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Bioorganic & Medicinal Chemistry 12 (2004) 2419–2439
Bioorganic & Medicinal Chemistry

Synthesis and biological activity of novel α-substituted β-phenylpropionic acids having pyridin-2-ylphenyl moiety as antihyperglycemic agents

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Received 23 October 2003; accepted 31 January 2004

Abstract—We previously reported the identification of novel oximes having 5-benzyl-2,4-thiazolidinedione with antihyperglycemic activity. We now report the synthesis and biological activity of a novel series of oximes and amides having α-substituted-β-phenylpropionic acids. In this series, we obtained potent PPARα/γ dual agonist (*S*)-**9d**, with which activation of PPARα and PPARγ was considerably more potent than that of the reference compounds GW9578 **22** and rosiglitazone **3**, respectively. This means (*S*)-**9d** is of the strongest class of PPARα/γ dual agonists. In the course of this study, we also obtained **8h**, which indicated potent plasma glucose lowering effect in spite of weak PPARα/γ agonistic activity.

1. Introduction

After the discovery of the thiazolidinedione (TZD)-based compound ciglitazone[1,2] as a novel oral antihyperglycemic agent having significant effects on improving peripheral insulin resistance, many reports on new TZD derivatives have appeared, and troglitazone (Sankyo) **1**,[3] pioglitazone (Takeda) **2**,[4] and rosiglitazone (GSK) **3**[5] (Fig. 1) have been developed and marketed. Since the launch of TZDs, however, several reports of treatment-related toxicity have been released. Troglitazone **1**, the first TZD approved, was withdrawn because of unacceptable levels of hepatotoxicity.[6] Rosiglitazone **3**, the second TZD marketed, has been associated with liver, cardiovascular, and hematological toxicity.[7]

The mechanism of action of TZDs is still not fully understood, but the recent identification that the TZDs and lipid lowering fibrates (e.g., bezafibrate) are high affinity ligands for the nuclear receptor peroxisome proliferators-activated receptor γ (PPARγ) and PPARα, respectively, has provided new tools for the discovery of novel compounds for the treatment of type 2 diabetes.[8,9] PPARα agonists are effective in lowering serum triglycerides and increasing HDL cholesterol, in some cases accompanied by lowering serum fibrinogen.[10] Furthermore, PPARα activation has also been shown to produce antiinflammatory effects in vascular cells.[11] The combined profile of a dual PPARα/γ agonist is thought to be beneficial for the treatment of hyperglycemia since it is accompanied by prevention of cardiovascular disease in type 2 diabetes. Several compounds have been reported to have both PPARα and PPARγ agonistic activity, and AZ-242 (Astrazeneca) **4**,[12] KRP-297 (Kyorin) **5**,[13] and MCC-555 (Mitsubishi Chemical) **6**[14] (Fig. 2) are now in clinical trial.

Historically, despite an exhaustive search to replace the TZD ring with other moieties, an effective replacement giving significant advantages over the TZD ring had remained unsuccessful for a long time. However,

Keywords: Antihyperglycemic agent; PPARα; PPARγ; KK mouse.
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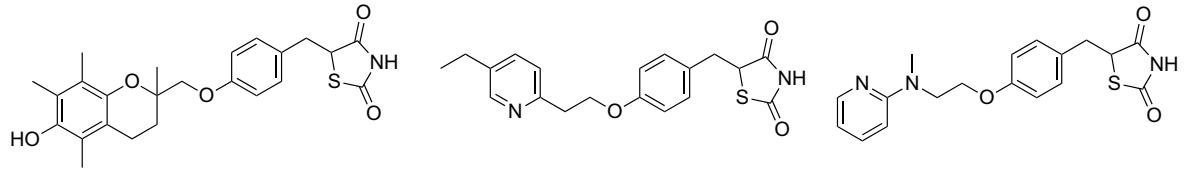
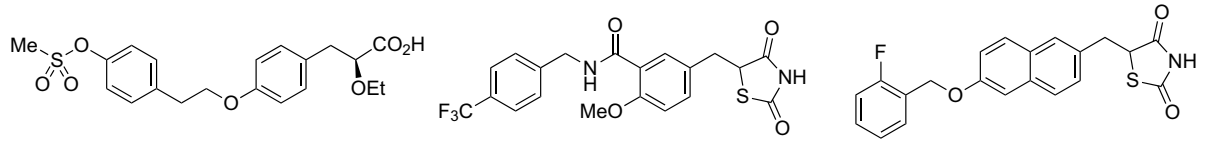
doi:10.1016/j.bmc.2004.01.048



Troglitazone **1** Pioglitazone **2** Rosiglitazone **3**

Figure 1.



AZ242 **4** KRP297 **5** MCC555 **6**

Figure 2.

research groups at Pfizer and Glaxo revealed that the TZD ring can be replaced by a substituted alkanoic acid moiety,[15–18] and recent reports showed these compounds have very potent in vitro and in vivo activities. On the other hand, we have already reported the TZD **7** (Fig. 3) having pyridin-2-ylphenyl moiety indicates potent PPARγ agonistic activity.[19] Using compound **7** as a template, we examined the effects of replacing TZD by various substituted phenylpropionic acids in activation of PPARα/γ.[20–22] Herein we describe our efforts to identify novel potent dual PPARα/γ agonists. The series was evaluated for antihyperglycemic activity in the genetically diabetic KK mice in vivo and in PPARα/γ transactivation in vitro assay to classify and characterize these compounds.

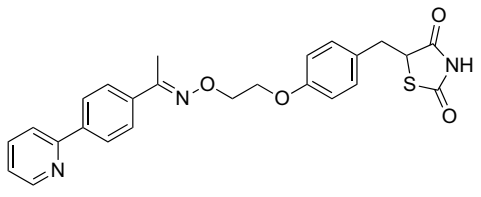


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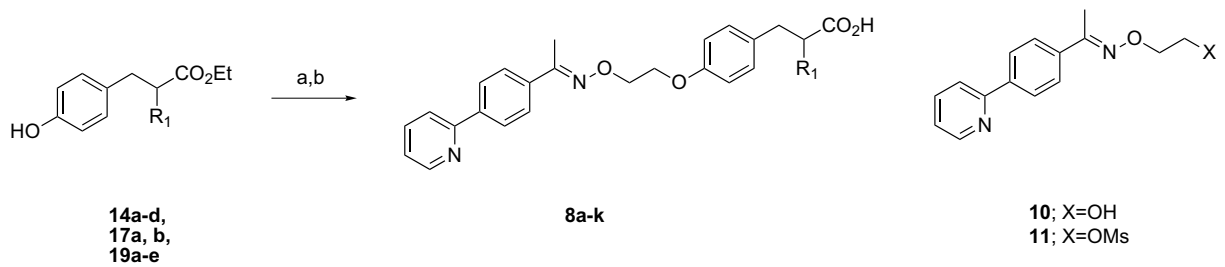
Figure 3.

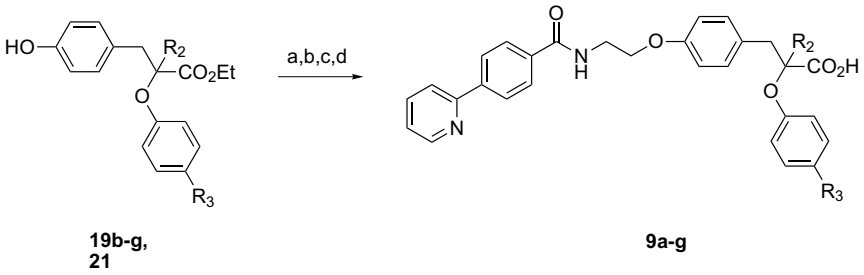
2. Chemistry

Oxime derivatives **8a**–**k** were prepared as follows (Scheme 1). Ethyl α-substituted β-(4-hydroxyphenyl)propionates **14a**–**d**, **17a**,**b**, **19a**–**e** were subjected to Mitsunobu reaction with the oxime alcohol **10** or alkylation with mesylate **11**. Subsequent alkaline hydrolysis gave the desired oxime derivatives **8a**–**k**. Amide derivatives **9a**–**g** were prepared as follows (Scheme 2). Ethyl α-(4-substituted phenoxy)-β-(4-hydroxyphenyl)propionates **19b**–**g**, **21** were subjected to Mitsunobu reaction with *N*-Boc-ethanolamine. Subsequent deprotection of the *N*-Boc group, acylation using diethyl phosphoryl cyanide (DEPC) and alkaline hydrolysis gave the desired amide derivatives **9a**–**g**. The starting materials were prepared as shown in Schemes 3–7. Ethyl α-alkyl and phenylalkyl-β-(4-hydroxyphenyl)propionates **14a**–**d** were prepared as follows (Scheme 3). Alkylation of ethyl α-alkyl malonates **12a**–**d** with 4-benzyloxybenzyl chloride gave **13a**–**d**, which were converted to **14a**–**d** by hydrolysis, decarboxylation, esterification, and subsequent removal of the benzyl group. Ethyl α-methylthio and phenylthio-β-(4-hydroxyphenyl)propionates **17a** and **17b** were, respectively, prepared from ethyl 3-(4-hydroxyphenyl)lactate **15** (Scheme 4). Compound **15** was converted to mesylate **16** after protection of the phenol group. Compound **16** was



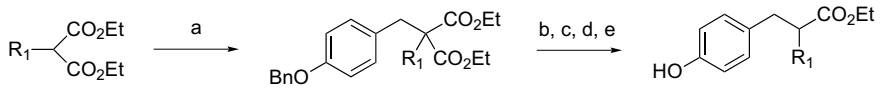
14a-d, 17a, b, 19a-e **8a-k** **10**; X=OH **11**; X=OMs

Scheme 1. Reagents and conditions: (a) DEAD, Ph_3P, **10** or NaH, **11**; (b) NaOH.



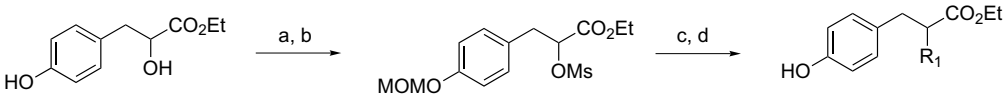
19b-g, 21 **9a-g**

Scheme 2. Reagents and conditions: (a) DEAD, Ph_3P, $BocNHCH_2CH_2OH$; (b) HCl, dioxane; (c) 2-Py-benzoic acid, Et_3N, DEPC; (d) NaOH.



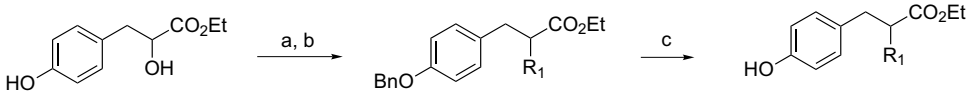
12a-d **13a-d** **14a-d**
R_1 =n-Pr, i-Pr, n-Bu, 3-Phenylpropyl

Scheme 3. Reagents and conditions: (a) NaH, 4-benzyloxybenzyl chloride; (b) KOH; (c) xylene, reflux; (d) H_2SO_4, EtOH; (e) H_2, Pd–C.



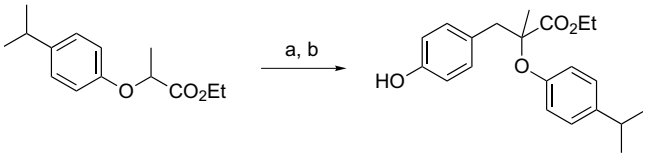
15 **16** **17a, b**
R_1=MeS, PhS

Scheme 4. Reagents and conditions: (a) methoxymethyl chloride, NaH; (b) MsCl, Et_3N; (c) MeSNa or $PhSH/K_2CO_3$; (d) HCl, dioxane.



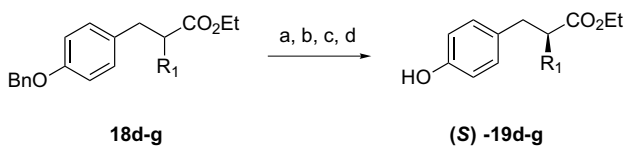
15 **18a-g** **19a-g**
R_1 =EtO, ArO

Scheme 5. Reagents and conditions: (a) benzyl bromide, K_2CO_3; (b) ArOH, DEAD, Ph_3P or NaH, EtI; (c) H_2, Pd–C or HBr in AcOH.



20 **21**

Scheme 6. Reagents and conditions: (a) lithium isopropylcyclohexylamide, 4-benzyloxybenzyl chloride; (b) H_2, Pd–C.



18d-g **(*S*) -19d-g**

Scheme 7. Reagents and conditions: (a) NaOH; (b) (−)-norephedrine; (c) H_2SO_4, EtOH; (d) H_2, Pd–C.

reacted with sodium thiomethoxide or benzenethiol. Compounds **17a**,**b** were obtained after removal of the methoxymethyl group. Ethyl α-ethoxy and phenoxy-β-(4-hydroxyphenyl)propionates **19a**–**g** were prepared as follows (Scheme 5). Protection of the phenol group followed by alkylation of **15** with ethyl iodide or Mitsunobu reaction with phenol gave **18a**–**g**. Subsequent removal of the benzyl group gave **19a**–**g**. Ethyl α-(4-isopropylphenoxy)-α-methyl-β-(4-hydroxyphenyl)propionate **21** was prepared by alkylation of ethyl α-(4-isopropylphenoxy)propionate **20**[23] with 4-benzyloxybenzyl

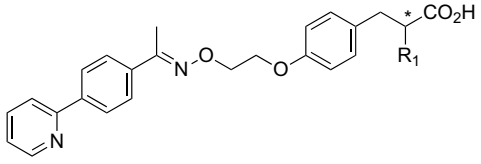
chloride and removal of the benzyl group (Scheme 6). Optically active ethyl α-aryloxy-β-(4-hydroxyphenyl)-propionates (*S*)-**19d**–**g** were prepared as follows (Scheme 7). Racemic ethyl α-aryloxy-β-(4-benzyloxy)phenylpropionates **18d**–**g** were hydrolyzed and optical resolution using (−)-norephedrine was performed. The optically active carboxylic acids obtained were subjected to esterification and removal of the benzyl group to give (*S*)-**19d**–**g** in >99% ee. The absolute configuration of (*S*)-**9d** was determined by chiral column HPLC analysis using an authentic sample synthesized from (*S*)-**19e** in a previous synthetic study.[24]

3. Results and discussion

The results of the biological activity of the synthesized compounds compared with GW9578 **22**[8] and rosiglitazone **3**, reported as a potent PPARα and γ agonist, respectively, are summarized in Tables 1 and 2. The oximes **8a**–**k** and amides **9a**–**g** prepared above were evaluated for their PPARα and γ agonistic activity and for their plasma glucose lowering activity in hyperglycemic KK mice. To compare the efficacy of PPARα and γ agonistic activity, maximum fold activation (% max) relative to the maximum efficacy of PPAR activation of GW9578 **22** and rosiglitazone **3** are listed. The maximum efficacy of PPAR activation of GW9578 **22** and rosiglitazone **3** are defined as 100% for PPARα and PPARγ, respectively.

