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Research Article

IN SILICO DESIGN OF QUINOXALINE BEARING THIAZOLIDINONE DERIVATIVES AS PPARγ AGONIST IN DIABETES MELLITUS

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ABSTRACT

Objective: Diabetes mellitus is a set of metabolic disease in which there is increased blood sugar level over a long period. The objective of the study is *in silico* design of quinoxaline bearing thiazolidinone derivatives as peroxisome proliferator-activated receptor gamma (PPARγagonist in diabetes mellitus.

Methods: *In silico* design of proposed derivatives was conducted by ACD Lab ChemSketch 12.0 and derivatives obeying Lipinski's rule of five were selected for docking studies. Docking was carried out using AutoDock Vina software.

Results: Molinspiration results revealed that the designed derivatives had physical and chemical properties meant for an orally available drug. Based on the docking results derivatives, QNT_1 and QNT_2 exhibited high docking score which indicates that these derivatives possess high-affinity and high polar interaction toward protein 1PRG (ligand-binding domain of human peroxisome proliferator-activated receptor gamma).

Conclusion: The designed quinoxaline 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.

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INTRODUCTION

Diabetes mellitus is a group of chronic metabolic disorders of multiple etiologies characterized by hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from relative or an absolute lack in insulin. Diabetes mellitus is of three types: Type 1 diabetes mellitus – an autoimmune disease in which the body's own immune system attacks the pancreas, making it unable to produce insulin, type 2 diabetes mellitus – in which a resistance to the effects of insulin or a defect in insulin secretion may be seen, and type 3 – gestational diabetes – is a condition in which blood sugar levels become high during pregnancy [1].

Currently used antidiabetic drugs include biguanides such as metformin, sulfonylureas such as glimepiride and glipizide, meglitinides such as repaglinide and nateglinide, and thiazolidinones such as pioglitazone and rosiglitazone [2-5]. Side effects of these drugs include kidney complications, weight gain, risk of liver disease, gas bloating, diarrhea, and anemia.

Quinoxaline derivatives constitute an important class of heterocycles in drug discovery. They are clinically effective as antibacterial, antifungal, anti-inflammatory, anticancer, antitubercular, and antineoplastic. It also shows hypoglycemic and antiglaucoma activity [6]. Thiazolidinones are an important scaffold with antidiabetic, anticancer, antibacterial, antiviral, and antioxidant properties [7].

PPARγ is a well-known target for diabetes and thiazolidinones which include rosiglitazone and pioglitazone, acts through PPARγ. PPARγ helps in glucose and lipid uptake, kindles glucose oxidation, decreases free fatty acid level, and improves insulin resistance. They are highly present in adipose tissues that play a significant role on insulin resistance, cell differentiation, and energy metabolism [8-10]. All the PPARs have similar structures and mechanism of action. Based on structure-function relationship, PPARs can be divided into three domains; (a) ligand binding domain which consists of 12 alpha helixes with a hydrophobic pocket, where the ligand binds, (b) trans-activating domain which is essential for transcriptional activation, and (c) DNA-binding domain which interacts with specific PPAR response elements in the promoter region of the target genes [11-14].

METHODS

ACD Lab ChemSketch 12.00 and molinspiration

It used for drawing chemical structures, 3D optimizing and calculating various physicochemical properties of the proposed derivatives. In this study, about 15 compounds were designed and from this, five derivatives possessed druglikeness properties and obeyed Lipinski rule of five. These five derivatives were selected for docking studies.

Protein data bank (PDB)

PDB is the single worldwide repository of information about the 3D structures of large biological molecules, including proteins and nucleic acid. Under Protien data bank: PDB ID is the 4-character unique identifier of every entry in the PDB. In this study, the selected protein is PPARγ shown in Fig. 1 and the PDB ID is 1PRG (ligand-binding domain of peroxisome proliferator-activated receptor gamma).

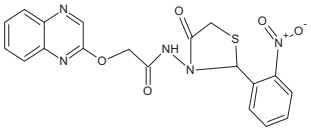
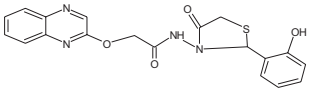
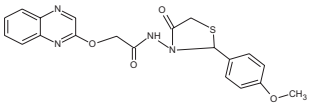
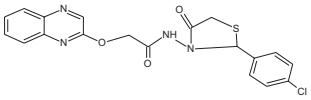
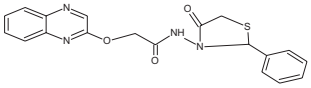
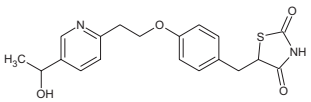
Molecular docking

Docking is the prediction of affinity and the activity of designed derivatives to the suitable protein targets. AutoDock Vina is an open source program for doing molecular docking. *PyMOL* was used for protein preparation and visualization. *PyRx* was used for docking [15].

