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Synthesis, Characterization and Biological Evaluation of Thiazolidinedione Derivative as Novel Antidiabetic Agents

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Thiazolidinedione derivative have Antihyperglycemic activity, they are agonists for the peroxisome proliferator-activated receptor (PPAR), which controls glucose synthesis, transport, and utilization via regulating the transcription of insulin-responsive genes. A number of novel insulin sensitizers are currently being researched. Several of these are derivatives of Thiazolidinedione, but others have different chemical structures. In this work, we created some new Thiazolidinedione derivative based on structure–activity relationship as closely as feasible. The Thiazolidine-2,4-Dione derivatives were manually developed and synthesized using the proper synthetic techniques, then tested in vitro for antihyperglycemic action using the Sucrose loading model (SLM) and the Alloxan induced diabetes model (AIDM). The newly synthesized Thiazolidine-2,4-Dione derivative was characterized using infrared (IR) and proton (H) nuclear magnetic resonance. In this study we found that Compound M-4 has a lot of antihyperglycemic action, thus it's a good idea to think about using it as a lead material for the creation of anti-diabetic drugs.

Keywords: Insulin action enhancers; peroxisome proliferator-activated receptor; thiazolidinediones; antidiabetic activity; Sucrose loaded model (SLM).

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1. INTRODUCTION

Diabetes mellitus is a significant medical condition with rising rates of occurrence and fatality. Diabetes mellitus is characterized by elevated plasma glucose concentrations resulting from insufficient insulin and insulin resistance [1]. According to the International Diabetes Federation (IDF), diabetes affected roughly 463 million persons over the age of 18 (9.3% of the global population) and 136 million people over the age of 65 in 2019 [2].

The following two categories can be used to categorize different forms of diabetes mellitus that have been described.

Type 1 is insulin-dependent diabetes mellitus (IDDM), Insulin-dependent diabetes mellitus (IDDM) is a type of diabetes in which the body produces no insulin. The most vulnerable are children and young adults. Approximately 5–10% of diabetics have type 1 diabetes.

Type 2 is noninsulin-dependent diabetes mellitus (NIDDM), Noninsulin-dependent diabetes mellitus (NIDDM) is the most prevalent kind of diabetes, in which the body does not make enough or improperly uses released insulin. accounting for 90–95% of diabetes. Due to an increase in the number of old individuals, as well as a higher incidence of obesity and sedentary lifestyles, type 2 diabetes is approaching epidemic proportions [3,4].

1.1 Diabetes Medication

If food, exercise, and a healthy body weight aren't enough to keep your blood sugar under control, you may need to start taking medication. Insulin is also included in diabetes medications. Oral medicines are rarely used by persons with Type 1 diabetes. Medications for Diabetic People with Type 2 diabetes who have had high blood sugar for less than ten years and are of normal weight or obesity are the greatest candidates [5].

1.1.1 Biguanide

Galega officinalis, a herbaceous plant, was discovered to contain guanidine, galegine, and biguanide, which were discovered to be useful in the treatment of diabetes in the Middle Ages, which decreased blood glucose levels, Metformin is a biguanide that is the main first-line oral drug of choice in the management of Type 2 diabetes across all age group, Metformin inhibits gluconeogenesis by activating adenosine monophosphate-activated protein kinase in the liver, inducing hepatic glucose absorption and reducing gluconeogenesis via complicated actions on mitochondrial enzymes. Metformin is well tolerated, with just a minor risk of hypoglycemia and a modest risk of weight gain [6].

1.1.2 GLP-1 receptor agonists

Exenatide and liraglutide are the only GLP-1 receptor agonists currently marketed. These medicines have a higher resistance to DPP4 enzymatic breakdown. In young patients with recent diagnosis of Type 2 diabetes, central obesity, and abnormal metabolic profile, one should consider treatment with GLP-1 analogs that would have a beneficial effect on weight loss and improve the metabolic dysfunction. In renal failure, GLP-1 analogues are not recommended [7].