At first, we prepared oximes **8a**–**k** having α-substituted-β-phenylpropionic acid. In the series of α-alkyl or phenylalkyl-β-phenylpropionic acids **8a**–**d**, α-propyl derivative **8a** indicated potent plasma glucose lowering activity compared with its isopropyl, butyl, and phenylpropyl analogues **8b**,**c**,**d**. All of these compounds showed only weak PPARα and γ agonistic activity and a longer alkyl or aralkyl chain in particular caused a marked decrease in PPARα and γ activity. Next, derivatives having an oxygen or sulfur atom at the α-position were synthesized (**8e**–**h**). α-Methylthio derivative **8e** showed better PPARα and γ agonistic activity than α-alkyl or phenylalkyl derivatives without affecting its in vivo activity. As reported in the literature,[16] α-ethoxy compound **8g** showed potent PPARγ agonistic activity comparable to rosiglitazone **3** and sufficient in vivo activity. Interestingly α-phenoxy compound **8h** also showed potent plasma glucose lowering activity in spite of weak PPARγ agonistic activity. On the other hand, its sulfur analogue **8f**, having greater PPARγ agonistic activity compared with **8h**, showed only a weak blood glucose lowering activity. Interested in the potent in vivo activity of **8h**, we synthesized substituted phenoxy compounds **8i**–**k**. Although PPARγ activation of these compounds was weak, their potent in vivo activities were confirmed. Pure *S* enantiomer (*S*)-**8j** was prepared to evaluate the enantiomeric effect on biological activity. Compound (*S*)-**8j** showed more potent in vivo and

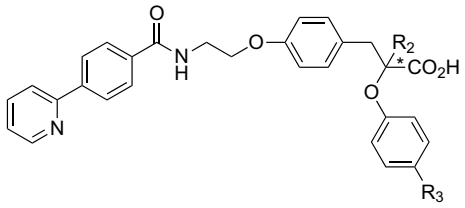
Table 1. PPARα and γ agonistic activity and antihyperglycemic activity of oximes



Compound	R_1	*	hPPARα EC_{50} (μM)	% Max[a]	hPPARγ EC_{50} (μM)	% Max[b]	PG[c] (%)
8a	*n*-Pr	*RS*	>10	11	>10	80	56
8b	*i*-Pr	*RS*	>10	39	>10	76	4
8c[d]	*n*-Bu	*RS*	>10	<5	>10	48	26
8d[d]	$PhCH_2CH_2CH_2$	*RS*	>10	<5	>10	11	47
8e	MeS	*RS*	>10	98	>10	148	20
8f	PhS	*RS*	>10	8	3.3	159	20
8g	EtO	*RS*	4.5	52	0.034	110	47
8h	PhO	*RS*	>10	<5	>10	40	65
8i	4-F-PhO	*RS*	>10	12	>10	46	64
8j	4-Me-PhO	*RS*	>10	72	>10	97	52
(*S*)-**8j**	4-Me-PhO	*S*	>10	15	4.6	42	62
8k	4-*t*-Bu-PhO	*RS*	>10	8	2.6	35	69
Rosiglitazone **3**			>10	10	0.054	100	66
GW9578 **22**			0.68	100	0.60	103	—

[a] The maximum efficacy of PPARα activation of GW9578 **22** is defined as 100%.
[b] The maximum efficacy of PPARγ activation of rosiglitazone **3** is defined as 100%.
[c] The test compounds were mixed with powdered feed F-2 (Funabashi Farms) in a ratio of 0.01% (about 10 mg/kg/day). The mixture was administered orally to hyperglycemic male KK mice (4–6 months of age) for 3 days. Values (mean ± SE) are the % change in plasma glucose concentration of the drug-treated mice relative to vehicle controls. All values are the mean of $n = 4$ or 5.
[d] Biological activities were evaluated as sodium salts.

Table 2. PPARα and γ agonistic activity and antihyperglycemic activity of amides



Compound	R_2	R_3	*	hPPARα EC_{50} (μM)	% Max[a]	hPPARγ EC_{50} (μM)	% Max[b]	PG[c] (%)
9a	H	H	*RS*	>10	<5	0.69	82	22
9b	H	Me	*RS*	>10	22	0.61	84	66
(*S*)-**9b**	H	Me	*S*	>10	57	0.10	81	69
9c	H	*i*-Pr	*RS*	1.0	141	0.070	98	64
(*R*)-**9c**	H	*i*-Pr	*R*	>10	53	5.8	55	52
(*S*)-**9c**	H	*i*-Pr	*S*	0.71	153	0.046	59	73
9d	H	*t*-Bu	*RS*	0.69	88	0.033	96	70
(*R*)-**9d**	H	*t*-Bu	*R*	>10	<5	>10	94	15
(*S*)-**9d**	H	*t*-Bu	*S*	0.21	103	0.011	72	62
9e	H	F	*RS*	>10	12	2.2	85	49
9f	H	Cl	*RS*	>10	11	8.7	132	60
(*S*)-**9f**	H	Cl	*S*	>10	47	2.5	73	73
9g	Me	*i*-Pr	*RS*	0.087	106	0.011	82	68
Rosiglitazone **3**				>10	10	0.054	100	66
GW9578 **22**				0.68	100	0.60	103	—

[a] The maximum efficacy of PPARα activation of GW9578 **22** is defined as 100%.

[b] The maximum efficacy of PPARγ activation of rosiglitazone **3** is defined as 100%.

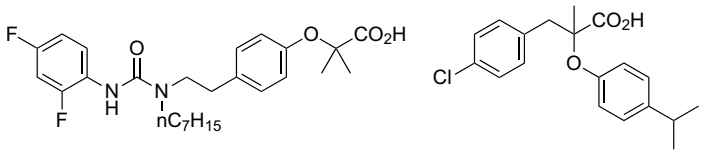
[c] The test compounds were mixed with powdered feed F-2 (Funabashi Farms) in a ratio of 0.01% (about 10 mg/kg/day). The mixture was administered orally to hyperglycemic male KK mice (4–6 months of age) for 3 days. Values (mean ± SE) are the % change in plasma glucose concentration of the drug-treated mice relative to vehicle controls. All values are the mean of $n = 4$ or 5.

in vitro activity than its racemate **8j**. The result gave good agreement with that of the Glaxo group.[25]

All the prepared oximes **8a**–**k** except for **8g** showed only weak PPARα and γ agonistic activities, but it is interesting that α-phenoxy derivatives **8h**–**k** showed potent plasma glucose lowering activity. Among these oxime derivatives, correlation between PPARγ agonistic activity and plasma glucose lowering activity was not clear. Compounds **8h**–**k** had no significant activity for PPARδ, and exerted only a little adipogenic activity in murine 3T3L1 cells in accordance with its weak PPARγ activity (data not shown). One possible explanation is that these compounds may be selective modulators of PPARγ.[26] Another possibility is that these compounds may activate another receptor, GPR40/FFAR, that is expressed in islet β cells.[27,28] Thus, the studies concerning binding for PPAR and other receptors, as well as in vivo pharmacological and pharmacokinetic profiles, would be needed to elucidate the plasma glucose lowering activity of these compounds.

Next, searching for our initial target dual PPARα/γ agonists, we synthesized compounds **9a**–**g**, which have the amide moiety instead of the oxime moiety. Although **9a** showed only moderate plasma glucose lowering activity, almost all of the 4-substituted phenoxy derivatives **9b**–**g** indicated potent in vivo activity, and there was a tendency that compounds having a more bulky group at the *para*-position of the α-phenoxy group had more potent PPARα and γ agonistic activity. The *S* enantiomers of **9b**–**d**,**f**, the 4-methylphenoxy, 4-isopropylphenoxy, 4-*tert*-butylphenoxy, and 4-chlorophenoxy derivatives and the *R* enantiomers of **9c**–**d** the 4-isopropylphenoxy and 4-*tert*-butylphenoxy derivatives were prepared to estimate the enantiomeric effect. Among these compounds, all of the *S* enantiomers had more potent PPARα and γ agonistic activity than their *R* enantiomers and racemates, and this tendency was also shown in plasma glucose lowering activity. The results indicate that PPARγ agonistic activity is essential for potent plasma glucose lowering activity compared with that of oxime series. Surprisingly, (*S*)-**9d**, having a 4-*tert*-butylphenoxy group at the α-position, indicated more potent PPARα and γ agonistic activity than the reference compounds **22** and **3**, respectively. This means (*S*)-**9d** is of the strongest class of PPARα/γ dual agonists.

Then, we prepared compound **9g** having a methyl group at the α-position of the propionic acid moiety. In designing **9g**, we referred to the structure of antihyperglycemic agent **23**[23] (Fig. 4) reported by the Pfizer research group. Its mechanism of action was suggested to involve the enhancement of the intrinsic activity of the glucose transporter GLUT1 or GLUT4. Our evaluation of **23** for PPARα and γ agonistic activity gave selective PPARα agonistic activity (data not shown). Interestingly, despite the racemic form, **9g** indicated the most potent PPARα and γ agonistic activity in our study



GW9578 **22** **23**

Figure 4.

with potent in vivo activity. A methyl group at the α-position might be important for PPARα activation. However, we selected (*S*)-**9d** for further investigation because of synthetic feasibility.

4. Conclusion

We synthesized and evaluated α-substituted β-phenylpropionic acids having a pyridin-2-ylphenyl moiety as antidiabetic agents. We obtained potent PPARα/γ dual agonists (*S*)-**9d** and **9g** in comparison with known PPARα and γ agonists. Compound (*S*)-**9d** was selected for further investigation because of synthetic feasibility. We also obtained **8h**, which indicated potent plasma glucose lowering effect in spite of weak PPARα/γ agonistic activity. Further development work on these compounds is in progress.

5. Experimental

5.1. PPARα and PPARγ transactivation assays

5.1.1. Plasmids. cDNA encoding the ligand binding domain of human PPARα (amino acids 168–468) or PPARγ2 (amino acids 175–475) was generated by reverse transcript polymerase chain reaction (RT-PCR) using total RNAs from human hepatocarcinoma HepG2 cells (ATCC HB-8065). The forward and reverse primers were 5′-GGATCCACAACGCGATTCGTTTT GGACGA-3′ and 5′-AAGCTTTGTGGCTGATCTGAAGGAACTCA-3′ toward PPARα, and 5′-GGATCCATAATGCCATCAGGTTTGGGCGG-3′ and 5′-AAGCTTCTAGTACAAGTCCTTGTAGATCTC-3′ toward PPARγ. The PCR products were cloned into pCRII (Invitrogen Corporation), and after sequence verification, subcloned into the pM vector (CLONTECH Laboratories, Inc.) including a yeast GAL4 (amino acids 1–147) sequence, at the BamHI-HindIII site. The plasmid, pM-hPPARα or pM-hPPARγ, including the PPARα or PPARγ ligand binding domain fused to the GAL4 DNA binding domain, was used for the PPARα or γ transactivation assay, respectively. A GAL4-responsive reporter plasmid, pFR-Luc, was also obtained from STRATAGENE Cloning Systems.

5.1.2. Assay. MG-63 (ATCC CRL 1427) cells were grown at 37 °C, 5% CO_2 in Dulbecco's modified Eagle's medium with 10% fetal calf serum and antibiotics in a 75 cm^2 flask. Under nearly confluent growth conditions, cells were transfected with 3 μg of pFR-Luc in combination with 12 μg of pM-hPPARα or pM-hPPARγ, using FuGENE6 transfection reagent (Roche Diagnostics). After 20–24 h of the transfection, cells were trypsinized, suspended in 250 mL of medium, seeded into 96-well plates at 100 μL/well, then incubated for 20–24 h. The test compound was dissolved in dimethylsulfoxide at a series of concentrations (1 μM–10 mM), and diluted to 1% (v/v) with the medium, then added to the cells at 10 μL/well. After 20–24 h of incubation, 100 μL of PicaGene LT2.0 Luminescence Reagent (Wako Pure Chemical Ltd.) was added, and luminescence was counted using a TopCount HTS (Packard Instruments).

5.1.3. Statistics. EC_{50} values were calculated via logistic sigmoidal regression using SigmaPlot 2001 software (SPSS Inc.). The results are expressed as means of $n = 4$. To obtain the maximum efficacy values (% max), the maximum efficacy of the reference PPAR agonist (GW9578 **22** and rosiglitazone **3** for PPARα and PPARγ, respectively) was defined as 100%, % max was calculated using the equation:

$$100 \times (L_{max}/L_{ref}),$$

where L_{max} is the mean luminescence of maximum response concentration in test compound-treated groups, and L_{ref} is the mean luminescence of maximum response concentration in reference PPAR agonist-treated groups.

5.1.4. In vivo studies. The test compounds were mixed with powdered feed F-2 (Funabashi Farms) in a ratio of 0.01% (about 10 mg/kg/day). The mixture was administered orally to hyperglycemic male KK mice (4–6 months of age) for 3 days. Values (mean ± SE) are the % change in plasma glucose concentration of the drug-treated mice relative to vehicle controls. All values are the mean of $n = 4$ or 5.

5.2. Synthesis

Melting points (mp) were determined with a Yanaco melting point apparatus and are not corrected. Infrared (IR) spectra were measured with a Nic 5SXCFT-IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or 500 spectrometer. Chemical shifts are expressed in δ ppm from the internal standard tetramethylsilane (TMS). All NMR spectra were consistent with the structures

assigned. MS or high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-D 300 mass spectrometer. HPLC spectra were obtained using a Shimadzu HPLC system consisting of the following: pump, LC-10Advp; and detector, SPD-M10Avp, measured at 254 nm. Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM). TLC analyses were performed on Merck reagent silica gel 60 F_{254} (0.25 mm thickness).

5.3. 2-[4-[2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoic acid (8a)

5.3.1. Diethyl 2-(4-benzyloxybenzyl)-2-propylmalonate (13a). A mixture of NaH (55% dispersion in oil) (1.13 g, 25.9 mmol), diethyl 2-propylmalonate **12a** (5.0 g, 24.7 mmol) in toluene (25 mL) and DMF (25 mL) was stirred at 40 °C for 1 h. 4-Benzyloxybenzyl chloride (6.32 g, 27.2 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 10/1) to give the title compound as a colorless syrup (9.85 g, yield 99%).

^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, $J = 7.0$ Hz), 1.23 (6H, t, $J = 7.0$ Hz), 1.24–1.38 (2H, m), 1.71–1.78 (2H, m), 3.18 (2H, s), 4.16 (2H, q, $J = 7.0$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 5.02 (2H, s), 6.86 (2H, d, $J = 8.5$ Hz), 6.99 (2H, d, $J = 8.5$ Hz), 7.30–7.44 (5H, m). IR ($CDCl_3$) cm^{-1} 2966, 2256, 1727, 1112, 1248, 1220, 1179. HRMS m/z 398.2086 (M^+) (calcd for $C_{24}H_{30}O_5$ 398.2094).

5.3.2. Ethyl 2-(4-benzyloxybenzyl)pentanoate. A mixture of diethyl ester **13a** (9.85 g, 24.7 mmol) and KOH (5.25 g, 80.0 mmol) in 2-methoxyethanol (100 mL) and H_2O (10 mL) was stirred at 130 °C for 2 h. The reaction mixture was evaporated in vacuo and mixed with toluene. The mixture was acidified with 6 N HCl and extracted with EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The obtained oil was dissolved in xylene (100 mL) and the solution was refluxed for 1 h. The solvent was removed in vacuo and the residue was dissolved in EtOH (100 mL). To this solution was added concd H_2SO_4 (2.0 mL) and the mixture was stirred at 80 °C for 16 h. The solvent was evaporated in vacuo, and the residue was extracted with EtOAc. The organic phase was washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the title compound was obtained after purification by column chromatography (hexane/EtOAc, 4/1) as a colorless syrup (4.11 g, yield 51%).

