REVIEW ARTICLE

A C G publications

Rec. Nat. Prod. 11:2 (2017) 92-113

records of natural products

Antileishmanial Marine Compounds: A Review

Paulo H.B. França[1,2], Edeildo F. da Silva-Júnior[1,2], Bárbara V.O. Santos[3], Magna S. Alexandre-Moreira[4], Lucindo J. Quintans-Júnior[5], Thiago M. de Aquino[1] and João X. de Araújo-Júnior[1,2*]

[1] *Chemistry and Biotechnology Institute, Federal University of Alagoas, CEP 57020-720, Maceió, AL, Brazil*

[2] *Laboratory of Medicinal Chemistry, School of Nursing and Pharmacy, Federal University of Alagoas, CEP 57020-720, Maceió, AL, Brazil.*

[3] *Post-Graduate Program in Natural Products and Bioactive Synthetics, Federal University of Paraiba, CEP 58051-900, João Pessoa, PB, Brazil*

[4] *Laboratory of Pharmacology and Immunity, Institute of Biological Sciences and Health, Federal University of Alagoas, CEP 57020-720, Maceió, AL, Brazil.*

[5] *Post-Graduate Program in Health Science, Federal University of Sergipe, CEP 57020-720, Aracaju, Brazil*

(Received January 21, 2016; Revised June 14, 2016; Accepted June 15, 2016)

Abstract: Leishmaniasis is widely ignored in discussions on the priorities of tropical diseases, and the already-existing drugs present high toxicity or teratogenicity, as well as reduced efficacy due to the emergence of resistant strains. Marine natural products have received increasing attention over the last few decades because of the isolation of metabolites found in many products, with structural pattern not available in terrestrial organisms. Several molecules of marine origin have been investigated in respect of their effects on different species of parasites that cause leishmaniasis. In this study, we review the pharmacological information obtained from the in vitro and in vivo assays on such metabolites.

Keywords: Leishmaniasis; marine compounds; inflammation.

1. Introduction

There are 3 main forms of leishmaniases: cutaneous, mucocutaneous and visceral. The disease is prevalent in 98 countries in 5 continents. Around 1.3 million cases occur annually, of which 1 million are cutaneous or mucocutaneous. More than 90% of the cases of visceral leishmaniasis, the most dangerous form of the disease, occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan. Cutaneous leishmaniasis, on the other hand, occurs mainly in Afghanistan, Algeria, Saudi Arabia, Brazil, Colombia, Iran, Pakistan, Syria and Tunisia, while mucocutaneous leishmaniasis occurs almost solely in Latin America, with around 90% of the cases in Bolivia, Brazil and Peru. It has been estimated that between 20.000 and 30.000 individuals are killed by visceral leishmaniasis annually [1].

*Corresponding author: E-Mail: jotaaraujo2004@gmail.com; Phone: +55-82-99901-9991.

The article was published by Academy of Chemistry of Globe Publications
www.acgpubs.org/rnp © Published 12/24/2016

Although the diversity of life in the terrestrial environment is extraordinary, the greatest biodiversity isin the world's oceans, with 34 of the 36 phyla of life represented. The oceans cover more than 70% of the earth's surface and contain more than 300.000 described species of plants and animals. In addition to the chemical novelty associated with these compounds [2-4], some of them also possess novel mechanisms of action [5,6].

In the early 1950s, the discovery and identification of spongothymidine and spongouridine from the Caribbean sponge *Tethya crypta* as bioactive molecules led research into natural products in a new direction. Since then, several molecules of marine origin have been investigated in pre-clinical and clinical assays with specific therapeutic purposes [7], culminating in the approval for the trade of drugs based on marine products [5].

A review of the methods for the discovery of natural products of marine origin targeting antileishmanial was developed by Tempone *et al*. in 2011 [8]. Additionally, Mayer *et al*. reviewed the pharmacological activities of marine metabolites between the years 2009 and 2011, including activities against protozoa [9]. However, some articles containing substances with antileishmanial potential have not been included in these reviews. Hence, we propose to update the pharmacological information available on marine metabolites, keeping the focus on activity related to antileishmanial and organizing the data for a better comparison of the results obtained.

2. Materials and Methods

The literature search was performed through specialized search databases (Scifinder,Scopus, Web of Science and Google Schoolar) using different combinations of the following keywords: "Leishmania", "marine", "metabolite(s)" and "activity". The manuscript selection was based on the following inclusion criteria: articles published in English and articles with the keywords in the title, abstract or full text, as well as studies with isolated compounds. There was no restriction concerning the publication periods and only the studies reviewed by two investigators were selected. This resulted in the identification of several studies. From these results, two independent investigators then selected articles according to the title. They then read the abstract, and if the article met the inclusion criteria completed an analysis of the full-text.

3. Results and Discussion

The information collected in the articles is shown in Table 1, in which the metabolites were organized by means of chemical classification into alkaloids, peptides, polyketides, steroids and terpenoids. The organisms from which the natural products were isolated were also included in this table. The IC_{50} values are related to the micromolar concentration for a better comparison of the pharmacological strength. To do this, the IC_{50} values of several compounds expressed in μM were converted into μg mL^{-1}. The molecular mass used in the conversion process was calculated based on the structures designed on the free application ACD/Chemsketch, considering up to two decimal places. The second decimal place was added to a unit when the value of the third place was higher or equal to 5.

3.1. Natural products with antileishmanial activity

3.1.1. Alkaloids

The alkaloids isolated from the sponge *Agelas mauritiana* showed inhibitory activity towards the promastigotes of *L. donovani*. The (−)-ageloxime D (**1**) compound presented an IC_{50} value of 29.28 μg mL^{-1} and an IC_{90} value of 33.96 μg mL^{-1}. The second alkaloid, ageloxime B (**2**), showed IC_{50} and IC_{90} values of 28.55 and 33.19 μg mL^{-1} respectively [10].

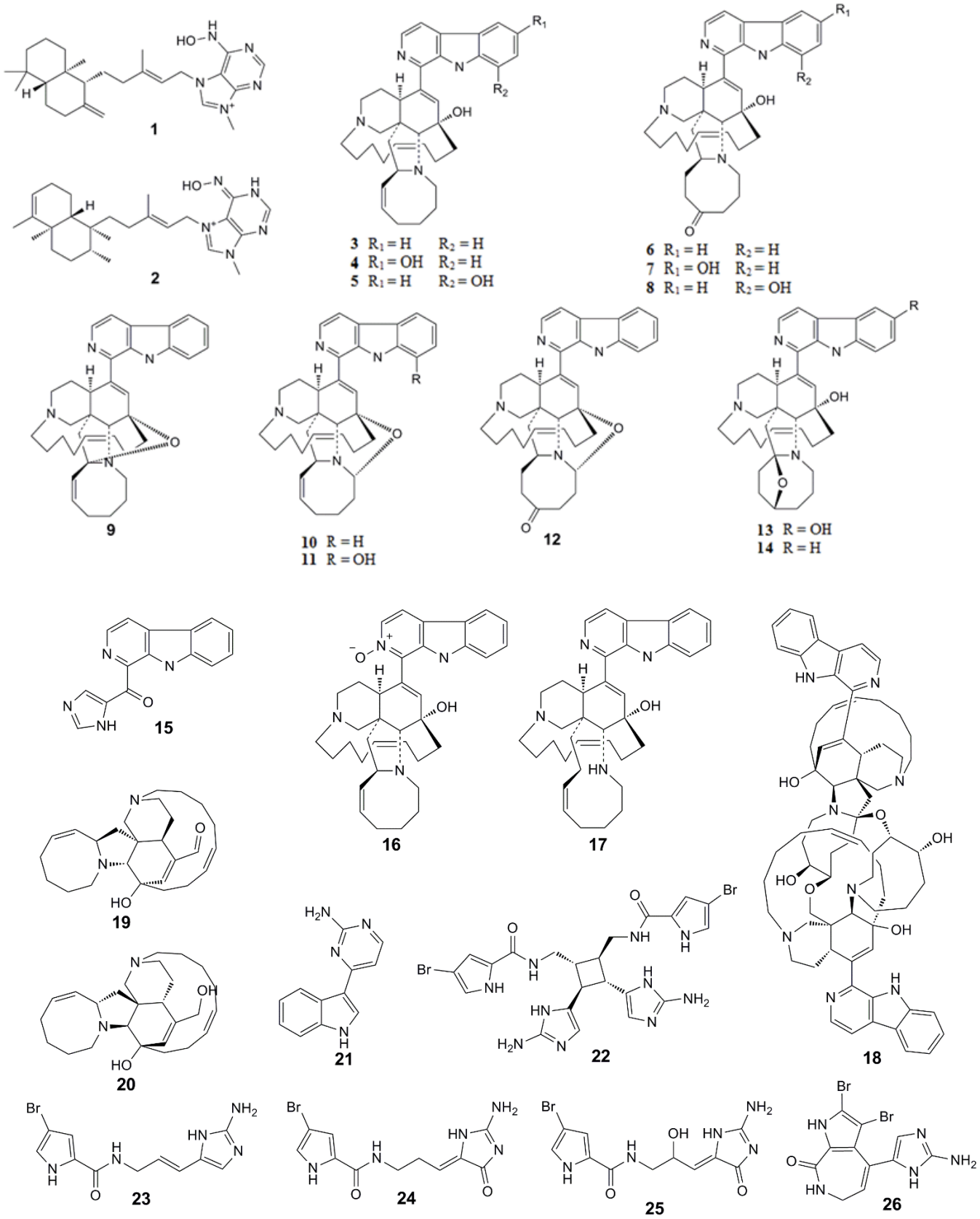

Figure 1. Alkaloids of marine origin with antileishmanial activity.

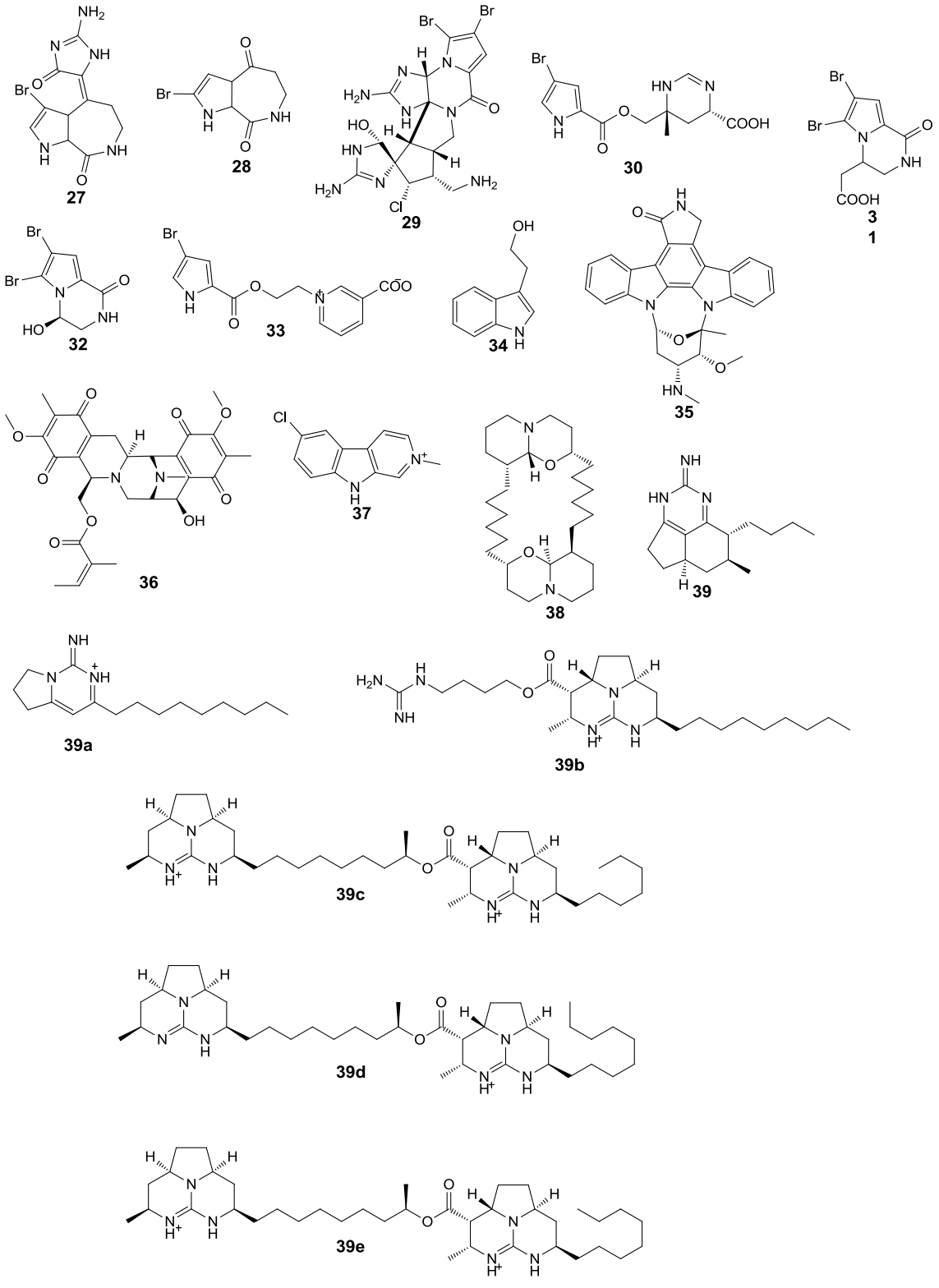

Figure 1. *Continuation*

Table 1. Metabolites of marine organisms with antileishmanial activity.

