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New antiprotozoal agents: Their synthesis and biological evaluations

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ABSTRACT

Here we report identification of new lead compounds based on quinoline and indenoquinolines with variable side chains as antiprotozoal agents. Quinolines **32**, **36** and **37** (Table 1) and indenoquinoline derivatives **14** and **23** (Table 2) inhibit the in vitro growth of the *Trypanosoma cruzi*, *Trypanosoma brucei*, *Trypanosoma brucei rhodesiense* subspecies and *Leishmania infantum* with IC_{50} = 0.25 μM. These five compounds have superior activity to that of the front-line drugs such as benznidazole, nifurtimox and comparable to amphotericin B. Thus these compounds constitute new 'leads' for further structure–activity studies as potential active antiprotozoal agents.

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Neglected tropical diseases (NTD)[1] include Chagas' disease (American trypanosomiasis[2]), human African trypanosomiasis HAT (sleeping sickness)[3] and leishmaniasis.[4] These are parasitic diseases caused by the parasitic protozoan's *Trypanosoma cruzi* (*T. cruzi*), *Trypanosoma brucei* (*T. brucei*) and *Leishmania* species, respectively. It is a serious health problem of today mainly in tropical countries and in Central and South American continent causing two million deaths per year.[5,6] The present treatment is not very effective in the chronic phase and has toxicity, side effects[7–15] and parasite resistance.[10–12,16–21]

Thus, there is a considerable potential in developing novel approaches for antitrypanosoma and antileishmania drugs. Molecular modeling,[22] enzymatic[23] and crystallographic studies[24] on tipifarnib (**1**, EC_{50} = 4 nM, Fig. 1) and its analogues (compounds **2** and **3**)[22,25–27] have shown role of quinoline and side chain in its biological activity. In these studies, the X-ray structure of cocrystal of compound **2** with *T. brucei* CYP51, has elegantly shown that the quinolone together with its imidazole ring side chain was coordinated with heme iron whereas the phenyl ring attached to quinolone occupying an additional CYP51 active-site cavity. Qunoline as a pharmacophore against *T. brucei* and *T. cruzi* is also interesting because tafenoquine (**3**, Fig. 1) is known to act on unique target such as cytochrome *c* reductase. As a part of our research project on antitubercular drug discovery, we have screened a library of 39 compounds based on a quinoline and indenoquinolines with various side chains for antiprotozoal activity, which have also shown anti-TB activity.[28–32] We have thus identified five compounds (**14**, **23**, **32**, **36** and **37**) that have shown excellent in vitro antitrypanosomal and antileishmanial activity as low as IC_{50} = 0.25 and 0.40 μM, respectively, which is superior to frontline drugs benznidazole[33] (IC_{50} = 3.66 μM), nifurtimox[34] (IC_{50} = 1.8 μM) and comparable to amphotericin B[35] (IC_{50} = 0.25 μM). The diverse structures of these active compounds further suggest that both quinoline and side chain variations are important for antiprotozoal activity.

Following the literature procedures compound **6** was prepared through functionalization of 4-OH of 6-bromo-2-(trifluoromethyl)quinolin-4-ol, **4**[36] (Scheme 1). Compound **4** was brominated by using PBr_3 in DMF to give 4,6-dibromo compound **5**[37] which was treated with strong base LDA followed by benzaldehyde in dry THF to obtain the desired compound **6**. To achieve the target compound **9** (Scheme 2), compound **7**[29] was treated with *m*-(trifluoromethyl) benzene sulfonyl chloride in presence of dry pyridine to give sulfonamide **8**. Carbonyl group of sulfonamide **8** was reduced by $NaBH_4$ to give hydroxy derivative **9**. To accomplish the synthesis of compounds **11**, **12**, **14** and **15** (Scheme 3),

Abbreviations: CC_{50}, concentration of inhibitor resulting in 50% parasite growth inhibition; DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EDC·HCl, 1-ethyl-3-(3-dimethyllaminopropyl)carbodiimide hydrochloride; Et_3N, triethylamine; EtOH, ethanol; MeOH, methanol; IC_{50}, concentration of inhibitor resulting in 50% inhibition; SI, Ratio of CC_{50} value/IC_{50}; NMR, nuclear magnetic resonance; SAR, structure–activity relationship; PFT, protein farnesyltransferase; PPA, polyphosphoric acid.

