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Synthesis of Some Novel 2,4-Thiazolidinedione Derivatives and Their Biological Screening as Antidiabetic Agents

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Six derivatives of 2,4-thiazolidinedione having dialkyl amine appendage at N-3 position were synthesized and their antidiabetic activity were evaluated. All derivatives were synthesized by the reaction of 2,4-thiazolidinedione with different aldehydes, which further react with different dialkylamine. All derivatives were evaluated for their glucose lowering capability in dexamethasone induced diabetic rat.

Key Words: 2,4-Thiazolidinedione, Anti-diabetic activity, Dexamethasone.

INTRODUCTION

2,4-Thiazolidinedione (TZD) or Rosiglitazones were found to possess oral hypoglycemic activity. They act mainly by increasing tissue sensitivity especially adipose tissue, to insulin. The present work is aimed to develop a series of 2,4-thiazolidinediones having dialkyl amine appendage at N-3 position with different aldehydes at C-5 position which might surmount the hepatic toxicity and also increases the production of insulin from the β-cells. All the synthesized compounds were evaluated for their glucose lowering capability in dexamethasone induced diabetic rat.

EXPERIMENTAL

All the chemicals used were of AR grade, procured from various chemical units like Merck, Mumbai, Qualigens, Mumbai, S.D. Fine Chemicals, Mumbai and CDH-New Delhi. Melting points were determined by open glass capillary method and are uncorrected. The infrared spectra were recorded on Perkin-Elmer BX1 (4000-450 cm^{-1}) in KBr discs. ^1H NMR spectra were recorded in Bruker Avance II (400 MHz) spectrometer; samples were run as solution in $CDCl_3$ and DMSO at ambient temperature and chemical shifts were recorded in ppm downfield from internal tetramethyl silane. TLC monitored the purity and completion of reaction. Chloroform: ethyl acetate (4:1) solvent system and silica gel-G coated on glass plates as solid support were used for the development of chromatogram.

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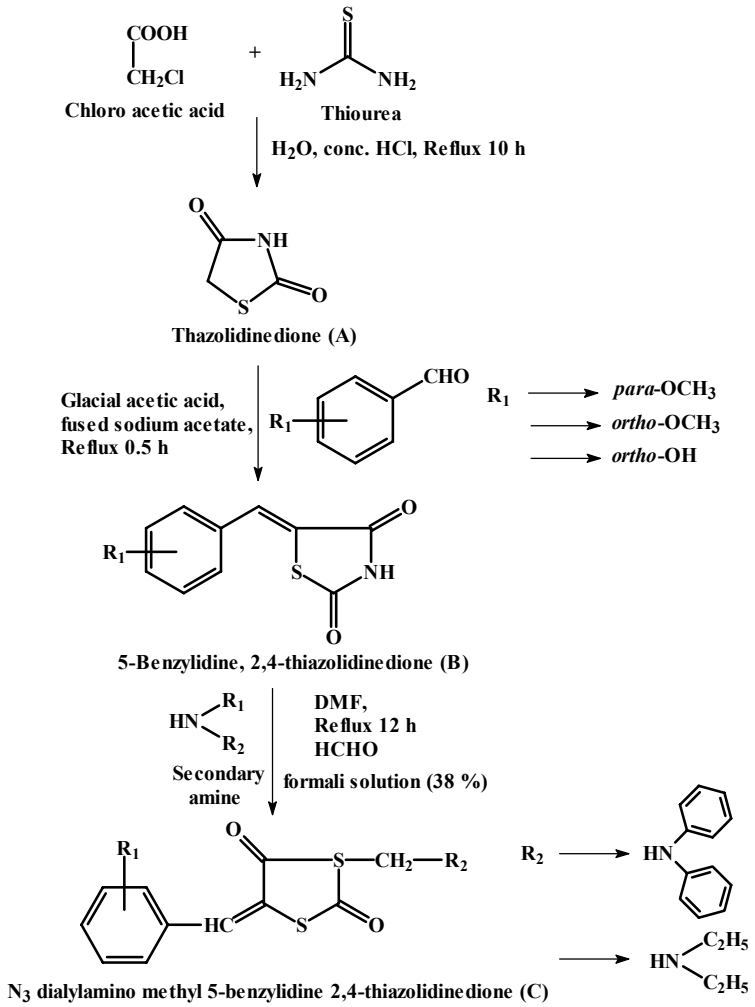
Synthesis of 2,4-thiazolidinedione[1] (A): In a 250 mL three-necked flask, placed a solution containing 56.5 g (0.6 M) of chloroacetic acid in 60 mL of water and 45.6 g (0.6 M) of thiourea dissolved in 60 mL of water. The mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. To the content of the flask 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 reflux from 8-10 h at 100-110 °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 was purified by recrystallization from ethyl alcohol. Yield: 85 %; m.p. 123-125 ºC; IR (KBr, ν_{max}, cm^{-1}): 3091 (NH), 2839 (C-H), 1713 (C=O) and 1234 (C-N).



