Polycyclic *N*-Heterocyclic Compounds 73: Synthesis and Evaluation of 5-Substituted 1,2-Dihydrofuro[2,3-*c*]isoquinolines as Inducers of Lipoprotein Lipase mRNA Expression

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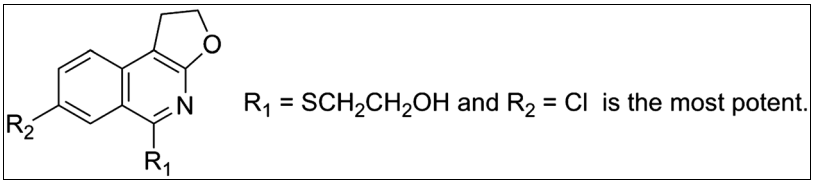

Several 5-substituted 1,2-dihydro[2,3-*c*]isoquinoline derivatives were synthesized as part of our research to develop new diabetes drugs. Amines and sulfanyls were used as substituents at the 5th-position. Evaluation of the effects of the newly synthesized compounds on lipoprotein lipase mRNA expression in 3T3-L1 preadipocytes revealed one promising candidate with potency comparable to that of troglitazone.

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INTRODUCTION

Recently, we reported that a Truce-Smiles rearrangement [1] of 2-(3-cyanopropoxy)benzonitriles (**1a–c**) followed by intramolecular cyclization produced 5-amino-1,2-dihydrofuro [2,3-*c*]isoquinolines (**2a–c**) in one step in moderate yields (Scheme 1) [2]. As part of our ongoing projects, we examined the effects of these compounds on lipoprotein lipase (LPL) mRNA expression, one of the key targets for diabetes drugs, using 3T3-L1 preadipocytes as an *in vitro* screening test for hyperlipemia [3]. Compound **2a** showed activity significantly different from the vehicle control, while **2b** and **2c** had no meaningful activity. Based on these results, we focused on compound **2a** as a lead structure to explore preparation of more active compounds. Here we describe the preparation of 5-subsituted 1,2-dihydrofuro[2,3-*c*]isoquinolines and the effects of these new analogues on LPL mRNA expression.

For derivatization of **2a**, we focused the amino group located at the 5th-position. To introduce nucleophiles at the 5th-position of **2a**, the 5-chloro derivative (**3**) was prepared from **2a** according to the literature procedure [2]. Compound **3** was a good starting material for preparation of various derivatives by substitution of the active 5-chloro group with potential pharmacophores. Thus, various nucleophiles such as 2-sulfanylethanol, 3-sulfanyl-1-propanol, ethyl sulfanylacetate, and ethyl 3-sulfanylpropionate were allowed to react with **3** to give **4–7**. All these derivatives have linear 5-subtituents. Compound **3** also was treated with morpholine, piperazine, and imidazole to produce cyclic 5-substituted products **8–10** (Scheme 2).

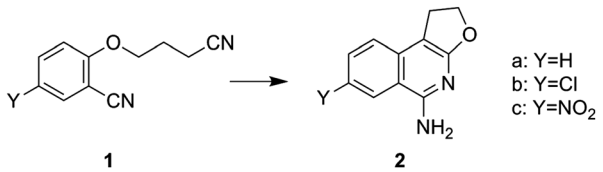
With these compounds in hand, their effects on LPL mRNA expression in 3T3-L1 preadipocytes were evaluated. Troglitazone [4] was employed as a reference compound and glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was chosen for the house keeping gene. The LPL/GAPDH mRNA ratio was evaluated as the relative values of LPL/GAPDH ratio from vehicle control group and tests were done in triplicate. The results including **2a–c** are shown in Table 1. Of these derivatives, **4** and **10** have significant potency.

