Marine pharmacology in 1998: Marine Compounds with Antibacterial, Anticoagulant, Antifungal, Anti-inflammatory, Anthelmintic, Antiplatelet, Antiprotozoal, and Antiviral Activities; with actions on the Cardiovascular, Endocrine, Immune, and Nervous Systems; and other Miscellaneous Mechanisms of Action.

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INTRODUCTION

During 1998 research on the pharmacology of marine chemicals included in this review involved investigators from 22 countries, namely Australia, Belgium, Bolivia, Brazil, Canada, China, France, Germany, India, Italy, Japan, the Netherlands, Norway, New Zealand, Philippines, Russia, Slovenia, Spain, Switzerland, United Kingdom, Uruguay and the United States. This review attempts to classify 59 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. Thirty marine chemicals had antibacterial, anticoagulant, antifungal, antihelminthic, antiplatelet, antiprotozoal or antiviral activities. An additional seventeen marine compounds were shown to have significant effects on the cardiovascular, immune or nervous system. Finally, twenty marine compounds were reported to act on a variety of molecular targets that could potentially contribute to various pharmacological classes. Thus, during 1998, marine organisms provided a variety of novel chemical leads for the potential development of new therapeutic agents for the treatment of multiple disease categories.

The purpose of this brief article was to review studies with bioactive marine natural products published exclusively during 1998 and to classify them into major pharmacological categories with the exception of marine chemicals with antitumor and cytotoxic properties that were recently reviewed (37). Only those articles reporting on the bioactivity and/or pharmacology of marine chemicals whose structures have been determined were included in the present review. Schmitz's chemical classification (56) was used to assign each marine compound to a major chemical class: polyketides, terpenes, nitrogen-containing compounds or polysaccharides. The publications reporting on antibacterial, anticoagulant, antifungal, antihelminthic, antiplatelet, antiprotozoal or antiviral properties of marine chemicals have been tabulated in *Table 1*. The articles reporting on marine compounds affecting the cardiovascular, immune or nervous system are grouped in *Table 2*. Finally marine compounds targeting a number of distinct cellular and molecular targets and mechanisms are presented in *Table 3*. Due to space limitations, publications on the pharmacological activity of marine extracts or as yet structurally uncharacterized marine compounds have been excluded from this article.

Table 1 includes reports on preclinical research on the antibacterial, anticoagulant, antifungal, antihelminthic, antiplatelet, antiprotozoal or antiviral activities of 30 marine compounds isolated from four major groups of organisms. It is noteworthy to highlight the fact that marine sponges yielded ten compounds, while twenty other marine chemicals were derived from corals, snails, mussels, crinoids, cucumbers and tunicates, fungi, marine algae and cyanobacteria. The marine natural products listed in *Table 1* represent all four chemical classes, namely polyketides (fatty acids, macrolides), terpenes (diterpenes, sesterterpenes, sesquiterpenes, sterols), nitrogen-containing compounds (indoles, proteins, depsipeptides, peptides, amides, pyrrols) and polysaccharides. Although preclinical pharmacological studies allowed classifying the marine compounds listed in *Table 1* into a particular drug class, i.e. antibacterial, anticoagulant, antifungal, antihelminthic, antiplatelet, antiprotozoal or antiviral, it should be noted that no detailed mechanism of action studies were reported for most of these marine compounds with only a few exceptions. Halisulfate and Suvanine inhibited the serine proteases thrombin and trypsin and are thus potentially novel anticoagulants (28); Mycalolide-B inhibited platelet aggregation by interfering with actin polymerization (58), and Didemnaketal inhibited the HIV-1 protease by an unusual mechanism, and might become part of a novel class of HIV-1 protease inhibitors (16). Furthermore, Cyanovirin-N (40) as well as Adociavirin (44) bound with high affinity to the HIV viral surface envelope glycoprotein 120 while a sulfoquinovosyldiacylglycerol (45) from a red alga inhibited HIV-reverse transcriptase type 1. Although all the pharmacological studies with the marine compounds listed in *Table 1* were of a preclinical nature (both *in vitro* and/or *in vivo*), Dolastin 10 advanced to clinical anticancer trials during 1998 (37, 64).

