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Original Article

DESIGN, *IN SILICO* DOCKING AND PREDICTIVE ADME PROPERTIES OF SOME THIAZOLIDINE-2, 4-DIONES DERIVATIVES AS PPARγ MODULATORS

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ABSTRACT

Objectives: Thiazolidinediones a promising and privileged scaffold in medicinal chemistry that has been popularly recognized for its antidiabetic activity. The objective of the current study is to explore the effects of substitution replacing the acidic hydrogen of thiazolidinedione ring.

Methods: The protocol adopted was (i) *In silico* enumeration of small chemical library, (ii) molecular docking simulation and (iii) selection of hits based on predicted ADME/TOX properties to support further synthetic enumeration of chemical compounds for biological evaluation.

Results: The results of the present study showed that all the designed compounds were found to be potent PPARγ modulators and shows promising lead like properties from the calculated ADME/TOX parameters. Rosiglitazone was taken as a standard for the comparison of *In silico* studies.

Conclusion: The design strategy adopted has predicted improved potency, less toxicity and a better binding mode prediction towards PPARγ.

Keywords: PPARγ, Pharmacokinetic parameters, Schrodinger, Structure-activity relationship, Molecular docking simulation, Pharmacokinetic parameters

INTRODUCTION

Type-2 diabetes mellitus (T2DM) is a complex metabolic disorder resulting due to the impaired secretion and development of insulin resistance. Despite the availability of various antidiabetic agents for the treatment of diabetes, the prevalence of the disease has been reported to increase significantly over the years and is expected to reach 380 million by 2025 [1].

The Peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor superfamily and are ligand activated transcription factors [2]. To date, there are three known major subtypes of PPARs named as PPAR-α (NR1C1), PPAR-β/δ (NR1C2), PPAR-γ (NR1C3) and encoded by different genes which can induce or repress different biochemical reactions [3, 4]. PPARs involved in the regulation of metabolism involving lipids and carbohydrates and hence have emerged as a target for various metabolic disorders [5, 6], diabetes, chronic inflammatory conditions and cancer [7-10]. Despite the challenges and major obstacles in the field of development of PPAR related drugs, PPARγ targeted agents still hold promising approach for the treating type-2 diabetes and associated metabolic disorders.

Many PPARγ agonists were available in the market for the treatment of diabetes, Adverse effects (cardiotoxicity and hepatotoxicity, bone marrow depression) associated with these drugs keeps the search on for the development of the safest agent [11, 12].

Compounds containing heterocyclic ring systems such as thiazolidine-2,4-dione are of great importance in different areas of medicinal chemistry [13]. TZDs are an important class of compounds which act as insulin sensitizers and promotes glucose utilization in peripheral tissues [14]. TZDs acts mainly by binding to PPARγ and thus leads to its activation, which justifies their role as antidiabetic compounds.

Rationale of designing potent PPAR γ modulators

In spite of their higher efficacy towards the target, the available drug shows a large number of targets related side effects such as weight gain, fluid retention, cardiovascular diseases and increased risk of bone fractures [15]. Table 1 summarizes their introduction, reported adverse effects and withdrawal from the market. Such safety related concerns, promoted us for the development of some novel PPARγ agonists.

Based on the earlier reports it is understood that any substitution on ring nitrogen is tolerated [16] a small chemical library containing a series of novel thiazolidinediones derivatives with substitution on ring nitrogen has been designed by partially keeping the pharmacophoric features reported for this class of drugs (fig. 1). The glitazones in the market were found to establish two H-bonding interaction with His323 and His449 (involving two carbonyl oxygen of ring) when there is no substitution on the ring nitrogen. The Effect of introducing a bulkier group has been the objective of the presented study. Molecular level interaction of the designed molecules was analyzed through molecular docking approach and was then compared with the standard drug Rosiglitazone. *In silico* ADME/TOX profiling of the designed series was performed to compare with the PPARγ agonists that are available in the market as well as those withdrawn due to adverse reactions [16].

Table 1: Current status of PPARγ marketed drugs

Drug	Year Introduced	Reported Adverse effects	Year Withdrawn	Ref
Ciglitazone	1982	Edema and Cardiotoxicity	NA	[17]
Troglitazone	US market in 1997	Idiosyncratic Hepatotoxicity	2000	[18]
Rosiglitazone	US and Mexico in June 1999	Cardiotoxicity, weight gain Edema	2010	[19]
Pioglitazone	US in 1999	Cardiotoxicity and Bladder Cancer	2009 *Used in UK	[20, 21]
Lobeglitazone	2013 (Korea)	Weight gain and edema	NA	[22]

