Electronic Supplementary Material (ESI) for Natural Product Reports.

Marine Alkaloids as Bioactive Agents Against Protozoal Neglected Tropical Diseases and Malaria

Andre G. Tempone,*[a] Pauline Pieper,[b] Samanta E. T. Borborema,[a] Fernanda Thevenard,[c] Joao Henrique G. Lago,[c] Simon L. Croft,*[d] Edward A. Anderson*[b]

[a]Centre for Parasitology and Mycology, Instituto Adolfo Lutz, 01246-000, São Paulo, Brazil. Email: andre.tempone@ial.sp.gov.br
[b]Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, UK. Email: edward.anderson@chem.ox.ac.uk
[c]Centre of Natural Sciences and Humanities, Federal University of ABC, 09210-580, Sao Paulo, Brazil
[d]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK. Email: simon.croft@lshtm.ac.uk

Supporting Information

Contents

Table S1. *In vitro* bioactivity of marine alkaloids and selected semi-synthetic / synthetic derivatives against *Leishmania* spp., *Trypanosoma* spp. and *Plasmodium falciparum*.

[a]*L. a. = Leishmania amazonensis; L. d. = Leishmania donovani; L. i. = Leishmania infantum; L. ma. = Leishmania major; L. me. = Leishmania mexicana; P. b. = Plasmodium berghei; P. f. = Plasmodium falciparum; T. b. b. = Trypanosoma brucei brucei; T. b. r. = Trypanosoma brucei rhodesiense; T. c. = Trypanosoma cruzi.*

NC = no cytotoxicity; ND = not determined; NS = no selectivity (<1). Selectivity Index = CC_{50} value / IC_{50} value; the value must be > 1.

Compd	Natural product	Source	Parasite[a]	IC_{50} value	CC_{50} value / Selectivity Index	Ref.
1	renieramycin	*Neopetrosia* sp.	*L. a.*	0.2 µg/mL	2.2 µg/mL / 11.0	43
2	araguspongin C	*Haliclona exigua*	*L. d.*	18.6-47.2 µg/mL	34.6 µg/mL / 1.9-NS	44, 45
3	8,9-dihydrocoscinamide B	*Conscinoderma* sp.	*L. d.*	>80% inhibition at 10.0 µg/mL	ND	46, 47
4	*des-N*-methylxestomanzamine A	Indonesian sponge	*L. d.*	35.0 µg/mL	NC	50
5	manzamine A	Indonesian sponge	*L. d.* *P. f.* *P. b.*	0.97 µg/mL 0.0045 µg/mL >97% suppression at 100 µmol/kg (*in vivo*)	1.2 µg/mL / 1.3 1.2 µg/mL / 266.7 ND	50 51
6	8-hydroxymanzamine A	Indonesian sponge	*L. d.* *P. f.*	6.2 µg/mL 0.006 µg/mL	1.1 µg/mL / NS 1.1 µg/mL / 183	50
7	manzamine E	Indonesian sponge	*L. d.* *P. f.*	3.8 µg/mL 3.4 µg/mL	NC	50
8	manzamine F	Indonesian sponge	*L. d.* *P. f.*	4.2 µg/mL 0.78 µg/mL	NC	50
9	12,34-oxamanzamine A	Indonesian sponge	*L. d.* *P. f.*	14.0 µg/mL 4.76 µg/mL	NC	50
10	6-deoxymanzamine X	Indonesian sponge	*L. d.* *P. f.*	3.2 µg/mL 1.3 µg/mL	4.76 µg/mL / 1.5 4.76 µg/mL / 3.6	50
11	manzamine X	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	5.7 µg/mL 0.9 µg/mL	NC	50
12	manzamine J	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	25.0 µg/mL 1.3 µg/mL	NC	52
13	manzamine A *N*-oxide	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	1.1 µg/mL 0.011 µg/mL	4.2 µg/mL / 3.8 4.2 µg/mL / 382	52
14	ircinal A	*Acanthostronglyophora* sp.	*L. d.*	4.6 µg/mL	NC	52
15	ircinol A	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	0.9 µg/mL 2.4 µg/mL	NC	52
16	6-hydroxymanzamine E	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	2.5 µg/mL 0.78 µg/mL	4.3 µg/mL / 1.7 4.3 µg/mL / 5.5	52
17	*neo*-kauluamine	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	4.2 µg/mL 1.7 µg/mL	NC	52
18	manzamine Y	*Acanthostronglyophora* sp.	*L. d.* *P. f.*	1.6 µg/mL 0.42 µg/mL	3.9 µg/mL / 2.4 3.9 µg/mL / 9.3	53
19	12,28-oxamanzamine A	*Acanthostronglyophora* sp.	*L. d.*	7.8 µg/mL	NC	53
20	12,28-oxa-8-hydroxymanzamine A	*Acanthostronglyophora* sp.	*L. d.*	24 µg/mL	NC	53

