SYNTHESIS, MOLECULAR DOCKING STUDIES AND BIOLOGICAL EVALUATION OF 5-[4-(SUBSTITUTED) BENZYLIDENE OR BENZYL] THIAZOLIDINE-2, 4-DIONE WITH THEIR ORAL HYPOGLYCEMIC ACTIVITY

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ABSTRACT

A new series of 5-[4-(substituted) benzylidene or benzyl] thiazolidine-2, 4-dione (TZDs) have been synthesized using economical synthetic routes. The aim of the synthesis based on modification of linker region and effector region of rosiglitazone. Among these newly synthesized compounds, based on their docking results, some compounds were selected for study of oral hypoglycemic activity on fructose induced hyperglycemia in Wistar rats. The results of selected compounds shows that, 5-[4-(2-amino-5-ethoxypyridine) sulphonyl benzylidene] thiazolidine-2, 4-dione and 5-[4-(2-amino-5-ethoxypyridine) ethoxy benzyl] thiazolidine-2, 4-dione have appreciable blood glucose-lowering effect compared to that of the reference drug, pioglitazone. Out of these two compounds, 5-[4-(2-amino-5-ethoxypyridine)ethoxy benzyl] thiazolidine-2, 4-dione shows better hydrogen bond interaction with amino acid residues of peroxisome proliferator activated receptor-gamma (PPAR γ) and also shows better oral hypoglycemic activity in this series.

Keywords: Thiazolidinediones (TZD's), Hyperglycemia, Docking, oral hypoglycemic activity.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder that affects 90 % of total diabetic population. This disease¹ is primarily characterized by insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion and hyperglycemia². Hyperglycemia should be controlled in a careful manner, otherwise higher morbidity and mortality have been found in the related diseases like retinopathy, nephropathy, neuropathy, dyslipidemia, coronary heart disease, hypertension and obesity. Many targets have been investigated to cure type II diabetes³. Among these targets, TZDs or glitazones⁴ are synthetic, high-affinity ligands of peroxisome proliferator activated receptor-gamma (PPAR γ)⁵. Of the thiazolidine-2, 4-dione compounds^{6,7}, pioglitazone and rosiglitazone are selective PPAR γ agonists⁸. Further comparative studies of both glitazones, rosiglitazone is associated with a significantly increased the risk of myocardial infarction, heart failure and death as a result of cardiovascular complication^{9,10}. A survey of TZDs class of PPAR γ agonists, three-dimensional quantitative structure-activity-relationships (3D-QSAR) studies and crystal structure information reveal that the pharmacophoric feature of these agents essentially consists of three parts: (i) an acidic head group, (ii) central aromatic region and (iii) a lipophilic side chain¹¹. The acidic head group containing TZD ring of rosiglitazone makes several specific hydrogen-bonding interactions, hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) with His449, Tyr473, His323, Ser289 and Gln286 protein residues of PPAR γ receptor (Figure 1)¹². A lipophilic side chain is an effector region of the PPAR γ receptor, which modifies the pharmacokinetic and toxicity profiles. This is an important region of the molecule where wide choice of lipophilic substituents can be made to design better antihyperglycemic agents. And there is linker region, which containing central aromatic ring is essential for activity. Because this region has a limited space and hence large substituted fragments in the central aromatic region leads to reduced activity¹³. Based on this conclusion, the present invention was aimed at the modification of effector

site and linker region of rosiglitazone without modification of TZDs towards development of better and safer glitazones than the available ones (Figure 1).

