



Published in final edited form as:

Comp Biochem Physiol C Toxicol Pharmacol. 2007 May ; 145(4): 553–581.

Marine pharmacology in 2003-4: Marine Compounds with Anthelmintic, 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

Alejandro M.S. Mayer¹, Abimael D. Rodriguez², Roberto G.S. Berlinck³, and Mark T. Hamann⁴

1 Department of Pharmacology, Chicago College of Osteopathic Medicine, Midwestern University, 555 31st Street, Downers Grove, Illinois 60515, U.S.A.

2 Department of Chemistry, University of Puerto Rico, San Juan, Puerto Rico 00931, U.S.A.

3 Instituto de Quimica de Sao Carlos, Universidade de Sao Paulo, Sao Carlos, 13560-970, Brazil

4 School of Pharmacy, The University of Mississippi, Faser Hall, University, Mississippi 38677, U.S.A.

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. Anthelmintic, 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

Author to whom correspondence should be addressed: Alejandro M.S. Mayer, Ph.D., Department of Pharmacology, Chicago College of Osteopathic Medicine, Midwestern University, 555 31st Street, Downers Grove, Illinois 60515, USA, Phone: (630) 515-6951, Fax: (630) 971-6414, Email: amayer@midwestern.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 anthelmintic, 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 *Sargassum 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 *anthelmintic* 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 ($LD_{99} = 3.1-8.3 \mu\text{g}/\text{mL}$) 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 (IC₅₀=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 methicillin-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 **dolabellin 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 dolabellin B2. Two papers reported on new antimicrobial peptides isolated from marine soft corals: Ata et al. (Ata et al., 2004) reported two new diterpenes, **pseudopterrosin 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 *Psammaphysilla 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 bicyclic **guanidine alkaloid (23)** from the marine sponge *Ptilocaulis spiculifer*, contributing a new member to the crambescic 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 known 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 (IC₅₀=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 **untenospongins 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 untenospongins B *in vivo* as well as its molecular mechanism of action.

Kossuga et al. (Kossuga et al., 2004) reported a new antifungal agent polyketide, **(2S, 3R)-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 (IC₅₀=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 unicellin class, **briarellins K hydroperoxide (41), D hydroperoxide (42) and L (43)**, isolated from the gorgonian *Briareum polyanthes* (IC₅₀=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 red octocoral *Eunicea* sp., (IC₅₀= 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 Streptomyces, Maskey et al. (Maskey et al., 2004) reported that the **trioxarcins 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 ($IC_{50}=0.2$ μ g/mL) while showing cytotoxicity at “*ten times higher concentration* ($IC_{50}=2.2$ μ g/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 ($LD_{50}=4.6-8.1$ μ g/mL), the authors proposed evaluation of this natural product as “*synergistic compound(s) for current antiprotozoan 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* ($ID_{50}=4-12$ μ M), which causes sleeping sickness, and the causative agent of cutaneous leishmaniasis, namely *Leishmania major* ($ID_{50}=12-45$ μ M), 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* H₃₇Rv ($MIC=12.5$ μ g/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* (H₃₇Rv, $MIC=0.91$ μ g/mL), comparing favorably with rifampin ($MIC=0.5$ μ g/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 8μ g/ml. A new scalarane-type bioactive sesterterpene, **12-deacetoxy scalarin 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 $MIC= 4$ μ M, comparing favorably with kanamycin sulfate ($MIC= 3.5-8.5$ μ M). 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., $IC_{50}=0.1 \mu M$; an *Oceanapiside* sp.-derived bromotyrosine compound (**56**), $IC_{50}=3 \mu M$; and the glycosphingolipid **oceanapiside (57)**, $IC_{50}=10 \mu M$. 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 **xestospongins 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 nummphaeus* 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* ($IC_{50}=1-3 \mu M$), 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 ($IC_{50}=3.2-5.6 \mu M$). 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 ($IC_{50}=10$ & $35 \mu M$, 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 ($IC_{50}=41.3-86.8 \mu M$), formation of giant cells ($IC_{50}=21.2-36.1 \mu M$) and recombinant reverse transcriptase *in vitro* ($IC_{50}=10.6-14.8 \mu M$).

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 E₂ 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 from a *Dysidea* sp. sponge, in several models of acute and chronic inflammation. The observation that bolinaquinone significantly inhibited cytokine, iNOS expression and eicosanoid (LTB₄, PGE₂) generation *in vitro* and *in vivo* in several models of inflammation through secretory PLA₂ 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 A₂. In mouse peritoneal macrophages *in vitro*, as well as in an *in vivo* model of inflammation, cacospongionolide B decreased nitric oxide, prostaglandin E₂ 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 I κ B- 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- κ B pathway and also exhibited *in vivo* activity. One novel iodinated **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 C₄₆ polyacetylenic alcohol isolated from the marine sponge *Petrosia* sp.. Petrocortyne A inhibited release of both TNF- α (IC₅₀=2.35 μ M) 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 E₂ and TNF- α both *in vitro* and *in vivo* while concomitantly inhibiting NF- κ B 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 A₂ (PLA₂) was investigated by mass spectrometry and molecular modelling approaches and demonstrated that petrosaspongiolides 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 *Pseudopteroorgia 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 *Pseudopteroorgia 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 B₂ (IC₅₀=4.7 μ M) 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 B₂ 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 decapeptide 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 (IC₅₀=0.44 μ M) 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 ($IC_{50}=0.1-2.7 \mu M$), was significantly more potent than that observed with the control agent herbimycin A ($IC_{50}=38 \mu M$). 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 polymannuroguronate (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 neurotogenic 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 $\mu\text{g/mL}$ 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 neurotogenic 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 *Cribrorchalina olemda*. Cribronic acid induced potent convulsive behavior in mice upon intracerebroventricular injection ($\text{ED}_{50} = 29 \pm 3.0$ pmol/mouse), as well as inhibited binding of an *N*-methyl-D-aspartic acid (NMDA) receptor ligand ($\text{IC}_{50} = 83 \pm 15$ 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 A₂ 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, Sudaralal et al. (Sudaralal 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 from 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**), *Atrium 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 et 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.

Acknowledgements

This publication was made possible by grant number 1R15 ES012654, from the National Institute of Environmental Health Sciences, NIH, to AMSM, and 1R01A136596, from the National Institute of Allergy and Infectious Diseases, NIH, and the Medicines for Malaria Venture (MMV), to MTH. Its content is solely the responsibility of the authors and does not necessarily represent the official views of the NIEHS, NIH. Additional financial support by Midwestern University is gratefully acknowledged. Jennifer Allman is acknowledged for her assistance with the preparation of Fig. 1 (MTH). The excellent support for literature searches in PubMed, Marinlit, Current Contents® and Chemical Abstracts®, as well as article retrieval by library staff members as well as medical and pharmacy students of Midwestern University is most gratefully acknowledged. The authors specially thank Ms. Mary Hall for carefully reviewing this manuscript.

References

- Agafonova IG, Aminin DL, Avilov SA, Stonik VA. Influence of cucumariosides upon intracellular $[Ca^{2+}]_i$ and lysosomal activity of macrophages. *J Agric Food Chem* 2003;51:6982–6986. [PubMed: 14611158]
- Aiello A, Borrelli F, Capasso R, Fattorusso E, Luciano P, Menna M. Conicamin, a novel histamine antagonist from the mediterranean tunicate *Aplidium conicum*. *Bioorg Med Chem Lett* 2003;13:4481–4483. [PubMed: 14643351]
- Alonso D, Khalil Z, Satkunanathan N, Livett BG. Drugs from the sea: conotoxins as drug leads for neuropathic pain and other neurological conditions. *Mini Rev Med Chem* 2003;3:785–787. [PubMed: 14529519]
- Aneiros A, Garateix A. Bioactive peptides from marine sources: pharmacological properties and isolation procedures. *J Chromatogr B Analyt Technol Biomed Life Sci* 2004;803:41–53.
- Ankisetty S, Amsler CD, McClintock JB, Baker BJ. Further membranolid diterpenes from the antarctic sponge *Dendrilla membranosa*. *J Nat Prod* 2004;67:1172–1174. [PubMed: 15270575]
- Aoki S, Wei H, Matsui K, Rachmat R, Kobayashi M. Pyridoacridine alkaloids inducing neuronal differentiation in a neuroblastoma cell line, from marine sponge *Biemna fortis*. *Bioorg Med Chem* 2003;11:1969–1973. [PubMed: 12670647]
- Ata A, Kerr RG, Moya CE, Jacobs RS. Identification of anti-inflammatory diterpenes from the marine gorgonian *Pseudopterogorgia elisabethae*. *Tetrahedron* 2003;59:4215–4222.
- Ata A, Win HY, Holt D, Holloway P, Segstro EP, Jayatilake GS. New antibacterial diterpenes from *Pseudopterogorgia elisabethae*. *Helvetica Chimica Acta* 2004;87:1090–1098.
- Bavington CD, Lever R, Mulloy B, Grundy MM, Page CP, Richardson NV, McKenzie JD. Anti-adhesive glycoproteins in echinoderm mucus secretions. *Comp Biochem Physiol B, Biochem & Molec Biol* 2004;139:607–617. [PubMed: 15581793]
- Bernan VS, Greenstein M, Carter GT. Mining marine microorganisms as a source of new antimicrobials and antifungals. *Curr Med Chem -Anti-infective Agents* 2004;3:181–195.
- Borrelli F, Campagnuolo C, Capasso R, Fattorusso E, Tagliatalata-Scafati O. Iodinated indole alkaloids from *Plakortis simplex* - New plakohypaphorines and an evaluation of their antihistamine activity. *Eur J Org Chem* 2004;1994;(15):3227–3232.
- Bugni TS, Singh MP, Chen L, Arias DA, Harper MK, Greenstein M, Maiese WM, Concepcion GP, Mangalindan GC, Ireland CM. Kalihinols from two *Acanthella cavernosa* sponges: inhibitors of bacterial folate biosynthesis. *Tetrahedron* 2004;60:6981–6988.
- Cao S, Gao Z, Thomas SJ, Hecht SM, Lazo JS, Kingston DG. Marine sesquiterpenoids that inhibit the lyase activity of DNA polymerase beta. *J Nat Prod* 2004;67:1716–1718. [PubMed: 15497946]
- Capasso A, Casapullo A, Randazzo A, Gomez-Paloma L. Petrosaspongiolide M reduces morphine withdrawal in vitro. *Life Sci* 2003;73:611–616. [PubMed: 12770615]
- Capon RJ, Skene C, Liu EH, Lacey E, Gill JH, Heiland K, Friedel T. Esmodil: an acetylcholine mimetic resurfaces in a Southern Australian marine sponge *Raspailia* (*Raspailia*) sp. *Nat Prod Res* 2004a;18:305–309. [PubMed: 15214481]
- Capon RJ, Skene C, Liu EH, Lacey E, Gill JH, Heiland K, Friedel T. Nematocidal thiocyanatins from a southern Australian marine sponge *Oceanapia* sp. *J Nat Prod* 2004b;67:1277–1282. [PubMed: 15332841]
- Carroll AR, Buchanan MS, Edser A, Hyde E, Simpson M, Quinn RJ. Dysinosins B-D, inhibitors of factor VIIa and thrombin from the Australian sponge *Lamellodysidea chlorea*. *J Nat Prod* 2004;67:1291–1294. [PubMed: 15332844]
- Cerqueira F, Watanadilok R, Sonchaeng P, Kijjoa A, Pinto M, Quarles vU, Kroes B, Beukelman C, Nascimento MS. Clionasterol: a potent inhibitor of complement component C1. *Planta Med* 2003;69:174–176. [PubMed: 12624828]
- Chang L, Whittaker NF, Bewley CA. Crambescidin 826 and dehydrocrambine A: new polycyclic guanidine alkaloids from the marine sponge *Monanchora* sp. that inhibit HIV-1 fusion. *J Nat Prod* 2003;66:1490–1494. [PubMed: 14640525]

