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Thiazolidine-2,4-diones derivatives as PPAR-γ agonists: Synthesis, molecular docking, in vitro and in vivo antidiabetic activity with hepatotoxicity risk evaluation and effect on PPAR-γ gene expression

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ABSTRACT

A library of conjugates of chromones and 2,4-thiazolidinedione has been synthesized by Knoevenagel condensation followed by reduction using hydrogen gas and Pd/C as a catalyst. Compounds **5c** and **5e** were most effective in lowering the blood glucose level comparable to standard drug pioglitazone. Compound **5e** exhibited potent PPAR-γ transactivation of 48.72% in comparison to pioglitazone (62.48%). All the molecules showed good glide score against the PPAR-γ target in molecular docking study. PPAR-γ gene expression was significantly increased by compound **5e** (2.56-fold) in comparison to standard drug pioglitazone. Compounds **5e** and **5c** did not cause any damage to the liver and may be considered as promising candidates for the development of new antidiabetic agents.

Type 2 diabetes is a complex metabolic syndrome resulting in high blood glucose due to impaired insulin action, which in turn stimulates glucose uptake in peripheral tissues such as muscle and fat. In normal humans, up to 80% of insulin-stimulated glucose disposal occurs in skeletal muscle, a major site of insulin resistance in type 2 diabetes.[1,2]

Recently, chemistry of 2,4-thiazolidinediones (TZDs) has attracted attention as they have been found to exhibit several biological activities,[3] such as antihyperglycemic,[4] anti-inflammatory,[5] antimalarial,[6] antioxidant,[7] antitumor,[8] cytotoxic,[9] antimicrobial,[10] and antiproliferative.[11] Thiazolidinediones are high-affinity ligands of peroxisome proliferator activated receptor-γ.[12] PPAR-γ, a member of a large family of ligand-activated nuclear hormone receptors is an important drug target for regulating glucose metabolism. PPAR-γ increases insulin sensitivity at adipose, muscle and hepatic tissues[13,14] thereby improving plasma glucose levels effectively.[15–17] PPAR-γ exists in two forms mainly PPAR-γ1, found in all the tissues except muscles and PPAR-γ2, found in adipose tissues and intestine. These are encoded by PPAR-γ gene in humans. Although TZDs are strong and specific activators of PPAR-γ capable of ameliorating diabetes mellitus by improving insulin resistance without inducing hypoglycaemia,[18] they are associated with side effects viz. weight gain, hepatotoxicity and fluid retention.[19]

Chromones are a group of naturally occurring compounds found in fruits and vegetables.[20,21] They are safe and are associated with low mammalian toxicity, making them excellent chemopreventive agents.[22] They are reported to exert an antihyperglycemic effect by promoting peripheral utilization of glucose or enhancing insulin sensitivity in diabetic animals.[23] Considering the biological importance of thiazolidinediones and chromones as antidiabetic agents, we have conjugated these two important ligands under one construct through a methylene linkage. We herein report the synthesis of thiazolidinedione and chromone based conjugates and their molecular docking studies and evaluation of their in vivo antidiabetic activity with hepatotoxicity risk evaluation, in vitro PPAR-γ activity and also the effect on the PPAR-γ gene expression.

Villsmeyer Hack reaction of substituted *o*-hydroxy acetophenones (**1a–k**) in presence of DMF and $POCl_3$ yielded 3-formyl

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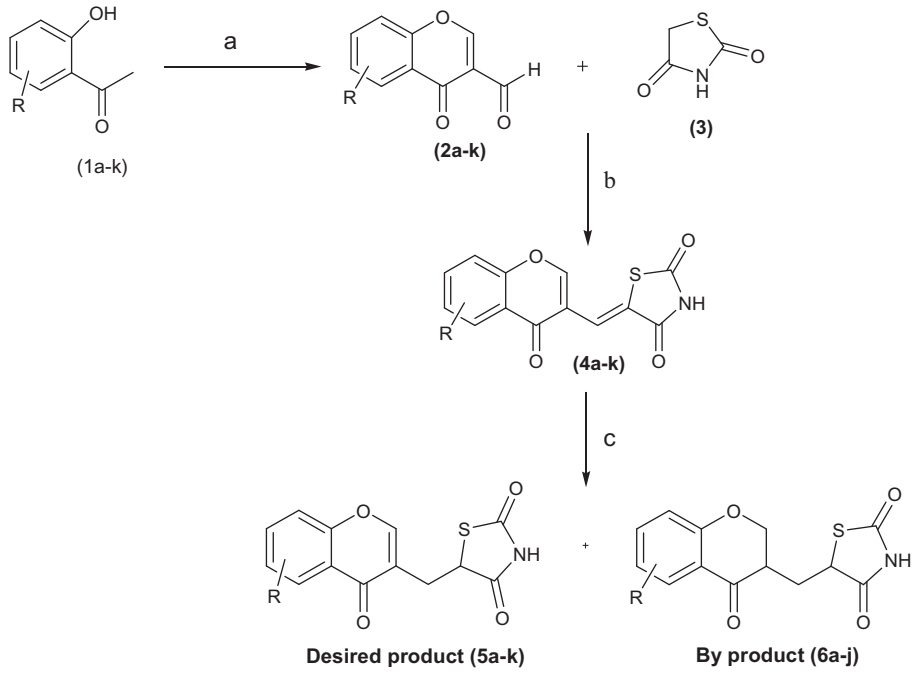

Scheme 1. Reagents and conditions:(a) DMF, $POCl_3$, 0-(−5)°C;(b) sodium acetate, acetic acid, 120–140 °C; (c) Pd/C, H_2 gas, 30 psi, rt, 10–12 h.

