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Review

Marine pharmacology in 2007–8: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action

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ABSTRACT

The peer-reviewed marine pharmacology literature in 2007–8 is covered in this review, which follows a similar format to the previous 1998–2006 reviews of this series. The preclinical pharmacology of structurally characterized marine compounds isolated from marine animals, algae, fungi and bacteria is discussed in a comprehensive manner. Antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis and antiviral activities were reported for 74 marine natural products. Additionally, 59 marine compounds were reported to affect the cardiovascular, immune and nervous systems as well as to possess anti-inflammatory effects. Finally, 65 marine metabolites were shown to bind to a variety of receptors and miscellaneous molecular targets, and thus upon further completion of mechanism of action studies, will contribute to several pharmacological classes. Marine pharmacology research during 2007–8 remained a global enterprise, with researchers from 26 countries, and the United States, contributing to the preclinical pharmacology of 197 marine compounds which are part of the preclinical marine pharmaceuticals pipeline. Sustained preclinical research with marine natural products demonstrating novel pharmacological activities, will probably result in the expansion of the current marine pharmaceutical clinical pipeline, which currently consists of 13 marine natural products, analogs or derivatives targeting a limited number of disease categories.

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1. Introduction

The current article presents the preclinical pharmacology of marine natural products during 2007–8 maintaining the format used in the previous reviews (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005; Mayer et al., 2007, 2009). The preclinical pharmacology of antitumor and cytotoxic marine compounds has been reported in separate reviews (Mayer, 1999; Mayer and Lehmann, 2001; Mayer and Gustafson, 2003, 2004, 2006, 2008). We have restricted the current as well as previous reviews to peer-reviewed articles reporting the bioactivity or pharmacology of structurally characterized marine compounds. As we have done previously, we have continued to use a modification of Schmitz’s chemical classification (Schmitz et al., 1993) to assign marine natural product structures to six major chemical classes, namely, polyketides, terpenes, peptides, alkaloids, shikimates, and sugars. Novel antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis and antiviral preclinical pharmacology of marine metabolites are presented in Table 1 with the corresponding structures shown in Fig. 1. Marine compounds that affect the immune and nervous systems, as well as those with anti-inflammatory effects are grouped in Table 2, with their corresponding structures presented in Fig. 2. Finally, marine compounds that have been demonstrated to affect a variety of cellular and molecular targets are exhibited in Table 3, and their structures depicted in Fig. 3. Several articles were published during 2007–8 reporting the preclinical pharmacology of extracts or structurally uncharacterized marine compounds, and although these have not been included in the present review, they probably may warrant further investigation: antimicrobial effects of the Turkish red alga Jania rubens (Karabay-Yavasoglu et al., 2007); antimicrobial activity in Portuguese marine cyanobacteria Synechocystis sp. and Synechococcus sp. extracts towards Gram-positive bacteria (Martins et al., 2008); antibacterial activity against human and fish bacteria from the sub-Arctic colonial ascidian Synoicum pulmonaria from northern Norway (Tadesse et al., 2008); strong antibiotic-producing potential in actinomycetes from sediments in the Trondheim fjord in Norway (Bredholt et al., 2008); antibacterial activity of deep-sea bacteria from sediments of the West Pacific Ocean (Xu et al., 2007); potent antimicrobial activity in the green alga Enteromorpha intestinalis collected in Gujarat, India (Nair et al., 2007); a nonhemolytic antimicrobial lipopeptide derived from the marine bacterium Bacillus circulans (Das et al., 2008); a T-antigen binding lectin with bioactivity against a broad spectrum of Gram-positive and Gram-negative bacteria from the sea cucumber Holothuria scabra (Gowda et al., 2008); anticoagulant activity of a 100–500 kDa polysaccharide isolated from the fermented red seaweed Lomentaria catenata which was greater than the clinical anticoagulant heparin (Pushpamali et al., 2008); antimycobacterial activity in long-chain fatty acids isolated from the red alga Polysiphonia virgata (Saravana-kumar et al., 2008); antileishmanial and anti-trichomonal activity in organic extracts of several Mexican red and brown algae (Freile-Pelegri et al., 2008; Moo-Puc et al., 2008); anti-HIV-1 activity of novel sulfated galactans isolated from the Chinese red alga Grateloupia longifolia and Grateloupia filicina (Wang et al., 2007); significant anti-herpes simplex virus activity in a 30 kDa polysaccharide isolated from the red alga Grateloupia corticata (Chattopadhyay et al., 2008); immunomodulatory effects of an enzymatic extract from the South Korean marine brown alga Ecklonia cava on murine splenocytes (Ahn et al., 2008); immunostimulant properties of a sulfated polysaccharide isolated from the Brazilian red alga Champaia feldmannii (Assreuy et al., 2008); antioxidant and antimicrobial activity of the Indian red and brown seaweed methanolic extracts with high phenolic contents (Deví et al., 2008); and decreased expression of key regulatory genes involved in cholesterol and fatty acid biosynthetic pathways by the lipid extract of the cyanobacterium Nostoc commune var. sphaeroides Kützing (Rasmussen et al., 2008).

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

Table 1 presents preclinical pharmacology reported during 2007–8 on the antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral pharmacology of the marine natural products (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74) shown in Fig. 1.

2.1. Antibacterial activity

Contributing to the global search for new antimicrobials to combat antibiotic-resistant strains of pathogenic bacteria, marine ecological niches have been described recently as “particularly promising” (Fischbach and Walsh, 2009). During 2007–8, 38 studies reported novel antibacterial marine natural products isolated from marine bacteria, fungi, sponges, worms and fish, a larger effort than the ones reported in previous years (Mayer et al., 2009), and previous reviews of this series.

Only six papers provided detailed mechanism of action studies with marine antimicrobial compounds. Kanoh et al. (2008b) reported the discovery of the novel bioactive spirodioxynaphthalene ascochytacin (1) isolated from cultures of a marine-derived fungus Ascochyta sp. NGB4, which inhibited B. subtilis growth (MIC = 0.3 μg/disk) by targeting the function of the bacterial growth regulatory system TCS (YycG/YycF). Kitani et al. (2008) discovered that the 120 kDa acidic glycoprotein l-aminoo acid oxidase termed SSAP (2), isolated from the rockfish Sebastes schlegelli (Kitani et al., 2007), acted selectively on Gram-negative bacteria (minimum inhibitory concentration (MIC) = 0.078–0.63 μg/mL). While H2O2 was shown to mediate the antibacterial action of SSAP, electron microscopy analysis revealed that SSAP induced cell surface damage and morphological changes in several bacterial species. Lee et al. (2007) reported that the 21-residue peptide arenicin-1 (3) isolated from the marine polychaete Arenicola marina exhibited significant antibacterial activity against P. aeruginosa and Staphylococcus aureus (MIC = 2 μg/mL). Interestingly, arenicin-1 induced release of calcin from PE/PG liposomes, thus suggesting that the bacterial cell membrane is the main molecular target of the peptide. Jang et al. (2007c) extended the pharmacology of the alkaloid isoaaptamine (4), isolated from the marine sponge Aaptos aaptos. Isoaaptamine inhibited sorbate A (IC50 = 3.7 μg/mL), an enzyme involved in S. aureus cell wall protein anchoring and virulence, thus potentially providing a novel lead compound for further development of potent antibacterials. Lee et al. (2008) isolated seven sesterterpenes (5, 6, 7, 8, 9, 10, 11) from a tropical sponge Dyside sp. which demonstrated antibacterial activity against B. subtilis (MIC = 1.56–12.5 μg/mL) by inhibiting isocitrate lyase activity, a key enzyme in the glyoxylate cycle which is present in most prokaryotes, lower eukaryotes and plants, but not in vertebrates. Kanoh et al. (2008a) described a new sulfoalkylresorcinol (12) isolated
Table 1

Marine pharmacology in 2007–8: marine compounds with antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral activities.

