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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and evaluation of the hypoglycemic and hypolipidemic activity of novel 5-benzylidene-2,4-thiazolidinedione analogs in a type-2 diabetes model

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Abstract This article reports synthesis and evaluation of two novel thiazolidinedione ring containing molecules namely (*Z*)-5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)-phenoxy)acetyl)-2-hydroxybenzamide (**4**) and (*Z*)-2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-*N*-(5-nitrothiazol-2-yl)acetamide (**7**). The new chemical entities were tested for hypoglycemic activity and for their total cholesterol (CHL) and triglyceride (TG) lowering effect in high-fat diet (HFD) fed Sprague–Dawley rats. The synthesized molecules showed significant reduction in blood glucose, CHL, and TG levels after 14 days of treatment.

Keywords Type-2 diabetes · 5-Benzylidene-2,4-thiazolidinedione · Knoevenagel condensation · Hypoglycemic activity · Streptozotocin

Introduction

Diabetes mellitus is a group of syndromes characterized by hyperglycemia. The World Health Organization (WHO) has designated diabetes mellitus as an epidemic, although it is a non-infectious disease. Nearly 2.3% of the world's population is estimated to be suffering from this disease, with an increasing trend of 4–5% every year. (Lohray and Lohray, 2007) Clinically, patients can be classified as having either type 1 (insulin-dependent diabetes mellitus or IDDM) or type 2 (non-insulin-dependent diabetes mellitus or NIDDM). The early stage of type-2 diabetes can be managed by diet and exercise. However, in addition to this insulin or oral hypoglycemic agents (OHAs), either alone or in combination are needed for good control over blood glucose. Clinically, insulin and its analogs, sulfonylureas, biguanides, and TZD class of drugs are widely used. Among these drugs, TZDs were found to be superior as they avoid hypoglycemia and act as insulin sensitizers (Skyler, 2004).

In the late 1990s, the TZD class of drugs was developed, of which troglitazone was the first candidate to be marketed. However, due to hepatotoxic events it was then voluntarily withdrawn (Williams and Lemke, 2005). The search was further continued and resulted in discovery of two molecules namely rosiglitazone and pioglitazone. These two are potent analogs giving optimum plasma glucose lowering profile. Both the drugs act as agonists upon binding to PPARγ which preferentially bind to DNA, activating transcription of a wide variety of metabolic regulators. These regulators increase expression of a number of genes involved in regulation of glucose and lipid metabolism (Williams and Lemke, 2005).

Food Drug and Administration has ordered new safety labels for pioglitazone and rosiglitazone (FDA Safety alerts for drugs, 2007). This is because recent papers have shown serious toxicity profile for these drugs, particularly for rosiglitazone (Scheen, 2001). Moreover, some papers claim that rosiglitazone is associated with hepatic failure (Forman *et al*., 2000). It has also been proven that rosiglitazone is associated with genotoxicity in rats (Bedir *et al*., 2006), data indicating that the rosiglitazone is able to induce primary DNA damage in rats, with greater damage being

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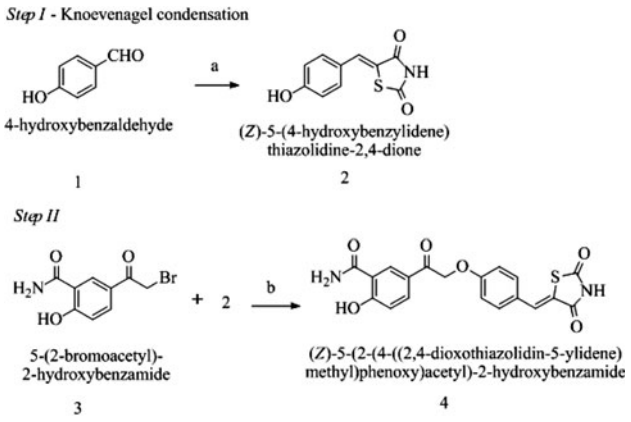
detected in liver cells than lymphocytes. The reports show that these drugs are associated with congestive heart failure and pulmonary edema (Kenned, 2003).

