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SYNTHESIS AND EVALUATION OF NEWER QUINOLINE DERIVATIVES OF THIAZOLIDINEDIONES FOR THEIR ANTIDIABETIC ACTIVITY

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ABSTRACT

In view of various biological activities of both thiazolidinediones and quinoline derivatives like antidiabetic, antifungal, antitumoral, anti-inflammatory, retinoidal, anti atherosclerotic activities, it was our interest to prepare various thiazolidinedione derivatives with a quinoline ring moiety and to evaluate them for antidiabetic activity. 5-(4-fluorobenzyl)-2,4-thiazolidinedione was synthesized by reaction of 4-fluoroaniline with methyl acrylate to give crude 2-Bromo-3-(4-fluoro-phenyl)-propionic acid methyl ester as an oil which was treated with thiourea in presence of sodium acetate and ethanol to give 5-(4-fluoro-benzyl)-2-imino-thiazolidine-4-one which on oxidation gave 5-(4-fluoro-benzyl)-thiazolidine-2,4-dione. This was condensed with the quinoline derivatives in presence of Tetrahydrofuran. Among the synthesized derivatives five of them were screened for oral hypoglycemic activity, the compounds SK, SK-3 were showing significant activity and compound SK-2 was showing moderate activity and compounds SK-4 and SK-5 were active. The structures of newly synthesized compounds were established on the basis of elemental analysis, TLC, IR and ^{1}H NMR spectral studies.

KEYWORDS

Thiazolidinediones, Quinolines, Antidiabetic agents, Chalcones.

INTRODUCTION

Insulin is a protein hormone secreted by the beta cells of islets of langerhans of pancreas. Deficiency of effective insulin in the body causes a disease called diabetes mellitus[1] in which there is a faulty carbohydrate metabolism. The metabolism of fats and proteins is also disturbed. This results in hyperglycemia (excessive sugar in the blood) and glucosuria (presence of sugar in the urine). Some other symptoms associated with disease are polydipsia (increased thirst), polyurea (increased urinary output), ketonemia and ketonuria (presence of ketone bodies in the blood and urine, respectively). As the disease progresses tissue or vascular damage ensues adding to severe diabetic complications such as retinopathy, nephropathy, neuropathy and ulceration, thus diabetes mellitus is a chronic and progressive condition associated with

serious micro vascular and macro vascular complications

Diabetes mellitus is a heterogeneous clinical disorder with numerous causes. Two main classifications of diabetes mellitus exist, idiopathic and secondary. Idiopathic diabetes is divided into two main types: Insulin dependent and Non-insulin dependent.

Insulin dependent diabetes mellitus (IDDM or type1 diabetes) is defined by the development of ketoacidosis in the absence of insulin therapy[2]. It is a severe form. It occurs most commonly in juveniles but can take place in adults also specifically those who are elderly. In this, circulating insulin is practically absent and β- cells of the pancreas do not respond to insulinogenic stimuli. It may have resulted from infection, toxic environment or autoimmune destruction of the beta cell of the pancreas. In this type insulin deficiency leads to rapid rise in the blood glucose concentration with subsequent loss of glucose with water and salt in urine.

Non insulin dependent diabetes mellitus (NIDDM or type2 diabetes) is characterized by milder hyperglycemia and rarely leads to ketoacidosis[3]. It occurs primarily in adults but occasionally in adolescence also. Circulating endogenous insulin is sufficient to prevent ketoacidosis but is often inadequate because of tissue insensitivity. In this the β cells do not respond to high levels of blood glucose it occurs more in obese individual than in non obese.

Insulin remains the main stay of therapy for treatment of type 1 diabetes. Various forms of insulin dosage forms are available, however incase of type2 diabetes, when dietary treatment and weight reduction fails to correct hyperglycemia, oral antidiabetic drugs on oral hypoglycemic agents are prescribed.

