DOCKING AND MOLECULAR DYNAMICS STUDIES IN THE DESIGN OF SELECTIVE INHIBITORS FOR *PLASMODIUM FALCIPARUM* SERINE HYDROXYMETHYL TRANSFERASE

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Serine Hydroxymethyl Transferase (SHMT) is a very conserved key enzyme in the folic cycle of most organisms. The only important difference between the active sites of the human and the *P. falciparum* enzyme is the position of the equivalent residues Asp146 of human SHMT and Glu137 of PfSHMT. While in human SHMT Asp146 is located at least 10 Å from the polyglutamate tail of the substrate (FFO), the equivalent residue in PfSHMT, Glu 137, is quite close to the tail of FFO. We have used molecular dynamics (MD) simulations (GROMACS 3.3.1), docking (AutoDock 3.0.5) and electrostatic surface complementarily studies (PyMol) to design new analogues of FFO as potential selective inhibitors of the parasite enzyme. More than 10 potential inhibitors were proposed, but the best designed potential selective inhibitors were 2,4,6-triaminopyrimidines with a 4-amidinephenyl tail separated by a C_3 or a C_4 spacer from the pyrimidine ring. Those compounds were tested using MD and docking simulations. The compound with the C_3 spacer bound the parasite active site 97% and the human enzyme only 3%. The compound with the C_4 spacer selected the parasite enzyme 84% of the time. These compounds are being synthesized to determine their experimental selectivity for the parasite enzyme. CNPq, FAPERJ, CAPES-MD (Pró-defesa).
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