N-(2-Benzoylphenyl)-L-tyrosine PPARγ Agonists. 1. Discovery of a Novel Series of Potent Antihyperglycemic and Antihyperlipidemic Agents

Brad R. Henke,*[,†] Steven G. Blanchard,[‖] Marcus F. Brackeen,[†,▽] Kathleen K. Brown,[#] Jeff E. Cobb,[†] Jon L. Collins,[†] W. Wallace Harrington, Jr.,[#] Mir A. Hashim,[⊥] Emily A. Hull-Ryde,[#] Istvan Kaldor,[†] Steven A. Kliewer,[‡] Debra H. Lake,[†] Lisa M. Leesnitzer,[‖] Jürgen M. Lehmann,[‡] James M. Lenhard,[#] Lisa A. Orband-Miller,[‖] John F. Miller,[†] Robert A. Mook, Jr.,[†] Stewart A. Noble,[†,◆] William Oliver, Jr.,[#] Derek J. Parks,[‖] Kelli D. Plunket,[‡] Jerzy R. Szewczyk,[†] and Timothy M. Willson[†]

Glaxo Wellcome Research and Development, Five Moore Drive, Research Triangle Park, North Carolina 27709

Received July 13, 1998

We have identified a novel series of antidiabetic *N*-(2-benzoylphenyl)-L-tyrosine derivatives which are potent, selective PPARγ agonists. Through the use of in vitro PPARγ binding and functional assays (2*S*)-3-(4-(benzyloxy)phenyl)-2-((1-methyl-3-oxo-3-phenylpropenyl)amino)-propionic acid (**2**) was identified as a structurally novel PPARγ agonist. Structure−activity relationships identified the 2-aminobenzophenone moiety as a suitable isostere for the chemically labile enaminone moiety in compound **2**, affording 2-((2-benzoylphenyl)amino)-3-(4-(benzyloxy)phenyl)propionic acid (**9**). Replacement of the benzyl group in **9** with substituents known to confer in vivo potency in the thiazolidinedione (TZD) class of antidiabetic agents provided a dramatic increase in the in vitro functional potency and affinity at PPARγ, affording a series of potent and selective PPARγ agonists exemplified by (2*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl}propionic acid (**18**), 3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]phenyl}-(2*S*)-((2-benzoylphenyl)amino)propanoic acid (**19**), and (2*S*)-((2-benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propanoic acid (**20**). Compounds **18** and **20** show potent antihyperglycemic and antihyperlipidemic activity when given orally in two rodent models of type 2 diabetes. In addition, these analogues are readily prepared in chiral nonracemic fashion from L-tyrosine and do not show a propensity to undergo racemization in vitro. The increased potency of these PPARγ agonists relative to troglitazone may translate into superior clinical efficacy for the treatment of type 2 diabetes.

Peroxisome proliferator-activated receptors (PPARs) are orphan receptors belonging to the steroid/thyroid/retinoid receptor superfamily of ligand-activated transcription factors. Three mammalian PPARs have been identified thus far and are termed PPARα, PPARγ, and PPARδ.[1−5] PPARs regulate expression of target genes by binding to DNA sequences termed PPAR response elements (PPREs). PPREs have been identified in the regulatory regions of a number of genes encoding proteins that are involved in lipid metabolism and energy balance, such as aP2,[6] phosphoenolpyruvate carboxykinase (PEPCK),[7] acyl-CoA synthetase,[8] and lipoprotein lipase (LPL).[9] The physiological role of the PPAR family in the regulation of lipid metabolism and storage has been the subject of several recent reviews.[10−15]

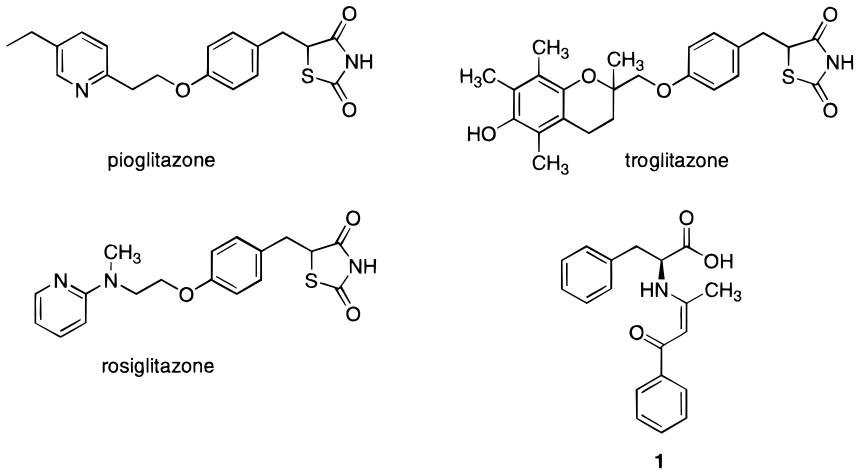
The PPARγ receptor subtype is predominantly expressed in adipose tissue and plays a pivotal role in adipocyte differentiation in vitro, suggesting that the PPARγ is an important component in the adipogenic signaling cascade and in lipid storage and utilization.[6,16,17] The human PPARγ gene structure has been characterized, and two isoforms with a common ligand binding domain, PPARγ1 and PPARγ2, have been identified. PPARγ1 is the predominantly expressed isoform both in man[18] and in rodents.[19] A number of naturally occurring fatty acids, eicosanoids, prostaglandins, and their metabolites have been shown to modulate PPARγ activity,[20−24] consistent with the hypothesis that fatty acids or their metabolites may be naturally occurring PPARγ ligands.

We recently identified a class of antidiabetic drugs, the thiazolidinediones (TZDs), as high-affinity PPARγ agonists,[25] which was subsequently corroborated by others.[22,26,27] In addition, we have demonstrated a correlation between the in vitro potency at the PPARγ receptor and the in vivo antihyperglycemic potency in C57 Bl/6 ob/ob mice for a series of TZDs.[28] These results suggest that PPARγ is the molecular target responsible for the antidiabetic activity of the thiazolidinedione class of agents. TZDs, or "glitazones", enhance the sensitivity of target tissues to insulin and also reduce lipid and insulin levels in animal models of type 2 diabetes and clinically in type 2 diabetics.[29−35] TZDs do not cause an increase in insulin secretion or in the number or affinity of insulin receptor binding sites, suggesting that

* Address correspondence to: Brad R. Henke, Glaxo Wellcome Research and Development, NORTH M2111, Five Moore Drive, Research Triangle Park, NC 27709. Tel: (919) 483-1363. Fax: (919) 315-5668. E-mail: brh14990@glaxowellcome.com.
† Department of Medicinal Chemistry.
‖ Department of Molecular Biochemistry.
‡ Department of Molecular Endocrinology.
⊥ Department of Molecular Pharmacology.
Department of Metabolic Diseases.
▽ Current address: MonomerChem Inc., Research Triangle Park, NC 27709.
◆ Current address: Synaptic Pharmaceutical Corp., Paramus, NJ 07652.

10.1021/jm9804127 CCC: $15.00
Published on Web 11/11/1998

Chart 1



TZDs amplify postreceptor events in the insulin signaling cascade.[36]

A number of TZDs have been advanced into the clinic for the treatment of type 2 diabetes without benefit of the knowledge of their molecular target, using in vivo assays to discriminate among the candidate molecules. The TZDs currently undergoing clinical evaluation include troglitazone,[37] pioglitazone,[38−40] and rosiglitazone (BRL 49653)[41,42] (Chart 1). The TZD class of compounds is not without drawbacks, however. Although troglitazone has been approved for use in the United States and Japan, it displays modest in vivo potency both in animal models of type 2 diabetes[43,44] and clinically,[29] suggesting that improvements in antidiabetic potency are feasible. A number of TZDs have been dropped from development due to their unacceptable side-effect profile.[45] It remains unclear whether the side effects are caused by the mechanism of action of these compounds or originate within the 2,4-thiazolidinedione chemical structure common to this class. Notably, all TZDs have been developed as racemates since the stereogenic center present in the 2,4-thiazolidinedione moiety is known to undergo facile racemization under physiological conditions.[46]

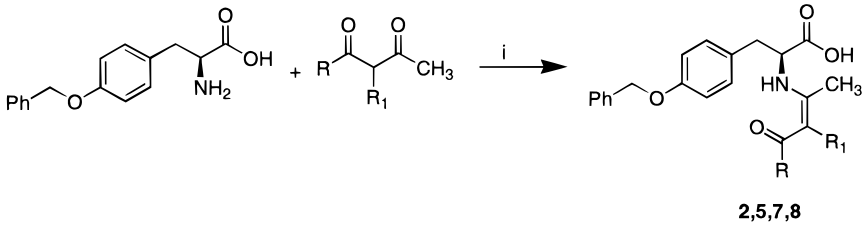
We were interested in developing a series of potent, selective, non-thiazolidinedione PPARγ agonists which might surmount the problems associated with the known thiazolidinediones and thus offer an advantage as an antidiabetic agent. This manuscript provides an account of the discovery of a novel set of tyrosine-based PPARγ agonists and describes the synthesis, initial structure−activity relationship (SAR) studies, and in vitro activity of this series of compounds. In addition, the in vivo antihyperglycemic activity of a subset of these compounds is described. The detailed SAR of these *N*-(2-benzoylphenyl)-L-tyrosine PPARγ agonists is the subject of the following two papers.

Chemistry

Synthesis of the vinylogous amide analogues **2**, **5**, **7**, and **8** (Table 1) was carried out by condensation of *O*-benzyltyrosine or its corresponding methyl ester with the requisite β-diketone in the presence of either dicyclohexylamine or molecular sieves as a catalyst (Scheme 1).[47,48] The remainder of *O*-benzyltyrosine analogues from Table 1 were prepared via a rhodium-catalyzed insertion reaction[49] of a suitable aniline derivative with 3-(4-(benzyloxy)phenyl)-2-diazopropionic acid methyl ester,[50] followed by saponification to the desired acid (Scheme 2).

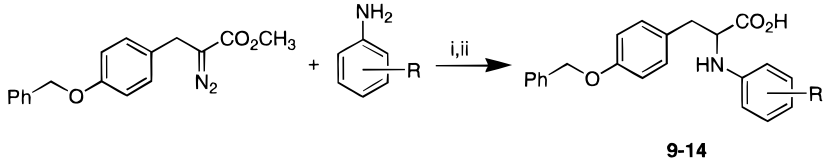
Analogues found in Table 2 were prepared via the general route depicted in Scheme 3. L-Tyrosine methyl ester and 2-benzoylcyclohexanone[51] were refluxed in anisole in the presence of 10% Pd/C with removal of

Scheme 1[a]



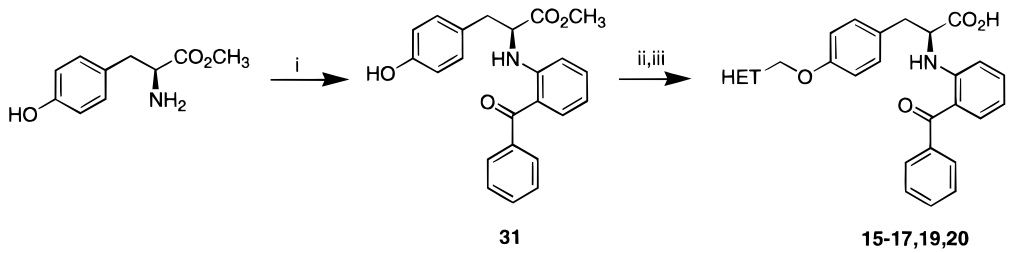
[a] Reagents: (i) dicyclohexylamine, MeOH, reflux, 24 h or 4-Å molecular sieves, MeOH, reflux, 72 h.

Scheme 2[a]



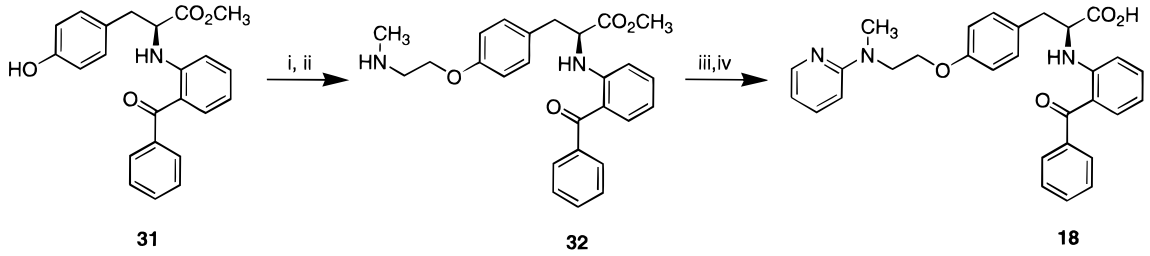
[a] Reagents: (i) $Rh_2(OAc)_4$, toluene, rt to 80 °C, 1−12 h; (ii) LiOH, THF/MeOH (3:1), rt, 4−24 h.

Scheme 3[a]



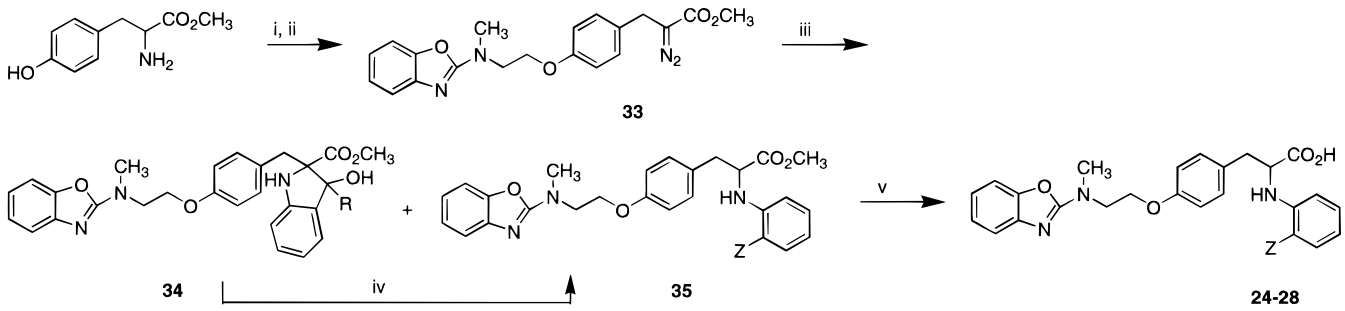
[a] Reagents: (i) 2-benzoylcyclohexanone, 10% Pd/C, anisole, reflux, 2 h; (ii) Ph_3P, DEAD, HET-OH, THF, rt, 6−18 h; (iii) LiOH, THF/MeOH (3:1), rt, 4−24 h.

