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Design, Synthesis and Biological Evaluation of 1,3-Diaminopropanes: A New Class of Polyamine Analogs as Leishmanicidal Agents[1]

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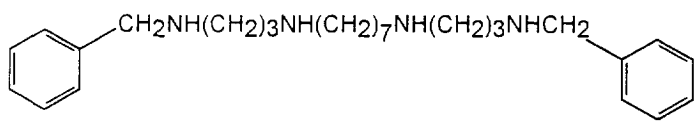
Abstract: *Analogs of 1,3-diaminopropane as inhibitors for the growth of Leishmania donovani have been synthesized and evaluated for their antileishmanial activity. Of the many active compounds, 1-(3-N,N-bis methoxycarbonyl guanidino)propyl-4-methylpiperidine piperazine (**4e,f**) exhibited significant in vivo inhibitory efficacy against L. donovani by oral and intraperitoneal route of administration.*

Natural polyamines like spermidine, spermine and putrescine etc. are responsible for the regulation of normal growth of leishmania parasites[2,3]. Based on the assumption that their synthetic analogs may interfere with the biosynthesis and function of natural polyamines of the leishmania parasites led Baumann et al[4,5] to design and synthesize bis(benzyl)polyamine MDL 27695 [1] as an antileishmanial agent. This compound when administered orally exhibited complete suppression of *Leishmania donovani* in BALB/c mice.

It may be assumed that the diaminoalkane moiety is the key pharmacophore responsible for eliciting antileishmanial activity in bis(benzyl)polyamines. In order to explore the potential of this key pharmacophore for designing antileishmanial agents, a number of derivative of 1,3-diaminopropane in which one of the nitrogen atom is simulated in a heterocyclic ring system and the other in an amidine group, have been synthesized and evaluated for their ability to inhibit the growth of leishmania parasites. The details of this study are presented here:

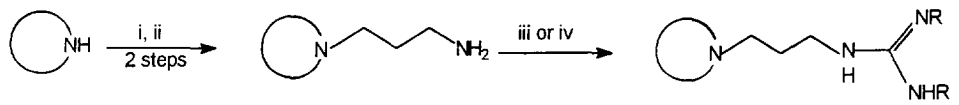


MDL 27695 [1]

Chemistry: The strategies for the synthesis of polyamine analogs are outlined in Schemes 1 & 2. Michael addition of substituted aliphatic secondary amine **[2a]** onto acrylonitrile yielded[6] 1-(2-cyanoethyl) piperidine in good yield (72%) which was subsequently

converted to 1,3-diaminopropane [**3a**] (70%) by hydrogenating it in presence of Raney-Ni and methanolic ammonia[6]. This diaminopropane derivative **3a** was then reacted with 1,3-bis (methoxycarbonyl)-S-methyl isothiourea to furnish the corresponding 1,3-bis carbomethoxy derivative **4a** (58%)[7]. The compound **3a** on treatment with S-methyl isothiouranium sulphate in presence of sodium hydroxide furnished the corresponding guanidine [**5a**] (62%)[7] (Scheme-1).

SCHEME 1



2 a-g **3 a-g** **4 a-g,** R=$COOCH_3$
5 a-g, R=H

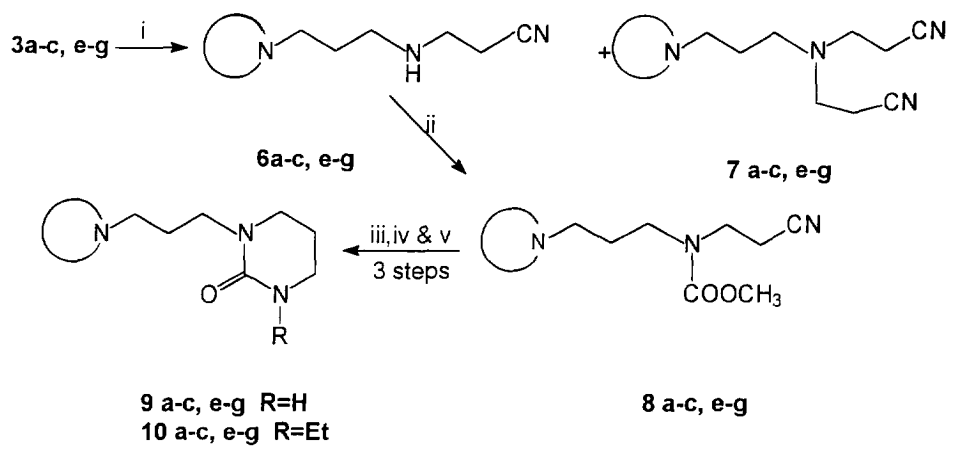
2	
a	Piperidine
b	(4-Phenyl)piperazine
c	(4-Phenyl)piperidine
d	4-(-2-Pyridyl)piperidine
e	(4-Methyl)piperidine
f	(4-Methyl)piperazine
g	Morpholine

Reagents and conditions

i) CH_2=CHCN, MeOH, 0°C; ii) H_2, Raney-Ni, MeOH/NH_3; iii) $CH_3SC(=NCOOCH_3)NHCOOCH_3$, EtOH, 25°C; iv) $CH_3SC(=NH)NH_2.1/2H_2SO_4$, NaOH, H_2O, 25°C.

