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In silico design, chemical synthesis and toxicological evaluation of 1,3-thiazolidine-2,4-dione derivatives as PPARγ agonists

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Abstract

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors involved in the metabolism of lipids and carbohydrates. The exogenous ligands of these receptors are thiazolidinediones (TZDs), which are used to treat type 2 diabetes mellitus (DM2). However, drugs from this group produce adverse effects such as hepatic steatosis. Hence, the aim of this work was to design a set of small molecules that can activate the γ isoform of PPARs while minimizing the adverse effects. The derivatives were designed containing the polar head of TZD and an aromatic body, serving simultaneously as the body and tail. Two ligands were selected out of 130 tested. These compounds were synthesized in a solvent-free reaction and their physicochemical properties and toxicity were examined. Acute oral toxicity was determined by administering these compounds to female Wistar rats in increasing doses (as per the OECD protocol 425). The median lethal dose (LD50) of the compound substituted with a hydroxyl heteroatom was above 2000 mg/kg, and that of the compound substituted with halogens was 700-1400 mg/kg. The results suggest that the compounds can interact with PPARγ and elicit biological responses similar to other TZDs, but without showing adverse effects. The compounds will be subsequently evaluated in a DM2 animal model.

Keywords:

PPARγ agonists, thiazolidinedione, *in silico* studies, chemical synthesis, acute toxicity.

Introduction

Type 2 diabetes mellitus (DM2) is a complex metabolic disease characterized by hyperglycemia (caused by a defect in pancreatic β cells), insulin resistance in peripheral tissues, and excessive accumulation of triglycerides and fatty acid derivatives in skeletal muscles and other tissues. The latter characteristic is highly correlated with the development of the chronic micro and macro vascular complications of the disease [1-13].

The treatment of DM2 has aimed to decrease hyperglycemia by improving insulin secretion or reducing insulin resistance in peripheral tissues, an effect found with thiazolidinediones (TZDs) [7,9,14-16]. These compounds, also known as glitazones, are used clinically as insulin sensitizers to lower the levels of blood glucose and circulating triglycerides [9,14,16-19]. To carry out these activities, TZDs act as full agonists of peroxisome proliferator-activated receptors (PPARs) γ. In addition to such beneficial functions, they are involved in the increase of adipocyte differentiation and improvement of fatty acids. Since these molecules have attracted the attention of several research groups worldwide, new strategies have been sought and discovered to synthesize them [14,16-18,20,21].

Three isoforms have been described for PPARs: α, β/δ and γ. Each of these regulate tissue-specific target genes involved in biological pathways for lipid and glucose homeostasis. Of the PPARs, PPARγ is particularly important in the pathology of various disorders, including DM2, obesity, dyslipidemia, atherosclerosis, neoplastic diseases and tumors, inflammatory conditions, and neurodegenerative diseases [8,14,16,22-33].

PPARγ is organized into domains, each associated with certain functions, such as ligand binding, activation, and DNA binding (Figure 1). The amino terminal A/B domain has a ligand-dependent transactivation function. The C domain is the central DNA-binding domain, which contains two zinc finger-like structures and one α helical DNA binding

68 motif. The E/F domain has the ligand-dependent transactivation function, which allows for
69 conformational changes in the presence of a ligand. This in turn leads to the recruitment of
70 co-activators and the release of co-repressors [16,22,34,35].
71
72 **Figure 1.** The main functional domains of PPARγ. A/B has the activation function 1 (AF-
73 1) and C is the DNA-binding domain (DBD). D serves as a hinge between C and E/F, the
74 latter of which is the ligand-binding domain (LBD) that contains AF-2, a ligand-binding
75 dimerization transactivation domain.
76
77 The PPARγ ligand-binding domain (LBD) contains a large binding pocket that permits
78 diverse types of ligands to enter and search for the proper resting conformation that enables
79 each of them to form a ligand-receptor complex. Fatty acids or their derivatives are natural
80 ligands of PPARγ. Synthetic ligands, such as TZDs, L-tyrosine analogs and some
81 nonsteroidal anti-inflammatory drugs, can be classified as either full or partial agonists [16-
82 18,22,26,34,36-40].
83 TZDs as well as most known PPARγ agonists share common features, including a
84 hydrophilic head group, a central hydrophobic body, and a flexible linker to a cyclic tail.
85 The hydrophilic head group has hydroxyl, carbonyl or carboxyl oxygen atoms that allow it
86 to form H bonds with the key amino acid residues: Tyr 473 (having an AF2 helix H12,
87 which appears to be crucial for maintaining the helix in an adequate conformation for
88 coactivator recruitment), His 449 (H11), His323 (H5), Ser289 (H3), and Gln286 (H3) of the
89 LBD. In this way, full agonists are able to generate an intermolecular network with the
90 receptor.

