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Antileishmanial Agents: An Updated Review

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ABSTRACT

Antileishmanial activity is associated with diverse heterocyclic nucleus such as piperazine, pyrimidine, quinoline, azoles (imidazole, 1, 2, 4 triazole, isoxazole, pyrazole, thiazole, thiadiazole), quinazoline, acridine and indole. This review article covers different heterocyclic nucleus with their antileishmanial activity on different species of Leishmania parasite. Considering the therapeutic potential of these nucleuses, new drugs can be synthesized as antileishmanial agent. These compounds act by efficacious mechanism of action and provide result for the future medicines.

Keywords: Azoles, antileishmanial activity, therapeutic potential.

INTRODUCTION

Leishmaniasis is an age-old parasitic disease transmitted to humans by the bite of the infected female phlebotomus sandfly. The sandfly vector is usually infected with flagellate protozoa belonging to the genus *Leishmania* [1]. 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 [2]. Leishmaniasis is a complex of disease syndromes that has classically been divided into visceral, cutaneous, diffuse and mucocutaneous forms [3-5]. The disease is endemic in many tropical and subtropical regions of the world [6]. It is estimated that 12 million people are infected by over 20 species with about two million cases reported annually and about 350 million people live in endemic areas under the risk of infection [7]. Leishmania parasite exists in two forms one is amastigote and second is Promastigote. The amastigote is ovoid and non flagellated form of Leishmania, while the promastigote is flagellated and found in sandfly [8]. Antileishmanial activity is performed against promastigote and then amastigote form of the parasite. Heterocyclic system may also form by fusion with other rings either carbocyclic

or heterocyclic. In this review article different compounds having heterocyclic nucleus have been shown to possess antileishmanial activity. It was found that among the important pharmacophores responsible for antileishmanial activity, the heterocyclic scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antileishmanial agents.

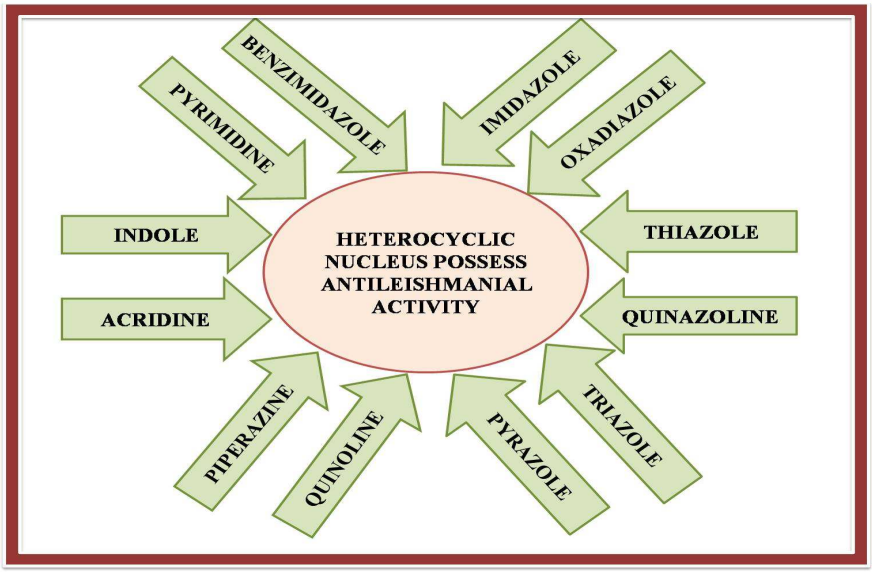


Fig.1: Different heterocyclic nucleus

Imidazole

Bhandari *et al* [9] synthesized a series of novel aryloxy cyclohexane based mono and bis-imidazoles **(1)** derivatives. Among all, the Bis-methylimidazole containing compound 1a 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.

Robert *et al* [10] introduced a new imidazolidin-2-one **(2)** derivatives. Which were evaluated against promastigotes of *Leishmania mexicana* and *Leishmania infantum*. Among the eighteen tested compounds , compound 2a showed a highest activity with IC_{50} value in the range of 16.0-9.5 $\mu molL^{-1}$. Then compound 2a was subjected to evaluate against amastigotes of *Leishmania mexicana* and showed the inhibiton at IC_{50} 2.4 $\mu molL^{-1}$.

Ferreira *et al* [11] synthesized N-substituted-phenyl-imidazole-5-difluoromethyl **(3)** derivatives. These compounds were tested against promastigote forms of *Leishmania amazonensis*. Among all imidazole derivatives, compound 3a showed most promising activity with IC_{50} 1.7 µM.

