DESIGN AND SYNTHESSES OF 2-OXIRANECARBOXYLATE DERIVATIVES AND THEIR HYPOGLYCEMIC ACTIVITIES\textsuperscript{†}

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Abstract - A series of 2-oxiranecarboxylate derivatives were prepared as carnitine palmitoyl transferase I (CPT-I) inhibitors for the development of new antiabetic agents. The syntheses and biological activities were reported. The most promising derivative (13\textsuperscript{b}) showed 2.5 times more hypoglycemic activity and 2 times lower acute toxicity compared to Etomoxir (3).

2-Oxiranecarboxylate derivatives such as Palmoxirate (1),\textsuperscript{1} Clomoxir (2)\textsuperscript{2} and Etomoxir (3)\textsuperscript{3,4} were reported as potent hypoglycemic agents in fasted animals and human\textsuperscript{5} (Figure 1). These compounds inactivate carnitine palmitoyl transferase I (CPT I), which is a rate limiting enzyme for transport of long chain acyl CoA into the mitochondria matrix for fatty $\beta$-oxidation.\textsuperscript{6} The mode of inactivation involves the irreversible binding with CPT I through a stable covalent modification.\textsuperscript{7} The inactivation of CPT I inhibits fatty acid oxidation, which gradually increases the utilization of glucose and finally the following decrement of gluconeogenesis leads hypoglycemic activity.\textsuperscript{8-10}

\[ \text{Palmoxirate (1)} \quad R^1 = \text{CH}_3 \quad R^2 = \text{CH}_3(\text{CH}_2)_{12}\text{CH}_2 \\
\text{Clomoxir (2)} \quad R^1 = \text{C}_2\text{H}_5 \quad R^2 = \text{Cl} - \text{CH}_2(\text{CH}_2)_3\text{CH}_2 \\
\text{Etomoxir (3)} \quad R^1 = \text{C}_2\text{H}_5 \quad R^2 = \text{Cl} - \text{OCH}_2(\text{CH}_2)_4\text{CH}_2 \\
\]

Figure 1

\textsuperscript{†} Dedicated to Prof. Teruaki Mukaiyama for the celebration of his 73\textsuperscript{nd} Birthday
Etomoxir has been most widely studied as a CPT I inhibitor in the series of 2-oxiranecarboxylates.\textsuperscript{4,11} It was reported that 3 is 7 and 15 times more effective compared with tolbutamide and buformin, respectively which are currently clinically using as hypoglycemic agents.\textsuperscript{4} Although Etomoxir had quite potent hypoglycemic effect, the drug development research was discontinued by its long-term toxicity such as myocardial hypertrophy.\textsuperscript{6} As a part of our program directed toward the development of new antidiabetic agents which have more potent activity and lower toxicity, we designed and synthesized a new series of 2-oxiranecarboxylate derivatives as CPT I inhibitors by modification of 3. The structure-activity relationship studies were carried out by comparison of the hypoglycemic activities of prepared derivatives.

Based on previous studies,\textsuperscript{9} the oxiran ring in 3 appeared to be essential for drug action. So we planned to modify the side chain of Etomoxir as a strategy for our SAR study. As shown in Schemes 1 and 2, we designed a new series of 2-oxiranecarboxylate derivatives (13a-j) by replacing the phenyl group in 3 with heterocyclic groups such as thiophene and furane. Also the length of the side chain was changed by increasing of the carbon number between heterocycle ring and oxygen.

**Scheme 1**

\[
\begin{align*}
\text{XOCH}_2\text{(CH}_2\text{)}_4\text{CH}_2\text{OX} \quad \xrightarrow{\text{i)} \quad \text{ROH (6)}} \quad \text{ROCH}_2\text{(CH}_2\text{)}_4\text{CH}_2\text{OMs} \\
\text{4} \quad \text{X = H} \quad \text{5} \quad \text{X = Ms}
\end{align*}
\]

\[R = \begin{array}{llll}
\text{a} & n = 0 & \text{d} & n = 1 \\
\text{b} & n = 1 & \text{e} & n = 2 \\
\text{c} & n = 2 & \text{f} & X = \text{CH}_3 \quad Y = \text{H} \\
& & \text{g} & X = \text{Cl} \quad Y = \text{H} \\
& & \text{h} & X = \text{H} \quad Y = \text{Cl} \\
& & \text{i} & X = \text{OCH}_3 \quad Y = \text{H}
\end{array}\]

Reagents: i) MsCl(2.2 eq.)/TEA/THF, rt, 1 h, (100%), iv) ROH (6a-j)/NaH/THF, rt, 16 h (50-78%)

The syntheses of 2-oxiranecarboxylate derivatives (13a-j) were accomplished in 6 steps starting from mesylate (7a-j) (Scheme 1). 1,6-Hexanediol (4) was dimesylated to give 5 and by using 5, the alcohols (6a-j), could be directly converted to 7a-j, respectively. Diethyl malonate was alkylated with 6a-j, followed by partial hydrolysis with one equivalent of KOH to give the half esters (9a-j).\textsuperscript{12} Treatment of half esters with Eschenmoser's salt\textsuperscript{13} in the presence of NaH produced ethyl 2-methylenecarboxylates (10a-j), which were dihydroxylated with 4-methylmorpholine N-oxide (NMO) and OsO\textsubscript{4}\textsuperscript{14} to afford the 2,3-dihydroxypropionates
(11a-j). The following tosylation and cyclization with excess K₂CO₃ furnished the desired ethyloxiranecarboxylates (13a-j) (Scheme 2).

**Scheme 2**

Reagents: i) diethyl malonate/NaH/THF, reflux, 16 h (63-100%), ii) KOH (1.0 eq.)/C₆H₅OH, rt, 1 h (60-89%), iii) Eschenmoser: salt/NaH/THF, reflux, 16 h (70-84%), iv) NMO/OsO₄/Acetone/H₂O/tert-C₆H₅OH, rt, 1 h, v) TsCl/Pyr, rt, 3 h, vi) K₂CO₃/C₆H₅OH, rt 5 h (62-85% from 10)

The oral hypoglycemic activities of the prepared derivatives compared with Etomoxir (3) were listed in Table I. Generally the replacement of benzene ring in 3 with thiophene showed comparable hypoglycemic activity to 3. Especially 13b showed the most potent hypoglycemic activity (75.9%) and the activity of 13e-h (30.7 - 42.2%) was similar to 3 (31.0%).

**Table 1. The oral hypoglycemic activity¹⁵,¹⁶ of prepared 2-oxiranecarboxylate derivatives (50 mg/kg).**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>Hypoglycemic activity (inhibition %)</th>
<th>Compd. No.</th>
<th>Hypoglycemic activity (inhibition %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>31.0</td>
<td>13a</td>
<td>21.4</td>
</tr>
<tr>
<td>13a</td>
<td>21.4</td>
<td>13f</td>
<td>33.7</td>
</tr>
<tr>
<td>13b</td>
<td>75.9</td>
<td>13g</td>
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<td>13c</td>
<td>5.6</td>
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<td>13d</td>
<td>9.3</td>
<td>13i</td>
<td>5.9</td>
</tr>
<tr>
<td>13e</td>
<td>42.2</td>
<td>13j</td>
<td>6.8</td>
</tr>
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</table>
Inspection of Table 1 showed that the hypoglycemic activity was dramatically changed by the length of alkyl linker chain between thiophene ring and oxygen (13a-c). For example the hypoglycemic activity of 13a, 13b and 13c were 21.4, 75.9 and 5.6% respectively. Similar result was observed in 3-substituted thiophene derivatives (13d, 13e). 13e showed 42.2% of hypoglycemic activity, whereas 13d showed only 9.3% of hypoglycemic activity. It is suggested that there is optimal length of the linker chain to maximize the binding interaction with CPT I. 3- or 5-Substituted derivatives (13g, 13h) with chlorine and methyl (13f) in thiophene ring resulted in comparable activities (32.7 - 33.7%) with 3, whereas substitution with 5-methoxy (13i) led loss of activity (5.9%). Replacement of furan moiety with thiophene moiety drastically decreased hypoglycemic activity (13j 6.8%; 13f 33.7%). Among the synthesized derivatives, 13b which showed the highest hypoglycemic activity was selected and the LD$_{50}$ was evaluated. The LD$_{50}$ of 13b was 487 mg/kg and that of etomoxir was 250 mg/kg. The 2.5-fold higher hyperglycemic activity and 2-fold lower acute toxicity of 13b compared with Etomoxir encouraged us to proceed with preclinical study for a new antidiabetic drug.

