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Design and Synthesis of Novel Antidiabetic Agents

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The synthesis and structure-activity relationships of a novel series of substituted quercetins that activates peroxisome proliferator-activated receptor gamma (PPARγ) are reported. The PPARγ agonistic activity of the most potent compound in this series is comparable to that of the thiazolidinedione-based antidiabetic drugs currently in clinical use.

Key words: Antidiabetic agents, Quercetin, Thiazolidinedione, Malonate

INTRODUCTION

Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all diabetes (Zimmet *et al.*, 2001). Currently 150 million people worldwide are afflicted with T2DM and the number is estimated to rise to over 220 million by the year 2010 partly due to a dramatic increase in the incidence of obesity and a sedentary lifestyle (Zimmet *et al.*, 2001). T2DM is a metabolic disorder that is associated with three basic pathophysiologic abnormalities: impaired insulin secretion, excessive hepatic glucose production, and insulin resistance in skeletal muscle, liver, and adipose tissue (DeFronzo *et al.*, 1992). Development of diabetes-specific microvascular pathology in the retina, renal glomerulus and peripheral nerve due to chronic hyperglycemia leads to blindness, end-stage renal disease and a variety of debilitating neuropathies. Diabetes is also associated with accelerated atherosclerotic macrovascular diseases such as myocardial infarction, stroke and limb amputation (Brownlee *et al.*, 2001; Porte *et al.*, 1996,). Since the completion of the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) it is now clear that aggressive control of hyperglycemia in patients with diabetes can prevents or delays the onset of complications such as retinopathy, nephropathy and neuropathy. Most T2DM patients require medication to achieve euglycemia even though they adhere to strict diet and increase physical activity. The pharmacologic agents available for the treatment of type 2 diabetes have focused primarily on reducing the hyperglycemia itself. Injectable insulin suppresses glucose production and augments glucose utilization, sulfonylureas and meglitinides increase insulin release from pancreatic islets, biguanides such as metformin act to reduce excessive hepatic glucose production, α-glucosidase inhibitors interfere with gastrointestinal glucose absorption, and peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists such as thiazolidinediones enhance insulin action (Nuss *et al.*, 2000). However, neither mono nor combination therapy of these agents is completely successful in ameliorating type 2 diabetes for many patients. These therapies have limited efficacy, limited tolerability and significant mechanism-based side effects, such as weight gain, hypoglycemia, lactic acidosis, gastrointestinal disturbances, edema and anemia (Marcus *et al.*, 2000a; Marcus *et al.*, 2000b). Thus more efficacious agents are desperately needed (Morral, 2003).

Antioxidants are being actively studied for their functional role in improving the diabetic status in experimentally induced diabetic rats. It has been demonstrated that antioxidant quercetin improved diabetic status in terms of urine volume, urine glucose, and fasting blood glucose possibly through improving secretion of insulin or by increasing glucose uptake by the tissues (Shetty *et al.*, 2004). Quercetin was reported to normalize blood glucose level, augment liver glycogen content and significantly reduce serum cholesterol and LDL concentration in alloxan-

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diabetic rats (Nuraliev *et al.*, 1992). A beneficial role of quercetin in improving diabetic cataracts by inhibiting aldose reductase has also been reported (Varma *et al.*, 1977).

After the synthesis of ciglitazone and its derivatives in 1982, it was discovered that the thiazolidinedione derivative could reduce insulin resistance in obese and diabetic animals (Sohda *et al.*, 1982; Fujita *et al.*, 1983). In 1995, it has been proven that peroxisome proliferator-activated receptors (PPARs) were the receptors through which the thiazolidinedione class of drugs mediate their biological activity (Lehmann *et al.*, 1995).

Two thiazolidinediones, pioglitazone (Momose *et al.*, 1991) and rosiglitazone (Cantello *et al.*, 1994), are now in clinical use for the treatment of type 2 diabetes in humans.

It has been reported that compounds with malonate in the place of thiazolidinedione displayed similar antihyperglycemic activity in the *ob/ob* mouse model of type 2 diabetes mellitus (Buckle *et al.*, 1996).

This background information led to the design of quercetin derivatives containing thiazolidinedione or malonate. This manuscript describes the synthesis and *in vitro* activity of a novel series of quercetin derivatives.

MATERIALS AND METHODS

Chemistry

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Dimethylformamide (DMF) was treated with molecular sieves (4Å) and used without distillation. Chromatography was performed using Merck 60, 70-230 mesh silica gel. Thin layer chromatography (TLC) was carried out using E. Merck Silica Gel 60 precoated plates. Melting points were determined by capillary method on Electrothermal IA9200 digital melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for ^{1}H-NMR were taken on Bruker AC80 or Varian UNITY *plus* 300 spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS) the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quertet, Q = quintet, m = multiplet, dd = doublet of doublet, bs = broad singlet. Mass spectra (MS) were obtained on Shimazu GCMS QP2000A instrument applying a electron-impact ionization (EI) method. Infrared spectra (IR) were determined neat or in pressed KBr disk on Jasco FT-IR instrument and reported in reciprocal centers.

5-[4'-(3-Chloropropyl)oxybenzylidene]thiazolidine-2,4-dione (1)

To a solution of *p*-hydroxybenzaldehyde (3 g, 24.57 mmol) and 1-bromo-3-chloropropane (2.43 mL, 24.57 mmol) in DMF (30 mL) was added K_2CO_3 (4.14 g, 31.94 mmol) and reacted at 40 °C for 24 h. The resulting mixture was extracted with CH_2Cl_2, washed with H_2O and brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 7:1) to give white oil (3.82 g, 78.4 %): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.78 (2H, Q, J = 6.0 Hz,$CH_2C\underline{H_2}CH_2$), 3.76 (2H, t, J = 6.0 Hz, $CH_2C\underline{H_2}Cl$), 4.21 (2H, t, J = 6.0 Hz, $CH_2C\underline{H_2}O$), 7.01 (2H, d, J = 9.0 Hz, aromatic H), 7.84 (2H, d, J = 9.0 Hz, aromatic H), 9.89 (1H, s, CHO); IR neat (cm^{-1}) 2836 (aliphatic CH), 1690 (C=O); MS (*m/z*, relative intensity) 198 (14.6), 121 (75.5), 69 (72.5), 57 (99.9).

