Design, Synthesis, and Biological Evaluation of Novel Constrained *meta*-Substituted Phenyl Propanoic Acids as Peroxisome Proliferator-Activated Receptor α and γ Dual Agonists

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In an effort to develop dual PPARα/γ activators with improved therapeutic efficacy, a series of diaryl α-ethoxy propanoic acid compounds comprising two aryl groups linked by rigid oxime ether or isoxazoline ring were designed and synthesized and their biological activities were examined. Most of the compounds possessing an oxime ether linker were more potent PPARγ activators than the lead PPARα/γ dual agonist, tesaglitazar in vitro. Compound **18**, one of the derivatives with an oxime ether linker, was found to selectively transactivate PPARγ (EC_{50} = 0.028 μM) over PPARα (EC_{50} = 7.22 μM) in vitro and lower blood glucose in *db*/*db* mice more than muraglitazar after oral treatment for 11 days.

Introduction

Peroxisome proliferator-activated receptors (PPARs[a]) regulate the lipid and glucose metabolism. PPARα agonists mainly improve dyslipidemia and PPARγ agonists improve insulin resistance.[1] Many synthetic dual PPARα/γ agonists have been developed to treat type 2 diabetes (T2D) and metabolic syndrome and have been shown to be beneficial as compared with selective PPARα or PPARγ agonists because they improve lipid and glucose homeostasis.[2] However, the adverse toxicity profiles of dual PPARα/γ activators have raised critical safety issues, which have caused developmental programs to be discontinued.[3]

Studies of the mechanisms responsible for these toxicities have not proved clearly whether these side effects identified are target- or compound-related,[4] and therefore we believe that the identification of a dual PPARα/γ agonist with a better pharmacological profile could provide a suitable therapeutic option in T2D. For example, the clinical development of tesaglitazar (a dual PPARα/γ agonist) was discontinued in 2006 due to potential kidney toxicity.[3a] Nevertheless, recent clinical investigations undertaken to fully define the beneficial effects of tesaglitazar revealed that it improves the atherogenic dyslipidemia associated with insulin resistance[5] and improves glycemic control and dyslipidemia when used as an add-on therapy in T2D patients that show poor response to existing sulfonylurea therapy.[6] We believe that these results support the relevance of further research into PPARα/γ dual agonists for the treatment of T2D, given that the safety issues are properly addressed.

The selective PPARα agonist fenofibrate, which acts by weakly modulating PPARα (EC_{50}= 20−30 μM), is known to effectively lower serum triglyceride and free fatty acid levels. In addition, fenofibrate has excellent tolerability in humans; in particular, it induced no significant adverse effects in T2D patients on long-term therapy.[7] On the other hand, PPARγ agonists have been proven to be clinically effective at reducing high plasma glucose levels in T2D, although some PPARγ agonists induce edema and body-weight gain, which are clinical disadvantages in T2D patients.[8] To improve blood glucose lowering and reduce weight gain, it has been suggested that compounds with marginal PPARα affinity but with selective PPARγ-modulating activity provide a possible solution.[9] PPARα/γ agonists usually possess essential pharmacophoric elements,[2,10] i.e., an acidic group attached to a central flat aromatic ring, a linker, and a large hydrophobic group (see Figure 1). On the other hand, dual PPARα/γ agonists possess a flexible alkyl ether linkage, which allows the molecule to adopt a bioactive U-shaped conformation that well fits into the arms of T- or Y-shaped PPAR active sites.[11] Furthermore, in recently reported studies, highly selective and active PPARα/γ dual agonists with nanomolar to picomolar EC_{50} values were obtained by replacing the alkyl ether central linker with a rigid linker composed of an alkenyl, alkynyl, or indole ring.[12]

In the present study, we undertook the design, synthesis, and biological evaluation of a novel series of dual PPARα/γ agonists to identify ligands with improved in vivo efficacy. The PPARα/γ dual agonist tesaglitazar was selected as the chemical lead, and accordingly, analogous compounds (Table 1) were designed and analyzed in terms of their binding modes by docking analysis. In terms of molecular design strategy, the α-(*S*)-ethoxy propanoic acid moiety of tesaglitazar was retained as an acidic head group and the chemical modifications made centered on linker rigidity and hydrophobic moiety type. Oxime ether (a bioisostere of alkene) and isoxazoline ring (a bioisostere of amide) were selected as potential rigid linker units. Phenyl and substituted phenyl groups were utilized as hydrophobic moieties. Comparisons of binding energy scores and binding modes identified the *meta*-substituted aryl structures (scaffolds E and F in Table 1) as the best candidate scaffolds. By varying substituent X in

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[a] Abbreviations: PPAR, peroxisome proliferator-activated receptor; T2D, type 2 diabetes; HOBT, 1-hydroxybenzotriazole; TFAA, trifluoroacetic anhydride; DEAD; diethyl azodicarboxylate; PTSA, *p*-toluenesulfonic acid.

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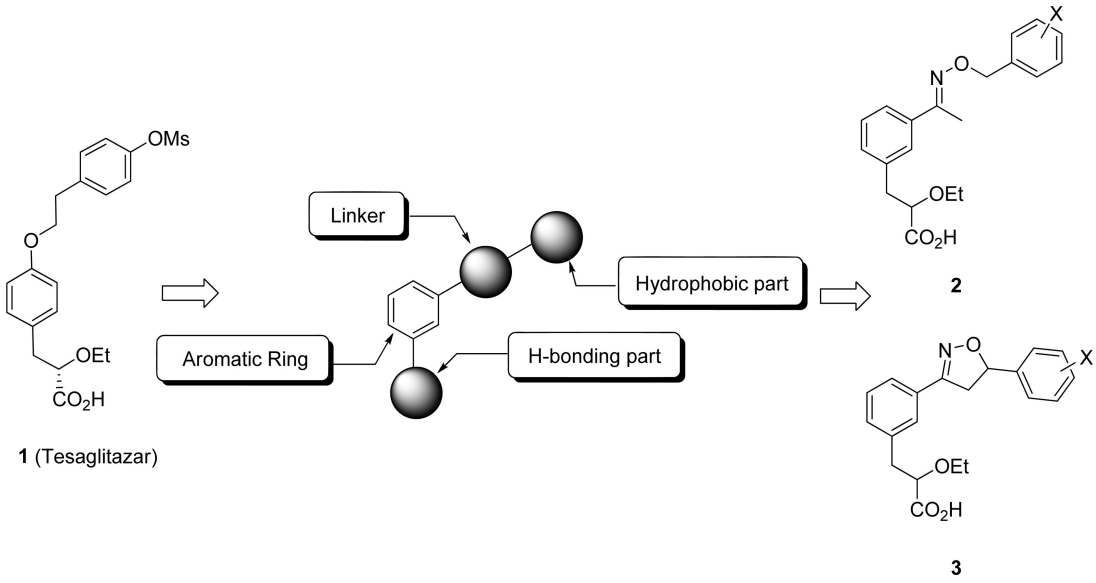


Figure 1. Designs of PPARα/γ Dual Agonists.

the phenyl ring, a series of compounds were synthesized (Figure 1) and subsequently their biological activities were examined. PPARα and γ agonistic activities were determined using in vitro PPARα/γ-GAL4 cotransfection reporter assays, and in vivo antihyperglycemic activities were also measured for several selected compounds. In particular, compound **18** (Table 4), which possesses an oxime linker, was identified as PPARα/γ dual agonist that more effectively lowers blood glucose level than muraglitazar in vivo.

Results and Discussion

Chemistry. Oxime ether analogues were expediently synthesized via a common intermediate, as outlined in Scheme 1. The key intermediate was synthesized from commercially available 3-acetylbenzonitrile (**4**). Sequential nitrile reduction to the aldehyde by DIBAL-H, and Wittig olefination gave **7**. Saturation of the double bond of **7** with hydrogen on Pd/C, removal of ketal, followed by hydrolysis, resulted in the racemic acid **10**, which was transformed into the optically pure amides via (*R*)-2-phenylglycinol coupling. Separation of the resulting two diastereomers, amide hydrolysis, and esterification afforded methyl esters **14** and **30**, respectively (Scheme 2). These intermediates were readily converted into various oxime ether analogues (**16**−**29** and **32**−**41**) by condensation with diverse hydroxyl amines followed by ester hydrolysis (Scheme 2).

The absolute configurations of these oxime ether analogues were confirmed by comparing the specific rotations of compound **44b** transformed from intermediate **45a** with that of **44a** prepared from known intermediate **42**, as described in Scheme 3. Known intermediate **42**, which could be prepared by enzymatic resolution[14] or using a synthetic approach,[2e] was readily converted to **44a** by triflation, followed by deoxygenation using Pd (II). Compound **44b** was prepared from compound **45a** by Baeyer−Villiger oxidation,[15] ester hydrolysis, and the deoxygenation protocol described above.

Some of the alkylhydroxylamines, used to prepare **15** and **31** in Scheme 2, were not commercially available and were prepared using the method described in Scheme 4. The reduction of commercially available substituted benzaldehydes to alcohols followed by the Mitsunobu reaction[16] afforded alkylhydroxylamines **50**, which were subsequently subjected to imide hydrolysis using hydrazine.

The racemic isoxazoline analogues were conveniently synthesized, as outlined in Scheme 5. Commercially available isophthalaldehyde (**51**) was converted to **53** by Wittig olefination and acetal formation. Hydrogenation and deprotection of **53** gave the aldehyde **55**, which was then transformed to oxime **56**, a precursor of [3 + 2] cycloaddition, by condensation with hydroxylamine salt. The cycloaddition of the oxime **56** with substituted styrene derivatives afforded various isoxazoline analogues **57**. As shown in Scheme 6, these analogues were further transformed into the diasteromeric mixtures of isoxazoline analogues containing optically pure (*R*)- or (*S*)-ethoxy propanoic acid using the resolution protocol used for oxime ether analogues, as depicted in Schemes 1 and 2.

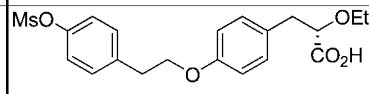
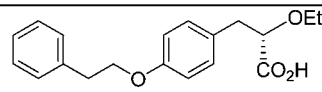
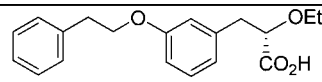
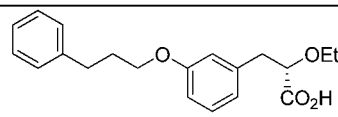
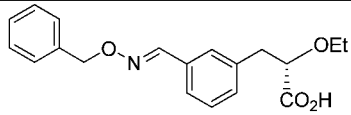
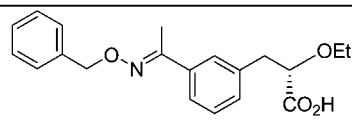
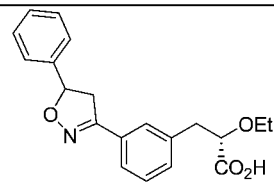
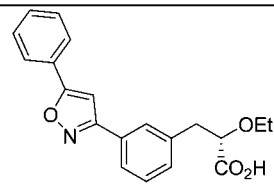
Isoxazole analogues were also synthesized from oxime **56**, which is commonly used to prepare isoxazoline analogues (Scheme 7). Cycloaddition of oxime with phenylacetylenes afforded isoxazole analogue,[17] which was then subjected to ester hydrolysis. This analogue was then transformed into the optically pure (*R*)- or (*S*)-isoxazole analogues using a resolution protocol analogous to that used for oxime ether analogues, as depicted in Schemes 1 and 2.

The absolute configuration of isoxazoline analogue was also confirmed by comparing the specific rotation of the compound **45b** transformed from optically pure isoxazole analogue with that of intermediate **45a**, prepared as described in Scheme 2. Isoxazoline analogue **62** was transformed to intermediate **45b** via ethyl ester formation followed by retroaldol condensation using molybdenum catalyst[18] (Scheme 8).

In Vitro Test. The in vitro receptor transactivation activities of the synthesized compounds were determined,[2a] and results are summarized in Tables, 2 and 3. Generally analogues containing (*S*)-ethoxy propanoic acid had higher activities than analogues containing (*R*)-ethoxy propanoic acid on both PPARα and PPARγ (Table 2). Most of the active compounds displayed higher potency at PPARγ than PPARα. Noticeably, most of analogues possessing an oxime ether linker were more potent PPARγ activators than the lead PPARα/γ dual agonist, (*S*)-tesaglitazar (Table 3).