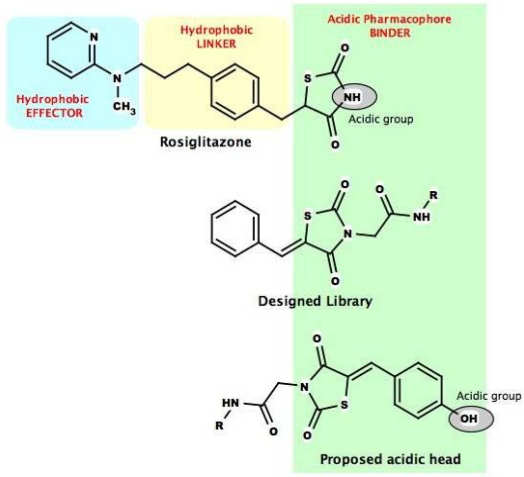


Fig. 1: Design of library and proposed new acidic binder

MATERIALS AND METHODS

All computational studies were carried out on a Dell Precision T3400n workstation with Intel core 2 quad processor, 8GB RAM, 500GB hard disk, running on the operating system Red Hat Enterprise 5.0 Linux (RHEL 5.0) platform. Simulations were carried out using Maestro-8.5 (Schrödinger LLC). *In silico* ADME/TOX profiling was performed using pkCSM [23] web server maintained by VLS3D (Cambridge University).

Molecular docking simulation procedures

Protein Preparation: In order to understand the interaction at the molecular level, compounds (1-20) were docked with X-ray crystal structure of PPARγ (PDB: 2PRG). The X-ray crystal structure of PPARγ (PDB: 2PRG) was downloaded from protein data bank (www. rcsb. org). It is a trimer (Chain A, B, C) having rosiglitazone as co-crystallized ligand. For the purpose of running the simulation, chain A was selected [24]. Protein preparation wizard Maestro-8.4 (Schrodinger LLC) was used to prepare the protein with default parameters and finally minimized using OPLS2005.

Grid generation

Using the energy-minimized structure of the protein obtained as output from the protein preparation wizard, a grid was generated for performing the molecular docking calculations. Centre of the grid was specified by locating the co-crystallized ligand, rosiglitazone through a pick ligand option in the Glide grid generation module. Grid for docking was generated using default parameters implemented in the module.

Ligand preparation

Structures of the ligands were sketched using build panel and were prepared for docking using Ligprep module implemented Maestro-8.5 (Schrodinger LLC). Once again default parameters in the module were used and energy minimization was carried out in OPLS 2005 force field.

Docking protocol

Extra precision protocol (Glide XP) implemented in Glide was used to run the docking simulation using default parameters. Write XP descriptor option was used to generate. xpdes file and the dockings were analyzed using XP visualizer.

ADMET parameters prediction

Rule of Five (Ro5) and Rule of Three (Ro3) violations

In 1997, Christopher A. Lipinski formulated a rule known as Lipinski's Rule of Five (Ro5), on the basis of his observation to evaluate the possibility of oral availability of a plausible therapeutic agent [25]. The Lipinski rule of five can be considered as an essential filtration tool to ensure drug like pharmacokinetics profile while using rational drug design. Jorgensen's Rule of Three (Ro3) is mainly found its application in fragment based drug design, where fragments were evaluated for Ro3 violations [26]. All the designed molecules were evaluated for their conformity with Ro5 and Ro3 using QikProp v3.0. Ligprep output was given as input for Qikprop and the results were presented in table 3.

ADMET parameters were predicted using pkCSM web server [23]. ADME parameters such as water solubility, CaCo2 permeability, intestinal absorption, P-glycoprotien, 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) [27] were predicted and presented in table 4. The properties were also predicted for standard drugs and used for comparison.

RESULTS AND DISCUSSION

Molecular docking simulation

Molecular docking simulation studies were carried out to understand the interaction of the designed molecules (1-20) with PPARγ at the atomic level. Before running the simulation with the designed molecules, redocking method was employed to validate the docking protocol and the RMSD for the cocrystallized ligand, Rosiglitazone was found to be 2.47 Å (fig. 2). Interaction of Rosiglitazone with its redocked pose revealed that its hydrophilic head part (Thiazolidinedione-carbonyl oxygen) establishing three H-bonding interaction Ser289, His323 and His449, while effector region establishing one H-bonding interaction with Ser342. The linker portion connecting them was showing hydrophobic interaction with nonpolar amino acids.