A solution of the above compound (3.82 g, 19.26 mmol) and thiazolidine-2,4-dione (2.26 g, 19.26 mmol) in toluene (40 mL) containing a piperidinium acetate (0.83 g, 5.78 mmol) was refluxed in Dean-Stark water trap for 5 h. The solution was cooled in a refrigerator and filtered and the precipitate washed with ether and dried under to give yellow solid (4.49 g, 78.3%): mp 137.3-145.7 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.18 (2H, Q, J = 6.4 Hz, $CH_2C\underline{H_2}CH_2$), 3.75 (2H, t, J = 6.4 Hz, $CH_2C\underline{H_2}Cl$), 4.18 (2H, t, J = 6.4 Hz, $CH_2C\underline{H_2}O$), 7.00 (2H, d, J = 8.8 Hz, aromatic H), 7.46 (2H, t, J = 6.4 Hz, aromatic H), 7.69 (1H, s, benzylidene H); IR neat (cm^{-1}) 3145 (NH), 3033 (aromatic CH), 2960 (aliphatic CH), 1689 (C=O); MS (*m/z*, relative intensity) 297(41.9), 226(88.7), 150(99.9), 149(59)

5-[4'-(3-Chloropropyl)oxybenzyl]thiazolidine-2,4-dione (2)

To a stirring solution of $CoCl_2{\cdot}6H_2O$ (80 mg, 0.336 mmol) and 2,2-dipyridyl (53 mg, 0.034 mmol) in H_2O (10 mL) was added 1.0 N NaOH (6 drop) followed by $NaBH_4$ (51 mg, 1.34 mmol), and resulting deep blue mixture was cooled to 0 °C. A solution of compound **1** (100 mg, 0.336 mmol) in DMF (5 mL) was added over 0.5 h. The mixture stirred for 18 h at room temperature. Acetic acid was added the mixture was approximately pH 6. The mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried, filtered, and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 7:1) to give white solid (85 mg, 84.3%): mp 91.5-93.7 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.22 (2H, Q, J = 6.4 Hz, $CH_2C\underline{H_2}CH_2$), 3.09 (1H, dd, J = 9.6 Hz, 16 Hz, benzylic H), 3.47 (1H, dd, J = 16 Hz, 4.8 Hz, benzylic H), 3.73 (2H, t, J = 6.4 Hz, $CH_2C\underline{H_2}Cl$), 4.03 (2H, t, J=6.4 Hz, $CH_2C\underline{H_2}O$), 4.50 (1H, dd, J = 4.8, 9.6 Hz, thiazolidine H), 6.85 (2H, d, J = 8.0Hz, aromatic H), 7.15 (2H, d, J = 8.0 Hz, aromatic H); IR neat (cm^{-1}) 3135 (NH), 3043 (aromatic CH), 2954 (aliphatic CH), 1685 (C=O).

Dimethyl 2-(4'-hydroxybenzylidene)malonate (3)

A solution of *p*-hydroxybenzaldehyde (4 g, 32.75 mmol)

and dimethyl malonate (5.35 mL, 39.3 mmol) in toluene (50 mL) containing a piperidinium acetate (1.41 g, 9.82 mmol) was refluxed in a Dean-Stark trap for 5 h. The solution was cooled in a refrigerator and filtered and precipitate washed with ether and dried under vacuum to a give pale yellow solid (6.7 g, 86.6%): mp 154.4-156.3 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.82 (3H, s, $COOCH_3$), 3.85 (3H, s, $COOCH_3$), 6.1 (1H, s, OH), 6.81(2H, d, J = 8.4 Hz, aromatic H), 7.32 (2H, d, J = 8.4 Hz, aromatic H), 7.69 (1H, s, benzylidene H); IR neat (cm^{-1}) 3340 (OH), 2950 (aliphatic CH), 1668 (C=O); MS (*m/z*, relative intensity) 236 (76.8), 205 (45.8), 176 (90.3), 137 (99.9), 118 (76.8)

Dimethyl 2-(4'-hydroxybenzyl)malonate (4)

A solution of compound **3** (1 g, 4.23 mmol) in a mixture of MeOH (4 mL) and 1,4-dioxane (20 mL) was stirred in the presence of 5% palladium on charcoal (0.3 g) under atmosphere of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filterate was evaporated under a vacuum to give dark yellow oil (1 g, 99.2%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.13 (2H, d, J = 7.7 Hz, benzylic H), 3.61 (2H, d, J = 7.7 Hz, COCHCO), 3.67 (6H, s, $CH_3COCHCOCH_3$), 6.93 (2H, d, J = 6.5 Hz, aromatic H), 7.03 (2H, d, J = 6.5 Hz, aromatic H); IR neat (cm^{-1}) 3442 (OH), 3016 (aromatic CH), 2954 (aliphatic CH), 1729 (C=O); MS (*m/z*, relative intensity) 238 (18.4), 147 (35.9), 107 (99.9).

Dimethyl 2-[4-(3-chloropropoxy)benzyl]malonate (5)

To a solution of compound **3** (3 g, 12.7 mmol) and 1-bromo-3-chloropane (1.26 mL, 12.7 mmol) in DMF (25 mL) was K_2CO_3 (2.28 g, 16.51 mmol) and reacted at 40 °C for 2 h. The resulting mixture was extracted with EtOAc, washed with H_2O and, brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The residue was separated by column chromatography (SiO_2, Hexane : EtOAc = 5 : 1) to give white solid (2.06 g, 52%): mp 78.9-82.4 °C; ^{1}H-NMR (80 MHz,$CDCl_3$) δ 2.23 (2H, Q, J = 6 Hz, $CH_2CH_2CH_2$), 3.69 (2H, t, J = 6 Hz, OCH_2CH_2), 3.82 (3H, s, $COCH_3$), 3.85 (3H, s, $COCH_3$), 4.14 (2H, t, J = 6 Hz, OCH_2CH_2), 6.89 (2H, d, J = 8.9 Hz, aromatic H), 7.39 (2H, d, J = 8.9 Hz, aromatic H), 7.69 (1H, s, benzylidene H); IR neat (cm^{-1}) 3079 (aromatic CH), 2964 (aliphatic CH), 1720 (C=O); MS (*m/z*, relative intensity) 312 (99.9), 281 (40.7), 252 (67), 176 (97.6), 137 (66.9).

