Design and Synthesis of α-Aryloxy-α-methylhydrocinnamic Acids: A Novel Class of Dual Peroxisome Proliferator-Activated Receptor α/γ Agonists

Yanping Xu,*,† Christopher J. Rito,*,†
Garret J. Etgen,*,† Robert J. Ardecky,‡
James S. Bean,† William R. Bensch,†
Jacob R. Bosley,† Carol L. Broderick,†
Dawn A. Brooks,† Samuel J. Dominianni,†
Patric J. Hahn,† Sha Liu,‡ Dale E. Mais,‡
Chahrzad Montrose-Rafizadeh,† Kathy M. Ogilvie,‡
Brian A. Oldham,† Mary Peters,† Deepa K. Rungta,‡
Anthony J. Shuker,† Gregory A. Stephenson,†
Allie E. Tripp,† Sarah B. Wilson,†
Leonard L. Winneroski,† Richard Zink,†
Raymond F. Kauffman,† and James R. McCarthy*,†

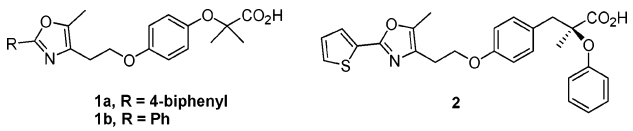
Lilly Research Laboratories, A Division of Eli Lilly & Company, Lilly Corporate Center, Indianapolis, Indiana 46285, and Ligand Pharmaceuticals, 10275 Science Center Drive, San Diego, California 92121

Received December 18, 2003

Abstract: The design and synthesis of the dual peroxisome proliferator activated receptor (PPAR) α/γ agonist (*S*)-2-methyl-3-{4-[2-(5-methyl-2-thiophen-2-yl-oxazol-4-yl)ethoxy]-phenyl}-2-phenoxypropionic acid (**2**) for the treatment of type 2 diabetes and associated dyslipidemia are described. **2** possesses a potent dual hPPAR α/γ agonist profile (IC_{50} = 28 and 10 nM; EC_{50} = 9 and 4 nM, respectively, for hPPARα and hPPARγ). In preclinical models, **2** substantially improves insulin sensitivity and potently reverses diabetic hyperglycemia while significantly improving overall lipid homeostasis.

Type 2 diabetes is a debilitating metabolic disorder affecting over 100 million people worldwide[1] that culminates in a range of progressive secondary complications.[2] Therapy for type 2 diabetes primarily has been aimed at improving glycemic control via a combination of diet, exercise, and the use of oral agents[3] including sulfonylureas, metformin, acarbose, and more recently thiazolidinediones (TZDs). Unlike other oral agents, the TZDs, which are high-affinity ligands for the peroxisome proliferator activated receptor γ, affect a key underlying feature of type 2 diabetes: insulin resistance.[4,5]

The peroxisome proliferator activated receptors (PPARs) are a highly conserved set of ligand-activated transcription factors in the nuclear hormone receptor superfamily.[6] Three distinct PPAR subtypes (PPARγ, PPARα, and PPARδ or PPARβ) have been identified in most mammalian species,[7] each forming a functional heterodimer complex with the 9-cis retinoid acid receptor (RXR). As noted above, PPARγ has been implicated as the primary receptor modulating the antidiabetic activity of the TZDs and at a cellular level is well-known for its role in adipogenesis.[8]



1a, R = 4-biphenyl
1b, R = Ph

2

Figure 1. Dual PPAR α/γ agonists.

