N-(2-Benzoylphenyl)-L-tyrosine PPARγ Agonists. 2. Structure−Activity Relationship and Optimization of the Phenyl Alkyl Ether Moiety

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We previously reported the identification of (2*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acid (**2**) (PPARγ pK_i = 8.94, PPARγ pEC$_{50}$ = 9.47) as a potent and selective PPARγ agonist. We now report the expanded structure−activity relationship around the phenyl alkyl ether moiety by pursuing both a classical medicinal chemistry approach and a solid-phase chemistry approach for analogue synthesis. The solution-phase strategy focused on evaluating the effects of oxazole and phenyl ring replacements of the 2-(5-methyl-2-phenyloxazol-4-yl)ethyl side chain of **2** with several replacements providing potent and selective PPARγ agonists with improved aqueous solubility. Specifically, replacement of the phenyl ring of the phenyloxazole moiety with a 4-pyridyl group to give 2(*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-pyridin-4-yloxazol-4-yl)ethoxy]phenyl}propionic acid (**16**) (PPARγ pK_i = 8.85, PPARγ pEC$_{50}$ = 8.74) or a 4-methylpiperazine to give 2(*S*)-((2-benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]ethoxy}phenyl)-propionic acid (**24**) (PPARγ pK_i = 8.66, PPARγ pEC$_{50}$ = 8.89) provided two potent and selective PPARγ agonists with increased solubility in pH 7.4 phosphate buffer and simulated gastric fluid as compared to **2**. The second strategy took advantage of the speed and ease of parallel solid-phase analogue synthesis to generate a more diverse set of phenyl alkyl ethers which led to the identification of a number of novel, high-affinity PPARγ ligands (PPARγ pK_i's 6.98−8.03). The combined structure−activity data derived from the two strategies provide valuable insight on the requirements for PPARγ binding, functional activity, selectivity, and aqueous solubility.

Introduction

Type 2 diabetes is a debilitating disease that arises from improper energy storage and utilization. The global incidence of this disease is estimated to be 120 million at present and is predicted to soar to over 200 million by the year 2010.[1] Type 2 diabetes is defined by high plasma glucose levels and is characterized by both peripheral insulin resistance and insufficient insulin secretion by the β-cells of the pancreas.[2] This disease is associated with a high degree of morbidity and mortality and is poorly controlled in the long run by diet, exercise, or current drug therapies such as sulfonylureas and insulin.[3]

An important treatment for type 2 diabetes has been the use of the sulfonylurea class of insulin secretagogues.[4] While these compounds can alleviate the hallmark hyperglycemia of the disease, they do not normalize glycemia and are subject to both primary and secondary failure.[3,5] In addition, given that hyperinsulinemia is a risk factor for ischemic heart disease,[6] increasing plasma insulin levels may not be the optimal therapeutic approach for treating type 2 diabetes. An alternative approach to improve hyperglycemia would be to alleviate insulin resistance rather than to stimulate insulin secretion. However, there are few good molecular targets for drug intervention to improve insulin resistance.

The thiazolidinedione (TZD) class of antidiabetics has been shown to improve insulin resistance in humans.[7−9] The only member of this class approved for use in humans to date is troglitazone (**1**) (Chart 1). This drug has been shown to increase insulin sensitivity in humans as measured directly by the hyperinsulinemic, euglycemic clamp protocol and indirectly by its ability to lower plasma glucose concomitant with a decrease in plasma insulin.[10,11] Troglitazone also reduces plasma levels of triglycerides, free fatty acids, and total cholesterol.[12] Although troglitazone reduces plasma glucose by an average 20%, it does not, as monotherapy, normalize plasma glucose in most type 2 diabetics.[10] While troglitazone shows much promise as an oral antidiabetic agent, there is still a need for improvement.

Troglitazone and related thiazolidinediones were discovered and optimized using in vivo models of type

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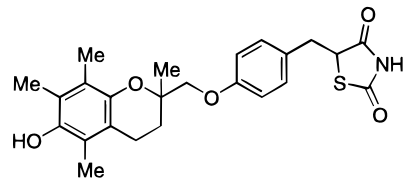
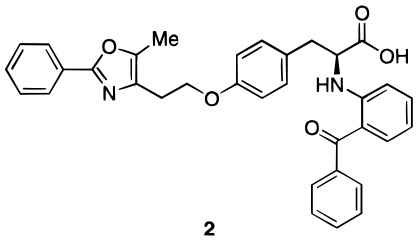
Chart 1



Troglitazone (1)



2

2 diabetes without knowledge of their mechanism of action.[7−9] Recently, we discovered that the thiazolidinedione rosiglitazone (BRL 49653) binds to and activates the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ).[12] Shortly thereafter, we demonstrated a correlation between the potency of binding to PPARγ and the in vivo antihyperglycemic potency in the ob/ob mouse of a number of thiazolidinediones.[13] We concluded from these data that PPARγ is the molecular target of the TZDs and is responsible for most, if not all, of their antihyperglycemic and insulin-sensitizing effects. While it is not yet clear why activation of PPARγ should lead to an improvement in insulin resistance, it is known to be present in insulin-sensitive tissues such as the adipocyte and muscle and to affect a number of genes involved in lipid and glucose metabolism.[14] PPARγ is most prevalent in adipose tissue where it plays an important role in adipocyte differentiation.[14,15]

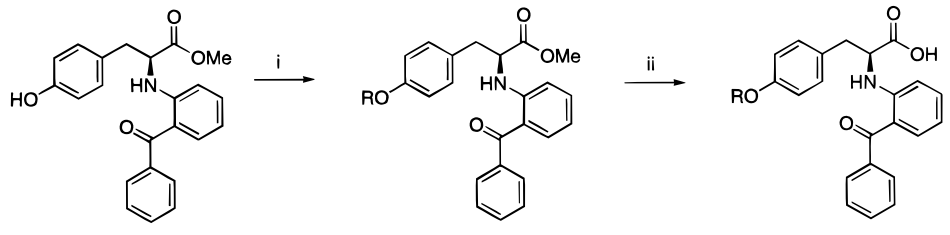
Troglitazone is a relatively weak PPARγ agonist (pK_i = 6.52);[16] therefore, we felt that a more potent molecule may have greater therapeutic efficacy in treating type 2 diabetes. In the preceding paper, we described the discovery and preliminary structure−activity data (SAR) of a series of novel, tyrosine-based non-thiazolidinedione PPARγ agonists.[16] Of the compounds evaluated, (2*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acid (**2**) emerged as the most potent PPARγ agonist in vitro and demonstrated antihyperglycemic and antihyperlipidemic activity in two rodent models of type 2 diabetes. Herein, we describe detailed SAR of the phenyl alkyl ether moiety of **2** using a combination of classical solution-phase analogue synthesis and high-throughput solid-phase synthesis. The goals were to maintain or improve in vitro activity and selectivity, improve aqueous solubility, and identify novel "left-hand" sides for this class of PPARγ ligands.

Chemistry

Solution-Phase Chemistry. All of the targeted analogues possessed the (*S*)-2-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid core structure shown in **2** in which a logical synthetic disconnection for these analogues was the tyrosine ether oxygen−alkyl bond. Thus, all of the analogues could be readily constructed via a Mitsunobu reaction as shown in Scheme 1. Exposure of (*S*)-2-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid methyl ester (**3**)[16] and a requisite alcohol to standard Mitsunobu coupling conditions provided the desired intermediates as the corresponding methyl esters. Saponification with LiOH in aqueous THF provided the desired targets with no evidence of racemization at the α-carbon as judged by chiral HPLC.

The required alcohols that addressed replacement of the oxazole ring in **2** (Table 1) were synthesized as shown in Schemes 2−5. The thiazole alcohol for **4** (Scheme 2) was synthesized following exposure of thiobenzamide to methyl 4-bromo-3-oxopentanoate[17] in hot toluene followed by ester reduction with LAH in THF. Imidazole alcohols for **5** and **6** (Scheme 3) were prepared from 2-phenyl-3-methylimidazole upon deprotonation with NaH in DMF followed by alkylation with the appropriate alkylating agent. Subsequent deprotonation with *n*-BuLi in THF and alkylation with ethylene oxide provided the targeted alcohols in modest yield. Following a Mitsunobu reaction with **3**, the 2-(trimethylsilyl)ethoxy group was efficiently removed upon treatment with BF_3−etherate in wet CH_3CN to provide **5**. *N*-Methylimidazole alcohol for **7** was prepared from 1-methyl-4-phenylimidazole[18] upon treatment with *n*-BuLi followed by trapping of the carbanion with ethylene oxide (Scheme 3). Pyrazole and triazole alcohols for **8** and **10** were prepared directly from 3-methyl-5-phenylpyrazole and 3-phenyl-5-methyl-[1,2,4]-triazole,[19] respectively, following deprotonation with NaH in DMF and subsequent N-alkylation with ethylene carbonate (Scheme 4). The assigned regiochemistry of the alkylation of **8** was confirmed by NMR spectroscopy using HMBC and NOESY experiments. *N*-Phenylpyrazole alcohol for **9** was prepared upon treatment of methyl 3,5-dioxohexanoate with phenylhydrazine and *p*-toluenesulfonic acid in methanol followed by reduction of the pendant ester group with LAH to give an inseparable mixture of isomeric alcohols (Scheme 5). Coupling with **3** using Mitsunobu conditions gave rise

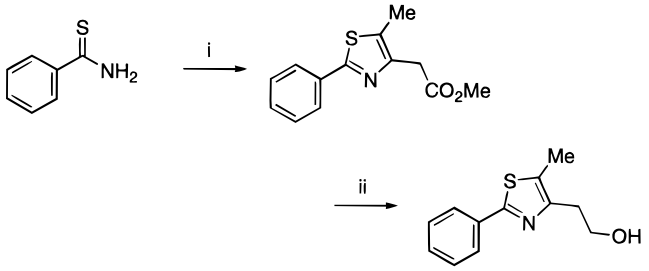
Scheme 1[a]



3

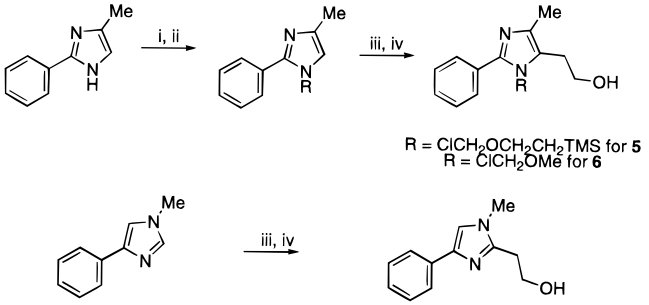
[a] Reagents: (i) ROH, Ph_3P, DEAD, THF; (ii) LiOH, THF, H_2O.

Scheme 2[a]



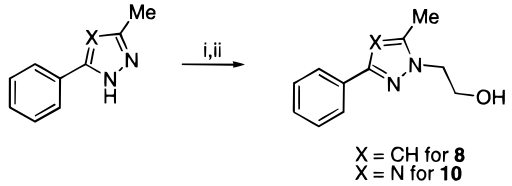
[a] Reagents: (i) methyl 4-bromo-3-oxopentanoate, toluene, 90 °C; (ii) LAH, THF, 0−25 °C.

Scheme 3[a]



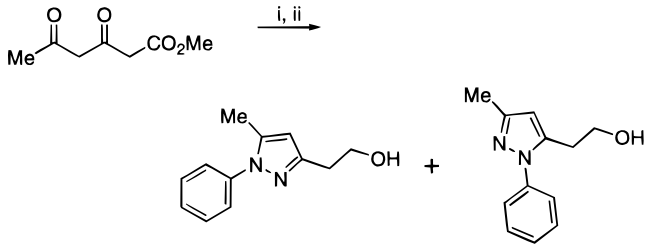
[a] Reagents: (i) NaH, DMF, 25 °C; (ii) $ClCH_2OCH_2CH_2TMS$ or $ClCH_2OMe$; (iii) *n*-BuLi, THF/hexanes, −78 °C; (iv) ethylene oxide, −78−25 °C.

Scheme 4[a]



[a] Reagents: (i) NaH, DMF, 0 °C; (ii) ethylene carbonate, 0−25 °C.

Scheme 5[a]

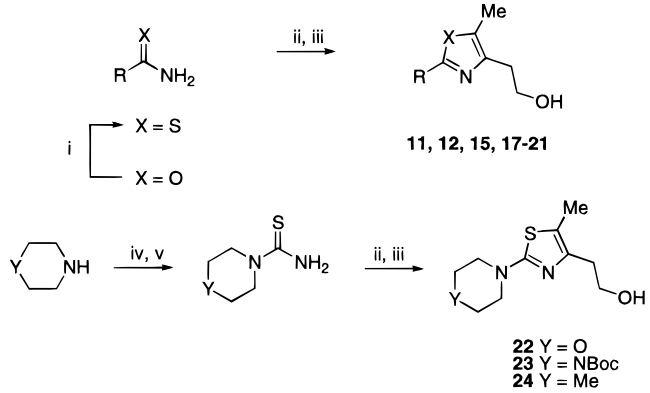


[a] Reagents: (i) $PhNHNH_2$, *p*-TsOH, MeOH; (ii) LAH, THF, 0−25 °C.

to isomeric pyrazoles that were separated by flash chromatography. The regiochemistry of the desired isomer was assigned by NMR spectroscopy following COSY and NOESY experiments on the Mitsunobu adducts.

