Journal of Saudi Chemical Society (2016) **20**, S196–S201

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Design and synthesis of novel thiazolidine-2,4-diones as hypoglycemic agents

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Received 30 August 2012; accepted 2 October 2012
Available online 7 November 2012

KEYWORDS

2D QSAR;
MLR;
Hypoglycemic activity;
Thiazolidinediones;
Diabetes;
Sucrose loaded model (SLM)

Abstract Thiazolidinediones are well known for causing reduction in blood glucose levels. A number of thiazolidinediones have been approved for clinical use in diabetes. Present research work is based on the synthesis of thiazolidinedione derivatives that were designed previously using 2D QSAR for antidiabetic activity. Thiazolidine-2,4-diones derivatives having carboxylic ester appendages at *N*-3 and 5-substituted benzylidene were studied and the syntheses of only four derivatives were performed that were predicted to have promising antidiabetic activities. Their effect on hypoglycemic activity was performed using a sucrose loaded model. Compounds **5a** and **5b** were found to have prominent activities at 100 mg/kg by oral route administration.

1. Introduction

According to the American Diabetes Association, the direct costs in 2007, of treating the estimated 23.6 million type 2 diabetes mellitus (T2DM) patients and the estimated 57 million pre-diabetic patients in the United States was approximately $116 billion with an additional $58 billion dollars in indirect costs (Hanrahan et al., 2012). 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 II DM) are characterized by tissue resistance to the effects of insulin secreted by pancreatic β cells (Rang et al., 2008).

From the pioneering discovery of ciglitazone (Defronzo, 2000), a new class of thiazolidinedione based compounds have been developed to treat diabetic patients that can reverse the insulin resistance in non-insulin dependent diabetes mellitus (NIDDM). Among various substituted benzyl-2,4-thiazolidinedione compounds, troglitazone (Yoshioka et al., 1989), pioglitazone (Momose et al., 1991), and rosiglitazone (Cantello et al., 1994), are potentially antidiabetic compounds that have been clinically examined. The first marketed thiazolidinedione, troglitazone (Krook et al., 2000), was withdrawn because of the increased risk of hepatotoxicity (Scheen, 2001). The potent side effect i.e., hepatotoxicity limits the use of thiazolidine derivatives as safe drug candidates.

Many drugs have been approved from this class for the treatment of diabetes like Rosiglitazone, Pioglitazone, Ciglitazone and many more. Though the marketed drugs show additive effect with other antihyperglycemic agents, they are also prone to show toxicity. For example, Rosiglitazone shows hepatotoxicity (Kahn et al., 2006). Hence there is a need to find more potent and orally safe thiazolidine 2,4-diones with less toxicity.

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Peer review under responsibility of King Saud University.

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http://dx.doi.org/10.1016/j.jscs.2012.10.010

In the present research work, we have performed the synthesis of thiazolidinedione derivatives that were designed previously using 2D QSAR for antidiabetic activity. Thiazolidine-2,4-diones derivatives having carboxylic ester appendages at *N*-3 and 5-substituted benzylidene were designed and the syntheses of only the best four derivatives were performed that were predicted to have promising antidiabetic activities.

2. Drug design

We have performed 2D QSAR on the series reported by Bhat et al. (2004) using software VLife MDS 3.5 in our laboratory. It gives the output as an equation containing descriptors such as alignment independent parameters and as an indicative of physicochemical properties required to show biological activity i.e., antihyperglycemic activity. The correlation between independent variables (descriptors) and dependent variables (pharmacological activity) was established (Puzyn et al., 2010). The output is in the form of regression equation showing descriptors are in the form of positive and negative contributions by using the equation as an output from the QSAR study, we have designed the following derivatives. And further their syntheses has been done followed by hypoglycemic activity using SLM model in rats.

3. Experimental

Derivatives under study as depicted in Fig. 1, shows R1 varied as either a 5 and 6 membered ring while R2 varied from H, methyl, or ethyl groups and the derivatives to be synthesized are based upon substitution on the benzene moiety next to thiazolidinedione (TZD) ring.

