Glycosylated metal chelators as anti-protozoa agents with tunable selectivity.

Sangenito, L.S[a]*.; Reddy, A[b].; Guedes, A.A[a].; Branquinha, M.H[a].; Kavanagh, K[c].; McGinley, J[d].; Santos, A.L.S[a] and Velasco-Torrijos, T[b]

* ibastefano@hotmail.com

a Department of General Microbiology, Microbiology Institute Paulo de Góes, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro, RJ, 21941-590, Brazil
b Department of Chemistry, Maynooth University, Maynooth, Co. Kildare, Ireland
c Department of Biology, Maynooth University, Maynooth, Co. Kildare, Ireland
d Department of Chemistry, University of Copenhagen, DK-2100 Copenhagen, Denmark

Abstract

Trypanosoma cruzi and *Leishmania amazonensis* are the causative agents of Chagas' disease and leishmaniasis, respectively. These conditions affect millions of people worldwide, especially in developing countries. As such, there is an urgent need for novel, efficient and cost-effective treatments for these diseases, given the growing resistance and side-effects of current therapies. This work details the evaluation of the anti-parasitic activity of novel amino- and imino pyridyl metal chelators, their glycosylated derivatives and some of their metal complexes. The library of eleven compounds was initially screened for inhibitory activity against the viability of *T. cruzi* trypomastigotes and the proliferation of *L. amazonensis* promastigotes at initial concentrations of 50 and 10 μM, respectively. The five most effective compounds against both parasites were then evaluated at appropriated concentrations. The classical drugs, Benznidazole and Amphotericin B, were also used as positive controls. Our results revealed the potent and metal-dependent activity for the amino pyridyl compounds: Cu(ii) complexes were most effective against *T. cruzi* trypomastigotes presenting an LD_{50} value of 1.7 μM, while Zn(ii) complexes presented excellent activity against *L. amazonensis* promastigotes, with as IC_{50} value of 1.3 μM. The treatment of trypomastigotes with the test compounds caused some significant morphological changes when compared to the typical appearance of non-treated parasites, including rounding in shape with reduced cell size, swelling of the cell body and shortening or loss of flagellum. In *L. amazonensis* promastigotes, the compounds induced the loss of flagellum and a reduced cell size. Further morphological alterations, such as a swelling and rounding of the cell, were also observed. In addition, the compounds showed excellent selectivity indexes and very low relative toxicity as judged by *in vitro* and *in vivo* studies, respectively, using RAW murine macrophages and *Galleria mellonella* larvae model. These preliminary studies suggest that these compounds could be extremely attractive candidates for further development as novel anti-kinetoplastid therapeutic agents.

Keywords: *Trypanosoma cruzi*, *Leishmania amazonensis*, Glycosylated metal chelators, anti-parasitic activity

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