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SYNTHESIS AND ANTIDIABETIC EVALUATION OF SOME THIAZOLIDINE-2, 4-DIONE DERIVATIVES

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Thiourea,

chloroacetic acid,

Thiazolidinedione,

Anti- diabetic activity

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ABSTRACT

Condensation of thiaourea with chloro acetic acid gave Thiazolidinedione which react with aromatic aldehyde and produce 5- benzylidine, 2, 4 Thiazolidinedione.To this different secondary amine was reacted and final derivatives was obtained. The structures of these compounds were established by means of IR, 1 H-NMR.All the compounds were evaluated for antidiabetic activities. Most of the compounds have shown significant antidiabetic activity when compared with the standard drug.

INTRODUCTION: Diabetes mellitus, long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st century. The incidence of the disease currently is estimated to reach 210 million by the year 2010 and 300 million by the year 2025 [1]. Most cases will be of type 2 diabetes, which is strongly associated with a sedentary life style and obesity.

Early stages of type 2 diabetes mellitus (Type 2 DM) are characterized by tissue resistance to the effects of insulin secreted by pancreatic beta cells. The ability of pancreatic beta cells to continue increased production of insulin diminishes over time. When insulin production declines in the face of insulin resistance glucose disposal from the muscle is diminished and suppression of hepatic glucose output is decreased[2]. Metformin, a biguanides, acts primarily by decreasing hepatic glucose output and increasing peripheral glucose utilization[6]. It is a first line therapeutic option for Type 2 DM. Another class of drugs, that is, sulfonylureas stimulates insulin secretion by blocking ATP-dependent potassium channels[7] but is associated with a significant risk of hypoglycemia. Since the pioneer thiazolidinedione compound, ciglitazone, was reported improving blood glucose level by increasing insulin sensitivity, several new Thiazolidine-2, 4-diones such as pioglitazone, rosiglitazone, was launched into market since 1997.

MATERIALS AND METODS:

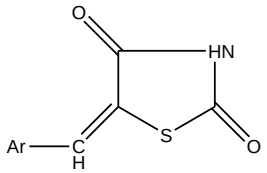
Antidiabetic Activity: The determination of blood sugar and plasma insulin level is most frequently carried out for screening of antidiabetic activity in biochemical laboratories. The methods generally used for blood glucose is determination by glucose oxidase/peroxidase method[3]. Wister rats (200-250 g) and Swiss mice (20-25 g) of either sex were used for the investigation. The animals were housed in controlled room under standard environmental conditions of temperature (25 $\pm$ 2°C), humidity (55 $\pm$ 10%) and light (12:12 h light/ dark cycle; lights on at 07.00h). Rats were supplied with standard pellet diet (Hindustan lever limited, Mumbai.) and tap water. The animals were handled and acclimatized to laboratory conditions 24 hrs before conducting experiments[4].

EXPERIMENTAL: 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-(Bruker) using DMSO as solvent and Tetramethylsilane as internal standards.

Synthesis of 2, 4-Thiazolidinedione[5, 6]: In a 250 ml three-necked flasks was placed, a solution containing 56.5g (0.6M) of chloroacetic acid in 60mL of water and 45.6g (0.6 M) of thiourea dissolved in 60mL of water. The mixture was stirred for 15 min to obtain a white precipitate, accompanied by considerable cooling. The 60mL of concentrated hydrochloric acid from a drooping funnel was added slowly to the content of flask. 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 hrs at 110°C. On cooling, the contents of the flask solidified into a cluster of white needles and product was filtered and washed with water to remove traces of hydrochloric acid and dried, purified by recrystallization with ethyl alcohol. Yield was 85% & m. p 123 ° C.

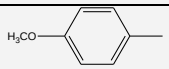
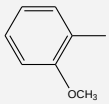
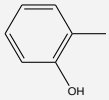
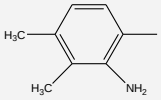
Synthesis of 5- (substituted) - 2, 4-thiazolidinedione: To a solution of Aryl aldehyde (0.25M) and 2, 4thiazolidinedione (0.25M) in hot glacial acid (50mL), fused sodium acetate (1.8g) was added and then it was refluxed for 1 hr with occasional shaking. It was poured in water (500mL), then product obtain

was filtered, washed with water, alcohol and ether and was recrystalized with glacial acetic acid. The physical property of synthesis compound is given table-1.

