Identification of G protein-coupled receptor 120-selective agonists derived from PPARγ agonists

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A weak, nonselective G protein-coupled receptor 120 (GPR120) agonist **10** was found by screening a series of carboxylic acids derived from the peroxisome proliferator-activated receptor γ (PPARγ) agonist **3**. Modification based on the homology model of GPR120 led to the first GPR120-selective agonist **12**. These results provide a basis for constructing new tools for probing the biology of GPR120 and for developing new candidate therapeutic agents.

Introduction

G protein-coupled receptor 40 (GPR40[a]) and GPR120 are members of a class of proteins known as G protein-coupled receptors, which are activated by long-chain free fatty acids (FFAs) such as α-linolenic acid (α-LA, **1**) (Chart 1), and these two receptors have very similar pharmacological properties.[1] GPR120 is expressed in intestines and, upon stimulation by long-chain FFAs, increases the secretion of glucagon-like peptide-1 (GLP-1) from intestinal endocrine cells,[1a] leading a glucose-dependent increase of insulin secretion from pancreatic β-cells, stimulation of insulin biosynthesis, and a decrease of glucagon secretion.[2] Moreover, GLP-1 has been reported to play a significant role in appetite and feeding control.[3] Thus, GPR120 has emerged as an attractive target for the treatment of type 2 diabetes and obesity.[4]

Although a number of GPR40 agonists have been identified to date,[5] including compound **2** (GW9508) (Chart 1),[5a] there are only a few reports on GPR120 agonists.[5a,b,6] Furthermore, GPR120-selective agonists, which are of interest as tools for investigating the biological functions of GPR120 and as candidate therapeutic agents having few side effects, have not been reported so far. We therefore initiated a search for GPR120-selective agonists and found a carboxylic acid derivative showing agonistic activity selective for GPR120 over GPR40. We describe here the design, synthesis, and activity of GPR120-selective agonists.

Chemistry. Of the 26 compounds included in this study (Tables 1−3), compounds **3**−**11** had previously been synthesized[7] and were available in our laboratories. Compounds **12**−**28** have not previously been described. Thus, these compounds were prepared as outlined in Scheme 1. 4-(4-Hydroxyphenyl-)butyric acid methyl ester (**29a**)[8] and 5-(4-hydroxyphenyl)pentanoic acid methyl ester (**29b**)[9] were converted to ethers **30** using the Mitsunobu reaction. Coupling between secondary amines and bromide **30** gave tertiary amines, and hydrolysis of the methyl esters afforded the desired carboxylic acids **12**−**28**.

Chart 1. Structures of α-LA (**1**) (Dual Agonist of GPR40 and GPR120) and **2** (GPR40-Selective Agonist)

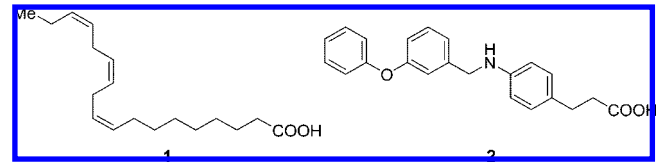
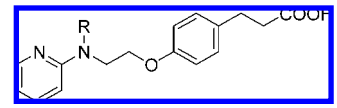


Table 1. GPR40- and GPR120-Agonistic Activity of Compounds **3**−**11**[a]



compound	R	GPR40[b]	GPR120[b]
α-LA (**1**)		100	100
3	*n*-nonyl	121	0
4	*n*-heptyl	99	0
5	*n*-hexyl	104	31
6	*n*-Bu	215	33
7	*n*-Pr	125	57
8	Et	147	45
9	Me	58	0
10	Ph	98	56
11	2-Py	0	0

[a] Values are means of at least three experiments. [b] The agonistic response elicited by 10 μM test compound as a percentage of the response evoked by 10 μM α-LA (**1**).