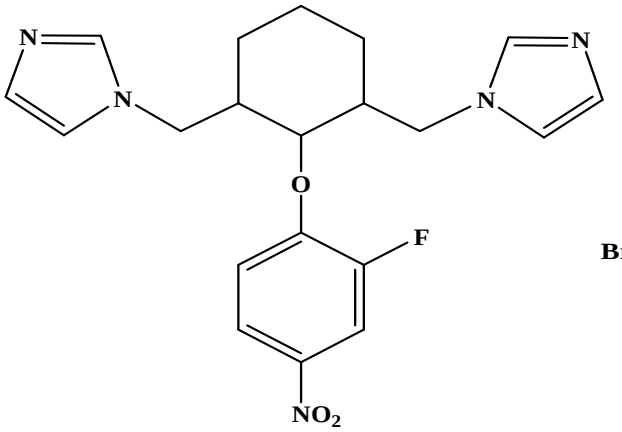
Borgne *et al* [2] prepared several 3-imidazolylalkyl indole **(4)** derivatives. All the synthesised compounds were evaluated *in-vitro* against Leishmania mexicana promastigotes and tested against intracellular amastigotes of *Leishmania mexicana*. It was observed that the most potent compound was 1-(2-bromobenzyl)-3-(1H-imidazole-1-ylmwthyl)-1H-indole (4a) 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 *et al* [12] introduced a series of 1-(4-X-phenyl)-N'-[(4-Y-phenyl)methylene]-1H-pyrazole-4-carbohydrazides **(5)** derivatives. In these compounds a lateral chain of 1H-pyrazole-4-carbohydrazide which probably contributes to their biological activity. In this series compound 5a and 5b showed a potent activity with 66% and 90% inhibition of *Lieshmania amazonensis* respectively.

Thiazole

Fillion *et al* [13] synthesized naphthothiophene quinones **(6)** containing a fused thiazole ring. These compounds were screened against promastigote forms of *Leishmania donovani* and *Leishmania major*. The compound 6a was found to be most significant due to less cytotoxicity against THP-1 cell line.



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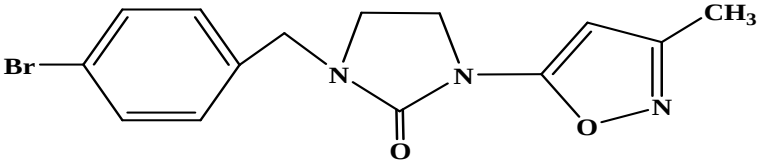

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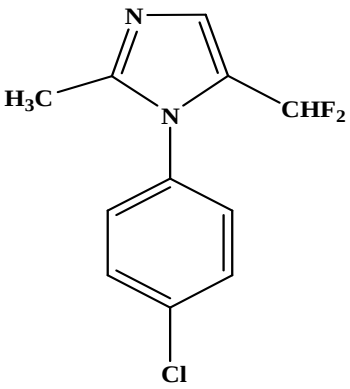
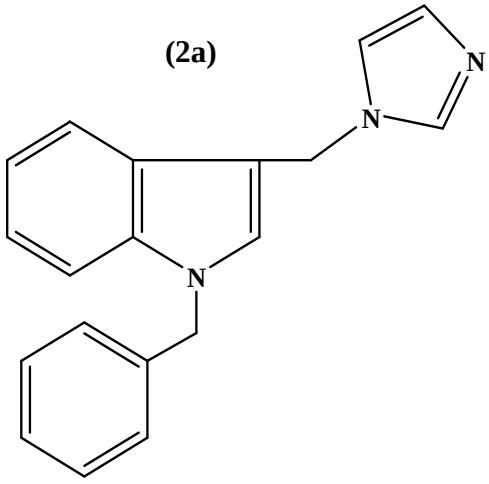
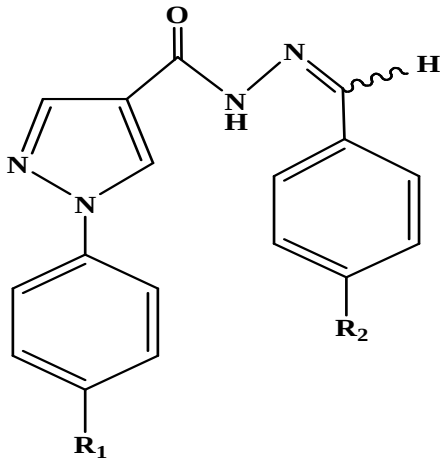


(3a)



(4a)



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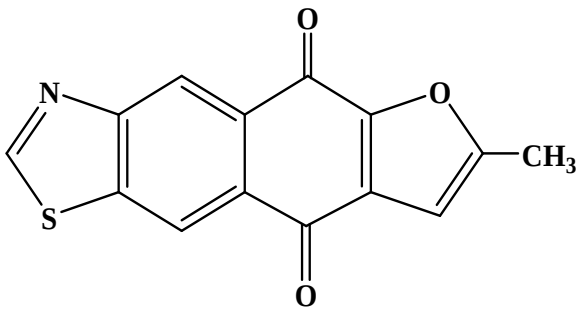
R_2=Br, R_2=F
(5)



(6a)

Thiadiazole

Ram *et al* [14] presented 2,4 disubstituted 1,3,4 thiadiazole **(7)** derivatives and evaluated for *in-vitro* antileishmanial activity. Among these, compound 7a showed 73% *in-vitro* inhibition of promastigote of *Leishmania donovani*.

