PYRIDINE AND QUINOLINE BASED SYNTHETIC AND NATURAL PRODUCTS AGAINST LEISHMANIASIS

Arindam Maity *

Dr B C Roy College of Pharmacy and AHS, Durgapur- 713206, West Bengal, India.
*Email of corresponding author: arindam.ju05@gmail.com

INTRODUCTION

Macrophages (Greek: big eaters, from makros "large" + phagein "eat"; abbr. M□) are cells produced by the differentiation of monocytes in tissues. They are phagocytes and function in both non-specific defense (innate immunity) as well as helps to initiate specific defense mechanisms (adaptive immunity) of vertebrate animals. Due to their role in phagocytosis, macrophages are involved in many diseases of the immune system. Leishmaniasis was one of the macrophage associated disease, caused by a parasite that is spread to people through the bite of the female phlebotomine sand fly (Fig.1). Upon phagocytosis by a macrophage, the Leishmania parasite finds itself in a phagocytic vacuole. Under normal circumstances, this phagocytic vacuole would develop into a lysosome and its contents would be digested. Leishmania alter this process and avoid being destroyed; instead, they make a home inside the vacuole. The diseases caused by at least 17 species of protozoan parasite Leishmania [1]. It has been estimated that there are 2 million new cases of leishmaniasis every year in the world, of which 1.5 million are categorized as cutaneous leishmaniasis and 0.5 million are visceral leishmaniasis. Epidemics occur when people are displaced into affected regions through war or migration or when people in affected regions experience high rates of disease or malnutrition. This disease has been identified as one of the six major tropical diseases and thus has been included in the special programme for research and training by the World Health Organization. The disease affects around 88 subtropical and tropical countries with 12 million people worldwide; with an annual incidence of approximately two million new cases and 350 million are living at risk to be infected [2]. Multiple factors such as the human immuno deficiency virus (HIV) epidemic, increase of international travel, a lack of effective vaccines, difficulties in controlling vectors, international conflicts and the development of resistance to chemotherapy could increase the cases of leishmaniasis [3]. The

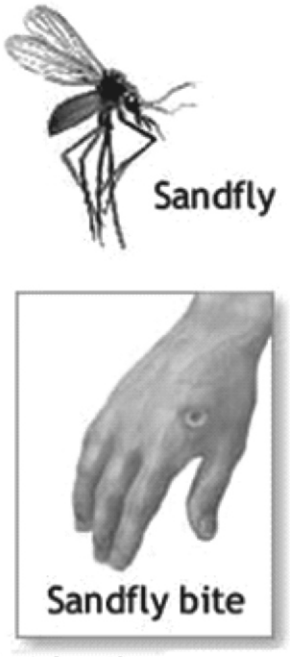


Fig.1 Sandfly

Leishmania are Kinetoplastid protozoans that cause four main clinical syndromes: Cutaneous Leishmaniasis; Mucocutaneous Leishmaniasis (also known as espundia); *Visceral Leishmaniasis* (VL; also known as kala-azar) and Difuse Leishmaniasis [4]. Leishmania species are transmitted by 30 species of sand fly and essentially requires two different hosts: an invertebrate insect vector, Phlebotomus (in the Old World) or Lutzomiya (in the New World) sandfly mosquito and a vertebrate host (human, dog or even a wild vertebrate) [5]. Leishmaniasis is divided into clinical syndromes according to which part of the body is affected most. In *Visceral Leishmaniasis* (VL), the parasite affects the organs of the body mainly the skin is the predominate site of infection. Mucocutaneous leishmaniasis occurs only in the New World and is most common in Bolivia, Brazil, and Peru. Leishmaniasis is prevalent in tropical and temperate regions of the world, ranging from rainforests in Central and South America to deserts in West Asia and the Middle East. The visceral leishmaniasis has an estimated incidence of 500,000 new cases and 60,000 deaths each year with more than 90 % of cases are centralized to India, Bangladesh, Nepal, Sudan, and Brazil [6]. Leishmania - HIV co-infection has been globally controlled in Southern Europe since 1997 by highly active anti retroviral therapy (HAART), but it appears to be an increasing problem in other countries such as Ethiopia, Sudan, Brazil or India where both infections are becoming more and more prevalent [7]. The situation is particularly alarming in southern Europe, where 50-75% of adult VL cases are HIV positive and among the 45 million people infected by HIV worldwide, an estimated one-third lives in the zones of endemic Leishmania infections [8]. Today, the greatest prevalence of HIV co-infection has been in the Mediterranean basin. Among more than 2,000 cases notified to the WHO, 90% of them belong to Spain, Italy, France and Portugal [9].

MORPHOLOGY AND LIFE CYCLE

Leishmania are the obligate intracellular parasites existing in two morphologic forms: promastigotes and amastigotes. Promastigotes are found in digestive tract of sandfly and are long spindle shaped with a single delicate flagellum (15-28 μM long) attached to cytoplasmic organelle called kinetoplast containing intertwined circular DNA (kDNA) molecules known as maxicircles and minicircles, which make up 5-10% of total DNA [10]. A fully developed promastigote measures about 114.3 to 20 □m in length and 1.5 to 1.8 □m at their widest part [11]. The

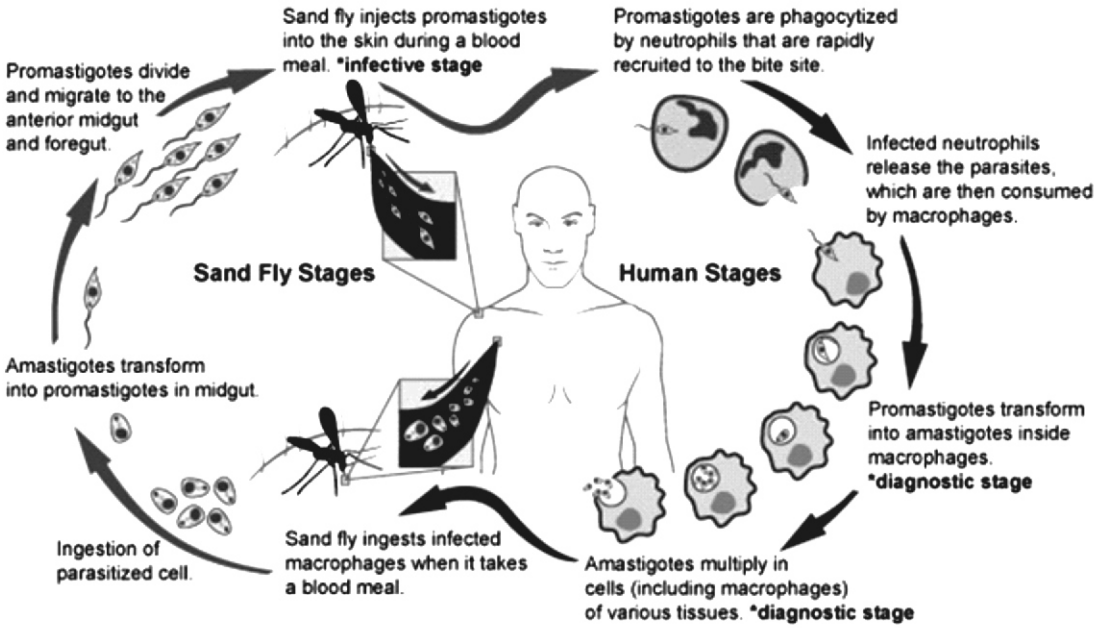


Fig 2: This figure shows life cycle of Leishmania parasite

small, round to oval bodies called amastigotes (2 to 3 μm in length) are the non-infective Leishmania parasites occurring in monocytes, polymorpho-nuclear leucocytes or endothelial cells of vertebrates (hosts) while promastigotes represent the infective stage in sandfly (vector). The Leishmania promastigotes are transmitted by sandfly to vertebrate hosts e.g. canines, marsupials, edentates and rodents. Once inside the bloodstream of reservoirs for the disease, promastigotes are phagocytosed by the mononuclear phagocytic cells and are transformed to amastigotes that multiply by means of binary fission. On lyses of host cell, the free parasites spread to new cells and tissues of different organs including the spleen, liver and bone marrow. Amastigotes in the blood as well as in the monocytes are ingested during a blood meal by female sandfly. Once ingested, the amastigotes migrate to the mid gut of the sand fly and transform into the promastigotes. After a period of four to five days, promastigotes move forward to the oesophagus reach to salivary glands of the sandfly. Infected sandfly during the second blood meal regurgitates the infectious promastigotes from its pharynx into the bloodstream of the host vertebrates and life cycle is repeated (fig-2) [12].

