marine drugs

MDPI

Review

Marine Pharmacology in 2012–2013: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis, and Antiviral Activities; Affecting the Immune and Nervous Systems, and Other Miscellaneous Mechanisms of Action †

Alejandro M. S. Mayer [1,*], Abimael D. Rodríguez [2], Orazio Taglialatela-Scafati [3] and Nobuhiro Fusetani [4]

1 Department of Pharmacology, Chicago College of Osteopathic Medicine, Midwestern University, 555 31st Street, Downers Grove, IL 60515, USA
2 Molecular Sciences Research Center, University of Puerto Rico, 1390 Ponce de León Avenue, San Juan, PR 00926, USA; abimael.rodriguez1@upr.edu
3 Department of Pharmacy, University of Naples "Federico II", Via D. Montesano 49, 80131 Napoli, Italy; scatagli@unina.it
4 Fisheries and Oceans Hakodate, Hakodate 041-8611, Japan; anobu@fish.hokudai.ac.jp
* Correspondence: amayer@midwestern.edu; Tel.: +1-630-515-6951; Fax: +1-630-971-6414
† This review is dedicated to the memory of the late Professor Ernesto Fattorusso on the occasion of what would have been his 80th birthday, and the late Professor Robert S. Jacobs on the occasion of what would have been his 84th birthday.

Received: 20 July 2017; Accepted: 21 August 2017; Published: 29 August 2017

Abstract: The peer-reviewed marine pharmacology literature from 2012 to 2013 was systematically reviewed, consistent with the 1998–2011 reviews of this series. Marine pharmacology research from 2012 to 2013, conducted by scientists from 42 countries in addition to the United States, reported findings on the preclinical pharmacology of 257 marine compounds. The preclinical pharmacology of compounds isolated from marine organisms revealed antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral and anthelmitic pharmacological activities for 113 marine natural products. In addition, 75 marine compounds were reported to have antidiabetic and anti-inflammatory activities and affect the immune and nervous system. Finally, 69 marine compounds were shown to display miscellaneous mechanisms of action which could contribute to novel pharmacological classes. Thus, in 2012–2013, the *preclinical* marine natural product pharmacology pipeline provided novel pharmacology and lead compounds to the *clinical* marine pharmaceutical pipeline, and contributed significantly to potentially novel therapeutic approaches to several global disease categories.

Keywords: drug; marine; chemical; metabolite; natural product; pharmacology; pharmaceutical; review; toxicology; pipeline

1. Introduction

The aim of the present review is to consolidate *preclinical* marine pharmacology in 2012–2013, with a format similar to the previous 8 reviews of this series, which cover the period 1998–2011 [1–8]. The peer-reviewed articles were retrieved from searches of several databases, including MarinLit, PubMed, Chemical Abstracts®, ISI Web of Knowledge and Google Scholar. The review only includes bioactivity and/or pharmacology of structurally characterized marine chemicals, which we have

classified using a modification of Schmitz's chemical classification [9] into six major chemical classes; namely, polyketides, terpenes, peptides, alkaloids, shikimates, and sugars. The preclinical antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral and anthelmintic pharmacology of marine chemicals is reported in Table 1, with the structures shown in Figure 1. Marine compounds that affect the immune and nervous systems, as well as those with antidiabetic and anti-inflammatory effects, are exhibited in Table 2, with their structures presented in Figure 2. Finally, marine compounds that affected a variety of cellular and molecular targets are noted in Table 3, and their structures presented in Figure 3.

A number of publications during 2012–2013 reported extracts or structurally uncharacterized marine compounds, with novel and interesting *preclinical* and/or *clinical* pharmacology: in vitro *antimalarial* activity in crude extracts from Fiji marine organisms using a semi-automated RNA fluorescence-based high-content live cell-imaging assay [10]; the first report of in vitro liver stage *antiplasmodial* activity and dual stage inhibitory potential of British seaweeds [11]; *anti-hepatitis C virus* activity affecting the viral helicase NS3 and replication, in crude extracts from the marine feather star *Alloeocomatella polycladia* [12]; *anti-herpes simplex* virus HSV-1 and HSV-2 activity in a purified sulfoglycolipid fraction from the Brazilian marine alga *Osmundaria obtusiloba* [13]; in vivo *anti-inflammatory* activity of a heterofucan from the Brazilian seaweed *Dictyota menstrualis* that inhibited leukocyte migration to sites of tissue injury by binding to the cell membrane [14]; in vivo *antinociceptive* and *anti-inflammatory* activity in a crude methanolic extract of the red alga *Bryothamnion triquetrum* [15]; in vivo *anti-inflammatory* activity in a sulfate polysaccharide fraction from the red alga *Gracilaria caudata* resulting in significant inhibition of neutrophil migration and cytokine release [16]; in vitro *anti-inflammatory* effect of a hexane-soluble fraction of the brown alga *Laminaria japonica* that inhibited nitric oxide, prostaglandin E_2, interleukin (IL)-1β and IL-6 release from lipopolysaccharide-stimulated macrophages via inactivation of nuclear factor-κB transcription factor [17]; in vivo *anti-inflammatory* of a polysaccharide-rich fraction from the marine red alga *Lithothamnion muelleri* that reduced organ injury and lethality, as well as pro-inflammatory cytokines and chemokines, associated with graft-versus-host disease in mice [18]; in vivo clinical effectiveness in an osteoarthritis trial by PCSO-524™, a nonpolar lipid extract from the New Zealand marine green lipped mussel *Perna canaliculus*, which may offer "potential alternative complementary therapy with no side effects for osteoarthritis patients" [19]; enhanced *antioxidant* activity of chitosan nanoparticles as compared to chitosan on hydrogen peroxide-induced stress injury in mouse macrophages in vitro [20]; induction of concentration-dependent *vasoconstrictive* activity on isolated rat aorta by a tentacle extract from the jellyfish *Cyanea capillata* [21]; significant *antioxidant* effect of a sulfated-polysaccharide fraction of the marine red alga *Gracilaria birdiae* which prevented naproxen-induced gastrointestinal damage in rats by reversing glutathione depletion [22]; in vitro *antioxidant* properties of a polysaccharide from the brown seaweed *Sargassum graminifolium* (Turn.) that was also observed to inhibit calcium oxalate crystallization, a constituent of urinary kidney stones [23]; *antioxidant* activity in organic extracts from 30 species of Hawaiian marine algae, with the carotenoid fucoxanthin identified as the major bioactive antioxidant compound in the brown alga *T. ornata* [24]; screening of *antioxidant activity* in 18 cyanobacteria and 23 microalgae cell extracts identified *Scenedesmus obliquus* strain M2-1, which protected against DNA oxidative damage induced by copper (II)-ascorbic acid [25]; *anxiolytic*-like effect of a salmon phospholipopeptidic complex composed of polyunsaturated fatty acids and bioactive peptides associated with strong free radical scavenging properties [26]; *antinociceptive* activity in extracts of the skin of the Brazilian planehead filefish *Stephanolepis hispidus* with partial activation of opioid receptors in the nervous system [27]; strong in vitro *acetylcholinesterase* inhibition, an enzyme targeted by drugs used to treat Alzheimer's disease, myasthenia gravis and glaucoma, by an extract from the polar marine sponge *Latrunculia* sp. [28]; *central nervous system* activity of a phlorotannin-rich extract from the edible brown seaweed *Ecklonia cava* targeting gamma-aminobutyric acid type A benzodiazepine receptors [29]; and novel *protease inhibitors* from Norwegian spring spawning herring determined by screening of marine extracts with assays combining fluorescence resonance energy transfer activity and surface plasmon resonance spectroscopy-based binding [30].

2. Marine Compounds with Antibacterial, Antifungal, Antiprotozoal, Antituberculosis, Antiviral and Anthelmintic Activities

Table 1 presents 2012–2013 preclinical pharmacological research on the antibacterial, antifungal, antiprotozoal, antituberculosis, antiviral and anthelmintic activities of marine natural products (**1**–**113**) shown in Figure 1.

Table 1. Marine pharmacology in 2012–2013: marine compounds with antibacterial, antifungal, antituberculosis, antiprotozoal, antiviral and anthelmintic activities.

Drug Class	Compound/Organism [a]	Chemistry	Pharmacologic Activity	IC_{50} [b]	MMOA [b]	Country [c]	References
Antibacterial	anthracimycin (**1**)/bacterium	Polyketide [d]	*B. anthracis* & *S. aureus* inhibition	0.03–0.06 μg/mL [+]	DNA/RNA inhibition	USA	[31]
Antibacterial	chrysophaentins (**2**,**3**)/alga	Shikimate [h]	Gram-negative & -positive bacterial inhibition	27–84 μM [+]	Competitive inhibition of FtsZ GTP-binding site	ESP, USA	[32]
Antibacterial	merochlorin A (**4**)/bacterium	Terpenoid [e]	*C. dificile* & *S. aureus* strains inhibition	0.3–2 μg/mL [+]	DNA, RNA, protein & cell wall synthesis inhibition	USA	[33]
Antibacterial	aflatoxin B2b (**5**)/fungus	Polyketide [d]	*B. subtilis* & *E. aerogenes* inhibition	1.7, 1.1 μM [+]	Undetermined	CHN	[34]
Antibacterial	ageloxime B (**6**)/sponge	Alkaloid/terpenoid [e]	*S. aureus* inhibition	7.2–9.2 μg/mL *	Undetermined	CHN, USA	[35]
Antibacterial	*Alternaria* sp. anthraquinones (**7**–**9**)/fungus	Polyketide [d]	*E. coli* & *V. parahemolyticus* inhibition	0.62–5 μM [+]	Undetermined	CHN	[36]
Antibacterial	antimycin B2 (**10**)/bacterium	Shikimate/Polyketide [d]	*L. hongkongensis* inhibition	8 μg/mL [+]	Undetermined	CHN	[37]
Antibacterial	*Aspergillus* sp. (−)sydonol (**11**)/fungus	Terpenoid [e]	*S. albus* & *M. tetragenus* inhibition	1.2–5 μg/mL [+]	Undetermined	CHN, NLD	[38]
Antibacterial	axistatins 1–3 (**12**–**14**)/sponge	Alkaloid/terpenoid [e]	*C. neoformans* & *S. aureus* inhibition	1–4 μg/mL [+]	Undetermined	AUS, USA	[39]
Antibacterial	bromophycoic acid A & E (**15**,**16**)/alga	Terpenoid [e]	*S. aureus* & *E. faecilis* inhibition	1.6 μg/mL [+]	Undetermined	FJI, USA	[40]
Antibacterial	cadeolides C–F (**17**–**20**)/tunicate	Shikimate [h]	*S. aureus* inhibition	0.13–3 μg/mL [+]	Undetermined	S. KOR	[41]
Antibacterial	cadiolides E–I (**21**–**23**)/ascidian	Shikimate [h]	*S. aureus* & *B. subtilis* inhibition	0.8–12 μg/mL [+]	Undetermined	S. KOR	[42]
Antibacterial	citreamicin θ A & B (**24**,**25**)/bacterium	Polyketide [d]	*S. aureus* inhibition	0.25–1 μg/mL *	Undetermined	CHN, SAU	[43]
Antibacterial	communol A & F (**26**,**27**)/fungus	Polyketide [d]	*E. coli* inhibition	4.1, 6.4 μg/mL [+]	Undetermined	CHN	[44]
Antibacterial	*D. spiralis* dolabellanes (**28**,**29**)/alga	Terpenoid [e]	*S. aureus* inhibition	2–8 μg/mL [+]	Undetermined	GRC, ESP, UK	[45]
Antibacterial	enhygrolide A (**30**)/bacterium	Shikimate [h]	*A. cristallopoietes* inhibition	4 μg/mL [+]	Undetermined	DEU	[46]
Antibacterial	eudistomin Y11 (**31**)/ascidian	Alkaloid [f]	*B. subtilis* & *S. typhimurium* inhibition	3.12 μg/mL [+]	Undetermined	S. KOR	[47]
Antibacterial	fradimycin B (**32**)/bacterium	Polyketide [d]	*S. aureus* inhibition	2.0 μg/mL [+]	Undetermined	CHN	[48]
Antibacterial	*Haliclona* diAPS (**33**–**35**)/sponge	Alkaloid [f]	*M. luteus* inhibition	3.1 μg/mL [+]	Undetermined	S. KOR	[49]
Antibacterial	hyrtimomine D (**36**)/sponge	Alkaloid [f]	*S. aureus* inhibition	4 μg/mL [+]	Undetermined	JPN	[50]
Antibacterial	ianthelliformisamine A (**37**)/sponge	Alkaloid [f]	*P. aeruginosa* inhibition	6.8 μM	Undetermined	AUS	[51]
Antibacterial	kocurin (**38**)/bacterium	Peptide [f]	MR *S. aureus* inhibition	0.25 μg/mL [+]	Undetermined	ESP, USA	[52]
Antibacterial	lamellarin O (**39**)/sponge	Alkaloid [f]	*B. subtilis* inhibition	2.5 μM	Undetermined	AUS	[53]
Antibacterial	*Laurencia* sesquiterpenes (**40**–**42**)/alga	Terpenoid [e]	*E. coli* & *S. aureus* inhibition	5–7 μg/disk [++]	Undetermined	CHN, USA	[54]
Antibacterial	lobophorin H (**43**)/bacterium	Terpenoid glycoside	*B. subtilis* inhibition	1.57 μg/mL [+]	Undetermined	CHN	[55]
Antibacterial	marthiapeptide A (**44**)/bacterium	Peptide [f]	*M. luteus* & *B. thuringiensis* inhibition	2.0 μg/mL *	Undetermined	CHN	[56]
Antibacterial	napyradiomycin A1 & B3 (**45**,**46**)/bacterium	Terpenoid/polyketide [d]	*S. aureus* inhibition	0.5–2 μg/mL [+]	Undetermined	CHN	[57,58]
Antibacterial	*Nigrospora* sp. anthraquinones (**47**,**48**)/fungus	Polyketide [d]	*E. coli* & *S. aureus* inhibition	0.6–0.7 μM [+]	Undetermined	CHN	[59]
Antibacterial	ohmyungsamycin A (**49**)/bacterium	Peptide [f]	*B. subtilis* inhibition	4.28 μM [+]	Undetermined	S. KOR	[60]
Antibacterial	penicifuran A (**50**)/fungus	Shikimate [h]	*S. albus* inhibition	3.1 μM [+]	Undetermined	CHN	[61]

Table 1. *Cont.*

Drug Class	Compound/Organism [a]	Chemistry	Pharmacologic Activity	IC_{50} [b]	MMOA [b]	Country [c]	References
Antifungal	crambescidin-816 (**51**)/sponge	Alkaloid [f]	*S. cerevisiae* growth inhibition	1 μM [+]	G2/M cell cycle arrest and apoptosis	ESP, FRA	[62]
Antifungal	neothyonidioside (**52**)/sea cucumber	Terpenoid glycoside	*S. cerevisiae* inhibition	1 μM [+]	Binding to plasma membrane sterols	NZL	[63]
Antifungal	ageloxime B (**6**)/sponge	Alkaloid/terpenoid	*C. neoformans* inhibition	4.9 μg/mL *	Undetermined	CHN, USA	[35]
Antifungal	aurantoside K (**53**)/sponge	Polyketide/alkaloid glycoside	*C. albicans* inhibition	1.95 μg/mL [+]	Undetermined	FJI	[64]
Antifungal	caulerprenylol B (**54**)/alga	Terpenoid [e]	*C. glabrata* & *C. neoformans* inhibition	4.0 μg/mL [+]	Undetermined	CHN	[65]
Antifungal	didymellamide A (**55**)/fungus	Alkaloid [f]	*C. albicans* inhibition	3.1 μg/mL [+]	Undetermined	JPN	[66]
Antifungal	hippolachnin A (**56**)/sponge	Polyketide [d]	*T. rubrum*, *M. gypseum* & *C. neoformans* inhibition	0.41 μM [+]	Undetermined	CHN	[67]
Antifungal	holotoxins F & G (**57**,**58**)/sea cucumber	Terpenoid glycoside	*C. albicans*, *Microsporum* & *Cryptococcus* inhibition	1.4–5.8 μM [+]	Undetermined	CHN, DEU	[68]
Antifungal	hyrtimomine D & E (**36**,**59**)/sponge	Alkaloid [f]	*C. albicans* & *C. neoformans* inhibition	4–16 μg/mL [+]	Undetermined	JPN	[50]
Antifungal	nagelamide Z (**60**)/sponge	Alkaloid [f]	*C. albicans* inhibition	0.25 μg/mL *	Undetermined	JPN	[69]
Antifungal	woodylide A (**61**)/sponge	Polyketide [d]	*C. neoformans* inhibition	3.7 μg/mL *	Undetermined	CHN	[70]
Antiprotozoal	araplysillin I (**62**)/sponge	Alkaloid [f]	*P. falciparum* FcB1 & 3D7 strain inhibition	4.5 μM	Undetermined	AUS, DEU, FJI, FRA	[71]
Antiprotozoal	ascidiathiazone A (**63**)/ascidian	Alkaloid [f]	*P. falciparum* K1 strain inhibition	3.3 μM	Undetermined	NZL, CHE	[72]
Antiprotozoal	axidjiferosides A–C (**64**–**66**)/sponge	Glycosphingolipid	*P. falciparum* FcB1strain inhibition	0.53 μM	Undetermined	FRA	[73]
Antiprotozoal	cytosporone E (**67**)/fungus	Polyketide [d]	*P. falciparum* inhibition	13 μM **	Undetermined	USA	[74]
Antiprotozoal	dicerandrol D (**68**)/fungus	Polyketide [d]	*P. falciparum* 3D7 strain inhibition	0.6 μM	Undetermined	CHN, TWN, USA	[75]
Antiprotozoal	dihydroingenamine D (**69**)/sponge	Alkaloid [f]	*P. falciparum* D6 & W2 strain inhibition	57–72 ng/mL	Undetermined	USA	[76]
Antiprotozoal	19-hydroxypsammaplysin E (**70**)/sponge	Alkaloid [f]	*P. falciparum* 3D7strain inhibition	6.4 μM	Undetermined	AUS, IDN	[77]
Antiprotozoal	kabiramide L (**71**)/sponge	Polyketide [d]	*P. falciparum* K1 strain inhibition	2.6 μM	Undetermined	THAI, AUT	[78]
Antiprotozoal	meridianin C & G (**72**,**73**)/tunicate	Alkaloid [f]	*P. falciparum* D6 & W2 strain inhibition	4.4–14.4 μM	Undetermined	IND	[79]
Antiprotozoal	orthidine F (**74**)/ascidian	Alkaloid [f]	*P. falciparum* K1 strain inhibition	0.90 μM	Undetermined	CHE, NZL	[80]
Antiprotozoal	plakortide U (**75**)/sponge	Polyketide [d]	*P. falciparum* FcM29 strain inhibition	0.8 μM	Undetermined	FRA, ITA	[81]
Antiprotozoal	thiaplakortone A (**76**)/sponge	Alkaloid [f]	*P. falciparum* 3D7 & Dd2 strain inhibition	0.006–0.051 μM	Undetermined	AUS	[82]
Antiprotozoal	tsitikammamine C (**77**)/sponge	Alkaloid [f]	*P. falciparum* 3D7 & Dd2 strain inhibition	13 & 18 nM	Undetermined	AUS	[83]
Antiprotozoal	urdamycinone E (**78**)/bacterium	Polyketide [d]	*P. falciparum* K1 strain inhibition	0.05 μg/mL	Undetermined	THAI	[84]
Antiprotozoal	almiramide (**79**,**80**)/bacterium	Peptide [f]	*T. brucei* inhibition	0.4–3.5 μM	Glycosome function inhibition	USA	[85]
Antiprotozoal	diazepinomicin (**81**)/bacterium	Alkaloid/terpenoid	*T. brucei* inhibition	13.5 μM	Rhodesain inhibition	EGY, DEU	[86]
Antiprotozoal	(−)-elatol (**82**)/alga	Terpenoid [e]	*T. cruzi* inhibition	1.5–3 μM *	Mitochondrial disfunction	BRA	[87]
Antiprotozoal	ascidiathiazone A (**63**)/ascidian	Alkaloid [f]	*T. b. rhodesiense* inhibition	3.1 μM	Undetermined	NZL, CHE	[72]
Antiprotozoal	coibacin A (**83**)/bacterium	Polyketide [d]	*L. donovani* inhibition	2.4 μM	Undetermined	USA, PAN	[88]
Antiprotozoal	cristaxenicin A (**84**)/gorgonian	Terpenoid [e]	*T. congolense* & *L. amazonensis* inhibition	0.25 & 0.088 μM	Undetermined	JPN	[89]
Antiprotozoal	manadoperoxide B analogues (**85**,**86**)/sponge	Polyketide [d]	*T. b. rhodesiense* inhibition	3–11 ng/mL	Undetermined	ITA, IDN, CHE, IRL	[90]

Table 1. *Cont.*

Drug Class	Compound/Organism [a]	Chemistry	Pharmacologic Activity	IC_{50} [b]	MMOA [b]	Country [c]	References
Antituberculosis	asperterpenoid A (**87**)/fungus	Terpenoid [e]	*M. tuberculosis* PTP inhibition	2.2 μM	Undetermined	CHN	[91]
Antituberculosis	brevianamide S (**88**)/fungus	Alkaloid [f]	BCG inhibition	6.25 μg/mL [+]	Undetermined	AUS, CHN	[92]
Antituberculosis	lobophorin G (**89**)/bacterium	Terpenoid [e] glycoside	BCG inhibition	1.56 μg/mL [+]	Undetermined	CHN	[93]
Antituberculosis	neamphamide B (**90**)/sponge	Peptide [f]	*M. bovis* inhibition	1.56 μg/mL [+]	Undetermined	JPN	[94]
Antituberculosis	*S. flava* diterpenes (**91**,**92**)/sponge	Terpenoid [e]	*M. tuberculosis* H37Rv inhibition	15, 32 μg/mL [+]	Undetermined	USA	[95]
Antituberculosis	urdamycinone E (**78**)/bacterium	Polyketide [d]	*M. tuberculosis* H37Ra inhibition	3.13 μg/mL [+]	Undetermined	THAI	[84]
Antiviral	halistanol sulfates (**93**,**94**)/sponge	Terpenoid [f]	Human *Herpes simplex* virus-1 inhibition	0.5–12.2 μg/mL	Attachment & penetration inhibition	ARG, BRA	[96]
Antiviral	*L. arboreum* metabolites (**95**–**97**)/ soft coral	Terpenoid/sphingolipid	HIV-1 protease inhibition	4.8–7.2 μM *	Molecular docking & HIV-1 protease receptor	ZAF	[97]
Antiviral	manoalide (**98**)/sponge	Terpenoid [e]	Hepatitis C virus inhibition	15–70 μM	RNA helicase and ATPase inhibition	JPN	[98]
Antiviral	*N. aculeata* metabolites (**99**,**100**)/alga	Polyketide [d]	Human rhinoviruses 2 & 3 inhibition	2.5–7.1 μg/mL	Cytopathic effect inhibition	S. KOR	[99]
Antiviral	stachybotrin D (**101**)/fungus	Alkaloid/terpenoid	HIV-1 replication inhibition	8.4 μM	Reverse transcriptase inhibition	CHN	[100]
Antiviral	streptoseolactone (**102**)/bacterium	Terpenoid [f]	Neuraminidase inhibition	3.9 μM	Noncompetitive inhibition	CHN	[101]
Antiviral	asperterrestide A(**103**)/fungus	Peptide [f]	H3N2 influenza virus inhibition	8.1 μM	Undetermined	CHN	[102]
Antiviral	*Cladosporium* sp. alkaloids (**104**,**105**)/fungus	Alkaloid [f]	H1N1 influenza virus inhibition	82–85 μM	Undetermined	CHN	[103]
Antiviral	isorhodoptilometrin-1-methyl ether (**106**)/fungus	Polyketide [d]	Hepatitis C NS3/4A protease inhibition	>1 ng/mL *	Undetermined	EGY	[104]
Antiviral	massarilactone H (**107**)/fungus	Polyketide [d]	Influenza virus neuraminidase inhibition	8.2 μM	Undetermined	CHN, MYS	[105]
Antiviral	pyronepolyene C-glucoside (**108**)/fungus	Polyketide [d]	H1N1 influenza virus inhibition	91.5 μM	Undetermined	CHN	[106]
Antiviral	*S. candidula* sterol (**109**,**110**)/soft coral	Terpenoid/sphingolipid	H5N1 avian influenza virus inhibition	1 ng/mL *	Undetermined	EGY	[107]
Antiviral	*S. vulgare* glycolipid (**111**)/alga	Glycolipid	Human herpes simplex virus-1 & 2 inhibition	<50 μg/mL	Undetermined	BRA	[108]
Anthelmintic	echinosides A & B (**112**,**113**)/ sea cucumber	Terpenoid glycoside	*S. mansoni* worm lethality	0.19, 0.27 μg/mL [+++]	Undetermined	EGY	[109]

([a]) **Organism**: *Kingdom Animalia*: ascidian (Phylum Chordata), gorgonian, coral (Phylum Cnidaria), sea cucumber (Phylum Echinodermata), sponge (Phylum Porifera); *Kingdom Monera*: bacterium (Phylum Cyanobacteria); *Kingdom Fungi*: fungus; *Kingdom Plantae:* alga; ([b]) **IC_{50}**: concentration of a compound required for 50% inhibition in vitro, *: estimated IC_{50}, **: IC_{90}, [+]: MIC: minimum inhibitory concentration, [++]: MID: minimum inhibitory concentration per disk; [+++]: LC_{50}: concentration of a compound required for 50% lethality; **MMOA**: molecular mechanism of action; ([c]) **Country**: ARG: Argentina; AUS: Australia; AUT: Austria; BRA: Brazil; CHE: Switzerland; CHN: China; DEU: Germany; EGY: Egypt; ESP: Spain; FJI: Fiji; FRA: France; GRC: Greece; IDN: Indonesia; IND: India; IRL: Ireland; ITA: Italy; JPN: Japan; MYS: Malaysia; NLD: The Netherlands; NZL: New Zealand; PAN: Panama; SAU: Saudi Arabia; S. KOR: South Korea; THAI: Thailand; TWN: Taiwan; UK: United Kingdom; ZAF: S. Africa; **Chemistry**: ([d]) Polyketide; ([e]) Terpene; ([f]) Nitrogen-containing compound; ([g]) Polysaccharide, ([h]) Shikimate; **Abbreviations**: BCG: Bacille Calmette-Guérin; diAPS: dialkylpyridinium; MR: methicillin-resistant.

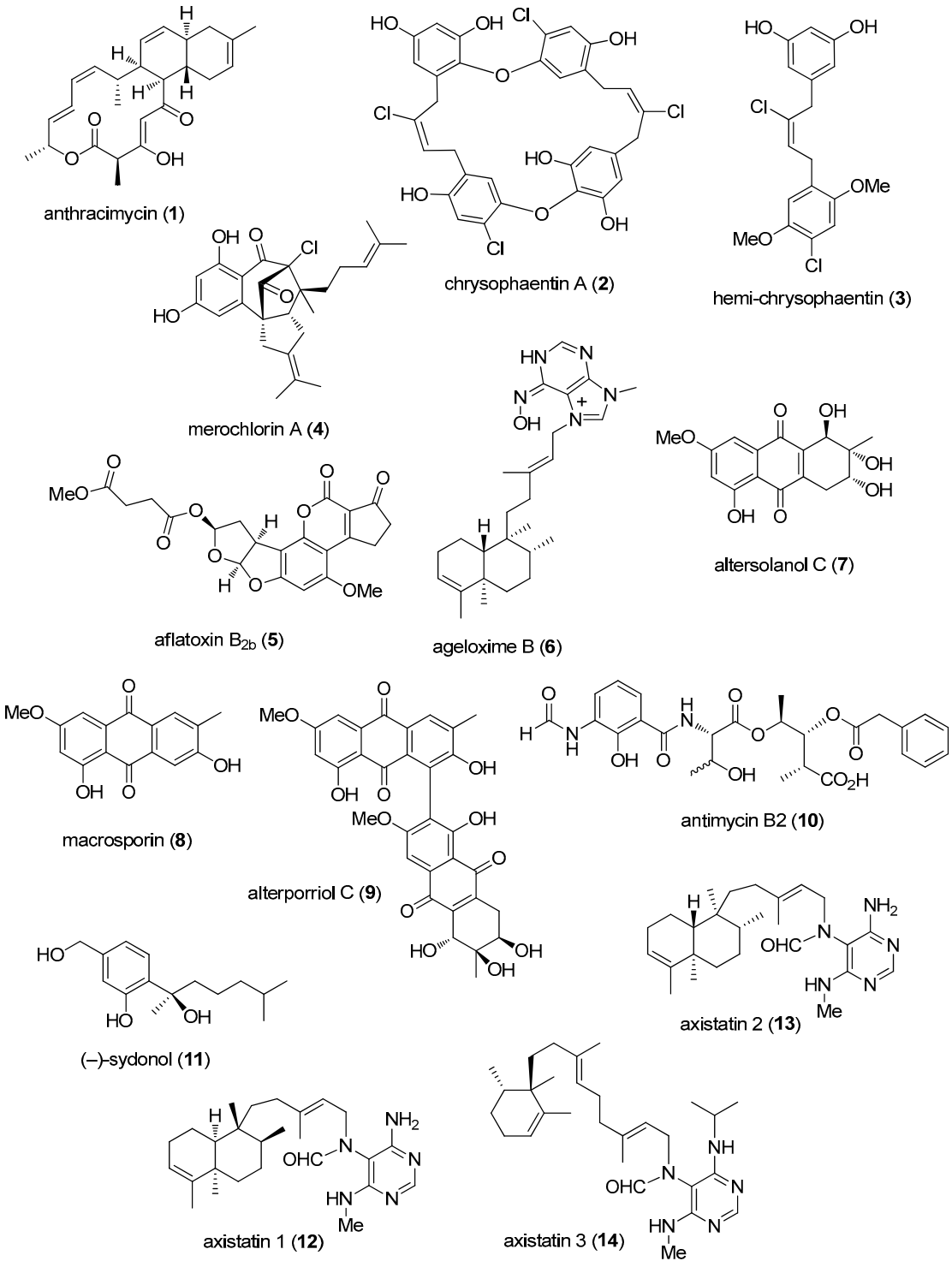
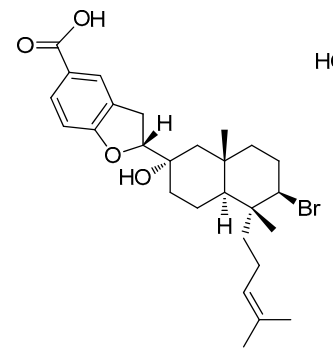
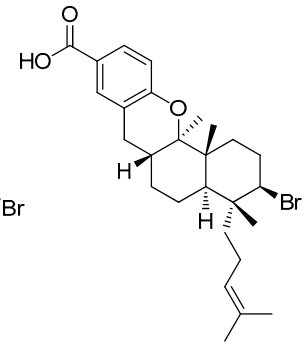


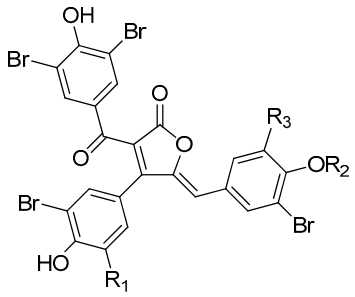
Figure 1. *Cont.*



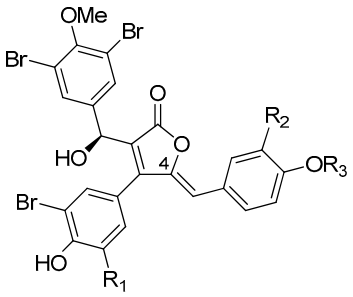
bromophycoic acid A (**15**)



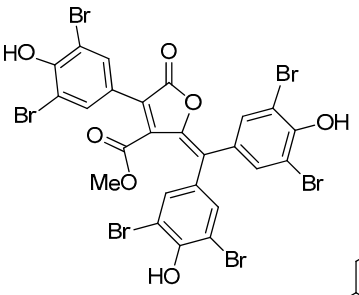
bromophycoic acid E (**16**)



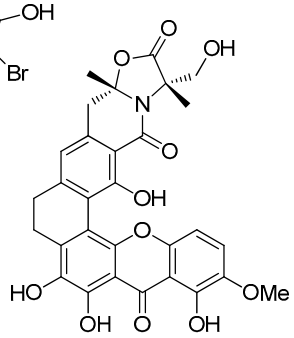
cadiolide C (**17**) $R_1 = R_2 = R_3 = H$
cadiolide D (**18**) $R_1 = Br$ $R_2 = R_3 = H$
cadiolide E (**19**) $R_1 = R_2 = H$ $R_3 = Br$
cadiolide F (**20**) $R_1 = R_3 = H$ $R_2 = Me$



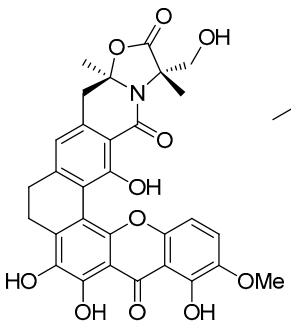
cadiolide G (**21**) $R_1 = R_3 = H$ $R_2 = Br$
4Z-cadiolide H (**22a**) $R_1 = Br$ $R_2 = H$ $R_3 = Me$
4E-cadiolide H (**22b**) $R_1 = Br$ $R_2 = H$ $R_3 = Me$



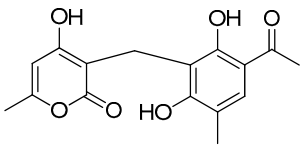
cadiolide I (**23**)



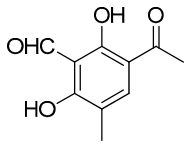
citreamicin θ A (**24**)



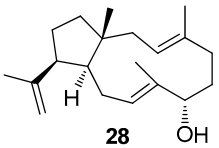
citreamicin θ B (**25**)



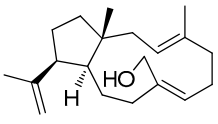
communol A (**26**)



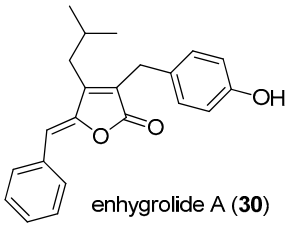
communol F (**27**)



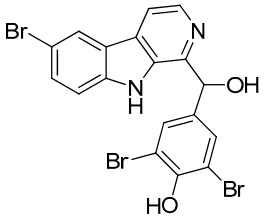
28



29



enhygrolide A (**30**)



eudistomin Y_{11} (**31**)

