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Syntheses of some novel 5-Substituted-Arylidene-3-Substituted-Benzyl-Thiazolidine-2, 4-Dione Analogues as Anti-Hyperglycemic Agents

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Abstract
A series of 5-substituted-arylidene-3-substituted-benzyl-thiazolidine-2, 4-dione derivatives were synthesized through Knoevenagel condensation and studied for their glucose lowering capability against alloxan induced diabetic rats. Some of the compounds showed appreciable antidiabetic activity comparable to standard drug rosiglitazone.

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Introduction

Diabetes mellitus is a syndrome characterized by chronic hyperglycaemia as a result of absolute or relative insulin deficiency (resistance) or both [1]. Today diabetes mellitus is a major health concern especially in urban world. Studies showed that there are 150 million people suffering from diabetes mellitus and by 2025 it is estimated that the figure would rise to 300 million [2]. Over 90 % of the diabetes mellitus patients are type-2 patients [3]. Type-2 diabetes mellitus is now considered as a life - style disease and is usually associated with urbanization, mechanization and change in life-style habits [4]. This disease is characterized by insulin resistance and cardiovascular dysmetabolic

syndrome. The conventional therapy of type-2 diabetes mellitus (sulphonylureas) has not been satisfactory as it is not successful in treating associated cardiovascular risk factors, which is the major cause of morbidity. The current trend is, therefore, to make the therapy better by choosing appropriate combination of available drugs. A parallel search for newer drugs is also being made. It is a well known fact that oxidative stress is increased in diabetes due to overproduction of ROS and decreased efficiency of antioxidant defenses, a process that starts very early and worsens over the course of the disease [5-9]. Thiazolidinediones or glitazones are oral hypoglycaemic agents which act mainly by increasing tissue sensitivity to insulin. Besides their anti-diabetic potency, these TZDs have been shown to exert antioxidant activity [10]. Pioglitazone inhibits O^{-2} radical production in endothelial cells. Rosiglitazone ameliorates the impaired coronary arteriolar dilation in mice with type 2 diabetes by reducing oxidative stress [11] This paper describes the synthesis and give the structural characteristics of several derivatives of the 5-substituted-arylidene-3-substituted-benzyl-thiazolidine-2, 4-dione substituted on the either benzylidene or benzyl moiety.

Chemistry

5-substituted-arylidene-3-substituted-benzyl-thiazolidine-2, 4-diones **1(a)-1(e)** and **2(a)-2(c)** were prepared by knoevenagel condensation of 3-benzyl-thiazolidine-2, 4-dione (2) with selected various substituted aromatic aldehydes [12]. Synthetic pathway is shown in Fig.1. Thiazolidinedione (A) was refluxed with substituted benzyl chloride like 4-nitrobenzyl bromide or 4-chloro benzyl chloride for about 18 hours [13] to get substituted 3-benzyl-thiazolidine-2, 4-dione (B).

