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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 2, 4-THIAZOLIDINEDIONES AS ANTIDIABETIC AGENTS

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ABSTRACT

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. At least 90% of all cases are accounts for type II diabetes mellitus. All new series of 2, 4 thiazolidinediones derivatives were synthesized by conventional as well as microwave irradiation method. The structures of these compounds were established by IR, H^1 NMR and elemental analysis. All these compounds (3a-3j) were screened for antidiabetic and antihyperlipidemic activity on albino rats. Most of these compounds shown significant activity when compared with standard drug Pioglitazone.

KEYWORDS: Thiazolidinediones, conventional method, microwave irradiation, pioglitazone.

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.[1] Patients with diabetes are at higher risk for cardiovascular events including strokes and atherosclerotic lesions in peripheral, coronary, cerebral arteries. Cataracts, retinopathy, renal diseases and nervous system damage are other complications. Type II diabetes is characterized by hyperglycemia, insulin resistance and progressive loss of β cell function and associated with dyslipidemia, hypertension and obesity that affects between 6% and 20% of the population in Western

industrialized societies. The thiazolidinediones also known as glitazones are a class of medications used in the treatment of type II diabetes mellitus.[2] The thiazolidinediones used in oral combination therapy in management of patients with type II diabetes that has insufficient glycaemic control despite maximal tolerated dose of oral mono-therapy with either metformin or sulphonylureas. These observations promoted us to synthesis the title compounds with incorporation of substituted aromatic aldehydes and aromatic amine. The thiazolidinediones nuclei would produce new compound with significant antidiabetic properties.[3]

