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Research Article

SYNTHESIS AND EVALUATION OF NOVEL THIAZOLIDINEDIONE DERIVATIVES FOR ANTIDIABETIC ACTIVITY

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ABSTRACT

The aim of study was to synthesize a new series of thiazolidinedione's. Thiazolidinedione's or glitziness forms a significant class of drugs which exhibit biological activities ranging from antidiabetic, anti-inflammatory, antibacterial, antifungal, antiviral and anticancer. In the present study reported a systematic synthesis of thiazolidinedione analogues. A new series of 2, 4-thiazolidinedione based derivatives have been synthesized by the condensation of various substituted phenoxy benzene amines and 4'-chlorosulphonyl 5-benzylidene-2, 4-thiazolidinedione. The structure of these compounds were established by IR and ^{1}H NMR. These new compounds *($F_1 – F_7$)* were evaluated for their antidiabetic activity on albino rats. Most of the compounds showed significant antidiabetic activity when compared with the standard drug metformin.

Keywords: Diabetes Mellitus, Thiazolidinedione, Antidiabetic activity.

INTRODUCTION

Diabetes Mellitus is a group of metabolic disorder characterized by chronic hyperglycemia. Symptoms of Diabetes Mellitus include frequent urination (polyuria), increased thirst (polydipsia), increased hunger (polyphagia) and weight loss. If left untreated, diabetes can cause complications. Long term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcer and damage to the eyes[1]. Diabetes mellitus is of two types, 1) Insulin dependent diabetes mellitus (IDDM) or juvenile diabetes or diabetes mellitus type 1 which result from the destruction of insulin producing beta cells in the pancreas.2) Noninsulin dependent diabetes mellitus(NIDDM) or adult onset diabetes or diabetes mellitus type 2 is characterized by insulin resistance or reduced insulin sensitivity. Although the frequency of diabetes is increasing only two classes of oral hypoglycemic agents are available: Sulfonylureas and Biguanides. Biguanides are banned in western countries due to its severe side effects mainly lactic acidosis. Sulfonylurea therapy has some problems such as primary or secondary failure of efficacy, enhancement of obesity and high incidence of hypoglycemia. A significant advancement has been made with the introduction of new class of compounds thiazolidine-2, 4-diones (TZDs) which act as insulin sensitivity enhancers[2].

The class of thiazolidinedione's (TZDs also called as "glitazones") was introduced in late 1990's as an adjunct therapy for type II diabetes mellitus and related diseases. 2, 4-thiazolidinediones (TZDs) have become a pharmacologically important class of heterocyclic compounds. Several studies have been reported that TZDs have acquired much importance because of their diverse pharmaceutical applications such as ant hyperglycemic, bactericidal, pesticidal, fungicidal, insecticidal, anticonvulsant, tuberculostatic, anti-inflammatory etc[3, 4]. The thiazolidinedione's are peroxisome proliferator-activated receptor agonist. The PPARγ receptor is a member of the nuclear hormone receptor of ligand activated transcription factors that regulate gene expression of several genes involved in fatty acid and carbohydrate metabolism and adipocyte differentiation. In addition to hypoglycemic activity, thiazolidinedione reduce insulin levels and improve insulin resistance, markedly reduce plasma free fatty acids, increase the storage of fat and often improve the blood lipid profile[5, 6].

MATERIALS AND METHODS[7, 8, 9]

The melting points were determined using open capillary tubes and are uncorrected. Purity of the all synthesized compounds was checked by thin layer chromatography technique (0.2 mm thickness of silica gelG plates) and iodine was used as visualizing agent. IR spectra were recorded on FT-IR3000A, Fourier Transform (Analytical Technologies) Infrared spectrophotometer using KBr disk method. ^{1}H NMR spectra were recorded on AVANCE (300 MHz) in dimethyl sulfoxide (DMSO) using tetramethylsilane (TMS) as an internal standard.

