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NEGLECTED TROPICAL DISEASE, LEISHMANIASIS - A REVIEW ON SYNTHETIC STRATEGIES

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ABSTRACT

Leishmaniasis is the neglected tropical diseases in several regions of the world and regarded as a serious hazard to public health. Major disease causing species *include Leishmania donovani (L.donovani), Leishmania infantum (L. infantum), Leishmania braziliensis (L. braziliensis), Leishmania chagasi(L.chagasi), Leishmania amazonensis (L. amazonensis)* among many other. Many natural and synthetic antileishmanial molecules have been described for disease treatment. Meticulous inspection and observation of scientific reports revealed that considerable molecules belonged to the heterocycles such as acridines, triazole, pyrazole, imidazole, indole, pyrimidine, β-carboline, quinoxaline, quinazoline and benzimidazole. In this present review, synthetic schemes of acridine molecules and metal complexes with special emphasis on structure activity relationship and antileishmanial activity in the form of IC_{50} values in comparison with reference standard like Amphotericin B of acridine molecules and metal complexes is discussed about.

KEYWORDS: Leishmaniasis, acridines, metal complexes.

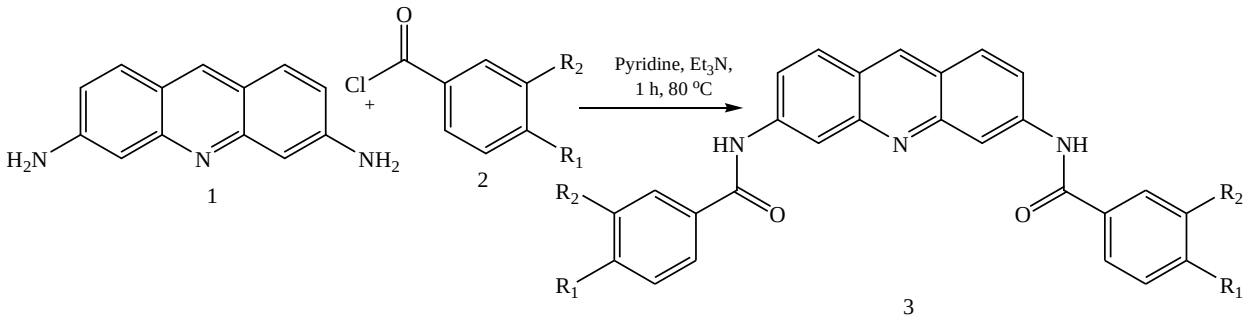
INTRODUCTION

Leishmaniasis is a parasitic borne disease which presents four main clinical syndromes: cutaneous leishmaniasis, mucocutaneous leishmaniasis, visceral leishmaniasis/kala azar and post kala azar dermal leishmaniasis. Causative Leishmania are protozoan parasites that are transmitted to mammalian hosts by phlebotomine sandflies. In mammalian hosts, parasite cells proliferate inside the host phagocytic cells as round amastigotes. After introduction into the insect gut, Leishmania amastigotes transform into elongated flagellated promastigotes that propagate in the insect gut. A new round of infection is initiated after the infected sandfly takes a blood meal from a naive mammalian host and introduces Leishmania parasites into the bite wound in the host dermis. Wide spread resistance to currently available treatments for leishmaniasis by Pentavalent antimonials, Amphotericin B, Paramomycin, Miltefosine calls for more research in the synthesis arena of new molecules which might overcome the resistance in near future.

Acridines

Due to their ability to interact with varied macromolecules, acridine chromophores have been widely synthesized and evaluated for their pharmacological activities including antibacterial, anticancer, and antiparasitic properties**.**

Two new series of diaminoacridinic derivatives obtained from proflavine and acetamide were synthesized and assessed for their cytotoxic and antileishmanial activities by Giorgio et al in 2007. Two compounds demonstrated highly specific antileishmanial properties against the intracellular amastigote form of the parasite. Structure activity relationships established the presence of two acetylamino or benzoylamino groups in 3, 6-di-substituted acridines strongly increased the specificity of the molecules for *Leishmania* parasite, suggesting that symmetric conformations could preferentially interfere with *Leishmania* metabolism (Scheme 1).

