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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* (Saravanakumar et al., 2008); antileishmanial and anti-trichomonal activity in organic extracts of several Mexican red and brown algae (Freile-Pelegrin et al., 2008; Moo-Puc et al., 2008); anti-HIV-1 activity of novel sulfated galactans isolated from the Chinese red algae *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 *Gracilaria 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 *Champia feldmannii* (Assreuy et al., 2008); antioxidant and antimicrobial activity of the Indian red and brown seaweed methanolic extracts with high phenolic contents (Devi 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 ascochytatin (**1**) isolated from cultures of a marine-derived fungus *Ascochyta* sp. NGB4, which inhibited *B. subtilis* growth (MID = 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-amino 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 H_2O_2 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 calcein 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 *Aaaptos aaptos*. Isoaaptamine inhibited sortase A (IC_{50} = 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 *Dysidea* 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}^{b}	MMOA[b]	Country[c]	References
Antibacterial	Ascochytatin (**1**)/fungus	Polyketide[d]	*B. subtilis* inhibition	0.3 μg^{++}	TCS (YycG and YycF) regulatory system	JPN	(Kanoh et al., 2008b)
Antibacterial	L-Amino acid oxidase SSAP (**2**)/rockfish	Protein[f]	*A. salmonicida*, *P. damselae* subsp. *piscida* and *V. parahaemolyticus* inhibition	0.078–0.63 μg/mL^{+}	H_2O_2 mediates the antibacterial action	JPN	(Kitani et al., 2008)
Antibacterial	Arenicin-1 (**3**)/polychaete	Peptide[f]	*P. aeruginosa* and *S. aureus* inhibition	2 μg/mL^{+}	Binding and disruption of cell membrane	S. KOR	(Lee et al., 2007)
Antibacterial	Isoaaptamine (**4**)/sponge	Alkaloid[f]	*S. aureus* inhibition	3.7 μg/mL	Sortase A inhibition and fibronectin binding	S. KOR	(Jang et al., 2007c)
Antibacterial	*Dysidea* sp. Sesterterpenes (**5**, **6**, **7**, **8**, **9**, **10**, **11**) /sponge	Terpenoid[e]	*B. subtilis* inhibition	1.56–12.5 μg/mL^{+}	Isocitrate lyase inhibition	S. KOR	(Lee et al., 2008)
Antibacterial	Sulfoalkylresorcinol (**12**)/fungus	Polyketide[d]	Methicillin-resistant *S. aureus* inhibition	12.5 μg/mL^{+}	FtsZ polymerization inhibition	JPN	(Kanoh et al., 2008a)
Antibacterial	Ambiguines H and I (**13**, **14**)/bacterium	Alkaloid[f]	*S. albus* and *B. subtilis* inhibition	0.08–1.25 μg/mL^{+}	Undetermined	ISR	(Raveh and Carmeli, 2007)
Antibacterial	Ariakemicins A and B (**15**, **16**)/bacterium	Polyketide[d]	*S. aureus* inhibition	0.46 μg^{++}	Undetermined	JPN	(Oku et al., 2008)
Antibacterial	Ayamycin (**17**)/bacterium	Polyketide[d]	Gram-positive and -negative bacteria inhibition	0.1 μg/mL^{+}	Undetermined	EGY, GBR	(El-Gendy et al., 2008a)
Antibacterial	Batzelladine L and M (**18**, **19**)/sponge	Alkaloid[f]	*S. aureus* and methicillin-resistant *S. aureus* inhibition	0.25–5.0 μg/mL^{+}	Undetermined	USA, CHN, ESP, NZL	(Hua et al., 2007)
Antibacterial	*L. herbacea* diphenyl ether (**20**)/sponge	Polyketide[d]	*B. subtilis* inhibition	0.1 μg^{++}	Undetermined	JPN, IDN, NLD	(Hanif et al., 2007)
Antibacterial	Essramycin (**21**)/bacterium	Alkaloid[f]	*B. subtilis*, *S. aureus* and *M. luteus* inhibition	1–85 μg/mL^{+}	Undetermined	EGY, DEU	(El-Gendy et al., 2008b)
Antibacterial	(+)-Isojaspic acid (**22**)/sponge	Terpenoid[e]	*S. epidermis* inhibition	2.5 μg/mL^{+}	Undetermined	USA, NLD	(Rubio et al., 2007)
Antibacterial	Lynamicins A–D (**23**, **24**, **25**, **26**)/bacterium	Alkaloid[f]	Methicillin-resistant *S. aureus* inhibition	1.8–9.5 μg/mL^{+}	Undetermined	USA	(McArthur et al., 2008)
Antibacterial	Lipoxazolidinones A and B (**27**, **28**)/bacterium	Polyketide[d]	*Staphylococcus* sp., *S. pneumoniae*, *E. faecalis* inhibition	0.5–16 μg/mL^{+}	Undetermined	USA	(Macherla et al., 2007)
Antibacterial	Marinopyrrole A (**29**)/bacterium	Alkaloid[f]	Methicillin-resistant *S. aureus* inhibition	0.31 μM^{+++}	Undetermined	USA	(Hughes et al., 2008)
Antibacterial	(−)-Microcionin-1 (**30**)/sponge	Terpenoid[e]	*M. luteus* inhibition	6 μg/mL^{+}	Undetermined	PRT, ESP	(Gaspar et al., 2008)
Antibacterial	Phomolide B (**31**)/fungus	Polyketide[d]	*E. coli* inhibition	5–10 μg/mL^{+}	Undetermined	CHN	(Du et al., 2008)
Antibacterial	Sargaquinoic acid derivative (**32**)/alga	Terpenoid[e]	*S. aureus* inhibition	2 μg/mL^{+}	Undetermined	JPN	(Horie et al., 2008)
Antibacterial	Tauramamide (**33**)/bacterium	Peptide[f]	*Enterococcus* sp. inhibition	0.1 μg/mL^{+}	Undetermined	CAN, PAP, USA	(Desjardine et al., 2007)
Anticoagulant	Anticoagulant polypeptide (TGAP) (**34**)/bivalve	Protein[f]	Inhibition of factor II- to IIa conversion	77.9 nM	Specific binding to factor Va and factor II	S. KOR	(Jung et al., 2007b)
Antifungal	*Odonthalia corymbifera* bromophenols (**35**, **36**, **37**)/alga	Polyketide[d]	*Magnaporthe grisea* inhibition	2.0–2.8 μM	Isocitrate lyase inhibition	S. KOR	(Lee et al., 2007)
Antifungal	Callipeltins J and K (**38**, **39**)/sponge	Peptide[f]	*C. albicans* inhibition	1 μM^{+}	Undetermined	ITA, FRA	(D'Auria et al., 2007)
Antifungal	Holothurin B (**40**)/sea cucumber	Triterpenoid glycoside[e]	*T. mentagrophytes* and *S. schenckii* inhibition	1.56 μg/mL^{+}	Undetermined	IND	(Kumar et al., 2007)
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[f]	*R. glutinis*, *S. cerevisae* and *C. albicans*	0.6–1.6 μg/mL^{+}	Undetermined	DEU	(Kunze et al., 2008)
Antifungal	Pseudoceratins A and B (**43**, **44**)/sponge	PKS/NRPS[f]	*C. albicans* and mutant *S. cerevisae* inhibition	6.5–8.0 μg^{++}	Undetermined	JPN	(Jang et al., 2007b)
Antimalarial	(*E*)-Oroidin (**45**) and (*E*)-oroidin TFA salt (**46**)/sponge	Alkaloid[f]	*P. falciparum* K1 strain inhibition	3.9–7.9 μg/mL	FabI inhibition	CHE, GBR, USA, TUR	(Tasdemir et al., 2007)
Antimalarial	Dragomabin (**47**)/bacterium	Peptide[f]	*P. falciparum* W2 strain inhibition	6.0 μM	Undetermined	PAN, USA	(McPhail et al., 2007)
Antimalarial	Venturamides A and B (**48**, **49**)/bacterium	Peptide[f]	*P. falciparum* W2 strain inhibition	5.6–8.2 μM	Undetermined	PAN, USA	(Linington et al., 2007)
Antimalarial	Nodulisporacid A (**50**)/fungus	Polyketide[d]	*P. falciparum* 94 strain inhibition	1–10 μM	Undetermined	THAI	(Kasettrathat 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	S. KOR, USA	(Na et al., 2008)
Antimalarial	Tumonoic acid I (**52**)/bacterium	Polyketide[d]	*P. falciparum* D6 and W2 strain inhibition	2 μM	Undetermined	PAP, USA	(Clark et al., 2008)
Antimalarial	Chaetoxanthone B (**53**)/fungus	Polyketide[d]	*P. falciparum* K1 strain inhibition	0.5 μg/mL	Undetermined	CHE	(Pontius et al., 2008a)
Antiprotozoal	Plakortide P (**54**)/sponge	Polyketide[e]	Inhibition of *L. chagasi* and *T. cruzi*	0.5–2.3 μg/mL	Undetermined, though not involving nitric oxide	BRA	(Kossuga et al., 2008)

(continued on next page)

Table 1 (*continued*)

Drug class	Compound/organism[a]	Chemistry	Pharmacologic activity	IC_{50}[b]	MMOA[b]	Country[c]	References
Antiprotozoal	Viridamides A and B (**55**, **56**)/bacterium	Peptide[f]	Inhibition of *L. mexicana* and *T. cruzi*	1.1–1.5 μM	Undetermined	PAN, USA	(Simmons et al., 2008)
Antiprotozoal	Chaetoxanthone B (**53**)/fungus	Polyketide[d]	*T. cruzi* Tulahuen C4 strain inhibition	1.5 μg/mL	Undetermined	CHE	(Pontius et al., 2008a)
Antituberculosis	Bipinnapterolide B (**57**)/coral	Terpenoid[e]	*M. tuberculosis* inhibition	128 μg/mL*	Undetermined	USA	(Ospina et al., 2007)
Antituberculosis	8′-*O*-Demethylnigerone (**58**) and 8′-*O*-demethylisonigerone (**59**)/fungus	Polyketide[d]	*M. tuberculosis* inhibition	21.5 and 43.0 μM	Undetermined	CHN	(Zhang et al., 2008)
Antituberculosis	Caribenols A and B (**60**, **61**)/soft coral	Terpenoid[e]	*M. tuberculosis* inhibition	63 and 128 μg/mL+	Undetermined	USA	(Wei et al., 2007)
Antituberculosis	Parguesterols A and B (**62**, **63**)/sponge	Triterpenoid[f]	*M. tuberculosis* inhibition	7.8 and 11.2 μg/mL+	Undetermined	USA	(Wei et al., 2007)
Antituberculosis	Spiculoic acids (**64**, **65**, **66**)/sponge	Polyketide[d]	*M. tuberculosis* inhibition	50 μg/mL+++	Undetermined	ESP, FRA	(Berrue et al., 2007)
Antiviral	Esculetin ethyl ester (**67**)/sponge	Polyketide[d]	SARS-Corona virus viral protease 3CL inhibition	46 μM	Undetermined	BRA, CAN	(de Lira et al., 2007)
Antiviral	*Cryptonemia crenulata* galactan (**68**)/alga	Polysaccharide[g]	Dengue type 2 inhibition	0.8–16 μg/mL	Inhibition of viral binding and cell penetration	ARG, BRA	(Talarico et al., 2007)
Antiviral	6,6′-Bieckol (**69**)/alga	Shikimate	Inhibition of HIV-1 infection	1.07–1.72 μM	Viral p24 antigen production and reverse transcriptase inhibition	CHN, S. KOR	(Artan et al., 2008)
Antiviral	Dolabelladienetriol (**70**)/alga	Terpenoid[e]	Inhibition of HIV-1 replication	8.4 μM	Noncompetitive inhibition of reverse transcriptase	BRA	(Cirne-Santos et al., 2008)
Antiviral	Mirabamides A, C and D (**71**, **72**, **73**)/sponge	Peptide[f]	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[g]	Inhibition of HIV-1 infection		Inhibition of HIV-1 Tat-induced angiogenesis	CHN	(Lu et al., 2007)

[a]Organism, *Kingdom Animalia*: polychaeta (Phylum Annelida), rockfish (Phylum Chordata), corals (Phylum Cnidaria), sea cucumber (Phylum Echinodermata), bivalve (Phylum Mollusca), sponge (Phylum Porifera); *Kingdom Monera*: bacterium (Phylum Cyanobacteria); *Kingdom Fungi*: fungus; *Kingdom Plantae*: alga; [b]IC_{50}: concentration of a compound required for 50% inhibition *in vitro*; *: estimated IC_{50}, ND: not determined; +MIC: minimum inhibitory concentration; ++MID: minimum inhibitory concentration per disk; +++MIC_{90}: minimum inhibitory concentration; [b]MMOA: molecular mechanism of action; [c]Country: 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: [d]polyketide; [e]terpene; [f]nitrogen-containing compound; [g]polysaccharide, modified as in the text.

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 ambiguine isonitriles H and I (**13** **14**) isolated from a marine cyanobacterium *Fischerella* sp. (Raveh and Carmeli, 2007); the polyketides ariakemicins A and B (**15**, **16**) isolated from a marine gliding bacterium *Rapidithrix* sp. (Oku et al., 2008); ayamycin (**17**) isolated from a bacterium *Nocardia* sp. ALAA 2000 (El-Gendy et al., 2008a); the alkaloids batzelladines L and M (**18**, **19**) isolated from the Caribbean sponge *Monanchora unguifera* (Hua et al., 2007); a diphenyl ether (**20**) isolated from the Indonesian sponge *Lamellodysidea herbacea* (Hanif et al., 2007); essramycin (**21**) obtained from the culture broth of a marine *Streptomyces* sp. isolate Merv8102 (El-Gendy et al., 2008b); a meroditerpene (+)-isojaspic acid (**22**) isolated from the Papua New Guinean sponge *Cacospongia* sp. (Rubio et al., 2007); the bisindole pyrroles lynamicins A–D (**23**, **24**, **25**, **26**) isolated from a novel marine actinomycete *Marinispora* sp. (McArthur et al., 2008); lipoxazolidinones A and B (**27**, **28**) isolated from a marine actinomycete *Marinispora* sp. (Macherla et al., 2007); marinopyrrole A (**29**) isolated from an obligate marine *Streptomyces* strain (Hughes et al., 2008); a furanosesquiterpene (−)-microcionin-1 (**30**) isolated from a marine sponge *Fasciospongia* sp. (Gaspar et al., 2008); a macrolide phomolide B (**31**) isolated from a fungus *Phomopsis* sp. (Du et al., 2008); a sargaquinoic acid derivative (**32**) isolated from the brown alga *Sargassum sagamianum* (Horie et al., 2008), and tauramamide (**33**), a lipopeptide isolated from the bacterium *Brevibacillus laterosporus* PNG276 (Desjardine et al., 2007).

Furthermore during this period, several novel marine metabolites with moderate antimicrobial activity (MIC or IC_{50} ranging from 10 to 50 μg/mL, or 10 to 50 μM, respectively), were also reported, but their weaker antibacterial activity precluded their inclusion in either Table 1 or Fig. 1: acetylmajapolene A (MIC = 20 μg/disk) (Vairappan et al., 2008), callophycoic acids A, B, G and H (MIC = 16–63.9 μg/mL) (Lane et al., 2007); corallidictyals A, B, C and D (MIC less than 20 μg/mL) (Grube et al., 2007); (*S*)-(+)-curcuphenol analogs (IC_{50} = 34–44 μM) (Gul et al., 2007); cyclomarazines A and B (MIC = 13–18 μg/mL) (Schultz et al., 2008); dehydroxychlorofusarielin B (MIC = 62.5 μg/mL) (Nguyen et al., 2007), nodosol (MIC = 16 μg/mL) (Kontiza et al., 2008); paeciloxanthone (MIC = 40 μg/disk) (Wen et al., 2008), palmitoleic acid (IC_{50} = 10–20 μM) (Desbois et al., 2008); puupehenone-metabolites (MIC = 8–16 μg/mL) (Ciavatta et al., 2007); *Tripalea clavaria* C-secosteroids (MIC = 25 μg/disk) (Rodriguez Brasco et al., 2007), shishididemniols A and B (MIC = 20 μg/disk) (Kobayashi et al., 2007b), and zafrin (MIC = 50–125 μg/mL) (Uzair et al., 2008).