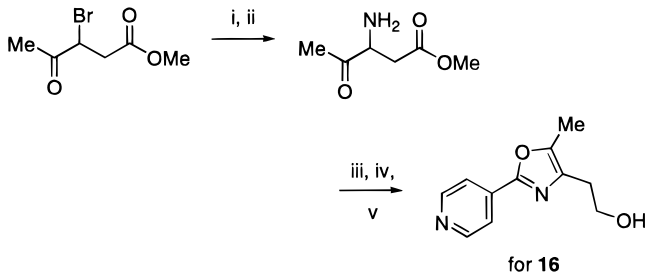
The targeted analogues with substitutions and replacements of the "left-hand" side phenyl ring (Table 2) were synthesized as shown in Schemes 6 and 7. In general, the oxazole or thiazole rings were synthesized directly from the amide, thioamide, or urea upon heating in the presence of methyl 4-bromo-3-oxopentanoate (Scheme 6). Simple reduction of the ester to the corresponding alcohol provided the Mitsunobu precursors in an efficient manner. In a number of cases the

Scheme 6[a]



[a] Reagents: (i) Lawesson's reagent, toluene, Δ; (ii) methyl 4-bromo-3-oxopentanoate, Δ; (iii) LAH, THF, 0−25 °C; (iv) thiocarbonyldiimidazole, THF; (v) NH_3, MeOH.

Scheme 7[a]

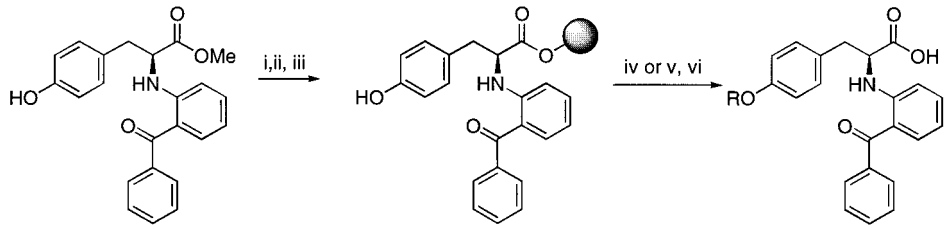


[a] Reagents: (i) NaN_3, DMF, 0−25 °C; (ii) 10% Pd/C, H_2, MeOH; (iii) isonicotinoyl chloride hydrochloride, Et_3N, CH_2Cl_2, 0−25 °C; (iv) $POCl_3$, toluene, Δ; (v) LAH, THF, 0−25 °C.

amide failed to cyclize to the corresponding oxazole (the oxazole analogue of **15** and compound **16**). Thus, we chose a thioamide as an alternative due to the increased nucleophilicity of the sulfur atom which, in turn, would allow more facile formation of an isosteric thiazole ring. Derivatives **22**−**24** were synthesized (Scheme 6) from the corresponding amines following treatment with thiocarbonyldiimidazole and ammonia to give an intermediate thiourea. Subsequent cyclization and ester reduction efficiently provided the desired analogues. The direct amide cyclization/reduction strategy for the synthesis of pyridyl analogue **16** failed; however, this analogue was readily synthesized from methyl 3-bromo-4-oxopentanoate via a five-step sequence (Scheme 7). Carefully controlled bromide displacement with sodium azide and subsequent reduction to the amine using hydrogen on palladium provided an intermediate amino ester. Acylation with isonicotinoyl chloride, cyclization with $POCl_3$, and ester reduction provided the targeted alcohol. Thiophene analogues **13** and **14** were prepared following a modification of the literature procedure.[20]

Solid-Phase Chemistry. The solution-phase chemistry approach described above focused on the synthesis of analogues around the phenyloxazole moiety of **2**. A second strategy was also pursued that utilized a solid-phase Mitsunobu reaction[21−24] between a resin-bound phenol and an alcohol for the generation of a more diverse and novel set of potential PPARγ agonists. A limited number of resins and linkers were evaluated for analogue synthesis including Wang, brominated Wang, Sasrin, and 2-chlorotrityl chloride polystyrene. Of these, 2-chlorotrityl chloride polystyrene resin proved optimal with respect to carboxylic acid loading, the

Scheme 8[a]



[a] Reagents: (i) LiOH, THF, MeOH, H_2O; (ii) $CsHCO_3$, MeOH, H_2O; (iii) trityl chloride resin, DMF, 50 °C, 20 h; (iv) excess ROH, Ph_3P, DEAD, THF; (v) excess ROH, Bu_3P, TMAD, THF, CH_2Cl_2; (vi) 10% TFA/CH_2Cl_2.

efficiency of the Mitsunobu reaction, and the mild conditions required for analogue cleavage from the resin. Toward this end, saponification of (*S*)-2-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid methyl ester (**3**) with LiOH in THF/MeOH/H_2O and heating the corresponding cesium carboxylate in the presence of 2-chlorotrityl chloride polystyrene (PS; 1.5 mmol/g) resin at 50 °C provided the desired ester-functionalized resin (Scheme 8).[25] Subjection of the resin-bound phenol to excess alcohol, triphenylphosphine, and diethyl azodicarboxylate (DEAD) in THF or to excess alcohol, tributylphosphine, and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD) in CH_2Cl_2/THF (1:1) effected formation of the key carbon−phenol oxygen bond. A total of 62 compounds were synthesized on solid phase, cleaved with 10% TFA in CH_2Cl_2, and analyzed by mass spectrometry and HPLC (Table 4). The purity of the crude compounds ranged from 16% to 98% with unreacted phenol (**27**) being present as the predominant byproduct in the majority of the crude products. Since pure **27** displayed no affinity for PPARγ when tested at 10 μM (Table 4, entry 1), we were not concerned with its presence in the crude mixture, and thus, affinity for PPARγ was measured using the unpurified compounds. Subsequently, a total of six of the compounds with pK_i > 6.00 were purified and tested in binding, transient transfection, and lipogenesis to confirm activity and determine functional potency and selectivity.

Biology

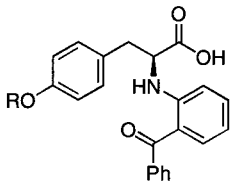
The targeted compounds were screened for both binding and functional activity in vitro. A detailed description of each assay is described in the previous paper.[16] Compounds were screened for PPARγ affinity in a competitive binding assay using [^{3}H]BRL 49653 as the radioligand. Functional activity and subtype selectivity were measured in a transient transfection assay using a chimeric receptor system containing the appropriate PPAR subtype. Compounds that elicited at least 70% activation versus rosiglitazone (BRL 49653) were considered full agonists. Additional characterization of PPARγ-specific functional activity was determined by measuring the ability of the compounds to promote differentiation of preadipocytes to adipocytes.

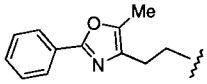
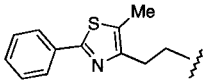
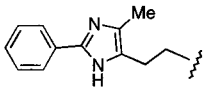
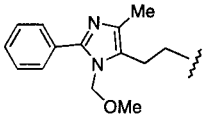
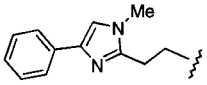
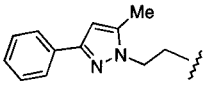
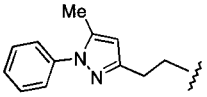
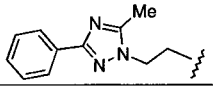
Results and Discussion

In the preceding paper we reported that hybridization of a novel tyrosine-based scaffold with "left-hand" sides from known thiazolidinediones (TZDs) provided potent, selective PPARγ agonists with **2** being the most potent agonist in vitro. Although potent and efficacious in vivo given po, compound **2** is a high-molecular-weight (>500) and highly lipophilic molecule with low aqueous solubility, and these physical properties have historically been considered suboptimal for the design of orally bioavailable compounds.[26] Thus, our goals were to (1) explore the SAR of the heterocyclic and phenyl rings of the 2-phenyloxazole moiety in compound **2** and (2) improve the aqueous solubility. Specifically, a series of compounds with replacements of the oxazole ring as well as replacements and substitutions of the phenyl ring of the 2-phenyloxazole moiety in **2** were targeted for evaluation as PPARγ agonists.

As shown in Table 1, replacement of the oxazole ring in **2** with a thiazole (**4**) provided a compound equipotent to **2** in vitro in all three assays which indicates that a thiazole is a suitable replacement for the oxazole. It is interesting to note that a similar thiazole in the thiazolidinedione series is a 10-fold less potent hypoglycemic agent in vivo as compared to the corresponding oxazole.[27] This information combined with the in vitro data for **4** suggests that any difference in in vitro and in vivo activity between a thiazole and an oxazole is not due to a difference in affinity for PPARγ. Replacement of the oxazole with an imidazole ring as in **5**−**7** provided high-affinity PPARγ ligands that were devoid of the weak affinity for PPARα observed with compounds **2** and **4**. Importantly, no functional activity at PPARδ was observed with these analogues or any of the other compounds described in this manuscript. The binding affinity data from compounds **5**−**7** suggested that the receptor might tolerate more basic ring structures; however, there was a consistent decrease in potency between the binding assay data and the functional assays with compounds **5**−**7**. One possible explanation for the weaker functional potency is poor cellular uptake of the ligands in the transient transfection and lipogenesis assays. However, a difference in receptor−ligand or co-activator−receptor−ligand interactions[28] between the assays, although unlikely, cannot be ruled out. Oxazole-to-pyrazole replacement as in **8** and **9** also provided high-affinity PPARγ ligands with selectivity comparable to **2**. Interestingly, there was no evidence of poor cellular uptake with compounds **8** and **9** as the magnitude of the corresponding activities was similar in both the cell-based and direct binding assays. Further replacement of the oxazole with triazole derivative **10** provided a potent PPARγ agonist with no detectable activity at PPARα up to 10 μM. Although compounds **2**, **4, 7,** and **8** were >1000-fold selective for PPARγ, submicromolar affinity for PPARα was also observed. Triazole analogue **10** and imidazole analogues **5** and **6**

Table 1. In Vitro Profile of PPARγ Agonists



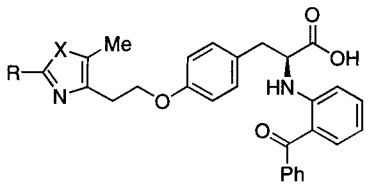
		Binding[a]		Transactivation[b]		Lipogenesis[c]
No.	R	PPARγ pK_i	PPARα pK_i	PPARγ pEC_{50}	PPARα pEC_{50}	pEC_{50}
2		8.94 ± 0.13 (8)	6.31 ± 0.02 (4)	9.47 ± 0.44 (11)	6.34 ± 0.10 (7)	8.83 ± 0.67 (7)
4		8.96 ± 0.11 (2)	6.90 ± 0.03 (2)	10. 00 ± 0.50 (4)	5.98 ± 0.07 (5)	8.67 ± 0.18 (5)
5		8.59 ± 0.05 (2)	<5.52 (2)	6.42 ± 0.29 (3)	<5.00 (2)	6.16 ± 0.02 (2)
6		8.70 ± 0.01 (2)	<5.52 (2)	7.09 ± 0.39 (3)	<5.00 (2)	6.92 ± 0.28 (2)
7		9.16 ± 0.04 (2)	6.86 (1)	8.03 ± 0.55 (4)	<5.00	8.19 ± 0.58 (3)
8		8.75 ± 0.24 (2)	6.76 ± 0.03 (3)	8.97 ± 0.42 (3)	6.18 ± 0.12 (3)	8.56 ± 0.48 (2)
9		8.90 ± 0.05 (2)	6.39 ± 0.10 (2)	8.43 ± 0.16 (3)	<5.00 (2)	7.74 ± 0.04 (2)
10		8.32 ± 0.02 (2)	<5.52 (2)	7.91 ± 0.22 (3)	<5.00 (2)	7.49 ± 0.45 (2)

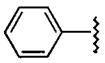
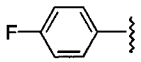
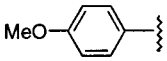
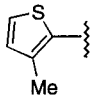
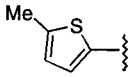
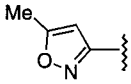
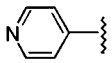
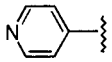
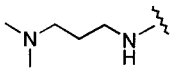
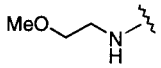
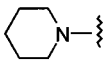
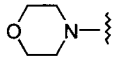
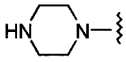
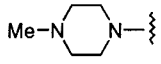
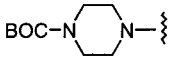
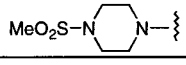
[a] pK_i, −log of the concentration of test compound required to achieve an apparent K_i value according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K_d is the dissociation constant for the radioligand at the receptor. [b] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity ± standard error (number of determinations). All compounds were functionally inactive at 10^{-5} M against PPARδ. [c] pEC_{50}, −log of the concentration of test compound required to induce 50% maxium lipogenic activity ± standard error (number of determinations).

were the only oxazole replacements that displayed no binding affinity or functional activity at PPARα up to 10 μM. Interestingly, only these three analogues possess an oxazole oxygen-to-heterocycle sp^2 nitrogen atom conversion that may be involved in a key isoform-specific interaction with PPARγ and not PPARα. Of the targeted oxazole replacements, only thiazole **4** and pyrazole **8** maintain comparable PPARγ affinity as well as functional potency in transient transfection and lipogenesis assays as compared to compound **2**.

