Poster Presentation

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Design, Synthesis, and Biological Evaluation of novel Alpha Glucosidase Inhibitors

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To develop a lead anti-diabetic compound, a series of 21 novel quinazoline derivatives have been synthesized and screened against alpha Glucosidase. The binding mode of the compounds at the active site of alpha Glucosidase was explored using Glide docking method. The binding model suggests one to four hydrogen bonding interactions between quinazoline derivatives and alpha-glucosidase. 6-Bromo-2- cyclopropyl quinazoline-4(3H)-one has been modified by C– C cross coupling to obtain nine different aryl scaffolds. These scaffolds further modified at C-4 position using amidation method to generate 21 compounds. These compounds were characterized by elemental analysis, IR, NMR spectral studies and X-ray single-crystal diffraction analysis. Based on the interaction profile and docking score, all these compounds were selected for in vitro enzymatic screening. Seven of the thirty six compounds showed <20 uM activity against alpha Glucosidase and among these, one compound showed the highest inhibition, with an IC50 of 3.4 uM. Insilico analysis was utilized to evaluate the diversity of the set of compounds against shape space, and relevant drug-like properties (Fig. 1).

The predicted binding mode of the highest active compound against the Alpha Glucosidase model retained hydrogen bond interactions occurred with conserved amino acids. Three hydrogen bond interactions of the highest active compound with Asp321, His591, and Asp199 residues of the homology modeled protein. The first hydrogen bond is observed between the hydroxyl group of the highest active compound and the COO group of Asp321 residue (–OH - O–CO, 2.44 A°). The second hydrogen bond is observed between the hydroxyl group of the highest active compound and the O–H of His591 (–HO - HN, 1.73 A°). The third hydrogen bond is observed between the hydroxyl group of the highest active compound and COO group of Asp199 residue (–OH - O–CO, 1.77 A °). The predicted binding mode, 2D interaction diagram of the highest active compound in homology modeled Alpha Glucosidase protein, is shown (Fig. 2). The docking studies of ligands with alpha-glucosidase revealed that the ligands are potent as a drug for target enzyme.

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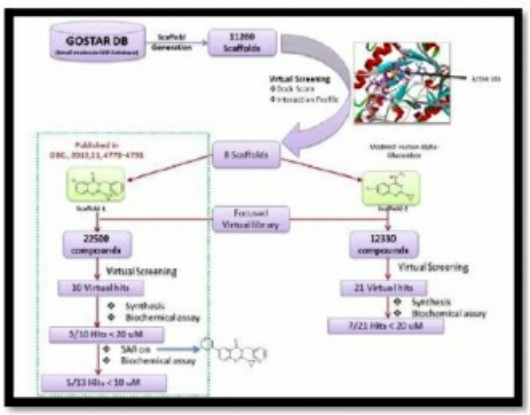

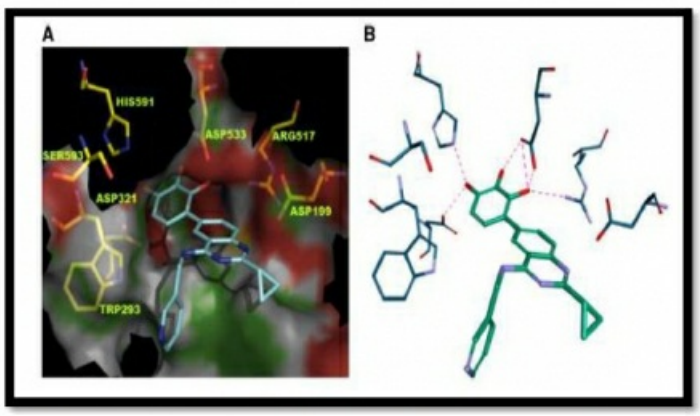

Fig1. A flow diagram for the focused library generation of Alpha Glucosidase inhibitors. Fig2. Predicted binding mode of compound

Keywords: Quinazoline Derivatives, Alpha Glucosidase inhibitors, Molecular docking.