Scheme 4[a]



[a] Reagents: (i) Ph_3P, DEAD, 2-(*N*-Boc-*N*-methylamino)ethanol, THF, rt, 6 h; (ii) trifluoroacetic acid, DCM, rt, 30 min; (iii) 2-fluoropyridine, reflux, 16 h; (iv) LiOH, THF/MeOH (3:1), rt, 7 h.

Scheme 5[a]



[a] Reagents: (i) NaH, 2-(2-benzoxazolylmethylamino)ethanol methylsulfonyl ester, DMF, 100 °C, 2 h; (ii) isoamyl nitrite, AcOH, $CHCl_3$, rt to 60 °C, 15 min; (iii) $Rh_2(OAc)_4$, Ar-NH_2, toluene, rt to 80 °C, 1−12 h; (iv) DBU, toluene, reflux, 1 h; (v) LiOH, THF/MeOH (3:1), rt, 4−24 h.

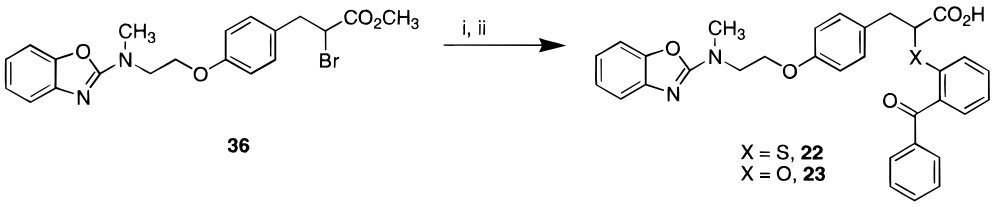
water via a Dean−Stark trap to effect condensation to the vinylogous amide and subsequent dehydrogenation to the benzophenone derivative **31** without loss of stereochemical integrity. The resulting (*S*)-2-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid methyl ester was then reacted with the desired heterocyclic alcohol via a Mitsunobu reaction to afford the intermediate methyl ester. Saponification with LiOH in THF afforded compounds **15**−**17**, **19**, and **20** in enantiomerically pure fashion. Synthesis of the requisite heterocyclic alcohol coupling partners was carried out via literature methods.[41,52,53]

We suspected compound **18** could not be prepared via the Mitsunobu coupling of **31** with 2-(*N*-methyl-*N*-pyridin-2-ylamino)ethanol as described in Scheme 3 due to competing intramolecular cyclization of the activated alcohol onto the pyridine nitrogen.[41] Therefore **18** was synthesized by the procedure outlined in Scheme 4 via Mitsunobu reaction with 2-(*N*-*tert*-butoxycarbonyl-*N*-methylamino)ethanol to afford **32**, followed by removal of the Boc group, addition to 2-fluoropyridine, and saponification. Synthesis of *ent*-**18** was carried out in identical fashion starting with D-tyrosine methyl ester. Analogues **29** and **30** (Table 4) were prepared from **18** via standard functional group transformations.

Most of the analogues in Table 4 were prepared as outlined in Scheme 5. Alkylation of tyrosine methyl ester with 2-(2-benzoxazolylmethylamino)ethanol methylsulfonyl ester[41] followed by treatment with isoamyl nitrite provided the key diazo intermediate **33**. Rhodium-catalyzed diazo insertion followed by treatment with LiOH or NaOH then afforded **24**−**28**. In most cases when a carbonyl was ortho to the amino moiety of the insertion partner, the desired benzophenone product was accompanied by a byproduct determined to be cyclic derivative **34**, which may arise from rearrangement of an epoxide intermediate. Intermediate **34** could be converted to the desired benzophenone species simply by refluxing with DBU in toluene to effect a formal retroaldol reaction. The cyclic derivative **34** appeared to be a single diastereomer by ^1H NMR, but assignment of relative stereochemistry was not attempted. Attempts at asymmetric insertion reactions using chiral rhodium catalysts[54−56] led to poor (<10% ee) asymmetric induction under all conditions tried.

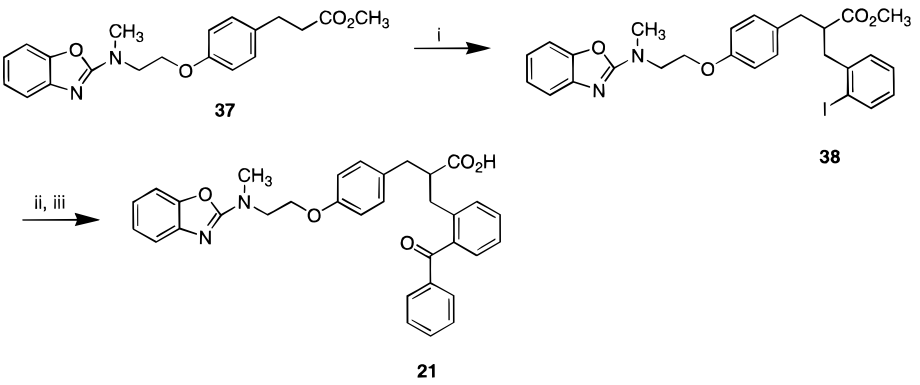
Compounds **22** and **23** were prepared by the route

Scheme 6[a]



[a] Reagents: (i) *t*-BuO$^-$K$^+$, 18-C-6, Ar-XH, THF, rt, 3 h; (ii) LiOH, THF/MeOH (3:1), rt, 4−7 h.

Scheme 7[a]



[a] Reagents: (i) $NaN(TMS)_2$, 2-iodobenzyl bromide, THF, −78 °C, 90 min; (ii) phenylboronic acid, $PdCl_2(PPh_3)_2$, CO(g), K_2CO_3, 1,4-dioxane, 95 °C, 22 h; (iii) LiOH, THF/MeOH (3:1), rt, 6 h.

outlined in Scheme 6 via alkylation of the known α-bromo ester **36**[57] with either 2-mercapto- or 2-hydroxybenzophenone[58] followed by saponification. Compound **21** was prepared by alkylation of the known ester **37**[57] with 2-iodobenzyl bromide, followed by palladium-catalyzed carbonylative cross-coupling[59] with phenylboronic acid to form the desired benzophenone derivative (Scheme 7). Saponification then afforded compound **21**.

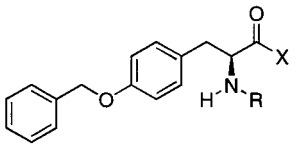
Biology

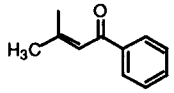
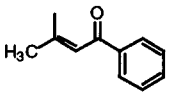
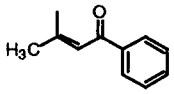
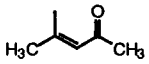
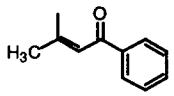
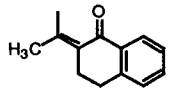
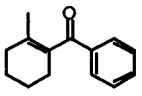
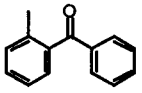
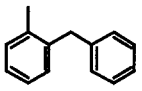
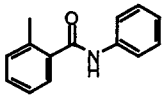
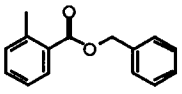
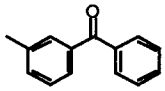
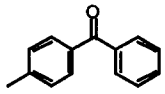
In Vitro. Compounds were evaluated in three separate in vitro assays to determine their binding and functional potency. Compounds were tested for their ability to bind to PPARγ using a scintillation proximity assay (SPA). The PPAR ligand binding domain (LBD) was expressed in *Escherichia coli* as polyHis-tagged fusion proteins and purified. The LBD was then labeled with biotin and immobilized on streptavidin-modified scintillation proximity beads. The beads were then incubated with a constant amount of the appropriate radioligand ([^{3}H]BRL 49653 for PPARγ) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads was measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabeled ligand, was subtracted from each data point. For each compound tested, plots of ligand concentration versus CPM of radioligand bound were constructed and apparent K_i values were estimated from nonlinear least-squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere.[60]

Compounds were screened for functional potency in a transient transfection assay in CV-1 cells for their ability to activate the three PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the three receptor subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results.[25] The ligand binding domains for murine and human PPARα, PPARγ, and PPARδ were each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and β-galactosidase as described previously.[25] After 16 h, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts were prepared and assayed for alkaline phosphatase and β-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the β-galactosidase activity as an internal standard. Compounds which elicited on average at least 70% activation of PPARγ versus rosiglitazone (positive control) were considered full agonists.

Certain compounds were also tested for their ability to promote differentiation of C3H10T1/2 stem cells to adipocytes via measurement of glucose incorporation into total lipid of the cells (lipogenesis assay). The amount of glucose uptake into lipid in these cells provides a measure of the cell differentiation and indirectly a measure of insulin sensitization mediated through activation of PPARγ. Several lines of evidence indicate the importance of the role PPARγ and insulin play in adipocyte differentiation. First, induction of PPARγ has been shown to be an early event in the course of differentiation of several preadipocyte cell lines and precedes the induction of other adipocyte markers

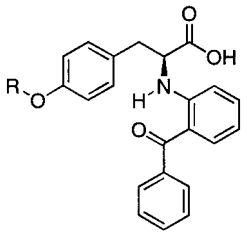
Table 1. In Vitro Profile of PPARγ Agonists

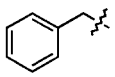
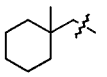
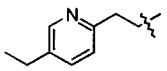
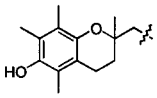
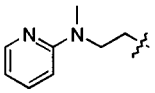
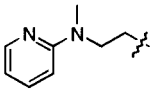
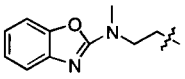
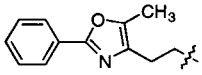


	Structures[a]		Binding[b]	Transactivation[c]
no.	X	R	hPPARγ pK_i	PPARγ pEC_{50}
2	OH		7.93 ± 0.01 (2)	6.64 ± 0.20 (2)
3	NH_2		5.88 ± 0.01 (2)	6.31 (1)
4	OCH_3		6.12 ± 0.03 (2)	6.16 ± 0.08 (3)
5	OH		5.71 ± 0.19 (2)	IA
6	OH	H	< 5.5 (2)	5.60 ± 0.24 (3)
ent-2	OH		< 5.5 (2)	4.66 (1)
7	OCH_3		< 5.5 (2)	IA
8	OH		6.10 ± 0.24 (2)	4.99 ± 1.13 (4)
9	OH		6.79 ± 0.04 (2)	4.78 ± 0.44 (5)
10	OH		< 5.5 (1)	IA
11	OCH_3		< 5.5 (2)	IA
12	OCH_3		< 5.5 (1)	IA
13	OH		< 5.5 (2)	IA
14	OH		5.90 ± 0.00 (2)	IA

[a] See figure. [b] pK_i, −log of the concentration of test compound required to achieve an apparent K_i value according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K_d is the dissociation constant for the radioligand at the receptor. [c] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity ± standard error (number of determinations); IA, inactive at 10^{-4} M.

Table 2. In Vitro Profile of PPARγ Agonists



	Structure[a]	Binding[b]	Transactivation[c]	Lipogenesis[d]
no.	R	PPARγ pK_i	PPARγ pEC_{50}	pEC_{50}
9		6.79 ± 0.04 (2)	4.78 ± 0.44 (5)	5.82 ± 0.04 (2)
15		7.29 ± 0.03 (3)	6.21 ± 0.20 (5)	5.94 ± 0.02 (2)
16		8.19 ± 0.032 (3)	7.30 ± 0.17 (5)	6.30 ± 0.05 (2)
17		8.28 ± 0.03 (3)	8.04 ± 0.11 (5)	6.44 ± 0.07 (2)
18		8.85 ± 0.02 (3)	8.04 ± 0.33 (7)	7.74 ± 0.29 (3)
ent-18		6.98 ± 0.04 (2)	6.41 ± 0.29 (7)	< 6.0 (1)
19		8.83 ± 0.05 (3)	8.58 ± 0.39 (8)	8.36 ± 0.41 (4)
20		8.94 ± 0.13 (8)	9.47 ± 0.44 (11)	8.83 ± 0.67 (7)

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

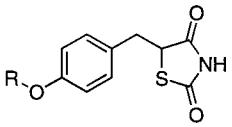
such as aP2 and C/EBPα.[6,16] Importantly, this differentiation was dependent on the presence of insulin in the media. Furthermore, ectopic expression of PPARγ in fibroblasts has been shown to induce adipocyte differentiation; this differentiation was significantly enhanced in the presence of weak PPARγ activators.[17] In addition, thiazolidinediones have been shown to induce the insulin-stimulated differentiation of preadipocyte cell lines,[61] which suggests that the insulin-enhancing action of TZDs in these cells is mediated through the PPARγ receptor.