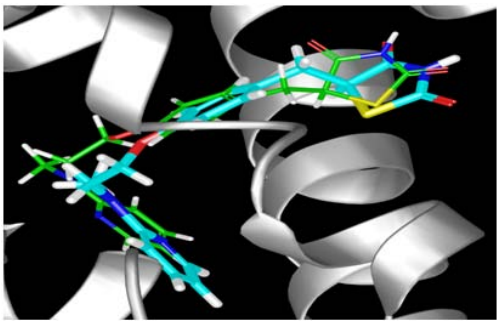


Fig. 2: Validation of docking protocol–Redocking 2PRG: The molecular docking calibration by Glide using Rosiglitazone as standard drug showing RMSD 2.47Å in comparison to crystal structure green colour)

Docked conformers of all the designed molecules were analyzed for the presence of similar interactions. In compounds 1-3, presence of bulkier phenyl, benzyl and phenyl ethyl substitutions found to push the hydrophilic head portion towards the hydrophobic region and orient differently in the pocket. Due to this the H-bonding interaction of TZD with Ser289, His323 and His449 were totally absent (fig. 4). In case of compounds 8-10, orientation greatly varies in comparison with compound 1. Compounds 9 & 10 reversed their orientation and could able to establish an H-bonding interaction with Ser342 (effector region).

Compounds 4 and 5, having cyclopropyl and cyclobutyl rings due to their smaller size could able to position side chain carbonyl oxygen of TZD in such a way to establish H-bonding interaction with Ser289 and His323. Moreover, carbonyl oxygen at 2nd position of TZD ring could able establish an H-bonding interaction with Tyr327. The three major interaction energies (VdW, ES, and HB) of these two compounds were found to be equivalent with Rosiglitazone (table 2). Increasing the ring size to 5 and 6 (compounds 6 and 7) resulted in conformation quite similar to the one having a phenyl ring (compound 1).

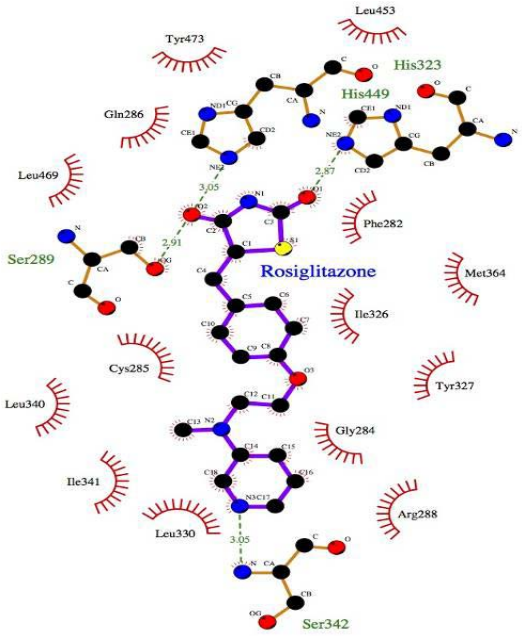


Fig. 3: 2D-plot of re-docked conformer of Rosiglitazone in the active site of 2PRG, Common Color coding of atoms in ball format: Black-carbon; Blue-nitrogen; Red-oxygen and Yellow-sulphur (fig. generated with LigPlot+v1.4.5)

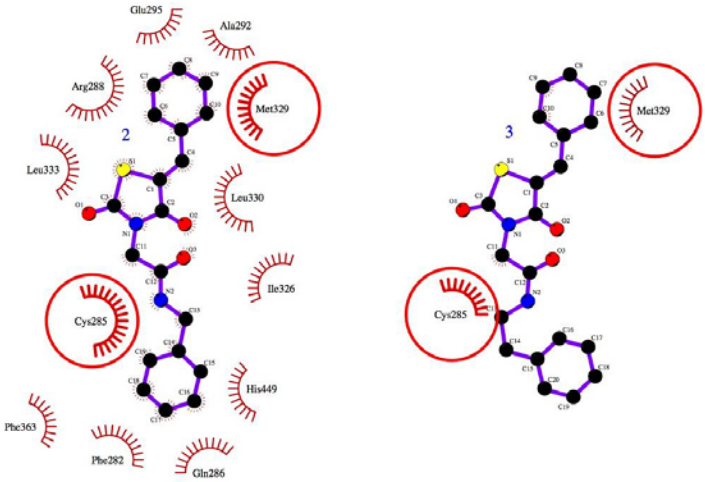


Fig. 4: 2D-plot of compounds 2 & 3 in complex with 2PRG. Common interacting residues were highlighted in red circles. Color coding of atoms in ball format: Black-carbon; Blue-nitrogen; Red-oxygen and Yellow-sulphur (fig. **generated with LigPlot+v1.4.5)**