21	12,28-oxamanzamine E	*Acanthostronglyophora* sp.	*L. d.*	18.0 µg/mL	NC	53
22	8-acetoxymanzamine A	Semi-synthetic	*L. d.* *P. f.*	3.4 µg/mL 0.0096 µg/mL	370 µg/mL / 109 370 µg/mL / 38542	54
23	8,12-diacetoxymanzamine A	Semi-synthetic	*L. d.* *P. f.*	16.0 µg/mL 1.3 µg/mL	NC	54
24	8-methoxymanzamine A	Semi-synthetic	*L. d.* *P. f.*	5.0 µg/mL 0.037 µg/mL	980 µg/mL / 196 980 µg/mL / 26486	54
25	zamamidine C	*Amphimedon* spp.	*T. b. b.* *P. f.*	0.27 µg/mL 0.58 µg/mL	14.1 µg/mL / 52 14.1 µg/mL / 24	49
26	3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A	*Amphimedon* spp.	*T. b. b.* *P. f.*	0.04 µg/mL 0.97 µg/mL	3.6 µg/mL / 90 3.6 µg/mL / 3.71	49
27	3,4-dihydromanzamine J *N*-oxide	*Amphimedon* spp.	*T. b. b.* *P. f.*	4.4 µg/mL 7.0 µg/mL	3.6 µg/mL / NS 3.6 µg/mL / NS	49
28	12-deoxyascididemin	*P. echinatum*	*T. b. b.*	0.077 µM	7.6 µM / 99	55
29	ascididemin	*P. echinatum*	*T. b. b.*	0.032 µM	1.5 µM / 47	55
30	eilatin	*P. echinatum*	*T. b. b.*	1.3 µM	ND	55
31	convolutamine I	*Amathia tortusa*	*T. b. b.*	1.1 µM	22 µM / 18	56
32	convolutamine J	*Amathia tortusa*	*T. b. b.*	13.7 µM	ND	56
33	psammaplysin F	*Hyatella* sp. *Pseudoceratina* sp.	*T. c.* *P. f.*	5.6 µM 1.9 µM	> 3.5 / NS 10.9 µM / 5.7	57 58
34	psammaplysin G	*Pseudoceratina* sp.	*P. f.*	5.2 µM	18.7 µM / 3.6	57
35	psammaplysin H	*Pseudoceratina* sp.	*P. f.*	0.4 µM	> 40 µM / > 97	58
36	dibromopalauamine	*Axinella verrucosa*	*T. b. r.* *P. f.* *L. d.* *T. c.*	0.5 µg/mL 1.5 µg/mL 1.1 µg/mL 69.0 µg/mL	4.5 µg/mL / 9 4.5µg/mL / 3 4.46 µg/mL / 4 4.46 µg/mL / NS	60
37	longamide B	*Agelas díspar*	*T. b. r.* *P. f.* *L. d.* *T. c.*	1.5 µg/mL 7.5 µg/mL 3.8 µg/mL 33.0 µg/mL	9.9 µg/mL / 6.6 9.9 µg/mL / 1.3 9.9 µg/mL / 2.6 9.9 µg/mL / NS	60
38	oroidin	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	12.2 µg/mL 7.9 µg/mL 15.4 µg/mL > 30.0 µg/mL	76.4 µg/mL / 6.3 76.4 µg/mL / 9.7 76.4 µg/mL / 4.9 ND	60
39	hymenidin	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	77.6 µg/mL 12.5 µg/mL 29.9 µg/mL 73.1 µg/mL	75.7 µg/mL / NS 75.7 µg/mL / 6.1 75.7 µg/mL / 2.5 75.7 µg/mL / 1.0	60
40	dispacamide B	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	40.1 µg/mL 1.3 µg/mL > 90.0 µg/mL > 90.0 µg/mL	> 90 µg/mL / > 2.2 > 90 µg/mL / > 69.2 ND ND	60
41	stevensine	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	25.3 µg/mL 4.9 µg/mL 75.8 µg/mL >90.0 µg/mL	> 90 µg/mL / > 3.5 > 90 µg/mL / > 18.3 > 90 µg/mL / > 1.2 > 90 µg/mL / > 1.0	60
42	spongiacidin B	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	13.5 µg/mL 1.1 µg/mL 41.6 µg/mL 72.2 µg/mL	35.6 µg/mL / 2.6 35.6 µg/mL / 32.3 35.6 µg/mL / NS 35.6 µg/mL / NS	60
43	sceptrin	*Axinella* sp. / *Agellas* sp.	*T. b. r.*	9.7 µg/mL	> 90 µg/mL / > 9.3	60

