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Synthesis, antileishmanial and antitrypanosomal activities of N-substituted tetrahydro-β-carbolines ☆

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ABSTRACT

A series of N-substituted tetrahydro-β-carbolines were synthesized and screened for antileishmanial activity through an in vitro assay that involves promastigotes and axenic amastigotes of *Leishmania donovani*, the causative agent for visceral leishmaniasis. The thiophen-2-yl analogs **9b** and **11f** and naphthyl analog **11h** were found to show significant activity against promastigotes with IC_{50} values of 12.7, 9.1 and 22.1 μM, respectively. Analogs **9b** and **11h** were also effective against axenic amastigotes with IC_{50} values of 62.8 and 87.6 μM, respectively. The antileishmanial activity of analogs was then tested in human macrophage cell line infected with *L. donovani* amastigotes and 2-naphthyl linked analog **11h** was found to be effective with IC_{50} value of 28.3 μM. Several analogs also displayed antitrypanosomal activity against *Trypanosoma brucei*, the causative agent for human African trypanosomiasis. Compounds **11e**, **11f** and **11h** were more effective than others with IC_{50} values of 1.0, 8.9 and 10.2 μM, respectively. All synthesized analogs were not cytotoxic towards mammalian cell lines including Vero (monkey kidney fibroblasts), HEPG2 (human hepatoma cells), LLC-PK_1 (pig kidney epithelial cells) and THP-1 (human macrophages).

The diseases caused by kinetoplastid parasites affect millions of people in the developing world. Leishmaniasis, African trypanosomiasis, and Chagas disease are the most prevalent kinetoplastid diseases that pose major human health challenge. Leishmaniasis is caused by protozoan parasites that belong to the genus *Leishmania* and is transmitted by the bite of certain species of sand fly (subfamily: phlebotominae). Most of the visceral leishmaniasis cases are observed in countries like India, Bangladesh, Sudan and Brazil.[1] Trypanosomiasis (also called as sleeping sickness) primarily occurs in sub-Saharan Africa; and is caused by the parasite *Trypanosoma brucei*, transmitted by tsetse flies.[2,3] Most of the current antiparasitic drugs are decades old and have many limitations, including the emergence of drug resistance.[4–9] There has always been a continuous search for new drugs for these diseases with improved efficacy and less side-effects.[10,11]

A large number of natural products have been reported to exhibit antileishmanial and antitrypanosomal activities.[12] The β-carboline alkaloids are widely distributed in plant kingdom and are also present in beverages and foods. This class of compounds exhibit psychopharmacological,[13] antitumor,[14,15] antileishmanial,[16] antitrypanosomal,[17,18] anti-HIV,[19] antiinflammatory,[20] and variety of other pharmacological activities. The β-carboline alkaloids harmane (**1**), harmine (**2**) and harmaline (**3**) have been reported to possess antileishmanial activity.[21] Harmane (**1**) and harmine (**2**) strongly inhibited the growth of intracellular amastigotes with IC_{50} values of 0.27 and 0.23 μM, respectively. Harmine (**2**) appeared the most efficient compound toward the promastigote stage of the parasite (IC_{50} = 3.7 μM). Harmane (**1**) and harmaline (**3**) showed comparatively lesser activity in promastigotes stage, with IC_{50} values of 19.2 and 116.8 μM, respectively.[21] Harmaline (**3**) showed an interesting amastigote-specific activity with an IC_{50} of 1.16 μM. The pyrimidine substituted β-carboline alkaloid annomontine (**4**) and *N*-hydroxy annomontine (**5**) were reported to show activity (IC_{50} = 34.8 and 252.7 μM, respectively) against *Leishmania brazilensis*.[22] The compound **6** has shown potent activity against *Trypanosoma cruzi* (IC_{50} 0.40 μM).[17] Harmine (**2**) was also reported to be effective against *T. brucei* (IC_{50} 74 μM).[18] Furthermore, structurally related canthin-6-one alkaloids have also shown trypanocidal activity in vivo in the mouse model of acute or chronic *T. brucei* infection.[23] The structures of β-carboline alkaloids **1**–**6** are shown in Figure 1.