Table 1
Physical data of the synthesized compounds

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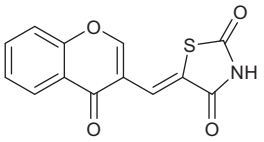
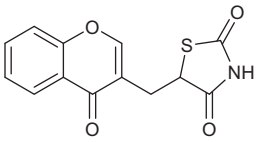
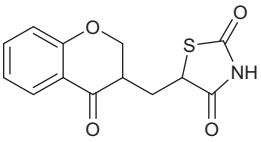
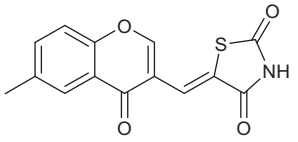
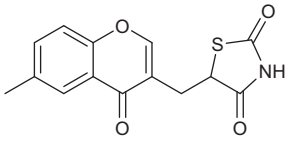
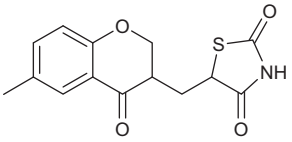
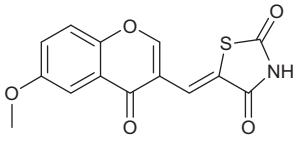
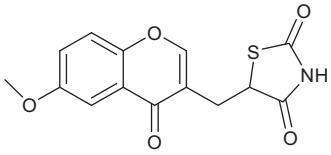
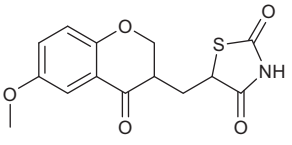
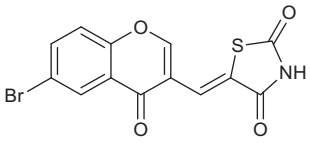
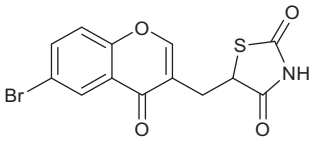
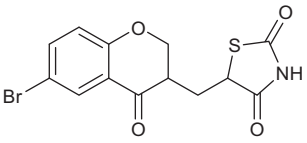
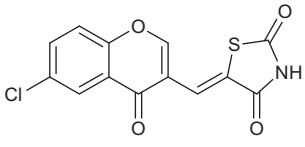
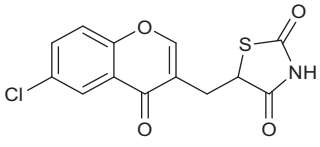
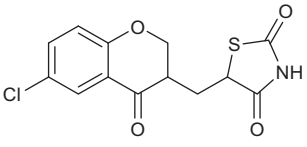
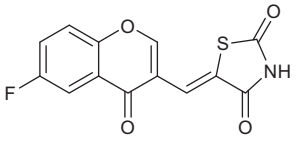
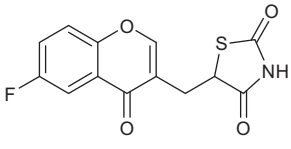
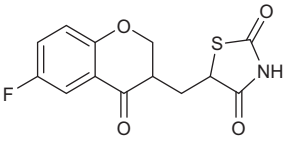
a			50		30
b			65		20
c			70		20
d			65		25
e			60		20
f			65		21

(*continued on next page*)

Table 1 (*continued*)

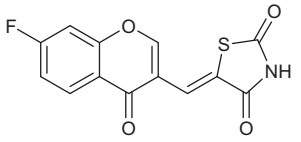
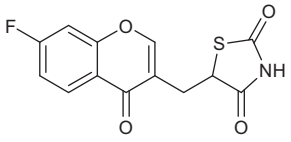
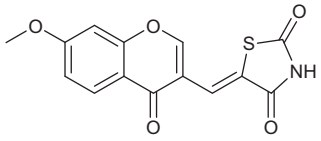
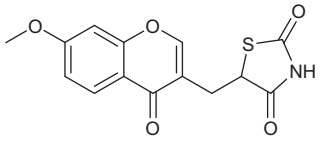
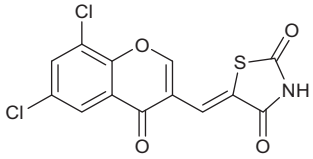
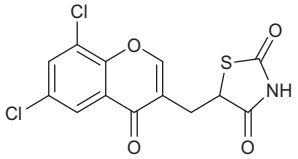
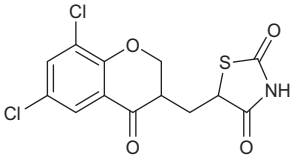
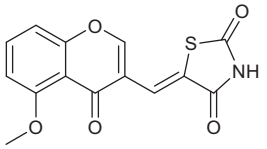
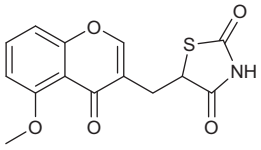
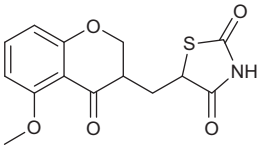
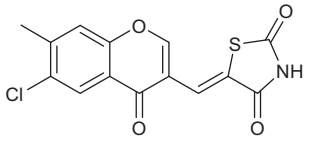
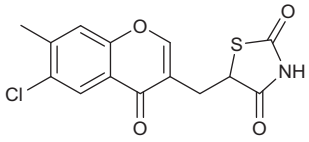
S.No.	Reactant (**4**)	Desired product (**5**)	yield (%)	By product (**6**)	Yield (%)
g			70	–	
h			75	–	
i			64		21
j			55		25
k			75	–	

Table 2
Docking score and ADME prediction of the compounds (**5a**–**k**) and (**6a**–**j**)

S.No.	Compd	G-Score	G-energy	Log*Po*/w	PSA	Log*S*
1	**5a**	**−7.33**	−40.52	0.929	108.199	−2.40
2	**5b**	**−7.29**	−40.47	1.382	107.495	−2.99
3	**5c**	**−7.57**	−58.16	1.274	116.677	−2.58
4	**5d**	**−7.41**	−52.80	1.669	106.747	−3.29
5	**5e**	**−7.76**	−50.96	1.684	106.759	−3.37
6	**5f**	**−7.42**	−51.44	1.405	107.749	−3.01
7	**5g**	**−6.91**	−37.80	1.395	107.691	−2.98
8	**5h**	**−6.69**	−42.66	1.402	117.276	−2.81
9	**5i**	**−7.69**	−40.13	2.218	106.201	−4.17
10	**5j**	**−7.18**	−43.18	1.472	113.399	−2.91
11	**5k**	**−6.64**	−36.21	1.967	108.344	−3.58
12	**6a**	−5.20	−38.83	0.944	105.035	−2.59
13	**6b**	**−7.20**	−41.01	1.321	107.229	−2.88
14	**6c**	**−7.11**	−41.06	1.2	115.614	−2.53
15	**6d**	**−7.04**	−41.39	1.57	105.684	−2.68
16	**6e**	**−7.34**	−40.80	1.513	107.042	−3.05
17.	**6f**	**−7.21**	−39.54	1.285	107.563	−3.35
18	**6i**	**−7.18**	−34.94	2.001	105.389	−3.91
19	**6j**	**−7.03**	−39.62	1.181	112.844	−2.38
Std.	Rosi	−5.77	−71.55	3.475	94.375	−4.49

The bold values signify the glide score of those compounds are higher than that of the standard drug Rosiglitazone.

chromones (**2a**–**k**) which upon Knoevenagel condensation with 2,4-thiazolidinedione (**3**) yielded chromonyl-2,4 thiazolidinediones (**4a**–**k**). The catalytic hydrogenation of chromonyl-2,4-thiazolidinediones (**4a**–**k**) using Pd/C in DMF at 30 psi (H_2 gas) for 10–12 h at ambient temperature afforded the desired products (**5a**–**k**) together with compounds (**6a**–**j**) as the by-products as shown in Scheme 1. A library of nineteen chromone and 2,4-thiazolidinedione conjugates (**5a**–**k**) and (**6a**–**j**) have been synthesized in good yields (Supplementary data).