We next sought to substitute or replace the phenyl ring of the 2-phenyloxazole or 2-phenylthiazole moiety in **2** and **4**, respectively, with more polar functionalities, and the results are shown in Table 2. We felt this might be an ideal location for modulation of the structure−activity relationship for potential improvement of potency, selectivity, and solubility. Since we had determined that the oxazole and thiazole were equipotent in binding and functional potency, we chose a number of thiazole-containing phenyl replacements instead of oxazole derivatives due to their relative ease of synthesis. Simple substitution of the phenyl ring with a 4-fluoro (**11**) or a 4-methoxy (**12**) had little effect on PPARγ affinity but does appear to increase PPARα binding slightly. Replacement of the phenyl ring of the 2-phenyloxazole or 2-phenylthiazole with a thiophene (**13** and **14**) or isoxazole (**15**) provided high-affinity PPARγ ligands with selectivity over PPARα remaining the same or slightly decreased. In contrast, incorporation of nitrogen into the 4-position of the phenyl ring to give a 2-(4-pyridyl)oxazole analogue **16** or the corresponding 2-(4-pyridyl)thiazole derivative **17** resulted in undetectable PPARα affinity up to 10 μM and functional activity accompanied by only a slight decrease in PPARγ activity. None of these substitutions or replacements resulted in a substantial improvement in PPARγ affinity or functional potency; however, selectivity over PPARα varied greatly (pK_i < 5.52−7.34) with more basic substitutions (**16**, **17**) completely abolishing any measurable PPARα affinity or functional activity.

Table 2. In Vitro Profile of PPARγ Agonists

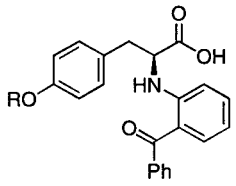


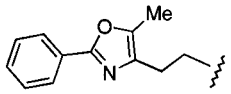
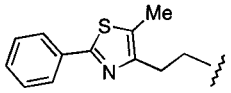
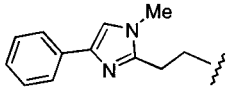
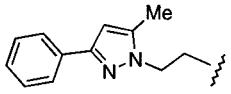
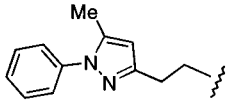
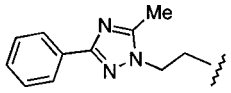
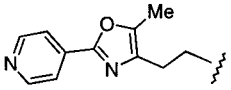
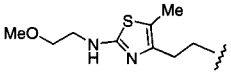
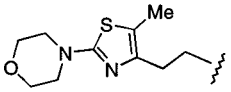
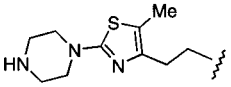
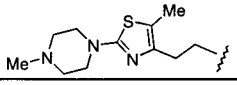
			Binding[a]		Transactivation[b]		Lipogenesis[c]
no.	R	X	PPARγ pK_i	PPARα pK_i	PPARγ pEC_{50}	PPARα pEC_{50}	pEC_{50}
2		O	8.94 ± 0.13 (8)	6.31 ± 0.02 (4)	9.47 ± 0.44 (11)	6.34 ± 0.10 (7)	8.83 ± 0.67 (7)
11		O	8.80 ± 0.06 (2)	7.25 ± 0.06 (2)	9.90 ± 0.47 (3)	6.59 ± 0.07 (2)	8.83 ± 0.42 (2)
12		O	8.96 ± 0.05 (2)	6.97 ± 0.06 (2)	9.22 ± 0.27 (3)	6.41 ± 0.04 (2)	8.75 ± 0.68 (2)
13		O	8.72 ± 0.05 (2)	6.33 ± 0.02 (2)	8.98 ± 0.15 (3)	5.56 ± 0.17 (2)	8.30 ± 0.68 (2)
14		O	9.07 ± 0.02 (2)	7.34 ± 0.05 (2)	9.61 ± 0.17 (3)	6.24 ± 0.41 (2)	8.75 ± 0.67 (2)
15		S	9.05 ± 0.07 (2)	6.75 ± 0.06 (2)	8.82 ± 0.33 (3)	5.74 ± 0.09 (3)	7.83 ± 0.34 (2)
16		O	8.85 ± 0.14 (2)	<5.52 (2)	8.74 ± 0.23 (3)	<5.00 (3)	8.04 ± 0.05 (2)
17		S	9.06 ± 0.05 (2)	<5.52 (3)	8.68 ± 0.07 (4)	<5.00 (4)	8.13 ± 0.10 (2)
18		S	7.56 ± 0.12 (2)	<5.52 (3)	5.91 ± 0.20 (3)	<5.00 (3)	6.41 ± 0.02 (2)
19		S	7.91 ± 0.06 (2)	<5.52 (2)	5.52 ± 0.24 (3)	<5.00 (2)	6.14 ± 0.04 (2)
20		S	8.59 ± 0.10 (2)	5.73 ± 0.11 (3)	7.51 ± 0.33 (3)	<5.00 (2)	6.75 ± 0.16 (2)
21		O	6.77 ± 0.04 (2)	<5.52 (3)	7.29 ± 0.13 (4)	<5.00 (2)	6.26 ± 0.08 (2)
22		S	9.11 ± 0.11 (2)	5.72 ± 0.10 (3)	8.74 ± 0.19 (4)	<5.00 (3)	7.81 ± 0.04 (2)
23		S	8.36 ± 0.16 (2)	<5.52 (3)	6.93 ± 0.22 (3)	<5.00 (2)	6.47 ± 0.07 (2)
24		S	8.66 ± 0.06 (2)	<5.52 (3)	8.89 ± 0.04 (3)	5.19 ± 0.06 (2)	8.44 ± 0.08 (2)
25		S	9.01 ± 0.01 (2)	<5.52 (3)	8.62 ± 0.36 (3)	<5.00 (2)	7.40 ± 0.20 (2)
26		S	8.58 ± 0.09 (2)	5.60 ± 0.08 (3)	7.63 ± 0.32 (3)	<5.00 (2)	6.29 ± 0.05 (2)

[a] 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. [b] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity ± standard error (number of determinations). All compounds were functionally inactive at 10^{-5} M against PPARδ. [c] pEC_{50}, −log of the concentration of test compound required to induce 50% maxium lipogenic activity ± standard error (number of determinations).

To evaluate replacement of the phenyl ring with polar aliphatic groups, compounds **18**−**26** were prepared. Replacement of the phenyl group with a *N*,*N*-dimethylamino group as in **18** or with an acyclic diamine as in **19** resulted in a >100-fold decrease in activity at PPARγ in all three assays. In contrast, substitution of the terminal amino group in **19** with a less basic methoxy group (compound **20**) resulted in a high-affinity PPARγ ligand, although an equivalent increase in functional activity was not observed. Reasoning that the conformational freedom at the 2-position of the oxazole with compounds **18**−**20** may be responsible for the decrease in activity, a set of more constrained cyclic amines (**21**−**26**) was prepared. Incorporation of a piperidine (**21**) resulted in a substantial decrease in affinity for PPARγ, while incorporation of a morpholine (**22**) provided a

Table 3. Solubility Data for PPARγ Agonists



		Solubility (mg/mL) [a]	
No.	R	simulated gastric fluid	pH 7.4 phosphate buffer
2		<0.001	<0.001
4		<0.001	0.002
7		<0.001	0.004
8		ND	0.004
9		ND	0.005
10		0.001	0.004
16		0.005	0.846
20		0.21	0.21
22		0.004	0.18
23		>10	0.025
24		>6	0.01

[a] See Experimental Section for solubility measurements; ND, not determined.

potent, selective PPARγ activator. One possible explanation for the >200-fold increase in affinity for PPARγ upon addition of the ring oxygen to **21** to provide **22** may be due to an additional hydrogen bond interaction with the receptor with **22** as compared to **21**. Extension of these modifications to piperazine (**23**), *N*-methylpiperazine (**24**), *N*-BOC-piperazine (**25**), or *N*-(methylsulfonyl)piperazine (**26**) led to high-affinity γ-ligands; however, compounds **23** and **26** showed decreased potency in the functional assays. *N*-Methylpiperazine **24** is the only compound within the piperazine series that is both a high-affinity ligand for PPARγ and a potent agonist in the functional assays. An explanation for the difference in activity between **23** and **24** will require further studies.

It is interesting to note that those phenyl ring replacements (compounds **18**−**26**) that possess a 2-amino-substituted heterocycle display much weaker affinity for PPARα relative to compounds **2** and **11**−**15**. Moreover, replacement of the oxazole oxygen in **2** with nitrogen as in imidazole **5**, imidazole **6**, and triazole **10** (Table 1) also results in compounds that are devoid of PPARα affinity when tested up to 3 μM. This information leads one to question why replacement with a polar nitrogen atom leads to improved selectivity for PPARγ versus PPARα. Although attempts have been made to rationalize the origin of the selectivity differences between these compounds and compounds **2** and **11**−**15**, no one hypothesis has prevailed.

Although compound **2** is extremely potent and selective, it is poorly soluble in aqueous media as evidenced by a measured solubility of <1 μg/mL in simulated gastric fluid (SGF; pH 1) and pH 7.4 phosphate buffer (Table 3). Thus, we were interested in determining the

effects of the "left-hand" side substitutions on the solubility of those compounds that were high-affinity ($pK_i > 8.0$) PPARγ ligands and were reasonably potent agonists ($pEC_{50} > 6.9$). As shown in Table 3, replacement of the oxazole moiety in compound **2** with a thiazole (**4**), *N*-methylimidazole (**7**), pyrazole (**8**, **9**), or triazole (**10**) did not improve the solubility of these compounds relative to **2** in either SGF or pH 7.4 phosphate buffer. In contrast, replacement of the phenyl ring of **2** with a 4-pyridyl group (**16**) resulted in a >800-fold increase in solubility in pH 7.4 phosphate buffer. Additionally, those analogues that possessed more basic 2-aminooxazole moieties (compounds **20**, **22**−**24**) not only were more soluble in pH 7.4 phosphate buffer but also were substantially more soluble in SGF as compared to **2**. In particular, *N*-methylpiperazine **24**, which is slightly less potent than **2** in the in vitro assays, is >6000 times more soluble in SGF. This increase in solubility in SGF is presumably due to the formation of a water-soluble ammonium ion in acidic media. In general, replacement of the oxazole did not result in a significant improvement in aqueous solubility relative to **2**; however, replacement of the phenyl ring with more polar groups did improve solubility considerably.

The chemistry utilized to evaluate the structure−activity around the 2-(5-methyl-2-phenyloxazol-4-yl)-ethyl side chain of compound **2** utilized a Mitsunobu coupling of phenol **3** with a requisite alcohol. In addition to our focused SAR described above, we also wanted to evaluate the SAR around a more diverse set of "left-hand" side analogues. To achieve this, an alternative strategy for analogue synthesis that utilized a solid-phase Mitsunobu reaction was undertaken in parallel with the solution-phase strategy. The impetus for choosing this strategy was primarily driven by the ease of phenyl alkyl ether synthesis on solid phase which would ultimately result in higher throughput analogue synthesis. Thus, a small library of tyrosine-based analogues was targeted that would provide additional insight on the requirements for PPARγ agonist activity. Starting from a list of alcohols derived from commercial sources and our internal chemistry stores, a second list of 970 alcohols was generated following elimination of undesired monomers based on four factors: (1) chemistry compatibility, (2) number of rotatable bonds, (3) excessive formal charge, and (4) molecular weight > 300. A three-dimensional virtual library was constructed and used to calculate the electrostatic potential mapped onto the molecular surface of each theoretical product. A space-fill experimental design[29] was then used to select a third list of 350 alcohols. The final set of 62 alcohols used to generate a small, focused library of potential PPARγ agonists was chosen from this list using availability and cost factors.