Whereas this H bond network stabilizes the receptor in the proper conformation, the acid head group of commercially available TZDs are prone to racemization under physiological conditions due to their stereogenic center at C5. Furthermore, it has been demonstrated that only the (S)-enantiomers bind to the receptor, which suggests that approximately 50% of the active substance is inactive.

The binding of these ligands causes conformational changes in the receptors, and this facilitates ligand interaction with co-activator proteins in the nucleus. The resulting protein complexes activate the transcription of specific target genes, inducing intracellular signaling cascades that mediate physiological effects [16-21,26,30,31,34,36-40].

Despite the excellent potency of TZDs, they have severe side effects such as fluid retention, weight gain, hepatotoxicity (only for troglitazone), plasma-volume expansion, hemodilution, edema, and congestive heart failure. Because of these unfavorable effects, the clinical application of TZDs has been limited, especially for diabetic patients suffering from cardiomyopathy [14,16,17,30,31,33,39-41].

The aim of the present study was to produce TZD derivatives that are effective for treating DM2, but with less side effects. There was a specific purpose for each aspect of the current contribution, including molecular docking, synthesis and acute toxicity. Molecular docking studies were performed on PPARγ with a series of TZD derivatives to predict the orientation within a targeted binding site. For chemical synthesis of the derivatives, high yield was sought within the context of a solvent-free reaction. The acute toxicity study was conducted to obtain relatively safe compounds that could be administrated to healthy animals.

Materials and methods

Docking studies

The structures of the compounds were drawn with ChemDraw Ultra v10.0 (Cambridge Soft Corporation, USA), then copied to Chem3D Ultra v10.0 to create a 3D model. Afterwards, they were subjected to energy minimization with Gaussian 09 and GaussView v5 (Gaussian Inc, USA) [42], using molecular mechanics (MM_2) in an AM1 platform. The minimization was executed until the root mean square gradient value became smaller than 0.001 kcal/mol. Corresponding pdb files were prepared by means of AutoDock Tools v1.5.6 [43].

The selection of the protein for molecular docking studies was based on several factors. The structure was determined by X-ray diffraction with a resolution between 2.0 and 2.5 Å. A co-crystallized ligand and a co-activator were required, protein breaches in the 3D structure were not permitted, and the LBD had to be complete [44,45]. In the crystal chosen, PDB entry 2PRG [46], rosiglitazone and SRC-1 were co-crystallized as the ligand and the coactivator, respectively. The LBD formed a homodimer in which both monomers had a nearly identical Cα conformation, allowing the "A" monomer to be selected for the docking studies. All water molecules and the crystallographic ligand were removed from the receptor. All hydrogen atoms were added, Kollman's charges assigned, and non-polar hydrogen atoms merged [43-48].

The active binding site region was defined as a 60 x 60 x 60 cube, with points separated by 0.375 Å. The Lamarckian genetic algorithm was applied for the search, utilizing default parameters. The LBD was considered as a rigid molecule and the ligands as flexible (all non-ring torsions were accepted). Before docking the proposed compounds, the docking protocols of AutoDock v4.0 and AutoGrid v4.0 were validated by predicting the binding mode of a well-known crystallographic ligand (rosiglitazone). Results were visualized with Pymol 1.0 and VMD v1.8.7 [6,20,23,29,39,43,47,48].

The physicochemical properties of the compounds were also evaluated and the predictive toxicity calculated by using online software: Molinspiration Cheminformatics [49] and Osiris Property Explorer [50].

