



Synthesis and Evaluation of Some New (E)-5-((E)-4-((E)-Benzylidene amino) Benzylidene) Thiazolidine-2,4-Dione Analogs as Aldose Reductase Inhibitors

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Received: 10 Oct 2018/ Accepted: 8 Nov 2018/ Published online: 01Jan 2019

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Abstract

Aldose reductase (ALR) enzyme plays a significant role in conversion of excess amount of glucose into sorbitol in diabetic condition through polyol pathway and responsible for the secondary complications. Thus, the inhibition of aldose reductase has basic approach to the prevention and treatment of diabetic complications. In this work we described the synthesis and the functional evaluation of a series of substituted (E)-5(4-aminobenzylidene) thiazolidine-2,4-dione (Ta 01-11) were synthesized and tested for in vitro aldose reductase inhibitory activity. ARI activity of synthesized compounds was found in the range of 38.29-69.12% at 10 µg/mL. Similarly, synthesized compounds decrease blood glucose level in the range of 130.20-173.20mg/dl at 15 mg/kg body weight. Hence (E)-5-((E)-4-((E)-benzylideneamino)benzylidene) thiazolidine-2,4-dione derivatives newer analogs shows comparable ARI as well as antidiabetic activity and devoid from the toxicity.

Keywords

Aldose reductase inhibitors, Diabetes mellitus (DM), 2, 4-thiazolidinedione.

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic metabolic disorders, characterized by elevated levels of blood glucose. According to WHO Global report on diabetes, the prevalence has been increasing frequently all over the world. It is estimated that 366 million people had diabetes in 2011; by 2030 this would have risen to 552 million.

The number of people with type 2 diabetes is increasing in every country with 80% of people with DM living in low- and middle-income countries. Diabetes caused 4.6 million deaths in 2011.¹ It is estimated that 439 million people would have type 2 diabetes by the year 2030. 2, 3 Diabetes is related with long-term complications due to uncontrolled

hyperglycemia lead to several diabetic complications such as retinopathy neuropathy, cataracts, nephropathy, and cardiovascular complication. Aldose reductase (AR) is plays a key role in development of secondary diabetic complications via polyol pathway.⁴ Aldose reductase (AR, EC 1.1.1.21) is the first and rate-controlling enzyme, in polyol pathway and in turn it has been a potential target for drug design therefore the inhibition of aldose reductase has been a safe approach to the prevention and treatment of diabetic complications.

Aldose reductase (AR; EC 1.1.1.21) is vital member of NADPH dependent aldo-keto reductase family. It is anacytosolic, monomeric oxidoreductase enzyme. This catalyzes the conversion of the glucose into sorbitol in first and rate-limiting step of polyol pathway. This is glucose metabolism^{5, 6, 7}. AR not only reduces the glucose into sorbitol although also reduces the production of toxic aldehydes^{8, 9}. In normal conditions, aldose reductase has low affinity for glucose, with so small percentage of total glucose (less than 3%), converted into sorbitol via this pathway.

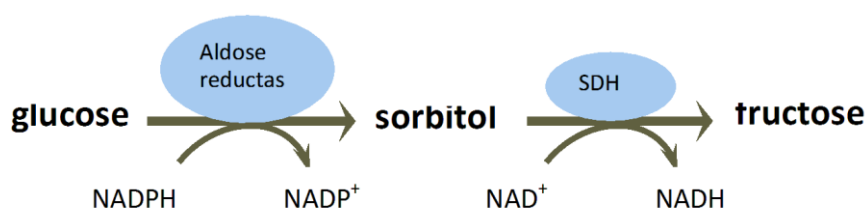


Fig1: Polyol pathway

In hyperglycemic conditions, there is an enhancement in enzymatic activity and production of sorbitol and result of this is overall reduction in NADPH¹⁰. Since increased polyol pathway flux leads to the accumulation of sorbitol in lens fiber. It leads to osmotic imbalances and oxidative stress. It causes swelling of fiber cell, liquefaction and development of cataract.¹¹ Hence, reduction of hyperglycemia induced polyol pathway flux by AR inhibitors (ARIs) might be a potential therapeutic opportunity for the treatment and prevention of diabetic complications. ARIs might be an emerging target for the management of complications developed by diabetes, by means of reduction of sorbitol flux through polyol pathway. Structurally, ARIs include carboxylic acid derivatives such as Epalrestat, Alrestatin, Zopalrestat, Zenarestat, Ponalrestat, Lidorestat, and Tolrestat), spirohydantoin and related cyclic amides such as Sorbinil, Minalrestat, and Fidarestat and phenolic derivatives (related to Benzopyran-4-one and Chalcone). Among these inhibitors, Epalrestat is the only commercially available inhibitor till date.¹² There is a need of a potent, selective aldose reductase inhibitors for the management of diabetic complication. Therefore, it is worthwhile to develop new analogues of aldose reductase inhibitors which are devoid from the toxicity. In previous work, numerous 5-arylidene-2, 4-thiazolidinediones derivatives synthesized and evaluated considerable ALR inhibition, but their

