

Development of cruzain selective inhibitors by structure based virtual screening

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Cruzain is the major *Trypanosoma cruzi* cysteine protease and is related to parasite nutrition and host cell invasion. Its inhibition is shown to decrease parasite infection in animal models but no medicine has been developed yet. Cruzain is homologous to human cathepsins, so, selectivity can be a challenge when developing drugs against this enzyme. In order to develop a selective inhibitor to cruzain we propose a virtual screening with docking. Glide (Schrodinger) was the chosen software, it has 3 precision levels that increases in accuracy in pose prediction, true positives recognition and computational cost (HTVS, SP and XP, in this order). The crystals structures we applied in our docking protocols have the following PDB IDs: 3KKU (cruzain), 3AI8 (human cathepsin B) and 1MHW (human cathepsin L). All the enzymes were prepared with Protein Preparation Wizard from Schrodinger. We downloaded the Leads Now compounds from ZINC and selected compounds that differ from each other with a Tanimoto cutoff of 0.9. A diversity set of 372,632 compounds was prepared with LigPrep (Schrodinger) and they were submitted to Glide HTVS against cruzain. Top 10% compounds were submitted to Glide SP against cruzain and top 10% were filtered based in the presence of some interactions between ligand and receptor, in this step we retrieved 2,025 compounds. These were submitted to Glide SP against both cathepsins and bottom 10% (489 molecules) were submitted to Glide XP against all the enzymes. Molecules were visually inspected and selected based in the occupancy S2 pocket of some portion of ligand; hydrogen bonding pattern; chemical diversity of compounds and purchasability of supposed hits. We selected 9 molecules to be purchase and test against cruzain and human cathepsins in order to check its activity against cruzain and its selectivity towards its humans homologous.

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