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Review Article

Antiprotozoal Activity of α,β-Unsaturated δ-Lactones: Promising Compounds for the Development of New Therapeutic Alternatives

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Abstract

The parasite resistance and side effects of drugs used to treat protozoal diseases have led to the search for new therapies, both natural and synthetic. Studies have shown that various α,β-unsaturated δ-lactones displayed high antiprotozoal activity and thus are promising compounds for new drug discovery and development. These compounds and their activity are examined in this review.

***Keywords*:** Lactones, Pyrones, Antiparasitic, Antiprotozoal, Leishmania, Malaria, Chagas, *Plasmodium falciparum*, *Tripanosoma cruzi*.

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INTRODUCTION

Protozoal diseases, particularly malaria, leishmaniasis and Chagas disease, represent major causes of mortality in various tropical and subtropical regions. These diseases remain significant health problems in many developing countries, and this situation is compounded by increasing treatment failures using current drugs.

Malaria causes more than 300 million acute illnesses and at least one million deaths annually. Resistance of the malaria parasites, *Plasmodium spp.*, to drugs such as chloroquine (and, more lately, quinine) occurs with increasing frequency [1,2]. This resistance underlies the necessity of developing new agents for malaria chemotherapy, with new modes of action to replace current ineffective drugs.

Leishmaniasis is a major health problem that affects approximately 12 million people worldwide, with 2 million new cases diagnosed every year [3]. The causative agents of this disease are parasites of the genus *Leishmania*, which infect and replicate in macrophages of the vertebrate host. Recently, a dramatic increase in the number of cases of leishmaniasis has been observed in patients with compromised T-cell function, such as those infected with the human immunodeficiency virus [4]. The chemotherapy of leishmaniasis has been based on pentavalent antimonials, sodium stibogluconate (pentostam) and meglumine antimonite (glucantime). These drugs contain multiple uncharacterized molecular structures with variable efficacies and toxicities, they are associated with moderate and severe side effects [5-7], prone to induce resistance [8,9] and require parenteral administration over a long period [10]. Second-line drugs, such as Amphotericin B and its lipid formulations, are either more toxic and expensive for routine use in developing countries.

Trypanosoma cruzi is a protozoa that causes Chagas disease (American trypanosomiasis); it is an obligate intracellular protozoan parasite that causes acute and chronic infection in several mammalian species including humans. This illness affects approximately 16 to 18 million people in tropical and sub-tropical Americas leading to the death of approximately 400.000 people per year [11]. Nifurtimox and benznidazole, the drugs currently in use against this disease, present several side effects and have limited efficacy [12]. Gentian violet, another compound for the prevention of Chagas disease by blood transfusion [13], leads to purple colouring of the blood and staining of patients' tissues. The use of gentian violet is limited due to its toxicity and other side effects such as alteration of skin color, mucous membranes and urine [14].

The development of new, effective, non-toxic and less expensive drugs is required to contribute to the world-wide control of these diseases. 6-Substituted 5,6-dihydro-α-pyrones, so-called α,β-unsaturated δ-lactones (see Fig **1**) of both natural and non-natural origin have been found to exhibit relevant pharmacological activities. We cite a few examples: pironetin (**1**) [15] has been found to inhibit cell cycle progression in the M phase. Callystatin A (**2**) [16] gonodiol (**3**) [17] obolactone (**4**) [18] and spicigerolide (**5**) [19], exhibit cytotoxic activity. Goniothalamin (**6**) [20] induce the apoptotic process. Fostriecin (**7**) is an anticancer agent [21]. Rugulactone (**8**) inhibits NF-KB activation pathway [22]. Lactones **9** [23] and **10** [24], as well as massoilactone (**11**) [25] and strictifolione (**12**) [26] have shown antifungal activity. Pectinolides A-C (**13**) exhibit significant antimicrobial and cytotoxic activity [27]. Phomalactone (**14**) displayed herbicidal, antibacterial and insecticidal activity [28] and kavalactones (**15**) display various and important biological properties such as sedative, anxiolytic, anti-inflammatory and analgesic effects [29,30].

