Arch Pharm Res Vol 27, No 11, 1099-1105, 2004

Archives of Pharmacal Research
http://apr.psk.or.kr

Synthesis and Biological Activity of Benzoxazole Containing Thiazolidinedione Derivatives

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(Received August 6, 2004)

The peroxisome proliferator-activated receptors (PPARs) are a primary regulator of lipid metabolism. Potency for activation of PPARγ, one of a subfamily of PPARs, particularly mirrors glucose lowering activity. We prepared thiazolidinediones featuring benzoxazole moiety for subtype selective PPARγ activators. 5-[4-[2-(Benzoxazol-2-yl-alkylamino)ethoxy]benzyl]thiazolidine-2,4-diones have been prepared by Mitsunobu reaction of benzoxazolylalkylaminoethanol **8** and hydroxybenzylthiazolidinedione **6** and their activities were evaluated. Most compounds tested were identified as potent PPARγ agonists.

Key words: Benzoxazole, Thiazolidinedione, PPAR

INTRODUCTION

Also known as noninsulin-dependent diabetes mellitus (NIDDM), Type 2 diabetes is a chronic and multifactorial disease characterized by insulin resistance in the liver and peripheral tissues (Defronzo *et al.*, 1992) and impaired insulin secretion from pancreatic β-cells (Defronzo, 1988). Hyperglycemia in type II diabetes leads to a gradual progression of complications, including neuropathy, nephropathy, retinopathy, arteriosclerosis, and coronary artery disease (Feldt-Rasmussen *et al.*, 1986; Dahl-Jorgensen *et al.*, 1986).

Primary therapy for type 2 diabetes includes caloric restriction and aerobic exercise which enhances tissue responsiveness to insulin (Ruderman and Scheneider, 1992). However, few patients are successful in the controlling of blood glucose level. The most widely used oral antihyperglycemic agents are sulfonylureas, which increase insulin secretion from pancreatic β-cells. A major drawback regarding this therapy is the adverse effect of severe hypoglycemia and weight gain (Holman and Turner, 1991).

Thus, insulin sensitivity enhancers represent an attractive approach to the treatment of type 2 diabetes. Clofibrate is the first such compound found to improve insulin resistance. It was followed by the discovery of thiazolidinediones (TZD), which are a class of oral insulin-sensitizing agents that improve glucose utilization without stimulating insulin secretion. Although the precise mechanism of action of TZDs remains unknown, a number of reports suggest that TZDs are high-affinity ligands of peroxisome proliferator activated receptor-γ (PPARγ) (Kletzien *et al.*, 1992; Ibrahimi *et al.*, 1994; Lehmann *et al.*, 1995). PPARs are members of the nuclear hormone receptor superfamily that consists of three members, PPAR-α, -δ, and γ and act as ligand-activated transcription factors, playing a major role in the regulation of lipid metabolism and storage (Desvergne and Wahli, 1999; Kersten *et al.*, 2000; Derger and Moller, 2002).

To date, a large number of compounds containing TZD moiety have been synthesized to produce new antidiabetic agents. Among them, troglitazone (Yoshioka *et al.*, 1989) was launched first in the market, but was subsequently withdrawn due to liver toxicity. Currently, rosiglitazone (Cantello *et al.*, 1994) and pioglitazone (Sohda *et al.*, 1990), the second and third TZDs marketed, are clinically used. However, these drugs have also been linked to liver, cardiovascular, and hematological toxicity, as well as body weight gain (Aronoff *et al*, 2000). Therefore, improvement of the TZD class of antidiabetic agents is still worth pursuing.

Many of the [[(heterocycloamino)alkoxy]benzyl]-2,4-thiazolidinediones represented in Fig. 1 have been already reported as potent antihyperglycemic agents. Of these compounds, benzoxazole derivatives such as BRL 48482 have been reported to have potent agonism to PPARγ

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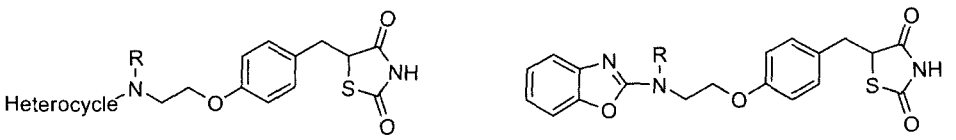


