Discovering Potent Inhibitors Against the Reductase of Sulfate-Reducing Bacteria to Control Biosulfide Generation by Docking and Virtual Screening

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ABSTRACT

Computational approaches that dock small molecules are commonly used for discovery novel enzyme inhibitors. Virtual screening has been used to find inhibitors for APS reductase (APSR), other sulfate reducing enzymes and carrying sulfate analogs. Different ligands were docked on the APSR molecular structure especially on the substrate-binding site of isoalloxazine ring of FAD. The metalloprotein APSR is an important enzyme to reduce sulfate-reducing bacteria (SRB) that utilize hydrogen, simple organic acids, alcohols and hydrocarbons. SRB play a significant role in the global cycling of carbon and sulfur especially in anaerobic conditions, however, are undesirable during the oil refining process, because the sulfides (H_2S and HS^-), cause corrosion. Here, we present the results of discovery of three novel substances with potential for inhibit the APSR from SRB. The X-ray crystal structure of adenylylsulfate (Adenosine 5'-phosphosulfate, APS) reductase in complex with APS was used in this study. Its code name in PDB is 2FJA and its crystallographic resolution is 2.5. The docking calculation on the specification of a binding pocket of the isoalloxazine ring of FAD, accommodated in the bottom of the channel accessible only from the outside. We obtain fifteen compounds for the target in suppliers 2D SDF files from databases ZINC, Pubchem and PDB-Ligand and were converting for pdb format using server web Prodrg, taking in consideration the physico-chemical properties of APS. The ligands and target have been geometry optimized by Steepest Descent and Gradient Conjugated algorithm. The AutoDock version 4.0 was used as a docking engine. AutoDock makes energy evaluation by archiving pre-calculating atomic affinity potential for each atom type in the substrate molecule. In the AutoGrid procedure the protein is embedded in three-dimensional grid and a probe atom is placed at each grid point. The energetic of a particular substrate configuration is then found by tri-linear interpolation of affinity values of eight grid points surrounding each the atoms in the substrate, similarly is evaluated interpolating the values of the electrostatic potential. The ligands and receptor were prepared for docking as described: All water molecules were removed from the structure of receptor; Polar hydrogen's were placed with AutoDockTools 1.5.1; Gasteiger charges were assigned to receptor atoms. We edit the partial charges on each metal atom to the clusters iron-sulfur. It were calculated with Gamess97 software using the Hartree-Fock theory with a set of minimum bases (RHF/STO-3G), without taking into account the cysteines atoms, which are covalently attached to iron atoms. For specification of the binding site we define a rectangular box oriented to axes of the coordinate system to define FAD atoms as being the binding site. The ligands and target were geometrically optimized by the Steepest Descent and Gradient Conjugated algorithm. For docking was Adopted Genetic Algorithm. All run were without APS and free energy binding of the APS ($DG° = -20.57$ kJ.mol^{-1}) for positive control. Compounds docked with binding energy above of positive control (binding energy APS) were rejected.