

Synthesis, Antidiabetic Evaluation and Molecular Docking Studies of Thiazolidine-2,4-Dione Analogues

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ABSTRACT

Introduction: Diabetes Mellitus is a disorder of metabolism described by high glucose levels. The disorder kills a larger number of individuals consistently than of malignant growth and AIDS combined. Presently available drugs have several drawbacks forcing to withdraw from treatment. The potent side effect i.e., hepatotoxicity and cardiovascular toxicity limits the use of thiazolidine-2,4-dione derivative as safe drugs. Our aim is towards the development of synthetic compounds as potential antidiabetic agents, particularly preparation and screening of new analogues of thiazolidine-2,4-dione (TZD) which are well established as oral insulin sensitizing agents that improve insulin resistance and are agonists of Peroxisome Proliferator Activated Receptor- γ (PPAR- γ). **Materials and Methods:** Proper substitution at C-5 position of thiazolidine-2,4-dione could produce better and potential antidiabetics with improved pharmacological properties, including toxicity. Our aim of this research work is towards this. **Results:** A series of C-5 substituted thiazolidine-2,4-dione analogues were synthesized. Structures of these new analogues were confirmed by IR, $^1\text{H-NMR}$ and MASS spectroscopy. Among the synthesized compounds, three compounds: 5-(2-pyridinylbenzylidene) thiazolidine-2,4-dione, 5-(3,4-dimethoxybenzylidene) thiazolidine-2,4-dione and 5-(2,3,4-trifluorobenzylidene) thiazolidine-2,4-dione showed significant antidiabetic activity in streptozotocin induced diabetic mice comparable with Pioglitazone drug. The molecular docking studies of these compounds performed using protein target showed amino acid interactions with Leu270, Gln283 and Arg288 similar with that of Rosiglitazone and Pioglitazone. The compounds did not show any toxic effect in mice even at 2000 mg/kg of dose. Therefore, synthesis of modified and better thiazolidine-2,4-dione containing drugs other than the currently available drugs is of importance in antidiabetic drug research.

Keywords: Thiazolidine-2,4-dione, Molecular docking, Antidiabetic evaluation, *Swiss albino* mice.

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Received: 25-11-2022;

Revised: 30-12-2022;

Accepted: 20-01-2023.

INTRODUCTION

Diabetes is an incredibly complex disease, influencing different age groups over the world.¹ Among several complications of the disease, the most predominant are kidney infections, visual impairment, hypertension, hypoglycemia, dyslipidemia and respiratory failure or stroke. More commonly used drugs for the treatment are belonging to the class of biguanide, sulfonylurea, thiazolidine-2,4-dione. Presently accessible medications have improper activity profile and pharmacokinetic properties.² Recent reports suggested that cardiovascular toxicity with Rosiglitazone and development of bladder cancer with Pioglitazone are of significant.³ Other drugs such as troglitazone, englitazone are not currently used for the treatment.⁴ Because of these drawbacks

associated with some of such glitazone drugs, new drugs with better activity profile are necessary for the treatment of diabetes, particularly type-2 disease. Among the variously C-5 substituted benzylidene-2,4-thiazolidine (TZD) compounds, Pioglitazone and Rosiglitazone are not drugs of choice, though rarely used clinically. Therefore, we report here the synthesis of variously C-5 substituted 2,4-thiazolidine (TZD) analogues and *in vivo* antidiabetic activity determined using *swiss albino* mice.

MATERIALS AND METHODS

Materials

The chemicals and reagents used for the synthesis were obtained from Sigma-Aldrich, Merck and Loba Chemicals and were used after their characterization. Melting points were taken in open capillary tube on Campbell Melting-point apparatus. The progress of reaction was monitored by TLC and purity of all the compounds were assessed by thin layer chromatography (Silica Gel G coated TLC plates). Fourier Transform Infrared (FT-IR)



DOI: 10.5530/ijper.57.1s.11

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spectra (cm^{-1}) were recorded in potassium bromide (KBr) disk on "Jasco FTIR 4100". Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were recorded in DMSO- d_6 using JEOL (500 MHz) with tetramethylsilane (TMS) as an internal standard. The mass spectra of compounds were recorded on Agilent 6460 Triple Quadrupole LC/MS System with Jet stream ESI ion source. Log p values were calculated using ChemBioDraw Ultra vs 14.0 software.