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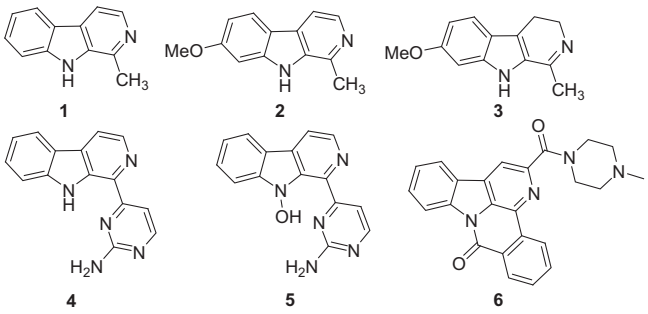


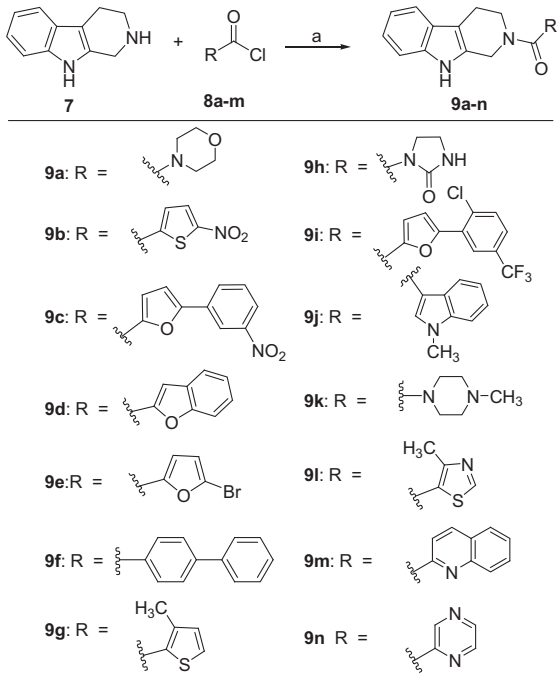
Figure 1. Structures of biologically active β-carboline alkaloids.

Based on the literature precedence for antileishmanial[21,22] and antitrypanosomal[17,18] activities of β-carboline alkaloids, herein we report the synthesis and evaluation of antileishmanial and anti-trypanosomal activities of a series of N-substituted tetrahydro-β-carbolines. For NH-substitutions, we have selected moieties such as *N*-methylpiperazine (which is present in **6**)[17] and its structural variants (e.g., morpholine). Furthermore, several antileishmanial scaffolds consists of benzoyl,[24–26] piperazinoyl,[17] furyl,[27] naphthyl[27] functionalities; thus various *CO*- and *CH*$_2$-linked aryl and heteroaryl moieties were incorporated to understand the structural requirements for antileishmanial activities.

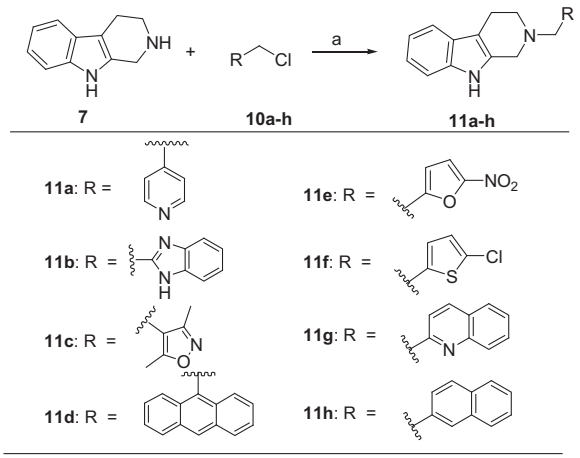
A series of tetrahydro-β-carboline analogs were synthesized starting from commercially available tetrahydro-β-carboline **7**. The reaction of tetrahydro-β-carboline **7** with different acyl halides in CH_2Cl_2 in presence of sodium hydroxide produced *N*-acyl β-carbolines **9a**–**n** in 63-82% yield (Scheme 1).

Similarly, a series of *N*-alkylated β-carbolines were synthesized by treatment of tetrahydro-β-carboline **7** with different heterocycle linked alkyl halides in acetonitrile in presence of potassium carbonate. The *N*-alkylated products **11a**–**h** were formed in 66–78% yield (Scheme 2).

All compounds were tested for in vitro antileishmanial, antitrypanosomal and cytotoxic activities.[26,28,29] The antileishmanial



Scheme 1. Reagents and conditions: (a) CH_2Cl_2, NaOH, 0 °C, 15 min then rt, 3 h, 63–82%.