effectiveness generally decreases in vivo, probably due to their poor penetrability to key target tissues, in particular, peripheral nerves. Thus, the aim of this work to develop new ARIs, active on relevant targets involved in the control of glucose level to hyperglycemic conditions, are presented as promising antidiabetic compounds. In this study, new active analogs of 5-arylidene-2, 4-dioxothiazolidines were identified and synthesized as potent ARI. In particular, 5-benzylidene moieties bearing substituted benzaldehyde gives respective imine derivatives (Schiff bases), which is potentially able to enhance stability or interaction of enzyme-inhibitor complex.

MATERIAL AND METHODS

Chemistry

All the chemicals used in the synthesis of designed compounds were of synthetic grade, and they were procured from Loba, Highmedia, and E. Merck. Reactions were monitored by thin layer chromatography (TLC) using silica gel-G on glass plate in different solvent systems. Iodine vapor and UV detector (long wavelength) were used as detecting agents. The purification of reaction intermediates and final compounds was carried out through recrystallization and column chromatography technique. For the purpose of chromatography glass column (high 18" with internal diameter 20 mm), column grade silica gel mesh #240-

400 as the stationary phase and appropriate solvent system as mobile phase were used. The melting points of synthesized compounds and intermediates were determined by open capillary method, which were uncorrected. The absorption maxima (λ_{max}) of the intermediate and synthesized compounds were determined on Shimadzu 1800 UV-visual © 2018 spectrophotometer by scanning the compound between 200 and 400 nm in methanol. IR spectra recorded on Shimadzu 8400s from BR Nahata college of Pharmacy, Mandsaur(M.P.) The samples for NMR and Mass were tested to IIT Indore, and nuclear magnetic resonance (Chemical shifts are given in δ units (ppm) relative to internal standard tetramethylsilane and refer to dimethyl sulfoxide (DMSO)-D6 solutions.

General method of synthesis

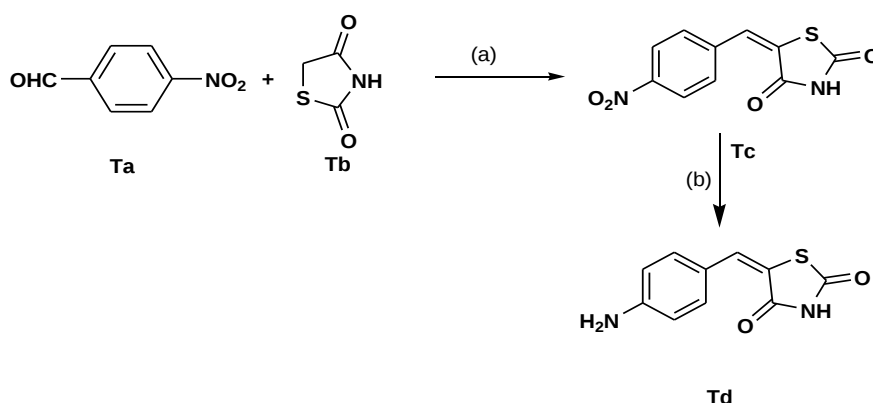
Synthesis of (E)-5-(4-nitrobenzylidene) thiazolidine 2-4 dione derivatives (C)

All the thiazolidinedione derivatives (Tf1–Tf6) were synthesized by Knoevenagel condensation¹³ by reacting equimolar concentration of derivative of 4-nitro benzaldehyde (0.025 mol) and

thiazolidinedione, (0.025 mol) were taken in round-bottomed flask containing glacial acetic acid. To this, a catalytic amount of sodium acetate (0.080 g) was added. The reaction mixture was stirred and heated at 100-105°C for 10-12 hrs. Progress of the reaction mixture was checked through TLC. After completion of reaction, the mixture was kept aside for overnight at RT. The crystalline product was filtered, washed with cold acetic acid and used in next step (Scheme 1).

