Synthesis and Biological Evaluation of 3-Aryl-3-(4-phenoxy)-propionic Acid as a Novel Series of G Protein-Coupled Receptor 40 Agonists

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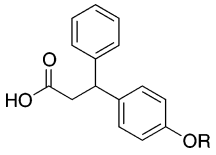
High-throughput screening of a subset of the J&J compound library containing the carboxylic acid functional group uncovered a bromophenyl derivative as a moderate potent GPR40 agonist. Chemical elaboration of this bromophenyl led to the discovery of a novel series of GPR40 agonists with submicromolar potency. Among them, **22** and **24** behaved as full agonists when compared to the endogenous GPR40 ligand linolenic acid in a functional Ca^{+2} flux assay in HEK cells expressing GPR40 receptor. Several GPR40 agonists have also demonstrated the ability to induce glucose-mediated insulin secretion in the mouse MIN6 pancreatic β-cell line. Our data supports the hypothesis that GPR40 may play an important role in fatty acid-mediated glucose-dependent insulin secretion. Compound **22** exhibited good pharmacokinetic profile in rat and may serve as a good candidate for in vivo study and may help to determine if GPR40 agonists would be beneficial in the treatment of type II diabetes.

Introduction

Fatty acids (FAs[a]) provide an important energy source and also act as signaling molecules. Acutely elevated FAs enhance insulin secretion in response to glucose,[1,2] however, chronically elevated FAs may impair pancreatic β-cell function, a phenomenon recognized as lipotoxicity.[3] FAs do not initiate insulin release, but amplify glucose-dependent insulin secretion. It is well-documented that glucose metabolism increases the ATP/ADP ratio, which closes ATP-sensitive potassium channels (K_{ATP} channels), activates voltage-gated calcium channels (Ca^{+2} channels), and results in calcium influx, which in turn induces the release of insulin.[4] The effects of FAs were thought to require transport across the plasma membrane and metabolized into long-chain FA-coenzyme A.[5,6] However, several recently published articles[7−10] suggested that FAs bind to and activate the G protein-coupled receptor 40 (GPR40). The activation of GPR40 leads to inositol triphosphate (IP3) production and mobilization of intracellular Ca^{+2} from the endoplasmic reticulum (ER). GPR40 activation also stimulates Ca^{+2} influx through Ca^{+2} channels. The resulting increase in $[Ca^{+2}]_i$ enhances glucose-dependent insulin secretion. Binding of FAs to GPR40 may also produce an increase in intracellular cAMP levels, which may antagonize the K_{ATP} channels activity and further enhance Ca^{+2} influx.[11]

GPR40 belongs to a family of FA binding GPCRs, which include GPR40, GPR41, GPR43, and GPR120. GPR41 and GPR43 are activated by short-chain FAs, GPR40 is activated by medium- and long-chain FAs, and GPR120 is activated by long-chain FAs.[7,8,12] GPR40 is highly expressed in pancreatic β-cells and insulin-secreting cell lines.[8−10] It is also found in several areas of the brain.[7] Treatment of MIN6 pancreatic β-cells with small interfering RNA (siRNA) specific for GPR40 prevents FA stimulation of insulin secretion.[8] This study further supported that GPR40 may serve as an attractive target[13] to mediate insulin secretion. Furthermore, agents that serve as GPR40 agonists may be useful for the treatment of type II diabetes. To date, there is only one series of GPR40 agonists (beyond the FAs) reported in the literature.[13,14] This article describes our research efforts in the identification of a novel series of GPR40 agonists.

Table 1. ED_{50} at the Human GPR40 Receptor[a]



cmpd	R	ED_{50}[b] μM (% max resp.)
3	*n*-C_3H_7	4.80 (68)
5	*n*-C_4H_9	1.20 (72)
7	*n*-C_5H_{11}	2.97 (60)
9	*n*-C_6H_{13}	2.88 (68)
11	*n*-C_7H_{15}	4.26 (70)
13	$(CH_2)_3CF_3$	3.16 (72)
15	CH_2-CH═CH-CH_3	2.71 (75)
17	$(CH_2)_3OCH_3$	7.58 (43)
19	$(CH_2)_2$-C(CH_3)═CH_2	2.71 (81)
20	$(CH_2)_2CH(CH_3)_2$	1.86 (77)
22	$CH_2CH(CH_3)C_2H_5$	0.30 (98)
24	$CH_2CH(C_2H_5)_2$	0.64 (96)

[a] Assay details were described in the Experimental Section. [b] Values represent the mean of two to three experiments.

Chemistry

The synthesis of 3-phenyl-3-(4-alkoxyphenyl)-propionic acid target molecules listed in Table 1 is shown in Scheme 1. The

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[a] Abbreviations: GPR, G protein-coupled receptor; FAs, fatty acids; Ca^{+2}, calcium; K_{ATP}, ATP-sensitive potassium; IP3, inositol triphosphate; ER, endoplasmic reticulum; siRNA, small interfering RNA; DMAP, dimethylaminopyridine; TFA, trifluoroacetic acid; NMP, 1-methyl-2-pyrrolidinone.

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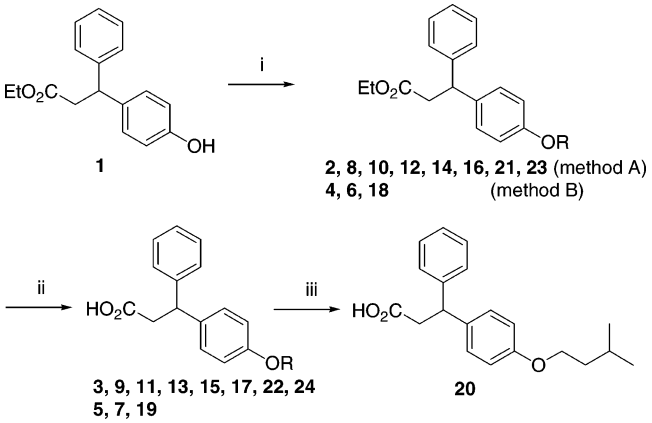
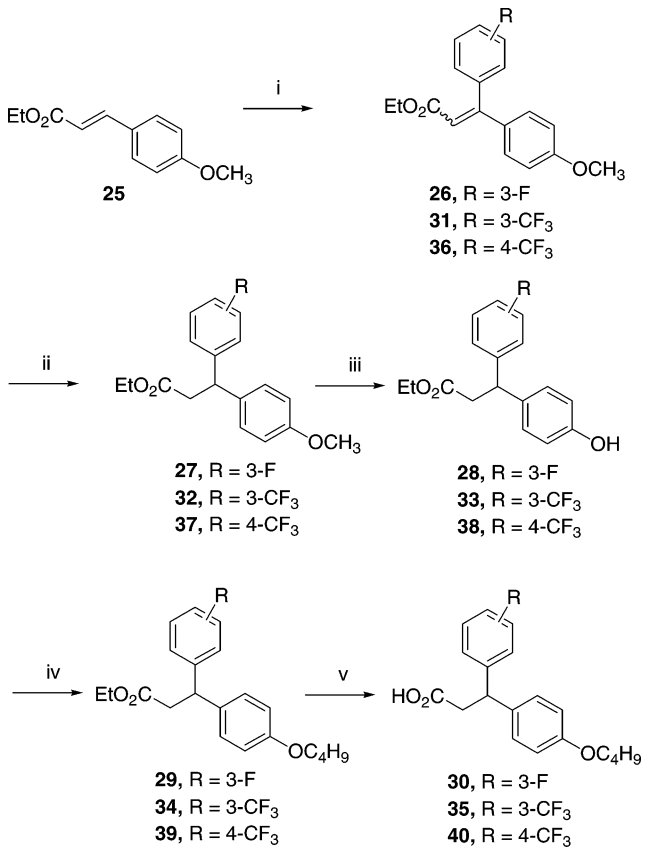
Scheme 1[a]



[a] Reagents and conditions: (i) method A, RX, CsF, DMF, 20 °C; method B, PPh_3, DIAD, ROH, THF; (ii) LiOH, THF/MeOH/H_2O; (iii) H_2, Pd/C, EtOH.

Scheme 2[a]

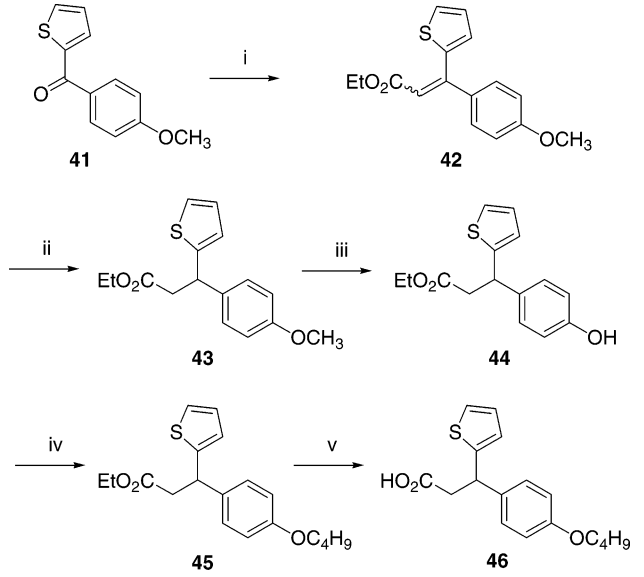


[a] Reagents and conditions: (i) R-C_6H_4Br, $Pd(OAc)_2$, TBAA, 130 °C; (ii) H_2, Pd/C, EtOH; (iii) BBr_3, CH_2Cl_2, −78 °C; (iv) *n*-BuI, CsF, DMF; (v) LiOH, THF/MeOH/H_2O.

ethyl esters of the target carboxylic acids were prepared easily from the known phenol **1**[15] by two methods: a direct base-promoted alkylation with the halides (method A) or a PPh_3/DIAD-mediated Mitsunobu reaction with the alcohols (method B). Base hydrolysis of these ethyl esters in a mixture of THF/MeOH/H_2O gave good yield of the products.

