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ARTICLE

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Design, Synthesis, and Biological Activity of Potent and Orally Available G Protein-Coupled Receptor 40 Agonists

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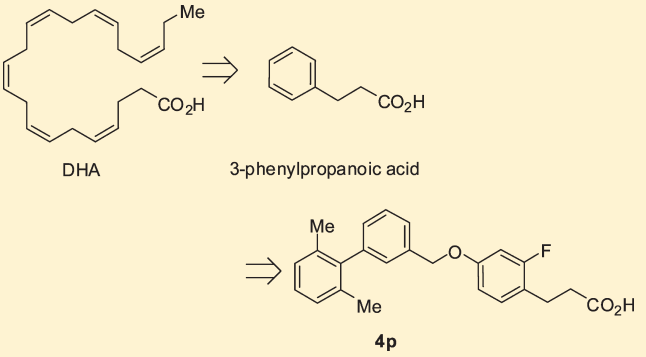
ABSTRACT: G protein-coupled receptor 40 (GPR40) is being recently considered to be a new potential drug target for the treatment of type 2 diabetes because of its role in the enhancement of free fatty acid-regulated glucose-stimulated insulin secretion in pancreatic β-cells. We initially identified benzyloxyphenylpropanoic acid (**1b**) (EC_{50} = 510 nM), which was designed based on the structure of free fatty acids, as a promising lead compound with GPR40 agonist activity. Chemical modification of compound **1b** led to the discovery of 3-{4-[(2′,6′-dimethylbiphenyl-3-yl)methoxy]-2-fluorophenyl}propanoic acid (**4p**) as a potent GPR40 agonist (EC_{50} = 5.7 nM). Compound **4p** exhibited acceptable pharmacokinetic profiles and significant glucose-lowering effects during an oral glucose tolerance test in diabetic rats. Moreover, no hypoglycemic event was observed even after administration of a high dose of compound **4p** to normal fasted rats. These pharmacological results suggest that GPR40 agonists might be novel glucose-dependent insulin secretagogues with little or no risk of hypoglycemia.



INTRODUCTION

Free fatty acids (FFAs) are not only an important energy source but they play key roles in the regulation of a range of physiological responses, including insulin secretion.[1−7] Acute administration of FFAs promotes glucose-stimulated insulin secretion (GSIS),[1,2] whereas chronic exposure to high levels of FFAs impairs β-cell function by induction of secretory failure and β-cell apoptosis.[3,4] Several possible mechanisms for FFA-amplified GSIS have been proposed, for example, that FFAs might simply provide energy to β-cells or that the intracellular metabolites of FFAs (fatty acyl-coenzyme A molecules) act to stimulate insulin secretion.[5−7] In the past decade, by using the G protein-coupled receptor (GPCR) deorphanizing strategy,[8] several studies have reported that a number of FFAs act as ligands for GPCRs, including GPR40, GPR41, GPR43, and GPR120.[9−13] GPR41 and GPR43 are activated by short-chain FFAs,[12] whereas GPR40 and GPR120 are activated by medium- or long-chain FFAs.[9−11,13] GPR40 is highly expressed in mouse, rat, and human pancreatic β-cells and is also found in several areas of the human brain.[9−11] GPR40 couples mainly with a G protein α-subunit of the Gq family (Gαq) and has been shown to amplify GSIS from pancreatic β-cells only under high-glucose concentration.[9]

Impaired insulin secretion is one of the major causes of type 2 diabetes, and several insulin secretagogues, such as sulfonylureas and glinides, are commonly used for its treatment.[14] However, these drugs promote insulin secretion independent of blood glucose levels, thereby leading to the risk of hypoglycemia and β-cell dysfunction.[14,15] The above-mentioned findings suggest that activation of GPR40 may lead to the enhancement of insulin secretion in a glucose-dependent manner and that small molecule agonists of GPR40 may serve as novel insulin secretagogues with little or no risk of hypoglycemia.

Recently, several studies have reported GPR40 agonists that contain acidic moieties such as a carboxylic acid or thiazolidinedione.[16,17] However, in 2002, we independently identified a range of synthetic agonists by ligand-based drug design methods.[18,19] We had previously reported that saturated and unsaturated long-chain FFAs have GPR40 agonist activity. Among them, docosahexaenoic acid (DHA), a polyunsaturated fatty acid, showed the most potent activity (EC_{50} = 1.1 μM), whereas the methyl ester of linoleic acid showed no activity (EC_{50} > 300 μM).[9] On the basis of these results, we speculated that both a hydrogen bond interaction of carboxylate and a $\pi-\pi$ interaction of olefin might have a great impact on the receptor−ligand interaction. We selected several commercially available arylalkanoic acids and screened them for their activity by using a fluorometric imaging plate reader (FLIPR) assay. Fortunately, we found that

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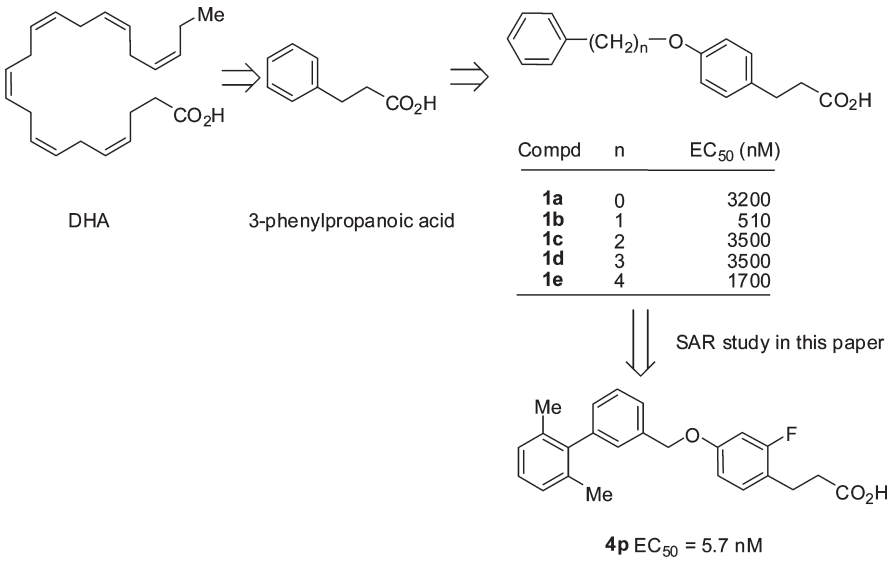
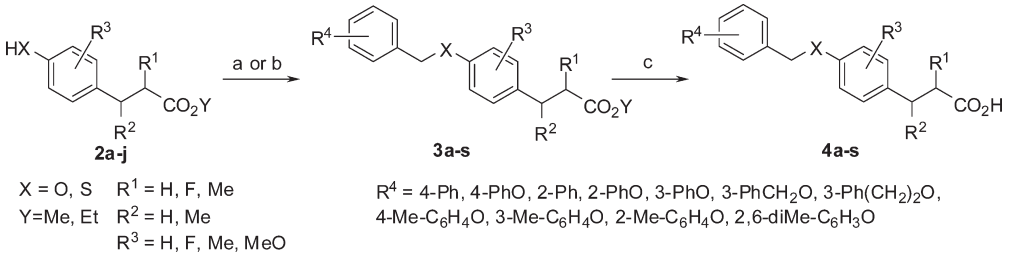


Figure 1. Optimization of GPR40 agonist.

Scheme 1[a]



[a] Reagents and conditions: (a) $R^4C_6H_4CH_2OH$, ADDP, P(*n*-Bu)$_3$, THF, rt; (b) $R^4C_6H_4CH_2Br$, NaH, DMF, 60 °C; (c) 2 M NaOH aq or LiOH aq, MeOH or EtOH, THF, rt, 5−85% (2 steps).

3-phenylpropanoic acid had modest agonist activity at a concentration of 100 μM. On the basis of this result, we synthesized or selected several phenylpropanoic acid derivatives having a phenylalkoxy side chain for an additional $\pi-\pi$ interaction with GPR40 and identified benzyloxyphenylpropanoic acid (**1b**) (EC_{50} = 510 nM) as a promising lead series (Figure 1). The optimization of compound **1b** led to the discovery of compound **4p** as a potent and orally bioavailable GPR40 agonist. In this paper, we describe our early efforts with regard to the synthesis, structure−activity relationship (SAR) study data, and pharmacological effects of phenylpropanoic acid derivatives.

CHEMISTRY

The synthesis of phenylpropanoic acid derivatives having an ether or thioether linker **4a**−**s** is summarized in Scheme 1. The phenoxy or phenylthio derivatives **2a**−**j** was condensed with appropriate alcohols using Mitsunobu reaction or with appropriate alkyl bromides in the presence of a base to give the intermediates **3a**−**s**. Subsequent basic hydrolysis of the intermediates **3a**−**s** afforded the desired carboxylic acids **4a**−**s**.

The biaryl analogues **6a**−**l**, **7**, and **9** were synthesized by standard palladium-catalyzed cross-coupling reactions as shown in Scheme 2. The key intermediate **5** was prepared by Mitsunobu reaction of 3-bromobenzyl alcohol with methyl 3-(4-hydroxyphenyl)propanoate (**2a**). Suzuki−Miyaura cross-coupling of bromide **5** with appropriate arylboronic acids followed by basic hydrolysis provided the biaryl analogues **6a**−**l**. Stille coupling of compound **5** with 2-(trimethylstannyl)pyridine followed by basic hydrolysis afforded pyridyl derivative **7**. Coupling of compound **5** with pinacolborane gave boronic ester **8**. Suzuki coupling of compound **8** with 2-bromothiazole followed by basic hydrolysis provided the thiazolyl derivative **9**.[20]

The synthesis of the 4-aminophenylpropanoic acid derivatives **11** and **12** is depicted in Scheme 3. Reductive amination of 2′,6′-dimethylbiphenyl-3-carbaldehyde (**22**) with methyl 3-(4-aminophenyl)propanoate (**2b**) gave intermediate **10**. Basic hydrolysis of intermediate **10** afforded the corresponding carboxylic acid **11**. Compound **12** was synthesized from intermediate **10** by methylation followed by basic hydrolysis.

Compound **17** was synthesized as shown in Scheme 4. 3-(Bromophenyl)acetic acid (**13**) was converted to the corresponding acyl chloride and then treated with ethyl 3-phenylpropanoate under Friedel−Crafts condition to give ketone **14**. Suzuki coupling of compound **14** with 2,6-dimethylphenylboronic acid followed by basic hydrolysis provided compound **15**. Reduction of the carbonyl group of compound **15** with sodium borohydride followed by dehydration under acidic conditions gave compound **16**. Hydrogenation of the double bond of compound **16** afforded compound **17**.

