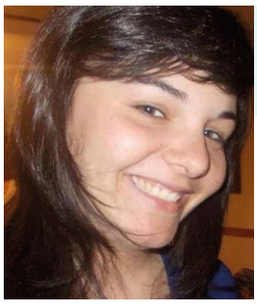

# Evaluation of the leishmanicidal activity of a series of Quinolin-4(1H)-imines

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## Abstract

Current practices to treat leishmaniasis suffer from poor efficacy and are associated with high toxicity. This induces side effects that make people discontinue treatments, leading to disease relapses and the emergence of resistant strains. Besides this, the high costs associated to most of the available therapeutic options are far from suitable for developing countries.

Searching for alternatives to current treatments, we have used a high content-based platform previously implemented in the lab to screen about 40 different compounds against intracellular amastigotes (in bone marrow-derived macrophages, BMDM). From this screening, a set of quinolin-4(1H)-imines, which were previously shown to display antiplasmodial activity [1], emerged as the most interesting family of compounds. The three most active (5P2, 7P2 and 22P2) presented half maximal inhibitory concentrations (IC50) of 0.9±0.1$\mu$M, 1.25±0.4$\mu$M and 0.7±0.2$\mu$M respectively, and selectivity indexes of 15-20 (host cell cytotoxicity evaluated also in BMDM). Interestingly, the efficiency exhibited by these compounds over intracellular amastigotes was more than tenfold superior to that observed against axenic amastigotes. We are investigating whether this occurs due to an inherent capacity of these compounds to directly activate macrophages, because the compounds are metabolized within these cells to a derivative more potent against *Leishmania* or, even, due to a metabolic alteration of intramacrophagic parasites, which become more prone to inhibition.

Quinolin-4(1H)-imines were initially designed to target mitochondrial cytochrome bc1 [1]. The observation that several of these compounds have an inhibitory effect on the basal oxygen consumption of intact *Leishmania* amastigotes suggests that their mode of action could also include inhibition of cytochrome bc1 and/or other respiratory chain enzymes. In short, this study suggests that quinolin-4(1H)-imines might be an interesting chemotype in the search of new anti-*Leishmania* leads.

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[1] a) Ressurreição, et al. *Med. Chem.* 2013, 56, 7679; b) Rodrigues, et al *Med. Chem.* 2013, 56, 4811.