NOVEL THIOPHENOL-THIOSEMICARBAZONES DERIVATIVES AS CRUZAIN INHIBITORS

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Chagas disease is recognized by WHO as one of the 13 most neglected tropical diseases in the world. In Latin America, Chagas disease is endemic and about 6 million to 7 million people are estimated to be infected worldwide. Cruzain is a cysteine protease present all stages of the life cycle of T. cruzi and it is essential for parasite survival, being a well validated therapeutic target. Previous works revealed that thiosemicarbazones have potential activity against T. cruzi and cruzain. This motivated us to synthesize novel anti-Chagas drug candidates which target cruzain. In this way, we synthesized a novel serie of twelve thiophenol-thiossemicarbazones with several replacements on the aromatic ring to establish a structure activity relationship (SAR) for this compound series. The compounds were evaluated against the cruzain and the enzymatic activity was measured based on the cleavage of the fluorogenic substrate Z-FR-AMC. Two molecules were active against enzyme, the 2,5-diMe-thiophenyl-thiossemicarbazones (IC50=3.3μM) and 3-Cl-thiophenol-thiossemicarbazones (IC50=19μM). Most compounds showed moderate inhibitory potential, about 50% at 100μM. No clear SAR trend was observed concerning the nature of the substituents or their position. More studies are required to establish the SAR for this serie in the search for more potent molecules against cruzain.

Keywords: cruzain, thiosemicarbazones, Chagas disease.