Class	Compound	Organism/Species	IC_{50} (μg mL^{-1})		Protozoa	Ref.[a]
			Promastigote	Amastigote		
Alkaloid	(−)-Ageloxime D (**1**)	Sponge (*Agelas mauritiana*)	29.28	NC	*L. donovani*	[10]
	Ageloxime B (**2**)	Sponge (*Agelas mauritiana*)	28.55	NC	*L. donovani*	[10]
	Manzamine A (**3**)	Sponge (*Acanthostrongylophora* sp. and *Petrosiidae* sp.)	0.9	NC	*L. donovani*	[11–13]
	Manzamine Y (**4**)	Sponge (*Acanthostrongylophora* sp.)	1.6	NC	*L. donovani*	[11]
	(+)-8-Hydroxymanzamine A (**5**)	Sponge (*Acanthostrongylophora* sp. and *Petrosiidae* sp.)	6.2	NC	*L. donovani*	[11–13]
	Manzamine E (**6**)	Sponge (*Acanthostrongylophora* sp. and *Petrosiidae* sp.)	3.8	NC	*L. donovani*	[11–13]
	6-Hydroxymanzamine E (**7**)	Sponge (*Acanthostrongylophora* sp.)	2.5	NC	*L. donovani*	[11,13]
	Manzamine F (**8**)	Sponge (*Acanthostrongylophora* sp. and *Petrosiidae* sp.)	4.2	NC	*L. donovani*	[11–13]
	12,34-oxamanzamine A (**9**)	Sponge (*Acanthostrongylophora* sp. and *Petrosiidae* sp.)	141	NC	*L. donovani*	[11,12]
	12,28-oxamanzamine A (**10**)	Sponge (*Acanthostrongylophora* sp.)	7.8	NC	*L. donovani*	[11]
	12,28-oxa-8-hydroxy-manzamine A (**11**)	Sponge (*Acanthostrongylophora* sp.)	24	NC	*L. donovani*	[11]
	12,28-Oxamanzamine E (**12**)	Sponge (*Acanthostrongylophora* sp.)	18	NC	*L. donovani*	[11]
	Manzamine X (**13**)	Sponge (*Petrosiidae* sp.)	5.7	NC	*L. donovani*	[12,13]
	6-Deoxymanzamine X (**14**)	Sponge (*Petrosiidae* sp.)	3.2	NC	*L. donovani*	[12,13]
	Des-*N*-methylxestomanzamine A (**15**)	Sponge (*Petrosiidae* sp.)	35	NC	*L. donovani*	[12]
	Manzamine A *N*-oxide (**16**)	Sponge (*Acanthostrongylophora* sp.)	1.1	NC	*L. donovani*	[13]
	manzamine J (**17**)	Sponge (*Acanthostrongylophora* sp.)	25	NC	*L. donovani*	[13]
	neo-kauluamine (**18**)	Sponge (*Acanthostrongylophora* sp.)	4.2	NC	*L. donovani*	[13]
	ircinal A (**19**)	Sponge (*Acanthostrongylophora* sp.)	4.6	NC	*L. donovani*	[11,13]
	ircinol A (**20**)	Sponge (*Acanthostrongylophora* sp.)	0.9	NC	*L. donovani*	[11,13]
	Meridianin G (**21**)	Ascidian (*Aplidium meridianum*)	64.86	NC	*L. donovani*	[14]
	Sceptrin (**22**)	Sponge (*Agelas conifera, Agelas clathrodes, Agelas longissima, A. dispar*)	NC	51.58	*L. donovani*	[15]
	Hymenidin (**23**)	Sponge (*Agelas conifera, Agelas*	NC	29.87	*L. donovani*	[15]

		clathrodes, Agelas longissima, A. dispar)				
	Dispacamide B (**24**)	Sponge (*Agelas conifera, Agelas clathrodes, Agelas longissima, A. dispar*)	NC	> 90	*L. donovani*	[15]
	Dispacamide D (**25**)	Sponge (*Agelas conifera, Agelas clathrodes, Agelas longissima, A dispar*)	NC	53.75	*L. donovani*	[15]
	Stevensin (**26**)	Sponge (*Axinella verrucosa*)	NC	75.86	*L. donovani*	[15]
	Spongiacidin B (**27**)	Sponge (*Axinella verrucosa*)	NC	41.59	*L. donovani*	[15]
	Bromoaldisin (**28**)	Sponge (*Axinella verrucosa*)	NC	> 90	*L. donovani*	[15]
	Dibromopalau'amine (**29**)	Sponge (*Axinella verrucosa*)	NC	1.09	*L. donovani*	[15]
	Manzacidin A (**30**)	Sponge (*Axinella verrucosa*)	NC	75.83	*L. donovani*	[15]
	Longamide A (**31**)	Sponge (*Agelas longissima*)	NC	3.85	*L. donovani*	[15]
	Longamide B (**32**)	Sponge (*Agelas dispar*)	NC	> 90	*L. donovani*	[15]
	Agelongine (**33**)	Sponge (*Agelas* spp. and *Axinella* sp.)	NC	43.22	*L. donovani*	[15]
	Tryptophol (**34**)	Sponge (*Ircinia spiculosa*)	NC	9.6	*L. donovani*	[16,17]
	Staurosporine (**35**)	Fungus (*Streptomyces* sp.)	2.47	NC	*L. major*	[18]
	Renieramycin A (**36**)	Sponge (*Neopetrosia* sp.)	0.2	NC	*L. amazonensis*	[19]
	Nostocarboline (**37**)	Cyanobacterium (Nostoc 78-12A)	NC	7.47	*L. donovani*	[20]
Peptide	Almiramide B (**40**)	Cyanobacterium (*Lyngbya majuscula*)	NC	1.74	*L. donovani*	[21]
	Almiramide C (**41**)	Cyanobacterium (*Lyngbya majuscula*)	NC	1.38	*L. donovani*	[21]
	Dragonamide A (**42**)	Cyanobacterium (*Lyngbya majuscula*)	NC	4.25	*L. donovani*	[22]
	Dragonamide E (**43**)	Cyanobacterium (*Lyngbya majuscula*)	NC	3.32	*L. donovani*	[22]
	Herbamide E (**44**)	Cyanobacterium (*Lyngbya majuscula*)	NC	2.42	*L. donovani*	[22]
	Kahalalide F (**45**)	Green seaweed (*Bryopsis* sp.) Mollusk (*Elysia rufescens*)	9.06 12.28	NC 43.64	*L. donovani* *L. pifanoi*	[25,26]
	Viridamide A (**46**)	Cyanobacterium (*Oscillatoria nigro-viridis*)	NC	1.29	*L. mexicana*	[25]
	Venturamide A (**47**)	Cyanobacterium (*Oscillatoria* sp.)	NC	> 9.77	*L. donovani*	[26]
	Venturamide B (**48**)	Cyanobacterium (*Oscillatoria* sp.)	NC	> 9.85	*L. donovani*	[26]
	Tachyplesin I (**49**)	Horseshoe crab (*Tachypleus tridentatus*)	168.57 (5 h) 10.65 (24 h) 21.07 (72 h)	NC	*L. braziliensis*	[29,30]
	Mytilin A (**50**)	Mussel (*Mytilus edulis*)	155.63 (24 h) 174.24 (72 h)	NC	*L. braziliensis*	[30,31]
	IB-01212 (**51**)	Fungus (*Clonostachys* sp.)	10.85 NC	NC 7.34	*L. donovani* *L. pifanoi*	[32,33]

	Valinomycin (**52**)	Fungus (*Streptomyces* sp.)	< 0.12	NC	*L. major*	[18]
Polyketide	(3*S*,6*R*,8*S*)-4,6-Diethyl-3,6-epidioxy-8-methyldodeca-4-enoic acid (**53**)	Sponge (*Plakorth* aff. *angulospiculatus*)	0.29	NC	*L. mexicana*	[32]
	3,6-Epidioxy-4,6,8,10-tetraethyltetradeca-7,11-dienoic acid (**54**)	Sponge (*Plakorth* aff. *angulospiculatus*)	1	NC	*L. mexicana*	[32]
	Methyl (2Z,6R,8S)-4,6-diethyl-3,6-epoxy-8-methydodeca-2,4-dienoate (**55**)	Sponge (*Plakorth* aff. *angulospiculatus*)	1.86	NC	*L. mexicana*	[32]
	Methyl (2Z,6R,8S)-3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**56**)	Sponge (*Plakorth* aff. *angulospiculatus*)	2.71	NC	*L. mexicana*	[32]
	Plakortide P (**57**)	Sponge (*Plakortis angulospiculatus*)	1.9	0.5	*L. chagasi*	[33]
	(2Z,6R,8R,9E)-Methyl 3,6-epoxy-4,6,8-tri-ethyl-2,4,9-dodecatrienoate (**58**)	Sponge (*Plakortis angulospiculatus*)	8.5	1.6	*L. chagasi*	[33]
	Spongosoritin A (**59**)	Sponge (*Plakortis angulospiculatus*)	2.5	3.1	*L. chagasi*	[33]
	(2E,6R,8S)-Methyl 3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**60**)	Sponge (*Plakortis angulospiculatus*)	3.9	3.4	*L. chagasi*	[33]
	Coibacin A (**61**)	Cyanobacterium (*Oscillatoria* sp.)	NC	0.68	*L. donovani*	[34]
	Coibacin B (**62**)	Cyanobacterium (*Oscillatoria* sp.)	NC	1.86	*L. donovani*	[34]
	Coibacin C (**63**)	Cyanobacterium (*Oscillatoria* sp.)	NC	4.99	*L. donovani*	[34]
	Coibacin D (**64**)	Cyanobacterium (*Oscillatoria* sp.)	NC	2.10	*L. donovani*	[34]
	Simplexolide B (**65**)	Sponge (*Plakortis simplex*)	13.82	NC	*L. donovani*	[35]
	(2Z,6R,8R,9E)-[3-ethyl-5-(2-ethyl-hex-3-enyl)-6-ethyl-5H-furan-2-ylidene]-acetic acid methyl ester (**66**)	Sponge (*Plakortis simplex*)	38.56	NC	*L. donovani*	[35]
	methyl (2Z,6R,8S)-4,6-diethyl-3,6-epoxy-8-methyldeca-2,4-dienoate (**67**)	Sponge (*Plakortis simplex*)	31.24	NC	*L. donovani*	[35]
	methyl (2Z,6R,8S)-3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**68**)	Sponge (*Plakortis simplex*)	20.2	NC	*L. donovani*	[35]
	(2Z,6R,8R,9E)[3-ethyl-5-(2-ethyl-	Sponge (*Plakortis simplex*)	7.11	NC	*L. donovani*	[35]