^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, $J = 7.0$ Hz), 1.14 (3H, t, $J = 7.0$ Hz), 1.20–1.70 (4H, m), 2.55–2.64 (1H, m), 2.68 (1H, dd, $J = 6.0$, 13.0 Hz), 2.86 (1H, dd, $J = 8.0$, 13.0 Hz), 4.05 (2H, q, $J = 7.0$ Hz), 5.04 (2H, s), 6.88 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.05$ Hz), 7.28–7.45 (5H, m). IR ($CDCl_3$) cm^{-1} 2961, 2931, 1722, 1511, 1239, 1176, 1026. HRMS m/z 326.1878 (M^+) (calcd for $C_{21}H_{26}O_3$ 326.1882).

5.3.3. Ethyl 2-(4-hydroxybenzyl)pentanoate (14a). A mixture of ethyl 2-(4-benzyloxybenzyl)pentanoate (4.0 g, 12.3 mmol) and 5% Pd–C (0.4 g) in EtOH (45 mL) was stirred under H_2 atmosphere at 50 °C for 2 h. The reaction mixture was filtered to remove Pd–C and the filtrate was concentrated in vacuo to afford the title compound as a colorless syrup (2.9 g, yield 99%).

^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 7.0$ Hz), 1.15 (3H, t, $J = 7.0$ Hz), 1.20–1.70 (4H, m), 2.53–2.62 (1H, m), 2.67 (1H, dd, $J = 6.0$, 13.0 Hz), 2.84 (1H, dd, $J = 8.5$, 13.0 Hz), 4.05 (2H, q, $J = 7.0$ Hz), 4.77–4.81 (1H, m), 6.72 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 3401, 2960, 2935, 1731, 1705, 1516, 1222. HRMS m/z 236.1408 (M^+) (calcd for $C_{14}H_{20}O_3$ 236.1413).

5.3.4. Ethyl 2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoate. A mixture of NaH (0.10 g, 2.33 mmol) and ethyl 2-(4-hydroxybenzyl)pentanoate **14a** (0.50 g, 2.11 mmol) in toluene (5.0 mL) and DMF (5.0 mL) was stirred at 40 °C for 1 h. 2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethyl mesylate **11** (0.74 g, 2.22 mmol) was added. The mixture was stirred at room temperature for 16 h. Water was added and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 7/3) to give the title compound as a colorless oil (1.0 g, yield 43%).

^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 7.0$ Hz), 1.15 (3H, t, $J = 7.0$ Hz), 1.20–1.70 (4H, m) 2.28 (3H, s), 2.52–2.62 (1H, m), 2.67 (1H, dd, $J = 6.0$, 13.0 Hz), 2.86 (1H, dd, $J = 8.0$, 13.0 Hz), 4.05 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.20–7.25 (1H, m), 7.75–7.78 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). IR ($CDCl_3$) cm^{-1} 2961, 2930, 1722, 1588, 1512, 1469, 1245. HRMS m/z 475.2609 ($M+H^+$) (calcd for $C_{29}H_{35}N_2O_4$ 475.2597).

5.3.5. 2-[4-[2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoic acid (8a). To a solution of ethyl 2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoate (0.43 g, 0.91 mmol) in ethanol (10 mL) was added 1 N NaOH (3.5 mL), and the mixture was stirred at room temperature for 16 h. After the reaction mixture was evaporated in vacuo, the residue was diluted with water and carefully acidified with 1 N HCl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The solids were collected by filtration using the mixture of isopropyl ether and hexane to give the title compound as a colorless solid (0.37 g, yield 92%).

Mp: 115–117 °C. ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, $J = 7.0$ Hz), 1.25–1.71 (4H, m), 2.27 (3H, s), 2.62–2.74 (2H, m), 2.86–2.95 (1H, m), 4.30 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.23–7.30 (1H, m), 7.65–7.81 (4H, m), 7.95 (2H, d, $J = 8.5$ Hz). 8.70 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2958, 1694, 1511, 1243, 953, 780. MS m/z 447 (M+H$^+$). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.44; H, 6.91; N, 6.27.

Similarly **8b–d** were prepared.

5.4. 3-Methyl-2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]butyric acid (8b)

5.4.1. Diethyl 2-(4-benzyloxybenzyl)-2-isopropylmalonate (13b). Colorless syrup (yield 92%). ^{1}H NMR ($CDCl_3$) δ 1.04 (6H, d, $J = 7.0$ Hz), 1.18 (6H, t, $J = 7.0$ Hz), 2.30 (1H, septet, $J = 7.0$ Hz), 3.19 (2H, s), 4.01–4.21 (4H, m), 5.02 (2H, s), 6.84 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.28–7.46 (5H, m). IR ($CDCl_3$) cm^{-1} 2981, 2929, 1719, 1510, 1263, 1239, 1179. HRMS m/z 398.2060 (M$^+$) (calcd for $C_{24}H_{30}O_5$ 398.2094).

5.4.2. Ethyl 2-(4-benzyloxybenzyl)-3-methylbutyrate. Colorless syrup (yield 53%). ^{1}H NMR ($CDCl_3$) δ 0.96–1.12 (9H, m), 1.84–1.98 (1H, m), 2.41 (1H, q, $J = 7.0$ Hz), 2.79 (2H, d, $J = 7.0$ Hz), 3.94–4.05 (2H, m), 5.03 (2H, s), 6.87 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.28–7.44 (5H, m). IR ($CDCl_3$) cm^{-1} 2964, 2929, 1721, 1511, 1239, 1176, 1025. HRMS m/z 326.1890 (M$^+$) (calcd for $C_{21}H_{26}O_3$ 326.1882).

5.4.3. Ethyl 2-(4-hydroxybenzyl)-3-methylbutyrate (14b). Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, $J = 7.0$ Hz), 1.02 (3H, d, $J = 7.0$ Hz), 1.12 (3H, t, 7.0 Hz), 1.83–2.01 (1H, m), 2.37–2.48 (1H, m), 2.71–2.82 (2H, m), 4.00 (2H, q, $J = 7.0$ Hz), 5.26–5.38 (1H, m), 6.68 (2H, d, $J = 8.5$ Hz), 7.00 (2H, d, $J = 8.5$ Hz). IR ($CDCl_3$) cm^{-1} 2965, 2933, 1718, 1614, 1515, 1375, 1173. HRMS m/z 236.1406 (M$^+$) (calcd for $C_{14}H_{20}O_3$ 236.1413).

5.4.4. Ethyl 3-methyl-2-[4-[2-[1-(4-pyridin-2-ylphenyl)-ethylideneaminooxy]benzyl]butyrate. Colorless syrup (yield 46%). ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, d, $J = 7.0$ Hz), 1.01 (3H, d, $J = 7.0$ Hz), 1.11 (3H, t, $J = 7.0$ Hz), 1.86–1.98 (1H, m), 2.28 (3H, s), 2.37–2.45 (1H, m), 2.79 (2H, d, $J = 7.0$ Hz), 3.94–4.06 (2H, m), 4.26 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.20–7.25 (1H, m), 7.71–7.78 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). IR ($CDCl_3$) cm^{-1} 2964, 2930, 1721, 1588, 1511, 1469, 1246. HRMS m/z 475.2601 (M+H$^+$) (calcd for $C_{29}H_{35}N_2O_4$ 475.2597).

5.4.5. 2-[4-[2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]-3-methylbutyric acid (8b). Mp: 100–102 °C (yield 88%). ^{1}H NMR ($CDCl_3$) δ 1.01–1.07 (6H, m), 1.88–2.02 (1H, m), 2.26 (3H, s), 2.43–2.51 (1H, m), 2.74–2.83 (2H, m), 4.30 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.23–7.28 (1H, m), 7.65–7.81 (4H, m), 7.94 (2H, d, $J = 8.5$ Hz), 8.68 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2960, 1722, 1512, 1470, 1246, 955, 783. MS m/z 447 (M+H$^+$). Anal. Calcd for $C_{27}H_{30}N_2O_4 \cdot 2/3H_2O$: C, 70.71; H, 6.89; N, 6.11. Found: C, 70.90; H, 6.69; N, 6.14.

5.5. 2-[4-[2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]hexanoic acid (8c)

5.5.1. Diethyl 2-(4-benzyloxybenzyl)-2-butylmalonate (13c). Mp: 72–73 °C (yield 92%). ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, $J = 7.0$ Hz), 1.24 (6H, t, $J = 7.0$ Hz), 1.20–1.37 (4H, m), 1.74–1.80 (2H, m), 3.18 (2H, s), 4.11–4.23 (4H, m), 5.02 (2H, s), 6.86 (2H, d, $J = 8.5$ Hz), 6.99 (2H, d, $J = 8.5$ Hz), 7.31–7.44 (5H, m). IR (KBr) cm^{-1} 2962, 1724, 1513, 1270, 1242, 1206, 1015. MS m/z 412 (M$^+$). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.65; H, 7.68.

5.5.2. Ethyl 2-(4-benzyloxybenzyl)hexanoate. Colorless syrup (yield 86%). ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, $J = 7.0$ Hz), 1.14 (3H, t, $J = 7.0$ Hz), 1.20–1.37 (4H, m), 1.40–1.70 (2H, m), 2.51–2.72 (2H, m), 2.85 (1H, dd, $J = 8.5$, 13.5 Hz), 4.05 (2H, q, $J = 7.0$ Hz), 5.03 (2H, s), 6.88 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.31–7.45 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.92, 14.23, 22.57, 29.51, 31.82, 37.76, 47.90, 60.03, 70.01, 114.70, 127.44, 127.87, 128.54, 129.85, 131.92, 137.17, 157.29, 175.78. IR (liquid film) cm^{-1} 2956, 2933, 1731, 1512, 1242, 1176, 1159. HRMS m/z 340.2044 (M$^+$) (calcd for $C_{22}H_{28}O_3$ 340.2039).

5.5.3. Ethyl 2-(4-hydroxybenzyl)hexanoate (14c). Colorless syrup (yield 95%). ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, $J = 7.0$ Hz), 1.16 (3H, t, $J = 7.0$ Hz), 1.20–1.35 (4H, m), 1.40–1.70 (2H, m), 2.53–2.72 (2H, m), 2.84 (1H, dd, $J = 8.5$, 13.5 Hz), 4.06 (2H, q, $J = 7.0$ Hz), 4.93 (1H, s), 6.72 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.91, 14.17, 22.55, 29.53, 31.87, 37.79, 48.15, 60.40, 115.24, 129.91, 131.06, 154.43, 176.57. IR (liquid film) cm^{-1} 3401, 2958, 2934, 1705, 1516. HRMS m/z 250.1568 (M$^+$) (calcd for $C_{15}H_{22}O_3$ 250.1569).

5.5.4. Ethyl 2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]hexanoate. Colorless syrup (yield 48%). ^{1}H NMR ($CDCl_3$) δ 0.87 (3H, t, $J = 7.0$ Hz), 1.16 (3H, t, $J = 7.0$ Hz), 1.20–1.40 (4H, m), 1.40–1.70 (2H, m), 2.28 (3H, s), 2.51–2.72 (2H, m), 2.86 (1H, d, d, $J = 8.5$, 13.5 Hz), 4.06 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 6.87 (2H, d, 8.5 Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.21–7.27 (1H,

m), 7.71–7.80 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.71 (1H, d, $J = 5.0$ Hz). HRMS m/z 489.2759 ($M+H^+$) (calcd for $C_{30}H_{37}N_2O_4$ 489.2753).

5.5.5. 2-[4-[2-[1-(4-Pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]hexanoic acid (8c). Colorless syrup (yield 78%). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, $J = 6.5$ Hz), 1.23–1.37 (4H, m), 1.43–1.73 (2H, m), 2.23 (3H, s), 2.60–2.74 (2H, m), 2.90 (1H, dd, $J = 8.5$, 13.5 Hz), 4.30 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz), 7.24–7.28 (1H, m), 7.68–7.81 (4H, m), 7.95 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 461.2445 ($M+H^+$) (calcd for $C_{28}H_{33}N_2O_4$ 461.2440).

The analytical sample was obtained as sodium salts as follows. To a solution of **8c** in EtOH (10 mL) was added 1 N NaOH (1.50 mL), and the reaction mixture was evaporated in vacuo. The residual water was removed by co-distillation with EtOH in vacuo. The Na salt of **8c** was collected by filtration using diethyl ether as a colorless solid (0.65 g, yield 90%).

^1H NMR (DMSO-d_6) δ 0.79 (3H, t, $J = 6.5$ Hz), 1.04–1.30 (5H, m), 1.30–1.49 (1H, m), 2.09–2.25 (1H, m), 2.23 (3H, s), 2.39 (1H, dd, $J = 7.5$, 13.5 Hz), 2.78 (1H, dd, $J = 7.5$, 13.5 Hz), 4.23 (2H, t, $J = 4.5$ Hz), 4.47 (2H, t, $J = 4.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.33–7.41 (1H, m), 7.80 (2H, d, $J = 8.5$ Hz), 7.85–7.95 (1H, m), 8.00 (1H, d, $J = 8.0$ Hz), 8.13 (2H, d, $J = 8.5$ Hz), 8.69 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2931, 1567, 1513, 1415, 1251, 1064, 779. MS m/z 505 ($M+Na^+$). Anal. Calcd for $C_{28}H_{32}N_2O_4Na$: C, 68.42; H, 6.56; N, 5.70; Na, 4.68. Found: C, 68.27; H, 6.37; N, 5.67; Na, 5.01.

5.6. 5-Phenyl-2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoic acid (8d)

5.6.1. Diethyl 2-(4-benzyloxybenzyl)-2-(3-phenylpropyl)-malonate (13d). Colorless syrup (yield 82%). ^1H NMR ($CDCl_3$) δ 1.21 (6H, t, $J = 7.0$ Hz), 1.57–1.66 (2H, m), 1.76–1.85 (2H, m), 2.61 (2H, t, $J = 6.5$ Hz), 3.14 (2H, s), 4.15 (4H, d, q, $J = 1.5$, 7.0 Hz), 5.01 (2H, s), 6.79 (2H, d, $J = 8.5$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.15–7.44 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 26.03, 31.03, 35.85, 37.07, 58.76, 61.11, 69.95, 114.57, 125.87, 127.46, 127.92, 128.35, 128.49, 128.56, 130.79, 137.08, 141.80, 157.71, 171.26. IR (liquid film) cm^{-1} 2980, 2938, 1731, 1512, 1245. HRMS m/z 475.2486 ($M+H^+$) (calcd for $C_{30}H_{35}O_5$ 475.2485).

5.6.2. Ethyl 2-(4-benzyloxybenzyl)-5-phenylpentanoate. Colorless syrup (yield 96%). ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, $J = 7.0$ Hz), 1.49–1.73 (4H, m), 2.56–2.71 (4H, m), 2.80–2.89 (1H, m), 4.04 (2H, q, $J = 7.0$ Hz), 5.03 (2H, s), 6.87 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.11–7.46 (10H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.22, 29.13, 31.62, 35.69, 37.72, 47.73, 60.11, 70.01, 114.71, 125.74, 127.44, 127.89, 128.29, 128.55, 129.86, 131.74, 137.16, 142.11, 157.32, 175.56. IR (liquid film) cm^{-1} 2938, 1730, 1511, 1241, 1177. HRMS m/z 402.2193 (M^+) (calcd for $C_{27}H_{30}O_3$ 402.2195).

5.6.3. Ethyl 2-(4-hydroxybenzyl)-5-phenylpentanoate (14d). Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, $J = 7.0$ Hz), 1.51–1.72 (4H, m), 2.53–2.70 (4H, m), 2.79–2.88 (1H, m), 4.05 (2H, q, $J = 7.0$ Hz), 4.84 (1H, s), 6.72 (2H, d, $J = 8.5$ Hz), 7.00 (2H, d, $J = 8.5$ Hz), 7.12–7.30 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.15, 29.13, 31.65, 35.64, 37.72, 47.95, 60.45, 115.24, 125.76, 128.30, 128.35, 129.91, 130.91, 142.05, 154.53, 176.29. IR (liquid film) cm^{-1} 3340, 2939, 1705, 1516, 1222. HRMS m/z 312.1715 (M^+) (calcd for $C_{20}H_{24}O_3$ 312.1726).