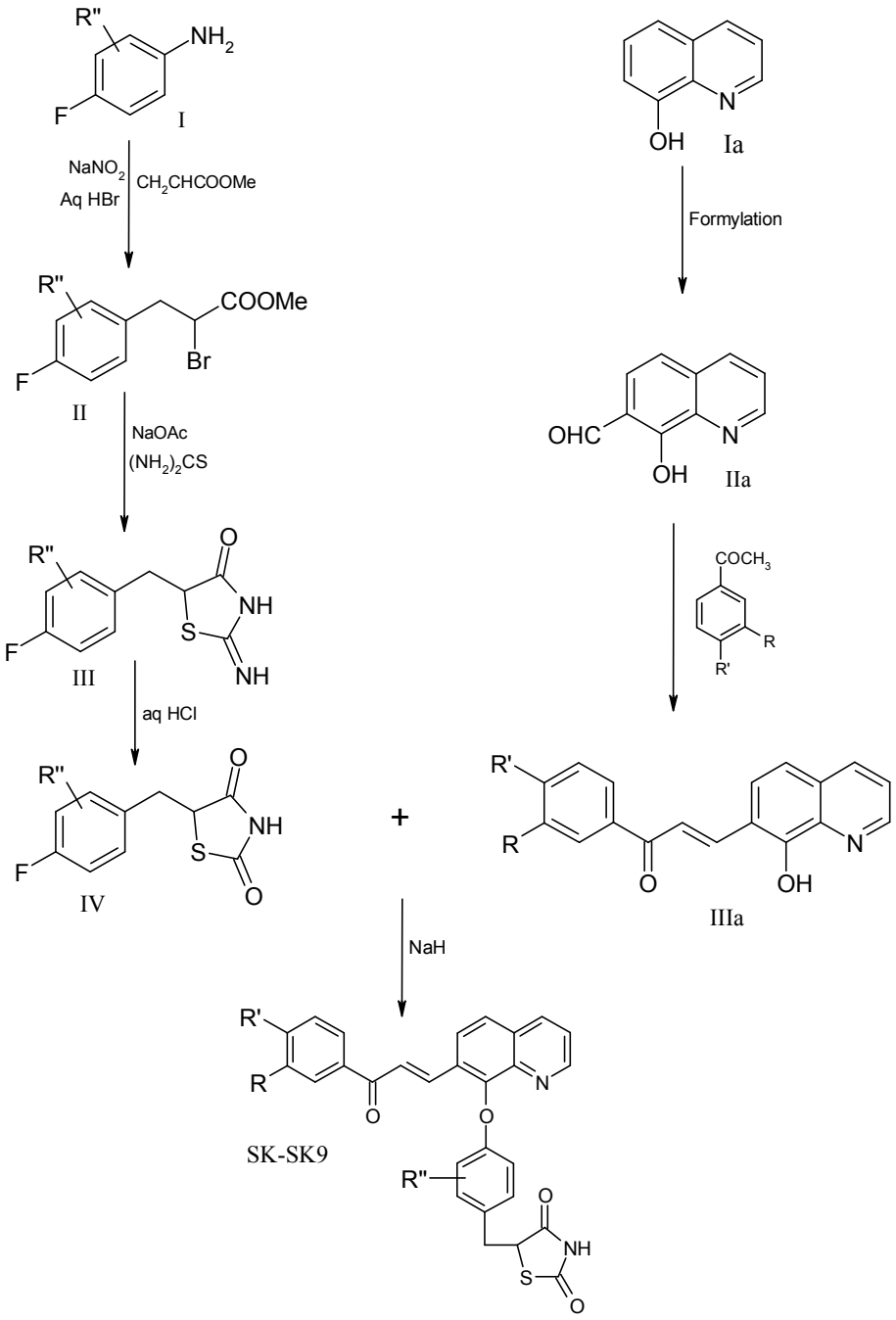
Recently thiazolidinedione derivatives have been reported to have antidiabetic/ hypoglycemic activities. Drugs available in the market under this class are Rosiglitazone, Pioglitazone. Various other activities like anticancer, retinoidal and anti-inflammatory have been reported.

