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Review

Marine pharmacology in 2001–2002: Marine compounds with anthelmintic, antibacterial, anticoagulant, antidiabetic, antifungal, anti-inflammatory, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems and other miscellaneous mechanisms of action

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Abstract

During 2001–2002, research on the pharmacology of marine chemicals continued to be global in nature involving investigators from Argentina, Australia, Brazil, Canada, China, Denmark, France, Germany, India, Indonesia, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Pakistan, the Philippines, Russia, Singapore, Slovenia, South Africa, South Korea, Spain, Sweden, Switzerland, Thailand, United Kingdom, and the United States. This current article, a sequel to the authors' 1998, 1999 and 2000 marine pharmacology reviews, classifies 106 marine chemicals derived from a diverse group of marine animals, algae, fungi and bacteria, on the basis of peer-reviewed preclinical pharmacology. Anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis or antiviral activities were reported for 56 marine chemicals. An additional 19 marine compounds were shown to have significant effects on the cardiovascular, immune and nervous system as well as to possess anti-inflammatory and antidiabetic effects. Finally, 31 marine compounds were reported to act on a variety of molecular targets and thus may potentially contribute to several pharmacological classes. Thus, during 2001–2002 pharmacological research with marine chemicals continued to contribute potentially novel chemical leads for the ongoing global search for therapeutic agents for the treatment of multiple disease categories.

Keywords: Chemical; Marine; Metabolites; Natural; Pharmacology; Products; Review; Toxicology

Contents

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1. Introduction

The purpose of this article is to review the 2001–2002 primary literature on pharmacological and toxicological studies with marine natural products using a similar format to the one used in our previous reviews of the marine pharmacology peer-reviewed literature (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004). Consistent with our previous reviews, only those articles reporting on the bioactivity and/or pharmacology of 106 marine chemicals whose structures have been published are included in the present review. We have used the same chemical classification as our previous reviews (Schmitz et al., 1993) to assign each marine compound to a major chemical class, namely, polyketides, terpenes, nitrogen-containing compounds or polysaccharides. Those publications reporting on anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis or antiviral properties of 56 marine chemicals have been tabulated in Table 1 with the corresponding structures shown in Fig. 1. The articles reporting on 19 marine compounds affecting the cardiovascular, immune and nervous systems, as well as those with anti-inflammatory and antidiabetic effects, are grouped in Table 2 and the structures presented in Fig. 2. Finally 31 marine compounds targeting a number of distinct cellular and molecular targets and mechanisms are shown in Table 3 and their structures depicted in Fig. 3. Publications on the biological and/or pharmacological activity of marine extracts or as yet structurally uncharacterized marine compounds have been excluded from the present review, though several promising reports were published during 2001–2002 (Duarte et al., 2001; Ermakova et al., 2001; Kaji et al., 2002; Liu et al., 2002b; Matou et al., 2002; Mohapatra et al., 2002; Preeprame et al., 2001; Suput et al., 2001; Trento et al., 2001).

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

Table 1 summarizes new pharmacological findings reported during 2001–2002 on the preclinical anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral pharmacology of the 56 marine natural products shown in Fig. 1.

2.1. Anthelmintic and antibacterial compounds

Two studies contributed to the search of novel *anthelmintic* marine natural products during 2001–2002. *Nafuredin* (1), an epoxy-δ-lactone with a methylated olefinic side chain isolated from the culture broth of *Aspergillus niger*, exerted anthelmintic activity against the ruminant parasite worm *Haemonchus contortus* and the dwarf tapeworm *Hymenolepsis nana* in mice (Omura et al., 2001). The mechanism of action involved inhibition at the nanomolar level of NADH-fumarate reductase activity, a "*unique anaerobic electron transport system in helminth mitochondria*". The marine natural product *onnamide F* (2), isolated from the Australian marine sponge *Trachycladus laevispirulifer*, showed potent inhibition of larval development of the parasitic nematode *Haemonchus contortus* with an in vitro LD_{99} value of 2.6 μg/mL (Vuong et al., 2001).

Reflecting the fact that the development of resistance toward current antibiotics continues to be a significant problem in the treatment of infectious diseases, during 2001–2002 thirteen studies contributed to the *antibacterial* pharmacology of marine natural products, a marked increase from 1998–2000 (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004). Two studies reported on the mechanism of action of two novel marine antibiotics. Torres et al. (2002) investigated the *arenosclerins A–C* (3–5) and *haliclonacyclamine E* (6), novel tetracyclic alkylpiperidine alkaloids isolated from the marine sponge *Arenosclera brasiliensis*. The investigators reported that differences in the stereochemistry at the bis-piperidine ring system played a significant role in the potent antibiotic activity of these compounds against antibiotic-resistant *Staphylococcus aureus* strains, observations that lead the authors to suggest that "*these compounds may be regarded as potentially useful new drug leads*". Linington et al. (2002) developed a high throughput assay to screen marine compounds for their ability to inhibit a type III secretory system which is an essential component of the pathogenicity of enteropathogenic and enterohermorragic *E. coli*. Their efforts resulted

Table 1
Marine pharmacology in 2001–2002: marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities

Drug class	Compound/organism[a]	Chemistry	Pharmacologic activity	MMOA[b]	Country[c]	References
Anthelmintic	Nafuredin (1)/fungus	Polyketide[d]	Inhibition of helminth NADH-fumarate reductase	Competes for the quinone-binding site in complex I	GER, JAPN	Omura et al., 2001
	Onnamide F (2)/sponge	Polyketide[d]	*H. contortus* inhibition	Undetermined	AUS	Vuong et al., 2001
Antibacterial	Arenosclerins A, B, C and haliclonacyclamine E (3, 4, 5, and 6)/sponge	Alkaloids[e]	*S. aureus* inhibition	Bis-piperidine ring stereochemistry related	BRA	Torres et al., 2002
	Caminoside A (7)/sponge	Lipopolysaccharide[f]	Antibiotic-resistant *S. aureus* and enterococci	Inhibition of bacterial type III secretory system	CAN, NETH	Linington et al., 2002
	Bogorol A (8)/bacterium	Peptide[e]	Antibiotic-resistant *S. aureus* and enterococci	Undetermined	CAN	Barsby et al., 2001
	Chalcomycin B (9)/bacterium	Macrolide[d]	*S. aureus* inhibition	Undetermined	GER	Asolkar et al., 2002
	Dicynthaurin (10)/tunicate	Peptide[e]	Gram-negative and Gram-positive inhibition	Undetermined	S. KOR, USA	Lee et al., 2001
	Halocidin (11)/tunicate	Peptide[e]	Antibiotic resistant *S. aureus* and MDR-resistant *P. Aeruginosa*	Undetermined	S. KOR	Jang et al., 2002
	Iyengaroside-A (12)/alga	Steroidal glycoside[g]	Gram-negative and Gram-positive inhibition	Undetermined	CAN, PAK	Ali et al., 2002
	Lembyne A (13)/alga	Halogenated acetogenins	Inhibition of marine bacteria	Undetermined	JAPN	Vairappan et al., 2001
	Pannosanol and pannosane (14 and 15)/alga	Sesquiterpene[g]	Inhibition of marine bacteria	Undetermined	JAPN	Suzuki et al., 2001
	Pestalone (16)/fungus	Halogenated benzophenone	Antibiotic-resistant *S. aureus* and enterococci inhibition	Undetermined	USA	Cueto et al., 2001
	Sumiki's acid (17)/fungus	Macrolide[d]	*B. subtilis* and *S. aureus* inhibition	Undetermined	GER	Jadulco et al., 2001
	Zamamistatin (18)/sponge	Bromotyrosine[e]	*Rhodospirillum salexigens* inhibition	Undetermined	JAPN	Takada et al., 2001
	Zopfiellamides A and B (19 and 20)/fungus	Polyketide[d]	Gram-negative and Gram-positive inhibition	Undetermined	GER, SWE	Dafemer et al., 2002
Anticoagulant	Galactan and fucans (21 and 22)/sea urchin	Sulfated galactans and fucans[f]	Coagulation inhibition	Enhancement of thrombin or factor Xa inhibition	BRA	Pereira et al., 2002
Antifungal	Basiliskamides A and B (23 and 24)/bacterium	Polyketide[d]	*C. albicans* and *A. fumigatus* inhibition	Undetermined	CAN	Barsby et al., 2002
	Corticatic acids A and E (25 and 26)/sponge	Polyacetylenic acid	*C. albicans* and *A. fumigatus* inhibition	Selective GGTase I inhibition	JAPN	Nishimura et al., 2002
	Swinhoeiamide A (27)/sponge	Polyketide[d]	*C. albicans* and *A. fumigatus* inhibition	Undetermined	GER, INDO, AUS, NETH	Edrada et al., 2002a

(continued on next page)

Table 1 (*continued*)

Drug class	Compound/organism[a]	Chemistry	Pharmacologic activity	MMOA[b]	Country[c]	References
Antifungal	Patagonicoside A (28)/sea cucumber	Triterpene glycoside[g]	*Cladosporium cucumerinum* inhibition	Sulfate groups in oligosaccharide related to activity	ARG	Murray et al., 2001
	Oxybis methyl phenol (29)/fungus	Polyketide[d]	*C. albican*, *T. rubrum* and *A. niger* inhibition	Undetermined	CHI	Liu et al., 2002a
	Polyester 15G256β (30)/fungus	Macrolide[d]	Cell wall biosynthesis inhibition	Undetermined	USA	Schlingmann et al., 2002
	Xestodecalactones B (31)/fungus	Macrolide[d]	*C. albicans* inhibition	Undetermined	GER, INDO	Edrada et al., 2002b
Antimalarial	Aigialomycin D (32)/fungus	Macrolide[d]	*P. falciparum* inhibition	Undetermined	THAI	Isaka et al., 2002
	Halorosellinic acid (33)/fungus	Sesterterpene[g]	*P. falciparum* inhibition	Undetermined	THAI	Chinworrungsee et al., 2001
	Heptyl prodigiosin (34)/bacterium	Pyrrole alkaloid[e]	*P. falciparum* and *P. berghei* inhibition in vitro and in vivo	Undetermined	FRA, PHIL	Lazaro et al., 2002
	ent-8-hydroxymanzamine A, manzamine F, and neo-kauluamine (35, 36, and 37)/sponge	Alkaloid[e]	*P. berghei* inhibition in vivo	Undetermined	N. ZEL, SING, USA	El Sayed et al., 2001
	(*S*)-(+)-15-hydroxycurcuphenol (38)/sponge	Sesquiterpene[e]	*P. falciparum* inhibition	Undetermined	N. ZEL, USA	El Sayed et al., 2002
	Jasplakinolide (39)/sponge	Cyclic peptide[e]	*P. falciparum* inhibition	Apical protrusion in merozoites, F-actin increase	JAPN	Mizuno et al., 2002
	Lepadins E-F (40 and 41)/tunicate	Alkaloid[e]	*P. falciparum* inhibition	Tyrosine kinase $p56^{lck}$ inhibition	GER, SWI	Wright et al., 2002
	Plakortide F (42)/sponge	Polyketide[d]	*P. falciparum* inhibition	Undetermined	USA	Gochfeld and Hamann, 2001
Antiprotozoal	Plakortolide G (43)/sponge	Polyketide[d]	*Toxomplasma gondii*	Undetermined	N. ZEL, USA	Perry et al., 2001
Antituberculosis	Cyanthiwigin C (44)/sponge	Diterpene[g]	*M. tuberculosis* inhibition	Undetermined	N. ZEL, USA	Peng et al., 2002
	Erogorgiaene and 7-hydroxyerogorgiaene (45 and 46)/sea whip	Diterpene[g]	*M. tuberculosis* inhibition	Undetermined	USA	Rodriguez and Ramirez, 2001
Antiplatelet	Alkylpyridinium (47)/sponge	Pyridine[e]	In vivo and in vitro platelet aggregation	Undetermined	SLO	Bunc et al., 2002
Antiviral	Clathsterol (48)/sponge	Sulfated sterol[g]	HIV reverse transcriptase inhibition	Undetermined	ISRA, S. AFR	Rudi et al., 2001
	Microspinosamide (49)/sponge	Depsipeptide[e]	HIV-growth inhibition	Undetermined	USA	Rashid et al., 2001
	Polyacetylenetriol (50)/sponge	Fatty acid[d]	RNA- and DNA-directed DNA polymerase inhibition	Reversible non-competitive inhibition, with hydrophobic interactions	ISRA	Loya et al., 2002
	Thalassiolins A–C (51, 52, and 53)/sea grass	Sulfated flavones[d,f]	HIV-1 integrase inhibition and HIV growth in vitro	Binding to catalytic domain of HIV-1 integrase	USA	Rowley et al., 2002
	Calyceramides A–C (54, 55, and 56)/sponge	Fatty acid[d]	Neuraminidase inhibition	Undetermined	JAPN	Nakao et al., 2001

