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In Silico Protein-Ligand Docking Studies on Thiazolidinediones analogs as Potential Aldose reductase Inhibitors

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ABSTRACT: Aldose reductase (ALR) enzyme plays a key role in polyol pathway, there is conversion of excess amount of glucose into sorbitol and inhibit secondary complication of diabetes mellitus. The docking study is explored the structural interaction between ligand and enzyme to developed more effective ALR inhibitors. The docking study was performed on a substituted thiazolidinedione derivatives as potential aldose reductase inhibitor and these compounds were carried out, by using Molegro Virtual Docker v 6.0 on a set of representative compounds within the active site region of 4lua. Based on the validations and hydrogen bond interactions with at least two key active site residues made by R substituents were considered for evaluation. The docking results of most stable binding ligand Thr 113, Lys 21 with Moldock score -136.518 involved in 2 hydrogen bonds with amino acid residues, 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. The docking simulation clearly predicted the binding mode that is nearly similar to the crystallographic binding mode with 1.5 A° RMSD. Hence it could a potent inhibitor of aldose reductase enzyme and thus be used for prevention/ treatment of diabetic complications.

Keywords: Aldose reductase (AR) enzyme, Molecular Docking, Thiazolidinediones, A Rinhibitors (ARI) Molegro Virtual Docker (MVD)

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INTRODUCTION

Molecular docking is very important tool in drug discovery and, to study complex biological and chemical systems. Docking methodology aims to explore experimental binding modes and affinities or ligand conformation of macromolecular targets within the binding site. A standard computational and experimental drug design is used for lead compound optimisation and in virtual screening studies to find novel biologically active molecules. Basically, docking methodology includes a sampling algorithms and scoring functions for generating and evaluating ligand poses (Guedes *et al.*, 2014; Ferreira *et al.*, 2015). So, docking is a well known tool, used for increasing the speed of drug designing process and easy to understand in structure function relationships, automated docking and virtual screening.

Globally, Diabetes mellitus is a metabolic disorder and its complications are leading causes of death. As per WHO, around 47.3% of India's 70 million diabetics people suffer from diabetes and that are not diagnosed and do not know they have high blood glucose levels lead to complications such as blindness, kidney failure, heart disease, stroke and foot amputation. 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 together with sorbitol dehydrogenase (SDH) forms the polyol pathway. In the polyol pathway, AR initially catalyzes the NADPH-dependent reduction of the aldehyde form of glucose to form sorbitol. Sorbitol dehydrogenase then utilizing NAD oxidizes the intermediate sorbitol to fructose. Though, the inhibition of aldose reductase has basic approach to the prevention and treatment of diabetic complications and a potential target for drug design. Currently there are very few drugs available used to treat diabetic complications, the biochemical problems address and do not those which are indicated clinically provide symptomatic relief.

Although a large no of synthetic ARIs have shown to inhibit the enzyme and have been tested in clinical trials, the clinical efficacy of these compounds is not satisfactory and some have also shown deleterious side effect. Sorbinil, extensively studied ARIs, induced hypersensitivity reaction. Other promising ARIs such as Tolrestat, Zopolrestat, Zenarestat and ponarestat were also withdrawn from clinical trials. Epalrestat is the only drug marketed to treat the diabetes complications (Zhu, 2013).

Furthermore, recent studies have demonstrated on AR inhibitors may be able to prevent diabetic complications. Some heterocyclic analogues like Thiazolidinediones, benzimidazole and rhodanine derivatives improve glycaemic control type 2 diabetes and an effective for antihyperglycaemic agent as well as AR2 inhibitors but, some of them have been reported to have hepatotoxicity.

There is a need of 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.

In the present docking study on Aldose reductase enzyme were employed on some thiazolidinedione derivatives. By in Silico docking method, determined predicted binding energies and different modes of interactions exhibited by recognized ligands. The X-ray crystal structure was obtained from the Brookhaven Protein Data Bank (http://www.rcsb.org/pdb) (PDB.ID: 4lua).

