

Research Article



In silico Design and Molecular Docking Studies of Benzimidazole Bearing thiazolidin-4-one Derivatives as PPAR γ 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 PPAR γ agonists in diabetes mellitus. *In silico* design of proposed derivatives were conducted by ACD lab Chemscketch 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, PPAR γ agonist, Docking, AutoDock Vina, Pioglitazone.

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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 blood¹. 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 pregnancy².

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 therapy³.

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 (sitagliptin, 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)⁴.

Peroxisome proliferator activated receptor gamma (PPAR γ) also known as glitazone receptor regulates the genes important for cell differentiation and various metabolic processes especially lipid and glucose homeostasis. Activation of PPAR γ causes insulin sensitization and enhances glucose metabolism. Activated PPAR γ in adipocytes secrete mediators of insulin action in peripheral tissues⁵.

PPAR γ 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, PPAR γ heterodimerizes with retinoid X receptor- α and activates the transcription of target genes through binding of PPRE response elements^{7,8}.

Thiazolidinediones (TZDs) are the important PPAR γ agonists that improve the glucose tolerance by enhancing insulin sensitivity and restoring the functions of β -cells in diabetic patients⁹. 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 ¹⁰.

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 ¹².

Molecular docking is a kind of bioinformatics modelling which involves the interaction of two or more molecules to give a stable adducts ¹³. 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 ¹⁴.

MATERIALS AND METHODS

ACD Lab Chemskevch 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.

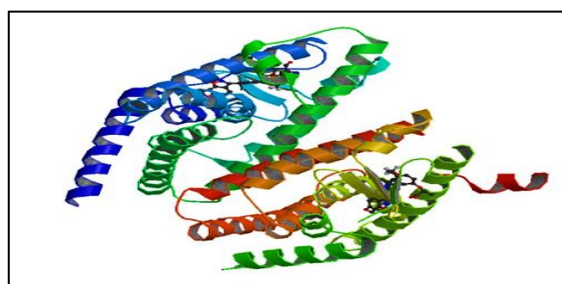


Figure 1: 3D structure of PPAR γ

The structure were generated after X- ray crystallography and NMR studies. In this study the protein selected is PPAR γ (PDB code 1PRG) ¹¹.

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, co-factors, 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 Chemskevch 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 ¹⁵.

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 Chemskevch 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.

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		400.89	6	1	2.65	4	0
BT-2		411.44	9	1	1.93	5	0
BT-3		396.97	7	1	2.03	5	0
BT-4		382.44	7	2	1.49	4	0
BT-5		366.45	6	1	1.97	4	0
Standard (pioglitazone)		356.45	5	1	3.07	7	0

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

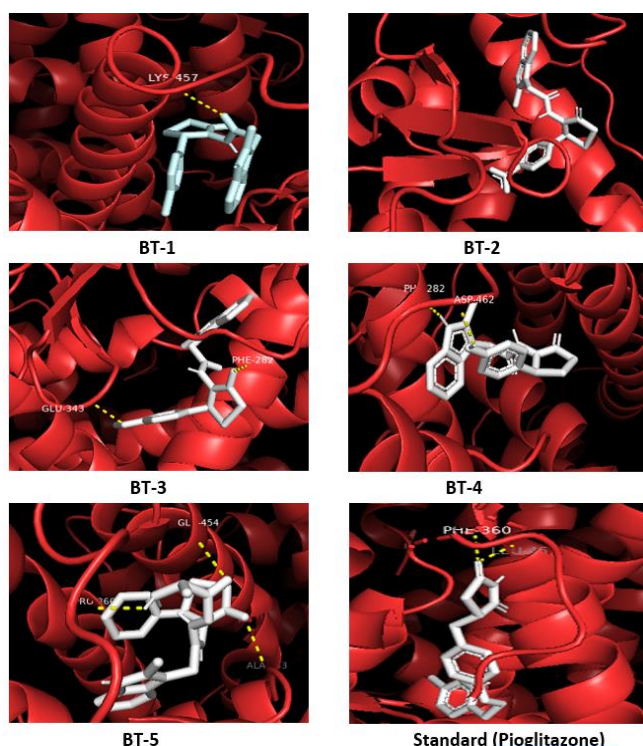


Figure 2: Docked images of derivatives and pioglitazone (white) with protein 1PRG (red). Hydrogen bonds are shown as yellow.

Lipinski's rule of five analysis revealed that all five derivatives were likely to have physical and chemical properties to be orally bioavailable. Docking studies of selected 5 derivatives were carried out using AutoDock Vina with protein 1PRG. Schematic 2D representation of docked

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 1PRG 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 PPAR γ agonists. Further modification can be carried out to develop better antidiabetic agents.

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