Chemistry

General Method of Synthesis of Thiazolidine-2,4-Dione

A solution containing chloroacetic acid (9.45 gm, 0.1 Mol) and thiourea (7.61 gm, 0.1 Mol) taken in excess of water was placed in round bottom flask under stirring. The mixture was stirred at low temperature for 15 min or until a white precipitate is formed. To the contents of the flask was then added slowly 3ml of conc. HCl through a dropping funnel, the mixture was then refluxed until a clear solution is obtained (10 -13 hr). Progress of reaction

was monitored by TLC. On cooling the contents, needle shaped solid product resulted and was filtered, washed several times with water and dried. It was purified by dichloromethane (DCM, 3 x 100 ml). Melting Point (M.P.) and spectral characteristics are recorded (Figure 1).^{5,6}

General Method of Synthesis of 5-Substituted Benzylidene Thiazolidine-2,4-Diones

To an equimolar ethanolic solution of thiazolidine-2,4-dione as obtained above, variously substituted benzaldehydes were added (m/m). A catalytic amount of piperidine (0.2 ml) was added. The mixture was stirred and refluxed for 4-6 hr.⁷ The completion of reaction was assessed by TLC (ClCH_3 : CH_3OH ; 9:1) and then, the reaction mixture was poured on to crushed ice. Few drops of glacial acetic acid were added to effect precipitation of product.^{8,9} The products thus obtained were filtered, washed with sufficient cold water and recrystallized from ethanol. Melting Point (M.P.) and spectral characteristics are recorded (Figure 2).

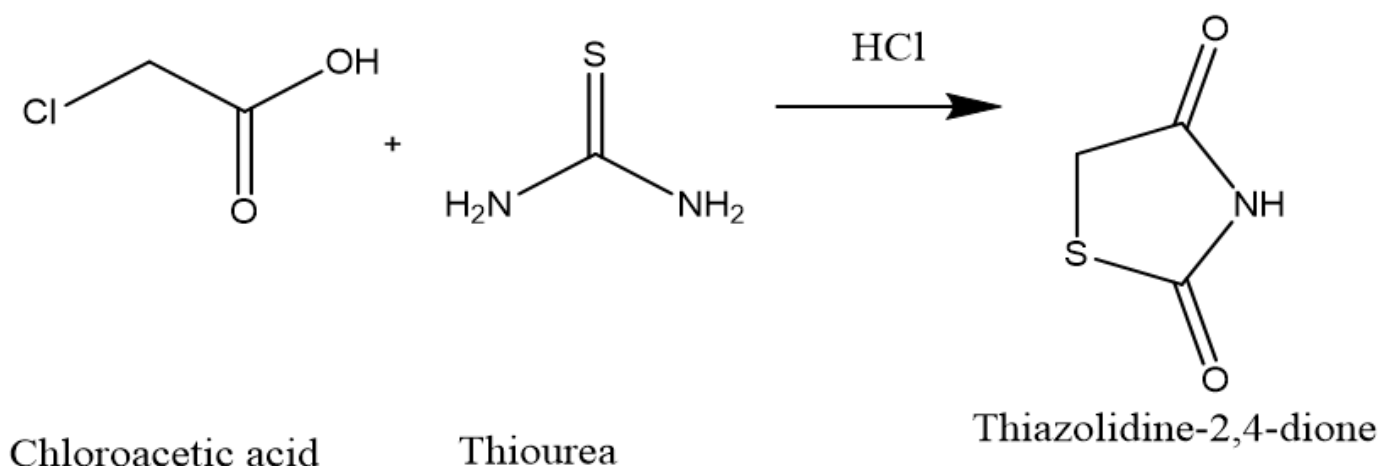


Figure 1: Synthesis of thiazolidine-2,4-dione.

