HETEROCYCLES, Vol. 71, No. 10, 2007, pp. 2131 - 2154. © The Japan Institute of Heterocyclic Chemistry
Received, 14th April, 2007, Accepted, 26th June, 2007, Published online, 29th June 2007. COM-07-11095

# DESIGN, SYNTHESIS, AND EVALUATION OF TETRAHYDROQUINOLINE-LINKED THIAZOLIDINEDIONE DERIVATIVES AS PPARγ SELECTIVE ACTIVATORS

**HyeSung Kim, HyoJin Gim, Mihi Yang, Jae-Ha Ryu, and Raok Jeon***

College of Pharmacy, Sookmyung Women's University, 52 Hyochangwon-Gil, Yongsan-Ku, Seoul 140-742, Korea

**Abstract** – A series of tetrahydroquinoline-linked thiazolidinediones was designed and synthesized and their peroxisome proliferator activated receptor-γ (PPARγ) agonistic activities were evaluated. A number of analogs were revealed to have significant PPARγ agonistic activity. Among these compounds, compound **1h** possessing *N*-heptyl moiety was found to be the most active in PPARγ transactivation assay. Molecular modeling suggested that the heptyl group of **1h** appropriately interacts with hydrophobic amino acid residues in the active site of PPARγ.

## INTRODUCTION

Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM), is a chronic and multifactorial disease characterized by insulin resistance in the liver and peripheral tissues[1] and impaired insulin secretion from pancreatic β-cells.[2] Hyperglycemia in type 2 diabetes leads to a gradual progression of complications, including neuropathy, nephropathy, retinopathy, arteriosclerosis, and coronary artery disease.[3-5] Primary therapy for type 2 diabetes is caloric restriction and aerobic exercise

which enhances tissue responsiveness to insulin.[6] However, few patients are successful in a control of blood glucose level. The most widely used oral antihyperglycemic agents are sulfonylureas which increase insulin secretion from pancreatic β-cells. A major drawback of this therapy is the adverse effects of severe hypoglycemia and weight gain.[7]

Thus, insulin sensitivity enhancer represents an attractive approach to the treatment of type 2 diabetes. Clofibrate is the first such compound found to improve insulin resistance.[8,9] It was followed by the discovery of thiazolidinediones (TZD),[10] which are a class of oral insulin-senstizing agents that improve glucose utilization without stimulating insulin secretion. Although the precise mechanism of the action of TZD remains unknown, a number of reports suggest that TZDs are high-affinity ligands of peroxisome proliferator activated receptor-γ (PPARγ).[11-14] The PPARs were cloned a decade ago as orphan members of the superfamily of nuclear transcription factors that govern lipid and glucose homeostasis playing a central role in cardiovascular diseases, obesity, and diabetes. The PPAR subfamily comprises three subtypes (PPARα, PPARβ/δ, and PPARγ) that exhibit different tissue distribution and physiological functions.[15-17] PPARγ is selectively expressed in adipocytes and shown to induce adipocyte differentiation and has been implicated as the primary receptor modulating the antidiabetic activity through insulin sensitization.[13,18] Therefore, PPARγ is a legitimate molecular target for the development of antidiabetic agents. TZDs have proven to be high-affinity ligands for PPARγ. To date, a large number of compounds containing TZD moiety have been synthesized to produce new antidiabetic agents. Among them, troglitazone[19] was launched first in the market, but had been withdrawn due to liver toxicity. Nowadays, rosiglitazone[20] and pioglitazone[21,22] the second and third TZDs marketed are clinically used. However, even these drugs sometimes have been reported to be associated with liver, cardiovascular, hematological toxicities and body weight gain in animals. Therefore, further improvement of the TZD class of antidiabetic agents in terms of biological activities or side effects is of great interest for drug discovery efforts worldwide.

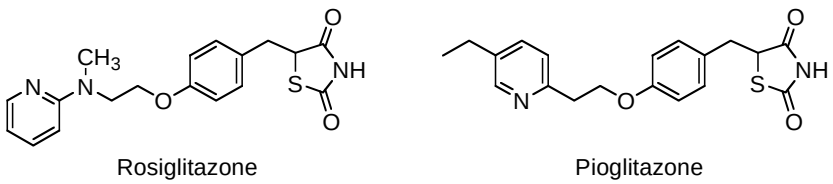



**Figure 1.** Structures of thiazolidinedione class of antidiabetic drugs

In this paper we describe the design, synthesis, and evaluation of novel tetrahydroquinoline-linked TZD derivatives as selective PPARγ activators. Conformationally constrained 1,2,3,4-tetrahydroquinoline-containing TZDs, which could make more potent agonists or partial agonists for PPARγ, were based on

the structure of rosiglitazone as a lead compound. Rosiglitazone, like most of PPARγ activators, can be divided into three key parts: (A) the acidic head group, (B) the linker group, and (C) the lipophilic tail group. We modified the lipophilic tail of rosiglitazone into a series of tetrahydroquinolines, in which the nitrogen on the spacer of rosiglitazone is included (Figure 2). We also expected that the introduction of an additional hydrophobic group into the lipophilic tail may increase the affinity for PPARγ. Therefore, alkyl groups of various lengths were introduced on the nitrogen of tetrahydroquinoline ring. Here, we report synthesis, SAR study and in vitro evaluation of a new series of tetrahydroquinoline-TZDs.

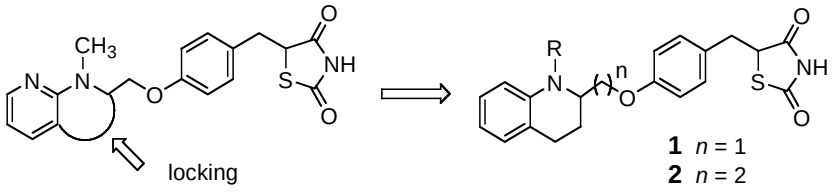
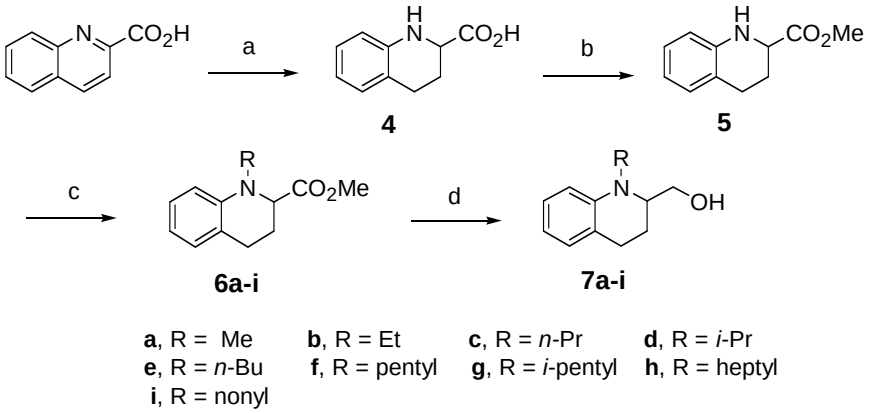



**Figure 2.** Structures of the target molecules derived from rosiglitazone.

## RESULTS AND DISCUSSION

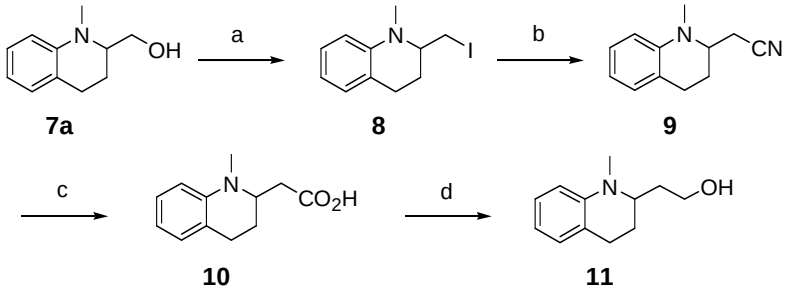
The synthesis of all compounds started with the preparation of *N*-alkylsubstituted tetrahydroquinoline **7a-i** (Scheme 1). Hydrogenation of the commercially available quinaldic acid in MeOH over platinum oxide under normal pressure of hydrogen followed by methylation with thionyl chloride in MeOH provided methyl tetrahydroquinoline-2-carboxylate (**5**).[23] Alkyl groups of various lengths were introduced at the tetrahydroquinoline ring by either *N*-alkylation or reductive amination.[24] Direct alkylation of compound **5** with suitable alkyl iodides was employed to give compounds **6a**,**d**,**e** while compounds **6b**,**c**,**f-i** were obtained by treating compound **5** with appropriate aldehydes and sodium cyanoborohydride. *N*-alkylated methyl esters **6a-i** were reduced to the corresponding alcohols **7a-i** with lithium aluminum hydride (LAH). 2-[1-Methyltetrahydroquinolin]ethanol (**11**), which contains one carbon-extended spacer unit, was prepared as outlined in Scheme 2. Alcohol **7a** was converted to intermediary crude iodide **8** by treatment of $I_2$/$PPh_3$/imidazole. Treatment of **8** with excess sodium cyanide followed by hydrolysis of the resulting cyanide **9** in refluxing hydrochloric acid provided acid **10**. Reduction of acid **10** with LAH afforded the desired alcohol **11**.[25]

The target compounds **1a-i** and **2** were prepared *via* Mitsunobu reaction of **7a-i** or **11** with **12** which was prepared from 4-hydroxybenzaldehyde by modification of the reported method,[26] followed by removal of



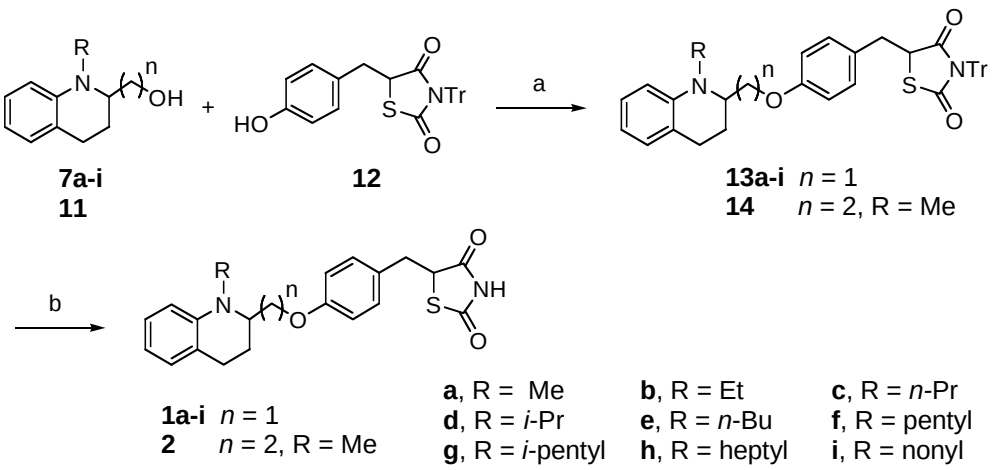

**Scheme 1.** Preparation of (*N*-alkyl-tetrahydroquinolin-2-yl)methanols

Reaction conditions : (a) $H_2$, $PtO_2$, MeOH, 3h; (b) $SOCl_2$, MeOH, rt, 12h; (c) base (NaH, $Cs_2CO_3$, TEA), RI, DMF or aldehyde, $NaBH_3CN$, AcOH, MeCN; (d) LAH, $Et_2O$, rt, 3h.




