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# Antileishmanial potential of alkaloids isolated from plants: an integrative review

# Potencial antileishmania de alcaloides isolados de plantas: uma revisão integrativa

# Potencial antileishmanial de alcaloides aislados de plantas: una revisión integradora

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## Abstract

Leishmaniasis treatment is often carried out with drugs of high toxic potential and high cost, and satisfactory therapeutic response is not usually observed. In this context, searching for therapeutic alternatives is urgent. This study seeks to evaluate the antileishmanial potential of alkaloids from plants. The search for scientific papers occurred at Pubmed, CAPES Journal Portal (PPC), Virtual Health Library (VHL) and COCHRANE using the descriptors: alkaloid and antileishmanial. The inclusion criteria were studies about alkaloids isolated from plants

and tested against *Leishmania* parasite. A total of 805 publications were found in Pubmed, 825 in PPC, 4 in VHL and none in COCRHANE. After reading the titles and abstracts, articles containing other biological evaluations (350), chemical studies such as docking and material characterizations (388), evaluation of extracts and fractions activities (406) which did not fit in this research or were in duplicate (377) were excluded. Acridone and all the naphthylisoquinolinic and tetrahydroisoquinolinic alkaloids were active or moderately active against *Leishmania* promastigotes or amastigotes, and indolizidine was active against both forms. The *β*-carbolines were inactive or moderately active against *Leishmania* promastigotes, with the exception of flavopereirine. The indolizidine alkaloid was the most promising as a future drug candidate, since it was very active against both forms of *Leishmania*.

**Keywords:** Alkaloids; Amastigote; Antileishmanial; Plants; Promastigote.

**Resumo**

O tratamento da leishmaniose costuma ser realizado com fármacos potencialmente tóxicos e de alto custo, não sendo habitualmente observada resposta terapêutica satisfatória. Nesse contexto, a busca por alternativas terapêuticas é urgente. Este estudo visa avaliar o potencial antileishmania de alcaloides de plantas. A busca de artigos científicos ocorreu no Pubmed, Portal de Periódicos CAPES (PPC), Biblioteca Virtual em Saúde (VHL) e COCHRANE utilizando os descritores: alcaloide e antileishmania. Os critérios de inclusão foram estudos sobre alcaloides isolados de plantas e testados contra o parasita *Leishmania*. Um total de 805 publicações foi encontrado no Pubmed, 825 no PPC, 4 no VHL e nenhum no COCRHANE. Após a leitura dos títulos e resumos, artigos contendo outras avaliações biológicas (350), estudos químicos como docking e caracterizações de materiais (388), avaliação de atividades de extratos e frações (406) que não se enquadraram nesta pesquisa ou estavam em duplicata (377) foram excluídos. A acridona e todos os alcaloides naftilisoquinolínicos e tetrahidroisoquinolínicos foram ativos ou moderadamente ativos contra promastigotas ou amastigotas de *Leishmania*, e a indolizidina foi ativa contra ambas as formas. As *β*-carbolinas foram inativas ou moderadamente ativas contra promastigotas de *Leishmania*, com exceção da flavopereirina. O alcaloide indolizidina foi o mais promissor como futuro candidato a fármaco, pois era muito ativo contra ambas as formas de *Leishmania*.

**Palavras-chave:** Alcaloides; Amastigota; Antileishmania; Plantas; Promastigota.

**Resumen**

El tratamiento de la leishmaniasis se realiza a menudo con fármacos de alto potencial tóxico y elevado coste, y no suele observarse una respuesta terapéutica satisfactoria. En este contexto, la búsqueda de alternativas terapéuticas es urgente. Este estudio busca evaluar el potencial antileishmania de los alcaloides de las plantas. La búsqueda de artículos científicos se realizó en Pubmed, CAPES Journal Portal (PPC), Virtual Health Library (VHL) y COCHRANE utilizando los descriptores: alcaloide y antileishmania. Los criterios de inclusión fueron estudios sobre alcaloides aislados de plantas y probados contra el parásito Leishmania. Se encontraron un total de 805 publicaciones en Pubmed, 825 en PPC, 4 en BVS y ninguna en COCRHANE. Después de leer los títulos y resúmenes, los artículos que contienen otras evaluaciones biológicas (350), estudios químicos como el atraque y caracterización de materiales (388), evaluación de extractos y actividades de fracciones (406) que no encajaban en esta investigación o estaban por duplicado (377) fueron excluidos. La acridona y todos los alcaloides naftilisoquinolínicos y tetrahidroisoquinolínicos fueron activos o moderadamente activos contra los promastigotes o amastigotes de *Leishmania*, y la indolizidina fue activa contra ambas formas. Las *β*-carbolinas fueron inactivas o moderadamente activas contra promastigotes de *Leishmania*, con la excepción de la flavopereirina. El alcaloide indolizidina fue el más prometedor como futuro fármaco candidato, ya que fue muy activo contra ambas formas de *Leishmania*.

**Palabras clave:** Alcaloides; Amastigote; Antileishmania; Plantas; Promastigote.

## 1. Introduction

About 1 billion people live in *Leishmania*-endemic areas under risk to contract the disease. Between 2013 and 2018, 1 million cases of cutaneous leishmaniasis were reported. Annually, there are 300,000 cases of visceral leishmaniasis, which can cause about 20,000 deaths (WHO, 2018). About 90% of visceral leishmaniasis cases occur in Brazil, India, Sudan, South Sudan, Ethiopia and Kenya. Five countries report three out of four new cases of cutaneous leishmaniasis: Afghanistan, Brazil, Iran, Iraq and Syria (Organización Panamericana de La Salud, 2019).

The drug treatment requires assessment of clinical conditions, electrocardiogram and accurate diagnosis (Alvarenga et al., 2010). There are several contraindications for the antimonial use, such as: patients who use beta-blockers and antiarrhythmic drugs, with renal

or hepatic failure and in pregnant women in the first two trimesters of pregnancy (Martins and Lima, 2013).

The parasite's resistance to antimonials, resulting in treatment failure up to 60% of patients, has been related to the following mechanisms: decreased drug entry into the cell; (2) drug efflux through phosphoglycoprotein (PGP) in the membrane or others ATP-dependent carrier proteins; (3) decreased drug activation or inactivation; (4) alteration in drug's target (Ouellette, 2004; Matrangolo, 2013). The therapeutic alternative is Amphotericin B, which can also cause several adverse events, among which are the most frequent and significant renal complications, since practically all patients under treatment presented in varying degrees (Berman, 1998).