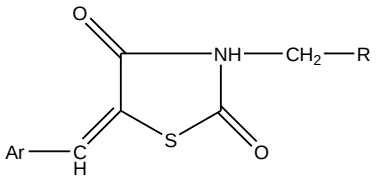


II

Table: 1; 5- (substituted) - 2, 4-thiazolidinedione

Ar	Yield (%)	Melting point
	76.22%	254^{0}C
	70%	252^{0}C
	75%	172^{0}C
	55%	183^{0}C

Synthesis of final compound: The compounds (II) (0.05 M) synthesis was dissolve in N, N-dimethyl formamide (15mL). Diethyl/ Diphenyl amine (0.05 M) was added followed by addition of formaline solution (38%) (0.05 M) and was refluxed for 15 hrs. The refluxed solution was kept in the refrigerator for 48 hrs. The product obtain was filtered dried and recrystallized using ethyl acetate[8, 9]. The list of final compounds synthesized is given in table-2.



III

Table: 2 Final compounds synthesized

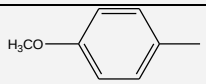
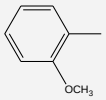
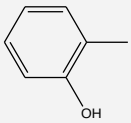
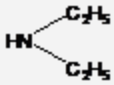
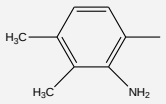
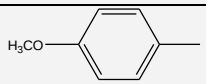
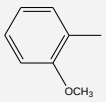
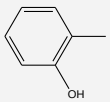
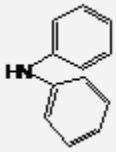
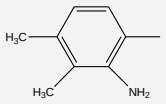
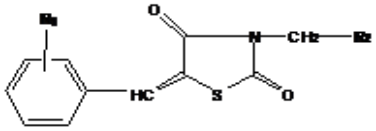
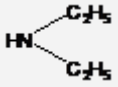
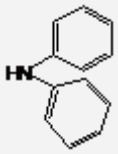
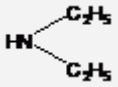
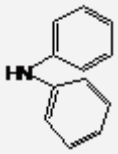
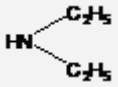
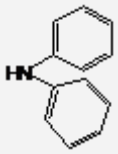
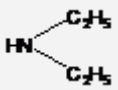
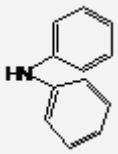
Ar	R	Yield	Melting Point
		75.21%	205^{0}C
		70%	210^{0}C
		77.34%	200^{0}C
		55%	222^{0}C
		62.25%	182^{0}C
		55.02%	179^{0}C
		64.03%	165^{0}C
		62.00%	188^{0}C

Table 3: Physical Data of the Synthesized Compound



Comp. code	Name of the compound	R_1	R_2	Molecular Formula	% yield	m. p. (°C)	Rf Value
FD-1	3-((diethylamino) methyl)-5-(4-methoxy benzylidene)-2,4-thiazolidinedione	p-OCH_3		$C_6H_{20}N_2O_3S$	75.21	200-205	0.57
FD-2	3((diphenylamino) methyl)-5-(4 methoxy benzylidene)-2,4-thiazolidinedione	p-OCH_3		$C_{24}H_{20}N_2O_3S$	62.25	180-182	0.72
FD-3	3-((diethylamino) methyl) -5-(2-methoxy benzylidene)-2,4-thiazolidinedione.	o-OCH_3		$C_{16}H_{20}N_2O_3S$	70.0	208-210	0.58
FD-4	3-((diphenylamino) methyl)-5-(2-methoxy benzylidene)-2,4-thiazolidinedione	o-OCH_3		$C_{27}H_{20}N_2O_3S$	55.02	179-180	0.70
FD-5	3-((diethylamino) methyl)-5-(2-hydroxy benzylidene)-2,4-thiazolidinedione	o-OH		$C_{15}H_{18}N_2O_3S$	77.34	198-200	0.50
FD-6	3-((diphenylamino) methyl)-5-(2-hydroxy benzylidene)-2,4-thiazolidinedione	o-OH		$C_{23}H_{18}N_2O_3S$	64.03	164-170	0.68
FD-7	5-(2-amino-3,4-dimethybenylidene) -3-((diethylamino) methyl) 2,4-thiazolidine -dione	o-NH_2, m-OCH_3, p-OCH_3		$C_{17}H_{23}N_3O_2S$	55.00	220-222	0.81
FD-8	5-(2-amino-3,4-dimethybenylidene)-3-((diphenylamino) methyl) 2,4-thiazolidinedione.	o-$_{NH2}$, o-OCH_3, p-OCH		$C_{25}H_{23}N_3O_2S$	62.00	187-190	0.85

