International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 9, Issue 4, 2017

Original Article

INSILICO STUDIES OF OXIME PRODRUG OF GLICLAZIDE AGAINST SULPHONYLUREA RECEPTORS (SUR 1)

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Received: 28 Jan 2017, Revised and Accepted: 20 Apr 2017

ABSTRACT

Objective: Objective of the study is to perform a molecular docking analysis of novel oxime prodrug of gliclazide against SUR1 receptor.

Methods: Sulfonylurea receptors (SUR) are membrane proteins which are the molecular targets of the sulfonylurea class of anti-diabetic drugs whose mechanism of action is to promote insulin release from pancreatic beta cells. Oxime prodrug of gliclazide a better soluble derivative of gliclazide is used for enhancement of bioavailability of gliclazide. Autodock 4.2 software was used for docking studies. Ligand 2D structures were drawn using ChemDraw Ultra 7.0. Binding sites, docking poses and interactions of the ligand with SUR1 receptors were studied by pymol software.

Results: The docking studies suggest that potential binding sites of oxime prodrug of gliclazide exhibiting all the major interactions such as hydrogen bonding, hydrophobic interaction and electrostatic interaction with GLU43, LEU11, LEU 40, ILE17 GLU 68, GLN72 residues of SUR1. The binding energy of complexes are also found to be minimal forming stable complexes.

Conclusion: *In silico* study of oxime prodrug of gliclazide conforms, the binding of oxime prodrug of glicalzide with SUR1 receptors which effectively controls the release insulin to regulate plasma glucose concentrations. Hence, the oxime prodrug of gliclazide could be a potent anti-diabetic target molecule which may be worth for further *in vitro* and *in vivo* studies.

Keywords: Insilico study, Oxime prodrug, Gliclazide, Sulphonylurea receptors

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DOI: http://dx.doi.org/10.22159/ijcpr.2017v9i4.20968

INTRODUCTION

Molecular docking describes the "best-fit" orientation of a ligand that binds to a particular protein of interest and is used to predict the structure of the intermolecular complex that has been formed between two or more molecules [1]. The most interesting case is the protein-ligand interaction, because of its applications in medicines. Ligand is a small molecule, which interacts with protein's binding sites [2]. Binding modes are several possible mutual conformations in which bindings may occur. These are commonly called binding modes [3]. Molecular docking provides useful information about drug receptor interactions and is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to envisage the binding affinity and activity of the small molecule [4].

Diabetes mellitus (DM), is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Type 2 diabetes occurs as a result of obesity lack of exercise and genetic factors [5]. Sulphonylurea compounds are the group of organic compounds used in the treatment of type 2 diabetes mellitus. Sulfonylureas bind to an ATP-sensitive K^+ (K_{ATP}) channel on the cell membrane of pancreatic beta cells. This inhibits a tonic, hyper polarizing efflux of potassium, and makes the electric potential over the membrane to become more positive. This depolarization opens voltage-gated Ca^{2+} channels [6]. The increase in intracellular calcium leads to augmented fusion of insulin granulae with the cell membrane resulting in increased secretion of (pro) insulin. The insulin released reduces plasma glucose concentrations. Sulphonylurea analogues exhibited better binding affinity in SUR1 receptors, a member of the adenosine-triphosphate-binding cassette protein superfamily [7, 8].

Sulfonylureas, including glyburide, glipizide, gliclazide and glimepiride or their antecedents were used for the treatment of T2DM since the 1960s. Since their inception in clinical practice, Sulfonylureas (SUs) exists as the backbone of pharmacotherapy in the management of type 2 diabetes mellitus (T2DM) [9]. A careful choice of SU, apt dosage, the timing of administration and suitable patient counseling will ensure that deserving patients are not deprived of the advantages of this well-established class of anti-diabetic agents. Considering their efficacy, safety and low cost of therapy, SUs were considered as drugs/agents of choice for the treatment of diabetes [10]. Modern SUs (Glimepiride and Gliclazide) are preferred over conventional SUs in view of the reduced mortality (all-cause and CV mortality), better CV outcomes (composite of acute myocardial infarction, stroke, and Cardio Vascular mortality), and renal protection n [11]. Gliclazide is poorly water soluble drug with low bioavailability hence in our previous paper we synthesised oxime prodrug of gliclazide, a more soluble and better bioavailable derivative of gliclazide [12]. In continuation of that in the present study, we have performed the molecular docking studies of the oxime prodrug of gliclazide with SUR1 receptors to study drug receptor interaction.