Scheme 2. Reagents and conditions: (a) K_2CO_3, CH_3CN, 3 h, rt, 66–78%.

activity of the compounds was tested in vitro against a culture of *Leishmania donovani* promastigotes, axenic amastigotes and macrophage amastigotes. Several compounds showed significant antileishmanial activity against promastigotes. As presented in Table 1, the thiophen-2-yl analogs **9b** and **11f** and naphthyl analog **11h** showed activity against promastigotes with IC_{50} values of 12.7, 9.1 and 22.1 μM, respectively. Other compounds displaying good anti-promastigote activity include benzofuran analog **9d** (IC_{50} 49.5 μM), biphenyl analogs **9f** and **9i** (IC_{50} values 75.3 and 39.6 μM), and anthracene analog **11d** (IC_{50} 16.0 μM). Compounds **9b**, **9d**, **9e**, **9f**, **9i**, **11e**, **11f** and **11h** also showed activity against axenic amastigotes. However, only compound **11h** displayed activity against macrophage amastigotes, with IC_{50} of 28.3 μM. None of the compounds were toxic to differentiated THP-1 macrophage cells.

The antitrypanosomal activity of all analogs was evaluated against a culture of *T. brucei*.[30] Results are shown in Table 1. Several compounds were effective in inhibiting the growth of *T. brucei* trypomastigotes. The 2-nitrofurn-2-yl linked analog **11e** was the most potent with IC_{50} value of 1.0 μM, and IC_{90} of 28.1 μM. Further, the thiophen-2-yl linked analog **11f** and naphthyl linked analog **11h** were found to possess promising antitrypanosomal activity with IC_{50}/IC_{90} values of 8.9/14.5 and 10.2/17.6 μM, respectively.

It is noteworthy to mention that thiophen-2-yl linked analogs **9b**, **9g** and **11f** displayed better antileishmanial activity in comparison to other analogs. Next, the anthracene and naphthyl linked analogs **11d** and **11h** were best antileishmanial agents among remaining analogs. The analog **11f** showed comparable anti-promastigote activity to that of reference drug pentamidine. Interestingly, thiophen-2-yl analog **11f** and anthracene and naphthyl linked analogs **11d** and **11h** also displayed better anti-trypanosomal activity than other analogs. Compounds **9e**, **11c**, **11d**, **11e**, **11f** and **11h** showed better antitrypanosomal activity than reference drug DFMO.

On comparison of biological data with harmanes **1**–**3**, it was observed that the analog **11f** displayed better anti-promastigote activity than harmane (**1**). Compounds **11e** and **11f** displayed better antitrypanosomal activity than harmine (**2**). The comparative antileishmanial and antitrypanosomal activity of harmane class of compounds **1**–**3** and N-substituted tetrahydro-β-carbolines **11f**–**11h** is shown in Table 2.

In order to investigate the selectivity of the synthesized compounds toward leishmania/trypanosoma parasites, their in vitro cytotoxicity,[29] was determined up to a highest concentration of 25 μg/mL against three mammalian cell lines (Vero: monkey kidney fibroblasts, HEPG2: human hepatoma cells and LLC-PK$_1$: pig kidney epithelial cells). Most of the compounds were not toxic

Table 1
In vitro antileishmanial and antitrypanosomal activity of tetrahydro β-carboline analogs[a,b]

Entry[a]	IC_{50}/IC_{90} (μM)			
	L. donovani			*T. brucei*
	Promastigotes	Axenic amastigotes	Macrophage amastigotes	Trypamastigotes
9b	12.7/36.6	62.8/107.3	na	na
9c	66.7/—	na	na	na
9d	49.5/120.2	116.2/—	na	na
9e	27.5/—	96.5/122.4	na	13.7/23.9
9f	75.3/111.2	83.4/110.0	na	na
9g	26.0/—	na	na	na
9i	39.6/69.1	37.1/76.0	na	na
9j	52.6/—	na	na	na
11a	121.3/—	na	na	26.2/—
11b	117.7/—	na	na	29.7/—
11c	na	na	na	15.9/26.3
11d	16.0/76.0	80.4/103.6	na	11.0/18.8
11e	33.8/—	116.7/—	na	1.0/28.1
11f	9.1/25.6	na	na	8.9/14.5
11h	22.1/28.1	87.59/—	28.3/>32	10.2/17.6
Pentamidine	4.8/6.1	>29.4/>29.4	2.0/3.1	0.0041/0.0070
Amph. B	0.3/0.4	0.3/0.4	0.2/0.5	nt
DFMO	nt	nt	nt	28.0/68.2

na, not active; nt, not tested;—IC_{90} was not obtained; DFMO, α-difluoromethylornithine.
[a] The general synthetic procedure and representative experimental data is shown in Refs. 31,32.
[b] Compounds **9a**, **9h**, **9k**, **9l**, **9m**, **9n** and **11g** were found to be inactive in all these assays, and thus are not listed in this table.