The results shown in Table 2 reveal the effects of the configuration of the acidic portion and of the conformational rigidity of the linker unit on activity. We prepared analogues containing isoxazoline or isoxazole linker instead of oxime

Table 1. Comparison of Calculated Binding Energy Scores for PPARα versus PPARγ[a]

ID	structure	*binding energy score (Gold score)	
		PPARα	PPARγ
Tesaglitazar		-206.30	-260.58
A		-199.74	-201.46
B		-211.68	-222.37
C		-229.20	-226.00
D		-231.23	-233.65
E		-240.00	-262.13
F		-234.00	-262.36
G		-221.36	-234.75

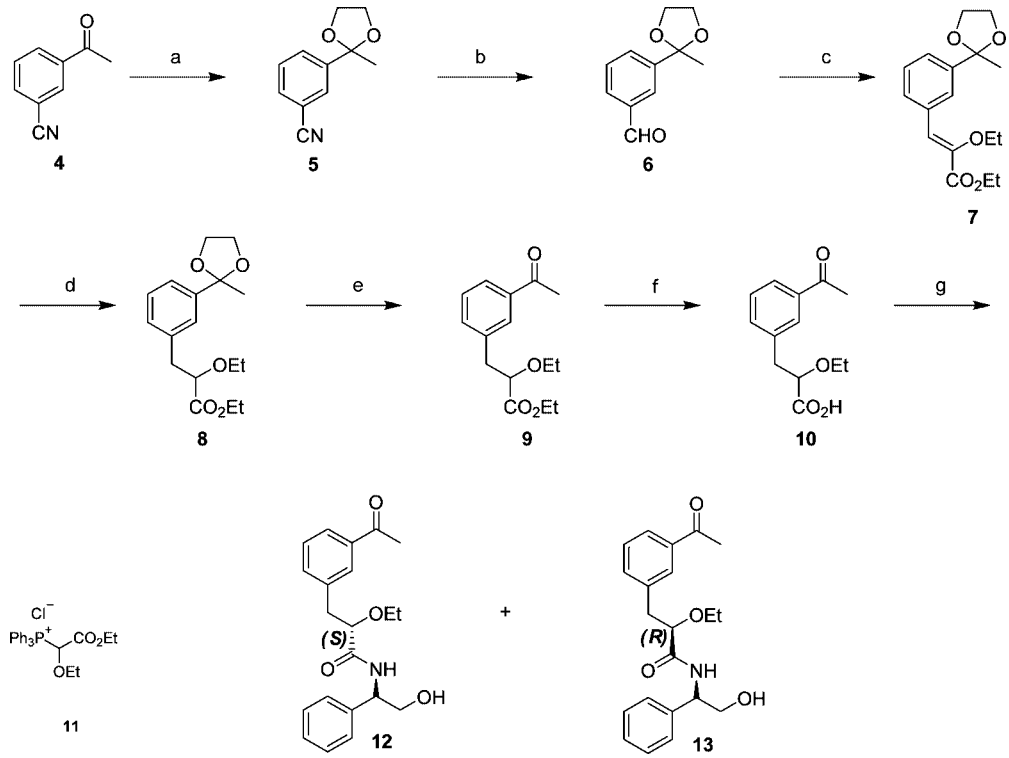
[a] * = Gold score[13] for the best docked conformation of each compound obtained using the FlexX docking.

ethers, and an ethoxy propanoic acid moiety of each analogue was prepared in the *R* and *S* configurations. Modulation of the conformational rigidity of the linking portion significantly affected PPARγ activity but only marginally affected PPARα activity. Moreover, when the linker unit was too rigid, PPARα and γ activities decreased. Replacement of the oxime ether with an isoxazole ring resulted in 30-fold decrease in PPARγ agonistic activity. Although the configuration at the ethoxy propanoic acid moiety dramatically affected agonistic activity, the rigidity of the linker unit was also found to have a substantial effect on PPAR activity. These present results obtained agreed well with the docking results shown in Table 1, in which lowest energy scores were obtained by docking oxime ether analogues into both PPARα and γ.

On the basis of in vitro transactivation assay results shown in Table 2, **16** and **60** were selected as primary leads for further optimization. We prepared derivatives with various *para* substituents (X) on the phenyl ring (Table 3) and examined their transactivation activities.

For oxime ether derivatives, the presence of an electron withdrawing group X at the *para*-position, such as halogen (Cl, Br, or I) or trifluoromethyl, improved PPARγ agonistic activity, whereas only iodine increased PPARα activity. In particular, the 4-chloro analogue **18** not only exhibited greatest PPARγ activity (EC_{50} = 28 nM) but also exhibited 260 times higher selectivity for PPARγ over PPARα. In contrast, the activities of analogues with an electron donating group decreased both at PPARα and γ. These results suggest that electronic effects of substituent groups influence the charge distribution in the hydrophobic tail group and the interaction between the drug and the PPARα/γ receptor cavities. We also examined whether the position of the chloro group on the phenyl ring affected the activity of **18** (see the Supporting Information Table S1) and found that at the *ortho*- and *meta*-positions, the introduction of

Scheme 1. Synthesis of the Chiral Intermediate Amide[a]



[a] Reagents and conditions: (a) $(CH_2OH)_2$, PTSA, benzene, reflux; (b) DIBAL-H, CH_2Cl_2, −40 °C; (c) **11**, tetramethylguanidine, CH_2Cl_2, 0 °C → rt; (d) 10% Pd/C, H_2, MeOH, rt; (e) 2N HCl, THF; (f) LiOH, H_2O/MeOH/THF, rt; (g) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylethylamine, HOBT, (*R*)-(−)-2-phenylglycinol, CH_2Cl_2, rt.

chlorine slightly improved PPARα/γ activity but that *para*-positioned chlorine provided the greatest selectivity for PPARγ.

In the case of isoxazoline analogues, the compound lacking *para*-substituent (**60**) showed rather high activity, indicating that the presence of a substituent on the phenyl ring in the hydrophobic region is not crucial for the interaction with PPARα/γ. We also examined the effect of the length of the linker between the isoxazoline and phenyl rings on activity (see Supporting Information Table S2). Methylene and ethylene linkages in this region decreased the interaction with PPARα/γ, indicating that direct bonding between isoxazoline and the hydrophobic portion provides optimal size for binding.

Oxime ether analogues had higher transactivation activities than isoxazoline analogues. When we compared the potencies of the two most potent analogues, it was found that the oxime ether **18** induced 10-fold more PPARγ activity than the isoxazoline **60** but that **18** induced about 2-fold less PPARα activity than **60**.

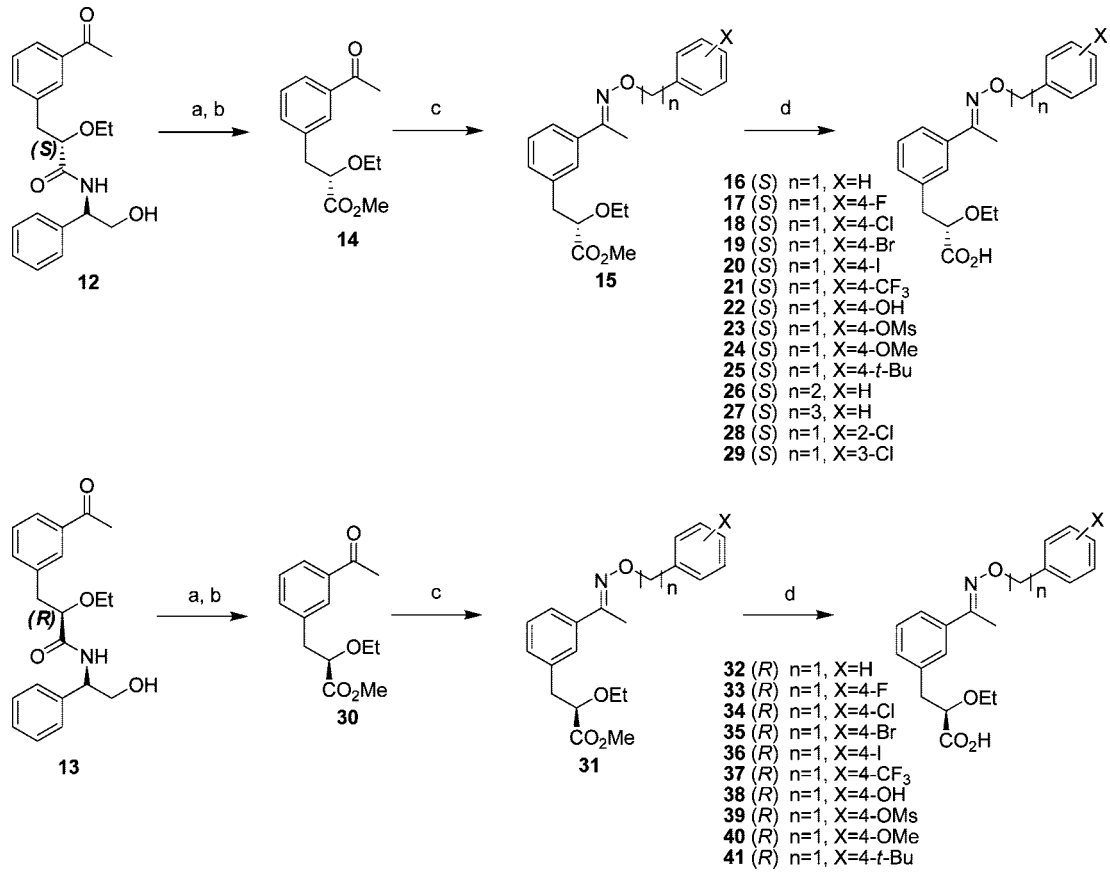
Docking analysis was used to investigate binding between **18** and **60** and the ligand binding domains of PPARγ and PPARα. As illustrated in Figure 2 (left), both **18** and **60** well-fitted the X-ray disposition of tesaglitazar in the bent cavity of PPARγ, which concurred with their highly selective interactions with PPARγ. Compounds **18** and **60** also well-fitted the tesaglitazar-binding pocket of PPARα. However, the binding positions of their hydrophobic moieties differed from that of tesaglitazar (Figure 2, right). Compound **60** adopts a U-shaped binding conformation, and its hydrophobic phenyl ring protrudes deeper into the inner hydrophobic pocket of PPARα, whereas the chloro-substituted phenyl group of **18** interacts with the upper portion of the hydrophobic pocket.

In Vivo Test. In the present study, we identified dual PPARα/γ agonists that induce marginal PPARα activity but excellent PPARγ activity in vitro. To determine whether these compounds have beneficial effects in a diabetes model, we evaluated the preliminary in vivo antihyperglycemic activities of several compounds in db/db mice for 5 days. This model serves as an obese model of T2D that is characterized by severe insulin resistance and marked hypertriglyceridemia; in vivo antihyperglycemic activities of the compounds examined are summarized in the Supporting Information Table S3. Of the compounds tested for 5 days, the oxime ether analogues **17** and **18** displayed potent antihyperglycemic activities and caused less weight gain side effect than muraglitazar. Therefore, we conducted a chronic 11-day study on **17** and **18** to confirm their desirable in vivo activities compared with muraglitazar and the results are summarized in Table 4. The oral administration of **17** and **18** significantly reduced blood glucose levels: 71% and 76% at 3 mg/kg, respectively. The blood-glucose reducing effect of **18** was more effective than muraglitazar, while that of **17** was similar to muraglitazar in vivo considering error values. Their effects on body weight gain, a well-known side effect of PPAR agonists,[19] were similar to muraglitazar after an 11-day treatment.

Conclusion

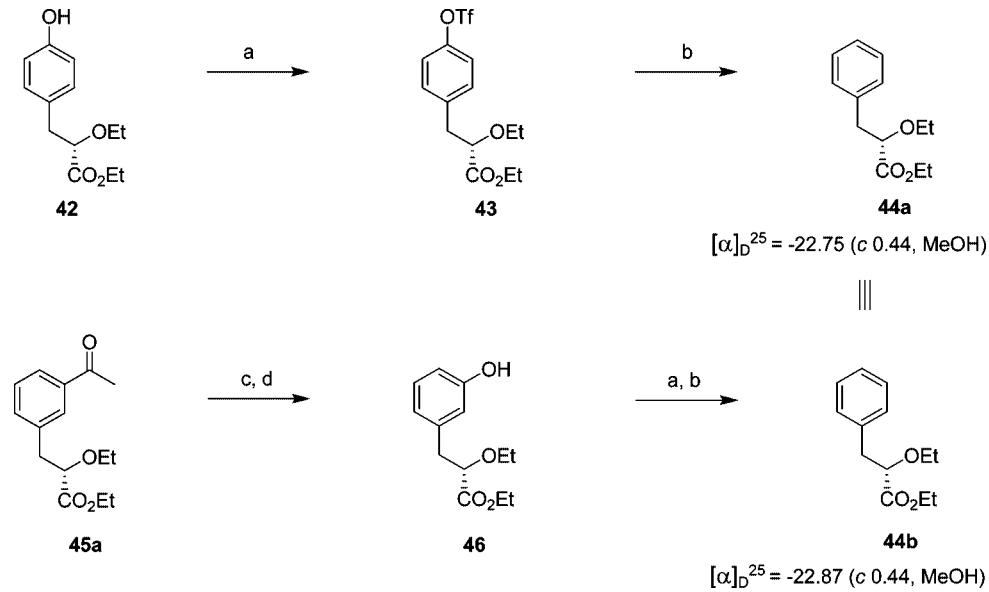
To identify dual PPARα/γ agonists with more beneficial biological activities than known dual agonists, we designed and prepared tesaglitazar analogues containing rigid oxime ether and isoxazoline ring linkers. The structure−activity relationships obtained by in vitro PPARα/γ transactivation assays allowed us to identify several oxime ether compounds with marginal PPARα activities and higher PPARγ activities than that induced by

Scheme 2. Synthesis of Oxime Ether Analogues by Condensation[a]



[a] Reagents and conditions: (a) *c*-H_2SO_4, dioxane/H_2O, reflux; (b) TMSCl, MeOH, reflux; (c) various hydroxylamines, pyridine, reflux; (d) LiOH, H_2O/MeOH/THF, rt.

Scheme 3. Confirmation of the Absolute Configurations of the Oxime Ether Analogues[a]



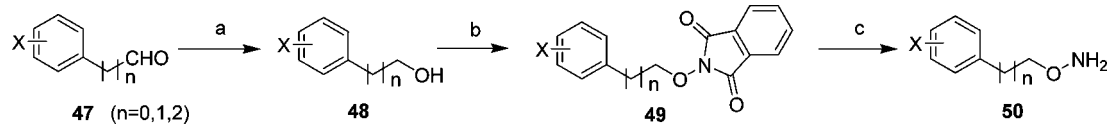
[a] Reagents and conditions: (a) Tf_2O, Et_3N, CH_2Cl_2, rt; (b) $Pd(OAc)_2$, Ph_3P, Et_3N, HCO_2H, DMF, 60 °C; (c) TFAA, sodium percarbonate, CH_2Cl_2, rt; (d) TMSCl, EtOH, reflux.

tesaglitazar. In particular, compounds, **18** were found to reduce blood glucose levels more than muraglitazar at 3 mg/kg oral dose.