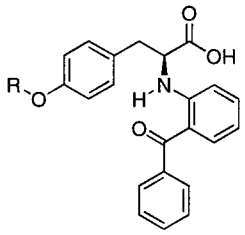
C3H10T1/2 cells were grown in a DME medium supplemented with 10% fetal calf serum. One day before reaching confluence, differentiation was induced by addition of insulin (200 nM) with or without test compound. Medium and compound were exchanged every 3 days. [^{3}H]Glucose was added to the cells after 3 days in culture. Cells treated with compound were evaluated for lipogenic activity after 7 days by determination of radioactive glucose uptake into total lipid and confirmed by accumulation of lipid droplets in the cytoplasm by staining with oil red O. The details of this assay have been recently reported.[62]

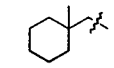
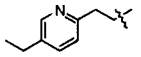
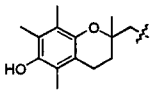
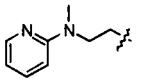
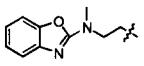
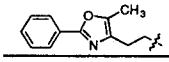
In Vivo. Compounds which showed potent PPARγ activation in vitro were evaluated for in vivo antidiabetic activity using two established rodent models of type 2 diabetes: the db/db mouse model and/or the Zucker diabetic fatty (ZDF) rat model.[63,64] Both models are characterized by a single-gene mutation (autosomal recessive trait) that results in a severe diabetic phenotype resembling human type 2 diabetes. The animals are hyperglycemic, hyperinsulinemic, hyperlipidemic, and insulin-resistant.

A. Db/db Mice. Test compound was administered to 60-day-old male db/db mice (n = 7/group) at a dose of 5 mg/kg bid for 14 days by oral gavage. Blood

Table 3. In Vitro Comparison of TZDs and Tyrosine PPARγ Agonists





		Thiazolidinediones			Tyrosines	
Structures[a]		Binding[b]	Transactivation[c]		Binding[b]	Transactivation[c]
R	no.	PPARγ pK_i	PPARγ pEC_{50}	no.	PPARγ pK_i	PPARγ pEC_{50}
	ciglitazone	5.51 ± 0.09 (3)	4.64 ± 0.30 (3)	**15**	7.29 ± 0.03 (3)	6.21 ± 0.20 (5)
	pioglitazone	5.91 ± 0.02 (3)	6.23 ± 0.05 (3)	**16**	8.19 ± 0.03 (3)	7.30 ± 0.17 (5)
	troglitazone	6.52 ± 0.06 (3)	6.27 ± 0.18 (3)	**17**	8.28 ± 0.03 (3)	8.04 ± 0.11 (5)
	rosiglitazone	7.33 ± 0.02 (12)	7.05 ± 0.19 (14)	**18**	8.85 ± 0.02 (3)	8.04 ± 0.33 (7)
	BRL 48482	7.57 ± 0.03 (3)	7.95 ± 0.39 (10)	**19**	8.83 ± 0.05 (3)	8.58 ± 0.39 (8)
	AD-7057	8.37 ± 0.04 (3)	8.50 ± 0.58 (5)	**20**	8.94 ± 0.13 (8)	9.47 ± 0.44 (11)

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

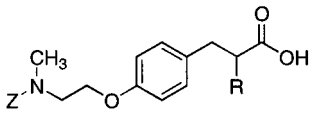
samples were obtained by cardiac puncture at days 0, 4, 7, and 14 and analyzed for plasma glucose, triglycerides (TGs), nonesterified free fatty acids (NEFAs), and insulin. A subset of mice was housed in metabolic cages to obtain baseline food and water consumption, body weight changes, and urine glucose and output. Values in Table 6 represent percent reduction from vehicle control animals at day 14, with the exception of body weight which is represented as a percent increase over vehicle controls.

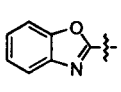
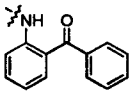
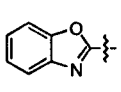
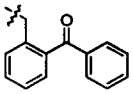
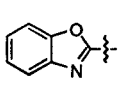
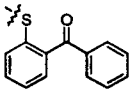
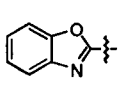
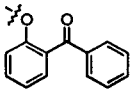
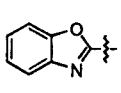
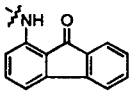
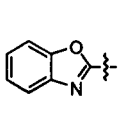
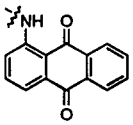
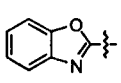
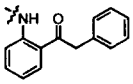
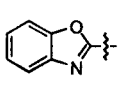
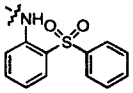
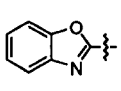
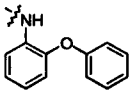
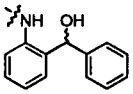
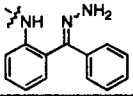
ZDF Rats. Male Zucker diabetic fatty (ZDF) rats at $8^1/_2$ weeks of age ($n = 6$/group) were baseline-matched for plasma glucose, and test compound was administered bid for 14 days by oral gavage. Blood samples were obtained by cardiac puncture at days 0, 4, 7, and 14 and analyzed for plasma glucose, glycosylated hemoglobin (HbA_{1c}), which is a surrogate marker for overall glycemic control, triglycerides (TGs), and nonesterified free fatty acids (NEFAs). Values in Table 7 represent percent reduction from vehicle control animals at day 14.

Results and Discussion

In general, structure−activity relationships were developed and pursued based primarily on binding affinity to PPARγ rather than on the cell-based functional assays (transactivation and lipogenesis). Interpretation of the latter assays can be complicated by differences in the ability of a given compound to permeate cell walls. In addition, a number of factors are known to influence PPARγ activity besides ligand binding. These include phosphorylation of PPARγ[65] and the presence of coactivator or corepressor proteins.[66] It is not known how well the in vitro cell-based assays mimic the in vivo expression of these modifying conditions. Thus there may be a number of reasons why a molecule with good binding affinity may not have analogous potency in the functional assays; however, the converse is rare. To date we have identified no molecules that are substantially more potent in the functional assays than in the binding assay. The functional assays are, nevertheless, extremely important in choosing molecules for further progression to in vivo assays. In particular, in our hands, compounds which have good potency in the lipogenesis assay also have good antihyperglycemic and antihyperlipidemic activity in vivo in rodent models of type 2 diabetes. Since adipose tissue is the major site for PPARγ expression, it is not surprising that an assay based on preadipocyte differentiation to adipocytes, a process in which PPARγ plays a major role,[67] would have good predictive value for in vivo activity by PPARγ agonists.

Table 4. In Vitro Profile of PPARγ Agonists



	Structure[a]		Binding[b]	Transactivation[c]	Lipogenesis[d]
no.	Z	R	PPARγ pK_i	PPARγ pEC_{50}	PEC_{50}
19			8.83 ± 0.14 (2)	8.58 ± 0.39 (8)	8.36 ± 0.41 (4)
21			7.55 ± 0.08 (2)	6.78 ± 0.77 (5)	6.02 ± 0.14 (3)
22			7.48 ± 0.01 (2)	5.86 ± 0.42 (4)	5.87 ± 0.01 (2)
23			7.49 ± 0.01 (2)	6.03 ± 0.38 (4)	5.94 ± 0.01 (2)
24			7.07 ± 0.73 (5)	6.31 ± 0.19 6)	6.24 ± 0.02 (2)
25			8.29 ± 0.06 (2)	8.30 ± 0.27 (6)	NT
26			8.48 ± 0.10 (2)	7.54 ± 0.36 (5)	7.33 (1)
27			6.91 ± 0.05 (2)	5.74 ± 0.46 (4)	5.66 ± 0.01 (2)
28			8.43 ± 0.02 (2)	6.97 ± 0.43 (4)	6.33 ± 0.10 (2)
29			NT	6.35 ± 0.20 (5)	5.88 ± 0.03 (2)
30			6.79 (1)	6.07 ± 0.20 (2)	5.91 ± 0.02 (2)

[a] See figure. [b] pK_i, −log of the concentration of test compound required to achieve an apparent K_i value according to the equation $K_i = IC_{50}/(1 + [L]/K_d)$, where IC_{50} is the concentration of test compound required to inhibit 50% of the specific binding of the radioligand, [L] is the concentration of the radioligand used, and K_d is the dissociation constant for the radioligand at the receptor; NT, not tested. [c] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum alkaline phosphatase activity ± standard error (number of determinations). [d] pEC_{50}, −log of the concentration of test compound required to induce 50% of the maximum lipogenic activity ± standard error (number of determinations); NT, not tested.

Our goal was to develop a potent (<10 nM), subtype-selective (>1000-fold) PPARγ agonist which (a) did not contain the 2,4-thiazolidinedione moiety, (b) either was achiral or could be prepared easily in chiral nonracemic fashion, and (c) displayed both antihyperglycemic and antihyperlipidemic activity in an established animal model of type 2 diabetes when dosed orally. A number of approaches toward finding an appropriate bioisostere

Table 5. In Vitro Profile of PPARγ Agonists **18**−**20**

	Binding[a]			Transactivation[b]					
no.	PPARγ pK_i	PPARα pK_i	PPARδ pK_i	hPPARγ pEC_{50}	hPPARα pEC_{50}	hPPARδ pEC_{50}	mPPARγ pEC_{50}	mPPARα pEC_{50}	mPPARδ pEC_{50}
18	8.84 ± 0.09 (2)	<5.5 (2)	6.15 ± 0.05 (2)	8.04 ± 0.33 (7)	IA	IA	7.88 ± 0.10 (2)	IA	IA
19	8.83 ± 0.14 (2)	5.92 ± 0.40 (2)	6.80 ± 0.00 (2)	8.58 ± 0.39 (8)	5.19 ± 0.60 (6)	IA	8.33 ± 0.07 (2)	IA	IA
20	8.94 ± 0.13 (8)	6.31 ± 0.02 (4)	6.07 ± 0.12 (3)	9.47 ± 0.44 (11)	6.34 ± 0.10 (7)	IA	9.45 ± 0.01 (2)	IA	IA

[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); IA, inactive at 10^{-4} M.

Table 6. In Vivo Activity of PPARγ Agonists **18**−**20** in db/db Mice

	Antihyperglycemic activity[a]	Antihyperlipidemic activity[b]		
no.	Plasma Glucose (% reduction)	Triglycerides (% reduction)	NEFAs (% reduction)	Body weight[c] (% increase)
18	58 ± 5	61 ± 4	46 ± 13	6 ± 3
19	41 ± 11	36 ± 9	38 ± 7	9 ± 1
20	65 ± 3	54 ± 8	56 ± 16	17 ± 2

[a] Antihyperglycemic activity of test compound dosed at 5 mg/kg bid via oral gavage for 14 days; values represent percent reduction as compared to vehicle control group on day 14, ± standard error. [b] Antihyperlipidemic activity of test compound dosed at 5 mg/kg bid via oral gavage for 14 days; values represent percent reduction as compared to vehicle control group on day 14, ± standard error. [c] Values represent percent body weight increase of drug-treated animals as compared to vehicle control group on day 14.

for the 2,4-thiazolidinedione ring have been described which have met with varying degrees of success,[68−72] and several suitable replacements have been reported.[73−75] We opted to "mine" the Glaxo Wellcome database in an attempt to identify a structurally novel PPARγ agonist which did not contain the 2,4-thiazolidinedione ring. Since PPARγ belongs to the steroid/thyroid family of nuclear receptors, we selected a subset of compounds from the database which contained the general size, shape, hydrophobicity, and hydrogen-bonding characteristics found in known steroid/thyroid ligands and screened them for in vitro activity. Compound **1** (Chart 1) emerged as the most chemically tractable from a set of several structurally novel agonists having micromolar potency at human PPARγ. Replacement of the L-phenylalanine in **1** with *O*-benzyl-L-tyrosine afforded compound **2** (Table 1) which displayed submicromolar (pK_i = 7.93, pEC_{50} = 6.64) potency at PPARγ in both binding and functional assays. Continuous iv infusion of **2** in glucose-matched 9-week old ZDF rats for 5 days (C_{ss} = 5 μM) produced a 46% decrease in postprandial plasma glucose levels compared to vehicle controls. In addition, the serum levels of triglycerides (TGs) and free fatty acids (FFAs) were significantly decreased in the treated animals as compared to vehicle controls. Having established that a compound selected solely on the basis of interaction with the PPARγ receptor in vitro displays antidiabetic activity in vivo, we began to explore the SAR around compound **2**.

We briefly explored the region around the phenyl enaminone and carboxylic acid moieties. Conversion of the carboxylic acid of **2** to either the primary amide **3** or the methyl ester **4** led to a considerable drop in binding affinity for the PPARγ receptor (Table 1). Only a small decrease in potency of activation in the transactivation assay was observed for both **3** and **4**; however, we believe the apparent discrepancy is due to conversion of both the ester and amide to **2** via cellular enzymes during the incubation time of the assay. Replacement of phenyl with methyl (compound **5**, Table 1) led to 100-fold loss in binding affinity and a compound which had no measurable agonist activity at concentrations up to 10 μM. Removal of the phenyl enaminone altogether to afford *O*-benzyltyrosine **6** also led to a complete abolishment of receptor affinity and activity. Finally, *ent*-**2** was only marginally active, suggesting that compounds with the (*S*)-configuration, derived from naturally occurring L-tyrosine, are more active at the PPARγ receptor. This result is in agreement with data published on a series of antidiabetic α-alkoxy- and α-thiophenylpropanoic acids in which both in vitro and in vivo activity was also shown to reside in the (*S*)-enantiomer.[74,76]

Despite the promising PPARγ activity of compound **2** and the ease in which analogues could be synthesized, this compound unfortunately suffered from poor pharmacokinetic properties. Oral administration of compound **2** in CD rats (5 mg/kg, n = 4) resulted in both low bioavailability (%F = 10%) and a short half-life ($t_{1/2}$ = 2.3 h). In addition, **2** lacked in vivo efficacy in lowering glucose and lipids in the db/db mouse assay when dosed orally, in contrast to the results seen with iv dosing (vide supra). We felt that the most plausible reason for the poor pharmacokinetics surrounding **2** was the potential lability of the enaminone moiety. Systematic structure−stability studies of enaminones suggest that these compounds are readily cleaved in acid.[77] Indeed, the enaminone moiety has been used as an acid-removable protecting group in peptide synthesis. The lability of this group might also explain the 20-fold loss in potency of **2** in the transactivation assay versus the binding assay (Table 1), as the transactivation assay requires extended incubation times in cell culture. We thus concentrated on analogues which would either stabilize or provide a suitable replacement for the enaminone moiety of **2**. Ring-constrained analogue **7** (Table 1) was completely inactive at the PPARγ receptor. The 2-benzoylcyclohexenyl derivative **8**, although approximately 70-fold less potent than **2**, still displayed weak agonist activity and offered hope that the steric environment around the enaminone was not too restric-

tive. Replacement of the cyclohexenyl ring of **8** with phenyl afforded benzophenone **9**, which was roughly equipotent to **8**. However, benzophenone **9** no longer contained the acid-labile vinylogous amide moiety and represented a chemically stable alternative to the enaminone **2**.

