Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 16 (2006) 6328–6333
Bioorganic & Medicinal Chemistry Letters

Synthesis and evaluation of aminomethyl dihydrocinnamates as a new class of PPAR ligands

Alan M. Warshawsky,* Charles A. Alt, Joseph T. Brozinick, Allen R. Harkness, Eric D. Hawkins, James R. Henry, Donald P. Matthews, Anne R. Miller, Elizabeth A. Misener, Chahrzad Montrose-Rafizadeh, Gary A. Rhodes, Quanrong Shen, Jennifer A. Vance, Uko E. Udodong, Minmin Wang, Tony Y. Zhang and Richard W. Zink

Eli Lilly and Co, Indianapolis, IN 46285, USA

Received 16 June 2006; revised 1 September 2006; accepted 6 September 2006
Available online 26 September 2006

Abstract—PPAR ligands with varied subtype selectivity have been synthesized using an achiral aminomethyl dihydrocinnamate template. Several compounds in this series have demonstrated potent plasma glucose and triglyceride lowering capability in rodent models of type 2 diabetes.

Modulation of the peroxisome proliferator-activated receptors (PPARs) has been advanced as a means to treat a number of diseases, ranging from metabolic and cardiovascular disorders to inflammation and cancer.[1] The PPARs belong to the superfamily of nuclear hormone receptors, and function as ligand-activated transcription factors through heterodimers with the retinoic acid X receptor (RXR), another nuclear hormone receptor. There are 3 known PPAR subtypes: α, δ, and γ. PPARα is expressed primarily in metabolic tissues. PPARα agonists, such as fenofibrate (**1**) and clofibrate (**2**), are used to lower serum triglycerides and raise HDL cholesterol in humans (Fig. 1). PPARδ is expressed broadly. While preclinical studies have determined a role for PPARδ in the regulation of cholesterol, PPARδ agonists have yet to reach the market.

PPARγ has been the most thoroughly studied PPAR subtype. It is found primarily in adipose tissue, and is expressed substantially in the liver, kidney, heart, and skeletal muscle as well as in the colon, intestines, pancreas, and spleen. The selective PPARγ agonists on the market today, rosiglitazone (**3**) and pioglitazone (**4**), belong to the thiazolidinedione (TZD) class of compounds and are currently used to treat type 2 diabetes (Fig. 1). These chiral compounds have been developed as racemates because of the propensity of their chiral centers to epimerize in vivo. As illustrated by rosiglitazone, this property leads to reduced compound efficiency since only the (*S*)-enantiomer was determined to be a high affinity ligand for PPARγ.[2] The TZD functionality participates in an extensive hydrogen bonding network within the receptor to promote functional activity.[3] Carboxylic acids can also participate in this hydrogen bonding interaction.[3a] The in vivo racemization potential of chiral carboxylic acid containing compounds varies by their overall structure.[4] A number of carboxylic acid-based PPARγ dominant agonists, GI 262570 (**5**),[5] BMS 298585 (**6**),[6] and LY519818 (**7**)[7] among others, have been advanced to clinical trials (Fig. 2). These PPAR agonists share common structural features: a 1,4-disubstituted benzene core and heteroatom substituents nestled around a terminal carboxylic acid group.

In this communication, we describe the synthesis and biological evaluation of a new class of PPAR agonists, the aminomethyl dihydrocinnamates (AMCs). As part of our overall effort to identify compounds with varied affinities for PPARs, we recognized certain favorable structural features of the AMC template (**8**) as a starting

Keyword: PPAR.
* Corresponding author. Tel.: +1 317 277 7226; e-mail: amw@lilly.com

0960-894X/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2006.09.011

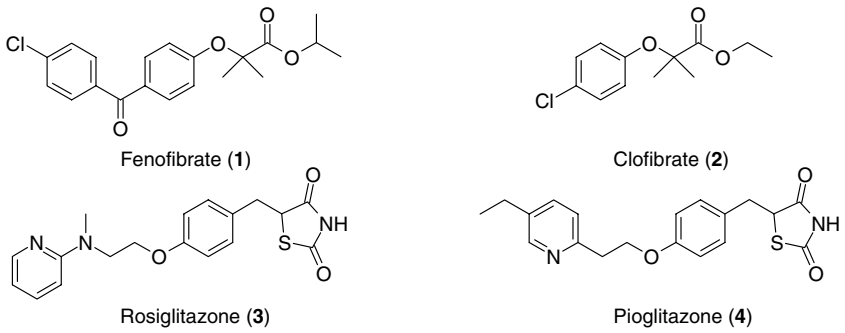


Figure 1. Marketed PPAR ligands.