Protein preparation

Structure which was taken from the PDB database could not fit as such for docking studies. Under Protein preparation: docking studies, because the structure consist of water molecule (HOH), detergents

Table 1: Structure and molecular descriptors of derivatives and standard (pioglitazone)

Compound code	Structure	MW (g/mol)	HA	HD	logP	rotb	Violation
QNT_1		425.43	10	1	2.77	6	0
QNT_2		396.43	8	2	2.80	5	0
QNT_3		410.45	8	1	2.91	6	0
QNT_4		414.87	7	1	3.54	5	0
QNT_5		380.43	7	1	2.86	5	0
Standard pioglitazone		372.4	6	2	1.72	7	0

(DSN), small molecules, cofactors and metal ions. Therefore, the PDB structure should be converted into suitable form for docking by addition of command "remove<>resn<>molecules" (HOH,DSN). 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* where both the protein and the derivative were loaded into the navigation pane. Then, the protein was converted into macromolecule whereas the derivative was converted into ligand molecule. After the preparation of protein and ligand, click the AutoDock Vina wizard start 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 result was displayed in a table. The binding affinity of the protein is indicated in Kcal/mol [16-18].

Visualization and analysis

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

RESULTS

Computer-assisted drug design (CADD) approach has contributed to the successful discovery of novel quinoxaline bearing thiazolidinone derivatives as antidiabetic agents. A series of structurally related compounds were designed. Those compounds obeying rule of five were selected for docking studies and they are illustrated in Table 1. The molecular docking analysis of the selected derivative with the receptor PPARγ(1PRG – ligand-binding domain of peroxisome proliferator-activated receptor gamma) has been performed. Schematic 3D representation of derivative with receptor PPARγ(1PRG) was visualized and shown in Fig. 2. The docking score of derivatives and the standard (pioglitazone) with the 1PRG is given in Table 2. QNT_1 shows hydrogen bond interaction with TYR-743, QNT_2 with THR-731, QNT_3 with LYS-728, QNT_4 with PHE-650, QNT_5 with LYZ-728, and the thiazolidinone

Table 2: Docking score of derivatives and standard (pioglitazone) with protein 1PRG (ligand binding domain of peroxisome proliferator-activated receptor gamma)

S. No.	Compound code	Docking score (Kcal/mol)
1.	QNT_1	−9.0
2.	QNT_2	−8.7
3.	QNT_3	−8.7
4.	QNT_4	−8.5
5.	QNT_5	−8.4
6.	Standard (pioglitazone)	−9.5

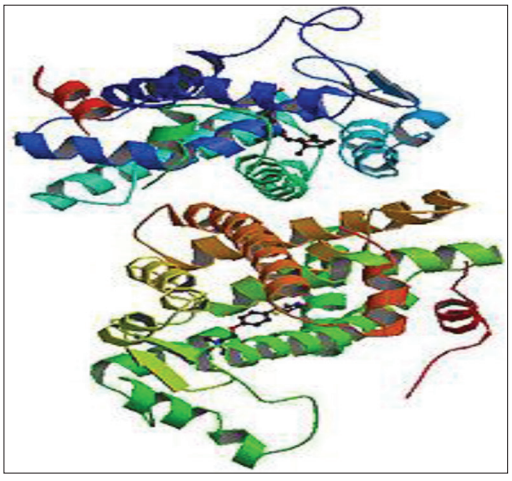


Fig. 1: Structure of PPARγ

ring present in the pioglitazone display hydrogen bond interaction with PHE-360 and LEU-246.