Results and Discussion

Since it has been reported that long-chain FFAs and peroxisome proliferator-activated receptor γ (PPARγ) agonists, such as ciglitazone and troglitazone, activate GPR120,[1a,5b] we focused initially on carboxylic acid **3** (Table 1), which we previously reported as a potent PPARγ agonist.[7] Compound **3** and its derivatives **4**−**11** (Table 1) were screened for GPR40- and

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[a] Abbreviations: GPR, G protein-coupled receptor; FFA, free fatty acid; α-LA, α-linolenic acid; GLP-1, glucagon-like peptide-1; PPAR, peroxisome proliferator-activated receptor; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; FLIPR, fluorometric imaging plate reader; ERK, extracellular signal-regulated kinase.

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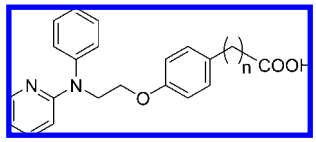
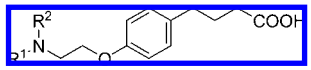
Table 2. GPR40- and GPR120-Agonistic Activity of Compounds **10**, **12**, and **13**[a]



compound	*n*	GPR40[b]	GPR120[b]
α-LA (**1**)		100	100
10	2	98	56
12	3	26	115
13	4	99	58

[a] Values are means of at least three experiments. [b] The agonistic response elicited by 10 μM test compound as a percentage of the response evoked by 10 μM α-LA (**1**).

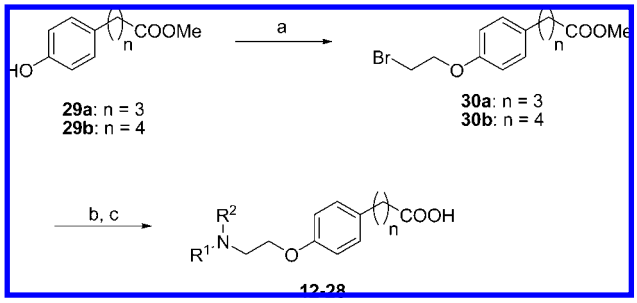
Table 3. GPR40- and GPR120-Agonistic Activity of compounds **12** and **14**−**28**[a]



compound	R^1	R^2	GPR40[b]	GPR120[b]
α-LA (**1**)			100	100
12	2-Py	Ph	26	115
14	2-Py	*n*-butyl	10	41
15	2-Py	Bn	26	56
16	2-Py	3-Py	1	65
17	2-Py	2-Naph	27	37
18	2-Py	4-F-Ph	23	59
19	2-Py	3-F-Ph	33	71
20	2-Py	4-Me-Ph	26	78
21	Ph	Ph	21	88
22	2-benzothiazolyl	Ph	32	73
23	2-benzoxazolyl	Ph	8	43
24	2-thiazolyl	Ph	30	106
25	4-Me-2-Py	Ph	43	81
26	6-Me-2-Py	Ph	34	81
27	4-Cl-2-Py	Ph	68	100
28	6-Cl-2-Py	Ph	32	70

[a] Values are means of at least three experiments. [b] The agonistic response elicited by 10 μM test compound as a percentage of the response evoked by 10 μM α-LA (**1**).

Scheme 1[a]



[a] Reagents: (a) 2-bromoethanol, DEAD, PPh_3, THF, rt, 19−41%; (b) NaH or Et_3N, R^1R^2NH, KI, DMF, 80 °C; (c) NaOH, H_2O, THF, MeOH, rt, 3−55% (two steps)

GPR120-agonistic activity by measuring the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) using a fluorometric imaging plate reader (FLIPR)-based assay in HEK293 cells expressing human GPR40 or human GPR120 (see the experimental procedure in the Supporting Information). α-LA (**1**) was used as the standard compound because it is a dual agonist of GPR40 and GPR120.[1] Efficacy was calculated as percent agonistic response elicited by 10 μM test compound with respect to the response evoked by 10 μM α-LA (**1**) (Table 1). Although the potent PPARγ agonist **3** showed high GPR40-agonistic activity, it was totally inactive against GPR120. Among compounds **4**−**11**, compound **7** with an *n*-propyl group and compound **10** with a phenyl group showed the most potent agonistic activity toward GPR120, and the GPR120/GPR40 selectivity of compound **10** was found to be the highest, although it was less than that of α-LA (**1**).

