Isoxazolidine-3,5-dione and Noncyclic 1,3-Dicarbonyl Compounds as Hypoglycemic Agents

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Isoxazolidine-3,5-dione **2** (JTT-501), one of the cyclic malonic acid derivatives, was found to decrease blood glucose at an oral dose of 38 mg/kg/day in KKA^y mice and is currently undergoing evaluation in phase II clinical trials. Further studies on a series of malonic acids and related compounds showed that the 1,3-dicarbonyl structure was important for insulin-sensitizing activity. Dimethyl malonate **10**, which was selected as a successor for **2**, was the optimum compound in a series of 1,3-dicarbonyl compounds and was more potent than the corresponding thiazolidine-2,4-dione **1**.

Introduction

Non-insulin-dependent diabetes (NIDDM) is a metabolic disorder characterized by hyperglycemia leading to chronic complications such as neuropathy, nephropathy, retinopathy, and premature atherosclerosis.[1] The recently completed NIH-sponsored Diabetes Control and Complications Trial demonstrated that tight blood glucose control was associated with a reduced incidence of diabetic complications.[2] Hyperglycemia in NIDDM is caused not only by impaired insulin secretion from the pancreas but also by the increased insulin resistance of peripheral tissues.[3] Hence, a decrease of insulin resistance is necessary for achieving tight blood glucose control. Since the thiazolidinedione-based compound ciglitazone (Chart 1) was reported as a novel oral hypoglycemic agent that apparently potentiated the peripheral action of insluin,[4] many reports on new analogues have appeared,[5] and troglitazone has been approved for use in Japan, the United Kingdom, and the United States. Many studies on replacement of the cyclohexyl portion of ciglitazone have been carried out. Compound **1** (Chart 1), one of the optimum compounds, possesses a (2-phenyl-4-oxazolyl)ethyl chain and is 500 times more potent than ciglitazone.[6] Numerous studies on replacement of the thiazolidine-2,4-dione ring have also been carried out. Replacement of the thiazolidine-2,4-dione ring has been tried with various acidic groups,[7] such as oxazolidine-2,4-dione rings,[8] 1-oxa-2,4-diazolidine-3,5-dione rings,[9] carbonylated hydroxyureas,[9] α-heteroatom-substituted carboxylic acids,[10,11a] and α-carbon-substituted carboxylic acids.[11b] Among these compounds, the α-alkoxy carboxylic acids have shown equipotent[10] or more potent[11a] activity compared to the thiazolidine-2,4-diones. Some interesting reports on the molecular mechanism of the insulin-sensitizing action of thiazolidinediones have been published. The Glaxo group showed that a thiazolidinedione was an agonist for peroxisome proliferator-activated receptor γ (PPARγ), a receptor subtype selectively expressed in adipocytes that induces adipocyte differentiation.[12,13] They proposed that PPARγ was a molecular target for the adipogenic effect of thiazolidinediones.

Here we report on the synthesis and biological actions of isoxazolidine-3,5-dione **2** (Chart 1) and its derivatives, noncyclic 1,3-dicarbonyl compounds. These compounds showed insulin-sensitizing activity in 3T3-L1 cells and hypoglycemic activity in genetically diabetic KKA^y mice. Isoxazolidine-3,5-dione **2** (JTT-501) is currently undergoing evaluation in phase II clinical trials, because no significant toxicity has been observed in earlier studies. Dimethyl malonate **10** was the optimum compound in a series of noncyclic 1,3-dicarbonyl compounds and was selected as a successor to JTT-501.

Chemistry

Scheme 1 shows the preparation of 1,3-dicarbonyl compounds containing isoxazolidine-3,5-dione **2**. Knoevenagel condensation between the aldehyde **19**[8] and dimethyl malonate gave the benzylidene **16**. Catalytic hydrogenation of **16** with 5% palladium on carbon gave dimethyl malonate **10**. The 1,3-diketone **15** was prepared from **10** and 2,4-pentanedione using the same procedure. Isoxazolidine-3,5-dione **2** was synthesized by coupling between **10** and hydroxylamine. Hydrolysis of **10** with more than 2 equiv of sodium hydroxide gave malonic acid **14**. The diamide **9** was prepared from **10** with ammonia using strongly basic catalysis. Partial hydrolysis of **10** with 1 equiv of sodium hydroxide gave the half-ester **12**. The Schotten−Baumann reaction between an acid chloride of **12** and ammonia gave the amide ester **4**. The amide acid **3** was prepared by hydrolysis of **4** or reduction of **2** with 5% palladium on carbon as the catalyst. Methylation of **10** with iodomethane gave the α-methylmalonate **17**.

The methyl oxazolylacetate **20**[14] was reduced with $LiBH_4$ and converted to methylsulfonyl ester **21**. The ester **6** was prepared by coupling between **21** and methyl 3-(*p*-hydroxyphenyl)propionate. Hydrolysis of **6** gave the carboxylic acid **5**. Conversion of **6** with ammonia gave the amide **7** (Scheme 2).

The triester **23** was prepared by coupling between **22** and ethyl bromoacetate. Reductive removal of benzyl groups from **23** and subsequent decarboxylation gave the monoethyl succinate **24**. The amide ester **8** was prepared by the Schotten−Baumann reaction between the acid chloride of **24** and ammonia (Scheme 3).