| Drug class | Compound/organism\(^a\) | Chemistry | Pharmacologic activity | IC\(_{50}\) | MMOA\(^b\) | Country\(^c\) | References |
|------------|-------------------------|-----------|------------------------|--------|---------|-----------|-----------|
| Antibacterial | Ascochyta tinctorium (1)/fungus | Polyketide\(^d\) | B. subtilis inhibition | 0.3 µg/mL\(^+\) | TCS (YycG and YyfF) regulatory system H\(_2\)O\(_2\) mediates the antibacterial action | JPN | (Kanoh et al., 2008b) |
| Antibacterial | L-Amino acid oxidase SSAP (2)/rockfish | Protein\(^f\) | A. salmonicida, P. damaelega subsp. piscida and V. parahaemolyticus inhibition | 0.078–0.63 µg/mL\(^+\) | Binding and disruption of cell membrane | S. KOR | (Lee et al., 2007) |
| Antibacterial | Arenicin-1 (3)/polyochaeta | Peptide\(^d\) | P. aeruginosa and S. aureus inhibition | 2 µg/mL\(^+\) | Sortase A inhibition and fibrinectin binding | L. herbacea | (Jang et al., 2007c) |
| Antibacterial | Isoaaptamine (4)/sponge | Alkaloid\(^d\) | S. aureus inhibition | 3.7 µg/mL | Sortase A inhibition and fibrinectin binding | Pedein A | (Lee et al., 2008) |
| Antibacterial | Dysiside sp. Sesterterpenes (5, 6, 7, 9, 10, 11)/sponge | Terpenoid\(^d\) | B. subtilis inhibition | 1.56–12.5 µg/mL\(^+\) | FtsZ polymerization inhibition | L-Amino acid oxidase SSAP | (Kanoh et al., 2008a) |
| Antibacterial | Ambiguines H and I (13, 14)/bacterium | Alkaloid\(^d\) | B. subtilis and S. aureus inhibition | 0.08–1.25 µg/mL\(^+\) | Undetermined | JPN | (Oko et al., 2008) |
| Antibacterial | Astatemycins A and B (15, 16)/bacterium | Polyketide\(^d\) | B. subtilis and M. luteus inhibition | 1–85 µg/mL\(^+\) | Undetermined | JPN | (Kobayashi et al., 2008b) |
| Antibacterial | Ayamycin (17)/bacterium | Polyketide\(^d\) | B. subtilis and M. luteus inhibition | 2.5 µg/mL\(^+\) | Undetermined | USA, NLD | (El-Gendi et al., 2008a) |
| Antibacterial | Batzelladine L and M (18, 19)/sponge | Polyketide\(^d\) | B. subtilis and S. aureus inhibition | 0.1 µg/mL\(^+\) | Undetermined | JPN, IDN | USA, CHN, ESP, NZL | (Hanif et al., 2007) |
| Antibacterial | Dysiside sp. Sesterterpenes (20)/sponge | Polyketide\(^d\) | B. subtilis and S. aureus inhibition | 0.1 µg/mL\(^+\) | Undetermined | JPN, IDN | USA, CHN, ESP, NZL | (Hanif et al., 2007) |
| Antibacterial | Esrawmycin (21)/bacterium | Alkaloid\(^d\) | B. subtilis, S. aureus and M. luteus inhibition | 1–85 µg/mL\(^+\) | Undetermined | CAN, PAP, USA | (McArthur et al., 2008) |
| Antibacterial | (+)-Isoaspic acid (22)/sponge | Terpenoid\(^d\) | S. epidermidis inhibition | 2.5 µg/mL\(^+\) | Undetermined | USA, NLD | (Rubio et al., 2007) |
| Antibacterial | Lymamicins A-D (23, 24, 25, 26)/bacterium | Polyketide\(^d\) | S. aureus and methicillin-resistant | 1.8–9.5 µg/mL\(^+\) | Undetermined | USA | (Machesky et al., 2007) |
| Antibacterial | Liposaxdinoliones A and B (27, 28)/bacterium | Polyketide\(^d\) | S. aureus and methicillin-resistant | 0.5–16µ g/mL\(^+\) | Undetermined | USA | (Machesky et al., 2007) |
| Antibacterial | Marinospyrole A (29)/bacterium | Alkaloid\(^d\) | S. aureus and methicillin-resistant | 0.31 µM\(^+\) | Undetermined | USA | (Hughes et al., 2008) |
| Antibacterial | (–)-Microcionin-1 (30)/sponge | Terpenoid\(^d\) | S. aureus and M. luteus inhibition | 6 µg/mL\(^+\) | Undetermined | JPN | (Gaspar et al., 2008) |
| Antibacterial | Phomolide B (31)/fungus | Polyketide\(^d\) | E. coli inhibition | 5–10 µg/mL\(^+\) | Undetermined | CHN | (Chen et al., 2008) |
| Antibacterial | Sargaucoonic acid derivative (32)/alga | Phenol\(^d\) | E. coli inhibition | 2 µg/mL\(^+\) | Undetermined | JPN | (Chen et al., 2008) |
| Antibacterial | Tauramamide (33)/bacterium | Peptide\(^e\) | Enterococcus sp. inhibition | 0.1 µg/mL\(^+\) | Undetermined | CAN, PAP, USA | (Desjardine et al., 2007) |
| Anticoagulant | Anticoagulant polyamide (TGAP) (34)/bivalve | Polyketide\(^d\) | Inhibition of factor IIb to IIa conversion | 77.9 nM | Specific binding to factor Va and factor IIb | S. KOR | (Kumar et al., 2007) |
| Antifungal | Odontolothu serybifera bromophenols (35, 36, 37)/alga | Terpenoid\(^d\) | Magnaporthe grisea isocitric acid inhibition | 2.0–2.8 µM | Undetermined | S. KOR | (Lee et al., 2007) |
| Antifungal | Callipeltis (38)/algae | Peptide\(^d\) | C. albicans inhibition | 1 µM\(^+\) | Undetermined | CAN, PAP, USA | (Dee et al., 2007) |
| Antifungal | Holothurin B (40)/sea cucumber | Triterpenoid glycoside\(^d\) | T. mentagrophytes and S. schencki inhibition | 1.56 µg/mL\(^+\) | Undetermined | IND | (Kunze et al., 2008) |
| Antifungal | Neopeltolide (41)/sponge | Polyketide\(^d\) | C. albicans inhibition | 0.62 µg/mL\(^+\) | Undetermined | USA | (Wright et al., 2007) |
| Antifungal | Pedein A (42)/bacterium | Peptide\(^d\) | C. albicans and C. glatii inhibition | 0.6–1.6 µg/mL\(^+\) | Undetermined | DEU | (Jang et al., 2008) |
| Antifungal | Pseudoceratins A and B (43, 44)/sponge | PKS/NRPS\(^d\) | C. albicans and mutant | 6.5–8.0 µg/mL\(^+\) | Undetermined | JPN | (Tasdemir et al., 2007) |
| Antimalarial | (E)-Orocin (45) and (E)-orocin (46)/sponge | Alkaloid\(^d\) | P. falciparum K1 strain inhibition | 3.9–7.9 µg/mL | Fibrinogen binding | CHE, CRR, USA, TUR | (McPhail et al., 2007) |
| Antimalarial | Dragomabin (47)/bacterium | Peptide\(^d\) | P. falciparum W2 strain inhibition | 6.0 µM | Undetermined | PAN, USA | (McPhail et al., 2007) |
| Antimalarial | Venturamides A and B (48, 49)/bacterium | Peptide\(^d\) | P. falciparum W2 strain inhibition | 5.6–8.2 µM | Undetermined | PAN, USA | (McPhail et al., 2007) |
| Antimalarial | Nodulisoracis A (50)/fungus | Polyketide\(^d\) | P. falciparum K4 strain inhibition | 1–10 µM | Undetermined | THAI | (Kasettrathath et al., 2008) |
| Antimalarial | Streptomyces sp. H668 polyether (51)/bacterium | Polyketide\(^d\) | P. falciparum D6 and W2 strain inhibition | 0.1–0.2 µg/mL | Undetermined | PAN, USA | (Na et al., 2008) |
| Antimalarial | Tumonic acid (52)/bacterium | Polyketide\(^d\) | P. falciparum D6 and W2 strain inhibition | 2 µM | Undetermined | S. KOR, USA | (Clark et al., 2008) |
| Antimalarial | Chaetoxanthone B (53)/fungus | Polyketide\(^d\) | P. falciparum K1 strain inhibition | 0.5 µg/mL | Undetermined | CHN | (Pontius et al., 2008a) |
| Antimalarial | Plakotide P (54)/sponge | Polyketide\(^d\) | Inhibition of L. chagasi and T. cruzi | 0.5–2.3 µg/mL | Undetermined | BRA | (Kosuga et al., 2008) |

(continued on next page)
from the marine-derived fungus Zygosporium sp. KNC52, which showed antimicrobial activity against methicillin-resistant S. aureus. The mechanism of action appeared to involve inhibition (IC$_{50}$ = 12.5 µg/mL) of the in vitro polymerization of FtsZ, a protein which is a structural homolog of eukaryotic tubulin, and that participates in bacterial cell division.

As shown in Table 1, several new marine antibacterials were also reported in 2007–8 (Fig. 1) with MICs less than 10 µg/mL against antibiotic-resistant bacterial strains, although no mechanism of action studies were reported: the alkaloids ambigunine isonitriles H and I (Lin et al., 2007); corallidictyls A, B, C and D (MIC less than 20 µg/mL) (Grube et al., 2007); (−)-mycalasin A (MIC=20 µg/mL) (Deschio et al., 2008); dehydroxychlorofusarielin B (MIC=8 µg/mL) (DeLira et al., 2007); dehydroxycolemanein A (MIC=8 µg/mL) (Simmons et al., 2008); demethylnigerone (MIC=8 µg/mL) (Desjardine et al., 2007).

Table 1 (continued)

| Drug class       | Compound/organism* | Chemistry | Pharmacologic activity | IC$_{50}$ | MMDOA* | Country* | References |
|------------------|--------------------|-----------|------------------------|-----------|--------|----------|------------|
| Antibacterial    | Viridamides A and B (55, 56)/bacterium | Peptide | Inhibition of L. mexicana and T. cruzi | 1.1–1.5 µM | Undetermined | PAN, USA | Simmons et al., 2008 |
| Antiprotozoal    | Chaetoxanthine B (53)/fungus | Polyketide | T. cruzi Tulahuen C4 strain inhibition | 1.5 µg/mL | Undetermined | CHE | Pontius et al., 2008 |
| Antituberculosis | Bipinnapterolide A (57)/coral | Terpenoid | M. tuberculosis inhibition | 128 µg/mL | Undetermined | USA | Ospina et al., 2007 |
| Antituberculosis | 8′-O-Demethyladriamycin (58) and 8′-O-demethylisonigromycin (59)/fungus | Polyketide | M. tuberculosis inhibition | 21.5 and 43.0 µM | Undetermined | CHN | Zhang et al., 2008 |
| Antituberculosis | Caribenos A and B (60, 61)/soft coral | Terpenoid | M. tuberculosis inhibition | 63 and 128 µg/mL | Undetermined | USA | Wei et al., 2007 |
| Antituberculosis | Parguesterols A and B (62, 63)/sponge | Triterpenoid | M. tuberculosis inhibition | 7.8 and 11.2 µg/mL | Undetermined | USA | Wei et al., 2007 |
| Antituberculosis | Spiculol acids (64, 65, 66)/sponge | Polyketide | M. tuberculosis inhibition | 50 µg/mL | Undetermined | ESP, FRA | Berrue et al., 2007 |
| Antiviral        | Esculetin ethyl ester (67)/sponge | Polysaccharide | Dengue type 2 inhibition | 0.8–16 µg/mL | Inhibition of viral binding and cell penetration | ARG, BRA | Cirne-Santos et al., 2008 |
| Antiviral        | Cryptomenia crenulata (68)/alga | Polysaccharide | Inhibition of HIV-1 infection | 1.07–1.72 µM | | CHN, S, KOR | Anart et al., 2008 |
| Antiviral        | Mirabamides A, C and D (71, 72, 73)/sponge | Peptide | Inhibition of HIV-1 fusion | 0.041–3.9 µM | Interaction with HIV-1 envelope glycoproteins | NZL, USA | Plaza et al., 2007 |
| Antiviral        | Sulfated SPMG (74)/alga | Polysaccharide | Inhibition of HIV-1 infection | | | CHN | Lu et al., 2007 |

