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Novel Design of Thiazolidinediones Derivatives as typical Antidiabetic Agents against Insulin Resistance

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Abstract: Recent years have seen a rise in interest in the study of heterocycles (hybrid molecules) due to claims that these compounds exhibit a wide range of pharmacological effects. As a result, it was decided to conduct research on and screen for the biological activities of heterocycles containing thiazolidinedione moieties. The goal of this study was to create novel lead compounds for drug development, namely new anti-diabetic medicines, by synthesising, purifying, characterising, and evaluating substituted thiazolidindione derivatives. This experimental study outlines a technique for synthesising a series of chemicals known as 2-amino (5' (4-sulfonylbenzylidine) 2, 4-thiazolidinedione) sulphonamide derivatives (C1-C5) utilising suitable synthetic processes. Results showed that the yield of the synthesised compounds was between 60% and 79%. The melting point and the presence of a single spot on the TLC confirmed the purity of the produced compounds.

1. INTRODUCTION

Diabetes mellitus[1]is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia[2], resulting from a diversity of etiologies, environmental and genetic, acting jointly. The underlying causes of diabetes are the defective production or action of insulin, a hormone that controls carbohydrate, fat and protein metabolism. Characteristically, diabetes is a long term disease with variable clinical manifestation and progression. Chronic hyperglycemia leads to a number of disorders including cardiovascular, renal, neurological as well as ophthalmic infections [3-5]

Diabetes mellitus[6]is a condition in which the pancreas no longer produces enough insulin or body cells stop responding to insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. Symptoms include frequent urination, lethargy, excessive thirst, and hunger. The treatment includes change in diet, oral medication and in some cases daily injection of insulin.

Thiazolidones and thiazolidinediones were the first parent compounds in which thiazole ring was recognized[7]. Frances E. Brown reported in 1961 a brief review on the close structural relationship among the various 4-thiazolidinones[8]. These compounds were found to be biologically active[9]. In the present work, we have synthesized 2-amino[5′(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole and screened them for their antidiabetic activity on diabetes induced albino rats. The thiazolidinediones[10,11]are currently licensed for use in oral combination therapy in management of patients with type-2 diabetes who have insufficient glycaemic control despite

maximal tolerated dose of oral mono-therapy with either Metformin or Sulphonylurea. It is generally recommended that thiazolidinediones are used in combination with Metformin only in obese patients.

Rosiglitazone[12-14], a member of the thiazolidinediones class of antidiabetic agents improves glycaemic control by improving insulin sensitivity. Rosiglitazone is a highly selective and potent agonist for the peroxisome proliferators activator receptor Gamma (PPAR)[11-15]. In humans, PPAR receptors are formed within the kidney and target tissues for insulinaction such as adipose, skeletal muscle and liver tissues. Activation of PPAR nuclear receptors regulates the transcription of insulin responsive genes involved in the control, production, transport and utilization of glucose. Rosiglitazone often is referred to as an "insulin sensitizer" because it attaches to the insulin receptors on cells throughout the body and causes the cells to become more sensitive (more responsive) to insulin and remove more glucose from the blood. At least some insulin must be produced by the pancreas in order for rosiglitazone to work. Rosiglitazone was approved by the FDA in May 1999.The most common side effects seen with rosiglitazone alone or in combination with metformin are upper respiratory tract infection, headache, back pain, hyperglycemia (elevated blood sugar), fatigue, sinusitis, diarrhoea, and hypoglycemia (low blood sugar).

With the available data from the literature and the co-crystallized structure of Rosiglitazone deposited in the protein data bank (eg. 1FM6, 3DZY, 2XKW and 4EMA) we can further optimise and design possibly a better analog of Rosiglitazone.

AIM AND OBJECTIVE

In current era the wing of innovative therapeutic molecules (hybrid molecules) synthesis, which comprises of linking two or more therapeutically verified molecules has gained wide appreciation. It was established that, when one heterocyclic system (i.e., ought to have any pharmacological activity) is attached to one more heterocyclic system, superior biological activity was produced. On basis of this important biological activity profile of several thiadiazoles, we intended to synthesize, characterize and evaluate the anti-diabetic activity of a few fused thiazolidinedione derivatives.

The primary objectives of present work:

To design and synthesize, new novel substituted thiazolidinedione small molecules.

