Journal of Pharmaceutical Chemistry
http://www.vensel.org/index.php/jphchem

Comparative Design, In Silico Dockingand Predictive ADME/ TOX Properties of Some Novel 2, 4-hydroxy Derivatives of Thiazolidine-2, 4-diones as PPARγ Modulator

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Abstract: Peroxisome proliferated receptors (PPARs) are important targets for drugs used in the treatment of various metabolic disorders. We have reported 4-hydroxy benzylidene derivatives of thiazolidine-2,4-diones with reversed orientation in the active site of PPARγin our earlier communication. With the reversed conformation of TZD, fitting the established pharmacophore was discussed. The current simulation studies revolves around the 2,4-dihydroxy benzylidene derivatives expecting H-bonding interactions similar to Rosiglitazone's acidic head. The docking protocol was validated by enrichment studies using decoys and actives from DUD. Designed compounds were showing interactions similar to the actives in the top 10%, 5% and 1%. They also exhibited H-bonding interactions similar to their monohydroxy counterparts without any additional H-bonding interactions due to introduction of additional hydroxy functional groups. Predicted ADMET report reveals that 5 molecules show favourable hERG-I and -II properties and nine compounds show best metabolic stability.

Keywords: PPARγ; virtual screening; enrichment study; molecular docking; predictive ADMET

1. Introduction

Non-insulin dependent diabetes mellitus (NIDDM) or Type-2 diabetes mellitus (T2DM) is a chronic multifactorial metabolic disorder manifested due to either impairment of secretion of insulin or development of resistance towards it.[1] Despite the availability of various antidiabetic agents for the treatment of T2DM, there is a growing concern as currently 285 million people worldwide were affected and its predicted to reach 400 million by 2030.[2] The available antidiabetic agents are classified as sulfonylurea, biguanides, α-glucosidase inhibitors, DPP IV and thiazolidinediones (TZDs). Amongst these, TZDs have gained popularity in the past decade as a class of drugs that improves insulin sensitivity of the target cells through the activation of Peroxisome Proliferator Activated Receptor γ (PPARγ).

The PPARγ is a member of the nuclear hormone receptor family of ligand dependent transcription factors. The PPARγ gene contains promoters that can be transcribed into three mRNA species, i.e. PPARγ1, PPARγ2 and PPARγ3. PPARγ1 shows the ubiquitous tissue expression, being present in adipose tissue, heart, large and small intestines, kidney, pancreas and skeletal muscle.[3] In divergence, PPARγ2 is predominantly present in adipose tissue, whereas PPARγ3 expression is limited to adipose tissue, macrophages and epithelial wall of the colon.[4-5] PPARγ primarily acts as a master gene regulator in various metabolic regulation by stimulating insulin sensitivity, lowering glucose and lipid management. Specifically, PPARγ can be considered as a key regulator of adipogenesis and adipocyte metabolism regulation.[6-7] In defiance of the challenges and hurdles present in the arena of development of PPARγ related drugs, it is still holding a strong propitious approach for the treatment of type-2 diabetes and associated metabolic disorders.

A number of natural and synthetic PPARγ ligands have been identified and reported till date, of which the most known are the TZDs.[8-9] Thiazolidine-2,4-dione are a class of heterocyclic ring system and plays an important role in different areas of medicinal chemistry.[10] As discussed earlier, TZDs act as PPARγ agonists by playing a role in insulin sensitization and also promoting glucose utilization in peripheral tissues. The history of TZDs came into the picture by the discovery of Ciglitazone in early 1982.[11] After that, several other glitazones such as Troglitazone,[12] Pioglitazone,[13] and Rosiglitazone,[14] came into existence. But the associated toxicity and side effects such as weight gain, hepatotoxicity, edema, cardiotoxicity and increased risk of bone fracture limits their use (Table1).