Table 2
Comparison of antileishmanial and antitrypanosomal activity of harmane class of compounds **1**–**3** and N-substituted tetrahydro-β-carbolines **11e**, **11f** and **11h**

Entry	IC_{50} (μM)		
	L. donovani		*T. brucei*
	Promastigotes	Axenic amastigotes	
1[a]	19.2	0.27	nr
2[a]	3.7	0.23	74
3[a]	116.8	1.16	nr
11e	33.83	116.66	1.01
11f	9.13	na	8.90
11h	22.11	87.59	10.16

[a] Data from literature; nr: data not available in literature; na: not active.

up to the concentration of 25 μg/mL (data not shown), except compounds **9b** and **9i**. Compound **9b** showed cytotoxicity to HEPG2 and LLC-PK1 cells with IC_{50} values of 20.8 (63.6 μM) and 18.3 (56 μM) μg/mL, respectively. Compound **9i** displayed cytotoxicity to HEPG2 with IC_{50} value of 10 μg/mL (25.52 μM). None of the analog was toxic to macrophages up to 10 μg/mL during antileishmanial testing (data not shown).

In summary, we have identified tetrahydro-β-carboline analogs possessing significant antileishmanial activity against *L. donovani* promastigotes. The thiophen-2-yl linked analog **11f** and naphthyl linked analog **11h** were most promising antileishmanial agents, exhibiting IC_{50} values of 9.1 and 22.1 μM, respectively. The naphthyl linked analog **11h** displayed promising antileishmanial activity against promastigotes, axenic amastigotes, macrophage amastigotes, and also displayed antitrypanosomal activity against *T. brucei*. This indicates its potential for further lead optimization towards the discovery of newer antileishmanial and antitrypanosomal agent(s).

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Supplementary data

Supplementary data (experimental procedures and spectral data scans) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.06.030.

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31. General procedure for the synthesis of N-substituted 1,2,3,4-tetrahydro-β-carbolines **9a–m.** To the suspension of 1,2,3,4-tetrahydro-β-carboline (**7**, 1.2 mmol) in CH_2Cl_2 (3 ml) at 0 °C was added slowly an aqueous solution of 4 N NaOH (1.2 mol). After 5 min stirring at 0 °C, aryl/heteroaryl or cycloalkyl acyl chloride (1.2 mmol) was added dropwise. The mixture was stirred for 15 min at 0 °C and further stirred at rt for 3 h. Completion of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with CH_2Cl_2 and was washed with water. Organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and crude product was purified by silica gel (#100–200) column chromatography using EtOAc: hexane as mobile phase to get desired aryl/cycloalkyl-carbonyl linked 1,2,3,4-tetrahydro-β-carbolines **9a–m** in 63–82% yield. The spectral data for representative compounds is provided here. 2-(5-Nitrothiophen-2-yl-carbonyl)-1,2,3,4-tetrahydro-beta carboline (**9b**). Red solid; yield 75%; mp 217–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.92 (br s, NH, 1H), 8.31 (s, 1H), 7.59 (s, 1H), 7.42 (d, J = 8 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 4.85 (br s, 2H), 3.94 (br s, 2H), 2.85 (br s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 161.6 (CO), 152.6 (C), 145.0 (C), 136.5 (C), 130.4 (C), 129.7 (CH), 128.7 (CH), 126.8 (C), 121.5 (CH), 119.1 (CH), 118.0 (CH), 111.6 (CH), 107.2 (C), 55.3 (CH_2), 46.2 (CH_2), 22.1 (CH_2); IR (KBr): ν_{max} 3392, 2921, 1614, 1536, 1507, 1448, 1415, 1346, 1334, 1232, 1032 cm^{-1}; ESI-MS: m/z 350.01 $[M+Na]^+$; HRMS: m/z 328.0728 calcd for $C_{16}H_{13}N_3O_3S+H^+$ (328.0750).