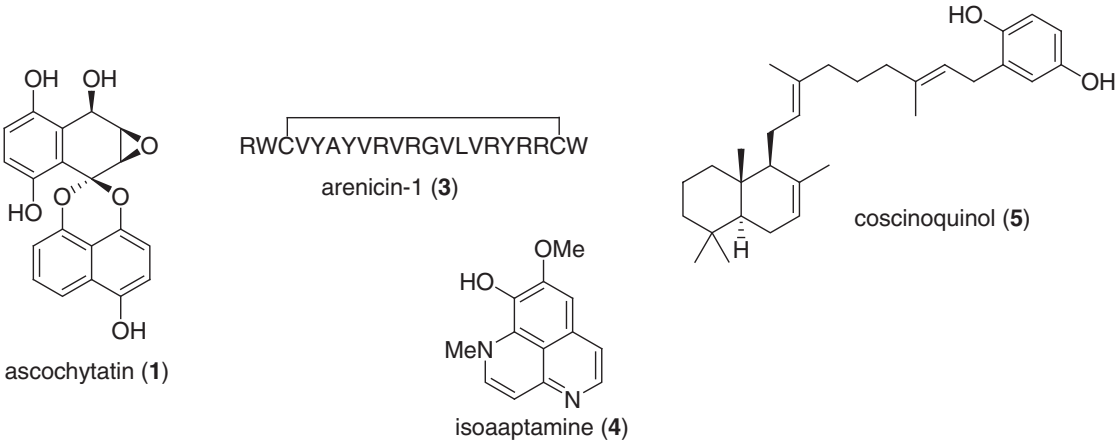
Noteworthy were reports of novel marine antimicrobial peptides: dicentracin, a new component of the moronecidin family isolated from head kidney leukocytes from the sea bass *Dicentrarchus labrax* (Salerno et al., 2007); hepcidins, three novel antimicrobial peptides isolated from the tilapia *Oreochromis 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 tunichromes, 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



MNIMKEKLAALETKLKAQEGKDGKKTNFQTEMNPHVVTWKLFAVSVLLLALYPSHAAAISLR
DNLADCLEDRDYDKLLHIAEFGLPNINTSHHVVIAGAGMAGLTAAKLLKEAGHKVTILEASSR
VGGRVETYRNEKEGWYAELGAMRIPSSHQIVRWYAKELGVKLNEFIMDDPNTFYLVNGVL
EKTETVQKDPDVLKYHVEASEKGKSADELLQHALQKVQDEVEASGCRAALLKYDRYSVKD
YLKEEGGLSSEAVRMLGDLLNQQSLMYTALSEMVYDQTDINDDVKYSEVTGGSDLLPKAFV
DVLDELGVPILLNSTVKRISQSDKGVIVSYEKGQQSSLTDLTADVVLVTTTTKAALFMDFDPP
LPIKKMEALRAAHYDSSTKILLTFSERFWEKDGIRGGKSITDGPSRYIYYPSHSFPTNKNIGV
LLASYTWSDDSLLFLGASDEDLKELALRDLAKIHGEHVRSLCTGVLVKKWSMDPYSLGAFA
LFTPYQHLEFAKELFRSEGRVHFAGEHTAFPHAWIEASLKSAIRAATNINKESARSPHDEL

SSAP (**2**)

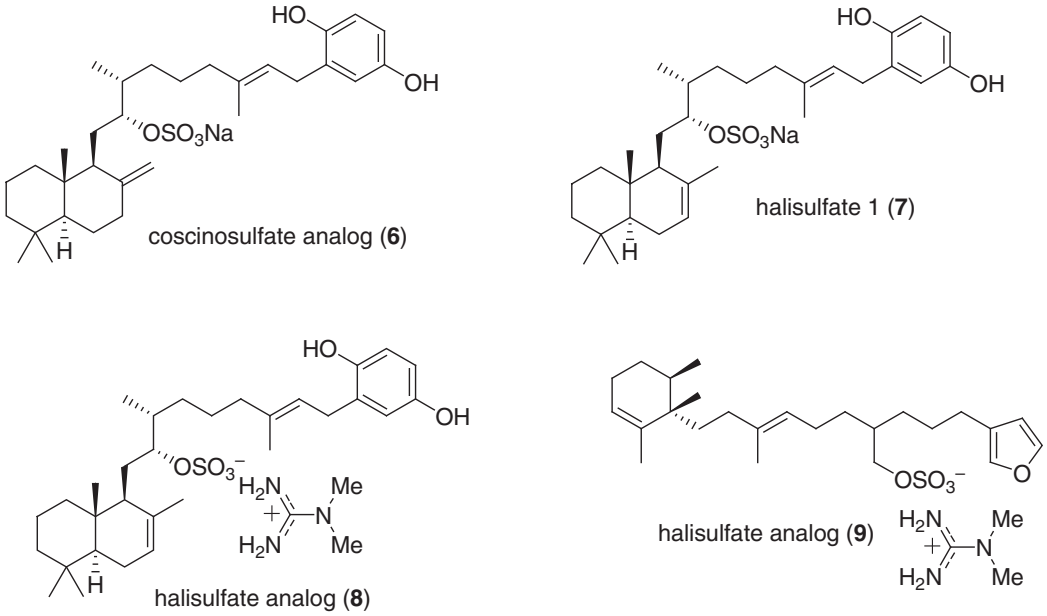
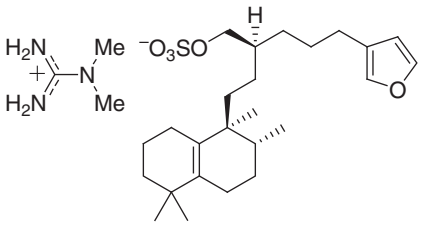
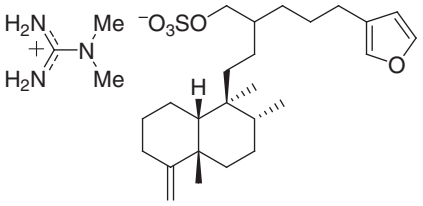


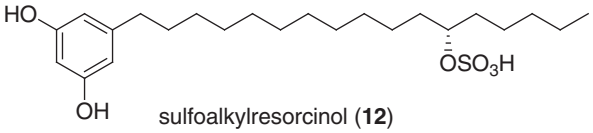
Fig. 1. Marine compounds with antibacterial, anticoagulant, antifungal, antimalarial, antiprotozoal, antituberculosis, and antiviral activities.



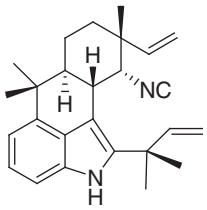
halisulfate analog (**10**)



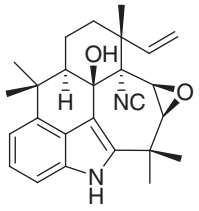
halisulfate analog (**11**)



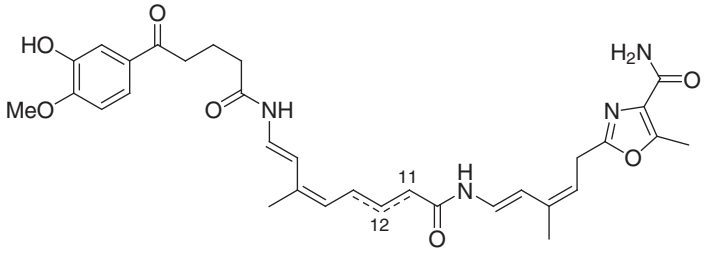
sulfoalkylresorcinol (**12**)



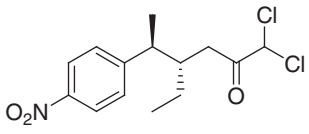
ambiguine H isonitrile (**13**)



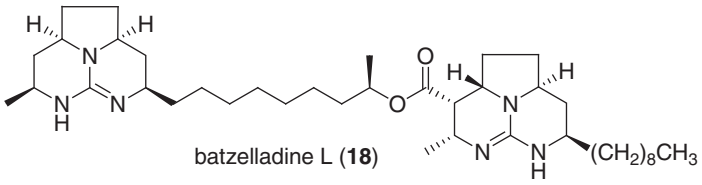
ambiguine I isonitrile (**14**)



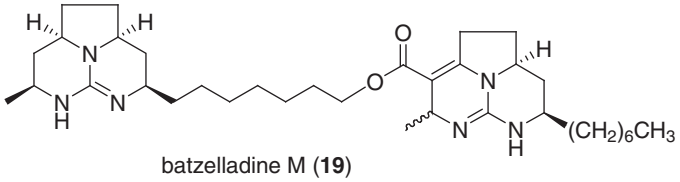
ariakemicin A; Δ^{12} (**15**)
ariakemicin B; Δ^{11} (**16**)



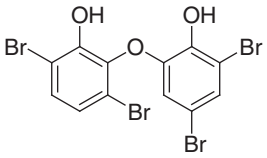
ayamycin (**17**)



batzelladine L (**18**)



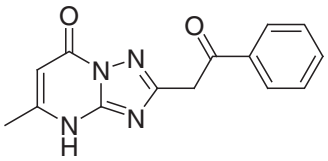
batzelladine M (**19**)



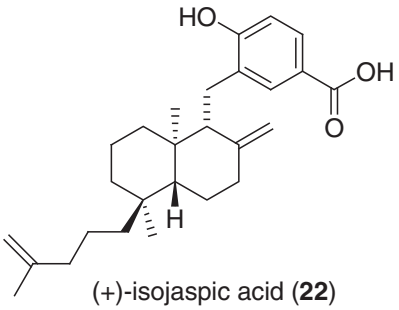
(**20**)

Fig. 1 (*continued*).

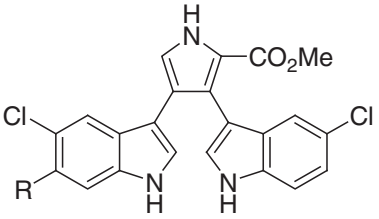
concentration-dependent manner (IC_{50} = 77.9 nM), thus resulting in prolonged prothrombin time. The same research group (Jung et al., 2007a) extended the anticoagulant pharmacology of a sulfated polysaccharide from the brown alga *E. cava.* The sulfated algal polysaccharide potently inhibited the biological activity of human blood coagulation factors IIa, VIIa and Xa in the presence of the glycoprotein antithrombin III in a dose-dependent manner (K_D = 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



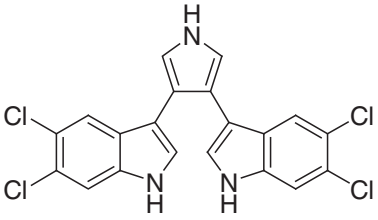
essramycin (**21**)



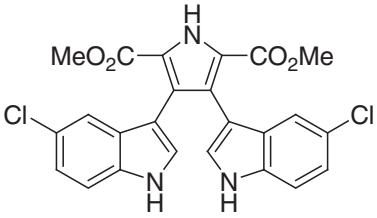
(+)-isojaspic acid (**22**)



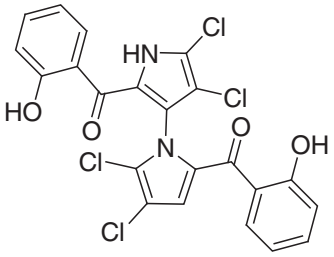
lynamicin A (**23**) R = H
lynamicin B (**24**) R = Cl



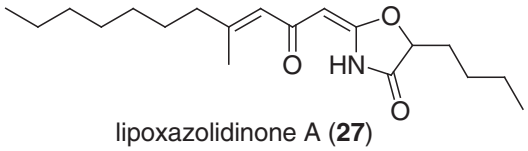
lynamicin C (**25**)



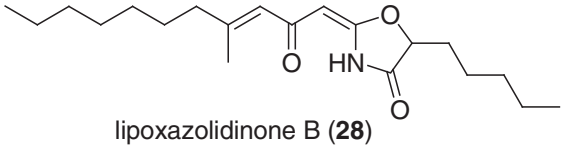
lynamicin D (**26**)



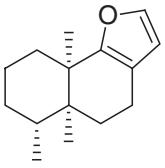
marinopyrrole A (**29**)



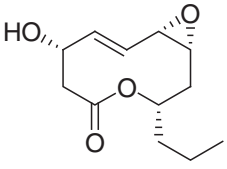
lipoxazolidinone A (**27**)



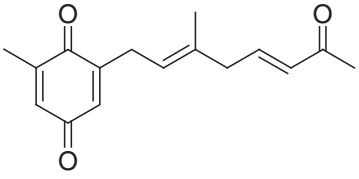
lipoxazolidinone B (**28**)



(–)-microcionin-1 (**30**)

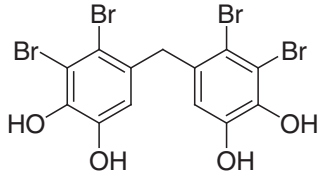


phomolide B (**31**)

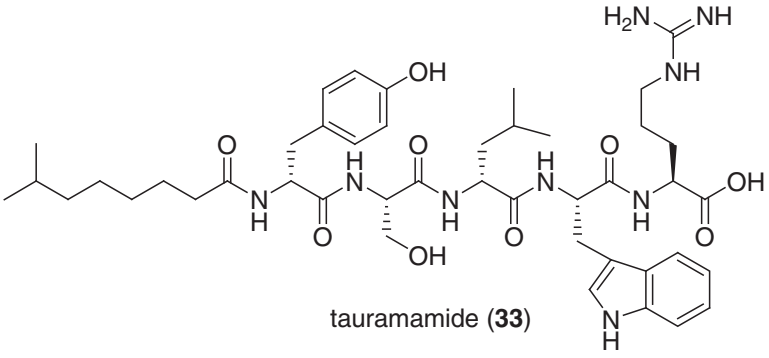


sargaquinoic acid derivative (**32**)

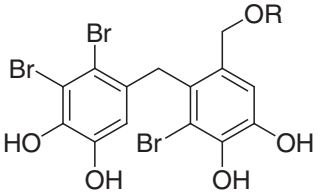
HTHLQRAPHPNALGYHGK
Partial sequence of TGAP (**34**)



bromophenol derivative (**35**)



tauramamide (**33**)



(**36**) R = H
(**37**) R = Me

Fig. 1 (*continued*).