Experimental Section

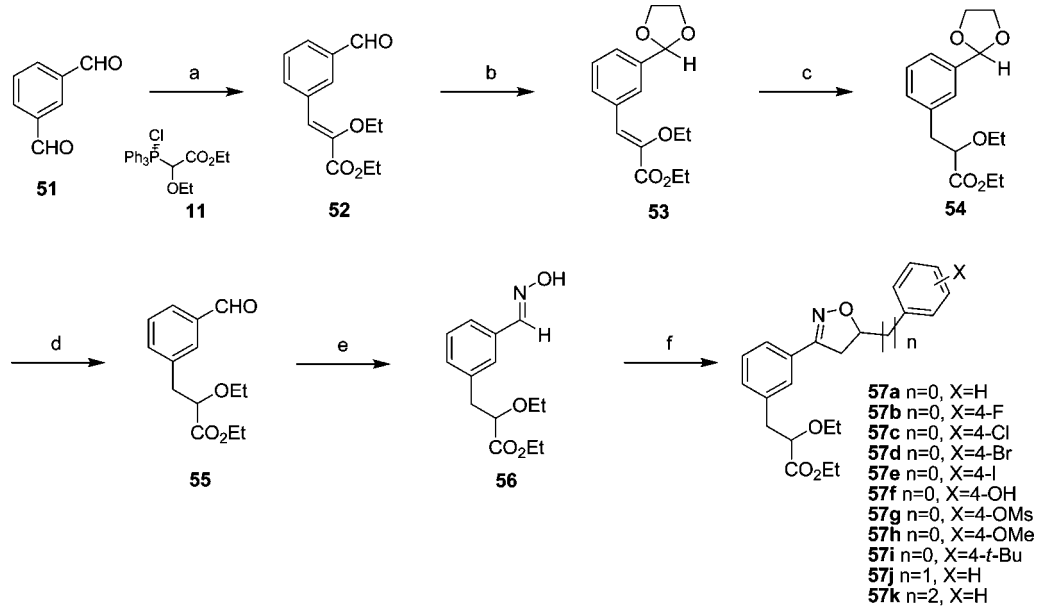
Chemistry. Unless noted otherwise, all starting materials and reagents were obtained commercially and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, acetonitrile, and pyridine were freshly distilled from calcium hydride. All solvents used for routine product isolation and chromatography were of reagent grade and glass distilled. Reaction flasks were dried at 100 °C before use, and air and moisture sensitive reactions were

Scheme 4. Synthesis of *O*-Alkylhydroxylamine Analogues[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C → rt; (b) DEAD, *N*-hydroxyphthalimide, PPh_3, THF, 0 °C → rt; (c) NH_2NH_2, CH_3CN, rt.

Scheme 5. Synthesis of Isoxazoline Analogues[a]



[a] Reagents and conditions: (a) **11**, tetramethylguanidine, CH_2Cl_2, 0 °C → rt; (b) $(CH_2OH)_2$, PTSA, benzene, reflux; (c) 10% Pd/C, H_2, THF, rt; (d) 2N HCl, THF, rt; (e) hydroxylamine HCl, pyridine, reflux; (f) various styrene derivatives, NaOCl, CH_2Cl_2, rt.

performed under argon. Flash column chromatography was performed using silica gel 60 (230−400 mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Optical rotations were measured using a JASCO DIP-1000 digital polarimeter at ambient temperature using 100 nm cells of 2 mL capacity. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained using a VG Trio-2 GC-MS instrument, and high resolution mass spectra were obtained using a JEOL JMS-AX 505WA unit. ^1H and ^{13}C NMR spectra were recorded on either a JEOL JNM-GCX 400 or JEOL JNM-LA 300 spectrometer in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^1H NMR data are reported in the order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and/or multiple resonance, numbers of protons, and coupling constants in hertz (Hz).

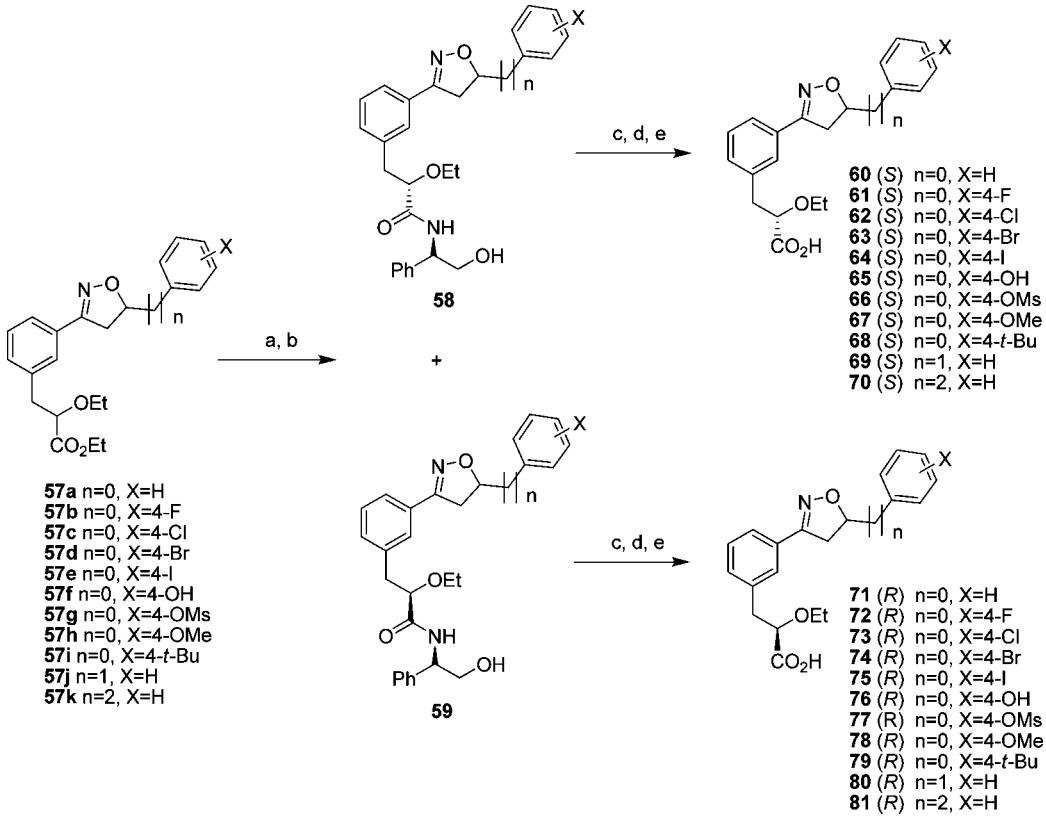
3-(2-Methyl-1,3-dioxolan-2-yl)benzonitrile (5). To a solution of 3-acetylbenzonitrile (**4**) (2 g, 13.8 mmol) in benzene (50 mL) were added *p*-toluenesulfonic acid (PTSA) (263 mg, 1.38 mmol) and ethylene glycol (1.54 mL, 27.6 mmol). The reaction mixture was then refluxed in a Dean & Stark apparatus for 3 h, cooled to room temperature, concentrated in vacuo, and diluted with EtOAc. The organic layer was washed with water and $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 1:5) afforded 2.46 g (94%) of **5** as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (t, 1H, J = 1.6 Hz), 7.70 (td, 1H, J = 1.6, 7.9 Hz), 7.57 (td, 1H, J = 1.5, 7.7 Hz), 7.43 (t, 1H, J = 7.8 Hz), 4.07−4.02 (m, 2H), 3.76−3.71 (m, 2H), 1.61 (s, 3H). LRMS (FAB) *m/z* 190 ($M + H^+$).

3-(2-Methyl-1,3-dioxolan-2-yl)benzaldehyde (6). DIBAL-H (1 M solution in toluene, 19.0 mL) was added dropwise at −40 °C to a solution of **5** (2.40 g, 12.7 mmol) in CH_2Cl_2 (45 mL), and stirred for 3 h. The reaction mixture was then quenched with MeOH (0.5 mL) and acidified with 2N HCl to pH 3. The mixture was then warmed to ambient temperature, stirred for 1 h, and diluted with CH_2Cl_2. The organic layer was washed with Rochelle's solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 1: 10) afforded 2.07 g (85%) of **6** as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.99 (t, 1H, J = 1.7 Hz), 7.81 (td, 1H, J = 1.5, 7.6 Hz), 7.74 (td, 1H, J = 1.5, 7.7 Hz), 7.50 (t, 1H, J = 7.7 Hz), 4.08−4.03 (m, 2H), 3.78−3.74 (m, 2H), 1.65 (s, 3H). LRMS (FAB) *m/z* 193 ($M + H^+$).

Ethyl 2-ethoxy-3-(3-(2-methyl-1, 3-dioxolan-2-yl)phenyl)acrylate (7). Tetramethylguanidine (10.0 mL, 79.8 mmol) was added dropwise at 0 °C to a solution of **6** (10.2 g, 53.2 mmol) in CH_2Cl_2 (100 mL) containing (1,2-diethoxy-2-oxoethyl)triphenylphosphonium chloride (27.4 g, 63.8 mmol). The mixture was then warmed to ambient temperature and stirred for 12 h. The organic layer was diluted with CH_2Cl_2, then washed with $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 1: 5) afforded 15.0 g (92%) of **7** as colorless oil. ^1H NMR (*E*/*Z* mixture of isomers, 300 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.73−7.71 (m, 1H), 7.50−7.30 (m, 2H), 6.98 (s, 1H), 4.28 (q, 2H, J = 7.1 Hz), 4.05−3.96 (m, 4H), 3.78−3.73 (m, 2H), 1.64 (s, 1H), 1.38 (t, 3H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.1 Hz). LRMS (FAB) *m/z* 307 ($M + H^+$).

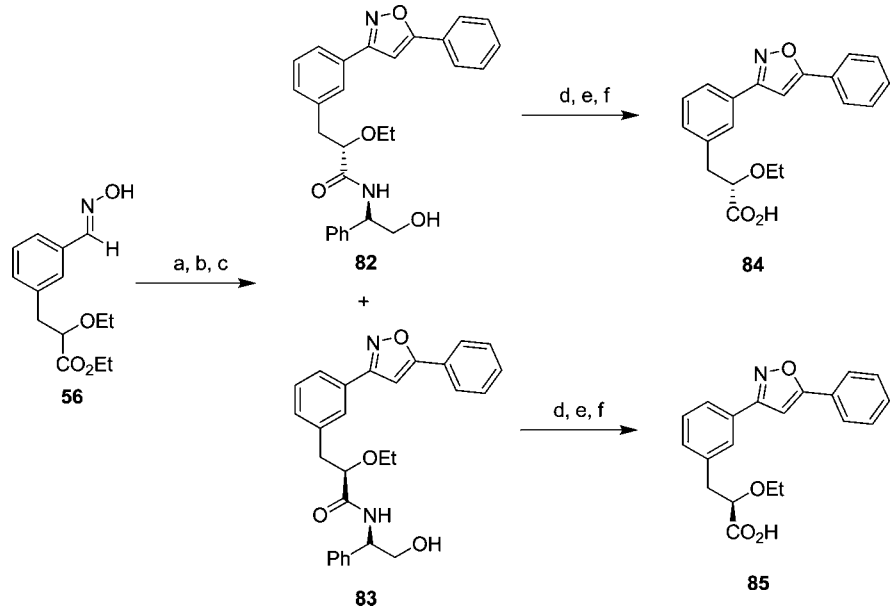
Ethyl 2-ethoxy-3-(3-(2-methyl-1, 3-dioxolan-2-yl)phenyl)propanoate (8). A catalytic amount of Pd on carbon under H_2 was added to a solution of **7** (15.0 g, 48.8 mmol) in MeOH (100 mL) and stirred for 13 h. The reaction mixture was then diluted with EtOAc, filtered using a celite pad, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 1: 5) afforded 15.0 g (99%) of **8** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 2H), 7.24 (t, 1H, J =

Scheme 6. Synthesis of Diastereomeric Isoxazoline Analogues Containing Optically Pure Ethoxy Propanoic acid Moiety[a]



[a] Reagents and conditions: (a) LiOH, H_2O, MeOH, THF, rt; (b) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylethylamine, HOBT, (*R*)-(−)-2-phenylglycinol, CH_2Cl_2, rt; (c) *c*-H_2SO_4, dioxane/H_2O, reflux; (d) TMSCl, MeOH, reflux; (e) LiOH, H_2O/MeOH/THF.

Scheme 7. Synthesis of Isoxazole Analogues[a]

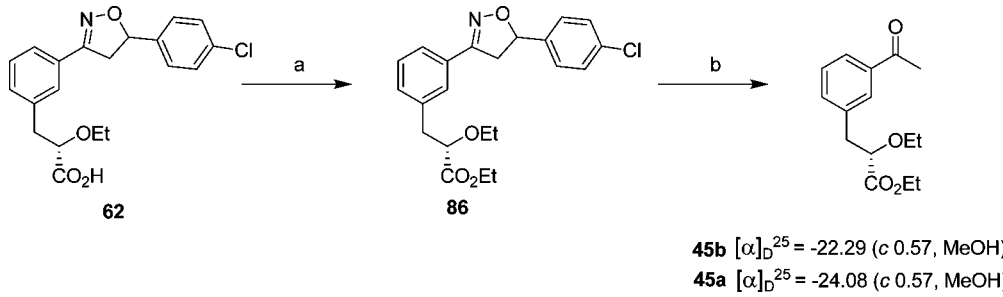


[a] Reagents and conditions: (a) phenylacetylene, NaOCl, CH_2Cl_2, rt; (b) LiOH, H_2O/MeOH/THF, rt; (c) 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylethylamine, HOBT, (*R*)-(−)-2-phenylglycinol, CH_2Cl_2, rt; (d) *c*-H_2SO_4, dioxane/H_2O, reflux; (e) TMSCl, MeOH, reflux; (f) LiOH, H_2O/MeOH/THF.

