Synthesis and Biological Activity of Novel 5-(ω-Aryloxyalkyl)oxazole Derivatives as Brain-Derived Neurotrophic Factor Inducers

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A novel series of 5-(ω-aryloxyalkyl)oxazole derivatives was prepared and their effects on brain-derived neurotrophic factor (BDNF) production were evaluated in human neuroblastoma (SK-N-SH) cells. Syntheses were performed by construction of an oxazole ring as a key reaction. Most of the 5-(ω-aryloxyalkyl)oxazole derivatives markedly increased BDNF production in SK-N-SH cells. 4-(4-Chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-[3-(2-methoxyphenoxy)propyl]-1,3-oxazole, one of the most promising compounds, showed potent activity (EC_{50}=7.9 μM) and the improvement of the motor nerve conduction velocity and the tail-flick response accompanied by a recovery of the brain-derived neurotrophic factor level in the sciatic nerve of streptozotocin (STZ)-diabetic rats.

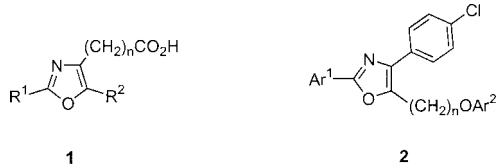
Key words 5-(ω-aryloxyalkyl)oxazole; brain-derived neurotrophic factor; diabetic neuropathy; diabetic complication; streptozotocin (STZ)-diabetic rat

Diabetes, obesity, and cardiovascular disease are risk factors for mortality and morbidity. The number of people with diabetes is growing rapidly and it is now estimated that about 5% of the population of developed countries is afflicted.[1)] Diabetes often leads to long-term complications such as neuropathy, nephropathy, retinopathy, cataract, and angiopathy. Among them, diabetic neuropathy is the most prevalent complication of diabetes mellitus in both type 1 and type 2 patients. The average prevalence of neuropathy in diabetic patients is estimated at 50% approximately.[2)] The maintenance of blood glucose at an appropriate level is a good way to prevent diabetic complications, because there is a link between hyperglycemia and the development of the disease.[3)] The practical control of blood glucose, however, has been difficult to achieve the normal level at present. Therefore, agents able to prevent or ameliorate diabetic complications without strict glycemic control are needed. While aldose reductase inhibitors, for example, have been extensively studied,[4,5)] they have had limited effects on the progression of neuropathy; or been withdrawn from the world markets excepting some countries because of adverse effects. Although positive symptoms such as pain can be treated with anticonvulsants or antidepressants, frequent side effects limit their usage for chronic pain.

The pathogenesis of diabetic neuropathy is still unclear though the disease is recognized to be multifactorial. There are many candidates of causative factor, including the activation of a polyol pathway, oxidative stress, insufficient blood supply to the nerves, autoimmune reactions, *etc.*[5)] Among them, a lack of neurotrophic support has been focused on because of its importance for the nervous system.[6)] Neurotrophic factors play pivotal roles in maintaining neural phenotypes and are already in clinical trials for the treatment of diseases of the peripheral nervous system. Neurotrophins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) that are released from the neuron itself or its target tissues,[7)] are a small gene family of structurally and functionally related neurotrophic factors. Among these neurotrophins, NGF has been tested the most extensively in animal models of diabetic neuropathy with encouraging results.[8—11)] Recombinant human nerve growth factor (rhNGF) was tested in clinical trials for the treatment of patients with diabetes.[12)] However, it has not shown clear efficacy probably because of limited delivery to the nervous system. Based upon these facts, we hypothesized that one way to treat diabetic neuropathy would be to increase the endogenous production of neurotrophic factors.

In the previous paper, Meguro and his colleagues reported that five-membered heteroaryl alkanoic acid derivatives, especially ω-oxazolylalkanoic acids (**1**), acted as antidiabetic agents promoting the glucose-dependent secretion of insulin (Chart 1).[13)] We found that a series of 5-(ω-aryloxyalkyl)oxazole derivatives (**2**, Chart 1), prepared in the course of studies on novel insulin secretagogues, increased the endogenous production of neurotrophic factors, especially BDNF, both *in vitro* and *in vivo*. It is well-known that BDNF supports the subsets of sensory neurons involved in mechanical pressure sensation and pain sensation.[14)] Furthermore, BDNF promotes the survival of motorneurons, unlike NGF.[15)] Therefore, compounds able to increase the endogenous production of BDNF might be clinically useful in the treatment of diabetic neuropathy.

We describe in this paper the syntheses and biological ef-



1 **2**

Chart 1

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fects on diabetic neuropathy of a novel class of 5-(ω-aryloxyalkyl)oxazole derivatives. The structure–activity relationships of these compounds are also discussed.

Chemistry

The general synthetic pathways for the preparation of 5-(ω-aryloxyalkyl)oxazole derivatives **13** listed in Table 3 are shown in Charts 2 and 3.

The key intermediates, 2-chlorooxazoles **7**, were synthesized from the starting acyl chlorides **3** *via* a six-step process (Chart 2). The Friedel–Crafts reaction of **3** with chlorobenzene gave ω-(4-chlorobenzoyl)alkanoic acid esters **4**. After bromination of **4**, subsequent treatment with sodium formate in methanol gave the corresponding α-hydroxyketones. Introduction of a phenoxycarbonyl moiety to the hydroxy group of α-hydroxyketones yielded α-phenoxycarbonyloxyketones **5**. Cyclization of **5** was carried out by a reaction with ammonium acetate in acetic acid to yield 4-(4-chlorophenyl)-oxazolones **6**. 2-Chlorooxazoles **7**, the key intermediates, were obtained by treatment of **6** with phosphoryl chloride in the presence of pyridine.

The routes used to synthesize the targeted 5-(ω-aryloxyalkyl)oxazole derivatives **13** from the key intermediates **7** are shown in Chart 3. Introduction of an azolyl group at the 2-position of the oxazole ring was achieved by reacting the 2-chlorooxazoles **7** with the corresponding azoles in the presence of potassium carbonate in *N*,*N*-dimethylformamide (DMF) to give the desired ω-(2-azolyloxazolyl)alkanoic acid esters **8** as shown in Table 1 (method A). A 2-phenyloxazole derivative (**8d**) was prepared by the Suzuki coupling reaction of **7a** with phenylboronic acid (method A). Introduction of the azolyl moiety at C-2 of the oxazole was also achieved *via* the corresponding carboxylic acids **10** (method B). After hydrolysis of **7**, the residual carboxylic acid derivatives **10** were treated with various azoles and subsequently esterified to give ω-(2-azolyloxazolyl)alkanoic acid esters **8**. Reduction of **8** with lithium aluminum hydride (LAH) afforded the corresponding alcohols **9** (Table 2), which were transformed into the desired 5-(ω-aryloxyalkyl)oxazole derivatives **13** by the Mitsunobu-type reaction[16] with the phenols possessing various substituents. Alternatively the 5-(ω-aryloxyalkyl)oxazoles **13** were also prepared by method C. Reduction of **7** with diisobutyl aluminum hydride (DIBAL-H) afforded the corresponding alcohols **11**. Conversion of the hydroxy group into the aryloxy group by the Mitsunobu-type reaction and subsequent introduction of an azolyl moiety onto the oxazole ring yielded the desired 5-(ω-aryloxyalkyl)oxazoles **13**.

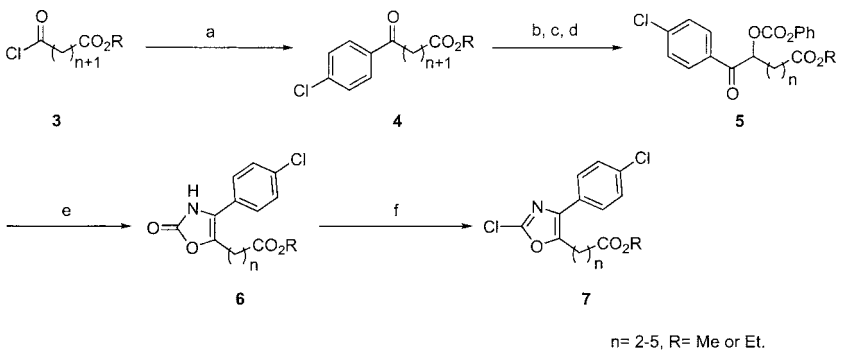
Biology

***In Vitro*. Cell Culture** Human neuroblastoma cells (SK-N-SH) were purchased from American Type Culture Collection (Rockville, MD, U.S.A.). The cells were maintained in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) fetal calf serum. Prior to treatment with compounds, 5×10^4/ml of the cells were seeded into poly-lysine-coated 48-well dishes at 0.3 ml/well and incubated for 8 d.