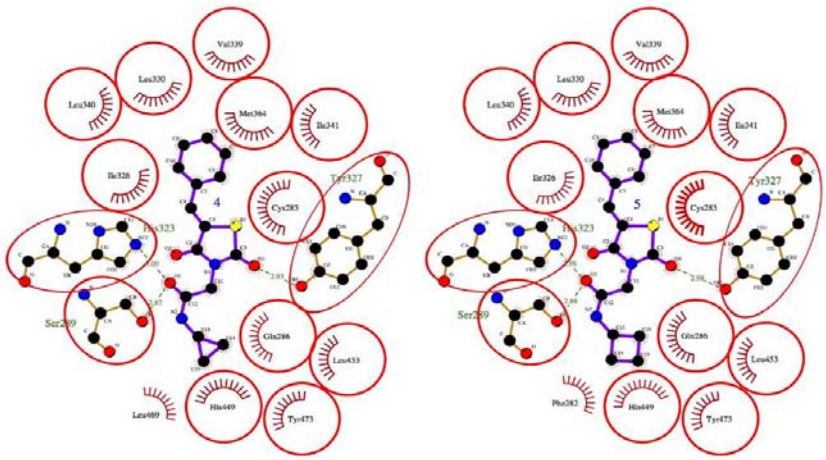


Fig. 5: 2D-plot of compounds 4 & 5 in complex with 2PRG. Common interacting residues were highlighted in red circles. The Side chain of amino acid residues establishing H-bonding interactions were shown in ball & stick model. H-bonds were shown in green dotted lines. Color coding of atoms in ball format: Black-carbon; Blue-nitrogen; Red-oxygen and Yellow-sulphur (fig. generated with LigPlot+v1.4.5)

In an effort to get an H-bonding interaction at the effector site similar to Rosiglitazone, we introduced a hydroxy functional group on the phenyl ring of benzylidene portion (Compounds 11-20). While analyzing the docked conformer we observed an interesting fact. Phenyl and benzyl derivatives (compounds 11 & 12) were having the orientation similar to compounds 1 & 2. While, all the other compounds (13-20) displayed a reversed orientation to place the hydroxy phenyl of benzylidene portion in the hydrophilic pocket (fig. 5). Moreover, they could also establish two H-bonding interactions with His323 and Tyr327. We also observe a drastic increase in electrostatic interaction (except compound 20, table 2) and this may be due to the presence of acidic phenolic OH and in the relatively polar and basic region lined by His323 and His449. A condition generally encountered with the natural substrates.

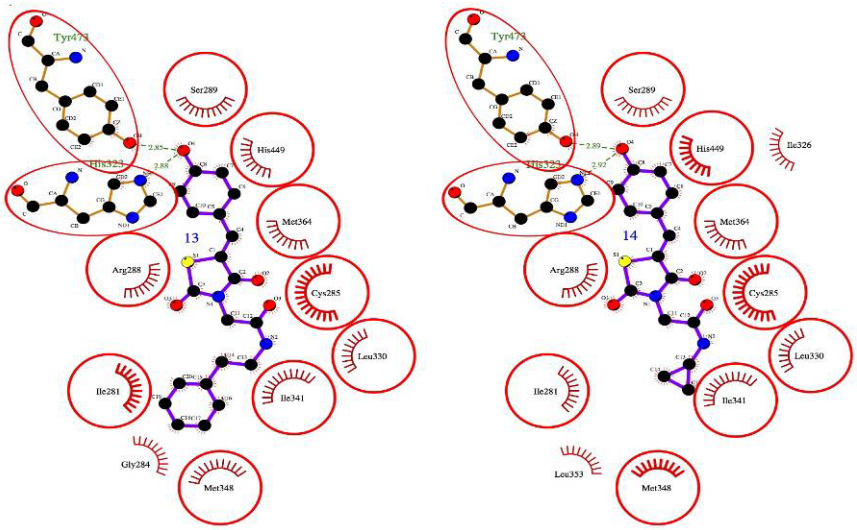
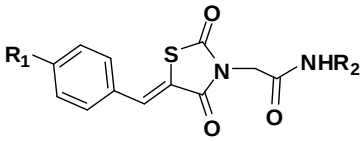


Fig. 6: 2D-plot of compounds 13&14 in complex with 2PRG. Common interacting residues were highlighted in red circles. The Side chain of amino acid residues establishing H-bonding interactions were shown in ball & stick model. H-bonds were shown in green dotted lines. Color coding of atoms in ball format: Black-carbon; Blue-nitrogen; Red-oxygen and Yellow-sulphur (fig. **generated with LigPlot+v1.4.5)**

In summary, the introduction of a hydroxy functional group on benzylidene phenyl ring improved the interaction with reversed orientation. This has made the benzylidene portion to behave as hydrophilic head, while pushing the TZD ring slightly towards a hydrophobic area. Yet TZD could able to establish H-bonding interaction with Tyr327. A revised pharmacophore structure can be written for this class as in fig. 6. Through this study, we proposed a new class of TZD targeting PPARγ for the treatment of diabetes.