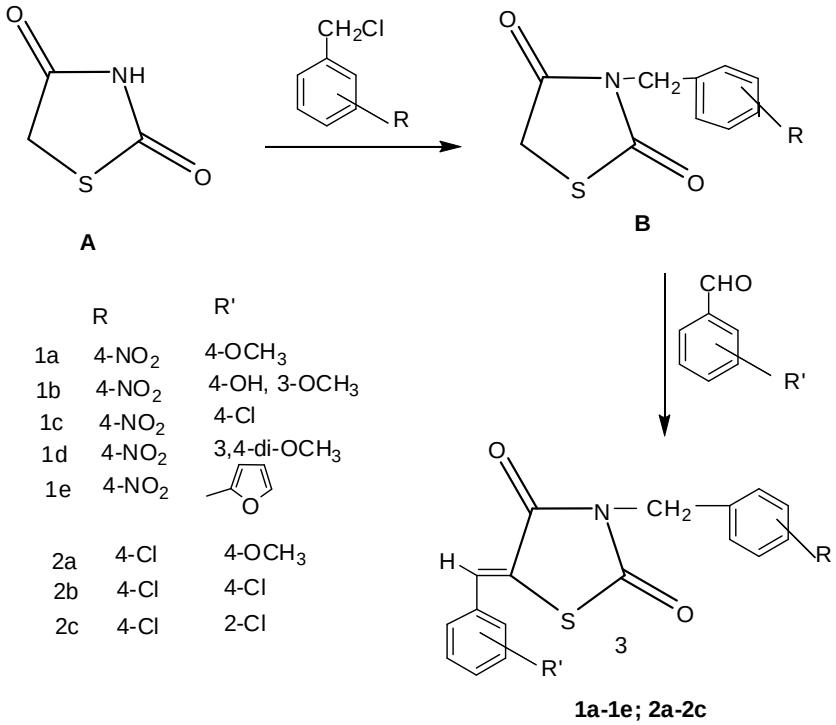

Fig.1. Synthetic pathway of 5- arylidene-3-benzyl-thiazolidine-2, 4-diones

Pharmacology

Male Wistar rats (150-200 g) were used for the study. The animals were kept under standard conditions i.e. temperature 25±1°C, relative humidity 55±10 % and 12 hours light and dark cycle [14]. The animals were provided with standard pellet diet and water *ad libitum* in animal house of BBDNITM, Lucknow, India. Initial body weight of each animal was

recorded and they were given seven days time to get acclimatized with the laboratory conditions. The animal handling was as per the protocol of the Institutional Animal Ethics Committee (IAEC) duly approved by CPCSEA. (CPCSEA approval number is BBDNITM/IAEC/CLEAR/12/2009).

Induction of Diabetes

Animals were fasted overnight before the day of experiment with free access to water. Fasting blood was collected for blood glucose estimation before the experiment. These animals were treated with an oral D-glucose load of 2 g/kg by means of stomach tube. Hyperglycemia was induced by a single intra peritoneal injection of freshly prepared alloxan (150 mg/kg body weight dissolved in 0.9% saline) for 3 consecutive days. Diabetes was confirmed on 4th day by determining the blood glucose concentration. Rats having BGL more than 250 mg/dl were used for study. Blood glucose levels were measured using a Glucometer (Accu Chek). Animals were divided into four groups of six rats each. Group I: normal rats (positive control), group II: diabetic rats (negative control), group III: diabetic rats received standard drug (rosiglitazone) and group IV-XI: diabetic rats treated with test compounds [15-17].

Determination of Antidiabetic Activity against Alloxan Induced Diabetes in Rats

All the test compounds were given once orally for 7 days (30 mg/kg dissolved in PEG) by using oral gastric gavages to the animals of group IV. Animals of group I and II received only vehicle. Animals of group III treated with standard drug at a dose of 3 mg/kg. The blood glucose concentrations of the animals were measured on 3rd, 5th and 7th day. Blood was collected from retro-orbital sinus under mild ether anesthesia.

Statistical analysis

All the values of the experimental results were expressed as mean±S.E.M with n=6. The values were analyzed by ANOVA (Dunnett's test) for the possible significant identification between various groups. * Significant at P<0.05, ** Significant at P<0.01 vs. diabetic control. Statistical analysis was carried out using Graph pad prism 3.0 (Graph pad software, San Diego, CA).

Table 1: Effect of 1, 3-thiazolidine-2, 4-dione derivatives on blood glucose level of alloxan induced diabetes in rats

Treatment (mg/kg, p.o.)	Blood Glucose Level (mg/dl)			
	0 day	3rd day	5th day	7th day
I	86.11±0.98	85.67±0.58	84.68±0.54	86.23±0.48
II	192.34±1.56	210.44±0.68	232.42±1.27	247.68±1.24
III	188.45±1.99	156.88±0.82**	125.77±1.45**	104.10±1.72**
IV	186.17±1.16	198.23±0.77**	162.47±1.22**	109.45±2.13**
V	191.18±1.06	208.58±0.76	198.57±1.42*	178.45±1.58**
VI	188.23±1.14	189.56±0.98	185±0.86*	182.36±1.25*
VII	189.35±1.18	206.38±0.86	192.30±1.24	188.36±1.23
VIII	187.56±1.15	194.23±0.96*	182.26±0.65**	172.36±0.98*
IX	188.68±1.23	195.35±1.16	175.65±0.86*	118.63±0.89**
X	194.99±1.70	207.45±0.69*	189.64±1.33**	172.38±2.24**
XI	185.35±1.16	195.65±0.89	158.56±1.56*	134.25±1.18**