A solution of the above compound (1.83 g, 5.85 mmol) in a mixture of MeOH (5 mL) and 1,4-dioxane (25 mL) was stirred in the presence of 5% palladium on charcoal (0.4 g) under atmosphere of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filterate was evaporated under a vacuum to give colorless oil (1.84 g, 100%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.20 (2H, Q, J = 6 Hz, $CH_2CH_2CH_2$), 3.15 (2H, d, J=7.7 Hz, benzylic H), 3.60 (2H, t, J = 7.7 Hz, COCHCO), 3.69 (6H, s, $CH_3COCHCOCH_3$), 3.90 (2H, t, J = 6 Hz, OCH_2CH_2), 4.07 (2H, t, J = 6 Hz, CH_2CH_2O), 6.8 (2H, d, J = 8.6 Hz, aromatic H), 7.1 (2H, d, J = 8.6 Hz, aromatic H); IR neat (cm^{-1}) 3040 (aromatic CH), 2954 (aliphatic CH), 1730 (C=O).

3',4',7-Tribenzylquercetin (6)

To a solution of quercetin·$2H_2O$ (5 g, 14.78 mmol) and benzyl bromide (5.27 mL, 44.34 mmol) in DMF (40 mL) was added K_2CO_3 (8.17 g, 59.12 mmol) at r. t. overnight. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, CH_2Cl_2) to give yellow solid (3.89 g, 46%): mp 148.8 - 151.5 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 5.07 (2H, s, benzylic H), 5.12 (2H, s, benzylic H), 5.18 (2H, s, benzylic H), 6.46 (2H, m, aromatic H), 7.197.64 (18H, m, aromatic H); IR neat (cm^{-1}) 3291 (OH), 3025 (aromatic CH), 2875 (aliphatic CH), 1654 (C=O)

3',4',7-Trimethoxymethylquercetin (7)

To a solution of quercetin·$2H_2O$ (5 g, 14.78 mmol) in DMF (50 mL) was added NaH (2.35 g, 59.12 mmol) and chloromethyl methyl ether (3.4 mL, 44.34 mmol) at ice-water bath. The resulting mixture was stirred at r. t. for 40 min. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 3 : 1) to give yellow solid (1.65 g, 25.7%): mp 121.1-123.6 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.27 (3H, s, CH_3OCH_2), 3.49 (3H, s, CH_3OCH_2), 3.54 (3H, s, CH_3OCH_2), 5.19 (2H, s, CH_3OCH_2), 5.22 (2H, s, CH_3OCH_2), 5.28 (2H, s, CH_3OCH_2), 6.44 (1H, d, J = 2.2 Hz, aromatic H), 6.61 (1H, d, 2 J = 2Hz, aromatic H), 7.12-7.82 (3H, m, aromatic H), 12.50 (1H, s, OH); IR neat (cm^{-1}) 3392 (OH), 2956 (aliphatic CH), 1654 (C=O).

3-*O*-(3-Chloropropyl)-3',4',7-trimethoxymethylquercetin (8)

To a flask containing a suspension of KH (0.9 g, 7.84 mmol, washed three times with hexane) was added a solution of compound **7** (1.3 g, 2.99 mmol) in DMF (9 mL) at ice-water bath under argon. After 30 min, a solution of 1-bromo-3-chloropropane (0.3 mL, 2.99 mmol) in DMF (1 mL) and NaI (0.45 g, 2.99 mmol) was added to a reaction flask. After removing ice-water bath, the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by

column chromatography (SiO_2, Hexane : EtOAc = 5 : 1) to give yellow solid (1.2 g, 79%): mp 84.6-86.2 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.29 (2H, Q, *J* = 6.1 Hz, $CH_2C\underline{H}_2CH_2$), 3.23 (3H, s, $CH_2OC\underline{H}_3$), 3.48 (3H, s, $CH_2OC\underline{H}_3$), 3.51 (3H, s, $CH_2OC\underline{H}_3$), 3.78 (2H, t, *J* = 6.2 Hz, $CH_2C\underline{H}_2CH_2$), 4.24 (2H, t, *J* = 5.9 Hz, $CH_2C\underline{H}_2CH_2$), 5.17 (2H, s, $C\underline{H}_2OCH_3$), 5.21 (2H, s, $C\underline{H}_2OCH_3$), 5.26 (2H, s, $C\underline{H}_2OCH_3$), 6.44 (1H, d, *J* = 2.2 Hz, aromatic H), 6.61 (1H, d, *J* = 2.2 Hz, aromatic H), 7.15 7.71 (3H, m, aromatic H), 12.48 (1H, s, O<u>H</u>); IR neat (cm^{-1}) 3448 (OH), 3100 (aromatic CH), 2934 (aliphatic CH), 1653 (C=O)

3',4',7-Tribenzyl-3-*O*-[3-[4'-(thiazolidine-2,4-dion-5-yl) methylenephenyloxy]propyl]quercetin (9)

To a flask containing a suspension of KH (1.2 g, 10.48 mmol, washed three times with hexane) was added a solution of compound **6** (1 g, 1.75 mmol) in DMF (8 mL) at ice-water bath under argon. After 30 min, a solution of compound **1** (0.52 g, 1.75 mmol) in DMF (3 mL) and NaI (0.52 g, 3.49 mmol) was added to a reaction flask. After removing ice-water bath, the reaction flask was heated to 50-60 °C and then was stirred for 2 h. The reaction flask was cooled to room temperature. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 3 :1) to give yellow solid (0.31 g, 37.4%): mp 148.1-150.7 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.22 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 4.03 (2H, t, *J* = 6 Hz, $OCH_2C\underline{H}_2$), 4.17 (2H, t, *J* = 6 Hz, $CH_2C\underline{H}_2O$), 5.0 (2H, s, benzylic H), 5.12 (2H, s, benzylic H), 5.19 (2H, s, benzylic H), 6.44 (1H, d, *J* = 2.1 Hz, aromatic H), 6.49 (1H, d, *J* = 1.8 Hz, aromatic H), 6.93 (2H, d, *J* = 9Hz, aromatic H), 6.97 (2H, d, *J* = 8.7Hz, aromatic H), 7.257.69 (18H, m, aromatic H), 12.69 (1H, s, O<u>H</u>).