*Organism, Kingdom Animalia: polychaeta (Phylum Annelida), rockfish (Phylum Chordata), corals (Phylum Cnidaria), sea cucumber (Phylum Echinodermata), bivalve (Phylum Mollusca), sponge (Phylum Porifera); kingdom Plantae: alga; IC$_{50}$: concentration of a compound required for 50% inhibition in vitro; *: estimated IC$_{50}$, ND: not determined; **MIC: minimum inhibitory concentration; **+MIC: minimum inhibitory concentration per disk; +MMDOA: molecular mechanism of action; cCountry: ARG: Argentina; BRA: Brazil; CAN: Canada; CHE: Switzerland; CHN: China; EGY: Egypt; ESP: Spain; FRA: France; DEU: Germany; GBR: United Kingdom; IND: India; ISR: Israel; ITA: Italy; JPN: Japan; NLD: The Netherlands; NZL: New Zealand; PAN: Panama; PAP: Papua New Guinea; PRT: Portugal; S. KOR: South Korea; THAI: Thailand; TUR: Turkey; Chemistry: *polyketide; +terpenoid; −nitrogen-containing compound; *polysaccharide, modified as in the text.

Noteworthy were reports of novel marine antibacterial peptides: dicerinactin, a new component of the moronecidin family isolated from head kidney leukocytes from the sea bass Dicentrarchus labrax (Salerno et al., 2007); hepcidins, three novel antimicrobial peptides isolated from the tilapia Oreochromis mossambicus, with MICs (50–100 µg/mL) against Listeria monocytogenes, S. aureus, and Enterococcus faecium (Huang et al., 2007); scygonadin, a novel anionic antimicrobial peptide from the seminal plasma of the mud crab, Scylla serrata (Wang et al., 2007), and tunicichromes, small dehydrodopamine-containing peptides found in hemocyte cells of the ascidian...
Ascidia nigra that are capable of crosslinking proteins in vitro (Cai et al., 2008).

2.2. Anticoagulant activity

Four articles published during 2007–8, reported anticoagulant marine natural products isolated from algae and clams, a number very similar to that reported in our previous review (Mayer et al., 2009), and other reviews of this marine pharmacology series.

Jung et al. (2007b) characterized a novel 7.7 kDa anticoagulant polypeptide termed TGAP with a partial sequence (34) from the muscle protein of the South Korean bivalve Tegillarca granosa. The anticoagulant polypeptide, which demonstrated low in vitro cytotoxicity to venous endothelial cells, specifically inhibited the blood coagulation factor Va, as well as the molecular interaction between factor IIa and factor Va in a...
concentration-dependent manner (IC$_{50}$ = 77.9 nM), thus resulting in prolonged prothrombin time. The same research group (Jung et al., 2007a) extended the anticoagulant pharmacology of a sulfated polysaccharide from the brown alga _E. cava_. The sulfated algal polysaccharide potently inhibited the biological activity of human blood coagulation factors IIa, VIIa and Xa in the presence of the glycoprotein antithrombin III in a dose-dependent manner (KD = 15.1, 45.0 and 65.0 nM, respectively). Yoon et al. (2007) reported the purification of a complex and heterogeneous sulfated fucan from the brown alga _Laminaria cichorioides_. The purified polysaccharide had potent anticoagulant activity which resulted from enhancement of thrombin inhibition by heparin cofactor II, within the same concentration range as the clinically used heparin. Mao et al. (2008) described two sulfated polysaccharides WF1 (870 kDa) and WF3 (70 kDa) from the marine green alga _Monostroma nitidum_ which demonstrated high anticoagulant activities. Interestingly, both polysaccharides inhibited
Fig. 1 (continued).
thrombin as well as potentiated antithrombin III-mediated inhibition of coagulation factor Xa.

2.3. Antifungal activity

Ten studies during 2007–8 reported on the antifungal activity of several novel marine natural products isolated from marine algae, bacteria, sponges and sea cucumbers, a decrease from our last review (Mayer et al., 2009), and previous reviews of this series.

As shown in Table 1, only one report extended the molecular pharmacology of novel antifungal marine metabolites. Lee et al. (2007) discovered that three bromophenols (\(^{35,36,37}\)) isolated from the red alga Odonthalia corymbifera potently inhibited isocitrate lyase (ICL) (IC\(_{50} = 2.0–2.8\) μM), an enzyme that is part of the glyoxylate cycle which is expressed during host infection by
pseudoceratin A (43)

pseudoceratin B (44)

(E)-oroidin (45)

(E)-oroidin TFA salt (46)

dragomabin (47)

venturamide A (48)

venturamide B (49)

nodulisporacid A (50)

E-isomer

Z-isomer

Streptomyces sp. H668 polyether (51)

tumonoic acid I (52)

chaetoxanthone B (53)

Fig. 1 (continued).
plakortide P (54)

bipinnapterolide B (57)

8'-O-demethylnigerone (58)

8'-O-demethylisonigerone (59)

caribenol A (60)

caribenol B (61)

viridamide A (55)

viridamide B (56)

parguesterol A (62)

parguesterol B (63)

24-norisospiculoic acid A (64) $R_1 = \text{Me}, R_2 = \text{Et}, R_3 = \text{Me}$

dinorspiculoic acid A (65) $R_1 = R_2 = R_3 = \text{Me}$

norspiculoic acid A (66) $R_1 = \text{Et}, R_2 = \text{Me}, R_3 = \text{Me}$

Fig. 1 (continued).
esculetin-4-carboxylic acid ethyl ester (67)

6,6'-bieckol (69)

dolabelladienetriol (70)

Fig. 1 (continued).
**Table 2**

Marine pharmacology in 2007-8: marine compounds with anti-inflammatory activity, and affecting the immune and nervous systems.