In an effort to discover new compounds for infectious diseases treatment, several α,β-unsaturated δ-lactones were evaluated and

found to have high antiprotozoal activity. Our finding are summarizes in this review.

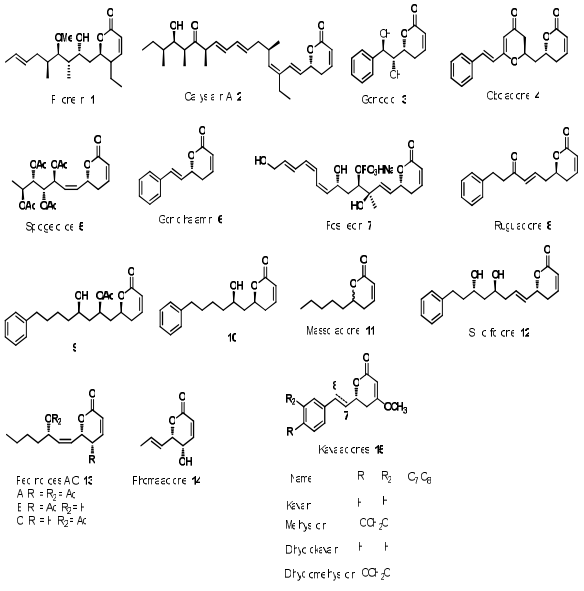

Fig 1: Structures of α,β-Unsaturated δ-lactone

ANTILEISHMANIAL ACTIVITY

Argentilactone (**16**) (Fig **2**) was isolated from *Aristolochia argentina* (*Aristolochiaceae*) [31], *Chorisia crispflora* (*Bombaceae*) [32], *Annona haema*tantha (*Annonaceae*) [33] and *Raimondia cf. (monoica)* [34]. This natural pyranone was shown to have *in vitro* leishmanicidal activity against *Leishmania panamensis* (ED_{50} = 51.5μM) [34] and *Leishmania amazonensis* (ED_{50} = 51.5 μM) [33]. Compound **16** displayed activity against promastigotes of *Leishmania Mexicana*. At 5μg/ml concentration, synthetic argentilactone leads to marked growth retardation in promastigote cultures, while at 10μg/ml, the parasites are unable to proliferate and die within 2-3 days [35].

Argentilactone exhibited *in vitro* activity against various strains of *Leishmania ssp.* at 10 μg/ml. BALB/c mice infected with *Leishmania amazonensis* were treated four weeks after infection with argentilactone by oral or subcutaneous routes for 14 days at 25 mg/kg daily. The reference drug, *N*-methylglucamine antimonate, was administered by subcutaneous injections at l00 mg/kg for 14 days. Under these conditions, argentilactone showed the same efficacy as the reference drug, reducing by 96 % the parasite loads in the lesion and by 50% the parasite burden in spleen [36]. Other studies showed that **16** exhibited cytotoxic activity against P-388 mouse leukemia cells (IC_{50} = 21.4μM) [32] and both enantiomers of argentilactone displayed antiproliferative activity against several human cancer cell lines [37]. Two argentilactone epoxides derivatives, **17** and **18** (Fig **2**) showed *in vitro* activity against *Leishmania amazonensis* (IC_{50} = 22.3 and 44.6 *m*g/mL, respectively), epoxide (**19**) displayed no activity [38].

Lactones (**20**) and (**21**) (Fig **2**) were isolated from dichloromethane extracts of both the roots and the leaves of *Raimondia cf. monoica.* These compounds showed *in vitro* leishmanicidal activities against *Leishmania panamensis* with ED_{50} of 1.9 and 0.42 μg/mL, respectively, and cytotoxicity on U-937 cells with LD_{50} of 2.1 and 1.0 μg/mL, respectively [34].

Passifloricin A was isolated from *Passiflora foetida* resin [39], its structure was revised as a consequence of a stereospecific synthesis [40]. Several natural, hemisynthetic and synthetic passifloricins were tested against *Leishmania panamensis* amastigotes [41,42] (Fig **2**). High leishmanicidal activity as well as toxicity were observed. Passifloricin A (**22**) showed activity (EC_{50}) and cytotoxicity (LC_{50}) of 0.36 and 2.3, respectively. Change in the C-12 configuration decreases both the activity and cytotoxicity (**22** vs **23**) (see Table **1**). Modifications in the hydroxyl substituents (acetylation, **26**, **27** and **45-47** (**vs 41-43**); cetalization, **28**; and oxidation, **48 vs 22**) decrease both activity and cytotoxicity.

