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RESEARCH ARTICLE

Molecular Docking Studies of Novel Thiazolidinedione derivatives as PPARγ Modulators

Deepak Shilkar [*†] and Sabina Yasmin [‡]

†Department of Pharmaceutical Sciences & Technology, Birla Institute of Technology, Mesra, Ranchi 835215, Jharkhand, India
‡Department of Pharmaceutical Chemistry, College of Pharmacy, King Khalid University, Abha 61441, Saudi Arabia
*Corresponding author. Email: deepakshilkar@live.com

Abstract

Thiazolidinediones (TZDs), a well-known target of peroxisome proliferated receptors (PPARγ), have been clinically used as antidiabetic agents. PPARs belong to the nuclear receptor superfamily and are important targets (PPARs) for drugs that treat various metabolic disorders such as diabetes. We present comparative research on the meta-para substitution of benzylidene derivatives of thiazolidine-2,4-diones to identify their potential as modulators of PPARγ. PPARs are key drug targets in treating a range of metabolic disorders. In our previous study, we described 4-hydroxy benzylidene derivatives of thiazolidine-2,4-diones that exhibited a reversed orientation in the active site of PPARγ. The established pharmacophore was also discussed concerning the reversed conformation of the TZD fitting. In current silico studies, a focus is placed on meta-para-substituted benzylidene derivatives to identify H-bonding interactions analogous to those observed in the acidic head of rosiglitazone. All designed compounds exhibited strong hydrogen bonding interactions and displayed superior interaction energies compared to their monohydroxy counterparts. The results of a predicted ADMET report indicated that all molecules exhibited favourable hERG I & II properties, suggesting excellent metabolic stability.

Keywords: PPARγ; thiazolidinediones; molecular docking; ADME-TOX

1. Introduction

Type-2 diabetes mellitus (T2DM) or non-insulin dependent diabetes mellitus (NIDDM) represents a significant concern affecting more than 180 million people worldwide,

and this number is expected to reach 366 million in 2030[1]. T2DM can be considered a complex disorder resulting from impaired insulin secretion or developing resistance. The most widely available antidiabetic medications can be classified into insulin secretagogues and sensitizers. The first category examples are sulfonylureas and meglitinides, while metformin and thiazolidinediones act as (TZDs) are insulin sensitizers. Following the discovery of PPARγ, the first class of synthetic ligands to bind it specifically consisted of thiazolidinediones-2,4-diones (TZDs) [2]. TZDs are crucial heterocyclic ring systems [3] that act as insulin sensitizers and promote glucose utilization in peripheral tissues [4]. The PPARγ is a nuclear hormone receptor family member that requires the ligand-binding recruitment of various coactivator proteins to stimulate further gene transcription machinery [5]. Being the most extensively studied receptor among the other two subtypes of PPAR, i.e., PPARα and PPARβ/δ, PPARγ is found to be involved in various metabolic-related applications and has three isoforms: PPARγ1, PPARγ2, and PPARγ3 [3]. The first subtype, i.e., PPARγ1, shows ubiquitous tissue expression, with its presence in adipose tissue, heart, large and small intestines, kidneys, pancreas, and skeletal muscle [6]. At the same time, PPARγ2 is predominantly present in adipose tissue, and PPARγ3 expression is limited to adipose tissue, macrophages, and the epithelial wall of the colon [7, 8].

