N-(2-Benzoylphenyl)-L-tyrosine PPARγ Agonists. 3. Structure−Activity Relationship and Optimization of the *N*-Aryl Substituent

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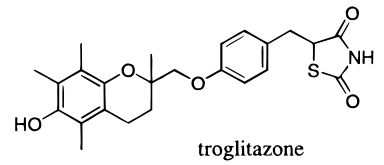
3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-(2*S*)-((2-benzoylphenyl)amino)propionic acid (**1**) and (2*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic acid (**2**) are peroxisome proliferator-activated receptor γ (PPARγ) agonists and have antidiabetic activity in rodent models of type 2 diabetes. As part of an effort to develop the SAR of the *N*-2-benzoylphenyl moiety of **1** and **2**, a series of novel carboxylic acid analogues, **23**−**66**, modified only in the *N*-2-benzoylphenyl moiety were synthesized from L-tyrosine and evaluated as PPARγ agonists. In general, only modest changes in the *N*-2-benzoylphenyl moiety of **1** and **2** are tolerated. More specifically, the best changes involve bioisosteric replacement of one of the two phenyl rings of this moiety. Addition of substituents to this moiety generally produced compounds that are less active in the cell-based functional assays of PPARγ activity although binding affinity to PPARγ may be maintained. A particularly promising set of analogues is the anthranilic acid esters **63**−**66** in which the phenyl ring in the 2-benzoyl group of **1** and **2** has been replaced by an alkoxy group. In particular, (*S*)-2-(1-carboxy-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic acid methyl ester (**63**) has a pK_i of 8.43 in the binding assay using human PPARγ ligand binding domain and a pEC_{50} of 9.21 in the in vitro murine lipogenesis functional assay of PPARγ activity. Finally, **63** was found to normalize glycemia when dosed at 3 mg/kg bid po in the Zucker diabetic fatty rat model of type 2 diabetes.

Introduction

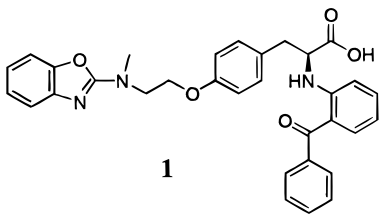
The PPARγ agonist troglitazone (Chart 1) was recently approved for the treatment of type 2 diabetes. This member of the thiazolidinedione (TZD) class of antidiabetics enhances insulin action in man and ameliorates the hyperglycemia characteristic of type 2 diabetes.[1] It also reduces plasma levels of triglycerides, free fatty acids, and total cholesterol. While troglitazone is an important advance in the treatment of type 2 diabetes, its use as a monotherapy does not normalize plasma glucose in most type 2 diabetics.[2] Troglitazone is a relatively weak PPARγ ligand (pK_i = 6.52).[3] We felt that a more potent molecule may have greater therapeutic efficacy in treating type 2 diabetics.

In the first paper of this series, we report a novel, potent class of antihyperglycemics that was discovered and optimized from a L-tyrosine-derived screening hit using in vitro assays of PPARγ activity.[3] These compounds are *N*-(2-benzoylphenyl)-L-tyrosine derivatives exemplified by compounds **1** and **2** (Chart 1). A number of structurally analogous α-heteroatom-substituted phenylpropanoic acids have also been reported to have antihyperglycemic activity.[4,5] These compounds resulted from research focused on finding alternative pharmacophores to the TZD moiety, but only in a

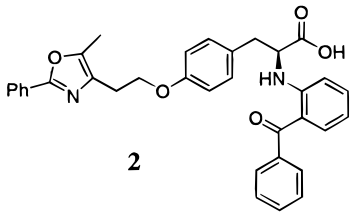
Chart 1



troglitazone



1



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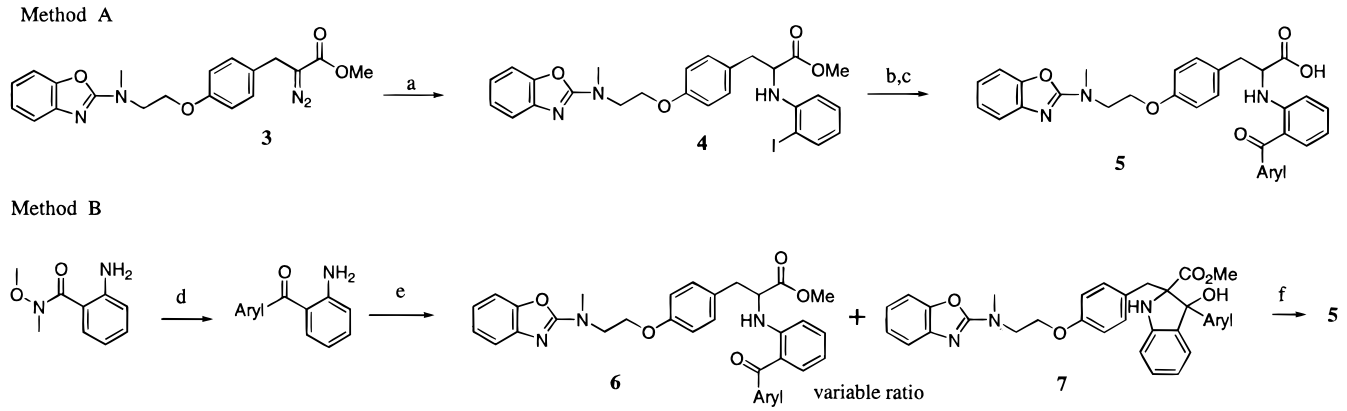
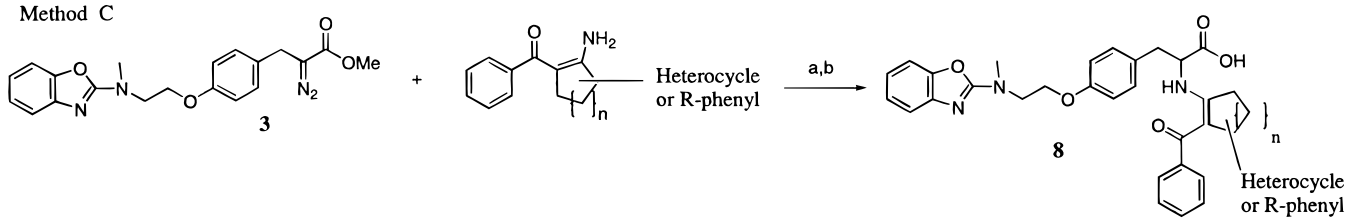
Scheme 1[a]



[a] Reagents: (a) 2-iodoaniline, $Rh_2(OAc)_4$, toluene, rt; (b) $PdCl_2(PPh_3)_2$, K_2CO_3, dioxane, CO (1 atm), 100 °C, arylboronic acid; (c) LiOH, MeOH, THF, H_2O; (d) arylLi, THF, −78 °C; (e) **3**, $Rh_2(OAc)_4$, toluene, 80 °C; (f) LiOH, MeOH, THF, H_2O or KOH, EtOH, 80 °C.

Scheme 2[a]



[a] Reagents: (a) $Rh_2(OAc)_4$, toluene, rt to 80 °C; (b) 1.0 M LiOH/THF/MeOH (1:3:1), rt.

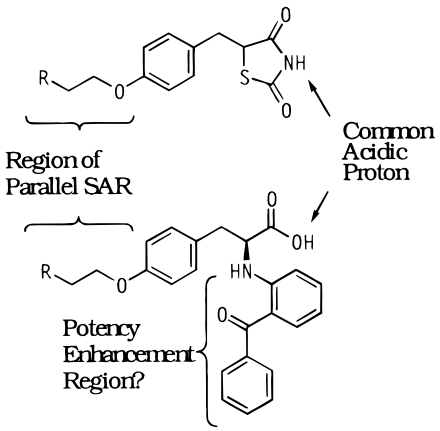


Figure 1. TZD and *N*-(2-benzoylphenyl)-L-tyrosine derivative comparison.

limited number of cases has their PPARγ affinity been reported.[5] In our efforts to optimize the potency of the *N*-(2-benzoylphenyl)-L-tyrosine derivatives against PPARγ, we found that they share a parallel structure−activity relationship (SAR) with the TZDs with respect to the alkyl portion of their common phenyl alkyl ether moiety as shown in Figure 1. In addition, the carboxylic acid proton of the tyrosine series occupies the same position in space as that of the acidic proton of the TZD heterocycle if their common structural features are overlaid.[4] The structural difference that distinguishes these new PPARγ agonists from the TZDs is the replacement of the TZD group by the *N*-(2-benzoylphenyl)glycine subunit. This larger, more lipophilic moiety probably accounts for the greater PPARγ affinity seen with our tyrosine derivatives when compared with the analogous TZDs. The *N*-2-benzoylphenyl moiety interacts with an area of the ligand-binding domain of PPARγ that is not accessible to the TZDs.[6]

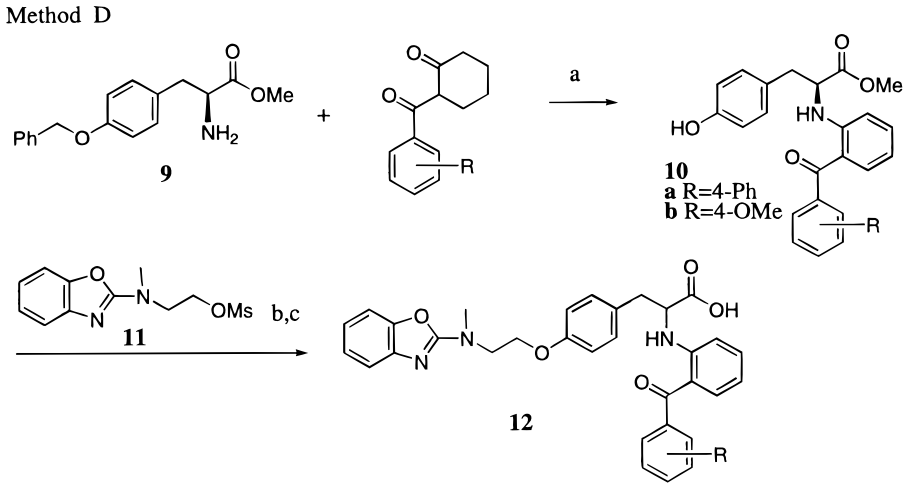
This paper reports our SAR studies on the *N*-aryl region of this new class of antihyperglycemics using **1** and **2** as starting points. Our goals were to develop their SAR, to maximize potency against PPARγ, and to improve the aqueous solubility of these highly lipophilic molecules.

Chemistry

The most expeditious routes to obtaining a variety of racemic analogues of **1** utilize rhodium carbenoid N−H insertions as a key step.[7] Scheme 1 shows two general routes to analogues of **1** bearing the generic structure **5** where the distal phenyl ring of the *N*-2-benzoylphenyl moiety has been derivatized or replaced by other rings. In method A, the iodoaniline **4**, generated by a N−H insertion of the rhodium carbenoid derived from **3**[8] with 2-iodoaniline, is converted into **5** using palladium-catalyzed carbonylative coupling with arylboronic acids under an atmosphere of CO followed by saponification.[9] Method B utilizes a functionalized *o*-aminobenzophenone, generated by the reaction of an aryllithium with the Weinreb amide of anthranilic acid,[10] as the substrate for the N−H insertion reaction. This process gives variable ratios of the desired product **6** and the cyclic derivative **7** as reported previously.[3] Both compounds can be converted into **5** with KOH in EtOH at 80 °C. The latter N−H insertion route was also used to make analogues modified on the proximal phenyl ring of the *N*-2-benzoylphenyl moiety of **1** as shown generically by structure **8** (Scheme 2, method C).

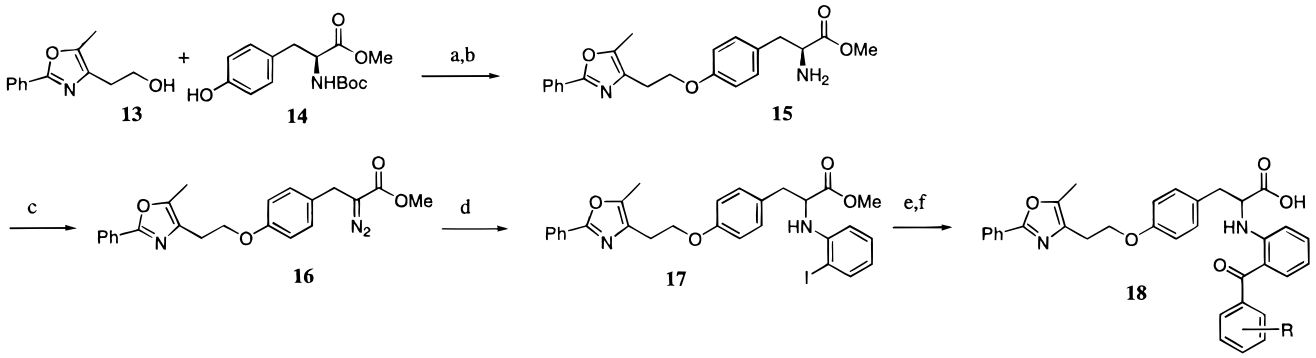
An alternative route to compounds of the generic structure **12** is shown in Scheme 3 (method D). Coupling of *O*-benzyl-L-tyrosine methyl ester (**9**) with a 2-benzoylcyclohexanone gives a vinylogous amide which is aromatized in situ with concomitant benzyl ether cleavage with 10% Pd/C at high temperature to give the

Scheme 3[a]



[a] Reagents: (a) toluene, Δ, DS trap, anisole, 10% Pd/C, Δ; (b) NaH, DMF, 80 °C; (c) LiOH, MeOH, THF, H_2O.