Table 2 includes reports on preclinical research on 17 marine chemicals affecting the cardiovascular, immune or nervous system. In contrast to *Table 1*, in addition to *in vitro* and/or *in vivo* preclinical pharmacological studies, 16 of these 17 marine compounds were characterized extensively at the molecular level. Interestingly, several marine chemicals, though belonging to *different* chemi-

Table 1: Marine pharmacology in 1998: Marine Compounds with Antibacterial, Anticoagulant, Antifungal, Antihelminthic, Antiplatelet, Antiprotozoal, and Antiviral Activities.

Drug Class	Compound	Organism	Chemistry	MMOA[o]	Country[v]	Ref[w]
Antibacterial	Flexibilide/ Sinulariolide	Coral[b]	Diterp.[k]	Undet.[p]	AUS,JPN, PHL,USA	2
Antibacterial	Hexadecenoid acid	Synthet.[a]	Fatty acid[l]	Undet.[p]	USA	8
Antibacterial	Indolequinones	Snail[c]	Indole[m]	Undet.[p]	JPN	19
Antibacterial	Lectin	Mussel[c]	Protein[m]	Undet.[p]	NRW	62
Anticoagulant	Halisulfate/ Suvanine	Sponge[d]	Sester.[k]	Ser.prot. Inhib.[h]	UK,JPN, USA	28
Anticoagulant	Chondroitin	Cucumber[e]	Polysac.[n]	Undet.[p]	BRZ,UK	42
Antifungal	Polylactones Lipodepsipeptide	Fungus[g]	Polyketide Depsip[m]	Undet.[p]	CHN,USA	1
Antifungal	Cyclolithistide A	Sponge[d]	Depsip[m]	Undet.[p]	USA	10
Antifungal	Lobanes	Coral[b]	Diterp.[k]	Undet.[p]	GER,NTH	14
Antifungal	Dolastatin 10	Tunicate[f]	Peptide[m]	Undet.[p]	USA	48
Antifungal	Spongistatin	Sponge[d]	Macrolide[l]	Undet.[p]	USA	47
Antifungal	Lipodepsipeptide	Fungus[g]	Depsip[m]	Undet.[p]	USA	54
Antifungal	Acanthosterols	Sponge[d]	Sterols[k]	Undet.[p]	JPN,NTH	61
Antihelmintic	Tetrahydrofuran	Alga[h]	Fatty acid[l]	Undet.[p]	AUS	6
Antihelmintic	Chondriamide C	Alga[i]	Indole[m]	Undet.[p]	URG	12
Antiplatelet	Mycalolide-B	Sponge[d]	Macrolide[l]	Actin pol.[r]	JPN	58
Antimalarial	Papuanoate	Sponge[d]	Terpene[k]	Undet.[p]	BOL,ITA,FRA	11
Antimalarial	Bistramides	Tunicate[f]	Amides[m]	Undet.[p]	FRA	20
Antimalarial	Kalihinol A	Sponge[d]	Diterp.[k]	Undet.[p]	JPN	39
Antiplasmodial	Oroidin	Sponge[d]	Pyrrol[m]	Undet.[p]	GER,SWZ	30
Antiviral	Didemnaketal	Tunicate[f]	Complex polyketide	HIV prot. Inhib.[s]	USA	16
Antiviral	Frondosin	Sponge[d]	Sesquit.[k]	Undet.[p]	USA	22
Antiviral	Sulfated polysacchride	Alga[h]	Polysac.[n]	Undet.[p]	JPN	24
Antiviral	Gymnochrome D	Crinoid[e]	Complex polyketide	Undet.[p]	JPN	32
Antiviral	Cyanovirin-N	Bacterium[j]	Protein[m]	HIV bind.[t]	USA	40
Antiviral	Adociavirin	Sponge[d]	Protein[m]	HIV bind.[t]	USA	44
Antiviral	Sulfoquinovosyl diacylglycerol	Alga[i]	Fatty acid[l]	HIV RT[u]	JPN	45

