marine drugs

MDPI

Review

Promising Antiparasitic Natural and Synthetic Products from Marine Invertebrates and Microorganisms

Mingyue Zhang [1], Qinrong Zhang [1], Qunde Zhang [1], Xinyuan Cui [1] and Lifeng Zhu [1,2,*]

[1] College of Life Sciences, Nanjing Normal University, Nanjing 210046, China
[2] School of Medicine & Holistic Integrative Medicine, Nanjing University of Chinese Medicine, Nanjing 210023, China
* Correspondence: zhulf2020@126.com

Abstract: Parasitic diseases still threaten human health. At present, a number of parasites have developed drug resistance, and it is urgent to find new and effective antiparasitic drugs. As a rich source of biological compounds, marine natural products have been increasingly screened as candidates for developing new antiparasitic drugs. The literature related to the study of the antigenic animal activity of marine natural compounds from invertebrates and microorganisms was selected to summarize the research progress of marine compounds and the structure–activity relationship of these compounds in the past five years and to explore the possible sources of potential antiparasitic drugs for parasite treatment.

Keywords: bioactive compound; antiparasitic drugs; marine sponges; cnidaria; bryozoa; marine bacteria; marine fungi; cyanophyta

Citation: Zhang, M.; Zhang, Q.; Zhang, Q.; Cui, X.; Zhu, L. Promising Antiparasitic Natural and Synthetic Products from Marine Invertebrates and Microorganisms. *Mar. Drugs* **2023**, *21*, 84. https://doi.org/10.3390/md21020084

Academic Editors: Saccoccia Fulvio and Carla Fernandes

Received: 12 January 2023
Revised: 19 January 2023
Accepted: 23 January 2023
Published: 25 January 2023

1. Introduction

Parasitic diseases common in the tropics and subtropics, including malaria, leishmaniasis, trypanosomiasis, and others, still threaten the lives and property of indigenous people [1].

Malaria, which occurs mainly in sub-Saharan Africa [2], is caused by *Plasmodium*. *Anopheles gambiae* is the principal vector of the disease in the Afrotropical Region [3]. *Plasmodium* enters human liver cells via infected female *Anopheles* and proliferates. Then, merozoites invade red blood cells and further cause disease [4], which is characterized by fever, headache, vomiting, diarrhea, chills, and muscle aches [5]. According to the World Health Organization, an estimated 240 million malaria cases were endemic in 84 countries worldwide in 2021 [6].

Leishmaniasis and trypanosomiasis are neglected tropical diseases (NTDs) that are associated with extreme poverty [7], spread in tropical and subtropical areas in 149 countries, and affect more than 2 billion poor people worldwide [8].

Leishmaniasis is affected by poor nutrition, poor sanitation, a weak immune system, and a lack of preventive measures [9]. This parasite occurs in Asia, Africa, the Americas, and the Mediterranean region. The main genera responsible for this disease are *Phlebotomus* and *Lutzomyia* [10]. Sand flies bite an infected animal host and acquires *Leishmania*, which multiplies in the gut. After 8 to 20 days, they become infectious and spread the disease by biting other hosts [11]. Leishmaniasis includes cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), and mucocutaneous leishmaniasis (MCL). CL is the most common form, while VL is the most severe and is characterized by fever, weight loss, enlargement of the spleen and liver, and anemia [12]. Currently, the only effective treatment for leishmania is pentavalent antimony [10].

Trypanosomiasis includes sleeping sickness and Chagas disease (American trypanosomiasis); sleeping sickness is common in 36 sub-Saharan African countries [13] and is

transmitted by blood-sucking tsetse flies. This parasite has two main forms: the slower-progressing form caused by *Trypanosoma brucei gambiense* and the faster-progressing form caused by *Trypanosoma brucei rhodesiense* [14]. A prominent feature of African trypanosomiasis is lethargy. *T. brucei* can circulate freely in the host's blood and tissue fluids until it reaches the central nervous system, where it is usually fatal. Therefore, therapeutics at this stage must cross the blood–brain barrier [4]. American trypanosomiasis occurs in the Americas (including Mexico, Central, and South America) and is caused by *Trypanosoma cruzi*, which is transmitted through reduviid bugs [15,16].

Because of the widespread use of drugs, many parasites have developed resistance to treatment. For example, artemisinin-based combination therapy (ACT), which combines artemisinin and quinolines [17], is considered a first-line treatment for *Plasmodium falciparum* malaria globally [18]. Unfortunately, in the Greater Mekong subregion, such as Cambodia, Thailand, and Myanmar, the efficacy of artemisinin derivatives and ACT partner drugs is decreasing [19–22]. Additionally, the parasite has resistance to inexpensive drugs such as chloroquine and sulfadoxine/pyrimethamine. Similar situations were also observed with praziquantel for the treatment of schistosomiasis infection [23] and ivermectin for worms [24]. In addition to drug resistance, the efficacy and toxicity of drugs also deserve attention. Benznidazole and nifurtimox, which are used to treat *Trypanosoma cruzi* infection, are highly toxic to adult patients and have low efficacy [25]. Moreover, although a large number of resources have been invested, no effective vaccine against parasitic diseases has been developed thus far [26]. These reasons are forcing researchers to find new safe and effective antiparasite drugs.

The ocean covers more than 70% of the Earth's surface area. Plants and animals, approximately 500,000 species in approximately 28 phyla, exist in this environment [27]. Compared with the terrestrial environment, the ocean has much richer biodiversity. The marine environment is more complex, and marine organisms have been in a harsh environment of high salinity, high pressure, lack of oxygen, limited food supply, and lack of photosynthesis for a long time [28]. Some organisms have evolved adaptations that allow them to synthesize toxic compounds or acquire toxic compounds from others. These toxic compounds can help protect marine life from predators [29]. Marine natural products are bioactive metabolites extracted from marine organisms, including marine animals, plants, and microorganisms [30]. Therefore, the ocean is an important source of bioactive compounds. Currently, compounds isolated from marine organisms mainly include terpenoids, alkaloids, polyketones, steroids, peptides, lactones, and so on [27,31], which have effective antibacterial, antifungal, anti-inflammatory, antiviral, antiparasitic, and other bioactivities [32,33].

We searched the Web of Science database from January 2017 to November 2022 for references with the keywords "marine-derived natural antiparasite products" and further screened the relevant research literature on invertebrates and microorganisms. We did not include meetings or review articles. In this review, we also used the following criteria to determine the activity of compounds:

1. When $IC_{50} > 20$ μM, the activity of the compounds was low or inactive; when $1 \leq IC_{50} \leq 20$ μM, the compounds showed moderate activity. When $IC_{50} < 1$ μM, they showed good potent activity [34];
2. When measured in μg/mL, if $IC_{50} > 20$ μM, the activity of the compounds was low or inactive; if $3 \leq IC_{50} \leq 10$ μg/mL, the compound showed moderate activity. If $IC_{50} < 3$ μg/mL, the compound showed good potent activity [35].

We screened 36 studies on the derivatives from invertebrates and microorganisms (Table 1) and six studies on their crude extracts (Table 2). We reviewed the literature on the purification of the derived compounds. Twelve invertebrate marine sponges came from 11 genera: *Aplysinella*, *Dysidea*, *Fascaplysinopsis*, *Hyrtios*, *Ircinia*, *Pseudoceratina*, *Mo-*

nanchora, *Mycale*, *Tedania*, and *Xestospongia*. Five genera, *Bebryce*, *Macrorhynchia*, *Plumarella*, and *Sinulari*, were included in the seven studies regarding cnidarians. Two genera, *Amathia* and *Orthoscuticella*, were involved in two bryozoan studies. For microorganisms, two genera, including *Streptomyces* and *Pseudomonas*, were studied in three bacterial studies. *Aspergillus*, *Cochliobolus*, *Exserohilum*, and *Paecilomyces* were involved in four fungal studies. Nine cyanobacteria studies involved *Caldora, Dapis, Leptolyngbya, Okeania, Salileptolyngbya,* and *Moorea*. Finally, we summarized the chemical structures with good potent activity (Figures 1–4) and the possible structure–activity relationships.

Table 1. Natural products or derivatives from marine invertebrates and microorganisms.

Category		Species	Compounds	Chemistry	Target parasite	Stage/strain	IC_{50}	Cytotoxicity		Site	Reference
								Type of cells	IC_{50}		
Invertebrate	sponges	*Aplysinella rhax*	**1** Psammaplin A	Bromotyrosine Alkaloids	*T. cruzi*	C2C4	30 μM	NT	NT	Fiji Islands	[36]
					P. falciparum	3D7	60 μM				
			2 Psammaplin D		*T. cruzi*	C2C4	43 μM				
					P. falciparum	3D7	67 μM				
			3 Bisaprasin		*T. cruzi*	C2C4	19 μM				
					P. falciparum	3D7	29 μM				
			Benznidazole*	-	*T. cruzi*	C2C4	2.6 μM	-	-	-	
			Chloroquine*	-	*P. falciparum*	3D7	0.017μM				
		Dysidea avara	**4** Avarone	Sesquiterpene Quinone Avarone	*P. falciparum*	D10	2.74 μM	Human microvascular endothelial cells, HMEC-1	62.19 μM	Bay of Izmir, Turkey	[37]
						W2	2.09 μM				
						3D7 elo1-pfs16-CBG99	15.53 μM				
					L. infantum	promastigote	28.21 μM	Human acute monocytic leukemia cells, THP-1	> 100 μM		
					L. tropica	promastigote	20.28 μM				
					L. infantum	amastigotes	7.64 μM				
					S. mansoni	schistosomula	42.77 μM				
			5 Thiazoavarone		*P. falciparum*	D10	0.38 μM	Human microvascular endothelial cells, HMEC-1	3.31 μM		
						W2	0.21 μM				
						3D7 elo1-pfs16-CBG99	15.01 μM				
					L. infantum	promastigote	8.78 μM	Human acute monocytic leukemia cells, THP-1	7.41 μM		
					L. tropica	promastigote	9.52 μM				
					L. infantum	amastigotes	4.99 μM				
					S. mansoni	schistosomula	5.90 μM				
			6 Avarol		*P. falciparum*	D10	0.96 μM	Human microvascular endothelial cells, HMEC-1	36.85 μM		
						W2	1.10 μM				
						3D7 elo1-pfs16-CBG99	9.30 μM				
					L. infantum	promastigote	7.42 μM	Human acute monocytic leukemia cells, THP-1	31.75 μM		
					L. tropica	promastigote	7.08 μM				
					L. infantum	amastigotes	3.19 μM				
					S. mansoni	schistosomula	33.97 μM				
			Chloroquine*	-	*P. falciparum*	D10	0.04 μM	-	-	-	
						W2	0.54 μM				
			Methylene blue*	-		3D7 elo1-pfs16-CBG99	0.155 μM				
			Amphotericin B*	-	*L. infantum*	promastigote	0.2 μM				

			L. tropica	promastigote	0.17 μM				
			L. infantum	amastigotes	0.189 μM				
Fascaplysinopsis reticulata	**7** 8-oxo-tryptamine	Tryptophan-Derived Alkaloids	*P. falciparum*	3D7	8.8 μg/mL	NT	NT	Mayotte	[38]
	8 The mixture of the known (E) and (Z)-6-bromo-2′-demethyl-3′-N-methylaplysinopsin				8.0 μg/mL				
	Artemisinin*	-			0.006 μg/mL	-	-	-	
Hyrtios erectus	**9** Smenotronic acid	Sesquiterpenoids	*P. falciparum*	Dd2	3.51 μM	NT	NT	Sesquiterpenoids	[39]
	10 Ilimaquinone				2.11 μM				
	11 Pelorol				0.80 μM				
Hyrtios sp.	**12** Hyrtiodoline A	Alkaloid	*T. brucei brucei*	-	48 h: 15.26 μM	J774.1 macrophages	> 200 μM	Red Sea at Sharm el-Sheikh, Egypt	[40]
					72 h: 7.48 μM				
Ircinia oros	**13** Ircinin-1	Linear Furanosesterterpenoids	*T. b. rhodesiense*	-	97 μM	L6 rat myoblast cells	150 μM	Gökçeada, Northern Aegean Sea, Turkey	[41]
			T. cruzi		120 μM				
			L. donovani		31 μM				
			P. falciparum		58 μM				
	14 Ircinin-2		*T. b. rhodesiense*		65 μM		140 μM		
			T. cruzi		110 μM				
			L. donovani		28 μM				
			P. falciparum		56 μM				
	15 Ircinialactam E		*T. b. rhodesiense*		130 μM		> 200 μM		
			P. falciparum		95 μM				
	16 Ircinialactam F		*T. b. rhodesiense*		130 μM		> 200 μM		
			L. donovani		95 μM				
	Melarsoprol*	-	*T. b. rhodesiense*	-	0.015 μM	-	-	-	
	Benznidazole*		*T. cruzi*		3.07 μM				
	Miltefosine*		*L. donovani*		0.51 μM				
	Chloroquine*		*P. falciparum*		0.009 μM				
	Podophyllotoxin*		-	-	-	L6 rat myoblast cells	0.010 μM		
Ircinia wistarii	**17** Ircinianin	Sesterterpenes	*P. falciparum*	NF54	25.4 μM	HeLa	> 64 μg/mL	Wistari Reef, Great Barrier Reef, Australia	[42]
			T. brucei rhodesiense	STIB900	82.8 μM				
			T. cruzi	C2C4	190.9 μM	L6	59.5 μg/mL		
			L. donovani	MHOM/ET/67/L82	16.6 μM				
	Chloroquine*	-	*P. falciparum*	NF54	0.006 μM	-	-	-	
	Melarsoprol*		*T. brucei rhodesiense*	STIB900	0.020 μM				