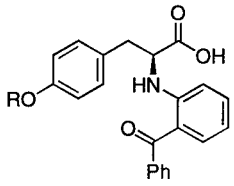
The compounds obtained from this library were prepared and screened as discretes for ligand binding to PPARγ. The results along with the crude analytical data are shown in Table 4. Since the major impurity in the crude reaction products was the starting phenol **27**, this compound was screened as a control and displayed no affinity for PPARγ (Table 4, entry 1). The majority of the compounds shown in Table 4 possess a substituted aromatic or heteroaromatic ring with a variable linker of 1−4 carbons between the aromatic ring and the phenol oxygen. Within the 1-carbon linker series (compounds **28**−**48**), the binding data indicate that the receptor does not tolerate multiple aromatic substitutions (compounds **39**, **40**, **42**, **46**−**48**), heteroaromatic rings (compounds **43**−**45**), or aromatic rings that are monosubstituted with hydrogen-bond acceptors (compounds **30**, **31**, **33**). The majority of the compounds within this series that have affinity for PPARγ possess aromatic rings that are monosubstituted with a hydrophobic group which suggests that these "left-hand" sides may be binding in a sterically compact or narrow hydrophobic pocket. As the linker is extended to 2 carbons (compounds **49**−**61**), the receptor becomes more tolerable as polar substitutions of an aromatic ring (compounds **50**, **51**) and heteroaromatic rings (compounds **56**, **57**, **59**) provide high-affinity ($pK_i < 6.45$) ligands for PPARγ. In the 3-atom linker series (compounds **62**−**79**), 13 of the 18 compounds synthesized that contain diverse aromatic or heteraromatic ring subsitutions display submicromolar affinity for PPARγ. As a general rule, further extension of the linker to 4 atoms provided inactive or low-affinity PPARγ ligands.

A total of six compounds in Table 4 were purified by reverse-phase HPLC and screened in binding, transient transfection, and lipogenesis assays in order to confirm affinity as well as to determine functional potency and selectivity. We were pleased to find that the binding data from the purified compounds in Table 5 versus the crude samples in Table 4 differed by less than 20-fold, and there was no association with the respective purities from the crude samples. As seen in Table 5, the compounds were all selective, high-affinity PPARγ ligands with a pK_i range of 6.98−8.03, and all six compounds were shown to be active in the functional assays. However, the activity in the cell-based assays was consistently lower than in the direct binding assay which may be a consequence of poor cell penetration. It is difficult to extract a defined structure−activity relationship from the compounds in Tables 4 and 5 due to the diverse set of functionalities present. Nonetheless, these data suggest that the binding pocket occupied by the "left-hand" side appears to accommodate a wide variety of structural diversity, which is supported by an X-ray crystal structure of various ligands cocrystallized with the ligand-binding domain of PPARγ.[30] Despite the fact that none of these compounds were superior to **2** in affinity or functional potency, the strategy utilized for analogue synthesis described above resulted in a number of novel "left-hand" side moieties. In the absence of thiazolidinedione literature precedent, this approach would have generated a number of potent, selective PPARγ agonists in a very short time frame.

Conclusion

The previous paper described the discovery of novel *N*-(2-benzoylphenyl)-L-tyrosine derivatives that are potent, selective PPARγ agonists.[16] In this paper, we have expanded the structure−activity relationship around the "left-hand" side moiety by pursuing two independent strategies. The first strategy focused on replacing both the oxazole and the phenyl ring of the 2-(5-methyl-2-phenyloxazol-4-yl)ethyl side chain of **2**. Replacement of the oxazole in **2** with various heterocycles resulted

Table 4. Analytical and PPARγ Binding Data of Analogues Synthesized via a Solid-Phase Mitsunobu Reaction



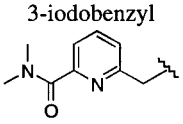
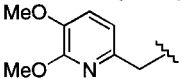
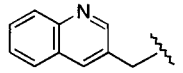
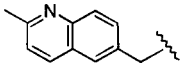
No.	R	Method [a]	Mol. Wt.	LRMS M^+ or MH^+	Crude HPLC Purity (%)[b]	Binding[c] PPARγ pK_i
27	H	--	361	362	99	IA
28	4-isopropylbenzyl	A	493	494	49	6.33 ± 0.02 (2)
29	4-chlorobenzyl	A	485	486	64	6.18 ± 0.02 (2)
30	4-thiomethylbenzyl	A	497	498	37	5.62 ± 0.01 (2)
31	4-methoxybenzyl	B	481	482	98	IA
32	4-ethylbenzyl	B	479	480	16	6.57 (1)
33	4-ethoxybenzyl	B	495	496	31	IA
34	3-methylbenzyl	A	465	466	50	6.01 ± 0.02 (2)
35	3-iodobenzyl	B	577	578	39	6.38 ± 0.02 (2)
36		B	523	524	ND	IA
37	2-methylbenzyl	A	465	466	44	6.43 ± 0.02 (2)
38	2-ethylbenzyl	B	479	480	31	5.86 ± 0.02 (2)
39	2,5-dimethylbenzyl	A	479	480	33	IA
40	3-bromo-4-methoxy-benzyl	B	560	561	75	IA
41	3-bromo-2-methoxy-benzyl	B	560	561	25	6.33 ± 0.01 (2)
42	3,4-dimethoxybenzyl	B	511	512	34	IA
43		B	512	513	ND	IA
44		B	502	503	ND	IA
45		B	530	531	ND	IA
46	2,4,5-trimethoxybenzyl	A	541	542	45	IA
47	3-bromo-4,5-dimethoxybenzyl	B	590	591	17	IA
48	2,3,5,6-tetramethylbenzyl	A	507	508	19	IA
49	2-(4-chlorophenyl)-ethyl	A	500	500	60	6.84 ± 0.02 (2)
50	2-(4-dimethylamino-phenyl)-ethyl	A	508	509	59	6.93 (1)
51	2-(4-trifluoromethoxy-phenyl)-ethyl	B	549	550	25	6.79 ± 0.02 (2)

Table 4 (Continued)

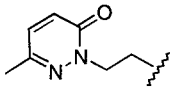
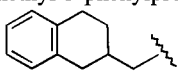
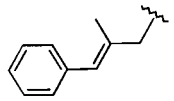
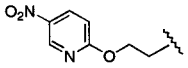
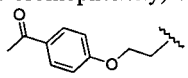
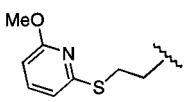
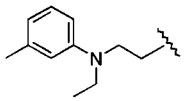
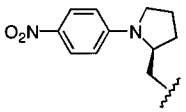
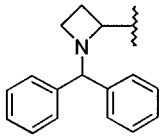
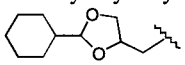
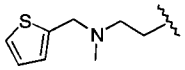
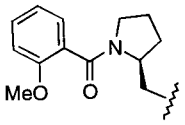
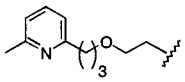
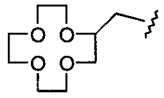
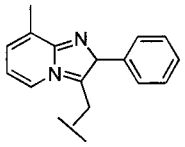
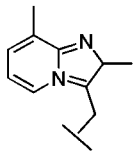
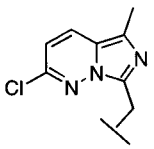
No.	R	Method [a]	Mol. Wt.	LRMS M^+ or MH^+	Crude HPLC Purity (%)[b]	Binding[c] PPARγ pK_i
52	2-(3-bromophenyl)-ethyl	A	544	544	33	6.17 ± 0.02 (2)
53	2-(3-fluorophenyl)-ethyl	B	483	484	97	6.95 ± 0.02 (2)
54	2-(2-methylphenyl)-ethyl	A	479	480	66	6.89 ± 0.25 (4)
55	2-(4-isopropyl-2-methylphenyl)- ethyl	B	521	522	27	IA
56	2-(2-pyridyl)-ethyl	B	466	467	60	6.45 ± 0.09 (4)
57	2-(4-methyl-5-thiazolyl)-ethyl	A	486	487	47	6.85 ± 0.02 (2)
58	2-(3-bromo-5-isoxazolyl)-ethyl	B	535	535	ND	IA
59		B	497	498	98	6.88 ± 0.02 (2)
60	2-methoxy-2-phenylethyl	A	495	496	41	6.10 ± 0.01 (2)
61	2-isopropyl-2-phenylethyl	B	507	508	95	6.26 ± 0.02 (2)
62	3-(4-pyridyl)-propyl	B	480	481	50	5.99 ± 0.02 (2)
63	3-(6-methyl-2-pyridyl)-propyl	A	494	495	34	5.99 ± 0.01 (2)
64	3-(4-methoxy-phenyl)-propyl	A	509	510	54	6.14 ± 0.02 (2)
65	3-(3,4-dimethoxy-phenyl)-propyl	A	539	540	35	6.92 ± 0.33 (4)
66	2-methyl-3-phenylpropyl	A	493	494	33	6.27 ± 0.35 (4)
67		B	505	506	24	6.84 ± 0.02 (2)
68		B	491	492	21	IA
69		B	527	528	44	7.04 ± 0.27 (4)
70	2-(4-bromophenoxy)-ethyl	A	560	560	27	7.14 ± 0.02 (2)
71		B	523	524	42	6.63 ± 0.02 (2)
72	2-(4-methylphenoxy)-ethyl	B	495	496	94	7.03 ± 0.02 (2)
73	2-(3-cyanophenoxy)-ethyl	B	506	507	20	6.43 ± 0.02 (2)
74	2-(2,6-dichlorophenoxy)-ethyl	A	550	550	23	5.86 ± 0.01 (2)
75		B	533	533	37	6.80 ± 0.02 (2)
76	2-(4-chlorothiophenoxy)-ethyl	A	532	532	44	6.70 ± 0.02 (2)

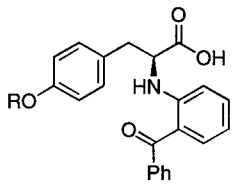
Table 4 (Continued)

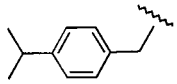
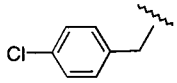
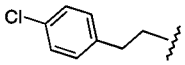
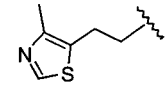
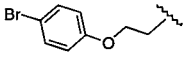
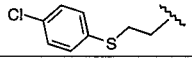
No.	R	Method [a]	Mol. Wt.	LRMS M^+ or MH^+	Crude HPLC Purity (%)[b]	Binding[c] PPARγ pK_i
77		A	522	523	20	6.97 ± 0.02 (2)
78		B	565	566	30	7.14 (1)
79		B	582	583	16	5.79 ± 0.02 (2)
80	2-(4-phenyl-5-thiazolyl)-ethyl	B	548	549	17	5.84 (1)
81	2-benzyloxy-ethyl	A	495	496	41	6.46 ± 0.19 (4)
82		B	515	516	30	IA
83		B	514	515	17	IA
84		A	578	579	39	6.02 ± 0.01 (2)
85		B	538	539	60	6.12 ± 0.02 (2)
86		B	549	550	28	5.93 ± 0.02 (2)
87		B	581	582	26	IA
88		B	519	520	33	IA
89		B	541	541	ND	IA

[a] See Experimental Section. [b] See Experimental Section; ND, not determined. [c] 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; IA, inactive at 3×10^{-5} M; ND, not determined.

in comparable or slightly decreased potency for PPARγ with thiazole **4** and pyrazole **8** being the only compounds prepared in this series that were of comparable potency to **2** in binding, transient transfection, and lipogenesis. Similarly, replacement of the phenyl ring with more polar groups resulted in compounds with variable affinity and functional activity at PPARγ with 4-pyridyl derivatives **16** and **17** and *N*-methylpiperazine **24** possessing in vitro activity comparable to that of **2**. Unfortunately, the more potent oxazole replacements **4** and **8** were not significantly more soluble in simulated gastric fluid or pH 7.4 phosphate buffer. However, replacement of the phenyl ring with a 4-pyridyl group (**16**, **17**) or a *N*-methylpiperazine (**24**) resulted in a significant improvement in aqueous solubility. The second strategy took advantage of the speed and ease

Table 5. In Vitro Profile of Select Mitsunobu Library Compounds



		Binding[a]		Transactivation[b]	Lipogenesis[c]
No.	R	PPARγ pK_i	PPARα pK_i	PPARγ pEC_{50}	pEC_{50}
28		6.98 ± 0.07 (2)	IA	6.62 ± 0.19 (3)	6.03 ± 0.05 (2)
29		7.41 ± 0.04 (2)	NT	5.96 ± 0.06 (3)	6.07 ± 0.04 (2)
49		8.03 ± 0.00 (2)	IA	6.98 ± 0.17 (3)	6.35 ± 0.07 (2)
57		7.73 ± 0.04 (2)	IA	6.49 ± 0.14 (3)	6.12 ± 0.01 (2)
70		7.71 ± 0.08 (2)	IA	6.57 ± 0.15 (3)	6.34 ± 0.09 (2)
76		7.94 ± 0.00 (2)	5.85 ± 0.03 (2)	6.72 ± 0.11 (3)	6.12 ± 0.06 (2)

[a] 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; IA, inactive at 3×10^{-5} M; NT, not tested. [b] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity ± standard error (number of determinations). [c] pEC_{50}, −log of the concentration of test compound required to induce 50% maximum lipogenic activity ± standard error (number of determinations).

of parallel solid-phase analogue synthesis to generate a more diverse set of tyrosine-based analogues that led to the identification of a number of novel, high-affinity PPARγ ligands. The information described herein combined with the information gained from the ligand-bound PPARγ crystal structure should prove useful not only for the design of other PPARγ-selective ligands but also for the fundamental understanding of the requirements for ligand-based modulation of PPARγ.

