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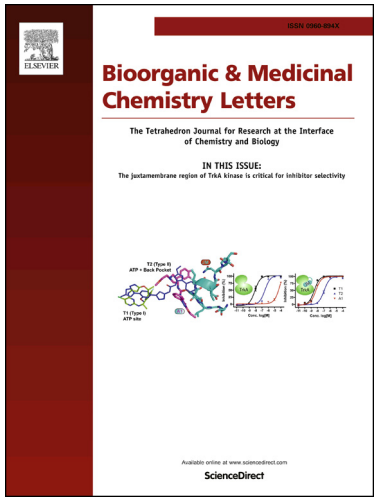

Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and *in silico* physico-chemical properties

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Anti-leishmanial and cytotoxic activities of amino acid-triazole hybrids: Synthesis, biological evaluation, molecular docking and *in silico* physico-chemical properties

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ABSTRACT

According to WHO, leishmaniasis is a major tropical disease, ranking second after malaria. Significant efforts have been therefore invested into finding potent inhibitors for the treatment. In this work, eighteen novel 1,2,3-triazoles appended with *L*-amino acid (Phe/Pro/Trp) tail were synthesized via azide-alkyne click chemistry with moderate to good yield, and evaluated for their anti-leishmanial activity against promastigote form of *Leishmania donovani* (Dd8 strain). Among all, compounds **40**, **43,** and **53** were identified with promising anti-leishmanial activity with IC_{50} = 88.83 ± 2.93, 96.88 ± 12.88 and 94.45 ± 6.51 μM respectively and displayed no cytotoxicity towards macrophage cells. Moreover, compound 43 showed highest selectivity index (SI = 8.05) among all the tested compounds. Supported by docking studies, the lead inhibitors (**40**, **43** and **53**) showed interactions with key residues in the catalytic site of trypanothione reductase. The results of pharmacokinetic parameters suggest that these selected inhibitors can be carried forward for further structural optimization and pharmacological investigation.

Leishmaniasis is poverty related most neglected zoonotic disease worldwide caused by protozoan parasites of the genus *Leishmania* and spread by the bite of infected female phlebotomine sandflies. Leishmaniasis is endemic in 98 countries placing 350 million people at risk. An estimated 0.9 –1.3 million new cases and 20 – 30 thousand deaths occur annually with many cases going undiagnosed. Three main forms of leishmaniasis – visceral (also known as kala-azar), cutaneous, and mucocutaneous are observed. Of these, visceral leishmaniasis (VL) is fatal if left untreated, is endemic in the Indian subcontinent and in East Africa. An estimated 0.2 to 0.4 million new cases of VL occur worldwide each year.[1-2]

Leishmaniasis control mainly depends on chemotherapy (Figure 1). The first-line therapy for leishmaniasis include pentavalent antimonial drugs like sodium stibogluconate (pentostam) and meglumine antimoniate (glucantime) being used for the last five decades. Unfortunately, about 60% of VL cases in India alone become un-responsive to pentavalent antimonial due to developed resistance.[3] Polyene antifungal drug amphotericin B, in spite of its adverse effects is the drug of choice where resistance to pentavalent antimonial is developed. Usefulness of second-line drugs such as paromomycin and pentamidine has been restricted.[4] Miltefosine (hexadecylphosphocholine [HePC]), an alkyl phosphocholine originally developed as anticancer agent, is widely used as an anti-leishmanial drug as it has a good oral profile,[5,6] causes apoptotic death[7] and exhibits activity against various *Leishmania* species.[8] However, toxicity, appearance of drug resistance and the relapse of the disease in some cases, even after 10 months of a full course of treatment with miltefosine[9] prompted health researchers to search for novel, safe and effective anti-leishmanial agents. In this regard, several studies with heterocyclic compounds as anti-leishmanial agents have been reported in the literature.[10-14] 1,2,3-triazoles flanked on each side by two randomized amino acids (peptidotriazoles) against *L. mexicana* cysteine protease has also been reported (Fig.1).[15] Peptidic compounds are susceptible to hydrolysis. However, the combination of peptides with rigid and hydrophobic molecular moieties can alter this process. Peptide based small molecules