MATERIALS AND METHODS

Materials

AutoDock 4.2software which perform the automated Docking of Flexible Ligands to Flexible Receptors, introduced by Garrett M. Morris *et al.*, [13] popularly known as Autodock with version 4.2 was used in the present study to study the molecular docking. Discovery Studio, a BIOVIA's software of comprehensive predictive science application for the Life Sciences, was used in the present study to separate the ligand from the protein. PyMOL an open-source, user-sponsored, molecular visualization system created by Warren Lyford De Lano, was used to visualize the docking positions in 3-dimensional images.

Ligand structure preparation

Ligand 2D structures were drawn using ChemDraw Ultra 7.0 (Chem Office 2002). Chem3D Ultra 7.0 was used to convert 2D structure into 3D and the energy minimised using the semi-empirical AM1 method. RMS gradient was set to a minimum value of 0.100 was set in each iteration to minimize energy. All structures were saved as

pdb file format for input to AutoDockTools (ADT) version 1.5.6. All the ligand structures were then saved in PDBQT file format, for input into AutoDock version 1.5.6.

Protein structure preparation

For the molecular docking study, protein structure was obtained from the RCSB protein data bank; PDB ID of SUR protein is 2E5Z which is a solution structure of surp2 domain in splicing factor.20 conformations were available for the protein structure, out of that top 10 conformations were chosen for the study. All hydrogen atoms were added, residue structures in lower occupancy state were deleted, and any incomplete side chains were replaced using the ADT version 1.5.6. Further ADT was used to remove crystal water, Gasteiger charges were added to each atom, non-polar hydrogen atoms were merged to the protein structure. The distance between donor and acceptor atoms that form a hydrogen bond was demarcated as 1.9 Å with a tolerance limit of 0.5 Å, and the acceptor–hydrogen–donor angle was not less than 120[0]. The structures were then saved in PDBQT file format, for input into AutoDock version 1.5.6.

Methodology

The Autodock 4.2 program was used to locate the appropriate binding orientations and conformations of oxime prodrug of gliclazide on sulphonyl urease receptors (SUR1). AutoDockis an extensively used automated procedure for predicting the interaction of small molecules, such as peptides, enzyme inhibitors, and drugs, to macromolecules, such as proteins, enzymes, antibodies, DNA, and RNA. The structure of the non-nucleoside binding site (NNBS) of sulphonyl urease was taken from Brookhaven Protein Data Bank with the entry code SUR1.

Molecular structures of oxime prodrug of gliclazide were built using the ChemBio draw ultra 11.0 version. Geometry optimizations of all derivatives were carried out using the Tripos force field with a distance-dependent dielectric and the Powell conjugate gradient algorithm. Gasteiger-Hückel charges were used.

Docking procedure

AUTOGRID 4.0 was used to calculate the grid maps with 40 X 40 X 40 points, a grid point spacing of 0.375 Å and the maps were centered on the ligand. The Lamarckian Genetic Algorithm (LGA) in Autodock 4.0 was used to explore the energy landscape. The hybrid search technique consists of a global optimizer modified from a genetic algorithm with 2-point crossover, random mutation, and a local optimizer with a Solis and Wets algorithm. A docking box of 40 X 40 X 40 points with a grid spacing of 0.375 Å was used in the calculations. Random conditions were used in the settings of seed, initial quaternion, coordinates, and torsions. A 0.2 Å step was used for translation and a 25-degree was used for quaternion and torsion. The maximum number of energy evaluation was set as 250000, and the maximum number of generations was fixed as 27000. The rate of gene mutation was 0.02, and the rate of crossover was 0.8. The number of cycles was fixed as 10. So a total of 10 docking configurations were determined in each docking calculation. A preferable docking configuration was chosen based on the lowest empirical binding free energy and the most frequent cluster.