CURE OF LEISHMANIASIS

Immunomodulator

Cure of leishmaniasis appears to be dependent upon the development of an effective immune response that activates macrophages to produce toxic nitrogen and oxygen metabolites to kill the intracellular amastigotes. This process is suppressed by the infection itself, which down regulates the requisite signaling between macrophage and T cell such as the interleukin (IL) 12, the interferon (IFN) and the presentation of major histocompatibility complex (MHC). One alternative in leishmaniasis treatment is the association of antileishmanial drugs with products that stimulate the immune system. The purpose is to enhance the immune response by the activation of macrophages and the increase of the nitric oxide production among other mechanisms to eliminate the infection [13]. The first report about the use of immunomodulator was the superiority of human IFN as an adjunct antimony therapy for VL, which was demonstrated in Kenya and India [14]. Amphotericin B in conjunction of IL-12 or IL-10 was more efficient than monotherapy and led to a reduction of the amphotericin dose. Other studies have been reported, using immunomodulator like BCG [15] and protein A [16]. Nevertheless, the price of immunomodulator is exorbitantly high for poor population [17]. Recently, a new generation of synthetic immunomodulator drugs has shown potential for Leishmaniasis treatment. A Schiff base forming compound, Tucaresol enhance TH1 response and the production of IL-12 and IFN-α in mice and human in patients with viral infections and cancer. Tucaresol also has activity against infection caused by *L. donovani* in BALB/c mice and C57BL/6 at a dose of 5 mg/Kg [18]. Iminoquimod, an imidazoquinoline, is the ingredient of a cream (AldaraTM) used for the treatment of genital warts. This drug has shown to induce nitric oxide production in macrophages and it was effective in vitro against *L. donovani* [19]. This field can be more explored with new products, aiming to validate the use of immunomodulator for treatment of leishmaniasis, particularly in patients infected with strains that can develop ML or other complications.

Combined Therapy

After increasing unresponsiveness to most of the monotherapeutic regimens, the combination therapy has found new scope in the treatment of leishmaniasis. The combination of antileishmanial drugs could reduce the potential toxic side effects and prevent drug resistance. Several works have shown that some drugs increase their antileishmanial effect in conjunction [20]. Paromomycin have been used extensively in Sudan in combination with sodium stibogluconate for the treatment of VL in a period of 17 days [21]. The superiority of this combination has been demonstrated in several studies [22, 23]. Combined chemotherapy against VL in Kenya was evaluated using oral allopurinol (21 mg/Kg, three times a day for 30 days) with endogenous pentostam (20mg/Kg once a day). The therapy was efficient, but relapses were found in the first

month after treatment [24]. This clinical evidence demonstrated the superiority of the combination therapy and can be a hope to develop new formulations.

DEVELOPMENT OF NEW DRUGS

During the past decades new impetus have been given to anti-leishmanial drug discovery; including (i) knowledge of biology, biochemical pathway and genome of parasite, (ii) a revolution in chemical techniques, (iii) several advances in bioinformatics tools and (iv) a higher number of networks, partnerships and consortia to support the development of new antileishmanial agents. Currently, the development of both synthetic and natural drugs has relevant importance in the search of new therapeutic alternatives.

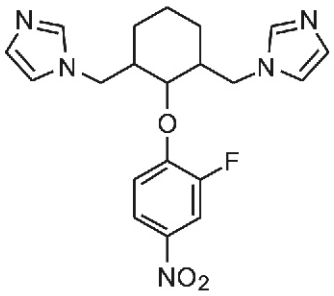
SCOPE OF SYNTHETIC COMPOUNDS

The medicinal chemistry is a recent applied science directed to the development of new drugs that evolved significantly due to recent technological advances, mainly in molecular, structural biology and computational chemistry areas. The generation of structural modifications in an initial molecule (called lead compound) to obtain new derivatives has been one successful approach for the design of new drugs based in known and validated molecular targets in the parasite. The knowledge about the physiochemical and structural properties of the leading compound and its relation to the pharmacological target or action have provided evidences about the initial pharmacophore group, which is essential to activity [25]. Derivatives with pharmacophore group can be obtained with the aim to increase the activity and modulate toxic and pharmacokinetic characteristics of the compounds. In parallel, the design of specific inhibitors has been explored as a possible means for controlling the parasites growth without damaging the host. A review about potential targets in Leishmania parasite has been written [26]. Some of the most promising targets are: topoisomerases [27], kinetoplast [28], mitochondria [29], trypanothione reductase [30], cysteine protease [31], and fatty acid and sterol pathways [32]. A plethora of compounds having different structural features have demonstrated their antileishmanial potentialities. This review is an attempt to summarize the accounts of promising antileishmanial compounds mainly based on pyridine

and quinoline core of both synthetic and natural origin that appeared in the literature.

IMIDAZOLE

A series of novel aryloxy cyclohexane based mono and bis-imidazoles derivatives were synthesized by Bhandari and co-workers [33]. Among all, the Bis-methylimidazole containing compound (1) with 2-fluoro, 4-nitro aryloxy group exhibited significant *in vivo* inhibition of Leishmania donovani (77.9%). This compound was better than sodium stibogluconate and pentamidine. Another new class of imidazolidin-2-one derivatives was introduced [34], which were evaluated against promastigotes of *Leishmania mexicana* and *Leishmania infantum*. Among the eighteen tested compounds, compound (2) showed a highest activity with IC_{50} value in the range of 16.0-9.5 $\mu molL^{-1}$. Then compound (2) was subjected to evaluate against amastigotes of *Leishmania mexicana* and showed the inhibiton at IC_{50} 2.4 $\mu molL^{-1}$. Ferreira et al. [35] synthesized N-substituted-phenyl-imidazole-5-difluoromethyl derivatives. These compounds were tested against promastigote forms of *Leishmania amazonensis*. Among all imidazole derivatives,



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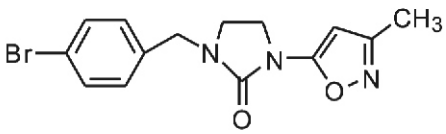

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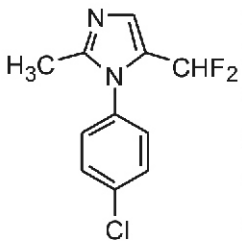

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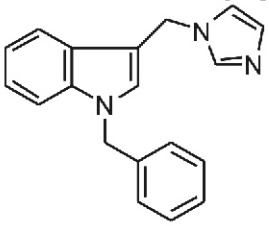

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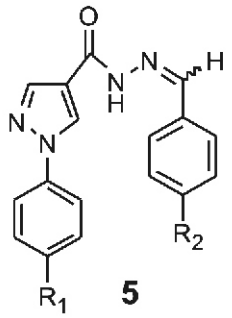
compound (3) showed most promising activity with IC_{50} 1.7 µM. Borgne and his group [36] prepared several 3-imidazolylalkyl indole derivatives. All the synthesized compounds were evaluated *in-vitro* against *Leishmania mexicana* promastigotes and tested against intracellular amastigotes of *Leishmania mexicana*. It was observed that the most potent compound was 1-(2-bromobenzyl)-3-(1H-imidazole-1-ylmethyl)-1H-indole (4) with IC_{50} value 0.011±0.003 µg/ml in pomastigotes and IC_{50} value 0.018±0.004 µg/ml in amastigotes.