Submitted on: 14 Feb 2017 Revised on: 28 Mar 2017 Accepted on: 23 Apr 2017
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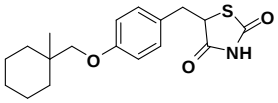
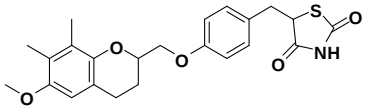
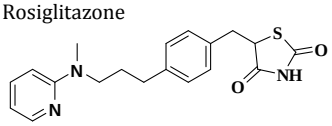
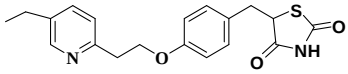
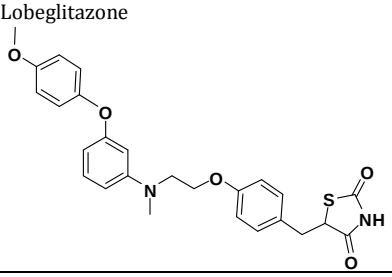
Table 1. PPARγ marketed drugs

Drug	Year Launched	Manufacturer	Reported Adverse Effects
Ciglitazone 	1982 (never marketed due to poor clinical assesment)	Takeda Pharmaceuticals	Edema and Cardiotoxicity[11, 15]
Troglitazone 	US 1997	Parke-Davis	Idiosyncratic Hepatotoxicity[12]
Rosiglitazone 	US andMexico1999	Takeda/Eli Lilly	Cardiotoxicity, weight gain and Edema[14]
Pioglitazone 	US 1999	SmithKlineBeecham	Cardiotoxicity and Bladder Cancer[16-17]
Lobeglitazone 	Korea 2013	ChongKun Dang Pharmaceutical Cooperation	Weight gain and edema[18]

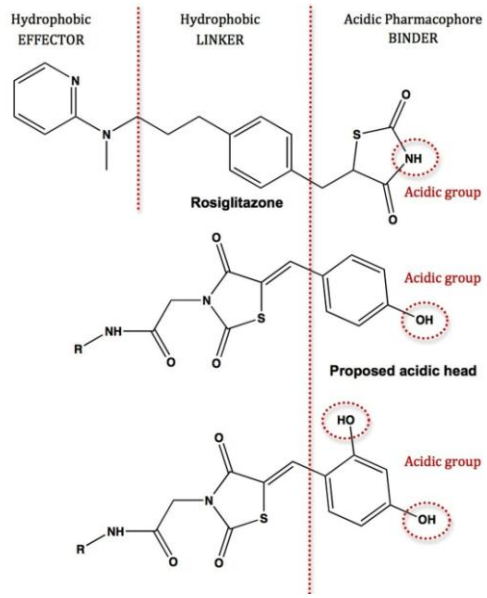


Figure 1. Dihydroxy benzylidene derivatives design
Figure was constructed with ChemDraw Ultra 2006

The safety related concerns is the driving force in encouraging the scientific community towards the development of novel and safe PPARγ agonists. Upon this background, we reported a series of benzylidene derivatives of TZD having a substitution at ring N-of TZD. We observed a reversed orientation with benzylidene derivatives having *para*-hydroxy substitution inside the active site establishing H-bond interactions similar to acidic head (TZD) of Rosiglitazone.[19] This prompted us to incorporate an additional hydroxy functional group at *ortho*-position of the benzylidene ring expecting additional H-bonding interactions matching with those of Rosiglitazone at acidic head side (Figure 1). Docking program and the molecular docking protocol have been validated through virtual screening enrichment study using the decoy and active sets available from DUD and literature.[20-24] Further the designed molecules were also subjected to predictive ADME-TOX studies.

2. Result and Discussion

2. 1. Enrichment study

Selection of Targets and Data Sets: The data sets of true and binding decoys for PPARγ used in this study were collected from the available literature[20] as well as from the publically available dataset, DUD[21-24]. The PPAR γ actives (164) were mixed with decoys (3127) to form a single library of 3291 molecules.[20-21] Ligprep utility in Maestro 11 (Schrodinger LLC) was used to prepare the ligands for docking with default parameters. The prepared ligands were then docked on 2PRG protein using SP protocol implemented in Glide Docking. Enrichment factor is calculated using the formula given by Pearlman and Charifson.[25]

$$EF^{x\%} = \frac{Hits_{Sampled}}{N_{Samples}} \times \frac{N_{Total}}{Hits_{Total}}$$

Where $Hits_{sampled}$ is the number of hits around at x% of the database screened, $N_{sampled}$ is the number of compounds screened at x% of the database, $Hits_{total}$ is the number of actives in entire database, and N_{total} is the number of compounds in the entire database. EF calculated for 10%, 5% and 1%. The data was presented in Table 2. The dataset displayed the best enrichment at top 1% with Enrichment factor of 7.90. Figure 2 highlights the binding pose of top actives and the designed compound **11** in PPARγ active site.