Figure 1. *Cont.*

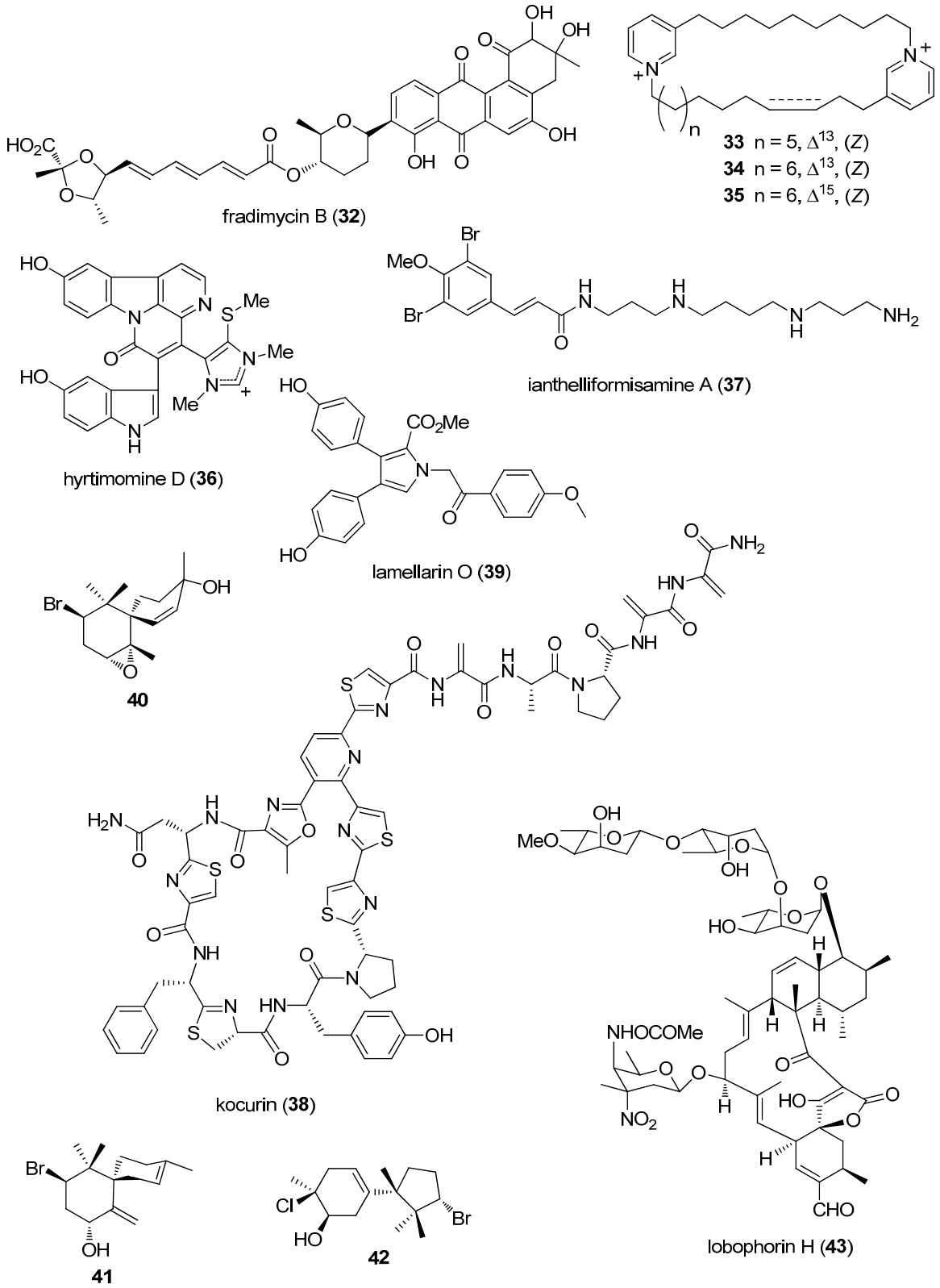


Figure 1. *Cont.*

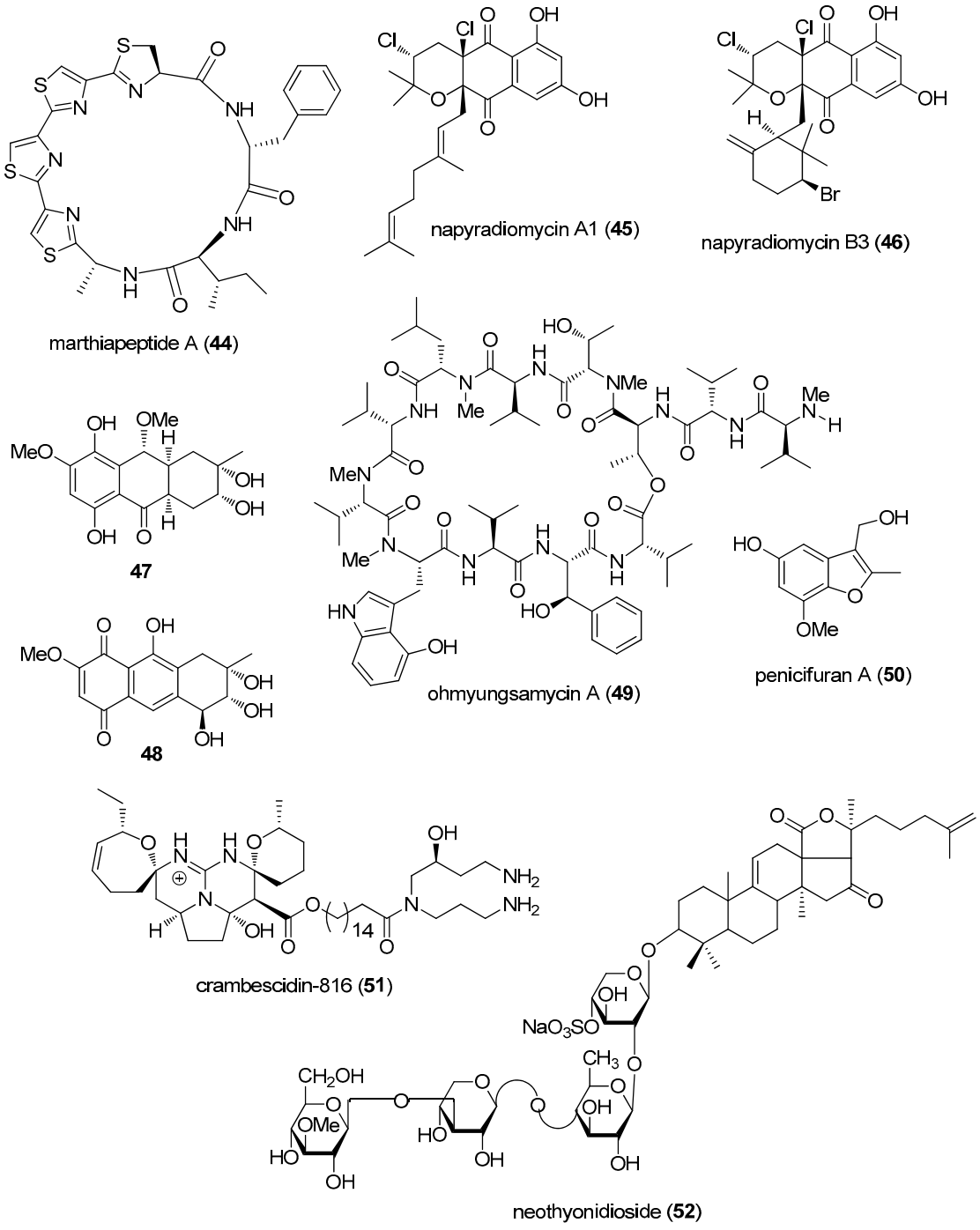


Figure 1. *Cont.*

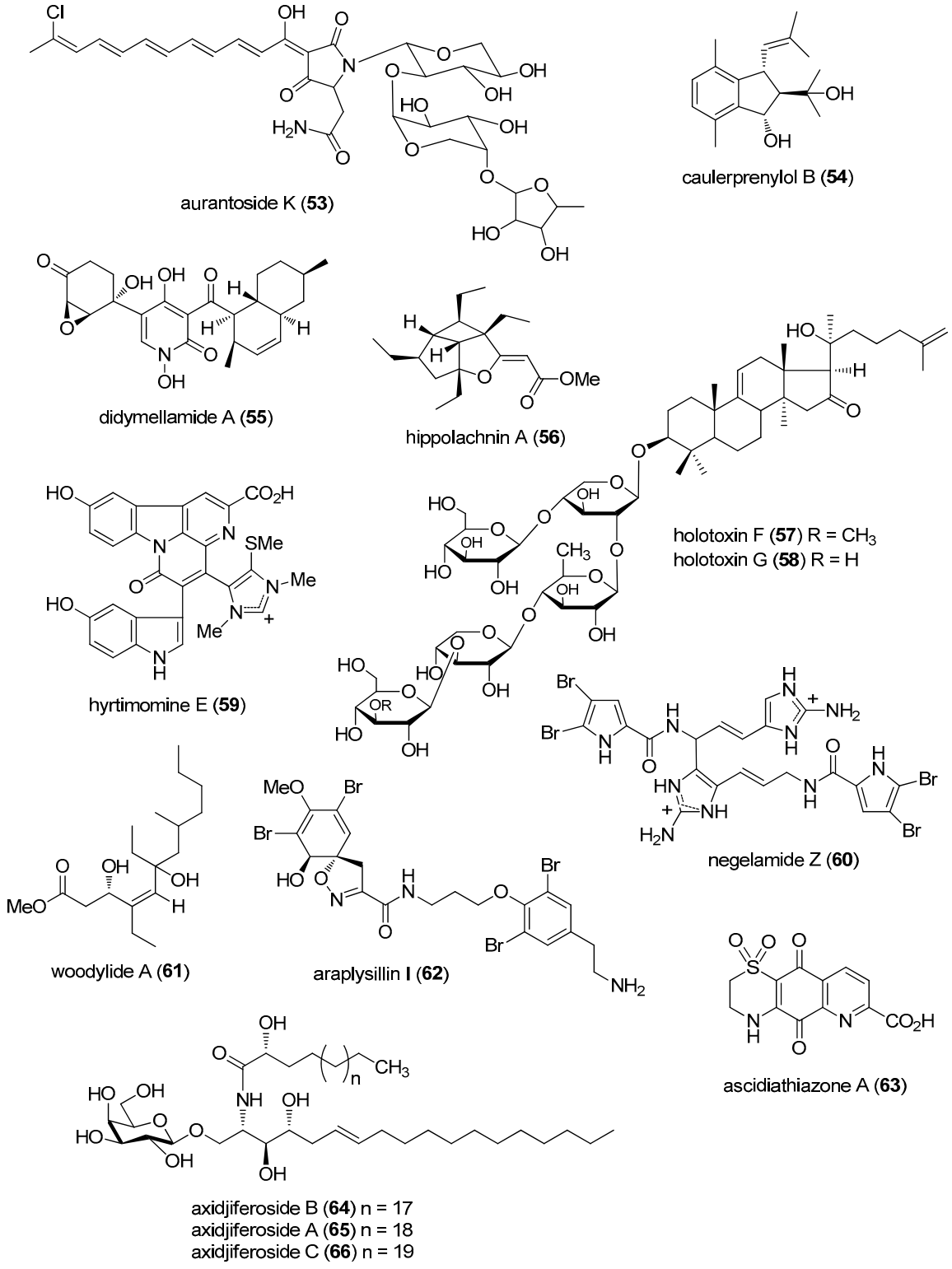


Figure 1. *Cont.*

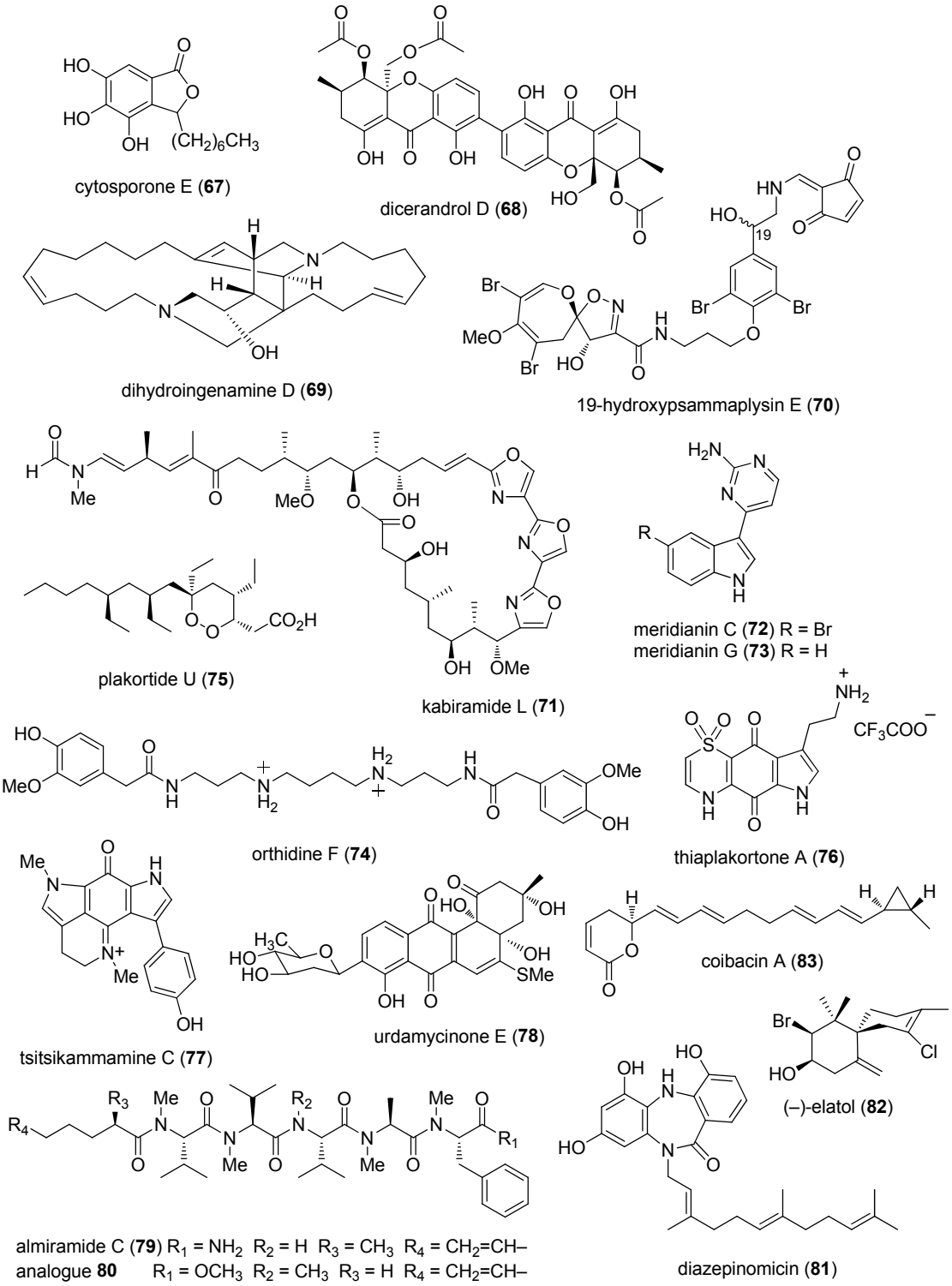


Figure 1. *Cont.*

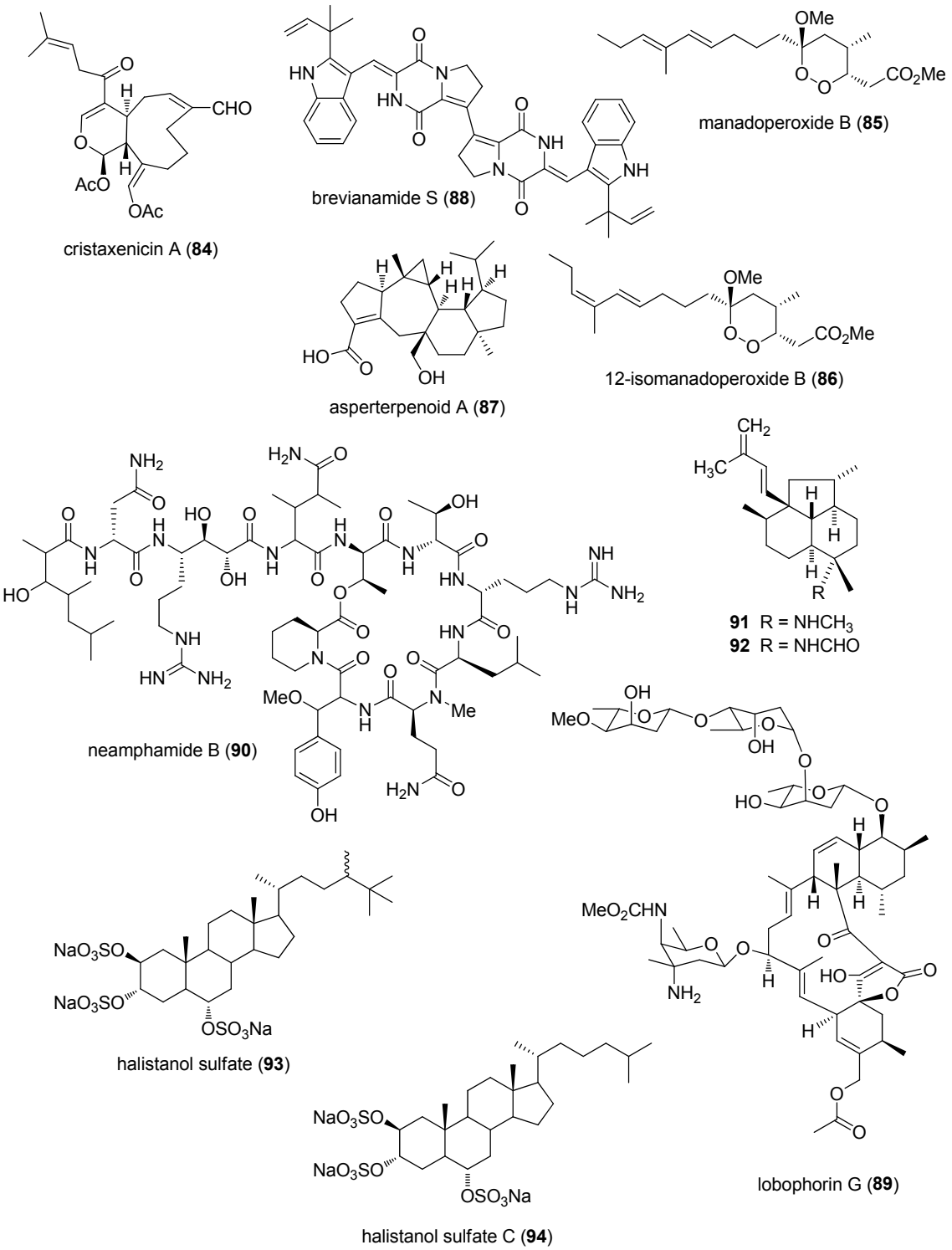
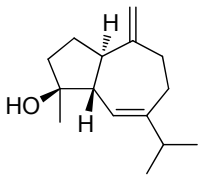
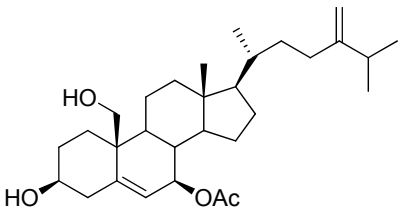


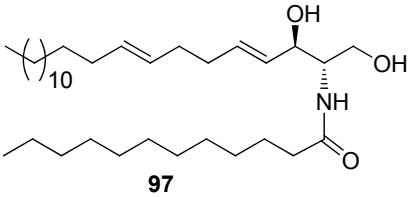
Figure 1. *Cont.*



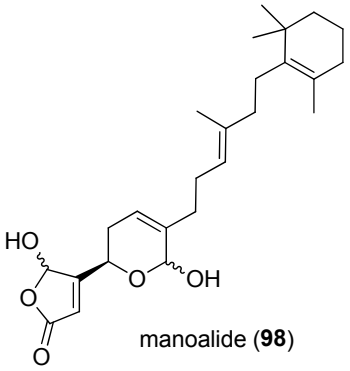
alismol (**95**)



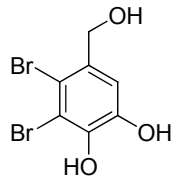
96



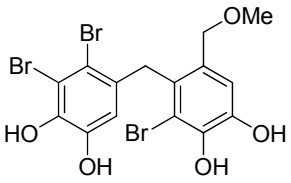
97



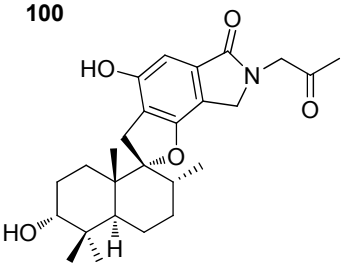
manoalide (**98**)



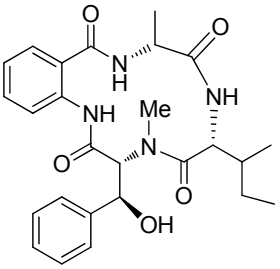
lanosol (**99**)



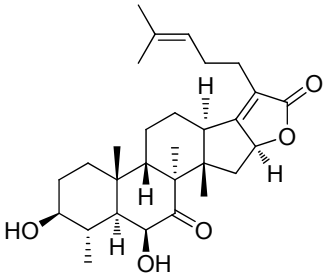
100



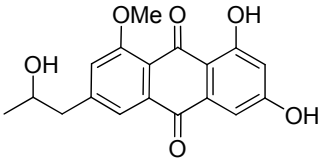
stachybotrin D (**101**)



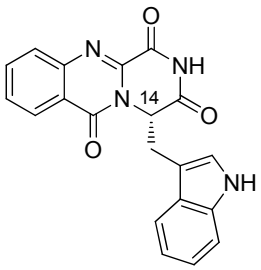
asperterrestide A (**103**)



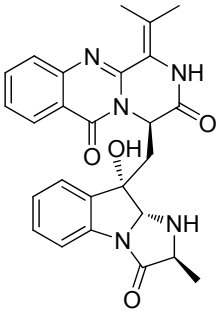
streptoseolactone (**102**)



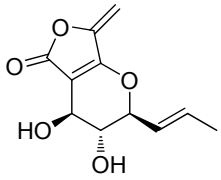
isorhodoptilometrin-1-methyl ether (**106**)



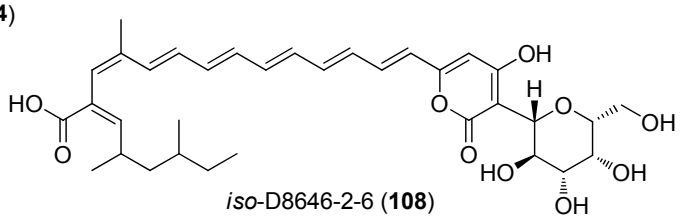
(14*S*)-oxoglyantrypine (**104**)



norquinadoline A (**105**)



massarilactone H (**107**)



iso-D8646-2-6 (**108**)

Figure 1. *Cont.*

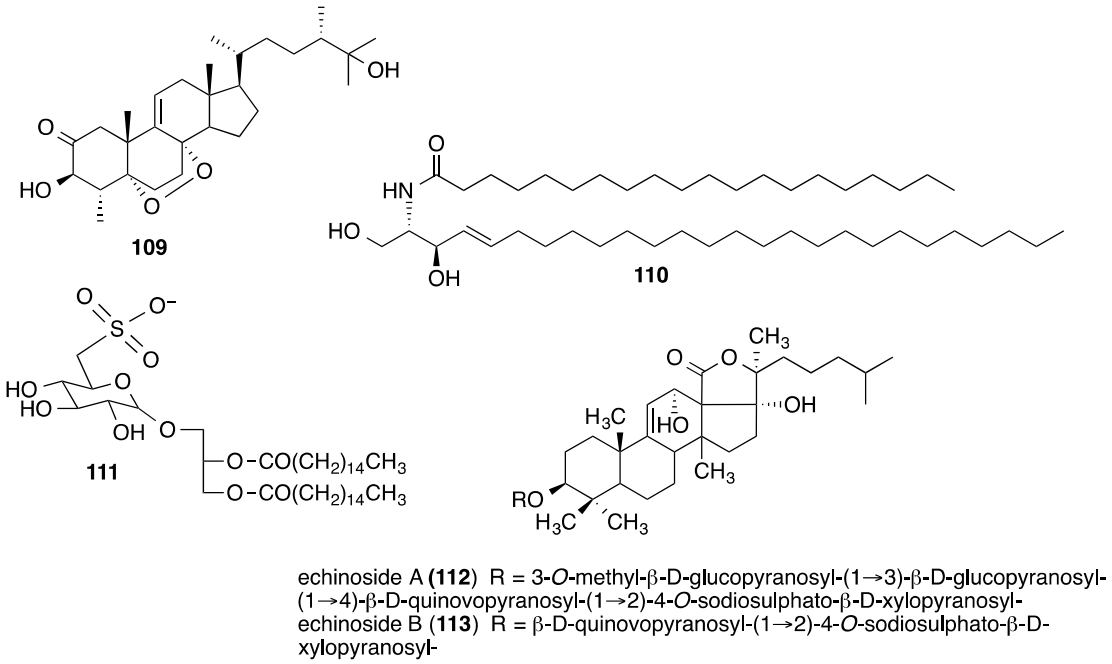


Figure 1. Marine pharmacology in 2012–2013: marine compounds with antibacterial, antifungal, antiprotozoal, antituberculosis, and antiviral activities.

2.1. Antibacterial Activity

During 2012–2013, 31 studies reported *antibacterial* marine natural products (**1**–**50**) isolated from bacteria, fungi, tunicates, sponges, and algae, a global effort that may contribute to the search for novel leads for developing newer drugs to treat drug-resistant bacterial infections.

As shown in Table 1 and Figure 1, three papers reported molecular mechanism of action studies with marine antibacterial compounds. Jang and colleagues reported a potent antianthrax antibiotic, anthracimycin (**1**), derived from a marine actinomycete with significant activity against *Bacillus anthracis*, by a mechanism that " ... remains to be fully defined ... " but that appears to involve DNA/RNA synthesis inhibition [31]. Keffer and colleagues extended the mechanism of action of *bis*-diarylbutene macrocycle chrysophaentins (**2**,**3**), isolated from the chrysophyte alga *Chrysophaeum taylori*, by determining that they competitively inhibited the biochemical activity of the Gram-positive and Gram-negative cell division protein FtsZ by binding to its GTP-binding site [32]. Sakoulas and colleagues reported the antibacterial activity of merochlorin A (**4**), a meroterpenoid isolated from a marine-derived actinomycete strain CNH189, which demonstrated activity against Gram-positive bacteria including *Clostridium difficile*, but not against Gram-negative bacteria, by a mechanism that appeared to involve " ... global inhibition of DNA, RNA, protein, and cell wall synthesis ... " [33].

As shown in Table 1 and Figure 1, 46 marine chemicals (**5**–**50**), some of them novel, were reported to exhibit antibacterial activity with MICs < 10 μg/mL or 10 μM against several bacterial strains, although the mechanism of action for these compounds remained undetermined: a novel aflatoxin B_{2b} (**5**), isolated from the fungus *Aspergillus flavus*; 092008, isolated from the root of the mangrove *H. tiliaceus* from Hainan, China [34]; a new alkaloid ageloxime B (**6**), isolated from the South China Sea marine sponge *Agelas mauritiana* [35]; several known yet bioactive compounds namely altersolanol C (**7**), macrosporin (**8**) and alterporriol C (**9**) isolated from a soft-coral derived from South China Sea fungus *Alternaria* sp. [36]; a novel antimycin A analogue, antimycin B2 (**10**), derived from the actinomycete *Streptomyces lusitanus*, isolated from the mangrove *Avicennia mariana* in Fujian, China [37]; a new bisabolane-type sesquiterpenoid (−)-sydonol (**11**) from a South China Sea sponge-derived fungus *Aspergillus* sp. [38]; three new pyrimidine diterpenes designated axistatins 1 (**12**), 2 (**13**) and 3 (**14**), isolated from the marine sponge *Agelas axifera* collected in the Republic of

Palau [39]; two new diterpene-benzoate compounds bromophycoic acid A (**15**) and E (**16**) from a Fijian red alga *Callophycus* sp. [40]; new butenolide cadiolides C–F (**17**–**20**) from a Korean tunicate *Pseudodistoma antinboja* [41]; novel tris-aromatic furanones cadiolides G-I (**21**–**23**) from the Korean dark red ascidian *Synoicum* sp. [42]; xanthones citreamicins θ A and B (**24**,**25**), isolated from the Red Sea marine *Streptomyces caelestis* [43]; two new aromatic polyketides, communols A and F (**26**,**27**), isolated from the marine *Penicillium commune* 518, associated with the gorgonian *Muricella abnormalis* [44]; two dolabellane diterpenes (**28**,**29**), isolated from the Greek brown alga *Dilophus spiralis* [45]; a novel enhygrolide A (**30**), isolated from the obligate marine myxobacterium *Enhygromyxa salina* from a mud sample from Prerow, Germany [46]; a new β-carboline alkaloid eudistomin Y_{11} (**31**), isolated from a purple-colored ascidian *Synoicum* sp. [47]; a new capoamycin-type antibiotic fradimycin B (**32**), isolated from the marine *Streptomyces fradiae* strain PTZ0025 [48]; three novel cyclic *bis*-1,3 dialkylpyridiniums (**33**–**35**) from a Korean sponge *Halyclona* sp. [49]; a novel bisindole alkaloid hyrtimomine D (**36**), isolated from an Okinawan marine sponge *Hyrtios* sp. [50]; a new bromotyrosine-derived metabolite, ianthellisformisamine A (**37**), reported from the Australian marine sponge *Suberea ianthelliformis* [51]; a new thiazolyl peptide kocurin (**38**) from the marine-derived bacterium *Kocuria palustris* [52]; the known alkaloid lamellarin O (**39**), isolated from a southern Australian sponge *Ianthella* sp. [53]; three new halogenated sesquiterpenes (**40**–**42**), isolated from the Chinese marine red alga *Laurencia okamurai* [54]; a new spirotetronate antibiotic, lobophorin H (**43**) from a South China Sea-*Streptomyces* sp. 12A35 [55]; a new cyclopeptide marthiapeptide A (**44**), isolated from the South China Sea-derived bacterium *Marinactinospora thermotolerans* [56]; two known napyradiomycin A1 (**45**) and napyradiomycin B3 (**46**) from a Chinese marine-derived *Streptomyces* sp. strain SCSIO [57,58]; two new hydroanthraquinone analogues 4a-*epi*-9α-methoxydihydrodeoxybostrycin (**47**) and 10-deoxy-bostrycin (**48**), isolated from a South China Sea marine-derived fungus *Nigrospora* sp., isolated from an unidentified sea anemone [59]; a novel cyclic peptide ohmyungsamycin A (**49**) from a Korean *Streptomyces* sp. strain SNJ042 [60]; and a novel benzofuran penicifuran A (**50**), obtained from a South China Sea sponge-derived fungus *Penicillium* sp. strain MWZ14-4 [61].

Furthermore, during 2012–2013, several other marine natural products, some of them novel, reported MICs or IC_{50}s ranging from 10 to 50 μg/mL, or 10–50 μM, respectively, and thus, because of their lower antibacterial potency, were excluded from Table 1 and Figure 1: guaiazulene-derived terpenoids from a Chinese gorgonian *Anthogorgia* sp. (MIC = 12.7–18 μg/mL) [110]; novel fulvynes antimicrobial polyoxygenated acetylenes from the Mediterranean sponge *Haliclona fulva* (IC_{50} = 12–60 μM) [111]; bioactive polyhydroxylated halicrasterols (MIC = 4–32 μg/mL) from the Chinese marine sponge *Haliclona crassiloba* [112]; hunanamycin A, an antibiotic (MIC = 12.4 μM), isolated from the Bahamanian marine-derived *Bacillus hunanensis* [113]; three new dimeric bromopyrrole alkaloids, nagelamides X–Z (MIC = 8–32 μg/mL) from an Okinawan marine sponge *Agelas* sp. [69]; a new anthraquinone-citrin derivative (MIC = 16 μg/mL), isolated from the sea fan-derived fungus *Penicillium citrinum* PSU-F51 [114]; and a new chlorinated benzophenone derivative, (±)-pestalachloride C (MIC = 5–20 μM) from a South China Sea soft coral-derived fungus *Pestalotiopsis* sp. [115]. Finally, during 2012–2013, the novel marine lipopeptides, peptidolipins B–F (MIC = 64 μg/mL), were isolated from an ascidian-derived Gram positive *Nocardia* sp. bacterium [116].

2.2. Antifungal Activity

Eleven studies during 2012–2013 reported on the *antifungal* activity of several novel marine natural products (**6**,**36**,**51**–**60**), isolated from marine fungi, sponges, sea cucumbers and algae, a slight decrease from our last review [7], and previous reviews of this series.

As shown in Table 1 and Figure 1, two reports described antifungal marine chemicals with novel mechanisms of action. Rubiolo and colleagues investigated the guanidine antifungal alkaloid crambescidin-816 (**51**), previously isolated from the Mediterranean sponge *Crambe crambe* [62]. Detailed cell cycle studies in the yeast *Saccharomyces cerevisiae* demonstrated that this compound induced G2/M cell cycle arrest followed by apoptosis and mitochondrial disfunction, suggesting

that although cytotoxic crambescidin-816 " ... .could serve as a lead compound to fight fungal infections". Yibmantasiri and colleagues investigated the molecular basis for the fungicidal action of the triterpene glycoside neothyonidioside (**52**) isolated from the sea cucumber *Australostichopus mollis* [63], demonstrating that neothyonidioside binds directly to fungal ergosterol affecting membrane curvature and fusion capability essential for membrane recycling and lysosomal degradation.

Furthermore, as shown in Table 1 and Figure 1, several marine natural products showed significant antifungal activity (i.e., MICs that were either less than 10 μg/mL, 10 μM, or 10 μg/disk), although no mechanism of action studies were reported in the published articles: a novel alkaloid ageloxime B (**6**), isolated from the South China Sea sponge *Agelas mauritiana* [35]; a novel tetramic acid glycoside, aurantoside K (**53**), isolated from a Fijian marine sponge *Melophlus* sp. [64]; a new prenylated *para*-xylene caulerprenylol A (**54**), isolated from the green alga *Caulerpa racemosa* collected in the Zhanjiang coastline, China [65]; a new 4-hydroxy-2-pyridone alkaloid didymellamide A (**55**), isolated from the Japanese marine-derived fungus *S. cucurbitacearum* [66]; a new polyketide hippolachnin A (**56**), reported from the South China Sea sponge *Hippospongia lachne* [67]; novel triterpene glycosides holotoxin F and G (**57**,**58**), isolated from the sea cucumber *Apostichopus japonicus* Selenka, "a traditional tonic with high economic value" in China [68]; a novel bisindole alkaloid hyrtimomine D and E (**36**,**59**), isolated from an Okinawan marine sponge *Hyrtios* sp. [50]; a novel dimeric alkaloid nagelamide Z (**60**), isolated from a Japanese sponge *Agelas* sp. [69]; and a new linear polyketide woodylide A (**61**), isolated from the South China Sea sponge *Plakortis simplex* [70]. Ongoing mechanism of action studies with these potent marine compounds will be required to characterize their molecular pharmacology.

Finally, several novel structurally-characterized marine molecules demonstrated MICs or IC_{50}s greater than 10 μg/mL, 10 μM, or 10 μg/disk, and therefore, because of the reported weaker antifungal activity, were excluded from Table 1 and Figure 1: three triterpene glycosides, cucumariosides A_1, A_6 and A_{15} (MIC = 20 μg/mL), isolated from the Pacific Sea cucumber *Eupentacta fraudatrix* [117]; a tetranorditerpenoid derivative isolated from *Aspergillus wentii* EN-48 (MIC = 16 μg/mL), a fungus isolated from an unidentified marine brown algae [118]; and bromophenol-aconitic acid adduct, symphyocladin G, isolated from the marine red alga *Symphyocladia latiuscula* (MIC = 10 μg/mL) [119]. These novel marine compounds may contribute to ongoing research for clinically useful antifungal agents.

2.3. Antiprotozoal and Antituberculosis Activity

As shown in Table 1, during 2012–2013 twenty five studies contributed to novel findings on *antiprotozoal* (*antimalarial*, *antileishmanial and antitrypanosomal*) and *antituberculosis* pharmacology of structurally characterized marine natural products (**62**–**92**), a decrease from previous 1998–2011 reviews [1–8].

Malaria, which is caused by protozoa of the genus *Plasmodium* (*P. falciparum*, *P. ovale*, *P. vivax* and *P. malariae*), affects millions of people worldwide. Contributing to the global search for novel antimalarial drugs, and as presented in Table 1, seventeen novel marine molecules (**62**–**78**), isolated from bacteria, ascidians, fungi, sponges, and tunicates, were shown during 2012–2013 to possess *antimalarial activity*, although mechanism of action studies were not reported for these compounds.