[a]Organism, *Kingdom Animalia*: sea urchin and cucumber (Phylum Echinodermata), sponge (Phylum Porifera), tunicate (Phylum Chordata), and sea whips (Phylum Cnidaria); *Kingdom Fungi*: fungus; *Kingdom Plantae*: alga and sea grass; and *Kingdom Monera*: bacterium (Phylum Cyanobacteria). [b]MMOA: molecular mechanism of action. [c]Country: ARG: Argentina; AUS: Australia; BRA: Brazil; CAN: Canada; CHI: China; FRA: France; GER: Germany; INDO: Indonesia; ISRA: Israel; ITA: Italy; JAPN: Japan; NETH: The Netherlands; N. ZEL: New Zealand; PAK: Pakistan; PHIL: The Philippines; SING: Singapore; S. AFR.: South Africa; S. KOR: South Korea; SLO: Slovenia; SWE: Sweden; SWZ: Switzerland; and THAI: Thailand. [d]Polyketides. [e]Nitrogen-containing compound. [f]Polysaccharide. [g]Terpene.

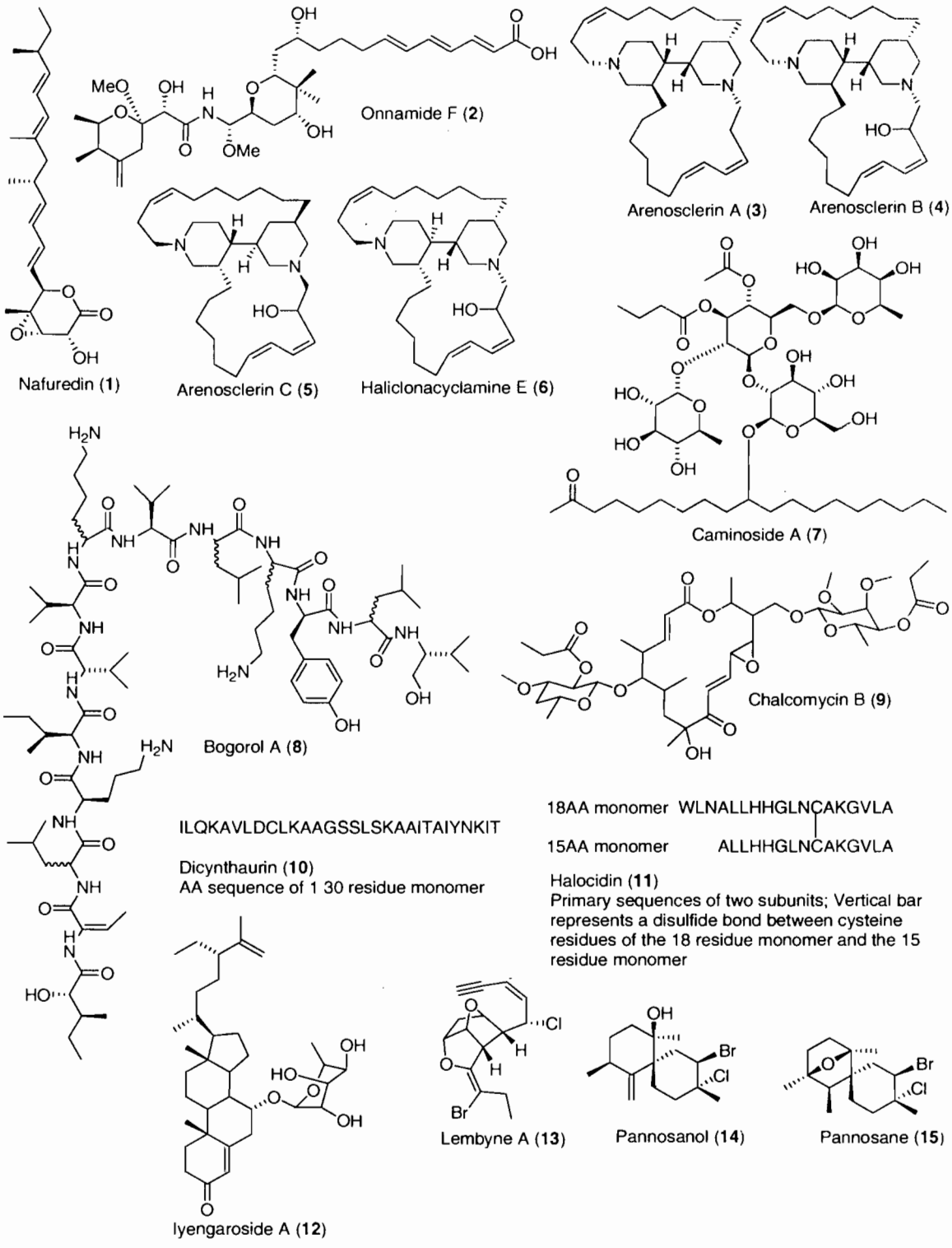


Fig. 1. Marine pharmacology in 2001–2002: marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities.

in the isolation of a novel antimicrobial glycolipid *caminoside A* (7) from the marine sponge *Caminus spaeroconia*. Caminoside A was "*reasonably potent*" against methicillin-resistant *S. aureus* (MIC=12 μg/mL) and vancomycin-resistant enterococcal strains (MIC=12 μg/mL).

Although additional novel marine antibiotics were reported in 2001–2002, no mechanism of action studies were reported for marine compounds (8–20). Nevertheless, the reports highlight the observations that potentially novel antibiotics are present in marine bacteria, tunicates, fungi,