A brief investigation into the structure−activity relationships of the benzophenone revealed that this moiety is fairly sensitive to structural changes. Removal of the ketone to afford compound **10** abolished all activity at PPARγ. Replacement of the phenyl ketone portion with either a phenyl amide (**11**) or a benzyl ester (**12**) also resulted in a loss of activity. In addition, the ortho orientation between the amine and ketone is important, as the corresponding *m*- and *p*-aminobenzophenones (**13** and **14**, Table 1) show reduced activity at PPARγ.

Having established compound **9** as a chemically stable alternative to **2**, we began to explore the "left-hand" portion of the molecule in an attempt to regain both the affinity and functional potency at PPARγ. We postulated that if the carboxylic acid moiety of **9** mimicked the 2,4-thiazolidinedione moiety of the glitazones, then the most expedient method for improving potency would be to replace the benzyl group of **9** with "left-hand" groups known to confer potency in the TZDs. Using this strategy a rapid improvement in potency at PPARγ was realized (Table 2). Replacement of the benzyl moiety with the "left-hand" portion of ciglitazone (compound **15**) resulted in a 50-fold improvement in functional potency at PPARγ and a modest improvement in binding affinity over **9**. Further increases in PPARγ potency and affinity were realized upon replacement of the benzyl moiety with the "left-hand" portions of pioglitazone (**16**), troglitazone (**17**), rosiglitazone (**18**), and BRL 48482 (**19**), affording compounds with binding pK_i and functional pEC_{50} values > 7.3. The "left-hand" group which proved to be the most potent was the 2-(5-methyl-2-phenyloxazol-4-yl)ethyl side chain first employed by Takeda.[78] Incorporation of this side chain onto the *N*-(2-benzoylphenyl)tyrosine framework afforded compound **20**, which displayed low-nanomolar binding to PPARγ and subnanomolar in vitro functional potency. As in the *O*-benzyl enaminone series, the enantiomer derived from L-tyrosine was considerably more potent than its antipode (compare entries **18** and *ent*-**18**). All the analogues in Table 2 were at least 500-fold selective for PPARγ over PPARα in both receptor affinity and in vitro functional agonism (Table 5, data not shown), and none of the compounds in Table 2 showed activity at PPARδ at concentrations up to 10 μM (data not shown). It was also reassuring to note that the rank order of potency in this series of compounds was maintained across the binding and transactivation assays, suggesting that this class of compounds has good cell permeability.

A comparison of the in vitro binding and functional potency of the *N*-(2-benzoylphenyl)tyrosine analogues found in Table 2 along with their corresponding thiazolidinediones is found in Table 3. Several interesting trends emerge from examination of these data. First, our *N*-(2-benzoylphenyl)tyrosine analogues show 5−600-fold greater affinity for hPPARγ than the corresponding thiazolidinediones. This trend also holds true for PPARγ functional potency, as the *N*-(2-benzoylphenyl)-tyrosine analogues are 5−50-fold more potent than their corresponding TZDs in the transactivation assay. These data suggest that the 2-benzoylphenylamino side chain is responsible for additional receptor interactions which the TZDs are unable to achieve. In addition, the rank order of potencies in both binding and transactivation assays conferred by a given "left-hand" is the same for both the TZDs and the *N*-(2-benzoylphenyl)tyrosine analogues. Ciglitazone, the least potent TZD, is also the least potent in our series, while the 2-(5-methyl-2-phenyloxazol-4-yl)ethyl side chain is the most potent in both series. This trend supports the hypothesis that the TZDs and our *N*-(2-benzoylphenyl)tyrosine series bind to the PPARγ receptor in a similar fashion.[79]

We selected the 2-aminobenzoxazole compound **19** as a template for exploring the SAR around the 2-aminobenzophenone portion of this series in greater detail. Replacement of the nitrogen atom with carbon, sulfur, or oxygen (Table 4, entries 1−4) led to a 10-fold decrease in affinity for PPARγ. An even greater decrease (>100 fold) in functional potency at PPARγ was observed in both the transactivation and lipogenesis assays, with the rank order of potency being N ≫ C > O > S. The origin of the difference between receptor affinity and functional potency of compounds **21**−**23** is unclear but may be due to poorer cellular uptake and/or increased metabolic lability of these analogues. Interestingly, conformational constraint of the benzophenone via the fluorenone derivative **24** led to roughly 100-fold decrease in both affinity and functional potency at PPARγ (Table 4, entry 1 versus 5), while constraint via the anthraquinone-type compound **25** afforded no loss of affinity or potency at PPARγ (Table 4, entry 1 versus 6). Insertion of a methylene unit between the distal phenyl ring and the carbonyl group afforded compound **26** which was 10-fold less potent than **19** in both functional assays, despite showing similar affinity for the PPARγ receptor. Finally, a short series of replacements for the carbonyl were explored (Table 4, entries 8−11). Replacement of the carbonyl with a sulfone, ether linkage, hydrazone, or carbinol all led to at least a 50-fold decrease in both functional potency and binding affinity versus the corresponding carbonyl analogues **18** and **19**.

The data in Tables 1 and 4 suggest that the pocket of the PPARγ protein which binds the 2-aminobenzophenone is fairly intolerant of stereoelectronic perturbations away from the parent 2-aminobenzophenone. We believe the amine and ketone moieties of the aminobenzophenone engage in both a critical internal hydrogen bond and additional hydrogen bond(s) with residues in the protein which help place the benzophenone phenyl rings in an optimal position within the binding pocket.

To evaluate receptor subtype selectivity of the tyrosine series, the most potent PPARγ agonists (analogues **18**−**20**) were tested for functional activity at the three human and murine PPAR subtypes as well as for binding affinity to PPARα and PPARδ. The data are shown in Table 5. All three compounds displayed at least 100-fold binding selectivity for PPARγ versus PPARα and PPARδ. Compound **19** showed the highest binding affinity for PPARδ of the three, while compound **20** displayed the most affinity for PPARα. All three compounds displayed almost identical functional po-

Table 7. In Vivo Activity of PPARγ Agonists **18** and **20** in Zucker Diabetic Fatty Rats

	Antihyperglycemic activity[a]		Antihyperlipidemic activity[b]	
no.	Plasma Glucose (% reduction)	HbA_{1C} (% reduction)	Triglycerides (% reduction)	NEFAs (% reduction)
troglitazone	61 ± 9	29 ± 4	87 ± 2	81 ± 2
18	68 ± 5	37 ± 2	87 ± 6	73 ± 2
20	65 ± 5	33 ± 4	77 ± 5	75 ± 4

[a] Antihyperglycemic activity of the maximum dose of test compound (5 mg/kg for **18** and **20**; 500 mg/kg for troglitazone) given bid via oral gavage for 14 days; values represent percent reduction as compared to vehicle control group on day 14, ± standard error. [b] Antihyperlipidemic activity of the maximum dose of test compound (5 mg/kg for **18** and **20**; 500 mg/kg for troglitazone) given bid via oral gavage for 14 days; values represent percent reduction as compared to vehicle control group on day 14, ± standard error.

tency at the murine PPARγ receptor versus the human PPARγ receptor, which is not surprising in view of the high degree of sequence homology between the two receptors.[18] In addition, all three compounds were functionally inactive against the murine PPARα and PPARδ receptors as well as human PPARδ at concentrations up to 10 μM. Compound **18** also was inactive at human PPARα; however, analogues **19** and **20** displayed weak affinity and activity at human PPARα. The origin of the observed potency difference of our analogues at murine versus human PPARα is unclear. The human and murine PPARα receptors show a lower degree of sequence homology within the ligand binding domain as compared to PPARγ, and key difference(s) in the amino acid sequence could be responsible for changing the promiscuity in the binding pocket of the receptor. However, differences in phosphorylation states and/or corepressor and coactivator proteins cannot be ruled out (vide supra). Nevertheless, it is noteworthy that **19** and **20** show greater than 1000-fold functional selectivity for PPARγ over PPARα and PPARδ.

On the basis of their in vitro PPARγ potency and selectivity, compounds **18**−**20** were evaluated for in vivo antihyperglycemic and antihyperlipidemic efficacy in the db/db mouse. The results are displayed in Table 6. Both **18** and **20** showed a marked ability to lower plasma glucose, serum triglycerides, and nonesterified free fatty acids (NEFAs) when dosed orally at 5 mg/kg bid for 14 days. Compound **19** was less efficacious in all respects than **18** and **20** at the same dose. Since **19** displayed comparable in vitro potency to **18** and **20**, the relatively poor in vivo efficacy is most likely due to suboptimal pharmacokinetics of this compound. All three compounds caused statistically significant weight gain despite showing no increase in food consumption (data not shown). This increase in weight mirrors that seen with insulin in rodent models of diabetes and correlates with the amelioration of glycosuria and the diabetic state of the animals.[80] This effect may be model-specific, as no significant weight gain has been seen in human clinical trials with the TZD troglitazone.[81]

Compounds **18** and **20** were also evaluated for in vivo antihyperglycemic and antihyperlipidemic efficacy in the ZDF rat. Results are listed in Table 7. Troglitazone at doses of 50, 150, and 500 mg/kg was used for comparison in this assay. When dosed orally at 5 mg/kg bid, both **18** and **20** reduced postprandial plasma glucose to 30−40% of the vehicle animals after 14 days of administration. Glycosylated hemoglobin (HbA_{1c}) of the drug-treated animals was also significantly reduced compared to vehicle controls. Both compounds also had marked effects on serum triglycerides and NEFAs.

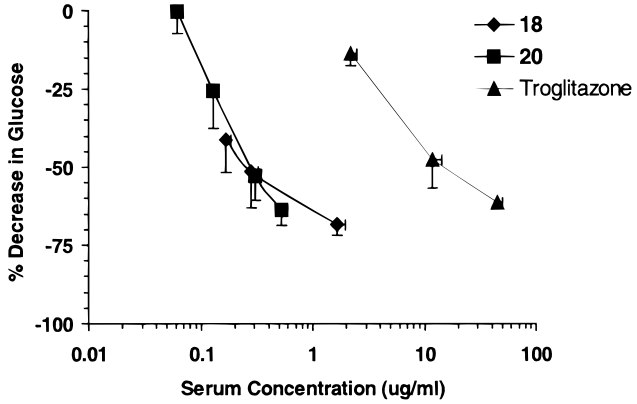


Figure 1. Plasma concentration−response curves for glucose lowering of compounds **18**, **20**, and troglitazone in Zucker diabetic fatty rats.

These compounds displayed efficacy similar to troglitazone dosed at 500 mg/kg. Figure 1 shows the plasma concentration−response curves for troglitazone and compounds **18** and **20**. Both **18** and **20** elicit glucose-lowering activity similar to troglitazone at plasma concentrations approximately 100-fold lower, which parallels their differences in binding and activation potencies at PPARγ. This provides further evidence that activity at PPARγ is a predictor of in vivo antihyperglycemic activity.[28]

Compounds **18** and **20** meet the criteria we initially outlined (vide supra) of being potent and selective PPARγ agonists which do not contain the 2,4-thiazolidinedione ring. These compounds are easily prepared in enantiomerically pure form via a convergent approach, using L-tyrosine as a commerically available source of chirality. Furthermore, the chemical structure of these compounds suggests that the facile racemization seen with the TZD class of agents is not likely to occur in this series. Data from our cell-based functional assays support this hypothesis. The marked difference in the functional potency of **18** and *ent*-**18** (Table 2) in both the transactivation and lipogenesis assays, which mirrors the difference in binding affinity, suggests these enantiomers do not racemize under the cell culture conditions of these assays. The in vivo chiral stability of these analogues will be reported elsewhere.

These *N*-(2-benzoylphenyl)tyrosine analogues represent a novel series of antidiabetic agents which were identified and optimized solely on the basis of in vitro potency at PPARγ. Concurrent with our work on this series, researchers at both Pfizer[74] and SmithKline Beecham[75] independently reported that α-heteroatom-substituted carboxylic acids function as effective replacements for the 2,4-thiazolidinedione. Although our series bears some structural resemblance to the afore-

mentioned series, it is worthwhile to note the contrast in the approaches taken to develop the respective series. Both the Pfizer and SmithKline groups sought specific replacements of the 2,4-thiazolidinedione moiety having already started with TZDs which displayed potent antidiabetic activity in vivo. Our approach utilized in vitro screening for a functional PPARγ agonist response to identify a novel isostere of the 2,4-thiazolidinedione ring first, and then potency was increased using the existing thiazolidinedione SAR. The in vivo activity of analogues **18** and **20** further supports the hypothesis that activation of PPARγ leads to potent antihyperglycemic and antihyperlipidemic effects in the diabetic state. Although the molecular target of these compounds has been identified, the downstream cellular mechanisms by which activation of PPARγ-regulated genes exert their antidiabetic effects remain to be discovered.[82]

Conclusion

We have identified a novel series of antidiabetic *N*-(2-benzoylphenyl)-L-tyrosine derivatives which are potent, selective PPARγ agonists. Starting from screening lead **1**, optimization of receptor potency and compound stability identified the 2-benzoylphenyl moiety as an optimal substituent on the tyrosine nitrogen. Compounds from this series show increased in vitro potency at PPARγ when compared to the corresponding thiazolidinedione antidiabetic agents, suggesting that the 2-benzoylphenylamino moiety occupies a previously undiscovered binding pocket in the PPARγ receptor. In addition, the β-phenylpropionic acid moiety functions as a suitable isosteric replacement for the benzyl 2,4-thiazolidinedione ring. Compounds **18** and **20** from this series are potent, efficacious antihyperglycemic and antihyperlipidemic agents when dosed orally in rodent models of type 2 diabetes. In addition, these analogues can be prepared in chiral nonracemic fashion from readily available L-tyrosine and do not show a propensity to undergo racemization in vitro. Additional structure−activity relationships of these *N*-(2-benzoylphenyl)-L-tyrosine antidiabetic agents are detailed in the following two papers. The increased potency of these PPARγ agonists versus the currently available TZDs may translate into superior clinical efficacy of these compounds for the treatment of type 2 diabetes, diabetic dyslipidemia, and cardiovascular risk management in diabetic patients.