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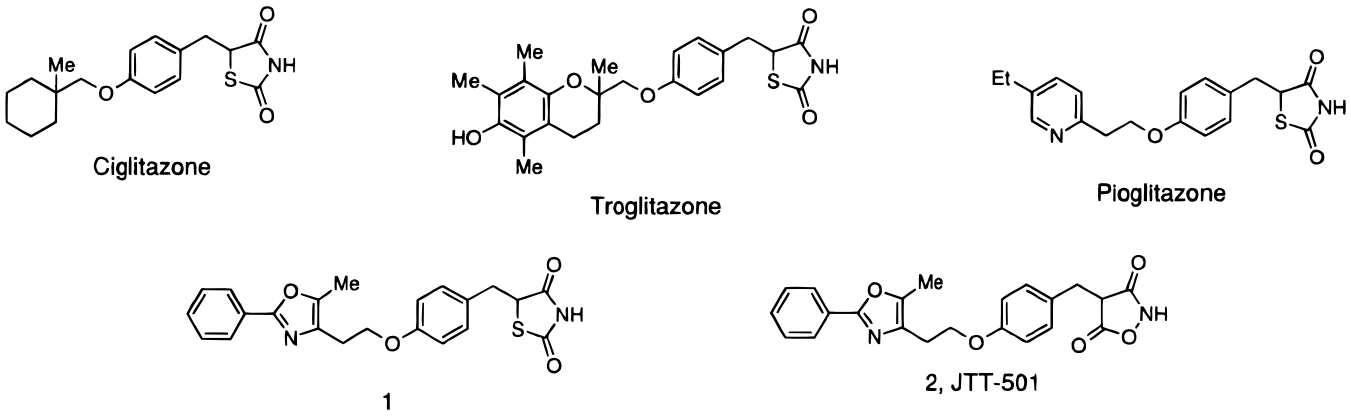
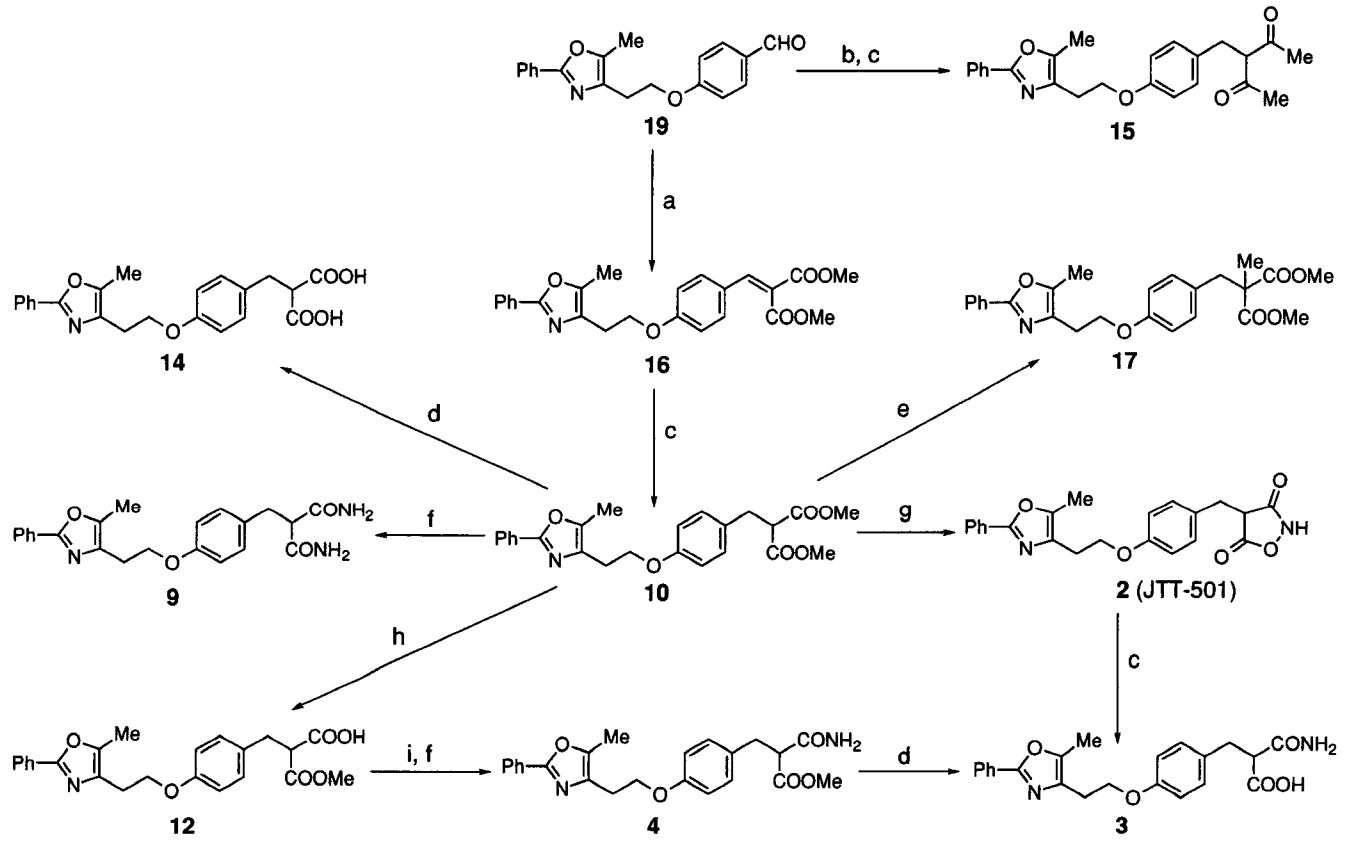
Chart 1



Scheme 1[a]



[a] Reagents: (a) dimethyl malonate, piperidinium acetate, toluene, reflux; (b) 2,4-pentanedione, piperidinium acetate, toluene, reflux; (c) H_2, Pd−C; (d) NaOH; (e) KCO_3, MeI; (f) 28% ammonium hydroxide; (g) hydroxylamine; (h) 1 equiv of NaOH; (i) thionyl chloride.