Alternatively, PPARα regulates lipid homeostasis via its role in fatty acid catabolism[9] including fatty acid binding, uptake, and oxidation as well as lipoprotein assembly and transport. PPARα agonists, e.g., gemfibrozil, have demonstrated the ability to reduce serum triglycerides and increase HDL cholesterol,[10] along with an ability to reduce serum fibrinogen and plasminogen activator inhibitor 1.[11] The pivotal role that these receptors play in the regulation of metabolism makes them inviting targets for the treatments of diabetes mellitus, atherosclerosis, and obesity,[12−15] as demonstrated by the TZDs and fibrates. Recently, however, there has been considerable interest in combining the beneficial activities of PPARα activation and PPARγ activation, since the dual agonist approach should be well suited for the treatment of insulin resistance and the cardiovascular disease prevalent in type 2 diabetes and syndrome X.[16] Compared to combination therapy, the dual agonist approach offers additional benefits, i.e., patient compliance, avoidance of potential drug−drug interactions. We have previously reported on a class of dual agonists derived from the fusion of the putative pharmacophores of the known PPARα and PPARγ agonists, represented by **1a**[16c] (Figure 1), and report the design, synthesis, and preclinical evaluation of a highly potent dual PPAR α/γ agonist (**2**, LY510929) that resulted from the rational elaboration of **1a**/**1b.**

The syntheses of **8a**−**e** and **10**−**17** are described in Scheme 1. Compound **3** was treated with LDA at −78 °C and quenched with 4-benzyloxybenzaldehyde to provide alcohol **4** as a mixture of diastereomers. Benzylic deoxygenation with $BF_3{\cdot}Et_2O/Et_3SiH$, followed by catalytic hydrogenation to remove the benzyl group, afforded the phenol **5**. The enantiomers of phenol **5** were separated by chiral chromatography using a Chiralpak AD 4.6 mm × 250 mm column. The structure of the *S* enantiomer was unequivocally established by X-ray crystallographic analysis of the (*R*)-α-methylbenzylamine salt (crystallized from methanol, data not shown). To complete the syntheses, **5** was treated with tosylates **6a**−**e**[16c,17] under basic conditions, followed by the saponification with 5 N NaOH to provide acids **8a**−**e**, **12**, and **13**. Optically pure isomers, **2**, **15**, and **17**, were prepared from the corresponding *S* enantiomer of phenol **5** (R^2 = Me), while **14** and **16** were prepared from the *R* enantiomer of **5** (R^2 = Me). The X-ray crystal structure of **2** was also obtained (see Figure 1 in the Supporting Information section).

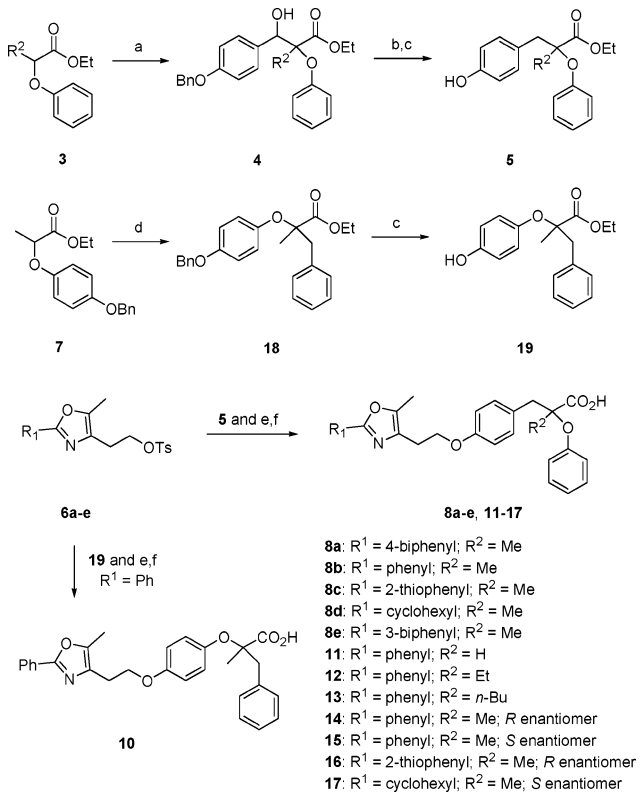
Access to the analogue **10** started with the α-benzylation of **7** by the treatment with LDA/BnBr to afford **18**. Cleavage of the benzyl ether using Pd/C yielded phenol **19**. Treatment of **19** with tosylate **6b** followed by a saponification of the resulting intermediate provided **10**.

