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Review

Marine pharmacology in 1999: compounds with antibacterial, anticoagulant, antifungal, anthelmintic, anti-inflammatory, antiplatelet, antiprotozoal and antiviral activities affecting the cardiovascular, endocrine, immune and nervous systems, and other miscellaneous mechanisms of action

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Abstract

This review, a sequel to the 1998 review, classifies 63 peer-reviewed articles on the basis of the reported preclinical pharmacological properties of marine chemicals derived from a diverse group of marine animals, algae, fungi and bacteria. In all, 21 marine chemicals demonstrated anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antituberculosis or antiviral activities. An additional 23 compounds had significant effects on the cardiovascular, sympathomimetic or the nervous system, as well as possessed anti-inflammatory, immunosuppressant or fibrinolytic effects. Finally, 22 marine compounds were reported to act on a variety of molecular targets, and thus could potentially contribute to several pharmacological classes. Thus, during 1999 pharmacological research with marine chemicals continued to contribute potentially novel chemical leads in the ongoing global search for therapeutic agents for the treatment of multiple disease categories.

Keywords: Marine; Pharmacology; 1999; Toxicology; Review; Secondary metabolites

1. Introduction

The purpose of this article is to review the 1999 primary literature on pharmacological and toxicological studies with marine natural products using a similar format to that used in our 1998 review (Mayer and Lehmann, 2000). The 1999 review corresponding to marine-derived compounds with antitumor and cytotoxic activity has recently been published (Mayer and Lehmann, 2001). Consistent with our 1998 review, only those articles reporting on the bioactivity and/or pharmacology of marine chemicals for which structures have been established are included in the present review. We have used the chemical classification of Schmitz et al. (1999) 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, antituberculosis or antiviral properties of marine chemicals are tabulated in Table 1 and the corresponding structures are shown in

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Fig. 1. The articles reporting on marine compounds affecting the cardiovascular, sympathomimetic and nervous systems, as well as those with anti-inflammatory, immunosuppressant and fibrinolytic effects, are grouped in Table 2 and the structures presented in Fig. 2.. Finally, marine compounds targeting a number of distinct cellular and molecular targets and mechanisms are shown in Table 3 and their structures are presented in Fig. 3. Although publications on the biological and/or pharmacological activity of marine extracts or as yet structurally uncharacterized marine compounds have not been included in the present review, several interesting reports appeared during 1999 (Berge et al., 1999; Cancre et al., 1999; Choi et al., 1999; Christophersen et al., 1999; Conquer et al., 1999; Fabregas et al., 1999; Horikawa et al., 1999; Matsuda et al., 1999; Siddhanta et al., 1999).

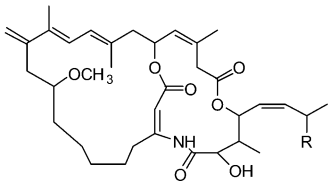
2. Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antituberculosis and antiviral activities

Table 1 summarizes 21 publications that reported on preclinical anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antituberculosis, and antiviral pharmacology of the 21 marine compounds shown in Fig. 1.

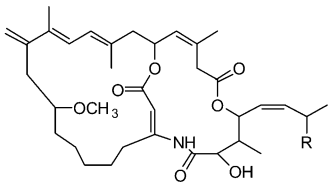
Two studies published during 1999 with the marine natural products amphilactams A–S and geodin A contributed to anthelmintic pharmacology. Four novel amphilactams, macrocyclic lactone/lactams isolated from the sponge *Amphimedon* spp. showed in vitro LD_{99} activity in the range 0.30–7.5 μg/ml (Ovenden et al., 1999). These investigators noted that the level of in vitro activity for amphilactams A, C and D was comparable to that of existing commercial anthelmintics, such as levamisole and closantel, but the mechanism of action of these compounds was not determined. A new macrocyclic polyketide lactam tetramic acid, geodin A Mg salt, was isolated from the sponge *Geodia* sp. (Capon et al., 1999). Although the mechanism of action of the pure Geodin A was not explored, this marine compound, which occurs naturally as the Mg salt, was nematocidal to the nematode *Haemonchus contortus* ($LD_{99}=1$ μg/ml).

Studies with loloatins A–D, myticin and psammaplin A contributed to the antibacterial pharmacology of marine natural products. The loloatins A–D, a family of new cyclic decapeptides isolated from a tropical marine bacterium, exhibited in vitro antimicrobial activity against methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and penicillin-resistant *Streptococcus pneumoniae* (Gerard et al., 1999). Although the molecular mechanism of action was not fully investigated, the authors suggested that their findings were an important contribution to the current search for novel drugs needed in the treatment of antibiotic-resistant strains of human bacterial pathogens. Two isoforms of a cysteine-rich antibacterial peptide myticin, isolated from hemocytes and plasma of the mussel *Mytilus galloprovincialis*, were characterized (Mitta et al., 1999). Although myticins A and B had marked activity against the Gram-positive strains *Micrococcus luteus*, *Bacillus megaterium* and *Enterococcus viridans*, other Gram-positive, Gram-negative bacteria and fungi were unaffected. Kim et al. (1999) reported that psammaplin A, a bromotyrosine derivative from the sponge *Psammaplysilla* sp. possessed antibacterial activity against methicillin-resistant Gram-positive *Staphylococcus aureus* that was ''…almost comparable to ciprofloxacin…'', a quinolone antibiotic currently used in the US. Furthermore, extensive mechanism-of-action studies completed by these investigators determined that psammaplin A did not bind to penicillin-binding proteins, but did inhibit DNA synthesis of *S. aureus* SG511 in a dose-dependent manner ($IC_{50}=2.83$ μg/ml), and inhibited the supercoiling activity of DNA gyrase, similar to the quinolones, although less efficiently than ciprofloxacin (Kim et al., 1999).

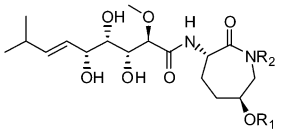
A detailed investigation on the anticoagulant pharmacology of algal and echinoderm marine sulfated furans and sulfated polysaccharides was reported during 1999. Pereira et al. (1999) investigated the possible correlation between structure and anticoagulant activity of echinoderm-derived and brown algae-derived fucans, noting that, while the highly branched sulfated fucans from brown algae directly inhibited thrombin, the linear fucans from echinoderms required the presence of antithrombin or heparin cofactor II for inhibition of thrombin, a molecular mechanism also observed with mammalian glycosaminoglycans (Pereira et al., 1999). These investigators support the use of structural analysis of sulfated polysaccharides from algae and echinoderms and their testing on specific biological assays as an important biochemical



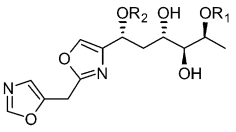
Amphilactam A R=H
Amphilactam B R=CH_3



Amphilactam C R=H
Amphilactam D R=CH_3

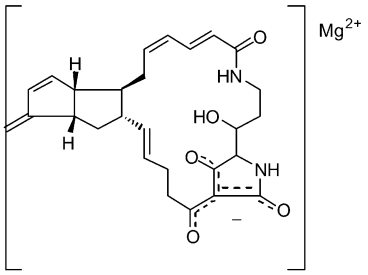


	R_1	R_2
Bengamide A	$CO(CH_2)_{12}CH_3$	H
Bengamide B	$CO(CH_2)_{12}CH_3$	Me
Bengamide E	H	H
Bengamide F	H	Me
Bengamide L	$CO(CH_2)_{11}CH(CH_3)_2$	H

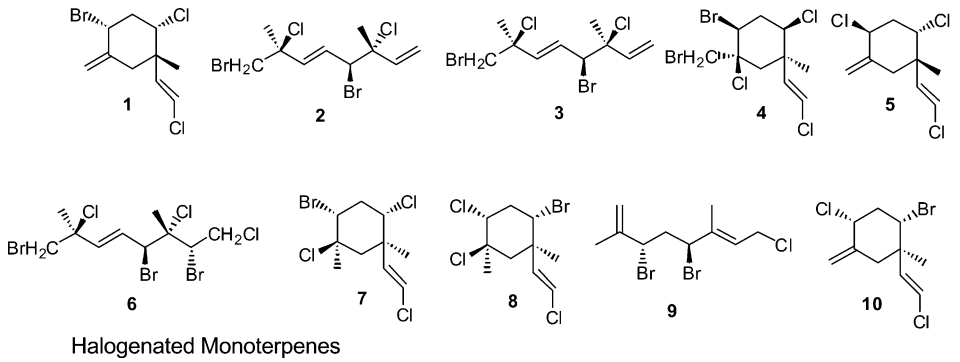


Bengazole

	R_1	R_2
1	$CO(CH_2)_{14}CH_3$	H
2	H	$CO(CH_2)_{14}CH_3$
3	$CO(CH_2)_{12}CH(CH_3)_2$	H
4	H	$CO(CH_2)_{12}CH(CH_3)_2$
5	$CO(CH_2)_{13}CH_3$	H
6	H	$CO(CH_2)_{13}CH_3$
7	$CO(CH_2)_{11}CH(CH_3)_2$	H
8	H	$CO(CH_2)_{11}CH(CH_3)_2$
9	$CO(CH_2)_{12}CH_3$	H
10	H	$CO(CH_2)_{12}CH_3$
11	H	H



Geodin A Mg salt



Halogenated Monoterpenes

Fig. 1. Marine pharmacology in 1999: compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antiplatelet, antimalarial, antituberculosis and antiviral activities.

