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Synthesis and anti-leishmanial activity of 1-aryl-β-carboline derivatives against *Leishmania donovani*

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ABSTRACT

β-carbolines from various natural and synthetic sources have been known to show diverse biological activities. As a part of our current ongoing project to search for potent natural product-derived anti-leishmanial compounds, we have synthesized a series of substituted 1-aryl-β-carboline derivatives. A total of 22 compounds were synthesized and tested in vitro against *Leishmania donovani*, out of which 6 compounds (**4**, **5**, **10**, **11**, **19** and **22**) showed notably more activity than the standard miltefosine (IC_{50} 12.07 ± 0.82 μM), with compound **4** being the most potent (IC_{50} 2.16 ± 0.26 μM).

Leishmaniasis, caused by the protozoan parasite of genus *Leishmania*, is a group of neglected parasitic disease. It is manifested in visceral, mucocutaneous, or cutaneous forms. Leishmaniasis is prevalent in 88 countries throughout the world and affects more than 12 million people with more than 90% of visceral leishmaniasis (VL) patients located in India, Sudan, Brazil and Bangladesh.[1] The drugs currently used for the treatment of leishmaniasis include miltefosine, sodium stibogluconate, meglumine antimoniate, pentamidine, amphotericin B, and paromomycin.[2] All of these drugs are either expensive or have too many side effects and are toxic. Besides, current treatment regimen is lengthy, has poor compliance and also resistance to these drugs have been observed in several cases.[3] Hence, there is a significant unmet need to identify and develop cheaper, safer and effective molecules for the treatment of leishmaniasis.

Natural products have always been a prolific starting point for many drug development programs, especially for anti-infective and antitumor agents.[4–6] Many alkaloids have been reported to be active against leishmaniasis, including β-carbolines (Fig 1).[3] The β-carboline alkaloid harmaline isolated from *Peganum harmala* (Syrian Rue) has been reported to show a strong amastigote specific activity with an IC_{50} of 1.16 μM.[7] The metabolite harmine occurring in same plant has also shown significant activity in vivo.[8] The pyrimidine-β-carboline alkaloid annomontine, isolated from *Annona foetida*, has been reported to show anti-leishmanial activity (IC_{50} 34.8 μM) against *Leishmania brazilensis*.[9] Moreover, several synthetically modified β-carboline derivatives have also been studied against leishmaniasis.[10–13] Our group had previously reported the synthesis of this group of compounds for anti-HIV activity.[14,15] As a part of our current ongoing project to search for potent natural product-derived anti-leishmanial compounds, we have synthesized a series of 1-aryl-β-carboline derivatives. In this Letter, we are reporting the results of synthesis and biological evaluation of novel 1-aryl-β-carboline derivatives against promastigotes of *Leishmania donovani*, the causative organism for visceral leishmaniasis.

The overall strategy for the synthesis of β-carboline derivatives is depicted in Scheme 1. Briefly, 1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indole-3-carboxylic acid (**1**) was obtained by Pictet–Spengler condensation, reacting DL-tryptophan and *p*-nitro-benzaldehyde in acidic conditions.[16] Compound **1** was aromatized and decarboxylated in a single step using Jones oxidation to give 1-(4-nitrophenyl)-9*H*-pyrido[3,4-*b*]indole (**2**). The 4-nitro group was reduced using stannous chloride to give the amino

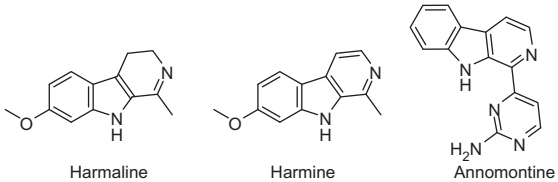

Figure 1. Anti-leishmanial β-carboline alkaloids.