RESULTS AND DISCUSSION

Potential binding sites of oxime prodrug of gliclazide: Glu 43, leu11, leu 40, Ile17 Glu 68, Gln72. The minimum binding energy indicated that the SUR1 (target protein) was successfully docked with oxime prodrug of gliclazide. The possible binding position of oxime prodrug of gliclazide at SUR1 active sites in models I to X have been shown in fig. Ten models of SUR1 were chosen and for each model, ten conformations of ligand in protein was studied. Comparative study of ten models and their respective ten conformations shown that conformation1 in model 1 exhibits minimum binding energy of-15.44 kcal/mol.

The docking of SUR1 target with oxime prodrug of gliclazide using docking procedure revealed that all the computationally predicted lowest energy complexes of SUR1 are stabilized by intermolecular hydrogen bonds, Vanderwaals force and stacking interactions. It is found that C11, O8, N13, H28, H32 are the ligand atoms involved in docking with the protein.

The AutoGrid model presented the most energetically favorable binding mode of oxime prodrug of gliclazide to SUR1. The oxime prodrug of gliclazide as a ligand is docked into the generated combined grids and the binding energies are evaluated, and it is observed that minimum binding free energy complex performs the best table 1 and 2. The ligand showed the best interaction with target proteins fig. 1-3. Docking results revealed that this oxime prodrug of gliclazide compound can effectively bind with SUR1 protein target which will regulate insulin secretion. Further *in-vitro* and preclinical in vivo studies are warranted to confirm the activity of oxime prodrug of gliclazide table 1-2.

Table 1: Intermolecular energy of various models of SUR1 I to X

Models	Intermolecular energy(kcal/mol)
1	-15.74
2	-15.43
3	-15.39
4	-14.98
5	-14.86
6	-14.84
7	-14.81
8	-14.81
9	-14.67
10	-14.55

Table 2: Binding energy of various models of SUR1 I to X

Model	Binding energy(kcal/mol)
1	-15.44
2	-11.99
3	-9.35
4	-11.43
5	96.54
6	26.38
7	385.92
8	52.1
9	570.94
10	7.93