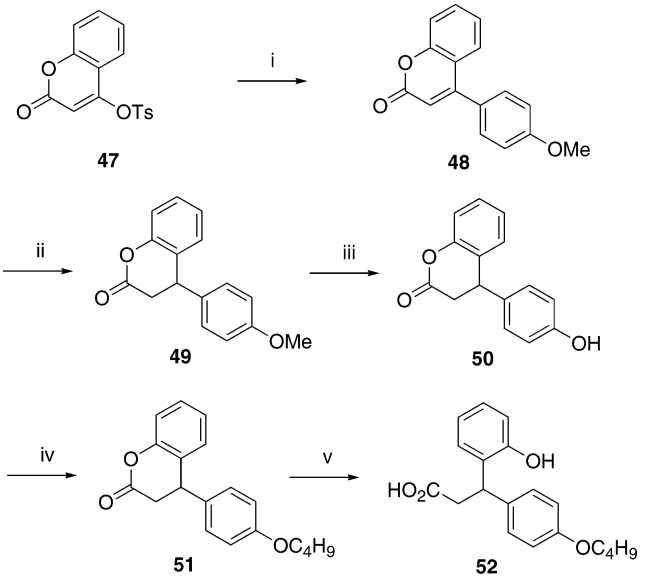
The synthesis of 3-substituted phenyl-3-(4-butoxyphenyl)-propionic acids (**30**, **35**, or **40**) is shown in Scheme 2. A palladium-catalyzed Heck reaction[16] of **25** with various halides gave a mixture of *E*/*Z* olefins (**26**, **31**, or **36**). Hydrogenation of the crude *E*/*Z* olefins in a Parr shaker gave the reduced intermediates (**27**, **32**, or **37**). Demethylation with BBr_3, followed

Scheme 3[a]



[a] Reagents and conditions: (i) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (ii) Et_3SiH, TFA, CH_2Cl_2; (iii) BBr_3, CH_2Cl_2, −78 °C; (iv) *n*-BuI, CsF, DMF; (v) LiOH, THF/MeOH/H_2O.

Scheme 4[a]



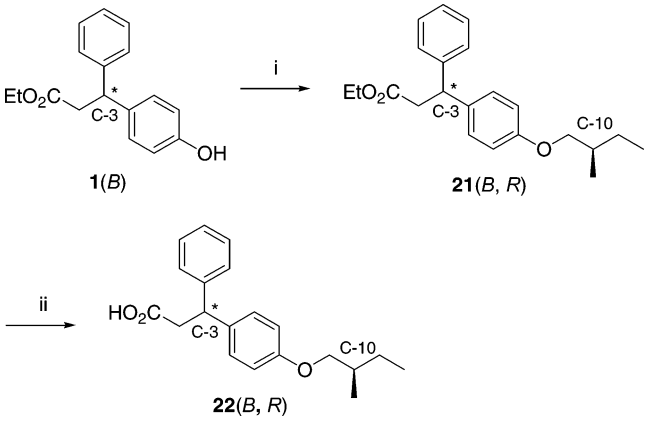
[a] Reagents and conditions: (i) 4-OMe-$C_6H_4B(OH)_2$, $PdCl_2(PPh_3)_2$, Na_2CO_3; (ii) H_2, Pd/C, EtOH; (iii) BBr_3, CH_2Cl_2, −78 °C; (iv) *n*-BuI, CsF, DMF; (v) LiOH, THF/MeOH/H_2O.

by base-promoted alkylation and hydrolysis, provided the desired 3-substituted phenyl products (**30**, **35**, or **40**).

The synthesis of 3-thiophen-3-(4-butoxyphenyl)-propionic acid **46** is described in Scheme 3. A Horner−Emmons−Wadsworth reaction[17] of **41** with the carbanion of (diethoxyphosphoryl)-acetic acid ethyl ester gave an *E*/*Z* mixture of **42**. Reduction of the crude **42**, followed by demethylation, alkylation, and hydrolysis gave **46**. The synthesis of 3-(2-hydroxyphenyl)-3-(4-butoxyphenyl)-propionic acid **52** is described in Scheme 4. A palladium-catalyzed Suzuki coupling reaction[18] of **47** with 4-methoxyphenylboronic acid gave **48**. Hydrogenation of **48**, followed by demethylation, alkylation, and hydrolysis provided the desired product **52**.

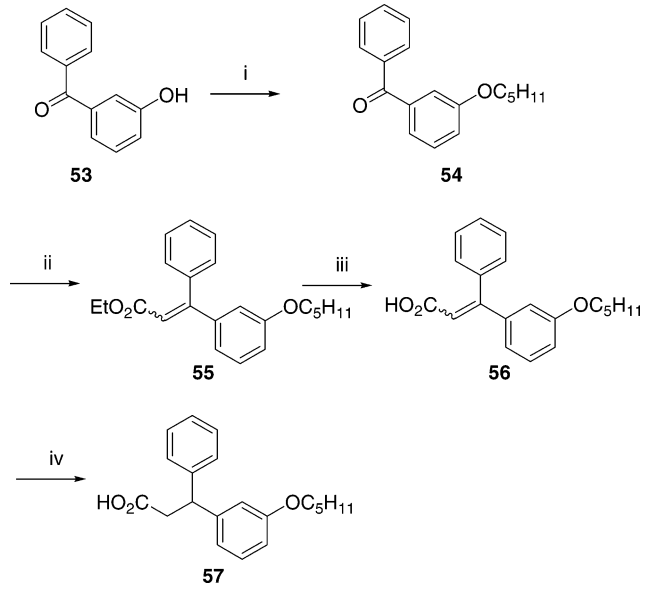
The general synthesis of chiral diastereoisomers of **22** is shown in Scheme 5. The chiral enantiomer **1**(*B*) was the second peak isolated from **1** from the HPLC with a chiral OJ column.

Scheme 5[a]



[a] Reagents and conditions: (i) PPh_3, DIAD, ROH, THF; (ii) LiOH, THF/MeOH/H_2O.

Scheme 6[a]



[a] Reagents and conditions: (i) PPh_3, DIAD, n-$C_5H_{11}OH$, THF; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (iii) LiOH, THF/MeOH/H_2O; (iv) H_2, Pd/C, EtOH.

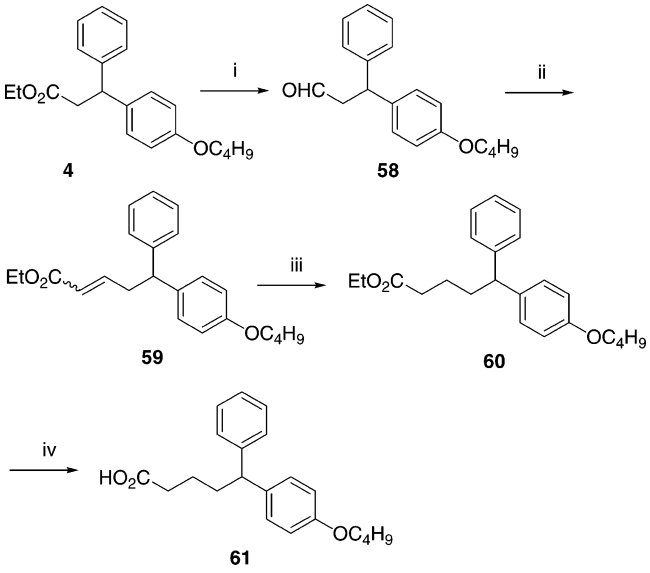
Because the absolute stereochemistry at C-3 was not determined, we used **1**(*B*) and **1**(*A*) to differentiate the two enantiomers based on the sequence isolated from the HPLC. *A* means the first peak coming out of the HPLC, and *B* means the second peak coming out of the HPLC. A Mitsunobu reaction of **1**(*B*) and (*R*)-2-methyl-butan-1-ol gave **21**(*B*, *R*). Hydrolysis of **21**(*B*, *R*) gave **22** (*B*, *R*).

The synthesis of 3-phenyl-3-(3-pentyloxyphenyl)-propionic acid **57** is shown in Scheme 6. A PPh_3/DIAD-mediated Mitsunobu reaction of **53** with *n*-pentyl alcohol gave **54**. A Horner−Emmons−Wadsworth reaction of **54**, followed by hydrolysis and hydrogenation gave **57**. Finally, DIBAL-H reduction of **4** gave the aldehyde **58**. Olefination of **58**, followed by hydrogenation and hydrolysis gave **61** (Scheme 7).

Results and Discussion

Lead Generation. Because long-chain FAs, including linoleic acid (ED_{50} = 24 μM, Figure 1), are endogenous ligands for GPR40, we envisioned that the carboxylic acid moiety may be the required pharmacophore for maintaing GPR40 agonist activity. A cell-based high-throughput screening of the carboxylic acid containing a sublibrary of the J&J chemical collection resulted in the discovery of 3-(4-bromophenyl)-3-phenyl-propionic acid as a moderately potent 40 agonist (ED_{50} = 9 μM, Figure 1). The bromide was served as a valuable intermediate for modification to various chemical series. We now report our efforts toward the identification of 3-aryl-3-(4-phenoxy)-propionic acid as a novel series of GPR40 agonist.

Scheme 7[a]



[a] Reagents and conditions: (i) DIBAL-H, CH_2Cl_2; (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF; (iii) H_2, Pd/C, MeOH; (iv) LiOH, THF/MeOH/H_2O.

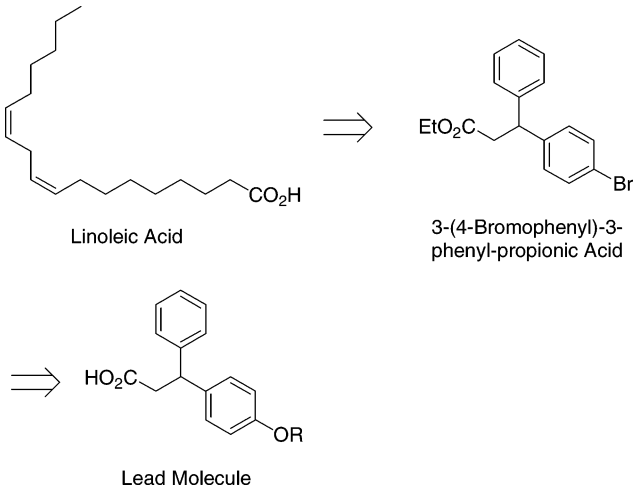
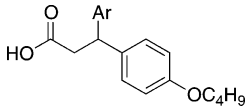


Figure 1. Generation of the lead molecule.

The first phenoxide synthesized, the *n*-propyl phenoxide **3**, showed about a 2-fold increase in potency (ED_{50} = 4.8 μM, Table 1) compared to the bromide (ED_{50} = 9 μM) focused library hit. The GPR40 activity of **3** is represented as a percentage of the maximal response relative to the activity produced by linoleic acid. Therefore, compound **3** may be considered as a partial agonist because of the 68% maximal response observed. Extension of the *n*-propyl phenoxide to *n*-butyl phenoxide increased the potency by 4-fold (**5**, ED_{50} = 1.2 μM). Further extension of the *n*-butyl phenoxide to a longer *n*-pentyl phenoxide (**7**, ED_{50} = 2.97 μM), *n*-hexyl phenoxide (**9**, ED_{50} = 2.88 μM), or *n*-heptal phenoxide (**11**, ED_{50} = 4.26 μM) reduced the potency steadily.