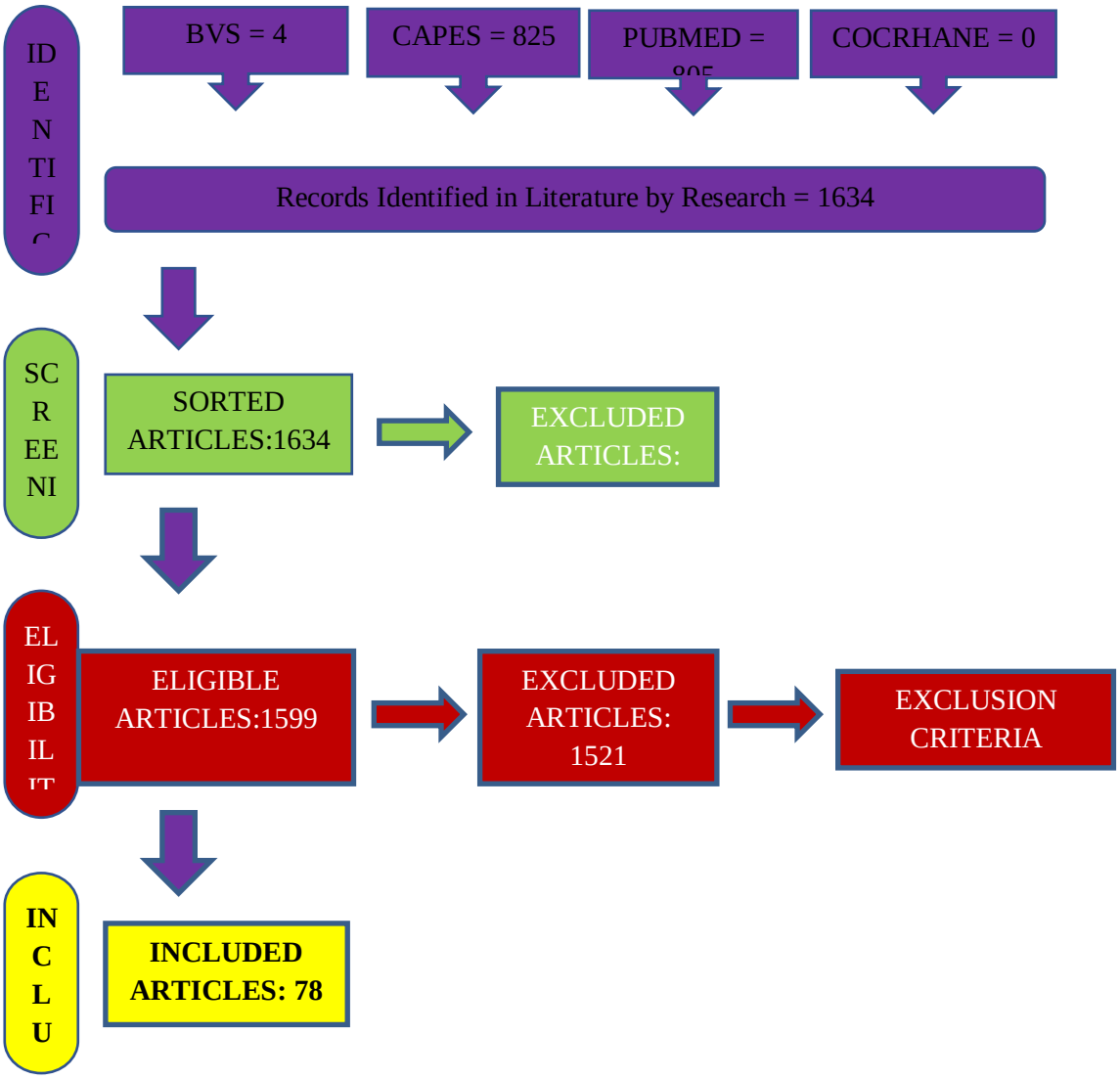
The search for therapeutic alternatives for leishmaniasis treatment is urgent and metabolites, especially alkaloids, isolated from medicinal plants have been promise to treat diseases caused by protozoa. The purpose of this integrative review is to assess the antileishmanial potential of alkaloids isolated from different plant species.

## 2. Methods

A survey was carried out to select scientific papers available at the Virtual Health Library (VHL), CAPES Journal Portal (PPC), PUBMED and COCHRANE, the year of publication was not limited. The search was performed in January 2020, and only articles in Portuguese, English and Spanish were considered. Exclusion criteria were adopted: articles in other languages, articles that did not address the proposed theme, that had tested extracts and fractions, alkaloids obtained through synthesis and other natural products (algae, fungi, etc.), articles that were not reviewed by specialists, which were not available in full and duplicate papers.

For searching the articles, representative descriptors, alkaloid and antileishmanial, were used. The preliminary search resulted in 1634 articles for screening (VHL = 4, PPC = 825, PUBMED = 805 and COCRHANE = 0), having as inclusion criteria the title adequacy to the investigated theme, and abstract compatible with this paper proposal, and the exclusion of duplicate articles. Thirty-five articles available on PPC were eliminated because were not reviewed by specialists, generating a total of 790 on this portal. After analyzing title and abstract, 1521 articles were excluded, and only 78 articles were selected to full reading and possible inclusion in the review. The procedures for identification, screening, eligibility and articles inclusion are described in Figure 1.

**Figure 1**. Flowchart of article selection, according to database.




Source**:** Veiga ASS, et al. (2020).

Two reviewers selected, independently, studies based on their title and abstract. Those papers considered potentially necessary were obtained in full for complete analysis. Any discrepancies were solved by consensus and a third reviewer was consulted to guarantee compliance with the inclusion requirements. At the end, 38 articles were selected for discussion and inclusion in the review (Figure 1), with 40 articles excluded from the 78 initially included.

The data analysis was done in two stages: in the first, a table was used to organize the following data: title and data contained in the abstract. In the second stage, papers were read in full and synthesized for further discussion.

In the results analysis, an active alkaloid was considered when the $IC_{50}$ was less than

or equal to 10 µg/mL against promastigote or amastigote form; moderately active when $IC_{50}$ was greater than 10 and less than 50 µg/ml and inactive when $IC_{50}$ was greater than 50 µg/ml. For choosing the most promising alkaloids, the substance should be active in both forms.

## 3. Results

The acridones derived from acridone Rhodesiacridone (1; Figure 2) and Gravacridonediol (2; Figure 2) were moderately active against promastigotes (11.8µg/mL and 18.4µg/mL, respectively) and active against *L. major* amastigotes (2.3µg/mL and 3.2µg/mL respectively; Table 1).