(a) synthet.: synthetic; **Organism**: *Kingdom Animalia*: (b) coral (Phylum Cnidaria), (c) snail and mussel (Phylum Mollusca), (d) sponge (Phylum Porifera), (e) crinoid and cucumber (Phylum Echinodermata); (f) tunicate (Phylum Chordata); *Kingdom Fungi*: (g) fungus; *Kingdom Plantae*: (h) alga (Phylum Phaeophyta), (i) alga (Phylum Rodophyta); *Kingdom Monera* : (j) bacterium (Phylum *Cyanobacteria*); **Chemistry**: (k)*Terpenes*: diterp: diterpenes, sester: sesterterpene, sesquit: sesquiterpene; (l) *Polyketides*;(m) *Nitrogen-containing compounds*: depsi: depsipeptide; (n) Polysac: *polysaccharide*; (o) **MMOA**: molecular mechanism of action; (p) undet.: undetermined mechanism of action;(q) ser.prot. inhib.: serine protease inhibition; (r) polym: polymerization; (s) HIV prot. Inhib.: HIV protease inhibition; (t)HIV bind.: HIV gp 120 binding; (u) HIV RT.: HIV reverse transcriptase binding ; (v)**Country**: AUS: Australia; BOL: Bolivia, BRZ: Brazil, CHN: China, FRA: France, GER: Germany, ITA: Italy, JPN: Japan, NTH: Netherlands, NRW: Norway, PHL: Philippines, URG: Uruguay, SWZ: Switzerland, UK: United Kingdom; (w) **Ref**: references.

Table 2: Marine pharmacology in 1998: Marine Compounds affecting the Cardiovascular, Immune and Nervous Systems

Drug Class	Compound	Organism	Chemistry	MMOA[n]	Country[y]	Ref[z]
Cardiovascular	Sapogenins	Seastar[b]	Sterol[k] and saponin[k]	Ca^{2+} influx	RUS	21
Cardiovascular	Zooxanthellatoxin-B	Dinoflag.[h]	Macrolide[l]	Ca^{2+} influx	JPN	41
Cardiovascular	B-90063	Bacterium[j]	Pyridine[m]	Endot. inhib.[o]	JPN	59
Antihistamine	Verongamine analogs	Synthet.[a]	Imidazole[m]	Histam. antag.[p]	USA	3
Anti-inflammatory	Decatetraenoic acids	Alga[i]	Fatty acid metab.[l]	Eicos. inhib.[q]	JPN	25
Anti-inflammatory	Pseudopterosins	Coral[c]	Diterp.[k]	Eicos. inhib.[q]	USA	36
Anti-inflammatory	Prenyl Hydroquinones	Synthet.[a]	Terpene	Eicosa inhib.[q] TNF-α inhib.[r]	SPA,ITA	60
Immunosuppressant	Palau'amine	Sponge[d]	Guanidine[m]	Undet.[s]	USA	29
Immunosuppressant	Pateamine A	Sponge[d]	Macrolide[l]	IL-2 inhib.[t]	USA	51
Nervous System	Conotoxin	Snail[e]	Peptide[m]	Serot. rec. inact.[u]	USA	15
Nervous System	Ciguatoxin	Dinoflag.[h]	Complex polyketide	Na^+ chan. inact.[v]	AUS	23
Nervous System	Anthopleurins	Tunicate[f]	Peptide[m]	Na^+ chan. inact.[v]	USA	27
Nervous System	Saxitoxin Tetrodotoxin	Dinoflag.[h] Fish[g]	Guanidine[m]	Na+ chan. inact.[v]	USA	46
Nervous System	Xestospongin D Araguspongin C	Sponge[d]	Quinol.[m]	NO synth. inhib.[w]	IND,USA	50
Autonomic Nervous System	Alkylpyridinium polymer	Sponge[d]	Pyridine[m]	Acetylch. inhib.[x]	FRA,SLOV	55