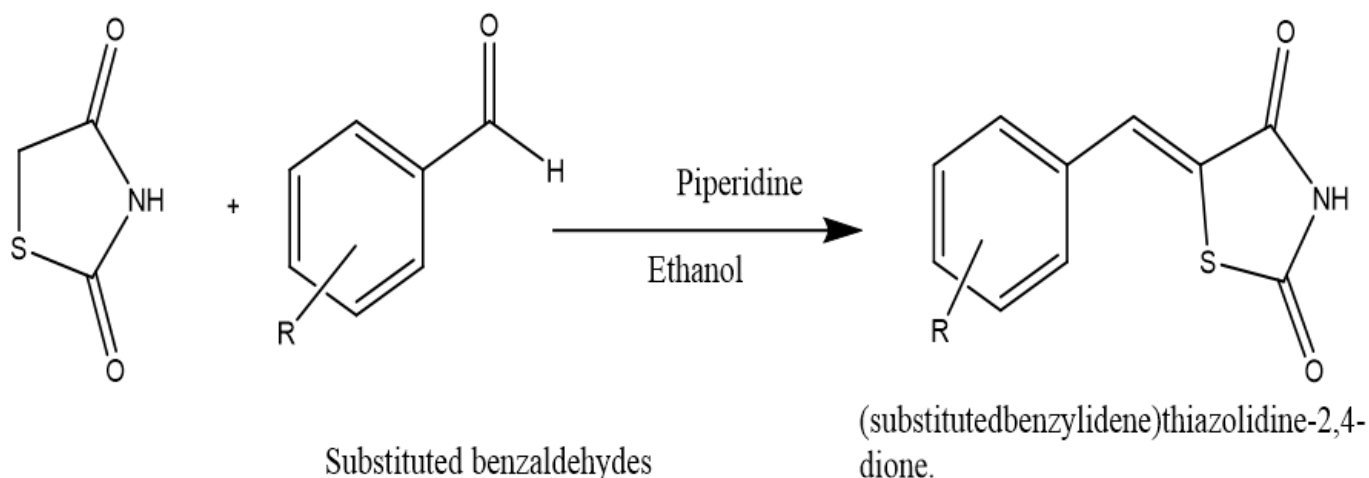


Figure 2: Synthesis of (substitutedbenzylidene)thiazolidine-2,4-dione.

Male Swiss Albino Mice with an average weight of 33 ± 5 gm were used. Animals were housed in propylene cages at an ambient temperature of $25 \pm 2^\circ\text{C}$ and 45-55% relative humidity with standard 12 hr light and dark cycle. They had a free access of feed and water. The guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA) Govt. of India were followed and earlier consent was observed from the institutional animal ethics committee.⁹ (IAEC approval no-PCP/IAEC/2021-22/ "1-11").

Acute Oral Toxicity Test

Oral acute toxicity test of the compounds was performed. The mice were fasted for 4 hr prior to administration of the synthesized compounds. After checking the solubility of the compounds at different dose levels, distilled water was used as a vehicle. The final compounds were given orally in sequential in the form of suspension which is prepared with 2% of acacia gum and water at a dose of 2000 mg/kg. The mice were observed for any signs of toxicity for 4 hr, with special attention. After that up to 48 hr periodically. Then daily thereafter, for 14 days for sign of toxicity and motility.¹⁰