	Benznidazole*		*T. cruzi*	C2C4	3.36 μM				
	Miltefosine*		*L. donovani*	MHOM/ET/67/L82	0.486 μM				
Pseudoceratina sp.	**18** Psammaplysin F	Bromotyrosine Alkaloid	*P. falciparum*	K1	3.77 μg/mL	MRC-5	12.65 μg/mL	Okinawa, Japan	[43]
				FCR3	2.45 μg/mL				
	19 Ceratinadin E			K1	1.03 μg/mL		15.99 μg/mL		
				FCR3	0.77 μg/mL				
	Chloroquine*	-		K1	0.34 μg/mL		> 25.80 μg/mL	-	
				FCR3	0.035 μg/mL				
	Artemisinin*			K1	0.010 μg/mL		> 14.12 μg/mL		
				FCR3	0.0088 μg/mL				
Monanchora unguiculata	**20** Unguiculin A	Acyclic Guanidine Alkaloid	*P. falciparum*	3D7	12.89 μM	KB Cells	7.66 μM	Mitsio Islands, Madagascar	[44]
	21 Ptilomycalin E	Pentacyclic Alkaloids			0.35 μM		0.85 μM		
	22 Ptilomycalin F				0.23 μM		1.61 μM		
	23 Ptilomycalins G+H				0.46 μM		0.92 μM		
	24 Crambescidin 800	Acyclic Guanidine Alkaloid			0.52 μM		1.31 μM		
	25 Fromiamycalin				0.24 μM		1.17 μM		
	Artemisinin*	-			0.004 μM	--	-	-	
Mycale sp. *SS5*	**26** Albanitrile A	Nitrile-Bearing Polyacetylenes	*Giardia duodenalis*	713	12 μM	Mammalian myeloma cell line NS-1	50 μM	Near Albany	[45]
						Normal nontumor NFF cells	100 μM		
	27 Albanitrile B				25 μM	Mammalian myeloma cell line NS-1	50 μM		
						Normal nontumor NFF cells	100 μM		
	28 Albanitrile C				90 μM	Mammalian myeloma cell line NS-1	180 μM		
						Normal nontumor NFF cells	90 μM		
	Metronidazole*				2.9 μM	-	-		
	Sparsomycin*	-	-	-	-	Mammalian myeloma cell line NS-1	0.55 μM	-	
						Normal nontumor NFF cells	1.7 μM		
	29 Pseudoceratidine		*P. falciparum*	3D7	EC_{50}= 1 μM		NT		[46]

						1.1 μM				
					K1	1.1 μM				
		30 Pseudoceratidine derivative		*P. falciparum*	3D7	EC_{50}= 6 μM				
		31 Pseudoceratidine derivative				EC_{50}= 4 μM				
		32 Pseudoceratidine derivative		*L. infantum*	promastigotes	EC_{50}= 24 μM		52 μM		
				L. amazonensis	promastigotes	EC_{50}= 19 μM				
				T. cruzi	epimastigotes	EC_{50}=7 μM				
		33 Pseudoceratidine derivative		*L. infantum*	promastigotes	EC_{50}=19 μM		> 100 μM		
				L. amazonensis	promastigotes	EC_{50}=7 μM				
				P. falciparum	3D7	EC_{50}=19 μM				
		34 Pseudoceratidine derivative		*P. falciparum*	3D7	EC_{50}=44 μM		NT		
		35 Pseudoceratidine derivative		*L. infantum*	promastigotes	EC_{50}=2 μM		66 μM		
				L. amazonensis	promastigotes	EC_{50}=3 μM				
				T. cruzi	epimastigotes	EC_{50}=24 μM				
		36 Pseudoceratidine derivative		*P. falciparum*	3D7	EC_{50}=7 μM		NT		
		37 Pseudoceratidine derivative		*L. infantum*	promastigotes	EC_{50}=20 μM		> 100 μM		
				L. amazonensis	promastigotes	EC_{50}=76 μM				
		38 Pseudoceratidine derivative		*L. infantum*	promastigotes	EC_{50}=23 μM		82 μM		
				L. amazonensis	promastigotes	EC_{50}=18 μM				
				P. falciparum	3D7	EC_{50}=3 μM		NT		
		Chloroquine*	-	*P. falciparum*	3D7	0.013 μM	-	-	-	
					K1	0.167 μM				
		Pyrimethamine*	-	*P. falciparum*	3D7	0.03 μM	-	-	-	
					K1	3.9 μM				
		Cycloguanil*	-	*P. falciparum*	3D7	0.010 μM	-	-	-	
					K1	0.54 μM				
		Artesunate*	-	*P. falciparum*	3D7	0.004 μM	-	-	-	
					K1	0.003 μM				
	Tedania brasiliensis	**39** Kaimanol	Bromopyrrole Alkaloids	*P. falciparum*	3D7	0.359 μM	Bone marrow-derived macrophages	> 100 μM	Cabo Frio, Rio de Janeiro state, Brazil	
		40 Saringosterol				0.00025 μM				
	Xestospongia sp.	**39** Kaimanol	Sterol			0.359 μM	NT	NT	Indonesia	[47]
		40 Saringosterol				0.00025 μM				
		Artemisinin*	-			5.207×10^{-3} nM	-	-	-	[48]
Cnidaria	*Alcyonium* sp.	**41** Alcyopterosin V	Illudalane Sesquiterpenes	*L. donovani*	-	7.0 μM	J774.A1 macrophages	110 μM	Scotia Arc of Antarctica	[49]
							Host cell lines HEK293T	220 μM		

						Host cell lines HepG2	288 μM		
	42 Alcyopterosin E				3.1 μM	J774.A1 macrophages	62 μM		
						Host cell lines HEK293T	570 μM		
						Host cell lines HepG2	331 μM		
	Miltefosine*	-			6.2 μM	-	-	-	
Bebryce grandis	**43** Bebrycin A	Diterpene	*P. falciparum*	Dd2	EC_{50} = 1.08 μM	HepG2 human hepatocyte carcinoma cell line	EC_{50} =21.8 μM	Southeast coast of Curacao, East of Fuikbaai	[50]
	44 Nitenin	C21 Degraded Terpene			EC_{50} = 0.29 μM		EC_{50} =18.3 μM		
Macrorhynchia philippina	**45** Isololiolide	Carotenoid Isololiolide	*T. cruzi*	trypomastigotes	31.9 μM	BMM cells	> 200 μM	São Sebastião Channel, Brazil	[51]
				amastigotes	40.4 μM				
	Benznidazole*	-		trypomastigotes	16.2 μM		> 200 μM	-	
				amastigotes	5.3 μM				
Plumarella delicatissima	**46** Keikipukalide A	Furanocembranoid Diterpenes	*L. donovani*	amastigotes	> 28 μM	Human lung carcinoma, cells, A549 cytotoxicity	> 50 μM	Stanley, Falkland Islands (Islas Malvinas), in the Southern Ocean	[52]
	47 Keikipukalide B				8.5 μM		> 50 μM		
	48 Keikipukalide C				8.8 μM		> 50 μM		
	49 Keikipukalide D				12 μM		> 50 μM		
	50 Keikipukalide E				8.8 μM		> 50 μM		
	51 Pukalide aldehyde				1.9 μM		> 50 μM		
	52 Norditerpenoid ineleganolide				4.4 μM		> 50 μM		
	Miltefosine*	-			6.2 μM	-	-	-	
Sinularia brassica	**53** Chlorinated steroid	Steroid	*L. donovaniamastigote*	amastigote	Inhibition of a growth of L. donovani at 50 μM = 58.7%	THP-1 cells at 50 μM	88.8%	Van Phong bay, Khanh Hoa province, Vietnam and Institute of Oceanography, Nha Trang, Vietnam	[53]
	54 Pinnaterpene C	Dibromoditerpene			Inhibition of a growth of L. donovani at 50 μM = 74.3%		106.2%		
	55 24-methylenecholestane-3β-5α,6β-triol-6-monoacetate	Steroid			Inhibition of a growth of L. donovani at 50μM = 54.7%		96.1%		

		56 Cholestane-3β-5α,6β-triol-6-monoacetate				Inhibition of growth of L. donovani at 50μM = 39.0%		92.7%		
	Sinularia sp.	**57** Sinuketal	Sesquiterpenoids	*P. falciparum*	3D7	80 μM	Jurkat MDA-MB-231 U2OS	24.9 μM 32.3 μM 41.7 μM	Yongxing Island (16°50′ N, 112°20′ E) of Xisha Islands in the South China Sea	[54]
		Dihydroartemisinine*	-			10 nM	-	-	-	
Bryozoa	*Amathia lamouroux*	**58** Convolutamines K	Brominated Alkaloids	*P. falciparum*	3D7	1.7 μM	Human embryonic kidney cell line, HEK293	17.01 μM	Rock pools of Woolgoolga, New South Wales, Australia	[55]
		59 Convolutamines L			3D7	11 μM		IA at 40 μM		
		60 Volutamides F			3D7	0.61 μM		IA at 40 μM		
					Dd2	0.75 μM				
		61 Volutamides G			3D7	0.57 μM		11 μM		
					Dd2	0.85 μM				
		62 Volutamides H			3D7	1.6 μM		IA at 40 μM		
					Dd2	1.9 μM				
		Chloroquine*	-		3D7	0.025 μM		67% at 4 μM	-	
					Dd2	0.18 μM				
		Dihydroartemisinin*	-		3D7	0.0020 μM		IA at 0.1 μM	-	
					Dd2	0.0020 μM				
		Puromycin*	-		3D7	0.11 μM		0.81 μM	-	
					Dd2	0.068 μM				
	Orthoscuticella ventricosa	**63** Orthoscuticellines A	Alkaloids	*P. falciparum*	3D7	10 μM	Human embryonic kidney cell line, HEK293	10 μM	Northern NSW, Australia	[56]
		64 Orthoscuticellines B				> 40 μM		> 40 μM		
		65 Orthoscuticellines D				14 μM		> 40 μM		
		66 Orthoscuticellines E				12 μM		> 40 μM		
		67 1-ethyl-4-methylsulfone-β-carboline				21 μM		> 40 μM		
		68 1-ethyl-β-carboline				18 μM		> 40 μM		
		Chloroquine*	-			0.007 μM		> 40 μM		
		Artesunate*	-			0.0003 μM	-	-	-	