Synthesis of (E)-5-(4-aminobenzylidene) thiazolidine-2, 4-dione (D)

The crude compound C (0.025 mol) and granulated tin (0.038 mol), were taken in round-bottomed flask equipped with reflux condenser. 10 mL concentrated hydrochloric acid was added in step to control vigorous reaction. After complete addition of HCl, the reaction mixture was heated on water bath and progress of the reaction mixture was checked through TLC. After completion of reaction gradually sodium hydroxide solution (7.5 g in 12 mL water) was added and amine was separated out. Synthesis of substituted

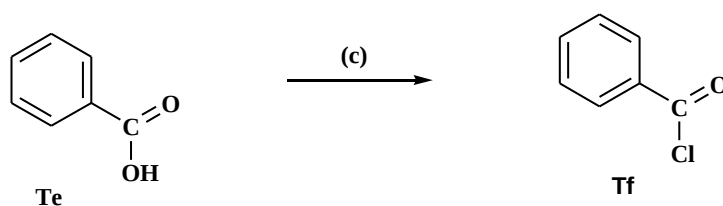


Scheme1: Reagents and conditions: (a) CH₃COONa, CH₃COOH, Reflux; (b) Tin granules, HCl, Heat, NaOH

Synthesis of benzoyl chloride (Tf)

Benzoic acid (0.01 mol) were refluxed with thionyl chloride for 3-4 hrs, and the reaction was monitored

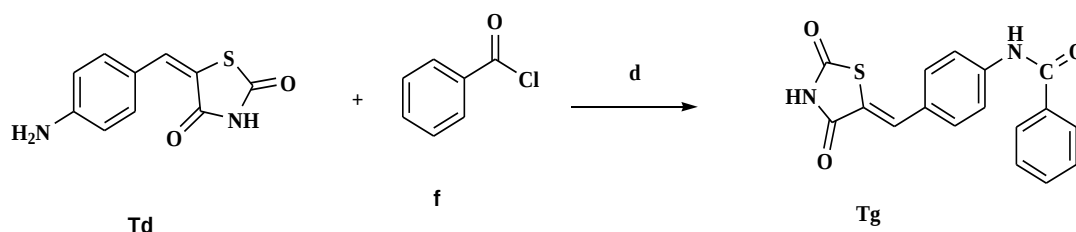
through TLC. After completion of reaction, evaporate excess of thionyl chloride under reduced pressure, and the crude solid was used as such in next step.



Reagents and conditions: (c) SOCl₂, Reflux

Method for the synthesis of N-(4-((Z)-(2, 4-dioxothiazolidin-5-ylidene) methyl) phenyl) benzamide (Tg): Benzoic acid were refluxed with thionyl chloride for 3-4 hr, and reaction was

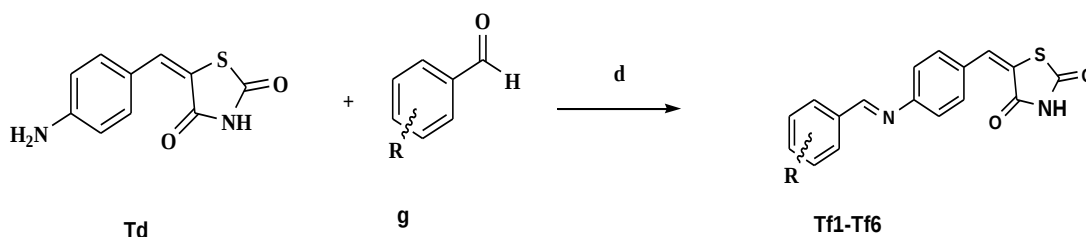
monitored through TLC. After completion of reaction, evaporate excess of thionyl chloride under pressure.



Reagents and conditions: (d) CH₂Cl₂, (C₂H₅)₃N, stirring

Synthesis of substituted (E)-5-(4-aminobenzylidene) thiazolidine-2, 4-dione derivatives (Tf1-Tf6): Equimolar concentration of compound Td and substituted benzaldehyde reflux with ethanobI (3.5ml), and acetic acid (2-3drop). The reaction

mixture was stirred and heated at 100-105 °C for 4 hrs. Progress of the reaction mixture was checked through TLC. After completion of reaction, product was filtered and washed.