As shown in Table 1 and Figure 1, potent (IC_{50} < 2 μM) to moderate (IC_{50} > 2–10 μM) *antimalarial* activity was reported for several marine natural products (**62**–**78**), isolated from ascidians, sponges, bacteria and fungi. Mani and colleagues reported antiplasmodial activity in the bromotyrosine derivative araplysillin I (**62**) from the South Pacific Solomon Islands sponge *Suberea ianthelliformis* [71]. Lam and colleagues extended the pharmacology of the New Zealand ascidian dioxothiazino-quinoline-quinone metabolite ascidiathiazone A (**63**) by demonstrating it to be a moderate growth inhibitor of chloroquine and a pyrimethamine resistant *P. falciparum* K1 strain, and noting that changing the quinolone-based structure to incorporate benzofuran or benzothiophene moieties yielded particularly potent antimalarials [72]. Farokhi and colleagues characterized new glycosphingolipids axidjiferoside A–C (**64**–**66**) from the Senegal marine sponge *Axinyssa djiferi* with potent antimalarial activity against chloroquine-resistant FcB1/Colombia *P. falciparum* strain [73]. Beau and colleagues reported that epigenetic tailoring of the marine fungus *Leucostoma persoonii*

enhanced production of the known polyketide cytosporone E (**67**), which inhibited *P. falciparum* with significant selectivity [74]. Calcul and colleagues reported a massive screening of Chinese mangrove endophytic fungi and discovered several new compounds, including a novel dimeric tetrahydroxanthone polyketide dicerandrol D (**68**), which was potent against "a robust and validated" drug-sensitive *P. falciparum* strain 3D7 [75]. Ilias and colleagues reported a novel pentacyclic ingamine alkaloid dihydroingenamine D (**69**), isolated from a sponge *Petrosid* Ng5 sp.5, which showed strong antiplasmodial activity against *P. falciparum* D6 and W2 strains [76]. Mudianta and colleagues reported that the novel alkaloid 19-hydroxypsammaplysin E (**70**) from the Indonesian marine sponge *Aplysinella strongylata* had notable antimalarial activity against the *P. falciparum* chloroquine-sensitive 3D7 strain [77]. Sirirak and colleagues reported a new trisoxazole macrolide kabiramide L (**71**) from the Thai marine sponge *Pachatrissa nux* that had moderate activity against a *P. falciparum* K1 multidrug-resistant strain [78]. Bharate and colleagues extended the pharmacology of the known meridianin C and G alkaloids (**72**,**73**), originally isolated from the marine tunicate *Aplidium meridianum*, by reporting that they inhibited both chloroquine-resistant D6 and sensitive W2 clones of *P. falciparum* [79]. Liew and colleagues identified orthidine F (**74**), a metabolite from the New Zealand ascidian *Aplidium orthium* of low toxicity and a moderate growth inhibitor of *P. falciparum* K1 strain dual drug-resistant strain [80]. Lin and colleagues isolated a new polyketide endoperoxide plakortide U (**75**) from the Fijian sponge *Plakinastrella mamillaris* with potent antimalarial activity against chloroquine-resistant *P. falciparum* FcM29 strain [81]. Davis and colleagues isolated several novel thiazine alkaloids from the Australian marine sponge *Plakortis lita*, one of which thiaplakortone A (**76**), showed potent activity against the human malaria parasite *Plasmodium falciparum* strains 3D7 and Dd2 with low cytotoxicity [82]. Davis and colleagues reported a novel bispyrroloiminoquinone alkaloid tsitikammamine C (**77**) from an Australian sponge *Zyzzya* sp. that displayed potent activity against *P. falciparum* chloroquine-sensitive 3D7 and -resistant dd2 strains [83]. Supong and colleagues reported a novel *C*-glycosylated benz[*a*]anthraquinone derivative, urdamycinone E (**78**) isolated from a marine *Streptomyces* sp. BCC45596 that potently inhibited *P. falciparum* K1 strain [84].

As shown in Table 1 and Figure 1, nine marine compounds (**79**–**86**) isolated from bacteria, ascidians, sponges, soft corals and algae were reported to possess bioactivity towards so-called neglected protozoal diseases, namely leishmaniasis, caused by the genus *Leishmania* (*L.*), amebiasis, trichomoniasis, and both African sleeping sickness (caused by *Trypanosoma* (*T.*) *brucei rhodesiense* and *T. brucei gambiense*) and American sleeping sickness or Chagas disease (caused by *T. cruzi*).

As shown in Table 1, three reports described four *antitrypanosomal* marine chemicals (**79**–**82**) as well as their mechanisms of action. Sanchez and colleagues examined the mode of action of almiramides (**79**,**80**), originally isolated from the cyanobacterium *Lyngbya majuscula*, and demonstrated for the first time that these compounds inhibited *T. brucei* by disrupting the parasite's glycosomal function by targeting two membrane proteins, and were thus considered "encouraging candidates for further lead development" [85]. Abdelmohsen and colleagues reported that the dibenzodiazepine alkaloid diazepinomicin (**81**) isolated from a strain of *Micromonospora* sp. RV115 associated with the Croatian marine sponge *Aplysina aerophoba* showed activity against *T. brucei* trypmastigote forms and inhibited the parasite protease rhodesain [86]. Desoti and colleagues extended the pharmacology of (−)-elatol (**82**), a sesquiterpene isolated from the Brazilian red alga *Laurencia dendroidea* shown to affect trypomastigotes of *T. cruzi*, demonstrating that it induced initial depolarization of the parasite's mitochondrial membrane, followed by an increase in superoxide generation, as well as loss of cell membrane and DNA integrity [87].

As shown in Table 1 and Figure 1, five marine natural products (**63**,**83**–**86**) were characterized to exhibit *antileishmanial* and *antiprotozoal* activity, although the mechanism of action remained undetermined. Lam and colleagues reported that the known dioxothiazino-quinoline-quinone metabolite ascidiathiazone A (**63**), isolated from a New Zealand ascidian, moderately inhibited the growth of *T. brucei rhodesiense*, but was ineffective against *T. cruzi* and *L. donovani* [72]. Balunas and colleagues isolated the polyketide coibacin A (**83**) from a Panamanian marine cyanobacterium *Oscillatoria* sp., and observed potent activity against *L. donovani* axenic amastigotes [88]. Ishigami and

colleagues isolated a new xenicane diterpenoid cristaxenicin A (**84**) from the deep-sea gorgonian *Acanthoprimnoa cristata*, which showed potent activity against *L. amazonensis* and *T. congolense* [89]. Chianese and colleagues completed structure-activity relationship studies with several natural and semisynthetic manadoperoxide B analogues (**85**,**86**), isolated from the Indonesian sponge *Plakortis* sfr. *lita*, and determined that both were highly active towards the parasite *T. brucei rhodesiense*, highlighting the 1,2-dioxane ring to be a key pharmacophore [90].

Because of the surge in drug-resistant strains of the intracellular pathogen *Mycobacterium tuberculosis* (*Mtb*), there is a global need for the development of novel drugs with novel mechanisms of action. As shown in Table 1 and Figure 1, seven novel marine natural products (**78**,**87**–**92**), isolated from bacteria, sponges and fungi, contributed to the ongoing global search for novel *antituberculosis* agents. Although these marine natural products were characterized to exhibit *antituberculosis* activity, unfortunately the mechanism of action of these compounds remained undetermined.

Huang and colleagues reported a novel sesterterpenoid asperterpenoid A (**87**) from a mangrove endophytic fungus *Aspergillus* sp. that demonstrated strong inhibitory activity against *M. tuberculosis* protein tyrosine phosphatase B, an enzyme that is " ... considered a promissory target for pulmonary tuberculosis cure" [91]. Song and colleagues isolated a new dimeric diketopiperazine, brevianamide S (**88**), from *Aspergillus versicolor* collected in the Bohai Sea, China, which demonstrated selective antibacterial activity against Bacille Calmette-Guérin (BCG), "suggestive of a new mechanism of action that could inform the development of next generation antitubercular drugs ... if translated to *M. tuberculosis* ... " [92]. Chen and colleagues reported a new spirotetronate, lobophorin G (**89**), from a marine-derived *Streptomyces* sp. MS100061 which exhibited strong anti-*M. bovis* BCG activity, providing relevant pharmacological information as this screen is thought to "serve as a useful screening surrogate for *M. tuberculosis*" [93]. Yamano and colleagues discovered a new cyclic depsipeptide neamphamide B (**90**) in a Japanese marine sponge *Neamphius* sp., which showed activity against *M. bovis* BCG in "both actively growing and dormant states" [94]. Avilés and colleagues isolated two new tricyclic diterpenes (**91**,**92**) from the Bahamian marine sponge *Svenzea flava* that displayed moderate antimycobacterial activity against *M. tuberculosis* H37Rv, the data suggesting that "the isoneoamphilectane backbone" may be "responsible for the observed activity" [95]. In addition to the antimalarial activity described earlier, Supong and colleagues reported that the novel *C*-glycosylated benz[*a*]anthraquinone derivative, urdamycinone E (**78**), inhibited *M. tuberculosis* strain H37Rv [84].

2.4. Antiviral Activity

As shown in Table 1 and Figure 1, thirteen reports were published during 2012–2013 on the *antiviral* pharmacology of marine natural products (**93**–**102**) against hepatitis C, human immunodeficiency virus type-1 (HIV-1), influenza virus, human rhinovirus (HRV) and herpes simplex virus (HSV).

As shown in Table 1, only six reports described antiviral marine chemicals and their mechanisms of action. Da Rosa Guimarães and colleagues extended the pharmacology of the known steroids halistanol sulfate (**93**) and halistanol sulfate C (**94**), isolated from the Brazilian marine sponge *Petromica citrina*, by demonstrating that the compounds inhibited attachment and penetration of the "early events of HSV-1 infection" [96]. Ellithey and colleagues investigated several known metabolites (**95**–**97**) from the Red Sea soft coral *Litophyton arboreum* and demonstrated selective inhibition of the HIV-1 protease by a mechanism that "confirms the contribution of the hydrophobicity of inhibitors of HIV protease" [97]. Salam and colleagues reported a novel pharmacological activity for the sesterterpene manoalide (**98**), which was observed to affect the hepatitis C virus NS3 helicase by inhibiting RNA binding and ATPase activity [98]. Park and colleagues reported that two polybromocatechol compounds (**99**,**100**), isolated from the red alga *Neorhodomela aculeate*, inhibited infection and cytopathic effects on a HeLa cell line by HRV2 and HRV3, causal agents of viral respiratory infections and common colds [99]. Ma and colleagues determined that the novel phenylspirodrimane stachybotrin D (**101**), isolated from the fungus *Stachybotrys chartarum* MXH-X73 derived from the Chinese marine sponge *Xestospongia testudinaria*, inhibited HIV-1 replication of wild-type and five non-nucleoside reverse transcriptase

inhibitor (NNRTI)-resistant HIV-1 strains by inhibiting the reverse transcriptase, and thus "provides a new class of chemotype for the search of NNRT inhibitors" [100]. Jiao and colleagues reported that streptoseolactone (**102**), derived from the actinomycete *Streptomyces seoulensis* strain isolated from the shrimp *Penasus orientalis*, inhibited neuraminidase by a noncompetitive mechanism, a finding "of value in terms of drug discovery for the treatment of influenza" [101].

As shown in Table 1 and Figure 1, several marine natural products (**103**–**111**) were characterized to exhibit antiviral activity, although the mechanism of action of these compounds remained undetermined. He and colleagues isolated a novel cyclic tetrapeptide asperterrestide A (**103**) from the marine-derived fungus *Aspergillus terreus* SCSGAF0162, which inhibited influenza virus strains H1N1 and H3N2 [102].

Two contributions by Peng and colleagues reported two novel indole alkaloids (**104**,**105**), produced by the mangrove-derived fungus *Cladosporium* sp. PJX-41, that inhibited influenza A virus H1N1 [103], and a new pyronepolyene *C*-glucoside iso-D8646-2-6 (**108**), from a sponge-associated fungus *Epicoccum* sp. JJY40, that also inhibited the influenza virus H1N1 [106]. Hawas and colleagues isolated the novel isorhodoptilometrin-1-methyl ether (**106**) from the Red Sea marine fungus *Aspergillus versicolor*, which exhibited hepatitis virus C NS3/4A protease activity [104]. Zhang and colleagues isolated a novel polyketide massarilactone H (**107**) from the marine-derived fungus *Phoma herbarum* which displayed moderate neuraminidase inhibitory activity [105]. Ahmed and colleagues purified a novel polyhydroxylated sterol (**109**) and a new ceramide (**110**) from the Red Sea soft coral *Sinularia candidula*, which inhibited the H5N1 avian influenza viral strain [107]. Plouguerné and colleagues characterized the antiviral activity of a sulfoquinovosyldiacylglycerol (**111**) from the Brazilian brown seaweed *Sargassum vulgare*, demonstrating that it inhibited both HSV-1 and HSV-2 more potently than acyclovir, a clinically used antiherpetic agent [108].

2.5. Anthelmintic Activity

As shown in Table 1, only one report was published during 2012–2013 on the *anthelmintic* pharmacology of marine natural products. Melek and colleagues isolated triterpene glycosides echinosides A and B (**112**,**113**) from the sea cucumbers *Actinopyga echinites* and *Holothuria polii* that displayed "potential in vitro schisotomicidal activity against worms of *Schistosoma mansoni*", suggesting that these compounds may be "promising lead compounds for the development of new schistosomicidal agents" [109].

3. Marine Compounds with Antidiabetic and Anti-Inflammatory Activity, and Affecting the Immune and Nervous System

Table 2 presents the 2012–2013 preclinical pharmacology of marine chemicals (**114**–**188**), which demonstrated either antidiabetic or anti-inflammatory activity, as well as those affecting the immune or nervous system; their structures are depicted in Figure 2.

Table 2. Marine pharmacology in 2012–2013: marine compounds with antidiabetic and anti-inflammatory activity; and affecting the immune and nervous system.

Drug Class	Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
Antidiabetic	octaphlorethol A (**114**)/alga	Polyketide [e]	Increased glucose uptake in rat myoblast cells	50 μM *	Glucose transporter 4 translocation	S. KOR	[120]
Anti-inflammatory	apo-9′-fucoxanthinone (**115**)/alga	Terpenoid [f]	Macrophage TNF-α, IL-6 & 12 expression inhibition	5–14 μM	MAPK pathway inhibition	S. KOR	[121]
Anti-inflammatory	astaxanthin (**116**)/alga	Terpenoid [f]	Macrophage cytokine inhibition	10 μM *	SHP-1 restoration	ITA	[122]
Anti-inflammatory	bengamide A & B (**117**,**118**)/sponge	Alkaloid [g]	Macrophage TNF-α & IL-6 inhibition	0.5 μM *	IkBα phosphorylation inhibition	USA	[123]
Anti-inflammatory	bis-*N*-norgliovictin (**119**)/fungus	Alkaloid [g]	Macrophage TNF-α, IL1-6, MCP-1 release inhibition in vitro	0.5 μg/mL *	Inflammatory gene inhibition	CHN	[124]
Anti-inflammatory	6,6′-bieckol (**120**)/alga	Polyketide [e]	Macrophage TNF-α & IL-6 expression inhibition	25 μM *	Inhibition of NFκB	S. KOR, USA	[125]
Anti-inflammatory	coibacin B (**121**)/bacterium	Polyketide [e]	Macrophage NO inhibition	5 μM	iNOS, TNF-α, IL-1, IL-6 transcription inhibition	USA, PAN	[88]
Anti-inflammatory	11-*epi*-sinulariolide acetate (**122**)/ soft coral	Terpenoid [f]	Macrophage COX-2 & IL-8 expression inhibition	10 μM	Ca^{2+} signaling inhibition	TWN	[126]
Anti-inflammatory	honaucin A (**123**)/bacterium	Polyketide [e]	Macrophage NO inhibition	4 μM	iNOS, TNF-α, IL-1, IL-6 transcription inhibition	USA, PAN	[127]
Anti-inflammatory	*Hymeniacidon* sp. amphilectanes (**124**,**125**)/sponge	Terpenoid [f]	Brain microglia TXB_2 inhibition	0.2 μM	SOX independent & COX dependent	USA	[128]
Anti-inflammatory	largazole (**126**)/bacterium	Peptide [g]	Modulation of human RA synovial fibroblasts in vitro	5 μM *	Enhanced HDAC6 & ICAM-1	USA	[129]
Anti-inflammatory	lemnalol (**127**)/soft coral	Terpenoid [f]	In vivo arthritis inhibition	30 mg/kg*	iNOS, COX-2 and c-Fos expression inhibition	TWN	[130]
Anti-inflammatory	neoechinulin A (**128**)/fungus	Alkaloid[g]	Macrophage PGE_2 and NO expression inhibition	25–50 μM *	Inhibition of NFκB & MAPK	S. KOR; CHN	[131]
Anti-inflammatory	penstyrylpyrone (**129**)/fungus	Shikimate/polyketide	Macrophage NO, PGE_2, IL1β inhibition	9.3–13.5 μM	PTP1B inhibition	S. KOR	[132]
Anti-inflammatory	perthamide C (**130**)/sponge	Peptide [g]	Carrageenan-induced paw edema inhibition	ND	Induction of proteome changes	ITA	[133]
Anti-inflammatory	R-prostaglandins (**131**,**132**)/soft coral	Polyketide [e]	Topical inflammation inhibition	ND	PMN elastase inhibition	COL	[134]
Anti-inflammatory	sinularin (**133**)/soft coral	Terpenoid [f]	Carrageenan-induced spinal neuroinflammation inhibition	0.1 μM *	iNOS & COX-2 inhibition	TWN	[135]
Anti-inflammatory	swinhosterol B (**134**)/sponge	Terpenoid [f]	Lymphocyte release of IL-10	10 μM *	Pregnane-X-receptor agonist	ITA, FRA	[136]
Anti-inflammatory	*A. polyacanthus* steroids (**135**,**136**)/starfish	Terpenoid [f]	Bone marrow-derived dendritic cells IL-6 and TNF-α inhibition	1.8–7.0 μM	Undetermined	S. KOR, VNM	[137]
Anti-inflammatory	barettin (**137**)/sponge	Alkaloid [g]	Macrophage anti-inflammatory IL-10 release in vitro	50 μg/mL	Undetermined	NOR	[138]
Anti-inflammatory	briarenolide F (**138**)/octocoral	Terpenoid [f]	Neutrophil superoxide inhibition	3.82 μg/mL	Undetermined	TWN	[139]
Anti-inflammatory	*Callyspongia* sp. diketopiperazine (**139**)/sponge	Peptide [g]	Macrophage IL1β release inhibition in vitro	5 μg/mL *	Undetermined	CHN	[140]
Anti-inflammatory	6-*epi*-cladieunicellin F (**140**)/octocoral	Terpenoid [f]	Neutrophil superoxide and elastase inhibition	10 μM *	Undetermined	TWN	[141]
Anti-inflammatory	crassarosteroside A (**141**)/soft coral	Terpenoid glycoside [f]	Macrophage iNOS protein inhibition	10 μM *	Undetermined	TWN	[142]

Table 2. *Cont.*

Drug Class	Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
Anti-inflammatory	cystodione A (**142**)/alga	Terpenoid [f]	Radical-scavenging and macrophage TNF-α inhibition in vitro	8–22 μM *	Undetermined	ESP, MAR	[143]
Anti-inflammatory	densanins A & B (**143**,**144**)/sponge	Alkaloid [g]	Macrophage NO release inhibition	1–2.1 μM	Undetermined	S. KOR	[144]
Anti-inflammatory	dissesterol (**145**)/soft coral	Terpenoid [f]	Bone marrow dendritic cells IL-12 release inhibition	4 μM	Undetermined	S. KOR, VNM	[145]
Anti-inflammatory	echinohalimane A (**146**)/gorgonian	Terpenoid [f]	Neutrophil elastase inhibition	0.38 μg/mL	Undetermined	TWN	[146]
Anti-inflammatory	eunicidiol (**147**)/gorgonian	Terpenoid [f]	PMA-induced mouse ear edema inhibition	100 μg/ear	Undetermined	CAN	[147]
Anti-inflammatory	flexibilisolide C (**148**)/soft coral	Terpenoid [f]	Macrophage COX-2 & iNOS expression inhibition	10 μM *	Undetermined	TWN	[148]
Anti-inflammatory	flexibilisquinone (**149**)/soft coral	Terpenoid [f]	Macrophage COX-2 & iNOS expression inhibition	10–20 μM *	Undetermined	TWN	[149]
Anti-inflammatory	lobocrassin F (**150**)/soft coral	Terpenoid [f]	Neutrophil elastase release inhibition	6.3 μM *	Undetermined	TWN	[150]
Anti-inflammatory	perthamide J (**151**)/sponge	Peptide [g]	Carrageenan-induced paw edema reduction	0.3 mg/kg *	Undetermined	ITA, FRA	[151]
Anti-inflammatory	pseudoalteromone A (**152**)/bacterium	Terpenoid [f]	Neutrophil elastase inhibition	10 μg/mL *	Undetermined	TWN	[152]
Anti-inflammatory	sarcocrassocolide M (**153**)/soft coral	Terpenoid [f]	Macrophage COX-2 & iNOS expression inhibition	10 μM *	Undetermined	TWN	[153]
Anti-inflammatory	sclerosteroids K & M (**154**,**155**)/ soft coral	Terpenoid [f]	Macrophage COX-2 & iNOS expression inhibition	10 μM *	Undetermined	TWN	[154]
Anti-inflammatory	seco-briarellinone (**156**)/octocoral	Terpenoid [f]	Macrophage NO release inhibition	4.7 μM	Undetermined	PAN	[155]
Anti-inflammatory	sinulariolside (**157**)/soft coral	Glycolipid	Macrophage NO release inhibition	30 μM *	Undetermined	ITA	[156]
Immune system	lobocrassin B (**158**)/soft coral	Terpenoid [f]	Dendritic cell activation inhibition	39 μM *	NF-κB translocation and TNF-α release inhibition	TWN	[157]
Immune system	penicacid B(**159**)/fungus	Polyketide [e]	T lymphocyte proliferation inhibition	0.23–20 μM	IMPDH inhibition	CHN	[158]
Nervous system	APETx2 peptide (**160**)/sea anemone	Peptide [g]	ASIC3 inhibition	61 nM	*N*- and *C*- termini truncation decrease inhibition	AUS	[159]
Nervous system	asteropsin A (**161**)/sponge	Peptide [g]	Enhancement of neuronal Ca^{2+} influx	14 nM	No binding with VGSC site 2	S. KOR, USA	[160]
Nervous system	BcsTx peptides (**162**,**163**)/ sea anemone	Peptide [g]	rKv1.1 inhibition	0.02–80 nM	Potassium influx inhibition	BRA, BEL	[161]
Nervous system	*C. consors* peptide (**164**)/cone snail	Peptide [g]	Muscle relaxation induction	0.15 μM	$Na_v1.4$ & $Na_v1.2$ channel inhibition	BEL, FRA, CHE, CHL, DEU, NLD,	[162]
Nervous system	*C. magnificus* conotoxin MfVIA(**165**)/cone snail	Peptide [g]	Neuronal Na^+ current inhibition	95 nM	$Na_v1.8$ and $Na_v1.4$ channel inhibition	AUS	[163]

Table 2. *Cont.*

Drug Class	Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
Nervous system	*C. regius* conotoxin RegIIA (**166**)/cone snail	Peptide [g]	ACH-current inhibition	33 nM	A2β2 ACH receptor	AUS, DEU, USA	[164]
Nervous system	*C. regularis* peptide (**167**)/cone snail	Peptide [g]	Antinociceptive activity	0.85 mg/kg *	$Ca_v2.2$ channel inhibition	MEX	[165]
Nervous system	convolutamydine A (**168**)/bryozoa	Alkaloid [g]	Antinociceptive activity	1 mg/kg	Cholinergic, opioid and nitric oxide	BRA	[166]
Nervous system	*H. crispa* polypeptides (**169**)/sea anemone	Peptide [g]	Antinociceptive and analgesic activity in vivo	0.01–0.1 mg/kg *	Inhibition of TRPV1 vanilloid 1 receptor	RUS	[167]
Nervous system	ianthellamide A (**170**)/sponge	Alkaloid [g]	Increased kynurenic acid in vivo	200 mg/kg *	Kynurenine 3- hydroxylase inhibition	AUS	[168]
Nervous system	leucettamine B (**171**)/sponge	Alkaloid [g]	Reduction of neurodegeneration in brain slices by analog leucettine L41	0.6–4.1 μM	Dual tyrosine phosphorylation kinase inhibition	FRA, UK, USA	[169]
Nervous system	pulchranin A (**172**)/sponge	Alkaloid [g]	TRPV1 receptor inhibition	41.2 μM	Ca^{2+} response inhibition	RUS, S. KOR	[170]
Nervous system	serinolamide B (**173**)/bacterium	Alkaloid [g]	CB_1 & CB_2 binding	**	cAMP accumulation inhibition	USA	[171]
Nervous system	arigsugacin I (**174**)/fungus	Terpenoid [f]	acetylcholinesterase inhibition	0.64 μM	Undetermined	CHN	[172]
Nervous system	asperterpenol A (**175**)/fungus	Terpenoid [f]	acetylcholinesterase inhibition	2.3 μM	Undetermined	CHN	[173]
Nervous system	cymatherelactone (**176**)/alga	Polyketide [e]	voltage-gated sodium channel inhibition	16 μM	Undetermined	USA	[174]
Nervous system	dictyodendrin H (**177**)/sponge	Alkaloid [g]	BACE inhibition	1 μM	Undetermined	AUS	[175]
Nervous system	geranylphenazinediol (**178**)/bacterium	Alkaloid [g]	acetylcholinesterase inhibition	2.62 μM	Undetermined	DEU	[176]
Nervous system	halomadurones C & D (**179**,**180**)/bacteria	Terpenoid [e]	Nrf2-ARE activation	3.7 μM *	Undetermined	USA	[177]
Nervous system	lamellarin O (**39**)/sponge	Alkaloid [g]	BACE inhibition	<10 μM	Undetermined	AUS	[53]
Nervous system	*Psammocinia* sp. ircinianin lactams (**181**,**182**)/sponge	Terpenoid [f]	A3 GlyR potentiation	8.5 μM	Undetermined	AUS, DEU	[178]
Nervous system	starfish polar steroids (**183**–**188**)/starfish	Terpenoid [f]	Neuritogenic and neuroprotective	1–100 nM	Undetermined	RUS	[179]

([a]) **Organism**: *Kingdom Animalia*: coral and sea anemone (Phylum Cnidaria); starfish (Phylum Echinodermata); cone snail (Phylum Mollusca); sponge (Phylum Porifera); *Kingdom Fungi*: fungus; *Kingdom Plantae:* alga; *Kingdom Monera*: bacterium; ([b]) **IC_{50}**: concentration of a compound required for 50% inhibition, *: apparent IC_{50}, **: *Ki* 16.4 and 2 μM, respectively; ([c]) **MMOA**: molecular mechanism of action; ([d]) **Country**: AUS: Australia; BEL: Belgium; BRA: Brazil; CHE: Switzerland; CHL: Chile; CHN: China; COL: Colombia; DEU: Germany; ESP: Spain; FRA: France; ITA: Italy; MAR: Morocco; MEX: Mexico; NLD: Netherlands; NOR: Norway; PAN: Panama; RUS: Russian Federation; S. KOR: South Korea; TWN: Taiwan; UK: United Kingdom; VNM: Vietnam; **Chemistry**: ([e]) Polyketide; ([f]) Terpene; ([g]) Nitrogen-containing compound; ([h]) polysaccharide. **Abbreviations**: ASIC3: pH-sensitive sodium ion channel 3; BACE: protease β-secretase; COX: cyclooxygenase; GlyR: glycine-gated chloride channel receptor; HDAC6: class II, histone deacetylase 6; ICAM: intercellular adhesion molecule-1; iNOS: inducible nitric oxide synthase; IMPDH: inosine 5′-monophosphate dehydrogenase; MAPK: mitogen-activated protein kinase pathway; NO: nitric oxide; Nrf2-ARE: nuclear transcription factor E2-related factor antioxidant response element; PTP1B: tyrosine protein phosphatase 1B; rKv1.1: voltage-gated potassium channel Kv subfamily; SHP1: SHP-1 protein tyrosine phosphatase; SOX: superoxide; TRPV1: transient receptor potential cationic channel of subfamily V.

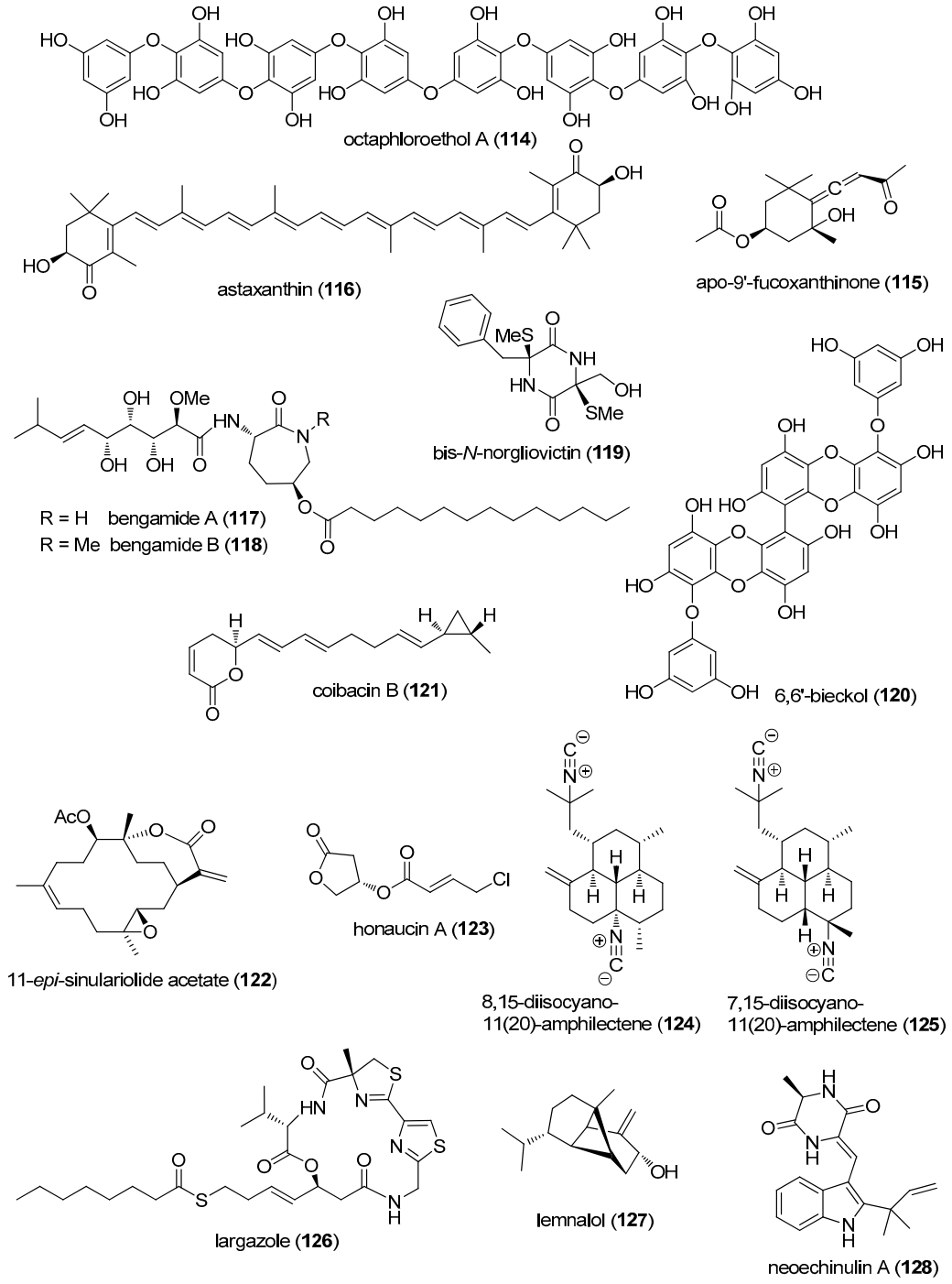


Figure 2. *Cont.*

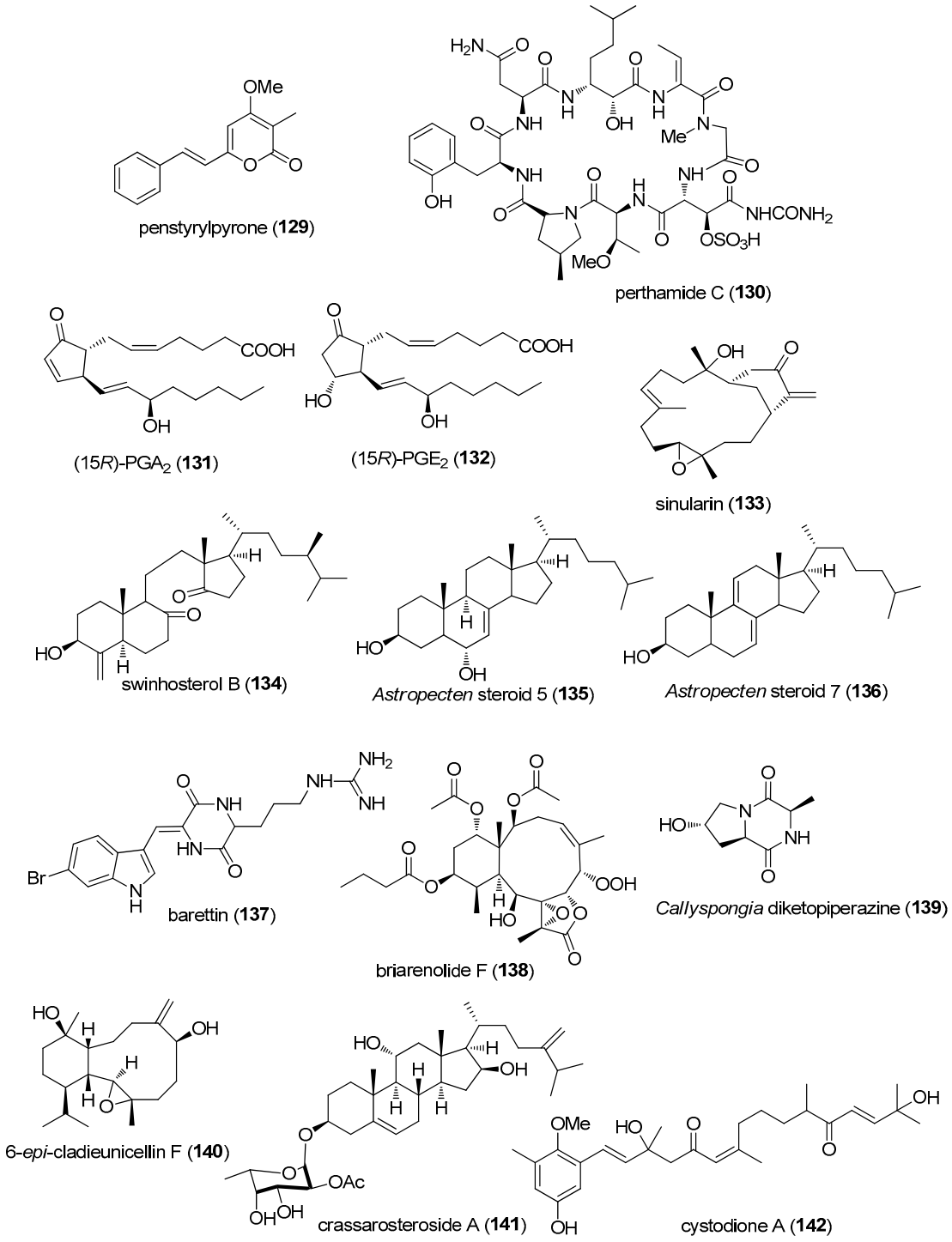


Figure 2. *Cont.*

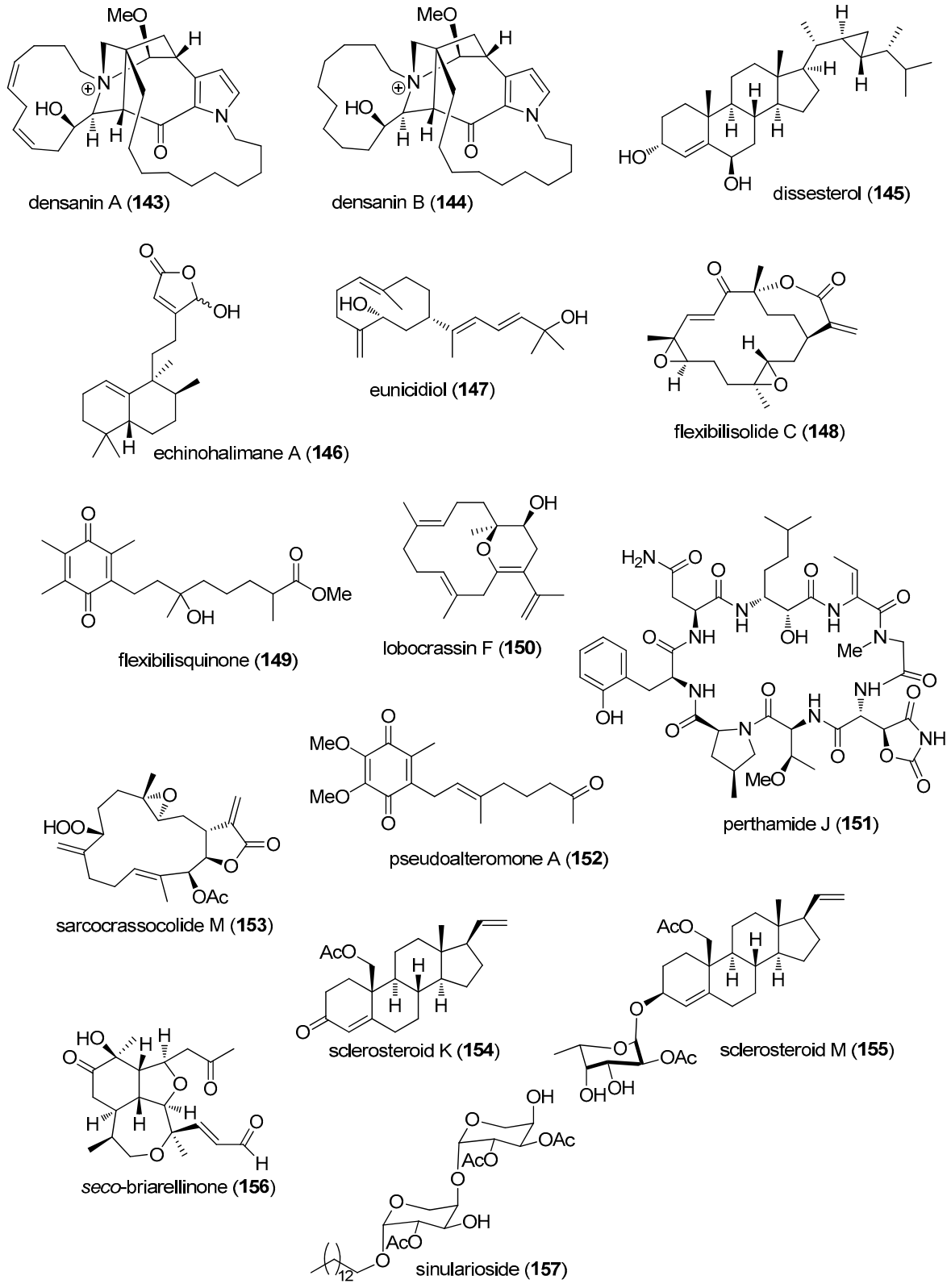
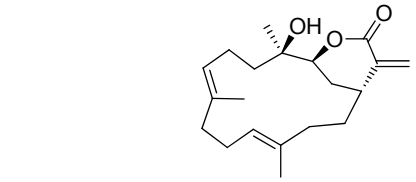
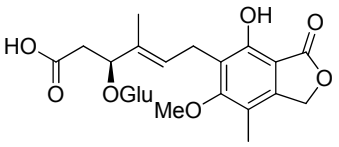