| Drug class | Compound/organism | Chemistry | Pharmacological activity | IC₅₀ | MMOA | Country | References |
|------------|-------------------|-----------|--------------------------|------|------|---------|------------|
| Anti-inflammatory | Ascidialthiazones A (75) and B (76)/ascidian | Alkaloid<sup>a</sup> | Human neutrophil free radical inhibition in vitro and in vivo | 0.44–1.55 μM | Superoxide anion inhibition | NZL | (Pearce et al., 2007a) |
| Anti-inflammatory | Crassauloids A and C (77, 78)/soft coral | Terpenoid<sup>b</sup> | Modulation of LPS-activated murine macrophage cell line | < 10 μM | Inducible NOS and COX-2 inhibition | TAJW | (Chao et al., 2008) |
| Anti-inflammatory | Durumolides A-C (79, 80, 81)/soft coral | Terpenoid<sup>b</sup> | Modulation of LPS-activated murine macrophage cell line | < 10 μM | Inducible NOS and COX-2 inhibition | TAJW | (Cheng et al., 2008) |
| Anti-inflammatory | Fruganoïdes B and C (82, 83)/coral | Terpenoid<sup>b</sup> | Human neutrophil free radical inhibition in vitro | > 10 μg/mL<sup>a</sup> | Superoxide anion and elastase inhibition | TAJW | (Shen et al., 2007) |
| Anti-inflammatory | Gruclaria verrucosa fatty acids (84, 85)/algae | Polyketide<sup>d</sup> | Modulation of LPS-activated murine macrophages in vitro | < 20 μg/mL<sup>a</sup> | | NO, IL-6 and TNF-α inhibition | S. KOR | (Dang et al., 2008) |
| Anti-inflammatory | Hypnea cervicornis lectin (86)/algae | Peptide<sup>x</sup> | Antinociception and anti-inflammatory effects in vivo | 0.1–1 mg/kg<sup>g</sup> | Carbohydrate-binding site interaction | BRA | (Bittencourt Fda S. et al., 2008) |
| Anti-inflammatory | Manzamine (MZA) (87), (-)-8-hydroxy MZA (88), hexahydro-8-hydroxy MZA (89)/sponge | Alkaloid<sup>a</sup> | Modulation of LPS-activated brain microglia in vitro | 0.25–1.97 μM | TXB₂ inhibition | USA | (El Sayed et al., 2008) |
| Anti-inflammatory | Perthulio cupuliforis quinine (94)/algae | Shikimate | Human neutrophil free radical release inhibition in vitro and in vivo | 2.1 μM | Superoxide anion inhibition | NZL | (Sansom et al., 2007) |
| Anti-inflammatory | PFF-B (95)/algae | Polyketide<sup>d</sup> | Rat basophilic leukemia cell histamine release inhibition | 7.8 μM | Inhibition of β-hexosaminidase release | JPN | (Sugiura et al., 2007) |
| Anti-inflammatory | Plakoride P (54)/sponge | Polyketide<sup>e</sup> | Modulation of LPS-activated brain microglia in vitro | 0.93 μM | TXB₂ inhibition | BRA | (Kossuga et al., 2008) |
| Anti-inflammatory | Rubroide O (96)/ascidian | Polyketide<sup>d</sup> | Human neutrophil free radical release inhibition in vitro | 35 μM | Superoxide anion inhibition | NZL | (Pearce et al., 2007b) |
| Anti-inflammatory | Stearidionic (97)/algae | Polyketide<sup>d</sup> | Inhibition of mouse ear inflammation | 160–314 μg/ear | Inhibition of edema, erythema and blood flow | S. KOR, JPN | (Khan et al., 2007) |
| Anti-inflammatory | Carteramine A (98)/bacterium | Alkaloid<sup>d</sup> | Neutrophil chemotaxis inhibition | 5 μM | Undetermined | JPN | (Kobayashi et al., 2007a) |
| Anti-inflammatory | Lyngbyatetins 5-7 (99, 100, 101)/bacterium | Peptide<sup>b</sup> | Elastase inhibition | 3–10 μM | Undetermined | USA | (Tao et al., 2007) |
| Anti-inflammatory | Salinemyre A (102)/bacterium | Polyketide<sup>d</sup> | Mouse spleen cell interleukin-5 inhibition | 10 μg/mL<sup>b</sup> | | | (Oh et al., 2008) |
| Immune system | Cycloprodigiosin hydrochloride (103)/bacterium | Alkaloid<sup>d</sup> | Interleukin-8 inhibition | 1 μM | P38 MAP protein kinase inhibition | JPN | (Kawauchi et al., 2007) |
| Immune system | Floridoside (104)/algae | Sugar<sup>d</sup> | Activation of classical complement pathway | 5.9–9.3 μg/mL<sup>b</sup> | | | (Courtois et al., 2008) |
| Immune system | Lamthasins (105, 106)/sponge | Polyketide<sup>d</sup> | Activation of Ca²⁺ mobilization | 0.48–1.3 μM | | | (Grewe et al., 2007) |
| Immune system | Prodigiosin (107)/bacterium | Alkaloid<sup>d</sup> | Macrophage iNOS inhibition | 0.1 μg/mL<sup>b</sup> | NF-κB transcription factor inhibition | CHN, USA | (Huh et al., 2007) |
| Immune system | Sulpholipid (108)/algae | Polyaspartamide<sup>d</sup> | Splenocyte proliferation increase | < 100 μg/mL<sup>a</sup> | | | (He et al., 2007) |
| Immune system | Frondoside A (109)/sea cucumber | Terpenoid glycocide | Lysosomal activity, phagocytosis and ROS activation | 0.1–0.001 μg/mL<sup>b</sup> | | | (Aminin et al., 2008) |
| Immune system | Hippopospong sp. quinones (110, 111, 112)/sponge | Terpenoid<sup>d</sup> | Enhancement of IL-8 release | > 1 μg/mL<sup>b</sup> | | | (Khan et al., 2007) |
| Immune system | Macrophosphedile M (113)/fungus | Polyketide<sup>d</sup> | Cell adhesion inhibition | 33.2 μM | | | (Oda et al., 2007) |
| Immune system | Physiopon B (114)/fungus | Terpenoid<sup>d</sup> | Cell adhesion inhibition | 11.8 μM | | | (Yamada et al., 2007) |
| Immune system | Quercifuramide C (115)/soft coral | Terpenoid<sup>d</sup> | Macrophage iNOS and COX-2 inhibition | > 1 μM | | | (Yamada et al., 2007) |
| Immune system | Spongopon s. diterpenoids (116, 117)/sponge | Terpenoid<sup>d</sup> | Murine spleen cells lysosome activation | > 10 μg/mL<sup>b</sup> | | | (Lu et al., 2008) |
| Immune system | Thalassosporamin B (118)/bacterium | Terpenoid<sup>d</sup> | Interleukin 5 inhibition | 5 μM | | | (Ono et al., 2007) |
| Nervous system | Lincoinoside L1 and L2 (119, 120)/sea star | Terpenoid glycocide | Induction of neurite outgrowth | 0.3 μM<sup>b</sup> | MAP kinase activation | ITA, RUS | (Kicha et al., 2007b) |
| Nervous system | Lincoinosides M-Q (121, 122, 123, 124, 125)/sea star | Terpenoid<sup>d</sup> | Induction of neurite outgrowth | < 10 μM<sup>b</sup> | | | (Han et al., 2007) |
| Nervous system | Phaeophyta A (126)/algae | Alkaloid/terpenoid | Induction of neurite outgrowth | < 3 μM<sup>b</sup> | MAP kinase activation | JPN | (Ito et al., 2007) |
| Nervous system | Comus francopos coenos cyanus Lp1.1 (127)/snail | Peptide<sup>e</sup> | Seizure and paralysis in goldfish | > 10 μM<sup>b</sup> | | | (Peng et al., 2008) |
| Nervous system | Damipepino (128) and damipetin (129)/sponge | Alkaloid<sup>d</sup> | Inhibition of serotonin receptor binding | < 1 μg/mL<sup>a</sup> | Ca²⁺ influx inhibition | ITA, DEU | (Hess et al., 2007) |
| Nervous system | 4-Acetoxy-plakinamine 8 (130)/sponge | Terpenoid alkaloid<sup>d</sup> | Allosteric cholinesterase inhibition | 3.75 μM | Mixed-competitive inhibition | THAI | (Langjau et al., 2007) |
| Nervous system | Sargarizinic acid (131) and sargachromenol (132)/algae | Terpenoid<sup>d</sup> | Butyrylcholinesterase inhibition | 26 μM | | | (Chai et al., 2007) |
| Nervous system | SPMG (74)/algae | Polyaspartamide<sup>d</sup> | Neuronal Ca²⁺-apoptosis inhibition | 10 μM | Decrease in caspase-3 activity | CHN | (Hui et al., 2008) |

<sup>a</sup>: Organism: Kingdom Animalia: coral (Phylum Cnidaria); ascidian (Phylum Chordata); sea star, cucumber (Phylum Echinodermata); clam, mussel, snail (Phylum Mollusca); sponge (Phylum Porifera); Kingdom Fungi: fungus; Kingdom Plantae: algae; Kingdom Monera: bacteria (Phylum Cyanobacteria);
<sup>b</sup>: %C:N: concentration of a compound required for 50% inhibition; *
<sup>c</sup>: not determined; **MNOA: molecular mechanism of action, NO: nitric oxide; ¹Country: AUS: Australia; BRA: Brazil; CHN: China; DEU: Germany; FRA: France; ITA: Italy; JPN: Japan; NZL: New Zealand; RUS: Russia; S. KOR: South Korea; TAIW: Taiwan; THAI: Thailand; Chemistry: epolyketide; terpene; nitrogen-containing compound; polyaspartamide, modified as in the text.
Fig. 2. Marine compounds with anti-inflammatory activity, and affecting the immune and nervous systems.
rubrolide O (96)

steardonic acid (97)

carteramine A (98)

lyngbystatin 5 (99) $R_1=R_2=H$
lyngbystatin 6 (100) $R_1=\text{Me}, R_2=\text{SO}_3\text{Na}$

lyngbystatin 7 (101)

salinipyrone A (102)

cycloprodigiosin hydrochloride (103)

floridoside (104)

iso-iantheran A (105) $R=H$
8-carboxy-iso-iantheran A (106) $R=\text{CO}_2\text{H}$

Fig. 2 (continued).
Fig. 2 (continued).
linckoside M (121)
linckoside N (122)
linckoside O (123)
linckoside P (124)
linckoside Q (125)

GCCARAACAGIHQELC*
*amidated terminus (127)

damippecolin (128)
phaeophytin A (126)
damituricin (129)
sargaquinoic acid (131)
sargachromenol (132)