1.1.3 DPP-4 Inhibitors

Dipeptidyl peptidase 4 inhibitors include sitagliptin, saxagliptin, vidagliptin, linagliptin and alogliptin. These drugs can be taken alone or in combination with metformin, sulfonylureas, and TZD. This treatment is similar to other oral diabetes medications. Gliptins have not been shown to increase the risk of hypoglycemia when compared to controls [8].

1.1.4 SGLT2 Inhibitors

Canagliflozin, dapagliflozin, and empagliflozin are novel glucosuric medicines that inhibit sodium-glucose cotransporter. By inhibiting SGLT2, these drugs promote insulin-independent glucose reduction by limiting glucose reabsorption in the proximal renal tubule [9].

1.1.5 Sulfonylureas

By inhibiting the K_{ATP} channels, sulfonylureas lower blood glucose levels by increasing insulin secretion in the pancreas. They also limit gluconeogenesis in the liver. Sulfonylureas slow the breakdown of lipids into fatty acids and lower insulin clearance in the liver. Sulfonylureas are currently prescribed as second line or add-on treatment options for management of Type 2 diabetes They are divided into two groups, first-generation agents, which includes chlorpropamide, tolazamide and tolbutamide and second-generation agents, which includes glipizide, glimepiride and glyburide [10].

1.1.6 Meglitinide

Meglitinides (repaglinide and nateglinide) are non-sulfonylurea secretagogues, which was approved as treatment for Type 2 diabetes in 1997. Meglitinide shares the same mechanism as that of sulfonylureas it also binds to the sulfonylurea receptor in ß-cells of the pancreas. In individuals with irregular meal schedules or those who have late postprandial hypoglycemia while taking a sulfonylurea, rapid-acting secretagogues (meglitinides) may be administered instead of sulfonylureas [11].

1.1.7 Thiazolidinedione

Like biguanides, TZDs improve insulin action. Rosiglitazone and pioglitazone are representative agents. TZDs are PPAR agonists that increase glucose absorption in a variety of tissues, including adipose, muscle, and liver. Mechanisms of action include diminution of free fatty acid accumulation, reduction in inflammatory cytokines, rising adiponectin levels, and preservation of ß-cell integrity and function, all leading to improvement of insulin resistance and ß-cell exhaustion. TZDs selectively enhance or partially mimic certain actions of insulin, causing a slowly generated anti hyperglycemic effect in Type 2 diabetic patients [12].

2. MATERIALS AND METHODS

All reactions were carried out under optimum laboratory conditions. Solvents and reagents used were of laboratory grade and were purified by distillation and crystallization techniques where ever necessary and their melting point were checked with the available literature. The synthesized compounds were purified by recrystallization. The open capillary method was used to determine the melting points of newly synthesized compounds, and the results were uncorrected. The final products were purified by recrystallization and purity was checked by TLC. Using a KBr pellet, the IR spectra of the compounds were recorded on a JASCO FT/IR-5300 spectrometer. 1H-NMR spectra were recorded BRUKER DPX-400 MHz on a spectrometer using TMS as internal standard. The spectra were obtained in chloroform and the chemical shift values are reported as values in ppm relative to TMS as internal standard.

2.1 Synthesis

2.1.1 General scheme for synthesis

Synthesis of all compounds have been carried out using the reaction of 4-formylbenzoic acid and thiazolidine-2,4-dione to produce the reaction intermediate (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzoic acid. Then intermediate was reacted with substituted aniline to produce the final product [13]. General scheme for synthesis of different derivative is given into Fig. 1

2.2 Procedure of Synthesis

2.2.1 Synthesis of (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzoic acid

A mixture of thiazolidine-2,4-dione (55 mg, 0.2 mmol), 4-carboxybenzaldehyde (30 mg,0.2 mmol), and a drop of piperidine in absolute ethanol (0.5 ml) was refluxed for 2 hrs. The reaction was monitored using thin layer chromatography (TLC) on silica gel-G coated plates with ethyl acetate and petroleum ether (3:7) as the solvent, and the results were observed under UV light. Solvent was evaporated, and the residue was crystallized from ethanol to yield the final product [14,15]. Fig. 2 depicts a chemical reaction.