^{1}H NMR, ^{13}C NMR and mass spectral data were found to be in agreement with the proposed structures of all the newly synthesized compounds (Supplementary data). Formation of chromonyl-2,4-thiazolidinediones (**4a**–**k**) by the Knoevenagel condensation was confirmed by the appearance of exocyclic olefinic proton as a singlet in the range of δ 7.57–7.79 in the ^{1}H NMR spectra of these compounds. Reduction of compounds (**4a**–**k**) with Pd/C resulted in the hydrogenation of the double bond between TZD and chromone ring leading to the formation of compounds (**5a**–**k**) as well as hydrogenation of both the double bonds, that is double bond between TZD and chromone ring and olefinic bond of chromone ring gave compounds (**6a**–**j**). Formation of compounds (**5a**–**k**) was confirmed by the disappearance of the singlet of exocyclic olefinic proton as seen in the ^{1}H NMR spectra of (**4a**–**k**) and the appearance of a characteristic pattern of three double doublets at δ 4.81–4.86, 3.28–3.32 and 2.70–2.85 in the ^{1}H NMR spectra of (**5a**–**k**) due to the newly generated methine and methylene protons, respectively. The formation of compounds (**6a**–**j**) was confirmed by the absence of singlet of the olefinic proton of chromone ring at δ 8.31–8.48 and appearance of double doublet of methylene protons of chromone ring at δ 4.30–4.66, double doublet of methine protons of TZD ring at δ 4.16–4.37 and a multiplet in the region δ 2.50–2.62 in the ^{1}H NMR spectra. The double doublets of methylene protons that appeared in the ^{1}H NMR spectra of compounds (**5a**–**k**) were not seen in the ^{1}H NMR spectra of (**6a**–**j**). Instead, a multiplet in the region δ 1.34–2.52 was observed for these protons confirming reduction of both the double bonds in these compounds (Table 1).

The synthesized compounds (**5a**–**k**) and (**6a**–**j**) were docked for in silico studies against PPAR-γ target (Supplementary data). Molecular docking studies were done to gain insights of molecular binding modes of the ligands with the large pocket of PPAR-γ receptors. The compounds were docked against grid generated by

Schrodinger glide software. In order to analyze the binding pattern and energies of new molecules & reference ligand (Rosiglitazone), they were docked individually against the generated grid. Initial docking of reference ligand (Rosiglitazone) against generated grid helped in validating the grid generated by software. Rosiglitazone is reported to have H-bonding with TYR 473, HIS 449 & CYS 285. Docking of Rosiglitazone against generated grid showed similar docking mode and H-bonds with RMSD value of 2.8 and hence validated the generated grid. The synthesized molecules docked against the grid showed good binding energies ranging from −58.16 to −34.9 kcal/mol. All the molecules showed good glide score but the most promising molecules were **5c**, **5d**, **5e**, **5f**, **5i**, **5j** and **6e** with best Glide score of −7.57, −7.41, −7.76, −7.42, −7.69, −7.18 and −7.34, respectively whereas glide score of Rosiglitazone was −5.77 kcal/mol with respect to same grid. All the molecules were predicted to bind with large binding site of PPAR-γ receptor with good binding scores with respect to Rosiglitazone. Compounds **5e**, **5f** and **5i** were found to form hydrogen bonding with SER 289 residue of the target protein whereas compounds **5c** and **5d** were found to be aligned perfectly with the hydrophobic pocket of the protein. The in silico ADME (Absorption, Distribution, Metabolism and Excretion) prediction of the synthesized library were found to be within the acceptable range (Table 2 and Fig. 1).

In order to validate the molecular docking results, all the synthesized compounds were screened for the in vivo antidiabetic activity in STZ induced diabetic rat model. The protocol for the in vitro and in vivo antidiabetic activity has been provided in the Supplementary data. As observed from the data of Figure 2 among the synthesized library, five compounds **5c**, **5d**, **5e**, **5f** and **5i** showed significant blood glucose lowering effect after 15 days of study. Compounds **5c** and **5e** were found to be more potent than standard drug Rosiglitazone but comparable to another standard drug Pioglitazone in lowering blood glucose level. Compounds **5d**, **5f** and **5i** also showed significant activity comparable to both the standards. Compounds **5c**, **5d**, **5e**, **5f**, **5i**, **5j** and **6e** with best