Microorganisms	Actinomy-cetes	*Streptomyces* sp. PBLC04	**69** Staurosporine	Alkaloid	*Acanthamoeba castellanii*	Trophozoites	0.265 μg/mL	Murine macrophage J774.A1 cell line	4.076 μM	Jambelí mangrove, Ecuador	[57]
						Cysts	0.771 μg/mL				
		Streptomyces sp.	**70** Marinopyrrole A	Alkaloids	*T. gondii*	Tachyzoites/Type I RH	0.31 μM	Human foreskin fibroblast (HFF)	> 50 μM	Marinopyrrole A was obtained from Sigma–Aldrich	[58]
								Human hepatocarcinoma (HepG2)	5.3 μM		
			71 RL002				0.17 μM	Human foreskin fibroblast (HFF)	> 50 μM		
								Human hepatocarcinoma (HepG2)	29.0 μM		
			72 RL003				0.09 μM	Human foreskin fibroblast (HFF)	> 50 μM		
								Human hepatocarcinoma (HepG2)	49.7 μM		
			73 RL125				0.16 μM	Human foreskin fibroblast (HFF)	> 50 μM		
								Human hepatocarcinoma (HepG2)	46.5 μM		
			Pyrimethamine*	-			0.61 μM	-	-	-	
	Proteobacteria	*Pseudomonas aeruginosa*	**74** 3-heptyl-3-hydroxy-1,2,3,4-tetrahydroquinoline-2.4-dione	Hydroxyquinoline	*P. falciparum*	Indochina W2	3.47 μg/mL	NT	NT	Pacific of Panama	[59]
			75 2-heptyl-4-hydroxyquinoline		*P. falciparum*	Indochina W2	2.57 μg/mL				
					T. cruzi	C4	3.66 μg/mL				
			76 2-nonyl-4-hydroxyquinoline		*P. falciparum*	Indochina W2	2.79 μg/mL				
					T. cruzi	C4	3.99 μg/mL				
			Chloroquine*	-	*P. falciparum*	Indochina W2	0.03 μg/mL	-	-	-	
			Nifurtimox*	-	*T. cruzi*	C4	1.6 μg/mL	-	-	-	
	Cyanophyta	*Caldora penicillata*	**77** Hoshinoamide C (natural)	Lipopeptide	*P. falciparum*	3D7	0.96 μM	Human cancer cells, HeLa and HL60	No cytotoxicity at 10 μM	Ikei Island, Okinawa, Japan	[60]
					T. brucei rhodesiense	IL-1501	2.9 μM				
			78 Hoshinoamide C(synthetic)		*P. falciparum*	3D7	3.2 μM				
					T. brucei rhodesiense	IL-1501	3.7 μM				
					P. falciparum	3D7	0.87 μM				

	79 43-epi-hoshinoamide C(synthetic)		*T. brucei rhodesiense*	IL-1501	4.4 μM				
	Atovaquone*	-	*P. falciparum*	3D7	0.00096 μM	-	-	-	
	Pentamidine*	-	*T. brucei rhodesiense*	IL-1501	0.001 μM	-	-	-	
Dapis sp.	**80** Iheyanone	Linear Peptides	*T. brucei rhodesiense*	IL-1501	35 μM	WI-38 cells	> 50 μM	Noho Island, Okinawa, Japan	[61]
	81 Peptides				33 μM		> 50 μM		
	82 Peptides				24 μM		> 50 μM		
	83 Peptides				15 μM		> 50 μM		
	84 Peptides				17 μM		> 50 μM		
	85 Peptides				6.2 μM		> 50 μM		
	Pentamidine*	-	*T. brucei rhodesiense*	IL-1501	0.05 μM	-	--	-	
Dapis sp.	**86** Iheyamides A	Linear Peptides	*T. b. rhodesiense*	IL-1501	1.5 μM	Normal human fibroblasts, WI-38 cells	18 μM	Noho Island, Okinawa, Japan	[62]
			T. b. brucei	221	1.5 μM				
			T. b. rhodesiense	IL-1501	> 20 μM		> 20 μM		
			T. b. brucei	221	> 20 μM				
			T. b. rhodesiense	IL-1501	> 20 μM		> 20 μM		
			T. b. brucei	221	> 20 μM				
	Pentamide*	-	*T. b. rhodesiense*	IL-1501	0.005 μM	-	-	-	
			T. b. brucei	221	0.001 μM				
Leptolyngbya sp.	**87** Motobamide	Cyclic Peptide	*T. b. rhodesiense*	IL-1501	2.3 μM	WI-38 cells	55 μM	Bise, Okinawa Island, Okinawa Prefecture, Japan	[63]
						HeLa or HL60 cells	IA at 10 μM		
Leptolyngbya sp.	**88** Palstimolide A	Polyhydroxy Macrolide	*P. falciparum*	Dd2	0.1725 μM	HepG2 human liver cell line	5.04 μM	Palmyra Atoll	[64]
			L. donovani	promastigotes	4.67 μM	B10R murine macrophages (L. donovani host cell toxicity)	> 10 μM		
Okeania sp.	**89** Ikoamide	Lipopeptide	*P. falciparum*	3D7	0.14 μM	HeLa cells or HL60 cells	No cytotoxicity at 10 μM	Iko-pier, Kuroshima Island, Okinawa, Japan	[65]
	Chloroquine*	-			6.9 nM	-	-	-	
	doxorubicin	-	-	-	-	HeLa cells	0.24 μM	-	
						HL60 cells	46 nM	-	
Okeania sp.	**90** Mabuniamide	Lipopeptide	*P. falciparum*	3D7	1.4 μM	L6 myotubes	No cytotoxicity at 10–40 μM	The coast of Odo, Okinawa, Japan	[66]
	91 Stereoisomer 2				1.4 μM				

		Chloroquine*	-			7.6 nM	-	-	-	
	Salileptolyngbya sp.	**92** Kinenzoline (natural)	Linear Depsipeptide	*T. b. rhodesiense*	IL-1501	5.0 μM	WI-38 cells	> 20 μM	Kinenhama beach, Kagoshima, Japan	[67]
		93 Kinenzoline (synthetic)				4.5 μM		> 100 μM		
		Pentamide*	-			0.001 μM	-	-	-	
		Adriamycin*	-	-	-	-	WI-38 cells	0.73 μM	-	
	Moorea producens	**94** Dudawalamide A	Cyclic Depsipeptides	*P. falciparum*	W2	3.6 μM	H-460 human lung cancer cell line	Little to no cytotoxicity	Papua New Guinea	[68]
				T. cruzi	Transgenic β-galactosidase-expressing strain	12% GI (Percentage growth inhibition) at 10 μg/mL				
				L. donovani	WR2810	> 10 μM				
		95 Dudawalamide B		*P. falciparum*	W2	8.0 μM				
				T. cruzi	Transgenic β-galactosidase-expressing strain	7% GI at 10 μg/mL				
				L. donovani	WR2810	> 10 μM				
		96 Dudawalamide C		*P. falciparum*	W2	10 μM				
		97 Dudawalamide D		*P. falciparum*	W2	3.5 μM				
				T. cruzi	Transgenic β-galactosidase-expressing strain	60% GI at 10 μg/mL				
				L. donovani	WR2810	2.6 μM				
Ascomycetes	*Aspergillus terreus* BCC51799	**98** Astepyrazinoxide	Alkaloid	*P. falciparum*	K-1	24.82 μM	MCF-7	34.70 μM	The marine fungus was isolated from a decayed wood sample at Hat Bang Pu, Khao Sam Roi Yot National Park, Prachuap Khiri Khan Province	[69]
							NCI–H187	5.98 μM		
							Vero	15.61 μM		
		99 Astechrome				0.94 μM	MCF-7	IA		
							NCI–H187	IA		
							Vero	7.9 μM		
		Dihydroartemisinin*	-			2.12×10^{-3} μM	-	-	-	
		Mefloquine*	-			0.422 μM	-	-	-	
		Ellipticine*	-	-	-	-	NCI–H187	9.87 μM	-	
							Vero	5.32 μM		
		Doxorubicin*	-	-	-	-	MCF-7	10.97 μM	-	

						NCI–H187	0.16 μM		
	Tamoxifen*	-	-	-	-	MCF-7	32.95 μM	-	
Cochliobolus lunatus TA26-46	**100** Derivatives	14-Membered Resorcylic Acid Lactone Derivatives	*P. falciparum*	HB3	12.59 μmol/L	HUVEC	NT	Marine-derived	[70]
	101 Derivatives				12.39 μmol/L		NT		
	102 Derivatives				11.55 μmol/L		NT		
	103 Derivatives				8.06 μmol/L		>100 μmol/L		
	104 Derivatives				6.69 μmol/L		>100 μmol/L		
	105 Derivatives				7.82 μmol/L		>100 μmol/L		
	106 Derivatives				9.72 μmol/L		>100 μmol/L		
	107 Derivatives				7.82 μmol/L		>100 μmol/L		
	108 Derivatives				7.25 μmol/L		>100 μmol/L		
	109 Acyl derivatives				9.18 μmol/L		NT		
	110 Acyl derivatives				6.91 μmol/L		>100 μmol/L		
	111 Acyl derivatives				3.54 μmol/L		>100 μmol/L		
	Chloroquine*	-			32.9 nmol/	-	-	-	
Exserohilum sp.	**112** Isocoumarins	Polyketide	*P. falciparum*	HB3	1.13 μM	Vero cells	87.5 μM	Zoanthid *Palythoa haddoni*	[71]
	113 Isocoumarins				11.7 μM		124.2 μM		
	114 Derivatives				0.77 μM		258.0 μM		
	115 Derivatives				0.38 μM		106.3 μM		
	116 Derivatives				2.58 μM		262.5 μM		
Paecilomyces sp. 7A22	**117** Harzialactone A	Polyketone	*L. amazonensis*	promastigotes	5.25 μg/mL	Peritoneal macrophages	35.21 μg/mL	Ascidian Aplidiopsis sp. collected from São Sebastião Channel in Brazil	[72]
				amastigotes	18.18 μg/mL				
	Amphotericin B*	-	*L. amazonensis*	promastigotes	0.119 μg/mL		22.41 μg/mL	-	
				amastigotes	0.095 μg/mL				

* Positive control; NT indicates not text; IA indicates inactive

Table 2. Crude extracts of marine invertebrates and microorganisms.

Category	Species	Extract type	Target parasite	Stage/strain	IC_{50}	Site	References
Cnidaria	*Linuche unguiculata*	Distilled water	*Giardia duodenalis*	Trophozoites, IMSS 0989:1 strain	63 μg/mL	Puerto Morelos Reef Lagoon, Mexico	[73]
Actinomycetes	*Nocardia* sp. UA 23	ISP2 medium	*Trypanosoma brucei*	TC 221	MIC, 72 h = 7.2 μg/mL	Coscinoderma mathewsi was collected from Ahia Reefs	[74]
	Micromonospora sp. W305	Resin, MeOH	*Antiplasmodial Activities*	Dd2	0.42 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Nocardiopsis sp. V671	ASE, MeOH	*Antiplasmodial Activities*	Dd2	0.88 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Streptomyces tendae V324	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.35 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Streptomyces sp. INV ACT2	Ethyl acetate	*T. gondii*	GFP-RH tachyzoites	Inhibition ≥ 80% at 120 μg/mL	Caño Aguas Negras	[76]
	Streptomyces sp. RM66	On ISP2, solid media with GlcNAc	*Trypanosoma brucei*	TC 221	MIC, 72 h = 4.7 μg/mL	Hurghada (Egypt)	[77]
	Streptomyces sp. *V881*	Resin, CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.062 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Streptomyces sp. E677	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.037 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Unidentified actinomycete V663	ASE, heptane	*Antiplasmodial Activities*	Dd2	0.89 μg/mL	The microbial population associated with deep-water invertebrates	[75]
Bacteroides	*Alcanivorax* sp. V174 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.969 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Alcanivorax sp. V193 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	1.079 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Endozoicomonas numazuensis H402 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.978 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Marinobacter sp. V184 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	1.008 μg/mL	The microbial population associated with deep-water invertebrates	[75]

