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Synthesis and biological evaluation of novel piperidine-benzodioxole derivatives designed as potential leishmanicidal drug candidates

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ABSTRACT

A novel series of ester and carbamate derivatives was synthesized and evaluated its activities against *Leishmania amazonensis*. All compounds exhibited weaker leishmanicidal activity than amphotericin B. However, results indicated that substituents on the aryl–acyl subunit are important for modulation of the leishmanicidal effect. The nitro derivative showed the highest activity of the series with an IC_{50} = 17.24 μM, and comparable potency to the 3,4-benzodioxole ester and *n*-hexyl carbamate derivatives. All compounds showed low toxicity against human cells. These results revealed interesting novel piperine-like molecular pattern for exploitation in search and development of effective and low toxic antileishmanial drug candidates.

Leishmaniasis is a parasitosis caused by protozoans of the *Leishmania* genus. As the major of parasitosis affecting human beings, leishmaniasis is considered a neglected disease and its occurrence is more common in underdeveloped countries or those with poor efforts in healthful politics, located in tropical and subtropical regions of the globe.[1,2] It is considered the second main cause of death among parasitic diseases caused by protozoa, falling behind only with malaria. New estimated cases, per year, is not certain and it is considered that the number of cases range from approximately 0.9 million to 1.6 million for cutaneous and visceral leishmaniasis worldwide.[3]

The disease is transmitted by *Leishmania*-infected sandflies, and could exhibit a broad spectrum of diseases including visceral (VL), cutaneous (CL) and mucocutaneous leishmaniasis (MCL). In VL, also known as Kalaazar, the most severe form of the disease, the patient is infected by parasites of *Leishmania donovani* complex, and is commonly fatal in the absence of an adequate treatment. *L. major*, *L. donovani*, *L. tropica*, *L. aethiopica* and *L. amazonensis* are the *Leishmania* species responsible for CL, whereas *L. braziliensis* is the etiologic agent for mucocutaneous leishmaniasis.[4,5] The current available treatment is restricted to few drugs of first choice as pentavalent antimonials, as miltefosine, amphotericin B with its derivatives and paromomicine. The main problem of conventional treatment is the intrinsic or acquired resistance by the protozoan. Other restrictions related to the available medicines are high incidence of adverse effects and toxicity.[6] The clinic symptoms are diverse, being associated to antigenic differences among the *Leishmania* species, despite host genetic and immunologic factors.[7–9]

Discovery and development of novel effective and lower toxic drug candidates remain a challenge for medicinal chemists. During the last decade, many studies have evidenced the pharmacological potential of natural products as drugs or structural models for drug design. Piperine (**1**, Fig. 1), for example, is an abundant piperidine alkaloid with a marked wide profile of biologic and pharmacologic activities,[10] including anti-inflammatory,[11] blockade of skeletal neuromuscular depolarization,[12] antimicrobial[13] and antifungal.[14] In addition, pharmacological studies revealed the in vitro inhibitory activity of piperine against Trypanosomatidae, such as *Leishmania*[15] and *Trypanosoma*[16] species. Some others structurally related piperidine derivatives have also shown leishmanicidal activity against *L. amazonensis*[17] and *L. donovani*.[18]

In a continuous search for new antileishmanial drug candidates, we elected the structure of piperine (**1**, Fig. 1) as a model for the design of a new series of piperidine-benzodioxole derivatives

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