Experimental Section

General. 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, CH_2Cl_2), chloroform ($CHCl_3$), trifluoroacetic acid (TFA), dimethylformamide (DMF), methanol (MeOH). All reactions except 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, 5% phosphomolybdic acid in 95% ethanol, or ninhydrin.

^{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 the positive ion mode under electrospray ionization (ESI) or fast atom bombardment (FAB) methods. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

General Procedure A for the Mitsunobu Reaction (Scheme 1). 2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenylthiazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. A solution of 243 mg (0.93 mmol) of triphenylphosphine in 1.8 mL of anhydrous THF at 0 °C was treated with 0.146 mL (0.93 mmol) of DEAD. After stirring for 5 min the cold solution was added to a solution of 348 mg (0.93 mmol) of **3** and 203 mg (0.93 mmol) of 2-(5-methyl-2-phenylthiazol-4-yl)ethanol in 1.8 mL of anhydrous THF at 25 °C. After stirring for 24 h, the reaction was concentrated in vacuo (<25 °C). The residue was purified by silica gel flash column chromatography using hexanes/EtOAc (3:1) as eluent to give 378 mg (71%) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1 H, J = 7.6), 7.87 (dd, 2 H, J = 8.0, 1.6), 7.59 (d, 2 H, J = 7.6), 7.54−7.28 (m, 8 H), 7.17 (d, 2 H, J = 8.6), 6.83 (d, 2 H, J = 8.6), 6.63 (d, 1 H, J = 8.8), 6.57 (t, 1 H, J = 7.2), 4.37 (dd, 1 H, J = 7.2, 6.0), 4.28 (t, 2 H, J = 6.8), 3.69 (s, 3 H), 3.24−3.06 (m, 4 H), 2.41 (s, 3 H); low-resolution MS (ES) *m/e* 599 (MNa^+), 577 (MH^+); TLC (hexanes/EtOAc (2:1)) R_f = 0.50. Anal. ($C_{35}H_{32}N_2O_4S \cdot 1.3H_2O$) C, H, N.

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyl-3*H*-imidazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. Prepared from **3** and 2-[3-((trimethylsilylethoxy)-methyl)-5-methyl-2-phenyl-3*H*-imidazol-4-yl]ethanol as in general procedure A to give impure silyl-protected intermediate. A solution of 830 mg (1.2 mmol) of protected imidazole in 12 mL of CH_3CN at 0 °C was treated with 0.222 mL (1.8 mmol) of $BF_3 \cdot OEt_2$. After the mixture stirred for 30 min at 0 °C and then at 25 °C for 1 h, an additional 0.444 mL (3.6 mmol) of $BF_3 \cdot OEt_2$ was added. After the mixture stirred for a further 1 h, an additional 0.444 mL (3.6 mmol) of $BF_3 \cdot OEt_2$ was added, and stirring was continued for 35 min. The reaction was

poured into saturated $NaHCO_3$, and the product was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using hexanes/EtOAc (1:1) as eluent to give 542 mg (39% overall) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (d, 1 H, J = 7.2), 7.79 (d, 2 H, J = 7.6), 7.62−7.25 (m, 10 H), 7.14 (d, 2 H, J = 8.4), 6.76 (d, 2 H, J = 8.4), 6.64 (d, 1 H, J = 8.8), 6.58 (t, 1 H, J = 7.6), 4.40 (dd, 1 H, J = 7.2, 6.0), 4.11 (t, 2 H, J = 7.2), 3.69 (s, 3 H), 3.20 (dd, 1 H, J = 14.0, 5.6), 3.12 (dd, 1 H, J = 14.0, 7.2), 2.98 (t, 2 H, J = 6.0), 2.19 (s, 3 H); low-resolution MS (ES) *m/e* 560 (MH^+); TLC (EtOAc/hexanes (2:1)) R_f = 0.29. Anal. ($C_{35}H_{33}N_3O_4 \cdot 1.3H_2O$) C, H, N.

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-pyridin-4-yloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. Prepared from **3** and 2-(5-methyl-2-pyridin-4-yloxazol-4-yl)ethanol according to general procedure A. Purification by silica gel flash chromatography using EtOAc/hexane (1:1 to 9:1) provided the title compound in 51% yield: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.83 (d, 1 H, J = 7.4), 8.63 (m, 2 H), 7.74 (m, 2 H), 7.60 (m, 2 H), 7.53 (m, 2 H), 7.45 (m, 1 H), 7.27 (m, 1 H), 7.10 (m, 2 H), 6.75 (m, 2 H), 6.55 (m, 2 H), 4.31 (m, 1 H), 4.13 (t, 2 H, J = 6.6), 3.63 (s, 3 H), 3.09 (m, 2 H), 2.90 (t, 2 H, J = 6.5), 2.32 (s, 3 H); low-resolution MS (ES) *m/e* 562 (MH^+).

General Procedure B for the Mitsunobu Reaction (Scheme 1). 2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-1-phenyl-1*H*-pyrazol-3-yl)ethoxy]phenyl}propionic Acid Methyl Ester. Prepared from **3** and 2-(5-methyl-3-phenylpyrazol-1-yl)ethanol according to general procedure A. After stirring for 15 h, the solvent was removed in vacuo. The residue was stirred vigorously for 1 h in 2:1 diethyl ether/1 N LiOH biphasic solution to effect selective removal of residual **3**. Workup as in general procedure A and purification with hexane/EtOAc (4:1 to 2:1) as eluent afforded the title compound as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (d, 1 H, J = 7.4), 7.60 (d, 2 H, J = 8.3), 7.45 (m, 6 H), 7.34 (m, 1 H), 7.19 (d, 2 H, J = 8.6), 6.87 (d, 2 H, J = 8.6), 6.63 (d, 1 H, J = 8.5), 6.57 (dd, 1 H, J = 7.5, 7.5), 4.38 (dd, 1 H, J = 7.2, 13.3), 4.22 (t, 2 H, J = 7.1), 3.70 (s, 3 H), 3.20 (dd, 1 H, J = 6.0, 13.7), 3.12 (m, 3 H), 2.31 (s, 3 H); low-resolution MS (FAB) *m/e* 561 (MH^+), 560 (M^+). Anal. ($C_{35}H_{33}N_3O_4$) C, H, N.

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-(4-fluorophenyl)oxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. Prepared from **3** and 2-[2-(4-fluorophenyl)-5-methyloxazol-4-yl]ethanol according to general procedure B. Purification with hexane/EtOAc (4:1 to 2:1) as eluent afforded the title compound in 48% yield as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1 H, J = 7.3), 7.95 (m, 2 H), 7.58 (d, 2 H) 7.44 (m, 4 H), 7.34 (m, 1 H), 7.17 (d, 2 H, J = 8.6), 7.10 (dd, 2 H, J = 8.7, 8.7), 6.82 (d, 2 H, J = 8.6), 6.62 (d, 1 H, J = 8.5), 6.57 (dd, 1 H, J = 7.5, 7.5), 4.36 (dd, 1 H, J = 7.2, 13.3), 4.19 (t, 2 H, J = 6.5), 3.69 (s, 3 H), 3.19 (dd, 1 H, J = 5.8, 13.7), 3.11 (dd, 1 H, J = 7.4, 13.7), 2.93 (t, 2 H, J = 6.5), 2.34 (s, 3 H); low-resolution MS (FAB) *m/e* 580 (MH^+), 579 (M^+). Anal. ($C_{35}H_{31}FN_2O_5$) C, H, N.

General Procedure C for the Mitsunobu Reaction (Scheme 1). 2(*S*)-((2-Benzoylphenyl)amino)-3-(4-{2-[2-[(3-(dimethylamino)propyl)amino]-5-methylthiazol-4-yl]-ethoxy}phenyl)propionic Acid Methyl Ester. A suspension of 715 mg (2.73 mmol, 1.10 equiv) of triphenylphosphine, 929 mg (2.48 mmol) of **3**, and 600 mg (2.48 mmol) of 2-[2-[(3-(dimethylamino)propyl)amino]-5-methylthiazol-4-yl]ethanol in 25 mL of dry toluene was heated to 95 °C for 15 min to effect dissolution of **3**. To this solution was added 452 mg (2.60 mmol, 1.05 equiv) of diethyl azodicarboxylate dropwise over 5 min. The reaction was then allowed to cool to room temperature and stir for 16 h. The toluene was removed in vacuo, and the residue was purified by silica gel flash column chromatography using EtOAc/MeOH (1:1) with 1% ammonium hydroxide as eluent to afford 770 mg (52% yield) of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1 H, J = 7.3), 7.60 (d, 2 H, J = 7.0), 7.48 (m, 3 H), 7.33 (m, 1 H), 7.16 (d, 2 H, J = 8.5), 6.81 (d, 2 H, J = 8.5), 6.63 (d, 1 H, J = 8.3), 6.58 (dd, 1 H, J = 7.5, 7.5), 4.38 (m, 1 H), 4.13 (t, 2 H, J = 7.0), 3.69 (s, 3 H), 3.26 (t, 2 H, J = 6.3), 3.19 (dd, 1 H, J = 5.9, 13.8), 3.11 (dd, 1 H, J = 7.4, 13.8), 2.90 (t, 2 H, J = 7.0), 2.39 (t, 2 H, J = 6.5), 2.22 (m, 8 H), 1.76 (m, 2 H); low-resolution MS (FAB) *m/e* 602 (MH^+), 601 (M^+).

2(*S*)-((2-Benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]ethoxy}phenyl)-propionic Acid Methyl Ester. Prepared from **3** and 2-[5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]ethanol according to general procedure C. Purification by silica gel flash column chromatography using EtOAc/MeOH (10:1) with 1% ammonium hydroxide as eluent afforded 3.06 g of the title compound as a yellow oil. Approximately 130 mg of the material was dissolved in Et_2O, and the pH was adjusted to 1.0 by the addition of a 1.0 M solution of HCl in Et_2O. The resulting yellow precipitate was filtered and dried under vacuum to afford 100 mg of the HCl salt: ^{1}H NMR (MeOH-d_4, 400 MHz) δ 7.57 (m, 3 H), 7.50 (m, 2 H), 7.41 (m, 2 H), 7.09 (d, 2 H, J = 8.5), 6.77 (m, 3 H), 6.61 (dd, 1 H, J = 7.5, 7.5), 4.62 (t, 1 H, J = 5.7), 4.19 (t, 2 H, J = 5.8), 3.73 (s, 3 H), 3.30 (m, 4 H), 3.20 (dd, 1 H, J = 5.3, 13.9), 3.11 (dd, 1 H, J = 6.2, 13.9), 3.04 (t, 2 H, J = 5.8), 2.97 (s, 3 H), 2.26 (s, 3 H); low-resolution MS (FAB) *m/e* 599 (MH^+); RP-HPLC (Dynamax C-8, 25 cm × 4.1 mm; 30−80% CH_3CN in H_2O with 0.1% TFA buffer; 30 min; 1 mL/min) t_R = 17.79 min.