			P. f. *L. d.* *T. c.*	11.1 µg/mL 51.6 µg/mL 60.0 µg/mL	> 90 µg/mL / > 8.1 > 90 µg/mL / > 1.7 > 90 µg/mL / > 1.5	
44	agelongine	*Axinella* sp. / *Agellas* sp.	*T. b. r.* *P. f.* *L. d.* *T. c.*	49.9 µg/mL 11.2 µg/mL 43.2 µg/mL >90.0 µg/mL	> 90 µg/mL / > 1.8 > 90 µg/mL / > 8.0 > 90 µg/mL / > 2 > 90 µg/mL / > 1	60
45	3-hydroxyacetylindole	*Bacillus pumilus* isolated from *Antipaties* sp.	*T. c.*	20.6 µM	ND	62
46	acetyl-β-oxotryptamine	*Bacillus pumilus* isolated from *Antipaties* sp.	*T. c.*	19.4 µM	66 µM / 3.4	62
47	3-formylindole	*Bacillus pumilus* isolated from *Antipaties* sp.	*T. c.*	26.9 µM	ND	62
48	fascaplysin	*Hyrtios cf. erecta*	*T. b. r.* *P. f.*	0.17 µg/mL 0.05 µg/mL	2.5 µg/mL / 14.7 2.5 µg/mL / 50	63
49	homofascaplysin	*Hyrtios cf. erecta*	*P. f.*	0.014 µg/mL	1.1 µg/mL / 78	63
50	staurosporine	*Streptomyces* sp.	*L. ma.* *T. b. b.*	5.3 µM 0.02 µM	1.3 µM / 0.25 1.3 µM / 65	64
51	tryptophol	*Spongia* sp. *and Ircinia* sp.	*L. d.* *T. c.* *T. b. b.* *P. f.*	9.6 µg/mL 49.4 µg/mL 5.9 µg/mL 5.1 µg/mL	63.5 µg/mL / 6.6 63.5 µg/mL / 1.3 63.5 µg/mL / 11 63.5 µg/mL / 13	65
52	didemnidine A	*Didemnum* sp.	*T. c.* *T. b. r.* *P. f.*	130.0 µM 59.0 µM 41.0 µM	24 µM / NS 24 µM / NS 24 µM / NS	66
53	didemnidine B	*Didemnum* sp.	*T. c.* *T. b. r.* *P. f.*	82.0 µM 44.0 µM 15.0 µM	25 µM / NS 25 µM / NS 25 µM / 1.7	66
54	diazepinomicin	*Micromonospora* sp. from *Aplysina aerophoba*	*T. b. b.*	13.6 µM	ND	67
55	paenidigyamycin A	*Paenibacillus* sp.	*L. ma.* *L. d.* *T. b. b.* *P. f.*	0.75 µM 7.0 µM 0.8 µM 9.1 µM	NC	68
56	viscosamine	*Haliclona viscosa*	*L. ma.* *L. me.* *T. b. b.* *P. f.*	0.7 µM 0.8 µM 0.4 µM 0.05 µM	26 µM / 37 26 µM / 33 26 µM / 65 26 µM / 520	70
57	3-tridecylpyridinium alkaloid	Synthetic	*L. ma* *L. me.* *T. b. b.* *P. f.*	0.8 µM 0.2 µM 0.2 µM 0.07 µM	16 µM / 20 16 µM / 80 16 µM / 80 16 µM / 229	70
58	3-tridecylpyridinium alkaloid	Synthetic	*L. ma.* *L. me.* *T. b. b.* *P. f.*	0.6 µM 1.1 µM 0.5 µM 0.2 µM	14 µM / 23 14 µM / 13 14 µM / 28 14 µM / 70	70
59	batzelladine A	*Monanchora arbuscula / Clathria calla*	*P. f.*	0.3 µM	2.9 µM / 9.7	71
60	norbatzelladine A	*Monanchora arbuscula / Clathria calla*	*P. f.*	0.2 µM	4.7 µM / 24	71
61	dinorbatzelladine A	*Monanchora arbuscula / Clathria calla*	*P. f.*	0.9 µM	ND	71
62	dinordehydrobatzelladine B	*Monanchora arbuscula / Clathria calla*	*P. f.*	0.8 µM	ND	71

