MOLECULAR DOCKING STUDIES OF NOVEL NITROPHENYL INHIBITOR AGAINST ALDOSE REDUCTASE

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ABSTRACT: *Aldose reductase is associated with diabetes. Many inhibitors are design that may be used as potential inhibitors for treatment of diabetes. Molecular docking is the most used tool in structure based drug-design. In the present study, we have tried to investigate novel Nitrophenyl derivative as aldose reductase inhibitor via in silico docking studies using AutoDock 4.2.6. In the docking studies three important parameters like Interaction Pattern, Binding Moeties and Binding Energy were determined. The results showed that the selected novel molecule shows binding energy i.e., (-1.90) kcal/mol and HIS110, TYR48, CYS80, LEU300, TRP111, CYS298, PHE1115, THR113, CYS303, TRP79 and PHE122 as binding moieties. Thus, Molecular docking study reveals that novel nitrophenyl derivative has good interaction pattern and exhibits aldose reductase inhibitory activity because of its structural properties. This molecular docking could lead to further development of potent aldose reductase inhibitor hence more in vivo studies required to validate inhibitor potentially for the treatment in diabetes.*

Key Words: *Molecular Docking, Nitrophenyl inhibitor, Aldose reductase, Drug-designing, Insilico docking, Interaction pattern.*

Introduction:

Diabetes Mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both (1). Type 1diabetes is caused by a lack of β-pancreatic cells insulin secretion (1). Type 2 diabetes is associated with obesity and is characterized by an early phase progressive insulin resistance, with ensuing reduction in the ability of pancreatic hormone to promote peripheral glucose disposal and to decrease hepatic glucose output (2, 3).

Aldose reductase (ALR2) belongs to aldoketo reductase group. It is a first rate limiting enzyme in polyol pathway during diabetes cause accumulation of osmotically active sorbitol results into osmotic as well as oxidative stress, leading to tissue injury (4, 5). Evidence shows the involvement of ALR2 in diabetic neuropathy, retinopathy, nephropathy and cataract emerged from several independent studies. Thus, inhibiting ALR2 activity appears to be an effective means to prevent the diabetic complications (6).

Drug design is an important tool in the field of medicinal chemistry where new compounds are synthesized by molecular or chemical changes of the lead moiety in order to produce highly active compounds with minimum steric effect (7). A huge breakthrough in the process of drug design was the development of *Insilico* method to predict about the therapeutic efficacy of the molecule (8, 9).

Molecular docking is a most common tool in computer aided structure-based rational drug design. It evaluates how ligands (nitrophenyl derivative) and the target macromolecule (ALR2 enzyme) fit together (10, 11). Factors such as binding energies, position of ligand in the enzyme binding site are determined in present study. This is useful in developing potential drug candidates and understanding binding nature. AutoDock 4.2.6 is the most recent version which has been widely used for virtual screening, due to its enhanced docking speed (12). Its default search function is based on Lamarckian Genetic Algorithm (LGA), a hybrid genetic algorithm with local optimization that uses a parameterized free energy scoring function to estimate the binding energy (13). The main objective of the study is to define *in silico* ALR2 inhibitory activity of novel nitrophenyl derivative.

Soft wares required:

Molecular graphics laboratory (MGL) tools and AutoDock 4.2.6 by Scripps research institute (http://AutoDock.scripps.edu/) was used to perform Docking studies, Openbabel GUI by BABEL (https://openbabel.org/docs/dev/GUI/GUI.html) was used to transform chemical structures and files into working formats, molecular modelling was performed using ACD/ChemSketch 2012 (https://www.acdlabs.com/resources/freeware/chemsketch/).

Materials and Methods:

Computational Methods:

PDB Structure Retrieval:

Crystal structure of ALR2 enzyme (EC: 1.1.1.21) receptor was downloaded from the PDB Protein Data Bank (http://www.rcsb.org/), the structure further utilized in docking study (14).