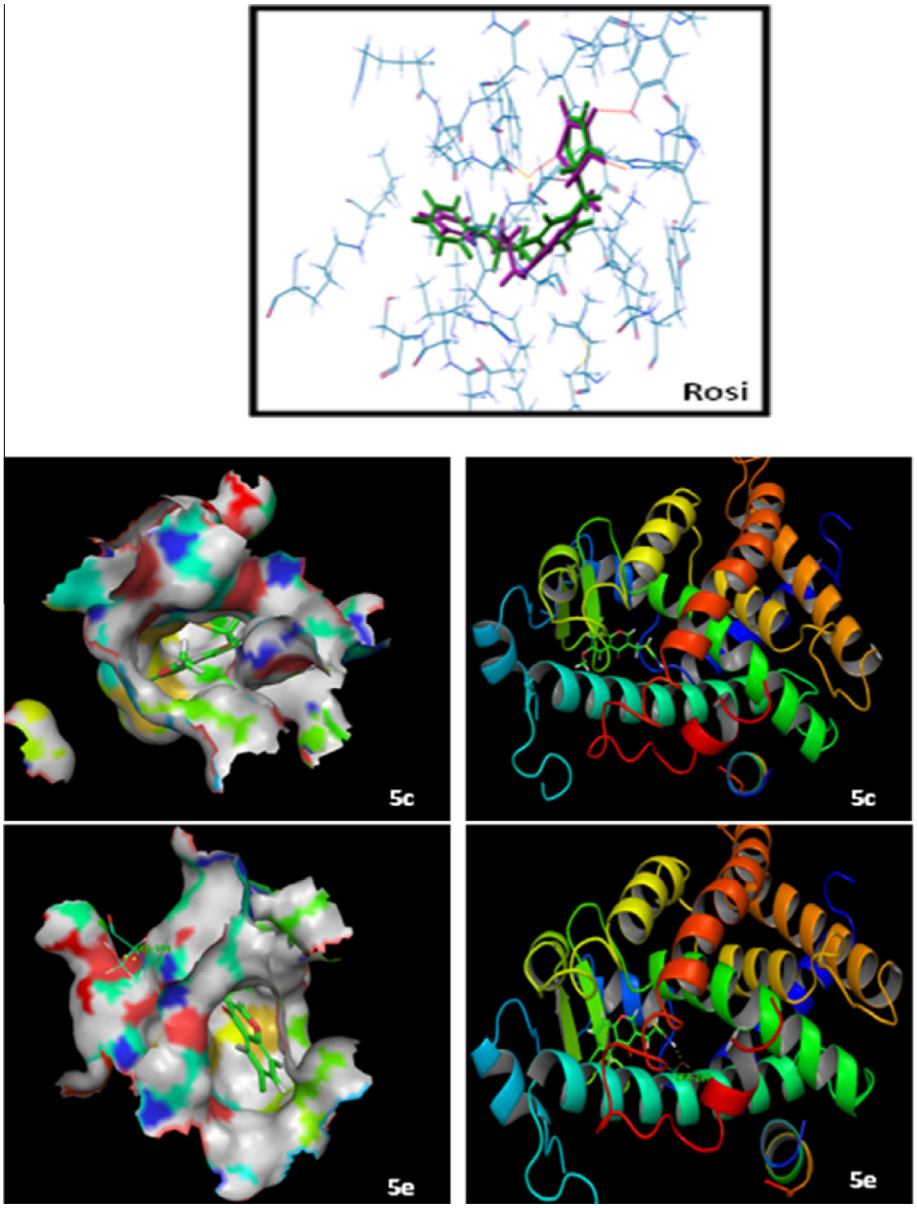


Figure 1. Molecular docking of the active compounds showing interactions with the hydrophobic pocket of the protein. Comparative binding orientation of crystallographic (green) & docked (purple) structure of Rosiglitazone as docked by Schrodinger software. Hydrogen bonding with Tyr473, His449 & Cys285 is highlighted in red colour. Compounds **5e**, **5i** and **5f** showing hydrogen bonding with SER 289 (yellow dotted line). Compounds **5c** and **5d** deeply buried into hydrophobic pocket of PPAR-γ.

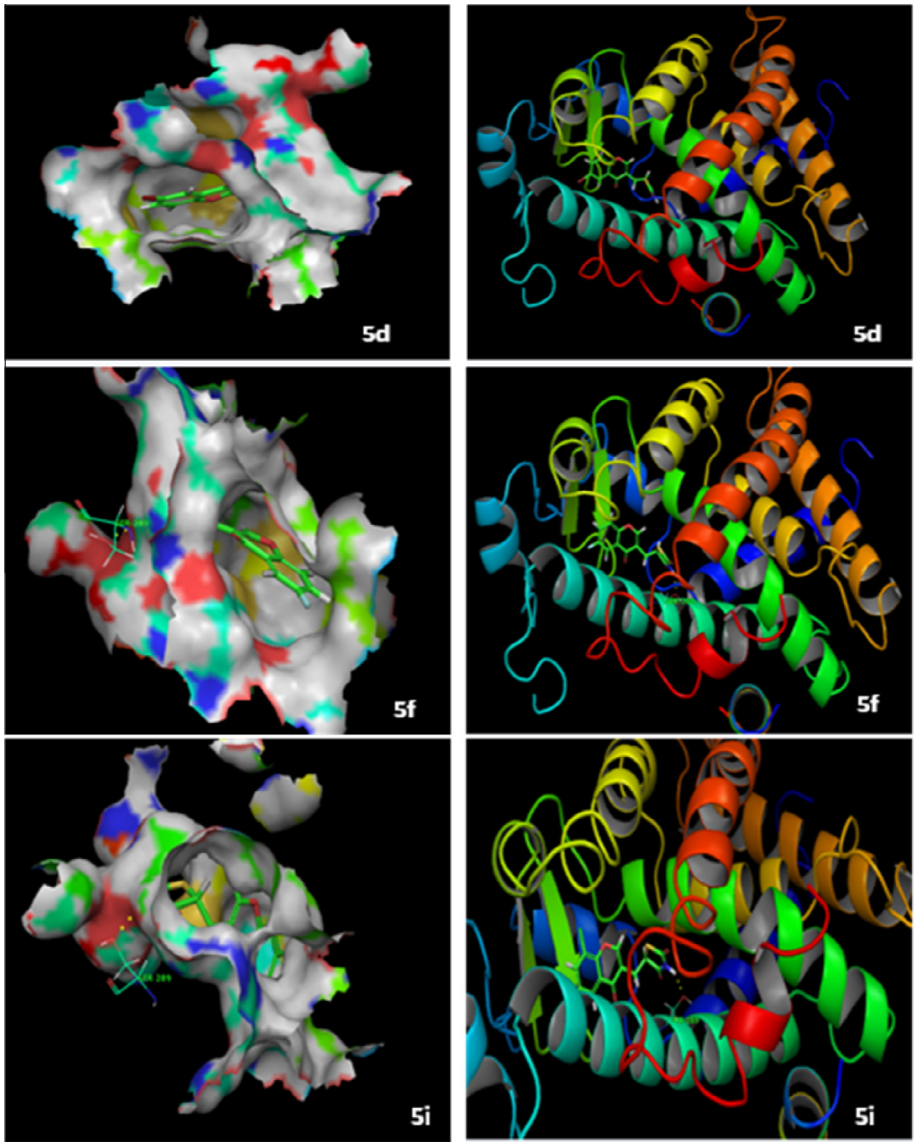


Fig. 1 (*continued*)

Glide scores showed significant blood glucose lowering activity. Compounds **5a**, **5b**, **6b**, **6c**, **6d**, **6f**, **6i** and **6j** although showing glide score more than the standard rosiglitazone showed moderate in vivo activity. Further from oral glucose tolerance test (Fig. 3), the administration of compound **5e** causes significant decrease in the blood glucose levels of diabetic rats at 120 min when compared to diabetic control rats indicating that glucose tolerance was improved by administration of compound **5e**. Insulin tolerance test (Fig. 3) showed that the blood glucose levels of **5e** treated diabetic rats were significantly lowered after 90 min of insulin administration as compared to diabetic rats indicating insulin resistance was improved by compound **5e**. These results suggest that the antihyperglycemic activity of **5e** may result from enhanced insulin and glucose resistance. As the PPAR-γ agonists are associated with body weight gain, **5e** was also tested for body weight gain study. Compound **5e** treated normal rats did not show any significant change in body weight as compared to normal control rats. However, oral administration of **5e** to diabetic rats for 15 days caused a significant improvement in body weight of diabetic rats (Fig. 4).