Through our in vitro screening efforts (see assays in Supporting Information), **9**[18] (Figure 2) was identified

* To whom correspondence should be addressed. For Y.X.: phone, 317-433-1113; fax, 317-277-2035; e-mail, xu_yanping@lilly.com. For C.J.R: phone, 317-276-4231; fax, 317-651-6510; e-mail, cjrito@lilly.com. For G.J.E.: phone, 317-276-9800; fax, 3170277-2035; e-mail, g.etgen@lilly.com. For J.R.M.: phone, 317-433-1345; fax, 317-277-2035; e-mail: jmccarthy@lilly.com.
† Lilly Research Laboratories.
‡ Ligand Pharmaceuticals.

10.1021/jm0342616 CCC: $27.50
Published on Web 04/10/2004

Scheme 1[a]



[a] Reagents and conditions: (a) LDA, −78 °C, then *p*-benzyloxybenzaldehyde (70%); (b) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2 (70%); (c) H_2, 5−10% Pd/C, EtOAc (100%); (d) LDA, BnBr, TBAI; (e) Cs_2CO_3, DMF, 55 °C (70%); (f) 5 N NaOH, EtOH, reflux (>99%).

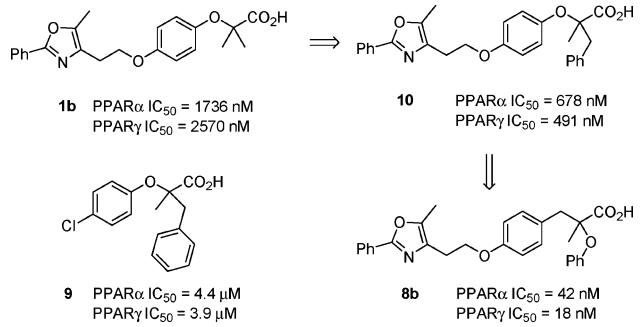


Figure 2. Early lead and SAR evolution.

as a moderate dual PPARα/γ agonist ($IC_{50}(\alpha) = 4.4\ \mu M$; $IC_{50}(\gamma) = 3.9\ \mu M$). This result was of particular interest to us because **9** possesses a bulky lipophilic group α to the carboxylic acid and binds to both hPPARα and hPPARγ receptors. From a standpoint of designing a novel dual PPARα/γ agonist, it suggested that the benzyl substitution α to the carboxylic acid of the prototypical dual agonist **1b** might improve in vitro binding. The α-benzyl analogue **10**[19] (Figure 2) did show increased binding to hPPARα and hPPARγ receptors relative to **1b**. The position of the oxygen atom α to the carboxylic acid and the quaternary stereogenic center were found to be critical for binding. Moving the ether oxygen in **10** to the alternative benzylic position provided the substantially more potent dual agonist **8b** (hPPARα IC_{50} = 42 nM and hPPARγ IC_{50} = 18 nM). Compound **11**, lacking the α-methyl group of **8b**, demonstrated substantially decreased binding at both hPPARα and hPPARγ receptors. Increasing the length of the α-alkyl group adjacent to the carboxylic acid from methyl to ethyl (**12**) or *n*-butyl (**13**) also resulted in decreased binding that was more pronounced with the longer alkyl chain.

Varying substitution (phenyl, 2-thiophenyl, and cyclohexyl) at the 2-position of the oxazole ring provided **8b**−**d**, which are essentially equipotent dual PPAR α/γ agonists. However, when larger groups were introduced to give *p*-biphenyl- and *m*-biphenyl-substituted analogues **8a** and **8e**, a significant diminution in binding at both receptors was observed.

To address the impact of chirality on receptor binding, the enantiomers **14**/**15** and **2**/**16** were compared with the corresponding racemates **8b** and **8c** (Table 1). The binding results show that the *S* enantiomers (**2** and **15**) have substantially better affinity at both the hPPAR α and γ receptors than the *R* counterparts (**14** and **16**). It is important to note that neither **2** nor any of the analogues demonstrated potent binding at the PPARδ receptor (>2 μM, Table 1). Thiophene analogue **2** had the best overall physical properties among the *S* enantiomers **2**, **15**, and **17**. The cyclohexyl analogue **17** could not be obtained in a crystalline form and was not suitable for formulation or production on a large scale. The thiophene analogue **2** exhibited adequate water solubility (100 μg/mL) and was selected for further in vivo evaluation.