Hypoglycemic study has been done using the animal model already reported in the literature. The animal model being used is Sucrose Loaded Model (Godkar and Godkar, 2003), though other models are available (Chaturvedi et al., 2008; Sharma et al., 2010; Ram et al., 2003), blood glucose estimation has been done using a glucometer (Pattan et al., 2009).

4. Chemistry

The synthetic protocol of thiazolidinedione derivatives presented here is shown in Scheme (Fig. 2). Thiazolidin-2,4-dione **1** (Prashantha et al., 2006) on reacting with benzaldehyde derivative **2** undergoes Knovengeal condensation giving benzylidene thiazolidinedione **3a**–**3b** (Bruno et al., 2002) which upon *N*-Alkylation with ethyl bromoacetate furnished alkyl 2,4-dioxothiazolidin-3-ethyl ester **4a**–**4b** (Goel et al., 2004), ethyl ester is being converted to acid derivative **5a**–**5d** using conc. HCl and glacial acetic acid.

Melting points were determined by open capillary tubes using VEEGO VMP-D Digital melting point apparatus and

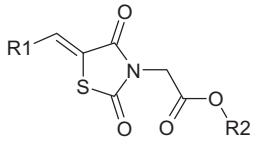


Figure 1 Thiazolidinediones.

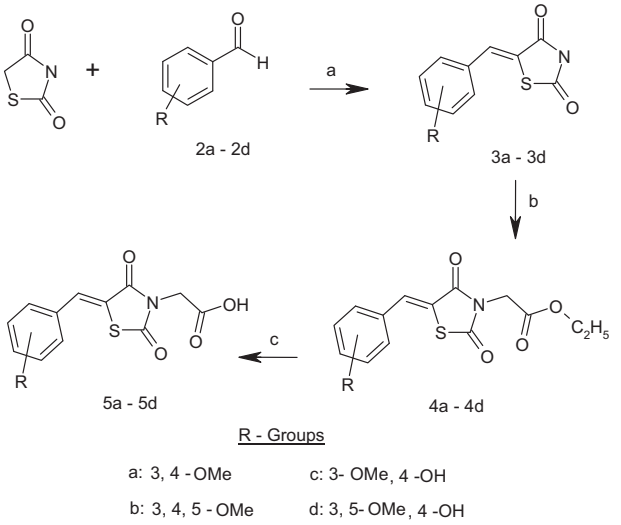


Figure 2 Scheme: Reagents: (a) Piperidine, Ethanol, CH_3-COOH; (b) NaH, ethyl bromoacetate, Dry DMF; (c) Conc. HCl, Glacial acetic acid.

are uncorrected. FTIR spectra of the powdered compounds were recorded using KBr on a JASCO FTIR 4100 series and are reported in cm^{-1} and ^1H NMR spectra were recorded on a Varian Mercury YH300 (300 MHz FT NMR) spectrophotometer using TMS as an internal reference (Chemical shift represented in dppm). Purity of the compounds was checked on TLC plates using silica gel G as stationary phase and iodine vapors as the visualizing agent.

*4.1. General procedure for 5-(substituted benzylidene)-2,4-thiazolidinediones, **3a**–**3d** (Bruno et al., 2002)*

A mixture of 2,4-thiazolidinedione **1** (2.4 g, 20 mmol), benzaldehyde derivative **2** (20 mmol), piperidine (1.4 g, 16 mmol) and ethanol (150 ml) was refluxed for 16–24 h. The reaction mixture was poured into H_2O and acidified with AcOH to give **3a**–**3d** as solids, which were recrystallized from methanol. Completion of reaction has been confirmed using TLC using Benzene:Ethyl acetate as solvent system (3:7).

*4.2. General procedure for [5-(substituted benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid ethyl ester, **4a**–**4b** (Bruno et al., 2002)*

Sodium hydride (0.576 g, 24 mmol) was added portion wise to a solution of 5-benzylidene-2,4-thiazolidinedione **3** (20 mmol) in dry DMF and the mixture was stirred at 80°C for 1.5 h. The mixture was cooled to room temperature and a solution of ethyl bromoacetate (3.7 g, 24 mmol) in dry DMF was added dropwise. After being stirred at 80°C for 15–20 h, the reaction mixture was poured into H_2O and the solid product filtered and recrystallized from EtOH/H_2O.

