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SYNTHESIS, CHARACTERIZATION OF THIAZOLIDINEDIONE DERIVATIVES AS ORAL HYPOGLYCEMIC AGENT

F. Alam*, Biplab Kr. Dey and Pallab Kalita

Dept. of Pharmacy, Assam Down Town University, Panikhaiti, Guwahati, Assam, 781026, India.

ABSTRACT

We have synthesized a new series of 5-(substituted benzylidene)-3-[(substituted)-methyl]-1,3-thiazolidine-2,4-dione derivative and the structures of the new compounds were confirmed by physical parameters like solubility, melting point, chromatographic methods (TLC) and at last spectroscopic methods (IR, ^{1}H NMR).The thiozolidinediones are improving insulin sensitivity and lowering blood glucose, free fatty acid, and triglyceride levels. The thiozolidinediones are PPARγ(peroxisome proliferator-activated receptor) agonist. Since our titled compounds are known to possess anti-diabetic activity. The antidiabetic activity of the synthesized compounds has been carried out by male Wister rats weighing between 80-150 gm using glibenclamide as standard drug. Apart from this it has also been reported that derivatives of 1,3-thiazolidine-2,4-dione condensed nucleus systems exert diverse pharmacological activities such as antimicrobial anti-inflammatory, anticancer, antidiabetic etc.

Keywords: Antidiabatic activity, 1,3-thiazolidine-2,4-dione, glibenclamide.

INTRODUCTION

Sulfonylureas and metformin are the most common antidiabetic agents that induce severe hypoglycemia and weight gain [1]. In addition, there are increased rates of both primary and secondary failures associated with them [2]. Hence, there is a need for developing insulin resistance upgrading drugs for type 2 diabetes. Troglitazone 50 [3], the first drug on the market failed to survive due to liver toxicity. 2, 4-thiazolidinedione class agents, pioglitazone 48 [4] and rosiglitazone 51 [5] are currently in clinical use. Ciglitazone 47 [6] has antihyperglycemic activity in insulin resistant animal models. But, anaemia, edema and body weight gain [7] are associated with 2,4-thiazolidinediones drugs. Drugs with more advanced profile are the focus of attention.

The thiozolidinediones are the most recently introduced class of oral agents for treatment of type 2-diabetes, improving insulin sensitivity and lowering blood glucose, free fatty acid, and triglyceride levels. The thiozolidinediones are peroxisome proliferator-activated receptor agonist. The PPARγ receptor is a member of the nuclear hormone receptor of ligand activated transcription factors that regulate gene expression of several genes involved in fatty acid and carbohydrate metabolism and adipocyte differentiation [19]. In addition to hypoglycemic activity, thiozolidinedione reduce insulin levels and improve insulin reistance, markedly reduce plasma free fatty acids, increase the storage of fat and often improve the blood lipid profile [8].

Besides, thiazolidine derivatives show anticancer [9,10], anti-inflammatory [11,12], anti-obesity [13], antifungal [14], anti-diabetic [15,16], cardiotonic [17] and anticonvulsant [18] activities.

METHODS AND METERIALS

All the chemicals and reagents were of synthetic grade and commercially procured from S.D. Fine Chem. Ltd. (Mumbai, India). The melting points were determined using open capillary tubes and are uncorrected. Purity of the all synthesized compounds was checked by thin layer chromatography technique (0.2 mm thickness of silica gel G plates) and iodine was used as visualizing agent. IR

Corresponding Author:- **Faruk Alam** Email: kalitapallab@gmail.com

spectra were recorded on FT-IR8400S, Fourier Transform (Shimadzu) Infrared spectrophotometer using KBr disk method. ^{1}H NMR spectra were recorded on JEOL (JNM-ECS400, 400 MHz) in dimethyl sulfoxide (DMSO-*d6*) using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on Shimadzu LC–MS 2010A Mass Spectrometer.

Synthesis of Thiazolidine-2,4-dione(1) [20,21]:

In a 250 ml three necked flask a solution of containing chloroacetic acid (0.6 mol) in a 60 ml of water and thiourea (0.6mol) dissolved in 60 ml of water. The mixture was stirred for 15 minutes to form a white precipitate, accompanied by considerable cooling. To content of the flux was now added slowly 60 ml conc.HCl from dropping funnel, the flux was concentrated with reflux condenser and gentle heat applied to effect complete solution,after with the reaction mixture was stirred and refluxed for 8-10 hrs at 100-110 ^{0}C.On cooling the content of the flux solidified to mass of cluster of white needles. The product was filtered and washed with water to remove traces of HCl and dried." It was recrystallized from ethanol.