In conclusion, a series of 2-oxiranecarboxylate derivatives bearing thiophene or furan moiety were prepared and their hypoglycemic activities were reported. Among this series, 13b showed the most potent hypoglycemic activity (75.9%) compared with 3 (31%). Also The LD$_{50}$ of 13b (478 mg/kg) was 2 times lower than 3 (250 mg/kg).

**EXPERIMENTAL**

**General method.**

$^1$H and $^{13}$C NMR spectra were measured with a Bruker ARX-300 spectrometer using TMS (Me$_3$Si) as the internal standard. MS spectra were obtained on a VG Trio-2 GC-MS instrument; high resolution MS spectra were obtained on a HP 5890 Series II. Microanalysis were performed with EA1110 CE INSTRUMENT. All reactions were carried out under argon atmosphere, using anhydrous solvents. Most reagents were obtained from the best commercial suppliers and used without further purification unless noted. Tetrahydrofuran was distilled from Na and benzophenone.

**1,6-Hexyl dimesylate (5).** To a tetrahydrofuran suspension (70 mL) of 1,6-hexanediol (4) (5 g, 42.3 mmol) was added methanesulfonyl chloride (7.2 mL, 93.1 mmol) and triethylamine (14.7 mL, 106.0 mmol) at 0 °C. The reaction mixture was stirred at rt (1.5 h). The excess solvent was removed in vacuo and the residue was extracted with methylene chloride (3 × 200 mL). The combined methylene chloride solution was washed with water (2 × 20 mL), aq. 5%-HCl (2 × 20 mL) and brine (2 × 20 mL), then dried over anhydrous MgSO$_4$. The solvent was removed in vacuo and the residue was purified by recrystallization (ethyl acetate and n-hexane) to give 5 as a colorless needle (10.7 g, 92%); mp 58-59 °C; $^1$H NMR (CDCl$_3$, 300 MHz) δ 1.50 (m, 4 H), 1.81 (m,
6-(2-Thiophenoxy)hexylmesylate (7a)

To a tetrahydrofuran (100 mL) suspension of 95% NaH (883 mg, 34.95 mmol) was added a tetrahydrofuran solution (10 mL) of 6a (3.50 g, 34.95 mmol) at 0 °C. The reaction mixture was stirred for 10 min and then (11.51 g, 41.94 mmol) was added to the reaction. The reaction mixture was stirred for 16 h at rt. The solvent was removed in vacuo and the residue was diluted with ethyl acetate (200 mL). The ethyl acetate solution was washed with water (2 x 50 mL) and brine (2 x 50 mL), then dried over anhydrous MgSO₄. The residue was purified by column chromatography (SiO₂, ethyl acetate : n-hexane = 1 : 4) to give 7a as a pale yellow oil (7.16 g, 73%). ¹H NMR (CDCl₃, 400 MHz) δ 1.50 (m, 4 H), 1.79 (m, 4 H), 3.01 (s, 3 H), 4.03 (t, J = 6.26 Hz, 2 H) 4.24 (t, J = 6.42 Hz, 2 H), 6.19 (br, 1 H), 6.54 (d, J = 5.60 Hz, 1 H), 6.71 (dd, J = 3.74, 5.60 Hz, 1 H). Anal. Calcd for C₁₁H₁₈O₄S₂: C, 47.46; H, 6.52. Found: C, 47.41; H, 6.47.

6-(2-Thiophenemethoxy)hexylmesylate (7b)

By using the preceding procedure and the utilization of 95% NaH (442 mg, 17.52 mmol) and 6b (5.80 g, 21.00 mmol), 5 (2.0 g, 17.52 mmol) gave 7b as a pale yellow oil (3.95 g, 77%). ¹H NMR (CDCl₃, 300 MHz) δ 1.40 1.58 (m, 4 H), 1.61 (m, 2 H), 1.85 (m, 2 H), 3.40 (t, J = 6.40 Hz, 2 H), 4.22 (t, J = 6.56 Hz, 2 H), 4.65 (s, 2 H) 6.95 (m, 2 H), 7.26 (m, 1 H). Anal. Calcd for C₁₂H₂₀O₄S₂: C, 49.29; H, 6.89. Found: C, 49.21; H, 6.81.

6-(2-Thiopheneethoxy)hexylmesylate (7c)

By using the preceding procedure and the utilization of 95% NaH (570 mg, 22.58 mmol) and 6c (2.89 g, 22.54 mmol), 5 (5.0 g, 18.22 mmol) gave 7c as a pale yellow oil (3.52 g, 51%). ¹H NMR (CDCl₃, 300 MHz) δ 1.41 (m, 4 H), 1.60 (m, 2 H), 1.76 (m, 2 H), 3.00 (s, 3 H), 3.09 (t, J = 6.60 Hz, 2 H), 3.46 (t, J = 6.40 Hz, 2 H), 3.64 (t, J = 6.60 Hz, 2 H), 4.22 (t, J = 6.52 Hz, 2 H), 6.85 (m, 1 H), 6.93 (dd, J = 3.47, 5.03 Hz, 1 H), 7.14 (dd, J = 1.00, 5.03 Hz, 1 H). Anal. Calcd for C₁₃H₂₂O₄S₂: C, 50.95; H, 7.24. Found: C, 50.24; H, 7.17.

6-(3-Thiophenemethoxy)hexylmesylate (7d)

By using the preceding procedure and the utilization of 95% NaH (332 mg, 13.14 mmol) and 6d (1.50 g, 13.14 mmol), 5 (4.33 g, 15.77 mmol) gave 7d as an oil (2.46 g, 64%). ¹H NMR (CDCl₃, 300 MHz) δ 1.41 (m, 4 H), 1.61 (m, 2 H), 1.74 (m, 2 H), 2.98 (s, 3 H), 3.45 (t, J = 6.40 Hz, 2 H), 4.21 (t, J = 6.50 Hz, 2 H), 4.49 (s, 2 H) 7.06 (d, J = 4.67 Hz, 1 H), 7.19 (s, 1 H), 7.29 (m, 1 H). Anal. Calcd for C₁₃H₂₀O₄S₂: C, 49.29; H, 6.89. Found: C 49.11; H, 6.75.
6-(3-Thiopheneethoxy)hexylmesylate (7e)
By using the preceding procedure and the utilization of 95% NaH (570 mg, 22.58 mmol) and 6e (2.89 g, 22.58 mmol), 5 (5.0 g, 18.22 mmol) gave 7e as a pale yellow oil (3.93 g, 57%). 1H NMR (CDCl3, 300 MHz) δ 1.40 (m, 4 H), 1.59 (m, 2 H), 1.75 (m, 2 H), 2.91 (t, J = 6.94 Hz, 2 H), 3.00 (s, 3 H), 3.44 (t, J = 6.46 Hz, 2 H), 3.63 (t, J = 7.04 Hz, 2 H), 4.22 (t, J = 6.55 Hz, 2 H), 6.98 (dd, J = 1.25, 4.90 Hz, 2 H), 7.02 (m, 1 H), 7.25 (dd, J = 3.10, 4.90 Hz, 1 H). Anal. Calcd for C13H22O4S2: C, 50.95; H, 7.24. Found: C, 50.73; H, 7.13.

6-(5-Methyl-2-thiophenemethoxy)hexylmesylate (7f)
By using the preceding procedure and the utilization of 95% NaH (138 mg, 5.47 mmol) and 6f (1.25 g, 5.47 mmol), 5 (1.5 g, 5.47 mmol) gave 7f as a pale yellow oil (1.60 g, 96%). 1H NMR (CDCl3, 300 MHz) δ 1.43 (m, 4 H), 1.60 (m, 2 H), 1.75 (m, 2 H), 2.30 (s, 3 H), 2.46 (d, J = 0.82 Hz, 3 H), 3.45 (t, J = 6.40 Hz, 2 H), 4.22 (t, J = 6.56 Hz, 2 H), 4.56 (s, 2 H), 6.60 (d, J = 3.36 Hz, 1 H), 6.76 (d, J = 3.36 Hz, 1 H). Anal. Calcd for C13H22O4S2: C, 50.95; H, 7.24. Found: C, 50.84; H, 7.23.