Table 2. Sensitivity of Calculated Enrichment Factor

Protein	Code	No of actives	No of decoys	Enrichment Factor		
				10%	5%	1%
PPARγ	2PRG	164	3127	2.74	3.91	7.90

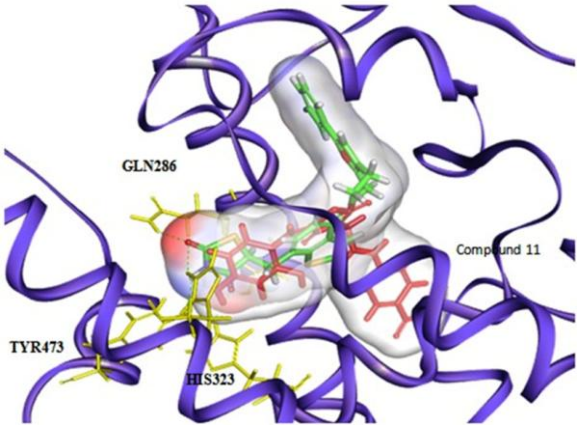


Figure 2. Binding models of PPARγtop active and designed compound **11**
Figure was constructed using Chimera [26]

2.2. Molecular Docking Analysis

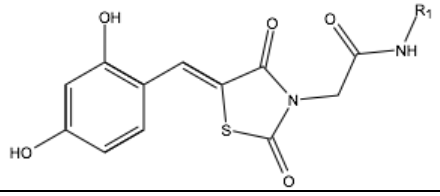
Molecular docking was carried out to understand the atomic level interaction and other structural features of designed compounds (**1**-**11**) with PPARγ receptor. The docking scores and energy calculations of the designed compounds are presented in Table **3**.

The results of docking revealed that compound **11** has the highest score of -8.971 and highest binding affinity towards the PPARγ active site, compared to the other ten docked compounds and the reference compound Rosiglitazone. The contributions of the electrostatic interactions, van der Waals forces and H-bond interaction towards the binding affinity of compound **11** were -216.99 kcal/mol, -6.33 kcal/mol and -1.33 kcal/mol, respectively. Figure 3 highlights the binding mode of active conformation for the highest-scoring compound **11** in the active site of PPARγ. The acidic pharmacophore (*ortho, para*-dihydroxy phenyl portion) of the compound **11** is involved in making hydrogen bonding interactions with the amino acid residues such as Tyr473 and His323.

The interaction of Rosiglitazone in its redocked conformation revealed that its acidic head region establishes three H-bonding interactions with Ser289, His323 and His449, while the effector region established one H-bonding interaction with Ser342 and hydrophobic interaction with Arg238, Gly284, Leu330 and Ile341 residues (Figure 4) similar interaction profile has been observed for compound **11** also (Figure 3).

Earlier it was observed that the presence of a *para*-hydroxy group in the benzylidene portion causes a dramatic reversal in the binding orientation when compared with unsubstituted benzylidine.[19] That has oriented *para*-hydroxy benzylidene portion of the molecule in a way that could able to establish two H-bonding interaction similar to TZD portion of Rosiglitazone. In an effort to get more effective PPARγ modulators, *ortho*,*para*-dihydroxy substitution was introduced to the phenyl ring of benzylidene portion. While analyzing the docked conformers, we observed an interesting fact that the introduction of *ortho*-hydroxy group was unable to establish new H-bonding interactions in the pocket that accommodates acidic pharmacophore (dihydroxy benzylidene portion). But the *para*-hydroxy functional group could able to display the H-bonding interactions (His323 & Tyr473) similar to the ones shown by the monohydroxy substituted molecules in our earlier publication.