Fig. 2 (continued).
| Compound/organism | Chemistry | Pharmacological activity | IC₅₀ | MMOA | Country | References |
|------------------|----------|--------------------------|------|------|---------|------------|
| Azumamide E | Peptide | Histone deacetylase inhibition | 50–80 nM | Selective inhibition of isoforms 1, 2, and 3 | ITA | (Maullucci et al., 2007) |
| 1-Deoxyrubralactone (134)/fungus | Shikimate | X and Y DNA polymerase inhibition | 12–60 μM | Specific inhibition of DNA polymerase | JPN | (Naganuma et al., 2008) |
| Fucoxanthin (135)/alga | Carotenoid | Antioxidant in vitro | 0.14–25 mg/mL | Hydroxyl and superoxide radical scavenging | JPN | (Sachindra et al., 2007) |
| Okadaic acid (136)/sponge | Polyketide | Protein phosphatase 1 and 2A inhibition | 0.96 nM | Okadaic acid binding to proteins OABP1 and OABP2 | JPN | (Sugiyama et al., 2007) |
| Saprosomol (137) and myxol (138)/bacterium | Polyketide | l-Glutamate toxicity inhibition | 3–8.1 μM | Lipid peroxidation inhibition | JPN | (Shindo et al., 2007a) |
| Sarcomastoidol (139)/fungus | Triterpenoid | L-Ascorbic acid oxidation | 3 μM | Alkaline phosphatase elevation | JPN | (Van Minh et al., 2007) |
| 3,6-Diapoxyoctadecanoid (140) | Triterpenoid | Reduced protein polyubiquitination | 0.4–0.7 μM | Protein phosphatase 2A inhibition | CAN | (Williams et al., 2007) |
| Stylopseudas A and B (143)/sponge | Alkaloid | Reduction of voltage-dependent Ca²⁺ entry | 4.5 μM | Irreversible effect requiring lipophilic brominated side chain | DEU | (Bickmeyer et al., 2007) |
| Symbiodinolide (144)/sponge | Polyketide | Voltage-dependent N-type Ca²⁺ channel activation | 7 nM | Cyclooxigenase 1 inhibition | JPN | (Kita et al., 2007) |
| Echinogorgia complexa (154, 155)/soft coral | Polyketide | Protein phosphatase 2A inhibition | 0.47 nM | Undetermined | ESP | (Antonov et al., 2007) |
| 19-iP-Oka-alkaid acid (156)/alginate | Polyketide | Activation of Ca²⁺ influx | 100 μg/mL | Undetermined | ITA | (Cruz et al., 2007) |
| Hippocampus kuda philhalates (159, 160, 161)/seahorse | Triterpenoid | Calcineurin inhibition | 59 μM | Undetermined | USA | (Matthew et al., 2008) |
| Irregular sulfate (162)/bacterium | Terpenoid | Elastase and chymotrypsin inhibition | 0.32–8.4 μM | Undetermined | USA | (Shindo et al., 2007) |
| Kemppeptins A and B (163, 164)/bacterium | Triterpenoid | Fertilization inhibition | <25 μg/mL | Undetermined | USA | (Shindo et al., 2007) |
| Linckoside L7 (165)/starfish | Triterpenoid | Histamine H₃ receptor agonists | 0.12–0.2 μM | Undetermined | CAN | (Kushida et al., 2007) |
| Lyngbyatin 4 (166)/bacterium | Peptide | Elastase and chymotrypsin inhibition | 0.03–0.3 μM | Undetermined | USA | (Matthew et al., 2007) |
| Malenamidic (167)/bacterium | Peptide | Extracellular Ca²⁺ channel inhibition | 9 μM | Undetermined | USA | (Adams et al., 2008) |
| Monodictyochromes A and B (169, 170)/fungus | Shikimic acid | CYP1A inhibition | 3.5–7.5 μM | Undetermined | USA | (Adams et al., 2008) |
| Penicillium sp. PF1270 A, B, and C | Alkaloid | Histamine H₃ receptor agonists | 0.12–0.2 μM | Undetermined | USA | (Adams et al., 2008) |
| Penicillium sp. anisols (171, 172, 173)/fungus | Polyketide | CYP3A4 inhibition | 0.02–0.2 μM | Undetermined | USA | (Adams et al., 2008) |
| Polysiphonia urceolata | Polyketide | DPPH radical scavenging activity | 6.1–8.1 μM | Undetermined | CAN | (Li et al., 2007, 2008) |
| Pompanopeptin A (181)/bacterium | Peptide | Trypsin inhibition | 2.4 μM | Undetermined | USA | (Matthew et al., 2008) |
| Purpuroe (182)/sponge | Polyketide | DPPH radical scavenging activity | 7 μM | Undetermined | USA | (Li et al., 2008) |
| Salinilactids A and B (183, 184)/bacterium | Polyketide | Ornithine decarboxylase inhibition | 1.9–7.8 μg/mL | Undetermined | USA | (Williams et al., 2007) |
| Sargassum siliquastrum monoglyceride (185)/alga | Triterpenoid | DPPH radical scavenging activity | 0.01-0.31 μg/mL | Undetermined | USA | (Chang et al., 2008) |
| Sargassum sagamianum meroditerpenoids | Polyketide | DPPH radical scavenging activity | 10.2–24 μM | Undetermined | CHN | (Duan et al., 2007) |
| Tenaxacins C and D (196, 197)/bacterium | Triterpenoid | Fe-binding (chelating) activity | 110–115 μM | Undetermined | JPN | (Jang et al., 2007a) |

*Organism, Kingdom Animalia: sea horse (Phylum Chordata); soft corals (Phylum Cnidaria); starfish (Phylum Echinodermata); sponge (Phylum Porifera); Kingdom Chromalveolata: dinoflagellates; Kingdom Fungi: fungus; Kingdom Plantae: alga; Kingdom Monera: bacterium; IC₅₀: concentration of a compound required for 50% inhibition in vitro; *: estimated IC₅₀; **: KD: concentration at which 50% of ligand binding sites are occupied; MMOA: molecular mechanism of action; Country: CAN: Canada; CHN: China; EGY: Egypt; ESP: Spain; DEU: Germany; IND: India; ITA: Italy; JPN: Japan; NLD: The Netherlands; PAP: Papua New Guinea; RUS: Russia; S. KOR: South Korea; VNM: Vietnam; Chemistry: epolyketide; terpene; polycyclic aromatic hydrocarbon; modified as in the text.*
Fig. 3. Marine compounds with miscellaneous mechanisms of action.
stylissadine A (144) \( R = \beta \)-H
stylissadine B (145) \( R = \alpha \)-H

symbiodinolide (146)

Fig. 3 (continued).
Although the investigators studied the effect of the algal bromophenols on the rice fungal pathogen *Magnaporthe grisea*, it is noteworthy that ICL has also been observed to be upregulated in *Mycobacterium tuberculosis*-infected human macrophages, and that *Candida albicans* requires ICL to be fully virulent to human hosts.
Fig. 3 (continued).
Furthermore, several marine natural products showed significant antifungal activity (i.e. MICs that were either less than 10 μg/mL, 10 μM, or 10 μg/disk) (Table 1 and Fig. 1; 38, 39, 40, 41, 42, 43, 44), although no mechanism of action studies were reported in the published articles: callipeltins J and K (38, 39), MIC = 1 μM (D’Auria et al., 2007), the triterpene glycoside holothurin B (40), MIC = 1.56 μg/mL (Kumar et al., 2007), the macrolide neopeltolide (41), MIC = 0.62 μg/mL (Wright et al., 2007), the cyclopeptide pedein A (42), MIC = 0.6–1.6 μg/mL (Kunze et al., 2008), and pseudoceratins A and B (43, 44), MIC = 6.5–8.0 μg/disk (Jang et al., 2007b). Hopefully, future studies on the molecular pharmacology of these marine compounds will elucidate their mechanisms of action.

Finally, several novel structurally characterized marine molecules isolated from sponges demonstrated MICs or IC50s greater than 10 μg/mL or 10 μM, and therefore, because of the reported weaker antifungal activity, they have been excluded from Table 1 and Fig. 1: eurysterols A and B (MIC = 15.6–62.5 μg/mL) (Boonlarppradab and Faulkner, 2007); nagelamides M and N (MIC = 33.3 μg/mL) (Kubota et al., 2008), nortetillapyrone (MIC = 31–62 μg/mL) (Wattanadilok et al., 2007), and Tydemania expeditionis triterpenoids (IC50 = 26–55 μM) (Jiang et al., 2008). These marine compounds may yet provide additional pharmacological leads in the ongoing global search for clinically useful antifungal agents.

2.4. Antimalarial, antiprotozoal, and antituberculosis activity

As shown in Table 1, during 2007–8 fourteen studies reported novel findings on the antimalarial, antiprotozoal and antituberculosis pharmacology of structurally characterized marine natural products,
an increase from our previous review (Mayer et al., 2009), and previous reviews of this series.

As shown in Table 1, nine marine molecules were shown during 2007–8 to possess significant antimalarial activity, although mechanism of action studies were reported for only two compounds. Tasdemir et al. (2007) reported that (E)-oroidin (45) and (E)-oroidin TFA salt (46) isolated from the Turkish marine sponge Agelas oroides potently inhibited cultures of multidrug resistant K1 strain of Plasmodium falciparum (IC\text{50} = 3.9 and 7.9 μg/mL, respectively) with concomitant inhibition of FabI (enoyl-ACP reductase), a key enzyme of the type II fatty acid synthase cascade (IC\text{50} = 0.3 and 5.0 μg/mL, respectively). Further studies revealed that oroidin free base appeared to bind to “the enzyme–substrate complex or enzyme–cofactor complex” by an uncompetitive mechanism, providing further
pharmacological characterization of the “first antimalarial marine natural product that targets *P. falciparum* FabI”.

Additional antimalarial activity was reported for seven marine compounds. Two reports were contributed during 2007 by the Panama International Cooperative Biodiversity Groups project: McPhail et al. (2007) isolated a novel linear lipopeptide dragomabin (47) from the cyanobacterium *Lyngbya majuscula* with moderate antimalarial activity ($IC_{50}=6.0 \mu M$), and significant differential toxicity between the malarial parasite and mammalian cells. Linington et al. (2007) discovered that the new cyclic hexapeptides venturamides A and B (48, 49) isolated from a Panamanian marine cyanobacterium *Oscillatoria* sp., demonstrated significant *in vitro* antiplasmodial activity against the W2 chloroquine-resistant strain of the parasite ($IC_{50}=5.6–8.2 \mu M$), with mild cytotoxicity to mammalian cells, the first “example of the identification of cyanobacterial peptides with selective antimalarial activity”. Kasettrathat et al. (2008) proved that a new tetronic acid, nodulisporacid A (50), from a marine-derived fungus *Nodulisporium* sp. CRIF1 isolated from a Thai soft coral, was moderately antiplasmodial ($IC_{50}=1–10 \mu M$) against chloroquine-resistant *P. falciparum* strain 94. Na et al. (2008) identified a new marine *Streptomyces* sp. H668 polyether (51) from Hawaii that showed *in vitro* antimalarial activity ($IC_{50}=0.1–0.2 \mu g/mL$) against both *P. falciparum* chloroquine-susceptible (D6) and -resistant
(W2) clones, with minimal cytotoxicity towards mammalian cells. Clark et al. (2008) found that a novel acylproline derivative, tunicamycin I (52) from the Papua New Guinean marine cyanobacterium Blnenothrix canthariduscum, showed moderate antimarialar activity against P. falciparum (IC50 = 2 μM). Pontius et al. (2008a) isolated a heterocyclic-stabilized xanthone, chaetoaxanthone B (53) from cultures of a marine-derived fungus Chaetomium sp. that showed selective activity towards P. falciparum K1 strain (IC50 = 0.5 μg/mL).