- Characterization of the synthesized small molecules by IR, NMR and Mass Spectrometry methods.
- Formulation of substituted thiazolidinedione small molecules for treatment diabetes.
- To enhance the bioavailability of these compounds at the site of action.
- *Invivo* pharmacokinetic and pharmacodynamic studies of the thiazolidinediones in albino wistar rats.

Experimental Work

Melting points are uncorrected. The IR spectra were recorded on Nicolet FT-IR spectrometer and 1H NMR spectra (DMSO-d6) were recorded on VXRO-300 MHz instrument using TMS as internal standard.

General procedure for synthesis of substituted 2-amino-6-fluro-7-chlorobenzothiazoles 1[16]

To gl. acetic acid (20 mL) cooled to 20°C, was added 8 g (0.08 mole) ofpotassium thiocyanate and 1.45 g (0.01 mole) of substituted 3-chloro-4-fluroaniline. The mixture was placed in freezing mixture of ice-salt and mechanically stirred. 1.6 mL of bromine in 6 mL of glacial acetic acid was added from a dropping funnel at such a rate that the temperature never rose beyond 0°C. After all the bromine was added (105 min), the solution was stirred for 2 hr below rt and at rt for 10hr. It was then allowed to stand overnight, during which period an orange precipitate settled at the bottom. Water (6 mL)was added quickly and the slurry was heated to 85°C on a steam-bath and filtered hot. The orange residue was placed in reaction flask and treated with 10 mL of gl. acetic acid heated again to 85°C and filtered. The combined filtrate was cooled and the precipitate was collected. These compounds can be recrystallized from benzene:ethanol (1:1) as reported

General procedure for the synthesis of2,4-thiazolidinediones2[17]

In a 250 mL three-necked flask was placed, a solution containing 56.5 g (0.6 M) of chloroacetic acid in 60 mL of water and 45.6 g (0.6M) of thiourea dissolved in 60 mL of water. The mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 mL of concentrated hydrochloric acid from a dropping funnel. The flask was then connected with a reflux condenser and gentle heat applied to effect complete dissolution, after which the reaction mixture was stirred and refluxed for 8-10 hr at 100-10°C. On cooling, the contents of the flask solidified into a cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It can be recrystallized from ethyl alcohol.

Synthesis of 5-benzylidine 2,4-thiazolidinediones 3[18].

In a 250 mL 3-necked round-bottomed flask provided with a Dean-Stark apparatus, benzaldehyde (20 g, 0.188 mole) and 2,4-thiazolidinedione (22 g, 0.188 mole) were together suspended in dry toluene. To this a catalytic amount of piperidine (1 mL) was added. The mixture was refluxed with stirring. After the complete removal of water and when the temperature crossed 110°C the reaction mixture was stirred for a further 1 hr. On cooling, the product precipitated out from toluene. The compound can be further purified with dry toluene and dry ethanol.

Synthesis of 4′-chlorosulphonylbenzylidene 2,4-thiazolidinedione 4[18].

Benzylidine-2,4-thiazolidinedione (8 g, 0.0388 mole) was placed in a 100 mL round-bottomed flask equipped with a condenser and a dropping funnel. Chlorosulphonic acid (18.08 g, 0.155 mole) was added at rt using the dropping funnel. The reaction was found to be exothermic. After addition of chlorosulfonic acid was over the reaction mixture was refluxed for 1 hr on a waterbath. The reaction mass was cooled and poured in a thin stream with stirring into crushed ice contained in a 1L beaker. It can be filtered and dried and purified by recrystallization from ethanol.

Synthesis of 2-amino [5′(4-sulphonylbenzylidine) -2,4- thiazolidinedione] – 7 – chloro – 6 -fluorobenzothiazole

Substituted 2-Amino-6-fluoro-7chlorobenzothiazole **1**(0.1 mole) and 4′-chloro-sulphonyl-benzylidine-2,4-thiazolidine dione **4**(0.1 mole) were added to a mixture of 4 mL of dry pyridine and 20 mL of acetic anhydride5. The mixture was refluxed for 2 hr, reaction mixture