Chemical synthesis

The reaction sequence employed for the synthesis of the proposed compounds was based on a Knoevenagel condensation, using equimolar concentrations and a catalytic amount of urea at 10 mol % in a solvent-free environment (Figure 2) [20,51,52]. 2,4-thiazolidinedione can undergo a Knoevenagel condensation with a variety of substituted aldehydes to produce 5-arylidene-2,4-thiazolidinediones (Figure 2). All the synthesized compounds were characterized by spectroscopic methods such as IR, ^{1}H NMR, ^{13}C NMR and MS [20].

Figure 2. Proposed synthesis methodology.

Acute Toxicity Study

Acute oral toxicity was performed as per the OECD (Organization of Economic Cooperation and Development) 425 guideline (Up & down method) [53]. Healthy female albino Wistar rats, nulliparous and not pregnant, were randomly divided into groups to be given increasing doses. The animals were housed individually at room temperature (22 ± 3° C) and 30-35% relative humidity. They were kept on a 12/12 h light/dark cycle, fed conventional rodent laboratory diet (Rat Chow 5012 formula), and provided drinking water *ad libitum* throughout the experiment.

The animals were acclimated to the lab conditions for 8 days prior to dosing. The day before the initial dose, animals were fasted overnight. To determine toxicity (by up and

down staircase), the compounds were administered orally via orogastric cannula, employing increasing doses with a 0.5 progression factor (175, 350, 700, 1400 and 2000 mg/kg). Doses were selected according to the original protocol (annex 2, paragraph 2), which states that in the absence of an available estimate of the lethality of a given substance, dosing should be initiated at 175 mg/kg. In most cases this dose is sub lethal and therefore serves to reduce the level of pain and suffering of the animals. The protocol also specifies that in case animal tolerances to the chemical are expected to be highly variable, an increase in the dose progression factor beyond the default 0.5 on a log dose scale (3.2 factor) should be considered. This led us to choose a 0.5 factor.

After administration of the compound, animals were watched to monitor their general behavior and possible neurological behavioral disturbances. This surveillance was carried out continuously for 5 h, frequently for another 5 h, and then occasionally for 24 or 48 h. The animals were kept under observation for 14 days to register survival and death [53,54].

The LD50 was estimated with the formula of Reed Muench: LD50 = log (inferior dose) + B x log A, where B = (50 – inferior mortality %) / (superior mortality % - inferior mortality %), and A = maximum dose / minimum dose.

Results

Docking studies

One hundred and thirty derivatives were designed and tested. The derivatives had the polar head of TZD and an aromatic mono and di-substituted body/tail portion. From 117 crystals encoded for PPARγ that are available in PDB, entry 2PRG was the most complete. This receptor was found co-crystallized with rosiglitazone as the ligand and SRC-1 as a

coactivator. This murine PPARγ protein is homologous to human PPARγ, having 95% identity at the amino acid level.

Like rosiglitazone, the head group of the tested compounds interacted with His323, His449, Tyr473, Ser289 and Gln286. The partially lipophilic tail was inserted into the hydrophobic pocket of the LBD (see Table 1).

Table 1. Docking scores for the pattern compounds and their derivatives.

In accordance with the physicochemical prediction, the proposed compounds proved to be more hydrophilic than those employed as patterns (rosiglitazone, pioglitazone and troglitazone), as well as having a lower molecular weight (Table 2).

Table 2. Physicochemical properties of the proposed compounds.