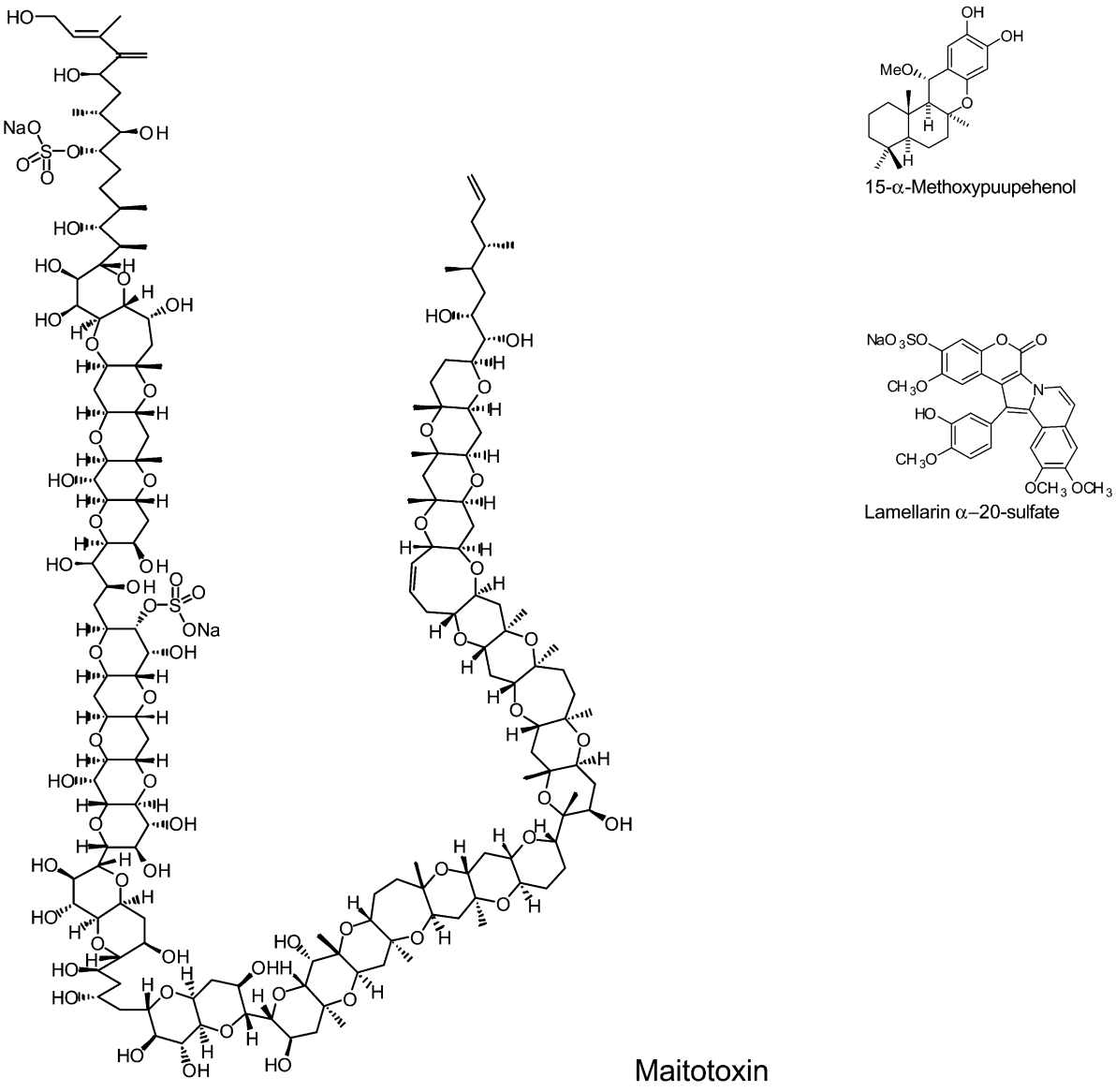
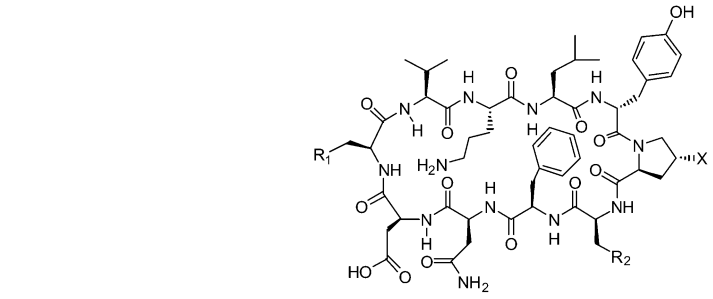


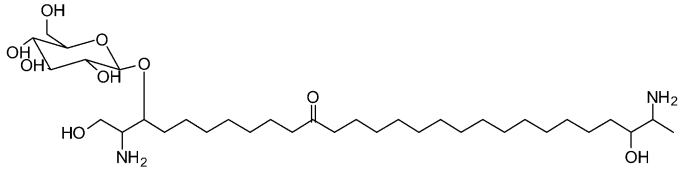
Fig. 1. (Continued).

approach to investigate molecular mechanisms of anticoagulant activity in mammalian systems.

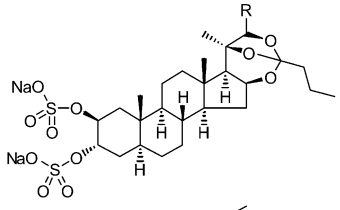
Five studies with the marine chemicals bengamide and bengazole derivatives, oceanapiside, spongistatin 1, tanikolide, and theopederins F–J resulted in novel contributions to antifungal pharmacology. Six new bengazole derivatives and a new bengamide L were reported from the sponge *Pachastrissa* sp. (Fernandez et al., 1999). Although no mechanism-of-action studies were completed, the bengazole derivatives were observed to be active against *Candida albicans* [minimum inhibitory concentration (MIC) 0.8–1.5 μg/ml]. Oceanapiside, a new glycosidic/amino alcohol lipid from the sponge *Oceanapia phillipensis*, demonstrated antifungal activity against the fluconazole-resistant yeast *Candida glabrata* (MIC 10 μg/ml) (Nicholas et al., 1999). Although additional mechanism-of-action studies remain to be completed with oceanapiside, these investigators noted that the aglycon exerted higher antifungal activity than the glycoside, possibly due to better cell penetration. In perhaps the most noteworthy study with a marine broad-spectrum anti-



	R_1	R_2	X
Loloatin A	–OH		H
Loloatin B			H
Loloatin C			H
Loloatin D			OH



Oceanapiside

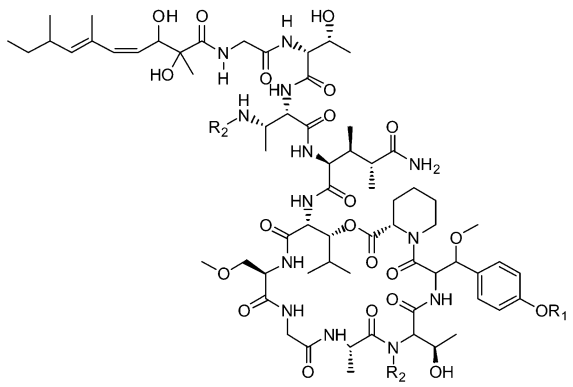


Orthosterol A R=

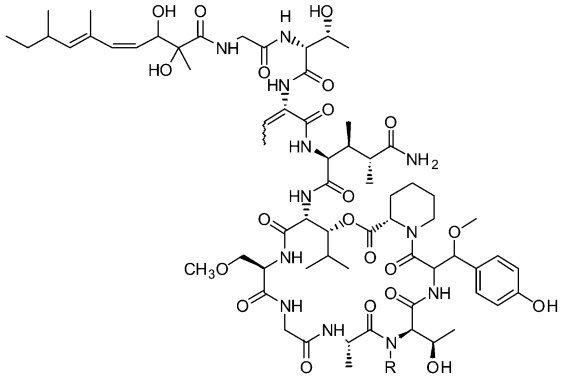
Orthosterol B R=

Orthosterol C R=

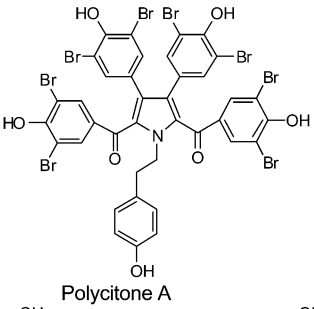
Fig. 1. (Continued).