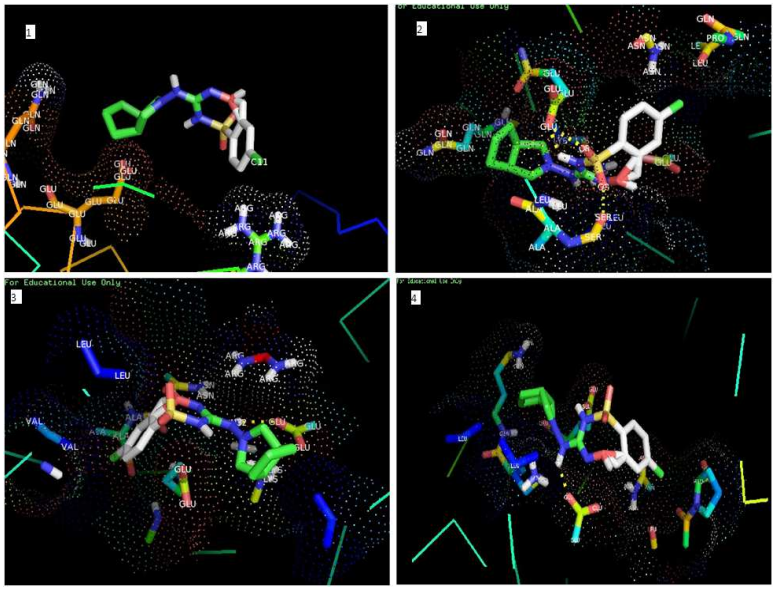

Fig. 1: Complex formed between ligand and model 1-4 of SUR1 receptors

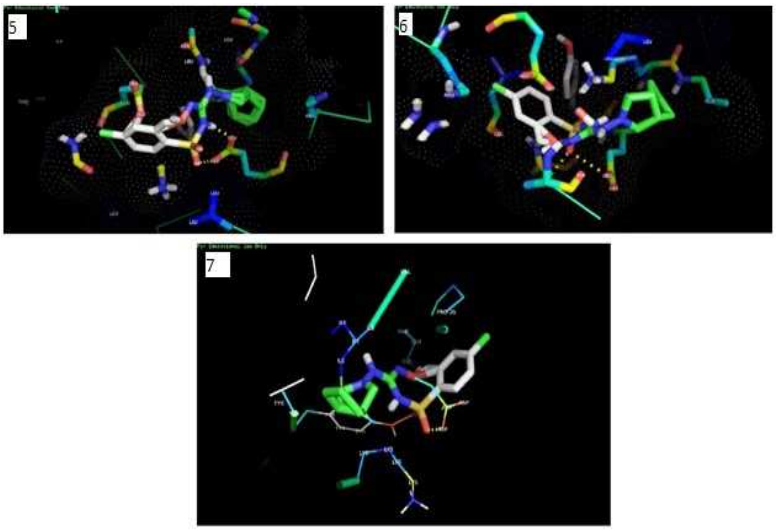

Fig. 2: Complex formed between ligand and model 5-7 of SUR1 receptors

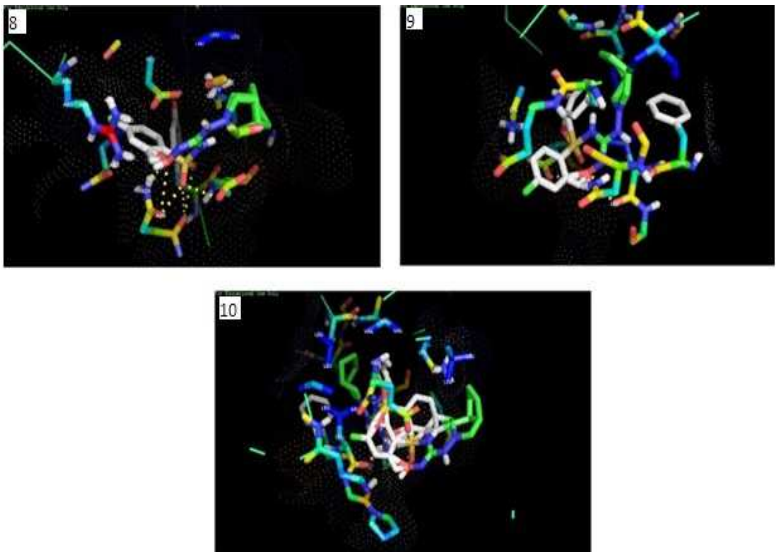

Fig. 3: Complex formed between ligand and model 8-10 of SUR1 receptors

CONCLUSION

In the present study docking of oxime prodrug of gliclazide was successfully done in the SUR1 receptor for antidiabetic activity. Molecular interactions and binding patterns were studied by Auto dock vina and Pymol software. Several docking poses of the ligand were trailed in ten models of SUR1 a member of ATP-binding cassette. Based on lowest binding free energy-15.44 kcal/mol, conformation 1 in the model I was chosen as the best dock. Therefore, the *in silico* study of oxime prodrug of gliclazide conforms, the ligand (a sulphonylurea analogue) binds effectively in ATP binding cassette of β cells of the pancreas and can effectively release insulin to regulate plasma glucose concentrations. Hence, it is concluded that that oxime prodrug of gliclazide could be a potent anti-diabetic target molecule which may be worth for further clinical trials.

CONFLICTS OF INTERESTS

Both authors have none to declare

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How to cite this article

- Surendran Vijayaraj, Kannekanti Chaithanya Veena. Insilico studies of oxime prodrug of gliclazide against sulphonylurea receptors (Sur1). Int J Curr Pharm Res 2017;9(4):100-103.