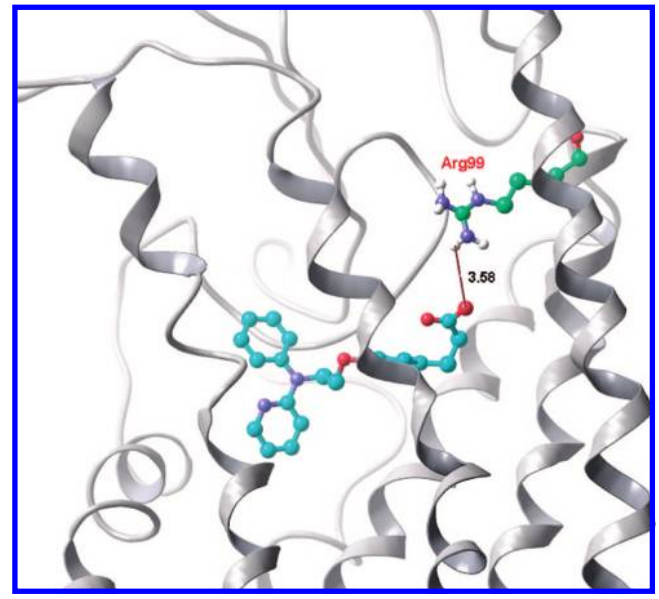


Figure 1. Model of compound **10** docked in the GPR120 homology model.

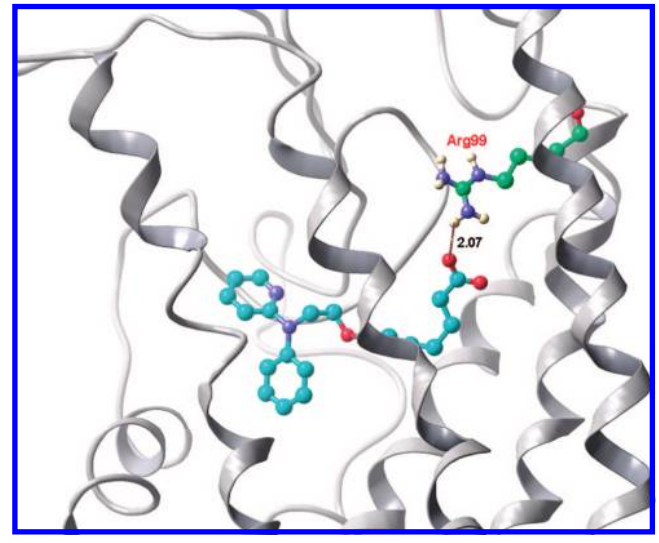


Figure 2. Model of compound **12** docked in the GPR120 homology model.

As a basis to improve the potency and selectivity for GPR120, we performed a binding mode study of compound **10** with the homology model of GPR120, which was developed based on a photointermediate model derived from the crystal structure of bovine rhodopsin (PDB code 1F88).[10] An inspection of the simulated GPR120/compound **10** complex showed that there appears to be an ionic interaction between the carboxylate anion of compound **10** and the guanidinium cation of Arg99 (Figure 1). However, the distance between the oxygen of the carboxylate and the hydrogen of the guanidine was 3.58 Å, which suggested that there is no hydrogen bond between the two atoms. Therefore, we designed compound **12** (Table 2) in which the number of methylene units in the linker is increased to 3. We anticipated that extension of the carbon chain would bring the carboxylate closer to Arg99 and allow it to interact more