Because the four-carbon chain length appeared to be optimal for GPR40 potency and activity, we decided to focus on the preparation of its close analogs. Replacement of the terminal

Table 2. ED_{50} at the Human GPR40 Receptor[a]



cmpd	R	ED_{50}[b] uM (% max resp.)
30	3-F-C_6H_5	1.44 (81)
35	3-CF_3-C_6H_5	2.84 (75)
40	4-CF_3-C_6H_5	>10 (3)
46		1.29 (79)
52	2-OH-C_6H_5	4.8 (66)

[a] Assay details were described in the Experimental Section. [b] Values represent the mean of two to three experiments.

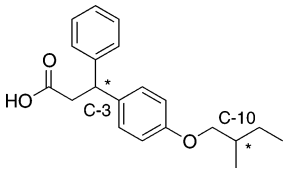
methyl group with the more lipophilic trifluoromethyl group, surprisingly, gave lower potency (**13**, ED_{50} = 3.16 μM versus **5**, ED_{50} = 1.2 μM). Decreasing the flexibility of the *n*-butyl group by installing a double bond in the middle of the four-carbon chain, still resulted in a 2-fold lower potency (**15**, ED_{50} = 2.71 μM). We then replaced the terminal methyl group with the more hydrophilic methoxy group; unfortunately, a 6-fold decrease of the potency and somehow lower activity was still observed (**17**, ED_{50} = 7.58 μM (43%)).

We next examined the impact of branched-chain on the potency. A methyl substitution on the remote carbon of the unsaturated or saturated four-carbon chain did not improve the potency (**19**, ED_{50} = 2.71 μM; **20**, ED_{50} = 1.86 μM). Surprisingly, a methyl substitution on the center carbon of the four-carbon chain increased the potency by 4-fold and also raised the activity (**22**, ED_{50} = 0.30 μM (98%)). Increasing the lipophilicity by replacing the methyl with an ethyl group exhibited no improvement in the potency but maintained the high activity (**24**, ED_{50} = 0.64 μM (96%)). We then examined the substitution effect on the second phenyl ring. While the fluoro substitution at the 3-position gave comparable potency (**30**, ED_{50} = 1.44 μM, Table 2) as compared to the parent **5** (ED_{50} =1.20 μM), the sterically bulkier trifluoromethyl substitution appears less favorable (**35**, ED_{50} = 2.84 μM). On the other hand, the trifluoromethyl substituent seems much less tolerable at the 4-position (**40**, ED_{50} >10 μM (3%)). Replacement of the phenyl ring with a thiophene bioisostere[19] provided an analog that was equipotent and good activity was also maintained (**46**, ED_{50} = 1.29 μM (79%)). Installation of a small polar hydroxyl group at the 2-position of the phenyl ring also lowered the potency (**52**, ED_{50} = 4.8 μM).

Up to this point, **22** is the most potent GPR40 agonist examined in this series. Based on the potencies observed for the four diastereoisomers (Table 3), it appeared that the stereochemistry at C-3 (but not C-10) determined the GPR40 agonist potency and activity exclusively. The close proximity of the C-3 substitution (rather than the C-10 substitution) to the hypothesized carboxylic acid pharmacophore of GPR40 seems consistent with these data. The importance of keeping the phenoxide side chain at the 4-position rather than shifting it to the 3-position was clearly demonstrated in **57** (ED_{50} > 10 μM (6%), Table 4). However, increasing the linker length between the carboxylic acid group and the biphenyl moiety from a one-carbon to a three-carbon chain completely abolished the GPR40 potency and activity (**61**, ED_{50} >10 μM (3%)).

Insulin Secretion from MIN6 Cells. It has been demonstrated that free FAs such as linoleic acid can produce a glucose-dependent insulin secretion from perfused pancreas, rat, or human islets and insulin-secreting cells.[6−8] Therefore, we decided to examine the stimulation of insulin release of these GPR40 small molecule agonists in the MIN6 mouse insulinoma cell line in the presence of both low glucose level (5 mM) and high glucose level (25 mM). As shown in Figure 2, addition of **7** (incubated at 30 μM concentration) resulted in a 122% increase (statistical nonsignificant) in insulin secretion in the presence of 25 mM glucose level as compared to 25 mM glucose alone. Under the same 25 mM glucose condition, a 137% increase (p < 0.05) in insulin secretion for **9**, a 155% increase (p < 0.01) for **24**, a 171% increase (p < 0.01) for **46**, and a 172% increase for linoleic acid (p < 0.01) were observed. On the other hand, all GPR40 agonists (**7**, **9**, **24**, and **46**) tested

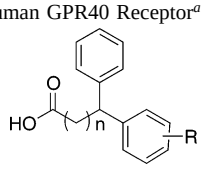
Table 3. ED_{50} at the Human GPR40 Receptor[a]



cmpd (C-3, C-10)	ED_{50}[b] uM (% max resp.)
22 (*B*, *R*)	0.71 (98)
22 (*B*, *S*)	0.56 (94)
22 (*A*, *R*)	>10 (3)
22 (*A*, *S*)	>10 (2)

[a] Assay details were described in the Experimental Section. [b] Values represent the mean of two to three experiments.

Table 4. ED_{50} at the Human GPR40 Receptor[a]



cmpd	*n*	R	ED_{50}[b] uM (% max resp.)
57	1	3-OC_5H_{11}	>10 (6)
61	3	4-OC_4H_9	>10 (3)

[a] Assay details were described in the Experimental Section. [b] Values represent the mean of two to three experiments.

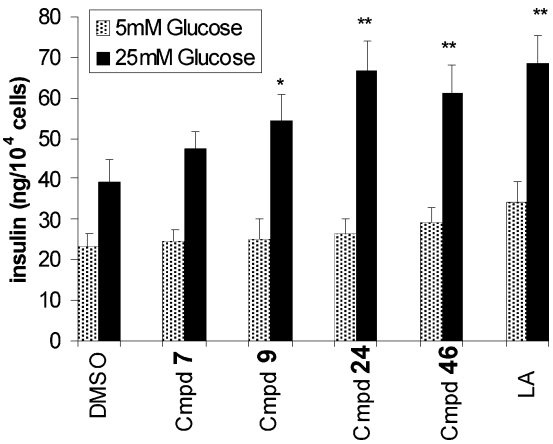


Figure 2. Activity of GRP40 agonists on basal and glucose-stimulated insulin release in MIN6 cells. Compounds were incubated at 30 μM in KRBH buffer containing 5 mM or 25 mM glucose for 2 h. Extracellular insulin concentration was determined by ELISA. Each data point is an average of three independent sample wells. * = p < 0.05, ** = p < 0.01 student's *t*-test compared to DMSO control.

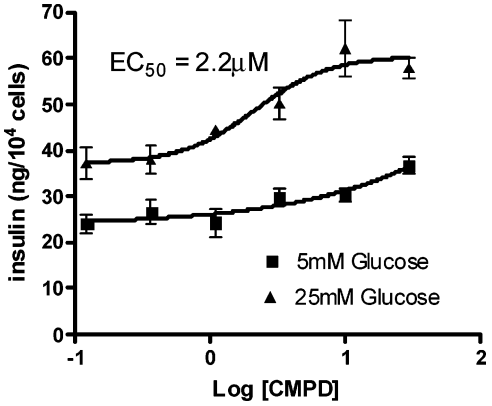


Figure 3. Dose-dependent effect of compound **24** on glucose-stimulated insulin release in MIN6 cells. Basal MIN6 cells were treated with varying compound **24** for 2 h in KRBH buffer containing 5 mM or 25 mM glucose. Extracellular insulin concentrations were determined by ELISA. EC_{50} analysis was done with GraphPad Prism. Each data point is an average of duplicate samples.

produced no significant increase in insulin secretion in the presence of 5 mM glucose level when compared to 5 mM glucose alone. Linoleic acid also produced a moderate increase (141%, nonsignificant) in insulin secretion at this low glucose level. This potentiation of insulin secretion observed at high glucose level following GPR40 activation was similar to that reported[13] in MIN6 cells.

While the mechanism behind the potentiation of insulin release by FAs remains debatable, several studies[20] reported that free FAs are able to potentiate insulin secretion, secondary to an increase in cytoplasmic Ca^{+2}. It is interesting to note that our data seems to support these findings. For example, while both **7** and **9** appeared to be partial agonists at GPR40 with respect to elevation of Ca^{+2} in HEK-293 cells (for **7**, 60% max, respectively, and for **9**, 68% max, respectively, Table 1), both compounds were less efficacious in potentiating glucose-mediated insulin release (for **7**, 122% increase, and for **9**, 137% increase, Figure 2). On the other hand, both **24** and linoleic acid appeared to be full GPR40 agonists with respect to the elevation of [Ca^{+2}] (for **24**, 96% max, respectively, and for LA, 100% max, respectively, Table 1), and were also found to be more efficacious in increasing glucose-mediated insulin secretion (for **24**, 155% increase, and for LA, 172% increase, Figure 2).

In addition, compound **24** produced a dose-dependent increase (EC_{50} = 2.2 μM) on insulin secretion in the presence of a high glucose level (25 mM), as shown in Figure 3. In contrast, **24** had a minimal effect on insulin release in the presence of a low glucose level (5 mM). This dose-dependent stimulation of insulin release by **24** in a glucose-sensitive manner in MIN6 cells suggests that small molecule activation of GPR40 enhances glucose-sensitive insulin secretion.

Pharmacokinetic Profile of 22. Most of the compounds in this series exhibited a good pharmacokinetic profile in rat. For example, compound **22** (*B, S*) showed very good oral bioavailability in rat (*F*% = 87, Table 5), with high maximum plasma concentration (C_{max} = 4758 ng/mL), rapid oral absorption (T_{max} = 0.5 h), high plasma drug exposure (AUC = 10742 ng·h/mL), long plasma duration ($t_{1/2}$ = 6.33 h), and reasonable systemic clearance (CL = 13.8 mL/min·kg). Compound **22** displayed no inhibition in the CYP450 screening assay (1A2, 2C9, 2C19, 2D6, and 3A4) with IC_{50} > 22 μM, indicating a low potential for drug−drug interactions. The good PK profile may allow these compounds to be useful candidates for in vivo study and may help to determine if GPR40 agonists would be beneficial in the treatment of type II diabetes.

Conclusion

High-throughput screening of the J&J sublibraries containing the carboxylic acid functional group resulted in the discovery of a bromophenyl derivative as a moderately potent GPR40 agonist. The chemical elaboration of this bromophenyl led to the discovery of a novel series of GPR40 agonists with submicromolar potency. Among them, **22** and **24** behaved as full agonists when compared to the endogenous GPR40 ligand linoleic acid in a functional calcium-flux assay in HEK-293 cells expressing GPR40. Several GPR40 agonists have also been demonstrated to induce glucose-mediated insulin secretion in the mouse MIN6 cells. Our data may support the hypothesis that GPR40 may play an important role in FA-induced glucose-sensitive insulin secretion. Compound **22** exhibited a good pharmacokinetic profile in rat and may serve as a good candidate for in vivo study and may help to determine if GPR40 agonists would be beneficial in the treatment of type II diabetes.