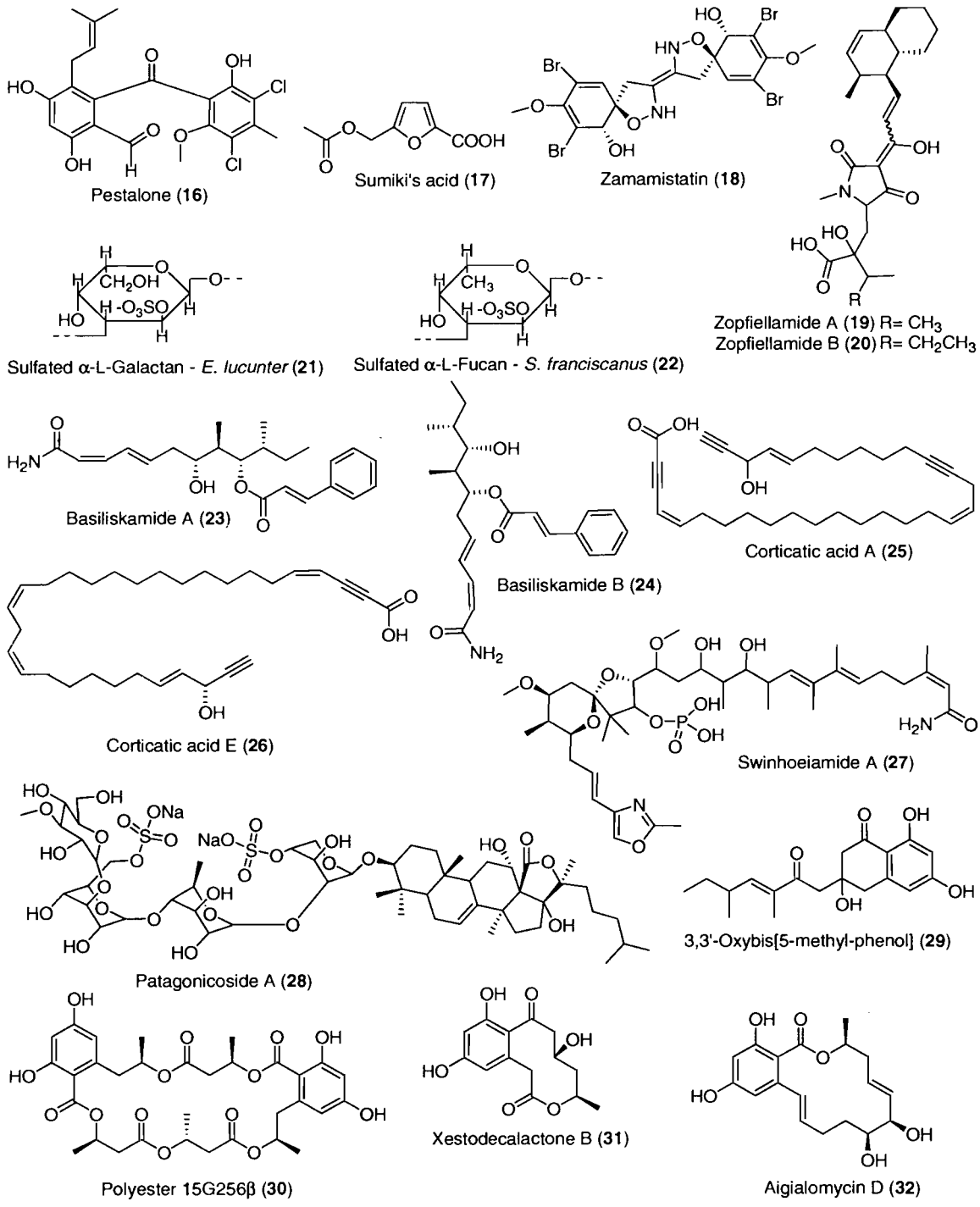
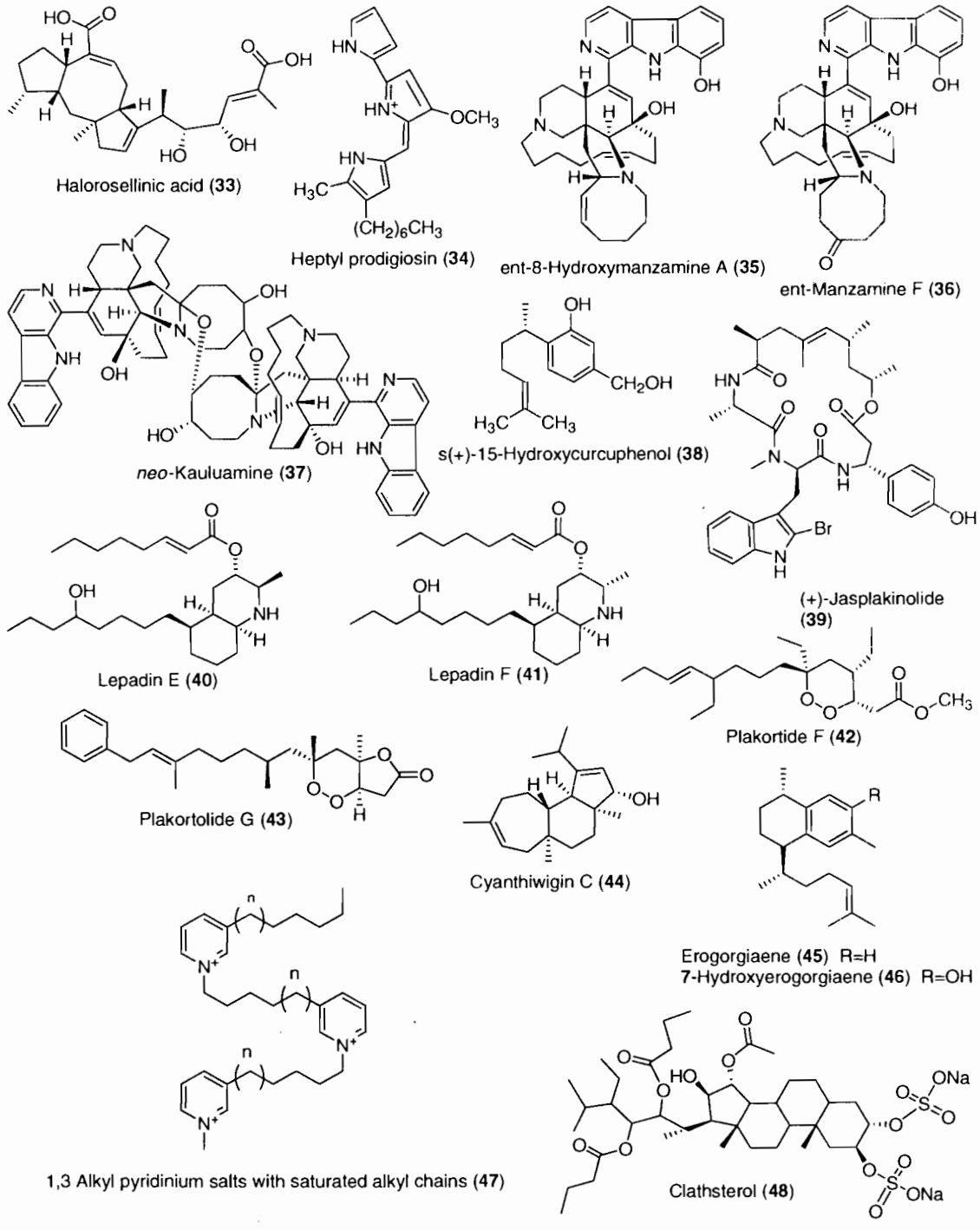


Fig. 1 (*continued*).

algae and sponges. Two papers reported on antibiotic activity in compounds isolated from marine bacteria: Barsby et al. (2001) reported the isolation of the peptide *bogorol A* (8) from a culture of a marine *Bacillus* sp., which was active against methicillin-resistant *S. aureus* (MIC=2 μg/mL) and vancomycin-resistant enterococcal strains (MIC=10 μg/mL). Because bogorol A represents a new cationic peptide antibiotic template the authors proposed that it might become "*an attractive lead structure for SAR optimization*". Asolkar et al. (2002) reported on the isolation of a novel macrolide antibiotic *chalcomycin B* (9) from the culture broth of a marine Streptomycete isolate which was particularly potent against *S. aureus* (MIC=0.39 μg/mL). Two papers reported on new antimicrobial peptides isolated from marine tunicates: Lee et al. (2001) discovered an unusual peptide, *dicynthaurin* (10), from hemocytes of the



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marine tunicate *Halocynthia aurantium*. Dicynthaurin (10), a peptide that contains an unpaired cysteine and forms covalent homodimers, was active against Gram-negative and Gram-positive bacteria. Jang et al. (2002) reported a new antimicrobial heterodimeric peptide *halocidin* (11) from the hemocytes of the solitary marine tunicate, *H. aurantium*, the same source of the peptide dicynthaurin. Although the investigators hypothesized that the main target of halocidin might be the bacterial cell membrane, this heterodimeric peptide demonstrated significant potency against methicillin-resistant *S. aureus* and multidrug-resistant *Pseudomonas aeruginosa*. Three papers reported on the presence of antibacterial compounds in marine algae: a novel steroidal glycoside, *iyengaroside-A* (12), was isolated from the marine green alga *Codium iyengarii* (Ali et al., 2002) and was shown to be slightly less potent than tetracycline against a

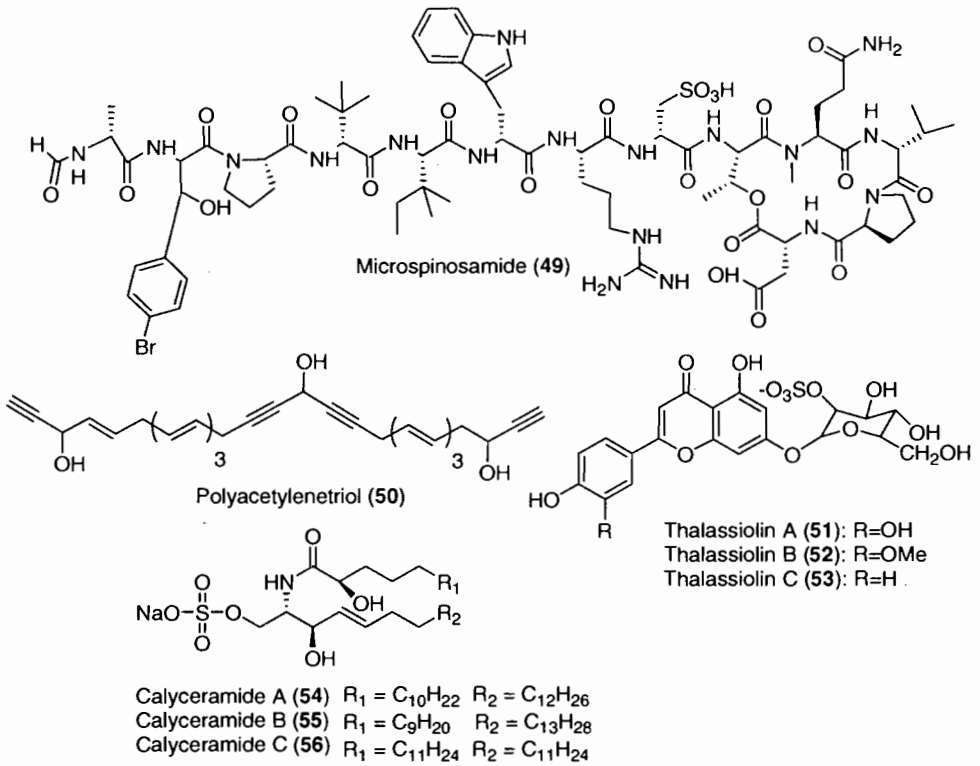


Fig. 1 (*continued*).

battery of Gram-negative and Gram-positive bacteria. Vairappan et al. (2001) reported a new halogenated G15 acetogenin, *lembyne-A* (13), from the marine red alga *Laurencia* sp. that had antibacterial activity against a panel of 13 species of marine bacteria isolated from algal habitats. Suzuki et al. (2001) contributed two novel halogenated sesquiterpenoids, *pannosanol* (14) and *pannosane* (15), from the red alga *Laurencia pannosa*, which demonstrated antibacterial activity against 13 species of marine bacteria. Three antibiotic compounds were isolated from marine fungi: a novel chlorinated benzophenone antibiotic, *pestalone* (16), was isolated from a member of the marine fungus genus *Pestalotia*, in response to a bacterial challenge (Cueto et al., 2001). Pestalone showed very potent antibiotic activity against methicillin-resistant *S. aureus* (MIC=37 ng/mL) and vancomycin-resistant *Enterococus faecium* (MIC=78 ng/mL), suggesting that pestalone should be evaluated in advanced models of infection. Jadulco et al. (2001) reported the isolation of a new furan carboxylic acid, an acetyl derivative of *sumiki's acid* (17) from the marine fungus *Cladosporium herbarum* that was found to be active against *Bacillus subtilis* and *S. aureus*. *Zopfiellamides A* and *B* (19 and 20), antimicrobial pyrrolidinone derivatives, were isolated from the marine fungus *Zopfiella latipes* (Daferner et al., 2002). Although the zopfiellamides appeared to be moderately antibacterial to Gram-positive and Gram-negative bacteria (MIC=2–10 μg/mL) they exhibited no cytotoxicity up to 100 μg/mL. Finally, the bromotyrosine antibiotic, *zamastatin* (18), was derived from the Okinawan sponge *Pseudoceratina purpurea* (Takada et al., 2001) and while zamastatin affected the growth of the marine biofouling bacteria *Rhodospirillum salexigens*, it remains to be demonstrated that this compound will affect antibiotic-resistant bacteria.

2.2. Anticoagulant compounds

One paper was published during 2001–2002 on the *anticoagulant* properties of two marine polysaccharides, a decrease from our previous reviews (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004). Pereira et al. (2002) reported a novel *sulfated α-L-galactan* (21) and a *sulfated α-L-fucan* (22) isolated from the crude egg jelly of the sea urchins *Echinometra lucunter* and *Strongylocentrotus franciscanus* collected in Brazil and the USA. Interestingly, only the sulfated galactan had potent anticoagulant activity as shown by the enhancement of thrombin or factor Xa inhibition by antithrombin or heparin cofactor II, similar to heparin.