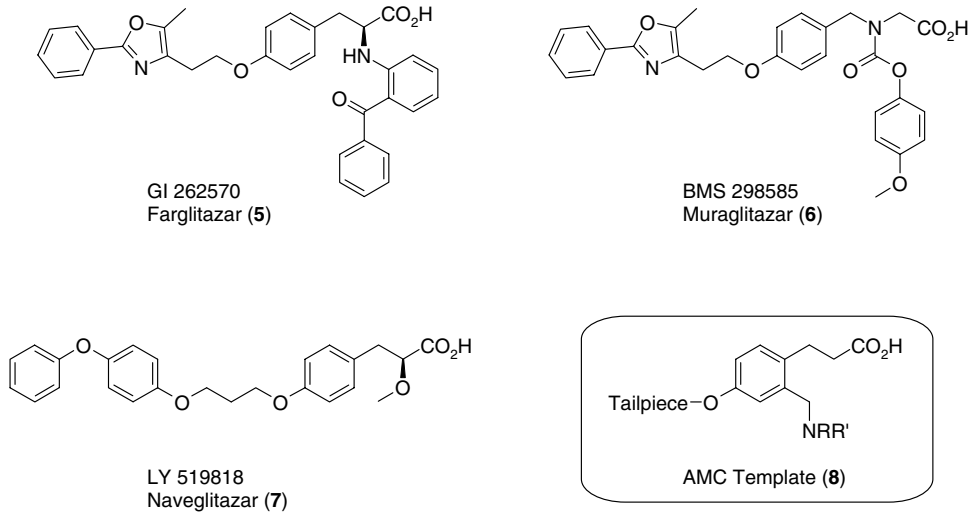


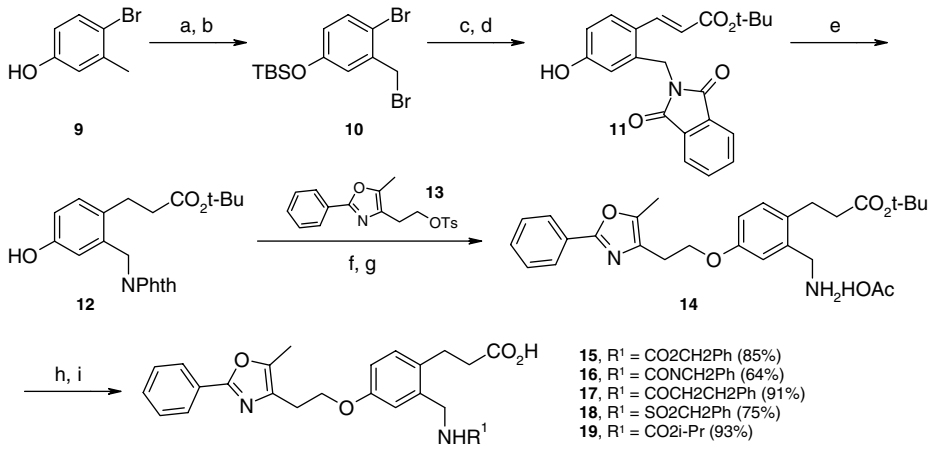
Figure 2. Non-TZD PPAR agonists in the clinic and a new PPAR ligand template.

point to develop novel PPAR ligands. This achiral template lacks the potential for racemization and maintains functionality for the key hydrogen bonding interactions with the receptors. The aminomethyl substitution on the phenyl ring permits interactions with the PPARs that are possible with the substituents alpha or beta to the carboxylic acid group in the compounds presented in Figure 2.