IR (KBr cm^{-1}): 1241 (C-N), 1492 (CH2), 1666, 1738 (C=O), 3121 (NH);^{1}H NMR $CDCl_3$: δ 4.2 (s, 2H, CH2), 9.1 (s, 1H, NH).

General procedure: Synthesis of substituted 5-(benzylidine)-2,4-Thiazolidinedione:

In 150 ml three necked round bottom flask attached with a Dean stark apparatus, equimolar quantity of substituted benzaldehyde and thiazolidinedione were taken and suspended in a dry toluene. To this catalytic amount of piperidine was added. The mixture was stirred and refluxed. After complete removal of water and when the temperature reached above 110^{0}C the reaction mixture was stirred for further 1 hrs. The completion of the reaction was checked by TLC using ethanol: acetone (9:1).The compound was filtered and washed with cold dry toluene and dry ethanol. Recrystallized from methanol.

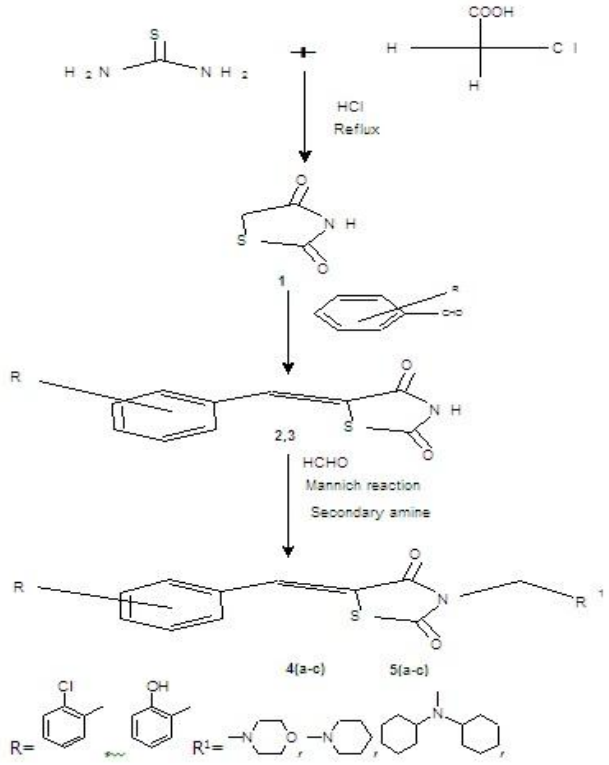
Synthesis of 5-(2-chloro benzylidine)-2,4-Thiazolidinedione(2):

IR (KBr cm^{-1}): 1341 (C-N), 1485 (-CH2), 1748 (C=O), 3138 (NH), 2834(C-Cl), 2345(C-S), 1612(C=C Ar);^{1}H NMR $CDCl_3$: δ 4.2 (s, 2H, CH2), 7.79 (s, 1H, NH),2.33 (s,1H,Benzylidene),7.08(m,4H,Ar-H).

Synthesis of 5-(2-hydroxy benzylidine)-2,4 – Thiazolidinedione(3):

IR (KBr cm^{-1}): 1346 (C-N), 1476 (-CH2), 1735 (C=O), 3438 (NH), 3041(OH), 2454(C-S), 1586(C=C Ar);^{1}H NMR $CDCl_3$: δ 4.5 (s, 2H, CH2), 7.9 (s, 1H, NH),2.5s,1H,Benzylidene),8.32(m,4H,Ar-H),7.04 (s,1H,O H).

Fig. 1. Synthetic Protocol Scheme



ANTIDIABETIC EVALUATION [22]

Experimental Animals

Adult Wister rats weighing (150–200 g) of either sex were used as experimental animals. All the animals were housed in cage at a temperature of 25 ±1^{0}C and a relative humidity of 45–55%. A 12 h dark and 12 h light cycle was followed during the experiments. Animals were allowed free access to food and water *ad libitum*. During the study period, guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Institutional Animals Ethics Committee (IAEC) were followed for the maintenance of animals.

Streptozotocin (STZ)-induced diabetic rats

The overnight fasted rats were made diabetic with STZ (sigma, St.Louis, MO.,USA;60 mg/kg body wt. i.p.).The STZ was freshly dissolved in citrate buffer (0.01M, pH 4.5) and maintained on ice prior to use; the injection volume was 1 mg/kg. Diabeties was confirmed in the STZ-treated rats by measuring the blood glucose concentration after 15hrs of fasting at 72 hrs post injection. The wister rats with blood glucose level above 250 mg/l were considered to be diabetic and used in the experiment.