About the antileishmanial activity of *β*-carbolinic alkaloids, there is a lack of studies to evaluate the activity against the intracellular form (amastigote), the studies found are only assays against promastigotes from different *Leishmania* species (Table 1). The alkaloids N-hydroxyannomontine (3; Figure 2) and Annomontine (5; Figure 2) were not promising against *Leishmania* promastigotes ($IC_{50}$ > 50 µg/mL). Harmine (6; Figure 2) was moderately active ($IC_{50}$ = 25 µg/mL), while flavopereirine (4; Figure 2) proved to be the most promising alkaloid in this class when evaluated against *L. amazonensis* promastigotes, being considered active ($IC_{50}$ = 0.23 µg/mL).

Indolic alkaloids are active against promastigotes from different species of *Leishmania* (Table 1; Figure 2). From the 18 substances found, two have no activity, 10-methoxygeissoschizol (9; $IC_{50}$ > 50 µg/mL) and Ajmaline (22; $IC_{50}$ > 97.92 µg/mL). However, studies evaluating the antiamastigote activity of these alkaloids are also scarce, only Coronaridine (7) has been evaluated against the two *Leishmania* forms, showing activity for both (Promastigota - $IC_{50}$ = 2,6 µg/mL; Amastigote – $IC_{50}$ = 1.6 µg/mL). Dihydrocorynantheine (8), Ramiflorine B (11), Corynantheine (12), Corynantheidine (13), 3,4-dihydro-hyrtiosulawesine (16), Corynanthine (17), a-yohimbine (18), Dihydrocorynantheine (19), Reserpine (20), Ajmalicine (21), Harmane (23) and Buchtienin (25) were active, as they presented $IC_{50}$ > 10 µg/mL. The alkaloids Corynantheine, Dihydrocorynantheine and Ajmalicine were the most active when evaluated against *L. major* promastigotes, with $IC_{50}$ of 0.41 µg/mL, 0.60 µg/mL and 0.20 µg/mL respectively. The other alkaloids Ramiflorine A (10), Pleiocarpine (14), and Pleiocarpin (24) showed moderate activity.

When analyzing the apomorphine isoquinoline alkaloids, only a few studies against *Leishmania* promastigotes (Table 1; Figure 2). Among the alkaloids Liriodenina (26),

Anonaine (27) and O-methylmoschatolina (28), only the Lyriodenine and Anonaine showed activity, the first was active only against *L. guyanensis* ($IC_{50}$ = 5.91 µg/mL), and the second only against *L. donovani* ($CI_{50}$ = 10 µg/mL), not being active for other *Leishmania* species tested (Table 1) indicating species-specific activity. Meanwhile, the bisbenzyltetrahydroisoquinoline alkaloids were active against *Leishmania* promastigotes, except for warifteine (30; Figure 2) which was inactive. It is noteworthy that both apomorphine and bisbenzyltetrahydroisoquinoline isoquinolinic alkaloids have not been tested against amastigote forms of *Leishmania* (Table 1).

In the analysis, the collected data about alkaloids from isoquinoline class, showed few active compounds (Table 1), however, with high antileishmanial potential. Among the 13 alkaloids tested against different species of *Leishmania*, Berberine (34; Figure 2), Cephaeline (37; Figure 2), Pseudoberberine (38; Figure 2) and Emetine (47; Figure 2) were the only active ones ($IC_{50}$>10 µg/mL). The cephaline presented the greatest antileishmanial activity (*L. donovani*) with $IC_{50}$ > 0.03 µg/mL. Berberine was the only compound evaluated in amastigotes, presenting activity against three different species of *Leishmania* (*L. tropica, L. infantum and L. major*). The alkaloids Northalidasina (40; Figure 2), Northalrugosidina (41; Figure 2), Talfoetidina (42; Figure 2), Northalfoetidina (43; Figure 2) and Taligosidina (44; Figure 2) presented only moderate antipromastigota activity and the other 3 alkaloides (+ - Preocoteína + - Thalicberina and Thaliglucinona) were inactive. When considering the naphthylisoquinolinic and tetrahydroisoquinolinic alkaloids, all were active or moderately active against *Leishmania* promastigotes or amastigotes (Table 1).

Similarly, quinolinic alkaloids also showed activities against *Leishmania* promastigotes and/or amastigotes (Table 1), with the exception of the Dictamnine (69; Figure 2), which was inactive against these two forms of *Leishmania*.

Other classes of alkaloids, such as the indolizidine 1,6-Juliprosopine (75; Figure 2), have been very active against *Leishmania* promastigotes (0.8 µg/mL) and amastigotes (1.8 µg/mL). Meanwhile, the other alkaloids classes researched in this study are active or moderately active against these forms of *Leishmania* (Table 1).