2.3. Antifungal compounds

Seven studies during 2001–2002 reported on the *antifungal* properties of 9 novel marine natural products, a slight increase from 1998–2000 (Mayer and Lehmann, 2000; Mayer and Hamann, 2002, 2004). Antifungal activity was noted in novel compounds isolated from marine bacteria, sponges, sea cucumbers and fungi.

Table 2
Marine pharmacology in 2001–2002: marine compounds with anti-inflammatory and antidiabetic activities and affecting the cardiovascular, immune and nervous systems

Drug class	Compound/organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
Anti-inflammatory	Halipeptins A and B (57 and 58)/sponge	Depsipeptides[d]	Inhibition of carrageenan-induced edema	Undetermined	ITA, FRA	Randazzo et al., 2001
	Hymenamide C (59)/sponge	Cyclopeptide[d]	Neutrophil and macrophage mediator modulation	Elastase, PGE_2 and NO inhibition	ITA, SPA	Napolitano et al., 2001
	Petrosaspongiolide (60)/sponge	Sesterterpene[e]	Phospholipase A_2 inhibition	Hydroxybutenolide required for PLA_2 inhibition	ITA	Dal Piaz et al., 2002
	Scytonemin (61)/bacterium	Amino acid[d]	Inhibition of PMA-induced mouse ear edema	Inhibition of polo-like kinase 1 and PKCβ1	USA	Stevenson et al., 2002b,a
Antidiabetic	Insulin (62)/shark	Peptide[d]	Glucose metabolism in sharks	High affinity binding to human insulin receptor	UK, USA, SWE, DEN	Anderson et al., 2002
Cardiovascular	Gramine analogue (TBG) (63)/bryozoa	Alkaloid[d]	Vasorelaxation of isolated rat aorta	Ca^{2+} inhibition and increase cyclic AMP	JAPN	Iwata et al., 2001
	Lepadiformine (64)/tunicate	Alkaloid[d]	Inhibition of cardiocirculatory system in vivo and in vitro	Reduction of inward K+ current	FRA	Juge et al., 2001
Immune system	Domoic acid (65)/ diatom	Amino acid[d]	Limited TNF-α and matrix metalloproteinase-9 release from brain microglia	Undetermined	USA	Mayer et al., 2001
Nervous system	Antillatoxin B (66)/bacterium	Lipopeptide[e]	Activator of voltage sensitive-sodium channel	Undetermined	USA	Nogle et al., 2001
	Dysiherbaine (67)/sponge	Amino acid[d]	Induction of convulsant action in mice	Inhibition of kainic acid and mGluR5 glutamate receptors	JAPN, USA	Sakai et al., 2001b
	N-3′-ethylaplysinopsin (68)/sponge	Alkaloid[d]	Undetermined	Binding to human serotonin 5-HT_{2C} receptor	N. ZEL, SING, USA	Hu et al., 2002
	Gangliosides HLG-1, HLG-2, HLG-3 (69–71)/sea cucumber	Glycosphingolipid[f]	In vitro neuritogenic assay	Undetermined	JAPN	Yamada et al., 2001
	Manoalide (72)/sponge	Sesterterpene[e]	Inhibition of seizures and epileptogenic properties of crotoxin	Dissociation of crotoxin complex	FRA	Dorandeu et al., 2002
	Neodysiherbaine A (73)/sponge	Amino acid[d]	Induction of convulsant action in mice	Inhibition of kainic acid glutamate receptors	JAPN	Sakai et al., 2001a
	Conantokin-G (74)/snail	Peptide[d]	In vitro NMDA receptor-transfected, oocyte electrophysiology	Interaction with NMDA glutamate-binding pocket	GER, USA	Wittekindt et al., 2001
	Conantokin-L (75)/snail	Peptide[d]	Anticonvulsant in mouse epilepsy model. Neuroprotective.	NMDA receptor antagonist	PHIL, USA	Jimenez et al., 2002

[a]Organism, *Kingdom Animalia*: bryozoa (Phylum Ectoprocta), sea anemones (Phylum Cnidaria), shark and tunicate (Phylum Chordata), sea cucumber (Phylum Echinodermata), snail (Phylum Mollusca), and sponge (Phylum Porifera); *Kingdom Plantae*: dinoflagellate and alga; and *Kingdom Monera*: bacterium (Phylum Cyanobacteria). [b]MMOA: molecular mechanism of action. [c]Country: DEN: Denmark; FRA: France; GER: Germany; ITA: Italy; JAPN: Japan; N. ZEL: New Zealand; PHIL: Philippines; SING: Singapore; SLO: Slovenia; SPA: Spain; SWE: Sweden; and UK: United Kingdom. [d]Nitrogen-containing compounds. [e]Terpenes. [f]Polyketides.

Two novel antifungal amides resulted from screening marine bacterial cultures against common fungal pathogens. Laboratory cultures of the marine bacterium *Bacillus laterosporus* produced the novel polyketides *basiliskamides A* and *B* (23 and 24) (Barsby et al., 2002). Both compounds showed potent activity against *Candida albicans* (MIC = 1.0 and 3.1 μg/mL, respectively) and *Aspergillus fumigatus* (MIC = 2.5 and 5.0 μg/mL, respectively), which was comparable to amphotericin B, an agent currently used for the treatment of systemic fungal infections. Interestingly, basiliskamide A was 4-fold less cytotoxic to normal human fibroblasts than amphotericin B.

Two novel polyacetylenic acids, *corticatic acids D* and *E* (25 and 26) isolated from the marine sponge *Petrosia*

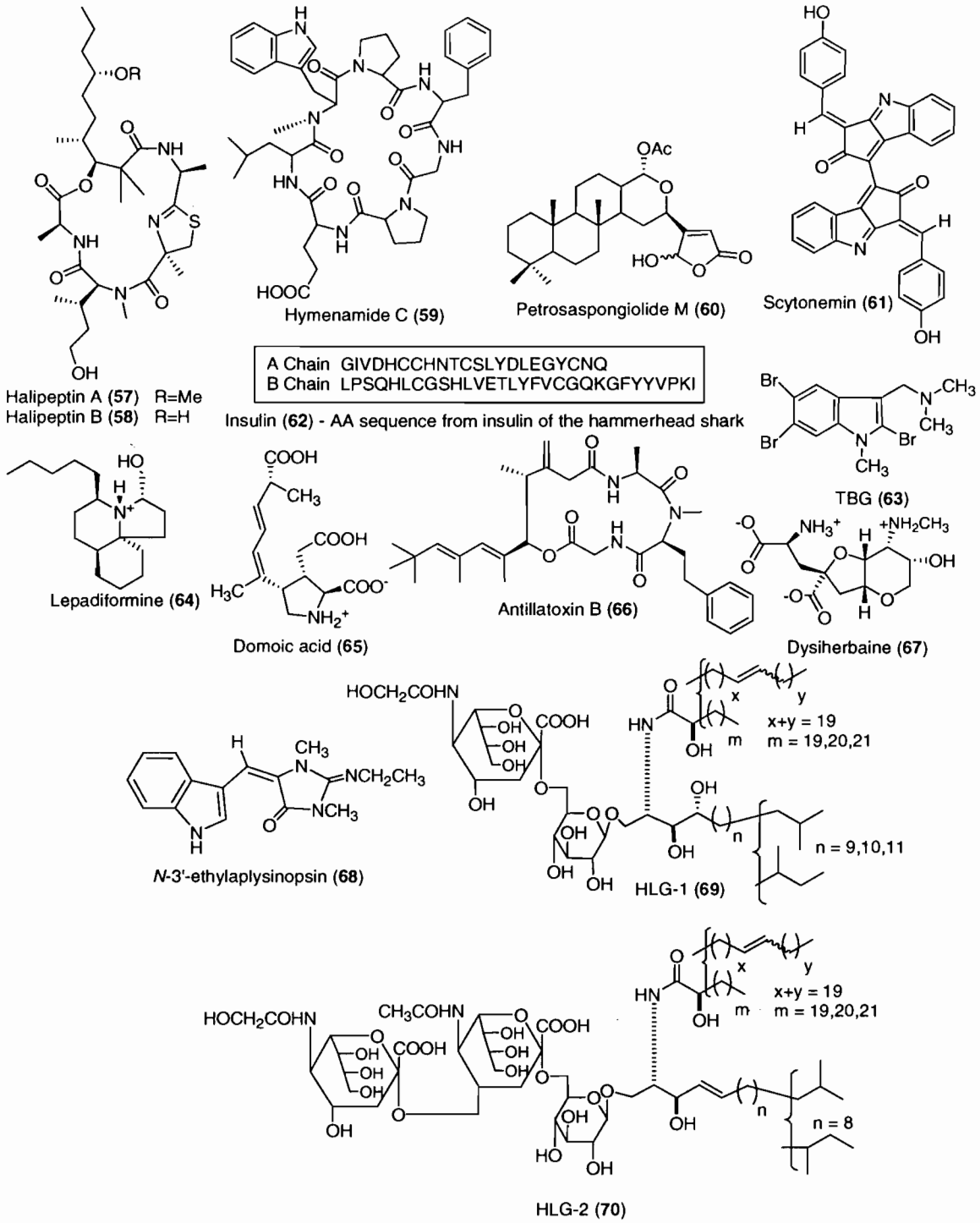
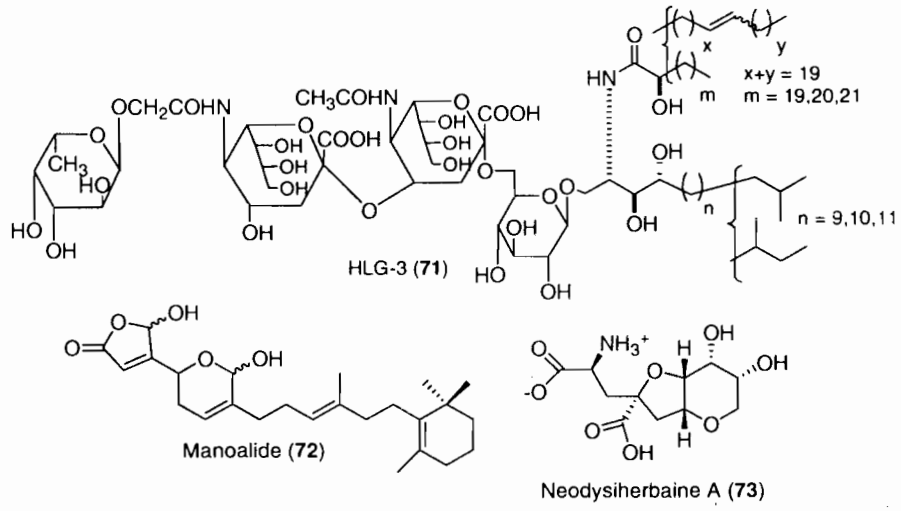