**Scheme 2.** Preparation of 2-(1-methyltetrahydroquinolin)ethanol

Reaction conditions : (a) I, $PPh_3$, imidazole, toluene/MeCN(5/1), 0℃, 10 min; (b) NaCN, DMF, 100℃, 24h; (c) 12N HCl, reflux, 5h; (d) LAH, $Et_2O$, rt, 3h.




**Scheme 3.** Synthesis of tetrahydroquinoline-*p*-thiazolidinediones

Reaction conditions ; (a) ADDP, $PBu_3$, THF/toluene, rt, 5h; (b) TFA, rt, 2h.

The agonist activities of the prepared compounds were measured in the cell-based transactivation assay (TA) using PPAR-GAL4 chimeric receptors and a reporter gene containing a GAL4 response element.

**Table 1.** Activity of the tested compounds in cell-based transactivation assay

| compound | R | Transactivation RR%[a] | |
|---|---|---|---|
| | | mPPARα | mPPARγ |
| **1a** | Me | NA | 10.7 |
| **1b** | Et | NA | 16.7 |
| **1c** | *n*-Pr | NA | 38.2 |
| **1d** | *i*-Pr | NA | 15.5 |
| **1e** | *n*-Bu | NA | 23.1 |
| **1f** | *n*-pentyl | NA | 29.5 |
| **1g** | *i*-pentyl | NA | 36.6 |
| **1h** | *n*-heptyl | NA | 57.5 |
| **1i** | *n*-nonyl | NA | 18.3 |
| **2** | Me | NA | 2.3 |
| GW409544 | | 100 | 100 |
| Tesaglitazar | | NA | 48.0 |
| Rosiglitazone | | NA | 69.3 |

[a]Prepared compounds (2 μM) were assayed for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CV-1 cells. [b]Data are represented as relative response (%), which is ((test drug-negative control)/(positive control-negative control)) x 100. GW409544 (30 μM for PPARα transactivation assay; 1 μM for PPARγ) and 0.1% DMSO were used as positive and negative controls, respectively. Tesaglitazar and rosiglitazone (2 μM) were assayed for the purpose of comparison. [c]NA: no activity.

Effect of the substitution with alkyl groups of various lengths at the 1-position of 1,2,3,4-tetrahydroquinoline ring is shown in Table 1. Most of the prepared TZD derivatives **1** revealed agonistic activity for PPARγ and not PPARα. It was found that the activity of compounds **1** was highly consisted with chain length, and the most active compound was heptyl **1h**, suggesting that introduction of extra hydrophobic group may increase the contact with the receptor in the hydrophobic subpocket of the active site of PPARγ. Further lengthening lowered the activity for PPARγ (compound **1i**). Importance of the linker size was also examined. The chain length between the tetrahydroquinoline ring and the oxygen

atom adjacent to the benzene ring had significant influence on the activity. When the chain was lengthened to that of ethylene ($n$ = 2), a dramatic loss of activity was observed (compound **2**). On the basis of this result, a methylene unit was selected as the best linker. This result suggests that optimal chain length is critical for controlling the conformation of the molecule and hence the way it binds to and activates PPARγ.

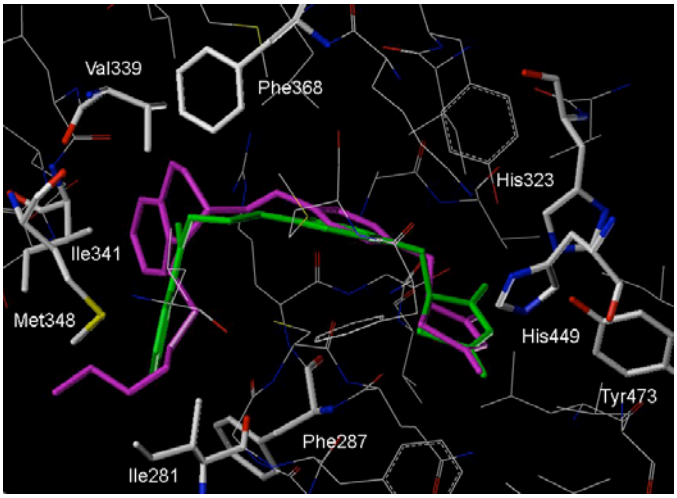



**Figure 3.** Comparison of the docked **1h** (magenta) with crystallographic rosiglitazone (green) complexed in the binding site of PPARγ.

We examined the mode of binding of compound **1h** to PPARγ. Compound **1h** was docked to the ligand binding domain (LBD) of PPARγ as identified in the crystal structure of PPARγ-rosiglitazone complex using Surflex-Dock module available in Sybyl 7.2.3. Reported crystal structures have shown that two carbonyl groups of thiazolidinedione are coordinated by two histidines (His323, His449) and a tyrosine (Tyr473) in the AF2 helix. The heptyl moiety of compound **1h** occupies the hydrophobic pocket formed by residues Ile281, Val339, and Met348, while the thiazolidinedione moiety is positioned in precisely the same manner as is that of rosiglitazone in the crystal structure. In addition, the tetrahydroquinoline of compound **1h** occupies another hydrophobic pocket formed by Phe287, Ile341, and Leu333 (Figure 3).

In summary, we designed and synthesized a new series of *N*-alkyltetrahydroquinoline-containing TZDs as selective PPARγ agonists. Among them, **1h** was found to be the most active in the transactivation assay. Molecular modeling suggested that the **1h** remains key hydrophilic interactions in the active site of PPARγ while heptyl group on tetrahydroquinoline ring appropriately interacts with hydrophobic amino acid residues. Compound **1h** and related analogs could represent promising candidates for the development of drugs against type 2 diabetes. Further detailed studies on these compounds are under way.

## EXPERIMENTAL

**Materials** Most of the reagents and solvents were purchased from Aldrich chemicals and used without purification, with the following exceptions. Ethyl ether ($Et_2O$) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Acetonitrile, methylene chloride, benzene, toluene, triethylamine, pyridine, dimethyl formamide, and diisopropylamine were distilled from calcium hydride under nitrogen atmosphere. Flash column chromatography (FCC) was performed using silica gel 60 (230-400 mesh, Merck) with the indicated solvents. Thin-layer chromatography (TLC) was performed using Kieselgel 60 $F_{254}$ plates (Merck). IR spectra were recorded on a JASCO FT/IR 430 spectrophotometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a Varian YH 400 spectrometer as solutions in $CDCl_3$, MeOH-$d_4$ or DMSO-$d_6$. Chemical shifts are expressed in parts per million (ppm, δ) downfield from an internal standard, tetramethylsilane. Microanalyses were carried out with Euro EA 3000 elemental analyzer.

### 1,2,3,4-Tetrahydroquinoline-2-carboxylic acid (4)

A solution of quinaldic acid (2 g, 11.55 mmol) in MeOH (40 mL) was reacted with hydrogen over $PtO_2$ (60 mg, 0.26 mmol) under atmospheric pressure at rt for 3 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated under reduced pressure to afford the title compound **4** as yellow oil, which was used for the next step without further purification; $R_f$ = 0.15 (EtOAc), IR (neat, $cm^{-1}$) 3393, 2927, 1719, 1606, 1495, 1221, 749; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.14 (br s, 1H), 7.01 (dt, 1H, *J* = 8.1,1.6 Hz), 6.97 (dd, 1H, *J* = 7.5, 0.9 Hz), 6.69 (dt, 1H, *J* =7.4, 1.1 Hz), 6.61 (dd, 1H, *J* = 8.0, 0.8 Hz), 4.09 (dd, 1H, *J* = 5.1, 3.7 Hz), 2.79 (m, 2H), 2.25 (m, 1H), 2.10 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 178.4, 142.2, 129.2, 127.1, 121.0, 118.3, 114.9, 53.8, 25.4, 24.3. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.43; H, 6.32; N, 7.81.

### 1,2,3,4-Tetrahydroquinoline-2-carboxylic acid methyl ester (5)

To a solution of carboxylic acid **4** (2.08 g, 11.74 mmol) in MeOH (30 mL) was added dropwise $SOCl_2$ (1.29 mL, 17.68 mmol) at 0 ℃. And the mixture was stirred overnight at rt and solvent was concentrated in vacuo. The residue was dispersed between EtOAc and saturated aqueous $NaHCO_3$ and the organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 9:1) to afford 1.7 g (8.89 mmol, 77 %) of title compound as a pale yellow powder; $R_f$ = 0.28 (*n*-hexane/EtOAc = 6:1); IR (neat, $cm^{-1}$) 3413, 3058, 3025, 1684, 1299; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.30-7.14 (m, 15H), 7.05 (m, 2H), 6.73 (m, 2H), 4.34 (dd, 1H, *J* = 8.8, 4.0 Hz), 3.37 (dd, 1H, *J* = 14.4, 4.0 Hz), 3.03 (dd, 1H,

*J* = 14.4, 8.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ174.0, 143.2, 129.3, 127.3, 120.7, 117.9, 114.8, 54.1, 52.6, 26.0, 24.9. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.22; H, 6.78; N, 7.62.