Based on the activities showed by compounds **4** and **10**, we prepared additional analogues in a search for higher potency. The 7-chlro substituted compound (**11**) [2] was selected as a starting material, and **12** and **13** were prepared as 7-chloro derivatives of **4** and **10**, respectively (Scheme 3). The pharmacological assays of **12** and **13** showed that **12** had the best activity, with potency comparable to that of troglitazone. We are currently exploring further structure–activity relationships with the goal of development of new diabetes drugs.

EXPERIMENTAL

General. All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. Fast atom bombardment (FAB)-mass spectra were obtained on a VG 70-SE mass spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. IR spectra were recorded on a Japan Spectroscopic FT/IR-200 spectrophotometer and frequencies are expressed in cm^{-1}. ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and *J* values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t,

Scheme 1. One step synthesis of 1,2-dihydrofuro[2,3-*c*]isoquinolines (**2**) by Truce-Smiles rearrangement.



Scheme 2. Preparation of **4–10.**

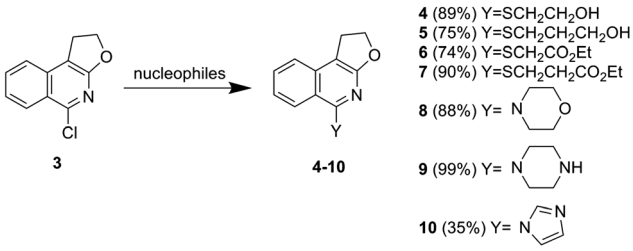


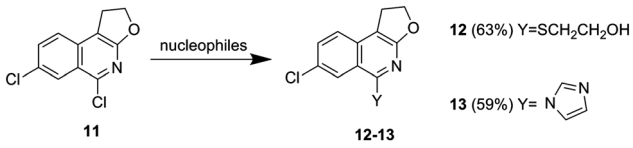
Table 1

Effects on LPL mRNA expression in 3T3-L1 preadipocytes.

Compd	LPL mRNA-fold	Compd	LPL mRNA-fold
2a	1.69 ± 0.19*	**7**	1.63 ± 0.42
2b	0.94 ± 0.09	**8**	1.68 ± 0.10*
2c	1.08 ± 0.10	**9**	1.57 ± 0.18**
3	1.49 ± 0.23	**10**	2.59 ± 0.62**
4	2.70 ± 0.01*	**11**	0.41 ± 0.05
5	2.01 ± 0.34*	**12**	4.14 ± 0.55*
6	1.70 ± 0.29	**13**	1.75 ± 0.02*
		Troglitazone	4.46 ± 0.02*

*$P < 0.05$.
**$P < 0.01$.

Scheme 3. Preparation of **12** and **13.**



triplet; q, quartet; quin, quintet; br, broad; m, multiplet. Column chromatography was performed on silica gel (Kieselgel 60, 70–230 mesh, Merck, Darmstadt, Germany). TLC was carried out on Kieselgel 60F254 (Merck) or silica gel 70FM (Wako).

5-(2-Hydroxyethylsulfanyl)-1,2-dihydrofuro[2,3-*c*]isoquinoline (4). To a solution of **3** (200 mg, 0.973 mmol) in dry DMF (4.0 mL) were added 2-sulfanylethanol (764 mg, 9.78 mmol) and K_2CO_3 (205 mg, 1.48 mmol) and the mixture was stirred for 3 h at 70°C. Ice-water (50 mL) was poured into the reaction mixture to precipitate solid, which was filtered off *in vacuo.* The solid was recrystallized from diethyl ether to give **4** (214 mg, 89%) as pale yellow needles, m.p. 92–93°C; IR (potassium bromide): 3400 (OH) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.45 (t, 2H, *J* = 8.9 Hz, H1), 3.54 (t, 2H, *J* = 5.5 Hz, H1′), 4.01 (t, 2H, *J* = 5.5 Hz, H2′), 4.78 (t, 2H, *J* = 8.9 Hz, H2), 7.34 (td, 1H, *J* = 8.4, 1.4 Hz, H7), 7.50–7.67 (m, 2H, H8 and 9), 8.17 (br d, 1H, *J* = 8.4 Hz, H6); FAB-MS *m/z*: 248 (MH^+); Analysis calculated for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.17; H, 5.47; N, 5.56.

