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Synthesis, anti-hyperglycaemic activity, and in-silico studies of *N*-substituted 5-(furan-2-ylmethylene) thiazolidine-2,4-dione derivatives

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Abstract Thiazolidinedione derivatives have been used as anti-hyperglycemic agents in diabetic patients since last decade. In the present study, a series of *N*-substituted-5-(furan-2-ylmethylene)thiazolidine-2,4-dione derivatives were synthesized and characterized by ^{1}H-NMR, ^{13}C-NMR and mass spectra. The introduction of the alkyl/haloalkyl moiety onto the amidic nitrogen of the thiazolidine-2,4-dione ring was intended to enhance the anti-hyperglycaemic activity, which was further tested in vivo by using alloxan-induced diabetic laca mice. Molecular docking simulation studies further helped in understanding the nature of the interactions and the binding mode of ligands inside the active site of the protein tyrosine phosphatase 1B enzyme, which negatively regulates the insulin signaling pathway. The compounds were screened for in-vivo anti-hyperglycaemic activity in which compounds **9** and **10** have exhibited significant decreases in blood glucose level comparable to that of pioglitazone.

Keywords Diabetes · *N*-substituted thiazolidine-2,4-dione · Anti-hyperglycaemic activity · Docking

Introduction

Diabetes mellitus has emerged as a major health care problem worldwide due to sedentary lifestyle, abrupt changes in human environment, culture, and rapid urbanization. Diabetes mellitus is a complex metabolic syndrome characterized by hyperglycemia and its severity often leads to poor wound healing, nephropathy, blurred vision, neuropathy, cardiovascular diseases, and premature death [1]. Diabetes Atlas 2015, a recent study by the International Diabetes Federation (IDF),

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has estimated the global occurrence of diabetes to be 415 million cases with another 318 million individuals suffering from impaired glucose tolerance, placing them at high risk of developing diabetes in the near future [2]. Diabetes is quickly gaining the status of a potential epidemic in the world, as its prevalence is predicted to double globally from 171 million in 2000 to 366 million in 2030, with a maximum increase in India [3, 4].

Glitazones, having a common structural framework with 2,4-thiazolidinediones (TZD), were approved as anti-hyperglycemic drugs in the last decade. This TZD moiety having sulphur atom in a five-membered ring has shown anti-hyperglycaemic activity and has also been reported as an insulin sensitizer, peroxisome proliferator-activator receptor γ (PPARγ) agonist, PTP1B inhibitor, and aldose reductase inhibitor. Thus, TZDs decrease the blood glucose concentration by ameliorating insulin resistance, promote glucose utilization in peripheral tissue, and thereby normalize elevated blood glucose levels [5]. Following the initial report of a novel antidiabetic agent called ciglitazone (benzylthiazolidinedione) from Takeda laboratories, TZD analogues have emerged as a new class of antidiabetic agents. Various substituted TZD analogues such as troglitazone, englitazone, rosiglitazone, and pioglitazone have been developed and used clinically for the treatment of type 2 diabetes (Fig. 1). However, except for pioglitazone, all others were withdrawn from clinical use due to serious side effects [6]. The side effects associated with TZD derivatives may have emerged due to the acidic amidic proton of the TZD nucleus, which imitates the carboxylate anion of the natural fatty acid ligands, enabling its binding to the peroxisome proliferator-activator receptor (PPAR) belonging to the steroid/thyroid/retinoid receptor super family of ligand-activated transcription factors. Hence, *N*-substituted TZD derivatives were expected to have lesser side effects as compared to the current glitazones [7, 8]. Bhattarai et al. [9, 10] have