Synthesis of 2, 4- Thiazolidinedione

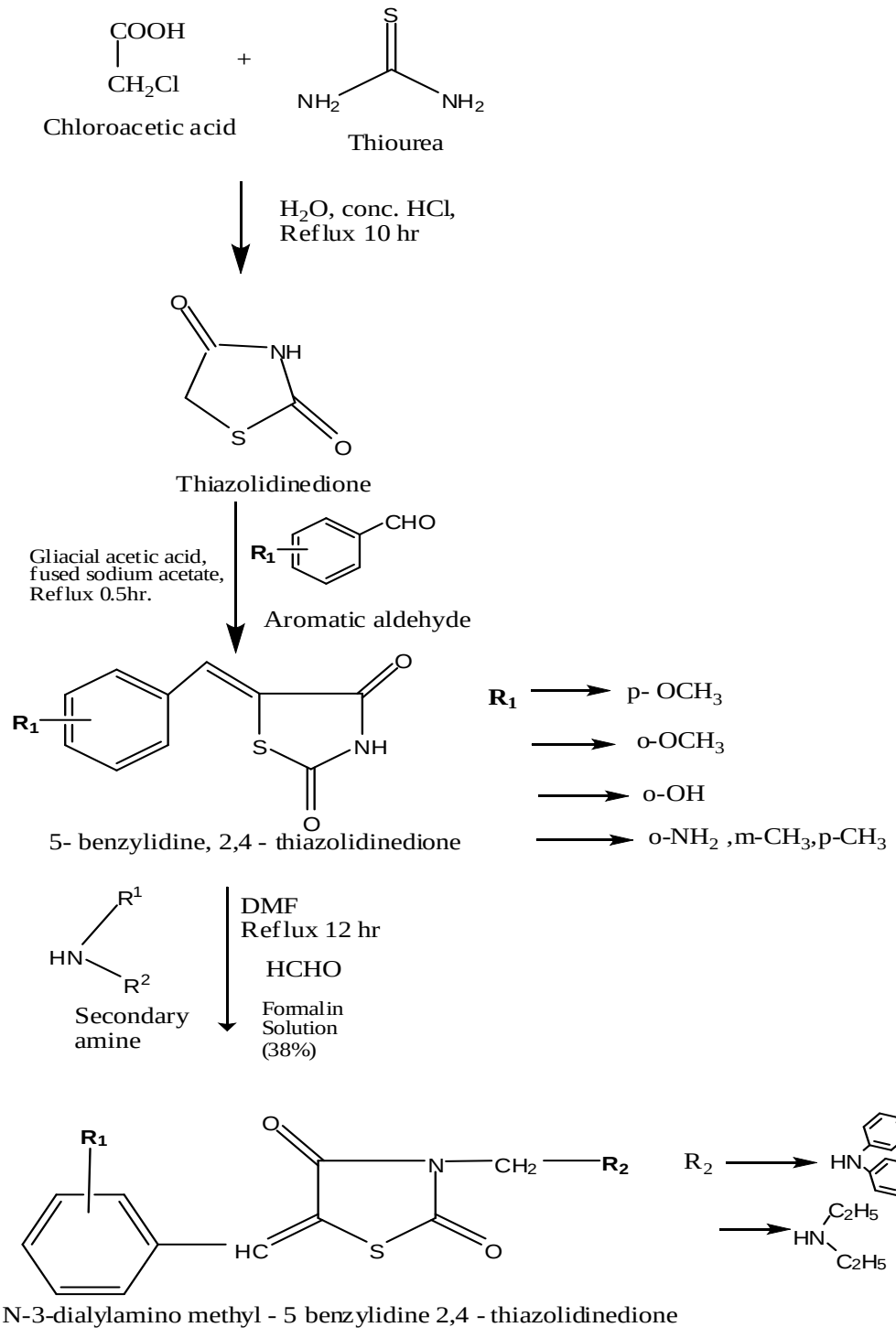


Table 4: Assignment of IR spectrum of synthesized compound

Compound Code	Wave number (cm^{-1})	Functional group
FD-1	3126.5	C-H Aro stretching
	2847.6,2769.6	C-H alkyl stretching
	1730.0, 1685.7	C=O (ring) stretching
	1593.9	C=C stretching
	1512.7	Mono substituted benzene
	1417.8	CH_2-N
	1081.5	Ali C-N stretching
FD-2	3121.7	C-H Aro stretching
	3011.7,2851.7,2754.3	C-H alkyl stretching
	1734.2, 1684.9	C=O (ring) stretching
	1591.5	C=C stretching
	1508.8	Mono substituted benzene
	1459.2	CH_2-N
	1256.5	Aro C-N stretching
FD-3	3136.6	C-H Aro stretching
	3029.8,2838.5,2768.5	C-H alkyl stretching
	1740.0, 1679.7	C=O (ring) stretching
	1588.4	C=C stretching
	1519.4	Mono substituted benzene
	1461.0	CH_2-N
	1048.6	Ali C-N stretching
FD-4	3134.9	C-H Aro stretching
	2839.0,2767.3	C-H alkyl stretching
	1739.8, 1678.1	C=O (ring) stretching
	1592.3	C=C stretching
	1516.8	Mono substituted benzene