Four marine compounds were reported to possess antiprototaxol activity. Kossuga et al. (2008) re-isolated the previously reported plakortide P (54) from the marine sponge Plakortis angulospiculatus. The compound displayed selective effects against both Leishmania chagasi (IC50 = 0.5–1.9 μg/mL) and Trypanosoma cruzi (IC50 = 2.3 μg/mL), with low concomitant hemolytic and cytotoxic activities towards human macrophages. Reportedly, the mechanism of action towards intracellular L. chagasi did not appear to involve nitric oxide. Simmons et al. (2008) found that two novel lipopeptides viridamides A and B (55, 56) were nearly “equipotent” in inhibiting both Leishmania mexicana (IC50 = 1.1 μM) and T. cruzi (IC50 = 1.5 μM). Besides the antimarialar activity, Pontius et al. (2008a) discovered that chaetoaxanthone B (53) had selective effects towards T. cruzi (IC50 = 1.5 μg/mL), with minimal cytotoxicity towards rat skeletal L6 myoblasts (IC50 = 47 μg/mL).

Ten new marine compounds were reported in the global search for novel antituberculosis agents, a considerable increase from our previous reviews (Mayer et al., 2009), and previous reviews of this series. Ospina et al. (2007) isolated a bioactive oxaoplycyclic diterpene bipinnapterolide B (57) from the Colorado gorgonian coral Pseudopterogorgia bipinnata which weakly inhibited growth of M. tuberculosis H37Rv (66% inhibition at 128 μg/mL). Zhang et al. (2008) identified two new dimeric naphtha-γ-pyrones 8′-O-demethylnigerone (58) and 8′-O-demethylenalogeron (59) from the marine-derived fungus Aspergillus carbonarius which showed weak antmycobacterial activity against M. tuberculosis (H37Rv, MIC = 43 and 21.5 μM, respectively). Interestingly, the presence of conjugated C=C-C=O bonds in the pyrene ring appeared to be crucial for antifungal activity. As a result of a continued investigation of the Caribbean sea whip Pseudopterogorgia elisabethae, Wei et al. (2007a) reported that the novel tricarbocyclic norditerpenes carbenolos A (60) and B (61) weakly inhibited M. tuberculosis (H37Rv, MIC = 128 and 63 μg/mL, respectively). Furthermore, Wei et al. (2007b) discovered two novel ring B aeo-sterols paugarestols A (62) and B (63) in the Caribbean sponge Svenzea zeai, which inhibited M. tuberculosis (H37Rv, MIC = 7.8 and 11.2 μg/mL, respectively). Hopefully future information on the selectivity index of these two compounds will provide additional information to support the notion that they might “constitute important lead structures for the development of novel tuberculosis drugs due to their strong activity, specificity, and low toxicity”. Berrue et al. (2007) noted that several bioactive polyketides, 24-norisorpsicicloic acid A (64), dinorspsicicloic acid A (65), and norspsicicloic acid A (66) from the Caribbean sponge Plakortis zygomyrna also inhibited M. tuberculosis (H37Rv, MIC = 50 μg/mL). Although all of these studies demonstrate that marine terpenes and polyketides constitute potentially novel antituberculosis leads, they unfortunately did not provide detailed mechanism of action pharmacology at the time of their publication.

2.5. Antiviral activity

As shown in Table 1, three reports were published on the antiviral pharmacology of novel marine natural products against severe acute respiratory syndrome (SARS) Corona virus, herpes simplex, and dengue virus during 2007–8. de Lira et al. (2007) discovered that the new esculatin-4-carboxylic acid ethyl ester (67) from the Brazilian marine sponge Axinella cf. corrugata inhibited the SARS 3CL protease (IC50 = 46 μM). This is a potentially significant finding because the 3CL protease is a “high profile target” in SARS drug development as it appears to be involved in the release of replicative viral proteins as well as the RNA polymerase. Talarico et al. (2007) reported that a D1-galactan hybrid C2S-3 (68) isolated from the Brazilian marine alga Cystonomia crenulata showed potent antiviral activity against three clinical strains of dengue virus serotype 2 (IC50 = 0.8–16 μg/mL), together with low cytotoxicity. Further mechanistic work determined that C2S-3 appeared to be a “promising DENV-2 entry inhibitor”. Mandal et al. (2008) described a sulfated xylomannan isolated from the Indian red seaweed Scinaia haiti which inhibited HSV-1 and HSV-2 (IC50 = 0.5–1.4 μg/mL), with low cytotoxicity, probably interfering with the HSV-1 multiplication cycle. Interestingly the “very good antiviral activity against the wide spectrum of HSV strains tested” suggested this compound might be a good candidate for further preclinical research.

Five reports contributed preclinical pharmacology of marine compounds active against the human immunodeficiency virus type-1 (HIV-1), the causative agent of the acquired immunodeficiency disease syndrome (AIDS), an increase from our previous reviews (Mayer et al., 2009), and previous reviews of this series. Artan et al. (2008) reported that the phlorglucinol derivative 6, 6′-bieckol (69) isolated from the brown alga E. cava inhibited HIV-induced syncytia formation (IC50 = 1.72 μM), viral p24 antigen production (IC50 = 1.26 μM), and the activity of the HIV reverse transcriptase (IC50 = 1.07 μM), with “no cytotoxicity” at concentrations that inhibited HIV replication “almost completely”. Cirne-Santos et al. (2008) extended the molecular pharmacology of the diterpene dolabelladienetriol (70) isolated from the marine brown alga Dictyota puffyi. The dolabellane diterpene blocked both synthesis and integration of the HIV-1 provirus by noncompetitively inhibiting the reverse transcriptase enzyme (Ki = 7.2 μM). The investigators proposed dolabelladienetriol (70) as a “potential new agent for anti-HIV-1 therapy”. Plaza et al. (2007) described three new depsipeptides miramibrides A, C and D (71, 72, 73) isolated from the sponge Siliquariaspongia mirabilis that potently inhibited both HIV-1 in neutralization (IC50 = 0.14–0.19 μM) and HIV-1 envelope-mediated cell fusion (IC50 = 0.14–3.9 μM), suggesting these compounds act at an early stage of HIV-1 cell infection, “presumably through interactions with HIV-1 envelope proteins”. Lu et al. (2007) added a “novel mechanistic profiling” of the previously reported sulfated polymannuronoguluronate (SPMG) (74), a polysaccharide with an average molecular weight of 8.0 kDa isolated from the brown alga Laminaria japonica, that has been reported to be in Phase II clinical trials in China as an anti-AIDS drug candidate. SPMG appeared to eliminate the viral gene product known as transactivator of transcription protein (Tat)-induced signal transduction as well as angiogenesis in AIDS-associated Kaposi's sarcoma cells. Furthermore, in 2008, Hui et al. (2008) demonstrated that SPMG appeared to show a neuroprotective effect because it decreased apoptosis caused by Tat-stimulated calcium overload in PC12 neuronal cells, thus suggesting SPMG might warrant further clinical studies in HIV-associated dementia.

3. Marine compounds with anti-inflammatory effects and affecting the immune and nervous systems

Table 2 summarizes the preclinical pharmacological research completed during 2007–8 with the marine compounds (75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132) shown in Fig. 2.