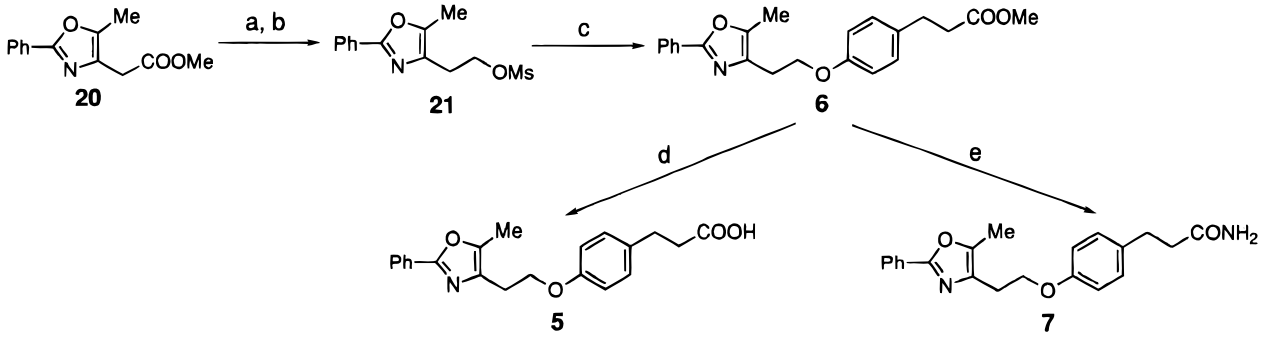
The dimethyl ester **18** was synthesized from **25**[15] using the same procedure as that used for preparing **10** (Scheme 4).

Results and Discussion

Because acidity of the thiazolidine-2,4-dione moiety is considered essential for its insulin-sensitizing activity,[7] we designed isoxazolidine-3,5-dione as a more acidic heterocyclic compound than thiazolidine-2,4-dione. The pK_a of thiazolidinedione and isoxazolidinedione was reported to be 6.82[16] and 1.86,[17] respectively. Insulin-sensitizing activity was evaluated from the hypoglycemic activity in genetically diabetic KKA^y mice[18] and by the effect on insulin-regulated differentiation, which was monitored from the rate of triglyceride accumulation in 3T3-L1 cells.[19] Isoxazolidine-3,5-dione **2** (JTT-501) caused a 50% increase of triglyceride accumulation in 3T3-L1 cells at a concentration of 1.1×10^{-7} M (Table 1) and a 25% decrease of blood glucose in KKA^y mice at an oral dose of 38 mg/kg/day (Table 2). The in vivo hypoglycemic activity of **2** was about 4 times more potent than that of troglitazone, and $^1/_8$ as potent as that of pioglitazone (Table 2). Compound **2** has advanced to clinical trials, because no significant toxicity, including cardiac hypertrophy, has been observed in rats, dogs, and monkeys.

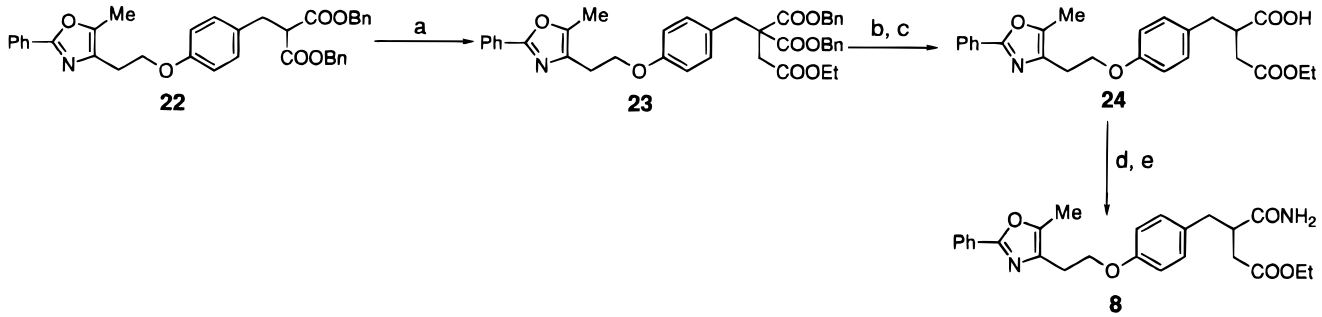
The main metabolite in humans was identified as malonic amide **3**, created by reductive cleavage of **2**. The

Scheme 2[a]



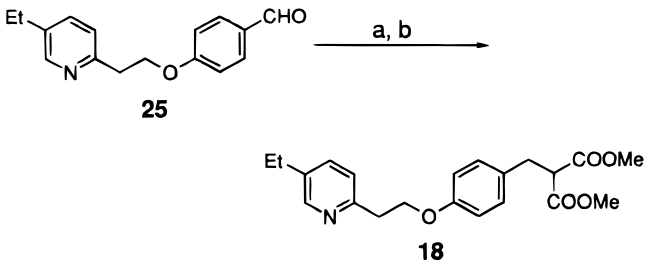
[a] Reagents: (a) $LiBH_4$; (b) methanesulfonyl chloride, triethylamine; (c) methyl 3-(*p*-hydroxyphenyl)propionate, NaH; (d) NaOH; (e) 28% ammonium hydroxide.

Scheme 3[a]



[a] Reagents: (a) NaH, ethyl bromoacetate; (b) H_2, Pd−C; (c) 150 °C; (d) thionyl chloride; (e) 28% ammonium hydroxide.

Scheme 4[a]



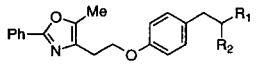
[a] Reagents: (a) dimethyl malonate, piperidinium acetate, toluene, reflux; (b) H_2, Pd−C.