6-(5-Chloro-2-thiophenemethyl)hexylmesylate (7g)
By using the preceding procedure and the utilization of 95% NaH (240 mg, 9.49 mmol) and 6g (1.41 g, 9.49 mmol), 5 (3.12 g, 11.39 mmol) gave 7g as a pale yellow oil (1.54 g, 50%). 1H NMR (CDCl3, 300 MHz) δ 1.41 (m, 4 H), 1.60 (m, 2 H), 1.74 (m, 2 H), 3.00 (s, 3 H), 3.46 (t, J = 6.30 Hz, 2 H), 4.22 (t, J = 6.53 Hz, 2 H), 4.54 (s, 2 H), 6.75 (d, J = 3.72 Hz, 1 H), 6.77 (d, J = 3.72 Hz, 1 H). Anal. Calcd for C13H19O4ClS2: C, 44.09; H, 5.86. Found: C, 43.85; H, 5.64.

6-(3-Chloro-2-thiophenemethoxy)hexylmesylate (7h)
By using the preceding procedure and the utilization of 95% NaH (250 mg, 9.11 mmol) and 6h (1.47 g, 9.89 mmol), 5 (3.26 g, 11.87 mmol) gave 7h as a colorless oil (1.07 g, 33%). 1H NMR (CDCl3, 300 MHz) δ 1.42 (m, 4 H), 1.62 (m, 2 H), 1.76 (m, 2 H), 3.00 (s, 3 H), 3.50 (t, J = 6.37 Hz, 2 H), 4.22 (t, J = 6.50 Hz, 2 H), 4.64 (s, 2 H), 6.90 (d, J = 5.20 Hz, 2 H), 7.27 (d, J = 5.20 Hz, 1 H). Anal. Calcd for C13H19O4ClS2: C, 44.09; H, 5.86. Found: C, 43.95; H, 5.94.

6-(5-Methoxy-2-thiophenemethoxy)hexylmesylate (7i)
By using the preceding procedure, 95% NaH (386 mg, 15.26 mmol) and 6i (2.0 g, 12.60 mmol), 5 (4.95 g, 18.03 mmol) gave 7i as an oil (0.67 g, 26%). 1H NMR (CDCl3, 300 MHz) δ 1.41 (m, 4 H), 1.57 (m, 2 H), 1.75 (m, 2 H), 3.00 (s, 3 H), 3.44 (m, 2 H), 3.87 (s, 3 H), 4.22 (m, 2 H), 4.48 (s, 2 H), 6.04 (d, J = 3.80 Hz, 1 H), 6.60 (d, J = 3.80 Hz, 1 H). Anal. Calcd for C13H22O5S2: C, 48.42; H, 6.88. Found: C, 48.39; H, 6.95.
6-(5-Methyl-2-furanemethoxy)hexylmesylate (7j)

By using the preceding procedure and the utilization of 95% NaH (572 mg, 22.65 mmol) and 6j (2.54 g, 22.65 mmol), 5 (7.46 g, 27.18 mmol) gave 7j as a pale yellow oil (2.79 g, 43%). ¹H NMR (CDCl₃, 300 MHz) δ 1.41 (m, 4 H), 1.61 (m, 2 H), 2.29 (d, J = 0.81 Hz, 3 H), 3.00 (s, 3 H), 3.46 (t, J = 6.54 Hz, 2 H), 4.22 (t, J = 6.53 Hz, 2 H), 4.37 (s, 2 H), 5.92 (m, J = 3.01 Hz, 1 H), 6.19 (d, J = 3.01 Hz, 1 H). Anal. Calcd for C₁₅H₂₂O₃S: C, 53.77; H, 7.64. Found: C, 51.88; H, 7.45.

Diethyl 6-(2-thiophenoxy)hexylmalonate (8a)

To a tetrahydrofuran (5 mL) suspension of 95% NaH (77 mg, 3.06 mmol) and diethyl malonate (490 mg, 3.06 mmol) was added a tetrahydrofuran solution (5 mL) of 7a (710 mg, 2.55 mmol) at 0 °C. The reaction mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 10 mL) and brine (2 × 10 mL), then dried over anhydrous MgSO₄. The residue was purified by column chromatography (SiO₂, ethyl acetate : n-hexane = 1 : 5) to give 8a as a pale yellow oil (84 mg, 94%). ¹H NMR (CDCl₃, 300 MHz) δ 1.27 (t, J = 7.10 Hz, 6 H), 1.35-1.45 (m, 6 H), 1.77 (m, 2 H), 1.89 (m, 2 H), 3.32 (t, J = 7.52 Hz, 1 H), 4.01 (t, J = 6.40 Hz, 2 H), 4.20 (q, J = 7.10 Hz, 4 H), 6.19 (dd, J = 1.28, 3.70 Hz, 4 H), 6.53 (dd, J = 1.28, 5.68 Hz, 1 H), 6.71 (dd, J = 3.70, 5.68 Hz, 1 H). Anal. Calcd for C₁₇H₂₆O₅S: C, 59.62; H, 7.65. Found: C, 58.34; H, 7.64.

Diethyl 6-(2-thiophenemethoxy)hexylmalonate (8b)

By using the preceding procedure and the utilization of 95% NaH (308 mg, 17.5 mmol) and diethyl malonate (1.85 mL, 12.19 mmol), 7b (3.24 g, 11.08 mmol) gave 8b as a pale yellow oil (3.50 g, 89%). ¹H NMR (CDCl₃, 300 MHz) δ 1.27 (t, J = 7.10 Hz, 6 H), 1.32 (m, 6 H), 1.60 (m, 2 H), 1.90 (m, 2 H), 3.30 (t, J = 7.56 Hz, 1 H), 3.46 (t, J = 6.50 Hz, 2 H), 4.20 (q, J = 7.10 Hz, 4 H), 4.65 (s, 2 H), 6.96-6.99 (m, 2 H), 7.28 (dd, J = 1.68, 4.77 Hz, 1 H). Anal. Calcd for C₁₉H₂₃O₅S: C, 60.65; H, 7.92. Found: C, 59.64; H, 7.51.

Diethyl 6-(2-thiopheneethoxy)hexylmalonate (8c)

By using the preceding procedure and the utilization of 95% NaH (319 mg, 12.64 mmol) and diethyl malonate (2.02 g, 12.64 mmol), 7c (3.52 g, 11.49 mmol) gave 8c as a pale yellow oil (4.29 g, 100%). ¹H NMR (CDCl₃, 300 MHz) δ 1.27 (t, J = 7.16 Hz, 6 H), 1.31 (m, 6 H), 1.58 (m, 2 H), 1.89 (m, 2 H), 3.09 (t, J = 6.80 Hz, 2 H), 3.31 (t, J = 7.58 Hz, 1 H), 3.44 (t, J = 6.56 Hz, 2 H), 3.64 (t, J = 6.80 Hz, 2 H), 4.20 (q, J = 7.16 Hz, 4 H), 6.85 m, 1 H), 6.93 (dd, J = 3.40, 5.10 Hz, 1 H), 7.14 (dd, J = 1.00, 5.10 Hz, 1 H). Anal. Calcd for C₁₉H₂₃O₅S: C, 1.59; H, 8.16. Found: C, 59.86; H, 8.04.

Diethyl 6-(3-thiophenemethoxy)hexylmalonate (8d)
By using the preceding procedure and the utilization of 95% NaH (255 mg, 10.09 mmol) and diethyl malonate (1.62 g, 10.09 mmol), 7d (2.46 g, 8.41 mmol) gave 8d as a pale yellow oil (2.60 g, 87%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.26 (t, $J = 7.04$ Hz, 6 H), 1.20-1.40 (m, 6 H), 1.59 (m, 2 H), 1.88 (m, 2 H), 3.31 (t, $J = 7.44$ Hz, 1 H) 3.44 (t, $J = 6.50$ Hz, 2 H), 4.19 (q, $J = 7.04$ Hz, 4 H), 4.50 (s, 2 H), 7.06 (d, $J = 4.75$ Hz, 1 H), 7.19 (br, 1 H) 7.29 (m, 1 H), Anal. Calcd for C$_{18}$H$_{28}$O$_5$S: C, 60.65; H, 7.92. Found: C, 59.42; H, 7.68.

