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Design and synthesis of indane-ureido-thioisobutyric acids: A novel class of PPARα agonists

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Abstract—A series of aminoindane derivatives were synthesized and shown to be potent PPARα agonists. The compounds were obtained as racemates in 12 steps, and tested for PPARα activation and PPARα mediated induction of the HD gene. SAR was developed by variation to the core structure as shown within. Oral bioavailability was demonstrated in a Sprague–Dawley rat, while efficacy to reduce plasma triglycerides and plasma glucose was demonstrated in *db*/*db* mice.

Peroxisome proliferators-activated receptors (PPARs) are members of a nuclear hormone receptor superfamily that are activated by endogenous saturated and unsaturated fatty acids, as well as synthetic ligands. To date, three nuclear receptor isoforms, PPARα, PPARδ, and PPARγ have been isolated in various species, with the PPARα-subtype being the first isoform cloned in multiple species, including rodent and humans. The PPARs as a whole play a central role in regulating the storage and catabolism of dietary fats,[1] with each PPAR receptor differentially expressed in a tissue-specific manner, subsequently playing a crucial role in lipid and lipoprotein homeostasis.[2,3] The PPARs have also been hypothesized to treat obesity-related syndromes, such as type 2 diabetes.[4]

PPARα is predominantly expressed in various metabolically active tissues, which include high levels of expression in the liver, kidney, heart, and brown adipose tissue, with lower levels of expression in muscle, testis, spleen, and the lung. The PPARα receptor is specifically involved in the regulation and expression of target genes responsible for lipid and lipoprotein metabolism. Upon ligand activation, the PPARα isoform forms a heterodimer with retinoid X receptor (RXR), with the heterodimer causing a downstream cascade effect that leads to the expression of target genes responsible for fatty acid degradation, such as fatty acid binding protein (FABP) and β-oxidation enzymes (acyl-CoA oxidase and 3-enoyl-hydroxyacyl CoA dehydrogenase (HD)). PPARα also regulates high-density lipoprotein (HDL) levels, which are involved in reverse cholesterol transport, by inducing the transcription of the major HDL apolipoproteins, apolipoprotein A-I and apolipoprotein A-II.[5]

The currently prescribed fibrates, such as clofibrate and fenofibrate (Fig. 1), are hypolipidemic agents effective at lowering elevated serum triglyceride levels. The triglyceride lowering activity of the fibrates is a result of increased lipoprotein lipolysis followed by β-oxidative degradation of fatty acids. The latter action combined with a reduction of fatty acid and triglyceride synthesis results in a decrease of VLDL production by the liver. Though the fibrates have been effective ligands of PPAR, their mechanism of action was not realized until the early 1990s. Consequently, the fibrates have weak affinities (>20 μM) in both rodent and human cloned PPARα receptors, with extremely poor subtype-selectiv-

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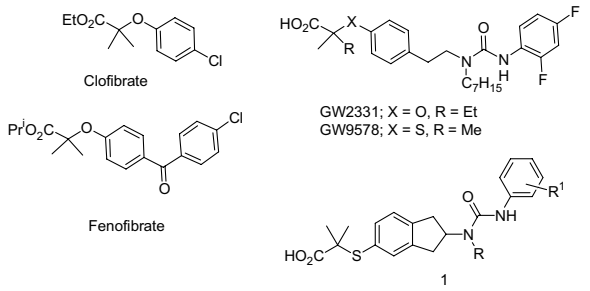
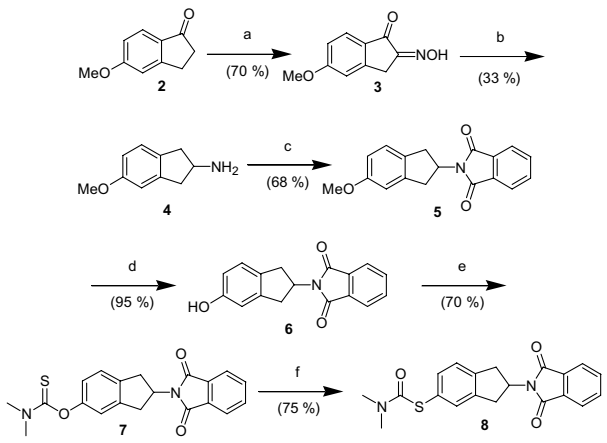