3',4',7-Trimethoxymethyl-3-*O*-[3-[4'-(thiazolidine-2,4-dione-5-yl)methylphenyloxy]propyl]quercetin (10)

To a flask containing a suspension of KH (0.33 g, 2.88 mmol, washed three times with hexane) was added a solution of compound **7** (0.5 g, 1.15 mmol) in DMF (5 mL) at ice-water bath under argon. After 30 min, a solution of compound **2** (0.34 g, 1.15 mmol) in DMF (2 mL) and NaI (0.34 g, 2.3 mmol) was added to a reaction flask. After removing ice-water bath, the reaction flask was warmed to 80-90 °C and then was stirred for 5 h. The reaction flask was cooled to room temperature. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 3 : 1) to give yellow solid (0.285g, 35.5%): mp 117.8-125.1 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.34 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.1 (1H, dd , *J* = 9.6 Hz, benzylic H), 3.21 (3H, s, $C\underline{H}_3OCH_2$), 3.41 (1H, dd, *J* = 3.9 Hz, benzylic H), 3.49 (3H, s, $C\underline{H}_3OCH_2$), 3.5 (3H, s, $C\underline{H}_3OCH_2$), 4.2 (2H, t, *J* = 6Hz, $OC\underline{H}_2CH_2$), 4.3 (2H, t, *J* = 6 Hz, $CH_2C\underline{H}_2O$), 4.48 (1H, dd, *J* = 3.9 Hz, thiazolidine H), 5.16 (2H, s, $CH_3OC\underline{H}_2$), 5.24 (2H, s, $CH_3OC\underline{H}_2$), 5.26 (2H, s, $CH_3OC\underline{H}_2$), 6.46 (1H, d, *J* = 2.1 Hz, aromatic H), 6.61 (1H, d, *J* = 2.4 Hz, aromatic H), 6.86 (2H, d, *J* = 8.4 Hz, aromatic H), 7.12 (2H, d, *J* = 8.7 Hz, aromatic H), 7.2 7.71 (3H, m, aromatic H), 12.5 (1H, s, O<u>H</u>); IR neat (cm^{-1}) 3432 (OH), 2924 (aliphatic CH), 1700 (C=O).

3-*O*-[3'-[4'-(Thiazolidine-2,4-dione-5-yl)methylphenyloxy] propyl] quercetin (11)

To a solution of compound **10** (64 mg, 0.092 mmol) and concentrated HCl (0.1 mL) in MeOH (7 mL) was refluxed for 1 h. After cooling and evaporation of the solvent, the mixture was extracted with EtOAc, washed with H_2O and, brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give yellow solid (49 mg, 94.4%): mp 201.5-208.2 °C; ^{1}H-NMR (300 MHz, DMSO-d_6) δ 2.21 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.03 (1H, dd, *J* = 6 Hz, benzylic H), 3.26 (1H, dd, *J* = 6 Hz, benzylic H), 4.19 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 4.83 (1H, dd, *J* = 4.5 Hz, 4.2 Hz, thiazolidine H), 6.2 (1H, d, *J* = 2.1 Hz, aromatic H), 6.47 (1H, d, *J* = 1.5 Hz, aromatic H), 6.91 (2H, d, *J* = 8.7 Hz, aromatic H), 6.96 (1H, d, *J* = 8.7 Hz, aromatic H), 7.14 (2H, d, *J* = 8.7 Hz, aroma tic H), 7.68 (1H, dd, *J* = 2 Hz, 1.8 Hz, aromatic H), 7.8 (1H, d, *J* = 2.1 Hz, aromatic H), 12.5 (1H, s, O<u>H</u>); IR neat (cm^{-1}) 3432 (OH), 2924 (aliphatic CH), 1700 (C=O).

Dimethyl 2-{4-(3-({7-(benzyloxy)-2-[3,4-bis(benzyloxy) phenyl]-5-hydroxy-4-oxo-4*H*-chromen-3-yl}oxy)propoxy] benzyl]malonate (12)

To a flask containing a suspension of KH (0.33 g, 2.84 mmol, washed three times with hexane) was added a solution of compound **6** (0.65 g, 1.14 mmol) in DMF (10 mL) at ice-water bath under argon. After 30 min, a solution of compound **5** (0.357 g, 1.14 mmol) in DMF (2 mL) and NaI (0.17 g, 1.14 mmol) was added to a reaction flask. After removing ice-water bath, the reaction flask was warmed to 80 °C and then was stirred for 3 h. The reaction flask was cooled to room temperature. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 3 : 1) to give yellow oil (0.26 g, 26.9%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.17 (2H, Q, *J* = 6Hz, $CH_2C\underline{H}_2CH_2$), 3.15 (2H, d, *J* = 7.6Hz, benzylic H), 3.61 (1H, t, *J* = 7.6 Hz, COC<u>H</u>CO), 3.66 (6H, s, $C\underline{H}_3COCHCOC\underline{H}_3$), 4.00 (2H, t, *J* = 6 Hz, $OC\underline{H}_2CH_2$), 4.15 (2H, t, *J* = 6 Hz, $CH_2C\underline{H}_2O$), 5.05 (2H, s, benzylic H), 5.09 (2H, s, benzylic H), 5.15 (2H, s, benzylic

H), 6.41 (1H, d, J = 2.2 Hz, aromatic H), 6.48 (1H, d, J = 2.1 Hz, aromatic H), 6.72-7.67 (22H, m, aromatic H), 12.68 (1H, s, OH); IR neat (cm^{-1}) 3448 (OH), 3100 (aromatic CH), 2941 (aliphatic CH), 1734 (C=O).

Dimethyl 2-[4-(3-{[2-[3,4-bis(methoxymethoxy)phenyl]-5-hydroxy-7-(methoxymethoxy)-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl]malonate (13)

To a flask containing a suspension of KH (0.9 g, 7.84 mmol, washed three times with hexane) was added a solution of compound **7** (1.3 g, 2.99 mmol) in DMF (9 mL) at ice-water bath under argon. After 30 min, a solution of 1-bromo-3-chloropropane (0.3 mL, 2.99 mmol) in DMF (1 mL) and NaI (0.45 g, 2.99 mmol) was added to a reaction flask. After removing ice-water bath, the reaction mixture was stirred at room temperature for 1 h. The resulting mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 5 : 1) to give yellow solid (1.2 g, 79%): mp 84.6-86.2 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.29 (2H, Q, J = 6.1 Hz, $CH_2C\underline{H}_2CH_2$), 3.23 (3H,s, $CH_2OC\underline{H}_3$), 3.48 (3H, s, $CH_2OC\underline{H}_3$), 3.51 (3H, s, $CH_2OC\underline{H}_3$), 3.78 (2H, t, J = 6.2 Hz, $CH_2C\underline{H}_2CH_2$), 4.24 (2H, t, J = 5.9 Hz, $CH_2C\underline{H}_2CH_2$), 5.17 (2H, s, $C\underline{H}_2OCH_3$), 5.21 (2H, s, $C\underline{H}_2OCH_3$), 5.26 (2H, s, $C\underline{H}_2OCH_3$), 6.44 (1H, d, J = 2.2 Hz, aromatic H), 6.61 (1H, d, J = 2.2 Hz, aromatic H), 7.15 7.71 (3H, m, aromatic H), 12.48 (1H, s, O$\underline{H}$); IR neat (cm^{-1}) 3448 (OH), 3100 (aromatic CH), 2934 (aliphatic CH), 1653 (C=O).