	Marinobacter sp. V201 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	1.091 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Marinobacter sp. V208 (G-)	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	1.091 μg/mL	The microbial population associated with deep-water invertebrates	[75]
Firmicutes	*Bacillus* sp. INV FIR35	Ethyl acetate	*T. gondii*	GFP-RH tachyzoites	Inhibition ≥ 80% at 48 μg/mL	Punta Betín	[76]
	Bacillus sp. INV FIR48	Ethyl acetate	*T. gondii*	GFP-RH tachyzoites	Inhibition ≥ 80% at 120 μg/mL	Caño Grande	[76]
	Fictibacillus sp. INV FIR149	Ethyl acetate	*T. gondii*	GFP-RH tachyzoites	Inhibition ≥ 80% at 1080 μg/mL	Caño Grande	[76]
	Paenibacillus sp. #91_7 (IN-CRY)	Waters™ Oasis® HLB extraction plates, with the sorbent Oasis® HLB, was equilibrated using methanol and HPLC grade water	*T. cruzi*	Tulahuen C4	97%	Isolated from marine sponges of the Erylus genus, collected in Portuguese waters	[78]
	Penicillium citrinum V170	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	1.069 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Penicillium sp. N161	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.266 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Penicillium sp. Z691	Resin, CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.049 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Talaromyces rotundus S920	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.677 μg/mL	The microbial population associated with deep-water invertebrates	[75]
	Tritirachium sp. V199	Resin, MeOH/CH_2Cl_2	*Antiplasmodial Activities*	Dd2	0.339 μg/mL	The microbial population associated with deep-water invertebrates	[75]
ɣ-Proteobacteria	*Enterococcus faecalis* #118_3 (IN-CRY)	EPA vials: Sepabeads® SP207ss resin, HPLC-grade water and acetone; medium IN-CRY	*T. cruzi*	Tulahuen C4	Percentage of growth inhibition = 81%	Isolated from marine sponges of the Erylus genus, collected in Portuguese waters	[78]
	Enterococcus faecalis #118_3 (IN-CRY)	Duetz extraction: Waters™ Oasis® HLB extraction plates, with the sorbent Oasis® HLB, was equilibrated using	*T. cruzi*	Tulahuen C4	Percentage of growth inhibition = 102%	Isolated from marine sponges of the Erylus genus, collected in Portuguese waters	[78]

		methanol and HPLC grade water; medium IN-CRY					
	Enterococcus faecalis #118_4 (IN-CRY)	Duetz extraction: Waters™ Oasis® HLB extraction plates, with the sorbent Oasis® HLB, was equilibrated using methanol and HPLC grade water; medium IN-CRY	*T. cruzi*	Tulahuen C4	Percentage of growth inhibition = 103%	Isolated from marine sponges of the Erylus genus, collected in Portuguese waters	[78]
	Pseudoalteromonas sp. INV PRT33	Ethyl acetate	*T. gondii*	GFP-RH tachyzoites	Inhibition ≥ 80% at 48 µg/mL	Caño Grande	[76]
Phaeophyta	*Cladostephus hirsutus*	Ethyl acetate	*T. brucei brucei*	-	27.2 µg/mL	North–west coast of Algeria	[79]
	Cystoseira sedoides	Hexane	*Acanthamoeba castellanii*	Trophozoite/Neff	1009 µg/mL	Tunisian coasts, Tabarka	[80]
		Ethyl acetate			860 µg/mL		
		Methanol			836 µg/mL		
	Dictyota ciliolata	Hexane	*Schistosoma mansoni*		Death Ratio = 100%	Espírito Santo State, Southeastern Brazil	[81]
		Chloroform			Death Ratio = 100%		
		Supercritical fluid			Death Ratio = 100%		

2. Marine Invertebrate-Derived Antiparasitic Compounds

Invertebrates make up a large part of the literature collected on antiparasitic compounds of marine origin (58.33%). Most of these compounds are alkaloids (including bromotyrosine alkaloids, tryptophan-derived alkaloids, acyclic guanidine alkaloids, etc.), sesquiterpenoids, diterpenoids, sterols, steroids, etc. (Table 1). Invertebrate-derived compounds against *P. falciparum* have highly effective bioactivity (Figure 1).

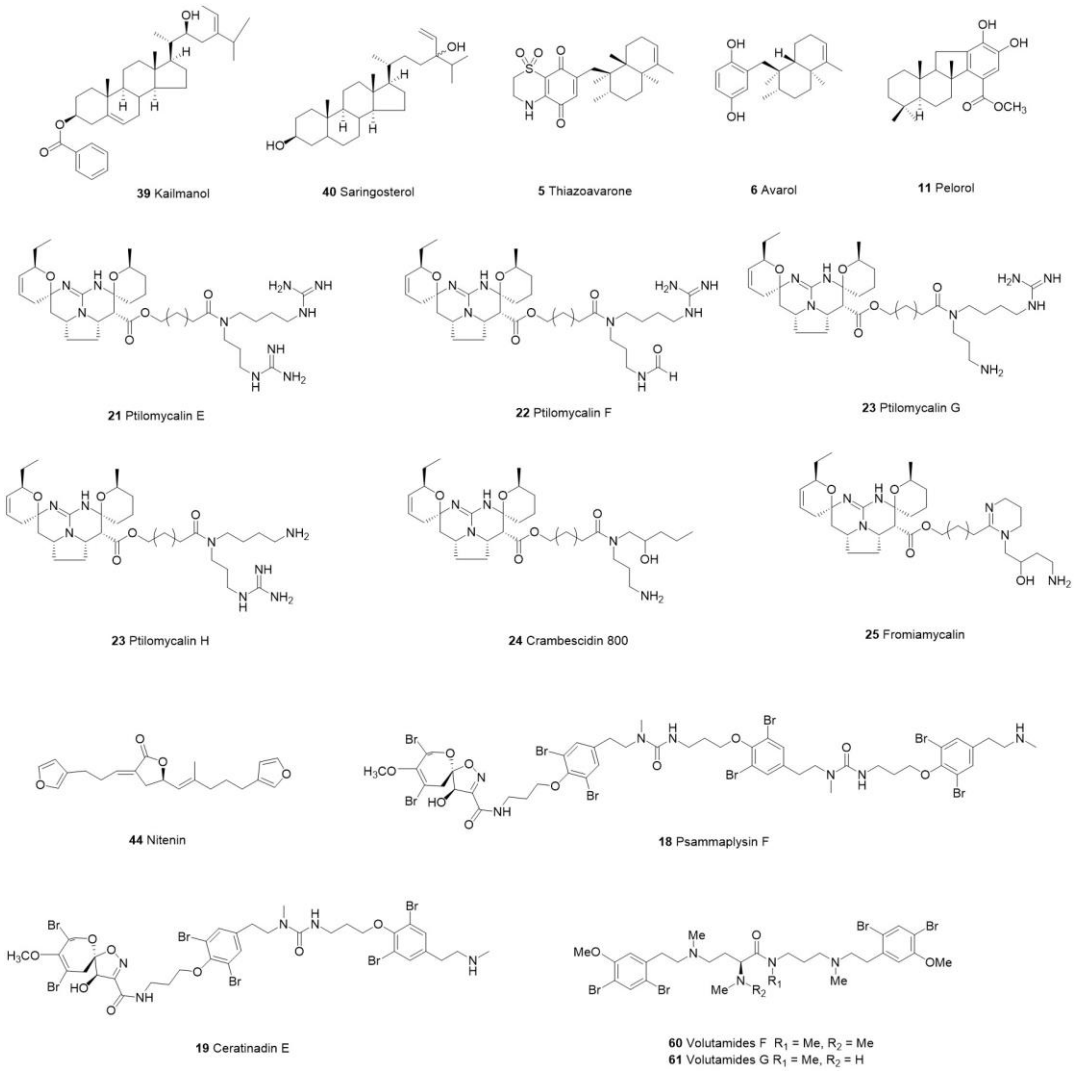


Figure 1. The structure of compounds with effective antiparasitic activity in invertebrates.

2.1. Alkaloid Compounds

Bromopyrrole alkaloids are a field worth exploring for antiparasitic drugs [46]. The bromotyrosine alkaloid bisaprasin (**3**) extracted from marine sponges was moderately effective against *T. cruzi* (IC_{50} = 0.61 μM) [36]. Pseudoceratidine (1) (**29**) and its derivatives extracted from *Tedania brasiliensis* have moderate efficacy against *P. falciparum*, *L. infantum*, *L. amazonensis*, and *T. cruzi* (Table 1). The antiplasmodium activity of this alkaloid is related to the length of the polyamine chain containing basic nitrogen and the presence of bromine atoms on the terminal portion of pyrrole or furan. Moreover, Parra et al. [46] found that pseudoceratidine (1) (**29**) had additive effects when used in combination with artesunate. Consequently, pseudoceratidine (1) (**29**) can be used as a promising source of antiplasmodial drugs.

Campos et al. [44] extracted pentacyclic alkaloids (ptilomycalin E, ptilomycalin F, and ptilomycalins G+H (**21**–**23**)) and acyclic guanidine alkaloids (crambescidin 800 (**24**)

and fromiamycalin (**25**)) from *Monanchora unguiculata* sponges, which have extremely high activity against the chloroquine-sensitive 3D7 strain of *P. falciparum* (IC_{50} were 0.35, 0.23, 0.46, 0.52, and 0.24 μM, respectively) [82]. The antimalarial activity of pentacyclic alkaloids is related to their five-ring structure. Unguiculin A (**20**), which has no five-ring structure, has lower antimalarial activity (IC_{50} = 12.89 μM). Ceratinadin E (**19**), a new bromotyrosine alkaloid, was isolated from the marine sponge *Pseudoceratina* by Kurimoto et al. [43] and showed good potent activity against the chloroquine-resistant strain FCR3 (IC_{50} = 0.77 μg/mL) and multidrug-resistant strain K1 (IC_{50} = 1.03 μg/mL) of *P. falciparum*. In 2019, Campos et al. [38] isolated 8-oxo-tryptamine (**7**) and the mixture of (E) with (Z)-6-bromo-2′-demethyl-3′-N-methylaplysinopsin (**8**), which showed moderate activity against the *P. falciparum* 3D7 strain ((IC_{50} were 8.8 and 8.0 μg/mL, respectively). These two aplysinopsins with antimalarial activity have a double bond between C-8 and C-1′, suggesting that antimalarial activity may be connected to the skeleton of the compounds.

Brominated alkaloids extracted from the bryozoan *Amathia lamourouxi* showed effective antimalarial activity against the *P. falciparum* 3D7 strain. Moreover, volutamide F (**60**) showed a higher selectivity index for the human embryonic kidney cell line HEK293. The antimalarial activity of volutamide H (**62**) (IC_{50} = 1.6 μM) was lower than that of volutamide F (**60**) (IC_{50} = 0.61 μM) and volutamide G (**61**) (IC_{50} = 0.57 μM), indicating that the presence of tertiary amides plays an important role against *Plasmodium* [55]. Alkaloids (orthoscuticellines A, D, E, 1-ethyl-β-carboline (**63, 65, 66, 68**)) isolated from *Orthoscuticella ventricosa*, another bryophyte, also had moderate antimalarial activity, ranging from 12-21 μM (Table 1). Ligand efficiency calculations showed that β-carboline was partly related to the antiplasmodium activity [56].

2.2. Terpenoids, Sesquiterpenoids, and Diterpenoids Compounds

Imperatore et al. [37] obtained the natural sesquiterpenoid quinone avarone (**4**) and avarol (**6**) from *Dysidea avara* sponges. They obtained the semisynthetic thiazinoquinone derivative thiazoavarone (**5**) by condensation reaction of avarone (**4**) with subtaurine. Compared with the two natural products, thiazoavarone (**5**) showed better activity against the chloroquine-resistant strain W2 (IC_{50} = 0.21 μM) and drug-sensitive strain D10 (IC_{50} = 0.38 μM) of *P. falciparum*. In addition, this derivative also had bioactivity against *Schistosoma mansoni* (IC_{50} = 5.90 μM). These results suggested that the substituent of the 1,1-dioxo-1,4-thiazine ring played a vital part in bioactivity.

Among the five new furan diterpenes keikipukalides (A–E) (**46–50**) isolated from *Plumarella delicatissima*, four keikipukalides (B–E) (**47–50**) showed moderate activity against *L. donovani* (IC_{50} were 8.5, 8.8, 12, and 8.8 μM, respectively). In addition, the two known compounds pukalide (**51**) and norditerpenoid (**52**) ineleganolide that were isolated, also showed good biological activity (IC_{50} were 1.9 and 4.4 μM, respectively). In particular, these compounds were not toxic to human lung carcinoma cells when they were below 50 μM. [52]. The sesquiterpenoids alcyopterosin V (**41**) and alcyopterosin E (**42**) obtained from another cnidarian *Alcyonium* sp. also had moderate activity against *L. donovani* (IC_{50} were 7.0 and 3.1 μM, respectively) [49].

2.3. Steroids and Sterols Compounds

Chlorinated steroid (3) (**53**), 24-methylenecholestane-3β-5α,6β-triol-6-monoacetate (**55**), and dibromoditerpene compounds pinnaterpene C (**54**) extracted from *Sinularia brassica* at 50 μM showed positive effects. The inhibitory effects of *L. donovaniamastigote* on amastigotes were 58.7%, 54.7%, and 74.3%, respectively. In addition, the three compounds showed little toxicity to THP-1 cells at these concentrations [53].

Two sterol compounds, kaimanol (**39**) and saringosterol (**40**), were extracted from the sponge *Xestospongia* sp. The antimalarial activity of kaimanol (**39**) was lower than that of saringosterol (**40**), suggesting that benzoyl may reduce the activity in the sterol structure [47]. The terpenoids extracted from the sponge *Hyrtios erectus* and the cnidarian *Bebryce grandis* showed moderate or greater activity against chloroquine-resistant Dd2 strains [39,

50]. It is worth noting that both compounds extracted from *B. grandis* act on the life cycle of *Plasmodium* parasites. They found that the addition of nitenin (**44**) before the ring transition to the early trophozoite stage inhibited the maturation of the parasites. Bebrycin A (**43**) prevented the parasite from maturing. Among the clinical antimalarial drugs, only artemisinin is active against the merozoite of *Plasmodium* [83]. Consequently, Wright et al. [50] noted that it might be possible to develop new artemisinin combination therapy partner drugs based on the properties of these two terpenoids.