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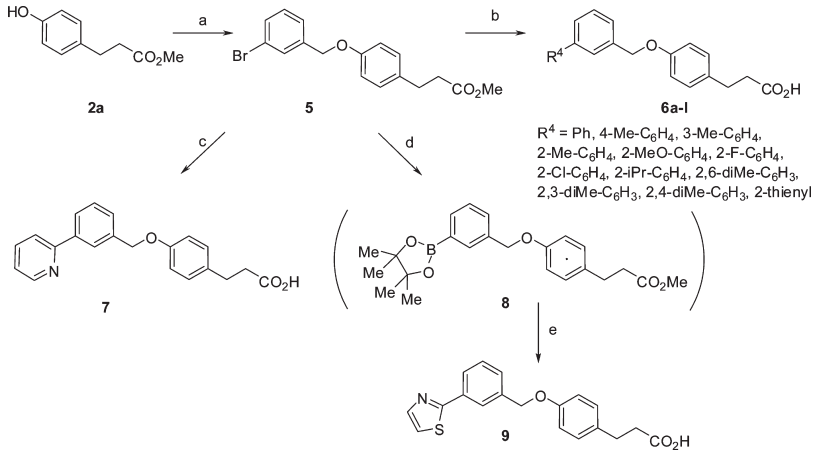
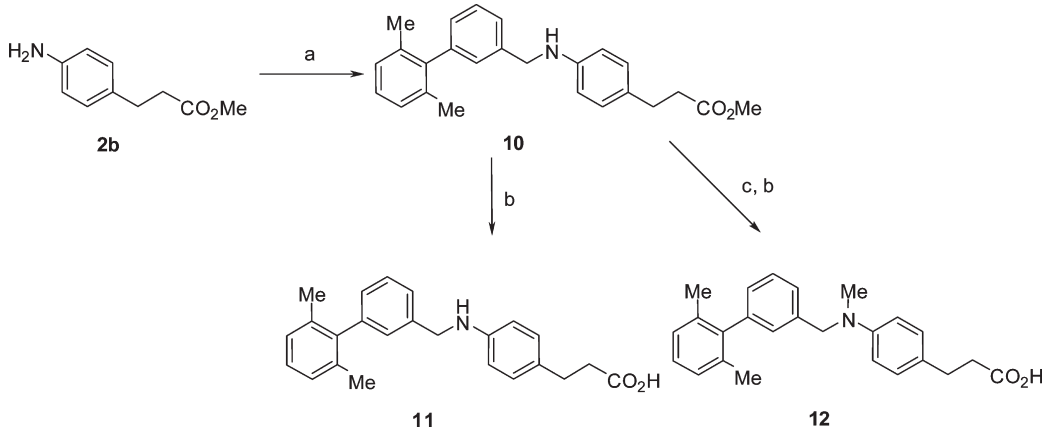
Scheme 2[a]



[a] Reagents and conditions: (a) 3-bromobenzyl alcohol, ADDP, P(*n*-Bu)$_3$, THF, rt, 68%; (b) (i) R^{4}B(OH)$_2$, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, toluene, MeOH, H$_2$O, reflux, (ii) LiOH·H$_2$O, MeOH, THF, H$_2$O, rt, 3−76% (2 steps); (c) (i) 2-(trimethylstannyl)pyridine, PdCl$_2$(PPh$_3$)$_2$, DMF, reflux, (ii) LiOH·H$_2$O, MeOH, THF, H$_2$O, rt, 19% (2 steps); (d) pinacolborane, PdCl$_2$(dppf), triethylamine, toluene, 100 °C; (e) (i) 2-bromothiazole, Pd(PPh$_3$)$_4$, Na$_2$CO$_3$, toluene, MeOH, H$_2$O, reflux, (ii) LiOH·H$_2$O, MeOH, THF, H$_2$O, rt, 31% (3 steps from **5**).

Scheme 3[a]



[a] Reagents and conditions: (a) 2′,6′-dimethylbiphenyl-3-carbaldehyde **22**, 4 Å molecular sieves, toluene, then NaBH$_3$CN, AcOH, THF, rt, 61%; (b) 2 M NaOH aq, MeOH, THF, rt, 57−70%; (c) MeI, K$_2$CO$_3$, acetone, reflux, 48%.

Scheme 5 illustrates the synthesis of benzyl alcohols **20**, **23**, and **25a**−**d**. Suzuki coupling of bromide **18** with 2, 4-dimethylphenylboronic acid followed by reduction of the ester group provided alcohol **20**. Compound **23** was synthesized from bromide **21** and 2,6-dimethylphenylboronic acid in the similar procedure. Ullmann coupling of bromide **21** with appropriate phenols provided the aldehydes **24a**−**d**, which were then reduced with NaBH$_4$ to give the alcohols **25a**−**d**.

The synthesis of the esters **2b**−**j** is outlined in Scheme 6. Esterification of acids **26a**−**b** with MeOH under acidic conditions afforded esters **2b** and **2j**. Heck coupling of bromophenol **27** with methyl acrylate followed by hydrogenation of the double bond provided compound **2c**. Horner−Emmons reaction of the protected benzaldehydes **28a**−**c**, **28e**, and ketone **29** using phosphonoacetate reagents followed by catalytic hydrogenation gave the corresponding phenylpropanoates. The protecting groups were, in case of necessity, subsequently removed[21] to afford the esters **2d**−**i**.

RESULTS AND DISCUSSION

The agonist activities of all synthesized compounds were measured by a FLIPR assay in Chinese hamster ovary (CHO) cells stably expressing human GPR40 in the presence of 0.1% bovine serum albumin (BSA).

As the first step of our chemical modification, we introduced a phenyl group or phenoxy group into the lead compound **1b** to potentiate the agonist activity due to an additional aromatic interactions (e.g., $\pi-\pi$, CH$-\pi$, and cation$-\pi$ interaction) with GPR40 (Table 1). Among the modifications, introduction of a substituent in the C3 position was more effective than that in the C2 or C4 position (**6a** vs **4a** and **4c**; **4e** vs **4b** and **4d**). Extending the length of the linker reduced the potency (**4e** vs **4f** and **4g**). These results indicated that the distance between the terminal benzene ring and the central benzene ring is important for the potent agonist activity. Furthermore, we replaced the terminal phenyl group of compound **6a** with a variety of heteroaromatic

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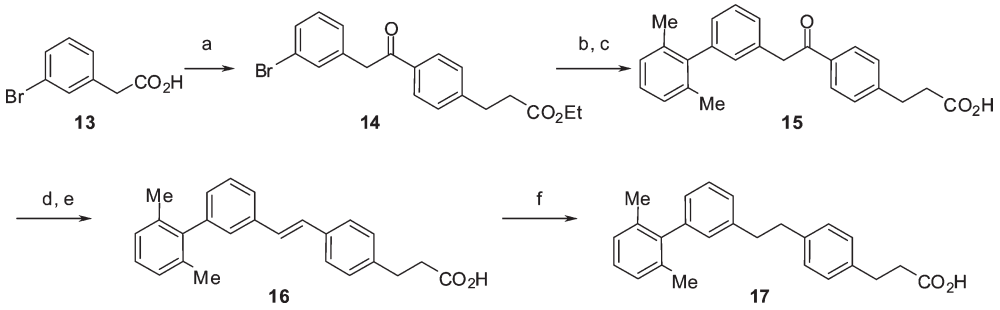
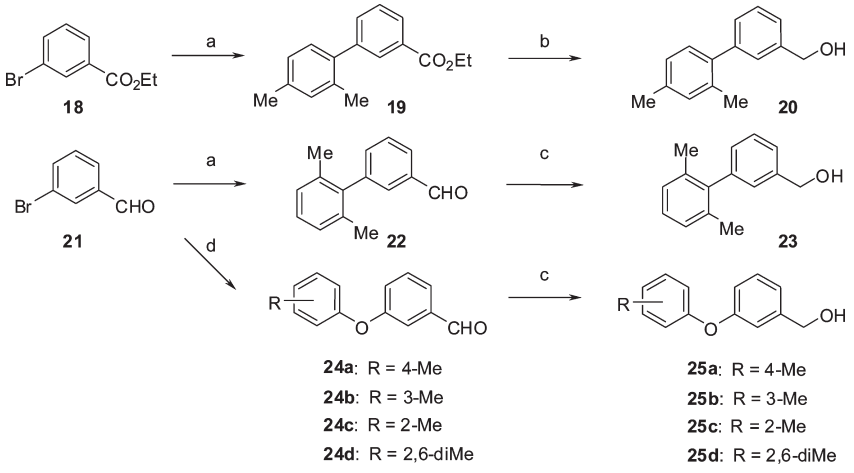
Scheme 4[a]



[a] Reagents and conditions: (a) (i) $(COCl)_2$, DMF, THF, rt, (ii) ethyl 3-phenylpropanoate, $AlCl_3$, nitromethane, rt, 61% (2 steps); (b) 2,6-dimethylphenylboronic acid, Na_2CO_3, $Pd(PPh_3)_4$, toluene, EtOH, H_2O, reflux; (c) 1 M NaOH aq, THF, EtOH, rt, 79% (2 steps); (d) $NaBH_4$, THF, EtOH, 0 °C; (e) *p*-TsOH·H_2O, toluene, reflux, 87% (2 steps); (f) H_2, Pd/C, THF, rt, 77%.

Scheme 5[a]



[a] Reagents and conditions: (a) 2,4-dimethylphenylboronic acid or 2,6-dimethylphenylboronic acid, $Pd(PPh_3)_4$, Cs_2CO_3 or 1 M Na_2CO_3 aq, toluene, EtOH, 70−80 °C, 97−100%; (b) $LiAlH_4$, THF, rt, 96%; (c) $NaBH_4$, DME, THF, 0 °C−rt, 24−84%; (d) RPhOH, CuO, K_2CO_3, pyridine, quinoline, 170 °C, 72−83%.

groups. Although replacement of the phenyl group with a 2-thienyl group maintained activity (**6a** vs **6l**), replacement with a 2-pyridyl group or a 2-thiazolyl group which has a lower Log *D* value was not tolerated (**6a** vs **7** and **9**). These results led us to speculate that the terminal aromatic ring contributed to the aromatic interactions and/or lipophilic interactions with GPR40.

In the next step of our chemical modification, we investigated the influence of substituents on the terminal benzene rings of derivative **4e** and **6a** (Table 2). Introduction of methyl group(s) at different positions of the terminal benzene ring of the phenoxy derivative **4e** hardly affected the agonist activity (**4e** vs **4h**−**k**). In contrast, introduction of a 2-methyl group in the phenyl derivative **6a** drastically increased the potency compared with a 3-methyl or a 4-methyl group (**6d** vs **6b**−**c**). Encouraged by the result of the 2-methyl derivative **6d**, we focused on the investigation of ortho-substituents in the terminal benzene ring of derivative **6a**. Introduction of a slightly smaller 2-fluoro group (**6f**) decreased the activity compared with a 2-methyl derivative **6d**, while incorporation of a bulkier substitution such as a 2-methoxy (**6e**), a 2-chloro (**6g**), or a 2-isopropyl (**6h**) group maintained the potent activity. In addition, introduction of a 2,6-dimethyl (**6i**), a 2,3-dimethyl (**6j**), or a 2,4-dimethyl (**6k**) group maintained the potent activity.