Fig. 1. General structure of [[(heterocycloamino)alkoxy]benzyl]-2,4-thiazolidinedione and benzoxazole analog

comparable to the well known antihyperglycemic agent, rosiglitazone. However, few studies have been done which were able to elicit the influence of the substituents of exocyclic nitrogen on the affinity of the compound to the receptor. First, we selected BRL 48482 as a seed compound. We now report the synthesis and biological activity of 5-[4-[2-(benzoxazol-2-yl-alkylamino)ethoxy]benzyl] thiazolidine-2,4-diones (**10**) together with a series of alkyl substituents on exocyclic nitrogen.

MATERIALS AND METHODS

Unless otherwise indicated, reagents and solvents were purchased from Aldrich chemicals and used without purification, with the following exceptions. Ethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Acetonitrile, methylene chloride, benzene, toluene, triethylamine, pyridine, dimethyl formamide, and diisopropylamine were distilled from calcium hydride under nitrogen. Flash column chromatography was performed using silica gel 60 (230-400 mesh, Merck) with indicated solvents. Thin-layer chromatography (TLC) was performed using Kieselgel 60 F_{254} plates (Merck). Melting points were measured on a Buchi melting point apparatus and were uncorrected. Infrared spectra were recorded on a Jasco FT/IR 430 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian YH 400 spectrometer as solutions in deuteriochloroform ($CDCl_3$), deuteriomethanol (CD_3OD) or deuteriodimethyl sulfoxide ($(CD_3)_2SO$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from an internal standard, tetramethylsilane. ^{1}H-NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonance), number of protons and coupling constant in hertz (Hz).

5-(4-Hydroxybenzylidene)thiazolidine-2,4-dione(2)

A mixture of 4-hydroxybenzaldehyde (5.18 g, 41.57 mmol), 2,4-thiazolidinedione (4.87 g, 41.57 mmol), benzoic acid (6.09 g, 49.88 mmol) and anhydrous toluene (50 mL) was stirred at 130 for 5 h. The reaction mixture was chilled and filtered. The filtercake was washed with the mixture solvent (water/methanol = 1:1 v/v) to afford 7.88 g (86 %) of the title compound as a yellow powder: R_f = 0.35 (*n*-hexane/ethyl acetate = 2:1); IR (neat) 3405, 3125, 3003, 2792 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.41 (br s, 1H), 10.27 (br s, 1H), 7.66 (s, 1H), 7.42 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz); ^{13}C-NMR δ (100 MHz, DMSO-d_6) 168.1, 167.6, 159.9, 132.4, 132.3, 123.9, 119.0, 116.3.

5-(4-Hydroxybenzyl)thiazolidine-2,4-dione (3)

Ten percent palladium/carbon (1.65 g) was added to a mixture of **2** (1.65 g, 7.04 mmol), dimethylformamide (20 mL), and methanol (30 mL). The resulting mixture was then vigorously shaken in 30 psi of hydrogen for 7 days. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford the tiltle compound as a yellow oil: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 11.95 (br s, 1H), 9.31 (br s, 1H), 6.99 (d, 2H, *J* = 8.4 Hz), 6.65 (d, 2H, *J* = 8.4 Hz), 4.78 (dd, 1H, *J* = 9.2, 4.0 Hz), 3.21 (dd, 1H, *J* = 14.0, 4.0 Hz), 2.95 (dd, 1H, *J* = 14.0, 9.2 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) 175.8, 171.8, 156.4, 130.3, 126.8, 115.2, 53.3, 36.4.

5-(4-Acetoxybenzyl)thiazolidine-2,4-dione (4)

Acetic anhydride (1.11 mL, 11.74 mmol) and pyridine (0.96 mL, 11.74 mmol) were added to a mixture of **3** (2.17 g, 9.08 mmol) and anhydrous toluene. The mixture was stirred at room temperature for 3 h. The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 2:1 v/v) to afford 1.24 g of title compound as a pale yellow powder: R_f = 0.39 (*n*-hexane/ethyl acetate = 2:1); IR (neat) 3414, 3068, 2782, 1755, 1698, 1197 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.02 (br s, 1H) 7.24 (d, 2H, *J* = 8.4 Hz), 7.03 (d, 2H, *J* = 8.4 Hz), 4.89 (dd, 1H, *J* = 9.2, 4.4 Hz), 3.34 (dd, 1H, *J* = 14.4, 4.4 Hz), 3.09 (dd, 1H, *J* = 14.4, 9.2 Hz) 2.21 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 175.7, 171.6, 169.2, 149.5, 134.3, 130.3, 121.8, 52.6, 36.5, 20.9.