PYRAZOLE

Amaral and its group introduced a series of 1-(4-X-phenyl)-N'-[(4-Y-phenyl) methylene] 1H-pyrazole-4-carbohydrazides (5) derivatives [37]. In these compounds a lateral chain of 1H-pyrazole-4-carbohydrazide probably contributed to their biological activity. In this series compound (5a) and (5b) showed a potent activity with 66% and 90% inhibition of *Lieshmania amazonensis*, respectively.

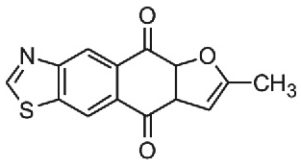


5

5a $R_1 = NO_2$, $R_2 = Cl$
5b $R_2 = Br$, $R_2 = F$

THIAZOLE

A new series of naphthothiophene quinones containing a fused thiazole ring was synthesized by Fillion and its group. These compounds were screened against promastigote forms of *Leishmania donovani* and *Leishmania major* [38]. The compound (6) was found to be most significant due to less cytotoxicity against THP-1 cell line.



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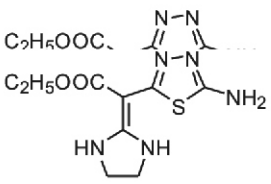
THIADIAZOLE

Ram and his co-worker presented 2, 4 disubstituted 1, 3, 4-thiadiazole derivatives and evaluated for *in vitro* antileishmanial activity [39].



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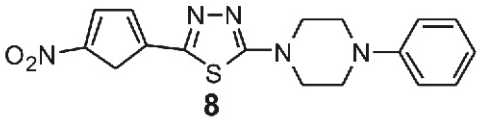
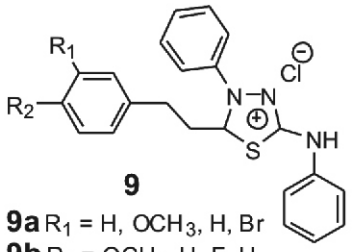


8

Among these, compound (7) showed 73% *in-vitro* inhibition of promastigote of *Leishmania donovani*. Another group of scientist reported a set of 2-(5-nitro-2-furyl) and 2-(5-nitro-2-thienyl)-5-substituted 1, 3, 4-thiadiazole derivatives [40]. The most active compound (8) was found to be significant with an IC_{50} 0.1 µM against *Leishmania major* promastigotes. Echeavarria et al. [41] prepared a class of 1, 3, 4-thiadiazolium-2-phenylamine (9) derivatives. This is a class of mesoinoic compounds. These were evaluated against *Leishmania amazonensis*. Compound 9a and 9b were more active than pentamidine against promastigote forms with IC_{50} value 0.17 and 0.04 µM, respectively. Compound 9c and 9d were more effective against amastigotes with IC_{50} value 5.37-5.48 µM.

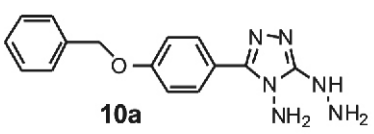


9

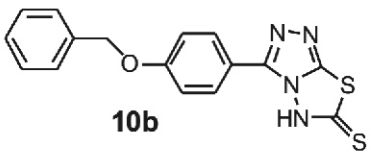
9a R_1 = H, OCH_3, H, Br
9b R_2 = OCH_3, H, F, H

TRIAZOLE

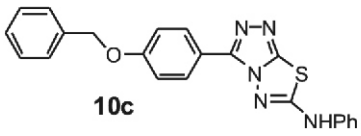
A series of 4-Amino-3-(4'-benzyloxyphenyl)-5-mercapto-1,2,4-triazole (10) compounds were prepared and screened for antileishmanial activity against *Leishmania Donovani* [42]. Among all these ten compounds, only 10a, 10b, 10c, 10d, and 10e showed 80-95% inhibition. Ferreira and its group [42a] introduced a series of compounds containing triazole rings. Form all the synthesized compounds



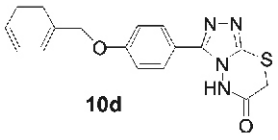
10a



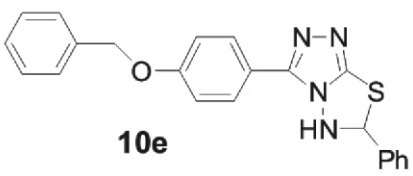
10b



10c

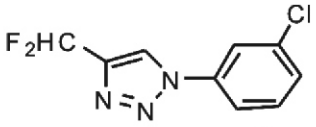


10d



10e

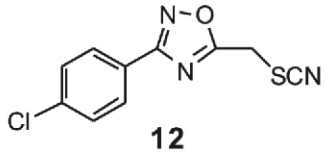
only compound (11) was found to be most active against promastigote form of *Leishmania amazonensis* with IC_{50} 2.6 µM.



11

OXADIAZOLE

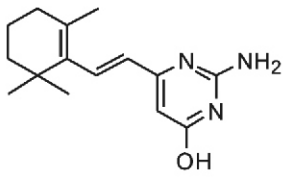
Werbovetz and co-workers synthesized a series of 3-aryl-5-thiocyanatomethyl-1,2,4-oxadiazoles [43]. These compounds were tested against amastigotes of *Leishmania donovani*. Among these compounds 3-(4-chlorophenyl)-5-(thiocyanatomethyl)-1,2,4 oxadiazole (12) showed more selectivity for *Leishmania donovani* (IC_{50}=4.5±1.8 µM).



12

PYRIMIDINE

A new series some novel terpenyl pyrimidine derivatives were demonstrated by Suryawanshi and co-workers [44]. The pyrimidine derivatives were screened for *in-vivo* antileishmanial activity against amastigotes of *Leishmania donovani* in hamsters. The compound (13) showed promising 63% *in-vivo* antileishmanial activity at 50 mg/kg dose. A similar series of novel N- substituted terpenyl pyrimidines were synthesized by same group [45]. These were screened for *in-vitro* antileishmanial activity profile in promastigote model. Among all compounds, compound (14) showed better activity with 98.8% inhibition at 1 µg/ml dose.



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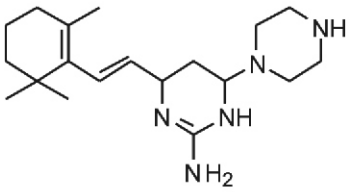
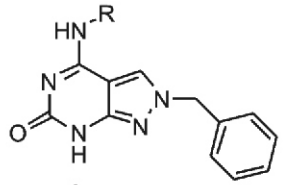


14

Bhakuni et al. [46] synthesized a series of 1/2-benzyl-4,6-disubstituted 1H /2H-pyrazolo [3,4-d] pyrimidines. Among these, compound 15a and 15b showed 60% and 55% inhibition respectively of amastigotes for *L. donovani* in hamster at the dose of 100 mg /ml.

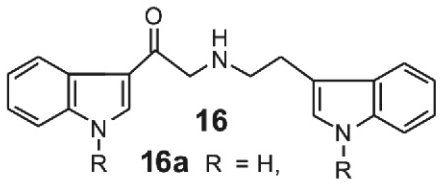


15

15a R = CH_2-CH_2-C_6H_4-Cl,
15b = H

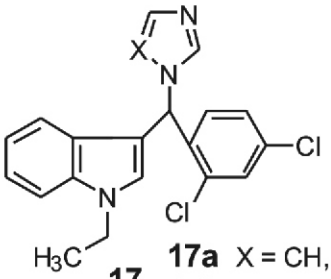
INDOLE

A series of marine alkaloid 8, 9-dihydrocoscinamide B, its analogues and indolylglyoxylamide derivatives (16) were synthesized by Chauhan and its group [47]. Among these, compound 16a and 16b have shown 99-100% inhibition against promastigotes and 97-98% inhibition against amastigotes at a concentration of 10 µg/ml. A similar approach was synthesized by Pagniez and its group [48] and evaluated two 3-(α-azolylbenzyl) indoles (17) against intracellular and axenic amastigotes. Compound 17a and 17b both were active against to intracellular and axenic amastigotes. Compound 17a and 17b showed IC_{50} value 4.4±0.1 and 6.4±0.1 µM, respectively.