Induction of Diabetes

On the basis of results of molecular docking study, three compounds were selected for *in vivo* antidiabetic activity. Diabetes was induced with streptozotocin (200 mg/kg), dissolved in 0.1M citrate buffer solution, i.p. after 15 min of injecting the nicotinamide (NIC) solution (110 mg/kg) for injection. The vehicle used for the nicotinamide solution is saline solution and for citrate buffer solution water was used as a vehicle. After injecting the streptozotocin, animals were allowed for free access to food and water. After 72 hr the blood glucose level of animals was determined using glucometer. The mice having blood glucose level beyond 250 mg/dL were considered for further investigation.^{11,12}

Molecular Docking Study

For this study, 3D structures of the compounds (Table 1) converted to pdbqt coordinate as per procedure. Before arrangement of auto dock configuration of protein, the water particles and the inhibitors were removed from it. Then, at that point utilizing polar hydrogen's were added, Koullman charges were assigned, and the obtained compound design was utilized as an information file for the AUTOGRID program. Each atom type in the ligand, maps were calculated with 0.375 \AA spacing between grid points and

Table 1: 5-substituted benzylidene-2,4-thiazolidinedione.

Sl. No	Compound Name	Amino acid Interactions	Binding energy (Kcal/mol)	Log P
1	Rosiglitazone	Ile281, Gln283, Leu270.	-7.5	3.21
2	Pioglitazone	Met348, Ile341, Glu259, Cys285, Leu330, Arg288, Tyr327, Ile326, Met364.	-7.6	3.58
	R substitution			
SD-1	Pyridin-2-yl	Ser342, Ile262, Phe247, Lys265, Ly261.	-7.2	1.83
SD-2	3-Br,4-F	Leu333, Leu330, Arg288, Gys285, His449, Met304.	-6.8	2.48
SD-3	3,4-(OCH ₃) ₂	Phe287, Leu270, Gly204, Arg288, Ser342, Gln283, Arg280.	-6.6	1.24
SD-4	4-Cl	His323, Tyr327, Cys285, Leu330, Met365, Arg288, Ile341.	-6.5	2.05
SD-5	2-OH, 3-OCH ₃	Glu259, Ile262, Leu255, Ile249, Ile341, Phe247, Gln271, Arg280.	-6.0	0.98
SD-6	4-OH	Gln271, Leu270, Arg288, Ser342, Phe287.	-6.4	1.1
SD-7	4-F.	Gln271, Leu270, Arg288, Ser342, Phe287.	-6.4	1.65
SD-8	3-Br.	Val339, Met394, Cys282, Gly284, Ile341, Argln288, Ser345.	-6.4	2.32
SD-9	2,3,4-(F) ₃	Gln470, Tyr473, Leu453.	-6.4	1.97
SD-10	2-NO ₂	Val339, Arg288, Gln47.	-5.2	1.98

Note: Log P value is calculated by using chem bio draw ultra vs 14.0 software.

the center of the grid box was placed at $x = 49.390$, $y = -34.847$, and $z = 14.992$. The components of the dynamic site box were set at $50 \times 50 \times 50 \text{ \AA}$. Flexible ligand dockings were achieved for the selected compounds. The best pose of each ligand was selected for analyzing the interactions between PPAR- γ and the inhibitor. The results were visualized using Discovery Studio 4.0 Client.

RESULTS AND DISCUSSION

A series of thiazolidinedione analogues were synthesized by reacting thiazolidine-2,4-dione (0.2 Mol) and various aromatic benzaldehydes (0.2 Mol). The structures of these compounds were confirmed by spectroscopy, IR, MASS and $^1\text{H-NMR}$. The title compounds (SD-1 to SD-9) were docked with the PPAR- γ receptor PDB ID: 2PRG. Then depending on the binding energy and amino acid interactions, three compounds (SD-1, SD-3 and SD-9) were selected for antidiabetic activity screening using streptozotocin induced diabetic mice.

