**In silico** Design and Molecular Docking Studies of Benzimidazole Bearing thiazolidin-4-one Derivatives as PPARγ Agonists in Diabetes Mellitus

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**ABSTRACT**

Diabetes mellitus (DM) is the major cause of mortality and morbidity in the world. The objective of the study is the in silico design and molecular docking studies of benzimidazole bearing thiazolidin-4-one derivatives as PPARγ agonists in diabetes mellitus. In silico design of proposed derivatives were conducted by ACD lab Chemsketch 12.0 and derivatives obeying Lipinski’s rule of five were selected for molecular docking studies by AutoDock Vina. Visualization and analysis were conducted by PyMOL. Molinspiration studies revealed that the designed derivatives had physical and chemical properties meant for an orally bioavailable drug. Based on the docking results, derivatives BT-1 and BT-3 showed high docking score which indicates that these derivatives possess high affinity and high polar interaction towards protein 1PRG (Ligand binding domain of human peroxisome proliferator activated receptor gamma). The designed Benzimidazole bearing thiazolidinone derivatives were found to possess good binding affinity and good interaction in the binding pocket of target 1PRG, so these derivatives are expected to exhibit good antidiabetic property with minimal side effects.

**Keywords:** Diabetes mellitus, PPARγ agonist, Docking, AutoDock Vina, Pioglitazone.

**INTRODUCTION**

The disease burden related to diabetes is high and rising in every country. Diabetes mellitus is a chronic condition associated with abnormally high level of glucose in the blood. Several pathogenic processes are involved in the development of diabetes. There are three types of diabetes mellitus. Type 1 diabetes mellitus is a chronic autoimmune condition in which the pancreas produces little or no insulin (insulin-dependent). Type 2 diabetes mellitus is a chronic condition that affects the way the body processes blood glucose. It is beginning with insulin resistance and lack of insulin may also develop (insulin-independent). Type 3 diabetes mellitus or Gestational diabetes is any degree of glucose intolerance that was first recognized during pregnancy. Hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of various organs such as eye, kidney, nerves, heart and blood vessels.

Diabetes mellitus is normally controlled by controlling of blood sugar through diet, exercise, oral medications and insulin therapy.

Currently available therapies for diabetes mellitus includes anti-diabetic agents such as Sulfonylureas (glimepiride), Biguanides (metformin), Meglitinides (repaglinide), GLP-1 agonists (lixisenatide, liraglutide), DPP-4 inhibitors (sitaglitpin, saxagliptin), Thiazolidinediones (pioglitazone) and alpha glucosidase inhibitors (acarbose). But these drugs had various side effects such as severe joint pain and heart failure (DPP-4 inhibitors), kidney dysfunction (metformin), hypoglycaemia (sulfonyl ureas), liver disease and weight gain (thiazolidinediones), diarrhoea and bloating (acarbose).

Peroxisome proliferator activated receptor gamma (PPARγ) also known as glitazone receptor regulates the genes important for cell differentiation and various metabolic processes especially lipid and glucose homeostasis. Activation of PPARγ causes insulin sensitization and enhances glucose metabolism. Activated PPARγ in adipocytes secrete mediators of insulin action in peripheral tissues.

PPARγ comprises of an agonist-dependent activation domain (AF-2), DNA binding domain and agonist-independent activation domain (AF-1)[6]. Upon the binding of agonists, PPARγ heterodimerizes with retinoid X receptor-α and activates the transcription of target genes through binding of PPRE response elements.

Thiazolidinediones (TZDs) are the important PPARγ agonists that improve the glucose tolerance by enhancing insulin sensitivity and restoring the functions of β-cells in diabetic patients. But these drugs have various side effects. So, the designed benzimidazole bearing thiazolidinone derivatives are expected to exhibit good antidiabetic activity with less side effects.
Benzimidazole is one of the oldest known nitrogen containing heterocyclic aromatic compound. This bicyclic compound is the fusion of benzene and imidazole nucleus. Benzimidazole nucleus explores variety of therapeutic uses including antitumor, antifungal, antidiabetic, analgesic, and antiinflammatory activity. Thiazolidinone is a five membered heterocyclic compound containing one nitrogen, one sulphur and three carbon atom, with a carbonyl group. It possesses broad spectrum of biological activities such as antidiabetic, anti-inflammatory, antihistaminic, antifungal, anthelmintic and as CNS stimulants. Molecular docking is a kind of bioinformatics modelling which involves the interaction of two or more molecules to give a stable adducts. Depending upon the binding properties of ligand and target, it predicts the three dimensional structure of the complex. The information obtained from the docking technique can be used to suggest the binding energy, free energy and stability of complexes.

**MATERIALS AND METHODS**

**ACD Lab Chemsketch 12.00**

Used for drawing chemical structures, 3D optimization and calculating various physicochemical properties of the proposed derivatives. The values obtained for the novel derivatives were compared with standard drug (Pioglitazone). About 15 derivatives were designed for molecular descriptor analysis and docking studies.