Synthesis of Thiazolidine-2, 4-dione (A)

In a 250 ml round bottomed flask transfer a 56.5 g of chloroacetic acid (0.6 ml) in a 60 ml of water and 45.6 g of thiourea (0.6mol) dissolved in 60 ml of water. The mixture was stirred for 15 minutes to form a white precipitate, accompanied by considerable cooling. To content of the flask, now added slowly 60 ml concentrated hydrochloric acid from dropping funnel. The flask was connected with reflux condenser and gentle heat applied to effect complete dissolution, after which

the reaction mixture was stirred and refluxed for 8-10 hrs. at 100-110^{0}C.On cooling the content of the flask solidified to mass of cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was recrystallized from ethanol. Yield: 73%: M.P: 124 – 126^{0}C.

Synthesis of 5-Benzylidene-2, 4-Thiazolidinedione (B)

In a 250 ml round bottomed flask benzaldehyde (20 g, 0.188 mole) and 2, 4-thiazolidinedione (22 g, 0.188 mole) were together suspended in dry toluene. To this catalytic amount of piperidine (1 ml) was added. The mixture was refluxed with stirring. After the complete removal of water and temperature crossed 110^0 C, the reaction mixture was stirred for a 1 hr. On cooling, the product precipitated from toluene. The compound was filtered and washed with cold, dry toluene and dry ethanol. Yield: 68%: M.P: 236 – 238^{0}C.

Synthesis of 4'-Chloro Sulphonyl -5-benzylidene-2, 4-Thiazolidinedione (C)

5-Benzylidene-2, 4-Thiazolidinedione (8 g, 0.0388 mole) was placed in a 100 ml round bottomed flask connected with a condenser and a dropping funnel. Chlorosulphonic acid (18.08 g, 0.155 mole) was added at room temperature using the dropping funnel. The reaction was found to be exothermic. After the addition of Chlorosulphonic acid was over the reaction mixture was refluxed for 1 hr. on a water bath. The reaction mixture was cooled and poured in a thin stream with stirring into crushed ice contained in a 1Lt beaker. It was filtered and purified by recrystallization from ethanol. Yield: 62%: M.P: 180 – 182^{0}C.

Synthesis of 4-Phenoxy nitrobenzene (D_1)

16 g (0.170 mol) of phenol and 8 g (0.143 mol) of potassium hydroxide were transferred to a 250 ml round bottomed flask and about 30 ml dimethyl formamide was added. The reaction mixture was heated to dissolve the solid. After cooling, about 1 g active copper and 15.8 g (0.1 mol) of 1-chloro-4-nitrobenzene were added, and the reaction mixture was refluxed for 2 hrs. maintaining the temperature at about 150^0 C. Then, it was cooled and poured into 50 ml of ice cold water and extracted twice with ethyl acetate (50 ml each time). The solvent was evaporated to get the green crystals of crude product.
Yield: 76%: M.P: 52 – 54^0 C
Similarly compounds **D_2 – D_8** were prepared by adopting similar procedure using appropriate phenol and 1-chloro-4-nitrobenzene.

Synthesis of 4-Phenoxy benzene amine (E1)

1.0 g (0.0046 mol) of 4-Phenoxy nitrobenzene (**D_1**) was transferred to a 250 ml round bottomed flask and about 15 ml of absolute alcohol was added. The reaction mixture was stirred to dissolve the solid. To this 4.73 g (0.0209 mol) of stannous chloride was added and refluxed for 4 hours. maintaining the temperature at about 78^0 C. Then, it was cooled and poured into 25 ml of ice-cold water and extracted twice with ethyl acetate (25 ml each time). The solvent was evaporated to get the crude product. It was purified by column chromatography using a mixture of pet ether: ethyl acetate (4:1) as an eluent to get a colorless solid. Yield: 93%: M.P: 62 – 65^{0}C.
Similarly compounds **E_2 – E_8** were prepared by adopting similar procedure using appropriate substituted 4- Phenoxy nitrobenzene.