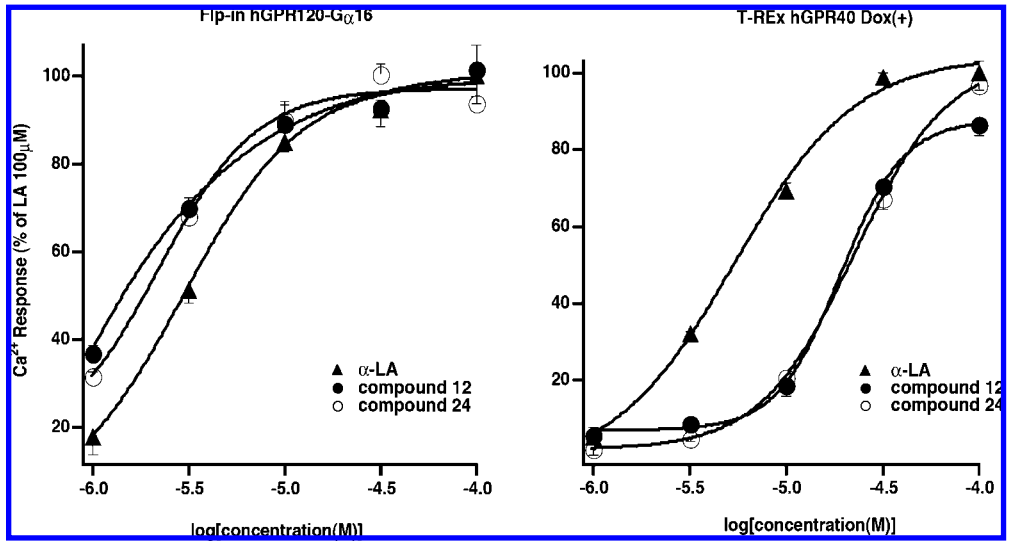


Figure 3. Dose-dependent $[Ca^{2+}]_i$ response induced by compounds **12** and **24** in HEK293 cells expressing GPR120 (left) or GPR40 (right).

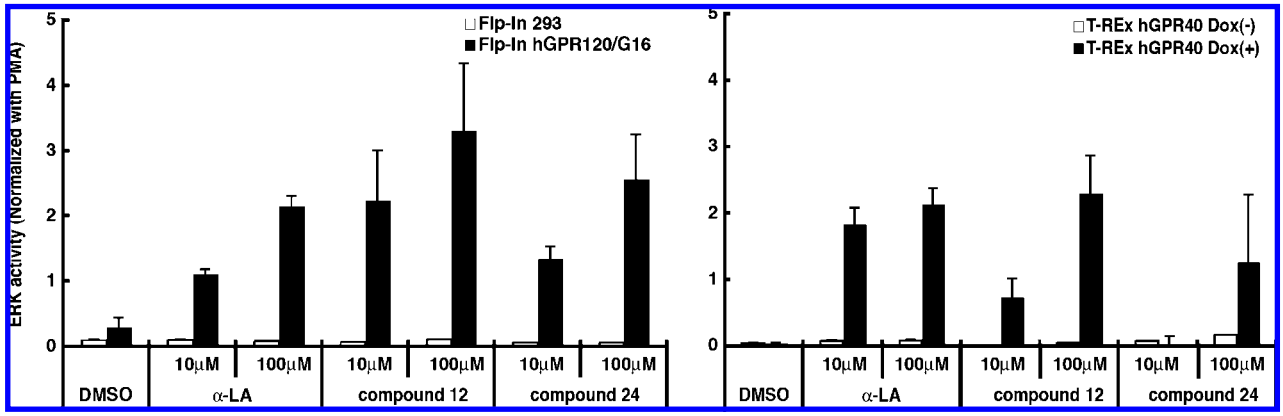


Figure 4. ERK activation induced by α-LA (**1**), compound **12**, and compound **24** in HEK293 cells expressing GPR120 (left) or GPR40 (right).