MATERIALS AND METHODS

A. Software Methodology

In the present molecular docking study, software Molegro Virtual Docker (MVD) v 6.0 (www.molegro.com), MVD tools was used to generate grid, calculate dock score and evaluate conformers. Molecular docking was performed using MolDock docking software. 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. 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 (Gehlhaar *et al.,* 1995).

B. Molecular Modeling

A set of 11 new thiazolidinedione derivatives listed in Table 1 were synthesized and modeled by using chem. draw software (Avupati *et al.,* 2010).

C. Ligand Preparation

The structures of thiazolidinediones derivatives were converted into suitable chemical information using Chemdraw 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)). (Berman *et al.,* 2000) (Table 1).

D. Protein Selection

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. Moreover, we considered ramachandran plot statistics as the important filter for protein selection that none of the residues present in disallowed regions (Wang *et al.,* 1993).

E. Protein Preparation

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 (Ramachandran and Sasisekharan, 1968).

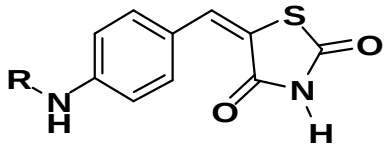
F. Software Method Validation

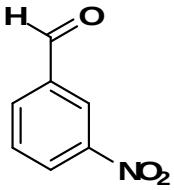
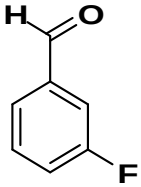
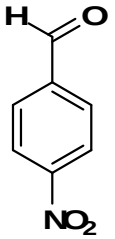
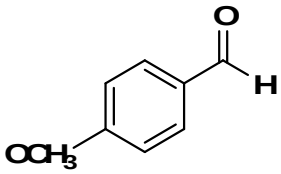
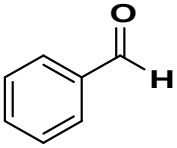
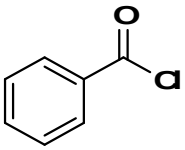
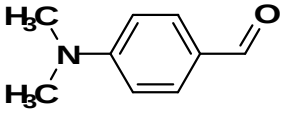
Software method validation was performed in MVD using Protein Data Bank (PDB) protein 4lua. The bio active co-crystallized bound ligand was docked with in the active site region on x-ray crystal structure of 4lua. The RMSD of all atoms between the two conformations is 1.5 A indicating that the parameters for docking simulation are good in reproducing X-ray crystal structure.

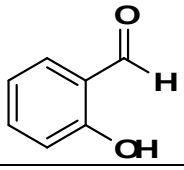
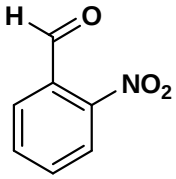
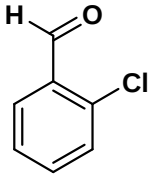
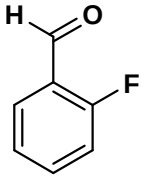
G. Molecular Docking

In the present investigation, 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.

