Bioorganic & Medicinal Chemistry Letters 20 (2010) 6191–6194

Synthesis and Biological Evaluation of Indolyl Glyoxylamides as a new class of Antileishmanial agents

Shikha S. Chauhan,[a] Leena Gupta,[a] Monika Mittal, [b] Preeti Vishwakarma, [b] Suman Gupta [b]and Prem M. S. Chauhan [a,]*

[a]Division of Medicinal and Process Chemistry, Central Drug Research Institute, CSIR, Lucknow 226001, India

[b]Parasitology Division, Central Drug Research Institute, CSIR, Lucknow 226001, India

*Corresponding author. Tel.: +91 522 2262411x4470; fax: +91 522 2623405;

E-mail: prem_chauhan_2000@yahoo.com; premsc58@hotmail.com

Keywords: Antileishmanial; Indolylglyoxylamides; Tetrahydro-β-carboline.

Abstract:

A series of indolylglyoxylamide derivatives have been synthesized and evaluated in vitro against amastigote form of *L. donovani.* Compound **8c** has been identified as the most active analog of the series with IC_{50} value of 5.17 μM and SI value of 31.48, and is several folds more potent than the standard drugs sodium stilbogluconate and pentamidine.

Leishmaniasis is one of the most neglected tropical diseases caused by an obligate intracellular protozoan parasite belonging to the genus *Leishmania.*[1] It is transmitted to mammals by the bite of an insect vector, namely, the phlebotomine sand fly. The parasite exists in two different forms, the motile flagellated form (promastigotes) found in the gut of the sand fly vector and the non-flagellated form (amastigotes) found in the mammalian host that is the cause of the acute disease.[2] It manifests mainly in three clinical forms: visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL).Visceral leishmaniasis (VL) commonly known as kala azar is caused by *Leishmania donovani* and is most lethal, if left untreated.[3] According to WHO estimations, 12 million people are infected worldwide, with 2 million new cases per year, out of which 5, 00,000 cases correspond to the visceral form.[4]
Unfortunately, treatment options for Leishmaniasis are very limited. Antimonials which have been the first line of treatment options for VL for more than 50 years suffer from major side effects including cardiac arrhythmia and pancreatitis.[5] The second line treatment option for VL includes pentamidine, miltefosine, and amphotericin B. However, all of these drugs suffer from

moderate to severe side effects. Pentamidine, which is an aromatic diamidine, can lead to renal, pancreatic, and hepatic toxicity along with hypotension and dysglycemia.[6] Miltefosine, a phosphocholine analogue, is the first oral antileishmanial agent used to cure both visceral and cutaneous leishmaniasis. Despite its great efficacy, miltefosine is limited by its extremely long half-life (6-8 days), low therapeutic index, and teratogenicity in animals.[7] In view of the foregoing facts, there is an urgent need for the development of antileishmanial agents based on new molecular scaffolds.

It has been reported earlier that indolylglyoxylamide derivatives have anticancer activity.[8] More recently, we have demonstrated indolylglyoxylamide derivatives as potent antileishmanial agents. Here, it was observed that indolylglyoxylamide derivatives, obtained from tryptamine were more active as compared to those obtained from cyclic/acyclic amines.[9] Based on the above report and our continuation of studies on chemotherapy of Leishmania, we planned to synthesize a series of indolylglyoxylamide derivatives using L- and D-tryptophan methyl ester, followed by the conversion of these esters into their corresponding acids (Table. 1).

Moreover, natural and synthetic β-carbolines and tetrahydro-β-carbolines alkaloids are well-known compounds that possess a variety of biological properties. [10] Recent studies have pointed β-carboline alkaloids as potential antileishmanial agents. [11] Further, our group has also synthesized some novel β-carboline derivatives showing good antileishmanial activity.[12] Prompted by this and in continuation of our efforts towards synthesis of novel indolylglyoxylamide derivatives as antileishmanial agents we further planned to synthesize another series of indolylglyoxylamide derivatives with various tetrahydro-β-carbolines (Table.1). All of these compounds were investigated for their in vitro antileishmanial activity. Many of these derivatives were found to possess strong inhibitory activity against *L. donovani* when compared to the standard drugs. In this communication, we have reported the synthesis of novel indolylglyoxylamide derivatives and their in vitro antileishmanial activity.