5.6.4. Ethyl 5-phenyl-2-[4-[2-[1-(4-pyridin-2-ylphenyl)-ethylideneaminooxy]ethoxy]benzyl]pentanoate. Mp: 53–55 °C (yield 89%). ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, $J = 7.0$ Hz), 1.49–1.75 (4H, m), 2.28 (3H, s), 2.56–2.71 (4H, m), 2.84 (1H, dd, $J = 7.5$, 12.5 Hz), 4.05 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.12–7.29 (6H, m), 7.75–7.78 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2944, 1733, 1249, 1163, 956. MS m/z 551 ($M+H^+$). Anal. Calcd for $C_{35}H_{38}N_2O_4$: C, 76.34; H, 6.96; N, 5.09. Found: C, 76.52; H, 6.88; N, 5.16.

5.6.5. 5-Phenyl-2-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]benzyl]pentanoic acid (8d). Colorless syrup (yield 93%). ^1H NMR ($CDCl_3$) δ 1.52–1.75 (4H, m), 2.25 (3H, s), 2.54–2.70 (4H, m), 2.86–2.93 (1H, m), 4.26 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.11–7.17 (3H, m), 7.22–7.26 (3H, m), 7.70–7.78 (4H, m), 7.94 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 523.2602 ($M+H^+$) (calcd for $C_{33}H_{35}N_2O_4$ 523.2597).

The sodium salt of **8d** was obtained by the same procedure as described for the preparation of the sodium salt of **8c**.

^1H NMR (DMSO-d_6) δ 1.40–1.67 (5H, m), 2.24 (3H, s), 2.36–2.51 (4H, m), 2.83 (2H, dd, $J = 7$, 13.5 Hz), 4.23 (2H, t, $J = 4.0$ Hz), 4.48 (2H, t, $J = 4.0$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 7.06–7.12 (5H, m), 7.17–7.23 (2H, m), 7.35 (1H, dd, $J = 5.0$, 6.0 Hz), 7.79 (2H, d, $J = 8.5$ Hz), 7.87 (1H, dt, $J = 1.5$, 8.0 Hz), 7.97 (1H, d, $J = 8.0$ Hz), 8.12 (2H, d, $J = 8.5$ Hz), 8.67 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 3403, 2935, 1556, 1413, 1249, 948, 783. MS m/z 567 ($M+Na^+$). Anal. Calcd for $C_{33}H_{33}N_2O_4Na$: C, 72.88; H, 6.15; N, 5.11; Na, 4.22. Found: C, 72.78; H, 6.11; N, 5.14; Na, 4.08.

5.7. 2-Methylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylfideneaminooxy]ethoxy]phenyl]propionic acid (8e)

5.7.1. Ethyl 2-hydroxy-3-[4-(methoxymethoxy)phenyl]propionate. After a mixture of NaH (55% dispersion in oil) (1.15 g, 26.5 mmol), ethyl 3-(4-hydroxyphenyl)lactate **15** (5.56 g, 26.5 mmol), and a catalytic amount of 18-crown-6 in toluene (25 mL) and DMF (25 mL) was stirred at room temperature for 1 h, a solution of chloromethylmethyl ether (4.42 mL, 58.2 mmol) in toluene (10 mL) was added. The reaction mixture was stirred at room temperature for 16 h. Water was added and the mixture was extracted with EtOAc. The organic phase was separated, washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 7/3) to give the title compound as a colorless syrup (1.98 g, yield 29%).

^{1}H NMR ($CDCl_3$) δ 1.29 (3H, t, $J = 7.0$ Hz), 2.73 (1H, d, $J = 6.0$ Hz), 2.92 (1H, dd, $J = 6.5$, 14.0 Hz), 3.08 (1H, dd, $J = 4.5$, 14.0 Hz), 3.47 (3H, s), 4.22 (2H, q, $J = 7.0$ Hz), 4.37–4.45 (1H, m), 5.15 (2H, s), 6.97 (2H, s, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 3469, 2957, 1738, 1512, 1234, 1200, 1007. HRMS m/z 254.1163 (M^+) (calcd for $C_{13}H_{18}O_5$ 254.1155).

5.7.2. Ethyl 2-methanesulfonyloxy-3-[4-(methoxymethoxy)phenyl]propionate (16). To a solution of ethyl 2-hydroxy-3-[4-(methoxymethoxy)phenyl]propionate (2.58 g, 10.2 mmol) and methanesulfonyl chloride (1.74 g, 15.2 mmol) in dichloromethane (30 mL) was added triethylamine (2.12 mL, 15.2 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 1 h. Water was added and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 2/1) to give the title compound as a colorless syrup (2.79 g, yield 68%).

^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, $J = 7.0$ Hz), 2.87 (3H, s), 3.10 (1H, dd, $J = 8.0$, 14.5 Hz), 3.23 (1H, dd, $J = 4.5$, 14.5 Hz), 3.47 (3H, s), 4.24 (2H, q, $J = 7.0$ Hz), 5.10–5.25 (3H, m), 6.99 (2H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 2940, 1754, 1513, 1365, 1176, 1003. HRMS m/z 332.0929 (M^+) (calcd for $C_{14}H_{20}O_7S$ 332.0930).

5.7.3. Ethyl 3-[4-(methoxymethoxy)phenyl]-2-methylthiopropionate. A mixture of **16** (1.0 g, 3.0 mmol), sodium thiomethoxide (257 mg, 3.7 mmol) in DMF (10 mL) was stirred at 50 °C for 6 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 4/1) to give the title compound as a colorless syrup (660 mg, yield 77%). ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, $J = 7.0$ Hz), 2.17 (3H, s), 2.91 (1H, dd, $J = 6.5$, 14.0 Hz), 3.15 (1H, dd, $J = 9.0$, 14.0 Hz), 3.41 (1H, dd, $J = 6.5$, 9.0 Hz), 3.47 (3H, s), 4.09–4.23 (2H, m), 5.15 (2H, s), 6.96 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 1727, 1512, 1235, 1153, 1079, 1007. HRMS m/z 284.1082 (M^+) (calcd for $C_{14}H_{20}O_4S$ 284.1083).

5.7.4. Ethyl 3-(4-hydroxyphenyl)-2-methylthiopropionate (17a). A mixture of the above-mentioned methoxymethyl ether (356 mg, 1.25 mmol) and 4 N HCl in dioxane (5.0 mL) was stirred at room temperature for 30 min. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give **17a** as solids. The solids were collected by filtration using hexane to afford the title compound as colorless solids (0.30 g, yield 99%).

Mp: 49–50 °C. ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, $J = 7.5$ Hz), 2.17 (3H, s), 2.89 (1H, dd, $J = 6.5$, 14.0 Hz), 3.13 (1H, dd, $J = 9.5$, 14.0 Hz), 3.41 (1H, dd, $J = 6.5$, 9.5 Hz), 4.09–4.20 (2H, m), 4.97–5.11 (1H, br s), 6.74 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz). IR (KBr) cm^{-1} 3400, 1702, 1520, 1251, 1178. HRMS m/z 241.0900 ($M+H^+$) (calcd for $C_{12}H_{17}O_3S$ 241.0899). Anal. Calcd for $C_{12}H_{16}O_3S$: C, 59.97; H, 6.71; S, 13.34. Found: C, 59.78; H, 6.56; S, 13.40.

5.7.5. Ethyl 2-methylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)-ethylideneaminooxy]ethoxy]phenyl]propionate. Colorless syrup (yield 91%). ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, t, $J = 7.0$ Hz), 2.16 (3H, s), 2.28 (3H, s), 2.90 (1H, dd, $J = 6.5$, 14 Hz), 3.15 (1H, dd, $J = 9.0$, 14.0 Hz), 3.40 (1H, dd, $J = 6.5$, 9.0 Hz), 4.13 (2H, dq, $J = 3.0$, 7.0 Hz), 4.28 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz), 7.22–7.27 (1H, m), 7.75–7.78 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.71 (1H, d, $J = 4.5$ Hz). HRMS m/z 479.2011 ($M+H^+$) (calcd for $C_{27}H_{31}N_2O_4S$ 479.2005).

5.7.6. 2-Methylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8e). Mp: 113–115 °C (yield 95%). ^{1}H NMR ($CDCl_3$) δ 2.22 (3H, s), 2.25 (3H, s), 2.91 (1H, dd, $J = 5.5$, 14.0 Hz), 3.18 (1H, dd, $J = 10.0$, 14.0 Hz), 3.44 (1H, dd, $J = 5.0$, 10.0 Hz), 4.33 (2H, t, $J = 4.5$ Hz), 4.55 (2H, t, $J = 4.5$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.15 (2H, d, $J = 8.5$ Hz), 7.26–7.32 (1H, m), 7.63 (2H, d, $J = 8.5$ Hz), 7.71–7.84 (2H, m), 7.87 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 4.5$ Hz). IR (KBr) cm^{-1} 2922, 1693, 1511, 1244, 952, 782. MS m/z 451 ($M+H^+$). Anal. Calcd for $C_{25}H_{26}N_2O_4S$: C, 66.65; H, 5.82; N, 6.22; S, 7.12. Found: C, 66.80; H, 5.84; N, 6.27; S, 7.03.

5.8. 2-Phenylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8f)

5.8.1. Ethyl 3-[4-(methoxymethoxy)phenyl]-2-phenylthiopropionate. A mixture of **16** (1.0 g, 3.0 mmol), benzenethiol (398 mg, 3.6 mmol), and K_2CO_3 (0.5 g, 3.61 mmol) in DMF (10 mL) was stirred at 50 °C for 1 h. Water was added and the mixture was extracted with

EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 4/1) to give the title compound as a colorless syrup (880 mg, yield 84%).

^{1}H NMR ($CDCl_3$) δ 1.09 (3H, t, $J = 7.0$ Hz), 3.01 (1H, dd, $J = 6.5$, 14.0 Hz), 3.15 (1H, dd, $J = 9.0$, 14.0 Hz), 3.48 (3H, s), 3.87 (1H, dd, $J = 6.5$, 9.0 Hz), 4.00–4.08 (2H, m), 5.15 (2H, s), 6.95 (2H, d, $J = 8.5$ Hz), 7.12 (2H, d, $J = 8.5$ Hz), 7.29–7.36 (3H, m), 7.44–7.48 (2H, m). IR (liquid film) cm^{-1} 1732, 1512, 1235, 1153, 1079, 1006. HRMS m/z 346.1229 (M^+) (calcd for $C_{19}H_{22}O_4S$ 346.1239).

5.8.2. Ethyl 3-(4-hydroxyphenyl)-2-phenylthiopropionate (17b). The same procedure as for the preparation of **17a** was performed.

Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, t, $J = 7.0$ Hz), 2.99 (1H, dd, $J = 6.5$, 14.0 Hz), 3.11 (1H, dd, $J = 9.5$, 14.0 Hz), 3.85 (1H, dd, $J = 6.5$, 9.5 Hz), 3.91–4.08 (2H, m), 6.72 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.16–7.40 (3H, m), 7.44 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 3406, 1729, 1710, 1516, 1232, 1175. HRMS m/z 302.0974 (M^+) (calcd for $C_{17}H_{18}O_3S$ 302.0977).

5.8.3. Ethyl 2-phenylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionate. To a solution of **17b** (303 mg, 1.0 mmol) in toluene (3.0 mL) were added **10** (384 mg, 1.5 mmol) and triphenylphosphine (393 mg, 1.5 mmol). To the mixture was added diethyl azodicarboxylate (590 μL, 1.5 mmol) slowly over 1 h at 0 °C, and the mixture was stirred for another 16 h at room temperature. The residue was subjected to column chromatography (hexane/EtOAc, 4/1 and 7/3) to give the title compound as a colorless syrup (420 mg, yield 78%).

^{1}H NMR ($CDCl_3$) δ 1.07 (3H, t, $J = 7.0$ Hz), 2.27 (3H, s), 3.00 (1H, dd, $J = 6.5$, 14.0 Hz), 3.14 (1H, dd, $J = 9.5$, 14.0), 3.85 (1H, dd, $J = 6.5$, 9.5 Hz), 3.98–4.06 (2H, m), 4.27 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.11 (2H, d, $J = 8.5$ Hz), 7.20–7.30 (4H, m), 7.40–7.45 (2H, m), 7.72–7.78 (4H, m), 8.00 (2H, d, $J = 8.5$ Hz), 8.69–8.71 (1H, m). IR ($CDCl_3$) cm^{-1} 2929, 1728, 1588, 1512, 1469, 1249. HRMS m/z 541.2167 (M+H$^+$) (calcd for $C_{32}H_{33}N_2O_4S$ 541.2161).

5.8.4. 2-Phenylthio-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8f). The same procedure as for the preparation of **8a** was performed.

Colorless foam (yield 83%). ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 3.01 (1H, dd, $J = 6.0$, 14.0 Hz), 3.15 (1H, dd, $J = 9.5$, 14.0 Hz), 3.87 (1H, dd, $J = 6.0$, 9.5 Hz), 4.30 (2H, t, $J = 4.5$ Hz), 4.54 (2H, t, $J = 4.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz), 7.23–7.32 (4H, m), 7.43–7.49 (2H, m), 7.64 (2H, d, $J = 8.5$ Hz), 7.68–7.80 (2H, m), 7.85 (2H, d, $J = 8.5$ Hz), 8.66 (1H, d, $J = 5.5$ Hz). IR (KBr) cm^{-1} 2930, 1719, 1511, 1437, 1247, 1066, 782. MS m/z 513 (M+H$^+$). Anal. Calcd for $C_{20}H_{28}N_2O_4S{\cdot}1/3H_2O$: C, 69.51; H, 5.57; N, 5.40; S, 6.19. Found: C, 69.31; H, 5.48; N, 5.27; S, 6.42.

5.9. 2-Ethoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8g)

5.9.1. Ethyl 3-(4-benzyloxyphenyl)lactate. A mixture of **15** (15.83 g, 75.3 mmol), benzyl chloride (10.73 mL, 90.4 mmol), and K_2CO_3 (25.0 g, 0.18 mol), in DMF (160 mL) was stirred at 60 °C for 4 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 7/3) to give the title compound as an oil (22.6 g, yield 99%).

^{1}H NMR ($CDCl_3$) δ 1.28 (3H, t, $J = 7.0$ Hz), 2.73 (1H, d, $J = 6.5$ Hz), 2.92 (1H, dd, $J = 6.5$, 14.0 Hz), 3.07 (1H, dd, $J = 4.5$, 14.0 Hz), 4.21 (2H, q, $J = 7.0$ Hz), 4.36–4.42 (1H, m), 5.04 (2H, s), 6.91 (2H, d, $J = 8.5$ Hz), 7.14 (2H, d, $J = 8.5$ Hz), 7.29–7.45 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.04, 39.51, 61.45, 69.80, 71.21, 114.59, 127.29, 127.74, 128.39, 128.55, 130.40, 136.93, 157.62, 174.15. IR (liquid film) cm^{-1} 3489, 1734, 1512, 1242, 1177, 1026. HRMS m/z 323.1257 (M+Na$^+$) (calcd for $C_{18}H_{20}O_4Na$ 323.1260).