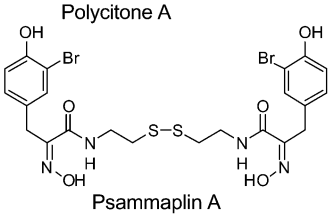
Papuamide A $R_1=R_2=H$; $R_3=CH_3$
Papuamide B $R_1=R_2=R_3=H$



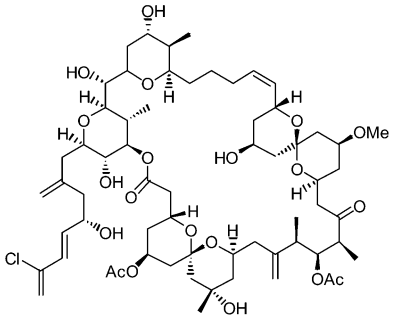
Papuamides C R=Me
Papuamides D R=H



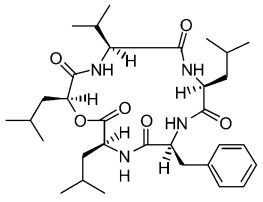
Polycitone A



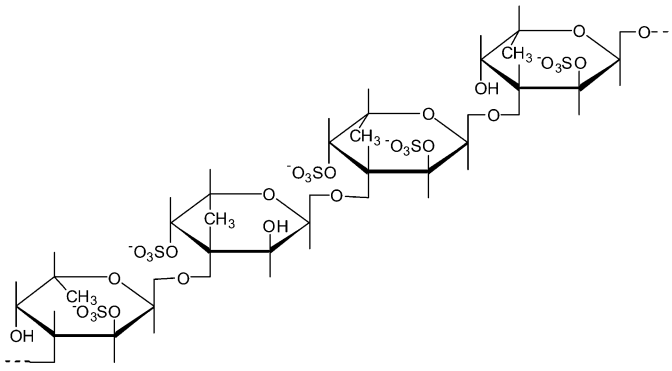
Psammaplin A



Spongistatin 1

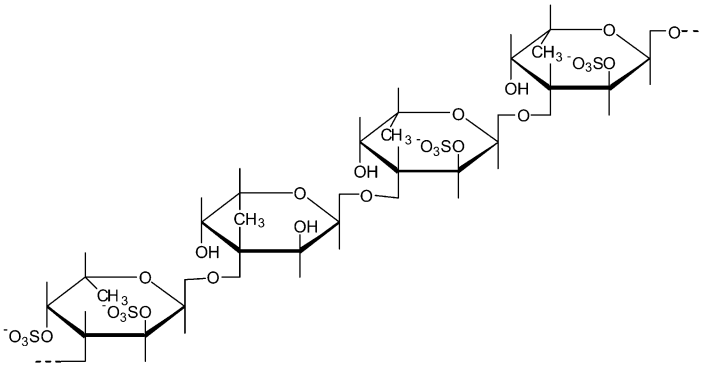


Sansalvamide

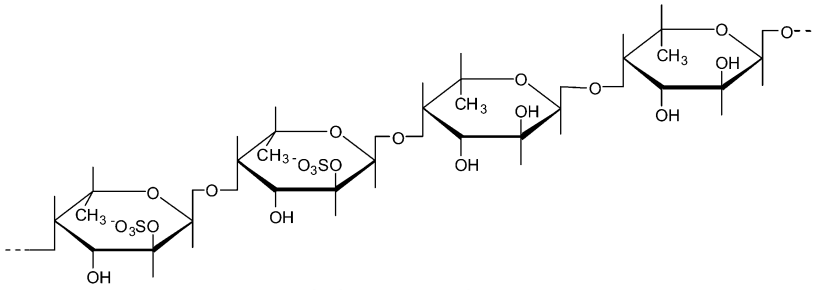


Sulfated L-Fucan from *L. variegates*

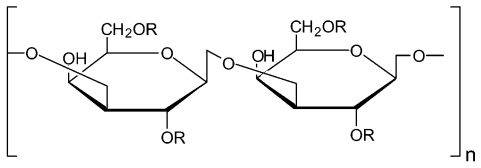
Fig. 1. (Continued).



Sulfated L-Fucan from the sea cucumber *L. grisea*

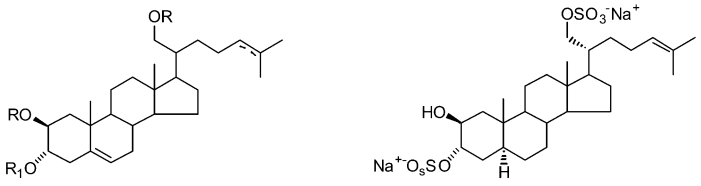


Sulfated L-Fucan from *A. lixula*



R=H or SO_3^-

Sulfated glactan



Sulphated polyhydroxysteroids and semisynthetic derivatives

1 R=$SO_3^-Na^+$; R_1=H, Δ^{24} **3**

1a R=$SO_3^-Na^+$; R_1=Ac, Δ^{24}

1b R= R_1=H, Δ^{24}

2 R=$SO_3^-Na^+$; R_1=H

Fig. 1. (Continued).

fungal compound, Ovechkina et al. (1999) demonstrated potent microtubule-severing activity with spongistatin 1, a macrocyclic lactone isolated from the sponge *Hyrtios erecta*. This appears to be an interesting observation because, if confirmed in future studies, the mechanism of action of

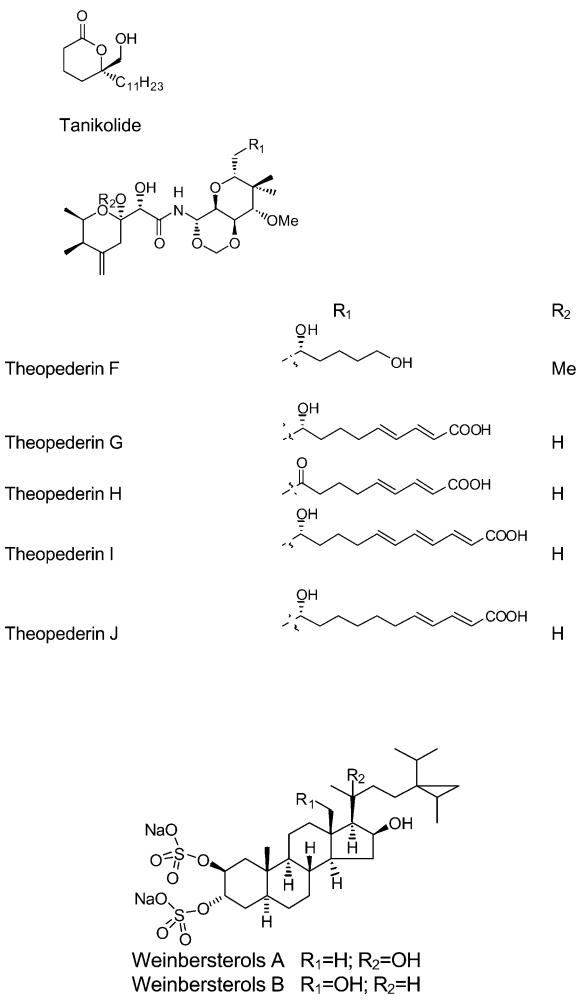
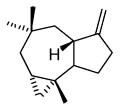


Fig. 1. (Continued).

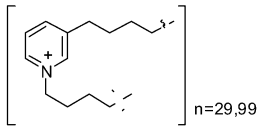
Spongistatin 1 would significantly differ from all other antimicrotubule agents studied to date. A new brine-shrimp toxic and antifungal lactone, tanikolide, was isolated from the marine cyanobacterium *Lyngbia majuscula* (Singh et al., 1999). Although the researchers observed a 13-mm-diameter zone of inhibition (100 μg/disk) when testing the effect of tanikolide on the fungus *Candida albicans*, further mechanistic research is necessary to determine if the toxicity of this compound might perhaps be responsible for the antifungal activity observed. Tsukamoto et al. (1999) isolated five new bioactive metabolites, theopederins F–J, from the sponge *Theonella swinhoei*. Although theopederin F was particularly effective against *Saccharomyces cerevisiae* at 1 μg/disk, no mechanistic studies were reported.

During 1999, three separate studies were reported in the area of antimalarial, antiplatelet and antituberculosis pharmacology of structurally characterized marine natural products. Although no mechanism-of-action studies were reported, the sesquiterpene 15-α-methoxypuupehenol isolated from the New Caledonian marine sponge *Hyrtios* sp. demonstrated antimalarial activity against chloroquine-susceptible and chloroquine-resistant strains of *Plasmodium falciparum* (IC_{50} = 0.4–1.4 μg/ml) (Bourguet-Kondracki et al., 1999). Detailed studies on the mechanism of platelet activation by the polyether maitotoxin, a Ca^{2+} channel-activating marine toxin causing ciguatera poisoning, were completed by Nakahata et al. (1999a). These researchers observed that the mechanism of action of maitotoxin was similar to U46619, a thromboxane A_2 receptor agonist. However, the effects of maitotoxin on Ca^{2+} mobilization, phosphoinositide hydrolysis and tyrosine phosphorylation in platelets were *strictly* dependent on the presence of external Ca^{2+}, an observation that could explain maitotoxin toxicity to platelets in vivo. In a bioactivity study with several polyhalogenated monoterpenes isolated from the tropical marine red alga *Plocamium hamatum*, Konig et al. (1999) observed that one of them was antitubercular towards *Mycobacterium tuberculosis* (MIC 32 μg/ml) and *Mycobacterium avium* (MIC 64 μg/ml).

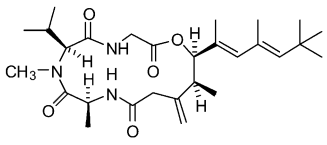
Interest in the antiviral pharmacology of marine natural products remained high during 1999, as evidenced by the seven papers published, a number similar to that reported in our 1998 review (Mayer and Lehmann, 2000). During the screening of diverse marine natural products for compounds against human immunodeficiency virus (HIV-1) integrase, one of the three enzymes encoded by the HIV virus, Reddy et al. (1999b) identified the alkaloid lamellarin α 20-sulfate in an unidentified ascidian that showed selective in vitro inhibition. The detailed mechanistic studies completed with lamellarin α 20-sulfate led these investigators to propose that their findings provided a new class of lead compounds for the potential development of clinically useful integrase inhibitors. Novel cyclic depsipeptides papuamides A, B, C and D were isolated from the sponges *Theonella mirabilis* and *Theonella swinhoei* (Ford et al., 1999). Papuamides A and B inhibited the infection of human T-lymphoblastoid cells by HIV-1 in vitro (EC_{50} = 3.6 ng/ml), a particularly interesting finding,



