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Short Communication

Synthesis and hypoglycemic activity of some substituted flavonyl thiazolidinedione derivatives—fifth communication: flavonyl benzyl substituted 2,4-thiazolidinediones☆

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Abstract

A new series of 3-benzyl(*p*-substituted benzyl)-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinediones (**8a**–**e**) were synthesized. These products were prepared by Knoevenagel reaction from 3′-flavone carboxaldehyde and 3-substituted 2,4-thiazolidinediones. In vitro insulinotropic activity was determined for compounds **6a**–**e**, **7a**–**e**, **8b** and **8c**.

Keywords: Flavonyl thiazolidinediones; Hypoglycemic activity; Synthesis

1. Introduction

Diabetes mellitus was classified into two groups, non-insulin dependent diabetes mellitus (NIDDM, type-2 diabetes) and insulin-dependent diabetes mellitus (IDDM, type-1 diabetes). NIDDM is a complex, chronic metabolic disorder mainly associated with three basic pathophysiologic abnormalities insulin resistance in target tissues, excessive hepatic glucose output and insulin resistance in skeletal muscle, liver and adipose tissue [1]. Insulin resistance and associated hyperinsulinaemia are being implicated increasingly in the development of other metabolic disorders such as obesity, dyslipidaemias and hypertension [2,3]. The primary therapy for NIDDM is caloric restriction and aerobic exercise. These regimes increase insulin sensitivity [4], but only a small percentage of patients adopt them with sufficient rigor to achieve a significant improvement in glycemic control. The pharmacological agents available for the treatment of type-2 diabetes have focused primarily on delaying gastrointestinal glucose absorption (α-glucosidase inhibitors), increasing insulin availability (sulfonylureas) or suppressing excessive hepatic glucose production (biguanides). Pharmacological intervention to enhance the biological activity of endogenous insulin (insulin sensitivity enhancers) represents an attractive and novel approach to the treatment of NIDDM. Since the pioneering discovery of ciglitazone by a group of scientists at Takeda [5], which normalizes the plasma glucose and effectively reduces insulin resistance by potentiating insulin action in genetically diabetic and/or obese animals [6] several new thiazolidine-2,4-diones have been developed. Pioglitazone [7,8], troglitazone (CS 045) [9,10], englitazone [11,12], rosiglitazone [13,14] and many others are in various stages of clinical development (Fig. 1).

2. Chemistry

In our previous papers, we reported the synthesis of some substituted flavonyl thiazolidinedione [15,16] and 3-benzyl(*p*-substituted benzyl)-5-(6- and 4′-flavonyl) thiazolidinedione derivatives (**6a**–**e**, **7a**–**e**) [17,18]. In

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the present work five additional compounds with similar structure 3-benzyl(p-substituted benzyl)-5-(3′-flavonyl)-thiazolidinediones **8a**–**e** (Scheme 1) were synthesized using the same method and antihyperglycemic activities of all compounds were investigated.

3. Experimental

Melting points were determined with a Büchi SMP-20 melting point apparatus (Büchi Laboratoriumstechnik, Flawil, Switzerland) and are uncorrected. IR spectra were recorded on a JASCO FT/IR 420 spectrophotometer (JASCO Corp., Tokyo, Japan) as potassium bromide discs. ^{1}H NMR spectra were measured with a Bruker DPX-400, 400 MHz instrument (Rheinstetten, Karlsruhe, Germany) using tetramethylsilane (TMS) internal standard and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. EI MS were obtained with a VG Platform II, Micromass spectrometer (Manchester, UK) with ionization energy maintained at 70 eV. Elemental analyses (C, H, N) were determined on a Leco CHNS 932 instrument (St. Joseph, USA), and were within ±0.4% of the theoretical values. Instrumental analysis were performed at Scientific and Technical Research Council of Turkey, Instrumental Analysis Center (Ankara, Turkey).The chemical reagents used in synthesis were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, MI, USA).