- Chaturvedula VSP, Gao ZJ, Thomas SH, Hecht SA, Kingston DGI. New norditerpenoids and a diterpenoid from a sponge that inhibit the lyase activity of DNA polymerase beta. *Tetrahedron* 2004;1994;60(44):9991–9995.
- Chill L, Rudi A, Aknin M, Loya S, Hizi A, Kashman Y. New sesterterpenes from Madagascar *Lendenfeldia* sponges. *Tetrahedron* 2004;60(47):10619–10626.
- Ciavatta ML, Gresa MPL, Manzo E, Gavagnin M, Wahidulla S, Cimino G. New C-21 Delta(20) pregnanes, inhibitors of mitochondrial respiratory chain, from Indopacific octocoral *Carijoa* sp. *Tetrahedron Lett* 2004;45:7745–7748.
- Cichewicz RH, Kenyon VA, Whitman S, Morales NM, Arguello JF, Holman TR, Crews P. Redox inactivation of human 15-lipoxygenase by marine-derived meroditerpenes and synthetic chromanes: Archetypes for a unique class of selective and recyclable inhibitors. *J Amer Chem Soc* 2004;1994;126(45):14910–14920. [PubMed: 15535718]
- Copp BR. Antimycobacterial natural products. *Nat Prod Rep* 2003;20:535–557. [PubMed: 14700198]
- De Oliveira JH, Grube A, Kock M, Berlinck RG, Macedo ML, Ferreira AG, Hajdu E. Ingenamine G and cyclostellatamines G-I, K, and L from the new Brazilian species of marine sponge *Pachychalina* sp. *J Nat Prod* 2004;67:1685–1689. [PubMed: 15497940]
- Dmitrenok AS, Radhika P, Anjaneyulu V, Subrahmanyam S, Rao PVS, Dmitrenok PS, Boguslavsky VM. New lipids from the soft corals of the Andaman Islands. *Russ Chem Bull* 2003;52:1868–1872.
- Donia M, Hamann MT. Marine natural products and their potential applications as anti-infective agents. *Lancet Infect Dis* 2003;3:338–348. [PubMed: 12781505]
- Edwards DJ, Marquez BL, Nogle LM, McPhail K, Goeger DE, Roberts MA, Gerwick WH. Structure and biosynthesis of the jamaicamides, new mixed polyketide-peptide neurotoxins from the marine cyanobacterium *Lyngbya majuscula*. *Chem Biol* 2004;11:817–833. [PubMed: 15217615]
- Endo T, Tsuda M, Okada T, Mitsuhashi S, Shima H, Kikuchi K, Mikami Y, Fromont J, Kobayashi J. Nagelamides A-H, new dimeric bromopyrrole alkaloids from marine sponge *Agelas* species. *J Nat Prod* 2004;67:1262–1267. [PubMed: 15332839]
- Erdogan-Orhan I, Sener B, De Rosa S, Perez-Baz J, Lozach O, Leost M, Rakhilin S, Meijer L. Polyprenyl-hydroquinones and -furans from three marine sponges inhibit the cell cycle regulating phosphatase CDC25A. *Nat Prod Res* 2004;18:1–9. [PubMed: 14974610]
- Fennell BJ, Carolan S, Pettit GR, Bell A. Effects of the antimitotic natural product dolastatin 10, and related peptides, on the human malarial parasite *Plasmodium falciparum*. *J Antimicrob Chemother* 2003;51:833–841. [PubMed: 12654761]
- Fernandez-Busquets X, Burger MM. Circular proteoglycans from sponges: first members of the spongican family. *Cell Mol Life Sci* 2003;60:88–112. [PubMed: 12613660]
- Frenz JL, Kohl AC, Kerr RG. Marine natural products as therapeutic agents: Part 2. *Exp Opin Therap Patents* 2004;14:17–33. Review
- Fujita M, Nakao Y, Matsunaga S, Seiki M, Itoh Y, Yamashita J, van Soest RW, Fusetani N. Ageladine A: an antiangiogenic matrix metalloproteinase inhibitor from the marine sponge *Agelas nakamurai*. *J Am Chem Soc* 2003a;125:15700–15701. [PubMed: 14677933]
- Fujita M, Nakao Y, Matsunaga S, van Soest RW, Itoh Y, Seiki M, Fusetani N. Callysponginol sulfate A, an MT1-MMP inhibitor isolated from the marine sponge *Callyspongia truncata*. *J Nat Prod* 2003b;66:569–571. [PubMed: 12713420]
- Gochfeld DJ, El Sayed KA, Yousaf M, Hu JF, Bartyzel P, Dunbar DC, Wilkins SP, Zjawiony JK, Schinazi RF, Schlueter WS, Tharnish PM, Hamann MT. Marine natural products as lead anti-HIV agents. *Mini Rev Med Chem* 2003;3:401–424. [PubMed: 12769693]
- Gompel M, Leost M, Kier Joffe EB, Puricelli L, Franco LH, Palermo J, Meijer L. Meridianins, a new family of protein kinase inhibitors isolated from the ascidian *Aplidium meridianum*. *Bioorg Med Chem Lett* 2004;14:1703–1707. [PubMed: 15026054]
- Goud TV, Reddy NS, Swamy NR, Ram TS, Venkateswarlu Y. Anti-HIV active petrosins from the marine sponge *Petrosia similis*. *Biol Pharm Bull* 2003a;26:1498–1501.
- Goud TV, Srinivasulu M, Reddy VL, Reddy AV, Rao TP, Kumar DS, Murty US, Venkateswarlu Y. Two new bromotyrosine-derived metabolites from the sponge *Psammaphysilla purpurea*. *Chem Pharm Bull (Tokyo)* 2003b;51:990–993. [PubMed: 12913243]

- Grant MA, Morelli XJ, Rigby AC. Conotoxins and structural biology: a prospective paradigm for drug discovery. *Curr Protein Pept Sci* 2004;5:235–248. [PubMed: 15320731]
- Gustafson KR, Oku N, Milanowski DJ. Antiviral Marine Natural Products. *Curr Med Chem* 2004;3:233–249.
- Hassan W, Edrada R, Ebel R, Wray V, Berg A, Van Soest R, Wiryowidagdo S, Proksch P. New imidazole alkaloids from the Indonesian sponge *Leucetta chagosensis*. *J Nat Prod* 2004;67:817–822. [PubMed: 15165143]
- Hirono M, Ojika M, Mimura H, Nakanishi Y, Maeshima M. Acylspermidine derivatives isolated from a soft coral, *Simularia* sp, inhibit plant vacuolar H(+)-pyrophosphatase. *J Biochem (Tokyo)* 2003;133:811–816. [PubMed: 12869538]
- Hong S, Kim SH, Rhee MH, Kim AR, Jung JH, Chun T, Yoo ES, Cho JY. In vitro anti-inflammatory and pro-aggregative effects of a lipid compound, petrocortyne A, from marine sponges. *Naunyn-Schmiedeberg's Arch* 2003;368:448–456.
- Hu J, Geng M, Li J, Xin X, Wang J, Tang M, Zhang J, Zhang X, Ding J. Acidic oligosaccharide sugar chain, a marine-derived acidic oligosaccharide, inhibits the cytotoxicity and aggregation of amyloid beta protein. *J Pharmacol Sci* 2004;95:248–255. [PubMed: 15215650]
- Iijima R, Kisugi J, Yamazaki M. A novel antimicrobial peptide from the sea hare *Dolabella auricularia*. *Dev Comp Immunol* 2003;27:305–311. [PubMed: 12590964]
- Isnansetyo A, Kamei Y. MC21-A, a bactericidal antibiotic produced by a new marine bacterium, *Pseudoalteromonas phenolica* sp. nov. O-BC30(T), against methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003;47:480–488. [PubMed: 12543647]
- Jacob MR, Hossain CF, Mohammed KA, Smillie TJ, Clark AM, Walker LA, Nagle DG. Reversal of fluconazole resistance in multidrug efflux-resistant fungi by the *Dysidea arenaria* sponge sterol 9alpha,11alpha-epoxycholest-7-ene-3beta,5alpha,6alpha,19-tetrol 6-acetate. *J Nat Prod* 2003;66:1618–1622. [PubMed: 14695809]
- Jiang YH, Ryu SH, Ahn EY, You S, Lee BJ, Jung JH, Kim DK. Antioxidant activity of (8E,13Z, 20Z)-strobilinin/(7E,13Z, 20Z)-felixinin from a marine sponge *Psammocinia* sp. *Nat Prod Sci* 2004;10:272–276.
- Jung M, Kim H, Lee K, Park M. Naturally occurring peroxides with biological activities. *Mini Rev Med Chem* 2003;3:159–165. [PubMed: 12570849]
- Kamei Y, Tsang CK. Sargaquinoic acid promotes neurite outgrowth via protein kinase A and MAP kinases-mediated signaling pathways in PC12D cells. *Int J Dev Neurosci* 2003;21:255–262. [PubMed: 12850058]
- Kaneko M, Kisa F, Yamada K, Miyamoto T, Higuchi R. Structure of a new neuritogenic-active ganglioside from the sea cucumber *Stichopus japonicus*. *Eur J Org Chem* 2003;(6):1004–1008.
- Kehraus S, Gorzalka S, Hallmen C, Iqbal J, Muller CE, Wright AD, Wiese M, Konig GM. Novel amino acid derived natural products from the ascidian *Atrium robustum*: identification and pharmacological characterization of a unique adenosine derivative. *J Med Chem* 2004;47:2243–2255. [PubMed: 15084123]
- Keyzers RA, Davies-Coleman MT. Anti-inflammatory metabolites from marine sponges. *Chem Soc Rev* 2005;34:355–365. [PubMed: 15778769]
- Keyzers RA, Northcote PT, Berridge MV. Clathriol B, a new 14 beta marine sterol from the New Zealand sponge *Clathria lissosclera*. *Australian Journal of Chemistry* 2003;56:279–282.
- Keyzers RA, Northcote PT, Zubkov OA. Novel anti-inflammatory spongian diterpenes from the New Zealand marine sponge *Chelonaplysilla violacea*. *Eur J Org Chem* 2004;1994:419–425.
- Kossuga MH, MacMillan JB, Rogers EW, Molinski TF, Nascimento GG, Rocha RM, Berlinck RG. (2S, 3R)-2-aminododecan-3-ol, a new antifungal agent from the ascidian *Clavelina oblonga*. *J Nat Prod* 2004;67:1879–1881. [PubMed: 15568780]
- Krishnaiah P, Reddy VL, Venkataramana G, Ravinder K, Srinivasulu M, Raju TV, Ravikumar K, Chandrasekar D, Ramakrishna S, Venkateswarlu Y. New lamellarin alkaloids from the Indian ascidian *Didemnum obscurum* and their antioxidant properties. *J Nat Prod* 2004;67:1168–1171. [PubMed: 15270574]

- Lakshmi V, Kumar R, Gupta P, Varshney V, Srivastava MN, Dikshit M, Murthy PK, Misra-Bhattacharya S. The antifilarial activity of a marine red alga, *Botryocladia leptopoda*, against experimental infections with animal and human filariae. *Parasitol Res* 2004;93:468–474. [PubMed: 15243801]
- Laurent D, Pietra F. Natural-product diversity of the New Caledonian marine ecosystem compared to other ecosystems: A pharmacologically oriented view. *Chem Biodiv* 2004;1:539–594. Review
- Lee EH, Yun MR, Wang WH, Jung JH, Im DS. Structure-activity relationship of lysophosphatidylcholines in HL-60 human leukemia cells. *Acta Pharmacol Sin* 2004;25:1521–1524. [PubMed: 15525477]
- Lippert H, Brinkmeyer R, Mulhaupt T, Iken K. Antimicrobial activity in sub-Arctic marine invertebrates. *Polar Biol* 2003;26:591–600.
- Livett BG, Gayler KR, Khalil Z. Drugs from the sea: conopeptides as potential therapeutics. *Curr Med Chem* 2004;11:1715–1723. [PubMed: 15279578]
- Lucas R, Casapullo A, Ciasullo L, Gomez-Paloma L, Paya M. Cycloamphilectenes, a new type of potent marine diterpenes: inhibition of nitric oxide production in murine macrophages. *Life Sci* 2003a; 72:2543–2552. [PubMed: 12650863]
- Lucas R, Giannini C, D'Auria MV, Paya M. Modulatory effect of bolinaquinone, a marine sesquiterpenoid, on acute and chronic inflammatory processes. *J Pharmacol Exp Ther* 2003b; 304:1172–1180. [PubMed: 12604694]
- Luescher-Mattli M. Algae, a possible source for new drugs in the treatment of HIV and other viral diseases. *Curr Med Chem* 2003;2:219–225.
- Marrero J, Rodriguez AD, Baran P, Raptis RG, Sanchez JA, Ortega-Barria E, Capson TL. Bielschowskysin, a gorgonian-derived biologically active diterpene with an unprecedented carbon skeleton. *Org Lett* 2004;6:1661–1664. [PubMed: 15128261]
- Maskey RP, Helmeke E, Kayser O, Fiebig HH, Maier A, Busche A, Laatsch H. anti-cancer and antibacterial trioxacarcins with high anti-malaria activity from a marine streptomycete and their absolute stereochemistry. *J Antibiot* 2004;57:771–779. [PubMed: 15745111]
- Masuno MN, Hoepker AC, Pessah IN, Molinski TF. 1-O-Sulfatobastadins-1 and -2 from *Ianthella basta* (Pallas). Antagonists of the RyR1-FKBP23 Ca⁺² Channel. *Marine Drugs* 2004;2:176–184.
- Matsubara K. Recent advances in marine algal anticoagulants. *Curr Med Chem* 2004;2:13–19.
- Mayer AMS, Hamann MT. Marine pharmacology in 1999: compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, anthelmintic, anti-inflammatory, antiplatelet, antiprotozoal and antiviral activities; affecting the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. *Comp Biochem Physiol C, Pharmacol Toxicol* 2002;132:315–339.
- Mayer AMS, Hamann MT. Marine pharmacology in 2000: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antituberculosis, and antiviral activities; affecting the cardiovascular, immune, and nervous systems and other miscellaneous mechanisms of action. *Mar Biotechnol (NY)* 2004;6:37–52. [PubMed: 14583811]
- Mayer AMS, Hamann MT. Marine pharmacology in 2001-2002: marine compounds with anthelmintic, antibacterial, anticoagulant, antidiabetic, antifungal, anti-inflammatory, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems and other miscellaneous mechanisms of action. *Comp Biochem Physiol C Toxicol Pharmacol* 2005;140:265–286. [PubMed: 15919242]
- Mayer AMS, Lehmann VKB. Marine pharmacology in 1998: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, anthelmintic, antiplatelet, antiprotozoal, and antiviral activities; with actions on the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. *Pharmacologist* 2000;42:62–69.
- McClelland D, Evans RM, Abidin I, Sharma S, Choudhry FZ, Jaspars M, Sepcic K, Scott RH. Irreversible and reversible pore formation by polymeric alkylpyridinium salts (poly-APS) from the sponge *Reniera sarai*. *Br J Pharmacol* 2003;139:1399–1408. [PubMed: 12922926]
- Meiyou G, Fuchuan L, Xianliang X, Jing L, Zuowei Y, Huashi G. The potential molecular targets of marine sulfated polymannuroguluronate interfering with HIV-1 entry. Interaction between SPMG and HIV-1 rgp120 and CD4 molecule. *Antiviral Res* 2003;59:127–135. [PubMed: 12895696]

