Thiosemicarbazone derivatives and their metal complexes as SARS-CoV-2 main protease inhibitors

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With the breakout of the pandemic caused by the SARS-CoV-2 virus in late 2019 and early 2020, the focus on drug design for the treatment of the severe respiratory syndrome caused by this virus was prompted. The main protease (MPro) of the virus has been stablished as one of the most accepted targets for the rational design of new drugs [1]. In this work, we present a series of organic compounds previously developed by our group, and their coordination complexes. Originally, these complexes had been designed as potential antiparasitic drugs, with the focus put on the main cysteine protease of the *T. cruzi* parasite, cruzipain. The compounds have been tested in an in vitro MPro inhibition essay and several structural redesign cycles have been performed, reaching 50% inhibition concentrations (IC_{50}) in the low micromolar and nanomolar range. Molecular docking of the ligands and metal complexes was performed using GOLD software. The results allowed us to understand the role of co-ligands and substituents in the potential inhibition mechanism and to purpose different inhibition pathways as for example covalent metal – protein interactions and the relevant poses of the substrates in the active site of the MPro.

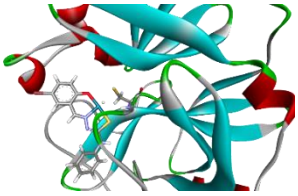

Figure 1 – Example of a docking pose of a MPro inhibitor coordination complex.

[1] L. Hong *et al.*, *Science.* **368** (2020) 1331.

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