The strategy for the synthesis of compounds in which one of the nitrogen atom of the diaminopropane chain is simulated in a heterocyclic ring system (Scheme 2) involved the Michael addition of **3b** to acrylonitrile[6]. This gave a mixture of two products, namely 1-(2-cyanoethyl)-1,3-diaminopropane [**6b**] (62%)[8] and 1-bis (2-cyanoethyl)-1,3-diaminopropane [**7b**] (11%). Monocyanoethylated product **6b** was further reacted with methylchloroformate to yield 1-[3-(2-cyanoethyl)-N-carbomethoxyaminopropyl]-4-phenylpiperazine [**8b**] (48%). This was then hydrogenated [6] in presence of Raney-Ni in methanolic ammonia to yield the corresponding amine which underwent facile intramolecular cyclization in presence of sodium methoxide to 1-[3-N-(4-phenylpiperazinyl)]propylhexahydropyrimidine-2-one [**9b**] (42%)[8]. The latter [**9b**] was finally subjected to N-alkylation using alkyl halide in presence of sodium hydride to furnish the corresponding N-alkylated product **10b** (28%).

SCHEME 2



9 a-c, e-g R=H
10 a-c, e-g R=Et

8 a-c, e-g

Reagents and conditions

i) CH_2=CHCN, MeOH, 0°C; ii) ClCOOMe, C_6H_6, NEt_3,25°C; iii) H_2,Raney-Ni, MeOH/ NH_3; iv) NaOMe, MeOH, reflux; v) EtI, NaH, C_6H_6, reflux.

Biological Activity: *In vivo* antileishmanial screening technique reported by Bhatnagar et al[9] was used. The method of infecting hamster *Mesocrietus auretus*, spleen biopsy, assessment of parasite counts in spleen,calculation of percent inhibition and preparation of drug suspension etc. similar to that used by Bhatnagar et al[9].

The selected compounds were tested at 50 mg/kg x 5 days dose intraperitoneal and oral route. Four or five hamsters were used at each dose level and 2-3 replicates were carried out. Stibanate (sodium stibogluconate) was simultaneously used at 20 mg/ kg x 5 (ip) dose regimens as standard drug.

Results and Discussion :Table 1 presents a compilation of the results of chemotherapeutic effect of synthesized compounds. Out of 28 compounds tested, 7 (4b,4d-g, 6a & 6f) have shown promising *in vivo* activity (70-85%) against *L. donovani* as evident from the observation period on day 7.

Table 1: *In vivo* % Inhibition of *Leishmania donovani* by 1,3-diaminopropane derivatives

COMPOUND NO.	DOSE (ip) mg/kg x 5	% INHIBITION ON DAY 7TH
3a	50	52.39
3b	50	37.20
3c	50	66.04
3d	50	48.72
3e	50	54.52
3f	50	66.94
3g	50	45.75
4a	50	56.18
4b	50	73.75
4c	50	66.46
4d	50	72.75
	25	73.18
4e	100	46.36
	50	78.42
	25	80.91
	50*	76.78
	25 *	77.59
4f	50	85.47
4g	50	80.18
5a	50	42.10
5c	50	57.74
5e	50	62.16
5f	50	45.14
6a	50	64.76
6b	50	71.05
	25	71.15
6c	50	43.43
6e	50	45.05
6f	50	78.06
9a	50	43.04
9e	50	60.80
9f	50	52.11
10a	50	41.24
10e	50	25.04
Stibenate	20	94.83

* Oral route

Analysis of the biological results have been made on the basis of three considerations. The first one is concerned with the influence on the antileishmanial activity in which one of the two nitrogen atoms of 1,3-diaminopropane chain has been incorporated in a cyclic system (**3a-g**). These exhibited moderate inhibition of *L. donovani* (37-66%). However, replacement of one of the hydrogen atoms of the primary amino group in **3a-c** & **e-g** by a **β**-cyanoethyl group led to improved leishmanicidal activities in compounds **6b** and **6f** respectively. Second consideration aims at ascertaining the influence of guanidine/biscarbomethoxy guanidine substituents present on the primary amino group. The diaminopropane substituted with biscarbomethoxy guanidine function (**4a-g**) were identified as most potent inhibitors having 46-85% reduction of amastigotes count on day 7. However, replacement of one of the two nitrogen atoms in the

diaminopropane chain with guanidine component gave **5a-f** which compared to **4a-g** were poor inhibitors (40-60%).The third consideration relates to the influence on the antileishmanial activity after the incorporation of the primary amino group of 1,3-diaminopropane in a cyclic system (**9,10**). Except **9e**, no other compounds showed significant effect on leishmania parasite.