*4.3. General procedure for [5-(substituted benzylidene)-2,4-dioxo-thiazolidin-3-yl]-acetic acid **5a**–**5d** (Bruno et al., 2002)*

A mixture of ethyl ester (10 mmol), glacial AcOH (40 ml) and HCl 12 N (10 ml) was refluxed for 2 h. After evaporation in

Table 1 Elemental analysis (C, H, N).

Compound no.	M.P. °C	% Yield	Theoretical value (%)			Observed value (%)		
			C	H	N	C	H	N
5a	218–220	60	52	4.02	4.33	54.9	5.26	4.70
5b	189–191	65	50.99	4.24	3.96	51.7	5.07	4.02
5c	181–183	57	50.48	3.55	4.53	50.9	4.21	5.12
5d	173–175	52	49.55	3.83	4.12	51.0	4.15	4.78

vacuo, the residue was refluxed again with AcOH (40 ml) and HCl (10 ml) for 2 h. After evaporation to dryness in vacuo, the crude solid was washed with H_2O and recrystallized from EtOH providing pure carboxylic acid.

For the above steps the yield obtained for each of the selected substituted thiazolidinediones and their physicochemical properties, and elemental analyses for C, H, N are shown in Table 1. Following are the spectral data obtained by FTIR and ^{1}H NMR studies.

*4.4. Synthesis of 5-(3,4-dimethoxy)benzylidine-2,4-thiazolidine dione, (**5a**)*

Benzaldehyde derivative used is Veratraldehyde (3,4-dimethoxybenzaldehyde) keeping the other reagents and lab conditions the same. Brownish solid. IR (KBr) ν cm^{-1} (C–O) 1301, (C═O) 1721, (Ar C–H) 3072, (OH) 3239, (C═C) 1581. ^{1}H NMR (DMSO) δ 1.2, (s, CH_2), 10.8 (s, COOH), 4.45 (s, C═C–H), 3.91 (s, O–CH_3), 6.8–7.5 (m, Ar–H).

*4.5. Synthesis of 5-(3,4,5-trimethoxy)benzylidine-2,4-thiazolidine dione (**5b**)*

Benzaldehyde derivative used is 3,4,5-Trimethoxybenzaldehyde while other reagents and other conditions have been kept the same. Faint brownish powder. IR (KBr) ν cm^{-1} (C–O) 1301, (C═O) 1721, (Ar C–H) 3072, (OH) 3239, (C═C) 1581. 1H NMR (DMSO) δ 1.2, (s, CH_2), 10.8 (s, COOH), 4.48 (s, C═C–H), 4.1 (s, O-CH_3), 6.85–7.5 (m, Ar–H).

*4.6. Synthesis of 5-(3-methoxy-4-hydroxy)benzylidine-2,4-thiazolidine dione (**5c**)*

Benzaldehyde derivative used is Vanillin (3-methoxy-4-hydroxy benzaldehyde) while other reagents and conditions have been kept the same. Faint brownish powder. IR (KBr) ν cm^{-1} (C–O) 1234, (C═O) 1737, (Ar C–H) 3012, (OH) 3544, (C═C) 1600. ^{1}H NMR (DMSO) δ 1.2, (s, CH_2), 10.8 (s, COOH), 3.95 (s, O–CH_3), 4.5 (s, C═C–H), 6.95–7.5 (m, Ar C–H), 1.6 (Ar–OH).