The mechanism for toxicity profile of these drugs is still unclear. From previous reports, we can infer that molecular modifications, apart from pharmacophore TZD, are responsible for its toxicity (Williams and Lemke, 2005). Thus, there is much more scope for development in this area. Therefore, in the present work, we have designed two novel molecules by modifying the non-pharmacophoric elements.

Materials and methods

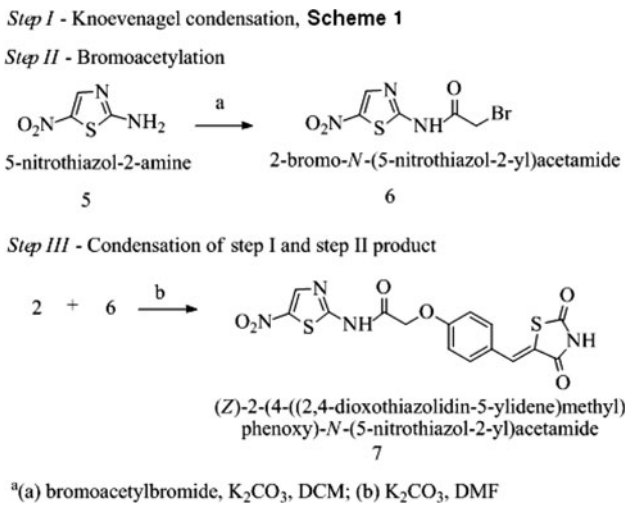
Chemistry

Antidiabetic TZDs are generally prepared by Knoevenagel condensation, in which aryl aldehydes are refluxed with TZD in the presence of bases like piperidinium benzoate (Lohray *et al*., 1998). As an alternative and more convenient route, we first synthesized **2** as a common intermediate. Compound **4**, having carbonyl carbon in the form of ketone in the linker chain, was synthesized by condensing **3** and Knoevenagel product **2** at room temperature (Scheme 1) (Reddy *et al*., 1999). For compound **7**, the intermediate **6** was obtained by a base-mediated bromoacetylation of 2-nitrothiazole. This bromoacetylated product was further condensed with **2** (Scheme 2) (Sengpracha, 2005).



[a](a) 2,4-TZD, piperidinium benzoate, toluene, reflux; (b) K_2CO_3, DMF

Scheme 1



[a](a) bromoacetylbromide, K_2CO_3, DCM; (b) K_2CO_3, DMF

Scheme 2

Biological evaluation

Materials

Streptozotocin was purchased from Sigma-Aldrich, USA. Pioglitazone hydrochloride was obtained from Cipla Ltd., India as a gift sample. The animal feed ingredients were of veterinary grade.

Animals

Male Sprague–Dawley rats with an average body weight of 190 ± 10 g were selected for the study. Animals were housed in polypropylene cages at an ambient temperature of 25 ± 2°C and 45–55% relative humidity with standard 12-h light and dark cycle. They had free access to feed and water. Animals were examined properly for infection and metabolic disorders. The guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Govt. of India were followed and prior permission was sought from the institutional animal ethics committee for conducting the study.

Experimental Design

Sprague–Dawley rats were randomly divided into seven groups with six animals each. Group 1 served as a normal control and received vehicle 1% Na-CMC (2 ml kg^{-1}, p.o.). Groups 2 and 3 served as drug control. Groups 4 and 5 comprised diabetic rats to which compounds **4** and **7** were administered in dose of 20 mg/kg/day, respectively, for 14 days. Group 6 served as standard and received pioglitazone hydrochloride, equivalent to 10 mg/kg/day of piogliatazone for 14 days.

Development of HFD-fed and STZ-treated type-2 diabetic rats

All groups were given HFD for a period of 2 weeks (Shrinivasan *et al*., 2005). Composition of this diet was 58% fat, 25% protein, and 17% carbohydrate as percentage of total Kcal.