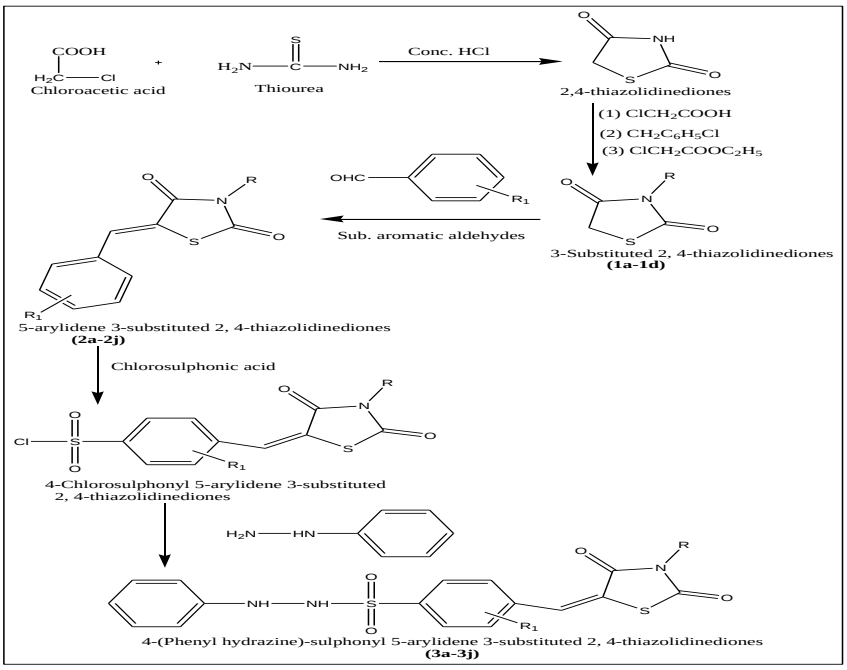
2. MATERIAL AND METHODS

2.1 Antidiabetic activity

Wistar rats either sex weighing between 150-200gm were used. The animals were housed under controlled conditions with standard diet and water ad libitum. The animals were kept fasted for 24hrs with water ad libitum, diabetes was induced by Alloxan monohydrate (120mg/kg i.p) in normal saline solution. A 5% dextrose solution was given in feeding bottle for a day to overcome early hypoglycemic phase. The blood glucose level was monitored by taking blood tail tip cut method on auto analyzer. After 72 hrs, the animals showing blood glucose level beyond 150mg/dl were segregated and were divided into 3 groups. viz…(i) vehicle treated group (ii) standard treated group, (iii) drug treated group comprised 5 subgroups for 20 test compounds. Each group as well as subgroup comprised of 6 animals. The quantity of 2, 4- thiazolidinediones derivatives equivalent to average human intake 200 mg/kg at a time was calculated for single dose 30 mg/kg. The test compounds were administered orally by mixing with CMC (0.25%) solution.[4] The blood glucose level was monitored at different times interval 0, 2, 4, 6, 8 days are shown in Table 1 and triglyceride, cholesterol, HDL level was monitored on 28th and 36th days are shown in Table 2, 3, 4 respectively.

2.2 Experimental

Scheme



R	R_1
-H	-H
$-ClCH_2COOH$	$3-NO_2$
$-CH_2C_6H_5Cl$	3-Cl
$-ClCH_2COOC_2H_5$	$3-OCH_3$
	2-Cl

Synthesis of 2, 4-thiazolidinediones

In a 250 ml three necked round-bottomed flask was place, solution containing (56.4gm, o.6 mol) of chloroacetic acid in 60 ml of water and (45.6gm, 0.6mol) 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 hydrochloric acid 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 hrs at 100-110□C. The completion of reaction was monitored by thin layer chromatography using mobile phase as chloroform: methanol (4.5:0.5). On cooling the content of the flask solidified to 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 ethanol. Melting point: 124°C. Yield: 93.12%. The compounds 1a-1d was synthesized following a similar procedure. The data of synthesized compounds are shown in Table 5.

Synthesis of 5-Arylidene-2, 4-thiazolidinediones

In a 250 ml three necked round-bottomed flask provided with a Dean-Stark apparatus, benzaldehyde (20gm, 0.188mol) and 2, 4-thiazolidinediones (22gm, 0.188mol) were together suspended in ethanol. To this a catalytic amount of piperidine (1ml) was added. The mixture was stirred and refluxed. The completion of reaction was monitored by thin layer chromatography using mobile phase as methanol: acetic acid (9:1). After the complete removal of water and when temperature reached above 110°C the reaction mixture was stirred for further 1hr. On cooling the product precipitated out from ethanol. The compound was filtered and washed with cold dry toluene and dry ethanol. Melting point: 240-242°C. Yield: 90.96%. The compounds 2a-2j was synthesized following a similar procedure.

Synthesis of 4-Chlorosulphonyl-5-Arylidene-2, 4-thiazolidinediones

Substituted 5-arylidene 2, 4-thiazolidinediones (8gm, 0.0388mol) was taken in 100ml of round bottomed flask equipped with a condenser and a dropping funnel. Chlorosulphonic acid (18.08gm, 0.155gm) was added at room temperature using the dropping funnel. The reaction was found to be exothermic. After addition of Chlorosulphonic acid the reaction was refluxed for 1hr on a water bath. The complication of reaction is monitored by thin layer chromatography using mobile phase as chloroform: methanol (4.5:0.5).The reaction was cooled and poured in a thin stream with stirring into crushed ice contained in a one liter beaker. The product was filtered and dried. It was purified by recrystallization from ethanol. Melting point: 180-181°C. Yield: 85%.

Synthesis of N-(4-(phenyl hydrazine)-sulphonyl)-5-Arylidene-2, 4-thiazolidinediones

A mixture of 5-(4-chlorosulphonyl)-arylidene) 3-sustituted-2, 4-thiazolidinediones (0.01mol), aromatic or aliphatic amines were taken in a beaker and made a homogeneous paste. The paste was exposed to microwave irradiation for 1-2min, at interval 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. Melting point: 174-176°C. Yield: 69%. The compounds 3a-3j was synthesized following a similar procedure.