In general, most fatty acids bind to serum albumin under physiological conditions.[23] Owing to the structural similarity to fatty acids, our GPR40 agonists readily bound to serum albumin. For that reason, we measured the agonist activity of selected compounds in both the absence (0%) and the presence (0.5%) of BSA to investigate the influence of binding to serum albumin on the pharmacological activity. As the result, the serum shift of the nonsubstituted biphenyl derivative (**6a** 282-fold) was significantly higher than these of the ortho-substituted biphenyl analogues (**6d** 38-fold and **6i** 36-fold) and the phenoxybenzene analogues (**4e**, **4j**, and **4k** 27−47-fold). Moreover, these effects of the serum shift were comparably correlated with the activity of these compounds (**6a** vs **4e**, **4j**, **4k**, **6d**, and **6i**) in the presence of 0.1% BSA. These results led us to hypothesize that a large dihedral angle of the 2,6-dimethylbiphenyl or the phenoxybenzene core was favorable for binding to the GPR40 receptor but on the other hand was unfavorable for binding to serum albumin. Conformational analyses of simple fragments (biphenyl, 2,6-dimethylbiphenyl, and phenoxybenzene) were performed using the MNDO-PM3 (MOPAC

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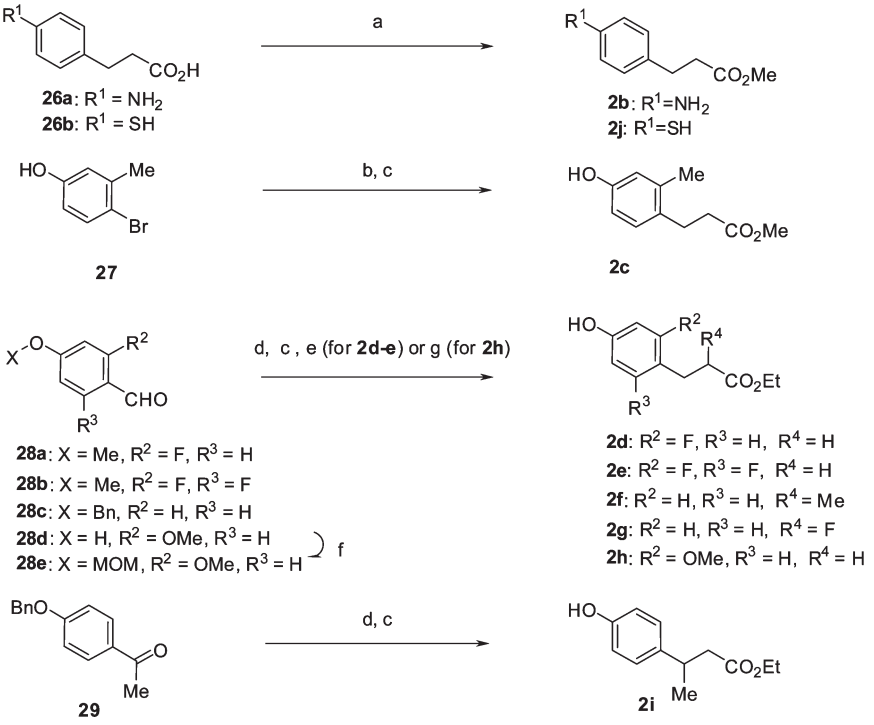
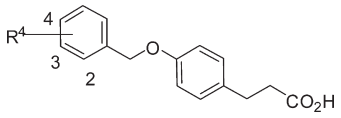
Scheme 6[a]



[a] Reagents and conditions: (a) $SOCl_2$, MeOH, rt, 99% (for **2b**) or H_2SO_4, MeOH, reflux, 86% (for **2j**); (b) methyl acrylate, $Pd(OAc)_2$, Bu_4NCl, DMF, 100 °C, 24−34%; (c) H_2, Pd/C, THF, MeOH or EtOH, 71−100% (for **2c**−**i**); (d) (method A) $(EtO)_2P(O)CH_2CO_2Et$ (for **2d**−**e** and **2h**−**i**) or $(EtO)_2P(O)CH(Me)CO_2Et$ (for **2f**), NaH, THF, (method B) $(EtO)_2P(O)CHFCO_2Et$ (for **2g**), *n*-BuLi, THF, rt, 52−100%; (e) $AlCl_3$, $CH_3(CH_2)_7SH$, CH_2Cl_2, rt, 83−91%; (f) MOMCl, NaH, DMF, 87%; (g) 3 M HCl aq, EtOH, reflux, 44%.

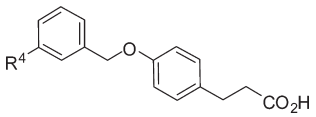
Table 1. Effect of Substituents in the Benzyl Moiety on GPR40 Agonist Activity



compd	R^4	EC_{50} (nM)[a]	Log D[b]	compd	R^4	EC_{50} (nM)[a]	Log D[b]
1b	H	510	1.96	**4f**	3-$PhCH_2O$	300	3.27
4a	4-Ph	300	3.41	**4g**	3-$Ph(CH_2)_2O$	260	3.63
4b	4-PhO	310	3.26	**7**	3-(2-pyridyl)	2700	1.94
4c	2-Ph	3600	3.25	**6l**	3-(2-thienyl)	530	3.22
4d	2-PhO	1100	3.32	**9**	3-(2-thiazolyl)	2700	2.11
6a	3-Ph	260	3.37				
4e	3-PhO	34	3.26				

[a] All values are averages of $n = 3$ in the presence of 0.1% BSA. [b] The Log D values were determined at pH 7.4 according to the reported method.[22]

Table 2. Effect of Substituents in the Terminal Benzene Ring on GPR40 Agonist Activity



compd	R^4	EC_{50} (nM)[a]	compd	R^4	EC_{50} (nM)[a]
4e	PhO	34	**6e**	2-MeO-C_6H_4	82
4h	4-Me-C_6H_4O	40	**6f**	2-F-C_6H_4	120
4i	3-Me-C_6H_4O	45	**6g**	2-Cl-C_6H_4	20
4j	2-Me-C_6H_4O	38	**6h**	2-^{i}Pr-C_6H_4	30
4k	2,6-diMe-C_6H_3O	47	**6i**	2,6-diMe-C_6H_3	8.8
			6j	2,3-diMe-C_6H_3	19
6a	Ph	260	**6k**	2,4-diMe-C_6H_3	9.9
6b	4-Me-C_6H_4	120			
6c	3-Me-C_6H_4	240			
6d	2-Me-C_6H_4	27			

[a] All values are averages of $n = 3$ in the presence of 0.1% BSA.

version 7.01) method in MOE.[24] The global minimum conformations are shown in Figure 2. The dihedral angle of biphenyl (orange) was almost planar, while that of 2,6-dimethylbiphenyl (green) and phenoxybenzene (blue) were orthogonal. These results were consistent with our hypothesis mentioned above.

Next, we examined the effects of a linker atom (X) between the biphenylylmethyl and the phenyl propanoic acid moiety (Table 3). Replacement of the oxygen atom (**6i**) with a nitrogen atom (**11**) maintained potent activity, whereas replacement with a carbon atom (**17**) and with a sulfur atom (**4l**) markedly reduced the agonist activity. These results suggest that the length of the

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linker region ($-CH_2X-$) is very important for the potent agonist activity. Moreover, introduction of a methyl group (**12**) on the nitrogen atom of compound **11** reduced the potency, implying that the substituent on the nitrogen atom may introduce an unfavorable steric interaction due to the limited space in the binding pocket.

While the compounds **6i** and **11** exhibited potent activities, unfortunately, these compounds showed poor PK profiles with high clearance (CLtotal) (**6i** 4816 mL/h/kg; **11** 1691 mL/h/kg) in rats. In addition, a β-oxidation product (**6i-1**) and its taurine conjugate (**6i-2**) were presumed to be major metabolites in the rat plasma and liver after oral administration of compound **6i** (10 mg/kg) as shown in Figure 3.

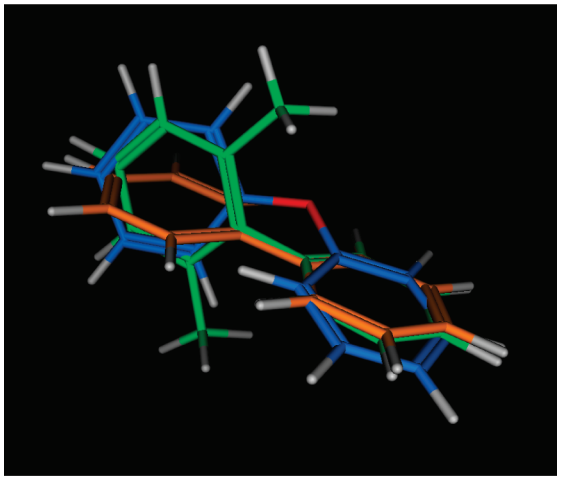
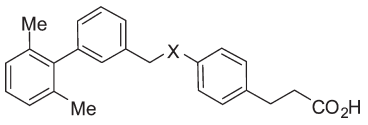


Figure 2. Overlap of minimized structures: 2,6-dimethylbiphenyl (carbon atoms colored green), biphenyl (orange), and phenoxybenzene (blue).

Table 3. Effect of a Linker Atom (X) on GPR40 Agonist Activity



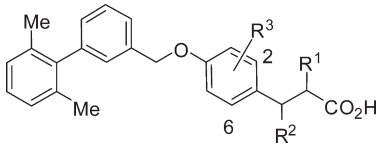
compd	X	EC_{50} (nM)[a]
6i	O	8.8
11	NH	6.3
12	NMe	520
17	CH_2	320
4l	S	1800

[a] All values are averages of $n = 3$ in the presence of 0.1% BSA.

Therefore, to block β-oxidation of compound **6i**, we focused on chemical modifications of the phenylpropanoic acid moiety (Table 4). Introduction of a fluoro group in the α-position of the carboxylic acid moiety remarkably reduced the activity (**6i** vs **4m**), indicating that an increasing acidity is unfavorable (calculated pK_a: **6i** = 4.7; **4m** = 2.6). Furthermore, introduction of a methyl group in either the α- or β-position reduced the activity (**6i** vs **4n** and **4o**). Next, we turned our attention to the effect of the substituent in the benzene ring of the phenylpropanoic acid moiety. Introduction of a fluoro group in the 2-position of the benzene ring maintained the potency (**6i** vs **4p**). Moreover, an additional incorporation of a fluoro group in the 6-position of compound **4p** reduced the activity (**4p** vs **4s**). Our hypothesis is that the benzene ring of the phenylpropanoic acid moiety plays a key role in the $\pi-\pi$ interaction with the GPR40 receptor. This interaction most likely contributes to the potent activity seen for this series. Therefore, we hypothesize that the drop in potency seen with compound **4s** is due to a decreased electron density of the benzene ring. However, introduction of a bulkier substituent in this position reduced the activity (**4p** vs **4q**−**r**). One possible explanation is that incorporation of a bulkier substituent moves the propanoic acid moiety into a different and less favorable conformation.

On the other hand, these steric or electronic effects of the substituents drastically improved the PK profiles with reduced

Table 4. Effect of Substituents in the Phenylpropanoic Acid Moiety on GPR40 Agonist Activity and Pharmacokinetic Profile[a]



compd	R^1	R^2	R^3	EC_{50} (nM)[b]	CL_{total} (mL/h/kg)	C_{max} (ng/mL)	AUC_{0-8h} (ng·h/mL)	F (%)
6i	H	H	H	8.8	4816	5.3	2.0	0.9
4m	F	H	H	170	528	300.9	1264.1	61.2
4n	Me	H	H	170	1136	268.7	848.4	94.0
4o	H	Me	H	32	914	256.2	1188.8	87.2
4p	H	H	2-F	5.7	900	86.0	249.0	21.5
4q	H	H	2-Me	30	187	939.5	4637.9	85.2
4r	H	H	2-MeO	30	42	1593.7	10275.3	40.3
4s	H	H	2,6-diF	35	207	472.8	2618.8	54.2

[a] Rat cassette dosing at 0.1 mg/kg, iv and 1 mg/kg, po. Average of 3 rats. [b] All values are averages of $n = 3$ in the presence of 0.1% BSA.

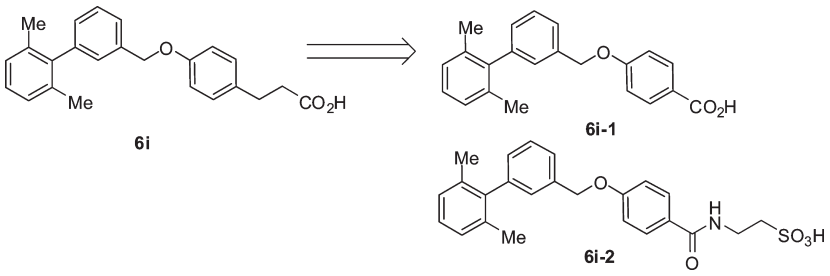


Figure 3. Presumed structures of metabolites in the plasma and liver after oral administration of compound **6i** at a dose of 10 mg/kg to rats.