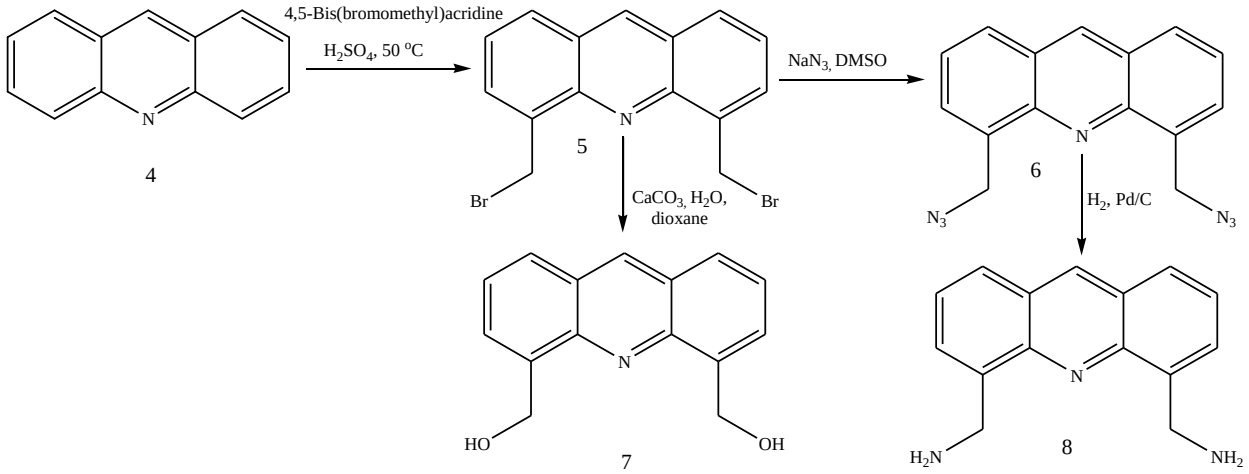


Scheme 1: Synthesis of 3, 6-di-substituted acridines.

Table 1: *In vitro* antileishmanial activities.

Sr. No.	R_1	R_2	IC_{50} value against *L. infantum* (µM)
3	Cl	H	0.11±0.03
Amphotericin B	-		0.38±0.1

Carole et al in 2005 synthesized mono-substituted and di-substituted acridines from which di-substituted acridines displayed interesting amastigote-specific activities through a mechanism of action other than intercalation to DNA (Scheme 2).

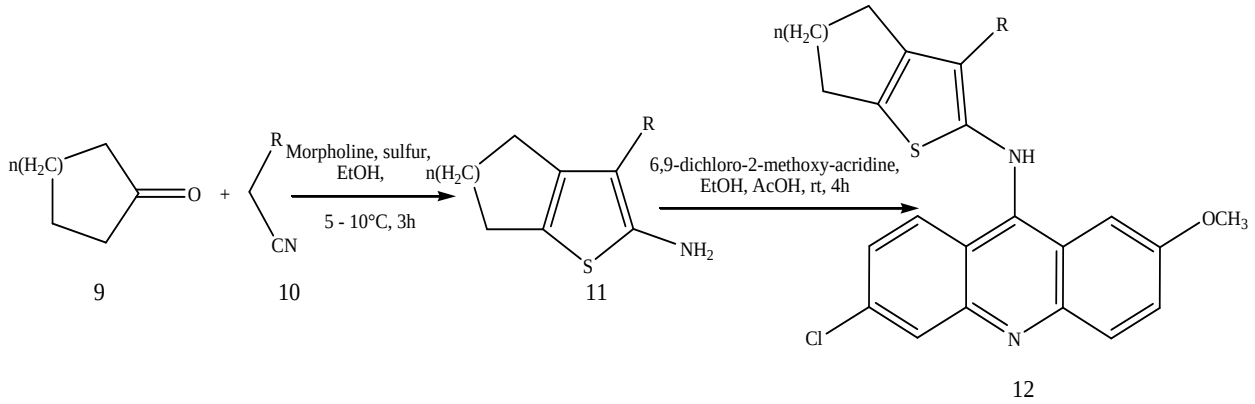


Scheme 2. Synthesis of 4, 5-disubstituted acridines.