To examine the PPAR-mediated pharmacodynamic effects of **2** in vivo, three preclinical models were utilized. Female Zucker (fa/fa) and male Zucker diabetic fatty (ZDF) rats were used to assess insulin sensitivity and antihyperglycemic potency, respectively. The human apolipoprotein A-1 transgenic (apoA-1 TG) mouse was used to measure alterations in HDL cholesterol and serum triglycerides.

Consistent with the potent PPARγ binding and receptor activation profile, **2** substantially lowered fasting insulin levels and improved insulin and glucose responses to a glucose challenge in obese insulin resistant female (fa/fa) Zucker rats (Figure 3). The compound potently improved hyperglycemia with a threshold glucose reduction at 0.003 mg/kg and glucose normalization at 0.03 mg/kg. The ED_{50} for glucose normalization was determined to be 0.0041 mg/kg (Figure 4).

The PPARα-mediated antidyslipidemic effects of **2** were assessed in the apoA-1 TG mouse model. In these mice, **2** dose-dependently elevated serum HDL cholesterol and lowered triglycerides (Figure 5). HDL cholesterol was elevated by 50% at a dose of 4.5 mg/kg, and similarly, the ED_{50} for triglyceride lowering was estimated to be ∼9 mg/kg in this model.

Despite the equivalent in vitro potency on hPPARα and hPPARγ, there is a notable difference in the in vivo dose−response relationship for the presumed PPARγ driven response in the ZDF rat and the PPARα driven response in the apoA-1 TG mouse. The relative insensitivity of the apoA-1 TG mouse correlates with the poor murine PPARα receptor activation profile observed for **2** (mPPARα $EC_{50} \approx 2\ \mu M$ vs hPPARα EC_{50} = 9 nM). Several key species-specific amino acid differences previously noted within the ligand binding domain of PPARα[20] most likely accounted for this human/murine potency divergence. This hypothesis has been further substantiated through an SAR study in which mPPARα

Table 1. Binding IC_{50} [a] and Cotransfection EC_{50} [b] Data[c] on Human and PPAR Receptor Subtypes

		hPPARα[f]		hPPARγ[g]		hPPARδ[f]	
compd	stereo[e]	IC_{50} (nM)	EC_{50} (nM)[d]	IC_{50} (nM)	EC_{50} (nM)	IC_{50} (nM)	EC_{50} (nM)[d]
2	*S*	28 ± 2	9 ± 4	10 ± 1	4 ± 1	5253 ± 230	na
8a	rac	503 ± 41	69 ± 6	169 ± 22	7 ± 1	nb	na
8b	rac	42 ± 6	12 ± 2	18 ± 3	8 ± 1	7113 ± 1908	na
8c	rac	45 ± 7	19 ± 2	24 ± 5	6 ± 1	5137 ± 650	na
8d	rac	73 ± 14	18 ± 3	51 ± 9	9 ± 2	nb	na
8e	rac	167 ± 25	7 ± 1	71 ± 3	6 ± 1	nb	na
10	rac	678 ± 92	549 ± 0	491 ± 32	1776 ± 0	4448 ± 216	na
11	rac	1106 ± 98	833 ± 254	128 ± 4	390 ± 35	7040 ± 1266	na
12	rac	473 ± 41	75 ± 22	290 ± 22	285 ± 52	5074 ± 1140	na
13	rac	1846 ± 109	2558 ± 108	2241 ± 13	2507 ± 50	7232 ± 968	na
14	*R*	1546 ± 36	390 ± 23	388 ± 174	382 ± 52	2685 ± 149	3014 ± 31
15	*S*	21 ± 4	5 ± 1	14 ± 2	3 ± 0	5519 ± 728	na
16	*R*	618 ± 42	67 ± 7	297 ± 47	121 ± 32	6749 ± 0	na
17	*S*	18 ± 3	1 ± 0	15 ± 2	1 ± 0	9688 ± 334	na