MATERIALS AND METHODS

All the solvents used were of analytical grade. Reactions were monitored with the help of thin layer chromatography using precoated silica gel as stationary phase, using appropriate solvent system as mobile phase and iodine vapors as visualizing agent. Melting points were determined in Elico melting point apparatus and are uncorrected. IR spectrum of all compounds was recorded on Shimadzu FTIR-8400S Spectrophotometer (MVPS's College of Pharmacy, Nashik, India) by using KBr pellet and values are expressed in cm⁻¹. NMR spectra were recorded on BROOK spectrophotometer (Analytical center, University of Pune, Pune, India) by using varian 800 MHz in DMSO-d₆ as solvent and chemical shift are reported in δ ppm. Mass spectrum were recorded on Shimadzu QP2010 (MGV college of Pharmacy, Nashik, India) and mass values were reported in m / z. The general strategies for synthesis of some new 5-[4-(substituted) benzylidene or benzyl] thiazolidine-2, 4-dione derivatives are illustrated in scheme 1 and 2 respectively. Structure of final compounds was shown in Table 1.

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

By cyclo addition of 1, 3 dipolar procedures reported in literature¹⁴.

Synthesis of 5-benzylidenethiazolidine-2, 4-dione (2)

Knoevenagel condensation reaction takes place between thiazolidine-2, 4-dione and benzaldehyde by using weakly basic amine as a catalyst (piperidine) and toluene as solvent¹⁴.

Synthesis of 5-(4-chlorosulphonyl benzylidene) thiazolidine-2, 4-dione (3)

Chlorosulphonation reaction with 5-benzylidenethiazolidine-2, 4-dione using chlorosulphonic acid¹⁴.

General Procedure for Synthesis of 5-[4-(substituted) sulfonyl benzylidene] thiazolidine-2, 4-dione (4a-4d)

Nucleophilic displacement reaction with 5-(4-chlorosulphonyl benzylidene) thiazolidine-2, 4-dione using primary amine containing substituted pyridine rings (R)¹⁴.

4a: M.p - 240⁰c, Yield – 65 %, R_f - 0.48, IR (KBr, cm⁻¹) 3389 (N-H TZD), 3245 (N-H sulfonamide), 3049 (C-H Ar), 1745 (C=O), 1606 (C=C Ar), 1437 (C=C, C=N pyridine), 1327 (S=O), 688 (C-S-C TZD).

4b: M.p - 208⁰c, Yield – 74 %, R_f - 0.53, IR (KBr, cm⁻¹) 3379 (N-H TZD), 3250 (N-H sulfonamide), 3051 (C-H Ar), 1749 (C=O), 1610 (C=C Ar), 1437 (C=C, C=N pyridine), 1331 (S=O), 1038 (C-Br Ar) 692 (C-S-C TZD).

4c: M.p - 170⁰c, Yield – 73 %, R_f - 0.83, IR (KBr, cm⁻¹) 3385 (N-H TZD), 3248 (N-H sulfonamide), 3050 (C-H Ar), 1748 (C=O), 1611 (C=C Ar), 1435 (C=C, C=N pyridine), 1329 (S=O), 1037 (C-Br Ar) 691 (C-S-C TZD), ¹H NMR (δ ppm): 8.4 (s, 1H, NH, TZD), 8.1 (s, 1H, NH, sulfonamide), 7.7 (t, 1H, pyridine), 7.4 (d, 1H, pyridine), 7.2 (d, 2H, 3 and 5 position, Ar.), 7.0 (d, 2H, 2 and 6 position, Ar.), 6.8 (d, 1H, pyridine), MS (m/z): 440 (M)⁺.

4d: M.p - 160⁰c, Yield – 75 %, R_f - 0.92, IR (KBr, cm⁻¹) 3386 (N-H TZD), 3251 (N-H sulfonamide), 3052 (C-H Ar), 1750 (C=O), 1612 (C=C Ar), 1436 (C=C, C=N pyridine), 1332 (S=O), 1230 (C-O-C Ar) 694 (C-S-C TZD), ¹H NMR (δ ppm): 8.5 (s, 1H, NH, TZD), 7.9 (s, 1H, NH, sulfonamide), 7.3 (d, 2H, 3 and 5 position, Ar.), 7.0 (d, 2H, 3 and 5 position, Ar.), 6.8 (d, 1H, pyridine), 6.6 (d, 1H, pyridine), 6.1 (s, 1H, pyridine), 3.99 (q, 2H, ethoxy-CH₂), 2.5 (t, 3H, ethoxy-CH₃).