Flavone-3′-carboxaldehyde [19], 2,4-thiazolidinedione [20], 3-benzyl-2,4-thiazolidinediones [21], 3-p-chlorobenzyl-2,4-thiazolidinediones [22], 3-p-bromobenzyl-2,4-thiazolidinediones [23], 3-p-fluorobenzyl-2,4-thiazolidinediones [20], 3-p-nitrobenzyl-2,4-thiazolidinediones [24] were prepared according to the literature.

3.1. General synthesis of compounds 8a–e

A mixture of flavone-3′-carboxaldehyde (**5**) (0.01 mol) and 3-benzyl(p-substituted benzyl) 2,4-thiazolidinedione (**2a**–**e**) (0.01 mol) was heated at 140–150 °C in the presence of 1 ml glacial acetic acid and sodium acetate (0.01 mol) for 12 h. The crude product was crystallized from DMF.

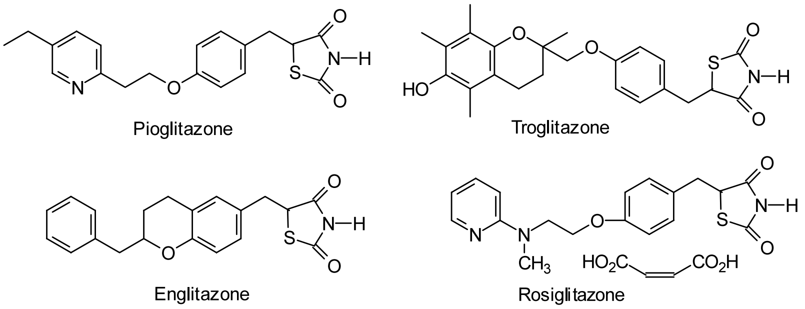
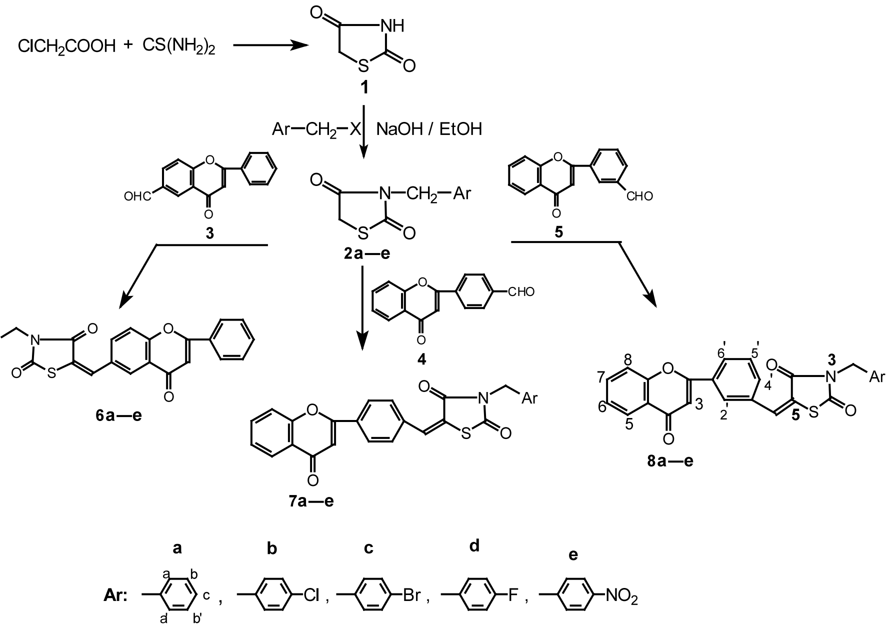


Fig. 1. Structures of several insulin-sensitizing thiazolidinediones.



Scheme 1. Synthesis of some substituted flavonyl thiazolidinedione derivatives.