2.4. Other Compounds

Sala et al. extracted several nitrile-containing polyacetylene secondary metabolites from the sponge *Mycale* sp.SS5; however, only albanitrile A (**26**) showed moderate bioactivity against *Giardia duodenalis* (IC_{50} =12 μM). The lower bioactivity of albanitrile B (**27**) than A **26** also suggested that the activity of antigenic animals depended on the chain length of the alkyl group [45].

Notably, isololiolide (**45**), which was extracted in the sponge *Macrorhynchia philippina*, had certain effects on *T. cruzi* trypomastigotes and amastigotes (IC_{50} = 31.9 and 40.4 μM, respectively). Lima et al. [51] studied the lethal mechanism of this compound and suggested that isololiolide (**45**) may cause damage to plasma membrane integrity and depolarization of mitochondrial membrane potential.

3. Marine Microorganisms-Derived Antiparasitic Compounds

3.1. Steroids and Sterols Compounds

Previous studies have shown that polyketones, alkaloids, fatty acids, terpenes, and other compounds isolated from marine bacteria have potential antibacterial, antifungal, and antiparasitic activities [74,84,85]. *Salinivibrio* and *Streptomyces* from Actinomycetes are Gram-positive bacteria [74], while *Pseudomonas* from Proteobacteria is Gram-negative bacteria [86]. The active compounds extracted from these bacteria mainly include alkaloids and quinoline (Table 1) (Figure 2).

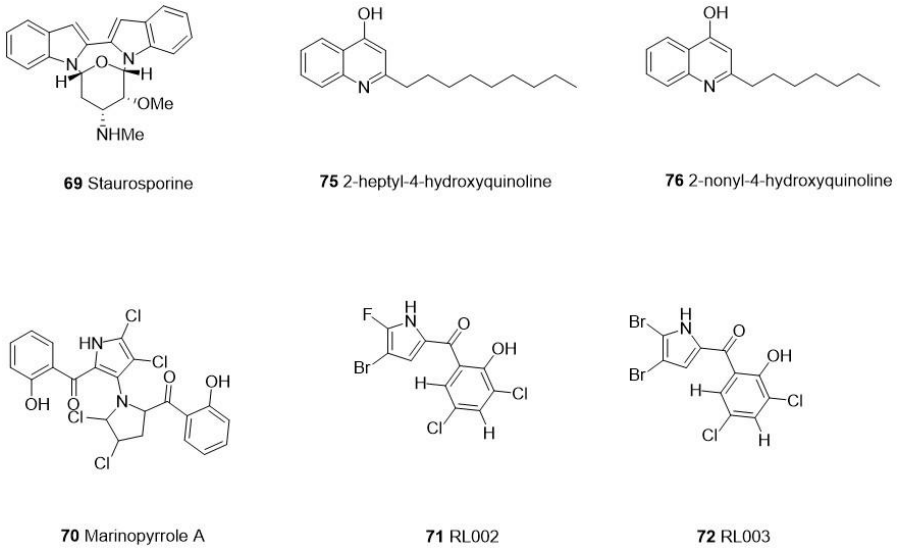


Figure 2. The structure of compounds with effective antiparasitic activity in marine bacteria.

Marinopyrrole A (**70**), an alkaloid compound found in marine *Streptomyces* sp., has strong antibacterial activity against methicillin-resistant *Staphylococcus aureus* [87]. Martens et al. [58] explored the activity of this compound against *Toxoplasma gondii*. In in vitro experiments, marinopyrrole A (**70**) showed potent inhibitory activity at 0.31 μM against *Toxoplasma gondii* tachyzoites. However, the anti-toxoplasma effect was inhibited when more than 20% bovine calf serum was added to the liquid medium. Based on compound

(**70**), they obtained three analogs, RL002, RL003, and RL125 (**71–73**), which showed 3.6- to 6.8-fold increased efficacy against toxoplasmosis ($P < 0.001$, Student's paired *t*-test) and decreased serum sensitivity. RL003 (**72**), the most inhibitory analog, is highly active against cysts in vitro (IC_{50} = 0.245 μM). Hence, further in vivo chronic studies are needed to assess the potential antiparasitic activity of RL003 (**72**) in the host. Another alkaloid, staurosporine (**69**), isolated from *Streptomyces* sp. PBLC04 can kill the trophozoites of *Acanthamoeba* (IC_{50} = 0.265 μg/mL) [57]. The cysts of *Acanthamoeba* allow the parasite to cope with harsh environments such as a lack of nutrients, high temperatures, and high osmotic pressure, so *Acanthamoeba*, in this stage is highly resistant [88, 89]. Notably, tarosporine also showed good potent inhibition against cysts (IC_{50} = 0.771 μg/mL). The protein kinase family is generally considered to be the main target of staurosporine (**69**) [90]. *Acanthamoeba* is rich in known kinase genes, which may explain the high activity of this compound against *Acanthamoeba*.

Martinez-Luis et al. [59] isolated five hydroxyquinoline compounds from P*seudomonas aeruginosa*, among which three compounds had good antiparasitic effects: 3-heptyl-3-hydroxy-1,2,3,4-tetrahydroquinoline-2.4-dione (2), 2-heptyl-4-hydroxyquinoline (3), and 2-nonyl-4-hydroxyquinoline (4) (**74–76**). These three compounds showed moderate and greater antimalarial activity against the chloroquine-resistant strain W2 of *P. falciparum* (IC_{50} = 3.47, 2.57, and 2.79 μg/mL, respectively). Compounds (3) (**75**) (IC_{50} = 3.66 μg/mL) and (4) (**76**) (IC_{50} = 3.99 μg/mL) also showed resistance to *Trypanosoma cruzi*. In addition, this study also found that the corresponding tautomers of compounds (3) (**75**) and (4) (**76**) showed strong activity against the chloroquine-sensitive D6 strain and chloroquine-resistant *Plasmodium falciparum* W2 strain [91], indicating that the hydroxyquinoline compounds maintained antimalarial activity independently of their tautomers [59].

3.2. Marine Fungi

Endophytes are microfungi that reside in the internal tissues of plants without causing any immediate obvious negative effects [92, 93]. Marine invertebrates, algae endophytes, or fungi found in marine sediments are also rich sources of bioactive natural products [94-96]. In the four studies on marine fungi from 2017 to 2022, the natural products were mostly polyketones and alkaloids (Table 1).

The compound harzialactone A (**117**) was extracted from *Paecilomyces* sp.7A22, a marine fungus isolated from sea squirts. This known polyketone compound has been isolated from *Trichoderma harzianum*, an endophytic fungus of the sponge *Halichondria okadai* [97]. Braun et al. [72] investigated the antiparasitic activity of this polyketone compound.

Harzialactone A (**117**) had the ability to overcome the transmembrane barriers to reach the macrophage phagolysosome, where amastigotes grow, and showed moderate activity against *L. amazonensis promastigotes* (IC_{50} = 5.25 μg/mL). In addition, another polyketone isolated from *Cochliobolus lunatus* by Xu et al. [70] (Derivatives **103-111**, Acyl derivatives **69**-**71**) showed moderate antiplasmodial activity (Table 1). The structure–activity relationships showed that biphenyl substituents at C-2, acetone at C-5 'and C-6', and triple or quadruple substitution of acyl groups increased antiplasmodium activity.

Isocoumarins (1) (**112**) and isocoumarins (3) (**113**) extracted from *Exserohilum* sp. (CHNSCLM-0008) fungus isolated from button coral *Palythoa haddon*i by Coronado et al. [71] showed moderate activity against chloroquine-sensitive HB3 strains of *Plasmodium falciparum* (IC_{50} values were 1.13 and 11.7 μM, respectively). Semisynthetic derivatives were obtained by changing the substituents of the aromatic ring and adipose chain to explore the structure–activity relationship of the compounds. The newly synthesized compounds, derivatives **114–116** (Figure 3), showed good potent activity against *P. falciparum* (IC50 values were 0.77, 0.38, and 2.58 μM, respectively). Among them, derivative **115** was an accidental ring-opening product obtained during the demethylation process, which had a very strong antimalarial effect. Moreover, structure–activity analysis demonstrated that the configuration of methoxy groups and *3R*, *4R*, and *10S* was necessary for antimalarial activity, and the lipid solubility of the side chain could help improve antimalarial

activity. On the one hand, derivative **115** can inhibit heme polymerization and reduce mitochondrial membrane potential in the parasite; on the other hand, they can inhibit DNA gyrase enzymes and thus inhibit DNA replication. In conclusion, this study suggested that derivatives **115** may be a potential lead agent for malaria treatment.

Bunbamrung et al. [69] isolated the fungus *Aspergillus terreus* BCC51799 from decaying wood samples in the ocean and extracted new natural products from this fungus. Among them, the alkaloid astechrome (**99**) (Figure 3) showed strong antimalarial activity (IC_{50}= 0.94 μM) (Table 1).

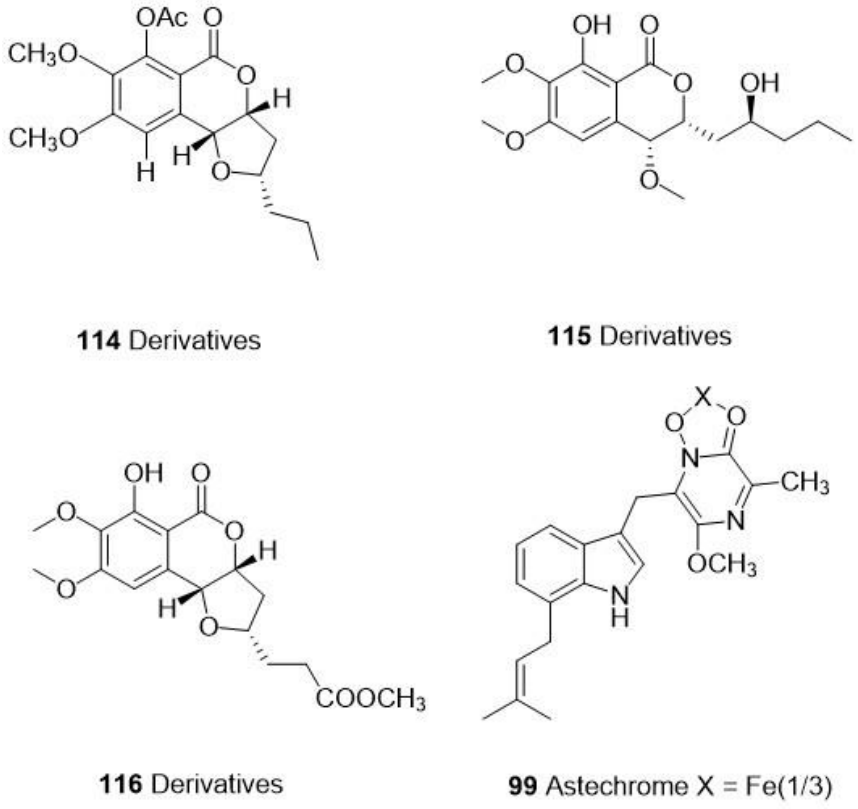


Figure 3. The structure of compounds with effective antiparasitic activity in marine fungi.

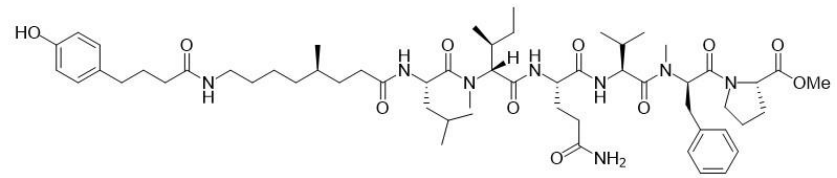
4. Cyanophyta

Cyanobacteria, also known as blue-green algae because of the presence of phycocyanin and chlorophyll, are the only prokaryotes that can produce oxygen through photosynthesis [98]. Some secondary metabolites in marine cyanobacteria have good activity and are considered lead compounds for drugs [99]. Some of these compounds are antimicrobial peptides, and cyanobacterial peptides can be divided into linear peptides, depsipeptides, and cyclic peptides according to their structure [98].