[a] Concentration of test compound required to displace 50% of tritiated ligand. [b] Concentration of test compound that produced 50% of the maximal reporter activity. [c] $n = 3-6$; nb = no binding; na = efficacy relative to control was less than 20% at 10 μM. [d] Gal4-hPPARα was used to eliminate interference by endogenous PPARγ receptors in CV-1 cells. [e] Stereochemistry of the chiral center. [f] Tritium-labeled PPARα/PPARδ agonist 2-(4-{2-[3-(2,4-difluorophenyl)-1-heptylureido]ethyl}phenoxy)-2-methylbutyric acid was used as radioligand for generating displacement curves and IC_{50} values. [g] Tritium labeled PPARγ agonist 5-{4-[2-(methylpyridin-2-ylamino)ethoxy]benzyl}thiazolidine-2,4-dione was used as radioligand for generating displacement curves and IC_{50} values.

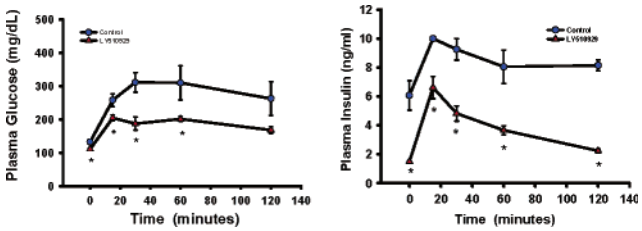


Figure 3. Glucose and insulin responses to an oral glucose challenge in female fa/fa rats.

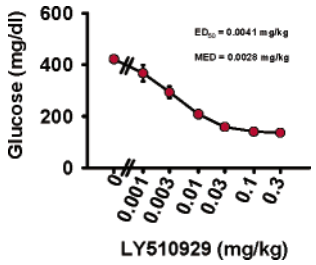


Figure 4. Glucose response in male ZDF rats.

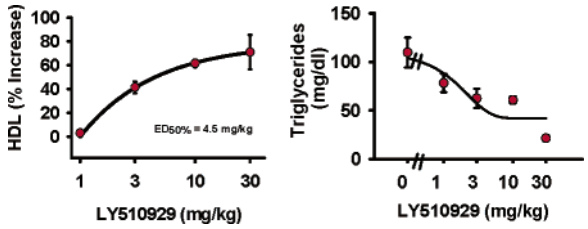


Figure 5. HDL cholesterol and triglyceride responses in ApoA-1 TG mice.

in vitro activity correlated with the PPARα driven in vivo results (manuscript in preparation). Thus, we suggest that **2** will display a potent balanced dual PPAR α/γ agonist profile in humans, and the true impact and therapeutic benefit of this compound will only be realized through clinical evaluation.

In summary, **2** was identified as a balanced dual PPAR α/γ agonist with high-affinity binding to hPPARα and hPPARγ and potent agonist activity in cell-based cotransfection assays. Preclinically, **2** exhibits remarkably potent activity on PPARγ-mediated endpoints (insulin-sensitization and glucose lowering) but appears discrepantly less potent on PPARα-mediated endpoints (HDL cholesterol elevation). This observation is believed to reflect the relative lack of cross-species consistency for PPARα activation by **2**. Overall, these results support the hypothesis that **2** will stimulate both PPARα and PPARγ at similar plasma exposures in the clinical setting, thus providing optimal control of both hyperglycemia and dyslipidemia. **2** was selected for advancement to clinical trials for the treatment of type 2 diabetes and associated dyslipidemia and is currently undergoing evaluation in man.

Acknowledgment. The authors thank Don Jett, Michael Denney, Robert Brickley, and Lawrence Goodwin for technical support.

Supporting Information Available: Synthetic procedures and characterization data for intermediates and final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Amos, A. F.; McCarty, D. J.; Zimmet, P. The rising global burden of diabetes and its complications: estimates and projections by 2010. *Diabetes Metab.* **1997**, *14* (Suppl. 5), S5−S85.