Shafiee *et al* [15] reported a set of 2-(5-nitro-2-furyl) and 2-(5-nitro-2thienyl)-5-substituted-1,3,4-thiadiazole **(8)** derivatives. The most active compound 8a was found to be significant with an IC_{50} 0.1 µM against *Leishmania major* promastigotes.

Echeavarria *et al* [16] 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.

Triazole

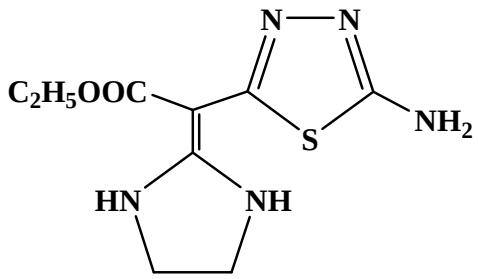
Rastogi *et al* [17] prepared a series of 4-Amino-3-(4'-benzyloxyphenyl)-5-mercapto-1,2,4-triazole **(10)** compounds. These were screened for their antileishmanial activity against *Leishmania donovani*. Compound 10a, 10b, 10c, 10d, 10e and 10f showed 80-95% inhibition among all ten compounds.

Ferreira *et al* [11] introduced a series of compounds containing triazole rings **(11).**The compound 11a was found to be most significant activity against promastigote form of *Leishmania amazonensis* with IC_{50} 2.6 µM.

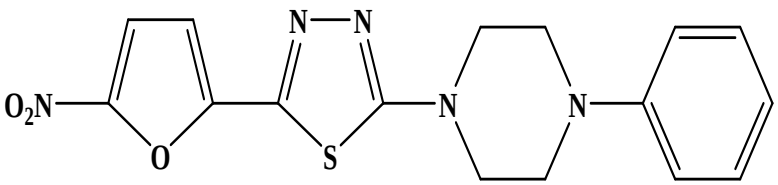
Oxadiazole

Werbovetz *et al* [18] synthesized a series of 3-aryl-5-thio cyanatomethyl-1,2,4-oxadiazoles **(12)**. These compounds were tested against amastigotes of *Leishmania donovani*. In these 3-(4-

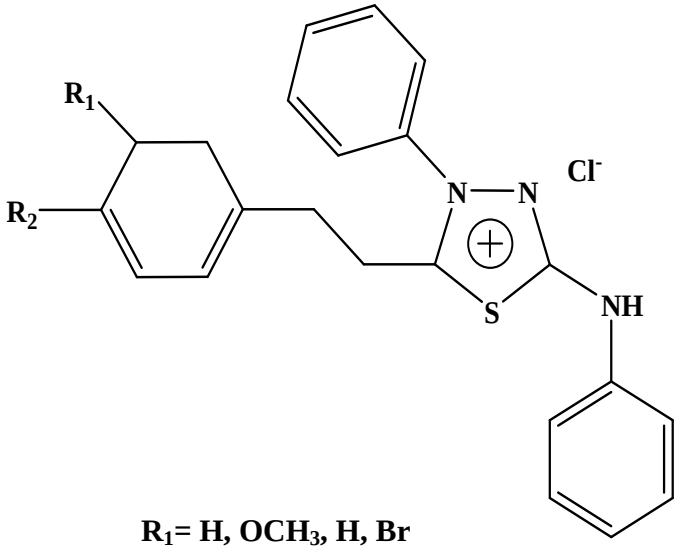
chlorophenyl)-5-(thiocyanatomethyl)-1, 2, 4 oxadiazole (12a) showed more selectivity for *Leishmania donovani* (IC_{50}=4.5±1.8 µM).



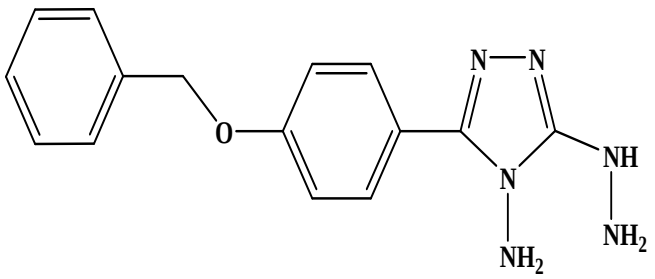
(7a)