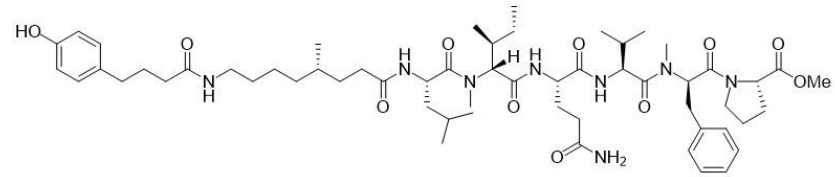
4.1. Linear Peptides

Ozaki et al. [66] isolated the linear peptides mabuniamide (1) (**90**) and stereoisomer **2** (**91**), from *Okeania* sp., which showed moderate activity (IC_{50} were both 1.4 μM) against the chloroquine-sensitive 3D7 strain of *P. falciparum*. In 2020, Iwasaki et al. [65] isolated another linear peptide, ikoamide (1) (**89**) (Figure 4), from *Okeania* and discovered strong activity against the *P. falciparum* 3D7 strain. Kurisawa et al. [62] isolated three linear peptides from the cyanobacteria *Dapis* sp. However, only iheyamides A (**86**) showed moderate activity against *T. b. rhodesiense* (IC_{50} = 1.5 μM) and *T. b. brucei* (IC_{50} = 1.5 μM). Structure–activity analysis proved that the C-terminal pyrrolinone moiety was vital for antiparasitic activity. The team then isolated the C-terminal part of iheyamide A (1) to obtain iheyanone

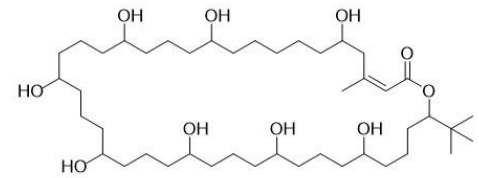
(2), which also showed some activity against *T. b. rhodesiense*. To further clarify the structure–activity relationship of this compound, Iswasaki et al. [61] synthesized a variety of compounds with different peptide chain lengths and found that longer lengths of the peptide chain were more effective in inhibiting the growth of *Trypanosoma.* Hoshinoamide C (**77**) (Figure 4), a natural product discovered by Iswasaki et al. [60] in *Caldora penicillate*, also had some effective activity against *P. falciparum* (IC_{50} = 0.96 μM) and *T. b. rhodesiense* (IC_{50} = 2.9 μM). Finally, the configuration at C-43 (Figure 4) did not affect antiparasitic activity when used to synthesize two possible isomers of hoshinoamide C (**77,78**). The linear peptide Kinenzoline (1) (**92**) isolated from *Salileptolyngbya* sp. showed moderate activity (IC_{50} = 5.0 μM) against the IL-1501 strain of *T. b. rhodesiense*. Kurisawa et al. [67] also identified a synthetic pathway for kinenzoline (1) (**92**) and showed that neither natural nor synthetic Kinenzoline (1) (**92,93**) was toxic to WI-38 cells.



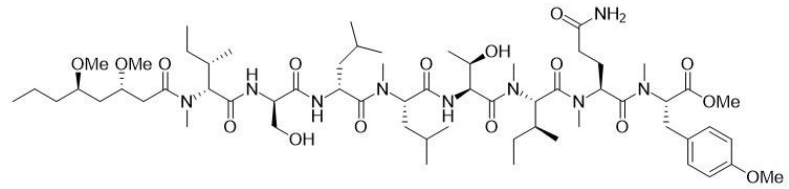
77,78 Hoshinoamide C



79 43-epi-Hoshinoamide C



88 Palstimolide A



89 Ikoamide

Figure 4. The structure of compounds with effective antiparasitic activity in Cyanophyta.

4.2. Cyclic Peptides

Cyclic peptides are likely to mimic peptide substrates or ligands of endogenous proteins (such as enzymes or receptors). Therefore, they are often considered "privileged structures" of bioactivity [100,101]. Motobamide (1) (**87**), a cyclic decapeptide isolated from *Leptolyngbya* sp., inhibited the growth of *T. b. rhodesiense*. Almaliti et al. [68] explored the relationship between the structure and activity of several dudawalamides **94–97**, which are cyclic depsipeptides isolated from the cyanobacterium *Moorea producens*. The

results indicated that the activity of Dhoya natural products was affected by the structure of the configuration and order of residues. Keller et al. [64] isolated Palstimolide A (**88**), a polyhydroxy macrolide compound from cyanobacteria, with an IC_{50} of 0.1725 μM against the Dd2 strain of P. falciparum, showing very high antiplasmodium activity. This compound also showed moderate activity against the promastigotes phase of *L. donovani* (IC_{50} = 4.67μM).

5. Conclusions

Our review of the literature published in the last five years found that sponges are still the major source of marine-derived compounds. Marine sponge-derived compounds have shown excellent activity against *Plasmodium falciparum* in in vitro studies. A total of 40 natural products or synthetic compounds from marine sponges were included in this study, among which 12 compounds had good potent activity. These sponges belong to *Xestospongia*, *Dyside*, *Hyrtios*, *Pseudoceratina*, and *Monanchora*. Approximately 17 compounds were derived from cnidarians, and one compound from *Bebryce* showed good potent activity. In addition, 11 compounds from bryophytes and two high bioactivity compounds were derived from *Amathia*. A total of 8 compounds from marine bacteria were collected, and seven compounds with effective bioactivity were extracted from *Streptomyces*, *Salinivibrio,* and *Pseudomonas*. Twenty compounds were identified from marine fungi, with three highly active compounds from *Exserohilum* and *Aspergillus.* Finally, 21 were derived from Cyanophyta, with 4 highly active compounds from *Caldora*, *Okeania*, and *Leptolyngbya*.

Naturally derived or semisynthetic molecular analogs can be developed by structure–activity relationship (SAR) analysis and tend to have higher bioactivity and less toxicity [102]. In addition, it has been shown that coupling natural products with nanomaterials may enhance the activity of compounds. Walvekar et al. used silver nanoparticles coupled with extracts of *Kappaphycus alvarezii*, which enhanced anti-acanthamoebic activity [103].

Although the association between the structure of some compounds and their antiparasitic activity has been explored through SAR, the molecular targets and mechanisms of some compound molecules have not been clarified [104]. At present, a large number of promising active antiparasitic compounds have been discovered, but translating them into a drug for clinical use still faces many difficulties: (1) if the purified antiparasitic product is not chemically synthesized, clinical studies and mass production of those compounds often require more biomass than discovering new compounds and (2) if the compounds can be obtained through chemical synthesis, it is also worth considering how to reduce the synthesis steps and reduce the cost of chemical synthesis.

Author Contributions: L.Z. conceived the ideas and methodology. M.Z., Q.Z. (Qunde Zhang), Q.Z.(Qinrong Zhang), and X.C. collected the data. M.Z. and L.Z. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: Financial support was provided by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Data Availability Statement: Not applicable.

Acknowledgments: We thank the team members for the help during data collection.

Conflicts of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Mostafa, O.; Al-Shehri, M.; Moustafa, M. Promising antiparasitic agents from marine sponges. *Saudi J. Biol. Sci.* **2021**, *29*, 217–227.
2. Greenwood, B.; Mutabingwa, T. Malaria in 2002. *Nature* **2002**, *415*, 670.
3. della Torre, A.; Tu, Z.; Petrarca, V. On the distribution and genetic differentiation of Anopheles gambiae ss molecular forms. *Insect Biochem. Mol. Biol.* **2005**, *35*, 755–769.
4. Horn, D.; Duraisingh, M.T. Antiparasitic chemotherapy–from genomes to mechanisms. *Annu. Rev. Pharmacol. Toxicol.* **2014**, *54*, 71.
5. Seo, E.B.; du Plessis, L.H.; Viljoen, J.M. Solidification of Self-Emulsifying Drug Delivery Systems as a Novel Approach to the Management of Uncomplicated Malaria. *Pharmaceuticals* **2022**, *15*, 120.
6. World Health Organization. *World Malaria Report 2022*; World Health Organization: Geneva, Switzerland, 2022.
7. Hotez, P.J.; Aksoy, S.; Brindley, P.J.; Kamhawi, S. *What Constitutes a Neglected Tropical Disease?* Public Library of Science: San Francisco, CA USA, 2020; Volume 14, p. e0008001.
8. Engels, D.; Zhou, X.-N. Neglected tropical diseases: An effective global response to local poverty-related disease priorities. *Infect. Dis. Poverty* **2020**, *9*, 1–9.
9. Pinheiro, A.C.; de Souza, M.V.N. Current leishmaniasis drug discovery. *RSC Med. Chem.* **2022**, *13*, 1029–1043.
10. Torres-Guerrero, E.; Quintanilla-Cedillo, M.R.; Ruiz-Esmenjaud, J.; Arenas, R. Leishmaniasis: A review. *F1000Research* **2017**, *6*, 22–25.
11. Desjeux, P. Leishmaniasis: Current situation and new perspectives. *Comp. Immunol. Microbiol. Infect. Dis.* **2004**, *27*, 305–318.
12. Pal, M.; Gutama, K.P.; Steinmetz, C.H.; Dave, P. Leishmaniasis: An Emerging and Re-emerging Disease of Global Public Health Concern. *Am. J. Infect. Dis.* **2022**, *10*, 22–25.
13. Shah, V.V.; Patel, V.M.; Vyas, P. Human African Trypanosomiasis–A rare case report from India. *Indian J. Med. Microbiol.* **2022**, *40*, 169–171.
14. Simarro, P.P.; Cecchi, G.; Paone, M.; Franco, J.R.; Diarra, A.; Ruiz, J.A.; Fèvre, E.M.; Courtin, F.; Mattioli, R.C.; Jannin, J.G. The Atlas of human African trypanosomiasis: A contribution to global mapping of neglected tropical diseases. *Int. J. Health Geogr.* **2010**, *9*, 1–18.
15. Chimelli, L.; Scaravilli, F. Trypanosomiasis. *Brain Pathol.* **1997**, *7*, 599–611.
16. Montgomery, S.P.; Parise, M.E.; Dotson, E.M.; Bialek, S.R. What do we know about Chagas disease in the United States? *Am. J. Trop. Med. Hyg.* **2016**, *95*, 1225.
17. Beteck, R.M.; Smit, F.J.; Haynes, R.K.; N'Da, D.D. Recent progress in the development of anti-malarial quinolones. *Malar. J.* **2014**, *13*, 1–10.
18. Ouji, M.; Augereau, J.-M.; Paloque, L.; Benoit-Vical, F. Plasmodium falciparum resistance to artemisinin-based combination therapies: A sword of Damocles in the path toward malaria elimination. *Parasite* **2018**, *25*, 24.
19. Thu, A.M.; Phyo, A.P.; Landier, J.; Parker, D.M.; Nosten, F.H. Combating multidrug-resistant Plasmodium falciparum malaria. *FEBS J.* **2017**, *284*, 2569–2578.
20. Duru, V.; Khim, N.; Leang, R.; Kim, S.; Domergue, A.; Kloeung, N.; Ke, S.; Chy, S.; Eam, R.; Khean, C. Plasmodium falciparum dihydroartemisinin-piperaquine failures in Cambodia are associated with mutant K13 parasites presenting high survival rates in novel piperaquine in vitro assays: Retrospective and prospective investigations. *BMC Med.* **2015**, *13*, 1–11.
21. Leang, R.; Taylor, W.R.; Bouth, D.M.; Song, L.; Tarning, J.; Char, M.C.; Kim, S.; Witkowski, B.; Duru, V.; Domergue, A. Evidence of Plasmodium falciparum malaria multidrug resistance to artemisinin and piperaquine in western Cambodia: Dihydroartemisinin-piperaquine open-label multicenter clinical assessment. *Antimicrob. Agents Chemother.* **2015**, *59*, 4719–4726.
22. AlKadi, H.O. Antimalarial drug toxicity: A review. *Chemotherapy* **2007**, *53*, 385–391.
23. da Silva, V.B.R.; Campos, B.R.K.L.; de Oliveira, J.F.; Decout, J.-L.; de Lima, M. d. C. A. Medicinal chemistry of antischistosomal drugs: Praziquantel and oxamniquine. *Bioorganic Med. Chem.* **2017**, *25*, 3259–3277.
24. Lespine, A.; Ménez, C.; Bourguinat, C.; Prichard, R.K. P-glycoproteins and other multidrug resistance transporters in the pharmacology of anthelmintics: Prospects for reversing transport-dependent anthelmintic resistance. *Int. J. Parasitol. Drugs Drug Resist.* **2012**, *2*, 58–75.
25. Bermudez, J.; Davies, C.; Simonazzi, A.; Real, J.P.; Palma, S. Current drug therapy and pharmaceutical challenges for Chagas disease. *Acta Trop.* **2016**, *156*, 1–16.
26. Versteeg, L.; Almutairi, M.M.; Hotez, P.J.; Pollet, J. Enlisting the mRNA vaccine platform to combat parasitic infections. *Vaccines* **2019**, *7*, 122.
27. Lu, W.-Y.; Li, H.-J.; Li, Q.-Y.; Wu, Y.-C. Application of marine natural products in drug research. *Bioorganic Med. Chem.* **2021**, *35*, 116058.
28. Danovaro, R.; Corinaldesi, C.; Dell'Anno, A.; Snelgrove, P.V. The deep-sea under global change. *Curr. Biol.* **2017**, *27*, R461–R465.
29. Thomas, T.R.A.; Kavlekar, D.P.; LokaBharathi, P.A. Marine drugs from sponge-microbe association—A review. *Mar. Drugs* **2010**, *8*, 1417–1468.
30. Nweze, J.A.; Mbaoji, F.N.; Li, Y.-M.; Yang, L.-Y.; Huang, S.-S.; Chigor, V.N.; Eze, E.A.; Pan, L.-X.; Zhang, T.; Yang, D.-F. Potentials of marine natural products against malaria, leishmaniasis, and trypanosomiasis parasites: A review of recent articles. *Infect. Dis. Poverty* **2021**, *10*, 1–19.

