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A Molecular Docking and Pharmacokinetic Prediction of Thiazolidine-2, 4-dione Derivatives: Toward Novel Therapeutic Targets for Type-2 Diabetes Mellitus

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a leading endocrine disorder that affects millions of people worldwide. It is characterized by hyperglycemia and high insulin resistance. The commonly prescribed oral therapeutic for insulin resistance in T2DM is Thiazolidine-2, 4-diones (TZDs). TZDs are a class of oral hypoglycemic agents that act on Peroxisome proliferator activating receptor-γ (PPAR-γ) receptors and are mainly expressed in the adipose tissues. In this work, we derive novel classes of TZDs and predict the nature of structural affinity using docking studies against the PPAR-γ.

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1. INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a leading endocrine disorder that affects millions of people worldwide [1, 2].While it is characterized by hyperglycemia and insulin resistance (IR) in which cells does not respond to insulin [3], it leads to impaired uptake and utilization of glucose in adipose tissue and skeletal muscle cells [4, 5]. The T2DM can be treated by several types of drugs associated with insulin, viz. sulfonylureas, meglitinides, biguanides, thiazolidinediones (TZDs), glucosidase inhibitors and few newer antidiabetic drugs such as glucagon-like peptide 1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, bile acid

sequestrants and sodium glucose transport protein-2 inhibitors [6, 7]. These agents increase the sensitivity of target organs to insulin by increasing its secretion and simultaneously reduce excessive hepatic glucose production and carbohydrate absorption in the intestines [8, 9]. While the commonly prescribed oral therapeutic agents for T2DM have varied limitations [10, 11], the PPAR-γ agonist, TZDs are known to be an effective agent that is mainly used in insulin-resistant diabetes.

The TZDs are heterocyclic compounds that have broad spectrum of biological activities [12, 13] that includes aldose reductase inhibitory, anti-bacterial, anti-fungal, anti-tubercular and anti-inflammatory activities [14, 15].While the TZDs are known to show therapeutic applications for diabetes, they are known to act as hypoglycemic agents leading to an increase in insulin sensitivity at specific tissues such as liver and skeletal muscles [16, 17]. A majority of TZDs are known to act on peroxisome proliferator activating receptor-γ (PPAR-γ), a ligand-activated transcription factors belonging to the nuclear receptor superfamily [18]. Whereas there are three known subtypes of PPAR receptors, viz. α, γ, and β/δ, they have varied influence on metabolism [19]. PPAR-α is expressed mainly in various organs such as liver, skeletal muscle and heart where it regulates genes that influence lipoprotein metabolism and fatty acid uptake and oxidation thereby serving as an agonist for diabetic ailments [20], while PPAR-γ is expressed mainly in adipose tissue and helps in regulation of adipocyte differentiation in addition to fatty acid uptake, storage and glucose uptake. The PPAR-δ is pervasively expressed and yet remains less understood among PPAR subtypes. A major focus, however, is on PPAR-γ inducing lipogenesis and fat storage affecting insulin sensitivity [21, 22]. Upon activation, PPAR-γ forms a heterodimer with the retinoid X receptor (RXR) and binds with DNA response elements called PPAR response elements (PPRE) in the promoter region of target genes and ultimately activate or suppress transcription of PPAR-γ target genes. After binding of endogenous ligands such as polyunsaturated fatty acids (PUFA), oxidized fatty acids and prostaglandins, PPARs undergo conformational changes, leading to recruitment of cofactor proteins and coactivators influencing the transcribed genes [23].

With PPAR-γ agonists acting as a key factor in various metabolic processes there is a need to understand it's efficacy towards improving insulin sensitivity for exerting anti-inflammatory and anti-atherosclerotic response [24-26]. Although the TZDs have similar effects on glycemic control, they are known to enhance insulin action and improve hyperglycemia in patients with T2DM, but they have also been reported to show severe adverse effects [27-29]. Therefore an inherent need to develop novel derivatives for TZDs would be of tremendous interest to the scientific community [30-33]. In this work, we discuss the effect of in silico derived TZDs using molecular modeling and docking approaches targeting PPAR-γ receptor.

2. METHODOLOGY

2.1. Designing of 3D structure of PPAR-γ protein and ligands:

The structure of PPAR-γ ligand binding domain, complex with Lanifibranor (PDB ID: 6ENQ) [34] at a resolution of 2.2 Å was retrieved from protein databank databank [35]. The structure of PPAR-γ constituting two polypeptide chains were used as a query (Accession: P37231.3) [36, 37] and the reference sequence of PPAR-γ protein was retrieved from NCBI database (Accession:- NP_619725.2) with help of Swissmodel [38, 39]. After checking for the sequence identity (100%), Global Model Quality Estimation scores (GMQE) (0.71), the template 3e00.1.B (419 aa) was taken and aligned with 6ENQ. The PDB was considered based on the proximity with side chain D (282 aa) and its similarity with template.