Fig. 2. Marine pharmacology in 2001–2002: marine compounds with anti-inflammatory and antidiabetic activities and affecting the cardiovascular, immune and nervous systems.

corticata (Nishimura et al., 2002) were shown to inhibit geranylgeranyltransferase type I (GGTase I), an enzyme involved in fungal cell wall biosythesis. Interestingly, while corticatic acids D and E inhibited *C. albicans* with IC_{50} values of 3.3 and 7.3 μM, the fact that there is little sequence identity between human and *Candida* GGTase I suggested that these marine compounds may become leads for novel and "*selective antifungal agents*". *Swinhoeiamide A* (27), a novel antifungal calyculin derivative was isolated from the marine sponge *Theonella swinhoei* (Edrada et al., 2002a). Swinhoeiamide A showed strong antifungal activity towards *C. albicans* and *A. fumigatus* (MIC=1.2 and 1.0 μg/mL, respectively). Murray et al. (2001) reported the novel disulfated triterpene glycoside *patagonicoside A* (28)



MHLYTYLYLLVPLVTFHLILGTGTLDDGGALTERRSADATALKAEPVLLQKSAARSTDDNGKDRLTQ

Conantokin-G (**74**) - precursor AA sequence

MQLYTYLYLLVPLVTFHLILGTGTLDHGGALTERRSTDAIALKPEPVLLQKSSARSTDDNGNDRLTQ

Conantokin-L (**75**) - precursor AA sequence

Fig. 2 (*continued*).

from the sea cucumber *Psolus patagonicus* that was active against the pathogenic fungus *C. cucumerinum* (apparent MIC=8 μg/spot), which may be the result of sulfate groups in the oligosaccharide chain.

Three novel marine antifungals resulted from screening marine fungal cultures against common fungal pathogens. An antifungal metabolite, *3,3'-oxybis[5-methyl-phenol]* (29) was isolated from the fermentation broth of the filamentous marine fungus *Keissleriella* sp. (Liu et al., 2002a,b). This novel metabolite moderately inhibited growth of the human pathogens *C. albicans*, *Tricophyton rubrum* and *A. niger* (MIC=10–80 μg/ml). A new antifungal *polyester 15G256β* (30) was isolated from the fermentation broth of the marine fungus *Hypoxylon oceanicum* (Schlingmann et al., 2002). Although the exact molecular mechanism responsible for the reported antifungal activity has not been established, the polylactone was observed to potently inhibit a variety of phytopathogenic fungi (MIC=2 μg/mL). Culture filtrates of *Penicillium* cf. *montanense* obtained from the marine sponge *Xestospongia exigua* yielded a novel decalactone *xestodecalactone B* (31) (Edrada et al., 2002b) which was found to be active against the yeast *C. albicans*.

2.4. Antimalarial, antiplatelet, antiprotozoal and antituberculosis compounds

During 2001–2002 and as shown in Table 1, 11 studies were reported in the area of *antimalarial, antiprotozoal* and *antituberculosis* pharmacology of structurally characterized marine natural products.

Eleven compounds depicted in Fig. 1 were shown to possess antimalarial activity. Moderate antimalarial activity (IC_{50}=6.6 μg/mL) against the multidrug resistant *Plasmodium falciparum* (K1 strain) was reported for *aigialomycins D* (32), a new 14-membered resorcyclic macrolide isolated from the marine mangrove fungus *Aigialus parvus* BCC 5311 (Isaka et al., 2002). As part of an ongoing program on biologically active substances from bioresources in Thailand, Chinworrungsee et al. (2001) reported the ophiobolane sesterterpene *halorosellinic acid* (33) from the marine fungus *Halorosellinia oceanica* BCC 5149. Halorosellinic acid demonstrated moderate antimalarial activity (IC_{50}=13 μg/mL) against the parasite *P. falciparum* (K1, multidrug resistant strain). In vitro and in vivo antimalarial studies were conducted with the trypyrrole bacterial pigment *heptyl prodigiosin* (34), purified from the culture of a proteobacteria from a marine tunicate in the Philippines (Lazaro et al., 2002). The investigators reported that the in vitro activity of heptyl prodigiosin against *P. falciparum* 3D7 was similar to chloroquine (IC_{50}=0.07 vs. 0.015 μM, respectively). Interestingly, a single subcutaneous administration of 5–20 mg/kg heptyl prodigiosin significantly extended survival of *P. berghei* ANKA strain-infected mice, suggesting that "*the molecule might be used as a lead compound*". New enantiomers of *ent-8-hydroxymanzamine A* (35), *manzamine F* (36) and *neo-kauluamine* (37) were isolated from an undescribed Indo-Pacific sponge (El Sayed et al., 2001). When assayed in vivo, *ent*-8-hydroxymanzamine A and *neo*-kauluamine reduced parasitemia in *P. berghei*-infected mice, with a concomitant

Table 3
Marine pharmacology in 2001–2002: marine compounds with miscellaneous mechanisms of action

Compound/organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
Aeroplysinin-1 (76)/sponge	Amino acid derived[d]	Antiangiogenic	Undetermined	SPA	Rodriguez-Nieto et al., 2002
Antillatoxin (77)/bacterium	Lipopeptide[d]	Voltage-dependent Na^+ channel activation	Sodium channel α subunit binding	JAPN, USA	Li et al., 2001
Aplysiallene (78)/sea hare	Polyketide[e]	Na^+, K^+–ATPase inhibition	Undetermined	JAPN	Okamoto et al., 2001a
Azaspiracid-1 (79)/alga	Polyketide[e]	Toxicity to lymphocytes and neuroblastoma cells	Decrease in F-actin pools and increased $[Ca^{2+}]_i$	SPA, JAPN	Roman et al., 2002
Bistratene A (80)/ascidian	Polyketide[e]	Induction of cell-cycle arrest in G_o/G_1 and G_2/M	Protein kinase C δ activation	AUS, USA	Frey et al., 2001
Bryoanthrathiophene (81)/bryozoa	Polyketide[e]	Angiogenesis inhibition	Undetermined	JAPN	Jeong et al., 2002
Bryostatin-1 (82)/bryozoa	Polyketide[e]	IgE synthesis inhibition	Iε germline transcription modulation	USA	Rabah et al., 2001
Coscinosulfate (83)/sponge	Sesquiterpene[f]	Cell cycle regulation	Dual specificity phosphatase CDC25 inhibition	FRA	Loukaci et al., 2001
Debromohymenialdisine (84)/sponge	Alkaloid[d]	G_2 checkpoint inhibition	Protein kinase Chk1 and Chk2 inhibition	CAN, UK, USA	Curman et al., 2001
Chlorogentisylquinone (85)/fungus	Polyketide[e]	Neutral sphingomyelinase inhibition	Undetermined	JAPN	Uchida et al., 2001
Discodermin A (86)/sponge	Peptide[d]	Permeabilization of plasma membrane	Undetermined	JAPN	Sato et al., 2001
Farnesylhydroquinone (87)/fungus	Terpene[f]	Radical scavenging	Undetermined	S. KOR	Son et al., 2002
Halenaquinol (88)/sponge	Polyketide	Na^+, K^+–ATPase inhibition	Oxidation of sulfhydryl groups	RUS	Gorshkova et al., 2001
Halenaquinone (89)/sponge	Polyketide[e]	Induction of apoptosis	Inhibition of phosphatidyl inositol 3-kinase	JAPN	Fujiwara et al., 2001
Hectochlorin (90)/bacterium	Peptide[d]	Inhibition of cell growth	Induction of actin polymerization	USA	Marquez et al., 2002
Iantherans A and B (91 and 92)/sponge	Peptide[d]	Na^+, K^+–ATPase and plasmin inhibition	Undetermined	JAPN	Okamoto et al., 2001b
Jaspaquinol (93)/sponge	Terpene[f]	Human 15-lipoxygenase inhibition	Undetermined	USA	Carroll et al., 2001
Jasplankinolide (39)/sponge	Peptide/ Polyketide[e]	Increased outflow facility in monkey eye	Undetermined	USA	Tian et al., 2001
Linckosides A and B (94 and 95)/starfish	Sterol glycoside[f]	Induction of neuritogenesis	Undetermined	JAPN	Qi et al., 2002
Maitotoxin (96)/alga	Complex polyketide[e]	Modulation of calcium and sodium influx	Undetermined	MEX	Morales-Tlalpan and Vaca, 2002
	Complex polyketide[e]	Regulation of excocytosis in *Xenopus laevis* oocytes	Activation of cation conductance	GER, RUS, UK, FRA	Diakov et al., 2001
Micropeptins (97)/bacterium	Depsipeptides[d]	Inhibition of trypsin and chymotrypsin	Undetermined	ISRA	Reshef and Carmeli, 2001
Pectenotoxin-6 (98)/alga	Macrolide[e]	Disruption of F-actin cytoskeletal	Induction of F-actin depolymerization	SPA, JAPN, ITA	Leira et al., 2002
Sculezonone-A and B (99 and 100)/fungus	Polyketide[e]	Inhibition of DNA polymerase α, β and γ	Differential electrostatic charges elicit different inhibition spectra	JAPN	Perpelescu et al., 2002
Scytonemin (61)/bacterium	Amino acid[d]	Inhibition of active cell proliferation	Inhibition of polo-like and cell-cycle kinases	USA	Stevenson et al., 2002a
Stolonoxides (101)/tunicate	Fatty acid[e]	Mitochondrial respiratory chain inhibition	Effect on mitochondrial complex II and III	ITA, SPA	Fontana et al., 2001
Swinholide A (102)/sponge	Complex Polyketide[e]	Increased outflow facility in monkey eye	Undetermined	USA	Tian et al., 2001
Wondonins A and B (103 and 104)/sponge	Alkaloid[d]	Modulation of angiogenesis in vitro	Undetermined	S. KOR	Shin et al., 2001
Xetospongin-C (105)/sponge	Alkaloid[d]	Inhibition of smooth muscle contraction	Voltage-dependent K^+ and L-type Ca^{2+} channel inhibition	JAPN	Ozaki et al., 2002
Yessotoxin (106)/alga	Polyketide[e]	Lymphocyte $[Ca^{2+}]_i$ homeostasis modulation	Inhibition of calcium channels	SPA	De la Rosa et al., 2001

[a]Organism. *Kingdom Animalia*: ascidians and tunicates (Phylum Chordata), anemones, corals and hydroids (Phylum Cnidaria), sea cucumber and starfish (Phylum Echinodermata), bryozoa (Phylum Ectoprocta), sea hares (Phylum Mollusca), and sponge (Phylum Porifera); *Kingdom Fungi*: fungus; *Kingdom Plantae*: alga; and *Kingdom Monera*: bacterium (Phylum Cyanobacteria). [b]MMOA: molecular mechanism of action. [c]Country: AUS: Australia; CAN: Canada; CHI: China; FRA: France; GER: Germany; ISRA: Israel; ITA: Italy; JAPN: Japan; MEX: Mexico; RUS: Russia; S. KOR: South Korea; SPA: Spain; and UK: United Kingdom. [d]Nitrogen-containing compounds. [e]Polyketides. [f]Terpenes. [g]Polysaccharides.
The structure for jasplankinolide (39) is shown in Fig. 1. The structure for scytonemin (61) is shown in Fig. 2.