Various indolylglyoxylamide derivatives **(6a-h)** were synthesized in high yield by reaction of D/L-tryptophan methyl ester **(2)** with different indole oxalyl chlorides **(5)** in presence of Et_3N in THF at room temperature for 4h and were then converted to their acid derivatives **(7a-h)** by refluxing them with 2N HCl and acetic acid (Scheme 1). The ester **(2)** was prepared by reaction of D/L-tryptophan **(1)** with thionyl chloride in methanol. Similarly, another series of indolylglyoxylamide derivatives **(8a-p)** were also synthesized in high yield by reaction of indole oxalyl chloride **(5)** with different tetrahydro-β-carboline derivatives by refluxing in THF in presence of K_2CO_3 (Scheme 2). These cis/trans isomers of β-carboline derivatives were prepared by the reaction of D/L tryptophan **(1)** with thionyl chloride in methanol and then the methyl ester **(2)** was cyclized by Pictet–Spingler cyclization in the presence of different aromatic aldehydes.[13] All the synthesized compounds are well characterized by spectroscopic method such as IR, mass, NMR and elemental analysis.[14]

For assessing the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J-774A.1) infected with promastigotes expressing luciferase firefly reporter gene was used. Cells were seeded in a 96-well plate (4×10^4 cells/100 μL/ well) in RPMI-1640 containing 10% foetal calf serum and the plates were incubated at 37°C in a CO_2 incubator. After 24h, the medium was replaced with fresh medium containing stationary phase promastigotes (4×10^5/100 μL/well). Promastigotes invade the macrophage and are transformed into amastigotes. The test material in appropriate concentrations (0.62-40 μM) in complete medium was added after replacing the previous medium and the plates were incubated at 37°C in a CO_2 incubator for 72h. After incubation, the drug containing medium was decanted and 50 μL

PBS was added in each well and mixed with an equal volume of Steady Glo® reagent. After gentle shaking for 1-2 min, the reading was taken in a luminometer.[15] The inhibition of parasitic growth is determined by comparison of the luciferase activity of drug treated parasites with that of untreated controls as described above. IC_{50} of antileishmanial activity were evaluated by logit regression analysis.

Indolylglyoxylamides derivatives **(6a-h)** prepared by combining L- and D-tryptophan methyl ester with substituted indole oxalyl chlorides, were evaluated in vitro against transgenic *L. donovani* amastigotes. Though, a few of these compounds showed up to 99-100% inhibition at 40 μM concentrations but on further screening, they were not selective against amastigote model and were overall found to be inactive and toxic. In order to increase the activity and decrease the toxicity we converted these indolylglyoxylamide derivatives **(6a-h)** into their corresponding acids **(7a-h)** but unfortunately this resulted into the complete loss in activity. Interestingly, the in vitro biological activities of indolylglyoxylamide derivatives **(8a-p)** prepared by combining tetrahydro-β-carbolines **(3)** with indole/5-bromo indole oxalyl chlorides, have shown encouraging results with IC_{50} values in the range of 3.79-8.04 μM (Table 2.).

