SYNTHESIS OF 1,2,3-TRIAZOLE NAPHTOQUINONES HYBRIDS AND EVALUATION OF THEIR TRYPANOCIDAL ACTIVITY

Rita Y. P. da Silva (PG),[1] Tagod M. S. Omer (Res),[2] Samara F. Ferreira (G),[1] Daniel K. Inaoka (Prof.),[2] Euzébio G. Barbosa (Prof),[1] Alessandro K. Jordão (Prof).[1]*

rita.yanka.pereira.108@ufrn.edu.br;

[1] *Department of Pharmacy, Federal University of Rio Grande do Norte, Natal, 59012-570, RN, Brazil;*

[2] *Department of Infection Biochemistry, Institute of Tropical Medicine (NEKKEN), Nagasaki University, 852-8523, Nagasaki, Japan*

Keywords: Trypanosomiasis, triazoles, naphtoquinones, molecular dynamics

ABSTRACT

Background: Chagas disease (CD) is a chronic, systemic, parasitic and often fatal disease caused by infection with the protozoan *Trypanosoma cruzi*. According to the World Health Organization, CD is the most common neglected tropical disease associated with poverty, the most significant parasitic disease, and the third most prevalent in Latin America. Currently, CD constitutes a global public health challenge, affecting 6 to 8 million people. However, available treatments are limited to two nitroheterocyclic drugs that were developed more than half a century ago. Triazoles are a group of molecules with reported antiparasitic activity and are possible drug candidates against trypanosomiasis. Virtual screening and molecular dynamics tools are methods that help direct the search for new drugs, standing out for their low cost and speed in delivering results. **Objectives:** The aim of this work is to evaluate the trypanocidal activity of 1,2,3-triazole naphthoquinones hybrids and their mode of interaction with the possible receptor. **Methods:** The molecules were synthesized using PEG 400 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the reaction medium, to which lawsone and azides were added. These molecules were subjected to an assay to evaluate the intracellular growth of amastigotes, as well as the dose-response curve with 4 different strains of *T. cruzi*. In addition, cytotoxicity in HeLa and HepG2 cells was measured. The molecule with the best result underwent virtual screening to predict its potential binding target. Using this target, a molecular dynamics analysis was conducted to evaluate its interaction with the receptor. **Results and discussion:** The synthesized compounds were prepared in good yields, purified by column chromatography and characterized by spectroscopic methods. In the assays to determine the dose-response curve, benznidazole was used as the reference drug. Considering toxicity and potency parameters, compound 1B (Figure 1) was the one that obtained the best results and was the only one tested against the 4 strains of *T. cruzi.* In this assay, it showed greater selectivity for the trypomastigote form. In the virtual screening, the target S-adenosylhomocysteine hydrolase of *T. cruzi* was identified as a possible target of interaction of the molecule. This target was used in molecular dynamics to predict the binding mode between the molecule and the receptor, and the presence of a cofactor (NADH) and interactions with amino acid residues were observed. **Conclusion:** The biological evaluation of the anti-trypanosma activity of naphthoquinones associated with the triazole nucleus was performed and one molecule was selected as the one with the best result. This compound was tested against four different strains of the parasite, showing greater selectivity for the trypomastigote form. An *in silico* study was also conducted to determine how the molecule interacts with the receptor, presenting a potential candidate for a new drug against Chagas disease.

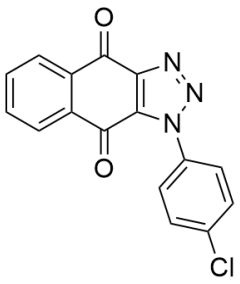

Figure 1: Compound 1B.