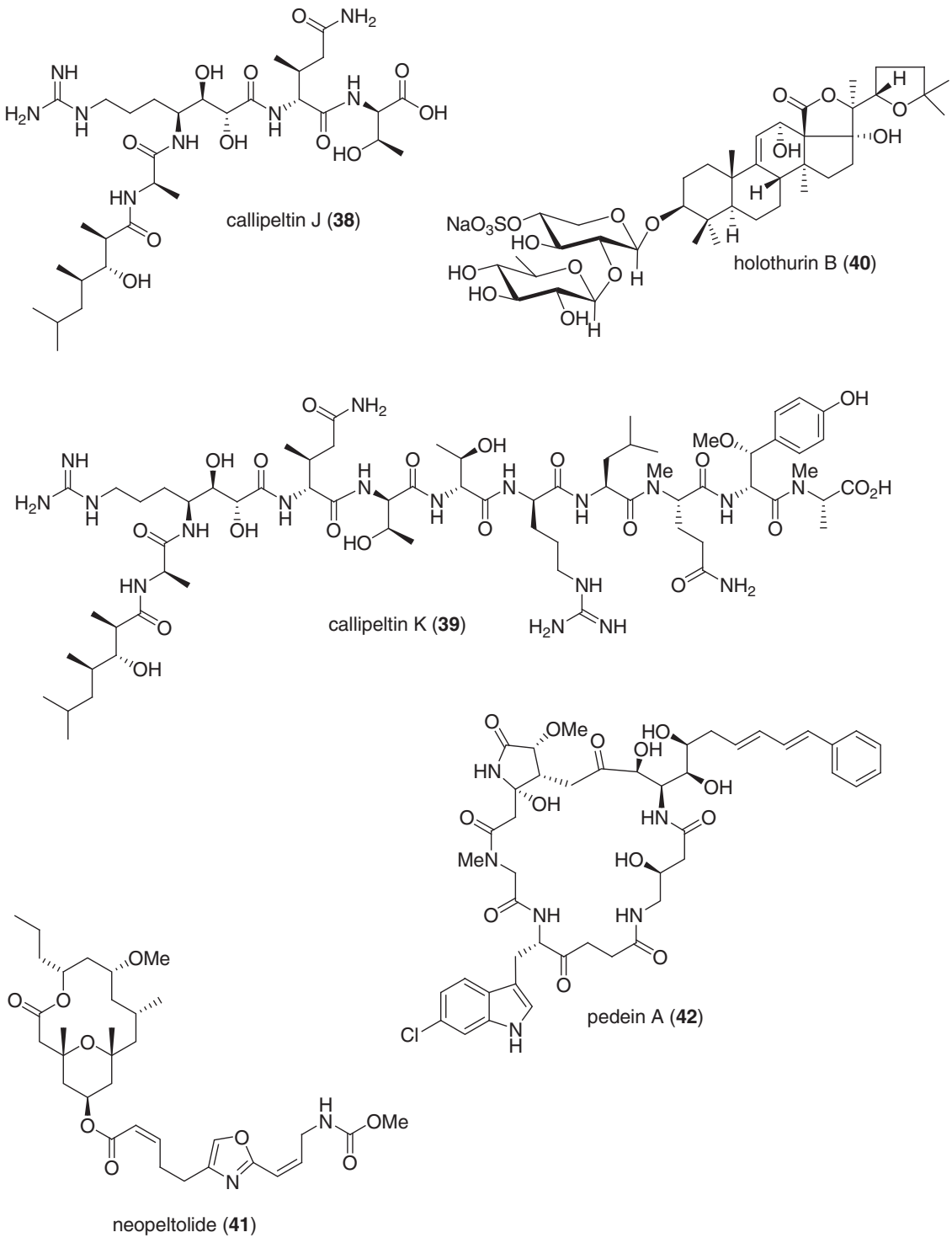


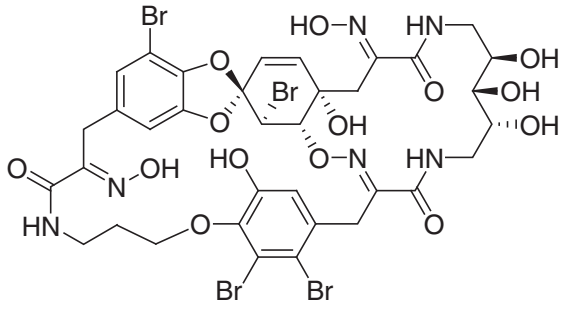
Fig. 1 (*continued*).

thrombin as well as potentiated antithrombin III-mediated inhibition of coagulation factor Xa.

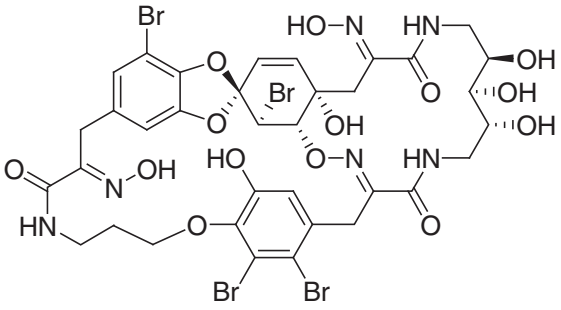
2.3. Antifungal activity

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.

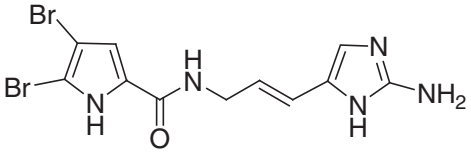
As shown in Table 1, only one report extended the molecular pharmacology of novel antifungal marine metabolites. Lee et al. (2007) discovered that three bromophenols (**35**, **36**, **37**) isolated from the red alga *Odonthalia corymbifera* potently inhibited isocitrate lyase (ICL) (IC_{50} = 2.0–2.8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



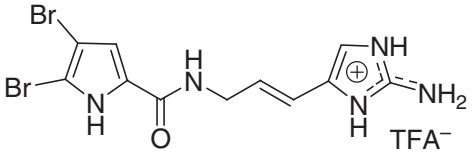
pseudoceratin A (**43**)



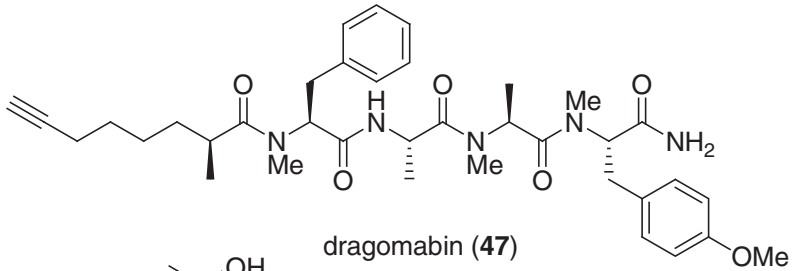
pseudoceratin B (**44**)



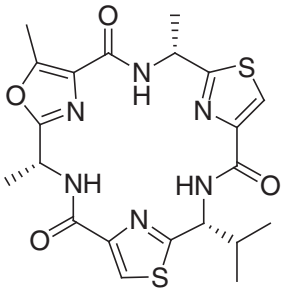
(*E*)-oroidin (**45**)



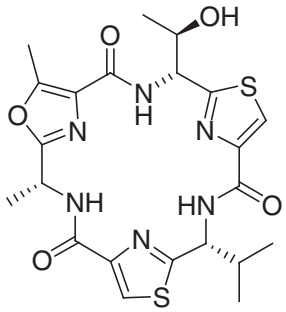
(*E*)-oroidin TFA salt (**46**)



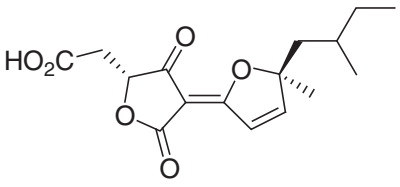
dragomabin (**47**)



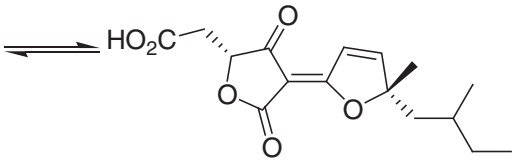
venturamide A (**48**)



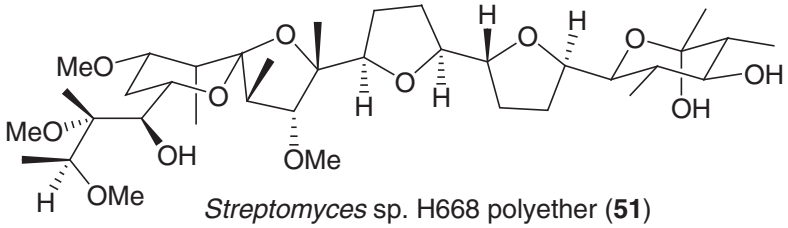
venturamide B (**49**)



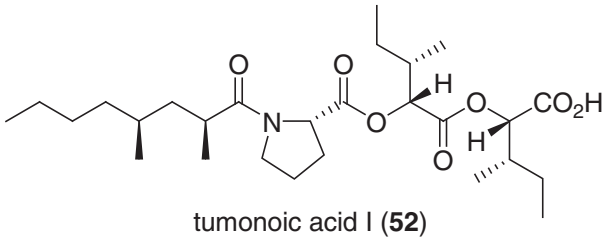
E-isomer



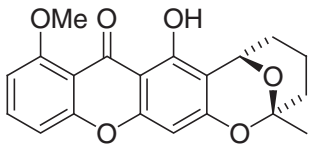
nodulisporacid A (**50**) *Z*-isomer



Streptomyces sp. H668 polyether (**51**)

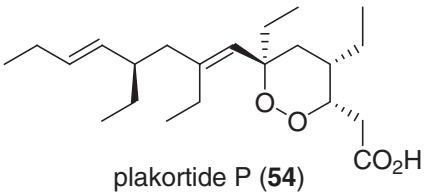


tumonoic acid I (**52**)

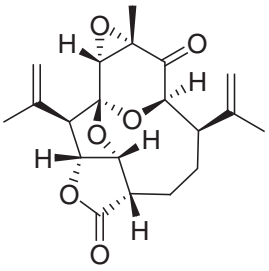


chaetoxanthone B (**53**)

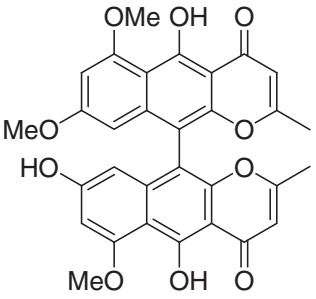
Fig. 1 (*continued*).



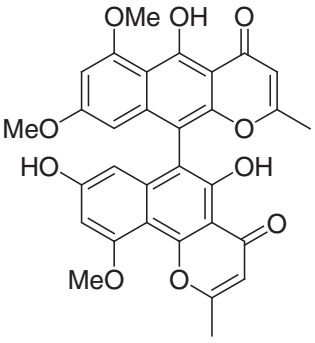
plakortide P (**54**)



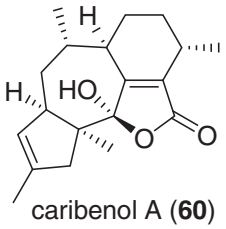
bipinnapterolide B (**57**)



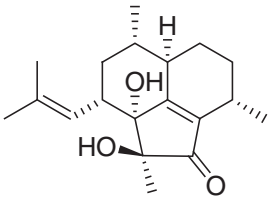
8'-*O*-demethylnigerone (**58**)



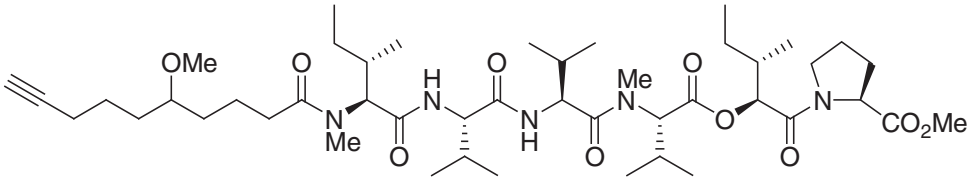
8'-*O*-demethylisonigerone (**59**)



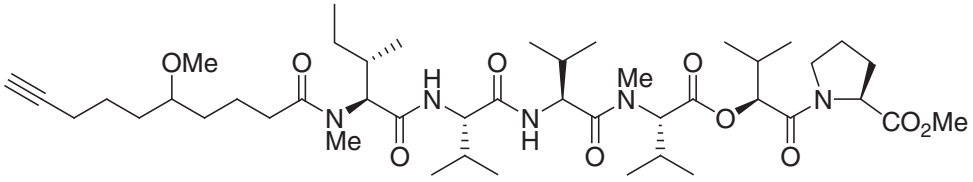
caribenol A (**60**)



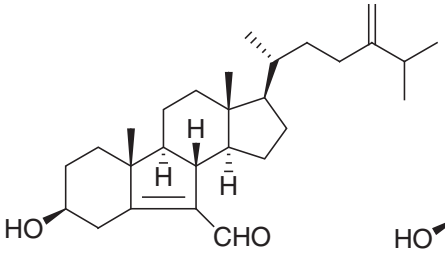
caribenol B (**61**)



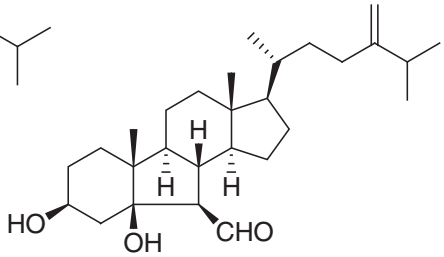
viridamide A (**55**)



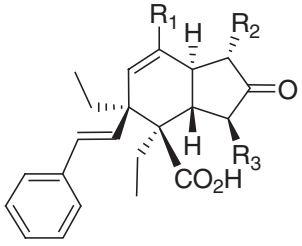
viridamide B (**56**)



parguesterol A (**62**)

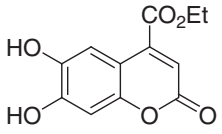


parguesterol B (**63**)

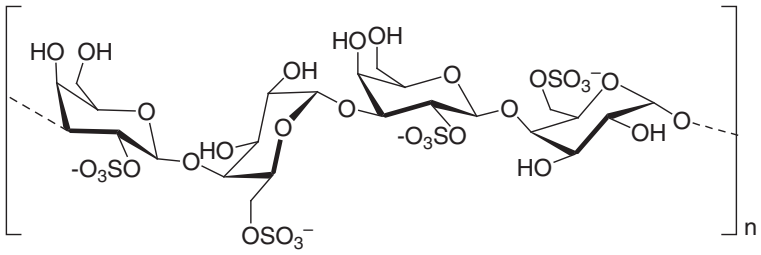


24-norisospiculoic acid A (**64**) R_1 = Me, R_2 = Et, R_3 = Me
dinorspiculoic acid A (**65**) $R_1 = R_2 = R_3$ = Me
norspiculoic acid A (**66**) R_1 = Et, R_2 = Me, R_3 = Me

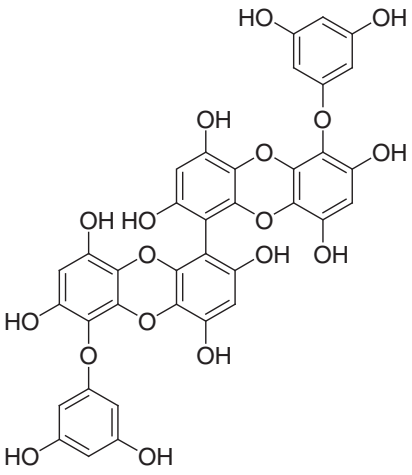
Fig. 1 (*continued*).



