In silico screening for Phospholipase A2 of Apis Mellifera with Fragment Library


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Phospholipases A2 (PLA2s) are enzymes that catalyze the hydrolysis of the sn-2 acyl bond of glycerophospholipids. PLA2s have been isolated from a variety of sources, including reptile and insect venoms, pancreatic juices, platelets, and synovial fluid. They have been assigned to groups I to XIV, according to differences in amino acid sequence. The primary structure of the group III PLA2 from honeybee (Apis mellifera) venom (bvPLA2), shows homology to other short PLA2s, except in the region of the catalytic histidine and aspartic acid residues, the calcium binding loop, and certain cysteine residues. Virtual screening is the use of high-performance computing to analyze large databases of chemical compounds in order to identify possible lead compounds. The Fragment Library is a collection of approximately 3,800 compounds rationally selected according to various diversity parameters and Astex Rule of Three considerations. The aim of this project was predict potential inhibitors against bvPLA2 and validate the possible interactions. Structure of bvPLA2 (1POC) was obtained from PDB database and analyzed using DS ViewerPro 5.0. Flexible docking was performed with GOLD 4.1 in order to propose novel potential inhibitors. GOLD software was used, as well, to perform virtual screening simulations with the virtual compounds collections of the Fragment Library database. It was selected the top-ranked orientations for each of the best 50 compounds simulated inside a sphere of 10 Å radius centered at the PHE67 carbon atom of the group and rescores were calculated. The molecular interaction fields were obtained using the software GRID. The parameters that define the ‘Rule of Five’ (RO5) were calculated for these proposals, and agreed with this rule. The best score compost has been named Molecule 593 (8,8-dimethyl-2-thioxo-1,2,3,6,8,9-hexahydro-4H-pyrano[3′,4′:5,6]pyrido[2,3-d]pyrimidin-4-one). The compounds will be used in further analysis in vivo or in vitro to confirm its potential to inhibit bvPLA2. The best twenty of fifty proposals were selected and also should be evaluated against bvPLA2.