7.6 Hz), 7.17−7.15 (m, 2H), 4.15 (q, 2H, J = 7.2 Hz), 4.03−3.98 (m, 3H), 3.76−3.73 (m, 2H), 3.61−3.57 (m, 1H), 3.34−3.30 (m, 1H), 3.00 (d, 2H, J = 6.8 Hz), 1.62 (s, 3H), 1.21 (t, 3H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) *m/z* 309 ($M + H^+$).

Ethyl 3-(3-acetylphenyl)-2-ethoxypropanoate (9). 2N HCl (40.8 mL) was added to a solution of **8** in THF (80 mL). The reaction mixture was then refluxed for 3 h, cooled to room temperature, and $NaHCO_3$ was added to quench the reaction. The mixture was then concentrated in vacuo, diluted with EtOAc, and the organic layer so obtained was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 1: 5) afforded 10.54 g (82%) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.80 (m, 2H), 7.45 (d, 1H, J = 7.5 Hz), 7.37 (t, 1H, J =

Scheme 8. Confirmation of the Absolute Configurations of Isoxazoline Analogues[a]



[a] Reagents and conditions: (a) TMSCl, EtOH, reflux; (b) $Mo(CO)_6$, CH_3CN/H_2O, reflux.

7.5 Hz), 4.17 (q, 2H, J = 7.1 Hz), 4.00 (dd, 1H, J = 7.8, 5.4 Hz), 3.66−3.56 (m, 1H), 3.36−3.26 (m, 1H), 3.11−2.98 (m, 2H), 2.58 (s, 1H), 1.22 (t, 3H, J = 7.1 Hz), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 265 ($M + H^+$).

3-(3-Acetylphenyl)-2-ethoxypropanoic Acid (10). $LiOH \cdot H_2O$ (970 mg, 23.2 mmol) was added to a solution of **9** (2.04 g, 7.72 mmol) in THF/H_2O/MeOH (3:1:1, 50 mL) and then stirred for 12 h at ambient temperature. The reaction was quenched with 2N HCl, and diluted with EtOAc. The organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 1.81 g (99%) of **10** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.81 (m, 2H), 7.47−7.36 (m, 2H), 4.09 (dd, 1H, J = 7.9, 4.2 Hz), 3.67−3.57 (m, 1H), 3.46−3.36 (m, 1H), 3.18 (dd, 1H, J = 14.1, 4.2 Hz), 3.06 (dd, 1H, J = 14.1, 7.9 Hz), 2.59 (s, 3H), 1.15 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 237 ($M + H^+$).

(2(*S*)-3-(3-Acetylphenyl)-2-ethoxy-*N*-((*R*)-2-hydroxy-1-phenylethyl)propanamide (12) and (2(*R*)-3-(3-acetylphenyl)-2-ethoxy-*N*-((*R*)-2-hydroxy-1-phenylethyl)propanamide (13). To a solution of **10** (9.97 g, 42.2 mmol) in CH_2Cl_2 (120 mL) at ambient temperature were added; *N*-(3-dimethylaminoproryl)-*N*′-ethylcarbodiimide hydrochloride (EDCI) (8.90 g, 46.4 mmol), (*R*)-(−)-2-phenylgycinol (6.37 g, 46.4 mmol), and HOBT (6.27 g, 46.4 mmol). Finally, diisopropylethylamine (8.09 mL, 46.4 mmol) was added dropwise at 0 °C. The reaction mixture was then stirred for 12 h at ambient temperature, quenched with saturated NH_4Cl solution, and diluted with CH_2Cl_2. The organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc: *n*-hexane = 2: 1) afforded 4.60 g (31%) of **12** as a colorless oil and 4.26 g (28%) of **13** as a white solid.

12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.82 (m, 2H), 7.47−7.06 (m, 7H), 5.00−4.94 (m, 1H), 4.00 (dd, 1H, J = 6.6, 4.0 Hz), 3.73−3.63 (m, 2H), 3.48 (q, 2H, J = 6.9 Hz), 3.21 (dd, 1H, J = 14.1, 3.8 Hz), 3.06 (dd, 1H, J = 13.9, 6.6 Hz), 2.59 (s, 3H), 1.11 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 356 ($M + H^+$).

13: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.75 (m, 2H), 7.39−7.17 (m, 5H), 7.02−6.99 (m, 2H), 5.01−4.96 (m, 1H), 4.04 (dd, 1H, J = 6.6, 3.9 Hz), 3.83 (d, 2H, J = 5.0 Hz), 3.63−3.48 (m, 2H), 3.16 (dd, 1H, J = 14.1, 3.8 Hz), 3.00 (dd, 1H, J = 14.1, 6.8 Hz), 2.46 (s, 3H), 1.18 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 356 ($M + H^+$).

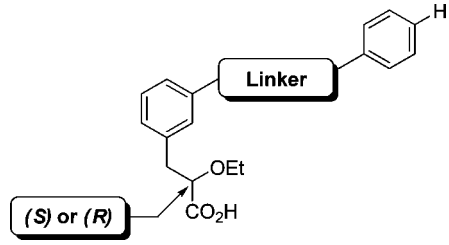
(*S*)-Methyl 3-(3-acetylphenyl)-2-ethoxypropanoate (14). *c*-H_2SO_4 (5 mL) was added dropwise to a solution of **12** (4.60 g, 13.0 mmol) in 1,4-dioxane:H_2O (10:1, 55 mL). The reaction mixture was refluxed for 8 h, cooled to room temperature, diluted with EtOAc, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 3.92 g of a brown oil. To a solution of this prepared acid in MeOH (50 mL), TMSCl (4.93 mL, 38.85 mmol) was added dropwise and the resulting mixture was refluxed for 8 h and then cooled to room temperature. $NaHCO_3$ was then added to quench the reaction. The reaction mix was then concentrated in vacuo, diluted with EtOAc, and the organic layer so obtained was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 2.37 g (73%) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.80 (m, 2H), 7.45−7.34 (m, 2H), 4.02 (dd, 1H, J = 7.9, 5.1 Hz), 3.71 (s, 3H), 3.65−3.55 (m, 1H), 3.35−3.25 (m, 1H), 3.11−2.98 (m, 2H), 2.58 (s, 3H), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 251 ($M + H^+$).

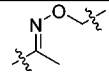
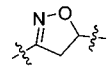
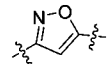
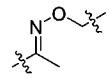
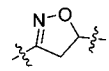
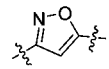
(*R*)-Methyl 3-(3-acetylphenyl)-2-ethoxypropanoate (30). *c*-H_2SO_4 (5 mL) was added dropwise to a solution of **13** (4.26 g, 12.0 mmol) in 1,4-dioxane: H_2O (10: 1, 55 mL). The reaction mixture was then refluxed for 8 h, cooled to room temperature, diluted with EtOAc, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 3.68 g of a brown oil. To a solution of this acid in MeOH (50 mL), TMSCl (4.56 mL, 35.9 mmol) was then added dropwise. The reaction mixture was refluxed for 8 h, cooled to room temperature, and the reaction was quenched with $NaHCO_3$. The mix was then concentrated in vacuo, diluted with EtOAc, and the organic layer so obtained was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 2.16 g (72%) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83−7.80 (m, 2H), 7.45−7.34 (m, 2H), 4.02 (dd, 1H, J = 7.9, 5.1 Hz), 3.71 (s, 3H), 3.65−3.55 (m, 1H), 3.35−3.25 (m, 1H), 3.11−2.98 (m, 2H), 2.58 (s, 3H), 1.13 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 251 ($M + H^+$).

Representative Procedure for the Synthesis of Compounds 16−29 and 32−41: The Preparation of (*S*)-3-(3-((*E*)-1-Benzyloxyiminoethyl)phenyl)-2-ethoxypropanoic Acid (16). *O*-Benzylhydroxylamine·HCl (25 mg, 0.16 mmol) was added to a solution of **14** (33 mg, 0.13 mmol) in pyridine (3 mL). The reaction mixture was refluxed for 5 h, cooled to room temperature, concentrated in vacuo, and diluted with EtOAc. The organic layer so obtained, was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 34 mg (72%) of ester as colorless oil. $LiOH \cdot H_2O$ (970 mg, 23.2 mmol) was then added to prepared ester (102 mg, 0.28 mmol) in THF/H_2O/MeOH (3:1:1, 10 mL) and stirred for 12 h at ambient temperature. The reaction was then quenched with 2N HCl, and diluted with EtOAc, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 94 mg (99%) of **16** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.42−7.21 (m, 7H), 5.22 (s, 2H), 4.08 (dd, 1H, J = 7.9, 4.0 Hz), 3.62−3.52 (m, 1H), 3.47−3.37 (m, 1H), 3.15 (dd, 1H, J = 14.1, 4.0 Hz), 2.99 (dd, 1H, J = 14.1, 7.9 Hz), 2.24 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 342 ($M + H^+$). HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ ($M + H^+$), 342.1705; found, 342.1708.

(*S*)-3-(3-((*E*)-1-(4-Fluorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (17). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.39−7.21 (m, 4H), 7.06−7.00 (m, 2H), 5.17 (s, 2H), 4.08 (dd, 1H, J = 7.9, 4.0 Hz), 3.63−3.53 (m, 1H), 3.47−3.37 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.2, 8.0 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 360 ($M + H^+$). HRMS (FAB) calcd for $C_{20}H_{23}FNO_4$ ($M + H^+$), 360.1611; found, 360.1621.

Table 2. In Vitro Transactivation Assay Results Showing the Effects of Linker Structure and Configuration of the Acidic Portion on Agonistic Activity



Compound id	Configuration of acid part	Linker	hPPARγ		hPPARα	
			$EC_{50}(\mu M)^a$	$E_{max}(\%)^b$	$EC_{50}(\mu M)^a$	$E_{max}(\%)^b$
16	S		0.121	141	2.91	71
60	S		0.220	115	3.99	78
84	S		3.29	164	5.60	162
32	R		1.89	135	NA	8
71	R		25.4	71	NA	-
85	R		37.4	106	30.4	48
rosiglitazone	-	-	0.033	100	3.46	56
gemfibrozil	-	-	147.8	79	193.3	100
(S)-tesaglitazar	S	-	0.704	98	3.124	94

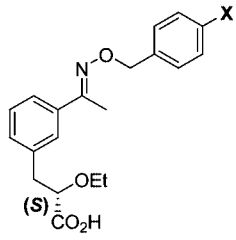
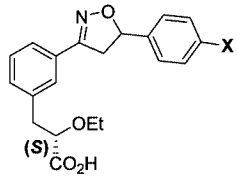
[a] EC_{50} values were calculated by logistic 4-parametric equation using the mean values of its intrinsic activation obtained from more than three independent experiments. [b] Relative maximum efficacies to the percentage of the standards.

(*S*)-3-(3-((*E*)-1-(4-Chlorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (18). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.35−7.22 (m, 6H), 5.18 (s, 2H), 4.07 (dd, 1H, J = 8.1, 4.0 Hz), 3.64−3.54 (m, 1H), 3.45−3.35 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.1, 8.0 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 376 (M + H^+). HRMS (FAB) calcd for $C_{20}H_{23}ClNO_4$ (M + H^+), 376.1316; found, 376.1309.

(*S*)-3-(3-((*E*)-1-(4-Bromobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (19). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.45 (m, 4H), 7.30−7.21 (m, 4H), 5.16 (s, 2H), 4.07 (dd, 1H, J = 7.9, 4.0 Hz), 3.63−3.53 (m, 1H), 3.47−3.37 (m, 1H), 3.14 (dd, 1H, J = 14.0, 4.1 Hz), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 420 (M + H^+). HRMS (FAB) calcd for $C_{20}H_{24}BrNO_4$ (M + H^+), 420.0810; found, 420.0815.

(*S*)-3-(3-((*E*)-1-(4-Iodobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (20). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.65 (m, 2H), 7.51−7.48 (m, 2H), 7.34−7.22 (m, 2H), 7.15−7.12 (m, 2H), 5.15 (s, 2H), 4.06 (dd, 1H, J = 7.9, 4.0 Hz), 3.64−3.54 (m, 1H), 3.45−3.35 (m, 1H), 3.13 (dd, 1H, J = 13.9, 4.0 Hz), 2.99 (dd, 1H, J = 14.1, 7.9 Hz), 2.23 (s, 3H),

Table 3. Transactivation Assay Results of Oxime Ether Compounds on Human PPAR α/γ

Compound id	Structure	X	Human PPAR γ		Human PPAR α	
			$EC_{50}(\mu M)^a$	$E_{max}(\%)^b$	$EC_{50}(\mu M)^a$	$E_{max}(\%)^b$
16		H	0.121	141	2.91	71
17		F	0.139	214	5.90	299
18		Cl	0.028	163	7.22	386
19		Br	0.036	160	2.70	150
20		I	0.040	146	0.674	139
21		CF_3	0.046	135	2.95	185
22		OH	2.94	222	58.8	58
23		OMs	1.61	129	13.1	165
24		OMe	0.175	155	4.06	179
25		t-Bu	0.279	155	12.1	137
60		H	0.220	115	3.99	78
61		F	1.16	158	24.4	119
62		Cl	0.816	167	6.78	125
63		Br	0.740	151	4.39	144
64		I	0.606	161	2.76	162
65		OH	38.6	83	ND	0
66		OMs	28.1	95	37.4	107
67		OMe	3.19	121	11.3	156
68		t-Bu	2.73	158	3.95	138
rosiglitazone	-	-	0.033	100	3.46	56
gemfibrozil	-	-	147.8	79	193.3	100
(S)-tesaglitazar	S	-	0.704	98	3.124	94

[a] EC_{50} values were calculated by logistic 4-parametric equation using the mean values of its intrinsic activation obtained from more than three independent experiments. [b] Relative maximum efficacies to the percentage of the standards.