Measurement of BDNF[17] in Culture Supernatant The growth medium was replaced with 0.2 ml of DMEM containing 1% (w/v) bovine serum albumin and incubated for another 2 d. The collected culture supernatants were kept at −80 °C until the BDNF assay. Human BDNF was measured using an enzyme-linked immuno-sorbent assay system built up with commercial items. Briefly, monoclonal anti-human BDNF antibody (R&D, Minneapolis, MN, U.S.A.) was coated on immunoplates at 1 μg/ml, and blocked with a commercial buffer (Promega, Madison, WI, U.S.A.). The collected culture supernatants were directly applied onto the plates, which were incubated at room temperature for 2 h. After repeated washes, the plates were incubated with the secondary anti-BDNF antibody (Promega) and successively with HRP-conjugated anti-goat IgG antibody (Promega). Color development was achieved by adding substrate solution (TMB peroxidase EIA substrate kit, Bio-Rad, Richmond, CA, U.S.A.). The BDNF concentration was determined by measuring absorbance at 450 nm. The concentration required for a 50% increase, the EC_{50}, was obtained from regression analysis.

***In Vivo*. Animals and Experimental Design** Six-week-old male Sprague Dawley rats (Clea Japan, Inc., Tokyo, Japan) were intravenously injected with 70 mg/kg of streptozotocin (STZ) (Sigma, St. Louis, MO, U.S.A.). Three weeks later, they were divided into 3 groups so that mean body weights and blood glucose levels were similar among the groups. In the treatment group, 10 mg/kg/d of compound **13a** suspended in 0.5% (w/v) methylcellulose at 5 ml/kg was orally administered for 4 weeks. For the untreated STZ-diabetic rats and normal rats, only 0.5% (w/v) methylcellulose was given.

Nerve Conduction Velocity At the end of the treatment



(a) PhCl, $AlCl_3$; (b) Br_2, CH_2Cl_2; (c) HCO_2Na, MeOH, (d) $ClCO_2Ph$, pyridine, THF; (e) NH_4OAc, AcOH; (f) $POCl_3$, pyridine.

Chart 2

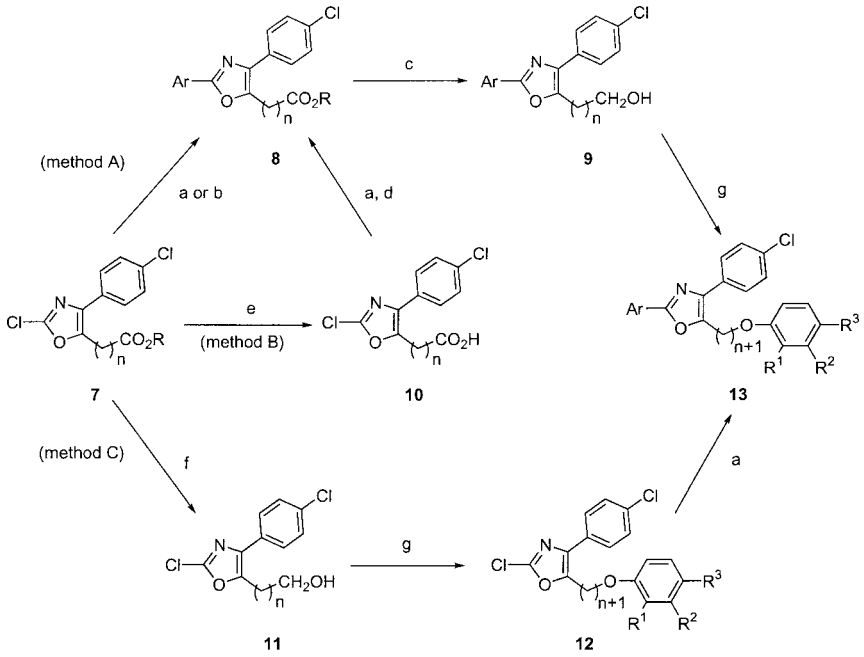
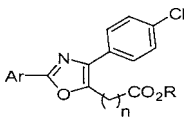


Chart 3

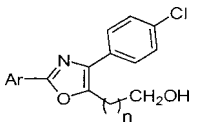
Table 1. Physical Data and Yields of ω-(5-Oxazolyl)alkanoates **8**



Compd.	Ar	*n*	R	Method[a]	Yield (%)	mp (°C)	Recryst. solvent[e]
8a		2	Et	B	76[c]	70—71	A-H
8b		2	Et	B	76[c]	67—68	A-IP
8c		2	Et	B	71[c]	99—100	A-IP
8d		2	Me	A[b]	88[d]	oil	—
8e		3	Et	B	67[c]	72—73	A-IP
8f		4	Et	A	88[d]	93—94	EA-IP
8g		5	Et	A	87[d]	oil	—

a) See Chart 3 and Chemistry section. *b*) Prepared by the Suzuki coupling reaction. *c*) Yield based on **10**. *d*) Yield based on **7**. *e*) A=acetone, EA=ethyl acetate, H=hexane, IP=isopropyl ether.

Table 2. Physical Data and Yields of ω-(5-Oxazolyl)alkyl Alcohols **9**



Compd.	Ar	*n*	Yield[a] (%)	mp (°C)	Recryst. solvent[c]
9a		2	77	130—131	A-IP
9b		2	68	114—115	A-IP
9c		2	29[b]	75—76	E-H
9d		2	42	139—140	ME-IP
9e		2	82	76—77	E-H
9f		3	88	110—111	A-IP
9g		4	79	94—95	EA
9h		5	90	70—71	A-IP

a) Yield based on **8**. *b*) Yield based on **7a** (See Experimental). *c*) A=acetone, E=diethyl ether, EA=ethyl acetate, H=hexane, IP=isopropyl ether, ME=methanol.

period, rats were anaesthetized with pentobarbital sodium (Dabbott laboratories) by intraperitoneal injection (50 mg/kg). Motor nerve conduction velocity was measured between sciatic notch and knee in the nerve branch to tibialis anterior muscle with Neuropack 2 (Nihon Kohden), which is representative of the whole sciatic nerve in terms of susceptibility to diabetes and treatment effects. Nerve temperature was monitored and regulated between 36.5 and 37.5 °C.

Tail Flick Response Each animal was gently held and its tail was exposed to the radiant heat of a specialized device to evoke a tail-flick response (Model 33, IITC Inc. Woodland Hills, CA, U.S.A.), and the latency until the tail flicked was automatically recorded.

Nerve BDNF Levels At the end of the experiment, the sciatic nerve was obtained and stored at −80 °C until further analysis. The protein level of BDNF in the sciatic nerve was determined by enzyme-linked immunosorbent assay (ELISA) as reported previously (Inoue *et al.*, 1997). Briefly, the supernatants from sciatic nerve homogenates were applied onto immunoplates coated with anti-BDNF antibody. After incubation and washes, the plates were incubated with biotinylated anti-BDNF antibody. Then, streptavidin-conjugated β-galactosidase was added to the plates, to be followed by an enzymic reaction with the substrate, 4-methylumbelliferyl-β-D-galactosidase, and the measurement of fluorescence produced by excitation at 355 nm and emission at 460 nm. The nonspecific reaction was quantified from a paralleled reaction in non-coated wells and subtraction from the specific antibody-coated wells.