Figure 1. Structures of clofibrate, fenofibrate, GW2331, GW-9578, and thioisobutyric acid **1**.

ity. Despite the low affinity for the PPARs, clofibrate has been shown to improve glucose tolerance in type 2 diabetes patients, with obesity a risk factor in the development of diabetes. With the uncertainty of whether the α- or γ-component (or the combination thereof) of clofibrate is responsible for the therapeutic effect, the need for a PPARα-selective agonist has been a large thrust amongst several groups in the last 10 years.[6–13] Recently, GlaxoSmithKline (GSK) reported the discovery of GW2331, a ureidofibrate, found to be a potent, dual PPARα/γ agonist.[14] Subsequently, a similar motif was revealed by GSK in the form of GW-9578, a ureidobutyric acid, which was disclosed to be a potent and selective PPARα agonist with favorable hypolipidemic activity in vivo compared to fenofibrate.[15,16] Herein, we report the design and synthesis of novel indane-ureido-thioisobutyric acids as PPARα agonists.

The synthetic approach utilized toward the synthesis of the indane-ureido-thioisobutyric acids is shown in Scheme 1. Treatment of 5-methoxy-1-indanone **2** with butyl nitrite at elevated temperature afforded oxime **3**, which was subsequently reduced to aminoindane **4** via catalytic hydrogenation, using carbon-activated palladium. Protection of aminoindane **4** was achieved using phthalic anhydride at elevated temperature to afford intermediate **5**. Demethylation of ether **5** using boron tribromide at reduced temperatures affords phenol **6**, which was further acylated with dimethylthiocarbamoyl chloride in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) to provide thiocarbamate **7**. Newman–Kwart rearrangement of thiocarbamate **7** to carbamate **8** was achieved at 340 °C in excellent yields.

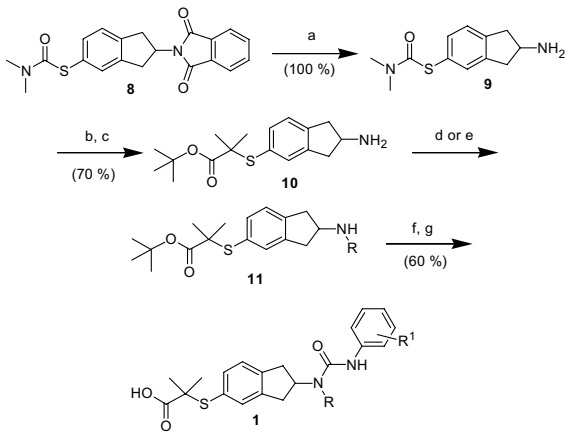


Scheme 1. (a) MeOH, HCl, $CH_3(CH_2)_3ONO$, 45 °C; (b) AcOH, H_2SO_4, Pd–C (10%), H_2, 60 psi, 18 h; (c) DMF, NaH (60%), 125 °C, 96 h; (d) CH_2Cl_2, BBr_3, −50 °C, 5 h; (e) DMF, DABCO, RT, 16 h; (f) neat, 340 °C, 12 min.