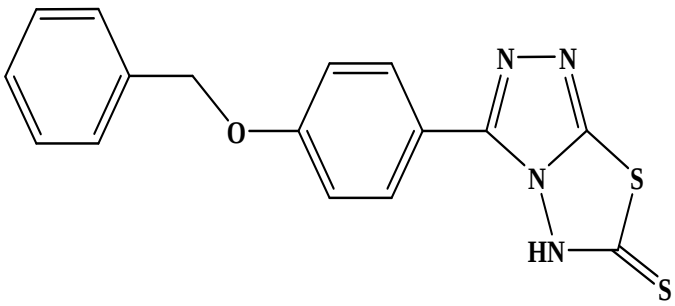
(8a)



R_1= H, OCH_3, H, Br
R_2= OCH_3, H, F, H
(9)



(10a)



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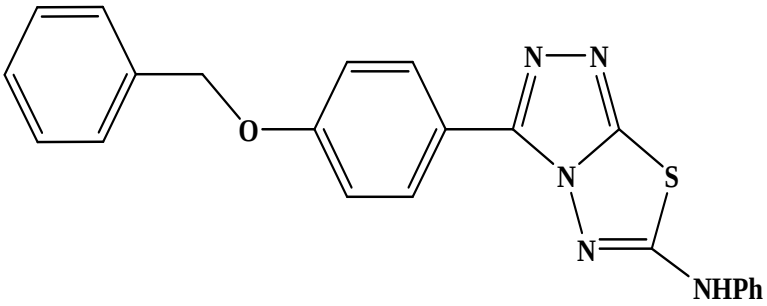

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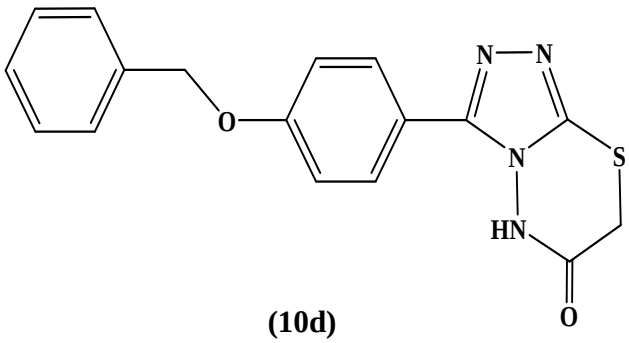
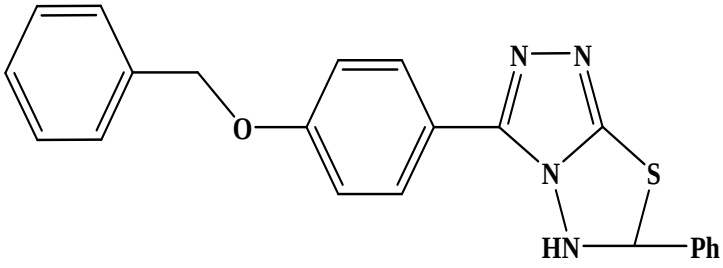
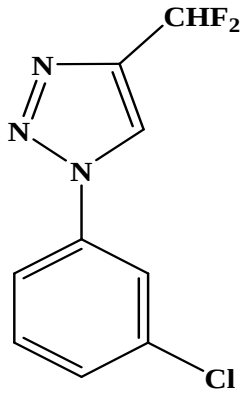


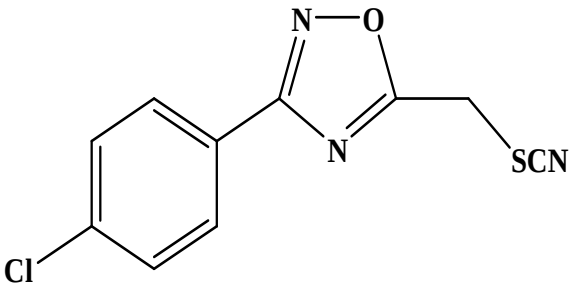
(10d)



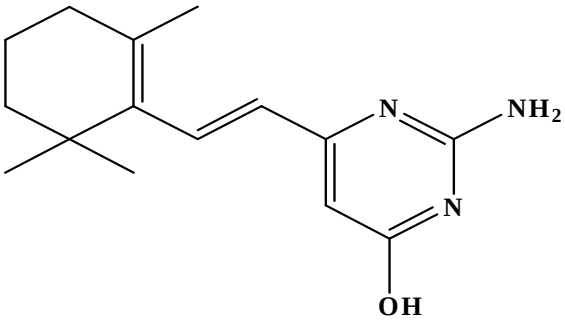
(10e)



(11a)



(12a)



(13a)

Pyrimidine

Suryawanshi *et al* [19] have synthesized some novel terpenyl pyrimidine derivatives **(13)**. The pyrimidine derivatives were screened for *in-vivo* antileishmanial activity against amastigotes of *Leishmania donovani* in hamsters. The compound 13a showed promising 63% *in-vivo* antileishmanial activity at 50 mg/kg dose.

Suryawanshi *et al* [20] introduced some novel N- and O- substituted terpenyl pyrimidines**(14).** These were screened for *in-vitro* antileishmanial activity profile in promastigote model. In all compounds, compound 14a showed better activity with 98.8% inhibition at 1 µg/ml dose.