Figure 2. *Cont.*



lobocrassin B (**158**)

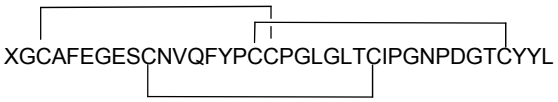


penicacid B (**159**)

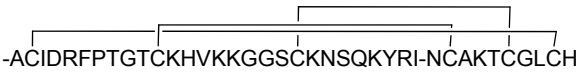
G1-S19 C20-D42

GTACSCGNSKGIYWFYRPS CPTCRGYTGSGRYFLGTCCTPAD

APETx2_1-42 (**160**)



asteropsin A (**161**)



BcsTx1 (**162**)

BcsTx2 (**163**)

ZGCCNGP--KG-CSSKWCRDHARCC

μCnIIIC (**164**)

RDCQEKWEYCIVPILGFVYCCPGLICGPFV CV

MfVIA (**165**)

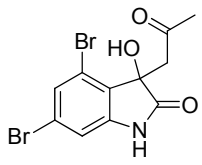
RegIIA (**166**)

CKGQSCSSCSTKEFCLSKGSRLMYDCCTGSCCGVKTAGVT

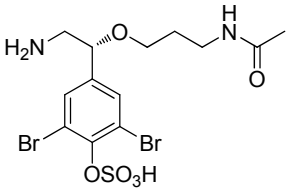
RsXXIVA (**167**)

GSICLEPKVVGPCTAYFRRFYFDSETGKCTVFIYGGCEGNGNNFETLRACRAICRA

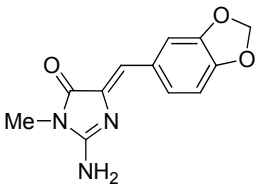
APHC1 (**169**)



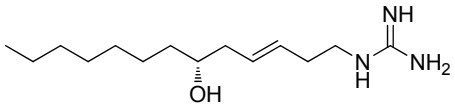
convolutamydine A (**168**)



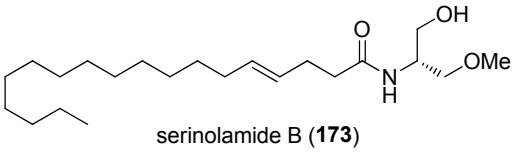
ianthellamide A (**170**)



leucettamine B (**171**)



pulchranin A (**172**)



serinolamide B (**173**)

Figure 2. *Cont.*

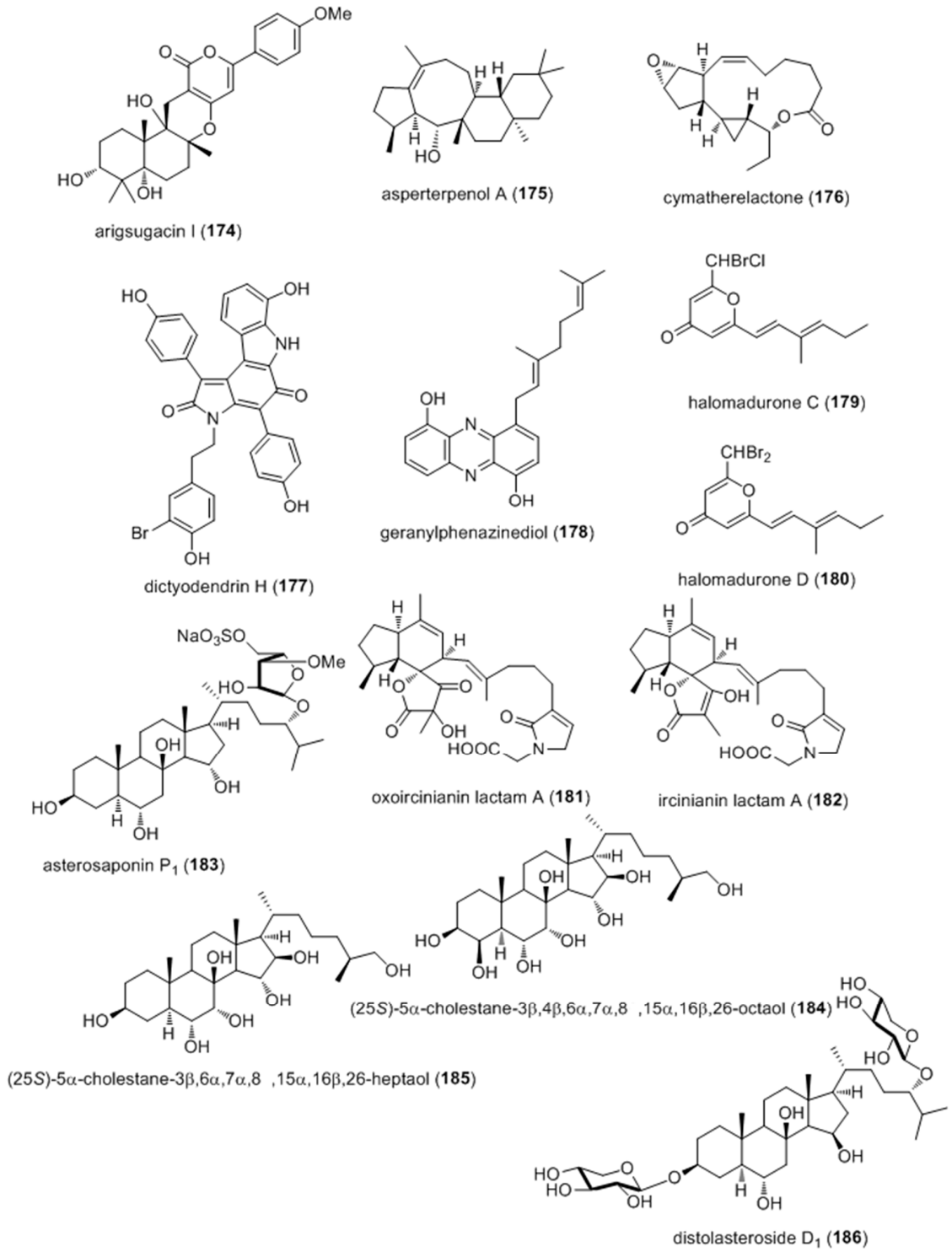


Figure 2. *Cont.*

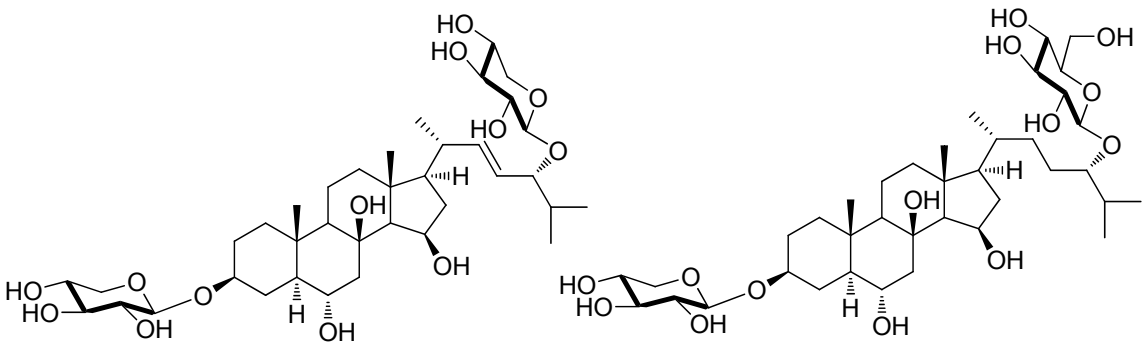


Figure 2. Marine pharmacology in 2012–2013: marine compounds with antidiabetic and anti-inflammatory activity; and affecting the immune and nervous system.

3.1. Antidiabetic Activity

Lee and colleagues reported the pharmacology of octaphlorethol A (**114**), a novel phenolic compound isolated from the marine brown alga *Ishige foliacea*, by showing that octaphlorethol A enhanced glucose uptake in L6 rat myoblast cells by increasing glucose transporter 4 translocation to the plasma membrane and protein kinase B and AMP-activated protein kinase activity [120].

3.2. Anti-Inflammatory Activity

As shown in Table 2 and Figure 2, there was a remarkable increase in marine anti-inflammatory pharmacology research during 2012–2013. The molecular mechanism of action of marine natural products (**115**–**134**) was investigated in both in vitro and in vivo preclinical pharmacological studies which were completed using a variety of in vitro models including bone marrow-derived macrophages, human U937 monocytic cells, murine RAW 264.7 macrophages, human epidermoid carcinoma A431 cell line, human polymorphonuclear leukocytes, rat brain microglia, and mouse peritoneal macrophages.

Chae and colleagues evaluated the anti-inflammatory properties of apo-9′-fucoxanthinone (**115**), isolated from the marine edible brown alga *Sargassum muticum* [121] in unmethylated CpG DNA-stimulated bone marrow-derived macrophages and dendritic cells. Inhibition of interleukin-12 p40, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) production, as well as concomitant attenuation of the mitogen-activated protein kinase pathways, was observed, leading the authors to conclude that apo-9′-fucoxanthinone may have "potential therapeutic use . . . for inflammatory disease". In a detailed mechanistic study, Speranza and colleagues investigated the antioxidant marine carotenoid astaxanthin (**116**), showing that it inhibited hydrogen peroxide-stimulated production of pro-inflammatory cytokines IL-1, IL-6 and TNF-α in a human U937 monocytic cell line by selectively restoring physiological levels and function of the tyrosine phosphatase SHP-1, thus proposing that astaxanthin might become a novel agent for the therapy of inflammatory diseases [122]. Johnson and colleagues identified the alkaloids bengamide A and B (**117**,**118**) as potent inhibitors of NFκB and LPS-induced expression of cytokines IL-6, TNF-α and chemokine monocyte chemoattractant protein-1 (MCP-1) release from murine RAW 264.7 macrophages, concluding that these compounds may "serve as therapeutic leads for immune disorders involving inflammation" [123]. Song and colleagues determined that bis-*N*-norgliovictin (**119**) derived from a marine fungus *S3-1-c* inhibited TNF-α, IL-6, interferon-β, and MCP-1 production by LPS-stimulated RAW 264.7 macrophages and affecting Toll-like receptor 4 (TLR-4) signal transduction pathways, as well as LPS-induced septic shock in mice, thus suggesting bis-*N*-norgliovictin might result in a useful therapeutic candidate for "sepsis and other inflammatory diseases" [124]. Investigations by Yang and colleagues with phlorotannin 6,6′-bieckol (**120**), isolated from the marine brown alga *Ecklonia cava*, showed that the compound inhibited expression and release of nitric oxide, prostaglandin E_2, TNF-α and IL-6 in LPS-stimulated

macrophages, with concomitant inhibition of NFκB activation, suggesting that compound **120** is potentially useful for the treatment of inflammatory diseases [125]. Balunas and colleagues determined that the polyketide coibacin B (**121**), isolated from the Panamanian marine cyanobacterium, cf. *Oscillatoria* sp. possessed not only antileishmanial activity, but also significant anti-inflammatory activity, as it significantly decreased LPS-induced nitric oxide, TNF-α and IL-6 release from RAW 264.7 macrophages [88]. Hsu and colleages reported that the soft coral *S. flexibilis*-derived 11-*epi*-sinulariolide acetate (**122**) inhibited cyclooxygenase-2 and interleukin-8 expression in human epidermoid carcinoma A431 cells in vitro by inhibition of Ca^{2+} signaling, suggesting that it might become a lead compound to target "store-operated calcium signaling-dependent inflammatory diseases" [126]. Choi and colleagues demonstrated that the novel honaucin A (**123**) from the Hawaiian cyanobacterium *Leptolyngbya crossbyana*, which inhibited LPS-induced nitric oxide production, and TNF-α, IL-1β, IL-6 and iNOS gene transcription in RAW 264.7 macrophages, had functional groups "critical for anti-inflammatory... activity" [127]. Rat brain microglia, a macrophage type involved in neuroinflammation and neurodegeneration [180] was used by Mayer and colleagues to investigate several known diterpene isocyanide amphilectane metabolites (**124**,**125**) from the Caribbean marine sponge *Hymeniacidon* sp., which potently inhibited thromboxane B_2 generation from LPS activated rat neonatal microglia in vitro, with concomitant low lactate dehydrogenase release and minimal mitochondrial dehydrogenase inhibition. The authors concluded that the potency of these compounds warranted "further investigation . . . as lead compounds to modulate . . . activated microglia in neuroinflammatory disorders" [128]. Ahmed and colleagues extended the pharmacology of largazole (**126**), originally isolated from a marine cyanobacterium *Symploca* sp., by reporting that largazole inhibited class I histone deacetylase 6 in vitro in human rheumatoid arthritis. Furthermore, largazole-enhanced expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 was observed to be mediated by activation of the p38 and Akt signal transduction pathways in synovial fibroblasts [129]. Lee and colleagues reported that the sesquiterpenoid lemnalol (**127**), isolated from the Japanese soft coral *Lemnalia tenuis*, attenuated monosodium urate-induced gouty rat arthritis, by a mechanism that involved inhibition of inducible nitric oxide synthase and cyclooxygenase-2, thus becoming a potential new candidate for "development of a new treatment for gout" [130]. Kim and colleagues reported that the diketopiperazine-type indole alkaloid neoechinulin A (**128**), isolated from an Antarctic marine fungus *Eurotium* sp. SF-5989, inhibited LPS-stimulated RAW264.7 macrophages expression, release of nitric oxide and prostaglandin E_2, with concomitant inhibition of NFκB activation, and reduced inhibitor NFκB and p38 mitogen-activated protein kinase (MAPK) phosphorylation [131]. In a detailed study, Lee and colleagues investigated penstyrylpyrone (**129**), isolated from a marine-derived fungus *Penicillium* sp. JF-55, and determined that the inhibition of LPS-treated murine peritoneal macrophage production of NO, PGE_2, TNF-α, IL-1β, was correlated with suppression of iκB-α and NF-κB and concomitant expression of heme oxygenase-1 [132]. Vilasi and colleagues extended the molecular pharmacology of the novel cyclic octapepetide perthamide C (**130**), isolated from the marine sponge *Theonella swinhoei*, by investigating its effect on the proteome of murine macrophages J774.A1 using two-dimensional proteomics, and determining differential effect on several cytosolic and ER-associated proteins, mainly involved in cellular folding processes, thus "shed(ding) more light on the . . . mechanisms of action" of this natural product [133]. Reina and colleagues reported that *R*-prostaglandins (**131**,**132**) isolated from the Caribbean Colombian soft coral *Plexaura homomalla* inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced mouse ear inflammation in vivo and decreased human polymorphonuclear leukocytes degranulation, as well as myeloperoxidase and elastase levels in vitro, thus concluding that prostaglandins from " . . . *P. homomalla* are promising molecules with an interesting anti-inflammatory activity profile" [134]. Huang and colleagues extended the pharmacology of the known compound sinularin (**133**), demonstrating that it modulates nociceptive responses and spinal neuroinflammation by a mechanism that may involve inhibition of leukocyte iNOS and cyclooxygenase-2 (COX-2) and the upregulation of the anti-inflammatory cytokine transforming growth factor-β [135]. Marino and colleagues reported

the molecular pharmacology of the novel polyhydroxylated steroid swinhosterol B (**134**) isolated from the Solomon Islands marine sponge *T. swinhoei* [136]. Swinhosterol B was shown to be a highly specific agonist for the human pregnane-X-receptor (PXR), and in transgenic PXR murine monocytes, it attenuated pro-inflammatory cytokine production in vitro, thus supporting "the exploitation of this compound in rodent model(s) of liver inflammation and cholestasis".

As shown in Table 2, and in contrast to the 20 marine compounds (**115**–**134**) with described anti-inflammatory mechanisms of action, for marine compounds (**135**–**157**), only anti-inflammatory activity, namely IC_{50}, was reported, but the molecular mechanism of action remained undetermined: *A. polyacanthus* steroids (**135**,**136**) [137]; barettin (**137**) [138]; briarenolide F (**138**) [139]; diketopiperazine (**139**) [140]; 6-*epi*-cladieunicellin F (**140**) [141]; crassarosteroside A (**141**) [142]; cystodione A (**142**) [143]; densanins A and B (**143**,**144**) [144]; dissesterol (**145**) [145]; echinohalimane A (**146**) [146]; eunicidiol (**147**) [147]; flexibilisolide C (**148**) [148]; flexibilisquinone (**149**) [149]; lobocrassin F (**150**) [150]; perthamide J (**151**) [151]; pseudoalteromone A (**152**) [152]; sarcocrassocolide M (**153**) [153]; sclerosteroids K and M (**154**,**155**) [154]; seco-briarellinone (**156**) [155]; and sinularioside (**157**) [156].

3.3. Marine Compounds with Activity on the Immune System

In 2012–2013 preclinical pharmacology of marine compounds that affected the *immune* system showed a decline as previously reported in this series.

Lin and colleagues reported that the cembrane-type diterpenoid lobocrassin B (**158**), isolated from the marine soft coral *Lobophytum crissum*, demonstrated immunomodulatory effects on bone marrow-derived dendritic cells (DC), a cell type known to be an important link between the innate and adaptive immune response [157]. Lobocrassin B was shown to attenuate DC maturation and activation with concomitant inhibition of toll-like receptor-stimulated translocation of NF-κB and TNF-α production, data that suggested that lobocrassin B might have "therapeutic applications in certain immune disfunctions". Chen and colleagues reported that a novel mycophenolic acid derivative, penicacid B (**159**), isolated from a South China sea fungus *Penicillium* sp. SOF07, inhibited splenocyte lymphocyte proliferation by a mechanism that involved inhibition of inosine 5′-monophosphate dehydrogenase, an essential rate-limiting enzyme in purine metabolic pathway and an "important drug target for immunosuppressive" activity [158].

3.4. Marine Compounds Affecting the Nervous System

In 2012–2013, the preclinical marine *nervous* system pharmacology with compounds (**160**–**188**), which is consolidated in Table 2 and Figure 2, was focused on sodium and potassium channels, nicotinic acetylcholine receptors, as well as, analgesia, antinociception, and neuroprotection.

Four marine compounds (**160**–**163**) were shown to bind to sodium (Na^+) and potassium (K^+) channels. Jensen and colleagues determined the effect of cyclisation on the stability of the sea anemone peptide APETx2 (**160**). Cyclization with either a six-, seven- or eight-residue linker appeared to be a "promising strategy" to increase protease resistance of APETx2, but it decreased its potency against non-voltage gated, pH-sensitive Na^+ channel ASIC3 (IC_{50} = 61 nM). Furthermore, truncation at either *N*- and *C*-terminus significantly affected APETx2 binding to ASIC3, demonstrating their critical role in this process [159]. Li and colleagues reported the discovery of a cysteine-crosslinked peptide asteropsin A (**161**), isolated from a Korean marine sponge *Asteropus* sp., that affected neuronal Ca^{2+} influx by a mechanism that involved murine cerebrocortical neurons agonist-induced Na^+ channel activation, and may thus represent " . . . a valuable contribution to the cysteine knot peptide-based drug development as a model scaffold" [160]. Orts and colleagues published the biochemical and electrophysiological characterization of two novel sea anemone type 1 potassium toxins, namely Bcs Tx1 (**162**) and Bcs Tx2 (**163**) isolated from the Atlantic sea anemone *Bunodosoma caissarum*, and demonstrated by electrophysiological screening of 12 subtypes of voltage-gated Kv K^+ channels, that BcsTx1 showed highest affinity for rKv1.2 (IC_{50} = 0.03 ± 0.006 nM) while Bcs Tx2 potently inhibited rKv1.6 (IC_{50} = 7.76 ± 1.90 nM) [161].

Four studies extended the pharmacology of conopeptides (**164**–**167**). Favreau and colleagues reported that a novel μ-conopeptide CnIIIIC (**164**) isolated from the venom of the marine snail *C. consors* strongly decreased mouse hemidiaphragm contraction by a mechanism that involved potently blocking muscle $Na_v1.4$ (IC_{50} = 1.3 nM) and rat brain $Na_v1.2$ (IC_{50} < 1 μM) voltage-gated Na^+ channels in a "virtually irreversible" manner, which will probably result in potential development of **164** " . . . as a myorelaxing drug candidate" [162]. Vetter and colleagues reported the isolation and characterization of a novel hydrophobic 32-residue μO-conotoxin MfVIA (**165**), isolated from the venom of marine snail *C. magnificus*, and by using a variety of electrophysiological techniques demonstrated that it preferentially inhibited Nav1.8 (IC_{50} = 96 nM) and Nav1.4 (IC_{50} < 81 nM) voltage-gated Na^+ channels, leading the authors to propose it as a "drug lead for development of improved analgesic molecules . . . to improve pain management" [163]. Franco and colleagues isolated an α4/7-conotoxin RegIIA (**166**) from the venom of the marine cone snail *C. regius*, and demonstrated that it potently inhibited α3β4 neuronal nicotinic acetylcholine receptors (IC_{50} = 33 nM) by a mechanism that will require continuous investigation to determine "the precise binding mode of this peptide" [164]. Bernáldez and colleagues described the isolation and biochemical characterization of the first *Conus regularis* conotoxin designated RsXXIVA (**167**) with an eight-cysteine framework, which "diverges from other known conotoxins" and that inhibited $Ca_v2.2$ channels (IC_{50} = 2.8 μM) in rat superior cervical ganglion neurons, and also displayed both analgesic and anti-nociceptive activity in the hot-plate and formalin murine in vivo assays, which may contribute to the "design of analgesic peptides" [165].

Two studies reported marine compounds (**168**,**169**) that contributed to nociceptive pharmacology. Figuereido and colleagues extended the pharmacology of convolutamydine A (**168**), isolated from the Floridian marine bryozoan *Amantia convoluta*, demonstrating that it caused peripheral anti-nociceptive and anti-inflammatory effects in several acute pain models, an effect probably mediated by the cholinergic, opioid and nitric oxide systems and "comparable to morphine's effects" [166]. Andreev and colleagues contributed an extensive in vitro and in vivo pharmacological study of two polypeptides APHC1 and PAHC3 (**169**), isolated from the sea anemone *Heteractis crispa*, shown to have significant anti-nociceptive and analgesic activity in a number of in vivo murine models with associated hypothermia. Furthermore, the two compounds were proposed as a new class of vanilloid 1 receptors modulators based on detailed in vitro biochemical studies [167].

Neuroprotective activity of marine compounds (**170**,**171**) was reported in two studies. Feng and colleagues observed that the novel octopamine derivative ianthellamide A (**170**), isolated from the Australian marine sponge *Ianthella quadrangulate*, increased endogenous kynurenic acid in rat brain, as well as selectively inhibited the kynurenine 3-hydroxylase in vitro, thus revealing that modulation of the kynurenine pathway of tryptophan metabolism by this compound suggested "potential as a neuroprotective agent" [168]. Burgy and colleagues completed an extensive pharmacological study on the selectivity, co-crystal structures and neuroprotective properties of the leucettines, analogues of the marine sponge alkaloid leucettamine B (**171**), originally isolated from the calcareous sponge *Leucetta microraphis.* An optimized product, leucettine L41, with multi-target selectivity that resulted in neuroprotective effects was proposed for "further optimization as potential therapeutics against neurodegenerative diseases such as Alzheimer's disease" [169].

As shown in Table 2, additional marine compounds (**172**–**174**) were shown to modulate other molecular targets, i.e., TRPV1 and cannabinoid receptors, and the acetylcholinesterase enzyme. Guzii and colleagues reported that a novel guanidine-containing compound pulchranin A (**172**), isolated from the marine sponge *Monanchora pulchra* inhibited TRPV1 receptor, an ionic channel involved in the regulation of pain and body temperature. Pulchranin A, "the first marine non-peptide inhibitor of TRPV1 channels", led to a decrease of Ca^{2+} response in a CHO cell line expressing the rat TRPV1 channel by a mechanism the authors propose may result from "direct action on the channel pore" [170]. Montaser and colleagues reported a new fatty acid amide, serinolamide B (**173**), isolated from the Guam cyanobacterium *Lyngbya majuscula* that bound with higher selectivity to cannabinoid receptor CB2 and inhibited forskolin-stimulated cAMP accumulation in Chinese hamster

ovary cells expressing the CB1 and CB2 receptors, a finding that "introduces a new structural lead to the cannabimimetic" field of research [171]. Huang and colleagues reported the isolation of a new α-pyrone meroterpene arigsugacin I (**174**), isolated from an endophytic fungus *Penicillium* sp. Sk5GW1L [172] that was observed to potently inhibit acetylcholinesterase, thus contributing to the "best-established treatment target for the design of anti-Alzheimer's drugs".

In contrast to the 15 marine compounds (**160**–**174**) affecting the nervous system with investigated mechanisms of action discussed above, for marine compounds **175**–**188**, only an IC_{50} was reported and consolidated in Table 2, but their respective molecular mechanisms of action remained undetermined: asperterpenol A (**175**) [173]; cymatherelactone (**176**) [174]; dictyodendrin H (**177**) [175]; geranylphenazinediol (**178**) [176]; halomadurones C and D (**179**,**180**) [177]; lamellarin O (**39**) [53]; ircinianin lactams A (**181**,**182**) [178]; and polar steroids (**183**–**188**) [179].

Finally, marine bioprospecting resulting from deep sequencing of transcriptomes of marine organisms may ultimately enhance the search for new nervous system drug candidates, as demonstrated by a study of the adult polyp transcriptomes of two cold-water sea anemone species that revealed 15 new neurotoxin peptide candidates [181].

4. Marine Compounds with Miscellaneous Mechanisms of Action

Table 3 presents 2012–2013 preclinical pharmacological research of 69 marine compounds (**189**–**257**) with miscellaneous mechanisms of action; their structures are shown in Figure 3. Because comprehensive pharmacological characterization data for these compounds were unavailable, it was not possible to assign these compounds to a particular drug class.

Table 3 presents a pharmacological activity, an IC_{50}, and a molecular mechanism of action for 36 marine natural products as reported in the peer-reviewed literature: astaxanthin (**189**) [182]; biselyngbyaside (**190**) [183]; *Callyspongia* sp. bisacetylenic alcohol (**191**) [184]; conicasterol E (**192**) [185]; 6″-debromohamacanthin A (**193**) [186]; dieckol (**194**) [187]; fructigenine A (**195**) [188]; geoditin A (**196**) [189]; gorgosterol (**197**) [190]; gracilioether B (**198**) [191]; gracilioether K (**199**) [192]; herdmanine K (**200**) [193]; hyrtioreticulin A (**201**) [194]; new Kunitz-type protease inhibitor InHVJ (**202**) [195]; jaspamide (**203**) [196]; latonduine A (**204**) [197]; leucettine L41 (**205**) [169]; manzamine A (**206**) [198]; nahuoic acid A (**207**) [199]; namalide (**208**) [200]; ningalins C and D (**209**,**210**) [201]; octaphlorethol A (**114**) [120]; petrosaspongiolide M (**211**) [202]; petrosiol A (**212**) [203]; phidianidine A (**213**) [204]; Poly-APS (**214**) [205]; *Pseudoceratina* sp. dibromotyrosine (**215**) [206]; pseudopterosin A (**216**) [207]; sargachromanol G (**217**) [208]; *S. graminifolium* polysaccharide (**218**) [209]; *S. patens* phloroglucinol (**219**) [210]; *S. xiamenensis* benzopyran (**220**) [211]; theonellasterol (**221**) [212]; toluquinol (**222**) [213]; and *U. lactuca* fatty acid (**223**) [214].

Also described in Table 3 is the pharmacological activity of 34 additional compounds. Albeit an IC_{50} for enzyme or receptor inhibition is provided, no mechanism of action studies were reported at the time of publication: alotaketal C (**224**) [215]; aspergentisyl A (**225**) [216]; *A. terreus* butyrolactone (**226**) [217]; caulerpine (**227**) [218]; conicasterol F (**228**) [219]; *D. avara* sesquiterpene (**229**) [220]; *D. gigantea* sterols (**230**,**231**) [221]; dysidavarone A (**232**) [222]; galvaquinone B (**233**) [223]; halicloic acids A and B (**234**,**235**) [224]; isochromophilone XI (**236**) [225]; leucettamols A and B (**237**,**238**) [226]; manadosterol A (**239**) [227]; marilines A1 and A2 (**240**,**241**) [228]; methyl sarcotroate B (**242**) [229]; *P. citrinum* sorbicillinoid (**243**) [230]; phosphoiodyn A (**244**) [231]; purpuroines A and D (**245**,**246**) [232]; santacruzamate A (**247**) [233]; sarcophytonolide N (**248**) [234]; sargassumol (**249**) [235]; sesquibastadin 1 (**250**) [236]; *S. glaucum* cembranoids (**251**–**253**) [237]; symplocin A (**254**) [238]; tsitsikammamine A derivative (**255**) [239]; *V. lanosa* bromophenol (**256**) [**240**]; and *X. testudinaria* fatty acid (**257**) [241].

Table 3. Marine pharmacology in 2012–2013: marine compounds with miscellaneous mechanisms of action.

Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
astaxanthin (**189**)/alga	Terpenoid [f]	Human sperm capacitation	2 μM *	Increased tyrosine phosphorylation	ITA	[182]
astaxanthin (**189**)/alga	Terpenoid [f]	Apoptosis reduction in retinal ganglion cells	2 μM	H_2O_2 inhibition	CHN	[242]
biselyngbyaside (**190**)/bacterium	Polyketide [e]	Osteoclast apoptosis induction	30 nM *	c-Fos and NFATc1 inhibition	JPN	[183]
Callyspongia sp. bisacetylenic alcohol (**191**)/sponge	Polyketide [e]	Lymphatic endothelial cell proliferation inhibition	0.11 μM	Cell cycle arrest	JPN, NLD	[184]
conicasterol E (**192**)/sponge	Terpenoid [f]	Bile acid detoxification	10 μM *	Farnesoid and pregnane receptor activity modulation	ITA, PYF	[185]
6′′-debromohamacanthin A (**193**)/sponge	Alkaloid [g]	Angiogenesis inhibition	14.8 μM	PI3K/AKT/mTOR signaling inhibition	CAN, S. KOR	[186]
dieckol (**194**)/alga	Polyketide [e]	Inhibition of melanin synthesis	>120 μM *	Cellular tyrosinase inhibition	S. KOR	[187]
fructigenine A (**195**)/fungus	Alkaloid [g]	PTP1B inhibition	10.7 μM	Noncompetitive inhibition	S. KOR	[188]
geoditin A (**196**)/sponge	Terpenoid [f]	Melanogenesis inhibition	1 μg/mL	cAMP-dependent signaling inhibition	CHN, USA	[189]
gorgosterol (**197**)/soft coral	Terpenoid [f]	FXR transactivation antagonism	10 μM	Inhibition of OSTα & BSEP genes	ITA	[190]
gracilioether B (**198**)/sponge	Polyketide [e]	PPARγ binding	5 μM *	Cys285 covalent binding	FRA, ITA	[191]
gracilioether K (**199**)/sponge	Polyketide [e]	PXR agonistic activity	10 μM *	Binding to LBD by molecular docking	ITA	[192]
herdmanine K (**200**)/ascidian	Alkaloid [g]	PPAR-γ agonist	1 μg/mL *	mRNAexpression of target genes	S. KOR	[193]
hyrtioreticulin A (**201**)/sponge	Alkaloid [g]	Ubiquitin-activating enzyme inhibition	2.4 μM	Putative ubiquitin-adenylate intermediate inhibition	IDN, JPN, NLD	[194]
InhVJ protease inhibitor (**202**)/ sea anemone	Peptide [g]	Trypsin and α-chymotrysin inhibition	**	Glu45 involved in InhVJ-trypsin complex	BEL, RUS	[195]
jaspamide (**203**)/sponge	Peptide [g]	Decreased cardiomyocyte activity and function	1–19 μM *	Kv1.5 channel inhibition	USA	[196]
latonduine A (**204**)/sponge	Alkaloid [g]	F508del-CTFR correction	1 μM *	PARP-3 inhibition	CAN	[197]
leucettine L41 (**205**)/sponge	Alkaloid [g]	DYR and CL tyrosine kinase inhibition	21–77 nM	Primary and secondary targets identified	FRA	[169]
manzamine A (**206**)/sponge	Alkaloid [g]	Cholesterol esters inhibition	4.1 μM	ACAT inhibition	JPN	[198]
nahuoic acid A (**207**)/bacterium	Polyketide [e]	SETDH inhibition	6.5 μM	Competitive inhibition	PNG, CAN	[199]
namalide (**208**)/sponge	Peptide [g]	Carbopeptidase A inhibition	0.25 μM	D-Lys presence required for activity	ITA, USA	[200]
ningalins C & D (**209**,**210**)/ascidian	Alkaloid [g]	CK1δ and GSK3β inhibition	0.2 μM	Binding to ATP binding site	AUS	[201]
octaphlorethol A (**114**)/alga	Polyketide [e]	Glucose tansporter 4 increase	10 μM *	AKT and AMPK activation	S. KOR	[120]
petrosaspongiolide M (**211**)/sponge	Terpenoid [f]	Proteasome inhibition	0.085–1.05 μM	Pro-apoptotic bax induction	ITA	[202]
petrosiol A (**212**)/sponge	Polyketide [e]	PDGF-induced DNA synthesis inhibition	0.73 μM	PDGF receptor-β signaling inhibition	JPN	[203]
phidianidine A (**213**)/mollusc	Alkaloid [g]	CXCR4 ligand antagonist	<50 μM	CXCL12-dependent DNA synthesis inhibition	ITA	[204]
Poly-APS (**214**)/sponge	Polyketide [e]	Thoracic aorta contraction inhibition in vitro	<10 μM *	Concentration-dependent LDH release	SVN	[205]
Pseudoceratina sp. Dibromotyrosine (**215**)/sponge	Alkaloid [g]	Apoptosis induction	5 μg/mL	Mitochondrial disfunction	EGY, TWN	[206]
pseudopterosin A (**216**)/soft coral	Terpenoid [f]	Increased HUVEC proliferation	13 nM	Enhancement potency by HPβCD	USA	[207]
sargachromanol G (**217**)/alga	Terpenoid [f]	Osteoclastogenesis inhibition	20 Mm *	NF-kB phosphorylation of MAPK kinases inhibition	S. KOR	[208]
S. graminifolium polysaccharide (**218**)/alga	Polysaccharide [h]	Improved mitochondrial disfunction and oxidative stress	25 mg/kg ***	Increased activity of antioxidant enzymes	CHN	[209]

Table 3. *Cont.*

Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
S. patens phloroglucinol (**219**)/alga	Polyketide [e]	α-amylase inhibition	3.2 μg/mL	Competitive α-amylase inhibitor	JPN	[210]
S. xiamenensis benzopyran (**220**)/bacterium	Mixed biogenesis	Fibrosis inhibition	30 μg/mL *	Anti-proliferation, anti-contractile and anti-adhesion activity	CHN	[211]
theonellasterol (**221**)/sponge	Terpenoid [f]	Farnesoid receptor transactivation inhibition	50 μM *	SAR showed OH at C-4 and oxidation at C-3 required	ITA, JPN	[212]
toluquinol (**222**)/fungus	Shikimate	Angiogenesis inhibition in vitro and in vivo	2.5 μM *	Cell cycle arrest induction	ESP	[213]
U. lactuca fatty acid (**223**)/alga	Polyketide [e]	ARE activator	10 μg/mL *	Nrf2 transcription factor activation	USA	[214]
alotaketal C (**224**)/sponge	Terpenoid [f]	cAMP signaling activation	6.5 μM	Undetermined	CAN	[215]
aspergentisyl A(**225**)/fungus	Polyketide [e]	DPPH radical-scavenging	9.3 μM	Undetermined	CHN	[216]
A. terreus butyrolactone (**226**)/fungus	Shikimate	β-glucuronidase inhibition	6.2 μM	Undetermined	LKA, PAK, USA	[217]
caulerpine (**227**)/alga	Alkaloid [g]	Spasmolytic effect on guinea pig ileum	0.05–0.13 μM	Undetermined	BRA	[218]
conicasterol F (**228**)/sponge	Terpenoid [f]	FXR antagonism	10 μM *	Undetermined	GBR, ITA	[219]
D. avara sesquiterpene (**229**)/sponge	Terpenoid [f]	FAK, IGF1 & ERBB2 kinase inhibition	1 μg/mL *	Undetermined	DEU, GBR, EGY, SAU	[220]
D. gigantea sterols (**230**,**231**)/soft coral	Terpenoid [f]	Farnesoid receptor transactivation inhibition	14–15 μM	Undetermined	S. KOR	[221]
dysidavarone A (**232**)/sponge	Terpenoid [f]	PTP1B inhibition	9.98 μM	Undetermined	CHN	[222]
galvaquinone B (**233**)/bacterium	Polyketide [e]	Epigenetic activity	1.0 μM	Undetermined	USA	[223]
halicloic acids A & B (**234**,**235**)/sponge	Terpenoid [f]	IDO1 inhibition	10 & 11 μM	Undetermined	CAN, NLD	[224]
isochromophilone XI (**236**)/fungus	Polyketide [e]	PD4 inhibition	8.3 μM	Undetermined	DEU	[225]
leucettamols A & B (**237**,**238**)/sponge	Terpenoid [f]	TRPA1 and TRPM8 channel inhibition	4.7–6.4 μM	Undetermined	ITA	[226]
manadosterol A (**239**)/sponge	Terpenoid [f]	Ubiquitin E2 enzyme UBc13-Uev1A complex inhibition	90 nM	Undetermined	IDN. JPN, NLD	[227]
marilines A_1 & A_2 (**240**,**241**)/fungus	Mixed biogenesis	HLE inhibition	0.86 μM	Undetermined	DEU, GRC, PAN	[228]
methyl sarcotroate B (**242**)/soft coral	Terpenoid [f]	PTP1B inhibition	6.97 μM	Undetermined	CHN	[229]
P. citrinum sorbicillinoid (**243**)/fungus	Polyketide [e]	Antioxidant	30 μM	Undetermined	JPN	[230]
phosphoiodyn A (**244**)/sponge	Polyketide [e]	hPPARδ inhibition	23.7 nM	Undetermined	AUS, S. KOR	[231]
purpuroines A & D (**245**,**246**)/sponge	Alkaloid [g]	LCK kinase inhibition	0.94, 2.35 μg/mL	Undetermined	DEU, CHN	[232]
santacruzamate A (**247**)/bacterium	Alkaloid [g]	HDAC2 inhibition	0.110 nM	Undetermined	PAN, USA	[233]
sarcophytonolide N (**248**)/soft coral	Terpenoid [f]	PTP1B inhibition	5.9 μM	Undetermined	CHN, ITA	[234]
sargassumol (**249**)/alga	Polyketide [e]	Antioxidant	47 μM	Undetermined	S. KOR	[235]
sesquibastadin 1 (**250**)/sponge	Alkaloid [g]	Protein kinases inhibition	0.1–6.5 μM	Undetermined	CHN, DEU	[236]

Table 3. *Cont.*

Compound/Organism [a]	Chemistry	Pharmacological Activity	IC_{50} [b]	MMOA [c]	Country [d]	References
S. glaucum cembranoids (**251**–**253**)/soft coral	Terpenoid [f]	Cytochrome P450 1A inhibition	12.7–3.7 nM *	Undetermined	EGY, SAU, USA	[237]
symplocin A (**254**)/bacterium	Peptide [g]	Cathepsin E inhibition	0.3 nM	Undetermined	USA	[238]
tsitsikammamine A derivative (**255**)/sponge	Alkaloid [g]	IDO1 inhibition	0.9 μM	Undetermined	BEL, FRA	[239]
V. lanosa bromophenol (**256**)/alga	Terpenoid [f]	Biochemical & cellular antioxidant activity	30 μg/mL	Undetermined	NOR	[240]
X. testudinaria fatty acid (**257**)/sponge	Polyketide [e]	Adipogenesis stimulation	2 μM	Undetermined	JPN	[241]

([a]) **Organism**: *Kingdom Animalia*: soft corals and sea anemone (Phylum Cnidaria), starfish (Phylum Echinodermata), mollusk (Phylum Mollusca); sponge (Phylum Porifera); *Kingdom Plantae:* alga; *Kingdom Monera*: bacterium; ([b]) **IC_{50}**: concentration of a compound required for 50% inhibition in vitro; *: estimated IC_{50}; **: *Ki* 7.4×10^{-8} M, and 9.9×10^{-7} M, respectively; ***: in vivo study; ([c]) **MMOA**: molecular mechanism of action; ([d]) **Country**: AUS: Australia; BEL: Belgium; BRA: Brazil; CAN: Canada; CHN: China; DEU: Germany; EGY: Egypt; FRA: France; ESP: Spain; GBR: United Kingdom; GRC: Greece; IDN: Indonesia; ITA: Italy; JPN: Japan; LKA: Sri Lanka; NLD: The Netherlands; NOR: Norway; PAN: Panama; PAK: Pakistan; PNG: Papua New Guinea; PYF: French Polynesia; RUS: Russian Federation; SAU: Saudi Arabia; S. KOR: South Korea; SVN: Slovenia; TWN: Taiwan; **Chemistry**: ([e]) Polyketide; ([f]) Terpene; ([g]) Nitrogen-containing compound; ([h]) polysaccharide; **Abbreviations**: ACAT: acyl-CoA:cholesterol acyl-transferase; Akt: protein kinase B; AMPK: AMP-activated protein kinase; ARE: antioxidant-response element; ASIC3: pH-sensitive sodium ion channel 3; CFTR: cystic fibrosis transmembrane conductance regulator; CXCR4: chemokine receptor; CKL: cdc2-like kinase; DYRK: dual-specificity, tyrosine phosphorylation regulated kinase; ERBB2: erb-b2 receptor tyrosine kinase; FAK: focal adhesion kinase; FXR: farnesoid-X-receptor; HDAC: histone deacetylase; HLE: human leukocyte elastase; HUVEC: human umbilical vein endothelial cells; HPβCD: hydroxypropyl-β-cyclodrextrin; IDO1: indoleamine 2, 3 dioxygenase; Kv1.5: Potassium voltage-gated ion channel; LBD: ligand binding domain; LCK: lymphocyte-specific protein tyrosine kinase; IGF1-R: insulin-like growth factor 1 receptor; PDGF: platelet-derived growth factor; PI3K: phosphoinositide 3-kinase; Poly-APS: polymeric 3-alkylpyridinium salts; PARP: poly(ADP-ribose) polymerase; PD4: phosphodiesterase 4; PPARγ: peroxisome proliferator-activated receptor γ; PTP1B: protein tyrosine phosphatase 1B; PXR: pregnane-X-receptor; SETDH: protein methyltransferase SETD8; TRPA1: ankyrin channel; TRPM8: melastin channel.

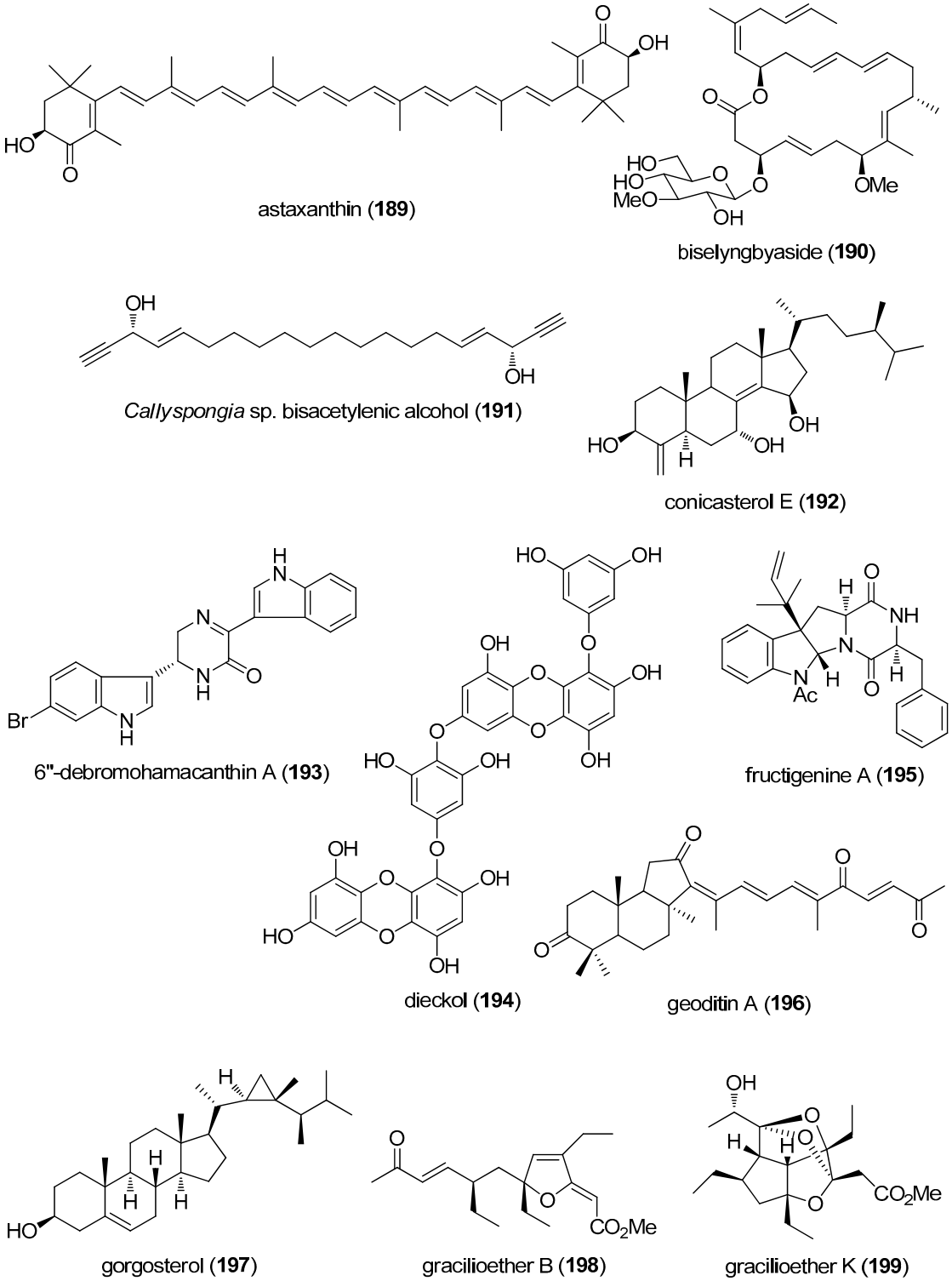
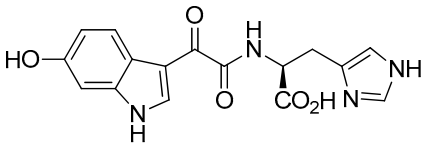
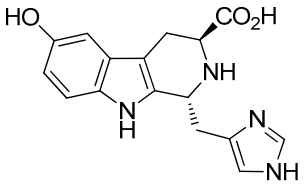


Figure 3. *Cont.*



herdmanine K (**200**)



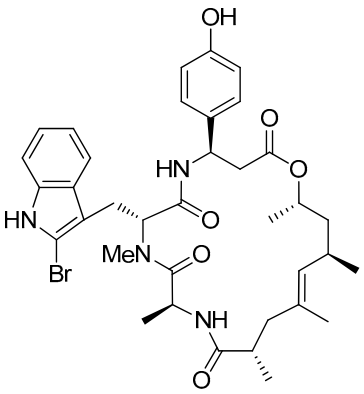
hyrtioreticulin A (**201**)

GSICLEPKVVGPCTAYFPR

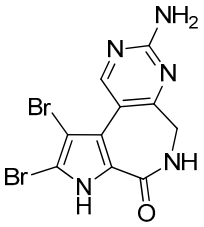
FYFDSETGKCTPFIYGGCE

GNGNNFETLHACRAICRA

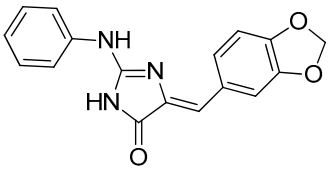
InhVJ protease inhibitor (**202**)



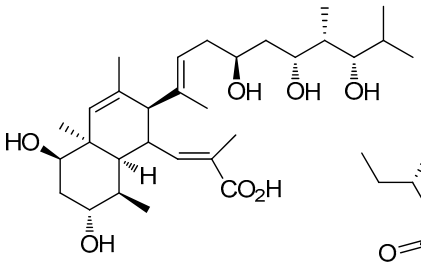
jaspamide (**203**)



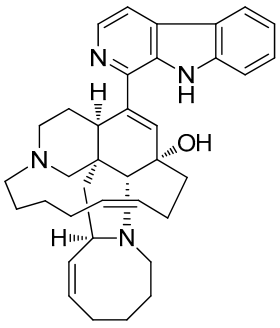
latonduine A (**204**)



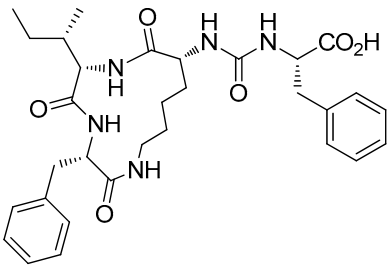
leucettine L41 (**205**)



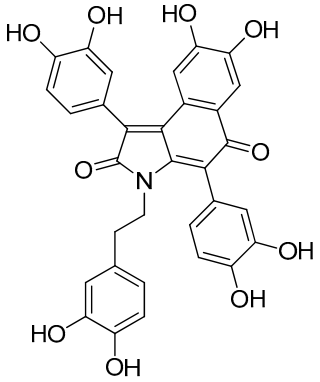
nahuoic acid A (**207**)



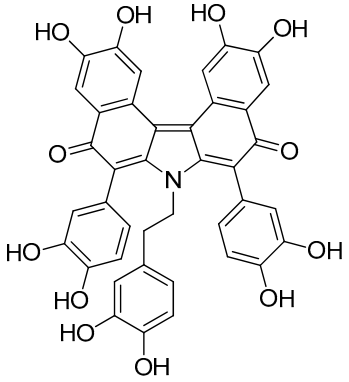
manzamine A (**206**)



namalide (**208**)

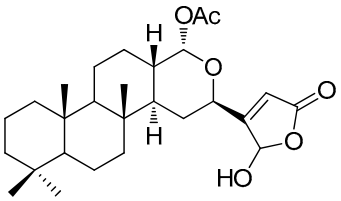


ningalin C (**209**)

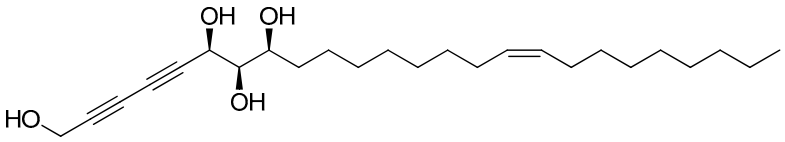


ningalin D (**210**)

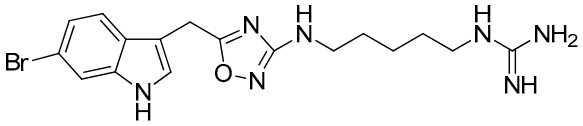
Figure 3. *Cont.*



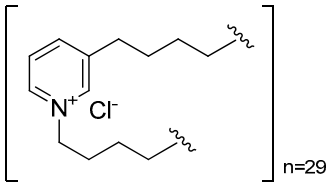
petrosaspongiolide M (**211**)



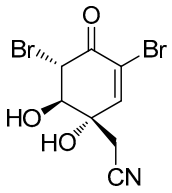
petrosiol A (**212**)



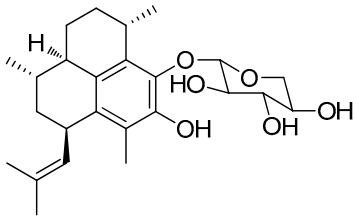
phidianidine A (**213**)



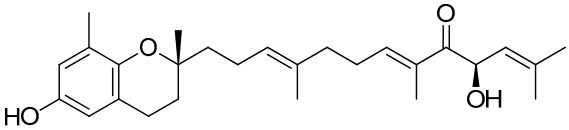
Poly-APS (**214**)



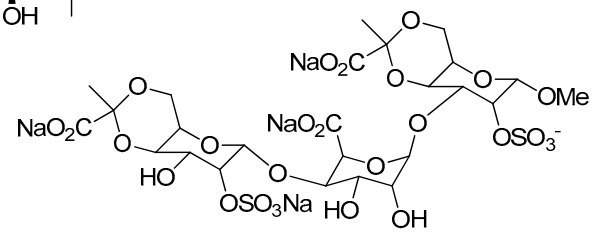
Pseudoceratina sp. dibromotyrosine (**215**)



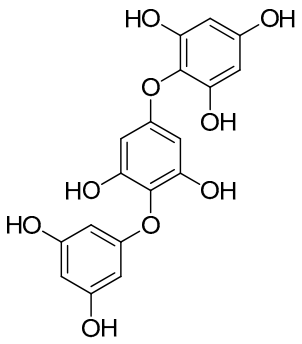
pseudopterosin A (**216**)



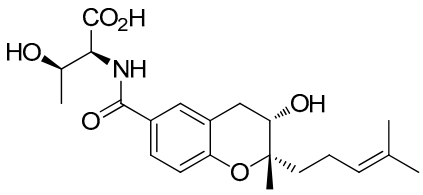
sargachromanol G (**217**)



S. graminifolium polysaccharide (**218**)

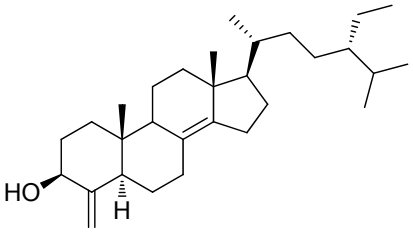


S. patens phloroglucinol (**219**)

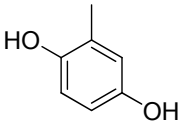


S. xiamenensis benzopyran (**220**)

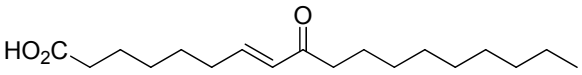
Figure 3. *Cont.*



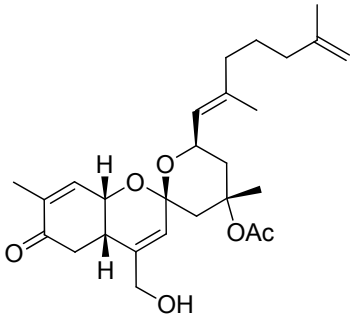
theonellasterol (**221**)



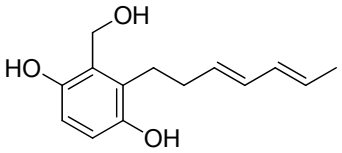
toluquinol (**222**)



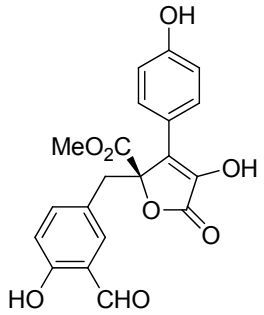
U. lactuca fatty acid (**223**)



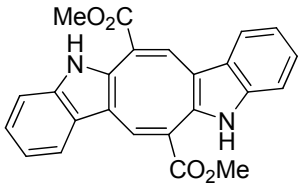
alotaketal C (**224**)



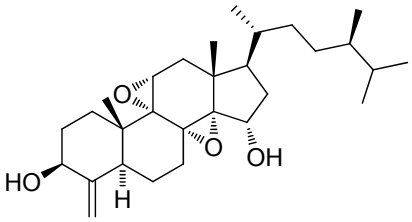
aspergentisyl A (**225**)



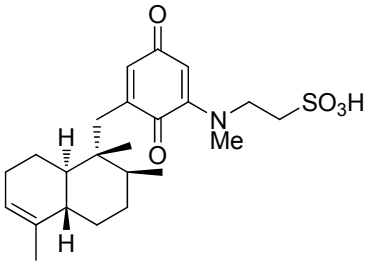
A. terreus butyrolactone (**226**)



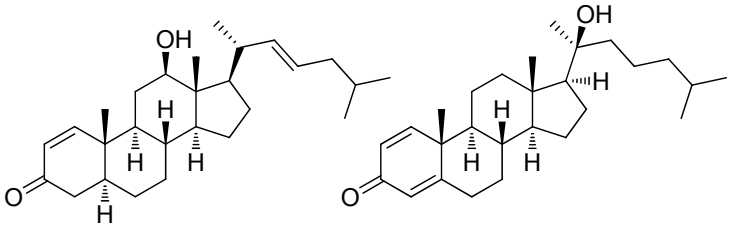
caulerpine (**227**)



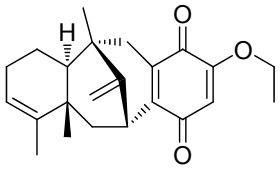
conicasterol F (**228**)



D. avara sesquiterpene (**229**)



D. gigantea sterols (**230**, **231**)



dysidavarone A (**232**)

Figure 3. *Cont.*

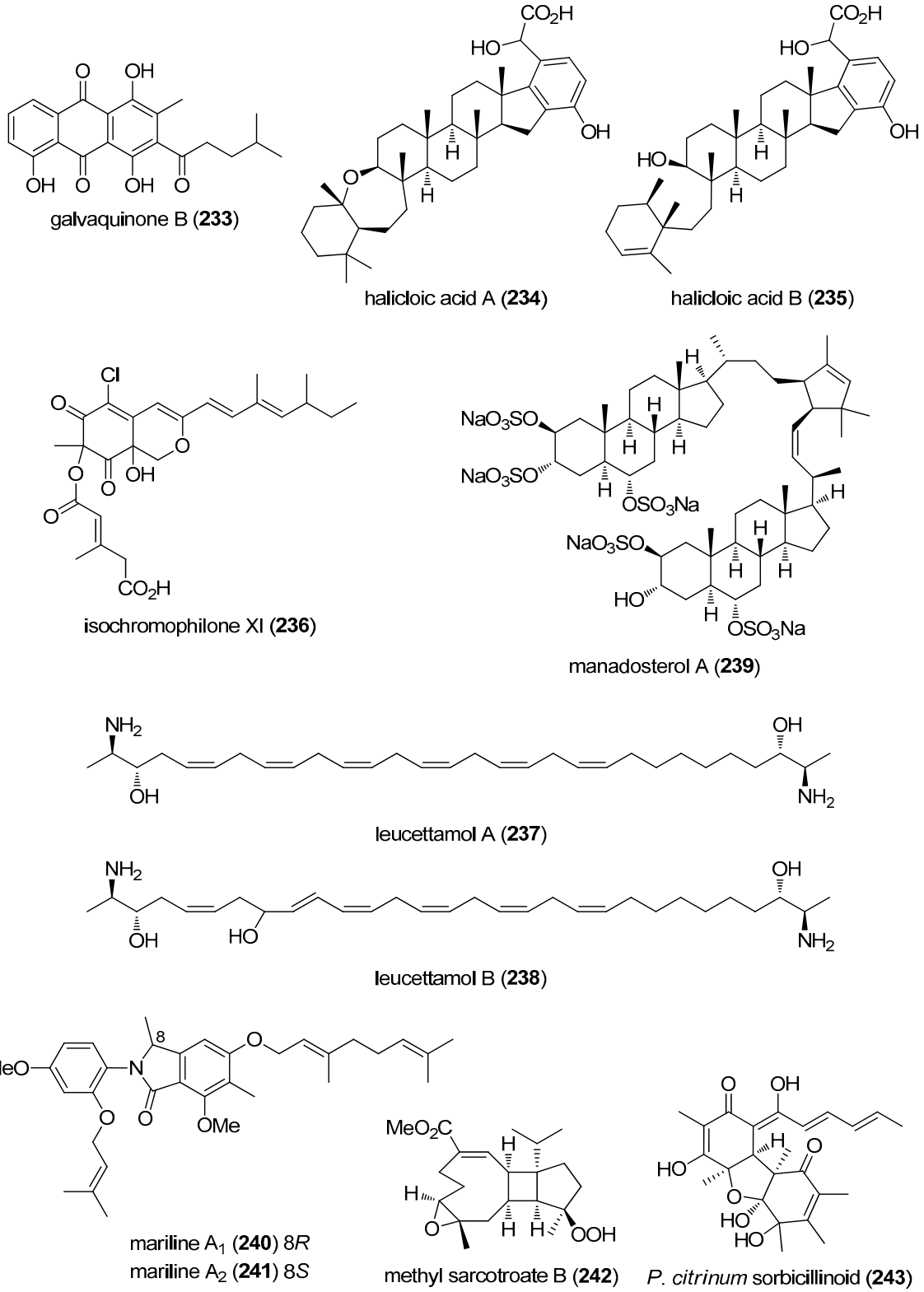
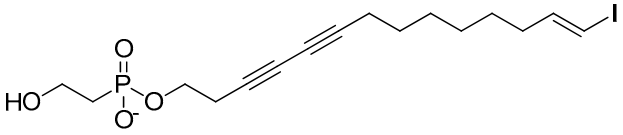
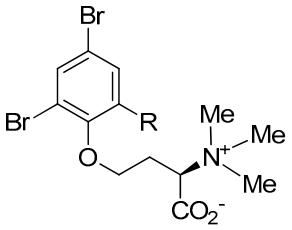


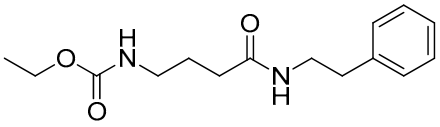
Figure 3. *Cont.*



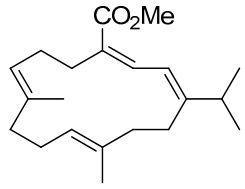
phosphoiodyn A (**244**)



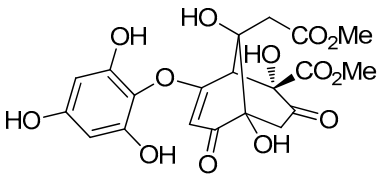
purpuroine A (**245**) R = Br
purpuroine D (**246**) R = I



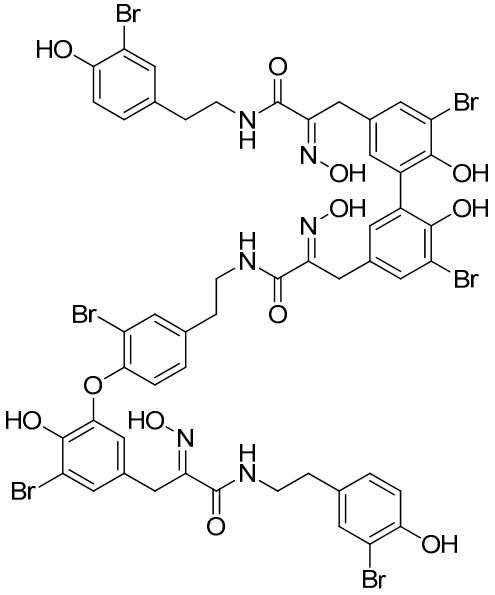
santacruzamate A (**247**)



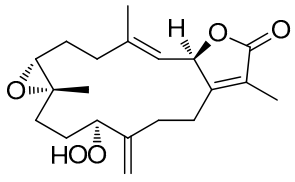
sarcophytonolide N (**248**)



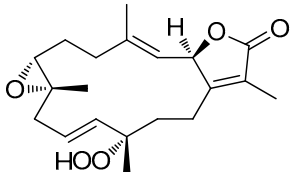
sargassumol (**249**)



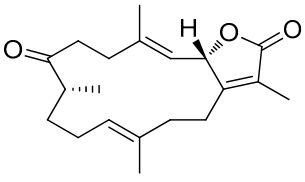
sesquibastadin 1 (**250**)



(**251**)



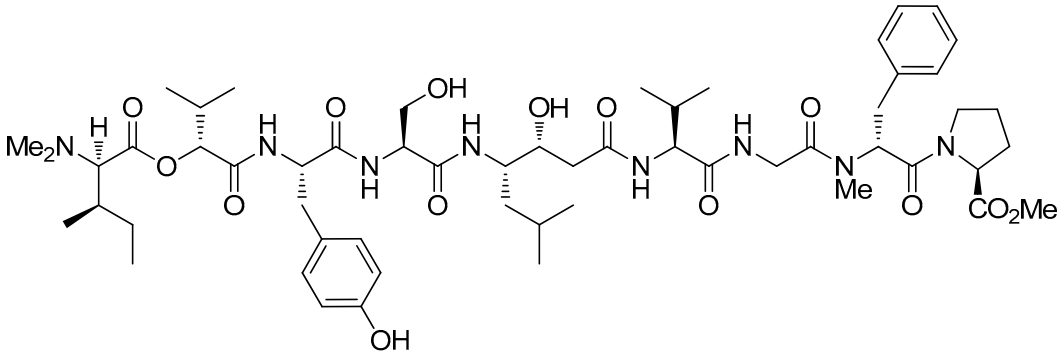
(**252**)



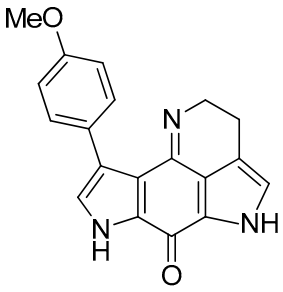
(**253**)

S. glaucum cembranoids

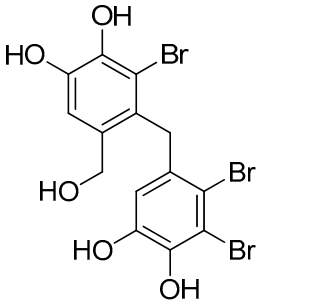
Figure 3. *Cont.*



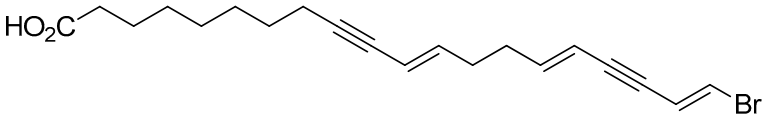
symplocin A (**254**)



tsitsikammamine A analog b (**255**)



V. lanosa bromophenol (**256**)



X. testudinaria fatty acid (**257**)

Figure 3. Marine pharmacology in 2012–2013: marine compounds with miscellaneous mechanisms of action.

5. Reviews on Marine Pharmacology

In 2012–2013, several reviews were published covering general and/or specific areas of marine preclinical pharmacology: (a) ***marine pharmacology and marine pharmaceuticals***: new marine natural products and relevant biological activities published in 2010 and 2011 [243,244]; natural products drug discovery as a continuing source of novel drug leads [245]; guiding principles for natural product drug discovery [246]; challenges and triumphs to genomic-based natural product discovery and pharmacology [247]; future of marine natural products drug discovery [248]; bioactive marine natural products from Antarctic and Arctic organisms [249]; biological activities of terpenes from the soft coral genus *Sarcophyton* [250]; pharmacologically active marine peptides from fish and shellfish [251]; preclinical pharmacology of marine diterpene glycosides [252]; bioactivity of fucoidan, a complex algal sulfated polysaccharide [253]; therapeutic application of marine fucanomics and galactanomics in drug development [254]; marine pharmacology of cosmopolitan brown alga *Cystoseira* genus secondary metabolites [255]; pharmacological activity of sulfated polysaccharides from marine algae [256]; biological activities and functions of halogenated organic molecules of red algae Rhodomelaceae [257]; pharmacological potential of marine cyanobacterial secondary metabolites [258]; pharmaceutical agents from filamentous marine cyanobacteria [259]; chemistry and preclinical pharmacology of sponge glycosides [260]; sea cucumbers as drug

candidates [261]; bioactives from microalgal dinoflagellates [262]; the global marine pharmaceutical pipeline in 2017: U.S. Food and Drug Administration-approved compounds and those in Phase I, II and III of clinical development http://marinepharmacology.midwestern.edu/clinPipeline.htm; (b) ***antimicrobial marine pharmacology***: antimicrobial non-ribosomal peptides from abundant α-, γ- and δ-marine Proteobacteria classes [263]; marine bacteria as potential sources for compounds to overcome methicillin-resistant *Staphylococcus aureus* [264]; marine coral alkaloids and antibacterial activities [265]; marine fish and invertebrates as sources of antimicrobial peptides [266]; marine actinomycetes as an emerging resource for drug development [267]; chemistry and biological activity of marine *Bacillus* sp. secondary metabolites [268]; marine compounds with therapeutic potential in Gram-negative sepsis [269]; antimicrobial properties of tunichromes [270]; drug discovery from marine microbes [271]; (c) ***antiviral marine pharmacology***: marine natural products with anti-HIV activities in the last decade [272]; fucoidans as potential inhibitors of human immunodeficiency virus type 1 (HIV-1) [273]; discovery of potent broad spectrum antivirals derived from marine Actinobacteria [274]; algal lectins for prevention of HIV transmission [275]; (d) ***antiprotozoal, antimalarial, antituberculosis and antifungal marine pharmacology***: trypanocidal activity of marine natural products [276]; natural sesquiterpenes as lead compounds for the design of trypanocidal drugs [277]; antifungal compounds from marine fungi [278]; (e) ***immuno- and anti-inflammatory marine pharmacology***: immunoregulatory properties of bryostatin [279]; bioactive marine peptides as potential anti-inflammatory therapeutics [280]; anti-inflammatory soft coral marine natural products from Taiwan [281]; marine natural products with potential for the therapeutics of inflammatory diseases [282]; antioxidant properties of crude extracts and compounds from brown marine algae [283]; (f) ***cardiovascular and antidiabetic marine pharmacology***: oxidation of marine omega-3 supplements and human health [284]; marine peptides for prevention of metabolic syndrome [285]; antidiabetic effect of marine brown algae-derived phlorotannins [286]; marine bioactive peptides as potential antioxidants [287]; cardioprotective peptides from marine sources [288]; antioxidant and antidiabetic pharmacology of fucoxantin [289]; marine-derived bioactive peptides as new anticoagulants [290]; (g) ***nervous system marine pharmacology***: marine neurotoxins, structures, molecular targets and pharmacology [291]; the phosphatase inhibitor okadaic acid as a tool to identify phosphoepitopes relevant to neurodegeneration [292]; marine toxins and drug discovery targeting nicotinic acetylcholine receptors [293]; marine-derived marine secondary metabolites and neuroprotection [294]; cone snail polyketides active in neurological assays [295]; and (h) ***miscellaneous molecular targets and uses***: small-molecule inhibitors of clinically validated protein and lipid kinases of marine origin [296]; natural products as kinase inhibitors [297]; marine natural products with protein tyrosine phosphatase 1B activity [298]; current development strategies for marine conotoxins and their mimetics as therapeutic leads [299]; therapeutic potential of novel conotoxins reported in 2007–2011 [300]; computational studies of marine toxins targeting ion channels [301]; marine invertebrates as sources of skeletal proteins for bone regeneration [302]; marine algal compounds in cosmeceuticals [303]; and marine sponge steroids as nuclear receptor ligands [304].