5-(4-Acetoxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (5)

Triethylamine (0.95 mL, 2.31 mmol) was added to a mixture of **4** (201.5 mg, 0.77 mmol), triphenylmethyl chloride (1.11 mL, 0.92 mmol) and anhydrous toluene (2

mL). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 1:1 v/v) to afford 1.24 g (49%) of the title compound as a pale yellow powder: R_f = 0.59 (*n*-hexane/ethyl acetate = 3:1); IR (neat) 3059, 1759, 1688, 1300, 1196, 737 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33-7.00 (m, 19H), 4.36 (dd, 1H, *J* = 9.2, 4.0 Hz), 3.46 (dd, 1H, *J* = 14.0, 4.0 Hz), 3.06 (dd, 1H, *J* = 14.0, 9.2 Hz), 2.28 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.1, 169.3, 169.3, 150.1, 141.5, 133.4, 130.4, 128.4, 127.6, 126.8, 121.9, 76.5, 50.2, 37.9, 21.1.

5-(4-Hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (6)

A mixture of **5** (197.4 mg, 0.39 mmol), sodium methoxide (24.5 mg, 0.43 mmol) and methanol (20 mL) was stirred at room temperature for 1 h. Water was added to the reaction mixture, followed by neutralization with dilute hydrochloric acid. The mixture was then extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 1:1 v/v) to afford 139.1 mg (77%) of title compound as a pale yellow powder: R_f = 0.50 (*n*-hexane/ethyl acetate = 1:3); IR (neat) 3413, 3058, 3025, 1684, 1299 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.3 (s, 1H), 7.33-7.10 (m, 15H), 6.93 (d, 2H, *J* = 8.4 Hz), 6.73 (d, 2H, *J* = 8.4 Hz), 4.34 (dd, 1H, *J* = 8.8, 4.0 Hz), 3.37 (dd, 1H, *J* = 14.4, 4.0 Hz), 2.99 (dd, 1H, *J* = 14.4, 8.8 Hz).

2-(Benzoxazol-2-yl-methylamino)ethanol (8a)

A solution of 2-chlorobenzoxazole (2.00 g, 13.02 mmol), 2-methylaminoethanol (1.47 g, 19.57 mmol) and triethylamine (1.98 g, 19.57 mmol) in tetrahydrofuran (30 mL) was stirred at 70°C for 2 h. The reaction mixture was then extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 1:1 v/v) to afford 2.24 g (89%) of the title compound as a yellow oil: R_f = 0.20 (*n*-hexane/ethyl acetate = 1:1); IR (neat) 3298, 3060, 2936, 2880, 1650, 1585, 742 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.26 (ddd, 1H, *J* = 7.9, 1.3, 0.6 Hz), 7.18 (ddd, 1H, *J* = 7.9, 1.3, 0.6 Hz), 7.09 (td, 1H, *J* = 7.7, 1.3 Hz), 6.95 (td, 1H, *J* = 7.7, 1.3 Hz), 4.12 (s, 1H), 3.85 (t, 2H, *J* = 5.4 Hz), 3.62 (t, 2H, *J* = 5.4 Hz), 3.18 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0, 148.7, 142.7, 123.9, 120.4, 115.7, 108.7, 60.7, 53.2, 36.6.