Chemical synthesis

For the chemical synthesis of compound 40 (C#40), the reagents were 1,3-thiazolidine-2,4-dione and salicylaldehyde. The reaction was carried out in a solvent-free environment at 120° C for 2 h. The product obtained was a yellow dust with an Rf of 0.26 (hexane-ethyl acetate, 6:4) and a final yield of 90.58%. It has a melting point at 275 ± 2°C and shows good solubility in acetone, ethyl acetate, methanol and dimethyl sulfoxide. The presence of the desired product was confirmed by IR, NMR and MS. IR (cm^{-1}): OH (3413.4), NH (3129), C=C-H (3015.3, 2795), C=O (1722.7, 1667) C=C (1590). ^{1}H NMR (300 MHz, DMSO-d6): δ/ppm 12.4 (a, 1H, OH), 10.52 (s, 1H, NH), 7.99 (s, 1H, H6), 7.31 (d, ^{2}J=1, 1H, H12), 7.28 (t, ^{3}J=3, 1H, H10), 6.94 (d, ^{2}J=2, 1H, H11), 6.92 (d, ^{2}J=1, 1H, H9). ^{13}C

NMR (75.4 MHz, DMSO-d6): δ/ppm 168.6 (C4), 168.0 (C2), 157.7 (C6), 132.7 (C11), 128.7 (C10), 127.4 (C12), 122.3 (C5), 120.3 (C9), 120.1 (C8), 116.5 (C7). MS= 221.01.

For the chemical synthesis of compound 81 (C#81), the reagents used were 1,3-thiazolidine-2,4-dione and 3-chloro-2-fluorobenzaldehyde. The reaction was carried out in a water solvent environment at 145° C for 7 h. The product obtained was a yellowish dust with an Rf of 0.66 (hexane-ethyl acetate, 6:4), a yield of 57.87%, and a melting point of 155 ± 2°C. It displays good solubility in ethyl acetate, methanol and dimethyl sulfoxide. The presence of the desired product was confirmed by IR, NMR and MS. IR (cm^{-1}): NH (3158.6), C=C-H (3031.2, 2755.2), C=O (1746.6, 1696.8), C=C-H (1608.6). ^{1}H NMR (300 MHz, DMSO-d6): δ/ppm 12.69 (a, 1H, NH), 7.68 (s, 1H, H6), 7.55 (td, ^{3}J (H-F)= 4, 1H, H10), 7.48 (m, ^{3}J (H-F)= 8, ^{5}J (H-F)= 4, 1H, H12), 7.39 (ddd, ^{4}J (H-F)= 8, 1H, H11). ^{13}C NMR (75.4 MHz, DMSO-d6): δ/ppm 167.6 (d, ^{5}J (C-F)= 4, C4), 166.9 (s, C2), 159.4 (d, ^{1}J (C-F)= 2, C8), 134.4 (d, ^{2}J (C-F)= 4, C7), 133.0 (d, ^{3}J (C-F)= 8, C10), 132.1 (s, C5), 126.5 (d, ^{3}J (C-F)= 2, C12), 123.7 (s, C11), 120.8 (d, ^{2}J (C-F)= 14, C9), 115.8 (d, ^{3}J (C-F)= 16, C6). MS= 257.96.

Acute Oral Toxicity Study

C#40 or (5Z)-5-(2-hydroxybenziliden)-1,3-thiazolidine-2,4-dione

The compound was administered at the doses of 175, 350, 700, 1400 and 2000 mg/kg by orogastric cannula. The vehicle was ethanol (10%) and isotonic saline solution (90%) in a final volume of 1 ml. For all doses, the animals exhibited normal behavior and no physical changes were observed. For the first dose (175 mg/kg), post-mortem analysis did not reveal any significant findings (Figure 3A). For the rest of the doses (≥350 mg/kg), fat deposits were found within the abdominal cavity (Figure 3B shows the 2000 mg/kg dose).

The results (Table 3) suggest that C#40 is adipogenic and capable of increasing body weight. By utilizing Reed Muench's formula, the LD50 for C#40 was estimated to be 77090.34 mg/kg.

Figure 3. Acute oral toxicity. Gross necropsy of a rat that received C#40 at: A) 175 mg/kg, and B) 2000 mg/kg.

Table 3. Trends in body weight and percentage of mortality for animals given C#40.