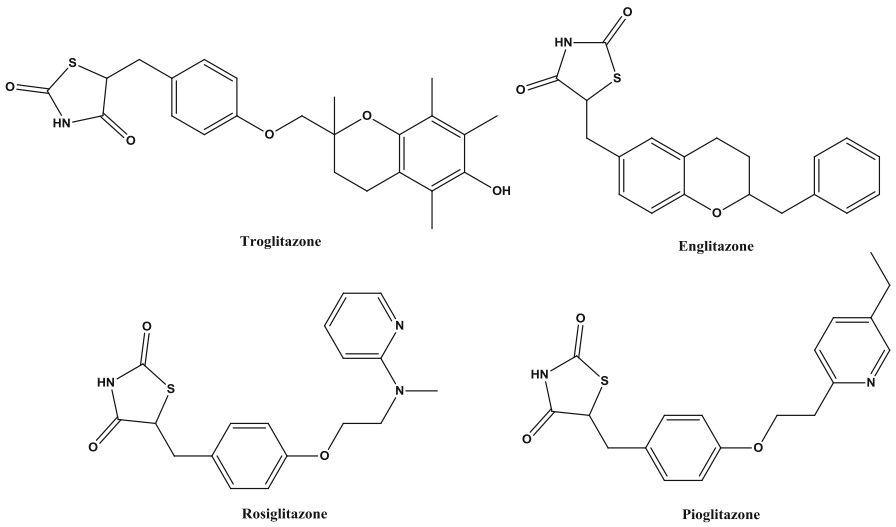


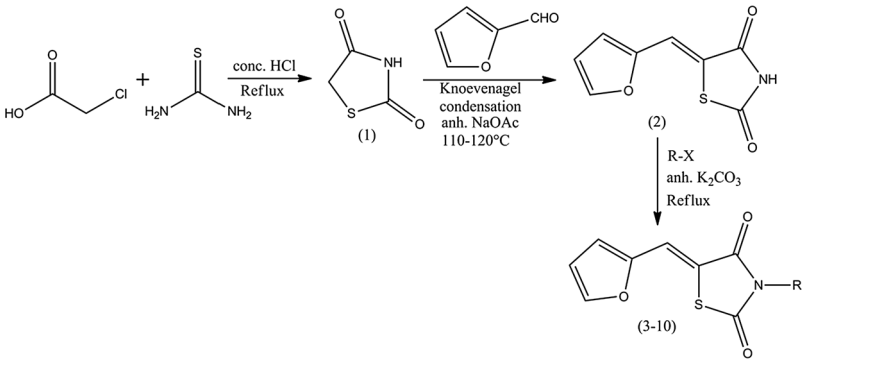
Fig. 1 Reported anti-hyperglycaemic agents having a TZD scaffold

reported significant PTP1B inhibitory and anti-hyperglycaemic activity of various TZD derivatives. Lakshminarayana et al. [11] have reported various furan carboxylic acids as potential antidiabetic agents. Therefore, it was envisaged to design a series of small molecule inhibitors by connecting both the furan and TZD nucleus by a vinylic linkage, and the amidic nitrogen of TZD was substituted by alkyl/haloalkyl groups. In the present investigation synthesis, characterization and in-vivo anti-hyperglycaemic activity of *N*-substituted 5-(furan-2-ylmethylene)thiazolidine-2,4-dione derivatives are herein reported. Docking studies were also carried out for supplementing the in-vivo results.

Experimental

Chemistry

All reagents were obtained commercially and were of the highest quality and used without further purification. Solvents were freshly distilled and used. Melting points were recorded on a Veego-540 melting-point apparatus and were uncorrected. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AC-400F, 400 MHz spectrometer for solutions in deuteriochloroform ($CDCl_3$), deuterated dimethylsulfoxide (DMSO-*d*6), and were reported in parts per million (ppm), downfield from tetramethylsilane (TMS) as an internal standard. Splitting patterns were designated as singlet (s), doublet (d), triplet (t), or multiplet (m). Chemical shift values are presented in parts per million (ppm). Mass spectroscopy (MS) was conducted using a Micromass LCT system. All reactions were monitored by TLC (silica gel-coated aluminum sheets). The N-substituted derivatives of thiazolidinedione have been synthesized as outlined in (Scheme 1).



Scheme 1 Synthesis of *N*-substituted 5-(furan-2-ylmethylene)thiazolidine-2,4-diones

*Synthesis of thiazolidine-2,4-dione (**1**)*

A mixture of chloroacetic acid (56.7 g, 0.6 mol) and thiourea (45.6 g, 0.6 mol) was dissolved in water (125.0 ml) and stirred for 15 min. Hydrochloric acid (conc., 60.0 ml) was added dropwise to this solution. The reaction mixture was refluxed for 12 h and then cooled in an ice bath. The product separated as white needles, was filtered, washed repeatedly with water to remove traces of hydrochloric acid, dried, and then recrystallised from methanol to yield 2,4-thiazolidinedione [12].

