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Synthesis, antileishmanial activity and docking study of *N′*-substitutedbenzylidene-2-(6,7-dihydrothieno[3,2-*c*] pyridin-5(4*H*)-yl)acetohydrazides

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ABSTRACT

A series of *N′*-substitutedbenzylidene-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetohydrazide derivatives is synthesized and evaluated for antileishmanial activity against *Leishmania donovani* promastigotes. Compounds **9a** and **9i** were shown significant antileishmanial when compared with standard sodium stilbogluconate. Antimicrobial study revealed that compound **9b** has potent as well as broad spectrum antibacterial activity when compared with ampicillin and compound **9e** showed promising antifungal activity when compared with miconazole. Also, none of the synthesized compounds showed cytotoxicity up to tested concentration. Further, docking study against pteridine reductase 1 enzyme of *L. donovani* showed good binding interactions. ADME properties of synthesized compounds were also analyzed and showed potential to develop as good oral drug candidates.

Leishmaniasis is a group of diseases caused by infection with intracellular species of the parasitic protozoan of the genus *Leishmania* with different clinical forms ranging from cutaneous leishmaniasis (CL) with skin lesions to visceral leishmaniasis (VL) with enlargement of liver, spleen, and bone marrow dysfunctions. According to the World Health Organization, leishmaniasis is an uncontrolled tropical disease with high morbidity and mortality rates in Africa, Asia, and the America.[1] The drugs currently in use are expensive, require long term treatment,[2] display high liver and heart toxicities, develop clinical resistance after few weeks of treatment and currently contribute to increase leishmaniasis-AIDS co-infections in some countries[3,4] and hence there is a need for new antileishmanials with improved efficacy and less side effects. Also, there are several classes of antimicrobial agents are available and used for clinical treatment, their advances in medical care are threatened by a natural phenomenon known as 'drug resistance'.[5,6] This has created an urgent need to devote our continuous efforts for the discovery and development of new antimicrobials with broader spectrum of activity and lower toxicity.[7,8]

Thieno[3,2-*c*]pyridine compounds are known to possess diverse range of pharmacological activities such as antimicrobials,[9–13] antiarrhythmic activity,[14] antiplatelet agent[15] and antidiabetic activity.[16] Compounds containing acetohydrazide group are reported to posses various pharmacological activities like antimicrobial,[17–21] anticancer,[22,23] anticonvulsant[24,25] and antileishmanial.[26] To reduce the economical burden of developing new antileishmanial drugs from scratch and limited understanding of leishmanial biology, a current strategy is to study drugs known to possess anti-infective activity.[27,28] Many leishmanicidal drugs in distinct phases of development are derived from this approach, including some in current clinical use such as the amphotericin B[29] (antifungal) and paromomycin[30] and sitamaquine[31] (antibacterial). Structures of some anti-infective agents bearing thieno[3,2-*c*]pyridine ring and acetohydrazide chain reported in literature are presented in Figure 1.

Taking into account all of the aforementioned and due to the urgent need for innovative drugs based on new molecular scaffolds, and as an extension of our earlier work on thieno[3,2-*c*]pyridine derivatives[9,10] and the increased interest on new antileishmanial agents due to the lack of effective drugs, we decided to synthesize and test the efficiency of *′N′*-substitutedbenzylidene-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetohydrazides **9**(**a**–**j**) for antimicrobial and antileishmanial activity. The computational parameters like docking study for

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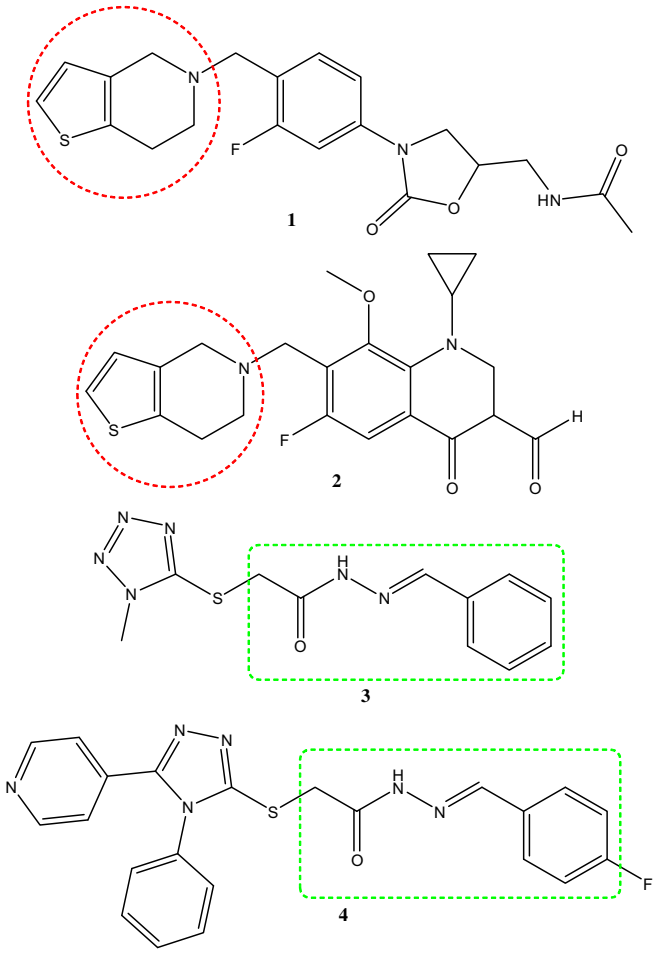