3.1.1. 3-Benzyl-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**8a**)

Yield: 65.0%, m.p: 250 °C. IR (KBr) cm^{-1}: 1636 (C=O, γ-pyrone), 1680, 1740 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): $\delta = 4.8$ (s, 2H, CH_2), 6.9 (s, 1H, 3-H), 7.2–7.3 (m, 5H, a,a′,b,b′,c), 7.4 (d.t.d, 1H, 6-H), 7.6–7.8 (m, 4H, 5′,6′,7,8-H), 7.9–8.1 (m, 3H, =CH, 4′,5-H), 8.2 (s, 1H, 2′-H). EI MS [*m/z* (rel. int. %)]:439 (100) [M^+], 279 (36.7), 278 (48.5), 221 (7.3), 158 (13.6), 121 (4.3), 91 (24.1). $C_{26}H_{17}NO_4S$ (439).

3.1.2. 3-(4-Chlorobenzyl)-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**8b**)

Yield: 72.4%, m.p: 257 °C. IR (KBr) cm^{-1}: 1645 (C=O, γ-pyrone), 1676, 1737 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): $\delta = 4.9$ (s, 2H, CH_2), 7.1 (s, 1H, 3-H), 7.4 (d, 2H, $J_{a,b} = J_{a',b'} = 8.27$ Hz, a,a′-H), 7.4 (d, 2H, $J_{b,a} = J_{b',a'} = 8.39$ Hz, b,b′-H), 7.5 (d.t.d, 1H, 6-H), 7.8–7.9 (m, 4H, 5′,6′,7,8-H), 8.0 (d, 1H, $J_{5,6} = 7.67$ Hz, 5-H), 8.1 (s, 1H, =CH), 8.2 (d, 1H, $J_{4',5'} = 6.86$ Hz, 4′-H), 8.4 (s, 1H, 2′-H). EI MS [*m/z* (rel. int. %)]: 278 (2.7), 221 (1.5), 168 (5.4), 158 (10.8), 125 (43.1), 121 (8.7), 92 (28.4), 73 (100). $C_{26}H_{16}ClNO_4S$ (473.5).

3.1.3. 3-(4-Bromobenzyl)-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**8c**)

Yield: 63.6%, m.p: 262 °C. IR (KBr) cm^{-1}: 1645 (C=O, γ-pyrone), 1676, 1736 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): $\delta = 4.9$ (s, 2H, CH_2), 7.1 (s, 1H, 3-H), 7.3 (d, 2H, $J_{a,b} = J_{a',b'} = 8.27$ Hz, a,a′-H), 7.5–7.6 (m, 3H, 6,b,b′-H), 7.8–7.9 (m, 4H, 7,8,5′,6′-H), 8.1 (d, 1H, $J_{5,6} = 6.55$ Hz, 5-H), 8.1 (s, 1H, =CH), 8.2 (d, 1H, $J_{4',5'} = 7.70$ Hz, 4′-H), 8.4 (s, 1H, 2′-H). EI MS [*m/z* (rel. int. %)]: 278 (2.8), 221 (1.6), 171 (39.1), 169 (40.6), 158 (32.2), 125 (10.2), 121 (31.9), 114 (21.5), 92 (75.1), 89 (100). $C_{26}H_{16}BrNO_4S$ (519).

3.1.4. 3-(4-Fluorobenzyl)-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**8d**)

Yield: 65.6%, m.p: 245 °C. IR (KBr) cm^{-1}: 1644 (C=O, γ-pyrone), 1675, 1738 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): $\delta = 4.9$ (s, 2H, CH_2), 7.1 (s, 1H, 3-H), 7.2 (d, 2H, $J_{a,b} = J_{a',b'} = 8.99$ Hz, a,a′-H), 7.3–7.4 (m, 3H, 6,b,b′-H), 7.8–7.9 (m, 4H, 7,8,5′,6′-H), 8.0–8.1 (m, 2H, =CH, 5-H), 8.2 (d, 1H, $J_{4',5'} = 7.23$ Hz, 4′-H), 8.4 (s, 1H, 2′-H). EI MS [*m/z* (rel. int. %)]: 457 (100) [M^+], 279 (37.9), 278 (34.9), 221 (6.3), 158 (13.5), 121 (3.9), 109 (41.8). $C_{26}H_{16}FNO_4S$ (457).