The profile of antileishmanial activity of 1,3-diaminopropane indicates that the nature of the ring system which incorporates one of the nitrogen atoms of 1,3-diaminopropane itself governs leishmanicidal action. Incorporation of N,N-dicarbomethoxy guanidine moiety in lieu of amino function invariably ameliorated the leishmanicidal action while compounds with guanidine substituents led to loss of activity. An invariable fall in leishmanicidal activity was noticed when both the amino functions became a part of the heterocyclic ring (**9,10**). One representative compound **4e** was selected for further study to ascertain its oral efficacy. This compound at 25 and 50 mg/kg p.o. exhibited significant leishmanicidal activity. Thus it indicate that this class of compounds exhibited lesihmanicidal activity through ip and p.o. routes. However, the dose dependent study of this compound revealed that at higher doses loss of leishmanicidal activity occured. Similar observations with other compounds subjected for general primary screening have also been made. The reason ascribed for this observation relates to the toxic effect of test compounds on macrophages. It thus became apperent that **4e**, though active by oral route, did exhibit toxic effect at higher concentrations.

Conclusion:It may be concluded that the substructural unit represented by 1,3-diaminopropane is a good backbone pharmacophore for designing antileishmanial agents. Incorporation of both the nitrogen atoms of 1,3-diaminopropane in cyclic system causes marked loss of leishmanicidal activity. However, if one of the nitrogen of the aminoalkyl chain remains as a free primary amino function and the other is retained in a cyclic frame work, the leishmanicidal efficacy is retained and the incorporation of the primary amine into the molecular framework of biscarbomethoxy guanidine moiety evoked maximum leishmanicidal activity. One of these compounds also show potent leishmanicidal action through oral route of administration.

Recently, Kandpal et al[10] has reported a clear correlation between the inhibition of arginine transport by the diamidines and their leishmanicidal potential. In view of this it may be concluded that compounds having molecular framework in which primary amino function is incorporated with biscarbomethoxy guanidine can be further evaluated as arginine transport inhibitors to provide its useful application in understanding possible mode of action.

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7. Spectroscopic data of some representative compounds of Scheme 1 are given as follows: Compound No., yield (%), m.p. (°C), IR (KBr, cm^{-1}), MS: m/z, ^1H NMR (400 MHz, $CDCl_3$ + DMSO-d_6, , ppm).

4e; 58; 65; 3300 (NH), 1745 (C=O); 314 (M^+); 0.84 (d, 3H, J=8Hz, CH_3), 1.20-1.89 (m, 7H, CH and 3 x C-CH_2), 2.38 (t, 2H, J=6Hz, N-CH_2), 2.92-3.50 (m, 6H, 3 x N-CH_2), 3.71 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 8.20, 11.5 (brs, 1H each, exchg D_2O, 2 x NH); (Found: C, 53.82, H, 8.44, N, 17.80. Calc. for $C_{14}H_{26}N_4O_4$: C, 53.50, H, 8.28, N, 17.83%).

5c; 62; 206; 3100 (NH), 3300 (NH); 260 (M^+); 1.52-1.89 (m, 7H, CH and 3 x C-CH_2), 2.20-2.52 (m, 6H, 3xN-CH_2), 3.55 (t, 2H, J=6Hz, N-CH_2), 3.56 (s, 1H, CH), 7.00-7.45 (m, 5H, ArH), 7.48, 8.52, (brs, 1H each , exchg. D_2O, 2 x NH), 9.79 (brs, 2H, exchg, D_2O, NH_2); (Found: C, 69.05, H, 9.22, N, 21.54. Calc. for $C_{15}H_{24}N_4$: C, 68.91, H, 9.45, N, 21.30%).

8. Spectroscopic data of some representative compounds of Scheme 2 are given as follows: Compound No., yield (%), m.p. (°C), IR (KBr, cm^{-1}), MS: m/z, ^1H NMR (300 MHz, $CDCl_3$, ,ppm).

6g ; 58; oil; 3100 (NH), 2200 (CN); 197 (M^+); 1.45-1.70 (m, 2H, C-CH_2), 1.92 (brs, 1H, exchg. D_2O, NH), 2.21-2.95 (m, 12H, 5xN-CH_2, CH_2CN), 3.64-3.81 (m, 4H, 2xOCH_2); (Found: C, 60.74, H, 9.89, N, 21.20. Calc. for $C_{10}H_{19}N_3O$: C, 60.91, H, 9.64, N, 21.31%).

9b; 42; 142; 1645 (C=O); 302 (M^+); 1.73-2.00 (m, 6H, 2xC-CH_2, N-CH_2), 2.40-2.45 (m, 2H, NH_2), 2.59-2.69 (m, 4H, 2xN-CH_2), 3.18-3.40 (m, 8H, 4XN-CH_2), 4.69 (brs, 1H each, exchg. D_2O, NH), 6.82-6.94 (m, 3H, ArH), 7.23-7.28 (m, 2H, ArH); (Found: C, 67.28, H, 8.68, N, 18.32. Calc. for $C_{17}H_{26}N_4O$: C, 67.54, H, 8.60, N, 18.54%).

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