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), 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, or 5% phosphomolybdic acid in 95% ethanol.

Final compounds were typically purified either by flash chromatography on silica gel (E. Merck, 40−63 mm) or by preparative reverse-phase high-pressure liquid chromatography (RP-HPLC) using a Waters model 3000 Delta Prep instrument equipped with a Delta-Pak radial compression cartridge (C-18, 300 A, 15 μm, 47 mm × 300 mm) as the stationary phase. The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier. Linear gradients were used in all cases, and the flow rate was 100 mL/min ($t_0 = 5$ min). Analytical purity was assessed by RP-HPLC using a Hewlett-Packard series 1050 system equipped with a diode array spectrometer (λ range 200−400 nm). The stationary phase was a Keystone Scientific BDS Hypersil C-18 column (5 μm, 4.6 mm × 200 mm). The mobile phase employed 0.1% aqueous TFA with acetonitrile as the organic modifier and a flow rate of 1.0 mL/min ($t_0 = 3$ min). Analytical data is reported as retention time, t_R, in minutes (% acetonitrile, time, flow rate).

^{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 for Formation of Vinylogous Amides 2, 3, 5, 7, and 8. A mixture of 1.0 equiv of *O*-benzyl-L-tyrosine (or the corresponding methyl ester or primary amide), 1.0 equiv of the requisite β-diketone, and 1.1 equiv of dicyclohexylamine were refluxed in methanol (solution concentration approximately 0.1 M) until the reaction was complete as judged by TLC (24−72 h). The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The crude reaction was purified either by trituration or by silica gel flash column chromatography.

3-(4-(Benzyloxy)phenyl)-(2*S*)-((1-methyl-3-oxo-3-phenylpropenyl)amino)propionic Acid (2). Trituration with cold (−20 °C) absolute ethanol three times yielded 7.60 g of a white solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.38 (d, 1 H, J = 8.9), 7.76 (d, 2 H, J = 5.8), 7.3 (m, 8 H), 7.09 (d, 2 H, J = 8.5), 6.84 (d, 2 H, J = 8.5), 5.53 (s, 1 H), 5.00 (s, 2 H), 4.02 (m, 1 H), 3.05 (dd, 1 H, J = 4.4, 12.9), 2.93 (m, 2 H), 2.76 (dd, 1 H, J = 8.4, 13.7), 1.92 (m, 4 H), 1.71 (s, 3 H), 1.66 (m, 4 H), 1.53 (d, 2 H, J = 12.7), 1.2 (m, 8 H), 1.03 m (2 H); low-resolution MS (FAB$^+$) *m/e* 597 (MH^+), 182 ($DCAH^+$). Anal. ($C_{26}H_{23}NO_4 \cdot (C_6H_{11})_2NH$) C, H, N.

2-Amino-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]-phenyl}propionic Acid Methyl Ester. To a stirred solution of 3.61 g (18.5 mmol) of (*S*)-tyrosine methyl ester and 0.81 g (20.4 mmol) of sodium hydride (60% suspension in mineral oil) in 50 mL of DMF at room temperature was added 5.0 g (18.5 mmol) of *N*-2-(*N*-methylaminoethyl 1-methylsulfonate)-1,3-benzoxazole.[41] The resulting solution was heated to 100 °C for 2 h. After cooling to room temperature, the solution was quenched with water and extracted with EtOAc. The combined organics were dried ($MgSO_4$) and solvent removed in vacuo. The residue was purified by silica gel chromatography using hexane/EtOAc (gradient of 3:7 to 0:1) as eluent to give 1.45 g (21% yield) of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, 1 H, J = 7.8), 7.18 (s, 1 H), 7.04 (m, 4 H), 6.76 (d, 2 H, J = 8.6), 4.18 (t, 2 H, J = 5.2), 3.88 (t, 2 H, J = 5.2), 3.64 (s, 3 H), 3.61 (m, 1 H), 3.29 (s, 3 H), 2.95 (m, 1 H), 2.74 (m, 1 H), 1.52 (bs, 2 H); low-resolution MS (ES$^+$) *m/e* 370 (MH^+); TLC (MeOH/EtOAc (1:9)) $R_f = 0.35$.

2-Diazo-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]-phenyl}propionic Acid Methyl Ester. *Safety note: Reaction was performed behind a blast shield.* To a stirred solution of 1.45 g of 2-amino-3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy]-phenyl}propionic acid methyl ester and 0.7 mL (11.8 mmol) of glacial acetic acid in 40 mL of chloroform was added 0.5

mL (3.93 mmol) of isoamyl nitrite. The resulting solution was heated to 60 °C for 0.25 h. The solution under went a color change to orange/brown after heating. The solution was cooled to room temperature, extracted with water, and then washed with a saturated solution of sodium bicarbonate. The organics were then dried ($MgSO_4$) and the solvent removed in vacuo to quantitatively yield the title compound which was used directly without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (d, 1 H, J = 7.7), 7.18 (s, 1 H), 7.08 (m, 3 H), 6.95 (m, 1 H), 6.77 (d, 2 H, J = 8.5), 4.18 (t, 2 H, J = 5.2), 3.88 (t, 2 H, J = 5.3), 3.71 (s, 3 H), 3.50 (s, 2 H), 3.28 (s, 3 H); TLC (EtOAc/hexane (3:7)) R_f = 0.23; low-resolution MS (ES^+) *m/e* 381 (MH^+), 353.

General Procedure for Diazo Insertion Reactions. *Safety note: This reaction should always be performed behind a blast shield.* To a stirred solution of 1.0 equiv (0.5−5 mmol) of the diazo ester and 1.1 equiv of the desired aniline in toluene at room temperature was added 5 mol % of rhodium(II) acetate dimer. The resulting greenish solution was stirred at room temperature for 15 min and then warmed to 80 °C until starting material was consumed as judged by TLC (1−12 h). The reaction was cooled to room temperature, and the solvent was removed in vacuo. The crude reaction was then purified by silica gel flash column chromatography.

3-(4-(Benzyloxy)phenyl)-2-((phenylcarbamoyl)phenylamino)propionic Acid Methyl Ester (11). Purification by flash chromatography using hexane/EtOAc (5:1) as eluent afforded 354 mg of the title compound: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (s, 1 H), 7.66 (d, 1 H, J = 7.9), 7.54 (d, 2 H, J = 8.0), 7.47 (d, 1 H, J = 7.9), 7.35 (m, 8 H), 7.13 (m, 3 H), 6.85 (d, 2 H, J = 8.6), 6.68 (t, 1 H, J = 7.5), 6.61 (d, 1 H, J = 8.4), 4.96 (s, 2 H), 4.30 (q, 1 H, J = 7.2), 3.64 (s, 3 H), 3.10 (m, 2 H); low-resolution MS (ES^+) *m/e* 481 (MH^+). Anal. ($C_{30}H_{27}N_2O_4 \cdot 0.7H_2O$) C, H, N.

(2*S*)-2-((2-Benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic Acid Methyl Ester (31). A stirred mixture of 92 g (0.45 mol) of 2-benzoylcyclohexanone,[51] 78 g (0.40 mol) of l-tyrosine methyl ester, and 17.0 g of palladium on activated carbon (10%) was refluxed for 2 h in 1 L of anisole while the resulting water was removed by a Dean−Stark apparatus. The mixture was cooled to 80 °C, and the Pd/C was filtered and washed with anisole (3 × 50 mL). The mixture was cooled to 40 °C; 1 L of hexane was added and the mixture kept at −20 °C for 48 h. The solid was filtered and washed with hexane (5 × 200 mL) to yield 89.0 g of crude (*S*)-2-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid methyl ester. This solid was mixed with 220 mL of methanol, and the slurry was refluxed for 30 min. The mixture was cooled to 0 °C; the product was filtered, washed with 50 mL of cold (−20 °C) methanol twice, and then dried under reduced pressure to yield 67.4 *g* the of the title compound: mp 185−6 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 9.27 (s, 1 H), 8.68 (d, 1 H, J = 7.8), 7.69−7.32 (m, 7 H), 7.00 (d, 2 H, J = 8.4), 6.82 (d, 1 H, J = 8.4), 6.65 (m, 3 H), 4.64 (m, 1 H), 3.67 (s, 3 H), 3.05 (m, 2 H); low-resolution MS (ES^+) *m/e* 376 (MH^+). Anal. ($C_{23}H_{21}NO_4$) C, H, N.

General Procedure for Mitsunobu Coupling with Phenol (31). A stirring solution of 1.0 equiv of (2*S*)-((2-benzoylphenyl)amino)-3-(4-hydroxyphenyl)propionic acid methyl ester, 1.1 equiv of the requisite alcohol, and 1.5 equiv of triphenylphosphine in THF (0.1 M total solution concentration) at room temperature was treated with 1.5 equiv of diethyl azodicarboxylate in 5−50 mL of THF via dropwise addition. The resulting solution was stirred for 6−18 h at room temperature, and then the solvent was removed in vacuo. The crude reaction mixture was purified as described below.

(2*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(*tert*-butoxycarbonyl)methylamino)ethoxy]phenyl}propionic Acid Methyl Ester. Purification by silica gel flash column chromatography using hexane/EtOAc (2:1) as eluent afforded 1.37 g (65%) of title compound as a viscous yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.91 (bs, 1 H), 7.59 (m, 2 H), 7.56−7.40 (m, 4 H), 7.33 (t, 1 H, J = 7.8), 7.19 (d, 2 H, J = 8.6), 6.81 (d, 2 H, J = 8.6), 6.63 (d, 1 H, J = 8.4), 6.58 (t, 1 H, J = 7.8), 4.37 (m, 1 H), 4.02 (m, 2 H), 3.70 (s, 3 H), 3.56 (m, 2 H), 3.16 (m, 2 H), 2.95 (s, 3 H), 1.44 (s, 9 H); low-resolution MS (ES^+) *m/e* 555 (MNa^+), 533 (MH^+); TLC (hexane/EtOAc (2:1)): R_f = 0.49. Anal. ($C_{31}H_{36}N_2O_6$) C, H, N.

(2*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid Methyl Ester. Purification by silica gel flash column chromatography using hexane/EtOAc (7:3): as eluent afforded 0.26 g (70%) of the title compound as a yellow foam: mp 55−60 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.66 (d, 1 H, J = 7.8), 7.91 (m, 2 H), 7.65−7.32 (m, 10 H), 7.12 (d, 2 H, J = 8.4), 6.84 (d, 3 H, J = 8.6), 6.64 (t, 1 H, J = 7.5), 4.68 (m, 1 H), 4.16 (t, 2 H, J = 6.7), 3.66 (s, 3 H), 3.11 (m, 2 H), 2.90 (t, 2 H, J = 6.6), 2.34 (s, 3 H); low-resolution MS (ES^+) *m/e* 561 (MH^+); TLC (hexane/EtOAc (7:3)) R_f = 0.50. Anal. ($C_{35}H_{32}N_2O_5 \cdot 0.2H_2O$) C, H, N.

2(*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl}propionic Acid Methyl Ester. A solution of 2.56 g (4.81 mmol) of 2(*S*)-((2-benzoylphenyl)-amino)-3-{4-[2-((*tert*-butoxycarbonyl)methylamino)ethoxy]-phenyl}propionic acid methyl ester in 56 mL of DCM at 25 °C was treated with 56 mL (0.73 mol, 152 equiv) of TFA. After stirring for 30 min, the solution was neutralized with saturated $NaHCO_3$ and extracted with DCM (2 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude amine was used immediately in the next reaction. A solution of 2.08 g (4.81 mmol) of the crude amine from above in 480 mL of 2-fluoropyridine was allowed to reflux for 16 h and then concentrated in vacuo. Purification by silica gel flash column chromatography using hexane/EtOAc (2:1) as eluent provided 1.85 g (76%) of the title compound as a yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1 H, J = 7.3), 8.14 (dd, 1 H, J = 1.6, 4.8), 7.59 (d, 2 H, J = 7.0), 7.45 (m, 5 H), 7.31 (dd, 1 H, J = 7.2, 7.2), 7.16 (d, 2 H, J = 8.6), 6.81 (d, 2 H, J = 8.6), 6.57 (m, 4 H), 4.37 (dd, 1 H, J = 6.0, 6.0), 4.14 (t, 2 H, J = 5.6), 3.95 (t, 2 H, J = 5.6), 3.68 (s, 3 H), 3.12 (m, 5 H); low-resolution MS (CI) *m/e* 511 (MH^+), 510 (M^+); TLC (hexane/EtOAc (2:1)) R_f = 0.40. Anal. ($C_{31}H_{31}N_3O_4$) C, H, N.

