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Discovery of Potential Aldose reductase Inhibitors using In Silico docking studies on Rhodanine derivatives

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Abstract

Molecular docking study was performed on a set of rhodanine (TA-01-TA-11) as potential aldose reductase inhibitors (ARI). In this study, docking of rhodanine analogs against AR have been performed using MVD software within the active site region of 4lua. For these compounds, the binding free energy (kcal/mol) was determined.The docking results of a set of compounds, showed that most stable binding ligand TA-01 (TA01-TA-11) with Moldock score -147.01 kcal/mol involved with selected aldose reductase crystal structures shows that it forms hydrogen bonds with at least 3 hydrogen bonds with key active site residues Thr 113, Trp 111, Gln 49 within the binding site region of 4lua. These molecular docking analyses could lead to the further development of potent aldose reductase inhibitors for the treatment of diabetes.

Keywords: Molecular Docking, rhodanine, Aldose reductase inhibitors (ARI), Molegro Virtual Docker (MVD), Moldock score

Introduction

Docking methodology aims to predict the experimental binding modes and affinities of small molecules within the binding site of particular receptor targets and is currently used as a standard computational tool in drug design for lead compound optimisation and in virtual screening studies to find novel biologically active molecules. The basic tools of a docking methodology include a search algorithm and an energy scoring function for generating and evaluating ligand poses.[1]

Diabetes mellitus (DM) is a chronic metabolic disorder in which prevalence has been increasing frequently all over the world. It is estimated that 366 million people had diabetes in 2011; by 2030 this would have risen to 552 million.The number of people with type 2 diabetes is increasing in every country with 80% of people with DM living in low- and middle-income countries. Diabetes caused 4.6 million deaths in 2011.[2] It is estimated that 439 million people would have type 2 diabetes by the year 2030.[3,4]

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Diabetes is associated with long-term complications that affect almost every organ of the body. The high blood glucose levels lead toseveral long-term complications, namely neuropathy, nephropathy, retinopathy, cataract, and cardiovascular.[5]

Aldose reductase (AR, EC 1.1.1.21) is responsible for the diabetes complications; first and rate-controlling enzyme in the polyol pathway. Aldose reductase (AR) is an enzyme of aldo-keto reductase super-family that catalyzes the conversion of glucose to sorbitol in the polyol pathway of glucose metabolism. In this pathway is catalyzed by sorbitol dehydrogenase, which catalyzes the NAD-linked oxidation of sorbitol to fructose. Thus, the polyol pathway results in conversion of glucose to fructose with stoichiometric utilization of NADPH and production of NADH.[6]

Decreased sorbitol flux through polyol pathway by ARIs could be an emerging target for the management of diabetes complications.[5]

Thus, the inhibition of aldose reductase has basic approach to the prevention and treatment of diabetic complications and a potential target for drug design the role of aldose reductase inhibitorsin the diabetic complications or use in the treatment and management of the major diabetic complications such as cataract, retinopathy, neuropathy,

nephropathy and cardiovascular. The ARIs developed vary structurally, and representative structural classes of ARIs include as carboxylic acid derivatives (such asEpalrestat, Alrestatin, Zopalrestat, Zenarestat, Ponalrestat, Lidorestat, and Tolrestat), ii) spirohydantoins and related cyclic amides (such as Sorbinil, Minalrestat, and Fidarestat), and iii) phenolic derivatives (related to Benzopyran-4-one and Chalcone). Among these inhibitors, Epalrestat is the only commercially available inhibitor till date. [5]There is a need of a potent, selective aldose reductase inhibitors for the management of diabetic complication. Therefore, it is worthwhile to develop new analogues of aldose reductase inhibitors which are devoid from the toxicity.

The aim of this study was to analyze the inhibitory action of aldose reductase enzyme orthe role of ARIs in management of diabetic complicationsbycomputational docking studies.There is an aldose reductase enzyme were employed on some rhodanine derivatives. In Silico docking study were determinedby predicted binding energies and different modes of ligands interactions.

Material and Methods

Software Methodology

In the present investigation, an attempt was made to understand the ligand-receptor interactions of rhodanine derivatives against aldose reductase as a target enzyme, by performing docking studies using Molegro Virtual Docker version 6.0 (MVD) (www.molegro.com), probably the most accurate predictive tool of binding geometry. MVD tools was used to generate grid, calculate dock score and evaluate conformers. Docking calculations were carried out using MVD on new ligand protein model.