Table 3. Glide and Qikprop reports for the designed compounds **1-11**



code	R_1	MW	MF	Glide score	Binding Energy (Kcal/mol)			Violations	
					$E_{electrostatic}$	E_{vdW}	$E_{H\text{-}bond}$	Ro5	Ro3
1	Phenyl	370	$C_{18}H_{14}N_2O_5S$	-8.279	-230.2	-5.30	-1.16	0	0
2	Benzyl	384	$C_{19}H_{16}N_2O_5S$	-8.239	-268.3	-5.64	-1.28	0	0
3	Phenylethyl	398	$C_{20}H_{18}N_2O_5S$	-7.559	-248.2	-5.55	-1.56	0	0
4	Cyclopropyl	334	$C_{15}H_{14}N_2O_5S$	-7.716	-215.2	-4.22	-1.03	0	0
5	Cyclobutyl	348	$C_{16}H_{16}N_2O_5S$	-7.646	-223.0	-4.81	-1.47	0	0
6	Cyclopentyl	362	$C_{17}H_{18}N_2O_5S$	-6.728	-241.1	-3.99	-1.33	0	0
7	Cyclohexyl	376	$C_{18}H_{20}N_2O_5S$	-7.514	-240.1	-4.94	-1.05	0	0
8	p-Cl-Phenyl	404	$C_{18}H_{13}ClN_2OS$	-7.446	-246.9	-5.83	-1.04	0	0
9	p-CH_3-phenyl	384	$C_{19}H_{16}N_2O_5S$	-7.874	-239.2	-4.94	-1.77	0	0
10	p-OCH_3-phenyl	400	$C_{19}H_{16}N_2O_6S$	-7.780	-254.3	-5.07	-1.65	0	0
11	p-NO_2-phenyl	415	$C_{18}H_{13}N_3O_7S$	-8.971	-217.0	-6.33	-1.33	0	0
Rosiglitazone		**357**	$C_{18}H_{19}N_3O_3S$	-7.990	-208.1	-5.91	-1.24	0	0

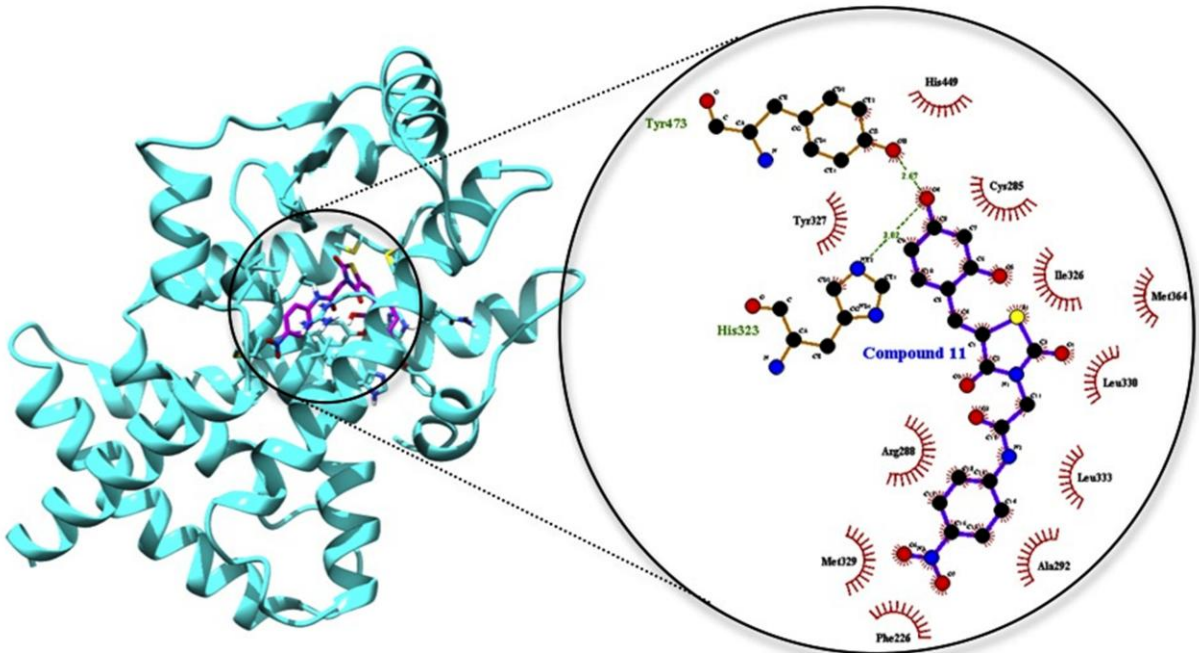


Figure 3. A depiction of compound **11** docked into the PPARγ active site and LigPlot highlighting compound 11 interactions with PPARγ active site residues.

