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Comparing multifunctional Mn(I) and Re(I) tricarbonyls as potential agents against Chagas disease

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Abstract

Chagas disease (American trypanosomiasis), caused by the protozoan parasite *Trypanosoma cruzi*, is considered neglected by the World Health Organization. The absence of effective chemotherapy underscores the urgent requirement for the development of novel, potent, and non-toxic drugs. Exploring organometallic compounds has emerged as a promising strategy in the pursuit of improved and safer chemotherapy to tackle this illness. Hybridization of an organometallic center with bioactive organic ligands frequently yields antiparasitic compounds with improved biological properties compared to free ligands and efficacy against multiple parasite targets. Our recent research focuses on the development of multifunctional Re(I) tricarbonyls and their Mn(I) counterparts, namely *fac*-[$M^{I}(CO)_3(NN)(CTZ)](PF_6)$. These compounds integrate two distinct ligands, both with demonstrated activity against *T. cruzi*: a bidentate 1,10-phenanthroline derivative (NN) and the monodentate Clotrimazole (CTZ). The compounds were synthesized *via* a stepwise procedure and were thoroughly characterized. Synthetic procedure, solution stability, lipophilicity, and biological properties of both families of metal(I) tricarbonyls were compared. The impact of the compounds on the molecular targets of the free ligands, specifically DNA and CYP51 lanosterol 14-α-demethylase, was investigated. Aiming to provide insights into the compounds' effect on metabolic pathways within the parasite, metallomics and proteomics studies on *T. cruzi* were conducted for the hit compounds of both series. The whole set of results will be scrutinized to uncover the potential of Mn(I) and Re(I) tricarbonyl compounds in advancing the development of drugs targeting the parasite.

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