**Diethyl 6-(3-thiopheneethoxy)hexylmalonate (8e)**

By using the preceding procedure and the utilization of 95% NaH (389 mg, 15.39 mmol) and diethyl malonate (2.47 g, 15.39 mmol), 7e (3.93 g, 12.83 mmol) gave 8e as a pale yellow oil (4.74 g, 100%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.27 (t, $J = 7.14$ Hz, 6 H), 1.33 (m, 6 H), 1.56 (m, 2 H), 1.89 (m, 2 H), 2.91 (t, $J = 7.00$ Hz, 2 H) 3.31 (t, $J = 7.56$ Hz, 1 H), 3.43 (t, $J = 6.59$ Hz, 2 H), 3.62 (t, $J = 7.00$ Hz, 2 H), 4.20 (q, $J = 7.14$ Hz, 4 H), 6.98 (dd, $J = 1.15$, 4.89 Hz, 1 H), 7.02 (m, 1 H), 7.25 (dd, $J = 3.90$, 4.89 Hz, 1 H). Anal. Calcd for C$_{19}$H$_{30}$O$_5$S: C, 61.59; H, 8.16. Found: C, 60.72; H, 8.20.

**Diethyl 6-(5-methyl-2-thiophenemethoxy)hexylmalonate (8f)**

By using the preceding procedure and the utilization of 95% NaH (145 mg, 5.74 mmol) and diethyl malonate (0.87 mL, 5.74 mmol), 7f (1.60 g, 5.22 mmol) gave 8f as a pale yellow oil (1.26 g, 65%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.26 (t, $J = 7.15$ Hz, 6 H), 1.32 (m, 6 H), 1.57 (m, 2 H), 1.87 (m, 2 H), 2.46 (d, $J = 0.91$ Hz, 3 H), 3.30 (t, $J = 7.58$ Hz, 1 H), 3.43 (t, $J = 6.58$ Hz, 2 H), 4.19 (m, 4 H), 4.56 (s, 2 H), 6.60 (d, $J = 3.36$ Hz, 1 H), 6.76 (d, $J = 3.36$ Hz, 1 H). Anal. Calcd for C$_{19}$H$_{30}$O$_5$S: C, 61.59; H, 8.16. Found: C, 60.45; H, 7.98.

**Diethyl 6-(5-chloro-2-thiophenemethoxy)hexylmalonate (8g)**

By using the preceding procedure and the utilization of 95% NaH (131 mg, 5.18 mmol) and diethyl malonate (0.79 mL, 5.18 mmol), 7g (1.54 g, 4.71 mmol) give 8g as a pale yellow oil (1.60 g, 87%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.26 (t, $J = 7.16$ Hz, 6 H), 1.33 (m, 6 H), 1.57 (m, 2 H), 1.88 (m, 2 H), 3.30 (t, $J = 7.53$ Hz, 1 H), 3.44 (t, $J = 6.50$ Hz, 2 H), 4.19 (q, $J = 7.16$ Hz, 4 H), 4.53 (s, 2 H), 6.74 (d, $J = 3.71$ Hz, 1 H), 6.77 (d, $J = 3.71$ Hz, 1 H). Anal. Calcd for C$_{19}$H$_{27}$O$_5$Cl S: C, 55.30; H, 6.96. Found: C, 54.80; H, 6.23.

**Diethyl 6-(3-chloro-2-thiophenemethoxy)hexylmalonate (8h)**

By using the preceding procedure and the utilization of 95% NaH (91 mg, 3.60 mmol) and diethyl malonate (0.55 mL, 3.60 mmol), 7h (1.07 g, 3.27 mmol) gave 8h as a pale yellow oil (1.05 g, 82%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.27 (t, $J = 7.11$ Hz, 6 H), 1.33 (m, 6 H), 1.58 (m, 2 H), 1.88 (m, 2 H), 3.30 (t, $J = 7.53$ Hz, 1 H), 3.48 (t, $J = 6.50$ Hz, 2 H), 4.19 (q, $J = 7.11$ Hz, 4 H), 4.63 (s, 2 H), 6.89 (d, $J = 5.20$ Hz, 1 H), 7.26 (d, $J = 5.20$ Hz, 1 H). Anal. Calcd for C$_{18}$H$_{27}$O$_5$Cl S: C, 55.30; H, 6.96. Found: C, 54.20; H, 6.15.
Diethyl 6-(5-methoxy-2-thiophenemethoxy)hexylmalonate (8i)

By using the preceding procedure and the utilization of 95% NaH (58 mg, 2.29 mmol) and diethyl malonate (0.35 mL, 2.29 mmol), 7i (0.67 g, 2.08 mmol) gave 8i as a pale yellow oil (0.34 g, 43%). \( ^1H \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.26 (t, \( J = 7.10 \) Hz, 6 H), 1.33 (m, 6 H), 1.55 (m, 2 H), 1.89 (m, 2 H), 3.42 (t, \( J = 6.55 \) Hz, 2 H), 3.87 (s, 3 H), 4.19 (q, \( J = 7.10 \) Hz, 4 H), 4.48 (s, 2 H), 6.03 (d, \( J = 3.76 \) Hz, 1 H), 6.60 (d, \( J = 3.76 \) Hz, 1 H). Anal. Calcd for C\(_{19}\)H\(_{30}\)O\(_6\)S: C, 59.04; H, 7.82. Found: C, 58.21; H, 7.76.

Diethyl 6-(5-methyl-2-furanmethoxy)hexylmalonate (8j)

By using the preceding procedure and the utilization of 95% NaH (267 mg, 10.57 mmol) and diethyl malonate (1.69 g, 10.57 mmol), 7j (2.79 g, 9.61 mmol) gave 8j as a pale yellow oil (3.66 g, 100%). \( ^1H \) NMR (CDCl\(_3\), 400 MHz) \( \delta \) 1.26 (t, \( J = 7.13 \) Hz, 6 H), 1.32 (m, 6 H), 1.58 (m, 2 H), 1.88 (m, 2 H), 2.29 (s, 3 H), 3.30 (t, \( J = 7.58 \) Hz, 1 H), 3.44 (t, \( J = 6.68 \) Hz, 2 H), 4.19 (q, \( J = 7.13 \) Hz, 4 H), 4.36 (s, 2 H), 5.91 (d, \( J = 3.01 \) Hz, 1 H), 6.18 (d, \( J = 3.01 \) Hz, 1 H). Anal. Calcd for C\(_{19}\)H\(_{30}\)O\(_6\): C, 64.38; H, 8.53. Found: C, 63.89; H, 8.35.

Ethyl 6-(2-thiophenoxy)hexylmalonate (9a)

To an ethanol solution (30 mL) of 8a (0.82 g, 2.40 mmol) was added a 85% potassium hydroxide (174 mg, 2.64 mmol) and the reaction mixture was stirred for 6 h at rt. The solvent was removed in vacuo and the residue was diluted with water (150 mL). The water solution was washed with ethyl acetate (20 mL x 3) to remove starting material. The \( \text{p} \)H was adjusted to 2.0 with aq. 5\%\- HCl solution, then extracted with ethyl acetate (3 x 50 mL). The combined ethyl acetate solution was washed with brine (2 x 20 mL), then dried over anhydrous MgSO\(_4\). The solvent was removed in vacuo to give 9a as a pale yellow oil (0.66 g, 88%). \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 1.29 (t, \( J = 7.06 \) Hz, 3 H), 1.40 (m, 6 H), 1.77 (m, 2 H), 1.93 (m, 2 H), 3.38 (t, \( J = 7.48 \) Hz, 1 H), 4.01 (t, \( J = 6.48 \) Hz, 2 H), 4.24 (q, \( J = 7.06 \) Hz, 2 H), 6.19 (dd, \( J = 1.30 \), 3.70 Hz, 1 H), 6.53 (dd, \( J = 1.30 \), 5.70 Hz, 1 H), 6.71 (dd, \( J = 3.70 \), 5.70 Hz, 1 H), 7.55 (br, 1 H). Anal. Calcd for C\(_{15}\)H\(_{22}\)O\(_5\)S: C, 57.30; H, 7.05. Found: C, 56.83; H, 6.86.