Bhakuni *et al* [21] synthesized a series of 1⁄2-benzyl-4,6-disubstituted 1H ⁄2H-pyrazolo[3,4-d] pyrimidines **(15)**. Among these, compound 15a and 15b showed 60% and 55% inhibition respectively of amastigotes of *Leishmania donovani* in hamster at the dose of 100 mg⁄ml.

Indole

Chauhan *et al* [8] synthesized a series of marine alkaloid 8,9-dihydrocoscinamide B, its analogues and indolylglyoxylamide derivatives **(16)**. 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.

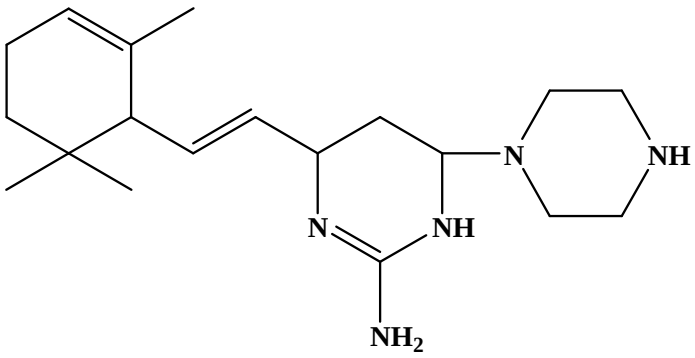
Pagniez et al [22] evaluated two 3-(α-azolylbenzyl)indoles **(17)** against intracellular and axenic amastigotes. Compound 17a and 17b both were active against intracellular and axenic amastigotes. Compound 17a and 17b showed IC_{50} value 4.4±0.1 and 6.4±0.1 µM respectively.

Acridine

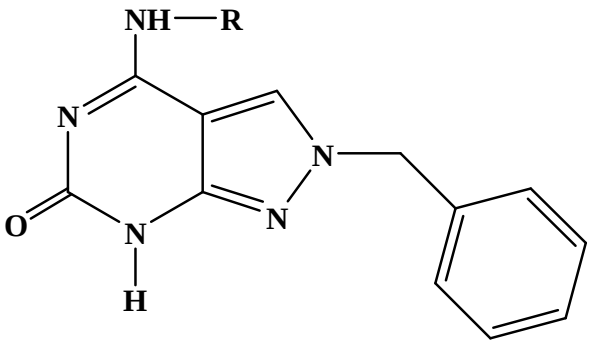
Carole *et al* [23] synthesized a number of 4,5 di substituted acridines. In these compounds 4,5-bis(hydroxymethyl)acridine **(18)** showed potent antileishmanial activity against *Leishmania infantum* amastigote form.

Benzimidazole

Vazquer *et al* [24] prepared a series of ten novel hybrids from benzimidazole and pentamidine by using a short synthetic route. Among these, 1,5-Bis[4-(5-methoxy-1H-benzimidazole-2-yl)phenoxy]pentane **(19)** was found to be 13-fold more active than pentamidine against *Leishmania mexicana*.

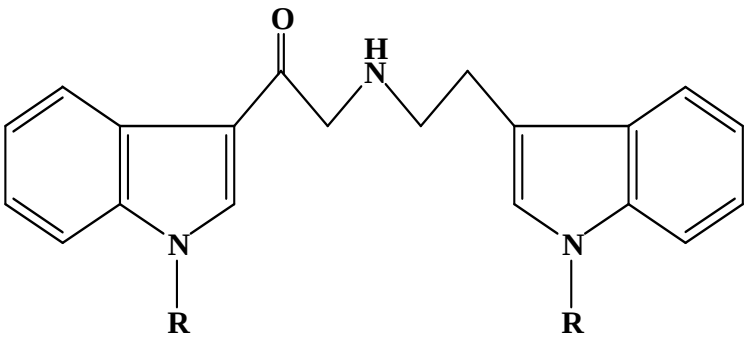


(14a)

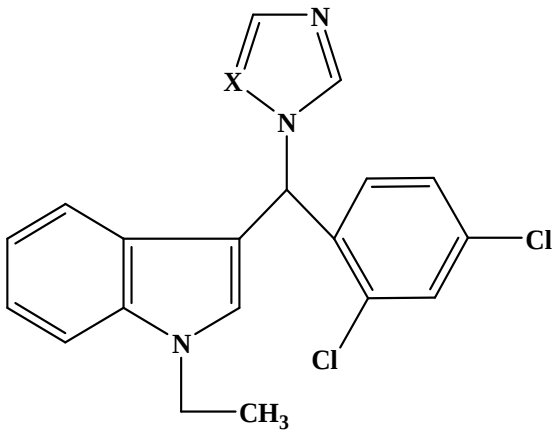


R= CH_2-CH_2-C_6H_4-Cl, H

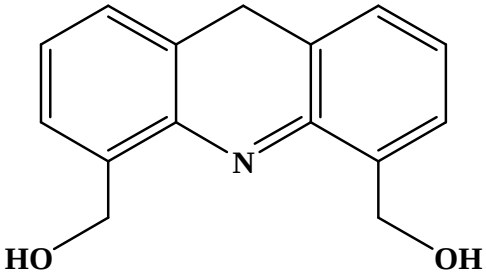
(15)