16

16a R = H,
16b = CH_3

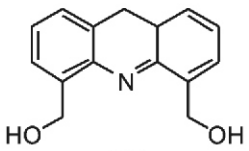


17

17a X = CH,
17b = N

ACRIDINE

Carole and its co-workers [49] synthesized a number of 4,5 di substituted acridines. In these compounds 4,5-bis-(hydroxymethyl) acridine (18) showed potent antileishmanial activity against *Leishmania infantum* amastigote form.

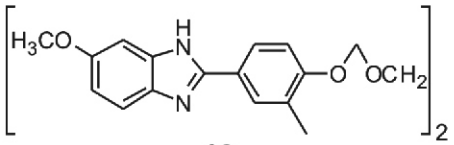


18

BENZIMIDAZOLE

A series of ten novel hybrids form of benzimidazole and pentamidine were prepared by Vazquer and its co-workers [50], using a short synthetic route. Among these,

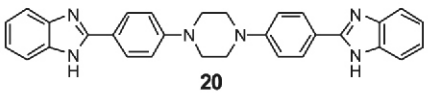
1,5-bis-[4-(5-methoxy-1H-benz-imidazole-2yl)phenoxy] pentane (19) was found to be 13-fold more active than pentamidine against *Leishmania mexicana*.



19

PIPERAZINE

A novel series of 1,4-diarylpiperazine derivatives were synthesized by Huang and its groups [51].



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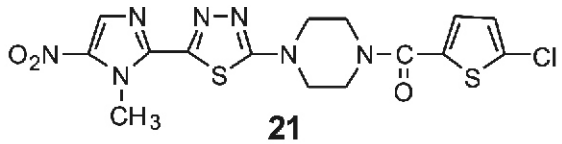
Among these compounds, 1,4-bis-[4-(1H- benzimidazol-2-yl) phenyl] piperazine (20) emerged as most active against Leishmania parasite. Foroumadi et al. [52] prepared a series of 1-[5-(1-methyl-5-nitro-1H-imidazole-2-yl)-1, 3, 4-thiadiazol-2-yl]-4-aroylpiperazines. The most active compound was 1-[(5-chloro-2-thienyl) carbonyl]-4-[5-(1-methyl- 5- nitro-1H- imidazol- 2- yl) -1,3,4-thiadiazol-

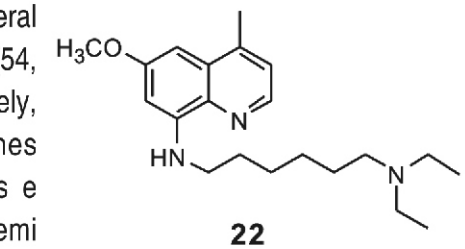


21

2-yl] piperazine (21) with IC_{50} value of 9.35±0.67 µM against Leishmania major promastigotes.

QUINOLINES

8-Aminoquinolines possess outstanding *in vivo* antileishmanial activity [53] and the 8-aminoquinoline sitamaquine (WR6026), compound (22) has been the subject of several VL drug trials [54, 55]. Unfortunately, 8-aminoquinolines can cause methemoglobinemia and hemolysis in populations where glucose-6-phosphate dehydrogenase deficiency is prevalent. The racemic 8-aminoquinoline NPC1161C and its pure enantiomers NPC1161A and NPC1161B (23) showed potent antileishmanial activity, with 23 displaying the best efficacy [56]. At an oral dose of 0.4 mg/kg/day for five days, 23 gave 61% suppression of liver parasitemia in *L. donovani* infected mice. 8-aminoquinolines 22 and 23 gave similar *in vivo* efficacy in the BALB/c VL model. When administered orally to beagles at a dose of 1.91 mg/kg/day for 4 days, NPC1161A induced 20% methemoglobinemia, while 22 did not appear to increase methemoglobin levels. For 23 or any other 8-aminoquinoline to be developed against Leishmania, low levels of hemolytic toxicity at higher doses should be demonstrated. Amodiaquine analogs were synthesized and evaluated against intracellular *L. donovani*. Compound 24 displayed an IC_{50} of 2.3mM against *L. donovani* and an IC_{50} of 12mM against KB cells [57]. A new group of compounds contains 4-Aminoquinaldine Analogues showed very good activity against leishmaniasis. Both compounds 24a, 24b showed profound antiparasitic activity against both Schwann cell membrane glycoprotein (SAG)-sensitive and-resistant strains of Leishmania in an *in vitro* and as well as an *in vivo* model. In this scenario, the efficacy of 24a and 24b against SAG-sensitive and -resistant parasites for oral



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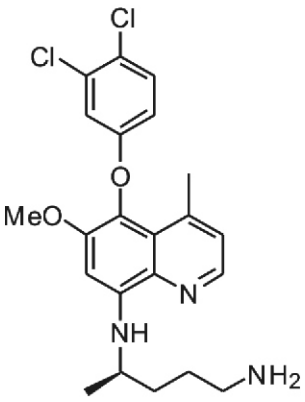

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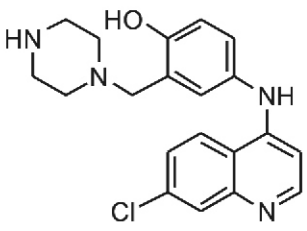

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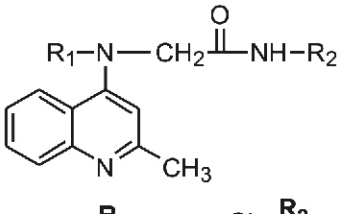
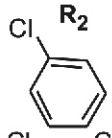
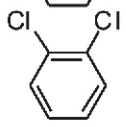
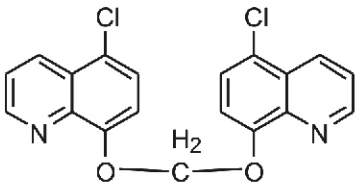
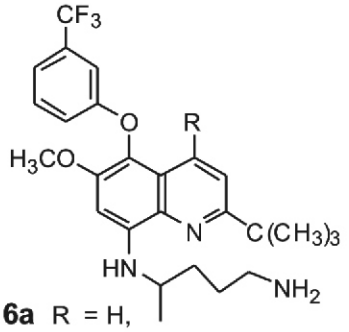


	R_1	R_2
24a	H	
24b	H	



25

treatment of experimental VL is remarkable [57a]. These two are promising preclinical development candidates for oral drug therapy for VL, alone or in combination with currently used antileishmanials, with prospects also for rescue treatment of antimony treatment failure. A series of bis-quinolines were synthesized and tested for antiparasitic activity [58]. Compound (25) displayed an IC_{50} of 2.1mg/mL (5.7mM) against intracellular *L. donovani*. When *L. donovani*-infected mice were given (25) by the i.p. route at a dose of 12.5 mg/kg starting one month post-infection and administered twice per week for one month, parasite load was reduced by 95% in the spleen and by 98% in the liver. Sodium antimony gluconate, given at a dose of 250 mg/kg by the same regimen as 25, resulted in only 57% inhibition in the spleen and 60% inhibition in the liver. Another series of 8-quinolinamine analogues (26) were synthesized and evaluated for antileishmanial activity [59]. Among all these compounds, 26a, 26b and 26c showed IC_{50} value 3.0, 3.4 and 2.9µg/mL in *Leishmania donovani*.