(a) synthet.:synthetic; **Organism**: *Kingdom Animalia*: (b) seastar (Phylum Echinodermata), (c) coral (Phylum Cnidaria), (d) sponge (Phylum Porifera), (e) snail (Phylum Mollusca, (f) tunicate and (g) fish (Phylum Chordata); *Kingdom Protista*: (h) dinoflagellate; *Kingdom Plantae*: (i) alga (Phylum Chlorophyta); *Kingdom Monera* : (j) bacterium (Phylum Bacteria); **Chemistry**: (k) *Terpenes*: diterp: diterpenes; (l) *Polyketides*: fatty acid metab.: fatty acid metabolites ;(m) *Nitrogen-containing compounds:* quinol.: quinolizidine; (n) **MMOA**: molecular mechanism of action; (o) endot. inhib.: endothelin converting enzyme inhibitor; (p) histam. antag.: histamine receptor antagonist; (q) eicos. inhib.: eicosanoid inhibition; (r) TNF-α inhib.: TNF-α inhibition; (s) undet: undetermined; (t) IL-2 inhib: interleukin-2 inhibition; (u) serot. rec. inact. : serotonin receptor inactivation; (v) Na^+ chan. inact.: Na^+ channel inactivation; (w) NO synth. Inhib.: nitric oxide synthase inhibition; (x) acetylch. inhib.: acetylcholinesterase inhibition; (y) **Country**: AUS: Australia, FRA: France, IND: India, ITA: Italy, JAPN: Japan, RUS: Russia, SPA: Spain, SLOV: Slovenia; (z) **Ref**: references.

Table 3: Marine pharmacology in 1998: Marine Compounds with Miscellaneous Mechanisms of Action

Compound	Organism	Chemistry	MMOA[l]	Country[aa]	Ref[bb]
Bistheonellide Swinholide	Sponge[a]	Macrolide[i]	Actin depol.[m]	JPN	52
AFP-2	Fish[b]	Protein[j]	Antifreeze	CAN	34
Microcystin	Bacterium[f]	Peptide[j]	Apoptosis	USA	38
Gymnodinium A3	Dinoflag.[g]	Polysac.[k]	Apoptosis	JPN	57
Mapacalcine	Sponge[a]	Protein[j]	Ca^{2+} chan. bind.[n]	FRA	63
Carboxymethyl-nicotinic acid	Sponge[a]	Pyridine[j]	Cyst. prot. inhib.[o]	JPN	35
Misakinolide	Sponge[a]	Macrolide[i]	Liver fenestra[p]	BEL,USA	5
Rhopaloic acid	Sponge[a]	Sester.[h]	Gastrul. inhib.[q]	JPN	65
Adociasulfate-2	Sponge[a]	Triterp..[h]	Kinesin inhib.[r]	USA	53
Palytoxin	Coral[d]	Complex Polyketide	MAP kin. activ.[s]	USA	33
Jaspisin	Urchin[c]	Tyr.[j]	Metallop. inhib.[t]	JPN	26
Norzoanthamine	Coral[d]	Alkaloid[j]	Osteop. inhib.[u]	JPN	31
Okadaic acid	Sponge[a]	Complex Polyketide	PI kin. activ.[v]	USA	9
Dragmacidins	Sponge[a]	Indole[j]	Phosph. inhib.[w]	AUS	7
Clavosines A-C	Sponge[a]	Amide[j]	Phosph. inhib.[w]	USA,NZ, CAN	18
Cacospongionolide	Sponge[a]	Sester.[h]	PLA inhib.[x]	ITA,SPA	13
Petrosaspongiolides	Sponge[a]	Sester.[h]	PLA inhib.[x]	ITA,FRA SPA	49
Cyclotheonamides	Sponge[a]	Peptides[j]	Ser. prot. inhib.[y]	JPN	43
Pulchellalactam	Fungus[e]	Amide[j]	Tyr. phosp.inhib.[z]	USA	4