	hex-3-enyl)-6-methyl-5H-furan-2-ylidene]-acetic acid methyl ester (**69**)					
	Pseudopyronine A (**70**)	Bacterium (*Pseudomonas* sp.)	NC	2.63	*L. donovani*	[38,39]
	Pseudopyronine B (**71**)	Bacterium (*Pseudomonas* sp.)	NC	1.38	*L. donovani*	[38,39]
	(*E*)-2-(Hept-1-enyl)-3-(hydroxymethyl)-5-(3-methylbut-2-enyl)benzene-1,4-diol (**72**)	Fungus (*Eurotium repens*)	19	NC	*L. donovani*	[38]
	Flavoglaucin (**73**)	Fungus (*Eurotium repens*)	23	NC	*L. donovani*	[38]
	Tetrahydroauroglaucin (**74**)	Fungus (*Eurotium repens*)	22	NC	*L. donovani*	[38]
	Dihydroauroglaucin (**75**)	Fungus (*Eurotium repens*)	20	NC	*L. donovani*	[38]
	Auroglaucin (**76**)	Fungus (*Eurotium repens*)	7.5	NC	*L. donovani*	[38]
	2-(2′,3-Epoxy-1′,3′-heptadienyl)-6-hydroxy-5-(3-methyl-2-butenyl)benzaldehyde (**77**)	Fungus (*Eurotium repens*)	6.2	NC	*L. donovani*	[38]
	Tetromycin derivative (**78**)	Fungus (*Streptomyces axinellae*)	31.68	NC	*L. major*	[39]
	Chaetoxanthone A (**79**)	Fungus (*Chaetomium* sp.)	NC	5.3	*L. donovani*	[40]
	Chaetoxanthone B (**80**)	Fungus (*Chaetomium* sp.)	NC	3.4	*L. donovani*	[40]
	Chaetoxanthone C (**81**)	Fungus (*Chaetomium* sp.)	NC	3.1	*L. donovani*	[40]
Steroid	Pandaroside A (**82**)	Sponge (*Pandaros acanthifolium*)	NC	15.70	*L. donovani*	[41]
	Pandaroside A methyl ester (**83**)	Sponge (*Pandaros acanthifolium*)	NC	53.77	*L. donovani*	[41]
	Pandaroside B (**84**)	Sponge (*Pandaros acanthifolium*)	NC	NC	*L. donovani*	[41]
	Pandaroside C (**85**)	Sponge (*Pandaros acanthifolium*)	NC	> 92.27	*L. donovani*	[41]
	Pandaroside C methyl ester (**86**)	Sponge (*Pandaros acanthifolium*)	NC	34.60	*L. donovani*	[41]
	Pandaroside D (**87**)	Sponge (*Pandaros acanthifolium*)	NC	18.81	*L. donovani*	[41]
	Pandaroside D methyl ester (**88**)	Sponge (*Pandaros acanthifolium*)	NC	8.50	*L. donovani*	[41]
	Pandaroside E (**89**)	Sponge (*Pandaros acanthifolium*)	NC	11.91	*L. donovani*	[41]
	Pandaroside E methyl ester (**90**)	Sponge (*Pandaros acanthifolium*)	NC	31.51	*L. donovani*	[41]
	Pandaroside F (**91**)	Sponge (*Pandaros acanthifolium*)	NC	3.23	*L. donovani*	[41]
	Pandaroside F methyl ester (**92**)	Sponge (*Pandaros acanthifolium*)	NC	20.50	*L. donovani*	[41]
	Pandaroside G (**93**)	Sponge (*Pandaros acanthifolium*)	NC	0.97	*L. donovani*	[41,42]
	Pandaroside G methyl ester (**94**)	Sponge (*Pandaros acanthifolium*)	NC	0.04	*L. donovani*	[41,42]
	Pandaroside H (**95**)	Sponge (*Pandaros acanthifolium*)	NC	35.07	*L. donovani*	[41]
	Pandaroside H methyl ester (**96**)	Sponge (*Pandaros acanthifolium*)	NC	12.62	*L. donovani*	[41]
	Pandaroside I (**97**)	Sponge (*Pandaros acanthifolium*)	NC	28.11	*L. donovani*	[41]
	Pandaroside I methyl ester (**98**)	Sponge (*Pandaros acanthifolium*)	NC	22.82	*L. donovani*	[41]
	Pandaroside J (**99**)	Sponge (*Pandaros acanthifolium*)	NC	28.19	*L. donovani*	[41]

	Pandaroside J methyl ester (**100**)	Sponge (*Pandaros acanthifolium*)	NC	16.45	*L. donovani*	[41]
	Pandaroside K (**101**)	Sponge (*Pandaros acanthifolium*)	NC	49.40	*L. donovani*	[42]
	Pandaroside K methyl ester (**102**)	Sponge (*Pandaros acanthifolium*)	NC	80.97	*L. donovani*	[42]
	Pandaroside L (**103**)	Sponge (*Pandaros acanthifolium*)	NC	63.53	*L. donovani*	[42]
	Pandaroside L methyl ester (**104**)	Sponge (*Pandaros acanthifolium*)	NC	40.81	*L. donovani*	[42]
	Pandaroside M (**105**)	Sponge (*Pandaros acanthifolium*)	NC	43.07	*L. donovani*	[42]
	Pandaroside M methyl ester (**106**)	Sponge (*Pandaros acanthifolium*)	NC	20.02	*L. donovani*	[42]
	18-Acetoxipregna-1,4,20-trien-3-one (**107**)	Octocoral (*Carijoa riisei*)	5.51	16.88	*L. chagasi*	[43]
	Pregna-1,4,20-trien-3-one (**108**)	Octocoral (*Carijoa riisei*)	NC	> 100	*L. braziliensis*	[44]
Terpene	(*S*)-(+)-curcuphenol (**109**)	Sponge (*Myrmekioderma styx*)	2.40	NC	*L. donovani*	[45]
	Cristaxenicin A (**110**)	Gorgonian (*Acanthoprimnoa cristata)*	0.07	NC	*L. amazonensis*	[46]
	Shagene A (**111**)	Octocoral (not identified)	NC	15.68 1.45	*L. donovani*	[47]
	Agelasine D (**112**)	Sponge (*Agelas* sp.)	NC	1.5	*L. infantum*	[48]
	Elatol (**113**)	Red seaweed (*Laurencia dendroidea*)	1.33	0.15	*L. amazonensis*	[49]
	Obtusol (**114**)	Red seaweed (*Laurencia dendroidea*)	6.20	3.90	*L. amazonensis*	[50]
	(4R,9S,14S)-4α-Acetoxy-9β,14α-dihydroxydolast-1(15),7-diene (**115**)	Brown seaweed (*Canistrocarpus cervicornis*)	2	12	*L. amazonensis*	[51]
	Furospinulosin-1 (**116**)	Sponge (*Spongia* sp. and *Ircinia* sp.)	NC	14.2	*L. donovani*	[16]
	Furospongin-1 (**117**)	Sponge (*Spongia* sp.)	NC	4.8	*L. donovani*	[16]
	Demethylfurospongin-4 (**118**)	Sponge (*Ircinia* sp.)	NC	10.2	*L. donovani*	[16]
	2-(Hexaprenylmethyl)-2-methylchromenol (**119**)	Sponge (*Spongia* sp.)	NC	15.9	*L. donovani*	[16]
	4-Hydroxy-3-octaprenylbenzoic acid (**120**)	Sponge (*Ircinia* sp.)	NC	5.6	*L. donovani*	[16]
	Heptaprenyl-*p*-quinol (**121**)	Sponge (*Spongia* sp.)	NC	18.9	*L. donovani*	[16]
	11ß-Acetoxyspongi-12-en-16-one (**122**)	Sponge (*Ircinia* sp.)	NC	0.75	*L. donovani*	[16]
	Dolabelladienetriol (**123**)	Seaweed (*Dictyota pfaffii*)	NC	14.16	*L. amazonensis*	[52]
	Lobocrasol A (**139**)	Soft coral (*Lobophytum* spp.)	NC	0.18	*L. donovani*	[53]
	Lobocrasol C (**140**)	Soft coral (*Lobophytum* spp.)	NC	0.17	*L. donovani*	[53]

NC: not calculated; [a]: Reference.

Several manzamine alkaloids isolated from *Acanthostrongylophora* sp. and *Petrosiidae* sp. (**3**-**17**) were screened for their antileishmanial activity. The IC_{50} values vary between 0.9 and 50 μg mL^{-1}, manzamine A being the most potent alkaloid. Pentamidine and amphotericin B had their IC_{50} values calculated at 2.1 and 0.06 μg mL^{-1}, respectively. Concerning the cytotoxicity against *Vero* cells, the metabolites manzamine A and (+)-8-hydroxymanzamine A were the most toxic, with IC_{50} values of 1.2 and 1.1 μg mL^{-1}, respectively [11–13].

Meridianine G (**21**), an indole alkaloid isolated from the tunicate *Aplidium meridianum*, was shown to be active against the promastigotes of *L. donovani*, with IC_{50} value of 64.86 μM [14].

Several bromopyrrole alkaloids (**22**-**33**) were obtained from different species of the genera *Agelas* and *Axinella*. The metabolites were screened for antileishmanial activity in axenic amastigotes of *L. donovani*. The IC_{50} values ranged from 1.09 to 75.86 μg mL^{-1}, and dibromopalauamine was the most potent compound. However, it was shown to be toxic with an IC_{50} value of 4.46 μg mL^{-1} in L6 cells [15].

The isoquinolinequinone renieramycin A (**36**) isolated from the sponge *Neopetrosia sp*. showed antileishmanial activity. Towards the promastigotes of *L. amazonensis*, it presented an IC_{50} value of 0.2 μg mL^{-1}, compared to 2.2 μg mL^{-1} for cytotoxic activity over leukemic P388 murine cells [19,54].

The β-carboline alkaloid, nostocarboline (**37**), derived from cyanobacterium Nostoc 78-12A, was synthetized and evaluated towards different parasites. Against axenic amastigotes of *L. donovani*, the alkaloid presented IC_{50} value of 34.3 μM. The cytotoxicity in L6 myoblast cells of rats was 120.9 μM [20].

The alkaloid araguspongin C (**38**), isolated from the sponge *Haliclona exigua*, showed inhibitory activity of 61.2 ± 6.3% against promastigotes in a concentration of 100 μg mL^{-1}. Towards the intracellular amastigotes, the inhibition at the same concentration was 48.6 ± 4.6%. In the *in vivo* assay with hamsters infected with *L. donovani*, the alkaloid also presented weak activity with an inhibition value of 38.7 ± 12% in a dose of 100 mg kg^{-1} day^{-1}. Miltefosine presented an IC_{50} value of 5.1 μg mL^{-1} in the assay against promastigotes, 45 ± 6.5% of inhibition in the concentration of 25 μg mL^{-1} against intracellular amastigotes, and 91.6 ± 1.4% inhibition of the *in vivo* infection in hamsters in a dose of 50 mg kg^{-1} day^{-1} [55].

The guanidine alkaloid mirabiline B (**39**), isolated from the sponge *Monanchora unguife*, presented activity against *L. donovani* with an IC_{50} value of 17 μg mL^{-1}. The evolving form was not reported [56]. Other tricyclic pyrimidine and guanidine alkaloids (**39a**-**39e**), monalidine A and batzelladines D, F, L and nor-L, were isolated from the sponge *Monanchora arbuscular* and their activity towards *L. infantum* promastigotes revealed IC_{50} values ranging from 2-4 μM, but no activity was detected for intracellular amastigotes [57].