White solid (Yield: 62.58 g, 88.2 %; m. p. 123–125 °C); R_f: 0.49 (Chloroform : Methanol :: 10 : 1); IR (KBr): 3132, 1739, 1662, 615 cm^{-1}; ^1H NMR (DMSO-d6, ppm): δ 11.98 (s, 1H, N*H*), δ 4.09 ppm (s, 2H, CH_2); ^{13}C NMR (DMSO-d6, ppm): δ 173.54 (*C*O), δ 172.79 (*C*O), δ 35.65 (Aromatic *C*).

*Synthesis of (Z)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**2**)*

A mixture of thiazolidine-2,4-dione (2.92 g, 25 mmol) and anhydrous sodium acetate (2.05 g, 25 mmol) in glacial acetic acid was refluxed at 110–120 °C for 20 min. Furfuraldehyde (2.07 ml, 25 mmol) was added into the mixture and refluxed for 36 h using a Dean–Stark apparatus to remove water from the reaction. The solvent was evaporated and the residue was added into crushed ice with stirring. The separated product was filtered, washed with water, and dried. It was crystallised from acetone to yield (*Z*)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione.

Dark brown solid (Yield: 1 g, 20.5 %); m. p.: 230–232 °C); R_f: 0.57 (hexane : ethylacetate :: 2:1); IR (KBr): 3143, 3030, 1725,1684 cm^{-1}; ^1H NMR (DMSO-d_6): δ 6.6 (q, 1H, Ar–H), 7.01 (d, 1H, Ar–*H*), 7.58 (s, 1H, =CH), 7.95 (d, 1H, Ar–*H*) and 12.39 (br s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 113.21 (Aromatic-C), 118.09 (Aromatic-C), 118.32 (>C=, TZD), 120.46 (=CH), 146.99 (Aromatic-C), 149.22 (Aromatic-C), 166.93 (*CO*, TZD) and 168.46 (*CO*, TZD) ppm.

*General procedure for synthesis of compounds **3–10***

A mixture of (*Z*)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (1.36 g, 7 mmol) and anh. potassium carbonate (2 g, 14 mmol) in acetone was refluxed for 20 min. Suitable alkyl/haloalkyl derivatives (10.5 mmol) were added to the mixture and refluxed for 24 h. The solvent was evaporated under reduced pressure to obtain a solid residue. The solid residue was mixed with crushed ice with stirring for 30 min. The product obtained was filtered, washed with water to remove traces of inorganic salt, and dried. It was recrystallized from acetone to afford the final compounds.

*(Z)-3-ethyl-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**3**)*

Light brown solid (Yield: 0.750 g, 48 %; m. p.: 119–121 °C); R_f: 0.62 (hexane:ethylacetate 2:1); IR (KBr): 3039, 2981, 1730, 1668, 1614, 1436 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (t, 3H, CH_3), 3.79 (q, 2H, CH_2 –N<), 6.5 (q, 1H, Ar–*H*), 6.78 (d, 1H, Ar–*H*), 7.63 (s, 1H, =CH) and 7.67 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 13.15 (CH_3), 36.91 (CH_2–N<), 113.13 (Aromatic-C), 117.63 (-Aromatic-C),

119.41 (>C=, TZD), 119.45 (=CH), 146.37 (Aromatic-C), 149.8 (Aromatic-C), 166.03 (*CO*, TZD) and 168.65 (*CO*, TZD) ppm; Mass (EI): *m/z* 223.04 $[M]^+$

*(Z)-3-(3-chloropropyl)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**4**)*

Light brown solid (Yield: 0.7 g, 37 %; m. p.: 116–118 °C); R_f: 0.59 (hexane:ethylacetate 2:1); IR (KBr): 3034, 2954, 1730, 1671, 1614, 1439 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (quint, 2H, CH_2), 3.56 (t, 2H, CH_2–Cl), 3.89 (t, 2H, CH_2–N<), 6.58 (q, 1H, Ar–*H*), 6.8 (d, 1H, Ar–*H*), 7.64 (s, 1H, =CH) and 7.67 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 30.69 (CH_2), 39.48 (CH_2–Cl), 41.85 (CH_2–N<), 113.21 (Aromatic-C), 117.97 (Aromatic-C), 118.49 (>C=, TZD), 119.86 (=CH), 146.54 (=CH–O–), 149.73 (Aromatic-C), 166.08 (*CO*, TZD) and 168.78 (*CO*, TZD) ppm; Mass (EI) : *m/z* 271 $[M]^+$, 273.02$[M+2]^+$.

