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Original Article

Studies on the Synthesis of Novel 2,4-Thiazolidinedione Derivatives with Antidiabetic Activity

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Abstract

A new series of thiazolidinedione derivatives were synthesized. The structures of these compounds were established by means of IR, ^{1}H-NMR and elemental analysis. All of the compounds were screened for antidiabetic activity on albino rats. Most of the compounds showed significant antidiabetic activity when compared with the standard drug glibenclamide.

Keywords: Antidiabetic activity; Microwave assisted synthesis; Thiazolidinedione.
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1. Introduction

Diabetes mellitus is a heterogeneous group of diseases, characterized by a state of chronic hyperglycemia [1, 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 manifestations and progression, chronic hyperglycemia from whatever cause, leads to a number of complications including cardiovascular such as hypertension, renal, neurological such as anxiety, stress, ocular and other such intercurrent infections [3-5]. Diabetes mellitus is a condition in which the pancreas no longer produces enough insulin or 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 changes in diet, oral medications and in some cases daily injection of insulin. A large number of 2,4-thiazolidinediones have been reported to be antifungal, antibacterial and antileukemic agents [6, 7]. These observations promoted us to synthesis the title compound with presumption that incorporation of aromatic amines and thiazolidinones nuclei would produce new compounds with significant antidiabetic properties. Lifestyle changes

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including weight loss and increased activity are the primary recommendations for treatment of type II diabetes. However, because of the progressive nature of the disease, the treatment of type 2 diabetes usually requires the stepwise introduction of oral hypoglycaemic drugs followed by insulin [8].

Thiazolidinediones act in a complex with the retinoid X receptor to increase the transcription of several insulin sensitive genes. These include lipoprotein lipase, the fatty acid transporter, adipocyte fatty acid binding protein, acyl CoA, malic enzyme and glucose transporter isoform GLUT-4. They also increase the uptake of glucose and fatty acids by adipocytes, promoting lipogenesis and adipogenesis (Figure 1). They also increase glucose uptake, glycogenesis and glucose utilization by the muscle tissue and may reduce glucose production by the liver [9].

2. Materials and method

2.1. Materials and instrumentation

Melting points were determined in open capillary method and are uncorrected. IR spectra were recorded on Thermo Nicolet IR 200 spectrophotometer using KBr disc method. The ^{1}H-NMR spectra were recorded on sophisticated multinuclear FT-NMR spectrometer model Avance-II (Bruker), using dimethylsulfoxide-d6 as solvent and tetramethylsilane as internal standard. The FT-NMR instrument is equipped with a cryomagnet of field strength 9.4 T. Its ^{1}H frequency is 400 MHz. The reactions were carried in microwave oven.

2.2. General synthesis procedure

In a 250 ml three-necked round-bottomed flask, was placed, solution containing (56.4 g, 0.6 mol) of chloracetic acid in 60 ml of water and (45.6 g, 0.6 mol) of thiourea dissolved in 60 ml of water. The mixture was stirred for 15 min. to form a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 ml of concentrated HCl from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 h at 100-110 °C. On cooling the contents of the flask solidified to a cluster of white needles (Figure 2). The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by

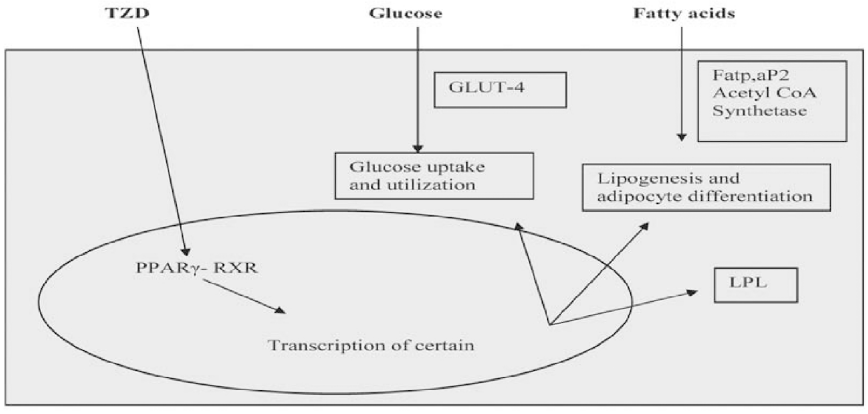


Figure 1. Diagramatic representation of cellular mechanism of action of thiazolidinediones on an adipocyte. TZD: thiazolidinedione; PPARγ: peroxisome proliferator-activated receptor-gamma; RXR: retinoid X receptor; GLUT-4: glucose transporter isoform 4; FATP: fatty acid transporter protein; aP2: adipocyte fatty acid binding protein; LPL: lipoprotein lipase.