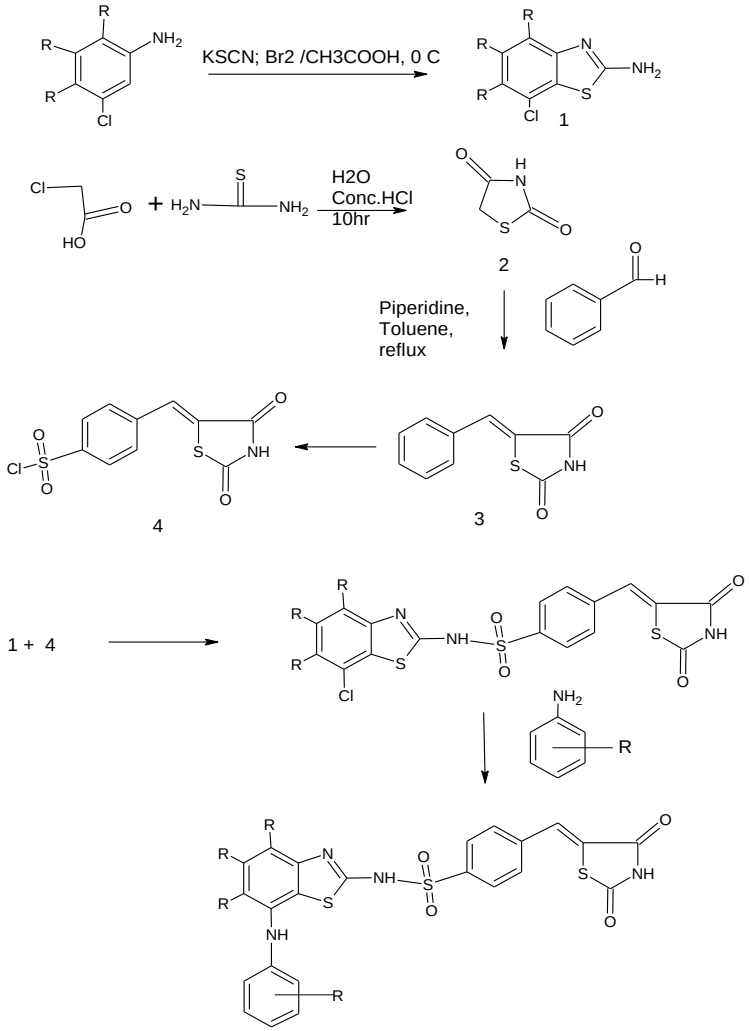
was then poured into 20 mL of ice-water and the solid obtained filtered and recrystallized from ethanol to give the desired product. This product can be treated with equimolar quantities of various substituted anilines, morpholine, piperazine and benzyl amine and in each case refluxed for 2 hr, in presence of DMF. The mixture was cooled and poured into crushed ice. The solid separated was filtered, washed with water and dried. It was purified by recrystallization from ethanolbenzene mixture (1:1).

Antidiabetic activity[19]

The acclimatized animals were kept fasting for 24 hr with water adlibitemandalloxan monohydrate (120 mg/Kg i.p.) in normal saline was then administered. After 1 hr of alloxan administration the animals were given ad libitem, 5% dextrose solution which was administered via feeding bottle for a day to overcome the early hypoglycemic phase. The blood glucose regulator was monitored after alloxination by withdrawing a drop of blood from the tail vein by tail tipping method. The blood was dropped on the dextrostrix reagent pad. The strip was inserted into microprocessor digital blood gluco meter and the readings were noted.

After 72 hr rats having blood glucose level beyond 150 mg/dL of blood were selected for the study and divided into 6 groups (n=6). The quantity of thiazolidinedione derivatives quivalent to average human intake of 200mg/kg at a time was calculated for a single dose of 36mg/kg (for acute study). The test compounds were administered orally by mixing with CMC (0.25 %) solution. The blood glucose level was monitored at 0 hr, 1 hr, 3 hr and 6 hr respectively

