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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, protease inhibition, and antileishmanial activity of new benzoxazoles derived from acetophenone or benzophenone and synthetic precursors

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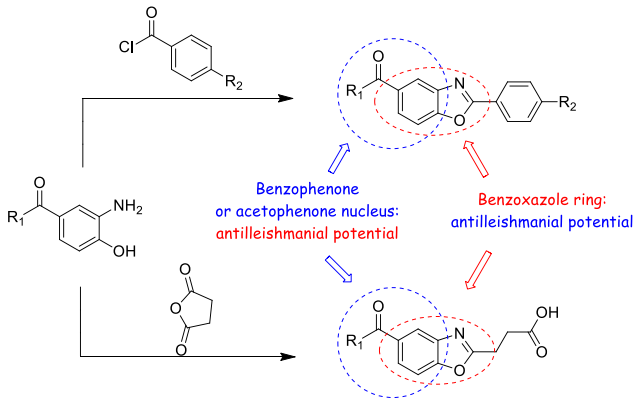
Abstract This work reports the synthesis, protease inhibition, and antileishmanial activity of ten benzoxazole derivatives, which were obtained in a three-step synthetic route from 4-hydroxy-acetophenone and 4-hydroxy-benzophenone. These benzoxazoles, the synthetic intermediates, and the starting ketones were evaluated for their inhibitory effect on the activity of cysteine (papain, rCPB2.8, and rCPB3.0) and serine (trypsin) proteases. All compounds showed significant values of IC_{50} against these enzymes (in the range of 0.0086–0.7612 μM for papain and 0.0075–0.5032 μM for trypsin), being more active than the standard inhibitors (1.7821 and 7.2318 μM, for E64 and TLCK, respectively). Following, all compounds were evaluated in vitro for their leishmanicidal activity against promastigote form of *Leishmania amazonensis*. The most active compounds were further evaluated against amastigote form and for its toxicity against murine macrophages. The benzoxazole **4d**, a benzophenone derivative, and the intermediate 4-hydroxy-3-nitroacetophenone **2b** showed significant antileishmanial activity ($IC_{50} = 90.3$ μM and $IC_{50} = 130.9$ μM, respectively) with selectivity indexes (5.22 and 18.09, respectively) compared to or better than those of two established leishmanicidal drugs, pentamidine (0.58) and amphotericin B (5.31).

Graphical Abstract



Keywords *Leishmania amazonensis* · Benzophenone · Acetophenone · Benzoxazoles · Proteases · Antiproteolytic activity

Introduction

Leishmaniosis is a group of infectious diseases caused by many protozoa of the genus *Leishmania*, which are transmitted to humans and small mammals by more than 30 different species of phlebotomine sandflies (Phillips and Stanley 2011). This disease can manifest as the less severe cutaneous form or as the lethal visceral form (Eschenlauer et al. 2009). According to the World Health Organization,

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