2.2.2 Synthesis of (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-phenyl benzamide derivatives

A solution of (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzoic acid (1mmol) in N, N-dimethylformamide (15 ml) was added to N-ethyl-N'-(dimethyl amino propyl)-carbodiimide hydrochloride (1.5 mmol), 1-hydroxybenzotriazol (1.5 mmol) and triethylamine (2.5 mmol), the mixture was stirred for 5 min at room temperature, then substituted amine (1.5 mmol) was added, the reaction mixture was stirred overnight at this temperature until the start material disappeared as monitored by TLC. The mixture was poured into ice water (80 ml) and extracted with ethyl acetate (4 – 30 ml). The combined organic extracts were washed with a 50 mL saturated sodium chloride aqueous solution, dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure; the residue was purified by column chromatography to get the final product [16]. Fig. 3 depicts a chemical reaction. Table 1 shows the structures of many synthesized derivatives.

2.3 Biological Evaluation

Experimental induction of diabetes mellitus in animal models is essential for the advancement

of our knowledge and understanding of the various aspects of its pathogenesis and ultimately finding new therapies and cure**.** As a result, animal models of diabetes are extremely valuable and beneficial in biomedical research since they promise fresh insights into human diabetes. Because of their tiny size, short generation interval, easy availability, and cost concerns, rats are used in the majority of accessible models. Diabetes mellitus is commonly produced in laboratory animals for research purposes. Experimental diabetes mellitus is generally induced in laboratory animals by several methods that include. chemical, surgical and genetic (immunological) manipulations [17].