Physical and Spectral Properties

Thiazolidine-2,4-dione (Scheme 1); White solid, yield: 89%, M.P 124-128°C; FT-IR (KBr) cm^{-1} : 3309 (N-H), 1746 (C=O), 1337 (C-N), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500 MHz, DMSO): 12.01 (s,1H, NH), 41 (s,1H,CH). MS: m/z 115.96 (Exp) [M^{-1}], 117 (cal). R_f : 0.9.

5-(2-pyridinylbenzylidene) thiazolidine-2,4-dione (Scheme 2); (SD-1); Yellow solid, Yield:84%, M.P 262-266°C; FT-IR (KBr) cm^{-1} : 3045 (Ar-CH), 3309 (N-H), 1746 (C=O), 1337 (C-N), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500 MHz, DMSO): 12.47 (s,1H, NH), 8.0 (d, 1H Alkene CH), 8.2 (s, 1H Alkene CH), 8.26 (d, 1H Alkene CH), 8.08 (s, 1H Alkene CH). MS: m/z 281.11 (Exp) [M^{-1}], 282.32 (cal). R_f : 0.6.

5-(3-bromo-4-fluorobenzylidene) thiazolidine-2,4-dione (SD-2); Yellow solid, Yield:92%, M.P 202-206°C; FT-IR (KBr) cm^{-1} : 3332 (N-H), 3066 (ArC-H), 1720 (C=O), 1309 (C-N), 756 (C-F), 699 (C-Br), 657 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500 MHz, DMSO): 12.47 (s, 1H, NH), 8.0 (d, 1H Alkene CH), 8.2 (s, 1H Alkene CH), 8.26 (d, 1H Alkene CH), 8.08 (s, 1H Alkene CH). MS: m/z 301 (Exp) [M^{-1}], 302 (cal). R_f : 0.7.

5-(3,4-dimethoxybenzylidene) thiazolidine-2,4-dione (SD-3); Yellow solid, Yield:84%, M.P 206-210°C; FT-IR (KBr) cm^{-1} : 3323 (N-H), 3229 (Ar-CH), 1746 (C=O), 1317 (C-N), 618 (C-S), 1033 (Ar-O-C). $^1\text{H-NMR}$ (δ -ppm) (500MHz DMSO): 12.5 (s,1H,NH), 7.19 (d,2H,Ar CH) 7.19 (s,1H Ar CH) 7.7 (s,1H alkene CH), 3.81 (s,6H,OCH₃). MS: m/z 264 (Exp) [M^{-1}], 265 (cal). R_f : 0.5.

5-(4-chlorobenzylidene) thiazolidine-2,4-dione (SD-4); Yellow solid, Yield:72%, M.P 184-188°C; FT-IR (KBr) cm^{-1} : 3323 (N-H), 3202 (ArC-H), 1717 (C=O), 1331 (C-N), 764 (C-Cl), 635 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz DMSO): 12.6 (s,1H,NH), 7.6 (d,4H

Ar-CH), 7.8 (s,1H alkene CH). MS: m/z 220 (Exp) [M^{-1}], 219 (cal). R_f : 0.5.

5-(2-hydroxy-3-methoxybenzylidene) thiazolidine-2,4-dione (SD-5); Pale green solid, Yield:86%, M.P 146-148°C; FT-IR (KBr) cm^{-1} : 3410 (O-H), 3121 (N-H), 3000 (Ar C-H), 1740 (C=O), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz DMSO): 12.4 (s,1H,NH), 13.80 (s,1H,OH), 7.17 (d,Ar CH) . 6.61 (d,Ar CH). 7.09 (t,Ar-CH). 8.34 (s,alkene CH), 3.81 (s,3H,OCH₃). MS: m/z 250 (Exp) [M^{-1}], 251 (cal). R_f : 0.5.