(2) (a) UK Prospective Diabetes Study (UKPDS) Group. Intensive blood−glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **1998**, *352*, 837−853. (b) Wei, M.; Gaskill, S. P.; Haffner, S. M.; Stern, M. P. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. *Diabetes Care* **1998**, *7*, 1167−1172. (c) Ebara, T.; Conde, K.; Kako, Y.; Liu, Y.; Xu, Y.; Ramakrishnan, R.; Goldberg, I. J.; Shachter, N. S. Delayed catabolism of apoB-48 lipoproteins due to decreased heparan sulfate proteoglycan production in diabetic mice. *J. Clin. Invest.* **2000**, *105*, 1807−1818. (d) Ginsberg, H. N. Insulin resistance and cardiovascular disease. *J. Clin. Invest.* **2000**, *106*, 453−458. (d) Knuiman, M. W.; Welborn, T. A.; McCann, V. J.; Stanton, K. G.; Constable, L. J. Prevalance of Diabetic Complications in Relation to Risk Factors. *Diabetes* **1986**, *35*, 1332−1339. (e) Feldt-Rasmussen, B.; Mathiesen, E.; Deckert, T. Effect of Two Years of Strict Metabolic Control on Progression of Incipient Nephropathy in Insulin-Dependent Diabetes. *Lancet* **1986**, *2*, 1300−1304. (f) Dahl-Jorgensen, K.; Brinchmann-Hansen, O.; Hanssen, K. F.; Ganes, T.; Kierulf, P.; Smeland, E.; Sandvik, L.; Agagenaes, O. Effect of Near-Normoglycemia for Two Years on Progression of Early Diabetic Retinopathy, Nephropathy, and Neuropathy: The Oslo Study. *Br. Med. J.* **1986**, *293*, 1195−1199.

(3) Gerich, J. E. Oral Hypoglycemic Agents. *N. Engl. J. Med.* **1989**, *321*, 1231−1245.