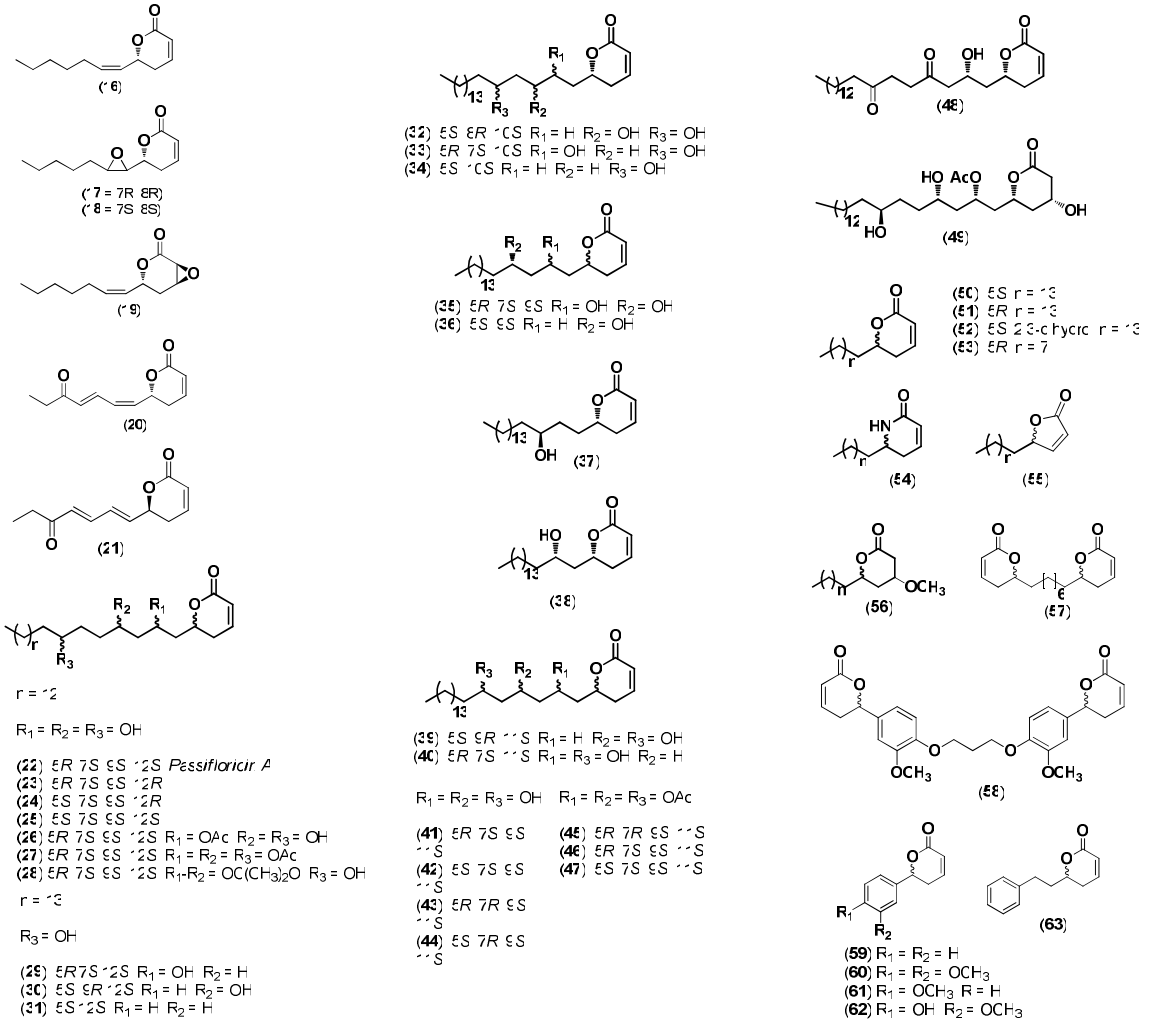

Fig 2: α,β-unsaturated δ-lactones with leishmanicidal activity

In general, most active compounds are those with two hydroxyl groups in the side chain (**29**, **32**, **33**, **35**, **39** and **40**). Compounds with hydroxyl group in side chains have a tendency to increase activity and decrease cytotoxicity when the hydroxyl group is farther from the closure of the lactone (**31**, **34** and **36-38**). However, a comparison of the biological profiles of these compounds indicate there is no tendency to increase activity against *L. panamensis* according to the number of hydroxyl groups.

Several aliphatic and aromatic lactones and two dimers were synthesized to establish a relationship between structure and activity (see Fig **2**) [43]. These compounds were active *in vitro* against intracellular amastigotes of *Leishmania panamensis* (see Table **1**).

Change in the stereochemistry of the lactone closure has no significant effect on the biological activity (**50** vs **51**). However, shortening the length of the side chain decreases it (**51** vs **53**). Lactam **54** exhibited lower leishmanicidal activity (3.4 µg/mL) than compound rac-**50** (0.8 µg/mL), but it displayed less cytotoxicity (45.1 µg/mL vs 3.5 µg/mL) and the selectivity index (SI) was