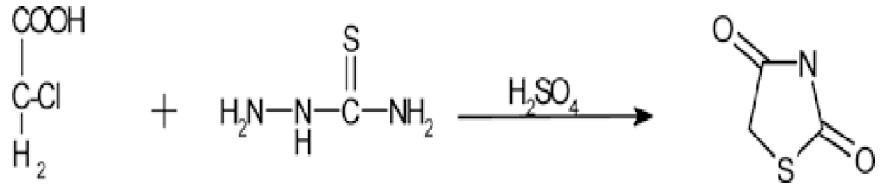


Figure 2. Synthesis of 2,4-thiazolidinedione.

recrystallization from ethyl alcohol. Yield: 85%; m.p.:123-125 °C.

In a 250 ml three-necked round-bottomed flask provided with a Dean-Stark apparatus, benzaldehyde (20 g, 0.188 mol) and 2,4-thiazolidinedione (22 g, 0.188 mol) were together suspended in ethanol. To this a catalytic amount of piperidine (1 ml) was added. The mixture was stirred and refluxed. After the complete removal of water and when the temperature reached above 110 °C the reaction mixture was stirred for a further 1 h. On cooling, the product precipitated out from ethanol (Figure 3). The compound was filtered and washed with cold dry toluene and dry ethanol. Yield: 93%; m.p.:240-242 °C.

Benzylidine-2,4-thiazolidinedione (8 g, 0.0388 mol) was placed in a 100 ml round-bottomed flask equipped with a condenser and a dropping-funnel. Chlorosulphonic acid (18.08 g, 0.155 mol) was added at room temperature using the dropping funnel. The reaction was found to be exothermic. After addition of chlorosulphonic acid was over the reaction mass was refluxed for 1 h on a water bath. The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a 1 L beaker. The product was filtered and dried [10, 11] (Figure 4). The product was purified by recrystallization from ethanol. Yield: 68%; m.p.:180-181 °C.

A mixture of 5-(4-Chlorosulfonyl benzylidene)-2, 4-Thiazolidenedione I (0.01 mole) and aromatic amines R (0.01 mole) (Table 1) were taken in a beaker and made a homogenous paste. The paste was exposed to microwave irradiation for 1-2 min., at intervals of 30 seconds. After the completion of reaction, ice-cold water was added to the reaction mixture and precipitated solid was separated by filtration, dried and recrystallized from ethanol (Figure 5).

A series of 2, 4-thiazolidinedione compounds (B_1-B_9) were synthesized and the structures were established by means of IR and ^{1}H-NMR. The yield, melting point and elemental analysis of synthesized compounds is illustrated (Table 2). Spectral data:

B_1: FT-IR (KBr disc) cm^{-1}: 3096.6 (Ar-CH-str.), 3437.6 (C=O-str.), 1286.4 (C-N-str.), 3452.6 (N -H -str.), 620.8 (C-S-str.)

^{1}H-NMR (δ ppm) (400 MHz, DMSO): 13.69 (1H,SO_2-NH-str.),12.45 (1H, NH, Thiazolidinedione),7.95 (1H,CH_2, Benzylidine), 6.58-7.68 (8H, Ar-CH), 5.32(2H, NH_2), R_F 0.60-0.62

B_2: FT-IR (KBr disc) cm^{-1}: 3098.2 (Ar-CH-str.), 3383.1 (C=O-str.), 1286.4 (C-N-str.), 1377.1 ($N0_2$ -str.), 628.8 (C-S-str.)

^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H,SO_2-NH-str.), 12.45 (1H, NH, Thiazolidinedione), 7.95 (1H,CH_2, Benzylidine), 7.66-8.32 (8H, Ar-CH), R_F 0.62-0.64

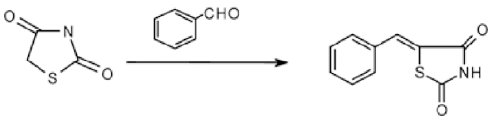


Figure 3. Synthesis of 5-benzylidine 2,4-thiazolidinedione.

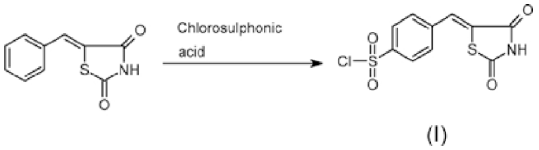


Figure 4. Synthesis of 5-(4-Chlorosulfonyl benzylidene) -2, 4- thiazolidenedione.