General Procedure D for the Saponification of the Methyl Ester (Scheme 1). 2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenylthiazol-4-yl)ethoxy]phenyl}-propionic Acid (4). To a solution of 350 mg (0.61 mmol) of 2(*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenylthiazol-4-yl)ethoxy]phenyl}propionic acid methyl ester in 5.6 mL of THF and 1.9 mL of H_2O at 0 °C was added 0.91 mL (0.91 mmol) of 1.0 N LiOH. The reaction was immediately warmed to 25 °C, stirred 2.5 h, and poured into EtOAc. The solution was acidified with 0.1 N HCl, and the product was extracted with EtOAc. The combined organic layers were concentrated in vacuo, and the residue was dissolved in $CHCl_3$, filtered, and concentrated in vacuo. Trituration with Et_2O/hexanes provided 283 mg (83%) of title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.62 (d, 1 H, J = 8.0), 7.82 (dd, 2 H, J = 6.0, <1.0), 7.60−7.36 (m, 9 H), 7.33 (d, 1 H, J = 8.0), 7.09 (d, 2 H, J = 8.8), 6.80 (t, 3 H, J = 8.4), 6.58 (t, 1 H, J = 7.6), 4.50 (dd, 1 H, J = 7.2, 6.0), 4.19 (t, 2 H, J = 6.8), 3.18−2.94 (m, 4 H), 2.37 (s, 3 H); low-resolution MS (ES) *m/e* 586 (MNa^+), 563 (M^+); RP-HPLC (C-18, 4.6 mm × 25 cm; 30−80% CH_3CN in H_2O with 0.1% TFA; 30 min; 1 mL/min) t_R = 28.9 min (t_0 = 3 min). Anal. ($C_{34}H_{30}N_2O_4S \cdot 0.3H_2O$) C, H, N, S.

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-pyridin-4-yloxazol-4-yl)ethoxy]phenyl}propionic Acid (16). Prepared from 2(*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-pyridin-4-yloxazol-4-yl)ethoxy]phenyl}propionic acid methyl ester according to general procedure D. Purification by silica gel chromatography using MeOH/CH_2Cl_2 (1:9) as eluent provided the title compound in 96% yield: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.75 (d, 1 H, J = 7.0), 8.68 (m, 2 H), 7.76 (m, 2 H), 7.52 (m, 1 H), 7.46 (m, 4 H), 7.28 (m, 2 H), 7.08 (m, 2 H), 6.73 (m, 3 H), 6.45 (m, 1 H), 4.22 (bm, 1 H), 4.07 (bm, 2 H), 3.17 (m, 1 H), 2.96 (m, 1 H), 2.86 (m, 2 H), 2.31 (s, 3 H); RP-HPLC (50−100% CH_3CN in water with 0.1% TFA buffer; 25 min) t_R = 7.58 min; chiral HPLC (Daicel chiralcel OD-H, 4.6 × 250 mL, 5 mm; 25% ethanol/hexane with 0.1% TFA; 1 mL/min; 30 min) t_R = 9.45 min, 96% ee; low-resolution MS (ES) *m/e* 548 (MH^+); high-resolution MS (EI) *m/e* 548.2194 (MH^+), $C_{33}H_{29}N_3O_5$ requires 548.2185.

2(*S*)-((2-Benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]ethoxy}phenyl)-propionic Acid Hydrochloride (24). Prepared from 2(*S*)-((2-benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]ethoxy}phenyl)propionic acid methyl ester according to general procedure D. Acidification of the reaction with 1 equiv of acetic acid and concentration in vacuo provided a residue. The residue was purified by silica gel chromatography using MeOH/EtOAc (gradient of 2:3 to 3:2 to

4:1) to give a yellow oil that was dissolved in minimal CH_2Cl_2 and filtered through filter paper. Concentration in vacuo and then acidification with 1 M HCl in Et_2O provided the title compound in 83% yield as a hydrochloride salt: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.05 (d, 1 H, J = 6.1), 7.56 (m, 2 H), 7.40 (m, 2 H), 7.30 (m, 1 H), 7.02 (m, 2 H), 6.80 (m, 1 H), 6.47 (m, 3 H), 4.42 (m, 1 H), 4.31 (m, 2 H), 3.11 (m, 6 H), 2.77 (m, 6 H), 2.43 (s, 3 H), 2.21 (s, 3 H); TLC (MeOH/EtOAc (2:3)) R_f = 0.17; RP-HPLC (50−100% CH_3CN in water with 0.1% TFA buffer; 25 min) t_R = 6.177 min; chiral HPLC (Daicel chiralcel OD-H, 4.6 × 250 mm, 5 mm; 25% ethanol/hexane with 0.1% TEA and 0.1% TFA; 1 mL/min; 30 min) t_R = 7.908 min, 96% ee; low-resolution MS (ES) *m/e* 585 (MH^+); high-resolution MS (EI) *m/e* 585.2541 (MH^+), $C_{33}H_{36}N_4O_4S$ requires 585.2536.

2-[3-((Trimethylsilylethoxy)methyl)-5-methyl-2-phenyl-3*H*-imidazol-4-yl]ethanol. A solution of 1.04 g (6.57 mmol) of 2-phenyl-3-methylimidazole in 25 mL of DMF at 0 °C was treated with 289 mg (7.23 mmol, 60% in oil) of NaH. After the mixture stirred for 5 min, 1.28 mL (7.23 mmol) of 2-(trimethylsilyl)ethoxymethyl chloride was added. The reaction was stirred for 10 min and then warmed to 25 °C and stirred overnight. The reaction was poured into H_2O, and the product was extracted with hexanes/EtOAc (1:1). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/MeOH (98:2) as eluent to give 1.18 g (62%) of protected intermediate. To 1.18 g (4.09 mmol) of protected imidazole in 16 mL of anhydrous THF at −78 °C was added 2.05 mL (5.11 mmol) of a 2.5 M *n*-BuLi in hexanes solution. After the mixture stirred for 45 min, 0.613 mL (12.3 mmol) of ethylene oxide was added, and stirring was continued for 15 min. The reaction was slowly warmed to 25 °C over a period of 2 h and then poured into H_2O. The product was extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/MeOH (95:5 to 9:1) as eluent to give 851 mg (63%) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, 1 H, J = 7.2), 7.48−7.38 (m, 3 H), 5.20 (s, 2 H), 3.82 (t, 2 H, J = 6.0), 3.45−3.35 (m, 2 H), 2.92 (t, 2 H, J = 6.0), 2.47 (s, 3 H), 0.90−0.80 (m, 2 H), −0.04 (s, 9 H); low-resolution MS (ES) *m/e* 233 (MH^+); TLC (EtOAc/MeOH (95:5)) R_f = 0.13. Anal. ($C_{18}H_{28}N_2O_2Si\cdot0.3H_2O$) C, H, N.

3-(Methoxymethyl)-5-methyl-2-phenyl-3*H*-imidazole. To a solution of 1.0 g (6.32 mmol) of 4-methyl-2-phenylimidazole in 25 mL of DMF at 0 °C was added 278 mg (6.95 mmol, 60% in oil) of NaH. After the mixture stirred for 5 min, 0.528 mL (6.95 mmol) of chloromethyl methyl ether was added, and the reaction was warmed to 25 °C and stirred 4 h. The reaction was poured into H_2O, and the product was extracted with hexanes/EtOAc (1:1). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography using hexanes/EtOAc (5:95) as eluent provided 816 mg (64%) of title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2 H, J = 7.2), 7.47−7.36 (m, 3 H), 6.84 (s, 1 H), 5.16 (s, 2 H), 3.36 (s, 3 H), 2.28 (s, 3 H); low-resolution MS (ES) *m/e* 225 (MNa^+), 203 (MH^+); TLC (EtOAc/MeOH (95:5)) R_f = 0.38.

2-(3-(Methoxymethyl)-5-methyl-2-phenyl-3*H*-imidazol-4-yl)ethanol. A solution of 710 mg (3.51 mmol) of 3-(methoxymethyl)-5-methyl-2-phenyl-3*H*-imidazole in 14 mL of anhydrous THF at −78 °C was treated with 1.7 mL (4.21 mmol) of a 2.5 M solution of *n*-BuLi in hexanes. The reaction was warmed to −65 °C and stirred 30 min. Upon cooling to −78 °C, 0.526 mL (10.53 mmol) of ethylene oxide was added, and stirring was continued for 15 min at −78 °C. The reaction was slowly warmed to 25 °C over 2 h and then poured into H_2O. The product was extracted with EtOAc, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/MeOH (93:7) as eluent to give 433 mg (50%) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (dd, 2 H, J = 8.0, 2.0), 7.45−7.35 (m, 3 H), 5.09 (s, 2 H), 3.76 (t, 2 H, J = 6.4), 3.22 (s, 3 H), 2.87 (t, 2 H, J = 6.4), 2.20 (s, 3 H); low-resolution MS (ES) *m/e* 269 (MNa^+), 247 (MH^+); TLC (EtOAc/MeOH (92:8)) R_f = 0.36. Anal. ($C_{14}H_{18}N_2O_2\cdot0.1H_2O$) C, H, N.

2-(1-Methyl-4-phenyl-1*H*-imidazol-2-yl)ethanol. A solution of 674 mg (4.26 mmol) of 1-methyl-4-phenylimidazole[18] in 8.5 mL of THF at −78 °C was treated with 1.9 mL (4.69 mmol) of a 2.5 M *n*-BuLi in hexanes solution. After the mixture stirred for 10 min, 1.1 mL (21.3 mmol) of ethylene oxide was added. The reaction was stirred for 5 min, then warmed to 25 °C, and stirred for 1 h. Upon cooling to 0 °C, 1.1 mL (21.3 mmol) of ethylene oxide was added, and the reaction was warmed to 25 °C and stirred overnight. The reaction was poured into H_2O and extracted with Et_2O. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/MeOH (95:5), and the collected product was recrystallized from CH_2Cl_2/EtOAc to give 178 mg (21%) of title compound as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, 2 H, J = 7.2), 7.36 (t, 2 H, J = 7.2), 7.22 (t, 1 H, J = 7.2), 7.08 (s, 1 H), 4.09 (t, 2 H, J = 5.6), 3.58 (s, 3 H), 2.87 (t, 2 H, J = 5.6); low-resolution MS (ES) *m/e* 225 (MNa^+), 203 (MH^+); TLC (EtOAc/MeOH (95:5)) R_f = 0.24. Anal. ($C_{12}H_{14}N_2O$) C, H, N.

2-(5-Methyl-3-phenylpyrazol-1-yl)ethanol. A solution of 497 mg (3.14 mmol) of 3-methyl-5-phenylpyrazole in 12.6 mL of DMF at 0 °C was treated with 138 mg (3.45 mmol, 60% in oil) of NaH. After the mixture stirred for 15 min, 1.38 g (15.7 mmol) of ethylene carbonate was added, and the reaction was warmed to 25 °C and stirred overnight. The reaction was diluted with H_2O, and the product was extracted with hexanes/EtOAc (1:1). The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using hexanes/EtOAc (1:3) as eluent to give 305 mg (48%) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 2 H, J = 7.2), 7.38 (t, 2 H, J = 7.2), 7.29 (t, 1 H, J = 7.2), 6.35 (s, 1 H), 4.18−4.10 (m, 2 H), 4.10−4.03 (m, 2 H), 2.31 (s, 3 H); low-resolution MS (ES) *m/e* 225 (MNa^+), 203 (MH^+); TLC (hexanes/EtOAc (1:3)): R_f = 0.31. Anal. ($C_{12}H_{14}N_2O$) C, H, N.

2-(5-Methyl-1-phenyl-1*H*-pyrazol-3-yl)ethanol. To a stirring solution of 150 mg (0.96 mmol) of methyl 3,5-dioxohexanoate in 5 mL of MeOH at room temperature was added 104 mg (0.96 mmol) of phenylhydrazine followed by 10 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred 15 min at room temperature and then allowed to reflux for 2 h. The reaction was cooled to room temperature, diluted with 10 mL of EtOAc, and washed with $NaHCO_3$ (1 × 10 mL). The organic layer was separated and dried ($MgSO_4$), and the solvents were removed in vacuo. Purification of the material by silica gel flash column chromatography using hexane/EtOAc (3:1) as eluent afforded 180 mg of the cyclized methyl ester. This material was dissolved in 5 mL of THF and cooled to 0 °C, and then 0.76 mL (0.76 mmol, 1.0 equiv) of a 1.0 M solution of $LiAlH_4$ in THF was added dropwise. The resulting solution was stirred at room temperature for 2 h, then cooled to 0 °C, and quenched by careful addition of 0.030 mL of H_2O, followed by addition of 0.030 mL of 15% NaOH and 0.090 mL of H_2O. The resulting slurry was filtered to remove the solids, and the filtrate was concentrated in vacuo to afford 150 mg of the title compound as a yellow oil which was used without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (m, 5 H), 6.10 (s, 1 H), 3.81 (t, 2 H, J = 6.5), 2.89 (t, 2 H, J = 6.5), 2.32 (s, 3 H).

2-(5-Methyl-3-phenyl-[1,2,4]triazol-1-yl)ethanol. A solution of 550 mg (3.45 mmol) of 3-phenyl-5-methyl-[1,2,4]-triazole[19] in 6.9 mL of DMF at 25 °C was treated with 345 mg (8.64 mmol, 60% in oil) of NaH in small portions. After the mixture stirred for 10 min, 1.5 g (17.3 mmol) of ethylene carbonate was added, and the reaction was stirred overnight. The reaction was poured into H_2O, and the product was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography using EtOAc/MeOH (95:5) as eluent and then recrystallized

from Et_2O to give 140 mg (20%) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (dd, 2 H, J = 8.0, 1.6), 7.45−7.34 (m, 3 H), 4.18 (t, 2 H, J = 4.6), 4.06 (t, 2 H, J = 4.6), 2.50 (s, 3 H); low-resolution MS (CI) *m/e* 204 (MH^+); TLC (EtOAc/MeOH (95:5)) R_f = 0.25. Anal. ($C_{11}H_{13}N_3O$) C, H, N.