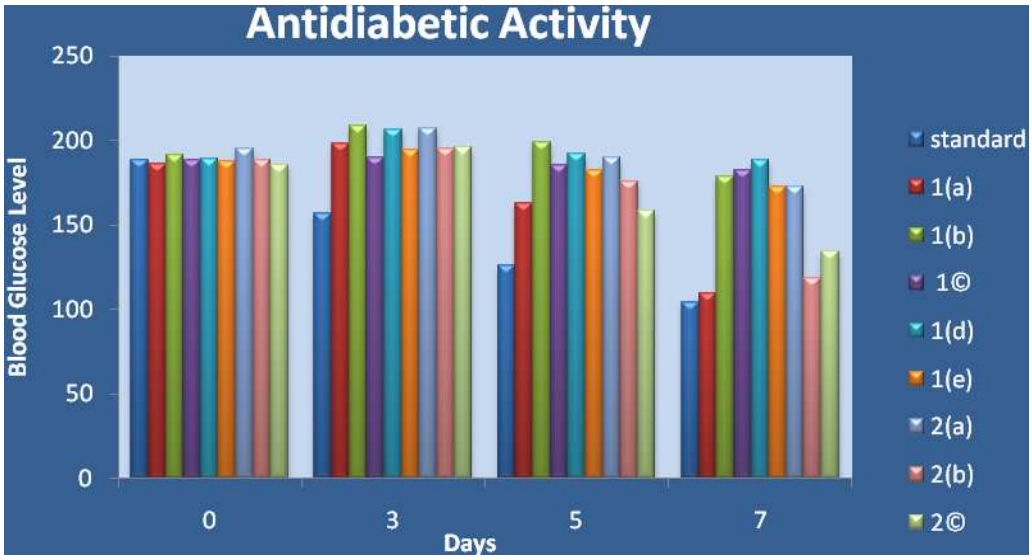

Figure 1: Antidiabetic activity of synthesized compounds

Results and Discussion

The synthesized compounds were confirmed by physical characterization and spectral analysis. The glucose lowering effects after oral administration for 7 days as aqueous suspension (in PEG 400) of new thiazolidinedione analogues **1(a)-1(e)** and **2(a)-2(c)** in alloxan diabetic rats are summarized in Table 1. The blood glucose concentrations of the animals were measured at the beginning of the study and the measurements were repeated on 0^{th}, 3^{rd}, 5^{th} and 7^{th} day after the initiation of the experiment. Blood was collected from retro-orbital sinus under mild ether anesthesia. The inference was made by comparing Blood Glucose Level. Compounds **1(a)**, **2(a)**, **2(c)** showed appreciable antidiabetic activity in comparison to standard drug rosiglitazone. The anisaldehyde based thiazolidinedione compounds **1(b)**, **1(c)**, **1(d)**, **1(e)**, **2(b)** and **2(c)** displayed very less activity as comparable to other compounds whereas 2-methoxy group containing compound **1(d)** showed least activity.

SAR studies revealed that compounds with methoxy group at para position on arylidene ring gave maximum activity **1(a)** and **2(a)**. However, addition of one more methoxy group decreased the activity to minimum among the series **1(d)**. Chloro at ortho position on arylidene with 4-chloro in benzyl ring showed remarkable activity **2(c)**.

Conclusion

The new 5-substituted-arylidene-3-substituted-benzyl-thiazolidine-2, 4-dione derivatives have shown promising glucose lowering activity at a dose of 30mg/kg close to that of the rosiglitazone.

Experimental Protocols [18-19]

5-substituted-arylidene-3-substituted-benzyl-thiazolidine-2, 4-diones (1a-1e) and (2a-2c): general procedure.

To a solution containing 0.01mole (0.143 g) of benzaldehyde and 0.01mole (0.25 g) of 3-substituted benzyl-thiazolidine-2, 4-dione in 1.0 ml of hot acetic acid, 0.01mole (0.338 g) of fused sodium acetate was added and the mixture was refluxed for 1.5 hours. The product was obtained by pouring the mixture into water and recrystallizing the resulting solid from ethanol.