B_3: FT-IR (KBr disc) cm^{-1}: 3094.6 (Ar-CH-str.), 1694.5 (C=O-str.), 1286.4 (C-N-str.), 1639.4 (C= C -str.), 628.8 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H,SO_2-NH-str.), 12.45 (1H, NH, Thiazolidinedione), 7.95 (1H,CH_2, Benzylidine), 7.40-7.66 (8H,Ar-CH), 6.95-6.99 (2H, CH alkyl), RF 0.58-0.60

B_4: FT-IR (KBr disc) cm^{-1}: 3095.4 (Ar-CH-str.),1694.5 (C=O-str.), 1298.0 (C-N-str.), 3394.6 (N -H -str.), 612.7 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H,SO_2-NH-str.), 12.45 (1H, NH, Thiazolidinedione), 7.42-7.75 (4H,Ar-CH), 6.13 (1H, NH), 7.41 (1H, tetrazole), 3.46 (CH_2,Benzylidine) , R_F 0.68-0.70

B_5: FT-IR (KBr disc) cm^{-1}: 3069.5 (Ar-CH-str.),1693.4 (C=O-str.), 1299.4 (C-N-str.), 3408.2 (N -H -str.), 612.8 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H,SO_2-NH-str.), 12.45 (1H, NH, Thiazolidinedione), 7.34-7.7 (4H, Ar-CH), 5.16 (1H, NH), 3.4-3.6 (Piperidine), 2.9 (CH2, Benzylidine), RF 0.71-0.73

B_6: FT-IR (KBr disc) cm^{-1}: 3084.5 (Ar-CH-str.),1695.2 (C=O-str.), 1299.6 (C-N-str.), 3408.2 (N -H -str.), 617.4 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H, SO2-NH-str.), 12.45 (1H, NH, Thiazolidinedione),11.3-7.7 (4H, Ar-CH), 5.15 (1H, NH), 3.8 (CH_2, Benzylidine), 3.06-3.08 (8H, Morpholine.), R_F 0.70-0.72

B_7: FT-IR (KBr disc) cm^{-1}: 3041.5 (Ar-CH-str.), 1698.2 (C=O-str.), 1301.3 (C-N-str.), 3408.2 (N -H -str.), 619.8 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 10.04(1H, SO_2-NH-str.), 12.45 (1H, NH Thiazolidinedione), 7.95 (1H, CH_2, Benzylidine), 7.12-7.68 (8H, Ar-CH) , R_F 0.73-0.75

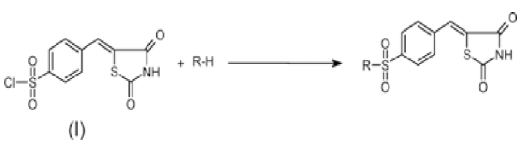
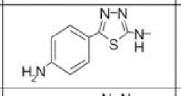
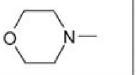
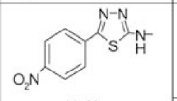
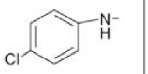
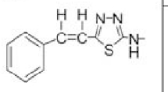
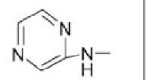
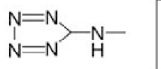
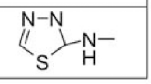
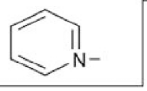


Figure 5. Synthesized 2-4, thiazolidinedione derivatives.

Table 1. Illustrated different aromatic amines.

	R		R
B1		B6	
B2		B7	
B3		B8	
B4		B9	
B5			

B_8: FT-IR (KBr disc) cm^{-1}: 3041.5 (Ar-CH-str.), 1696.2 (C=O-str.), 1300.8 (C-N-str.), 3406.4 (N -H -str.), 619.8 (C-S-str.)
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 11.27 (1H,SO_2-NH-str.),12.45-(1H, NH Thiazolidinedione), 7.95 (1H, CH_2, Benzylidine), 8.35-8.40 (3H, pyrazine), 7.66-7.68 (8H, Ar-CH), RF 0.70-0.72

B_9: FT-IR (KBr disc) cm^{-1}: 3041.5 (Ar-CH-str.), 1698.4 (C=O-str.), 1300.8 (C-N-str.), 3409.2 (N -H -str.), 619.8 (C-S-str.), R_F 0.63-0.65
^{1}H-NMR (δ ppm): (400 MHz, DMSO): 13.69 (1H,SO_2 NH-str.), 12.45 (1H, NH Thiazolidinedione), 7.95(1H,CH_2, Benzylidine), 9.16 (2H, thiadiazole), 7.66-7.68 (8H, Ar-CH), RF 0.63-0.65

2.2. General antidiabetic activity procedure

The acclimatized animals were kept fasting for 24 h with water *ad libutm* and alloxan monohydrate (120 mg/Kg; i.p.) in normal saline was administered. After one hour of alloxan administration, the animals were given *ad libitum*. A 5% dextrose solution was given in feeding bottle for a day to overcome the

Table 2. Characterization data of compounds synthesized.