2-(Benzoxazol-2-yl-ethylamino)ethanol (8b)

This compound was prepared using the same procedure as described for the preparation of **8a**: Yield 83%; R_f = 0.32 (*n*-hexane/ethyl acetate = 1:1); IR (neat) 3298, 2975, 2935, 1639, 1582 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.27 (dt, 1H, *J* = 7.9, 0.6 Hz), 7.20 (dt, 1H, *J* = 7.9, 0.6 Hz), 7.10 (td, 1H, *J* = 7.7, 1.3 Hz), 6.97 (td, 1H, *J* = 7.7, 1.3 Hz), 4.11 (s, 1H), 3.87 (t, 2H, *J* = 5.4 Hz), 3.64 (t, 2H, *J* = 5.4 Hz), 3.58 (q, 2H, *J* = 7.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 162.7, 148.6, 142.5, 123.9, 120.4, 115.7, 108.7, 61.4, 51.4, 44.7, 13.4.

2-(Benzoxazol-2-yl-propylamino)ethanol (8c)

This compound was prepared using the same procedure as described for the preparation of **8a**: Yield 95%; R_f = 0.34 (*n*-hexane/ethyl acetate = 1:1); IR (neat) 3334, 3061, 2964, 2875, 1638, 1581, 1461, 1243 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, 1H, *J* = 7.9, 0.6 Hz), 7.24 (dd, 1H, *J* = 7.9, 0.6 Hz), 7.14 (td, 1H, *J* = 7.7, 0.9 Hz), 6.99 (td, 1H, *J* = 7.7, 1.1 Hz), 3.91 (t, 2H, *J* = 4.9 Hz), 3.71 (t, 2H, *J* = 4.9 Hz), 3.51 (t, 2H, *J* = 7.5 Hz), 1.70 (sextet, 2H, *J* = 7.5 Hz), 0.95 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0, 148.5, 142.4, 123.9, 120.4, 115.7, 108.5, 61.5, 52.0, 51.63, 21.4, 11.0.

2-(Benzoxazol-2-yl-butylamino)ethanol (8d)

This compound was prepared using the same procedure as described for the preparation of **8a**: Yield 91%; IR (neat) 3310, 3060, 2958, 2932, 2872, 1639, 1582, 1462, 1242 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.28 (dt, 1H, *J* = 7.9, 0.6 Hz) 7.22 (dt, 1H, *J* = 7.9, 0.6 Hz), 7.12 (td, 1H, *J* = 7.7, 0.9 Hz), 7.0 (td, 1H, *J* = 7.7, 1.1 Hz), 3.89 (t, 2H, J = 4.9 Hz), 3.67 (t, 2H, *J* = 4.9 Hz), 3.53 (t, 2H, *J* = 7.5 Hz), 1.63 (quintet, 2H, *J* = 7.5 Hz), 1.35 (sextet, 2H, *J* = 7.5 Hz), 0.95 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.0, 148.6, 142.3, 124.0, 120.5, 115.8, 108.7, 61.8, 52.1, 49.9, 30.7, 19.8, 13.8

5-[4-[2-(Benzoxazol-2-yl-methylamino)ethoxy]benzyl]-3-(2,2,2-triphenylmethyl)thiazolidine-2,4-dione (9a)

Tributylphosphine (1.2 mL, 0.6 M in dry toluene, 0.60 mmol) in anhydrous toluene was added dropwise to a mixture of the alcohol **8a** (57.7 mg, 0.30 mmol), 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**6**) (93.1 mg, 0.20 mmol), azodicarbonyldipiperidine (151.4 mg, 0.60 mmol) and anhydrous toluene (2 mL). The resulting mixture was then stirred at room temperature for 6 h. Insoluble materials were filtered away and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-

hexane/ethyl acetate = 3:1 v/v) to afford 49.8 mg (37%) of the title compound as a yellow oil: R_f = 0.43 (*n*-hexane/ethyl acetate = 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-6.91 (m, 21H), 6.74 (d, 2H, *J* = 8.4 Hz), 4.27 (dd, 1H, *J* = 9.0, 4.0 Hz), 4.16 (t, 2H, *J* = 4.9 Hz), 3.87 (t, 2H, *J* = 4.9 Hz), 3.31 (dd, 1H, J = 14.0, 4.0 Hz), 3.26 (s, 3H), 2.97 (dd, 1H, *J* = 14.0, 9.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.4, 168.8, 160.4, 158.2, 149.0, 143.7, 115.7, 114.9, 108.7, 76.6, 66.4, 50.8, 48.0, 45.4, 37.2.