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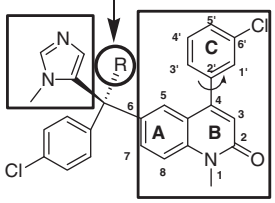
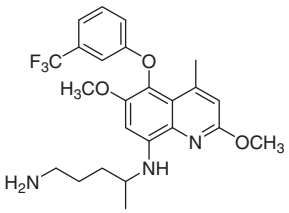
R = NH_2 binds to mammalian PFT *via* farnesyl diphosphate
R = OCH_3 binds to *T.cruzi* 14DM



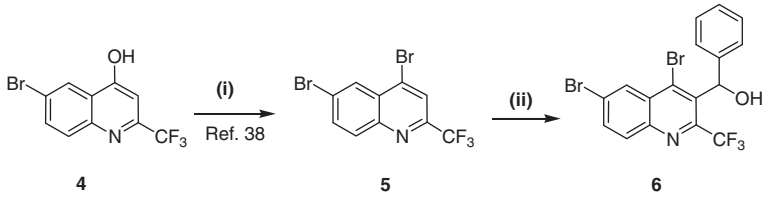
1: R = NH_2, Tipifarnib (EC_{50} = 4 nM) *T. cruzi protein farnesyltransferase (PFT); human (hPFT* IC_{50}= 0.7 nM)

2: R = OCH_3 (EC_{50} = 0.6 nM) *T. cruzi (PFT); human (hPFT* IC_{50}>5000 nM)

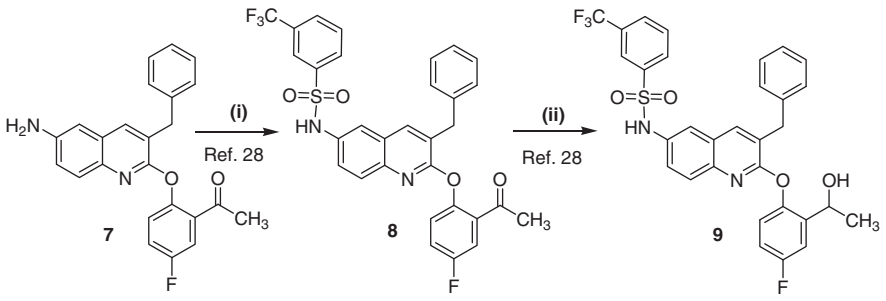


3: Tafenoquine (IC_{50} = 5.6 μM) against *L. donovani* *Target: mitochondrial dysfunction through cytochrome c reductase*

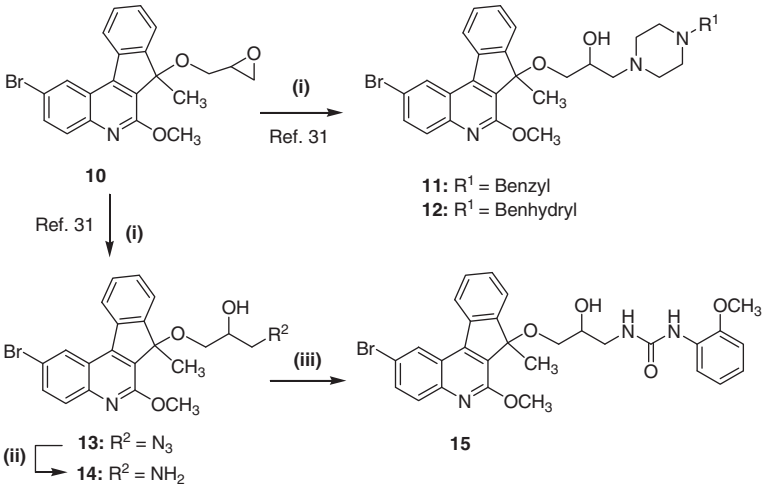
Figure 1. Quinoline based antiparasitic lead molecules (**1**–**3**) under clinical trials.



Scheme 1. Reagents and conditions: (i) dry DMF, PBr_3 at 0 °C then at rt, 4 h, 82%; (ii) LDA, dry THF, 30 min, PhCHO, −78 °C, 2 h, 16%.



Scheme 2. Reagents and conditions: (i) 3-(trifluoromethyl)benzene-1-sulfonyl chloride, dry pyridine, rt, 12 h, 54%; (ii) $NaBH_4$, EtOH–THF (2:1, 6 mL), rt, 2 h, 53%.



Scheme 3. Reagents and conditions: (i) *iso*-propanol, 1-benzyl piperazine for **11**, 1-benzhydryl piperazine for **12**, and NaN_3 for **13**, reflux, 12 h, (**11**, 26%; **12**, 27% and **13**, 61%); (ii) dry THF, PPh_3, reflux, 15 h, 58%; (iii) dry DCM, 2-methoxyphenyl isocyanate, dry Et_3N, 0 °C–rt, 1 h, 9%.

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