5.9.2. Ethyl 3-(4-benzyloxyphenyl)-2-ethoxypropionate (18a). A mixture of NaH (55% dispersion in oil) (2.76 g, 63.3 mmol) and ethyl 3-(4-benzyloxyphenyl)lactate (17.3 g, 57.5 mmol) in toluene (100 mL) and DMF (100 mL) was stirred at 40 °C for 1 h. Ethyl iodide (2.76 g, 69.0 mmol) was added and the mixture was stirred at room temperature for 16 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 5/1) to give the title compound as a colorless syrup (10.6 g, yield 56%).

^{1}H NMR ($CDCl_3$) δ 1.17 (3H, t, $J = 7.0$ Hz), 1.21 (3H, t, $J = 7.0$ Hz), 2.95 (2H, d, $J = 6.5$ Hz), 3.30–3.41 (1H, m), 3.55–3.66 (1H, m), 3.97 (1H, d, $J = 6.5$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 5.04 (2H, s), 6.89 (2H, d, $J = 8.5$ Hz), 7.16 (2H, d, $J = 8.5$ Hz), 7.27–7.44 (5H, m). HRMS m/z 329.1749 (M+H$^+$) (calcd for $C_{20}H_{25}O_4$ 329.1753).

5.9.3. Ethyl 2-ethoxy-3-(4-hydroxyphenyl)propionate (19a). The same procedure as for the preparation of **14a** was performed.

Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz), 2.94 (2H, d, $J = 6.5$ Hz), 3.31–3.42 (1H, m), 3.55–3.66 (1H, m), 3.98 (1H, t, $J = 6.5$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 6.74 (2H,

d, $J = 8.5$ Hz), 7.10 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.18, 15.02, 38.44, 61.05, 66.28, 80.45, 115.24, 128.65, 130.49, 154.71, 172.98. IR (KBr) cm^{-1} 3405, 2980, 1730, 1517, 1116. HRMS m/z 239.1279 ($M+H^+$) (calcd for $C_{13}H_{19}O_4$ 239.1284).

5.9.4. Ethyl 2-ethoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)-ethylideneaminooxy]ethoxy]phenyl]propionate. The same procedure as for the preparation of the ethyl ester of **8a** was performed.

Mp: 59–61 °C (yield 77%). ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, t, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz), 2.28 (3H, s), 2.95 (2H, d, $J = 6.5$ Hz), 3.29–3.40 (1H, m), 3.54–3.65 (1H, m), 3.97 (1H, t, $J = 6.5$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.28 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.16 (2H, d, $J = 8.5$ Hz), 7.22–7.27 (1H, m), 7.75–7.80 (2H, m), 7.76 (2H, d, $J = 8.5$ Hz), 8.01 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 477.2383 ($M+H^+$) (calcd for $C_{28}H_{33}N_2O_5$ 477.2390).

5.9.5. 2-Ethoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8g). The same procedure as for the preparation of **8a** was performed.

Mp: 133–135 °C (yield 80%). ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, $J = 7.0$ Hz), 2.28 (3H, s), 2.95 (1H, dd, $J = 7.5$, 14.0 Hz), 3.08 (1H, dd, $J = 4.5$, 14.0 Hz), 3.39–3.50 (1H, m), 3.55–3.66 (1H, m), 4.04 (1H, dd, $J = 4.5$, 7.5 Hz), 4.29 (2H, t, $J = 5.0$ Hz), 4.56 (2H, t, $J = 5.0$ Hz), 6.89 (2H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.5$ Hz), 7.25–7.30 (1H, m), 7.74 (2H, d, $J = 8.5$ Hz), 7.76–7.80 (2H, m), 7.96 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 4.5$ Hz). IR (KBr) cm^{-1} 2939, 2479, 1918, 1718, 1514, 1240, 950. MS m/z 449 ($M+H^+$). Anal. Calcd for $C_{26}H_{28}N_2O_5$: C, 69.69; H, 6.29; N, 6.25. Found: C, 69.53; H, 6.42; N, 6.09.

5.10. 2-Phenoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8h)

5.10.1. Ethyl 3-(4-benzyloxyphenyl)-2-phenoxypropionate (18b). To a solution of ethyl 3-(4-benzyloxyphenyl)lactate (300 mg, 1.0 mmol), phenol (113 mg, 1.2 mmol), and triphenylphosphine (315 mg, 1.2 mmol) in toluene (3.5 mL) was added diethyl azodicarboxylate (40% solution in toluene) (471 μL, 1.2 mmol) at 0 °C and the mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated in vacuo and purified by column chromatography (hexane/EtOAc, 20/1 and 10/1) to give the title compound as an oil (215 mg, yield 57%).

^{1}H NMR ($CDCl_3$) 1.18 (3H, t, $J = 7.0$ Hz), 3.12–3.24 (2H, m), 4.16 (2H, q, $J = 7.0$ Hz), 4.71–4.79 (1H, m), 5.04 (2H, s), 6.81–6.98 (5H, m), 7.20–7.47 (9H, m). IR (liquid film) cm^{-1} 1753, 1512, 1495, 1240, 1179, 1754. HRMS m/z 376.1677 (M^+) (calcd for $C_{24}H_{24}O_4$ 376.1675).

5.10.2. Ethyl 3-(4-hydroxyphenyl)-2-phenoxypropionate (19b). The same procedure as for the preparation of **14a** was performed.

Mp: 67–68 °C (yield 96%). ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 3.11–3.22 (2H, m), 4.17 (2H, q, $J = 7.0$ Hz), 4.72–4.76 (1H, m), 4.92 (1H, s), 6.75 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 6.95 (1H, t, $J = 8.5$ Hz), 7.16 (2H, d, $J = 8.5$ Hz), 7.25 (2H, t, $J = 8.5$ Hz). IR (KBr) cm^{-1} 3406, 1728, 1516, 1488, 1277, 1267, 1224. MS m/z 286 (M^+). Anal. Calcd for $C_{17}H_{18}O_4 \cdot 1/10$ *n*-hexane: C, 71.67; H, 6.63. Found: C, 71.76; H, 6.63.

5.10.3. Ethyl 2-phenoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)-ethylideneaminooxy]ethoxy]phenyl]propionate. The same procedure as for the preparation of the ethyl ester of **8f** was performed.

Colorless syrup (yield 69%). ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 2.26 (3H, s), 3.17–3.20 (2H, m), 4.17 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 5.0$ Hz), 4.54 (2H, t, $J = 5.0$ Hz), 4.74 (1H, dd, $J = 5.5$, 6.5 Hz), 6.82–6.96 (5H, m), 7.21–7.26 (5H, m), 7.74–7.77 (4H, m), 8.01 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 525.2385 ($M+H^+$) (calcd for $C_{32}H_{33}N_2O_5$ 525.2390).

5.10.4. 2-Phenoxy-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenylpropionic acid (8h). The same procedure as for **8a** was performed.

Mp: 138–140 °C (yield 93%). ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.22 (2H, d, $J = 6.0$ Hz), 4.29 (2H, t, $J = 4.5$ Hz), 4.54 (2H, t, $J = 4.5$ Hz), 4.81 (1H, t, $J = 6.0$ Hz), 6.86–6.97 (5H, m), 7.21–7.31 (5H, m), 7.67–7.89 (6H, m), 8.72 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2926, 1727, 1600, 1512, 1491, 1237, 1058. MS m/z 497 ($M+H^+$). Anal. Calcd for $C_{30}H_{28}N_2O_5$: C, 72.56; H, 5.68; N, 5.64. Found: C, 72.37; H, 5.77; N, 5.56.

Similarly **8i–k** were prepared.

5.11. 2-(4-Fluorophenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8i)

5.11.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-fluorophenoxy)propionate (18c). Colorless syrup (yield 76%). ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, $J = 7.0$ Hz), 3.16 (2H, d, $J = 6.5$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 4.66 (1H, t, $J = 6.5$ Hz), 5.04 (2H, s), 6.72–6.80 (2H, m), 6.89–6.97 (4H, m), 7.21 (2H, d, $J = 8.5$ Hz), 7.31–7.48 (5H, m). IR (KBr) cm^{-1} 1734, 1504, 1243, 1020, 830. HRMS m/z 417.1484 ($M+Na^+$) (calcd for $C_{24}H_{23}FO_4Na$ 417.1443). Anal. Calcd for $C_{24}H_{23}FO_4 \cdot 1/10H_2O$: C, 72.75; H, 5.90; F, 4.79. Found: C, 72.87; H, 5.83; F, 4.75.

5.11.2. Ethyl 2-(4-fluorophenoxy)-3-(4-hydroxyphenyl)-propionate (19c). Mp: 80–81 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 3.15 (2H, d,

$J = 6.5$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.65 (1H, t, $J = 6.5$ Hz), 4.76 (1H, s), 6.71–6.80 (4H, m), 6.87–6.95 (2H, m), 7.16 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 3412, 1735, 1506, 1205, 830. HRMS m/z 305.1188 ($M+H^+$) (calcd for $C_{17}H_{18}FO_4$ 305.1189).

5.11.3. Ethyl 2-(4-fluorophenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionate. Colorless syrup (yield 84%). ^1H NMR ($CDCl_3$) δ 1.19 (3H, s), 2.27 (3H, s), 3.16 (2H, d, $J = 6.5$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.28 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 4.66 (1H, t, $J = 6.5$ Hz), 6.77 (2H, dd, $J = 4.5$, 9.0 Hz), 6.90 (2H, d, $J = 8.5$ Hz), 6.91 (2H, dd, $J = 8.5$, 9.0 Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.24–7.27 (1H, m), 7.74–7.77 (4H, m), 8.00 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 543.2291 ($M+H^+$) (calcd for $C_{28}H_{32}N_2FO_5$ 543.2295).

5.11.4. 2-(4-Fluorophenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8i). Mp: 88–90 °C (yield 94%). ^1H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.20 (1H, d, $J = 7.0$ Hz), 3.21 (1H, d, $J = 5.5$ Hz), 4.30 (2H, t, $J = 5.0$ Hz), 4.55 (2H, t, $J = 5.0$ Hz), 4.72 (1H, dd, $J = 5.5$, 7.0 Hz), 6.81 (2H, dd, $J = 4.5$, 9.0 Hz), 6.89 (2H, d, $J = 8.5$ Hz), 6.91 (2H, dd, $J = 8.5$, 9.0 Hz), 7.22 (2H, d, $J = 8.5$ Hz), 7.27–7.32 (1H, m), 7.69 (2H, d, $J = 8.5$ Hz), 7.72 (1H, d, $J = 7.5$ Hz), 7.80 (2H, dd, $J = 2.0$, 7.5 Hz), 7.86 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2930, 1728, 1505, 247, 1204. MS m/z 515 ($M+H^+$). Anal. Calcd for $C_{30}H_{27}FN_2O_5$: C, 70.03; H, 5.29; F, 3.69; N, 5.44. Found: C, 69.92; H, 5.18; F, 3.84; N, 5.43.

5.12. 2-(4-Methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8j)

5.12.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-methylphenoxy)propionate (18d). Colorless syrup (yield 56%). ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, $J = 7.0$ Hz), 2.30 (3H, s), 3.15–3.28 (2H, m), 4.15–4.25 (2H, m), 4.70–4.79 (1H, m), 5.08 (2H, s), 6.78 (2H, d, $J = 8.5$ Hz), 6.95 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.26 (2H, d, $J = 8.5$ Hz), 7.32–7.60 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.10, 20.46, 38.28, 61.18, 69.98, 78.37, 114.78, 115.28, 127.89, 128.54, 128.77, 129.90, 130.49, 130.96, 137.07, 155.71, 157.77, 171.38. IR (liquid film) cm^{-1} 1752, 1510, 1239, 1178, 1026. HRMS m/z 413.1738 ($M+Na^+$) (calcd for $C_{25}H_{26}O_4Na$ 413.1729).

5.12.2. Ethyl 3-(4-hydroxyphenyl)-2-(4-methylphenoxy)propionate (19d). Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 2.25 (3H, s), 3.09–3.18 (2H, m), 4.16 (2H, q, $J = 7.0$ Hz), 4.64–4.72 (1H, m), 4.76 (1H, br s), 6.65–6.79 (4H, m), 7.02 (2H, d, $J = 8.5$ Hz), 7.16 (2H, s, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.07, 20.46, 38.25, 61.41, 78.44, 115.31, 115.36, 127.87, 129.94, 130.57, 131.07, 155.03, 155.63, 171.84. IR (KBr) cm^{-1} 3443, 1719, 1509, 1267, 1222. HRMS m/z 301.1431 ($M+H^+$) (calcd for $C_{18}H_{21}O_4$ 301.1440).

5.12.3. Ethyl 2-(4-methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionate. Colorless syrup (yield 42%). ^1H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 2.25 (3H, s), 2.26 (3H, s), 3.15–3.18 (2H, m), 4.16 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 4.5$ Hz), 4.54 (2H, t, $J = 4.5$ Hz), 4.69 (1H, dd, $J = 5.5$, 6.5 Hz), 6.72 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz), 7.22–7.27 (1H, m), 7.73–7.80 (4H, m), 7.99 (2H, d, $J = 8.5$ Hz), 8.70 (1H, d, $J = 5.0$ Hz). HRMS m/z 539.2540 ($M+H^+$) (calcd for $C_{33}H_{35}N_2O_5$ 539.2546).

5.12.4. 2-(4-Methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8j). Mp: 54–56 °C (yield 66%). ^1H NMR ($CDCl_3$) δ 2.25 (6H, s), 3.21 (2H, d, $J = 6.0$ Hz), 4.29 (2H, t, $J = 4.5$ Hz), 4.55 (2H, t, $J = 4.5$ Hz), 4.78 (1H, t, $J = 6.0$ Hz), 6.77 (2H, d, $J = 8.5$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.26–7.31 (1H, m), 7.69–7.83 (4H, m), 7.89 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 2926, 1510, 1241, 1178, 1070. MS m/z 511 ($M+H^+$). Anal. Calcd for $C_{31}H_{30}N_2O_5 \cdot 1/2H_2O$: C, 71.66; H, 6.01; N, 5.39. Found: C, 71.89; H, 5.89; N, 5.24.

5.13. 2-(4-*tert*-Butylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8k)

5.13.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionate (18e). Colorless syrup (yield 50%). ^1H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 1.26 (9H, s), 3.12–3.21 (2H, m), 4.17 (2H, q, $J = 7.0$ Hz), 4.70 (1H, dd, $J = 5.5$, 7.5 Hz), 5.04 (2H, s), 6.76 (2H, d, $J = 8.5$ Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.20–7.26 (4H, m), 7.31–7.45 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.12, 31.46, 34.08, 38.31, 61.19, 69.98, 78.23, 114.78, 126.25, 127.42, 127.89, 128.54, 128.82, 130.51, 137.07, 144.31, 155.54, 157.77, 171.43. IR (liquid film) cm^{-1} 2962, 1754, 1512, 1240, 1186. HRMS m/z 455.2203 ($M+Na^+$) (calcd for $C_{28}H_{32}O_4Na$ 455.2199).

5.13.2. Ethyl 2-(4-*tert*-butylphenoxy)-3-(4-hydroxyphenyl)propionate (19e). Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.26 (9H, s), 3.13–3.20 (2H, m), 4.18 (2H, q, $J = 7.0$ Hz), 4.69 (1H, dd, $J = 5.5$, 7.5 Hz), 4.81 (1H, br s), 6.75 (2H, d, $J = 8.5$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.11, 31.46, 34.09, 38.29, 61.30, 78.28, 114.80, 115.26, 126.29, 128.50, 130.68, 144.39, 154.57, 155.51, 171.59. IR (liquid film) cm^{-1} 3421, 2963, 1731, 1514, 1238, 1187. HRMS m/z 365.1739 ($M+Na^+$) (calcd for $C_{21}H_{26}O_4Na$ 365.1729).