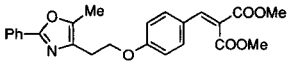
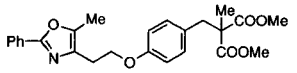
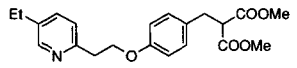
in vitro insulin-sensitizing activity of **3** was as potent as that of **2** (Table 1). However, the nonacidic amide ester **4** was 100 times more potent than **2** or **3**. Therefore, we questioned the necessity for acidity of these compounds and focused on the 1,3-dicarbonyl structure, which was common to the compounds (**2**−**4**). The SmithKline Beecham group reported that a malonate derivative, one of the α-substituted carboxylic acids, showed hypoglycemic activity.[11b] However, their compound was less potent in vivo than the parent thiazolidine-2,4-dione, BRL 48482, and they neither focused on the 1,3-dicarbonyl structure nor carried out any further investigations. We first investigated whether the 1,3-dicarbonyl structure was essential. The monocarbonyl compounds **5**−**7** and the 1,4-dicarbonyl compound **8** showed decreased activity, indicating the importance of the 1,3-dicarbonyl structure. Therefore, we carried out further studies on 1,3-dicarbonyl compounds in order to optimize the 1,3-dicarbonyl moiety and to obtain a successor for **2**.

The nonacidic diamide **9** also showed equipotent activity with amide ester **4**. The dicarboxylic acid **14**, with a pK_a of less than 3, was less potent than the nonacidic compounds **4** and **9**, indicating that an acidic functionality of the 1,3-dicarbonyl moiety was not essential. The diesters (**10** and **11**) and the half-esters (**12** and **13**) were more potent than amide ester **4**, diamide **9**, and dicarboxylic acid **14**. The 1,3-diketone **15** showed decreased potency relative to the dicarboxyl compounds (**10**−**14**). This may have been attributable to the presence of keto−enol tautomerism. The keto content of **15** was 37%, when measured in $CDCl_3$ by ^1H NMR. Comparison between the methyl esters (**10** and **12**) and the ethyl esters (**11** and **13**) disclosed that the minimal methyl group was more favorable than the ethyl group. Among the 1,3-dicarbonyl compounds, dimethyl malonate **10** and monomethyl malonate **12** showed the highest potency in vitro. This indicated that a methyl ester combined with another methyl ester or a carboxylic acid was the optimum structure. Since **10** can be partially hydrolyzed to **12** in vitro, and since both **10** and **12** are probably hydrolyzed to the less potent dicarboxylic acid **14**, it is difficult to decide which is the best combination: methyl ester plus methyl ester or methyl ester plus carboxylic acid.

The dimethyl malonate **10** caused a 50% increase of triglyceride accumulation in 3T3-L1 cells at a concentration of 5.9×10^{-11} M and was about 7 times more potent than the corresponding thiazolidinedione **1**. The corresponding dimethyl malonate **18** of pioglitazone was also about twice as potent as the parent compound with respect to in vitro insulin-sensitizing activity. Therefore, the dimethyl malonate structure was considered to be superior to the thiazolidinedione structure. In KKA^y mice, the oral ED_{25} values of **10** and **12** were 0.011 and 0.024 mg/kg/day, respectively, while the oral ED_{50} values were 0.17 and 0.12 mg/kg/day, respectively. The dispersion of the in vivo data may be attributable to the

Table 1. Effect of Triglyceride Accumulation in 3T3-L1 Cells



compd	R_1	R_2	EC_{50}[a]
2	–CO–NH–O–CO–		1.1×10^{-7}
3	$-CONH_2$	–COOH	1.3×10^{-7}
4	$-CONH_2$	–COOMe	1.3×10^{-9}
5	–COOH	–H	2.3×10^{-7}
6	–COOMe	–H	3.7×10^{-7}
7	$-CONH_2$	–H	3.5×10^{-7}
8	$-CONH_2$	$-CH_2COOEt$	4.0×10^{-7}
9	$-CONH_2$	$-CONH_2$	1.4×10^{-9}
10	–COOMe	–COOMe	5.9×10^{-11}
11	–COOEt	–COOEt	2.1×10^{-10}
12	–COOMe	–COOH	8.7×10^{-11}
13	–COOEt	–COOH	4.0×10^{-10}
14	–COOH	–COOH	4.4×10^{-9}
15	–COMe	–COMe	1.1×10^{-7}
16			1.7×10^{-8}
17			5.4×10^{-8}
18			8.1×10^{-8}
1	–CO–NH–CO–S–		4.5×10^{-10}
Troglitazone			1.3×10^{-7}
Pioglitazone			1.6×10^{-7}

[a] Effective concentration for 50% enhancement of insulin-induced triglyceride accumulation in 3T3-L1 cells.

Table 2. Hypoglycemic Effect in KKA^y Mice

compd	ED_{25}[a] (mg/kg/day)	ED_{50}[a] (mg/kg/day)
2 (JTT-501)	38	
10	0.011	0.17
12	0.024	0.12
14	0.44	2.7
troglitazone	170	
pioglitazone	4.6	19

[a] Effective doses for 25% and 50% blood glucose decreases were estimated from the dose–response curves obtained with three doses.

unstable ester structure, which is readily hydrolyzed in vivo by esterases.

The benzylidene derivative **16** showed decreased potency as well as the thiazolidinediones.[6,14] This was considered to be caused by inappropriate conformational restriction and/or electronic influence resulting from conjugation of the double bond on the carbonyl moiety and the phenyl moiety. Introduction of a methyl group at the 2-position of the malonate moiety (**17**) also decreased the potency, possibly as a result of increasing steric congestion adjacent to the methyl ester groups.

In conclusion, we have discovered the potent antihyperglycemic activity of a series of 1,3-dicarbonyl compounds which could replace the thiazolidine-2,4-dione structure. The initial lead compound, isoxazolidine-3,5-dione **2** (JTT-501), has advanced to clinical development. Dimethyl malonate **10**, which was one of the optimum compounds, has been selected as a successor for **2**.