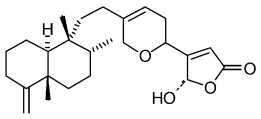
Africanene



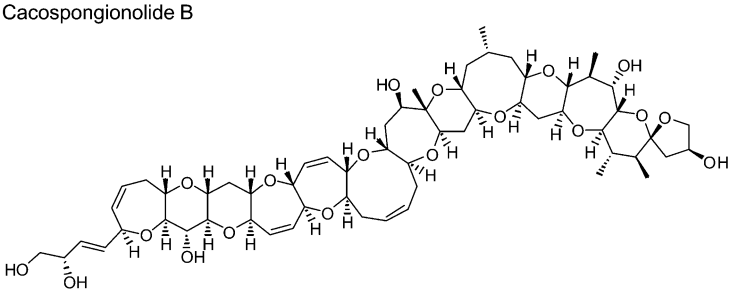
3-Alkylpridinium polymers n head-to-tail linked N-butyl-3-butyl pyridinium units



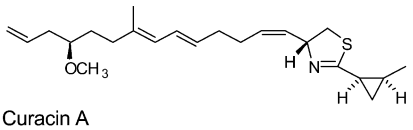
Antillatoxin



Cacospongionolide B



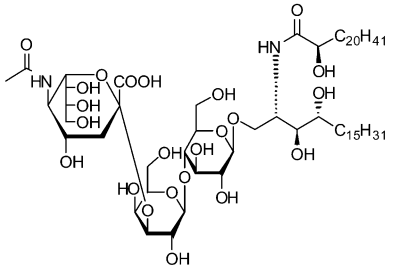
Ciguatoxin



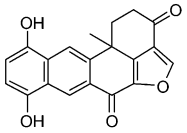
Curacin A

Fig. 2. Marine pharmacology in 1999: compounds with anti-inflammatory, immunosuppressant and fibrinolytic effects and affecting the cardiovascular, simpathomimetic and nervous systems.

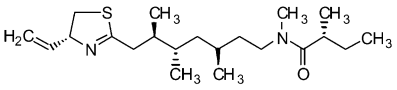
because this is the first report of peptides from the sponge *Theonella* that inhibit HIV. However, the mechanism of action of papuamides A and B was not studied. An extensive report detailed new mechanism-of-action studies with polycitone A, an aromatic alkaloid isolated from the ascidian *Polyc-*



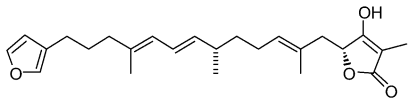
Glycosphingolipids



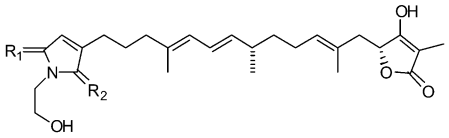
Halenaquinol



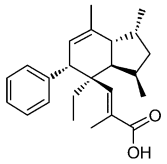
Kalkitoxin



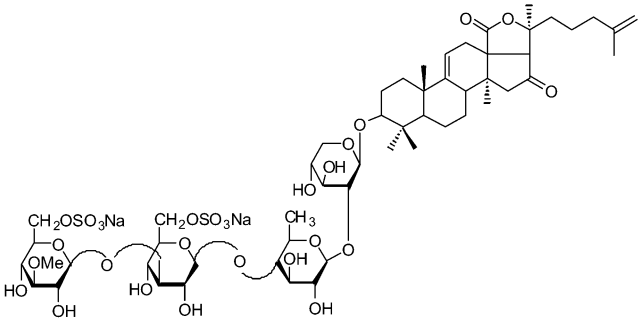
Palinurin



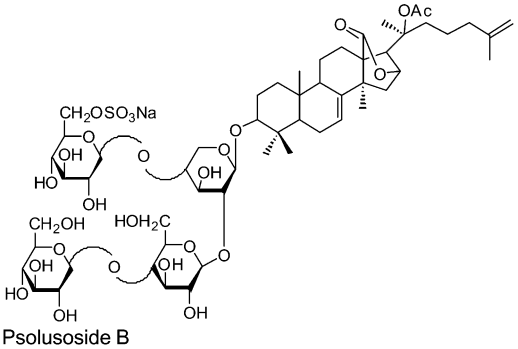
	R_1	R_2
Palinurine A	H_2	O
Palinurine B	O	H_2



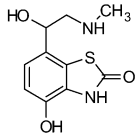
Plakotenin



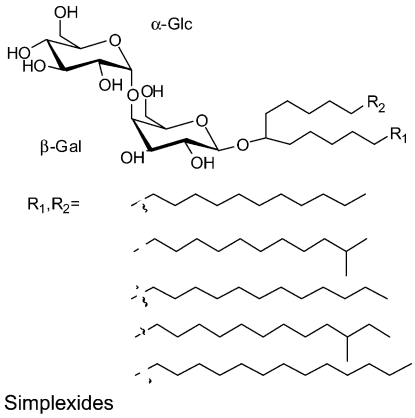
Psolusoside A



Psolusoside B

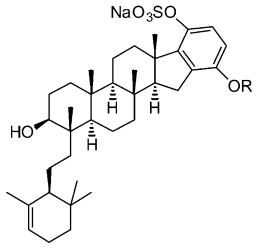


S1319

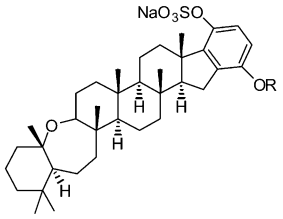


Simplexides

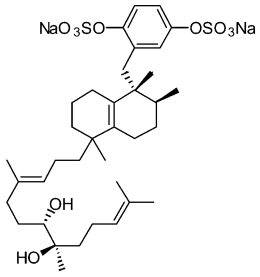
Fig. 2. (Continued).



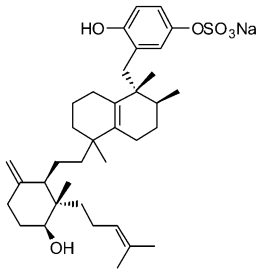
Adociasulfate **1** R = SO_3Na
Adociasulfate **5** R = H



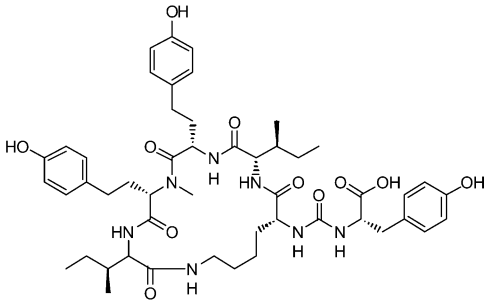
Adociasulfate **2** R = SO_3Na
Adociasulfate **6** R = H



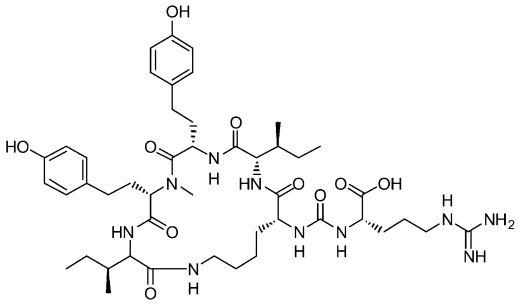
Adociasulfate **3**



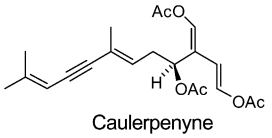
Adociasulfate **4**



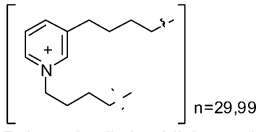
Anabaenopeptins G



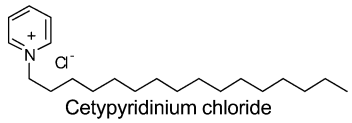
Anabaenopeptins H



Caulerpenyne

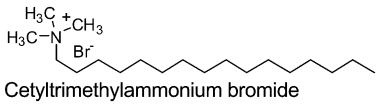


Polymeric alkylpyridinium salts

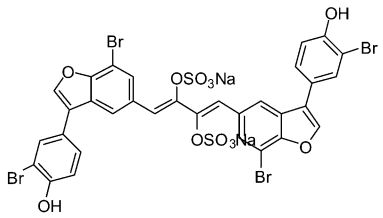


Cetypyridinium chloride

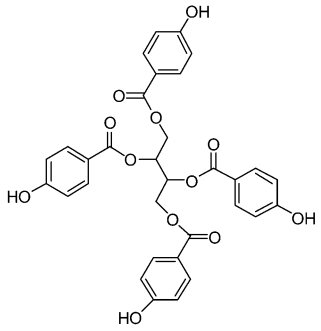
Fig. 3. Marine pharmacology in 1999: compounds with miscellaneous mechanisms of action.



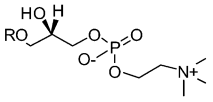
Cetyltrimethylammonium bromide



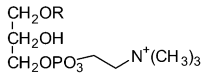
Iantheran A



Kelletinin I

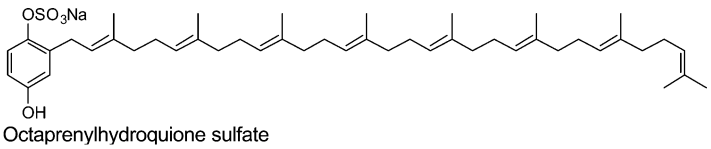


Lyso-PAF Analogues



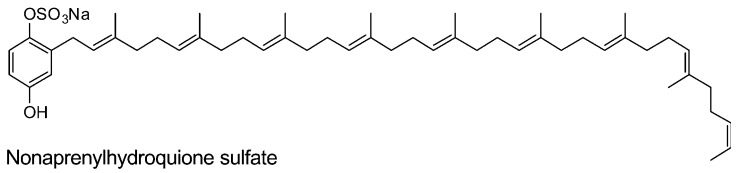
Lysophosphatidylcholines

R =
1 =
2 =
3 =
4 =
5 =
6 =
7 =

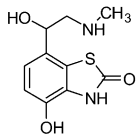


Octaprenylhydroquione sulfate

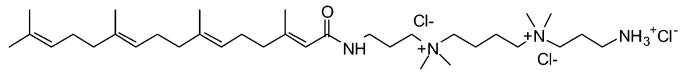
Fig. 3. (Continued).