The thiazolidinediones, also known as “glitazones,” are sometimes referred to as insulin enhancers. They are exemplified by ciglitazone, the first of the glitazones. Ciglitazone’s antihyperglycemic effects were discovered serendipitously. The first drug in this class to be marketed is the drug troglitazone, introduced in the United States in1997. While clinical studies did indicate hepatic and cardiac toxicity the toxicities were not considered severe and it was felt that the drug could be used if liver functions were closely monitored. In a 96-week study in type 2 diabetics, little or no cardiac toxicity was noted. Unfortunately, rare cases of liver failure, liver transplants, and deaths were reported during post marketing use and the drug was voluntarily withdrawn. More recently two new glitazones have been approved and marketed. These include rosiglitazone and pioglitazone. Both drugs have been approved for monotherapy and combination therapy with metformin, sulphonylureas or insulin. The glitazones lower blood glucose concentrations by improving sensitivity to insulin in target tissue, which includes adipose tissue, skeletal muscle and liver. These agents are dependent upon insulin for their activity[4].

In view of these valid observations in our present study, we have synthesized some new quinoline derivatives bearing thiazolidinedione nucleus as shown in scheme-I and screened them for antidiabetic activity.

MATERIALS AND METHODS

SCHEME- I [5, 6, 7]



The various synthesized derivatives were characterized by determination of melting point T.L.C, I.R and N.M.R. Melting point – By Theil's melting point apparatus. T.L.C. – By using Chloroform: methanol (1:1).I.R. - By using KBr pellet method. N.M.R. – Bruker 200 spectrospin.

Synthesis of 2-Bromo-3-(4-fluoro-phenyl)-propionic acid methyl ester (II): A solution of $NaNO_2$ (2.31 gm) in H_2O (10 ml) was added to a stirred and ice cooled mixture of 4-Fluoroaniline (3.5 gm), 47% HBr (14 ml), and MeOH-Acetone (1:1, v/v, 100 ml). The mixture was stirred at 5° C for 30 min, and then methyl acrylate (15.5 gm) was added to the mixture. The temperature was raised to 35°C and Cu_2O (0.3 gm) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo, diluted with H_2O, neutralized with conc. NH_4OH, and extracted with Ethyl acetate. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo* to give crude 2-Bromo-3-(4-fluoro-phenyl)-propionic acid methyl ester as an oil.

Synthesis of 5-(4-fluoro-benzyl)-2-imino-thiazolidine-4-one (III):
A Mixture of the oil, Thiourea (1.98 gm), Sodium acetate (2.13 gm), and ethanol (50 ml) was refluxed for 5 hrs. The reaction mixture was poured into water to give crystals, which were collected by filtration and washed with Di ethyl ether.

Synthesis of 5-(4-fluoro-benzyl)-thiazolidine-2, 4-dione (IV): A mixture of 5-(4-fluoro-benzyl)-2-imino-thiazolidine-4-one, 2N HCl (20 ml) and ethanol (20 ml) was stirred under reflux for 12 hrs. The reaction mixture was concentrated *in vacuo.* The residue was diluted with H_2O, neutralized with saturated aqueous $NaHCO_3$, and extracted with chloroform. The chloroform extract was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give the title compound.

Synthesis of 8-Hydroxy-quinoline-7-carbaldehyde (IIa): Equip a 1-liter three-necked flask with a separatory funnel, a sealed mechanical stirrer and a reflux condenser. Place 50 gm of 8-hydroxy quinoline and 150 ml of rectified spirit in the flask, start the stirrer and rapidly add a solution of 100 gm of NaOH in 210 ml of water. Heat the resulting solution to 70-80°C on a water bath, and place 62 gm (42 ml) of pure chloroform in the separatory funnel. Introduce the chloroform drop wise until reaction commences (indicated by the formation of deep blue color) remove the water bath and continue the addition of chloroform at such a rate that the mixture refluxes gently (about 1.5 hrs). The sodium salt of phenolic aldehyde separates near the end of the addition continue the stirring for a further 1 hr. set the condenser for downward distillation (but retaining the stirrer) and distill off the excess chloroform and alcohol. Treat the residue, with stirring, drop wise with concentrated HCl until the contents of the flask are acid to Congo red paper (about 88 ml are required) a dark oil, accompanied by a considerable amount of NaCl separates. Add sufficient water to dissolve the salt, extract the oil with ether, wash the ethereal solution with water, dry with anhydrous $MgSO_4$ and remove the solvent. Distill the residue under reduced pressure and collect the slightly colored aldehyde at 177-180°C/20mmHg it solidifies on cooling. Recrystallise the solid from about 40 ml of ethanol.