Compound	m.p. °C	Yield %	Elemental analysis calculated (found)		
			C	H	N
B_1	174-176	68%	47.05 (46.68)	2.85 (2.57)	15.24 (14.96)
B_2	180-182	54%	44.17 (43.89)	2.27 (1.97)	14.31 (13.94)
B_3	118-120	62%	51.05 (50.76)	3.00 (2.80)	11.91 (11.75)
B_4	199-200	64%	40.94 (40.77)	3.44 (3.14)	22.03 (21.56)
B_5	241-243	56%	49.58 (49.18)	3.61 (3.33)	11.56 (11.26)
B_6	234-237	52%	46.99 (46.63)	4.47 (4.31)	10.96 (10.78)
B_7	222-223	56%	48.67 (48.37)	2.81 (2.56)	7.09 (6.88)
B_8	180-182	55%	46.40 (46.32)	2.78 (2.48)	15.46 (15.21)
B_9	192-193	63%	38.91 (38.55)	2.72 (2.38)	15.12 (14.96)

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 readings were noted.

After 72 h, 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 2,4-thiazolidinedione derivatives equivalent to average human intake 200-mg/kg at a time was calculated for single dose 36 mg/kg (for acute study). The test compounds were administered orally by mixing with CMC (0.25 %) solution [12]. The blood glucose level was monitored at different times 0 h, 1 h, 3 h, 6 h, respectively (Table 3). The results were calculated by measuring the mean±SE and '*p*' value.

3. Results and discussion

A series of thiazolidinedione derivatives were synthesized by reacting 5-(4-chlorosulfonyl benzylidene)-2, 4-thiazolidene dione I (0.01 mole) and aromatic amines R (0.01 mole). The structures of these compounds were established by means of IR, ^{1}H NMR, and elemental analysis.

The title compounds were screened for their antidiabetic activity 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 out in six difference groups.

Out of nine compounds synthesized (B_1-B_9). The drug B_1, B_2, B_4, B_7, B_8, and B_9 showed significant antidiabetic activity. The drug B_3, B_5 and B_6 showed moderate antidiabetic activity on oral administration (Table 3).

4. Conclusion

Deciding when a thiazolidinedione is appropriate requires consideration of their advantages and disadvantages. Potentially, the thiazolidinediones could be useful in the treatment of type II diabetes as they act to improve insulin sensitivity. However, the clinical evidence supporting their use is still very limited [13]. There is no current evidence to suggest that the glucose-lowering actions of thiazolidinediones are greater than those of other oral hypoglycaemic drugs. Thiazolidinediones might be shown to preserve-cell function, alleviate many of the components of the metabolic syndrome/insulin resistance states, and offer cardiovascular protection. There are evidences of chemical structures of thiazolidinedione when compared to rosiglitazone which is considered as oral hypoglycemic agents. In this regard, we have planed to synthesize some more potent oral hypoglycemic agents.

Acknowledgement

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Table 3. Statistical analysis is done by one-way ANOVA followed by Dunnet's't' test. Standard drug: glibenclamide.

Compound.	Blood glucose level mg/dl (Mean±SE)			
	0 h	1 h	3 h	6 h
B_1	296.7±4.05	292.7±4.25	187.7±15.6**	148.0±7.8**
B_2	300.5±0.12**	134.5±2.72	123.5±5.23	116.5±5.90**
B_3	320.5±15.81**	145.5±2.26	137.0±3.80	123.5±1.10*
B_4	213.5±8.78	140.7±3.30*	106.3±6.91	95.75±6.06**
B_5	283.5±43.76	205.75±49.7	166.3±38.92	124.5±13.16*
B_6	295.3±7.42*	233.3±23.8	193.0±13.86	159.3±12.12
B_7	289.2±9.98	280.6±9.29*	244.2±9.04**	180.4±1.99**
B_8	203.7±13.79	156.2±13.5	123.3±4.3*	101.5±4.5**
B_9	217.0±3.01	213.0±2.53	164.3±4.74*	146.0±2.19**
Control	123.3±6.00	120.7±5.54	122.3±5.81	123.0±6.4
Std.	385.8±21.37	230.8±12.35**	156.8±10.87**	93.4±4.98**

**$p<0.01$ (considered as significant), *$p<0.05$

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