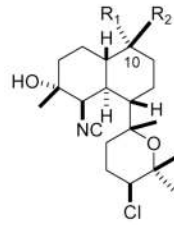
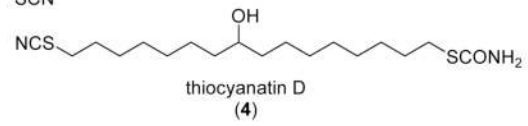
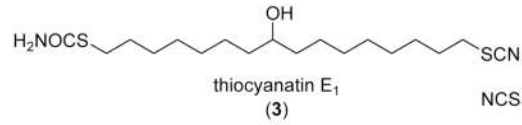
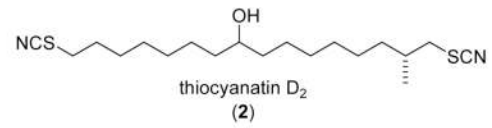
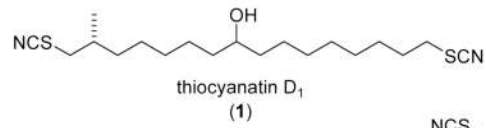
- Melo FR, Pereira MS, Foguel D, Mourao PA. Antithrombin-mediated anticoagulant activity of sulfated polysaccharides: different mechanisms for heparin and sulfated galactans. *J Biol Chem* 2004;279:20824–20835. [PubMed: 14996843]
- Miao B, Geng M, Li J, Li F, Chen H, Guan H, Ding J. Sulfated polymannuroguluronate, a novel anti-acquired immune deficiency syndrome (AIDS) drug candidate, targeting CD4 in lymphocytes. *Biochem Pharmacol* 2004;68:641–649. [PubMed: 15276071]
- Miljanich GP. Ziconotide: neuronal calcium channel blocker for treating severe chronic pain. *Curr Med Chem* 2004;11:3029–3040. [PubMed: 15578997]
- Molinski TF. Antifungal Compounds from Marine Organisms. *Curr Med Chem* 2004;3:197–220.
- Monti MC, Casapullo A, Riccio R, Gomez-Paloma L. Further insights on the structural aspects of PLA (2) inhibition by gamma-hydroxybutenolide-containing natural products: a comparative study on petrosaspongiolides M-R. *Bioorg. Med Chem* 2004;12:1467–1474.
- Mourao PA. Use of sulfated fucans as anticoagulant and antithrombotic agents: future perspectives. *Curr Pharm Des* 2004;10:967–981. [PubMed: 15078127]
- Mukku VJ, Edrada RA, Schmitz FJ, Shanks MK, Chaudhuri B, Fabbro D. New sesquiterpene quinols from a Micronesian sponge *Aka* sp. *J Nat Prod* 2003;66:686–689. [PubMed: 12762808]
- Nakao Y, Shiroiwa T, Murayama S, Matsunaga S, Goto Y, Matsumoto Y, Fusetani N. Identification of Renieramycin A as an Antileishmanial substance in a marine sponge *Neopetrosia* sp. *Mar Drugs* 2004;2:55–62.
- Nakao Y, Maki T, Matsunaga S, van Soest RW, Fusetani N. Penasulfate A, a new alpha-glucosidase inhibitor from a marine sponge *Penares* sp. *J Nat Prod* 2004;67:1346–1350. [PubMed: 15332853]
- Namikoshi M, Suzuki S, Meguro S, Nagai H, Koike Y, Kitazawa A, Kobayashi H, Oda T, Yamada J. Manoalide derivatives from a marine sponge *Luffariella* sp collected in Palau. *Fisheries Sci* 2004;70:152–158.
- Newman DJ, Cragg GM, Snader KM. Natural products as sources of new drugs over the period 1981-2002. *J Nat Prod* 2003;66:1022–1037. [PubMed: 12880330]
- Nicholas GM, Eckman LL, Newton GL, Fahey RC, Ray S, Bewley CA. Inhibition and kinetics of mycobacterium tuberculosis and mycobacterium smegmatis mycothiol-S-conjugate amidase by natural product inhibitors. *Bioorg Med Chem* 2003;11:601–608. [PubMed: 12538025]
- Nika K, Mulloy B, Carpenter B, Gibbs R. Specific recognition of immune cytokines by sulphated polysaccharides from marine algae. *Eur J Phycol* 2003;38:257–264.
- Nishimura S, Matsunaga S, Shibazaki M, Suzuki K, Furihata K, van Soest RW, Fusetani N. Massadine, a novel geranylgeranyltransferase type I inhibitor from the marine sponge *Stylissa* aff. *massa*. *Org Lett* 2003;5:2255–2257. [PubMed: 12816422]
- Ohgami K, Shiratori K, Kotake S, Nishida T, Mizuki N, Yazawa K, Ohno S. Effects of astaxanthin on lipopolysaccharide-induced inflammation in vitro and in vivo. *Invest Ophthalmol Vis Sci* 2003;44:2694–2701. [PubMed: 12766075]
- Oku N, Gustafson KR, Cartner LK, Wilson JA, Shigematsu N, Hess S, Pannell LK, Boyd MR, McMahon JB. Neamphamide A, a new HIV-inhibitory depsipeptide from the Papua New Guinea marine sponge *Neamphius huxleyi*. *J Nat Prod* 2004;67:1407–1411. [PubMed: 15332865]
- Ospina CA, Rodriguez AD, Ortega-Barria E, Capson TL. Briarellins J-P and polyanthellin A: new eunicellin-based diterpenes from the gorgonian coral *Briareum polyanthes* and their antimalarial activity. *J Nat Prod* 2003;66:357–363. [PubMed: 12662092]
- Ovchinnikova TV, Aleshina GM, Balandin SV, Krasnosdembkaya AD, Markelov ML, Frolova EI, Leonova YF, Tagaev AA, Krasnodembsky EG, Kokryakov VN. Purification and primary structure of two isoforms of arenicin, a novel antimicrobial peptide from marine polychaeta *Arenicola marina*. *FEBS Lett* 2004;577:209–214. [PubMed: 15527787]
- Pan W, Liu X, Ge F, Han J, Zheng T. Perinerin, a novel antimicrobial peptide purified from the clamworm *Perinereis aibuhitensis* grube and its partial characterization. *J Biochem (Tokyo)* 2004;135:297–304. [PubMed: 15113828]
- Pascual I, Gil-Parrado S, Cisneros M, Joseph-Bravo P, Diaz J, Possani LD, Charli JL, Chavez M. Purification of a specific inhibitor of pyroglutamyl aminopeptidase II from the marine annelide *Hermodice carunculata*. in vivo effects in rodent brain. *Int J Biochem Cell Biol* 2004;36:138–152. [PubMed: 14592539]

- Patrzykat A, Douglas SE. Gone gene fishing: how to catch novel marine antimicrobials. Trends Biotechnol 2003a;21:362–369. [PubMed: 12902173]
- Patrzykat A, Gallant JW, Seo JK, Pytyck J, Douglas SE. Novel antimicrobial peptides derived from flatfish genes. Antimicrob Agents Chemother 2003b;47:2464–2470. [PubMed: 12878506]
- Pereira HS, Leao-Ferreira LR, Moussatche N, Teixeira VL, Cavalcanti DN, Costa LJ, Diaz R, Frugulhetti IC. Antiviral activity of diterpenes isolated from the Brazilian marine alga *Dictyota menstrualis* against human immunodeficiency virus type 1 (HIV-1). Antiviral Res 2004;64:69–76. [PubMed: 15451181]
- Perez M, Sadqi M, Munoz V, Avila J. Inhibition by Aplidine of the aggregation of the prion peptide PrP¹⁰⁶⁻¹²⁶ into beta-sheet fibrils. Biochim Biophys Acta 2003;1639:133–139. [PubMed: 14559120]
- Pettit RK, Fakoury BR, Knight JC, Weber CA, Pettit GR, Cage GD, Pon S. Antibacterial activity of the marine sponge constituent cribrostatin 6. J Med Microbiol 2004;53:61–65. [PubMed: 14663107]
- Pimentel SM, Bojo ZP, Roberto AV, Lazaro JE, Mangalindan GC, Florentino LM, Lim-Navarro P, Tasdemir D, Ireland CM, Concepcion GP. Platelet aggregation inhibitors from philippine marine invertebrate samples screened in a new microplate assay. Mar Biotechnol (NY) 2003;5:395–400. [PubMed: 14719168]
- Posadas I, De Rosa S, Terencio MC, Paya M, Alcaraz MJ. Cacospongionolide B suppresses the expression of inflammatory enzymes and tumour necrosis factor-alpha by inhibiting nuclear factor-kappa B activation. Br J Pharmacol 2003a;138:1571–1579. [PubMed: 12721113]
- Posadas I, Terencio MC, Randazzo A, Gomez-Paloma L, Paya M, Alcaraz MJ. Inhibition of the NF-kappaB signaling pathway mediates the anti-inflammatory effects of petrospongionolide. M Biochem Pharmacol 2003b;65:887–895.
- Proksch P, Ebel R, Edrada RA, Schupp P, Lin HW, Sudarsono, Wray V, Steube K. Detection of pharmacologically active natural products using ecology. Selected examples from Indopacific marine invertebrates and sponge-derived fungi. Pure Appl Chem 2003a;75:343–352.
- Proksch, P.; Ebel, R.; Edrada, RA.; Wray, V.; Steube, K. SPONGES: (PORIFERA). 2003b. Bioactive natural products from marine invertebrates and associated fungi; p. 117-142.
- Qi J, Ojika M, Sakagami Y. Linckosides C-E, three new neurotogenic steroid glycosides from the Okinawan starfish *Linckia laevigata*. Bioorg Med Chem 2004;12:4259–4265. [PubMed: 15246102]
- Radhika P, Cabeza M, Bratoeff E, Garcia G. 5 alpha-Reductase inhibition activity of steroids isolated from marine soft corals. Steroids 2004;69:439–444. [PubMed: 15246773]
- Rao KV, Santarsiero BD, Mesecar AD, Schinazi RF, Tekwani BL, Hamann MT. New manzamine alkaloids with activity against infectious and tropical parasitic diseases from an Indonesian sponge. J Nat Prod 2003;66:823–828. [PubMed: 12828469]
- Rifai S, Fassouane A, Kijjoa A, Van Soest R. Antimicrobial activity of untenospongin B, a metabolite from the marine sponge *Hippospongia communis* collected from the Atlantic coast of Morocco. Mar Drugs 2004;2:147–153.
- Roch P, Beschin A, Bernard E. Antiprotozoan and Antiviral Activities of Non-cytotoxic Truncated and Variant Analogues of Mussel Defensin. Evid Based Complement Alternat Med 2004;1:167–174. [PubMed: 15480442]
- Rodriguez II, Rodriguez AD. Homopseudopteroxazole, a new antimycobacterial diterpene alkaloid from *Pseudopteroxorgia elisabethae*. J Nat Prod 2003;66:855–857. [PubMed: 12828474]
- Rodriguez II, Shi YP, Garcia OJ, Rodriguez AD, Mayer AM, Sanchez JA, Ortega-Barria E, Gonzalez J. New pseudopterosin and seco-pseudopterosin diterpene glycosides from two Colombian isolates of *Pseudopteroxorgia elisabethae* and their diverse biological activities. J Nat Prod 2004;67:1672–1680. [PubMed: 15497938]
- Sakai R, Matsubara H, Shimamoto K, Jimbo M, Kamiya H, Namikoshi M. Isolations of N-methyl-D-aspartic acid-type glutamate receptor ligands from Micronesian sponges. J Nat Prod 2003;66:784–787. [PubMed: 12828462]
- Sakai R, Suzuki K, Shimamoto K, Kamiya H. Novel betaines from a micronesian sponge *Dysidea herbacea*. J Org Chem 2004;69:1180–1185. [PubMed: 14961668]
- Sandsdalen E, Haug T, Stensvag K, Styrvold OB. The antibacterial effect of a polyhydroxylated fucophlorethol from the marine brown alga, *Fucus vesiculosus*. World J Microbiol Biotechnol 2003;19:777–782.