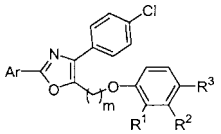
Results and Discussion

The effects on BDNF production of the novel 5-(ω-aryloxyalkyl)oxazole derivatives described above are summarized in Table 3. The 2-azolyloxazole derivatives **13a**—**g** strongly promoted the production. The 2-methylimidazolyl (**13a**, EC_{50}=7.9 μM), imidazolyl (**13b**, EC_{50}=5.7 μM), pyrazolyl (**13e**, EC_{50}=6.5 μM), and benzimidazolyl (**13g**, EC_{50}=5.1 μM) derivatives were also highly active. On the other hand, compound **13f** with a 1,2,4-triazolyl group at the 2-position on the oxazole ring exhibited a slight loss of activity (EC_{50}=13.9 μM). With regard to the substituent of the imidazole ring at C2 on the oxazole ring, introduction of a relatively bulky group such as a 2-ethyl (**13c**, EC_{50}=9.8 μM) or a 2-propyl (**13d**, EC_{50}=9.7 μM) group resulted in a minor decrease in activity. It is worth noting that replacement of the C2 azolyl moiety by a phenyl group (**13h**) significantly reduced the BDNF level (EC_{50}>50.0 μM). These findings indicated that an azolyl moiety of the proper size at the 2-position on the oxazole ring was necessary for a good effect on BDNF production by the 5-(ω-aryloxyalkyl)oxazole series.

We next directed our attention to a substituent on the benzene ring, which was linked by an oxygen atom with the 5-alkylene chain of the oxazole ring. Compound **13m** with a 2-methylthio moiety (EC_{50}=11.0 μM), which was very similar to a 2-methoxy group, showed less activity than compound **13a**, whereas replacement of the 2-methoxy group of **13a** by a 2-ethoxy group (**13k**, EC_{50}=6.5 μM) resulted in retention of activity. Furthermore, replacement of the methoxy group of **13a** by a cyano (**13n**, EC_{50}=5.5 μM) and a methyl group (**13o**, EC_{50}=6.1 μM) slightly increased activity. Removal of the 2-methoxy group, however, resulted in a reduction of the BDNF content (**13i**, EC_{50}=13.1 μM). In addition, compound **13j** replaced by a hydroxy group (EC_{50}=36.0 μM) was less active than compound **13a**. Compounds with a relatively bulky group such as an iso-propoxy (**13l**, EC_{50}=9.4 μM) or an iso-propyl (**13p**, EC_{50}>50.0 μM) group exhibited decreased activity. It is of note that the position of the substitution on the benzene ring greatly influenced potency. The *para*-isomer (**13r**, EC_{50}=6.7 μM) was as active as the corresponding *ortho*-isomer **13o**, whereas the *meta*-analogue (**13q**, EC_{50}=10.3 μM) was about 1.7 times less active than **13o**. In addition, compounds possessing two substituents such as **13s** (EC_{50}=46.8 μM) or **13t** (EC_{50}=14.8 μM) showed reduced activity compared with the corresponding monosubstituted derivative **13o**. These results showed that a lipophilic substituent of the proper size, especially at the 2-position on the benzene ring, was required for an optimal effect on BDNF production by the 5-(ω-aryloxyalkyl)oxazole derivatives. The length of the methylene chain between the oxazole ring and the phenoxy moiety was also investigated. Compound **13u** (EC_{50}=29.8 μM) with a tetramethylene unit (m=4) was about 5-fold less active than compound **13o**. As compounds **13v** (m=5, EC_{50}>50.0 μM) and **13w** (m=6, EC_{50}>50.0 μM) show, the activity reduced in accordance with prolonging length of the methylene chain between the oxazole ring and the phenoxy group.

Compound **13a**, one of the most promising compounds, was examined for oral therapeutic effects on diabetic neuropathy in STZ-diabetic rats as a typical type 1 diabetic model. Furthermore, the tissue level of BDNF was evaluated after oral administration of **13a**. As shown in Table 4, the un-

Table 3. Physical Data, Yields, and BDNF Production Activities of 5-(ω-Aryloxyalkyl)oxazoles **13**



Compd.	Ar	R^1	R^2	R^3	*m*	Yield[a] (%)	mp (°C)	Recryst. solvent[d]	BDNF production activity EC_{50} (μM)[e]
13a		OMe	H	H	3	54	84—85	E-H	7.9
13b		OMe	H	H	3	34	109—110	EA-H	5.7
13c		OMe	H	H	3	53[b]	78—79	A-IP	9.8
13d		OMe	H	H	3	39[b]	89—90	A-H	9.7
13e		OMe	H	H	3	51	103—104	A-H	6.5
13f		OMe	H	H	3	42	106—107	A-H	13.9
13g		OMe	H	H	3	77[b]	116—117	A-IP	5.1
13h		OMe	H	H	3	36	88—89	IP-H	>50.0
13i		H	H	H	3	33	76—77	E-H	13.1
13j		OH	H	H	3	50[c]	110—111	A-IP	36.0
13k		OEt	H	H	3	57	96—97	EA-H	6.5
13l		O^{i}Pr	H	H	3	93	76—77	A-IP	9.4
13m		SMe	H	H	3	60	118—119	A-H	11.0
13n		CN	H	H	3	82	136—137	A-IP	5.5
13o		Me	H	H	3	60	110—111	A-IP	6.1
13p		^{i}Pr	H	H	3	80	83—84	E-IP	>50.0
13q		H	Me	H	3	56	62—63	A-IP	10.3
13r		H	H	Me	3	58	oil	—	6.7
13s		Me	Me	H	3	49	102—104	E-IP	46.8
13t		Me	H	Me	3	39	76—77	A-IP	14.8
13u		Me	H	H	4	66	71—72	A-IP	29.8
13v		Me	H	H	5	66	61—62	E-IP	>50.0
13w		Me	H	H	6	62	70—71	E-H	>50.0

a) Yield based on **9**. *b*) Yield based on **12**. *c*) Yield from **13l** (See Experimental). *d*) A=acetone, E=diethyl ether, EA=ethyl acetate, H=hexane, IP=isopropyl ether. *e*) Concentration required to induce BDNF production by 50%.

Table 4. Effects of **13a** Treatment on Body Weight, Plasma Glucose, MNCV, Tail-Flick Response and BDNF Level

Rat	Treatment	Body weight (g)	Plasma glucose (mg/dl)	MNCV (m/s)	Tail-flick response (s)	BDNF (pg/g wet tissue)
Normal	—	470±36**	148±12**	44.90±3.70**	3.99±0.41	2.76±0.62
STZ-diabetic	—	294±24	528±38	36.24±2.69	4.54±0.82	2.50±0.49
STZ-diabetic	**13a**	299±32	588±125	42.08±3.69**	3.25±0.64**	3.45±0.47**

Three weeks after injection with STZ-diabetic rats were treated with or without 10 mg/kg/d (*p.o.*) of **13a** for 4 weeks. Data are means and S.D. (n=6—8). ** $p<0.01$, compared with untreated STZ-diabetic rats (t-test).

treated STZ-diabetic rats showed the significantly reduced motor nerve conduction velocity (MNCV). They also exhibited the impaired tail-flick response, which is one of the indicators of the function of sensory neurons. Treatment with **13a** (10 mg/kg/d *p.o.*, for 4 weeks) significantly improved both the MNCV and the tail-flick response without changing the plasma glucose level. The level of nerve BDNF declined in the untreated STZ-diabetic rats compared with normal rats, but administration of **13a** significantly restored BDNF production.

In summary, we showed that a series of 5-(ω-aryloxyalkyl)oxazole derivatives enhance BDNF production in human neuroblastoma cells. The results of the SAR studies identified that the azolyl moiety at the 2-position on the oxazole ring and the lipophilic substituent of the proper size, especially at the 2-position on the benzene ring connected with the propyloxy-spacer to the oxazole ring, were required for an optimal effect on BDNF production by the 5-(ω-aryloxyalkyl)oxazole derivatives. Compound **13a**, one of the most promising compounds, produced on improvement in both the MNCV and the tail-flick response accompanied by a recovery of the BDNF level in STZ-diabetic rats. These results suggest that 5-(ω-aryloxyalkyl)oxazole derivatives might be clinically useful in the treatment of diabetic neuropathy. Further investigation of this series as a remedy for diabetic neuropathy is underway.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus, and are uncorrected. The ^{1}H-NMR spectra were recorded on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts are given in δ values (ppm) using tetramethylsilane as an internal standard, and coupling constants (J) are given in hertz. Elemental Analyses were performed by Takeda Analytical Research Laboratories, Ltd. and results obtained were within ±0.4% of the theoretical values. Column chromatography was performed using SiO_2 (Merck Kieselgel 60, 70—230 mesh).