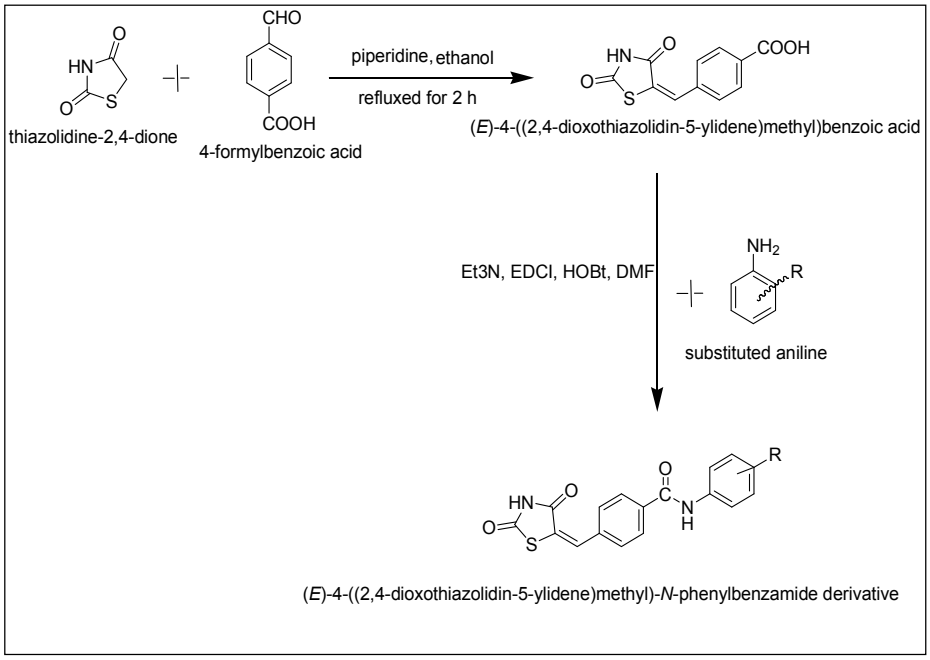


Fig. 1. General scheme for synthesis of different derivative

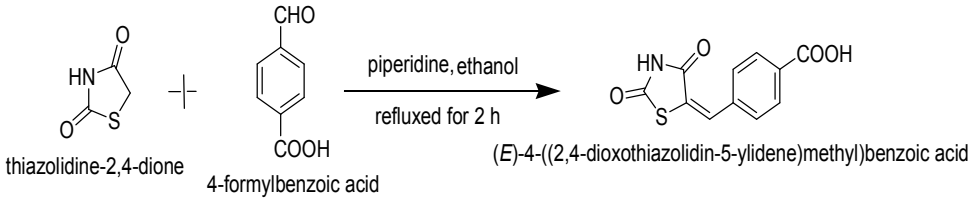


Fig. 2. Synthetic scheme of (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzoic acid

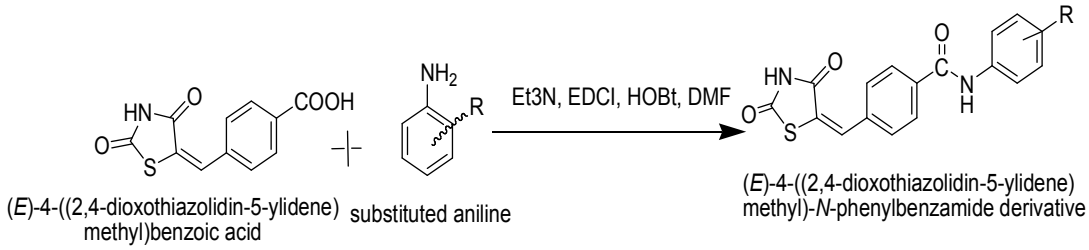
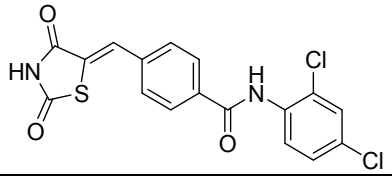
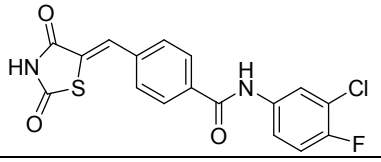
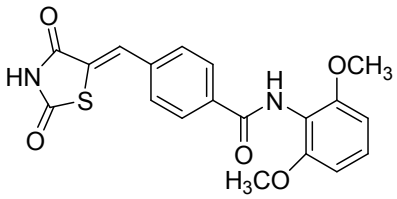
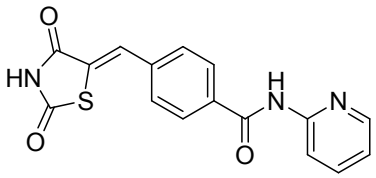
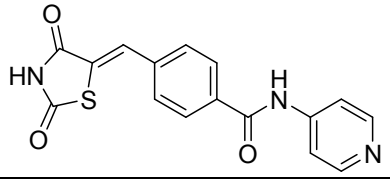
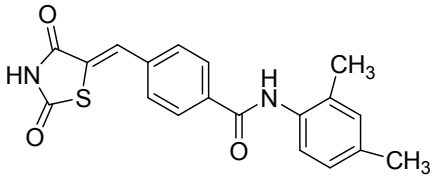
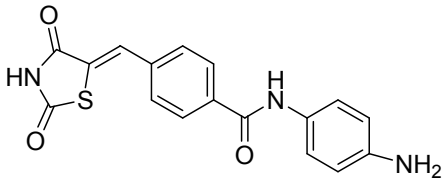


Fig. 3. Synthetic scheme of (E)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-phenyl benzamide derivative