Among all the indolylglyoxylamide derivatives **(8a-h)**, synthesized by combining indole oxalyl chlorides with tetrahydro-β-carbolines, most of them showed better inhibitory activity with the IC_{50} values in the range of 3.79-8.04 μM and S.I. values in the range of 2.60-31.48 when compared to the standard drugs like Pentamidine (IC_{50}= 20.43, S.I. = 2.58) and SSG (IC_{50}= 71.90, S.I. = 5.53). Among these indolylglyoxylamides, compound **8c** having ethyl group at the para position of the phenyl ring of tetrahydro-β-carboline has emerged as the most promising candidate of this series which possess strong inhibitory activity with IC_{50} of 5.17μM and high selectivity index of 31.48. This lead molecule is 12- and 5-fold more selective than the standard drugs Pentamidine and Sodium stibogluconate (SSG), respectively. With the aim to study the influence of structural parameters on the antileishmanial activity, we made several structural modifications in the molecules. In order to find the influence of stereochemical modulations on the antileishmanial activity of these indolylglyoxylamide derivatives, we used different isomers of tetrahydro-β-carbolines but no significant change was observed in its activity. Variation at the phenyl ring of tetrahydro-β-carbolines showed remarkable influence on the antileishmanial activity of these indolylglyoxylamide derivatives. It was observed that an electron withdrawing group at phenyl ring resulted in the decrease in IC_{50} values of these compounds. Compound **8g**, with chloro group at para position of the phenyl ring showed IC_{50} of 4.36 μM and compound **8h** with bromo group at the ortho position of the phenyl ring showed IC_{50} of 3.76 μM. These values are much lower than their corresponding analog **8b** having methyl group at para position of phenyl ring with IC_{50} of 6.79 μM.

Further, to investigate the SAR effect of electron withdrawing substituent on indole, we synthesized another set of indolylglyoxylamides **(8i-p)** by combining 5-bromoindole oxalyl chloride with same tetrahydro-β-carbolines as above. These compounds also showed good inhibitory activity with IC_{50} values in the range of 3.91-5.86 μM and these values were lower than their analogous derivatives **(8a-h).** Moreover, compound **8j**, with methyl-substituted phenyl ring of tetrahydro-β-carboline showed IC_{50} of 4.79 μM and their corresponding analogs **8o** and **8p** with chloro and bromo-substituted phenyl ring showed slightly low IC_{50} of 4.02 μM and 4.09 μM respectively. It reflects that an electron withdrawing group at the phenyl ring of tetrahydro-β-carboline showed similar effect on the IC_{50} value as in above case. But, by analyzing their in vitro activity data, it was found that though their IC_{50} was lower than that of their corresponding analogs **(8a-h),** they were more toxic and less selective. All these results clearly indicate that

inclusion of 5-bromo indole in place of indole in indolylglyoxylamide significantly increases the toxicity of the final compounds **(8i-p).**

In conclusion, this study has identified indolylglyoxylamides of tetrahydro-β-carbolines as an entirely new structural class of indolylglyoxylamides with antileishmanial activity. The potent activity and simple synthesis of these indolylglyoxylamides suggest that they are potential candidates for the development of new antileishmanial drugs and have opened a new avenue for further exploration.

Acknowledgements

S.S.C and L.G. thanks ICMR and UGC, New Delhi, for financial assistance and to the Sophisticated Analytical Instrument Facility, CDRI, Lucknow for providing spectroscopic data.

References and notes:

[1] Akopyants, N. S.; Kimblin, N.; Secundino, N.; Patrick, R.; Peters, N.; Lawyer, P.; Dobson, D. E.; Beverley, S. M.; Sacks, D. L. *Science* **2009**, *324*, 265.

[2] Rogers, M.; Kropf, P.; Choi, B. S.; Dillon, R.; Podinovskaia, M.; Bates, P.; Muller, I. *PLoS Pathog.* **2009**, *5*, e1000555.

[3] a) http://www.who.int/tdr/diseases/leish/diseaseinfo.htm. b) Sharma, U.; Singh, S. *Indian J. Exp. Biol.* **2009**, *47*, 412.

[4] WHO, Available at: http://www.who.int/leishmaniasis/burden/en.

[5] Murray, H. W.; Berman, J. D.; Davies, C. R.; Saravia, N. G. *Lancet* **2005**, *366*, 1561.

[6] Poola, N. R.; Kalis, M.; Plakogiannis, F. M.; Taft, D. R. J. *Antimicrob. Chemother.* **2003**, *52*, 397.

