Binding mode characterization of PfFNT' inhibitors through Docking and MD simulations

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Malaria is a key threat to public health worldwide. Recently, Plasmodium-faciparum formate-nitrite-transporter (PfFNT) has been identified as the malaria parasite's lactate transporter and as a novel drug target[1]. A few putative inhibitors for PfFNT have been identified[2]. However, their mechanism of binding and inhibition is not well understood. Here, we used molecular dynamics simulation to study the function and inhibition of PfFNT at an atomic level. The ligands MMV007839 and BH267.meta have been identified as potential inhibitors. For these ligands, we derived new parameters based on GAFF2. To do this, we used the HTMD Parameterize tool[3] complemented with Stochastic Conformational Analysis at the semi-empirical level with ab initio refinement. The new parameters reproduce the dihedral potentials of these ligands at the DF-MP2-aug-cc-pVTZ level of theory. This is a remarkable improvement relative to initial GAFF2 parameters. In silico, we docked the ligands into the putative binding site in the PfFNT structure. Our initial simulations are in agreement with the reported experimental results.

[1] A. Golldack et al., PLoS Pathogens 13, 1-18 (2017).

[2] P. Walloch et al., Journal of Medicinal Chemistry 63, 9731-9741 (2020).

[3] R. Galvelis et al., Journal of Chemical Information and Modeling 59 3485-3493 (2019)