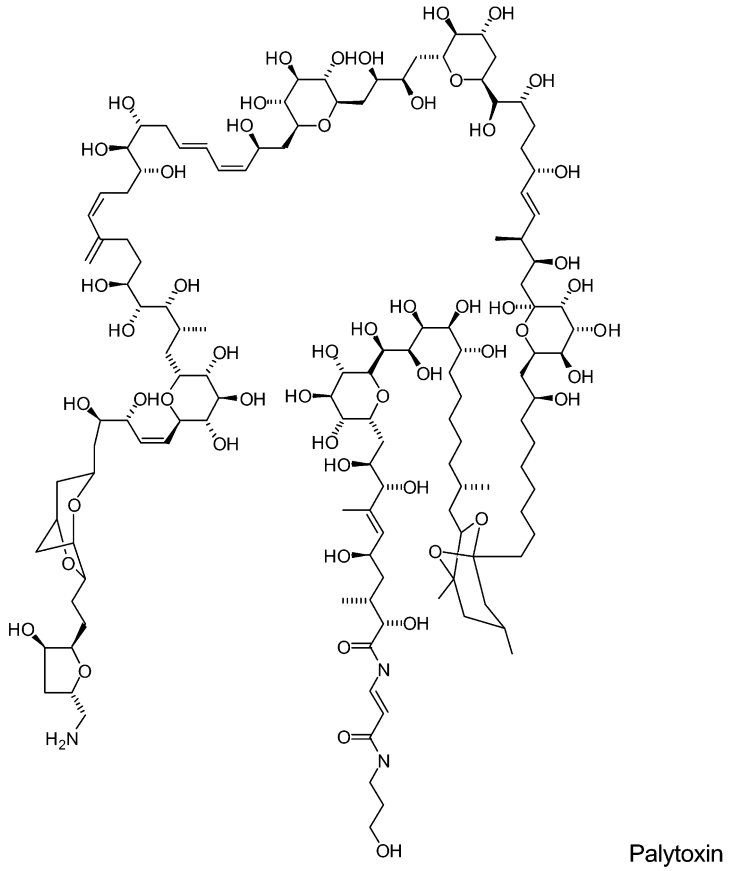
Nonaprenylhydroquione sulfate



S1319



Sinulamide



Palytoxin

Fig. 3. (Continued).

itor sp., that is a potent inhibitor of the reverse transcriptase of HIV and both C and B retroviruses, as well as a general inhibitor of cellular DNA polymerases (Loya et al., 1999). Although it appears that, because polycitone A is a general inhibitor of DNA polymerases it cannot serve as

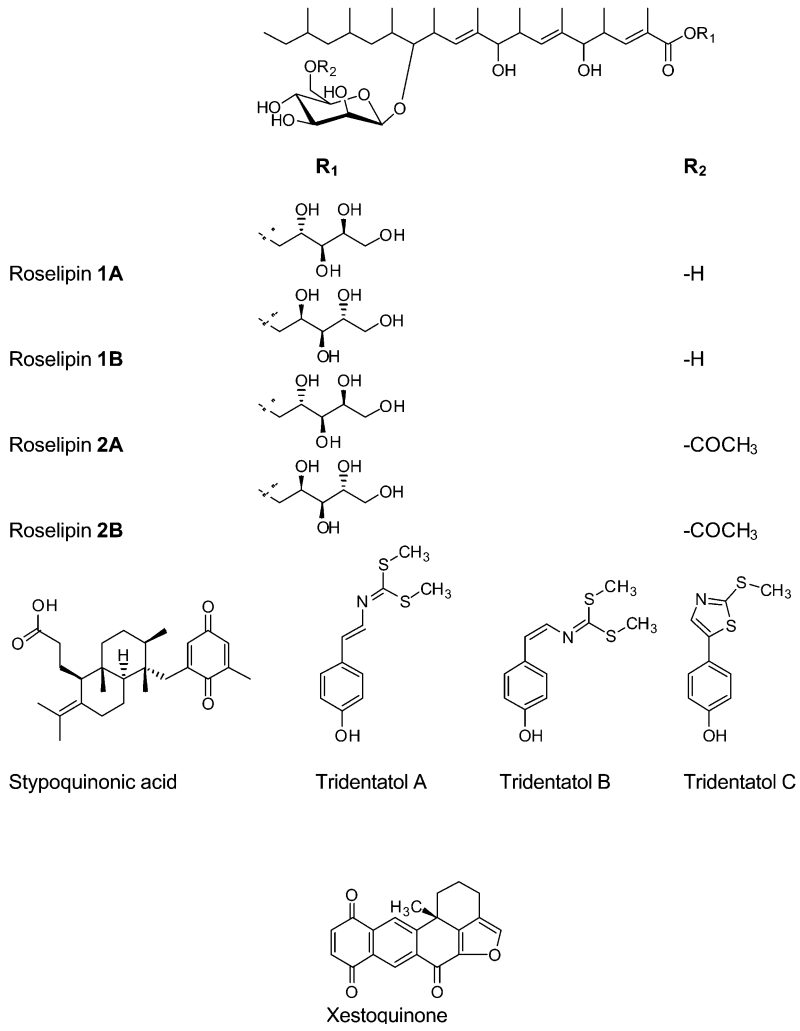


Fig. 3. (Continued).

an anti-HIV drug, structural modifications of polycitone A could lead towards the rational design of new derivatives with anti-HIV reverse transcriptase activity. The synthesis of sulfated derivatives of a glycosaminoglycan isolated from the marine bacterium *Pseudomonas* sp. and their testing against two strains of influenza virus types A and B were described by Ahmad et al. (1999). The authors noted that introduction of the sulfate groups into the polysaccharides containing L-glutamic acid resulted in antiviral activity against influenza virus type A, but not against type B, and that this activity was similar to that of ribavirin, an antiviral drug that is clinically used in the US to treat influenza A infections. Amornrut et al. (1999) isolated a novel sulfated β-galactan from the marine clam *Meretrix petechialis* and examined its anti-HIV activity in an in vitro assay. The sulfated galactan inhibited $CD4^+$ HeLa cells from forming syncytia, an observation that was interpreted as probably the result of a ‘‘…direct interaction of the polysaccharide with the HIV binding site at the membrane protein receptor CD4’’. Comin et al. (1999) evaluated natural disulfated polyhydroxysteroids isolated from the Antarctic ophiuroid *Astrotoma agassizii* against three pathogenic human viruses, namely herpes simplex type 2 (HSV-2), Junin (JV) and polio type 3 (PV-3) viruses. The investigators concluded that the steroids with sulfate groups at C-21 and C-2 or C-3 were very effective against HSV-2, PV-3 and JV. Sansalvamide A, a cyclic depsipeptide isolated

Table 1
Marine pharmacology in 1999: compounds with anthelmintic, antibacterial, anticoagulant, antifungal, antimalarial, antiplatelet, antituberculosis and antiviral activities

Drug class	Compound	Organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
Anthelmintic	Amphilactams	Sponge	Macrolide[d]	*H. contortus* inhibition	Undetermined	AUS	Ovenden et al., 1999
Anthelmintic	Geodin A	Sponge	Macrolide[d]	*H. contortus* inhibition	Undetermined	AUS	Capon et al., 1999
Antibacterial	Loloatins A–D	Bacterium	Cyclic peptide[f]	*S. aureus*, *S. pneumoniae* and enterococci inhibition	Undetermined	CAN	Gerard et al., 1999
Antibacterial	Myticin	Mussel	Peptide/ proteins[f]	*M. luteus*, *B. megaterium*, *E. viridans* inhibition	Undetermined	FRA	Mitta et al., 1999
Antibacterial	Psammaplin A	Sponge	Tyrosine-based[f]	*S. aureus* inhibition	DNA gyrase and synthesis inhibition	S. KOR	Kim et al., 1999
Anticoagulant	Sulfated fucans	Alga and cucumber	Sulfated polysaccharide[g]	Thrombin inhibition	Inhibition direct or with antithrombin or heparin cofactor II	BRA, UK	Pereira et al., 1999
Antifungal	Bengazole, bengamide	Sponge	Polyketide[d]	*C. albicans* inhibition	Undetermined	FRA	Fernandez et al., 1999
Antifungal	Oceanapiside	Sponge	Polyketide[d]	*C. glabrata* inhibition	Undetermined	USA	Nicholas et al., 1999
Antifungal	Spongistatin I	Sponge	Macrolide[d]	*A. nidulans* inhibition	Induces microtuble fragmentation	USA	Ovechkina et al., 1999
Antifungal	Tanikolide	Bacterium	Fatty acid[d]	*C. albicans* inhibition	Undetermined	USA	Singh et al., 1999
Antifungal	Theopederins F–J	Sponge	Polyketide[d]	*S. cerevisiae* inhibition	Undetermined	JPN	Tsukamoto et al., 1999
Antimalarial	15-α-Methoxy-puupehenol	Sponge	Sesquiterpene[e]	*P. falciparum* inhibition	Undetermined	FRA	Bourguet-Kondracki et al., 1999
Antiplatelet	Maitotoxin	Alga	Polyketide[d]	Platelet activation	Highly dependent on external Ca^{2+}	JPN	Nakahata et al., 1999a
Antituberculosis	Monoterpenes	Alga	Terpene[e]	*M. tuberculosis* inhibition	Undetermined	GER, SWZ	Konig et al., 1999
Antiviral	Lamellarin α-20-sulfate	Tunicate	Tyrosine-based[f]	In vitro HIV infection inhibition	HIV integrase inhibition	IND, USA	Reddy et al., 1999b
Antiviral	Papuamides A–D	Sponge	Depsipeptide[f]	In vitro HIV infection inhibition	Undetermined	CAN, USA	Ford et al., 1999
Antiviral	Polycitone A	Tunicate	Tyrosine-based[f]	In vitro anti-RT inhibition	DNA polymerase inhibition	ISR	Loya et al., 1999
Antiviral	Glycosaminoglycan	Bacterium	Sulfated polysaccharide[g]	In vitro anti-influenza A and B inhibition	Only influenza A virus inhibition	JPN	Ahmad et al., 1999
Antiviral	Sulfated β-galactan	Clam	Sulfated polysaccharide[g]	In vitro syncitia formation inhibition	Inhibition of HIV binding to CD4	S. KOR, JPN, USA	Amornrut et al., 1999
Antiviral	Poly-hydroxysteroids	Brittle star	Sterol[e]	In vitro reduction of HSV-2, JV, PV plaque formation	Sulfate at C-21, C-2 and C-3 critical for inhibition	ARG	Comin et al., 1999
Antiviral	Sansalvamide	Fungus	Depsipeptide[f]	*Molluscum contagiosum* virus topoisomerase inhibition	DNA binding and relaxation inhibition	USA	Hwang et al., 1999