Experimental Section

Chemistry. Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer 2400 Series II CHNS/O analyzer, and all values are within ±0.4% of the calculated values. ^1H NMR spectra were recorded on a Jeol JNM-A300W, Bruker AMX 300, or Bruker ARX 400 spectrometer in solutions of either $CDCl_3$ or DMSO-d_6 using tetramethylsilane as the internal standard. Chemical shifts are expressed as δ (ppm) values for protons relative to the internal standard; all compounds gave spectra consistent with their assigned structures.

Dimethyl 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-benzylidenemalonate (16). A solution of **19** (2.94 g, 10 mmol) and dimethyl malonate (1.39 g, 10 mmol) in toluene (30 mL) containing a catalytic quantity of piperidinium acetate was refluxed in a Dean–Stark trap for 4 h. After cooling to room temperature, the solution was concentrated. The residue was crystallized from methanol to give **16** as a colorless solid (2.5 g, 60%): mp 105.9–106.7 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.99 (t, J = 6.6 Hz, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.28 (t, J = 6.6 Hz, 2H), 6.88–6.91 (m, 2H), 7.35–7.46 (m, 5H), 7.69 (s, 1H), 7.96–7.99 (m, 2H). Anal. ($C_{24}H_{23}NO_6$) C, H, N.

Dimethyl 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-benzylmalonate (10). A solution of **16** (2.5 g, 60 mmol) in a mixture of methanol (4 mL) and 1,4-dioxane (20 mL) was stirred in the presence of 5% palladium on charcoal (150 mg) under an atmosphere of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The residue was crystallized from methanol to give **10** as a colorless solid (2.15 g, 85%): mp 87.9–88.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.96 (t, J = 6.6 Hz, 2H), 3.15 (d, J = 8.1 Hz, 2H), 3.62 (t, J = 7.5 Hz, 1H), 3.69 (s, 6H), 4.21 (t, J = 6.6 Hz, 2H), 6.80–6.83 (m, 2H), 7.07–7.10 (m, 2H), 7.40–7.45 (m, 3H), 7.96–7.99 (m, 2H). Anal. ($C_{24}H_{25}NO_6$) C, H, N.

Diethyl 4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzylmalonate (11). Using the above procedure, **11** was prepared from diethyl malonate. The residue was crystallized from ethyl acetate/hexane to give **11** as a colorless solid (5.23 g, 55%): mp 69.8–70.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H), 2.43 (s, 3H), 3.02 (t, J = 6.7 Hz, 2H), 3.20 (d, J = 7.8 Hz, 2H), 3.64 (t, J = 7.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.21 (q, J = 7.1 Hz, 2H), 4.27 (t, J = 6.8 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 8.6 Hz, 2H), 7.47 (m, 3H), 8.04 (m, 2H). Anal. ($C_{26}H_{29}NO_6$) C, H, N.

4-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-3,5-isoxazolidinedione (2). Hydroxylamine (1 mL, 17.5 mmol, 50% solution in water) and sodium carbonate (3.7 g, 35 mmol) were added to a solution of **10** (1.5 g, 3.5 mmol) in a mixture of tetrahydrofuran (15 mL) and methanol (15 mL). The mixture was heated at 60 °C for 3 h. After cooling and evaporation of the solvent, 1 N hydrogen chloride (50 mL) was added to the residue. The mixture was extracted with ethyl acetate (2 × 50 mL), dried over sodium sulfate, and concentrated. The crude product was crystallized from methanol to give **2** as a colorless solid (1.1 g, 80%): mp 154.6–155.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.92 (t, J = 6.5 Hz, 2H), 3.23–3.27 (m, 2H), 3.50 (t, J = 4.9 Hz, 1H), 4.11 (t, J = 6.7 Hz, 2H), 6.77–7.95 (m, 9H). Anal. ($C_{22}H_{20}N_2O_5$) C, H, N.

2-(Methoxycarbonyl)-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionic Acid (12). A 2 N aqueous solution of sodium hydroxide (11 ml, 22 mmol) was added to a solution of **10** (8.46 g, 20 mmol) in a mixture of methanol (80 mL) and tetrahydrofuran (40 mL) at 0 °C. The mixture was stirred for 90 min at room temperature, and then the solvent was removed under a vacuum. The residue was dissolved in saturated aqueous sodium bicarbonate (50 mL) and washed with ethyl acetate (50 mL). The aqueous solution was acidified to pH 2–3 with dilute hydrochloric acid and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated. The residue was crystal-

lized from ethyl acetate/hexane (1:2) to give an off-white solid (5.9 g, 72%): mp 126.0−127.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.96 (t, J = 6.5 Hz, 2H), 3.18 (d, J = 7.5 Hz, 2H), 3.65 (t, J = 7.5 Hz, 1H), 3.71 (s, 3H), 4.15 (t, J = 6.6 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.38−7.48 (m, 3H), 7.90−8.00 (m, 2H). Anal. ($C_{23}H_{23}NO_6$) C, H, N.

2-(Ethoxycarbonyl)-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionic acid (13). Using the above procedure, **13** was prepared from **11** as a colorless solid (2.91 g, 67%): mp 95.1−96.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 6H), 2.30 (s, 3H), 2.90 (t, J = 6.6 Hz, 2H), 3.12 (d, J = 7.6 Hz, 2H), 3.58 (t, J = 7.6 Hz, 1H), 4.07−4.14 (m, 4H), 6.74 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.36 (m, 3H), 7.90 (m, 2H). Anal. ($C_{24}H_{25}NO_6$) C, H, N.