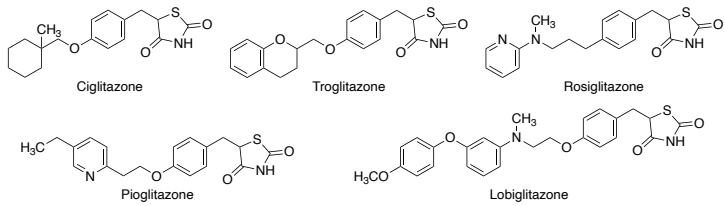


Figure 1. PPARγ marketed drugs

As discussed earlier, TZDs, commonly called "glitazones", act as PPARγ agonists by playing a role in insulin sensitization and lowering glucose and fatty acid levels in type 2 diabetic patients (**Fig.** 1). The history of TZDs came into the picture in the early 1960s and 1970s, when various research groups explored anti-TB, anticonvulsants, and various other toxicological and pharmacological aspects [9–14]. However, in 1982, the research on TZDs gained high standards when Sohda and co-workers reported ciglitazone for clinical evaluation in hyperglycemia [15], which later failed to reach a clinical trial. Continuous research on TZDs resulted in Troglitazone [16], Pioglitazone [17], and rosiglitazone [18, 19], and the associated toxicity and side effects such as weight gain, hepatotoxicity, oedema, cardiotoxicity, and increased risk of bone fracture limit their use. This safety-related concern encourages us toward the search for and development of a novel PPARγ modulator. Based on this background, we reported a series of benzylidene derivatives of TZD having a substitution at ring N- of TZD. Based on the earlier observation of orientation and other *in silico* studies in the case of para hydroxy substitution, we designed and studied the introduction of other possible substitutions (**Fig.** 2).

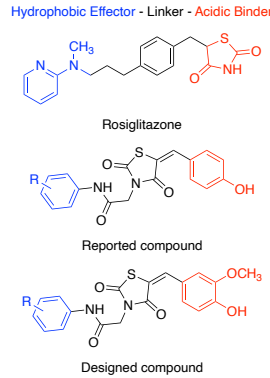


Figure 2. PPARγ modulator design

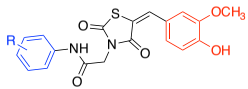
2. Results & discussion

2.1 Molecular docking simulation

Molecular docking simulation studies were conducted to understand the atomic level interaction and other structural features of designed molecules (1-11) with PPARγ (PDB: 2PRG) receptor (**Table** 1). Before starting the simulation with the designed molecules, the redocking method was carried out to validate the docking protocol, and the root-mean-square deviation (RMSD) for the co-crystallized ligand, rosiglitazone, was obtained as 2.33 . Interaction of rosiglitazone with its re-docked pose shows its lipophobic head region, establishing three H-bonding interactions with Ser289, His323, and His449. In comparison, the effector region establishes one H bonding nonpolar interaction with Ser342 (**Fig.** 3). Earlier, it was observed that the presence of the para hydroxy group in the benzylidene portion causes a dramatic reversal in the binding orientation compared with unsubstituted benzylidine. To get more effective PPARγ modulators, we tried to introduce meta-para substitution on the phenyl ring of the benzylidene portion. While analyzing the docked conformers, we observed an interesting fact that the introduction of the methoxy group at the meta position could not produce any new hydrogen bonding interaction compared with previously designed molecules. It was observed that the presence of the para hydroxy group is only interacting with the catalytic residues. Surprisingly, there are some variations in the energy potential of certain molecules compared to simple para hydroxy-substituted benzylidiene compounds. It was also observed that the orientation of binding for all the designed molecules aligned in the same arrangement and were found to bind into the ligand-binding domain (LBD), thus sharing a very similar mode when compared with PPARγ full agonist, rosiglitazone (**Fig.** 4).

The three primary interaction energies (van der Waals, electrostatic, and hydrogen bonding) of all the docked compounds were determined to be more potent than those of rosiglitazone (**Table** 1). Increasing the ring size (compounds 2 and 3) led to interactions similar to that of rosiglitazone (**Fig.** 3).

Table 1. Predicted ADME (Quickprop) parameters and molecular docking score of designed molecules