[a] Organism: kingdom Animalia: brittle star and cucumber (Echinodermata); clam and mussel (Mollusca); sponge (Porifera); tunicate (Chordata); kingdom Fungi: fungus; kingdom Plantae: alga; kingdom Monera: bacterium (Cyanobacteria).

[b] MMOA: molecular mechanism of action.

[c] Country: ARG, Argentina; AUS, Australia; BRA, Brazil; CAN, Canada; FRA, France; GER, Germany; IND, India; ISR, Israel; JPN, Japan; S. KOR, South Korea; SWZ, Switzerland; UK, United Kingdom.

[d] Polyketide.

[e] Terpene.

[f] Nitrogen-containing compound.

[g] Polysaccharide.

from the marine fungus *Fusarium* sp., inhibited the topoisomerase of the pathogenic poxvirus *Molluscum contagiosum* (MCV) (Hwang et al., 1999), an important finding, because MCV may cause severe lesions in AIDS patients. This is a particularly significant study, because it determined that sansalvamide A inhibited MCV topoisomerase by inhibition of topoisomerase-catalyzed DNA relaxation, DNA-binding and covalent complex formation. This finding represents the first identification

Table 2
Marine pharmacology in 1999: compounds with anti-inflammatory, immunosuppressant and fibrinolytic effects and affecting the cardiovascular, nervous and sympathomimetic systems

Drug class	Compound	Organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
Anti-inflammatory	Africanene	Coral	Sesquiterpene[e]	In vivo rat paw edema inhibition	Undetermined	IND	Reddy et al., 1999a
Anti-inflammatory	Cacospongiolide B	Sponge	Sesterterpene[e]	In vivo and in vitro inflammation assays	Human $sPLA_2$ inhibition	ITAL, SPA	Pastor et al., 1999
Anti-inflammatory	Palinurin, palinurines A, B	Sponge	Sesterterpene[e]	In vitro modulation of activated rat brain microglia	Thromboxane B_2 inhibition	USA, NZ	El Sayed et al., 1999
Anti-inflammatory	Plakotenin	Sponge	Polyketide[d]	Synovial fibroblast proliferation inhibition	Undetermined	USA	Qureshi et al., 1999
Cardiovascular	Equinatoxin	Anemone	Protein[f]	Cardiotoxic	LDH release	SLOV	Bunc et al., 1999
Cardiovascular	Halenaquinol	Sponge	Polyketide[d]	Cardioactivity at the cellular level	Na^+, K^+ and Ca^{2+} ATPase inhibition	RUS	Gorshkova et al., 1999a
Cardiovascular	Seal oil	Seal	Fatty acids[d]	Reduced cardiovascular disease in humans	Rise in serum EPA and DHA	CAN	Conquer et al., 1999
Fibrinolytic	*C. latum* protease	Alga	Protein[f]	Fibrinolysis of human fibrinogen	Specificity for Arg and Lys residues	JPN	Matsubara et al., 1999
Immuno-suppressant	Simplexides	Sponge	Fatty acid metabolites[d]	Lymph node cell proliferation inhibition	Undetermined	ITA	Costantino et al., 1999
Nervous system	3-Alkyl-pyridinium	Sponge	Pyridines[f]	Acetylcholinesterase inhibition	Aggregation and multisite binding	SLOV, FRA	Sepcic et al., 1999
Nervous system	Ciguatoxin-1	Dinoflagellate	Polyketide[d]	Differential action on Na^+ channel subtypes	Modulation of Na^+ gating	AUS	Strachan et al., 1999
Nervous system	Conantokin-G, T	Snail	Peptide[f]	Neuronal NMDA-receptor inhibition	Current inhibition	USA	Klein et al., 1999
Nervous system	Conotoxin CcTX	Snail	Peptide[f]	Axon and motor nerve terminals	Na^+ channel activation	FRA	Le Gall et al., 1999
Nervous system	k-Conotoxin-PVIIA	Snail	Peptide[f]	K^+ channel inactivation	Competitive lysine interaction	MEX, AUS	Garcia et al., 1999
Nervous system	Curacin-A, antillatoxin, kalkitoxin	Bacterium	Polyketide/peptide[f]	Cytotoxicity to rat cerebellar granule cells	NMDA-mediated toxicity	USA	Berman et al., 1999
Nervous system	Psolusosides A, B	Sea cucumber	Triterpene glycosides[e]	Na^+,K^+-ATPase inhibition	Irreversible, with cholesterol affinity	RUS	Gorshkova et al., 1999b
Nervous system	Glycosphingolipids	Seastar	Glycoside[g]	Neuritogenic to rat pheochromocytoma	Undetermined	JPN	Kawatake et al., 1999
Sympathomimetic	S1319	Sponge	Tyrosine-based[f]	Potent relaxation of guinea pig tracheal muscle	β_2-selective adrenoreceptor agonist	JPN	Suzuki et al., 1999

[a] Organism: kingdom Animalia: coral (Cnidaria); snail (Mollusca); sponge (Porifera); seastar and sea cucumber (Echinodermata); seal (Chordata); kingdom Plantae: dinoflagellate and alga; kingdom Monera: bacterium (Cyanobacteria).
[b] MMOA: molecular mechanism of action.
[c] Country: AUS, Australia; CAN, Canada; FRA, France; IND, India; ITA, Italy; JPN, Japan; NZ, New Zealand; MEX, Mexico; RUS, Russia; SLOV, Slovenia; SPA, Spain.
[d] Polyketide.
[e] Terpene.
[f] Nitrogen-containing compound.
[g] Polysaccharide.

of a new inhibitor against *Molluscum contagiosum* topoisomerase in vitro.

3. Marine compounds with anti-inflammatory, immunosuppressant and fibrinolytic effects, and affecting the cardiovascular, nervous and sympathomimetic systems

Table 2 lists the preclinical pharmacological research completed on 23 marine chemicals shown in Fig. 2, affecting the cardiovascular, immune and nervous systems, as well as possessing anti-inflammatory, immunosuppressant, lipid-lowering and sympathomimetic effects.

The anti-inflammatory pharmacology of marine natural products during 1999 involved studies with africanene, cacospongiolide B, palinurin, palinurine A and B, and plakotenin, an increase of one compound compared to 1998 (Mayer and Leh-

mann, 2000). Reddy et al. (1999a) conducted an extensive bioactivity screen with the sesquiterpene africanene, isolated from the soft coral *Sinularia leptoclados*, that included an investigation of its anti-inflammatory activity. In acute inflammation studies utilizing the carrageenan-induced rat edema assay, an oral in vivo dose of 10 mg/kg body weight of africanene resulted in a more potent reduction of paw volume than that produced by 100 mg/kg body weight of ibuprofen, strongly suggesting that africanene may be worthy of further anti-inflammatory characterization studies. Pastor et al. (1999) extended the pharmacology of cacospongionolide B, a novel sesterterpene inhibitor of human synovial phospholipase A_2 isolated from the sponge *Fasciospongia cavernosa*, studying its mechanism of action in several assays for both in vitro (secretory and cytosolic phospholipase A_2, leukotriene B_4, cyclooxygenase I and II, nitric oxide) and in vivo inflammation (rat air pouch, mouse ear edema, mouse paw edema and mouse air pouch). Their results indicated that cacospongionolide B irreversibly inhibited both secretory PLA_2 in vitro and group II secretory PLA_2 in vivo. Perhaps the fact that cacospongionolide B was bioavailable by the oral route and had an effect on cytokine generation suggests that further research on this marine compound may lead to a novel anti-inflammatory agent. El Sayed et al. (1999) used microbial transformation of palinurin, a linear furanosesterterpene isolated from the marine sponge *Ircinia echinata* to produce two novel metabolites, palinurine A and B (El Sayed et al., 1999). The effect of these three compounds on thromboxane B_2 (TXB_2) and superoxide anion (O_2^-) release from activated rat neonatal microglia was investigated because these potentially neurotoxic mediators appear to be involved in neuroinflammatory conditions (Mayer et al., 1999). The investigators noted that, while palinurin inhibited TXB_2 ($IC_{50}=0.21$ μM) and O_2^- ($IC_{50}=5$ μM) generation, palinurine A and B were relatively ineffective inhibitors of both TXB_2 and O_2^-, thus suggesting that the furan ring appears to be required for the pharmacological activity of palinurin observed. Furthermore, the authors suggested that palinurin, by becoming a ''…lead compound for development as an anti-inflammatory medication'', could contribute to the current search for novel drugs to treat neuroinflammatory conditions (Mayer, 1998). Qureshi et al. (1999) investigated the inhibition of proliferation of arthritic cells with the carboxylic acid homoplakotenin, as well as the known compound plakotenin derived from the palauan sponge *Plakortis lita*. Although both compounds inhibited the ability of rheumatoid synovial fibroblasts to proliferate in response to platelet-derived growth factor at concentrations of 1 μg/ml, they were unable to inhibit proliferation at 0.1 μg/ml, suggesting that the compounds are active over a limited range of concentrations.