	1459.7	CH_2-N
	1250.6	Aro C-N stretching

FD-5	3410.7	O-H stretching
	3060	C-H Aro stretching
	2923.5,2838.7,2768.9	C-H alkyl stretching
	1723.0, 1685.7	C=O (ring) stretching
	1593.8	C=C stretching
	1515.5	Mono substituted benzene
	1447.6	CH_2-N
	1061.0	Ali C-N stretching
FD-6	3407.1	O-H stretching
	3037.1	C-H Aro stretching
	2861.4	C-H alkyl stretching
	1720.4, 1662.8	C=O (ring) stretching
	1595.3	C=C stretching
	1517.6.	Mono substituted benzene
	1456.8	CH_2-N
	1241.9	Aro C-N stretching
FD-7	3386.6	N-H stretching
	3165.1	C-H Aro stretching
	2901.1,2795.9,2713.7	C-H alkyl stretching
	1721.4, 1663.7	C=O (ring) stretching
	1596.7	C=C stretching
	938.4(S),1580.3(m)	1,2,3-trisubstituted benzene
	1433.0	CH_2-N
	1064.1	Ali C-N stretching
FD-8	3344.4	N-H stretching
	3037.6	C-H Aro stretching
	2913.7,2823.3	C-H alkyl stretching
	1657.2	C=O (ring) stretching
	1522.7	C=C stretching
	910.3(S),1582.4(m)	1,2,3-trisubstituted benzene
	1441.4	CH_2-N
	1237.9.6	Aro C-N stretching

