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Synthesis and biological evaluation of chalcones as potential antileishmanial agents

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ABSTRACT

Antileishmanial activities of thirty-five synthetic chalcones have been examined. Among them, ten compounds (**4**, **6**, **16**, **22**, **23**, **24**, **25**, **29**, **35** and **37**) exhibited potent in vitro activity (IC_{50} range from 1.70 to 8 μM) against extracellular promastigotes and intracellular amastigotes form of *Leishmania donovani*. Two promising compounds **22** and **37** were tested in vivo in *L. donovani*/hamster model. Chalcone **37** showed 83.32% parasite inhibition at a dose of 50 mg/kg for 10 days whereas, 75.89% parasite inhibition at 100 mg/kg dose for 5 days by intraperitoneal route at day 7 post-treatment.

1. Introduction

Leishmaniasis is a group of disease transmitted by the bite of *Leishmania*-infected female sand flies. It is classified as cutaneous, muco-cutaneous and visceral leishmaniasis (VL) depending on the parasite species and cellular immune system of the patient [1,2]. This disease has been recognized as an increasing health problem worldwide by the World Health Organization (WHO) [3]. Many parts of Asia and Africa are vulnerable to leishmaniasis [4]. The first line treatment options for the visceral form of leishmaniasis are limited and involve the administration of pentavalent antimonials (sodium stibogluconate (SSG) and meglumine antimoniate) and amphotericin B [5]. Second line drugs include, pentamidine, paromomycin and miltefosine, but these drugs have not experienced widespread use due to the severe toxicities, parenteral administration and resistance issues [5]. Presently, more than 60% VL patients in Bihar (India) are unresponsive to the antimonials [6]. Amphotericin B and its formulations are quite effective for VL; however, these are very expensive, highly toxic and have a longer half-life [7]. Pentamidine presents several side effects, including renal and hepatic toxicities, pancreatitis, hypotension and cardiac abnormalities [8]. Paromomycin has limited use for the treatment of VL [7]. Miltefosine, an orally effective drug also suffers from nephrotoxicity, hepatotoxicity and teratogenicity [7]. So far, no vaccine has been clinically approved for human use [9]. Therefore, there is an urgent need for the development of new, low-cost, effective and safe drugs for the treatment of VL. The discovery of new lead compounds for this disease is a pressing concern for global health programs. In this respect, several synthetic or natural plant/marine product inspired compounds have shown promising efficacy for the treatment of visceral leishmaniasis [10].

Chalcones, or 1,3-diaryl-2-propen-1-ones (Fig. 1), are prominent secondary metabolite precursors of flavonoids and isoflavonoids in plants. Natural and synthetic chalcones are described in the literature with different pharmacological profiles, such as antiinflammatory [11], antibacterial [12], antiviral [13], antimalarial [14], anticancer [15], antileishmanial [16], antituberculosis [17], anti-HIV [18] and antifungal activities [19]. A thorough assessment of structural requirements for antileishmanial activities of chalcones is vital to develop and designing of novel drug like candidate [20]. Licochalcone A (II), is an oxygenated chalcone (Fig. 1), isolated from Chinese licorice, efficiently inhibits proliferation of *Leishmania donovani* and *Leishmania major* promastigotes and amastigotes in vitro by interfering with the function of the parasite mitochondria. As a part of our drug discovery program on antileishmanial agents from Indian medicinal plants, we have reported the isolation

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