To obtain better potential binding sites in the protein, a maximum of five cavities were detected using parameters such as molecular surface (expanded van der Waals), maximum number of cavities (n = 5), minimum cavity volume (10), probe size (1.20), maximum number of ray checks (n = 16), minimum number of ray hits (n = 12), and grid resolution (0.80) The active binding site region was defined as a spherical region which encompasses all protein within 15.0 A of bound crystallographic ligand atom with selected co-ordinates of X, Y and Z axes, respectively. Default settings were used for all the calculations. Docking was performed using a grid resolution of 0.30 A and for each of the 10 independent runs; a maximum number of 1500 of iterations were executed on a single population of 50 individuals.

One pose per run was retained based on root mean square division clustering using a heavy atom threshold set at 2.0 A° and an energy penalty of 100. All the poses were examined manually and the best poses were retained.

The active binding site was considered as a rigid molecule, whereas the ligands were treated as being flexible, i.e. all non-ring torsions were allowed. [7,8]

Preparation of Ligand

The initial structure of ligands were drawn on ChemDrawChemdraw ultra v 10.0 (Cambridge software), copied to Chem3D ultra v 10.0 to create a 3D model and, finally subjected to energy minimization using molecular mechanics (MM2)and MOPAC. Such energy minimized structures are considered for docking and corresponding pdb files were prepared using Chem3D ultra v 10.0 integral option (save as /Protein Data Bank (pdb))[9](Table 1)

Selection of Protein

The X-ray crystal structure of the aldose reductase enzyme (2PDG) was retrieved from protein data bank. The selection of protein for docking studies is based on several factors i.e. structure should be examined by X-ray diffraction, and resolution should be between 2.0-2.5 A, it should contain a co-crystallized ligand; the selected protein should not have any protein breaks in their 3D structure. All the water molecules were removed from the enzyme and subsequently protein was prepared. Moreover, we considered ramachandran plot statistics as the important filter for protein selection that none of the residues present in disallowed regions.[10]

Preparation of Protein

All aldose reductase enzyme crystal structures were held from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb). Subsequent to screening for the above specific standards the resultant protein target (PDB Code: 4lua) was selected and prepared for molecular docking simulation in such a way that all heteroatoms (i.e., nonreceptor atoms such as water, ions, etc.) were removed.[11]

Software Method Validation

Software method validation was performed in MVD using Protein Data Bank (PDB) protein 4lua. The bio active co-crystallized bound ligand was docked with in the active site region on x-ray crystal structure of 4lua. Docking protocol was validated by comparing the RMSD of crystal structure conformation of ligand with docked conformation of the ligand obtain through docking methodology. The RMSD of all atoms between the two conformations is 1.3 A which is under acceptable limit and indicating that the

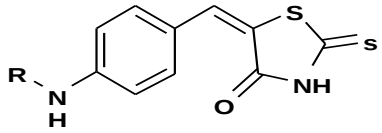
parameters for docking simulation are good in reproducing X-ray crystal structure.

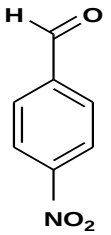
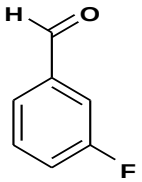
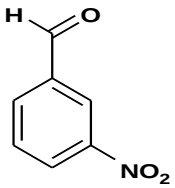
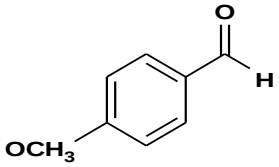
Molecular modeling and Docking

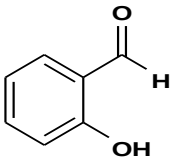
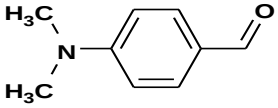
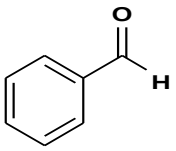
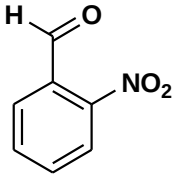
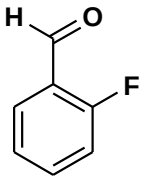
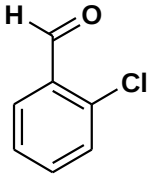
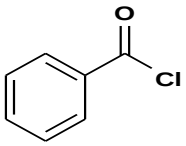
A set of 11 new rhodanine derivativeslisted in Table 1 were synthesized and modeled by using chem. draw software. [5]