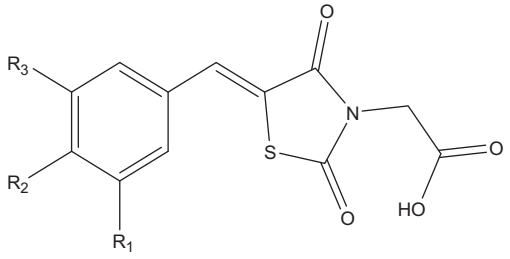
*4.7. Synthesis of 5-(3,5-dimethoxy-4-hydroxy)benzylidine-2,4-thiazolidine dione (**5d**)*

The derivative used is syringaldehyde (3,5-dimethoxy-4-hydroxy benzaldehyde) while other reagents and other conditions have been kept the same. Very dark brown powder. IR (KBr) ν cm^{-1} (C–O) 1249, (C═O) 1731, (Ar C–H) 3055, (OH) 3619, (C═C) 1687. 1H NMR (DMSO) δ 1.2, (s, CH_2), 10.4 (s, COOH), 3.95 (s, O–CH_3), 4.5 (s, C═C–H), 6.95–7.5 (m, Ar C–H), 1.6 (Ar–OH).

5. Biology

5.1. Sucrose loaded model (SLM) (Godkar and Godkar, 2003)

Wistar rats weighing in the range 250–300 g were obtained from National center for cell science (NCCS), Pune, India. In this study a group of six male Wistar rats were used per dose per compound. Animals were housed in standard cages, under standard ambient conditions, temperature (25 ± 2 °C), and relative humidity of 50 ± 5%. A 12:12 h light: dark cycle was maintained. All the animals were allowed to have free access to water and standard palletized laboratory. The blood glucose of each animal was checked after 16 h starvation using glucose strips and glucometer. Animals showing blood glucose between 135 and 150 mg/dl were selected as suitable for the test. Dose given is as reported in the literature. Rats of the experimental group were administered in the form of suspension of the desired compound orally made in 1.0% gum acacia for a dose of 100 mg/kg-body weight. Animals of the control



Compound Code	R_1	R_2	R_3
5a	-OCH_3	-OCH_3	H
5b	-OCH_3	-OCH_3	-OCH_3
5c	-OCH_3	-OH	H
5d	-OCH_3	-OH	-OCH_3

Figure 3 The designed thiazolidinedione analogs using 2D QSAR.

group were given an equal amount of 1.0% gum acacia. A sucrose load of 2.0 g/kg was given to each animal orally initially. Thirty minutes later to sucrose administration, the test compound was administered orally. After the test compounds are administered, blood glucose profile of each rat was determined at 30, 60, 90, and 120 min by using glucose strips and the glucometer. Food but not water was withheld from the cages during the course of experimentation. Pioglitazone has been used as the reference standard during the course of experimentation. All the experimental procedures and protocols used in these studies were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of College, Pune, constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India. Animals were not sacrificed during the course of experimentation. Percentage hypoglycemic activity has been determined by AUC method.

6. Results and discussion

As per the 2D QSAR studies performed for the thiazolidinedione series in our lab, the following descriptors were used in the design.

The term **T_2_T_6** contributes negatively toward activity, which signifies the count of any double bonded atom separated from any atom by a six-bond distance. While **T_T_N_5** also shows a negative contribution toward biological activity, which signifies the count of any atom (single, double or triple bonded) separated from any nitrogen atom (single or double bonded) by a 5-bond distance. Next descriptor we obtained is the **SssCH2 count**, which contributes negatively toward

Table 2 Blood glucose levels in experimental animals (mg/dl).

Compound no.	Time (min)				
	0	30	60	90	120
DMSO	145	156	150	147	141
Pioglitazone	139	105	110	112	115
5a	141	112	117	118	112
5b	147	110	112	107	104
5c	133	117	115	119	123
5d	136	114	119	121	127

Table 3 Decrease in blood glucose levels by AUC method.