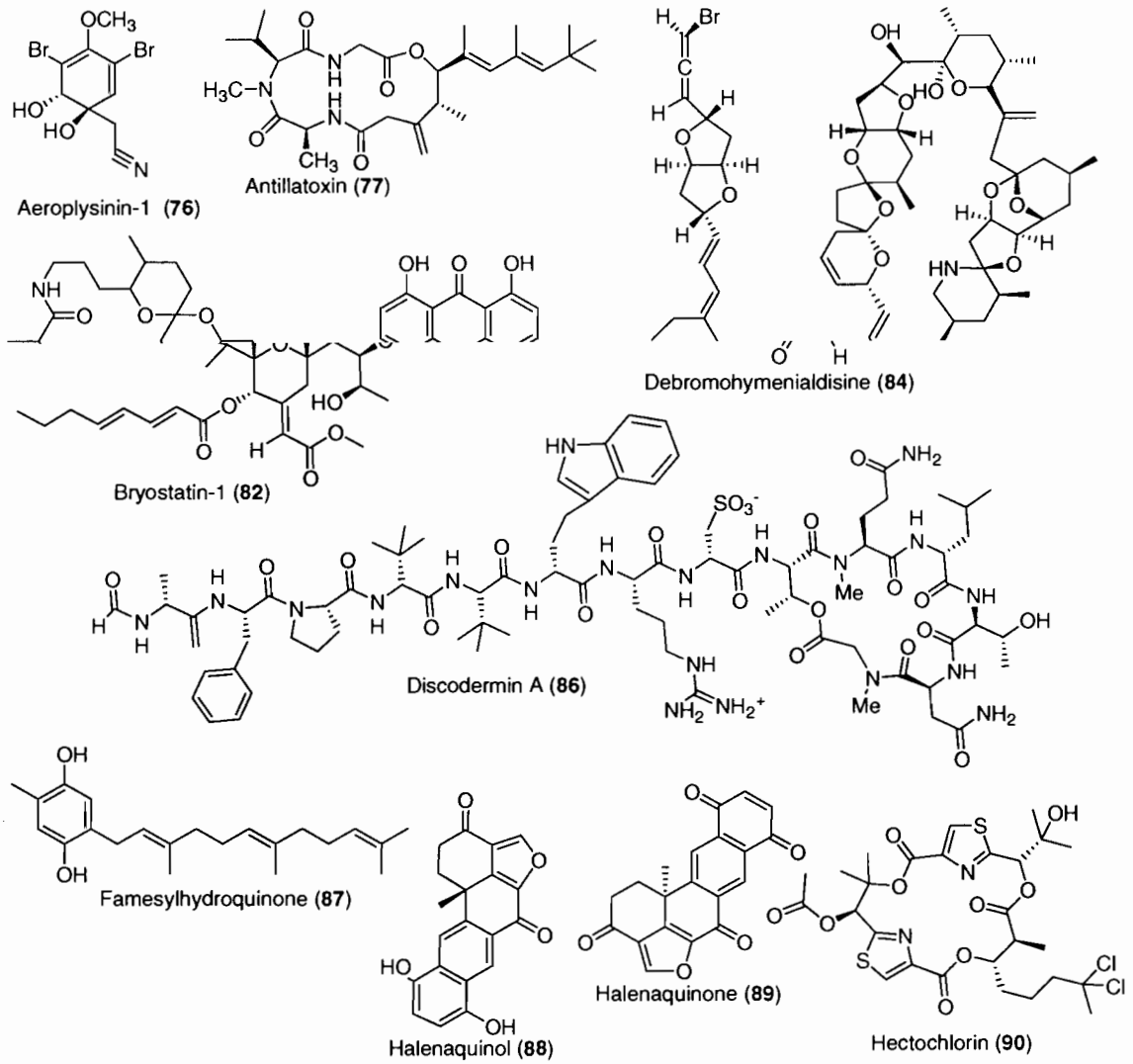


Fig. 3. Marine pharmacology in 2001–2002: marine compounds with miscellaneous mechanisms of action.

increase in survival; additionally *ent*-8-hydroxymanzamine A and manzamine F inhibited *Mycobacterium tuberculosis* (MIC < 12.5 μg/mL). In vitro antimalarial activity (MIC = 3.8–2.9 μg/mL) against *P. falciparum* (D6 and W2 clones) was reported for *(S)-(+)-15-hydroxycurcuphenol* (38), a microbial transformation product of the sesquiterpene (*S*)-(+)-curcuphenol isolated from the Jamaican sponge *Didiscus oxeata* and transformed using *Kluyveromyces marxianus* var. *lactis* (El Sayed et al., 2002). Mizuno et al. (2002) extended the pharmacology of *jasplakinolide* (39), a cyclic peptide isolated from the marine sponge *Jaspis* sp. These investigators observed that

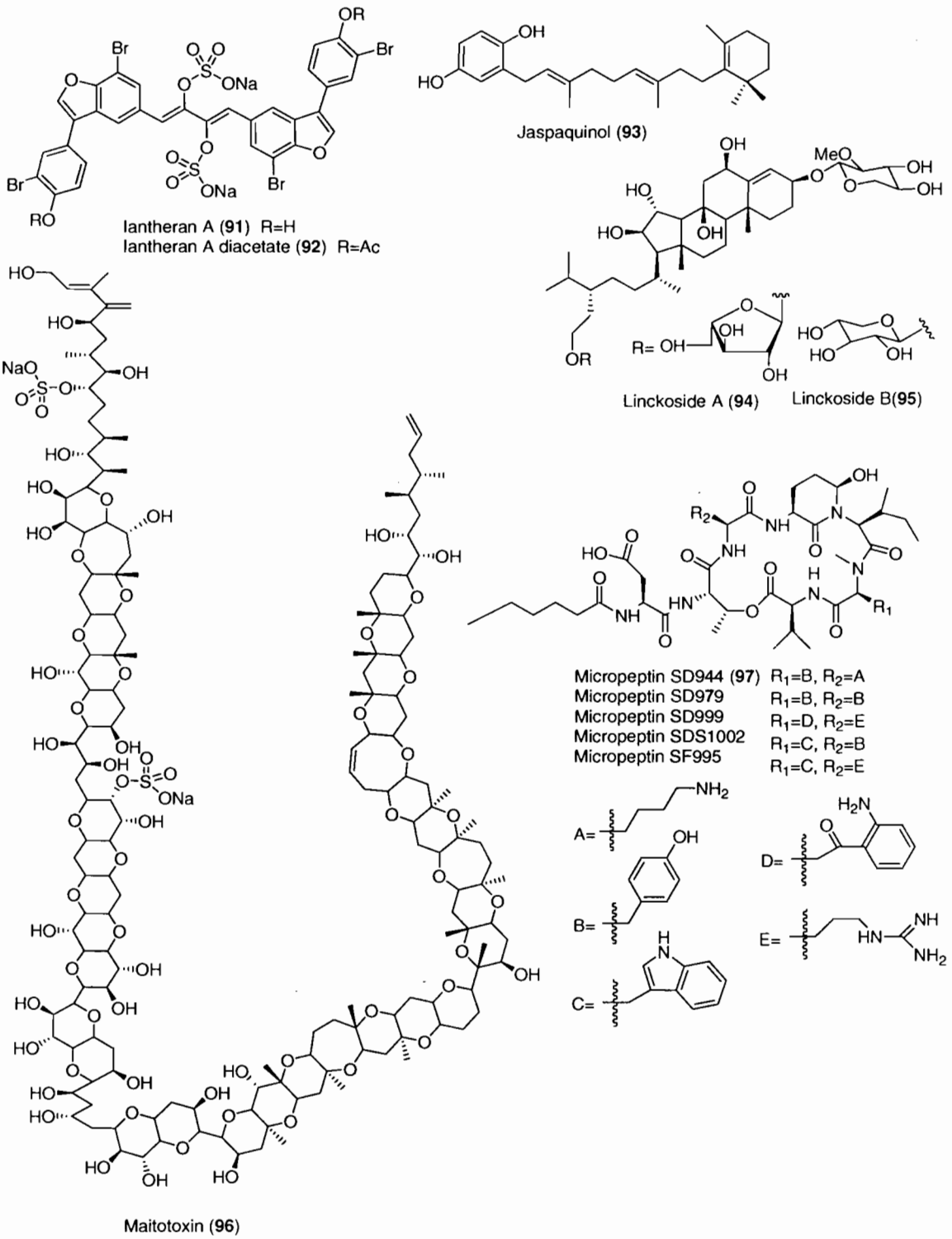


Fig. 3 (*continued*).

jasplakinolide markedly decreased parasitemia of *P. falciparum* by virtue of "*an apical protrusion that appears to interfere with the erythrocyte invasion by the merozoites*" and whose mechanism of formation is possibly related to an increase in F-actin content of the merozoites treated with this marine agent. Wright et al. (2002) reported an extensive study on two novel alkaloids, *lepadins E* (40) and *F* (41) isolated from a tropical marine tunicate *Didemnum* sp., which showed significant antiplasmodial activity. Interestingly, the bioactivity of the two molecules against two *P. falciparum* strains (strain K1: IC_{50}=0.4 and 0.2 μg/mL, respectively; strain NF5: IC_{50}=0.9 and 0.3 μg/