5.13.3. Ethyl 2-(4-*tert*-butylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionate. Colorless syrup (yield 77%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.26 (9H, s), 2.27 (3H, s), 3.15–3.18 (2H, m), 4.17 (2H, q, $J = 7.0$ Hz), 4.27 (2H, t, $J = 5.0$ Hz), 4.53 (2H, t, $J = 5.0$ Hz), 4.70 (1H, dd, $J = 5.5$, 7.5 Hz), 6.76 (2H, d, $J = 8.5$ Hz), 6.92 (2H, d, $J = 8.5$ Hz), 7.20–7.27 (5H, m), 7.74–7.77 (4H, m), 8.00 (2H, d, $J = 8.5$ Hz), 8.71 (1H, d, $J = 4.5$ Hz). HRMS m/z 581.3009 (M+H$^+$) (calcd for $C_{36}H_{41}N_2O_5$ 581.3016).

5.13.4. 2-(4-*tert*-Butylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (10k). Mp: 148–150 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.30 (9H, s), 2.31 (3H, s), 3.26 (2H, d, $J = 6.0$ Hz), 4.34 (2H, t, $J = 5.0$ Hz), 4.59 (2H, t, $J = 5.0$ Hz), 4.84 (1H, t, $J = 6.0$ Hz), 6.86 (2H, d, $J = 9.0$ Hz), 6.93 (2H, d, $J = 8.5$ Hz), 7.25–7.35 (5H, m), 7.74–7.88 (4H, m), 7.95 (2H, d, $J = 8.5$ Hz), 8.76 (1H, d, $J = 4.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.79, 31.45, 34.05, 38.10, 66.60, 72.61, 77.99, 114.63, 114.76, 121.56, 122.63, 126.26, 126.51, 127.26, 128.98, 130.54, 137.23, 137.78, 138.92, 144.25, 148.91, 154.86, 155.49, 156.63, 157.79, 174.74. IR (KBr pellet) cm^{-1} 2960, 1512, 1242, 1185, 1071, 783. HRMS m/z 553.2698 (M+H$^+$) (calcd for $C_{34}H_{37}N_2O_5$ 553.2703). Anal. Calcd for $C_{34}H_{36}N_2O_5$: C, 73.89; H, 6.57; N, 5.07. Found: C, 74.02; H, 6.57; N, 4.99.

5.14. 2-Phenoxy-3-[4-[2-[(4-pyridin-2-ylbenzoyl)-amino]ethoxy]phenyl]propionic acid (9a)

5.14.1. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)-phenyl]-2-phenoxypropionate. To a solution of 3-(4-hydroxyphenyl)-2-phenoxypropionate **19b** (291 mg, 1.02 mmol) in toluene (3.0 mL) were added *N*-(*tert*-butoxycarbonyl)aminoethanol (410 mg, 2.54 mmol) and triphenylphosphine (666 mg, 2.54 mmol). To the mixture, was slowly added a solution of DEAD (40% solution in toluene) (996 μL, 2.54 mmol) over 1 h at 0 °C, and the mixture was stirred for another 16 h at room temperature. The organic solvent was removed in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 9/1 and 7/3) to give the title compound as a colorless syrup (421 mg, yield 96%).

^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 1.45 (9H, s), 3.13–3.23 (2H, m), 3.49–3.53 (2H, m), 3.99 (2H, t, $J = 5.0$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.73 (1H, dd, $J = 5.5$, 7.5 Hz), 4.98 (1H, br s), 6.82 (2H, d, $J = 8.5$ Hz), 6.83 (2H, d, $J = 8.5$ Hz), 6.94 (1H, t, $J = 7.5$ Hz), 7.21–7.25 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.116, 28.39, 38.23, 40.13, 61.28, 67.15, 78.04, 79.50, 114.39, 115.31, 121.67, 128.85, 129.47, 130.57, 155.88, 157.57, 157.77, 171.21. IR (liquid film) cm^{-1} 3392, 2979, 1513, 1243, 1177. HRMS m/z 452.2056 (M+Na$^+$) (calcd for $C_{24}H_{31}NO_6Na$ 452.2049).

5.14.2. Ethyl 2-phenoxy-3-[4-[2-[(4-pyridin-2-ylbenzoyl)-amino]ethoxy]phenyl]propionate. A mixture of the above-mentioned ester (421 mg, 0.98 mmol) and 4 N HCl in dioxane (4.0 mL) was stirred at room temperature for 1 h. The solvent was removed in vacuo and the residual HCl was removed by co-distillation with toluene several times to give the HCl salt of ethyl 3-[4-(2-aminoethoxy)phenyl]-2-phenoxypropionate. To the HCl salt were added DMF (4.0 mL) and Et_3N (410 μL, 2.94 mmol), and the mixture was stirred for 10 min. Then 4-(pyridin-2yl)benzoic acid (205 mg, 1.03 mmol) and diethylphosphoryl cyanide (DEPC, 168 μL, 1.03 mmol) were added and the mixture was stirred for 1 h. The reaction mixture was diluted with EtOAc. The organic phase was separated, washed with water, aq $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 1/1 and 2/3) to give the title compound as colorless crystals (155 mg, yield 33%).

Mp: 119–120 °C. ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 3.17–3.22 (2H, m), 3.89 (2H, dt, $J = 5.0$, 5.5 Hz), 4.13–4.22 (4H, m), 4.74 (1H, dd, $J = 5.5$, 7.0 Hz), 6.63–6.69 (1H, m), 6.84 (2H, d, $J = 9.0$ Hz), 6.87 (2H, d, $J = 9.0$ Hz), 6.94 (1H, t, $J = 7.5$ Hz), 7.20–7.30 (5H, m), 7.75–7.80 (2H, m), 7.90 (2H, d, $J = 8.5$ Hz), 8.07 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 4.5$ Hz). IR (KBr) cm^{-1} 3352, 1748, 1633, 1543, 1246. HRMS m/z 511.2246 (M+H$^+$) (calcd for $C_{31}H_{31}N_2O_5$ 511.2233). Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49. Found: C, 73.05; H, 5.98; N, 5.46.

5.14.3. 2-Phenoxy-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]-ethoxy]phenyl]propionic acid (9a). The same procedure as for the preparation of **8a** was performed.

Mp: 149–151 °C (yield 91%). ^{1}H NMR ($CDCl_3$) δ 3.21 (2H, d, $J = 7.0$ Hz), 3.87 (2H, dt, $J = 5.0$, 5.5 Hz), 4.14–4.18 (2H, m), 4.74 (1H, t, $J = 7.0$ Hz), 6.84–6.94 (6H, m), 7.19–7.31 (5H, m), 7.75–7.80 (2H, m), 7.88 (2H, d, $J = 8.5$ Hz), 8.05 (2H, d, $J = 8.5$ Hz), 8.71 (1H, d, $J = 4.5$ Hz). HRMS m/z 483.1928 (M+H$^+$) (calcd for $C_{29}H_{27}N_2O_5$ 483.1920). Anal. Calcd for $C_{29}H_{26}N_2O_5 \cdot 1/2H_2O$: C, 70.60; H, 5.56; N, 5.68. Found: C, 70.60; H, 5.56; N, 5.68.

Similarly **9b**–**g** were prepared.

5.15. 2-(4-Methylphenoxy)-3-[4-[2-[(4-pyridin-2-yl-benzoyl)amino]ethoxy]phenyl]propionic acid (9b)

5.15.1. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)-phenyl]-2-(4-methylphenoxy)propionate. Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.45 (9H, s), 2.25 (3H, s), 3.12–3.18 (2H, m), 3.45–3.55 (2H, m), 3.99 (2H, t, $J = 5.0$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.69 (1H, dd, $J = 5.5$, 7.5 Hz), 4.96 (1H, br s), 6.72 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.13, 20.47, 28.39, 38.25, 40.13, 61.22, 67.15, 78.35, 79.50, 114.37, 115.27, 128.95, 129.91, 130.55, 130.99, 155.71,

155.89, 157.55, 171.36. IR (KBr) cm^{-1} 3393, 2979, 1715, 1511, 1243. HRMS m/z 466.2196 ($M+Na^+$) (calcd for $C_{25}H_{33}NO_6Na$ 466.2206).

5.15.2. Ethyl 2-(4-methylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Colorless syrup (yield 90%). ^1H NMR ($CDCl_3$) δ 1.23 (3H, t, $J = 7.0$ Hz), 2.28 (3H, s), 3.14–3.22 (2H, m), 3.88–3.96 (2H, m), 4.11–4.27 (4H, m), 4.73 (1H, t, $J = 6.0$ Hz), 6.62–6.71 (1H, m), 6.76 (2H, d, $J = 8.5$ Hz), 6.90 (2H, d, $J = 8.5$ Hz), 7.05 (2H, d, $J = 8.5$ Hz), 7.22–7.33 (3H, m), 7.78–7.83 (2H, m), 7.92 (2H, d, $J = 8.5$ Hz), 8.11 (2H, d, $J = 8.5$ Hz), 8.71–8.78 (1H, m). IR (KBr) cm^{-1} 3360, 1741, 1644, 1510, 1233. MS m/z 525 (M+H). Anal. Calcd for $C_{32}H_{32}N_2O_5$: C, 73.26; H, 6.15; N, 5.34. Found: C, 73.07; H, 6.23; N, 5.34.

5.15.3. 2-(4-Methylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)-amino]ethoxy]phenyl]propionic acid (9b). Mp: 129–131 °C (yield 99%). ^1H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.21 (2H, d, $J = 6.0$ Hz), 3.81–3.90 (2H, m), 4.15–4.21 (2H, m), 4.80 (1H, t, $J = 6.0$ Hz), 6.68–6.75 (1H, m), 6.79 (2H, d, $J = 8.5$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 7.03 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.29–7.36 (1H, m), 7.70–7.88 (4H, m), 7.92 (2H, d, $J = 8.5$ Hz), 8.69–8.73 (1H, m). HRMS m/z 497.2076 ($M+H^+$) (calcd for $C_{30}H_{29}N_2O_5$ 497.2077). Anal. Calcd for $C_{30}H_{28}N_2O_5 \cdot 1/2H_2O$: C, 71.27; H, 5.78; N, 5.54. Found: C, 71.54; H, 5.51; N, 5.47.

5.16. 2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-yl-benzoyl)amino]ethoxy]phenyl]propionic acid (9c)

5.16.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-isopropylphenoxy)propionate (18f). Colorless syrup (yield 56%). ^1H NMR ($CDCl_3$) δ 1.16–1.20 (9H, m), 2.78–2.87 (1H, m), 3.10–3.20 (2H, m), 4.12–4.21 (2H, m), 4.68 (1H, dd, $J = 5.5$ Hz, 7.5 Hz), 5.02 (2H, s), 6.73 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.23–7.41 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.11, 24.12, 33.26, 38.32, 61.19, 69.98, 78.32, 114.79, 115.19, 127.28, 127.42, 127.89, 128.54, 128.82, 130.51, 137.07, 142.07, 155.89, 157.78, 171.43. IR (KBr) cm^{-1} 2959, 1753, 1511, 1239, 1179. HRMS m/z 441.2048 ($M+Na^+$) (calcd for $C_{27}H_{30}O_4Na$ 441.20).

5.16.2. Ethyl 3-(4-hydroxyphenyl)-2-(4-isopropylphenoxy)propionate (19f). Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.13–1.22 (9H, m), 2.75–2.88 (1H, m), 3.11–3.18 (2H, m), 4.17 (2H, q, $J = 7.5$ Hz), 4.69 (1H, dd, $J = 5.5$ Hz, 7.5 Hz), 4.77 (1H, br s), 6.76 (4H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.17 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.09, 24.13, 33.27, 38.31, 61.32, 78.41, 115.22, 115.31, 127.31, 128.11, 130.63, 142.15, 154.94, 155.85, 171.71. IR (liquid film) cm^{-1} 3419, 2962, 1733, 1512, 1374. HRMS m/z 351.1567 ($M+Na^+$) (calcd for $C_{20}H_{24}O_4Na$ 351.1573).

5.16.3. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)-phenyl]-2-(4-isopropylphenoxy)propionate. Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.18–1.22 (9H, m), 1.44 (9H, s), 2.78–2.83 (1H, m), 3.10–3.20 (2H, m), 3.47–3.52 (2H, m), 3.95–3.98 (2H, m), 4.13–4.20 (2H, m), 4.67 (1H, dd, $J = 5.5$ Hz, 7.5 Hz), 4.96 (1H, br s), 6.74 (2H, d, $J = 8.5$ Hz), 6.79 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz). IR (KBr) cm^{-1} 3335, 2961, 1719, 1512, 1247. HRMS m/z 494.2516 ($M+Na^+$) (calcd for $C_{27}H_{37}NO_6Na$ 494.2519). Anal. Calcd for $C_{27}H_{37}NO_6 \cdot 1/7H_2O$: C, 68.40; H, 7.93; N, 2.95. Found: C, 68.47; H, 7.78; N, 2.92.

5.16.4. Ethyl 2-(4-isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 77–79 °C (yield 90%). ^1H NMR ($CDCl_3$) δ 1.14–1.25 (9H, m), 2.72–2.90 (1H, m), 3.12–3.19 (2H, m), 3.89 (2H, dt, $J = 5.0$, 5.5 Hz), 4.11–4.22 (4H, m), 4.69 (1H, dd, $J = 5.5$, 7.5 Hz), 6.65 (1H, br t), 6.75 (2H, d, J =8.5 Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.08 (2H, d, $J = 8.5$ Hz), 7.20–7.31 (3H, m), 7.76–7.81 (2H, m), 7.88 (2H, d, $J =$ 8.5 Hz), 8.07 (2H, d, $J = 8.5$ Hz), 8.69–8.75 (1H, m). IR (KBr) cm^{-1} 3363, 2959, 1510, 1241, 1182. MS m/z 553 (M+H). Anal. Calcd for $C_{34}H_{36}N_2O_5 \cdot 1/6H_2O$: C, 73.51; H, 6.59; N, 5.04. Found: C, 73.89; H, 6.57; N, 5.07.

5.16.5. 2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-yl-benzoyl)amino]ethoxy]phenyl]propionic acid (9c). Mp: 84–85 °C (yield 99%). ^1H NMR ($CDCl_3$) δ 1.16 (6H, d, $J = 7.0$ Hz), 2.70–2.88 (1H, m), 3.19 (2H, d, $J = 6.0$ Hz), 3.80–3.89 (2H, m), 4.11–4.18 (2H, m), 4.77 (1H, t, $J = 6.0$ Hz), 6.77–6.88 (5H, m), 7.07 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.25–7.35 (1H, m), 7.70 (1H, d, $J = 8.5$ Hz), 7.75–7.86 (3H, m), 7.89 (2H, d, $J = 8.5$ Hz), 8.70–8.77 (1H, m). HRMS m/z 525.2374 ($M+H^+$) (calcd for $C_{32}H_{33}N_2O_5$ 525.2390). Anal. Calcd for $C_{32}H_{32}N_2O_5 \cdot 1/2H_2O$: C, 72.03; H, 6.23; N, 5.25. Found: C, 72.01; H, 6.06; N, 5.22.