6. Conclusions

The purpose of the current marine pharmacology review was to continue the marine *preclinical* pharmacology pipeline review series that was initiated in 1998 [1–8] by consolidating preclinical marine pharmacological research published during 2012–2013 in the global literature. The large number of peer-reviewed publications we have reviewed demonstrates that the global research effort involved chemists and pharmacologists from 43 countries, namely, Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, China, Colombia, Egypt, Fiji, France, French Polynesia, Germany, Greece, India, Indonesia, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Morocco, the Netherlands, New Zealand, Norway, Pakistan, Panama, Papua New Guinea, Russian Federation, Saudi Arabia, Slovenia, South Africa, South Korea, Spain, Sri Lanka, Switzerland, Taiwan, Thailand, United Kingdom, Vietnam, and the United States. Thus, during 2012–2013 the marine *preclinical*

pharmaceutical pipeline continued to provide novel pharmacological lead compounds that enriched the marine *clinical* pharmaceutical pipeline. Currently, the *clinical* pharmaceutical pipeline consists of 6 pharmaceuticals approved by the U.S. Food and Drug Administration, and 29 compounds in Phase I, II and III of clinical pharmaceutical development, as shown at a dedicated website: http://marinepharmacology.midwestern.edu/clinPipeline.htm.

Acknowledgments: We thank the contributions of Hillary Kerns, Michelle Nguyen, and Patrycja Kalwajtys from the Chicago College of Pharmacy for database and literature retrieval. We also thank the secretarial assistance of Victoria Sears, Laura Phelps and Mary Hall from the Pharmacology Department, CCOM for careful review of this manuscript. We gratefully acknowledge financial support from Midwestern University to AMSM; and NIH-SC1 Award (Grant 1SC1GM086271-01A1) of the University of Puerto Rico to ADR, and Italian MIUR (Grant 20154JRJPP) to OTS. The content of this review is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Article retrieval by library staff members, and students from the Chicago College of Pharmacy, Midwestern University, is gratefully acknowledged. The authors are especially grateful to Mary Hall for her careful review of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Mayer, A.M.S.; Lehmann, V.K.B. 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. *Pharmacologist* **2000**, *42*, 62–69.
2. Mayer, A.M.S.; Hamann, M.T. Marine pharmacology in 1999: Compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, anthelmintic, anti-inflammatory, antiplatelet, antiprotozoal and antiviral activities; affecting the cardiovascular, endocrine, immune, and nervous systems; and other miscellaneous mechanisms of action. *Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol.* **2002**, *132*, 315–339.
3. Mayer, A.M.S.; Hamann, M.T. Marine pharmacology in 2000: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antituberculosis, and antiviral activities; affecting the cardiovascular, immune, and nervous systems and other miscellaneous mechanisms of action. *Mar. Biotechnol.* **2004**, *6*, 37–52. [PubMed]
4. Mayer, A.M.S.; Hamann, M.T. 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. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2005**, *140*, 265–286. [PubMed]
5. Mayer, A.M.S.; Rodriguez, A.D.; Berlinck, R.G.; Hamann, M.T. Marine pharmacology in 2003-4: Marine compounds with anthelmintic antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiplatelet, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2007**, *145*, 553–581. [PubMed]
6. Mayer, A.M.S.; Rodriguez, A.D.; Berlinck, R.G.; Hamann, M.T. Marine pharmacology in 2005-6: Marine compounds with anthelmintic, antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the cardiovascular, immune and nervous systems, and other miscellaneous mechanisms of action. *Biochim. Biophys. Acta* **2009**, *1790*, 283–308. [PubMed]
7. Mayer, A.M.S.; Rodriguez, A.D.; Berlinck, R.G.; Fusetani, N. Marine pharmacology in 2007-8: Marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action. *Comp. Biochem. Physiol. C Toxicol. Pharmacol.* **2011**, *153*, 191–222. [PubMed]
8. Mayer, A.M.S.; Rodriguez, A.D.; Taglialatela-Scafati, O.; Fusetani, N. Marine Pharmacology in 2009–2011: Marine Compounds with Antibacterial, Antidiabetic, Antifungal, Anti-Inflammatory, Antiprotozoal, Antituberculosis, and Antiviral Activities; Affecting the Immune and Nervous Systems, and other Miscellaneous Mechanisms of Action. *Mar. Drugs* **2013**, *11*, 2510–2573. [PubMed]

9. Schmitz, F.J.; Bowden, B.F.; Toth, S.I. Antitumor and Cytotoxic Compounds from Marine Organisms. In *Marine Biotechnology, Pharmaceutical and Bioactive Natural Products*; Attaway, D.H., Zaborsky, O.R., Eds.; Plenum Press: New York, NY, USA; London, UK, 1993; pp. 197–308.
10. Cervantes, S.; Stout, E.P.; Prudhomme, J.; Engel, S.; Bruton, M.; Cervantes, M.; Carter, D.; Tae-Chang, Y.; Hay, M.E.; Aalbersberg, W.; et al. High content live cell imaging for the discovery of new antimalarial marine natural products. *BMC Infect. Dis.* **2012**, *12*, 1. [CrossRef] [PubMed]
11. Spavieri, J.; Allmendinger, A.; Kaiser, M.; Itoe, M.A.; Blunden, G.; Mota, M.M.; Tasdemir, D. Assessment of dual life stage antiplasmodial activity of british seaweeds. *Mar. Drugs* **2013**, *11*, 4019–4034. [CrossRef] [PubMed]
12. Yamashita, A.; Salam, K.A.; Furuta, A.; Matsuda, Y.; Fujita, O.; Tani, H.; Fujita, Y.; Fujimoto, Y.; Ikeda, M.; Kato, N.; et al. Inhibition of hepatitis C virus replication and viral helicase by ethyl acetate extract of the marine feather star *Alloeocomatella polycladia*. *Mar. Drugs* **2012**, *10*, 744–761. [CrossRef] [PubMed]
13. De Souza, L.M.; Sassaki, G.L.; Romanos, M.T.; Barreto-Bergter, E. Structural characterization and anti-HSV-1 and HSV-2 activity of glycolipids from the marine algae *Osmundaria obtusiloba* isolated from Southeastern Brazilian coast. *Mar. Drugs* **2012**, *10*, 918–931. [CrossRef] [PubMed]
14. Albuquerque, I.R.; Cordeiro, S.L.; Gomes, D.L.; Dreyfuss, J.L.; Filgueira, L.G.; Leite, E.L.; Nader, H.B.; Rocha, H.A. Evaluation of Anti-Nociceptive and Anti-Inflammatory Activities of a Heterofucan from *Dictyota menstrualis*. *Mar. Drugs* **2013**, *11*, 2722–2740. [CrossRef] [PubMed]
15. Cavalcante-Silva, L.H.; da Matta, C.B.; de Araujo, M.V.; Barbosa-Filho, J.M.; de Lira, D.P.; de Oliveira Santos, B.V.; de Miranda, G.E.; Alexandre-Moreira, M.S. Antinociceptive and anti-inflammatory activities of crude methanolic extract of red alga *Bryothamnion triquetrum*. *Mar. Drugs* **2012**, *10*, 1977–1992. [CrossRef] [PubMed]
16. Chaves, L.S.; Nicolau, L.A.; Silva, R.O.; Barros, F.C.; Freitas, A.L.; Aragao, K.S.; Ribeiro, R.A.; Souza, M.H.; Barbosa, A.L.; Medeiros, J.V. Antiinflammatory and antinociceptive effects in mice of a sulfated polysaccharide fraction extracted from the marine red algae *Gracilaria caudata*. *Immunopharmacol. Immunotoxicol.* **2013**, *35*, 93–100. [CrossRef] [PubMed]
17. Lee, J.Y.; Lee, M.S.; Choi, H.J.; Choi, J.W.; Shin, T.; Woo, H.C.; Kim, J.I.; Kim, H.R. Hexane fraction from *Laminaria japonica* exerts anti-inflammatory effects on lipopolysaccharide-stimulated RAW 264.7 macrophages via inhibiting NF-kappa B pathway. *Eur. J. Nutr.* **2013**, *52*, 409–421. [CrossRef] [PubMed]
18. Rezende, B.M.; Bernardes, P.T.; Resende, C.B.; Arantes, R.M.; Souza, D.G.; Braga, F.C.; Castor, M.G.; Teixeira, M.M.; Pinho, V. *Lithothamnion muelleri* controls inflammatory responses, target organ injury and lethality associated with graft-versus-host disease in mice. *Mar. Drugs* **2013**, *11*, 2595–2615. [CrossRef] [PubMed]
19. Zawadzki, M.; Janosch, C.; Szechinski, J. Perna canaliculus lipid complex PCSO-524 demonstrated pain relief for osteoarthritis patients benchmarked against fish oil, a randomized trial, without placebo control. *Mar. Drugs* **2013**, *11*, 1920–1935. [CrossRef] [PubMed]
20. Wen, Z.S.; Liu, L.J.; Qu, Y.L.; Ouyang, X.K.; Yang, L.Y.; Xu, Z.R. Chitosan nanoparticles attenuate hydrogen peroxide-induced stress injury in mouse macrophage RAW264.7 cells. *Mar. Drugs* **2013**, *11*, 3582–3600. [CrossRef] [PubMed]
21. Wang, B.; Zhang, B.; Wang, Q.; Zhang, Z.; Nie, F.; Liu, G.; Zheng, J.; Xiao, L.; Zhang, L. Pharmacological studies of tentacle extract from the jellyfish *Cyanea capillata* in isolated rat aorta. *Mar. Drugs* **2013**, *11*, 3335–3349. [CrossRef] [PubMed]
22. Silva, R.O.; Santana, A.P.; Carvalho, N.S.; Bezerra, T.S.; Oliveira, C.B.; Damasceno, S.R.; Chaves, L.S.; Freitas, A.L.; Soares, P.M.; Souza, M.H.; et al. A sulfated-polysaccharide fraction from seaweed *Gracilaria birdiae* prevents naproxen-induced gastrointestinal damage in rats. *Mar. Drugs* **2012**, *10*, 2618–2633. [CrossRef] [PubMed]
23. Zhang, C.Y.; Wu, W.H.; Wang, J.; Lan, M.B. Antioxidant properties of polysaccharide from the brown seaweed *Sargassum graminifolium* (Turn.), and its effects on calcium oxalate crystallization. *Mar. Drugs* **2012**, *10*, 119–130. [CrossRef] [PubMed]
24. Kelman, D.; Posner, E.K.; McDermid, K.J.; Tabandera, N.K.; Wright, P.R.; Wright, A.D. Antioxidant activity of Hawaiian marine algae. *Mar. Drugs* **2012**, *10*, 403–416. [CrossRef] [PubMed]
25. Guedes, A.C.; Giao, M.S.; Seabra, R.; Ferreira, A.C.; Tamagnini, P.; Moradas-Ferreira, P.; Malcata, F.X. Evaluation of the antioxidant activity of cell extracts from microalgae. *Mar. Drugs* **2013**, *11*, 1256–1270. [CrossRef] [PubMed]

26. Belhaj, N.; Desor, F.; Gleizes, C.; Denis, F.M.; Arab-Tehrany, E.; Soulimani, R.; Linder, M. Anxiolytic-like effect of a salmon phospholipopeptidic complex composed of polyunsaturated fatty acids and bioactive peptides. *Mar. Drugs* **2013**, *11*, 4294–4317. [CrossRef] [PubMed]
27. Carvalho, V.; Fernandes, L.; Conde, T.; Zamith, H.; Silva, R.; Surrage, A.; Frutuoso, V.; Castro-Faria-Neto, H.; Amendoeira, F. Antinociceptive activity of *Stephanolepis hispidus* skin aqueous extract depends partly on opioid system activation. *Mar. Drugs* **2013**, *11*, 1221–1234. [CrossRef] [PubMed]
28. Turk, T.; Ambrozic, A.J.; Batista, U.; Strugar, G.; Kosmina, R.; Civovic, S.; Janussen, D.; Kauferstein, S.; Mebs, D.; Sepcic, K. Biological activities of ethanolic extracts from deep-sea Antarctic marine sponges. *Mar. Drugs* **2013**, *11*, 1126–1139. [CrossRef] [PubMed]
29. Cho, S.; Han, D.; Kim, S.B.; Yoon, M.; Yang, H.; Jin, Y.H.; Jo, J.; Yong, H.; Lee, S.H.; Jeon, Y.J.; et al. Depressive Effects on the Central Nervous System and Underlying Mechanism of the Enzymatic Extract and Its Phlorotannin-Rich Fraction from *Ecklonia cava* Edible Brown Seaweed. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 163–168. [CrossRef] [PubMed]
30. Christopeit, T.; Overbo, K.; Danielson, U.H.; Nilsen, I.W. Efficient screening of marine extracts for protease inhibitors by combining FRET based activity assays and surface plasmon resonance spectroscopy based binding assays. *Mar. Drugs* **2013**, *11*, 4279–4293. [CrossRef] [PubMed]
31. Jang, K.H.; Nam, S.J.; Locke, J.B.; Kauffman, C.A.; Beatty, D.S.; Paul, L.A.; Fenical, W. Anthracimycin, a potent anthrax antibiotic from a marine-derived actinomycete. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 7822–7824. [CrossRef] [PubMed]
32. Keffer, J.L.; Huecas, S.; Hammill, J.T.; Wipf, P.; Andreu, J.M.; Bewley, C.A. Chrysophaentins are competitive inhibitors of FtsZ and inhibit Z-ring formation in live bacteria. *Bioorg. Med. Chem.* **2013**, *21*, 5673–5678. [CrossRef] [PubMed]
33. Sakoulas, G.; Nam, S.J.; Loesgen, S.; Fenical, W.; Jensen, P.R.; Nizet, V.; Hensler, M. Novel Bacterial Metabolite Merochlorin A Demonstrates in vitro Activity against Multi-Drug Resistant Methicillin-Resistant *Staphylococcus aureus*. *PLoS ONE* **2012**, *7*, e29439. [CrossRef] [PubMed]
34. Wang, H.; Lu, Z.; Qu, H.J.; Liu, P.; Miao, C.; Zhu, T.; Li, J.; Hong, K.; Zhu, W. Antimicrobial aflatoxins from the marine-derived fungus *Aspergillus flavus* 092008. *Arch. Pharm. Res.* **2012**, *35*, 1387–1392. [CrossRef] [PubMed]
35. Yang, F.; Hamann, M.T.; Zou, Y.; Zhang, M.Y.; Gong, X.B.; Xiao, J.R.; Chen, W.S.; Lin, H.W. Antimicrobial metabolites from the Paracel Islands sponge *Agelas mauritiana*. *J. Nat. Prod.* **2012**, *75*, 774–778. [CrossRef] [PubMed]
36. Zheng, C.J.; Shao, C.L.; Guo, Z.Y.; Chen, J.F.; Deng, D.S.; Yang, K.L.; Chen, Y.Y.; Fu, X.M.; She, Z.G.; Lin, Y.C.; et al. Bioactive hydroanthraquinones and anthraquinone dimers from a soft coral-derived *Alternaria* sp. fungus. *J. Nat. Prod.* **2012**, *75*, 189–197. [CrossRef] [PubMed]
37. Han, Z.; Xu, Y.; McConnell, O.; Liu, L.; Li, Y.; Qi, S.; Huang, X.; Qian, P. Two antimycin A analogues from marine-derived actinomycete *Streptomyces lusitanus*. *Mar. Drugs* **2012**, *10*, 668–676. [CrossRef] [PubMed]
38. Li, D.; Xu, Y.; Shao, C.L.; Yang, R.Y.; Zheng, C.J.; Chen, Y.Y.; Fu, X.M.; Qian, P.Y.; She, Z.G.; de Voogd, N.J.; et al. Antibacterial bisabolane-type sesquiterpenoids from the sponge-derived fungus *Aspergillus* sp. *Mar. Drugs* **2012**, *10*, 234–241. [CrossRef] [PubMed]
39. Pettit, G.R.; Tang, Y.; Zhang, Q.; Bourne, G.T.; Arm, C.A.; Leet, J.E.; Knight, J.C.; Pettit, R.K.; Chapuis, J.C.; Doubek, D.L.; et al. Isolation and structures of axistatins 1–3 from the Republic of Palau marine sponge *Agelas axifera* Hentschel. *J. Nat. Prod.* **2013**, *76*, 420–424. [CrossRef] [PubMed]
40. Teasdale, M.E.; Shearer, T.L.; Engel, S.; Alexander, T.S.; Fairchild, C.R.; Prudhomme, J.; Torres, M.; Le, R.K.; Aalbersberg, W.; Hay, M.E.; et al. Bromophycoic acids: Bioactive natural products from a Fijian red alga *Callophycus* sp. *J. Org. Chem.* **2012**, *77*, 8000–8006. [CrossRef] [PubMed]
41. Wang, W.; Kim, H.; Nam, S.J.; Rho, B.J.; Kang, H. Antibacterial butenolides from the Korean tunicate *Pseudodistoma antinboja*. *J. Nat. Prod.* **2012**, *75*, 2049–2054. [CrossRef] [PubMed]
42. Won, T.H.; Jeon, J.E.; Kim, S.H.; Lee, S.H.; Rho, B.J.; Oh, D.C.; Oh, K.B.; Shin, J. Brominated aromatic furanones and related esters from the ascidian *Synoicum* sp. *J. Nat. Prod.* **2012**, *75*, 2055–2061. [CrossRef] [PubMed]
43. Liu, L.L.; Xu, Y.; Han, Z.; Li, Y.X.; Lu, L.; Lai, P.Y.; Zhong, J.L.; Guo, X.R.; Zhang, X.X.; Qian, P.Y. Four new antibacterial xanthones from the marine-derived actinomycetes *Streptomyces caelestis*. *Mar. Drugs* **2012**, *10*, 2571–2583. [CrossRef] [PubMed]

44. Wang, J.; Liu, P.; Wang, Y.; Wang, H.; Li, J.; Zhuang, Y.; Zhu, W. Antimicrobial Aromatic Polyketides from Gorgonian-Associated Fungus, *Penicillium commune* 518. *Chin. J. Chem.* **2012**, *30*, 1236–1242. [CrossRef]
45. Ioannou, E.; Quesada, A.; Rahman, M.M.; Gibbons, S.; Vagias, C.; Roussis, V. Structures and Antibacterial Activities of Minor Dolabellanes from the Brown Alga *Dilophus spiralis*. *Eur. J. Org. Chem.* **2012**, *2012*, 5177–5186. [CrossRef]
46. Felder, S.; Kehraus, S.; Neu, E.; Bierbaum, G.; Schaberle, T.F.; Konig, G.M. Salimyxins and enhygrolides: Antibiotic, sponge-related metabolites from the obligate marine myxobacterium *Enhygromyxa salina*. *Chembiochem* **2013**, *14*, 1363–1371. [CrossRef] [PubMed]
47. Won, T.H.; Jeon, J.E.; Lee, S.H.; Rho, B.J.; Oh, K.B.; Shin, J. Beta-carboline alkaloids derived from the ascidian *Synoicum* sp. *Bioorg. Med. Chem.* **2012**, *20*, 4082–4087. [CrossRef] [PubMed]
48. Xin, W.; Ye, X.; Yu, S.; Lian, X.Y.; Zhang, Z. New capoamycin-type antibiotics and polyene acids from marine *Streptomyces fradiae* PTZ0025. *Mar. Drugs* **2012**, *10*, 2388–2402. [CrossRef] [PubMed]
49. Lee, Y.; Jang, K.H.; Jeon, J.E.; Yang, W.Y.; Sim, C.J.; Oh, K.B.; Shin, J. Cyclic Bis-1,3-dialkylpyridiniums from the sponge *Haliclona* sp. *Mar. Drugs* **2012**, *10*, 2126–2137. [CrossRef] [PubMed]
50. Tanaka, N.; Momose, R.; Takahashi, Y.; Kubota, T.; Takahashi-Nakaguchi, A.; Gonoi, T.; Fromont, J.; Kobayashi, J. Hyrtimomines D and E, bisindole alkaloids from a marine sponge *Hyrtios* sp. *Tetrahedron Lett.* **2013**, *54*, 4038–4040. [CrossRef]
51. Xu, M.; Davis, R.A.; Feng, Y.; Sykes, M.L.; Shelper, T.; Avery, V.M.; Camp, D.; Quinn, R.J. Ianthelliformisamines A–C, antibacterial bromotyrosine-derived metabolites from the marine sponge *Suberea ianthelliformis*. *J. Nat. Prod.* **2012**, *75*, 1001–1005. [CrossRef] [PubMed]
52. Martin, J.; da S Sousa, T.; Crespo, G.; Palomo, S.; Gonzalez, I.; Tormo, J.R.; de la Cruz, M.; Anderson, M.; Hill, R.T.; Vicente, F.; et al. Kocurin, the true structure of PM181104, an anti-methicillin-resistant *Staphylococcus aureus* (MRSA) thiazolyl peptide from the marine-derived bacterium *Kocuria palustris*. *Mar. Drugs* **2013**, *11*, 387–398. [CrossRef] [PubMed]
53. Zhang, H.; Conte, M.M.; Huang, X.C.; Khalil, Z.; Capon, R.J. A search for BACE inhibitors reveals new biosynthetically related pyrrolidones, furanones and pyrroles from a southern Australian marine sponge, *Ianthella* sp. *Org. Biomol. Chem.* **2012**, *10*, 2656–2663. [CrossRef] [PubMed]
54. Li, X.D.; Miao, F.P.; Li, K.; Ji, N.Y. Sesquiterpenes and acetogenins from the marine red alga *Laurencia okamurai*. *Fitoterapia* **2012**, *83*, 518–522. [CrossRef] [PubMed]
55. Pan, H.Q.; Zhang, S.Y.; Wang, N.; Li, Z.L.; Hua, H.M.; Hu, J.C.; Wang, S.J. New spirotetronate antibiotics, lobophorins H and I, from a South China Sea-derived *Streptomyces* sp. 12A35. *Mar. Drugs* **2013**, *11*, 3891–3901. [CrossRef] [PubMed]
56. Zhou, X.; Huang, H.; Chen, Y.; Tan, J.; Song, Y.; Zou, J.; Tian, X.; Hua, Y.; Ju, J. Marthiapeptide A, an anti-infective and cytotoxic polythiazole cyclopeptide from a 60 L scale fermentation of the deep sea-derived *Marinactinospora thermotolerans* SCSIO 00652. *J. Nat. Prod.* **2012**, *75*, 2251–2255. [CrossRef] [PubMed]
57. Wu, Z.; Li, S.; Li, J.; Chen, Y.; Saurav, K.; Zhang, Q.; Zhang, H.; Zhang, W.; Zhang, W.; Zhang, S.; et al. Antibacterial and cytotoxic new napyradiomycins from the marine-derived *Streptomyces* sp. SCSIO 10428. *Mar. Drugs* **2013**, *11*, 2113–2125. [CrossRef] [PubMed]
58. Cheng, Y.B.; Jensen, P.R.; Fenical, W. Cytotoxic and Antimicrobial Napyradiomycins from Two Marine-Derived *Streptomyces* Strains. *Eur. J. Org. Chem.* **2013**, 3751–3757. [CrossRef] [PubMed]
59. Yang, K.L.; Wei, M.Y.; Shao, C.L.; Fu, X.M.; Guo, Z.Y.; Xu, R.F.; Zheng, C.J.; She, Z.G.; Lin, Y.C.; Wang, C.Y. Antibacterial anthraquinone derivatives from a sea anemone-derived fungus *Nigrospora* sp. *J. Nat. Prod.* **2012**, *75*, 935–941. [CrossRef] [PubMed]
60. Um, S.; Choi, T.J.; Kim, H.; Kim, B.Y.; Kim, S.H.; Lee, S.K.; Oh, K.B.; Shin, J.; Oh, D.C. Ohmyungsamycins A and B: Cytotoxic and Antimicrobial Cyclic Peptides Produced by *Streptomyces* sp. from a Volcanic Island. *J. Org. Chem.* **2013**, *78*, 12321–12329. [CrossRef] [PubMed]
61. Qi, J.; Shao, C.L.; Li, Z.Y.; Gan, L.S.; Fu, X.M.; Bian, W.T.; Zhao, H.Y.; Wang, C.Y. Isocoumarin derivatives and benzofurans from a sponge-derived *Penicillium* sp. fungus. *J. Nat. Prod.* **2013**, *76*, 571–579. [CrossRef] [PubMed]
62. Rubiolo, J.A.; Ternon, E.; Lopez-Alonso, H.; Thomas, O.P.; Vega, F.V.; Vieytes, M.R.; Botana, L.M. Crambescidin-816 acts as a fungicidal with more potency than crambescidin-800 and -830, inducing cell cycle arrest, increased cell size and apoptosis in *Saccharomyces cerevisiae*. *Mar. Drugs* **2013**, *11*, 4419–4434. [CrossRef] [PubMed]

63. Yibmantasiri, P.; Leahy, D.C.; Busby, B.P.; Angermayr, S.A.; Sorgo, A.G.; Boeger, K.; Heathcott, R.; Barber, J.M.; Moraes, G.; Matthews, J.H.; et al. Molecular basis for fungicidal action of neothyonidioside, a triterpene glycoside from the sea cucumber, *Australostichopus mollis*. *Mol. Biosyst.* **2012**, *8*, 902–912. [CrossRef] [PubMed]
64. Kumar, R.; Subramani, R.; Feussner, K.D.; Aalbersberg, W. Aurantoside K, a new antifungal tetramic acid glycoside from a Fijian marine sponge of the genus *Melophlus*. *Mar. Drugs* **2012**, *10*, 200–208. [CrossRef] [PubMed]
65. Liu, A.H.; Liu, D.Q.; Liang, T.J.; Yu, X.Q.; Feng, M.T.; Yao, L.G.; Fang, Y.; Wang, B.; Feng, L.H.; Zhang, M.X.; et al. Caulerprenylols A and B, two rare antifungal prenylated para-xylenes from the green alga *Caulerpa racemosa*. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2491–2494. [CrossRef] [PubMed]
66. Haga, A.; Tamoto, H.; Ishino, M.; Kimura, E.; Sugita, T.; Kinoshita, K.; Takahashi, K.; Shiro, M.; Koyama, K. Pyridone alkaloids from a marine-derived fungus, *Stagonosporopsis cucurbitacearum*, and their activities against azole-resistant *Candida albicans*. *J. Nat. Prod.* **2013**, *76*, 750–754. [CrossRef] [PubMed]
67. Piao, S.J.; Song, Y.L.; Jiao, W.H.; Yang, F.; Liu, X.F.; Chen, W.S.; Han, B.N.; Lin, H.W. Hippolachnin A, a New Antifungal Polyketide from the South China Sea Sponge *Hippospongia lachne*. *Org. Lett.* **2013**, *15*, 3526–3529. [CrossRef] [PubMed]
68. Wang, Z.; Zhang, H.; Yuan, W.; Gong, W.; Tang, H.; Liu, B.; Krohn, K.; Li, L.; Yi, Y.; Zhang, W. Antifungal nortriterpene and triterpene glycosides from the sea cucumber *Apostichopus japonicus* Selenka. *Food Chem.* **2013**, *132*, 295–300. [CrossRef] [PubMed]
69. Tanaka, N.; Kusama, T.; Takahashi-Nakaguchi, A.; Gonoi, T.; Fromont, J.; Kobayashi, J. Nagelamides X–Z, dimeric bromopyrrole alkaloids from a marine sponge *Agelas* sp. *Org. Lett.* **2013**, *15*, 3262–3265. [CrossRef] [PubMed]
70. Yu, H.B.; Liu, X.F.; Xu, Y.; Gan, J.H.; Jiao, W.H.; Shen, Y.; Lin, H.W. Woodylides A–C, new cytotoxic linear polyketides from the South China Sea sponge *Plakortis simplex*. *Mar. Drugs* **2012**, *10*, 1027–1036. [CrossRef] [PubMed]
71. Mani, L.; Jullian, V.; Mourkazel, B.; Valentin, A.; Dubois, J.; Cresteil, T.; Folcher, E.; Hooper, J.N.; Erpenbeck, D.; Aalbersberg, W.; et al. New antiplasmodial bromotyrosine derivatives from *Suberea ianthelliformis* Lendenfeld, 1888. *Chem. Biodivers.* **2012**, *9*, 1436–1451. [CrossRef] [PubMed]
72. Lam, C.F.; Pearce, A.N.; Tan, S.H.; Kaiser, M.; Copp, B.R. Discovery and evaluation of thiazinoquinones as anti-protozoal agents. *Mar. Drugs* **2013**, *11*, 3472–3499. [CrossRef] [PubMed]
73. Farokhi, F.; Grellier, P.; Clement, M.; Roussakis, C.; Loiseau, P.M.; Genin-Seward, E.; Kornprobst, J.M.; Barnathan, G.; Wielgosz-Collin, G. Antimalarial activity of axidjiferosides, new beta-galactosylceramides from the African sponge *Axinyssa djiferi*. *Mar. Drugs* **2013**, *11*, 1304–1315. [CrossRef] [PubMed]
74. Beau, J.; Mahid, N.; Burda, W.N.; Harrington, L.; Shaw, L.N.; Mutka, T.; Kyle, D.E.; Barisic, B.; van, O.A.; Baker, B.J. Epigenetic tailoring for the production of anti-infective cytosporones from the marine fungus *Leucostoma persoonii*. *Mar. Drugs* **2012**, *10*, 762–774. [CrossRef] [PubMed]
75. Calcul, L.; Waterman, C.; Ma, W.S.; Lebar, M.D.; Harter, C.; Mutka, T.; Morton, L.; Maignan, P.; van, O.A.; Kyle, D.E.; et al. Screening mangrove endophytic fungi for antimalarial natural products. *Mar. Drugs* **2013**, *11*, 5036–5050. [CrossRef] [PubMed]
76. Ilias, M.; Ibrahim, M.A.; Khan, S.I.; Jacob, M.R.; Tekwani, B.L.; Walker, L.A.; Samoylenko, V. Pentacyclic ingamine alkaloids, a new antiplasmodial pharmacophore from the marine sponge *Petrosid* Ng5 Sp5. *Planta Med.* **2012**, *78*, 1690–1697. [CrossRef] [PubMed]
77. Mudianta, I.W.; Skinner-Adams, T.; Andrews, K.T.; Davis, R.A.; Hadi, T.A.; Hayes, P.Y.; Garson, M.J. Psammaplysin derivatives from the Balinese marine sponge *Aplysinella strongylata*. *J. Nat. Prod.* **2012**, *75*, 2132–2143. [CrossRef] [PubMed]
78. Sirirak, T.; Brecker, L.; Plubrukarn, A. Kabiramide L, a new antiplasmodial trisoxazole macrolide from the sponge *Pachastrissa nux*. *Nat. Prod. Res.* **2013**, *27*, 1213–1219. [CrossRef] [PubMed]
79. Bharate, S.B.; Rammohan, R.Y.; Khan, S.I.; Tekwani, B.L.; Jacob, M.R.; Khan, I.A.; Vishwakarma, R.A. Meridianin G and its analogs as antimalarial agents. *Med. Chem. Commun.* **2013**, *4*, 1042–1048. [CrossRef]
80. Liew, L.P.; Kaiser, M.; Copp, B.R. Discovery and preliminary structure-activity relationship analysis of 1,14-sperminediphenylacetamides as potent and selective antimalarial lead compounds. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 452–454. [CrossRef] [PubMed]

81. Festa, C.; De Marino, S.; D'Auria, M.V.; Taglialatela-Scafati, O.; Deharo, E.; Petek, S.; Zampella, A. New antimalarial polyketide endoperoxides from the marine sponge *Plakinastrella mamillaris* collected at Fiji Islands. *Tetrahedron* **2013**, *69*, 3706–3713. [CrossRef]
82. Davis, R.A.; Duffy, S.; Fletcher, S.; Avery, V.M.; Quinn, R.J. Thiaplakortones A-D: Antimalarial thiazine alkaloids from the Australian marine sponge *Plakortis lita*. *J. Org. Chem.* **2013**, *78*, 9608–9613. [CrossRef] [PubMed]
83. Davis, R.A.; Buchanan, M.S.; Duffy, S.; Avery, V.M.; Charman, S.A.; Charman, W.N.; White, K.L.; Shackleford, D.M.; Edstein, M.D.; Andrews, K.T.; et al. Antimalarial activity of pyrroloiminoquinones from the Australian marine sponge *Zyzzya* sp. *J. Med. Chem.* **2012**, *55*, 5851–5858. [CrossRef] [PubMed]
84. Supong, K.; Thawai, C.; Suwanborirux, K.; Choowong, W.; Supothina, S.; Pittayakhajonwut, P. Antimalarial and antitubercular *C*-glycosylated benz[a]anthraquinones from the marine-derived *Streptomyces* sp. BCC45596. *Phytochem. Lett.* **2012**, *5*, 651–656. [CrossRef]
85. Sanchez, L.M.; Knudsen, G.M.; Helbig, C.; De, M.G.; Mascuch, S.M.; Mackey, Z.B.; Gerwick, L.; Clayton, C.; McKerrow, J.H.; Linington, R.G. Examination of the mode of action of the almiramide family of natural products against the kinetoplastid parasite *Trypanosoma brucei*. *J. Nat. Prod.* **2013**, *76*, 630–641. [CrossRef] [PubMed]
86. Abdelmohsen, U.R.; Szesny, M.; Othman, E.M.; Schirmeister, T.; Grond, S.; Stopper, H.; Hentschel, U. Antioxidant and anti-protease activities of diazepinomicin from the sponge-associated *Micromonospora* strain RV115. *Mar. Drugs* **2012**, *10*, 2208–2221. [CrossRef] [PubMed]
87. Desoti, V.C.; Lazarin-Bidoia, D.; Sudatti, D.B.; Pereira, R.C.; Alonso, A.; Ueda-Nakamura, T.; Dias Filho, B.P.; Nakamura, C.V.; Silva, S.O. Trypanocidal action of (−)-elatol involves an oxidative stress triggered by mitochondria dysfunction. *Mar. Drugs* **2012**, *10*, 1631–1646. [CrossRef] [PubMed]
88. Balunas, M.J.; Grosso, M.F.; Villa, F.A.; Engene, N.; McPhail, K.L.; Tidgewell, K.; Pineda, L.M.; Gerwick, L.; Spadafora, C.; Kyle, D.E.; et al. Coibacins A–D, antileishmanial marine cyanobacterial polyketides with intriguing biosynthetic origins. *Org. Lett.* **2012**, *14*, 3878–3881. [CrossRef] [PubMed]
89. Ishigami, S.T.; Goto, Y.; Inoue, N.; Kawazu, S.; Matsumoto, Y.; Imahara, Y.; Tarumi, M.; Nakai, H.; Fusetani, N.; Nakao, Y. Cristaxenicin A, an antiprotozoal xenicane diterpenoid from the deep sea gorgonian *Acanthoprimnoa cristata*. *J. Org. Chem.* **2012**, *77*, 10962–10966. [CrossRef] [PubMed]
90. Chianese, G.; Scala, F.; Calcinai, B.; Cerrano, C.; Dien, H.A.; Kaiser, M.; Tasdemir, D.; Taglialatela-Scafati, O. Natural and semisynthetic analogues of manadoperoxide B reveal new structural requirements for trypanocidal activity. *Mar. Drugs* **2013**, *11*, 3297–3308. [CrossRef] [PubMed]
91. Huang, X.; Huang, H.; Li, H.; Sun, X.; Huang, H.; Lu, Y.; Lin, Y.; Long, Y.; She, Z. Asperterpenoid A, a new sesterterpenoid as an inhibitor of Mycobacterium tuberculosis protein tyrosine phosphatase B from the culture of *Aspergillus* sp. 16–5c. *Org. Lett.* **2013**, *15*, 721–723. [CrossRef] [PubMed]
92. Song, F.; Liu, X.; Guo, H.; Ren, B.; Chen, C.; Piggott, A.M.; Yu, K.; Gao, H.; Wang, Q.; Liu, M.; et al. Brevianamides with antitubercular potential from a marine-derived isolate of *Aspergillus versicolor*. *Org. Lett.* **2012**, *14*, 4770–4773. [CrossRef] [PubMed]
93. Chen, C.; Wang, J.; Guo, H.; Hou, W.; Yang, N.; Ren, B.; Liu, M.; Dai, H.; Liu, X.; Song, F.; et al. Three antimycobacterial metabolites identified from a marine-derived *Streptomyces* sp. MS100061. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 3885–3892. [CrossRef] [PubMed]
94. Yamano, Y.; Arai, M.; Kobayashi, M. Neamphamide B, new cyclic depsipeptide, as an anti-dormant mycobacterial substance from a Japanese marine sponge of *Neamphius* sp. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 4877–4881. [CrossRef] [PubMed]
95. Aviles, E.; Rodriguez, A.D.; Vicente, J. Two rare-class tricyclic diterpenes with antitubercular activity from the Caribbean sponge *Svenzea flava*. Application of vibrational circular dichroism spectroscopy for determining absolute configuration. *J. Org. Chem.* **2013**, *78*, 11294–11301. [CrossRef] [PubMed]
96. Da Rosa Guimaraes, T.; Quiroz, C.G.; Borges, C.R.; de Oliveira, S.Q.; de Almeida, M.T.; Bianco, E.M.; Moritz, M.I.; Carraro, J.L.; Palermo, J.A.; Cabrera, G.; et al. Anti HSV-1 activity of halistanol sulfate and halistanol sulfate C isolated from Brazilian marine sponge *Petromica citrina* (Demospongiae). *Mar. Drugs* **2013**, *11*, 4176–4192. [CrossRef] [PubMed]
97. Ellithey, M.S.; Lall, N.; Hussein, A.A.; Meyer, D. Cytotoxic, cytostatic and HIV-1 PR inhibitory activities of the soft coral *Litophyton arboreum*. *Mar. Drugs* **2013**, *11*, 4917–4936. [CrossRef] [PubMed]