The protein structure was then refined by subtracting water molecules and the addition of hydrogen bond and gasteiger-huckel charges using Autodock [40] (Table 1). The template for TZDs was retrieved from Pubchem and the TZDs (TZD 1-9) were designed using Marvin sketch and Marvin view by substituting the thiazolidinedione ring towards increasing their nuclear receptor activity and ranked based on their molecular screening properties. The minimization of energies was set in designing new ligand molecules considering addition of gasteiger-huckel charges, polar hydrogen and saved as .mol2 and .pdb extension files (Figure 1).

2.2. Docking Methodology

Autodock and Swissdock tools were utilized to predict the ligand-protein interaction for docking studies. The 3D structure of protein (PPAR-γ) was prepared by removing the water molecules, metals and ligand for docking analysis. Subsequently charges and H-bonds were added to the molecule. Similarly the ligand molecule was prepared by adding charges and H-bonds to the molecule. Following the preparation of receptor and ligand molecules, the binding site was selected and grid was formed. The TZDs (1-9) were docked against PPAR-γ (PDB ID: 6ENQ) with the protein held rigid. A template TZD molecule

(Pioglitazone) was used as a standard to crosscheck the docking activity. The docking was carried out using Autodock and Swissdock and consensus was attempted to evaluate the structural affinity.

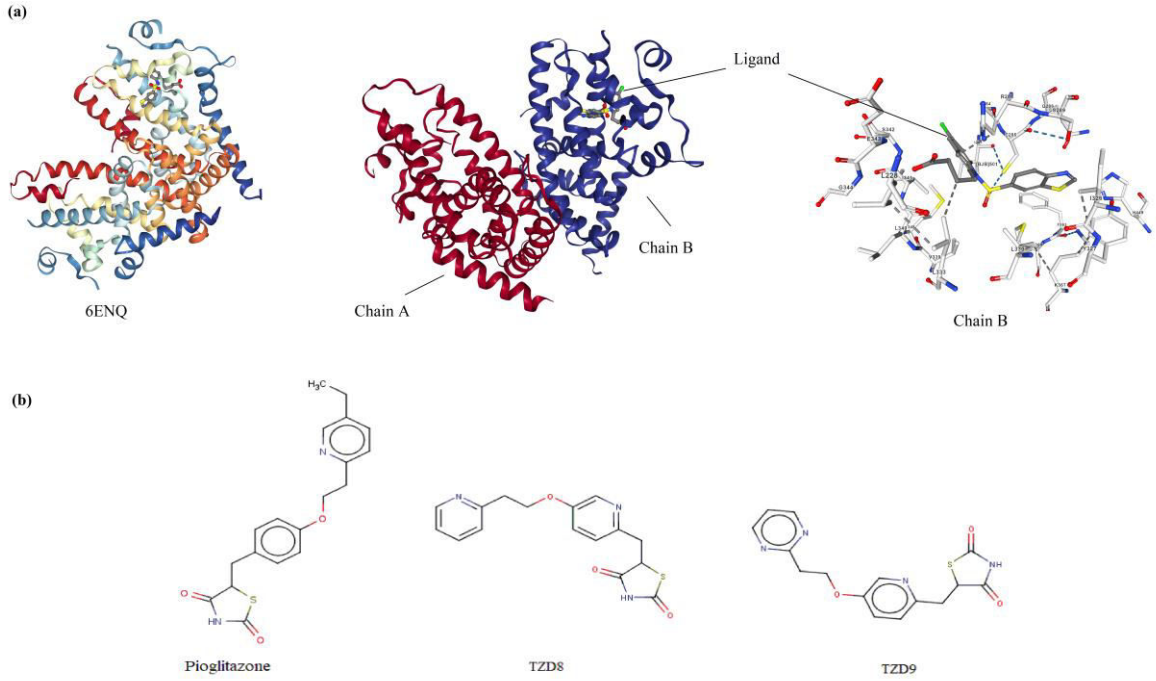

Figure 1: (a) The structure of PPAR-γ protein (PDB ID: 6ENQ) with a known ligand (ref- grey colour). The hydrogen bonded residues of 6ENQ are shown as catalytic domain structure of 6ENQ. The secondary structure elements are shown in red helices (chain A) and blue helices (chain B) with a ligand binding site in ball and stick model (grey). (b) The structures of TZDs designed for this study.