5-[4-[2-(Benzoxazol-2-yl-ethylamino)ethoxy]benzyl]-3-(2,2,2-triphenylmethyl)thiazolidine-2,4-dione (9b)

This compound was prepared using the same procedure as described for the preparation of **9a**: Yield 37 %; R_f= 0.34 (*n*-hexane/ethyl acetate = 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-6.88 (m, 21H), 6.73 (d, 2H, *J* = 8.4 Hz), 4.24 (dd, 1H, *J* = 9.0, 4.0 Hz), 4.14 (t, 2H, *J* = 4.9 Hz), 3.83 (t, 2H, *J* = 4.9 Hz), 3.64 (q, 2H, *J* = 7.1 Hz), 3.28 (dd, 1H, *J* = 14.0, 4.0 Hz), 2.96 (dd, 1H, *J* = 14.0, 9.0 Hz), 1.23 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 169.8, 162.1, 158.2, 149.0, 143.7, 116.2, 114.9, 109.0, 76.6, 66.4, 50.8, 48.4, 45.4, 37.8, 13.7.

5-[4-[2-(Benzoxazol-2-yl-propylamino)ethoxy]benzyl]-3-(2,2,2-triphenylmethyl)thiazolidine-2,4-dione (9c)

This compound was prepared using the same procedure as described for the preparation of **9a**: Yield 40%; R_f= 0.26 (*n*-hexane/ethyl acetate = 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39-6.97 (m, 21H), 6.81 (d, 2H, *J* = 8.4 Hz), 4.33 (dd, 1H, *J* = 9.0, 4.0 Hz), 4.23 (t, 2H, *J* = 4.9 Hz), 3.92 (t, 2H, *J* = 4.9 Hz), 3.62 (t, 2H, *J* = 7.5 Hz), 3.37 (dd, 1H, *J* = 14.0, 4.0 Hz), 3.04 (dd, 1H, *J* = 14.0, 9.0 Hz), 1.76 (sextet, 2H, *J* = 7.5 Hz), 1.24 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.1, 168.5, 160.9, 156.8, 147.6, 141.0, 140.4, 129.5, 127.4, 127.0, 126.9, 126.1, 122.9, 119.4, 114.9, 113.5, 107.7, 75.3, 64.9, 50.8, 49.4, 47.4, 36.5, 20.3, 10.1.

5-[4-[2-(Benzoxazol-2-yl-butylamino)ethoxy]benzyl]-3-(2,2,2-triphenylmethyl)thiazolidine-2,4-dione (9d)

This compound was prepared using the same procedure as described for the preparation of **9a**: Yield 36%; R_f = 0.20 (*n*-hexane/ethyl acetate = 3:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37-6.99 (m, 21H), 6.73 (d, 2H, *J* = 8.4 Hz), 4.25 (dd, 1H, *J* = 9.0, 4.0 Hz), 4.15 (t, 2H, *J* = 4.9 Hz), 3.84 (t, 2H, *J* = 4.9 Hz), 3.57 (t, 2H, *J* = 7.5 Hz), 3.29 (dd, 1H, *J* = 14.0, 4.0 Hz), 2.96 (dd, 1H, *J* = 14.0, 9.0 Hz), 1.63 (quintet, 2H, *J* = 7.5 Hz), 1.31 (sextet, 2H, *J* = 7.5 Hz), 0.88 (t, 3H, *J* = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.4, 169.8, 162.5, 158.2, 149.1, 143.7, 141.8, 130.8, 128.7, 128.3, 127.8, 127.0, 124.1, 120.5, 116.3, 114.8, 108.9, 76.6, 66.3, 50.8, 50.2, 48.6, 37.9, 30.6, 20.2, 14.2.

5-[4-[2-(Benzoxazol-2-yl-methylamino)ethoxy]benzyl]thiazolidine-2,4-dione (10a)