5.17. 2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-yl-benzoyl)amino]ethoxy]phenyl]propionic acid (9d)

5.17.1. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)-phenyl]-2-(4-*tert*-butylphenoxy)propionate. Colorless syrup (yield 99%). ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, $J = 7.0$ Hz), 1.26 (9H, s), 1.45 (9H, s), 3.13–3.19 (2H, m), 3.51 (2H, q, $J = 5.0$ Hz), 3.99 (2H, t, $J = 5.0$ Hz), 4.18 (2H, q, $J = 7.0$ Hz), 4.66–4.72 (1H, m), 4.90–5.02 (1H, m), 6.76 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.22 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.14, 28.39, 31.46, 34.08, 38.27, 40.13, 61.21, 67.15, 78.22, 79.47, 114.37, 114.77, 126.25, 128.99, 130.57, 144.35, 155.53, 155.88, 157.54, 171.40. IR (liquid film) cm^{-1} 3392, 2966, 1716, 1512, 1244. HRMS m/z 508.2674 ($M+Na^+$) (calcd for $C_{28}H_{39}NO_6Na$ 508.2675).

5.17.2. Ethyl 2-(4-*tert*-butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Colorless

foam (yield 90%). ^{1}H NMR ($CDCl_3$) δ 1.21 (3H, t, $J = 7.0$ Hz), 1.25 (9H, s), 3.15–3.20 (2H, m), 3.89 (2H, q, $J = 5.0$ Hz), 4.10–4.22 (4H, m), 4.69 (1H, dd, $J = 5.5$, 7.5 Hz), 6.66 (1H, t, $J = 5.0$ Hz), 6.76 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.23–7.30 (5H, m), 7.74–7.80 (2H, m), 7.89 (2H, d, $J = 8.5$ Hz), 8.07 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 4.5$ Hz). IR (KBr) cm^{-1} 3362, 2961, 1511, 1243, 1186. HRMS m/z 567.2858 (M+H$^+$) (calcd for $C_{35}H_{39}N_2O_5$ 567.2859). Anal. Calcd for $C_{35}H_{38}N_2O_5 \cdot 1/9H_2O$: C, 73.90; H, 6.78; N, 4.92. Found: C, 73.93; H, 6.81; N, 4.83.

5.17.3. 2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9d). Mp: 94–96 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.24 (9H, s), 3.20 (2H, d, $J = 6.0$ Hz), 3.80–3.90 (2H, m), 4.13–4.20 (2H, m), 4.79 (1H, t, $J = 6.0$ Hz), 6.76 (1H, t, $J = 5.0$ Hz), 6.82 (2H, d, $J = 8.0$ Hz), 6.85 (2H, d, $J = 8.0$ Hz), 7.22 (2H, d, $J = 8.0$ Hz), 7.25 (2H, d, $J = 8.0$ Hz), 7.28–7.35 (1H, m), 7.70–7.90 (4H, m), 7.91 (2H, d, $J = 8.5$ Hz), 8.73 (1H, d, $J = 4.5$ Hz). HRMS m/z 539.2548 (M+H$^+$) (calcd for $C_{33}H_{35}N_2O_5$ 539.2546). Anal. Calcd for $C_{33}H_{34}N_2O_5 \cdot 1/2H_2O$: C, 72.38; H, 6.44; N, 5.12. Found: C, 72.58; H, 6.55; N, 4.98.

5.18. 2-(4-Fluorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9e)

5.18.1. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-fluorophenoxy)propionate. Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.45 (9H, s), 3.16 (2H, d, $J = 7.0$ Hz), 3.38–3.59 (2H, m), 3.99 (2H, t, $J = 5.0$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.65 (1H, t, $J = 7.0$ Hz), 4.93–5.02 (1H, m), 6.70–6.79 (2H, m), 6.82 (2H, d, $J = 8.5$ Hz), 6.88–6.95 (2H, m), 7.20 (2H, d, $J = 8.5$ Hz). IR (liquid film) cm^{-1} 3386, 2979, 1713, 1507, 1246. HRMS m/z 470.1952 (M+Na$^+$) (calcd for $C_{24}H_{30}FNO_6Na$ 470.1955).

5.18.2. Ethyl 2-(4-fluorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 116–118 °C (yield 90%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 3.17 (2H, d, $J = 6.5$ Hz), 3.80–3.91 (2H, m), 4.08–4.21 (4H, m), 4.66 (1H, t, $J = 6.5$ Hz), 6.62–6.70 (1H, m), 6.70–6.80 (2H, m), 6.80–6.92 (4H, m), 7.20–7.30 (3H, m), 7.71–7.80 (2H, m), 7.88 (2H, d, $J = 8.5$ Hz), 8.07 (2H, d, $J = 8.5$ Hz), 8.71 (1H, d, $J = 5.0$ Hz). IR (KBr) cm^{-1} 3358, 1632, 1543, 1503, 1198. HRMS m/z 529.2135 (M+H$^+$) (calcd for $C_{31}H_{30}FN_2O_5$ 529.2139).

5.18.3. 2-(4-Fluorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9e). Mp: 139–140 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 3.20 (2H, d, $J = 6.5$ Hz), 3.80–3.91 (2H, m), 4.16–4.22 (2H, m), 4.74 (1H, t, $J = 6.5$ Hz), 6.69–6.77 (1H, m), 6.77–6.92 (6H, m), 7.19 (2H, d, $J = 8.5$ Hz), 7.30–7.37 (1H, m), 7.69–7.80 (3H, m), 7.80–7.90 (3H, m), 8.71 (1H, d, $J = 4.0$ Hz). HRMS m/z 501.1828 (M+H$^+$) (calcd for $C_{29}H_{26}FN_2O_5$ 501.1826). Anal. Calcd for $C_{29}H_{25}FN_2O_5 \cdot 1/3H_2O$: C, 68.75; H, 5.11; N, 5.53; F, 3.75. Found: C, 68.93; H, 4.84; N, 5.43; F, 3.69.

5.19. 2-(4-Chlorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9f)

5.19.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-chlorophenoxy)propionate (18g). The same procedure as for **18b** was performed.

Mp: 63–64 °C (yield 56%). ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, t, $J = 7.0$ Hz), 3.17 (2H, d, $J = 6.5$ Hz), 4.16 (2H, q, $J = 7.0$ Hz), 4.69 (1H, t, $J = 6.5$ Hz), 5.04 (2H, s), 6.75 (2H, d, $J = 9.0$ Hz), 6.91 (2H, d, $J = 8.5$ Hz), 7.13–7.23 (4H, m), 7.25–7.55 (5H, m). IR (KBr) cm^{-1} 1736, 1513, 1491, 1244, 826. HRMS m/z 410.1260 (M$^+$) (calcd for $C_{24}H_{23}ClO_4$ 410.1285). Anal. Calcd for $C_{24}H_{23}ClO_4$: C, 70.15; H, 5.64; Cl, 8.63. Found: C, 69.96; H, 5.60; Cl, 8.56.

5.19.2. Ethyl 2-(4-chlorophenoxy)-3-(4-hydroxyphenyl)propionate (19g). A mixture of **18g** (3.45 g, 8.40 mmol) and 30 wt % HBr solution in AcOH (35 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo and purified by column chromatography (hexane/EtOAc, 4/1) to give a mixture of the title compound and ethyl 3-(4-acetoxyphenyl)-2-(4-chlorophenoxy)propionate. To this mixture were added EtOH (30 mL) and K_2CO_3 (2.8 g, 20.3 mmol), and the mixture was stirred at 60 °C for 4 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The title compound was collected by filtration using isopropyl ether and hexane (1.94 g, yield 78%).

Mp: 90–93 °C. ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, t, $J = 7.0$ Hz), 3.16 (2H, d, $J = 6.5$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.69 (1H, t, $J = 6.5$ Hz), 4.95 (1H, br s), 6.76 (4H, d, $J = 8.5$ Hz), 7.15 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz). HRMS m/z 343.0730 (M+Na$^+$) (calcd for $C_{17}H_{17}ClO_4Na$ 343.0713). Anal. Calcd for $C_{17}H_{17}ClO_4$: C, 63.65; H, 5.34; Cl, 11.05. Found: C, 63.65; H, 5.36; Cl, 11.02.

5.19.3. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-chlorophenoxy)propionate. Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 1.45 (9H, s), 3.17 (2H, t, $J = 6.5$ Hz), 3.43–3.57 (2H, m), 3.99 (2H, t, $J = 5.0$ Hz), 4.17 (2H, q, $J = 7.0$ Hz), 4.69 (1H, t, $J = 6.5$ Hz), 4.96 (1H, br s), 6.76 (2H, d, $J = 8.5$ Hz), 6.82 (2H, d, $J = 8.5$ Hz), 7.10–7.20 (4H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.12, 28.40, 38.16, 40.13, 61.42, 67.17, 78.42, 79.53, 114.44, 116.70, 126.66, 128.61, 129.38, 130.54, 155.88, 156.41, 157.65, 170.82. IR (liquid film) cm^{-1} 3369, 2979, 1713, 1513, 1492. HRMS m/z 486.1659 (M+Na$^+$) (calcd for $C_{24}H_{30}ClNO_6Na$ 486.1660).

5.19.4. Ethyl 2-(4-chlorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 134–135 °C (yield 90%). ^{1}H NMR ($CDCl_3$) δ 1.20 (3H, t, $J = 7.0$ Hz), 3.17 (2H, d, $J = 6.5$ Hz), 3.83–3.92 (2H, m), 4.08–4.21 (4H, m), 4.69 (1H, t, $J = 6.5$ Hz), 6.60–6.68 (1H, m), 6.75 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.13–7.30 (5H, m), 7.72–7.79 (2H, m), 7.89 (2H, d, $J = 8.5$ Hz), 8.08 (2H, d, $J = 8.5$ Hz), 8.70–8.73 (1H, m). IR (KBr) cm^{-1} 3346, 2936, 1740, 1490, 1239. HRMS m/z 545.1849 (M+H$^+$) (calcd for $C_{31}H_{30}ClN_2O_5$ 545.1834). Anal. Calcd for $C_{31}H_{29}ClN_2O_5$: C, 68.32; H, 5.36; Cl, 6.50; N, 5.14. Found: C, 68.15; H, 5.22; Cl, 6.41; N, 5.32.

5.19.5. 2-(4-Chlorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9f). Mp: 155–156 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 3.21 (2H, d, $J = 6.0$ Hz), 3.80–3.90 (2H, m), 4.12–4.22 (2H, m), 4.76 (1H, t, $J = 6.0$ Hz), 6.70–6.88 (5H, m), 7.15 (2H, d, $J = 8.5$ Hz), 7.20 (2H, d, $J = 8.5$ Hz), 7.30–7.38 (1H, m), 7.79–7.90 (6H, m), 8.70–8.74 (1H, m). HRMS m/z 517.1519 (M+H$^+$) (calcd for $C_{29}H_{26}ClN_2O_5$ 517.1530). Anal. Calcd for $C_{29}H_{25}ClN_2O_5 \cdot 1/6H_2O$: C, 67.00; H, 4.91; N, 5.39; Cl, 6.82. Found: C, 67.09; H, 4.87; N, 5.42; Cl, 6.86.

5.20. 2-(4-Isopropylphenoxy)-2-methyl-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9g)

5.20.1. Ethyl 3-(4-benzyloxyphenyl)-2-(4-isopropylphenoxy)-2-methylpropionate. To a solution of *N*-isopropylcyclohexylamine (18.1 mL, 0.11 mol) in THF (300 mL) was slowly added 1.54 M *n*-butyl lithium in hexane (71.4 mL, 0.11 mol) at −78 °C. After removal of the cooling bath, the mixture was stirred for 1 h at room temperature and then cooled again to −78 °C. To the mixture was added a solution of 23.63 g (0.10 mol) of ethyl 2-(4-isopropylphenoxy)propionate **22** in THF (20 mL) dropwise over 30 min. The reaction mixture was stirred at −78 °C for 20 min and then added a solution of 4-benzyloxybenzyl chloride (46.5 g, 0.20 mol) in THF (100 mL). The reaction mixture was stirred overnight at −78 °C and allowed to warm to room temperature. After removal of the solvent in vacuo, the residue was treated with water, and then the pH was adjusted to 5–6 with 2 N HCl. The mixture was extracted with EtOAc and the organic phase was washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography (hexane/EtOAc, 9/1) to give the title compound as a colorless syrup (23 g, yield 53%).

^{1}H NMR ($CDCl_3$) δ 1.20 (6H, d, $J = 7.0$ Hz), 1.21 (3H, t, $J = 7.5$ Hz), 1.38 (3H, s), 2.83 (1H, septet, $J = 7.0$ Hz), 3.11 (1H, d, $J = 13.5$ Hz), 3.25 (1H, d, $J = 13.5$ Hz), 4.20 (2H, q, $J = 7.5$ Hz), 5.05 (2H, s), 6.75 (2H, d, $J = 8.5$ Hz), 6.91 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz), 7.30–7.45 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.70, 20.60, 24.10, 33.29, 44.89, 61.29, 69.98, 82.04, 114.40, 119.38, 126.90, 127.46, 127.90, 128.02, 128.55, 131.69, 137.10, 142.66, 153.27, 157.85, 173.87. IR ($CDCl_3$) cm^{-1} 2963, 1731, 1510, 1116, 909. HRMS m/z 455.2198 (M+Na$^+$) (calcd for $C_{28}H_{32}O_4Na$ 455.2199).

5.20.2. Ethyl 3-(4-hydroxyphenyl)-2-(4-isopropylphenoxy)-2-methylpropionate (21). Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.20 (6H, d, $J = 7.0$ Hz), 1.22 (3H, t, $J = 7.5$ Hz), 1.38 (3H, s), 2.83 (1H, septet, $J = 7.0$ Hz), 3.10 (1H, d, $J = 13.5$ Hz), 3.24 (1H, d, 13.5 Hz), 4.20 (2H, q, $J = 7.5$ Hz), 4.81 (1H, s), 6.75 (4H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.13 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 20.55, 24.10, 33.30, 44.97, 58.49, 82.17, 114.98, 119.47, 126.93, 131.77, 142.76, 153.22, 155.05, 174.14. IR (liquid film) cm^{-1} 2962, 1732, 1509, 1232, 1112. HRMS m/z 342.1821 (M$^+$) (calcd for $C_{21}H_{26}O_4$ 342.1831).

5.20.3. Ethyl 3-[4-(2-*tert*-butoxycarbonyaminoethoxy)-phenyl]-2-(4-isopropylphenoxy)-2-methyl-propionate. Colorless syrup (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.15–1.28 (9H, m), 1.37 (3H, s), 1.45 (9H, s), 2.83 (1H, septet, $J = 7.0$ Hz), 3.10 (1H, d, $J = 13.5$ Hz), 3.25 (1H, d, $J = 13.5$ Hz), 3.46–3.58 (2H, m), 4.00 (2H, t, $J = 5.0$ Hz), 4.21 (2H, q, $J = 7.0$ Hz), 4.95–5.05 (1H, m), 6.75(2H, d, $J = 8.5$ Hz), 6.81 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz). 7.17 (2H, d, $J = 8.5$ Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.09, 20.61, 21.46, 24.10, 28.41, 33.30, 40.16, 44.82, 61.32, 67.13, 79.51, 82.01, 113.99, 119.40, 126.91, 131.76, 137.86, 142.70, 153.25, 155.90, 157.60, 173.88. IR (liquid film) cm^{-1} 3392, 2963, 1718, 1509, 1245. HRMS m/z 508.2686 (M+Na$^+$) (calcd for $C_{28}H_{39}NO_6Na$ 508.2675).