(4) (a) Hauner, H. The mode of action of thiazolidinediones. *Diabetes Metab. Res. Rev.* **2002**, *18*, S10−S15. (b) Smith, U. Pioglitazone: mechanism of action. *Int. J. Clin. Pract.* **2001**, Suppl. 121, 13−18. (c) Bailey, C. J.; Day, C. Thiazolidinediones today. *Br. J. Diabetes Vasc. Dis.* **2001**, *1*, 7−13.
(5) Lenhard, J. M. PPARγ/RXR as a molecular target for diabetes. *Recept. Channels* **2001**, 249−258.
(6) (a) Mangelsdorf, D. J.; Evans, R. M. The RXR heterodimers and orphan receptors. *Cell* **1995**, *83*, 841−850. (b) Green, S.; Wahli, W. Peroxisome proliferator-activated receptors: finding the orphan a home. *Mol. Cell. Endocrinol.* **1994**, *100*, 149−153.
(7) (a) Dreyer, C.; Krey, G.; Keller, H.; Givel, F.; Helftenbein, G.; Wahli, W. Control of the Peroxisomal β-Oxidation Pathway by a Novel Family of Nuclear Hormone Receptors. *Cell* **1992**, *68*, 879−887. (b) Kliewer, S. A.; Xu, H. E.; Lambert, M. H.; Willson, T. M. Peroxisome Proliferator-Activated Receptors: From Genes to Physiology. *Recent Prog. Horm. Res.* **2001**, *56*, 239−263. (c) Berger, J.; Moller, D. E. The Mechanism of Action of PPARs. *Annu. Rev. Med.* **2002**, *53*, 409−435.
(8) (a) Tong, Q.; Hotamisligil, G. S. Molecular Mechanism of Adipocyte Differentiation. *Endocr. Metab. Disord.* **2001**, *2*, 349−355. (b) Rose, E. D.; Walkey, C. J.; Puigserver, P.; Spiegelman, B. M. Transcriptional regulation of adipogenesis. *Genes Dev.* **2000**, *14*, 1293−1307.
(9) Torra, I. P.; Gervois, P.; Staels, B. Peroxisome Proliferator-Activated Receptor alpha in Metabolic Disease, Inflammation, Atherosclerosis and Aging. *Curr. Opin. Lipidol.* **1999**, *10*, 151−159.
(10) Frick, M. H.; Elo, O.; Haapa, K.; Heinonen, O. P.; Heinsalmi, P.; Helo, P.; Huttunen, J. K.; Kaitaniemi, P.; Koskinen, P.; Manninen, V.; Maenpaa, H.; Malkonen, M.; Manttari, M.; Norola, S.; Pasternack, A.; Pikkarainen, J.; Romo, M.; Sjoblom, T.; Nikkila, E. A. Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men with Dyslipidemia. *N. Engl. J. Med.* **1986**, *314*, 488.
(11) Kaneko, T.; Fujii, S.; Matsumoto, A.; Goto, D.; Ishimori, N.; Watano, K.; Furumoto, T.; Sugawara, T.; Sobel, B. E.; Kitabatake, A. Induction of Plasminogen Activator Inhibitor-1 Endothelial Cells by Basic Fibroblast Growth Factor and Its Modulation by Fibric Acid. *Arterioscler., Thromb., Vasc. Biol.* **2002**, *22*, 855.
(12) (a) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. The PPARs: From Orphan Receptors to Drug Discovery. *J. Med. Chem.* **2000**, *43*, 527. (b) Berger, J.; Moller, D. E. The Mechanism of Action of PPARs. *Annu. Rev. Med.* **2002**, *53*, 409.
(13) (a) Seedorf, U.; Assmann, G. The Role of PPARα in Obesity. *Nutr. Metab. Cardiovasc. Dis.* **2001**, *11*, 189. (b) Youssef, J. A.; Badr, M. Z. Peroxisome Proliferator-Activated Receptors From Orphanage to Fame in a Decade. *Saudi Pharm. J.* **2001**, *9*, 1. (c) Kersten, S. Peroxisome proliferator activated receptors and obesity. *Eur. J. Phamacol.* **2002**, *440*, 223.
(14) (a) Rushforth, N. B.; Miller, N.; Bennett, P. H. Fasting and Two-Hour Post-Load Glucose Levels for the Diagnosis of Diabetes. The Relationship between Glucose Levels and Complications of Diabetes in the Pima Indians. *Diabeologia* **1979**, *16*, 373−379. (b) Knuiman, M. W.; Welborn, T. A.; McCann, V. J.; Stanton, K. G.; Constable, L. J. Prevalance of Diabetic Complications in Relation to Risk Factors. *Diabetes* **1986**, *35*, 1332−1339.
(15) (a) Feldt-Rasmussen, B.; Mathiesen, E.; Deckert, T. Effect of Two Years of Strict Metabolic Control on Progression of Incipient Nephropathy in Insulin-Dependent Diabetes. *Lancet* **1986**, *2*, 1300−1304. (b) Dahl-Jorgensen, K.; Brinchmann-Hansen, O.; Hanssen, K. F.; Ganes, T.; Kierulf, P.; Smeland, E.; Sandvik, L.; Agagenaes, O. Effect of Near-Normoglycemia for Two Years on Progression of Early Diabetic Retinopathy, Nephropathy, and Neuropathy: The Oslo Study. *Br. Med. J.* **1986**, *293*, 1195−1199. (c) Pirart, J. Diabetes Mellitus and Its Degenerative Complications. A Prospective Study of 4,400 Patients Observed between 1947 and 1973. *Diabetes Care* **1978**, *1*, 168−188. (d) Pirart, J. Diabetes Mellitus and Its Degenerative Complications. A Prospective Study of 4,400 Patients Observed between 1947 and 1973. *Diabetes Care* **1978**, *1*, 252−263.