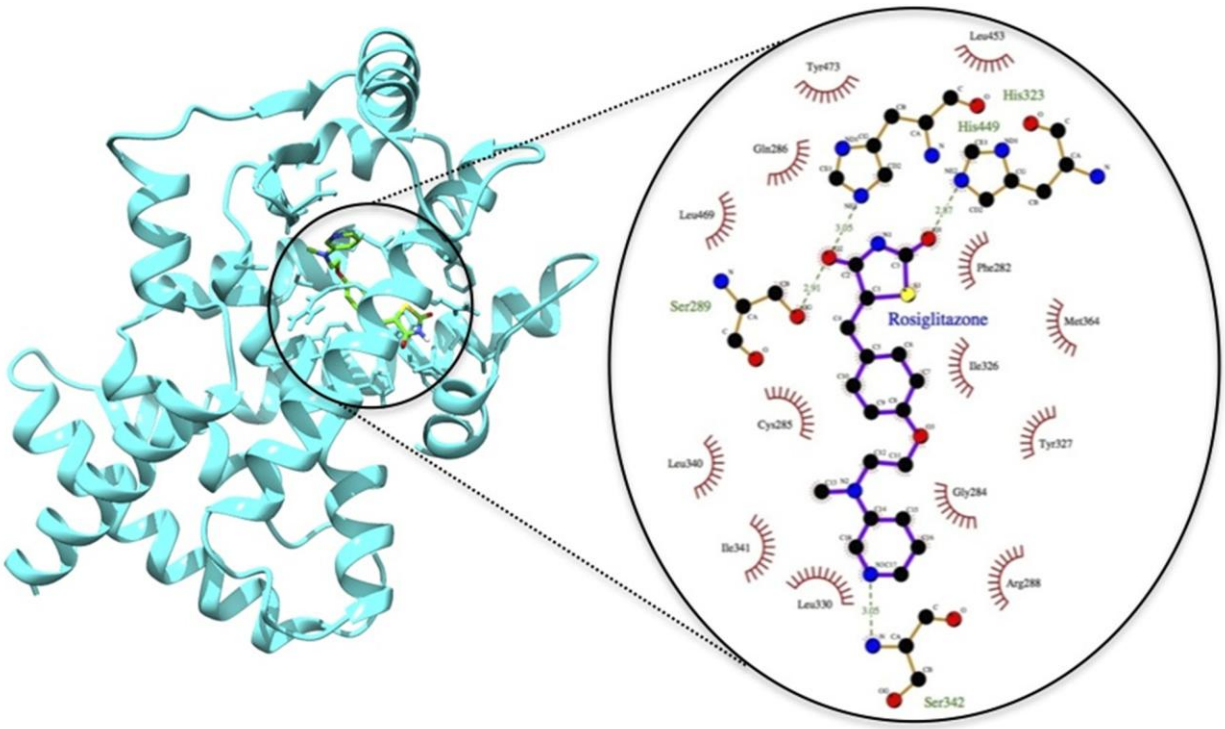


Figure 4. A depiction of Rosiglitazone docked into the PPARγ active site and LigPlot highlighting Rosiglitazone interactions with PPARγ active site residues.

