Synthetic oxoisoaporphine alkaloids: in vitro, in vivo and in silico assessment of antileishmanial activities.

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Leishmaniasis is a growing health problem worldwide. As there are certain drawbacks with the drugs currently used to treat human leishmaniasis and resistance to these drugs is emerging, there is a need to develop novel antileishmanial compounds, among which isoquinoline alkaloids are promising candidates. In this study, 18 novel oxoisoaporphine derivatives were synthesized and their possible antileishmanial activity was evaluated. The in vitro activity of these derivatives against Leishmania amazonensis axenic amastigotes was first evaluated, and the selected compounds were then tested in an inhibition assay with promastigotes of L. infantum, L. braziliensis, L. amazonensis and L. guyanensis, and with intracellular amastigotes of L. infantum and L. amazonensis. Finally, the most active compounds, OXO 1 (2,3-dihydro-7H-dibenzo[de,h]quinolin-7-one) and OXO 13 (2,3,8,9,10,11-hexahydro-7H-dibenzo[de,h]quinolin-7-one), were tested in BALB/c mice infected with L. infantum. Treatment of mice at a dose of 10 mg/kg with OXO 1 yielded significant reductions ($p<0.05$) in parasite burden in liver and spleen (99% and 78%, respectively) whereas with OXO 13 were not significant. Although previous reports suggest that this family of molecules displays

inhibitory activity against monoamine oxidase A and acetylcholinesterase, these enzymes were not confirmed as targets for antileishmanial activity on the basis of the present results. However, after development of a new bioinformatics model to analyze the Leishmania proteome, we were able to identify other putative targets for these molecules. The most promising candidates were four proteins: two putative pteridine reductase 2 (1MXF and 1MXH), one N-myristoyltransferase (2WUU) and one type I topoisomerase (2B9S).