98. Salam, K.A.; Furuta, A.; Noda, N.; Tsuneda, S.; Sekiguchi, Y.; Yamashita, A.; Moriishi, K.; Nakakoshi, M.; Tsubuki, M.; Tani, H.; et al. Inhibition of hepatitis C virus NS3 helicase by manoalide. *J. Nat. Prod.* **2012**, *75*, 650–654. [CrossRef] [PubMed]
99. Park, S.H.; Song, J.H.; Kim, T.; Shin, W.S.; Park, G.M.; Lee, S.; Kim, Y.J.; Choi, P.; Kim, H.; Kim, H.S.; et al. Anti-human rhinoviral activity of polybromocatechol compounds isolated from the rhodophyta, *Neorhodomela aculeata*. *Mar. Drugs* **2012**, *10*, 2222–2233. [CrossRef] [PubMed]
100. Ma, X.; Li, L.; Zhu, T.; Ba, M.; Li, G.; Gu, Q.; Guo, Y.; Li, D. Phenylspirodrimanes with anti-HIV activity from the sponge-derived fungus *Stachybotrys chartarum* MXH-X73. *J. Nat. Prod.* **2013**, *76*, 2298–2306. [CrossRef] [PubMed]
101. Jiao, R.H.; Xu, H.; Cui, J.T.; Ge, H.M.; Tan, R.X. Neuraminidase Inhibitors from marine-derived actinomycete *Streptomyces seoulensis*. *J. Appl. Microbiol.* **2013**, *114*, 1046–1053. [CrossRef] [PubMed]
102. He, F.; Bao, J.; Zhang, X.Y.; Tu, Z.C.; Shi, Y.M.; Qi, S.H. Asperterrestide A, a cytotoxic cyclic tetrapeptide from the marine-derived fungus *Aspergillus terreus* SCSGAF0162. *J. Nat. Prod.* **2013**, *76*, 1182–1186. [CrossRef] [PubMed]
103. Peng, J.; Lin, T.; Wang, W.; Xin, Z.; Zhu, T.; Gu, Q.; Li, D. Antiviral alkaloids produced by the mangrove-derived fungus *Cladosporium* sp. PJX-41. *J. Nat. Prod.* **2013**, *76*, 1133–1140. [CrossRef] [PubMed]
104. Hawas, U.W.; El-Beih, A.A.; El-Halawany, A.M. Bioactive anthraquinones from endophytic fungus *Aspergillus versicolor* isolated from red sea algae. *Arch. Pharm. Res.* **2012**, *35*, 1749–1756. [CrossRef] [PubMed]
105. Zhang, G.F.; Han, W.B.; Cui, J.T.; Ng, S.W.; Guo, Z.K.; Tan, R.X.; Ge, H.M. Neuraminidase inhibitory polyketides from the marine-derived fungus *Phoma herbarum*. *Planta Med.* **2012**, *78*, 76–78. [CrossRef] [PubMed]
106. Peng, J.; Jiao, J.; Li, J.; Wang, W.; Gu, Q.; Zhu, T.; Li, D. Pyronepolyene *C*-glucosides with NF-kappaB inhibitory and anti-influenza A viral (H1N1) activities from the sponge-associated fungus *Epicoccum* sp. JJY40. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3188–3190. [CrossRef] [PubMed]
107. Ahmed, S.; Ibrahim, A.; Satar Arafa, A. Anti-H5N1 virus metabolites from the Red Sea soft coral, *Sinularia candidula*. *Tetrahedron Lett.* **2013**, *54*, 2377–2381. [CrossRef]
108. Plouguerne, E.; de Souza, L.M.; Sassaki, G.L.; Cavalcanti, J.F.; Villela Romanos, M.T.; da Gama, B.A.; Pereira, R.C.; Barreto-Bergter, E. Antiviral Sulfoquinovosyldiacylglycerols (SQDGs) from the Brazilian brown seaweed *Sargassum vulgare*. *Mar. Drugs* **2013**, *11*, 4628–4640. [CrossRef] [PubMed]
109. Melek, F.R.; Tadros, M.M.; Yousif, F.; Selim, M.A.; Hassan, M.H. Screening of marine extracts for schistosomicidal activity in vitro. Isolation of the triterpene glycosides echinosides A and B with potential activity from the Sea Cucumbers *Actinopyga echinites* and *Holothuria polii*. *Pharm. Biol.* **2012**, *50*, 490–496. [CrossRef] [PubMed]
110. Chen, D.; Yu, S.; Van, O.L.; Proksch, P.; Lin, W. Anthogorgienes A–O, new guaiazulene-derived terpenoids from a Chinese gorgonian *Anthogorgia* species, and their antifouling and antibiotic activities. *J. Agric. Food Chem.* **2012**, *60*, 112–123. [CrossRef] [PubMed]
111. Nuzzo, G.; Ciavatta, M.L.; Villani, G.; Manzo, E.; Zanfardino, A.; Varcamonti, M.; Gavagnin, M. Fulvynes, antimicrobial polyoxygenated acetylenes from the Mediterranean sponge *Haliclona fulva*. *Tetrahedron* **2012**, *68*, 754–760. [CrossRef]
112. Cheng, Z.B.; Xiao, H.; Fan, C.Q.; Lu, Y.N.; Zhang, G.; Yin, S. Bioactive polyhydroxylated sterols from the marine sponge *Haliclona crassiloba*. *Steroids* **2013**, *78*, 1353–1358. [CrossRef] [PubMed]
113. Hu, Y.; Wang, K.; MacMillan, J.B. Hunanamycin A, an antibiotic from a marine-derived *Bacillus hunanensis*. *Org. Lett.* **2013**, *15*, 390–393. [CrossRef] [PubMed]
114. Khamthong, N.; Rukachaisirikul, V.; Phongpaichit, S.; Preedanon, S.; Sakayaroj, J. Bioactive polyketides from the sea fan-derived fungus *Penicillium citrinum* PSU-F51. *Tetrahedron* **2012**, *68*, 8245–8250. [CrossRef]
115. Wei, M.Y.; Li, D.; Shao, C.L.; Deng, D.S.; Wang, C.Y. (+/−)-Pestalachloride D, an antibacterial racemate of chlorinated benzophenone derivative from a soft coral-derived fungus *Pestalotiopsis* sp. *Mar. Drugs* **2013**, *11*, 1050–1060. [CrossRef] [PubMed]
116. Wyche, T.P.; Hou, Y.; Vazquez-Rivera, E.; Braun, D.; Bugni, T.S. Peptidolipins B–F, antibacterial lipopeptides from an ascidian-derived *Nocardia* sp. *J. Nat. Prod.* **2012**, *75*, 735–740. [CrossRef] [PubMed]

117. Silchenko, A.S.; Kalinovsky, A.I.; Avilov, S.A.; Andryjaschenko, P.V.; Dmitrenok, P.S.; Martyyas, E.A.; Kalinin, V.I. Triterpene glycosides from the sea cucumber *Eupentacta fraudatrix*. Structure and biological action of cucumariosides I1, I3, I4, three new minor disulfated pentaosides. *Nat. Prod. Commun.* **2013**, *8*, 1053–1058. [PubMed]
118. Sun, H.F.; Li, X.M.; Meng, L.; Cui, C.M.; Gao, S.S.; Li, C.S.; Huang, C.G.; Wang, B.G. Asperolides A–C, tetranorlabdane diterpenoids from the marine alga-derived endophytic fungus *Aspergillus wentii* EN-48. *J. Nat. Prod.* **2012**, *75*, 148–152. [CrossRef] [PubMed]
119. Xu, X.; Yin, L.; Gao, L.; Gao, J.; Chen, J.; Li, J.; Song, F. Two new bromophenols with radical scavenging activity from marine red alga *Symphyocladia latiuscula*. *Mar. Drugs* **2013**, *11*, 842–847. [CrossRef] [PubMed]
120. Lee, S.H.; Kang, S.M.; Ko, S.C.; Lee, D.H.; Jeon, Y.J. Octaphlorethol A, a novel phenolic compound isolated from a brown alga, *Ishige foliacea*, increases glucose transporter 4-mediated glucose uptake in skeletal muscle cells. *Biochem. Biophys. Res. Commun.* **2012**, *420*, 576–581. [CrossRef] [PubMed]
121. Chae, D.; Manzoor, Z.; Kim, S.C.; Kim, S.; Oh, T.H.; Yoo, E.S.; Kang, H.K.; Hyun, J.W.; Lee, N.H.; Ko, M.H.; et al. Apo-9′-fucoxanthinone, isolated from *Sargassum muticum*, inhibits CpG-induced inflammatory response by attenuating the mitogen-activated protein kinase pathway. *Mar. Drugs* **2013**, *11*, 3272–3287. [CrossRef] [PubMed]
122. Speranza, L.; Pesce, M.; Patruno, A.; Franceschelli, S.; de Lutiis, M.A.; Grilli, A.; Felaco, M. Astaxanthin treatment reduced oxidative induced pro-inflammatory cytokines secretion in U937: SHP-1 as a novel biological target. *Mar. Drugs* **2012**, *10*, 890–899. [CrossRef] [PubMed]
123. Johnson, T.A.; Sohn, J.; Vaske, Y.M.; White, K.N.; Cohen, T.L.; Vervoort, H.C.; Tenney, K.; Valeriote, F.A.; Bjeldanes, L.F.; Crews, P. Myxobacteria versus sponge-derived alkaloids: The bengamide family identified as potent immune modulating agents by scrutiny of LC-MS/ELSD libraries. *Bioorg. Med. Chem.* **2012**, *20*, 4348–4355. [CrossRef] [PubMed]
124. Song, Y.; Dou, H.; Gong, W.; Liu, X.; Yu, Z.; Li, E.; Tan, R.; Hou, Y. Bis-N-norgliovictin, a small-molecule compound from marine fungus, inhibits LPS-induced inflammation in macrophages and improves survival in sepsis. *Eur. J. Pharmacol.* **2013**, *705*, 49–60. [CrossRef] [PubMed]
125. Yang, Y.I.; Shin, H.C.; Kim, S.H.; Park, W.Y.; Lee, K.T.; Choi, J.H. 6,6′-Bieckol, isolated from marine alga *Ecklonia cava*, suppressed LPS-induced nitric oxide and PGE(2) production and inflammatory cytokine expression in macrophages: The inhibition of NFkappaB. *Int. Immunopharmacol.* **2012**, *12*, 510–517. [CrossRef] [PubMed]
126. Hsu, W.L.; Chiu, S.J.; Tsai, Y.T.; Chang, C.M.; Wang, J.Y.; Wang, E.T.; Hou, M.F.; Huang, C.Y.; Sheu, J.H.; Chang, W.C. A soft coral natural product, 11-episinulariolide acetate, inhibits gene expression of cyclooxygenase-2 and interleukin-8 through attenuation of calcium signaling. *Molecules* **2013**, *18*, 7023–7034. [CrossRef] [PubMed]
127. Choi, H.; Mascuch, S.J.; Villa, F.A.; Byrum, T.; Teasdale, M.E.; Smith, J.E.; Preskitt, L.B.; Rowley, D.C.; Gerwick, L.; Gerwick, W.H. Honaucins A–C, potent inhibitors of inflammation and bacterial quorum sensing: Synthetic derivatives and structure-activity relationships. *Chem. Biol.* **2012**, *19*, 589–598. [CrossRef] [PubMed]
128. Mayer, A.M.; Aviles, E.; Rodriguez, A.D. Marine sponge *Hymeniacidon* sp. amphilectane metabolites potently inhibit rat brain microglia thromboxane B_2 generation. *Bioorg. Med. Chem.* **2012**, *20*, 279–282. [CrossRef] [PubMed]
129. Ahmed, S.; Riegsecker, S.; Beamer, M.; Rahman, A.; Bellini, J.V.; Bhansali, P.; Tillekeratne, L.M. Largazole, a class I histone deacetylase inhibitor, enhances TNF-alpha-induced ICAM-1 and VCAM-1 expression in rheumatoid arthritis synovial fibroblasts. *Toxicol. Appl. Pharmacol.* **2013**, *270*, 87–96. [CrossRef] [PubMed]
130. Lee, H.P.; Huang, S.Y.; Lin, Y.Y.; Wang, H.M.; Jean, Y.H.; Wu, S.F.; Duh, C.Y.; Wen, Z.H. Soft coral-derived lemnalol alleviates monosodium urate-induced gouty arthritis in rats by inhibiting leukocyte infiltration and iNOS, COX-2 and c-Fos protein expression. *Mar. Drugs* **2013**, *11*, 99–113. [CrossRef] [PubMed]
131. Kim, K.S.; Cui, X.; Lee, D.S.; Sohn, J.H.; Yim, J.H.; Kim, Y.C.; Oh, H. Anti-inflammatory effect of neoechinulin a from the marine fungus *Eurotium* sp. SF-5989 through the suppression of NF-small ka, CyrillicB and p38 MAPK Pathways in lipopolysaccharide-stimulated RAW264.7 macrophages. *Molecules* **2013**, *18*, 13245–13259. [CrossRef] [PubMed]
132. Lee, D.S.; Jang, J.H.; Ko, W.; Kim, K.S.; Sohn, J.H.; Kang, M.S.; Ahn, J.S.; Kim, Y.C.; Oh, H. PTP1B inhibitory and anti-inflammatory effects of secondary metabolites isolated from the marine-derived fungus *Penicillium* sp. JF-55. *Mar. Drugs* **2013**, *11*, 1409–1426. [CrossRef] [PubMed]

133. Vilasi, A.; Monti, M.C.; Tosco, A.; De Marino, S.; Margarucci, L.; Riccio, R.; Casapullo, A. Differential in gel electrophoresis (DIGE) comparative proteomic analysis of macrophages cell cultures in response to perthamide C treatment. *Mar. Drugs* **2013**, *11*, 1288–1299. [CrossRef] [PubMed]
134. Reina, E.; Ramos, F.A.; Castellanos, L.; Aragon, M.; Ospina, L.F. Anti-inflammatory R-prostaglandins from Caribbean Colombian soft coral *Plexaura homomalla*. *J. Pharm. Pharmacol.* **2013**, *65*, 1643–1652. [CrossRef] [PubMed]
135. Huang, S.Y.; Chen, N.F.; Chen, W.F.; Hung, H.C.; Lee, H.P.; Lin, Y.Y.; Wang, H.M.; Sung, P.J.; Sheu, J.H.; Wen, Z.H. Sinularin from indigenous soft coral attenuates nociceptive responses and spinal neuroinflammation in carrageenan-induced inflammatory rat model. *Mar. Drugs* **2012**, *10*, 1899–1919. [CrossRef] [PubMed]
136. De, M.S.; Ummarino, R.; D'Auria, M.V.; Chini, M.G.; Bifulco, G.; D'Amore, C.; Renga, B.; Mencarelli, A.; Petek, S.; Fiorucci, S.; et al. 4-Methylenesterols from *Theonella swinhoei* sponge are natural pregnane-X-receptor agonists and farnesoid-X-receptor antagonists that modulate innate immunity. *Steroids* **2012**, *77*, 485–495.
137. Thao, N.P.; Cuong, N.X.; Luyen, B.T.; Quang, T.H.; Hanh, T.T.; Kim, S.; Koh, Y.S.; Nam, N.H.; Van, K.P.; Van, M.C.; et al. Anti-inflammatory components of the starfish *Astropecten polyacanthus*. *Mar. Drugs* **2013**, *11*, 2917–2926. [CrossRef] [PubMed]
138. Lind, K.F.; Hansen, E.; Osterud, B.; Eilertsen, K.E.; Bayer, A.; Engqvist, M.; Leszczak, K.; Jorgensen, T.O.; Andersen, J.H. Antioxidant and anti-inflammatory activities of barettin. *Mar. Drugs* **2013**, *11*, 2655–2666. [CrossRef] [PubMed]
139. Hong, P.H.; Su, Y.D.; Su, J.H.; Chen, Y.H.; Hwang, T.L.; Weng, C.F.; Lee, C.H.; Wen, Z.H.; Sheu, J.H.; Lin, N.C.; et al. Briarenolides F and G, new briarane diterpenoids from a *Briareum* sp. octocoral. *Mar. Drugs* **2012**, *10*, 1156–1168. [CrossRef] [PubMed]
140. Chen, J.H.; Lan, X.P.; Liu, Y.; Jia, A.Q. The effects of diketopiperazines from *Callyspongia* sp. on release of cytokines and chemokines in cultured J774A.1 macrophages. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3177–3180. [CrossRef] [PubMed]
141. Chen, Y.H.; Hwang, T.L.; Su, Y.D.; Chang, Y.C.; Chen, Y.H.; Hong, P.H.; Hu, L.C.; Yen, W.H.; Hsu, H.Y.; Huang, S.J.; et al. New 6-hydroxyeunicellins from a soft coral *Cladiella* sp. *Chem. Pharm. Bull.* **2012**, *60*, 160–163. [CrossRef] [PubMed]
142. Chao, C.H.; Chou, K.J.; Huang, C.Y.; Wen, Z.H.; Hsu, C.H.; Wu, Y.C.; Dai, C.F.; Sheu, J.H. Steroids from the soft coral *Sinularia crassa*. *Mar. Drugs* **2012**, *10*, 439–450. [CrossRef] [PubMed]
143. De Los, R.C.; Zbakh, H.; Motilva, V.; Zubia, E. Antioxidant and anti-inflammatory meroterpenoids from the brown alga *Cystoseira usneoides*. *J. Nat. Prod.* **2013**, *76*, 621–629. [CrossRef] [PubMed]
144. Hwang, B.S.; Oh, J.S.; Jeong, E.J.; Sim, C.J.; Rho, J.R. Densanins A and B, new macrocyclic pyrrole alkaloids isolated from the marine sponge *Haliclona densaspicula*. *Org. Lett.* **2012**, *14*, 6154–6157. [CrossRef] [PubMed]
145. Thao, N.P.; Nam, N.H.; Cuong, N.X.; Tai, H.; Quang, T.H.; Ngan, N.T.; Luyen, B.T.T.; Yang, S.Y.; Choi, C.H.; Kim, S.; et al. Steroidal Constituents from the Soft Coral *Sinularia dissecta* and Their Inhibitory Effects on Lipopolysaccharide-Stimulated Production of Pro-inflammatory Cytokines in Bone Marrow-Derived Dendritic Cells. *Bull. Korean Chem. Soc.* **2013**, *34*, 949–952.
146. Chung, H.M.; Hu, L.C.; Yen, W.H.; Su, J.H.; Lu, M.C.; Hwang, T.L.; Wang, W.H.; Sung, P.J. Echinohalimane A, a bioactive halimane-type diterpenoid from a Formosan gorgonian *Echinomuricea* sp. (Plexauridae). *Mar. Drugs* **2012**, *10*, 2246–2253. [CrossRef] [PubMed]
147. Marchbank, D.H.; Berrue, F.; Kerr, R.G. Eunicidiol, an anti-inflammatory dilophol diterpene from *Eunicea fusca*. *J. Nat. Prod.* **2012**, *75*, 1289–1293. [CrossRef] [PubMed]
148. Shih, H.J.; Tseng, Y.J.; Huang, C.Y.; Wen, Z.H.; Dai, C.F.; Sheu, J.H. Cytotoxic and anti-inflammatory diterpenoids from the Dongsha Atoll soft coral *Sinularia flexibilis*. *Tetrahedron* **2013**, *68*, 244–249. [CrossRef]
149. Lin, Y.F.; Kuo, C.Y.; Wen, Z.H.; Lin, Y.Y.; Wang, W.H.; Su, J.H.; Sheu, J.H.; Sung, P.J. Flexibilisquinone, a new anti-inflammatory quinone from the cultured soft coral *Sinularia flexibilis*. *Molecules* **2013**, *18*, 8160–8167. [CrossRef] [PubMed]
150. Lee, C.H.; Kao, C.Y.; Kao, S.Y.; Chang, C.H.; Su, J.H.; Hwang, T.L.; Kuo, Y.H.; Wen, Z.H.; Sung, P.J. Terpenoids from the octocorals *Menella* sp. (Plexauridae) and *Lobophytum crassum* (Alcyonacea). *Mar. Drugs* **2012**, *10*, 427–438. [CrossRef] [PubMed]

151. Festa, C.; De Marino, S.; D'Auria, M.V.; Monti, M.C.; Bucci, M.; Vellecco, V.; Debitus, C.; Zampella, A. Anti-inflammatory cyclopeptides from the marine sponge *Theonella swinhoei*. *Tetrahedron* **2012**, *68*, 2851–2857. [CrossRef]
152. Chen, Y.H.; Lu, M.C.; Chang, Y.C.; Hwang, T.L.; Wang, W.H.; Weng, C.F.; Kuo, J.; Sung, P.J. Pseudoalteromone A: A novel bioactive ubiquinone from a marine bacterium *Pseudoalteromonas* sp. CGH2XX (Pseudoalteromonadaceae). *Tetrahedron Lett.* **2012**, *53*, 1675–1677. [CrossRef]
153. Lin, W.Y.; Lu, Y.; Chen, B.W.; Huang, C.Y.; Su, J.H.; Wen, Z.H.; Dai, C.F.; Kuo, Y.H.; Sheu, J.H. Sarcocrassocolides M–O, bioactive cembranoids from the Dongsha Atoll soft coral *Sarcophyton crassocaule*. *Mar. Drugs* **2012**, *10*, 617–626. [CrossRef] [PubMed]
154. Fang, H.Y.; Hsu, C.H.; Chao, C.H.; Wen, Z.H.; Wu, Y.C.; Dai, C.F.; Sheu, J.H. Cytotoxic and anti-inflammatory metabolites from the soft coral *Scleronephthya gracillimum*. *Mar. Drugs* **2013**, *11*, 1853–1865. [CrossRef] [PubMed]
155. Gomez-Reyes, J.F.; Salazar, A.; Guzman, H.M.; Gonzalez, Y.; Fernandez, P.L.; Ariza-Castolo, A.; Gutierrez, M. Seco-Briarellinone and briarellin S, two new eunicellin-based diterpenoids from the Panamanian octocoral *Briareum asbestinum*. *Mar. Drugs* **2012**, *10*, 2608–2617. [CrossRef] [PubMed]
156. Putra, M.Y.; Ianaro, A.; Panza, E.; Bavestrello, G.; Cerrano, C.; Fattorusso, E.; Taglialatela-Scafati, O. Sinularioside, a triacetylated glycolipid from the Indonesian soft coral *Sinularia* sp., is an inhibitor of NO release. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2723–2725. [CrossRef] [PubMed]
157. Lin, C.Y.; Lu, M.C.; Su, J.H.; Chu, C.L.; Shiuan, D.; Weng, C.F.; Sung, P.J.; Huang, K.J. Immunomodulatory effect of marine cembrane-type diterpenoids on dendritic cells. *Mar. Drugs* **2013**, *11*, 1336–1350. [CrossRef] [PubMed]
158. Chen, Z.; Zheng, Z.; Huang, H.; Song, Y.; Zhang, X.; Ma, J.; Wang, B.; Zhang, C.; Ju, J. Penicacids A–C, three new mycophenolic acid derivatives and immunosuppressive activities from the marine-derived fungus *Penicillium* sp. SOF07. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3332–3335. [CrossRef] [PubMed]
159. Jensen, J.E.; Mobli, M.; Brust, A.; Alewood, P.F.; King, G.F.; Rash, L.D. Cyclisation increases the stability of the sea anemone peptide APETx2 but decreases its activity at acid-sensing ion channel 3. *Mar. Drugs* **2012**, *10*, 1511–1527. [CrossRef] [PubMed]
160. Li, H.; Bowling, J.J.; Fronczek, F.R.; Hong, J.; Jabba, S.V.; Murray, T.F.; Ha, N.C.; Hamann, M.T.; Jung, J.H. Asteropsin A: An unusual cystine-crosslinked peptide from porifera enhances neuronal Ca^{2+} influx. *Biochim. Biophys. Acta* **2013**, *1830*, 2591–2599. [CrossRef] [PubMed]
161. Orts, D.J.; Peigneur, S.; Madio, B.; Cassoli, J.S.; Montandon, G.G.; Pimenta, A.M.; Bicudo, J.E.; Freitas, J.C.; Zaharenko, A.J.; Tytgat, J. Biochemical and electrophysiological characterization of two sea anemone type 1 potassium toxins from a geographically distant population of *Bunodosoma caissarum*. *Mar. Drugs* **2013**, *11*, 655–679. [CrossRef] [PubMed]
162. Favreau, P.; Benoit, E.; Hocking, H.G.; Carlier, L.; D' hoedt, D.; Leipold, E.; Markgraf, R.; Schlumberger, S.; Cordova, M.A.; Gaertner, H.; et al. A novel micro-conopeptide, CnIIIC, exerts potent and preferential inhibition of NaV1.2/1.4 channels and blocks neuronal nicotinic acetylcholine receptors. *Br. J. Pharmacol.* **2012**, *166*, 1654–1668. [CrossRef] [PubMed]
163. Vetter, I.; Dekan, Z.; Knapp, O.; Adams, D.J.; Alewood, P.F.; Lewis, R.J. Isolation, characterization and total regioselective synthesis of the novel muO-conotoxin MfVIA from *Conus magnificus* that targets voltage-gated sodium channels. *Biochem. Pharmacol.* **2012**, *84*, 540–548. [CrossRef] [PubMed]
164. Franco, A.; Kompella, S.N.; Akondi, K.B.; Melaun, C.; Daly, N.L.; Luetje, C.W.; Alewood, P.F.; Craik, D.J.; Adams, D.J.; Mari, F. RegIIA: An α4/7-conotoxin from the venom of *Conus regius* that potently blocks α3β4 nAChRs. *Biochem. Pharmacol.* **2012**, *83*, 419–426. [CrossRef] [PubMed]
165. Bernaldez, J.; Roman-Gonzalez, S.A.; Martinez, O.; Jimenez, S.; Vivas, O.; Arenas, I.; Corzo, G.; Arreguin, R.; Garcia, D.E.; Possani, L.D.; et al. A *Conus regularis* conotoxin with a novel eight-cysteine framework inhibits CaV2.2 channels and displays an anti-nociceptive activity. *Mar. Drugs* **2013**, *11*, 1188–1202. [CrossRef] [PubMed]
166. Figueiredo, G.S.; Zardo, R.S.; Silva, B.V.; Violante, F.A.; Pinto, A.C.; Fernandes, P.D. Convolutamydine A and synthetic analogues have antinociceptive properties in mice. *Pharmacol. Biochem. Behav.* **2013**, *103*, 431–439. [CrossRef] [PubMed]
167. Andreev, Y.A.; Kozlov, S.A.; Korolkova, Y.V.; Dyachenko, I.A.; Bondarenko, D.A.; Skobtsov, D.I.; Murashev, A.N.; Kotova, P.D.; Rogachevskaja, O.A.; Kabanova, N.V.; et al. Polypeptide modulators of TRPV1 produce analgesia without hyperthermia. *Mar. Drugs* **2013**, *11*, 5100–5115. [CrossRef] [PubMed]

168. Feng, Y.; Bowden, B.F.; Kapoor, V. Ianthellamide A, a selective kynurenine-3-hydroxylase inhibitor from the Australian marine sponge *Ianthella quadrangulata*. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3398–3401. [CrossRef] [PubMed]
169. Burgy, G.; Tahtouh, T.; Durieu, E.; Foll-Josselin, B.; Limanton, E.; Meijer, L.; Carreaux, F.; Bazureau, J.P. Chemical synthesis and biological validation of immobilized protein kinase inhibitory Leucettines. *Eur. J. Med. Chem.* **2013**, *62*, 728–737. [CrossRef] [PubMed]
170. Guzii, A.G.; Makarieva, T.N.; Korolkova, Y.V.; Andreev, Y.A.; Mosharova, I.V.; Tabakmaher, K.M.; Denisenko, V.A.; Dmitrenok, P.S.; Ogurtsova, E.L.; Antonov, A.S.; et al. Pulchranin A, isolated from the Far-Eastern marine sponge, *Monanchora pulchra*: The first marine non-peptide inhibitor of TRPV-1 channels. *Tetrahedron Lett.* **2013**, *54*, 1247–1250. [CrossRef]
171. Montaser, R.; Paul, V.J.; Luesch, H. Marine cyanobacterial fatty acid amides acting on cannabinoid receptors. *Chembiochem* **2012**, *13*, 2676–2681. [CrossRef] [PubMed]
172. Huang, X.; Sun, X.; Ding, B.; Lin, M.; Liu, L.; Huang, H.; She, Z. A new anti-acetylcholinesterase alpha-pyrone meroterpene, arigsugacin I, from mangrove endophytic fungus *Penicillium* sp. sk5GW1L of Kandelia candel. *Planta Med.* **2013**, *79*, 1572–1575. [PubMed]
173. Xiao, Z.; Huang, H.; Shao, C.; Xia, X.; Ma, L.; Huang, X.; Lu, Y.; Lin, Y.; Long, Y.; She, Z. Asperterpenols A and B, new sesterterpenoids isolated from a mangrove endophytic fungus *Aspergillus* sp. 085242. *Org. Lett.* **2013**, *15*, 2522–2525. [CrossRef] [PubMed]
174. Choi, H.; Proteau, P.J.; Byrum, T.; Pereira, A.R.; Gerwick, W.H. Cymatherelactone and cymatherols A–C, polycyclic oxylipins from the marine brown alga *Cymathere triplicata*. *Phytochemistry* **2012**, *73*, 134–141. [CrossRef] [PubMed]
175. Zhang, H.; Conte, M.M.; Khalil, Z.; Huang, X.C.; Capon, R.J. New dictyodendrins as BACE inhibitors from a southern Australian marine sponge, *Ianthella* sp. *RSC Adv.* **2012**, *2*, 4209–4214. [CrossRef]
176. Ohlendorf, B.; Schulz, D.; Erhard, A.; Nagel, K.; Imhoff, J.F. Geranylphenazinediol, an acetylcholinesterase inhibitor produced by a *Streptomyces* species. *J. Nat. Prod.* **2012**, *75*, 1400–1404. [CrossRef] [PubMed]
177. Wyche, T.P.; Standiford, M.; Hou, Y.; Braun, D.; Johnson, D.A.; Johnson, J.A.; Bugni, T.S. Activation of the nuclear factor e2-related factor 2 pathway by novel natural products halomadurones a–d and a synthetic analogue. *Mar. Drugs* **2013**, *11*, 5089–5099. [CrossRef] [PubMed]
178. Balansa, W.; Islam, R.; Fontaine, F.; Piggott, A.M.; Zhang, H.; Xiao, X.; Webb, T.I.; Gilbert, D.F.; Lynch, J.W.; Capon, R.J. Sesterterpene glycinyl-lactams: A new class of glycine receptor modulator from Australian marine sponges of the genus *Psammocinia*. *Org. Biomol. Chem.* **2013**, *11*, 4695–4701. [CrossRef] [PubMed]
179. Palyanova, N.V.; Pankova, T.M.; Starostina, M.V.; Kicha, A.A.; Ivanchina, N.V.; Stonik, V.A. Neuritogenic and neuroprotective effects of polar steroids from the Far East starfishes *Patiria pectinifera* and *Distolasterias nipon*. *Mar. Drugs* **2013**, *11*, 1440–1455. [CrossRef] [PubMed]
180. Mayer, A.M.S.; Murphy, J.; Macadam, D.; Osterbauer, C.; Baseer, I.; Hall, M.L.; Feher, D.; Williams, P. Classical and Alternative Activation of Cyanobacterium *Oscillatoria* sp. Lipopolysaccharide-Treated Rat Microglia in vitro. *Toxicol. Sci.* **2016**, *149*, 484–495. [CrossRef] [PubMed]
181. Urbarova, I.; Karlsen, B.O.; Okkenhaug, S.; Seternes, O.M.; Johansen, S.D.; Emblem, A. Digital marine bioprospecting: Mining new neurotoxin drug candidates from the transcriptomes of cold-water sea anemones. *Mar. Drugs* **2012**, *10*, 2265–2279. [CrossRef] [PubMed]
182. Dona, G.; Kozuh, I.; Brunati, A.M.; Andrisani, A.; Ambrosini, G.; Bonanni, G.; Ragazzi, E.; Armanini, D.; Clari, G.; Bordin, L. Effect of astaxanthin on human sperm capacitation. *Mar. Drugs* **2013**, *11*, 1909–1919. [CrossRef] [PubMed]
183. Yonezawa, T.; Mase, N.; Sasaki, H.; Teruya, T.; Hasegawa, S.; Cha, B.Y.; Yagasaki, K.; Suenaga, K.; Nagai, K.; Woo, J.T. Biselyngbyaside, isolated from marine cyanobacteria, inhibits osteoclastogenesis and induces apoptosis in mature osteoclasts. *J. Cell. Biochem.* **2012**, *113*, 440–448. [CrossRef] [PubMed]
184. Shirouzu, T.; Watari, K.; Ono, M.; Koizumi, K.; Saiki, I.; Tanaka, C.; van Soest, R.W.; Miyamoto, T. Structure, synthesis, and biological activity of a C-20 bisacetylenic alcohol from a marine sponge *Callyspongia* sp. *J. Nat. Prod.* **2013**, *76*, 1337–1342. [CrossRef] [PubMed]
185. Sepe, V.; Ummarino, R.; D'Auria, M.V.; Chini, M.G.; Bifulco, G.; Renga, B.; D'Amore, C.; Debitus, C.; Fiorucci, S.; Zampella, A. Conicasterol E, a small heterodimer partner sparing farnesoid X receptor modulator endowed with a pregnane X receptor agonistic activity, from the marine sponge *Theonella swinhoei*. *J. Med. Chem.* **2012**, *55*, 84–93. [CrossRef] [PubMed]