*(Z)-3-(2-bromoethyl)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**5**)*

Brown solid (Yield: 0.64 g, 30 %; m. p.: 120–122 °C); R_f: 0.55 (hexane:ethylacetate 2:1); IR (KBr): 3042, 2959, 1736, 1672, 1613, 1429 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.51 (t, 2H, CH_2–Br), 4.07 (t, 2H, CH_2–N<), 6.52 (q, 1H, Ar–*H*), 6.74 (d, 1H, Ar–*H*), 7.56 (s, 1H, =CH) and 7.61 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 26.93 (CH_2–Br), 42.52 (CH_2–N<), 113.27, 118.21 (Aromatic-C), 118.56 (>C=, TZD), 120.22 (=CH), 146.68, 149.67 (Aromatic-C), 165.72 (CO, TZD) and 168.56 (CO, TZD) ppm; Mass (ESI) : *m/z* 302.78 $[M]^+$, 304.78$[M+2]^+$.

*(Z)-5-(furan-2-ylmethylene)-3-propylthiazolidine-2,4-dione (**6**)*

Brown solid (Yield: 0.80 g, 51 %; m. p.: 110–112 °C); R_f: 0.49 (hexane : ethylacetate :: 2:1); IR (KBr): 3038, 2955, 1727, 1674, 1610, 1432 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, 3H, CH_3), 1.60 (m, 2H, CH_2), 3.62 (t, 2H, CH_2–N<), 6.49 (q, 1H, Ar–*H*), 6.70 (d, 1H, Ar–*H*), 7.56 (s, 1H, =CH) and 7.59 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 11.17 (CH_3), 21.16 (CH_2), 43.39 (CH_2–N<), 113.11, 117.59 (Aromatic-C), 119.37 (>C=, TZD), 119.46 (=CH), 146.35, 149.85 (Aromatic-C), 166.27 (CO, TZD) and 168.83 (CO, TZD) ppm; Mass (EI): *m/z* 238.56$[M+1]^+$.

*(Z)-3-butyl-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**7**)*

Light yellow solid (Yield: 1.50 g, 85 %; m. p.: 95–97 °C); R_f: 0.64 (hexane : ethylacetate :: 2:1); IR (KBr): 3042, 2958, 1734,1667,1615,1430 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.63 (quint, 2H, CH_2), 3.72 (t, 2H, CH_2–N<), 6.56 (q, 1H, Ar–*H*), 6.77 (d, 1H, Ar–*H*), 7.63 (s, 1H, =CH) and 7.66 (d,1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 13.61 (CH_3), 19.97 (CH_2), 29.83 (CH_2), 41.67 (CH_2–N<), 113.11, 117.57 (Aromatic-C), 119.38 (>C=, TZD), 119.42 (=CH), 146.34, 149.84 (Aromatic-C), 166.22 (*CO*, *TZD*) and 168.76 (CO, TZD) ppm; Mass (ESI): *m/z* 251.53 $[M]^+$.

*(Z)-5-(furan-2-ylmethylene)-3-methylthiazolidine-2,4-dione (**8**)*

Brown solid (Yield: 0.96 g, 65.6 %; m. p.: 129–131 °C); R_f: 0.60 (hexane : ethylacetate :: 2:1); IR (KBr): 3043, 2956, 1729, 1671, 1614,1421 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.22 (s, 3H, CH_3), 6.57 (q, 1H, Ar–*H*), 6.78 (d, 1H, Ar–*H*), 7.64 (s, 1H, =CH–),7.67 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 27.78 (CH_3), 113.15, 117.80 (Aromatic-C), 119.19 (>C=, TZD), 119.59 (=CH), 146.44, 149.73 (Aromatic-C), 166.28 (*CO*, TZD), 168.88 (*CO*, TZD) ppm; Mass (ESI): *m*/*z* 210.46 $[M+1]^+$.

*(Z)-3-(2-chloroethyl)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**9**)*

Brown solid (Yield: 0.70 g, 38 %; m. p.: 87–89 °C); R_f: 0.57 (hexane : ethylacetate :: 2:1); IR (KBr): 3039, 1737, 1677, 1617, 1424 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.75 (t, 2H, CH_2–Cl), 4.08 (t, 2H, CH_2–N<), 6.58 (q, 1H, –Ar–*H*), 6.81 (d, 1H, Ar–*H*), 7.66 (s, 1H, =CH–),7.68 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 39.87 (CH_2–Cl), 42.66 (CH_2–N<), 113.27, 118.22 (Aromatic-C), 118.55 (>C=, TZD), 120.19 (=CH), 146.68, 149.66 (Aromatic-C), 165.84 (*CO*, TZD), 168.68 (*CO*, TZD) ppm; Mass (EI): *m*/*z* 257.73 $[M]^+$, 258.67 $[M+1]^+$.