Table 4. GPR40- and GPR120-Agonistic Activity of Compounds **12** and **24**[a]

compound	EC_{50} (GPR120) (μM)	EC_{50} (GPR40) (μM)	SI[b]
α-LA (**1**)	2.6	5.2	2
12	1.2	19	16
24	1.7	21	12

[a] Values are means of at least three experiments. [b] SI (selectivity index) = EC_{50} (GPR40)/EC_{50} (GPR120).

strongly with the guanidine of Arg99 via ionic and hydrogen bonding (Figure 2), which might lead to a more potent activation of GPR120. We also expected that compound **12** would show increased GPR120/GPR40 activity ratio because it was reported that extension of the methylene chain of **2** significantly decreases the GPR40-agonistic activity.[5c] As expected, the GPR120-agonistic activity and the GPR120/GPR40 selectivity of compound **12** were significantly increased as compared with those of α-LA (**1**) and compound **10** (Table 2). On the other hand, further extension of the methylene chain (compound **13**) resulted in reduction of both the potency and the selectivity, which can be explained by the steric hindrance between the carboxylate of **13** and Arg99.

Next, we looked at the effect of replacing the phenyl or 2-pyridine ring with several substituents (Table 3). We initially converted the phenyl group of compound **12** to alkyl (**14** and **15**), aromatic (**16** and **17**), and 3- or 4-substituted phenyl (**18**−**20**) groups, but these compounds displayed weak GPR120 activity as compared with compound **12**. Among compounds **14**−**20**, compound **16** exhibited a superior selectivity toward GPR120, although the activity of compound **16** is less than that of compound **12**. These results indicate that compound **16** may be a lead compound suitable for further structural optimization. Then, we changed the 2-pyridine ring of compound **12** to other aromatic rings. Phenyl **21**, 2-benzothiazole **22**, and 2-benzoxazole **23** derivatives exhibited GPR120-agonistic activity less potent than that of compound **12**, whereas the 2-thiazole **24** retained the activity and selectivity to some extent, highlighting the importance of the nitrogen atom at the 2-position and of the ring size. Introduction of a methyl group (**25** and **26**) or a chloro group (**27** and **28**) into the 2-pyridine ring resulted in a significant decrease in GPR120 activity or GPR120/GPR40 selectivity.

The dose dependency of compounds **12**, **24**, and α-LA (**1**) is shown in Figure 3, clarifying the GPR120 selectivity of compounds **12** and **24**. The EC_{50} values of compound **12** for GPR120 and GPR40 were 1.2 and 19 μM, respectively, and the selectivity index (SI, GPR40 EC_{50}/GPR120 EC_{50}) was 16, which substantially exceeded that of α-LA (**1**) (SI = 2.0) (Table 4).

Since it has been reported that long-chain FFAs stimulate the extracellular signal-regulated kinase (ERK) and Akt/protein kinase through GPR40 or GPR120,[11] we examined the effects

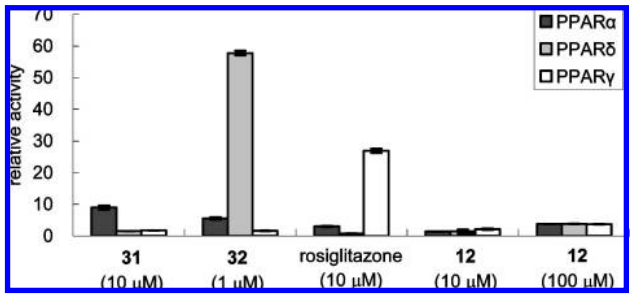


Figure 5. PPAR transactivation activity of compound **12**. [4-Chloro-6-(2,3-xylidino)-2-pyrimidinylthio]acetic acid **31** (WY14643) (PPARα agonist),[12] {2-methyl-4-[4-methyl-2-(4-trifluoromethylphenyl)thiazol-5-ylmethylsulfanyl]phenoxy}acetic acid **32** (GW501516) (PPARδ agonist),[13] and rosiglitazone (PPARγ agonist) were used as positive controls.