Table 2: Docking score and energy calculations of designed molecules



Compound	R_1	R_2	Glide score	Electrostatic Energy (Kcal/mol)	Lipophilic evdw energy (Kcal/mol)	H-bond energy (Kcal/mol)
1	H	Phenyl	-6.431	-214.0	-4.5	-0.31
2	H	Benzyl	-6.626	-256.1	-4.8	-0.40
3	H	Phenylethyl	-6.977	-238.4	-4.5	-0.70
4	H	Cyclopropyl	-7.499	-209.0	-4.8	1.31
5	H	Cyclobutyl	-7.421	-210.7	-4.6	1.32
6	H	Cyclopentyl	-6.959	-233.0	-4.7	-1.01
7	H	Cyclohexyl	-6.623	-232.5	-4.6	-0.62
8	H	Anisidine	-6.877	-237.8	-4.9	-0.35
9	H	Toulidine	-7.249	-223.0	-5.2	-1.10
10	H	Nitroaniline	-6.577	-244.0	-4.4	-1.11
11	OH	Phenyl	-8.939	-194.6	-6.0	-1.10
12	OH	Benzyl	-7.393	-283.8	-5.3	-0.62
13	OH	Phenylethyl	-9.163	-269.6	-6.3	-1.33
14	OH	Cyclopropyl	-7.966	-239.1	-5.0	-1.33
15	OH	Cyclobutyl	-8.165	-240.8	-5.1	-1.33
16	OH	Cyclopentyl	-6.940	-262.5	-5.6	-1.32
17	OH	Cyclohexyl	-8.501	-262.3	-5.4	-1.33
18	OH	Anisidine	-9.157	-267.7	-6.3	-1.32
19	OH	Toulidine	-7.231	-253.1	-6.0	-1.33
20	OH	Nitroaniline	-9.062	-224.8	-6.2	-1.33
Rosiglitazone			-7.990	-208.09	-5.91	-1.24

ADMET parameters

All the compounds were evaluated for Ro5 and Ro3 violation using Qikprop v3.0 (Schrodinger LLC). All the molecules were found to obey both Ro5 and Ro3 (table 3). As Ro5 compliance ensures the oral bioavailability, the molecules in the designed library were assumed to have better intestinal permeability.

ADME parameters were predicted using pkCSM webserver and are presented in table 5. Intestinal absorption (human, % absorbed) predicted to be more than 90% for all the molecules except compound 20 (79.43%). The parameters related to distribution and excretion were found to be favourable for all the designed molecules and are comparable to that of the standard drugs.

Table 3: Predicted ADME parameters of some novel thiazolidinediones-ones derivatives using QikProp

Compound	Mol. formula	Mol. weight	Lipinski's violations	Jorgensen's violations
1	$C_{19}H_{18}N_2O_3S$	354	0	0
2	$C_{20}H_{20}N_2O_3S$	368	0	0
3	$C_{15}H_{16}N_2O_3S$	304	0	0
4	$C_{18}H_{18}N_2O_3S$	318	0	0
5	$C_{17}H_{20}N_2O_3S$	332	0	0
6	$C_{18}H_{22}N_2O_3S$	346	0	0
7	$C_{19}H_{18}N_2O_4S$	370	0	0
8	$C_{19}H_{18}N_2O_3S$	354	0	0
9	$C_{18}H_{15}N_3O_5S$	385	0	0
10	$C_{19}H_{18}N_2O_4S$	370	0	0
11	$C_{20}H_{20}N_2O_3S$	384	0	0
12	$C_{15}H_{16}N_2O_4S$	320	0	0
13	$C_{16}H_{18}N_2O_4S$	334	0	0
14	$C_{17}H_{20}N_2O_4S$	348	0	0
15	$C_{18}H_{22}N_2O_4S$	362	0	0
16	$C_{19}H_{18}N_2O_5S$	386	0	0
17	$C_{19}H_{18}N_2O_4S$	370	0	0
18	$C_{18}H_{15}N_2O_4S$	401	0	0
Cigltazone	$C_{18}H_{23}NO_3S$	333	0	0
Troglitazone	$C_{24}H_{27}NO_5S$	441	1	2
Rosiglitazone	$C_{18}H_{19}N_3O_3S$	357	0	1
Pioglitazone	$C_{19}H_{20}N_2O_3S$	356	1	0
Lobeglitazone	$C_{26}H_{26}N_2O_5S$	478	1	1