Table 1: Activity against *Leishmania panamensis* and *Plasmodium falciparum* of α,β-unsaturated δ-lactones

Compound	Cytotoxicity LC_{50} (µg/mL)	Leismanicidal Activity		Antiplasmodial Activity
		EC_{50} (µg/mL)	SI	IC_{50} (µg/mL)
22	2.3	0.36	6.4	20.9
Passifloricin A				
23	4.9	0.93	5.3	53.6
24	2.1	0.13	16.2	23.1
25	2.1	0.44	4.8	41.9
26	2.8	0.60	4.7	-
27	3.5	0.60	5.8	-
28	2.6	1.40	1.9	-
29	2.2	0.07	31.4	90.6
30	1.5	0.23	6.3	26.7
31	2.8	0.70	4.0	63.5
32	2.9	0.09	32.2	40.1
33	2.0	0.25	8.0	45.8
34	3.9	0.60	6.5	108.9
35	6.6	0.50	13.2	50.1
36	2.9	0.54	5.4	19.8
37	2.0	0.25	8.0	81.3
38	1.2	0.50	2.4	54.5
39	2.0	0.30	6.7	94.0
40	1.0	0.03	33.3	39.0
41	7.4	0.93	8.0	85.2
42	8.2	0.97	8.5	51.3
43	3.2	0.50	6.4	32.3
44	3.1	0.74	4.2	-
45	8.2	6.30	1.3	97.8
46	8.3	0.95	8.7	84.6
47	6.8	1.20	5.7	49.0
48	15.0	3.50	4.3	-
49	24.0	10.3	2.3	-
50	4.0	0.22	18.1	69.1
51	3.7	0.20	18.5	-
Rac-50	3.5	0.80	4.4	-
52	30.1	19.9	1.5	-
53	10.5	1.8	5.8	-
54	45.1	3.4	13.2	-
55	33.9	2.8	12.1	-
56	51.2	47.2	1.1	-
57	1.0	1.4	0.7	-
58	54.1	22.2	2.4	-
59	1.4	4.5	0.3	-
60	0.4	1.6	0.3	-
61	1.0	8.6	0.1	-
62	27.6	37.9	0.7	-
63	2.5	7.5	0.3	-
Rac-6	2.2	1.9	1.2	-
Glucantime	416.4	6.70	59.6	-
Cloroquine	-	-	-	1.1

LC_{50} = Lethal concentration at 50 %; EC_{50} = Effective concentration at 50 %; SI = selectivity index, ratio of cytotoxic activity against leishmanicidal activity (SI = LC_{50}/EC_{50}); IC_{50} = Inhibitory Concentration 50