Synthesis of (E)-3-(8-Hydroxy-quinoline-7-yl-1-phenyl-propeonone (IIIa): Aqueous NaOH (50%, 20 ml) was added a little at a time to a solution of 8-Hydroxy-quinoline-7-carbaldehyde (0.02 mol) and p-nitro acetophenone (0.01 mol) in ethanol (50 ml) over a period of 30 min. the contents of the flask were stirred for 3 hrs at 10°C. The reaction mixture was neutralized with 1% dilute hydrochloric acid and kept at 0°C for one day. The colored solid was filtered off under suction and dried on a desiccator[5, 6].

Synthesis of 5-{4-[7-((E)-3-Oxo-3-phenyl-propenyl)-quinolin-8-yloxy]-benzyl}-thiazolidine-2, 4-dione (SK-SK9): Sodium hydride (60% in oil, 0.20 g) was added gradually to a stirred and ice-cold solution of derivatives of (E)-3-(8-Hydroxy-quinoline-7-yl-1-phenyl-propeonone (1.45 g) and 5-(4-Fluoro-benzyl)-thiazolidine-2, 4-dione (1.125 g) in tetrahydrofuran (THF 20 ml). After stirring for 2

hrs the reaction mixture was poured in water and extracted with Diethyl ether. The extract was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residual crystals were recrystallized from hexane to give colorless prisms[7].

5-(4-{7-[(E)-3-(4-Ethyl-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione. (Sk): IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.063 δ (1H, s, NH), 7.121-7.142 δ (2H, d, CH=CH), 6.192-8.05 δ (13H, m, ArH), 4.556–4.588 δ (2H, q, CH_2), 4.168–4.194 δ (3H, t, CH_3).

5-(4-{7-[(E)-3-(3-Nitro-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione. (Sk2)

IR (KBr) (cm^{-1}) : 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.627 δ (1H, s, NH), 7.638-7.658 δ (2H, d, CH=CH), 7.099-7.730 δ (13H, m, ArH), 2.868–2.899 δ (2H, d, CH_2), 2.014 – 2.026 δ (1H, t, CH).

5-(4-{7-[(E)-3-(4-Amino-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione. (Sk3)

IR (KBr) (cm^{-1}) : 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm) : 8.75 δ (1H, s, NH), 7.609 δ (2H, s, NH_2), 7.540-7.547 δ (2H, d, CH=CH), 6.965–7.717 δ (13H, m, ArH), 2.975 – 2.986 δ (2H, d, CH_2), 2.472 – 2.579 δ (1H, t, CH).

5-(4-{7-[(E)-3-(4-Nitro-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione. (Sk4)

IR (KBr) (cm^{-1}) : 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.651 δ (1H, s, NH), 7.202-7.216 δ (1H, d, =CH), 7.222-7.236 δ (1H, d, =CH-CO), 6.953 – 7.659 δ (13H, m, ArH), 3.447 – 3.491 δ (2H, d, CH_2), 2.958 – 3.018 δ (1H, t, CH).

5-(4-{7-[(E)-3-(4-Methoxy-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione. (Sk5)

IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.902 δ (1H, s, NH), 7.061-8.690 δ (13H, m, ArH), 4.57-4.615 δ (1H, t, CH), 1.181 – 1.232 δ (2H, d, CH_2).

5-{4-[7-((E)-3-Oxo-3-p-tolyl-propenyl)-quinolin-8-yloxy]-benzyl}-thiazolidine-2, 4-dione. (Sk6)

IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.627 δ (1H, s, NH), 7.638-7.658 δ (2H, d, CH=CH), 7.099-7.730 δ (13H, m, ArH), 2.868–2.899 δ (2H, d, CH_2), 2.35 δ (3H, s, CH_3), 2.014 – 2.026 δ (1H, t, CH).