63	dihomodehydrobatzelladine C	*Monanchora arbuscula* / *Clathria calla*	*P. f.*	4.5 μM	ND	71
64	clathriadic acid	*Monanchora arbuscula* / *Clathria calla*	*P. f.*	2.3 μM	ND	71
65	ptilomycalin A	*Monanchora arbuscula* / *Clathria calla*	*P. f.*	0.1 μM	0.1 μM / 1	71
66	batzelladine L	*Monanchora arbuscula*	*P. f.* *T. c.* *L. i.*	0.3 μM 2.0 μM 2.0 μM	< 0.1 μM / NS 22 μM / 11 22 μM / 11	71 72 72
67	norbatzelladine L	*Monanchora arbuscula*	*P. f.* *T. c.* *L. i.*	0.4 μM 7.0 μM 2.0 μM	ND 85 μM / 12 85 μM / 43	71 72 72
68	batzelladine F	*Monanchora arbuscula*	*T. c.* *L. i.*	5.0 μM 4.0 μM	10 μM / 2 10 μM / 2.5	72
69	batzelladine D	*Monanchora arbuscula*	*T. c.* *L. i.*	64.0 μM 2.0 μM	130 μM / 2.0 130 μM / 65	72
70	monalidine A	*Monanchora arbuscula*	*T. c.* *L. i.*	8.0 μM 2.0 μM	26 μM / 3.3 26 μM / 13	72
71	ptilomycalins E	*Monanchora unguiculata*	*P. f.*	0.35 μM	0.85 μM / 2.4	73
72	ptilomycalins F	*Monanchora unguiculata*	*P. f.*	0.23 μM	1.61 μM / 7	73
73 / **74**	ptilomycalin G / H	*Monanchora unguiculata*	*P. f.*	0.46 μM	0.92 μM / 2	73
75	crambescidin 800	*Monanchora unguiculata*	*P. f.*	0.52 μM	1.31 μM / 2.5	73
76	fromiamycalin	*Monanchora unguiculata*	*P. f.*	0.24 μM	1.17 μM / 5	73
77	unguilicin A	*Monanchora unguiculata*	*P. f.*	12.89 μM	7.66 μM / NS	73
78	tricyclic guanidinium ion batzelladine mimic	Synthetic	*T. c.* *L. i.*	4.0 μM 59.0 μM	84 μM / 21 84 μM / 1.4	74
79	tricyclic guanidinium ion batzelladine mimic	Synthetic	*T. c.* *L. i.*	9.0 μM 2.0 μM (amastigote) 34 μM (promastigote)	45 μM / 5 45 μM / 22 45 μM / 1.3	74
80	spiroaminal guanidinium ion	Synthetic	*L. i.*	8.0 μM	> 150 μM / > 19	74
81	lissoclinotoxin E	Philippine didemnid ascidian	*T. c.* *L. d.* *L.d.* *T. b. b.*	3.9 μM 0.7 (promastigote) 4.4 μM (amastigote) 0.6 μM	NC	57
82	thiaplakortone A	*Plakortis lita*	*T. c.* *T. b. b.* *P. f.*	4.3 μM 3.9 μM 0.051 μM	NS NS 3.9 μM / 76	57 57 75
83	thiaplakortone B	*Plakortis lita*	*P. f.*	0.65 μM	> 40 μM / > 62	75
84	thiaplakortone C	*Plakortis lita*	*P. f.*	0.30 μM	> 40 μM / > 133	75
85	thiaplakortone D	*Plakortis lita*	*P. f.*	0.28 μM	> 80 μM / > 285	75
86	thiaplakortone A analogue	Synthetic	*T. c.* *T. b. b.*	3.5 μM 0.7 μM	ND	57
87	8-oxo-tryptamine	*Fascaplysinopsis reticulata*	*P. f.*	8.8 μg/mL	ND	76
(*E*/*Z*)-88	(*E*)/(*Z*)-bromo-2'-demethyl-3'-*N*-methylaplysinopsin	*Fascaplysinopsis reticulata*	*P. f.*	8.0 μg/mL	ND	76
89	hyrtiodoline A	*Hyrtios* sp.	*T. b. b.*	15.2 μM	> 200 μM / > 13	77
90	caulidamine A	*Caulibugula intermis*	*P. f.*	8.3 μM	ND	78
91	caulidamine B	*Caulibugula intermis*	*P. f.*	12.9 μM	ND	78