TZDs are reported to cause hepatotoxicity which is the major drawback encountered with this class of drug. The synthesized compounds have therefore been assayed for AST, ALT and ALP levels and hepatotoxicity. It has been reported that the levels of these enzymes are significantly increased in STZ rats indicating the toxic effect of STZ on liver.[24] The elevation of these enzymes might be due to increased protein catabolism followed by gluconeogenesis as ALT and AST are directly involved in the amino acid conversion to ketoacids. It was observed that the levels of serum AST, ALT and ALP significantly increased in STZ treated rats were significantly decreased to near normal level after treatment with the active compounds **5c**, **5d**, **5e**, **5f** and **5i** as shown in Figure 5. Compounds **5c**, **5d**, **5e**, and **5f** were found to be more potent in lowering the AST, ALT and ALP levels than the standard Pioglitazone whereas compound **5i** was equally potent to Pioglitazone thereby these compounds have protective effect on liver. Histopathological study of the liver of the treated animals also showed that two compounds **5e** and **5c** did not cause any damage to the liver. Compound **5d** and **5f** caused mild damage to the liver that is they caused mild dilation in sinusoidal space and compound **5i** having disubstituted halogen and standard drug Pioglitazone caused significant damage to the liver (Fig. 6). TZDs are associated with cardiovascular risks and are the leading cause for the withdrawal

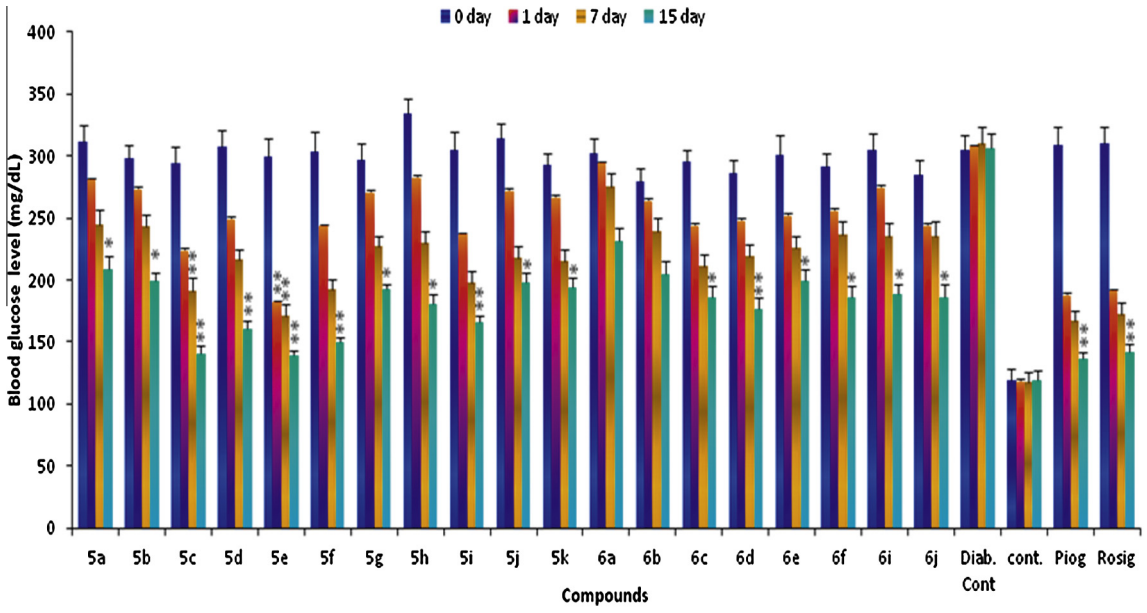


Figure 2. Antidiabetic activity of the synthesized compounds (**5a–k**) and (**6a–j**) in STZ induced diabetic rats. Data is analyzed by one way ANOVA followed by Dunnett's '*t*' test and expressed as mean ± SEM from five observations; **indicates p <0.01 & *indicates p <0.05 versus diabetic control.

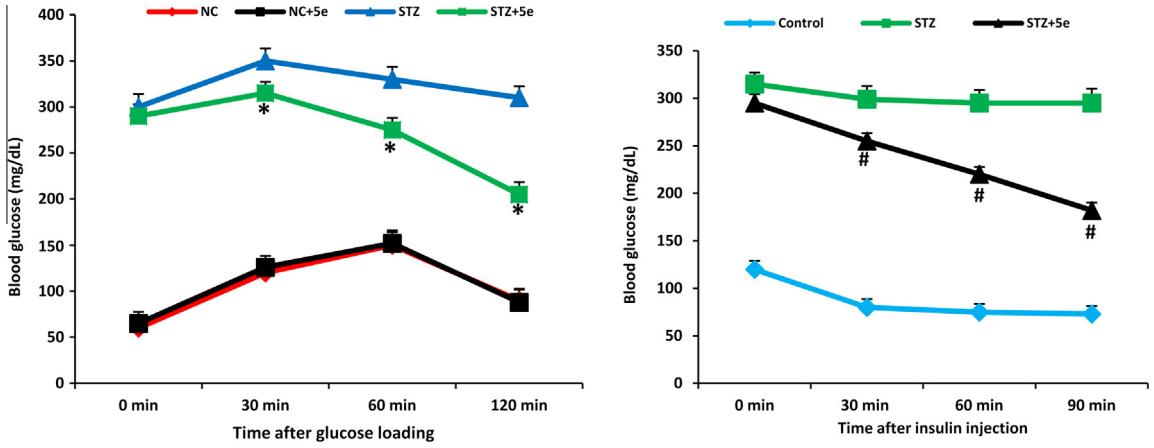


Figure 3. Effect of compound **5e** on Oral Glucose Tolerance test and Insulin Tolerance test. Data is analyzed by one way ANOVA followed by Dunnett's '*t*' test and expressed as mean ± SEM from five observations; *indicates p <0.001 versus diabetic control. #indicates p <0.05 versus diabetic control. NC: Normal control; NC + 5e: normal control + 5e; STZ: diabetic control; STZ + 5e: 5e treated diabetic rats.

of these drugs from the market. We therefore tested compound **5e** for hERG inhibition. It has been reported that compounds with an IC_{50} >10 μM do not inhibit hERG significantly and hence have no cardiotoxicity. Since compound **5e** was found to have an IC_{50} of 135 μM, indicating that compound **5e** would not be associated with cardiotoxicity.

In order to confirm the mode of action of the active compounds, the active compounds were tested for in vitro PPAR-γ transactivation study. It was observed from the Figure 7 that these compounds were found to be PPAR-γ active. Compound **5e** was most potent among the synthesized compounds followed by **5c** and **5d**. From these results, it was clear that the compounds may have exerted the blood glucose lowering effect by activating PPAR-γ receptors. The synthesized compounds **5c–5f** and **5i** exerted similar or lower blood glucose levels than Pioglitazone and Rosiglitazone but lower PPAR-γ transactivation activity than Pioglitazone and Rosiglitazone. The absence of linear correlation between in vivo pharmacological profile in albino rats and in vitro PPARγ transactivation assays may be attributed to several reasons. For example, the test compounds **5c–5f** and **5i** are administered orally and therefore absorption, metabolism, excretion, etc. of the test compounds might have contributed in exerting the significant lowering in blood glucose level (Reddy et al. 1999).[25] Also, compounds **5c–5f** and **5i** might be exhibiting their antihyperglycemic activity through other mechanisms, in addition to binding to PPAR-γ. Similar kind of results have been reported by other groups working with TZDs,[25] which showed superior euglycemic and hypolipidemic profiles in *db*/*db* mice but not significant in vitro PPAR-γ transactivation activity than the standard drug troglitazone.