Experimental Section

Chemistry. ^{1}H NMR spectra were measured on a Bruker AC-300 (300 MHz) spectrometer using tetramethylsilane as an internal standard. Elemental analyses were obtained by Quantitative Technologies Inc. (Whitehouse, New Jersey), and the results were within 0.4% of the calculated values unless otherwise mentioned. Melting points were determined in open capillary tubes with a Thomas−Hoover apparatus and were uncorrected. Electrospray mass spectra (MS-ES) were recorded on a Hewlett-Packard 59987A spectrometer. High-resolution mass spectra (HRMS) were obtained on a Micromass Autospec. E. spectrometer.

General Procedure for the Synthesis of 2, 8, 10, 12, 14, 16, 21, and 23 (Method A). 3-Phenyl-3-(4-propoxy-phenyl)-propionic Acid Ethyl Ester (2). To a mixture of **1** (189 mg, 0.70 mmol) in DMF (7 mL) with CsF (320 mg, 2.10 mmol) was added 1-iodopropane (143 mg, 0.84 mmol). The reaction was stirred at room temperature overnight. Water was added, and the mixture was extracted with EtOAc thrice. The combined extracts were washed with H_2O and brine and dried over Na_2SO_4. The reaction mixture was concentrated and the crude product was purified by column chromatography on silica gel (10:1 hexane/EtOAc) to give 146 mg (67%) of **2** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81 (d, J = 6.0 Hz, 2H), 4.49 (t, J = 9.0 Hz, 1H), 4.00 (q, J = 6.0 Hz, 2H), 3.87 (t, J = 6.0 Hz, 2H), 3.01 (d, J = 9.0 Hz, 2H), 1.77 (tq, J = 6.0, 6.0 Hz, 2H), 1.11 (t, J = 6.0 Hz, 3H), 1.01 (t, J = 6.0 Hz, 3H); MS (ES) m/z 335 ($M + Na^+$).

3-(4-Hexyloxy-phenyl)-3-phenyl-propionic Acid Ethyl Ester (8). Using 1-iodohexane and following the procedure as in the preparation of **2** gave **8** (84%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, J = 9.0 Hz, 2H), 4.49 (t, J = 7.5 Hz, 1H), 4.03 (q, J = 6.0 Hz, 2H), 3.90 (t, J = 6.0 Hz, 2H), 3.01 (d, J = 7.5 Hz, 2H), 1.79−1.68 (tt, J = 6.0, 6.0 Hz, 2H), 1.47−1.23 (m, 6H), 1.11 (t, J = 6.0 Hz, 3H), 0.91 (t, J = 6.0 Hz, 3H); MS (ES) m/z 355 ($M + H^+$).

3-(4-Heptyloxy-phenyl)-3-phenyl-propionic Acid Ethyl Ester (10). Using 1-iodoheptane and following the procedure as in the preparation of **2** gave **10** (89%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, J = 9.0 Hz, 2H), 4.49 (t, J = 7.5 Hz, 1H), 4.03 (q, J = 6.0 Hz, 2H), 3.90 (t, J = 6.0 Hz, 2H), 3.01 (d, J = 7.5 Hz, 2H), 1.79−1.65 (m, 2H), 1.47−1.21 (m, 8H), 1.11 (t, J = 6.0 Hz, 3H), 0.88 (t, J = 6.0 Hz, 3H); MS (ES) m/z 369 ($M + H^+$).

3-Phenyl-3-[4-(4,4,4-trifluoro-butoxy)-phenyl]-propionic Acid Ethyl Ester (12). Using 4-bromo-1,1,1-trifluoro-butane and following the procedure as in the preparation of **2** gave **12** (68%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.11 (m, 7H), 6.79 (d, J = 9.0 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 4.03 (q, J = 7.2

Table 5. Pharmacokinetic Profile of Compound **22**

species	route[a]	dose[b] (mg/kg)	C_{max}[c] (ng/mL)	T_{max}[d] (h)	AUC[e] (ng·h/mL)	$t_{1/2}$[f] (h)	CL[g] (mL/min·kg)	F[h] (%)
rat	iv	2	5781 ± 1954	0.08 ± 0	2476 ± 421	4.78 ± 1.37	13.8 ± 2.5	
	po	10	4758 ± 767	0.5 ± 0	10742 ± 1973	6.33 ± 2.96		87

[a] 20% cyclodextrin in water. [b] $n = 4$. [c] Maximum plasma concentration, each value is the mean ± SD. [d] Time to reach the maximum concentration. [e] Estimated area under the plasma concentration vs time curve. [f] Calculated terminal half-life. [g] Systemic clearance. [h] Oral bioavailability.

Hz, 2H), 3.97 (t, $J = 6.0$ Hz, 2H), 3.01 (d, $J = 8.0$ Hz, 2H), 2.38−2.20 (m, 2H), 2.06−1.95 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H); MS (ES) m/z 403 ($M + Na^+$).

3-(4-But-2-enyloxy-phenyl)-3-phenyl-propionic Acid Ethyl Ester (14). Using 1-bromo-but-2-ene and following the procedure as in the preparation of **2** gave **14** (83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.89−5.64 (m, 2H), 4.56−4.38 (m, 3H), 4.03 (q, $J = 6.0$ Hz, 2H), 3.01 (d, $J = 9.0$ Hz, 2H), 1.74 (d, $J = 6.0$ Hz, 3H), 1.11 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 347 ($M + Na^+$).

3-[4-(3-Methoxy-propoxy)-phenyl]-3-phenyl-propionic Acid Ethyl Ester (16). Using 1-bromo-3-methoxy-propane and following the procedure as in the preparation of **2** gave **16** (80%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81 (d, $J = 9.0$ Hz, 2H), 4.49 (t, $J = 9.0$ Hz, 1H), 4.08−3.95 (m, 4H), 3.53 (t, $J = 6.0$ Hz, 2H), 3.33 (s, 3H), 3.01 (d, $J = 9.0$ Hz, 2H), 2.08−1.95 (m, 2H), 1.11 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 343 ($M + H^+$).

3-[4-(2-Methyl-butoxy)-phenyl]-3-phenyl-propionic Acid Ethyl Ester (21). Using 1-bromo-2-methylbutane and following the procedure as in the preparation of **2** gave **21** (65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, $J = 8.7$ Hz, 2H), 4.49 (t, $J = 8.0$ Hz, 1H), 4.03 (q, $J = 7.2$ Hz, 2H), 3.77 (dd, $J = 9.0$, 6.0 Hz, 1H), 3.68 (dd, $J = 9.0$, 6.5 Hz, 1H), 3.01 (d, $J = 8.0$ Hz, 2H), 1.89−1.63 (m, 1H), 1.35−1.16 (m, 2H), 1.11 (t, $J = 7.2$ Hz, 3H), 0.99 (d, $J = 7.4$ Hz, 3H), 0.93 (t, $J = 7.4$ Hz, 3H); MS (ES) m/z 341 ($M + H^+$).

3-[4-(2-Ethyl-butoxy)-phenyl]-3-phenyl-propionic Acid Ethyl Ester (23). Using 1-bromo-2-ethylbutane and following the procedure as in the preparation of **2** gave **23** (53%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 7.13 (d, $J = 6.6$ Hz, 2H), 6.81 (d, $J = 6.6$ Hz, 2H), 4.49 (t, $J = 8.0$ Hz, 1H), 4.03 (q, $J = 7.2$ Hz, 2H), 3.79 (d, $J = 5.7$ Hz, 2H), 3.01 (d, $J = 8.0$ Hz, 2H), 1.69−1.53 (m, 1H), 1.50−1.38 (m, 4H), 1.11(t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 6H); MS (ES) m/z 355 ($M + H^+$).

General Procedure for the Synthesis of 3, 5, 7, 9, 11, 13, 15, 17, 19, 22, and 24. 3-Phenyl-3-(4-propoxy-phenyl)-propionic Acid (3). A solution of **2** (128 mg, 0.41 mmol) in THF/MeOH/H_2O (4:1:1 v/v/v, 12 mL) was treated with LiOH (1 M in H_2O, 2.0 mL, 2.0 mmol). The mixture was stirred at room temperature overnight. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na_2SO_4. The reaction mixture was concentrated, and the crude product was purified by column chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to give 90 mg (77%) of the acid **3** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.09 (m, 7H), 6.81 (d, $J = 6.0$ Hz, 2H), 4.47 (t, $J = 9.0$ Hz, 1H), 3.87 (t, $J = 6.0$ Hz, 2H), 3.06 (d, $J = 9.0$ Hz, 2H), 1.77 (tq, $J = 6.0$, 6.0 Hz, 2H), 1.01 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 307 ($M + Na^+$); FAB-HRMS ($M + H^+$) calcd, 284.1412; found, 284.1416.

3-(4-Butoxy-phenyl)-3-phenyl-propionic Acid (5). Using **4** and following the procedure as in the preparation of **3** gave **5** (89%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.09 (m, 7H), 6.80 (d, $J = 6.0$ Hz, 2H), 4.46 (t, $J = 6.0$ Hz, 1H), 3.90 (t, $J = 6.0$ Hz, 2H), 3.04 (d, $J = 6.0$ Hz, 2H), 1.74 (tt, $J = 6.0$, 6.0 Hz, 2H), 1.46 (tq, $J = 6.0$ Hz, $J = 6.0$ Hz, 2H), 0.95 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 321 ($M + Na^+$). Anal. ($C_{19}H_{22}O_3 \cdot 0.2H_2O$) C, H, N.

3-(4-Pentyloxy-phenyl)-3-phenyl-propionic Acid (7). Using **6** and following the procedure as in the preparation of **3** gave **7** (81%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.09 (m, 7H), 6.80 (d, $J = 8.0$ Hz, 2H), 4.46 (t, $J = 7.5$ Hz, 1H), 3.90 (t, $J = 6.0$ Hz, 2H), 3.04 (d, $J = 7.5$ Hz, 2H), 1.82−1.65 (m, 2H), 1.46−1.25 (m, 4H), 0.91 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 335 ($M + Na^+$); FAB-HRMS ($M + H^+$) calcd, 312.1743; found, 312.1734. Anal. ($C_{20}H_{24}O_3 \cdot 0.1H_2O$) C, H, N.

3-(4-Hexyloxy-phenyl)-3-phenyl-propionic Acid (9). Using **8** and following the procedure as in the preparation of **3** gave **9** (84%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, $J = 8.0$ Hz, 2H), 4.47 (t, $J = 9.0$ Hz, 1H), 3.90 (t, $J = 6.0$ Hz, 2H), 3.05 (d, $J = 9.0$ Hz, 2H), 1.74 (tt, $J = 6.0$, 6.0 Hz, 2H), 1.48−1.26 (m, 6H), 0.89 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 349 ($M + Na^+$). Anal. ($C_{21}H_{26}O_3$) C, H, N.