3.1. Anti-inflammatory marine compounds

The anti-inflammatory pharmacology of marine compounds reported during 2007–8 showed a considerable increase from our previous review (Mayer et al., 2009), and previous reviews of this
series. Several marine natural products were shown in preclinical pharmacological studies to target arachidonic metabolism in neutrophils and macrophages. Pearce et al. (2007a) reported two new tricyclic alkaldols ascidiahalone A (75) and B (76) isolated from a New Zealand ascidian Aplidium species that affected superoxide production by human neutrophils in vitro (IC$_{50}$ = 0.44–1.55 μM), as well as murine peritoneal neutrophils ex vivo, with concomitant “low or nonexistent” liver and renal toxicity, thus suggesting that these two compounds might become “potential anti-inflammatory pharmaceutical” leads. Chao et al. (2008) identified the new ceramides crassumolides A and C (77, 78) from the soft coral Lobophyllum crassum which inhibited expression of iNOS and COX-2 (apparent IC$_{50}$ 10 μM), as well as murine peritoneal neutrophils ex vivo, with concomitant “low or nonexistent” liver and renal toxicity, thus suggesting that these two compounds might become “potential anti-inflammatory pharmaceutical” leads. Cheng et al. (2008) found that new ceramides from the soft coral Lobophyllum duru, durumolides A–C (79, 80, 81) inhibited both the iNOS and COX-2 proteins in LPS-activated RAW 264.7 cells in vitro (apparent IC$_{50}$ less than 10 μM), suggesting that the α-methylene-γ-lactone moiety of these compounds was necessary for the observed activity. Shen et al. (2007) showed that new briarane-type diterpenoids frajunolides B and C (82, 83), isolated from the Taiwanese gorgonian Juncella fragilis, significantly inhibited superoxide anion and elastase generation from human neutrophils in vitro (apparent IC$_{50}$ greater than 10 μg/mL). Dang et al. (2008) demonstrated that the previously described fatty acids (84, 85) from the South Korean marine red alga Gracilaria verrucosa inhibited release by LPS-activated murine macrophages of the inflammatory nitric oxide, tumor necrosis factor α and interleukin-6 (apparent IC$_{50}$ less than 20 μg/mL), thus revealing that the conjugated enone moiety played a critical role in the anti-inflammatory activity observed in vitro. Bittencourt et al. (2008) contributed novel preclinical pharmacology on a previously reported 90 amino acid polypeptide (86) isolated from the red alga Hypnea cervicornis. The mucin-binding agglutinin, which was extensively characterized with several in vivo models of nociception and inflammation, probably exerted its anti-inflammatory activity (apparent IC$_{50}$ = 0.1–1 mg/kg) via interaction of the polypeptide with the lectin carbohydrate-binding site, although the exact mechanism of action remains undetermined. El Sayed et al. (2008) demonstrated that manzamine A (87), (−)-8-hydroxymanzamine A (88), and hexahydro-8-hydroxymanzamine A (89) potentiated inhibited TNF-$\alpha$ generation (IC$_{50}$ = 0.25, less than 0.1, and 1.97 μM, respectively) in brain microglia. These findings provide further support to the notion that manzamine alkaloids appear to be “viable anti-inflammatory leads” for the preclinical pharmaceutical development of agents to modulate both activated brain microglia and eicosanoid generation. Treschow et al. (2007) investigated four novel α-3 polysaturated fatty acids (90, 91, 92, 93) from the New Zealand green-lipped mussel Perna canaliculus with an in vitro bioassay that used stimulated human neutrophil 5-lipoxygenase, demonstrating that the putative anti-inflammatory potential of these compounds might be related to inhibition of leukotriene and prostaglandin metabolite production. Sansom et al. (2007) reported a bis-prenylated quinone (94) from the New Zealand brown alga Perichthia capillaris which inhibited superoxide anion production in human neutrophils (IC$_{50}$ = 2.1 μM) in vitro, with low toxicity. An explanation as to why the authors decided not to investigate the quinone “as an anti-inflammatory lead” remains unclear, although it was strongly cytotoxic towards human leukemia cells (IC$_{50}$ = 0.34 μM). Sugura et al. (2007) characterized a novel anti-inflammatory polypeptide containing an allergenic polypeptide (95) from the edible brown alga Eiseania arborea. PFF-B, isolated from β-2,4-diaminobutyric acid release from rat basophilic leukemia cells (IC$_{50}$ = 7.8 μM) in vitro, thus showing higher potency than Trypanlast (Rizaben®) (IC$_{50}$ = 46.6 μM), a pharmaceutical agent used for treatment of allergic disorders such as asthma, allergic rhinitis and atopic dermatitis in Japan and South Korea. Kossuga et al. (2008) demonstrated that the polyketide plakortide P (94) isolated from the Brazilian sponge P. angulospiculatus, potentely inhibited thromboxane $\beta_2$ release (IC$_{50}$ = 0.93 μM) from activated rat brain microglia, thus extending the preclinical pharmacology of this compound, which besides being antiparasitic as discussed earlier in this review, also appears to be a potentially “novel antineuroinflammatory agent”. Pearce et al. (2007b) examined a halogenated furanone rubrolide O (96) isolated from a New Zealand ascidian Synoicum n. sp., which inhibited superoxide anion production in human neutrophils (IC$_{50}$ = 35 μM) in vitro with low toxicity. Although rubrolides have been reported to be cytotoxic and antibacterial, the authors proposed that the anti-inflammatory activity for these tunicate metabolites though moderate was “unprecedented”. Khan et al. (2007) identified a o-3 polysaturated fatty acid stearidonic acid (97) from the South Korean brown seaweed Undaria pinnatifida, which was shown to be very active against PMA-induced mouse ear inflammation symptoms, edema, erythema and blood flows (IC$_{50}$ = 160, 314 and 235 μg/per ear, respectively). The in vivo data compared well with indomethacin which was used as a positive control (IC$_{50}$ = 90, 172, 179 μg/per ear, respectively), and thus supported claims that this “seaweed can be used as a remedy for inflammation-related symptoms”. Kobayashi et al. (2007a) discovered a novel dimeric oroidin derivative carteramine A (98) in the marine sponge Styliosa carteri, and showed that it inhibited neutrophil chemotaxis (IC$_{50}$ = 5 μM). The authors suggested that because carteramine A has no structural resemblance to known compounds that inhibit neutrophil chemotaxis, their finding provides a “novel platform to develop a new class of anti-inflammatory agents”. Taori et al. (2007) identified three new analogues of dolastatin 13, lyngbyastatins 5–7 (99, 100, 101), isolated from marine cyanobacteria Lyngbya spp. from South Florida. Although the three compounds selectively and potently inhibited porcine pancreatic elastase (IC$_{50}$ = 3–10 nM), suggesting a potential therapeutic use in pathophysiological conditions where elastase overactivity is involved, no mechanism of action studies were reported at the time. Oh et al. (2007) purified a novel polyketide salinipyrone A (102) from the marine actinomycete Salinispora pacifica, which moderately inhibited interleukin-5 (IC$_{50}$ = 10 μg/mL) in a mouse splenocyte model of allergic inflammation, with low cell cytotoxicity.

### 3.2. Marine compounds affecting the immune system

The pharmacology of the marine compounds reporting activity on the immune system during 2007–2008 showed a considerable increase from our previous review (Mayer et al., 2009), and previous reviews of this series.

Kawachii et al. (2007) investigated the red pigment cycloprodigiosin hydrochloride (103) isolated from the marine bacterium Pseudoalteromonas dermatitica. Interestingly, the compound suppressed activator protein 1 (AP-1) (apparent IC$_{50}$ = 1 μM), and downstream gene expression of interleukin 8, a chemokine involved in the innate immune system. Courtois et al. (2008) assessed the effect of the known compound floridoside (104), isolated from the French red alga Mastocarpus stellatus on the complement system. Floridoside was observed to potently activate the classical complement pathway (apparent IC$_{50}$ = 5.9–9.3 μg/mL) by recruiting immunoglobulin M (IgM), suggesting that the compound might be an “important step in the development of a potent new antimcomplementary agent” useful in therapy aimed at addressing complement depletion. Greve et al. (2007) reported that the novel iso-iantheran A and 8-carboxy-iso-iantheran A (105, 106) purified from the Australian marine sponge Ianthella quadrangulata demonstrated in vivo activity at P2Y$_{11}$ receptors (IC$_{50}$ = 1.29 and 0.48 μM, respectively). This finding represents an interesting contribution to ionotropic purine receptor P2Y$_{11}$ pharmacology, because these receptors have been shown to affect the maturation and differentiation of dendritic cells. Huh et al. (2007) extended the pharmacology of prodigiosin (107) isolated from the marine bacterium Halitella chejuensis collected in South Korea. Prodigiosin inhibited INOS mRNA expression and NO production.
production (apparent IC\textsubscript{50} = 0.1 \mu g/mL) by a mechanism that involved inhibition of NF-\kappa B and p38 MAPK and JNK phosphorylation. He et al. (2007) characterized the pharmacology of a water soluble polysaccharide (\textbf{108}) isolated from the mollusc \textit{Arca subcrenata} Lischke, a popular Chinese seafood, and named it ASLP. ASLP stimulated mouse spleen lymphocyte proliferation in a concentration-dependent manner (apparent IC\textsubscript{50} less than 100 \mu g/mL), and with the “branches of ASLP” being required for the immunomodulatory bioactivity. Aminin et al. (2008) described the immunostimulant activity of frondoside A (\textbf{109}), a triterpene glycoside isolated from the sea cucumber \textit{Cucumaria frondosa}. The glycoside was shown to stimulate lymososomal activity and phagocytosis in mouse macrophages, as well as reactive oxygen species formation. Oda et al. (2007) provided novel information on the molecular mechanisms affected by sennosponginone, sennospongiaraine and sennospongine (\textbf{110, 111, 112}), sesqui-terpene quinones previously isolated from a Palauan marine sponge \textit{Hippopospongia} sp. The observation that at 10 \mu g/mL, these compounds promoted interleukin-8 release, a member of the C–X–C chemokine superfamily which is involved in tumor progression and metastasis, suggested that “the functional group at C-18” might play a yet undetermined role in the observed results. Yamada et al. (2007) isolated the novel macropheride M (\textbf{113}) and peribysin J (\textbf{114}) from \textit{Periconia byssoides}, a fungal strain discovered from the sea hare \textit{Aplysia kurodai}. Significantly, both fungal metabolites inhibited the adhesion of human promyelocytic leukemia HL-60 cells to human umbilical vein endothelial cells (IC\textsubscript{50} = 33.2 and 11.8 \mu M, respectively) more potently than herbimycin A (IC\textsubscript{50} = 38 \mu M). The latter compound, a benzochinoid ansamycin antibiotic isolated from \textit{Streptomyces} sp. was used as a positive control in these studies. Liu et al. (2008) contributed a novel cembranoid querciformide C (\textbf{115}) from the soft coral \textit{Simularia querciformis}, which significantly inhibited the activation of the iNOS and COX-2 enzymes (apparent IC\textsubscript{50} less than 10 \mu M) in LPS-activated murine macrophages in vitro. Pononarenko et al. (2007) discovered that new diterpenoids (\textbf{116}, \textbf{117}) isolated from a Northern Cook Islands marine sponge \textit{Spongia} (\textit{Heterosbria}) sp. moderately activated murine splenocytes lysosomes (apparent IC\textsubscript{50} greater than 100 \mu g/mL). Oh et al. (2007) characterized a novel cyclic peptide thalassosipiramide B (\textbf{118}) isolated from a marine bacterium \textit{Thalassospira} sp., which showed immunosuppressive activity in an interleukin-5 (IL-5) inhibition assay (IC\textsubscript{50} = 5 \mu M); an interesting finding because IL-5 is expressed both in eosinophils and mast cells in asthmatic patients.

### 3.3. Marine compounds affecting the nervous system

Pharmacological studies with marine compounds affecting the nervous system involved three areas of neuropharmacology: the stimulation of neurogenesis, the targeting of receptors, and other miscellaneous activities on the nervous system.