Scheme 4[a]



[a] Reagents: (a) Ph_3P, DEAD, THF, 0 °C to rt (45%); (b) TFA, CH_2Cl_2; (c) isoamyl nitrite, HOAc, $CHCl_3$, Δ (61%); (d) 2-iodoaniline, $Rh_2(OAc)_4$, toluene, rt (86%); (e) $PdCl_2(PPh_3)_2$, K_2CO_3, dioxane, CO (1 atm), 100 °C, arylboronic acid; (f) LiOH, MeOH, THF, H_2O.

methyl L-tyrosine derivative **10**. Subsequent coupling with the mesylate **11**[11] and saponification give **12**. Although this route commences with chiral, nonracemic material, the final products are racemic. We believe that racemization occurs during the mesylate coupling reaction.

Rhodium carbenoid N−H insertions also play a key role in synthesizing derivatives of **2**. A route to the generic compound **18** is shown in Scheme 4. The alcohol **13**[12] is coupled to *N*-Boc-L-tyrosine methyl ester (**14**) using Mitsunobu conditions followed by Boc group removal with TFA to produce **15**. Treatment of **15** with isoamyl nitrite produces the key intermediate diazo compound **16**.[13] Using analogous chemistry to that reported above (Scheme 1, method A), **18** is generated via the iodoaniline **17**.

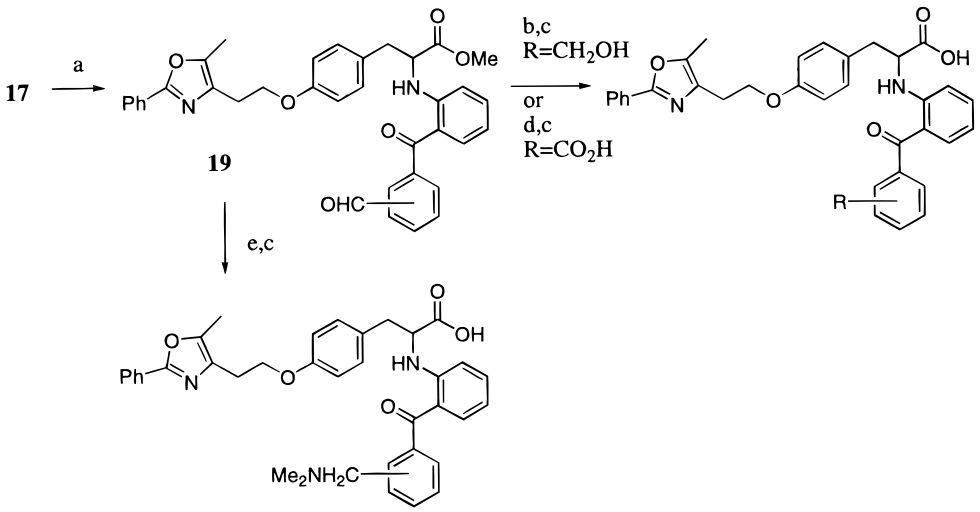
This same chemistry is also exploited in Scheme 5 to provide the key intermediate **19** bearing an aldehyde moiety which is converted into several analogues of **2** using standard chemical manipulations. The utility of N−H insertions is shown again in Scheme 6 where it is used to generate analogues of **2** where the phenyl ring of the benzoyl group of the *N*-2-benzoylphenyl moiety is replaced with cyclohexyl or pyridyl rings (compounds **56** and **20**, respectively).

Scheme 7 details the synthesis of analogues of **2** where the *N*-2-benzoylphenyl moiety is replaced by a *N*-2-carboxyphenyl moiety producing anthranilate derivatives. The iodoaniline **17** is carboxylated using Pd catalysis under 200 psi of CO in the presence of water to provide a racemic anthranilic acid which can be either saponified directly to give the diacid **60** or converted into an amide using EDC and the appropriate amine followed by saponification to give **61** or **62**. Molecules of the anthranilate class can also be made in a chiral, nonracemic fashion. Condensation of the L-tyrosine derivative **15** with methyl cyclohexanone-2-carboxylate in toluene at 130 °C gives a vinylogous carbamate. The toluene is then replaced with anisole, and 10% Pd/C is added. Heating this mixture to 190 °C results in aromatization to the anthranilate derivative **21** with little or no racemization. The alkyl methyl ester of **21** can be selectively saponified to **63** if the reaction is carefully monitored and the reaction time is short. The corresponding diacid is obtained with longer reaction times. The diacid, in turn, can be selectively esterified on the alkyl acid moiety using HCl in MeOH. The remaining carboxylic acid moiety can then be converted into various esters by reaction with alkyl iodides and K_2CO_3 in DMF. The methyl ester is then selectively saponified to give the generic stucture **22**.

Biology

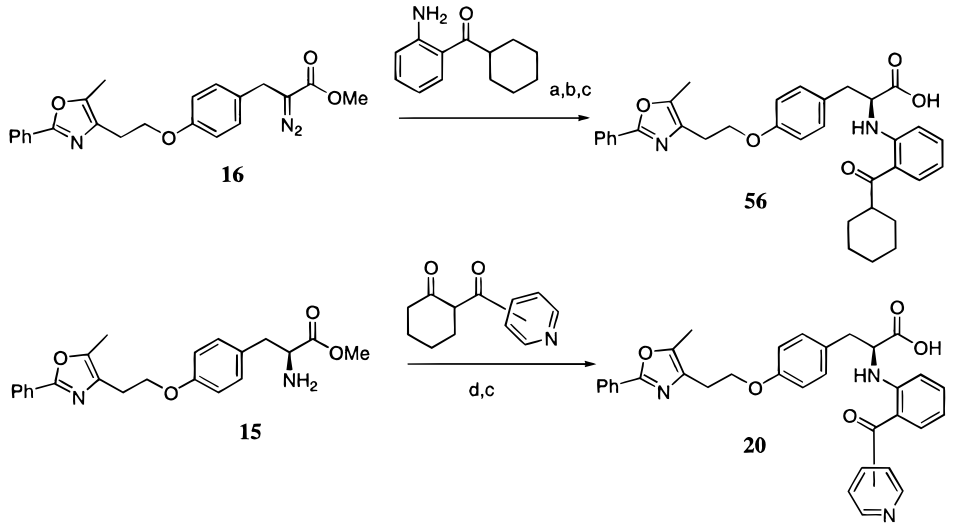
In Vitro. The PPARγ binding assay and the cell-based transactivation and lipogenesis assays of PPARγ activity are as reported in the first paper of this series.[3]

Scheme 5[a]



[a] Reagents: (a) formylbenzeneboronic acid, $PdCl_2(PPh_3)_2$, K_2CO_3, dioxane, CO (1 atm), 100 °C; (b) $NaBH_4$, THF; (c) LiOH, MeOH, THF, H_2O; (d) Jones' reagent, acetone; (e) Me_2NH, HOAc, MeOH, THF, $NaCNBH_3$.

Scheme 6[a]



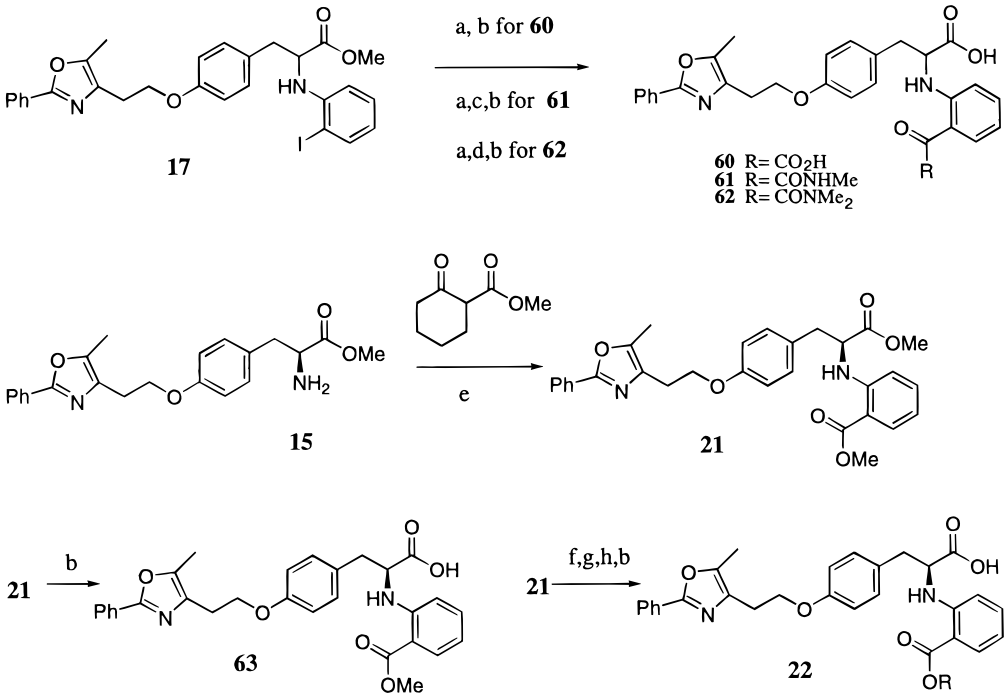
[a] Reagents: (a) $Rh_2(OAc)_4$, toluene, rt; (b) chiral chromatography on Chiral OD column; (c) 1.0 M LiOH/THF/MeOH (1:3:1), rt; (d) 10% Pd/C, anisole, 212 °C.

In Vivo. Nine-week-old male Zucker diabetic fatty (ZDF) rats[14] (n = 8/group) were baseline-matched for plasma glucose, and the test compounds were administered twice daily for 17 days by oral gavage. Blood samples were obtained by tail venipuncture at days 0, 3, 7, and 17 and analyzed for plasma glucose, insulin, triglycerides, and nonesterified free fatty acids (NEFAs). Glycosylated hemoglobin was measured on day 17 of the study. Data presented in Table 7 represent the mean ± SEM for the percent reduction from the vehicle control animals at day 17.

Results and Discussion

SAR Studies. Table 1 lists a set of compounds where the distal phenyl ring of the *N*-2-benzoylphenyl moiety of **1** has been derivatized. Compounds **23**−**31** were made to probe the influence of electronic effects on binding affinity. This set was generated by 'walking' a trifluoromethyl, a methyl, or a methoxy group around the phenyl ring. Interestingly, none of these compounds differ greatly from any other one in the series (pK_i range: 8.25−8.76) or from the parent **1** (pK_i = 8.83). As a group, however, they are less active in the functional assays. Attachment of large lipophilic groups to this phenyl ring (compounds **32**−**34**) results in a substantial loss of activity. Several compounds were made when the phenyl ring was replaced with alternative rings (Table 2). The cyclopentane (**35**) and cyclohexane (**36**) replacements had little effect on binding affinity, but the larger cycloheptane (**38**) shows lower affinity. In the case of the cyclohexane analogue, the enantiomers (**36**, **37**) were separated by chiral chromatography and most of the activity was found in the enantiomer **36** which is assigned the *S*-configuration by analogy with **1** made from L-tyrosine.[3] The two possible thiophene analogues (**39**, **40**) are similar in binding affinity to PPARγ although functional activity is decreased relative to **1**. Finally, the naphthalene analogue **41** retains good binding affinity and potency in the lipogenesis assay. No analogue in the series **23**−**41** has greater affinity for PPARγ than does **1**, and a number of them have substantially lower activity, especially in

Scheme 7[a]



[a] Reagents: (a) $PdCl_2(PPh_3)_2$, K_2CO_3, dioxane, water, CO (200 psi), 125 °C; (b) 1.0 M LiOH/THF/MeOH (1:3:1), 2 h, rt; (c) EDC, HOBt, TEA, aq $MeNH_2$, CH_2Cl_2; (d) EDC, HOBt, TEA, aq Me_2NH, CH_2Cl_2; (e) toluene, 130 °C; 10% Pd/C, anisole, 190 °C; (f) 1.0 M LiOH/THF/EtOH (1:4:1), 30 h; (g) HCl, MeOH, 70 °C; (h) K_2CO_3, RI, DMF.

the functional assays. The overall profile of the cyclohexane analogue **36** is comparable, however.