3.1.5. 3-(4-Nitrobenzyl)-5-[3′-(4H-4-oxo-1-benzopyran-2-yl)-benzylidene]-2,4-thiazolidinedione (**8e**)

Yield: 55.5%, m.p: 280 °C. IR (KBr) cm^{-1}: 1644 (C=O, γ-pyrone), 1676, 1739 (C=O, thiazolidinedione ring). ^{1}H NMR (DMSO-d_6): $\delta = 5.0$ (s, 2H, CH_2), 7.1 (s, 1H, 3-H), 7.5 (d.t.d, 1H, 6-H), 7.6 (d, 2H, $J_{a,b} = J_{a',b'} = 8.69$ Hz, a,a′-H), 7.7–7.9 (m, 5H, 7,8,4′,5′,6′-H), 8.1 (d, 1H, $J_{5,6} = 7.64$ Hz, 5-H), 8.1 (s, 1H, =CH), 8.2 (d, 2H, $J_{b,a} = J_{b',a'} = 8.69$Hz, b,b′-H), 8.4 (s, 1H, 2′-H). EI MS [*m/z* (rel. int. %)]: 484 (10.1) [M^+], 438 (100), 278 (31.5), 221 (6.5), 158 (11.9), 121 (2.3), 114 (3.1), 109 (1.1), 92(2.6). $C_{26}H_{16}N_2O_6S$ (484).

3.2. Biological activity

3.2.1. Cell culture

INS-1 cells generously provided by Dr. C. Wollheim, Geneva, Switzerland, were grown in plastic culture bottles or micro-wells for 4–6 days (half confluence: $1–2 \times 10^6$ cells per ml) in RPMI medium supplemented with 10% (v/v) fetal calf serum, 100 U of penicillin per ml and 0.1 mg of streptomycin per ml. Prior to the experiment cells were washed two times and then incubated in Krebs–Ringer buffer containing 10 mmol l^{-1} HEPES and 0.5% bovine serum albumin (KRBH).

3.2.2. Insulin release

To measure insulin secretion, half-confluent cells in micro-wells were incubated for 90 min at 37 °C in the aforementioned KRBH buffer. Insulin released into the medium was assayed with a radioimmunoassay using rat insulin (Novo Nordisk, Bagsvaerd, Denmark) as a standard, (mono-^{125}I-Tyr A^{14})-porcine insulin as the labeled compound (Hoechst, Frankfurt, Germany) and anti-insulin antibodies from Linco (St. Louis, USA). Each compound had been checked for non-interference with the insulin radioimmunoassay. The data were corrected for the effects of solubilizing compounds (ethanol, DMSO).

4. Results and discussion

For the synthesis of the target compounds, the reaction sequences outlined in Scheme 1 were followed. Methylenyl group linker between the flavone and 2,4-thiazolidinedione derivatives were synthesized by Knoevenagel condensation of the 3′-flavone carboxaldehyde and 2,4-thiazolidinedione ring.

The structure of the compounds was confirmed on the basis of data IR, ^{1}H NMR spectral data, mass and elemental analysis. The IR spectra showed three bands in the 1740–1636 cm^{-1} region due to the vibrations of γ-pyrone and thiazolidinedione ring C=O groups. ^{1}H NMR spectra, 4H-benzopyran and flavone B rings protons were observed between 6.93 and 8.41 ppm. Benzylic protons were seen at 4.84–5.02 ppm as a singlet.