3.1.3. Peptides

From the cyanobacterium *Lyngbya majuscula*, the peptides almiramide A-C were isolated. The analogous B (**40**) and C (**41**) were active against *L. donovani* and showed IC_{50} values of 2.4 and 1.9 μM, respectively. None of these compounds were cytotoxic towards mammalian *Vero* cells (IC_{50} 33.1 – 113.1 μM). Almiramide B presented an SI of 21.8 [21].

Other peptides isolated from *Lyngbya majuscula* were the compounds dragonamide A (**42**), dragonamide E (**43**) and herbamide B (**44**). These were tested against axenic amastigotes of *L. donovani* and showed IC_{50} values of 6.5, 5.1 and 5.9 μM, respectively [22].

The peptide kahalalide F (**45**), previously isolated from the mollusk *Elysia rufescens*, and its food, the algae *Bryopsis* sp. [23], was synthesized and the antileishmanial activity was investigated. Towards the promastigotes of *L. donovani* and *L. pifanoi*, the metabolite presented IC_{50} values of 6.13 ± 0.16 and 8.31 ± 0.40 μM, respectively. For the reference drugs miltefosine and amphotericin B, the IC_{50} values, calculated for *L. donovani*, were 12.5 and 0.08 μM, respectively. The peptide also presented activity comparable to miltefosine towards amastigotes of *L. pifanoi*, with IC_{50} value of 29.53 ± 1.07 μM, compared to 26.3 μM. For amphotericin B, the value obtained was 0.2 μM. The cytotoxicity of kahalalide F was verified in peritoneal macrophages and bovine aortic endothelial cells (BAEC), and the IC_{50} values were respectively 10.23 ± 1.02 and 25.80 ± 0.11 μM [24].

The peptide viridamide A (**46**) was isolated from the cyanobacterium *Oscillatoria nigro-viridis* and presented activity against axenic amastigotes of *L. mexicana*. The IC_{50} value calculated was 1.5 ± 0.15 μM, compared to the 0.1 ± 0.01 value of the amphotericin B [25].

The peptides venturamides A (**47**) and B (**48**) were isolated from the cyanobacterium *Oscillatoria* sp. Both were evaluated in respect of activity against axenic amastigotes of *L. donovani*, but the IC_{50} values were not obtained until the concentration of 20 and 19 μM for the venturamides A and B, respectively. The toxicity in Vero cells was investigated, and the IC_{50} values were 86 and 56 μM, respectively [26].

The peptides tachyplesin I (**49**), isolated from the Atlantic horseshoe crab *Tachypleus tridentatus* [27], and mytiline A (**50**), isolated from the blue mussel *Mytilus edulis* [29], were active against promastigotes of *L. braziliensis*. Tachyplesin showed IC_{50} values of 74.4 μM, 4.7 μM and 9.3 μM, related to the incubation periods of 5, 24 and 72 hours, respectively. Mytiline was shown to be less active, with IC_{50} values of 43.5 and 48.7 μM for the respective periods of 24 and 72 hours [28]. In spite of showing haemolytic activity towards concentrations higher than 2.5 μM, tachyplesin did not show any cytotoxic effect, until 40 μM, against mammalian cell strains such as *Vero*, MA-104 and Hep-2 [58].

The depsipeptide IB-01212 (**51**) was isolated from the fungus *Clonostachys* sp. [30].The peptidic metabolite showed IC_{50} values of 7.1 ± 0.4 μM against axenic amastigotes of *L. pifanoi*, 10.5 ± 1.3 μM against promastigotes of *L. donovani*, and 18.3 ± 0.1 μM against peritoneal macrophages. That compound induces an apoptosis-like process, but that does not alter plasmatic membrane permeability. Fragmentation of the parasite DNA was seen along with the depolarization of the mitochondrial electrochemical gradient and progressive depletion of ATP, thus suggesting the involvement of an intracellular target [31].

The heterocyclic peptide balgacyclamide B (**126**), isolated from the cyanobacterium *Microcystis aeruginosa* EAWAG 251, presented an IC_{50} value of 28 μM against *L. donovani*, but the evolving form of the parasite was not mentioned. Against rats,´ L6 myoblastic cells, balgacyclamide B did not show cytotoxicity until a concentration of 150 μM [59].

The investigation of the tunicate *Didemnum molle* resulted in the isolation of the peptide molamide B (**127**), whose activity against *L. donovani* was assessed. The IC_{50} and IC_{90} values obtained for the marine metabolite were 18 and 35 μg/mL. The evolving form was not mentioned [60].

The peptides ciliatamides A and B (**128**-**129**), isolated from the sponge *Aaptos ciliate*, were weakly active against *L. major*, inhibiting the growth of promastigotes by 50 and 45.5%, respectively, in a concentration of 10 μg mL^{-1} [61].

3.1.4. Polyketides

Polyketides were isolated from the sponge *Plakorth* aff. *angulospiculatus* and their antileishmanial activity was evaluated *in vitro* against promastigotes of *L. mexicana*. The cyclic endoperoxide (3*S*,6*R*,8*S*)-4,6-diethyl-3,6-epidioxy-8- methyldodeca-4-enoic acid (**53**) showed an IC_{50} value of 0.29 μg mL^{-1}. Another polyketide isolated from the sponge, 3,6-epidioxy-4,6,8,10-tetraethyltetradeca-7,11-dienoic acid (**54**), containing also a cyclic endoperoxide, was less potent and showed an IC_{50} value of 1.00 μg mL^{-1}. Additionally, the compounds containing furanic rings instead of cyclic endoperoxide methyl (2*Z*,6*R*,8*S*)-4,6-diethyl-3,6-epoxy-8-methydodeca-2,4-dienoate (**55**) and methyl (2*Z*,6*R*,8*S*)-3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**56**) also showed less potency, with IC_{50} values of 1.86 and 2.71 μg mL^{-1}, respectively. The reference compound used was cetoconazol, which showed an IC_{50} value of 0.06 μg mL^{-1} [32].

From the sponge *Plakortis angulospiculatus*, other polyketides showed activity against *L. chagasi*. The compounds plakortide P (**57**), (2*Z*,6*R*,8*R*,9*E*)-methyl 3,6-epoxy-4,6,8-tri-ethyl-2,4,9-dodecatrienoate (**58**), spongosoritin A (**59**) and (2*E*,6*R*,8*S*)-methyl 3,6-epoxy-4,6,8-triethyldodeca-2,4-dienoate (**60**) were active against promastigote forms with IC_{50} values between 1.9 – 8.5 μg mL^{-1}, and plakortide P was the most potent polyketide. In the assay, against intracellular amastigote forms, the same compounds showed IC_{50} values in the range of 0.50 – 3.40 μg mL^{-1}, with a higher potency observed again for plakortide P. The cytotoxicity assessment in human macrophages through the MTT assay showed an SI of 31.6 for plakortide P. Moreover, it did not promote haemolysis in erythrocytes of mice.

The mechanism of action was not determined, but investigations indicate it does not involve NO up-regulation. The morphological alterations in promastigotes were highlighted by means of electronic transmission microscopy [33].

Four polyketides were isolated from the cyanobacterium *Oscillatoria* sp. The evaluation of the activity against axenic amastigotes of *L. donovani* revealed IC_{50} values between 2.4 and 18.7 μM, and the coibacin A compound (**61**) was the most potent. The cytotoxicity test using NCI-H460 cells showed IC_{50} value ranging between11.4 and 31.5 μM [34].