Code	R	Mol. Wt	Mol. Form.	Lipinski's violations	Jorgensen's violations	Glide Score	Component energy (Kcal/mol)		
							Electrostatic	Lipophilic	H-bond
1	Phenyl	384	$C_{19}H_{16}N_2O_5S$	0	0	-7.55	-237.17	-5.8	-1.94
2	Benzyl	398	$C_{20}H_{18}N_2O_5S$	0	0	-8.99	-264.91	-5.7	-1.92
3	Phenylethyl	412	$C_{21}H_{20}N_2O_5S$	0	0	-9.37	-241.94	-6.3	-1.69
4	Cyclopropyl	348	$C_{16}H_{16}N_2O_5S$	0	0	-6.84	-227.42	-5	-1.48
5	Cyclobutyl	362	$C_{17}H_{18}N_2O_5S$	0	0	-7.23	-229.94	-5.34	-2.02
6	Cyclopentyl	376	$C_{18}H_{20}N_2O_5S$	0	0	-7.52	-249.07	-4.82	-1.5
7	Cyclohexyl	390	$C_{19}H_{22}N_2O_5S$	0	0	-7.57	-245.17	-5.7	-1.93
8	p-Cl-Phenyl	418	$C_{19}H_{15}ClN_2OS$	0	0	-7.86	-249.43	-5.4	-1.55
9	Anisidine	414	$C_{20}H_{18}N_2O_6S$	0	0	-7.54	-249.07	-5.9	-1.92
10	Toluidine	398	$C_{20}H_{18}N_2O_5S$	0	0	-7.78	-246.44	-5.89	-1.66
11	Nitroaniline	429	$C_{19}H_{15}N_3O_7S$	0	0	-7.72	-214.93	-4.7	-1.91
Rosiglitazone (R)		357	$C_{18}H_{19}N_3O_3S$	0	1	-7.99	-208.09	-5.91	-1.24
Cigltazone (C)		333	$C_{18}H_{23}NO_3S$	0	0				
Lobeglitazone (L)		478	$C_{26}H_{26}N_2O_5S$	1	1				
Troglitazone (T)		441	$C_{24}H_{27}NO_5S$	1	2				
Pioglitazone (P)		356	$C_{19}H_{20}N_2O_3S$	1	0				

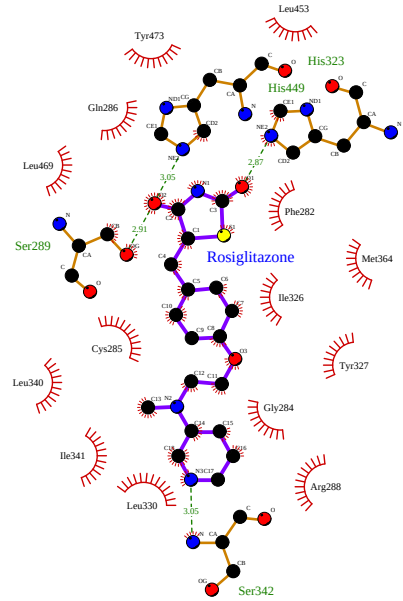


Figure 3. 2D-plot of compound Rosiglitazone in complex with 2PRG

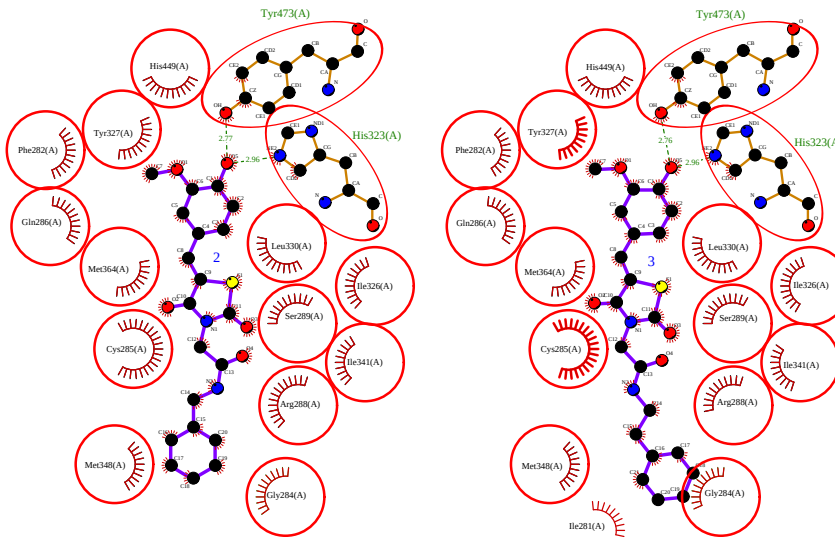


Figure 4. 2D-plot of compound 2 & 3 in complex with 2PRG

2.2 ADME/Tox parameters

All the designed derivatives were evaluated for Lipinski and Jorgensen's violation using QikProp v3.0 (Schrödinger LLC). All the molecules in the designed library were found to obey the desired characteristic and thus assumed to have better drug-like properties (**Table** 1). Some other ADMET properties were evaluated once again in the continuation of our previously reported work using the pkCSM webserver (https://biosig.lab.uq.edu.au/pkcsm/) and are presented in **Table** 2. It has been observed that incorporating the meta methoxy group, all designed compounds showed better intestinal absorption and thus supported the strong drug-like behaviour of the designed molecules. The other parameters related to distribution and excretion were also in the acceptable range and showed some remarkable differences from earlier designed molecules. One of the paramount parameters that received significant attention pertains to cardiotoxicity (hERG-I and II), which was observed to be within acceptable limits. This indicates that introducing meta-para substitution in the phenyl ring of the benzylidene moiety of thiazolidinedione derivatives results in a notable improvement in the ADME/TOX profile.

