Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 6744–6749
Bioorganic & Medicinal Chemistry Letters

Design and synthesis of novel and potent amide linked PPARγ/δ dual agonists

Qing Shi,* Emily J. Canada, Yanping Xu, Alan M. Warshawsky, Garret J. Etgen, Carol L. Broderick, Cathleen K. Clutinger, Lynnie A. Irwin, Michael E. Laurila, Chahrzad Montrose-Rafizadeh, Brian A. Oldham, Minmin Wang, Leonard L. Winneroski, Chaoyu Xie, Jeremy S. York, Nathan P. Yumibe, Richard W. Zink and Nathan Mantlo

Eli Lilly and Company, Lilly Research Labs, Lilly Corporate Center, Indianapolis, IN 46285, USA

Received 15 July 2007; revised 14 October 2007; accepted 15 October 2007
Available online 18 October 2007

Abstract—A series of potent amide linked PPARγ/δ dual agonists (**1a**) has been discovered through rational design. In the ZDF rat model of type 2 diabetes, compound (*R*)-3-[4-(3-{1-[(5-chloro-1,3-dimethyl-1*H*-indole-2-carbonyl)-amino]-ethyl}-5-fluoro-phenoxy)-2-ethyl-phenyl]-propionic acid (**42**) from this series has demonstrated glucose lowering efficacy comparable to the marketed PPARγ agonist rosiglitazone with less weight gain.

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily of ligand-modulated transcription factors. There are three PPAR subtypes, namely PPARα, γ, and δ. PPARs play a central role in regulating the storage and catabolism of dietary fats.[1] PPARα agonists, such as fenofibrate, are effective at lowering serum triglycerides and raising high-density lipoprotein (HDL) cholesterol.[1,2] The role of PPARγ has been extensively studied and is known to be involved with glucose homeostasis, insulin sensitization, and fat storage. PPARγ agonists, such as rosiglitazone, 5-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-benzyl}-thiazolidine-2,4-dione, increase insulin sensitivity and have been approved for the treatment of type 2 diabetes.[3] While not as extensively studied as the other subtypes, the role of PPARδ has become clearer recently with the generation of potent, selective ligands for this PPAR subtype. As exemplified in studies with GW501516, {2-methyl-4-[4-methyl-2-(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid, PPARδ activation appears to increase fatty acid β-oxidation, insulin sensitivity, and HDL cholesterol.[4,5]

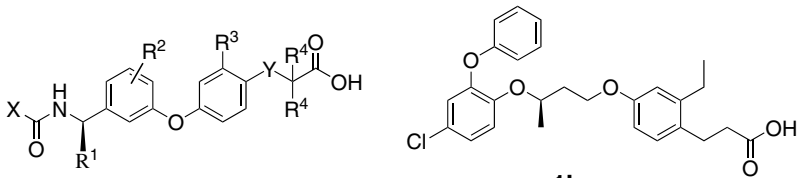
The primary goals of the present work were to develop a PPAR agonist to treat type 2 diabetes and to prevent associated cardiovascular disease while reducing the weight gain typically observed with PPARγ activation. We hypothesized that a PPARγ/δ dual agonist could effectively lower glucose and hemoglobin A1c levels while improving the dyslipidemia commonly seen in diabetic patients by simultaneously activating both receptor subtypes.[6] In addition, we hypothesized that beneficial effects could be achieved with a reduced weight gain profile due to PPARδ induced activation of fatty acid β-oxidation and a reduced need to drive efficacy solely through PPARγ activation. Recently, we reported the design and synthesis of a series of novel ether linked PPARγ/δ dual agonists, analogs of compound **1b** (Fig. 1), and showed that a PPARγ/δ dual agonist with a properly controlled γ/δ ratio can be efficacious on glucose control while producing less weight gain than rosiglitazone in animal models of diabetes.[6,7]

In an earlier effort to identify structurally novel PPAR ligands, PPARγ, δ dual agonist **5** was discovered. Through extensive SAR studies around **5**, we identified molecules with a wide range of PPARγ/δ in vitro activity. Herein, we report the design, synthesis, and biological evaluation of these novel amide linked PPARγ/δ dual agonists (**1a**, Fig. 1).