Methyl 5-(4-Chlorophenyl)-5-oxopentanoate (4a, n=2) A mixture of methyl glutaryl chloride (**3a**, 57.9 g, 0.352 mol), aluminum chloride (93.9 g, 0.704 mol), and chlorobenzene (158 g, 1.40 mol) was stirred at room temperature for 2 h, poured into 1 N HCl and extracted with ethyl acetate (AcOEt). The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**4a**, 77.0 g, 91%) as colorless crystals. mp 34—35 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.1 (2H, m), 2.45 (2H, t, J=7 Hz), 3.03 (2H, t, J=7 Hz), 3.69 (3H, s), 7.44 (2H, d, J=8.5 Hz), 7.91 (2H, d, J=8.5 Hz). Ethyl 7-(4-chlorophenyl)-7-oxoheptanoate (**4c**, n=4) and ethyl 8-(4-chlorophenyl)-8-oxooctanoate (**4d**, n=5) were obtained similarly.

4c: Yield 97% (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.3—1.8 (6H, m), 2.32 (2H, t, J=7 Hz), 2.95 (2H, t, J=7.5 Hz), 4.13 (2H, q, J=7 Hz), 7.44 (2H, d, J=8.5 Hz), 7.90 (2H, d, J=8.5 Hz).

4d: Yield 90% (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.2—1.9 (8H, m), 2.2—2.4 (2H, m), 2.93 (2H, t, J=7.5 Hz), 4.13 (2H, q, J=7 Hz), 7.43 (2H, d, J=8.5 Hz), 7.90 (2H, d, J=8.5 Hz).

Methyl 5-(4-Chlorophenyl)-5-oxo-4-(phenoxycarbonyloxy)pentanoate (5a, n=2) Bromine (51.1 g, 320 mmol) was added dropwise to a stirred solution of **4a** (77.0 g, 320 mmol) in CH_2Cl_2 (400 ml) at room temperature. The reaction mixture was washed successively with aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and water. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to give methyl 4-bromo-5-(4-chlorophenyl)-5-oxopentanoate (89.5 g, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.3—2.6 (2H, m), 3.71 (3H, s), 5.3—5.4 (1H, m), 7.48 (2H, d, J=8.5 Hz), 7.98 (2H, d, J=8.5 Hz).

A mixture of methyl 4-bromo-5-(4-chlorophenyl)-5-oxopentanoate (89.5 g, 280 mmol) and HCO_2Na (76.2 g, 1.12 mol) in MeOH (400 ml) was refluxed for 12 h. After removal of the solvent, the residue was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give an oil. The oil was dissolved in tetrahydrofuran (THF) (400 ml) and then pyridine (22.0 g, 278 mmol) was added. After addition of $ClCO_2Ph$ (43.8 g, 280 mmol) to the ice-cooled mixture, the resultant was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**5a**, 61.2 g, 56%) as colorless crystals. mp 97—98 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.85 (4H, m), 3.70 (3H, s), 5.93 (1H, dd, J=3, 9 Hz), 7.1—7.45 (5H, m), 7.48 (2H, d, J=7.5 Hz), 8.02 (2H, d, J=7.5 Hz). *Anal.* Calcd for $C_{19}H_{17}ClO_6$: C, 60.57; H, 4.55. Found: C, 60.81; H, 4.60. Ethyl 7-(4-chlorophenyl)-7-oxo-6-(phenoxycarbonyloxy)-heptanoate (**5c**, n=4) and ethyl 8-(4-chlorophenyl)-8-oxo-7-(phenoxycarbonyloxy)octanoate (**5d**, n=5) were obtained similarly.

5c: Yield 58% from **4c** (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.45—2.05 (6H, m), 2.32 (2H, t, J=7 Hz), 4.12 (2H, q, J=7 Hz), 5.79 (1H, t, J=6 Hz), 7.15—7.45 (5H, m), 7.47 (2H, d, J=8.5 Hz), 7.90 (2H, d, J=8.5 Hz).

5d: Yield 24% from **4d** (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.25—1.7 (6H, m), 1.85—2.0 (2H, m), 2.29 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7 Hz), 5.79 (1H, t, J=6 Hz), 7.15—7.45 (5H, m), 7.48 (2H, d, J=8.5 Hz), 7.90 (2H, d, J=8.5 Hz).

Methyl 6-(4-Chlorophenyl)-6-oxo-5-(phenoxycarbonyloxy)hexanoate (5b, n=3) A mixture of methyl adipoyl chloride (**3b**, 17.9 g, 100 mmol), aluminum chloride (26.7 g, 200 mmol), and chlorobenzene (33.8 g, 300 mmol) was stirred at room temperature for 2 h, poured into 1 N HCl and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give colorless crystals. The crystals were dissolved in CH_2Cl_2 (200 ml) and bromine (16.0 g, 100 mmol) was added dropwise to the solution at room temperature. The reaction mixture was washed successively with aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and water. The organic layer was separated, dried ($MgSO_4$), and concentrated *in vacuo* to give methyl 5-bromo-6-(4-chlorophenyl)-6-oxohexanoate (31.7 g, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.05 (2H, m), 2.1—2.3 (2H, m), 2.42 (2H, t, J=7 Hz), 3.68 (3H, s), 5.08 (1H, dd, J=6.5, 8 Hz), 7.47 (2H, d, J=8.5 Hz), 7.96 (2H, d, J=8.5 Hz).

A mixture of methyl 5-bromo-6-(4-chlorophenyl)-6-oxohexanoate (31.7 g, 95 mmol), HCO_2Na (25.8 g, 379 mmol), and MeOH (150 ml) was refluxed for 12 h. After removal of the solvent, the residue was diluted with water and extracted with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give an oil. The oil was dissolved in THF (200 ml) and then pyridine (8.27 g, 105 mmol) was added. After addition of $ClCO_2Ph$ (16.4 g, 105 mmol) to the mixture with cooling, the resultant was stirred at room temperature for 1 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oil which was purified by column chromatography on SiO_2 (200 g) with AcOEt–hexane (1 : 4, v/v) to give the title compound (**5b**, 24.8 g, 63% yield from **3b**) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.1 (4H, m), 2.40 (2H, t, J=7 Hz), 3.67 (3H, s), 5.82 (1H, dd, J=4.5, 7.5 Hz), 7.15—7.45 (5H, m), 7.48 (2H, d, J=9 Hz), 7.91 (2H, d, J=9 Hz).

Methyl 3-[4-(4-Chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]propionate (6a, n=2) A mixture of **5a** (61.2 g, 162 mmol), NH_4OAc (62.6 g, 812 mmol), and AcOH (300 ml) was refluxed for 2 h. The reaction mixture was concentrated, and diluted with water to give the title compound (**6a**,

36.3 g, 79%) as colorless crystals. mp 147—148 °C (MeOH). ^{1}H-NMR ($CDCl_3$) δ: 2.71 (2H, t, J=7 Hz), 2.97 (2H, t, J=7 Hz), 3.68 (3H, s), 7.35—7.5 (4H, m), 9.75 (1H, br s). *Anal.* Calcd for $C_{13}H_{12}ClNO_4$: C, 55.43; H, 4.29; N, 4.97. Found: C, 55.48; H, 4.37; N, 5.00. Methyl 4-[4-(4-chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]butyrate (**6b**, n=3), ethyl 5-[4-(4-chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]pentanoate (**6c**, n=4), and ethyl 6-[4-(4-chlorophenyl)-2-oxo-2,3-dihydro-5-oxazolyl]hexanoate (**6d**, n=5) were obtained similarly.

6b: Yield 69%. mp 121—122 °C (acetone–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.1 (2H, m), 2.41 (2H, t, J=7 Hz), 2.71 (2H, t, J=7 Hz), 3.65 (3H, s), 7.34 (2H, d, J=9 Hz), 7.43 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{14}H_{14}ClNO_4$: C, 56.86; H, 4.77; N, 4.74. Found: C, 56.97; H, 4.77; N, 4.81.