5-(4-hydroxybenzylidene) thiazolidine-2,4-dione (SD-6); Yellow solid, Yield: 94%, M.P 172-176°C; FT-IR (KBr) cm^{-1} : 3410 (O-H), 3121 (N-H), 1724 (C=O), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz, DMSO): 12.45 (s,1H,NH), 10.30 (t,1H,OH), 6.95 (d,2H Ar CH), 7.45 (m,2H,Ar CH), 7.61 (s,alkene CH). MS: m/z 220 (Exp) [M^{-1}], 221 (cal). R_f : 0.7.

5-(4-fluorobenzylidene) thiazolidine-2,4-dione (SD-7); Brown sticky, Yield:76%, M.P 206-210°C; FT-IR (KBr) cm^{-1} : 3428 (N-H), 2934 (Ar-CH), 1736 (C=O), 1516 (C-F), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz,DMSO): 12.47 (s,1H,NH), 7.72 (d,2H Ar CH), 7.76 (s,1H alkene CH), 7.40 (d,2H Ar CH). MS: m/z 222 (Exp) [M^{-1}], 223 (cal). R_f : 0.8.

5-(3-bromobenzylidene) thiazolidine-2,4-dione (SD-8); White solid, Yield:92%, M.P 216-220°C; FT-IR (KBr) cm^{-1} : 3400 (N-H), 3200 (Ar C-H), 1730 (C=O), 1343 (C-N), 698 (C-Br), 628 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz,DMSO): 12.47 (s,1H,NH), 7.56 (s,1H Ar CH), 7.46 (d,1H Ar CH), 7.32 (m,1H Ar CH), 7.60 (d,1H Ar CH), 8.6 (s,1H Alkene CH). MS: m/z 283.13 (EXP) [M^{-1}]. 284.14 (cal). R_f : 0.6.

5-(2,3,4-trifluorobenzylidene) thiazolidine-2,4-dione (SD-9); Yellow solid, Yield:89%, M.P 230-234; FT-IR (KBr) cm^{-1} : 3462 (N-H), 3127 (Ar C-H), 1745 (C=O), 792 (C-F), 620 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz, DMSO): 12.79 (s,1H,NH), 7.80 (d,1H alkene CH), 7.67 (s,1H Ar CH), 7.59 (d,1H Ar CH). MS: m/z 258 (Exp) [M^{-1}], 259 (cal). R_f : 0.6.

5-(4-nitrobenzylidene) thiazolidine-2,4-dione (SD-10); Brown solid, Yield:60%, M.P 172-174; FT-IR (KBr) cm^{-1} : 3397 (N-H), 2968 (Ar-CH), 1703 (C=O), 1526 (N-O), 1314 (C-N), 621 (C-S). $^1\text{H-NMR}$ (δ -ppm) (500MHz, DMSO): 12.47 (s,1H,NH), 8.37 (d,2H Ar-CH), 8.03 (d,2H Ar -CH), 7.61 (s,alkene CH). MS: m/z 249.07 (Exp) [M^{-1}], 250 (Cal). R_f : 0.7

Molecular Docking

To study the interaction of synthesized compounds in the active site of PPAR- γ , a docking study was performed using crystal structure complexed with Rosiglitazone which has major interactions with Ile 281, Gln283 and Leu270. The most potent compounds: SD-1, SD-3 and SD-ss9 have amino acid interactions. The benzyl ring of the compound SD-1 shows the

π - π cation with Phe247 and Tyr265, van der Waals interaction are with N of pyridynyl ring. Lys261 shows the π -cation interaction with thiazolidinedione ring. In addition, the phenyl ring of the compound SD-3, shows the π -sigma interaction with Leu270. The substituted methoxy group shows van der Waals interaction with the Gln 283 and alkyl interaction with the Arg280. The π -sulphur interaction is observed with Phe287 and π -sigma interaction with Arg 288. Finally, the carbonyl function of thiazolidinedione compound shows conventional hydrogen bond interaction with the Arg288. These interactions can be observed in Figures 3 to 6. Other interactions are given in Table 1.