5-(3-Hydroxypropylsulfanyl)-1,2-dihydrofuro[2,3-*c*] isoquinoline (5). To a solution of **3** (300 mg, 1.46 mmol) in dry DMF (3.0 mL) were added 3-sulfanyl-1-propanol (1.35 g, 14.6 mmol) and K_2CO_3 (302 mg, 2.19 mmol) and the mixture was stirred for 9 h at 70°C. Ice-water (150 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (150 mL ×3). The organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of benzene-ethyl acetate (9:1) was evaporated and recrystallized from diethyl ether to give **5** (286 mg, 75%) as pale yellow needles, m.p. 95–96°C; IR (potassium bromide): 3400 (OH) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 2.00 (quin, 2H, *J* = 5.9 Hz, H2′), 3.43 (t, 2H, *J* = 8.9 Hz, H1), 3.50 (t, 2H, *J* = 5.9 Hz, H1′), 3.71 (t, 2H, *J* = 5.9 Hz, H3′), 4.78 (t, 2H, *J* = 8.9 Hz, H2), 7.32 (td, 1H, *J* = 8.4, 1.4 Hz, H7), 7.50 (dd, 1H, *J* = 8.4, 1.4 Hz, H6), 7.62 (td, 1H, *J* = 8.4, 1.4 Hz, H8), 8.16 (br d, 1H, *J* = 8.4 Hz, H9); FAB-MS *m/z*: 262 (MH^+); Analysis calculated for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.05; H, 5.70; N, 5.04.

Ethyl 2-(1,2-dihydrofuro[2,3-*c*]isoquinolin-5-yl) sulfanylacetate (6). To a solution of **3** (250 mg, 1.22 mmol) in dry DMF (5.0 mL) were added ethyl sulfanylacetate (1.46 g, 12.1 mmol) and K_2CO_3 (252 mg, 1.82 mmol) and the mixture was stirred at room temperature for 69 h. Ice water (150 mL) was added to the reaction mixture and the precipitated solid was collected on a filter. The solid was recrystallized from ethyl acetate-*n*-hexane to give **6** (260 mg, 74%) as pale yellow needles, m.p. 93–94°C; IR (potassium bromide): 1740 (CO) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.30 (t, 3H, *J* = 7.1 Hz, Me), 3.43 (t, 2H, *J* = 8.9 Hz, H1), 4.14 (s, 2H, SCH_2), 4.24 (q, 2H, *J* = 7.1 Hz, CH_2Me), 4.76 (t, 2H, *J* = 8.9 Hz, H2), 7.33 (td, 1H, *J* = 8.5, 1.5 Hz, H7), 7.48–7.65 (m, 2H, H6 and 8), 8.13 (br d, 1H, *J* = 8.5 Hz, H9); FAB-ms *m/z*: 290 (MH^+). Analysis calculated for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.30; H, 5.19; N, 4.56.

Ethyl 3-(1,2-dihydrofuro[2,3-*c*]isoquinolin-5-yl) sulfanylpropionate (7). To a solution of **3** (300 mg, 1.46 mmol) in dry DMF (2.0 mL) were added ethyl 3-sulfanylpropionate (1.96 g, 14.6 mmol) and K_2CO_3 (302 mg, 2.19 mmol) and the mixture was stirred for 7 h at 70°C. Ice-water (200 mL) was poured into the reaction mixture which was then extracted with benzene (70 mL ×3). The organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo.* The residue was chromatographed on silica gel. The eluate of petroleum ether-diethyl ether (9:1) was evaporated and recrystallized from *n*-hexane to give **7** (397 mg, 90%) as pale yellow needles, m.p. 66–67°C; IR (potassium bromide):1730 (CO) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 1.26 (t, 3H, *J* = 7.1 Hz, Me), 2.86 (t, 2H, *J* = 6.9 Hz, H2′), 3.44 (t, 2H, *J* = 8.9 Hz, H1), 3.60 (t, 2H, *J* = 6.9 Hz, H1′), 4.16 (q, 2H, *J* = 7.1 Hz, OCH_2), 4.77 (t, 2H, *J* = 8.9 Hz, H2), 7.30 (td, 1H, *J* = 8.5, 1.5 Hz, H7), 7.48–7.64 (m, 2H, H8 and 9), 8.11 (br d, 1H, *J* = 8.5 Hz, H6).; FAB-MS *m/z*: 304 (MH^+). Analysis