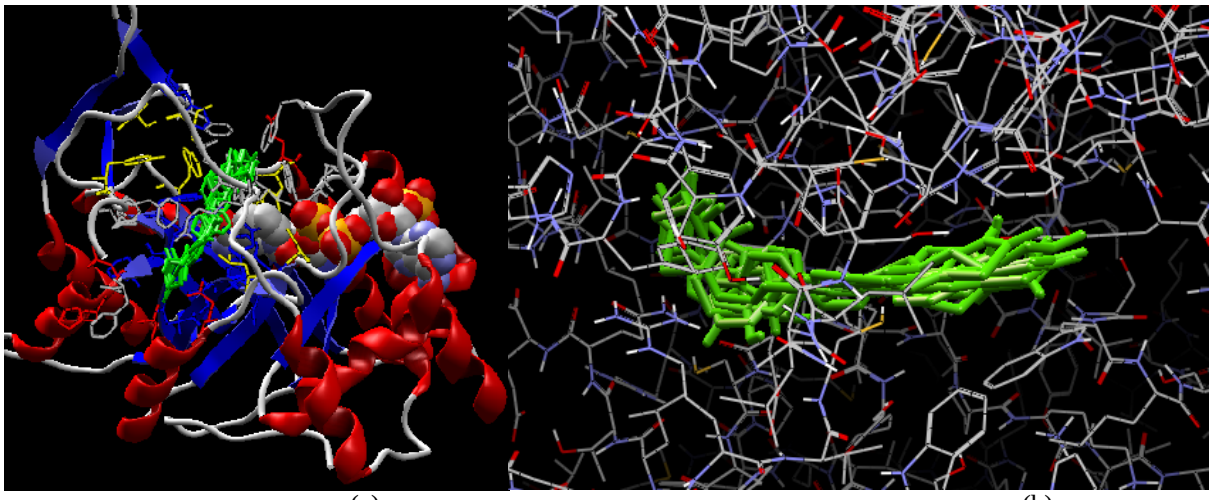
Table 1: Thiazolidinediones derivatives with their Moldock Scores (kcal/mol) and H-bonds interactions against aldose reductase receptor.



Ligand Code (comp)	**R Group Substituent**	**Moldock Score (kcal/mol)**	**Rerank score**	**H-Bond**	**No. of H-Bonds / H-bond Interacting Residues**
TA-01		-130.838	-107.512	-0.506198	Thr 113
TA-02		-135.278	-106.422	4.08248	-
TA-03		**-136.518**	**-99.513**	**-0.356862**	**Lys 21 Thr 113**
TA-04		-135.798	-104.14	-1.89071	Thr113
TA-05		-119.595	-96.0286	1.19951	Thr113
TA-06		-129.013	-102.572	-1.0025	Thr113
TA-07		-135.919	-99.1938	-0.57916	-

Ligand Code (comp)	**R Group Substituent**	**Moldock Score (kcal/mol)**	**Rerank score**	**H-Bond**	**No. of H-Bonds / H-bond Interacting Residues**
TA-08		-121.854	-99.9901	0	Thr113
TA-09		-139.283	-103.2305	-0.54232	Thr 113
TA-10		-130.395	-102.2330	-0.9927	Thr 113
TA-11		-132.766	-109.574	-0.5731	-

We used MVD because it showed higher docking accuracy than other stages of the docking products (MVD: 87%, Glide: 82%, Surflex: 75%, FlexX: 58%) in the market (Avupati *et al.*, 2010; Storn and Price 1995). Molecular docking studies was employed to dock the designed thiazolidinediones derivatives listed in (Table 1) against aldose reductase enzyme using MVD to locate the interaction between various compounds and aldose reductase enzyme. MVD requires the receptor and ligand coordinates in PDB format. Non polar hydrogen atoms were removed from the receptor file and their partial charges were added to the corresponding carbon atoms. Molecular docking was performed using MolDock docking engine of Molegro software.



(a) (b)

Fig. 1. (a, b) Superimposed binding orientation of docked conformer.

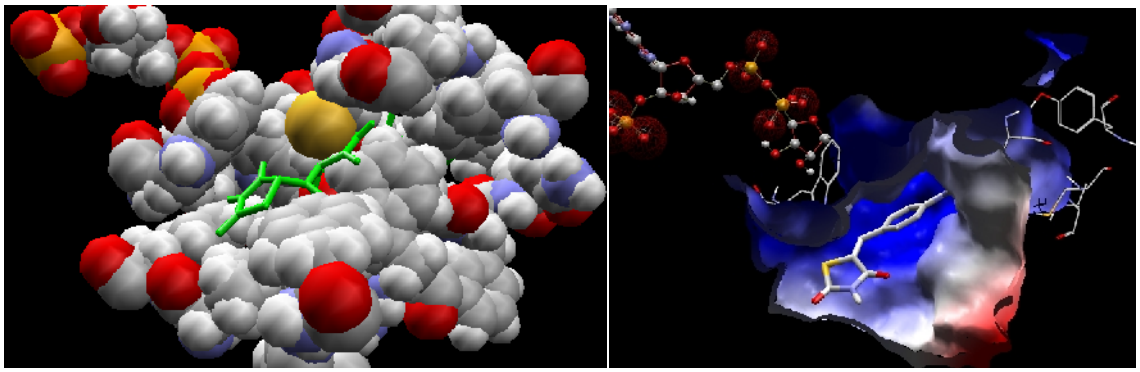
The binding site was defined as a spherical region which encompasses all protein atoms within 15.0 A° of bound crystallographic ligand atom (dimensions X (32.11 A°), Y (-77.21 A°), Z (-11.45 A°) axes, respectively). Default settings were used for all the calculations. Docking was performed using a grid resolution of 0.3 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.