[7] Herwaldt, B. L. *N. Engl. J. Med.* **1999**, *341*, 1840.

[8] Li, W. T.; Hwang, D. R.; Chen, C. P.; Shen, C. W.; Huang, C. L.; Chen, T. W.; Lin, C. H.; Chang, Y. L.; Chang, Y. Y.; Lo, Y. K.; Tseng, H. Y.; Lin, C. C.; Song, J. S.; Chen, H. C.; Chen, S.; Wu, S. H.; Chen, C. T. *J. Med. Chem.* **2003,** *46,* 1706; b) James, D. A.; Koya, K.; Li, H.; Liang, G.; Xia, Z.; Ying, W.; Wu, Y.; Sun, L. *Bioorg. Med. Chem. Lett.* **2008,** *18*, 1784; c) Li, W. T.; Hwang, D. R.; Song, J. S.; Chen, C. P.; Chuu, J. J.; Hu, C. B.; Lin, H. L.; Huang, C. H.; Huang, C. Y.; Tseng, H. Y.; Lin, C. C.; Chen, T. W.; Lin, C. H.; Wang, H. S.; Shen, C. C.; Chang, C. M.; Chao, Y. S.; Chen, C. T. *J. Med. Chem.* **2010**, *53*, 2409.

[9] Gupta, L.; Talwar, A.; Nishi; Palne, S.; Gupta, S.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2007,** *17*, 4075.

[10] a) Srivastava, S. K.; Agarwal, A.; Chauhan, P. M. S.; Agarwal, S. K.; Bhaduri, A. P.; Singh, S. N.; Fatima, N.; Chatterjee, R. K. *J. Med. Chem.* **1999**, *42*, 1667; b) Kuo, P. C.;

Shi, L. S.; Damu, A. G.; Su, C. R.; Huang, C. H.; Ke, C. H.; Wu, J. B.; Lin, A. J.; Bastow, K. F.; Lee, K. H.; Wu, T. S. *J. Nat. Prod*. **2003**, *66*, 1324; c) Sun, B.; Morikawa, T.; Matsuda, H.; Tewtrakul, S.; Wu, L. J.; Harima, S.; Yoshikawa, M. *J. Nat. Prod*. **2004**, *67*, 1464; d) Wang, Y-H.; Tang, J-G.; Wang, R-R.; Yang, L-M.; Dong, Z-J.; Du, L.; Shen, X.; Liu, J-K.; Zheng, Y-T. Biochem. *Biophys. Res. Commun*. **2007**, *355*, 1091; e) Gupta, L.; Srivastava, K.; Singh, S.; Puri, S. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3306; f) Rook, Y.; Schmidtke, K-U.; Gaube, F.; Schepmann, D.; Wunsch, B.; Heilmann, J.; Lehmann, J.; Winckler, T. *J. Med. Chem.* **2010**, *53*, 3611.

[11] a) Kam, T. S.; Sim, K. M.; Koyano, T.; Komiyama, K. *Phytochemistry* **1999,** *50*, 75; b) Lala, S.; Pramanick, S.; Mukhopadhyay, S.; Bandyopadhyay, S.; Basu, M.K. *J. Drug Target*. **2004,** *12*, 165; c) Costa, E. V.; Pinheiro, M. L. B.; Xavier, C. M.; Silva, J. R. A.; Amaral, A. C. F.; Souza, A. D. L.; Barison, A.; Campos, F. R.; Ferreira, A. G.; Machado, G. M. C.; Leon, L. L. P. *J. Nat. Prod*. **2006**, *69*, 292.

[12] a) Kumar, R.; Khan, S.; Verma, A.; Srivastava, S.; Viswakarma, P.; Gupta, P.; Meena, S.; Singh, N.; Sarkar, J.; Chauhan, P. M. S. *Eur. J. Med. Chem.* **2010***, 45,* 3274; b) Kumar, A.; Katiyar, S. B.; Gupta, S.;Chauhan**,** P. M. S. *Eur. J. Med. Chem.* **2006**, *41,* 106.