In ^{13}C NMR, the configuration could be determined by the vicinal coupling constant between ethylene proton and carbone of the carbonyl group (C-4) of thiazolidinediones. The value of this constant characterizes which isomer was formed. According to the

Table 1
Effects of various compounds on glucose-mediated insulin release from INS-1 cells

Comp.	İnsulin release (%)
Glucose (3.0 mM)	62.96±5.68 (11)
Glucose (5.6 mM)	100 (11)
Plus **6a** (1 μg ml^{-1})	90.85±1.02 (4)
Plus **6a** (10 μg ml^{-1})	47.91±0.91 (3)
Plus **6b** (1 μg ml^{-1})	85.31±5.73 (3)
Plus **6b** (10 μg ml^{-1})	66.66±4.98 (3)
Plus **6c** (1 μg ml^{-1})	98.75±10.09 (3)
Plus **6c** (10 μg ml^{-1})	95.06±22.68 (3)
Plus **6d** (1 μg ml^{-1})	101.3±9.73 (3)
Plus **6d** (10 μg ml^{-1})	105.10±6.59 (3)
Plus **6e** (1 μg ml^{-1})	99.68±8.99 (3)
Plus **6e** (10 μg ml^{-1})	117.70±9.61 (3)
Plus **7a** (1 μg ml^{-1})	100.70±2.41 (4)
Plus **7a** (10 μg ml^{-1})	29.79±1.04 (4)
Plus **7b** (1 μg ml^{-1})	110.80±3.64 (4)
Plus **7b** (10 μg ml^{-1})	110.40±3.72 (4)
Plus **7c** (1 μg ml^{-1})	105.10±20.30 (4)
Plus **7c** (10 μg ml^{-1})	140.3±9.64 (4)
Plus **7d** (1 μg ml^{-1})	66.60±10.50 (3)
Plus **7d** (10 μg ml^{-1})	114.20±10.73 (3)
Plus **7e** (1 μg ml^{-1})	117.90±9.42 (3)
Plus **7e** (10 μg ml^{-1})	85.98±17.32 (3)
Plus **8b** (1 μg ml^{-1})	93.12±4.78 (3)
Plus **8b** (10 μg ml^{-1})	88.21±5.47 (3)
Plus **8c** (1 μg ml^{-1})	126.30±4.99 (3)
Plus **8c** (10 μg ml^{-1})	90.93±3.22 (3)
Glibenclamide (1 μg ml^{-1})	210.4±15.6 (11)
Troglitazone	no effect

INS-1 cells in multi-wells were washed three times and incubated in KRBH-buffer for 90 min at 5.6 mM glucose. The results are expressed as percent insulin release at 5.6 mM glucose alone. Values obtained in the presence of 3.0 mM glucose (substimulatory concentration) and glibenclamide (1 μg ml^{-1}) served as controls. Each value represents the mean±SEM, number of independent experiments in parentheses.

literature findings arylidene thiazolidinediones and imidazolidinediones were in the Z configuration (sulfur and phenyl of benzylidene group are on the same side of the double bond) [25,26]. In this study, only one isomer was obtained. However, due to the low solubility of the compounds and the difficulties of getting suitable crystals for X-ray analysis, the isomer could not be analyzed structurally in detail. On the other hand, it was observed [8] that there was no significant difference of antidiabetic activity the two isomers.

Compounds **6a**–**e**, **7a**–**e**, **8b**–**c** were evaluated for their in vitro insulin releasing activity by using INS-1 cells (Table 1). Inhibitory effects were observed using some compounds, especially using the higher concentrations of compounds **6a**, **6b** and **7a**. Compounds **6d**, **6e**, **7b**, **7c** and **7d** were able to increase insulin release at the higher concentrations.

Insulin release at 8.3 mM glucose was normalized to 100%. Control experiments were performed with either low glucose (3.0 mM) or glibenclamide (1 μg ml^{-1}) at 8.3 mM glucose, one of the leading sulfonylureas in treatment of diabetes. Substimulatory glucose (3.0 mM) has a low effect (63.0% of that at 8.3 mM glucose). 1 μg ml^{-1} glibenclamide at 8.3 mM glucose increased insulin release from 100 to 210.4%. This is to compare the effects of various compounds with that of an established control compound.

N–H, methyl and ethyl substituted analogs of 2,4-thiazolidinedione rings of **8a**–**e** series were synthesized before and then tested antihyperglycemic effects with the same method [15,16]. When the result which are obtained from this study compared with the result of analog compounds, it was found that they show inhibitory effects such as other analogs of **8b** and **8c** at the high concentrations.

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