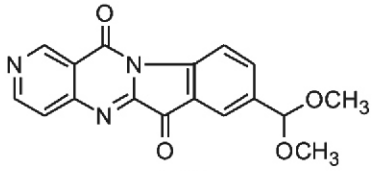


26a R = H,
26b = CH_3,
26c = C_2H_5

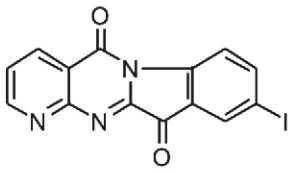
26

QUINAZOLINE

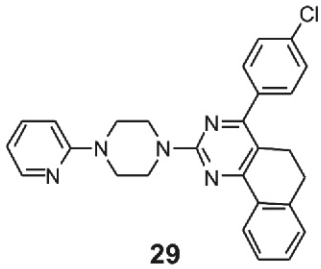
Sahu and its co-workers [60] synthesized a series of new class of 4-(hetero)aryl-2-piperazino quinazolines (27). These were accessed for *in vitro* activity against intracellular amastigotes of *Leishmania donovani*. Among all the evaluated compounds, compound 28a showed potent action. Bhattacharjee et al. [61] analysed stereoelectronic properties of synthetic indolo [2,1-b] quinazoline-6,12-dione derivatives. These compounds exhibited remarkable activity at concentrations below 100ng/mL when tested against *in vitro* Leishmania donovani amastigotes. Among these, compound 28a and 28b were the most active against Leishmania in this study, with IC_{50} value of 16ng/mL. A series of dihydro and tetrahydroquinazolines was prepared as potential antileishmanial dihydrofolate reductase (DHFR) inhibitors [62]. Compound 29 was the most potent, displaying an IC_{50} value of 2.7mg/mL (5.8mM) against intracellular *L. donovani*.



28a



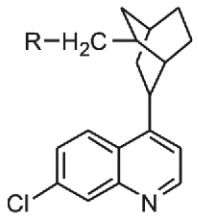
28b



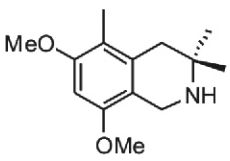
29

ISOQUINOLINE

Khan and its group designed and synthesized a series of semi rigid analogs of the antimalarial drug chloroquines [63]. All analogs demonstrated significant antileishmanial activity against *Leishmania donovani* but compounds 30 and 31 being the most potent. Naphthyl isoquinolines were synthesized and investigated for their activity against intracellular *L. donovani* [64]. A precursor to the naphthyl isoquinoline target compounds (32) displayed the best activity (IC_{50}=2.4mM, selectivity index of 28



30 R = H,
31 R = $-N(CH_3)_2$



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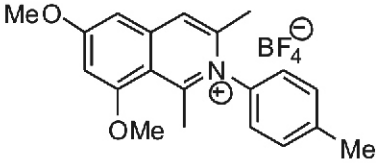
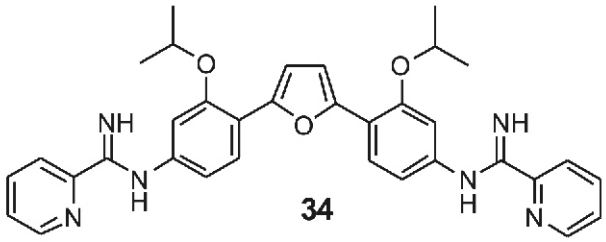


33

when compared to L6 rat myoblasts). N,C coupled aryl isoquinolinium salts related to the natural product ancistrocladinium A showed far better activity, with 33 displaying an EC_{50} value of 92nM against intracellular *L. major*[65].

ARYLIMIDAMIDES

A host of diamidines related to pentamidine have been prepared and evaluated for antimicrobial activity.

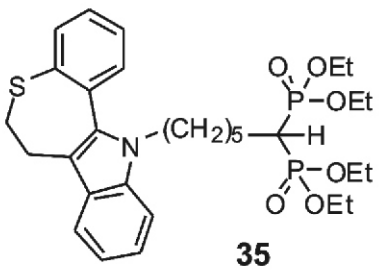


34

Although diamidines often display potent activity against axenic Leishmania, they typically possess limited efficacy against intracellular parasites [66], perhaps due to their polarity. Arylimidamides contain amidine groups but have lower pKa values and are more hydrophobic than diamidines because of their amidine nitrogen atom being bound to an aromatic linker. DB766 (34) displays an IC_{50} value of 36 nM against intracellular *L.donovani* (approximately two fold more potent than amphotericin B in this assay) [67]. Compound 34, when given orally at 100 mg/ kg/day × 5, resulted in 71% and 89% reduction of liver parasitemia in *L. donovani*-infected mice and hamsters, respectively. No change in marker enzymes was observed in a mouse toxicology study when 34 were given orally at 100 mg/kg/day × 5.

BISPHOSPHONATES

Bisphosphonates, which inhibit the isoprene biosynthesis pathway enzyme farnesyl pyrophosphate synthase (FPPS), are commonly used in bone resorption therapy and also possess outstanding *in vivo* antileishmanial activity [68]. Several tetracyclic N-substituted dihydrobenzothiepino and dihydrobenzoxepino indole derivatives were screened against *L. donovani*. Compounds featuring tetra esters showed better activity against intracellular organisms when compared to 1-hydroxy bisphosphonates, with compound 35 displaying 78% inhibition of the parasites at a concentration of 16mM [69].



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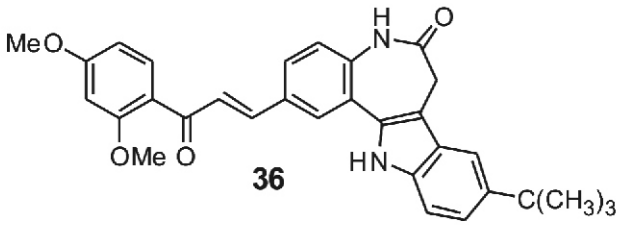
CHALCONES

Chalcones have long been known to possess

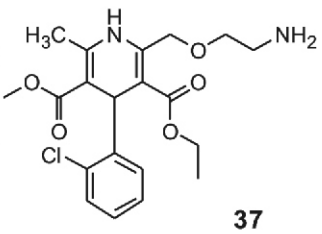


36

antileishmanial activity [70]. Novel dihydro-a-ionone based chalcones were synthesized and evaluated against intracellular *L. donovani*. Compound 36 inhibited parasitemia by 88% at a concentration of 2mg/mL (6.3mM) [71]. Modification of the paullone core with a 2-(3-aryl-3-oxopropenyl) group together with a 9-tert-butyl group resulted in compounds that showed good activity in the *L. donovani*-infected macrophage assay and generally displayed low toxicity against uninfected THP-1 cells. The most effective compound in this study, 36, reduced parasitemia within *L. donovani*-infected THP-1 cells by 86% at a concentration of 5mM while having no discernable effect on uninfected host cells at the same concentration [72].

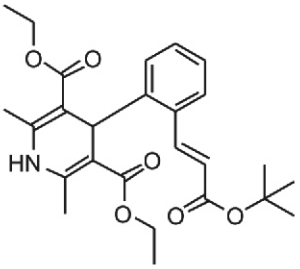
DIHYDROPYRIDINE ANTIHYPERTENSIVES

Amlodipine (37) and lacidipine (38), two dihydropyridine containing antihypertensive agents, displayed IC_{50} values of 2.1mg/mL (5.3mM) and 2.8mg/mL (6.1mM) against intracellular *L. donovani*. When given to *L. donovani* infected mice orally at 10 mg/kg in single weekly doses for four weeks, 8 and 9 resulted in 86% and 72% inhibition of liver parasitemia, respectively [73]. While



37

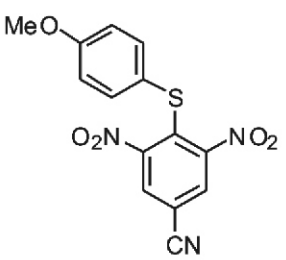
these compounds clearly merit further investigation as antileishmanial candidates, comparison of the antileishmanial efficacy of the dihydropyridines to that of control antileishmanial drugs is needed.