*(Z)-5-(furan-2-ylmethylene)-3-pentylthiazolidine-2,4-dione (**10**)*

Light brown solid (Yield: 0.99 g, 54 %; m.p.: 62–64 °C); R_f: 0.56 (hexane:ethylacetate 2:1); IR (KBr): 3042, 2929, 1735, 1669, 1430 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89 (t, 3H, CH_3), 1.32 (m, 4H, CH_2–CH_2), 1.65 (quint, 2H, CH_2), 3.72 (t, 2H, CH_2–N<), 6.57 (q, 1H, Ar–*H*), 6.77 (d, 1H, Ar–*H*), 7.63 (s, 1H, =CH), 7.66 (d, 1H, Ar–*H*) ppm; ^{13}C NMR ($CDCl_3$): δ 13.92 (CH_3), 22.24 (CH_2), 27.48 (CH_2), 28.81 (CH_2), 41.90 (CH_2–N<), 113.12, 117.61 (Aromatic-C), 119.37 (>C=, TZD), 120.19 (=CH), 146.36, 149.84 (Aromatic-C), 165.24 (*CO*, TZD), 168.80 (*CO*, TZD) ppm; Mass (EI): *m*/*z* 265.12 $[M]^+$.

In-vivo anti-hyperglycaemic activity

Albino mice (Laca strain) of either sex, bred in the Central Animal House Facility of Panjab University, were used in the present antidiabetic screening. Animals were housed in polypropylene cages. They were housed (six mice per cage) under standard (25 ± 2 °C, 60–70 % humidity) laboratory conditions, maintained on a 12-h natural day-night cycle, with free access to standard food and water. Animals were acclimatized to laboratory conditions for 1 week before the experiment. The experimental protocol was approved by the Institutional Animal Ethics Committee (PU/IAEC/S/14/105) and conducted according to the CPCSEA guidelines.

Diabetes was induced in overnight-fasted mice by a single i.p. injection of Alloxan (150 mg/kg) dissolved in normal physiological saline. Animals were fed with 5 % glucose solution for the first 12 h to prevent hypoglycemia. A blood glucose monitoring system (eBsensor blood glucose meter, Visgeneer Inc. Taiwan) was used for measurement of blood glucose concentration. The elevated blood

glucose levels determined at 72 h confirmed hyperglycemia. Animals with blood glucose concentrations greater than 250 mg/dl were selected for the study [11, 13].

Acute study

In the acute study, animals were fasted overnight and the fasting blood glucose level at 0 h was calculated. All the test compounds (homogenized suspension in 0.5 % CMC and a permissible amount of Tween 80) and the standard drug pioglitazone were administered orally at a fixed dose of 30 mg/kg body weight. Animals of the vehicle-treated group were given an equal amount of 0.5 % CMC and those of the control group were kept as such. Using the tail prick method, the blood glucose level was monitored at 2, 4, 6, and 24 h after administration of test compounds. The % reduction in blood glucose level was calculated with respect to the control group. A 10 % reduction in serum glucose level versus control group levels was considered as a positive screening result.

Subacute study

In the subacute study, the test compounds (homogenized suspension in 0.5 % CMC and a permissible amount of Tween 80) and the standard drug pioglitazone were administered once daily by oral gavage at a fixed dose of 30 mg/kg body weight for 7 days at a fixed time. After 7 days, blood samples were taken from animals and percentage change in blood sugar level was determined. The data obtained were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's test. The results were expressed as mean ± standard error of mean (SEM) for each group. Statistical significance of differences between groups was determined by one-way ANOVA followed by Dunnett's test. A probability (P) value of less than 0.05 indicated statistically significant difference between the treatment groups.