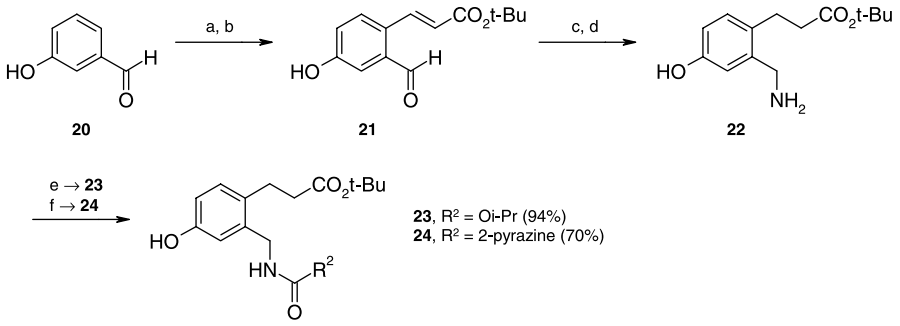
Compounds **15**–**19** and **33**–**38** were synthesized by the routes detailed in Schemes 1–4. The general synthetic strategy involved the reaction of a phenolic headpiece and a tailpiece tosylate. The specific method used to elaborate the aminomethyl substitution is presented in Scheme 1. Silyl ether protection of phenol **9** and subsequent radical bromination using NBS gave benzyl bromide **10**. Treatment with potassium phthalimide introduced the latent amino group. Heck coupling and fluoride ion mediated silyl ether cleavage provided hydroxycinnamate **11**. Hydrogenation yielded the dihydrocinnamate (**12**), which was coupled with tailpiece tosylate **13**[8] using cesium carbonate in DMF. The phthalimide protecting group was removed under mild reductive-hydrolysis conditions to give the amine salt **14**. The free amine was released with saturated aqueous bicarbonate and treated with the appropriate electrophile to afford final compounds **15**–**19** after ester cleavage using trifluoroacetic acid.

An alternate approach for the headpiece preparation is described in Scheme 2. Phenol **20** was brominated and subjected to Heck coupling conditions to provide cinnamate **21**. The aldehyde group was converted to the corresponding oxime; hydrogenation yielded aminomethyl hydroxy-dihydrocinnamate **22**. The amine function was modified selectively with isopropyl chloroformate to give carbamate **23** or with 2-pyrazine carboxylic acid and EDC to give amide **24**. Synthetic routes toward tailpiece variations are given in Scheme 3. Aryl bromide **25**[9] was transformed to boronate **26**, which underwent Suzuki coupling with 2-chloropyrimidine to give **27**. Alternately, the benzyl ether of **25** was reacted with phenol via palladium catalysis to provide phenyl ether **29**. Hydrogenolysis gave the primary alcohol, which was treated with tosyl chloride to give tosylate **30**. Tosylate **31** was prepared from the corresponding alcohol obtained via Suzuki coupling of **25** with phenyl boronic acid.[9] Tosylation of the known thiazole alcohol[5b] provided **32**. Reacting headpiece phenols **23** and **24** with tailpiece tosylates **28** and **30**–**32** using cesium carbonate in DMF followed by treatment with trifluoroacetic acid gave final compounds **33**–**38** in good overall yields (Scheme 4).