**1-Methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6a)**

To a solution of methyl ester **5** (219.9 mg, 1.15 mmol) in DMF (5 mL) was added NaH (60 % dispersion in mineral oil, 138 mg, 3.45 mmol) with stirring at 0 ℃ under nitrogen. The mixture was stirred for 30 min, and MeI (excess) was added at 0 ℃. The mixture was stirred at rt for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 9:1) to afford 223.08 mg (1.09 mmol, 95 %) of the title compound as a pale yellow oil; $R_f$ = 0.47 (*n*-hexane/EtOAc = 6:1); IR (neat, cm$^{-1}$) 2948, 1746, 1500, 1213, 1163, 746; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, 1H, *J* = 7.6 Hz), 6.96 (d, 1H, *J*= 7.3 Hz), 6.65 (t, 1H, *J* = 7.2 Hz), 6.59 (d, 1H, *J* = 8.1Hz), 4.35 (s, 1H), 4.05 (dd, 1H, *J* = 8.6, 2.9 Hz), 3.78 (s, 3H), 2.78 (m, 2H), 2.29 (m, 1H), 2.10 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.2, 129.3, 127.3, 120.7, 117.9, 114.8, 54.1, 52.6, 26.0, 24.9. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.01; H, 7.15; N, 6.99.

**1-Ethyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6b)**

A mixture of methyl ester **5** (207.10 mg, 1.08 mmol) and $NaBH_3CN$ (204.17 mg, 3.25 mmol) in MeCN (3 mL) was added acetaldehyde (181.62 μL, 3.25 mmol) and stirred at rt for 10 min. To the mixture was added AcOH (2 mL) and stirred at rt for 30 min. And the reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 6:1) to afford 221.50 mg (93 %) of the title compound as a pale yellow oil; $R_f$ = 0.48 (*n*-hexane/EtOAc = 6:1); IR (neat, cm$^{-1}$) 2970, 1748, 1602, 1500, 1196, 1161, 744; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, 1H, *J* = 7.5 Hz), 6.94 (d, 1H, *J* = 7.1 Hz), 6.65 (d, 1H, *J* = 8.1 Hz), 6.60 (t, 1H, *J* = 7.1Hz), 4.12 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.71 (s, 3H), 3.53 (m, 1H), 3.18 (m, 1H), 2.67 (m, 2H), 2.29 (m, 1H), 2.01(m, 1H), 1.17 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.7, 129.2, 127.6, 121.8, 116.2, 110.6, 60.3, 52.3, 25.3, 25.0, 12.3. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.52; H, 7.73; N, 6.13.

**1-Propyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6c)**

Reaction of methyl ester **5** (420.30 mg, 2.20 mmol) with propionaldehyde (479.89 μL, 6.59 mmol) in MeCN (4 mL), as described above, gave **6c** (476.8 mg , 2.04 mmol, 93 %) as a pale yellow oil; $R_f$ = 0.50

(*n*-hexane/EtOAc = 6:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.3 Hz), 6.93 (d, 1H, *J* = 7.0 Hz), 6.60 (d, 1H, *J* = 8.3 Hz), 6.58 (t, 1H, *J* = 7.1 Hz), 4.12 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.70 (s, 3H), 3.46 (m, 1H), 2.97 (m, 1H), 2.66 (m, 2H), 2.27 (m, 1H), 2.05 (m, 1H), 1.63 (m, 2H), 0.92 (t, 3H, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.2, 143.6, 128.9, 127.2, 121.2, 115.8, 110.4, 60.9, 52.8, 52.0, 24.8, 24.4, 20.1, 11.4. Anal. Calcd for $C_{14}H_{19}NO_2$ : C, 72.07; H, 8.21; N, 6.00. Found: C, 72.43; H, 8.51; N, 6.13.

**1-Isopropyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6d)**

To a solution of methyl ester **5** (680 mg, 3.56 mmol) in DMF (5 mL) was added TEA and stirred at rt for 30 min. Then iodopropane (1.06 mL, 10.67 mmol) was added to the mixture and boiled under reflux for 3 days. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 9:1) to afford 520.31 mg (2.23 mmol, 63 %) of the title compound as a pale yellow oil; $R_f$ = 0.5 (*n*-hexane/EtOAc = 6:1); IR(neat, $cm^{-1}$) 2966, 1751, 1727, 1493, 1193, 1158, 743; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, 1H, *J* = 7.5 Hz), 6.96 (d, 1H, *J* = 7.1 Hz), 6.77 (d, 1H, *J* = 8.1 Hz), 6.60 (t, 1H, *J* = 7.1 Hz), 4.24 (dd, 1H, *J* = 4.8, 3.3 Hz), 4.20 (m, 1H), 3.69 (s, 3H), 2.66 (m, 2H), 2.26 (m, 1H), 1.86 (m, 1H), 1.19 (d, 3H, *J* = 6.6 Hz), 1.16 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 175.5, 143.8, 129.5, 127.5, 122.1, 116.0, 111.3, 53.6, 52.2, 47.9, 25.2, 24.9, 20.2, 10.4. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.38; H, 8.01; N, 6.43.

**1-Butyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6e)**

To a mixture of methyl ester **5** (575 mg, 3.01 mmol), $Cs_2CO_3$ (2.45g, 7.52 mmol) and DMAP (95.51 mg, 0.78 mmol) in DMF (6 mL) was added iodobutane (1.03 mL, 9.02 mmol) and stirred at 80 ℃ for 12 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 25:1) to afford 506.61 mg (2.05 mmol, 68 %) of the title compound as a pale yellow oil; $R_f$ = 0.53 (*n*-hexane/EtOAc = 6:1); IR (neat, $cm^{-1}$) 2953, 1748, 1730, 1500, 1193, 743; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.3 Hz), 6.93 (d, 1H, *J* = 7.0 Hz), 6.62 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.1 Hz), 4.10 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.69 (s, 3H), 3.49 (m, 1H), 3.01 (m, 1H), 2.66 (m, 2H), 2.28 (m, 1H), 2.04 (m, 1H), 1.59 (m, 2H), 1.36 (m, 2H), 0.94 (t, 3H, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.6, 128.8, 127.2, 121.2, 115.8, 110.3, 60.7, 52.0, 50.8, 29.0, 24.8, 24.4, 20.3, 13.9. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.56; H, 8.79; N, 5.45.

**1-Pentyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6f)**

Reaction of methyl ester **5** (601.90 mg, 3.15 mmol) with valeraldehyde (1.00 mL, 9.44 mmol) in MeCN (5 mL), as described above, gave **6f** (736.81 mg, 2.82 mmol, 95 %) as a pale yellow oil; $R_f$ = 0.24 (*n*-hexane/EtOAc = 25:1); IR (neat, $cm^{-1}$) 2952, 1748, 1731, 1500, 1210, 1193, 1162, 743; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.08 (t, 1H, *J* = 7.3 Hz), 6.93 (d, 1H, *J* = 7.0 Hz), 6.62 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.3 Hz), 4.11 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.70 (s, 3H), 3.48 (m, 1H), 3.51 (m, 1H), 2.66 (m, 2H), 2.28 (m, 1H), 2.04 (m, 1H), 1.59 (m, 2H), 1.34 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.2, 143.6, 128.9, 127.2, 121.2, 115.8, 110.3, 60.8, 52.0, 51.1, 29.3, 26.6, 24.9, 22.6, 14.1. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.34; H, 8.63; N, 5.54.

**1-Isopentyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6g)**

Reaction of methyl ester **5** (530.90 mg, 2.78 mmol) with isovaleraldehyde (837.4 mL, 8.33 mmol) in MeCN (5 mL), as described above, gave **6g** (614 mg , 2.35 mmol, 85 %) as a pale yellow oil; $R_f$ = 0.23 (*n*-hexane/EtOAc = 25:1); IR (neat, $cm^{-1}$) 2953, 1749, 1731, 1500, 1211, 1193, 1163, 743; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.3 Hz), 6.92 (d, 1H, *J* = 7.0 Hz), 6.81 (d, 1H, *J* = 8.2 Hz), 6.58 (dt, 1H, *J* = 7.3, 1.0 Hz), 4.09 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.69 (s, 3H), 3.49 (m, 1H), 3.04 (m, 1H), 2.65 (m, 2H), 2.27 (m, 1H), 2.01 (m, 1H), 1.59 (m, 1H), 1.49 (m, 2H), 0.96 (d, 3H, *J* = 6.6 Hz), 0.93 (d, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.1, 143.5, 128.8, 127.2, 121.2, 115.7, 110.2, 60.5, 51.9, 49.3, 35.4, 26.2, 24.8, 24.5, 22.8, 22.4. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.76; H, 8.48; N, 5.57.

**1-Heptyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6h)**

Reaction of methyl ester **5** (487 mg, 2.54 mmol) with heptaldehyde (1.07 mL, 7.64 mmol) in MeCN (4 mL), as described above, gave **6h** (612.11 mg, 2.12 mmol, 65 %) as a pale yellow oil; $R_f$ = 0.28 (*n*-hexane/EtOAc = 25:1); IR (neat, $cm^{-1}$) 2927, 1750, 1731, 1500, 1195, 1162, 742; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.06 (t, 1H, *J* = 7.3 Hz), 6.96 (d, 1H, *J* = 6.8 Hz), 6.61 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.3Hz), 4.11 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.69 (s, 3H), 3.48 (m, 1H), 3.00 (m, 1H), 2.66 (m, 1H), 2.28 (m, 1H), 1.65 (m, 2H), 1.29 (m, 8H), 0.88 (t, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.2, 143.6, 128.8, 127.2, 121.2, 115.8, 110.3, 60.7, 52.0, 51.1, 31.8, 29.2, 27.1, 26.9, 24.9, 24.5, 22.6, 14.0. Anal. Calcd for $C_{18}H_{27}NO_2$: C, 74.70; H, 9.40; N, 4.84. Found: C, 74.43; H, 9.61; N, 4.97.

**1-Nonyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid methyl ester (6i)**

Reaction of methyl ester **5** (580 mg, 3.03 mmol) with nonylaldehyde (1.56 mL, 9.09 mmol) in MeCN (5 mL), as described above, gave **6i** (774.60 mg, 2.44 mmol, 70 %) as a pale yellow oil; $R_f$ = 0.30 (*n*-

hexane/EtOAc = 25:1); IR (neat, $cm^{-1}$) 2925, 1750, 1731, 1500, 1194, 1162, 742; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.08 (t, 1H, *J* = 7.3 Hz), 6.93 (d, 1H, *J* = 6.8 Hz), 6.61 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.3Hz), 4.11 (dd, 1H, *J* = 4.8, 3.3 Hz), 3.70 (s, 3H), 3.48 (m, 1H), 3.00 (m, 1H), 2.66 (m, 2H), 2.28 (m, 1H), 2.03 (m, 1H), 1.59 (m, 2H), 1.28 (m, 12H), 0.88 (t, 3H, *J* = 7.0 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.2, 143.6, 128.9, 127.2, 121.2, 115.8, 110.3, 60.8, 52.0, 51.1, 31.8, 29.6, 29.2, 27.1, 26.9, 24.9, 24.5, 22.6, 14.0. Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.93; H, 9.65; N, 4.52.