Several analogues of **1** were made in which the proximal phenyl ring of the *N*-2-benzoylphenyl moiety was modified or replaced by a heterocycle (Table 3). Compounds **42** and **43,** which have a methyl or a chloro substituent para to the amino group, show a modest decrease in binding affinity. Replacement of the phenyl ring by three different thiophene isomers (compounds **44**−**46**) also shows modest decreases in binding affinity (pK_i range: 7.63−8.59). A pyridine analogue, **47**, was found to be substantially less potent than **1**. Finally, the thiazole analogue **48** also has decreased affinity. In general, the syntheses of these molecules were difficult and gave racemic products. As this class of analogues showed no in vitro advantage over **1**, they were not pursued further.

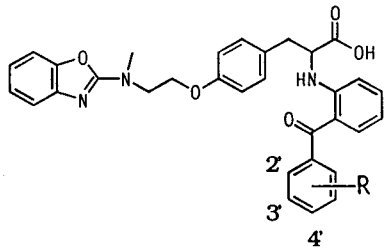
At this point in our SAR work, we discovered that **2** had superior glucose-lowering effects in vivo at a given dose versus **1** despite their similar in vitro profiles.[3] It was assumed that this difference is due to these molecules having different pharmacokinetic profiles. Because of this result, subsequent analogues were made bearing the 2-(5-methyl-2-phenyloxazo-4-yl)ethyl side chain of **2** rather than the 2-(2-benzoxazoylmethylamino)ethyl side chain of **1**.

In an effort to decrease the lipophilicity of **2** and to increase aqueous solubility, a series of compounds were made that appended polar groups onto the distal phenyl ring of the *N*-2-benzoylphenyl moiety (Table 4). At either the meta or para position, either a hydroxymethyl group, a carboxyl group, or a dimethylamino group was attached (compounds **49**−**51** for the para series and compounds **52**−**54** for the meta series). In both cases, the hydroxymethyl group is tolerated with only a modest decrease in affinity. The benzoic acids, however, are over 500-fold less potent. The *p*-dimethylaminomethyl-appended analogue **51** is 10-fold less potent than **2**, while the meta analogue **54** is 1000-fold less potent. Finally, addition of a *m*-amino group (compound **55**) gave little change in affinity. All compounds in this set have decreased activity in the functional assays relative to **2**.

In another series of analogues of **2**, the distal phenyl ring of the *N*-2-benzoylphenyl moiety was replaced by other groups (Table 5). As was seen in compound **36**, cyclohexyl is a good replacement (enantiomeric compounds **56** and **57**). Again, the more active enantiomer **56** (pK_i = 8.79) is assigned the *S*-configuration by analogy to **2** made from L-tyrosine. Other replacements for the phenyl group that maintain good affinity for PPARγ include the 3-pyridyl (**58**, pK_i = 9.03) and the 4-pyridyl (**59**, pK_i = 8.74), although they are substantially less active in the lipogenesis assay. Table 5 also reports a series of anthranilate analogues of **2**. The parent anthranilic acid **60** is inactive in the binding assay (pK_i > 5.5), while the corresponding methylamide **61** and dimethylamide **62** are >10- and >100-fold less active than **2**, respectively. Interestingly, the ester analogues **63**−**66** have comparable potency to **2** (pK_i range: 8.43−9.01). Of even greater interest, these compounds have good potency in the functional assays. For example, **63** and **64** have pEC_{50}'s of 9.21 and 9.37 in the lipogenesis assay, respectively, versus a pEC_{50} of 8.83 for **2**. In the transactivation assay, compounds **63**−**66** all have a pEC_{50} > 9, which compares favorably with the value of 9.47 seen for **2**. In this series the compounds with the best in vitro profiles are **56** and the anthranilate esters **63**−**66**.

Aqueous Solubility. One goal of our work was to increase the aqueous solubility of our molecules. As can be seen in Table 6, the highly lipophilic **2** has very poor

Table 1. In Vitro Profile of PPARγ Agonists **23**−**34**



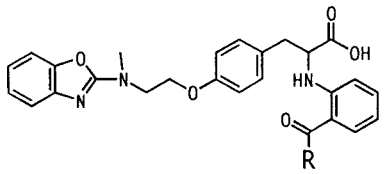
	Structure[a]		Binding[b]	Transactivation[c]	Lipogenesis[d]
#	SC	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
1	S	H	8.83 ± 0.14 (2)	8.58 ± 0.39 (8)	8.36 ± 0.41 (4)
23	R/S	2'-CF_3	8.57 ± 0.04 (2)	7.40 ± 0.40 (3)	7.15 ± 0.15 (2)
24	R/S	3'-CF_3	8.58 ± 0.00 (2)	7.93 ± 0.46 (3)	7.57 ± 0.82 (2)
25	R/S	4'-CF_3	8.29 ± 0.23 (2)	7.62 ± 0.05 (3)	7.16 ± 0.13 (2)
26	R/S	2'-CH_3	8.65 ± 0.03 (2)	8.03 ± 0.10 (3)	8.16 ± 0.07 (4)
27	R/S	3'-CH_3	8.57 ± 0.02 (2)	7.78 ± 0.30 (3)	7.84 ± 0.96 (2)
28	R/S	4'-CH_3	8.55 ± 0.15 (2)	8.07 ± 0.06 (3)	7.91 ± 0.86 (4)
29	R/S	2'-OCH_3	8.76 ± 0.05 (2)	7.42 ± 0.23 (3)	6.30 ± 0.87 (4)
30	R/S	3'-OCH_3	8.64 ± 0.01 (2)	6.93 ± 0.41 (3)	6.81 ± 0.13 (3)
31	R/S	4'-OCH_3	8.25 ± 0.04 (2)	7.49 ± 0.33 (3)	7.02 ± 0.41 (3)
32	R/S	3'-OCH_2Ph	7.27 ± 0.10 (2)	6.13 ± 0.11 (3)	6.05 ± 0.01 (2)
33	R/S	4'-OCH_2 Ph	7.18 ± 0.02 (2)	6.12 ± 0.37 (3)	6.17 ± 0.01 (2)
34	R/S	4'- Ph	7.31 ± 0.02 (2)	7.62 ± 0.04 (5)	6.47 ± 0.29 (3)

[a] See Figure. [b] pK_i −log of the concentration of test compound required to achieve an apparent K_i value according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K_d is the dissociation constant for the radioligand at the receptor. [c] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity. [d] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum lipogenic activity ± standard error (number of determinations); SC, stereochemistry.

solubility in simulated gastric fluid (pH 1.2) or in pH 7.4 phosphate buffer (<0.001 mg/mL). The former is an estimate of solubility in the stomach and the latter that of the small intestine. Although **2** is orally active and potent in rodent diabetes models, we believed that molecules with improved aqueous solubility could have improved pharmacokinetic and pharmaceutic properties. Not surprisingly, these carboxylic acids are more soluble at higher pH when the carboxylate moiety is largely ionized. The solubilities of a number of analogues of **2** are also shown in Table 6. Of the compounds listed, the pyridine-containing analogue **59** has the best solubility in simulated gastric fluid (0.087 mg/mL), while the most soluble compound at pH 7.4 is the *m*-hydroxymethyl analogue **52** (1.34 mg/mL). Interestingly, the *p*-hydroxymethyl analogue **49** is much less soluble at pH 7.4 (0.075 mg/mL). The compound with the best overall solubility is **59**. The methyl anthranilate analogue **63**, while still poorly soluble in simulated gastric fluid, is much more soluble in the pH 7.4 buffer (0.300 mg/mL) than is **2**.

In Vivo Results. Due to its overall favorable in vitro profile, **63** was chosen for in vivo evaluation in the Zucker diabetic fatty (ZDF) rat.[14] This was a 17-day dose-ranging study with **63** given at 0.3, 1, 3, and 5 mg/kg bid po. The positive standard was troglitazone given at 500 mg/kg bid po, a dose which normalizes glucose in this model. A summary of the day 17 results with the 5 mg/kg dose of **63** and troglitazone is shown in Table 7. The two compounds gave similar results.

Table 2. In Vitro Profile of PPARγ Agonists **35**−**41**



	Structure[a]		Binding[b]	Transactivation[c]	Lipogenesis[d]
#	SC	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
1	S	Ph	8.83 ± 0.14 (2)	8.58 ± 0.39 (8)	8.36 ± 0.41 (4)
35	R/S	cyclopentyl	8.19 ± 0.04 (2)	7.74 ± 0.35 (4)	7.62 ± 0.85 (2)
36	S	cyclohexyl	8.39 ± 0.11 (2)	8.54 ± 1.21 (3)	8.07 ± 1.31 (3)
37	R	cyclohexyl	5.81 ± 0.04 (2)	< 5 (2)	< 5.3 (2)
38	R/S	cycloheptyl	7.40 ± 0.13 (2)	8.11 ± 0.52 (4)	7.18 ± 0.02 (2)
39	R/S	2-thienyl	8.56 ± 0.02 (2)	7.34 ± 0.16 (3)	7.11 ± 0.07 (2)
40	R/S	3-thienyl	8.63 ± 0.03 (2)	7.20 ± 0.34 (3)	7.14 ± 0.01 (2)
41	R/S	1-naphthyl	8.49 ± 0.04 (2)	7.07 ± 0.51 (3)	8.57 ± 0.04 (2)

[a−d] See Table 1.

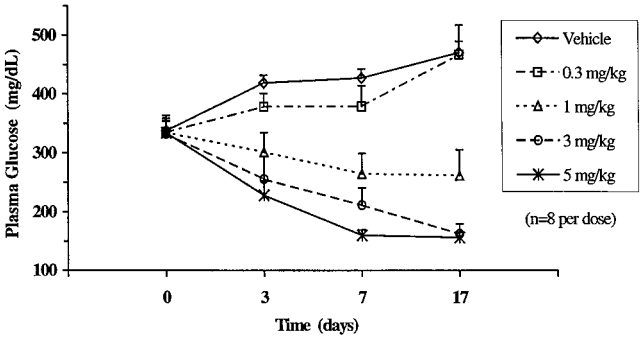


Figure 2. Compound **63**'s effects on plasma glucose in ZDF rats.

Plasma glucose was reduced by 67%, hemoglobin A1C (HbA_{1C}) by 40%, triglycerides by 82%, and nonesterified fatty acids by 87% versus control by **63**. HbA_{1C} is a glycated form of hemoglobin and is a marker of long-term glucose exposure.[15] The 17-day values for ZDF rats dosed with **63** (5 mg/kg) were 156 mg/dL for postprandial glucose and 5.74% for HbA_{1C}. We consider both of these values to be within the normal range. Figure 2 shows the time and dose dependence for glucose lowering in this study. Consistent with previous studies in the ZDF rat, the vehicle-treated animals show progressive worsening of their diabetes over the course of the study. Normalization of plasma glucose was seen with the highest dose, 5 mg/kg, by day 7, and the lower dose of 3 mg/kg also normalized plasma glucose by day 17. Thus this lower dose was equally effective but took longer to produce the maximum effect. The dose response is very steep, with no response seen at 0.3 mg/kg and a full response seen at 3 mg/kg. This seems to be characteristic of PPARγ agonists in this model. The in vivo efficacy of **63** is comparable with that of **2**.

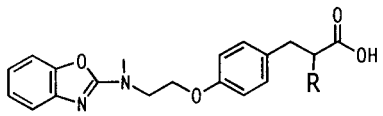
Conclusions

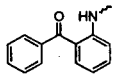
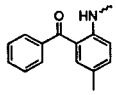
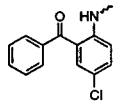
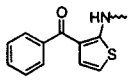
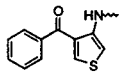
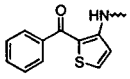
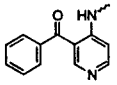
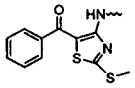
This report details a SAR study of the *N*-2-benzoylphenyl region of the lead compounds **1** and **2**. We found that, in general, only modest changes to this moiety are tolerated by PPARγ. More specifically, the best changes involve isosteric replacement of the distal phenyl ring of this moiety by thiophene, cyclohexane, or pyridine. Addition of substituents to the *N*-2-benzoylphenyl moiety tended to produce compounds that are less active in the cell-based functional assays, although binding affinity was retained in a number of instances. The most important molecules to emerge from these SAR studies may be the lower-molecular-weight analogues of **2**, the anthranilate esters **63**−**66**. In particular, **63** has an in vitro profile similar to that of **2** in the PPARγ assays, improved aqueous solubility, and good efficacy in the ZDF rat model of type 2 diabetes. Further information on this new class of tyrosine-based PPARγ agonists will be reported in due course.