SCHEME

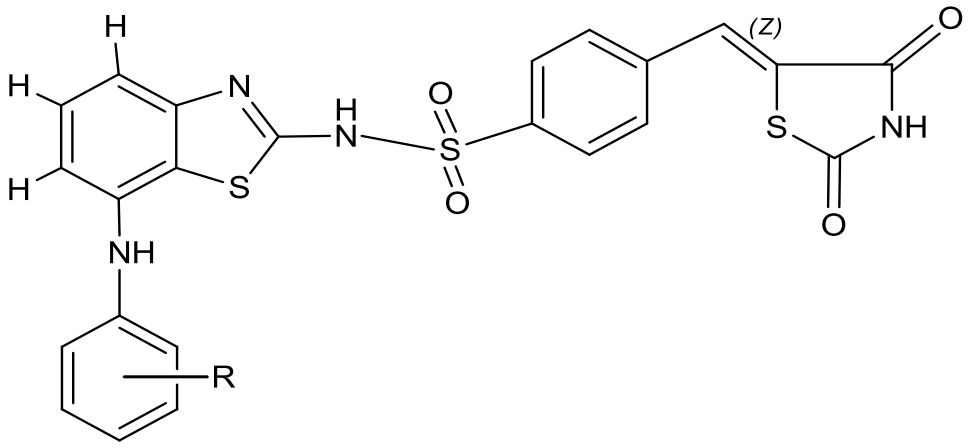


2. RESULTS AND DISCUSSION

In our current research, different derivatives of thiadiazoles (A1-A4) were synthesized. Compounds were identified and characterized by their physic-chemical data i.e., melting point and R_f values.

The structure of the synthesized compounds were established by spectral (IR, ^{1}H NMR) data interpretation. The fine points of Physico-Chemical data, structural characterization, anti-diabetic activity study results of the synthesized compounds are discussed below section.

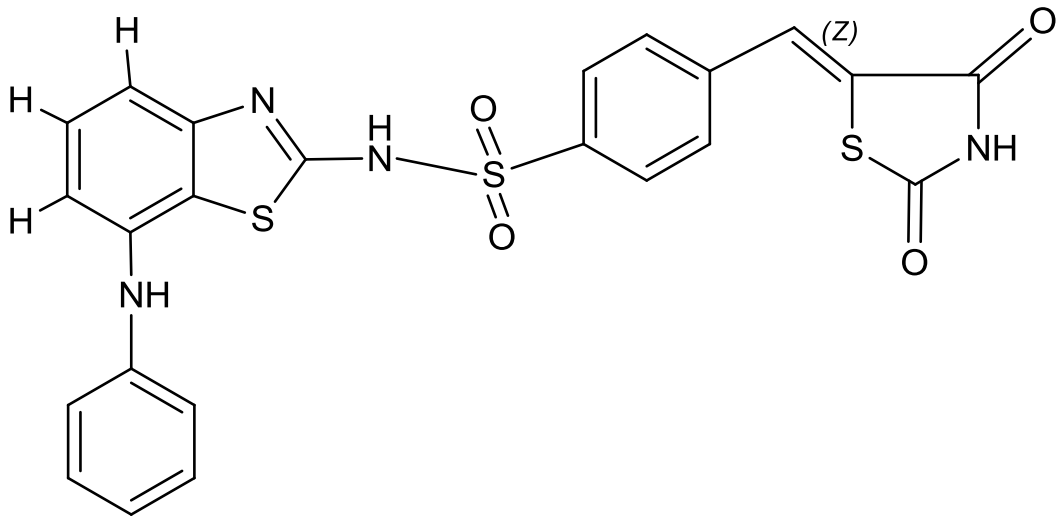
IDENTIFICATION AND CHARACTERIZATION OF SYNTHESIZED COMPOUNDS Physico-chemical data of thiazolidinedione derivatives (A1-A5)



Compound	R	Molecular formula	Mol. Wt.	Yield (%)	Melting point(^{0}C)	Solubility	R_f value
A_1	H	$C_{23}H_{15}N_4O_4S_3F$	526	62	120-124	DMSO	0.75*
A_2	m-NO_2	$C_{23}H_{14}N_5O_6S_3F$	571	79	218-220	DMSO	0.50*
A_3	p-COOH	$C_{24}H_{15}N_4O_6S_3F$	570	68	200	DMSO	0.32**
A_4	$NHCH_2$-C_6H_6	$C_{24}H_{17}N_4O_4S_3F$	540	65	115-119	DMSO	0.48*