Immunosuppresant activity was reported for the novel glycolipids simplexides, isolated from the sponge *Plakortis simplex* (Costantino et al., 1999). Simplexides showed a 43% inhibitory effect on lymph node cell proliferation at 10 ng/ml. Interestingly, this immunosuppressive activity that was not related to cytotoxicity is probably attributable to its sugar head, and very probably involves an interaction with ''…glycoproteins involved in the immune mechanism''.

Cardiovascular pharmacology of marine natural products during 1999 involved studies with equinatoxin, halenaquinol and seal oil. Bunc et al. (1999) studied the mechanism of cardiotoxicity of equinatoxin II, a toxic basic protein isolated from the sea anemone *Actinia equina* (L.). The investigators observed that equinatoxin II was very potent, because in the nanomolar range it had clear dose-dependent, direct cardiotoxic effects, but, because it also caused lactate dehydrogenase release, it appeared that cytotoxicity probably played an important part in the toxin's cardiotoxic effects. Gorshkova et al. (1999a) extended the pharmacology of halenaquinol, a natural pentacyclic hydroquinone isolated from the sponge *Petrosia seriata* with previously known cardiotonic action. Halenaquinol inhibited membrane transport enzymes, such as rat brain Na^+, K^+-ATPase and rabbit muscle sarcoplasmic reticulum Ca^{2+}-ATPase, enzymatic systems involved in muscle contraction regulation. Furthermore, structure–activity relationship studies with halenaquinol determined that the inhibition of Na^+, K^+-ATPase observed was dependent on the presence of a naphthohydroquinone fragment in the molecule. Conquer et al. (1999) completed a 6-week double-blind trial with 19 healthy male subjects on the effects of seal oil, which contains omega-3 fatty acids, on cardiovascular disease risk factors. A marked increase in both eicosapentanoic acid and docosahexaenoic acid levels in serum phospholipid and non-esterified fatty acids was observed, an interesting finding

in view of the fact that both docosahexaenoic acid and non-esterified fatty acids possess antiplatelet aggregatory and antiarrhythmic effects. Furthermore, the authors noted that seal oil had a slight beneficial effect on fibrinogen and protein C levels, and thus proposed that seal oil supplementation may influence the balance between plasma procoagulant and anticoagulant activity in healthy volunteers in the direction of reduced cardiovascular disease (Conquer et al., 1999).

Reports on nervous system pharmacology of marine natural products increased slightly over 1998 (Mayer and Lehmann, 2000), with the 1999 studies involving 10 marine compounds, namely 3-alkyl-pyridinium, antillatoxin, ciguatoxin-1, conantokin-G and -T, conotoxin CcTX, κ-conotoxin, curacin-A, kalkitoxin and psolusosides A and B. Sepcic et al. (1999) investigated the mechanism of inhibition of the water-soluble cholinesterase inhibitors 3-alkylpyridinium polymers isolated from the marine sponge *Reniera sarai*. The investigators' extensive work determined that the apparently non-specific mechanism of acetylcholinesterase inhibition was strong and irreversible, and was not due to conformational changes of the protein and/or its unfolding, but rather the result of multisite binding between the two molecules, resulting in aggregation. Strachan et al. (1999) completed an extensive pharmacological investigation of the effect of ciguatoxin-1, an abundant and potent cyclic polyether ciguatoxin isolated from the marine dinoflagellate *Gambierdiscus toxicus*, on sodium channel subtypes in rat dorsal-root ganglion sensory neurons using whole-cell patch-clamp techniques. The investigators observed that ciguatoxin-1 acted in a ''…differential manner on the two types of sodium channel subtypes found in rat dorsal root ganglion neurons'', and therefore would appear to modulate sodium channel gating, thus providing a possible explanation for the enhanced degree of neuronal excitation and disturbance in nerve conduction observed in ciguatera patients.

Three studies extended the toxicology of the conotoxins, a family of small peptide toxins derived from the venom of marine snails of the genus *Conus* that have been shown to bind to excitable tissue (Olivera, 1997). Klein et al. (1999) evaluated the effect of the marine cone snail toxins conantokin-G and -T on *N*-methyl-D-aspartate (NMDA) ionotropic glutamate receptors in mouse primary hippocampal neuronal cultures using the whole-cell patch-clamp technique. The researchers observed that both toxins non-competitively inhibited NMDA-evoked currents, a fact that is of importance because NMDA receptors play a critical role in a number of physiological processes in the central nervous system, as well as in neuropathological states, such as stroke, chronic pain, Parkinson's disease and amyotrophic lateral sclerosis. Conotoxin CcTX, a new 30-amino-acid peptide was isolated from the Indo-Pacific fish-hunting marine snail *Conus consors* (Le Gall et al., 1999). The investigators demonstrated that CcTX showed particular selectivity to axons and motor nerve terminals, because it activated neuronal voltage-gated sodium channels and produced Na^+ entry into nerve terminals and axons without directly affecting skeletal muscle fibers. Interestingly, because conotoxin CcTX has an unusual sequence compared with previously reported classes of conotoxins, it defines a novel family of conotoxins. Garcia et al. (1999) extended the pharmacology of the marine snail *Conus purpurascens* κ-conotoxin-PVIIA (κ-PVIIA), a 27-residue peptide venom component that inhibits voltage-gated K channels. While studying the mechanism by which this peptide inhibited K channels expressed in *Xenopus* oocytes Garcia et al. (1999) determined that there was a ''…purely competitive interaction…'' with ''…a positively charged side chain, possibly a lysine, interacting electrostatically with K^+ ions from the intracellular side of the channel''. Interestingly, the investigators noted a putative convergence between κ-PVIIA and evolutionary distant scorpion toxins of the α-KTx family towards a common mechanism of action on K channels.

Berman et al. (1999) reported on the nervous system pharmacology of curacin-A, the lipopeptide antillatoxin and the thiazoline-containing lipid kalkitoxin, compounds isolated from the pantropical marine cyanobacterium *Lyngbia majuscula*. During studies designed to determine the neurotoxic activity of these compounds in primary cultures of rat cerebellar granule cells, curacin-A was non-toxic, while under similar experimental conditions both antillatoxin and kalkitoxin produced concentration-dependent cytotoxicity ($LC_{50} = 20.1 \pm 6.4$ and 3.86 ± 1.91 nM, respectively), although clearly involving ''…distinct temporal patterns''. Additional mechanism-of-action studies determined that the neurotoxicity induced by both toxins appeared to involve ionotropic

glutamate receptor-dependent excitotoxic mechanisms, probably mediated by *N*-methyl-D-aspartate receptor blockage. Gorshkova et al. (1999b) extended the pharmacology of psolusosides A (PsA) and B (PsB), two membranolytic triterpene glycosides isolated from the holothurian *Psolus fabricii* that form a complex with membrane sterols as well as ''…solitary ion channels and large aqueous pores''. As part of their effort to characterize the membranotropic properties of these compounds, they determined that both PsA and PsB differed in their inhibiting action on rat brain Na^+,K^+-ATPase, ''…possibly irreversible'' and probably explained by their chemical structure and particular affinity to membrane cholesterol. Kawatake et al. (1999) isolated a glycosphingolipid from the starfish *Luidia maculata* that appears similar to the mammalian ganglioside GM_3. Interestingly, in rat pheochromocytoma PC-12 cells treated with 10 μg/ml of this active glycoside, neurite outgrowth was induced.

A novel benzothiazole-2-one (S319) sympathomimetic agent was isolated from the marine sponge *Dysidea* sp. (Suzuki et al., 1999). While investigating its tracheal-relaxing activity, the investigators determined that this compound was more potent than isoproterenol. Because its pharmacological effect appeared to be mediated through β_2-adrenoceptors, the authors suggested that this compound might become a clinically useful and potent bronchodilator (Suzuki et al., 1999).

4. Marine compounds with miscellaneous mechanisms of action

Table 3 lists 22 marine compounds with miscellaneous mechanisms of action in Fig. 3. Interestingly, and in contrast to the chemicals included in Tables 1 and 2, this third group of marine compounds includes nitrogen-containing compounds (i.e. proteins, peptides, pyridines, tyrosine-based metabolites), terpenes and polyketides, but not polysaccharides.

For some of these marine chemicals, namely alkylpyridinium polymers, caulerpenyne, CEL-1, CEL-2, equistatin, eucheuma isolectins, maitotoxin, obelin, palytoxin, *Ptilota serrata* lectin, sinulamide, tridentatols and xestoquinone, both the pharmacological activity and a molecular mechanism of action have been investigated. For the anabaenopeptins G and H, kelletinin A, roselipin and stypoquinonic acid, only the pharmacological activity has been investigated so far. Finally, although adociasulfates 1–6, iantheran A, lyso-PAF analogues and octa- and nonaprenylhydroquinone sulfates have been explored at the molecular level, no pharmacological activity has been clearly identified at this time. Hopefully, ongoing studies with these compounds will permit their assignment to a particular therapeutic class in the near future.