A mixture of **9a** (49.8 mg, 0.12 mmol) and trifluoroacetic acid (0.42 mL, 5.45 mmol) was stirred at room temperature for 3 h. The reaction mixture was diluted with ethyl acetate and neutralized by the addition of saturated potassium carbonate solution, extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (eluant, *n*-hexane/ethyl acetate = 3:1 v/v) to afford 13.8 mg (45%) of the title compound as a yellow oil: IR (neat) 3167, 3030, 2973, 2934, 2875, 2763 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.33 (dd, 1H, *J* = 7.9, 0.6 Hz), 7.23 (d, 1H, *J* = 8.4 Hz), 7.14 (dd, 1H, *J* = 7.7, 1.1 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 6.98 (dt, 1H, *J* = 7.9, 1.1 Hz), 6.79 (d, 2H, *J* = 8.4 Hz), 4.45 (dd, 1H, *J* = 9.2, 4.0 Hz), 4.19 (t, 2H, *J* = 4.9 Hz), 3.54 (t, 2H, *J* = 4.9), 3.38 (dd, 1H, *J* = 14.1, 4.0 Hz), 3.31 (s, 3H), 3.08 (dd, 1H, *J* = 14.1, 9.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.4, 162.6, 159.9, 158.1, 150.4, 149.1, 130.7, 128.2, 124.2, 120.7, 116.3, 114.9, 108.9, 66.4, 53.8, 50.3, 37.9, 37.6.

5-[4-[2-(Benzoxazol-2-yl-ethylamino)ethoxy]benzyl]thiazolidine-2,4-dione (10b)

This compound was prepared using the same procedure as described for the preparation of **10a**: Yield 61%; R_f = 0.25 (*n*-hexane/ethyl acetate = 3:1); IR (neat) 3166, 3029, 2973, 2934, 2876, 2762, 1698, 1638, 1244, 754 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.27 (d, 1H, J = 7.9 Hz), 7.17 (d, 1H, *J* = 8.4 Hz), 7.09 (d, 1H, *J* = 7.7 Hz), 7.05 (d, 2H, *J* = 8.4 Hz), 6.92 (dt, 1H, *J* = 7.9, 1.1 Hz) 6.75 (d, 2H, *J* = 8.4 Hz), 4.38 (dd, 1H, *J* = 9.2, 4.0 Hz), 4.11 (t, 2H, *J* = 4.9 Hz), 3.82 (t, 2H, *J* = 4.9 Hz), 3.64 (q, 2H, *J* = 7.1 Hz), 3.31 (dd, 1H, *J* = 14.1, 4.0 Hz), 3.00 (dd, 1H, *J* = 14.1, 9.2 Hz), 1.23 (t, 3H, *J* = 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 175.1, 171.3, 162.1, 158.1, 148.9, 143.0, 130.7, 128.1, 124.3, 120.7, 116.1, 114.8, 108.9, 66.3, 53.9, 48.4, 45.4, 37.8, 14.4.

5-[4-[2-(Benzoxazol-2-yl-propylamino)ethoxy]benzyl]thiazolidine-2,4-dione (10c)

This compound was prepared using the same procedure as described for the preparation of **10a**: Yield 36%; R_f = 0.26 (*n*-hexane/ethyl acetate = 3:1); IR (neat) 3172, 3030, 2973, 2932, 2875, 2761, 1698, 1637, 1580, 1243, 742 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 7.33 (d, 1H, *J* = 7.9 Hz), 7.23 (d, 1H, *J* = 8.4 Hz), 7.14 (d, 1H, *J* = 7.7 Hz), 7.10 (d, 2H, *J* = 8.4 Hz), 6.98 (t, 1H, *J* = 7.9 Hz), 6.80 (d, 2H, *J* = 8.4 Hz), 4.43 (dd, 1H, *J* = 9.2, 4.0 Hz), 4.18 (t, 2H, *J* = 4.9 Hz), 3.89 (t, 2H, *J* = 4.9 Hz), 3.59 (t, 2H, *J* = 7.5 Hz), 3.38 (dd, 1H, *J* = 14.1, 4.0 Hz), 3.06 (dd, 1H, *J* = 14.1, 9.2 Hz), 1.74 (sextet, 2H, *J* = 7.5 Hz), 0.95

(t, 3H, J = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.3, 171.1, 162.1, 158.2, 148.9, 142.5, 130.7, 128.2, 124.2, 120.7, 116.1, 114.9, 108.9, 76.1, 66.1, 53.9, 52.1, 48.7, 37.8, 11.4.