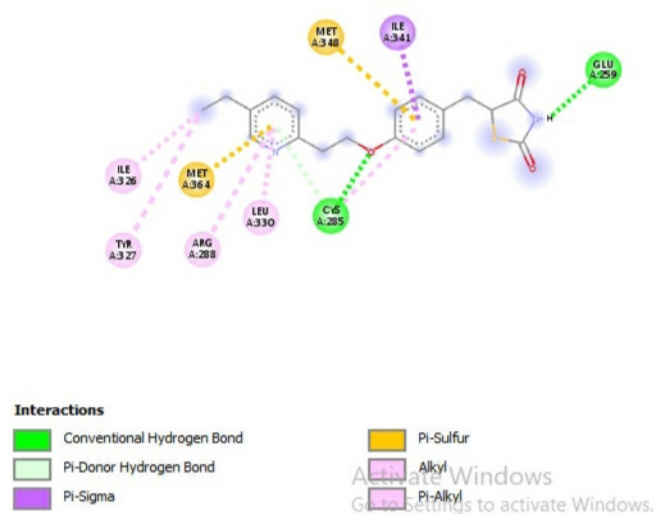


Figure 3: Amino acid interactions of Pioglitazone.

Acute Oral Toxicity Test

The acute oral toxicity test of molecules SD-1, SD-3 and SD-9 were performed and found no toxic effect even at 2000 mg/kg. It is confirmed thus that our compounds do not show any side effect even at the higher dose.

Antidiabetic Activity

Three compounds: SD-1, SD-3 and SD-9 exhibited significant reduction in fasting blood glucose levels after 8 days of treatment compared to standard drug Pioglitazone. (Table 2).

Antidiabetic Activity in Mice

Further, to understand structure activity relationship log *p* values were calculated by the One-Way ANOVA (Dunnet hoc test) test

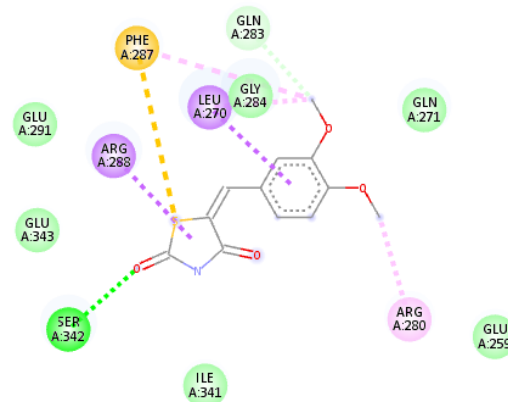


Figure 5: Amino acid interactions of 5-(3,4-dimethoxybenzylidene)-2,4-thiazolidinedione. (SD-3).

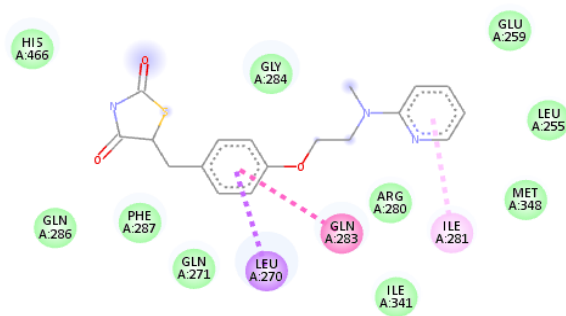


Figure 4: Amino acid interactions of Rosiglitazone.

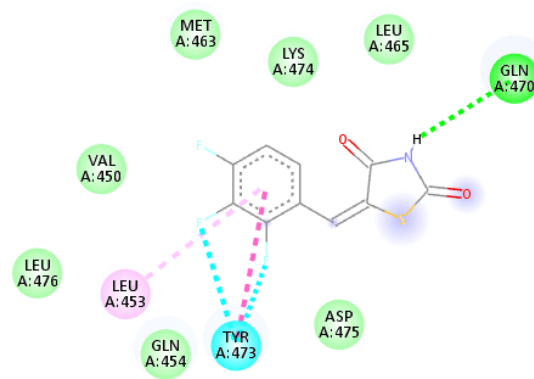


Figure 6: Amino acid interactions of 5-(2,3,4-trifluorobenzylidene)-2,4-thiazolidinedione (SD-9).