Experimental design

Animals were divided into 7 groups of 10 animals (n=10): Group1: diabetic animals (vehicle) received 0.5% CMC (1ml); Group 2: diabetic animals received glibenclamide 20mg/kg. Group (3-7) diabetic animals

received test drugs (4a-4c and 5a-5c) in a single dose of 50 mg/kg b.w., p.o respectively for 7 days continuously (Table 3) [23].

RESULTS AND DISCUSSION

Change in blood glucose in treatment of diabetic rats with synthesized compound was presented in table no 1.A significant increase in blood glucose level was observed in diabetic rats. Oral administration of synthesized compounds (Compound 1,2,3) for 7^{th} and 10^{th} day show reduction in blood glucose as compared to control diabetic rats.Compound 3 did not shown significant blood glucose reduction on 7^{th} days like other test drugs.Compound 1 and compound 2 was found to be hypoglycemic agent like the standard drug Glibenclamide in reducing the blood glucose level.

CONCLUSION

In conclusion, we have described a simple protocol for the synthesis of 5-(2-chlorobenzylidene)-3-(substituted methyl)-1,3-thiazolidine-2,4-dione derivatives with remarkable yields. All the synthesized compounds were screened for their in-vitro anti-diabetic activities and found most of them having significant anti diabetic activities. The pharmacological activities exhibited by synthesized novel thiozolidinediones derivatives have confirmed that these compounds may serve the purpose of being accepted as the novel therapeutic agents. Furthermore, an extensive toxicological study of these derivatives are highly recommended to assess the safety and pharmacological efficacy of the compounds studied.

Table 1. Physical data of the synthesized compounds

Compd.	Mol. formula	Mol.Wt.	m.p. 0C	Yield%	Rf	Elemental analysis					
						Calculated			Found		
						C	H	N	C	H	N
1	C3H3NO2S	117	123-125	87	0.57	30.76	2.58	11.96	30.46	2.55	11.92
2	C10H6ClNO2S	239	208-210	64	0.68	50.11	2.52)	5.84	49.81	2.49	5.85
3	C10H7NO3S	221	220-222	69	0.69	54.29	3.19	6.33	54.20	3.09	6.23
4a	C15H15ClN2O3S	338	198-201	56	0.61	53.17	4.46	8.27	53.37	3.96	8.26
4b	C16H17ClN2O2S	336	215-217	58	0.77	57.05	5.09	8.32	57.12	5.13	8.33
4c	C23H29ClN2O2S	433	230-232	74	0.73	63.80	6.75	6.47	63.00	6.70	6.40
5a	C15H16N2O4S	320	206-207	72	0.72	56.24	5.03	8.74	55.84	5.09	7.94
5b	C16H18N2O3S	318	260-263	74	0.79	60.36	5.70	8.80	60.13	5.68	8.87
5c	C23H30N2O3S	414	227-229	75	0.58	66.64	7.29	6.76	66.58	7.22	6.75