Experimental Section

General Methods. All commercial chemicals and solvents are reagent grade and were used without further purification unless otherwise specified. The following solvents and reagents have been abbreviated: tetrahydrofuran (THF), ethyl ether (Et_2O), dimethyl sulfoxide (DMSO), ethyl acetate (EtOAc), dichloromethane (DCM), trifluoroacetic acid (TFA), dimethylformamide (DMF), methanol (MeOH). All reactions except

Table 3. In Vitro Profile of PPARγ Agonists **42**−**48**



	Structure[a]		Binding[b]	Transactivation[c]	Lipogenesis[d]
#	SC	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
1	S		8.83 ± 0.13 (2)	8.58 ± 0.39 (8)	8.36 ± 0.41 (4)
42	R/S		7.87 ± 0.04 (2)	6.64 ± 0.44 (4)	7.20 ± 1.30 (3)
43	R/S		8.06 ± 0.02 (2)	7.05 ± 0.18 (3)	6.75 ± 0.05 (2)
44	R/S		7.63 ± 0.04 (2)	7.42 ± 0.54 (3)	7.02 ± 0.26 (3)
45	R/S		8.59 ± 0.07 (2)	8.08 ± 0.60 (3)	8.84 ± 0.74 (4)
46	R/S		8.01 ± 0.02 (2)	7.92 ± 0.02 (2)	8.46 ± 0.34 (2)
47	R/S		6.81 ± 0.07 (2)	5.03 ± 0.22 (2)	6.14 (1)
48	R/S		7.37 ± 0.11 (2)	5.39 ± 0.25 (3)	< 5.6 (2)

[a−d] See Table 1.

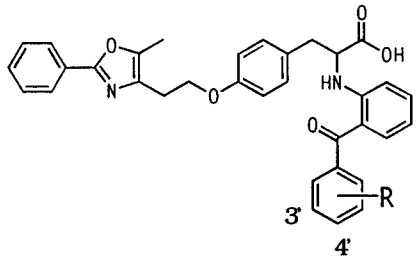
those in aqueous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography on 0.25-mm silica gel plates (60F-254, E. Merck) and visualized with UV light, iodine vapors, or 5% phosphomolybdic acid in 95% ethanol.

Final compounds were typically purified either by flash chromatography on silica gel (E. Merck, 40−63 mm) or by preparative reverse-phase high-pressure liquid chromatography (RP-HPLC) using a Waters model 3000 Delta Prep equipped with a Delta-pak radial compression cartridge (C-18, 300 Å, 15 μm, 47 mm × 300 mm) as the stationary phase. The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier. Linear gradients were used in all cases, and the flow rate was 100 mL/min (t_0 = 5 min). Analytical purity was assessed by RP-HPLC using a Hewlett-Packard series 1050 system equipped with a diode array spectrometer (λ range 200−400 nm). ^{1}H NMR spectra were recorded on either a Varian VXR-300, a Varian Unity-400, or a Varian Unity-300 instrument. Chemical shifts are reported in parts per million (ppm, δ units). Coupling constants are reported in units of hertz (Hz). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Low-resolution mass spectra (MS) were recorded on a JEOL JMS-AX505HA, JEOL SX-102, or SCIEX-APIiii spectrometer. High-resolution mass spectra were recorded on an AMD-604 (AMD Electra GmbH) high-resolution double focusing mass spectrometer (Analytical Instrument Group, Raleigh, NC). Mass spectra were acquired in either positive or negative ion mode under electrospray ionization (ESI), fast atom bombardment (FAB), or chemical ionization (CI) methods. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

Benzeneboronic acids which are not commercially available were synthesized from the corresponding aryl Grignard reagent and trimethyl borate. 2-Aminobenzophenones which are not commercially available were synthesized from the corresponding aryllithium reagents and the Weinreb amide of anthranilic acid as reported by Frye.[10]

2-(2-Iodophenyl)-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]phenyl}propionic Acid Methyl Ester (4). To a solution of 2.88 g (13.15 mmol) of 2-iodoaniline stirred in 50 mL of toluene under a nitrogen atmosphere at 25 °C was added 26.3 mL of a 0.1 M solution of 2-diazo-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]phenyl}propionic acid methyl ester (**3**)[8] in toluene, followed by 58 mg (0.132 mmol) of rhodium(II) acetate dimer. The resulting solution was stirred for 16 h at 25 °C and then concentrated in vacuo to a dark-brown oil. The

Table 4. In Vitro Profile of PPARγ Agonists **49**−**55**



	Structure[a]		Binding[b]	Transactivation[c]	Lipogenesis[d]
#	SC	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
2	S	H	8.94 ± 0.13 (8)	9.47 ± 0.44 (11)	8.83 ± 0.67 (7)
49	R/S	4'-CH_2OH	8.38 ± 0.07 (2)	7.76 ± 0.56 (3)	6.76 ± 0.08 (2)
50	R/S	4'-CO_2H	6.19 ± 0.00 (2)	5.12 ± 0.52 (3)	< 5.3 (3)
51	R/S	4'-CH_2NMe_2	7.81 ± 0.04 (2)	6.39 ± 0.07 (3)	6.01 ± 0.16 (3)
52	R/S	3'-CH_2OH	8.47 ± 0.01 (2)	7.61 ± 0.09 (3)	6.12 ± 0.27 (3)
53	R/S	3'-CO_2H	6.09 ± 0.01 (2)	6.68 ± 0.57 (5)	5.80 ± 0.21 (3)
54	R/S	3'-CH_2NMe_2	5.94 (1)	6.38 ± 0.07 (3)	5.93 ± 0.49 (3)
55	R/S	3'-NH_2	8.49 ± 0.047 (2)	8.05 ± 0.07 (3)	6.88 ± 0.26 (2)

[a−d] See Table 1.

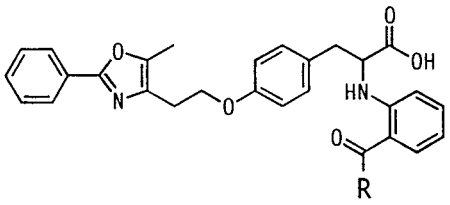
crude product was chromatographed over silica gel eluting with CH_2Cl_2 to obtain 1.12 g (75%) of **4** as a clear foam: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.60 (d, 1 H), 7.35 (d, 1 H), 7.24 (d, 1 H), 7.17−7.04 (m, 4 H), 6.96 (t, 1 H), 6.82 (d, 2 H), 6.56 (d, 1 H), 6.41 (t, 1 H), 4.67 (d, 1 H), 4.34 (q, 1 H), 4.19 (t, 2 H), 3.85 (t, 2 H), 3.19 (s, 3 H), 3.05 (m, 2 H); MS (API) *m/e* 573 $(MH)^+$; TLC (hexanes/EtOAc; 70:30) R_f = 0.34.

Method A: 3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[2-(4-(trifluoromethyl)benzoyl)phenylamino]propionic Acid (25). A solution of **4** (250 mg, 0.44 mmol), K_2CO_3, (182 mg, 1.3 mmol), $PdCl_2(PPh_3)_2$ (9.2 mg, 0.013 mmol), and 4-(trifluoromethyl)benzeneboronic acid (91.4 mg, 0.48 mmol) in dioxane (4.4 mL) was stirred under CO (1 atm, balloon) at 100 °C for 20 h. The resulting brown heterogeneous mixture was partitioned between water (50 mL) and EtOAc (50 mL). The EtOAc solution was washed with 2.0 M NaOH and brine (25 mL each), dried over $MgSO_4$, and concentrated to a brown oil. This material was chromatographed on silica gel (75 g) with EtOAc/hexane (1:2) as eluent to afford 3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[2-(4-(trifluoromethyl)benzoyl)phenylamino]propionic acid (**25**) methyl ester (206.9 mg, 76%) as a yellow oil: MS (ES^+) *m/e* 618 $(MH)^+$; TLC (EtOAc/hexane (1:1)) R_f = 0.51. A solution of this methyl ester (206.9 mg, 0.335 mmol) in THF/EtOH/1.0 M LiOH (3:1:1, 5 mL) was stirred under N_2 for 18 h. The solution was diluted with water (25 mL), acidified with 2.0 M HCl (2 mL), and extracted with EtOAc (50 mL). This extract was washed with brine (10 mL), dried over $MgSO_4$, and concentrated to afford **25** (175 mg, 86%) as a yellow solid: mp 177−178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.13 (d, 1 H, J = 7.0), 7.66−7.61 (m, 4 H), 7.45−7.38 (m, 3 H), 7.24 (d, 1 H, J = 7.9), 7.16−7.11 (m, 3 H), 7.01 (t, 1 H, J = 7.8), 6.80 (d, 1 H, J = 8.6), 6.77 (d, 2 H, J = 8.6), 6.61 (t, 1 H, J = 7.6), 4.06−4.01 (m, 1 H), 3.85−3.78 (m, 3 H), 3.27 (s, 3 H), 3.24−3.18 (m, 2 H); MS (ES^+) *m/e* 604 $(MH)^+$. Anal. ($C_{33}H_{28}F_3N_3O_5 \cdot 1.0H_2O$) C, H, N.

Method B: 3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[2-(4-(phenylmethoxy)benzoyl)phenylamino]propionic Acid (33). *Reaction was performed behind a blast shield.* To a stirred solution of 0.52 g (1.37 mmol) of 2-diazo-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]phenyl}-propionic acid methyl ester (**3**) and 0.50 g of 2-amino-4′-(phenylmethoxy)benzophenone in 13.7 mL of toluene at room temperature was added 29.5 mg (68 μmol) of $Rh_2(OAc)_4$. The resulting solution was stirred for 1 h, the solvent was removed in vacuo, and the resulting residue was purified by silica gel chromatography using ethyl acetate/hexane (gradient of 3:7 to 1:1) to yield 600 mg (67% yield) of a mixture consisting primarily of the cyclic derivative **7** and **33** methyl ester. Data for **7** (aryl = 4-(phenylmethoxy)phenyl): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (m, 8 H), 7.24 (m, 3 H), 7.15 (m, 2 H), 7.08 (m, 1 H), 7.01 (m, 2 H), 6.82 (m, 5 H), 5.09 (s, 2 H), 4.38 (s, 1 H), 4.22 (t, 2H, J = 5.2), 3.93 (t, 2H, J = 5.2), 3.75 (s, 3 H), 3.34 (s, 3 H), 2.60 (s, 1 H), 2.52 (d, 1H, J = 13.4), 2.32 (d, 1H, J = 13.4) (note: these last two doublets are characteristic of the cyclic compound); MS (ES) *m/e* 656.0 $(MH)^+$.

To a stirred solution of 600 mg (0.91 mmol) of the above mixture in 11 mL of ethanol was added 0.51 g (9.1 mmol) of potassium hydroxide, and the resulting solution was heated to 80 °C for 0.25 h. The solution was cooled to room temperature and diluted with 10 mL of water. Glacial acetic acid was then added dropwise to pH 5. A precipitate was collected, washed with ethyl acetate/hexane (5:95), and then washed with hexane. The solid was dried under vacuum at 40 °C for 1 h and further purified by thin layer silica gel chromatography preparatory plates (20 in. × 20 in.) using methanol/dichloromethane (5:95) as eluent to yield 108 mg (18% yield) of **33**

Table 5. In Vitro Profile of PPARγ Agonists **56**−**66**



		Structure[a]	Binding[b]	Transactivation[c]	Lipogenesis[d]
#	SC	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
2	S	Ph	8.94 ± 0.13 (8)	9.47 ± 0.44 (11)	8.83 ± 0.67 (2)
56	S	cyclohexyl	8.79 ± 0.04 (2)	9.55 ± 0.06 (3)	8.51 ± 0.03 (2)
57	R	cyclohexyl	6.72 ± 0.21 (2)	7.82 ± 0.24 (6)	6.43 ± 0.01 (2)
58	S	3-pyridyl	9.03 ± 0.03 (2)	8.83 ± 0.38 (3)	7.77 ± 0.13 (3)
59	S	4-pyridyl	8.74 ± 0.02 (2)	9.04 ± 0.17 (4)	6.97 ± 0.52 (5)
60	R/S	OH	< 5.5 (3)	5.31 ± 0.04 (2)	< 5 (1)
61	R/S	NHMe	7.81 ± 0.12 (2)	7.49 ± 0.43 (3)	6.44 ± 0.01 (3)
62	R/S	NMe_2	6.60 ± 0.14 (2)	6.25 ± 0.36 (3)	< 6 (3)
63	S	OMe	8.43 ± 0.02 (2)	9.15 ± 0.30 (9)	9.21 ± 0.04 (6)
64	S	OEt	8.52 ± 0.03 (2)	9.04 ± 0.66 (5)	9.37 ± 0.27 (2)
65	S	OPr	8.62 ± 0.03 (2)	9.52 ± 0.41 (5)	7.89 ± 0.28 (2)
66	S	OiPr	9.01 ± 0.00 (2)	9.24 ± 0.42 (3)	8.49 ± 0.62 (2)

[a−d] See Table 1.