3-(4-Heptyloxy-phenyl)-3-phenyl-propionic Acid (11). Using **10** and following the procedure as in the preparation of **3** gave **11** (79%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.09 (m, 7H), 6.80 (d, $J = 6.0$ Hz, 2H), 4.47 (t, $J = 7.5$ Hz, 1H), 3.90 (t, $J = 6.0$ Hz, 2H), 3.05 (d, $J = 7.5$ Hz, 2H), 1.74 (tt, $J = 6.0$, 6.0 Hz, 2H), 1.48−1.22 (m, 8H), 0.88 (t, $J = 6.0$ Hz, 3H); MS (ES) m/z 363 ($M + Na^+$).

3-Phenyl-3-[4-(4,4,4-trifluoro-butoxy)-phenyl]-propionic Acid (13). Using **12** and following the procedure as in the preparation of **3** gave **13** (50%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, $J = 8.6$ Hz, 2H), 4.47 (t, $J = 7.8$ Hz, 1H), 3.96 (t, $J = 6.0$ Hz, 2H), 3.05 (d, $J = 7.8$ Hz, 2H), 2.36−2.20 (m, 2H), 2.08−1.96 (m, 2H); MS (ES) m/z 375 ($M + Na^+$); FAB-HRMS ($M + H^+$) calcd, 352.1286; found, 352.1291.

3-(4-But-2-enyloxy-phenyl)-3-phenyl-propionic Acid (15). Using **14** and following the procedure as in the preparation of **3** gave **15** (70%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.82 (d, $J = 9.0$ Hz, 2H), 5.89−5.64 (m, 2H), 4.56−4.38 (m, 3H), 3.05 (d, $J = 9.0$ Hz, 2H), 1.74 (d, $J = 6.0$ Hz, 3H); MS (ES) m/z 319 ($M + Na^+$).

3-[4-(3-Methoxy-propoxy)-phenyl]-3-phenyl-propionic Acid (17). Using **16** and following the procedure as in the preparation of **3** gave **17** (75%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81 (d, $J = 9.0$ Hz, 2H), 4.46 (t, $J = 9.0$ Hz, 1H), 4.00 (t, $J = 6.0$ Hz, 2H), 3.53 (t, $J = 6.0$ Hz, 2H), 3.33 (s, 3H), 3.04 (d, $J = 9.0$ Hz, 2H), 2.01 (tt, $J = 6.0$, 6.0 Hz, 2H); MS (ES) m/z 333 ($M + Na^+$).

3-[4-(3-Methyl-but-3-enyloxy)-phenyl]-3-phenyl-propionic Acid (19). Using **18** and following the procedure as in the preparation of **3** gave **19** (56%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.81 (d, $J = 8.0$ Hz, 2H), 4.82 (s, 1H), 4.78 (s, 1H), 4.47 (t, $J = 8.0$ Hz, 1H), 4.03 (t, $J = 8.0$ Hz, 2H), 3.05 (d, $J = 8.0$ Hz, 2H), 2.47 (t, $J = 8.0$ Hz, 2H), 1.79 (s, 3H); MS (ES) m/z 333 ($M + Na^+$).

3-[4-(2-Methyl-butoxy)-phenyl]-3-phenyl-propionic Acid (22). Using **21** and following the procedure as in the preparation of **3** gave **22** (56%) as a white solid. Due to the two chiral centers, the ^{1}H NMR is complex. For clean ^{1}H NMR, please see **22**(*B*, *R*), **22**(*B*, *S*), **22**(*A*, *R*), and **22**(*A*, *S*).

3-[4-(2-Ethyl-butoxy)-phenyl]-3-phenyl-propionic Acid (24). Using **23** and following the procedure as in the preparation of **3** gave **24** (51%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 7.12 (d, $J = 6.6$ Hz, 2H), 6.81 (d, $J = 6.6$ Hz, 2H), 4.46 (t, $J = 8.0$ Hz, 1H), 3.79 (d, $J = 5.7$ Hz, 2H), 3.04 (d, $J = 8.0$ Hz, 2H), 1.69−1.53 (m, 1H), 1.50−1.38 (m, 4H), 0.91 (t, $J = 7.4$ Hz, 6H); MS (ES) m/z 349 ($M + Na^+$). Anal. ($C_{21}H_{26}O_3$) C, H, N.

General Procedure for the Synthesis of 4, 6, 18, 21(*B*, *R*), 21(*B*, *S*), 21(*A*, *R*), and 21(*A*, *S*) (Method B). 3-(4-Butoxy-

phenyl)-3-phenyl-propionic Acid Ethyl Ester (4). A solution of **1** (135 mg, 0.50 mmol), 1-butanol (37 mg, 0.50 mmol), and PPh_3 (157 mg, 0.60 mmol) in THF (3 mL) was treated with DIAD (107 mg, 0.53 mmol). The reaction was stirred at room temperature for 7 h. The reaction mixture was concentrated, and the crude product was purified by column chromatography on silica gel (20:1 hexane/EtOAc) to give 103 mg (63%) of **4** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, J = 6.0 Hz, 2H), 4.49 (t, J = 6.0 Hz, 1H), 4.02 (q, J = 6.0 Hz, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.01 (d, J = 6.0 Hz, 2H), 1.73 (tt, J = 6.0, 6.0 Hz, 2H), 1.52−142 (m, 2H), 1.11 (t, J = 6.0 Hz, 3H), 0.95 (t, J = 6.0 Hz, 3H); MS (ES) m/z 327 (M + H^+).

3-(4-Pentyloxy-phenyl)-3-phenyl-propionic Acid Ethyl Ester (6). Using 1-pentanol and following the procedure as in the preparation of **4** gave **6** (69%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.80 (d, J = 8.0 Hz, 2H), 4.49 (t, J = 7.5 Hz, 1H), 4.02 (q, J = 6.0 Hz, 2H), 3.90 (t, J = 6.0 Hz, 2H), 3.01 (d, J = 7.5 Hz, 2H), 1.75 (tt, J = 6.0, 6.0 Hz, 2H), 1.45−1.27 (m, 4H), 1.10 (t, J = 6.0 Hz, 3H), 0.93 (t, J = 6.0 Hz, 3H); MS (ES) m/z 341 (M + H^+).

3-[4-(3-Methyl-but-3-enyloxy)-phenyl]-3-phenyl-propionic Acid Ethyl Ester (18). Using 3-methyl-but-3-en-1-ol and following the procedure as in the preparation of **4** gave **18** (64%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.82 (d, J = 9.0 Hz, 2H), 4.82 (s, 1H), 4.78 (s, 1H), 4.49 (t, J = 9.0 Hz, 1H), 4.08−3.99 (m, 2H), 3.01 (d, J = 9.0 Hz, 2H), 2.47 (t, J = 6.0 Hz, 2H), 1.78 (s, 3H), 1.11 (t, J = 6.0 Hz, 3H); MS (ES) m/z 361 (M + Na^+).

(3*B*)-{4-[(2*R*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid Ethyl Ester (21(*B, R*)). Using **1**(*B*), which was the second peak separated from the chiral HPLC (OJ column, using 100% MeOH as the eluent and 80 mL/min as the flow rate, retention time ∼ 22.9 min) of **1**, and (*R*)-2-methyl-butan-1-ol and following the procedure as in the preparation of **4** gave **21**(*B, R*) as a colorless oil (44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81 (d, J = 8.7 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.76 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.01 (d, J = 8.0 Hz, 2H), 1.86−1.76 (m, 1H), 1.60−1.49 (m, 1H), 1.30−1.19 (m, 1H), 1.13 (t, J = 7.1 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); MS (ES) m/z 341 (M + H^+).

(3*B*)-{4-[(2*S*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid Ethyl Ester (21(*B, S*)). Using **1**(*B*) and (*S*)-2-methyl-butan-1-ol and following the procedure as in the preparation of **4** gave **21**(*B, S*) as a colorless oil (81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81(d, J = 8.7 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.01 (d, J = 8.1 Hz, 2H), 1.86−1.76 (m, 1H), 1.60−1.49 (m, 1H), 1.30−1.19 (m, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); MS (ES) m/z 341 (M + H^+); $[\alpha]_D$ = 5.5 (*c* 1, $CHCl_3$).

(3*A*)-{4-[(2*R*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid Ethyl Ester (21(*A, R*)). Using **1**(*A*), which was the first peak separated from the chiral HPLC (OJ column, using 100% MeOH as the eluent and 80 mL/min as the flow rate, retention time ∼ 19.1 min) of **1**, and (*R*)-2-methyl-butan-1-ol and following the procedure as in the preparation of **4** gave **21**(*A, R*) as a colorless oil (50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81-(d, J = 8.7 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.01 (d, J = 8.1 Hz, 2H), 1.86−1.76 (m, 1H), 1.60−1.48 (m, 1H), 1.30−1.15 (m, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); MS (ES) m/z 341 (M + H^+).

(3*A*)-{4-[(2*S*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid Ethyl Ester (21(*A, S*)). Using **1**(*A*) and (*S*)-2-methyl-butan-1-ol and following the procedure as in the preparation of **4** gave **21**(*A, S*) as a colorless oil (76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81(d, J = 8.7 Hz, 2H), 4.49 (t, J = 8.0 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.01 (d, J = 8.1 Hz, 2H), 1.86−1.76 (m, 1H), 1.60−1.49 (m, 1H), 1.30−1.19 (m, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); MS (ES) m/z 341 (M + H^+).

(3*B*)-{4-[(2*R*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid (22(*B, R*)). Using **21**(*B, R*) and following the procedure as in the preparation of **3** gave **22**(*B, R*) as a colorless oil film (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81 (d, J = 8.6 Hz, 2H), 4.48 (t, J = 7.8 Hz, 1H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.06 (d, J = 7.9 Hz, 2H), 1.86−1.76 (m, 1H), 1.60−1.49 (m, 1H), 1.30−1.19 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); MS (ES) m/z 335 (M + Na^+). Anal. ($C_{20}H_{24}O_3$) C, H, N.

(3*B*)-{4-[(2*S*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid (22(*B, S*)). Using **21**(*B, S*) and following the procedure as in the preparation of **3** gave **22**(*B, S*) as a white solid (92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81(d, J = 8.6 Hz, 2H), 4.47 (t, J = 7.8 Hz, 1H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.05 (d, J = 7.9 Hz, 2H), 1.88−1.76 (m, 1H), 1.60−1.46 (m, 1H), 1.31−1.18 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); MS (ES) m/z 335 (M + Na^+).

(3*A*)-{4-[(2*R*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid (22(*A, R*)). Using **21**(*A, R*) and following the procedure as in the preparation of **3** gave **22**(*A, R*) as a white solid (94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81(d, J = 8.6 Hz, 2H), 4.47 (t, J = 7.8 Hz, 1H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.05 (d, J = 7.9 Hz, 2H), 1.88−1.76 (m, 1H), 1.60−1.46 (m, 1H), 1.31−1.18 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); MS (ES) m/z 335 (M + Na^+).