of compounds **12** and **24** on the accumulation of phosphorylated ERK (p44/42) in HEK293 cells expressing human GPR40 or human GPR120 by means of Western blotting analysis (see the experimental procedure in the Supporting Information). Consistent with the results obtained in the FLIPR-based assay, compounds **12** and **24** did not activate ERK compared with α-LA (**1**) in HEK293 cells expressing GPR40 but increased the amount of phosphorylated ERK more than did α-LA (**1**) in HEK293 cells expressing GPR120 (Figure 4).

We also examined the agonistic activity of compound **12**, the most potent and selective GPR120 agonist among these compounds, toward PPARs (other long-chain FFA receptors). As a result, compound **12** proved to be totally inactive toward PPARs (Figure 5).

Conclusion

In conclusion, we have identified a GPR120-selective agonist **12**, which was derived from PPARγ agonist **3**. To our knowledge, compound **12** is the first GPR120-selective agonist and therefore represents a lead compound from which it should be possible to develop more potent and selective GPR120 agonists, which are expected to be useful as tools for probing the biology of GPR120 and as candidate therapeutic agents with potentially fewer side effects.

Experimental Section

Synthesis of 4-[4-(2-Bromoethoxy)phenyl]butyric Acid Methyl Ester (30a). To a solution of 4-(4-hydroxyphenyl)butyric acid methyl ester (**29a**) (5.0 g, 25.7 mmol), 2-bromoethanol (3.5 g, 28.0 mmol), and 2.2 M diethyl azodicarboxylate solution in toluene (15.3 mL, 33.7 mmol) in THF (65 mL) was slowly added triphenylphosphine (8.8 g, 33.6 mmol) at 0 °C and the solution was stirred at room temperature for 4 h. After that, the reaction mixture was concentrated in vacuo and purification by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/8) gave 1.50 g (19%) of **30a** as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz, δ; ppm) 7.10 (2H, d, J = 8.9 Hz), 6.84 (2H, d, J = 8.9 Hz), 4.27 (2H, t, J = 6.4 Hz), 3.66 (3H, s), 3.63 (2H, t, J = 6.4 Hz), 2.59 (2H, t, J = 7.6 Hz), 2.32 (2H, t, J = 7.6 Hz), 1.92 (2H, quintet, J = 7.6 Hz).

Synthesis of 4-{4-[2-(Phenyl-2-pyridinylamino)ethoxy]phenyl}butyric Acid (12). To a solution of *N*-phenylpyridin-2-amine (305 mg, 1.79 mmol) in 3 mL of DMF was added NaH (60%, 86 mg, 2.15 mmol), and the mixture was stirred at 60 °C for 30 min. Then, to the reaction mixture were added KI (150 mg, 0.90 mmol) and 4-[4-(2-bromoethoxy)phenyl]butanoic acid methyl ester (**30a**) (539 mg, 1.79 mmol) obtained above, and the mixture was stirred at 80 °C for 2 h. After cooling to room temperature, the reaction mixture was diluted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/6) gave 150 mg (21%) of 4-{4-[2-(phenyl-2-pyridinylamino)ethoxy]phenyl}
butyric acid methyl ester as a colorless oil.