Table 2: Effect of Test Compounds on Streptozotocin Induced Diabetic Mice.

Group	Blood Glucose level(mg/dl) 1 st day	Blood Glucose level(mg/dl) after 72 hr of STZ administration	Blood Glucose level(mg/dl) after 8 days of treatment
NC	160	----	154
DC	170	238	245
SD-1	158	236	133
SD-3	152	230	124
SD-9	160	231	125
Pioglitazone	165	222	127

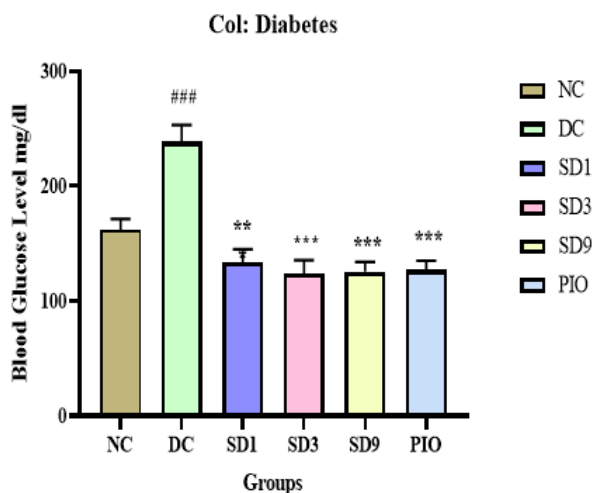


Figure 7: Effect of SD-1, SD-3, SD-9 and Standard Drug Blood Glucose Level in Streptozotocin Induced Diabetic Mice. $p < 0.0001$ Which is Significant and Indicated in Terms of ***. NC= Normal control, DC= Diabetic control, PIO= Std drug Pioglitazone.

using Prism Software. Significant p value of all three compounds is < 0.001 . The results are shown in Figure 7. The compounds having Log p value between 1-2 show good antidiabetic activity in mice.

CONCLUSION

Recent studies have indicated that cardiovascular toxicity with Rosiglitazone and increase in bladder cancer with Pioglitazone. These drugs are no longer drugs of choice. To obtain better and safe drugs containing thiazolidine-2,4-dione moiety, we have attempted modification by introducing suitable substituents at C-5 of thiazolidine-2,4-dione nucleus.¹³ A novel series of thiazolidine-2,4-dione analogues has been thus synthesized. The structures of these compounds were established by IR, ¹H-NMR and MASS spectrometry. The acute oral toxicity test of these molecules were performed and found no toxic effect even at 2000mg/kg of drug. Three compounds were tested for antidiabetic activity in swiss albino mice. The synthesized compounds were then docked with the PPAR- γ (PDB ID: 2PRG) using Auto Dock Vina software. The results indicated interaction

with Gly283 and Leu270 comparable with Rosiglitazone. Among all the synthesized compounds, three derivatives; SD-1, SD-3 and SD-9 have similar amino acid interactions as of Rosiglitazone and Pioglitazone. These compounds also showed better glucose lowering effect.

ACKNOWLEDGEMENT

Dolly Pardeshi thanks Clean Chem Laboratories, Navi-Mumbai for providing facilities to work in their laboratories. Authors are grateful to Principal Dr. Atmaram Pawar and to Dr. Urmila Aswar for pharmacology assistance.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Pardeshi DR, Kulkarni VM, Pathare SS. Synthesis, Antidiabetic Evaluation and Molecular Docking Studies of Thiazolidine-2,4-Dione Analogues. *Indian J of Pharmaceutical Education and Research*. 2023;57(1s):s98-s104.