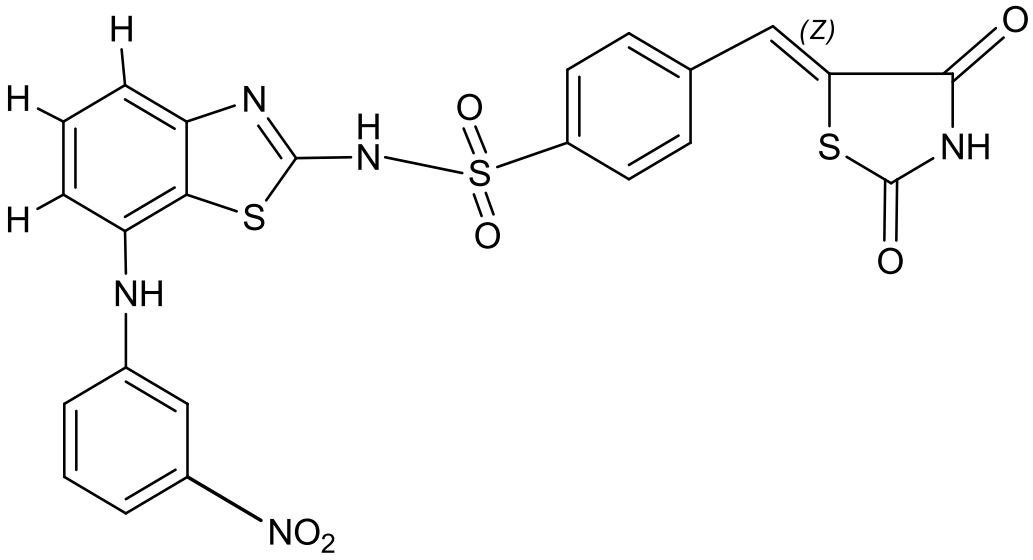
Mobile phase A1: n-hexane: Ethyl acetate (1.4:0.6); A2 & A4: n-hexane: Ethyl acetate (1.6:0.4); A3: n-hexane: Ethyl acetate (0.4:1.6).

A1



IUPAC Name	(Z)-4-((2,4-dioxothiazolidin-5-ylidine)methyl)-N-(phenylamino)benzo(d)thiazol-2-yl)benzenesulfonamide
Molecular Formula	$C_{23}H_{15}N_4O_4S_3F$
Molecular Weight	526
Colour	Black
Appearance	Flakes
IR Spectra data	(C—NH str) 3414.82cm^{-1}; (Ar C-H str 1900.10cm^{-1}; (C=C str in Aromatic Hydrocarbon) 1654.13cm^{-1}; (C=N str) 1494.41cm^{-1}; (C-S-C str) 679.06cm^{-1}; (S=O str) 1420.91 cm^{-1};(C=O str) 1689.
NMR Spectra data	^{1}HNMR-2.5 (3H, t, 3NH), 7.5-7.35 (2H, m, Aryl-H), 7.50 (5H,m, Aryl-H), 7.74-7.7 (4H, m, ArylH), 2.25 (1H, d, C=H).

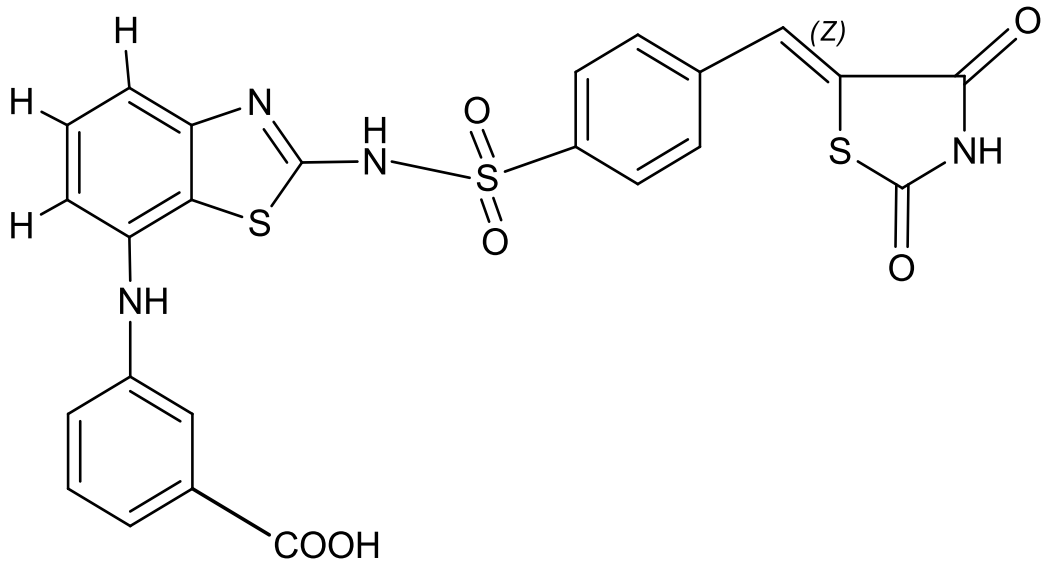
A2



IUPAC Name	(Z)-4-((2,4-dioxothiazolidin-5-ylidine)methyl)-N-(7-((3-nitrophenyl amino)benzo(d)thiazol-2-yl)benzenesulfonamide
Molecular Formula	$C_{23}H_{14}N_5O_6S_3F$
Molecular Weight	571

