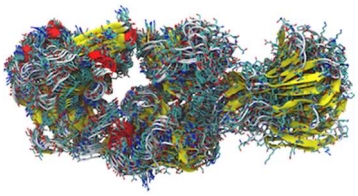

IV ASBioSim – Advanced School on Biomolecular Simulation: Protein Engineering with Rosetta, from fundamental principles to tutorials
05 to 10/May, 2019, Recife/PE, Brazil

The enzyme 3-hydroxykynurenine transaminase from *Aedes aegypti* as target for 1,2,4-oxadiazoles

Larissa G. Maciel

Universidade Federal de Pernambuco

Abstract: The *Aedes aegypti* mosquito is the vector of arboviruses such as Dengue and Zika fever, major public health threats. Chemical control remains one of the current strategies to decrease mosquito population despite inducing long-term insect resistance mechanisms. In some cases, the target of these substances are important enzymes for the vector and susceptible to inhibition by small molecules. One of the detoxification pathways in living organisms is the kynurenine pathway, through which 3-hydroxykynurenine (oxygen and nitrogen reactive species) is converted into xanthurenic acid (atoxic substance) by the enzyme 3-hydroxykynurenine transaminase (HKT). Substances containing the 1,2,4-oxadiazole scaffold have shown larvicide activity with evidence that these molecules are potential HKT inhibitors. Therefore, we aim to investigate the potential of HKT as a molecular target for 1,2,4-oxadiazole derivatives by combining molecular biology, biochemistry, and biophysics techniques. Towards this end, recombinant HKT has been cloned and expressed in *Escherichia coli* and its 2.5 Å 3D structure has been determined by X-ray crystallography. In addition, a new, faster and cheaper methodology for detection of HKT activity has been developed which is based on absorbance spectrophotometry of xanthurenic acid-Fe^{3+} complex to characterize HKT kinetic parameters and determine the IC_{50} of 1,2,4-oxadiazoles. From this, we could verify that these synthetic compounds are HKT inhibitors. The further evolution of this work will rely on computational simulations of molecular dynamics and free energy calculations the novel HKT crystallographic structure in complex with the most promising 1,2,4-oxadiazole compounds in order to identify critical functional groups in the inhibitor and amino acids in the protein for optimal inhibitory activity in relation to HKT.