5-[4-[2-(Benzoxazol-2-yl-butyl-amino)-ethoxy]-benzyl]-thiazolidine-2,4-dione (10d)

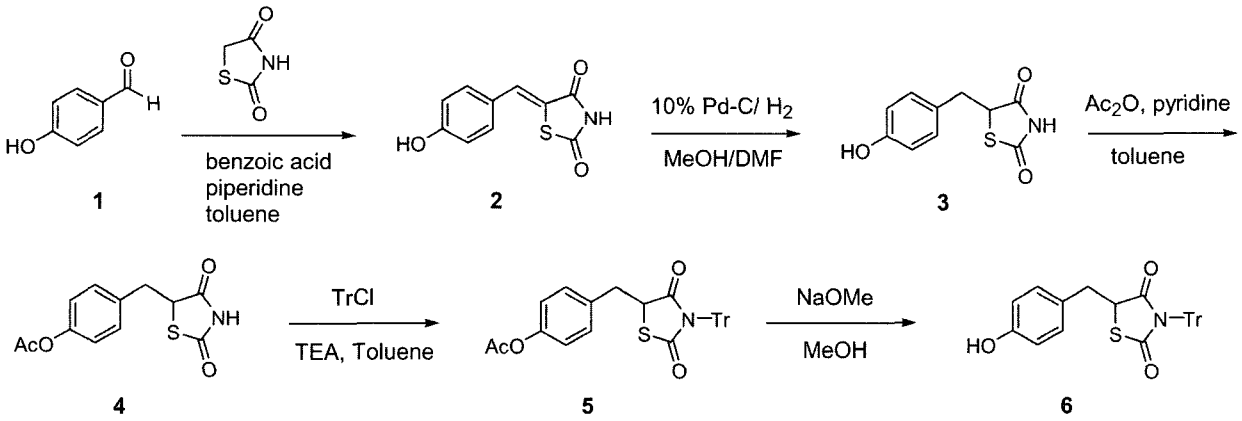
This compound was prepared using the same procedure as described for the preparation of **10a**: Yield 31%; R_f= 0.26 (*n*-hexane/ethyl acetate = 3:1); IR (neat) 3167, 3058, 3024, 2957, 2870, 2760, 1699, 1637, 1579, 1242, 742 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.34 (d, 1H, J = 7.9 Hz), 7.25 (d, 1H, J = 8.4 Hz), 7.16 (d, 1H, J = 7.7 Hz), 7.13 (d, 2H, J = 8.4 Hz), 6.99 (dt, 1H, J = 7.9, 1.1 Hz), 6.82 (d, 2H, J = 8.4 Hz), 4.45 (dd, 1H, J = 9.2, 3.8 Hz), 4.20 (t, 2H, J = 4.9 Hz), 3.90 (t, 2H, J = 4.9Hz), 3.65 (t, 2H, J = 7.5 Hz), 3.40 (dd, 1H, J = 14.1, 3.8 Hz), 3.08 (dd, 1H, J = 14.1. 9.2 Hz), 1.71 (quintet, 2H, J = 7.5 Hz), 1.40 (sextet, 2H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 174.9, 171.1, 162.4, 158.2, 148.9, 143.2, 130.7, 128.2, 124.2, 120.6, 116.1, 114.8, 108.9, 66.1, 60.7, 53.9, 50.2, 48.6, 37.9, 30.5, 20.1, 14.1.

