The HGPRT AND XPRT ENZYMES FROM *Leishmania donovani:* MOLECULAR MODELING AND STUDY OF DUAL INHIBITORS.

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INTRODUCTION

Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT) and Xanthine Phosphoribosyltransferase (XPRT) are classified in the type I PRTases family, which are responsible for purine recycling in the organism to which they belong. Protozoans of the order Kinetoplastidae such as *Leishmania spp.* cannot make *de novo* purine synthesis, and they have only the recovery route. The aim of this work was to perform molecular homology modeling of both HGPRT and XPRT targets, as well as to perform a virtual screening in order to search dual inhibitor for both enzymes.

METHODS

Molecular modeling by homology

The molecular modeling of LdHGPRT and LdXPRT was performed taking into account the crystallographic structures with the best identity and resolution (Å), PDB: 1PZM and PDB: 6AR9, respectively.

Ligand-based virtual screening

The ROC curve was plotted to determine the *cutoff*. Five type I PRTase inhibitors were submitted to the ROCS program (Openeye Scientific Software) against a database with 57,000 chemical compounds from natural sources extracted from the ZINC15 database.

Receptor-based virtual screening

Molecular docking for LdHPGRT and LdXPRT with 1,825 compounds returned from the previous step (LBVS); evaluation of the five best compounds using Lipinski's five characteristic rule, affinity energy (Kcal / mol), *in silico* prediction for toxicity and druglikeness.

Molecular dynamics simulations

Molecular dynamics simulations were also performed with the best compound (ZINC2150030) evaluated on both targets, considering a simulation time of 50 ns.

RESULTS AND DISCUSSION

In LdHGPRT and LdXPRT, the QMEAN values of the modeled structures are determined at -1.09 and -1.83, respectively. The graph of the ROC curve reveals an area on the curve (AUC) equal to 0.90 ± 0.10 (figure 1). The search for compounds by the program returned a total of 1825 compounds. After calculations of molecular docking, the best evaluated compound (ZINC2150030) (figure 2 and 3) obtained an affinity energy of -10.5 Kcal / mol for LdHGPRT and -11.5 Kcal / mol for LdXPRT.

The same compound showed no toxicity due to in silico prediction and obtained an ideal value for druglikeness. Molecular dynamics calculations showed that the compound remained within the active site of both enzymes for 50 ns (figure 4).

The compound interacted and made hydrogen bonds mainly with bonds II and III for the two targets. Type I PRTases have active sites made up of four loops. It is described in the literature that the ideal is the search for an inhibitor or drug that inhibits loop III of type I PRTases.