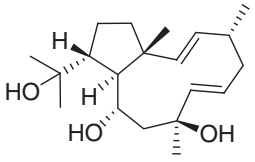
esculetin-4-carboxylic acid ethyl ester (**67**)



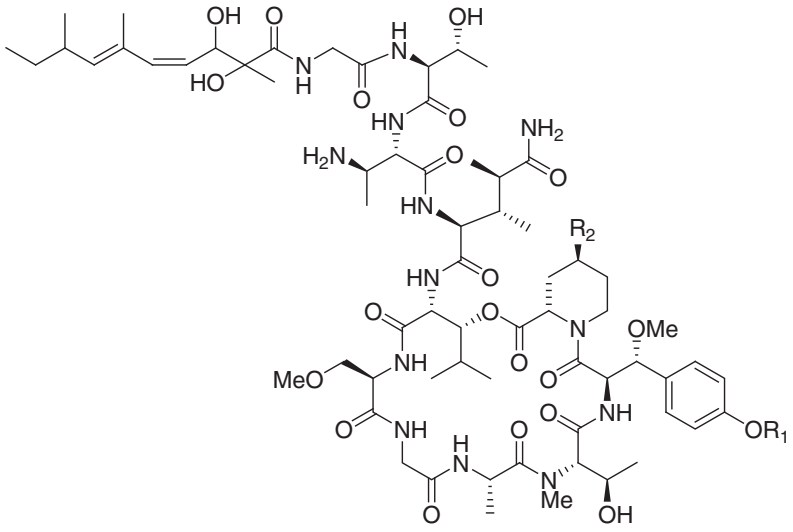
D,L-galactan hybrid C2S-3 (**68**)

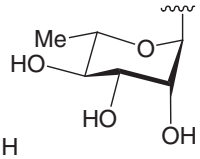


6,6'-bieckol (**69**)

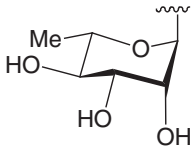


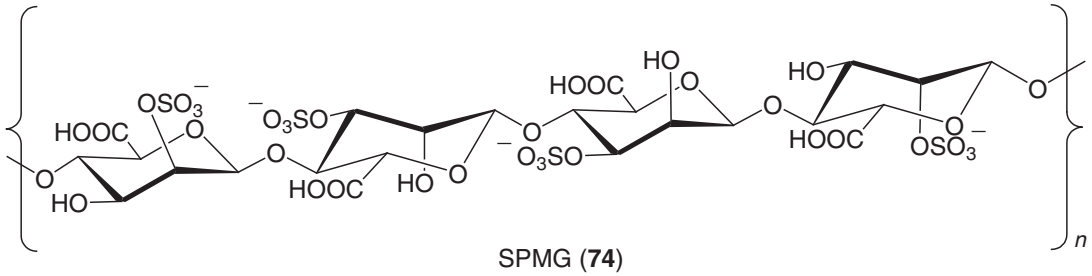
dolabelladienetriol (**70**)



mirabamide A (**71**) R_1 =  R_2 = Cl

mirabamide C (**72**) R_1 = H R_2 = Cl

mirabamide D (**73**) R_1 =  R_2 = H



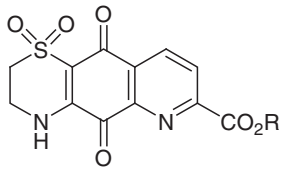
SPMG (**74**)

Fig. 1 (*continued*).

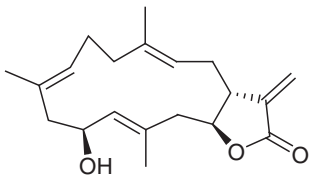
Table 2
Marine pharmacology in 2007–8: marine compounds with anti-inflammatory activity, and affecting the immune and nervous systems.

Drug class	Compound/organism[a]	Chemistry	Pharmacological activity	IC_{50}[b]	MMOA[c]	Country[d]	References
Anti-inflammatory	Ascidiathiazones A (**75**) and B (**76**)/ascidian	Alkaloid[g]	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	Crassumolides A and C (**77**, **78**)/soft coral	Terpenoid[e]	Modulation of LPS-activated murine macrophage cell line	<10 μM	Inducible NOS and COX-2 inhibition	TAIW	(Chao et al., 2008)
Anti-inflammatory	Durumolides A-C (**79**, **80**, **81**)/soft coral	Terpenoid[e]	Modulation of LPS-activated murine macrophage cell line	<10 μM	Inducible NOS and COX-2 inhibition	TAIW	(Cheng et al., 2008)
Anti-inflammatory	Frajunolides B and C (**82**, **83**)/coral	Terpenoid[e]	Human neutrophil free radical inhibition *in vitro*	>10 μg/mL*	Superoxide anion and elastase inhibition	TAIW	(Shen et al., 2007)
Anti-inflammatory	*Gracilaria verrucosa* fatty acids (**84**, **85**)/alga	Polyketide[d]	Modulation of LPS-activated murine macrophages *in vitro*	<20 μg/mL*	NO, IL-6 and TNF-α inhibition	S. KOR	(Dang et al., 2008)
Anti-inflammatory	*Hypnea cervicornis* lectin (**86**)/alga	Peptide[g]	Antinociception and anti-inflammatory effects *in vivo*	0.1–1 mg/kg*	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[g]	Modulation of LPS-activated brain microglia *in vitro*	0.25–1.97 μM	TXB_2 inhibition	USA	(El Sayed et al., 2008)
Anti-inflammatory	ω-3 PUFA (**90**, **91**, **92**, **93**)/mussel	Polyketide[d]	Human neutrophil lipoxygenase inhibition *in vitro*	ND	LTB4 and 5-HETE inhibition	AUS	(Treschow et al., 2007)
Anti-inflammatory	*Perithalia capillaris* quinone (**94**)/alga	Shikimate	Human neutrophil free radical release inhibition *in vitro*	2.1 μM	Superoxide anion inhibition	NZL	(Sansom et al., 2007)
Anti-inflammatory	PFF-B (**95**)/alga	Polyketide[d]	Rat basophilic leukemia cell histamine release inhibition	7.8 μM	Inhibition of β-hexosaminidase release	JPN	(Sugiura et al., 2007)
Anti-inflammatory	Plakortide P (**54**)/sponge	Polyketide[e]	Modulation of LPS-activated brain microglia *in vitro*	0.93 μM	TXB_2 inhibition	BRA	(Kossuga et al., 2008)
Anti-inflammatory	Rubrolide O (**96**)/ascidian	Polyketide[d]	Human neutrophil free radical release inhibition *in vitro*	35 μM	Superoxide anion inhibition	NZL	(Pearce et al., 2007b)
Anti-inflammatory	Stearidonic (**97**)/alga	Polyketide[d]	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**)/sponge	Alkaloid[g]	Neutrophil chemotaxis inhibition	5 μM	Undetermined	JPN	(Kobayashi et al., 2007a)
Anti-inflammatory	Lyngbyastatins 5–7 (**99**, **100**, **101**)/bacterium	Peptide[g]	Elastase inhibition	3–10 nM	Undetermined	USA	(Taori et al., 2007)
Anti-inflammatory	Salinipyrone A (**102**)/bacterium	Polyketide[e]	Mouse splenocyte interleukin-5 inhibition	10 μg/mL	Undetermined	USA	(Oh et al., 2008)
Immune system	Cycloprodigiosin hydrochloride (**103**)/bacterium	Alkaloid[g]	Interleukin-8 inhibition	1 μM	AP-1 transcription factor inhibition	JPN	(Kawauchi et al., 2007)
Immune system	Floridoside (**104**)/alga	Sugar[h]	Activation of classical complement pathway	5.9–9.3 μg/mL*	IgM mediated-effect	FRA	(Courtois et al., 2008)
Immune system	Iantherans (**105**, **106**)/sponge	Polyketide[d]	Activation of Ca^{2+}-mobilization	0.48–1.3 μM	Ionotropic $P2Y_{11}$ receptor activation	DEU, USA	(Greve et al., 2007)
Immune system	Prodigiosin (**107**)/bacterium	Alkaloid[g]	Macrophage iNOS inhibition	0.1 μg/mL*	NF-κB transcription factor inhibition	S. KOR	(Huh et al., 2007)
Immune system	ASLP (**108**)/clam	Polysaccharide[h]	Splenocyte proliferation increase	<100 μg/mL*	Undetermined	CHN	(He et al., 2007)
Immune system	Frondoside A (**109**)/sea cucumber	Terpenoid glycoside	Lysosomal activity, phagocytosis and ROS activation	0.1–0.001 μg/mL	Undetermined	RUS, USA	(Aminin et al., 2008)
Immune system	*Hippospongia* sp. quinones (**110**, **111**, **112**)/sponge	Terpenoid[f]	Enhancement of IL-8 release	>1 μg/mL*	Undetermined	JPN	(Oda et al., 2007)
Immune system	Macrosphelide M (**113**)/fungus	Polyketide[d]	Cell adhesion inhibition	33.2 μM	Undetermined	JPN	(Yamada et al., 2007)
Immune system	Peribysin J (**114**)/fungus	Terpenoid[f]	Cell adhesion inhibition	11.8 μM	Undetermined	JPN	(Yamada et al., 2007)
Immune system	Querciformolide C (**115**)/soft coral	Terpenoid[f]	Macrophage iNOS and COX-2 inhibition	<10 μM*	Undetermined	TAIW	(Lu et al., 2008)
Immune system	*Spongia* sp. diterpenoids (**116**, **117**)/sponge	Terpenoid[f]	Murine spleen cell lysosome activation	>100 μg/mL*	Undetermined	RUS	(Ponomarenko et al., 2007)
Immune system	Thalassospiramide B (**118**)/bacterium	Peptide[g]	Interleukin 5 inhibition	5 μM	Undetermined	USA	(Oh et al., 2007)
Nervous system	Linckosides L1 and L2 (**119**, **120**)/sea star	Triterpenoid glycoside[f]	Induction of neurite outgrowth	0.3 μM*	Undetermined	ITA, RUS	(Kicha et al., 2007b)
Nervous system	Linckosides M–Q (**121**, **122**, **123**, **124**, **125**)/sea star	Triterpene[f]	Induction of neurite outgrowth	<10 μM*	Dependent on xylose on side chain	JPN	(Han et al., 2007)
Nervous system	Phaeophytin A (**126**)/alga	Alkaloid/terpenoid	Induction of neurite outgrowth	<3.9 μM*	MAP kinase activation	JPN	(Ina et al., 2007)
Nervous system	*Conus leopardus* conotoxin Lp1.1 (**127**)/snail	Peptide[g]	Seizure and paralysis in goldfish	<10 μM*	Slow block of α6α3β2 and α3β2 nicotinic receptor	CHN, USA	(Peng et al., 2008)
Nervous system	Damipipecolin (**128**) and damituricin (**129**)/sponge	Alkaloid[g]	Inhibition of serotonin receptor binding	1 μg/mL*	Ca^{2+} influx inhibition	ITA, DEU	(Aiello et al., 2007)
Nervous system	4-Acetoxy-plakinamine B (**130**)/sponge	Triterpenoid alkaloid[g]	Acetylcholinesterase inhibition	3.75 μM	Mixed-competitive inhibition	THAI	(Langjae et al., 2007)
Nervous system	Sargaquinoic acid (**131**) and sargachromenol (**132**)/alga	Terpenoid[f]	Butyrylcholinesterase inhibition	26 nM	Undetermined	S. KOR	(Choi et al., 2007)
Nervous system	SPMG (**74**)/alga	Polysaccharide[h]	Neuronal Ca^{2+}-apoptosis inhibition		Decrease in caspase-3 activity	CHN	(Hui et al., 2008)

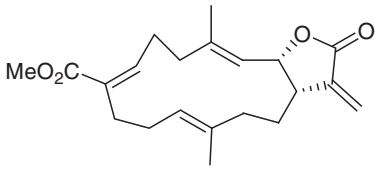
[a]Organism: *Kingdom Animalia*: coral (Phylum Cnidaria); ascidian (Phylum Chordata), sea star, cucumber (Phylum Echinodermata); clam, musse, snail (Phylum Mollusca); sponge (Phylum Porifera); *Kingdom Fungi*: fungus; *Kingdom Plantae*: alga; *Kingdom Monera*: bacterium (Phylum Cyanobacteria); [b]IC_{50}: concentration of a compound required for 50% inhibition; *: apparent IC_{50}; ND: not determined; [c]MMOA: molecular mechanism of action, NO: nitric oxide; [d]Country: 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: [e]polyketide; [f]terpene; [g]nitrogen-containing compound; [h]polysaccharide, modified as in the text.



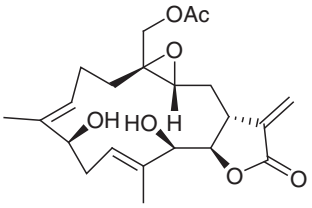
ascidiathiazone A (**75**) R = H
ascidiatthiazone B (**76**) R = Me



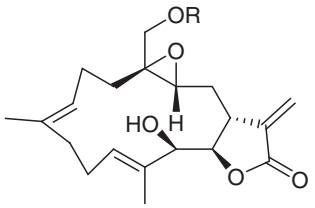
crassumolide A (**77**)



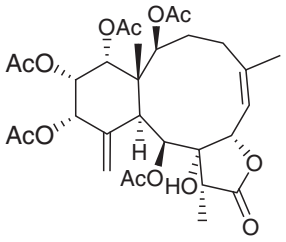
crassumolide C (**78**)



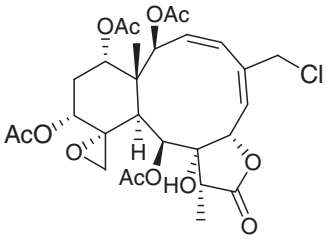
durumolide A (**79**)



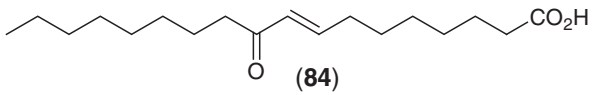
durumolide B (**80**) R = Ac
durumolide C (**81**) R = H



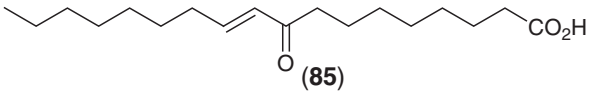
frajunolide B (**82**)



frajunolide C (**83**)



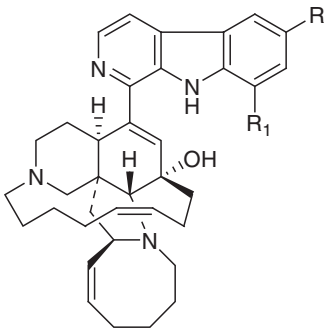
(**84**)



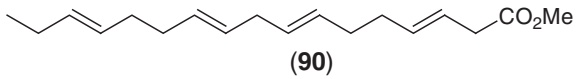
(**85**)

ZKACTMDYFPVCCQIVLGGGAYTAGNPCSC
QGFVASKGTCDNPYPCPCTTEAQFPVCCTT
QWGLVSATGNCACGCMGGVPVSDGPCPEVY

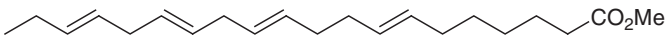
(**86**)



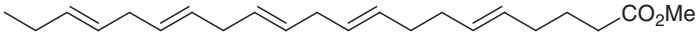
manzamine A (**87**) R=R$_1$=H
8-hydroxymanzamine A (**88**) R=H, R$_1$=OH



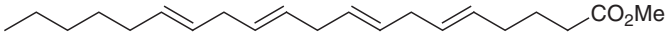
(**90**)



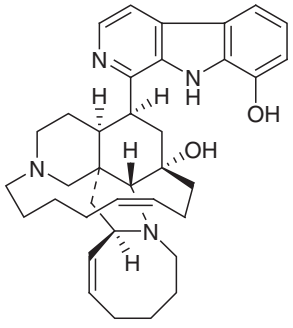
(**91**)



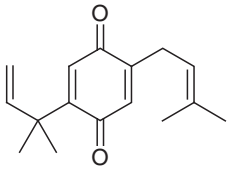
(**92**)



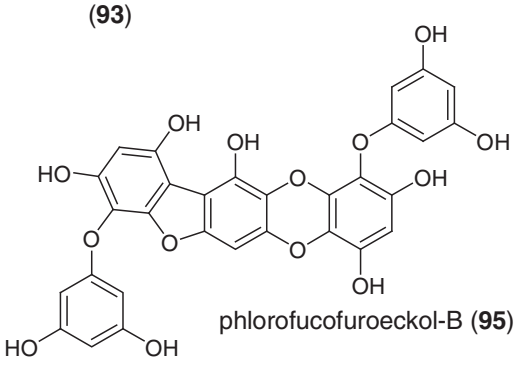
(**93**)



10,11,15,16,32,33-hexahydro-
8-hydroxymanzamine A (**89**)

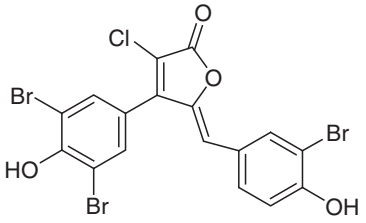


bis-prenylated quinone (**94**)

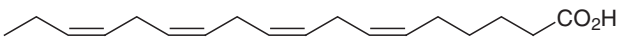


phlorofucofuroeckol-B (**95**)

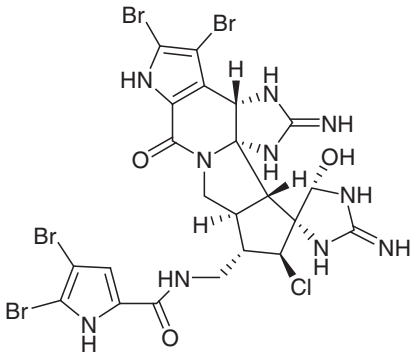
Fig. 2. Marine compounds with anti-inflammatory activity, and affecting the immune and nervous systems.