RESULTS AND DISCUSSION

The docking process is to perform docking using an ensemble of static receptor conformations it is a most convenient way to incorporate protein flexibility. Recently, this approach is applicable for virtual screening. This approach applied using a collection of selected AR crystal structures with different bound ligands to give different conformations of the protein and allow for structural changes in the protein upon ligand binding.

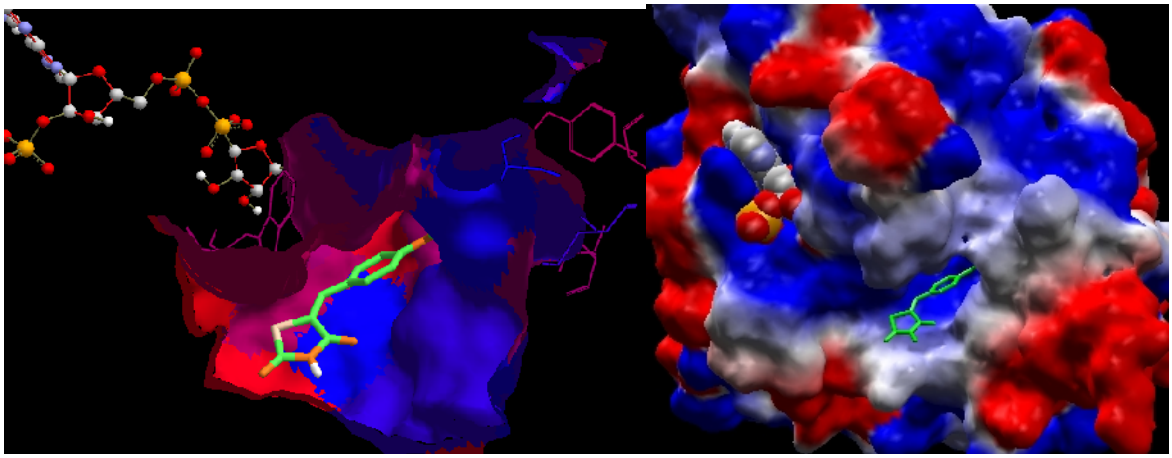
In docking study the compound with least binding energy against target. Protein is expressed as 'hit compound'. Thus, it is possible to understand how the compounds with observed inhibition interact with the target protein. The results come out of this study can be used to establish the possible inherent mechanism of action of thiazolidinediones as potential aldose reuctase inhibitors.

The ligand-protein inverse docking simulation technique was performed with 11synthetic ligands thiazolidinediones derivatives with basic α,β-unsaturated ketone and thiazolidine-2,4-dione moieties reported to be having aldose reductase inhibitory activity by using MVD program. Docking simulations with 4lua bound ligand resulted in a Moldock score of -136.518kcal/mol and a RMSD value of 1.5 A° showed 2 hydrogen bond interactions with in the active binding site region.



(c) (d)

Fig.1. (c) Most stable ligand (green) within the active binding site region. (d) electrostatic interaction with active binding site of AR.



(e) (f)

Fig. 1. (e) hydrophobic region occurs and showing space active site cavity for interaction of active stable compound in fig (f).