A general synthetic scheme is illustrated in Scheme 1. Nitriles **2**[8] were hydrogenated in the presence of 5% Pd/C or Raney nickel to give the corresponding amines

Keywords: PPAR; Diabetes; Dyslipidemia.
* Corresponding author. Tel.: +1 317 277 9158; fax: +1 317 276 1417; e-mail: shi_qing@lilly.com

0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.10.047



1a

X=Ar, heteroAr
R^1=H, Me
R^2=H, Me, F
R^3=Me, Et
Y=CH_2, O
R^4=H, Me

1b

Figure 1. Amide linked series **1a** and ether linked compound **1b**.

(**3**). Coupling **3** with a variety of aryl carboxylic acids (**4**)[8] and subsequent hydrolyses afforded carboxylic acids **5**–**24**. Indole derivatives **25**–**33** were prepared in an analogous fashion starting from **3** and various indole-2-carboxylic acids.[8]

Pure more active enantiomers of benzyl-substituted compounds **42** and **43** were prepared as described in Scheme 2. Commercially available 1,3-dibromo-5-fluoro-benzene **34** and 3-(2-ethyl-4-hydroxy-phenyl)-propionic acid ethyl ester **35**[8] were subjected to a 2,2,6,6,-tetramethylheptane-3,5-dione accelerated Ullmann reaction to give diaryl ether **36**.[9] Stille coupling of **36** and tributyl (1-ethoxyvinyl) tin in the presence of dichlorobis (triphenylphosphine) palladium (II) and subsequent hydrolysis provided ketone **37**. The ketone was reduced enantioselectively to the corresponding alcohol (**38**) using *N*,*N*-diethylaniline-borane and a catalytic amount of (*R*)-2-methyl-oxazaborolidine (MeCBS).[10] Treatment of alcohol **38** with diphenyl phosphorazidate (dppa) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded a mixture of the desired azide (**39**) and a phosphate intermediate, which was also converted to azide **39** using trimethylsilyl azide in the presence of fluoride anion. Reduction of azide yielded amine **40**. This enatiomerically enriched compound (*R* configuration, 67–85% ee) was purified by chiral chromatography with a Chiralcel OD column (eluent: 0.2% DMEA in MeOH) to give **40** as a single enantiomer (100% ee). Coupling amine **40** with 5-chloro-1,3-dimethyl-1*H*-indole-2-carboxylic acid[8] or commercially available 5-chloro-3-methyl-benzo [*b*]thiophene-2-carboxylic acid **41** and subsequent hydrolyses provided carboxylic acids **42** and **43**, respectively.

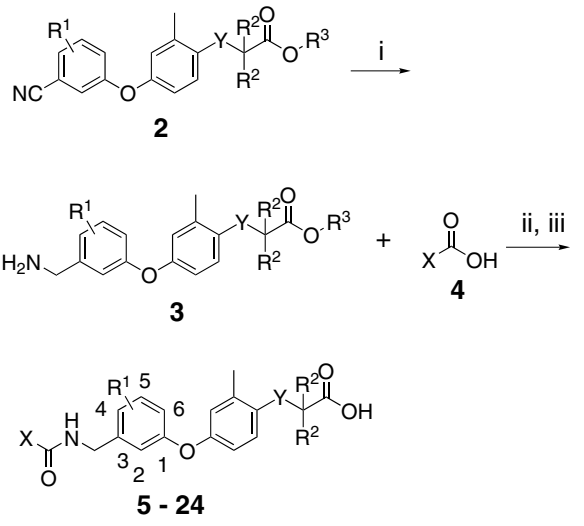
The final compounds were tested for PPAR binding (IC_{50})[11] and receptor transactivation (EC_{50})[12] activities (Tables 1–3). Based on the SAR results from our previously reported ether linked series (**1b**),[2,3] we examined the effects of ortho substitution on the tailpiece phenyl of **5** (Table 1). Substitutions of Me, Et, Cl, F, Br, and OMe were all well tolerated for PPARγ/δ activities (**6**–**10** and **13**). Fluorine (**9**) and methoxy (**13**) substitution led to increased PPARα activities. While a strong electron withdrawing group, CF_3, was detrimental to all PPAR activity (**11**), the sterically demanding phenoxy group (**12**) attenuated only PPARγ/δ activities.

Compound **6** was identified as a potent and selective PPARγ/δ dual agonist. Replacement of the CF_3 substituent in **6** by Me, Cl, and OMe resulted in compounds **14**, **15**, and **17**, which had significantly reduced PPARδ functional activities ($EC_{50}\delta$ = 286, 254, and 376 nM, respectively). The OCF_3 analog (**16**) showed attenuated PPARγ/δ affinity ($IC_{50}\gamma$ = 47 nM; $IC_{50}\delta$ = 54 nM). Removing the CF_3 group from **6** was detrimental to PPARδ potency (**18**, $EC_{50}\delta$ = 1878 nM).

Substitution on the spacer phenyl ring resulted in compounds **19**–**23**. Compared to parent compound **9** ($EC_{50}\delta$ = 22 nM), PPARδ functional activity was improved by 5-Me substitution (**20**, $EC_{50}\delta$ = 4 nM). The 5-F substituted compound (**22**) had comparable PPARα, γ, and δ activities to **9**. Substitution at C-4 and C-6 on the spacer phenyl ring (**19**, **21**, and **23**) reduced PPARδ functional activity.

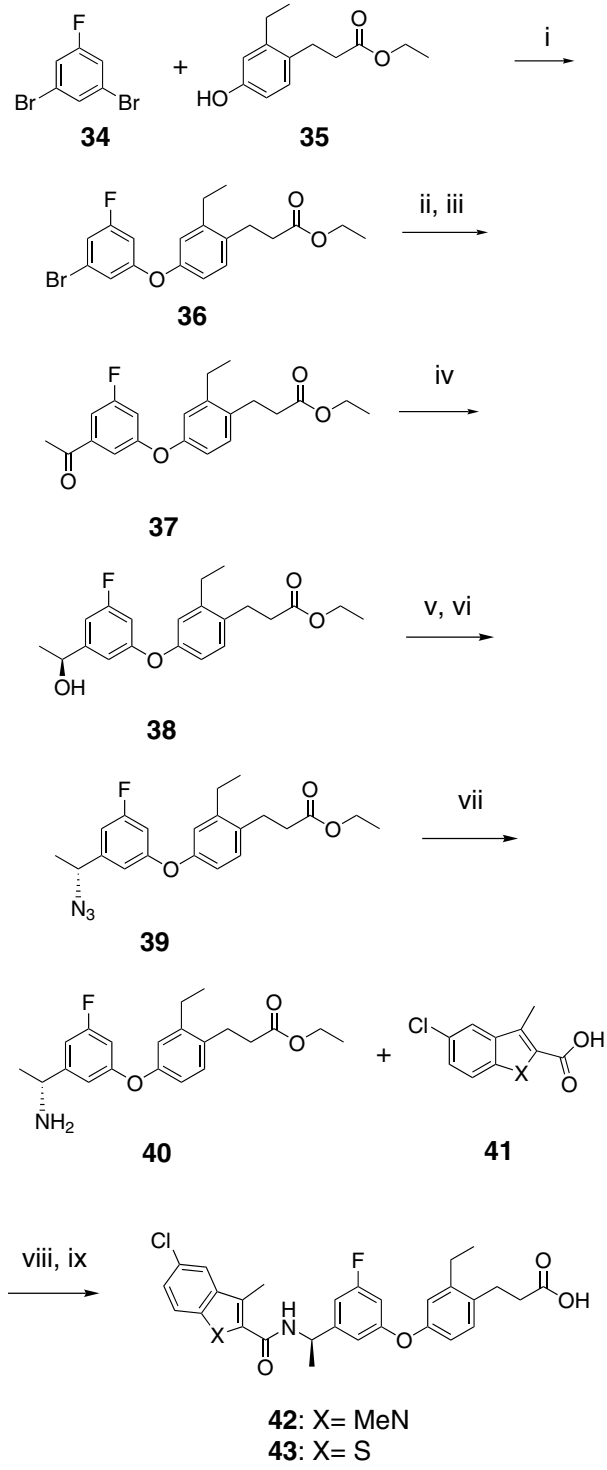
Variation at the carboxylic acid headpiece influenced the PPAR activity of these ligands. With the dihydrocinnamic acid headpiece, **24** showed comparable PPARδ activity and reduced PPARα and γ activities versus fibrate-based **6**.

To further reduce PPARα activity and increase PPARδ activity, we examined the tailpiece SAR through a set of substituted indoles (**25**–**33**) using the dihydrocinnamic acid headpiece (Table 2). Among the monosubstituted indoles, 5-Cl substitution afforded the most potent and selective PPARγ/δ dual agonist (**26**). The 5,6-dichloro-indole **30** showed attenuated PPARγ activity. With 5-Cl substitution, N-methylation (**31**) tended to further reduce PPARα and γ activity. Methylation at C-3 (**32**) increased PPARα activity, maintained PPARγ activity, and significantly improved PPARδ functional activity. The combined trisubstituted indole compound (**33**) proved to be a potent and selective PPARγ/δ dual agonist as shown in Table 2, especially showed improved δ activity compared with substituted phenyl compounds.



5: X= 4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
6: X= 2-Me-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
7: X= 2-Et-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
8: X= 2-Cl-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
9: X= 2-F-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
10: X= 2-Br-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
11: X= 2-CF_3-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
12: X= 2-OPh-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
13: X= 2-OMe-4-CF_3-phenyl, R^1=H, Y=O, R^2=Me
14: X= 2-Me-4-Me-phenyl, R^1=H, Y=O, R^2=Me
15: X= 4-Cl-2-Me-phenyl, R^1=H, Y=O, R^2=Me
16: X= 2-Me-4-OCF_3-phenyl, R^1=H, Y=O, R^2=Me
17: X= 4-OMe-2-Me-phenyl, R^1=H, Y=O, R^2=Me
18: X= 2-Me-phenyl, R^1=H, Y=O, R^2=Me
19: X= 2-F-4-CF_3-phenyl, R^1=6-Me, Y=O, R^2=Me
20: X= 2-F-4-CF_3-phenyl, R^1=5-Me, Y=O, R^2=Me
21: X= 2-F-4-CF_3-phenyl, R^1=4-Me, Y=O, R^2=Me
22: X= 2-F-4-CF_3-phenyl, R^1=5-F, Y=O, R^2=Me
23: X= 2-F-4-CF_3-phenyl, R^1=4-F, Y=O, R^2=Me
24: X= 2-Me-4-CF_3-phenyl, R^1=H, Y=CH_2, R^2=H

Scheme 1. Reagents and conditions: (i) H_2, HOAc, 5% Pd/C, rt, 60 Psi, overnight or Raney nickel, 2 N NH_3 in MeOH, 40 °C, 60 Psi, overnight; (ii) EDC, HOBT, DIEA; (iii) LiOH, H_2O, 1,4-dioxane.



42: X= MeN
43: X= S

Scheme 2. Reagents and conditions: (i) 2,2,6,6-tetramethyl-3,5-heptanedione, Cs_2CO_3/NMP, CuCl, 120 °C, overnight; (ii) tributyl (1-ethoxyvinyl) tin, Pd $(PPh_3)_2Cl_2$, toluene; (iii) 1 N HCl; (iv) (*R*)-MeCBS, *N*,*N*-diethylaniline-borane, toluene; (v) dppa, DBU, toluene; (vi) $TMSN_3$, TBAF (1 M in THF), 40 °C; (vii) Ph_3P, THF, H_2O; (viii) EDC, HOBT, DIEA; (ix) LiOH, H_2O, dioxane.

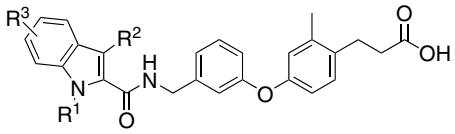
Further modifications included substitution at the benzylic carbon of the linker and evaluation of the benzothiophene tailpiece (Table 3). We used the ethyl instead of methyl substituted dihydrocinnamic acid headpiece to hinder β-oxidation.[6] Benzothiophene **43** exhibited a similar in vitro profile compared with indole **42**, both being potent and selective PPARγ/δ dual agonists with more relaxed γ activity compared with compound **33**.

Compound **42** (~99% ee) was studied for in vivo evaluation in the male ZDF rat, a model of type 2 diabetes.[6] As shown in Figure 2, **42** dose-dependently lowered plasma glucose levels in this model. Compound **42** demonstrated 50% glucose normalization (ED_{50}) at 0.82 mg/kg compared to 1 mg/kg for rosiglitazone. Moreover, compound **42** showed significantly ($p < 0.05$) less weight gain than rosiglitazone at the

Table 1. Binding IC_{50}[11] and receptor transactivation EC_{50}[12] data[13] on human PPARs of compounds **5–24**

Compound	hPPARα IC_{50} (nM)	hPPARα EC_{50} (nM)	hPPARγ IC_{50} (nM)	hPPARγ EC_{50} (nM)	hPPARδ IC_{50} (nM)	hPPARδ EC_{50} (nM)
5	3487	1253	18	42	6	95
6	1763	921	9	24	3	38
7	1127	828	10	57	4	81
8	1230	836	15	49	3	59
9	640	466	12	24	4	22
10	1594	590	12	43	3	36
11	10,313	n.a.	203	1058	40	2870
12	1483	706	114	479	32	409
13	463	329	7	16	4	30
14	1749	1042	7	25	4	286
15	7154	2205	9	28	6	254
16	4850	420	47	10	54	50
17	4200	1504	8	26	12	376
18	n.b.	2727	20	125	64	1878
19	188	792	5	24	3	96
20	313	544	12	37	5	4
21	331	877	17	43	6	86
22	728	754	8	22	3	48
23	384	1053	8	28	3	119
24	n.b.	2888	126	345	5	33
Rosiglitazone	n.b.	n.a.	67	308	n.b.	n.a.

Table 2. Binding IC_{50}[11] and receptor transactivation EC_{50}[12] data[13] on human PPARs of compounds **25–33**



Compound	R^1	R^2	R^3	hPPARα IC_{50} (nM)	hPPARα EC_{50} (nM)	hPPARγ IC_{50} (nM)	hPPARγ EC_{50} (nM)	hPPARδ IC_{50} (nM)	hPPARδ EC_{50} (nM)
25	H	H	4-Cl	n.b	2997	258	1088	12	1300
26	H	H	5-Cl	10,034	2459	13	25	3	47
27	H	H	6-Cl	1132	588	233	348	3	80
28	H	H	5-Br	7457	2770	8	32	4	93
29	H	H	7-Br	4865	2404	37	158	9	527
30	H	H	5,6-di-Cl	4352	1887	95	238	5	59
31	Me	H	5-Cl	n.b.	2735	98	135	3	87
32	H	Me	5-Cl	2104	558	27	24	3	6
33	Me	Me	5-Cl	n.b.	2654	35	44	3	4

Table 3. Binding IC_{50}[11] and receptor transactivation EC_{50}[12] data[13] on human PPARs of compounds **42** and **43**

Compound	X	hPPARα IC_{50} (nM)	hPPARα EC_{50} (nM)	hPPARγ IC_{50} (nM)	hPPARγ EC_{50} (nM)	hPPARδ IC_{50} (nM)	hPPARδ EC_{50} (nM)
42	MeN	10,257	2824	39	116	5	1
43	S	9336	n.a.	50	163	5	7

same doses (Fig. 3). Additionally, compound **42** significantly lowered plasma triglycerides and plasma free fatty acids at 3 mg/kg dose compared with the control group (Figs. 4 and 5).

In summary, we have presented the synthesis and in vitro characterization of a novel series of potent and selective PPARγ/δ dual agonists. In the ZDF rat model, **42** demonstrated efficacy in lowering plasma glucose levels comparable to rosiglitazone with a significantly reduced weight gain side effect at the same doses. These results further supported our initial hypothesis that a PPARγ/δ dual agonist with a properly controlled PPARγ/δ in vitro profile can reduce the weight gain side effect associated with marketed PPARγ agonists.

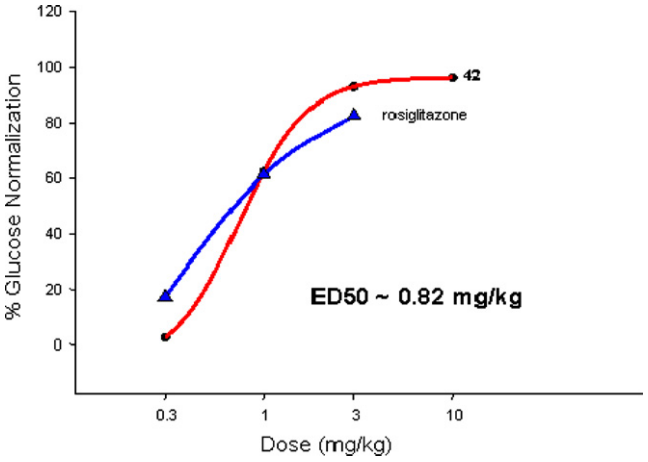


Figure 2. Dose–response for effects of compound **42** and rosiglitazone on glucose normalization in ZDF rats after 7 days of oral gavage dosing.

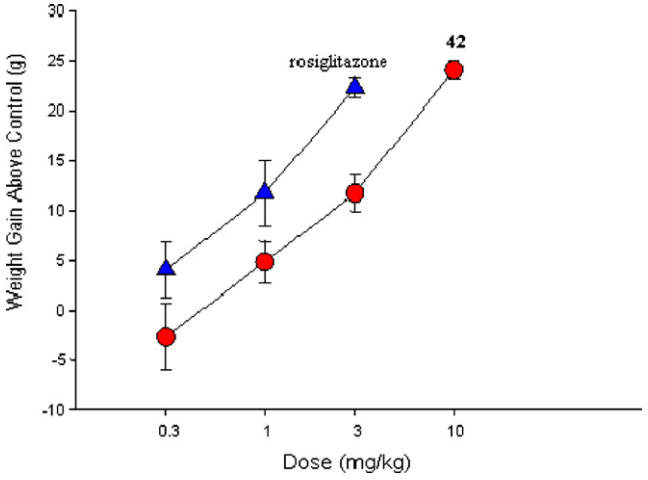


Figure 3. Dose–response for effects of compound **42** and rosiglitazone on body weight in ZDF rats after 7 days of oral gavage dosing.

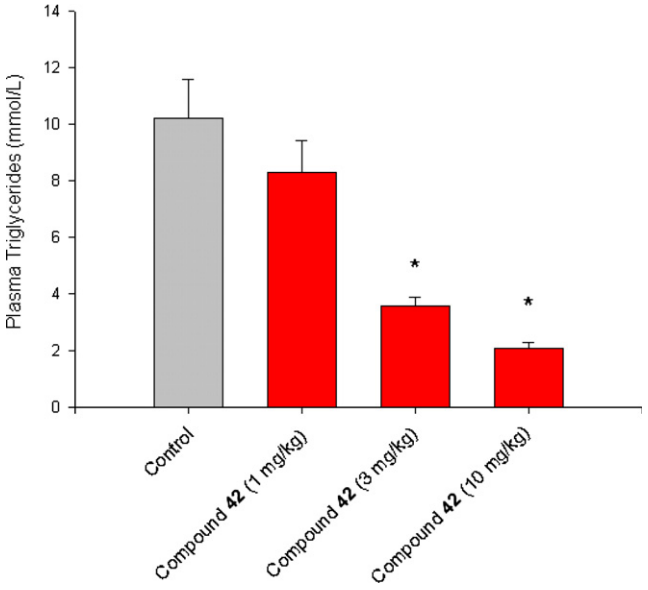


Figure 4. Dose–response for effects of compound **42** on plasma triglycerides in ZDF rats after 7 days of oral gavage dosing.

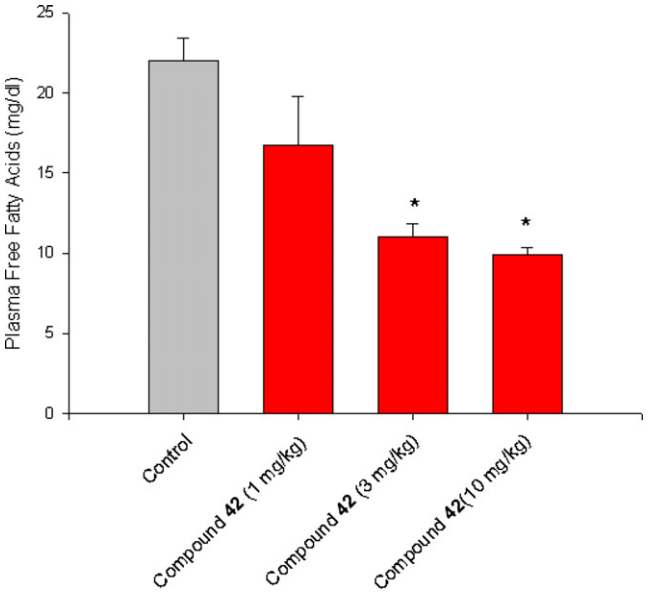


Figure 5. Dose–response for effects of compound **42** on fatty acids in ZDF rats after 7 days of oral gavage dosing.

Acknowledgment

Q.S. thanks James R. McCarthy for valuable discussions regarding the research.

References and notes

1. Willson, T.; Brown, P.; Sternbach, D.; Henke, B. *J. Med. Chem.* **2000**, *43*, 527.
2. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J.-C. *Circulation* **1998**, *98*, 2088.
3. Lehmann, J.; Moore, L.; Smith-Oliver, T.; wilkison, W.; Willson, T.; Kliewer, S. *J. Biol. Chem.* **1995**, *270*, 12953.
4. Lee, C.-H.; Olson, P.; Hevener, A.; Mehl, I.; Chong, L.-W.; Olefsky, J.; Gonzalez, F.; Jungyeob, H.; Kang, H.; Peters, J.; Evans, R. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 3444.
5. Oliver, W.; Shenk, J.; Snaith, M.; Russell, C.; Plunket, K.; Bodkin, N.; Lewis, M.; Winegar, D.; Sznaidman, M.; Lambert, M.; Xu, H.; Sternbach, D.; Kliewer, S.; Hansen, B.; Willson, T. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 5306.
6. Xu, Y.; Etgen, G. J.; Broderick, C. L.; Canada, E. J.; Gonzalez, I.; Lamar, J.; Montrose-Rafizadeh, C.; Oldham, B. A.; Osborne, J. J.; Xie, C.; Shi, Q.; Winneroski, L. L.; York, J.; Yumibe, N.; Zink, R.; Mantlo, N. *J. Med. Chem.* **2006**, *49*, 5649.
7. Gonzalez, I. C.; Lamar, J.; Iradier, F.; Xu, Y.; Winneroski, L. L.; York, J.; Yumibe, N.; Zink, R.; Montrose-Rafizadeh, C.; Etgen, G. J.; Broderick, C. L.; Oldham, B. A.; Mantlo, N. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1052.
8. Canada, E. J.; Gossett, L.; Mantlo, N.; Shi, Q.; Wang, M.; Warshawsky, A. M.; Xu, Y. WO 2005054176.
9. Buck, E.; Song, Z.; Tschaen, D.; Dormer, P.; Volante, R.; Reider, P. *Org. Lett.* **2002**, *4*, 1623.
10. Salunkhe, A.; Burkhardt, E. *Tetrahedron Lett.* **1997**, *38*, 1523.
11. IC_{50}: Concentration of test compound required to displace 50% of tritiated ligand: tritium labeled PPARα/PPARδ agonist, 2-(4-{2-[3-(2,4-difluoro-phenyl)-1-heptyl-ureido]-

ethyl}-phenoxy)-2-methyl-butyric acid, and tritium labeled PPARγ agonist, 2-methyl-2-(4-{3-{propyl-(5-pyridin-2-yl-thiophene-2-sulfonyl)-amino}-propyl}-phenoxy)-propionic acid, were used; n.b.: $IC_{50} > 10$ μM.

12. EC_{50}: Concentration of test compound required to produce 50% of the maximal reporter activity. Gal4-hPPARα was used to eliminate interference by endogenous PPARγ receptors in CV-1 cells; n.a.: $EC_{50} > 10$ μM.
13. Minimum significant ratio (MSR, smallest ratio of affinities/potencies for statistical significance in assay data) for PPARα, γ, and δ: IC_{50}: 1.5, 2.6, 1.3; EC_{50}: 2.5, 1.8, 2.9.