Table 2: *In vitro* antileishmanial activities.

Sr. No.	IC_{50} value against *L. infantum* (µM)
7	0.6±0.05
8	3.4±0.4
Amphotericin B	0.32±0.05

Serafim et al in 2018 synthesized hybrids of thiophene with acridine. *In silico* molecular docking findings suggested a significant correlation between the observed values of IC_{50} and pyruvate kinase enzyme inhibition, wherein the presence of ring thiophene with ester and nitrile motifs were crucial for interaction with the target. In addition, the methoxy-acridine nucleus was able to intercalate into the DNA and also interacted with the enzyme pyruvate kinase through its methoxyl, which indicated the duality of mechanism of action of the new derivatives (Scheme 3).



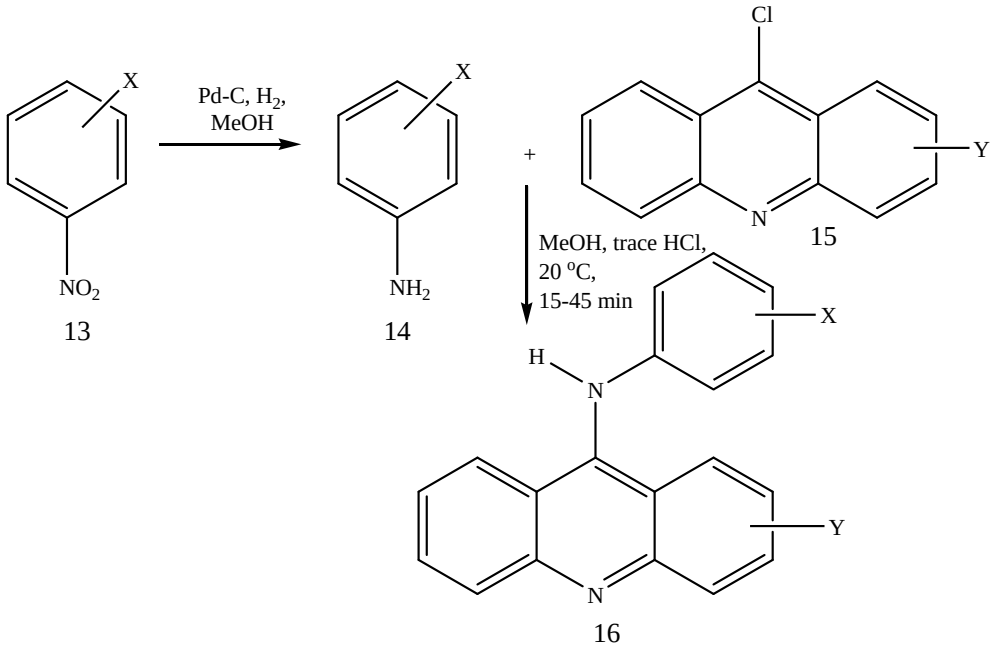
9 10 11 12

Scheme 3: Synthesis of thiophene-acridine hybrid.

Table 3: *In vitro* antileishmanial activities.

Sr. No.	$(CH_2)n$	R	IC_{50} value against *L. amazonensis* (µM)
12	1	CN	9.60±3.19
	2	CN	10.95±3.96
Trivalent antimony	-		14.77±0.52
Amphotericin B			0.19±0.09

Gamage et al in 1997 synthesized 9-anilinoacridine analogs having topoisomerase-II inhibitory activity. SAR revealed that 3, 6-dimethylamino grouping greatly increased toxicity to *L. major* without altering mammalian toxicity (Scheme 4).