**(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7a)**

To a solution of compound **6a** (193.2 mg, 0.94 mmol) in $Et_2O$ (3 mL) was added LAH (89.31 mg, 2.35 mmol) at 0 ℃ and stirred at rt for 3 h. The resulting mixture was quenched by addition of saturated ammonium chloride solution. And then mixture was extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 3:1) to afford 162 mg (0.91 mmol, 97 %) of the title compound as a pale yellow oil; $R_f$ = 0.21 (*n*-hexane/EtOAc = 3:1); IR (neat, $cm^{-1}$) 3366, 2931, 1601, 1499, 745; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.10 (dt, 1H, *J* = 7.6, 1.3 Hz), 6.98 (td, 1H, *J* = 7.1, 0.9 Hz), 6.63 (t, 2H, *J* = 7.2 Hz), 3.68 (m, 2H), 3.37 (m, 1H), 3.01 (s, 3H), 2.75 (m, 1H), 2.70 (m, 1H), 2.01 (m, 1H) 1.89 (m, 1H); $^{13}C$ NMR (100 M Hz, $CDCl_3$) δ 145.6, 128.8, 127.4, 122.7, 116.4, 111.6, 63.6, 60.3, 38.9, 24.5, 23.2. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.59; H, 8.11 N, 7.78.

**(1-Ethyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7b)**

Reaction of compound **6b** (207.9 mg, 0.95 mmol) with LAH (89.95 mg, 2.37 mmol) in $Et_2O$ (3 mL), as described above, gave **7b** (172.31 mg, 0.91 mmol, 95 %) as a pale yellow oil; $R_f$ = 0.21 (*n*-hexane/EtOAc = 3:1); IR (neat, $cm^{-1}$) 3368, 3066, 1601, 1498, 744; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.12 (t, 1H, *J* = 7.5 Hz), 7.02 (d, 1H, *J* = 7.1 Hz), 6.70 (d, 1H, *J* = 8.1 Hz), 6.64 (t, 1H, *J* = 7.1 Hz), 3.60 (m, 2H), 3.52 (m, 1H), 3.90 (m, 1H), 3.31 (m, 1H), 2.71 (m, 2H), 2.13 (m, 1H) 1.79 (m, 1H), 1.21 (t, 3H, *J* = 7.1 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 143.7, 128.9, 126.9, 122.1, 115.5, 114.4, 62.9, 60.3, 57.8, 45.0, 23.8, 22.3, 12.1. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.21; H, 8.54; N, 7.21.

**(1-Propyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7c)**

Reaction of compound **6c** (476.8 mg, 2.05 mmol) with LAH (194.70 mg, 5.13 mmol) in $Et_2O$ (4 mL), as described above, gave **7c** (397.32 mg, 1.94 mmol, 94 %) as a pale yellow oil; $R_f$ = 0.22 (*n*-hexane/EtOAc = 5:1); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.05 (t, 1H, *J* = 7.3 Hz), 6.97 (d, 1H, *J* = 7.0 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.1Hz), 3.54 (m, 2H), 3.40 (m, 2H), 3.14 (m, 1H), 2.74 (m, 1H), 2.66 (m, 1H),

2.04 (m, 1H) 1.81 (m, 1H), 1.64 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.2, 109.0, 127.0, 121.9, 115.6, 111.8, 63.0, 58.5, 53.2, 23.9, 22.2, 20.3, 11.3. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.43; H, 9.21; N, 6.97.

**(1-Isopropyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7d)**

Reaction of compound **6d** (155 mg, 0.66 mmol) with LAH (194.70 mg, 5.13 mmol) in $Et_2O$ (3 mL), as described above, gave **7d** (130 mg, 0.63 mmol, 95 %) as a pale yellow oil; $R_f$ = 0.44 (*n*-hexane/EtOAc = 3:1); IR (neat, cm$^{-1}$) 3364, 2965, 1600, 1492, 746; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.5 Hz), 6.98 (d, 1H, *J* = 7.1 Hz), 6.88 (d, 1H, *J* = 8.1 Hz), 6.66 (t, 1H, *J* = 7.1 Hz), 4.11 (m, 2H), 3.53 (m, 2H), 3.45 (m, 1H), 2.71 (m, 1H), 1.98 (m, 1H), 1.89 (m, 1H), 1.68 (m, 1H), 1.30 (d, 3H, *J* =6.6 Hz), 1.12 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.9, 127.1, 123.7, 117.3, 116.2, 62.9, 51.9, 50.6, 23.6, 22.1, 22.0, 19.8. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Found: C, 76.41; H, 9.12; N, 6.96.

**(1-Butyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7e)**

Reaction of compound **6e** (107.78 mg, 0.41 mmol) with LAH (39.13 mg, 1.03 mmol) in $Et_2O$ (2 mL), as described above, gave **7e** (81 mg, 0.37 mmol, 90 %) as a pale yellow oil; $R_f$ = 0.44 (*n*-hexane/EtOAc = 5:1); IR (neat, cm$^{-1}$) 3335, 2920, 1600, 1497, 743; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.3 Hz), 6.97 (d, 1H, *J* = 7.0 Hz), 6.64 (d, 1H, *J* = 8.2 Hz), 6.59 (dt, 1H, *J* = 7.1, 1.0 Hz), 3.60 (m, 2H), 3.45 (m, 2H), 3.19 (m, 1H), 2.77 (m,1H), 2.67 (m, 1H), 2.05 (m, 1H), 1.81 (m, 1H), 1.59 (m, 2H), 1.35 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.1, 129.0, 126.9, 121.9, 115.5, 111.6, 63.3, 58.8, 51.4, 29.6, 24.2, 22.6, 20.7, 14.3, 11.7. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.43; H, 9.59; N, 6.21.

**(1-Pentyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7f)**

Reaction of compound **6f** (493.3 mg, 1.89 mmol) with LAH (179.10 mg, 4.72 mmol) in $Et_2O$ (4 mL), as described above, gave **7f** (411.2 mg, 1.76 mmol, 94 %) as a pale yellow oil; $R_f$ = 0.268 (*n*-hexane/EtOAc = 5:1); IR (neat, cm$^{-1}$) 3365, 2928, 1601, 1497, 1037, 742; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, 1H, *J* = 7.3 Hz), 6.95 (d, 1H, *J* = 7.0 Hz), 6.61 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.3 Hz), 3.55 (m, 2H), 3.42 (m, 2H), 3.15 (m, 1H), 2.70 (m, 2H), 2.18 (s, 1H), 2.02 (m, 1H), 1.77 (m, 1H), 1.59 (m, 2H), 1.31 (m, 4H), 0.91 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.1, 129.1, 126.9, 121.9, 115.5, 111.7, 62.9, 58.4, 51.3, 29.2, 26.7, 23.8, 22.5, 22.2, 14.0. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.53; H, 9.67; N, 6.21.

**(1-Isopentyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7g)**

Reaction of compound **6g** (396.9 mg, 1.52 mmol) with LAH (144.16 mg, 3.80 mmol) in $Et_2O$ (4 mL), as described above, gave **7g** (332.5 mg, 1.42 mmol, 94 %) as a pale yellow oil; $R_f$ = 0.27 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3364, 2953, 1601, 1499, 1038, 742; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.06 (t, 1H, *J* = 7.3 Hz), 6.96 (d, 1H, *J* = 7.0 Hz), 6.62 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.3 Hz), 3.59 (m, 2H), 3.44 (m, 2H), 3.20 (m, 1H), 2.75 (m, 1H), 2.65 (m, 1H), 2.04 (m, 1H), 1.88 (s, 1H), 1.77 (m, 1H), 1.60 (m, 1H), 1.48 (m, 2H), 0.95 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.2, 129.1, 127.0, 122.2, 115.7, 111.8, 63.2, 58.3, 49.7, 35.7, 26.3, 24.0, 22.8, 22.5, 22.4. Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.19; H, 9.71; N, 6.24.

**(1-Heptyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7h)**

Reaction of compound **6h** (456 mg, 1.66 mmol) with LAH (157.35 mg, 4.15 mmol) in $Et_2O$ (5 mL), as described above, gave **7h** (412 mg, 1.58 mmol, 96 %) as a pale yellow oil; $R_f$ = 0.28 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3356, 2927, 1601, 1499, 1456, 742; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.06 (t, 1H, *J* = 7.3 Hz), 6.96 (d, 1H, *J* = 6.8 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.3 Hz), 3.59 (m, 2H), 3.42 (m, 2H), 3.17 (m, 1H), 2.76 (m,1H), 2.66 (m, 1H), 2.04 (m, 1H), 1.79 (m, 1H), 1.59 (m, 2H), 1.29 (m, 8H), 0.89 (t, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.2, 129.1, 127.0, 122.1, 155.7, 112.0, 63.2, 58.5, 51.5, 31.8, 29.2, 27.2, 27.1, 23.9, 22.6, 22.3, 14.0. Anal. Calcd for $C_{17}H_{27}NO$: C, 78.11; H, 10.41; N, 5.36. Found: C, 77.98; H, 10.32; N, 5.49.

**(1-Nonyl-1,2,3,4-tetrahydroquinolin-2-yl)methanol (7i)**

Reaction of compound **6i** (671 mg, 2.11 mmol) with LAH (200.53 mg, 5.28 mmol) in $Et_2O$ (5 mL), as described above, gave **7i** (593 mg, 2.05 mmol, 97 %) as a pale yellow oil; $R_f$ = 0.31 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3347, 2925, 1601, 1499, 1457, 742; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.04 (t, 1H, *J* = 7.3 Hz), 6.94 (d, 1H, *J* = 6.8 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 3.59 (m, 2H), 3.41 (m, 2H), 3.14 (m, 1H), 2.74 (m, 1H), 2.63 (m, 1H), 2.46 (br, 1H), 2.03 (m, 1H), 1.75 (m, 1H) 1.57 (m, 2H), 1.27 (m, 12H), 0.88 (t, 3H, *J* = 7.0 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 144.0, 129.0, 126.9, 121.8, 115.4, 111.5, 62.8, 58.4, 51.2, 31.7, 29.5, 29.4, 29.2, 27.1, 25.6, 23.8, 22.6, 22.1. Anal. Calcd for $C_{19}H_{31}NO$: C, 78.84; H, 10.79; N, 4.84. Found: C, 78.71; H, 10.94; N, 4.66.