Table 2. Spectral data of the synthesized compounds

Compd.	IR	NMR	MS
4a	IR (cm^{-1}): 3042 (C-H Ar); 2918, 2828 (CH_2); 1700, 1716 (C=O); 2362(C-S);1514 (C=C) 1120 (C-O-C); 1315 (C-N); 738 (C-Cl).	7.08-7.24(m,8H,Ar-H); 2.50 (s,1H,Benzylidene); 4.55 (s,2H,CH_2); 2.37 (m, 4H, morpholine); 3.67 (m, 4H, morpholine),	m/z:- 337(M-1) $^{+}$;338$(M)^{+}$
4b	IR (cm^{-1}): 3056 (C-H Ar); 2922, 2865 (CH_2); 1315 (C-N) ; 1710 (C=O);1565 (C=CAr),2341 (C-S) ;740 (C-Cl)	7.04-7.34 (m,8H,Ar-H), 3.66 (s1H,Benzylidene), 4.50 (s,2H,CH_2), 1.5 to 2.37 (m, 10H, piperidine),	m/z:- 336$(M)^{+}$; 337$(M+1)^{+}$
4c	IR (cm^{-1}): 3056 (C-HAr); 2934, 2843(CH_2); 1728 (C=O) ; 1353 (C-N);1541 (C=CAr),2360 (C-S) ;762 (C-Cl)	7.12-7.23(m,8H,Ar-H),2.50 (s1H,Benzylidene),1.55 to 2.6 (m, 20H, dicyclohexane) ,4.48(s,2H,CH_2)	m/z:- 433$(M)^{+}$
5a	IR (cm^{-1}): 3142 (C-H Ar); 2938, 2920 (CH_2); 1736 (C=O); 2457(C-S); 1126 (C-O-C); 2796(C=C) ; 1321 (C-N); 3038 (OH).	6.62-7.23 (m,4H,Ar-H),2.50 (s1H,Benzylidene), 4.55 (s,2H,CH2) ,9.41 (s,1H,OH); 2.32 (m, 4H, morpholine); 3.65 (m, 4H, morpholine).	m/z:-;320$(M)^{+}$,322$(M+2)^{+}$
5b	IR (cm^{-1}): 3156 (C-H Ar); 2934 (CH_2); 1753 (C=O); 2450(C-S); 1128 (C-O-C); 2789(C=C) ; 1332 (C-N);1534 (C=CAr)3042 (OH).	6.64-7.14 (m,4H,Ar-H), 3.46 (s1H,Benzylidene), 4.44 (s,2H,CH_2), 9.34 (s,1H,OH); 1.45 to 2.42 (m, 10H, piperidine),	m/z:- 318$(M)^{+}$
5c	IR (cm^{-1}): 3142 (C-H Ar); 2938, 2920 (CH_2); 1736 (C=O); 2457(C-S); 1126 (C-O-C); 2796(C=C) ; 1513 (C=CAr) ,1321 (C-N); 3038 (OH).	6.12-7.42 (m,4H,Ar-H), 2.53 (s1H,Benzylidene),1.45 to 2.55 (m, 20H, dicyclohexane) ,4.47(s,2H,CH_2)	m/z:- 414$(M)^{+}$

Table 3. Measurement of Blood Glucose Level of Control, Standard and Compound Treated Rat

Treatment(mg/kg b.w., p.o)	Blood glucose Level(mg/dl)			
	0-Day	3-Day	7-Day	10-Day
Control(0.5%CMC)	86±4.35	420±7.19	413.32±8.35	410±19.86
Glibenclamide-20	89±5.34	411±13.11	227.45±10.38**	109±13.16**
Compound 4a	85±5.22	425±9.34	233.52±19.15**	119±18.54**
Compound 4b	87±4.31	429±7.77	246.66±13.78**	112±10.13**
Compound 4c	88±4.21	422±7.41	396.16±6.30	370±16.96NS
Compound5a	82±5.22	418±9.34	232.52±19.15**	120±18.54**
Compound5b	80±4.31	416±7.77	240.66±13.78**	117±10.13**
Compound5c	84±4.21	420±7.41	380.16±6.30	348±16.96NS

Values are expressed as mean ±SEM n=10, data were analysed using one way ANOVA followed by Tukey-kramer multiple comparison test; **p<0.001 compared to diabetic control.