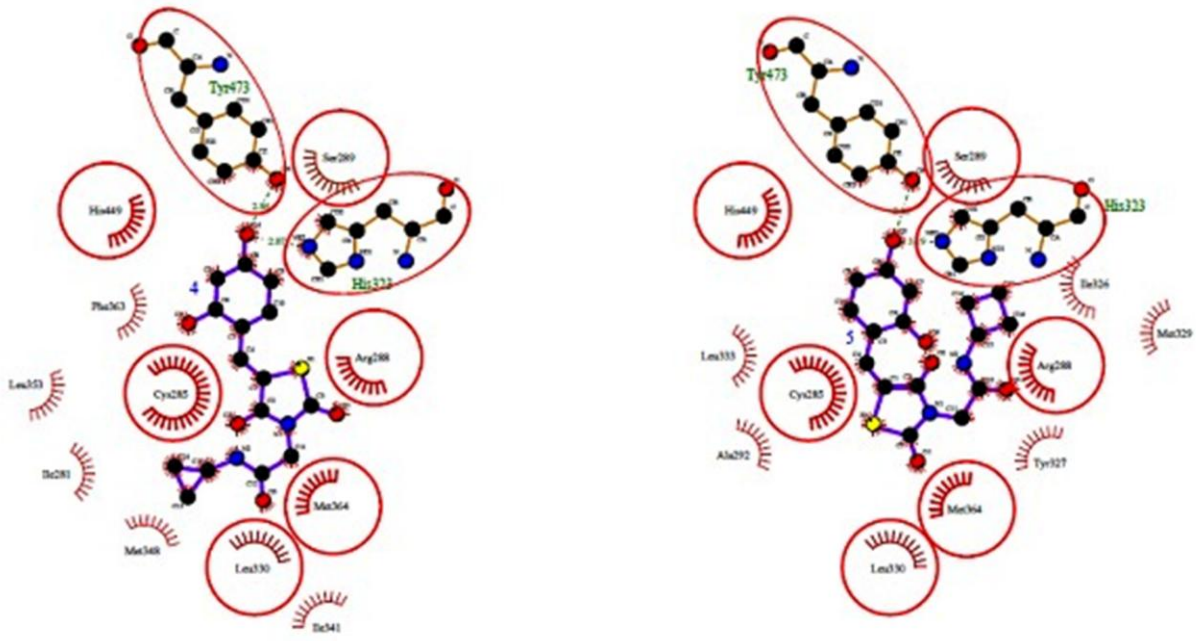


Figure 5. 2D-plot of compounds **4** and **5** in complex with 2PRG. Common interacting residues were highlighted in circles. (Figure was generated with LigPlot+ v1.4.5)

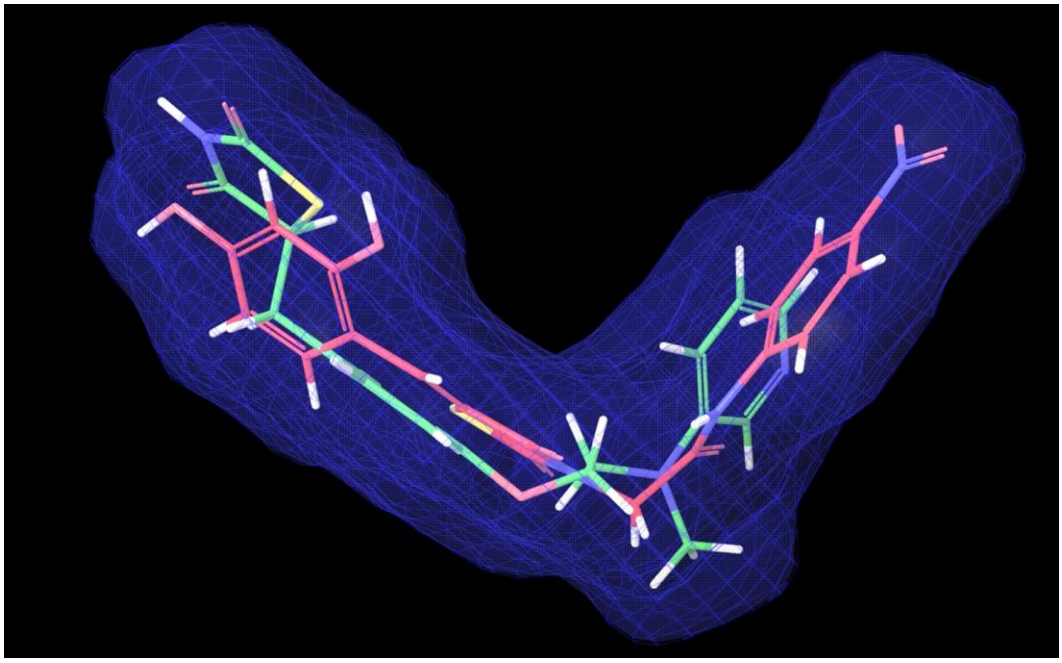


Figure 6. Rosiglitazone and top scorer compound **11** takes U-shape in the Y-shaped active site of PPARγ.

Compounds **2**-**11** exhibited similar orientation in the active site. Compounds **4-7** having cycloalkyl groups at R_1 position exhibited low VdW interaction (Figure 5, Table 3) in comparison with the others that are having aromatic ring at that position (compounds **1**-**3** & **8**-**10**). Compounds **1**-**3** displayed decreased Glide score with increasing carbon in the R_1 side chain. This can be attributed to increased electrostatic interaction (Table 3). In case of compounds **1** & **8**-**11**, a similar trend has been observed. Compounds with electron pumping groups at *para*-position of R_1 side chain phenyl ring (**8**-**10**) have shown increased electrostatic interaction leading to decreased Glide score. Compound **11** having electron withdrawing nitro group at *para*-position has significantly reduced the electrostatic interaction to the level as that of Rosiglitazone (Table 3). This along with best VdW interaction, compound **11** exhibited the best Glide score. It was also observed that the top scorer compound **11** has well aligned with Rosiglitazone in the U-shaped conformation in the active site of PPARγ (Figure 6), thus highlighting a binding confirmation similarity between the two compounds.