(3*A*)-{4-[(2*S*)-Methyl-butoxy]-phenyl}-3-phenyl-propionic Acid (22(*A, S*)). Using **21**(*A, S*) and following the procedure as in the preparation of **3** gave **22**(*A, S*) as a colorless oil film (98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.10 (m, 7H), 6.81(d, J = 8.6 Hz, 2H), 4.47 (t, J = 7.8 Hz, 1H), 3.77 (dd, J = 9.0, 6.0 Hz, 1H), 3.68 (dd, J = 9.0, 6.6 Hz, 1H), 3.05 (d, J = 7.9 Hz, 2H), 1.88−1.76 (m, 1H), 1.60−1.46 (m, 1H), 1.31−1.18 (m, 1H), 0.98 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); MS (ES) m/z 335 (M + Na^+).

3-[4-(3-Methyl-butoxy)-phenyl]-3-phenyl-propionic Acid (20). A mixture of compound **19** (15 mg, 0.05 mmol) in EtOH (5 mL) with Pd/C (10% w/w, 20 mg) was shaken under H_2 (55 psi) for 5 h in a Parr shaker. Filtration though Celite and concentration gave the crude. The crude product was purified by column chromatography on silca gel (20:1 CH_2Cl_2/MeOH) to give 10 mg (66%) of the acid **20** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 5H), 7.12 (d, J = 9.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 4.46 (t, J = 7.5 Hz, 1H), 3.93 (t, J = 6.0 Hz, 2H), 3.04 (d, J = 7.5 Hz, 2H), 1.87−1.72 (m, 1H), 1.64 (dt, J = 6.0, 6.0 Hz, 2H), 0.94 (d, J = 6.0 Hz, 6H); MS (ES) m/z 335 (M + Na^+).

General Procedure for the Synthesis of 27, 32, and 37. 3-(3-Fluoro-phenyl)-3-(4-methoxy-phenyl)-propionic Acid Ethyl Ester (27). Tetrabutylammonium bromide (1.64 g) was melted at 130 °C. Compound **25** (618 mg, 3.0 mmol), 1-bromo-3-fluoro-benzene (788 mg, 4.5 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol), and then tetrabutylammonium acetate (2.26 g, 7.5 mmol) were added. The mixture was stirred at 130 °C for 30 h. Water was added to the cooled mixture and it was extracted with hexane thrice. The combined extracts were washed with water (×2) and brine and dried over Na_2SO_4. The reaction mixture was concentrated, and the crude product was purified by column chromatography (10:1 hexane/EtOAc) to give 839.2 mg of a mixture containing **26**. The mixture (826 mg) was dissolved in EtOH (50 mL) with Pd/C (10% w/w, 450 mg) and then was shaken under H_2 in a Parr shaker overnight. Filtration through Celite and concentrated. The crude product was purified by column chromatography on silica gel (20:1 hexane/EtOAc) to give 421 mg (46% for 2 steps) of **27** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 1H), 7.14 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.0 Hz, 1H), 6.92−6.84 (m, 2H), 6.83 (d, J = 8.0 Hz, 2H), 4.49 (t, J = 7.8 Hz, 1H), 4.04 (q, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.99 (d, J = 7.8 Hz, 2H), 1.12 (t, J = 8.0 Hz, 3H); MS (ES) m/z 325 (M + Na^+).

3-(4-Methoxy-phenyl)-3-(3-trifluoro-methyl-phenyl)-propionic Acid Ethyl Ester (32). Using 1-bromo-3-trifluoromethylbenzene and following the procedure as in the preparation of **27** gave **32** (9% for 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.36 (m, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 4.54 (t, J = 7.8 Hz, 1H), 4.04 (q, J = 8.0 Hz, 2H), 3.77 (s, 3H), 3.02 (d, J = 7.8 Hz, 2H), 1.11 (t, J = 8.0 Hz, 3H); MS (ES) m/z 353 (M + H$^+$).

3-(4-Methoxy-phenyl)-3-(4-trifluoro-methyl-phenyl)-propionic Acid Ethyl Ester (37). Using 1-bromo-4-trifluoromethylbenzene and following the procedure as in the preparation of **27** gave **37** (36% for 2 steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.5 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 2H), 6.83 (d, J = 7.5 Hz, 2H), 4.56 (t, J = 9.0 Hz, 1H), 4.04 (q, J = 7.5 Hz, 2H), 3.77 (s, 3H), 3.03 (d, J = 9.0 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H).

General Procedure for the Synthesis of 28, 33, and 38. 3-(4-Hydroxy-phenyl)-3-(3-trifluoro-methyl-phenyl)-propionic Acid Ethyl Ester (33). Compound **32** (188 mg, 0.53 mmol) in CH_2Cl_2 (6 mL) at −78 °C was treated with BBr_3 (1.0 M in CH_2Cl_2, 0.80 mL, 0.80 mmol). The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. Saturated $NaHCO_3$ aqueous solution was added to the cooled (0 °C) reaction mixture. The mixture was extracted with EtOAc thrice. The combined extracts were washed with H_2O and brine and dried (Na_2SO_4). Concentration and chromatography on silica gel (4:1 hexane/EtOAc) give 75 mg (42%) of **33** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.36 (m, 3H), 7.07 (d, J = 8.0 Hz, 2H), 6.74 (d, J = 8.0 Hz, 2H), 5.16 (s, 1H, OH), 4.54 (t, J = 7.8 Hz, 1H), 4.03 (q, J = 8.0 Hz, 2H), 3.02 (d, J = 7.8 Hz, 2H), 1.12 (t, J = 8.0 Hz, 3H); MS (ES) m/z 339 (M + H$^+$).

3-(3-Fluoro-phenyl)-3-(4-hydroxy-phenyl)-propionic Acid Ethyl Ester (28). Using **27** and following the procedure as in the preparation of **33** gave **28** (96%) as a colorless oil.

3-(4-Hydroxy-phenyl)-3-(4-trifluoro-methyl-phenyl)-propionic Acid Ethyl Ester (38). Using **37** and following the procedure as in the preparation of **33** gave **38** (87%) as a colorless oil.

General Procedure for the Synthesis of 29, 34, and 39. 3-(4-Butoxy-phenyl)-3-(3-trifluoromethyl-phenyl)-propionic Acid Ethyl Ester (34). Compound **33** (22 mg, 0.07 mmol) in DMF (0.6 mL) with CsF (30 mg, 0.20 mmol) was treated with *n*-butyl iodide (15 mg, 0.08 mmol). The mixture was stirred at room temperature overnight. Chromatography of the mixture on silica gel (20:1 hexane/EtOAc) gave 22 mg (86%) of **34** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.36 (m, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 4.55 (t, J = 7.8 Hz, 1H), 4.04 (q, J = 8.0 Hz, 2H), 3.92 (t, J = 6.0 Hz, 2H), 3.02 (d, J = 7.8 Hz, 2H), 1.75 (tt, J = 6.0, 6.0 Hz, 2H), 1.47 (tq, J = 6.0, 6.0 Hz, 2H), 1.11 (t, J = 8.0 Hz, 3H), 0.96 (t, J = 6.0 Hz, 3H); MS (ES) m/z 395 (M + H$^+$).

3-(4-Butoxy-phenyl)-3-(3-fluoro-phenyl)-propionic Acid Ethyl Ester (29). Using **28** and following the procedure as in the preparation of **34** gave **29** (78%) as a colorless oil.

3-(4-Butoxy-phenyl)-3-(4-trifluoromethyl-phenyl)-propionic Acid Ethyl Ester (39). Using **38** and following the procedure as in the preparation of **34** gave **39** (83%) as a colorless oil.

General Procedure for the Synthesis of 30, 35, and 40. 3-(4-Butoxy-phenyl)-3-(3-fluoro-phenyl)-propionic Acid (30). A solution of **29** (46 mg) in THF/MeOH/H_2O (4:1:1 v/v/v, 6.0 mL) was treated with LiOH (1.0 mL, 1.0 mmol, 1 N). The mixture was stirred at room temperature overnight. Aqueous 1 N HCl solution was added and it was extracted with EtOAc three times. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave 25 mg (58%) of the acid **30** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.20 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.00 (d, J = 8.0 Hz, 1H), 6.90−6.83 (m, 2H), 6.82 (d, J = 8.0 Hz, 2H), 4.45 (t, J = 7.8 Hz, 1H), 3.92 (t, J = 8.0 Hz, 2H), 3.02 (d, J = 7.8 Hz, 2H), 1.78−1.69 (m, 2H), 1.52−1.40 (m, 2H), 0.96 (t, J = 8.0 Hz, 3H); MS (ES) m/z 339 (M + Na$^+$).

3-(4-Butoxy-phenyl)-3-(3-trifluoromethyl-phenyl)-propionic Acid (35). Using **34** and following the procedure as in the preparation of **30** gave **35** (65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.35 (m, 3H), 7.11 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 4.52 (t, J = 7.5 Hz, 1H), 3.92 (t, J = 6.0 Hz, 2H), 3.06 (d, J = 7.5 Hz, 2H), 1.74 (tt, J = 6.0, 6.0 Hz, 2H), 1.47 (tq, J = 6.0, 6.0 Hz, 2H), 0.96 (t, J = 6.0 Hz, 3H); MS (ES) m/z 367 (M + H$^+$).

3-(4-Butoxy-phenyl)-3-(4-trifluoromethyl-phenyl)-propionic Acid (40). Using **39** and following the procedure as in the preparation of **30** gave **40** (85%) as a colorless sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, J = 6.0 Hz, 2H), 7.32 (d, J = 6.0 Hz, 2H), 7.10 (d, J = 9.0 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 4.51 (t, J = 7.5 Hz, 1H), 3.91 (t, J = 6.0 Hz, 2H), 3.06 (d, J = 7.5 Hz, 2H), 1.72 (tt, J = 6.0, 6.2 Hz, 2H), 1.46 (tq, J = 6.0, 6.2 Hz, 2H), 0.95 (t, J = 6.0 Hz, 3H); MS (ES) m/z 389 (M + Na$^+$).