Colour	Black
Appearance	Flakes
IR Spectra data	(C—NH str) 3424.22cm^{-1}; (C-H str in Cycloalkanes 2902.01cm^{-1}; (C=C str in Aromatic Hydrocarbon) 1645.18cm^{-1}; (C=N str) 1459.14cm^{-1}; (C-S-C str) 669.06cm^{-1}.(N-O str) 1530.03cm^{-1}; (S=O str) 1410.71 cm^{-1}
NMR Spectra data	^{1}HNMR-2.5 (3H, t, 3NH), 7.5-7.35 (2H, m, Aryl-H), 7.50 (4H,m, Aryl-H), 7.7-7.5 (4H, m, Aryl-H), 2.25 (1H, d, C=H).

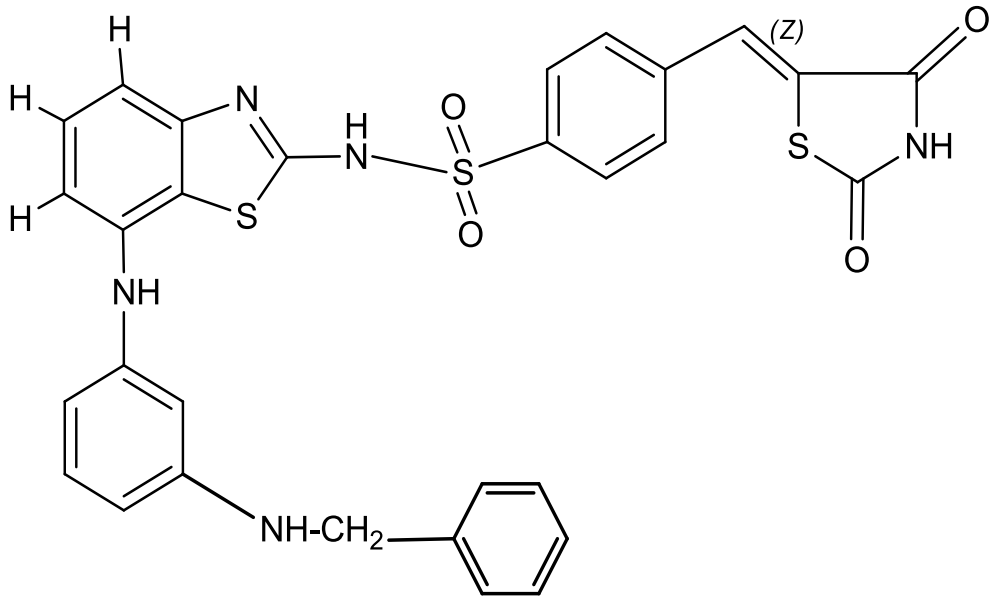
A3



IUPAC Name	(Z)-3-((2-(4-((2,4-dioxothiazolidin-5-ylidine)methyl)phenyl sulfonamide)benzo(d)thiazol-7-yl)amino)benzoic acid
Molecular Formula	$C_{24}H_{15}N_4O_6S_3F$
Molecular Weight	570
Colour	Black
Appearance	Flakes
IR Spectra data	(C—NH str) 3420.02cm^{-1}; (C-H str in Cycloalkanes 2927.07cm^{-1}; (C=C str in Aromatic Hydrocarbon) 1645.12cm^{-1}; (C=N str) 1449.41cm^{-1}; (C-S-C str) (S=O str) 1410.01 cm^{-1} 689.00cm^{-1}; (OH str) 2890.32cm^{-1}; (C=O str) 1718.69 cm-^{1}

NMR Spectra data	^{1}HNMR-2.5 (3H, t, 3NH), 7.4-7.35 (2H, m, Aryl-H),7.5-7.6 (4H,m, Aryl-H), 7.7-7.5 (4H, m, ArylH), 7.47 (1H of COOH), 2.25 (1H, d, C=H).