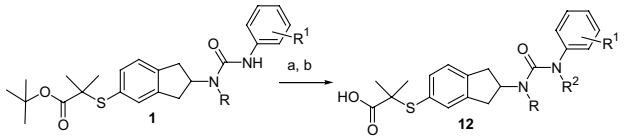
The synthesis of structure **1** was completed using the chemistry outlined in Scheme 2. Deprotection of phthalimide **8** to afford 2-aminoindane **9** was achieved using hydrazine at elevated temperatures. In one-pot, deprotection of the thiophenol (not shown) was accomplished using standard base hydrolysis conditions, followed by immediate treatment with *tert*-butyl 2-bromoisobutyrate to afford thiobutyrate **10**. Acylation of amine **10** with acid chlorides followed by reduction of the resultant amide with boron–THF complex provided secondary amine **11**, which was further acylated with arylisocyanates and deprotected under acidic conditions to afford analogs of **1**.

Alternatively, intermediate amine **10** was reductively aminated with aldehydes or ketones, using sodium triacetoxyborohydride as the reducing agent, to afford secondary amines **11**, which were subsequently converted to final products **1**.

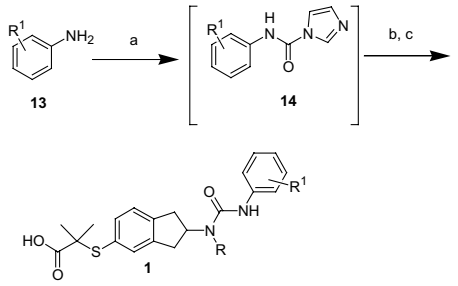
In the event that alkylation of the second urea nitrogen is desired, the chemistry shown in Scheme 3 was utilized. Alkylation of urea **1** using sodium hydride and the appropriate alkyl halide afforded *tert*-butyl protected



Scheme 2. (a) EtOH, H_2NNH_2, 78 °C, 30 min; (b) MeOH, KOH, 65 °C, 5 h; (c) *tert*-butyl 2-bromoisobutyrate, RT, 18 h; (d) i—CH_2Cl_2, TEA, RC(O)Cl, 0 °C, 16 h; ii—THF, borane–THF (1.0 M), RT, 5 h; (e) DCE, RCHO, $NaBH(OAc)_3$, RT, 18 h; (f) CH_2Cl_2, R^1PhNCO, RT, 16 h; (g) CH_2Cl_2, TFA, RT, 1 h.



Scheme 3. (a) DMF, NaH (60%), R^2-Br, RT, 5 h; (b) CH_2Cl_2, TFA, RT, 1 h.

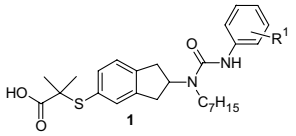


Scheme 4. (a) THF, CDI, 50 °C, 15 min; (b) THF, **11**, 50 °C, 2 h; (c) CH_2Cl_2, TFA, RT, 1 h.

intermediates (isolated), which were subsequently deprotected to afford compounds **12.**

In instances when the required isocyanates are not commercially available, the requisite analogs were synthesized using the chemistry shown in Scheme 4. Anilines **13** were treated with carbonyldiimidazole, at elevated temperatures, to afford intermediate **14**, to which was added a solution of compound **11**, to afford the *tert*-butyl protected esters, which were deprotected to afford compounds **1**.

Table 1. Biological data for aminoindane derivatives



Compound[a]	R^1	PPARα-HD[18] EC_{50} (μM)
15	2,4-diF	>10
16	H	>10
17	2-F	>10
18	2-CH_3	7.54
19	2-CF_3	6.39
20	2-OCF_3	4.99
21	2-SCF_3	1.96
22	3-F	2.67
23	3-Cl	2.09
24	3-CF_3	2.73
25	3-OCH_3	1.11
26	4-OCH_3	0.910
27	4-CF_3	1.27
28	4-SCH_3	0.419
29	4-SCF_3	0.210
30	4-*i*-Pr	0.229
31	4-$N(CH_3)_2$	0.252 (0.700)
32	4-OCF_3	0.294
(*R*)-(−)-32[b]	4-OCF_3	0.169
(*S*)-(+)-32[b]	4-OCF_3	>13
GSK-9578		0.166

[a] Target compounds were purified by reverse-phase semi-prep HPLC, isolated, and tested as carboxylic acids unless otherwise noted. Purities were judged by reverse-phase HPLC/MS at 215 and 254 nm (YMC J'Sphere C-18 column, 0.4 × 5 cm; mobile phase: MeCN–H_2O). All compounds were characterized by ESI-MS and 400-MHz ^1H NMR.