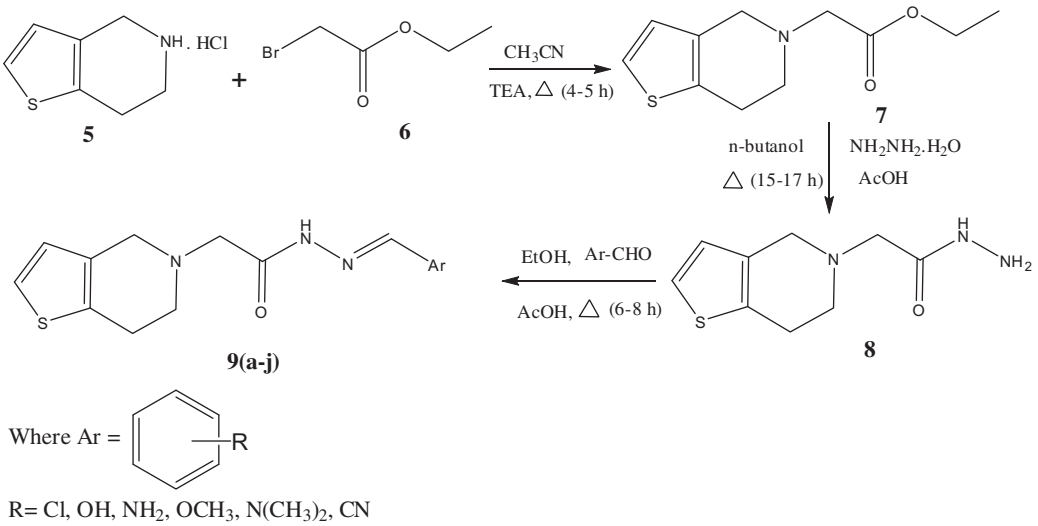
Figure 1. Structures of some anti-infective agents reported in literatures **1**–**4**.

antileishmanial and ADME prediction of synthesized compounds were also performed. The results suggest that the compound could be exploited as an antileishmanial drug.

The synthetic protocols employed for the synthesis of *N*′-substitutedbenzylidene-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetohydrazides **9**(**a**–**j**) are presented in Scheme 1. The ethyl-2(6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-yl)acetate (**7**) was obtained via reaction of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine hydrochloride (**5**) with ethyl-2-bromoacetate (**6**) using triethyl amine as catalyst. Ethyl-2(6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-yl)acetate (**7**) was reacted with hydrazine hydrate to give the compound 2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetohydrazide (**8**).[9]

Further, to expand the series, *N*′-substitutedbenzylidene-2-(6,7-dihydrothieno[3,2-*c*]pyridin-5(4*H*)-yl)acetohydrazides **9**(**a**–**j**) were prepared reacting the compound (**8**) with various substituted aromatic aldehydes in ethanol using glacial acetic acid as catalyst. The physical data of the synthesized compounds are presented in Table 1. All the reactions proceeded well in 6–8 h to give products in very good yields (74–90%). The purity of the synthesized compounds was checked by TLC and melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus and are uncorrected. All synthesized derivatives **9**(**a**–**j**) were characterized using IR, ^{1}H NMR, ^{13}C NMR and Mass spectra.

The title compounds **9**(**a**–**j**) were tested for their in vitro antileishmanial activity against a culture of *Leishmania donovani* promastigotes (NHOM/IN/80/DD8). Parasite viability was evaluated using a modified 3-(4,5-dimethylthiazol-2 yl)-2,5-diphenyl tetrazolium bromide (MTT) assay wherein the amount of formazan produced is directly proportional to the number of metabolically active cells.[32] The concentration that decreased cell growth by 50% (IC_{50}) was determined by graphic interpolation and data obtained depicted in Table 2. Sodium stibogluconate and pentamidine were used as standard drugs. Compounds **9**(**a**–**j**) showed varying degrees of antileishmanial activities with IC_{50} ranging between 93.75 and 265 μg/mL. Amongst all tested compounds **9a** and **9i** were found to be most promising compounds showing IC_{50} value of 98.75 μg/mL and 93.75 μg/mL, respectively when compared with sodium stilbogluconate. All the synthesized compounds showed better activity than standard sodium stibogluconate (IC_{50} = 490 μg/mL) against *L. donovani* promastigotes. Structure activity relationship revealed that the activity mainly depends upon the presence of substituent on phenyl ring. If we compare the activity of most active member of the series, compounds with 2-chloro **9a** and 4-*N*,*N*-dimethylamino substituted phenyl ring **9i** showed significant antileishmanial activity against *L. donovani* promastigotes. Introduction of 4-chloro **9b** or 2,6-dichloro **9c** on phenyl ring showed decrease in activity. Substitution of methoxyl group on various position of phenyl ring contributed no significant



Scheme 1. Synthetic protocol for title compounds.