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Article

Targeting the Trypanothione Reductase of Tissue-Residing *Leishmania* in Hosts' Reticuloendothelial System: A Flexible Water-Soluble Ferrocenylquinoline-Based Preclinical Drug Candidate

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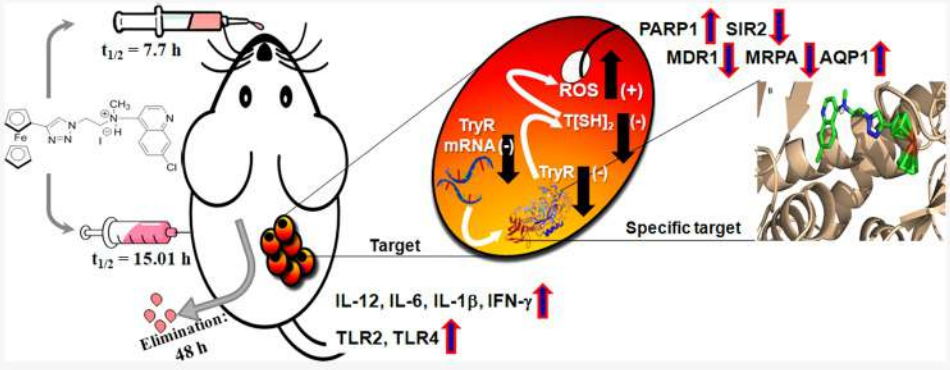

ABSTRACT: Since inception, the magic bullets developed against leishmaniasis traveled a certain path and then dropped down due to either toxicity or the emergence of resistance. The route of administration is also an important concern. We developed a series of water-soluble ferrocenylquinoline derivatives, targeting *Leishmania donovani*, among which CQFC1 showed the highest efficacy even in comparison to other drugs, in use or used, both in oral and intramuscular routes. It did not induce any toxicity to splenocytes and on hematopoiesis, induced protective cytokines, and did not hamper the drug-metabolizing enzymes in hosts. It acts through the reduction and the inhibition of parasites' survival enzyme trypanothione reductase of replicating amastigotes in hosts' reticuloendothelial tissues. Unlike conventional drugs, this molecule did not induce the resistance-conferring genes in laboratory-maintained resistant *L. donovani* lines. Experimentally, this easily bioavailable preclinical drug candidate overcame all of the limitations causing the discontinuation of the other conventional antileishmanial drugs.

INTRODUCTION

Leishmania, the protozoan parasite causing the disease complex, leishmaniases, presumably originated during the Mesozoic era and is presumed to have established its transmission worldwide along with the human migration in early ages.[1] The two subgenera *L.* (*Leishmania*) and *L.* (*Viannia*) diverged approximately 54−25 million years ago, after the geographical split of Africa from South America.[1] During the journey through this long period, adaptability in the parasites developed through genome plasticity, particularly evidenced by the differences in copy number variations (CNVs) of resistance-associated genes or chromosomes.[2] The three major clinical forms of leishmaniases are visceral leishmaniasis (VL), cutaneous leishmaniasis (CL), and mucocutaneous leishmaniasis (MCL). The global variations of *Leishmania* species and related tissue tropism are another concern as the parasitic fitness counteracts with the hosts' cellular complexity. The fitness of *Leishmania* in mammalian hosts depends on the ability of parasites to evade the host's effector mechanisms. *Leishmania chagasi* could resist the nitric oxide (NO) defense mechanism of macrophages by a simultaneous increase in parasite-specific glucose-6-phosphate dehydrogenase and the decrease in host arginase and glutathione peroxidase.[3] The fitness of *Leishmania* cumulatively turned into acquired drug resistance as evidenced by the variable expressions of enzymes linked with glucose, sterol, and trypanothione metabolic pathways and, more importantly, alteration in membrane fluidity, causing the upregulation or downregulation of certain receptors responsible for drug influx

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