38

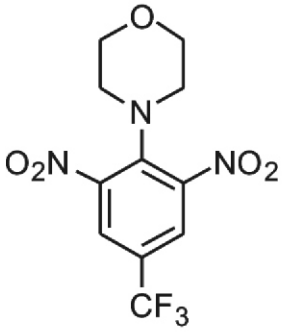
NITROAROMATIC COMPOUNDS

Analogs of a dinitroaryl lead compound identified by *in silico* screening were synthesized that demonstrated activity against intracellular Leishmania. Compound 39 displayed an IC_{50} value of 2.6mM against intracellular *L. amazonensis* but produced only 29% inhibition of liver parasitemia when administered i.p. to *L. donovani* infected BALB/c mice at 50 mg/kg/day × 5 [74].



39

The antileishmanial activity of the dinitroaniline herbicide trifluralin was demonstrated in 1990 [75], but it has little potential as an antileishmanial agent due to poor solubility. A series of novel trifluralin analogs were synthesized in an attempt to improve trifluralin's physicochemical properties and efficacy against VL. Compound 40 displayed an IC_{50} of approximately 0.5mM against intracellular *L. infantum*, but did not clear parasites from infected cells. The length of the alkylamino chain on the amino group was critical for activity in the intracellular assays, and the introduction of an oxygen atom on the heterocyclic ring dramatically improved activity [76]. 5-Nitrofuran (41) reduced the parasitemia in *L. major* infected macrophages by approximately 70% percent compared to the control at a concentration of 11mM [77]. Further synthesis of compounds in this series yielded (42), which reduced the number of amastigotes per macrophage by approximately 80% compared to the control at a concentration of 9.4mM [78].



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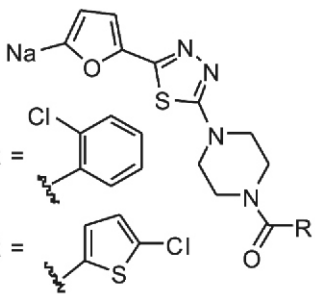
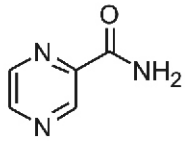


41 R =

42 R =

PYRAZINAMIDE

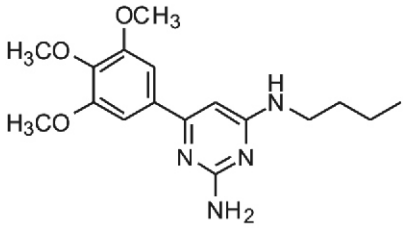
The antimycobacterial drug pyrazinamide (43) displayed activity against intracellular *L. major* (MIC= 8.2mM) and reduced lesion sizes in *L. major* infected C57BL/6 mice when given orally at 150 mg/kg in fifteen doses [79].



43

PYRIMIDINES AND TRIAZINES

A series of pyrimidines and triazines designed as dihydrofolate reductase inhibitors were synthesized and evaluated for activity against *L. donovani*. Pyrimidines featuring a 3, 4, 5-trimethoxyphenyl group at the 4-position of the pyrimidine ring showed better activity than compounds lacking this substituent. Compound 44 displayed 54% inhibition of parasitemia in *L. donovani* infected hamsters when administered i.p. at a dose of 50 mg/kg/day×5 [80]. A. Kumar et al [81] identified some β-carboline-triazine derivatives as potent and less toxic antileishmanial agents. These compounds can be better than the standard drug (sodium stibogluconate). Standard drug belongs to the antimonial class and is associated with nephrotoxicity and liver toxicity while β-



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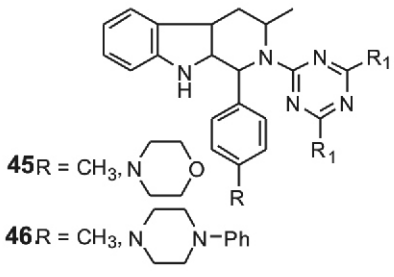


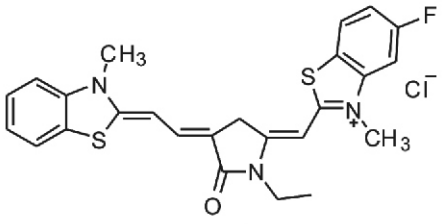
45 R = CH_3,

46 R = CH_3,

carboline-triazine derivatives 45, 46 do not have any type of metallic atom, so these molecules can be used as lead molecules for optimization work. These β-carboline-triazine derivatives will be useful in developing new potential antileishmanial agents.

RHODACYANINE DYES

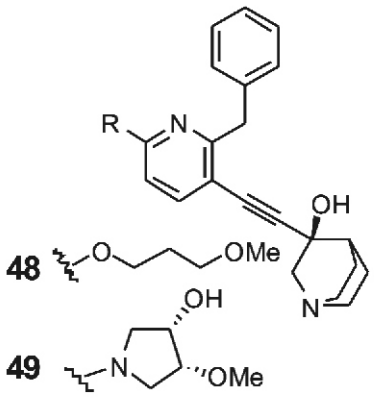
Various rhodacyanine derivatives were synthesized and evaluated for their activity against *L. donovani* both *in vitro* and *in vivo* [82]. Compound 47 displayed an IC_{50} of 0.35 mM against intracellular *L. donovani*. Intravenous treatment of *L. donovani* infected mice with 47 at 4.1 mg/kg/day×5 resulted in 97% inhibition of parasitemia. Oral activity in animal models of leishmaniasis must now be demonstrated with these rhodacyanine compounds or their derivatives.



47

STEROL METABOLISM INHIBITORS

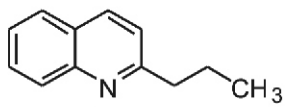
Two quinuclidine-containing inhibitors of human squalene synthetase, ER-119884 (48) and E5700 (49), displayed potent and selective activity against intracellular amastigotes of *L. amazonensis* [83]. The former compound was more potent, exhibiting an IC_{50} value of 0.5 nM against these parasites and showing no adverse effects against the host murine peritoneal macrophages at 500 nM concentrations. Compounds (48) and (49) were nanomolar inhibitors of *de novo* sterol biosynthesis in *L. amazonensis* promastigotes, while 48 also affected the cell cycle in these parasites.



SCOPE OF NATURAL PRODUCTS

ALKALOIDES

The alkaloids constitute an important class of natural products exhibiting significant anti-leishmanial activities. The quinoline alkaloids, 2-*n*-propylquinoline 50, chimanine D 51 and chimanine-B 52, isolated from *Galipea longiflora* (Rutaceae), exhibit antileishmanial activity against *L.braziliensis* promastigotes with an IC_{90} values of 50, 25 and 25μg/mL, respectively. Oral *in vivo* studies were performed on BALB/c mice demonstrates 99.9% suppression of liver parasites while subcutaneous treatment with 52 causes 86.6% parasite suppression when given for 10 days at 0.54 mmol/kg [84]. However, oral treatment given for 5 days resulted in 72.9% parasite suppression only. Likewise, dictylomide-A 53 and B 54 isolated from the bark of *Dictyoloma peruviana* (Rutaceae), causes total lyses of *L. amazonensis* promastigotes at 100 μg/mL concentration [85].



