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Original article

Evaluation of the leishmanicidal and cytotoxic effects of inhibitors for microorganism metabolic pathway enzymes

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ABSTRACT

Chemotherapy for leishmaniosis a neglected parasitic disease, is based on few drugs, which are toxic and present resistance issues. Efforts for the development of new therapies are essential for the control of leishmaniasis. Metabolic pathway enzymes are promising targets for new drugs against parasites. The search for effective drugs against key enzymes can take advantage of the similarities between metabolic pathways in different microorganisms trypanosomatids *Trypanosoma cruzi* and *Leishmania* and fungus *Saccharomyces cerevisiae*. In this report, leishmanicidal activity of the metabolic pathway enzymes inhibitors (IDs) of dihydroorotate dehydrogenase (DHODH), glyceraldehyde 3-phosphate dehydrogenase and cruzain-cysteine protease from *T. cruzi* and scitalona-desidratase, adenosine deaminase, succinate dehydrogenase complex II and hydroxynaphthalene reductase from *S. cerevisiae* was performed on *Leishmania amazonensis* extracellular promastigotes and amastigotes within macrophages. The most promising compound, ID195, which is a DHODH inhibitor was toxic against promastigotes and was selective for amastigotes over host cells.

1. Introduction

Leishmaniosis are a group of endemic diseases caused by the intramacrophage parasite *Leishmania*; promastigote is the lifecycle form found in the insect vector and amastigote lives in host macrophage parasitophorous vaculoles (PV) [1]. The severity of diseases varies, ranging from cutaneous or mucosal to visceral infection [2,3]. *Leishmania amazonensis* is transmitted mainly in the Amazon region and, is one of the species involved in localized and diffuse cutaneous leishmaniosis in Brazil [2,4]. The diseases are neglected by the pharmaceutical industry although chemotherapy remains the mainstream treatment for the leishmaniosis [3]. Currently there are only a few drugs for the treatment of cutaneous mucocutaneous and visceral leishmaniosis. Organic salt of pentavalent antimony has been the cornerstone for the treatment of all forms of leishmaniasis since the 1940s [5]. The compounds have to be given daily for at least three weeks and antimony therapy causes side effects such as weakness and myalgia, hepatotoxicity along with the most important one cardiopathy (Frezard et al.). Drug resistance is another reported problem [6]. Antimonial pentavalent is thought to act as a pro-drug that is reduced within the organism into more toxic and active SbIII, and the anti-*Leishmania* mechanism is probably related to its interaction with suphydryl containing biomolecules including thiols, peptides, proteins and enzymes [6]. Amphotericin B is a polyene antibiotic also used as a treatment for leishmaniosis since the 1960s [7] its side effects are fever chills, bone pain and renal toxicity [8]; this drug binds to ergosterol the predominant sterol in *Leishmania* but also recognizes cholesterol in human cells [9]. Aiming to decrease the adverse effects lipid formulations of amphotericin B are available, although the production is very expensive which makes their use difficult in poor countries [10]. More recently, miltefosine, an alkylphosphocholine has been used as an alternative drug for visceral leishmaniosis Nevertheless, there are disvantages to this treatment, including teratogenic effects and emergence of resistance [10,11]. In this scenario new and safe drugs are necessary to treat leishmaniosis. Yet, the discovery drug for the treatment of leishmaniosis is difficult due to several factors: the intracellular location of the parasite, the acidic pH of PV in host macrophage, and the multiple *Leishmania* species which infect humans. One strategy is to identify active low-molecular-mass ligands that modify the biological functions of

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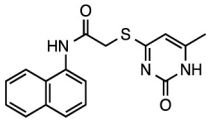
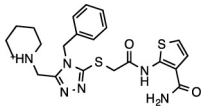
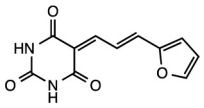
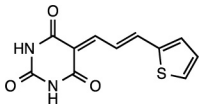
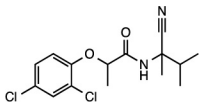
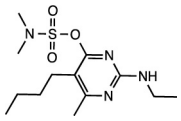
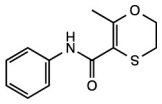
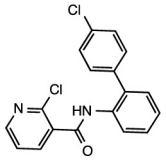
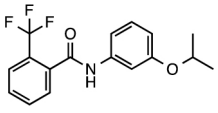
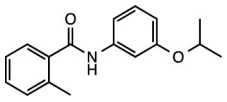
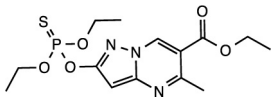
Table 1
In vitro activity of synthetic inhibitors of metabolic enzymes against *L. amazonensis* promastigotes.

Compound	Chemical structure	Enzyme target (microorganism)	IC50 (μM)[a]
ID16		Glyceraldehyde-3-phosphate dehydrogenase (*T. cruzi*)	>100
ID42		Cruzain (*T. cruzi*)	>100
ID71		Dihydroorotate dehydrogenase (*T. cruzi*)	82.30 ± 0.34
ID130		Dihydroorotate dehydrogenase (*T. cruzi*)	85.90 ± 2.30
ID185		Scitalone dehydratase (*Saccharomyces cerevisiae*)	>200
ID186		Adenosine deaminase (*S. cerevisiae*)	>100
ID187		Succinate dehydrogenase complex II (*S. cerevisiae*)	>200
ID188		Adenosine deaminase (*S. cerevisiae*)	>200
ID189		Succinate dehydrogenase complex II (*S. cerevisiae*)	>200
ID190		Succinate dehydrogenase complex II (*S. cerevisiae*)	>200
ID192		Scitalone dehydratase (*S. cerevisiae*)	>200
ID193		Hydroxynaphthalene reductase (*S. cerevisiae*)	>200