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Abstract

Biological Evaluation of Arylamine Mannich Base Derivatives with Potent In Vivo Activity as Potent Antichagasic Agents †

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Chagas disease (CD) is a neglected tropical disease caused by the parasite *Trypanosoma cruzi* [1]. About 6–7 million people are infected worldwide, mainly in Latin America [1]. Benznidazole and Nifurtimox are the only available drugs for this disease but the problems with those drugs are related to their variable antiparasitic activity, the undesired side effects and long treatment duration among others [2]. Therefore, there is a great need for the development of new, effective, safe and affordable drugs for the treatment of CD.

In this context, our group is focused on identifying new agents to fight against CD. So, twenty new derivatives were synthetized and tested in epimastigote, amastigote and trypomastigote forms in three different *T. cruzi* strains (SN3, Arequipa and Tulahuen). The cytotoxicity was also determined to establish their selectivity index (SI). The lead compound showed in vitro SI ranging from 99 to 258 times higher than Benznidazol in the amastigote form and from 333 to 2810 in the trypomastigote form of the parasites. The tested compounds in the SOS/umu screening test were non-genotoxic, whereas the reference drugs showed genotoxicity in the tested conditions. Regarding the studies of their mechanism of action, it seems that this family could be inhibitors of the Fe-SOD exclusive antioxidant defense trypanosomatids.

According to their in vitro biological activity and preliminary toxicological studies, four out of twenty derivatives were selected for an in vivo assay in a murine mice model. The in vivo acute model showed that the compounds decrease the parasitemia from the beginning of the treatment and parasites were not detected from day 25 post-infection. Moreover, none of the compounds showed reactivation after immunosuppression with the dose used with the reference drug (100 mg/kg) and the lead compounds showed no reactivation also at 50 mg/kg [3].

Considering the in vivo results, three out of four derivatives were selected for their mutagenicity evaluation and were non-mutagenic in the Ames test. Moreover, the absorption, distribution, metabolism, and excretion (ADME)/Tox and Pharmacokinetic (PK) evaluations are ongoing and the results will be presented in this congress.

Up to now, these results have encouraged us to propose these compounds as promising molecules for developing new anti-Chagas agents and they will be transferred to an in vivo bioluminescence model in collaboration with the London School of Hygiene and Tropical Medicine.

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