Synthesis of 5-[4'-(substituted) sulphonylbenzylidene] 2, 4-Thiazolidinedione (F1)

4-Phenoxy benzene amine **E_1** (0.1 mole) and 4'-Chloro Sulphonyl -5-benzylidene-2, 4-Thiazolidinedione **C** (0.1 mole) were added to a mixture of 4ml of dry pyridine and acetic anhydride. The mixture was refluxed for 2hrs, reaction mixture was poured into 20 ml of ice water and solid obtained was filtered and recrystallized from ethanol.
Similarly compounds **F_2 – F_8** were prepared by adopting similar procedure using appropriate substituted 4-Phenoxy benzene amine.

General Procedure Of Anti Diabetic Activity[10, 11]

Wistar albino rats of either sex weighing 180 -300 g were selected for the study. After which animals were fasted for 24 hours. Alloxan monohydrate dissolved in normal saline and administered through intra peritoneal route at a dose of 150 mg/kg. After 1hr of alloxan administration rats were given 5% w/v dextrose solution in feeding bottle for a day to overcome early hypoglycemic phase. After 72 hours. rats with blood glucose level greater than 200 mg/dl and less than 400 mg/dl were selected. Such animals were divided into test, standard and control groups. Each group was consisting of six animals. Then test compounds were administered at 50 mg/kg oral dose in 0.25% w/v CMC solution. The blood glucose levels were observed at different time intervals of 0hr, 3hr and 6hr. The anti-diabetic activities of test compounds were given in Table 3.

RESULTS

A series of thiazolidinedione derivatives were synthesized by reacting 4'-Chloro Sulphonyl -5-benzylidene-2,4-Thiazolidinedione (c) (0.1 mole) and various substituted phenoxy benzene amines (0.1 mole). The structures of these compounds were established by means of IR and ^{1}H NMR. Infra-Red and ^{1}H-NMR spectral study of the synthesized compounds are shown in Table 2**.** The title compounds were screened for their antidiabetic activity by alloxan induced tail tipping method**.** The albino rats of either sex weighing between 180-300 g were selected. Blood glucose changes in treatment of diabetic rats with synthesized TZD derivatives are presented in Table 3**.**

Table: 1: Physical data of compounds F_1 – F_8

Compound	R	Molecular Formula	Molecular Weight (gm)	M.P (^{0}C)	%Yield
F_1	H	$C_{22}H_{16}N_2O_5S_2$	452	238 – 240	72
F_2	4-OCH_3	$C_{23}H_{18}N_2O_6S_2$	482	180 – 182	68
F_3	4-Cl	$C_{22}H_{15}N_2O_5S_2Cl$	486.5	216 – 218	65
F_4	4-CH_3	$C_{23}H_{18}N_2O_5S_2$	466	178 – 180	56
F_5	4-OC_2H_5	$C_{24}H_{20}N_2O_6S_2$	496	192 – 194	64
F_6	2-OCH_3	$C_{23}H_{18}N_2O_6S_2$	482	162 – 164	57
F_7	2-Cl	$C_{22}H_{15}N_2O_5S_2Cl$	486.5	172 – 174	55
F_8	2-CH_3	$C_{23}H_{18}N_2O_5S_2$	466	154 - 156	53