**2-Iodomethyl-1-methyl-1,2,3,4-tetrahydroquinoline (8)**

A mixture of alcohol **7a** (563.5 mg, 3.18 mmol), triphenylphospine (2.09 g, 7.9483 mmol), imidazole (541.12 mg, 7.95 mmol) in toluene/MeCN (5:1, 5 mL) was added to a solution of iodine (1.61 g, 6.36 mmol) in toluene/MeCN (5:1, 2.2 mL). And the mixture was stirred at 0 ℃ for 30 min. The reaction

mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 40:1) to afford 552 mg (1.92 mmol, 60 %) of the title compound as a pale yellow oil; $R_f$ = 0.51 (*n*-hexane/EtOAc = 20:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.16 (dd, 1H, *J* = 8.04, 7.52 Hz), 7.06 (bd, 1H, *J* = 7.04 Hz), 6.71 (dd, 1H, *J* = 7.52, 7.04 Hz), 6.62 (d, 1H, *J* = 8.04 Hz), 3.58~3.65 (m, 1H), 3.39~3.43 (m, 1H), 3.10~3.15 (m, 1H), 3.05 (s, 3H), 2.73~2.80 (m, 2H), 2.38~2.46 (m, 1H), 1.91~2.02 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.1, 128.8, 127.3, 121.8, 116.3, 110.5, 59.9, 37.9, 23.8, 22.6, 7.6. Anal. Calcd for $C_{11}H_{14}IN$: C, 46.01; H, 4.91; N, 4.88. Found: C, 46.37; H, 4.58; N, 4.73.

**(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)acetonitrile (9)**

A mixture of compound **8** (512 mg, 1.78 mmol) and NaCN (349.56 mg, 7.13 mmol) in DMF (8 mL) was boiled under reflux for 4 h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent; *n*-hexane/EtOAc = 2:1) to afford 280 mg (1.68 mmol, 94 %) of the title compound as a pale yellow oil.; $R_f$ = 0.13 (*n*-hexane/EtOAc = 2:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, 1H, *J* = 7.3 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.65 (dt, 1H, *J* = 7.3, 1.0 Hz), 6.55 (d, 1H, *J* = 8.0 Hz) 3.68 (m, 1H), 2.94 (s, 3H), 2.75 (m, 2H), 2.53 (m, 1H), 2. 33 (m, 1H), 2.03 (m, 2H), 1.27 (m, 12H), 0.88 (t, 3H, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.5, 128.7, 127.3, 120.9, 118.0, 116.7, 111.2, 55.7, 37.8, 24.8, 22.6, 19.4. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.03; H, 7.76; N, 15.21.

**(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)acetic acid (10)**

A solution of acetonitrile **9** (250 mg, 1.50 mmol) in 35% HCl (5 mL) was stirred at 120 ℃ for 3 h. The resulting mixture was quenched by addition of saturated aqueous $NaHCO_3$. And then mixture was extracted with EtOAc. 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 (eluent; EtOAc) to afford 243 mg (1.18 mmol, 79 %) of the title compound as a pale yellow oil; $R_f$ = 0.33 (EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, 1H, *J* = 7.3 Hz), 7.05 (d, 1H, *J* = 7.3 Hz), 6.69 (t, 1H, *J* = 7.3 Hz), 6.62 (d, 1H, *J* = 8.2 Hz), 3.78 (m, 1H), 2.95 (s, 3H), 2.85 (m, 1H), 2.74 (m, 1H), 2.64 (m, 1H), 2.46 (m, 1H), 2.06 (m, 1H), 1.93 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 177.0, 144.4, 129.0, 127.3, 122.2,117.3, 112.6, 55.9, 38.5, 36.0, 25.0, 23.2. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.97; H, 7.21; N, 6.97.

**2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethanol (11)**

To a solution of acetic acid **10** (240 mg, 1.17 mmol) in $Et_2O$ (4 mL) was added LAH (110.93 mg, 2.92 mmol) at 0 ℃, and the mixture was stirred at rt for 3 h. The resulting mixture was quenched by addition of saturated aqueous $NH_4Cl$ solution. And then mixture was extracted with EtOAc. 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 (eluent; *n*-hexane/EtOAc = 2:1) to afford 190 mg (1.07 mmol, 92 %) of the title compound as a pale yellow oil; $R_f$ = 0.33 (*n*-hexane/EtOAc = 2:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, 1H, *J* = 7.3 Hz), 6.96 (d, 1H, *J* = 7.3 Hz), 6.64 (dt, 1H, *J* = 7.3, 1.0 Hz), 6.56 (d, 1H, *J* = 8.2 Hz), 3.69 (m, 2H), 3.44 (m, 1H), 2.93 (s, 3H), 2.79 (m, 1H), 2.67 (m, 1H), 2.24 (br s, 1H), 1.87 (m, 3H), 1.61 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.2, 128.7, 127.0, 122.0, 115.9, 111.6, 60.1, 55.9, 38.7, 34.3, 24.6, 23.5. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.38; H, 8.72; N, 7.52.

**5-[4-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13a)**

To a mixture of the alcohol **7a** (91.1 mg, 0.51 mmol), 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (239.29 mg, 0.51 mmol) and 1,1'-(azodicarbonyl)dipiperidine (394.56 mg, 1.54 mmol) in THF (3 mL) was added dropwise tributylphosphine (380.46 μL, 1.54 mmol) in toluene (0.3 mL). And the mixture was stirred at rt for 5 h. The reaction mixture was filtered and washed with $Et_2O$ and the filtrate extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent; *n*-hexane/EtOAc = 6:1) to afford **13a** (78.5 mg, 0.12 mmol, 24 %) of the title compound as a white powder; $R_f$ = 0.70 (*n*-hexane/EtOAc = 2:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.08 (m, 18H), 6.99 (d, 1H, *J* = 7.1Hz), 6.81 (d, 2H, *J* = 8.4 Hz), 6.62 (t, 1H, *J* = 7.3 Hz), 6.57 (d, 1H, *J* = 8.2 Hz), 4.36 (dd, 1H, *J* = 9.0, 3.8 Hz), 4.01 (m, 1H), 3.91 (m, 1H), 3.74 (m, 1H), 3.41 (m, 1H), 3.08 (dd, 1H, *J* = 8.8, 2.2 Hz), 3.05 (s, 3H), 2.75 (m, 2H), 2.19 (m, 1H), 1.97 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 113.4, 169.8, 158.5, 145.0, 141.8, 130.8, 129.0, 128.7, 128.1, 127.8, 127.5, 126.9, 76.6, 67.9, 60.6, 58.0, 50.8, 38.7, 37.9, 23.8, 23.0. Anal. Calcd for $C_{40}H_{36}N_2O_3S$: C, 76.89; H, 5.81; N, 4.48. Found: C, 77.03; H, 5.78; N, 4.32.

**5-[4-(1-Ethyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13b)**

Reaction of the alcohol **7b** (42 mg, 0.22 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (102.23 mg, 0.22 mmol), 1,1'-(azodicarbonyl)dipiperidine (166.88 mg, 0.66 mmol) and tributylphosphine (133.28 μL, 0.66 mmol) in THF (2.5 mL), as described above, gave **13b** (74 mg, 0.11 mmol, 51 %) as a white powder; $R_f$ = 0.71 (*n*-hexane/EtOAc = 2:1); $^1$H NMR (400 MHz, $CDCl_3$) δ

7.32~7.08 (m, 18H), 6.99 (d, 1H, *J* =7.1 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 6.63 (d, 1H, *J* = 8.2 Hz), 6.59 (t, 1H, *J* = 7.3 Hz), 4.35 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.87 (m, 1H), 3.76 (m, 1H), 3.54 (m, 1H), 3.37 (m, 2H), 3.06 (m, 1H), 2.74 (m, 2H), 2.22 (m, 1H), 1.83 (m, 1H), 1.19 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 143.4, 141.5, 130.6, 129.2, 128.5, 27.9, 127.5, 127.2, 126.7, 121.4, 115.3, 114.6, 110.7, 76.4, 67.9, 55.9, 50.5, 44.8, 37.6, 23.6, 22.5, 12.4. Anal. Calcd for $C_{41}H_{38}N_2O_3S$: C, 77.09; H, 6.00; N, 4.39. Found: C, 77.32; H, 6.21; N, 4.48.

**5-[4-(1-Propyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13c)**

Reaction of the alcohol **7c** (60 mg, 0.27 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (127.4 mg, 0.27 mmol), 1,1'-(azodicarbonyl)dipiperidine (166.6 mg, 0.82 mmol) and tributylphosphine (253.54 μL, 0.82 mmol) in THF (3 mL), as described above, gave **13c** (49.96 mg, 0.07 mmol, 27 %) as a white powder; $R_f$ = 0.57 (*n*-hexane/EtOAc = 3:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.98 (d, 1H, *J* = 7.0 Hz), 6.81 (d, 2H, *J* = 8.4 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.57 (t, 1H, *J* = 7.1 Hz), 4.34 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.93 (m, 1H), 3.85 (m, 1H), 3.77 (m, 1H), 3.43 (m, 2H), 3.18 (m, 1H), 3.06 (m, 1H), 2.76 (m, 2H), 2.22 (m, 1H), 1.88 (m, 1H), 1.66 (m, 2H), 0.94 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 143.7, 141.5, 130.6, 129.2 , 128.5, 127.9, 127.5, 127.1, 126.7, 121.2, 115.3, 114.7, 110.9, 76.4, 67.7, 56.5, 52.7, 50.5, 37.7, 23.5, 22.3, 20.4, 11.4. Anal. Calcd for $C_{42}H_{40}N_2O_3S$: C, 77.27; H, 6.18; N, 4.29. Found: C, 77.51; H, 6.43; N, 4.12.

