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DOCKING STUDY ON DERIVATIVES OF METHAZOLAMIDE AS INHIBITORS OF CARBONIC ANHYDRASE II

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Abstract

Carbonic anhydrase II catalyses the reversible hydration of carbon dioxide into bicarbonate. Increase in the intraocular pressure of eye cause the disease glaucoma and this increase is due to the excessiveness of carbonic anhydrase II. We identified the inhibitors of carbonic anhydrase II which are used against glaucoma disease. We docked the derivatives of methazolamide with carbonic anhydrase II.

Keywords: *Carbonic anhydraseII, glaucoma, methazolamide, discoverystudio, molecular docking*

Introduction

Glaucoma is the optic nerve diseases that are involving in loss of retinal ganglion cells in a characteristic pattern of optic neurotherapy. Glaucoma has been nick named "the sneak thief of sight" [1]. Carbonic anhydrase is responsible for the reversible hydration of carbon dioxide into carbonic acid. Its excessiveness is responsible for removal of water. And removal of water increased the intraocular pressure of eye resulting in glaucoma disease. Inhibitors of carbonic anhydrase II reduces the risk of glaucoma disease by reducing the intraocular pressure [2,3].

Methazolamide is the inhibitor for carbonic anhydrase II. Its original derivatives have less effectiveness than its modified derivatives. Three derivatives were identified and modified and docked with protein carbonic anhydase. These derivatives have shown to decrease the risk of glaucoma by its activity on the carbonic anhydrase II. These reduce the enzyme and then reduces the intraocular pressure by reducing the water removal.

Methods

Docking study with discovery studio and auto dock: Three-dimensional structure of enzyme carbonic anhydrase II (pdb.id 2VVB) was obtained from RCSB protein data bank as PDB file. Active sites of protein structure were analysed and residues were identified. The ligand (methazolamide derivatives) compounds were obtained from zinc database. The protein was modified in discovery studio. In discovery studio, we removed the already attached ligand and save this file as pdb. In autodock we add hydrogen and remove water from protein and then save this file as pdbqt. In autodock we made grid of protein and noted the values. In the similar way, the ligand structure was modified in discovery studio and autodock. First, we replace elements in the ligand structure in discovery studio and save this file as pdb. Then we make torsion of modified ligand in autodock and save this file as pdbqt. After obtaining the PDB and PDBqt files, protein structure (carbonic anhydrase II) were docked with ligand (modified methazolamide derivatives). Results were obtained. The modified ligand show affinity with carbonic anhydrase II and has shown to inhibit the activity of carbonic anhydrase II and it shown to be reduce the risk of glaucoma disease. The original derivatives has less affinity as compared to modified derivatives. The interaction of protein with modified ligands can be viewed in paymol.

ADME/ Toxicity Testing:

ADMET properties are calculated on MedChem designer. We open the structure of modified ligands on MedChem and then calculate the properties.

Results

In assessment using Discovery studio 1.7, CAII exhibit good binding with methazolamide derivatives. The possible active site was identified using Discovery studio.

Discussion

Docking study shows that the derivatives of methazolamide inhibitor are effective against carbonic anhydrase II. They treat glaucoma. These inhibitor reduces the concentration of carbonic anhydrase II. In this way, water removal is low, imtraocular pressure is maintained and glaucoma do not develop. Carbonic anhydrase II is the most recent potent drug target for glaucoma. The active site residues of CAII was predicted and refined models of CAII and methazolamide derivatives were obtained after energy minimization using Discovery studio software. The CAII stable molecule was further used in virtual docking of methazolamide derivatives.

References

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Table 1: Original ligand affinity with carbonic ahnydraseII

Original ligands	Affinity
Ligand 1	5.6
Ligand 2	5.7
Ligand 3	5.1

Table 2: Modified ligand affinity with carbonic anhydrase II

Modified ligand	Affinity
Ligand 1	5.7
Ligand 2	5.5
Ligand 3	5.7

Table 3: ADMET properties of modified ligands

Structure name	Ligand 1	Ligand 3
Mlog P	-2.473	-1.562
S+log P	-4.066	-2.708
S+log D	-3.893	-2.702
Rule of 5	2.000	1.000
Role of 5-code	Hb	Hb
Mwt	317.344	185.184
MNO	11.000	6.000
TPSA	168.460	121.930
HBDH	7.000	6.000

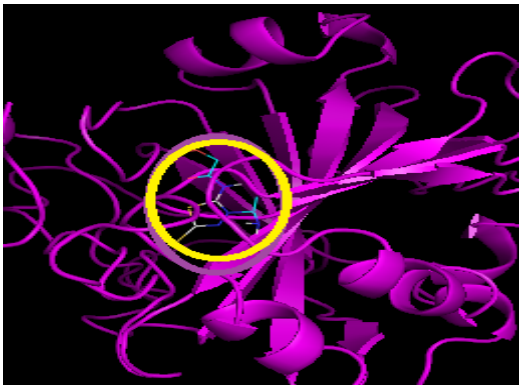

Figure 1: Interaction of protein with modified ligand 1

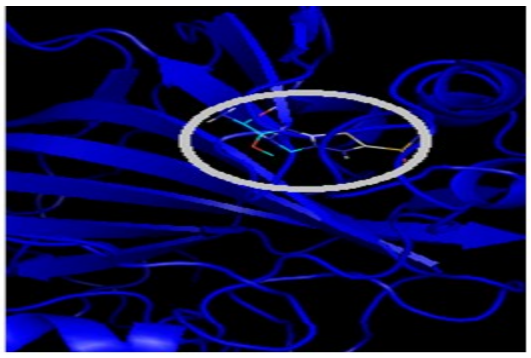

Figure 2: Interaction of protein with modified ligand 2

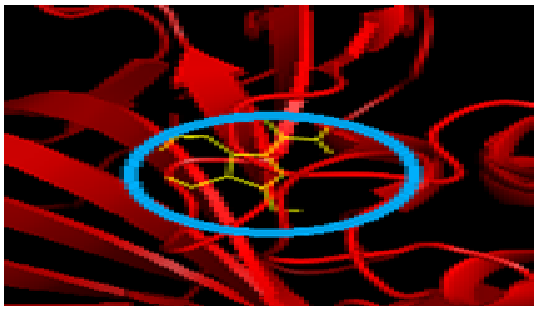

Figure 3: Interaction of protein with modified ligand 3

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