Table-5: Assignment of ^{1}H-NMR Spectra

Compound code	Shift values δ (ppm)	Nature of protons
FD-1	6.85-7.42	m, 4H, Ar-H
	3.77-3.86	s, 3H, O-CH_3
	7.8	s, 1H,-C=CH
	4.59	s,2H, N-CH_2
	2.57-2.79	t, 6H, -CH_3
	1.57-1.68	q,, 4H,-CH_2-
FD-2	6.85-7.42	m, 14H, Ar-H
	3.77-3.86	s, 3H, O-CH_3
	7.87	s, 1H,-C=CH
	5.36	s,2H, N-CH_2
FD-3	6.85-7.42	m, 4H, Ar-H
	3.77-3.86	s, 3H, O-CH_3
	7.87	s, 1H,-C=CH
	4.59	s,2H, N-CH_2
	2.57-2.79	t, 6H, -CH_3
	1.57-1.68	q, 4H,-CH_2-
FD-4	6.55-7.42	m, 4H, Ar-H
	3.82-3.88’	s, 3H, O-CH_3
	8.15	s, 1H,-C=CH
	4.79	s,2H, N-CH_2
FD-5	6.90-7.28	m, 4H, Ar-H
	8.38	s, 3H, O-CH_3
	5.39	s, 1H,-C=CH
	2.17-2.36	s,2H, N-CH_2
	1.15-1.38	q,4H ,-CH_2-
FD-6	7.26-7.73	m, 4H, Ar-H
	9.70	s, 3H, O-CH_3
	8.75	s, 1H,-C=CH
	5.35	s,2H, N-CH_2

FD-7	6.57-7.37	m,4H, Ar-H
	2.25	s,3H,Ar-CH_3
	2.90-2.92	s,3H, Ar, -CH_3
	5.87	s,3H , Ar-NH_2
	9.73	s, 1H,-C=CH-
	4.47	s, 2H,-N-CH_2
	2.40-2.62	t, 6H, -CH_3
	1.20-1.42	q, 4H,-CH_2-
FD-8	6.90-7.79	m, 4H, Ar-H
	3.04-3.08	s, 3H, O-CH_3
	2.90-2.92	s, 1H,-C=CH
	9.73	s,2H, N-CH_2

Table 7: Effect of the different dialkyl / diaryl amino methyl-5-(o/m/p- substituted benzylidine)-2, 4-thiazolidinedione derivatives on the Alloxan induced hyperglycemia

Comp Code	Dose (mg/ kg)	Mean blood glucose levels in mg/dl		Percentage reduction in blood glucose	
		After 1st h.	After 2nd h.	After 1st h.	After 2nd h.
FD-1	200	174.7±25.58	101.0±2.082	45.96	155.44
FD-2	200	157.7±22.81	114.7±2.028	61.69	124.93
FD-3	200	178.7±27.76	127.0±14.15	42.69	103.14
FD-4	200	152.0±18.15	128.7±3.383	67.76	100.46
FD-5	200	224.0±1.155	151.3±12.78	13.80	70.52
FD-6	200	236.7±22.58	152.7±10.41	7.73	66.88
FD-7	200	202.7±14.38	172.0±6.110	25.80	50.00
FD-8	200	222.0±21.70	180.3±24.06	14.86	43.09
ROS	200	136.0±10.79	105.3±10.65	87.50	145.01

RESULT & DISCUSSION: Thiazolidinedione derivatives were synthesized and the structures of the compounds were established by means of IR and ^{1}HNMR. The ant diabetic activity was determined using an Alloxan induced hyperglycaemia model, and it was found that the compound containing active (FD-1 and FD-2) than the compound –O-CH3 at ortho-position (FD-3 & FD-4). Substitution with –OH group at ortho- position also produces compounds which causes great decrease in blood glucose level (FD-5 & FD-6) but this decrease in blood glucose level is less than the compound FD-1 & FD-2, FD-3 & FD-4.

Compounds which are substituted with NH2 at ortho-position along with the substitution of –OCH3 at Meta & Para-position show minimal hypoglycaemic effects which are not very much significant. Hence we conclude that the compound FD-1, FD-2, FD-3 & FD-4 possess maximal hypoglycaemic activity (155.44, 124.93, 103.14, 100.46), compound FD-5 and FD-6 possess moderate hypoglycaemic activity (70.52, 68.88) which compound FD-7 & FD-8 have least hypoglycaemic activity (50.00%, 43.09%) in composition with the standard drug Resiglitazone (145.01).

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