*****Mean, n=6

C#81 or (5Z)-5-(3-chloro-2-fluorobenziliden)-1,3-thiazolidine-2,4-dione

The compound was administered at doses of 175, 350, 700, 1400 and 2000 mg/kg by orogastric cannula, leading to distinct results according to the dose (Table 4). The vehicle was dimethyl sulfoxide (2%) and isotonic saline solution (98%) in a final volume of 1 ml. The animals given the 175 and 350 mg/kg doses exhibited normal behavior, with no physical changes detected. The post-mortem analysis did not reveal anything significant (Figure 4A). Three of the animals receiving 700 mg/kg (with the same vehicle used for the previous animals) presented normal behavior with no observable physical changes. The post-mortem analysis revealed nothing significant. The two remaining animals with the same dose displayed severe lethargy immediately after administration, with sedation beginning at 24 h and full recovery as of 48 h. Post-mortem analysis was carried out without significant findings. The 1400 mg/kg dose was applied to two animals by following the aforementioned procedure. The first animal with this dose had normal behavior and no physical changes. Nothing significant was found with the post-mortem analysis. The other

259 animal with the same dose manifested severe lethargy that began immediately after
260 administration and lasted approximately 5 h. Hypnosis was seen at 10 h post-
261 administration, and then a coma state set in at 12 h post-administration, showing cyanotic
262 inferior extremities. Post-mortem analysis demonstrated stomach fundus hardening, which
263 was due to the jamming of the compound in the lumen of the gastroesophageal sphincter,
264 thus impairing the normal respiration of the animal.
265 Finally, the two animals receiving 2000 mg/kg (using the same procedure) exhibited severe
266 lethargy immediately after administration, followed by hyperventilation, cyanosis, and
267 death within 5 h. Post-mortem analysis evidenced stomach fundus hardening, mainly due to
268 the jamming of the compound in the lumen of the gastroesophageal sphincter, leading to
269 impaired respiration (Figure 4B). Since these results were derived from a physical rather
270 than toxicological mechanism, only doses 175-1400 mg/kg were considered.
271
272 **Figure 4.** Acute oral toxicity**.** Gross necropsy of a rat administered C#81 at: A) 175 mg/kg
273 and B) 2000 mg/kg. The latter dose highlights the hardening of the stomach fundus.
274
275 **Table 4.** Trends in body weight and percentage of mortality for animals given C#81.
276 *Mean, n=2
277 **Mean, n=3
278
279 By using Reed Muench's formula, it was found that the estimated LD50 for C#81 is
280 1389.95 mg/kg. The results suggest that C#81 does not affect body weight.
281
282 **Discussion and conclusion**

Pioglitazone is the only PPARγ agonist commercially available worldwide. In a few countries, its sale has been restricted by the U.S. Food and Drug Administration (FDA) because of being related to several cases of urinary bladder cancer. The other TZDs, rosiglitazone and troglitazone, are no longer on the world market. Since rosiglitazone was associated with a significant increase in myocardial infarction and death from cardiovascular diseases, the European Medicines Agency withdrew approval for this medication in 2010, and the FDA restricted its prescription in the United States [55-60].

For the *in silico* studies, the proposed compounds were substituted with electron-withdrawing or electron-donating heteroatoms according to previous findings by Avupati, *et al.* [20], who showed that an *ortho*, *meta*, and *para* substitution on the phenyl ring with a hydroxyl group may enhance hypoglycemic activity. This was also found for a *para* substitution with halogens such as chlorine [20]. Accordingly, the proposed compounds C#40 and C#81 proved to be very good candidates.

The present results indicate that when the aromatic body is substituted with electron-withdrawing heteroatoms, the compound attains a better interaction through hydrogen bonding between the pharmacophore (TZD head) and the LBD of PPARγ. Approximately 2.3 Å in length, these hydrogen bonds are with the main residues Tyr473, Ser289, His323 and His449, notably changing the position of the H12 helix. This crucial helical component of the receptor LBD provides a suitable surface for co-activator interaction and thereby generates the transcriptional activity of the AF-2 domain [61,62]. Hence, the proposed compounds interact in a way similar to the ones that served as patterns (rosiglitazone, pioglitazone and troglitazone, as previously reported by several authors) [6,15,17,34,38,40], meaning that they may also act in a comparable manner biologically.