[13] Tseng, M. C.; Liang, Y. M.; Chu, Y. Ho. *Tetrahedron Lett.* **2005**, *46*, 6131; b) Wang, Liu. T.; Huang, H.; Ye, Z. L.; Wu, Y.; Wang, X. C. *Synth. Commun*. **2006**, *36*, 2627; c) Muthukrishnan, M.; More, S. V.; Garud, D. R.; Ramana, C. V. J. *Heterocycl. Chem.* **2006**, *43*, 767; (d) Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Tetrahedron Lett.* **2007**, *48*, 1379.

[14] Spectroscopic data for **8b:** Yield: 72.0%; ESMS: 492 (M+1); mp: 160–162°C; IR(KBr) 3366, 3055, 2950, 1738, 1625, 1516, 1239, 822, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 9.00(bs, 1NH), 8.38-7.09(m, 14H), 6.36(s, 1H), 4.90-4.83 (m, 1H), 3.67(s, 3H), 3.63-3.47(m, 2H), 2.15(s, 3H); ^{13}C ($CDCl_3$, 50 MHz): 186.53, 170.86, 149.87, 138.33, 137.34, 136.91, 136.69, 135.20, 128.73, 127.89, 127.52, 122.34, 120.98, 119.07, 118.75, 112.12, 109.56, 55.61, 52.40, 51.73, 24.55, 21.89; Anal. Calcd for $C_{30}H_{25}N_3O_4$: Calculated: C: 73.30; H: 5.13; N: 8.55. Found: C: 73.42; H: 5.26; N: 8.28. Spectroscopic data for **8c:** Yield: 74.0%; ESMS: 506 (M+1); mp: 172-174°C; IR (KBr) 3358, 3018,2924, 1740, 1624, 1517, 1216, 831, 761 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 9.05(bs, 1NH), 7.89-7.30(m, 14H), 6.87(s, 1H), 5.05-5.02(m, 1H), 3.67-3.25(m, 5H), 2.67-2.63(m, 2H), 1.29(t, 3H, J=5.80 Hz); ^{13}C ($CDCl_3$, 50 MHz): 185.35, 171.14, 144.57, 136.21, 135.94, 134.82, 130.14, 129.12, 127.86, 126.51, 124.38, 122.58, 119.83, 118.68, 119.98, 11.12, 107.92, 53.98, 52.13, 51.63, 28.54, 21.78, 15.67; Anal. Calcd for $C_{31}H_{27}N_3O_4$: Calculated: C: 73.65; H: 5.38; N: 8.31. Found: C: 73.99; H: 5.15; N: 8.09. Spectroscopic data for **8e:** Yield: 70.0%; ESMS: 520 (M+1); mp: 162–164°C; IR (KBr) 3378, 3057, 2958, 1742, 1623, 1515, 1239, 831, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 9.01(bs, 1NH), 8.36-7.02(m, 14H), 6.82(s, 1H), 5.02-5.00(m, 1H), 3.23-2.87(m, 8H), 1.26(d, 6H, J= 6.88 Hz); ^{13}C ($CDCl_3$, 75 MHz): 185.31, 169.86, 168.55, 149.13, 136.30, 136.09, 135.89, 134.91, 130.17, 129.07, 126.50, 126.22, 124.37, 122.57, 122.08, 121.97, 119.81, 118.66, 114.60, 111.99, 111.10, 107.85, 56.18, 51.90, 51.55, 33.82, 23.93, 23.61; . Anal. Calcd for $C_{32}H_{29}N_3O_4$: Calculated: C: 73.97; H: 5.63; N: 8.09. Found: C: 73.47; H: 5.97; N: 8.32. Spectroscopic data for **8f:** Yield: 73.0%; ESMS: 520 (M+1); mp: 158-160°C; IR (KBr) 3362, 3056, 2957, 1737, 1625, 1516, 1238, 829, 746 cm^{-1}; ^1H NMR