**5-[4-(1-Isopropyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13d)**

Reaction of the alcohol **7d** (60.2 mg, 0.29 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (136.54 mg, 0.29 mmol), 1,1'-(azodicarbonyl)dipiperidine (222.84 mg, 0.88 mmol) and tributylphosphine (217.04 μL, 0.88 mmol) in THF (3 mL), as described above, gave **13d** (63.21 mg, 0.09 mmol, 32 %) of the title compound as a white powder; $R_f$ = 0.73 (*n*-hexane/EtOAc = 2:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42~7.05 (m, 18H), 6.98 (d, 1H, *J* = 7.3 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 8.1 Hz), 6.61 (t, 1H, *J* = 7.1 Hz), 4.36 (dd, 1H, *J* = 9.0, 3.8 Hz), 4.15 (m, 1H), 3.93 (m, 1H), 3.82 (m, 2H), 3.38 (m, 1H), 3.05 (m, 1H), 2.73 (m, 2H), 2.27 (m, 1H), 1.65 (m, 1H),1.31(m, 3H), 1.17 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 144.3, 141.5, 130.5, 129.8, 128.4, 127.7, 127.5, 126.9, 126.6, 122.0, 116.0, 114.6, 113.7, 76.3, 67.6, 50.5, 49.8, 47.9, 37.6, 23.0, 21.7, 21.4, 19.5. Anal. Calcd for $C_{42}H_{40}N_2O_3S$: C, 77.27; H, 6.18; N, 4.29. Found: C, 77.31; H, 6.43; N, 4.17.

**5-[4-(1-Butyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13e)**

Reaction of the alcohol **7e** (78 mg, 0.36 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (165.6 mg, 0.36 mmol), 1,1'-(azodicarbonyl)dipiperidine (270.2 mg, 1.07 mmol) and tributylphosphine (263.2 μL, 1.07 mmol) in THF (3 mL), as described above, gave **13e** (64 mg, 0.10 mmol, 27 %) as a white powder; $R_f$ = 0.58 (*n*-hexane/EtOAc = 3:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.88 (d, 1H, *J* = 7.3 Hz), 6.80 (d, 2H, *J* = 8.4 Hz), 6.60 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.1 Hz), 4.32 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.93 (m, 1H), 3.85 (m, 1H), 3.78 (m, 1H), 3.45 (m, 1H), 3.37 (m, 1H), 3.20 (m, 1H), 3.05 (m, 1H), 2.77 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.61 (m, 2H), 1.35 (m, 2H), 0.95 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.1, 169.4, 158.3, 143.6, 141.5, 130.5, 129.2, 128.5, 127.8, 127.5, 127.1, 126.6, 121.1, 115.3, 114.6, 110.8, 72.4, 67.6, 56.4, 50.5, 50.4, 37.6, 29.3, 23.4, 22.3, 20.3, 12.9. Anal. Calcd for $C_{43}H_{42}N_2O_3S$: C, 77.45; H, 6.35; N, 4.20. Found: C, 77.71; H, 6.23; N, 4.41.

**5-[4-(1-Pentyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13f)**

Reaction of the alcohol **7f** (74.8 mg, 0.32 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (149.2 mg, 0.32 mmol), 1,1'-(azodicarbonyl)dipiperidine (243.57 mg, 0.96 mmol) and tributylphosphine (237.2 μL, 0.96 mmol) in THF (3 mL), as described above, gave **13f** (58.99 mg, 0.09 mmol, 28 %) as a white powder; $R_f$ = 0.49 (*n*-hexane/EtOAc = 5:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.97 (d, 1H, *J* = 7.3 Hz), 6.81 (d, 2H, *J* = 8.4 Hz), 6.60 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.31 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.47 (m, 1H), 3.39 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.72 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.62 (m, 2H), 1.35 (m, 4H), 0.90 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 143.7, 141.5, 130.5, 129.2, 128.5, 127.8, 127.5, 127.2, 126.7, 121.2, 115.3, 114.7, 110.8, 76.4, 67.6, 56.4, 50.8, 50.5, 37.6, 29.3, 26.9, 23.4, 22.6, 22.3, 14.1. Anal. Calcd for $C_{44}H_{44}N_2O_3S$: C, 77.61; H, 6.51; N, 4.11. Found: C, 77.47; H, 6.68; N, 4.53.

**5-[4-(1-Isopentyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13g)**

Reaction of the alcohol **7g** (60.9 mg, 0.26 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (121.5 mg, 0.26 mmol), 1,1'-(azodicarbonyl)dipiperidine (198.33 mg, 0.78 mmol) and tributylphosphine (193.17 μL, 0.78 mmol) in THF (3 mL), as described above, gave **13g** (43.2 mg, 0.06 mmol, 24 %) as a white powder; $R_f$ = 0.48 (*n*-hexane/EtOAc = 5:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.90 (d, 1H, *J* = 7.3 Hz), 6.81 (d, 2H, *J* = 8.4 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.57 (t, 1H, *J* = 7.3 Hz), 4.33 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.48 (m, 1H), 3.38 (m, 1H), 3.26 (m, 1H), 3.05 (m, 1H), 2.73 (m, 2H), 2.22 (m, 1H), 1.84 (m, 1H), 1.53 (m, 2H), 0.96

(m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 143.6, 141.5, 130.5, 129.2, 128.5, 127.9, 127.5, 127.2, 126.7, 121.2, 115.3, 114.6, 110.7, 76.4, 67.7, 56.2, 50.5, 49.1, 37.6, 35.8, 26.3, 23.5, 22.8, 22.5, 22.4. Anal. Calcd for $C_{44}H_{44}N_2O_3S$: C, 77.61; H, 6.51; N, 4.11. Found: C, 77.43; H, 6.76; N, 4.29.

**5-[4-(1-Heptyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13h)**

Reaction of the alcohol **7h** (60.9 mg, 0.26 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (121.5 mg, 0.26 mmol), 1,1'-(azodicarbonyl)dipiperidine (198.33 mg, 0.78 mmol) and tributylphosphine (193.17 μL, 0.78 mmol) in THF (3 mL), as described above, gave **13h** (80.6 mg, 0.11 mmol, 19.56 %) as a white powder; $R_f$ = 0.24 (*n*-hexane/EtOAc = 9:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.97 (d, 1H, *J* = 7.3 Hz), 6.81 (m, 2H), 6.59 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.33 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.93 (m, 1H), 3.86 (m, 1H), 3.76 (m, 1H), 3.47 (m, 1H), 3.39 (m, 1H), 3.22 (m, 1H), 3.05 (m, 1H), 2.75 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.62 (m, 2H), 1.21 (m, 8H), 0.88 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.3, 143.7, 141.5, 130.5, 129.2, 128.5, 127.9, 127.5, 127.2, 126.7, 121.1, 115.3, 114.6, 110.8, 76.4, 67.6, 56.4, 50.8, 50.5, 37.6, 31.8, 29.2, 27.2, 27.1, 23.4, 22.6, 22.3, 14.1. Anal. Calcd for $C_{46}H_{48}N_2O_3S$: C, 77.93; H, 6.82; N, 3.95. Found: C, 77.51; H, 6.79; N, 3.57.

**5-[4-(1-Nonyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]-3-tritylthiazolidine-2,4-dione (13i)**

Reaction of alcohol **7i** (86.16 mg, 0.30 mmol) with 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (138.69 mg, 0.30 mmol), 1,1'-(azodicarbonyl)dipiperidine (226.39 mg, 0.89 mmol) and tributylphosphine (220.50 μL, 0.89 mmol) in THF (3 mL), as described above, gave **13i** (45.5 mg, 0.060 mmol, 20.28 %) as a white powder; $R_f$ = 0.26 (*n*-hexane/EtOAc = 9:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32~7.05 (m, 18H), 6.97 (d, 1H, *J* = 7.0 Hz), 6.80 (m, 2H), 6.60 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.35 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.93 (m, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.43 (m, 2H), 3.22 (m, 1H), 3.06 (m, 1H), 2.34 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.62 (m, 2H), 1.27 (m, 12H), 0.88 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.6, 158.6, 143.7, 141.5, 130.6, 129.2, 128.5, 127.9, 127.5, 127.2, 126.7, 121.2, 115.3, 114.7, 110.8, 76.4, 67.7, 56.4, 50.9, 50.6, 37.7, 31.8, 29.6, 29.5, 29.4, 29.3, 27.1, 26.0, 22.6, 22.3, 14.1. Anal. Calcd for $C_{48}H_{52}N_2O_3S$: C, 78.22; H, 7.11; N, 3.80. Found: C, 78.52; H, 7.13; N, 3.71.

**5-[4-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1a)**

To a compound **13a** (78.5 mg, 0.12 mmol) was added trifluoroacetic acid (0.7 mL) and stirred at rt for 2 h. The reaction mixture was diluted with water, neutralized by the addition of saturated aqueous $K_2CO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with

water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent; *n*-hexane/EtOAc = 4:1) to afford 42.64 mg (0.11 mmol, 91 %) of the title compound as a yellow oil; $R_f$ = 0.39 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3202, 3064, 2929, 1698, 1500, 1244, 749; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.11 (d, 2H, *J* = 8.4 Hz), 7.10 (t, 1H, *J* = 7.6 Hz), 6.98 (d, 1H, *J* = 7.1 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.62 (t, 1H, *J* = 7.3 Hz), 6.57 (d, 1H, *J* = 8.2 Hz), 4.47 (dd, 1H, *J* = 9.0, 3.8 Hz), 4.01(m, 1H), 3.89 (t, 1H, *J* = 8.4Hz), 3.72 (m, 1H), 3.42 (m, 1H), 3.08 (dd, 1H, *J* = 8.8, 2.2Hz), 3.03 (s, 3H), 2.76 (m, 2H), 2.17 (m, 1H), 1.98 (m, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.8, 171.1, 158.5, 145.0, 130.6, 129.0, 128.1, 127.5, 121.7, 116.1, 115.0, 110.7, 67.9, 60.7, 57.9, 53.9, 38.7, 37.9, 23.8, 23.0; LRMS (FAB) *m/z* 382.2 $(M)^+$; HRMS (FAB) Calcd for $C_{21}H_{23}N_2O_3S$ $(M+H)^+$ 383.4910, Found; 383.4921. Anal. Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.95; H, 5.80; N, 7.32. Found: C, 65.87; H, 5.61; N, 7.54.