Compound no.	Time (min)				% Reduction in blood glucose level
	30	60	90	120	
DMSO	+11	+05	+02	−04	+3.17
Pioglitazone	−34	−39	−29	−26	−23.07
5a	−29	−25	−24	−27	−21.71
5b	−37	−35	−28	−24	−22.84
5c	−16	−18	−14	−10	−10.3
5d	−22	−17	−15	−09	−10.51

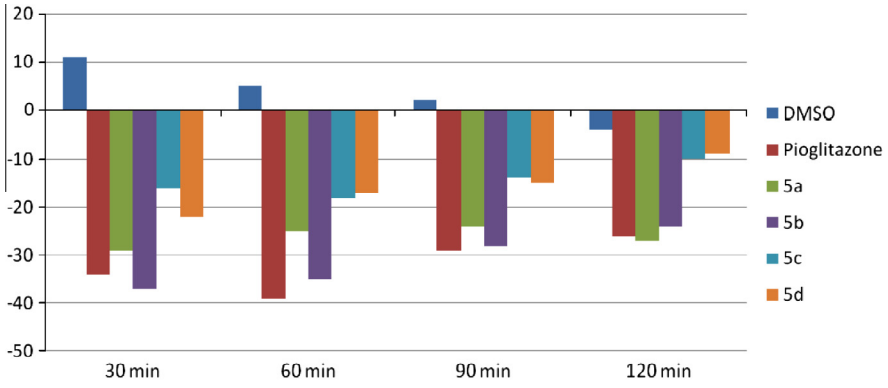


Figure 4 AUC's of decrease in blood glucose level for DMSO (control), Pioglitazone, **5a**–**d**.

antihyperglycemic activity; it signifies the total number of $-CH_2$ group connected with two single bonds. **T_T_O_3** is the next negatively contributing descriptor which determines the count of any atom (single, double or triple bonded) separated from any oxygen atom (single or double bonded) by a three-bond distance. In 2D QSAR equation, a positively contributing descriptor called the **H Count** indicates the number of H atoms in a molecule. The following molecules were designed as given in Fig. 3.

The design includes strategies such as the selection of substituents that will have as the maximum part, hydrogen. Functional groups where maximum hydrogen occurs are found as alkyl and not aryl groups. Tert butyl and secondary butyl, would be more preferred over *n*-butyl as primary selection criteria. The virtual molecules were predicted on the basis of 2D QSAR equation generated. It was required that oxygen should be at a distance of one or two or larger than three, but not a three bond distance. In such stringent criteria the methoxy group would be ideal for substitution. Further negative impact of the $SssCH_2$ count suggests that CH_2 groups should not be preferred. Thus designed analogs are the composition of the methoxy group. Replacement of the methoxy group to the hydroxyl group has been made to find the optimal position of the methoxy group. The results obtained from the biological study have been given in following Tables 2 and 3.

It has been seen that Pioglitazone showed a decrease in BGL in 30 min. while **5a** and **5b** shows a sudden decrease in BGL within a span of 30 min, and then a constant decrease appeared. While **5c** and **5d** showed a decrease in first 30 min, but after that they fail to show a decrease in the blood glucose level (BGL) and a further increase in BGL has been observed.

Fig. 4 shows a decrease in blood glucose level by the AUC method w.r.t. a time interval of 30 min. On the *X* axis, the responses for 30, 60, 90, 120 min are shown for DMSO (control), Pioglitazone (standard), and the synthesized compounds (**5a**–**5d**). From the AUC graph, it can be observed that **5a** and **5b** showed a maximum reduction and consistent reduction in blood glucose level for 120 min, while **5c** and **5d** shows a poor response of reduction in blood glucose levels.

7. Conclusion

By using 2D QSAR, the physicochemical properties required for hypoglycemic activity have been used to synthesize new derivatives. The hypoglycemic activities of 5-substituted benzylidene thiazolidine-2,4-dione-3-acetic acids were evaluated by the SLM model. The dimethoxy and trimethoxy derivatives have shown nearly equal hypoglycemic activities comparable with the standard used Pioglitazone. But when one $-OCH_3$ group of each of the derivatives has been replaced by –OH group, there is decrease in hypoglycemic activity.

Acknowledgement

The authors are very thankful to the AICTE for providing economical support for the research work. Also many thanks are given to Dr. K.G. Bothara (Principal, SIOP, Pune) for making the facilities available in the institute's laboratory. Authors are also sincerely thankful to the VLife Pvt. Ltd. for providing the demo version required for carrying out the present research work.

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