R=H, CH_3
(16)



X= CH, N
(17)



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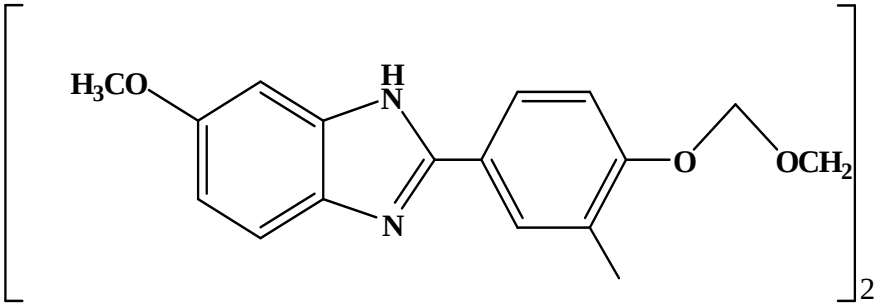


(19)

Piperazine

Huang *et al* [25] have been introduced a series of 1,4-diarylpiperazine derivatives **(20)**. Among these compounds, 1,4-Bis[4-(1H-benzimidazol-2-yl)phenyl] piperazine (20a) emerged as most active against Leishmania parasite.

Foroumadi *et al* [26] prepared a series of 1-[5-(1-methyl-5-nitro-1H-imidazole-2-yl)-1,3,4-thiadiazol-2-yl]-4-aroylpiperazines **(21).** 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-2-yl]piperazine (21a) with IC_{50} value of 9.35±0.67 µM against *Leishmania major* promastigotes.

Quinoline

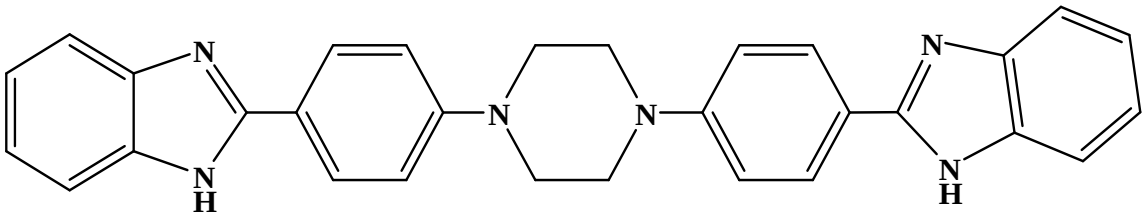
Mondal *et al* [27] synthesized some novel Bis-quinolines **(22)** by under phase transfer catalysed condition using 8-hydroxy quinoline as substrate. The synthesized analogues were evaluated for antileishmanial activity against *Leishmania donovani* promastigotes and amastigotes. Among all these, 1,1-Bis-[(5-chloro-8-quinolyl)oxy]methane (22a) showed significant activity.

Jain *et al* [28] introduced a series of some 8-quinolinamine analogues **(23).**These all were evaluated for antileishmanial activity. Among all these compounds, 23a, 23b and 23c showed IC_{50} value 3.0, 3.4 and 2.9 µg/mL in *Leishmania donovani*.

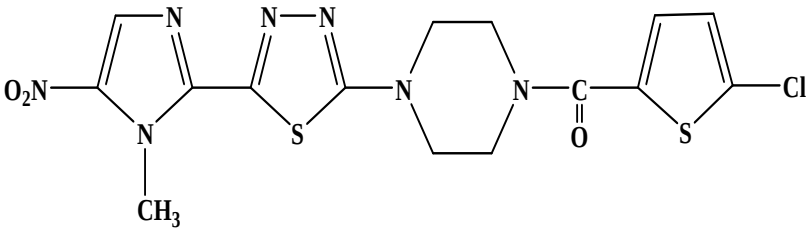
Quinazoline

Sahu *et al* [29] synthesized a series of new class of 4-(hetero) aryl-2-piperazino quinazolines (**24**). These were accessed for *in-vitro* activity against intracellular amastigotes of *Leishmania donovani*. Among all the evaluated compounds, compound 24a showed potent action.

