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Abstract

Docking Study on *T. cruzi* Trypanothione Reductase and Iron-Superoxide Dismutase Isoforms of a Series of Imidazole-Based Derivatives as an Approach towards the Design of New Potential Inhibitors †

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Chagas disease (CD) or American trypanosomiasis is a widespread parasitic disease throughout the world. It is part of the group of 17 Neglected Tropical Diseases (NTD), classified by the World Health Organization (WHO) [1]. CD is caused by the flagellate protozoan parasite *Trypanosoma cruzi* (*T. cruzi*), which is mainly transmitted to humans by the faeces of blood-sucking *Triatomine* insects. Nowadays, CD is one of the most significant health problems in Central and South America in terms of epidemiological and human health repercussions. CD is potentially lethal (12,000 deaths/year), so it involves significant socioeconomic repercussions for the concerned countries [2]. Currently, only two drugs are available to treat CD in the acute phase: Nifurtimox (NFX) and Benznidazol (BNZ). However, both of them have significant toxic effects and variable clinical efficacy during the chronic phase of CD [3]. For those reasons, there is an urgent necessity to find new compounds that are safer, more effective and more affordable than the existing ones to eradicate *T. cruzi*, preventing the progression and reducing the risk of transmission of this disease.

Despite efforts, actions and strategies by the WHO and several organizations, the research of new potential treatments against CD remains a challenge in drug discovery programmes [4]. Nowadays, one of the strategies is based on the search for molecules enabling interference with enzymes that are involved in the survival of the parasite. Thus, many enzymes have been studied and reported as potential targets for the discovery and design of new compounds for the treatment of CD [5].

Due to the intracellular nature of the parasite, it is highly sensitive to Reactive Oxygen Species (ROS), so our research group focuses on two targets that protect it against oxidative damage: trypanothione reductase (TR) and iron-superoxide dismutases (Fe-SODs) isoforms (one cytosolic and one mitochondrial). Therefore, we design and synthesize new potential inhibitors against these two targets for the therapy of CD [6]. In this context, we carried out a docking study of a new series of imidazole-based derivatives with the ability to inhibit these two exclusive targets that regulate *T. cruzi* redox metabolism.

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References

1. WHO. Neglected Tropical Diseases. Available online: http://www.who.int/neglected_diseases/diseases/en/ (accessed on 25 May 2017).
2. WHO. Chagas Disease (American Trypanosomiasis)/Fact Sheet March 2017. Available online: http://www.who.int/mediacentre/factsheets/fs340/es/ (accessed on 25 May 2017).
3. Bermúdez, J.; Davies, C.; Simonazzi, A.; Real, J.P.; Palma, S. Current drug therapy and pharmaceutical challenges for Chagas disease. *Acta Trop.* **2016**, *156*, 1–16.
4. Paucar, R.; Moreno-Viguri, E.; Pérez-Silanes, S. Challenges in Chagas Disease Drug Discovery: A Review. *Curr. Med. Chem.* **2016**, *23*, 1–17.
5. Beltrán-Hortelano, I.; Pérez-Silanes, S.; Galiano, S. Trypanothione Reductase and Superoxide Dismutase as Current Drug Targets for *Trypanosoma cruzi*: An Overview of Compounds with Activity against Chagas Disease. *Curr. Med. Chem.* **2017**, *24*, 1066–1138.
6. Moreno-Viguri, E.; Jiménez-Montes, C.; Martín-Escolano, R.; Santivañez-Veliz, M.; Martín-Montes, A.; Azqueta, A.; Jimenez_Lopez, M.; Zamora-Ledesma, S.; Cirauqui, N.; López de Cerain, A.; et al. In Vitro and in Vivo Anti-*Trypanosoma cruzi* Activity of New Arylamine Mannich Base-Type Derivatives. *J. Med. Chem.* **2016**, *59*, 10929–10945.