92	eudistidine C	*Eudistoma* sp.	*P. f.*	2.8-4.2 μM	NC	79
93	eudistidine A	*Eudistoma* sp.	*P. f.*	1.4 μM	NC	79, 80
94	eudistidine C analogue	synthetic	*P. f.*	1.1 μM	NC	79
95	netamine K	*Biemna laboutei*	*P. f.*	2.4 μM	> 1 μM / NS	81
95	mirabilin A	*Biemna laboutei*	*P. f.*	21.0 μM	> 1 μM / NS	81
97	mirabilin B	*Monanchora unguifera*	*L. d.*	17.6 μg/mL	NC	82
98	1,8a;8b,3a-didehydro-8b-hydroxyptilocaulin	*Monanchora unguifera*	*P. f.*	3.8 μg/mL	NC	82
99	1,8a;8b,3a-didehydro-8a hydroxyptilocaulin	*Monanchora unguifera*	*P. f.*	3.8 μg/mL	NC	82
100	netamine O	*Biemna laboutei*	*P. f.*	17.0 μM	> 0.01 μM / NS	83
101	netamine P	*Biemna laboutei*	*P. f.*	33.0 μM	> 0.01 μM / NS	83
102	netamine Q	*Biemna laboutei*	*P. f.*	8.4 μM	> 0.01 μM / NS	83
103	nortopsentin A	*Spongosorites*	*P. f.*	0.4 μM	6.6 μM / 14	84
104	ingamine A	*Petrosid Ng5 Sp5*	*P. f.* *L. d.*	0.09 μg/mL 5.98 μg/mL	> 10 μg/mL / > 111 > 10 μg/mL / > 1.7	86
105	hydroxyingamine A	*Petrosid Ng5 Sp5*	*P. f.* *L. d.*	0.22 μg/mL 5.83 μg/mL	> 10 μg/mL / > 45 > 10 μg/mL / > 1.7	86
106	dihydroingenamine D	*Petrosid Ng5 Sp5*	*P. f.* *L. d.*	0.078 μg/mL 3.12 μg/mL	> 10 μg/mL / > 128 > 10 μg/mL / > 3.2	86
107	neopetrosiamine A	*Neopetrosia proxima*	*P. f.*	2.3 μM	ND	87
108	marinacarboline A	*Marinactinospora thermotolerans*	*P. f.*	1.9 μM	> 50 μM / > 26	88
109	marinacarboline B	*Marinactinospora thermotolerans*	*P. f.*	15.6 μM	> 50 μM / > 3.2	88
110	marinacarboline C	*Marinactinospora thermotolerans*	*P. f.*	3.4 μM	> 50 μM / > 15	88
111	marinacarboline D	*Marinactinospora thermotolerans*	*P. f.*	3.6 μM	> 50 μM / > 14	88
112	13-N-demethyl-methylpendolmycin	*Marinactinospora thermotolerans*	*P. f.*	18.7 μM	> 50 μM / > 2.7	88
113	methylpendolmy-cin-14-O-α-glucoside	*Marinactinospora thermotolerans*	*P. f.*	5.0 μM	> 50 μM / > 5	88
114	meridianin A	*Psammopemma* sp. / *Aplidium meridianum*	*P. f.*	12 μM	15.0 μM / 1.2	89
115	4-methoxymeridianin A	synthetic	*P. f.*	40 μM	> 420 μM / > 10	89
116	meridoquin	synthetic	*P. f.*	200 μM	> 333 μM / > 1.7	89
117	meridianin C	*Aplidium meridianum*	*P. f.*	14.4 μM	> 87 μM / > 6.0 μM	91
118	meridianin G	*Aplidium meridianum*	*P. f.*	9.7 μM	> 119 μM / > 11 μM	91
119	monamphilectine A	*Hymeniacidon* sp.	*P. f.*	0.04 μM	ND	92
120	lepadin D	*Didemnum* sp.	*T. b. r.* *T. c.* *P. f.*	5.6 μg/mL 37.2 μg/mL 10.0 μg/mL	> 30 μg/mL / > 5.4 > 30 μg/mL / NS > 30 μg/mL / > 3	93
121	lepadin E	*Didemnum* sp.	*T. b. r.* *T. c.* *P. f.*	0.38 μg/mL 2.2 μg/mL 0.9 μg/mL	16.2 μg/mL / 43 16.2 μg/mL / 7.4 16.2 μg/mL / 18	93
122	lepadin F	*Didemnum* sp.	*T. b. r.* *T. c.* *P. f.*	0.23 μg/mL 2.6 μg/mL 0.3 μg/mL	18.43 μg/mL / 80 18.43 μg/mL / 7.1 18.43 μg/mL / 61	93

Table S2: *Plasmodium falciparum* Top hits by IC_{50}: <~1 µg / mL or <~1 µM, and SI>10, ordered by Selectivity Index.

Compound	Natural product	*Source*	IC_{50} value	SI	Ref.
8	manzamine F	*Indonesian sponge*	0.78 µg/mL	NC	48
11	manzamine X	*Acanthostronglyophora* sp.	0.9 µg/mL	NC	48
94	eudistidine C analogue	synthetic	1.1 µM	NC	79
22	8-acetoxymanzamine A	Semi-synthetic	0.0096 µg/mL	38542	54
24	8-methoxymanzamine A	Semi-synthetic	0.037 µg/mL	26486	54
56	viscosamine	*Haliclona viscosa*	0.05 µM	520	70
13	manzamine A N-oxide	*Acanthostronglyophora* sp.	0.011 µg/mL	382	52
85	thiaplakortone D	*Plakortis lita*	0.28 µM	>285	75
5	manzamine A	*Indonesian sponge*	0.0045 µg/mL	266.7	48
57	3-tridecylpyridinium alkaloid	Synthetic	0.07 µM	229	70
6	8-hydroxymanzamine A	Indonesian sponge	0.006 µg/mL	183	48
84	thiaplakortone C	*Plakortis lita*	0.30 µM	>133	75
106	dihydroingenamine D	*Petrosid Ng5 Sp5*	0.078 µg/mL	>128	86
104	ingamine A	*Petrosid Ng5 Sp5*	0.09 µg/mL	>11	86
35	psammaplysin H	*Pseudoceratina* sp.	0.4 µM	>97	59
49	homofascaplysin	*Hyrtios cf. erecta*	0.014 µg/mL	78	63
82	thiaplakortone A	*Plakortis lita*	0.051 µM	76	75
58	3-tridecylpyridinium alkaloid	Synthetic	0.2 µM	70	70
83	thiaplakortone B	*Plakortis lita*	0.65 µM	>62	75
122	lepadin F	*Didemnum* sp.	0.3 µg/mL	61	93
48	fascaplysin	*Hyrtios cf. erecta*	0.05 µg/mL	50	63
105	hydroxyingamine A	*Petrosid Ng5 Sp5*	0.22 µg/mL	> 45	86
25	zamamidine C	*Amphimedon* spp.	0.58 µg/mL	24	47
121	lepadin E	*Didemnum* sp.	0.9 µg/mL	18	93
103	nortopsentin A	*Spongosorites*	0.4 µM	14	84
67	norbatzelladine L	*Monanchora arbuscula*	0.4 µM	ND	71
119	monamphilectine A	*Hymeniacidon* sp.	0.04 µM	ND	92