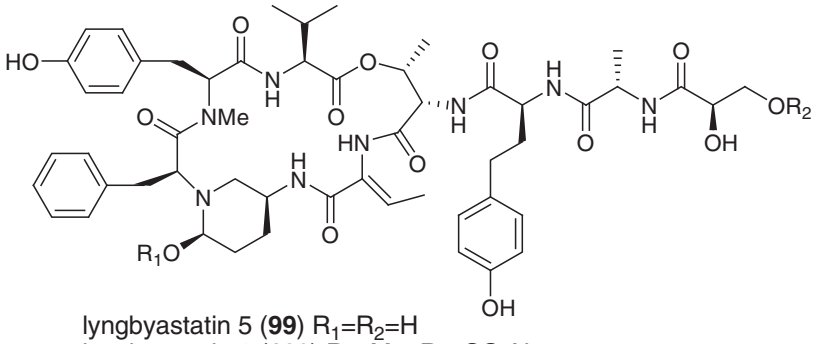
rubrolide O (**96**)



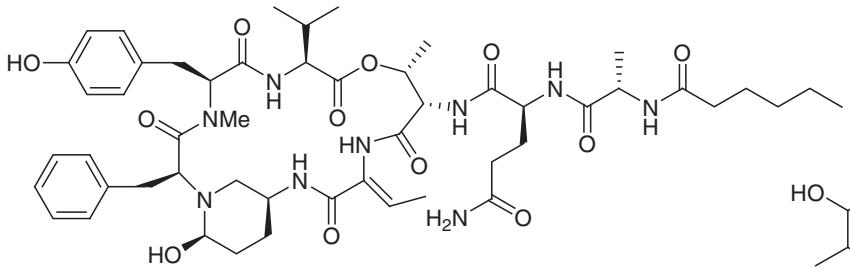
stearidonic acid (**97**)



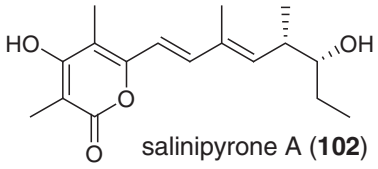
carteramine A (**98**)



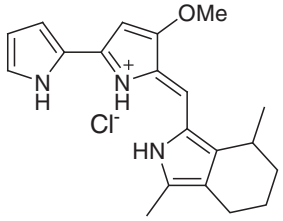
lyngbyastatin 5 (**99**) R_1=R_2=H
lyngbyastatin 6 (**100**) R_1=Me, R_2=SO_3Na



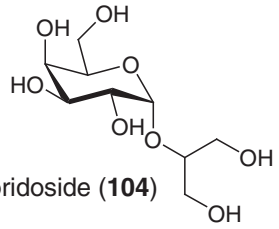
lyngbyastatin 7 (**101**)



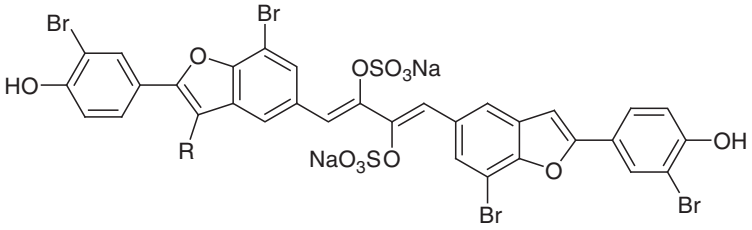
salinipyrone A (**102**)



cycloprodigiosin hydrochloride (**103**)

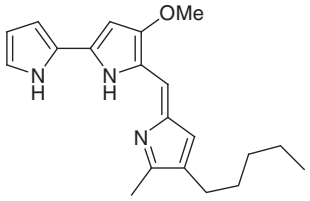


floridoside (**104**)



iso-iantheran A (**105**) R = H
8-carboxy-iso-iantheran A (**106**) R = CO_2H

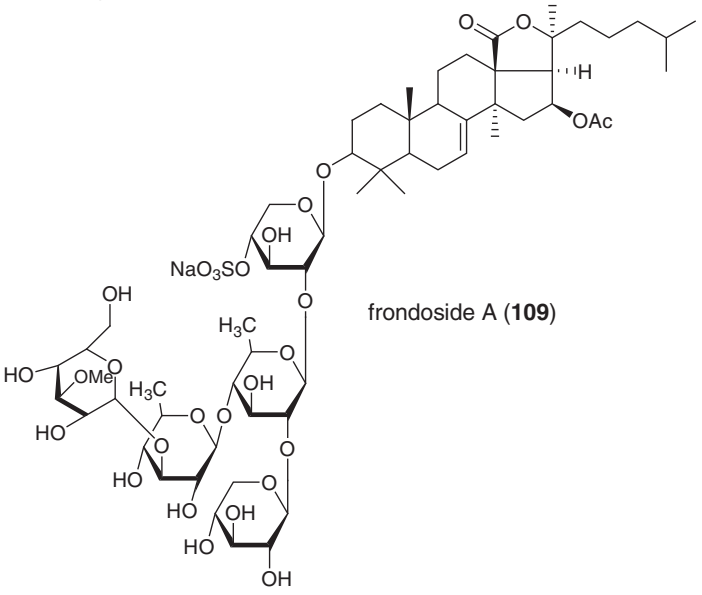
Fig. 2 (*continued*).



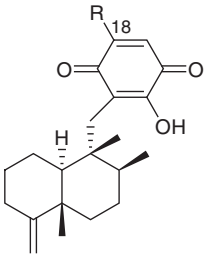
prodigiosin (**107**)

α-D-Glc*p*-(1-->6)-α-D-Glcp-(1-->6)-α-D-Glc*p*
↓ 1
↓ 6
[4)-α-D-Glcp-(1-->4)-α-D-Glc*p*-(1-->4)-α-D-Glc*p*-(1-->4)-α-D-Glc*p*-(1]

polysaccharide ASLP (**108**)



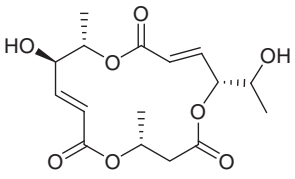
frondoside A (**109**)



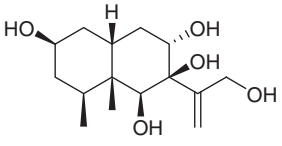
smenospongidine (**110**)
R = $NHCH_2CH_2Ph$

smenospongiarine (**111**)
R = $NHCH_2CH_2CHMe_2$

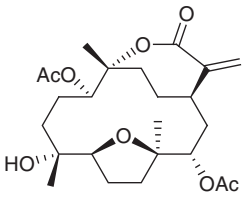
smenospongine (**112**)
R = NH_2



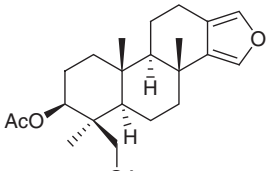
macrosphelide M (**113**)



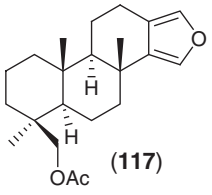
peribysin J (**114**)



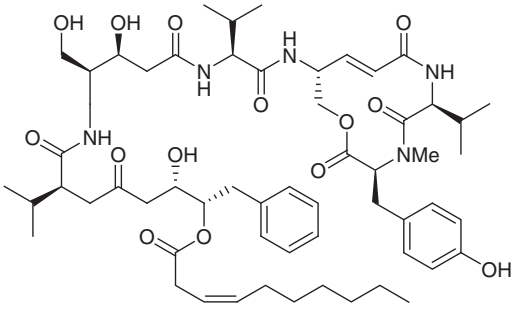
querciformolide C (**115**)



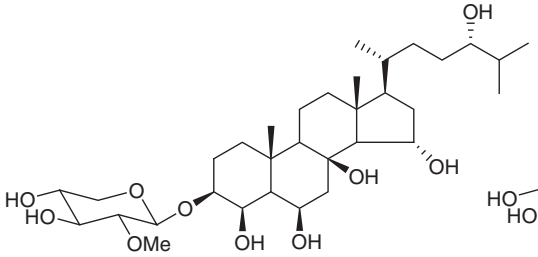
(**116**)



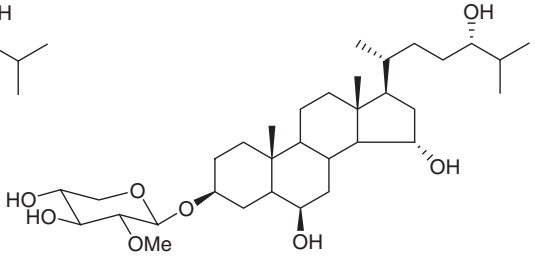
(**117**)



thalassospiramide B (**118**)

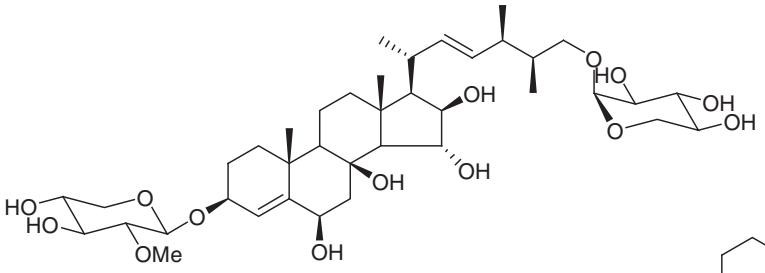


linckoside L1 (**119**)

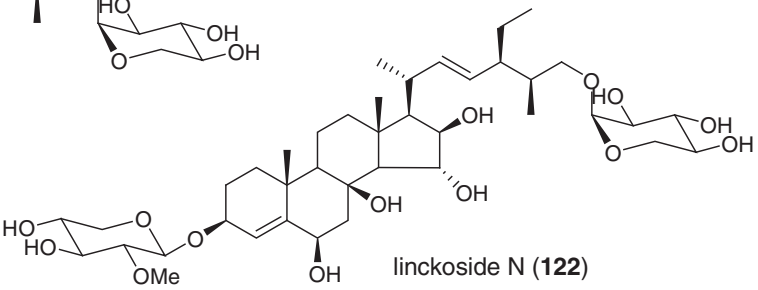


linckoside L2 (**120**)

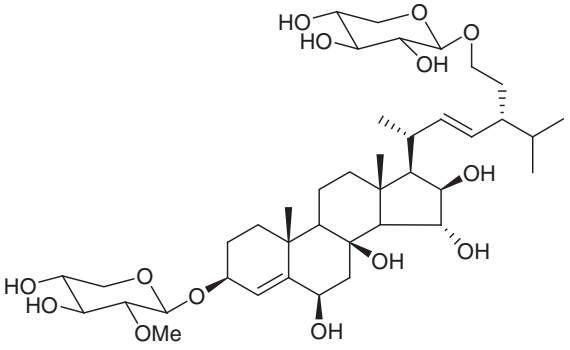
Fig. 2 (*continued*).



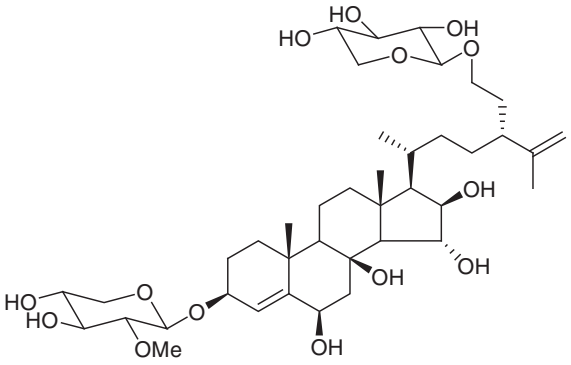
linckoside M (**121**)



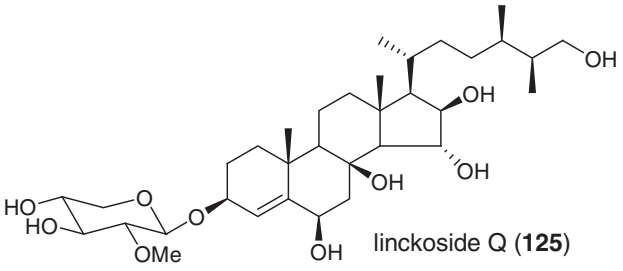
linckoside N (**122**)



linckoside O (**123**)



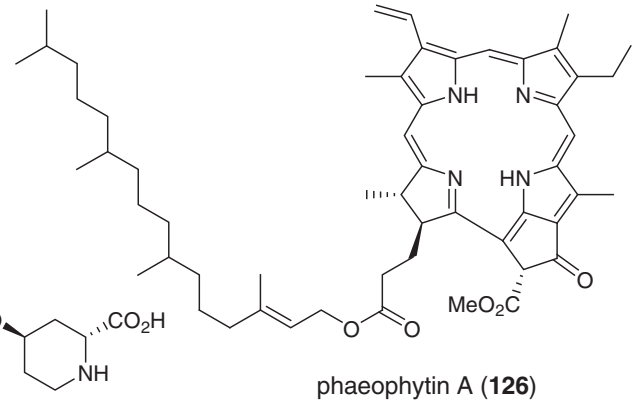
linckoside P (**124**)



linckoside Q (**125**)

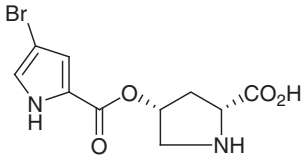
GCCARAACAGIHQELC*

Conus leopardus conotoxin Lp1.1
* amidated terminus (**127**)

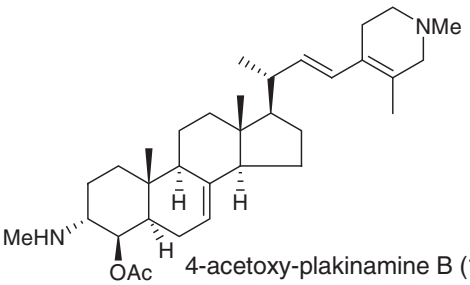


phaeophytin A (**126**)

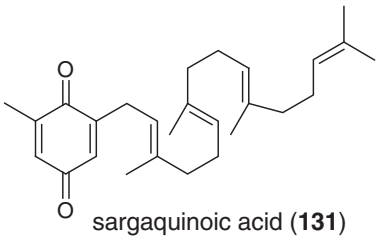
damipipecolin (**128**)



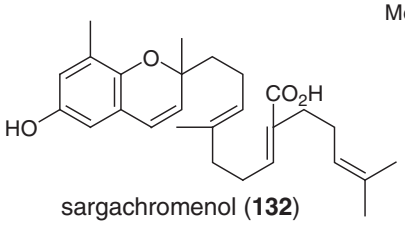
damituricin (**129**)



4-acetoxy-plakinamine B (**130**)



sargaquinoic acid (**131**)



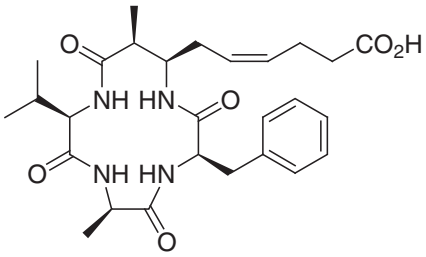
sargachromenol (**132**)

Fig. 2 (*continued*).