3. Conclusion

In the continuation of introducing *meta-para* substitution, all the designed thiazolidinediones derivatives (1-11) were more potent and better selective PPARγ agonists. The results obtained by docking studies could be utilized to develop more potent, effective novel 2,4-thiazolidinediones derivatives with PPARγ modulatory activity. All the designed derivatives showed significant differences in glide docking scores compared with the marketed drugs. The interactions of all the designed derivatives with the receptors show a promising path by introducing a *meta-para* substitution group and showing a path to designing more potent PPARγ modulators. The ADMET properties of most of the designed compounds show major differences to behave as more potent and have lead-like properties compared with the *para*-substituted hydroxy group. Predicted cardiotoxicity studies show that molecules having a TZD ring with *N*-substitution may serve as a better alternative to the existing drugs in the PPARγ market. The design strategy adopted has significantly improved the permeability characteristics compared to rosiglitazone.

4. Experimental

Materials and methods:

All computational studies were conducted on a Dell Precision workstation running an RHEL-5.0 Operating System, equipped with an Intel Core 2 Quad processor, 8 GB RAM, and a 500 GB hard disk. Simulations utilized Maestro-8.5 (Schrödinger LLC). In silico ADME/TOX profiling was executed using the pkCSM [20] web server, hosted by VLS3D (Cambridge University). The 2D plots were generated using Ligplot [21].

Table 2. ADME/TOX Profile of designed derivatives and marketed drugs

Prop.	Molecular Descriptors	1	2	3	4	5	6	7	8	9	10	11	R	C	L	T	P
A	Water solubility (log mol/L)	-4.72	-4.62	-4.80	-3.40	-3.70	-3.99	-4.28	-5.39	-4.96	-5.02	-5.36	-4.12	-5.25	-5.37	-6.05	-4.53
	Caco2 permeability (log Papp in 10-6cm/s)	0.37	0.39	0.41	0.13	0.31	0.37	0.43	0.32	0.28	0.43	0.05	1.04	1.41	0.29	1.05	1.04
	Intestinal absorption (human %Absorbed)	80.11	78.35	77.56	72.30	77.90	78.64	79.00	81.94	79.13	81.50	77.90	97.36	95.13	90.97	92.97	96.76
	P-glycoprotein substrate	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
	P-glycoprotein II inhibitor	Y	Y	Y	N	N	N	N	Y	Y	Y	Y	N	N	Y	Y	Y
D	VD_{SS} (human, log L/kg)	-0.64	-0.59	-0.55	-0.40	-0.31	-0.28	-0.25	-0.68	-0.78	-0.35	-0.96	-0.42	-0.08	-1.04	-0.20	-0.34
	Fraction unbound (human)	0.16	0.17	0.15	0.32	0.36	0.33	0.31	0.16	0.17	0.17	0.09	0.26	0.12	0.08	0.00	0.18
	BBB permeability (log BB)	-1.09	-1.04	-1.02	-1.13	-1.13	-1.16	-1.18	-1.28	1.11	-1.11	-1.13	-0.64	-0.04	-1.32	-0.40	-0.49
	CNS permeability (log PS)	-2.56	-2.72	-2.78	-3.1	-2.9	-2.85	-2.76	-2.45	-2.51	-2.51	-2.49	-2.69	-2.11	-3.11	-1.89	-2.48
M	CYP2D6 substrate	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior	Y	Y	Y	N	Y	Y	N	N	N	N	N	N	Y	N	N	Y
	CYP2C9 inhibitior	N	N	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	N
E	Total Clearance (log mL/min/kg)	-0.03	-0.01	-0.10	-0.10	-0.04	-0.03	-0.05	0.00	-0.06	-0.15	-0.01	-0.11	-0.07	-0.11	-0.48	-0.04
	Renal OCT2 substrate	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
T	AMES toxicity	Y	N	N	Y	Y	N	N	N	N	N	Y	N	N	N	Y	N
	Max. tolerated dose (human log mg/kg/day)	0.82	0.81	0.81	0.50	0.37	0.31	0.24	0.72	0.73	0.77	0.76	0.68	0.88	0.58	0.61	0.85
	Oral rat acute toxicity (LD_{50} mol/kg)	2.5	2.4	2.4	2.6	2.6	2.6	2.7	2.5	2.4	2.5	2.5	2.6	2.7	2.5	2.5	2.5
	Oral rat chronic toxicity (log mg/kg_bw/day)	2.08	2.11	2.21	1.56	1.53	1.51	1.49	2.06	2.08	2.07	2.38	1.54	1.86	1.89	2.2	1.81
	Minnow toxicity (log mM)	0.61	0.67	0.43	2.01	1.50	1.38	1.26	0.61	1.00	0.95	0.23	1.18	-0.48	0.15	-0.77	0.50
	hERG I inhibitor	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	hERG II inhibitor	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N	Y	Y	Y	N