Table 1. Synthesized Thiazolidinedione derivatives

Code	Structure	IUPAC Name
M1		**(**Z)-N-(2,4-dichlorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide
M2		**(**Z)-N-(3-chloro-4-fluorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide
M3		(Z)-N-(2,6-dimethoxyphenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide
M4		(Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-(pyridin-2-yl) benzamide
M5		(Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-(pyridin-4-yl) benzamide
M6		**(**Z)-N-(2,4-dimethylphenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide
M7		(Z)-N-(4-aminophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide

Animal Models for Diabetes

- Chemically induced diabetes
  1. Streptozocin (STZ) induced diabetes
  2. Alloxan induced diabetes
  3. Goldthioglucose obese diabetic mouse model
  4. Atypical antipsychotic-induced diabetic model
- Surgically induced diabetes
- Genetically induced diabetic animal model
- Virus induced diabetic animal model
- Oral sucrose loading animal model

Most commonly used methods for evaluation of diabetic drugs are sucrose loaded model alloxan induced diabetic model and streptozotocin induced diabetic model.

Alloxan is also called as mesozalylurea, mesoxalylcarbamide 2, 4, 5, 6-tetraoxohexa hydro pyrimidine or pyimidinetetrone. It's a uric acid derivative that's extremely unstable in water at neutral pH but quite stable at pH 3. With its reduction product, dialuric acid, alloxan generates reactive oxygen species in a cyclic redox process. Autoxidation of dialuric acid generates superoxide radicals, hydrogen peroxide and, in a final iron-catalyzed reaction step, hydroxyl radicals. These hydroxyl radicals are ultimately responsible for the death of the beta cells, which have a particularly low antioxidative defense capacity, and ensure state of insulin-dependent alloxan diabetes [18,19,20].

Oral sucrose loading method is often referred to as physiological induction of diabetes mellitus because the blood glucose level of the animal is transiently increased with no damage to the pancreas. In the clinical setting, it is known as Oral sucrose e tolerance test has been widely used for the diagnosis of impaired sucrose tolerance, diabetes mellitus and gestational diabetes [21].

Streptozocin (STZ) is a glucosamine-nitrosourea compound that has been in clinical trial since 1967. Intra-venous injection of 60mg/kg dose of streptozotocin in adult rats causes swelling of pancreas followed by degeneration of Langerhans islet beta cells and induces experimental diabetes mellitus in the 2-4 days. Three days after degeneration of beta cells, diabetes was induced in all animals [22].

3. RESULTS & DISCUSSION

According to scheme, derivative of thiazolidine-2,4-dione was synthesized with good percentage yield. The melting points of synthesized compounds were determined by open capillary method and are uncorrected.

3.1 Structure features of Synthesized Compounds

From structure-activity relationship study it has been observed that glitazones normally need to possess a polar thiazolidinedione ring system as a head followed by hydrophobic benzyloxy moiety as trunk linked by a two-carbon atom linker and a hydrophobic ring as a tail for better antihyperglycemic activity. The keto group in the thiazolidinedione is the group that is complementary in binding with the PPARγ binding site [23]. Keeping all the above structural features in mind we have designed newer compound in which lipophilic moiety is substituted by heterocyclic ring and substituted benzene which gives a better antihyperglycemic activity. It is also found when we attached Pyridine ring with ethyl ether linkage and thiazolidinedione moiety resulting compound show dramatically improvement in hypoglycemic activity compared to glitazones [24]. So due to this we also designed and synthesizes 2 Compounds M4 and M5 Which Contain Pyridine ring. Fig. 4 depicts pharmacophore structure of PPARγ agonists and Fig. 5 Show General structure of Synthesized Compounds.