From the biological data, the structure activity relationship (SAR) can be drawn as follows. Compounds (**6a–j**) having reduced olefinic bond of chromone ring did not show promising blood glucose lowering effect as compared to compounds (**5a–k**) wherein the olefinic bonds remained intact in the chromone ring. Therefore, olefinic bond of the chromone ring is necessary for the blood glucose lowering effect. The activity is also dependent on the nature and position of the substituents on chromone ring as well. Halo

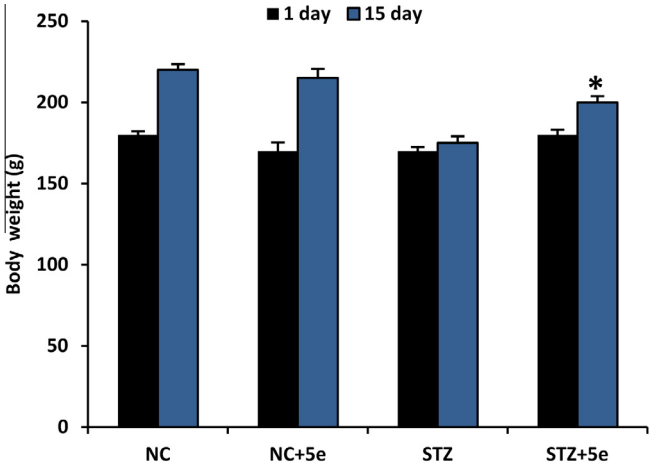


Figure 4. Effect of compound **5e** on body weight in albino wistar rats. Data is analyzed by one way ANOVA followed by Dunnett's '*t*' test and expressed as mean ± SEM from five observations; *indicates p <0.01 versus diabetic control. NC: Normal control; NC + 5e: normal control + 5e; STZ: diabetic control; STZ + 5e: 5e treated diabetic rats.

substituted compounds exhibited potent activity whereas methoxy substitution on aromatic ring exhibited good activity. Among the halogens, the activity was observed in the following order-Cl > Br > F. Substitution at position 6 of the chromone ring was more favourable for the activity. Methoxy and halogen substitution at position 6 exhibited significant blood glucose lowering and PPAR-γ activity than substitution at position 5 and 7. While 6,8-dichloro substituted compound **5i** shows good blood glucose lowering effect and PPAR-γ activity but caused significant hepatotoxicity. This may be due to the steric hindrance on the aromatic ring by the two halogens.

Since compound **5e** was found to be most PPAR-γ active, it was further subjected to PPAR-γ gene expression study. The PPAR-γ gene expression study was done to know the impact of compound **5e** on PPAR-γ gene. The protocol for the gene expression study has been provided in the Supplementary data. It was observed that the PPAR-γ expression was significantly increased in presence of compound **5e** (2.56-fold) in comparison to standard drug Pioglitazone (Fig. 8). The increase in PPAR-γ expression supports the results of in vitro PPAR-γ transactivation study. It is thus clear that the in vitro PPAR-γ transactivation and in vivo blood glucose lowering activity of compound may be due to increase in the PPAR-γ gene expression. It has reported that TZDs improve insulin action by effects on gene transcription in the fat cell that lead to diminished plasma levels of free fatty acids (FFAs) and an increase in the level of adiponectin, an adipokine that activates AMPK.[26–28] The increase in gene expression by compound **5e** might be due to the activation of AMPK. The overexpression of PPAR-γ in mature 3T3-L1 adipocytes increases the amount of the mRNA for the ubiquitous GLUT1, whose expression is reported to be downregulated during adipocyte differentiation.[29] The reduction of insulin-stimulated glucose transport in 3T3-L1 adipocytes overexpressing PPAR-γ may be due to the reduced expression of IR, IRS1, IRS2, and GLUT4. Thus, compound **5e** increase the gene expression by maintaining insulin sensitivity in mature 3T3-L1 adipocytes by regulating the expression of genes that encode components of the insulin signaling pathway as well as by increasing the expression levels of GLUT1 and GLUT4 in these cells.

In summary, a library of nineteen compounds have been synthesized out of which two compounds 5[(6-methoxy-4-oxo-4*H*-chromen-3yl) methyl] thia zolidine-2,4-dione (**5c**) and 5[(6-chloro-4-oxo-4*H*-chromen-3yl) methyl]thiazolidine-2,4-dione (**5e**) exhibited significant in vivo blood glucose lowering effect as well as in vitro PPAR-γ transactivation which is comparable with the standard drug Pioglitazone and Rosiglitazone. Compounds **5c**

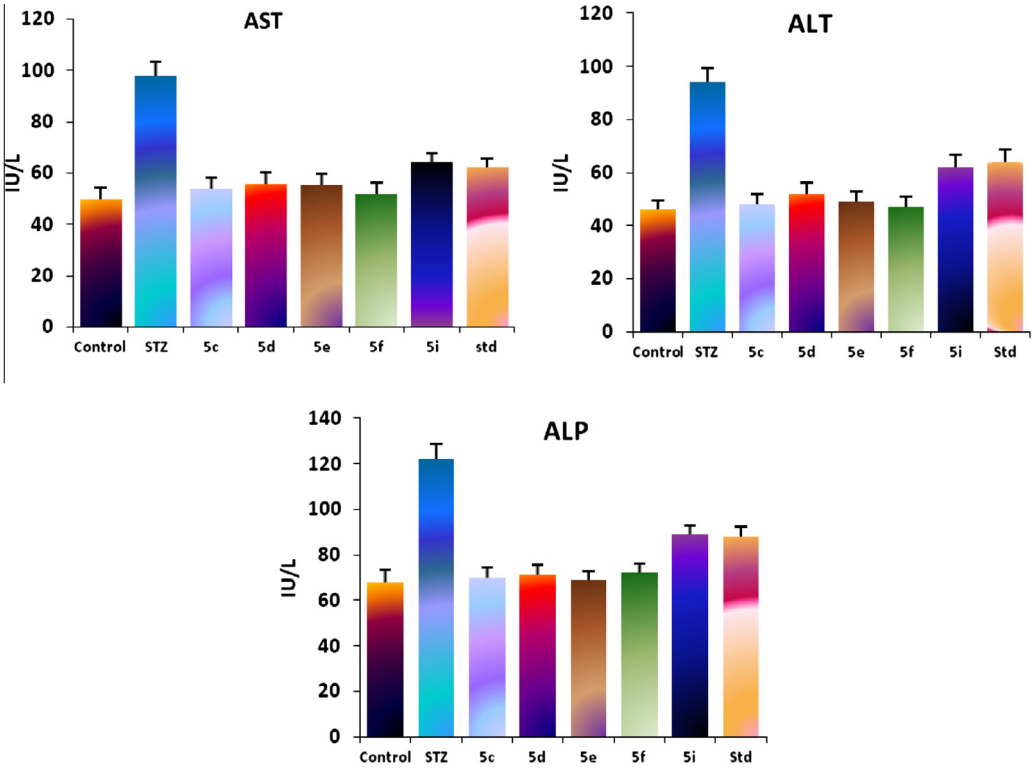


Figure 5. Effect of compounds on serum AST, ALT and ALP activities. Values are given as mean ± SD.