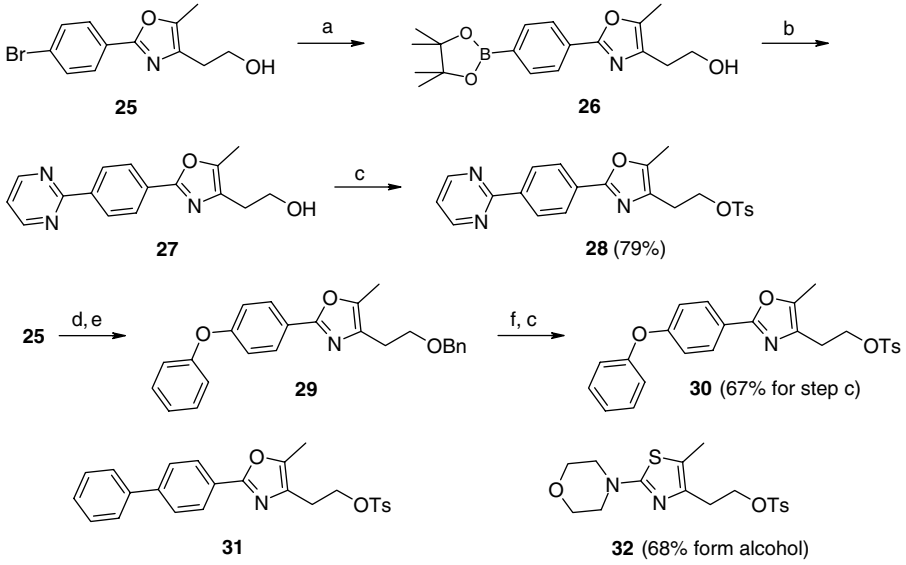
AMC derivatives **15**–**19** and **33**–**38** were evaluated in binding and co-transfection (CTF) assays to determine intrinsic receptor affinities (IC_{50}) and functional activities



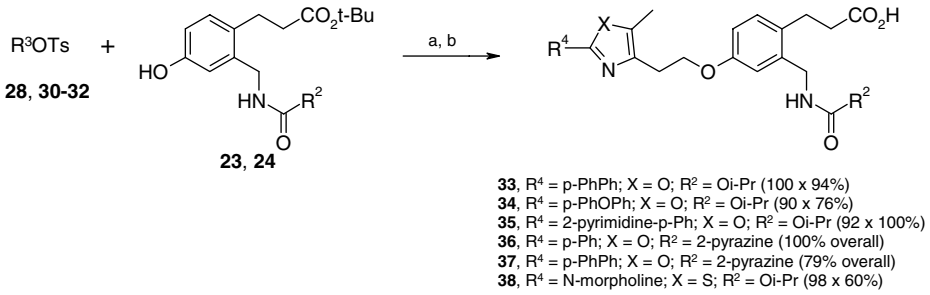
Scheme 1. Aminomethyl dihydrocinnamate synthesis: amino substitution variation. Reagents: (a) TBSCl, TEA, CH_2Cl_2 (98%); (b) NBS, AIBN, DCE (100%); (c) PhthNK, DMF (68%); (d) **1**. *t*-Bu acrylate, $Pd(OAc)_2$, $(o\text{-Tol})_3P$, $i\text{-Pr}_2NEt$, EtCN; **2**. TBAF, THF (87%); (e) 5% Pd–C, 60–75 psi H_2, EtOAc (87%); (f) **13**, Cs_2CO_3, DMF (71%); (g) 1—$NaBH_4$, IPA; 2—HOAc (79%); (h) 1—aqueous $NaHCO_3$, CH_2Cl_2; 2—RNCO, RSO_2Cl, or RCOCl, TEA, CH_2Cl_2; (i) TFA, *p*-anisole, CH_2Cl_2.



Scheme 2. Alternate headpiece synthesis. Reagents: (a) Br_2, CH_2Cl_2 (63%); (b) *tert*-butyl acrylate, $Pd(OAc)_2$, $(o\text{-Tol})_3P$, $i\text{-Pr}_2NEt$, EtCN (81%); (c) H_2NOH–HCl, pyr, EtOH (55%); (d) 10% Pd–C, 50 psi H_2, EtOH (87%); (e) *i*-PrOCOCl, TEA, CH_2Cl_2; (f) pyrazine-2-carboxylic acid, EDC, HOBt, CH_2Cl_2.



Scheme 3. Synthesis of tailpieces. Reagents and conditions: (a) pinacol diborane, $PdCl_2$(dppf), KOAc, DMSO (67%); (b) 2-chloroprimidine, $PdCl_2$(dppf), CsF, dioxane (41%); (c) TsCl, DMAP, TEA, CH_2Cl_2; (d) $PhCH_2Br$, NaH, THF (89%); (e) PhOH, $Pd(OAc)_2$, 2-BiPhP(*t*-Bu)$_2$, K_3PO_4, EtOH, Tol (72%); (f) H_2, Pd(OH)–C, EtOH (70%).