Organism: *Kingdom Animalia*: (a) sponge (Phylum Porifera), (b) fish (Phylum Chordata), (c) sea urchin (Phylum Echinodermata), (d) coral (Phylum Cnidaria); *Kingdom Fungi*: (e) fungus; *Kingdom Monera:* (f) bacterium (Phylum Cyanobacteria); *Kingdom Protista:* (g) dinoflagellate; **Chemistry**: (h) *Terpenes:* triterp: triterpene, sester: sesterterpene; (i) *Polyketides*;(j) *Nitrogen-containing compounds*: tyr. tyrosine-based metabolite; (k) Polysac: *polysaccharide*; (l) **MMOA**: molecular mechanism of action; (m) actin depol: actin depolimerizing; (n) Ca^{2+} chan. bind.: Ca^{2+} channel binding; (o) cyst. prot. inhib.: cysteine protease inhibition; (p) liver fenestra: liver fenestra formation; (q) gastrul. inhib.: gastrulation inhibition; (r) kinesin inhib.: kinesin inhibition; (s) MAP kin. Activ.: MAP kinase activation; (t) metallop. Inhib.: metalloprotease inhibition; (u) osteop. inhib.: osteoporosis inhibition; (v) PI kin. activ.: phosphatidylinositol 3'-kinase activation; (w) phosph. inhib.: phosphatase inhibition; (x) PLA inhib.: phospholipase A inhibition; (y) ser. prot. inhib.: serine protease inhibition; (z) tyr. phosp. inhib.: tyrosine phosphatase inhibition; (aa) **Country**: AUS: Australia, BEL: Belgium, CAN: Canada, FRA: France, ITA: Italy, JAPN: Japan, SPA: Spain, NZ: New Zealand; (bb) **Ref**.: References.

cal classes and marine Phyla, shared *similar* pharmacological properties. Thus inhibition of Ca^{2+} influx was affected by both the sapogenins, sterols derived from a seastar that showed stimulatory action on the isolated molluscan heart (21), and zooanthellatoxin-B, a macrolide derived from a dinoflagellate that caused a concentration-dependent contraction of rabbit isolated aorta (41). Similarly, eicosanoid inhibition was observed in MC/9 mouse mast cells with hexa- and octadecatetraenoic acids, fatty acid metabolites isolated from edible marine algae (25), in mouse peritoneal macrophages with the pseudopterosins, diterpenes derived from soft corals (36); and in human neutrophils and mouse macrophages with prenyl hydroquinones analogs of sponge terpenes (60). Finally, sodium channel inactivation was observed in rat parasympathetic neurons with ciguatoxin, a complex polyketide derived from benthic dinoflagellates (23); in murine neuroblastoma and rat tumor cell lines expressing cardiac and neuronal sodium channel isoforms with the anthopleurins, peptides isolated from a sea anemone (27); and in skeletal muscle sodium channel α-subunit expressed in Xenopus oocytes with ciguatoxin and tetrodotoxin, marine guanidines produced by dinoflagellates and fish (46).

Table 3 lists 20 marine compounds which have been particularly well investigated at the molecular level. Although for all these marine chemicals, a particular mechanism of action has been identified, they have not been proposed for preclinical studies in a particular pharmacological drug class at this time. Interestingly, as was the case with the chemicals included in *Table 1*, twelve of these marine compounds were isolated from sponges (Phylum Porifera), and though most were nitrogen-containing compounds (i.e. proteins, peptides, pyridines, tyrosine-based metabolites, alkaloids, indoles and amides), terpenes, polyketides and polysaccharides are also represented. Noteworthy are the variety of molecular targets that have been identified and studied during 1998, which suggests that some of these marine chemicals might affect one or more pharmacological class, e.g. pulchellalactam, a tyrosine phosphatase inhibitor.

In conclusion, this brief overview clearly documents that research into the preclinical pharmacological potential of marine chemicals was an extremely active scientific enterprise during 1998, involving collaborations between natural product chemists and pharmacologists from 22 foreign countries and the United States. We thus concur with conclusions of the author of a recent review on marine pharmacology that "… *pharmacological research involving marine organisms is intrinsically slower and has disadvantages compared with a program based on synthesis, but the number and quality of the leads generated more than justify research on marine pharmacology…*" (17).

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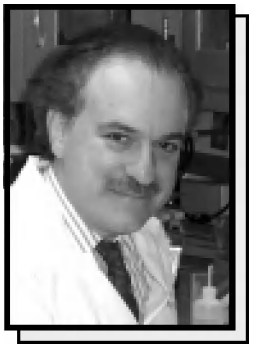
Acknowledgments

This paper was funded in part by a grant to A.M.S.M. from the National Sea Grant College Program, National Oceanic and Atmospheric Administration, U.S. Department of Commerce, under grant number NA66RG0477, project R/MP 73 through the California Sea Grant College System, which is gratefully acknowledged. The views expressed herein are those of the authors and do not necessarily reflect the views of NOAA or any of its sub-agencies. The U.S. Government is authorized to reproduce and distribute for governmental purposes.



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