**Table 1.** Antileishmanial activity of alkaloids.

| Name (class) | Antileishmanial activity ($IC_{50}$ µg/mL) | | *Leishmania* species | Data analysis | Reference |
|---|---|---|---|---|---|
| | **Promastigote** | **Amastigote*** | | | |
| **Acridone Alkaloid Derivatives** | | | | | |
| Rhodesiacridone [1]<br>Gravacridonediol [2] | 11,8<br>18,4 | 2,3<br>3,2 | *L. major*<br>*L. major* | Moderately active/Active<br>Moderately active /Active | Ahua et al., 2004; Sangshetti et al.,2015 |
| ***β*-carboline alkaloid** | | | | | |
| N-hydroxyannomontine [3] - pyrimidine-*β*-carboline alkaloid | 70,06<br>121,31 | ND<br>ND | *L. braziliensis*<br>*L. guyanensis* | Inactive<br>Inactive | Costa et al., 2006 |
| Flavopereirine [4] | 0.23 ± 0.10 | ND | *L. amazonensis* | Active | Silva-Silva et al.,2019 |
| Annomontine [5] - pyrimidine-*β*-carboline alkaloid | 911,8<br>>16060 | ND<br>ND | *L. braziliensis*<br>*L. guyanensis* | Inactive<br>Inactive | Costa et al., 2006 |
| Harmine [6] (7-methoxy 1-methyl beta-carboline) | 25 µg | ND | *L. donovani* (AG83) | Moderately active | Lala et al., 2004 |
| **Indole alkaloid** | | | | | |
| Coronaridine [7] | 2,6 | 1,2 | *L. amazonensis* | Active/Active* | Delorenzi et al.,2001; Delorenzi et al.,2002 |
| Dihydrocorynantheine [8] | 1,10 | ND | *L. major* | Active | Chan-Bacab and Pena-Rodriguez, 2001; Mishra et al.,2009 |
| 10-methoxygeissoschizol [9] | >320<br>>320 | ND<br>ND | *L. braziliensis*<br>*L. amazonensis* | Inative<br>Inative | Tanaka et al.,2007 |
| Ramiflorine A [10] | 16.3±1.6<br>16.3±1.6<br>16.3 | ND<br>ND<br>ND | *L. amazonensis*<br>*L. braziliensis*<br>*L. amazonensis* | Moderately active<br>Moderately active<br>Moderately active | Tanaka et al.2007; Mishra et al.,2009; Gutiérrez-Rebolledo et al.,2017 |
| Ramiflorine B [11] | 4.9±0.9<br>4.9±0.9<br>4.9 | ND<br>ND<br>ND | *L. amazonensis*<br>*L. braziliensis*<br>*L. amazonensis* | Active<br>Active<br>Active | Tanaka et al.2007; Mishra et al.,2009; Gutiérrez-Rebolledo et al.,2017 |
| Corynantheine [12] | 1,09<br>0,41 ± 0.4 | ND<br>ND | *L. major*<br>*L. major* | Active<br>Active | Chan-Bacab and Pena-Rodriguez, 2001; Staerk et al.2000; Mishra et al.,2009 |
| Corynantheidine [13] | 1,10<br>1,03 ± 0.4 | ND<br>ND | *L. major*<br>*L. major* | Active<br>Active | Chan-Bacab and Pena-Rodriguez, 2001; Staerk et al., 2000; Mishra et al.,2009. |
| Pleiocarpine [14] | < 25 | ND | *L. donovani* | Moderately active | Mishra et al.,2009 |
| Hyrtiosulawesine [15]<br>3,4-dihydro-hyrtiosulawesine [16] | 14,81 a 17,29 | ND | *L. amazonensis* | Moderately active | Pereira et al.,2017 |
| Corynanthine [17] | 8,29 | ND | *L. major* | Active | Staerk et al.,2000 |
| a-yohimbine [18] | 8,43 ± 2.6 | ND | *L. major* | Active | Staerk et al.,2000 |

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|---|---|---|---|---|---|
| Dihydrocorynantheine [19] | 0,60 ± 0.3 | ND | *L. major* | Active | Staerk et al.,2000 |
| Reserpine [20] | 9,98 ± 2.3 | ND | *L. major* | Active | Staerk et al.,2000 |
| Ajmalicine [21] | 0,20 ± 0.1 | ND | *L. major* | Active | Staerk et al.,2000 |
| Ajmaline [22] | >97,92 | ND | *L. major* | Inactive | Staerk et al.,2000 |
| Harmane [23]<br>Pleiocarpin [24]<br>Buchtienin [25] | 6.25<br>25<br>1.56 | ND<br>ND<br>ND | *L. donovani*<br>*L. donovani*<br>*L. donovani* | Active<br>Moderately active<br>Active | Mishra et al.,2009; Polonio, T., Efferth, 2008; Singh et al.,2014; Gutiérrez-Rebolledo et al.,2017. |
| **Isoquinoline alkaloid - aporphine alkaloid kind** | | | | | |
| Liriodenine [26] | 16,10 ± 1.8<br>5,91 ± 0.4<br>100<br>100<br>100 | ND<br>ND<br>ND<br>ND<br>ND | *L. braziliensis*<br>*L. guyanensis*<br>*L. braziliensis*<br>*L. amazonensis*<br>*L. donovani* | Moderately active<br>Active<br>Inactive<br>Inactive<br>Inactive | Costa et al.,2006; Queiroz et al.,1996 |
| Anonaine [27] | 50<br>25<br>100<br>10 | ND<br>ND<br>ND<br>ND | *L. brasiliensis*,<br>*L. amazonensis*<br>*L. donovani*<br>*L. donovani* | Moderately active<br>Moderately active<br>Inactive<br>Active | Costa et al.,2006; Queiroz et al.,1996 |
| O-methylmoschatoline [28] | 103,7 ± 3.1<br>33,31 ± 3.4 | ND<br>ND | *L. braziliensis*<br>*L. guyanensis* | Inactive<br>Inactive | Costa et al.,2006 |
| **Benzylisoquinoline alkaloid** | | | | | |
| O-methylarmepavine [29] | 23.3 | 25.4 | *L. chagasi* | Moderately active / Moderately active * | Vila-Nova et al.,2011 |
| **Bisbenzylisoquinoline alkaloid** | | | | | |
| Warifteine [30] | 80 | ND | *L. chagasi* | Inactive | Silva et al.,2012 |
| **Bisbenzyltetrahydroisoquinoline Alkaloid** | | | | | |
| Northalrugosidine [31] | 0,17 | ND | *L. donovani* | Active | Naman et al.,2015 |
| Thalrugosidine [32] | 0,63 | ND | *L. donovani* | Active | Naman et al.,2015 |
| Thalidasine [33] | 6,59 | ND | *L. donovani* | Active | Naman et al.,2015 |
| **Isoquinoline alkaloid** | | | | | |
| Berberine [34] | ND<br>2.9 ± 0.05<br>2.7 ± 0.05<br>13 | 10<br>4.7 ± 0.1<br>3.9 ± 0.1<br>ND | *L. major*<br>*L. tropica*<br>*L. infantum*<br>*L. major* | Active<br>Active/Active*<br>Active/Active*<br>Active | Chan-Bacab and Pena-Rodriguez, 2001; Vennerstrom et al.,1990; Ropivia et al.,2010; Mahmoudvand et al.,2014 |
| Protoberberine [35] | 444,0<br>535,5 | ND<br>ND | *L. donovani* (AG83)<br>*L. donovani* (GE1) | Inactive<br>Inactive | Kumar et al., 2016 |
| Isoguattouregidine [36] | 100<br>100 | ND<br>ND | *L. donovani*<br>*L. amazonensis* | Inactive<br>Inactive | Mishra et al.,2009; Chan-Bacab and Pena-Rodriguez, 2001 |