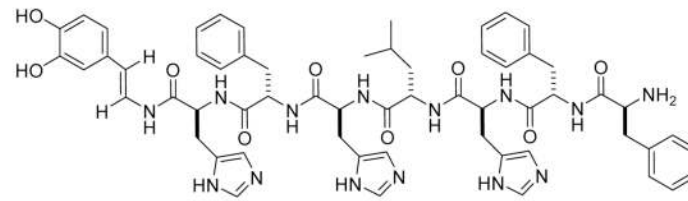
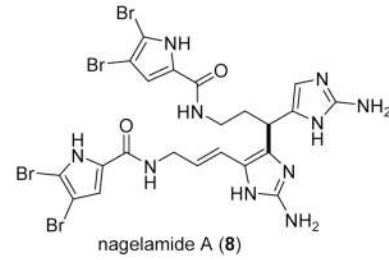
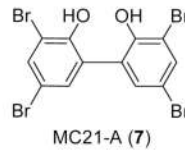
- Satitpatipan V, Suwanborirux K. New nitrogenous Germacrane from a Thai marine sponge, *Axinyssa n. sp.* J Nat Prod 2004;67:503–505. [PubMed: 15043445]
- Savoia D, Avanzini C, Aliche T, Callone E, Guella G, Dini F. Antimicrobial activity of euplotin C, the sesquiterpene taxonomic marker from the marine ciliate *Euplotes crassus*. Antimicrob Agents Chemother 2004;48:3828–3833. [PubMed: 15388442]
- Schmitz, FJ.; Bowden, BF.; Toth, SI. Antitumor and cytotoxic compounds from marine organisms. In: Attaway, DH.; Zaborsky, OR., editors. Marine Biotechnology, Pharmaceutical and Bioactive Natural Products, vol 1. Plenum Press; New York: p. 197-308.
- Schupp P, Poehner T, Edrada R, Ebel R, Berg A, Wray V, Proksch P. Eudistomins W and X, two new beta-carbolines from the micronesian tunicate *Eudistoma* sp. J Nat Prod 2003;66:272–275. [PubMed: 12608864]
- Sharpe IA, Palant E, Schroeder CI, Kaye DM, Adams DJ, Alewood PF, Lewis RJ. Inhibition of the norepinephrine transporter by the venom peptide chi-MrIA. Site of action, Na⁺ dependence, and structure-activity relationship. J Biol Chem 2003;278:40317–40323. [PubMed: 12885787]
- Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, Fisher R, Bryce DA, Mangieri EA, Luther RR, Mayo M, McGuire D, Ellis D. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS - A randomized controlled trial. J Amer Med Ass 2004;291:63–70.
- Sudarslal S, Majumdar S, Ramasamy P, Dhawan R, Pal PP, Ramaswami M, Lala AK, Sikdar SK, Sarma SP, Krishnan KS, Balaram P. Sodium channel modulating activity in a delta-conotoxin from an Indian marine snail. FEBS Lett 2003;553:209–212. [PubMed: 14550575]
- Takada K, Uehara T, Nakao Y, Matsunaga S, van Soest RW, Fusetani N. Schulzeines A-C, new alpha-glucosidase inhibitors from the marine sponge *Penares schulzei*. J Am Chem Soc 2004;126:187–193. [PubMed: 14709083]
- Takamatsu S, Hodges TW, Rajbhandari I, Gerwick WH, Hamann MT, Nagle DG. Marine natural products as novel antioxidant prototypes. J Nat Prod 2003;66:605–608. [PubMed: 12762791]
- Tincu JA, Menzel LP, Azimov R, Sands J, Hong T, Waring AJ, Taylor SW, Lehrer RI. Plicatamide, an antimicrobial octapeptide from *Styela plicata* hemocytes. J Biol Chem 2003;278:13546–13553. [PubMed: 12569105]
- Tincu JA, Taylor SW. Antimicrobial peptides from marine invertebrates. Antimicrob Agents Chemother 2004;48:3645–3654. [PubMed: 15388415]
- Tosuji H, Fusetani N, Seki Y. Calyculin A causes the activation of histone H1 kinase and condensation of chromosomes in unfertilized sea urchin eggs independently of the maturation-promoting factor. Comp Biochem Physiol C, Toxicol Pharmacol 2003;135:415–424. [PubMed: 12965186]
- Trevisi L, Cargnelli G, Ceolotto G, Papparella I, Semplicini A, Zampella A, D'Auria MV, Luciani S. Callipeltin A: sodium ionophore effect and tension development in vascular smooth muscle. Biochem Pharmacol 2004;68:1331–1338. [PubMed: 15345322]
- Tsang CK, Kamei Y. Sargaquinoic acid supports the survival of neuronal PC12D cells in a nerve growth factor-independent manner. Eur J Pharmacol 2004;488:11–18. [PubMed: 15044030]
- Tsukamoto S, Miura S, Yamashita Y, Ohta T. Aspermytin A: a new neurotrophic polyketide isolated from a marine-derived fungus of the genus *Aspergillus*. Bioorg Med Chem Lett 2004a;14:417–420. [PubMed: 14698172]
- Tsukamoto S, Tatsuno M, van Soest RW, Yokosawa H, Ohta T. New polyhydroxy sterols: proteasome inhibitors from a marine sponge *Acanthodendrilla* sp. J Nat Prod 2003;66:1181–1185. [PubMed: 14510593]
- Tsukamoto S, Yamashita Y, Yoshida T, Ohta T. Parguerol and Isoparguerol Isolated from the Sea Hare, *Aplysia kurodai*, Induce Neurite Outgrowth in PC-12 Cells. Mar Drugs 2004b;2:170–175.
- Tucker SJ, McClelland D, Jaspars M, Sepcic K, MacEwan DJ, Scott RH. The influence of alkyl pyridinium sponge toxins on membrane properties, cytotoxicity, transfection and protein expression in mammalian cells. Biochim Biophys Acta 2003;1614:171–181. [PubMed: 12896810]
- Tziveleka LA, Vagias C, Roussis V. Natural products with anti-HIV activity from marine organisms. Curr Top Med Chem 2003;3:1512–1535. [PubMed: 14529524]
- Uchida T, Yamasaki T, Eto S, Sugawara H, Kurisu G, Nakagawa A, Kusunoki M, Hatakeyama T. Crystal structure of the hemolytic lectin CEL-III isolated from the marine invertebrate *Cucumaria*

- echinata*: implications of domain structure for its membrane pore-formation mechanism. *J Biol Chem* 2004;279:37133–37141. [PubMed: 15194688]
- Verbitski SM, Mullally JE, Fitzpatrick FA, Ireland CM. Punaglandins, chlorinated prostaglandins, function as potent Michael receptors to inhibit ubiquitin isopeptidase activity. *J Med Chem* 2004;47:2062–2070. [PubMed: 15056003]
- Vetvicka V, Yvin JC. Effects of marine beta-1,3 glucan on immune reactions. *Int Immunopharmacol* 2004;4:721–730. [PubMed: 15135314]
- Villar RM, Gil-Longo J, Daranas AH, Souto ML, Fernandez JJ, Peixinho S, Barral MA, Santafe G, Rodriguez J, Jimenez C. Evaluation of the effects of several zoanthamine-type alkaloids on the aggregation of human platelets. *Bioorg Med Chem* 2003;11:2301–2306. [PubMed: 12713841]
- Wang CY, Wang BG, Wiryowidagdo S, Wray V, Van Soest R, Steube KG, Guan HS, Proksch P, Ebel R. Melophlins C-O, thirteen novel tetramic acids from the marine sponge *Melophlus sarassinorum*. *J Nat Prod* 2003;66:51–56. [PubMed: 12542345]
- Wang L, Geng M, Li J, Guan H, Ding J. Studies of marine sulfated polymannuroguluronate on endothelial cell proliferation and endothelial immunity and related mechanisms. *J Pharmacol Sci* 2003;92:367–373. [PubMed: 12939521]
- Wei XM, Rodriguez AD, Baran P, Raptis RG, Sanchez JA, Ortega-Barria E, Gonzalez J. Antiplasmodial cembradiene diterpenoids from a Southwestern Caribbean gorgonian octocoral of the genus *Eunicea*. *Tetrahedron* 2004;60:11813–11819.
- Williams DE, Lapawa M, Feng X, Tarling T, Roberge M, Andersen RJ. Spirastrellolide A: revised structure, progress toward the relative configuration, and inhibition of protein phosphatase 2A. *Org Lett* 2004a;6:2607–2610. [PubMed: 15255702]
- Williams DE, Telliez JB, Liu J, Tahir A, Van Soest R, Andersen RJ. Meroterpenoid MAPKAP (MK2) inhibitors isolated from the Indonesian marine sponge *Acanthodendrilla* sp. *J Nat Prod* 2004b;67:2127–2129. [PubMed: 15620270]
- Wonganuchitmeta SN, Yuenyongsawad S, Keawpradub N, Plubrukarn A. Antitubercular sesterterpenes from the Thai sponge *Brachiaster* sp. *J Nat Prod* 2004;67:1767–1770. [PubMed: 15497961]
- Xu N, Fan X, Yan X, Li X, Niu R, Tseng CK. Antibacterial bromophenols from the marine red alga *Rhodomela confervoides*. *Phytochemistry* 2003;62:1221–1224. [PubMed: 12648540]
- Yamada T, Iritani M, Minoura K, Kawai K, Numata A. Peribysins A-D, potent cell-adhesion inhibitors from a sea hare-derived culture of *Periconia* species. *Org Biomolec Chem* 2004;2:2131–2135.
- Yang SW, Buiovich A, Chan TM, Smith M, Lachowicz J, Pomponi SA, Wright AE, Mierzwa R, Patel M, Gullo V, Chu M. A new sterol sulfate, Sch 572423, from a marine sponge, *Topsentia* sp. *Bioorg Med Chem Lett* 2003a;13:1791–1794. [PubMed: 12729666]
- Yang SW, Chan TM, Pomponi SA, Chen G, Loebenberg D, Wright A, Patel M, Gullo V, Pramanik B, Chu M. Structure elucidation of a new antifungal sterol sulfate, Sch 575867, from a deep-water marine sponge (Family: Astroscleridae). *J Antibiot (Tokyo)* 2003b;56:186–189. [PubMed: 12715881]
- Yang SW, Chan TM, Pomponi SA, Chen G, Wright AE, Patel M, Gullo V, Pramanik B, Chu M. A new bicyclic guanidine alkaloid, Sch 575948, from a marine sponge, *Ptilocaulis spiculifer*. *J Antibiot (Tokyo)* 2003c;56:970–972. [PubMed: 14763564]
- Yang SW, Chan TM, Pomponi SA, Gonsiorek W, Chen G, Wright AE, Hipkin W, Patel M, Gullo V, Pramanik B, Zavodny P, Chu M. A new sesterterpene, Sch 599473, from a marine sponge, *Ircinia* sp. *J Antibiot (Tokyo)* 2003d;56:783–786. [PubMed: 14632288]
- Yim JH, Kim SJ, Ahn SH, Lee CK, Rhie KT, Lee HK. Antiviral effects of sulfated exopolysaccharide from the marine microalga *Gyrodinium impudicum* strain KG03. *Mar Biotechnol (NY)* 2004;6:17–25. [PubMed: 14508657]
- Yoo HD, L D, Sanghara J, Daley D, Van Soest R, Andersen RJ. Isoarenarol, A New Protein Kinase Inhibitor from the Marine Sponge *Dysidea arenaria*. *Pharm Biol* 2003;41:223–225.
- Zancan P, Mourao PA. Venous and arterial thrombosis in rat models: dissociation of the antithrombotic effects of glycosaminoglycans. *Blood Coagul Fibrinol* 2004;15:45–54.
- Zhang W, Xue S, Zhao Q, Zhang X, Li J, Jin M, Yu X, Yuan Q. Biopotentials of marine sponges from China oceans: past and future. *Biomol Eng* 2003;20:413–419. [PubMed: 12919827]

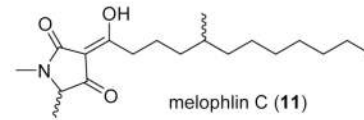
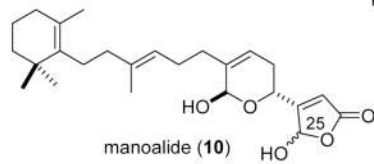
Zhu W, Chiu LC, Ooi VE, Chan PK, Ang PO Jr. Antiviral property and mode of action of a sulphated polysaccharide from *Sargassum patens* against herpes simplex virus type 2. *Int J Antimicrob Agents* 2004;24:279–283. [PubMed: 15325432]



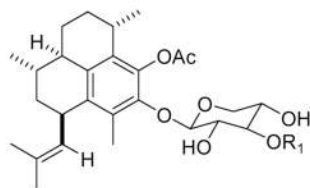
kalihinol Y (5) R₁, R₂ = CH₂
kalihinol X (6) R₁ = NCS, R₂ = Me



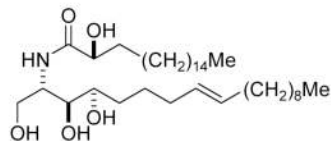
plicatamide (9)



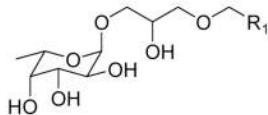
SHQDCYEALHKCMASHKPFSCSMKFMCLQQQ
dolabellarin B2 (13)



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

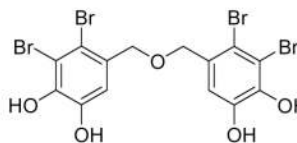


methyl 2-hydroxyoctadecanoate (**16**)

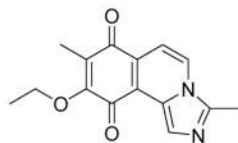


lipid 4a (**17**) $R_1=(CH_2)_{16}Me$

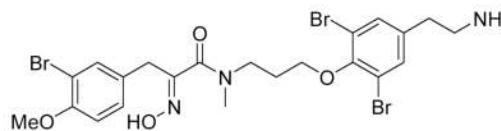
lipid 5a (**18**) $R_1=(CH_2)_{14}Me$



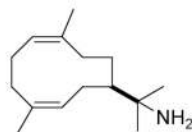
bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**19**)



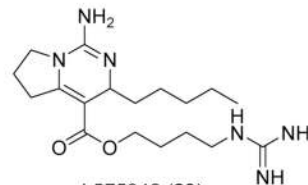
cribrostatin 6 (**20**)



