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Influence of Molecular Dynamics in the Docking of Dialkylphosphorylhydrazones in *Leishmania braziliensis* Hexokinase

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Abstract: Leishmaniasis, caused by parasites of the genus Leishmania, is one of the so-called neglected diseases. A previous study of our group with a series of dialklyphosphorylhydrazones (DAPH), **4a-4o**, some of which showed leishmanicidal activity both *in vivo* and *in vitro*, indicated hexokinase as a probable target of action of the compounds [1]. Using molecular docking and semi-empirical quantum calculations, we have previously studied the interactions between DAPH and a homology model of *L. braziliensis* hexokinase (LbHK), in the form of a dimer (chains A and B). The results indicated the ligands **4i, 4k** and **4n** (figure 1) as the most promising as potential inhibitors of LbHK. The objective of this work is to refine the LbHK model by molecular dynamics (MD) and apply the refined model in molecular docking studies, in order to verify the influence of the use of MD on the quality of the results of these studies. The MD simulations were done through the Gromacs 5.1.2.2 program [2], with the OPLS force field and the tip4p model for water, with a production phase of 50 ns. An alignment of the pre-MD homologous structure with its post-MD structure was performed, resulting in a RMSD value of 9.08 Å, which indicates a substantial conformational change. In order to evaluate if there were significant changes in the catalytic site of the parasite enzyme or emergence of new sites, a blind docking procedure using the ligand **4k**, the best of the three ligands mentioned above, was performed in both structures. In the blind docking procedure, the search space for protein-ligand interaction corresponds to the total surface of the protein, which allows a complete search of possible sites on the surface of the protein. This procedure was made with the SWISSDOCK web server [3]. The protein-ligand conformations given by the docking are grouped in clusters, and cluster 0 is the one that presents the most favorable Gibbs free energy of interaction (ΔG_{int}). The cluster 0 for the pre-MD model is located in the B chain's active site and has a small energy difference (-2,32 kcal mol^{-1}) when compared to an adjacent site. However, in the post-MD model, the cluster in the adjacent site does not exist, indicating that the active site is the most relevant presenting a ΔG_{int} = -8.78 kcal mol^{-1} for the cluster's best solution. The blind docking predicted interaction poses of **4k** in the active site in both LbHK conformations, providing favorable interaction energy values for both, being the interaction with the post-MD structure the most favorable. Then, a restricted docking with

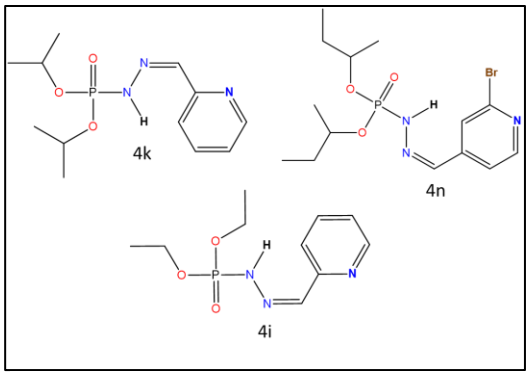

Figure 1: ligands 4i, 4k and 4n.

the 15 ligands was performed in the post-MD structure, where the search grid was restricted to the region of the active site, in order to compare with the pre-MD docking results. The restricted docking were performed with GOLD 5.4 [4] program (CCDC). The results showed that the **4i**, **4k** and **4n** ligands remained the best among the 15. The absence of one of the poses clusters shows that the results of blind docking were significantly influenced by the MD treatment of the structure obtained by homology modeling, indicating that this treatment of the models must be adopted prior to the doping studies, at least in the case of proteins with high flexibility like LbHK. The next step of this work is to propose changes in the structure of the ligands above mentioned to further improve their activity as inhibitors of the parasite's enzyme.

Key-words: Leishmanicide, hexokinase, dialkylphosphorylhydrazones, Blind docking, Molecular Dynamics.
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