1. 5-(4-Methoxy-benzylidene)-3-(4-nitro-benzyl)-thiazolidine-2, 4-dione(1a)

$C_{18}O_5N_2SH_{14}$, yield: 83.2%, M.Pt. 180-183˚C. TLC ethanol: chloroform (9:1) R_f: 0.62. IR cm^{-1} (KBr): ν

1595, 1670, 1650, 3050, 1550, 1020. MS (FAB) m/z: 370 (M^+), 371 (M^++1, 100%).

2. 5-(4-Hydroxy-3-methoxy-benzylidene)-3-(4-nitro-benzyl)-thiazolidine-2, 4-dione (1b)

$C_{18}O_6N_2SH_{14}$, yield: 78.5%, M.Pt. 195-200˚C. TLC ethanol: chloroform (9:1) R_f: 0.55. IR cm^{-1} (KBr): ν 1540, 1520, 3045, 1675, 1720, 3000, 1100, 3320. MS (FAB) m/z: 386 (M^+), 386 (M^+, 100%).

3. 5-(4-Chloro-benzylidene)-3-(4-nitro-benzyl)-thiazolidine-2, 4-dione (1c)

$C_{17}O_4N_2SClH_{11}$, yield: 85.7%, M.Pt. 205-210˚C. TLC ethanol: chloroform (9:1) R_f: 0.72. IR cm^{-1} (KBr): ν 1522 & 1379, 1605, 976 & 886, 3416, 2946, 703 & 663. MS (FAB) m/z: 374 (M^+), 375 (M^++1, 100%).

4. 5-(3, 4-Dimethoxy-benzylidene)-3-(4-nitro-benzyl)-thiazolidine-2, 4-dione (1d)

$C_{19}O_6N_2SH_{16}$, yield: 81.3%, M.Pt. 172-179˚C. TLC ethanol: chloroform (9:1) R_f: 0.50. IR cm^{-1} (KBr): ν 1575, 1675 & 1480, 3060, 1575, 1740, 3010, 1150. MS (FAB) m/z: 400 (M^+), 401 (M^++1, 100%).

5. 5-(Furfural-benzylidene)-3-(4-nitro-benzyl)-thiazolidine-2, 4-dione (1e)

$C_{15}O_5N_2SH_{10}$, yield: 74.4%, M.Pt. 165-170˚C. TLC ethanol: chloroform (9:1) R_f: 0.45. IR cm^{-1} (KBr): ν1390 & 1535, 1570, 3080, 1690, 1630, 700, 3110. MS (FAB) m/z: 330 (M^+), 331 (M^++1, 100%).

6. 5-(4-methoxy-benzylidene)-3-(4-chloro-benzyl)-thiazolidine-2, 4-dione (2a)

$C_{18}O_3NSClH_{14}$, yield: 80.3%, M.Pt. 193-198˚C. TLC ethanol: chloroform (9:1) R_f: 0.52. IR cm^{-1} (KBr): ν 763, 1608, 1381, 1686, 1753, 669, 3022, 1150. MS (FAB) m/z: 359 (M^+), 360 (M^++1, 100%).

7. 5-(4-Chloro-benzylidene)-3-(4-chloro-benzyl)-thiazolidine-2, 4-dione (2b)

$C_{17}O_2NSCl_2H_{11}$, yield: 82.1%, M.Pt. 185-190˚C. TLC ethanol: chloroform (9:1) R_f: 0.48. IR cm^{-1} (KBr): ν 603 & 537, 3069, 667, 1676, 1751. MS (FAB) m/z: 363 (M^+), 364 (M^++1, 100%).

8. 5-(2-Chloro-benzylidene)-3-(4-chloro-benzyl)-thiazolidine-2, 4-dione (2c)

$C_{17}O_2NSCl_2H_{11}$, yield: 75.9%, M.Pt. 168-175˚C. TLC ethanol: chloroform (9:1) R_f: 0.66. IR cm^{-1} (KBr): ν 763, 1603 & 1381, 1686, 1753, 669, 3021. MS (FAB) m/z: 363 (M^+), 364 (M^++1, 100%).

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