MM001-VALIDATION OF SEMI-EMPIRICAL METHODOLOGY FOR GEOMETRY OPTIMIZATION OF HIV-IN INHIBITORS.

EDUARDO B. DE MELO (PG)[(1)]; ALINE T. BRUNI(PQ)[(2)]; MÁRCIA M. C. FERREIRA(PQ)[(3)]

[(1)]UNIOESTE; [(2)]IBILCE/UNESP; [(3)]IQ/UNICAMP.

The integrase (IN) is indispensable for the replication of HIV. The only HIV-IN/inhibitor complex is the PDB 1QS4 (5CITEP/IN). When not much crystallographic informations are avaliable, the best starter point for a theoretical study are the most stable calculated geometries. In this trial were selected the best semi-empirical theory (AM1 or PM3) for the optimization of this compounds. The comparison criteria utilized were: the bond lengths of 5CITEP PDB; properties of the optimized geometries; and literature data. The 5CITEP, a keto-enol, were optimized for these two theories. The bond lenghts of the obtained geometries were similar to the 5CITEP PDB. Overlap between AM1 and PM3 geometries showed that they were identical. HOMO, LUMO and dipole moment (D) values are also similar. However, the heats of formation values (ΔH_f) presented great difference (Δ = 43 Kcal/mol). The same was observed for the partial charges of the atoms. In the literature, the AM1 theory is described as capable to compute most exacts values for D, HOMO and partial charges that the PM3. Furthermore, is indicate for the study of keto-enols. Therefore, AM1 is the semi-empirical theory indicated for a molecular modeling study of keto-enols inhibitors of HIV-IN.

Supervisor: Márcia M. C. Ferreira.

MM002-TRYPANOTHIONE-REDUCTASE: DOCKING STUDIES OF PEPTIDE ANALOG INHIBITORS

SAMUEL SILVA DA ROCHA PITA (PG)[1]; MAGALY GIRÃO ALBUQUERQUE (PQ)[1]; JOSÉ JAIR VIANNA CIRINO (PQ)[1]; RICARDO BICCA DE ALENCASTRO (PQ)[1]; CARLOS RANGEL RODRIGUES (PQ)[1]; HELENA CARLA CASTRO (PQ)[2]

[1] Instituto de Química – UFRJ [2] Instituto de Biologia – UFF

Trypanothione-reductase (TR) is an enzyme of *T. cruzi*, the etiological agent of Chagas' Disease (CD), and a promising target to drug design. McKie *et al*. [Amino Acids 2001 20:145] showed that 21 peptide analogs block TR in a reversible and selective manner. This work aims to study the binding mode of these analogues at the TR active site by a docking method. Calculations were carried out using FlexX/Sybyl. The complex TR-trypanothione structure was taken from Protein Data Bank (1BZL) as a reference. The ligands were docked after hydrogen atoms addition, charges assignment, and minimization. All docked complexes contained the inhibitor and the active site residues included in a 12Å radius of each inhibitor atoms, and the best binding modes were evaluated based on an energy score. Comparing with the experimental results, the most potent inhibitors were not necessarily the best scored by FlexX, but the least ones, were the worst scored. In addition, some of the achieved binding modes revealed new insights to propose new peptide analogues as potential inhibitors of TR on the development of drugs against CD.

Support: CAPES – CNPq – FAPERJ – FUJB
Advisors: MGA, CRR