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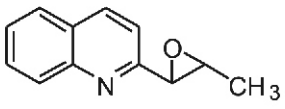

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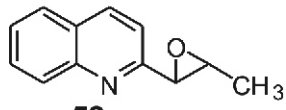

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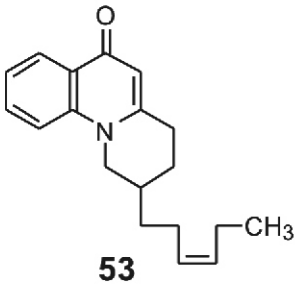

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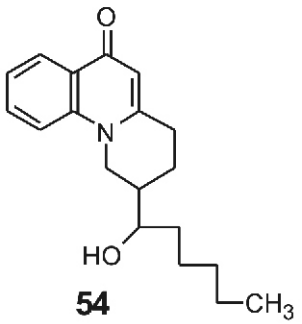
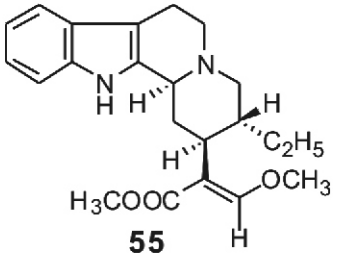


54

Indole alkaloids Dihydrocorynantheine 55, corynantheine 56 and corynantheidine 57 isolated from the bark of *Corynanthe pachyceras* (Rubiaceae) are the respiratory chain inhibitors exhibiting IC_{50} of 3 μM against *L. major*. Pleiocarpine isolated from stem bark of *Kopsia griffithii* (Apocynaceae), shows *in vitro*



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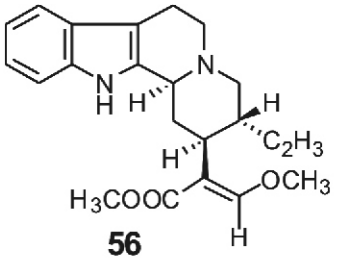
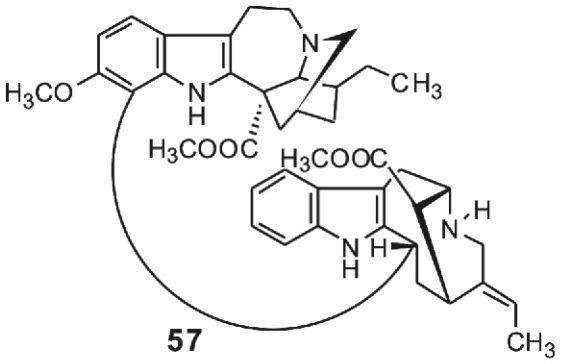


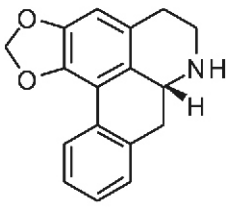
56

antileishmanial activity with an IC_{50}<25□g/mL against *L. donovani* promastigotes. Gabunine, a bis-indole alkaloid obtained from stem bark of *Peschiera van heurkii* (Apocynaceae), exhibits *in vitro* activity with an IC_{50} 25□g/mL against *L. amazonensis* amastigotes [86].



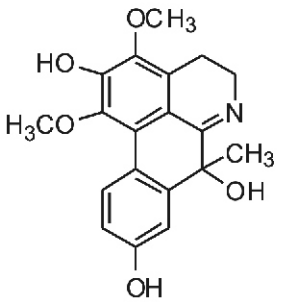
57

Isoquinoline alkaloids liriodenine 58 and O-methylmoschatoline 59, isolated from *Annona foetida* (Annonaceae), display *in vitro* activity against promastigote forms of L. braziliensis with an IC_{50} < 60μM [87]. The SAR study among these oxoaporphine alkaloids reveals that methylenedioxy moiety is eight times more active against *L. braziliensis* and *L. guyanensis* than the O-methylmoschatoline.



58

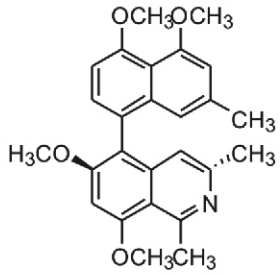
Berberine, occurring in many plant species of Annonaceae, Menispermaceae and Berberifaceae, exhibits in vivo leishmanicidal activity with an IC_{50} value of 10 μg/mL against *L. major*. Isoguattouregidine isolated from *Guatteria foliosa* (Annonaceae), shows activity at 100 μg/mL concentrations against *L. donovani* and *L. amazonensi*. Anonaine isolated from *Annona* spinescens (Annonaceae), exhibits activity against promastigotes of *L. braziliensis* and *L. donovani* [88]. The alkaloids, (+) neolitsine and cryptodorine, isolated from *Guatteria dumetorum* (Annonaceae), display significant activity against promastigotes of *L. maxicana* at 15 and 3 μM concentrations, respectively. Xylopine, an aporphine alkaloid isolated from *Guatteria amplifolia* (Annonaceae) shows activity against promastigotes of *L. mexicana* (IC_{50} value 3 μM) and *L. panamensis* (IC_{50} value 6 μM) [89]. Unonopsine, a dimeric aporphine alkaloid isolated from the *Unonopsis buchtienii* (Annonaceae), displays antileishmanial activity (IC_{100} value 25μg/mL) against *L. donovani* promastigotes [90].



59

NAPHTHYL ISOQUINOLINE ALKALOIDS :

Among the naphthylisoquinoline alkaloids, ancistroealaine-A 60 isolated from *Ancistrocladus ealaensis* (Ancistrocladaceae), exhibits activity against *L. donovani* promastigotes with an IC_{50} value 4.10 μg/mL. Ancistrocladinium A 61 and B 62 isolated from yet undescribed Congolese Ancistrocladaceae species, require 2.61 and 1.52 μg/mL concentrations, respectively to reach the IC_{50} towards *L. major* promastigotes. An apoptosis-like death pathway is the possible mode of action for above compounds.



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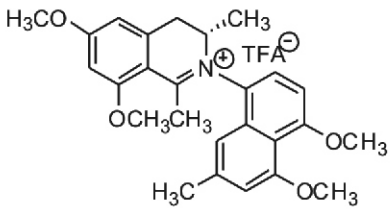

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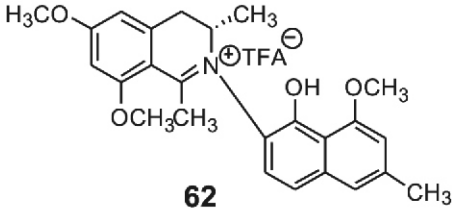
Ancistrocladidine, isolated from *Ancistrocladus tanzaniensis* (Ancistrocladaceae) shows relatively weak activity by a factor of 2 against *L. donovani* when compared to ancistrotanzanine-B (IC_{50} = 1.6 μg/mL), while by a factor of 10 in comparison to miltefosin (positive control). Likewise, ancistrotanazanine-A exhibits activity



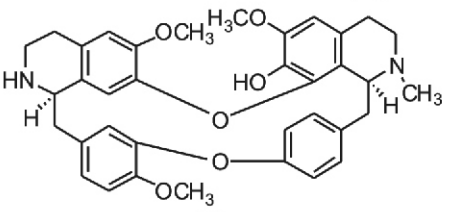
62

against promastigotes of *L. donovani* .

SAR based studies among the alkaloids suggest that the compound bearing C,C-biaryl axis connecting the naphthyl and isoquinoline moiety shows weak or no leishmanicidal activity.

BISBENZYL ISOQUINOLINE ALKALOIDS :

Daphanandrine 63 isolated from *Albertisia papuana* obaberine 64 obtained from *Pseudoxandra sclerocarpa* (Annonaceae), gyrocarpine 65 produced by *Gyrocarpus americanus* (Hernandiaceae) and limacine 66 isolated from *Caryomene olivasans* (Menispermaceae), display activity against *L. donovani*, *L. braziliensis* anamazonensis with an IC_{100} of ~50 μg/mL.SAR studies among these alkaloids demonstrate that alkaloids with methylated nitrogen are more active than those with non-substituted or aromatic nitrogens while quaternization of one or more nitrogen atoms results in the loss of antileishmanial activity [91].