6c: Yield 71%. mp 143—144 °C (acetone–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H t, J=7 Hz), 1.55—1.85 (4H, m), 2.25—2.4 (2H, m), 2.6—2.7 (2H, m), 4.12 (2H, q, J=7 Hz), 7.31 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz), 10.05 (1H, br s). *Anal.* Calcd for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.60; N, 4.33. Found: C, 59.22; H, 5.55; N, 4.38.

6d: Yield 87%. mp 113—114 °C (acetone–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.3—1.8 (6H, m), 2.29 (2H, t, J=7.5 Hz), 2.63 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7 Hz), 7.31 (2H, d, J=8.5 Hz), 7.42 (2H, d, J=8.5 Hz), 9.91 (1H, br s). *Anal.* Calcd for $C_{17}H_{20}ClNO_4$: C, 60.45; H, 5.97; N, 4.15. Found: C, 60.37; H, 5.80; N, 4.17.

Methyl 3-[2-Chloro-4-(4-chlorophenyl)-5-oxazolyl]propionate (7a, n=2) A mixture of **6a** (74.0 g, 263 mmol), phosphoryl chloride (161 g, 1.05 mol), and pyridine (20.8 g, 263 mmol) was stirred at 125 °C for 1.5 h. The reaction mixture was concentrated, and diluted with ice-water. After stirring at room temperature for 0.5 h, the resultant was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**7a**, 57.4 g, 73%) as colorless crystals. mp 71—72 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.72 (2H, d, J=7 Hz), 3.18 (2H, d, J=7 Hz), 3.68 (3H, s), 7.37 (2H, d, J=8.5 Hz), 7.58 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.69; N, 4.67. Found: C, 52.21; H, 3.68; N, 4.71. Methyl 4-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]butyrate (**7b**, n=3), ethyl 5-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]pentanoate (**7c**, n=4), and ethyl 6-[2-chloro-4-(4-chlorophenyl)-5-oxazolyl]hexanoate (**7d**, n=5) were obtained similarly.

7b: Yield 78%. mp 73—74 °C (acetone–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 2.41 (2H, t, J=7 Hz), 2.92 (2H, t, J=7.5 Hz), 3.67 (3H, s), 7.40 (2H, d, J=8.5 Hz), 7.56 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{14}H_{13}Cl_2NO_3$: C, 53.52; H, 4.17; N, 4.46. Found: C, 53.71; H, 4.12; N, 4.58.

7c: Yield 78% (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.6—1.85 (4H, m), 2.34 (2H, t, J=6.5 Hz), 2.86 (2H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 7.39 (2H, d, J=8.5 Hz), 7.53 (2H, d, J=8.5 Hz).

7d: Yield 70% (a colorless oil). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.3—1.85 (6H, m), 2.31 (2H, t, J=7.5 Hz), 2.85 (2H, t, J=7.5 Hz), 4.13 (2H, q, J=7 Hz), 7.39 (2H, d, J=8.5 Hz), 7.53 (2H, d, J=8.5 Hz).

General Procedure for Method A. Ethyl 5-[4-(4-Chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-oxazolyl]pentanoate (8f) A mixture of **7c** (10.0 g, 29.2 mol), 2-methylimidazole (7.20 g, 87.7 mmol), K_2CO_3 (12.1 g, 87.5 mmol), and DMF (80 ml) was stirred at 120—130 °C for 2 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**8f**, 9.97 g, 88%) as colorless crystals. mp 93—94 °C (AcOEt–isoPr$_2$O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.7—1.9 (4H, m), 2.36 (2H, t, J=7 Hz), 2.77 (3H, s), 2.94 (2H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 7.01 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.48 (1H, d, J=1.5 Hz), 7.60 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 5.72; N, 10.83. Found: C, 62.06; H, 5.72; N, 10.85. Compound **8g** was obtained similarly. The yield was displayed in Table 1.

8g: ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 1.35—1.9 (6H, m), 2.31 (2H, t, J=7.5 Hz), 2.77 (3H, s), 2.91 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7 Hz), 7.01 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.48 (1H, d, J=1.5 Hz), 7.60 (2H, d, J=8.5 Hz).

Methyl 3-[4-(4-Chlorophenyl)-2-phenyl-5-oxazolyl]propionate (8d) A mixture of **7a** (1.50 g, 5.0 mmol), phenylboronic acid (650 mg, 7.05 mmol), $NaHCO_3$ (1.68 g, 20.0 mmol), tetrakis(triphenylphosphine)palladium (0) (250 mg, 0.22 mmol), water (25 ml), EtOH (25 ml), and toluene (50 ml) was refluxed for 12 h under N_2. The reaction mixture was concentrated and the residue was purified by chromatography on SiO_2 (50 g) with hexane–AcOEt (6 : 1,v/v) to give the title compound (**8d**, 1.50 g, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 2.82 (2H, t, J=7.5 Hz), 3.29 (2H, t, J=7.5 Hz), 3.70 (3H, s), 7.3—7.5 (5H, m), 7.69 (2H, d, J=8.5 Hz), 8.0—8.1 (2H, m).

General Procedure for Method B. 3-[2-Chloro-4-(4-chlorophenyl)-5-oxazolyl]propionic Acid (10a, n=2) To an ice-cooled suspension of **7a** (56.6 g, 189 mmol) in EtOH (300 ml) was added dropwise 1 N NaOH (226 ml). After stirring at room temperature for 1 h, the reaction mixture was poured into ice-water and acidified with 6 N HCl (40 ml) to give the title compound (**10a**, 51.6 g, 96%) as colorless crystals. mp 167—168 °C (AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.81 (2H, t, J=7 Hz), 3.20 (2H, t, J=7 Hz), 7.41 (2H, d, J=8.5 Hz), 7.58 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.43; H, 3.16; N, 4.96. 4-[2-Chloro-4-(4-chlorophenyl)-5-oxazolyl]butyric acid (**10b**, n=3) was similarly obtained from **7b** in 76% yield. mp 150—151 °C (acetone–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.2 (2H, m), 2.48 (2H, t, J=7 Hz), 2.94 (2H, t, J=7 Hz), 7.39 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{13}H_{11}Cl_2NO_3$: C, 52.02; H, 3.69; N, 4.67. Found: C, 52.12; H, 3.48; N, 4.89.

Ethyl 3-[4-(4-Chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-oxazolyl]propionate (8a) A mixture of **10a** (10.0 g, 35 mmol), 2-methylimidazole (17.2 g, 209 mmol), K_2CO_3 (24.2 g, 175 mmol), and DMF (80 ml) was stirred at 120—130 °C for 10 h. The reaction mixture was poured into water and adjusted pH at 6 with 2 N HCl to give colorless crystals. Recrystallization from MeOH gave 3-[4-(4-chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-oxazolyl]propionic acid (9.79 g, 84%) as colorless prisms. mp 196—197 °C. ^{1}H-NMR (dimethyl sulfoxide (DMSO)-d_6) δ: 2.64 (3H, s), 2.73 (2H, t, J=7 Hz), 3.19 (2H, t, J=7 Hz), 6.99 (1H, d, J=1.5 Hz), 7.55 (2H, d, J=8.5 Hz), 7.66 (1H, d, J=1.5 Hz), 7.76 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.69; H, 4.22; N, 12.69.

A mixture of 3-[4-(4-chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-oxazolyl]propionic acid (500 mg, 1.51 mmol), K_2CO_3 (310 mg, 2.24 mmol), iodoethane (350 mg, 2.24 mmol), and DMF (10 ml) was stirred at room temperature for 16 h. The reaction mixture was poured into water and extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the title compound (**8a**, 495 mg, 90%) as colorless crystals. mp 70—71 °C (acetone–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.77 (3H, s), 2.77 (2H, t, J=7.5 Hz), 3.27 (2H, t, J=7.5 Hz), 4.16 (2H, q, J=7 Hz), 7.01 (1H, d, J=1.5 Hz), 7.43 (2H, d, J=8.5 Hz), 7.46 (1H, d, J=1.5 Hz), 7.66 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{18}H_{18}ClN_3O_3$: C, 60.09; H, 5.04; N, 11.68. Found: C, 59.82; H, 4.87; N, 11.70. Compounds **8b**, **8c**, and **8e** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 1.