Methyl 2-Carbamoyl-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionate (4). Thionyl chloride (375 μL, 6.12 mmol) was added to a solution of **12** (2.1 g, 5.1 mmol) in benzene (20 mL) at room temperature. Then the mixture was heated at 80 °C for 90 min. After cooling to room temperature, the solvent was removed under a vacuum. To a solution of the residue in acetone (2 mL) was added 28% ammonia solution (5 mL) at room temperature. The mixture was stirred for 30 min, and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL), washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. The crude product was crystallized from ethyl acetate/hexane (1:5) to give **4** as a colorless solid (700 mg, 40%): mp 154.8−155.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.96 (t, J = 6.7 Hz, 2H), 3.09−3.24 (m, 2H), 3.47 (dd, J = 6.7 and 8.2 Hz, 1H), 3.65 (s, 3H), 4.21 (t, J = 6.7 Hz, 2H), 5.43 (br s, 1H), 6.38 (br s, 1H), 6.81 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 7.35−7.46 (m, 3H), 7.91−8.00 (m, 2H). Anal. ($C_{23}H_{24}N_2O_5$) C, H, N.

2-Carbamoyl-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)-ethoxy]-phenyl]propionic Acid (3). A 2.5 N solution of aqueous sodium hydroxide (2.5 ml, 41 mmol) was added to a solution of **4** (1.8 g, 41 mmol) in a mixture of methanol (20 mL) and tetrahydrofuran (20 mL). The mixture was stirred for 15 h at room temperature, and then the solvent was removed under a vacuum. The residue was dissolved in 10% aqueous sodium hydroxide (50 mL) and washed with ethyl acetate (3 × 30 mL). The aqueous solution was acidified to pH 2−3 with 3 N hydrochloric acid, and the precipitate was collected by filtration. The crude solid was washed with water and dried under a vacuum to give **3** as a colorless solid (1.7 g, 98%): mp 138.1−138.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (s, 3H), 2.83−3.00 (m, 4H), 3.40 (t, J = 5.6 Hz, ^{1}H), 4.17 (t, J = 5.0 Hz, 2H), 6.82 (d, J = 6.5 Hz, 2H), 6.96 (br s, ^{1}H), 7.09 (d, J = 6.5 Hz, 2H), 7.40 (br s, ^{1}H), 7.41−7.52 (m, 3H), 7.82−7.95 (m, 2H), 12.39 (br s, 1H). Anal. ($C_{22}H_{22}N_2O_5$) C, H, N.

3 was also synthesized using the following procedure. A solution of **2** (5.0 g, 12.7 mmol) in a mixture of tetrahydrofuran (50 mL) and methanol (25 mL) was stirred in the presence of 5% palladium on charcoal (0.5 g) under 3 kg/cm^2 of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The residue was washed with hexane (100 mL) and with a mixture of ethyl acetate (25 mL) and acetone (25 mL) to give **3** as a colorless solid (4.2 g, 83%).

2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-malonic Acid (14). A 2 N aqueous solution of sodium hydroxide (17.7 mL, 35.5 mmol) was added to a solution of **10** (6 g, 14.2 mmol) in a mixture of methanol (60 mL) and tetrahydrofuran (30 mL). Then the mixture was stirred for 68 h at room temperature. After evaporation of the organic solvent, water (100 mL) was added to the residual solution, and the mixture was acidified with 1 N hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried under a vacuum. The crude product was crystallized from ethyl acetate/hexane (1:5) to give **14** as a colorless solid (3 g, 53%): mp 173.3−174.6 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.34 (s, 3H), 2.82−3.00 (m, 4H), 3.49 (t, J = 8.0 Hz, 1H), 4.16 (t, J = 6.8 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 7.41−7.56 (m, 3H), 7.82−7.92 (m, 2H). Anal. ($C_{22}H_{21}NO_6$) C, H, N.

2-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-malonamide (9). A 28% ammonia solution (20 mL) and 1 N aqueous sodium hydroxide (30 mL) were added to a solution of **10** (3.0 g, 7.1 mmol) in a mixture of methanol (50 mL) and tetrahydrofuran (50 mL). The mixture was stirred for 1 h at room temperature, and the solvent was removed under a vacuum. A mixture of tetrahydrofuran (50 mL) and ethyl acetate (50 mL) was added to the residue. The mixture was washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated to give **9** as an off-white solid (2.5 g, 90%): mp 222.5−223.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.80−2.92 (m, 4H), 3.22 (t, J = 7.5 Hz, 1H), 4.15 (t, J = 6.7 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 6.96 (br s, 2H), 7.07 (d, J = 8.4 Hz, 2H), 7.19 (br s, 2H), 7.40−7.52 (m, 3H), 7.82−7.95 (m, 2H). Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

Dimethyl 2-Methyl-2-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]malonate (17). 10 (4.24 g, 10 mmol) was added to a suspension of sodium hydride (480 mg, 12 mmol, 60% dispersion) in dry dimethylformamide (40 mL) at 0 °C. When hydrogen evolution ceased, iodomethane (0.93 mL, 15 mmol) was added, and the mixture was stirred at room temperature for 2.5 h. Then the solution was poured into iced water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated to give **17** as an off-white solid (2.71 g, 62%): mp 75.1−76.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (s, 3H), 2.36 (s, 3H), 2.96 (t, J = 6.6 Hz, 2H), 3.15 (s, 2H), 3.71 (s, 6H), 4.21 (t, J = 6.3 Hz, 2H), 6.79 (d, J = 6.6 Hz, 2H), 6.99 (d, J = 6.6 Hz, 2H), 7.38−7.48 (m, 3H), 7.94−8.01 (m, 2H). Anal. ($C_{25}H_{27}NO_6$) C, H, N.