32. General procedure for the synthesis of N-substituted 1,2,3,4-tetrahydro-β-carbolines **11a–d**. To the solution of 1,2,3,4-tetrahydro-β-carboline (**7**, 1.2 mmol) in acetonitrile was added K_2CO_3 (1.8 mmol) followed by addition of corresponding heterocyclic alkyl chloride (1.2 mmol). The reaction mixture was stirred at rt for 3 h. Completion of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was diluted with ethyl acetate and was washed with water. The organic layer was separated and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and crude product was purified by silica gel (#100–200) column chromatography using EtOAc: hexane as mobile phase to get desired aryl methylene linked 1,2,3,4-tetrahydro-β-carbolines **9a–d** in 66–78% yield. 2-(Anthracen-10-yl-methyl)-1,2,3,4-tetrahydro-beta-carboline (**11d**). yellow solid; yield 66%; mp 222–225 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.50 (br s, NH, 1H), 8.70 (s, 1H), 8.60 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 8.0 Hz, 2H), 7.85–7.51 (m, 4H), 7.25 (d, J = 7.7 Hz, 1H), 7.21 (d, J = 8.0 Hz,1H), 6.97 (t, J = 7.5 Hz, 1H), 6.92 (t, J = 7.7 Hz, 1H), 4.85 (s, 2H), 3.65 (s, 2H), 2.98 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 166.8 (C), 135.7 (C), 132.7 (C), 131.6 (C), 131.4 (CH), 130.9 (C), 130.7 (C), 129.8 (C), 128.6 (CH), 127.1 (CH), 126.5 (C), 125.7 (CH), 125.0 (CH), 120.1 (CH), 118.1 (CH), 117.2 (CH), 110.7 (CH) 106.3 (C), 64.9 (CH_2), 52.5 (CH_2) 50.6 (CH_2), 49.5 (CH_2); IR (KBr): ν_{max} 3401, 3054, 2959, 2931, 2872, 1723, 1623, 1598, 1453, 1380, 1286, 1122, 1073 cm^{-1}; ESI-MS: m/z 363.17 $[M+H]^+$; HRMS: m/z 363.1823 calcd for $C_{26}H_{23}N_2+H^+$ (363.1855). 2-(5-Chlorothiophen-2-yl-methyl)-1,2,3,4-tetrahydro-beta-carboline (**11f**). white solid; yield 73%; mp 191–193 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm): δ 10.70 (br s, NH, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 7.02–6.90 (m, 4H), 3.92 (s, 2H), 3.60 (s, 2H), 2.90 (t, J = 5.6 Hz, 2H), 2.65 (t, J = 5.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm): δ 142.6 (C), 135.7 (C), 132.2 (C), 127.1 (C), 126.6 (CH), 126.1 (C), 125.2 (CH), 120.2 (CH), 118.1 (CH), 117.2 (CH), 110.7 (CH), 106.1 (C), 55.6 (CH_2), 50.0 (CH_2), 49.4 (CH_2), 20.8 (CH_2); IR (KBr): ν_{max} 3152, 2922, 2848, 2805, 1620, 1448, 1328,1236, 1204, 1100, 1006 cm^{-1}; ESI-MS: 303 $[M+H]^+$; HRMS: m/z 303.0708 calcd for $C_{16}H_{16}ClN_2S+H^+$ (303.0717). 2-(Naphthalen-2-yl-methyl)-1,2,3,4-tetrahydro-beta-carboline (**11h**). white solid; yield 80%; mp165–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.85–7.82 (m, 3H), 7.63–7.57 (m, 2H), 7.50–7.45 (m, 2H), 7.29–7.27 (m, 2H), 7.14–7.04 (m, 2H), 3.94 (s, 2H), 3.70 (s, 2H), 2.97 (t, 2H, J = 5.0 Hz), 2.85 (t, 2H, J = 5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$ ppm): δ 136.6 (c), 136.0 (C), 133.3 (C), 132.8 (C), 131.8 (C), 128.0 (CH), 127.9 (C), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.3 (CH), 126.0 (CH), 125.6 (CH), 121.3 (CH), 119.3 (CH), 117.9 (CH), 110.6 (CH), 108.4 (C), 62.1 (2CH), 51.0 (2CH), 50.2 (2CH), 21.2 (2CH); IR ($CHCl_3$): ν_{max} 3401, 2923, 2852, 2353, 1625, 1454, 1384, 1019, 741 cm^{-1}; ESI-MS: m/z 313.03 $[M+H]^+$; HRMS: m/z 313.1730 calcd for $C_{22}H_{21}N_2+H^+$ (313.1699).