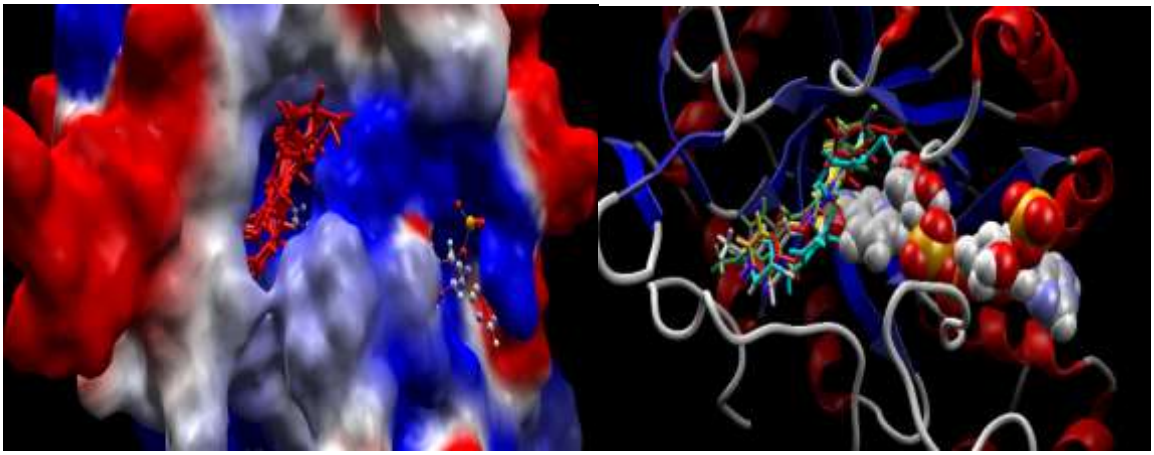
In the present study, we make use of a docking algorithm called MolDock based on a new hybrid search algorithm, called guided differential evolution. The guided differential evolution algorithm combines the differential evolution optimization technique with a cavity prediction algorithm. We used MVD because it showed higher docking accuracy than other stages of the docking products in the market. [12,13,14]

Table 2: Rhodanine derivatives with their Moldock Scores (kcal/mol) and H-bonds interactions against aldose reductase receptor



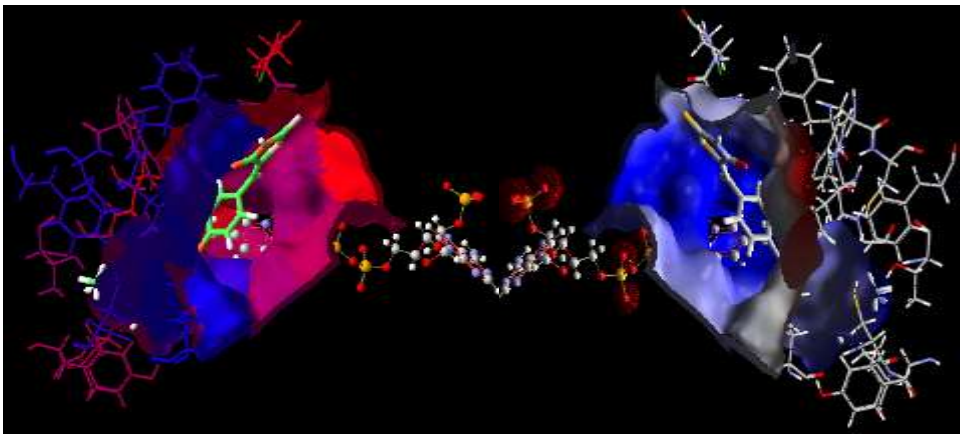
Ligand ' Code	R' Group Substituent	Moldock Score (kcal/mol)	Rerank score	H-bond	No. of H-Bonds / H-bond Interacting Residues
TA-01		**-147.03**	**-115.879**	**-0.442227**	**Thr113 Trp 111 Gln49**
TA-02		-141.416	-90.4969	-2.59791	-
TA-03		-133.336	-111.67	-2.74287	Thr 113 Cys303
TA-04		-142.742	-113.261	-0.268945	Trp11 Gln49

TA-05		-142.014	-119.227	-2.63005	Cys 80
TA-06		-145.424	-104.698	-2.78968	Thr113
TA-07		-140.496	-115.318	-2.78968	-
TA-08		-131.875	-112.072	-0.9952	Thr 113
TA-09		-145.097	-101.221	-2.6551	Cys 80
TA-10		-128.752	-114.132	0	Thr 113
TA-11		-134.453	-132.223	-1.2382	-



(a) (b)

Fig. 2 (a,b)Superimposed binding orientation of docked conformer in active site AR



(c) (d)

Most stable ligand (green) within the active binding with hydrophobic (Fig c) and electrostatic interaction (Fig d)

Results and Discussion

Molecular docking is a most convenient way to incorporate protein flexibility. The process of docking involves sampling the coordinate space of the target binding site and scoring each possible ligand pose within that site, the highest scoring poses then taken as the predicted binding mode for that compound.