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plasma clearance compared to the original compound **6i** (**6i** vs **4m**−**s**). These results demonstrate the utility of our strategy to improve PK profiles by introduction of substituents in the phenylpropanoic acid moiety. One of the speculations for the improved PK profiles of these compounds is that they might be resistant to β-oxidation, as we hypothesized above. Among them, the most potent compound (**4p**) (EC_{50} = 5.7 nM) showed moderate bioavailability (F = 21.5%). To assess the utility of compound **4p** as a tool compound for in vivo studies, we examined a direct insulinotropic effect of compound **4p**. Compound **4p** enhanced glucose-stimulated insulin secretion (GSIS) in rat insulinoma INS-1 833/15 cells (EC_{50} = 0.38 μM) and rat isolated pancreatic islets (at 3 μM) (data not shown). Encouraged by these results, compound **4p** was selected to test the antidiabetic efficacy in rats.

In vivo efficacy of compound **4p** was evaluated by the oral glucose tolerance test (OGTT) in male N-STZ-1.5 rats, a model for nonobese type 2 diabetes with impaired insulin secretion.[25] As a result, compound **4p** apparently reduced glucose excursion at doses above 3 mg/kg (Figure 4A) in parallel with increased insulin levels in the early phase (Figure 4B) when administered 0.5 h before an oral glucose challenge (1 g/kg). Similarly, outstanding efficacy of compound **4p** (3 mg/kg) was observed in female Wistar fatty rats, a model that develops obesity and obesity-related features such as impaired glucose tolerance, hyperinsulinemia, and hyperlipidemia[26] (data not shown). In addition, the risk of hypoglycemia was assessed in fasted healthy Sprague−Dawley rats by oral administration of compound **4p** (30 mg/kg) and nateglinide (50 mg/kg), a well-known nonsulfonylurea rapid insulin secretagogue which acts on the ATP-sensitive potassium channel in pancreatic β-cells.[27] As expected, with the glucose-dependent insulinotropic action of the GPR40 agonists,[9,28] no significant differences were observed in the normal fasting glucose levels between compound **4p**-treated and control groups despite the remarkable hypoglycemic effects seen in the nateglinide-treated group (Figure 5A). Nateglinide also potently enhanced plasma insulin levels in these rats, while compound **4p** showed a slight increase in plasma insulin levels which did not affect plasma glucose levels (Figure 5B). These results indicate that compound **4p** may be a novel glucose-dependent insulin secretagogue with little or no risk of hypoglycemia.

CONCLUSION

Optimization of the lead compound **1b**, which was identified from FFAs by ligand-based drug design, led to the discovery of the phenylpropanoic acid derivative **4p** as a potent and orally bioavailable GPR40 agonist. The important aspects that led to the discovery of compound **4p** were as follows: (1) introduction of ortho-substituents in the terminal benzene ring of compound **6a** increased the agonist activities and reduced serum shifts, and (2) introduction of a substituent in the phenylpropanoic acid moiety dramatically improved PK profiles with reduced plasma clearance. Compound **4p** showed a significant glucose-lowering effect during OGTT in diabetic rats. In addition, oral administration of compound **4p** in healthy rats neither increased insulin secretion nor changed the normal fasting blood glucose levels, even at a high dose. These results indicated that GPR40 agonists may be safe insulin secretagogues with little or no risk of hypoglycemia. To improve the PK profiles, further optimizations

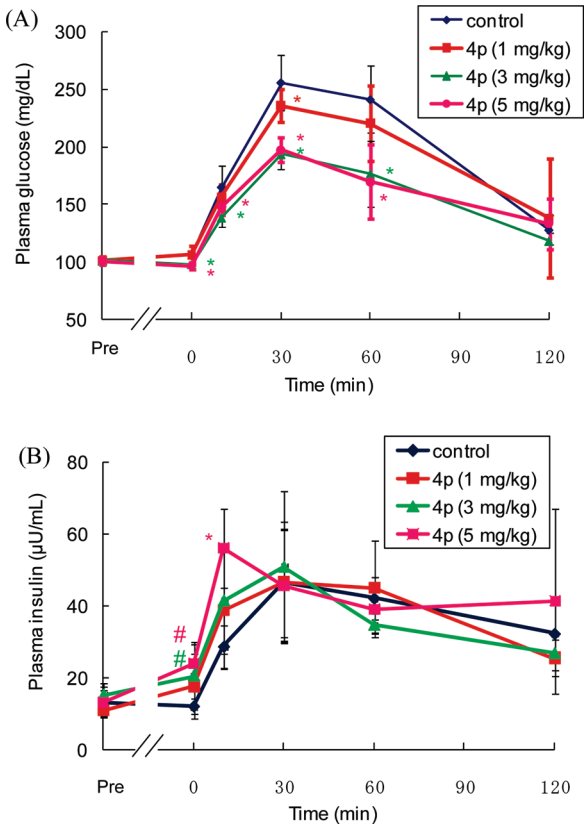

Figure 4. Effects of compound **4p** on plasma glucose and insulin levels during an OGTT in male N-STZ-1.5 rats. (A) and (B) show time-dependent changes of plasma glucose and plasma insulin levels after oral administration of compound **4p** followed by 1 g/kg oral glucose challenge, respectively. Values are mean ± SD (n = 6). *:$p \leq 0.025$ versus control by one-tailed Williams' test. *:$p \leq 0.025$ versus control by Shirley-Williams' test.

of the phenylpropanoic acid moiety of compound **4p** were performed, which was published recently.[29]

EXPERIMENTAL SECTION

Melting points were determined on a BÜCHI B-545 melting point apparatus and were uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Ultra Shield-300 (300 MHz) instruments. Chemical shifts are given in parts per million (ppm) with tetramethylsilane as an internal standard. Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublets of doublet, br = broad. Coupling constants (J values) are given in hertz (Hz). Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd. and were within 0.4% of the theoretical values unless otherwise noted. Low-resolution mass spectra (MS) were determined on a Waters liquid chromatography−mass spectrometer system (MS), using a CAPCELL PAK UG-120 ODS (Shiseido Co., Ltd.) column (2.0 mm i.d. × 50 mm) with aqueous CH_3CN (10−95%) containing 0.05% trifluoroacetic acid (TFA) and an HP-1100 (Agilent Technologies) apparatus for monitoring at 220 nm. All MS experiments were performed using electrospray ionization (ESI) in positive ion mode. Analytical HPLC was performed on a Shimadzu LC-VP instrument, equipped with CAPCELL PAK C18 UG120 S-3 μm, 2.0 mm × 50 mm column with a 4 min linear gradient from 90/10 to 5/95 and subsequently with a 1.5 min isocratic elution 5/95 A/B, where A = H_2O−0.1%TFA, B = CH_3CN−0.1%TFA, at a flow rate of 0.5 μL/min, with UV detection at 220, at column temperature of 25 °C. Reaction

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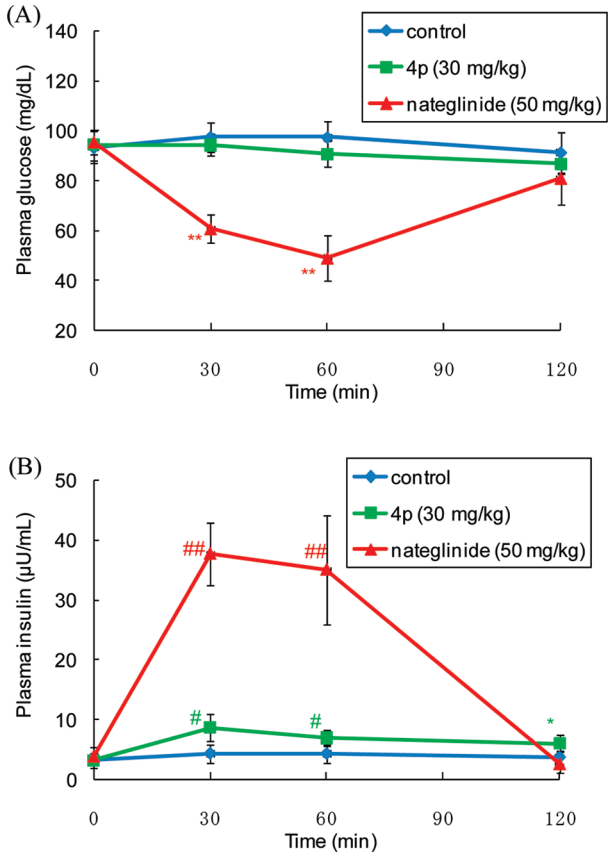

Figure 5. Effects of compound **4p** (30 mg/kg, po) and nateglinide (50 mg/kg, po) on fasting plasma glucose and insulin levels in healthy Sprague−Dawley rats. (A) and (B) show time-dependent changes of plasma glucose and plasma insulin level after oral administration of compound **4p** or nateglinide, respectively. Values are mean ± SD (n = 6). *: $p \leq 0.05$ and **: $p \leq 0.01$ versus control by Dunnett's test. #: $p \leq 0.05$ and ##: $p \leq 0.01$ versus control by Steel test.

progress was determined by thin layer chromatography (TLC) analysis on Merck Kieselgel 60 F254 plates or Fuji Silysia NH plates. Chromatographic purification was carried out on silica gel columns [(Merck Kieselgel 60, 70−230 mesh or 230−400 mesh, Merck) or (Chromatorex NH-DM 1020, 100−200 mesh)] or on Purif-Pack (SI 60 μm or NH 60 μm, Fuji Silysia Chemical, Ltd.). The purities of all compounds tested in biological systems were assessed as being >95% using analytical HPLC or elemental analyses.

3-[4-(Biphenyl-4-ylmethoxy)phenyl]propanoic Acid (4a). Step 1: To a solution of methyl 3-(4-hydroxyphenyl)propanoate (**2a**) (500 mg, 2.06 mmol) in DMF (10 mL) was added sodium hydride (NaH) (60% in oil, 144 mg, 3.61 mmol). After stirring for 0.5 h, 4-(bromomethyl)biphenyl (753 mg, 3.05 mmol) was added to the solution. After stirring at 60 °C for 5 h, the reaction mixture was poured into water. The organic materials were extracted with THF and EtOAc. The extract was washed with water and brine, dried over magnesium sulfate ($MgSO_4$), and concentrated to give **3a** as a colorless oil. Step 2: A mixture of **3a** and 2 M NaOH (10 mL, 20 mmol) in MeOH (30 mL) was stirred for 6 h under refluxed condition. After concentration, the mixture was diluted with water, acidified with aqueous HCl, and extracted with EtOAc. The extract was dried over $MgSO_4$ and concentrated. The residue was recrystallized from THF−hexane to give **4a** (60 mg, 11%) as colorless crystals; mp 187−189 °C. ^{1}H NMR ($CDCl_3$) δ 2.66 (t, J = 7.7 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 5.08 (s, 2H), 6.93 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.30−7.50 (m, 5H), 7.50−7.60 (m, 4H). Anal. Calcd for $C_{22}H_{20}O_3 \cdot 0.5\,H_2O$: C, 77.40; H, 6.20. Found: C, 77.25; H, 6.17.