4.1 Molecular docking simulation

4.1.1 Preparation of protein

To understand the molecular-level interactions, molecular docking simulations of compounds (1-11) were conducted using the X-ray crystal structure of PPARγ (PDB: 2PRG), obtained from the Protein Data Bank (https://www.rcsb.org/). The 2PRG structure is a trimer (A, B, and C) and contains the protein with rosiglitazone as a co-crystallized ligand. For the molecular simulation studies, chain A was chosen [22]. The Protein Preparation Wizard in Maestro-8.4 (Schrödinger LLC) was employed to prepare the protein using default parameters, followed by minimization using OPLS2005.

4.1.2 Generation of Grid

The minimized protein structure was utilized to generate a grid, with the co-crystallized ligand rosiglitazone as the reference to identify the drug's binding sites on the target. The grid for docking was created with default parameters from the module. This generated grid was then employed for the subsequent docking of new molecules.

4.1.3 Preparation of Ligands

The ligand structures were initially sketched in 3D format using a building panel and subsequently refined for docking using the LigPrep module. These molecules underwent energy minimization using the OPLS-2005 force field to yield a single low-energy 3D structure for each input compound.

4.1.4 Docking protocol

The docking simulation was conducted using the Glide XP (Extra Precision) protocol in Glide, employing the default parameters. The "Write XP descriptors" option was enabled to create the .xpdes file. The resulting favourable ligand poses were then analyzed using the XP visualizer.

4.2 ADMET/ TOX parameters prediction

In 1997, Christopher A. Lipinski formulated the rule of drug-likeness known as Lipinski's Rule of Five (Ro5). This rule can be considered a necessary filtration tool to ensure a drug-like pharmacokinetics profile for designing a plausible therapeutic agent [23]. Jorgensen's Rule of Three (Ro3) is also an additional tool for evaluating the designed compounds in the search for drug-like properties evaluation [24]. All the designed molecules were evaluated for their conformity with Ro5 and Ro3 using QikProp v3.0. Ligprep output was used as input for QikProp, and the results were presented in **Table** 1.

ADMET parameters were predicted using the pkCSM web server [20]. ADME/TOX parameters such as water solubility, CaCo2 permeability, intestinal absorption, P-glycoprotein, the volume of distribution, blood-brain barrier (BBB), and CNS permeability, along with toxicity parameters such as AMES toxicity (mutagenicity) and cardiotoxicity (hERG-I & II inhibition) [25] were predicted and presented in **Table** 2. The properties were also predicted for standard drugs and used for comparison.

5. Declarations

5.1 Ethics approval and consent to participate

Not applicable.

5.2 Consent for publication

Not applicable.

5.3 Availability of data and materials

Not applicable.

5.4 Competing interests

The authors declare that they have no competing interests.

5.5 Funding

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5.6 Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: D. Shilkar, S. Yasmin; data collection: S. Yasmin; analysis and interpretation of results: D. Shilkar, S. Yasmin; draft manuscript preparation: S. Yasmin. All authors reviewed the results and approved the final version of the manuscript.

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