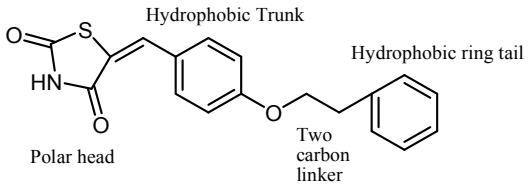


Fig. 4. Pharmacophore structure of PPARγ agonists

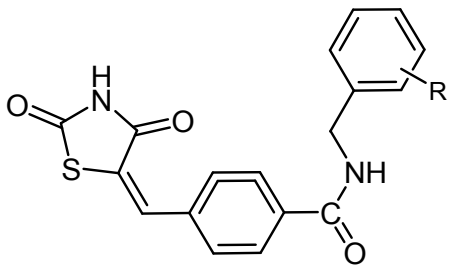


Fig. 5. General structure of synthesized compounds

3.2 Chemistry

3.2.1 Characterization of (Z)-N-(2,4-dichlorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide M1

Melting point: 162-164°C, Molecular Weight: 395.26 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{17}H_{13}Cl_2N_2O_3S$. R_f = 0.37. The IR spectrum of the compound by KBr methods. It exhibits intense bands at 3428 cm^{-1} (N-H stretching), 1732 cm^{-1} (C=O stretching), 2920 cm^{-1} (C-H), 1645 cm^{-1} (C-C) 1120 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 3.61(s, 3H); 6.81-7.29 (m, 9H); 8.53 (s, 1H); 7.71(s, 1H).

3.2.2 Characterization of (Z)-N-(3-chloro-4-fluorophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide M2

Melting point: 140-142°C, Molecular Weight: 378 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{17}H_{12}FClN_2O_3S$. R_f = 0.47. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3419 cm-^{1} (N-H stretching), 1712 cm^{-1} (C=O stretching),2982 cm^{-1} (Ar C-H), 1080 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H): 8.98 (d, 2H).

3.2.3 Characterization of (Z)-N-(2,6-dimethoxyphenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide M3

Melting point: 140-142°C, Molecular Weight: 384 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{19}H_{16}N_2O_5S$. R_f = 0.35. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3421 cm^{-1} (N-H stretching), 1705 cm^{-1} (C=O stretching), 3050 cm^{-1} (Ar C-H), 1085 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 3.49 (s, 2H); 3.51 (s, 3H); 3.72 (s, 3H); 3.73 (s, 3H); 3.82 (s, 2H); 6.84 (m, 1H); 6.90(m, 1H); 6.94 (m, 1H); 7.08 (m, 1H); 7.18 (m, 1H); 7.30 (m, 2H).

3.2.4 Characterization of (Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-(pyridin-2-yl) benzamide M4

Melting point: 140-144°C, Molecular Weight: 327.36 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{16}H_{13}N_3O_5S$. R_f = 0.40. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3426 cm^{-1} (N-H stretching), 1728 cm^{-1} (C=O stretching), 2917 cm^{-1} (C-H), 1115 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68, (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 7.98 (d, 2H).

3.2.5 Characterization of (Z)-4-((2,4-dioxothiazolidin-5-ylidene) methyl)-N-(pyridin-4-yl) benzamide M5

Melting point: 142-146°C, Molecular Weight: 327.36 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{16}H_{13}N_3O_5S$. R_f = 0.40. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3428 cm^{-1} (N-H stretching), 1726 cm^{-1} (C=O stretching), 2915 cm^{-1} (C-H), 1112 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 3.49 (s, 3H); 3.69 (s, 2H); 3.84 (s, 6H); 6.88 (t, 1H); 7.20 (d, 2H); 7.28 (m, 2H); 7.39 (m, 2H).

3.2.6 Characterization of (Z)-N-(2,4-dimethylphenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide M6

Melting point: 143-148°C, Molecular Weight: 353 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{19}H_{16}N_2O_3S$. R_f = 0.47. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3426 cm^{-1} (N-H stretching), 1728 cm^{-1} (C=O stretching), 1640 cm^{-1} (C-C), 2917 cm^{-1} (C-H), 1115 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 2.46 (s, 3H); 3.47 (s, 3H); 3.68 (s, 2H); 7.27 (m, 2H); 7.39 (m, 4H); 8.80 (d, 2H).