1. RESULT AND DISCUSSION

A series of thiazolidinediones derivatives were synthesized. The structures of these compounds were established by means of IR, ^{1}H-NMR and elemental analysis. Infra red/^{1}H-NMR spectral studies of the synthesized compounds are shown in Table 6. The title compounds were screened for their antidiabetic activity by alloxan induced tail cutting

method. The albino rats of either sex weighing between 150-200 gm were selected. The blood glucose level was induced and the study was carried out in six different groups. Out of ten synthesized (3a-3j) compounds, the compounds 3a, 3b, 3f, 3t are shown significant decrease in blood glucose level, compounds 3a, 3f, 3t are shown significant decrease in triglyceride level, compounds 3a, 3b, 3f, 3t are shown significant decrease in cholesterol level and compounds 3a, 3b, 3f, 3k, 3t are shows significant decrease in HDL-Cholesterol level on oral administration. The results were calculated by measuring the mean ± SEM.

Table 1: Blood glucose level of synthesized compounds.

Compounds	Blood glucose level (mg/dl) mean±SEM				
	0th day	2nd day	4th day	6th day	8th day
Negative control	232±2.31	233±2.97	231±1.24	233±2.86	230±2.46
Control	115±1.44	116±2.67	118±1.45	114±2.45	115±2.45
Standard	202±2.28	188±2.21	153±1.99	128±2.27	116±1.51
3a	208±0.78	194±1.67	160±1.89	135±2.90	121±2.45
3b	210±2.45	195±1.56	164±1.45	134±1.23	120±2.89
3c	210±4.55	209±4.78	149±1.23	150±1.90	148±3.65
3d	230±2.54	210±3.32	191±2.65	175±1.45	160±3.89
3e	208±3.56	199±2.67	167±2.89	133±1.43	119±3.54
3f	232±2.34	204±1.89	188±3.87	159±1.90	148±4.98
3g	231±1.67	209±1.756	189±2.54	153±1.87	142±4.09
3h	229±1.89	200±1.78	164±2.45	141±1.97	132±1.09
3i	230±1.55	191±4.89	188±2.09	158±2.87	145±1.65
3j	212±3.09	198±3.32	161±2.11	136±2.45	124±1.45

Table 2: Triglyceride level of synthesized compounds.

Compounds	Triglyceride level mg/dl (Mean±SEM)	
	28 day	36 day
Negative control	224±2.87	226±2.93
Control	124±1.44	122±2.67
Std	151±2.88	125±2.45
3a	177±0.78	138±1.67
3b	209±1.55	200±4.89
3d	208±4.55	199±4.78
3e	200±2.54	190±3.32
3f	163±3.46	133±2.43
3k	201±2.34	199±1.89
3m	202±1.67	200±1.756
3p	196±1.89	180±1.78
3s	223±3.56	198±2.67
3t	175±1.82	134±1.99

Table 3: Cholesterol level of synthesized compounds.

Drug	Cholesterol level mg/dl (Mean±SEM)	
	28 day	36 day
Negative control	130±1.37	132±1.64
Control	52±1.44	50±2.67
Std	91±2.88	52±2.45
3a	98±4.55	61±4.78
3b	100±2.45	60±1.56
3d	125±3.56	120±2.67
3e	113±2.54	96±3.32
3f	96±2.34	63±1.89
3k	130±1.37	128±1.61
3m	129±1.67	121±1.756
3p	117±1.89	98±1.78
3s	112±1.55	101±4.89
3t	94±1.82	61±1.99

Table 4: HDL-Cholesterol level of synthesized compounds.

Drug	HDL level mg/dl (Mean±SEM)	
	28 day	36 day
Negative Control	45±2.15	48±2.64
Control	21±1.44	20±2.67
Std	30±2.88	21±2.45
3a	38±0.78	29±1.67
3b	36±2.45	27±1.56
3d	41±4.55	40±4.78
3e	45±2.54	43±3.32
3f	56±3.56	31±2.67
3k	40±2.34	28±1.89
3m	65±1.67	63±1.756
3p	44±1.89	40±1.78
3s	49±1.55	46±4.89
3t	40±1.82	38±1.99

Statistical analysis is done by one-way ANOVA followed by Dunnett test.