Table 6. Solubilities of Selected Analogues of **2** (mg/mL)

Compd	Simulated Gastric Fluid	pH 7. 4 Phosphate Buffer
2	<0.001	<0.001
49	0.022	0.075
52	not done	1.34
54	0.009	0.009
55	0.003	0.525
57	0.002	0.052
58	0.018	0.055
59	0.087	1.15
63	<0.002	0.300

Table 7. In Vivo Activity of PPARγ Agonist **63** in Zucker Diabetic Fatty Rats

	Antihyperglycemic Activity[a] (% reduction)		Antihyperlipidemic Activity[b] (% reduction)	
Compd	Plasma Glucose	HbA_{1C}	Triglycerides	NEFAs
troglitazone	59 ± 9	35 ± 6	85 ± 1	81 ± 2
63	67 ± 2	40 ± 2	82 ± 1	87 ± 1

[a] Antihyperglycemic activity of the maximum dose of test compound (5 mg/kg for **63**; 500 mg/kg for troglitazone) given bid via oral gavage for 17 days; values represent percent reduction as compared to vehicle control group on day 17, ± standard error. [b] Antihyperlipidemic activity of the maximum dose of test compound (5 mg/kg for **63**; 500 mg/kg for troglitazone) given bid via oral gavage for 17 days; values represent percent reduction as compared to vehicle control group on day 17, ± standard error.

as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.65 (d, 1H, J = 7.3), 7.37 (m, 9 H), 7.22 (m, 2 H), 7.08 (m, 5 H), 6.96 (m, 1 H), 6.80 (m, 3 H), 6.55 (m, 1 H), 5.14 (s, 2 H), 4.50 (m, 1 H), 4.16 (m, 2 H), 3.84 (m, 2 H), 3.18 (s, 3 H), 3.08 (m, 2 H); MS (ES) *m/e* 642.0 $(MH)^+$. Anal. ($C_{39}H_{35}N_3O_6 \cdot 0.5H_2O$) C, H, N.

Method D: 3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[2-(4-phenylphenylcarbonyl)phenylamino]-propionic Acid (34). (Note: Chiral HPLC of the final compounds made using this method show they are racemic. Racemization is assumed to occur during the reaction of **10** with **11**.) A solution of 1.83 g (5.7 mmol) of *O*-benzyl-L-tyrosine methyl ester and 1.59 g (5.7 mmol) of 2-(4-phenylbenzoyl)cyclohexanone[16] in toluene (125 mL) was refluxed overnight with azeotropic removal of water. Concentration and purification by silica gel chromatography provided 1.53 g of a vinylogous amide: MS (CI) *m/e* 546 $(MH)^+$; TLC (EtOAc/hexanes, 1:1) R_f = 0.45. An anisole (100 mL) solution of this intermediate (1.48 g, 2.7 mmol) was refluxed under nitrogen in the presence of 1.4 g of 10% palladium on carbon and monitored for completion by TLC. The solution was filtered, concentrated, and purified by silica gel chromatography eluting with 1:9 EtOAc/hexanes

to yield 0.83 g of 3-(4-hydroxyphenyl)-2-[2-(4-phenylphenylcarbonyl)phenylamino]propionic acid methyl ester (**10a**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.69−7.3 (m, 13 H), 7.14 (d, 2 H, J = 8.5), 6.74 (d, 2 H, J = 8.6), 6.6 (m, 2 H), 4.38 (dd, 1 H, J = 1.0, 7.0), 3.71 (s, 3 H), 3.16 (m, 2 H); MS (CI) *m/e* 452 $(MH)^+$; TLC (EtOAc/hexanes, 50:50) R_f = 0.62.

To a DMF solution (5 mL) of **10a** (0.78 g, 1.73 mmol) was added 57 mg of 80% NaH followed by 0.47 g (1.73 mmol) of **11**[11] in 5 mL of DMF. The mixture was stirred for 18 h at 80 °C, quenched with water (5 mL), concentrated to dryness, and extracted from 30 mL of water with EtOAc (3 × 30 mL). The organics were dried ($MgSO_4$), concentrated, and purified by silica gel chromatography eluting with 1:1 EtOAc/hexanes to give 0.90 g of **34** methyl ester: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.85 (d, 1 H, J = 7.4), 7.7−6.9 (multiplet, 15 H), 7.18 (d, 2 H, J = 8.6), 6.8 (d, 2 H, J = 8.6), 6.6 (m, 2 H), 4.38 (m, 1 H), 4.2 (t, 2 H, J = 5.2), 3.91 (t, 2 H, J = 5.1), 3.7 (s, 3 H), 3.32 (s, 3 H), 3.16 (m, 2 H); MS (CI) *m/e* 626 $(MH)^+$; TLC (EtOAc/hexanes, 1:1) R_f = 0.57.

To a solution of 0.9 g (1.44 mmol) of **34** methyl ester in 5 mL of water and 50 mL of MeOH was added 0.6 g (14.4 mmol) of LiOH. The mixture was refluxed for 0.5 h, concentrated, and partitioned between pH 7 phosphate buffer solution and EtOAc. The concentrated organics were purified by silica gel chromatography eluting with 0−5% MeOH in CH_2Cl_2 to yield **34** as a yellow solid: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.00 (bs, 1 H), 7.7−7.6 (m, 7 H), 7.5−7.35 (m, 5 H), 7.2−6.95 (m, 5 H), 6.75 (m, 3 H), 6.63 (t, 1 H, J = 7.5), 4.45 (bs, 1 H), 3.27 (s, 3 H), 3.2 (d, 2 H, J = 5.7); MS (CI) *m/e* 612 $(MH)^+$; high-resolution MS (FAB^+) *m/e* $(MH)^+$ calcd for $C_{38}H_{33}N_3O_5$ 612.2498, found 612.2483; reverse-phase HPLC (Supelco Supelcosil ABZ + Plus C18, 15 cm × 4.6 mm; gradient of 10−100% acetonitrile/water (25 min) with 0.1% formic acid) t_R = 22.3 min; estimated purity >95%. Anal. ($C_{38}H_{33}N_3O_5 \cdot 0.2H_2O$) C, H, N.

(*S*)-3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-(2-(cyclohexylcarbonyl)phenylamino)propionic Acid (36) and (*R*)-3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-(2-(cyclohexylcarbonyl)phenylamino)propionic Acid (37). The racemic mixture of **36** and **37** was synthesized using method B from **3** and (2-aminophenyl)cyclohexylmethanone[17] in 58% overall yield and isolated as a yellow solid. The racemic mixture was resolved using chiral chromatography (Daicel Chiracel OD-H column (5.0 × 50 cm, 20 μm; 60% IPA in hexanes with 0.1% TFA buffer; 30 min; 6 mL/min) t_R = 9.54 min for **36** and t_R = 20.38 min for **37**) in 73% yield. Data for **36**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.10 (bd, 1 H), 7.86 (d, 2H, J = 7.6), 7.34 (m, 2 H), 7.24 (m, 1 H), 7.03 (m, 4 H), 6.78 (d, 2H, J = 8.4), 6.70 (d, 1H, J = 8.7), 6.61 (m, 1 H), 4.39 (m, 1 H), 4.18 (m, 2 H), 3.85 (m, 2 H), 3.34 (bm, 1 H), 3.20 (s, 3 H), 3.00 (m, 2 H), 1.67 (bm, 5 H), 1.36 (bm, 4 H), 1.29 (m, 1 H); MS (ES^+) *m/e* 542.0 (MH^+); high-resolution MS (FAB^+) *m/e* $(MH)^+$ calcd for $C_{32}H_{35}N_3O_5$ 542.2655, found 542.2641; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 30−80% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 22.86 min (t_0 = 3 min); purity = 98%; Daicel Chiracel OD-H (4.6 × 250 mm; 60% IPA in hexanes with 0.1% TFA buffer; 30 min; 0.7 mL/min) t_R = 9.54 min; 99.7% ee. Data for **37**: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.09 (bd, 1 H), 7.86 (d, 2H, J = 7.9), 7.34 (m, 2 H), 7.24 (m, 1 H), 7.03 (m, 4 H), 6.79 (d, 2H, J = 8.4)), 6.70 (d, 1H, J = 8.7), 6.61 (m, 1 H), 4.39 (m, 1 H), 4.18 (m, 2 H), 3.85 (m, 2 H), 3.34 (bm, 1 H), 3.20 (s, 3 H), 3.00 (m, 2 H), 1.67 (bm, 5 H), 1.36 (bm, 4 H), 1.29 (m, 1 H); MS (ES^+) *m/e* 542.1 $(MH)^+$; high-resolution MS (FAB^+) *m/e* $(MH)^+$ calcd for $C_{32}H_{35}N_3O_5$ 542.2655, found 542.2643; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 30−80% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 22.49 min (t_0 = 3 min); purity = 98%; Chiralpak AD (4.6 × 250 mm; 60% IPA in hexanes with 0.1% TFA buffer; 30 min; 0.7 mL/min) t_R = 20.38 min; 99.3% ee.

Method C: 3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-((3-benzoylthien-2-yl)amino)propionic Acid (44). To a solution of **3** (137 mg, 0.36 mmol) and 2-amino-3-benzoylthiophene[18] (104 mg, 0.51 mmol) in 3.6 mL of toluene at room temperature was added $Rh_2(OAc)_4$ (5 mg, 0.011 mmol). The resulting solution was stirred for 12 h at room temperature. The reaction solvents were removed in vacuo, and the residue was purified by silica gel flash column chromatography using hexane/EtOAc (7/3) as eluent to afford **44** methyl ester (145 mg, 73%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62 (d, 1 H, J = 8.4), 7.64 (m, 2 H), 7.44 (m, 3 H), 7.26 (m, 2 H), 7.13 (m, 3 H), 7.02 (m, 2 H), 6.84 (m, 2 H), 6.12 (d, 1 H, J = 5.8), 4.22 (m, 3 H), 3.92 (m, 2 H), 3.72 (s, 3 H), 3.33 (s, 3 H), 3.20 (m, 2 H); MS (ES^+) *m/e* 556.0 (MH^+). To a solution of **44** methyl ester (145 mg, 0.26 mmol) in 3 mL of THF and 1 mL of H_2O was added lithium hydroxide (14 mg, 0.34 mmol). The resulting solution was stirred for 3 h at room temperature and then acidified to pH 2, and the solvents were removed in vacuo. Purification by silica gel flash column chromatography using DCM/MeOH (95:5 to 90:10) as eluent afforded **44** (77 mg, 54%) as a yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.44 (d, 1 H, J = 8.2), 7.54 (m, 5 H), 7.36 (d, 1 H, J = 7.9), 7.25 (d, 1 H, J = 7.7), 7.14 (m, 3 H), 6.96 (m, 1 H), 6.84 (m, 3 H), 6.40 (d, 1 H, J = 5.7), 3.85 (m, 2 H), 3.20 (m, 4 H), 3.17 (m, 1 H); MS (ES^-) *m/e* 539.9 $(M - H)^-$; high-resolution MS (FAB^+) *m/e* $(MH)^+$ calcd for $C_{30}H_{27}N_3O_5$ 542.1750, found 542.1757; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 30−80% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 18.16 min (t_0 = 3 min); purity = 98%.

(*S*)-Amino-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (15). A solution of 11.6 mL (73.80 mmol) of diethyl azodicarboxylate and 19.3 g (73.8 mmol) of triphenylphosphine in 100 mL of THF at 0 °C was added rapidly to a stirred mixture of 15.0 g (73.8 mmol) of 2-(5-methyl-2-phenyloxazol-4-yl)ethanol (**13**)[10] and 21.8 g (73.8 mmol) of *N*-Boc-L-tyrosine methyl ester in 200 mL of THF at room temperature. The reaction was stirred at room temperature for 16 h and the solvent removed in vacuo to dryness. The residue was taken up in 600 mL of diethyl ether/water (2:1) and 5.4 g (128.7 mmol) of lithium hydroxide monohydrate added at once. After stirring for 2 h at room temperature, the layers were separated, the aqueous layer was extracted with diethyl ether, and all the organics were combined. The organics were dried ($MgSO_4$), the solvent was removed in vacuo, and the residue was purified by silica gel chromatography using diethyl ether/dichloromethane (1:19) to give 15.92 g (45% yield) of Boc-protected **15**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, 2 H, J = 8.4), 7.35 (m, 3 H), 6.94 (d, 2 H, J = 8.4), 6.76 (d, 2 H, J = 8.5), 4.87 (m, 1 H), 4.46 (m, 1 H), 4.15 (t, 2 H, J = 6.7), 3.64 (s, 3 H), 2.92 (m, 4 H), 2.31 (s, 3 H), 1.35 (s, 9 H); low-resolution MS (ES) *m/e* 481 $(MH)^+$; TLC (diethyl ether/dichloromethane (1:9)) R_f = 0.56.