8b: ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz), 2.77 (2H, d, J=7.5 Hz), 3.26 (2H, d, J=7.5 Hz), 4.16 (2H, q, J=7 Hz), 7.20 (1H, dd, J=1, 1.5 Hz), 7.43 (2H, d, J=8.5 Hz), 7.58 (1H, t, J=1.5 Hz), 7.65 (2H, d, J=8.5 Hz), 8.23 (1H, t, J=1 Hz), 8.91 (1H, s). *Anal.* Calcd for $C_{17}H_{16}ClN_3O_3$: C, 59.05; H, 4.66; N, 12.15. Found: C, 59.14; H, 4.64; N, 12.22.

8c: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 2.82 (2H, t, J=7.5 Hz), 3.30 (2H, t, J=7.5 Hz), 4.15 (2H, q, J=7 Hz), 7.45 (2H, d, J=8.5 Hz), 7.69 (2H, d, J=8.5 Hz), 8.18 (1H, s), 8.91 (1H, s). *Anal.* Calcd for $C_{16}H_{15}ClN_4O_3$: C, 55.42; H, 4.36; N, 16.16. Found: C, 55.63; H, 4.40; N, 16.30.

8e: ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7 Hz), 2.0—2.2 (2H, m), 2.43 (2H, t, J=7 Hz), 2.78 (3H, s), 2.99 (2H, t, J=7.5 Hz), 4.12 (2H, q, J=7 Hz), 7.01 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.48 (1H, d, J=1.5 Hz), 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{19}H_{20}ClN_3O_3$: C, 61.04; H, 5.39; N, 11.24. Found: C, 61.23; H, 5.46; N, 11.41.

3-[4-(4-Chlorophenyl)-2-(2-methyl-1*H*-imidazol-1-yl)-5-oxazolyl]-1-propanol (9a) Lithium aluminum hydride (1.20 g, 31.6 mmol) was added portionwise to a stirred solution of **8a** (10.8 g, 0.030 mol) in THF (120 ml) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with water (3 ml) and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* to give colorless crystals. Recrystallization from acetone–isoPr$_2$O gave the title compound (**9a**, 7.35 g, 77%) as colorless prisms, mp 130—131 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.60 (1H, br s), 1.95—2.1 (2H, m), 2.78 (3H, s), 3.06 (2H, t, J=7.5 Hz), 3.7—3.8 (2H, m), 7.00 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.47 (1H, d, J=1.5 Hz), 7.66 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{16}H_{16}ClN_3O_2$: C, 60.48; H, 5.07; N, 13.22. Found: C, 60.48; H, 4.89; N, 13.16. Compounds **9b** and **9d**—**h** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 2.

9b: ^{1}H-NMR ($CDCl_3$) δ: 1.86 (1H, br s), 1.95—2.1 (2H, m), 3.06 (2H, t, J=7.5 Hz), 3.77 (2H, t, J=6 Hz), 7.19 (1H, br s), 7.42 (2H, d, J=8.5 Hz), 7.59 (1H, t, J=1.5 Hz), 7.65 (2H, d, J=8.5 Hz), 8.23 (1H, br s). *Anal.* Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.51; H, 4.60; N, 13.84.

9d: ^{1}H-NMR ($CDCl_3$) δ: 1.46 (1H, br s), 2.0—2.15 (2H, m), 3.11 (2H, t,

J=7.5 Hz), 3.75—3.8 (2H, m), 7.44 (2H, d, J=8.5 Hz), 7.68 (2H, d, J=8.5 Hz), 8.18 (1H, s), 8.91 (1H, s). *Anal.* Calcd for $C_{14}H_{13}ClN_4O_2$: C, 55.18; H, 4.30; N, 18.39. Found: C, 55.12; H, 4.29; N, 18.38.

9e: ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 3.07 (2H, t, J=7.5 Hz), 3.77 (2H, t, J=7.5 Hz), 7.3—7.6 (5H, m), 7.70 (2H, d, J=9 Hz), 8.15—8.2 (2H, m). *Anal.* Calcd for $C_{18}H_{16}ClNO_2$: C, 68.90; H, 5.14; N, 4.46. Found: C, 68.93; H, 5.02; N, 4.51.

9f: ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.95 (5H, m), 2.77 (3H, s), 2.96 (2H, t, J=7.5 Hz), 3.65—3.8 (2H, m), 7.00 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.47 (1H, d, J=1.5 Hz), 7.62 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.79; H, 5.60; N, 12.90.

9g: ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.9 (7H, m), 2.77 (3H, s), 2.93 (2H, t, J=7.5 Hz), 3.6—3.75 (2H, m), 7.00 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.48 (1H, d, J=1.5 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{18}H_{20}ClN_3O_2$: C, 62.52; H, 5.83; N, 12.15. Found: C, 62.55; H, 5.73; N, 12.12.

9h: ^{1}H-NMR ($CDCl_3$) δ: 1.3—1.9 (9H, m), 2.77 (3H, s), 2.91 (2H, t, J=7.5 Hz), 3.65 (2H, t, J=7.5 Hz), 7.01 (1H, d, J=1.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.47 (1H, d, J=1.5 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{19}H_{22}ClN_3O_2$: C, 63.42; H, 6.16; N, 11.68. Found: C, 63.46; H, 6.25; N, 11.71.

3-[4-(4-Chlorophenyl)-2-(1*H*-pyrazol-1-yl)-5-oxazolyl]-1-propanol (9c) A mixture of **10a** (1.50 g, 5.24 mmol), pyrazole (1.43 g, 21.0 mmol), K_2CO_3 (2.90 g, 21.0 mmol), and DMF (30 ml) was stirred at 120—130 °C for 5 h. The reaction mixture was poured into water and adjusted pH at 6 with 2 N HCl to give 3-[4-(4-chlorophenyl)-2-(1*H*-pyrazol-1-yl)-5-oxazolyl]propionic acid (1.44 g, 87%) as colorless crystals. mp 171—172 °C (MeOH). ^{1}H-NMR (DMSO-d_6) δ: 2.70 (2H, t, J=7.5 Hz), 3.20 (2H, t, J=7.5 Hz), 6.67 (1H, t, J=2 Hz), 7.57 (2H, d, J=9 Hz), 7.80 (2H, d, J=2 Hz), 7.92 (1H, d, J=2 Hz), 8.48 (1H, d, J=2 Hz). *Anal.* Calcd for $C_{15}H_{12}ClN_3O_3$: C, 56.70; H, 3.81; N, 13.23. Found: C, 56.56; H, 3.61; N, 13.13. Lithium aluminum hydride (190 mg, 5.01 mmol) was added portionwise to a stirred solution of 3-[4-(4-chlorophenyl)-2-(1*H*-pyrazol-1-yl)-5-oxazolyl]propionic acid (1.44 g) in THF (30 ml) at 0 °C. After stirring at the same temperature for 2 h, the reaction mixture was quenched with water (0.5 ml) and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on SiO_2 (40 g). Elution with AcOEt–hexane (2 : 3, v/v) gave colorless crystals. Recrystallization from Et_2O–hexane gave the title compound (**9c**, 450 mg, 33%) as colorless prisms, mp 75—76 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.15 (2H, m), 3.08 (2H, t, J=7.5 Hz), 3.76 (2H, t, J=7 Hz), 6.53 (1H, dd, J=2, 2.5 Hz), 7.42 (2H, d, J=8.5 Hz), 7.69 (2H, d, J=8.5 Hz), 7.81 (1H, dd, J=0.5, 2 Hz), 8.27 (1H, dd, J=0.5, 2.5 Hz). *Anal.* Calcd for $C_{15}H_{14}ClN_3O_2$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.19; H, 4.62; N, 13.58.