3-{4-[(4-Phenoxybenzyl)oxy]phenyl}propanoic Acid (4b). Step 1: To a solution of (4-phenoxyphenyl)methanol (300 mg, 1.50 mmol) and **2a** (324 mg, 1.80 mmol) in THF (20 mL) were added tributylphosphine (607 mg, 3.00 mmol) and 1,1′-(azodicarbonyl)-dipiperidine (757 mg, 3.00 mmol). After stirring overnight, the mixture was concentrated and diluted with diisopropyl ether (i-Pr_2O). The precipitate was filtered off, washed with i-Pr_2O, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 12/1) to give **3b** (500 mg, 92%) as a white powder. Step 2: A mixture of **3b** (490 mg, 1.35 mmol) and litium hydroxide monohydrate ($LiOH \cdot H_2O$) (170 mg, 4.06 mmol) in THF (12 mL), MeOH (8 mL), and water (8 mL) was stirred at room temperature for 3 h. The mixture was diluted with water, neutralized with aqueous HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOAc−hexane to give **4b** (242 mg, 51%) as colorless crystals; mp 144−145 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 5.00 (s, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.00−7.03 (m, 4H), 7.08−7.15 (m, 3H), 7.34 (t, J = 8.3 Hz, 2H), 7.39 (d, J = 8.6 Hz, 2H). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.79; H, 5.73.

3-[4-(Biphenyl-2-ylmethoxy)phenyl]propanoic Acid (4c). Compound **4c** was prepared in a manner similar to that described for **4a** in 23% yield as colorless crystals; mp 103−104 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.63 (t, J = 7.9 Hz, 2H), 2.88 (t, J = 7.9 Hz, 2H), 4.91 (s, 2H), 6.79 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.6 Hz, 2H), 7.33−7.50 (m, 8H), 7.60−7.70 (m, 1H). Anal. Calcd for $C_{22}H_{20}O_3 \cdot 0.1H_2O$: C, 79.07; H, 6.09. Found: C, 79.00; H, 6.11.

The following compounds **4d**−**s** were also prepared as described for **4b** from the appropriate alcohols and **2a**−**i** as colorless crystals.

3-{4-[(2-Phenoxybenzyl)oxy]phenyl}propanoic Acid (4d). Yield 43%; mp 114−115 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.63 (t, J = 7.9 Hz, 2H), 2.89 (t, J = 7.9 Hz, 2H), 5.13 (s, 2H), 6.86−6.92 (m, 3H), 6.95−7.00 (m, 2H), 7.06−7.12 (m, 3H), 7.16 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 7.24−7.36 (m, 3H), 7.58 (dd, J = 7.5 Hz, 1.4 Hz, 1H). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.67; H, 5.86.

3-{4-[(3-Phenoxybenzyl)oxy]phenyl}propanoic Acid (4e). Yield 33%; mp 94−95 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.64 (t, J = 7.9 Hz, 2H), 2.90 (t, J = 7.9 Hz, 2H), 5.01 (s, 2H), 6.86−6.90 (m, 2H), 6.88−6.98 (m, 1H), 7.00−7.03 (m, 2H), 7.08−7.17 (m, 5H), 7.30−7.36 (m, 3H). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.68; H, 5.77.

3-(4-{[3-(Benzyloxy)benzyl]oxy}phenyl)propanoic Acid (4f). Yield 67%; mp 107−108 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.9 Hz, 2H), 2.90 (t, J = 7.9 Hz, 2H), 5.01 (s, 2H), 5.07 (s, 2H), 6.87−6.94 (m, 3H), 7.01 (d, J = 7.6 Hz, 1H), 7.06−7.13 (m, 3H), 7.26−7.45 (m, 6H). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.20; H, 6.21.

3-(4-{[3-(2-Phenylethoxy)benzyl]oxy}phenyl)propanoic Acid (4g). Yield 41%; mp 96−97 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.64 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 3.09 (t, J = 7.1 Hz, 2H), 4.18 (t, J = 7.1 Hz, 2H), 5.00 (s, 2H), 6.83−6.92 (m, 3H), 6.97−7.00 (m, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.21−7.35 (m, 6H). Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.30; H, 6.26.

3-(4-{[3-(4-Methylphenoxy)benzyl]oxy}phenyl)propanoic Acid (4h). Yield 50%; mp 133−134 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 4.99 (s, 2H), 6.86−6.93 (m, 5H), 7.05 (s, 1H), 7.10−7.15 (m, 5H), 7.31 (t, J = 7.8 Hz, 1H). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.18; H, 6.24.

3-(4-{[3-(3-Methylphenoxy)benzyl]oxy}phenyl)propanoic Acid (4i). Yield 32%; mp 94−95 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.65 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 5.01 (s, 2H), 6.79−6.96 (m, 6H), 7.06−7.24 (m, 5H), 7.33 (t, J = 7.8 Hz, 1H). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.31; H, 6.23.

3-(4-{[3-(2-Methylphenoxy)benzyl]oxy}phenyl)propanoic Acid (4j). Yield 15%; mp 105−106 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.65 (t, J = 7.8 Hz, 2H), 2.90 (t, J = 7.8 Hz, 2H), 4.99 (s, 2H), 6.79−6.94 (m, 4H), 6.98 (m, 1H), 7.03−7.21 (m, 5H), 7.21−7.33 (m, 2H). Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 75.92; H, 6.21.

3-(4-{[3-(2,6-Dimethylphenoxy)benzyl]oxy}phenyl)propanoic Acid (4k). Yield 32%; mp 132−133 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 6H), 2.65 (t, J = 7.8 Hz, 2H), 2.90 (t, J = 7.8 Hz, 2H), 4.97 (s, 2H), 6.67 (dd, J = 2.1, 7.8 Hz, 1H), 6.81−6.91 (m, 3H), 7.00−7.15 (m, 6H), 7.24 (t, J = 7.8 Hz, 1H). Anal. Calcd for $C_{24}H_{24}O_4 \cdot 0.1H_2O$: C, 75.84; H, 6.39. Found: C, 75.73; H, 6.43.

3-(4-{[(2′,6′-Dimethylbiphenyl-3-yl)methyl]sulfanyl}phenyl)-propanoic Acid (4l). Yield 58%; mp 100−101 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 6H), 2.62 (t, J = 7.7 Hz, 2H), 2.89 (t, J = 7.7 Hz, 2H), 4.09 (s, 2H), 6.97−7.01 (m, 2H), 7.04−7.09 (m, 4H), 7.11−7.17 (m, 1H), 7.20−7.29 (m, 3H), 7.31−7.36 (m, 1H). Anal. Calcd for $C_{24}H_{24}O_2S \cdot 0.2H_2O$: C, 75.83; H, 6.47. Found: C, 75.84; H, 6.44.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]phenyl}-2-fluoropropanoic Acid (4m). Yield 34%; mp 143−144 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 6H), 2.98−3.37 (m, 2H), 4.97−5.26 (m, 3H), 6.93 (d, J = 8.5 Hz, 2H), 7.05−7.22 (m, 7H), 7.34−7.50 (m, 2H). Anal. Calcd for $C_{24}H_{23}FO_3$: C, 76.17; H, 6.13. Found: C, 76.01; H, 6.11.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]phenyl}-2-methylpropanoic Acid (4n). Yield 30%; mp 95−96 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J = 6.6 Hz, 3H), 2.01 (s, 6H), 2.58−2.76 (m, 2H), 3.00 (dd, J = 13.2, 6.3 Hz, 1H), 5.09 (s, 2H), 6.87−6.92 (m, 2H), 7.07−7.20 (m, 7H), 7.38−7.47 (m, 2H). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.21; H, 6.94.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]phenyl}butanoic Acid (4o). Yield 45%; mp 143−144 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 1.28 (d, J = 6.9 Hz, 3H), 2.00 (s, 6H), 2.49−2.66 (m, 2H), 3.15−3.29 (m, 1H), 5.09 (s, 2H), 6.88−6.93 (m, 2H), 7.08−7.19 (m, 7H), 7.38−7.46 (m, 2H). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 79.98; H, 7.04.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]-2-fluorophenyl}propanoic Acid (4p). Yield 29%; mp 107−107.5 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6H), 2.63 (t, J = 7.6 Hz, 2H), 2.90 (t, J = 7.6 Hz, 2H), 5.06 (s, 2H), 6.63−6.70 (m, 2H), 7.06−7.18 (m, 6H), 7.36−7.46 (m, 2H). Anal. Calcd for $C_{24}H_{23}FO_3$: C, 76.17; H, 6.13. Found: C, 76.07; H, 6.09.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]-2-methylphenyl}propanoic Acid (4q). Yield 38%; mp 79−80 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 6H), 2.28 (s, 3H), 2.60 (t, J = 7.8 Hz, 2H), 2.89 (t, J = 7.8 Hz, 2H), 5.08 (s, 2H), 6.73−6.80 (m, 2H), 7.04−7.20 (m, 6H), 7.38−7.46 (m, 2H). Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.18; H, 7.00. Found: C, 80.35; H, 6.75.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]-2-methoxyphenyl}propanoic Acid. (4r). Yield 5%; mp 118−119 °C (from i-Pr_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 6H), 2.62 (t, J = 7.6 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 3.77 (s, 3H), 5.08 (s, 2H), 6.45−6.52 (m, 2H), 7.02−7.21 (m, 6H), 7.38−7.47 (m, 2H). Anal. Calcd for $C_{25}H_{26}O_4 \cdot 0.2H_2O$: C, 76.20; H, 6.75. Found: C, 76.18; H, 6.75.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]-2,6-difluorophenyl}propanoic Acid (4s). Yield 85%; mp 112−113 °C (from Et_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 6H), 2.61 (t, J = 7.8 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 5.06 (s, 2H), 6.50 (d, J = 9.6 Hz, 2H), 7.08−7.48 (m, 7H). Anal. Calcd for $C_{24}H_{22}F_2O_3$: C, 72.71; H, 5.59. Found: C, 72.54; H, 5.64.

Methyl 3-{4-[(3-Bromobenzyl)oxy]phenyl}propanoate (5). Compound **5** was prepared in a manner similar to that described for **4b** (step 1) in 68% yield as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 3.66 (s, 3H), 5.00 (s, 2H), 6.88 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.21−7.27 (m, 1H), 7.34 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H).

3-[4-(Biphenyl-3-ylmethoxy)phenyl]propanoic Acid (6a). Step 1: To a mixture of **5** (600 mg, 1.72 mmol), sodium carbonate (547 mg, 5.16 mol), and phenylboronic acid (251 mg, 2.06 mmol) in toluene (25 mL), MeOH (5 mL), and water (5 mL) was added tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (99 mg, 0.086 mmol) at room temperature. The resulting mixture was refluxed with stirring overnight under argon atmosphere. Then the reaction mixture was concentrated under reduced pressure, diluted with water, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 18/1) to give methyl 3-[4-(biphenyl-3-ylmethoxy)phenyl]propanoate (547 mg, 92%) as a white powder. ^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 3.66 (s, 3H), 5.10 (s, 2H), 6.92 (d, J = 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 7.35−7.47 (m, 5H), 7.54−7.65 (m, 4H). Step 2: A mixture of 3-[4-(biphenyl-3-ylmethoxy)phenyl]propanoate (547 mg, 1.58 mmol) and $LiOH \cdot H_2O$ (199 mg, 4.74 mmol) in THF (9 mL), MeOH (6 mL), and water (6 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water, neutralized with aqueous HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOAc−hexane to give **6a** (253 mg, 48%) as colorless crystals; mp 125−126 °C. ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 5.10 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.30−7.47 (m, 5H), 7.50−7.61 (m, 3H), 7.65 (s, 1H). Anal. Calcd for $C_{22}H_{20}O_3 \cdot 0.3H_2O$: C, 78.22; H, 6.15. Found: C, 77.90; H, 5.88.