[b] >98% enantiomeric purity by chiral HPLC (Chiralcel OD column, 0.46 × 25 cm; mobile phase: 95:5: hexanes/*i*-PrOH, with 0.1% TFA; flow rate: 1 mL/min).

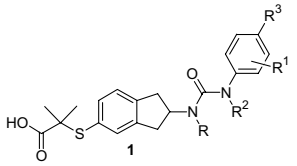
To determine the role of stereochemistry on gene activation, compounds **32**, **33**, and **35** were resolved by chiral HPLC to yield each enantiomer in >98% ee. The absolute configuration of the (*S*)-(+) enantiomer of **35** was initially characterized by vibrational circular dichroism (VCD).[17] The results in Tables 1 and 2 indicate that (*R*)-(−) enantiomer of **35** is the preferred absolute configuration in all three cases.

Compounds **15**–**32** were evaluated for their agonist activity by using a rat hepatoma cell line for the induction of PPARα target gene, 3-enoyl-hydroxyacyl CoA dehydrogenase (HD).[18] The results obtained in Table 1 were compared with corresponding data for GW-9578 (PPARα agonist) as a reference compound. The direct analogue of GSK-9578, **15**, exhibited no activity in the HD gene induction assay. However, introduction of o-substitution, such as a 2-trifluoromethyl group, as in **19**, enhanced receptor affinity (EC_{50} = 6.4 μM). Improved HD induction was realized through the introduction of a *p*-trifluoromethyl, as in **27** (EC_{50} = 1.2 μM). Methylthio analogue **28** demonstrated an additional 3-fold increase in potency over **27**, while trifluoromethyl thio analogue **29**, isopropyl analogue **30**, dimethylamino analogue **31**, and trifluoromethoxy analogue **32** show a further 5-fold enhancement in potency in the HD induction assay. Each of the enantiomers of **32**, (*R*)-(−)-**32**and (*S*)-(+)-**32**, was tested, with only enantiomer (*R*)-**(−)-32** demonstrating notable PPARα receptor activity (EC_{50} = 0.172 μM).

Using analogue **32** as a starting point, the length of the urea side chains (R and R^2) as well as the substitution pattern on the urea-phenyl moiety (R^1), as shown in Table 2, was explored. *Des*-heptyl analogue **33** demonstrated comparable affinity to **32** in the HD gene induction assay. Varying the chain length indicated that the smaller, aliphatic chains were favored. For example, ethyl analogues **35** (4-fold), **36** (7-fold), and **37** (9-fold) demonstrated a significant enhancement in potency compared to **32**, while octyl analogue **54** showed a 6-fold loss of activity. Branching of the aliphatic side chain was tolerated when the branched portion was several carbon atoms removed away from the urea, as in **57** (EC_{50} = 0.479 μM), albeit branching was not an optimal substitution. Substitution of the second urea nitrogen (R^2), demonstrated by compounds **39** and **46**, with aliphatic chains afforded inactive compounds. Further exploration of the structure–activity relationship of the trifluoromethoxyphenyl moiety afforded analogues **60**–**63**. Additional substitution on the urea-phenyl ring led to either less potent or inactive compounds. Each enantiomer of **35**, (*R*)-(−)-**35** and (*S*)-(+)-**35**, was studied, and both enantiomers furnished notable PPARα receptor potency (EC_{50} = 0.014 and 0.171 μM, respectively). However, (*R*)-(−) was 10-fold more potent than the (*S*)-(+).