Scheme 2: General synthesis scheme of substituted benzylidene 2, 4-dioxothiazolidin derivatives

In vitro biological evaluation

Enzyme preparation¹⁴.

A purified goat lens extract was prepared in accordance with the method of Hayman and Kinoshita. Lenses were quickly removed from goat eye following euthanasia and homogenized (Glass-Potter) in 5 volume of cold deionized water. The homogenate was centrifuged at 10,400 rpm at 0-4°C for 30 minutes. Saturated ammonium sulfate solution was added to the supernatant fraction to form a 40% solution, which was stirred for 30 minutes at 0-4°C and then centrifuged at 10,400 rpm for 20 minutes. Following this same procedure, the recovered supernatant was subsequently fractionated with saturated ammonium sulfate solution using first a 50%, and then a 75% salt saturation. The precipitate recovered from the 75% saturated fraction, possessing ALR2 activity, was Redissolved in 0.05 M NaCl and dialyzed overnight in

0.05 M NaCl. The dialyzed material was used for the enzymatic assay.

Enzymatic assay

ALR2 activity has been assayed at 30°C in a reaction mixture containing 0.75 mL of 10 mM D,L-glyceraldehyde, 0.5 ml of 0.104 mM NADPH, 0.75 mL of 0.1 M sodium phosphate buffer (pH=6.2), 0.3 mL of enzyme extract and 0.7 mL of deionized water in a total volume of 3 ml. All the above reagents, except D, L-glyceraldehyde, were incubated at 30°C for 10 minutes; then substrate was added to start the reaction, which was monitored for 5 minutes. Enzyme activity calibrated by diluting the enzymatic solution to obtain an average reaction rate of 0.011±0.0010 absorbance units/minute for the sample. AR percentage inhibitory activity of the synthesized compounds (15 µL, 5 µg/mL) has been determined using same procedure.

in vivo biological evaluation

Induction of noninsulin dependent DM:

The acclimatized animals have been kept fasting for 24 hours with water *ad-libitum*. Saline 1% W/V has been used in control group. Diabetes was induced by alloxan monohydrate (120 mg/kg *i.p*). After 72 hours of alloxan administration, the animals were got diabetes. A 5% dextrose solution was given in feeding bottle for a day to overcome the early hypoglycemic phase. The blood glucose regulator has been monitored after alloxination by withdrawing a drop of blood from the tail vein by Tail tipping method. The blood dropped on the dextrostix reagent pad. The strip was inserted into microprocessor digital blood glucometer and readings were noted.

EXPERIMENTAL PROTOCOLS

All experimental protocols were reviewed and accepted by the Institutional Animal Ethical Committee (IAEC) prior to the initiation of the experiment.

Wistar adult rats, weighing between 120-150 gram was taken for pharmacological activity and females of the same strain for LD₅₀ calculation. The rats were kept in animal house at a standard environmental condition (temperature-22 ± 1°C relative humidity-55 ± 5% and 12h light/12 h dark cycle). Animals were fed *ad libitum* with standard food and water except when fasting was required in the course of study. The animals were acquired from the local market. Animals were kept in standard environmental conditions and had free access to feed and water. All the animals were acclimatized to laboratory condition for a week before commencement of experiment.

Experimental design

Antidiabetic activity of the synthesized compounds was carried out on 6 rats in each group. The animals found diabetic after induction of alloxan monohydrate have been selected for the further study. Group 1 for diabetic control (Alloxan induced), Group 2 for reference standard (rosiglitazone 4 mg/kg body weight) and Group 3-8 for synthesized compounds (15 mg/kg body weight for acute study). Antidiabetic activities of the synthesized compounds were tested by using alloxan induced diabetic model in Wistar rats. The dose of the synthesized compounds (15 mg/kg body weight) and rosiglitazone (4 mg/kg body weight) were administered orally in 2% acacia. The blood glucose level was monitored at different times 0, 1, 3, and 9 hours respectively.

RESULT AND DISCUSSION

The analytical data of synthesized compounds are as follows:

(Tf1)(*E*)-5-((*E*)-4-((*E*)-benzylideneamino) benzylidene) thiazolidine-2, 4-dione.