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

Property	Molecular descriptors	1	2	3	4	5	*C	*T	*P	*R	*L
Absorption	Water solubility (log mol/l)	-4.81	-4.68	-4.8	-3.3	-3.6	-5.25	-6.05	-4.53	-4.115	-5.369
	Caco2 permeability (log Papp in10-6 cm/s)	1.04	1.07	1.08	0.95	0.95	1.405	1.048	1.035	1.035	0.291
	Intestinal absorption (human) (%Absorbed)	92.75	94	94.3	94.5	94.1	95.13	92.97	96.76	97.363	90.971
	P-glycoprotein substrate (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor (Y/N)	Y	Y	Y	N	Y	N	Y	Y	Y	Y
	P-glycoprotein II inhibitor(Y/N)	N	N	Y	N	N	N	Y	Y	N	Y
Distribution	VDss (human) (log L/kg)	-0.31	-0.26	-0.2	-0.01	-0.01	-0.082	-0.2	-0.34	-0.419	-1.036
	Fraction unbound (human)	0.125	0.14	0.12	0.35	0.33	0.117	0	0.177	0.258	0.076
	BBB permeability (log BB)	-0.09	-0.11	-0.13	-0.13	-0.12	-0.035	-0.4	-0.494	-0.641	-1.315
	CNS permeability (log PS)	-2.21	-2.36	-2.43	-2.68	-2.59	-2.11	-1.888	-2.484	-2.694	-3.112
Metabolism	CYP2D6 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior (Y/N)	N	Y	N	N	N	Y	N	Y	N	N
	CYP2C9 inhibitior(Y/N)	N	N	N	N	N	Y	Y	N	N	Y
Excretion	Total Clearance(log ml/min/kg)	-0.043	-0.02	-0.06	-0.05	-0.02	0.07	-0.48	-0.04	-0.11	-0.11
	Renal OCT2 substrate(Y/N)	N	N	N	N	N	N	N	N	N	N
Toxicity	AMES toxicity (Y/N)	N	N	N	Y	N	N	Y	N	N	N
	Max. tolerated dose (human) (log mg/kg/day)	1.038	1.001	1.016	0.637	0.572	0.876	0.61	0.85	0.68	0.58
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.5	2.49	2.43	2.43	2.6	2.65	2.47	2.48	2.64	2.47
	Oral RatChronicToxicity (log mg/kg_bw/day)	2.01	2.12	2.22	1.56	1.54	1.86	2.2	1.81	1.54	1.89
	Minnow toxicity(log mM)	N	0.377	0.135	1.321	1.204	-0.48	-0.77	0.5	1.18	0.15
	hERG I inhibitor (Y/N)	N	N	N	N	N	N	N	N	N	N
	hERG II inhibitor (Y/N)	Y	Y	Y	N	N	Y	Y	N	N	Y

Where *C: Ciglitazone, *T: Troglitazone, *P: Pioglitazone, *R: Rosigltazone, *L: Lobiglitazone

One of the toxicity parameter was given much attention, cardiotoxicity due to which few marketed TZD were withdrawn from the market. Eleven molecules (4-6, 8, 12-18, 20) were predicted not to inhibit hERG-I and II, and are predicted to be devoid of cardiotoxicity. Eight of the hydroxy benzylidene derivatives were found to have this favourable characteristic.

When compared with the marketed drugs such as Ciglitazone, Rosiglitazone, Pioglitazone, Troglitazone and lobeglitazone the various associated toxicity related factors such as cardiotoxicity, oral rat acute toxicity, oral rat chronic toxicity, minnow toxicity our designed compounds were showing good pharmacokinetic as well as nice ADMET properties. One of the most important factors that is absorption, is found all around very much similar with the marketed drugs. The others associated factors such as maximum tolerated dose, and blood brain permeability are also in the acceptable range of all the designed molecules.

In summary, the introduction of the hydroxy group in the phenyl ring of benzylidene portion of the TZD derivatives predicted improved their ADME/TOX profile. They were all found to have better intestinal absorbtion and devoid of cardiotoxicity.

Compared with earlier reported thiazolidinediones, in the presented simulation study, we observed a reversed orientation of molecules having a hydroxy benzylidene portion inside the active site of PPARγ. Due to this the polar hydroxy group containing benzylidene portion tends to occupy the acidic head of classical pharmacophore establishing H-bonding interaction similar to Rosiglitazone (TZD portion). This has prompted us to rewrite the pharmacophore for compounds of this class and it has been represented in fig. 1.

The interaction of this class of molecules with PPARγ has been established *In silico* and its effect as agonist, partial agonist or antagonist is required to be established through suitable experimental protocols. Moreover, for the first time the compound class was evaluated for their cardiotoxicity (hERGI & II) in a predictive model using pKCSM and most of the compounds were found to be better than the marketed drugs.

Table 4: ADME/TOX Profile of designed derivatives and marketed drugs (contd….)