Collection of blood and analytical methods

For blood glucose estimations, rats were given mild ether anesthesia followed by collection of blood from the retro orbital plexus. Blood was collected in sodium fluoride anticoagulant containing vials and glucose was analyzed by glucose oxidase method. For triglycerides (TG) and cholesterol (CHL) analysis, blood was collected in plain tubes to obtain serum and estimation was carried out using standard biochemistry kits.

Biological activity

We carried out acute toxicity studies for compounds **4** and **7** before testing hypoglycemic activity of both the compounds. We tried different doses upto 500 mg/kg. Hypoglycemic and hypolipidemic activities were carried out using a combination of high-fat diet (HFD) and low dose of STZ-treated male Sprague–Dawley rats. The animals were fed HFD for a period of 2 weeks. After 2 weeks of dietary manipulation, rats were injected intraperitoneally (i.p.) with low dose of STZ (35 mg/kg), while respective control rats were given vehicle 1% Na-CMC (2 ml/kg, p.o.). Blood glucose (BG) was estimated just before study, 1 week after STZ injection and at the end of 14 days treatment. Rats with non-fasting plasma glucose level more than 250 mg dl^{-1} were considered diabetic and 42 rats were selected for further pharmacological studies. For hypolipidemic activity, CHL and TG estimations were carried out prior to study, after 2 weeks of HFD and at the end of drug treatment.

Diabetic rats were randomly divided into four groups, i.e., from group 4 to 7. The diabetic rats were either treated with test compound (20 mg/kg once daily for 14 days) or with pioglitazone hydrochloride (equivalent to 10 mg/kg of pioglitazone once daily for 14 days).

Results

Design of novel molecules

Every molecule has a typical group or groups of atoms that interact with a receptor. This group of atoms which is responsible for interaction, through various bondings, is known as pharmacophore and plays a vital role in elucidating pharmacological response. Structural elements other than pharmacophore usually account for non-receptor events like pharmacokinetics, toxicity, etc.

Thus, in our work, we retained the pharmacophore (Sohda *et al*., 1982), i.e., TZD ring and made the changes in lipophilic group to develop new congeners with better efficacy and less toxicity. The general structure of the TZD class of molecules (Fig. 1) can be depicted as follows:

The present work includes modification at three stages

1. Novel lipophilic moiety in **A** part.
2. Introduction of carbonyl carbon in **B** part.
3. Unsaturation in **D** part.

Tanis *et al*. (1996) have synthesized the putative ketone metabolite of pioglitazone (Fig. 2) and have described its potential as a pioglitazone antihyperglycemic congener with somewhat greater potency and a better metabolic profile. Based on these findings, we designed compound **4**, which incorporates a carbonyl carbon as ketone in the linker chain.

We further extended our work and introduced carbonyl carbon as an amide linkage for compound **7** considering its simpler metabolic pathway.

It has been reported that both *p*-alkoxybenzyl and *p*-alkoxybenzylidene moieties were effective as linkers between benzene and TZD ring (Memose *et al*., 1991). We prepared benzylidene TZD analogues and evaluated them for biological activity.