1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 468 ($M + H^+$). HRMS (FAB) calcd for $C_{20}H_{24}INO_4$ ($M + H^+$), 468.0672; found 468.0662.

(*S*)-3-(3-((*E*)-1-(4-Trifluoromethylbenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (21). Colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.61−7.48 (m, 6H), 7.31−7.22 (m, 2H), 5.27 (s, 2H), 4.07

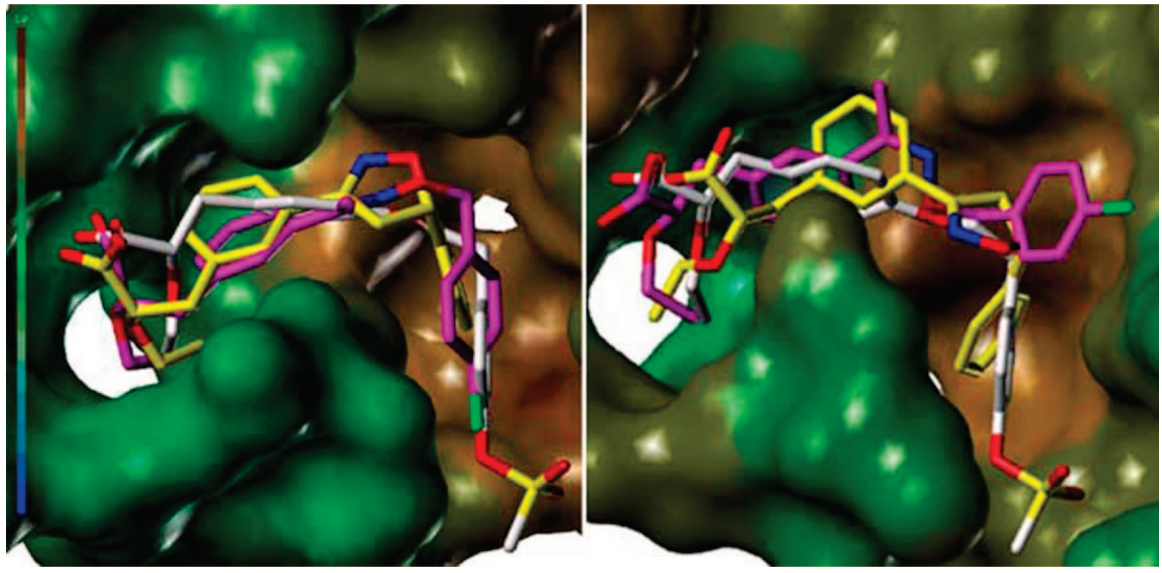


Figure 2. Binding dispositions of **18** (magenta) and **60** (yellow) in the PPARγ (left) and PPARα (right) binding pockets as compared with that of tesaglitazar (gray). Solvent-accessible protein surfaces are colored by lipophilicity potential. The color code is shown on the left: lipophilicity increases from blue (hydrophilic) to brown (lipophilic).

Table 4. Antihyperglycemic Activities and Weight Gain in *db*/*db* Mice (In Vivo Data after an 11-Day Study)

		% inhibition of blood glucose			weight gain (g) vs day 1		
compd ID	dose (mg/kg)	day 4	day 7	day 11	day 4	day 7	day 11
lean					0.6 ± 0.1	0.4 ± 0.2	0.9 ± 0.3
db/db control		0 ± 14	0 ± 9	0 ± 10	0.6 ± 0.6	1.0 ± 0.7	2.4 ± 0.8
Muraglitazar	3	53 ± 2[a]	67 ± 1[a]	68 ± 2[a]	2.0 ± 0.6	3.6 ± 0.7[a]	6.3 ± 0.9[a]
17	0.3	39 ± 13	58 ± 4[a]	68 ± 2[a]	1.9 ± 0.6	3.6 ± 0.6[a]	5.6 ± 0.8[a]
	3	64 ± 1[a]	73 ± 1[a]	71 ± 5[a]	2.1 ± 1.0	3.6 ± 1.0	5.6 ± 1.0[a]
18	0.3	63 ± 2[a]	60 ± 7[a]	71 ± 1[a]	1.9 ± 0.2	3.7 ± 0.4[a]	6.0 ± 0.5[a]
	3	61 ± 4[a]	73 ± 1[a]	76 ± 1[a]	2.5 ± 0.4[a]	3.7 ± 0.3[a]	5.3 ± 0.5[a]

[a] $P < 0.05$ vs db/db control. Data are expressed as mean ± SEM.

(dd, 1H, J = 7.9, 4.0 Hz), 3.62−3.52 (m, 1H), 3.46−3.36 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.26 (s, 3H), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 410 ($M + H^+$). HRMS (FAB) calcd for $C_{21}H_{22}F_3NO_4$ ($M + H^+$), 410.1579; found, 410.1575.

(*S*)-3-(3-((*E*)-1-(4-Hydroxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (22). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.49 (m, 2H), 7.31−7.19 (m, 4H), 6.82−6.79 (m, 2H), 5.13 (s, 2H), 4.08 (dd, 1H, J = 7.9, 4.0 Hz), 3.63−3.53 (m, 1H), 3.47−3.37 (m, 1H), 3.14 (dd, 1H, J = 13.9, 4.0 Hz), 3.00 (dd, 1H, J = 14.0, 8.0 Hz), 2.21 (s, 3H), 1.15 (t, 3H, J = 7.04 Hz). LRMS (FAB) m/z 358 ($M + H^+$). HRMS (FAB) calcd for $C_{20}H_{23}NO_5$ ($M + H^+$), 358.1654; found, 358.1644.

(*S*)-3-(3-((*E*)-1-(4-Methanesulfonyloxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (23). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.43 (m, 4H), 7.30−7.22 (m, 4H), 5.21 (s, 2H), 4.07 (dd, 1H, J = 7.7, 4.2 Hz), 3.63−3.53 (m, 1H), 3.46−3.36 (m, 1H), 3.17−3.11 (m, 4H), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.24 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 436 ($M + H^+$). HRMS (FAB) calcd for $C_{21}H_{25}NO_7S$ ($M + H^+$), 436.1430; found, 436.1418.

(*S*)-3-(3-((*E*)-1-(4-Methoxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (24). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.36−7.21 (m, 4H), 6.90−6.87 (m, 2H), 5.15 (s, 2H), 4.08 (dd, 1H, J = 8.1, 4.0 Hz), 3.79 (s, 3H), 3.63−3.53 (m, 1H), 3.46−3.36 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.1, 8.0 Hz), 2.21 (s, 3H), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 372 ($M + H^+$). HRMS (FAB) calcd for $C_{21}H_{25}NO_5$ ($M + H^+$), 372.1811; found, 372.1815.

(*S*)-3-(3-((*E*)-1-(4-(*tert*-Butylbenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (25). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.50 (m, 2H), 7.40−7.22 (m, 6H), 5.20 (s, 2H), 4.08 (dd, 1H, J = 8.1, 4.0 Hz), 3.63−3.53 (m, 1H), 3.47−3.37 (m, 1H), 3.15 (dd, 1H, J = 14.2, 3.9 Hz), 2.99 (dd, 1H, J = 14.0, 8.0 Hz), 2.24 (s, 3H), 1.31 (s, 9H), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 398 ($M + H^+$). HRMS (FAB) calcd for $C_{24}H_{31}NO_4$ ($M + H^+$), 398.2331; found, 398.2318.

(*S*)-3-(3-((*E*)-1-Phenethyloxyiminoethyl)phenyl)-2-ethoxypropanoic Acid (26). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.50 (m, 2H), 7.31−7.18 (m, 6H), 4.39 (t, 2H, J = 7.0 Hz), 4.08 (dd, 1H, J = 8.0, 4.0 Hz), 3.64−3.54 (m, 1H), 3.48−3.38 (m, 1H), 3.16 (dd, 1H, J = 14.2, 3.9 Hz), 3.06−2.97 (m, 3H), 2.19 (s, 3H), 1.16 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 356 ($M + H^+$). HRMS (FAB) calcd for $C_{21}H_{25}NO_4$ ($M + H^+$), 356.1862; found, 356.1856.

(*S*)-3-(3-((*E*)-1-(3-Phenylpropoxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (27). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.31−7.14 (m, 6H), 4.20 (t, 2H, J = 6.5 Hz), 4.08 (dd, 1H, J = 7.9, 4.0 Hz), 3.63−3.53 (m, 1H), 3.47−3.37 (m, 1H), 3.15 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.0, 8.0 Hz), 2.73 (t, 2H, J = 7.8 Hz), 2.22 (s, 3H), 2.09−1.99 (m, 2H), 1.15 (t, 3H, J = 6.96 Hz). LRMS (FAB) m/z 370 ($M + H^+$). HRMS (FAB) calcd for $C_{22}H_{27}NO_4$ ($M + H^+$), 370.2018; found, 370.2024.

(*S*)-3-(3-((*E*)-1-(2-Chlorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (28). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.46−7.43 (m, 1H), 7.38−7.21 (m, 5H), 5.34 (s, 2H), 4.08 (dd, 1H, J = 7.9, 4.0 Hz), 3.60−3.52 (m, 1H), 3.47−3.39 (m, 1H), 3.15 (dd, 1H, J = 14.3, 4.0 Hz), 2.99 (dd, 1H, J = 14.1, 7.9 Hz), 2.28 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 376 ($M + H^+$). HRMS (FAB) calcd for $C_{20}H_{23}ClNO_4$ ($M + H^+$), 376.1316; found, 376.1309.

(*S*)-3-(3-((*E*)-1-(3-Chlorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (29). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2H), 7.38 (m, 1H), 7.31−7.24 (m, 5H), 5.18 (s, 2H), 4.07 (dd, 1H, J = 7.8, 4.1 Hz), 3.60−3.55 (m, 1H), 3.45−3.39 (m, 1H), 3.14 (dd, 1H, J = 13.8, 3.8 Hz), 3.00 (dd, 1H, J = 14.4, 7.8 Hz), 2.25 (s, 3H), 1.14 (t, 3H, J = 7.05 Hz). LRMS (FAB) m/z 376 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{23}ClNO_4$ (M + H$^+$), 376.1316; found, 376.1305.

(*R*)-3-(3-((*E*)-1-Benzyloxyiminoethyl)phenyl)-2-ethoxypropanoic Acid (32). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.42−7.25 (m, 7H), 5.22 (s, 2H), 4.07 (dd, 1H, J = 8.1, 4.0 Hz), 3.64−3.54 (m, 1H), 3.45−3.35 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.0 Hz), 3.00 (dd, 1H, J = 14.0, 8.1 Hz), 2.24 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 342 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ (M + H$^+$), 342.1705; found, 342.1709.

(*R*)-3-(3-((*E*)-1-(4-Fluorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (33). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.48 (m, 2H), 7.39−7.22 (m, 4H), 7.06−7.00 (m, 2H), 5.17 (s, 2H), 4.07 (dd, 1H, J = 8.1, 4.0 Hz), 3.64−3.54 (m, 1H), 3.45−3.35 (m, 1H), 3.14 (dd, 1H, J = 14.0, 4.1 Hz), 3.00 (dd, 1H, J = 14.1, 8.1 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 360 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{23}FNO_4$ (M + H$^+$), 360.1611; found, 360.1614.

(*R*)-3-(3-((*E*)-1-(4-Chlorobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (34). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.48 (m, 2H), 7.35−7.25 (m, 6H), 5.18 (s, 2H), 4.07 (dd, 1H, J = 7.8, 3.9 Hz), 3.61−3.53 (m, 1H), 3.46−3.38 (m, 1H), 3.14 (dd, 1H, J = 14.1, 4.2 Hz), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 376 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{23}ClNO_4$ (M + H$^+$), 376.1316; found, 376.1305.

(*R*)-3-(3-((*E*)-1-(4-Bromobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (35). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.45 (m, 4H), 7.30−7.25 (m, 4H), 5.16 (s, 2H), 4.08 (dd, 1H, J = 7.8, 4.1 Hz), 3.60−3.52 (m, 1H), 3.47−3.39 (m, 1H), 3.15 (dd, 1H, J = 14.1, 3.8 Hz), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.23 (s, 3H), 1.14 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 420 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{24}BrNO_4$ (M + H$^+$), 420.0810; found, 420.0810.

(*R*)-3-(3-((*E*)-1-(4-Iodobenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (36). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.13 (m, 8H), 5.15 (s, 2H), 4.09 (m, 1H), 3.57 (m, 1H), 3.43 (m, 1H), 3.16−3.13 (m, 1H), 3.00 (m, 1H), 2.23 (s, 3H), 1.14 (t, 3H, J = 6.50 Hz). LRMS (FAB) m/z 468 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{24}INO_4$ (M + H$^+$), 468.0672; found, 468.0662.

(*R*)-3-(3-((*E*)-1-(4-Trifluoromethylbenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (37). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61−7.48 (m, 6H), 7.30−7.22 (m, 2H), 5.26 (s, 2H), 4.07 (dd, 1H, J = 8.0, 4.1 Hz), 3.63−3.53 (m, 1H), 3.45−3.35 (m, 1H), 3.13 (dd, 1H, J = 14.1, 4.0 Hz), 2.99 (dd, 1H, J = 14.2, 8.0 Hz), 2.26 (s, 3H), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 410 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{22}F_3NO_4$ (M + H$^+$), 410.1579; found, 410.1575.

(*R*)-3-(3-((*E*)-1-(4-Hydroxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (38). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.31−7.20 (m, 4H), 6.82−6.79 (m, 2H), 5.13 (s, 2H), 4.08 (dd, 1H, J = 7.98, 3.93 Hz), 3.60−3.52 (m, 1H), 3.48−3.38 (m, 1H), 3.15 (dd, 1H, J = 14.1, 3.9 Hz), 3.00 (dd, 1H, J = 14.0, 7.8 Hz), 2.21 (s, 3H), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 358 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{23}NO_5$ (M + H$^+$), 358.1654; found, 358.1651.