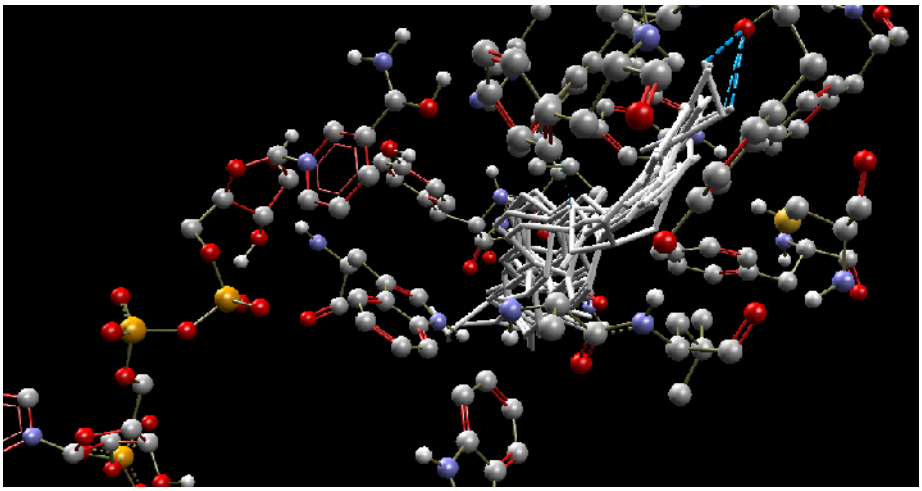


Fig. 1. (g) Active binding mode and H-bond interactions of docked conformers against AR.

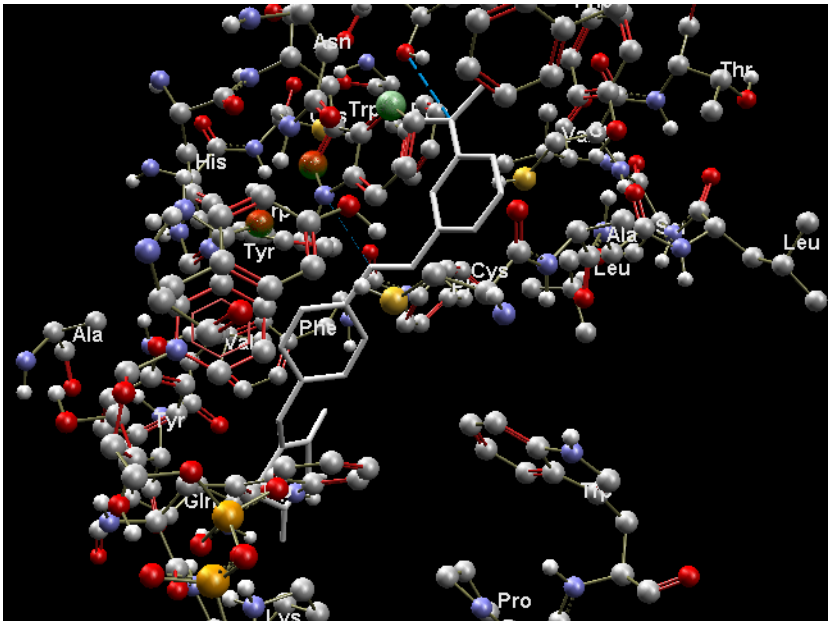


Fig.1. (h) H-bond interactions of active docked conformer (TA-03) against AR.

Docking studies on experimental compounds (Table 1) showed that most stable binding ligand TA-04 with Moldock score -136.518kcal/mol involved in 2 hydrogen bonds with amino acid residues Thr 113, Lys21 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

The docking studies detailed above provide estimates of the inhibitory activities of the docked ligand. The results show that thiazolidinedione derivatives (TA01-11) observed with inhibitory activity of aldose reductase enzyme and also interact with the residues in the active site which are important for their biological activity, thus, thiazolidinedione derivative (TA-03) compound could be a putative inhibitor of aldose reductase and can be used to prevent the onset/treatment of diabetic complication.

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