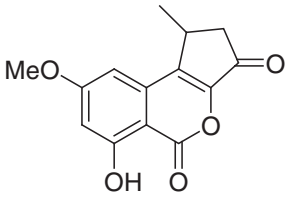
Table 3
Marine pharmacology in 2007–8: marine compounds with miscellaneous mechanisms of action.

Compound/organism[a]	Chemistry	Pharmacological activity	IC_{50}^{b}	MMOA[c]	Country[d]	References
Azumamide E (**133**)/sponge	Peptide[g]	Histone deacetylase inhibition	50–80 nM	Selective inhibition of isoforms 1, 2, and 3	ITA	(Maulucci et al., 2007)
1-Deoxyrubralactone (**134**)/fungus	Shikimate	X and Y DNA polymerase inhibition	12–60 μM	Specific inhibition of DNA polymerase β and κ	JPN	(Naganuma et al., 2008)
Fucoxanthin (**135**)/alga	Carotenoid	Antioxidant *in vitro*	0.14–2.5 mg/mL	Hydroxyl and superoxide radical scavenging	JPN	(Sachindra et al., 2007)
Okadaic acid (**136**)/sponge	Polyketide[e]	Protein phosphatase 1 and 2A inhibition	0.96 nM**	Okadaic acid binding to proteins OABP1 and OABP2	JPN	(Sugiyama et al., 2007)
Saproxanthin (**137**) and myxol (**138**)/bacterium	Polyketide[e]	L-Glutamate toxicity inhibition	3.1–8.1 μM	Lipid peroxidation inhibition	JPN	(Shindo et al., 2007a)
Sarcomilasterol (**139**)/sponge	Triterpene[f]	Osteoblast growth stimulation	3 μM	Alkaline phosphatase elevation	S. KOR, VNM	(Van Minh et al., 2007)
Spirastrellolides C, D, and E (**140**, **141**, **142**)/sponge	Polyketide[e]	Premature mitosis inhibition	0.4–0.7 μM	Protein phosphatase 2A inhibition	CAN	(Williams et al., 2007)
Spongia sesterterpenoid (**143**)/sponge	Terpenoid[f]	Hypercholesterolemia antagonist	2.4 μM	Farnesoid X-activated receptor coactivator peptide inhibition	S. KOR	(Nam et al., 2007)
Stylissadines A and B (**144**, **145**)/sponge	Alkaloid[g]	Reduction of voltage-dependent Ca^{2+} entry	4.5 μM	Irreversible effect requiring lipophilic brominated side chain	DEU	(Bickmeyer et al., 2007)
Symbiodinolide (**146**)/dinoflagellate	Polyketide[e]	Voltage-dependent N-type Ca^{2+} channel activation	7 nM	Cyclooxygenase 1 inhibition	JPN	(Kita et al., 2007)
Asterias amurensis saponin (**147**)/starfish	Triterpene[f]	Osteoblast cell proliferation	50 μM*	Undetermined	CHN	(Liu et al., 2008)
Botrytis sp. α-pyrone derivative (**148**)/fungus	Polyketide[e]	Tyrosinase inhibition	4.5 μM	Undetermined	CHN, S. KOR	(Zhang et al., 2007)
Cephalosporolides H and I (**149**, **150**)/fungus	Polyketide[e]	Xanthine oxidase and steroid dehydr. inhib.	<0.29 mM	Undetermined	CHN, DEU	(Li et al., 2007)
Chaetominedione (**151**)/fungus	Alkaloid[g]	$p56^{lck}$ tyrosine kinase inhibition	<200 μg/mL*	Undetermined	EGY	(Abdel-Lateff A., 2008)
Circumdatin I (**152**)/fungus	Alkaloid[g]	Ultraviolet A-protecting	98 μM	Undetermined	S. KOR	(Zhang et al., 2008)
Diapolycopenedioic acid xylosyl ester (**153**)/bacterium	Terpenoid[f]	Lipid peroxidation inhibition	4.6 μM	Undetermined	JPN	(Shindo et al., 2007)
Echinogorgia complexa furanosesquiterpenes (**154**, **155**)/soft coral	Terpenoid[f]	Mitochondrial respiratory chain inhibition	2.5–4.3 μM	Undetermined	ESP, IND, ITA	(Manzo et al., 2007)
19-*epi*-Okadaic acid (**156**)/dinoflagellate	Polyketide[e]	Protein phosphatase 2A inhibition	0.47 nM	Undetermined	ESP	(Cruz et al., 2007)
Erylosides F and F1 (**157**, **158**)/coral	Terpenoid[f]	Activation of Ca^{2+} influx	100 μg/mL*	Undetermined	ITA, RUS	(Antonov et al., 2007)
Hippocampus kuda phthalates (**159**, **160**, **161**)/seahorse	Polyketide[e]	Cathepsin B inhibition	0.18–.29 mM	Undetermined	CHN, S. KOR	(Li et al., 2008)
Irregularasulfate (**162**)/bacterium	Terpenoid[f]	Calcineurin inhibition	59 μM	Undetermined	CAN, NLD, PAP	(Carr et al., 2007)
Kempopeptins A and B (**163**, **164**)/bacterium	Peptide[g]	Elastase and chymotrypsin inhibition	0.32–8.4 μM	Undetermined	USA	(Taori et al., 2008)
Linckoside L7 (**165**)/starfish	Triterpenoid glycoside[f]	Fertilization inhibition	<25 μg/mL*	Undetermined	RUS	(Kicha et al., 2007a)
Lyngbyastatin 4 (**166**)/bacterium	Peptide[g]	Elastase and chymotrypsin inhibition	0.03–0.3 μM	Undetermined	USA	(Matthew et al., 2007)
Malevamide E (**167**)/bacterium	Peptide[g]	Extracellular Ca^{2+} channel inhibition	9 μM*	Undetermined	USA	(Adams et al., 2008)
Monodictysin C (**168**)/fungus	Shikimate	CYP1A inhibition	3.0 μM	Undetermined	DEU	(Krick et al., 2007)
Monodictyochromes A and B (**169**, **170**)/fungus	Shikimate	CYP1A inhibition	5.3–7.5 μM	Undetermined	DEU	(Pontius et al., 2008b)
Penicillium waksmanii PF1270 A, B, and C (**171**, **172**, **173**)/fungus	Alkaloid[g]	Histamine H3 receptor agonists	0.12–0.2 μM	Undetermined	JPN	(Kushida et al., 2007)
Penicillium sp. anisols (**174**, **175**, **176**)/fungus	Polyketide[e]	CYP3A4 inhibition	0.4–2 μg/mL	Undetermined	JPN	(El-Beih et al., 2007)
Polysiphonia urceolata bromophenols (**177**, **178**, **179**, **180**)/alga	Polyketide[e]	DPPH radical scavenging activity	6.1–8.1 μM	Undetermined	CHN	(Li et al., 2007, 2008)
Pompanopeptin A (**181**)/bacterium	Peptide[g]	Trypsin inhibition	2.4 μM	Undetermined	USA	(Matthew et al., 2008)
Purpurone (**182**)/sponge	Alkaloid[g]	DPPH radical scavenging activity	7 μM	Undetermined	CHN, S. KOR, USA	(Liu et al., 2008)
Saliniketals A and B (**183**, **184**)/bacterium	Polyketide[e]	Ornithine decarboxylase induction	1.9–7.8 μg/mL	Undetermined	USA	(Williams et al., 2007)
Sargassum sagamianum monoglyceride (**185**)/alga	Polyketide[e]	Phospholipase A_2 and COX-2 inhibition	ND	Undetermined	S. KOR	(Chang et al., 2008)
Sargassum siliquastrum meroditerpenoids (**186**, **187**, **188**, **189**, **190**, **191**)/alga	Terpenoid[f]	DPPH radical scavenging activity	0.1–0.31 μg/mL*	Undetermined	S. KOR	(Jung et al., 2008)
Symphyocladia latiuscula bromophenols (**192**, **193**, **194**, **195**)/alga	Polyketide[e]	DPPH radical scavenging activity	10.2–24 μM	Undetermined	CHN	(Duan et al., 2007)
Tenacibactins C and D (**196**, **197**)/bacterium	PKS/NRPS	Fe-binding (chelating) activity	110–115 μM	Undetermined	JPN	(Jang et al., 2007a)

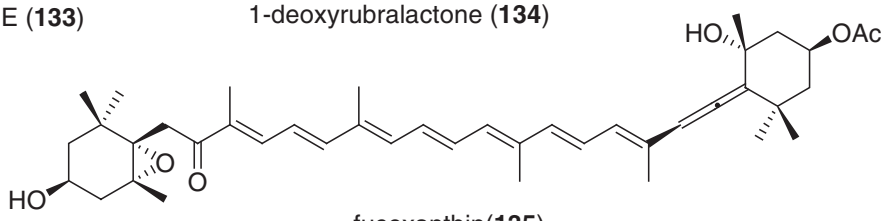
[a]Organism, *Kingdom Animalia*: sea horse (Phylum Chordata), soft corals (Phylum Cnidaria), starfish (Phylum Echinodermata), sponge (Phylum Porifera); *Kingdom Chromalveolata*: dinoflagellates; *Kingdom Fungi*: fungus; *Kingdom Plantae*: alga; *Kingdom Monera*: bacterium; [b]IC_{50}: concentration of a compound required for 50% inhibition *in vitro*; *: estimated IC_{50}; ** Kd: concentration at which 50% of ligand binding sites are occupied; MMOA: molecular mechanism of action ;[d]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: [e]polyketide; [f]terpene; [g]nitrogen-containing compound; [h]polysaccharide, modified as in the text.



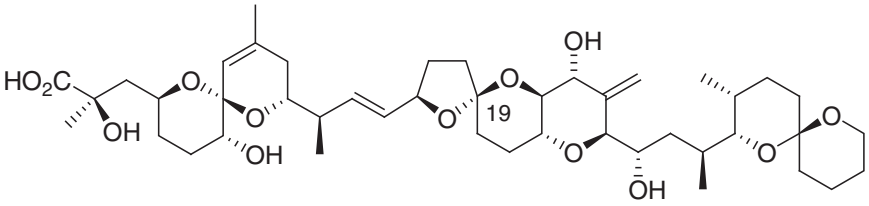
azumamide E (**133**)



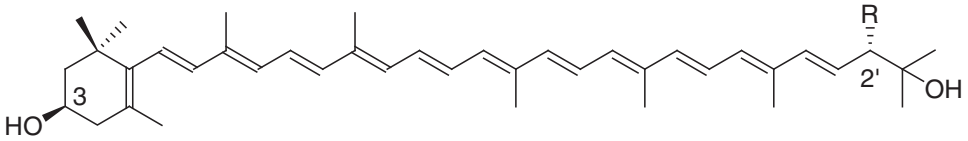
1-deoxyrubralactone (**134**)



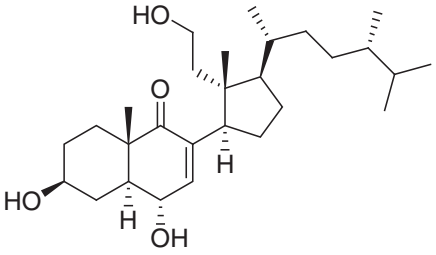
fucoxanthin(**135**)



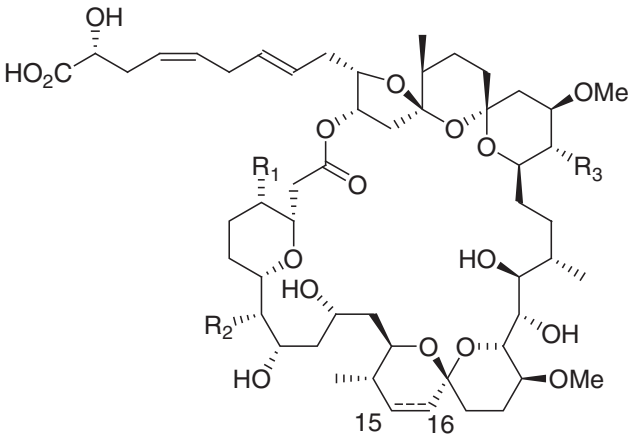
okadaic acid (**136**)
19-*epi*-okadaic acid (**156**)



(3*R*)-saproxanthin(**137**) R=H
(3*R*,2'*S*)-myxol (**138**) R=OH

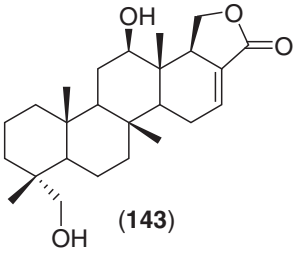


sarcomilasterol (**139**)

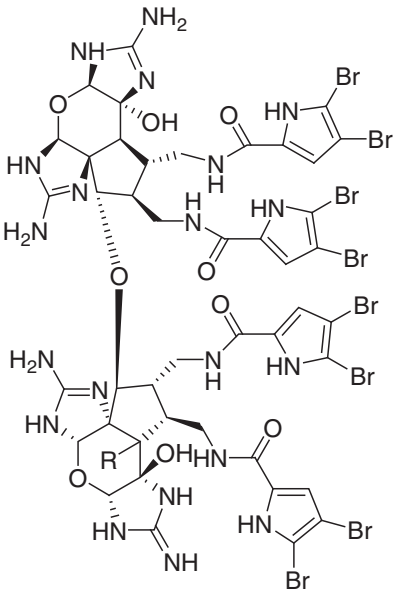


spirastrellolide C (**140**) R_1=R_3=H, R_2=OH
spirastrellolide D (**141**) R_1=R_3=Cl, R_2=H, $\Delta^{15,16}$
spirastrellolide E (**142**) R_1=R_2=R^3=H, $\Delta^{15,16}$

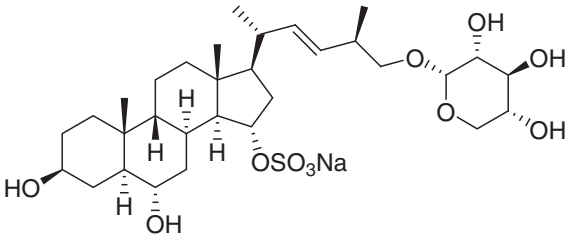
Fig. 3. Marine compounds with miscellaneous mechanisms of action.