5-{4-[7-((E)-3-Oxo-3-phenyl-propenyl)-quinolin-8-yloxy]-benzyl}-thiazolidine-2, 4-dione. (Sk7)

IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.75 δ (1H, s, NH), 7.540-7.547 δ (2H, d, CH=CH), 6.965–7.717 δ (13H, m, ArH), 2.975 – 2.986 δ (2H, d, CH_2), 2.472 – 2.579 δ (1H, t, CH).

5-(4-{7-[(E)-3-(3-Amino-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione (Sk8)

IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.75 δ (1H, s, NH), 7.609 δ (2H, s, NH_2), 7.540-7.547 δ (2H, d, CH=CH), 6.965–7.717 δ (13H, m, ArH), 2.975 – 2.986 δ (2H, d, CH_2), 2.472 – 2.579 δ (1H, t, CH).

5-(4-{7-[(E)-3-(3-Methoxy-phenyl)-3-oxo-propenyl]-quinolin-8-yloxy}-benzyl)-thiazolidine-2, 4-dione (Sk9)

IR (KBr) (cm^{-1}): 3431.71 cm^{-1} (N-H str), 3040.23 cm^{-1} (C-H str, aromatic), 1652.70 cm^{-1} (C = O str), 1724.05 cm^{-1} (C = N str), 1605.45 cm^{-1} (N-H bending)

^{1}H-NMR (DMSO, 400MHz), δ (ppm): 8.902 δ (1H, s, NH), 7.061-8.690 δ (13H, m, ArH), 4.57-4.615 δ (1H, t, CH), 1.181 – 1.232 δ (2H, d, CH_2).

Structures of Various Derivatives

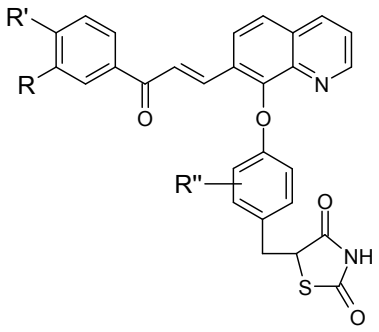


Table 1

Sl No	Compound Code	R	R^1	R^{11}
1.	SK	H	C_2H_5	H
2.	SK2	$-NO_2$	H	H
3.	SK3	H	$-NH_2$	H
4.	SK4	H	$-NO_2$	H
5.	SK5	H	$-OCH_3$	H
6.	SK6	H	$-CH_3$	H
7	SK7	H	H	H
8	SK8	$-NH_2$	H	H
9	SK9	$-OCH_3$	H	H

Table 2
***Physical data of various derivatives**:*

Sl no	Compound code	*Mol formula*	Mol weight	Melting point(^{0}C)	Yield (%)	Rf value
1	SK	$C_{30}H_{24}N_2O_4S$	508.60	205^{o}C	67.25	0.69
2	SK2	$C_{28}H_{19}N_3O_6S$	525.54	216^{o}C	61.55	0.64
3	SK3	$C_{28}H_{21}N_3O_4S$	495.56	240^{o}C	74.50	0.67
4	SK4	$C_{28}H_{19}N_3O_6S$	525.54	180^{o}C	56.66	0.65
5	SK5	$C_{29}H_{22}N_2O_5S$	510.57	220^{o}C	65.00	0.62
6	SK6	$C_{29}H_{22}N_2O_4S$	494.57	190^{o}C	72.33	0.68
7	SK7	$C_{28}H_{20}N_2O_4S$	480.55	240^{o}C	63.28	0.63
8	SK8	$C_{28}H_{21}N_3O_4S$	495.56	185^{o}C	66.44	0.65
9	SK9	$C_{29}H_{22}N_2O_5S$	510.57	235^{o}C	57.22	0.64

ANTIDIABETIC ACTIVITY

Hypoglycemic Activity by Tail Vein Method[8, 9].

Estimation of Glucose

Span diagnostic kit was used for the estimation of glucose, which followed enzymatic colorimetric procedure.

Reaction Parameters

Reaction type- Oxidation/ End point (indicated by a color change).

Wavelength-505nm, Hg 546, Optical path- 1cm, Temperature- 37^0C, Measurement –Against reagent blank

Table 3

Estimation of Blood Glucose.