Synthesis of 4-[2-(bromoethoxy)] acetanilide (6)

To dry ethanol (533 ml), sodium metal (20.4 g, 0.88 mol) was added slowly in small pieces. Then the resulting hot reaction mixture was cooled on a water-bath. Above cooled mixture, paracetamol (120 g, 0.88 mol) was added followed by slow addition of ethylene dibromide (153 g, 0.88 mol). Then the reaction mixture was refluxed for 3-4 h. After completion of the reaction, the reaction mixture was dumped into ice cold water, and the precipitated solid was collected by filtration under suction. Yield 65 %.

General Procedure Synthesis of 4-[2-(substituted) ethoxy] acetanilide (7a-7d)

To a solution of a primary amine containing substituted pyridine rings (R) (0.025 mol) in dry Dimethylformamide (37.5 ml) at 25⁰C was added an appropriate base (0.027 mol) and the reaction mixture stirred for 0.25-1 h. A solution of 4-[2-(bromoethoxy)] acetanilide (0.025 mol) in dry Dimethylformamide (12.5 ml) was added and stirred further 0.25-6 h. The reaction mixture was dumped into ice cold water and precipitated solid was filtered under suction and dried in oven. Yield 67 to 75 %.

General Procedure Synthesis of 4-[2-(substituted) ethoxy] aniline (8a-8g)

A mixture of 4-(2-(substituted) ethoxy) acetanilide (0.016 mol), 4N potassium hydroxide (75 ml) and ethanol (75 ml) was refluxed for 24 h and dumped in ice cold water and precipitated solid were filtered and dried in oven. Yield 35 to 40 %.

General Procedure Synthesis of Methyl-2-bromo-3-[4-(substituted) ethoxybenzyl] propionate (9a-9d)

Meerwein arylation of 4-[2-(substituted) ethoxy] aniline take place in presence of sodium nitrite, aqueous hydrobromic acid, methyl acrylate and powdered cuprous oxide¹⁵.

General Procedure Synthesis of 2-imino-5-[4-(substituted)ethoxybenzyl] thiazolidine-2,4-diones (10a-10d)

Methyl-2-bromo-3-[4-(substituted) ethoxybenzyl] propionate converted into imines form by using thiourea and sodium acetate¹⁵.

General Procedure Synthesis of 5-[4-(substituted) ethoxybenzyl] thiazolidine-2, 4-diones (11a-11d)

In the presence of 2 N ethanolic hydrochloric acid solution, hydrolysis of 2-imino-5-[4-(substituted) ethoxybenzyl] thiazolidine-2, 4-diones take places¹⁵.

11a: M.p - 220⁰c, Yield – 62 %, R_f - 0.15, IR (KBr, cm⁻¹) 3420 (N-H TZD), 3345 (N-H sec.amine of ethoxy linkage), 3010 (C-H Ar), 2958 (C-H alkane) 1740 (C=O), 1600 (C=C Ar), 1432 (C=C, C=N pyridine), 1334 (C-N sec. amines), 1032 (C-O-C phenyl alkyl ether) 735 (C-S-C TZD).

11b: M.p - 270⁰c, Yield – 60 %, R_f - 0.30, IR (KBr, cm⁻¹) 3425 (N-H TZD), 3350 (N-H sec.amine of ethoxy linkage), 3015 (C-H Ar), 2963 (C-H alkane) 1745 (C=O), 1620 (C=C Ar), 1433 (C=C, C=N pyridine), 1339 (C-N sec. amines), 1064 (C-Br Ar) 1037 (C-O-C phenyl alkyl ether) 740 (C-S-C TZD).