3-(4-Methoxy-phenyl)-3-thiophen-2-yl-propionic Acid Ethyl Ester (43). (Diethoxy-phosphoryl)-acetic acid ethyl ester (3.36 g, 15.0 mmol) was added dropwise to a suspension of NaH in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 30 min. A solution of **41** (1.09 g, 5.0 mmol) in THF (5 mL) was added. The reaction mixture was stirred at 60 °C overnight. The cooled mixture was poured into a saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc thrice. The combined extracts were washed with H_2O and brine and dried (Na_2SO_4). Concentration gave 0.806 g of the crude **42** as yellowish oil. The crude **42** (0.806 g) was dissolved in CH_2Cl_2 (30 mL) and treated with Et_3SiH (10.7 mL, 67.2 mmol). Trifluoroacetic acid (21.5 mL, 280 mmol) was added at room temperature. After it was stirred at room temperature for 2 h, the reaction mixture was concentrated and then azeotroped with $CHCl_3$ three times. The residue was purified by column chromatography on silica gel (4:1 hexane/EtOAc) to afford 800 mg (55% for 2 steps) of **43** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ7.20 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.91−6.87 (m, 1H), 6.86−6.78 (m, 3H), 4.72 (t, J = 8.0 Hz, 1H), 4.05 (q, J = 8.0 Hz, 2H), 3.78 (s, 3H), 3.08 (dd, J = 16.0, 8.0 Hz, 1H), 2.98 (dd, J = 16.0, 8.0 Hz, 1H), 1.14 (t, J = 8.0 Hz, 3H); MS (ES) m/z 291 (M + H$^+$).

3-(4-Hydroxy-phenyl)-3-thiophen-2-yl-propionic Acid Ethyl Ester (44). A solution of **43** (1.273 g, 4.39 mmol) in CH_2Cl_2 (45 mL) at −78 °C was treated with BBr_3 (1.0 M in CH_2Cl_2, 6.6 mL, 6.6 mmol). The reaction mixture was stirred at room temperature overnight. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with CH_2Cl_2 thrice. The combined extracts were washed with H_2O and brine and dried (Na_2SO_4). Concentration and chromatography on silica gel (4:1 hexane/EtOAc) gave 361 mg (30%) of **44** as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−7.10 (m, 3H), 6.90 (dd, J = 8.0, 4.0 Hz, 1H), 6.81 (d, J = 4.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 4.69 (t, J = 8.0 Hz, 1H), 4.05 (q, J = 8.0 Hz, 2H), 3.09 (dd, J = 16.0, 8.0 Hz, 1H), 2.99 (dd, J = 16.0, 8.0 Hz, 1H), 1.14 (t, J = 8.0 Hz, 3H); MS (ES) m/z 299 (M + Na$^+$).

3-(4-Butoxy-phenyl)-3-thiophen-2-yl-propionic Acid Ethyl Ester (45). Compound **44** (79 mg, 0.29 mmol) in DMF (1.5 mL) with CsF (130 mg, 0.86 mmol) was treated with *n*-butyl iodide (79 mg, 0.43 mmol). The mixture was stirred at room temperature overnight. Chromatography of the mixture on silica gel (20:1 hexane/EtOAc, then 10:1 hexane/EtOAc) gave 69 mg (72%) of **45** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.90 (dd, J = 8.0, 4.0 Hz, 1H), 6.86−6.80 (m, 3H), 4.70 (t, J = 8.0 Hz, 1H), 4.05 (q, J = 8.0 Hz, 2H), 3.93 (t, J = 8.0 Hz, 2H), 3.08 (dd, J = 16.0, 8.0 Hz, 1H), 2.98 (dd, J = 16.0, 8.0 Hz, 1H), 1.75 (tt, J = 6.5 Hz, 2H), 1.49 (tq, J = 8.0, 8.0 Hz, 2H), 1.14 (t, J = 8.0 Hz, 3H) 0.96 (t, J = 8.0 Hz, 3H); MS (ES) m/z 333 (M + H$^+$).

3-(4-Butoxy-phenyl)-3-thiophen-2-yl-propionic Acid (46). Compound **45** (61 mg, 0.18 mmol) in THF/MeOH/H_2O (4:1:1 v/v/v, 6 mL) was treated with LiOH (1 M in H_2O, 1.0 mL, 1.0 mmol). The mixture was stirred at room temperature overnight. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc

thrice. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave 43 mg (77%) of the acid **46** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20−7.11 (m, 3H), 6.93−6.80 (m, 4H), 4.69 (t, J = 7.6 Hz, 1H), 3.93 (t, J = 6.5 Hz, 2H), 3.13 (dd, J = 15.9, 7.6 Hz, 1H), 3.03 (dd, J = 15.9, 7.6 Hz, 1H), 1.75 (tt, J = 6.5 Hz, 2H), 1.53−1.45 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); MS (ES) m/z 305 (M + H$^+$); FAB-HRMS (M + H$^+$) calcd, 304.1152; found, 304.1146.

4-(4-Methoxy-phenyl)-chromen-2-one (48). To a mixture of compound **47** (1.58 g, 5.0 mmol) and 4-methoxyphenylboronic acid (1.52 g, 10.0 mmol) in THF (40 mL) was added $PdCl_2(PPh_3)_4$ (176 mg, 0.25 mmol), followed by Na_2CO_3 (2.0M in H_2O, 40 mL, 80 mmol). The reaction mixture was stirred at 60 °C overnight. The cooled reaction mixture was extracted with EtOAc twice. The combined organic phase was washed successively with H_2O and brine and dried (Na_2SO_4). Concentration and chromatography on silica gel (4:1 hexane/CH_2Cl_2, 4:1 hexane/EtOAc, then 2:1 hexane/EtOAc) gave 644 mg (51%) of **48** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J = 9.0 Hz, 1H), 7.55 (t, J = 9.0 Hz, 1H), 7.45−7.39 (m, 3H), 7.24 (t, J = 9.0 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 6.36 (s, 1H), 3.90 (s, 3H); MS (ES) m/z 253 (M + H$^+$).

4-(4-Hydroxy-phenyl)-chroman-2-one (50). A mixture of **48** (600 mg, 2.4 mmol) in EtOAc (50 mL) with Pd/C (10% w/w, 300 mg) was shaken under H_2 (55 psi) for 24 h. Filtration through Celite and concentration gave 538 mg of the crude **49** as white solid. The crude solid **49** (127 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) at −78 °C was treated with BBr_3 (1.0 M in CH_2Cl_2, 0.75 mL, 0.75 mmol). The reaction mixture was stirred at −78 °C for 1 h, then at room temperature for 2 h. Saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with EtOAc thrice. The combined extracts were washed with brine and dried (Na_2SO_4). Concentration and chromatography on silica gel (2:1 hexane/EtOAc) gave 80 mg (59% for 2 steps) of **50** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.6 Hz, 1H), 7.15−7.06 (m, 2H), 7.10−6.96 (m, 3H), 6.79 (d, J = 8.6 Hz, 2H), 5.79 (s, 1H), 4.28 (t, J = 6.7 Hz, 1H), 3.10−2.94 (m, 2H); MS (ES) m/z 263 (M + Na$^+$).

4-(4-Butoxy-phenyl)-chroman-2-one (51). Compound **50** (36 mg, 0.15 mmol) in DMF (1.0 mL) with CsF (69 mg, 0.45 mmol) was treated with *n*-butyl iodide (42 mg, 0.23 mmol). The mixture was stirred at room temperature overnight. Chromatography of the mixture on silica gel (10:1 hexane/EtOAc) gave 36 mg (81%) of **51** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (t, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 7.10−7.01 (m, 3H), 6.98 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.7 Hz, 2H), 4.29 (dd, J = 8.1, 6.1 Hz, 1H), 3.94 (t, J = 6.5 Hz, 2H), 3.05 (dd, J = 15.8, 6.1 Hz, 1H), 2.99 (dd, J = 15.8, 8.1 Hz, 1H), 1.76 (tt, J = 6.5, 6.0 Hz, 2H), 1.55−1.42 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); MS (ES) m/z 297 (M + H$^+$).

3-(4-Butoxy-phenyl)-3-(2-hydroxy-phenyl)-propionic Acid (52). Compound **51** (36 mg, 0.12 mmol) in THF/MeOH/H_2O (4:1:1 v/v/v, 6.0 mL) was treated with LiOH (1 M in H_2O, 1.0 mL, 1.0 mmol). The mixture was stirred at room temperature overnight. Aqueous 1 N HCl solution was added and it was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave 19 mg (51%) of the acid **52** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18−7.03 (m, 4H), 6.90−6.75 (m, 4H), 4.74 (t, J = 7.6 Hz, 1H), 3.91 (t, J = 6.5 Hz, 2H), 3.00−2.98 (m, 2H), 1.73 (tt, J = 6.5, 6.5 Hz, 2H), 1.53−1.40 (m, 2H), 0.95 (t, J = 7.4, 3H); MS (ES) m/z 337 (M + Na$^+$).

(3-Pentyloxy-phenyl)-phenyl-methanone (54). To a solution of **53** (0.990 g, 5.0 mmol), *n*-pentyl alcohol (0.440 g, 5.0 mmol), and PPh_3 (1.574 g, 6.0 mmol) in THF (20 mL) was added DIAD (1.112 g, 5.5 mmol). The solution was stirred at room temperature overnight. Concentration and chromatography on silica gel (20:1 hexane/EtOAc) gave 0.940 g (70%) of **54** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.51−7.46 (m, 2H), 7.39−7.31 (m, 3H), 7.13 (m, 1H), 7.14−7.10 (m, 1H), 4.01 (t, J = 8.0 Hz, 2H), 1.81 (tt, J = 8.0, 8.0 Hz, 2H), 1.57−1.43 (m, 4H), 0.93 (t, J = 8.0 Hz, 3H); MS (ES) m/z 269 (M + H$^+$).

3-(3-Pentyloxy-phenyl)-3-phenyl-acrylic Acid (56). (Diethoxy-phosphoryl)-acetic acid ethyl ester (258 mg, 1.15 mmol) was added dropwise to a suspension of NaH (60% w/w in mineral oil, 43 mg, 1.07 mmol) in THF (3 mL) at 0 °C. The mixture was stirred at room temperature for 30 min. A solution of **54** (103 mg, 0.38 mmol) in THF (2 mL) was added. The reaction mixture was stirred at 60 °C overnight. The cooled mixture was poured into a saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc thrice. The combined extracts were washed with H_2O and brine and dried (Na_2SO_4). Concentration and chromatography on silica gel (20:1 hexane/EtOAc) gave 128 mg (33%) of a 1:1 *Z*/*E* mixture of **55** as a colorless oil. Compound **55** (128 mg, 0.38 mmol) in THF/MeOH/H_2O (4:1:1 v/v/v, 12 mL) was treated with LiOH (1 M in H_2O, 2.0 mL, 2.0 mmol). The mixture was stirred at room temperature for overnight. Saturated NH_4Cl aqueous solution was added and it was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave 97 mg (82%) of the acid **56** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.16 (m, 6H), 6.91−6.72 (m, 3H), 6.31 (s, 1H), 3.91 (q, J = 6.0 Hz, 2H), 1.81−1.69 (m, 2H), 1.48−1.30 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); MS (ES) m/z 333 (M + Na$^+$).