To a flask containing a suspension of NaH (0.31 g, 7.83 mmol, washed three times with hexane) was added a solution of compound **3** (1.4 g, 5.87 mmol) in DMF (10 mL) at ice-water bath under argon. After 30 min, a solution of the above product (1 g, 1.96 mmol) in DMF (2 mL) and NaI (0.61 g, 3.91 mmol) was added to a reaction flask. After removing ice-water bath, the reaction flask was warmed to 100 °C and then was stirred for 3 h. The reaction flask was cooled to room temperature. The reaction mixture was quenched with H_2O, extracted with EtOAc, washed with H_2O and brine, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was separated by column chromatography (SiO_2, Hexane : EtOAc = 3 : 1) to give yellow oil (0.43 g, 30.8%): ^{1}H-NMR (80 MHz, $CDCl_3$) d 2.30 (2H, Q, J = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.09 (2H, d, J = 7.7 Hz, benzylic H), 3.25 (3H, s, $CH_2OC\underline{H}_3$), 3.49 (3H, s, $CH_2OC\underline{H}_3$), 3.53 (3H, s, $CH_2OC\underline{H}_3$), 3.62 (1H, t, J = 7.7 Hz, COC$\underline{H}$CO), 3.69 (3H, s, $C\underline{H}_3COCHCOC\underline{H}_3$), 3.82 (2H, t, J = 6 Hz, $OC\underline{H}_2CH_2$), 4.25 (2H, t, J = 6 Hz, $CH_2C\underline{H}_2O$), 5.18 (2H, s, $C\underline{H}_2OCH_3$), 5.23 (2H, s, $C\underline{H}_2OCH_3$), 5.27 (2H, s, $C\underline{H}_2OCH_3$), 6.46 (1H, d, J = 2.2 Hz, aromatic H), 6.15 (1H, d, J = 2.2 Hz, aromatic H), 6.66 7.71 (3H, m, aromatic H), 12.49 (1H, s, O$\underline{H}$).

Dimethyl 2-[4-(3-{[2-(3,4-dihydroxyphenyl)-5,7-hydroxy-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl]malonate (14)

To a solution of compound **13** (47 mg, 0.066 mmol) and concentrated HCl (0.1 mL) in MeOH (7 mL) was refluxed for 1 h. After cooling and evaporation of the solvent, the mixture was extracted with EtOAc, washed with H_2O and, brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give yellow green solid (49 mg, 94.4%): mp 134.5-146.4 °C; ^{1}H-NMR (80 MHz, DMSO-d_6) δ 2.26 (2H, Q, J = 5.5 Hz, $CH_2C\underline{H}_2CH_2$), 3.00 (2H, d, J = 5 Hz, benzylic H), 3.68 (1H, t, J = 5 Hz, COC$\underline{H}$CO), 3.59 (6H, s, $C\underline{H}_3COCHCOC\underline{H}_3$), 3.78 (2H, t, J = 5.7 Hz, $OC\underline{H}_2CH_2$), 4.16 (2H, t, J = 4.6 Hz, $CH_2C\underline{H}_2O$), 6.19 (1H, d, J = 2 Hz, aromatic H), 6.65 (1H, d, J = 2 Hz, aromatic H), 6.67 7.75 (7H, m, aromatic H), 12.54 (1H, s, O$\underline{H}$); IR neat (cm^{-1}) 3442 (OH), 2953 (aliphatic CH), 1719 (OH).

2-[4-(3-{[2-[3,4-Bis(methoxyoxymethoxy)phenyl]-5-hydroxy-7-(methoxymethoxy)-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl]malonic acid (15)

A 2*N* aqueous solution of lithium hydroxide (0.4 mL, 0.8 mmol) was added to a solution of compound **13** (110 mg, 0.15 mmol) in a mixture of MeOH (4 mL) and THF (2 mL) at room temperature. The mixture was refluxed for 20 h. The reaction flask was cooled to room temperature, and then the solvent was removed under vacuum. After evaporation of organic solvent, water was added to the residual solution, and the mixture was acidified with 1*N* hydrochloric acid. EtOAc was added to the residue. The mixture was washed water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give a yellow oil (99 mg, 92.5 %): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.30 (2H, Q, J = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.13 (2H, d, J = 7.5 Hz, benzylic H), 3.18 (3H, s, $OCH_2OC\underline{H}_3$), 3.48 (6H, s, $OCH_2OC\underline{H}_3$), 3.66 (1H, t, J = 7.4 Hz, COC$\underline{H}$CO), 4.17 (2H, t, J = 6.1 Hz, $OC\underline{H}_2CH_2$), 4.27 (2H, t, J = 6.3 Hz, $CH_2C\underline{H}_2O$), 5.09 (2H, s, $OC\underline{H}_2OCH_3$), 5.22 (2H, s, $OC\underline{H}_2OCH_3$), 5.23 (2H, s, $OC\underline{H}_2OCH_3$), 6.45 (1H, Q, J = 2.2 Hz, aromatic H), 6.61 (1H, d, J = 2.2 Hz, aromatic H), 6.76 7.68 (7H, m, aromatic H).

2-[4-(3-{[2-[3,4-Bis(methoxyoxymethoxy)phenyl]-5-hydroxy-7-(methoxymethoxy)-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl]malonamide (16)

A 28% ammonia solution (1 mL) and 1*N* aqueous sodium hydroxide (2 mL) was added to a solution of compound **13** (106 mg, 0.148 mmol) in a mixture of MeOH (5 mL) and THF (5 mL). The mixture was stirred for 5 h at r. t., and then the solvent was removed under vacuum. After evaporation of organic solvent, water was added to the residual solution, and the mixture was acidified with 1*N* hydrochloric acid. EtOAc was added to the residue. The

mixture was washed water and brine, dried over $MgSO_4$, and evaporated *in vacuo* to give yellow oil (99 mg, 92.8 %): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 2.29 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.12 (2H, d, *J* = 7.5 Hz, benzylic H), 3.18 (3H, s, $OCH_2OC\underline{H}_3$), 3.48 (6H, s, $OCH_2OC\underline{H}_3$), 3.62 (1H, t, *J* = 7.4 Hz, $COC\underline{H}CO$), 4.07 4.25 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 5.10 (2H, s, $OC\underline{H}_2OCH_3$), 5.21 (2H, s, $OC\underline{H}_2OCH_3$), 5.23 (2H, s, $OC\underline{H}_2OCH_3$), 6.45 (1H, d, *J* = 2.2 Hz, aromatic H), 6.60 (1H, d, *J* = 2.2 Hz, aromatic H), 6.76 7.63 (7H, m, aromatic H).