This compound was prepared according to general procedure and it was obtained as light orange solid, mp 250–255°C. The λ_{max} of the compound was determined in methanol and it was found to be 364 nm. IR (KBr, cm⁻¹) 3369 (N-H), 1741 (C=O), 1693 (C=C), 1560(C=N), 3053(C-H); ¹H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.65 (s, 1H), 8.13 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 7.44 – 7.26 (m, 5H).m/e: 308.06; Elemental Anal.C, 66.22; H, 3.92; N, 9.08; O, 10.38; S, 10.40

Tf2(*5E*)-5-((*E*)-4-(2-nitrobenzylideneamino) benzylidene) thiazolidine-2, 4-dione.

This compound was prepared according to general procedure and it was obtained as orange solid, mp 248–252°C. The λ_{max} of the compound was determined in methanol and it was found to be 362 nm. IR (KBr, cm⁻¹) 3005 (N-H), 1609(C=O), 1369 (C=C), 1660(C=N), (C-H) 2985; ¹H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.6 (s, 1H), 8.13 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.56 (s, 1H), 7.44 – 7.26 (m, 5H).m/e: 353.05 C, 57.78; H, 3.14; N, 11.89; O, 18.11; S, 9.07

Tf3(*E*)-5-((*E*)-4-((*E*)-3-nitrobenzylideneamino) benzylidene) thiazolidine-2, 4-dione.

This compound was prepared according to general procedure and it was obtained as orange solid, mp 240–250°C. The λ_{max} of the compound was determined in methanol and it was found to be 302 nm. IR (KBr, cm⁻¹) 3377 (N-H), 1739 (C=O), 1369 (C=C), 1516(C=N), (C-H) 3005, m/e: 353.05; ¹H NMR (400 MHz, DMSO) δ 15.43 (s, 1H), 8.73 (s, 1H), 8.32 – 8.14 (m, 2H), 7.92 – 7.74 (m, 2H), 7.39 – 7.20 (m, 4H), 7.12 (s, 1H).Elemental Anal. C, 57.78; H, 3.14; N, 8.64; O, 11.89; S, 9.07,

Tf4(*E*)-5-((*E*)-4-((*E*)-4-nitrobenzylideneamino) benzylidene) thiazolidine-2, 4-dione.

This compound was prepared according to general procedure and it was obtained as orange solid, mp 240–248°C.The λ_{max} of the compound was determined in methanol and it was found to be 386 nm. IR (KBr, cm⁻¹) 3304 (N-H), 1867(C=O), 1344 (C=C), 1559(C=N), (C-H) 3005 ¹H NMR (400 MHz, DMSO) δ 15.42 (s, 1H), 8.83 (s, 1H), 8.62 (s, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.55 (s, 1H), 7.31 – 7.24 (m, 4H), 7.14 (s, 1H). m/e: 353.05; Elemental Anal. C, 57.78; H, 3.14; N, 8.64; O, 11.89; S, 9.07

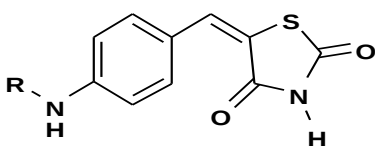
Tf5(*E*)-5-((*E*)-4-((*E*)-3-(dimethylamino) benzylideneamino)benzylidene)thiazolidine-2,4-dione.

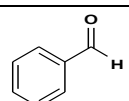
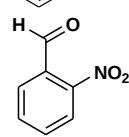
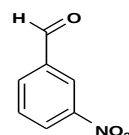
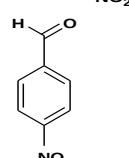
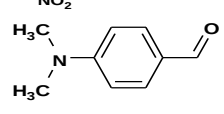
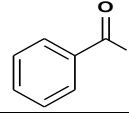
This compound was prepared according to general procedure and it was obtained as dark orange solid, mp 280–282°C. The $\lambda_{\max}$ of the compound was determined in methanol and it was found to be 388 nm. IR (KBr, cm⁻¹) 3304 (N-H), 1741 (C=O), 1369 (C=C), 1665 (C=N), (C-H) 3028 ¹H NMR (400 MHz, DMSO) δ 15.47 (s, 1H), 8.59 (s, 1H), 7.40–7.24 (m, 4H), 7.12 (d, *J* = 5.9 Hz), 6.97 (s, 1H), 6.90 (s, 1H), 6.65 (s, 1H), 2.91–2.86 (m, 6H) m/e: 351.10, C, 64.94; H, 4.88; N, 11.96; O, 9.11; S, 9.12

Tf6(E)-N-(4-((2, 4-dioxothiazolidin-5-ylidene) methyl) phenyl) benzamide.