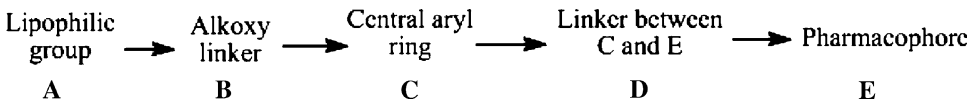


Fig. 1 Generalized structure of TZD class

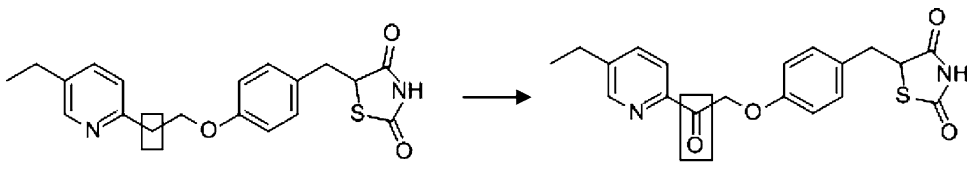


Fig. 2 Pioglitazone and its putative metabolite

Experimental section

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on Varian 300 MHz instrument using TMS as internal standard. Chemical shift values are reported in δ, ppm. Elementary analyses were performed on FLASH EA 1112 series (Thermo finnigan, Italy) CHNS analyzer. Mass spectra were recorded on Waters Quattro Premier XE Micromass in positive ion mode. All reactions as well as column chromatography were followed by TLC using Merck pre-coated silica gel 60 F_{254} plates and spots were visualized by observing in UV cabinet under short UV. IR spectra were recorded on FTIR-8400S instrument with KBr pellets and only the principal absorption levels (cm^{-1}) have been listed. All reagents were used as received unless otherwise stated.

Synthesis of the Knoevenagel product: 5-(4-hydroxybenzylidenethiazolidine-2,4-dione) (**2**)

A solution of *p*-hydroxy benzaldehyde (5 g, 40 mmol) and 2,4- TZD (4.8 g, 40 mmol) with catalytic quantity of piperidinium benzoate was refluxed in toluene with continuous removal of water using Dean–Stark apparatus for 4 h. The reaction mixture was cooled to 25°C and solid separated was collected by filtration. Yield: 93%; R_f: 0.70 (6:1, chloroform/ ethanol); IR (KBr, cm^{-1}): 1718 and 1683 (C=O stretching vibrations of cyclic imides), 1510 (NH bending), 1338, 1213 (C–O stretching); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.9 (d, 2H, J = 8.4 Hz, aromatic), 7.44 (d, 2H, J = 8.4 Hz, aromatic), 7.67 (s, 1H, benzylidene proton).

Synthesis of 2-bromo-*N*-(5-nitrothiazole-2-yl) acetamide (**6**)

5-Nitrothiazole-2-amine (3 g, 20 mmol) and anhydrous K_2CO_3 (4.85 g, 35 mmol) were taken in 20 ml of dichloromethane (DCM). Reaction mixture was cooled between 2 and 5°C and to this bromoacetyl bromide (2.7 ml, 30 mmol) in DCM (20 ml), was added dropwise. Reaction was stirred overnight at room temperature. Water was added to the reaction mixture and organic layer was separated. Organic layer was passed through anhydrous Na_2SO_4 and subsequently distilled out. Shiny yellow colored needle-shaped crystals were collected. Yield: 82%; R_f: 0.65 (20:1, chloroform/ ethanol); IR (KBr, cm^{-1}): 1687 (C=O stretching), 1350 (Aromatic C-NO_2 stretching), 497 (C-Br stretching); ^{1}H NMR ($CDCl_3$) δ (ppm): 4.4 (s, 2H, CH_2-Br), 8.36 (s, 1H, aromatic), 10.07 (bs, 1H, NH).

Synthesis of 5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetyl)-2-hydroxybenzamide (**4**)