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|---|---|---|---|---|---|
| Benzoquinolizidine cephaeline [37] | 0,03 | ND | *L. donovani* | Active | Muhammad et al.,2003; Salem and Werbovetz, 2006 |
| Pseudoberberine [38] | 3.5 | ND | *L. major* | Active | Ropivia et al.,2010 |
| Preocoteine [39] | 100 | ND | *L. major* | Inactive | Ropivia et al.,2010 |
| Northalidasine [40] | 27 | ND | *L. major* | Moderately active | Ropivia et al.,2010 |
| Northalrugosidine [41] | 30 | ND | *L. major* | Moderately active | Ropivia et al.,2010 |
| Thalfoetidine [42] | 17 | ND | *L. major* | Moderately active | Ropivia et al.,2010 |
| Northalfoetidine [43] | 39 | ND | *L. major* | Moderately active | Ropivia et al.,2010 |
| Thaligosidine [44] | 38 | ND | *L. major* | Moderately active | Ropivia et al.,2010 |
| Thalicberine [45] | 55 | ND | *L. major* | Inactive | Ropivia et al.,2010 |
| Thaliglucinone [46] | 63 | ND | *L. major* | Inactive | Ropivia et al.,2010 |
| Emetine [47] | 0.42 | ND | *L. donovani* | Active | Muhammad et al.,2003; Salem and Werbovetz, 2006 |
| **Naphthylisoquinoline alkaloids** | | | | | |
| Dioncophylline A [48] | 17,73 ± 20.70 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Dioncophylline C [49] | 13,26 ± 3.55 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Dioncopeltine A [50] | >37,94 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Ancistrocladidine [51] | >40,55 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Ancistroheynine B [52] | 12,92 ± 4.29<br>22.3 | ND<br>ND | *L. major*<br>*L. donovani* | Moderately active<br>Moderately active | Ponte-Sucre et al., 2007<br>Bringmann et al.,2004 |
| Ent-dioncophylleine A [53] | 12,05 ± 0.00 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| 5'-O-demethyl-ent-dioncophylleine A [54] | > 35,92 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Dioncophylleine D [55] | 37,34 | ND | *L. major* | Moderately active | Ponte-Sucre et al.,2007 |
| Ancistroealaine A ou Ancistrotanzanine B [56] | 41,95<br>ND<br>ND | ND<br>4.1<br>1.6 | *L. major*<br>*L. donovani*<br>*L. donovani* | Moderately active<br>Active*<br>Active* | Bringmann et al.,2000; Ponte-Sucre et al.,2007; Bringmann et al.,2003; Bringmann et al., 2004. |
| Ancistroealaines B [57] | ND | 10 | *L. donovani* | Active* | Bringmann et al.,2000 |
| Ancistrocladiniums A [58] | 2,05 ± 2,93 | ND | *L. major* | Active | Ponte-Sucre et al.,2007 |
| Ancistrocladiniums B [59] | 0,64 ± 0,15 | ND | *L. major* | Active | Ponte-Sucre et al.,2007 |
| Ancistrotanazanine A [60] | ND | 1.8 | *L. donovani* | Active* | Bringmann et al.,2003; Bringmann et al.,2004 |
| Ancistrotectoriline A [61] | ND | >10 | *L. donovani* | Active* | Bringmann et al., 2003 |
| Ancistrocladidine [62] | 2.9 | ND | *L. donovani* | Active | Bringmann et al., 2004 |
| Ancistrolikokine D [63] | ND | 5.9 | *L. donovani* | Active* | Bringmann et al.,2003 |
| Ancistrogriffines A [64] | ND | 3.1 | *L. donovani* | Active* | Salem and Werbovetz, 2006 |
| Ancistrogriffines C [65] | ND | 18 | *L. donovani* | Moderately active * | Salem and Werbovetz, 2006 |
| **Terpenoid tetrahydroisoquinoline alkaloid** | | | | | |
| Klugine [66] | 0,4 | ND | *L. donovani* | Active | Muhammad et al.,2003 |