Molecular docking study

Protein tyrosine phosphatase 1B enzyme has emerged as a therapeutic target for the management of type 2 diabetes, as it negatively regulated the insulin signaling pathway. A number of TZD derivatives have been reported as PTP1B inhibitors that control hyperglycemia [7, 9, 10]. Therefore, a 3D structure of the PTP1B enzyme was used as the receptor for the docking studies. The crystal structure of protein tyrosine phosphatase 1B (PDB ID: 2NT7) was downloaded from the protein data bank. Another 3D structure of the enzyme peroxisome proliferator-activated receptor gamma (PPARγ) was also downloaded from the PDB (2XKW) for carrying out additional docking studies with this receptor. Using a protein preparation wizard, bond orders were assigned, hydrogens were added, bonds to metals were deleted, the formal charges on the metal and the neighboring atoms were adjusted, and finally, waters that were more than 5 Å in distance were deleted. The receptor structure was refined by using restrained minimization. The receptor grid was set up and the co-crystallized ligand was excluded for defining the receptor structure. The

grids were defined by keeping the co-crystallized ligand as a center and using the default box size. The XP (extra precision) docking mode of Glide 5.8 (Schrodinger LLC., New York) was utilized for the molecular docking of low-energy conformers into the binding pocket of PTP1B [14–16]. Receptor structure was kept rigid, whereas the ligands were kept flexible during the docking. The final evaluation was done with a glide docking score, and a single best pose was generated for each ligand.

Ligand-receptor binding energy study

The binding free energy of the ligand-receptor complex was determined by using the MM/GBSA (molecular mechanics/generalized born model and solvent accessibility) module of Prime 3.1 (Schrodinger LLC., New York) [17–19].

$$\Delta G_{\text{bind}} = G_{\text{complex}} - G_{\text{receptor}} - G_{\text{ligand}}$$

ΔG_{bind} = Ligand-receptor binding free energy change; G_{complex} = Free energy of ligand-receptor complex; G_{receptor} = Free energy of receptor; G_{ligand} = Free energy of ligand.

ADME prediction study

Qikprop 3.5 (Schrodinger LLC., New York) module was utilized for the prediction of physico-chemical descriptors and pharmacokinetically important properties of the synthesized compounds [20].

Results and discussion

The designed compounds were synthesized by using known synthetic approaches. Thiazolidine-2,4-dione (**1**) was synthesized by condensing chloroacetic acid and thiourea in the presence of conc. HCl. Knoevenagel condensation of thiazolidine-2,4-dione and furan-2-carboxaldehyde was carried out to afford (*Z*)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**2**). Compound **2** was subjected to *N*-alkylation under basic conditions to give the final compounds (**3–10**). The synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopy. The exocyclic double bond was Z-configuration in all the synthesized compounds, which were also supported by the NMR data [21, 22]. The vinylic proton appeared within 7.56–7.64 ppm in ^{1}H-NMR, which confirmed the synthesis of Z-isomers. Disappearance of the NH peak in ^{1}H-NMR and appearance of aliphatic alkyl protons confirmed the synthesis of the final compounds.

In-vivo anti-hyperglycemic activity of the synthesized compounds was carried out using an alloxan-induced diabetic mice model taking pioglitazone as a positive control. The % reduction in blood sugar level of the test compound-treated groups showed similar profile types (Table 1) as that of pioglitazone. The blood sugar level was decreased from 2 up to 4 h and then again gradually increased up to 24 h. The

Table 1 In-vivo anti-hyperglycaemic activity of synthesized compounds

Compounds	Effect of compound **3**–**10** (30 mg/kg) on alloxan-induced diabetic mice				
	2 h	4 h	6 h	24 h	7th day
Control	1.16 ± 0.70	1.35 ± 0.47	2.31 ± 0.42	6.76 ± 1.52	8.02 ± 0.70
Pioglitazone	−36.02 ± 0.87	−44.78 ± 1.66	−40.27 ± 1.49	−34.93 ± 0.79	−34.87 ± 2.15
3	−17.21 ± 1.66	−25.75 ± 1.63	−20.40 ± 2.23	−11.55 ± 0.88	−12.48 ± 1.69
4	−31.83 ± 1.82	−36.38 ± 2.08	−33.12 ± 1.25	−29.58 ± 1.04	−28.82 ± 1.54
5	−14.61 ± 0.98	−23.79 ± 1.15	−16.67 ± 1.49	−8.24 ± 2.00	−9.89 ± 1.50
6	−11.9 ± 1.46	−17.73 ± 1.47	−14.74 ± 1.83	−10.80 ± 2.07	−8.93 ± 1.53
7	−21.88 ± 1.49	−28.30 ± 1.73	−27.21 ± 1.30	−20.21 ± 1.47	−17.62 ± 1.88
8	−12.13 ± 1.14	−18.54 ± 1.53	−19.86 ± 1.60	−9.10 ± 2.27	−9.95 ± 1.41
9	−35.51 ± 1.47	−43.72 ± 2.08	−39.43 ± 0.94	−30.06 ± 1.35	−34.92 ± 1.15
10	−37.89 ± 1.13	−43.11 ± 1.56	−39.39 ± 1.74	−31.83 ± 1.62	−32.97 ± 1.52