Conversion of Ligand Molecule:

Ligand molecule which was molidated from previous QSAR study was having non-functional format (.mol) for AutoDock 4.2.6 software. It was first converted to its working format (.pdb) for further Docking studies using Openbabel GUI by BABEL (https://openbabel.org/docs/dev/GUI/GUI.html) software (15).

Docking Studies:

A docking validation has been performed using MGL tools and AutoDock 4.2.6 developed by The Scripps research institute. Lamarckian genetic algorithm (14) for ligand conformational searching is used for the docking, which is a hybrid of genetic algorithm and local search algorithm. This algorithm first builds a population of individuals, each being a different random conformation of the docked molecule. Local search algorithm then performs energy minimizations on a user-specified proportion of the individuals. An extended PDB format, termed as PDBQT file was used for coordinate files which includes atomic partial charges. AutoDock tools were used for generating PDBQT files from traditional PDB files (16).

The Nitrophenyl derivative (Active molecule Mol 20) molidated from previous QSAR study was used as Ligand and a PDBQT file was created using AutoDock tools. The optimized ligand molecule was docked into ALR2 receptor module in AutoDock 4.2.6 (17).

The preparation of target protein with AutoDock tools software involved adding all hydrogen atoms to the macromolecule, which is a step necessary for correct calculation of partial atomic charges. Gasteiger charges are calculated for each atom of the macromolecule. In Grid parameter function a grid box has been designed using values of 17.889, (-7.359) and 14.599 as X, Y and Z center grid size.

The selected important docking parameters for the LGA as follows: population size of 150 individuals, maximum of 27000 generations, number of top individuals to automatically survive to next generation of 1, mutation rate of 0.0, crossover rate of 0.8, 10 docking runs, 2.5 million energy evaluations and random initial positions and confirmations. The probability of performing local search on an individual in the population was set to 0.06.

AutoDock was run to get various docked confirmations and used to analyse the predicted docking energy. 10 best poses were generated and scored using AutoDock 4.2.6 scoring functions (14).

Results and discussion:

Docking interactions:

Insilico docking study, was carried out to identify the inhibiting potential of selected nitrophenyl molecule against aldose reductase enzyme. The docking studies were performed by the use of AutoDock 4.2.6. The docking poses were ranked according to their docking scores and both the ranked list of docked ligand and their corresponding binding poses (14). This ranking of the compounds were based on their binding energy with the enzyme. If the binding energy of the compound is less, then the particular compound has more active in nature. In figure (A) docked pose of ALR2 enzyme with the selected ligand demonstrated the binding positions of the ligand with the enzyme.