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REFERENCES

1. Holman RR and Turner RC. Textbook of Diabetes. Pickup JC and Williams G (Eds). *Blackwell Scientific Publications*, London, UK, 1991, 462–76.
2. Harrower AD. Comparison of efficacy, secondary failure rate, and complications of sulfonylureas.*J Diabetes Complications*, 8, 1994, 201-3.
3. Yoshioka T, Fujita T, Kanai T, Aizawa Y, Kurumada T, Hasegawa K and Horikoshi H. Studies on hindered phenols and analogues. Hypolipidemic and hypoglycemic agents with ability to inhibit lipid peroxidation. *J Med Chem*, 32, 1989, 421-8.
4. Sohda T, Momose Y, Meguro K, Kawamatsu Y, Sugiyama Y and Ikeda H. Studies on antidiabetic agents. Synthesis and hypoglycemicactivity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones. *Arzneimittelforschung*, 40, 1990, 37-42.
5. Cantello BC, Cawthorne MA, Cottam GP, Duff PT, Haigh D, Hindley RM, Lister CA, Smith SA and Thurlby PL. [[omega-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J Med Chem*, 37, 1994, 3977-85.
6. Sohda T, Mizuno K, Imamiya E, Sugiyama Y, Fujita T and Kawamatsu Y. Studies on antidiabetic agents. II. Synthesis of5-[4-(1-methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and its derivatives. *Chem Pharm Bull (Tokyo)*, 30, 1982, 3580-600.
7. Rakowitz D, Maccari R, Ottana R and Vigorita MG. In vitro aldose reductase inhibitory activity of 5-benzyl-2,4-thiazolidinediones. *Bioorg Med Chem*, 14, 2006, 567-74.
8. Adams M, Montague CT, J B Prins, J C Holder, S A Smith, J E Digby, C P Sewter, M A Lazar, V K K Chatterjee, S. O'Rahilly. Activators of peroxisome proliferator-activated receptor gamma have depot-specific effects on human preadipocyte differentiation. *J Clin. Invest*, 100, 1997, 3149-3153
9. Patil V, Tilekar K, Mehendale-Munj S, Mohan R and Ramaa CS. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4- thiazolidinedione derivatives. *Eur J Med Chem*, 45, 2010, 4539-44.
10. V. Patil, K. Tilekar , S. Mehendale-Munj, R. Mohan ,C. S. Ramaa. Synthesis and primary cytotoxicity evaluation of new 5-benzylidene-2,4-thiazolidinedione derivatives. *Eur J Med Chem*, 45, 2010, 4539-44
11. Nastasa C, Tiperciuc B, Parvu A, Duma M, Ionut I and Oniga O. Synthesis of new N-substituted 5-arylidene-2,4-thiazolidinediones as anti-inflammatory and antimicrobial agents. *Arch Pharm (Weinheim)*, 346, 2013, 481-90.|
12. Nastasa C, B. Tiperciuc , A. Parvu , M. Duma , I. Ionut , O.Oniga. Synthesis of new N-substituted 5-arylidene-2,4-thiazolidinediones as anti-inflammatory and antimicrobial agents. *Arch Pharm* (Weinheim), 346, 2013, 481-90.
13. Bhattarai BR, Kafle B, Hwang JS, Ham SW, Lee KH, Park H, Han IO and ChoH. Novel thiazolidinedione derivatives with anti-obesity effects, dualaction as PTP1B inhibitors and PPAR-gamma activators. *Bioorg Med Chem Lett*, 20, 2010, 6758-63.
14. Lima MC, Costa DL, Goes AJ, Galdino SL, Pitta IR and Luu-Duc C.[Synthesis and antimicrobial activity of chlorobenzylbenzylideneimidazolidinedione derivatives and substituted thiazolidinediones]. *Pharmazie*, 1992, 47, 182-4.
15. Maccari R, Ciurleo R, Giglio M, Cappiello M, Moschini R, Corso AD, MuraU and Ottana R. Identification of new non-carboxylic acid containing inhibitors of aldose reductase. *BioorgMed Chem*, 18, 2010, 4049-55.

16. R. Maccari, R. Ciurleo , M. Giglio , M. Cappiello , R. Moschini , A. D. Corso , U. Mura R. Ottana, Identification of new non-carboxylic acid containing inhibitors of aldose reductase. *Bioorg Med Chem*, 18, 2010, 4049-55.
17. Andreani A, Rambaldi M, Locatelli A, Leoni R, Bossa M, ChiericozziI, Galatulas G and Salvatore A. Synthesis of lactams with potentialcardiotonic activity. *Eur J Med Chem*, 28, 1993, 825-9.
18. El-Feky SA. Synthesis and anticonvulsant properties of some novelquinazolinonethiazolidine and 4-thiazolidone derivatives. *Pharmazie,* 48, 1993, 894-6.
19. Way JM, Harrington WW, Brown KK, Gottschalk WK, Sundseth SS, Mansfield TA, Ramachandran RK, Willson TM, Kliewer SA. *Endocrinology,* 142, 2001, 1269-1277.
20. Pattan SR, Reddy VVK, Pawar PD, Dighe NS, Bhawar SB. Synthesis and evaluation of some substituted phenyl thiazoles and derivatives for antitubercular activities. *Indian Drugs,* 2007, 44(4).
21. Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogel's text book of practical organic chemistry, 5th ed.2005, pp.1260, Pearson Education Pvt Ltd. Singapore.
22. Chattergee TK. Hand book on laboratory Mice and Rats. 1st Edn, 1993, 71.
23. Tatiana Schoenfelder, Thayse Marcon Cirimbelli, Vanilde Citadini-Zanette. Acute effect of Trema micrantha (Ulmaceae) on serum glucose levels in normal and diabetic rats. *Journal of Ethnopharmacology*, 2006, 107, 456-459.