most pronounced effect was obtained after 4 h of treatment with the test compounds. After 7 days of treatment, the % reduction in blood sugar level ranged from 8.93 to 34.97 as compared to 34.87 for pioglitazone. Compounds **9** and **10** were observed to lower the blood sugar level by 32.85 and 34.97 %, respectively, and are comparable to the in-vivo activity of standard drug pioglitazone. The in-vivo data was depicted in (Fig. 2). At 4 h, the decrease in sugar level was the same for compound **10** and pioglitazone. A probability (*P*) value of less than 0.05 indicated a statistically significant difference between the treatment groups.

The probable binding conformation of the active compounds (**9** and **10**) in the binding pocket of PTP1B was studied by docking. A common binding orientation of all the ligands was observed inside the PTP1B active site. Both compounds **9** and **10** have shown H-bonding interaction with the catalytic active site residue Gly220. The top-ranked binding pose of the active compounds and docking interactions of

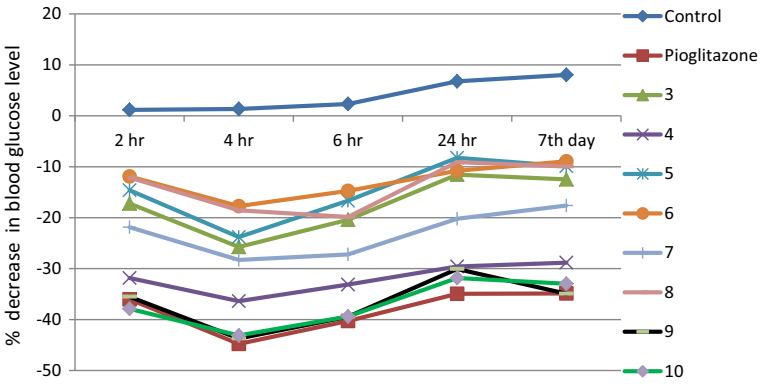


Fig. 2 Graphical representation of in-vivo anti-hyperglycemic activity of synthesized compounds

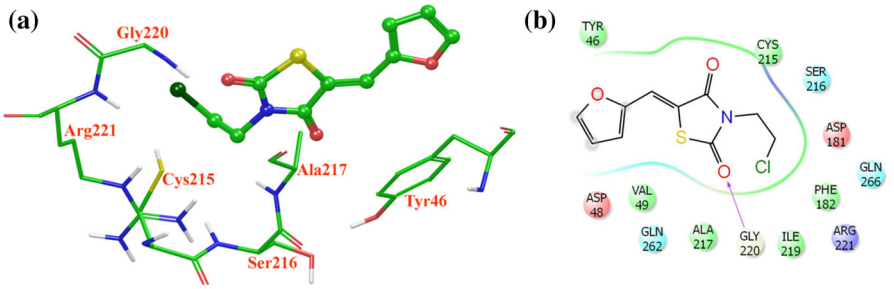


Fig. 3 Binding pose of compound **9** and docking interactions inside the binding pocket residues of PTP1B

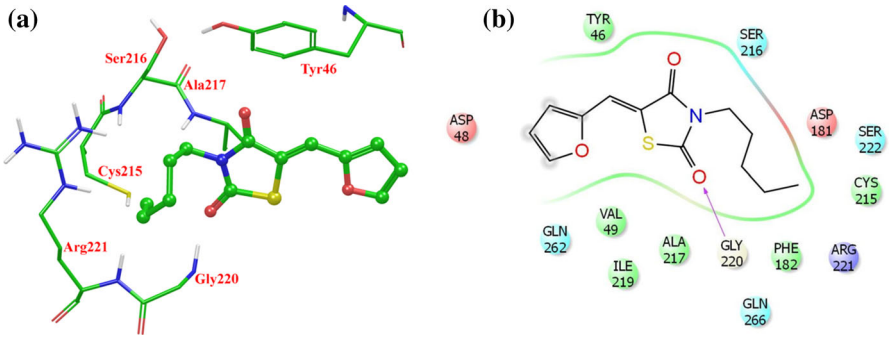


Fig. 4 Binding pose of compound **10** and docking interactions inside the binding pocket residues of PTP1B

compound **9** and **10** were depicted in (Figs. 3, 4), respectively. The amidic nitrogen of the TZD ring was found away from the catalytic residues site (His214–Arg221), and the N-alkyl region did not show any H–bonding network with binding site residues. This may be due to the substitution of amidic nitrogen with lipophilic alkyl groups.

