Multifunctional Mn(I) and Re(I) tricarbonyls as prospective antiparasitic compounds: a comparative study

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Diseases caused by the trypanosomatid parasites *Trypanosoma cruzi* and *Leishmania spp* are considered neglected by the World Health Organization. The lack of suitable chemotherapy underscores the pressing need for the development of novel, potent, and non-toxic drugs. The exploration of organometallic compounds has emerged as a promising strategy in the quest for enhanced and safer chemotherapy for addressing these illnesses. Our team has played a role in showcasing that the hybridization strategy involving an organometallic center and a bioactive organic ligand often results in antiparasitic compounds with enhanced biological properties compared to the free ligands and efficacy against multiple parasite targets. Our recent work has involved the development of five multifunctional Re(I) tricarbonyls and their Mn(I) counterparts, *fac*-$[M^{I}(CO)_3(NN)(CTZ)](PF_6)$. These compounds incorporate two distinct bioactive ligands with proven activity against *T. cruzi*: a bidentate 1,10-phenanthroline derivative (NN) and the monodentate azole Clotrimazole (CTZ).[1-3] The compounds were synthesized through a stepwise procedure starting from $[M^{I}Br(CO)_5]$ and were fully characterized. A comparative analysis of the synthetic procedure, in solution stability, lipophilicity, and biological properties of both families of metal(I) tricarbonyls was performed. Impact of the complexes on the molecular targets of the free ligands, namely DNA and CYP51 lanosterol 14-α-demethylase, was investigated. Furthermore, metallomics studies, focusing on the uptake and association with various parasite biomolecule fractions, along with proteomics analyses on *T. cruzi*, were conducted for the hit compounds *fac*-$[M^{I}(CO)_3(tmp)(CTZ)](PF_6)$, where tmp represents 3,4,7,8-tetramethyl phenanthroline. These investigations aimed to provide insights into the compounds' effect on metabolic pathways within the parasite. The whole set of results will be analyzed to shed light into the potential of Mn(I) and Re(I) tricarbonyl compounds for advancing the development of antitrypanosomatid parasite drugs.

Acknowledgments: Agencia Nacional de Investigación e Innovación (ANII, Uruguay), grants FCE_1_2019_155971 and FCE_1_2021_1_166665. CDM acknowledges ANII, grant POS_FCE_2021_1_1010807 and CAP-UdelaR.

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