The following compounds **6b**−**l** were also prepared as described for **6a** from the appropriate arylboronic acid as colorless crystals.

3-{4-[(4′-Methylbiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6b). Yield 64%; mp 150−151 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.65 (t, J = 7.9 Hz, 2H), 2.90 (t, J = 7.9 Hz, 2H), 5.09 (s, 2H), 6.85−6.96 (m, 2H), 7.13 (d, J = 8.7 Hz, 2H), 7.21−7.29 (m, 2H), 7.35−7.57 (m, 5H), 7.63 (s, 1H). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.49. Found: C, 79.58; H, 6.53.

3-{4-[(3′-Methylbiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6c). Yield 57%; mp 102−103 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.65 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H), 5.10 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.12−7.18 (m, 3H), 7.30−7.47 (m, 5H), 7.54 (dt, J = 7.3 Hz, 1.6 Hz, 1H), 7.64 (s, 1H). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.49. Found: C, 79.53; H, 6.35.

3-{4-[(2′-Methylbiphenyl-3-yl)methoxy]phenyl}propanic Acid (6d). Yield 41%; mp 135−136 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.65 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 5.09 (s, 2H), 6.92 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.23−7.31 (m, 5H), 7.39−7.45 (m, 3H). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.67; H, 6.57.

3-{4-[(2′-Methoxybiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6e). Yield 45%; mp 128−129 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 3.79 (s, 3H), 5.08 (s, 2H), 6.90−7.05 (m, 4H), 7.13 (d, J = 8.6 Hz, 2H), 7.29−7.50 (m, 5H), 7.58 (s, 1H). Anal. Calcd for $C_{23}H_{22}O_4 \cdot 0.25H_2O$: C, 75.29; H, 6.18. Found: C, 75.38; H, 6.28.

3-{4-[(2′-Fluorobiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6f). Yield 58%; mp 112−113 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.66 (t, J = 7.9 Hz, 2H), 2.91 (t, J = 7.9 Hz, 2H), 5.10 (s,

2H), 6.93 (d, J = 8.6 Hz, 2H), 7.12−7.24 (m, 4H), 7.29−7.36 (m, 1H), 7.42−7.54 (m, 4H), 7.61 (s, 1H). Anal. Calcd for $C_{22}H_{19}FO_3$: C, 75.41; H, 5.47. Found: C, 74.33; H, 5.33.

3-{4-[(2′-Chlorobiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6g). Yield 24%; mp 127−128 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 7.8 Hz, 2H), 2.91 (t, J = 7.8 Hz, 2H), 5.10 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.28−7.50 (m, 8H). Anal. Calcd for $C_{22}H_{19}ClO_3$: C, 72.03; H, 5.22. Found: C, 71.92; H, 5.09.

3-(4-{[2′-(1-Methylethyl)biphenyl-3-yl]methoxy}phenyl)-propanoic Acid (6h). Yield 3%; mp 120−121 °C (from Et_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 6H), 2.65 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H), 2.97−3.06 (m, 1H), 5.09 (s, 2H), 6.91 (d, J = 8.6 Hz, 2H), 7.11−7.26 (m, 5H), 7.31−7.45 (m, 5H). Anal. Calcd for $C_{25}H_{26}O_3 \cdot 0.1H_2O$: C, 79.80; H, 7.02. Found: C, 79.87; H, 7.01.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6i). Yield 45%; mp 136−137 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 6H), 2.64 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 5.09 (s, 2H), 6.90 (d, J = 8.6 Hz, 2H), 7.08−7.25 (m, 7H), 7.35−7.50 (m, 2H). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.88; H, 6.74.

3-{4-[(2′,3′-Dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6j). Yield 43%; mp 146−147 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.33 (s, 3H), 2.65 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 5.08 (s, 2H), 6.90−6.93 (m, 2H), 7.09−7.16 (m, 5H), 7.24−7.27 (m, 1H), 7.36−7.42 (m, 3H). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.83; H, 6.73.

3-{4-[(2′,4′-Dimethylbiphenyl-3-yl)methoxy]phenyl}propanoic Acid (6k). Yield 76%; mp 104−105 °C (from Et_2O−hexane) ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H), 2.36 (s, 3H), 2.65 (t, J = 7.6 Hz, 2H), 2.91 (t, J = 7.6 Hz, 2H), 5.08 (s, 2H), 6.91 (d, J = 8.4 Hz, 2H), 7.00−7.46 (m, 9H). Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.97; H, 6.71. Found: C, 79.99; H, 6.78.

3-(4-{[3-(Thiophen-2-yl)benzyl]oxy}phenyl)propanoic Acid (6l). Yield 17%; mp 127−128 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H), 5.07 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.08 (dd, J = 4.5 Hz, 3.5 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.27−7.41 (m, 4H), 7.57 (dt, J = 7.4 Hz, 1.6 Hz, 1H), 7.66 (s, 1H). Anal. Calcd for $C_{20}H_{18}O_3S$: C, 70.98; H, 5.36. Found: C, 70.79; H, 5.26.

3-{4-[(3-Pyridin-2-ylbenzyl)oxy]phenyl}propanoic Acid (7). To a solution of **5** (700 mg, 2.00 mmol) and 2-(trimethylstannyl)pyridine (598 mg, 2.40 mmol) in DMF (20 mL) was added dichlorobis(triphenylphosphane)palladium(II) (70 mg, 0.1 mmol). The mixture was refluxed with stirring overnight under argon atmosphere. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 5/1) to give a colorless oil. A mixture of this oil and $LiOH \cdot H_2O$ (87 mg, 2.01 mmol) in a mixture of THF (9 mL), MeOH (6 mL), and water (6 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water, neutralized with aqueous HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOAc−hexane to give **7** (130 mg, 19% in 2 steps) as colorless crystals; mp 160−161 °C. ^{1}H NMR ($CDCl_3$) δ 2.63 (t, J = 8.0 Hz, 2H), 2.90 (t, J = 8.0 Hz, 2H), 5.12 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.24−7.29 (m, 1H), 7.46−7.52 (m, 2H), 7.71−7.81 (m, 2H), 7.87−7.91 (m, 1H), 8.05 (s, 1H), 8.72−8.75 (m, 1H). Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.67; H, 5.85; N, 4.16.

3-(4-{[3-(1,3-Thiazol-2-yl)benzyl]oxy}phenyl)propanoic Acid (9). To a solution of **5** (0.80 g, 2.3 mmol), pinacolborane (0.50 mL, 3.4 mmol), and triethylamine (0.70 g, 6.9 mmol) in toluene (20 mL) was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($PdCl_2$(dppf)) (0.056 g, 0.069 mmol). The mixture was stirred at 100 °C under argon atmosphere overnight. After cooling to room temperature, the reaction mixture was diluted with aqueous ammonium chloride and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was diluted with toluene (25 mL), MeOH (5 mL), and water (6 mL), and added 2-bromothiazole (0.49 g, 3.0 mmol), sodium carbonate (0.73 g, 6.8 mmol), and $Pd(PPh_3)_4$ (0.13 g, 0.12 mmol) at room temperature. The resulting mixture was refluxed with stirring overnight under argon atmosphere. Then the reaction mixture was diluted with water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 3/1) to give methyl 3-(4-{[3-(1,3-thiazol-2-yl)benzyl]oxy}phenyl)propanonate (310 mg, 38%) as a colorless oil. A mixture of this oil and $LiOH \cdot H_2O$ (110 mg, 2.63 mmol) in a mixture of THF (12 mL), MeOH (9 mL), and water (9 mL) was stirred at room temperature for 3 h. The reaction mixture was diluted with water, neutralized with aqueous HCl, and extracted with EtOAc. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was recrystallized from EtOAc−hexane to give **9** (241 mg, 81%) as colorless crystals; mp 126−127 °C (from EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 2.65 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 8.0 Hz, 2H), 5.10 (s, 2H), 6.93 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 7.35 (d, J = 3.3 Hz, 1H), 7.43−7.52 (m, 2H), 7.88−7.92 (m, 2H), 8.04 (s, 1H). Anal. Calcd for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.18; H, 5.22; N, 3.85.

Methyl 3-(4-{[(2′,6′-Dimethylbiphenyl-3-yl)methyl]amino}-phenyl)propanoate (10). To a solution of **2j** (3.33 g, 18.6 mmol) and **22** (3.91 g, 18.6 mmol) in toluene (40 mL) were added molecular sieves (0.4 nm, beads, 7.2 g), and the mixture was stirred at room temperature for 55 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in THF (100 mL). Sodium cyanoborohydride (2.53 g, 40.3 mmol) and acetic acid (2.31 mL, 40.3 mmol) were successively added, and the mixture was stirred under a nitrogen atmosphere at room temperature for 3 h. The reaction mixture was weakly acidified with 10% aqueous citric acid solution and extracted with EtOAc. The extract was washed with brine, dried over sodium sulfate (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 9/1−3/2) to give **10** (4.24 g, 61%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.56 (t, J = 7.8 Hz, 2H), 2.83 (t, J = 7.8 Hz, 2H), 3.66 (s, 3H), 4.01 (s, 1H), 4.35 (s, 2H), 6.57 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 7.03−7.17 (m, 5H), 7.31−7.34 (m, 1H), 7.39 (t, J = 7.5 Hz, 1H).

3-(4-{[(2′,6′-Dimethylbiphenyl-3-yl)methyl]amino}phenyl)-propanoic Acid (11). To a solution of **10** (0.486 g, 1.30 mmol) in a mixture of MeOH (6 mL) and THF (6 mL) was added 2 M NaOH (2 mL), and the mixture was stirred at room temperature for 21 h. Water was added to the reaction mixture, and the mixture was weakly acidified with 10% aqueous citric acid solution and then extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 70/30−0/100) and recrystallized from EtOAc−hexane to give **11** (0.266 g, 57%) as colorless needle-like crystals; mp 87−88 °C. ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 6H), 2.61 (t, J = 7.7 Hz, 2H), 2.84 (t, J = 7.7 Hz, 2H), 4.35 (s, 2H), 6.57 (d, J = 8.5 Hz, 2H), 6.98−7.17 (m, 7H), 7.30−7.35 (m, 1H), 7.39 (t, J = 7.5 Hz, 1H). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.03; H, 7.20; N, 3.88.

3-{4-[[(2′,6′-Dimethylbiphenyl-3-yl)methyl](methyl)amino]-phenyl}propanoic Acid (12). To a solution of **10** (0.598 g, 1.60 mmol) and iodomethane (0.498 mL, 8.00 mmol) in acetone (10 mL) was added potassium carbonate (0.332 g, 2.40 mmol), and the mixture was heated under reflux under a nitrogen atmosphere for 6 h. After cooling, the

reaction mixture was concentrated under reduced pressure. Water was added to the obtained residue, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 100/0−75/25) to give a yellow oil. To a solution of this oil in a mixture of MeOH (4 mL) and THF (4 mL) was added 2 M NaOH (1.2 mL), and the mixture was stirred at room temperature for 3 days. Water was added to the reaction mixture, and the mixture was weakly acidified with 10% aqueous citric acid solution and extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by HPLC to give **12** (0.198 g, 28% in 2 steps) as a brown viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 6H), 2.61 (t, J = 7.7 Hz, 2H), 2.85 (t, J = 7.7 Hz, 2H), 2.99 (s, 3H), 4.53 (s, 2H), 6.68 (d, J = 8.7 Hz, 2H), 6.98−7.16 (m, 7H), 7.20 (d, J = 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H). MS m/z 374 $(M + H)^+$. HPLC (220 nm) 96.4%.