Table S3: *Trypanosoma* Top hits by IC_{50}: <~1 µg / mL or <~1 µM, and SI>~10, ordered by Selectivity Index.

Compd	Natural product	*Source*	*Parasitea*	IC_{50} value	SI	Ref.
28	12-deoxyascididemin	*P. echinatum*	*T. b. b.*	0.077 µM	99	54
26	3,4-dihydro-6-hydroxy-10,11-epoxymanzamine A	*Amphimedon* spp.	*T. b. b.*	0.04 µg/mL	90	47
57	3-tridecylpyridinium alkaloid	Synthetic	*T. b. b.*	0.2 µM	80	70
122	lepadin F	*Didemnum* sp.	*T. b. r.* *T. c.*	0.23 µg/mL 2.6 µg/mL	80 7.1	93
50	staurosporine	*Streptomyces* sp.	*T. b. b.*	0.02 µM	65	64
56	viscosamine	*Haliclona viscosa*	*T. b. b.*	0.4 µM	65	70
25	zamamidine C	*Amphimedon* spp.	*T. b. b.*	0.27 µg/mL	52	47
29	ascididemin	*P. echinatum*	*T. b. b.*	0.032 µM	47	55
121	lepadin E	*Didemnum* sp.	*T. b. r.* *T. c.*	0.38 µg/mL 2.2 µg/mL	43 7.4	93
48	fascaplysin	*Hyrtios cf. erecta*	*T. b. r.*	0.17 µg/mL	14.7	63
58	3-tridecylpyridinium alkaloid	Synthetic	*T. b. b.*	0.5 µM	28	70
36	dibromopalauamine	*Axinella verrucosa*	*T. b. r.* *T. c.*	0.5 µg/mL 69.0 µg/mL	9 NS	60
86	thiaplakortone A analogue	Synthetic	*T. c.* *T. b. b.*	3.5 µM 0.7 µM	ND ND	57

Table S4: *Leishmania* Top hits by IC_{50}: <~1 µg / mL or <~1 µM, and SI>~10, ordered by Selectivity Index.

Compd	Natural product	*Source*	*Parasitea*	IC_{50} value	SI	Ref.
15	ircinol A	*Acanthostronglyophora* sp.	*L. d.*	0.9 µg/mL	NC	52
57	3-tridecylpyridinium alkaloid	Synthetic	*L. ma* *L. me.*	0.8 µM 0.2 µM	20 80	70
56	viscosamine	*Haliclona viscosa*	*L. ma.* *L. me.*	0.7 µM 0.8 µM	37 33	70
58	3-tridecylpyridinium alkaloid	Synthetic	*L. ma.* *L. me.*	0.6 µM 1.1 µM	23 13	70
1	renieramycin	*Neopetrosia* sp.	*L. a.*	0.2 µg/mL	11.0	41

References *(note: Reference numbering corresponds to that in the review article).*

43 Y. Nakao, T. Shiroiwa, S. Murayama, S. Matsunaga, Y. Goto, Y. Matsumoto and N. Fusetani, *Mar. Drugs*, 2004, **2**, 55-62.

44 Y. Venkateswarlu, M. V. R. Reddy and J. V. Rao, *J. Nat. Prod.*, 1994, **57**, 1283-1285.

45 A. Dube, N. Singh, A. Saxena and V. Lakshmi, *Parasitology Res.*, 2007, **101**, 317-324.

46 H. R. Bokesch, L. K. Pannell, T. C. McKee and M. R. Boyd, *Tetrahedron Lett.*, 2000, **41**, 6305-6308.

47 L. Gupta, A. Talwar, Nishi, S. Palne, S. Gupta and P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4075-4079.

49 M. Yamada, Y. Takahashi, T. Kubota, J. Fromont, A. Ishiyama, K. Otoguro, H. Yamada, S. Ōmura and J. i. Kobayashi, *Tetrahedron*, 2009, **65**, 2313-2317.

