TARGET FISHING AND MOLECULAR DYNAMICS SIMULATIONS OF ANTITUBERCULAR 1*H*-1,2,3-TRIAZOLE-4-CARBOHYDRAZIDE

Samara F. Ferreira (G),[1] Alessandro K. Jordão (Prof),[1]Euzébio G. Barbosa (Prof)[1].

samara.felinto.123@ufrn.edu.br

[1] *Universidade Federal do Rio Grande do Norte, Natal/RN, Brasil*

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ABSTRACT

Introduction: 1*H*-1,2,3-Triazole molecules, belonging to the class of *N*-heterocyclic compounds, have been widely studied due to their biological properties, including antithrombotic, antipsychotic, tuberculostatic, anti-venom and antiviral activities. Recent studies highlight that the combination of 1*H*-1,2,3-triazole with carbohydrazide presents promising results in combating tuberculosis and herpes, highlighting the therapeutic potential of this synergy. To explore this potential, the use of inverted virtual screening and molecular dynamics techniques becomes essential in the identification of possible therapeutic targets and in the understanding of the molecular interactions involved. Thus, it has proven to be an important tool in the elucidation of mechanisms of action, biochemical processes and cellular pathways, in addition to contributing to the rational design of new compounds based on triazole-carbohydrazide analogues, thus promoting the discovery of innovative therapeutic alternatives. **Objective:** To evaluate, through molecular dynamics, the interaction between triazole-carbohydrazide compounds and molecular targets identified by inverted virtual screening. Additionally, the compounds will be optimized based on the receptor structure, aiming to increase their affinity for the target and improve their therapeutic efficacy. **Methods**: Compound (1), a 1,2,3-triazole-carbohydrazide derivative, was subjected to a target fishing process, which resulted in the identification of targets related to tuberculostatic activity. Among the identified targets, the receptors TbCYP126A1 and TbPANK (4BFU) were selected for molecular dynamics studies. The structures were obtained from the PDB databases and, when necessary, refined through the Alphafold repository. Molecular docking was performed using the AutoDock Vina software, and the best molecular positions were defined based on the affinity scores. The ligand parameters were generated by ATB Topology, and the simulations were conducted in the GROMACS software. **Results:** Two molecular dynamics simulations were performed, each corresponding to one of the identified targets. In the case of the TbCYP126A1 protein, the interaction was considered insufficient, since the ligand left the interaction site during the simulation, indicating low affinity and disqualifying this target as promising. On the other hand, the interaction with the TbPanK protein was satisfactory, with the molecule remaining stable throughout the simulation and without presenting significant displacements. This behavior suggests that the intermolecular bonds were strong enough to ensure the stability necessary for the effective interaction between the compound and the receptor residues. We are currently estimating the free energy of interaction to confirm the viability of the complex, in addition to planning new optimized ligands for future synthesis. **Conclusion:** The results indicate that compound (1) presents greater affinity for the TbPanK target, since molecular dynamics revealed stronger and more stable molecular interactions, with the molecule remaining in the site throughout the simulation. Considering that the PanK protein is directly involved in the metabolite growth of the causative agent of tuberculosis, the studied analogue represents a promising candidate for the development of new tuberculostatic drugs. The optimization of these compounds, based on the receptor structure, aims to design new ligands that will be synthesized by our research group.