306 Since there are no heteroatoms susceptible to forming hydrogen bonding between the tail of
307 the compound and the LBD, the head of the compound (TZD) was directed toward the
308 main residues of this domain. Consequently, the aromatic tail assumed an equilibrated
309 position in relation to the hydrophobic residues in Arm I of the LBD, such as Leu, Ile, Ala
310 and Met, through Van der Waals forces [63].
311 Based on the current general synthesis methodology, the reaction was favored when the
312 benzaldehyde was substituted with electron-donating heteroatoms, and delayed in the cases
313 that the substituents were electron-withdrawing heteroatoms. This is mainly a consequence
314 of the two-step Knoevenagel condensation, in which a nucleophilic attack is followed by
315 dehydration. The nucleophilic attack is facilitated by the electron donors, and dehydration
316 by electron withdrawal [64-66]. It has been previously demonstrated that water, in the
317 presence of halogens, can facilitate the formation of nucleophilic species derived from the
318 acid head. For this reason, water was herein used as a solvent for the reaction of C#81, the
319 acid head in this case being TZD. The nucleophilic species could then attack the carbon of
320 the aldehyde [66].
321 According to the acute toxicity study, C#40 has adipogenic activity [7-9,15,19] at doses
322 over 350 mg/kg. This may result from the effect of PPARγ agonists on brown fat
323 differentiation, which was previously found with pioglitazone and other TZD-type drugs
324 [30,55]. However, there were no evident toxic effects in any animal except one that was
325 given 2000 mg/kg. Thus, the compound was classified as non-toxic and harmless at doses
326 under 2000 mg/kg, according to the Globally Harmonized System of Classification and
327 Labelling of Chemicals (GHS).
328 On the other hand, C#81 exhibited sedative effects at doses over 700 mg/kg, which could
329 be due to several factors. First, this compound is structurally similar to lamotrigine,

bromazepam and clonidine, which are central nervous system (CNS) depressors with partial sedative effects. Since doses over 700 mg/kg led to higher mortality of the animals, the compound was classified as harmful in case of intake according to the GHS.

In conclusion, the two TZD derivatives, C#40 and C#81, were successfully designed, synthesized and tested for safe usage in healthy animals. They acted as PPARγ agonists and therefore may be beneficial for treating DM2. In a future study, these compounds will be evaluated in a DM2 animal model.

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Conflict of interest

The authors have no conflict of interests concerning the use of any of the materials or techniques mentioned herein. The authors alone are responsible for the content and writing of the article.

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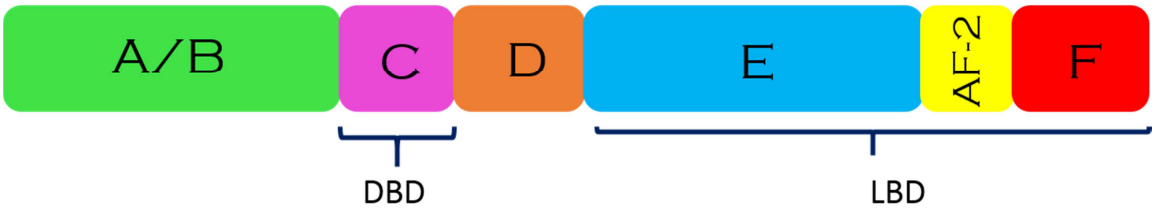
553