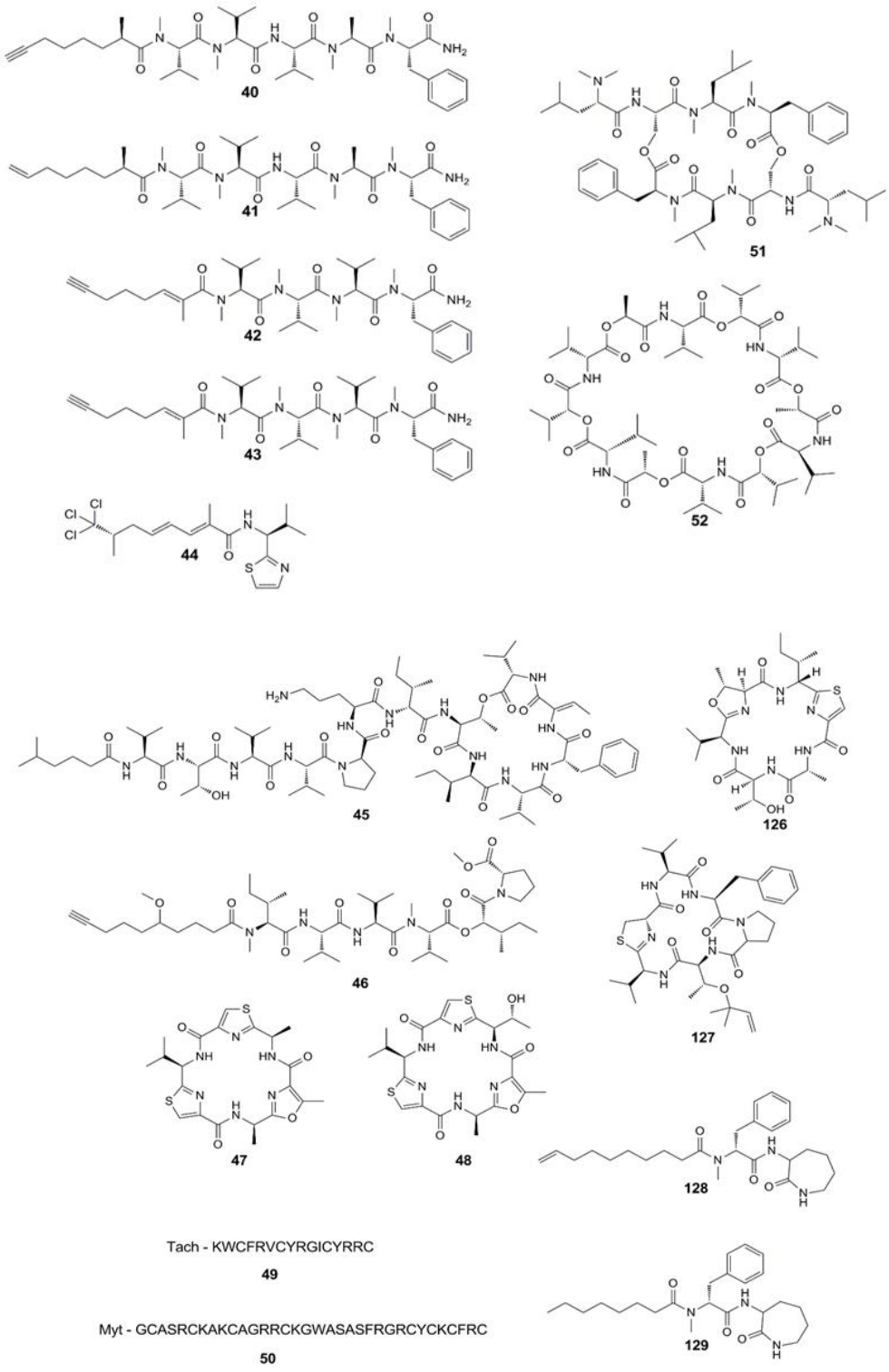

Figure 2. Marine peptides with antileishmanial activity

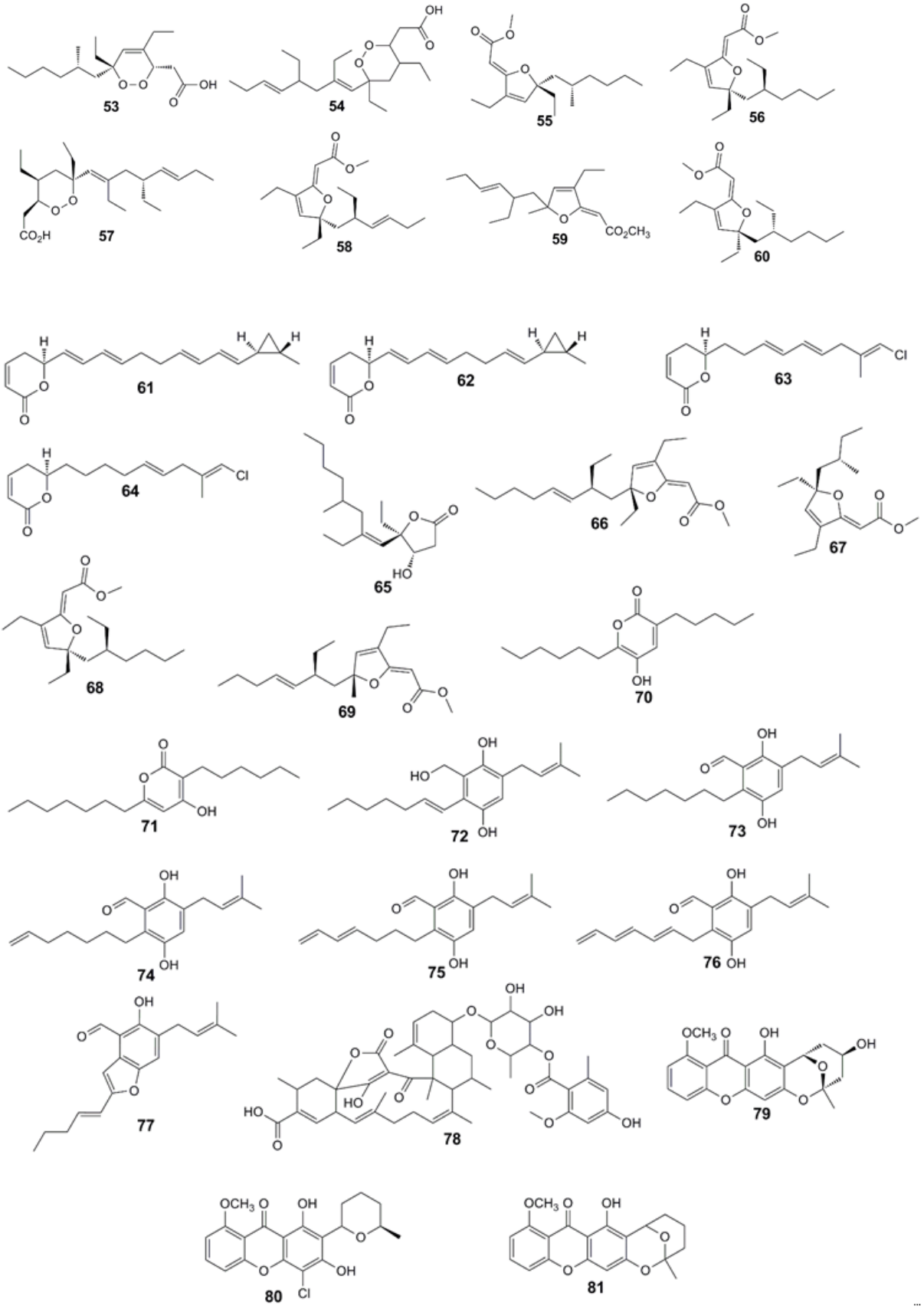

Figure 3. Polyketides of marine origin with antileishmanial activity.

Polyketides isolated from the sponge *Plakortis simplex* (**65-69**) were investigated concerning their activity over promastigotes of *L. donovani*. The IC_{50} values ranged between 7.11 – 38.56 μg mL^{-1}, compared to 0.34 μg mL^{-1} of amphotericin B and 1.62 μg mL^{-1} of pentamidine. The most potent compound (2*Z*,6*R*,8*R*,9*E*)[3-ethyl-5-(2-ethyl-hex-3-enyl)-6-methyl-5H-furan-2-ylidene]-acetic acid methyl ester (**69**) was not cytotoxic towards any of the strains of tumoral cells used in the study [35].

The pseudopyronine pyrones A (**70**) and B (**71**) isolated from the marine bacterium *Pseudomonas* sp. F92S91 were synthesized, and presented activity against axenic amastigotes of *L. donovani*, with IC_{50} values of 2.63 and 1.38 μg mL^{-1}, respectively. Against L6 myoblastic cells, the IC_{50} values for the pseudopyronines A and B were 23.2 and 17.9 μg mL^{-1} respectively. Miltefosine showed an IC_{50} value of 0.15 μg mL^{-1} [36].

From the fungus *Eurotium repens*, several secondary metabolites were isolated (**72-77**) with antileishmanial activity. The IC_{50} values obtained ranged between 6.2 and 23 μg mL^{-1}, compared to 1 μg mL^{-1} of pentamidine. None of these polyketides presented cytotoxicity towards the *Vero* cells [38].

A derivative of tetromicin (**78**) was isolated from the marine fungus *Streptomyces axinellae* Pol001. The investigation of its antileishmanial activity revealed that this compound is active against promastigotes of *L. major*, with an IC_{50} value of 36.80 μM. However, the cytotoxicity assays showed that the IC_{50} values towards the 293T renal cells and J774.1 macrophages were ~~respectively~~ 33.38 and 25.72 μM, respectively [39].

Investigations led to the isolation of new xanthones substituted with a tetrahydropyran ring, the chaetoxanthones A-C (**79-81**), from the marine fungus *Chaetomium* sp. The evaluation of the antileishmanial activity revealed that the IC_{50} values ranged between 3.1-5.3 μg mL^{-1}. Miltefosine presented an IC_{50} value of 0.125 μg mL^{-1} [40].

3.1.5. Steroids

Several saponines were isolated from the sponge *Pandaros acanthifolium*, the pandarosides A-J and their esters (**82-100**). The investigation of the effects of these compounds over several protozoa revealed their antileishmanial potential. Among them, the esterified derivative of pandaroside G showed high potency against axenic amastigotes, with an IC_{50} value of 0.051 μM, which is 10 times higher than the one shown by the standard drug, miltefosine (0.51 μM). However, this compound also showed the most toxic potential in the cytotoxicity assay with L6 cells, with IC_{50} of 0.22 μM. The IC_{50} value for podophyllotoxin was 0.012 μM. [41].

In another chemical study on the sponge *Pandaros acanthifolium*, the pandarosides K-M and their esters (**101-106**) were also isolated. The IC_{50} values for these compounds ranged between 26.1 and 63.1 μM, in comparison to 0.51 of the reference drug miltefosine. None of these compounds were cytotoxic towards the L6 cells up to a concentration of 100 μM [42].

A steroid isolated from octocorallia *Carijoa riisei*, 18-acetoxipregna-1,4,20-trien-3-one (**107**), showed activity against *L. chagasi in vitro*. Against the promastigote forms, the steroidal metabolite presented an IC_{50} value of 5.51 μg mL^{-1}, in comparison to 0.17 μg mL^{-1}, obtained for pentamidine. Concerning the amastigote forms, the IC_{50} value, shown by the steroid, was 16.88 μg mL^{-1}, which was lower than the value of 29.55 obtained for glucantime. The IC_{50} value for the cytotoxic effect of the natural product was set at 10.68 μg mL^{-1} and the haemolytic activity at 2.3% in the concentration of 25 μg mL^{-1} [43].

The norselic acid steroids A-E (**130-134**) were isolated from *Crella* sp. All the acids presented activity in low concentrations against *Leishmania*, with IC_{50} values ranging between 2.0 and 3.6 μM. However, neither the species nor the evolving form of the parasite were revealed [62].

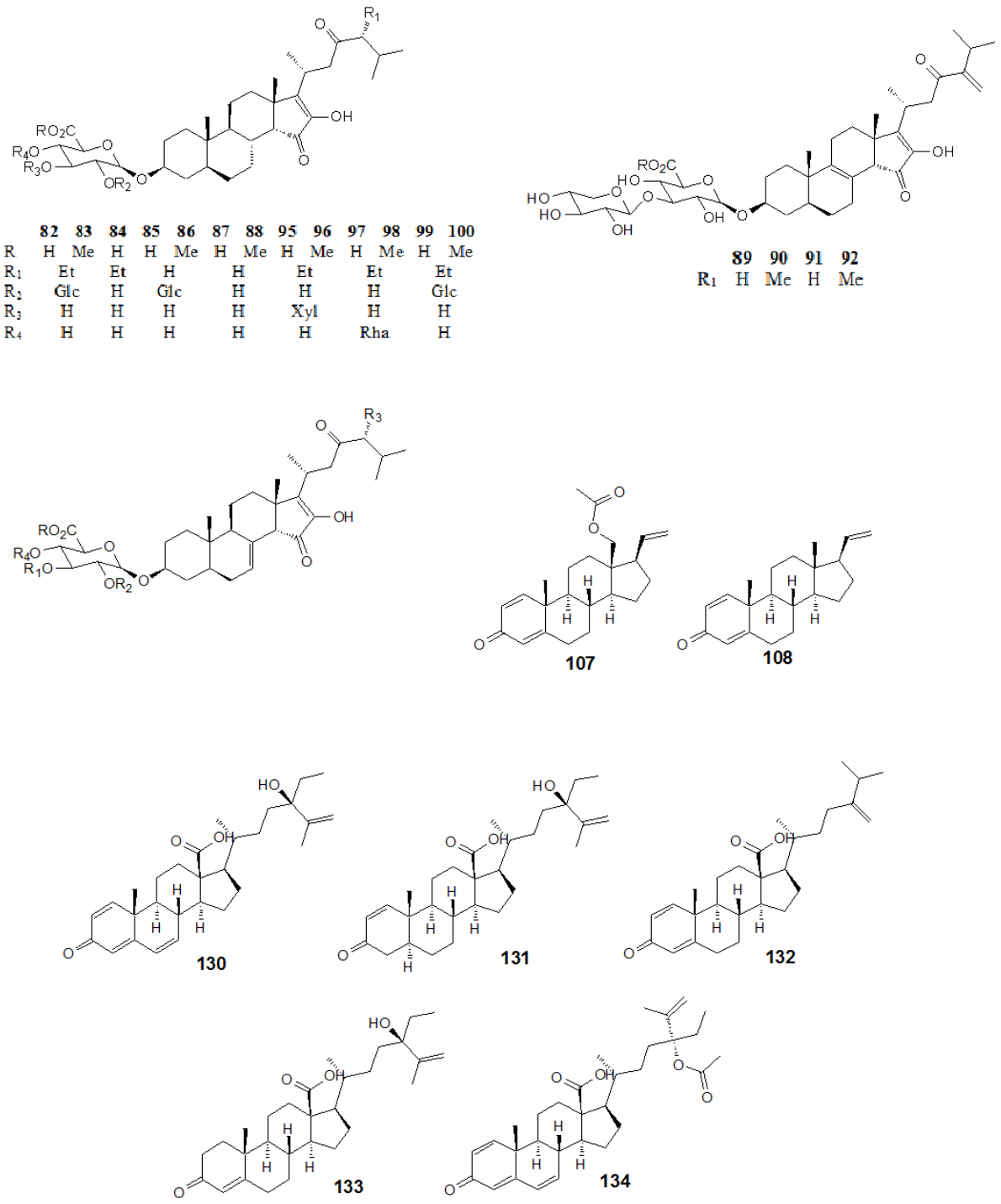

Figure 4. Steroids of marine organisms with potential antileishmanial activity.

3.1.6.Terpenes

The diterpene cristaxenicin A (**110**) was isolated from the gorgonian *Acanthoprimnoa cristata*. Against promastigotes of *L. amazonesis*, the terpenoid showed potent activity, with an IC_{50} value of 0.088 µM. Cytotoxicity was evaluated in tumoral cells of human cervical cancer (HeLa) and leukemic cells of murines (P388); the IC_{50} values calculated for cristaxenicin A, this way, were 2.1 and 4.7 µM, [46].