Pipette into test tubes	Blank	Standard	Test
Serum/Plasma	----	----	10 µl
Glucose standard	----	10 µl	----
Working Glucose reagent	1000 µl	1000 µl	1000 µl

Preparation of Working Reagent and Procedure

Fresh clear serum with no hemolysis was used for estimation. Mixed well and read the absorbance of test and standard at 505nm after 10 min incubation, against reagent blank. The final reaction mixture is stable for at least 1 hour.

CALCULATION

With standard

Glucose (mg/dl) = (Absorbance of sample/Absorbance of STD) X 100

Table 4

Animals used for screening antidiabetic activity

Species	Albino rats
Strain	Wister
Age	3 Months
Body weight	150-275 Gram
No. Of animals in each groups	Six
No of groups	Twelve
Water and food	*Ad Libitum*

PROCEDURE

The various steps followed in procedure for screening antidiabetic activity of analogues are as follows
The test dose of samples were calculated on the basis of the LD_{50}

1. ***Dose and preparation of test sample*:** LD_{50} was found to be 0.8mg/kg in rats so a dose of 0.2mg/kg was taken for each analogue to carryout pharmacological evaluation of antidiabetic activity; thus drug (analogue) at the dose of 0.2mg/kg was administered orally as an aqueous suspension; the drug suspension were made in 2% Tween 80.

2. ***Animals*:** Adult male and female albino rats weighing between 150 – 275 gm were used for present study. Animals were 90-110 days old at the start of the experiment. All the rats were fed on standard chow pellets with filtered water *ad libitum.*

3. ***Selection Criterion for Animals*:** Initially a group of healthy albino rats of either sex were selected and were divided into 3 groups, viz., group 1, group 2 and group 3. Group- 1(n = 6) received solvent dose orally, served as control. The Group 2 (n = 6) served as standard group in which Rosiglitazone was used. Group 3 served as a test group for screening derivatives for their hypoglycemic activity.

4. ***Drug Treatment Schedule:*** For screening quinoline derivatives of 2, 4-thiazolidinediones the group 3 was subdivided into 5 groups. The number of animals in each group to be screened for hypoglycemic activity was 6. The thiazolidinedione derivatives were administered by oral route.

5. ***Method:*** Animals were fasted 16 hrs before measuring serum blood glucose level in all the groups however water was given *ad libitum*. During this period serum blood glucose level in groups 2 and 3 were determined after 2 hr of the treatment with standard and quinoline derivatives of thiazolidinedione derivatives respectively. The blood sample from each rat was collected by tail vein method. Blood glucose was determined by using semi auto analyzer (Qualigen GSK). All readings were recorded in mg/dL of glucose content.

6. ***Statistical Analysis*** :

The statistical analysis of data was carried out by one way ANOVA test followed by Bonferonni's multiple comparision test i.e. The results are expressed as mean ± S.E.M.