(*R*)-3-(3-((*E*)-1-(4-Methanesulfonyloxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (39). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51−7.43 (m, 4H), 7.31−7.22 (m, 4H), 5.21 (s, 2H), 4.07 (dd, 1H, J = 7.7, 4.0 Hz), 3.61−3.55 (m, 1H), 3.45−3.40 (m, 1H), 3.17−3.13 (m, 4H), 3.00 (dd, 1H, J = 14.1, 7.7 Hz), 2.24 (s, 3H), 1.14 (t, 3H, J = 6.9 Hz). LRMS (FAB) m/z 436 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{25}NO_7S$ (M + H$^+$), 436.1430; found, 436.1418.

(*R*)-3-(3-((*E*)-1-(4-Methoxybenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (40). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53−7.50 (m, 2H), 7.36−7.25 (m, 4H), 6.90−6.87 (m, 2H), 5.15 (s, 2H), 4.09−4.05 (m, 1H), 3.79 (s, 3H), 3.64−3.54 (m, 1H), 3.46−3.36 (m, 1H), 3.14 (dd, 1H, J = 13.9, 3.8 Hz), 3.00 (dd, 1H, J = 14.1, 8.1 Hz), 2.21 (s, 3H), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 372 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{25}NO_5$ (M + H$^+$), 372.1811; found, 372.1815.

(*R*)-3-(3-((*E*)-1-(4-(*tert*-Butylbenzyloxyimino)ethyl)phenyl)-2-ethoxypropanoic Acid (41). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54−7.51 (m, 2H), 7.40−7.26 (m, 6H), 5.20 (s, 2H), 4.09 (dd, 1H, J = 7.8, 4.0 Hz), 3.60−3.52 (m, 1H), 3.50−3.41 (m, 1H), 3.16 (dd, 1H, J = 13.9, 3.8 Hz), 3.00 (dd, 1H, J = 14.1, 7.9 Hz), 2.24 (s, 3H), 1.31 (s, 9H), 1.15 (t, 3H, J = 6.96 Hz). LRMS (FAB) m/z 398 (M + H$^+$). HRMS (FAB) calcd for $C_{24}H_{31}NO_4$ (M + H$^+$), 398.2331; found, 398.2318.

4-((*S*)-2-(Ethoxycarbonyl)-2-ethoxyethyl)phenyltrifluoromethanesulfonate (43). To a solution of (*S*)-ethyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate(**42**)[14] (94 mg, 0.394 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added triethylamine (0.22 mL, 1.58 mmol) and triflic anhydride (Tf_2O) (dropwise 0.1 mL, 0.591 mmol). The mixture was warmed to ambient temperature and stirred for several hours until the starting material had been fully consumed as verified by TLC (EtOAc:*n*-hexane = 1:2). The reaction was then quenched with H_2O and CH_2Cl_2. The organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 118 mg (81%) of **43** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.29 (m, 2H), 7.20−7.16 (m, 2H), 4.15 (q, 2H, J = 7.1 Hz), 3.97 (dd, 1H, J = 7.6, 5.7 Hz), 3.7−3.6 (m, 1H), 3.37−3.27 (m, 1H), 3.05−2.99 (m, 2H), 1.20 (t, 3H, J = 6.8 Hz), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 371 (M + H$^+$).

(*S*)-Ethyl-2-ethoxy-3-phenylpropanoate (44a). To a solution of **43** (118 mg, 0.319 mmol), triphenylphosphine (20 mg, cat), and $Pd(OAc)_2$ (18 mg, cat) in anhydrous DMF (2 mL) were added triethylamine (0.14 mL, 0.957 mmol) and formic acid (0.04 mL, 0.957 mmol). The mixture was then warmed to 60 °C, stirred for several hours until the starting material had been fully consumed (confirmed by TLC (EtOAc:*n*-hexane = 1:5)). The reaction mixture was then quenched with brine and Et_2O. The organic layer so obtained, was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:10) afforded 13 mg (42%) of **44** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.17 (m, 5H), 7.20−7.16 (m, 2H), 4.15 (dd, 2H, J = 7.1, 7.0 Hz), 3.99 (dd, 1H, J = 7.1, 6.4 Hz), 3.63−3.53 (m, 1H), 3.38−3.28 (m, 1H), 3.00−2.98 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 223 (M + H$^+$). $[\alpha]_D^{25}$ = −22.75 (c 0.44, MeOH).

(*S*)-Ethyl 2-ethoxy-3-(3-hydroxyphenyl)-2-ethoxypropanoate (46). To a solution of (*S*)-ethyl 3-(3-acetoxyphenyl)-2-ethoxypropanoate **45a** (281 mg, 1.06 mmol), which was prepared from **14** by transesterification using TMSCl and EtOH mentioned below, in CH_2Cl_2 (25 mL) were added sodium percarbonate (2.50 mg, 15.95 mmol) and trifluoroacetic anhydride (0.6 mL, 4.25 mmol). The mixture was then stirred for several hours at ambient temperature until the starting material had been fully consumed (confirmed by TLC (EtOAc:*n*-hexane = 1:2)). The reaction mixture was then quenched with H_2O and CH_2Cl_2 was added. The organic layer so obtained, was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:2) afforded 140 mg (47%) of ester as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−6.93 (m, 4H), 4.15 (dd, 2H, J = 7.1, 7.0 Hz), 3.98 (dd, 1H, J = 7.5, 5.9 Hz), 3.64−3.54 (m, 1H), 3.38−3.28 (m, 1H), 3.06−2.97 (m, 2H), 2.27 (s, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) $m/$z 281 (M + H$^+$).

TMSCl (0.2 mL, 1.58 mmol) was added to a solution of provided ester (140 mg, 0.525 mmol) in EtOH (10 mL), and stirred for several hours at 80 °C until the starting material had been fully consumed

(confirmed by TLC (EtOAc:*n*-hexane = 1:2)). The reaction mixture was the concentrated in vacuo and purification of this residue by flash column chromatography (EtOAc:*n*-hexane = 1:2) afforded 95 mg (81%) of **46** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16−7.10 (m, 1H), 6.80−6.67 (m, 3H), 4.82 (s, 1H), 4.16 (q, 2H, J = 7.1 Hz), 3.99 (dd, 1H, J = 7.2, 6.0 Hz), 3.64−3.54 (m, 1H), 3.40−3.30 (m, 1H), 2.95−2.93 (m, 2H), 1.21 (t, 3H, J = 7.1 Hz), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 239 ($M + H^+$).

(*S*)-Ethyl 2-ethoxy-3-phenylpropanoate (44b). Compound **44b** was prepared (24% yield for a 2-stage process) from **46** using the procedure described for compound **44a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.17 (m, 5H), 7.20−7.16 (m, 2H), 4.15 (dd, 2H, J = 7.1, 7.0 Hz), 3.99 (dd, 1H, J = 7.1, 6.4 Hz), 3.63−3.53 (m, 1H), 3.38−3.28 (m, 1H), 3.00−2.98 (m, 2H), 1.20 (t, 3H, J = 7.1 Hz), 1.14 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 223 ($M + H^+$). $[\alpha]_D^{25} = -22.87$ (c 0.44, MeOH).

Ethyl 2-Ethoxy-3-(3-formylphenyl)acrylate (52). Tetramethylguanidine (4.01 mL, 32.0 mmol) was added dropwise to a solution of commercially available isophthalaldehyde **51** (2.86 g, 21.3 mmol) in CH_2Cl_2 (100 mL) and (1,2-diethoxy-2-oxoethyl)triphenylphosphonium chloride **11** (8.23 g, 19.2 mmol) at 0 °C. The mixture was warmed to ambient temperature and then stirred for several hours until the starting material had been fully consumed (verified by TLC (EtOAc:*n*-hexane = 1:2)). After adding CH_2Cl_2, the organic layer so obtained, was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 4.03 g (85%) of **52** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.29 (s, 1H), 8.01 (d, 1H, J = 7.7 Hz), 7.81 (d, 1H, J = 7.5 Hz), 7.51 (t, 1H, J = 7.7 Hz), 6.98 (s, 1H), 4.30 (q, 2H, J = 7.1 Hz), 4.05 (q, 2H, J = 6.9 Hz), 1.37 (t, 3H, J = 7.0 Hz), 1.37 (t, 3H, J = 7.0 Hz).

Ethyl 3-(3-(1,3-Dioxolan-2-yl)phenyl)-2-ethoxyacrylate (53). To a solution of **52** (4.03 g, 16.2 mmol) in benzene (50 mL) were added *p*-toluenesulfonic acid (PTSA) (308 mg, 1.62 mmol) and ethylene glycol (1.81 mL, 32.5 mmol). The reaction mixture was then refluxed in a Dean & Stark apparatus for several hours until the starting material had been fully consumed (verified by TLC (EtOAc:*n*-hexane = 1:2)). The mixture was then cooled to room temperature and concentrated in vacuo, and EtOAc was added. The organic layer so obtained, was washed with H_2O and $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 4.75 g (100%) of **53** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80−7.76 (m, 1H), 7.42−7.33 (m, 2H), 6.98 (s, 1H), 4.28 (q, 2H, J = 7.1 Hz), 4.16−4.00 (m, 4H), 3.98 (q, 2H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.0 Hz), 1.35 (t, 3H, J = 7.0 Hz).

Ethyl 3-(3-(1,3-Dioxolan-2-yl)phenyl)-2-ethoxypropanoate (54). A catalytic amount of Pd on carbon was added to a solution of **53** (4.75 g, 48.8 mmol) in THF (35 mL) under H_2, and stirred for several hours at ambient temperature until the starting material had been fully consumed (verified by TLC (EtOAc:*n*-hexane = 1:2)). EtOAc was then added, and the mixture was filtered using a Celite pad and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 4.74 g (99%) of **54** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76−7.73 (m, 1H), 7.53−7.41 (m, 1H), 7.35−7.18 (m, 2H), 5.77 (s, 1H), 4.20−3.96 (m, 6H), 3.72 (s, 1H), 3.64−3.53 (m, 1H), 3.35−3.25 (m, 1H), 3.09−2.94 (m, 2H), 1.20 (t, 3H, J = 7.0 Hz), 1.13 (t, 3H, J = 7.0 Hz).

Ethyl 2-Ethoxy-3-(3-formylphenyl)propanoate (55). 2N HCl (5 mL) was added to a solution of **54** (4.78 g, 16.3 mmol) in THF (25 mL). The mixture was then refluxed for several hours until the starting material had been fully consumed (verified by TLC (EtOAc:*n*-hexane = 1:2)), then cooled to room temperature, quenched with $NaHCO_3$, and concentrated in vacuo. EtOAc was then added and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, then concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 3.04 g (75%) of **55** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 7.76−7.73 (m, 2H), 7.53−7.41 (m, 2H), 4.16 (q, 2H, J = 7.0 Hz), 4.04−3.99 (m, 1H), 3.67−3.57 (m, 1H), 3.37−3.27 (m, 1H), 3.13−3.01 (m, 2H), 1.22 (t, 3H, J = 7.0 Hz), 1.13 (t, 3H, J = 7.0 Hz).

Ethyl 2-Ethoxy-3-(3-benzaldehyde-(*E*)-oxime)propanoate (56). Hydroxylamine HCl (1.01 g, 14.6 mmol) was added to a solution of **55** (3.04 g, 12.2 mmol) in pyridine (25 mL). The mixture was refluxed for 5 h, cooled to room temperature, and concentrated in vacuo. EtOAc was then added, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 3.14 g (97%) of **56** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.96−7.42 (m, 2H), 7.32−7.27 (m, 1H), 4.15 (q, 2H, J = 7.0 Hz), 4.02−3.97 (m, 1H), 3.65−3.55 (m, 1H), 3.37−3.27 (m, 1H), 3.07−2.94 (m, 2H), 1.20 (t, 3H, J = 7.0 Hz), 1.13 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 266 ($M + H^+$).

Representative Procedure for the Synthesis of 57a−k: The Preparation of Ethyl-2-ethoxy-3-(3-(5-phenyl-4,5-dihydroisoxazole-3-yl)phenyl)propanoate (57a). NaOCl (10−13% solution, 2 mL) was added to a solution of **56** (879 mg, 3.31 mmol) and styrene (0.42 mL, 3.64 mL) in CH_2Cl_2 (25 mL). The mixture was stirred for 2 h at ambient temperature and then CH_2Cl_2 was added. The organic layer so obtained was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 1.00 g (82%) of **57a** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.52 (m, 2H), 7.39−7.29 (m, 7H), 5.72 (dd, 1H, J = 10.9, 8.2 Hz), 4.16 (q, 2H, J = 7.0 Hz), 3.99 (dd, 1H, J = 7.3, 5.7 Hz), 3.76 (ddd, 1H, J = 16.7, 11.0, 0.9 Hz), 3.65−3.55 (m, 1H), 3.36−3.26 (m, 2H), 3.07−2.94 (m, 2H), 1.22 (t, 3H, J = 7.1 Hz), 1.16 (dt, 3H, J = 2.73, 6.96 Hz). LRMS (FAB) m/z 368 ($M + H^+$).

Representative Procedure for the Synthesis of 58a−k and 59a−k: The Preparation (*S*)-3-(3-(5-Benzyl-4,5-dihydroisoxazole-3-yl)phenyl)-ethoxy-*N*-((*S*)-2-hydroxy-1-phenylethyl) propanamide (58a) and (*R*)-3-(3-(5-benzyl-4,5-dihydroisoxazole-3-yl)phenyl)-ethoxy-*N*-((*S*)-2-hydroxy-1-phenylethyl)propanamide (59a). To a solution of **57** (920 mg, 2.71 mmol) in CH_2Cl_2 (25 mL) at ambient temperature were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, diisopropylethylamine (572 mg, 2.98 mmol), (*R*)-(−)-2-phenylgycinol (409 mg, 2.98 mmol), and HOBT (403 mg, 2.98 mmol). The mixture was then cooled to 0 °C and diisopropylethylamine (0.52 mL, 2.98 mmol) was added dropwise. The reaction mixture was then stirred for 18 h at ambient temperature and quenched with brine. CH_2Cl_2 was then added, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:1) afforded 482 mg (39%) of **58a** as a colorless oil and 461 mg (37%) of **59a** also as a colorless oil.