To a stirred solution of 15.92 g (33.1 mmol) of Boc-protected **15** in 300 mL of dichloromethane at room temperature was added 33 mL (10% volume) of trifluoroacetic acid. After stirring for 5 h, the reaction was quenched with 0.1 N NaOH, and the layers were separated. The organics were washed with water, the layers separated, and the organics dried ($MgSO_4$), and the solvent was removed in vacuo to give **15** as the trifluoroacetate salt: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.33 (bs, 3 H), 7.89 (m, 2 H), 7.48 (m, 3 H), 7.10 (d, 2 H, J = 8.7), 6.89 (d, 2 H, J = 8.5), 4.25 (m, 1 H), 4.18 (t, 2 H, J = 6.5), 3.67 (s, 3 H), 3.99 (m, 2 H), 2.90 (t, 2 H, J = 6.5), 2.35 (s, 3 H); MS (ES) *m/e* 381 $(MH)^+$; chiral HPLC (Daicel chiralcel, 4.6 × 250 mm, 10 mm; 10% 2-propanol/hexane with 0.1% TEA; 1 mL/min) t_R = 15.033 min; >99% ee.

2-Diazo-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (16). *Reaction was performed behind a blast shield.* A 500-mg (1.01 mmol) portion of **15** trifluoroacetate salt was free-based with saturated Na_2CO_3. The resulting **15** was taken up in 8 mL of chloroform and 170 mL (3.03 mmol) of acetic acid, and 140 mL (1.01 mmol) of fresh isoamyl nitrite was added. The resulting solution was heated to reflux for 3 h. After cooling to room temperature, the reaction was diluted with water, the layers were separated, the organics were washed with saturated $NaHCO_3$, the organics were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using ethyl acetate/hexane (3:7) as eluent to give 240 mg (61% yield)

of **16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (m, 2 H), 7.35 (m, 3 H), 7.07 (d, 2 H, J = 8.6), 6.79 (d, 2 H, J = 8.5), 4.16 (t, 2 H, J = 6.8), 3.71 (s, 3 H), 3.50 (s, 2 H), 2.91 (t, 2 H, J = 6.8), 2.31 (s, 3 H); MS (ES) *m/e* 364 $(M - N_2)^+$.

2-[(2-Iodophenyl)amino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (17). To a solution of **16** (3.08 g, 7.87 mmol) and 2-iodoaniline (2.07 g, 9.44 mmol) in toluene (80 mL) was added slowly $Rh_2(OAc)_4$ (100 mg). A gentle gas evolution was noted which ceased about 10 min after the last of the catalyst was added. This solution was stirred under N_2 for 30 min. The toluene was removed by rotary evaporation and the resulting brown residue flash chromatographed on silica gel (300 g) with hexane/EtOAc (85:15) to obtain **17** (3.93 g, 86% yield) as a pale-orange oil: ^{1}H NMR ($CDCl_3$,400 MHz) δ 8.12 (bs, 2 H), 7.65 (d, 1 H, J = 7.7), 7.49−7.48 (m, 3 H), 7.15 (t, 1 H, J = 8.1), 7.08 (d, 1 H, J = 8.5), 6.83 (d, 1 H, J = 8.6), 4.66 (bs, 1 H), 4.30−4.27 (m, 3 H), 3.68 (s, 3 H), 3.10−3.05 (m, 4 H), 2.42 (s, 3 H); MS (ES^+) *m/e* 583 $(MH)^+$; TLC (hexane/EtOAc (6:1)) R_f = 0.14.

2-[2-(4-Formylbenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester (19a). A suspension of K_2CO_3 (356 mg, 2.58 mmol) in dioxane (13 mL) containing **17** (500 mg, 0.86 mmol), 4-formylphenylboronic acid (193 mg, 1.29 mmol), and $PdCl_2(PPh_3)_2$ (18.0 mg, 26 mmol) was heated (100 °C) under 1 atm of CO for 24 h. After cooling to room temperature, the mixture was partitioned between 50 mL each of water and EtOAc. The EtOAc solution was washed with 0.5 M NaOH (50 mL), water (50 mL), and brine (25 mL). This solution was dried over $MgSO_4$ and concentrated to a brown oil which was flash chromatographed on silica gel (150 g) with hexane/EtOAc (85:15) to obtain unreacted **17** (0.32 g, 64% yield) and **19a** (99.1 mg, 168 mmol, 20% yield) as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.10 (s, 1 H), 9.03 (d, 2 H, J = 7.4), 8.03 (m, 2 H), 7.96 (d, 2 H, J = 8.1), 7.71 (d, 2 H, J = 8.0), 7.40 (m, 5 H), 7.17 (d, 2 H, J = 8.6), 6.83 (d, 2 H, J = 8.6), 6.64 (d, 1 H, J = 8.4), 6.57 (t, 1 H, J = 7.6), 4.39 (q, 1 H, J = 6.2), 4.23 (t, 2 H, J = 6.5), 3.70 (s, 3 H), 3.21 (dd, 1 H, J = 5.6, 13.8), 3.12 (dd, 1 H, J = 8.6, 13.8), 3.00 (t, 2 H, J = 6.5), 2.37 (s, 3 H); MS (ES) *m/e* 589 $(MH)^+$; TLC (hexane/EtOAc (2:1)) R_f = 0.29.

2-[2-(4-(Hydroxymethyl)benzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (49). To a solution of **19a** (167.4 mg, 284 μmol) in THF (20 mL) was added $NaBH_4$ (10.8 mg, 284 μmol). The resulting mixture was stirred under N_2 for 30 min, and acetone (1 mL) was added. After the mixture stirred for an additional 30 min, EtOAc (50 mL) was added and the solution washed with 2.0 M NaOH, 1.0 M $NaHCO_3$, and water (20 mL each). The organic solution was dried over $MgSO_4$ and concentrated to a dark-brown oil which was flash chromatographed on 25 g of silica gel using EtOAc/hexane (2:3) as eluent. **49** methyl ester was isolated (128.9 mg, 77%) as a yellow oil: MS (ES) *m/e* 591.4 $(MH)^+$. A solution of **49** methyl ester (31.6 mg, 53.5 μmol) in THF/MeOH/1.0 M LiOH (3:1:1, 5 mL) was stirred under N_2 for 16 h. Water (10 mL) was added, and the organic solvents were removed by rotary evaporation. The residual aqueous solution was washed with ether (10 mL). The aqueous solution was acidified to pH 1 with 2.0 M HCl and extracted with EtOAc (50 mL). This extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated to afford **49** (28.6 mg, 93%) as a yellow solid: mp 91−93 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.56 (s, 1 H), 7.97 (bd, 2 H, J = 3.6), 7.55−7.21 (m, 9 H), 7.13 (d, 2 H, J = 8.3), 6.71−6.58 (m, 4 H), 4.76 (s, 2 H), 4.35 (bs, 1 H), 4.00 (t, 2 H, J = 6.2), 3.25 (dd, 1 H, J = 5.5, 14.0), 3.10 (dd, 1 H, J = 7.4, 13.9), 2.91 (t, 2 H, J = 6.1), 2.33 (s, 3 H); MS (ES) *m/e* 577.3 $(MH)^+$. Anal. ($C_{35}H_{32}N_2O_6 \cdot 1.25H_2O$) C, H, N.

4-(2-{1-Carboxy-2-[4-(2-{5-methyl-2-phenyloxazol-4-yl}ethoxy)phenyl]ethylamino}benzoyl)benzoic Acid (50). To a solution of **19a** (98.5 mg, 167 μmol) in acetone (5 mL) was added dropwise Jones' reagent (62.6 μL of 2.67 M solution, 167 μmol). The resulting dark-green solution was stirred for 2 h and ^{i}PrOH (1 mL) added. After stirring for an additional 15 min, the mixture was partitioned between EtOAc (50 mL) and 1.0 M HCl (20 mL). The EtOAc layer was washed with water (20 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated to a brown oil which was flash chromatographed on silica gel (20 g) with EtOAc/$CHCl_3$ (1:1) with 0.1% HOAc as eluent. **50** methyl ester was isolated (57.2 mg, 57%) as a yellow foam: MS (ES) *m/e* 605.3 $(MH)^+$. A solution of **50** methyl ester (27.7 mg, 45.8 μmol) in THF/MeOH/1.0 M LiOH (3:1:1, 5 mL) was stirred under N_2 for 16 h. Water (10 mL) was added, and the organic solvents were removed by rotary evaporation. The residual aqueous solution was extracted with EtOAc (20 mL) and then acidified to pH 1 with 2.0 M HCl and extracted with EtOAc (50 mL). This extract was dried over $MgSO_4$ and concentrated to afford **50** (24.7 mg, 91%) as a yellow solid: mp 154−157 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.1 (bs, 2 H), 8.74 (d, 1 H, J = 6.4), 8.03 (d, 2 H, J = 8.0), 7.88 (d, 2 H, J = 7.8), 7.60 (d, 2 H, J = 8.3), 7.49−7.40 (m, 4 H), 7.29 (d, 1 H, J = 8.0), 7.09 (d, 2 H, J = 8.5), 6.84−6.79 (m, 3 H), 6.58 (t, 1 H, J = 7.3), 4.54 (q, 1 H, J = 7.3), 4.12 (t, 2 H, J = 6.6), 3.14 (dd, 1 H, J = 5.4, 13.9), 3.02 (dd, 1 H, J = 6.6, 14.2), 2.86 (t, 2 H, J = 6.6), 2.30 (s, 3 H); MS (ES) *m/e* 591.2 $(MH)^+$. Anal. ($C_{35}H_{30}N_2O_7 \cdot 1.0H_2O$) C, H, N.

2-[2-(4-(Dimethylaminomethyl)benzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}-propionic Acid Hydrochloride (51). To a solution of **19a** (96 mg, 163 μmol), dimethylamine (0.85 mL, 171 μmol), and HOAc (3.7 μL, 65 μmol) in MeOH/THF (3:1) (4 mL) was added sodium cyanoborohydride (20 mg, 326 μmol). The resulting solution was stirred under N_2 for 6 h. The solution was diluted with EtOAc (50 mL) and washed with 1.0 M $NaHCO_3$ (20 mL) and brine (20 mL). This solution was dried over $MgSO_4$ and concentrated to a yellow semisolid which was flash chromatographed on silica gel with EtOAc to elute the less polar products and then with EtOAc/MeOH (98:2) to elute the product **51** methyl ester: MS (ES) *m/e* 618 $(MH)^+$; TLC (EtOAc) R_f 0.13. This material was saponified by dissolution in THF/EtOH/1.0 M LiOH (3:1:1) (5 mL) and stirring under N_2 for 16 h. This solution was diluted with water (10 mL) and extracted with EtOAc (2 × 25 mL). These extracts were combined and washed with 1.0 M HCl (10 mL). This solution was dried over Na_2SO_4 and concentrated to give **51** (28.0 mg, 27% for two steps) as a yellow solid: mp 103−105 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.94 (bs, 2 H), 7.90−7.36 (m, 9 H), 7.16 (d, 2 H, J = 8.2), 6.82−6.77 (m, 3 H), 6.57 (t, 1 H, J = 7.3), 4.52 (t, 1 H, J = 5.4), 4.39 (s, 2 H), 4.18 (t, 2 H, J = 6.3), 3.24 (dd, 1 H, J = 4.6, 13.7), 3.10 (dd, 1 H, J = 6.8, 13.8), 2.94 (t, 2 H, J = 6.3), 2.89 (s, 6 H), 2.33 (s, 3 H); MS (ES) *m/e* 604 $(MH)^+$; high-resolution MS (FAB^+) *m/e* $(MH)^+$ calcd for $C_{37}H_{37}N_3O_5$ 604.2811, found 604.2816; reverse-phase HPLC (Keystone Scientific BDS Hypersil C-18 column (5 μm, 200 × 4.6 mm); gradient of 30−80% acetonitrile/water with 0.1% TFA (25 min); 1 mL/min) t_R = 17.3 min; estimated purity 90%. Anal. ($C_{37}H_{37}N_3O_5 \cdot HCl \cdot 0.33EtOAc \cdot 2.0H_2O$) C, H, N.

2-[2-(3-Aminobenzoyl)phenylamino]-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (55). A stirred solution of 400 mg (2.58 mmol) of 3-aminobenzeneboronic acid, 710 mg (5.15 mmol) of potassium carbonate, and 36.0 mg (0.52 mmol) of $Pd(Cl)_2(PPh_3)_2$ was evacuated and flushed with nitrogen. To this stirred solution was added 1.0 g (1.72 mmol) of **17** in 26 mL of anhydrous 1,4-dioxane. The reaction was heated to 100 °C and stirred under 1 atm of carbon monoxide for 16 h. After cooling to room temperature, the solvent was removed in vacuo. The residue was purified by silica gel chromatography using ethyl acetate/hexane (2:3) as eluent to give 640 mg (65% yield) of **55** methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.77 (d, 1 H, J = 7.3), 7.90 (m, 2 H), 7.45 (m, 1 H), 7.35 (m, 3 H), 7.25 (m, 1 H), 7.12 (m, 3 H), 6.88 (m 2 H), 6.76 (m, 3 H), 6.51 (m, 2 H), 4.29 (m, 1 H), 4.13 (t, 2 H, J = 6.7), 3.71 (bs, 2 H), 3.62 (s, 3 H), 3.13 (dd, 1 H, J = 5.7, 13.9), 3.03 (dd, 1 H, J = 7.4, 13.7), 2.88 (t, 2 H, J = 6.6), 2.29 (s, 3 H); MS (ES) *m/e* 576 $(MH)^+$; TLC (ethyl acetate/hexane (2:3)) R_f = 0.20. To a stirred solution of 73 mg (0.13 mmol) of **55** methyl ester in 1 mL of THF/methanol/water (3:1:1) was added 19 mg (0.39 mmol) of lithium hydroxide monohydrate.