Property	Molecular descriptors	6	7	8	9	10	*C	*T	*P	*R	*L
Absorption	Water solubility (log mol/l)	-4.80	-4.33	-5.00	-5.09	-4.55	-5.25	-6.05	-4.53	-4.115	-5.369
	Caco2 permeability (log Papp in10-6 cm/s)	0.95	0.95	1.06	1.04	1.05	1.405	1.048	1.035	1.035	0.291
	Intestinal absorption (human) (%Absorbed)	92.74	93.28	92.74	92.48	89.86	95.13	92.97	96.76	97.363	90.971
	P-glycoprotein substrate (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor (Y/N)	Y	Y	Y	N	Y	N	Y	Y	Y	Y
	P-glycoprotein II inhibitor(Y/N)	N	N	Y	N	N	N	Y	Y	N	Y
Distribution	VDss (human) (log L/kg)	-0.06	-0.09	-0.45	-0.28	-0.50	-0.082	-0.2	-0.34	-0.419	-1.036
	Fraction unbound (human)	0.302	0.278	0.125	0.106	0.16	0.117	0	0.177	0.258	0.076
	BBB permeability (log BB)	-0.10	-0.09	-0.62	-0.08	-0.89	-0.035	-0.4	-0.494	-0.641	-1.315
	CNS permeability (log PS)	-2.54	-2.37	-2.39	-2.56	-2.40	-2.11	-1.888	-2.484	-2.694	-3.112
Metabolism	CYP2D6 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior (Y/N)	N	N	N	Y	Y	Y	N	Y	N	N
	CYP2C9 inhibitior(Y/N)	N	N	N	Y	Y	Y	Y	N	N	Y
Excretion	Total Clearance(log ml/min/kg)	-0.02	-0.03	-0.01	-0.10	-0.16	0.07	-0.48	-0.04	-0.11	-0.11
	Renal OCT2 substrate(Y/N)	N	N	N	N	N	N	N	N	N	N
Toxicity	AMES toxicity (Y/N)	N	N	N	N	N	N	N	N	N	N
	Max. tolerated dose (human) (log mg/kg/day)	0.50	0.44	0.92	0.97	0.93	0.876	0.61	0.85	0.68	0.58
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.70	2.75	2.55	2.59	2.53	2.65	2.47	2.48	2.64	2.47
	Oral RatChronicToxicity (log mg/kg_bw/day)	1.52	1.50	2.00	1.95	2.09	1.86	2.2	1.81	1.54	1.89
	Minnow toxicity(log mM)	1.08	0.97	0.317	0.26	0.70	-0.48	-0.77	0.5	1.18	0.15
	hERG I inhibitor (Y/N)	N	N	Y	N	Y	N	N	N	N	N
	hERG II inhibitor (Y/N)	Y	N	Y	Y	N	Y	Y	N	N	Y

Where *C: Ciglitazone, *T: Troglitazone, *P: Pioglitazone, *R: Rosigltazone, *L: Lobiglitazone

Table 4: ADME/TOX Profile of designed derivatives and marketed drugs (contd….)

Property	Molecular descriptors	11	12	13	14	15	*C	*T	*P	*R	*L
Absorption	Water solubility (logmol/l)	-5.49	-4.44	-4.58	-3.13	-3.45	-5.25	-6.05	-4.53	-4.115	-5.369
	Caco2 permeability (log Papp in10-6 cm/s)	0.27	1.08	1.09	0.96	1.05	0.96	1.048	1.035	1.035	0.291
	Intestinal absorption (human) (%Absorbed)	85.71	91.06	91.44	91.58	91.16	95.13	92.97	96.76	97.363	90.971
	P-glycoprotein substrate (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor (Y/N)	Y	Y	Y	Y	N	N	Y	Y	Y	Y
	P-glycoprotein II inhibitor(Y/N)	Y	N	Y	Y	N	N	Y	Y	N	Y
Distribution	VDss (human) (log L/kg)	-0.64	-0.45	-0.40	-0.19	-0.16	-0.082	-0.2	-0.34	-0.419	-1.036

	Fraction unbound (human)	0.058	0.172	0.153	0.38	0.36	0.117	0	0.177	0.258	0.076
	BBB permeability (log BB)	-0.92	-0.84	-0.88	-0.91	-0.93	-0.035	-0.4	-0.494	-0.641	-1.315
	CNS permeability (log PS)	-2.39	-2.55	-2.62	-2.87	-2.78	-2.11	-1.888	-2.484	-2.694	-3.112
Metabolism	CYP2D6 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior (Y/N)	Y	N	Y	Y	N	Y	N	Y	N	N
	CYP2C9 inhibitior(Y/N)	Y	N	N	N	N	Y	Y	N	N	Y
Excretion	Total Clearance(log ml/min/kg)	-0.02	-0.13	-0.11	-0.13	-0.17	0.07	-0.48	-0.04	-0.11	-0.11
	Renal OCT2 substrate(Y/N)	N	N	N	N	N	N	N	N	N	N
Toxicity	AMES toxicity (Y/N)	N	N	N	N	N	N	N	N	N	N
	Max. tolerated dose (human) (log mg/kg/day)	0.94	0.94	0.91	0.56	0.49	0.876	0.61	0.85	0.68	0.58
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.39	2.46	2.45	2.56	2.67	2.65	2.47	2.48	2.64	2.47
	Oral RatChronicToxicity (log mg/kg_bw/day)	2.56	1.50	2.00	1.95	2.09	1.86	2.2	1.81	1.54	1.89
	Minnow toxicity(log mM)	0.06	0.72	0.317	0.26	0.70	-0.48	-0.77	0.5	1.18	0.15
	hERG I inhibitor (Y/N)	Y	N	Y	N	Y	N	N	N	N	N
	hERG II inhibitor (Y/N)	N	N	Y	Y	N	Y	Y	N	N	Y

Where *C: Ciglitazone, *T: Troglitazone, *P: Pioglitazone, *R: Rosigltazone, *L: Lobiglitazone

Table 4: ADME/TOX Profile of designed derivatives and marketed drugs (contd….)