Table: 2: Spectral data of compounds $F_1 – F_8$

Compound	R	^{1}H – NMR (δ ppm)	IR (KBr) χ (cm^{-1})
F_1	H	8.4 (s, 1H, NH Tzd), 8.1 (s, 1H, NH Sulfonamide), 6.6 – 7.5 (m, 13 H, Ar), 2.9 (s,1H, Benzylidene)	3309.22 (NH), 1636.70 (C=O)
F_2	4-OCH_3	9.1 (s, 1H, NH Tzd), 8.2 (s, 1H, NH Sulfonamide), 6.8 – 7.8 (m, 12 H, Ar),3.8 (s, 3H, Methoxy), 3.0 (s,1H, Benzylidene)	3285.28 (NH), 1642.23 (C=O), 1301.78 (S=O), 692.68 (C-S-C Tzd)
F_3	4-Cl	8.4 (s, 1H, NH Tzd), 8.0 (s, 1H, NH Sulfonamide), 6.9 – 7.6 (m, 12 H, Ar), 3.0 (s,1H, Benzylidene)	3298.70 (NH), 1638.83 (C=O), 1301.51 (S=O), 692.29 (C-S-C Tzd)
F_4	4-CH_3	8.8 (s, 1H, NH Tzd), 8.3 (s, 1H, NH Sulfonamide), 6.9 – 7.4 (m, 12 H, Ar), 2.5 (s,1H, Benzylidene), 2.1 (s, 3H, Methyl)	3311.84 (NH), 1640.73 (C=O), 1302.20 (S=O), 6923.79 (C-S-C Tzd)
F_5	4-OC_2H_5	8.8 (s, 1H, NH Tzd), 8.0 (s, 1H, NH Sulfonamide), 6.1 – 7.8 (m, 13 H, Ar), 3..9 (q,2H, Ethoxy –CH_2), 3.0 (t, 3H, Ethoxy –CH_3)	3317.2857 (NH), 1648.11 (C=O)
F_6	2-OCH_3	8.4 (s, 1H, NH Tzd), 8.2 (s, 1H, NH Sulfonamide), 6.9 – 7.9 (m, 12 H, Ar), 3.9 (s, 3H, Methoxy), 3.0 (s,1H, Benzylidene)	3327.37 (NH), 1648.25 (C=O)
F_7	2-Cl	8.8 (s, 1H, NH Tzd), 7.7 (s, 1H, NH Sulfonamide), 6.9 – 7.5 (m, 12 H, Ar), 2.5 (s,1H, Benzylidene)	3282.95 (NH), 1637.42 (C=O), 1301.78 (S=O), 695.67 (C-S-C Tzd)
F_8	2-CH_3	8.9 (s, 1H, NH Tzd), 8.2 (s, 1H, NH Sulfonamide), 6.9 – 7.5 (m, 12 H, Ar), 2.5 (s,1H, Benzylidene), 2.1 (s, 3H, Methyl)	3292.24 (NH), 1648.42 (C=O), 1298.41 (S=O), 688.16 (C-S-C Tzd)

Table: 3: Antidiabetic Activity of Compounds $F_1 – F_7$

Compound	Blood glucose level mg/dl (Mean±SE)		
	0 hr.	3 hr.	6 hr.
F_1	354.2±5.856	342.5±5.464	321.7±10.96*
F_2	343±5.797	313.8±9.411**	303.2±9.827***
F_3	351.8±7.007	340.3±4.580	318±9.299*
F_4	341.5±6.158	320.5±6.737	313.3±9.500**
F_5	353.7±6.026	315.8±8.109*	311.2±9.297**
F_6	357.7±6.677	348.0±5.882	340.7±3.593
F_7	358.3±8.597	346.3±5.981	342.8±3.544
Positive Control	335.7±5.168	345.5±5.488	354.3±8.135
Normal Control	125.0±4.494	126.3±4.047	127.7±3.703
Standard (Metformin)	343.3±6.206	322.8±4.989**	292.0±7.767****

Values are expressed as mean ± S.E.M; n = 5; *(*** p < 0.0001*)*, *(**p < 0.01*)*, *(* p < 0.05*)*

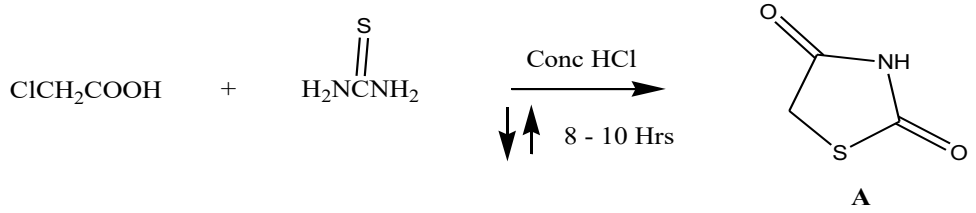


Figure: 1: Synthesis of 2, 4 – Thiazolidinedione (A)