4-(4-Chlorophenyl)-5-[3-(2-methoxyphenoxy)propyl]-2-(2-methyl-1*H*-imidazol-1-yl)oxazole (13a) A solution of diethyl azodicarboxylate in toluene (40%, 875 mg, 2.01 mmol) was added dropwise to a stirred solution of **9a** (320 mg, 1.01 mmol), 2-methoxyphenol (250 mg, 2.01 mmol), and tributylphosphine (405 mg, 2.00 mmol) in THF (10 ml) at room temperature. After stirring for 4 h, the reaction mixture was concentrated *in vacuo* to give an oil which was purified by chromatography on SiO_2 (40 g). Elution with AcOEt–hexane (1 : 1, v/v) gave the title compound (**13a**, 230 mg, 54%) as colorless crystals. mp 84—85 °C (Et_2O–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.4 (2H, m), 2.76 (3H, s), 3.19 (2H, t, J=7 Hz), 3.84 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—6.95 (4H, m), 6.99 (1H, d, J=1.5 Hz), 7.35 (2H, d, J=8.5 Hz), 7.43 (1H, d, J=1.5 Hz), 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{22}ClN_3O_3$: C, 65.17; H, 5.23; N, 9.91. Found: C, 65.18; H, 5.18; N, 9.98. Compounds **13b**, **13e**, **13f**, **13h**, **13i**, and **13k**—**w** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 3.

13b: ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.4 (2H, m), 3.19 (2H, t, J=7 Hz), 3.84 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—7.0 (4H, m), 7.19 (1H, br s), 7.35 (2H, d, J=8.5 Hz), 7.55 (1H, s), 7.61 (2H, d, J=8.5 Hz), 8.19 (1H, s). *Anal.* Calcd for $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.40; H, 5.06; N, 10.20.

13e: ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.4 (2H, m), 3.21 (2H, t, J=7 Hz), 3.85 (3H, s), 4.09 (2H, t, J=6 Hz), 6.51 (1H, dd, J=1.5, 2.5 Hz), 6.8—7.0 (4H, m), 7.32 (2H, d, J=8.5 Hz), 7.65 (2H, d, J=8.5 Hz), 7.81 (1H, d, J=1.5 Hz), 8.22 (1H, d, J=2.5 Hz). *Anal.* Calcd for $C_{22}H_{20}ClN_3O_3$: C, 64.47; H, 4.92; N, 10.25. Found: C, 64.41; H, 4.98; N, 10.22.

13f: ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.4 (2H, m), 3.23 (2H, t, J=7 Hz), 3.84 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—7.0 (4H, m), 7.35 (2H, d, J=8.5 Hz), 7.65 (2H, d, J=8.5 Hz), 8.17 (1H, s), 8.86 (1H, s). *Anal.* Calcd for $C_{21}H_{19}ClN_4O_3$: C, 61.39; H, 4.66; N, 13.64. Found: C, 61.52; H, 4.63; N, 13.77.

13h: ^{1}H-NMR ($CDCl_3$) δ: 2.25—2.4 (2H, m), 3.20 (2H, t, J=7 Hz), 3.86 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—7.0 (4H, m), 7.34 (2H, d, J=8.5 Hz), 7.4—7.5 (3H, m), 7.67 (2H, d, J=8.5 Hz), 7.95—8.1 (2H, m). *Anal.* Calcd for $C_{25}H_{22}ClNO_3$: C, 71.51; H, 5.28; N, 3.34. Found: C, 71.36; H, 5.35; N, 3.37.

13i: ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.35 (2H, m), 2.76 (3H, s), 3.16 (2H, t, J=7 Hz), 4.05 (2H, t, J=6 Hz), 6.85—7.0 (2H, m), 7.00 (1H, d, J=2 Hz), 7.2—7.3 (3H, m), 7.36 (2H, d, J=8.5 Hz), 7.42 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{22}H_{20}ClN_3O_2 \cdot 3/4H_2O$: C, 64.86; H, 5.32; N, 10.31. Found: C, 65.10; H, 4.99; N, 10.40.

13k: ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7 Hz), 2.2—2.35 (2H, m), 2.75 (3H, s), 3.16 (2H, t, J=7 Hz), 4.0—4.15 (4H, m), 6.8—6.95 (4H, m), 6.99 (1H, d, J=2 Hz), 7.36 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=2 Hz), 7.64 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{24}H_{24}ClN_3O_3$: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.85; H, 5.41; N, 9.62.

13l: ^{1}H-NMR ($CDCl_3$) δ: 1.32 (6H, d, J=6 Hz), 2.2—2.3 (2H, m), 2.76 (3H, s), 3.19 (2H, t, J=7 Hz), 4.09 (2H, t, J=6 Hz), 4.4—4.55 (1H, m), 6.8—6.95 (4H, m), 6.99 (1H, d, J=2 Hz), 7.36 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=2 Hz), 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{26}ClN_3O_3$: C, 66.44; H, 5.80; N, 9.30. Found: C, 66.33; H, 5.92; N, 9.53.

13m: ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.35 (2H, m), 2.43 (3H, s), 2.79 (3H, s), 3.25 (2H, t, J=7 Hz), 4.11 (2H, t, J=6 Hz), 6.77 (1H, d, J=8 Hz), 6.95—7.2 (4H, m), 7.35 (2H, d, J=8.5 Hz), 7.44 (1H, d, J=2 Hz), 7.65 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{22}ClN_3O_2S$: C, 62.79; H, 5.04; N, 9.55. Found: C, 62.46; H, 5.30; N, 9.67.

13n: ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.4 (2H, m), 2.76 (3H, s), 3.26 (2H, t, J=7 Hz), 4.11 (2H, t, J=6 Hz), 6.86 (1H, d, J=8.5 Hz), 6.95—7.1 (2H, m), 7.36 (2H, d, J=8.5 Hz), 7.4—7.5 (1H, m), 7.5—7.6 (2H, m). 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{19}ClN_4O_2$: C, 65.95; H, 4.57; N, 13.38. Found: C, 65.86; H, 4.66; N, 13.35.

13o: ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s), 2.25—2.35 (2H, m), 2.76 (3H, s), 3.18 (2H, t, J=7 Hz), 4.07 (2H, t, J=6 Hz), 6.77 (1H, d, J=8 Hz), 6.88 (1H, t, J=8 Hz), 6.99 (1H, d, J=2 Hz), 7.1—7.2 (2H, m), 7.34 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{22}ClN_3O_2$: C, 67.73; H, 5.44; N, 10.30. Found: C, 67.71; H, 5.45; N, 10.38.

13p: ^{1}H-NMR ($CDCl_3$) δ: 1.22 (6H, t, J=7 Hz), 2.2—2.4 (2H, m), 2.77 (3H, s), 3.19 (2H, t, J=7 Hz), 3.3—3.4 (1H, m), 4.08 (2H, t, J=6 Hz), 6.79 (1H, d, J=8 Hz), 6.9—7.0 (1H, m), 7.00 (1H, d, J=2 Hz), 7.1—7.3 (2H, m), 7.36 (2H, d, J=8.5 Hz), 7.42 (1H, d, J=2 Hz), 7.62 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{26}ClN_3O_2 \cdot 1/4H_2O$: C, 68.18; H, 6.06; N, 9.54. Found: C, 68.39; H, 6.12; N, 9.77.

13q: ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.3 (2H, m), 2.32 (3H, s), 2.76 (3H, s), 3.15 (2H, t, J=7 Hz), 4.03 (2H, t, J=6 Hz), 6.65—6.75 (1H, m), 6.75—6.85 (1H, m), 7.00 (1H, d, J=2 Hz), 7.1—7.2 (2H, m), 7.36 (2H, d, J=8.5 Hz), 7.42 (1H, d, J=2 Hz), 7.62 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{23}H_{22}ClN_3O_2$: C, 67.73; H, 5.44; N, 10.30. Found: C, 67.77; H, 5.41; N, 10.27.

13r: ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.3 (2H, m), 2.29 (3H, s), 2.76 (3H, s), 3.15 (2H, t, J=7 Hz), 4.02 (2H, t, J=6 Hz), 6.76 (2H, d, J=8.5 Hz), 6.99 (1H, d, J=2 Hz), 7.08 (2H, d, J=8.5 Hz), 7.36 (2H, d, J=8.5 Hz), 7.42 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz).