Primarily using PPARα activity, human liver microsomal stability,[19] and structural diversity to triage compounds, several compounds were selected as potential candidates for in vivo profile. Table 3 shows the in vitro metabolism (human liver microsomal stability) and pharmacokinetic profiles in rats at doses of

Table 2. PPARα-mediated HD gene induction and PPARα-Gal4 co-transfection data



Compound[a]	R	R_1	R_2	R_3	PPARα-HD[18] EC_{50} (μM)
33	H	H	H	OCF_3	0.096
(*R*)-(−)-33[b]	H	H	H	OCF_3	0.146
(*S*)-(+)-33[b]	H	H	H	OCF_3	1.11
34	CH_3	H	H	OCF_3	2.85
35	CH_2CH_3	H	H	OCF_3	0.033
(*R*)-(−)-35[b]	CH_2CH_3	H	H	OCF_3	0.002
(*S*)-(+)-35[b]	CH_2CH_3	H	H	OCF_3	0.165
36	CH_2CH_3	H	H	*i*-Pr	0.032
37	CH_2CH_3	H	H	SCF_3	0.023
38	CH_2CH_3	H	H	$N(CH_3)_2$	0.117
39	CH_2CH_3	H	CH_3	OCF_3	>1.0
40	$(CH_2)_2CH_3$	H	H	OCF_3	0.158
41	$(CH_2)_3CH_3$	H	H	OCF_3	0.195
42	$(CH_2)_3CH_3$	H	H	*i*-Pr	0.260
43	$(CH_2)_3CH_3$	H	H	SCF_3	0.160
44	$(CH_2)_3CH_3$	H	H	$N(CH_3)_2$	0.561
45	$(CH_2)_4CH_3$	H	H	OCF_3	0.105
46	H	H	$(CH_2)_4CH_3$	OCF_3	>5.0
47	$(CH_2)_4CH_3$	H	H	*i*-Pr	0.159
48	$(CH_2)_4CH_3$	H	H	SCF_3	0.046
49	$(CH_2)_4CH_3$	H	H	$N(CH_3)_2$	0.141
50	$(CH_2)_5CH_3$	H	H	OCF_3	0.166
51	$(CH_2)_5CH_3$	H	H	*i*-Pr	0.180
52	$(CH_2)_5CH_3$	H	H	SCF_3	0.249
53	$(CH_2)_5CH_3$	H	H	$N(CH_3)_2$	0.219
54	$(CH_2)_7CH_3$	H	H	OCF_3	1.03
55	$CH(CH_3)_2$	H	H	OCF_3	>5.0
56	$CH_2CH(CH_3)_2$	H	H	OCF_3	2.34
57	$(CH_2)_2CH(CH_3)_2$	H	H	OCF_3	0.386
58	$(CH_2)_2OCH_3$	H	H	OCF_3	0.425
59	$(CH_2)_3CF_3$	H	H	OCF_3	0.707
60	CH_2CH_3	2-CH_3	H	OCF_3	0.598
61	CH_2CH_3	2-Br	H	OCF_3	>1.0
62	CH_2CH_3	3-Cl	H	OCF_3	>3.0
63	CH_2CH_3	3-Br	H	OCF_3	>3.0
GSK-9578					0.084
Fenofibrate					>10
Ciprofibrate					>10

[a] Target compounds were purified by reverse-phase semi-prep HPLC, isolated, and tested as carboxylic acids unless otherwise noted. Purities were judged by reverse-phase HPLC/MS at 215 and 254 nm (YMC J'Sphere C-18 column, 0.4 × 5 cm; mobile phase: MeCN–H_2O). All compounds were characterized by ESI-MS and 400-MHz ^{1}H NMR. Compounds are racemates unless otherwise noted by stereochemical assignment.

[b] >98% enantiomeric purity by chiral HPLC (Chiralcel OD column, 0.46 × 25 cm; mobile phase: 95:5: hexanes/*i*-PrOH, with 0.1% TFA; flow rate: 1 mL/min).