calculated for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.43; H, 5.80; N, 4.66.

5-Morpholino-1,2-dihydrofuro[2,3-*c*]isoquinoline (8). To a solution of **3** (260 mg, 1.26 mmol) in dry 1,4-dioxane (10 mL) was added morpholine (2.20 g, 25.3 mmol) and the reaction was stirred for 16 h at 70°C. After evaporation of solvent and excess morpholine *in vacuo*, ice-water (150 mL) was poured into the residue to precipitate a solid, which was collected on a filter. The solid was recrystallized from *n*-hexane to give **8** (285 mg, 88%) as yellow prisms, m.p. 148–150°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.40 (t, 2H, *J* = 8.8 Hz, H1), 3.41 (t, 4H, *J* = 4.7 Hz, CH_2NCH_2), 3.95 (t, 4H, *J* = 4.7 Hz, CH_2OCH_2), 4.75 (t, 2H, *J* = 8.8 Hz, H2), 7.27 (td, 1H, *J* = 8.4, 1.9 Hz, H7), 7.48–7.64 (2H, m, H8 and 9), 8.11 (br d, 1H, *J* = 8.4 Hz, H6); FAB-MS *m/z*: 257 (MH^+). Analysis calculated for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.57; H, 6.35; N, 10.91.

5-(1-Piperazinyl)-1,2-dihydrofuro[2,3-*c*]isoquinoline (9). To a mixture of piperazine (1.88 g, 21.8 mmol) and K_2CO_3 (302 mg, 2.19 mmol) in dry 1,4-dioxane (10 mL) was added **3** (300 mg, 1.46 mmol) in dry 1,4-dioxane (10 mL) dropwise and the reaction was then stirred for 70 h at 70°C. After evaporation of solvent, ice-water (300 mL) was poured into the residue which was then extracted with benzene (100 mL ×3). The combined organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was recrystallized from ethyl acetate to give **9** (368 mg, 99%) as yellow prisms, m.p. 134–135°C; IR (potassium bromide): 3230, 3065 (NH) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.14, 3.40 (each m, each 4H, piperazine 4× CH_2), 3.40 (t, 2H, *J* = 8.8 Hz, H1), 4.74 (t, 2H, *J* = 8.8 Hz, H2), 7.26 (td, 1H, *J* = 8.4, 1.7 Hz, H7), 7.46–7.60 (m, 2H, H8 and 9), 8.11 (br d, 1H, *J* = 8.4 Hz, H6); FAB-MS *m/z*: 256 (MH^+). Analysis calculated for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.51; H, 6.71; N, 16.24.