31. Lenz, K.D.; Klosterman, K.E.; Mukundan, H.; Kubicek-Sutherland, J.Z. Macrolides: From toxins to therapeutics. *Toxins* **2021**, *13*, 347.
32. Rushdi, M.I.; Abdel-Rahman, I.A.; Attia, E.Z.; Abdelraheem, W.M.; Saber, H.; Madkour, H.A.; Amin, E.; Hassan, H.M.; Abdelmohsen, U.R. A review on the diversity, chemical and pharmacological potential of the green algae genus Caulerpa. *S. Afr. J. Bot.* **2020**, *132*, 226–241.
33. Nweze, J.A.; Mbaoji, F.N.; Huang, G.; Li, Y.; Yang, L.; Zhang, Y.; Huang, S.; Pan, L.; Yang, D. Antibiotics development and the potentials of marine-derived compounds to stem the tide of multidrug-resistant pathogenic bacteria, fungi, and protozoa. *Mar. Drugs* **2020**, *18*, 145.
34. Murillo, T.; Schneider, D.; Fichtel, C.; Daniel, R. Dietary shifts and social interactions drive temporal fluctuations of the gut microbiome from wild redfronted lemurs. *ISME Commun.* **2022**, *2*, 1–11.
35. Ioset, J.-R.; Brun, R.; Wenzler, T.; Kaiser, M.; Yardley, V. Drug Screening for Kinetoplastid Diseases: A Training Manual for Screening in Neglected Diseases. *DNDi.* **2009**; 1–74.
36. Oluwabusola, E.T.; Tabudravu, J.N.; Al Maqbali, K.S.; Annang, F.; Pérez-Moreno, G.; Reyes, F.; Jaspars, M. Antiparasitic activity of bromotyrosine alkaloids and new analogues isolated from the Fijian marine sponge Aplysinella rhax. *Chem. Biodivers.* **2020**, *17*, e2000335.
37. Imperatore, C.; Gimmelli, R.; Persico, M.; Casertano, M.; Guidi, A.; Saccoccia, F.; Ruberti, G.; Luciano, P.; Aiello, A.; Parapini, S. Investigating the antiparasitic potential of the marine sesquiterpene avarone, its reduced form avarol, and the novel semisynthetic thiazinoquinone analogue thiazoavarone. *Mar. Drugs* **2020**, *18*, 112.
38. Campos, P.-E.; Pichon, E.; Moriou, C.; Clerc, P.; Trepos, R.; Frederich, M.; De Voogd, N.; Hellio, C.; Gauvin-Bialecki, A.; Al-Mourabit, A. New antimalarial and antimicrobial tryptamine derivatives from the marine sponge Fascaplysinopsis reticulata. *Mar. Drugs* **2019**, *17*, 167.
39. Ju, E.; Latif, A.; Kong, C.-S.; Seo, Y.; Lee, Y.-J.; Dalal, S.R.; Cassera, M.B.; Kingston, D.G. Antimalarial activity of the isolates from the marine sponge Hyrtios erectus against the chloroquine-resistant Dd2 strain of Plasmodium falciparum. *Z. Für Nat. C* **2018**, *73*, 397–400.
40. Shady, N.H.; Fouad, M.A.; Ahmed, S.; Pimentel-Elardo, S.M.; Nodwell, J.R.; Kamel, M.S.; Abdelmohsen, U.R. A new antitrypanosomal alkaloid from the Red Sea marine sponge Hyrtios sp. *J. Antibiot.* **2018**, *71*, 1036–1039.
41. Chianese, G.; Silber, J.; Luciano, P.; Merten, C.; Erpenbeck, D.; Topaloglu, B. l.; Kaiser, M.; Tasdemir, D. Antiprotozoal linear furanosesterterpenoids from the marine sponge Ircinia oros. *J. Nat. Prod.* **2017**, *80*, 2566–2571.
42. Majer, T.; Bhattarai, K.; Straetener, J.; Pohlmann, J.; Cahill, P.; Zimmermann, M.O.; Hübner, M.P.; Kaiser, M.; Svenson, J.; Schindler, M. Discovery of Ircinianin Lactones B and C—Two New Cyclic Sesterterpenes from the Marine Sponge Ircinia wistarii. *Mar. Drugs* **2022**, *20*, 532.
43. Kurimoto, S.-i.; Ohno, T.; Hokari, R.; Ishiyama, A.; Iwatsuki, M.; Ōmura, S.; Kobayashi, J. i.; Kubota, T. Ceratinadins E and F, new bromotyrosine alkaloids from an Okinawan marine sponge Pseudoceratina sp. *Mar. Drugs* **2018**, *16*, 463.
44. Campos, P.-E.; Wolfender, J.-L.; Queiroz, E.F.; Marcourt, L.; Al-Mourabit, A.; Frederich, M.; Bordignon, A.; De Voogd, N.; Illien, B.; Gauvin-Bialecki, A. Unguiculin A and ptilomycalins E–H, antimalarial guanidine alkaloids from the marine sponge Monanchora unguiculata. *J. Nat. Prod.* **2017**, *80*, 1404–1410.
45. Sala, S.; Fromont, J.; Gomez, O.; Vuong, D.; Lacey, E.; Flematti, G.R. Albanitriles A–G: Antiprotozoal Polyacetylene Nitriles from a Mycale Marine Sponge. *J. Nat. Prod.* **2019**, *82*, 3450–3455.
46. Parra, L.L.; Bertonha, A.F.; Severo, I.R.; Aguiar, A.C.; de Souza, G.E.; Oliva, G.; Guido, R.V.; Grazzia, N.; Costa, T.R.; Miguel, D.C. Isolation, derivative synthesis, and structure–activity relationships of antiparasitic bromopyrrole alkaloids from the marine sponge Tedania brasiliensis. *J. Nat. Prod.* **2018**, *81*, 188–202.
47. Murtihapsari, M.; Salam, S.; Kurnia, D.; Darwati, D.; Kadarusman, K.; Abdullah, F.F.; Herlina, T.; Husna, M.H.; Awang, K.; Shiono, Y. A new antiplasmodial sterol from Indonesian marine sponge, Xestospongia sp. *Nat. Prod. Res.* **2021**, *35*, 937–944.
48. Fro¨hlich, T.; Çapcı Karago¨z, A.; Reiter, C.; Tsogoeva, S.B. Artemisinin-derived dimers: Potent antimalarial and anticancer agents. *J. Med. Chem.* **2016**, *59*, 7360–7388.
49. Limon, A.-C. D.; Patabendige, H.M.; Azhari, A.; Sun, X.; Kyle, D.E.; Wilson, N.G.; Baker, B.J. Chemistry and Bioactivity of the Deep-Water Antarctic Octocoral Alcyonium sp. *Mar. Drugs* **2022**, *20*, 576.
50. Wright, A.E.; Collins, J.E.; Roberts, B.; Roberts, J.C.; Winder, P.L.; Reed, J.K.; Diaz, M.C.; Pomponi, S.A.; Chakrabarti, D. Antiplasmodial compounds from deep-water marine invertebrates. *Mar. Drugs* **2021**, *19*, 179.
51. Lima, M.L.; Romanelli, M.M.; Borborema, S.E.; Johns, D.M.; Migotto, A.E.; Lago, J.H.G.; Tempone, A.G. Antitrypanosomal activity of isololiolide isolated from the marine hydroid Macrorhynchia philippina (Cnidaria, Hydrozoa). *Bioorganic Chem.* **2019**, *89*, 103002.
52. Thomas, S.A.; Von Salm, J.L.; Clark, S.; Ferlita, S.; Nemani, P.; Azhari, A.; Rice, C.A.; Wilson, N.G.; Kyle, D.E.; Baker, B.J. Keikipukalides, furanocembrane diterpenes from the Antarctic deep sea octocoral Plumarella delicatissima. *J. Nat. Prod.* **2018**, *81*, 117–123.
53. Pham, G.N.; Kang, D.Y.; Kim, M.J.; Han, S.J.; Lee, J.H.; Na, M. Isolation of sesquiterpenoids and steroids from the soft coral sinularia brassica and determination of their absolute configuration. *Mar. Drugs* **2021**, *19*, 523.
54. Qin, G.-F.; Tang, X.-L.; Sun, Y.-T.; Luo, X.-C.; Zhang, J.; Van Ofwegen, L.; Sung, P.-J.; Li, P.-L.; Li, G.-Q. Terpenoids from the soft coral Sinularia sp. collected in Yongxing Island. *Mar. Drugs* **2018**, *16*, 127.

