Computational Drug Design applied towards the treatment of Human African Trypanosomiasis

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Human African Trypanosomiasis (HAT), also known as sleeping sickness, is a tropical disease affecting 37 sub-Saharan countries. *Trypanosoma brucei gambiense* is the parasite that causes the chronic form of the disease in central and western Africa. *T.b.gambiense* is in the trypanosome family, a group of flagellate protozoan parasites that proliferate in the midgut of the tsetse fly. Once bitten by the tsetse fly, the trypanosomes enter the blood and lymphatic system of the mammalian host. In the second stage of the disease, the parasites cross the blood brain barrier and enter the central nervous system. Symptoms include fevers, irregular sleep cycles, and eventually coma and death.

Currently, only two treatments are able to cure a human with second stage HAT. Melarsoprol is an arsenic compound proven effective in the majority of cases, however it is immediately deadly in 5% of patients. Eflornithine (DFMO) is the only drug recently developed for the treatment of HAT. Eflornithine is not practical for disease treatment in Africa as it costs around $500 per patient and must be administered over a 14 day period.

Eflornithine is suicide inhibitor of *T.b. gambiense* ornithine decarboxylase (*Tb*ODC), a PLP-dependent enzyme that catalyzes the rate-controlling step in polyamine synthesis. Without the presence of intracellular polyamines, the parasites are unable to survive in the host. Eflornithine covalently binds to both the cofactor (PLP) and a cysteine residue in the active site. The goal of our project is to use computational drug design to create a pro-drug of eflornithine that is a more effective inhibitor of *Tb*ODC.

First, we evaluated the X-ray crystal structure of *Tb*ODC bound to PLP and DFMO using the Molprobity program. Using the X-ray crystal structure, we used HF/6-31G* level quantum mechanics to optimize the geometry of the drug and the cofactor (PLP). Then we used AMBER's Antechamber to generate the charges for the non-standard residues and parmchk to fill in the missing parameters. All the Antechamber and parmchk files for the non-standard residues were changed from the generalized AMBER force field (GAFF) to the parm94 force field before running the system through LEaP. Using the LEaP output files, we performed Sander minimizations followed by heating and molecular dynamics production runs on the enzyme bound to the non-standard residues.

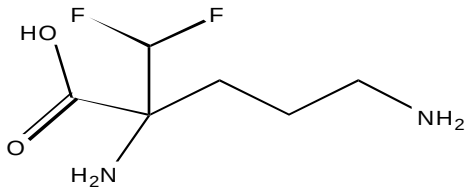

Figure 1. DFMO

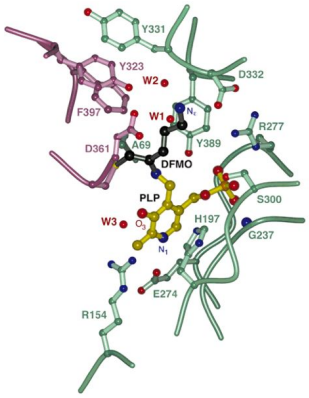

Figure 2. Active site of TbODC with PLP and DFMO