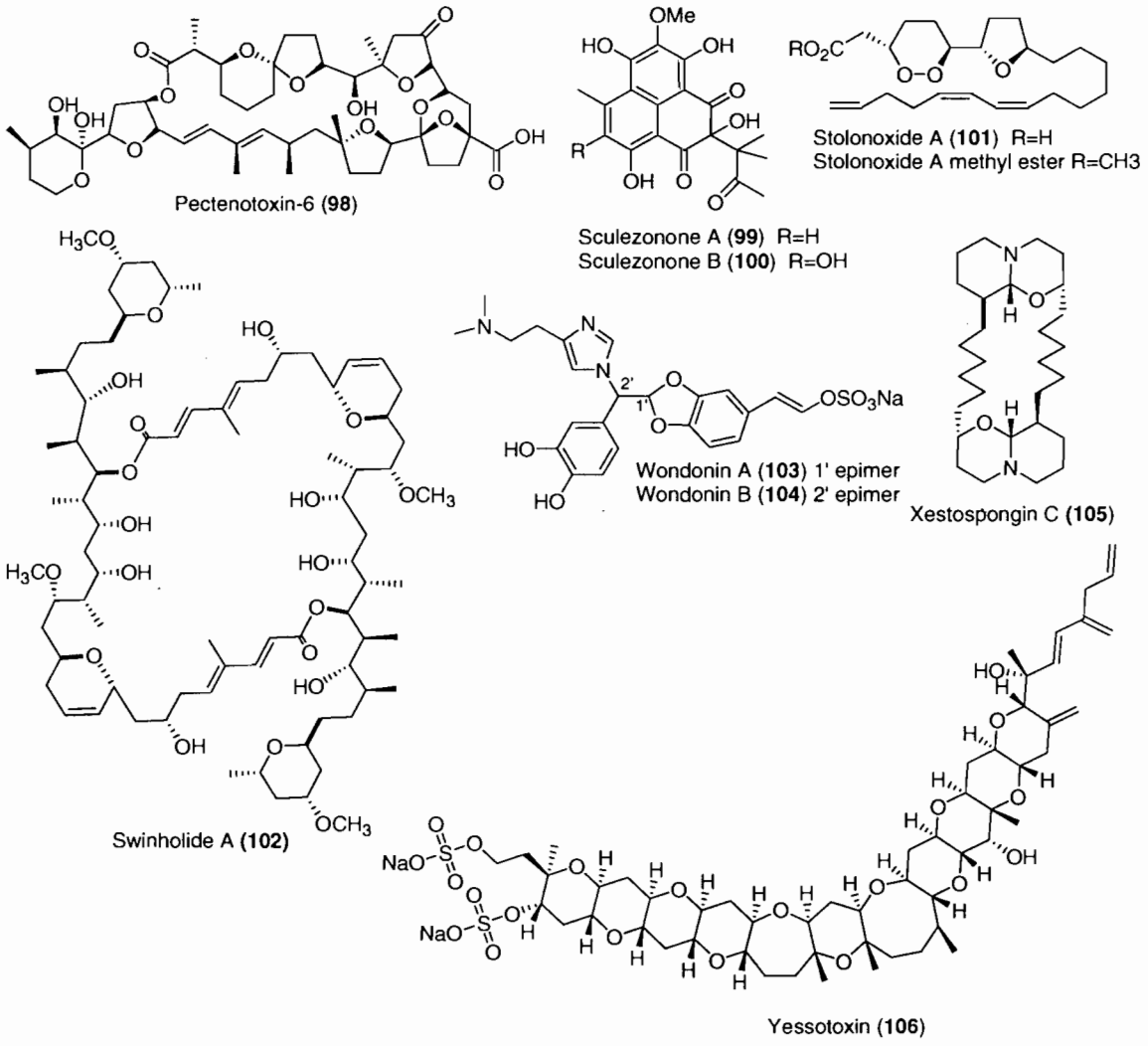


Fig. 3 (*continued*).

mL, respectively) appeared to be dependent on the configuration at C-2 and the nature of the functionality at C-3 in the decahydroquinoline, as well as the moderate inhibition of the $p56^{lck}$ tyrosine kinase. A peroxide-containing metabolite, *plakortide F* (42) was isolated from the Jamaican sponge *Plakortis* sp. (Gochfeld and Hamann, 2001). The fact that plakortide F had significant in vitro activity against *P. falciparum* (D6 and W2 clones: IC_{50}=0.48 and 0.39 μg/mL, respectively) suggested that the peroxide is necessary for antimalarial activity of this compound.

Perry et al. (2001) contributed to *antiprotozoal* pharmacology by reporting the isolation of *plakortolide G* (43), a new peroxylactone from the Jamaican sponge *Plakinastrella onkodes*. Plakortolide G at 10 μM exhibited 100% inhibition of infection by the obligate intracellular parasite *Toxoplasma gondii*, the cause of toxoplasmosis and concomitant serious pathology, including hepatitis, pneumonia, blindness, and severe neurological disorders that is especially true in individuals whose immune systems are compromised (e.g., AIDS patients).

Three novel compounds were contributed to the search for novel *antituberculosis* agents. A new bioactive diterpene, *cyanthiwigin C* (44), was isolated from the Jamaican sponge *Myrmekioderma styx* (Peng et al., 2002). At 6.25 μg/mL, cyanthiwigin C inhibited the growth of *M. tuberculosis* by 50%. Two new serrulatane diterpenes, *erogorgiaene* (45) and *7-hydroxyerogorgiaene* (46), inhibited *M. tuberculosis* growth by 96% and 77% at a concentration of 12.5 and 6.25 μg/mL, respectively (Rodriguez and Ramirez, 2001).

Bunc et al. (2002) contributed to the antiplatelet pharmacology of the water soluble polymeric *3-alkylpyridinium salts* (47) isolated from the marine sponge *Raniera sarai*. These salts, previously shown to be cholinesterase inhibitors, appeared to aggregate in vivo inducing formation of "*non-covalently bound supra-molecular structures*", ultimately inducing blood coagulation, platelet aggregation and cytotoxicity in rats.

2.5. Antiviral compounds

As shown in Table 1, interest in the *antiviral* pharmacology of marine natural products remained high during 2001–2002. During this two-year period, six novel marine compounds (Fig. 1) were reported to possess antiviral properties against human immunodeficiency (HIV), herpes simplex (HSV) and influenza viruses. Rudi et al. (2001) reported the isolation of *clathsterol* (48), a novel and active sulfated sterol from the Red Sea sponge *Clathria* sp., which was active against HIV-1 reverse transcriptase at 10 μM. An HIV-inhibitory cyclic depsipeptide, *microspinosamide* (49) was isolated from the marine sponge *Sidonops microspinosa* (Rashid et al., 2001). Microspinosamide inhibited the cytopathic effect of HIV-1 infection in a cell-based in vitro assay with an EC_{50} of 0.2 μg/mL. Loya et al. (2002) reported an extensive study on the mechanism of action of *polyacetylenetriol* (50), isolated from the marine sponge *Petrosia* sp. Polyacetylenetriol evidenced selective inhibition of the RNA- and DNA-dependent DNA polymerase activities of retroviral reverse transcriptases (IC_{50}=0.95 μM), as compared to cellular DNA polymerases (IC_{50}=2.6 μM). Furthermore, a reversible non-competitive mechanism involving a putative hydrophobic interaction was shown to play a critical role in the inhibition of the HIV-1 reverse transcriptase enzyme. Although polyacetylenetriol lacked sufficient specificity and thus could probably not be used as an anti-HIV agent, the authors concluded that "*...structural modification of the side chains of the lead polyacetylenic molecule may produce new potent and selective anti-AIDS drugs*". As a result of an ongoing program focused on the discovery of new "*small molecule*" inhibitors of HIV-1 integrase, Rowley et al. (2002) reported on the discovery of the sulfated-flavone glycosides, *thalassiolins A–C* (51, 52, and 53), isolated from the Caribbean sea grass *Thalassia testudinum*. Thalassiolin A, the most active compound of this series, inhibited HIV integrase catalyzed strand transfer (IC_{50}=0.4 μM) as well as HIV replication in cell culture (IC_{50}=30 μM). Interestingly, the presence of sulfated β-D-glucose functionality increased potency against the HIV integrase, while molecular modeling studies indicated that the probable binding site of the molecule was the catalytic core domain of the HIV-1 integrase.

As part of their search for novel influenza virus neuraminidase inhibitors, Nakao et al. (2001) reported three active sulfated *calyceramides A–C* (54, 55, and 56) isolated from the marine sponge *Discodermia calyx*. Interestingly, calyceramides A–C inhibited neuraminidase from bacterium *Clostridium perfringens* with IC_{50} values of 0.4, 0.2 and 0.8 μg/mL, respectively, which was slightly more potent than 4-acetyl neuraminic acid (IC_{50}=1.5 mg/mL). It remains to be determined if these compounds will also inhibit influenza virus neuraminidase with similar potency.

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

Table 2 summarizes preclinical pharmacological research completed during 2001–2002 with the 19 marine chemicals shown in Fig. 2.

3.1. Anti-inflammatory compounds

The *anti-inflammatory* pharmacology of the marine compounds *halipeptins A* and *B*, *hymenamide C*, *petrosaspongiolide* and *scytonemin* was reported during 2001–2002, a slight decrease from our previous report (Mayer and Hamann, 2004).

Two anti-inflammatory 17-membered cyclic depsipeptides, *halipeptins A* and *B* (57 and 58) were isolated from the marine sponge *Haliclona* sp. (Randazzo et al., 2001). Halipeptin A at 300 μg/kg potently and dose-dependently inhibited carrageenan-induced paw edema in a mouse model of inflammation. Although no mechanism of action study was reported, interestingly, indomethacin and naproxen showed an ED_{50} of 12 and 40 mg/kg, respectively, in the same in vivo assay, thus suggesting that halipeptin A was "*40 and 130 times more potent*" than these clinically used non-steroidal anti-inflammatory agents. The immunomodulating activity of the marine cyclopeptide *hymenamide C* (59), isolated from the marine sponge *Axinella carteri*, was explored investigating its effects on neutrophils and macrophages (Napolitano et al., 2001). Although hymenamide C inhibition of human neutrophil degranulation (IC_{50}=18 μM) was not particularly impressive, the authors noted that cyclosporine, a clinically used immunosuppressive cyclopeptide, exerted "*weaker inhibitory effect on elastase release*". A structure–activity relationship study completed with this cyclopeptide concluded a "*non-receptorial mode of action*" for hymenamide C and its synthetic analogs (Napolitano et al., 2002). Dal Piaz et al. (2002) reported an extensive investigation of the mechanism of phospholipase A_2 (PLA_2) inactivation by the novel marine sesterterpene *petrosaspongiolide M* (60), a bioactive sesterterpene isolated from the marine sponge *Petrosaspongia nigra*. The reported results suggest that the PLA_2 α-amino terminal group of the *IIe-1* residue is the only covalent binding site for petrosaspongiolide M, a compound that inhibits bee venom PLA_2 with an IC_{50}=0.6 μM. Stevenson et al. (2002a,b) extended the pharmacology of *scytonemin* (61), a yellow-pigment isolated from marine cyanobacteria which demonstrated interesting anti-inflammatory and anti-proliferative activities. In vitro, scytonemin inhibited both polo-like kinase 1 (IC_{50}=2.3 μM) and protein kinase C β1 (IC_{50}=5.4 μM), while in vivo, topical application of this novel pharmacophore reduced phorbol-ester induced mouse ear edema (IC_{50}=10.9 μg/ear).

3.2. Antidiabetic and cardiovascular compounds

Only 3 reports during 2001–2002 contributed to the *antidiabetic* and *cardiovascular* pharmacology of marine natural products.

Anderson et al. (2002) reported the purification, characterization and biological activity of *insulins* (62) from the European spotted dogfish, *Scyliorhinus canalicula*, and the hammerhead shark, *Sphyrna lewini*. Although the elasmobranch insulins were noted to be markedly different from human insulin, with 17 amino acid substitutions identified, all residues that are required for binding to the recombinant human insulin receptor were shown to be conserved. The bolus arterial injection of dogfish insulin caused a significant drop in blood glucose only after 12 h but it persisted for 48 h, indicating metabolic actions similar to those "*described for mammalian insulin*".