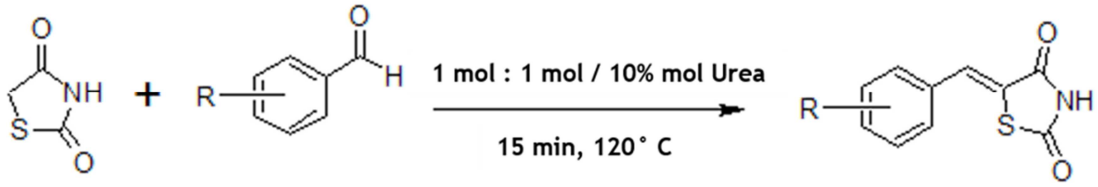
Compound	Molecular formula	Docking (kcal/mol)	No. of H bonds, residues and distances
Rosiglitazone	$C_{18}H_{19}N_3O_3S$	-10.68	5 (His323/1.99 Å, His449/2.09 Å, Tyr473/3.01 Å, Ser289/1.72 Å, Gln286/1.86 Å)
Pioglitazone	$C_{19}H_{20}N_2O_3S$	-11.03	5 (His323/1.92 Å, His449/2.00 Å, Tyr473/3.07 Å, Ser289/1.70 Å, Gln286/1.88 Å)
Troglitazone	$C_{24}H_{27}NO_5S$	-11.67	5 (His323/1.80 Å, His449/1.83 Å, Tyr473/3.35 Å, Ser289/1.88 Å, Gln286/2.24 Å)
40	$C_{10}H_7NO_3S$	-7.26	5 (His323/1.91 Å, His449/2.06 Å, Tyr473/3.01 Å, Ser289/2.07 Å, Gln286/1.83 Å)
81	$C_{10}H_5ClFNO_2S$	-7.51	5 (His323/1.85 Å, His449/1.85 Å, Tyr473/2.89 Å, Ser289/1.72 Å, Gln286/2.01 Å)

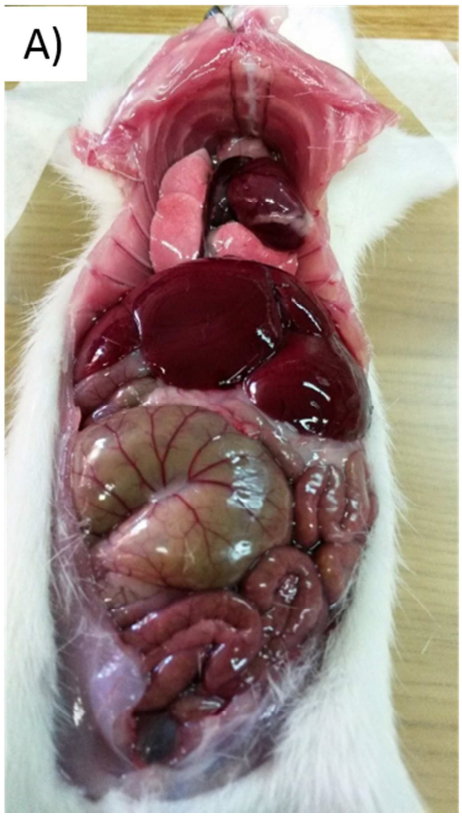
Compound	Molecular formula	Molecular weight	Polar surface (Å)	H donors	H acceptors	log P
Rosiglitazone	$C_{18}H_{19}N_3O_3S$	357.435	71.533	1	6	2.346
Pioglitazone	$C_{19}H_{20}N_2O_3S$	356.447	68.295	1	5	3.071
Troglitazone	$C_{24}H_{27}NO_5S$	441.546	84.865	2	6	5.031
40	$C_{10}H_7NO_3S$	221.237	70.161	2	4	1.423
81	$C_{10}H_5ClFNO_2S$	257.673	49.933	1	3	2.228

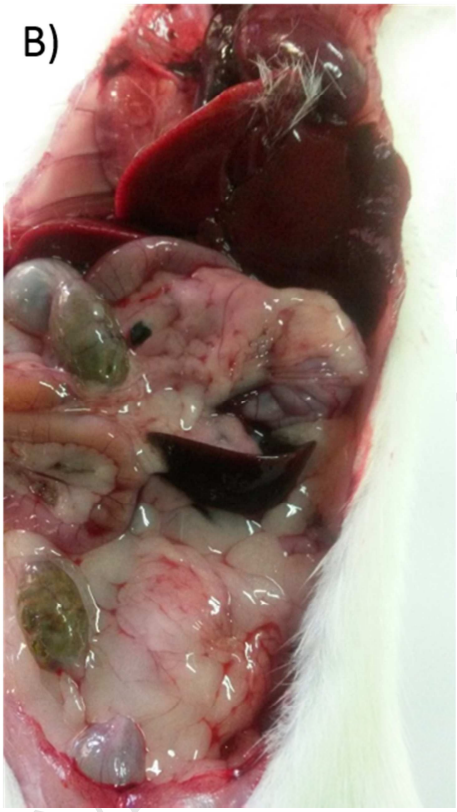
Dose (mg/kg)	Initial weight (g)	Final weight (g)	Weight increase (g)	Dead	Alive	Mortality %
175	183.6	204.3	20.7	0	1	0
350	195.3	218.7	23.4	0	1	0
700	216.2	263.3	47.1	0	1	0
1400	222.0	274.4	52.4	0	1	0
2000	234.7*	286.1*	51.4*	1	5	20