3.2.7 Characterization of (Z)-N-(4-aminophenyl)-4-((2,4-dioxothiazolidin-5-ylidene) methyl) benzamide M7

Melting point: 142-144°C, Molecular Weight: 339.37 g, Solid, Solubility In DMSO, Ethanol etc. was analyzed for $C_{17}H_{13}N_3O_3S$. R_f = 0.49. The IR spectrum of the compound by KBr methods. It exhibits intense bands at It exhibits intense bands at 3427 cm^{-1} (N-H stretching), 1718 cm^{-1} (C=O stretching), 2961 cm^{-1} (Ar C-H), 1079 cm^{-1} (C-O-C), 1H-NMR spectrum in DMSO, it shows peaks at δ (ppm): 3.52 (s, 3H); 3.73 (s, 2H); 7.94 (t, 2H); 7.31 (m, 3H); 7.43 (m, 3H); 8.51 (m, 1H); 8.58 (m, 2H); 8.76 (m, 2H).

Table 2. Biological evaluation of synthesized compound

Sr. No.	Groups	Compounds	AlBGL*(mg/dl)	Average blood glucose level(mg/dl) at different hours					
			0 hrs	1 hrs	2 hrs	3 hrs	4 hrs	5 hrs	6 hrs	24 hrs
1.	Group-1	Normal	282.44±1.41	293.8±2.09	282.64±1.49	283.1±1.7	284.36±1.47	282.06±1.1	281±1	283±2.09
2.	Group-2	Control	287.12±1.87	283.72±1.7	282.5±2.97	282.92±2.4	282.3±1.91	283.14±1.7	281.9±3	282.2±2.9
3.	Group-3	M1	291.6±4.6	281. ±2.22	264.52±2.01	251.62±2.5	241.84±1.1	223±1.58	202.4±1	266.2±2.0
4.	Group-4	M2	294.8±3.4	270.48±3.8	244.7±1.700	244.88±1.4	214.88±2.11	224.26±2.1	190.6±2	255.66±2.
5.	Group-5	M3	287.9±6.3	274.34±3.3	268.2±1.898	223.06±2.4	197.44±1.51	191.6±4.03	175.2±1	166.4±3.5
6.	Group-6	M4	285.7±1.9	266.88±1.0	222.08±1.63	179±2.77	162.84±2.08	152.88±2.1	142.8±2	229.68±4
7.	Group-7	M5	286.8±1.4	261.98±1.	243.28±2.02	221.714±1.	198.62±1.50	163±1.92	154.4±1	243.84±2
8.	Group-8	M6	287.5±6.1	261.8±3.64	253.66±2.74	231.62±1.5	212.42±1.54	198.22±1.4	166.9±1	284.4±1.1
9.	Group-9	M7	288.9±3.7	274.28±3.3	244.32±3.99	214±2.454	189.24±1.56	171.64±5.0	161.6±2	254.54±1.
10.	Group-10	Rosiglitazone	286.2±4.6	257.98±3.3	224.28±3.28	202.34±2.5	179.8±1.484	158.52±0.7	145.9±3	233.7±1.6

**AlBGL – Alloxan Induced Blood Glucose Level*

3.3 Pharmacological Study

3.3.1 Test animals

An animal study was performed after getting the permission from Institutional An. Albino rats (160 ± 20 g) of either sex was acclimatized for at least 7 days prior to commencement of any experiment. Rats were randomly distributed into eight groups, five animals in each group. All animals were placed in polypropylene cages and maintained on standard pallet laboratory animal feed and water ad libitum. Animals were maintained at 22±2°C in light controlled (14h light/10h dark) room.

3.3.2 Preparation of dose

Each of the synthesized compounds was suspended in 1% gum acacia and the 40% sucrose solution was prepared in distill water.

3.3.3 Chemicals

Alloxan monohydrate (CDH, New Delhi; hyperglycemic agent Rosiglitazone (Franco-Indian Pharmaceutical Pvt Ltd., Mumbai, antihyperglycemic agent), Saline (0.9% NaCl).