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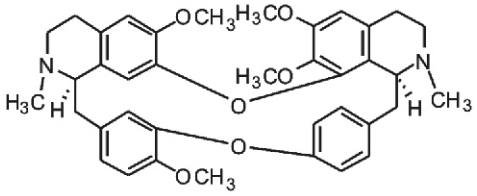

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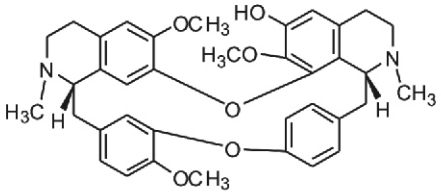

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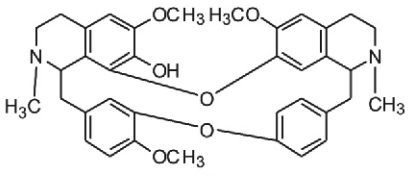
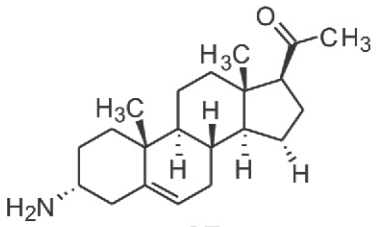


66

STEROIDAL ALKALOIDS :

Among the alkaloids, holamine 67, 15-α hydroxyholamine, holacurtine 68 and N-desmethylholacurtine obtained from *Holarrhena curtisii* (Apocynaceae), the metabolite holamine exhibits strongest activity against *L. donovani* ($1.56>IC_{50}>0.39$μg/mL) in compared to holacurtine and N-desmethyl holacurtine ($6.25>IC_{50}>1.56$ μg/mL) [92]. Benzoquinolizidine Alkaloids: Klugine 69, cephaeline 70, isocephaeline 71 and emetine 72 demonstrating significant leishmanicidal activities against *L. donovani* have been isolated from *Psychotria klugii* (Rubiaceae). Among these metabolites, klugine (IC_{50} of 0.40 μg/mL) and isocephaline (IC_{50} 0.45 μg/mL) exhibit <13- and <15 fold less potent activity in compared to cephaline with IC_{50} of 0.03 μg/mL demonstrates >20- and >5-fold more *in vitro* activity against *L. Donovani* when compared to pentamidine and amphotericin-B, respectively. Emetine exhibits activity against *L. donovani* with an IC_{50} value 0.03 μg/mL, however produces toxicity in treatment of cutaneous leishmaniasis caused by *L. major* [93].



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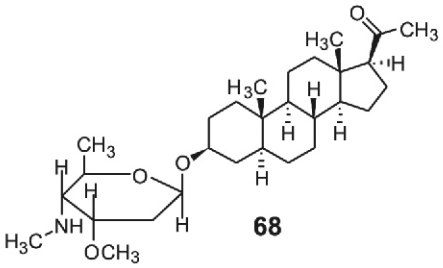

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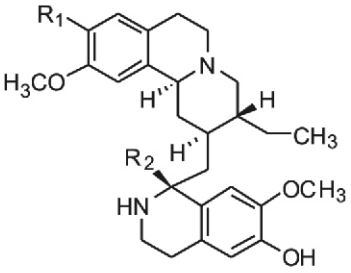
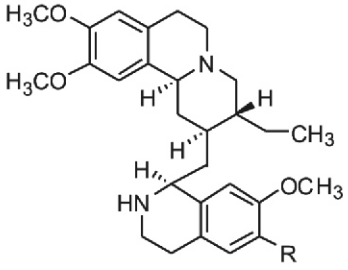


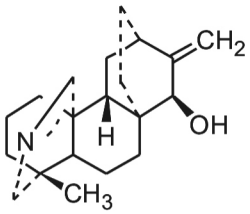
69 R_1 = OH; R_2 = OH
70 R_1 = OCH3; R_2 = H



71 R = OCH_3
72 R = OH

DITERPENE ALKALOIDS :

The alkaloids, 15, 22-O-Diacetyl19-oxo-dihydroatisine, azitine 73 and isoazitine 74, isolated from Aconitum, Delphinium and Consolida species, show significant leishmanicidal activities. The metabolite isoazitine exhibits strongest activity against promastigotes of L. infantum with IC_{50} values 44.6, 32.3 and 24.6 μM at 24, 48 and 72 h of culture, respectively. Azitine with IC_{50} values of 33.7 and 27.9 μM at 72 h of culture, respectively, exhibit activity against promastigotes of L. infantum [94].



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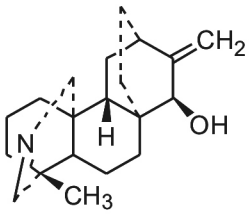
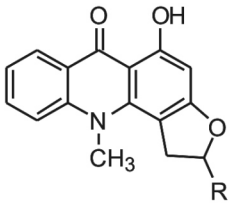


74

ACRIDONE ALKALOIDS :

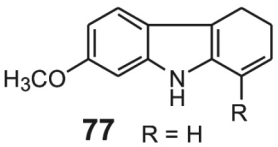
The rhodesiacridone 75 and gravacridonediol 76 isolated from *Thamnosma rhodesica* (Rutaceae), exhibit 69% and 46% inhibition at 10 μM concentration, respectively against promastigote of *L. major*. The compounds also display activity against *L. major* amastigotes and cause over 90% and 50% inhibition at 10 and 1 μM concentration, respectively.



75 R = $C(OH)(CH_2OH)COCH_3$
76 R = $C(OH)(CH_3)CH_2OH$

β-CARRBONILINE ALKALOIDS :

The harmaline 77, isolated from *Peganum harmala* (Nitrariaceae), exhibits amastigotespecific activity (IC_{50} of 1.16 μM). Harmine 78 isolated from same plant species reduces spleen parasite load by approximately 40, 60, 70 and 80% in free, liposomal, niosomal and nanoparticular forms, respectively in mice model.

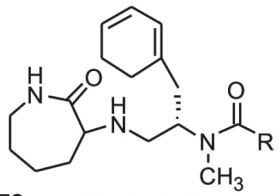


77 R = H
78 R = CH_3

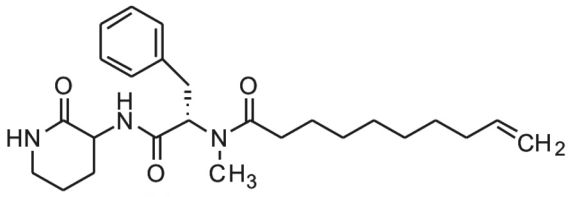
Canthin-6-one and 5methoxycanthin-6-one occurring in plant species of Rutaceae and Simaroubaceae, demonstrate *in vivo* activity against *L. amazonensis* in BALB/c mice model. N- hydroxyannomontine and annomontine isolated from Annona foetida (Annonaceae), show efficient leishmanicidal potentials.

ALKALOIDS FROM MARINE SOURCE :

Marine sponges e.g. Amphimedonviridis, Acanthostrongylophora species, *Neopetrosia species*, *Plakortis angulospiculatus* and *Pachymatisma johnstonii* serve as rich sources of alkaloids with significant antileishmanial potentials. Renieramycin A isolated from *Neopetrosia species*, is a La/egfp (expressing enhanced green fluorescent protein)



79 R = $(CH_2)_7CHCH_2$
80 R = $(CH_2)_5CH_3$



81

inhibitor that shows efficient antileishmanial activity against *L.amazonensis* with IC_{50} 0.2 μg/mL. Araguspongin C, isolated from a marine sponge *Haliclona exigua*, displays leishmanicidal activity against promastigotes as well as amastigotes at 100 μg/mL concentrations [95]. Among the ciliatamides A-C 79, 80, 81 isolated from *Aaptos ciliate*, the peptide ciliatamides at 10.0 μg/mL concentrations inhibit 50% growth *L. major* promastigotes [96].

CONCLUSION

Despite the advances in the parasitological and biochemical researches using various species of Leishmania, the treatment options available against leishmaniasis are far from satisfactory. Still now several promising antileishmanial leads based on pyridine or quinoline, have been reported over the past few years in

various test systems. Some of the compounds have very promising *in vivo* results. But in current situation, development of new drugs to combat leishmaniasis require increase input from the disciplines of chemistry, pharmacology, toxicology and pharmaceutics to complement the advances in molecular biology that have been made in past 21 years. A safe, non-toxic and cost-effective drug is urgently required to eliminate this problem from every corner of world. A safer, shorter & cheaper treatment, identification of the most cost effective surveillance system and control strategies, drug resistance, suitable vector control approach are among some important aspect for the control and complete eradication of this deadly disease. There is every expectation that this review will provide some valuable information to the synthetic and natural chemist and biologist community such that the work on this topic will continue near future.

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