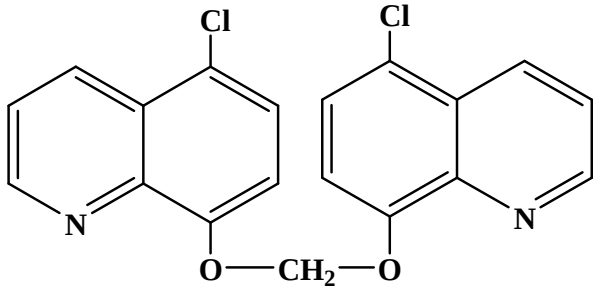
Bhattacharjee *et al* [30] analysed stereoelectronic properties of synthetic indolo [2,1-b] quinazoline-6,12-dione derivatives**(25)**. These compounds exhibited remarkable activity at concentrations below 100 ng/mL, when tested against *in-vitro Leishmania donovani* amastigotes. Among these, compound 25a and 25b were the most active against Leishmania in this study, with IC_{50} value of 16 ng/mL.



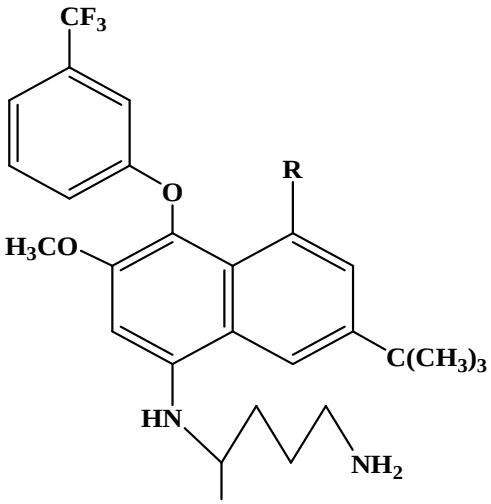
(20a)



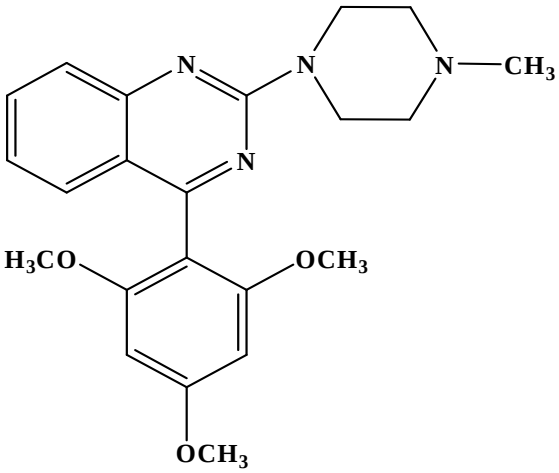
(21a)



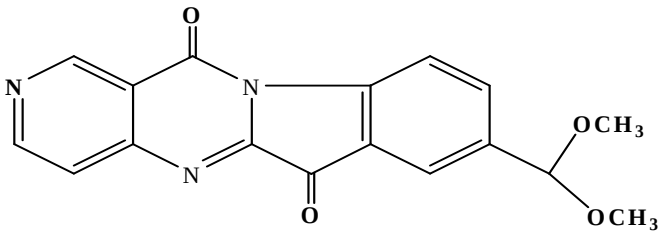
(22a)



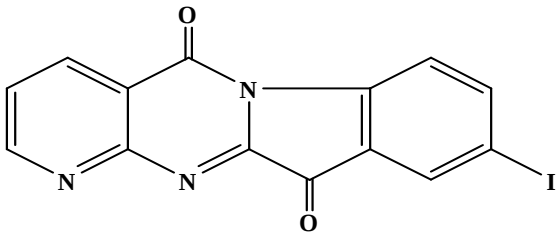
R=H, CH_3, C_2H_5
(23)



(24a)



(25a)



(25b)

CONCLUSION

It has been concluded that in most of the drugs used in the treatment of Leishmaniasis, heterocyclic nucleus is present. Any structural changes on the moiety provide better drug for the chemotherapy. From the review it was known that heterocyclic nucleus are potential targets for drug discovery of antileishmanial drugs. These all nucleus containing compounds represent new pharmacophore for the development of novel antileishmanial drugs.