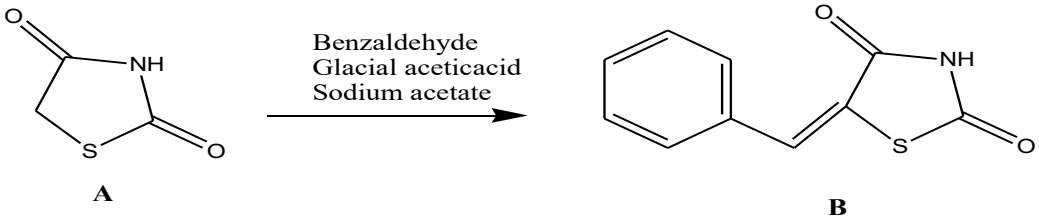


Figure: 2: Synthesis of 5 – Benzylidene - 2, 4 – Thiazolidinedione (B)

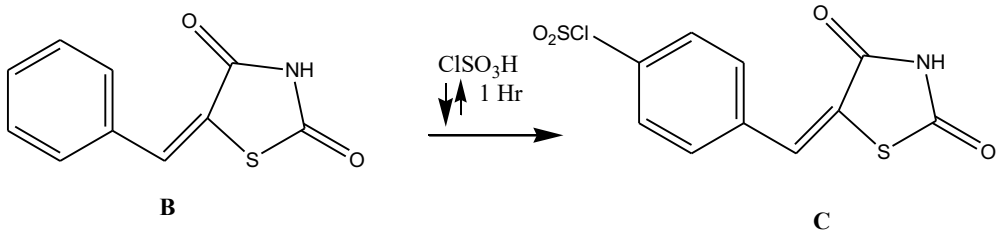
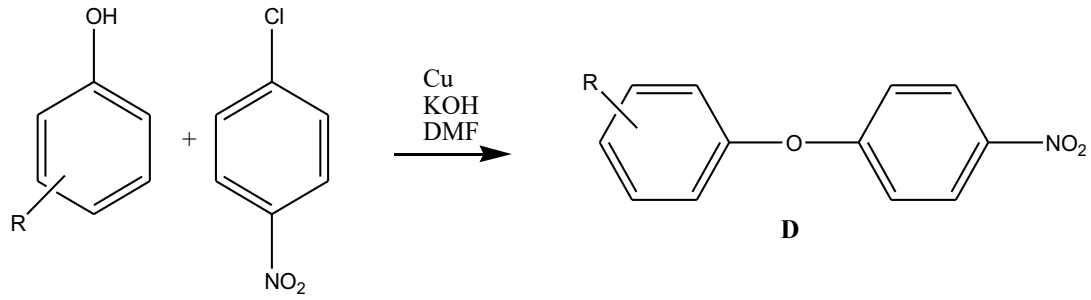
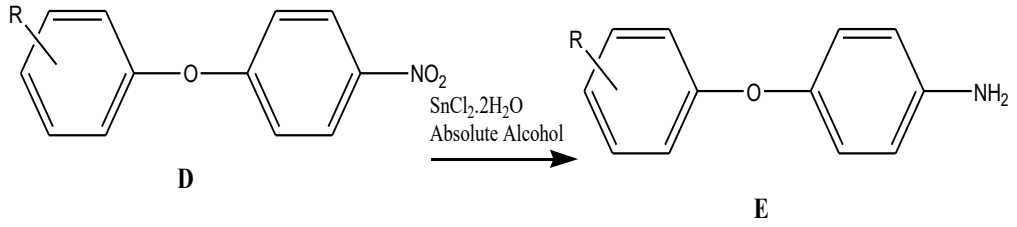


Figure: 3: Synthesis of 4'- Chlorosulphonyl -5- Benzylidene-2, 4-Thiazolidinedione (C