11c: M.p - 265⁰c, Yield – 60 %, R_f - 0.43, IR (KBr, cm⁻¹) 3424 (N-H TZD), 3344 (N-H sec.amine of ethoxy linkage), 3014 (C-H Ar), 2963 (C-H alkane) 1744 (C=O), 1610 (C=C Ar), 1434 (C=C, C=N pyridine), 1338 (C-N sec. amines), 1063 (C-Br Ar) 1036 (C-O-C phenyl alkyl ether) 739 (C-S-C TZD).

11d: M.p - 240⁰c, Yield – 62 %, R_f - 0.62, IR (KBr, cm⁻¹) 3423 (N-H TZD), 3343 (N-H sec.amine of ethoxy linkage), 3013 (C-H Ar), 2951 (C-H alkane) 1743 (C=O), 1603 (C=C Ar), 1436 (C=C, C=N pyridine), 1337 (C-N sec. amines), 1265 (C-O-C Ar) 1035 (C-O-C phenyl alkyl ether) 738 (C-S-C TZD). ¹H NMR (δ ppm) 8.80 (s, 1H, NH, TZD), 8.50 (s, 1H, pyridine), 8.2 (d, 1H, pyridine) 7.7 (s, 1H, pyridine), 7.29 (d, 2H, 3 and 5 position, Ar.), 6.92 (d, 2H, 2 and 6 position, Ar.), 4.52 (t, 1H, CH, TZD), 4.02 (t, 2H, αH to oxo, ethoxy), 3.90 (q, 2H, CH₂, ethoxy), 3.20 (m, 2H, α H to amino ethoxy) 2.60 (t, 3H, CH₃, ethoxy) 0.88 (s, 1H, NH, sec.amine), MS (m/z): 387 (M)⁺.

Molecular Docking Studies**Ligand Preparation**

The ligands were prepared using Lig prep 2.5 module of the Schrodinger suite using OPLS-2005 force field.

Protein Preparation

The structure of PPAR-γ protein (PDB ID: 2PRG) was download from the protein data bank, <http://www.rcsb.org/pdb>, where the residues were bonded more closely to the rosiglitazone agonist, co-crystallized with PPAR-γ. In this crystal structure, the LBD forms a homodimer in which both monomers have nearly identical Cα conformations. The structure of the “A” monomer of the LBD homodimer was chosen as the target for docking studies. The rosiglitazone agonist was extracted from the complex structure of the “A” monomer of the LBD homodimer. The structure of the “A” monomer of the LBD

homodimer was prepared by multistep process through the protein preparation wizard of maestro 9.2.

software of Schrodinger Maestro Module Glide Version 9.2^{16,17}.

Docking Studies

Docking studies on LigPrep treated ligands were carried out to predict the binding pocket of 2PRG using the docking program, Glide used a series of hierarchical filters to search for possible locations for the ligand in the active site region of the receptor. For the grid-based ligand docking, the receptor grid generation file was used. For protein structure, during the calculations of active site was determined within a grid box of X = 49.19, Y = -37.08, Z = 19.00 and grid box range X = 24.30, Y = 24.30, Z = 24.30 with a (default inner box) grid box ligand range X = 10, Y = 10, Z = 10 was centered on the corresponding co-crystallized ligand. Default parameters were used and no constraints were included. All prepared ligands were docked using the standard precision (SP). The docking analyses of synthetic compounds, pioglitazone and rosiglitazone were carried out on docking

Anti-hyperglycemic Activity Evaluation

The compounds 4a-4d and 11a-11d was evaluated for their antihyperglycemic activity in fructose-induced hyperglycemia Male albino rats of Wistar strain. The rats weighing in the range (130-230 g) from Bharat Serum Vaccine Put Ltd, Thane and maintained at 25 ± 2 °C and also its relative humidity (50 ± 5 %) with 12 h light / 12 h dark cycles. The rats were given standard laboratory chow and water ad libitum. The Institutional Animal Ethical Committee of MVPS's College of Pharmacy approved the proposal. Fructose and Pioglitazone were purchased from Merck laboratory. Glucose estimation kits were from Accusure, TaiDoc Technology Corporation, Taiwan. Reagents and chemicals used in the study were of analytical grade. Test agents and standard drug were formulated in suspension by using 2 % w / v sodium carboxy methyl cellulose (CMC) and distilled water before dosing.