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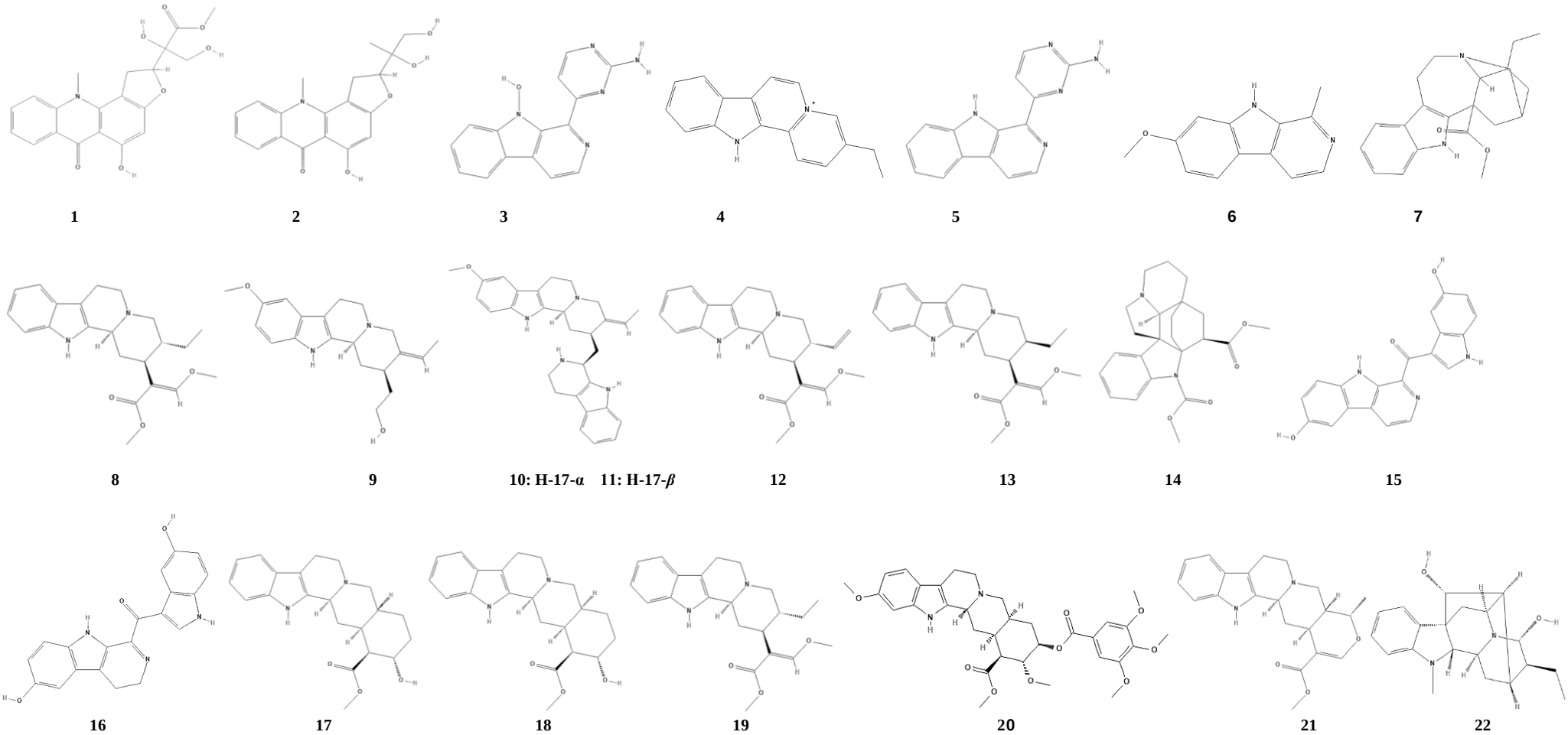
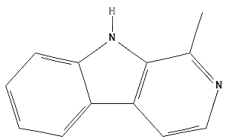
|---|---|---|---|---|---|
| | | | | | Salem and Werbovetz, 2006 |
| Isocephaeline [67] | 0,45 | ND | *L. donovani* | Active | Muhammad et al.,2003<br>Salem and Werbovetz, 2006 |
| **Quinoline alkaloid** | | | | | |
| N-methyl-2-phenoxyquinolin-4(1H)-one (heptaphyllone A) [68] | >30 | >30 | *L. panamensis* | Moderately active /<br>Moderately active * | Barrera et al.,2011 |
| Dictamnine [69] | > 100 | > 75 | *L. panamensis* | Inactive | Barrera et al.,2011 |
| N-methyl-8-methoxyflindersine[70] | 14.3 ± 4.3 | >30 | *L. panamensis* | Moderately active /<br>Moderately active * | Barrera et al.,2011 |
| y-Fagarine[71] - furoquinoline alkaloid | 7,17 ± 1.4 | ND | *L. amazonensis* | Active | Costa et al.,2018 |
| kokusaginine[72] - furoquinolone alkaloid | 30 | >30 | *L. panamensis* | Moderately active /<br>Moderately active * | Barrera et al.,2011 |
| Cryptolepine[73] - indoloquinoline alkaloid | 0,37 µg/mL | ND | *L. donovani* (AG83) | Active | Hazra et al.,2012 |
| 2,7-Dibromocryptolepine[74] - indoloquinoline alkaloid | 0,19 ± 0.1 | ND | *L. donovani* (AG83) | Active | Hazra et al.,2012 |
| **Other alkaloids classes** | | | | | |
| 1,6-Juliprosopine[75]- indolizidine alkaloid | 0.8 | 1.8 | *L. donovani* | Active/Active* | Rahman et al.,2011 |
| Phyllanthidine[76] - (+) Securinega alkaloid | 82.37 | 49.11 | *L. amazonensis* | Inactive/<br>Moderately active * | Moraes et al., 2015 |
| Holamine[77] - steroidal alkaloids | 0,38 a 1,55 | ND | *L. donovani* | Active | Kam et al.,1998; Sangshetti et al.,2015 |
| Ichangin[78]- Limonoids alkaloid (agliconas) | > 100 | >30 | *L. panamensis* | Inative/<br>Moderately active * | Barrera et al.,2011 |
| Mahanine[79] - carbazole alkaloid | 3,9 ± 0,8<br>10,10 ± 1,3 | ND<br>ND | *L. donovani* (AG83)<br>*L. donovani* (GE1) | Active<br>Moderately active | Roy et al.,2018 |
| Julocrotine [80]- glutarimide alkaloid | 21,19 | 6,26 | *L. amazonensis* | Moderately active | Guimarães et al.,2010 |
| Dihydrochelerythrine[81] - quaternary benzophenanthridine alkaloids | 0,78 | ND | *L. donovani* | Active | Fotie et al.,2007; Sangshetti et al.,2015 |

Legend: ND- not determined; µg- micrograms; mL- milliliter
Source: Veiga ASS, et al. (2020)

**Figure 2**. Chemical structures of alkaloids.





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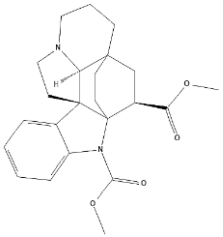

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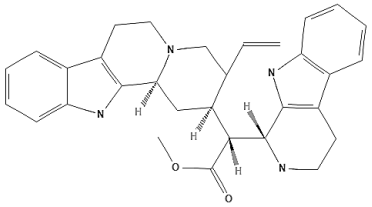

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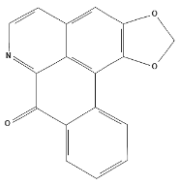

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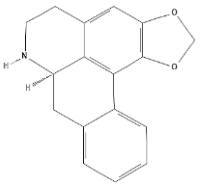

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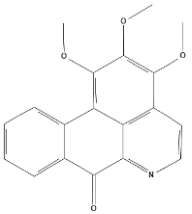

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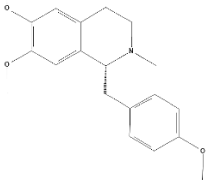

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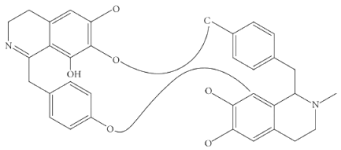

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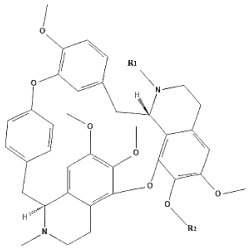
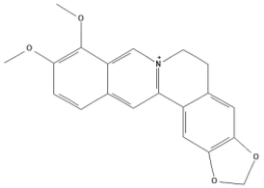


**31-33**

**31 $R_1$=H, $R_2$= H**

**32 $R_1$=Me, $R_2$=H**



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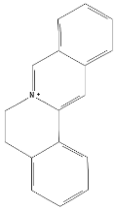

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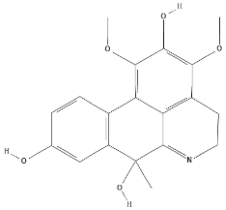

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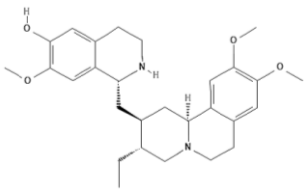

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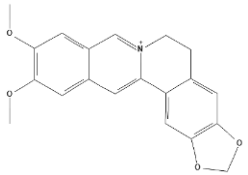

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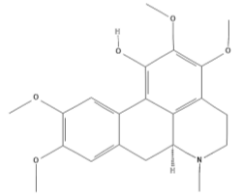