The terpenoid shagene A (**111**) was isolated from an unidentified octocorallia. The authors report that the species was an organism related neither to the genera nor to the families of the subclass

Octocorallia which are currently known. The terpene showed an IC_{50} value of 5 μM for the intracellular amastigotes and 54 μM for axenic amastigotes of *L. donovani*; it was not toxic towards the macrophages J774.A-1 up to a concentration of 345 μM, which represents an SI > 70 [47].

The terpenoid agelasine D (**112**), previously isolated from the sponge *Agelas* sp., showed an IC_{50} of 1.5 μg mL^{-1} against amastigotes of *L. infantum*, in comparison to 0.24 μg mL^{-1} of miltefosine. The SI of agelasine D was 4.5 in relation to fibroblasts MRC-5 [48].

The sesquiterpene elatol (**113**) was isolated from the alga *Laurencia dendroidea*. Its effects over *L. amazonensis* were revealed to present an IC_{50} of 4.0 μM over the promastigote forms and 0.45 μM over the amastigote forms, after 72 hours of exposure. Amphotericin B showed IC_{50} values of 0.06 and 0.31 μM against promastigotes and amastigotes respectively. The IC_{50} of the cytotoxic activity against macrophages J774G8 was 1.4 μM, which is equivalent to a selectivity index of 3 regarding the intracellular forms. The observation of the parasite under electronic transmission microscopy revealed structural alterations that include the destabilization of the plasmatic membrane, the onset of autophagic vacuoles, as well as changes in organelles [49].

Against *L. amazonensis*, obtusol (**114**), another terpenoid isolated from *Laurencia dendroidea*, showed IC_{50} values of 6.2 ± 0.5 and 3.9 ± 0.5 μg mL^{-1} towards intracellular promastigotes and amastigotes, respectively. The values for the cytotoxicity tests were 133.5 ± 3.7 and 139.3 ± 5.5 μg mL^{-1} for the peritoneal macrophages and nodal cells, respectively [50].

The terpenoid (4*R*,9*S*,14*S*)-4α-acetoxy-9β,14α-dihydroxydolast-1(15),7-diene (**115**) isolated from the alga *Canistrocarpus cervicornis* was screened for action towards *L. amazonensis*. It presented IC_{50} values of 2.0 and 12 μg mL^{-1} for the axenic promastigotes and amastigotes respectively, after 72 hours of incubation, in comparison to 0.06 μg mL^{-1} of amphotericin B. The cytotoxicity in macrophages of the J774G8 strain was 186.0 ± 3.29 μg mL^{-1}, revealing an SI of 93 when the comparison is made with promastigotes. In addition, the IC_{50} value obtained for the diterpene was 4 μg mL^{-1} on intracellular amastigotes after 24-hour incubation. The mitochondrial tumescence and depolarization were observed by means of electronic transmission microscopy and flow cytometry [51].

Several terpenoids (**116-122**) were isolated from the species of sponge of the genera *Spongia* sp. and *Ircinia* sp. Many of them were shown to be active against axenic amastigotes, with IC_{50} values ranging between 0.75 and 18.9 μg mL^{-1}; 11β-acetoxyspongi-12-en-16-one (**122**) was the most potent compound, in comparison to 0.20 μg mL^{-1} of miltefosine. The cytotoxicity of the most active terpenoid was set in L6 cells and presented an IC_{50} of 3.32 μg mL^{-1} [16].

The terpenoid dolabelladienetriol (**123**) isolated from the alga *Dictyota pfaffii* presented an IC_{50} of 43.9 μM against intracellular amastigotes of *L. amazonensis*. Against promastigotes of the same species, dolabelladienotriol inhibited the growth in 84 and 95.5% in concentrations of 50 and 100 μM [52].

The sesquiterpene euplotine C (**135**) was isolated from the ciliate *Euplotes crassus* and its effects over the promastigotes of *L. major* were investigated. In a concentration of 100 μg mL^{-1}, the terpenoid promoted inhibition of 94% in the growth and viability of the parasites after 2 hours of exposure. The irreversibility of the effect after 48 hours suggests leishmanicidal activity [63].

Two tripertenic glycosides were isolated from sea cucumber *Actinopyga lecanora* by means of biomonitored fractionation. The compounds holoturin A (**136**) and holoturin B (**137**) showed activity both *in vitro* and *in vivo* against *L. donovani*. Holoturin A showed inhibition of 73.2 ± 6.8% and 65.8 ± 6% for intracellular promastigotes and amastigotes respectively, in a concentration of 100 μg mL^{-1}. Holoturin B presented better activity against intracellular promastigotes and amastigotes in the same concentration with respective inhibition values of 82.5 ± 11.6 and 78 ± 10.2%. In the *in vivo* assays with hamsters, holoturin B presented better efficacy at doses of 100 $mg.kg^{-1}.day^{-1}$, being capable of inhibiting the infection with a value of 71.5 ± 12.8%, whereas the analogous A showed an inhibition value of 44.6 ± 10.6% at the same dose. Miltefosine, the drug used as reference, presented inhibition of 93.9 ± 2.6% at a dose of 40 mg kg^{-1} day^{-1} [64].

The sulfated meroterpenoid isoakaterpin (**138**), isolated from the sponge *Callyspongia* sp. is able to inhibit the adenosine phosphoribosyltransferase enzyme of leishmaniasis parasites with an IC_{50} of 1.05 μM [65].

The cembrane diterpenes, lobocrasol A (**139**) and lobocrasol (**140**) C isolated from the Vietnamese soft corals *Lobophytum crassum* and *L. laevigatum* showed potent antileishmanial effect against axenic amastigotes of *L. donovani*, with IC_{50} values of 0.18 and 0.17 μM, respectively [53].

3.1.7. Miscellaneous

The shikimate 3,5-dibromo-*N,N,N,O*-tetramethyltyrosinium was isolated from the sponge *Aiolochroia crassa* and in a concentration of 20 μM was able to promote 42.0 ±8.5 of inhibition in axenic amastigotes of *L. panamensis* [66].

Interactions between lecithins and parasites of the family *tripanosomatidae* have been studied over recent years. A lecithin (CaL) with specificity for lactose was isolated from the sponge *Cinachyrella apion* and the agglutination test with promastigotes of *L. chagasi* showed that 1 μg of the protein was able to lead to the agglutination of 6.7 x 10^5 cells [67].

A glycoprotein, isolated from the sponge *Pachymatisma johnstonii*, pachymatismin, was shown to be active against promastigotes of different species of *Leishmania* and axenic amastigotes of *L. mexicana*, with IC_{50} values ranging between 0.6 and 2.5 μg mL^{-1} [68]. Sulfated polysaccharides from different species of algae were tested against promastigotes of *L. amazonensis*. The metabolites of *Caulerpa racemosa*, *Botryocladia occidentalis* and *Solieria filiformis* presented respectively IC_{50} values of 34.5, 63.7 and 137.4 μg mL^{-1} and selectivity indexes of 1.42, 0.42 and 0.72 [69].

Table 2. Selectivity indexes for the marine metabolites of higher potency against amastigotes

Compound	*IC_{50} against amastigotes ($\mu g\ mL^{-1}$)*	*SI*[a]	*Cellular strain*
Plakortide P (**57**)	0.5	31.6	Peritoneal macrophages
Coibacin A (**61**)	0.68	13.1	NCI-H460 tumoral cells
Pandaroside G (**93**)	0.97	4.1	L6 cells
Pandaroside G methylester (**94**)	0.04	4.2	L6 cells
Elatol (**113**)	0.15	3.1	J774G8 macrophages
11ß-Acetoxyspongi-12-en-16-one (**122**)	0.75	4.4	L6 cells

[a]:Selectivity index

Fucoidans consist of sulfated polysaccharides composed mainly of L-fucose. They are metabolites of marine origin extracted from brown algae of different genera and from some invertebrates [70]. The administration of fucoidan to BALB/c rats, infected with strains of *L. donovani* susceptible and resistant to the antimonium, revealed inhibitory effects over the amastigote forms of both strains and resulted in a pronounced reduction of the parasitic load in an oral dose of 200 mg kg^{-1} day^{-1} three times daily. Additionally, it was demonstrated that fucoidan induced a protective response from the host by means of the production of cytokines and a significant increment in the levels of reactive species of oxygen and NO in infected macrophages, which may be involved in the reduction of the parasite multiplication observed [71].

According to the World Health Organization, a ligand compound against *Leishmania* must present an IC_{50} value lower than 0.5 μg mL^{-1} for axenic amastigotes or lower than 1 μg mL^{-1} for intracellular amastigotes, with selectivity indexes higher than 20 [72]. Based on the natural products of marine origin with antileishmanial activity described in Table 1, only six metabolites meet the criteria of potency against the amastigote forms.

If we also consider the selectivity indexes shown in Table 2, plakortide P can be thought of as a potential ligand compound, as all the others presented selectivity indexes lower than 20. Even though these metabolites cannot be classified as ligands, they may serve as a starting point for the development of new prototypes. In the case of the pandarosides, the obtaining of several metabolites with analogous structures allowed us to observe that the esterified derivatives are more active and more toxic towards the mammalian cells, and may possibly act as pro-drugs by being hydrolyzed to the corresponding fatty acids [41]. The investigation into the structure-activity relation of these natural products may provide information to allow the optimization of the molecules and the obtaining of more selective derivatives for the leishmaniasis cells.

The verification of the activity against promastigotes is generally used in a preliminary way. Primary trials frequently aim at this phase of the parasite because of the easy culture and manipulation. Indeed, promastigotes from several species of *Leishmania* are easily kept in *in vitro* cell suspension. However, once the promastigotes are the parasite form in the vector insect, that is not the appropriate target for an antileishmanial drug [73]. In order to facilitate the study in the evolving stage of the

parasite responsible for the disease in humans, culture conditions for axenic amastigotes have been developed [74].

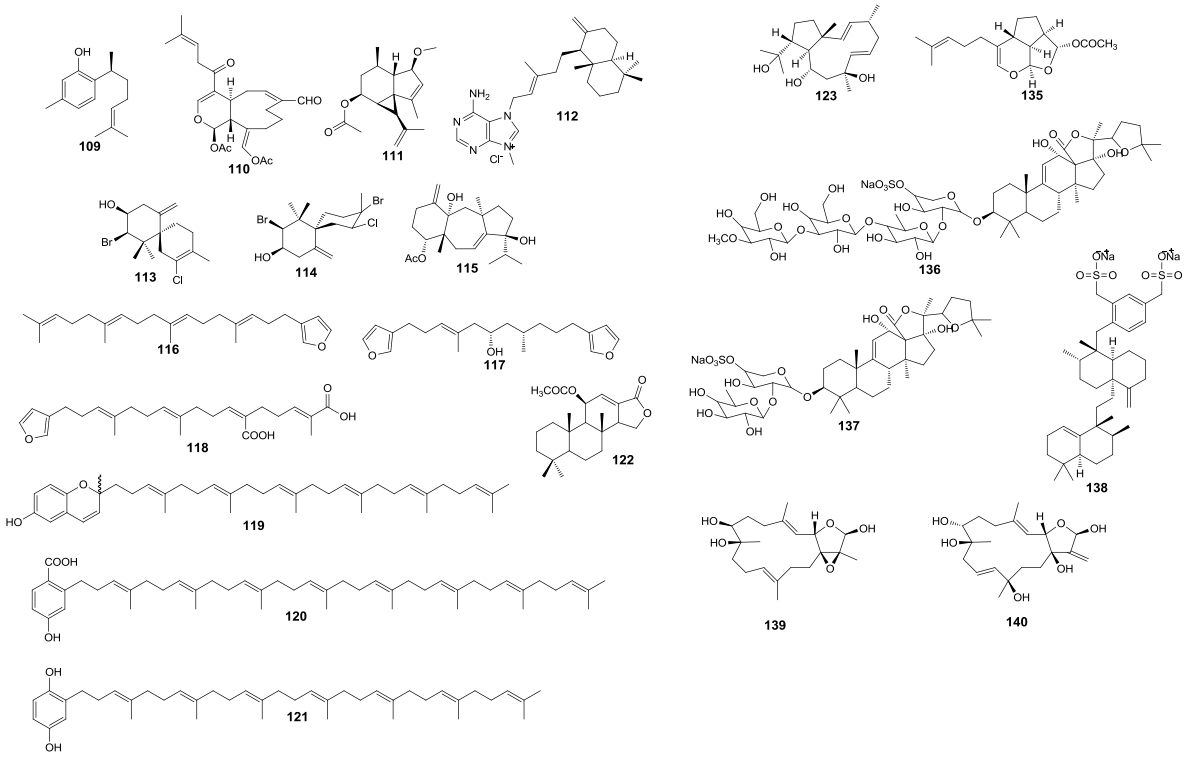

Figure 5. Marine terpenoids with antileishmanial activity

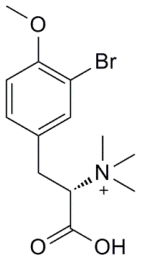

Figure 6. Structure of the shikimate 3,5-dibromo-*N*,*N*,*N*,*O*-tetramethyltyrosinium

The *in vitro* system can be potentially used for the compounds that possess direct lethal action over the parasite, but the compounds that are efficient through their metabolites or whose action is mediated through the host´s defense system do not present *in vitro* activity [75]. On the other hand, the *in vitro* assay results, at times, may not be transferrable to the *in vivo* situation, as the active compounds against axenic forms can be unable to reach an intracellular amastigote due to their incapacity to cut through the host cell membranes or to keep stability in low pH [76].