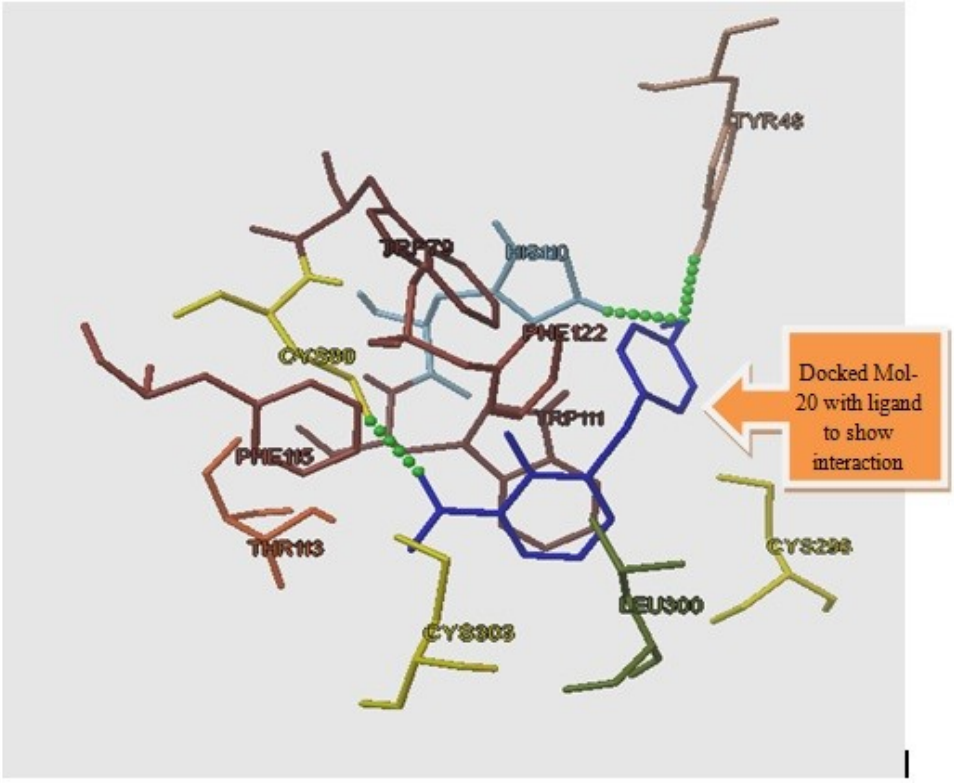

FIGURE A: Docked pose (Binding pattern) of ALR-2 enzyme with selected ligand molecule.

Binding energy of the compound was calculated by using the following formula:

Binding energy = A+B+C-D

[Where A denotes final intermolecular energy+ van der walls energy (vdW) + hydrogen bonds + desolvation energy + electrostatic energy (kcal/mol), B denotes final total internal energy (kcal/mol), C denotes torsional free energy (kcal/mol) and D denotes unbound system's energy (kcal/mol).]

The binding sites of the ligand molecule was found to be HIS110, TYR48, CYS80, LEU300, TRP111, CYS298, PHE115, THR113, CYS303, TRP79 and PHE122. This proves that the effective binding sites are present in the selected Nitrophenyl derivative when compared to standard (18). It proves the ability of inhibiting the ALR2 enzyme by the selected Nitrophenyl derivative.

Analysis of the Receptor/Ligand complex models generated after successful docking of the Nitrophenyl derivative was based on the parameters such as hydrogen bond interactions, π-π interactions, binding-energy, RMSD of active site residues and orientation of the docked compound within the active site (13).

As a general rule, in most of the potent anti-inflammatory compounds, both hydrogen bond and π-π hydrophobic interactions between the compound and the active sites of the receptor have been found to be responsible for mediating the biological activity. Analysis of the receptor/ligand complex models generated after successful docking of the Nitrophenyl derivative was based on the parameters such as binding energy, hydrogen bond interactions, π-π interactions, orientation of the docked compound within the active site and RMSD of active site residues (19, 20).

According to the results of AutoDock the summary of all the significant factors affected Docking studies have been described below:-

A total of 10 modules have been run from which **Module-1** with the lowest Free Binding energy is shown:

Estimated Free Energy of Binding = -1.90 kcal/mol [= (1) + (2) + (3) - (4)]

Estimated Inhibition Constant, Ki = 40.29 mM (millimolar) [Temperature = 298.15 K]

(1) Final Intermolecular Energy = -3.10 kcal/mol
vdW + Hbond + desolv Energy = -8.84 kcal/mol
Electrostatic Energy = +5.75 kcal/mol

(2) Final Total Internal Energy = -0.13 kcal/mol

(3) Torsional Free Energy = +1.19 kcal/mol

(4) Unbound System's Energy [= (2)] = -0.13 kcal/mol

Conclusions:

Molecular docking studies using AutoDock 4.2.6 Tools was performed to explore the binding mechanism of the nitropenyl derivative with Aldose reductase enzyme. In the present molecular docking study, results clearly demonstrated that the novel designed nitrophenyl derivative have a similar binding sites and interactions with Aldose reductase. The molecular interaction & energy level of designed molecules shows good inhibitory activity than available analogs. Thus novel designed molecule may be used as alternative and effective means of inhibitors for aldose reductase.

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