Reaction Scheme

Synthesis of 5-(*p*-methoxy benzylidine)-2,4-thiazolidinedione[2,3] (B): To a solution of *p*-methoxy benzaldehyde (0.25 M) and compound **A** (0.25 M) in hot glacial acetic acid (50 mL), fused sodium acetate (1.8 g) was added and then it was refluxed for 1 h with occasional shaking. It was poured in water (500 mL), then product obtain was filtered, washed with water, alcohol and ether. The product was recrystallized from glacial acetic acid to obtain yellowish brown needle like crystal. Yield: 89-93 %; m.p. 240-45 °C; IR (KBr, ν_{max}, cm^{-1}): 3091 (NH), 1730 (C=O), 1593 (C=C) and 1234 (C-N).

Synthesis of 3-((diethylamino)methyl)-5-(4-methoxybenzylidine)thiazolidine-2,4-dione[4,5] (C): Compound **B** (0.05 M) was dissolve in N,N′-dimethylformamide (15 mL). Diethyl amine (0.05 M) was added followed by addition of formaline solution (38 %) (0.05 M). The mixture was refluxed for 15 h. The refluxed solution was kept in the refrigerator for 48 h. The product obtain was filtered dried and recrystallized using ethyl acetate. Yield: 75.21 %, m.p 205 °C; IR (KBr, ν_{max}, cm^{-1}): 1730 (C=O), 1593 (C=C), 1417.8 (CH_2-N) and 1081 (C-N), ; ^{1}H NMR 6.85-7.42 (m, 4H, Ar-H), 3.77 (s, 3H, O-CH_3), 7.80 (s, 1H, -C=CH), 4.59 (s, 2H, N-CH_2).

Other compound FD-1 to FD-6 were synthesized similarly using compound **B** as a precursor by treatment with various amine and their characterization data were presented in Table-1.

Biological screening

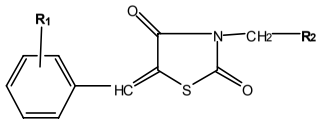
Acute toxicity study: All the compounds were screened for acute oral toxicity study according to OECD guidelines[6]. All the synthesized compounds (FD-1 to FD-6) were found to have LD_{50} in range 200mg/kg b.w. (OECD: Organization for economic co-operation and development).

Antidiabetic studies: The compound synthesized FD-1 to FD-6 was screened for their antidiabetic activity. The experimental induction of diabetes were carried out in rats by subcutaneous injection of dexamethasone DEX (1 mg/kg for 5 days)[7]. Effect of compound FD-1 to FD-6 on the dexamethasone induced hyperglycaemic rats were compared with the control and standard drug (Rosiglitazone). In order to confirm hyperglycaemia the blood glucose levels were determined according to GOD-POD method by withdrawing 0.5 mL of blood sample from the retro-orbital plexus (capillary method) under light ether anaesthesia. The compounds synthesized were suspended in 5% gum acacia solution and given orally at a dose of 50mg/kg b.w. (GOD-POD: Glucose oxidase-peroxidase method).

RESULTS AND DISCUSSION

In the present work, compounds FD-1 to FD-6 were synthesized and their characterization were done by physical and spectral methods. The purity were checked by TLC. The synthesized compounds show remarkable antidiabetic activity by GOD-POD method at dose level 50 mg/kg b.w. The compound FD-1 and FD-3 possess remarkable hypoglycemic activity (Table-2), which indicates that the substitution of α-amino methyl group at position-3 show different hypoglycemic activity from that of the standard compound. However, there is no clear-cut relation between the structure and activity.