Ethyl 3-{4-[(3-Bromophenyl)acetyl]phenyl}propanoate (14). (3-Bromophenyl)acetic acid (**13**) (4.00 g, 18.6 mmol) in THF (30 mL) containing a catalytic amount of DMF was treated with oxalyl chloride (2.83 g, 22.3 mmol) at room temperature. After evolution of gas ceased, the reaction mixture was evaporated to dryness, and the residue was dried under vacuum. To a stirred solution of the residue and aluminum chloride (5.46 g, 40.9 mmol) in nitromethane (30 mL), ethyl 3-phenylpropanoate (3.32 g, 18.6 mmol) was added dropwise and the mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with ice-cold 2 M HCl and extracted with EtOAc. The extract was washed successively with water, saturated aqueous sodium bicarbonate ($NaHCO_3$) and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 1/5) to give **14** (4.25 g, 61%) as colorless crystals; mp 69−70 °C. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 2.64 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 8.0 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 4.22 (s2H,), 7.18−7.41 (m, 6H), 7.93 (d, J = 8.2 Hz, 1H). Anal. Calcd for $C_{19}H_{19}BrO_3$: C, 60.81; H, 5.10. Found: C, 60.67; H, 5.05.

3-{4-[(2′,6′-Dimethylbiphenyl-3-yl)acetyl]phenyl}propanoic Acid (15). Compound **15** was prepared in a manner similar to that described for **6a** in 79% yield as colorless crystals; mp 143−144 °C (EtOAc−hexane). ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 6H), 2.69 (t, J = 7.6 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 4.28 (s, 2H), 7.01−7.40 (m, 9H), 7.93 (d, J = 8.4 Hz, 1H).

3-{4-[(*E*)-2-(2′,6′-Dimethylbiphenyl-3-yl)ethenyl]phenyl}-propanoic Acid (16). To a solution of **15** (2.00 g, 5.37 mmol) in EtOH (50 mL) was added sodium borohydride (50 mg, 1.32 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into water, neutralized with 2 M HCl, and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give a white powder. A mixture of the powder, *p*-toluenesulfonic acid monohydrate (0.285 g, 1.90 mmol), and toluene (30 mL) was heated under reflux for 0.5 h. The reaction mixture was concentrated, and the residue was recrystallized from EtOAc−hexane to give **16** as colorless crystals (0.97 g, 87%); mp 178−179 °C. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 6H), 2.69 (t, J = 8.0 Hz, 2H), 2.97 (t, J = 8.0 Hz, 2H), 7.02−7.46 (m, 13H). Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 84.08; H, 7.00.

3-{4-[2-(2′,6′-Dimethylbiphenyl-3-yl)ethyl]phenyl}propanoic Acid (17). Compound **16** (0.40 g, 1.12 mmol) was hydrogenated on 10% palladium on carbon (0.1 g, containing 50% water) in THF (40 mL) under hydrogen atmosphere (balloon pressure) at room temperature overnight. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (acetone−hexane = 1/3−1/2) to give **17** as colorless crystals (0.31 g, 77%); mp 178−179 °C (from Et_2O−hexane). ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 6H), 2.62−2.67 (m, 2H), 2.88−2.93 (m, 6H), 6.87−7.34 (m, 11H). Anal. Calcd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 83.46; H, 7.56.

Ethyl 2′,4′-Dimethylbiphenyl-3-carboxylate (19). Ethyl 3-bromobenzoate (**18**) (4.3 g, 18.8 mmol), 2,4-dimethylphenylboronic acid (3.0 g, 20.0 mmol), and cesium carbonate (9.8 g, 30.0 mmol) were dissolved in a mixture of EtOH (20 mL) and toluene (80 mL). After argon substitution, $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) was added. The reaction mixture was stirred under an argon atmosphere at 70 °C for 18 h. The reaction mixture was cooled, and insoluble material was filtered off through Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc−hexane = 1/10) to give **19** (5.0 g, 100%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.39 (t, J = 7.0 Hz, 3H), 2.23 (s, 3H), 2.37 (s, 3H), 4.38 (q, J = 7.0 Hz, 2H), 7.02−7.54 (m, 5H), 8.00−8.05 (m, 2H).

(2′,4′-Dimethylbiphenyl-3-yl)methanol (20). To a solution of **19** (5.0 g, 19.7 mmol) in anhydrous THF (50 mL) was added lithium aluminum hydride (0.91 g, 24.0 mmol) under ice-cooling, and the mixture was stirred at room temperature for 3 h. The reaction solution was ice-cooled, and sodium sulfate decahydrate (8.0 g, 24.8 mmol) was added. The mixture was stirred at room temperature for 1 h. The precipitated insoluble material was filtered off through Celite, and the filtrate was concentrated under reduced pressure to give **20** as a colorless oil (4.16 g, 96%). ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 2.36 (s, 3H), 4.73 (d, J = 6.0 Hz, 2H), 7.00−7. 45 (m, 7H).

2′,6′-Dimethylbiphenyl-3-carbaldehyde (22). 3-Bromobenzaldehyde (**21**) (18.5 g, 100 mmol) and (2,6-dimethylphenyl)boronic acid (21.0 g, 140 mmol) were dissolved in a mixture of 1 M aqueous sodium carbonate solution (200 mL), EtOH (100 mL), and toluene (200 mL). After argon substitution, $Pd(PPh_3)_4$ (5.78 g, 5.00 mmol) was added. The reaction mixture was stirred under argon atmosphere at 80 °C for 20 h. The reaction mixture was cooled, and water was added to the reaction mixture. The mixture was diluted with EtOAc, and the insoluble material was filtered through Celite. The organic layer of the filtrate was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 0/100−10/90) to give **22** (20.4 g, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.02 (s, 6H), 7.11−7.23 (m, 3H), 7.42−7.46 (m, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.68−7.69 (m, 1H), 7.86−7.90 (m, 1H), 10.06 (s, 1H).

(2′,6′-Dimethylbiphenyl-3-yl)methanol (23). Compound **22** (18.5 g, 88.0 mmol) was dissolved in a mixture of DME (100 mL) and THF (100 mL), and sodium borohydride (1.66 g, 44.0 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 3 h and further stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous HCl and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 0/100−50/90) to give **23** (15.6 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.66 (t, J = 5.9 Hz, 1H), 2.03 (s, 6H), 4.74 (d, J = 5.9 Hz, 2H), 7.07−7.19 (m, 5H), 7.35 (d, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H).

[3-(4-Methylphenoxy)phenyl]methanol (25a). Step 1: To a solution of 4-methylphenol (3.57 g, 33.0 mol) and 3-bromobenzaldehyde (**21**) (5.55 g, 30.0 mmol) in a mixture of pyridine (40 mL) and quinoline (20 mL) under nitrogen were added potassium carbonate (6.22 g, 45.0 mmol) and cupric oxide (3.58 g, 45.0 mol). The mixture was heated at 170 °C with vigorous stirring for 24 h. After cooling, pyridine was evaporated and the residue was diluted with EtOAc. The insoluble material was removed by filtration, and the filtrate was washed with 1 M HCl and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 0/100−10/90) to give 3-(4-methylphenoxy)benzaldehyde **24a** as a yellow oil (5.29 g, 83%). ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 6.94 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.24−7.28 (m, 1H), 7.41−7.43 (m, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.55−7.59 (m, 1H), 9.95 (s, 1H). Step 2: To a solution of **24a** (5.29 g, 24.9 mmol) in THF (30 mL) and DME (30 mL) was added portionwise sodium borohydride (473 mg, 12.5 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was poured into 1 M HCl, and extracted with EtOAc. The

extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 10/90−50/50) to give **25a** as a colorless oil (4.59 g, 86%). ^{1}H NMR ($CDCl_3$) δ 1.62 (t, J = 6.1 Hz, 1H), 2.34 (s, 3H), 4.66 (d, J = 6.1 Hz, 2H), 6.88−6.94 (m, 3H), 6.98 (s, 1H), 7.06 (d, J = 7.7 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 7.30 (t, J = 7.7 Hz, 1H).

[3-(3-Methylphenoxy)phenyl]methanol (25b). Compound **25b** was prepared in a manner similar to that described for **25a** in 69% yield as a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.66 (t, J = 6.0 Hz, 1H), 2.33 (s, 3H), 4.67 (d, J = 6.0 Hz, 2H), 6.79−6.83 (m, 2H), 6.90−6.94 (m, 2H), 7.01 (s, 1H), 7.09 (d, J = 7.5 Hz, 1H), 7.19−7.34 (m, 2H).

[3-(2-Methylphenoxy)phenyl]methanol (25c). Compound **25c** was prepared in a manner similar to that described for **25a** in 43% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.62 (t, J = 6.0 Hz, 1H), 2.24 (s, 3H), 4.66 (d, J = 6.0 Hz, 2H), 6.82 (dd, J = 2.2, 8.0 Hz, 1H), 6.87−6.97 (m, 2H), 7.03−7.22 (m, 3H), 7.22−7.32 (m, 2H).

[3-(2,6-Dimethylphenoxy)phenyl]methanol (25d). Compound **25d** was prepared in a manner similar to that described for **25a** in 23% yield as yellow crystals. ^{1}H NMR ($CDCl_3$) δ 1.60 (t, J = 6.0 Hz, 1H), 2.12 (s, 6H), 4.64 (d, J = 6.0 Hz, 2H), 6.65 (dd, J = 2,7 Hz, 8.1 Hz, 1H), 6.80 (s, 1H), 6.97 (d, J = 7.5 Hz, 1H) 7.02−7.13 (m, 3H), 7.22 (d, J = 7.5 Hz, 1H).

Methyl 3-(4-Aminophenyl)propanoate (2b). Under ice-cooling, thionyl chloride (15 mL, 206 mmol) was added dropwise to MeOH (60 mL), and the mixture was stirred for 10 min. 3-(4-Aminophenyl)propanoic acid (**26a**) (10.1 g, 61.1 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 18 h. The solvent and excess thionyl chloride was evaporated under reduced pressure, water and saturated aqueous $NaHCO_3$ were added, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4, and concentrated. The obtained solid was washed with hexane to give **2b** (10.9 g, 99%) as pale-brown prism crystals. ^{1}H NMR ($CDCl_3$) δ 2.57 (t, J = 7.8 Hz, 2H) 2.84 (t, J = 7.8 Hz, 2H) 3.56 (br s, 2H) 3.66 (s, 3H) 6.62 (d, J = 8.5 Hz, 2H) 6.99 (d, J = 8.5 Hz, 2H).

Methyl 3-(4-Sulfanylphenyl)propanoate (2j). To a solution of 3-(4-sulfanylphenyl)propanoic acid (**26b**) (2.19 g, 12.0 mmol) in MeOH (10 mL) was added concentrated sulfuric acid (1.2 mL, 22.5 mmol) and refluxed for 3 h. After concentration, the mixture was diluted with EtOAc, washed successively with water, saturated aqueous $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (EtOAc−hexane = 0/100−20/80) to give **2j** as colorless crystals (2.02 g, 86%). ^{1}H NMR ($CDCl_3$) δ 2.60 (t, J = 7.7 Hz, 2H), 2.90 (t, J = 7.7 Hz, 2H), 3.40 (s, 1H), 3.66 (s, 3H), 7.07 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H).