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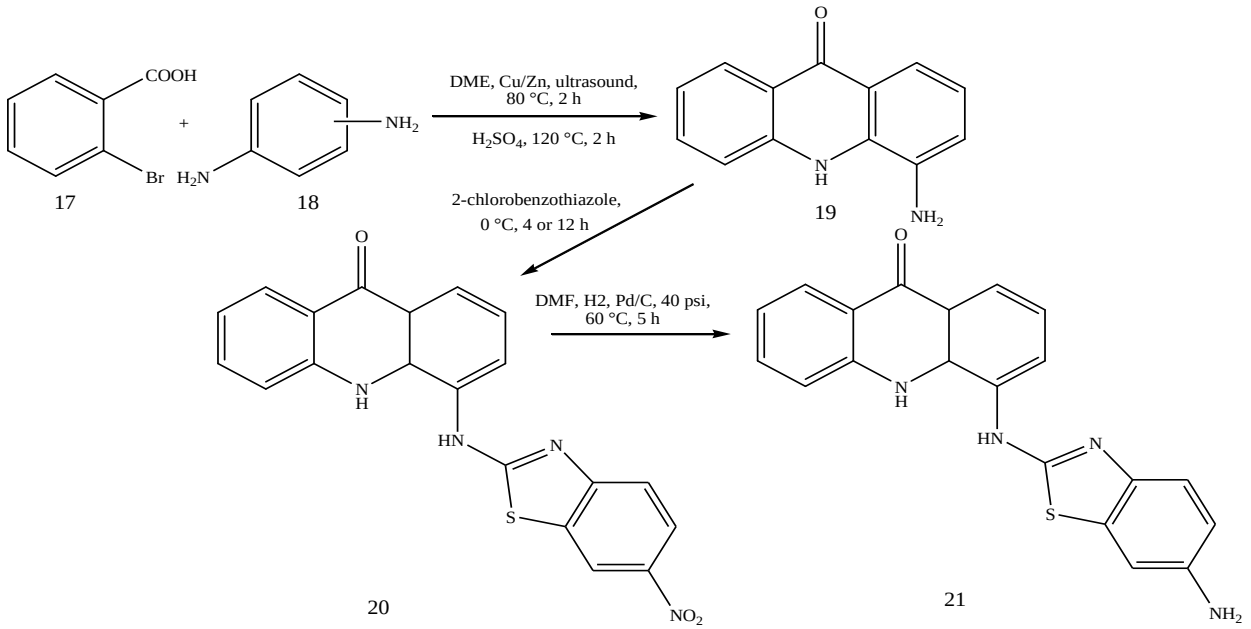
Scheme 4: Synthesis of 9-anilinoacridine analogs.

Table 4: *In vitro* antileishmanial activities.

Sr. No.	X	Y	IC_{50} value against *L. major* (µM)
16	1'H	3,6-di$N(CH_3)_2$	0.03
	1'-$NH(CH_2)_5CH_3$	3,6-di$N(CH_3)_2$	0.16
	1'H-$N(CH_3)(CH_2)_5CH_3$	3,6-di$N(CH_3)_2$	0.07
Sodium stibogluconate	-		46.7±2.8

Delmas et al in 2004 synthesized acridinone analogs. Results suggested that the addition of a benzothiazole group on a parent amino-9-(10H)-acridinone ring enhanced antileishmanial abilities and the presence of a 6-amino-benzothiazole group on position 2 amino chain or a 6-nitro-benzothiazole group on position 4 amino chain was essential for specific anti-amastigote properties (Scheme 5).



Scheme 5: Synthesis of acridinone analogs.

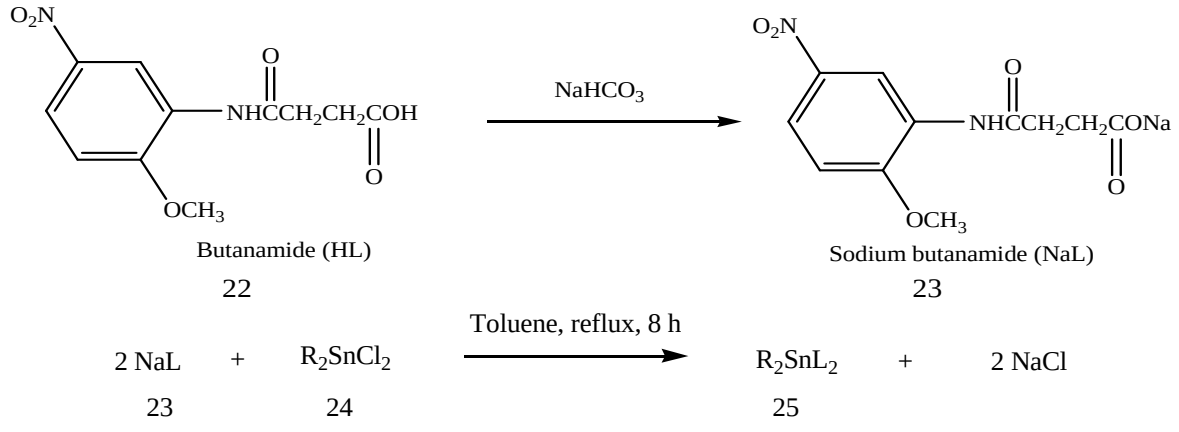
Table 5: *In vitro* antileishmanial activities.