($CDCl_3$, 200 MHz): 8.93(bs, 1NH), 8.33-6.95(m, 14H), 6.39(s, 1H), 5.10-5.09(m, 1H), 3.66-2.67(m, 8H), 1.21(d, 6H, J=6.90 Hz); ^{13}C ($CDCl_3$, 50 MHz): 184.36, 170.99, 148.99, 148.20, 136.58, 136.28, 136.23, 135.51, 132.50, 128.71, 126.92, 126.43, 124.09, 123.10, 122.48, 122.02, 119.89, 118.44, 111.89, 111.22, 107.52, 57.62, 52.96, 52.62, 33.67, 23.89, 23.60; Anal. Calcd for $C_{32}H_{29}N_3O_4$: Calculated: C: 73.97; H: 5.63; N: 8.09. Found: C: 73.48; H: 5.08; N: 8.17. Spectroscopic data for **8g:** Yield: 72.0%; ESMS: 512 (M+1); mp: 162–164°C; IR (KBr) 3390, 3022, 2936, 1732, 1625, 1518, 1218, 769 cm^{-1}; ^1H NMR ($CDCl_3$+CD_3OD, 200 MHz): 9.12(bs, 1NH), 9.05(bs, 1NH), 7.10-8.31(m, 13H), 6.41(s, 1H), 4.81(m, 1H), 3.73(s, 3H), 3.59-3.34(m, 2H); ^{13}C ($CDCl_3$+CD_3OD, 50 MHz): 188.33, 176.06, 144.67, 137.90, 136.86, 135.76, 132.53, 130.12, 129.96, 127.97, 127.06, 125.86, 123.36, 123.23, 122.11, 117.83, 116.10, 115.28, 108.23, 61.39, 56.39, 52.67, 51.81, 26.51; Anal. Calcd for $C_{29}H_{22}ClN_3O_4$: Calculated: C: 68.04; H: 4.33; N: 8.21. Found: C: 68.24; H: 4.06; N: 8.39.

[15] Porwal, S.; Chauhan, S. S.; Chauhan, P. M. S.; Shakya, N.; Verma, A.; Gupta, S. *J. Med. Chem.* **2009,** *52,* 5793.

Table 1. All the synthesized compounds **(6a-h), (7a-h)** and **(8a-h)**

Compd No.	Isomer	R^1	R^2	R^3	R^4
6a	L	H	H	-	-
6b	D	H	H	-	-
6c	L	H	Cl	-	-
6d	D	H	Cl	-	-
6e	L	Br	H	-	-
6f	D	Br	H	-	-
6g	L	OCH_3	H	-	-
6h	D	OCH_3	H	-	-
7a	L	H	H	-	-
7b	D	H	H	-	-
7c	L	H	Cl	-	-
7d	D	H	Cl	-	-