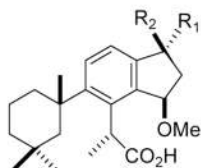
purpuramine L (**21**)



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



sch575948 (**23**)



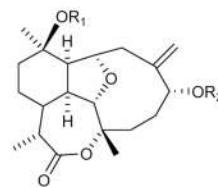
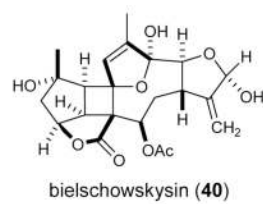
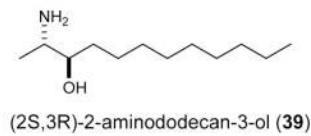
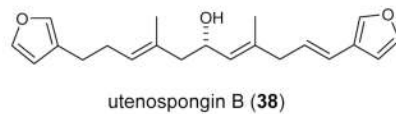
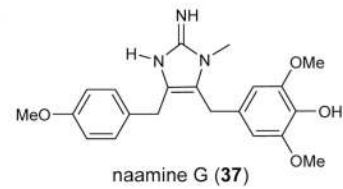
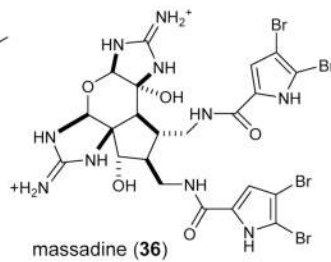
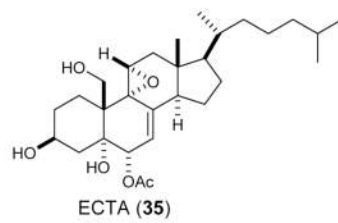
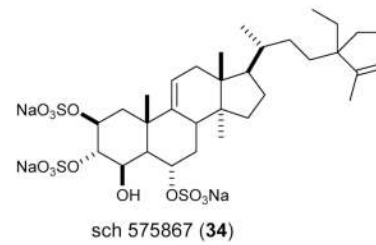
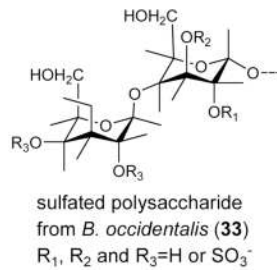
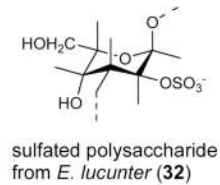
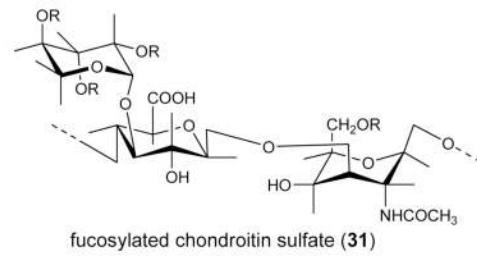
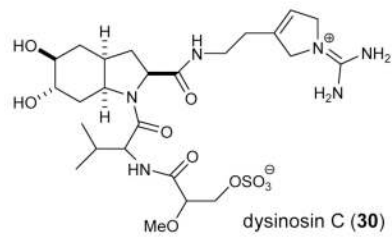
membranolid C (**24**) $R_1=OMe, R_2=H$
membranolid D (**25**) $R_1=H, R_2=OMe$

RWCYAYVRVGRVLRVYRRCW
arenicin-1 (**26**)

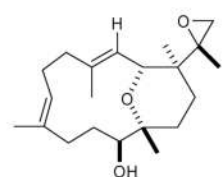
RWCYAYVRIRIGVLRVYRRCW
arenicin-2 (**27**)

FNKLKQGSSKRTCAKCFRKIMPSVHE
LDERRRGANRWAGFRKCVSSICRY
perinerin (**28**)

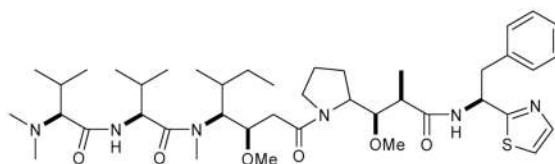
GWRTLLKKAIEVKTVGKLLKHYL-NH₂
Hippoglossoides peptide (**29**)



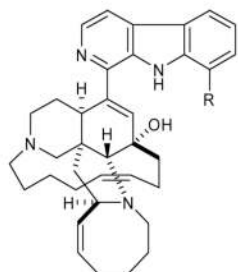
briarellin D hydroperoxide (**42**) R₁ = COC₃H₇, R₂ = OH
briarellin L (**43**) R₁ = COC₃H₇, R₂ = Ac



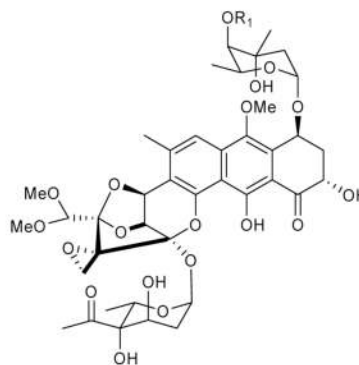
11(S*)-Hydroxy-
2(R*),12(R*),15(S*),17-
diepoxy-(3E,7E)-1(S*)-
cembra-3,7-diene (**44**)



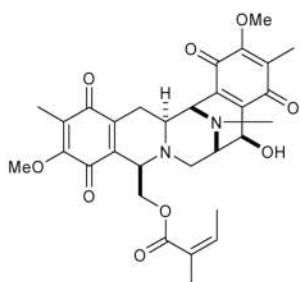
dolastatin 10 (**45**)



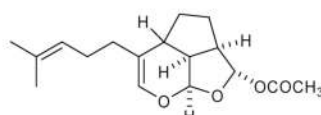
manzamine A (**46**) R = H
8-Hydroxymanzamine A (**47**) R = OH



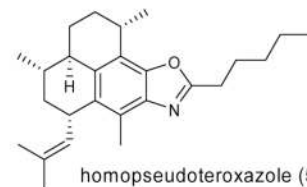
Trioxacarcin A (**48**) R₁=Ac
Trioxacarcin D (**49**) R₁=H



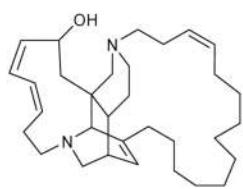
renieramycin A (**50**)



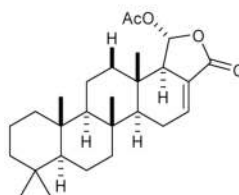
euplotin C (**51**)



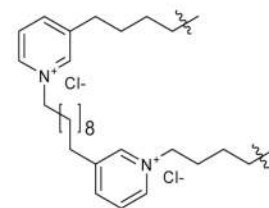
homopseudoteroxazole (**52**)



ingenamine G (**53**)



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



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

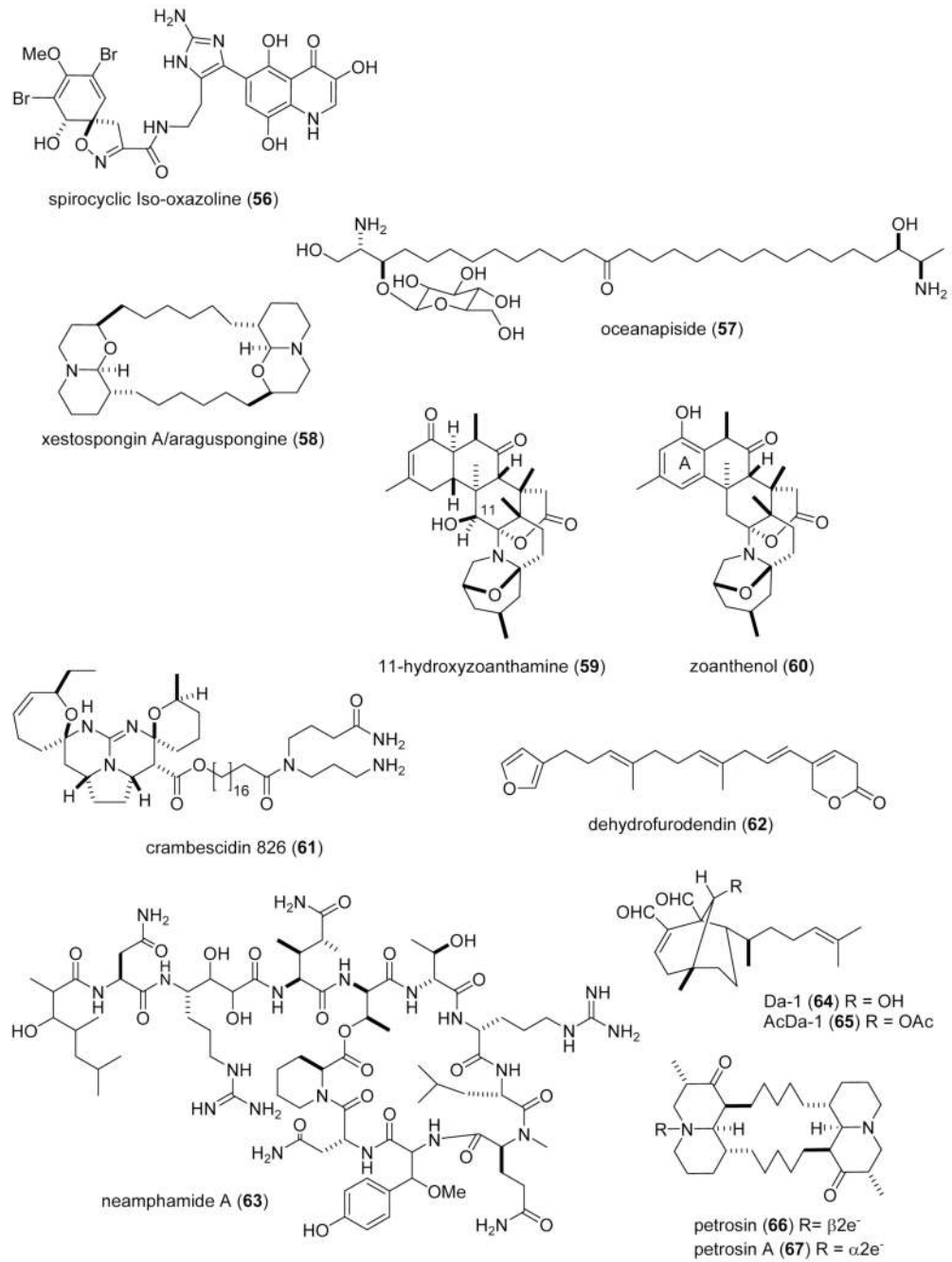
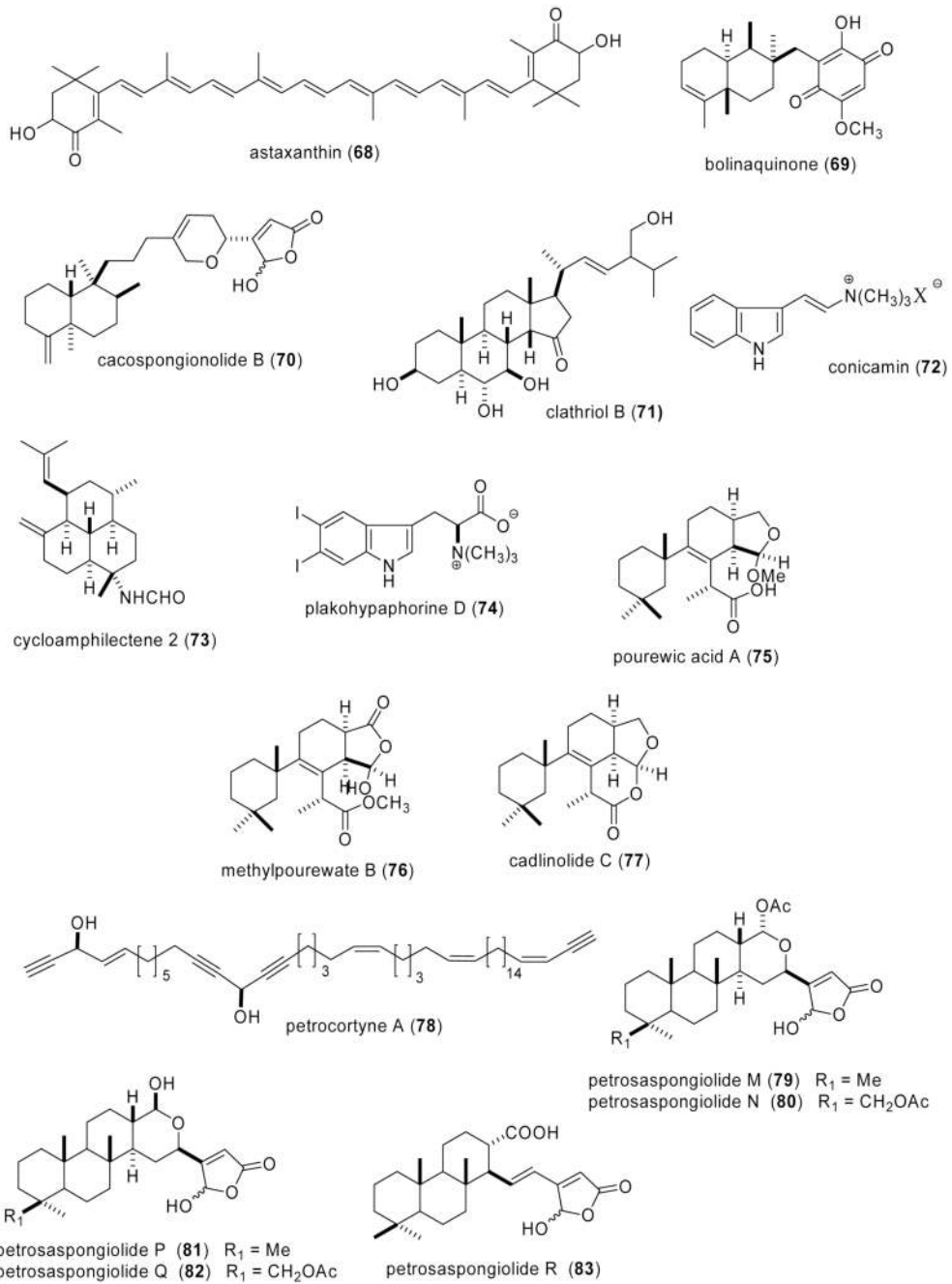
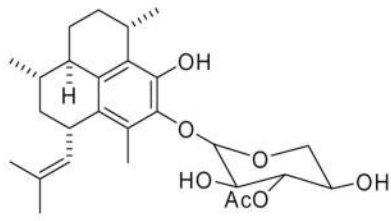
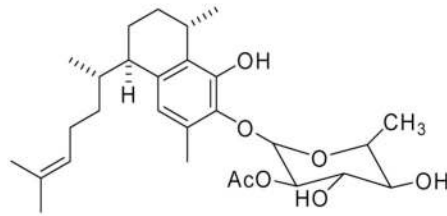


Figure 1.