After stirring at room temperature for 2 h, the solvent was removed in vacuo. The residue was taken up in ethyl acetate and diluted with water. The resulting mixture was acidified to pH 3 with concentrated HCl, layers were separated, organics were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography with methanol/dichloromethane (gradient of 1:19 to 1:4) as eluent to give a yellow solid. This solid was further purified by trituration with methanol/hexane (1:19) and then ethyl acetate/hexane (1:9) to give 35 mg (48% yield) of **55** as a yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.64 (d, 1 H, J = 7.1), 7.88 (m, 2 H), 7.46 (m, 3 H), 7.27 (m, 2 H), 7.08 (m, 3 H), 6.69 (m, 4 H), 6.56 (d, 1 H, J = 7.3), 6.42 (m, 1 H), 5.28 (bs, 2 H), 4.09 (m, 3 H), 3.09 (m, 1 H) 2.87 (m, 3 H), 2.29 (m, 3 H); MS (ES) m/e 562 $(MH)^+$; high-resolution MS (FAB) m/e $(MH)^+$ calcd for $C_{34}H_{31}N_3O_5$ 562.2342, found 562.2348; RP-HPLC (0−100% CH_3CN in water with 0.1% TFA buffer; 25 min) t_R = 16.51 min; estimated purity 93%.

(*S*)-2-(2-(Cyclohexylcarbonyl)phenylamino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (56) and (*R*)-2-(2-(Cyclohexylcarbonyl)phenylamino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (57). To a stirring solution of 3.03 g (7.75 mmol) of **16** in 77.5 mL of toluene and 2.07 g (10.51 mmol, 1.4 equiv) of (2-aminophenyl)cyclohexylmethanone[19] at room temperature was added 69 mg (0.008 mmol, 0.01 equiv) of $Rh_2(OAc)_4$. The resulting solution was stirred for 12 h at room temperature. The reaction solvents were removed in vacuo. Purification by silica gel flash column chromatography using DCM to 1:99 diethyl ether/DCM as eluent afforded 2.89 g of the racemic methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.38 (d, 1 H, J = 7.3), 7.96 (m, 2 H), 7.79 (d, 1 H, J = 7.8), 7.40 (m, 3 H), 7.12 (d, 2 H, J = 8.6), 6.81 (d, 2 H, J = 8.3), 6.59 (m, 2 H), 4.29 (m, 1 H), 4.20 (t, 2 H, J = 6.7), 3.64 (s, 3 H), 3.27 (m, 1 H), 3.10 (m, 2 H), 2.95 (t, 2 H, J = 6.7), 2.36 (s, 3 H), 1.81 (bm, 4 H), 1.40 (bm, 6 H); MS (ES) m/e 567.4 $(MH)^+$. The enantiomers of this material were then separated on a Daicel Chiracel OD-H column (5.0 × 50 cm, 20 μm; 60% EtOH in hexanes with 0.1% TFA buffer; 30 min; 6 mL/min). Data for **56** methyl ester: NMR, MS, HPLC identical to racemate; Daicel Chiral OD-H (4.6 × 250 mm, 5 μm; 0.7 mL/min; inj vol 3 mL; 60% IPA in hexanes; 30 min) t_R = 8.52 min; 99.99% ee. Data for **57** methyl ester: NMR, MS, HPLC identical to racemate; Daicel Chiral OD-H (4.6 × 250 mm, 5 μm; 0.7 mL/min; inj vol 3 μL, 60% IPA in hexanes; 30 min) t_R = 18.75 min; 99.9% ee.

To a stirring solution of 1.08 g (1.90 mmol) of **56** methyl ester in 10 mL of THF and 5 mL of H_2O was added 120 mg (2.86 mmol, 1.5 equiv) of lithium hydroxide. The resulting solution was stirred for 4 h at room temperature and then acidified to pH 2, and the solvents were removed in vacuo. Purification by silica gel flash column chromatography using DCM/MeOH (95:5) as eluent afforded 750 mg of **56** as a yellow foam: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.10 (d, 1 H, J = 7.4), 7.88 (m, 3 H), 7.46 (m, 3 H), 7.28 (m, 1 H), 7.03 (d, 2 H, J = 8.4), 6.75 (d, 2 H, J = 8.6), 6.66 (d, 1 H, J = 8.4), 6.55 (m, 1 H), 4.12 (m, 3 H), 3.17 (m, 1 H), 2.87 (m, 3 H), 2.31 (s, 3 H), 1.68 (bm, 5 H), 1.30 (bm, 5 H); MS (ES) m/e 551.2 $(M - H)^-$; high-resolution MS (FAB+) m/e (MH^+) calcd for $C_{34}H_{36}N_2O_5$ 553.2702, found 553.2691; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 50−100% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 20.20 min (t_0 = 3 min); purity = 92%; Daicel Chiral OD-H (4.6 × 250 mm, 5 μm; 0.7 mL/min; inj vol 3 μL; UV 230 nm; 60% IPA in hexanes with 0.1% TEA, 0.1% TFA; 30 min) t_R = 7.44 min; 99.9% ee.

57 methyl ester was saponified using the above procedure to produce **57** as a yellow foam: NMR and MS identical to **56**; high-resolution MS (FAB^+) m/e (MH^+) calcd for $C_{34}H_{36}N_2O_5$ 553.2702, found 553.2686; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 50−100% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 20.20 min (t_0 = 3 min); purity = 92%; Daicel Chiral OD-H (4.6 × 250 mm, 5 μm; 0.7 mL/min; inj vol 3 μL; UV 230 nm; 60% IPA in hexanes with 0.1% TEA, 0.1% TFA; 30 min) t_R = 11.67 min; 98.3% ee.

3-{4-[2-(5-Methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}-2(*S*)-[2-(pyridin-3-ylcarbonyl)phenylamino]propionic Acid (58). To a −78 °C THF solution (20 mL) of cyclohexanone (2.07 mL, 20 mmol) was slowly added LDA (10 mL, 2.0 M in THF). After 30 min at −78 °C, nicotinoyl chloride in THF (20 mL) cooled to −78 °C was added. The mixture was stirred for 15 min, quenched with 1 N HCl, and brought to room temperature. The crude reaction was basified with aqueous saturated sodium bicarbonate, extracted with EtOAc (3 × 50 mL), dried $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatograph eluting with 50% EtOAc in hexanes gave 2.14 g of 2-(3-pyridinylcarbonyl)cyclohexanone and an apparent dimer (by MS) in a 1:2 ratio: MS (ES) m/e 204.1 $(MH)^+$; R_f = 0.26 (50% EtOAc in hexanes). Diagnostic peaks in the NMR: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.07 (s, 1 H), 8.77 (m, 1 H), 8.18 (d, 1 H, J = 8.1), 7.41 (m, 1 H), 4.32 (dd, 1 H, J = 9.3, 5.8), 2.42 (m, 3 H), 1.64 (m, 2 H).

To a solution of **15** (1.30 g, 2.63 mmol) and the above 2-(3-pyridinylcarbonyl)cyclohexanone (estimated 1.07 g, 5.26 mmol) in anisole (20 mL) was added 1 g of 10% palladium on carbon. The reaction mixture was heated at 212 °C with a Dean−Stark trap containing 4A sieves for 4 h. The reaction was filtered through a pad of Celite washed with MeOH and concentrated in vacuo. Purification by silica gel flash column chromatography using hexane to 1:1 hexane/ethyl acetate as eluent afforded 0.54 g of **58** methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.99 (d, 1 H, J = 7.4), 8.82 (s, 1 H), 8.73 (dd, 1 H, J = 1.6, 4.7), 7.95 (m, 2 H), 7.40 (m, 7 H), 7.16 (d, 2 H, J = 8.7), 6.82 (d, 2 H, J = 8.7), 6.60 (m, 2 H), 4.38 (m, 1 H), 4.20 (m, 2 H), 3.70 (s, 3 H), 3.16 (m, 2 H), 2.95 (m, 2 H), 2.38 (s, 3 H); MS (ES) m/e 562.2 $(MH)^+$.

To a stirring solution of 0.54 g (0.96 mmol) of **58** methyl ester in 15 mL of THF and 2 mL of H_2O was added 122 mg (2.88 mmol, 3.0 equiv) of lithium hydroxide. The resulting solution was stirred for 2.5 h at room temperature and then acidified to pH 2, and the solvents were removed in vacuo. Purification by silica gel flash column chromatography using DCM/MeOH (90:10) as eluent afforded 506 mg of racemic **58**. The enantiomers were separated on a Daicel Chiracel OD-H column (5.0 × 50 cm, 20 μm; 50% IPA in hexanes with 0.1% TFA buffer; 30 min; 5 mL/min; t_R = 30.4 min for **58** and 45.5 min for ***ent*-58**). **58** was isolated in 76% yield as an amber gum: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.80 (bs, 1 H), 8.08 (d, 1 H, J = 7.9), 7.87 (m, 3 H), 7.67 (m, 1 H), 7.46 (m, 5 H), 7.33 (d, 1H, J = 7.3), 7.10 (d, 3H, J = 8.5), 6.82 (m, 3 H), 6.61 (m, 1 H), 4.56 (bs, 1 H), 4.12 (m, 2 H), 3.08 (m, 2 H), 2.87 (m, 2 H), 2.31 (s, 3 H); MS (ES^-) m/e 546 $(M - H)^-$; high-resolution MS (FAB^+) calcd for $C_{33}H_{29}N_3O_5$ 548.2185, found 548.2185; RP-HPLC (Vydac C-18, 25 cm × 4.6 mm; 30−80% CH_3CN in H_2O with 0.1% TFA buffer; 25 min; 1 mL/min) t_R = 17.31 min (t_0 = 3 min); purity = 98%; Daicel Chiracel OD-H (4.6 × 250 mm; 50% IPA in hexanes with 0.1% TFA buffer; 30 min; 0.87 mL/min) t_R = 8.53 min; 96% ee.

2-(1-(Methoxycarbonyl)-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic Acid (60). A suspension of K_2CO_3 (267 mg, 1.9 mmol) in dioxane (50 mL) and water (0.1 mL) containing **17** (375.2 mg, 0.64 mmol) and $Pd(Cl)_2(PPh_3)_2$ (22.6 mg, 0.032 mmol) in a 250-mL volume Parr bomb was stirred at 125 °C under CO (200 psi) for 16 h. After cooling to room temperature and venting the CO, the resulting mixture was diluted with EtOAc (250 mL) and washed with 2.0 M HCl and brine (50 mL each). The organic solution was dried over $MgSO_4$ and concentrated to a brown oil which was flash chromatographed on silica gel (50 g) with EtOAc/hexane (1:1 with 0.1% HOAc) to afford **60** methyl ester (110 mg, 34%) as a white solid: mp 173−174 °C (EtOAc/hexane); ^{1}H NMR (acetone-d_6, 400 MHz) δ 11.05 (bs, 1 H), 8.34 (d, 1 H, J = 7.8), 8.02−7.91 (m, 3 H), 7.51−7.45 (m, 3 H), 7.35 (t, 1 H, J = 8.6), 7.16 (d, 2 H, J = 8.7), 6.85 (d, 2 H, J = 8.5), 6.70 (d, 1 H, J = 8.5), 6.63 (t, 1 H, J = 7.7), 4.50−4.45 (m, 1 H), 4.22 (t, 2 H, J = 6.9), 3.65 (s, 3 H), 3.15 (dd, 1 H, J = 5.8, 13.7), 3.08 (dd, 1 H, J = 6.8, 13.7), 2.94 (t, 2 H, J = 6.7), 2.38 (s, 3 H); MS (ES^+) m/e 501 $(MH)^+$. Anal. ($C_{29}H_{28}N_2O_6$) C, H, N. A solution of **60** methyl ester (78.3 mg, 156 μmol) in THF/MeOH/1.0 M

LiOH (3:1:1, 5 mL) was stirred under N_2 for 16 h. Water (10 mL) was added, and the organic solvents were removed by rotary evaporation. The residual aqueous solution was washed with EtOAc (10 mL). The aqueous solution was acidified to pH 1 with 2.0 M HCl and extracted with EtOAc (50 mL). This extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated to a white solid. Recrystallization of this material from MeOH provided **60** (44.6 mg, 59%) as a white solid: mp 214−217 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.85 (bs, 1 H), 12.65 (bs, 1 H), 8.13 (d, 1 H, J = 7.7), 7.90 (d, 2 H, J = 7.9), 7.77 (d, 1 H, J = 7.8), 7.49−7.47 (m, 3 H), 7.32 (t, 3 H, J = 7.9), 7.11 (d, 2 H, J = 8.4), 6.82 (d, 2 H, J = 8.4), 6.65 (d, 1 H, J = 8.5), 6.57 (t, 1 H, J = 7.5), 4.36 (q, 1 H, J = 6.3), 4.15 (t, 2 H, J = 6.5), 3.08 (dd, 1 H, J = 5.3, 13.8), 2.98 (dd, 1 H, J = 6.6, 13.6), 2.89 (t, 2 H, J = 6.5), 2.33 (s, 3 H); MS (ES) m/e 487.2 $(MH)^+$. Anal. ($C_{28}H_{26}N_2O_6$) C, H, N.