Scheme 4. Coupling of headpieces and tailpieces. Reagents: (a) Cs_2CO_3, DMF; (b) TFA, *p*-anisole, CH_2Cl_2.

(% efficacy; EC_{50}), respectively, for each PPAR subtype (Table 1). Compounds with efficacies greater than 50% were considered agonists. Most of the AMC compounds with IC_{50} values less than 1 μM were found to be agonists. Data for PPARδ are not included in the table, since none of the compounds demonstrated significant binding or efficacy.

Variations at the aminomethyl substituent were evaluated. Within an initial series of related phenyl-substituted carbamate, urea, amide, and sulfonamide compounds **15**–**18**, SAR trends became evident. With respect to binding, carbamate **15** was the most potent for both PPARγ and α. The corresponding amide (**17**) and related sulfonamide (**18**) exhibited PPARγ binding similar to carbamate **15**, but showed ~10-fold weaker affinity for PPARα. The urea analog (**16**) showed the weakest binding for PPARγ but offered the greatest selectivity versus PPARα. PPARα functional activities among these compounds derived from the cell-based CTF assay roughly followed the trends in binding results. While the PPARγ binding affinity and functional potency were equivalent for carbamate **15**, larger differences (4- to 7-fold) were noted with **16**–**18**. These data suggest the potential value in using the AMC template in PPAR ligand design.

A dramatic improvement in both binding and CTF activities was realized by going from the benzyl to the isopropyl carbamate substituent (**15** vs **19**); the 5-fold PPARγ/α selectivity in binding was maintained. Changing the amide substituent also led to a compound (**36**) with a greatly improved in vitro profile. For pyrazine carboxamide **36**, the PPARγ/α binding selectivity was reduced to 3-fold.

Tailpiece modifications were evaluated also. Phenyl, phenoxy, and 2-pyrimidinyl substitution on the tailpiece phenyl group provided compounds (**33**–**35** and **37**) with PPARγ binding similar to that of the parent compound but with greater PPARγ/α selectivity. The 2-pyrimidine-containing AMC (**35**) was found to be a potent and selective PPARγ agonist with 200-fold binding and

Table 1. Binding IC_{50},[a,c] co-transfection efficacy and EC_{50},[b,c] and in vivo data

Compound	hPPARγ			hPPARα			In vivo	
	IC_{50} (nM)	EC_{50} (nM)	CTF %Eff	IC_{50} (nM)	EC_{50}[d] (nM)	CTF %Eff	*db*/*db* mouse versus (**3**)[e]	ZDF rat ED_{50} mpk[f]
15	91 ± 27	115 ± 20	65 ± 2	441 ± 124	515 ± 86	54 ± 2		
16	706 ± 188	2684 ± 34	24 ± 2	>10,000	NC	5 ± 0.5		
17	161 ± 32	1019 ± 186	52 ± 2	4962 ± 842	2801 ± 127	32 ± 1		
18	72 ± 22	527 ± 64	56 ± 2	3390 ± 1064	2940 ± 46	33 ± 3		
19	26 ± 6	8 ± 2	72 ± 4	146 ± 33	70 ± 13	51 ± 2	58 (33)	Not tested
33	47 ± 16	19 ± 10	92 ± 4	3489 ± 917	845 ± 66	52 ± 3	56 (49)	0.02 ± 0.06
34	50 ± 27	2 ± 1	80 ± 2	516 ± 161	78 ± 11	46 ± 2	Not tested	0.05 ± 0.04
35	50 ± 21	4 ± 1	85 ± 4	9940 ± 60	900 ± 143	37 ± 1	52 (36)	0.04 ± 0.01
36	17 ± 5	7 ± 1	70 ± 6	53 ± 17	35 ± 4	60 ± 4		
37	26 ± 15	2 ± 0.3	84 ± 4	449 ± 195	198 ± 53	68 ± 2	87 (33)	0.03 ± 0.01
38	22 ± 1	28 ± 6	57 ± 3	1495 ± 342	986 ± 118	37 ± 1	58 (49)	0.12 ± 0.03
3	67 ± 8	308 ± 21	100	>10,000	NC	9		0.41 ± 0.12
1b[g]	>10,000	NC	9 ± 4	>10,000	2646 ± 78	35 ± 1		