Table 5: Physical data of synthesized compounds.

Compounds	Mole. Formula	Mole. wt.	m.p. (˚c)	Yield (%)	Elemental analysis (calculated)					
					C	H	O	N	S	Cl
3a	$C_{16}H_{13}N_3O_4S_2$	375.42	174-176	72.62	51.19	3.49	17.05	11.19	17.08	….
3b	$C_{16}H_{12}N_4O_6S_2$	420.42	172	65.08	45.71	2.88	22.83	13.33	15.25	….
3c	$C_{16}H_{12}ClN_3O_4S_2$	409.87	172	68.00	46.89	2.95	15.61	10.25	15.65	8.65
3d	$C_{17}H_{15}N_3O_5S_2$	405.45	174-178	70.29	50.36	3.73	19.73	10.36	15.82	….
3e	$C_{18}H_{15}N_3O_6S_2$	433.46	170	74.91	49.24	3.70	24.16	9.07	13.84	….
3f	$C_{23}H_{19}N_3O_4S_2$	465.54	172	68.00	59.34	4.11	13.75	9.03	13.78	….
3g	$C_{23}H_{18}ClN_3O_4S_2$	499.99	170	71.46	55.25	3.63	12.80	8.40	12.80	7.09
3h	$C_{20}H_{19}N_3O_6S_2$	461.51	170	72.54	52.05	4.15	20.80	9.10	13.90	….
3i	$C_{20}H_{18}ClN_3O_6S_2$	495.96	174	70.00	48.43	3.66	19.36	8.47	12.93	7.15
3j	$C_{21}H_{21}N_3O_7S_2$	491.54	176	65.84	57.31	4.31	22.78	8.55	13.05	….

Table 6: Infra Red/ ^{1}H-NMR spectral study of synthesized compounds.

Compounds	IR (cm^{-1})	^{1}H-NMR (δ, ppm)
2c	3304.51 (NH stretch), 1658.78 (C=O), 1608.68(C=C), 1573.91(N-H bend), 750.31(C-Cl)	------
3c	3223.05 (NH stretch), 2970.38 (CH stretch), 1666.50(C=C stretch), 1359.82(C-C bending), 750.31 (C-Cl)	------
2b	2926.01 (Ar-CH stretch), 2700.99 (S-H stretch), 1778.37 (C=O), 1672.28(C=C stretch)	------
3b	3207.62 (NH stretch), 2962.66(Ar-CH stretch), 2425.05 (CH stretch),1670.35 (C=O), 1348.24 (-NO_2), 1145.72 (OH stretch), 729.09(NH bend)	10.0 (1H, NH imid), 7.26-8.51 (3H CH aromatic benzene), 2.0 (1H NH amine), 4.0 (1H NH aromatic C-NH), 6.66-7.18 (5H CH aromatic benzene), 7.68 (1H 1-ethylene) [1:8:1:1:1]

2. CONCLUSION

Structures of title compounds were confirmed by different spectroscopic techniques like IR, ^{1}HNMR and Mass spectroscopy. Compounds phenyl hydrazine-(4-sulphonyl)-5-benzylidine-2, 4-thiazolidinediones (3a), phenyl hydrazine-(4-sulphonyl)-5-(2-nitro-benzylidine)-2, 4-thiazolidinediones (3b), Phenyl hydrazine (4-sulphonyl) - 5-benzylidene-3-acetic acid-2, 4-thiazolidinediones (3f), phenyl hydrazine-(4-sulphonyl)-5-(3-methoxy)-benzylidene)-3-ethyl acetate-2, 4-thiazolidinediones (3t) shows significant decrease in blood glucose, triglyceride, cholesterol and HDL- cholesterol levels.

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