From the drug development perspective, medicinal chemists also take into account some chemical characteristics, in addition to the power of the bioactive molecule, since these features allow the tendency of a particular molecule to be lead-like or drug-like to be predicted. Thus, despite the high potency of various terpenoids and steroid derivatives, their elevated LogP values and low polar surface area values cause concern in respect of the ease with which this class of molecules is able to cross the blood-brain barrier.

In addition, various structurally related alkaloids have been isolated and their biological effects on protozoa studied, which has provided important information on their structure-activity relationship. In a recent review, several structural characteristics associated with the antileishmanial activity of the alkaloid manzamine were identified.

Another important aspect is the viability of synthetic bioactive molecules. The total synthesis of the alkaloid manzamine involved 18 steps in the shortest route, which substantially increases the production process.

Despite there being several promising molecules from a biological point of view, long synthetic routes make it difficult to obtain these compounds and their derivatives and analogues to investigate the structure-activity relationship. Therefore, a need exists for additional studies to determine the mechanisms of action and develop molecular simplifications.

Acknowledgments

The authors would like to thank the financial support given by CNPq, CAPES, FINEP and FAPEAL.

References

[1] WHO (2013). Sustaining the drive to overcome the global impact of neglected tropical diseases, *World Heal Organ.* **2,** 67-71.

[2] D. Liu, Y. Huang, C. Li, L. Ma, X. Pan and D. Ferreira (2016). A new sesquiterpenoid derivative from the coastal saline soilfungus A*spergillus fumigatus*, *Rec Nat Prod.* **10**, 708–713.

[3] B. Wu, G. Chen, Z.G. Liu and Y. Pei (2015). Two new alkaloids from a marine-derived fungus *Neosartorya fischeri*, *Rec Nat Prod.* **9**, 271–275.

[4] X. Tian, H. Tang, Y. Li, H. Lin, X. Zhang and J. Feng (2014). Studies on the chemical constituents from marine *Bryozoan Cryptosula pallasiana*, *Rec Nat Prod.* **9**, 628–632.

[5] R. Montaser and H. Luesch (2011). Marine natural products: a new wave of drugs?, *Future Med Chem.* **3**, 1475–89.

[6] M. Donia and M.T. Hamann (2003). Marine natural products and their potential applications as anti-infective agents, *Lancet Infect Dis.* **3**, 338–348.

[7] D.J. Newman and G.M. Cragg (2004). Marine natural products and related compounds in clinical and advanced preclinical trials, *J Nat Prod.* **67,** 1216-1238.

[8] A.G. Tempone, C. Martins De Oliveira and R.G.S. Berlinck (2011). Current approaches to discover marine antileishmanial natural products, *Planta Med.* **77**, 572–585.

[9] A.M.S. Mayer, A.D. Rodríguez, O. Taglialatela-Scafati and N. Fusetani (2013). Marine pharmacology in: marine compounds with antibacterial, antidiabetic, antifungal, anti-inflammatory, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous systems, and other miscellaneous mechanisms, *Mar Drugs.* **11**, 2510–2573.

[10] F. Yang, M.T. Hamann, Y. Zou, M.Y. Zhang, X.B. Gong and J.R. Xiao (2012). Antimicrobial metabolites from the paracel islands sponge *Agelas mauritiana*, *J Nat Prod.* **75**, 774–778.

[11] K. V Rao, M.S. Donia, J. Peng, E. Garcia-palomero, D. Alonso and A. Martinez (2006). Manzamine B and E and ircinal a related alkaloids from an indonesian *Acanthostrongylophora* Sponge and their activity against Infectious, tropical parasitic and alzheimer ' s diseases, *J Nat Prod.* **44,** 1034–1040.

[12] K. V Rao, B.D. Santarsiero, A.D. Mesecar, R.F. Schinazi, B.L. Tekwani and M.T. Hamann (2003). New manzamine alkaloids with activity against infectious and tropical parasitic diseases from an Indonesian sponge, *J Nat Prod.* **66**, 823–828.

[13] K. V Rao, N. Kasanah, S. Wahyuono, B.L. Tekwani, R.F. Schinazi and M.T. Hamann (2004). Three new manzamine alkaloids from a common Indonesian sponge and their activity against infectious and tropical parasitic diseases, *J Nat Prod.* **67**, 1314–1318.

[14] S.B. Bharate, R.R. Yadav, S.I. Khan, B.L. Tekwani, M.R. Jacob and I.A. Khan (2013). Meridianin G and its analogs as antimalarial agents, *Medchemcomm* **4,** 1042–1048.

[15] F. Scala, E. Fattorusso, M. Menna, O. Taglialatela-Scafati, M. Tierney and M. Kaiser (2010). Bromopyrrole alkaloids as lead compounds against protozoan parasites, *Mar Drugs.* **8,** 2162–2174.

[16] I. Orhan, B. Sener, M. Kaiser, R. Brun and D. Tasdemir (2010). Inhibitory activity of marine sponge-derived natural products against parasitic protozoa., *Mar Drugs.* **8,** 47–58.

[17] I. Erdorgan, B. Sener and T. Higa (2000). Tryptophol, a plant auxin isolated from the marine sponge Ircinia spinulosa., *Biochem Syst Ecol.* **28**, 793–794.

[18] S.M. Pimentel-Elardo, S. Kozytska, T.S. Bugni, C.M. Ireland, H. Moll and U. Hentschel (2010). Anti-parasitic compounds from Streptomyces sp. strains isolated from Mediterranean sponges, *Mar Drugs.***8**, 373–380.

[19] Y. Nakao, T. Shiroiwa, S. Murayama, S. Matsunaga, Y. Goto and Y. Matsumoto (2004). Identification of renieramycin A as an antileishmanial substance in a marine sponge Neopetrosia sp, *Mar Drugs* **2**, 55–62.

[20] D. Barbaras, M. Kaiser, R. Brun and K. Gademann (2008). Potent and selective antiplasmodial activity of the cyanobacterial alkaloid nostocarboline and its dimers., *Bioorg Med Chem Lett.* **18**, 4413–4415.

[21] L.M. Sanchez, D. Lopez, B.A. Vesely, G. Della Togna, W.H. Gerwick and D.E. Kyle (2010). Almiramides A-C: Discovery and development of a new class of leishmaniasis lead compounds, *J Med Chem.* **53**, 4187–4197.

[22] M.J. Balunas, R.G. Linington, K. Tidgewell, A.M. Fenner, L.-D. Urena and G. Della Togna (2010). Dragonamide E, a Modified Linear Lipopeptide from Lyngbya majuscula with Antileishmanial Activity, *J Nat Prod.* **73**, 60–66.

[23] M.T. Hamann, P.J. Scheuer and F. Kahalalide (1993). A bioactive depsipeptide from the sacoglossan mollusk Elysia rufescens and the green alga Bryopsis sp, *J Am Chem Soc.* **115**, 5825–5826.

[24] L.J. Cruz, J.R. Luque-Ortega, L. Rivas and F. Albericio (2009). Kahalalide F, an antitumor depsipeptide in clinical trials, and its analogues as effective antileishmanial agents, *Mol Pharm.* **6**, 813–824.

[25] T.L. Simmons, N. Engene, L.D. Ureña, L.I. Romero, E. Ortega-Barría and L. Gerwick (2008). Viridamides A and B, lipodepsipeptides with antiprotozoal activity from the marine cyanobacterium Oscillatoria nigro-viridis, *J Nat Prod.* **71**, 1544–1550.

[26] R.G. Linington, J. Gonzalez, L.-D. Urena, L.I. Romero, E. Ortega-Barria and W.H. Gerwick (2007). Venturamides A and B: Antimalarial constituents of the Panamanian Marine Cyanobacterium Oscillatoria sp, *J Nat Prod.* **70**, 397–401.

[27] T. Nakamura, H. Furunaka, T. Miyata, F. Tokunaga, T. Muta and S. Iwanaga (1988). Tachyplesin, a class of antimicrobial peptide from the hemocytes of the horseshoe crab (*Tachypleus tridentatus*). Isolation and chemical structure., *J Biol Chem.* **263**, 16709–16713.

[28] S.E. Löfgren, L.C. Miletti, M. Steindel, E. Bachère and M.A. Barracco (2008). Trypanocidal and leishmanicidal activities of different antimicrobial peptides (AMPs) isolated from aquatic animals, *Exp Parasitol.* **118**, 197–202.

[29] M. Charlet, S. Chernysh, H. Philippe, C. Hetru, J.A. Hoffmann and P. Bulet (1996). Innate immunity. Isolation of several cysteine-rich antimicrobial peptides from the blood of a mollusc, *Mytilus edulis*, *J Biol Chem.* **271**, 21808–21813.

[30] L.J. Cruz, M.M. Insua, J.P. Baz, M. Trujillo, R.A. Rodriguez-Mias and E. Oliveira (2006). IB-01212, a new cytotoxic cyclodepsipeptide isolated from the marine fungus Clonostachys sp. ESNA-A009, *J Org Chem.* **71,** 3335–3338.

[31] J.R. Luque-Ortega, L.J. Cruz, F. Albericio and L. Rivas (2010). The antitumoral depsipeptide IB-01212 kills Leishmania through an apoptosis-like process involving intracellular targets, *Mol Pharm.* **7**, 1608–1617.

[32] R.S. Compagnone, I.C. Piña, H.R. Rangel, F. Dagger, A.I. Suárez and M.V.R. Reddy (1998). Antileishmanial cyclic peroxides from the palauan sponge *Plakortis aff. angulospiculatus*, *Tetrahedron* **54**, 3057–3068.

[33] M.H. Kossuga, A.M. Nascimento, J.Q. Reimao, A.G. Tempone, N.N. Taniwaki and K. Veloso (2008). Antiparasitic, antineuroinflammatory, and cytotoxic polyketides from the marine sponge plakortis angulospiculatus collected in Brazil, *J Nat Prod.* **71**, 334–339.

[34] M.J. Balunas, M.F. Grosso, F.A. Villa, N. Engene, K.L. McPhail and K. Tidgewell (2012). Coibacins A-D, antileishmanial marine cyanobacterial polyketides with intriguing biosynthetic origins, *Org Lett.* **14**, 3878–3881.