(16) (a) Nomura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunoda, M.; Miyachi, H.; Awana, K. (3-Substituted benzyl)-thiazolidine-2,4-diones as structurally new antihyperglycemic agents. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 533−538. (b) Lohray, B. B.; Lohray, V. B.; Bajji, A. C.; Kalchar, S.; Poondra, R. R.; Padakanti, S.; Chakrabarti, R.; Vikramadithyan, R. K.; Misra, P.; Juluri, S.; Mamidi, N. V.; Rajagopalan, R. (−)3-[4-[2-(Phenoxazin-10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid [(−)DRF 2725]: A Dual PPAR Agonist with Potent Antihyperglycemic and Lipid Modulating Activity. *J. Med. Chem.* **2001**, *44*, 2675−2678. (c) Brooks, D. A.; Etgen, G. J.; Rito, C. J.; Shuker, A. J.; Dominianni, S. J.; Warshawsky, A. M.; Ardecky, R.; Paterniti, J. R.; Tyhonas, J.; Karanewsky, D. S.; Kauffman, R. F.; Broderick, C. L.; Oldham, B. A.; Montrose-Rafizadeh, C.; Winneroski, L. L.; Faul, M. M.; McCarthy, J. R. Design and synthesis of 2-methyl-2-[4-(2-[5-methyl-2-aryloxazol-4-yl]ethoxy)phenoxy]-propionic acids: a new class of dual PPAR α/γ agonists. *J. Med. Chem.* **2001**, *44*, 2061−2064. (d) Desai, R. C.; Han, W.; Metzger, E. J.; Bergman, J. P.; Gratale, D. F.; MacNaul, K. L.; Berger, J. P.; Doebber, T. W.; Leung, K.; Moller, D. E.; Heck, J. V.; Sahoo, S. P. 5-Aryl thiazolidine-2,4-diones: discovery of PPAR dual α/γ agonists as antidiabetic agents. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2795−2798. (e) Desai, R. C.; Gratale, D. F.; Han, W.; Koyama, H.; Metzger, E. J.; Lombardo, V. K.; MacNaul, K. L.; Doebber, T. W.; Berger, J. P.; Leung, K.; Franklin, R.; Moller, D. E.; Heck, J. V.; Sahoo, S. P. Aryloxazolidinediones: identification of potent orally active PPAR dual α/γ agonists. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3541−3544. (f) Sauerberg, P.; Pettersson, I.; Jeppesen, L.; Bury, P. S.; Mogensen, J. P.; Wasserman, K.; Brand, C. L.; Sturis, J.; Woeldike, H. F.; Fleckner, J.; Andersen, A.-S. T.; Mortensen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Snidelar, K.; Panajotova, V.; Ynddal, L.; Wulff, E. M. Novel Tricyclic-a-alkyloxyphenylpropionic Acids: Dual PPAR α/γ Agonists with Hypolipidemic and Antidiabetic Activity. *J. Med. Chem.* **2002**, *45*, 789−804. (g) Ebdrup, S.; Pettersson, I.; Rasmussen, H. B.; Deussen, H.-J.; Jensen, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. Synthesis and Biological and Structural Characterization of the Dual-Acting Peroxisome Proliferator-Activated Receptor α/γ Agonist Ragaglitazar. *J. Med. Chem.* **2003**, *46*, 1306−1317.
(17) Synthesis of the alcohol precursors to tosylates **6a**−**e**: Godfrey, A. G.; Brooks, D. A.; Hay, L. A.; Peters, M.; McCarthy, J. R.; Mitchell, D. Application of the Dakin−West reaction for the synthesis of oxazole-containing dual PPARα/γ agonists. *J. Org. Chem.* **2003**, *68*, 2623−2632.
(18) (a) Lilly, Eli and Co. GB 1176339, 1970. (b) Kennard, C. H.; Smith, G.; White, A. H. *Acta Crystallogr., Sect. B* **1981**, 1314−1317.
(19) Brooks, D. A.; Connor, S. E.; Dominianni, S. J.; Godfrey, A. G.; Gossett, L. S.; Rito, C. J.; Tripp, A. E.; Warshawsky, A. M.; Winneroski, L. L.; Zhu, G. Oxazolyl-aryloxyacetic acid derivatives and thiazole analogs and their uses as PPAR agonists, e.g., as antidiabetics and hypolipidemics. WO 2002018355, 2002.
(20) (a) Keller, H. J.; Devchand, P. R.; Perroud, M.; Wahli, W. PPARα structure−functional relationships derived from species-specific differences in responsiveness to hypolipidemic agents. *Biol. Chem. Hoppe−Seyler* **1997**, *378*, 651−655. (b) Lewis, D. F. V.; Jacobs, M. N.; Lake, B. G. Molecular modeling of the peroxisome proliferator-activated receptor α (PPARα) from human, rat and mouse, based on homology with the human PPARγ crystal structure. *Toxicol. in Vitro* **2002**, *16*, 275−280.

JM0342616