5.20.4. Ethyl 2-(4-isopropylphenoxy)-2-methyl-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp:89–90 °C (yield 90%). ^{1}H NMR ($CDCl_3$) δ 1.19 (6H, d, $J = 7.0$ Hz), 1.23 (3H, t, $J = 7.0$ Hz), 1.37 (3H, s), 2.83 (1H, septet, $J = 7.0$ Hz), 3.10 (1H, d, $J = 13.5$ Hz), 3.26 (1H, d, $J = 13.5$ Hz), 3.90 (2H, dt, $J = 5.0$, 5.0 Hz), 4.17 (2H, t, $J = 5.0$), 4.21 (2H, q, $J = 7.0$ Hz), 6.69 (1H, br t, $J = 5.0$ Hz), 6.75 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.26–7.32 (1H, m), 7.76–7.82 (2H, m), 7.89 (2H, d, $J = 8.5$ Hz), 8.08 (2H, d, $J = 8.5$ Hz), 8.71–8.73 (1H, m). IR (KBr) cm^{-1} 3374, 2959, 1734, 1636, 1509. MS m/z 567 (M+H$^+$). Anal. Calcd for $C_{35}H_{38}N_2O_5$: C, 74.18; H, 6.76; N, 4.94. Found: C, 74.04; H, 6.81; N, 4.92.

5.20.5. 2-(4-Isopropylphenoxy)-2-methyl-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid (9g). Mp: 141–143 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.20 (6H, d, $J = 7.0$ Hz), 1.43 (3H, s), 2.84 (1H, septet, $J = 7.0$ Hz), 3.15 (1H, d, $J = 14.0$ Hz), 3.25 (1H, d, $J = 14.0$ Hz), 3.83–3.93 (2H, m), 4.17 (2H, t, $J = 5.0$ Hz), 6.70 (1H, br t, $J = 6.0$ Hz), 6.85 (2H, d, $J = 8.5$ Hz), 6.86 (2H, d, $J = 8.5$ Hz), 7.09 (2H, d, $J = 8.5$ Hz), 7.21 (2H, d, $J = 8.5$ Hz), 7.27–7.33 (1H, m), 7.27–7.80 (2H, m), 7.83 (2H, d, $J = 8.5$ Hz), 8.00 (2H, d, $J = 8.5$ Hz), 8.72 (1H, d, $J = 4.5$ Hz). HRMS m/z

539.2545 ($M+H^+$) (calcd for $C_{33}H_{35}N_2O_5$ 539.2546). Anal. Calcd for $C_{33}H_{34}N_2O_5 \cdot 4/5H_2O$: C, 71.67; H, 6.49; N, 5.07. Found: C, 71.69; H, 6.12; N, 5.26.

5.21. (*S*)-2-(4-Methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid ((*S*)-8j)

5.21.1. 3-(4-Benzyloxyphenyl)-2-(4-methylphenoxy)propionic acid. To a solution of **18d** (0.36 g, 0.91 mmol) in ethanol (10 mL) was added 1 N NaOH (3.5 mL), and the mixture was stirred at room temperature for 16 h. After the reaction mixture was evaporated in vacuo, the residue was diluted with water and carefully acidified with 1 N HCl and extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The solids obtained were collected by filtration using the mixture of isopropyl ether and hexane to give the title compound as a colorless solid (0.33 g, yield 92%).

Mp: 129–130 °C. ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, s), 3.18 (2H, d, $J = 6.0$ Hz), 4.74 (1H, t, $J = 6.0$ Hz), 5.00 (2H, s), 6.71 (2H, d, $J = 8.5$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.01 (2H, d, $J = 8.5$ Hz), 7.18 (2H, d, $J = 8.5$ Hz), 7.22–7.40 (5H, m). MS m/z 385 ($M+Na^+$). IR (KBr) cm^{-1} 3031, 1731, 1711, 1511, 1232. Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.31; H, 6.13.

5.21.2. (*S*)-3-(4-Benzyloxyphenyl)-2-(4-methylphenoxy)propionic acid. To a solution of the above racemic propionic acid (114 g, 313 mmol) in EtOH (300 mL) was added (−)-norephedrine (23.7 g, 157 mmol) and the mixture was refluxed for 1 h and then allowed to cool to room temperature. The white precipitates were collected by filtration and washed with EtOH. Repeated crystallization from EtOH gave 51.4 g of (−)-norephedrine salt of the title compound. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). To the obtained (−)-norephedrine salt was added 1 N HCl until the mixture became acidified and the product was extracted with EtOAc. The organic phase was washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the title compound was collected by filtration using isopropyl ether (36.2 g, 32%).

Mp: 118–119 °C. The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{23}H_{22}O_4 \cdot 1/10H_2O$: C, 75.85; H, 6.14. Found: C, 75.85; H, 6.03.

5.21.3. Ethyl (*S*)-3-(4-benzyloxyphenyl)-2-(4-methylphenoxy)propionate. A solution of the (*S*)-propionic acid (36.2 g, 100 mmol) and concd H_2SO_4 (2.0 mL) in ethanol (360 mL) was stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was extracted with EtOAc. The organic phase was washed with water and brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the title compound was obtained as a colorless syrup (39.0 g, 99%).

The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.21.4. Ethyl (*S*)-3-(4-hydroxyphenyl)-2-(4-methylphenoxy)propionate ((*S*)-19d). Mp: 64–65 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{18}H_{20}O_4 \cdot 1/5H_2O$: C, 70.89; H, 7.07. Found: C, 71.03; H, 7.23.

5.21.5. Ethyl (*S*)-2-(4-methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionate. Colorless syrup (yield 84%). ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.21.6. (*S*)-2-(4-Methylphenoxy)-3-[4-[2-[1-(4-pyridin-2-ylphenyl)ethylideneaminooxy]ethoxy]phenyl]propionic acid (8j). Mp: 54–56 °C (yield 94%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{31}H_{30}N_2O_5 \cdot 1/3H_2O$: C, 72.06; H, 5.98; N, 5.42. Found: C, 72.10; H, 5.98; N, 5.35.

5.22. (*S*)-2-(4-Methylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9b)

5.22.1. Ethyl (*S*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-methylphenoxy)propionate. Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.22.2. Ethyl (*S*)-2-(4-methylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 102–103 °C (yield 90%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{32}H_{32}N_2O_5$: C, 73.26; H, 6.15; N, 5.34. Found: C, 73.07; H, 6.01; N, 5.36.

5.22.3. (*S*)-2-(4-Methylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9b). Mp: 76–78 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{30}H_{28}N_2O_5 \cdot 1/2H_2O$: C, 71.27; H, 5.78; N, 5.54. Found: C, 71.22; H, 5.75; N, 5.49.

5.23. (*R*)-2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*R*)-9c)

5.23.1. 3-(4-Benzyloxyphenyl)-2-(4-isopropylphenoxy)propionic acid. Alkaline hydrolysis of **18f** was performed.

Mp: 118–119 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.19 (6H, d, $J = 7.0$ Hz), 2.82 (1H, septet, $J = 7.0$ Hz), 3.19 (2H, d, $J = 6.0$ Hz), 4.74 (1H, t, $J = 6.0$ Hz), 5.00 (2H, s), 6.75 (2H, d, $J = 9.0$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.07 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 9.0$ Hz), 7.21–7.40 (5H, m). MS m/z 413 ($M+Na^+$). IR (KBr) cm^{-1} 2958, 1727, 1511, 1231, 827. Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.87; H, 6.69.

5.23.2. (*R*)-3-(4-Benzyloxyphenyl)-2-(4-isopropylphenoxy)propionic acid. Resolution of the racemate was done using (+)-norephedrine.

Mp: 88–89 °C. The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.69; H, 6.88.

5.23.3. Ethyl (*R*)-3-(4-benzyloxyphenyl)-2-(4-isopropylphenoxy)propionate ((*R*)-18f). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.23.4. Ethyl (*R*)-3-(4-hydroxyphenyl)-2-(4-isopropylphenoxy)propionate ((*R*)-19f). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.23.5. Ethyl (*R*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-isopropylphenoxy)propionate. Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.23.6. Ethyl (*R*)-2-(4-isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Colorless syrup (yield 90%). ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.23.7. (*R*)-2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*R*)-9c). Mp: 100–101 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{32}H_{32}N_2O_5 \cdot 1/3H_2O$: C, 72.44; H, 6.20; N, 5.28. Found: C, 69.47; H, 5.97; N, 5.11.

5.24. (*S*)-2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9c)

The same procedure for the preparation of (*R*)-**9c** was performed except using (−)-norephedrine for optical resolution.

5.24.1. (*S*)-3-(4-Benzyloxyphenyl)-2-(4-isopropylphenoxy)propionic acid. Mp: 88–89 °C. The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 77.05; H, 6.56.

5.24.2. Ethyl (*S*)-3-(4-benzyloxyphenyl)-2-(4-isopropylphenoxy)propionate ((*S*)-18f). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.24.3. Ethyl (*S*)-3-(4-hydroxyphenyl)-2-(4-isopropylphenoxy)propionate ((*S*)-19f). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.24.4. Ethyl (*S*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-isopropylphenoxy)propionate. Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.24.5. Ethyl (*S*)-2-(4-isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Colorless syrup (yield 90%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.24.6. (*S*)-2-(4-Isopropylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9c). Mp: 100–101 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{32}H_{32}N_2O_5 \cdot H_2O$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63; H, 6.26; N, 5.11.

5.25. (*R*)-2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*R*)-9d)

5.25.1. 3-(4-Benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionic acid. Mp: 124–125 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 1.26 (9H, s), 3.19 (2H, d, $J = 6.0$ Hz), 4.75 (1H, t, $J = 6.0$ Hz), 5.01 (2H, s), 6.75 (2H, d, $J = 9.0$ Hz), 6.87 (2H, d, $J = 8.5$ Hz), 7.19 (2H, d, $J = 8.5$ Hz), 7.24 (2H, d, $J = 9.0$ Hz), 7.28–7.40 (5H, m). MS m/z 427 ($M+Na^+$). IR (KBr) cm^{-1} 2963, 1718, 1512, 1248, 1232. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.09; H, 7.05.

5.25.2. (*R*)-3-(4-Benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionic acid. (+)-Norephedrine was used as an optical resolution agent.

Mp: 90–91 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{26}H_{28}O_4$: C, 76.90; H, 6.71. Found: C, 77.34; H, 7.04.

5.25.3. Ethyl (*R*)-3-(4-benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionate ((*R*)-18e). Colorless syrup (yield

99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.25.4. Ethyl (*R*)-2-(4-*tert*-butylphenoxy)-3-(4-hydroxyphenyl)propionate ((*R*)-19e). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.25.5. Ethyl (*R*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-*tert*-butylphenoxy)propionate. Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.25.6. Ethyl (*R*)-2-(4-*tert*-butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 72–73 °C (yield 90%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{35}H_{38}N_2O_5 \cdot 1/5H_2O$: C, 73.71; H, 6.79; N, 4.91. Found: C, 73.88; H, 6.88; N, 4.77.

5.25.7. (*R*)-2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*R*)-9d). Mp: 93–95 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{33}H_{34}N_2O_5 \cdot 1/2H_2O$: C, 72.38; H, 6.44; N, 5.12. Found: C, 72.40; H, 6.59; N, 5.20.

5.26. (*S*)-2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9d)

The same procedure as for the preparation of (*R*)-**9d** was performed using (−)-norephedrine as an optical resolution agent.

5.26.1. (*S*)-3-(4-Benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionic acid. Mp: 90–91 °C. The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.14; H, 7.03.

5.26.2. Ethyl (*S*)-3-(4-benzyloxyphenyl)-2-(4-*tert*-butylphenoxy)propionate ((*S*)-18e). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.26.3. Ethyl (*S*)-2-(4-*tert*-butylphenoxy)-3-(4-hydroxyphenyl)propionate ((*S*)-19e). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.26.4. Ethyl (*S*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-*tert*-butylphenoxy)propionate. Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.26.5. Ethyl (*S*)-2-(4-*tert*-butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 72–73 °C (yield 90%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{35}H_{38}N_2O_5$: C, 74.18; H, 6.76; N, 4.94. Found: C, 74.32; H, 6.82; N, 4.87.

5.26.6. (*S*)-2-(4-*tert*-Butylphenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9d). Mp: 93–95 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{33}H_{34}N_2O_5 \cdot 1/2H_2O$: C, 72.38; H, 6.44; N, 5.12. Found: C, 73.59; H, 6.36; N, 5.20.

5.27. (*S*)-2-(4-Chlorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionic acid ((*S*)-9f)

The same procedure as for the preparation of **9f** was performed from (*S*)-**19g**.

5.27.1. 3-(4-Benzyloxyphenyl)-2-(4-chlorophenoxy)propionic acid. Mp: 129–130 °C (yield 99%). ^{1}H NMR ($CDCl_3$) δ 3.14–3.26 (2H, m), 4.73 (1H, dd, $J = 5.0$, 6.5 Hz), 5.01 (2H, s), 6.74 (2H, d, $J = 9.0$ Hz), 6.88 (2H, d, $J = 8.5$ Hz), 7.15–7.18 (4H, m), 7.27–7.40 (5H, m). MS m/z 405 ($M+Na^+$). IR (KBr) cm^{-1} 3032, 1724, 1490, 1236, 1227. Anal. Calcd for $C_{22}H_{19}ClO_4 \cdot 1/2H_2O$: C, 68.89; H, 5.01; Cl, 9.24. Found: C, 68.93; H, 4.87; Cl, 9.26.

5.27.2. (*S*)-3-(4-Benzyloxyphenyl)-2-(4-chlorophenoxy)propionic acid. Mp: 129–130 °C (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{22}H_{19}ClO_4$: C, 69.02; H, 5.00; Cl, 9.26. Found: C, 69.03; H, 4.85; Cl, 9.22.

5.27.3. Ethyl (*S*)-3-(4-benzyloxyphenyl)-2-(4-chlorophenoxy)propionate ((*S*)-18g). Colorless syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.27.4. Ethyl (*S*)-2-(4-chlorophenoxy)-3-(4-hydroxyphenyl)propionate ((*S*)-19g). Mp: 93–94 °C (yield 78%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{17}H_{17}ClO_4 \cdot 1/3H_2O$: C, 62.53; H, 5.45; Cl, 10.86. Found: C, 62.55; H, 5.47, Cl, 10.98.

5.27.5. Ethyl (*S*)-3-[4-(2-*tert*-butoxycarbonyaminoethoxy)phenyl]-2-(4-chlorophenoxy)propionate. Colorless

syrup (yield 99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate.

5.27.6. Ethyl (*S*)-2-(4-chlorophenoxy)-3-[4-[2-[(4-pyridin-2-ylbenzoyl)amino]ethoxy]phenyl]propionate. Mp: 135–136 °C (yield 90%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. Anal. Calcd for $C_{31}H_{29}ClN_2O_5$: C, 68.32; H, 5.36; Cl, 6.50; N, 5.14. Found: C, 68.20; H, 5.35; Cl, 6.51; N, 5.12.

5.27.7. (*S*)-2-(4-Chlorophenoxy)-3-[4-[2-[(4-pyridin-2-yl-benzoyl)amino]ethoxy]phenylpropionic acid ((*S*)-9f). Mp: 152–155 °C (99%). The ^{1}H NMR, IR, and mass spectra were identical to the racemate. The enantiomeric excess was determined as >99% ee by HPLC analysis using Chiralpak OJ-R (CH_3CN/pH 2.2 buffer solution of phosphoric acid and Et_3N, 7/3). Anal. Calcd for $C_{29}H_{25}ClN_2O_5$: C, 67.38; H, 4.87; Cl, 6.86; N, 5.42. Found: C, 67.26; H, 4.90; Cl, 6.82; N, 5.39.

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