RESULTS AND DISCUSSIONS

Table 5

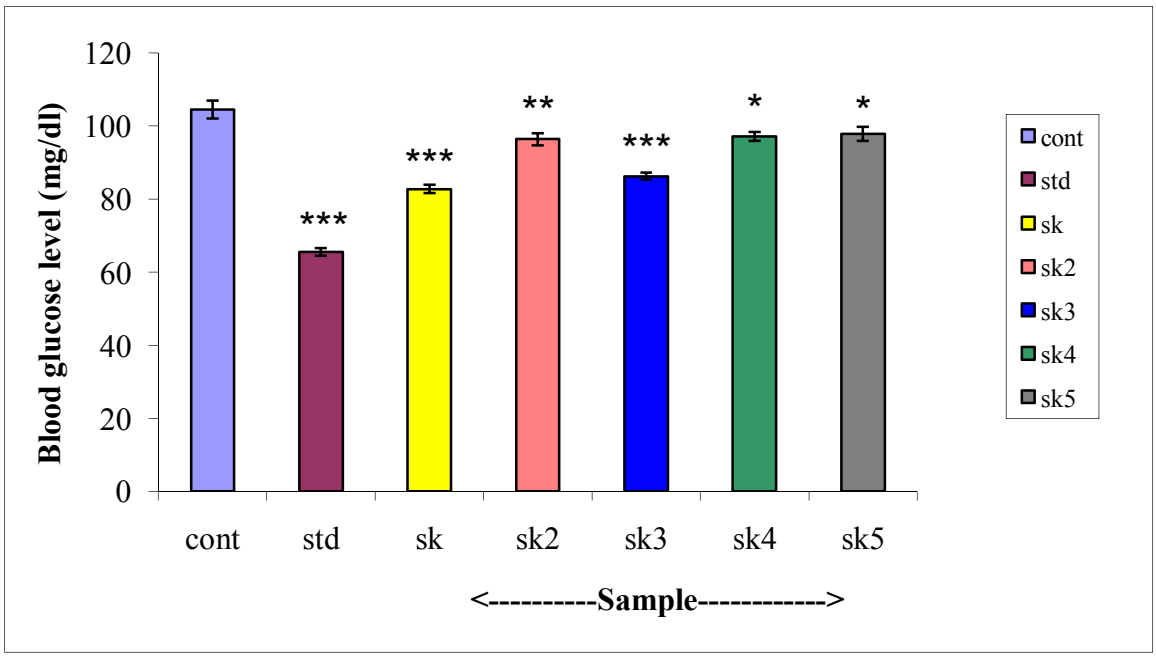
Hypoglycemic Activity of Different Derivatives with Standard Rosiglitazone and Control (mg/dl)

Control	Std	Sk	Sk2	Sk3	Sk4	Sk5
104.55 ± 2.409	65.58 ± 1.013 ***	82.81 ± 1.115 ***	96.5 ± 1.62 **	86.31 ± 0.993 ***	87.21 ± 1.233 *	97.91 ± 1.870 *

*** P<0.05 **P<0.01 ***P<0.001**

The values are represented by Column graph in Fig. 1

Figure 1



All the values are mean ± S.E.M., n = 6, a= p < 0.001 vs. vehicle control, * p < 0.05, ** p < 0.01, *** p < 0.001 vs. Rosiglitazone std.

CONCLUSION

The work which has been carried out as per the objective is concluded as follows:
5-(4-fluorobenzyl)-2,4-thiazolidinedione was synthesized by reaction of 4-fluoroaniline with methyl acrylate to give crude 2-Bromo-3-(4-fluoro-phenyl)-propionic acid methyl ester as an oil which was treated with thiourea in presence of sodium acetate and ethanol to give 5-(4-fluoro-benzyl)-2-imino-thiazolidine-4-one which on oxidation gave 5-(4-fluoro-benzyl)-thiazolidine-2,4-dione. This was condensed with the quinoline derivatives in presence of Tetrahydrofuran.

The synthesized derivatives were then screened for their hypoglycemic activity by determining their blood glucose concentration which was compared to that of the standard drug Rosiglitazone. The test was performed on rats.
The results obtained are as follows:

- Derivatives SK 4 and SK 5 were found to be active.
- Derivatives SK2 was found to possess moderate activity.
- Derivatives SK, and SK3 were found to have comparable activity with that of Rosiglitazone.

The results showed that the derivatives **SK, SK3, SK4and SK5** have decreased the blood glucose levels in rats, which confirmed the hypoglycemic activity of these derivatives.

Table 6

Hypoglycemic Activity of Synthesized Derivatives

Sl No	*Compound Code*	R	R^1	R^{11}	Pharmacological activity
1.	SK	H	C_2H_5	H	Significant
2.	SK2	$-NO_2$	H	H	Moderate
3.	SK3	H	$-NH_2$	H	Significant
4.	SK4	H	$-NO_2$	H	Active
5.	SK5	H	$-OCH_3$	H	Active
6.	SK6	H	$-CH_3$	H	*
7	SK7	H	H	H	*
8	SK8	$-NH_2$	H	H	*
9	SK9	$-OCH_3$	H	H	*

* Not screened for activity.

It can be concluded that the presence of ethyl and amino groups at R' position showed significant activity where as nitro and methoxy groups at R' showed activity but not significant and presence of nitro group at R position showed moderate activity. So the further studies will be required with various similar substituents.

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