REFERENCES

[1] DG Rando; MA Avery; BL Tekwani; SI Khan; EI Ferreira. *Biorg. Med. Chem.*, **2008**, 16, 6724.
[2] YM Na; N Lebouvier; ML Borgne; F Pagniez; N Alvarez; P L Pape; GL Baut. *J. Enz. Inhib. Med. Chem.*, **2004**, *19*, 451.
[3] MLAA Vasconcellos; TP Barbosa; CGL Junior; FPL Silva; HM Lopes; LRF Figueiredo; SCO Sousa; GN Batista, TG da Silva; TMS Silva; MR de Oliveira. *Eur. J. Med. Chem.*, **2009**, 44, 1726.
[4] LC Rios; SM Luis; GD Togna; PD Coley; TA Kursar; WH Gerwick. *J. Nat. Prod.*, **2008**, 71, 2011.
[5] SN Suryawanshi; N Chandra; P Kumar; J Porwal; S Gupta. *Eur. J. Med. Chem*., **2008**, 43, 2473.
[6] ED Olmo; O Rebollo; G Ruiz; JLL Perez; A Gimenez; AS Feliciano. *Biorg. Med. Chem. Lett*., **2008**, 18, 184.
[7] RF Rodrigues; EF da Silva; A Echevarria; RF Bonin; VF Amaral ; LL Leon; MM Canto-Cavalheiro. *Eur. J. Med. Chem*., **2007**, 42, 1039.
[8] L Gupta; A Talwar; MS Chauhan; S Palne; S Gupta. *Biorg. Med. Chem. Lett*., **2007**, 17, 4075.
[9] K Bhandari; N Srinivas; S Gupta; S Palne. *Biorg. Med. Chem. Lett*., **2009**, 19, 324.
[10] JH Robert; C Sabourin; N Alvarez; S Robert- Pissard; GL Baut; PL Pape. *Eur. J. Med. Chem*., **2003**, 38, 711.
[11] VF Ferreira; SB Ferreira; MS Costa; N Boechat; RJS Bezerra; MS Genestra; MM Canto-Cavalheiro; WB Kover. *Eur. J. Med. Chem.*, **2007**, 42, 1388.

[12] VF Amaral; AMR Bernardino; AO Gomes; KS Charret; ACC Freitas; GMC Machado; LL Leon. *Eur. J. Med. Chem.*, **2006**, 41, 80.
[13] H Fillion; N Walchshofer; RA Tapia; L Alegrea; CD Pessoa; C Salas; MJ Cortes; JA Valderrama; ME Sarciron; F Pautet. *Bioorg. Med. Chem.*, **2003**, 11, 2175.
[14] VJ Ram; A Goel; M Kandpal. *Biorg. Med. Chem. Lett*., **1997**, 7, 651.
[15] A Foroumadi; S Pournourmohammadi; F Soltani; S dabri; A Kharazmi; A Shafiee; M Asgharian-Rezaee. *Biorg. Med. Chem. Lett*., **2005**, 15, 1983.
[16] EF da Silva; MM Canto-Cavalheiro;VR Braz; L Cysne-Finkelstein; LL Leon; A Echevarria. *Eur. J. Med. Chem.*, **2002**, 37, 979.
[17] N Rastogi; RS Varma; AP Singh. *Indian J. Heterocycl. Chem.*, **2006**, 16, 112.
[18] KA Werbovetz; DM Cottrell; J Capers; MM Salem; KD Fradley; SL Croft. *Bioorg. Med. Chem.*, **2004**, 12, 2815.
[19] SN Suryawanshi; S Pandey; S Gupta; VML Srivastava. *Eur. J. Med. Chem*. **2004,** 39, 969.
[20] SN Suryawanshi; S Gupta; N Chandra; N Goyal. *Eur.J. Med. Chem.*, **2005,** 40, 552.
[21] DS Bhakuni; RP Tripathi; LM Ojha; A Mishra.. *Indian J. Heterocycl. Chem*. **1991**, 1, 51.
[22] F Pagniez; HA Valencia; P Marchand; ML Borgne; GL Baut; SR Piessard; PL Pape. *J. Enz. Inhib. Med. Chem.*, **2006**, 21, 277.
[23] DG Carole; DM. Michel; C Julien; D Florence; N Anna; J Severine; D Gerard; TD Pierre; GJ Pierre. *Bioorg. Med. Chem*., **2005**, 13, 5560.
[24] HT Gomez; GN Vazquez; EH Nunez; IL Rivera; JH Alvarez; RC Rivera; RM Puc; RA Ramos. *Bioorg. Med. Chem. Lett.*, **2008**, 18, 3147.
[25] TL Huang; A Mayence; JJV Eynde; L Lecour; LA Walker; BL Tekwani. *Eur. J. Med. Chem.*, **2004**, 39, 547.
[26] F Poorajab; SK Ardestani; S Emami; M Behrrouzi-fardmoghadam; A Shafiee; A Foroumad. *Eur. J. Med. Chem.*, **2009**, 44, 1758.
[27] NB Mondal; SG Dastidar; P Palit; P Paira; A Hazra; S Banerjee; AD Gupta. *Eur. J. Med. Chem.*, **2009**, 44, 845.
[28] R Jain; M Jain; SI Khan; BL Tekwani; MR Jacob; S Singh; PP Singh. *Bioorg. Med. Chem.*, **2005**, 13, 4458.
[29] DP Sahu; S Kumar; N Shakya; S Gupta; J Sarkar. *Bioorg. Med. Chem. Lett.*, **2009**, 19, 2542.
[30] KA Werbovetz; AK Bhattacharjee; DJ Skanchy; B Jennings; TH Hudson; JJ Brendle. *Bioorg. Med. Chem.*, **2002**, 10, 1979.