Methyl 3-(4-Hydroxy-2-methylphenyl)propanoate (2c). To a solution of 4-bromo-3-methylphenol (**27a**) (10.4 g, 55.6 mmol) in DMF (200 mL) was added methyl acrylate (7.18 g, 83.4 mmol), $NaHCO_3$ (11.7 g, 139 mmol), and tetrabutylammonium chloride (30.9 g, 111 mmol), and the solution was degassed and filled with argon. To this mixture was added palladium acetate(II) (375 mg, 1.67 mmol) and then heated under argon atmosphere at 100 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was diluted with EtOAc, washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 1/10−1/4) to give yellow crystals. These crystals were dissolved in MeOH (20 mL) and THF (30 mL) and hydrogenated on 10% palladium on carbon (127 mg, containing 50% water) under hydrogen atmosphere (balloon pressure) at room temperature for 16 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 1/15−1/8) to give **2c** (2.25 g, 21% in 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.55 (t, J = 8.4 Hz, 2H), 2.87 (t, J = 8.4 Hz, 2H), 3.68 (s, 3H), 4.69 (s, 1H), 6.59−6.65 (2H, m), 6.99 (d, J = 8.1 Hz, 1H).

Ethyl 3-(2-Fluoro-4-hydroxyphenyl)propanoate (2d). Step 1: To an ice-cooled solution of ethyl diethylphosphonoacetate (9.45 g, 42.1 mmol) in THF (50 mL) was added NaH (60% in mineral oil, 1.54 g, 38.5 mmol), and the mixture was stirred for 15 min. A solution of 2-fluoro-4-methoxybenzaldehyde (**28a**) (5.00 g, 32.4 mmol) in THF (30 mL) was added dropwise. The mixture was stirred at room temperature for 2 h, and water was added. The mixture was extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 4/1) to give a colorless oil. Step 2: A mixture of this oil, THF (50 mL), EtOH (5 mL), and platinum dioxide (300 mg) was stirred overnight under a hydrogen atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 4/1) to give ethyl 3-(2-fluoro-4-methoxyphenyl)propanoate (5.97 g, 81% in 2 steps) as a colorless oil. Step 3: To a solution of this oil (57.4 g, 254 mmol) and aluminum chloride (101 g, 761 mmol) in dichloromethane (250 mL) was added dropwise 1-octanethiol (74.3 g, 508 mmol), and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into ice water and the mixture was stirred for 30 min. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 4/1) to give **2d** (44.6 g, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 2.58 (t, J = 8.1 Hz, 2H), 2.89 (t, J = 8.1 Hz, 2H), 4.12 (q, J = 7.2 Hz, 2H), 6.51−6.56 (m, 2H), 7.01−7.06 (m, 1H).

Ethyl 3-(2,6-Difluoro-4-hydroxyphenyl)propanoate (2e). Compound **2e** was prepared from **28b** by a similar to that described for **2d** in 25% yield (3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.55 (t, J = 7.8 Hz, 2H), 2.92 (t, J = 7.8 Hz, 2H), 3.76 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 6.42 (d, J = 9.6 Hz, 2H).

Ethyl 3-(4-Hydroxyphenyl)-2-methylpropanoate (2f). Compound **2f** was prepared from **28c** by a similar to that described for **2d** (step 1 and step 2) in 81% yield (2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 6.3 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H), 2.57−2.73 (m, 2H), 2.85−2.99 (m, 1H), 4.09 (q, J = 7.2 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H).

Ethyl 2-Fluoro-3-(4-hydroxyphenyl)propanoate (2g). Step 1: A solution of ethyl diethylphosphono-2-fluoroacetate (4.90 g, 20.2 mmol) in THF (40 mL) was stirred under a nitrogen atmosphere at 0 °C, and 1.6 M *n*-butyllithium/hexane solution (13.1 mL, 21.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min, and a solution of 4-(benzyloxy)benzaldehyde (**28c**) (4.29 g, 20.2 mmol) in THF (20 mL) was added dropwise. The mixture was stirred at room temperature for 3 h, and ice-cooled aqueous ammonium chloride solution was added. The mixture was extracted with EtOAc, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 97/3−80/20) to give a colorless oil. Step 2: A mixture of this oil, THF (30 mL), EtOH (30 mL), and 10% palladium on carbon (4.9 g, containing 50% water) was stirred overnight under a hydrogen atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 90/10−60/40) to give **2g** (1.75 g, 50% in 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22−1.30 (m, 3H), 3.00−3.25 (m, 2H), 4.17−4.27 (m, 2H), 4.76−4.78 (m, 1H), 4.92−5.15 (m, 1H), 6.74−6.81 (m, 2H), 7.08−7.15 (m, 2H).

2-Methoxy-4-(methoxymethoxy)benzaldehyde (28e). To a solution of 4-hydroxy-2-methoxybenzaldehyde (**28d**) (5.00 g, 32.9 mmol) in DMF (100 mL) was added NaH (60% in mineral oil, 1.45 g, 36.2 mmol) at room temperature. After stirring for 0.5 h, chloromethyl methyl ether (3.97 g, 49.4 mmol) was added and the mixture was stirred at room temperature for 16 h. The reaction mixture was poured into

water. The organic materials were extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 6/1) to give **28e** (5.58 g, 87%) as a colorless powder. ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 3H), 3.91 (s, 3H), 5.24 (s, 2H), 6.61 (d, J = 2.2 Hz, 1H), 6.64−6.70 (m, 1H), 7.80 (d, J = 8.6 Hz, 1H), 10.31 (s, 1H).

Ethyl 3-(4-Hydroxy-2-methoxyphenyl)propanoate (2h). To an ice-cooled solution of ethyl diethylphosphonoacetate (8.28 g, 36.9 mmol) in THF (50 mL) was added NaH (60% in mineral oil, 1.37 g, 34.1 mmol), and the mixture was stirred for 30 min. A solution of 2-methoxy-4-(methoxymethoxy)benzaldehyde **28e** (5.58 g, 28.4 mmol) in THF (30 mL) was added dropwise. The mixture was stirred at room temperature for 45 min. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 7/1) to give a colorless oil. A mixture of this oil, THF (100 mL), EtOH (100 mL), and 10% palladium on carbon (742 mg, containing 50% water) was stirred overnight under a hydrogen atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated to give an oil. To a solution of this oil in EtOH (100 mL) was added 40 mL of 3 M HCl. The resulting mixture was refluxed after 30 min and then poured into cold water and extracted with EtOAc. The extract was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane−EtOAc = 4/1) to give **2h** (2.76 g, 44%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.55 (t, J = 8.0 Hz, 2H), 2.85 (t, J = 8.0 Hz, 2H), 3.78 (s, 3H), 4.12 (q, J = 7.2 Hz, 2H), 4.80 (s, 1H), 6.31 (dd, J = 8.1 Hz, 2.4 Hz, 1H), 6.38 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.1 Hz, 1H).

Ethyl 3-(4-Hydroxyphenyl)butanoate (2i). Compound **2i** was prepared from **29** by a similar to that described for **2d** (step 1 and step 2) in 89% yield (2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3H), 1.61 (d, J = 3.4 Hz, 2H), 2.46−2.60 (m, 2H), 3.16−3.28 (m, 1H), 4.07 (q, J = 7.2 Hz, 2H), 4.94 (br s, 1H), 6.73−6.77 (m, 2H), 7.06−7.10 (m, 2H).

Ca Influx Activity of CHO Cells Expressing Human GPR40 (FLIPR Assay). CHO dhfr cells stably expressing human GPR40 (accession no. NM_005303) were plated and incubated overnight in 5% CO_2 at 37 °C. Then, cells were incubated in loading buffer (recording medium containing 2.5 μg/mL fluorescent calcium indicator Fluo 4-AM (Molecular Devices), 2.5 mmol/L probenecid (Dojindo), and 0.1% fatty acid-free BSA (Sigma)) for 60 min at 37 °C. Various concentrations of test compounds or γ-linolenic acid (Sigma) were added into the cells, and increase of the intracellular Ca^{2+} concentration after addition was monitored by FLIPR Tetra system (Molecular Devices) for 90 s. The agonistic activities of test compounds and γ-linolenic acid on human GPR40 were expressed as $[(A - B)/(C - B)] \times 100$ (increase of the intracellular Ca^{2+} concentration (A) in test compounds-treated cells, (B) in vehicle-treated cells, and (C) in 10 μM γ-linolenic acid-treated cells). EC_{50} value of each compound was obtained with Prism 5 software (GraphPad).

Pharmacokinetic Analyses in Rat Cassette Dosing. Test compounds were administered as a cassette dosing to nonfasted rats. After oral and intravenous administration, blood samples were collected. The blood samples were centrifuged to obtain the plasma fraction. The plasma samples were deproteinized with acetonitrile containing an internal standard. After centrifugation, the supernatant was diluted and centrifuged again. The compound concentrations in the supernatant were measured by LC/MS/MS.

Pharmacological Evaluation in Healthy and Diabetic Rats. Male Sprague−Dawley rats (Jcl:SD) were obtained from CLEA Japan Inc. (Tokyo, Japan). Male N-STZ-1.5 rats were obtained from Takeda RABICS (Osaka, Japan). The N-STZ-1.5 rats were generated by subcutaneous injection of 120 mg/kg of streptozotocin (STZ) into male Wistar Kyoto rats 1−2 days after birth. All rats were fed regular chow CE-2 (CLEA, Japan) and tap water ad libitum and were housed in cages in a room with controlled temperature (23 ± 1 °C), humidity (55 ± 5%), and lighting (lights on from 07:30 to 19:30). The care and use of the animals and the experimental protocols used in this research were approved by the Experimental Animal Care and Use Committee of Takeda Pharmaceutical Company (Osaka, Japan).

Oral Glucose Tolerance Test in Diabetic Rats. Twenty-week-old male N-STZ-1.5 rats were fasted overnight, and blood samples were collected from tail vein, followed by measuring plasma glucose levels (referred to as time point pre) by the automatic analyzer Hitachi 7080 (Hitachi, Japan). Rats were divided into four groups based on body weight and plasma glucose levels (n = 6). Compound **4p** (1, 3, or 5 mg/kg) or 0.5% methylcellulose was orally administered 30 min before oral glucose load (1 g/kg). Blood samples were collected from the tail vein 0 (just before glucose load), 10, 30, 60, and 120 min after the glucose load. Plasma glucose levels were measured as described above, and plasma insulin levels were measured with insulin RIA kit (SHIONOGI & Co., Ltd., Japan) according to the manufacturer's instruction. Statistical differences versus control were analyzed with one-tailed Williams' test or Shirley−Williams' test.

Effects on Normal Fasting Plasma Glucose and Insulin Levels in SD Rats. Eight-week-old male SD rats were fasted overnight, and blood was collected from tail vein, followed by measuring plasma glucose levels (referred to as time point 0) by the automatic analyzer Hitachi 7080 (Hitachi, Japan). Rats were divided into three groups based on body weight and plasma glucose levels (n = 6). Compound **4p** (30 mg/kg), nateglinide (50 mg/kg), or vehicle (0.5% methylcellulose) was orally administered, and blood was collected from tail vein at time points 30, 60, and 120 min after the administrations. Plasma glucose and insulin levels were measured as described above. Statistical differences versus control were analyzed with Dunnett's test or Steel test.

Rotamer Analyses. Conformational analyses of biphenyl, 2,6-dimethylbiphenyl, biphenyl, and phenoxyphenyl were performed using MNDO-PM3 (MOPAC version 7.01) method in MOE. Each focused bond was fixed and the other part of each compound was fully optimized. Energy curves around each focused bond were obtained by plotting calculated total energies against an axis of a dihedral angle.

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ABBREVIATIONS USED

GPCR, G-protein coupled receptor; GSIS, glucose-stimulated insulin secretion; FFAs, free fatty acids; OGTT, oral glucose tolerance test; DHA, docosahexaenoic acid; FLIPR, fluorometric imaging plate reader; PK, pharmacokinetic; BSA, bovine serum albumin; CHO, Chinese hamster ovary

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