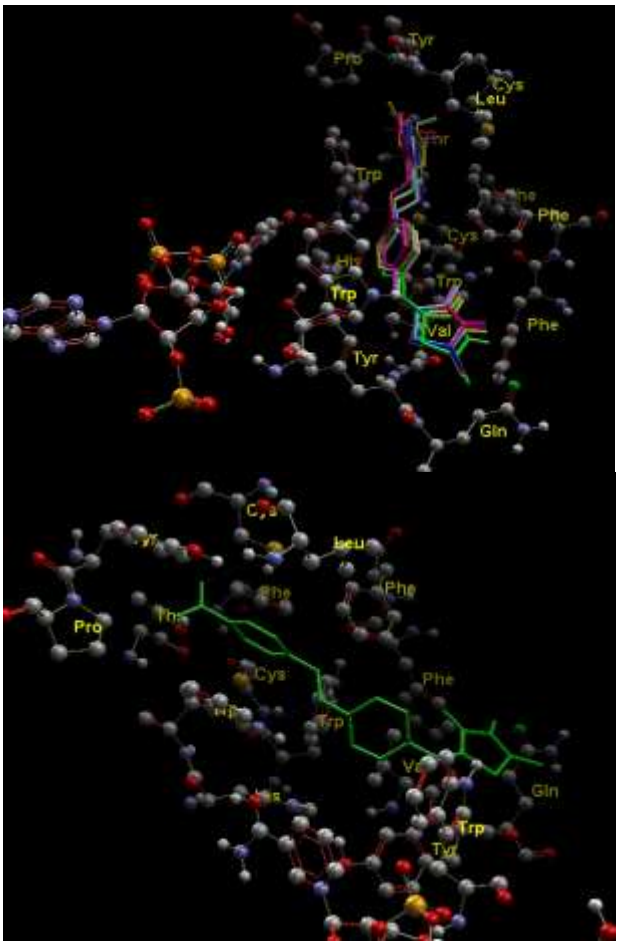
Molecular docking is a powerful tool in drug design, which could predict the best mode by which a given compound fits well into a binding site of a macromolecular target [15].

Table 1 presents the experimental values of MolDock score and the hydrogen bond interaction between inhibitor obtained after docking. Thus, it confirms that, the experimental values moderately agree with theoretical values, which suggest that the parameters for docking simulation are optimum in reproducing experimental orientation of these compounds. Protein-ligand molecular docking with ARI and interaction analysis. The main aim of docking study is to predict the orientation into AR and interaction of analogues with their active site residues.

Thus, it is possible to understand how the compounds with observed inhibition interact with the target protein. The results come out of this study can be used to establish the possible inherent mechanism of action of rhodamine analogs as potential aldose reuctase inhibitors.

The ligand-protein inverse docking simulation technique was performed with 11 synthetic ligands rhodanine derivativeswith basic α, β-unsaturated ketone andoxathiazole moieties reported to be having aldose reductase inhibitory activity by using MVD program. In the studies reported here, MVD was used, because it showed higher docking accuracy when benchmarked against other available docking

programs (MD: 87%, Glide: 82%, Surflex: 75%, FlexX: 58%) and has been shown to be successful in several recent studies, but also for reasons of cost and user-friendliness [16]



(e) **(f)**

Hydrogen bond interaction of docked conformers (fig f) and active comp in green(fig f)

The docking study applied to the database of 11compounds in the present study for finding 'best fit' (hit identification) against AR. The compound with least binding energy against target protein is considered for further study. By this means, it is possible to understand how the compounds interact with the target protein. The results emerging out of this study can be used to identify the binding properties of compounds.

The docking studies on experimental compounds (Table 1) showed that most stable binding ligand TA-01 with Moldock score -147.01kcal/mol involved in 3 hydrogen bonds with amino acid residues Thr 113, Trp 111, Gln 49 within the binding site region of 4lua. Although, other H-bond interactions exist, these hydrogen bonds are relevant for inducing intrinsic activity towards highly selective and AR specific inhibitory property.

Conclusion

Docking analysis revealed that rhodanine analog (TA-01) docks well with aldose reductase (ALR) and it interacts through hydrogen bonding. This interaction leads to the formation of stable ALR-rhodaninecomplex. Thus, it is a good molecule and it can be considered for developing into a potent aldose reductase inhibitor to treatment of long term diabetes complications.

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