PPAR transactivation assay

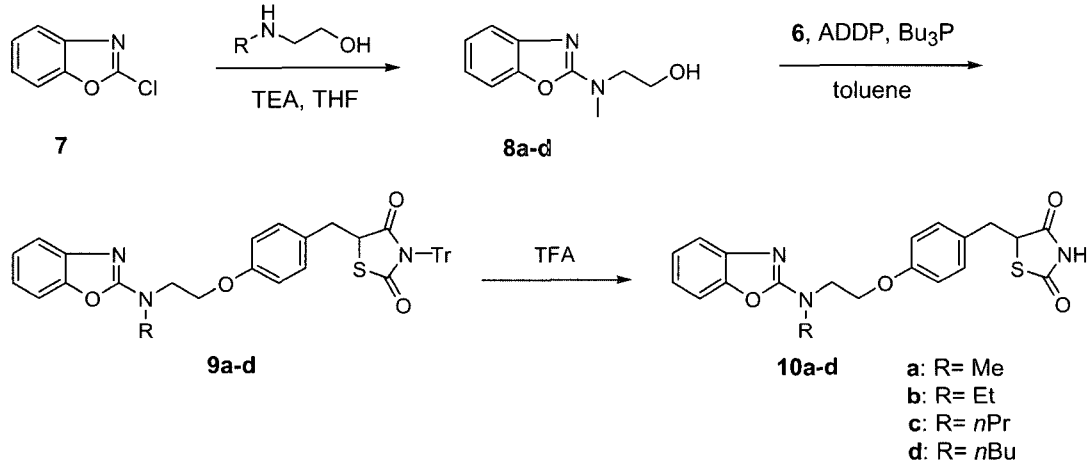
CV-1 cells were seeded at 2×10^4 cells/well and cultured for 24 h at 37°C. Cells were cotransfected for 3 h at 37°C with pUAS, pRL-TK, pCMX-GalPx. Transfected cells were then treated with test compounds for 24 h. DMSO (0.1%) was used as the blank. GW409544 was used as positive control. Luciferase activity was determined as fold activation relative to positive control.

RESULTS AND DISCUSSION

5-(4-Hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**6**) was prepared using a modified form of the reported method (Morita *et al*, 1998) as outlined in Scheme 1. 4-Hydroxybenzaldehyde was reacted with thiazolidine-2,4-dione to produce 5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (**2**). This was subsequently reduced in the presence of 10% Pd/C under hydrogen pressure to yield 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**3**). Acetylation



Scheme 1. Preparation of 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione



Scheme 2. Preparation of 5-[4-[2-(benzoxazol-2-yl-alkylamino)ethoxy]benzyl]thiazolidine-2,4-diones

Table I. *In vitro* PPARγ activities of the compounds[a]

Compd	R	transactivation RR %[b]	
		PPARα	PPARγ
10a (BRL 48482)	Me	NA	113.2
10b	Et	NA	78.0
10c	*n*Pr	NA	86.0
10d	*n*Bu	NA	51.0
GW409544		100	100
KRP-297		NA	63.3

[a]Compounds were assayed for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CV-1 cells as described. [b]Data is represented as relative response (%), which is [(test drug-negative control)/(positive control-negative control)]x100. GW409544 was used as positive control. DMSO was used as negative control.

of the phenol **3**, *N*-tritylation of the thiazolidinedione **4**, and deprotecting of the acetyl group afforded 5-(4-hydroxybenzyl)-3-triphenylmethylthiazolidine-2,4-dione (**6**).

The methods used to prepare the desired thiazolidinediones **10** are outlined in Scheme 2. The reaction of 2-chlorobenzoxazole with an appropriately substituted alkylamino alcohol generated the amino alcohol **8**. Mitsunobu reaction of **8** with 5-(4-hydroxybenzyl)thiazolidine-2,4-dione (**6**) in the presence of azodicarbonyldipiperidine and tributylphosphine gave **9**. Removal of the protecting trityl group by treating trifluoroactic acid afforded the desired product **10**.

The final compounds **10** were evaluated for the ability to activate PPARα and PPARγ in a transactivation assay in CV-1 cells, respectively. The results are shown in Table I. All compounds revealed significant PPARγ activities, although known BRL 48482 showed the most potent agonism to PPARγ. It was found that methyl substituent on the exocyclic nitrogen was the most suitable for PPARγ activities. We initially considered that increased bulk at this position may provide additional sites of interaction at the hydrophobic region of the active site, thus giving better activity. Unexpectedly, activities of the compounds-decreased along with the lengthening of the *N*-substituents.

In conclusion, we synthesized [[(benzoxazolylalkylamino) alkoxy]benzyl]thiazolidinediones with different alkyl substituents on the exocyclic nitrogen and observed that the lengthening of the *N*-alkyl substituents lowered activation of PPARγ. Further SAR study of the TZD analog with various steric and electrostatic functional groups at the exocyclic nitrogen is currently under investigation.

ACKNOWLEDGEMENTS

This study was supported by a grant (01-PJ1-PG3-21500-0019) from the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea. The authors would like to thank Dr. Yong Ho Ahn and Dong-A Pharm. Co., Ltd. for the PPAR transactivation data.

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