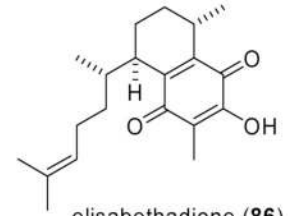




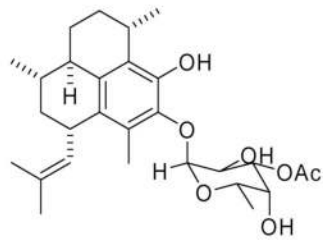
pseudopterosin N (84)



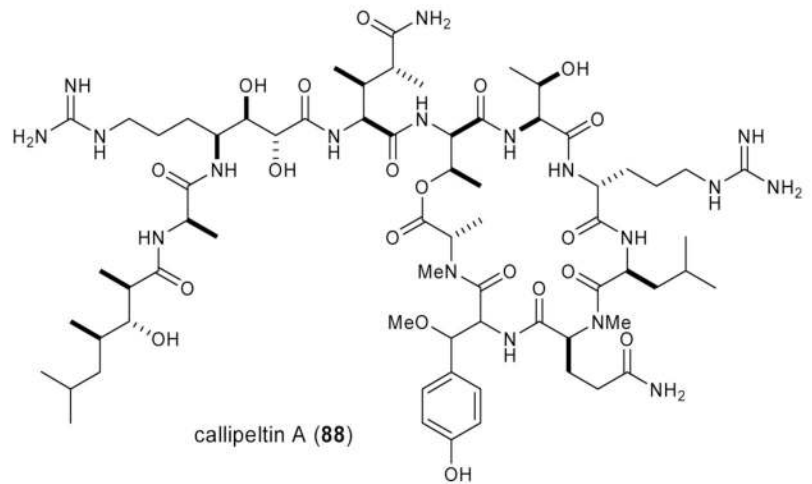
seco-pseudopterosin E (85)



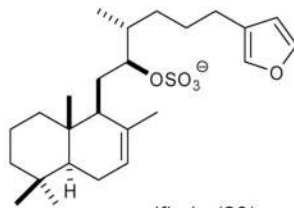
elisabethadione (86)



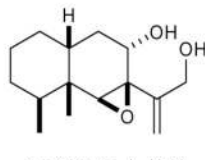
pseudopterosin R (87)



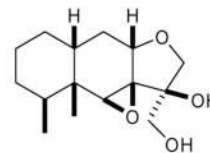
callipeltin A (88)



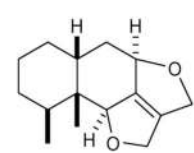
sulfircin (89)



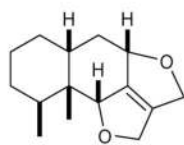
peribysin A (90)



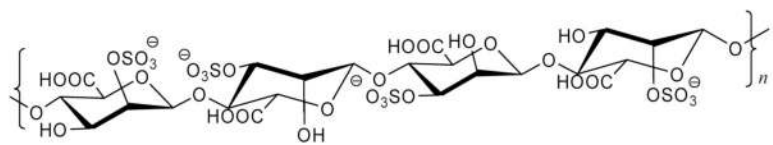
peribysin B (91)



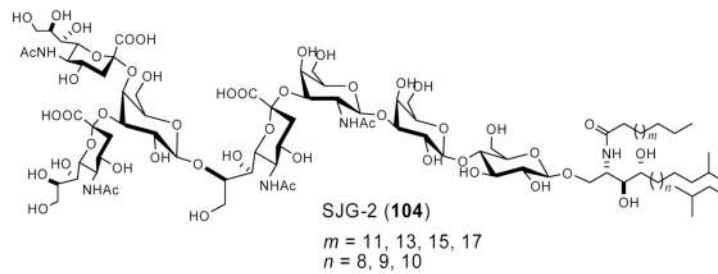
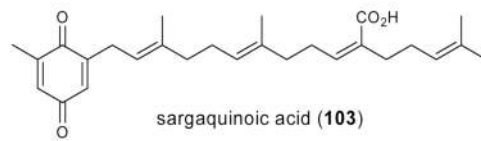
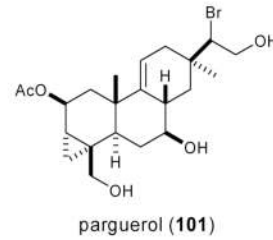
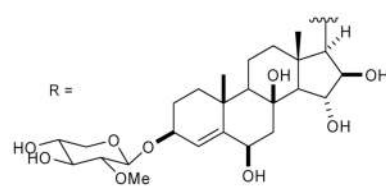
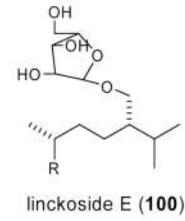
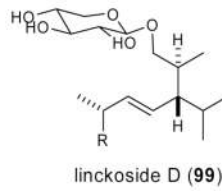
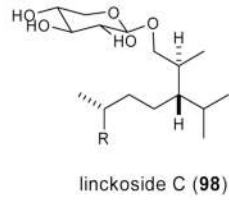
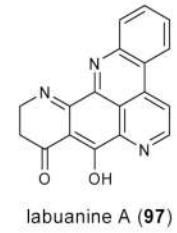
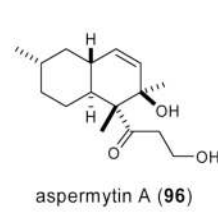
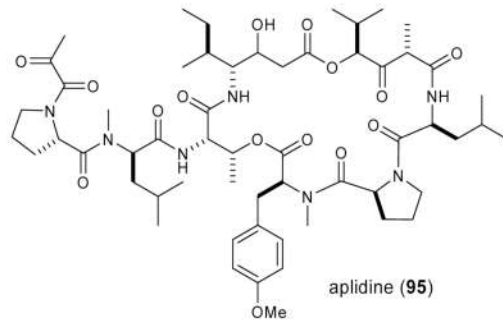
peribysin C (92)

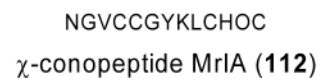
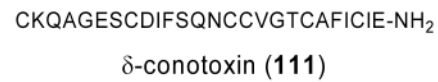
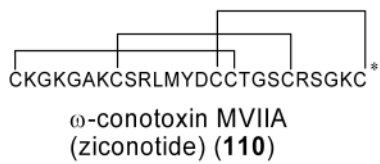
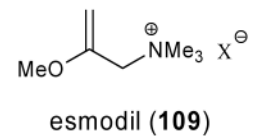
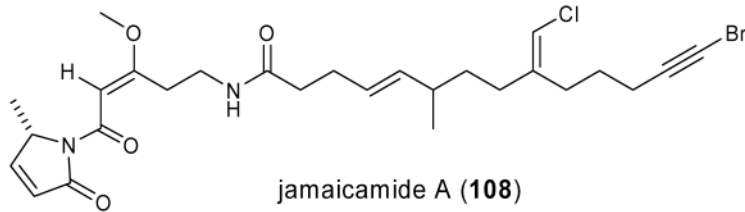
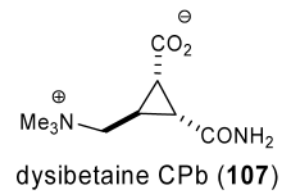
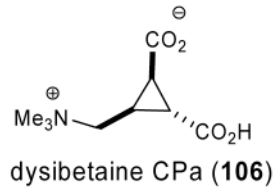
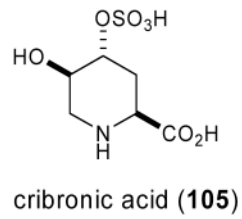


peribysin D (93)



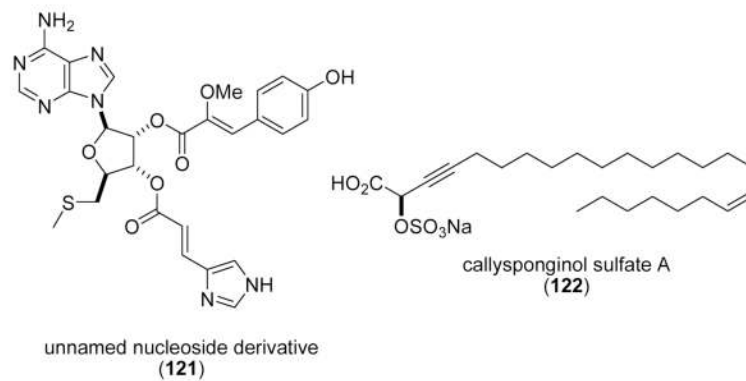
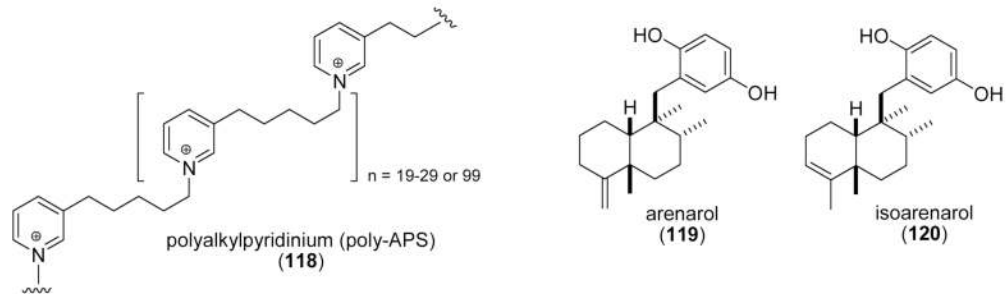
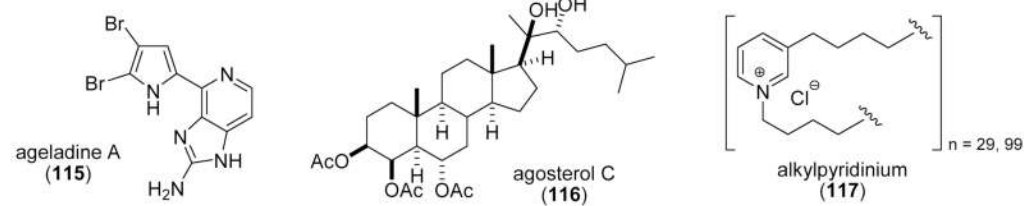
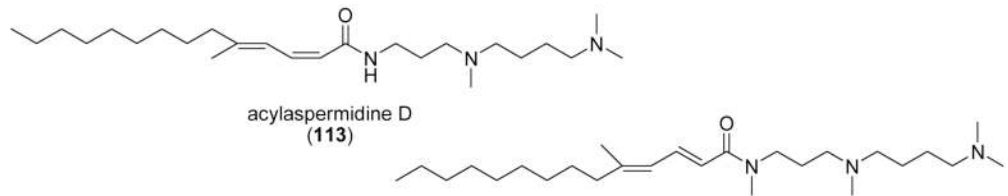
SPMG (94)

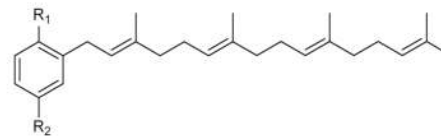
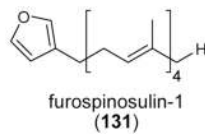
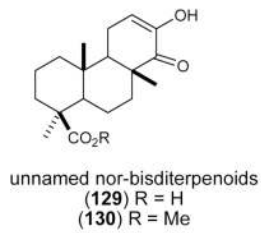
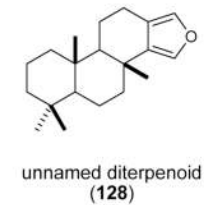
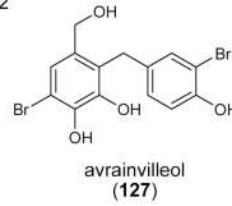
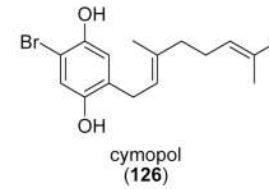
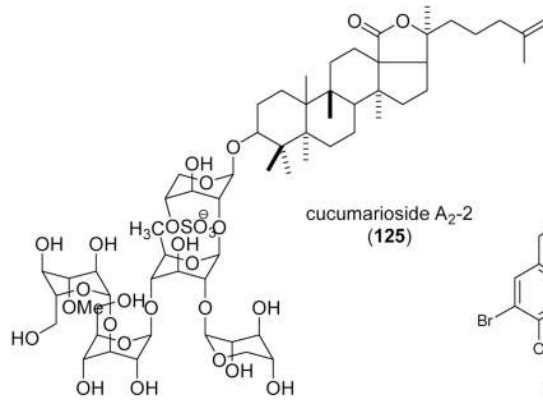
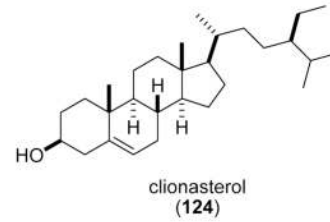
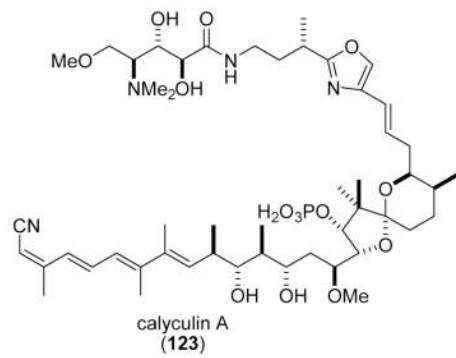




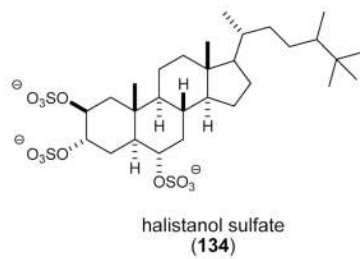
The bars represent the disulfide bonds and the asterisk represents an amidated C-terminus.