**5-[4-(1-Ethyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1b)**

Reaction of **13b** (70.8 mg, 0.11 mmol) with trifluoroacetic acid (0.65 mL), as described above, gave **1b** (39.57 mg, 0.10 mmol, 92 %) as a yellow oil; $R_f$ = 0.40 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3206, 3065, 2927, 1754, 1696, 1245, 749; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), 6.98 (d, 1H, *J* = 7.1 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 6.68 (d, 1H, *J* = 7.1 Hz), 6.58 (t, 1H, *J* = 7.1 Hz), 4.47 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.87 (t, 1H, *J* = 8.4 Hz), 3.78 (m, 1H), 3.55 (m, 1H), 3.38 (m, 2H), 3.06 (m, 1H), 2.73 (m, 2H), 2.22 (m, 1H), 1.82 (m, 1H), 1.19 (t, 3H, *J* = 6.6 Hz) ;$^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.5, 170.8, 158.3, 143.3. 130.3, 129.1, 127.8, 127.2, 121.4, 115.3, 114.7, 110.7, 67.9, 55.8, 53.7, 44.8, 37.6, 23.5, 22.4, 12.3; LRMS (FAB) *m/z* 397.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{22}H_{25}N_2O_3S$ $(M+H)^+$ 397.5180, Found; 397.5191. Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.78; H, 6.32; N, 7.18.

**5-[4-(1-Propyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1c)**

Reaction of **13c** (28 mg, 0.04 mmol) with trifluoroacetic acid (0.25 mL) as described above, gave **1c** (915.17 mg, 0.037 mmol, 88 %) as a yellow oil; $R_f$ = 0.43 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3197, 3035, 2929, 1697, 1510, 1242, 746; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.13 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.3 Hz), 6.98 (d, 1H, *J* = 7.0 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.57 (t, 1H, *J* = 7.1 Hz), 4.49 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.87 (t, 1H, *J* = 8.4 Hz), 3.77 (m, 1H), 3.45 (m, 2H), 3.15 (m, 2H), 2.75 (m, 2H), 2.21 (m, 1H), 1.87 (m, 1H), 1.66 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 173.84, 170.0, 158.4, 143.7, 130.4, 129.2, 127.8, 127.2, 121.2, 115.4, 114.8, 110.9, 67.7, 56.6, 53.7, 52.7, 37.7, 23.5, 22.3, 20.4, 11.4; LRMS (FAB) *m/z* 411.2 $(M+H)^+$; HRMS (FAB)

Calcd for $C_{23}H_{27}N_2O_3S$ $(M+H)^+$ 411.5449, Found; 411.5461. Anal. Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82. Found: C, 67.53; H, 6.21; N, 6.78.

**5-[4-(1-Isopropyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1d)**

Reaction of **13d** (63 mg, 0.09 mmol) with trifluoroacetic acid (0.6 mL), as described above, gave **1d** (34.71 mg, 0.085 mmol, 90 %) as a yellow oil; $R_f$ = 0.43 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3203, 3061, 2964, 1753, 1698, 750; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.11 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.99 (d, 1H, *J* = 7.1 Hz), 6.82 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 1H, *J* = 8.1 Hz), 6.61 (t, 1H, *J* = 7.1 Hz), 4.48 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.90 (m 1H), 3.80 (m, 2H), 3.43 (m, 1H), 3.08 (m, 1H), 2.74 (m, 2H), 2.25 (m,1H), 1.66 (m, 1H), 1.31 (d, 3H, *J* = 6.6 Hz), 1.44 (d, 3H, *J* = 6.6 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.5, 170.7, 158.6, 144.6, 130.5, 130.1, 127.9, 127.2, 122.3, 116.3, 114.9, 113.9, 67.9, 53.9, 50.1, 48.2, 37.9, 23.3, 20.0, 19.7; LRMS (FAB) *m/z* 411.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{23}H_{27}N_2O_3S$ $(M+H)^+$ 411.5449, Found; 411.5461. Anal. Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82. Found: C, 67.61; H, 6.27; N, 6.98.

**5-[4-(1-Butyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1e)**

Reaction of **13e** (47.6 mg, 0.07 mmol) with trifluoroacetic acid (0.45 mL), as described above, gave **1e** (26.83 mg, 0.063 mmol, 91 %) as a yellow oil; $R_f$ = 0.44 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3196, 3033, 2956, 2930, 1753, 1698, 748; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.3 Hz), 6.98 (d, 1H, *J* = 7.3 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.60 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.3 Hz), 4.49 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.86 (t, 1H, *J* = 8.4 Hz), 3.75 (m, 1H), 3.46 (m, 2H), 3.22 (m, 1H), 3.10 (m, 1H), 2.75 (m, 2H), 2.20 (m, 1H), 1.87 (m, 1H), 1.64 (m, 2H), 1.38 (m, 2H), 0.95 (t, 3H, *J* = 7.3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 174.0, 158.4, 143.7, 130.3, 130.2, 129.2, 127.8, 127.2, 121.2, 115.3, 114.8, 110.9, 67.7, 56.4, 53.7, 50.6, 37.7, 29.4, 23.5, 22.3, 20.2, 14.0; LRMS (FAB) *m/z* 425.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{24}H_{29}N_2O_3S$ $(M+H)^+$ 425.5719, Found; 425.5730. Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.77; H, 6.84; N, 6.71.

**5-[4-(1-Pentyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1f)**

Reaction of **13f** (29.9 mg, 0.04 mmol) with trifluoroacetic acid (0.3 mL), as described above, gave **1f** (16.9 mg, 0.038 mmol, 92 %) as a yellow oil; $R_f$ = 0.15 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3201, 3065, 2930, 2870, 1698, 1511, 1245; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.3 Hz), 6.98 (d, 1H, *J* = 7.3 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.59 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.48 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.86 (t, 1H, *J* = 8.4 Hz), 3.75 (m, 1H), 3.46 (m, 2H), 3.22 (m, 1H), 3.08 (m,1H), 2.75 (m, 2H), 2.21 (m, 1H), 1.86 (m, 1H), 1.63 (m, 2H), 1.34 (m, 4H),

0.91 (t, 3H, *J* = 7.1 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.6, 150.3, 143.6, 130.3, 129.2, 127.8, 127.1, 121.2, 115.3, 114.7, 110.8, 67.6, 56.4, 53.7, 50.8, 37.7, 29.3, 26.8, 23.4, 22.6, 22.2, 14.1; LRMS (FAB) *m/z* 439.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{25}H_{31}N_2O_3S$ $(M+H)^+$ 439.5989, Found; 439.6000. Anal. Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.39. Found: C, 68.31; H, 6.76; N, 6.51.

**5-[4-(1-Isopentyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1g)**

Reaction of **13g** (43.2 mg, 0.06 mmol) with trifluoroacetic acid (0.4 mL), as described above, gave **1g** (22.5 mg, 0.05 mmol, 84 %) as a yellow oil; $R_f$ = 0.14 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3197, 3064, 2954, 2869, 1698; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.3 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.83 (d, 2H, *J* = 8.4 Hz), 6.60 (d, 1H, *J* = 8.2 Hz), 6.58 (t, 1H, *J* = 7.3 Hz), 6.00 (br s, 1H), 4.48 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.87 (t, 1H, *J* = 8.4 Hz), 3.74 (m, 1H), 3.46 (m, 2H), 3.26 (m,1H), 3.08 (m, 1H), 2.78 (m, 1H), 2.68 (m, 1H), 2.21 (m,1H), 1.83 (m, 1H), 1.50 (m, 2H), 0.97 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 6.6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.7, 158.3, 143.6, 130.2, 129.2, 127.8, 127.2, 121.3, 115.3, 114.7, 110.7, 67.7, 56.2, 53.8, 49.0, 37.7, 35.7, 26.3, 23.5, 22.8, 22.5, 22.4; LRMS (FAB) *m/z* 439.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{25}H_{31}N_2O_3S$ $(M+H)^+$ 439.5989, Found; 439.6000. Anal. Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.39. Found: C, 68.21; H, 7.04; N, 6.59.

**5-[4-(1-Heptyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1h)**

Reaction of **13h** (52.9 mg, 0.073 mmol) with trifluoroacetic acid (0.5 mL), as described above, gave **1h** (30.4 mg, 0.065 mmol, 89 %) as a yellow oil; $R_f$ = 0.24 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3204, 3065, 2927, 2854, 1698; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* = 7.3 Hz), 6.97 (d, 1H, *J* = 7.3 Hz), 6.83 (m, 2H), 6.60 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.48 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 1H), 3.86 (t, 1H, *J* = 8.4 Hz), 3.75 (m, 1H), 3.46 (m, 2H), 3.22 (m, 1H), 3.08 (m, 1H), 2.74 (m, 2H), 2.21 (m, 1H), 1.85 (m, 1H), 1.61 (m, 2H), 1.30 (m, 8H), 0.88 (t, 3H, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.3, 170.6, 158.3, 143.6, 130.2, 129.2, 127.8, 127.1, 121.1, 115.2, 114.7, 110.8, 67.6, 56.4, 53.7, 50.8, 37.7, 31.9, 29.2, 27.1, 27.0, 23.4, 22.6, 22.2, 14.1; LRMS (FAB) *m/z* 467.2 $(M+H)^+$; HRMS (FAB) Calcd for $C_{27}H_{35}N_2O_3S$ $(M+H)^+$ 467.6529, Found; 467.6540. Anal. Calcd for $C_{27}H_{34}N_2O_3S$: C, 69.49; H, 7.34; N, 6.00. Found: C, 69.31; H, 7.57; N, 6.23.

**5-[4-(1-Nonyl-1,2,3,4-tetrahydroquinolin-2-ylmethoxy)benzyl]thiazolidine-2,4-dione (1i)**

Reaction of **13i** (45.5 mg, 0.06 mmol) with trifluoroacetic acid (0.42 mL), as described above, gave **1i** (20.6 mg, 0.042 mmol, 69 %) as a yellow oil; $R_f$ = 0.26 (*n*-hexane/EtOAc = 5:1); IR (neat, $cm^{-1}$) 3207, 3065, 2925, 2853, 1698; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 2H, *J* = 8.4 Hz), 7.07 (t, 1H, *J* =

7.3 Hz), 6.94 (d, 1H, *J* = 7.0 Hz), 6.84 (m, 2H), 6.60 (d, 1H, *J* = 8.2 Hz), 6.56 (t, 1H, *J* = 7.3 Hz), 4.27 (dd, 1H, *J* = 9.0, 3.8 Hz), 3.94 (m, 2H), 3.86 (t, 1H, *J* = 8.4 Hz), 3.76 (m, 1H), 3.46 (m, 2H), 3.22 (m, 1H), 3.08 (m, 1H), 2.75 (m, 2H), 2.21 (m, 1H), 1.87 (m, 1H), 1.63 (m, 2H), 1.28 (m, 12H), 0.88 (t, 3H, *J* = 7.0 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.4, 170.6, 158.6, 143.6, 130.3, 130.2, 129.2, 127.1, 121.1, 115.2, 114.7, 110.8, 68.0, 56.4, 53.7, 50.8, 37.7, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 27.1, 26.0, 22.2, 14.1; LRMS (FAB) *m/z* 495.3 $(M+H)^+$; HRMS (FAB) Calcd for $C_{29}H_{39}N_2O_3S$ $(M+H)^+$ 495.7069, Found; 495.7079. Anal. Calcd for $C_{29}H_{38}N_2O_3S$: C, 70.41; H, 7.74; N, 5.66. Found: C, 70.49; H, 7.43; N, 5.87.