[a] Concentration of test compound to required to displace 50% of tritiated ligand: PPARα/PPARδ agonist, 2-(4-{2-[3-(2,4-difluoro-phenyl)-1-heptyl-ureido]-ethyl}-phenoxy)-2- methyl-butyric acid and PPARγ agonist, 2-methyl-2-(4-{3-[propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino]-propyl}-phenoxy)-propionic acid.

[b] Concentration of test compound to that produces 50% of the maximal reporter activity as determined in CV-1 cells; maximum efficacy as % of maximum efficacy of a standard: unlabeled ligands in note a.

[c] Mean of at least 3 determinations ± standard error; NC, not calculated for efficacy <20% standard at 10μM.

[d] Gal4-hPPARα was used to eliminate interference by endogenous PPARγ.

[e] *db*/*db* mice were dosed orally 30 mg/kg for 7 days using 30 mg/kg rosiglitazone (**3**) as a standard; % normalization = [(vehicle − compound)/(vehicle − 200)] × 100.

[f] ED_{50} values in mg/kg were calculated from the day 7 change-from-baseline data versus dose by regression-based MED analysis.

[g] Fenofibric acid (**1b**) is the active metabolite of fenofibrate (**1**).

CTF selectivities versus PPARα. The improved gamma selectivity of these substituted tailpieces can result from differences in the receptor binding as seen through molecular docking studies with **15** and **35** into PPARγ (PDB: 1fm9) and PPARα (PDB: 1k7l).[10] Substitution on the terminal phenyl ring introduced unfavorable steric interactions with the PPARα LBD Tyr334, Cys275, and Leu254 side chains; this steric effect is absent with the corresponding Glu343, Gly 284, and Ile262 side chains in PPARγ. Finally, incorporation of the morpholinothiazole-based tailpiece led to a potent PPARγ agonist (**38**). Compared to the phenyloxazole-based tailpiece analog (**19**), AMC **38** had equivalent PPARγ binding but 11-fold greater PPARγ/α selectivity.

The functional potencies (EC_{50}s) of these more tightly bound ligands were consistently less than or equal to the IC_{50} values, and the ratios between these values varied considerably. The many parameters involved in the CTF assay; cell type, response element, co-activators, nuclear and cell membrane penetrability, among others; may account for these differences. While in vitro characterization helped to prioritize compounds for in vivo study, the in vitro data did not correlate rigorously with in vivo responses (vide infra).

Two rodent models of type 2 diabetes responsive to PPARγ modulation, the *db*/*db* mouse[11a] and the male Zucker diabetic fatty (ZDF) rat,[11b] were used to evaluate several of these AMC compounds (Table 1). In *db*/*db* mice, compounds were dosed orally at 30 mg/kg for 7 days, and % glucose normalizations relative to plasma glucose levels of lean animals were determined using rosiglitazone (**3**) as an internal standard in each study. Dose–response studies in ZDF rats (7 days at 0.3, 1, 3, and 10 mg/kg) generated ED_{50} values. The AMC PPARγ in vitro profiles translated nicely into in vivo responses. The AMC compounds tested in *db*/*db* mice produced plasma glucose reductions similar to or substantially better than rosiglitazone. All of the AMC compounds tested in the ZDF rat normalized plasma glucose and were significantly more potent than rosiglitazone with ED_{50} values ranging from 0.02 to 0.12 mg/kg versus 0.41 mg/kg, respectively. A concomitant lowering of plasma triglycerides with reductions in plasma glucose was observed in both rodent models.

