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SULFONE-MODIFIED AMIDOXIMES AS POTENTIAL ANTILEISHMANIAL AGENTS AGAINST *LEISHMANIA AMAZONENSIS*

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Abstract

Current treatments for leishmaniasis rely on a limited therapeutic arsenal associated with severe side effects, resistance, and therapeutic failure. Therefore, the search for new therapies is essential. Our research group has been investigating the antileishmanial effects of various amidoxime derivatives, as these compounds can function as drugs or prodrugs due to their reduction to amidines and subsequent transformation by multiple enzymes into amides, leading to the release of NO. Additionally, amidoximes exhibit better bioavailability compared to amidines. These modifications were designed to enhance the physicochemical properties of these compounds. In this study, six derivatives (OSC series) were synthesized, allowing substitutions primarily at position 2 of the 4,5-dihydrofuran scaffold, for comparison with *4-(5-benzyl-3-(4-fluorophenyl)sulfonyl)-5-methyl-4,5-dihydrofuran-2-yl)-N'-hydroxybenzimidamide*, our HIT compound. At position 2, ortho-nitrobenzamide, picolinamide, N'-hydroxy-2-nitrobenzimidamide, and N'-hydroxypicolinimidamide were evaluated. Positions 3 and 5 were modified by introducing a pyridine moiety (OSC151, OSC258). Antileishmanial activity was assessed in *Leishmania amazonensis* promastigotes, with IC_{50} values ranging from 7.4 to 39.7 µM. Among the tested derivatives, OSC151 (IC_{50} = 30.7 ± 3.3 µM) and OSC258 (IC_{50} = 39.7 ± 9.6 µM) exhibited lower activity, suggesting high sensitivity to pyridine modifications at positions 3 and 5, which reduced efficacy compared to the HIT compound. Conversely, OSC260 (IC_{50} = 11.8 ± 1.3 µM), OSC275 (IC_{50} = 9.4 ± 0.6 µM), and OSC276 (IC_{50} = 11.3 ± 1.6 µM), which involved modifications at position 2, showed comparable activity. Notably, the picolinamide derivative OSC272 (IC_{50} = 7.4 ± 0.9 µM) was the most active in this series. Further studies will be conducted to evaluate the activity of these derivatives in intracellular amastigotes and to elucidate their structure-activity relationship and mechanism of action.

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