General Procedure E for Oxazole or Thiazole Ring Formation. [2-(4-Fluorophenyl)-5-methyloxazol-4-yl]-acetic Acid Methyl Ester. A mixture of 667 mg (4.80 mmol) of 4-fluorobenzamide and 1.0 g (4.80 mmol) of methyl 4-bromo-3-oxopentanoate[17] in 6 mL of dry toluene was heated at 120 °C for 16 h. The resulting dark slurry was cooled to room temperature, diluted with 10 mL of EtOAc, and washed with $NaHCO_3$ (1 × 10 mL). The organic layer was separated and dried ($MgSO_4$), and the solvents were removed in vacuo. Purification of the material by silica gel flash column chromatography using hexane/EtOAc (4:1) as eluent afforded 308 mg of the title compound as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (m, 2 H), 7.11 (m, 2 H), 3.73 (s, 3 H), 3.56 (s, 2 H), 2.36 (s, 3 H).

[2-(4-Methoxyphenyl)-5-methyloxazol-4-yl]acetic Acid Methyl Ester. Prepared according to general procedure E except 4-methoxybenzamide was heated in neat 4-bromo-3-oxopentanoate at 120 °C for 2 h. Purification by silica gel flash column chromatography using hexane/EtOAc (3:1) as eluent afforded 189 mg of the title compound in 14% yield as a yellow solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, 2 H, J = 8.9), 6.93 (d, 2 H, J = 8.9), 3.85 (s, 3 H), 3.73 (s, 3 H), 3.56 (s, 2 H), 2.34 (s, 3 H); low-resolution MS (FAB) *m/e* 285 (MH^+), 284 (M^+).

[5-Methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]acetic Acid Methyl Ester. Prepared from 4-methylpiperazine-1-thiocarboxamide in refluxing 1,4-dioxane as in general procedure E. Purification by silica gel chromatography using methanol/ethyl acetate (3:17) as eluent afforded the title compound in 64% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (s, 3 H), 3.47 (s, 2 H), 3.35 (t, 4 H, J = 5.2), 2.42 (t, 4 H, J = 5.2), 2.67 (s, 3 H), 2.17 (s, 3 H); low-resolution MS (ES) *m/e* 270 (MH^+); TLC (MeOH/EtOAc (1:9)) R_f = 0.15.

General Procedure F for LAH reduction. 2-[2-(4-Fluorophenyl)-5-methyloxazol-4-yl]ethanol. To a stirring solution of 300 mg (1.20 mmol) of [2-(4-fluorophenyl)-5-methyloxazol-4-yl]acetic acid methyl ester in 5 mL of THF at 0 °C was added 1.20 mL (1.20 mmol, 1.0 equiv) of a 1.0 M solution of $LiAlH_4$ in THF. The resulting solution was stirred at room temperature for 45 min, then cooled to 0 °C, and quenched by careful addition of 0.045 mL of H_2O, followed by addition of 0.045 mL of 15% NaOH and 0.135 mL of H_2O. The resulting slurry was filtered to remove the solids, and the filtrate was concentrated in vacuo to afford 248 mg (93% yield) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (m, 2 H), 7.12 (m, 2 H), 3.92 (d, 2 H, J = 5.0), 3.21 (s, 1 H), 2.71 (t, 2 H, J = 5.6), 2.32 (s, 3 H); low-resolution MS (FAB) *m/e* 221 (M^+).

2-(5-Methyl-2-pyridin-4-yloxazol-4-yl)ethanol. Prepared from (5-methyl-2-pyridin-4-yloxazol-4-yl)acetic acid methyl ester according to general procedure F. Purification by silica gel column chromatography using MeOH/EtOAc (1:19) as eluent afforded the title compound in 80% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (d, 2 H, J = 6.0), 7.76 (d, 2 H, J = 6.2), 3.88 (m, 2 H), 2.72 (m, 2 H), 2.32 (s, 3 H); low-resolution MS (ES) *m/e* 205 (MH^+).

2-[5-Methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl]-ethanol. Prepared from [5-methyl-2-(4-methylpiperazin-1-yl)-thiazol-4-yl]acetic acid methyl ester according to general procedure F. Purification by silica gel flash column chromatography using $CHCl_3$/MeOH (10:1) as eluent afforded 2.20 g of the title compound as a clear colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.42 (bs, 1 H), 3.85 (m, 2 H), 3.41 (m, 4 H), 2.67 (t, 2 H, J = 5.4), 2.49 (m, 4 H), 2.34 (s, 3 H), 2.20 (s, 3 H).

Methyl 3-((5-Methyl-2-thienyl)amino)-4-oxopentanoate. A slurry of 19.3 g (0.136 mol) of 5-methyl-2-thiophenecarboxylic acid in 200 mL of toluene was treated with 10.9 mL (0.15 mol) of thionyl chloride. The resulting mixture was heated to 70 °C for 16 h and then concentrated in vacuo. The resulting oil was added in portions to a solution of 25.0 g (0.136 mol) of β-methylaspartic acid hydrochloride in 80 mL of pyridine at 0 °C at a rate to maintain a temperature < 10 °C. After the addition was complete, the solution was allowed to stir at 25 °C for 1 h, treated with 50 mL of acetic anhydride, and heated to 90 °C for 2 h. The mixture was then cooled to 25 °C, poured into 700 mL of 1 N HCl, and extracted three times with EtOAc. The combined organic phases were washed three times with 3 N HCl, once with water, once with 5% aqueous $NaHCO_3$, and finally with brine. The solution was dried (Na_2SO_4) and then chromatographed over silica gel eluting with hexanes/EtOAc (3:2) to obtain 9.1 g (25%) of the title compound as a clear yellow oil: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.81 (d, 1 H, J = 7.9), 7.57 (d, 1 H, J = 3.7), 6.85 (dd, 1 H, J = 2.4, 1.0), 4.64 (m, 1 H), 3.57 (s, 3 H), 2.85 (dd, 1 H, J = 16.3, 6.3), 2.61 (dd, 1 H, J = 16.3, 7.3), 2.45 (s, 3 H), 1.97 (s, 3 H); MS (ES+) *m/e* 270 (MH^+).

(5-Methyl-2-(5-methyl-2-thienyl)oxazo-4-yl)acetic Acid Methyl Ester. A solution of 3.97 g (14.7 mmol) of methyl 3-((5-methyl-2-thienyl)amino)-4-oxopentanoate in 100 mL of anhydrous CH_3CN was treated with 4.1 mL (44.2 mmol) of phosphorus oxychloride and heated at reflux for 5 h. The solution was cooled to 25 °C, and a dark oil was decanted from the tar at the bottom of the flask. The solution was concentrated in vacuo and diluted with water and EtOAc. The aqueous layer was saturated with $KHCO_3$, the layers were separated, and the solution was extracted twice more with ethyl acetate. The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo to give an orange oil, which was chromatographed over silica gel eluting with CH_2Cl_2/EtOAc (20:1). After concentration in vacuo, the residue was rechromatographed over silica gel eluting with hexane/EtOAc (2:1) to obtain 2.94 g (79%) of the title compound as a pink-orange oil: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.38 (d, 1 H, J = 3.6), 6.86 (d, 1 H, J = 3.4), 3.61 (s, 3 H), 3.57 (s, 3 H), 2.48 (s, 3 H), 2.29 (s, 3 H); MS (API+) *m/e* 252 (MH^+).

5-Methylisoxazole-3-thiocarboxamide. A suspension of 525 mg (4.16 mmol) of 5-methylisoxazole-3-carboxamide and 1.85 g (4.58 mmol, 1.1 equiv) of Lawesson's reagent in 15 mL of dry toluene was heated to reflux for 5 h, during which time the reaction mixture became a clear yellow color. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. Purification of the material by silica gel flash column chromatography using a gradient of hexane/EtOAc (5:1 to 1:1) as eluent followed by trituration with CH_3CN, filtration to remove the solid Lawesson's reagent byproducts, and removal of solvent afforded 614 mg of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (bs, 2 H), 6.52 (s, 1 H), 2.46 (s, 3 H).

3-Azido-4-oxopentanoic Acid Methyl Ester. To a solution of 2.23 g (10.67 mmol) of 3-bromo-4-oxopentanoic acid methyl ester in 11 mL of DMF at 0 °C was added 690 mg (10.67 mmol) of sodium azide. After warming to room temperature over 2.5 h, the reaction was diluted with H_2O and extracted with Et_2O/hexane (1:1). The layers were separated, the organics were dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using Et_2O/hexane (gradient of 1:4 to 2:3) to give 1.07 g (58% yield) of the title compound: ^{1} H NMR ($CDCl_3$, 400 MHz) δ 4.18 (dd, 1 H, J = 7.3, 5.6), 3.67 (s, 3 H), 2.87 (dd, 1 H, J = 17.0, 5.5), 2.73 (dd, 1 H, J = 16.9, 7.3), 2.28 (s, 3 H); low-resolution MS (FAB) *m/e* 172 (MH^+); IR (cm^{-1}) 2104, 1737, 1258.

3-Amino-4-oxopentanoic Acid Methyl Ester. A solution of 1.0 g (5.8 mmol) of 3-azido-4-oxopentanoic acid methyl ester in 25 mL of MeOH was evacuated and flushed with argon. To the solution was added 290 mg (30 wt %) of palladium on carbon (10%). The resulting slurry was evacuated and flushed with argon. After stirring under 1 atm of hydrogen for 4 h, the reaction was filtered through Celite under a stream of nitrogen. The organics were collected, and the solvent was removed in vacuo to give 940 mg (90% yield) of the title compound which was used without further purification: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.37 (bs, 2 H), 4.29 (m, 1 H),

3.64 (s, 3 H), 3.08 (m, 2 H), 2.24 (s, 3 H); low-resolution MS (ES) *m/e* 146 (MH^+).

4-Oxo-3-[(pyridin-4-ylcarbonyl)amino]pentanoic Acid Methyl Ester. To a stirred solution of 940 mg (5.18 mmol) of 3-amino-4-oxopentanoic acid methyl ester in 52 mL of CH_2Cl_2 at 0 °C was added 2.9 mL (20.72 mmol) of triethylamine. After the mixture stirred for 5 min, 1.0 g (5.69 mmol) of isonicotinoyl chloride hydrochloride was added, and the reaction was allowed to warm to room temperature overnight. The stirred solution was diluted with H_2O, the layers were separated, organics were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using MeOH/EtOAc (0:1 to 1:19) to give 360 mg (28% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (d, 2 H, J = 6.0), 7.59 (d, 2 H, J = 6.2), 4.86 (m, 1 H), 3.65 (s, 3 H), 3.06 (dd, 1 H, J = 17.2, 4.1), 2.87 (dd, 1 H, J = 17.3, 4.8), 2.25 (s, 3 H); low-resolution MS (ES) *m/e* 251 (MH^+); TLC (MeOH/EtOAc (1:19)) R_f = 0.49.

(5-Methyl-2-pyridin-4-yloxazol-4-yl)acetic Acid Methyl Ester. To a stirred solution of 250 mg (1.0 mmol) of 4-oxo-3-[(pyridin-4-ylcarbonyl)amino]pentanoic acid methyl ester in 7 mL of anhydrous toluene was added 0.28 mL (3.0 mmol) of $POCl_3$ (fresh ampule), and the reaction was heated to reflux for 16 h. After cooling to room temperature, the reaction was diluted with EtOAc, the organics were washed with saturated $NaHCO_3$ and dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using MeOH/EtOAc (1:19 with 0.1% NH_4OH) as eluent to give 180 mg (78% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.63 (d, 2 H, J = 6.0), 7.76 (d, 2 H, J = 6.0), 3.67 (s, 3 H), 3.53 (s, 2 H), 2.33 (s, 3 H); low-resolution MS (ES) *m/e* 233 (MH^+).

General Procedure G for Thiourea Synthesis. 1-Morpholinethiocarboxamide. To a stirring solution of 2.0 g (11.20 mmol, 1.15 equiv) of thiocarbonyldiimidazole in 30 mL of THF at room temperature was added 932 mg (10.70 mmol) of morpholine. The reaction mixture was stirred at room temperature for 2 h and then heated to 55 °C for 1 h. The reaction mixture was cooled to room temperature, and approximately 20 mL of THF was removed in vacuo; then 10 mL of a 2.0 M solution of ammonia in MeOH was added, and the reaction mixture was sealed and stirred for 15 h. An additional 10 mL of 2.0 M ammonia in MeOH was then added, and the reaction was stirred in a warm water bath for 8 h, during which time a white precipitate appeared. The precipitate was filtered, rinsed with Et_2O, collected, and dried to provide 745 mg of the title compound: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.41 (bs, 2 H), 3.69 (m, 4 H), 3.52 (m, 4 H); low-resolution MS (FAB) *m/e* 147 (MH^+).