Property	**Molecular descriptors**	**16**	**17**	**18**	**19**	**20**	***C**	***T**	***P**	***R**	***L**
Absorption	Water solubility (logmol/l)	-3.77	-4.08	-4.77	-4.82	-5.24	-5.25	-6.05	-4.53	-4.115	-5.369
	Caco2 permeability (log Papp in10-6 cm/s)	0.96	0.96	0.37	1.06	0.078	1.405	1.048	1.035	1.035	0.291
	Intestinal absorption (human) (%Absorbed)	90.74	90.40	80.76	89.65	79.46	95.13	92.97	96.76	97.363	90.971
	P-glycoprotein substrate (Y/N)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	P-glycoprotein I inhibitor (Y/N)	N	N	Y	Y	Y	N	Y	Y	Y	Y
	P-glycoprotein II inhibitor(Y/N)	N	N	Y	Y	Y	N	Y	Y	N	Y
Distribution	VDss (human) (log L/kg)	-0.13	-0.10	-0.64	-0.47	-0.82	-0.082	-0.2	-0.34	-0.419	-1.036
	Fraction unbound (human)	0.33	0.315	0.16	0.14	0.09	0.117	0	0.177	0.258	0.076
	BBB permeability (log BB)	-0.96	-0.98	-1.09	-0.90	-1.11	-0.035	-0.4	-0.494	-0.641	-1.315
	CNS permeability (log PS)	-2.69	-2.60	-2.56	-2.32	-2.58	-2.11	-1.888	-2.484	-2.694	-3.112
Metabolism	CYP2D6 substrate (Y/N)	N	N	N	N	N	N	N	N	N	N
	CYP1A2 inhibitior (Y/N)	N	N	N	Y	N	Y	N	Y	N	N
	CYP2C9 inhibitior(Y/N)	N	N	N	Y	N	Y	Y	N	N	Y
Excretion	Total Clearance(log ml/min/kg)	-0.009	-0.08	-0.13	-0.22	-0.47	0.07	-0.48	-0.04	-0.11	-0.11
	Renal OCT2 substrate(Y/N)	N	N	N	N	N	N	N	N	N	N
Toxicity	AMES toxicity (Y/N)	N	N	N	N	Y	N	N	N	N	N
	Max. tolerated dose (human) (log mg/kg/day)	0.42	0.35	0.82	0.86	0.85	0.876	0.61	0.85	0.68	0.58
	Oral Rat Acute Toxicity (LD50) (mol/kg)	2.67	2.72	2.50	2.57	2.54	2.65	2.47	2.48	2.64	2.47
	Oral RatChronicToxicity (log mg/kg_bw/day)	1.52	1.51	1.50	2.01	2.39	1.86	2.2	1.81	1.54	1.89
	Minnow toxicity(log mM)	1.43	1.31	0.66	0.61	0.28	-0.48	-0.77	0.5	1.18	0.15
	hERG I inhibitor (Y/N)	N	N	N	N	N	N	N	N	N	N
	hERG II inhibitor (Y/N)	Y	N	N	Y	N	Y	Y	N	N	Y

Where *C: Ciglitazone, *T: Troglitazone, *P: Pioglitazone, *R: Rosigltazone, *L: Lobiglitazone

CONCLUSION

All the designed Thiazolidinediones derivatives (1-20) were found to be potent and selective PPARγ agonists. The results obtained by docking studies could be utilized for development of more potent, effective novel 2, 4 thiazolidinediones derivatives with PPARγ modulator activity. All the designed derivatives were showing good glide docking score as compared with the marketed drugs. The interactions of all the designed derivatives with the receptors show a very good promising path that they can be considered as potent PPARγ modulators. The ADMET properties of most of the designed compounds are in an acceptable range and having lead like properties. Predicted cardiotoxicity shows that molecules having TZD ring N-substitution may serve as better alternatives to the existing drugs in the PPARγ market.

The design strategy adopted has significantly improved the permeability characteristics in comparison with Rosiglitazone. This study gives an idea to design and discover some new, safer and less toxic analogs in the field of PPARγ.

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CONFLICT OF INTERESTS

Declared none

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