A mixture of Knoevenagel product (**2**) and anhydrous K_2CO_3 (1.55 g, 11 mmol) in DMF (7 ml) was stirred for 30 min. 5-(2-Bromoacetyl)-2-hydroxybenzamide (**3**) (3.5 g, 13 mmol) was added to above mixture and reaction was stirred at room temperature for further 4 h. Water (50 ml) was added and mixture was stirred at room temperature for 1 h, extracted with ethyl acetate (3 × 20 ml). Combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give title compound. Yield: 84%; R_f: 0.45 (6:1, chloroform/ ethanol); IR (KBr, cm^{-1}): 3390 (OH stretching), 1737 and 1672 (C=O stretching vibrations of cyclic imides), 1211 (C–O stretching), 1093; ^{1}H NMR: (300 MHz, DMSO-d_6) δ (ppm): 5 (s, 2H, CO–CH_2–O), 6.32 (d, 1H, J = 9 Hz, aromatic), 6.94 (d, 2H, J = 8.7 Hz, aromatic), 7.54 (d, 2H, J = 8.7 Hz, aromatic), 7.6 (d, 1H, J = 8.7 Hz, aromatic), 7.88 (s, 1H, aromatic), 8.42 (s, 1H, benzylidene proton), 10.6 (bs, 1H, phenolic OH); ^{13}C NMR: (300 MHz, DMSO-d_6) δ (ppm): 172.8 (C=O), 167.4 (C=O), 165.7 (C=O), 160.2, 145.8, 136.7, 133.7, 132.7, 127.4, 123.9, 116.8, 116.5, 46.2; MS (ESI^+) *m/z* (rel. intensity): 407 (M + H, 100%); Anal. Calc. for $C_{15}H_{10}N_4O_6S_2$, %: C, 44.33; H, 2.48; N, 13.79. Found, %: C, 43.95; H, 2.42; N, 13.48.

Synthesis of 2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)-N-(5-nitrothiazol-2-yl)acetamide (**7**)

The title compound was prepared from Knoevenagel product (**2**) (1.7 g, 7 mmol), 2-bromo-*N*-(5-nitrothiazole-2-yl)acetamide (**6**) (2 g, 7 mmol), anhydrous K_2CO_3 (1.55 g, 11 mmol) in DMF (7 ml) by a procedure analogous to that described for the preparation of 5-(2-(4-((2,4-dioxothiazolidin-5-ylidene)methyl)phenoxy)acetyl)-2-hydroxybenzamide (**4**). Yield: 50%; R_f: 0.60 (4:1, chloroform/ ethanol); IR (KBr, cm^{-1}): 3382 (NH stretching), 1716 and 1664 (C=O stretching vibrations of cyclic imides), 1575; ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 4.71 (s, 2H, CO–CH_2–O), 6.94 (d, 2H, J = 8.7 Hz, aromatic), 7.54 (d, 2H, J = 8.4 Hz, aromatic), 7.90 (s, 1H, benzylidene proton), 8.66 (s, 1H, aromatic), 10.44 (s, 1H, NH of linker), 13.60 (bs, 1H, NH of TZD ring). ^{13}C NMR: (300 MHz, DMSO-d_6) δ (ppm): 188.2 (C=O), 170.4 (C=O), 169.6 (C=O), 167.3 (C=O), 165.6, 160.6, 134.2, 133.0, 131.8, 131.2, 127.0, 123.6, 122.5, 121.9, 119.6, 116.6, 116.2, 116.0, 47.2; MS (ESI^+) *m/z* (rel. intensity): 399 (M + H, 100%); Anal. Calc. for $C_{19}H_{13}N_2O_6S$, %: C, 57.28; H, 3.54; N, 7.03. Found, %: C, 56.97; H, 3.26; N, 7.12.

Statistics

The results were calculated with help of GraphPad InStat using one-way ANOVA and Dunetts' test and are expressed as mean ± SEM. The percent reduction was calculated using the equation (Lohray *et al.,* 2001): [1 − (TT/OT)/(TC/OC)] × 100, where TT is test day treated, OT is zero day treated, TC is test day control, and OC is zero day control.

Discussion

We have used HFD fed, low dose STZ model, as it perfectly mimics the insulin resistance in humans characterized by obesity, mild hyperglycemia, and hypercholesterolemia. Hypoglycemic activity for compounds **4** and **7**, carried out for 14 days in STZ-induced HFD fed rats, gave 64 and 56 % reduction in blood glucose when compared to vehicle control. It is pertinent to mention that an efficient control of TG and CHL levels in type-2 diabetic patients has shown beneficial effects in diabetes-related complications especially atherosclerosis and cardiovascular diseases. Thus, the drugs which control both TG and CHL would be more suitable candidates for further development for the treatment of type-2 diabetes (Lohray *et al*., 1999). In our study, both the compounds, **4** and **7**, were evaluated for its TG and CHL lowering activity. TG, CHL data were, however, not used in concluding results, since observed TG, CHL lowering effect of pioglitazone hydrochloride were not reported in clinical trials (Sauerberg *et al*., 2002).