3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2(*S*)-((2-benzoylphenyl)amino)propionic Acid Methyl Ester. A solution of 319 mg (0.60 mmol) of 2(*S*)-((2-benzoylphenyl)amino)-3-{4-[2-((*tert*-butoxycarbonyl)methylamino)ethoxy]-phenyl}propionic acid methyl ester in 7 mL of DCM at 25 °C was treated with 7 mL (90.9 mmol, 152 equiv) of TFA. After stirring for 30 min, the solution was neutralized with saturated $NaHCO_3$ and extracted with DCM (2 × 50 mL). The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude amine was used immediately in the next reaction. To a solution of 259 mg (0.60 mmol) of the above amine in 6 mL of THF at 25 °C was added 0.250 mL (1.80 mmol, 3 equiv) of Et_3N followed by 0.103 mL (0.90 mmol, 1.5 equiv) of 2-chlorobenzoxazole. After stirring for 24 h, the reaction was diluted with EtOAc, poured into saturated $NaHCO_3$, and extracted with EtOAc. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by silica gel flash column chromatography eluting with hexane/EtOAc (2:1 to 1:1) provided 244 mg (74%) of the title compound as a yellow solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.88 (d, 1 H, J = 6.9), 7.62−7.55 (m, 2 H), 7.54−7.10 (m, 10 H), 7.00 (t, 1 H, J = 7.7), 6.81 (d, 2 H, J = 8.4), 6.62 (d, 1 H, J = 8.7), 6.57 (t, 1 H, J = 7.5), 4.37 (m, 1 H), 4.22 (t, 2 H, J = 5.2), 3.93 (t, 1 H, J = 5.2), 3.68 (s, 3 H), 3.33 (s, 3 H), 3.15 (m, 2 H); low-resolution MS (ES^+) *m/e* 572 (MNa^+), 550 (MH^+); TLC (hexane/EtOAc (2:1)) R_f = 0.24. Anal. ($C_{33}H_{31}N_3O_5$) C, H, N.

3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[(2-(benzoylphenyl)thio]propionic Acid Methyl Ester. To a solution of 360 mg (1.68 mmol) of 2-mercaptobenzophenone and 18-crown-6 (50 mg) in 5 mL of THF was added dropwise 1.55 mL (1.55 mmol) of 1.0 M potassium *tert*-butoxide in THF. After 5 min, the resulting red solution was concentrated by rotary evaporation to give a red foam which was redissolved in THF (5 mL). To this solution was added a solution of 560 mg (1.29 mmol) of 2-bromo-3-{4-[2-(benzoxazol-

2-ylmethylamino)ethoxy]phenyl}propionic acid methyl ester[57] in 2 mL of THF. The resulting orange solution was stirred for 3 h at room temperature and then diluted with EtOAc (75 mL). This mixture was washed with 2.0 M NaOH (4 × 25 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated to a brown oil. This material was flash chromatographed on silica gel (75 g) and the product eluted with hexane/EtOAc (2:1) to afford 600 mg of the title compound as a white foam: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 2 H, J = 7.2), 7.56 (t, 2 H, J = 6.8), 7.45−7.35 (m, 6 H), 7.16 (t, 1 H, J = 7.6), 7.00 (m, 3 H), 6.74 (d, 2 H, J = 8.6), 4.21 (t, 2 H, J = 5.3), 3.93 (t, 2 H, J = 5.1), 3.83 (dd, 1 H, J = 9.7, 6.0), 3.52 (s, 3 H), 3.34 (s, 3 H), 3.01 (dd, 1 H, J = 9.9, 14.1), 2.86 (dd, 1 H, J = 6.0, 13.8); low-resolution MS (ES$^+$) *m/e* 567 (MH$^+$).

3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-[(2-benzoylphenyl)methyl]propionic Acid Methyl Ester. To a solution of 1.56 g (4.42 mmol) of 3-{4-[2-(benzoxazol-2-ylmethylamino)ethoxy}phenyl}propionic acid methyl ester in 75 mL of THF maintained at −78 °C was added dropwise 6.62 mL of 1.0 M sodium hexamethyldisilazide in THF. The resulting pale-yellow solution was stirred at −78 °C for 90 min, and then 1.97 g (6.62 mmol) of 2-iodobenzyl bromide was added. The solution was stirred for an additional 90 min at −78 °C and was then quenched by the addition of saturated NH_4Cl (50 mL). This mixture was warmed to room temperature and extracted with EtOAc (200 mL). This extract was washed with saturated NH_4Cl and brine (50 mL each), dried over $MgSO_4$, and concentrated to a pale-yellow oil which was flash chromatographed on silica gel. The product 2-(2-iodobenzyl)propionic acid methyl ester was eluted with hexane/EtOAc (3:1) and isolated as a colorless oil (0.48 g, 19%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, 1 H, J = 7.9), 7.36 (d, 1 H, J = 7.7), 7.24−7.14 (m, 4 H), 7.08 (d, 2 H, J = 8.5), 7.00 (t, 1 H, J = 7.7), 6.88 (t, 1 H, J = 7.7), 6.80 (d, 2 H, J = 7.7), 4.23 (t, 2 H, J = 5.3), 3.94 (t, 2 H, J = 5.2), 3.46 (s, 3 H), 3.34 (s, 3 H), 3.04−2.76 (m, 5 H); low-resolution MS (ES$^+$) *m/e* 571 (MH$^+$).

A solution of the above iodide (213 mg, 0.37 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.011 mmol), phenylboronic acid (50 mg, 0.41 mmol), and K_2CO_3 (153 mg, 1.12 mmol) in 8 mL of 1,4-dioxane was warmed to 95 °C and stirred under 1 atm of CO(g) for 22 h. The resulting tan suspension was diluted with EtOAc (75 mL), washed with water (10 mL) and brine (20 mL, 2×), dried over $MgSO_4$, and concentrated to a yellow oil which was flash chromatographed on silica gel eluted with hexane/EtOAc (7:3) to afford 144 mg of the title compound as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2 H, J = 7.20), 7.56 (t, 1 H, J = 7.8), 7.45−7.24 (m, 8 H), 7.16 (t, 1 H, J = 7.6), 7.00 (t, 1 H, J = 7.7), 6.94 (d, 2 H, J = 8.6), 6.72 (d, 2 H, J = 8.6), 4.21 (t, 2 H, J = 5.3), 3.93 (t, 2 H, J = 5.2), 3.39 (s, 3 H), 3.34 (s, 3H), 2.95 (m, 3 H), 2.82 (dd, 1 H, J = 8.0,13.9), 2.66 (dd, 1 H, J = 5.4,13.8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.22, 175.23, 162.45, 156.95, 149.00, 143.42, 138.52, 138.46, 137.75, 133.19, 131.36, 130.78, 130.35, 130.25, 129.84, 129.16, 128.40, 125.89, 123.96, 120.36, 116.08, 114.28, 108.71, 66.11, 51.3, 50.06, 49.73, 37.82, 37.38, 35.70; low-resolution MS (ES$^+$) *m/e* 549 (MH$^+$).

General Procedure for Ester Hydrolysis To Form Compounds 9, 10, and 13−27. A stirred solution of 1.0 equiv of the appropriate methyl ester in THF/MeOH (3:1) was treated with 1.5 equiv of a 1.0 M solution of LiOH in H_2O. The resulting solution was stirred at room temperature until reaction was complete as judged by TLC (4−24 h). The reaction mixture was then poured into 1 N HCl and extracted with EtOAc. The organic layer was separated and dried ($MgSO_4$), and the solvents were removed in vacuo. The crude reaction was then purified as outlined below.

2-((2-Benzoylphenyl)amino)-3-(4-(benzyloxy)phenyl)-propionic acid (9). Purification by silica gel flash column chromatography using DCM/MeOH (9:1) afforded 133 mg of the title compound: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.87 (bs, 1 H), 7.60 (d, 2 H, J = 6.0), 7.94−7.32 m (10 H), 7.23 (d, 2 H, J = 3.9), 6.90 (m, 2 H), 6.67−6.56 (m, 2 H), 4.98 (s, 2 H), 4.39 (m, 1 H), 3.30−3.10 (m, 2 H); low-resolution MS (FAB$^+$) *m/e* 452 (MH$^+$). Anal. ($C_{29}H_{25}NO_4$) C, H, N.

(2*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl}propionic Acid (18). Trituration of the crude reaction mixture with EtOAc followed by filtration and drying gave 1.24 g of the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.04 (s, 1 H), 8.71 (d, 1 H, J = 7.5), 8.11 (dd, 1 H, J = 1.2, 5.1), 7.69−7.52 (m, 6 H), 7.48 (t, 1 H, J = 7.8), 7.41 (dd, 1 H, J = 1.8, 8.0), 7.15 (d, 2 H, J = 8.7), 7.73−6.81 (m, 3 H), 6.75 (d, 1 H, J = 8.7), 6.71−6.60 (m, 2 H), 4.59 (m, 1 H), 4.12 (t, 2 H, J = 5.9), 3.93 (t, 2 H, J = 5.9), 3.15 (m, 2 H), 3.11 (s, 3 H); low-resolution MS (CI) *m/e* 518 (MNa$^+$), 496 (MH$^+$); TLC (EtOAc/AcOH (99:1)) R_f = 0.13; SFC (Chiralpak AD, 4.6 mm × 25 cm; 75% CO_2/25% MeOH with 0.1% DEA; 35 min; 1 mL/min; 3000 psi, 40 °C) t_R = 24.3 min (t_0= 3 min); >99% ee. Anal. ($C_{30}H_{29}N_3O_4\cdot 0.8H_2O$) C, H, N.

3-{4-[2-(Benzoxazol-2-ylmethylamino)ethoxy]phenyl}-(2*S*)-((2-benzoylphenyl)amino)propionic Acid (19). Trituration of the crude reaction with Et_2O/hexane followed by filtration and drying provided 209 mg of the title compound as a yellow solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 13.1 (bs, 1 H), 8.71 (d, 1 H, J = 7.5), 7.68−7.36 (m, 8 H), 7.32 (d, 1 H, J = 7.2), 7.23−7.12 (m, 3 H), 7.03 (dt, 1 H, J = 2.1, 7.7), 6.92−6.82 (m, 3 H), 6.66 (t, 1 H, J = 7.5), 4.58 (m, 1 H), 4.23 (t, 2 H, J = 5.4), 3.91 (t, 2 H, J = 5.4), 3.25 (s, 3 H), 3.15 (m, 2 H); low-resolution MS (CI) *m/e* 558 (MNa$^+$), 536 (MH$^+$); TLC (EtOAc/MeOH (9:1)) R_f = 0.23; HPLC (Chiralcel OD-H, 4.6 mm × 25 cm; 23%EtOH/hexane/0.1%TFA; 45 min; 1 mL/min) t_R = 9.3 min (t_0= 3 min); >98% ee. Anal. ($C_{32}H_{29}N_3O_5\cdot 1.1H_2O$) C, H, N.

(2*S*)-((2-Benzoylphenyl)amino)-3-{4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]phenyl}propionic Acid (20). Trituration of the crude reaction with Et_2O/hexane followed by filtration and drying provided 202 mg of the title compound: mp 148−50 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 8.66 (d, 1 H, J = 7.8), 7.91 (m, 2 H), 7.64−7.33 (m, 10 H), 7.13 (d, 2 H, J = 8.3), 6.82 (m, 3 H), 6.62 (t, 1 H, J = 7.5), 4.54 (m, 1 H), 4.15 (t, 2 H, J = 6.5), 3.10 (m, 2 H), 2.90 (t, 2 H, J = 6.5), 2.34 (s, 3 H); low-resolution MS (ES$^+$) *m/e* 547 (MH$^+$); TLC (DCM/MeOH (95:5)) R_f = 0.49. Anal. ($C_{34}H_{30}N_2O_5\cdot 0.3H_2O$) C, H, N.

(2*S*)-3-{4-[2-(1,3-Benzoxazol-2-ylmethylamino)ethoxy]-phenyl}-2-(2-phenoxyanilino)propionic Acid Sodium Salt (28). A stirred solution of 210 mg (0.40 mmol) of (2*S*)-3-{4-[2-(1,3-benzoxazol-2-ylmethylamino)ethoxy]phenyl}-2-(2-phenoxyanilino)propionic acid methyl ester in 5 mL of THF was treated with 0.60 mL (0.60 mmol) of a 1.0 M solution of LiOH in H_2O. The resulting solution was stirred at room temperature for 17 h. The reaction mixture was then poured into 15 mL of 1 N HCl and extracted with EtOAc (2 × 15 mL). The organics were separated and dried ($MgSO_4$) and the solvents removed in vacuo. The resulting tan foam was dissolved in 2 mL of dry methanol, and 1 equiv of NaH was added. The resulting solution was stirred at room temperature for 1 h; then the solvent was removed in vacuo. Purification of the residue by trituration with ether/DCM (1:1) followed by filtration and drying (house vacuum, 50 °C) afforded 170 mg of the sodium salt of the title compound as a white solid: mp 210−4 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.37 (d, 1 H, J = 7.9), 7.12 (dd, 1 H, J = 7.5, 7.5), 7.00−6.89 (m, 5 H), 6.79 (d, 2 H, J = 8.0), 6.69 (d, 1 H, J = 7.1), 6.61 (d, 2 H, J = 8.6), 6.50 (d, 1 H, J = 8.0), 6.42 (dd, 1 H, J = 7.7, 7.7), 5.42 (d, 1 H, J = 5.7), 4.12 (t, 2 H, J = 5.4), 3.83 (t, 2 H, J = 5.4), 3.64 (m, 1 H), 3.19 (s, 3 H), 2.98 (dd, 1H, J = 5.1, 14.5), 2.86 (dd, 1 H, J = 4.6, 14.5); low-resolution MS (ES$^+$) *m/e* 569 (MNa$^+$), 546 (M$^+$). Anal. ($C_{31}H_{28}N_3O_5Na\cdot 2.0H_2O$) C, H, N.