Differences between human and mouse PPARα have been documented in the literature.[12] The AMC compounds in Table 1 uniformly lacked functional mouse PPARα activity as determined through CTF assays, precluding their evaluation in our PPARα responsive animal model.

In summary, the value of the AMC template in PPAR ligand design has been demonstrated. By varying the substitution on the amino group and the tailpiece, compounds were identified having potent PPARγ binding affinity and functional activity with varying degrees of PPARα activity. Reductions in plasma triglycerides and glucose by these compounds in rodents models of type 2 diabetes sensitive to PPARγ were observed. Further SAR studies with the AMC template will be reported in due course.

References and notes

1. PPAR reviews: (a) Staels, B.; Fruchart, J.-C. *Diabetes* **2005**, *54*, 2460; (b) Etgen, G. J.; Mantlo, N. *Curr. Top. Med. Chem.* **2003**, *3*, 1649; (c) Miller, A. R.; Etgen, G. J. *Expert Opin. Investig. Drugs* **2003**, *12*, 1489; (d) Willson, T. M.; Brown, P. J.; Sternbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527.
2. Parks, D. J.; Tomkinson, N. C. O.; Villeneuve, M. S.; Blanchard, S. G.; Willson, T. M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3657.
3. (a) Gampe, R. T.; Montana, V. G.; Lambert, M. H.; Miller, A. B.; Bledsoe, R. K.; Milburn, M. V.; Kliewer, S. A.; Willson, T. M.; Xu, H. E. *Mol. Cell* **2000**, *5*, 545; (b) Nolte, R. T.; Wisely, G. B.; Westin, S.; Cobb, J. T.; Lambert, M. H.; Kurokawa, R.; Rosenfeld, M. G.; Willson, T. M.; Glass, C. K.; Milburn, M. V. *Nature* **1998**, *395*, 137.
4. Haigh, D.; Allen, G.; Birrell, H. C.; Buckle, D. R.; Cantello, B. C. C.; Eggleston, D. S.; Haltiwanger, R. C.; Holder, J. C.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Sime, J. T.; Smith, S. A.; Sweeney, J. D. *Bioorg. Med. Chem.* **1999**, *7*, 821.
5. (a) Henke, B. R.; Blanchard, S. G.; Brackeen, M. F.; Brown, K. K.; Cobb, J. E.; Collins, J. L.; Harrington, W. W., Jr.; Hashim, M. A.; Hull-Ryde, E. A.; Kaldor, I.; Kliewer, S. A.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Miller, J. F.; Mook, R. A.; Noble, S. A.; Oliver, W.; Parks, D. J.; Plunket, K. D.; Szewczyk, J. R.; Willson, T. M. *J. Med. Chem.* **1998**, *41*, 5020; (b) Collins, J. L.; Blanchard, S. G.; Boswell, G. E.; Charifson, P. S.; Cobb, J. E.; Henke, B. R.; Hull-Ryde, E. A.; Kazmierski, W. M.; Lake, D. H.; Leesnitzer, L. M.; Lehmann, J.; Lenhard, J. M.; Orband-Miller, L. A.; Gray-Nunez, Y.; Parks, D. J.; Plunket, K. D.; Tong, W.-Q. *J. Med. Chem.* **1998**, *41*, 5036; (c) Cobb, J. E.; Blanchard, S. G.; Boswell, G. E.; Brown, K. K.; Cooper, J. P.; Collins, J. L.; Dezube, M.; Henke, B. R.; Hull-Ryde, E. A.; Lake, D. H.; Leesnitzer, L. M.; Lenhard, J. M.; Oliver, W., Jr.; Oplinger, J.; Pentti, M.; Parks, D. J.; Plunket, K. D.; Tong, W.-Q. *J. Med. Chem.* **1998**, *41*, 5055; (d) Sorbera, L. A.; Leeson, P. A.; Martin, L.; Castaner, J. *Drugs Future* **2001**, *26*, 354.
6. (a) Harrity, T.; Farrelly, D.; Tieman, A.; Chu, C.; Kunselman, L.; Gu, L.; Ponticiello, R.; Cap, M.; Qu, F.; Shao, C.; Wang, W.; Zhang, H.; Fenderson, R.; Chen, S.; Devasthale, P.; Jeon, Y.; Seethala, R.; Yang, W.-P.; Ren, J.; Zhou, M.; Biller, S.; Mookhtiar, K. A.; Wetterau, J.; Gregg, R.; Cheng, P. T.; Hariharan, N. *Diabetes* **2006**, *55*, 240; (b) McIntyre, J. A.; Castaner, J. *Drugs Future* **2004**, *29*, 1084.
7. Martin, J. A.; Brooks, D. A.; Prieto, L.; Gonzalez, R.; Torrado, A.; Rojo, I.; Lopez de Uralde, B.; Lamas, C.; Ferritto, R.; Dolores Martin-Ortega, M.; Agejas, J.; Parra, F.; Rizzo, J. R.; Rhodes, G. A.; Robey, R. L.; Alt, C. A.; Wendel, S. R.; Zhang, T. Y.; Reifel-Miller, A.; Montrose-Rafizadeh, C.; Brozinick, J. T.; Hawkins, E.; Misener, E. A.; Briere, D. A.; Ardecky, R.; Fraser, J. D.; Warshawsky, A. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 51.
8. Shinkai, H.; Onogi, S.; Tanaka, M.; Shibata, T.; Iwao, M.; Wakitani, K.; Uchida, I. *J. Med. Chem.* **1998**, *41*, 1927, preparation of mesylate.
9. 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. *J. Med. Chem.* **2001**, *44*, 2061.