**Molinspiration**

It is used to calculate the molecular properties and bioactivity for prediction of Lipinski’s rule of five. Lipinski’s rule of five or rule of thumb helps to determine whether the compound is likely to have the physical and chemical properties to be orally bioavailable. 15 derivatives designed were analysed by molinspiration and those derivatives obeying Lipinski’ rule of 5 were selected for docking studies.

**Protein Data Bank (PDB)**

PDB is the only crystallographic database meant for obtaining the 3D structural data of large molecules such as proteins and nucleic acids.

The structure were generated after X-ray crystallography and NMR studies. In this study the protein selected is PPARy (PDB code 1PRG).

**Molecular Docking**

Docking is the prediction of affinity and activity of derivatives to suitable protein targets. AutoDock Vina, an open-source docking program was selected for docking studies. PyMOL was used for protein preparation and visualization. PyRx was used for docking analysis.

**Protein Preparation**

Structure taken from the PDB database could not fit as such for docking studies. Because it consists of water molecules (HOH), detergents (DSN), small molecules, cofactors, metal ions etc. Therefore, the PDB structure should be converted into suitable form for docking by addition of command “remove >resn< >molecules” (HOH, DSN etc). Hydrogen atoms should be added to the protein structure.

**Ligand Preparation**

The structures of derivatives were drawn using ACD Lab Chemsketch 12.0 and converted into 3D PDB format using Corina online software.

**Docking by AutoDock Vina**

Docking was performed using PyRx by loading the protein and derivatives into the navigation pane. The protein was then converted into macromolecule and derivative was converted into ligand molecule. After preparation of protein and ligand, click the AutoDock Vina Wizard button and adjust the grid size. The accuracy of the result depends on the number of exhaustiveness. Exhaustiveness is the number of times the ligand must be docked against the protein in different positions. After the completion of process, the results are displayed in the table. The binding affinity of the protein is indicated in Kcal/mol. RMSD upper and lower band indicates the position of the ligand which binds in the protein.

**Visualization and Analysis**

The PyMOL molecular graphics system was used to analyse the hydrogen bond, hydrophobic and pi-pi interactions. PyMOL can produce high quality 3D images of small molecules and macromolecules such as protein.

**RESULTS AND DISCUSSION**

A series of structurally related derivatives were designed using ACD Lab Chemsketch 12.0. Those derivatives obeying rule of 5 were selected for docking studies. The structures and molecular descriptors of selected derivatives and standard are depicted in the Table 1.

![Figure 1: 3D structure of PPARy](image-url)
Table 1: Structure and molecular descriptors of derivatives and standard (Pioglitazone)

| Compound Code | Structure | MW (g/mol) | HA | HD | Log P | rot b | Violation |
|---------------|-----------|------------|----|----|-------|-------|-----------|
| BT-1          | ![Structure Image] | 400.89     | 6  | 1  | 2.65  | 4     | 0         |
| BT-2          | ![Structure Image] | 411.44     | 9  | 1  | 1.93  | 5     | 0         |
| BT-3          | ![Structure Image] | 396.97     | 7  | 1  | 2.03  | 5     | 0         |
| BT-4          | ![Structure Image] | 382.44     | 7  | 2  | 1.49  | 4     | 0         |
| BT-5          | ![Structure Image] | 366.45     | 6  | 1  | 1.97  | 4     | 0         |
| Standard (pioglitazone) | ![Structure Image] | 356.45     | 5  | 1  | 3.07  | 7     | 0         |

HA = number of hydrogen bond acceptor  
HB = number of hydrogen bond donor

Complex of selected 5 derivatives and standard (pioglitazone) with protein 1PRG was visualized using PyMOL (Figure 2). Docking score of derivatives and standard pioglitazone with protein 1PRG is shown in Table 2.

Table 2: Docking score of derivatives and standard (Pioglitazone) with 1PRG

| Sl. No | Compound code | Docking score (Kcal/mol) |
|--------|---------------|--------------------------|
| 1      | BT-1          | -9.0                     |
| 2      | BT-2          | -8.7                     |
| 3      | BT-3          | -8.9                     |
| 4      | BT-4          | -8.5                     |
| 5      | BT-5          | -8.1                     |
| 6      | Standard (Pioglitazone) | -9.5                   |

Docking results revealed that BT-1 and BT-3 explored high negative docking score which indicates that these two derivatives possess high affinity and very good interaction within the binding site of 1PRG. The five derivatives and standard exhibited high binding energy due to polar interaction like hydrogen bonding. BT-1 displays hydrogen bond interaction with LYS-457, BT-3 with PHE-282 and GLU-343, BT-4 with ASP-462 and PHE-282 and BT-5 with GLU-454, ALA-343 and PRO-368. The standard pioglitazone displays hydrogen bond interaction with PHE-360 and LEU-246. Hence these derivatives were expected to have good in vitro and in vivo antidiabetic activity.
CONCLUSION
From the docking studies, we have found that derivatives BT-1 and BT-3 bound to the active pockets of PPARγ in good manner. The good binding affinity of the derivatives was due to polar interactions, mainly by hydrogen bonding. So, derivatives BT-1 and BT-3 were expected to give in vitro and in vivo antidiabetic activity. This may be considered in the design and discovery of ideal PPARγ agonists. Further modification can be carried out to develop better antidiabetic agents.

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