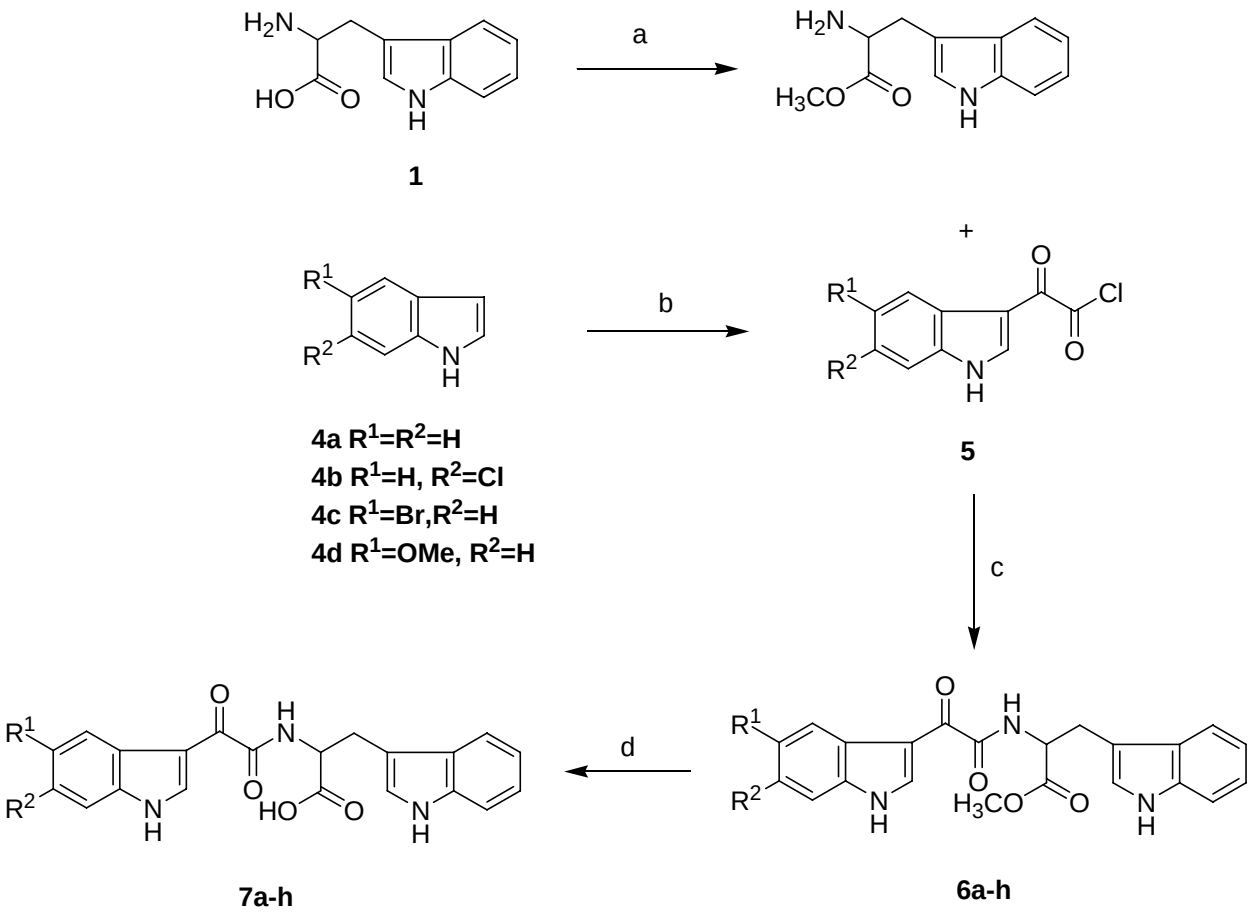
7e	L	Br	H	-	-
7f	D	Br	H	-	-
7g	L	OCH_3	H	-	-
7h	D	OCH_3	H	-	-
8a	L/cis	H	H	CH_3	H
8b	L/trans	H	H	CH_3	H
8c	D/cis	H	H	C_2H_5	H
8d	D-trans	H	H	C_2H_5	H
8e	D/cis	H	H	$CH(CH_3)_2$	H
8f	D/trans	H	H	$CH(CH_3)_2$	H
8g	L-trans	H	H	Cl	H
8h	L-trans	H	H	H	Br
8i	L/cis	Br	H	CH_3	H
8j	L/trans	Br	H	CH_3	H
8k	D/cis	Br	H	C_2H_5	H
8l	D/trans	Br	H	C_2H_5	H
8m	D/cis	Br	H	$CH(CH_3)_2$	H
8n	D/trans	Br	H	$CH(CH_3)_2$	H
8o	L/trans	Br	H	Cl	H
8p	L/trans	Br	H	H	Br