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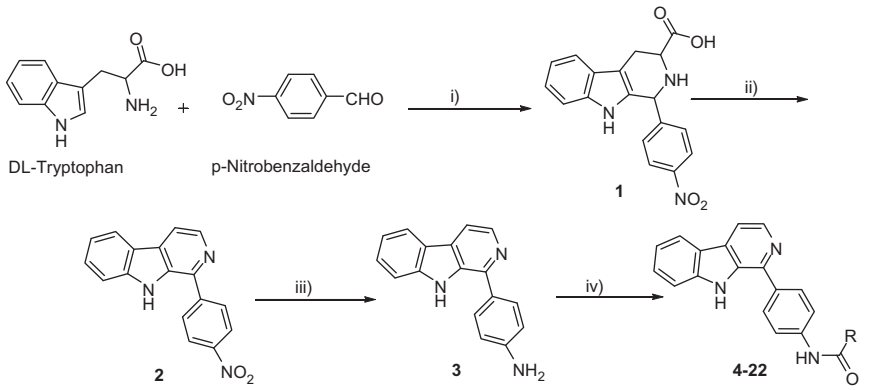

Scheme 1. Synthesis of 1-aryl-β-carboline derivatives by Pictet-Spengler route: Reagents and conditions: (i) 1 N H_2SO_4, H_2O, EtOH, reflux, 4 h, 84%; (ii) $K_2Cr_2O_7$, glacial-CH_3COOH, 5 min, 90% (iii) $SnCl_2$/HCl, EtOH, 70 °C, 30 min, 85%; (iv) Acyl chloride, anhydrous CH_2Cl_2, rt, 1–5 h, 60–89%.

compound (**3**), which was reacted with various substituted acyl chlorides using anhydrous dichloromethane as solvent to give the desired compounds (**4**–**22**) in good yields (60–89%).

The synthesized compounds were evaluated against promastigotes of *Leishmania donovani* according to the protocol described by Chollet et al.[17] The compounds **1** and **2** did not exhibit any anti-leishmanial activity (IC_{50} >100 μM), however when **2** was converted to **3**, it showed moderate anti-leishmanial activity (IC_{50} 46.57 ± 9.36 μM), suggesting that 4-amino group on the phenyl moiety gave better anti-leishmanial activity compared to the nitro derivative (**2**). Various substituted derivatives (**4**–**22**) were prepared to further improve the activity of the core moiety (Fig 2). The activity of the compounds is graphically presented in Figure 3. It was observed that long chain β-carboline anilides (**9**, **12** and **18**) did not show any anti-leishmanial activity (IC_{50} >100 μM), however compound containing methyl group (**4**) (IC_{50} 2.16 ± 0.26 μM) was the most active compound in the series. The un-substituted aryl derivative (**11**) and the cinnamoyl derivative (**19**) also showed a better anti-leishmanial activity than the standard drug (miltefosine, IC_{50} 12.07 ± 0.82 μM) with IC_{50} of 9.68 ± 0.87 and 7.70 ± 0.79 μM respectively. The stearic properties of the napthyl substituent in case of compound **5** and **7** were important, as 1-napthyl derivative (**7**) was totally inactive whereas 2-napthyl derivative (**5**) showed potent anti-leishmanial activity (IC_{50} 8.84 ± 0.34 μM). The compound containing furan ring (**10**) also exhibited potent anti-leishmanial activity (IC_{50} 6.38 ± 0.12 μM), whereas the compound containing a substituted furan ring (**20**) showed moderate activity (IC_{50} 30.08 ± 6.16 μM). The compound containing isostere of furan that is thiophene (**8**), however showed less activity compared to the furan derivative (**10**). Modifications of E ring also showed some interesting results. The substitution of halogen atoms on the E ring was also important as 2,4-difluoro derivative (**13**) was inactive, whereas 3,4-difluoro derivative (**14**) showed activity comparable to that of the standard drug (13.1 ± 0.43 μM). The compound containing 4-cyano group (**22**) on the E ring was the second most active compound in the series with an IC_{50} of 5.31 ± 0.70 μM. Compound containing an electron donating group like methyl or methoxy at the para posi-