5. Reviews on marine pharmacology

During 1999, several reviews covering selected aspects of marine pharmacology were published: the patent literature (Kerr and Kerr, 1999); the literature of marine natural product chemistry for 1997 (Faulkner, 1999); the biochemistry and biomedical applications of giant keyhole limpet hemocyanin (Harris and Markl, 1999); sea anemone toxins as templates for new immunosuppressant drugs (Kem et al., 1999); the pharmacology of polyketides from dinoflagellates (Rein and Borrone, 1999); the biochemistry and pharmacology of the anti-inflammatory phospholipase A_2 inhibitor manoalide (Soriente et al., 1999); and the current state of knowledge of actin-binding marine natural products (Spector et al., 1999).

Kerr and Kerr (1999) reviewed the patent literature in the field of marine natural products covering the period 1996–April 1999, noting that the majority of the patents focused on antitumor agents, although some covered antiviral and anti-inflammatory activities. Phylum Porifera was the source of the majority of metabolites described in the patents.

In an extensive review, Faulkner (1999) discussed some 749 novel marine compounds reported during 1997 and derived from organisms belonging to four kingdoms, namely Animalia (Echinodermata, Cnidaria, Porifera, Mollusca, Chordata), Fungi, Plantae (Chlorophyta, Phaeophyta, Rhodophyta) and Monera (Cyanobateria), some of which possessed interesting ''… biological and pharmacological properties''.

1999 saw the completion of an extensive review of the biochemistry, structure and cellular immunology of keyhole limpet hemocyanin (KLH) (Harris and Markl, 1999), a copper-containing respiratory protein isolated from the marine gastropod *Megathura crenulata*. Although the review provides extensive information on the use of KLH for tumor immunotherapy, as a pharmaceutical carrier for vaccines and antigens and as a tool for

Table 3
Marine pharmacology in 1999: compounds with miscellaneous mechanisms of action

Compound	Organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
Adociasulfates 1–6	Sponge	Sulfated triterpene[e]	Undetermined	Kinesin motor protein inhibition	USA	Blackburn et al., 1999
Alkylpyridinium polymer	Sponge	Pyridine[f]	Cytolytic to bovine erythrocytes	5.8-nm pores in membranes	SLO	Malovrh et al., 1999
Anabaenopeptins G and H	Bacterium	Peptide[f]	Carboxypeptidase A inhibition	Undetermined	JPN	Itou et al., 1999
Caulerpenyne	Alga	Sesquiterpene[e]	Pancreatic lipase inhibition	Competitive inhibition of enzyme	JPN	Bitou et al., 1999
CEL-1	Sea cucumber	Protein[f]	Hemolysis of rabbit erythrocytes	Ca^{2+}-dependent binding to carbohydrates	JPN	Hatakeyama et al., 1999
CEL-III	Sea cucumber	Protein[f]	Hemolysis of rabbit erythrocytes	Ca^{2+}-dependent binding to carbohydrates	JPN	Oda et al., 1999
Equistatin	Anemone	Protein[f]	Cysteine proteinase and cathepsin D inhibition	Inhibitory activity of first, second and third domains determined	SLO	Lenarcic and Turk, 1999
Eucheuma isolectins	Alga	Protein[f]	Hemagglutination and mitogenesis	Lectins with affinity for mannose glycans	JPN	Kawakubo et al., 1999
Iantheran A	Sponge	Polyketide[d]	Undetermined	Na,K-ATPase inhibition	JPN	Okamoto et al., 1999
Kelletinin A	Mollusc	Complex polyketide[d]	Differentiation promoter in *Hydra*	Undetermined	ITA	De Petrocellis et al., 1999
Lyso-PAF analogues	Sponge	Polyketide[d]	Undetermined	Cholesterol biosynthesis inhibition	S. KOR	Shin et al., 1999
Maitotoxin	Alga	Complex polyketide[d]	Ca^{2+} increase in erythrocyte ghosts	Blocked by gangliosides	JPN	Konoki et al., 1999
Maitotoxin	Alga	Complex polyketide[d]	Cytotoxicity and cell death	Ca^{2+}-dependent ERK1/ERK2 activation	JPN, ITA	Malaguti et al., 1999
Maitotoxin	Alga	Complex polyketide[d]	Phosphoinositide hydrolysis	Dependent on extracellular Ca^{2+}	JPN	Nakahata et al., 1999b
Maitotoxin	Alga	Complex polyketide[d]	Ca^{2+} increase in single hepatocytes	Dependent on extracellular Ca^{2+}	UK, JPN	Woods et al., 1999
Obelin	Cnidaria	Protein[f]	Bioluminescence-based immunoassay for small peptides	Competition with obelin-octapeptide fusion protein	USA	Matveev et al., 1999
Octa/nonaprenyl hydroquinone sulfates	Sponge	Prenylated hydroquinone sulfate[d,e]	Undetermined	α1,3-Fucosyl transferase VII inhibition	JPN, AUS	Wakimoto et al., 1999
Palytoxin	Coral	Macrolide[d]	Induction of non-selective cation channel in megakaryocytes	Sensitivity to oubain, $NiCl_2$ and amiloride derivatives	JPN	Ichida et al., 1999
Ptilota serrata lectin	Alga	Protein[f]	Hemagglutination inhibition assays	Activity dependent on divalent cations	UK, BRA	Sampaio et al., 1999
Roselipins	Fungus	Polyketide	Diacylglycerol	Undetermined	JPN	Tomoda et al., 1999

Table 3 *(Continued)*

Compound	Organism[a]	Chemistry	Pharmacological activity	MMOA[b]	Country[c]	References
		glycoside[d]	acyltransferase inhibition			
Sinulamide	Coral	Diterpene[e]	Cytotoxic to murine leukemia cells	H,K-ATPase inhibition	JPN	Sata et al., 1999
Stypoquinonic acid	Alga	Complex polyketide[d]	Tyrosine kinase inhibition	Undetermined	GER	Wessels et al., 1999
Tridentatols	Hydroid	Tyrosine-based[f]	Antioxidant	Inhibition of lipid peroxidation of LDL	USA	Johnson et al., 1999
Xestoquinone	Sponge	Complex polyketide[d]	Induction of sarcoplasmic reticulum Ca^{2+} release	Modification of sulfhydryl groups	JPN	Ito et al., 1999

[a] Organisms: kingdom Animalia: anemones, corals and hydroids (Cnidaria); mollusc (Mollusca); sea cucumber (Echinodermata); sponge (Porifera); kingdom Fungi: fungus; kingdom Plantae: alga; kingdom Monera: bacterium (Cyanobacteria).

[b] MMOA: molecular mechanism of action.

[c] Country: AUS, Australia; BRA, Brazil; GER, Germany; ITA, Italy; JPN, Japan; S. KOR, South Korea; SLO, Slovenia; SWZ, Switzerland; UK, United Kingdom.

[d] Polyketide.

[e] Terpene.

[f] Nitrogen-containing compound.

the investigation of immune competence in both animal and human health, the authors suggest that a number of critically important questions currently remain to be addressed by the suppliers of KLH for both experimental and clinical use.

Kem et al. (1999) reviewed a novel class of sea anemone K channel toxins as a potential template for the design of novel immunosuppressant drugs. The article is quite thought-provoking, because it focuses upon a relatively novel immunosuppressant strategy that is based on the inhibition of K channels to control T-lymphocyte proliferation. The authors propose that the use of novel immunosuppressant agents incorporating the anemone toxin pharmacophore could potentially lead to new pharmacologic treatments for autoimmune diseases, such as multiple sclerosis, type 1 diabetes and systemic lupus, as well as therapy for organ transplantation.

In an extensive review on human immunodeficiency virus reverse-transcriptase inhibitors of natural origin, these inhibitors were grouped according to their source organism, i.e. plant, micro-organism and marine organism (Matthee et al., 1999). The section on marine-derived reverse transcriptase (RT) inhibitors describes 20 marine chemicals, as well as algal extracts showing antiviral activities. The authors conclude their review by suggesting that marine compounds remain a poorly investigated source of HIV-RT inhibitors, and thus could potentially represent a resource of lead structures.

The biological activities of dinoflagellates polyketides are varied and include cytotoxic, antitumor, antibiotic, antifungal, immunosuppressant, and neurotoxic activities (Rein and Borrone, 1999). As to future directions in dinoflagellate polyketide pharmacology, the authors suggest that studies aimed at ''…identifying biosynthetic potential at the genomic level'' may ultimately allow the discovery of novel biosynthetic capability in these organisms.

The chemistry and pharmacology of manoalide, a potent analgesic and anti-inflammatory sesterterpene isolated from *Luffariella variabili*, were comprehensively reviewed (Soriente et al., 1999). This report emphasizes the chemistry of manoalide and its analogues, structure–activity relationships, mechanism-of-action studies of manoalide and related compounds on phospholipase A_2 and an extensive discussion of the in vitro and in vitro pharmacology of manoalide. Because this review includes more than 100 peer-reviewed articles, it appears to be the most comprehensive to date on manoalide chemistry and pharmacology.

Spector et al. (1999) described the current state of knowledge of actin-targeted marine natural products. In recent years, these investigators have identified several marine chemicals, namely the latrunculins, jasplakinolides, swinholide A, misakinolide A, halichondramides and pectenotoxin II, that bind to actin. The use of these chemicals to study fenestrae formation in liver endothelial cells provides an example of the ''…new insights into specific aspects of actin-mediated cellular processes'' that can be gained using these actin-binding marine natural products.

6. Conclusion

Although during 1999 no new marine natural product was approved for patient care by the US Food and Drug Administration, the present report clearly documents the fact that during 1999 preclinical pharmacological research with marine chemicals continued to be an extremely active, as well as multinational, effort involving collaborations between natural product chemists and pharmacologists from more than 18 countries, including the United States.

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