55. Kleks, G.; Holland, D.C.; Kennedy, E.K.; Avery, V.M.; Carroll, A.R. Antiplasmodial alkaloids from the Australian bryozoan Amathia lamourouxi. *J. Nat. Prod.* **2020**, *83*, 3435–3444.
56. Kleks, G.; Duffy, S.; Lucantoni, L.; Avery, V.M.; Carroll, A.R. Orthoscuticellines A–E, β-Carboline Alkaloids from the Bryozoan Orthoscuticella ventricosa Collected in Australia. *J. Nat. Prod.* **2020**, *83*, 422–428.
57. Cartuche, L.; Sifaoui, I.; Cruz, D.; Reyes-Batlle, M.; López-Arencibia, A.; Javier Fernández, J.; Díaz-Marrero, A.R.; Piñero, J.E.; Lorenzo-Morales, J. Staurosporine from Streptomyces sanyensis activates programmed cell death in Acanthamoeba via the mitochondrial pathway and presents low in vitro cytotoxicity levels in a macrophage cell line. *Sci. Rep.* **2019**, *9*, 1–12.
58. Martens, M.C.; Liu, Y.; Sanford, A.G.; Wallick, A.I.; Warner, R.C.; Li, R.; Davis, P.H. Analogs of Marinopyrrole A Show Enhancement to Observed In Vitro Potency against Acute Toxoplasma gondii Infection. *Antimicrob. Agents Chemother.* **2022**, *66*, e00794-21.
59. Martínez-Luis, S.; Cherigo, L.; Spadafora, C.; Gutiérrez, M. Antiparasitic Compounds from the Panamanian Marine Bacterium Pseudomonas aeruginosa. *Nat. Prod. Commun.* **2019,** *14*, 1934578X1901400109.
60. Iwasaki, A.; Ohtomo, K.; Kurisawa, N.; Shiota, I.; Rahmawati, Y.; Jeelani, G.; Nozaki, T.; Suenaga, K. Isolation, structure determination, and total synthesis of hoshinoamide c, an antiparasitic lipopeptide from the marine cyanobacterium Caldora penicillata. *J. Nat. Prod.* **2020**, *84*, 126–135.
61. Iwasaki, A.; Teranuma, K.; Kurisawa, N.; Rahmawati, Y.; Jeelani, G.; Nozaki, T.; Gerwick, W.H.; Suenaga, K. First Total Synthesis and Structure–Activity Relationship of Iheyamide A, an Antitrypanosomal Linear Peptide Isolated from a Dapis sp. Marine Cyanobacterium. *J. Nat. Prod.* **2021**, *84*, 2587–2593.
62. Kurisawa, N.; Iwasaki, A.; Jeelani, G.; Nozaki, T.; Suenaga, K. Iheyamides A–C, antitrypanosomal linear peptides isolated from a marine Dapis sp. cyanobacterium. *J. Nat. Prod.* **2020**, *83*, 1684–1690.
63. Takahashi, H.; Iwasaki, A.; Kurisawa, N.; Suzuki, R.; Jeelani, G.; Matsubara, T.; Sato, T.; Nozaki, T.; Suenaga, K. Motobamide, an antitrypanosomal cyclic peptide from a Leptolyngbya sp. marine cyanobacterium. *J. Nat. Prod.* **2021**, *84*, 1649–1655.
64. Keller, L.; Siqueira-Neto, J.L.; Souza, J.M.; Eribez, K.; LaMonte, G.M.; Smith, J.E.; Gerwick, W.H. Palstimolide A: A complex polyhydroxy macrolide with antiparasitic activity. *Molecules* **2020**, *25*, 1604.
65. Iwasaki, K.; Iwasaki, A.; Sumimoto, S.; Matsubara, T.; Sato, T.; Nozaki, T.; Saito-Nakano, Y.; Suenaga, K. Ikoamide, an antimalarial lipopeptide from an Okeania sp. marine cyanobacterium. *J. Nat. Prod.* **2020**, *83*, 481–488.
66. Ozaki, K.; Iwasaki, A.; Sezawa, D.; Fujimura, H.; Nozaki, T.; Saito-Nakano, Y.; Suenaga, K.; Teruya, T. Isolation and total synthesis of mabuniamide, a lipopeptide from an Okeania sp. marine cyanobacterium. *J. Nat. Prod.* **2019**, *82*, 2907–2915.
67. Kurisawa, N.; Otomo, K.; Iwasaki, A.; Jeelani, G.; Nozaki, T.; Suenaga, K. Isolation and Total Synthesis of Kinenzoline, an Antitrypanosomal Linear Depsipeptide Isolated from a Marine Salileptolyngbya sp. Cyanobacterium. *J. Org. Chem.* **2021**, *86*, 12528–12536.
68. Almaliti, J.; Malloy, K.L.; Glukhov, E.; Spadafora, C.; Gutiérrez, M.; Gerwick, W.H. Dudawalamides A–D, antiparasitic cyclic depsipeptides from the marine cyanobacterium Moorea producens. *J. Nat. Prod.* **2017**, *80*, 1827–1836.
69. Bunbamrung, N.; Intaraudom, C.; Dramae, A.; Komwijit, S.; Laorob, T.; Khamsaeng, S.; Pittayakhajonwut, P. Antimicrobial, antimalarial and anticholinesterase substances from the marine-derived fungus Aspergillus terreus BCC51799. *Tetrahedron* **2020**, *76*, 131496.
70. Xu, W.-F.; Wu, N.-N.; Wu, Y.-W.; Qi, Y.-X.; Wei, M.-Y.; Pineda, L.M.; Ng, M.G.; Spadafora, C.; Zheng, J.-Y.; Lu, L. Structure modification, antialgal, antiplasmodial, and toxic evaluations of a series of new marine-derived 14-membered resorcylic acid lactone derivatives. *Mar. Life Sci. Technol.* **2022**, *4*, 88–97.
71. Coronado, L.; Zhang, X.-Q.; Dorta, D.; Escala, N.; Pineda, L.M.; Ng, M.G.; Del Olmo, E.; Wang, C.-Y.; Gu, Y.-C.; Shao, C.-L. Semisynthesis, antiplasmodial activity, and mechanism of action studies of isocoumarin derivatives. *J. Nat. Prod.* **2021**, *84*, 1434–1441.
72. Braun, G.H.; Ramos, H.P.; Candido, A.C.; Pedroso, R.C.; Siqueira, K.A.; Soares, M.A.; Dias, G.M.; Magalhães, L.G.; Ambrósio, S.R.; Januário, A.H. Evaluation of antileishmanial activity of harzialactone a isolated from the marine-derived fungus Paecilomyces sp. *Nat. Prod. Res.* **2021**, *35*, 1644–1647.
73. Morales-Landa, J.L.; Lazcano-Pérez, F.; Cedillo-Rivera, R.; Sánchez-Rodríguez, J. Ultrastructure and molecular toxicological effects of the Coronate Scyphomedusa Linuche unguiculata Venom on Giardia duodenalis. *Biologia* **2021**, *76*, 1033–1039.
74. Shamikh, Y.I.; El Shamy, A.A.; Gaber, Y.; Abdelmohsen, U.R.; Madkour, H.A.; Horn, H.; Hassan, H.M.; Elmaidomy, A.H.; Alkhalifah, D.H.M.; Hozzein, W.N. Actinomycetes from the Red Sea sponge Coscinoderma mathewsi: Isolation, diversity, and potential for bioactive compounds discovery. *Microorganisms* **2020**, *8*, 783.
75. McCarthy, P.J.; Roberts, B.F.; Carbonell, A.; Roberts, J.; Wright, A.E.; Chakrabarti, D. Marine microbiome as a source of antimalarials. *Trop. Med. Infect. Dis.* **2019**, *4*, 103.
76. Quintero, M.; Blandón, L.M.; Vidal, O.M.; Guzman, J.D.; Gómez-Marín, J.E.; Patiño, A.D.; Molina, D.A.; Puerto-Castro, G.M.; Gómez-León, J. In vitro biological activity of extracts from marine bacteria cultures against Toxoplasma gondii and Mycobacterium tuberculosis. *J. Appl. Microbiol.* **2022**, *132*, 2705–2720.
77. Alkhalifah, D.H.M. Sponge-associated sp. RM66 metabolome induction with N-acetylglucosamine: Antibacterial, antifungal and anti-trypanosomal activities. *Saudi J. Biol. Sci.* **2021**, *28*, 4691–4698.
78. Santos, J.D.; Vitorino, I.; de la Cruz, M.; Díaz, C.; Cautain, B.; Annang, F.; Pérez-Moreno, G.; Gonzalez, I.; Tormo, J.R.; Martin, J. Diketopiperazines and other bioactive compounds from bacterial symbionts of marine sponges. *Antonie Van Leeuwenhoek* **2020**, *113*, 875–887.

79. Ghania, A.; Nabila, B.-B.; Larbi, B.; Elisabeth, M.; Philippe, G.; Mariem, B.; Khadidja, K.-K.; Wacila, B.-R.; Fawzia, A.-B. Antimicrobial and antiparasitic activities of three algae from the northwest coast of Algeria. *Nat. Prod. Res.* **2019**, *33*, 742–745.
80. Chiboub, O.; Ktari, L.; Sifaoui, I.; López-Arencibia, A.; Reyes-Batlle, M.; Mejri, M.; Valladares, B.; Abderrabba, M.; Piñero, J.E.; Lorenzo-Morales, J. In vitro amoebicidal and antioxidant activities of some Tunisian seaweeds. *Exp. Parasitol.* **2017**, *183*, 76–80.
81. Stein, E.M.; Tajú, S.G.; Miyasato, P.A.; de Freitas, R.P.; Tallarico, L. d. F.; Dos Santos, G.S.; Luiz, G.L.; Rofatto, H.K.; da Silva, F.N.; Colepicolo, P. The prospective use of Brazilian marine macroalgae in schistosomiasis control. *Mar. Drugs* **2021**, *19*, 234.
82. Saini, A.; Kumar, S.; Raj, R.; Chowdhary, S.; Gendrot, M.; Mosnier, J.; Fonta, I.; Pradines, B.; Kumar, V. Synthesis and antiplasmodial evaluation of 1H-1, 2, 3-triazole grafted 4-aminoquinoline-benzoxaborole hybrids and benzoxaborole analogues. *Bioorganic Chem.* **2021**, *109*, 104733.
83. Wilson, D.W.; Langer, C.; Goodman, C.D.; McFadden, G.I.; Beeson, J.G. Defining the timing of action of antimalarial drugs against Plasmodium falciparum. *Antimicrob. Agents Chemother.* **2013**, *57*, 1455–1467.
84. Dalisay, D.S.; Williams, D.E.; Wang, X.L.; Centko, R.; Chen, J.; Andersen, R.J. Marine sediment-derived Streptomyces bacteria from British Columbia, Canada are a promising microbiota resource for the discovery of antimicrobial natural products. *PLoS One* **2013**, *8*, e77078.
85. Subramani, R.; Aalbersberg, W. Marine actinomycetes: An ongoing source of novel bioactive metabolites. *Microbiol. Res.* **2012**, *167*, 571–580.
86. Hancock, R.E. Resistance mechanisms in Pseudomonas aeruginosa and other nonfermentative gram-negative bacteria. *Clin. Infect. Dis.* **1998,** *27* (Suppl. 1), S93–S99.
87. Haste, N.M.; Hughes, C.C.; Tran, D.N.; Fenical, W.; Jensen, P.R.; Nizet, V.; Hensler, M.E. Pharmacological properties of the marine natural product marinopyrrole A against methicillin-resistant Staphylococcus aureus. *Antimicrob. Agents Chemother.* **2011**, *55*, 3305–3312.
88. Khan, N.A. Pathogenesis of Acanthamoeba infections. *Microb. Pathog.* **2003**, *34*, 277–285.
89. Lorenzo-Morales, J.; Martín-Navarro, C.M.; López-Arencibia, A.; Arnalich-Montiel, F.; Piñero, J.E.; Valladares, B. Acanthamoeba keratitis: An emerging disease gathering importance worldwide? *Trends Parasitol.* **2013**, *29*, 181–187.
90. Antonsson, A.; Persson, J.L. Induction of apoptosis by staurosporine involves the inhibition of expression of the major cell cycle proteins at the G2/M checkpoint accompanied by alterations in Erk and Akt kinase activities. *Anticancer Res.* **2009**, *29*, 2893–2898.
91. Wang, B.; Waters, A.L.; Sims, J.W.; Fullmer, A.; Ellison, S.; Hamann, M.T. Complex marine natural products as potential epigenetic and production regulators of antibiotics from a marine Pseudomonas aeruginosa. *Microb. Ecol.* **2013**, *65*, 1068–1075.
92. Aly, A.H.; Debbab, A.; Proksch, P. Fungal endophytes: Unique plant inhabitants with great promises. *Appl. Microbiol. Biotechnol.* **2011**, *90*, 1829–1845.
93. Hyde, K.; Soytong, K. The fungal endophyte dilemma. *Fungal Divers* **2008**, *33*, e173.
94. Bhadury, P.; Mohammad, B.T.; Wright, P.C. The current status of natural products from marine fungi and their potential as anti-infective agents. *J. Ind. Microbiol. Biotechnol.* **2006**, *33*, 325.
95. Debbab, A.; Aly, A.H.; Proksch, P. Bioactive secondary metabolites from endophytes and associated marine derived fungi. *Fungal Divers.* **2011**, *49*, 1–12.
96. Singh, R.P.; Kumari, P.; Reddy, C. Antimicrobial compounds from seaweeds-associated bacteria and fungi. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 1571–1586.
97. Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; NUMATA, A. Cytotoxic substances produced by a fungal strain from a sponge: Physico-chemical properties and structures. *J. Antibiot.* **1998**, *51*, 33–40.
98. Rivas, L.; Rojas, V. Cyanobacterial peptides as a tour de force in the chemical space of antiparasitic agents. *Arch. Biochem. Biophys.* **2019**, *664*, 24–39.
99. Demay, J.; Bernard, C.; Reinhardt, A.; Marie, B. Natural products from cyanobacteria: Focus on beneficial activities. *Mar. Drugs* **2019**, *17*, 320.
100. Niedermeyer, T.H.J. Anti-infective natural products from cyanobacteria. *Planta Med.* **2015**, *81*, 1309–1325.
101. Horton, D.A.; Bourne, G.T.; Smythe, M.L. Exploring privileged structures: The combinatorial synthesis of cyclic peptides. *J. Comput. -Aided Mol. Des.* **2002**, *16*, 415–431.
102. Sawadogo, W.R.; Boly, R.; Cerella, C.; Teiten, M.H.; Dicato, M.; Diederich, M. A survey of marine natural compounds and their derivatives with anti-cancer activity reported in 2012. *Molecules* **2015**, *20*, 7097–7142.
103. Walvekar, S.; Anwar, A.; Anwar, A.; Lai, N.J.Y.; Yow, Y.-Y.; Khalid, M.; Siddiqui, R.; Khan, N.A. Conjugation with Silver Nanoparticles Enhances Anti-Acanthamoebic Activity of Kappaphycus alvarezii. *J. Parasitol.* **2021**, *107*, 537–546.
104. Mayer, A.M.; 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. Part C: Toxicol. Pharmacol.* **2005**, *140*, 265–286.