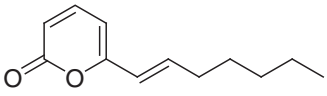
(**143**)



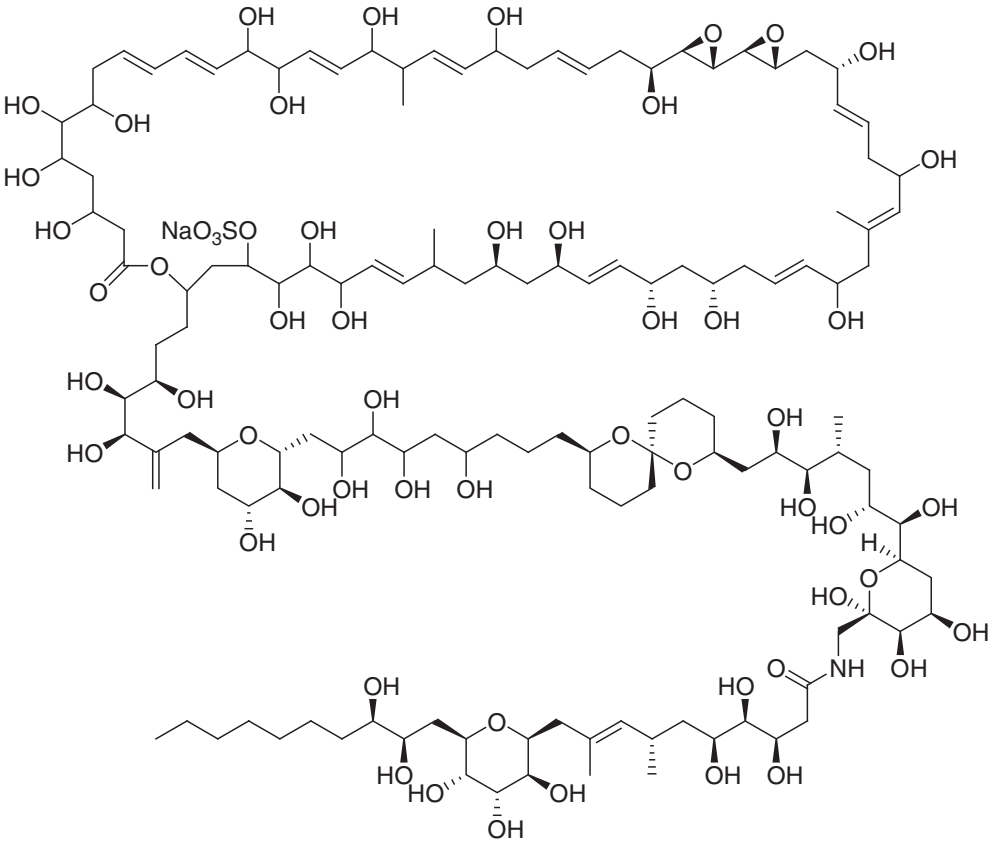
stylissadine A (**144**) R= β-H
stylissadine B (**145**) R= α-H



(**147**)

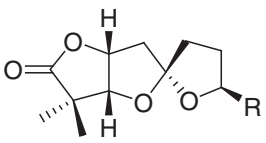


(**148**)

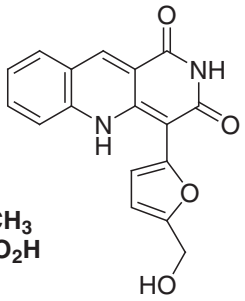


symbiodinolide (**146**)

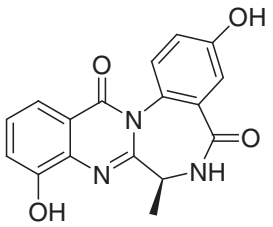
Fig. 3 (*continued*).



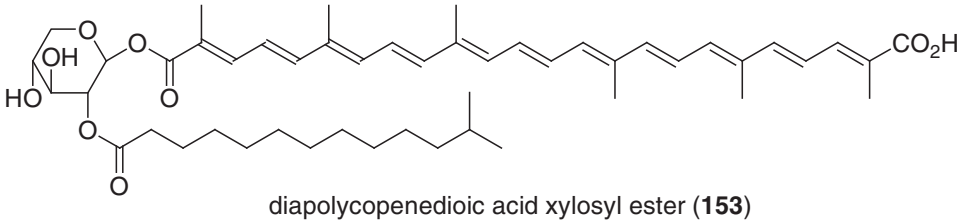
cephalosporolide H (**149**) **R=$(CH_2)_6CH_3$**
cephalosporolide I (**150**) **R=$(CH_2)_3CO_2H$**



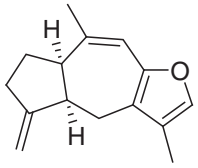
chaetominedione (**151**)



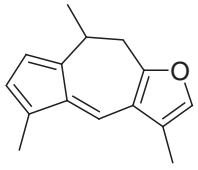
circumdatin I (**152**)



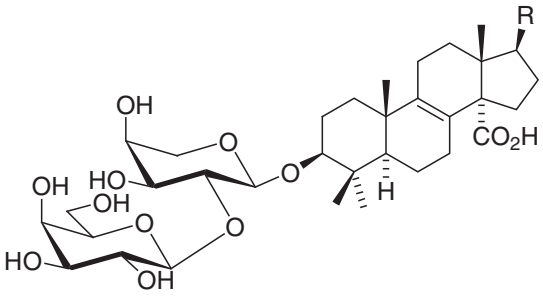
diapolycopenedioic acid xylosyl ester (**153**)



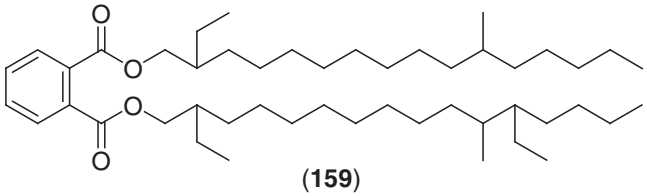
iso-echinofuran (**154**)



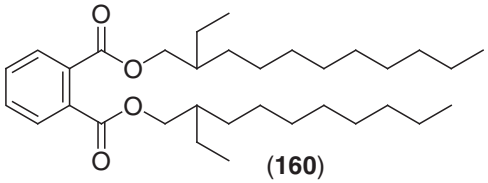
8,9-dihydro-linderazulene (**155**)



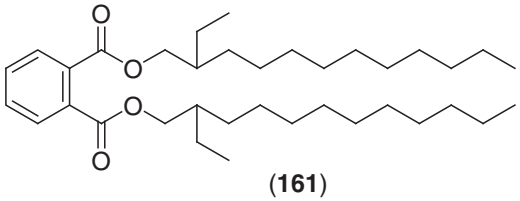
eryloside F (**157**) **R=**
eryloside F_1 (**158**) **R=**



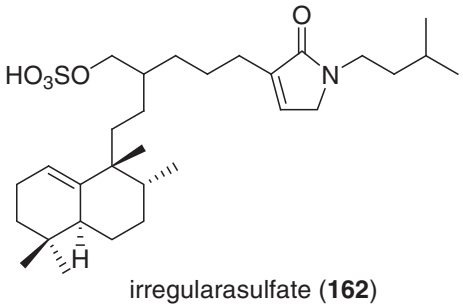
(**159**)



(**160**)



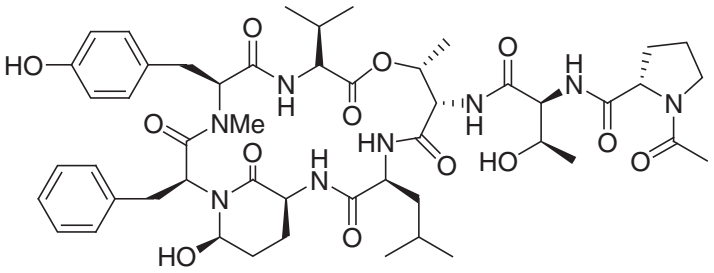
(**161**)



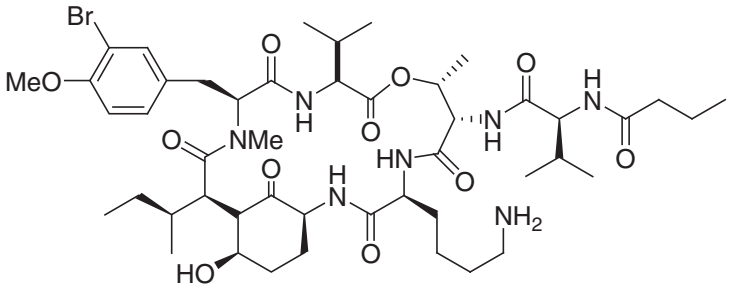
irregularasulfate (**162**)

Fig. 3 (*continued*).

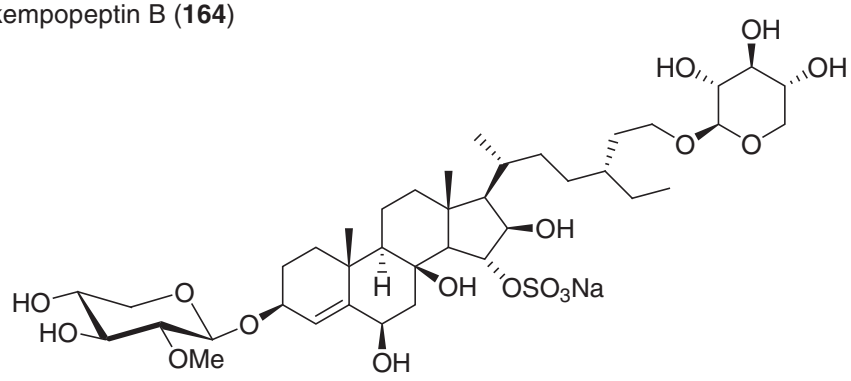
diverse pathogenic fungi. Although the investigators studied the effect of the algal bromophenols on the rice fungal pathogen *Magnaporthe grisea*, it is noteworthy that ICL has also been observed to be upregulated in *Mycobacterium tuberculosis*-infected human macrophages, and that *Candida albicans* requires ICL to be fully virulent to human hosts.



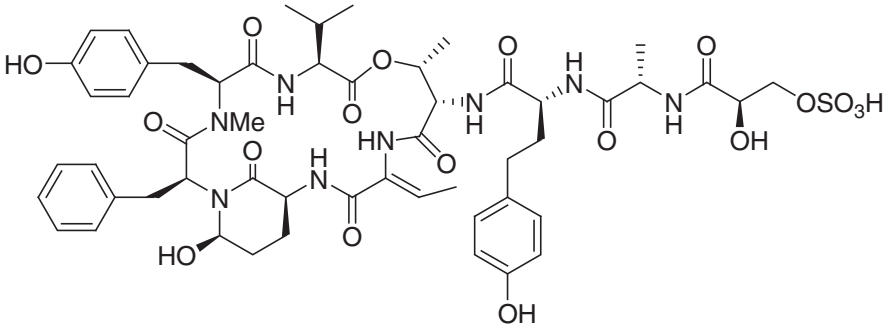
kempopeptin A (**163**)



kempopeptin B (**164**)

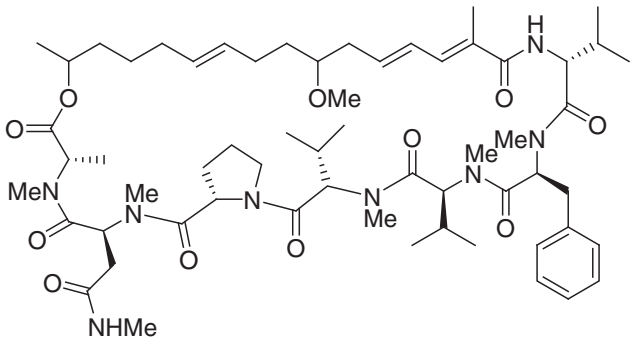


linckoside L7 (**165**)

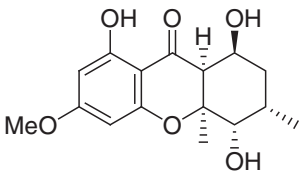


lyngbyastatin 4 (**166**)

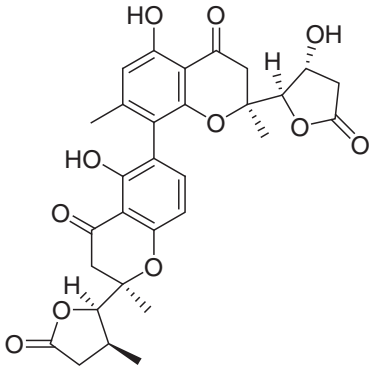
Fig. 3 (*continued*).



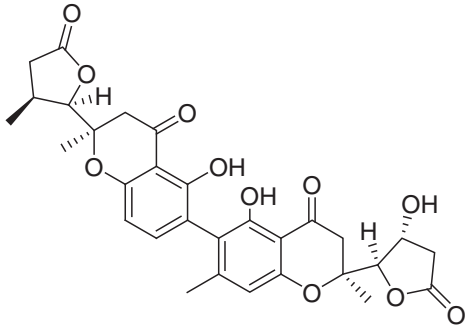
malevamide E (**167**)



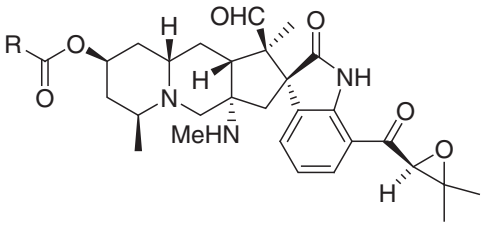
monodictysin C (**168**)



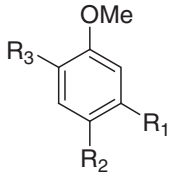
monodictyochrome A (**169**)



monodictyochrome B (**170**)



PF1270 A (**171**) R=$CH_2CH_2CH_3$
PF1270 B (**172**) R=CH_2CH_3
PF1270 C (**173**) R=CH_3



(**174**) R_1=OH, R_2=R_3=H
(**175**) R_1=R_3=H, R_2=CH_2CO_2H
(**176**) R_1=OH, R_2=H, R_3=NHCOMe

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 IC_{50}s 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 (IC_{50} = 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,

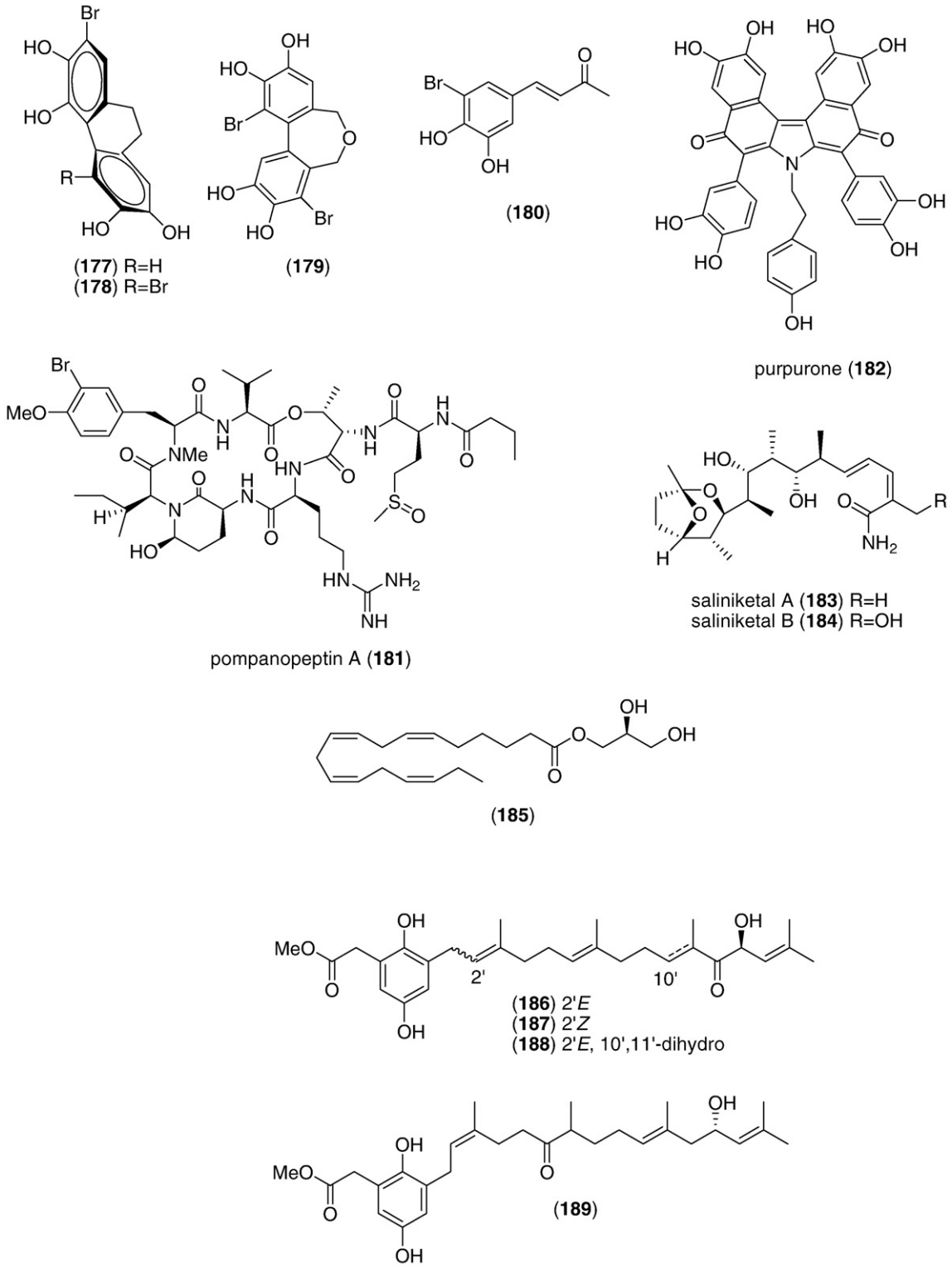
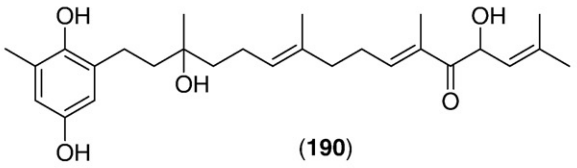


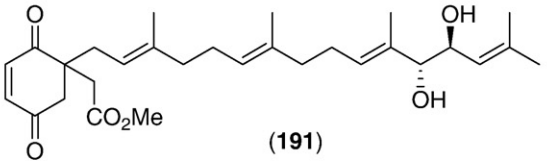
Fig. 3 (*continued*).

an increase from our previous review (Mayer et al., 2009), and previous reviews of this series.