10. Compounds were docked into the PPAR LBDs using CDocker: Vieth, M.; Hirst, J. D.; Kolinski, A.; Brooks, C. L., III. *J. Comput. Chem.* **1998**, *19*, 1612; Vieth, M.; Hirst, J. D.; Dominy, B. N.; Daigler, H.; Brooks, C. L., III. *J. Comput. Chem.* **1998**, *19*, 1623.
11. (a) *db*/*db* mouse studies. Five-week-old *db*/*db* mice were purchased from Jackson Laboratories (Bar Harbor, ME, USA). After a 2-week acclimation period, the mice were pre-bled and assigned to three groups (vehicle, rosiglitazone, and test compound; 5 animals per group) based on starting plasma glucose and body weight (day −1); (b) Zucker diabetic fatty (ZDF) rat studies. Male ZDF rats were obtained from Charles River (Genetic Models, Inc, Indianapolis, IN, USA) at 6 weeks of age. After a 2-week acclimation period, rats were pre-bled and assigned to four groups (5 animals per group; vehicle, test compound at the stated dose, or rosiglitazone at 10.0 mg/kg/day) based on starting plasma glucose levels and body weight (day −1). In both animal models, compounds were administered daily by oral gavage between 8:30 and 9:30 AM for 7 days. The dosing vehicle was 1% w/v CMC, 0.25% Tween 80. Blood samples were obtained 1 hour post-dose on day 7; following centrifugation of blood samples, plasma was used for measurements of glucose and triglyceride levels. Statistical significance was determined by one-way ANOVA. When statistical significance was detected with this method, group differences were determined by Neuman–Keuls post hoc analyses.
12. (a) Wang, M.; Winneroski, L. L.; Ardecky, R. J.; Babine, R. E.; Brooks, D. A.; Etgen, G. J.; Hutchison, D. R.; Kauffman, R. F.; Kunkel, A.; Mais, D. E.; Montrose-Rafizadeh, C.; Ogilvie, K. M.; Oldham, B. A.; Peters, M. K.; Rito, C. J.; Rungta, D. K.; Tripp, A. E.; Wilson, S. B.; Xu, Y.; Zink, R. W.; McCarthy, J. R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6113; (b) Keller, H.; Devchnad, P. R.; Perroud, M.; Wahli, W. *Biol. Chem.* **1997**, *378*, 651; (c) Mukherjee, R.; Jow, L.; Noonan, D.; McDonnell, D. P. *J. Steroid Biochem. Mol. Biol.* **1994**, *51*, 157.