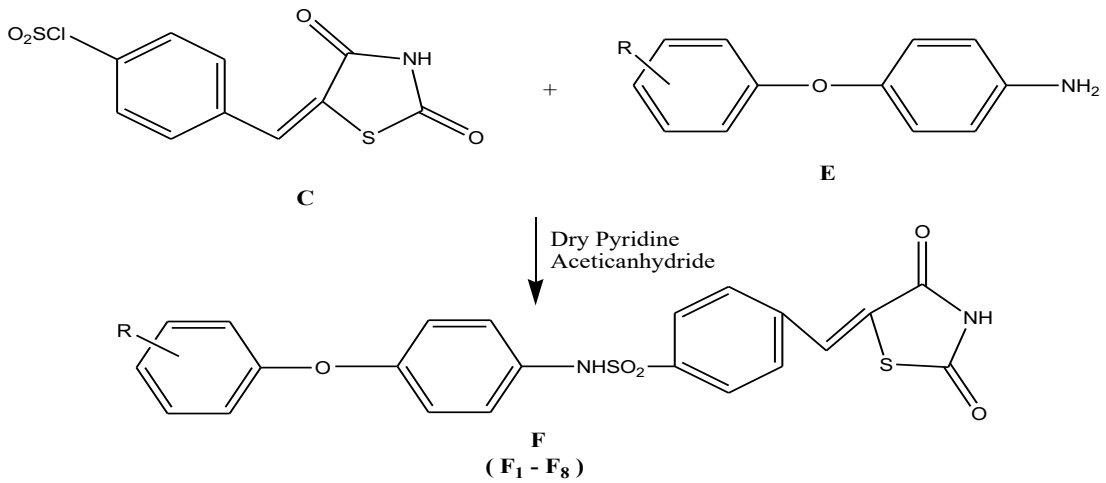


R = -H (D_1), 4-OCH_3 (D_2), 4-Cl (D_3), 4-CH_3 (D_4), 4-OC_2H_5 (D_5), 2-OCH_3 (D_6), 2-Cl (D_7), 2-CH_3 (D_8)

Figure: 4: Synthesis of Substituted 4-Phenoxy Nitrobenzene (D)



R = -H (E_1), 4-OCH_3 (E_2), 4-Cl (E_3), 4-CH_3 (E_4), 4-OC_2H_5 (E_5), 2-OCH_3 (E_6), 2-Cl (E_7), 2-CH_3 (E_8)
Figure: 5: Synthesis of Substituted 4-Phenoxy Amino benzene (E)



R = -H (F_1), 4-OCH_3 (F_2), 4-Cl (F_3), 4-CH_3 (F_4), 4-OC_2H_5 (F_5), 2-OCH_3 (F_6), 2-Cl (F_7), 2-CH_3 (F_8)
Figure: 6: Synthesis of 5-[4'-(substituted) sulphonyl benzylidene] 2, 4-Thiazolidinedione (F)

DISCUSSION

The new TZD derivatives were prepared and screened for antidiabetic activity using the alloxan induced tail tipping method. The albino rats of either sex weighing between 180-300 g were selected. Hyperglycemia was induced by alloxan monohydrate at dose of 150 mg/kg, intra peritoneal route. Then test compounds were administered at 50 mg/kg oral dose in 0.25% w/v CMC solution. Metformin was used as reference drug at dose of 100 mg/kg. Statistical comparisons between the groups were performed on all the groups using two-way ANOVA and Dun net's multiple comparison test on Graph Pad Prism 6.0 software for Windows. Blood glucose changes in treatment of diabetic rats with synthesized TZD derivatives are presented in Table 3. Out of eight compounds synthesized, seven compounds were screened (F_1- F_7) for their antidiabetic activity. The drugs F_2, F_4 and F_5 showed significant antidiabetic activity. The drugs $F_1$and F_3 showed moderate antidiabetic activity on oral administration. After 6 hours.' the compound **F_2** decreased blood glucose level which is highly significant ($p<0.0001$) and **F_4, F5** exhibited significant hypoglycemic activity ($p<0.05$).

All the synthesized 2, 4-Thiazolidinedione derivatives were screened for their in-vitro anti-diabetic activities and found most of them having significant anti diabetic activities. The pharmacological activities exhibited by synthesized novel thiazolidinedione's derivatives have confirmed that these compounds may serve the purpose of being accepted as the novel therapeutic agents. Furthermore, these novel thiazolidinedione's derivatives may be optimized by their toxicity and SAR studies.

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