(2*S*)-2-[2-(Hydroxyphenylmethyl)anilino]-3-{4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl}propionic Acid (29). To a stirred solution of 5 mg (0.13 mmol) of $NaBH_4$ in 1 mL of absolute ethanol was added 50 mg (0.10 mmol) of **18** in 1 mL of absolute ethanol. The resulting solution was stirred 30 min at room temperature, then an additional 5 mg $NaBH_4$ was added, and the solution was stirred an additional 30 min. The reaction was quenched by addition of 0.1 N HCl and then

poured into brine (15 mL) and extracted with EtOAc (2 × 15 mL). The organic layers were combined and dried ($MgSO_4$), and solvent was removed in vacuo. Purification of the cream-colored foam via silica gel flash column chromatography using $CHCl_3$/MeOH (9:1) as eluent afforded 25 mg of the title compound as a pale-yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.06 (d, 1 H, J = 3.3), 7.46 (m, 1 H), 7.28 (d, 2 H, J = 7.3), 7.21 (dd, 2 H, J = 7.1, 7.1), 7.12 (m, 1 H), 7.02 (d, 1 H, J = 7.1), 6.92 (m, 3 H), 6.64 (m, 3 H), 6.54 (dd, 1 H, J = 5.0, 6.8), 6.46 (dd, 1 H, J = 7.3, 7.3), 6.40 (d, 1 H, J = 8.0), 5.58 (s, 1 H), 4.04 (t, 2 H, J = 6.0), 3.86 (t, 2 H, J = 6.0), 3.72 (m, 1 H), 3.05 (s, 3 H), 2.90 (dd, 1 H, J = 4.8, 13.5), 2.69 (m, 1 H); low-resolution MS (ES) *m/e* 499 (MH^+), 498 (M^+), 481, 480, 436. Anal. ($C_{30}H_{31}N_3O_4$·HCl) C, H, N.

(2*S*)-2-[2-(Hydrazonophenylmethyl)anilino]-3-{4-[2-(methylpyridin-2-ylamino)ethoxy]phenyl}propionic Acid (30). A solution of 150 mg (0.30 mmol) of **18** in 5 mL of anhydrous hydrazine was heated to 80 °C for 9 h. The reaction was then cooled to room temperature, poured into EtOAc/water, and acidified to pH 2 by addition of 1 N HCl. The layers were separated; then the aqueous layer was adjusted to pH 6 by addition of aqueous $NaHCO_3$. The aqueous layer was extracted with DCM (2 × 15 mL). The organics were dried ($MgSO_4$), and the DCM was removed in vacuo to afford a tan solid. Purification via trituration with ether/hexane (1:1) afforded 48 mg of a cream-colored solid: ^{1}H NMR (DMSO-d_6, 400 MHz, 1:1 mixture of hydrazone isomers) δ 8.94 (d, 0.5 H, J = 7.4), 8.06 (m, 1 H), 7.55−7.45 (m, 2 H), 7.32−7.10 (m, 5 H), 7.03−6.23 (m, 12.5 H), 5.87 (m, br, 0.5 H), 4.28 (m, 1 H), 4.17 (m, 0.5 H), 4.05 (m, 1.5 H), 3.95 (m, 0.5 H), 3.86 (m, 2 H), 3.10−2.82 (m, 5 H); low-resolution MS (ES^+) *m/e* 511 (MH^+), 510 (M^+). Anal. ($C_{30}H_{31}N_5O_3$) C, H, N.

Acknowledgment. We gratefully acknowledge Roderick Davis, Doug Minick, Peter Kitrinos, Larry Shampine, and Manon Villeneuve for analytical support. We also thank Thomas Consler and Bruce Wisely for PPAR protein expression and purification.

Supporting Information Available: Table of physical data for compounds **2**−**30** and experimental data for all compounds which were not included in the Experimental Section (13 pages). Ordering information is given on any current masthead page.

References

(1) Greene, M. E.; Blumberg, B.; McBride, O. W.; Yi, H. F.; Kronquist, K.; Kwan, K.; Hsieh, L.; Greene, G.; Nimer, S. D. Isolation of the human peroxisome proliferator activated receptor gamma cDNA: expression in hematopoietic cells and chromosomal mapping. *Gene Express.* **1995**, *4*, 281−99.

(2) Issemann, I.; Green, S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* **1990**, *347*, 645−50.

(3) Kliewer, S. A.; Forman, B. M.; Blumberg, B.; Ong, E. S.; Borgmeyer, U.; Mangelsdorf, D. J.; Umesono, K.; Evans, R. M. Differential expression and activation of a family of murine peroxisome proliferator-activated receptors. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 7355−9.

(4) Schmidt, A.; Endo, N.; Rutledge, S. J.; Vogel, R.; Shinar, D.; Rodan, G. A. Identification of a new member of the steroid hormone receptor superfamily that is activated by a peroxisome proliferator and fatty acids. *Mol. Endocrinol.* **1992**, *6*, 1634−41.

(5) Zhu, Y.; Alvares, K.; Huang, Q.; Rao, M. S.; Reddy, J. K. Cloning of a new member of the peroxisome proliferator-activated receptor gene family from mouse liver. *J. Biol. Chem.* **1993**, *268*, 26817−20.

(6) Tontonoz, P.; Hu, E.; Graves, R. A.; Budavari, A. I.; Spiegelman, B. M. mPPARγ2: tissue-specific regulator of an adipocyte enhancer. *Genes Dev.* **1994**, *8*, 1224−34.

(7) Tontonoz, P.; Hu, E.; Devine, J.; Beale, E. G.; Spiegelman, B. M. PPAR-γ2 regulates adipose expression of the phosphoenolpyruvate carboxykinase gene. *Mol. Cell. Biol.* **1995**, *15*, 351−7.

(8) Schoonjans, K.; Watanabe, M.; Suzuki, H.; Mahfoudi, A.; Krey, G.; Wahli, W.; Grimaldi, P.; Staels, B.; Yamamoto, T.; Auwerx, J. Induction of the acyl-coenzyme A synthetase gene by fibrates and fatty acids is mediated by a peroxisome proliferator response element in the C promoter. *J. Biol. Chem.* **1995**, *270*, 19269−76.

(9) Schoonjans, K.; Peinado-Onsurbe, J.; Lefebvre, A.-M.; Heyman, R. A.; Briggs, M.; Deeb, S.; Staels, B.; Auwerx, J. PPARα and PPARγ activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J.* **1996**, *15*, 5336−48.

(10) Schoonjans, K.; Martin, G.; Staels, B.; Auwerx, J. Peroxisome proliferator-activated receptors, orphans with ligands and functions. *Curr. Opin. Lipidol.* **1997**, *8*, 159−66.

(11) Willson, T. M.; Wahli, W. Peroxisome proliferator-activated receptor agonists. *Curr. Opin. Chem. Biol.* **1997**, *1*, 235−41.

(12) Staels, B.; Schoonjans, K.; Fruchart, J. C.; Auwerx, J. The effects of fibrates and thiazolidinediones on plasma triglyceride metabolism are mediated by distinct peroxisome proliferator activated receptors (PPARs) *Biochimie* **1997**, *79*, 95−9.

(13) Mandrup, S.; Lane, M. D. Regulating adipogenesis. *J. Biol. Chem.* **1997**, *272*, 5367−70.

(14) Latruffe, N.; Vamecq, J. Peroxisome proliferators and peroxisome proliferator activated receptors (PPARs) as regulators of lipid metabolism. *Biochimie* **1997**, *79*, 81−94.

(15) Devchand, P. R.; Wahli, W. PPARα: tempting fate with fat. *Horm. Signaling* **1998**, *1*, 235−56.

(16) Chawla, A.; Schwarz, E. J.; Dimaculangan, D. D.; Lazar, M. A. Peroxisome proliferator-activated receptor (PPAR)γ: adipose-predominant expression and induction early in adipocyte differentiation. *Endocrinology* **1994**, *135*, 798−800.

(17) Tontonoz, P.; Hu, E.; Spiegelman, B. M. Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. *Cell* **1994**, *79*, 1147−56.

(18) Fajas, L.; Auboeuf, D.; Raspe, E.; Schoonjans, K.; Lefebvre, A.-M.; Saladin, R.; Najib, J.; Laville, M.; Fruchart, J.-C.; Deeb, S.; Vidal-Puig, A.; Flier, J.; Briggs, M. R.; Staels, B.; Vidal, H.; Auwerx, J. The organization, promoter analysis, and expression of the human PPARγ gene. *J. Biol. Chem.* **1997**, *272*, 18779−789.

(19) Xue, J.-C.; Schwarz, E. J.; Chawla, A.; Lazar, M. A. Distinct stages in adipogenesis revealed by retinoid inhibition of differentiation after induction of PPARγ. *Mol. Cell. Biol.* **1996**, *16*, 1567−75.

(20) Yu, K.; Bayona, W.; Kallne, C. B.; Harding, H. P.; Ravera, C. P.; McMahon, G.; Brown, M.; Lazar, M. A. Differential activation of peroxisome proliferator-activated receptors by eicosanoids. *J. Biol. Chem.* **1995**, *270*, 23975−83.

(21) Kliewer, S. A.; Lenhard, J. M.; Willson, T. M.; Patel, I.; Morris, D. C.; Lehmann, J. A prostaglandin J2 metabolite binds peroxisome proliferator-activated receptor γ and promotes adipocyte differentiation. *Cell* **1995**, *83*, 813−9.

(22) Forman, B. M.; Tontonoz, P.; Chen, J.; Brun, R. P.; Spiegelman, B. M.; Evans, R. M. 15-Deoxy-Δ12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ. *Cell* **1995**, *83*, 803−12.

(23) Krey, G.; Braissant, O.; L′Horset, F.; Kalkhoven, E.; Perroud, M.; Parker, M. G.; Wahli, W. Fatty acids eicosanoids, and hypolipidemic agents identified as ligands of peroxisome proliferator-activated receptors by coactivator-dependent receptor ligand assay. *Mol. Endocrinol.* **1997**, *11*, 779−91.

(24) Ricote, M.; Li, A. C.; Willson, T. M.; Kelly, C. J.; Glass, C. K. The peroxisome proliferator-activated receptor-γ is a negative regulator of macrophage activation. *Nature* **1998**, *391*, 79−82.

(25) Lehmann, J. M.; Moore, L. B.; Simth-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). *J. Biol. Chem.* **1995**, *270*, 12953−6.

(26) Lambe, K. G.; Tugwood, J. D. A human peroxisome-proliferator-activated receptor-γ is activated by inducers of adipogenesis, including thiazolidinedione drugs. *Eur. J. Biochem.* **1996**, *239*, 1−7.

(27) Berger, J.; Bailey, P.; Biswas, C.; Cullinan, C. A.; Doebber, T. W.; Hayes, N. S.; Saperstein, R.; Smith, R. G.; Leibowitz, M. D. Thiazolidinediones produce a conformational change in peroxisomal proliferator-activated receptor-γ: binding and activation correlate with antidiabetic actions in db/db mice. *Endocrinology* **1996**, *137*, 4189−95.

(28) Willson, T. M.; Cobb, J. E.; Cowan, D. J.; Wiethe, R. W.; Correa, I. D.; Prakash, S. R.; Beck, K. D.; Moore, L. B.; Kliewer, S. A.; Lehmann, J. M. The Structure−Activity Relationship between Peroxisome Proliferator-Activated Receptor γ. Agonism and the Anti-Hyperglycemic Activity of Thiazolidinediones. *J. Med. Chem.* **1996**, *39*, 665−8.

(29) Spencer, C. M.; Markham, A. Troglitazone. *Drugs* **1997**, *54*, 89−101.

(30) Grossman, S. L.; Lessem, J. Mechanisms and clinical effects of thiazolidinediones. *Exp. Opin. Invest. Drugs* **1997**, *6*, 1025−40.