2.3. ADME/TOX parameters

All the designed compounds were evaluated for Lipinski's and Jorgensen's rule violation using Qikprop v3.0 (Schrodinger LLC) and the results are presented in Table 3. It was observed that all the molecules in the designed library obeyed the desired characteristics and thus assumed to have better drug-like properties in comparison to the reference compound.

Other ADMET properties were once again using pkCSM webserver and are presented in Table 4. It was observed that the incorporation of one more hydroxy group at *ortho*-position leads to the decrease in intestinal absorption and increase of blood brain permeability, thus does not support the strong drug-like behavior of the designed molecules. Other parameters related to distribution and excretion did not show a remarkable difference in comparison with earlier designed compounds. One of the most important parameters which were given more attention, related with cardiotoxicity (hERG-I and -II) and was found to be at an acceptable level. In summary, the introduction of *ortho*,*para*-dihydroxy group in the phenyl ring of a benzylidiene portion of thiazolidinedione derivatives have shown less improvement in ADME/TOX profile.

Conclusion

Enrichment study has been carried out to validate the docking program and docking protocol. It was showing the best enrichment at top 1% of the HITs. All the designed compounds were showing interactions similar to the one exhibited by the actives in the top 1%, predicting the high probability for the designed molecule to be a PPARγ agonist. Introduction of additional hydroxy functional group did not favour establishment of any additional H-bonding interaction as expected. But all thecompouds displayed interaction pattern quite similar to their moohydric counterparts reported by us. Predictive ADME-TOX calculations revealed that out of eleven compounds nine were having good metabolic stability in comparison with the standard molecules.

3. Experimental

Materials and Methods: All computational studies were carried out on a Ubuntu Linux 12.04 Operating system installed on Dell Precision Tower 5810 825W TPM workstation with Intel Xeon Processor E5-1660 v3 and 32GB DDR4 RAM. Simulations were carried out using Maestro 11(Schrödinger LLC).[27] *In silico* ADME/TOX profiling was performed using pkCSM web server maintained by VLS3D (Cambridge University).[28]Two-dimensional plots were drawn with Ligplot.[29]

3.1. Molecular Docking

Preparation of Protein*:* In an attempt to understand the possible ligand-receptor interaction at the molecular level, molecular docking simulation of compounds **(1-11)** was carried out with the X-ray crystal structure of PPARγ (PDB: 2PRG)[30]which was downloaded from Protein Data Bank (www.rcsb.org). PDB 2PRG is a three chain (A, B and C) containing protein having rosiglitazone as a co-crystallized ligand. For the purpose of molecular docking studies, chain A was selected [30]due to the presence of ligand binding domain.Preparation of the protein was done with protein preparation wizard ofMaestro 11(Schrodinger LLC) with default parameters and finally minimized using OPLS-2005.[27]

Grid Generation: Aminimized structure of the protein obtained as output from the protein preparation wizard was used for grid generation, which involves co-crystallized ligand, Rosiglitazone as the reference as it signifies the binding sites of drug with respect to the target. The grid for docking was generated using default parameters implemented in the module. The generated grid was used for further docking of new molecules.

Preparation of Ligands: Structures of theligands were sketched in using build panel and were prepared for docking using Ligprepmodule implemented in Maestro 11 (Schrodinger LLC). The molecules were subjected to energy minimization with OPLS-2005 force field[27]to generate single low energy 3-D structure for each input structure. For enrichment studies the structures of decoys and actives were downloaded from DUD (http://dud.docking.org/r2/) web page in sdf format. Both the decoys and actives were mixed to form a single library and prepared for docking using Ligprep utility.

Docking Protocol: Enrichment study was carried out using SP (Standard Precision) protocol implemented in Glide. For designed molecules Extra precision protocol (Glide XP) implemented in Glide[27] was used to carry-out the docking simulation using default parameters. Write XP descriptor option was used to generate .xpdes file,to understand the different docking related parameters. Generated favorable ligand poses were analyzed using XP visualizer.