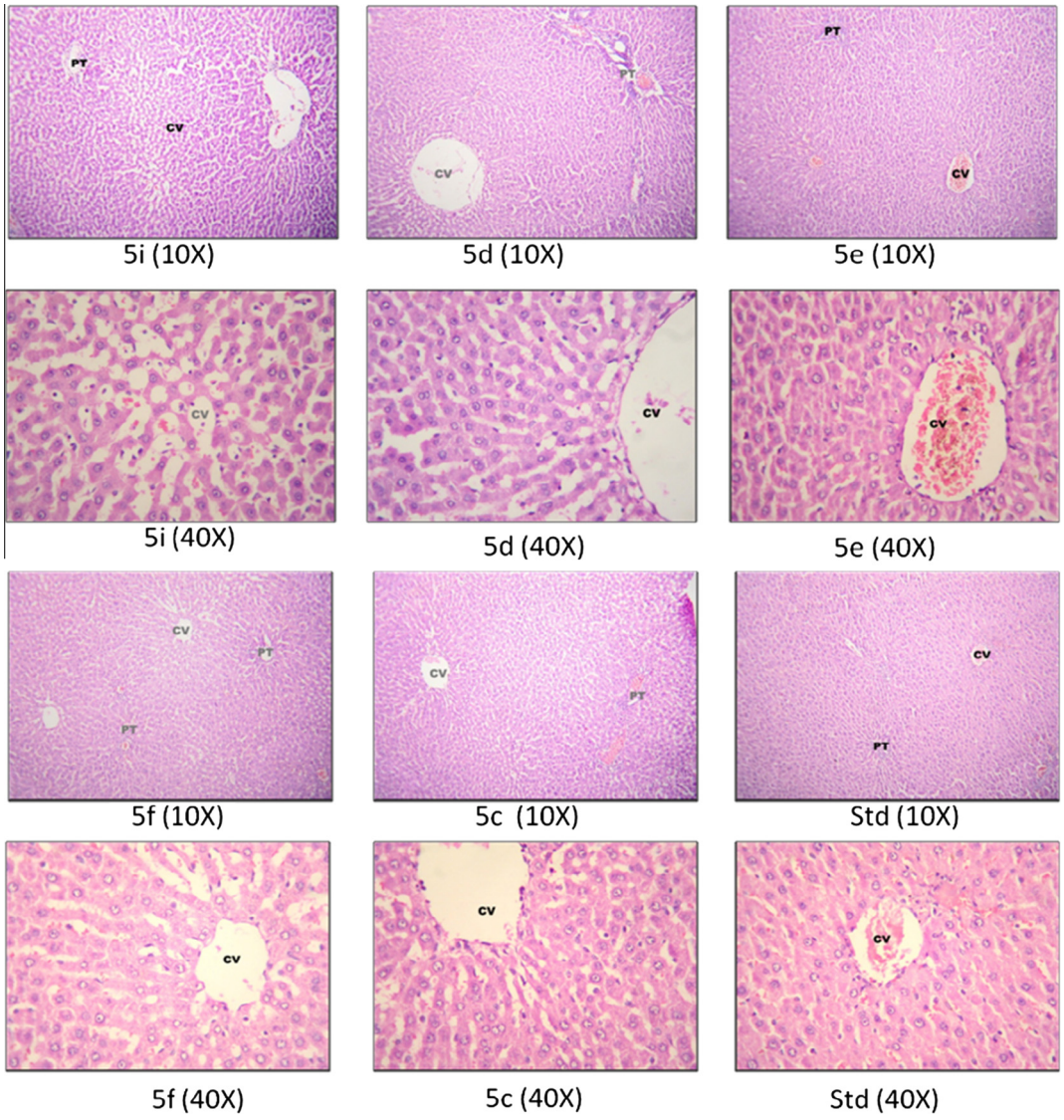


Figure 6. Haematoxylin and eosin immunohistochemical staining of liver after administration of synthesized drugs. Histopathology report of rat liver. As illustrated in above figure, Low and high power photomicrograph of liver from animal treated groups **5c**, **5d**, **5e**, **5f**, **5i** and standard 10×. Low power photomicrograph of liver from corresponding animal **5c**, **5d**, **5e**, **5f**, **5i** and standard treated groups showing normal arrangement of cells in the liver lobule. PT = Portal Triad and CV = Central vein 40×. High power photomicrograph of liver from animal treated groups **5c**, **5d**, **5e**, **5f**, **5i** and standard showing normal arrangement of hepatocytes in the centrizonal area. CV = Central Vein. Compounds **5c** and **5e** treated groups showing normal arrangement of cells in the liver lobule and normal arrangement of hepatocytes in the centrizonal area. **5d**, **5f** and pioglitazone treated groups showing a mild dilatation of sinusoidal spaces around the central vein, **5i** treated group showing evident centrizonal sinusoidal dilatation and thinning of liver cell plates.

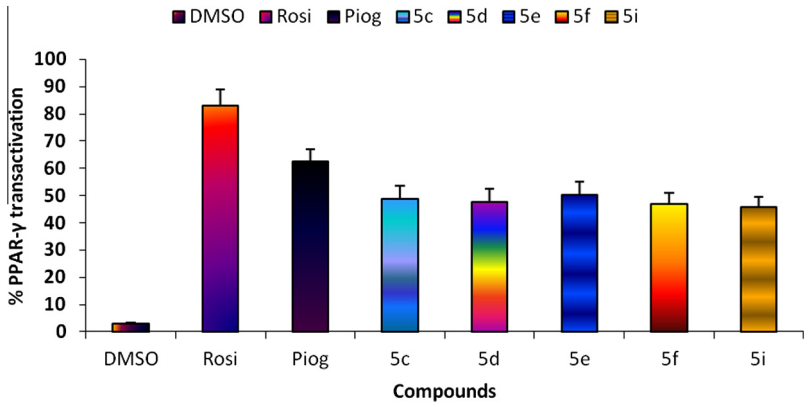


Figure 7. PPAR-γ transactivation assay of active synthesized compounds. Values are expressed as mean ± SE from three experiments conducted in triplicate at 10 μM.