50 K. V. Rao, B. D. Santarsiero, A. D. Mesecar, R. F. Schinazi, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod.*, 2003, **66**, 823-828.

51 K. Ang, M. Holmes and U. Kara, *Parasitology Res.*, 2001, **87**, 715-721.

52 K. V. Rao, N. Kasanah, S. Wahyuono, B. L. Tekwani, R. F. Schinazi and M. T. Hamann, *J. Nat. Prod.*, 2004, **67**, 1314-1318.

53 K. V. Rao, M. S. Donia, J. Peng, E. Garcia-Palomero, D. Alonso, A. Martinez, M. Medina, S. G. Franzblau, B. L. Tekwani, S. I. Khan, S. Wahyuono, K. L. Willett and M. T. Hamann, *J. Nat. Prod.*, 2006, **69**, 1034-1040.

54 A. G. Shilabin, N. Kasanah, B. L. Tekwani and M. T. Hamann, *J. Nat. Prod.*, 2008, **71**, 1218-1221.

55 Y. Feng, R. A. Davis, M. L. Sykes, V. M. Avery, A. R. Carroll, D. Camp and R. J. Quinn, *Tetrahedron Lett.*, 2010, **51**, 2477-2479.

56 R. A. Davis, M. Sykes, V. M. Avery, D. Camp and R. J. Quinn, *Bioorg. Med. Chem.*, 2011, **19**, 6615-6619.

57 B. Zulfiqar, A. Jones, M. Sykes, T. Shelper, R. Davis and V. Avery, *Molecules*, 2017, **22**, 1715-1715.

58 X. Yang, R. A. Davis, M. S. Buchanan, S. Duffy, V. M. Avery, D. Camp and R. J. Quinn, *J. Nat. Prod.*, 2010, **73**, 985-987.

59 M. Xu, K. T. Andrews, G. W. Birrell, T. L. Tran, D. Camp, R. A. Davis and R. J. Quinn, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 846-848.

60 F. Scala, E. Fattorusso, M. Menna, O. Taglialatela-Scafati, M. Tierney, M. Kaiser and D. Tasdemir, *Mar. Drugs*, 2010, **8**, 2162-2174.

62 S. Martínez-Luis, J. F. Gómez, C. Spadafora, H. M. Guzmán and M. Gutiérrez, *Molecules*, 2012, **17**, 11146-11155.

63 G. Kirsch, G. M. König, A. D. Wright and R. Kaminsky, *J. Nat. Prod.*, 2000, **63**, 825-829.

64 S. M. Pimentel-Elardo, S. Kozytska, T. S. Bugni, C. M. Ireland, H. Moll and U. Hentschel, *Mar. Drugs*, 2010, **8**, 373-380.

65 I. Orhan, B. Şener, M. Kaiser, R. Brun and D. Tasdemir, *Mar. Drugs*, 2010, **8**, 47-58.

66 R. Finlayson, A. N. Pearce, M. J. Page, M. Kaiser, M.-L. Bourguet-Kondracki, J. L. Harper, V. L. Webb and B. R. Copp, *J. Nat. Prod.*, 2011, **74**, 888-892.

67 U. R. Abdelmohsen, M. Szesny, E. M. Othman, T. Schirmeister, S. Grond, H. Stopper and U. Hentschel, *Mar. Drugs*, 2012, **10**, 2208-2221.

68 E. Osei, S. Kwain, G. Mawuli, A. Anang, K. Owusu, M. Camas, A. Camas, M. Ohashi, C.-N. Alexandru-Crivac, H. Deng, M. Jaspars and K. Kyeremeh, *Mar. Drugs*, 2019, **17**, 1-13.

69 B. Rodenko, M. I. Al-Salabi, I. A. Teka, W. Ho, N. El-Sabbagh, J. A. M. Ali, H. M. S. Ibrahim, M. J. Wanner, G.-J. Koomen and H. P. de Koning, *ACS Med. Chem. Lett.*, 2011, **2**, 901-906.

71 R. m. Laville, O. P. Thomas, F. Berrué, D. Marquez, J. Vacelet and P. Amade, *J. Nat. Prod.*, 2009, **72**, 1589-1594.

72 M. F. C. Santos, P. M. Harper, D. E. Williams, J. T. Mesquita, É. G. Pinto, T. A. da Costa-Silva, E. Hajdu, A. G. Ferreira, R. A. Santos, P. J. Murphy, R. J. Andersen, A. G. Tempone and R. G. S. Berlinck, *J. Nat. Prod.*, 2015, **78**, 1101-1112.

73 P.-E. Campos, J.-L. Wolfender, E. F. Queiroz, L. Marcourt, A. Al-Mourabit, M. Frederich, A. Bordignon, N. De Voogd, B. Illien and A. Gauvin-Bialecki, *J. Nat. Prod.*, 2017, **80**, 1404-1410.