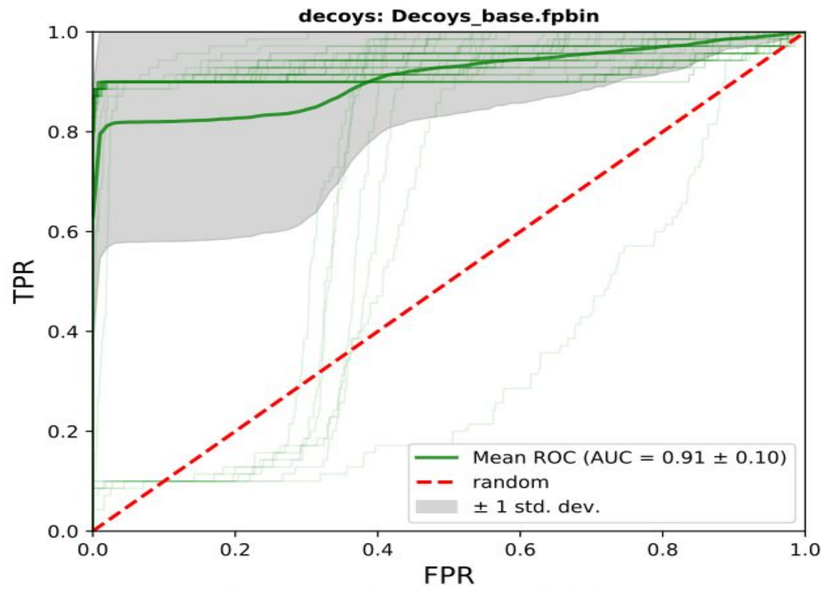

Figure 1. Graph of the ROC curve

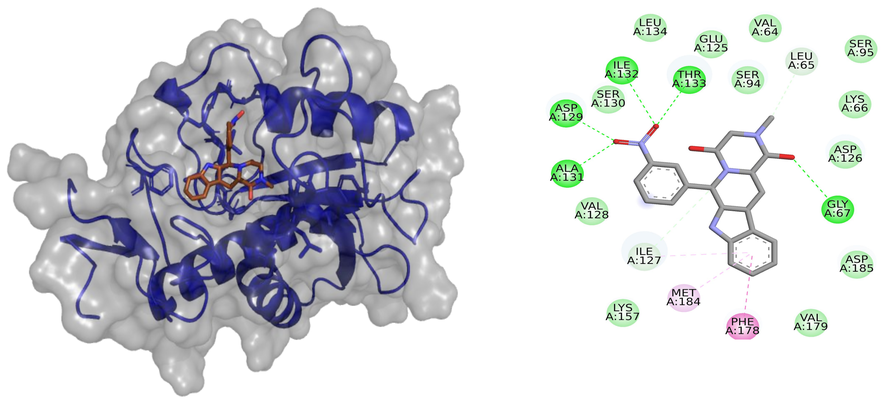

Figure 2. ZINC2150030 in complex with LdHGPRT

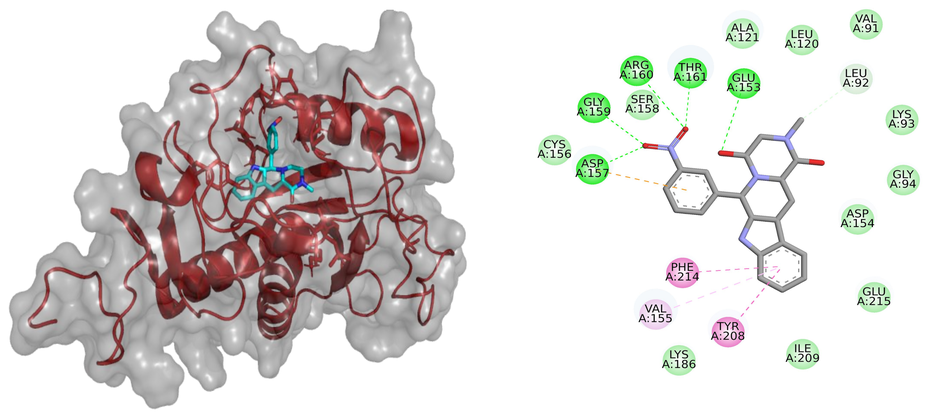

Figure 3. ZINC2150030 in complex with LdXPRT

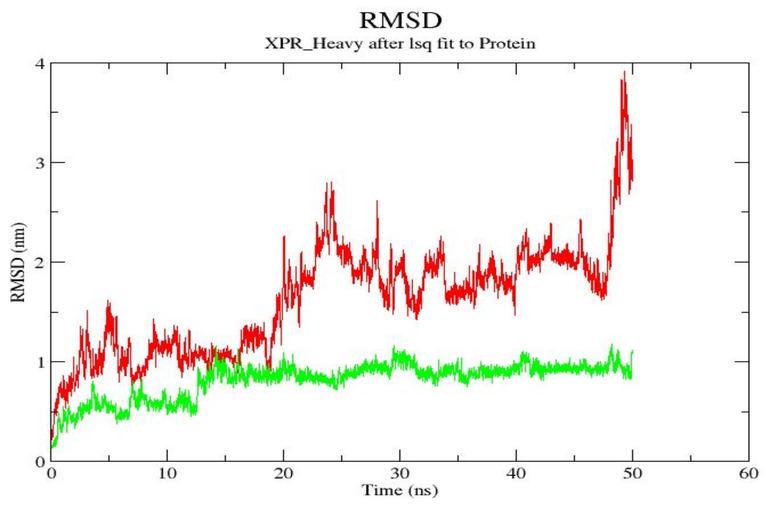

Figure 4. RMSD graph of the molecular dynamics simulation of the ligand in both targets.

CONCLUSION

After in silico studies, this inhibitor candidate can be tested in vitro and in vivo as a new treatment option for leishmaniasis.

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