[35] X.F. Liu, Y. Shen, F. Yang, M.T. Hamann, W.H. Jiao and H.J. Zhang (2012). Simplexolides A-E and plakorfuran A, six butyrate derived polyketides from the marine sponge Plakortis simplex, *Tetrahedron* **68**, 4635–4640.

[36] A.C. Giddens, L. Nielsen, H.I. Boshoff, D. Tasdemir, R. Perozzo and M. Kaiser (2008). Natural product inhibitors of fatty acid biosynthesis: synthesis of the marine microbial metabolites pseudopyronines A and B and evaluation of their anti-infective activities, *Tetrahedron* **64**, 1242–1249.

[37] F. Kong, M.P. Singh and G.T. Carter (2005). Pseudopyronines A and B, alpha-pyrones produced by a marine *Pseudomonas sp.* F92S91, and evidence for the conversion of 4-hydroxy-alpha-pyrone to-3-furanone, *J Nat Prod.* **68**, 920–923.

[38] J. Gao, M.M. Radwan, F. León, X. Wang, M.R. Jacob and B.L. Tekwani (2012). Antimicrobial and antiprotozoal activities of secondary metabolites from the fungus *Eurotium repens*, *Med Chem Res.* **21**, 3080–3086.

[39] S.M. Pimentel-Elardo, V. Buback, T.A.M. Gulder, T.S. Bugni, J. Reppart and G. Bringmann (2011). New tetromycin derivatives with anti-trypanosomal and protease inhibitory activities, *Mar Drugs.* **9**, 1682–1697.

[40] A. Pontius, A. Krick, S. Kehraus, R. Brun and G.M. König (2008). Antiprotozoal activities of heterocyclic-substituted xanthones from the marine-derived fungus Chaetomium sp, *J Nat Prod.* **71**, 1579–1584.

[41] E.L. Regalado, D. Tasdemir, M. Kaiser, N. Cachet, P. Amade and O.P. Thomas (2010). Antiprotozoal steroidal saponins from the marine sponge *Pandaros acanthifolium*, *J Nat Prod.* **73**, 1404–1410.

[42] E.L. Regalado, T. Turk, D. Tasdemir, M. Gorjanc, M. Kaiser and O.P. Thomas (2011). Cytotoxic and haemolytic steroidal glycosides from the Caribbean sponge *Pandaros acanthifolium*, *Steroids.* **76**, 1389–1396.

[43] J.Q. Reimão, A.E. Migotto, M.H. Kossuga, R.G.S. Berlinck and A.G. Tempone (2008). Antiprotozoan activity of Brazilian marine cnidarian extracts and of a modified steroid from the octocoral *Carijoa riisei*, *Parasitol Res.* **103**, 1445–1450.

[44] M.T.R. de Almeida, M.L. Tonini, T.R. Guimarães, E.M. Bianco, M.I.G. Moritz and S.Q. Oliveira (2012). Anti-infective pregnane steroid from the octocoral Carijoa riisei collected in South Brazil, *Lat Am J Pharm*. **31**, 1489–1495.

[45] W. Gul, N.L. Hammond, M. Yousaf, J. Peng, A. Holley and M.T. Hamann (2007). Chemical transformation and biological studies of marine sesquiterpene (*S*)-(+)-curcuphenol and its analogs, *Biochim Biophys Acta.* **1770**, 1513–1519.

[46] S.-T. Ishigami, Y. Goto, N. Inoue, S.-I. Kawazu, Y. Matsumoto and Y. Imahara (2012). Cristaxenicin A, an antiprotozoal xenicane diterpenoid from the deep sea *Gorgonian Acanthoprimnoa cristata*, *J Org Chem.* **77**, 10962–10966.

[47] J.L. Von Salm, N.G. Wilson, B.A. Vesely, D.E. Kyle, J. Cuce and B.J. Baker (2014). Shagenes A and B, new tricyclic sesquiterpenes produced by an undescribed antarctic octocoral, *Org Lett.* **16**, 2630–2633.

[48] A. Vik, A. Proszenyak, M. Vermeersch, P. Cos, L. Maes and L.L. Gundersen (2009). Screening of agelasine D and analogs for inhibitory activity against pathogenic protozoa; identification of hits for visceral leishmaniasis and chagas disease, *Molecules* **14**, 279–288.

[49] A.O. Dos Santos, P. Veiga-Santos, T. Ueda-Nakamura, B.P. Dias Filho, D.B. Sudatti and É.M. Bianco (2010). Effect of elatol, isolated from red seaweed *Laurencia dendroidea*, on Leishmania amazonensis, *Mar Drugs.* **8**, 2733–2743.

[50] F.L. Da Silva MacHado, W. Pacienza-Lima, B. Rossi-Bergmann, L.M. De Souza Gestinari, M.T. Fujii and J.C. Paula (2011). Antileishmanial sesquiterpenes from the Brazilian red alga *Laurencia dendroidea*, *Planta Med.* **77**, 733–735.

[51] A.O. Dos Santos, E.A. Britta, E.M. Bianco, T. Ueda-Nakamura, B.P. Dias Filho and R.C. Pereira (2011). 4-Acetoxydolastane diterpene from the Brazilian brown alga *Canistrocarpus cervicornis* as antileishmanial agent, *Mar Drugs.* **9**, 2369–2383.

[52] D.C. Soares, T.C. Calegari-Silva, U.G. Lopes, V.L. Teixeira, I.C.N.P. Paixão and C. Cirne-Santos (2012). Dolabelladienetriol, a compound from *Dictyota pfaffii* algae, inhibits the infection by *Leishmania amazonensis*, *PLoS Negl Trop Dis.* **6**, e1787.

[53] P.T. Nguyen, B.T.T. Luyen, R. Brun, M. Kaiser, P. Van Kiem and C. Van Minh (2015). Anti-Protozoal Activities of Cembrane-Type Diterpenes from *Vietnamese Soft Corals*, *Molecules.* **20**, 12459–12468.

[54] T. Ozturk and G. Cordell (2000). Alkaloids Containing An Isoquinolinequinone Unit. Academic Press, San Diego.

[55] A. Dube, N. Singh, A. Saxena and V. Lakshmi (2007). Antileishmanial potential of a marine sponge, *Haliclona exigua* (Kirkpatrick) against experimental visceral leishmaniasis, *Parasitol Res.* 101317–101324.

[56] H. Hua, J. Peng, F.R. Fronczek, M. Kelly and M.T. Hamann (2004). Crystallographic and NMR studies of antiinfective tricyclic guanidine alkaloids from the sponge Monanchora unguifera, *Bioorg Med Chem.* **12**, 6461–6464.

[57] M.F.C. Santos, P.M. Harper, D.E. Williams, J.T. Mesquita, E.G. Pinto and T.A. Costa-Silva (2015). Anti-parasitic Guanidine and Pyrimidine Alkaloids from the Marine Sponge *Monanchora arbuscula*, *J Nat Prod.* **78**, 1101–1112.

[58] M.C. Carriel-Gomes, J.M. Kratz, M.A. Barracco, E. Bachére, C.R.M. Barardi and C.M.O. Simões (2007). In vitro antiviral activity of antimicrobial peptides against herpes simplex virus 1, adenovirus, and rotavirus, *Mem Inst Oswaldo Cruz.* **102**, 469–472.

[59] C. Portmann, S. Sieber, S. Wirthensohn, J.F. Blom, L. Da Silva and E. Baudat (2014). Balgacyclamides, antiplasmodial heterocyclic peptides from *Microcystis aeruginosa* EAWAG 251, *J Nat Prod.* **77**, 557–562.

[60] M.S. Donia, B. Wang, D.C. Dunbar, P. V Desai, A. Patny and M. Avery (2008). Mollamides B and C,

cyclic hexapeptides from the indonesian tunicate *Didemnum molle*, *J Nat Prod.* **71**, 941–945.
[61] Y. Nakao, S. Kawatsu, C. Okamoto, M. Okamoto, Y. Matsumoto and S. Matsunaga (2008). Ciliatamides A-C, bioactive lipopeptides from the deep-sea sponge *Aaptos ciliata*, *J Nat Prod.* 71469–71472.
[62] W.S. Ma, T. Mutka, B. Vesley, M.O. Amsler, J.B. McClintock and C.D. Amsler (2009). Norselic acids A-E, highly oxidized anti-infective steroids that deter mesograzer predation, from the antarctic sponge *Crella sp*, *J Nat Prod.* **72**, 1842–1846.
[63] D. Savoia, C. Avanzini, T. Allice, E. Callone, G. Guella and F. Dini (2004). Antimicrobial activity of euplotin C, the sesquiterpene taxonomic marker from the marine ciliate Euplotes crassus, *Antimicrob Agents Chemother* **48**, 3828–3833.
[64] N. Singh, R. Kumar, S. Gupta, A. Dube and V. Lakshmi (2008). Antileishmanial activity in vitro and in vivo of constituents of sea cucumber Actinopyga lecanora, *Parasitol Res.* **103**, 351–354.
[65] C.A. Gray, L.S.P. de, M. Silva, E.F. Pimenta, O.H. Thiemann and G. Oliva (2006). Sulfated meroterpenoids from the Brazilian sponge *Callyspongia sp.* are inhibitors of the antileishmaniasis target adenosine phosphoribosyl transferase, *J Org Chem.* **71**, 8685–8690.
[66] E. Galeano, A. Martínez, O.P. Thomas, S. Robledo and D. Munoz (2012). Antiparasitic bromotyrosine derivatives from the caribbean marine sponge aiolochroia crassa, *Quim Nova.* **35**, 1189–1193.
[67] D.S. Medeiros, T.L. Medeiros, J.K.C. Ribeiro, N.K. V Monteiro, L. Migliolo and A.F. Uchoa (2010). A lactose specific lectin from the sponge *Cinachyrella apion*: Purification, characterization, N-terminal sequences alignment and agglutinating activity on Leishmania promastigotes, *Comp Biochem Physiol - B Biochem Mol Biol.* **15**, 5211–5216.
[68] P. Le Pape, M. Zidane, H. Abdala and M.-T. More (2000). A glycoprotein isolated from the sponge, *Pachymatisma johnstonii*, has anti-leishmanial activity, *Cell Biol Int.* **24,** 51–56.
[69] C. Lehnhardt Pires, S.D. Rodrigues, D. Bristot, H.H. Gaeta, D.O. Toyama and W.R.L. Farias (2013). Evaluation of macroalgae sulfated polysaccharides on the *Leishmania* (L.) *amazonensis* promastigote, *Mar Drugs.* **11**, 934–943.
[70] B. Li, F. Lu, X. Wei and R. Zhao (2008). Fucoidan: structure and bioactivity, *Molecules* **13**, 1671–1695.
[71] S. Kar, G. Sharma and P.K. Das (2011). Fucoidan cures infection with both antimony-susceptible and -resistant strains of Leishmania donovani through Th1 response and macrophage-derived oxidants, *J Antimicrob Chemother.* **66,** 618–625.
[72] WHO (2007). TDR Lead Discovery for Drugs, *Business Plan.* 2008-2013.
[73] L. Fumarola, R. Spinelli and O. Brandonisio (2004). In vitro assays for evaluation of drug activity against *Leishmania spp*, *Res Microbiol.* **155**, 224–230.
[74] P.S. Doyle, J.C. Engel, P.F. Pimenta, P.P. da Silva and D.M. Dwyer (1991). *Leishmania donovani*: Long-term culture of axenic amastigotes at 37 degrees C, *Exp Parasitol.* **73**, 326–334.
[75] S. Gupta and Nishi (2011). Visceral leishmaniasis: Experimental models for drug discovery, *Indian J Med Res.* **13**, 327–339.
[76] M. Vermeersch, R.I. da Luz, K. Toté, J.P. Timmermans, P. Cos and L. Maes (2009). In vitro susceptibilities of Leishmania donovani promastigote and amastigote stages to antileishmanial reference drugs: practical relevance of stage-specific differences, *Antimicrob Agents Chemother* **53**, 3855–3859.