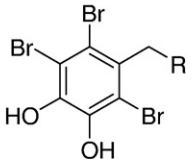
As shown in Table 1, nine marine molecules were shown during 2007–8 to possess significant *antimalarial* activity, although mechanism of action studies were reported for only two compounds. Tasdemir et al. (2007) reported that (*E*)-oroidin (**45**) and (*E*)-oroidin TFA salt (**46**) isolated from the Turkish marine sponge *Agelas oroides* potently inhibited cultures of multidrug resistant K1 strain of *Plasmodium falciparum* (IC_{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_{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

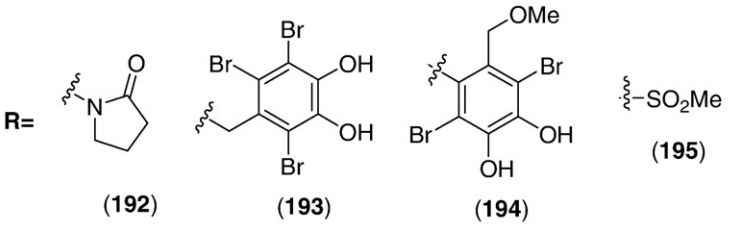


(**190**)

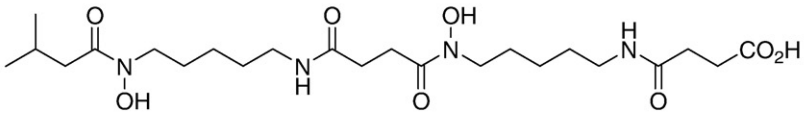


(**191**)

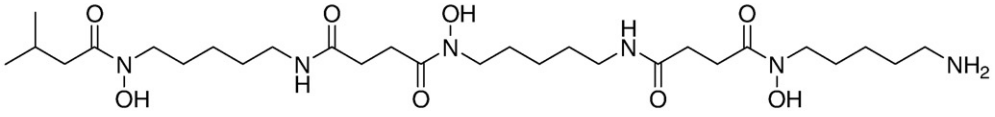




(**192**) (**193**) (**194**) (**195**)



tenacibactin C (**196**)



tenacibactin D (**197**)

Fig. 3 (*continued*).

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 μM), 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 chloroquinone-resistant strain of the parasite (IC_{50} = 5.6–8.2 μM), 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 μM) 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 μg/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, tumonoic acid I (**52**) from the Papua New Guinean marine cyanobacterium *Blennothrix cantharidosmum*, showed moderate antimalarial activity against *P. falciparum* (IC_{50} = 2 μM). Pontius et al. (2008a) isolated a heterocyclic-substituted xanthone, chaetoxanthone B (**53**) from cultures of a marine-derived fungus *Chaetomium* sp. that showed selective activity towards *P. falciparum* K1 strain (IC_{50} = 0.5 μg/mL).

Four marine compounds were reported to possess *antiprotozoal* 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* (IC_{50} = 0.5–1.9 μg/mL) and *Trypanosoma cruzi* (IC_{50} = 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* (IC_{50} = 1.1 μM) and *T. cruzi* (IC_{50} = 1.5 μM). Besides the antimalarial activity, Pontius et al. (2008a) discovered that chaetoxanthone B (**53**) had selective effects towards *T. cruzi* (IC_{50} = 1.5 μg/mL), with minimal cytotoxicity towards rat skeletal L6 myoblasts (IC_{50} = 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 oxapolycyclic diterpene bipinnapterolide B (**57**) from the Colombian gorgonian coral *Pseudopterogorgia bipinnata* which weakly inhibited growth of *M. tuberculosis* $H_{37}Rv$ (66% inhibition at 128 μg/mL). Zhang et al. (2008) identified two new dimeric naphtha-γ-pyrones 8′-*O*-demethylnigerone (**58**) and 8′-*O*-demethylisonigerone (**59**) from the marine-derived fungus *Aspergillus carbonarius* which showed weak antimycobacterial activity against *M. tuberculosis* ($H_{37}Rv$, MIC = 43 and 21.5 μM, respectively). Interestingly, the presence of conjugated C=C–C=O bonds in the pyrane 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 caribenols A (**60**) and B (**61**) weakly inhibited *M. tuberculosis* ($H_{37}Rv$, MIC = 128 and 63 μg/mL, respectively). Furthermore, Wei et al. (2007b) discovered two novel ring B abeo-sterols parguesterols A (**62**) and B (**63**) in the Caribbean sponge *Svenzea zeai*, which inhibited *M. tuberculosis* ($H_{37}Rv$, 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-norisospiculoic acid A (**64**), dinorspiculoic acid A (**65**), and norspiculoic acid A (**66**) from the Caribbean sponge *Plakortis zyggompha* also inhibited *M. tuberculosis* ($H_{37}Rv$, MIC_{99} = 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 esculetin-4-carboxylic acid ethyl ester (**67**) from the Brazilian marine sponge *Axinella* cf. *corrugata* inhibited the SARS 3CL protease (IC_{50} = 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 D,L-galactan hybrid C2S-3 (**68**) isolated from the Brazilian marine alga *Cryptonemia crenulata* showed potent antiviral activity against three clinical strains of dengue virus serotype 2 (IC_{50} = 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 hatei* which inhibited HSV-1 and HSV-2 (IC_{50} = 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 (IC_{50} = 1.72 μM), viral p24 antigen production (IC_{50} = 1.26 μM), and the activity of the HIV reverse transcriptase (IC_{50} = 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 pfaffii*. The dolabellane diterpene blocked both synthesis and integration of the HIV-1 provirus by noncompetitively inhibiting the reverse transcriptase enzyme (K_i = 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 mirabamides A, C and D (**71**, **72**, **73**) isolated from the sponge *Siliquariaspongia mirabilis* that potently inhibited both HIV-1 in neutralization (IC_{50} = 0.14–0.19 μM) and HIV-1 envelope-mediated cell fusion (IC_{50} = 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 polymannuroguluronate (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 alkaloids ascidiathiazone 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 neutrophis *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 cembranolides crassumolides A and C (**77**, **78**) from the soft coral *Lobophytum crassum* which inhibited expression of iNOS and COX-2 (apparent IC_{50} less than 10 μM). Similarly, from the same university, Cheng et al. (2008) found that new cembranolides from the soft coral *Lobophytum 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 *Junceella 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**) potently inhibited TXB_2 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 ω-3 polyunsaturated 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 *Perithalia 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). Sugiura et al. (2007) characterized a novel anti-allergic phlorotannin phlorofucofuroeckol B (PFF-B) (**95**) from the edible brown alga *Eisenia arborea*. PFF-B, inhibited β-hexosaminidase release from rat basophilic leukemia cells (IC_{50} = 7.8 μM) *in vitro*, thus showing higher potency than Tranilast (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 (**54**) isolated from the Brazilian sponge *P. angulospiculatus*, potently inhibited thromboxane B_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 ω-3 polyunsaturated 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 *Stylissa 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. (2008) 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 2007–8 showed a considerable increase from our previous review (Mayer et al., 2009), and previous reviews of this series.

Kawauchi et al. (2007) investigated the red pigment cycloprodigiosin hydrochloride (**103**) isolated from the marine bacterium *Pseudoalteromonas denitrificans*. 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 anticomplementary 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 agonist 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 *Hahella chejuencis* collected in South Korea. Prodigiosin inhibited iNOS mRNA expression and NO

production (apparent IC_{50} = 0.1 μg/mL) by a mechanism that involved inhibition of NF-κB and p38 MAPK and JNK phosphorylation. He et al. (2007) characterized the pharmacology of a water soluble polysaccharide (**108**) isolated from the mollusc *Arca subcrenata* Lischke, a popular Chinese seafood, and named it ASLP. ASLP stimulated mouse spleen lymphocyte proliferation in a concentration-dependent manner (apparent IC_{50} less than 100 μg/mL), and with the "branches of ASLP" being required for the immunomodulatory bioactivity. Aminin et al. (2008) described the immunostimulant activity of frondoside A (**109**), a triterpene glycoside isolated from the sea cucumber *Cucumaria frondosa*. The glycoside was shown to stimulate lysosomal 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 smenospongidine, smenospongiarine and smenospongine (**110**, **111**, **112**), sesquiterpene quinones previously isolated from a Palauan marine sponge *Hippospongia* sp. The observation that at 10 μg/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 macrosphelide M (**113**) and peribysin J (**114**) from *Periconia byssoides*, a fungal strain discovered from the sea hare *Aplysia kurodai*. Significantly, both fungal metabolites inhibited the adhesion of human promyelocytic leukemia HL-60 cells to human umbilical vein endothelial cells (IC_{50} = 33.2 and 11.8 μM, respectively) more potently than herbimycin A (IC_{50} = 38 μM). The latter compound, a benzochinoid ansamycin antibiotic isolated from *Streptomyces* sp. was used as a positive control in these studies. Lu et al. (2008) contributed a novel cembranolide querciformolide C (**115**) from the soft coral *Sinularia querciformis*, which significantly inhibited the activation of the iNOS and COX-2 enzymes (apparent IC_{50} less than 10 μM) in LPS-activated murine macrophages *in vitro*. Ponomarenko et al. (2007) discovered that new diterpenoids (**116**, **117**) isolated from a Northern Cook Islands marine sponge *Spongia* (*Heterofibria*) sp. moderately activated murine splenocytes lysosomes (apparent IC_{50} greater than 100 μg/mL). Oh et al. (2007) characterized a novel cyclic peptide thalassospiramide B (**118**) isolated from a marine bacterium *Thalassospira* sp., which showed immunosuppressive activity in an interleukin-5 (IL-5) inhibition assay (IC_{50} = 5 μM); 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 (**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 (**119**) and L2 (**120**) isolated from the Vietnamese blue sea star *Linckia laevigata*. All three glycosides (apparent IC_{50} = 0.3 μM) 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 (**121**, **122**, **123**, **124**, **125**) from the Japanese sea star *L. laevigata.* Linckoside P (**124**) induced neurite outgrowth in 55% of rat pheochromocytoma PC12 cells at 10 μM in the presence of nerve growth factor (NGF), while linckosides M–O appeared less active (21–32%), suggesting the importance of "the xylose on a side chain". Ina et al. (2007) characterized pheophytin A (**126**) purified from the Japanese brown alga *Sargassum fulvellum* as a novel neurodifferentiation compound. Pheophytin A at 3.9 μg/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 (**127**, **128**, **129**) were reported to target receptors in the nervous system. Peng et al. (2008) reported on the preclinical pharmacology of the α4/7-conotoxin Lp1.1 (**127**) originally isolated from the marine cone snail *Conus leopardus*. The conotoxin induced seizure and paralysis in goldfish, and selectively yet reversibly inhibited acetylcholine-evoked currents in *Xenopus* oocytes expressing rat α6α3β2 and α3β2 nicotinic receptors (apparent IC_{50} less than 10 μM). Aiello et al. (2007) characterized two novel bromopyrrole alkaloids damipipecolin (**128**) and damituricin (**129**) isolated from the Mediterranean sponge *Axinella damicornis* that were observed to modulate serotonin receptor activity *in vitro*. Although damipipecolin inhibited Ca^{2+} entry in neurons (apparent IC_{50} = 1 μg/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 (**74** and **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, Langjae et al. (2007) reported a new stigmastane-type steroidal alkaloid 4-acetoxy-plakinamine B (**130**), isolated from a Thai marine sponge *Corticium* sp. that significantly inhibited acetylcholinesterase (IC_{50} = 3.75 μM). 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, sargaquinoic acid (**131**) and sargachromenol (**132**) isolated from the brown alga *S. sagamianum.* Sargaquinoic acid potently inhibited butyrylcholinesterase (IC_{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) (**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 (**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_{50}, and a molecular mechanism of action affected by the respective compound: azumamide E (**133**), 1-deoxyrubralactone (**134**), fucoxanthin (**135**), okadaic acid (**136**), saproxanthin and myxol (**137**, **138**), sarcomilasterol (**139**), spirastrellolides C, D, and E (**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 IC_{50} 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-pyrone derivative (**148**), cephalosporolides H and I (**149**, **150**), chaetominedione (**151**), circumdatin I (**152**), diapolycopenedioic acid xylosyl ester (**153**), *Echinogorgia complexa* furanosesquiterpenes (**154**, **155**), 19-*epi*-okadaic acid (**156**), erylosides F and F_1 (**157**, **158**), *Hippocampus kuda* phthalates (**159**, **160**, **161**), irregularasulfate (**162**), kempopeptins A and B (**163**, **164**), linckoside L7 (**165**), lyngbyastatin 4 (**166**), malevamide E (**167**), monodictysin C (**168**), monodictyochromes A and B (**169**, **170**), *Penicillium waksmanii* PF1270 A, B, and C (**171**, **172**, **173**), *Penicillium* sp. anisols (**174**, **175**, **176**), *Polysiphonia urceolata* bromophenols (**177**, **178**, **179**, **180**), pompanopeptin A (**181**), purpurone (**182**), saliniketals A and B (**183**, **184**), *S. sagamianum* monoglyceride (**185**), *Sargassum siliquastrum* meroditerpenoids (**186**, **187**, **188**, **189**, **190**, **191**), *Symphyocladia 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 (Gademann 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 fucoidans (Kusaykin et al., 2008; Li et al., 2008a); potential pharmacological uses of the marine green alga polysaccharide ulvan (Lahaye and Robic, 2007); pharmacological properties of marine bis- and tris-indole alkaloids (Gupta et al., 2007); (b) *antimicrobial marine pharmacology*: a renaissance of genomics in antibacterial discovery from actinomycetes (Baltz 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); neuritogenic 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 http://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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