Ethyl 6-(2-thiophenemethoxy)hexylmalonate (9b)

By using the preceding procedure 8b (3.52 g, 9.82 mmol) gave 9b as an oil (2.54 g, 79%). \( ^1H \) NMR (CDCl\(_3\), 300 MHz) \( \delta \) 1.28 (t, \( J = 7.15 \) Hz, 3 H), 1.34 (m, 6 H), 1.60 (m, 2 H), 1.90 (m, 2 H), 3.36 (t, \( J = 7.43 \) Hz, 1 H), 3.46 (t, \( J = 6.50 \) Hz, 2 H), 4.22 (q, \( J = 7.15 \) Hz, 2 H), 4.66 (s, 2 H), 6.95-6.99 (m, 2 H), 7.28 (dd, \( J = 1.50 \), 4.85 Hz, 1 H). Anal. Calcd for C\(_{16}\)H\(_{23}\)O\(_5\)S: C, 58.51; H, 7.37. Found: C, 58.31; H, 7.45.

Ethyl 6-(2-thiopheneethoxy)hexylmalonate (9c)
By using the preceding procedure 8e (4.29 g, 11.52 mmol) gave 9e as an oil (2.08 g, 52%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, $J = 6.96$ Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.09 (t, $K = 6.70$ Hz, 2 H), 3.38 (t, $J = 7.37$ Hz, 1 H), 3.44 (t, $J = 6.75$ Hz, 2 H), 3.65 (t, $J = 6.70$ Hz, 2 H), 4.24 (q, $J = 6.96$ Hz, 2 H), 6.85 (br, 1 H), 6.93 (m, 1 H), 7.14 (br, 1 H), 7.83 (br, 1 H). Anal. Calcd for C17H26O5S: C, 59.62; H, 7.65. Found: C, 59.45; H, 7.62.

**Ethyl 6-(3-thiophenemethoxy)hexylmalonate (9d)**

By using the preceding procedure 8d (2.60 g, 7.29 mmol) gave 9d as an oil (2.13 g, 89%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, $J = 7.15$ Hz, 3 H), 1.34 (m, 6 H), 1.59 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, $J = 7.24$ Hz, 1 H), 3.45 (t, $J = 6.77$ Hz, 2 H), 4.23 (q, $J = 7.15$ Hz, 2 H), 4.50 (s, 2 H), 7.07 (br, 1 H), 7.20 (br, 1 H), 7.29 (m, 1 H). Anal. Calcd for C16H26O5S: C, 58.51; H, 7.37. Found: C, 58.32; H, 7.21.

**Ethyl 3-thiopheneethoxy)hexylmalonate (9e)**

By using the preceding procedure 8e (4.74 g, 12.72 mmol) gave 9e as an oil (3.26 g, 74%). 1H NMR (CDCl3, 300 MHz) δ 1.28 (t, $J = 7.12$ Hz, 3 H), 1.34 (m, 6 H), 1.57 (m, 2 H), 1.91 (m, 2 H), 2.91 (t, $J = 7.08$ Hz, 2 H), 3.37 (t, $J = 7.46$ Hz, 1 H), 3.44 (t, $J = 6.60$ Hz, 2 H), 3.64 (t, $J = 7.08$ Hz, 2 H), 4.22 (q, $J = 7.12$ Hz, 2 H), 6.98 (dd, $J = 1.17, 4.90$ Hz, 1 H), 7.02 (dd, $J = 1.0, 2.96$ Hz, 1 H), 7.25 (dd, $J = 2.96, 4.90$ Hz, 1 H), 8.3 (br, 1 H). Anal. Calcd for C15H28O5S: C, 59.62; H, 7.65. Found: C, 59.36; H, 7.62.

**Ethyl 6-(6-(5-methyl-2-thiophenemethoxy)hexylmalonate (9f)**

By using the preceding procedure 8f (1.26 g, 3.38 mmol) gave 9f as an oil (0.61 g, 59%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, $J = 7.10$ Hz, 3 H), 1.33 (m, 6 H), 1.55 (m, 2 H), 1.91 (m, 2 H), 2.46 (t, $J = 0.80$ Hz, 3 H), 3.37 (t, $J = 7.37$ Hz, 1 H), 3.44 (t, $J = 6.55$ Hz, 2 H), 4.23 (q, $J = 7.10$ Hz, 2 H), 4.56 (s, 2 H), 6.60 (d, $J = 3.36$ Hz, 1 H), 6.76 (d, $J = 3.36$ Hz, 1 H). Anal. Calcd for C17H26O5S: C, 59.62; H, 7.65. Found: C, 59.47; H, 7.64.

**Ethyl 5-chloro-2-thiophenemethoxy)hexylmalonate (9g)**

By using the preceding procedure 8g (1.59 g, 4.07 mmol) gave 9g as an oil (1.25 g, 85%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, $J = 7.16$ Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, $J = 7.47$ Hz, 1 H), 3.45 (t, $J = 6.38$ Hz, 2 H), 4.23 (q, $J = 7.16$ Hz, 2 H), 4.54 (s, 2 H), 6.75 (m, 2 H). Anal. Calcd for C16H22O5ClS: C, 52.96; H, 6.39. Found: C, 52.54; H, 6.32.

**Ethyl 6-(3-chloro-2-thiophenemethoxy)hexylmalonate (9h)**

By using the preceding procedure 8h (1.05 g, 2.69 mmol) gave 9h as an oil (0.77 g, 79%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, $J = 7.07$ Hz, 3 H), 1.35 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 3.37 (t, $J = 7.43$ Hz, 1 H),
3.47 (t, J = 6.50 Hz, 2 H), 4.23 (q, J = 7.07 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.16 Hz, 1 H), 7.26 (d, J = 5.16 Hz, 1 H). Anal. Calcd for C_{16}H_{27}O_{2}S: C, 52.96; H, 6.39. Found: C, 52.74; H, 6.35.

Ethyl 6-(5-methoxy-2-thiophenemethoxy)hexylmalonate (9i)
By using the preceding procedure 8i (340 mg, 0.88 mmol) gave 9i as an oil (260 mg, 83%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.28 (t, J = 7.16 Hz, 3 H), 1.32 (m, 6 H), 1.57 (m, 2 H), 1.95 (m, 2 H), 3.42 (m, 3 H), 3.89 (s, 3 H), 4.24 (q, J = 7.16 Hz, 2 H), 4.48 (s, 2 H), 6.03 (d, J = 3.54 Hz, 1 H), 6.60 (d, J = 3.54 Hz, 1 H). Anal. Calcd for C\(_{17}\)H\(_{26}\)O\(_6\)S: C, 56.96; H, 7.31. Found: C, 56.83; H, 7.38.

Ethyl 6-(5-methyl-2-furanmethoxy)hexylmalonate (9j)
By using the preceding procedure 8j (3.66 g, 10.27 mmol) gave 9j as an oil (1.76 g, 52%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.29 (t, J = 7.08 Hz, 3 H), 1.34 (m, 6 H), 1.58 (m, 2 H), 1.91 (m, 2 H), 2.29 (s, 3 H), 3.37 (t, J = 7.28 Hz, 1 H), 3.45 (t, J = 6.50 Hz, 2 H), 4.24 (q, J = 7.08 Hz, 2 H), 4.37 (s, 2 H), 5.91 (s, 1 H), 6.18 (d, J = 2.46 Hz, 1 H). Anal. Calcd for C\(_{17}\)H\(_{28}\)O\(_6\): C, 62.56; H, 8.03. Found: C, 62.46; H, 7.94.