13s: ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 2.2—2.35 (2H, m), 2.28 (3H, s), 2.76 (3H, s), 3.18 (2H, t, J=7 Hz), 4.04 (2H, t, J=6 Hz), 6.65 (1H, d, J=8 Hz), 6.80 (1H, d, J=8 Hz), 6.99 (1H, d, J=2 Hz), 7.03 (1H, t, J=8 Hz), 7.35 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.13; H, 5.76; N, 10.10.

13t: ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.3 (2H, m), 2.20 (3H, s), 2.26 (3H, s), 2.76 (3H, s), 3.17 (2H, t, J=7 Hz), 4.03 (2H, t, J=6 Hz), 6.65 (1H, d, J=8.5 Hz), 6.9—7.0 (3H, m), 7.34 (2H, d, J=8.5 Hz), 7.41 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.09; H, 5.61; N, 10.08.

13u: ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.1 (4H, m), 2.20 (3H, s), 2.77 (3H, s), 3.01 (2H, t, J=7 Hz), 4.02 (2H, t, J=6 Hz), 6.75—6.9 (2H, m), 7.01 (1H, d, J=2 Hz), 7.1—7.2 (2H, m), 7.37 (2H, d, J=8.5 Hz), 7.46 (1H, d, J=2 Hz), 7.60 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{24}H_{24}ClN_3O_2$: C, 68.32; H, 5.73; N, 9.96. Found: C, 68.18; H, 5.65; N, 9.85.

13v: ^{1}H-NMR ($CDCl_3$) δ: 1.6—1.9 (6H, m), 2.18 (3H, s), 2.77 (3H, s), 2.95 (2H, t, J=7 Hz), 3.97 (2H, t, J=6 Hz), 6.75—6.9 (2H, m), 7.00 (1H, d, J=2 Hz), 7.1—7.2 (2H, m), 7.41 (2H, d, J=8.5 Hz), 7.46 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{26}ClN_3O_2$: C, 68.88; H, 6.01; N,

9.64. Found: C, 68.89; H, 5.99; N, 9.58.

13w: ^{1}H-NMR ($CDCl_3$) δ: 1.4—1.6 (4H, m), 1.7—1.9 (4H, m), 2.21 (3H, s), 2.77 (3H, s), 2.92 (2H, t, J=7 Hz), 3.95 (2H, t, J=6 Hz), 6.75—6.9 (2H, m), 7.00 (1H, d, J=2 Hz), 7.1—7.2 (2H, m), 7.41 (2H, d, J=8.5 Hz), 7.46 (1H, d, J=2 Hz), 7.61 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{26}H_{28}ClN_3O_2$: C, 69.40; H, 6.27; N, 9.34. Found: C, 69.28; H, 6.13; N, 9.21.

4-(4-Chlorophenyl)-5-[3-(2-hydroxyphenoxy)propyl]-2-(2-methyl-1*H*-imidazol-1-yl)oxazole (13j) To a solution of **13l** (200 mg, 0.44 mmol) in CH_2Cl_2 (5 ml) was added titanium tetrachloride (380 mg, 2.0 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 1 h, quenched with saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give pale yellow crystals. Recrystallization from acetone–isoPr$_2$O gave the title compound (**13j**, 90 mg, 50%) as pale yellow prisms, mp 110—111 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.2—2.4 (2H, m), 2.79 (3H, s), 3.16 (2H, t, J=7 Hz), 4.15 (2H, t, J=6 Hz), 5.55 (1H, br s), 6.8—7.0 (4H, m), 6.97 (1H, d, J=2 Hz), 7.38 (2H, d, J=8.5 Hz), 7.43 (1H, d, J=2 Hz), 7.58 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{22}H_{20}ClN_3O_3 \cdot 1/4H_2O$: C, 63.77; H, 4.99; N, 10.14. Found: C, 64.00; H, 5.03; N, 9.81.

General Procedure for Method C. 3-(2-Chloro-4-chlorophenyl-5-oxazolyl)-1-propanol (11, *n*=2) A solution of diisobutylaluminum hydride in hexane (1.0 M, 65.0 ml, 65.0 mmol) was added dropwise to a stirred solution of **7a** (9.00 g, 30.0 mol) in THF (100 ml) at −78 °C followed by stirring at 0 °C for 1 h. The reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ (10.0 g) and the insoluble material was removed by filtration. The filtrate was concentrated *in vacuo* to give the title compound (**11**, 7.00 g, 86%) as an amorphous powder. ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.1 (2H, m), 2.99 (2H, t, J=7 Hz), 3.73 (2H, t, J=6 Hz), 7.38 (2H, d, J=8.5 Hz), 7.53 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{12}H_{11}Cl_2NO_2$: C, 52.96; H, 4.07; N, 5.15. Found: C, 53.35; H, 4.09; N, 5.28.

2-Chloro-4-(4-chlorophenyl)-5-[3-(2-methoxyphenoxy)propyl]oxazole (12, *n*=2) A mixture of **11** (1.28 g, 4.70 mmol), 2-methoxyphenol (931 mg, 7.50 mol), tributylphosphine (1.52 g, 7.50 mmol), 1,1′-(azodicarbonyl)dipiperidine (1.90 g, 7.50 mmol), and THF (10 ml) was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by chromatography on SiO_2 to give the title compound (**12**, 1.00 g, 56%) as colorless crystals. mp 81—82 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.3 (2H, m), 3.12 (2H, t, J=7 Hz), 3.86 (3H, s), 4.06 (2H, t, J=6 Hz), 6.8—7.0 (4H, m), 7.31 (2H, d, J=8.5 Hz), 7.55 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{19}H_{17}Cl_2NO_3$: C, 60.33; H, 4.53; N, 3.70. Found: C, 60.39; H, 4.52; N, 3.81.

4-(4-Chlorophenyl)-2-(2-ethyl-1*H*-imidazol-1-yl)-5-[3-(2-methoxyphenoxy)propyl]oxazole (13c) A mixture of **12** (1.00 g, 2.64 mol), 2-ethylimidazole (960 mg, 10.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and DMF (20 ml) was stirred at 120—130 °C for 2 h. The reaction mixture was poured into water to give crude crystals. Recrystallization from acetone–isoPr$_2$O gave the title compound (**13c**, 618 mg, 53%) as pale yellow prisms, mp 78—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.2—2.35 (2H, m), 2.72 (2H, t, J=7 Hz), 3.15 (2H, q, J=7 Hz), 3.19 (2H, t, J=7 Hz), 3.84 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—6.95 (4H, m), 7.02 (1H, d, J=2 Hz), 7.35 (2H, d, J=8.5 Hz), 7.42 (1H, d, J=2 Hz), 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{24}H_{24}ClN_3O_3$: C, 65.82; H, 5.52; N, 9.60. Found: C, 65.94; H, 5.41; N, 9.54. Compounds **13d** and **13g** were obtained similarly. The yields, recrystallization solvents, and melting points were listed in Table 3.

13d: ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz), 1.75—1.95 (2H, m), 2.25—2.40 (2H, m), 3.11 (2H, t, J=7 Hz), 3.19 (2H, t, J=7 Hz), 3.84 (3H, s), 4.10 (2H, t, J=6 Hz), 6.8—6.95 (4H, m), 7.01 (1H, d, J=2 Hz), 7.35 (2H, d, J=8.5 Hz), 7.40 (1H, d, J=2 Hz), 7.63 (2H, d, J=8.5 Hz). *Anal.* Calcd for $C_{25}H_{26}ClN_3O_3 \cdot 1/4H_2O$: C, 65.79; H, 5.85; N, 9.21. Found: C, 65.84; H, 5.76; N, 9.15.

13g: ^{1}H-NMR ($CDCl_3$) δ: 2.30—2.40 (2H, m), 3.26 (2H, t, J=6.5 Hz), 3.83 (3H, s), 4.14 (2H, t, J=6 Hz), 6.8—7.0 (4H, m), 7.35—7.5 (4H, m), 7.70 (2H, d, J=8.5 Hz), 7.8—7.9 (1H, m), 8.2—8.3 (1H, m), 8.50 (1H, s). *Anal.* Calcd for $C_{26}H_{22}ClN_3O_3$: C, 67.90; H, 4.82; N, 9.14. Found: C, 67.65; H, 4.81; N, 9.01.

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