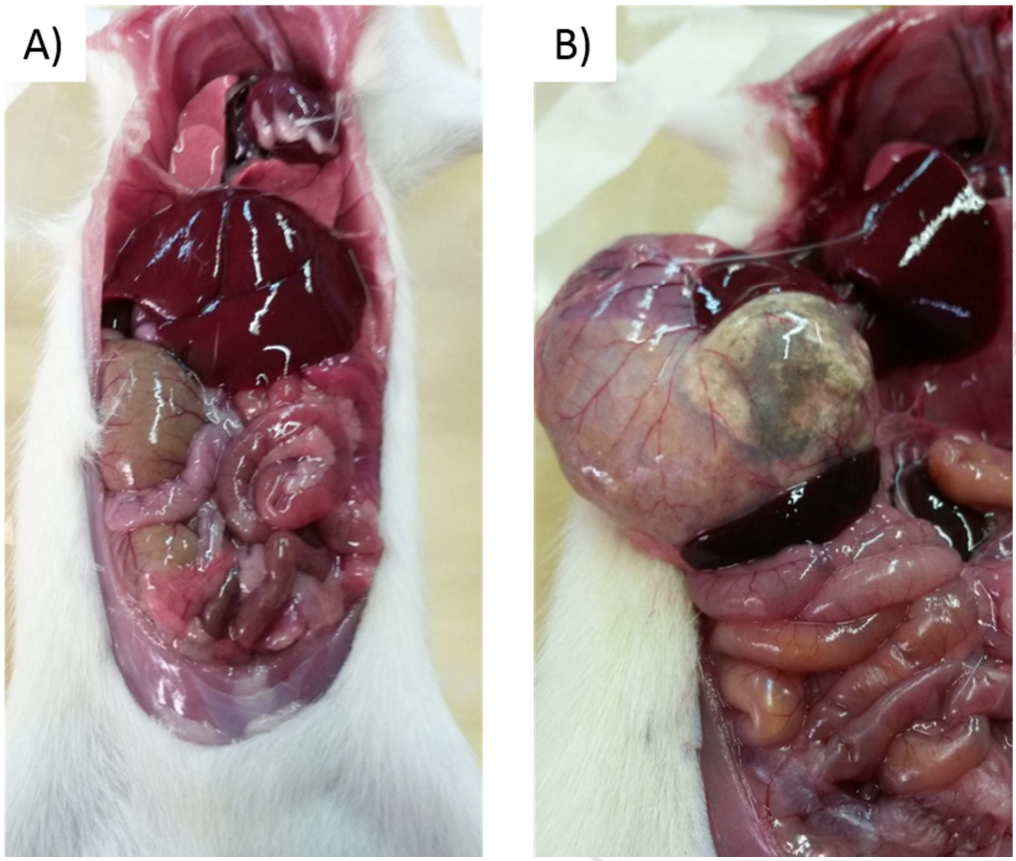
Dose (mg/kg)	Initial weight (g)	Final weight (g)	Weight increase (g)	Dead	Alive	Mortality %
175	186.1	204.3	18.2	0	1	0
350	189.5	211.9	22.4	0	1	0
700	204.6**	231.7**	27.1**	0	3	0
1400	212.2*	232.6*	20.4*	1	1	50











Highlights

1. Thiazolidinediones have been shown to produce severe adverse effects.
2. Derivatives were designed with the polar head of TZD and an aromatic body.
3. Two ligands were selected *in silico* to be synthesized in a solvent-free reaction.
4. Acute oral toxicity was determined by using healthy Wistar rats.
5. The compounds may elicit biological responses similar to other thiazolidinediones.