3-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]-pentane-2,4-dione (15). A solution of **19** (7 g, 10 mmol) and 2,4-pentanedione (1.2 g, 12 mmol) in toluene (40 mL) containing a catalytic quantity of piperidinium acetate was refluxed in a Dean−Stark trap for 5 h and the concentrated. Chromatography of the residue on silica gel eluted with ethyl acetate/hexane (1:1) gave 3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]-benzylidene]pentane-2,4-dione as a yellow oil (2.3 g, 60%). A solution of the oil (2 g, 5.1 mmol) in methanol (30 mL) was stirred in the presence of 5% palladium on charcoal (400 mg) under 3 kg/cm^2 of hydrogen at room temperature until hydrogen uptake ceased. Then the solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The crude product was chromatographed on silica gel eluted with ethyl acetate/hexane (2:3) to give the yellow oil **15** (1.74 g, 87%) as a keto−enol tautomer (the keto content at equilibrium was 37%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3.78H), 2.11 (s, 2.22H), 2.37 (s, 3H), 2.92−3.03 (m, 2H), 3.08 (d, J = 7.8 Hz, 0.74H), 3.57 (s, 1.26H), 3.95 (t, J = 7.5 Hz, 0.37H), 4.18−4.26 (m, 2H), 6.78−6.94 (m, 2H), 6.99−7.08 (m, 2H), 7.37−7.50 (m, 3H), 7.93−8.01 (m, 2H).

2-(5-Methyl-2-phenyl-4-oxazolyl)ethanol Methanesulfonyl Ester (21). Lithium borohydride (6.6 g, 0.3 mmol) was added gradually to a solution of **20** (34.7 g, 0.15 mmol) in dry tetrahydrofuran (120 mL) at room temperature. Then the mixture was heated at 50 °C for 3 h. After cooling to room temperature, the solution was poured into iced water (150 mL), acidified with 2 N hydrochloric acid, and extracted with ethyl acetate (2 × 200 mL). The organic extract was dried over sodium sulfate and concentrated to give 2-(5-methyl-2-phenyl-4-oxazolyl)ethanol as a crude solid (25.1 g, 82%). To a solution of the product (20.3 g, 0.1 mol) in dry dichloromethane (100 mL) was added methanesulfonyl chloride (12.6 g, 0.11 mol) at 0 °C. Triethylamine (11.3 g, 0.11 mol) was added dropwise to the mixture, and stirring was continued at room temperature for 8 h. The solution was washed with 2 N hydrogen chloride (2 × 100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), dried over sodium sulfate, and concentrated to give **21** as a colorless solid (28.1 g, 100%): mp 90.2−91.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.96 (s,

3H), 2.96 (t, J = 6.5 Hz, 2H), 4.53 (t, J = 6.6 Hz, 2H), 7.38−7.50 (m, 3H), 7.90−8.02 (m, 2H). Anal. ($C_{13}H_{15}NO_4S$) C, H, N.

Methyl 3-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]-phenyl]propionate (6). Methyl 3-(*p*-hydroxyphenyl)propionate (15.9 g, 88.1 mmol) was added to a suspension of sodium hydride (2.11 g, 88.1 mmol, 60% dispersion) in dry dimethylformamide (50 mL) at 0 °C. When hydrogen evolution ceased, a solution of **21** (15.7 g, 56 mmol) in dry dimethylformamide (50 mL) was added, and the mixture was stirred at room temperature for 5 h. Then the solution was poured into iced water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (15:85) to give **6** as a colorless solid (14.0 g, 68%): mp 50.2-51.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.58 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 7.5 Hz, 2H), 2.96 (t, J = 6.7 Hz, 2H), 3.65 (s, 3H), 4.22 (t, J = 6.7 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.41 (m, 3H), 7.96 (m, 2H). Anal. ($C_{22}H_{23}NO_4$) C, H, N.

3-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-propionic Acid (5). A 1 N aqueous sodium hydroxide (50 mL, 50 mmol) was added to a solution of **6** (13 g, 35.6 mmol) in methanol (400 mL). The reaction mixture was stirred for 15 h at room temperature, and the solvent was removed under a vacuum. Then the residue was dissolved in water (200 mL) and washed with ethyl acetate (50 mL). The aqueous solution was acidified with 1 N hydrochloric acid to pH 2−3. The precipitate was collected by filtration, washed with water, and dried under a vacuum to give **5** as a colorless solid (12 g, 96%): mp 141.8−144.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H**),** 2.62 (t, J = 7.5 Hz, 2H), 2.89 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 6.7 Hz, 2H), 4.21 (t, J = 6.7 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 8.6 Hz, 2H), 7.41 (m, 3H), 7.96 (m, 2H). Anal. ($C_{21}H_{21}NO_4$) C, H, N.

3-[4-[2-(5-Methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]-propionamide (7). 6 (0.6 g, 1.64 mmol) was dissolved in a mixture of 28% ammonium hydroxide (20 mL) and methanol (30 mL). The mixture was stirred at room temperature overnight, and the solvent was removed under a vacuum. Ethyl acetate (50 mL) was added to the residue, and the mixture was washed with 1 N aqueous sodium hydroxide (50 mL), water (50 mL), and brine (50 mL), dried over sodium sulfate, and concentrated to give **7** as a colorless solid (0.47 g, 80%): mp 139.2−140.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.48 (t, J = 7.5 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 6.7 Hz, 2H), 4.22 (t, J = 6.7 Hz, 2H), 5.20 (br s, 2H), 6.82 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.5 Hz, 2H), 7.39−7.46 (m, 3H), 7.94−7.99 (m, 2H). Anal. ($C_{21}H_{22}N_2O_3$) C, H, N.