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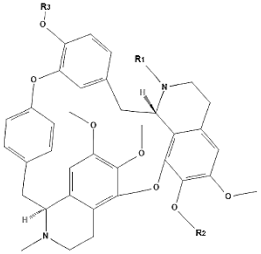
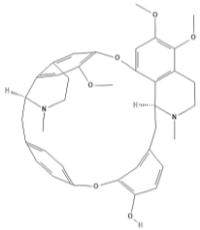


**40-44**

**40** R1= H, R2= Me, R3= Me

**41** R1= H, R2= H, R3= Me

**42** R1= Me, R2= Me, R3= H



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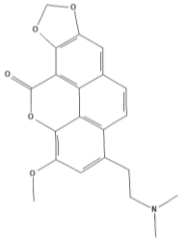

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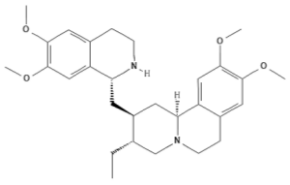

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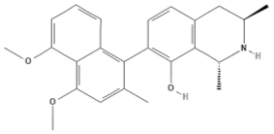

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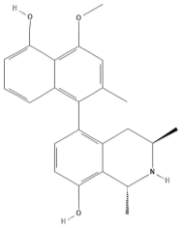

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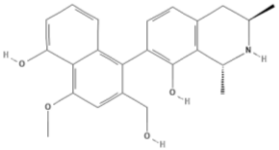

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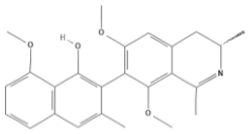

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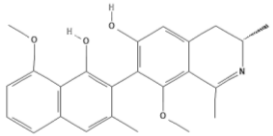

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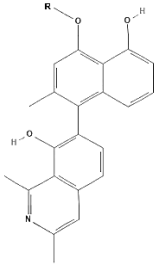
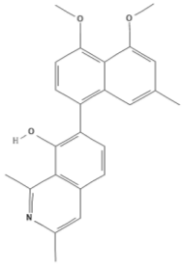


**53 R=Me 54 R=H**



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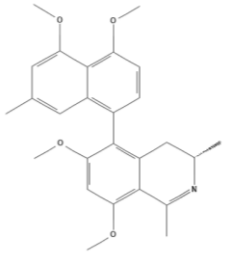

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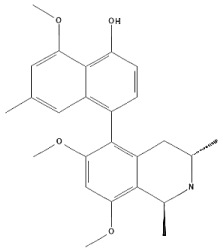

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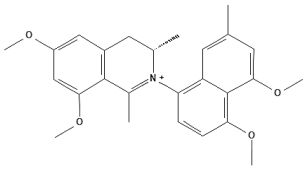

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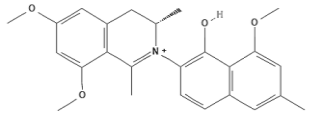

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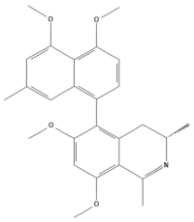

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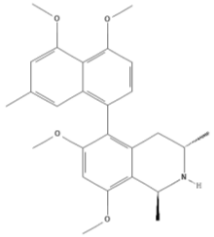

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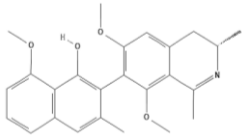

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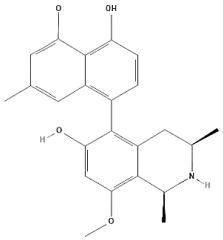

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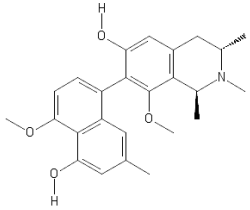

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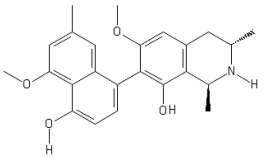

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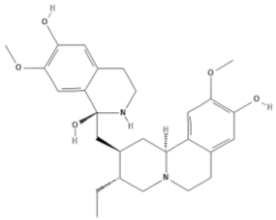

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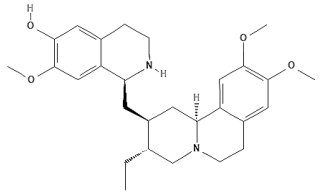

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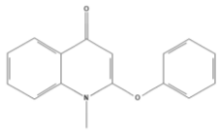

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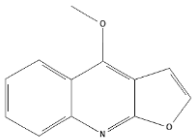

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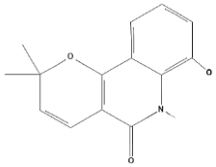

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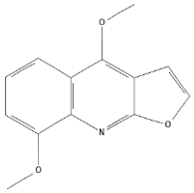

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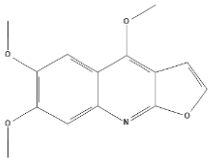

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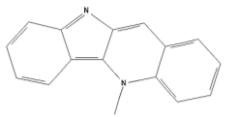

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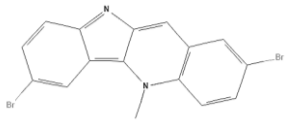

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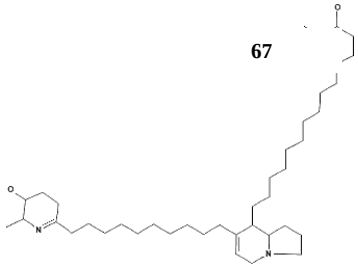

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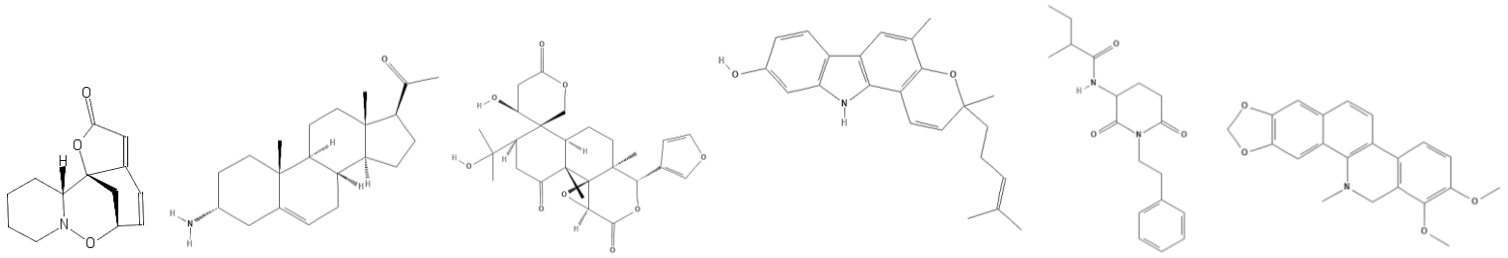