**5-{4-[2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethoxy]benzyl}-3-tritylthiazolidine-2,4-dione (14)**

To a mixture of the alcohol **11** (48.1 mg, 0.27 mmol), 5-(4-hydroxy-benzyl)-3-tritylthiazolidine-2,4-dione **12** (126.35 mg, 0.27 mmol) and 1,1'-(Azodicarbonyl)dipiperidine (206.25 mg, 0.81 mmol) in THF (3 mL) was added dropwise tributylphosphine (200.90 μL, 0.81 mmol) in toluene (0.3mL). And the mixture was stirred at rt for 5 h. The reaction mixture was filtered and washed with $Et_2O$ and the filtrate extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent; *n*-hexane/EtOAc = 9:1) to afford 49.1 mg (0.786 mmol, 29 %) of the title compound as a white powder; $R_f$ = 0.23 (*n*-hexane/EtOAc = 8:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35~7.07 (m, 18H), 6.98 (d, 1H, *J* = 7.3 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 6.60 (t, 1H, *J* = 7.3 Hz), 6.53 (d, 1H, *J* = 8.2 Hz), 4.36 (dd, 1H, *J* = 9.0, 3.8 Hz), 4.00 (t, 1H, *J* = 6.0 Hz), 3.61 (m, 1H), 3.41 (dd, 1H *J* = 14.1, 4.0 Hz), 3.07 (dd, 1H, *J* = 14.0, 9.0 Hz), 2.94 (s, 3H), 2.85 (m, 1H), 2.68 (m, 1H), 2.01~1.81 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 173.2, 169.5, 158.4, 145.1, 141.6, 130. 6, 128.8, 128.5, 127.8, 127.5, 127.2, 126.7, 121.5, 115.6, 114.7, 110.9, 76.5, 65.1, 55.7, 50.5, 38.5, 37.7, 31.6, 24.9, 23.5, 14.2. Anal. Calcd for $C_{41}H_{40}N_2O_3S$: C, 76.84; H, 6.29; N, 4.37. Found: C, 76.61; H, 6.48; N, 4.51.

**5-{4-[2-(1-Methyl-1,2,3,4-tetrahydroquinolin-2-yl)ethoxy]benzyl}thiazolidine-2,4-dione (2)**

To a compound **14** (49.1 mg, 0.075 mmol) was added trifluoroacetic acid (0.40 mL, 5.25 mmol) and stirred at rt for 2 h. The reaction mixture quenched by addition of water and neutralized by the addition of saturated aqueous $K_2CO_3$ solution, extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (eluent; *n*-hexane/EtOAc = 5:1) to afford 26.10 mg (0.066 mmol, 88 %) of the title compound as a yellow oil; $R_f$ = 0.48 (*n*-hexane/EtOAc = 2:1); IR (neat, $cm^{-1}$) 3199, 3019, 2928, 1752, 1697, 750; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, 2H, *J* = 8.4 Hz), 7.08 (t, 1H, *J* = 7.3 Hz), 6.98 (d, 1H, *J* = 7.1 Hz), 6.85 (d, 2H, *J* = 8.4 Hz), 6.60 (t, 1H, *J* = 7.3 Hz), 6.54 (d, 1H, *J* = 8.2 Hz), 4.49 (dd, 1H, *J* = 9.0, 3.8 Hz), 4.00 (t, 1H, *J* = 6.0 Hz), 3.60 (m, 1H), 3.45 (dd,

1H, *J* = 14.1, 4.0 Hz), 3.10 (dd, 1H, *J* = 14.0, 3.3 Hz), 3.03 (s, 3H), 2.85 (m, 1H), 2.73 (m, 1H), 2.01~1.81 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.2, 170.4, 158.4, 145.1, 130.3, 128.8, 127.8, 127.2, 121.6, 115.7, 114.8, 110.9, 65.1, 55.8, 53.7, 38.5, 37.8, 31.5, 24.8, 23.5; LRMS (FAB) *m/z* 396.2 $(M)^+$; HRMS (FAB) Calcd for $C_{22}H_{25}N_2O_3S$ $(M+H)^+$ 397.5180, Found; 397.5191. Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.58; H, 6.37; N, 7.25.

**PPAR Transactivation Assay**

GAL4 fusions were made by fusing murine PPAR ligand binding domain to the C-terminal end of yeast GAL4 DNA binding domain. CV-1 cells were seeded at 2 x $10^4$ cells/well and cultured for 24 h at 37 ºC. Cells were cotransfected for 3 h at 37 ºC with pUAS, pRL-TK, and pCMX-GalPx. Transfected cells were treated with 2 μM of the test compounds for 24 h. DMSO (0.1%) was used as a blank. GW409544, which is a potent full agonist on both PPARα and PPARγ was used as positive control with 30 μM for PPARα transactivation assay and 1 μM for PPARγ, respectively. 2 μM of Tesaglitazar and rosiglitazone were run together to compare the activity of the test compounds. Luciferase activity was determined as 'fold activation' relative to positive control.

**ACKNOWLEDGEMENTS**

This work was supported by the SRC program of MOST/KOSEF (RESEARCH CENTER FOR WOMEN'S DISEASES).

**REFERENCES**

1. R. A. DeFronzo, R. C. Bonadonna, and E. Ferrannini, *Diabetes Care*, 1992, **15**, 318.
2. R. A. DeFronzo, *Diabetes*, 1988, **37**, 667.
3. B. Feldt-Rasmussen, E. R. Mathiesen, and T. Deckert, *Lancet*, 1986, **2**, 1300.
4. K. Dahl-Jorgensen, O. Brinchmann-Hansen, K. F. Hanssen, T. Ganes, P. Kierulf, E. Smeland, L. Sandvik, and O. Aagenaes, *Br. Med. J. (Clin. Res. Ed.)*, 1986, **293**, 1195.
5. J. Pirart, *Diabetes care*, 1978, **1**, 139.
6. N. B. Ruderman and S. H. Schneider, *Diabetes care*, 1992, **15**, 1787.
7. R. R. Holman, J. Steemson, and R. C. Turner, *Diabetes Res.*, 1991, **18**, 149.
8. C. Ferrari, G. P. Testori, A. Bertazzoni, M. Romussi, R. Caldara, and S. Frezzati, *Horm. Metab. Res.*, 1978, vol. 10, p. 4.
9. D. Barnett, J. G. Craig, D. S. Robinson, and M. P. Rogers, *Br. J. Clin. Parmacol.*, 1977, **4**, 455.

10. T. Fujita, Y. Sugiyama, S. Taketomi, T. Sohda, T. Kawamatsu, H. Iwatsuka, and Z. Suzuoki, *Diabetes*, 1983, **32**, 804.
11. R. F. Kletzien, S. D. Clarke, and R. G. Ulrich, *Mol. Pharmacol*., 1992, **41**, 393.
12. A. Ibrahimi, L. Teboul, D. Gaillard, E. Z. Amri, G. Ailhaud, P. Young, M. A. Cawthorne, and P. A. Grimaldi, *Mol. Pharmacol*., 1994, **46**, 1070.
13. G. Martin, K. Schoonjans, B. Staels, and J. Auwerx, *Atherosclerosis*, 1998, **137 Suppl**, S75.
14. J. M. Lehmann, L. B. Moore, T. A. Smith-Oliver, W. O. Wilkison, T. M. Willson, and S. A. Kliewer, *J. Biol. Chem*., 1995, **270**, 12953.
15. B. Desvergne and W. Wahli, *Endocr. Rev*., 1999, **20**, 649.
16. S. Kersten, B. Desvergne, and W. Wahli, *Nature*, 2000, **405**, 421.
17. J. Berger and D. E. Moller, *Annu. Rev. Med*., 2002, **53**, 409.
18. E. D. Rosen and B. M. Spiegelman, *J. Biol. Chem*., 2001, **276**, 37731.
19. T. Yoshioka, T. Fujita, T. Kanai, Y. Aizawa, T. Kurumada, K. Hasegawa, and H. Horikoshi, *J. Med. Chem*., 1989, **32**, 421.
20. B. C. Cantello, M. A. Cawthorne, G. P. Cottam, P. T. Duff, D. Haigh, R. M. Hindley, C. A. Lister, S. A. Smith, and P. L. Thurlby, *J. Med. Chem*., 1994, **37**, 3977.
21. T. Sohda, Y. Momose, K. Meguro, Y. Kawamatsu, Y. Sugiyama, and H. Ikeda, *Arzneimittel-Forschung*, 1990, **40**, 37.
22. H. Ikeda, S. Taketomi, Y. Sugiyama, Y. Shimura, T. Sohda, K. Meguro, and T. Fujita, *Arzneimittel-Forschung*, 1990, **40**, 156.
23. R. Nagata, N. Tanno, T. Kodo, N. Ae, H. Yamaguchi, T. Nishimura, F. Antoku, T. Tatsuno, T. Kato, and Y. Tanaka, *J. Med. Chem*., 1994, **37**, 3956.
24. T. Miki, M. Kori, A. Fujishima, H. Mabuchi, R. Tozawa, M. Nakamura, Y. Sugiyama, and H. Yukimasa, *Bioorg. Med. Chem*., 2002, **10**, 385.
25. B. A. Bhat, S. Ponnala, D. P. Sahu, P. Tiwari, B. K. Tripathi, and A. K. Srivastava, *Bioorg. Med. Chem*., 2004, **12**, 5857.
26. B. Hu, J. Ellingboe, I. Gunawan, S. Han, E. Largis, Z. Li, M. Malamas, R. Mulvey, A. Oliphant, F. W. Sum, J. Tillett, and V. W. Wong, *Bioorg. Med. Chem. Lett*., 2001, **11**, 757.