2-(1-Carboxy-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)-ethoxy]phenyl}ethylamino)benzoic Acid Methyl Amide (61). To a solution of **60** methyl ester (49.5 mg, 100 μmol), HOBt (6.7 mg, 49 μmol), triethylamine (41.3 μL, 300 μmol), and methylamine (12.8 μL (40% solution in water), 150 μmol) in CH_2Cl_2 was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (22.7 mg, 120 μmol). The resulting solution was stirred for 16 h under N_2 and then diluted with EtOAc (50 mL) and washed with 20 mL each of 0.5 M HCl (2×), saturated NH_4Cl, water, and 2.0 M $NaHCO_2$ (2×). This solution was dried over $MgSO_2$ and concentrated to a yellow oil which was flash chromatographed on silica gel (10 g) with EtOAc/hexane (1:1) to afford 33.8 mg (67%) of **61** methyl ester as a colorless oil: MS (ES^+) m/e 514 (MH^+); TLC (hexane/EtOAc (1:1)) R_f = 0.31. A solution of this material in THF/EtOH/1.0 M LiOH (3:1:1, 5 mL) was stirred under N_2 for 16 h. The resulting mixture was diluted with EtOAc (25 mL) and washed with 1.0 M HCl (10 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$ and concentrated to afford **61** (33.4 mg, 100%) as a white solid after trituration with ether: mp 85−90 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.71 (s, 1 H), 8.24−8.20 (m, 2 H), 7.90−7.88 (m, 2 H), 7.49−7.45 (m, 4 H), 7.21 (t, 1 H, J = 7.2), 7.10 (d, 2 H, J = 8.5), 6.82 (d, 2 H, J = 8.6), 6.60−6.53 (m, 2 H), 4.23−4.22 (m, 1 H), 4.15 (t, 2 H, J = 6.5), 3.02 (dd, 1 H, J = 5.6, 13.8), 2.92−2.87 (m, 3 H), 2.69 (d, 3 H, J = 4.5), 2.33 (s, 3 H); MS (ES^+) m/e 500 $(MH)^+$; high-resolution MS (FAB^+) m/e (MH^+) calcd for $C_{29}H_{29}N_3O_5$ 500.2185, found 500.2184. Anal. ($C_{29}H_{29}N_3O_5 \cdot 0.75Et_2O$) C, H, N.

(*S*)-2-(1-(Methoxycarbonyl)-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic Acid Methyl Ester (21). A solution of **15** (664 mg, 1.75 mmol) and methyl cyclohexanone-2-carboxylate (300 mg, 1.92 mmol) in toluene (50 mL) was refluxed for 16 h under N_2 into a Dean−Stark trap (oil bath temperature of 130 °C). The toluene was then removed by rotary evaporation and replaced with anisole (50 mL). To this solution was added 10% palladium on carbon (250 mg), and the resulting suspension was heated to 190 °C and stirred for 6 h under N_2. After cooling to room temperature the catalyst was removed by filtration through a pad of Celite (5 g) with an EtOAc wash (200 mL). The filtrate was concentrated to a brown oil which was flash chromatographed on silica gel (100 g) with hexane/EtOAc (4:1) to provide **21** (590 mg, 66%) as a white solid: mp 102−103 °C (ether/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.17 (d, 1 H, J = 7.3), 7.98−7.96 (m, 2 H), 7.89 (d, 1 H, J = 8.1), 7.45−7.39 (m, 3 H), 7.30 (t, 1 H, J = 7.8), 7.12 (d, 2 H, J = 8.6), 6.82 (d, 2 H, J = 8.5), 6.61 (t, 1 H, J = 7.6), 6.54 (d, 1 H, J = 8.6), 4.32 (q, 1 H, J = 6.9), 4.21 (t, 2 H, J = 6.8), 3.85 (s, 3 H), 3.66 (s, 3 H), 3.16 (dd, 1 H, J = 6.1, 14.0), 3.08 (dd, 1 H, J = 7.1, 13.9), 2.96 (t, 2 H, J = 6.4), 2.36 (s, 3 H); MS (ES^+) m/e 515 $(MH)^+$; TLC (hexane/EtOAc (2:1)) R_f = 0.60; chiral chromatography (Chiralcel OD-H, 4.6 × 250 mm; EtOH/hexane (3:7); 0.7 mL/min) t_R = 11.5 min (major enantiomer), 13.9 min (minor enantiomer); 99% ee; $[\alpha]_D$ = −37.1°, α = −0.412°, c = 1.1 (CH_2Cl_2). Anal. ($C_{30}H_{30}N_2O_6$) C, H, N.

(*S*)-2-(1-Carboxy-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic Acid Methyl Ester (63). A solution of **21** (582 mg, 1.13 mmol) in THF/EtOH/1.0 M LiOH (3:1:1, 15 mL) was stirred under N_2 for 2 h. A solution of 0.4 M HCl (25 mL) was added, and the mixture was then extracted with EtOAc (150 mL). This extract was washed with brine (25 mL), dried over Na_2SO_4, and concentrated to a white solid. This material was flash chromatographed on silica gel with EtOAc (containing 0.1% HOAc) to produce **63** (450 mg, 80%) as a white solid: mp 140−141 °C (EtOAc); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.95 (bs, 1 H), 7.94−7.88 (m, 3 H), 7.77 (d, 1 H, J = 8.0), 7.49−7.45 (m, 3 H), 7.35 (t, 1 H, J = 7.9), 7.08 (d, 2 H, J = 8.5), 6.82 (d, 1 H, J = 8.6), 6.69 (d, 1 H, J = 8.6), 6.59 (t, 1 H, J = 7.5), 4.42−4.38 (m, 1 H), 4.15 (t, 2 H, J = 6.7), 3.75 (s, 3 H), 3.09 (dd, 1 H, J = 5.3, 13.9), 2.96 (dd, 1 H, J = 6.1, 14.0), 2.89 (t, 2 H, J = 6.6), 2.32 (s, 3 H); MS (ES^+) m/e 501 $(MH)^+$; TLC (EtOAc) R_f = 0.51; chiral chromatography (Chiralcel OD-H, 4.6 × 250 mm; EtOH/hexane (3:7) and 0.1% TFA; 0.7 mL/min) t_R = 7.8 min (major enantiomer), 7.2 min (minor enantiomer); 88% ee; $[\alpha]_D$ = −9.8°, α = −0.109°, c = 1.11 (CH_2Cl_2) (not corrected for ee). Anal. ($C_{29}H_{28}N_2O_6$) C, H, N.

(*S*)-2-(1-Carboxy-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic Acid Ethyl Ester (64). A solution of 0.97 g (1.94 mmol) of **21** in THF (40 mL) and EtOH (10 mL) was treated with 1 M LiOH (10 mL). The reaction was stirred for 30 h. Water (50 mL) and 1 N HCl (5 mL) were added. The reaction was extracted with EtOAc (3 × 100 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was suspended in toluene (3 × 40 mL) and concentrated to afford 900 mg (1.85 mmol, 95%) of the diacid (*S*)-**60** as an off-white solid.

A suspension of 0.432 g (0.889 mmol) of (*S*)-**60** in methanol (15 mL) was treated with concentrated HCl (1 mL) and heated to 70 °C. The solution was stirred for 4 h and then concentrated and the residue purified by flash chromatography (EtOAc with 0.1% AcOH) to afford 0.166 g (0.332 mmol, 37%) of 2(*S*)-(1-(methoxycarbonyl)-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}ethylamino)benzoic acid as a yellow foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (m, 2 H), 7.95 (d, 1 H, J = 6.3), 7.44 (m, 3 H), 7.33 (t, 1 H, J = 6.8), 7.08 (d, 2 H, J = 8.6), 6.83 (d, 2 H, J = 8.7), 6.64 (d, 1 H, J = 7.5), 6.53 (t, 1 H, J = 8.4), 4.34 (m, 1 H), 4.23 (t, 2 H, J = 6.7), 3.69 (s, 3 H), 3.13 (ddd, 2 H, J = 5.6, 8.1, 8.1), 2.36 (s, 3 H); MS m/e 501 $(MH)^+$.

A solution of 0.059 g (0.118 mmol) of the above (*S*)-(1-(methoxycarbonyl)-2-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]-phenyl}ethylamino)benzoic acid in DMF (2 mL) was treated with 0.018 g (0.130 mmol) of K_2CO_3 and 0.037 g (0.236 mmol) of ethyl iodide. The solution was stirred at room temperature for 16 h, diluted with EtOAc (25 mL), washed with water (3 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford 0.053 g (0.100 mmol, 85%) of **64** methyl ester as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, 1 H, J = 8.7), 8.00 (m, 2 H), 7.91 (d, 1 H, J = 8.0), 7.43 (bd, 3 H), 7.30 (t, 1 H, J = 7.0), 7.11 (d, 2 H, J = 8.6), 6.81 (d, 2h, J = 8.5), 6.61 (d, 1 H, J = 7.6), 6.53 (t, 1 H, J = 8.4), 4.41 (m, 3 H), 4.23 (t, 2 H, J = 6.5 Hz), 3.65 (s, 3 H), 3.16 (ddd, 2 H, J = 5.8, 7.9, 7.9), 2.99 (t, 2 H, J = 6.5), 2.37 (s, 3 H), 1.35 (t, 3 H, J = 7.1); MS m/e 529 $(MH)^+$.

To a solution of 0.082 g (0.154 mmol) of **64** methyl ester in THF (1 mL) was added 1 M LiOH (1 mL). The reaction was stirred for 2 h and then the pH adjusted to 3.5 with 1 N HCl. The reaction was extracted with EtOAc (3 × 25 mL). The combined organics were washed with water (2 × 15 mL) and brine (mL), dried over $MgSO_4$, filtered, and concentrated to afford 0.087 g (0.165 mmol, 61%) of **64** as an off-white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (bd, 1 H), 7.88 (bd, 2 H), 7.38−7.30 (m, 3 H), 7.26 (t, 2 H, J = 7), 7.10 (d, 2 H, J = 8.5), 6.72 (d, 2 H, J = 8.5), 6.60 (t, 1 H, J = 7.6), 6.52 (d, 1 H, J = 8.3), 4.25 (q, 3 H, J = 7.1), 4.10 (t, 2 H, J = 7), 3.19 (ddd, 2 H, J = 5.6, 7.0, 7.0), 2.88 (t, 2 H, J = 6.5), 2.30 (s, 3 H), 1.30 (t, 3 H, J = 7.2); MS m/e 513 $(M - H)^-$; chiral chromatography (Chiralcel OD-H, 4.6 × 250 mm; ^{i}PrOH/hexane (1:9) and 0.1% TFA; 1.0 mL/min) t_R = 19.2 min (major enantiomer), 24.6 min (minor enantiomer); 90% ee. Anal. ($C_{30}H_{30}N_2O_6 \cdot 0.5H_2O$) C, H, N.

Solubility Determinations. Solubilities were determined by equilibrating an excess of solid material in 500 μL of simulated gastric fluid (USP; pH 1.2) or pH 7.4 phosphate buffer (0.06 M) in temperature-controlled shaking water baths. Samples were drawn, filtered through a 0.22-μm filter (Ultrafree-MC 0.22-μm filter unit; Millipore, Bedford, MA), diluted using water/acetonitrile (60:40) mixture, and assayed by HPLC (Zorbax SB-phenyl column (250 × 4.6 mm, 5 μm); mobile phase 60:40 0.05% TFA in water/5% TFA in acetonitrile; flow rate of 1 mL/min; detected at the wavelength of UV maximum of individual compounds). HPLC determinations were performed using Waters 510 HPLC pumps, a Waters 715 ultra WISP automatic sample injection system, a Waters 490E programmable multiwavelength detector, and a Waters ExpertEase chromatography system.

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Supporting Information Available: Synthetic routes and spectral data for compounds **19a**, **23**, **24**, **26**−**32**, **35**, **38**−**43**, **45**−**49**, **52**−**54**, **59**, **62**, **65**, and **66** (14 pages). Ordering information is given on any current masthead page.

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