This compound was prepared according to general procedure and it was obtained as white creamish solid, mp 240–244°C, the $\lambda_{\max}$ of the compound d was determined in methanol and it was found to be 350 nm. IR (KBr, cm⁻¹) 3323 (N-H), 1869 (C=O), 1541 (C=C), 1689 (C=N), (C-H) 2808; ¹H NMR (400 MHz, DMSO) δ 15.19 (s, 1H), 8.42 (s, 1H), 7.77–7.53 (m, 2H), 7.01 (s, 1H), 7.13 (s, 1H) 7.74–7.32 (m, 6H), m/e: 324.06; C, 62.95; H, 3.73; N, 8.64; O, 14.80; S, 9.89

Table 1: Structure, molecular weight, percentage yield, and retardation factor (Rf) of synthesized (4-aminobenzylidene) thiazolidine-2, 4-dione



Comp no.	R	MW	%Yield	Rf value	$\lambda_{\max}$ (nm) in Methanol
Tf ₁		250–255°C	60	0.52	364
Tf ₂		248–252°C	42.2	0.60	302
Tf ₃		240–250°C	45	0.62	386
Tf ₄		240–248°C	55	0.72	362
Tf ₅		280–282°C	75.5	0.35	388
Tf ₆		240–244°C	70.5	0.79	350

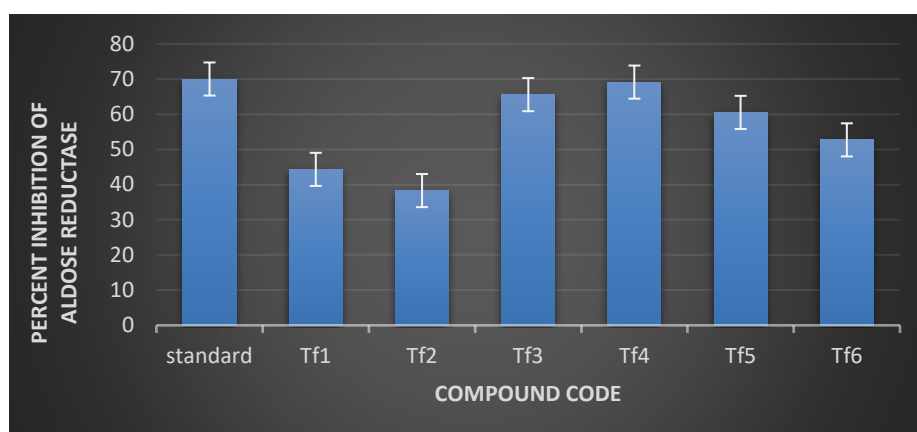
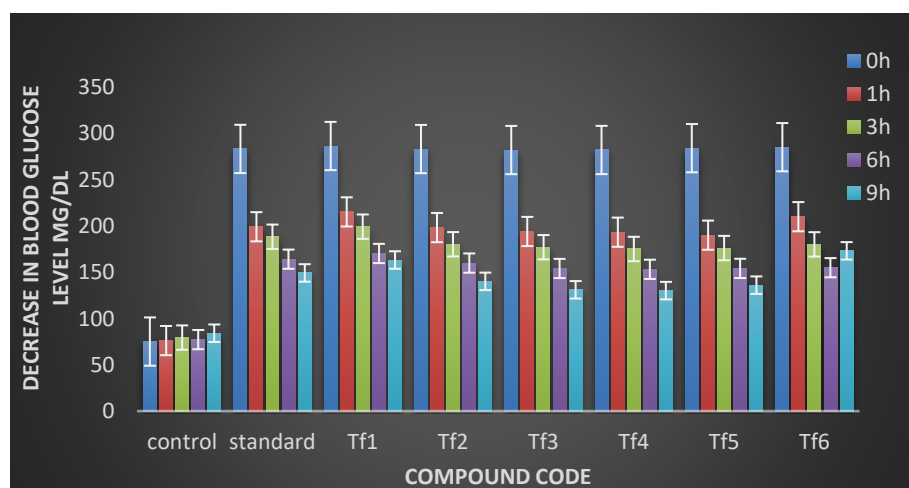
Aldose reductase Inhibitory activity

