Identification of druggable binding sites in ribose-5-phosphate isomerase of *Trypanosoma cruzi*

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Diseases caused by the trypanosome family members are a major public health problem in tropical and subtropical regions of developing countries, particularly in Brazil. The World Health Organization estimated that approximately 10 million people are infected with Trypanosoma cruzi, the etiologic agent of Chagas disease, with most cases found in Latin America. Unfortunately, there are no vaccines to control Chagas disease, and the two currently available drugs, nifurtimox, and benznidazole are inadequate for several reasons. For instance, these drugs present significant toxicity, act only in the acute phase of the infection, and some strains of the parasite have developed resistance to the available treatment. Hence, the search for new treatment strategies for Chagas disease is crucial to the development of more efficient drugs. The enzyme ribose 5-phosphate isomerase (R5PI) is an interesting molecular target. The R5PI enzyme is part of the pentose phosphate pathway, and its role is to protect the parasite against oxidative stress and production of nucleotides and NADPH precursors. Despite presenting functional resemblance with its human counterpart (HsR5PI), R5PI shows differences in its primary and tertiary structures. In this work, we applied a structure-based rational design approach, which included the search for cavities on the surface of R5PI and the analysis of the potential druggability of these cavities. Our purpose here is to investigate the possibility of agonizing or antagonize the protein through another binding site not yet described. A 100ns molecular dynamic simulation of R5PI (PDB ID 3K70) without the D-ribulose-5-Phosphate (substrate) showed that Glu 121 and His 23 undergo conformation changes transiently to prevent the formation of the catalytic pocket reducing its druggability. From the simulation, we clustered the structures in 3 groups and, afterward, chose the most representative one to search for potential allosteric sites. From the analysis, ten possible allosteric sites emerged, but only 3 presented high druggability according to the Pockdrug server, with values ranging from 0.72 to 0.84 and associated volumes close to 450 Å3. However, only two were stable concerning druggability and can be used in virtual screening studies to evaluate allosterically. Although the majority of inhibitor candidates act in the active site of an enzyme, in this work we searched for other potential binding sites where ligands could bind and act indirectly by provoking conformational changes in the protein to the point of altering some biological properties. The results obtained from our combined methodology may help in the development of alternative therapies against Chagas disease.