A4



IUPAC Name	(Z)-N-(7-((3-(benzylamino)phenyl)amino)benzo((2,4-(d)thiazol-2-yl)-4-((2,4-dioxothiazolidin-ylidine)methyl)benzene sulfonamideamino)benzoic acid
Molecular Formula	$C_{24}H_{17}N_4O_4S_3F$
Molecular Weight	540
Colour	Black
Appearance	Flakes
IR Spectra data	(C—NH str) 3414.82cm^{-1}; (C-H str in Cycloalkanes 2929.10cm^{-1}; (C=C str in Aromatic Hydrocarbon) 1654.13cm^{-1}; (C=N str) 1449.41cm^{-1}; (C-S-C str) 669.06cm^{-1}; (S=O str) 1400.72 cm^{-1}
NMR Spectra data	^{1}HNMR-2.5 (3H, s, 3NH), 7.27 (5H, s, Aryl), 7.35 (1H, m, Aryl-H), 7.50 (1H,d, Aryl-H), 7.74-7.7 (2H, d, Aryl-H), 7.83 (1H, d, Aryl-H), 7.84-7.8 (1H,d, Aryl-H), 2.25 (2H, d, C-H)

ANTI-DIABETIC ACTIVITY of the synthesized thiazolidinedione (A1-A4) in Albinowistar rats

Comp	Time in hours			
	0	1	3	6
A1	300.5±10.12**	134.5±2.723	123.5±5.236	116.5±5.90**
A2	320±15.811**	145.5±2.26	137±3.80	123.5±1.109*
A3	311±10.496	134.5±3.70	125.75±4.36	116.2±2.17**
A4	283±43.76*	205.75±49.7	166±38.92	124.5±13.16*
CONTROL	184±10.51	163±6.51	155.5±4.80	150.25±4.008

* P < 0.05, **P<0.01

The mean± S E of the blood glucose level was calculated for each group and the results were analysed by ANNOVA and student t-test by comparing the results of 1, 3 and 6 hr with 0hr. This test is applied to assess the statistical significance of difference between two independently drawn sample means.

The P<0.05 indicates statistically significant. P<0.01 indicates statistically more significant.
The title compounds were synthesized as shown in scheme. The compounds A1-4 were screened for their antidiabetic by alloxan induced tail tipping method. The albino rats of either sex weighing between 150-200 g were selected. The blood glucose level was induced and the study was carried in six different groups.

3. SUMMARY AND CONCLUSION

In recent times heterocycles (hybrid molecules) are reported to show broad spectrum of pharmacological properties and have attracted much attention towards them. Therefore it was planned to investigate heterocycles bearing thiazolidinedione moieties and screen for their biological activites.

The main focus of this research work was to synthesize, purify, characterize and evaluate substituted thiazolidindione derivatives that can be potentially used as new lead compounds in drug discovery particularly as anti-diabetic agents.

A series of compounds titled 2-amino (5’ (4-sulfonylbenzylidine) 2, 4-thiazolidinedione) sulphonamide derivatives (C1-C5) are being synthesized using appropriate synthetic procedures as per the scheme given in the experimental work.

The yield of the synthesized compounds was found to be in range of 60-79% .The synthesized compounds purity was ascertained by melting point determination and appearance of single spot in the TLC.

The structure of the synthesized compounds was confirmed by different spectrophotometrical methods. Specific peak was identified for all the compounds denoting aromatic, CH, C-N, C-S, NH, C=N, S=O and COOH group etc. ^{1}H NMR study of the synthetic compounds gave confirmation about the presence of specific proton in certain environment. Splitting content and area under peak denotes the chemical environment and number of protons. NMR data confirms the synthesis of targeted compounds.

The synthesized compounds were screened for anti- diabetic activity. All the derivatives A1-A4 (H, m-NO_2, p-COOH, $NHCH_2C_6H_6$ respectively) showed significant activity.

All the four compounds A1-4 showed good anti-iabetic activity. The results were obtained by measuring the mean SE± and p values. The title compound and their derivatives were found to be promising anti-diabetic agents. So, it can be considered as lead molecule for further biological investigation in development of new antitubercular drugs.

Acknowledgement
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