58a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2H), 7.40−7.26 (m, 9H), 7.17−7.15 (m, 2H), 7.05 (d, 1H, J = 7.1 Hz), 5.73 (dd, 1H, J = 11.0, 8.3 Hz), 5.00−4.93 (m, 1H), 4.01 (dd, 1H, J = 6.0, 4.1 Hz), 3.84−3.75 (m, 1H), 3.71−3.61 (m, 2H), 3.49 (q, 2H, J = 7.0 Hz), 3.40−3.28 (m, 1H), 3.18 (dd, 1H, J = 14.1, 2.9 Hz), 3.05 (dd, 1H, J = 14.2, 6.1 Hz), 1.16 (dt, 3H, J = 0.7, 7.0 Hz). LRMS (FAB) m/z 459 ($M + H^+$).

59a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.01 (m, 14H), 5.69 (m, 1H), 4.98 (m, 1H), 4.04 (m, 1H), 3.83−3.82 (m, 2H), 3.66−3.45 (m, 3H), 3.24−3.10 (m, 2H), 2.99 (m, 1H), 3.02 (dd, 1H, J = 14.4, 7.7 Hz), 1.18 (dt, 3H, J = 3.8, 7.0 Hz). LRMS (FAB) m/z 459 ($M + H^+$).

Representative Procedure for the Synthesis of Compounds 60−81: Preparation of (2(*S*)-2-Ethoxy-3-(3-(5-phenyl-4,5-dihydroisoxazole-3-yl)phenyl)propanoic Acid (60). c-H_2SO_4 (4 mL) was added dropwise to a solution of **58** (482 mg, 1.05 mmol) in 1,4-dioxane:H_2O (15:4, 19 mL). The mixture was then refluxed for 6 h, cooled to room temperature, and concentrated in vacuo. EtOAc was added and the organic layer was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 537 mg of **60**

as a crude oil. To a solution of provided acid (537 mg) in MeOH (15 mL), TMSCl (0.6 mL, 4.75 mmol) was added dropwise. The reaction mixture was then refluxed for 2 h, cooled to room temperature, quenched with $NaHCO_3$, and concentrated in vacuo. EtOAc was then added and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 323 mg (87% yield for the two steps) of ester as a colorless oil. $LiOH \cdot H_2O$ (75 mg, 1.78 mmol) was then added to a solution of (2*S*)-ethyl 2-ethoxy-3-(3-(5-phenyl-4,5-dihydroisoxazol-3-yl)phenyl)propanoate (314 mg, 0.89 mmol) in THF/H_2O/MeOH (15:3:7, 25 mL) and stirred for 5 h at ambient temperature. The reaction was quenched with 2*N*-HCl and concentrated in vacuo. EtOAc was then added and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 302 mg (100%) of **60** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.53 (m, 2H), 7.37−7.28 (m, 7H), 5.72 (dd, 1H, J = 10.8, 8.3 Hz), 4.08 (dd, 1H, J = 7.70, 4.2 Hz), 3.76 (dd, 1H, J = 16.7, 11.0 Hz), 3.66−3.56 (m, 1H), 3.47−3.40 (m, 1H), 3.32 (dd, 1H, J = 16.7, 8.2 Hz), 3.14 (dd, 1H, J = 14.1, 4.2 Hz), 3.01 (dd, 1H, J = 14.0, 7.8 Hz), 1.15 (dt, 3H, J = 2.2, 7.0 Hz). LRMS (FAB) m/z 340 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{21}NO_4$ (M + H$^+$), 340.1549; found, 340.1553.

(*S*)-2-Ethoxy-3-(3-(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (61). Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.52 (m, 2H), 7.37−7.28 (m, 4H), 7.08−7.00 (m, 2H), 5.70 (dd, 1H, J = 10.9, 8.3 Hz), 4.08 (dd, 1H, J = 7.8, 4.3 Hz), 3.75 (dd, 1H, J = 16.7, 10.8 Hz), 3.66−3.56 (m, 1H), 3.48−3.38 (m, 1H), 3.28 (dd, 1H, J = 16.7, 8.2 Hz), 3.14 (dd, 1H, J = 14.1, 4.2 Hz), 3.02 (dd, 1H, J = 14.0, 7.8 Hz), 1.15 (dt, 3H, J = 2.2, 7.0 Hz). LRMS (FAB) m/z 358 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}FNO_4$ (M + H$^+$), 358.1455; found, 358.1445.

(*S*)-2-Ethoxy-3-(3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (62). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.52 (m, 2H), 7.35−7.29 (m, 6H), 5.70 (dd, 1H, J = 11.0, 8.1 Hz), 4.09 (dd, 1H, J = 7.4, 4.3 Hz), 3.76 (dd, 1H, J = 16.7, 11.0 Hz), 3.65−3.55 (m, 1H), 3.51−3.43 (m, 1H), 3.27 (dd, 1H, J = 16.7, 8.2 Hz), 3.15 (dd, 1H, J = 14.1, 4.2 Hz), 3.02 (dd, 1H, J = 14.1, 7.5 Hz), 1.16 (dt, 3H, J = 2.0, 7.0 Hz). LRMS (FAB) m/z 374 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}ClNO_4$ (M + H$^+$), 374.1159; found, 374.1167.

(*S*)-2-Ethoxy-3-(3-(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (63). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.47 (m, 4H), 7.36−7.27 (m, 4H), 5.68 (dd, 1H, J = 11.0, 8.1 Hz), 4.10 (dd, 1H, J = 7.3, 4.2 Hz), 3.76 (dd, 1H, J = 16.8, 11.1 Hz), 3.62−3.48 (m, 2H), 3.26 (dd, 1H, J = 16.6, 8.2 Hz), 3.16 (dd, 1H, J = 14.3, 4.05 Hz), 3.02 (dd, 1H, J = 14.2, 7.2 Hz), 1.17 (dt, 3H, J = 1.9, 7.0 Hz). LRMS (FAB) m/z 418 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}BrNO_4$ (M + H$^+$), 418.0654; found, 418.0643.

(*S*)-2-Ethoxy-3-(3-(5-(4-iodophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (64). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.57−7.51 (m, 2H), 7.35−7.28 (m, 2H), 7.13−7.11 (m, 2H), 5.67 (dd, 1H, J = 10.9, 8.0 Hz), 4.09 (dd, 1H, J = 7.5, 4.4 Hz), 3.76 (dd, 1H, J = 16.5, 11.0 Hz), 3.65−3.55 (m, 1H), 3.48−3.42 (m, 1H), 3.26 (dd, 1H, J = 16.7, 8.0 Hz), 3.15 (dd, 1H, J = 14.0, 4.3 Hz), 3.02 (dd, 1H, J = 14.0, 7.6 Hz), 1.16 (dt, 3H, J = 2.1, 7.1 Hz). LRMS (FAB) m/z 466 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}INO_4$ (M + H$^+$), 466.0515; found, 466.0517.

(*S*)-2-Ethoxy-3-(3-(5-(4-hydroxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (65). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.53 (m, 2H), 7.35−7.22 (m, 4H), 6.82−6.80 (m, 2H), 5.65 (dd, 1H, J = 10.8, 8.4 Hz), 4.08 (dd, 1H, J = 7.7, 4.0 Hz), 3.70 (dd, 1H, J = 16.7, 10.8 Hz), 3.65−3.55 (m, 1H), 3.48−3.38 (m, 1H), 3.29 (dd, 1H, J = 16.8, 8.4 Hz), 3.14 (dd, 1H, J = 14.0, 4.5 Hz), 3.01 (dd, 1H, J = 14.2, 7.6 Hz), 1.16 (dt, 3H, J = 1.2, 7.1 Hz). LRMS (FAB) m/z 356 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{21}NO_5$ (M + H$^+$), 356.1498; found, 356.1508.

(*S*)-2-Ethoxy-3-(3-(5-(4-methanesulfonyloxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (66). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.52 (m, 2H), 7.45−7.42 (m, 2H), 7.36−7.27 (m, 4H), 5.74 (dd, 1H, J = 10.8, 7.7 Hz), 4.09 (dd, 1H, J = 7.4, 4.1 Hz), 3.79 (dd, 1H, J = 16.7, 11.0 Hz), 3.66−3.56 (m, 1H), 3.50−3.40 (m, 1H), 3.29 (dd, 1H, J = 16.7, 7.9 Hz), 3.18−3.13 (m, 4H), 3.02 (dd, 1H, J = 14.2, 7.4 Hz), 1.16 (dt, 3H, J = 1.8, 7.0 Hz). LRMS (FAB) m/z 434 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{23}NO_7S$ (M + H$^+$), 434.1273; found, 434.1276.

(*S*)-2-Ethoxy-3-(3-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (67). Colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 2H), 7.36−7.28 (m, 4H), 6.90−6.87 (m, 2H), 5.67 (dd, 1H, J = 10.7, 8.7 Hz), 4.09 (dd, 1H, J = 7.6, 4.3 Hz), 3.79 (s, 3H), 3.70 (dd, 1H, J = 16.6, 10.9 Hz), 3.65−3.55 (m, 1H), 3.51−3.43 (m, 1H), 3.30 (dd, 1H, J = 16.7, 8.6 Hz), 3.15 (dd, 1H, J = 14.1, 4.2 Hz), 3.02 (dd, 1H, J = 14.2, 7.6 Hz), 1.16 (dt, 3H, J = 1.4, 7.0 Hz). LRMS (FAB) m/z 370 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{23}NO_5$ (M + H$^+$), 370.1654; found, 370.1653.

(*S*)-2-Ethoxy-3-(3-(5-(4-(*tert*-butylphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (68). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 2H), 7.40−7.24 (m, 6H), 5.70 (dd, 1H, J = 10.8, 8.4 Hz), 4.10 (dd, 1H, J = 7.5, 4.2 Hz), 3.72 (dd, 1H, J = 16.6, 10.9 Hz), 3.62−3.44 (m, 2H), 3.33 (dd, 1H, J = 16.7, 8.4 Hz), 3.16 (dd, 1H, J = 14.0, 4.3 Hz), 3.02 (dd, 1H, J = 14.0, 7.4 Hz), 1.30 (s, 9H), 1.16 (dt, 3H, J = 1.5, 7.0 Hz). LRMS (FAB) m/z 396 (M + H$^+$). HRMS (FAB) calcd for $C_{24}H_{29}NO_4$ (M + H$^+$), 396.2175; found, 396.2185.

(*S*)-3-(3-(5-Benzyl-4,5-dihydroisoxazol-3-yl)phenyl)-2-ethoxypropanoic Acid (69). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.34−7.24 (m, 7H), 4.98 (m, 1H), 4.08−4.07 (m, 1H), 3.61−3.56 (m, 1H), 3.47−3.44 (m, 1H), 3.29 (dd, 1H, J = 16.7, 10.3 Hz), 3.20−3.12 (m, 2H), 3.07−2.99 (m, 2H), 2.87 (dd, 1H, J = 13.7, 7.3 Hz), 1.15 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 354 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{23}NO_4$ (M + H$^+$), 354.1705; found, 354.1710.

(*S*)-2-Ethoxy-3-(3-(4,5-dihydro-5-phenethylisoxazol-3-yl)phenyl-)propanoic Acid (70). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.51 (m, 2H), 7.34−7.19 (m, 7H), 4.72 (m, 1H), 4.09 (dd, 1H, J = 7.8, 4.1 Hz), 3.63−3.55 (m, 1H), 3.47−3.33 (m, 2H), 3.15 (dd, 1H, J = 14.0, 3.9 Hz), 3.05−2.91 (m, 2H), 2.83−2.74 (m, 2H), 2.11−2.08 (m, 1H), 1.92 (m, 1H), 1.16 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 368 (M + H$^+$). HRMS (FAB) calcd for $C_{22}H_{25}NO_4$ (M + H$^+$), 368.1862; found, 368.1855.

(*R*)-2-Ethoxy-3-(3-(4,5-dihydro-5-phenylisoxazole-3-yl)phenyl-)propanoic Acid (71). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60−7.53 (m, 2H), 7.38−7.31 (m, 7H), 5.73 (dd, 1H, J = 10.8, 8.3 Hz), 4.09 (dd, 1H, J = 7.9, 4.2 Hz), 3.76 (dd, 1H, J = 16.7, 11.0 Hz), 3.66−3.56 (m, 1H), 3.48−3.38 (m, 1H), 3.32 (dd, 1H, J = 16.7, 8.2 Hz), 3.15 (dd, 1H, J = 14.1, 4.0 Hz), 3.01 (dd, 1H, J = 14.2, 7.8 Hz), 1.15 (dt, 3H, J = 2.1, 7.0 Hz). LRMS (FAB) m/z 340 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{21}NO_4$ (M + H$^+$), 340.1549; found, 340.1554.

(*R*)-2-Ethoxy-3-(3-(5-(4-fluorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (72). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.53 (m, 6H), 7.37−7.28 (m, 4H), 7.08−7.01 (m, 2H), 5.70 (dd, 1H, J = 10.9, 8.34 Hz), 4.08 (dd, 1H, J = 7.61, 4.31 Hz), 3.75 (dd, 1H, J = 16.7, 10.8 Hz), 3.66−3.56 (m, 1H), 3.49−3.38 (m, 1H), 3.28 (dd, 1H, J = 16.6, 8.3 Hz), 3.14 (dd, 1H, J = 14.0, 4.3 Hz), 3.02 (dd, 1H, J = 14.0, 7.6 Hz), 1.16 (dt, 3H, J = 2.2, 7.0 Hz). LRMS (FAB) m/z 358 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}FNO_4$ (M + H$^+$), 358.1455; found, 358.1445.