These compounds have been additionally docked with PPAR gamma (2XKW), the X-ray structure of which was available in the protein data bank. The docking scores ranged from −5.7 to −5.0 (PPARγ) as compared to −3.8 to −2.7 (PTP1B), suggesting that the synthesized compounds more favorably interacted with PPAR gamma than with PTP1B.

The docking results were quantified in terms of ΔG binding energy, ΔG bind coulomb, Δ*G* bind H-bond, Δ*G* bind Lipo, and Δ*G* bind VdW. The Δ*G* binding energy of the ligand-receptor complex showed good correlation with their docking score and measured the ligand-receptor affinity. For the present compounds, binding energy ranged from −60.426 to −43.16 kcal/mol. The binding free energy of the ligand-receptor complex was determined by MM/GBSA method and was presented in Table 2.

Table 2 Binding free energy study of ligand-receptor complex

Compound	MMGBSA_dG_Bind	MMGBSA_dG_Bind_Coulomb	MMGBSA_dG_Bind_Covalent	MMGBSA_dG_Bind_Hbond	MMGBSA_dG_Bind_Lipo	MMGBSA_dG_Bind_vdW
3	−48.704	−9.776	0.227	−0.843	−27.219	−34.093
4	−57.006	−14.736	1.911	−0.79	−37.566	−34.152
5	−51.671	−12.799	3.898	−0.78	−31.735	−35.313
6	−52.851	−10.019	0.791	−0.929	−31.339	−36.603
7	−46.419	−10.783	4.131	−0.729	−32.767	−33.675
8	−43.16	−10.993	0.842	−0.775	−22.369	−30.751
9	−60.426	−16.568	−0.004	−0.831	−34.337	−34.471
10	−50.849	−9.283	3.392	−0.719	−35.081	−32.257

Table 3 Predicted ADME parameters

Compound	QPlogPw	QPlogPo/w	QPlogS	QPPCaco	QPlogBB	% Human oral absorption	Rule of five	Rule of three
3	5.27	1.969	−2.147	1403.647	−0.289	94.803	0	0
4	5.216	2.803	−3.434	1408.958	−0.219	100	0	0
5	5.153	2.536	−2.945	1404.322	−0.183	100	0	0
6	5.13	2.27	−2.644	1408.219	−0.377	96.593	0	0
7	4.989	2.666	−3.107	1408.827	−0.466	100	0	0
8	5.516	1.549	−2.062	1052.907	−0.32	90.11	0	0
9	5.358	2.449	−2.974	1405.442	−0.132	100	0	0
10	4.848	3.061	−3.571	1408.842	−0.554	100	0	0

The ADME prediction study helps in generating drug-like candidates that are less likely to be rejected during clinical trials. A number of physico-chemical and pharmacokinetic descriptors (QPlogPw, QPlogPo/w, QPlogS, QPPCaco, QPlogBB, % Human oral absorption, rule of five, and rule of three) were predicted. The ADME parameters were within the acceptable range defined for human use, exhibiting their druggable nature, and were presented in Table 3.

Conclusion

A series of *N*-substituted 5-(furan-2-ylmethylene)thiazolidine-2,4-dione derivatives were synthesized and tested in vivo for anti-hyperglycaemic activity. Introduction of chloroethyl and pentyl group on amidic nitrogen of TZD produced (*Z*)-3-(2-chloroethyl)-5-(furan-2-ylmethylene)thiazolidine-2,4-dione (**9**) and (*Z*)-5-(furan-2-ylmethylene)-3-pentylthiazolidine-2,4-dione (**10**), respectively, which were found to be significantly potent like pioglitazone. Additional docking studies were also carried out to predict the binding nature of these compounds inside the binding pocket of the PTP1B enzyme. These preliminary results would be helpful in designing and optimizing a more potent TZD scaffold containing anti-hyperglycemic agents.

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