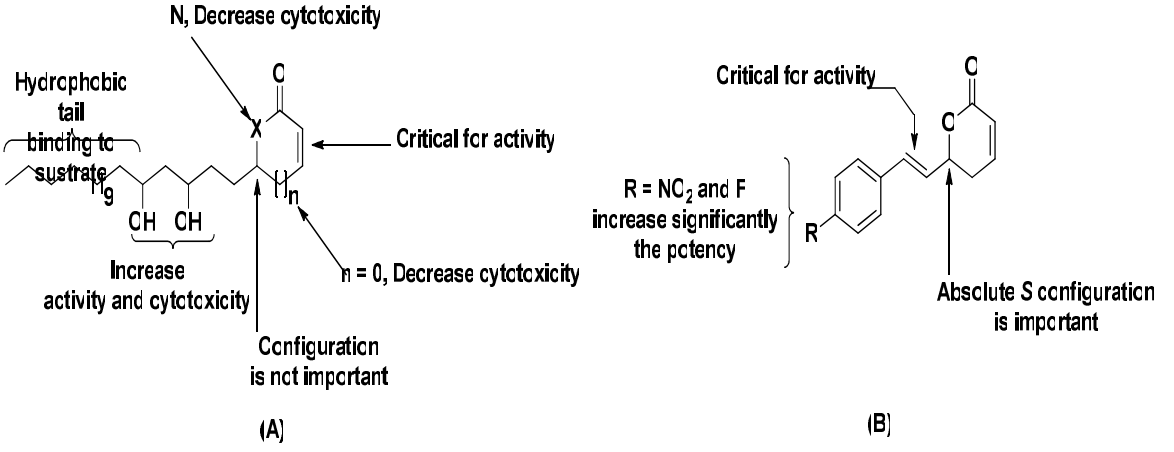

Fig 3: Pharmacophoric groups of passifloricin A (**A**) responsible for its leismanicidal activity and goniothalamin (**B**) for its trypanocidal activity against *Trypanosoma cruzi*

almost three times. Regarding changes in the lactone ring, the reduction of the ring size (compound **55**) leads to a considerable decrease in cytotoxicity (3.5 µg/mL vs 33.9 µg/mL, rac-**50** vs **55**), but its activity is three times lower (0.8 µg/mL vs 2.8 µg/mL compounds rac-**50** vs **55**). However, the γ-lactone shows a higher SI than δ-lactone. Not only the presence of an α,β-unsaturated lactone, but also a less polar portion which can be a long aliphatic chain (compound rac-**50**) or an aromatic ring (compounds **59,63**) appears essential for leishmanicidal activity.

The change of the aliphatic side chain (compound rac-**50**) for an aromatic ring (compounds **59-63**) led to an increase in cytotoxicity and a decrease in activity. Additionally, functionalization causes change in biological activity, which is affected by the relative position in the aromatic ring (**59** vs **60** and **61**), although cytotoxicity is still high. On the other hand, a large molecule such as dimer **58** is less active, even though it has two lactone rings, probably due to steric hindrance of the interaction with a putative receptor, but dimer **57,** which also has two lactone rings, displays a significant activity, even though it is smaller than compound **58.** However, dimer **57** has a similar activity to compound rac-**50,** but improved cytotoxicity. Perhaps, the improved activity of **57** is related to the lipophilic central chain joining the lactone rings. However, the central chain cannot be as large as in the case of dimeric molecule **58,** otherwise activity will be compromised. Activity against *Leishmania* amastigotes practically disappears in the Michael adducts (compounds **49, 52** and **56**). Both, the increased hydrophilicity (**60** vs **62**) and the reduction of the exocyclic double bond (**63** vs **rac-6**) lead to a decrease in activity (Fig **2**).

The structure-activity relationship showed the importance of the aliphatic side chain to enhance the biological activity and to obtain lower cytotoxicity. It was also observed that a decrease in the size of the lactone ring increases the selectivity index. Synthesis of analogs **23** to **53** allowed identification of the pharmacophoric groups responsible for the high antileishmanial activity shown by *passifloricin A* (**22**) against the *Leishmania panamensis* amastigotes (see Fig **3**).