To a solution of 4-{4-[2-(phenyl-2-pyridinylamino)ethoxy]phenyl}butyric acid methyl ester (149 mg, 0.382 mmol) obtained above in 2 mL of MeOH and 2 mL of THF was added aqueous 2 N NaOH (0.6 mL), and the solution was stirred overnight at room temperature. The mixture was neutralized with 0.6 mL of 2 N HCl and concentrated in vacuo. The residue was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 19/1) to give 115 mg (80%) of **12** as a colorless solid: mp 98−99 °C. ^{1}H NMR ($CDCl_3$, 500 MHz, δ; ppm) 8.21 (1H, d, J = 4.0 Hz), 7.41 (2H, t, J = 7.3 Hz), 7.33 (2H, d, J = 7.4 Hz), 7.30−7.20 (2H, m), 7.04 (2H, d, J = 8.6 Hz), 6.79 (2H, d, J = 8.6 Hz), 6.60 (1H, t, J = 7.0 Hz), 6.41 (1H, d, J = 8.9 Hz), 4.32 (2H, t, J = 5.2 Hz), 4.26 (2H, t, J = 5.8 Hz), 2.59 (2H, t, J = 7.4 Hz), 2.34 (2H, t, J = 7.4 Hz), 1.91 (2H, quintet, J = 7.4 Hz). MS (EI) m/z: 376 (M^+). HRMS calcd for $C_{23}H_{24}N_2O_3$ 376.179, found 376.178. Anal. ($C_{23}H_{24}N_2O_3$) C, H, N.

Synthesis of 4-{4-[2-(*n*-Butyl-2-pyridinylamino)ethoxy]phenyl}butyric Acid (14). A solution of 4-[4-(2-bromoethoxy)phenyl]butyric acid methyl ester (**30a**) (956 mg, 3.17 mmol), *N*-*n*-butylpyridin-2-amine[7] (1.4 g, 9.32 mmol), Et_3N (0.88 mL, 6.33 mmol), and KI (530 mg, 3.19 mmol) in THF (3 mL) was stirred overnight at reflux temperature. After cooling to room temperature, the reaction mixture was diluted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Filtration, concentration in vacuo, and purification by silica gel flash column chromatography (AcOEt/*n*-hexane = 1/6) gave 272 mg (23%) of 4-{4-[2-(*n*-butyl-2-pyridinylamino)ethoxy]phenyl}butyric acid methyl ester as a colorless oil.

To a solution of 4-{4-[2-(*n*-butyl-2-pyridinylamino)ethoxy]phenyl}butyric acid methyl ester methyl ester (272 mg, 0.734 mmol) obtained above in 4 mL of MeOH and 4 mL of THF was added aqueous 2 N NaOH (1.1 mL), and the solution was stirred overnight at room temperature. The mixture was neutralized with 1.1 mL of 2 N HCl and concentrated in vacuo. The residue was purified by silica gel flash column chromatography ($CHCl_3$/MeOH = 19/1) to give 128 mg (49%) of **14** as colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz, δ; ppm) 8.14 (1H, d, J = 4.0 Hz), 7.41 (1H, dt, J = 1.9, 7.1 Hz), 7.06 (2H, d, J = 8.6 Hz), 6.82 (2H, d, J = 8.5 Hz), 6.51 (1H, t, J = 4.9 Hz), 6.50 (1H, d, J = 7.4 Hz), 4.14 (2H, t, J = 6.1 Hz), 3.91 (2H, t, J = 5.8 Hz), 3.49 (2H, t, J = 7.7 Hz), 2.60 (2H, t, J = 7.3 Hz), 2.34 (2H, t, J = 7.3 Hz), 1.92 (2H, quintet, J = 7.7 Hz), 1.62 (2H, quintet, J = 7.7 Hz), 1.37 (2H, sextet, J = 7.7 Hz), 0.96 (3H, t, J = 7.3 Hz). MS (EI) m/z: 356 (M^+). HRMS calcd for $C_{21}H_{28}N_2O_3$ 356.210, found 356.211.

Compounds **13** and **16**−**28** were prepared from **30** and an appropriate amine using the procedure described for **12**, and compound **15** was prepared from **30a** and *N*-benzylpyridin-2-amine using the procedure described for **14**.

Compounds **3**−**11** were available in our laboratories and have been previously described.[7]

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Supporting Information Available: Experimental details for the synthesis of compounds **12**−**28**, spectroscopic data, elemental analysis results, experimental procedures for the biological testing, and a brief description of the molecular modeling. This material is available free of charge via the Internet at http://pubs.acs.org.

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