3.0 mg/kg (iv) and 30.0 mg/kg (po). The results shown in Table 3 suggest the compounds have reasonable oral bioavailability, though the highest exposures of drug were seen with **35** and **38**. Both **35** and **38** exhibited oral bioavailability in rats (59% and 58%, respectively), with acceptable oral $t_{1/2}$ (4.0 and 4.4 h, respectively), and relatively low clearance (0.1 and 0.11 mL/min/kg, respectively). The pharmacokinetic and in vitro pharmacological properties of **35** warranted assessment in pharmacological models in mice.

The hypolipidemic and hypoglycemic effects of compound **35** were demonstrated in *db*/*db* mice, an obese rodent model of type 2 diabetes characterized by severe hyperglycemia, hypertriglyceridemia, and insulin resistance.[20] The 6- to 7-week-old female *db*/*db* mice were treated with compound **35** by oral gavage at 1.0 mg/kg for 11 days. Compound **35** demonstrated a significant hypotriglyceridemic and hypoglycemic effect, with a reduction in plasma triglycerides (56%), plasma glucose (60%), and plasma insulin (53%) levels suggesting that the compound may improve insulin sensitivity. In the same study, **35** reduced the body weight of the mice by 59%. Similarly, (*R*)-(−)-**35** was dosed by oral gavage at 0.1 mg/kg in *db*/*db* mice (6- to 7-week-old female mice; 11-day dosing regimen). Even at this low dose,

Table 3. Pharmacokinetic profiles of **35**–**38**, **45**, **48**, and **49**[a]

Compound	HLM stability[b] ($t_{1/2}$, min)	C_{max} ± SE (μg/mL)	AUC ± SE (μg h/mL)	$t_{1/2}\beta$ (h)	CL_{tot} (mL/min/kg)	BA[c] (%)
35	100	39.27 ± 7.87	290.28 ± 93.49	4.0 ± 1.27	0.10	59
36	12	32.36 ± 19.48	37.13 ± 16.68	2.92 ± 1.01	0.81	34
37	100	5.67 ± 1.29	101.02 ± 50.3	3.84 ± 1.84	0.30	100
38	80	72.3 ± 32.17	273.46 ± 82.4	4.46 ± 1.12	0.11	58
45	100	16.63 ± 8.62	121.36 ± 59.85	7.19 ± 1.35	0.25	24
48	76	8.02 ± 3.36	54.72 ± 28.76	4.05 ± 0.55	0.55	59
49	94	20.79 ± 7.00	63.58 ± 24.07	2.60 ± 0.56	0.47	62

[a] Compounds were dosed in fasted rats, $n = 6$, po @ 30 mg/kg, iv @ 3 mg/kg.
[b] HLM, human liver microsome. Compounds were incubated at 37 °C at 5 μM and 1 mg protein/mL microsomal prep.[19]
[c] BA = Oral bioavailability.

Table 4. Selectivity of (*R*)-(−)-**35** for PPAR subtypes

Compound	PPARα-HD[18] ED_{50} (μM)	PPARα-Gal4[21] EC_{50} (μM)	PPARδ-Gal4[21] EC_{50} (μM)	PPARγ-Gal4[21] EC_{50} (μM)	PPARγ-aP2[22] (% BRL-49653)
(*R*)-(−)-**35**	0.002	0.170	2.1	>10	3.8%
GSK-9578	0.084	0.45	0.15	0.5	0.46%
Rosiglitazone				0.19	0.12 μM

compound (*R*)-(−)-**35** demonstrated a significant decrease in both serum triglycerides (43%) and serum insulin (49%), with a modest decrease in serum glucose (16%).