74 L. F. Martins, J. T. Mesquita, E. G. Pinto, T. A. Costa-Silva, S. E. T. Borborema, A. J. Galisteo Junior, B. J. Neves, C. H. Andrade, Z. A. Shuhaib, E. L. Bennett, G. P. Black, P. M. Harper, D. M. Evans, H. S. Fituri, J. P. Leyland, C. Martin, T. D. Roberts, A. J. Thornhill, S. A. Vale, A. Howard-Jones, D. A. Thomas,

H. L. Williams, L. E. Overman, R. G. S. Berlinck, P. J. Murphy and A. G. Tempone, *J. Nat. Prod.*, 2016, **79**, 2202-2210.

75 R. A. Davis, S. Duffy, S. Fletcher, V. M. Avery and R. J. Quinn, *J. Org. Chem.*, 2013, **78**, 9608-9613.

76 P.-E. Campos, E. Pichon, C. Moriou, P. Clerc, R. Trépos, M. Frederich, N. De Voogd, C. Hellio, A. Gauvin-Bialecki and A. Al-Mourabit, *Mar. Drugs*, 2019, **17**, 167-167.

77 N. H. Shady, M. A. Fouad, S. Ahmed, S. M. Pimentel-Elardo, J. R. Nodwell, M. S. Kamel and U. R. Abdelmohsen, *J. Antibiot.*, 2018, **71**, 1036-1039.

78 D. J. Milanowski, N. Oku, L. K. Cartner, H. R. Bokesch, R. T. Williamson, J. Saurí, Y. Liu, K. A. Blinov, Y. Ding, X.-C. Li, D. Ferreira, L. A. Walker, S. Khan, M. T. Davies-Coleman, J. A. Kelley, J. B. McMahon, G. E. Martin and K. R. Gustafson, *Chem. Sci.*, 2018, **9**, 307-314.

79 S. T. S. Chan, R. R. Nani, E. A. Schauer, G. E. Martin, R. T. Williamson, J. Saurí, A. V. Buevich, W. A. Schafer, L. A. Joyce, A. K. L. Goey, W. D. Figg, T. T. Ransom, C. J. Henrich, T. C. McKee, A. Moser, S. A. MacDonald, S. Khan, J. B. McMahon, M. J. Schnermann and K. R. Gustafson, *J. Org. Chem.*, 2016, **81**, 10631-10640.

80 S. T. S. Chan, P. R. Patel, T. R. Ransom, C. J. Henrich, T. C. McKee, A. K. L. Goey, K. M. Cook, W. D. Figg, J. B. McMahon, M. J. Schnermann and K. R. Gustafson, *J. Am. Chem. Soc.*, 2015, **137**, 5569-5575.

81 E. Gros, A. Al-Mourabit, M.-T. Martin, J. Sorres, J. Vacelet, M. Frederich, M. Aknin, Y. Kashman and A. Gauvin-Bialecki, *J. Nat. Prod.*, 2014, **77**, 818-823.

82 H.-m. Hua, J. Peng, F. R. Fronczek, M. Kelly and M. T. Hamann, *Bioorg. Med. Chem.*, 2004, **12**, 6461-6464.

83 E. Gros, M.-T. Martin, J. Sorres, C. Moriou, J. Vacelet, M. Frederich, M. Aknin, Y. Kashman, A. Gauvin-Bialecki and A. Al-Mourabit, *Chem. Biodivers.*, 2015, **12**, 1725-1733.

84 S. Alvarado, B. F. Roberts, A. E. Wright and D. Chakrabarti, *Antimicrob. Agents Chemother.*, 2013, **57**, 2362-2364.

86 M. Ilias, M. Ibrahim, S. Khan, M. Jacob, B. Tekwani, L. Walker and V. Samoylenko, *Planta Med.*, 2012, **78**, 1690-1697.

87 X. Wei, K. Nieves and A. D. Rodríguez, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5905-5908.

88 H. Huang, Y. Yao, Z. He, T. Yang, J. Ma, X. Tian, Y. Li, C. Huang, X. Chen, W. Li, S. Zhang, C. Zhang and J. Ju, *J. Nat. Prod.*, 2011, **74**, 2122-2127.

89 M. D. Lebar, K. N. Hahn, T. Mutka, P. Maignan, J. B. McClintock, C. D. Amsler, A. van Olphen, D. E. Kyle and B. J. Baker, *Bioorg. Med. Chem.*, 2011, **19**, 5756-5762.

91 R. R. Yadav, S. I. Khan, S. Singh, I. A. Khan, R. A. Vishwakarma and S. B. Bharate, *Eur. J. Med. Chem.*, 2015, **98**, 160-169.

92 E. Avilés and A. D. Rodríguez, *Org. Lett.*, 2010, **12**, 5290-5293.

93 A. D. Wright, E. Goclik, G. M. König and R. Kaminsky, *J. Med. Chem.*, 2002, **45**, 3067-3072.