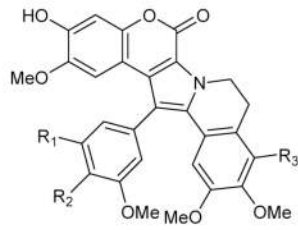
Figure 2.





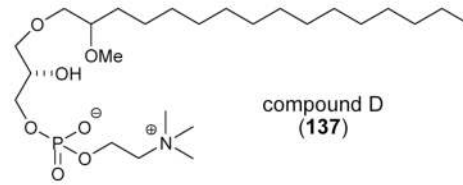
4-OH-3-tetraprenylphenylacetic acid (132) R₁ = OH, R₂ = CH₂CO₂H
4-OAc-3-tetraprenyl benzoic acetate (133) R₁ = OAc, R₂ = CO₂H



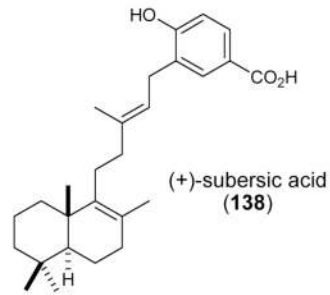


135 R₁ = OMe, R₂ = H, R₃ = OH
136 R₁ = H, R₂ = OMe, R₃ = OMe

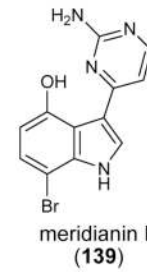
lamellarin G (**135**)
 lamellarin I (**136**)



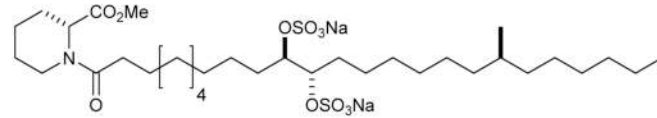
compound D
(137)



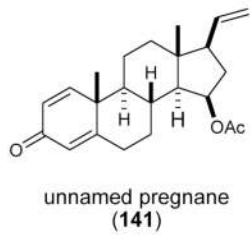
(+)-subersic acid
(138)



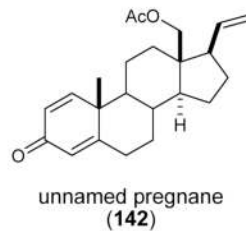
meridianin E
(139)



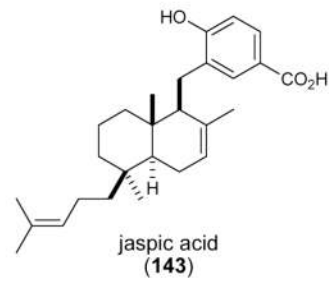
penasulfate A
(140)



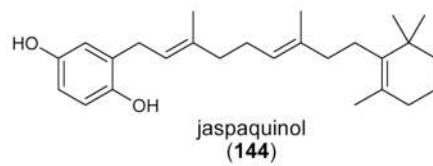
unnamed pregnane
(141)



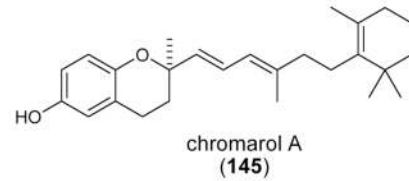
unnamed pregnane
(142)



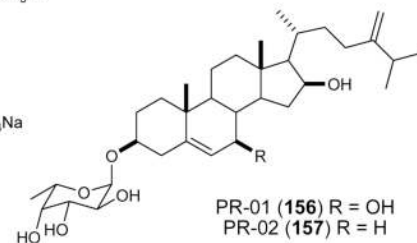
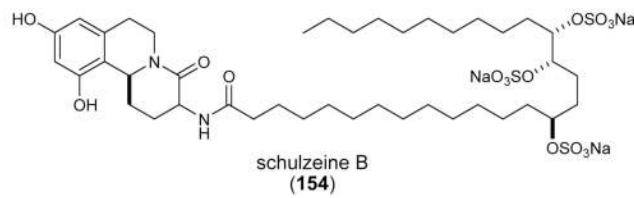
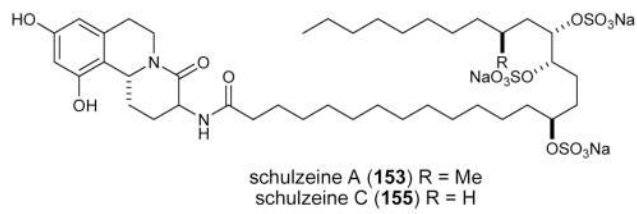
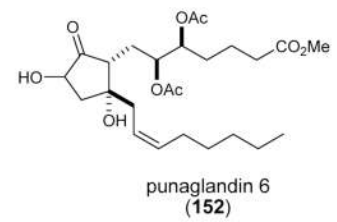
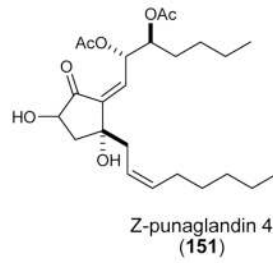
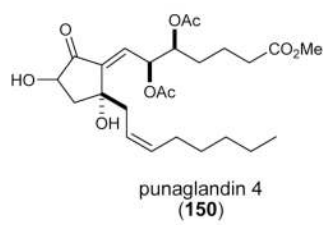
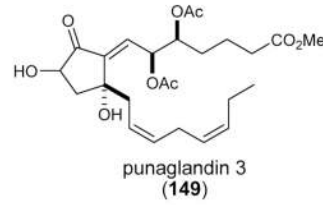
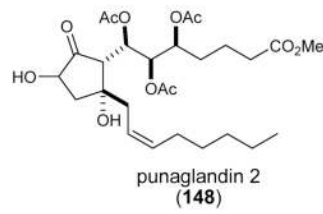
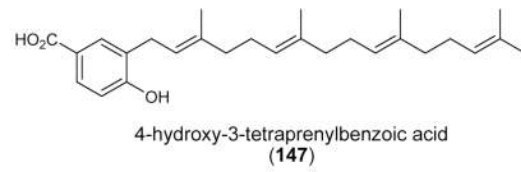
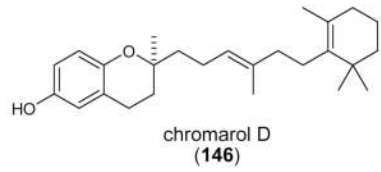
jaspic acid
(143)



jaspaquinol
(144)



chromarol A
(145)



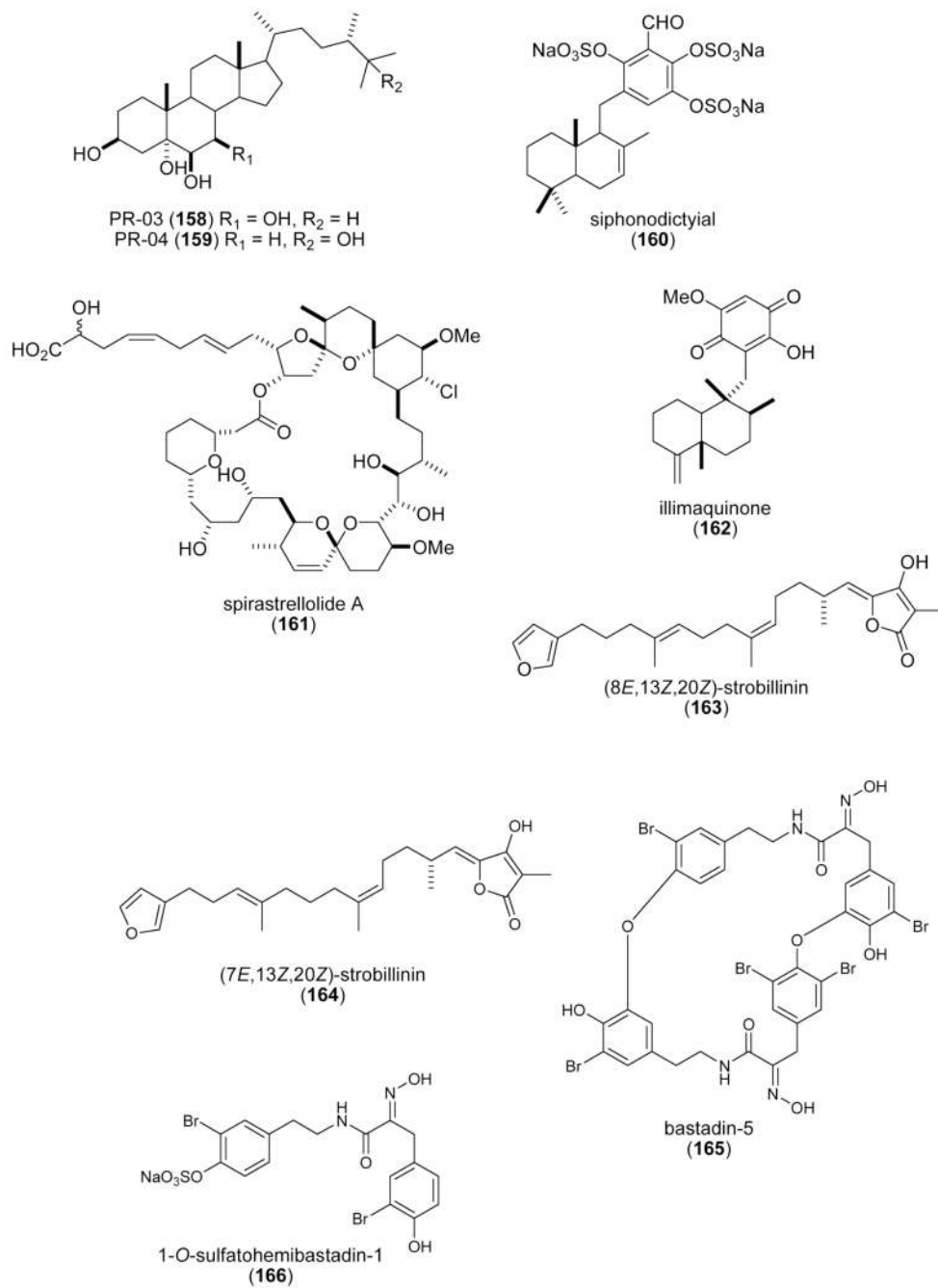


Figure 3.