In addition, (*R*)-(−)-**35** was assessed for its ability to stimulate various human PPAR subtypes (α, γ, δ; Table 4) with receptor activation assessed in co-transfection assays. For this purpose, Gal4 PPAR chimeric receptors were expressed in transiently transfected HEK293 cells.[21] Further selectivity of (*R*)-(−)-**35** was determined by evaluating the induction of aP2 (PPARγ-aP2) mRNA in human preadipocytes (Table 3).[22] As demonstrated in Table 4, (*R*)-(−)-**35** is potent toward the activation of the PPARα co-transfection assay ($EC_{50} = 0.170$ μM) and demonstrates high selectivity over the δ- and γ-receptors in the PPARδ and PPARγ-Gal4 co-transfection assays, as well as the aP2 induction assay. PPAR agonists GSK-9578 (PPARα) and Rosiglitazone (PPARγ-selective) were assessed in these assays as well.

In conclusion, we have investigated a series of indane-ureido-thioisobutyric acids as potent and efficacious PPARα agonists. We identified (*R*)-(−)-**35** as a highly selective PPARα receptor agonist and demonstrated that this compound has excellent oral efficacy in *db*/*db* mice, with the ability to significantly decrease hypotriglyceridemic and hypoglycemic effects, at a low dose (1.0 mg/kg). On the basis of an assortment of preclinical data, (*R*)-(−)-**35** was advanced into development as a selective PPARα agonist that could be useful for the treatment of several clinical indications for which the marketed fibrates are used.

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17. BioTools, 17546 Bee Line Hwy, Jupiter, FL 33458. X-ray crystallography of an advanced intermediate of *R*-(−)-**35** was obtained to verify the absolute configuration and will be published in a separate manuscript.
18. *HD bDNA assay*. H4IIE rat hepatoma cell line was obtained from ATCC. Cells were cultured in a tissue culture rack with culture medium, maintained at 37 °C and 5% CO_2. Twenty-four hours after initial seeding, the HD gene induction assay was initiated. The media was removed and replaced with low serum culture media containing vehicle or test compounds. The cells were incubated for 24 h, to which was added lysis buffer with HD gene specific CE, LE, BL prbles to initiate the bDNA HD mRNA assay. At the end of the assay, the luminescence was quantitated in a Dynex MLX microtiter plate luminometer. EC50 full dose–response data were obtained using a 15-pt curve (10^{-12} M to 10^{-5} M).
19. Compounds were tested by Absorption Systems, in Exton, PA.
20. *db*/*db* mouse female *db*/*db* mice (C57 BLK S/J-m+/+Lepr^{db}, Jackson Labs, Bar Harbor, ME), 6–7 weeks of age used. Female *db*/*db* diabetic mice (8/group) were orally gavaged once a day for 11 days with either 0.5% methylcellulose in dH_2O (vehicle) or test compound (0.5% hydroxypropyl-methylcellulose) at doses of 0.03, 0.1, 0.3, 1, 3, 10 mg/kg/day. The body weight was measured in the mornings on day 1, prior to dosing, and on day 12 before bleeding (18–24 h after the final dose for each group, the mice were anesthetized with CO_2/O_2 (70:30) and bled by retro-orbital sinus puncture into microtubes containing *c*log activator and put on ice. The serum samples were prepared by centrifugation). Serum glucose and triglycerides were determined using COBAS Mira Plus blood chemistry analyzer (Roche Diagnostics, NJ). Serum insulin was measured using ALPCO insulin ELISA kit.
21. *General transfection assay and method for PPARα, δ, γ receptors.* HEK293 cells were grown in DMEM/F-12 media supplemented with 10% FBS and glutamine. The cells were co-transfected with DNA for PPAR-Gal4 receptor and Gal4-Luciferase Reporter using DMRIE-C reagent. After 18 h, the DNA-containing medium was replaced with 5% charcoal treated FBS growth medium, which, after 6 h, was seeded in a 96-well plate and incubated at 37 °C in a CO_2 incubator overnight. The cells were challenged with test compounds, incubated for 24 h at 37 °C. The luciferase activity was assayed using the Steady-Glo Luciferase Assay Kit from Promega.
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