Dimethyl 2-{4-[3-({7-(benzyloxy)-2-[3,4-bis(benzyloxy) phenyl]-5-hydroxy-4-oxo-4*H*-chromen-3-yl}oxy) propoxy]benzyl}-2-methylmalonate (17)

Compound **12** (120 mg, 0.136 mmol) was added to a suspension of NaH (13 mg, 0.326 mmol) in dry DMF (4 mL) at 0 °C. When hydrogen evolution ceased, iodomethane (0.02 mL, 0.2 mmol) was added, and the mixture was stirred at room temperature for 2.5 h. then the solution was poured into ice water and extracted with EtOAc. The combined extracts were washed water and brine, dried over $MgSO_4$, and concentrated to give a pale yellow solid (89 mg, 75.8%): mp 155.2-158.3 °C; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.32 (3H, s, $CC\underline{H}_3$), 2.18 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.15 (2H, s, benzylic H), 3.70 (6H, s, $C\underline{H}_3COCHCOC\underline{H}_3$), 3.95-4.16 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 5.08 (2H, s, benzylic H), 5.12 (2H, s, benzylic H), 5.16 (2H, s, benzylic H), 6.72-8.72 (9H, m, aromatic H); IR neat (cm^{-1}) 3448 (OH), 3100 (aromatic CH), 2941 (aliphatic CH), 1734 (C=O).

Dimethyl 2-[4-(3-{[2-[3,4-bis(methoxymethoxy)phenyl]-5-hydroxy-7-(methoxymethoxy)-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl]-2-methylmalo-nate (18)

Compound **13** (97 mg, 0.136 mmol) was added to a suspension of NaH (13 mg, 0.326 mmol) in dry DMF (4 mL) at 0 °C. When hydrogen evolution ceased, iodomethane (0.02 mL, 0.2 mmol) was added, and the mixture was stirred at room temperature for 2.5 h. then the solution was poured into ice water and extracted with EtOAc. The combined extracts were washed water and brine, dried over $MgSO_4$, and concentrated to give yellow oil (77 mg, 78%): ^{1}H-NMR (80 MHz, $CDCl_3$) δ 1.32 (3H, s, $CC\underline{H}_3$), 2.31 (2H, Q, *J* = 6 Hz, $CH_2C\underline{H}_2CH_2$), 3.15 (2H, s, benzylic H), 3.23 (3H, s, $OCH_2OC\underline{H}_3$), 3.49 (3H, s, $OCH_2OC\underline{H}_3$), 3.50 (3H, s, $OCH_2OC\underline{H}_3$), 3.71 (6H, s, $C\underline{H}_3COCHCOC\underline{H}_3$), 4.09-4.36 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$), 5.51 (2H, s, $OC\underline{H}_2CH_3$), 5.55 (2H, s, $OC\underline{H}_2CH_3$), 5.56 (2H, s, $OC\underline{H}_2CH_3$), 6.72-8.72 (9H, m, aromatic H); IR neat (cm^{-1}) 3448 (OH), 2924 (aliphatic CH), 1734 (C=O); IR neat (cm^{-1}) 3448 (OH), 3100 (aromatic CH), 2934 (aliphatic CH), 1653 (C=O).

Biology

Plasmids

The mammalian expression vectors of mouse PPARγ (pCDM8-mPPARγ), mouse RXRa (pcDNA3.1-mRXRa), and pcDNA3.1-lacZ were prepared. For PPRE-driven transcriptional activity assay, pPPRE(x3)-tk-luc (5'-GTC GAC AGG GGA CCA GGA CAA GGT CAC GTT CGG GGA GTC GAC-3', X3) reporter vector was used.

Cell culture

The CV1 (mouse kidney fibroblast) cells were cultured in 96 well plate in DMEM supplemented with 10% FBS, 100 mg/mL penicillin, and 100 mg/mL streptomycin in 95% O_2/5% CO_2, at 37°C.

Transfections

The CV1 cells were plated in 96 well plates at 1.2×10^4 cells/well and cultured until 70-80% confluency for 16 h. The cells were transiently transfected with pCDM8-mPPARγ, pcDNA3.1-mRXRa, pPPRE(x3)-tk-luc and pcDNA3.1-lacZ by liposomal delivery using GenePORTER2 transfection kit (GTS). After 16 h incubation, the cells were washed and changed to fresh complete medium. The cells were treated with the indicated chemicals (the ligand candidates) at a final concentration of 10 mM. After 24 h treatment, the cells were harvested in luciferase lysate buffer and cellular luciferase activity was determined using luciferase assay kit (Promega). The results were normalized to the β-galactosidase activity to correct the transfection efficiencies.