In conclusion, most of the compounds had a significant activity against *L. panamensis* amastigotes, exhibiting an EC_{50} lower than 5.0 µg/mL (Table **1**). Regarding the selectivity index (SI = LC_{50}/EC_{50}>10.0), **55** (12.1), **35** (13.2), **54** (13.2), **24** (16.2), **50** (18.1), **32** (32.2), **29** (31.4)

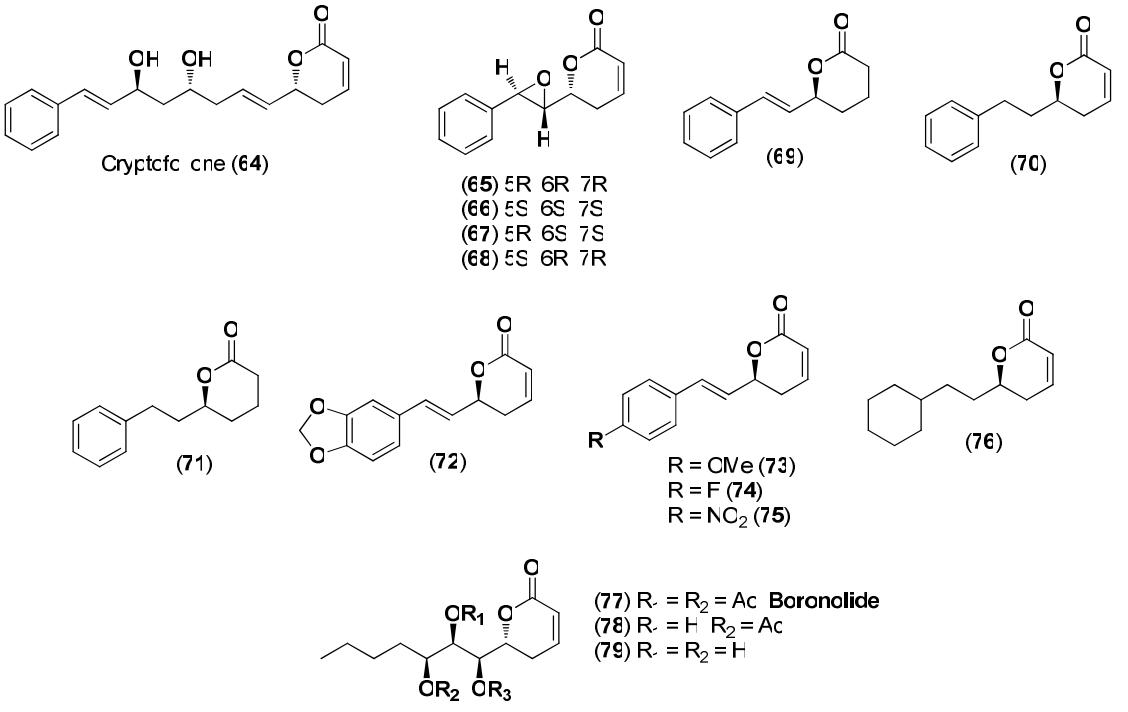

Fig 4: α,β-unsaturated δ-lactones with tripanocidal and antiplasmodial activity

and **40** (33.7) are the most promising compounds.

TRYPANOCIDAL ACTIVITY

Cryptofolione (**64**) was isolated from the fruits of *Cryptocarya alba* (see Fig **4**). In the trypanocidal test, this compound reduced the number of *Trypanosoma cruzi* trypomastigotes by 77 % at a concentration of 250 µg/mL. Under the same conditions, gentian violet lysed 100 % of the parasites. At the lowest concentration tested, 25 µg/mL this compound showed a moderate effect on *T. cruzi* amastigotes infecting mice peritoneal macrophages at the cytotoxic IC_{50}. As the trypanocidal effect and cytotoxicity values are similar, the compound presented little selectivity. However, this compound showed a moderate effect against *Leishmania* spp promastigotes (< 70 % of lysis) [44].

A structure–activity relationship study established the relevant structural features for the trypanocidal activity of goniothalamin (**6**), goniothalamin oxide (**65**) and argentilactone (**16**) analogues against *T. cruzi* (Fig **4**).The results showed that non-natural forms of goniothalamin (**ent-6,** IC_{50} = 0 .35 mM) and argentilactone (**ent-16,** IC_{50} = 0.94 mM) were more active than natural compounds (**6 and 16,** IC_{50} = 1.30 and 0.94 mM, respectively). This shows the importance of the absolute configuration for trypanocidal activity. However, **ent-6** and **6** showed lower activity when compared with crystal violet (IC_{50} = 0.08 mM) [45].