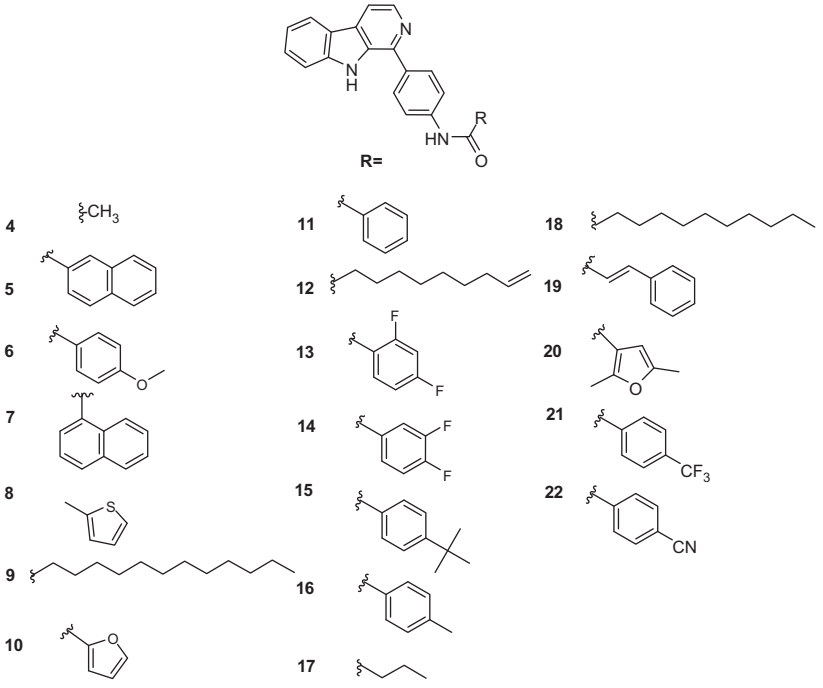

Figure 2. Synthesized 1-aryl-β-carboline derivatives.

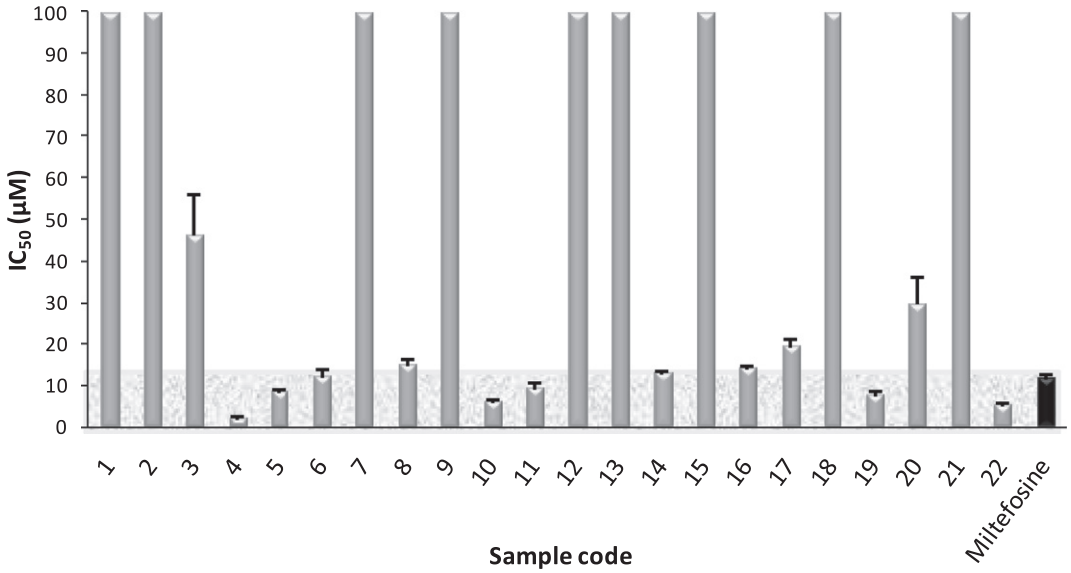

Figure 3. Anti-leishmanial activities of the synthesized compounds: Results are expressed as the concentration inhibiting parasite growth by 50% (IC_{50}) after a 3-day incubation period ($n = 3$). Standard (miltefosine) showed IC_{50} of 12.07 ± 0.82 μM, six compounds (shown in the shaded region) showed an IC_{50} less than the standard.

tion in the E ring (**6** and **16**) showed activity comparable to that of standard (12.35 ± 1.58 and 14.26 ± 0.33 μM) whereas those containing bulkier group like *tert*-butyl (**15**) were inactive. The cytotoxicity of the compounds was evaluated on peritoneal murine macrophages according to procedure adapted from Peyron et al.[18] with an incubation period of 72 h. The CC_{50} (cytotoxic concentrations 50%) of all compounds were more than 50 μM, indicating that the selectivity index (CC_{50}/IC_{50}) of the most active compound (**4**) was greater than 20.

In conclusion, six compounds (**4**, **5**, **10**, **11**, **19**, and **22**) showed anti-leishmanial activity that was better than the standard miltefosine and three compounds (**6**, **14** and **16**) showed activity that was comparable to standard, suggesting that this group of compounds can be further explored for getting potent anti-leishmanial compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.04.115.

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