Ethyl 2-[6-(2-thiophenoxy)hexyl]-2-methylidenepropionate (10a)
To a tetrahydrofuran (10 mL) suspension of 9a (650 mg, 2.07 mmol) at 0 °C. The reaction mixture was stirred for 30 min and then Eschenmosher’s salt (459 mg, 2.48 mmol) was added to the reaction. The reaction mixture was refluxed for 16 h. The solvent was removed in vacuo and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 × 10 mL), 1 N-aq. HCl (2 × 10 mL), 5% aq.-NaHCO\(_3\) (2 × 10 mL) and brine (2 × 10 mL), then dried over anhydrous MgSO\(_4\). After the solvent was removed in vacuo, the residue was purified by column chromatography (SiO\(_2\), ethyl acetate : n-hexane = 1 : 5) to give 10a as a pale yellow oil (400 mg, 68%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.31 (t, J = 7.14 Hz, 3 H), 1.35-1.55 (m, 6 H), 1.80 (m, 2 H), 2.31 (br, 2 H), 4.02 (t, J = 6.46 Hz, 2 H), 4.21 (q, J = 7.14 Hz, 2 H), 5.52 (m, 1 H), 6.13 (d, J = 1.36 Hz, 1 H), 6.19 (dd, J = 1.47, 3.75 Hz, 1 H), 6.53 (dd, J = 1.47, 5.75 Hz, 1 H), 6.71 (dd, J = 3.75, 5.75 Hz, 1 H). Anal. Calcd for C\(_{15}\)H\(_{22}\)O\(_3\)S: C, 68.80; H, 7.85. Found: C, 68.78; H, 7.92.

Ethyl 2-[6-(2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10b)
By using the preceding procedure 9b (2.42 g, 7.37 mmol) gave 10b as an oil (1.82 g, 83%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.30 (t, J = 7.14 Hz, 3 H), 1.35 (m, 4 H), 1.45 (m, 2H), 1.60 (m, 2 H), 2.29 (m, 2 H), 3.47 (t, J = 6.52 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 4.65 (s, 2H), 5.50 (m, 1 H), 6.12 (m, 1 H), 6.96-6.99 (m, 2 H), 7.28 (dd, J = 1.57, 4.65 Hz, 1 H). Anal. Calcd for C\(_{16}\)H\(_{24}\)O\(_3\)S: C, 64.83; H, 8.16. Found: C, 64.78; H, 8.09.
Ethyl 2-[6-(2-thiopheneethoxy)hexyl]-2-methylidenepropionate (10c)

By using the preceding procedure 9c (2.08 g, 6.04 mmol) gave 10c as an oil (880 mg, 47%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (t, $J = 7.14$ Hz, 3 H), 1.35 (m, 4 H), 1.47 (m, 2H), 1.58 (m, 2 H), 2.29 (m, 2 H), 3.10 (t, $J = 6.70$ Hz, 2 H), 3.45 (t, $J = 6.51$ Hz, 2 H), 3.65 (t, $J = 6.70$ Hz, 2 H), 4.21 (q, $J = 7.14$ Hz, 2H), 5.51 (s, 1 H), 6.13 (s, 1 H), 6.85 (br, 1 H), 6.93 (br, 1 H), 7.14 (m, 1 H). Anal. Calcd for C$_{13}$H$_{26}$O$_5$S: C, 65.77; H, 8.44. Found: C, 65.53; H, 8.39.

Ethyl 2-[6-(3-thiophenemethoxy)hexyl]-2-methylidenepropionate (10d)

By using the preceding procedure 9c (2.07 g, 6.30 mmol) gave 10d as an oil (1.24 g, 66%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (t, $J = 7.07$ Hz, 3 H), 1.35 (m, 4 H), 1.47 (m, 2H), 1.60 (m, 2 H), 2.29 (m, 2 H), 3.45 (t, $J = 6.48$ Hz, 2 H), 4.20 (q, $J = 7.07$ Hz, 2 H), 4.50 (s, 2 H), 5.50 (s, 1 H), 6.12 (s, 1 H), 7.07 (d, $J = 4.38$ Hz, 1 H), 7.20 (br, 1 H), 7.20 (br, 1 H), 7.28 (m, 1 H). Anal. Calcd for C$_{16}$H$_{28}$O$_5$S: C, 64.83; H, 8.16. Found: C, 64.68; H, 8.16.

Ethyl 2-[3-thiopheneethoxy]hexyl]-2-methylidenepropionate (10e)

By using the preceding procedure 9c (3.26 g, 9.46 mmol) gave 10e as an oil (2.29 g, 78%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (t, $J = 7.13$ Hz, 3 H), 1.34 (m, 4 H), 1.47 (m, 2H), 1.58 (m, 2 H), 2.29 (m, 2 H), 2.91 (t, $J = 7.0$ Hz, 2 H), 3.44 (t, $J = 6.63$ Hz, 2 H), 3.63 (t, $J = 7.0$ Hz, 2 H), 4.21 (q, $J = 7.13$ Hz, 2 H), 6.99 (dd, $J = 1.17$, 4.90 Hz, 1 H), 7.02 (m, 1 H), 7.25 (dd, $J = 3.0$, 4.90 Hz, 1 H). Anal. Calcd for C$_{13}$H$_{26}$O$_5$S: C, 65.77; H, 8.44. Found: C, 65.53; H, 8.43.

Ethyl 2-[6-(5-methyl-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10f)

By using the preceding procedure 9f (610 mg, 1.77 mmol) gave 10f as an oil (2.54 g, 79%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (t, $J = 7.15$ Hz, 3 H), 1.22-1.58 (m, 8 H), 2.29 (br, 2 H), 2.46 (d, $J = 0.83$ Hz, 3 H), 3.44 (t, $J = 6.59$ Hz, 2 H), 4.20 (q, $J = 7.15$ Hz, 2 H), 4.56 (s, 2 H), 5.50 (m, 1 H), 6.12 (d, $J = 1.56$ Hz, 1 H), 6.60 (m, 1 H), 6.76 (d, $J = 3.35$ Hz, 1 H). Anal. Calcd for C$_{17}$H$_{26}$O$_5$S: C, 65.77; H, 8.44. Found: C, 65.46; H, 8.35.

Ethyl 2-[6-(5-chloro-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10g)

By using the preceding procedure 9g (1.25 g, 3.44 mmol) gave 10g as an oil (0.90 g, 79%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 1.30 (t, $J = 7.13$ Hz, 3 H), 1.20-1.80 (m, 8 H), 2.29 (br, 2 H), 3.45 (t, $J = 6.53$ Hz, 2 H), 4.20 (q, $J = 7.13$ Hz, 2 H), 4.54 (s, 2 H), 5.51 (m, 1 H), 6.13 (d, $J = 1.33$ Hz, 1 H), 6.74 (d, $J = 3.74$ Hz, 1 H), 6.77 (d, $J = 3.74$ Hz, 1 H), Anal. Calcd for C$_{16}$H$_{23}$O$_5$S: C, 58.08; H, 7.01. Found: C, 57.97; H, 6.95.

Ethyl 2-[6-(3-chloro-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10h)
By using the preceding procedure 9h (770 mg, 2.12 mmol) gave 10h as an oil (540 mg, 77%). 1H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.07 Hz, 3 H), 1.20-1.80 (m, 6 H), 1.91 (m, 2 H), 3.37 (br, 1H), 3.47 (br, 2 H), 4.23 (q, J = 7.07 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.16 Hz, 1 H), 7.26 (d, J = 5.16 Hz, 1 H). Anal. Calcd for C₁₆H₂₅O₂ClS: C, 58.08; H, 7.01. Found: C, 58.02; H, 7.14.

**Ethyl 2-[(5-methoxy-2-thiophenemethoxy)hexyl]-2-methylidenepropionate (10i)**

By using the preceding procedure 9i (260 mg, 0.73 mmol) gave 10i as an oil (200 mg, 84%). 1H NMR (CDCl₃, 300 MHz) δ 1.30 (t, J = 7.13 Hz, 3 H), 1.28-1.57 (m, 8 H), 2.29 (m, 2 H), 3.43 (t, J = 6.62 Hz, 2 H), 3.87 (s, 3H), 4.20 (q, J = 7.13 Hz, 2 H), 4.48 (s, 2 H), 5.50 (d, J = 1.18 Hz, 1 H), 6.03 (d, J = 3.77 Hz, 1 H), 6.12 (s, 1 H), 6.59 (d, J = 3.77 Hz, 1 H). Anal. Calcd for C₁₇H₂₆O₄S: C, 62.55; H, 8.03. Found C, 62.39; H, 8.10.