Contributions to the *cardiovascular* pharmacology of the marine natural products *2,5,6-tribromo-1-methylgramine* (*TBG*) and *lepadiformine* were reported during 2001–2002. Iwata et al. (2001) extended the pharmacology of *2,5,6-tribromo-1-methylgramine* (*TBG*) (63), a compound isolated from the marine bryozoan *Zoobotryon pellucidum*, by examining its effect on the contraction of the rat aorta. Interestingly, while at concentrations up to 10 μM the halogen-containing gramine analogue inhibited muscle contraction by affecting Ca^{2+} entry, at 30 μM the inhibitory mechanism involved an increase in intracellular cyclic AMP. Juge et al. (2001) investigated the cardiovascular effects of *lepadiformine* (64), an alkaloid isolated from the marine ascidians *Clavelina lepadiformis* and *C. moluccensis*. Using in vivo arterial blood pressure recordings and electrocardiograms in anaesthetised rats and in situ peripheral vascular pressure recordings in perfused rabbit ear, they observed that lepadiformine had marked effects on the cardiocirculatory system, inducing bradycardia, prolonging electrocardiogram parameters, producing a transient fall of blood pressure in the rat and decreasing blood flow in the rabbit ear. The authors concluded that the pharmacological effects of lepadiformine might result from a reduction of the inward rectifying K^+ current, suggesting that this marine compound has "*antiarrhythmic properties*" that warrant further investigation.

3.3. Compounds affecting the immune system

Mayer et al. (2001) extended the pharmacology of the marine excitatory amino acid *domoic acid* (65), a glutamate and kainic acid analog which can cause amnesic shellfish poisoning in humans and is produced by the widely distributed marine diatom genus *Pseudo-nitzschia*. Domoic acid at in vitro concentrations that were toxic to neuronal cells (1 mM) was shown to trigger a limited activation of rat brain microglia, an immune cell type that contributes to circa 10% of the total glial population in the central nervous system, and the concomitant release of two potentially neurotoxic mediators, namely TNF-α and matrix metalloproteinase-9.

3.4. Compounds affecting the nervous system

Reports on both *central* and *autonomic nervous system* pharmacology of marine natural products during 2001–2002 studies involved *antillatoxin B*, *dysiherbaine*, *N-3'-ethylaplysinopsin*, *neodysiherbaine A*, *gangliosides* of *Holothuria leucospilota*, the peptides *conantokins-G* and *L* and *manoalide*.

Bioassay-guided fractionation of organic extracts from the marine cyanobacterium *Lyngbya majuscula* led to the isolation of the neurotoxic lipopeptide *antillatoxin B* (66), an analogue of the potent neurotoxin antillatoxin (Nogle et al., 2001). Although antillatoxin B was a potent activator of voltage-sensitive sodium channel in a mouse neuro-2a neuroblastoma cell line (EC_{50}=1.77 μM), its biological activity was 10-fold less than that of antillatoxin, probably as a result of a substitution of a larger *N*-methyl homophenylalanine residue for an *N*-methyl valine residue in the peptide-derived metabolite. An extensive characterization of the pharmacological properties of the potent epileptogenic amino acid *dysiherbaine* (67), isolated from the marine sponge *Dysidea herbacea* was reported by Sakai et al. (2001b). Dysiherbaine, which demonstrated "*potent convulsant activity*", caused seizures upon injection into mice (ED_{50}=13 pmol/mouse i.c.v) and was shown to be a non-NMDA-type glutamate receptor agonist with high selectivity for kainic acid receptors (IC_{50}=210 nM) as well as mGluR5 receptors. The authors concluded that this novel marine amino acid might be useful for the evaluation of "*physiological and pathological roles of non-NMDA receptors, especially kainic acid receptors, in the central nervous system*". A new indole alkaloid, *N-3'-ethylaplysinopsin* (68), isolated from the Jamaican sponge *Smenospongia aurea*, was shown to potently bind to the human serotonin 5-HT_{2C} receptor subtype expressed in a mammalian cell line (Hu et al., 2002). The authors suggest that the R2 functional groups at position 2′ may play an important role in regulating subtype selective binding to the 5-HT_{2C} receptor, a receptor found in high density in the choroid plexus, the site of cerebrospinal fluid production.

Yamada et al. (2001) reported new *gangliosides* (*HLG-1*, *HLG-2*, and *HLG-3*) (69–71) from the sea cucumber *Holothuria leucospilota* which induced neurite growth outgrowth. Although the molecular mechanism remains unexplored the ganglioside species displayed neuritogenic activity at 10 μM in the presence of nerve growth factor. Dorandeu et al. (2002) presented novel information on potential anticonvulsant pharmacology of the nonsteroidal sesterterpene *manoalide* (72), a well-known phospholipase A_2 inhibitor isolated from the marine sponge *Luffariella variabilis*. Manoalide was reported to fully and irreversibly inhibit the catalytic activity of crotoxin, the heterodimeric β-neurotoxin from the venom of the South American rattlesnake *Crotalus durissus terrificus*, preventing central neurotoxicity after intracerebroventricular injection and peripheral toxicity after intravenous injection. Sakai et al. (2001a)

reported the isolation of a *neodysiherbaine A* (73), a new excitatory amino acid from the sponge *D. herbacea*. Neodysiherbaine A was observed to be a potent epileptogenic amino acid (ED_{50}=15 pmol/mouse i.c.v), comparable to dysiherbaine, and a potent and novel non-NMDA-type glutamate receptor agonist with high selectivity for kainic acid receptors (IC_{50}=66 nM). Two studies extended the pharmacology of the marine *conantokins*, the only natural biochemically characterized peptides known to be *N*-methyl-D-asparate (NMDA) antagonists and potent anticonvulsants. Wittekindt et al. (2001) investigated the binding of *conantokin-G* (74), a peptide derived from the venom of the marine cone snail *Conus geographus*, on recombinant NMDA receptors carrying point mutations within the glycine and glutamate binding pockets of the NR1 and NR2B subunits. Because mutations located in the glutamate binding site of the NR2B subunit were found to significantly affect conantokin-G binding, the investigators concluded that this peptide inhibited the NMDA receptor currents at the "*glutamate binding site via a competitive mechanism*". A new member of the conantokin peptide family, *conantokin-L* (75), was isolated and characterized from a heretofore unexamined species, the marine fish-hunting cone snail *Conus lynceus* (Jimenez et al., 2002). Conantokin-L had extensive sequence identities with conantokin-R and was a potent NMDA receptor antagonist in mammalian CNS neurons in culture. However, conantokin-L was a far less potent anticonvulsant in the audiogenic mouse model of epilepsy, probably as a result of the lack of C-terminal acids. The authors note that the discovery of conantokin-L will definitely contribute to the development of a "*clinically effective and well-tolerated NMDA antagonist that possesses both anticonvulsant and neuroprotective properties*".

4. Marine compounds with miscellaneous mechanisms of action

The structures of marine compounds with miscellaneous mechanisms of action are presented in Fig. 3. Interestingly and in contrast with the 75 chemicals included in Figs. 1 and 2, this third group of 31 marine compounds includes not only nitrogen-containing compounds (i.e. proteins, peptides), terpenes and polyketides but also a few polysaccharides.

As shown in Table 3, for some of these marine natural products, namely *antillatoxin* (77), *azaspiracid-1* (79), *bistratene A* (80), *bryostatin-1* (82), *coscinosulfate* (83), *debromohymenialdisine* (84), *halenaquinol* (88), *halenaquinone* (89), *hectochlorin* (90), *maitotoxin* (96), *pectenotoxin-6* (98), *sculezonone A* and *B* (99 and 100), *scytonemin* (61), *stolonoxides* (101), *xetospongin-C* (105) and *yessotoxin* (106), both the pharmacological activity and molecular mechanism of action were reported.

In contrast, for the marine compounds *aeroplysinin-1* (76), *aplysiallene* (78), *bryoanthrathiophene* (81), *chlorogentisylquinone* (85), *discodermin A* (86), *farnesylhydroquinone* (87), *iantherans A* and *B* (91 and 92), *jaspaquinol* (93), *jasplankinolide* (39), *linckosides A* and *B* (94 and 95), *micropeptins* (97), *swinholide A* (102) and *wondonins A* and *B* (103 and 104), while a pharmacological activity was investigated, no additional information was reported on the molecular mechanism of action.

5. Reviews on marine pharmacology

Several reviews covering selected aspects of marine pharmacology and toxicology were published during 2001–2002: the chemistry and biological function of natural marine toxins (Yasumoto, 2001); a retrospective on the conotoxins (Olivera and Cruz, 2001); α-conotoxins as pharmacological tools and potential drug leads (Dutton and Craik, 2001); ciguatera fish poisoning (Hokama and Yoshikawa-Ebesu, 2001); toxic marine microalgae (Daranas et al., 2001); advances in chemical and biological research with marine indoles and carbazole alkaloids (Pindur and Lemster, 2001); biologically active marine proteins (O'Keefe, 2001); bioactive marine compounds from coral reef invertebrates (Higa et al., 2001); glycolipids with immunomodulating activity from marine sponges (Costantino et al., 2001); marine lipids and coronary heart disease (Colquhoun, 2001); anticoagulant properties of sulfated glycosaminoglycans (Pavao, 2002); sea-anemone pore-forming proteins and their pharmacological and medical use (Anderluh and Menestrina, 2001); cytolytic peptide and protein toxins from sea anemones (Anderluh and Macek, 2002); okadaic acid as the archetypal serine/threonine protein phosphatase inhibitor (Dounay and Forsyth, 2002) and useful tool for studying cellular processes (Fernandez et al., 2002); marine microorganisms for the production of bioactive metabolites (Wagner-Dobler et al., 2002); cyanobacterial toxins and their implications for human health (Rao et al., 2002); the pharmacological activity of fish venoms (Church and Hodgson, 2002); and the chemistry of marine natural products (Faulkner, 2001; Faulkner, 2002).

6. Conclusion

Although during 2001–2002 no new marine natural product was approved for patient care by the U.S. Food and Drug Administration, the present review documents the fact that during 2001–2002 preclinical pharmacological research with marine chemicals continued to proceed at a very active pace, involving both natural product chemists and pharmacologists from 29 countries including the United States. Although this review has mainly focused on recent developments in the preclinical pharmacology of 106 marine natural products, the reader should be aware that concomitant to the mechanistic characterization of marine natural products, the issues of supply, formulation, and manufacturing represent important challenges that need to be met for the successful

development of novel pharmaceutical agents. These issues were approached in 2002 by three companies involved in the development of novel pharmaceuticals from marine sources (Fenical et al., 2002; Garcia-Fernandez et al., 2002; Mayer, 2002; Sennett et al., 2002).

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