Results showed three factors increasing trypanocidal activity: when the endocyclic double bond is removed (**ent-6 vs 69 and 71,** IC_{50} = 0.21 and 0.19 mM, respectively), when the exocyclic double bond in the molecule remains (**ent-6 vs 70** IC_{50} = 0.91 mM) and by the presence of electron withdrawing groups in the aromatic ring (**ent-6 vs 74, 75,** IC_{50} =

0.12 and 0.09 mM, respectively). Compounds with electron-rich aromatic rings such as **72 (**IC_{50} = 2.39 mM) and **73** (IC_{50} = 6.27 mM) were significantly less potent when compared to **ent-6.**

Finally, substitution of the aromatic group by cyclohexyl group in analogue **76 (**IC_{50} = 0.22 mM) as well the use of isogoniothalamin oxide (**67,** IC_{50} = 0.25 mM) or its enantiomer **68** (IC_{50} = 0.26 mM) provided lower IC_{50} values than **ent-6** but were still not as effective as derivatives **74** and **75** (Table **3**). However, epoxides **67** and **68** presented higher activity than their corresponding stereoisomers **65** (IC_{50} = 0.41 mM) and **66 (**IC_{50} = 1.50 mM). These results allowed the identification of the pharmacophoric groups in goniothalamin (**6**) (Fig **3**)

ANTIPLASMODIAL ACTIVITY

Passifloricin derivatives display activity against *Plasmodium falciparum* (Table **1**) [42]. All of these compounds exhibit lower activity than cloroquine. Promising compounds (IC_{50} < 50.0 mg/mL) are compounds **36** (19.8 µg/mL), passifloricin A, **22** (20.9 µg/mL), **24** (23.1 µg/mL) and **30** (26.7 µg/mL) exhibit the best activity. Products **43** (32.3 µg/mL) **40** (39.0 µg/mL), **32** (40.1 µg/mL), **33** (45.8 µg/mL) and **35** (50.1 µg/mL) show marginal activity. However, a comparison of the biological profiles of these compounds indicate a tendency to increase activity against *P. falciparum* according to the number of hydroxy groups (**50**, **38**, **35** and **22**); this is the opposite result to that found against leishmaniasis. There is no clear relationship between antimalarial activity and structural features such as the distance of the hydroxyl at the closure of the lactone (**38**, **37**, **36**, **34** and **31**), changing the stereochemistry at the stereocenters (**22**, **23**, **24** and **25**), acetylation (**41**-**47**), and o deoxygenation (**29**, **30**, **32**, **39** and **40**) in the side chain.

(+)-Boronolide (**77**), isolated from the bark and branches of *Tetradenia fruticosa* and from the leaves of *Tetradenia barberae*, has been used as a traditional medicine in Madagascar and South Africa. In addition, a partially deacetylated analogue (**78)** and the totally deacetylated analogue (**79)** have also been obtained from *Tetradenia riparia* (Fig **4**), a Central African species traditionally employed by the Zulus as an emetic, and whose leaf infusions have also been reported to be effective against malaria [46]. Argentilactone (**16**) showed *in vitro* antimalarial activity against *Plasmodium falciparum* (ED_{50} = 0.l mg/mL) [34].

CONCLUDING REMARKS

In this review, we have presented the antiprotozoal activity of several α,β-unsaturated δ-lactones. The results shows that the α,β-unsaturated-δ-lactone moiety is essential for biological activity. This is due to the fact that this unit is an excellent potential Michael acceptor for nucleophilic amino acid residues (cysteine, lysine, serine or threonine) and N7 of guanine present in biomolecules of the natural receptors interacting with these compounds [47,48]. Several compounds showed high antiprotozoal activity, but cytotoxic properties were also observed. The synthesis of structural and functional lactones analogs is needed to obtain compounds with high selectivity index for validation as potential antiparasitic drugs.

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