Table 1: Physical Characterization of All Synthesized TZDs Compounds

Comp Code	R	X	Double Bond	Protein Residues	H-bond Length	Docking Score
4a		-SO ₂ -	Yes	Ser 289	2.067	-9.206
				His 449	2.350	
				Tyr 473	2.473	
4b		-SO ₂ -	Yes	Ser 289	2.043	-9.344
				His 449	2.396	
4c		-SO ₂ -	Yes	Gln 286	2.064	-9.070
				His 449	2.348	
				Tyr 473	2.471	
4d		-SO ₂ -	Yes	Ser 289	2.053	-9.156
				His 449	2.397	
				Tyr 473	2.499	
11a		-OC ₂ H ₅ -	No	Gln 286	1.770	-10.727
				Ser 289	2.041	
				His323	2.114	
				Tyr 473	2.398	
11b		-OC ₂ H ₅ -	No	Gln 286	2.045	-10.481
				Ser 289	1.774	
				His323	2.112	
				Tyr 473	2.410	
11c		-OC ₂ H ₅ -	No	Gln 286	2.049	-10.377
				Ser 289	1.760	
				His323	2.100	
				Tyr 473	2.389	
11d		-OC ₂ H ₅ -	No	Gln 286	2.077	-10.518
				Ser 289	1.761	
				His323	2.065	
				Tyr 473	2.374	
	Pioglitazone			Gln 286	2.083	-10.734
				Ser 289	1.758	
				His323	2.095	
				Tyr 473	2.377	

Table 2: Anti Hyperglycemic Effect of Test Compounds and the Standard Drug Pioglitazone in Fructose Loaded Hyperglycemic Rats

Groups	Blood glucose level (mg / dl)		
	0 h	2 h	5 h
Normal control	93.50 ± 2.28	94.16 ± 1.88	96.58 ± 2.24
Positive control	153.20 ± 0.98	155.90 ± 1.68	152.12 ± 2.30
Pioglitazone	152.80 ± 1.92	104.72 ± 1.79 ^a	108.36 ± 2.14 ^a
Test compound 4d	147.00 ± 1.86	124.60 ± 2.21 ^a	109.20 ± 2.40 ^a
Test compound 11a	157.62 ± 2.08	113.32 ± 1.73 ^a	120.40 ± 2.26 ^a
Test compound 11b	154.78 ± 1.65	112.28 ± 2.87 ^a	119.60 ± 2.29 ^a
Test compound 11c	150.87 ± 2.72	126.84 ± 2.94 ^a	124.60 ± 2.29 ^a
Test compound 11d	152.02 ± 2.19	107.80 ± 1.61 ^a	105.00 ± 2.70 ^a

Test compound = 100 mg / kg, p.o. Reference standard, Pioglitazone = 20 mg / kg, p.o. The results are expressed as mean ± SEM. The data is analyzed using one-way Analysis of Variance (ANOVA) followed by Dunnett's test. ($n = 5$), ^a Pioglitazone and test compounds compared to positive control ($P < 0.05$).

Figure-1: Based on 3DQ SAR correlations, designed of 5-[4-(substituted) benzylidene or benzyl] thiazolidine-2,4-dione

Scheme 2. Reagents and conditions : (i) Ethylene dibromide, NaOC₂H₅, reflux, 3-4 h; (ii) Primary amine substituted pyridine rings, DMF, base, stir, then DMF, 4-[2-(bromo ethoxy)]acetanilide, stir, 6 h; (iii) 4N ethanolic KOH, reflux, 24 h; (iv) Aqueous HBr, NaNO₂, then methyl acrylate, Cu₂O; (v) thiourea, sodium acetate, reflux; (vi) EtOH, conc. HCl, reflux.