TABLE-1
3-DIALKYL/DIARYL AMINO METHYL-5- (*o*/*m*/*p*-SUBSTITUTED BENZYLIDINE)-2,4-THIAZOLIDNEDIONE



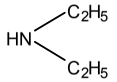
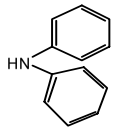
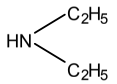
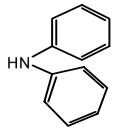
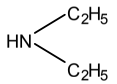
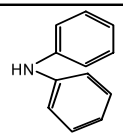
Compd. code	R_1	R_2	m.f. / (yield, %)	m.p. (°C) / (R_f value)	IR (KBr, ν_{max}, cm^{-1})	^{1}H NMR
FD-1	*p*-OCH_3		$C_6H_{20}N_2O_3S$ (75.21)	200-205 (0.57)	(N-H) 3150, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (CH_2-N) 1444, (C-N) 1259, (-OCH_3) 1055, (C-S) 778	CH_3-3.83 (s), C=C-H 7.80 (s), -N-CH 3.58 (s), CH_2 1.55 (m), CH_3 1.56 (m), Ar-H 6.9- 7.62 (m).
FD-2	*p*-OCH_3		$C_{24}H_{20}N_2O_3S$ (62.25)	180-182 (0.72)	(N-H) 3150, (Ar C-H) 3010, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (CH_2-N) 1444, (C-N) 1259, (-OCH_3) 1055, (C-S) 778	CH_3-3.83 (s), C=CH 7.87 (s), CH 6.16 (m) Ar-H 6.9- 7.62 (m).
FD-3	*o*-OCH_3		$C_{16}H_{20}N_2O_3S$ (70.0)	208-210 (0.58)	(N-H) 3150, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (mono substituted benzene) 1511, (CH_2-N) 1444, (C-N) 1259, -OCH_3 1055, (C-S) 778	CH_3-3.83 (S), C=C-H 7.80 (S), -N-CH 3.58 (s), CH_2 1.55 (m), CH_3 1.56 (m), Ar-H 6.9- 7.62 (m).
FD-4	*o*-OCH_3		$C_{27}H_{20}N_2O_3S$ (55.02)	179-180 (0.70)	(N-H) 3150, (Ar C-H) 3010, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (mono substituted benzene) 1510, (CH_2-N) 1444, (C-N) 1259, (-OCH_3) 1055, (C-S) 778	CH 6.16 (s), C=CH8.34 (m), CH_3 3.83 (S), Ar-H 6.96-7.66 (m).
FD-5	*o*-OH		$C_{15}H_{18}N_2O_3S$ (77.34)	198-200 (0.50)	(C-OH) 3414, (N-H) 3150, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (CH-N) 1259, (C-S) 778	C-OH 9.43 (m) CH_2 2.64 (m), CH_3 1.02 (S), N-CH_2-N 4.55 (S), C-H 8.07 (m), Ar-H 6.65-7.56 (m).
FD-6	*o*-OH		$C_{23}H_{18}N_2O_3S$ (64.03)	164-170 (0.68)	(C-OH) 3414, (N-H) 3150, (Ar C-H) 3010, (Aliph. C-H) 2837, (C=O) 1686, (C=C) 1583, (CH_2-N) 1259, (C-S) 778	C-OH 9.43 (s), N-CH_2-N 5.25 (s), C-H 8.07 (m), Ar–H 6.65- 7.56 (m)

TABLE-2
HYPOGLYCEMIC ACTIVITY OF DERIVATIVES

Compd. No.	Dose (mg/kg)	Mean blood glucose level (mg/dl)			% Reduction in blood glucose level	
		Before 1st dose	After 2 h	After 4 h	After 2 h	After 4 h
Std. dose (rosiglitazone)	50	400	56	48	86	88
FD-1	50	275	132	116	52	58
FD-2	50	312	122	156	61	50
FD-3	50	275	63	79	72	65
FD-4	50	196	88	101	55	48
FD-5	50	350	231	252	34	28
FD-6	50	294	167	179	43	39

Experimental animal rats; Route of administration = Subcutaneous;
Number of animals in each group = six.

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