Table 2. Antileishmanial *in vitro* activity against intracellular amastigotes

Compd no.	Antiamastigote activity IC_{50}(μM)	Cytotoxicity CC_{50} (μM)	Selectivity index [a] (SI)
8a	7.37	27.43	3.72
8b	6.79	34.40	5.07
8c	5.17	162.76	31.48
8d	8.04	30.90	3.84
8e	6.74	32.65	4.84
8f	6.02	15.09	2.51
8g	4.36	11.35	2.60
8h	3.79	30.09	7.94
8i	5.18	10.08	1.95
8j	4.79	8.83	1.84
8k	5.36	11.62	2.17
8l	5.86	9.48	1.62
8m	3.91	7.77	1.99
8n	4.44	9.04	2.04
8o	4.02	7.64	1.90
8p	4.09	7.25	1.77
Pentamidine®	20.43	52.82	2.58
SSG®	71.90	398.26	5.53

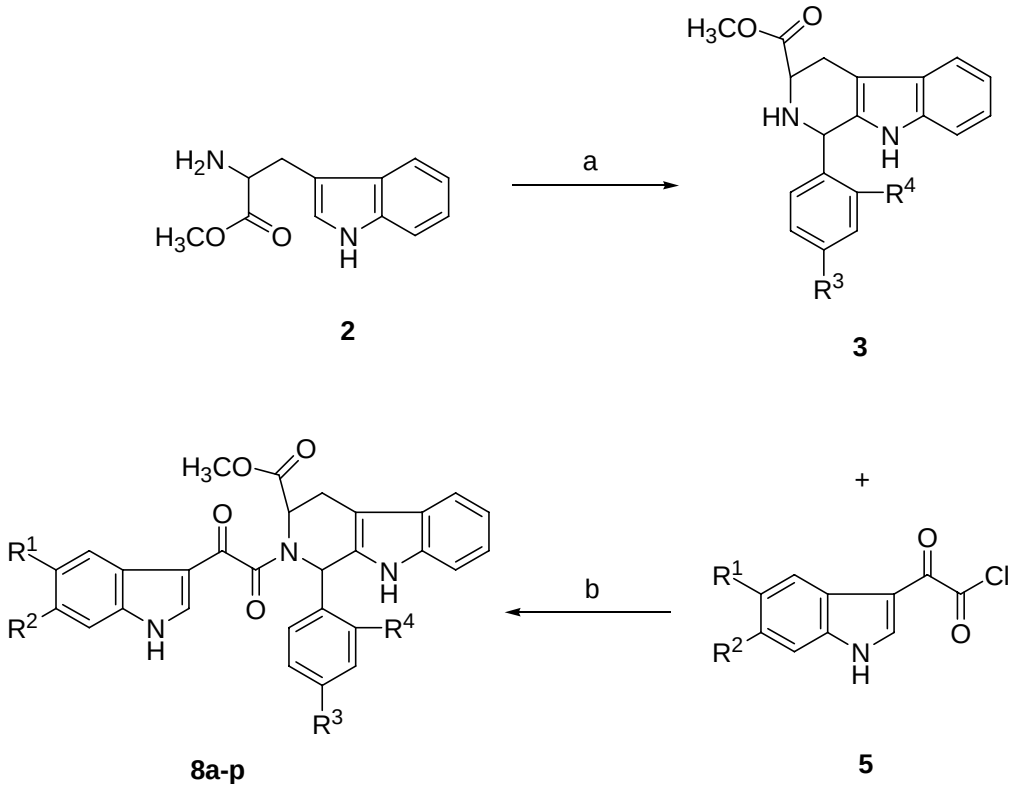
SSG® = sodium stibogluconate.
[a]Selectivity index (SI) defined by the ratio CC50 (J-774 A-1 cells)/IC50 (Leishmania amastigotes).

Scheme 1:



Reagents and conditions: a) $SOCl_2$, MeOH, reflux; b) $(COCl)_2$, THF, 0°C; c) THF, Et_3N, r.t., 4h; d) 2N HCl, acetic acid, reflux, 2h.

Scheme 2:



Reagents and conditions: a) different aromatic aldehyde, MeOH, reflux; b) THF, K_2CO_3, reflux, 5h