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SYNTHESIS AND LEISHMANICIDAL ACTIVITY OF CINNAMIC ACID ESTERS: STRUCTURE-ACTIVITY RELATIONSHIP

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BACKGROUND

Leishmaniasis is a major health problem that affects approximately 12 million people worldwide, with 2 million new cases diagnosed every year (3). Caffeic acid (1), 3,4-dihydroxy cinnamic acid, and its esters derivatives exhibit a broad spectrum of biological activities, including leishmanicidal activity (1,5).

OBJECTIVE

In the search for active compounds with low toxicity for the treatment of leishmaniasis seventeen cinnamic acid esters were synthesized via Fischer esterification of cinnamic acid derivatives with aliphatic alcohols (2) and their antileishmanial and cytotoxic activity were determined against Leishmania (Viannia) panamensis amastigotes and mammalian U-937 cells, respectively, following the method previously reported in the literature (4-8).

RESULTS

Eight compounds were active against intracellular parasites with EC_{50} of 2.9, 3.2, 10.4, 12.3, 18.3, 25.2, 26.5 and 60.2 µg/ml, and although toxic for mammalian cells, 6.7, 9.9, 10.4, 25.5, 28.5, 49.7, 69.1 and 85.3 µg/ml, respectively, they still are potential candidates for antileishmanial drug development. A SAR analysis indicates that first, while smaller alkyl chains lead to higher selectivity indices; second, the degree of oxygenation is essential for activity, primarily in positions 3 and 4; and third, hydroxyl groups increase both activity and cytotoxicity. On the other hand, the presence of a double bond in the side chain is crucial for cytotoxicity and leishmanicidal activity.

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CONCLUSION

However, further studies are required to optimize the structure of the promising molecules and to validate the *in vitro* activity against Leishmania demonstrated here with *in vivo* studies.

Keywords Leishmaniasis, antiprotozoal, caffeic acid, cinnamic acid ester.

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