RESULTS AND DISCUSSION

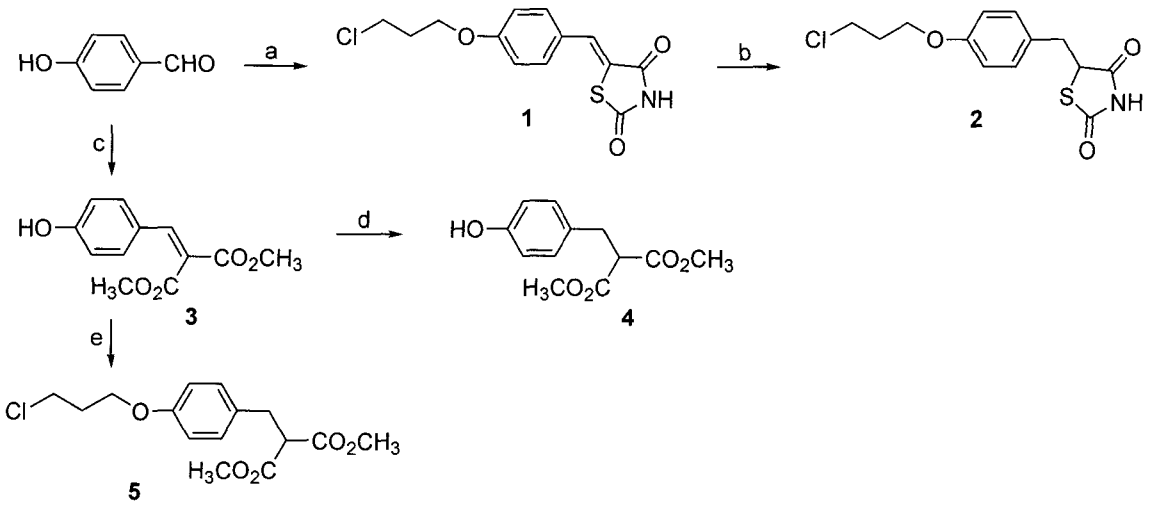
Propyl group was chosen as a linker between 5-(4'-hydroxybenzyl)thiazolidine-2,4-dione and quercetin. Accordingly 5-[4'-3-(chloropropyl)oxybenzylidene]thiazolidine-2,4-dione (**1**) was prepared from [4'-(3-chloropropyl)oxy] benzaldehyde, obtained from 4-hydoxybenzaldehyde and 1-bromo-3-chloropropane in DMF containing K_2CO_3 at 40 °C, and thiazolidine-2,4-dione in refluxing toluene in the presence of piperidinium acetate as a catalyst. The reduction of benzylidene portion in **1** was carried out using $NaBH_4$, $CoCl_2$, and 2,2'-dipyridyl (Satyanarayana *et al.*, 1984; Clark *et al.*, 1991) to afford 5-[4'-(3-chloropropyl) oxybenzyl]thiazolidine-2,4-dione (**2**). Dimethyl malonate instead of thiazolidine-2,4-dione ring containing compounds **4** and **5** were prepared following a similar procedure as above. Knoevenagel condensation between 4-hydroxybenzaldehyde and dimethyl malonate gave dimethyl 2-(4'-hydroxybenzylidene)malonate (**3**) and catalytic hydrogenation of **3** with 5% palladium on carbon gave dimethyl 2-(4'-hydroxybenzyl)malonate (**4**). While alkylation of compound **3** with 1-bromo-3-chloropropane in DMF containing

K_2CO_3 at 40°C for 2 h gave dimethyl 2-[4'-(3-chloropropyl) oxybenzylidene]malonate that underwent catalytic hydrogenation (5% Pd/C) to provide dimethyl 2-[4-(3-chloropropyl) oxybenzyl]malonate (**5**) (Scheme 1).

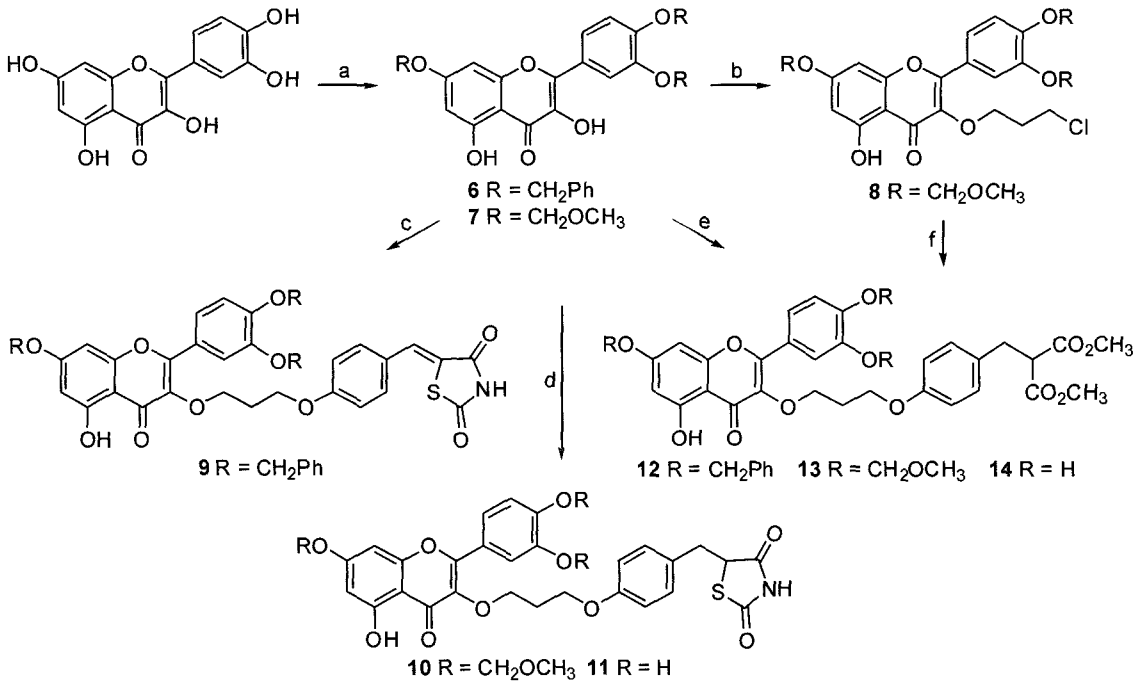
Quercetin has four phenolic and one non-phenolic hydroxyl group and the non-phenolic hydroxyl group was utilized to connect to 5-(4'-hydroxybenzyl)thiazolidine-2,4-dione moiety through the linker. Protection of the phenolic hydroxyl groups with excess benzyl bromide in the presence of K_2CO_3 in DMF provided 3',4',7-tribenzylated quercetin (**6**). The tribenzylated quercetin (**6**) was alkylated with **1** in the presence of KH, and NaI to yield 3',4',7-tribenzyl-3-*O*-[3-[4'-(thiazolidine-2,4-dion-5-yl)methylene-phenyloxy]propyl]quercetin (**9**). The compound **9** was then treated in the presence of 5% Pd/C as a catalyst in 1,4-dioxane under hydrogen atmosphere (balloon) expecting to debenzylate as well as to reduce the benzylidene double bond but the hydrogenation reaction gave a mixture of products. Methoxymethyl protecting group was chosen instead of benzyl group to protect the phenolic hydroxyl groups since it requires different deprotection methods. 3',4',7-Trimethoxymethyl-3-*O*-[3-[4'-(thiazolidine-2,4-dione-5-yl)methylphenloxy]propyl] quercetin (**10**) was synthesized by coupling 3',4',7-trimethoxymethylquercetin (**7**), prepared from quercetin and excess chloromethyl methyl ether, with **2** in the presence of KH and NaI. The three phenol protecting groups were then cleaved by treating **10** in methanol at refluxing temperature in the presence of trace amount of concentrated HCl to afford 3-*O*-[3-[4'-(thiazolidine-2,4-dione-5-yl)methylphenyloxy]propyl] quercetin (**11**). A coupling reaction of **6** with **5** in DMF afforded **12**. 3-*O*-(3-Chloropropyl)-3',4',7-trimethoxymethyl-quercetin (**8**), prepared from **7** and 1-bromo-3-chloropropane in the presence of KH and NaI, reacted with **4** to yield **13**. The methoxymethyl protecting group of **13** was removed with a trace amount of concentrated HCl in methanol to give dimethyl 2-[4-(3-{[2-(3,4-dihydroxyphenyl)-5,7-hydroxy-4-oxo-4*H*-chromen-3-yl]oxy}propoxy)benzyl] malonate (**14**) (Scheme 2).