(*R*)-2-Ethoxy-3-(3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (73). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.52 (m, 2H), 7.36−7.30 (m, 6H), 5.70 (dd, 1H, J = 10.9, 8.0 Hz), 4.10 (dd, 1H, J = 7.5, 4.2 Hz), 3.76 (dd, 1H, J = 16.6, 11.1 Hz), 3.63−3.55 (m, 1H), 3.49−3.44 (m, 1H), 3.27 (dd, 1H, J = 16.8, 8.2 Hz), 3.15 (dd, 1H, J = 14.0, 4.3 Hz), 3.02 (dd, 1H, J = 14.1, 7.3 Hz), 1.16 (dt, 3H, J = 2.0, 7.0 Hz). LRMS (FAB) m/z 374 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}ClNO_4$ (M + H$^+$), 374.1159; found, 374.1169.

(*R*)-2-Ethoxy-3-(3-(5-(4-bromophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (74). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57−7.47 (m, 4H), 7.36−7.27 (m, 4H), 5.68 (dd, 1H, J

= 11.0, 8.1 Hz), 4.10 (dd, 1H, J = 7.4, 4.3 Hz), 3.76 (dd, 1H, J = 16.7, 11.0 Hz), 3.65−3.55 (m, 1H), 3.51−3.43 (m, 1H), 3.26 (dd, 1H, J = 16.7, 8.2 Hz), 3.15 (dd, 1H, J = 14.1, 4.2 Hz), 3.02 (dd, 1H, J = 14.0, 7.4 Hz), 1.16 (dt, 3H, J = 2.1, 7.0 Hz). LRMS (FAB) m/z 418 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}BrNO_4$ (M + H$^+$), 418.0654; found, 418.0646.

(*R*)-2-Ethoxy-3-(3-(5-(4-iodophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (75). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.57−7.51 (m, 2H), 7.35−7.28 (m, 2H), 7.13−7.11 (m, 2H), 5.66 (dd, 1H, J = 11.0, 8.1 Hz), 4.09 (dd, 1H, J = 7.5, 4.2 Hz), 3.76 (dd, 1H, J = 16.7, 11.0 Hz), 3.65−3.55 (m, 1H), 3.50−3.42 (m, 1H), 3.26 (dd, 1H, J = 16.7, 8.0 Hz), 3.14 (dd, 1H, J = 14.2, 4.3 Hz), 3.02 (dd, 1H, J = 14.2, 7.4 Hz), 1.16 (dt, 3H, J = 2.1, 7.0 Hz). LRMS (FAB) m/z 466 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{20}INO_4$ (M + H$^+$), 466.0515; found, 466.0524.

(*R*)-2-Ethoxy-3-(3-(5-(4-hydroxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (76). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.53 (m, 2H), 7.35−7.22 (m, 4H), 6.83−6.80 (m, 2H), 5.65 (dd, 1H, J = 10.7, 8.7 Hz), 4.09 (dd, 1H, J = 7.5, 4.4 Hz), 3.70 (dd, 1H, J = 16.8, 10.9 Hz), 3.65−3.55 (m, 1H), 3.49−3.41 (m, 1H), 3.29 (dd, 1H, J = 16.8, 8.5 Hz), 3.14 (dd, 1H, J = 14.0, 4.1 Hz), 3.02 (dd, 1H, J = 13.8, 7.6 Hz), 1.16 (dt, 3H, J = 1.1, 7.0 Hz). LRMS (FAB) m/z 356 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{21}NO_5$ (M + H$^+$), 356.1498; found, 356.1508.

(*R*)-2-Ethoxy-3-(3-(5-(4-methanesulfonyloxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (77). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.52 (m, 2H), 7.45−7.42 (m, 2H), 7.36−7.27 (m, 4H), 5.74 (dd, 1H, J = 10.8, 7.9 Hz), 4.09 (dd, 1H, J = 7.4, 4.1 Hz), 3.79 (dd, 1H, J = 16.7, 11.0 Hz), 3.66−3.56 (m, 1H), 3.51−3.41 (m, 1H), 3.29 (dd, 1H, J = 16.7, 7.9 Hz), 3.18−3.13 (m, 4H), 3.02 (dd, 1H, J = 14.2, 7.4 Hz), 1.16 (dt, 3H, J = 1.7, 7.0 Hz). LRMS (FAB) m/z 434 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{23}NO_7S$ (M + H$^+$), 434.1273; found, 434.1279.

(*R*)-2-Ethoxy-3-(3-(5-(4-methoxyphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (78). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 2H), 7.36−7.29 (m, 4H), 6.91−6.87 (m, 2H), 5.67 (dd, 1H, J = 10.9, 8.7 Hz), 4.09 (dd, 1H, J = 7.6, 4.3 Hz), 3.79 (s, 3H), 3.70 (dd, 1H, J = 16.7, 10.8 Hz), 3.66−3.55 (m, 1H), 3.50−3.40 (m, 1H), 3.30 (dd, 1H, J = 16.7, 8.6 Hz), 3.15 (dd, 1H, J = 14.1, 4.2 Hz), 3.02 (dd, 1H, J = 14.2, 7.6 Hz), 1.16 (dt, 3H, J = 1.4, 7.0 Hz). LRMS (FAB) m/z 370 (M + H$^+$). HRMS (FAB) calcd for $C_{21}H_{23}NO_5$ (M + H$^+$), 370.1654; found, 370.1653.

(*R*)-2-Ethoxy-3-(3-(5-(4-(*tert*-butylphenyl)-4,5-dihydroisoxazol-3-yl)phenyl)propanoic Acid (79). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59−7.54 (m, 2H), 7.40−7.27 (m, 6H), 5.70 (dd, 1H, J = 10.8, 8.6 Hz), 4.10 (dd, 1H, J = 7.5, 4.2 Hz), 3.72 (dd, 1H, J = 16.6, 10.9 Hz), 3.65−3.44 (m, 2H), 3.33 (dd, 1H, J = 16.7, 8.6 Hz), 3.16 (dd, 1H, J = 14.0, 4.1 Hz), 3.02 (dd, 1H, J = 14.0, 7.4 Hz), 1.30 (s, 9H), 1.16 (dt, 3H, J = 1.6, 7.0 Hz). LRMS (FAB) m/z 396 (M + H$^+$). HRMS (FAB) calcd for $C_{24}H_{29}NO_4$ (M + H$^+$), 396.2175; found, 396.2185.

(*R*)-3-(3-(5-Benzyl-4,5-dihydroisoxazol-3-yl)phenyl)-2-ethoxypropanoic Acid (80). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52−7.49 (m, 2H), 7.33−7.24 (m, 7H), 5.00−4.98 (m, 1H), 4.10−4.06 (m, 1H), 3.62−3.56 (m, 1H), 3.47−3.41 (m, 1H), 3.29 (dd, 1H, J = 16.7, 10.3 Hz), 3.19−3.11 (m, 2H), 3.07−2.99 (m, 2H), 2.87 (dd, 1H, J = 13.8, 7.2 Hz), 1.15 (t, 3H, J = 7.1 Hz). LRMS (FAB) m/z 354 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{24}NO_4$ (M + H$^+$), 354.1705; found, 354.1710.

(*R*)-2-Ethoxy-3-(3-(4,5-dihydro-5-phenethylisoxazol-3-yl)phenyl-)propanoic Acid (81). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55−7.51 (m, 2H), 7.35−7.16 (m, 7H), 4.75−4.70 (m, 1H), 4.09 (dd, 1H, J = 7.7, 4.2 Hz), 3.65−3.55 (m, 1H), 3.47−3.33 (m, 2H), 3.15 (dd, 1H, J = 14.1, 4.2 Hz), 3.05−2.91 (m, 2H), 2.83−2.74 (m, 2H), 2.16−2.03 (m, 1H), 1.97−1.92 (m, 1H), 1.16 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 368 (M + H$^+$). HRMS (FAB) calcd for $C_{22}H_{25}NO_4$ (M + H$^+$), 368.1862; found, 368.1857.

(*S*)-2-Ethoxy-3-(3-(5-phenylisoxazole-3-yl)phenyl)propanoic Acid (84). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84−7.72 (m, 4H), 7.51−7.33 (m, 5H), 6.81 (s, 1H), 4.14−4.06 (m, 1H), 3.68−3.54 (m, 1H), 3.49−3.39 (m, 1H), 3.23−3.03 (m, 2H), 1.16 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 338 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{19}NO_4$ (M + H$^+$), 338.1392; found, 338.1382.

(*R*)-2-Ethoxy-3-(3-(5-phenylisoxazole-3-yl)phenyl)propanoic Acid (85). Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.84−7.72 (m, 4H), 7.51−7.33 (m, 5H), 6.83−6.82 (m, 1H), 4.14−4.06 (m, 1H), 3.67−3.57 (m, 1H), 3.51−3.29 (m, 1H), 3.24−3.03 (m, 2H), 1.17 (t, 3H, J = 7.0 Hz). LRMS (FAB) m/z 338 (M + H$^+$). HRMS (FAB) calcd for $C_{20}H_{19}NO_4$ (M + H$^+$), 338.1392; found, 338.1404.

(2(*S*)-Ethyl-3-(3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl)-2-ethoxy Propanoate (86). TMSCl (0.3 mL, 2.29 mmol) was added dropwise to a solution of (*S*)-2-ethoxy-3-(3-(5-(4-chlorophenyl)-4,5-dihydroisoxazol-3-yl)phenyl) propanoic acid **62** (285 mg, 0.76 mmol) in EtOH (20 mL). The reaction mixture was refluxed for 15 h, cooled to room temperature, quenched with $NaHCO_3$, and concentrated in vacuo. EtOAc was then added, and the organic layer so obtained was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (EtOAc:*n*-hexane = 1:5) afforded 273 mg (89%) of **86** as a colorless oil.

(*S*)-Methyl 3-(3-acetylphenyl)-2-ethoxypropanoate (45b). Mo(CO)$_6$ (88 mg, 0.33 mmol) was added to a solution of **86** (133 mg, 0.33 mmol) in CH_3CN/H_2O (100:1, 5 mL). The reaction mixture was refluxed for 14 h, cooled to room temperature, concentrated, and EtOAc was added. The mixture was then filtered using a celite pad and concentrated in vacuo. The residue so obtained, was purified by flash column chromatography (EtOAc:*n*-hexane = 1:5) to afford 44 mg (51%) of **14** as a colorless oil.

Biology. In Vitro Transactivation Assay. PPAR transactivation assays were conducted as previously described.[2a,e] The ligand binding domains (LBD) of human PPARα and PPARγ receptors were fused to the DNA binding domain (DBD) of the yeast transcription factor Gal4. Briefly, CV-1 cells were transiently transfected with an expression vector for the respective PPAR chimera and with a reporter construct containing five copies of the Gal4DNA binding site and with pRL-TK as a control vector (Promega). Test compounds were dissolved in DMSO and diluted 1:1000 in media. Cells were treated with test compounds at seven concentrations ranging from 0.03 to 100 μM for 24 h and then subjected to a dual luciferase assay using Dual-Glo luciferase reagent (Promega). EC_{50}values were calculated by nonlinear regression using SigmaPlot 4.0 (SPSS).

In Vivo Assay. Male obese *db*/*db* mice and lean control C57BL/6 mice were obtained from Japan SLC (Shizuoka, Japan). All mice were provided with a standard diet and tap water ad libitum. All mice (n = 6) were 12 weeks old when drug administration started. Each compound was administered orally for 11 days. At the end of the treatment period (4, 7, and 11-day), body weights were measured, blood samples were collected, and then blood glucose levels were measured using AccuChek Active (Roche, Germany).

Molecular Docking. The designed derivatives, including all hydrogen atoms, were built and minimized using Gasteiger-Hückel charge and Tripos force field in the SYBYL software suite.[13] Docking analysis was conducted using the FlexX algorithm to examine the binding modes of the designed derivatives at the active sites of PPARα and PPARγ. The crystal structures of PPARα and PPARγ compexed with tesaglitazar[11] were used in this study (pdb entry = 1I7G and 1I7I, respectively). The COOH group of tesaglitazar and the designed derivatives are bound by PPARα and PPARγ in the form of a carboxylate anion. Thus, COOH groups were calculated in an anionic form, which in situ shares its negative charge with two oxygens. The active sites in PPARα and PPARγ were defined as a collection of protein residues enclosed within a 6.5Å radius sphere centered by bound tesaglitazar. The energy-minimized structure of tesaglitazar was initially docked into PPARα and PPARγ to determine how well the FlexX algorithm reproduces the experimentally determined binding conformation of tesaglitazar at the active sites. A superpositioning of docked tesaglitazar onto crystallographic dispositions of the PPARα and PPARγ active sites yielded root-mean-square (rms) deviations of 1.59 Å and 1.22 Å, respectively, revealing that FlexX successfully reproduced the binding conformations of PPARα and PPARγ. To

calculate binding affinities between the designed derivatives and PPARα or PPARγ, we used a consensus scoring program that integrates multiple well-known scoring functions, i.e., a GOLD-like function, a DOCK-like function, ChemScore, a PMF function, and FlexX. In docking/scoring outputs, conformers with high GOLD-scores (obtained using hydrogen bonding, complex, and internal energies) were analyzed and compared with tesaglitazar cocrystallized in the PPARα and PPARγ active site.

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Supporting Information Available: Information on the in vitro transactivation assays on additional oxime ether and isoxazoline analogues, in vivo antihyperglycemic activities of several compounds in db/db mice, and HRMS and HPLC data for the target compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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