Figure 2: Hydrogen Bond Interactions between (S) 5-[4-(2-amino-5-ethoxy pyridine) ethoxy benzyl] thiazolidine-2, 4-dione (11d) and PPAR-γ

Figure 3: Hydrogen Bond Interactions between (S) Pioglitazone and PPAR-γ

Fructose-induced Hyperglycemia in Rats

Animals were divided into four groups, a normal control, positive control, standard drug and test compounds. Each groups (i.e. normal control, positive control and standard drug) and sub-groups of test compound 4g and 11a-11d were consisting of five rats per group. The normal control group fed with normal diet without fructose, it was also given sodium carboxy methyl cellulose (2 % w / v) in distilled water through oral gavage. Whereas, all remaining groups fed with normal diet 40 % w / v aq. fructose solution (4 g / kg / day), by oral gavage for 0-21 days. The induction of hyperglycemia was confirmed by measuring the blood glucose level on 0, 7, 14 and 21 day of the experiment. On 21st day, all groups of rats were fasted for 8 h at night. After which blood glucose levels of all animals were measured (taken as 0 h) and immediately thereafter drug treatment was given orally at earlier desired dose levels and followed by monitoring of blood glucose level at different time interval 2 and 5 h (Table 2).¹⁸

RESULTS AND DISCUSSION

The selection of effector site R of newly synthesized TZD's compounds is based on effector site of rosiglitazone. The linker moiety is also changed; para sulphonyl benzylidene is replaced in some compounds by ethoxybenzyl linkage, to study its effect on SAR. Because, the nitrogen of primary amine containing various substituted pyridine moieties so that the acidity of the hydrogen of amino group and TZD moiety changes marginally that may have effect in binding of molecule with the receptor. Like many other TZDs reported in literature, the activity of TZDs compounds probably depend on two parameters, these are docking score and specific hydrogen bonds interaction. Higher negative value of docking score indicated enhanced binding affinity of the ligand with the receptor. While TZD acidic head group allowing several specific hydrogen-bonding interactions with His449, Tyr473, His323, Ser289 and Gln286 residues and producing quite significant activity. These hydrogen bond interactions indicating that if the hydrogen bond interaction was more, the binding affinity of the ligand was higher. The docking score, specific hydrogen bond interactions and hydrogen bond (H-bond) length profile of all compounds 4a-4d and 11a-11d was compared with the profile of the pioglitazone molecule are listed in Table 1. Based on the comparative study, selection of some compounds 4d and 11a-11d, testing of their oral hypoglycemic activity, were reported in Table 2. The results of Table 2 indicate that, compounds 4d and 11a-11d were significantly ($p < 0.05$) reduce the rise in blood glucose levels in comparison with positive control group. Out of these selected compounds 4d and 11a-11d activity studies, compound 4d shows less significant activity after 2 h in comparisons with test compound 11d and standard drug containing pioglitazone. This compound 4d also shows closely similar activity after 5 h in comparison with the activity of standard drug of pioglitazone at considerably higher doses. The compound 11d have more appreciable blood glucose-lowering effect compared to that of the reference drug, pioglitazone after 2 h and 5 h at considerably higher doses (100 mg / kg body weight). Analysis of docking results of the compounds (Table 1), compound 11d (Figure 2) shows H-bond interactions was more at head end and also show the binding affinity of this ligand was higher. Because, H-bond interaction of compound 11d with protein residues of PPAR- γ same as standard drug pioglitazone (Figure 3). But the distance of compound 11d H-

bond is less compared with standard drug. This less distance of compound 11d indicate that, the presence of favorable interactions between ligand 11d and receptor of PPAR- γ . Probably based on this region, compound 11d shows more effective binding with PPAR- γ than standard drug, pioglitazone. The result of blood glucose lowering effect (Table 2) shows compound 11d and standard drug pioglitazone have closely similar effect. But, considerably at higher dose this may be due to differences in H-bonding and other bonding of compound 11d at central flat ring and tail end of the molecule.

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