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
Anthelmintic	thiocyanatins (1-4)/sponge	Polyketide ^d	Nematocidal activity to <i>Haemonchus contortus</i>	Undetermined	AUS	(Capon, R. J. et al. 2004b)
Antibacterial	kalihinol Y & X (5,6)/sponge	Diterpene ^e	<i>B. subtilis</i> inhibition	Folate biosynthesis inhibition	PHIL, USA	(Bugni, T. S. et al. 2004)
Antibacterial	MC21A (7)/bacterium	Bromophenol	Methicillin-resistant <i>S. aureus</i> inhibition comparable to vancomycin	Permeabilization of cell membrane	JAPAN	(Ishinsetyo, A. et al. 2003)
Antibacterial	nagelamide A (8)/sponge	Alkaloid ^f	<i>M. luteus</i> , <i>B. subtilis</i> & <i>E. coli</i> inhibition	Protein phosphatase 2A inhibition	AUS, JAPAN	(Endo, T. et al. 2004)
Antibacterial	plicatamide (9)/tunicate	Peptide ^f	Methicillin-resistant <i>S. aureus</i> , <i>L. monocytogenes</i> , <i>E. coli</i> & <i>P. aeruginosa</i> inhibition	Bind to plasma membrane causing K ⁺ efflux & depolarization	USA	(Tincu, J. A. et al. 2003)
Antibacterial	manoalide (10)/sponge	Sesterterpene ^e	<i>S. aureus</i> inhibition	Undetermined	JAPAN	(Namikoshi, M. et al. 2004)
Antibacterial	melophlin C (11)/sponge	Polyketide ^d	<i>B. subtilis</i> & <i>S. aureus</i> inhibition	Undetermined	CHI, INDO, GER, NETH	(Wang, C. Y. et al. 2003)
Antibacterial	eudistomin X (12)/tunicate	Alkaloid ^f	<i>S. aureus</i> , <i>B. subtilis</i> & <i>E. coli</i> inhibition	Undetermined	GER	(Schupp, P. et al. 2003)
Antibacterial	dolabellamin B2 (13)/sea hare	Peptide ^f	<i>B. subtilis</i> , <i>H. influenza</i> & <i>V. vulnificus</i> inhibition	Undetermined	JAPAN	(Iijima, R. et al. 2003)
Antibacterial	pseudopterrosin X & Y (14,15)/soft coral	Diterpene ^e	<i>S. aureus</i> , <i>S. pyogenes</i> , & <i>E. faecalis</i> inhibition	Undetermined	CAN, USA	(Ara, A. et al. 2004)
Antibacterial	<i>Sinularia</i> lipids (16-18)/soft coral	Polyketide ^d	<i>B. subtilis</i> , <i>B. pumilus</i> , <i>E. coli</i> and <i>P. aeruginosa</i> inhibition	Undetermined	RUS	(Dmitrenok, A. S. et al. 2003)
Antibacterial	<i>Rhodomela bromophenol</i> (19)/alga	Bromophenol	<i>S. aureus</i> , <i>S. epidermidis</i> and <i>P. aeruginosa</i> inhibition	Undetermined	CHI	(Xu, N. et al. 2003)
Antibacterial	eribrostatin 6 (20)/sponge	Alkaloid ^f	<i>S. pneumoniae</i> inhibition	Undetermined	USA	(Pettit, R. K. et al. 2004)
Antibacterial	purpuramine L (21)/sponge	Bromotyrosine Alkaloids ^f	<i>S. aureus</i> , <i>B. subtilis</i> & <i>C. violaceum</i> inhibition	Undetermined	IND	(Goud, T. V. et al. 2003b)
Antibacterial	germacrane (22)/sponge	Sesquiterpene ^e	<i>S. aureus</i> & <i>B. subtilis</i> inhibition	Undetermined	THAI	(Satitpaippan, V. et al. 2004)
Antibacterial	<i>Ptilocaulis guanidine</i> (23)/sponge	Alkaloid ^f	<i>S. aureus</i> inhibition	Undetermined	USA	(Yang, S. W. et al. 2003c)
Antibacterial	membranolidides C & D (24,25)/sponge	Diterpene ^e	<i>S. aureus</i> & <i>E. coli</i> inhibition	Undetermined	USA	(Ankisetty, S. et al. 2004)
Antibacterial	arenicins 1 & 2 (26,27)/polychaeta	Peptide ^f	<i>E. coli</i> , <i>L. monocytogenes</i> & <i>C. albicans</i> 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	<i>Hippoglossoides peptide</i> (29)/American plaice	Peptide ^f	<i>P. aeruginosa</i> & <i>S. aureus</i> inhibition	Undetermined	CAN	(Pattrzykat, A. et al. 2003b)
Anticoagulant	dysinoin 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 <i>in vivo</i>	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	<i>Astrocleridae sterol</i> (34)/sponge	Sterol sulfate ^d	<i>S. cerevisiae</i> inhibition	Undetermined	USA	(Yang, S. W. et al. 2003b)
Antifungal	<i>Dysidea arenaria sterol</i> (35)/sponge	Terpene ^e	Fluconazole resistance reversal in <i>C. albicans</i>	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	<i>C. herbarum</i> inhibition	Undetermined	GER, NETH	(Hassan, W. et al. 2004)
Antifungal	utenospongin B (38)/sponge	Diterpene ^e	<i>C. tropicales</i> & <i>F. oxysporum</i> inhibition	Undetermined	NETH, MOR, PORT	(Rifai, S. et al. 2004)
Antifungal	(2S,3R)-2-aminododecan-3-ol (39)/ascidian	Polyketide ^d	<i>C. albicans</i> inhibition	Undetermined	BRA, USA	(Kossuga, M.H. et al. 2004)
Antimalarial	bielschowskysin (40)/coral	Diterpene ^e	<i>P. falciparum</i> inhibition	Undetermined	PAN, USA	(Marrero, J. et al. 2004)
Antimalarial	briarellins (41-43)/coral	Diterpene ^e	<i>P. falciparum</i> inhibition	Undetermined	PAN, USA	(Ospina, C. A. et al. 2003)
Antimalarial	cembradienes (44)/sea whip	Diterpene ^e	<i>P. falciparum</i> inhibition	Undetermined	PAN, USA	(Wei, X. M. et al. 2004)
Antimalarial	dolostatin 10 (45)/sea hare	Peptide ^f	<i>P. falciparum</i> FCH5.C2 inhibition	Microtubule & mitotic inhibition	USA	(Fennell, B. J. et al. 2003)
Antimalarial	manzamine A (46)/sponge	Alkaloid ^f	<i>P. falciparum</i> D6 & W2 inhibition	Undetermined	USA	(Rao, K. V. et al. 2003)
Antimalarial	trioxarcarin A & D (48,49)/bacterium	Glycoside	<i>P. falciparum</i> strains NF54 & K1 inhibition	Undetermined	NETH, GER	(Maskey, R. P. et al. 2004)
Antiprotozoal	renieramycin A (50)/sponge	Alkaloid ^f	<i>Leishmania amazonensis</i> inhibition	Undetermined	JAPN	(Nakao, Y. et al. 2004)
Antiprotozoal	euploin C (51)/ciliate	Sesquiterpene ^e	<i>Leishmania major</i> & <i>infantum</i> inhibition	Undetermined	ITA	(Savoia, D. et al. 2004)
Antiprotozoal	defensins /mussel	Peptide ^f	<i>T. brucei</i> & <i>L. major</i> inhibition	Undetermined	BEL, FRA	(Roeh, P. et al. 2004)
Antituberculosis	(+)-8-hydroxymanzamine A (47)/sponge	Alkaloid ^f	<i>M. tuberculosis</i> inhibition	Undetermined	USA	(Rao, K. V. et al. 2003)
Antituberculosis	homopseudopteroxazole (52)/soft coral	Diterpene ^e	<i>M. tuberculosis</i> inhibition	Undetermined	USA	(Rodriguez, I. I. et al. 2003)
Antituberculosis	ingenamine G (53)/sponge	Alkaloid ^f	<i>S. aureus</i> , <i>E. coli</i> & <i>resistant S. aureus</i> inhibition	Undetermined	BRA, GER	(de Oliveira, J. H. et al. 2004)
Antituberculosis	12-deacetoscalarin 19-acetate (54)/sponge	Sesterterpene ^e	<i>M. tuberculosis</i> inhibition	Undetermined	THAI	(Wonganuchitmeta, S. N. et al. 2004)
Antituberculosis	<i>Oceanapiptide</i> 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 <i>in vitro</i>	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	ncamphamide A (63)/sponge	Depsipeptide ^f	HIV-growth inhibition	Undetermined	USA	(Oku, N. et al. 2004)
Antiviral	<i>Dictyota</i> 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 zoanths (Phylum Cnidaria); *Kingdom Monera*: bacteria (Phylum Cyanobacteria); *Kingdom Plantae*: algae; *Kingdom Protista*: ciliates (Phylum Ciliophora).

^b**MIMOA**: 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 Philippines; PORT: Portugal; RUS: Russia; SPA: Spain; THAI: Thailand.

^dPolyketide.

^eTerpene.

^fNitrogen-containing compound.

^gPolysaccharide.

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

Table 2

Drug Class	Compound/Organism ^a	Chemistry	Pharmacological Activity	MMOA ^b	Country ^c	References
Anti-inflammatory	astaxanthin (68)/salmon, sea stars	Tetraterpene ^e	Inhibition of endotoxin-induced uveitis in rats	iNOS, NO, TNF- α & PGE ₂ inhibition	JAPN	(Ohgami, K. et al. 2003)
Anti-inflammatory	bolinaquinone (69)/sponge	Merosequiterpene ^e	Inhibition of cytokine, iNOS and eicosanoids	sPLA ₂ inhibition	SPA, ITA	(Lucas, R. et al. 2003b)
Anti-inflammatory	carospongionolide B (70)/sponge	Sesterterpene ^e	Nitric oxide, PGE ₂ & TNF- α inhibition <i>in vitro</i> and <i>in vivo</i>	Nuclear factor- κ B 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	cycloamphillectene 2 (73)/sponge	Diterpene ^e	Nitric oxide inhibition	Inhibition of NF- κ B 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 & methypourewate B (75,76)/sponge	Diterpene ^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	petrospongolide M (79)/sponge	Sesterterpene ^e	Nitric oxide, PGE ₂ & TNF- α inhibition <i>in vitro</i> and <i>in vivo</i>	Nuclear factor- κ B inhibition	ITA, SPA	(Posadas, I. et al. 2003b)
Anti-inflammatory	petrospongolides M-R (79-83)/sponge	Sesterterpene ^e	Macrophage inflammatory mediator inhibition	PLA ₂ inhibition	ITA	(Monti, M. C. et al. 2004)
Anti-inflammatory	pseudopteroin N (84)/sea whip	Diterpene ^e	Inhibition of mouse ear inflammation	Undetermined	USA	(Ata, A. et al. 2003)
Anti-inflammatory	seco-pseudopteroin 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	pseudopteroin R (87)/sea whip	Diterpene ^e	Microglia thromboxane B ₂ inhibition	Undetermined	USA	(Rodríguez, I. I. et al. 2004)
Cardiovascular	callipeltin A (88)/sponge	Depside ^f	Affected resting aorta contraction	Na ⁺ -ionophore action	ITA	(Trevisi, L. et al. 2004)
Immune system	<i>Codium fragile</i> polysaccharide/alga	Polysaccharide ^g	Binding to IL-2, IL-7 and INF- γ	Undetermined	UK	(Nika, K. et al. 2003)
Immune system	sulfirin (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	perbybins A-D (90-93)/fungus	Sesquiterpene ^e	Inhibition of human leukemia cell adhesion	IL-1, IL-6 & TNF- α synthesis	FRA, USA	(Yamada, T. et al. 2004)
Immune system	phyccarine/alga	Polysaccharide ^g	Stimulation of macrophage phagocytosis	Binding to CD4 receptor on lymphocytes	CHI	(Vetvicka, V. et al. 2004)
Immune system	sulfated PMG (94)/alga	Polysaccharide ^g	Inhibition of HIV virus infection of lymphocytes	Interaction with CD4 receptor	CHI	(Meiyu, G. et al. 2003)
Immune system	sulfated PMG (94)/alga	Polysaccharide ^g	Binding to lymphocytes	Undetermined	CHI	(Miao, B. et al. 2004)
Nervous system	petrospongolide M (79)/sponge	Sesterterpene ^e	Reduction of morphine withdrawal <i>in vitro</i>	Undetermined	ITA	(Casspo, 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 peptide 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 neurite 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	sargaquinolic acid (103)/alga	Meroditerpene ^e	Induction of neurite outgrowth	PL-3 kinase independent; TrKA-MAP kinase and adenylylate 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	Undetermined	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 MrlA (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.

⁸Polysaccharide.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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

Table 3

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 ₂ -P- and V-type H ⁺ + ATPases and cytosolic pyrophosphatase	JAPN	(Hirono, M. et al. 2003)
agehadine 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 ; 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 & isoarenerol (119, 120)/sponge	merosquiter pene ^f	Protein kinases inhibition	4-7 μM	Undetermined	NETH, CAN	(Yoo, H. D. Leung D. et al. 2003)
<i>Arritolium robustum</i> 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	Stero ^f	Complement component C1 inhibition	4.1 μM	Undetermined	THAI, NETH, PORT	(Cerreira, F. et al. 2003)
cucumaroside 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 ^e	Antioxidant	4.0-6.1 μM	Undetermined	USA	(Takamatsu, S. et al. 2003)
<i>Dicyoceratida</i> 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	Stero ^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)

Compound/Organism ^a	Chemistry	Pharmacological Activity	IC ₅₀ ^b	MMOA ^c	Country ^d	References
(+)-subersic acid (138)/sponge	Meroterpenes ^f	MAPKAP Kinase 2 inhibition	9.6-20 μM	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)
<i>Psammocinia</i> spp. diterpenes (143-147)/sponge	Terpenes ^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	0.04-0.37 μM	P53 accumulation & ubiquitin isopeptidase activity <i>in vivo</i> & <i>in vitro</i>	USA	(Verbiski, S. M. et al. 2004)
schulzeines A-C (153-155)/sponge	Alkaloid/polyketide ^g	α-glucosidase inhibition	0.048-0.1 μM	Undetermined	JAPN, NETH	(Takada, K. et al. 2004)
<i>Simularia & Lobophytum</i> 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	Meresesquiterpene ^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)
<i>Spongia sesquiterpenoid</i> (162)/sponge	Meresesquiterpene ^f	DNA polymerase B lyase activity inhibition	16.2 μg/mL	Undetermined	USA	(Cao, S. et al. 2004)
stroblin-felixinin (163, 164)/sponge	Sesterterpene ^f	Antioxidant and radical scavenger	ND	Superoxide scavenging inhibition & H ₂ O ₂ induced DNA strand scission	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	protection 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 IC₅₀: 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.

f polysaccharide.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript