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2-Alkoxydihydrocinnamates as PPAR agonists. Activity modulation by the incorporation of phenoxy substituents

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Abstract—Herein we describe a series of potent and selective PPARγ agonists with moderate PPARα affinity and little to no affinity for other nuclear receptors. In vivo studies in a NIDDM animal model (ZDF rat) showed that these compounds are efficacious at low doses in glucose normalization and plasma triglyceride reduction. Compound **1b** (**LY519818**) was selected from our SAR studies to be advanced to clinical evaluation for the treatment of type II diabetes.

1. Introduction

Noninsulin dependent diabetes mellitus (NIDDM) is a major progressive metabolic disorder that affects 5–10% of adults over the age of 30 in most populations.[1] The prevailing incidence of the disease is in the elderly population of developed countries with the main cause being a high-fat western diet combined with a sedentary lifestyle.[2] This etiology is shared by other major diseases such as obesity and cardiovascular disorders. The disease is characterized by malfunctions in insulin-mediated glucose uptake in muscle and adipose tissues. The basic approach to treating NIDMM focuses on the control of blood glucose levels in order to reduce the incidence of the microvascular and macrovascular complications that define this syndrome.[3] Some treatments are based on the administration of insulin secretagogues, such as sulfonyl ureas, to produce an increase in insulin levels that eventually overcome the impaired glucose transport system.[4] Other treatments which are based on the decrease of plasma glucose without the increase of insulin levels include α-glycosidase inhibitors and metformin.[5]

Recently, compounds containing the thiazolidinedione (glitazone) moiety, were found to reduce plasma glucose levels in both animal models of diabetes and in human patients with NIDDM without increasing plasma insulin levels and without causing hypoglycemia.[6] Pioglitazone and rosiglitazone are marketed currently as treatments for NIDMM. The molecular target of the glitazones was unknown until the first compounds of the class were in the late-stages of clinical development.[7] These compounds were determined to be potent agonists of the peroxisome proliferator-activated receptor gamma (PPARγ), a member of a super family of nuclear transcription factors that include steroid, retinoid, and thyroid hormone receptors.[8] There are three known PPAR subtypes; PPARα, PPARγ, and PPARδ (also

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known in the literature as PPARβ). With its primary function related to lipid homeostasis, PPARα is distributed mainly in the liver, heart, and kidney. In contrast, PPARγ is predominantly expressed in adipose tissue and muscle, and PPARδ is expressed ubiquitously. Although the exact mechanism for insulin sensitization by PPARγ ligands remains unclear, it is known that the differentiation of preadipocytes to adipocytes is induced in cultured cells following the binding of synthetic ligands to the receptor.[9]

In our investigations, we sought PPARγ agonists outside the glitazone class that would produce improved glycemic and lipid control in animal models of diabetes that could be translated to man. During our search, we found that the *para*-biphenoxypropoxy 2-methoxyhydrocinnamic acid **1a**[10] was a high affinity ligand for PPARγ, which behaved as an agonist in the cell-based efficacy assay. Furthermore, **1a** showed modest PPARα agonist activity, which could lead to an improved triglyceride and cholesterol profile.[11] Greater than 65-fold selectivity versus PPARδ was observed. Compound **1a** also showed a promising in vivo potency (ED_{50} = 1.6 mg/kg) in the Zucker diabetic fatty rat, our primary model to evaluate glucose and triglyceride lowering.

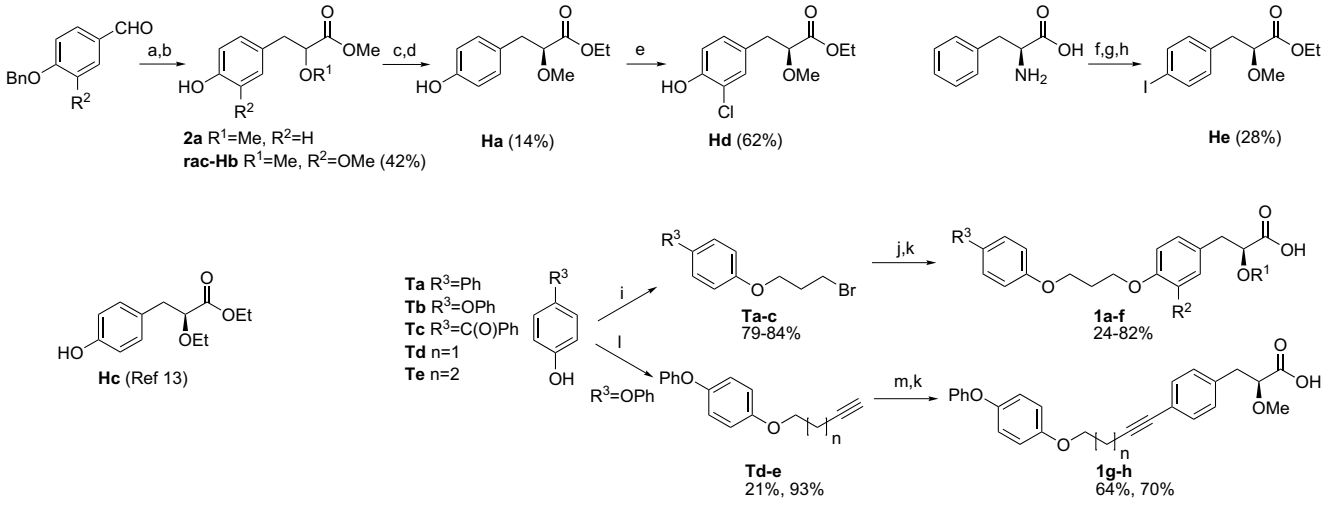
In this paper, we describe new SAR findings around the lipophilic tailpiece of the 2-alkoxydihydrocinnamate class that led to potent PPARγ agonists in vitro and effective compounds for the control of glucose and lipid levels in a diabetes animal model.

2. Chemistry

Compounds **1a**–**h** were synthesized as described in Scheme 1. The aldol condensation of 4-benzyloxybenzaldehyde and methyl alkoxyacetate derivatives gave the trifluoroacetic ester after a direct quench with trifluoroacetic anhydride. Exhaustive hydrogenolysis gave the racemic headpiece **2a**. Resolution of the headpiece **2a** was achieved by crystallization of the acid derivative obtained by saponification of **2a**-acid as cinchonidine salt. After isolation of the free acid, treatment with ethanol and sulfuric acid provided the desired ester head piece **Ha**. Racemic headpiece **rac-Hb** was prepared in a similar two-step synthesis by elimination of the aldol derivative using mesyl chloride/triethylamine, followed by olefin reduction with magnesium in methanol prior to the debenzylation.[12,10d] The further synthesis using this headpiece (see below) gave the racemic final compound that was resolved by chiral HPLC to afford compound **1e**. Compound **Hc** was prepared according with the method previously described.[13] The 3-chloro analog **Hd** was obtained from **Ha** directly by chlorination with *N*-chlorosuccinimide.

Tailpieces **Ta**–**c** containing di-ether linkers were prepared using the corresponding phenols, 1,3-dibromopropane, and powdered potassium carbonate in methyl ethyl ketone. **Ta**–**c** and **Ha**–**d** were coupled using powdered potassium carbonate in DMF at room temperature. Subsequent hydrolysis, without purification of the coupled product, afforded **1a**–**f**.

For compounds with monoether linkers (**1g**–**h**), palladium catalyzed Sonogashira conditions for the coupling of alkynes with the aryl iodo-headpiece were employed. Specifically, L-*p*-iodophenylalanine[14] was converted into the methoxylated aryl iodide **He** via sequential hydroxydeamination and O-methylation. This compound served as a pivotal starting material for the preparation of compounds with a triple bond in the linker.



Scheme 1. (a) Reagents and conditions: methyl α-methoxyacetate, NaHDMS, THF, −78 °C, then TFAA for **2a**, or MsCl/TEA for **Hb**; (b) H_2, Pd–C, EtOAc for **2a**, or Mg/MeOH and then H_2, Pd–C, MeOH for **Hb**; (c) saponification of **2a**, cinchonidine crystallization, and acid isolation; (d) H_2SO_4, ethanol; (e) NCS, CH_3CN; (f) I_2, $NaIO_3$, H_2SO_4, AcOH; (g) $NaNO_2$, H_2SO_4; (h) MeI, NaH, THF; (i) 1,3-dibromopropane, 3-butynyl *p*-toluenesulfonate, or 5-chloro-1-pentyne, K_2CO_3, MEK; (j) **Ha-d**, K_2CO_3, DMF, rt, or MeCN at 85 °C; (k) 5 N NaOH, EtOH. For **1e**, chiral HPLC separation; (l) K_2CO_3, MEK; (m) **He**, $Pd(PPh_3)_4$, CuI, piperidine.

3. Results and discussion

Several series of nonTZD PPARγ agonists have been described.[15] Some of these series contain the 2-alkoxycinnamate head piece containing different aromatic tailpieces.[10] In our efforts to further investigate the influence of the distal aromatic ring on euglycemic activity, we found that compound **1a** (Table 1), containing a *para*-biphenyloxy tailpiece,[16] was a selective PPARγ agonist (binding $IC_{50} = 21$ nM, CTF potency[11a] $EC_{50} = 154$ nM) with weak human PPARα and weaker PPARδ activities and with no activity for any other nuclear receptor evaluated (RARα, RXRα, AR, PR, ERα, GR, MR). The in vivo potency of **1a** measured in the ZDF model was approximately 3.6-fold lower than rosiglitazone ($ED_{50} = 0.41$ mg/kg). Encouraged by this preliminary result, we synthesized a series of analogs of **1a** in order to improve its in vitro and in vivo parameters. The results are summarized in Table 1.

Replacement of the biphenyl moiety by phenoxyphenyl to give **1b** produced a 4-fold decrease in PPARα affinity while the PPARγ binding is maintained; however, **1b** showed more than 10-fold improvement in the in vivo potency. The change of the biphenoxy moiety by the benzophenone group (**1c**) resulted in an increase in affinity for both PPARα and PPARγ but did not translate to further improvement in the in vivo potency. Substitution of the methoxy group at the C-2 position of the propanoic acid for an ethoxy (**1d** versus **1b**) gave a 3-fold decrease in PPARγ binding but did not change other in vitro parameters substantially. However, the in vivo potency for the ethoxy compound improved approximately 7-fold. Similar effects resulting from a change of the methoxy to the ethoxy group have been observed previously in a related series.[10a,17] This effect could be due to a difference in exposure. Plasma levels of compound in the efficacy studies (single point determination after 7 days of treatment) are approximately 2-fold higher for **1d** than for **1b** at 0.1, 0.3, and 1 mg/kg doses. The variation of the central ring by introducing a substituent at the 2-position did not produce notable changes in the in vitro parameters or an improvement in the in vivo potency (**1e** versus **1b** and **1c** versus **1f**). A chlorine atom does not change substantially the affinity while the introduction of a methoxy group slightly increases (3-fold) the PPARγ affinity.

The linker that joins the two aromatic ends of the molecule was also examined. Conceptually, modification of the linker could change the conformation of the molecule substantially, and therefore, alter its PPAR binding, selectivity, and functional activity as well as its in vivo profile.[18] The oxygen directly bound to the central aryl ring was replaced by an alkyne moiety to provide compounds **1g** and **1h**. Compound **1h** demonstrated slightly better (3-fold) PPAR binding than **1b** with comparable in vivo potency. Interestingly, the length of the linker does not affect the PPARα/PPARγ selectivity profile of **1g** and **1h**. These compounds with the alkyne linkers are still flexible enough to be adapted to both PPARα and PPARγ receptors.

Figure 1 shows the in vivo profile of compound **1b** after daily oral administration to Zucker diabetic fatty rats at different doses. Figure 1 (left) shows the plasma glucose change from vehicle compared with rosiglitazone treated animals at 7 days of treatment, and the graph on the right shows the corresponding parameters for plasma triglyceride. Both rosiglitazone and compound **1b** normalized plasma glucose at 3 mg/kg (plasma glucose values of 180 and 179 mg/dl, respectively). A calculated ED_{50} for compound **1b** of 0.10 ± 0.04 mg/kg was significantly lower than the ED_{50} of the standard compound Rosiglitazone (0.41 ± 0.10 mg/Kg).[19] The triglyceride lowering parallels the glucose reduction at each dose, in agreement with a PPARγ mediated effect in the ZDF rat. Compound **1b** is a weak h-PPARα agonist,

Table 1. Binding IC_{50}, cotransfection efficacy, and in vivo data for compounds **1a**–**h**

$R^1/R^2/R^3$ or (n)		h-PPARγ			h-PPARα			h-PPARδ[d]	In vivo
		IC_{50}[a,b]	EC_{50}[a,b]	CTF eff (%)[c]	IC_{50}[a,b]	EC_{50}[a,b]	CTF eff (%)[c]	IC_{50}[a,b]	ZDF rat ED_{50} (mg/Kg)[f]
Rosiglitazone		70	268	100	>10,000	—	9.11	—	0.41 ± 0.10
Fenofibric acid		>10,000	—	11 ± 5	>10,000	>10,000	75 ± 20	NT	NT
1a	Me/H/Ph	21 ± 3	154 ± 30	84 ± 2	568 ± 50	1100 ± 147	42 ± 2	1391 ± 127	1.5[e]
1b	Me/H/OPh	34 ± 3	361 ± 35	77 ± 5	2711 ± 364	2816 ± 35	43 ± 4	1916 ± 148	0.10 ± 0.04
1c	Me/H/C(O)Ph	5 ± 1	260 ± 20	76 ± 8	470 ± 20	2870 ± 32	27 ± 2	2324 ± 476	0.18 ± 0.06
1d	Et/H/OPh	44 ± 9	282 ± 29	85 ± 4	1686 ± 168	2754 ± 76	30 ± 2	1569 ± 447	0.015 ± 0.04
1e	Me/MeO/OPh	13 ± 1	185 ± 25	87 ± 2	1349 ± 357	2152 ± 87	35 ± 1	7502 ± 1505	0.12 ± 0.02
1f	Me/Cl/C(O)Ph	5 ± 1	305 ± 34	83 ± 2	309 ± 38	2713 ± 30	36 ± 3	1507 ± 23	0.29 ± 0.09
1g	(**1**)	13 ± 2	103 ± 11	74 ± 3	1154 ± 182	1880 ± 86	33 ± 1	3938 ± 206	0.08 ± 0.02
1h	(**2**)	7 ± 2	239 ± 45	77 ± 4	770 ± 156	2622 ± 94	35 ± 2	4123 ± 163	0.07 ± 0.02

Head- and tailpieces of the compounds (see Scheme 1).

[a] Mean for at least three determinations ± standard error.

[b] Values given in nM. Competitive displacement binding assays were performed using scintillation proximity assay (SPA) technology, PPAR receptors, and corresponding radiolabeled ligands.

[c] Maximum efficacy as % of the maximum efficacy of the standard.

[d] None of the compounds were efficacious in the PPARδ CTF assay.

[e] Estimated value.

[f] Statistical significance was determined by one-way analysis of variance (ANOVA). When statistical significance was detected with this method, group differences were determined by Neuman–Keuls post-hoc analyses.

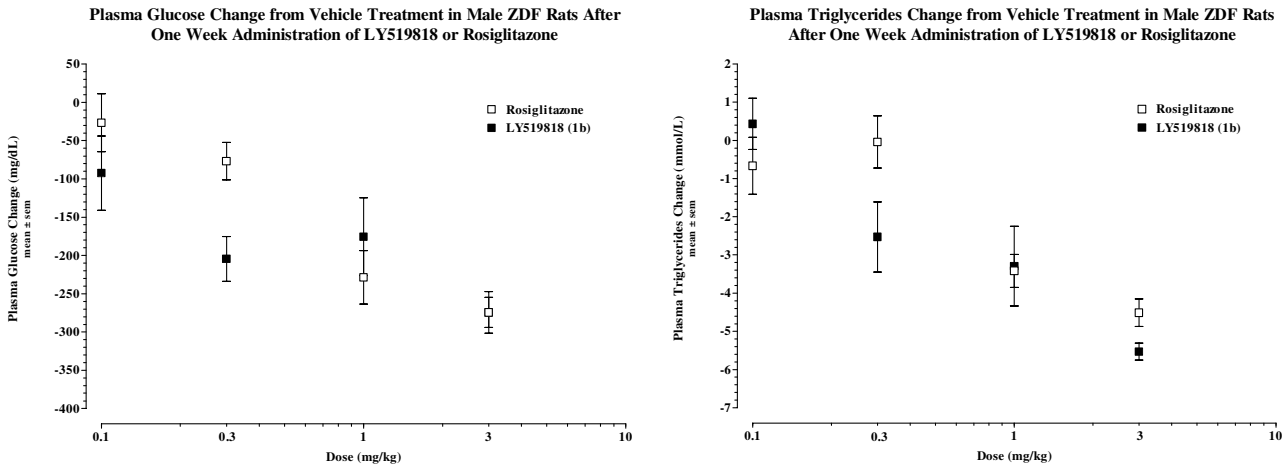


Figure 1. Plasma glucose (left) and triglycerides (right) changes from vehicle treatment in 8-week-old male ZDF rats dosed with vehicle (1% carboxymethylcellulose/0.25% Tween 80), LY519818, or rosiglitazone for 7 days ($N = 5$ per group). Blood samples were taken via tail snip, and plasma was analyzed on a Hitachi 912 metabolic analyzer for glucose and triglyceride content. Plasma glucose and triglyceride levels for vehicle treated rats were 456 mg/dL and 6.9 mmol/L, respectively.

which could lead to a better cholesterol profile in humans. Compound **1b** has better affinity for h-PPARα and more potent although less efficacious agonist activity than the well characterized PPARα agonist fenofibrate (Table 1). Because fenofibrate lowers total cholesterol, LDL-C, VLDL-C, and total triglycerides in addition to increasing HDL-C following administration to humans,[20] we anticipate that compound **1b** could demonstrate beneficial lipid parameters in addition to its anti-diabetic activities when tested in patients with type 2 diabetes. The lack m-PPARα efficacy in our cotransfection assay ($14 \pm 4\%$) precluded evaluation in our PPARα responsive animal model; however, we consider compound **1b** as a PPARγ-dominant dual agonist with confirmation of its beneficial PPARα activities coming from on-going clinical trials.

4. Conclusions

From SAR studies around the 2-alkoxydihydrocinnamate scaffold that incorporates a phenoxyphenyl-ether tailpiece, we have identified a number of compounds with high PPARγ affinity and in vivo potency in ZDF rat. Changes in the *para* substituent of the terminal phenyl ring of the tailpiece and conformational restriction in the linker were found to modulate PPAR potency and selectivity. The compounds reported herein show modest binding and CTF potency for human PPARα, which could be beneficial to overcome the cardiovascular problems usually associated with NIDDM. Compound **1b** (**LY519818**) was selected from our SAR studies to be advanced to clinical evaluation for the treatment of type 2 diabetes.

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References and notes

1. Turner, N. C.; Clapham, J. C. In *Progress in Drug research*; Jucker, E., Ed.; Virkhauser-Verlag, 1998; pp 35–94.
2. Harris, M. L.; Flegal, K. M.; Cowie, C. C.; Eberhardt, M. S.; Goldstein, D. E.; Little, R. R.; Weidmeyer, H. M.; Byrd-Holt, D. D. *Diabetes Care* **1998**, *21*, 518–524.
3. Reaven, G. M. *Experimental and Clinical Endocrinology & Diabetes* **2000**, *108*, S274–S280.
4. (a) Goldman, J. M. *Drugs Today* **1989**, *25*, 689–695; (b) Kolterman, O. G.; Pronce, M. J.; Olefsky, J. M. *Am. J. Med.* **1983**, *74*(Suppl 1A), 82–101.
5. Göke, B. *Experimental and Clinical Endocrinology & Diabetes* **2000**, *108*, S243–S249.
6. Hulin, B.; McCarthy, P. A.; Gibbs, E. M. *Curr. Pharm. Des.* **1996**, *2*, 85–102.
7. Lehmann, J. M.; Kliewer, S. A. *J. Biol. Chem.* **1995**, *270*, 12953–12956.
8. (a) Issemann, I.; Green, S. *Nature* **1990**, *347*, 645–650; (b) Mangelsdorf, D. J.; Evans, R. M. *Cell* **1995**, *83*, 841–850; (c) Willson, T. M.; Brown, P. J.; Sterbach, D. D.; Henke, B. R. *J. Med. Chem.* **2000**, *43*, 527–550.
9. Kletzien, R. F.; Clarke, S. D.; Ulrich, R. G. *Mol. Pharmacol.* **1992**, *41*, 393.
10. Previous work on the 2-alkoxy-3-phenylpropionic acid pharmacophore: (a) Hulin, B.; Newton, L. S.; Lewis, D. M.; Genereux, P. E.; Gibs, E. M.; Clark, D. A. *J. Med. Chem.* **1996**, *39*, 3897–3907; (b) Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K.; Failer, A.; Haigh, D.; Hindley, R. M.; Jefcott, L. J.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Smith, D. G.; Smith, S. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2121–2126; (c) Buckle, D. R.; Cantello, B. C. C.; Cawthorne, M. A.; Coyle, P. J.; Dean, D. K.; Failer, A.; Haigh, D.; Hindley, R. M.; Jefcott, L. J.; Lister, C. A.; Pinto, I. L.; Rami, H. K.; Smith, D. G.; Smith, S. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2127–2130; (d) Cronet, P.; Petersen, J. F. W.; Folmer, R.; Blomberg, N.; Sjöblom, K.; Karlsson, U.; Lindstedt, E.; Bamberg, K. *Structure* **2001**, *9*, 699–706; (e) Takeno, H.; Ikemoto, T.; Saitoh, I.; Watanabe, K. (Sumimoto) WO9638415, 1996; (f) 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. S. R.; Rajagopalan *J. Med. Chem* **2001**, *44*, 2675–2678; (g) Sauerberg, P.; Pettersson, I.; Jeppesen, L.; Bury, P. S.; Mogensen, J. P.; Wassermann, K.; Brand, C. L.; Sturis, J.; Woeldike, H. F.; Fleckner, J.; Andersen, A. T.; Mortensen, S. B.; Svensson, L. A.; Rasmussen, H. B.; Lehmann, S. V.; Polivka, Z.; Sindelar, K.; Panajotova, V.; Ynddal, L.; Wulff, E. M. *J. Med. Chem.* **2002**, *45*, 789–804; (h) Ebdrup, S.; Pettersson, I.; Rasmussen, H. B.; Deussen, H.; Jensen, A. F.; Mortensen, S. B.; Fleckner, J.; Pridal, L.; Nygaard, L.; Sauerberg, P. *J. Med. Chem.* **2003**, *46*, 1306–1317; (i) Ljung, B.; Bamberg, K.; Dahllof, B.; Kjellstedt, A.; Oakes, N. D.; Ostling, J.; Svensson, L.; Camejo, G. *J. Lipid Res.* **2002**, *43*, 1855–1863; (j) Cronet, P.; Petersen, J. F. W.; Folmer, R.; Blomberg, N.; Sjoblom, K.; Karlsson, U.; Lindstedt, E.-L.; Bamberg, K. *Structure* **2001**, *9*, 699–706; (k) Mogensen, J. P.; Jeppesen, L.; Bury, P. S.; Pettersson, I.; Fleckner, J.; Nehlin, J.; Frederiksen, K. S.; Albrektsen, T.; Din, N.; Mortensen, S. B.; Svensson, L. A.; Wassermann, K.; Wulff, E. M.; Ynddal, L.; Sauerberg, P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 257–260; (l) Das, S. K.; Reddy, K. A.; Abbineni, C.; Iqbal, J.; Suresh, J.; Premkumarb, M.; Chakrabartib, R. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 399–403; (m) Vikramadithyan, R. K.; Hiriyan, J.; Suresh, J.; Gershome, C.; Babu, R. K.; Misra, P.; Rajagopalan, R.; Chakrabarti, R. *Obesity Res.* **2003**, *11*, 292–303; (n) Miyachi, H.; Nomura, M.; Tanase, T.; Takahashi, Y.; Ide, T.; Tsunoda, M.; Murakami, K.; Awano, K. *Bioorg. Med. Chem. Lett.* **2001**, *12*, 77–80; (o) Nomura, M.; Tanase, T.; Ide, T.; Tsunoda, M.; Suzuki, M.; Uchiki, H.; Murakami, K.; Miyachi, H. *J. Med. Chem.* **2003**, *46*, 3581–3599; (p) Sauerberg, P.; Bury, P. S.; Mogensen, J. P.; Deussen, H.; Pettersson, I.; Fleckner, J.; Nehlin, J.; Frederiksen, K. S.; Albrektsen, T.; Din, N.; Svensson, L. A.; Ynddal, L.; Wulff, E. M.; Jeppesen, L. *J. Med. Chem.* **2003**, *46*, 4883–4894; (q) Liu, K. G.; Smith, J. S.; Ayscue, A. H.; Henke, B. R.; Lambert, M. H.; Leesnitzer, L. M.; Plunket, K. D.; Willson, T. M.; Sternbachb, D. D. *J. Med. Chem.* **2003**, *46*, 4883–4894.

11. (a) Brooks, D. A.; Etgen, G. J.; Rito, C. J.; Shuker, A. J.; Dominianni, S. J.; Warshawsky, A. M.; Ardecky, R.; Paternity, J. R.; Tyhonas, J.; Karanewsky, D. S.; Kauffman, R. F.; Broderick, C. L.; Oldham, B. A.; Montrose-Rafizadeh, C.; Winnerowski, L. L.; Faul, M. M.; McCarthy, J. R. *J. Med. Chem.* **2001**, *44*, 2061–2064; (b) Etgen, G. J.; Oldham, B. A.; Johnson, W. T.; Broderick, C. L.; Montrose, C. R.; Brozinick, J. T.; Misener, E. A.; Bean, J. S.; Bensch, W. R.; Brooks, D. A.; Shuker, A. J.; Rito, C. J.; McCarthy, J. R.; Ardecky, R. J.; Tyhonas, J. S.; Dana, S. L.; Bilakovics, J. M.; Paterniti, J. R., Jr.; Ogilvie, K. M.; Liu, S.; Kauffman, R. F. *Diabetes* **2002**, *51*, 1083–1087.
12. Hiersemann, M. *Synthesis* **2000**, *9*, 1279–1290.
13. Andersson, K.; Lindstedt Alstermark, E. WO 9962870, 1999.
14. Lei, H.; Stoakes, M. S.; Herath, K. P. B.; Lee, J.; Schwabacher, A. W. *J. Org. Chem.* **1994**, *59*, 4206–4210.
15. (a) Henke, B. R.; Adkison, K. K.; Blanchard, S. G.; Leesnitzer, L. M.; Mook, R. A., Jr.; Plunket, K. D.; Ray; John, A.; Roberson, C.; Unwalla, R.; Willson, T. M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3329–3334; (b) Liu, K. G.; Lambert, M. H.; Leesnitzer, L. M.; Oliver, W.; Ott, R. J.; Plunket, K. D.; Stuart, L. W.; Brown, P. J.; Willson, T. M.; Sternbach, D. D. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2959–2962; (c) Liu, K. G.; Lambert, M. H.; Ayscue, A. H.; Henke, B. R.; Leesnitzer, L. M.; Oliver, W. R., Jr.; Plunket, K. D.; Xu, H. E.; Sternbach, D. D.; Willson, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3111–3113; (d) Rybczynski, P. J.; Zeck, R. E.; Combs, D. W.; Turchi, I.; Burris, T. P.; Xu; Jun, Z.; Yang, M.; Demarest, K. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2359–2362; (e) 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. M.; 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*, 5020–5036; (f) Collins, J. L.; Blanchard, S. G.; Boswell, G.; Evan, C.; Paul, 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.; Plunkett, K. D.; Tong, W. *J. Med. Chem.* **1998**, *41*, 5037–5054; (g) Cobb, J. E.; Blanchard, S. G.; Boswell, E. G.; Brown, K. K.; Charifson, P. S.; Cooper, J. P.; Collins, J. L.; Dezube, M.; Henke, B. R.; Hull-Ryde, E. A.; Lake, D. H.; Lenhard, J. M., Jr.; Oliver, W., Jr.; Oplinger, J.; Pentti, M.; Parks, D. J.; Plunket, K. D.; Tong, W. *J. Med. Chem.* **1998**, *41*, 5055–5069; (h) Rami, H. K.; Smith, S. A. *Exp. Opin. Ther. Patents* **2000**, *10*, 623–634; (i) Imoto, H.; Imamiya, E.; Momose, Y.; Sugiyama, Y.; Kimura, H.; Sohda, T. *Chem. Pharm. Bull.* **2002**, *50*, 1349–1357; (j) Imoto, H.; Sugiyama, Y.; Kimura, H.; Momose, Y. *Chem. Pharm. Bull.* **2003**, *51*, 138–151; (k) Rybczynski, P. J.; Zeck, R. E.; Dudash, J., Jr.; Combs, D. W.; Burris, T. P.; Yang, M.; Osborne, M. C.; Chen, X.; Demarest, K. T. *J. Med. Chem.* **2004**, *47*, 196–209; (l) Takamura, M.; Sakurai, M.; Yamada, E.; Fujita, S.; Yachi, M.; Takagi, T.; Isobe, A.; Hagisawa, Y.; Fujiwara, T.; Yanagisawa, H. *Bioorg. Med. Chem.* **2004**, *12*, 2419–2439.
16. During the preparation of this manuscript, a paper on glitazone compounds containing phenoxy tailpieces has been published: 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. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2795–2798.
17. Haigh, D.; Allen, G.; Birrell, H. C.; Buckle, D. L.; 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*, 821–830.
18. Reddy, K. A.; Lohray, V. B.; Reddy, A. S.; Madimi, N. V.; Reddy, P. P.; Saibaba, V.; Reddy, N. J.; Suryaprakash, A.; Misra, P.; Vikramadithyan, R. K.; Rajagopalan, R. *J. Med. Chem.* **1999**, *42*, 3265–3278.
19. ED_{50} values for glucose lowering were obtained from analysis of the day seven change-from-baseline data versus dose by regression-based MED analysis.
20. Brown, W. V.; Dujovne, C. A.; Fraquhar, J. W.; Feldman, E. B.; Grundy, S. M.; Knopp, R. H.; Lasser, N. L.; Mellies, M. J.; Palmer, R. H.; Samuel, P.; Schonfeld, G.; Superko, H. R. *Arteriosclerosis (Dallas, Tex.)* **1986**, 670–678.