Both the test compounds **4** and **7** gave significant blood glucose reduction. Thus, introduction of carbonyl carbon in the form of ketone and amide, in linker chain, may serve as a useful strategy in drug design in the area of antidiabetic TZDs. Both the compounds are expected to show a better metabolic profile due to ketone and amide functional groups, thus reducing the chances of toxicity. In our synthetic scheme, we made Knoevenagel product separately as a common intermediate and combined it with lipophilic group. The same strategy could be further extended to combinatorial synthesis, wherein addition of only one component, i.e., different lipophilic groups would be needed (Table 1, 2, 3, 4, 5).

Table 1 Composition of HFD

Ingredients	Diet (g/kg)
Powdered normal feed diet	365
Lard	310
Casein	250
Cholesterol	10
Vitamin and mineral mix	60
DL-Methionine	03
Yeast powder	01
Sodium chloride	01

Table 2 Body weight in grams—before and after HFD

	Normal rats	HFD rats
1–10	188.8 ± 3.18	214 ± 4.76
11–20	190.5 ± 3.37	228 ± 8.30
21–30	197 ± 3.59	232 ± 7.42
31–40	197.3 ± 4.72	232 ± 8.73
41–50	194.2 ± 4.11	230 ± 6.29

Table 3 Cholesterol levels mg/dl—before and after 2 weeks of HFD

	Normal rats	HFD rats
1–10	59.2 ± 3.77	183.4 ± 4.49
11–20	58.2 ± 3.82	187.7 ± 4.35
21–30	56.9 ± 2.915	178.1 ± 5.08
31–40	53.2 ± 2.95	183.8 ± 6.13
41–50	54.5 ± 3.17	180.9 ± 5.21

Table 4 Triglyceride levels mg/dl—after 2 weeks of HFD

	Normal rats	HFD rats
1–10	84 ± 3.30	157.6 ± 7.20
11–20	67.5 ± 4.32	152.8 ± 5.91
21–30	73.9 ± 5.74	173.1 ± 4.14
31–40	82.6 ± 3.04	150.6 ± 4.72
41–50	70.5 ± 4.01	162.8 ± 5.90

Conclusion

Two new chemical entities belonging to the series of benzylidene thiazolidinedione were synthesized and characterized. Molecules were then screened for antidiabetic and hypolipidemic activity in STZ-induced diabetic animal model. Compounds **4** and **7** showed 64 and 56% blood glucose lowering activity, respectively, relative to vehicle control group. They could serve as lead molecules for molecular modifications to get improved activity and toxicity profile.

Table 5 In vivo efficacy in HFD-fed male Sprague–Dawley rats after oral treatment for 14 days

Compound No.	BG[a] % max reduction	TG[b] % max reduction	CHL[c] % max reduction
4	64.43 ± 1.26[N.S.]	74.18 ± 4.64*	89.70 ± 0.77**
7	56.08 ± 2.04[N.S.]	78.11 ± 1.46**	92.46 ± 0.54**
Pioglitazone hydrochloride	51.57 ± 3.15**	78.38 ± 1.80*	86.83 ± 3.24**

Male Sprague–Dawley rats ($n = 6$) were treated once a day by oral gavage for 14 days. Compounds **4** and **7** were tested at dose of 20 mg/kg/day; pioglitazone hydrochloride at 10 mg/kg/day. "% max reduction" is the maximum achieved reduction relative to vehicle control group ± SEM

N.S. non significant

[a] Blood glucose after 14 days treatment

[b] Triglycerides after 14 days treatment

[c] Cholesterol after 14 days treatment

* $P < 0.05$, ** $P < 0.01$

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