Marine natural products reported to be neuritogenic, might be used to treat damaged neuronal cells, and potentially neurodegenerative diseases. As shown in Table 2, compounds (\textbf{119, 120, 121, 122, 123, 124, 125, 126}) isolated from sea stars and a brown alga were observed to enhance the neuritogenic properties of nerve growth factor (NGF), a compound that has a critical role in differentiation, survival, and neuronal regeneration. Kicha et al. (2007b) contributed two new steroid glycosides, linckosides L1 (\textbf{119}) and L2 (\textbf{120}) isolated from the Vietnamese blue sea star \textit{Linckia laevis}. All three glycosides (apparent IC\textsubscript{50} = 0.3 \mu M) showed synergistic effects on NGF-induced (2 ng/mL) neurite outgrowth of murine neuroblastoma C-1300 cells. Han et al. (2007) contributed the novel steroid glycosides linckosides M–Q (\textbf{121, 122, 123, 124, 125}) from the Japanese sea star \textit{L. laevis}. Linckoside P (\textbf{124}) induced neurite outgrowth in 55% of rat pheochromocytoma PC12 cells at 10 \mu M in the presence of nerve growth factor (NGF), while linckosides M–Q appeared less active (21–32%), suggesting the importance of “the xylose on a side chain”. Ina et al. (2007) characterized pheophytin A (\textbf{126}) purified from the Japanese brown alga \textit{Sargassum fulvellum} as a novel neurodifferentiation compound. Pheophytin A at 3.9 \mu g/mL was observed to synergize with NGF (50 ng/mL) in promoting neurite outgrowth in rat pheochromocytoma PC12 cells by a mechanism that appeared to involve activation of mitogen-activated protein kinase signaling.

As shown in Table 2, during 2007–8, three marine compounds (\textbf{127, 128, 129}) were reported to target receptors in the nervous system. Peng et al. (2008) reported on the preclinical pharmacology of the \textit{\alpha}4/7-conotoxin Lp1.1 (\textbf{127}) originally isolated from the marine cone snail \textit{Conus leopardus}. The conotoxin induced seizure and paralysis in goldfish, and selectively yet reversibly inhibited acetylcholine-evoked currents in \textit{Xenopus} oocytes expressing rat \textit{cS}3/2 and \textit{cS}3/2 nicotinic receptors (apparent IC\textsubscript{50} less than 10 \mu M). Aiello et al. (2007) characterized two novel bromopyrrole alkaloids damipiceline (\textbf{128}) and damitircine (\textbf{129}) isolated from the Mediterranean sponge \textit{Axinella damicornis} that were observed to modulate serotonin receptor activity in vitro. Although damipiceline inhibited Ca\textsuperscript{2+} entry in neurons (apparent IC\textsubscript{50} = 1 \mu g/mL), the serotonin receptor subtype involved in the mechanism of action remains undetermined.

Finally, as shown in Table 2, during 2007–8, additional marine compounds (\textbf{74} and \textbf{130, 131, 132}) were reported to have miscellaneous effects on components of the nervous system. Contributing to the ongoing search for acetylcholinesterase inhibitors useful in the treatment of Alzheimer’s disease, Langjje et al. (2007) reported a new stigmastane-type steroidal alkaloid 4-acetoxy-plakinamine B (\textbf{130}), isolated from a Thai marine sponge \textit{Corticium} sp. that significantly inhibited acetylcholinesterase (IC\textsubscript{50} = 3.75 \mu M). Compound 130 was reported to be the “first marine-derived acetylcholinesterase-inhibiting steroidal alkaloid” with a mechanism of action involving an unusual mixed-competitive mode of inhibition. Choi et al. (2007) extended the molecular pharmacology of two known meroditerpenes, sarguquinic acid (\textbf{131}) and sargachromenol (\textbf{132}) isolated from the brown alga \textit{S. sagamianum}. Sargauquinic acid potently inhibited butyrylcholinesterase (IC\textsubscript{50} = 26 nM), a novel target for the treatment of Alzheimer’s disease, with potency comparable to or greater than anticholinesterases in current clinical use. Hui et al. (2008) further characterized the neuroprotective effects of the polysaccharide sulfated polymannuroguluronate (SPMG) (\textbf{74}), noted earlier as currently being in Phase II clinical trials in China as an anti-AIDS drug candidate. SPMG appeared to decrease the Tat-stimulated calcium overload in PC12 neuronal cells as well as concomitant apoptosis-signaling cascades, thus demonstrating a potential for further clinical development as a therapeutic intervention in HIV-associated dementia.

### 4. Marine compounds with miscellaneous mechanisms of action

Table 3 lists 65 marine compounds with miscellaneous pharmacological mechanisms of action, and their respective structures (\textbf{133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197) are presented in Fig. 3. Because during 2007–8 additional pharmacological data were unavailable, it was not possible to assign these marine compounds to a particular drug class as was possible with the compounds included in Tables 1 and 2.

Table 3 shows 14 marine natural products that the peer-reviewed literature reported with a pharmacological activity, an IC\textsubscript{50}, and a molecular mechanism of action affected by the respective compound: azumamide E (\textbf{133}), 1-deoxyrubralactone (\textbf{134}), fuxoanthin (\textbf{135}), okadaic acid (\textbf{136}), saproxanthin and myxol (\textbf{137, 138}), sarcosilaster (\textbf{139}), spirastrellolides C, D, and E (\textbf{140, 141, 142}), Spongia
sesterterpenoid (143), stylissadines A and B (144, 145) and symbiodinolide (146).

In contrast, although a pharmacological activity was described, and an IC₅₀ for inhibition of an enzyme or receptor determined, detailed molecular mechanism of action studies were unavailable at the time of publication for the following 51 marine compounds included in Table 3: Asterias amurensis saponin (147), Botrytis sp. α-lycynine derivative (148), cephalosporolides H and I (149, 150), chaetominedione (151), circumdatin B (152), diapolyphenic acid xylosyl ester (153), Echinogorgia complexa furanosousquinones (154, 155), 19-epi-okadaic acid (156), eriodysides F and Fr (157, 158), Hippocampus kuda phthalates (159, 160, 161), irgarolar sulfate (162), kempeptides A and B (163, 164), linckoside L7 (165), lyngbyastatin 4 (166), malevamide E (167), monodictyacin C (168), monodictychomes A and B (169, 170), Penicillium waksmanii PF1270 A, B, and C (171, 172, 173), Penicillium sp. anisols (174, 175, 176), Polyphytopha urceolata bromophenols (177, 178, 179, 180), pompanopeptin A (181), purpureone (182), saliniketals A and B (183, 184), S. sagamianum monoglyceride (185), Sargassum siliquastrum meroterpenoids (186, 187, 188, 189, 190, 191), Symphyotrichia latiuscula bromophenols (192, 193, 194, 195), and tenacibactins C and D (196, 197).

5. Reviews on marine pharmacology

Several reviews covering both general and specific subject areas of marine pharmacology were published during 2007–8: (a) general marine pharmacology: marine natural products with an emphasis on source organisms and relevant biological activities (Blunt et al., 2007, 2008); the value of natural products to future pharmaceutical discovery (Baker et al., 2007); the structures and bioactivities of secondary metabolites from cyanobacteria (Cademann and Portmann, 2008); bioactive natural products from marine cyanobacteria for drug discovery (Tan L.T., 2007); bioactive compounds from fungi in the South China Sea (Pan et al., 2008); biochemical and pharmacological functions of β-carboline alkaloids (Cao et al., 2007); pharmacological properties of lamellarin alkaloids (Kluza et al., 2008); biological activity of brown seaweed fucoids (Kusaykin et al., 2008; Li et al., 2008a); potential pharmacological uses of the marine green alga polysaccharide ulvan (Lahaye and Robic, 2007); (b) antitumor marine pharmacology: a renaissance of genomics in antibacterial discovery from actinomycetes (Balz R.H., 2008); mining marine genomics for novel drug discovery from phytosymbionts of marine invertebrates (Dunlap et al., 2007); (c) anticoagulant and cardiovascular pharmacology: structure, biology, evolution and medical importance of sulfated fucans and galactans as potential antithrombotic compounds (Pomin and Mourao, 2008); (d) antituberculosis, antimalarial and antifungal marine pharmacology: natural product growth inhibitors of Mycobacterium tuberculosis (Copp and Pearce, 2007); new advances in novel marine fatty acids as antimalarials, antimycobacterial and antifungal agents (Carballeira N.M., 2008); depsipeptides from microorganisms as a new class of antimalarials (Fotie and Morgan, 2008); the manzamine alkaloids for the control of malaria and tuberculosis (Hamann M.T., 2007); (e) immuno- and anti-inflammatory marine pharmacology: chemistry and biology of anti-inflammatory marine natural products (Abad et al., 2008); marine natural products as targeted modulators of the transcription factor NF-κB (Folmer et al., 2008); glycolipids as immunostimulating agents (Wu et al., 2008); (f) nervous system marine pharmacology: marine-derived drugs in neurology (Martinez A., 2007); neurotrophic gangliosides from marine echinoderms (Higuchi et al., 2007); (g) miscellaneous molecular targets: enzyme inhibitors from marine invertebrates (Nakao and Fusetani, 2007); natural products as aromatase inhibitors (Balunas et al., 2008); biology of the aeruginosin family of serine protease inhibitors (Ersmark et al., 2008); and marine natural products affecting membrane and intracellular processes, and ion channels (Folmer et al., 2007).

6. Conclusion

Six years after the approval of the marine compound ziconotide (Prialt®) by the U.S. Food and Drug Administration (Williams et al., 2008), the global marine preclinical pharmaceutical pipeline remains very active. The marine pharmaceutical clinical pipeline is available at marinepharmacology.midwestern.edu/clinDev.htm and has recently been reviewed (Mayer et al., 2010).

The current marine preclinical pipeline review contributes to the annual review series which was initiated in 1998 (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004, 2005; Mayer et al., 2007, 2009) and reveals the breadth of preclinical pharmacological research during 2007–8, which resulted from the global effort of natural products chemists and pharmacologists from Argentina, Australia, Brazil, Canada, China, Egypt, France, Germany, India, Israel, Italy, Japan, the Netherlands, New Zealand, Panama, Papua New Guinea, Portugal, Russia, South Korea, Spain, Switzerland, Taiwan, Thailand, Turkey, United Kingdom, Vietnam, and the United States. Thus, it appears that the marine preclinical pharmaceutical pipeline continues to contribute novel pharmacological lead compounds that will probably enable a future expansion of the marine clinical pharmaceutical pipeline, which currently consists of 13 compounds in Phase I, II and III of clinical development (Mayer et al., 2010).

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