Hydrolysis of **13** with more than 5 equiv. of 2*N* lithium hydroxide provided malonic acid derivatives **15**. The diamide **16** was prepared from **13** in the presence of ammonium hydroxide. Methylation of **12** and **13** with iodomethane gave the a-methylmalonate analogs **17** and **18** respectively (Scheme 3).

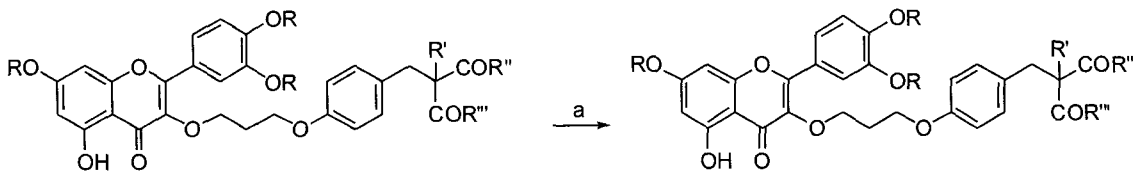
As shown in the Table I, compound **13** showed similar *in vitro* agonistic activity for PPARγ as troglitazone and this might mean that the thiazolidinedione and the vitamin E portion of troglitazone could be replaced with dimethyl malonate and trimethoxymethylated quercetin respectively. Compound without methoxymethyl groups, such as compound **14**, displayed lower activity. This may indicate that the binding site is rather lipophilic in the case of dimethyl malonate containing compounds **12**, **13**, and **14**. But further increase in lipophilicity did not improve agonistic activity. Compound **12**, which has tribenzylated quercetin moiety, displayed even lower activity than compound **14**. Benzyl groups in compound **12** may be too bulky or lipophilic for the receptor. Complete hydrolysis of the dimethyl malonate ester of **13** provided the malonic acid derivative, **15**, which had no PPARγ agonistic activity. This trend of decreasing activity by gradual hydrolysis of dimethyl malonate to malonic acid has been observed previously (Shinkai *et al.*, 1998). Conversion of the



Scheme 1. Reagents: (a) (i) 1-Bromo-3-chloropropane, K_2CO_3, DMF, 40°C, 24 h, 78%. (ii) Thiazolidine-2,4-dione, piperidinium acetate, toluene, Dean-Stark, reflux, 5 h, 78%. (b) $NaBH_4$, $CoCl_2$, 2,2-dipyridyl, r.t., 18 h, 84%. (c) Dimethyl malonate, piperidinium acetate, toluene, Dean-Stark, reflux, 5 h, 87%. (d) H_2 (balloon), 5% Pd/C, MeOH : 1,4-dioxane = 1 : 5, 99%. (e) (i) 1-Bromo-3-chloropropane, K_2CO_3, DMF, 40°C, 2 h, 52%. (ii) H_2 (balloon), 5% Pd/C, MeOH : 1,4-dioxane = 1 : 5, 99%.



Scheme 2. Reagents: (a) Benzyl bromide, K_2CO_3, DMF, r.t., 16 h, 46% for **6**.; Chloromethyl methyl ether, NaH, DMF, r.t., 40 min, 26% for **7**. (b) 1-Bromo-3-chloropropane, KH, DMF, NaI, r.t., 1 h, 79%. (c) **1**, KH, NaI, DMF, 50-60°C, 2 h, 37%. (d) (i) **2**, KH, NaI, DMF, 80-90°C, 5 h, 36%. (ii) *conc.* HCl, MeOH, reflux, 1 h, 94%. (e) **5**, KH, NaI, DMF, 80°C, 3 h, 27% for **12**. (f) (i) **4**, NaH, NaI, DMF, 100°C, 3 h, 31%. (ii) conc. HCl, MeOH, reflux, 1 h, 94%.



Scheme 3. Reagents: (a) 5.2eq of 2*N* LiOH, THF: MeOH= 1:2, reflux, 20 h, for **15** (93%); 28% Ammonium hydroxide, 1*N* NaOH, THF: MeOH= 1:1, r.t., 5 h, for **16** (96%); CH_3I, NaH, DMF, r.t., 2.5 h, for **17** (78%) and **18** (76%).

Table I. Effect of compounds on CV1 cells transfected with pPPRE-luc, RXR and PPARγ

Compound	% control[a]	Compound	% control[a]
9	76	**15**	15
10	61	**16**	24
11	88	**17**	51
12	69	**18**	37
13	94	Troglitazone	100
14	79	Rosiglitazone	90

[a]The data were mean±S.D of triplicate experiment.

malonic acid to the amide, from compound **15** to compound **16**, did not improve the activity. Methylation at the alpha carbon of the malonate (compounds **17** and **18**) decreased activity compared to the parent compounds (compounds **12** and **13** respectively).

Thiazolidinedione derivatives with substituted quercetin moiety, such as **9**, **10**, and **11** generally showed good agonistic activity. Compound **11**, which has non-protected quercetin unit, was the most active in this series of compounds while methoxymethylated quercetin derivatives (compound **10**) showed lower activity unlike the malonate derivatives (*cf.* compounds **13** and **14**).

CONCLUSION

Quercetin derivatives were synthesized and tested for

their PPARγ agonistic activity. Substituted quercetin with malonate (compound **13**) showed better activity than quercetin with thiazoldinedione (compound **11**). In the case of thiazoldinedione, un-substituted quercetin derivatives displayed better activity.

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