Table 1: Tabular representation of the tools used for in silico analysis of TZD derivatives

Protein 3D structure	• **RCSB Protein Data Bank (https://www.rcsb.org)**
Ligand Structure (Thiazolidine-2, 4-dione)	• **Pubchem (https://pubchem.ncbi.nlm.nih.gov/)**
Model consensus and Docking	• **Swissmodel (https://swissmodel.expasy.org/)** • **Swissdock (http://www.swissdock.ch/)** • **Autodock (http://autodock.scripps.edu/)**
Preparing novel ligands	• **Marvinsketch/Marvinview (https://chemaxon.com/products/marvin)**
ADMET properties Prediction	• **AdmetSAR (http://lmmd.ecust.edu.cn/admetsar1)**
Bioactivity score prediction	• **Molinspiration (http://www.molinspiration.com/)**
Molecular properties prediction	• **Medchem Designer (https://www.simulations-plus.com/software/medchem-designer/)**
Target Predication	• **SwissTargetPrediction (http://www.swisstargetprediction.ch/)**

2.3. Pharmacokinetic Properties

An ADMET property plays an important in safety assessment and development of drugs. All ligands were checked for using admetSAR [41] in order to ascertain the lead identification and optimization. The activity scores of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase and a host of inhibitors were obtained using molinspiration. In addition, Lipinski's RO-5 was used to establish pharmacological and biological properties that play major role in an orally active drug like moiety for humans. The molecular properties such as molecular weight, hydrogen bond donor, hydrogen bond acceptor, logP of novel targeted ligands were calculated using Medchem Designer. All the pharmacokinetics scores are in comparison with the standard drug Pioglitazone.

3. RESULTS AND ANALYSIS

3.1. Docking

A set of nine compounds with core TZD moieties, were docked with PPAR-γ using AutoDock [40] and Swissdock [42] (Figure 2). We have considered the docking interaction of Pioglitazone as standard with the binding activity of -7.59 Kcal/Mol with four hydrogen bonds binded within the active site. While comparing the binding activity of Pioglitazone to the derived ligands, we observed that TZD2 (-8.99 Kcal/Mol), TZD5 (-8.46 Kcal/Mol), TZD6 (-8.22 Kcal/Mol), TZD7 (-9.9 Kcal/Mol) have 8,1,4 and 8 number of hydrogen bonds respectively and ranged from -6.0 Kcal/Mol to -10 Kcal/Mol. Although we aimed to focus on TZ8 and TZ9 for their activity, our focus was on the favorable ligands bound to PPAR-γ protein (Table 2). However, we also checked the activity of other ligands, for example TZD7 shown to have a respectable ΔG is surrounded by eight H- Bonds at the binding site. Similarly, using swissdock, we have observed that TZD4, TZD5, TZD6, TZD8 and TZD9 have comparable estimated ΔG and full fitness energy score as compared to Pioglitazone (Supplementary Table 1).

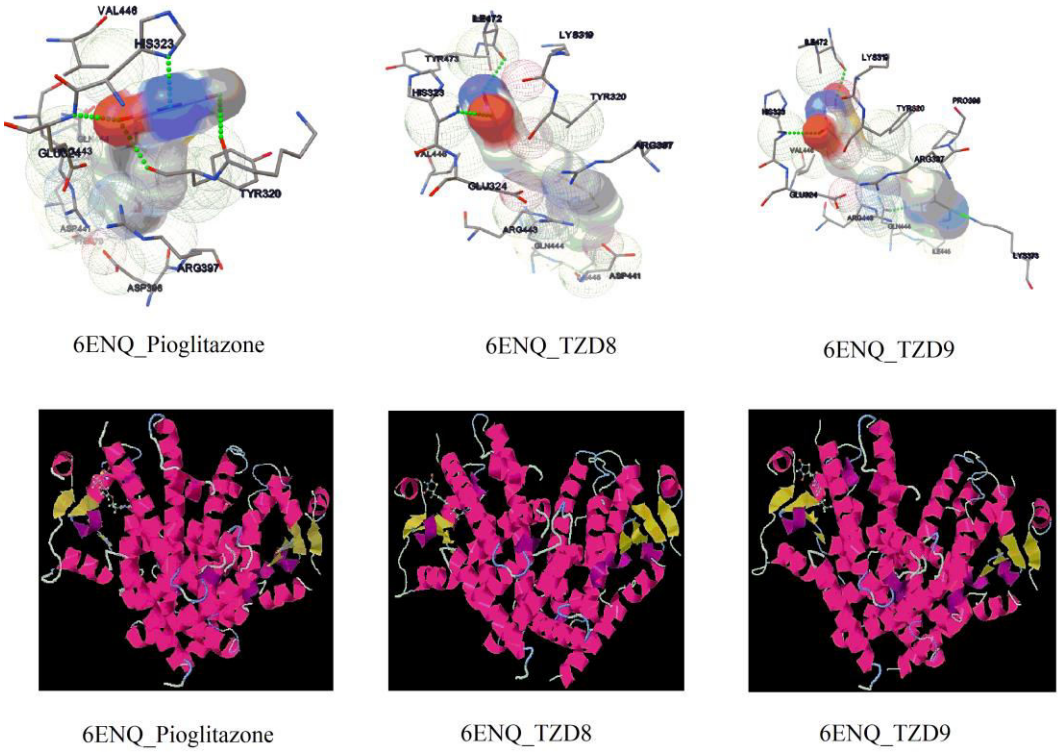

Figure 2: The figure representing the binding sites of the PPAR-γ protein (6ENQ) comparable to that of TZDs.