3-(3-Pentyloxy-phenyl)-3-phenyl-propionic Acid (57). A mixture of **56** (58 mg, 0.19 mmol) in EtOH (10 mL) with Pd/C (10% w/w, 50 mg) was shaken under H_2 (55 psi) for 2.5 h. Filtration through Celite and concentration gave the crude product. The crude product was purified by column chromatography on silica gel (20:1 CH_2Cl_2/MeOH) to give 51 mg (86%) of the acid **57** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.15 (m, 6H), 6.83−6.70 (m, 3H), 6.31 (s, 1H), 4.48 (t, J = 8.0 Hz, 1H), 3.90 (q, J = 8.0 Hz, 2H), 3.07 (d, J = 8.0 Hz, 2H), 1.75 (tt, J = 8.0, 8.0 Hz, 2H), 1.46−1.32 (m, 4H), 0.90 (t, J = 8.0 Hz, 3H); MS (ES) m/z 335 (M + Na$^+$).

3-(4-Butoxy-phenyl)-3-phenyl-propionaldehyde (58). To a solution of compound **4** (311 mg, 0.95 mmol) in CH_2Cl_2 (9 mL) at −78 °C was added dropwise DIBAL-H (1.0 M in CH_2Cl_2, 2.50 mL, 2.50 mmol). The reaction mixture was stirred at −78 °C for 1 h. Saturated Rochelle's salt aqueous solution was added and it was stirred vigorously at room temperature until the two layers became clear. It was extracted with EtOAc thrice and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel (10:1 hexane/EtOAc) to give 179 mg (67%) of the aldehyde **58** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.30−7.16 (m, 5H), 7.12 (d, J = 8.0 Hz, 2H), 6.82 (d, J = 8.0 Hz, 2H), 4.56 (t, J = 8.0 Hz, 1H), 3.91 (t, J = 7.0 Hz, 2H), 3.12 (d, J = 8.0 Hz, 2H), 1.73 (tt, J = 7.0, 7.0 Hz, 2H), 1.44 (tq, J = 7.0, 7.0 Hz, 2H), 0.96 (t, J = 7.0 Hz, 3H); MS (ES) m/z 305 (M + Na$^+$).

5-(4-Butoxy-phenyl)-5-phenyl-pent-2-enoic Acid Ethyl Ester (59). A mixture of the aldehyde **58** (88 mg, 0.31 mmol) and (triphenylphosphanylidene)-acetic acid ethyl ester (230 mg, 0.62 mmol) in toluene (8 mL) was heated at reflux for 1.5 h. Concentration and chromatography on silica gel (10:1 hexane/EtOAc) gave 106 mg (96%) of **59** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.16 (m, 5H), 7.10 (d, J = 8.0 Hz, 2H), 6.84 (dt, J = 16.0, 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 2H), 5.80 (d, J = 16.0 Hz, 1H), 4.12 (q, J = 8.0 Hz, 2H), 4.04 (t, J = 8.0 Hz, 1H), 3.91 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 8.0 Hz, 2H), 1.74 (tt, J = 7.0 Hz, 2H), 1.47 (tq, J = 7.0 Hz, 2H), 1.24 (t, J = 8.0 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H); MS (ES) m/z 353 (M + H$^+$).

5-(4-Butoxy-phenyl)-5-phenyl-pentanoic Acid Ethyl Ester (60). Compound **59** (96 mg, 0.27 mmol) was dissolved in MeOH (15 mL) with Pd/C (10% w/w, 90 mg) and it was shaken under H_2 (55 psi) for 2 h. Filtration through Celite and concentration gave the crude. The crude product was purified by column chromatography on silica gel (10:1 hexane/EtOAc) gave 89 mg (92%) of **60** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.15 (m,

5H), 7.11 (d, $J = 8.0$ Hz, 2H), 6.80 (d, $J = 8.0$ Hz, 2H), 4.10 (q, $J = 7.0$ Hz, 2H), 3.91 (t, $J = 8.0$ Hz, 2H), 3.85 (t, $J = 8.0$ Hz, 2H), 2.31 (t, $J = 8.0$ Hz, 2H), 2.03 (dt, $J = 8.0$, 8.0 Hz, 2H), 1.73 (tt, $J = 8.0$ Hz, 2H), 1.63−1.55 (m, 2H), 1.46 (tq, $J = 8.0$, 8.0 Hz, 2H), 1.24 (t, $J = 7.0$ Hz, 3H), 0.95 (t, $J = 8.0$ Hz, 3H); MS (ES) m/z 377 ($M + Na^+$).

5-(4-Butoxy-phenyl)-5-phenyl-pentanoic Acid (61). Compound **60** (71 mg, 0.20 mmol) in THF/MeOH/H_2O (4:1:1 v/v/v, 6 mL) was treated with LiOH (1 M in H_2O, 1.0 mL, 1.0 mmol). The mixture was stirred at room temperature overnight. Aqueous 1 N HCl solution was added to neutralize the reaction mixture and then it was extracted with EtOAc thrice. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and column chromatography on silica gel (20:1 CH_2Cl_2/MeOH) gave 51 mg (78%) of the acid **61** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 730−7.15 (m, 5H), 7.12 (d, $J = 9.0$ Hz, 2H), 6.80 (d, $J = 9.0$ Hz, 2H), 3.91 (t, $J = 6.0$ Hz, 2H), 3.84 (t, $J = 9.0$ Hz, 2H), 2.35 (t, $J = 7.5$ Hz, 2H), 2.05 (dt, $J = 9.0$, 7.5 Hz, 2H), 1.75 (tt, $J = 6.0$ Hz, 2H), 1.64−1.54 (m, 2H), 1.47 (tq, $J = 7.5$, 6.0 Hz, 2H), 0.95 (t, $J = 7.5$ Hz, 3H); MS (ES) m/z 349 ($M + Na^+$).

Biology. GPR40 FDSS Assay, Methods and Materials. Human embryonic kidney (HEK293) cells expressing human GPR40 receptors were grown in Dulbecco's modified Eagles medium (DMEM)/F12 media supplemented with 10% fetal bovine serum (FBS) and glutamine (Invitrogen Corp., Carlsbad, CA) and maintained in an atmosphere of 5% CO_2/95% O_2 at 37 °C. Changes in ligand-induced calcium-dependent intracellular fluorescence were measured with a fluorometric plate reader (FDSS; Hamamatsu Corp., Bridgewater, NJ). For the assay, cells were grown in black clear-bottom 96-well plates and loaded with fluo-4 dye (2 μM; Molecular Probes, Inc., Eugene, OR) in buffer (25 mM HEPES, 125 mM NaCl, 1 gm/l glucose, 0.01% BSA, 5 mM KCl, 0.5 mM $CaCl_2$, 0.5 mM $MgCl_2$, pH 7.45). During the assay procedure in the FDSS, cells were treated first with the compounds to measure agonist activity followed 3 min later with addition of the known GPR40 agonist linoleic acid (10 μM; Sigma Chemical, St. Louis, MO) to measure compound antagonist activity. Linoleic acid and compounds were solubilized in dimethylsulfoxide (DMSO), which was then serially diluted in buffer so that the cells were exposed to 1.5% DMSO.

MIN6 Insulin Secretion Assay. MIN6 cells were maintained in DMEM (high glucose; Herndon,VA) containing 15% heat-inactivated fetal calf serum and 50 μM β-mercaptoethanol. Cells were seeded into 96-well plates (40 000 cells per well) and cultured for 24 h at 37 °C in humidified 5% CO_2/95% air. Media was removed from the cells and they were washed twice with glucose-free Krebs−Ringers HEPES (120 mM NaCl, 2 mM $CaCl_2$, 2 mM $MgCl_2$, 4 mM KH_2PO_4, 25 mM $NaHCO_3$, and 10 mM HEPES (pH 7.4) containing 0.05% (wv^{-1}) FA free bovine serum albumin (KRBH). Washed cells were incubated with KRBH containing 2.5 mM glucose for 1 h at 37 °C. Subsequently, the plates were washed an additional two times with glucose-free Krebs, and 100 mL of KRBH containing glucose at the desired concentration, plus or minus compound, was added. Following a 2 h incubation, the KRBH solution in each well was removed and the insulin content of an aliquot of each sample supernatant was determined using an ultrasensitive insulin ELISA kit (LINCO Research Cat. No. EZRMI-13K) according to the manufacturer's instructions.

CYP450 Inhibition Screening Assay. The P450 inhibition screening assay was performed in 96-well microtiter plates by using cDNA expressed human enzymes (CYP1A2, 2C9, 2C19, 2D6, and 3A4). The test compounds (prepared in acetonitrile) were serially diluted in phosphate buffer (pH 7.4) containing an electron generating system (glucose-6-phosphate, $NADP^+$, and glucose-6-phosphate dehydogenase). The enzymatic reaction was initiated by adding individual P450 enzymes premixed with P450-specific fluorescent substrates and stopped by adding acetonitrile to the reaction mixture after incubation at 37 °C for a given amount of time. The fluorescence of metabolites was measured on a Biotek fluorescence reader. The results were expressed as inhibition percentage relative to the control. IC_{50} values were estimated from the concentration response curve. The P450 substrates used for the assay include dibenzylfluorescein (DBF for CYP2C9, 2C19, and 3A4), 3-cyano-7-ethoxycoumarin (CEC, for CYP1A2), 3-[2-(*N*,*N*-diethyl-*N*-methylamino)ethyl]-7-methoxy-4-methylcoumarin (AMMC, for CYP2D6), benzyloxyquinoline (BQ), and 7-benzyloxy-4-trifloromethylcoumarin (BFC, for CYP3A4).

Pharmacokinetic Assay. Rats, dogs, monkeys, or other species are normally dosed intravenously (IV) at levels of 1−3 mg/kg and by oral gavage at a level of 10−30 mg/kg with drug candidate. Drug compound is typically formulated for IV dosing as a solution in 10% w/v Solutol in 5% dextrose in sterile water vehicle (D5W). Drug compound is typically formulated for oral dosing as a uniform suspension in 0.5% methylcellulose vehicle. Blood samples (0.5 mL) are collected into heparinized tubes post dose via orbital sinus puncture. Blood samples are centrifuged for cell removal, and precisely 200 μL of plasma supernatant is then transferred to a clean vial, placed on dry ice, and subsequently stored in a −70 °C freezer prior to analysis.

Plasma samples are normally prepared as follows. Acetonitrile (400 μL) containing internal standard is added to 200 μL of plasma to precipitate proteins. Samples are centrifuged at 5000 × G for 3 min and supernatant is removed for analysis by LC-MS-MS. Calibration standards are prepared by adding appropriate volumes of stock solution directly into plasma and treated identically to collected plasma samples. Calibration standards are typically prepared in the range of 0.1 to 10 mM for quantitation. LC-MS-MS analysis is performed using either multiple reaction or selected ion monitoring for detection of characteristic ions for each drug candidate, and the internal standard used is propranolol.

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Supporting Information Available: Elemental analyses data for key target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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