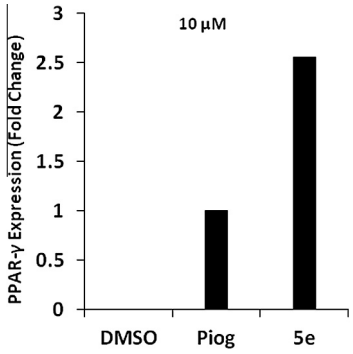


Figure 8. Effect of compound **5e** on PPAR-γ gene expression.

and **5e** recovered the activity of serum AST, ALT and ALP level and did not cause any damage to the liver. Compound **5e** has significant effect on PPAR-γ gene expression as it increases the PPAR-γ expression by 2.56-fold in comparison to Pioglitazone. Compounds **5c** and **5e** may be considered as promising candidate for development of new antidiabetic agents.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.05.034.

References and notes

1. Rotella, D. P. *J. Med. Chem.* **2004**, *47*, 4111.
2. Liu, K.; Xu, L.; Szalkowski, D.; Li, Z.; Ding, V.; Kwei, G.; Huskey, S.; Moller, D. E.; Heck, J. V.; Zhang, B. B.; Jones, A. B. *J. Med. Chem.* **2000**, *43*, 3487.
3. Avupati, V. R.; Yejella, R. P.; Akula, A.; Guntuku, G. S.; Doddi, B. R.; Vutla, V. R.; Anagani, S. R.; Adimulam, L. S.; Vyricharla, A. K. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6442.
4. Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. *J. Med. Chem.* **1994**, *37*, 3977.
5. Prabhakar, C.; Madhusudhan, G.; Sahadev, K.; Maheedhara Reddy, C.; Sarma, M. R.; Om Reddy, G.; Chakrabarti, R.; Seshagiri Rao, C.; Dileep Kumar, T.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2725.
6. Sunduru, N.; Srivastava, K.; Rajakumar, S.; Puri, S. K.; Saxena, J. K.; Chauhan, P. M. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2570.
7. Reddy, K. A.; Lohray, B. B.; Bhushan, V.; Reddy, A. S.; Kishore, P. H.; Rao, V. V.; Saibaba, V.; Bajji, A. C.; Rajesh, B. M.; Reddy, K. V.; Chakrabarti, R.; Rajagopalan, R. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 999.
8. Hafez, H. N.; ElGazzar, A. R. B. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4143.
9. Patil, V.; Tilekar, K.; Munj, S. M.; Mohan, R.; Ramaa, C. S. *Eur. J. Med. Chem.* **2010**, *45*, 4539.
10. Bonde, C. G.; Gaikwad, N. J. *Bioorg. Med. Chem.* **2004**, *12*, 2151.
11. Fan, Y. H.; Chen, H.; Natarajan, A.; Guo, Y.; Harbinski, F.; Iyasere, J.; Christ, W.; Aktasa, H.; Halperina, J. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2547.
12. Jeon, R.; Park, S. Y. *Arch. Pharm. Res.* **2004**, *27*, 1099.
13. Rikimaru, K.; Wakabayashi, T.; Abe, H.; Imoto, H.; Maekawa, T.; Ujikawa, O.; Murase, K.; Matsuo, T.; Matsumoto, M.; Nomura, C.; Tsuge, H.; Arimura, N.; Kawakami, K.; Sakamoto, J.; Funami, M.; Mol, C. D.; Snell, G. P.; Bragstad, K. A.; Sang, B. C.; Dougan, D. R.; Tanaka, T.; Katayama, N.; Horiguchi, Y.; Momose, Y. *Bioorg. Med. Chem.* **2012**, *20*, 714.
14. Willson, T. M.; Lambert, M. H.; Kliewer, S. A. *Annu. Rev. Biochem.* **2001**, *70*, 341.
15. Hong, W. L.; Joong, B. A.; Sung, K. K.; Soon, K. A.; Deok, C. H. *Org. Process Res. Dev.* **2007**, *11*, 190.
16. Packiavathy, A. S. C.; Ramalingam, M.; Devi, C. A. *Orient. J. Chem.* **2013**, *3*, 7.
17. Jawale, D. V.; Pratap, U. R.; Mane, R. A. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 924.
18. Iqbal, A. K. M.; Khan, A. Y.; Kalashetti, M. B.; Belavagi, N. S.; Gong, Y. D.; Khazi, I. A. M. *Eur. J. Med. Chem.* **2012**, *53*, 308.
19. Nesto, R. W.; Bell, D.; Bonow, R. O.; Fonseca, V.; Grundy, S. M.; Horton, E. S.; Winter, M. L.; Porte, D.; Semenkovich, C. F.; Smith, S.; Young, L. H.; Kahn, R. *Diabetes Care* **2004**, *27*, 256.
20. Hollman, P. C.; Katan, M. B. *Food Chem. Toxicol.* **1999**, *37*, 937.
21. Beecher, G. R. *J. Nutr.* **2003**, *133*, 3248S.
22. Moon, Y. J.; Wang, X.; Morris, M. E. *Toxicology* **2006**, *20*, 187.
23. Xie, W.; Wang, W.; Su, H.; Xing, D.; Pan, Y.; Du, L. *Comp. Biochem. Physiol. C: Toxicol. Pharmacol.* **2006**, *143*, 429.
24. Shinde, U. A.; Goyal, R. K. *J. Cell. Mol. Med.* **2003**, *7*, 332.
25. Reddy, K. A.; Lohray, B. B.; Bhushan, V.; Reddy, A. S.; Rao Mamidi, N. V.; Reddy, P. P.; Saibaba, V.; Reddy, N. J.; Suryaprakash, A.; Misra, P.; Vikramadithyan, R. K.; Rajagopalan, R. *J. Med. Chem.* **1999**, *42*, 3265.
26. Yamauchi, T.; Kamon, J.; Waki, H.; Murakami, K.; Motojima, K.; Komeda, K.; Ide, T.; Kubota, N.; Terauchi, Y.; Tobe, K.; Miki, H.; Tsuchida, A.; Akanuma, Y.; Nagai, R.; Kimura, S.; Kadowaki, T. *J. Biol. Chem.* **2001**, *276*, 41245.
27. Maeda, N.; Takahashi, M.; Funahashi, T.; Kihara, S.; Nishizawa, H.; Kishida, K.; Nagaretani, H.; Matsuda, M.; Komuro, R.; Ouchi, N.; Kuriyama, H.; Hotta, K.; Nakamura, T.; Shimomura, I.; Matsuzawa, Y. *Diabetes* **2001**, *50*, 2094.
28. Nathan, K. L.; Kelly, M.; 1 Tsao, T.; Farmer, S. R.; Saha, A. K.; Ruderman, N. B.; Tomas, E. *Am. J. Physiol. Endocrinol. Metab.* **2006**, *291*, E175.
29. Wu, Z.; Rosen, E. D.; Brun, R.; Hauser, S.; Adelmant, G.; Troy, A. E.; McKeon, C.; Darlington, G. J.; Spiegelman, B. M. *Mol. Cell* **1999**, *3*, 151.