Table 2: The binding energy and contacting residues of TZD8 and TZD9 in comparison to Pioglitazone.

Analogues	Binding Energy (Kcal/Mol)	Estimated ΔG (kcal/mol)	Full Fitness (kcal/mol)	Contacting residues in Docked Position	No. of H-Bond
Pioglitazone	-7.59	-8.53	-3010.37	Val446, His323, Tyr320, Arg397, Asp396, Glu324	4
TZD8	-7.77	-8.27	-3005.52	Ile472, Lys319, Tyr320, Arg397, Tyr473, His323, Val446, Glu324, Arg443, Gln444, Asp441	2
TZD9	-7.44	-8.31	-3021.26	Ile472,Lys319, Tyr320, Pro398, Arg397, His323, Val446, Glu324, Gln444	4

3.2 Bioactivity and molecular properties

To gain insight into the bioactivity and molecular stability, predictions on TZD analogues test were carried out using Molinspiration to check bioactivity scores. These compounds used against major drug targets such as GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand, protease inhibitor and enzyme inhibitor data were in agreement with Pioglitazone (Table 3). The activity score of TZD8 and TZD9 were found to be comparable to that of activity score of Pioglitazone. As PPAR-γ protein is a nuclear receptor, we assume that the derived TZDs could be potentially PPAR-γ agonists. The molecular properties of different TZDs were evaluated for Lipinski's rule of five (RO5) using Medchem designer and were found to be comparable with Pioglitazone with respect to molecular weight, log P values, topological polar surface area (Table 3). Absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties were predicted for their role in pharmacokinetic, pharmacodynamics and clinical safety of drugs for TZDs using admetSAR [41] (Supplementary table 2).

Table 3: The activity scores and molecular properties prediction of Pioglitazone and derived TZDs.

Bioactivity Scores	**Pioglitazone**	**TZD8**	**TZD9**
GPCR ligand	0.25	0.33	0.25
Ion channel modulator	-0.51	-0.3	-0.44
Kinase inhibitor	-0.71	-0.47	-0.57
Nuclear receptor ligand	**0.64**	**0.64**	**0.52**
Protease inhibitor	-0.09	-0.1	-0.29
Enzyme inhibitor	0.05	0.1	0.07
Molecular Properties			
Predicted logP	1.832	0.347	-0.256
Predicted log of the octanol/water partition coefficient	3.045	2.073	1.243
Predicted logD at pH 7.4	2.792	1.752	0.884
No. of Lipinski's rule of 5 violations	0	0	0
Molecular weight	356.446	329.379	330.367
Count of Nitrogen and Oxygen	5	6	7
Topological Polar Surface Area	68.29	81.18	94.07
No. of OH and NH hydrogen bond donor protons	1	1	1

3.3. Targeted ligand binding sites predictions

Keeping in view of these findings, we hypothesize that the TZDs have a major role of PPAR-γ's efficacy towards receptors. TZDs are known as a regulator of adipogenesis, modulator of lipid metabolism and insulin sensitivity. Furthermore, the analyzed TZDs may have a potential role in limb fat adipogenesis as these could be associated with characteristic Asian Indian T2DM phenotype. This has already allowed us to build the systems phenome interactome networks taking them as contexts [43]. On the other hand, the TZDs we have analyzed may show effect towards the inflammatory responses, expression of key biomarkers thereby serving as serological, if not prognostic markers.

4. CONCLUSION

In this work, we have made an attempt to derive TZD analogues and check for the structural affinity against PPAR receptors. We observe that TZD8 and TZD9 could serve as better ligands as it's molecular and bioactivity properties with predictions of binding sites of ligand in PPAR-γ protein. Although the intended targets of PPAR-γ agonist have been studied, we further intended to check for their efficacy considering the nature of PPARG to be bound to coactivators/receptors. We argue that the binding sites in PPAR-γ protein are comparable to that of the already available drug Pioglitazone and assume that the TZD8 and TZD9 have potential activity towards PPAR-γ agonists.

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AUTHOR CONTRIBUTIONS

PT, SG and RS contributed equally to the project. PT designed the TZD analogues with RS predicting the docking and affinity. PC and PSS worked on docking affinity. PT and RS wrote the initial draft followed by SG, SM, PSS and BM extending the discussions. BM and RS worked on chemical modeling with the ligand. All authors agreed before submitting the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

SUPPLEMENTARY FILES

1. Supplementary Table 1
2. Supplementary Table 2

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