**Ethyl 2-[(5-methyl-2-furanmethoxy)hexyl]-2-methylidenepropionate (10j)**

By using the preceding procedure 9j (1.76 g, 5.36 mmol) gave 10j as an oil (720 mg, 45%). 1H NMR (CDCl₃, 300 MHz) δ 1.30 (t, J = 7.14 Hz, 3 H), 1.32-1.50 (m, 8 H), 1.44 (m, 2 H), 1.57 (m, 2 H), 2.29 (s, 3 H), 3.45 (t, J = 6.67 Hz, 2 H), 4.20 (q, J = 7.14 Hz, 2 H), 4.37 (s, 2 H), 5.50 (s, 1 H), 5.91 (br, 1 H), 6.12 (s, 1 H), 6.18 (d, J = 2.55 Hz, 1 H). Anal. Calcd for C₁₇H₂₆O₄: C, 69.36; H, 8.90. Found: C, 69.29; H, 8.81.

**Ethyl 2-[(2-thiophenoxo)hexyl]oxirane-2-carboxylate (13a)**

To the acetone-H₂O (1 : 1) solution (12 mL) of NMO (60%, 0.27 mL, 1.56 mmol) and 10a (400 mg, 1.41 mmol) was added 2.5% t-BuOH solution of OsO₄ (0.71 mL, 0.07 mmol). The reaction mixture was stirred for 1.5 h at rt. The excess NMO was quenched by addition of Na₂S₂O₅. The solvent was removed in vacuo and the residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 x 20 mL) and brine (2 x 20 mL), then dried over anhydrous MgSO₄. After the solvent was removed in vacuo, almost pure diol (11a, 440 mg) was obtained and the following tosylation was proceeded without further purification. To a pyridine solution (5 mL) of 11a (440 mg, 1.40 mmol) was added p-toluenesulfonyl chloride (3.0 g, 16 mmol) at 0 °C. The reaction mixture was stirred for 3 h. The excess solvent was removed in vacuo and the residue was diluted with ethyl acetate (150 mL). The ethyl acetate solution was washed with 1 N-aq. HCl soln. (2 x 20 mL), 5% aq.-NaHCO₃ (2 x 20 mL), water (2 x 20 mL) and brine (2 x 10 mL), then dried over anhydrous MgSO₄. The residue was dissolved in anhydrous ethanol (10 mL) and anhydrous K₂CO₃ (1.0 g) was added to the reaction. The reaction mixture was stirred for 6 h at rt. The excess K₂CO₃ was removed by filtration and the excess ethanol was removed in vacuo. The residue was diluted with ethyl acetate (100 mL). The ethyl acetate solution was washed with water (2 x 20 mL) and brine (2 x 20 mL), then dried over anhydrous MgSO₄. After the solvent was removed in vacuo, the residue was purified by column chromatography (SiO₂, ethyl acetate : n-hexane = 1 : 5) to give 13a as a colorless oil (360 mg, 85 %). 1H NMR
(CDCl₃, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.80 (m, 9 H), 2.11 (m, 1 H), 2.78 (d, J = 5.90 Hz, 1 H) 3.03 (d, J = 5.90 Hz, 1 H), 4.02 (t, J = 6.44 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 6.19 (dd, J = 1.45, 3.75 Hz, 1 H), 6.53 (dd, J = 1.45, 5.75 Hz, 1 H), 6.71 (dd, J = 3.75, 5.75 Hz, 1 H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.10 24.65, 25.65, 28.99, 29.13, 31.12, 51.83, 56.97, 61.58, 73.74, 104.50, 111.67, 124.65, 165.72, 170.39. MS (EI m/z 298 [M⁺]; HRMS (EI) 298.122 72 [M⁺] (caled for C₁₅H₂₂O₅S 298.123 96).Anal. Caled for C₁₅H₂₂O₅S: C 60.38; H, 7.43. Found: C, 60.15; H, 7.37.

**Ethyl 2-[(6-(2-thiophenemethoxy)hexyl)oxirane-2-carboxylate (13b)**

By using the preceding procedure 10b (1.82 g, 6.14 mmol) gave 13b as an oil (1.65 g, 86%). ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.16 Hz, 3 H), 1.30-1.50 (m, 6 H), 1.54-1.70 (m, 3 H), 2.08 (m, 1 H), 2.78 (d, J = 5.9 Hz, 1 H), 3.02 (d, J = 5.93 Hz, 1 H), 3.46 (t, J = 6.50 Hz, 2 H), 4.22 (q, J = 7.16 Hz, 2 H), 4.65 (s, 2 H), 6.95-6.99 (m, 2 H), 7.28 (dd, J = 1.58, 4.79 Hz, 1 H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.13, 24.72, 25.93, 29.32, 29.5(31.17, 51.84, 57.04, 61.59, 67.31, 70.00, 125.63, 126.15, 126.58, 141.45, 170.45. MS (EI) m/z 312 [M⁺]; HRMS (EI) 312.140 21 [M⁺] (caled for C₁₆H₂₄O₄S 312.139 62). Anal. Caled for C₁₆H₂₄O₄S: C, 61.51; H, 7.74 Found: C, 61.39; H, 7.68.

**Ethyl 2-[(6-(2-thiopheneethoxy)hexyl)oxirane-2-carboxylate (13c)**

By using the preceding procedure 10c (880 mg, 7.37 mmol) gave 13c as an oil (574 mg, 62%). ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.08 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H) 3.02 (d, J = 5.90 Hz, 1 H), 3.08 (t, J = 6.81 Hz, 2 H), 3.44 (t, J = 6.52 Hz, 2 H), 3.64 (t, J = 6.81 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 6.84 (dd, J = 1.04, 3.58 Hz, 1 H), 6.92 (dd, J = 3.58, 5.08 Hz, 1 H), 7.13 (dd, J = 1.04 5.08 Hz, 1 H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.01, 24.62, 25.84, 29.21, 29.42, 30.36, 31.06, 51.71, 56.91, 61.45, 70.83, 71.25, 123.46, 124.90, 124.49, 141.29, 170.31. MS (EI) m/z 326 [M⁺]; HRMS (EI) 326.154 92 [M⁺] (caled for C₁₇H₂₆O₄S 326.155 28). Anal. Caled for C₁₇H₂₆O₄S: C, 62.55; H, 8.03. Found: C, 61.98; H, 8.32.

**Ethyl 2-[(6-(3-thiophenemethoxy)hexyl)oxirane-2-carboxylate (13d)**

By using the preceding procedure 10d (1.24 g, 4.18 mmol) gave 13d as an oil (1.01 g, 78%). ¹H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.36 (m, 6 H), 1.60 (m, 3 H), 2.06 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H), 3.02 (d, J = 5.90 Hz, 1 H), 3.44 (t, J = 6.55 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 4.50 (s, 2 H), 7.07 (br, 1 H), 7.20 (br, 1 H), 7.30 (dd, J = 1.97, 4.82 Hz, 1 H). ¹³C NMR (CDCl₃, 75 MHz) δ 14.06, 24.66, 25.92, 29.27, 29.51, 31.11, 51.75, 56.96, 61.50, 68.04, 70.19, 122.46, 125.81, 127.24, 139.74, 170.37. MS (EI) m/z 312 [M⁺]; HRMS (EI) 312.140 50 [M⁺] (caled for C₁₆H₂₆O₄S 312.139 62). Anal. Caled for C₁₆H₂₆O₄S: C, 61.51; H, 7.74. Found: C, 61.35; H, 7.86.
Ethyl 2-[3-thiopheneethoxy]hexyl|oxirane-2-carboxylate (13e)
By using the preceding procedure 10e (2.29 g, 7.33 mmol) gave 13e as an oil (1.80 mg, 87%). 1H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.16 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.10 (m, 1 H), 2.78 (d, J = 5.92 Hz, 1 H), 2.91 (t, J = 7.10 Hz, 2 H), 3.03 (d, J = 5.92 Hz, 1 H), 3.43 (t, J = 6.59 Hz, 2 H), 3.62 (t, J = 7.10 Hz, 2 H), 4.22 (q, J = 7.16 Hz, 2 H), 6.98 (dd, J = 1.34, 4.90 Hz, 1 H), 7.02 (m, 1 H), 7.26 (dd, J = 2.99, 4.90 Hz, 1 H). 13C NMR (CDCl₃, 75 MHz) δ 14.02, 24.62, 25.87, 29.23, 29.45, 30.63, 31.07, 51.73, 56.93, 61.48, 70.80, 70.86, 120.91, 125.04, 128.39, 139.24, 170.34. MS (EI) m/z 326 [M⁺]; HRMS (EI) 326.154 10 [M⁺] (calcd for C₁₇H₂₆O₅S 326.155 28). Anal. Calcd for C₁₇H₂₆O₅S: C, 62.55; H, 8.03. Found: C, 62.49; H, 8.02.

