Design, Synthesis, and Biological Evaluation of Thiophene-Acridine Derivatives as Potential Anti-Leishmanial Agents

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ABSTRACT

Background: Leishmaniasis is an infectious disease caused by parasites and treated with antiprotozoal agents that cause serious side effects **Objectives**: This study proposes the development of new drugs, thiophene-acridine derivatives, by non-classical bioisosterism to treat leishmaniasis. **Methods:** Organic synthesis was performed through the *Gewald reaction*, both in a full and convergent way, The ACS series, sourced from the LSVM library, contains a thiophene ring linked to an acridine core with OCH_3 and Cl substitutions. The MAL series, derived by molecular simplification, lacks these substituents on the acridine ring. The compounds had structural elucidation by FTIR, MS, and NMR. After structural identification, *in vitro* cytotoxicity assays were performed using the MTT method in J774 cells, followed by the evaluation of the leishmanicidal potential in the promastigote and amastigote forms of *Leishmania amazonensis*. Also, the best selectivity profiles were identified. In parallel, we evaluate Th_1, Th_2 responses and the expression of reactive oxygen and nitrogen species in macrophages infected with *L. amazonensis*. **Results and discussion**: The MAL synthesis yielded values ranging from 81.54% to 91.95%. Cytotoxicity profiles for the ACS and MAL series ranged from 15.76 to 31.24 µM and 37.40 to 50.55 µM, respectively. The ACS series exhibited antileishmanial activity against promastigotes (IC50 = 2.95–6.02 µM) and amastigotes (IC_{50} = 4.00–25.47 µM) with selectivity indices between 0.62 and 6.58. The MAL series showed IC_{50} values of 9.56–9.98 µM and 27.44 –35.93 µM against promastigotes and amastigotes, respectively, with selectivity indices between 0.94 and 1.63. Despite the ACS series potential, the MAL series was selected for further study due to its novelty, action against promastigotes, immunomodulatory profile, and better cytotoxicity. Then, cell viability studies were performed using Annexin-PI, and it was observed that none of the molecules exhibited cytotoxic profiles against J774 macrophages, corroborating the results obtained in MTT. Finally, studies related to the immunomodulatory profile analyzed the expression of ROS, NOS and cytokines related to the Th_1 and Th_2 response. High secretion of nitric oxide and ROS was obtained, as well as an immunomodulatory profile based on the increase in IL-2, INF-γ and a discrete action by TNF-α followed by the reduction of IL-4 and IL-10 cytokines, with MAL 3 being the best candidate, as it acted at the lowest concentrations. **Conclusion:** MAL3 is listed as a potential molecule for the treatment of *L. amazonensis* infection due to its best immunomodulation profiles, presenting the highest selectivity index among the MAL series.