(31) Leutenegger, M.; Sacca, L.; Alderton, C.; Eckland, D.; Lettis, S. Double-masked, placebo-controlled, dose-ranging study of troglitazone 10 to 200 mg once daily in non-insulin-dependent diabetes mellitus. *Curr. Ther. Res.* **1997**, *58*, 403−416.
(32) Levin, K.; Thye-Roenn, P.; Foot, E.; Beck-Nielsen, H. Metabolic effects of troglitazone in NIDDM patients. *Endocrinol. Metab.* **1997**, *4*, 255−64.
(33) Sironi, A. M.; Vichi, S.; Gastaldelli, A.; Pecori, N.; Anichini, R.; Foot, E.; Seghieri, G.; Ferrannini, E. Effects of troglitazone on insulin action and cardiovascular risk factors in patients with noninsulin-dependent diabetes. *Clin. Pharmacol. Ther.* **1997**, *62*, 194−202.
(34) Fujiwara, T.; Yoshioka, S.; Yoshioka, T.; Ushiyama, I.; Horikoshi, H. Characterization of new oral antidiabetic agent CS-045. Studies in KK and ob/ob mice and Zucker fatty rats. *Diabetes* **1988**, *37*, 1549−58.
(35) Chaiken, R. L.; Eckert-Norton, M.; Pasmantier, R.; Boden, G.; Ryan, I.; Gelfand, R. A.; Lebovitz, H. E. Metabolic effects of darglitazone, an insulin sensitizer, in NIDDM subjects. *Diabetologia* **1995**, *38*, 1307−12.
(36) Colca, J. R.; Morton, D. R. In *Antihyperglycemic thiazolidinediones: ciglitazone and its analogues*; Colca, J. R., Morton, D. R., Eds.; Smith-Gordon: New York, 1990; pp 255−261.
(37) Yoshioka, T.; Fujita, T.; Kanai, T.; Aizawa, Y.; Kurumada, T.; Hasegawa, K.; Horikoshi, H. Studies on hindered phenols and analogues. 1. Hypolipidemic and hypoglycemic agents with ability to inhibit lipid peroxidation. *J. Med. Chem.* **1989**, *32*, 421−8.
(38) Ikeda, H.; Taketomi, S.; Sugiyama, Y.; Shimura, Y.; Sohda, T.; Meguro, K.; Fujita, T. Effects of pioglitazone on glucose and lipid metabolism in normal and insulin resistant animals. *Arzneim.-Forsch.* **1990**, *40*, 156−62.
(39) Sohda, T.; Momose, Y.; Meguro, K.; Kawamatsu, Y.; Sugiyama, Y.; Ikeda, H. Studies on antidiabetic agents. Synthesis and hypoglycemic activity of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones. *Arzneim.-Forsch.* **1990**, *40*, 37−42.
(40) Momose, Y.; Meguro, K.; Ikeda, H.; Hatanaka, C.; Oi, S.; Sohda, T. Studies on antidiabetic agents. X. Synthesis and biological activities of pioglitazone and related compounds. *Chem. Pharm. Bull.* **1991**, *39*, 1440−5.
(41) Cantello, B. C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. [[ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **1994**, *37*, 3977−85.
(42) Cantello, B. C. C.; Cawthorne, M. A.; Haigh, D.; Hindley, R. M.; Smith, S. A.; Thurlby, P. The synthesis of BRL 49653 − a novel and potent antihyperglycemic agent. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1181−4.
(43) Horikoshi, H.; Yoshioka, T.; Kawasaki, T.; Nakamura, K.-i.; Matsunuma, N.; Yamaguchi, K.; Sasahara, K. Troglitazone (CS-045), a New Antidiabetic Drug. *Annu. Rep. Sankyo Res. Lab.* **1994**, *46*, 1−57.
(44) Fujiwara, T.; Yoshioka, S.; Yoshioka, T.; Ushiyama, I.; Horikoshi, H. Characterization of New Oral Antidiabetic Agent CS-045. *Diabetes* **1988**, *37*, 1549−58.
(45) Henry, R. R. Thiazolidinediones. *Endocrinol. Metab. Clin. North Am.* **1997**, *26*, 553−73.
(46) Sohda, T.; Mizuno, K.; Kawamatsu, Y. Studies on antidiabetic agents. VI. Asymmetric transformation of (±)-5-[4-(1-methylcyclohexylmethoxy)benzyl]-2,4-thiazolidinedione(ciglitazone) with optically active 1-phenylethylamines. *Chem. Pharm. Bull.* **1984**, *32*, 4460−5.
(47) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. The Enamine Alkylation and Acylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **1963**, *85*, 207−22.
(48) Westheimer, F. H.; Taguchi, K. Catalysis by molecular sieves in the preparation of ketimines and enamines. *J. Org. Chem.* **1971**, *36*, 1570−2.
(49) Adams, J.; Spero, D. M. Rhodium(II) catalyzed reactions of diazocarbonyl compounds. *Tetrahedron* **1991**, *47*, 1765−808.
(50) Kawamatsu, Y.; Asakawa, H.; Saraie, T.; Imamiya, E.; Nishikawa, K.; Hamuro, Y. Studies on antihyperlipidemic agents. II. Synthesis and biological activities of 2-chloro-3-arylpropionic acids. *Arzneim.-Forsch.* **1980**, *30*, 585−9.
(51) Denny, W. A.; Cain, B. F. Potential antitumor agents. 27. Quantitative structure-antileukemic (L1210) activity relationships for the ω[4-(9-acridinylamino)phenyl]alkanoic acids. *J. Med. Chem.* **1978**, *21*, 430−7.
(52) Hulin, B.; Clark, D. A.; Goldstein, S. W.; McDermott, R. E.; Dambek, P. J.; Kappeler, W. H.; Lamphere, C. H.; Lewis, D. M.; Rizzi, J. P. Novel thiazolidine-2,4-diones as potent euglycemic agents. *J. Med. Chem.* **1992**, *35*, 1853−64.
(53) Horner, M.; Nissen, A. 2-Hydroxyalkylchromans. Ger. Offen., 1981.
(54) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; et al. Enantioselective Intramolecular Cyclopropanations of Allylic and Homoallylic Diazoacetates and Diazoacetamides Using Chiral Dirhodium(II) Carboxamide Catalysts. *J. Am. Chem. Soc.* **1995**, *117*, 5763−75.
(55) Doyle, M. P.; Zhou, Q. L.; H., S. S.; Lynch, V. Dirhodium(II) tetrakis[alkyl 2-oxaazetidine-4(S)-carboxylates]. A new set of effective chiral catalysts for asymmetric intermolecular cyclopropanation reactions with diazoacetates. *Synlett* **1996**, 697−8.
(56) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. Intramolecular Regioselective Insertion into Unactivated Prochiral Carbon−Hydrogen Bonds with Diazoacetates of Primary Alcohols Catalyzed by Chiral Dirhodium(II) Carboxamidates. Highly Enantioselective Total Synthesis of Natural Lignan Lactones. *J. Org. Chem.* **1996**, *61*, 9146−55.
(57) Haigh, D. Heterocyclic compounds and their use in the treatment of type 2 diabetes. PCT Int. Appl., 1993.
(58) Brieaddy, L. E.; Donaldson, K. H. The synthesis of *cis*-6,12-diaryl-6H,12H-dibenzo[b,f][1,5]dithiocin-6,12-imine and *cis*-6,12-diphenyl-6,12-epoxy-6H,12H-dibenzo[b,f][1,5]dithiocin. *J. Heterocycl. Chem.* **1995**, *32*, 1683−6.
(59) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. Synthesis of unsymmetrical biaryl ketones via palladium-catalyzed carbonylative cross-coupling reaction of arylboronic acids with iodoarenes. *Tetrahedron Lett.* **1993**, *34*, 7595−8.
(60) Nichols, J. S.; Parks, D. J.; Consler, T. G.; Blanchard, S. G. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain. *Anal. Biochem.* **1998**, *257*, 112−9.
(61) Hiragun, A.; Sato, M.; Mitsui, H. Preadipocyte differentiation in vitro: identification of a highly active adipogenic agent. *J. Cell. Physiol.* **1988**, *134*, 124−30.
(62) Lenhard, J. M.; Kliewer, S. A.; Paulik, M. A.; Plunket, K. D.; Lehmann, J. M.; Weiel, J. E. Effects of troglitazone and metformin on glucose and lipid metabolism. Alterations of two distinct molecular pathways. *Biochem. Pharmacol.* **1997**, *54*, 801−8.
(63) Shafrir, E. Animal models of noninsulin-dependent diabetes. *Diabetes/Metab. Rev.* **1992**, *8*, 179−208.
(64) Bailey, C. J.; Flatt, P. R. In *Animal Models of Diabetes*; Bailey, C. J., Flatt, P. R., Eds.; Churchill Livingstone: Edinburgh, 1986; Vol. 2, pp 71−89.
(65) (a) Hu, E.; Kim, J. B.; Sarraf, P.; Spiegelman, B. M. Inhibition of adipogenesis through MAP kinase-mediated phosphorylation of PPARγ. *Science* **1996**, *274*, 2100−3. (b) Adams, M.; Reginato, M. J.; Shao, D.; Lazar, M. A.; Chatterjee, V. K. Transcriptional activation by peroxisome proliferator-activated receptor γ is inhibited by phosphorylation at a consensus mitogen-activated protein kinase site. *J. Biol. Chem.* **1997**, *272*, 5128−32. (c) Zhang, B.; Berger, J.; Zhou, G.; Elbrecht, A.; Biswas, S.; White-Carrington, S.; Szalkowski, D.; Moller, D. E. Insulin- and mitogen-activated protein kinase-mediated phosphorylation and activation of peroxisome proliferator-activated receptor γ. *J. Biol. Chem.* **1996**, *271*, 31771−4. (d) Camp, H. S.; Tafuri, S. R. Regulation of peroxisome proliferator-activated receptor γ activity by mitogen-activated protein kinase**.** *J. Biol. Chem.* **1997**, *272*, 10811−16.
(66) (a) Puigserver, P.; Wu, Z.; Park, C. W.; Graves, R.; Wright, M.; Spiegelman, B. M. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. *Cell* **1998**, *92*, 829−9. (b) Zhu, Y.; Qi, C.; Calandra, C.; Rao, M.; Sambasiva, R.; Janardan, K. Cloning and identification of mouse steroid receptor coactivator-1 (mSRC-1), as a coactivator of peroxisome proliferator-activated receptor γ. *Gene Express.* **1996**, *6*, 185−95. (c) Direnzo, J.; Soderstrom, M.; Kurokawa, R.; Ogliastro, M.-H.; Ricote, M.; Ingrey, S.; Horlein, A.; Rosenfeld, M. G.; Glass, C. K. Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors. *Mol. Cell. Biol.* **1997**, *17*, 2166−76.
(67) Brun, R. P.; Kim, J. B.; Hu, E.; Spiegelman, B. M**.** Peroxisome proliferator-activated receptor gamma and the control of adipogenesis. *Curr. Opin. Lipidol.* **1997**, *8*, 212−8.
(68) Ellingboe, J. W.; Alessi, T. R.; Dolak, T. M.; Nguyen, T. T.; Tomer, J. D.; Guzzo, F.; Bagli, J. F.; McCaleb, M. L. Antihyperglycemic activity of novel substituted 3H-1,2,3,5-oxathiadiazole 2-oxides. *J. Med. Chem.* **1992**, *35*, 1176−83.
(69) Ellingboe, J. W.; Lombardo, L. J.; Alessi, T. R.; Nguyen, T. T.; Guzzo, F.; Guinosso, C. J.; Bullington, J.; Browne, E. N. C.; Bagli, J. F. Antihyperglycemic activity of novel naphthalenylmethyl-3H-1,2,3,5-oxathiadiazole 2-oxides. *J. Med. Chem.* **1993**, *36*, 2485−93.
(70) Sohda, T.; Mizuno, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. Studies on antidiabetic agents. I. Synthesis of 5-[4-(2-methyl-2-phenylpropoxy)benzyl]thiazolidine-2,4-dione (AL-321) and related compounds. *Chem. Pharm. Bull.* **1982**, *30*, 3563−73.

(71) Kees, K. L.; Caggiano, T. J.; Steiner, K. E.; Fitzgerald, J. J., Jr.; Kates, M. J.; Christos, T. E.; Kulishoff, J. M.; Moore, R. D.; McCaleb, M. L. Studies on New Acidic Azoles as Glucose-Lowering Agents in Obese, Diabetic db/db Mice. *J. Med. Chem.* **1995**, *38*, 617−28.

(72) Kees, K. L.; Fitzgerald, J. J., Jr.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. New Potent Antihyperglycemic Agents in db/db Mice: Synthesis and Structure−Activity Relationship Studies of (4-Substituted benzyl)-(trifluoromethyl)pyrazoles and -pyrazolones. *J. Med. Chem.* **1996**, *39*, 3920−8.

(73) Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. Benzyloxazolidine-2,4-diones as potent hypoglycemic agents. *J. Med. Chem.* **1991**, *34*, 1538−44.

(74) Hulin, B.; Newton, L. S.; Lewis, D. M.; Genereux, P. E.; Gibbs, E. M.; Clark, D. A. Hypoglycemic Activity of a Series of α-Alkylthio and α-Alkoxy Carboxylic Acids Related to Ciglitazone. *J. Med. Chem.* **1996**, *39*, 3897−907.

(75) (a) Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K.; Faller, A.; Haigh, D.; Hindley, R. M.; Jefcott, L. J.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Smith, D. G.; Smith, S. A. Nonthiazolidinedione antihyperglycemic agents. 1: α-Heteroatom substituted *β*-phenylpropanoic acids. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2121−6. (b) Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K.; Faller, A.; Haigh, D.; Hindley, R. M.; Lefcott, L. J.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Smith, D. G.; Smith, S. A. Nonthiazolidinedione antihyperglycemic agents. 2: α-Carbon substituted *β*-phenylpropanoic acids. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2127−30.

(76) Young, P. W.; Buckle, D. R.; Cantello, B. C. C.; Chapman, H.; Clapham, J. C.; Coyle, P. J.; Haigh, D.; Hindley, R. M.; Holder, J. C.; Kallender, H.; Latter, A. J.; Lawrie, K. W. M.; Mossakowska, D.; Murphy, G. J.; Cox, L. R.; Smith, S. A. Identification of high-affinity binding sites for the insulin sensitizer Rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for Peroxisomal Proliferator-Activated Receptor *γ*. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 751−9.

(77) (a) Naringrekar, V. H.; Stella, V. J. Mechanism of hydrolysis and structure−stability relationship of enaminones as potential prodrugs of model primary amines. *J. Pharm. Sci.* **1990**, *79*, 138−46. (b) Larsen, J. D.; Bundgaard, H. Prodrugs as drug delivery systems. 49. Hydrolysis kinetics of enaminones derived from various amino acids and 1,3-diketones, keto-esters and keto-amides. *Arch. Pharm. Chem., Sci. Ed.* **1986**, *14*, 52−63.

(78) Sohda, T.; Mizuno, K.; Momose, Y.; Ikeda, H.; Fujita, T.; Meguro, K. Studies on antidiabetic agents. 11. Novel thiazolidinedione derivatives as potent hypoglycemic and hypolipidemic agents. *J. Med. Chem.* **1992**, *35*, 2617−26.

(79) X-ray crystallographic analysis of ligands from each series cocrystallized with the ligand binding domain of hPPAR*γ* indicates that the carboxylic acid moiety of the *N*-(2-benzoylphenyl)tyrosines and the 2,4-thiazolidinedione moiety of the TZDs interact with the same portion of the ligand binding domain in the hPPAR*γ* receptor, with the benzophenone occupying a pocket which remains empty in the PPAR*γ*−TZD complex (M. Milburn, unpublished results from these laboratories).

(80) Brown, K. K.; Henke, B. R.; Blanchard, S. G.; Cobb, J. E.; Kaldor, I.; Kliewer, S. A.; Lehmann, J. M.; Lenhard, J. M.; Harrington, W.; Novak, P. J.; Binz, J.; Hashim, M. A.; Oliver, W. O.; Brown, H. R.; Parks, D. J.; Plunket, K. D.; Tong, T.; Menius, A.; Adkison, K. K.; Noble, S. A.; Willson, T. M. Novel N-aryl tyrosine activators of PPAR*γ* reverse the diabetic phenotype of the zucker diabetic fatty rat. *Diabetes*, submitted for publication.

(81) Kumar, S.; Boulton, A. J. M.; Beck-Nielsen, H.; Berthezene, F.; Muggeo, M.; Persson, B.; Spinas, G. A.; Donoghue, S.; Lettis, S.; Stewart-Long, P. Troglitazone, an insulin action enhancer, improves metabolic control in NIDDM patients. *Diabetologia* **1996**, *39*, 701−709.

(82) For an excellent discussion on the possible downstream mechanism of action of PPAR*γ* activators, see: Spiegelman, B. M. PPAR-*γ*: Adipogenic regulator and thiazolidinedione receptor. *Diabetes* **1998**, *47*, 507−4.

JM9804127