186. Kim, G.D.; Cheong, O.J.; Bae, S.Y.; Shin, J.; Lee, S.K. 6′′-Debromohamacanthin A, a bis (indole) alkaloid, inhibits angiogenesis by targeting the VEGFR2-mediated PI3K/AKT/mTOR signaling pathways. *Mar. Drugs* **2013**, *11*, 1087–1103. [CrossRef] [PubMed]
187. Kang, S.M.; Heo, S.J.; Kim, K.N.; Lee, S.H.; Yang, H.M.; Kim, A.D.; Jeon, Y.J. Molecular docking studies of a phlorotannin, dieckol isolated from *Ecklonia cava* with tyrosinase inhibitory activity. *Bioorg. Med. Chem.* **2012**, *20*, 311–316. [CrossRef] [PubMed]
188. Sohn, J.H.; Lee, Y.R.; Lee, D.S.; Kim, Y.C.; Oh, H. PTP1B inhibitory secondary metabolites from marine-derived fungal strains *Penicillium* spp. and *Eurotium* sp. *J. Microbiol. Biotechnol.* **2013**, *23*, 1206–1211. [CrossRef] [PubMed]
189. Cheung, F.W.; Guo, J.; Ling, Y.H.; Che, C.T.; Liu, W.K. Anti-melanogenic property of geoditin A in murine B16 melanoma cells. *Mar. Drugs* **2012**, *10*, 465–476. [CrossRef] [PubMed]
190. Putra, M.Y.; Bavestrello, G.; Cerrano, C.; Renga, B.; D'Amore, C.; Fiorucci, S.; Fattorusso, E.; Taglialatela-Scafati, O. Polyhydroxylated sterols from the Indonesian soft coral *Sinularia* sp. and their effect on farnesoid X-activated receptor. *Steroids* **2012**, *77*, 433–440. [CrossRef] [PubMed]
191. Festa, C.; Lauro, G.; De Marino, S.; D'Auria, M.V.; Monti, M.C.; Casapullo, A.; D'Amore, C.; Renga, B.; Mencarelli, A.; Petek, S.; et al. Plakilactones from the marine sponge *Plakinastrella mamillaris*. Discovery of a new class of marine ligands of peroxisome proliferator-activated receptor gamma. *J. Med. Chem.* **2012**, *55*, 8303–8317. [CrossRef] [PubMed]
192. Festa, C.; D'Amore, C.; Renga, B.; Lauro, G.; De Marino, S.; D'Auria, M.V.; Bifulco, G.; Zampella, A.; Fiorucci, S. Oxygenated polyketides from *Plakinastrella mamillaris* as a new chemotype of PXR agonists. *Mar. Drugs* **2013**, *11*, 2314–2327. [CrossRef] [PubMed]
193. Li, J.L.; Xiao, B.; Park, M.; Yoo, E.S.; Shin, S.; Hong, J.; Chung, H.Y.; Kim, H.S.; Jung, J.H. PPAR-gamma agonistic metabolites from the ascidian *Herdmania momus*. *J. Nat. Prod.* **2012**, *75*, 2082–2087. [CrossRef] [PubMed]
194. Yamanokuchi, R.; Imada, K.; Miyazaki, M.; Kato, H.; Watanabe, T.; Fujimuro, M.; Saeki, Y.; Yoshinaga, S.; Terasawa, H.; Iwasaki, N.; et al. Hyrtioreticulins A–E, indole alkaloids inhibiting the ubiquitin-activating enzyme, from the marine sponge *Hyrtios reticulatus*. *Bioorg. Med. Chem.* **2012**, *20*, 4437–4442. [CrossRef] [PubMed]
195. Gladkikh, I.; Monastyrnaya, M.; Leychenko, E.; Zelepuga, E.; Chausova, V.; Isaeva, M.; Anastyuk, S.; Andreev, Y.; Peigneur, S.; Tytgat, J.; et al. Atypical reactive center Kunitz-type inhibitor from the sea anemone *Heteractis crispa*. *Mar. Drugs* **2012**, *10*, 1545–1565. [CrossRef] [PubMed]
196. Schweikart, K.; Guo, L.; Shuler, Z.; Abrams, R.; Chiao, E.T.; Kolaja, K.L.; Davis, M. The effects of jaspamide on human cardiomyocyte function and cardiac ion channel activity. *Toxicol. In Vitro* **2013**, *27*, 745–751. [CrossRef] [PubMed]
197. Carlile, G.W.; Keyzers, R.A.; Teske, K.A.; Robert, R.; Williams, D.E.; Linington, R.G.; Gray, C.A.; Centko, R.M.; Yan, L.; Anjos, S.M.; et al. Correction of F508del-CFTR trafficking by the sponge alkaloid latonduine is modulated by interaction with PARP. *Chem. Biol.* **2012**, *19*, 1288–1299. [CrossRef] [PubMed]
198. Eguchi, K.; Fujiwara, Y.; Hayashida, A.; Horlad, H.; Kato, H.; Rotinsulu, H.; Losung, F.; Mangindaan, R.E.; de Voogd, N.J.; Takeya, M.; et al. Manzamine A, a marine-derived alkaloid, inhibits accumulation of cholesterol ester in macrophages and suppresses hyperlipidemia and atherosclerosis in vivo. *Bioorg. Med. Chem.* **2013**, *21*, 3831–3838. [CrossRef] [PubMed]
199. Williams, D.E.; Dalisay, D.S.; Li, F.; Amphlett, J.; Maneerat, W.; Chavez, M.A.; Wang, Y.A.; Matainaho, T.; Yu, W.; Brown, P.J.; et al. Nahuoic acid A produced by a *Streptomyces* sp. isolated from a marine sediment is a selective SAM-competitive inhibitor of the histone methyltransferase SETD8. *Org. Lett.* **2013**, *15*, 414–417. [CrossRef] [PubMed]
200. Cheruku, P.; Plaza, A.; Lauro, G.; Keffer, J.; Lloyd, J.R.; Bifulco, G.; Bewley, C.A. Discovery and synthesis of namalide reveals a new anabaenopeptin scaffold and peptidase inhibitor. *J. Med. Chem.* **2012**, *55*, 735–742. [CrossRef] [PubMed]
201. Plisson, F.; Conte, M.; Khalil, Z.; Huang, X.C.; Piggott, A.M.; Capon, R.J. Kinase inhibitor scaffolds against neurodegenerative diseases from a Southern Australian ascidian, *Didemnum* sp. *ChemMedChem* **2012**, *7*, 983–990. [CrossRef] [PubMed]

202. Margarucci, L.; Tosco, A.; De Simone, R.; Riccio, R.; Monti, M.C.; Casapullo, A. Modulation of proteasome machinery by natural and synthetic analogues of the marine bioactive compound petrosaspongiolide M. *Chembiochem* **2012**, *13*, 982–986. [CrossRef] [PubMed]
203. Choi, B.K.; Cha, B.Y.; Yagyu, T.; Woo, J.T.; Ojika, M. Sponge-derived acetylenic alcohols, petrosiols, inhibit proliferation and migration of platelet-derived growth factor (PDGF)-induced vascular smooth muscle cells. *Bioorg. Med. Chem.* **2013**, *21*, 1804–1810. [CrossRef] [PubMed]
204. Vitale, R.M.; Gatti, M.; Carbone, M.; Barbieri, F.; Felicita, V.; Gavagnin, M.; Florio, T.; Amodeo, P. Minimalist hybrid ligand/receptor-based pharmacophore model for CXCR4 applied to a small-library of marine natural products led to the identification of phidianidine a as a new CXCR4 ligand exhibiting antagonist activity. *ACS Chem. Biol.* **2013**, *8*, 2762–2770. [CrossRef] [PubMed]
205. Lunder, M.; Drevensek, G.; Hawlina, S.; Sepcic, K.; Ziberna, L. Cardiovascular effects induced by polymeric 3-alkylpyridinium salts from the marine sponge *Reniera sarai*. *Toxicon* **2012**, *60*, 1041–1048. [CrossRef] [PubMed]
206. Su, J.H.; Chen, Y.C.; El-Shazly, M.; Du, Y.C.; Su, C.W.; Tsao, C.W.; Liu, L.L.; Chou, Y.; Chang, W.B.; Su, Y.D.; et al. Towards the small and the beautiful: A small dibromotyrosine derivative from *Pseudoceratina* sp. sponge exhibits potent apoptotic effect through targeting IKK/NFkappaB signaling pathway. *Mar. Drugs* **2013**, *11*, 3168–3185. [CrossRef] [PubMed]
207. Day, D.R.; Jabaiah, S.; Jacobs, R.S.; Little, R.D. Cyclodextrin formulation of the marine natural product pseudopterosin A uncovers optimal pharmacodynamics in proliferation studies of human umbilical vein endothelial cells. *Mar. Drugs* **2013**, *11*, 3258–3271. [CrossRef] [PubMed]
208. Yoon, W.J.; Kim, K.N.; Heo, S.J.; Han, S.C.; Kim, J.; Ko, Y.J.; Kang, H.K.; Yoo, E.S. Sargachromanol G inhibits osteoclastogenesis by suppressing the activation NF-kappaB and MAPKs in RANKL-induced RAW 264.7 cells. *Biochem. Biophys. Res. Commun.* **2013**, *434*, 892–897. [CrossRef] [PubMed]
209. Zhang, C.Y.; Kong, T.; Wu, W.H.; Lan, M.B. The protection of polysaccharide from the Brown Seaweed *Sargassum graminifolium* against ethylene glycol-induced mitochondrial damage. *Mar. Drugs* **2013**, *11*, 870–880. [CrossRef] [PubMed]
210. Kawamura-Konishi, Y.; Watanabe, N.; Saito, M.; Nakajima, N.; Sakaki, T.; Katayama, T.; Enomoto, T. Isolation of a new phlorotannin, a potent inhibitor of carbohydrate-hydrolyzing enzymes, from the brown alga *Sargassum patens*. *J. Agric. Food Chem.* **2012**, *60*, 5565–5570. [CrossRef] [PubMed]
211. Xu, M.J.; Liu, X.J.; Zhao, Y.L.; Liu, D.; Xu, Z.H.; Lang, X.M.; Ao, P.; Lin, W.H.; Yang, S.L.; Zhang, Z.G.; et al. Identification and characterization of an anti-fibrotic benzopyran compound isolated from mangrove-derived *Streptomyces xiamenensis*. *Mar. Drugs* **2012**, *10*, 639–654. [CrossRef] [PubMed]
212. Sepe, V.; Ummarino, R.; D'Auria, M.V.; Taglialatela-Scafati, O.; Marino, S.D.; D'Amore, C.; Renga, B.; Chini, M.G.; Bifulco, G.; Nakao, Y.; et al. Preliminary structure-activity relationship on theonellasterol, a new chemotype of FXR antagonist, from the marine sponge *Theonella swinhoei*. *Mar. Drugs* **2012**, *10*, 2448–2466. [CrossRef] [PubMed]
213. Garcia-Caballero, M.; Mari-Beffa, M.; Canedo, L.; Medina, M.A.; Quesada, A.R. Toluquinol, a marine fungus metabolite, is a new angiosuppresor that interferes with the Akt pathway. *Biochem. Pharmacol.* **2013**, *85*, 1727–1740. [CrossRef] [PubMed]
214. Wang, R.; Paul, V.J.; Luesch, H. Seaweed extracts and unsaturated fatty acid constituents from the green alga *Ulva lactuca* as activators of the cytoprotective Nrf2-ARE pathway. *Free Radic. Biol. Med.* **2013**, *57*, 141–153. [CrossRef] [PubMed]
215. Daoust, J.; Chen, M.; Wang, M.; Williams, D.E.; Garcia Chavez, M.A.; Wang, Y.A.; Merchant, C.E.; Fontana, A.; Kieffer, T.J.; Andersen, R.J. Sesterterpenoids isolated from a northeastern Pacific *Phorbas* sp. *J. Org. Chem.* **2013**, *78*, 8267–8273. [CrossRef] [PubMed]
216. Sun, S.W.; Ji, C.Z.; Gu, Q.Q.; Li, D.H.; Zhu, T.J. Three new polyketides from marine-derived fungus *Aspergillus glaucus* HB1-19. *J. Asian Nat. Prod. Res.* **2013**, *15*, 956–961. [CrossRef] [PubMed]
217. Haroon, M.H.; Premaratne, S.R.; Choudhry, M.I.; Dharmaratne, H.R. A new beta-glucuronidase inhibiting butyrolactone from the marine endophytic fungus *Aspergillus terreus*. *Nat. Prod. Res.* **2013**, *27*, 1060–1066. [CrossRef] [PubMed]

218. Cavalcante-Silva, L.H.; de Carvalho Correia, A.C.; Barbosa-Filho, J.M.; da Silva, B.A.; de Oliveira Santos, B.V.; de Lira, D.P.; Sousa, J.C.; de Miranda, G.E.; de Andrade, C.F.; Alexandre-Moreira, M.S. Spasmolytic effect of caulerpine involves blockade of Ca^{2+} influx on guinea pig ileum. *Mar. Drugs* **2013**, *11*, 1553–1564. [CrossRef] [PubMed]
219. Chini, M.G.; Jones, C.R.; Zampella, A.; D'Auria, M.V.; Renga, B.; Fiorucci, S.; Butts, C.P.; Bifulco, G. Quantitative NMR-derived interproton distances combined with quantum mechanical calculations of 13C chemical shifts in the stereochemical determination of conicasterol F, a nuclear receptor ligand from *Theonella swinhoei*. *J. Org. Chem.* **2012**, *77*, 1489–1496. [CrossRef] [PubMed]
220. Hamed, A.N.; Watjen, W.; Schmitz, R.; Chovolou, Y.; Edrada-Ebel, R.; Youssef, D.T.; Kamel, M.S.; Proksch, P. A new bioactive sesquiterpenoid quinone from the Mediterranean Sea marine sponge *Dysidea avara*. *Nat. Prod. Commun.* **2013**, *8*, 289–292. [PubMed]
221. Shin, K.; Chin, J.; Hahn, D.; Lee, J.; Hwang, H.; Won, D.H.; Ham, J.; Choi, H.; Kang, E.; Kim, H.; et al. Sterols from a soft coral, *Dendronephthya gigantea* as farnesoid X-activated receptor antagonists. *Steroids* **2012**, *77*, 355–359. [CrossRef] [PubMed]
222. Jiao, W.H.; Huang, X.J.; Yang, J.S.; Yang, F.; Piao, S.J.; Gao, H.; Li, J.; Ye, W.C.; Yao, X.S.; Chen, W.S.; et al. Dysidavarones A–D, new sesquiterpene quinones from the marine sponge *Dysidea avara*. *Org. Lett.* **2012**, *14*, 202–205. [CrossRef] [PubMed]
223. Hu, Y.; Martinez, E.D.; MacMillan, J.B. Anthraquinones from a marine-derived *Streptomyces spinoverrucosus*. *J. Nat. Prod.* **2012**, *75*, 1759–1764. [CrossRef] [PubMed]
224. Williams, D.E.; Steino, A.; de Voogd, N.J.; Mauk, A.G.; Andersen, R.J. Halicloic acids A and B isolated from the marine sponge *Haliclona* sp. collected in the Philippines inhibit indoleamine 2,3-dioxygenase. *J. Nat. Prod.* **2012**, *75*, 1451–1458. [CrossRef] [PubMed]
225. Jansen, N.; Ohlendorf, B.; Erhard, A.; Bruhn, T.; Bringmann, G.; Imhoff, J.F. Helicusin E, isochromophilone X and isochromophilone XI: New chloroazaphilones produced by the fungus *Bartalinia robillardoides* strain LF550. *Mar. Drugs* **2013**, *11*, 800–816. [CrossRef] [PubMed]
226. Chianese, G.; Fattorusso, E.; Putra, M.Y.; Calcinai, B.; Bavestrello, G.; Moriello, A.S.; De Petrocellis, L.; Di Marzo, V.; Taglialatela-Scafati, O. Leucettamols, bifunctionalized marine sphingoids, act as modulators of TRPA1 and TRPM8 channels. *Mar. Drugs* **2012**, *10*, 2435–2447. [CrossRef] [PubMed]
227. Ushiyama, S.; Umaoka, H.; Kato, H.; Suwa, Y.; Morioka, H.; Rotinsulu, H.; Losung, F.; Mangindaan, R.E.; de Voogd, N.J.; Yokosawa, H.; et al. Manadosterols A and B, sulfonated sterol dimers inhibiting the Ubc13-Uev1A interaction, isolated from the marine sponge *Lissodendryx fibrosa*. *J. Nat. Prod.* **2012**, *75*, 1495–1499. [CrossRef] [PubMed]
228. Almeida, C.; Hemberger, Y.; Schmitt, S.M.; Bouhired, S.; Natesan, L.; Kehraus, S.; Dimas, K.; Gutschow, M.; Bringmann, G.; Konig, G.M. Marilines A–C: Novel phthalimidines from the sponge-derived fungus *Stachylidium* sp. *Chemistry* **2012**, *18*, 8827–8834. [CrossRef] [PubMed]
229. Liang, L.F.; Kurtan, T.; Mandi, A.; Yao, L.G.; Li, J.; Zhang, W.; Guo, Y.W. Unprecedented diterpenoids as a PTP1B inhibitor from the Hainan soft coral *Sarcophyton trocheliophorum* Marenzeller. *Org. Lett.* **2013**, *15*, 274–277. [CrossRef] [PubMed]
230. Kawahara, T.; Takagi, M.; Shin-Ya, K. JBIR-124: A novel antioxidative agent from a marine sponge-derived fungus *Penicillium citrinum* SpI080624G1f01. *J. Antibiot.* **2012**, *65*, 45–47. [CrossRef] [PubMed]
231. Kim, H.; Chin, J.; Choi, H.; Baek, K.; Lee, T.G.; Park, S.E.; Wang, W.; Hahn, D.; Yang, I.; Lee, J.; et al. Phosphoiodyns A and B, unique phosphorus-containing iodinated polyacetylenes from a Korean sponge *Placospongia* sp. *Org. Lett.* **2013**, *15*, 100–103. [CrossRef] [PubMed]
232. Shen, S.; Liu, D.; Wei, C.; Proksch, P.; Lin, W. Purpuroines A–J, halogenated alkaloids from the sponge *Iotrochota purpurea* with antibiotic activity and regulation of tyrosine kinases. *Bioorg. Med. Chem.* **2012**, *20*, 6924–6928. [CrossRef] [PubMed]
233. Pavlik, C.M.; Wong, C.Y.; Ononye, S.; Lopez, D.D.; Engene, N.; McPhail, K.L.; Gerwick, W.H.; Balunas, M.J. Santacruzamate A, a potent and selective histone deacetylase inhibitor from the Panamanian marine cyanobacterium cf. *Symploca* sp. *J. Nat. Prod.* **2013**, *76*, 2026–2033. [CrossRef] [PubMed]
234. Liang, L.F.; Gao, L.X.; Li, J.; Taglialatela-Scafati, O.; Guo, Y.W. Cembrane diterpenoids from the soft coral *Sarcophyton trocheliophorum* Marenzeller as a new class of PTP1B inhibitors. *Bioorg. Med. Chem.* **2013**, *21*, 5076–5080. [CrossRef] [PubMed]

235. Kim, C.; Lee, I.K.; Cho, G.Y.; Oh, K.H.; Lim, Y.W.; Yun, B.S. Sargassumol, a novel antioxidant from the brown alga *Sargassum micracanthum*. *J. Antibiot.* **2012**, *65*, 87–89. [CrossRef] [PubMed]
236. Niemann, H.; Lin, W.; Muller, W.E.; Kubbutat, M.; Lai, D.; Proksch, P. Trimeric hemibastadin congener from the marine sponge *Ianthella basta*. *J. Nat. Prod.* **2013**, *76*, 121–125. [CrossRef] [PubMed]
237. Hegazy, M.E.; Gamal Eldeen, A.M.; Shahat, A.A.; Abdel-Latif, F.F.; Mohamed, T.A.; Whittlesey, B.R.; Pare, P.W. Bioactive hydroperoxyl cembranoids from the Red Sea soft coral *Sarcophyton glaucum*. *Mar. Drugs* **2012**, *10*, 209–222. [CrossRef] [PubMed]
238. Molinski, T.F.; Reynolds, K.A.; Morinaka, B.I. Symplocin A, a linear peptide from the Bahamian cyanobacterium *Symploca* sp. Configurational analysis of *N*,*N*-dimethylamino acids by chiral-phase HPLC of naphthacyl esters. *J. Nat. Prod.* **2012**, *75*, 425–431. [CrossRef] [PubMed]
239. Dolusic, E.; Larrieu, P.; Meinguet, C.; Colette, D.; Rives, A.; Blanc, S.; Ferain, T.; Pilotte, L.; Stroobant, V.; Wouters, J.; et al. Indoleamine 2,3-dioxygenase inhibitory activity of derivatives of marine alkaloid tsitsikammamine A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 47–54. [CrossRef] [PubMed]
240. Olsen, E.K.; Hansen, E.; Isaksson, J.; Andersen, J.H. Cellular Antioxidant Effect of Four Bromophenols from the Red Algae, *Vertebrata lanosa*. *Mar. Drugs* **2013**, *11*, 2769–2784. [CrossRef] [PubMed]
241. Matsunaga, S.; Akiyama, T.; Takada, K.; Oikawa, T.; Matsuura, N.; Ise, Y.; Okada, S.; Matsunaga, S. Stimulators of adipogenesis from the marine sponge *Xestospongia testudinaria*. *Tetrahedron* **2013**, *69*, 6560–6564.
242. Dong, L.Y.; Jin, J.; Lu, G.; Kang, X.L. Astaxanthin attenuates the apoptosis of retinal ganglion cells in db/db mice by inhibition of oxidative stress. *Mar. Drugs* **2013**, *11*, 960–974. [CrossRef] [PubMed]
243. Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2012**, *29*, 144–222. [CrossRef] [PubMed]
244. Blunt, J.W.; Copp, B.R.; Keyzers, R.A.; Munro, M.H.; Prinsep, M.R. Marine natural products. *Nat. Prod. Rep.* **2013**, *30*, 237–323. [CrossRef] [PubMed]
245. Cragg, G.M.; Newman, D.J. Natural products: A continuing source of novel drug leads. *Biochim. Biophys. Acta* **2013**, *1830*, 3670–3695. [CrossRef] [PubMed]
246. Camp, D.; Davis, R.A.; Evans-Illidge, E.A.; Quinn, R.J. Guiding principles for natural product drug discovery. *Future Med. Chem.* **2012**, *4*, 1067–1084. [CrossRef] [PubMed]
247. Jensen, P.R.; Chavarria, K.L.; Fenical, W.; Moore, B.S.; Ziemert, N. Challenges and triumphs to genomics-based natural product discovery. *J. Ind. Microbiol Biotechnol.* **2013**, *41*, 203–209. [CrossRef] [PubMed]
248. Gerwick, W.H.; Moore, B.S. Lessons from the past and charting the future of marine natural products drug discovery and chemical biology. *Chem. Biol.* **2012**, *19*, 85–98. [CrossRef] [PubMed]
249. Liu, J.T.; Lu, X.L.; Liu, X.Y.; Gao, Y.; Hu, B.; Jiao, B.H.; Zheng, H. Bioactive natural products from the antarctic and arctic organisms. *Mini Rev. Med. Chem.* **2013**, *13*, 617–626. [CrossRef] [PubMed]
250. Liang, L.F.; Guo, Y.W. Terpenes from the soft corals of the genus *Sarcophyton*: Chemistry and biological activities. *Chem. Biodivers.* **2013**, *10*, 2161–2196. [CrossRef] [PubMed]
251. Harnedy, P.A.; FitzGerald, R.J. Bioactive peptides from marine processing waste and shellfish: A review. *J. Funct. Foods* **2013**, *4*, 6–24. [CrossRef]
252. Berrue, F.; McCulloch, M.W.; Kerr, R.G. Marine diterpene glycosides. *Bioorg. Med. Chem.* **2011**, *19*, 6702–6719. [CrossRef] [PubMed]
253. Morya, V.K.; Kim, J.; Kim, E.K. Algal fucoidan: Structural and size-dependent bioactivities and their perspectives. *Appl. Microbiol. Biotechnol.* **2012**, *93*, 71–82. [CrossRef] [PubMed]
254. Pomin, V.H. Fucanomics and galactanomics: Marine distribution, medicinal impact, conceptions, and challenges. *Mar. Drugs* **2012**, *10*, 793–811. [CrossRef] [PubMed]
255. Gouveia, V.; Seca, A.M.; Barreto, M.C.; Pinto, D.C. Di- and sesquiterpenoids from *Cystoseira* genus: Structure, intra-molecular transformations and biological activity. *Mini Rev. Med. Chem.* **2013**, *13*, 1150–1159. [CrossRef] [PubMed]
256. Ngo, D.H.; Kim, S.K. Sulfated polysaccharides as bioactive agents from marine algae. *Int. J. Biol. Macromol.* **2013**, *62*, 70–75. [CrossRef] [PubMed]
257. Wang, B.G.; Gloer, J.B.; Ji, N.Y.; Zhao, J.C. Halogenated organic molecules of Rhodomelaceae origin: Chemistry and biology. *Chem. Rev.* **2013**, *113*, 3632–3685. [CrossRef] [PubMed]
258. Nagarajan, M.; Maruthanayagam, V.; Sundararaman, M. A review of pharmacological and toxicological potentials of marine cyanobacterial metabolites. *J. Appl. Toxicol.* **2012**, *32*, 153–185. [CrossRef] [PubMed]

259. Tan, L.T. Pharmaceutical agents from filamentous marine cyanobacteria. *Drug Discov. Today* **2013**, *18*, 863–871. [CrossRef] [PubMed]
260. Kalinin, V.I.; Ivanchina, N.V.; Krasokhin, V.B.; Makarieva, T.N.; Stonik, V.A. Glycosides from marine sponges (Porifera, Demospongiae): Structures, taxonomical distribution, biological activities and biological roles. *Mar. Drugs* **2012**, *10*, 1671–1710. [CrossRef] [PubMed]
261. Kiew, P.L.; Don, M.M. Jewel of the seabed: Sea cucumbers as nutritional and drug candidates. *Int. J. Food Sci. Nutr.* **2011**, *63*, 616–636. [CrossRef] [PubMed]
262. Gallardo-Rodriguez, J.; Sanchez-Miron, A.; Garcia-Camacho, F.; Lopez-Rosales, L.; Chisti, Y.; Molina-Grima, E. Bioactives from microalgal dinoflagellates. *Biotechnol. Adv.* **2012**, *30*, 1673–1684. [CrossRef] [PubMed]
263. Desriac, F.; Jegou, C.; Balnois, E.; Brillet, B.; Le, C.P.; Fleury, Y. Antimicrobial peptides from marine proteobacteria. *Mar. Drugs* **2013**, *11*, 3632–3660. [CrossRef] [PubMed]
264. Eom, S.H.; Kim, Y.M.; Kim, S.K. Marine bacteria: Potential sources for compounds to overcome antibiotic resistance. *Appl. Microbiol. Biotechnol.* **2013**, *97*, 4763–4773. [CrossRef] [PubMed]
265. Gao, C.; Yi, X.; Huang, R.; Yan, F.; He, B.; Chen, B. Alkaloids from corals. *Chem. Biodivers.* **2013**, *10*, 1435–1447. [CrossRef] [PubMed]
266. Hoang, V.L.; Kim, S.K. Antimicrobial peptides from marine sources. *Curr. Protein Pept. Sci.* **2013**, *14*, 205–211. [CrossRef] [PubMed]
267. Zotchev, S.B. Marine actinomycetes as an emerging resource for the drug development pipelines. *J. Biotechnol.* **2012**, *158*, 168–175. [CrossRef] [PubMed]
268. Mondol, M.A.; Shin, H.J.; Islam, M.T. Diversity of secondary metabolites from marine *Bacillus* species: Chemistry and biological activity. *Mar. Drugs* **2013**, *11*, 2846–2872. [CrossRef] [PubMed]
269. Solov'eva, T.; Davydova, V.; Krasikova, I.; Yermak, I. Marine compounds with therapeutic potential in gram-negative sepsis. *Mar. Drugs* **2013**, *11*, 2216–2229. [CrossRef] [PubMed]
270. Sugumaran, M.; Robinson, W.E. Structure, biosynthesis and possible function of tunichromes and related compounds. *Comp. Biochem. Physiol. B Biochem. Mol. Biol.* **2012**, *163*, 1–25. [CrossRef] [PubMed]
271. Gerwick, W.H.; Fenner, A.M. Drug discovery from marine microbes. *Microb. Ecol.* **2013**, *65*, 800–806. [CrossRef] [PubMed]
272. Zhou, X.; Liu, J.; Yang, B.; Lin, X.; Yang, X.W.; Liu, Y. Marine natural products with anti-HIV activities in the last decade. *Curr. Med. Chem.* **2013**, *20*, 953–973. [PubMed]
273. Prokofjeva, M.M.; Imbs, T.I.; Shevchenko, N.M.; Spirin, P.V.; Horn, S.; Fehse, B.; Zvyagintseva, T.N.; Prassolov, V.S. Fucoidans as potential inhibitors of HIV-1. *Mar. Drugs* **2013**, *11*, 3000–3014. [CrossRef] [PubMed]
274. Raveh, A.; Delekta, P.C.; Dobry, C.J.; Peng, W.; Schultz, P.J.; Blakely, P.K.; Tai, A.W.; Matainaho, T.; Irani, D.N.; Sherman, D.H.; et al. Discovery of potent broad spectrum antivirals derived from marine actinobacteria. *PLoS ONE* **2013**, *8*, e82318. [CrossRef] [PubMed]
275. Huskens, D.; Schols, D. Algal lectins as potential HIV microbicide candidates. *Mar. Drugs* **2012**, *10*, 1476–1497. [CrossRef] [PubMed]
276. Jones, A.J.; Grkovic, T.; Sykes, M.L.; Avery, V.M. Trypanocidal activity of marine natural products. *Mar. Drugs* **2013**, *11*, 4058–4082. [CrossRef] [PubMed]
277. Saeidnia, S.; Gohari, A.R.; Haddadi, A. Biogenic trypanocidal sesquiterpenes: Lead compounds to design future trypanocidal drugs—A mini review. *J. Fac. Pharm. Tehran Univ. Med. Sci.* **2013**, *21*, 35. [CrossRef] [PubMed]
278. Bladt, T.T.; Frisvad, J.C.; Knudsen, P.B.; Larsen, T.O. Anticancer and antifungal compounds from *Aspergillus*, *Penicillium* and other filamentous fungi. *Molecules* **2013**, *18*, 11338–11376. [CrossRef] [PubMed]
279. Ruan, B.F.; Zhu, H.L. The chemistry and biology of the bryostatins: Potential PKC inhibitors in clinical development. *Curr. Med. Chem.* **2012**, *19*, 2652–2664. [CrossRef] [PubMed]
280. Kim, J.A.; Kim, S.K. Bioactive peptides from marine sources as potential anti-inflammatory therapeutics. *Curr. Protein Pept. Sci.* **2013**, *14*, 177–182. [CrossRef] [PubMed]
281. Wei, W.C.; Sung, P.J.; Duh, C.Y.; Chen, B.W.; Sheu, J.H.; Yang, N.S. Anti-inflammatory activities of natural products isolated from soft corals of Taiwan between 2008 and 2012. *Mar. Drugs* **2013**, *11*, 4083–4126. [CrossRef] [PubMed]

282. D'Orazio, N.; Gammone, M.A.; Gemello, E.; De, G.M.; Cusenza, S.; Riccioni, G. Marine bioactives: Pharmacological properties and potential applications against inflammatory diseases. *Mar. Drugs* **2012**, *10*, 812–833. [CrossRef] [PubMed]
283. Balboa, E.M.; Conde, E.; Moure, A.; Falque, E.; Dominguez, H. In vitro antioxidant properties of crude extracts and compounds from brown algae. *Food Chem.* **2013**, *138*, 1764–1785. [CrossRef] [PubMed]
284. Albert, B.B.; Cameron-Smith, D.; Hofman, P.L.; Cutfield, W.S. Oxidation of marine omega-3 supplements and human health. *Biomed. Res. Int.* **2013**, *2013*, 464921. [CrossRef] [PubMed]
285. Ko, S.C.; Jeon, Y.J. Marine peptides for preventing metabolic syndrome. *Curr. Protein Pept. Sci.* **2013**, *14*, 183–188. [CrossRef] [PubMed]
286. Lee, S.H.; Jeon, Y.J. Anti-diabetic effects of brown algae derived phlorotannins, marine polyphenols through diverse mechanisms. *Fitoterapia* **2013**, *86*, 129–136. [CrossRef] [PubMed]
287. Ngo, D.H.; Kim, S.K. Marine bioactive peptides as potential antioxidants. *Curr. Protein Pept. Sci.* **2013**, *14*, 189–198. [CrossRef] [PubMed]
288. Harnedy, P.A.; FitzGerald, R.J. Cardioprotective peptides from marine sources. *Curr. Protein Pept. Sci.* **2013**, *14*, 162–172. [CrossRef] [PubMed]
289. D'Orazio, N.; Gemello, E.; Gammone, M.A.; De Girolamo, M.; Ficoneri, C.; Riccioni, G. Fucoxantin: A treasure from the sea. *Mar. Drugs* **2012**, *10*, 604–616.
290. Nasri, R.; Nasri, M. Marine-derived bioactive peptides as new anticoagulant agents: A review. *Curr. Protein Pept. Sci.* **2013**, *14*, 199–204. [CrossRef] [PubMed]
291. Cusick, K.D.; Sayler, G.S. An overview on the marine neurotoxin, saxitoxin: Genetics, molecular targets, methods of detection and ecological functions. *Mar. Drugs* **2013**, *11*, 991–1018. [CrossRef] [PubMed]
292. Medina, M.; Avila, J.; Villanueva, N. Use of okadaic acid to identify relevant phosphoepitopes in pathology: A focus on neurodegeneration. *Mar. Drugs* **2013**, *11*, 1656–1668. [CrossRef] [PubMed]
293. Molgo, J.; Araoz, R.; Benoit, E.; Iorga, B.I. Physical and virtual screening methods for marine toxins and drug discovery targeting nicotinic acetylcholine receptors. *Expert Opin. Drug Discov.* **2013**, *8*, 1203–1223. [CrossRef] [PubMed]
294. Pangestuti, R.; Kim, K. Marine-derived bioactive materials for neuroprotection. *Food Sci. Biotechnol.* **2013**, *22*, 1175–1186. [CrossRef]
295. Lin, Z.; Torres, J.P.; Ammon, M.A.; Marett, L.; Teichert, R.W.; Reilly, C.A.; Kwan, J.C.; Hughen, R.W.; Flores, M.; Tianero, M.D.; et al. A bacterial source for mollusk pyrone polyketides. *Chem. Biol.* **2013**, *20*, 73–81. [CrossRef] [PubMed]
296. Bharate, S.B.; Sawant, S.D.; Singh, P.P.; Vishwakarma, R.A. Kinase inhibitors of marine origin. *Chem. Rev.* **2013**, *113*, 6761–6815. [CrossRef] [PubMed]
297. Liu, J.; Hu, Y.; Waller, D.L.; Wang, J.; Liu, Q. Natural products as kinase inhibitors. *Nat. Prod. Rep.* **2012**, *29*, 392–403. [CrossRef] [PubMed]
298. Jiang, C.S.; Liang, L.F.; Guo, Y.W. Natural products possessing protein tyrosine phosphatase 1B (PTP1B) inhibitory activity found in the last decades. *Acta Pharmacol. Sin.* **2012**, *33*, 1217–1245. [CrossRef] [PubMed]
299. Brady, R.M.; Baell, J.B.; Norton, R.S. Strategies for the development of conotoxins as new therapeutic leads. *Mar. Drugs* **2013**, *11*, 2293–2313. [CrossRef] [PubMed]
300. Essack, M.; Bajic, V.B.; Archer, J.A. Conotoxins that confer therapeutic possibilities. *Mar. Drugs* **2012**, *10*, 1244–1265. [CrossRef] [PubMed]
301. Rashid, M.H.; Mahdavi, S.; Kuyucak, S. Computational studies of marine toxins targeting ion channels. *Mar. Drugs* **2013**, *11*, 848–869. [CrossRef] [PubMed]
302. Green, D.W.; Padula, M.P.; Santos, J.; Chou, J.; Milthorpe, B.; Ben-Nissan, B. A therapeutic potential for marine skeletal proteins in bone regeneration. *Mar. Drugs* **2013**, *11*, 1203–1220. [CrossRef] [PubMed]
303. Thomas, N.V.; Kim, S.K. Beneficial effects of marine algal compounds in cosmeceuticals. *Mar. Drugs* **2013**, *11*, 146–164. [CrossRef] [PubMed]
304. Fiorucci, S.; Distrutti, E.; Bifulco, G.; D'Auria, M.V.; Zampella, A. Marine sponge steroids as nuclear receptor ligands. *Trends Pharmacol. Sci.* **2012**, *33*, 591–601. [CrossRef] [PubMed]