Dibenzyl 2-[(Ethoxycarbonyl)methyl]-2-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]benzyl]malonate (23). 22 (26.0 g, 45.2 mmol) was added to a suspension of sodium hydride (2.2 g, 54.2 mmol, 60% dispersion) in dry tetrahydrofuran (250 mL) at 0 °C. When hydrogen evolution ceased, a solution of ethyl bromoacetate (9.0 g, 54.2 mmol) in dry tetrahydrofuran (50 mL) was added. The mixture was stirred at room temperature for 1 h. The solution was poured into iced water (200 mL) and extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (200 mL) and brine (200 mL), dried over sodium sulfate, and concentrated. The residue was chromatographed on silica gel eluted with ethyl acetate/hexane (1:3) to give **23** as a colorless oil (30.2 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (q, J = 7.1 Hz, 3H), 2.36 (s, 3H), 2.85 (s, 2H), 2.95 (t, J = 6.7 Hz, 2H), 3.33 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 4.18 (t, J = 6.7 Hz, 2H), 5.10 (d, J = 13.1 Hz, 1H), 5.12 (d, J = 13.1 Hz, 1H), 6.69 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 7.20−7.33 (m, 10H), 7.41 (m, 3H), 7.98 (m, 2H).

2-[(Ethoxycarbonyl)methyl]-3-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]propionic Acid (24). A solution of **23** (29.5 g, 44.6 mmol) in methanol (150 mL) was stirred in the presence of 5% palladium on charcoal (2.0 g) under 3 kg/cm^2 of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The residue was heated at 150 °C for 30 min and chromatographed on silica gel eluted with chloroform/methanol (20:1) to give **24** as a yellow oil (15.0 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (t, J = 7.1 Hz, 3H), 2.37 (s, 3H), 2.38 (dd, J = 4.8 and 16.8 Hz, 1H), 2.55−2.78 (m, 2H), 2.90−3.17 (m, 4H), 4.09 (q, J = 7.1 Hz, 2H), 4.20 (t, J = 6.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 7.44 (m, 3H), 7.97 (m, 2H).

Ethyl 3-Carbamoyl-4-[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]butyrate (8). A mixture of thionyl chloride (30 mL) and **24** (4.5 g, 10.3 mmol) was stirred at 40 °C for 1 h. After evaporation of the solvent, 28% ammonia solution (15 mL) was added to a solution of the residue in tetrahydrofuran (25 mL) at 0 °C, and the mixture was stirred for 10 min. The solution was acidified with 1 N sodium hydrogensulfate, and the precipitate was collected by filtration. The crude product was crystallized from ethyl acetate to give **8** as a colorless solid (2.9 g, 64%): mp 141.8−142.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (q, J = 7.2 Hz, 3H), 2.38 (s, 3H), 2.42 (dd, J = 3.8 and 16.7 Hz, 1H), 2.60−2.90 (m, 4H), 2.97 (t, J = 6.5 Hz, 2H), 4.10 (q, J = 7.2 Hz, 2H), 5.20 (br s, 1H), 5.44 (br s, 1H), 6.83 (d, J = 9.0 Hz, 2H), 7.09 (d, J = 9.0 Hz, 2H), 7.43 (m, 3H), 7.97 (m, 2H). Anal. ($C_{25}H_{28}N_2O_5$) C, H, N.

Dimethyl 5-[4-[2-(5-Ethyl-2-pyridyl)ethoxy]benzyl]malonate (18). A solution of **25**[15] (8.0 g, 31.4 mmol) and dimethyl malonate (6.21 g, 47.1 mmol) in toluene (100 mL) containing a catalytic quantity of piperidinium acetate was refluxed in a Dean−Stark trap for 40 min, and then concentrated. A solution of the residue in a mixture of methanol (30 mL) and 1,4-dioxane (30 mL) was stirred in the presence of 5% palladium on charcoal (1.0 g) under 3.5 kg/cm^2 of hydrogen at room temperature until hydrogen uptake ceased. The solution was filtered through Celite, and the filtrate was evaporated under a vacuum. The residue was chromatographed on silica gel eluting with ethyl acetate/hexane (3:7) to give **18** as a yellow oil (4.60 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.6 Hz, 3H), 2.63 (q, J = 7.5 Hz, 2H), 3.14 (d, J = 7.5 Hz, 2H), 3.21 (t, J = 6.6 Hz, 2H), 3.61 (t, J = 6.8 Hz, 1H), 3.69 (s, 6H), 4.31 (t, J = 6.8 Hz, 2H), 6.81 (d, J = 9.6 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.1 Hz, 1H), 7.45 (dd, J = 2.1 and 7.8 Hz, 1H), 8.39 (d, J = 2.1 Hz, 1H).

Biological Procedure. 1. In Vitro Enhancement of Triglyceride Accumulation in 3T3-L1 Cells. The effect of each compound on insulin-regulated differentiation 3T3-L1 cells was monitored by the rate of triglyceride accumulation. Confluent 3T3-L1 cells were incubated in 5% fetal calf serum with isobutylmethylxanthine (0.5 mM) and dexamethasone (1 μM) for 48 h. Cultures were then incubated in Dulbecco's modified Eagle's medium/2% fetal calf serum for 4 days with insulin (10 ng/mL) and the test compounds (10^{-5}−10^{-9} M). Cellular triglycerides were extracted with 2-propanol and assayed by the enzymatic method using a commercially available kit (MPR2 Triglycerides GPO-PAP, Boehringer Mannheim).

2. In Vivo Hypoglycemic Activity. The hypoglycemic activity of each compound was evaluated using genetically diabetic KKA^y mice (male, 8 weeks old) obtained from Clea Japan Inc., Tokyo, Japan. The mice were divided into experimental groups of six or seven animals each according to their blood glucose levels. The test compounds were mixed in CRF-1 powdered diet (Oriental Yeast Co. Ltd., Tokyo, Japan) and were given for 4 days. A control group was treated in parallel with the CRF-1 powdered diet alone. After 4 days of this dietary administration to the mice, blood samples were taken from the orbital vein, and the blood glucose level was determined using the glucose oxidase method. The decrease of blood glucose was calculated as the percent change relative to the level in the control group.

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