Sr. No.	IC_{50} value against *L. infantum* (µM)
20	>200
21	10.2
Amphotericin B	0.08

Metal complexes

The distinctive biological properties of many organometallic compounds have assisted in the growth and expansion of new drugs based on metal complexes for diseases like cancer along with bacterial, viral and parasitic diseases. Some metal based-drugs like tri- and penta- valent antimonials are promising leishmanicidal agents which are currently under use. Cu(II), Ni(II) and Co(II) derivatives were slightly active in vitro against *L. braziliensis* and *L. infantum* amastigotes and some complexes were also active *in vivo* against the *Leishmania* infection.

Sirajuddin et al in 2014 synthesized organotin (IV) carboxylate derivatives from substituted butanamides. The antileishmanial activity was may be due the interference with the function of parasite mitochondria (Scheme 6).

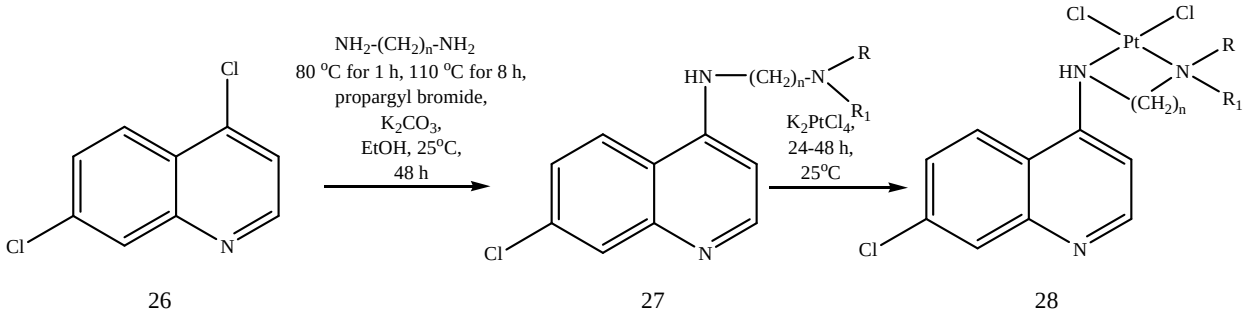


Scheme 6: Synthesis of organotin (IV) carboxylate derivatives.

Table 6: *In vitro* antileishmanial activities.

Sr. No.	R	IC_{50} value against *L. major* (µM)
25	C_8H_{17}	0.98 ± 0.06
Amphotericin B	-	0.29 ± 0.05

Carmo et al in 2011 synthesized 4-aminoquinoline analogs with platinum complexes. SAR studies indicated the presence of the amine group is essential to the mechanism of action of such compounds against *Leishmania*, since the addition of the alkyl-groups, either mono or di-alkyne substituents, resulted in loss of antileishmanial activity, unfortunately, only one of the platinum complexes tested was more active against *Leishmania.* (Scheme 7).



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Scheme 7: Synthesis of 4-aminoquinoline analogs with platinum complex.

Table 7: *In vitro* antileishmanial activities.

Sr. No.	n	R	R_1	IC_{50} value against *L. chagasi* (µM)
28	3	H	H	3.5
	2	CH_2CCH	CH_2CCH	4.2
Amphotericin B	-			1.90

CONCLUSION

So not limiting the usage to antimony metal, synthesis of other metal complexes involving stannous and platinum and acridines have also been found beneficial and library of compounds may be synthesized and can be evaluated further *in vivo* for its efficacy in humans.

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