DISCUSSION

Designed quinoxaline bearing thiazolidinone possessing druglikeness property and obeying Lipinski rule of five were selected for docking studies. The values of the parameters of Lipinski rule of five are shown

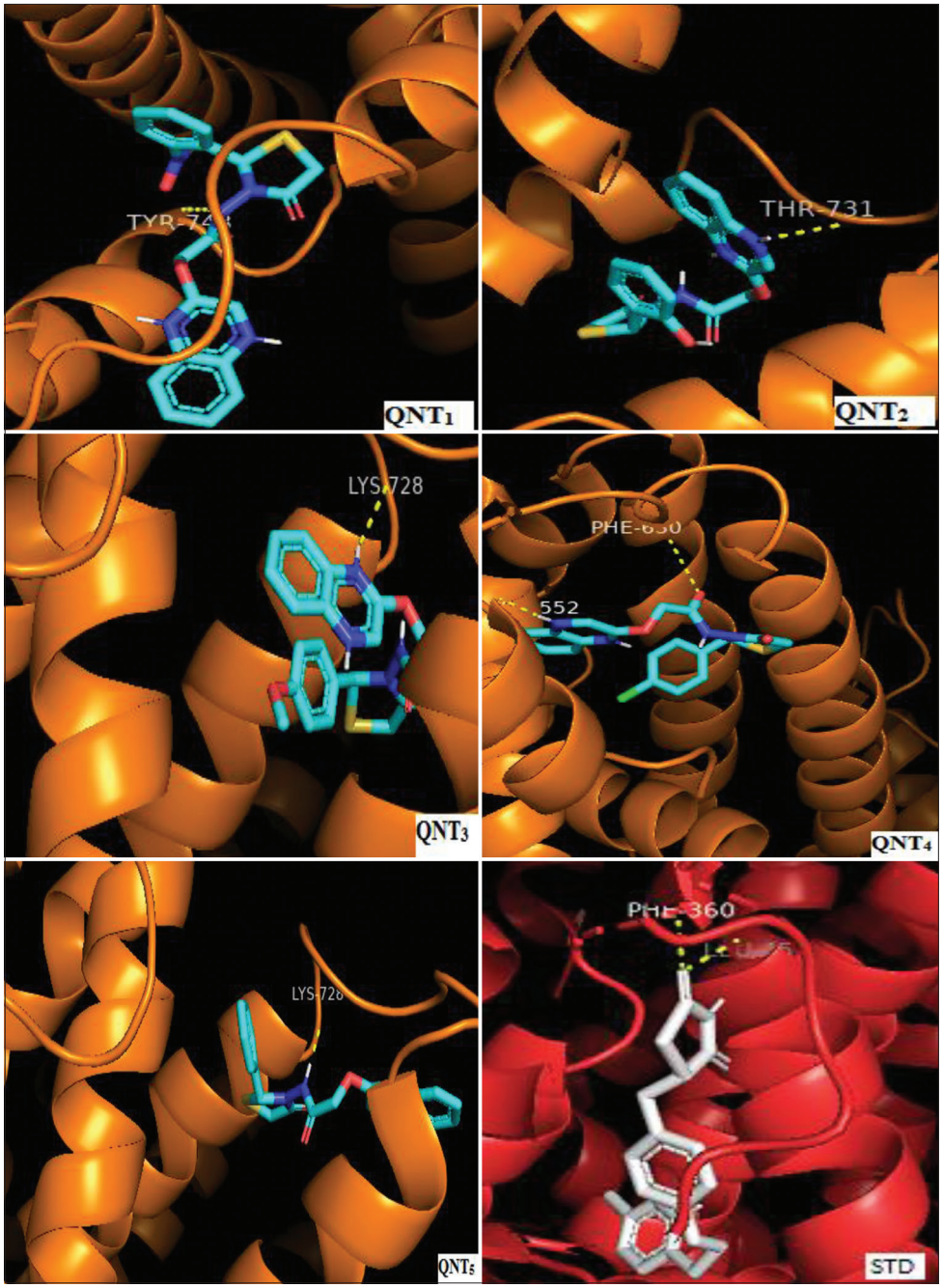


Fig. 2: Docked images of derivatives and standard (pioglitazone) with protein 1PRG (ligand-binding domain of peroxisome proliferator-activated receptor gamma)

in Table 1. Since there was no violation in rule of five, these derivatives are found to possess physical and chemical property to be orally bioavailable. Docking analysis reveals that these derivatives exhibit good hydrogen bond interaction with protein 1 PRG. Docking score is shown in Table 2 and docking images of five derivatives and standard are shown in Fig. 2. Hence, these derivatives are expected to have good *in vivo* and *in vitro* antidiabetic activity.

CONCLUSION

The designed quinoxaline bearing thiazolidinone derivatives are found to have good interaction in the binding pocket of target 1 PRG so these compounds are expected to possess good antidiabetic property with minimum side effects.

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AUTHORS' CONTRIBUTIONS

The 1st and 2nd author contributed to the entire work and drafted the manuscript and the 3rd author participated in docking studies.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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