3.4 Antihyperglycemic Activity

3.4.1 Sucrose loaded model (SLM)

Antihyperglycemic activity was studied in sucrose loaded hyperglycemic rats. Animals were divided into Ten groups (normal, control, standard and seven experimental) of five animals in each. The standard group received Rosiglitazone (20mg/kg), normal group received nothing and the untreated control group animals received only vehicle. Remaining groups were treated with 30 mg/kg of various synthesized compounds suspended in 1% gum acacia. 0 h blood sugar level was determined from overnight fasted animals. After 30 min of the drug treatment animals were fed with sucrose (2 g/kg) and blood glucose was determined after 30 min, 60 min, 90 min, and 120 min of the sucrose load. Blood glucose concentration was estimated by the glucose oxidase enzymatic method using a commercial glucometer and test-strips (Accu-chek Active TM Test meter).

3.4.2 Alloxan induced diabetic model (AIDM)

The diabetes in albino rats was experimentally induced by intraperitoneal administration of alloxan monohydrate (dose 120mg/kg body weight) in saline (0.9% NaCl). Prior to this, rats were fasted for 18 h but were allowed free access to drinking water. The rats were kept for next 24 h on 5% glucose solution in bottles in their cages to prevent hypoglycaemia. The blood glucose level was checked after 72 hrs. Animals with serum glucose levels 200–350 mg/dl were considered diabetic and were used for the study. After the induction of diabetes, the rats were divided into eight groups each containing five animals as discussed earlier.

The diabetic rats were fasted for 18 hrs. before treatment and blood samples were collected by puncture of retro-orbital plexus immediately with capillary tube under ether anesthesia. The blood glucose level was measured at 0 h (before treatment) and 1, 2, 3, 4, 5, 6, 24 hrs. (after treatment). The percentage fall in blood glucose level was calculated.

3.4.3 Estimation of blood glucose

Blood glucose level was estimated using electronic glucometer. The blood sample was placed on test strip and then test strip was inserted in glucometer. The blood glucose level (mg/dl) was displayed on the screen of glucometer. The test is based on the amperometry principle. The glucose dehydrogenase enzyme in the presence of coenzyme on the test strip converts the glucose in blood sample to gluconolactone. This reaction creates harmless electrical current that meter interprets for blood glucose. Result of antihyperglycemic activity is given into Table 2.

4. CONCLUSION

Diabetes is a metabolic illness that can be regarded as a major source of substantial economic loss, obstructing national progress. Furthermore, untreated diabetes causes a slew of long-term problems, including blindness, heart failure, and kidney failure. In order to prevent this alarming health problem, the development of research into new hypoglycemic and potentially antidiabetic agents are of great interest. Keeping all the above strategy in mind, we have synthesized and characterized Thiazolidine-2,4-dione derivative having structures similar to template pharmacophore structure. The physicochemical properties (Solubility, Melting point and molecular weight) of synthesized compounds were determined. The synthesized compounds were characterized by IR, 1H-NMR.

Result of biological activity confirmed that the compound number M4**,** M5 is highly active compound as compared to standard compound (Rosiglitazone) M4 and M5 contain Pyridine Ring which gives more % reduction of blood sugar level with compare to Rosiglitazone Finally, it was concluded that result obtained from in vivo biological activity on rat are significantly, so the compound M4 and M5 can be used as a lead molecule for the further development of more potent Thiazolidine-2,4-dione derivatives as oral hypoglycemic agent.

CONSENT

Not applicable.

ETHICAL APPROVAL

Biological Evaluation was done in Sumandeep Vidyapeeth deemed to be University which has Animal house facility, comprising of institutional animal ethics committee, which is being approved by Animal Regulatory body of Indian Government (Registration No: 947/PO/ERe/S/06/CPCSEA).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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