5-(Imidazol-1-yl)-1,2-dihydrofuro[2,3-*c*]isoquinoline (10). To a solution of **3** (200 mg, 0.973 mmol) in dry 1,4-dioxane (10 mL) were added imidazole (200 mg, 2.94 mmol) and K_2CO_3 (203 mg, 1.47 mmol) and the reaction was stirred for 48 h at 70°C. After evaporation of solvent *in vacuo*, ice-water (150 mL) was poured into the reaction mixture which was then extracted with ethyl acetate (50 mL ×3). The combined organic layer was washed with saturated brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed on silica gel. The eluate of ethyl acetate-benzene (1:1) was evaporated *in vacuo* and the residue was recrystallized from ethyl acetate-*n*-hexane to give **10** (81.0 mg, 35%) as colorless needles, m.p. 172–173°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.58 (t, 2H, *J* = 8.9 Hz, H1), 4.88 (t, 2H, *J* = 8.9 Hz, H2), 7.27 (br d, 1H, *J* = 1.4 Hz, imidazole H4), 7.40 (td, 1H, *J* = 8.7, 2.5 Hz, H7), 7.50 (br d, 1H, *J* = 1.4 Hz, imidazole H5), 7.63–7.74 (m, 2H, H8 and 9), 7.95 (br d, 1H, *J* = 8.7 Hz, H6), 8.04 (br s, 1H, imidazole H2); FAB-MS *m/z*: 238 (MH^+). Analysis calculated for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.75; H, 4.76; N, 17.38.

7-Chloro-5-(2-hydroxyethylsulfanyl)-1,2-dihydrofuro[2,3-*c*]isoquinoline (12). To a solution of **11** (200 mg, 0.833 mmol) in dry DMF (4.0 mL) were added 2-sulfanylethanol (647 mg, 8.28 mmol) and K_2CO_3 (172 mg, 1.24 mmol) and the mixture was stirred for 3 h at 70°C. Ice-water (200 mL) was poured into the reaction mixture to precipitate a solid, which was filtered off *in vacuo*. The solid was recrystallized from *n*-hexane to give **12** (147 mg, 63%) as pale yellow needles, m.p. 132–134°C; IR (potassium bromide): 3450 (OH) cm^{-1}; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.30 (br s, 1H, deuterium oxide exchangeable, OH), 3.44 (t, 2H, *J* = 8.9 Hz, H1), 3.54 (t, 2H, *J* = 5.5 Hz, H1′), 3.99 (t, 2H, *J* = 5.5 Hz, H2′), 4.78 (t, 2H, *J* = 8.9 Hz, H2), 7.46 (d, 1H, *J* = 9.2 Hz, H9), 7.55 (dd, 1H, *J* = 9.2, 2.0 Hz, H8), 8.16 (d, 1H, *J* = 2.0 Hz, H6); FAB-MS *m/z*: 282 (MH^+), 284 (MH^+ + 2); Analysis calculated for $C_{13}H_{12}ClNO_2S$: C, 55.42; H, 4.29; N, 4.97. Found: C, 55.22; H, 4.41. N, 4.79.

7-Chloro-5-(imidazol-1-yl)-1,2-dihydrofuro[2,3-*c*]isoquinoline (13). To a solution of **11** (180 mg, 0.750 mmol) in dry 1,4-dioxane (10 mL) were added imidazole (153 mg, 2.25 mmol) and K_2CO_3 (155 mg, 1.12 mmol) and the mixture was stirred for 27 h at 70° C. After evaporation of solvent *in vacuo*, ice-water (200 mL) was poured into the reaction mixture. The precipitated solid was filtered off and recrystallized from ethyl acetate to give **13** (120 mg, 59%) as colorless needles, m.p. 170–172°C; ^{1}H-NMR (200 MHz, deuterochloroform): δ 3.58 (t, 2H, *J* = 8.9 Hz, H1), 4.89 (t, 2H, *J* = 8.9 Hz, H2), 7.30 (br t, 1H, *J* = 1.5 Hz, imidazole H4), 7.48 (br t, 1H, *J* = 1.5 Hz, imidazole H5), 7.61–7.63 (m, 2H, H8 and 9), 7.92 (br s, 1H, H6), 8.03 (br t, 1H, *J* = 1.5 Hz, imidazole H2); FAB-MS *m/z*: 272 (MH^+), 274 (MH^+ + 2). Analysis calculated for $C_{14}H_{10}ClN_3O$: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.89; H, 3.93; N, 15.08.

Effects on lipoprotein lipase mRNA expression in 3T3-L1 preadipocytes. This assay was performed according to the literature procedure [3].

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