4-(*tert*-Butoxycarbonyl)piperazine-1-thiocarboxamide. Prepared from 1-(*tert*-butoxycarbonyl)piperazine according to general procedure G. Trituration with Et_2O afforded 1.5 g (38% yield) of the title compound as an off-white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.67 (bs, 2 H), 3.78 (bs, 4 H), 3.49 (m, 4 H), 1.41 (s, 9 H); low-resolution MS (ES) *m/e* 246 (MH^+).

4-Methylpiperazine-1-thiocarboxamide. Prepared from 1-methylpiperazine according to general procedure G. Trituration with Et_2O provided the title compound in 43% yield as an off-white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (bs, 2 H), 3.78 (bs, 4 H), 2.42 (t, 4 H, J = 5.2), 2.28 (s, 3 H); low-resolution MS (ES) *m/e* 160.1 (MH^+).

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-piperazin-1-ylthiazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. To a stirred solution of 650 mg (0.95 mmol) of 2(*S*)-((2-benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-(*tert*-butoxycarbonyl)piperazin-1-yl)thiazol-4-yl]ethoxy}phenyl)-propionic acid methyl ester in 10 mL of CH_2Cl_2 was added 1 mL of trifluoroacetic acid. After stirring for 1.5 h, the reaction was washed with water and saturated $NaHCO_3$. The layers were separated, the organics were dried (4), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using MeOH/EtOAc (1:4) as eluent to give 176 mg (32% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (d, 1 H, J = 7.1), 7.53 (m, 2 H), 7.42 (m, 4 H), 7.27 (m, 1 H), 7.10 (d, 2 H, J = 8.5), 6.75 (d, 2 H, J = 8.6), 6.54 (m, 2 H), 4.30 (m, 1 H), 4.09 (t, 2 H, J = 7.0), 3.63 (s, 3 H), 3.28 (m, 4 H), 3.13 (dd, 1 H, J = 5.9, 13.9), 3.05 (dd, 1 H, J = 7.5, 13.8), 2.87 (m, 6 H), 2.16 (s, 3 H); low-resolution MS (ES) *m/e* 607 (MNa^+), 585 (MH^+); TLC (MeOH/EtOAc (1:4)) R_f = 0.10.

2(*S*)-((2-Benzoylphenyl)amino)-3-(4-{2-[5-methyl-2-(4-(methylsulfonyl)piperazin-1-yl)thiazol-4-yl]ethoxy}-phenyl)propionic Acid Methyl Ester. To a stirred solution of 170 mg (0.29 mmol) of 2(*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-piperazin-1-ylthiazol-4-yl)ethoxy]phenyl}-propionic acid methyl ester in 3 mL of CH_2Cl_2 at 0 °C was added 0.07 mL (0.87 mmol) of pyridine and 0.025 mL (0.32 mmol) of methanesulfonyl chloride. After warming to room temperature, the reaction was washed with saturated $NaHCO_3$ and H_2O. The layers were separated, the organics were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using EtOAc/hexane (2:1) as eluent to give 140 mg (74% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, 1 H, J = 7.5), 7.53 (m, 2 H), 7.41 (m, 4 H), 7.27 (m, 1 H), 7.10 (d, 2 H, J = 8.6), 6.74 (d, 2 H, J = 8.5), 6.53 (m, 2 H), 4.31 (m, 1 H), 4.08 (t, 2 H, J = 7.0), 3.63 (s, 3 H), 3.45 (m, 4 H), 3.25 (m, 4 H), 3.13 (m, 1 H), 3.05 (m, 1 H), 2.84 (t, 2 H, J = 6.9), 2.73 (s, 3 H), 2.17 (s, 3 H); low-resolution MS (ES) *m/e* 663 (MH^+); TLC (EtOAc/hexane (2:1)) R_f = 0.21.

2(*S*)-((2-Benzoylphenyl)amino)-3-(4-hydroxyphenyl)-propionic Acid (27). A solution of 1.79 g (4.66 mmol) of **3** in 15 mL of MeOH/THF/H_2O (2:2:2; v/v) was treated with 390 mg (9.33 mmol) of lithium hydroxide monohydrate and allowed to react for 3 h at room temperature. The solvents were removed in vacuo, and the residue was extracted with ethyl acetate/0.1 N NaOH. The aqueous layer was then acidified with citric acid and extracted with EtOAc. This organic fraction was washed with H_2O, separated, and dried ($MgSO_4$), and the solvents were removed in vacuo to afford 1.63 g (95%) of the title compound: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.22 (bs, 1 H), 8.64 (d, 1 H, J = 7.7), 7.59−7.48 (m, 5 H), 7.40 (dd, 1 H, J = 7.2), 7.33 (d, 1 H, J = 7.6), 6.97 (d, 2 H, J = 8.3), 6.80 (d, 1 H, J = 8.5), 6.59 (m, 3 H), 4.48 (m, 1 H), 3.08 (dd, 1 H, J = 5.3, 13.9), 2.96 (dd, 1 H, J = 6.5, 13.9); C_{18} RPHPLC (YMC, 250 mm × 4.6 mm i.d., S-5 μm; 0−100% CH_3CN in H_2O with 1% TFA; 30 min; 1.5 mL/min) t_R = 16.44 min (t_0 = 2.4 min); low-resolution MS (ES^+) *m/e* 384 (MNa^+). Anal. ($C_{22}H_{19}NO_4 \cdot 0.25H_2O$) C, H, N.

***2*(*S*)-((2-Benzoylphenyl)amino)-3-(4-hydroxyphenyl)-propionic Acid (2-Chlorophenyl)diphenylmethyl Ester Attached to Polystyrene Resin.** A solution of 1.63 g (4.4 mmol) of 2(*S*)-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)-propionic acid in 10 mL of MeOH and 5 mL of H_2O was treated with 0.852 g (4.4 mmol) of cesium bicarbonate. After stirring for 10 min at room temperature, the reaction was concentrated and the resulting cesium salt dried in vacuo. A slurry of 480 mg (0.72 mmol) of 2-chlorotrityl chloride resin (polysytrene; 1.5 mmol/g) in 4 mL of dry DMF was treated with 60 mg (∼1 mmol) of the cesium salt and agitated for 20 h at 50 °C. The reaction was drained and the resin washed with DMF, DMF/ethanol (1:1), ethanol, and Et_2O, resulting in 550 mg of the dry acid-loaded resin. A substitution of 0.49 mmol/g was calculated based on the combustion analysis (C, H, N).

General Procedure for Solid-Phase Analogue Synthesis for Compounds 27−89. A Whatman syringeless filter (PTFE "Autovial", 12-mL capacity with a 0.45-μm PTFE membrane with glass microfiber) was charged with 100 mg (1.1 mmol) of phenol resin followed by 4 mL of THF, the appropriate alcohol (5 mmol), DEAD (5 mmol), and Ph_3P (5 mmol) for method A. Method B used TMAD (1,1′-azobis(*N*,*N*-dimethylformamide)) (5 mmol) and tributylphosphine (5 mmol) in CH_2Cl_2/THF (1:1) as a solvent. After the reactions were rotated on an orbit shaker for ∼1.5 h, the reaction was drained and the resin was washed with THF, MeOH, THF, DMF, and DCM. After drying for 30 min, the resin was treated with 10% trifluoroacetic acid in DCM for 1 h. The filtrate was then

concentrated under N_2 and dried under high vacuum for 24 h affording crude products that were tested as is. Purities (analytical column: YMC-Pack ODS AA1 2S05-2520WT, 250 mm × 4.6 mm i.d., S-5 mm, 120 Å; 0−100% CH_3CN in H_2O with 0.1% TFA buffer; 30 min; 1.5 mL/min; 220 nm) are as described in Table 4.

Purification of select compounds by reverse-phase HPLC (C_{18} Waters Delta Prep 3000, column: YMC-Pack ODS AA12S05-2520WT, 250 mm × 20 mm i.d., S-5 mm, 120 Å; 0−100% CH_3CN in H_2O with 0.1% TFA buffer; 30 min; 18 mL/min; 220 nm) provided the compounds in Table 5 with purity > 95% and satisfactory NMR and low-resolution mass spectra.

The following compounds were prepared in an analogous fashion:

2-((2-Benzoylphenyl)amino)-3-[4-(4-isopropylbenzyloxy)phenyl]propionic Acid (28). Prepared from 4-isopropylbenzyl alcohol and afforded the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.69 (d, 1 H), 7.51−7.09 (m, 15 H), 6.83 (m, 2 H), 6.57 (t, 1 H), 4.94 (s, 2 H), 4.47 (b, 1 H), 3.13 (m, 1 H), 3.03 (m, 1 H), 2.85 (m, 2H), 1.16 (d, 6H); MS (ESP+) *m/e* 516 (MNa^+), 494 (MH^+); HPLC t_R = 23.36 min; >95% pure.

2-((2-Benzoylphenyl)amino)-3-[4-(4-chlorobenzyloxy)phenyl]propionic Acid (29). Prepared from 4-chlorobenzyl alcohol and afforded the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.72 (d, 1 H), 7.57−7.29 (m, 8 H), 7.11 (d, 2 H), 6.76 (m, 4 H),6.52 (t, 1 H) 4.98 (s, 2 H), 4.34 (b, 1 H), 3.13 (m, 1 H), 2.98 (m, 1 H); MS (ESP+) *m/e* 486 (MH^+); HPLC t_R = 21.95 min; >95% pure.

2-((2-Benzoylphenyl)amino)-3-{4-[2-(4-chlorophenyl)ethoxy]phenyl}propionic Acid (49). Prepared from 2-(4-chlorophenyl)ethanol to give the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.63 (m, 1 H), 7.59−6.49 (m, 16 H), 4.49 (m, 1 H), 4.11 (m, 2 H), 2.97 (m, 2 H); MS (ESP+) *m/e* 538 (MH^+); HPLC t_R = 22.43 min; >95% pure.

2-((2-Benzoylphenyl)amino)-3-{4-[2-(4-methylthiazol-5-yl)ethoxy]phenyl}propionic Acid (57). Prepared from 2-(4-methylthiazol-5-yl)ethanol to give the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.82 (d, 1 H), 7.81−6.62 (m, 12 H), 4.51 (b, 1 H), 4.09 (m, 2 H), 3.15 (m, 4 H), 2.31 (s, 3H); MS (ESP+) *m/e* 487 (MH^+); HPLC t_R = 17.43 min; >95% pure.

2-((2-Benzoylphenyl)amino)-3-{4-[2-(4-bromophenoxy)ethoxy]phenyl}propionic Acid (70). Prepared from 2-(4-bromophenoxy)ethanol to give the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.65 (d, 1 H), 7.65−7.26 (m, 8 H), 7.13 (d, 1 H), 6.91 (d, 1 H), 6.81 (m, 2 H) 6.58 (t, 1 H), 4.52 (m, 1 H), 4.22 (m, 2 H), 3.15 (m, 1 H), 3.05 (m, 1 H); MS (ESP+) *m/e* 560 (MH^+); HPLC t_R = 21.28 min; >95% pure.

2-((2-Benzoylphenyl)amino)-3-{4-2-(4-chlorophenylsulfanyl)ethoxy]phenyl}propionic Acid (76). Prepared from 2-(4-chlorophenylsulfanyl)ethanol to give the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.72 (d, 1 H), 7.57−7.29 (m, 8 H), 7.11 (d, 2 H), 6.76 (m, 4 H), 6.52 (t, 1 H), 4.98 (s, 2 H), 4.34 (b, 1 H), 3.13 (m, 1 H), 2.98 (m, 1 H); MS (ESP+) *m/e* 532 (MH^+); HPLC t_R = 22.65 min; >95% pure.

Solubility Determinations. The solubilities of PPARγ compounds 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 (0.06M) in temperature-controlled shaking water baths. Samples were drawn, filtered through a 0.22-μm filter (Ultra-free-MC 0.22-μm filter unit; Millipore, Bedford, MA), diluted using water/acetonitrile (60:40) mixture, and assayed by HPLC after 3 days of equilibration. The concentration of PPARγ compounds in solution was determined by reversed-phase HPLC using a Zorbax SB-phenyl column (250 mm × 4.6 mm, 5 μm) and a mobile phase consisting of 60:40 05% TFA in water/0.05% TFA in acetonitrile, with a flow rate of 1 mL/min and 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: Experimental data for all compounds which were not included in the Experimental Section (24 pages). Ordering information is given on any current masthead page.

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