3.2. ADMET/ TOX Parameters Prediction

Rule of five (Ro5) also known as a Lipinski's rule of drug-likeness[31]was formulated by C. A. Lipinski in 1997. Based on trends in the Ro5, it can be considered as a basis for the required possible evaluation of oral availability for a plausible therapeutic agent[32]. Ro5 is explored in terms of drug-like physicochemical features, drug-likeness related to structural features,comparison of drug-like and nondrug-like properties in drug discovery and development.[33]

Table 4. ADME/TOX Profile of designed derivatives and marketed drugs

	Molecular Descriptors	1	2	3	4	5	6	7	8	9	10	11	R
A	Water solubility (logmol/L)	-4.36	-4.27	-4.4	-3.1	-3.4	-3.66	-3.94	-4.98	-4.58	-4.6	-5.0	-4.11
	Caco2 permeability (log Papp in10-6cm/s)	0.27	0.29	0.31	0.13	0.1	0.26	0.33	0.22	0.18	0.33	0.09	1.03
	Intestinal absorption (human, %Absorbed)	76.11	73.7	72.9	72.3	73.2	74	74.8	77.3	74.5	76.5	73	97.36
	P-glycoprotein substrate (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor (Y/N)	N	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y
	P-glycoprotein II inhibitor(Y/N)	N	Y	Y	N	N	N	N	Y	Y	Y	Y	N
D	VDss (human, log L/kg)	-0.68	-0.64	-0.2	-0.40	-0.01	-0.33	-0.32	-0.73	-0.35	-0.35	-0.99	-0.41
	Fraction unbound (human)	0.19	0.2	0.19	0.32	0.33	0.37	0.35	0.16	0.17	0.17	0.13	0.25
	BBB permeability (log BB)	-1.06	-1.02	-1.11	-1.13	-0.12	-1.14	-1.16	-1.23	1.11	-1.11	-1.06	-0.64
	CNS permeability (log PS)	-2.59	-2.74	-2.82	-3.1	-2.59	-2.288	-2.79	-2.81	-2.51	-2.51	-2.59	-2.69
M	CYP2D6 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior (Y/N)	N	Y	Y	N	N	N	N	N	N	N	N	N
	CYP2C9 inhibitior (Y/N)	N	N	N	N	N	N	N	N	N	N	N	N
E	Total Clearance (log ml/min/kg)	-0.09	-0.07	-0.1	-0.1	-0.02	-0.033	-0.02	-0.06	-0.06	-0.15	-1.29	-0.11
	Renal OCT2 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N	N	N
T	AMES toxicity (Y/N)	N	N	N	Y	N	N	N	N	N	N	N	N
	Max.tolerated dose (human, log mg/kg/day)	0.83	0.81	0.82	0.5	0.43	0.360	0.28	0.82	0.73	0.77	0.77	0.68
	Oral Rat Acute Toxicity (LD_{50}, mol/kg)	2.48	2.4	2.34	2.61	2.66	2.6	2.6	2.66	2.43	2.52	2.5	2.64
	Oral Rat Chronic Toxicity (log mg/kg_ bw/day)	2.01	2.13	2.23	1.56	1.54	1.53	1.50	1.94	2.08	2.07	2.39	1.54
	Minnow toxicity (log mM)	1.05	1.06	0.82	2.01	1.20	1.77	1.65	0.82	1	0.95	0.62	1.18
	hERG I inhibitor (Y/N)	N	N	N	N	N	N	N	N	N	N	N	N
	hERG II inhibitor (Y/N)	Y	Y	Y	N	N	N	N	Y	Y	N	Y	N

Where A-Absorption; D-Distribution; M-Metabolism; E-Excretion; T-Toxicity; R-Rosigltazone

Jorgensen's rule of three (Ro3)[34]is an additional tool for evaluating the designed compounds during the process of selection for a drug candidate to act as a drug.It mainly finds its application in fragment-based drug design, where fragments are evaluated for Ro3 violations[34]. All the designed molecules were evaluated for their conformity with Ro5 and Ro3 using QikProp v3.0[30]. Ligprep output wasgiven as input for Qikprop and the results were presented in Table **3**. ADMET parameters were predicted using pkCSM web server [28]. ADME/TOX parameters such as water solubili ty, CaCo2 permeability, intestinal absorption, P-glycopr otein which determines and modulates significant phar macokinetic implications for P-gp substrates, volume of distribution, blood brain barrier (BBB) and CNS permeability along with toxicity parameters such as AMES toxicity (mutagenicity) and cardio-toxicity (hERG-I & II inhibition)[35], were predicted and presentedin Table **3**.Such properties were also predicted for standard drugs and were used for comparison.

Acknowledgement

First author acknowledges the University Grants Commission, New Delhi (MANF) for financial assistance of this work.

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