Ethyl 2-[6-(5-methyl-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13f)
By using the preceding procedure 10f (196 mg, 0.63 mmol) gave 13f as an oil (144 mg, 70%). 1H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.14 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.08 (m, 1 H), 2.46 (s, 3 H), 2.78 (d, J = 5.98 Hz, 1 H), 3.02 (d, J = 5.98 Hz, 1 H), 3.44 (t, J = 6.57 Hz, 2 H), 4.22 (q, J = 7.14 Hz, 2 H), 4.56 (s, 2 H), 6.60 (m, 1 H), 6.76 (d, J = 3.35 Hz, 1 H). 13C NMR (CDCl₃, 75 MHz) δ 14.13, 14.72, 24.72, 25.93, 29.32, 29.50, 31.17, 51.84, 57.04, 61.59, 67.31, 70.00, 125.63, 126.58, 141.45, 142.12, 170.45. MS (EI) m/z 326 [M⁺]; HRMS (EI) 326.155 10 [M⁺] (calcd for C₁₇H₂₆O₅S 326.155 28). Anal. Calcd for C₁₇H₂₆O₅S: C, 62.55; H, 8.03. Found: C, 62.39; H, 8.34.

Ethyl 2-[5-chloro-2-thiophenemethoxy]hexyl|oxirane-2-carboxylate (13g)
By using the preceding procedure 10g (900 mg, 2.72 mmol) gave 13g as an oil (774 mg, 82%). 1H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.45 (m, 6 H), 1.77 (m, 3 H), 2.11 (m, 1 H), 2.78 (d, J = 5.91 Hz, 1 H), 3.03 (d, J = 5.86 Hz, 1 H), 4.02 (t, J = 6.44 Hz, 2 H), 4.20 (q, J = 7.13 Hz, 2 H), 6.19 (dd, J = 1.44, 3.75 Hz, 1 H), 6.53 (dd, J = 1.45, 5.75 Hz, 1 H), 6.71 (dd, J = 3.76, 5.75 Hz, 1 H). 13C NMR (CDCl₃, 75 MHz) δ 14.10, 24.68, 25.88, 29.27, 29.44, 31.14, 51.79, 56.99, 61.54, 67.53, 70.07, 125.27, 125.52, 129.91, 140.48, 170.40. MS (EI) m/z 346 [M⁺]; HRMS (EI) 346.098 72 [M⁺] (calcd for C₁₆H₂₃O₄ClS 346.100 69). Anal. Calcd for C₁₆H₂₃O₄ClS: C, 55.40; H, 6.68. Found: C, 55.32; H, 6.75.

Ethyl 2-[6-(3-chloro-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13h)
By using the preceding procedure 10h (540 mg, 1.63 mmol) gave 13h as an oil (487 mg, 86%). 1H NMR (CDCl₃, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.37 (m, 6 H), 1.60 (m, 3 H), 2.08 (m, 1 H), 2.77 (d, J = 5.91 Hz, 1 H), 3.02 (d, J = 5.91 Hz, 1 H), 3.49 (t, J = 6.51 Hz, 2 H), 4.22 (q, J = 7.13 Hz, 2 H), 4.63 (s, 2 H), 6.89 (d, J = 5.30 Hz, 1 H), 7.26 (d, J = 5.30 Hz, 1 H). 13C NMR (CDCl₃, 75 MHz) δ 14.09, 24.68, 25.85, 29.25, 29.41, 31.14, 51.77, 56.99, 61.53, 64.80, 70.34, 123.41, 124.67, 127.46, 134.10, 170.39. MS (EI) m/z 346 [M⁺]; HRMS (EI) 346.101 55 [M⁺] (calcd for C₁₆H₂₃O₄ClS 346.100 69). Anal. Calcd for C₁₆H₂₃O₄ClS: C, 55.40; H,

**Ethyl 2-[6-(5-methoxy-2-thiophenemethoxy)hexyl]oxirane-2-carboxylate (13i)**

By using the preceding procedure 10i (200 mg, 0.61 mmol) gave 13i as an oil (157 mg, 75%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, J = 7.14 Hz, 3 H), 1.30-1.80 (m, 9 H), 2.07 (m, 1 H), 2.77 (d, J = 5.90 Hz, 1 H), 3.02 (d, J = 5.90 Hz, 1 H), 3.42 (t, J = 6.55 Hz, 2 H), 3.87 (s, 3 H), 4.21 (q, J = 7.14 Hz, 2 H), 4.48 (s, 2 H), 6.03 (d, J = 3.75 Hz, 1 H), 6.60 (d, J = 3.75 Hz, 1 H). 13C NMR (CDCl3, 75 MHz) δ 14.08, 24.68, 25.91, 29.29, 29.46 31.14, 51.77, 56.99, 61.15, 61.52, 68.01, 69.54, 102.83, 124.09, 127.40, 166.68, 170.40. MS (EI) m/z 342 [M+] HRMS (EI) 342.148 56 [M+](calcd for C_{17}H_{26}O_{3}S 342.150 18). Anal. Calcd for C_{17}H_{26}O_{3}S: C, 59.62; H, 7.65. Found: C, 59.37; H, 7.52.

**Ethyl 2-[6-(5-methyl-2-furanmethoxy)hexyl]oxirane-2-carboxylate (13j)**

By using the preceding procedure 10j (720 mg, 2.43 mmol) gave 13j as an oil (547 mg, 72%). 1H NMR (CDCl3, 300 MHz) δ 1.29 (t, J = 7.13 Hz, 3 H), 1.30-1.70 (m, 9 H), 2.07 (m, 1 H), 2.28 (s, 3 H), 2.77 (d, J = 5.92 Hz, 1 H), 3.02 (d, J = 5.92 Hz, 1 H), 3.44 (t, J = 6.65 Hz, 2 H), 4.21 (q, J = 7.13 Hz, 2 H), 4.36 (s, 2 H), 5.90 (br, 1 H) 6.17 (d, J = 2.96 Hz, 1 H). 13C NMR (CDCl3, 75 MHz) δ 13.50, 13.98, 24.58, 25.77, 29.18, 29.32, 31.03, 51.63 56.87, 61.43, 64.68, 69.93, 105.98, 109.90, 150.01, 152.31, 170.28. MS (EI) m/z 310 [M+]; HRMS (EI) 310.178 59 [M+] (calcd for C_{17}H_{26}O_{3} 310.178 08). Anal. Calcd for C_{17}H_{26}O_{3}: C, 65.78; H, 8.44. Found: C, 65.57; H, 8.21.

**Biological Assay**

The hypoglycemic activity test was performed as follows. Male sprague-Dawley rats (200 - 250 g) were housed in stainless-steel cages in a room maintained at 20-24°C with a 12 h light/dark cycle. The rats received food and water ad libitum except for the specified periods. Diabetes was induced using streptozotocin (STZ). After a 24 h-fast, rats were injected intravenously with 45 mg/kg STZ (Sigma Chem Co., St. Louis. MO) which was freshly prepared in a cold 0.1 M citrate buffer (pH 4.5). Antidiabetic effects were studied only using the rats showing serum glucose levels of over 350 mg/dl on day 7 after STZ administration. Vehicle or synthetic compounds (50 mg/kg) dissolved in 5% ethanol-saline were administered orally. Blood samples were obtained 2 h after drug administration and serum glucose concentrations determined using an enzymatic kit from Young-Dong Pharm. Corp (Seoul, Korea).

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REFERENCES AND NOTES


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