**76** **77** **78** **79** **80** **81**

**Legend:** 1- Rhodesiacridone; 2- Gravacridonediol; 3- N-hydroxyannomontine; 4- Flavopereirine; 5- Annomontine; 6- Harmine; 7- Coronaridine; 8- Dihydrocorynantheine; 9-10-methoxygeissoschizol; 10- Ramiflorine A; 11- Ramiflorine B; 12- Corynantheine; 13- Corynantheidine; 14- Pleiocarpine; 15- Hyrtiosulawesine; 16- 3,4-dihydro-hyrtiosulawesine; 17- Corynanthine; 18- a-yohimbine; 19- Dihydrocorynantheine; 20- Reserpine; 21- Ajmalicine; 22- Ajmaline; 23- Harmane; 24- Pleiocarpin; 25- Buchtienin; 26- Liriodenine; 27- Anonaine; 28- O-methylmoschatoline; 29- O-methylarmepavine; 30- Warifteine; 31- Northalrugosidine; 32- Thalrugosidine; 33- Thalidasine; 34- Berberine; 35- Protoberberine; 36- Isoguattouregidine; 37- Benzoquinolizidine cephaeline; 38- Pseudoberberine; 39- Preocoteine; 40- Northalidasine; 41- Northalrugosidine; 42- Thalfoetidine; 43- Northalfoetidine; 44- Thaligosidine; 45- Thalicberine; 46- Thaliglucinone; 47- Emetine; 48- Dioncophylline A; 49- Dioncophylline C; 50- Dioncopeltine A; 51- Ancistrocladidine; 52- Ancistroheynine B; 53- Ent-dioncophylleine A; 54- 5'-O-demethyl-ent-dioncophylleine A ; 55- Dioncophylleine D; 56- Ancistroealaine A ou Ancistrotanzanine B; 57- Ancistroealaines B; 58- Ancistrocladiniums A; 59- Ancistrocladiniums B; 60- Ancistrotanazanine A; 61- Ancistrotectoriline A; 62- Ancistrocladidine; 63- Ancistrolikokine D; 64- Ancistrogriffines A; 65- Ancistrogriffines C; 66- Klugine; 67- Isocephaeline; 68- N-methyl-2-phenoxyquinolin-4(1H)-one (heptaphyllone A); 69- Dictamnine; 70- N-methyl-8-methoxyflindersine; 71- y-Fagarine; 72- kokusaginine; 73- Cryptolepine; 74- 2,7-Dibromocryptolepine; 75- 1,6-Juliprosopine; 76- Phyllanthidine; 77- Holamine; 78- Ichangin; 79- Mahanine; 80- Julocrotine; 81- Dihydrochelerythrine.
Source**:** Veiga ASS, et al., (2020).

## 4. Discussion

The acridones derived from acridone (Ahua et al., 2004; Sangshetti et al., 2015) were moderately active against promastigotes and active against *L. major* amastigotes (Table 1). Authors observed that the greatest activity against the *Leishmania* amastigote form occurred more intensely in acridones that had the benzoylamino group in positions 3 and 6, this group seems to be essential for a greater specificity against amastigote than promastigote (selective antileishmanial activity; Sangshetti et al., 2015). Another study showed that substituted 6-mono and 3,6-disubstituted acridones are antileishmania agents, the most active of which are acridones 3,6 disubstituted with benzoylamino groups in positions 3 and 6, as they demonstrate strong activity against both forms (promastigotes and amastigotes; Di Giorgio et al., 2007).

Indolic alkaloids are active against promastigotes from different species of *Leishmania* (Table 1; Figure 2). The leishmanicidal mechanism of action of indolic alkaloids is not known yet, but there is an association of this activity with a chemical structure (Rodrigues et al., 2008). Some authors claim the oxidation state and nature of the nitrogen substitution are important for antileishmanial activity, as quartering one or more nitrogen atoms result in activity loss (Camacho et al., 2002). A tetracyclic planar structure imparts antiparasitic activity to these compounds (Staerk et al., 2000). In a study with indolic and bisindolic alkaloids from *Ervatamia coronaria*, the lack of quartering in their nitrogen, and a relatively planar structure are responsible for the activity of these alkaloids on amastigotes of *L. braziliensis* (Rodrigues et al., 2008).

When analyzing the apomorphine isoquinoline alkaloids, only a few studies against *Leishmania* promastigotes (Table 1; Figure 2). Studies with bisbenzylisoquinolic alkaloids have observed that the oxidation state and the substitution of nitrogen atoms are important in leishmanicidal activity as the quartering of one or more nitrogen atoms result in activity loss, a substitution in each monomer of the molecule can influence the activity and, also, the presence of phenolic hydroxy groups can cause increased activity (Camacho et al., 2002). Which could explain the difference in activity, against promastigotes, between these different types of alkaloids.

In the analysis, the collected data about alkaloids from isoquinoline class, showed few active compounds (Table 1), however, with high antileishmanial potential. In general, the naphthylisoquinolinic alkaloids that had an axial biaryl C, C attached to the naphthyl or isoquinolinic portion of the molecule, had little or no leishmanicidal activity (Ponte-Sucre et al., 2007) against promastigotes (T 1), while the ones with axial hetero-biaryl C, N attached to the naphthyl or isoquinolinic portion (Ponte-Sucre et al., 2007) had a high leishmanicidal activity (Table 1; Figure 2) such as Ancistrocladiniums A (2.05 µg/mL) and Ancistrocladiniums B (0.64 µg/mL).

Other classes of alkaloids (Figure 2; Rahman et al., 2011), have been very active against *Leishmania* promastigotes and amastigotes. The presence of a double bond between C1 and C2 in both

piperidine rings, as seen in 1,6-Juliprosopine, conferred potent leishmanicidal activity against *L. donovani* promastigotes and amastigotes (Rahman et al., 2011).

Through a literature review of scientific articles in order to obtain scientific quality in the respective subject, we observed that indolizidine alkaloids, as 1,6-Juliprosopine, among all the classes studied, were the most promising as a future drug candidates, since they were active against the two forms of *Leishmania* (promastigotes and amastigote). This literature review also found that more studies about the anti-amastigote activity need to be carried out since this is the infective form for humans, responsible for the clinical manifestations of the disease.

## Conflict of interest

The authors declare that there is no conflict of interest.

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