All the synthesized 5 aryl 2, 4-dioxothiazolidin derivatives were evaluated for their ability to inhibit the in vitro reduction of D, Lglyceraldehydes by partially purified ALR from goat lenses; sorbinil was used as a reference drug (Table 2 and Fig. 2). Inhibitory data indicate that 2-substitution on benzamido moiety shows more potent inhibitory activity as compare to un-substituted, 4-substituted

or 3,4 di-substituted analogs. In vivo biological evaluation of all the synthesized thiazolidinedione also evaluated for their antidiabetic activity using rosiglitazone as reference drug. The decrease in blood glucose level against each compound is shown in Table 3 and Fig. 3. Inhibitory data indicate that the synthesized compounds show almost similar activity to reference compound.

Table 2: Aldose reductase percentage inhibitory activity of synthesized 5 aryl 2, 4- thiazolidinedione analogs

Compound	% Inhibition ($\pm$ standard)
Standard (Sorbiniil)	70
Tf1	44.32
Tf2	38.29
Tf3	65.55
Tf4	69.12
Tf5	60.51
Tf6	52.70


Fig. 2: Graphical representation of aldose reductase inhibitory activity of 5 aryl benzylidene2, 4-thiazolidinedione analogs

Fig. 3: Graphical representation of antidiabetic activity of 5 aryl benzylidene2, 4-thiazolidinedione analogs
Table3: Antidiabetic activities of the synthesized 5arylbenzylidene 2, 4-thiazolidinedioneanalogs

Comp.	Decrease in blood glucose level mg/dl				
	0 hrs	1 hrs	3 hrs	6 hrs	9 hrs
Control	75.20±1.306	76.25±1.240	79.50±1.205	77.32±1.255	84.20±1.300
Std (roziglitazone)	283.35±1.250***	195.25±2.220**	176.45±2.120**	154.20±1.230***	135.35±1.185***
Tf1	286.51±2.520**	215.31±2.250**	199.35±2.325**	170.38±3.322*	163.30±1.340***
Tf2	283.22±1.530**	198.35±3.140*	180.33±2.130**	160.00±1.335***	140.25±2.300**
Tf3	282.15±1.410***	194.15±1.230***	177.12±1.220***	154.17±1.300***	131.11±1.150****
Tf4	282.20±1.220***	193.36±2.040**	175.23±2.100***	153.25±2.233**	130.20±1.200***
Tf5	284.15±1.400**	199.15±1.235***	184.22±1.225***	165.26±2.325**	146.15±1.280***
Tf6	285.24±2.420**	210.15±1.250***	180.22±2.330**	155.00±3.320*	173.20±1.300***

CONCLUSION

5 aryl benzylidene thiazolidinedione derivatives have been synthesized & demonstrated as aldose reductase inhibitors. All synthesized thiazolidinedione derivatives have been evaluated for ability to inhibit the *in-vitro* reduction. The synthesized compounds on comparison to aryl benzylidene thiazolidinedione derivatives, it has been identified as a Schiff base with various substitutions on the benzylidene moiety, to increase the inhibitory effectiveness. Schiff bases are characterized by an imine group $-N=CH-$, which helps to clarify the mechanism of transamination and racemization reaction in biological system. The substituted Schiff bases like nitro & phenyl derivatives possess more active although, activity has been found lesser than the standard drug in antidiabetic drug. The compounds with para nitro group substitution with iminium ion, produces effective inhibition. Particularly, 4 paranitro substituted derivative (Tf6) proved to be the most active among all substituted compounds.

The synthesized compound showed ARI activity in range of 38.21-69.12%. Similarly, synthesized compounds decrease blood glucose level in range of 130.20-173.20mg/dl at 15 mg/kg body. The *in vivo* study of thiazolidinedione derivatives has been carried out by alloxan induced tail tipping method. From the above-mentioned present study, it is recommended to evaluate these compounds with other existing Anti-diabetic drugs for further more enhancements.

ACKNOWLEDGEMENT

I take this opportunity to sincerely acknowledge the Bhagwant University, Ajmer for granting permission to conduct the study. I am also extremely indebted to my guide Dr. Girendra Gautam and Dr. Arun Kumar Gupta for valuable guidance and advice. I feel deep

thanks to PBRI laboratories, Bhopal for providing laboratory facilities to carry out the entire experiments.

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