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Phenoxyacetic acids as PPARδ partial agonists: Synthesis, optimization, and in vivo efficacy

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ABSTRACT

A series of phenoxyacetic acids as subtype selective and potent hPPARδ partial agonists is described. Many analogues were readily accessible via a single solution-phase synthetic route which resulted in the rapid identification of key structure–activity relationships (SAR), and the discovery of two potent exemplars which were further evaluated in vivo. Details of the SAR, optimization, and in vivo efficacy of this series are presented herein.

The peroxisome proliferator activated receptors (PPARs) are important members of the nuclear receptor superfamily. These receptors are ligand activated transcription factors known to play a key role in the catabolism and storage of dietary fats. Three receptor subtypes, PPARα, PPARγ, and PPARδ, exhibiting distinct tissue expressions have been identified, and represent attractive therapeutic targets with promising clinical potential.[1] PPARδ remains the least understood PPAR subtype and currently no marketed PPARδ agonists exist. However, evidence implicating PPARδ as a key regulator of lipid homeostasis and glucose disposal is growing.[2] For example, the full PPARδ agonist GW501516[3] (**1**) has been shown to reduce serum triglycerides and prevent the decrease of HDL-c and apoA-1 levels observed in sedentary human volunteers.[2c] These positive results suggest that PPARδ is a promising target for the novel treatment of metabolic diseases.

While the number of PPARδ selective agonists described in the literature has grown in recent years, additional chemical tool compounds with a range of functional activity profiles are still needed to further elucidate the biologic roles of PPARδ and provide additional insights into potential therapeutic utilities of modulating this receptor.

As part of our effort to identify PPARδ partial agonists,[4] we searched our internal database of PPAR program compounds for potential templates to exploit. The goal of this effort was to identify potent and selective partial PPARδ agonists for testing across a panel of in vivo models. Standard PPAR binding and cell-based reporter assays were used as primary screens to profile compounds. Phenoxyacetic acid **2** (hPPARδ binding $pIC_{50} = 5.9$, hPPARδ $pEC_{50} = 6.8$, 75%max) was identified as a compound with modest potency and submaximal efficacy that could serve as a promising starting point for SAR exploration.[5]

A number of structural modifications of agonist **2** were initially designed and implemented. This ultimately resulted in the preparation of compound **3** (Fig. 1) which was in fact a potent and selective partial agonist of PPARδ (hPPARδ binding $pIC_{50}\ \delta = 7.3$; hPPARδ functional $pEC_{50} = 7.6$, 56%max). Compound **3** also demonstrated promising pharmacokinetic properties in the mouse via oral administration ($DNAUC_{0-24\ h} = 575$ ng h/mL/mg/kg).[6] This compound became our new partial agonist lead compound in order to more fully explore the structure–activity relationships of this new series, as well as to further optimize for potency, oral exposure, and in vivo efficacy.

Systematic structural modifications of this template at five positions of diversity were primarily achieved through a solution-phase synthesis as described in Scheme 1. The appropriate phenol **4** was treated with substituted bromoacetate **5** and potassium carbonate in *N*,*N*-dimethylformamide (DMF) under microwave conditions to afford the phenoxyacetic acid ester **6**. Immediately following treatment of **6** with chlorosulfonic acid,

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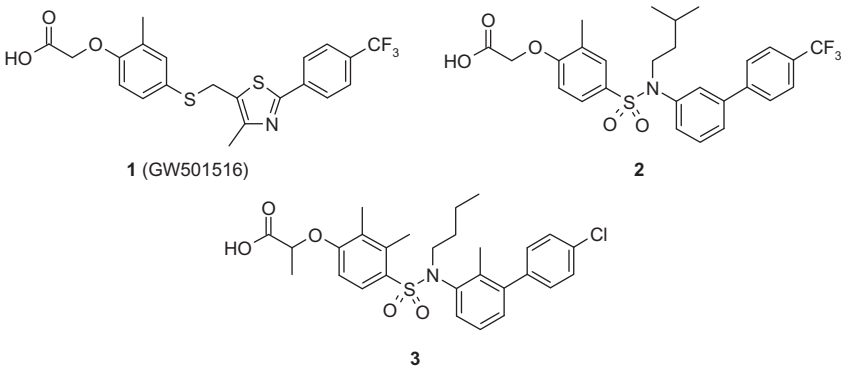
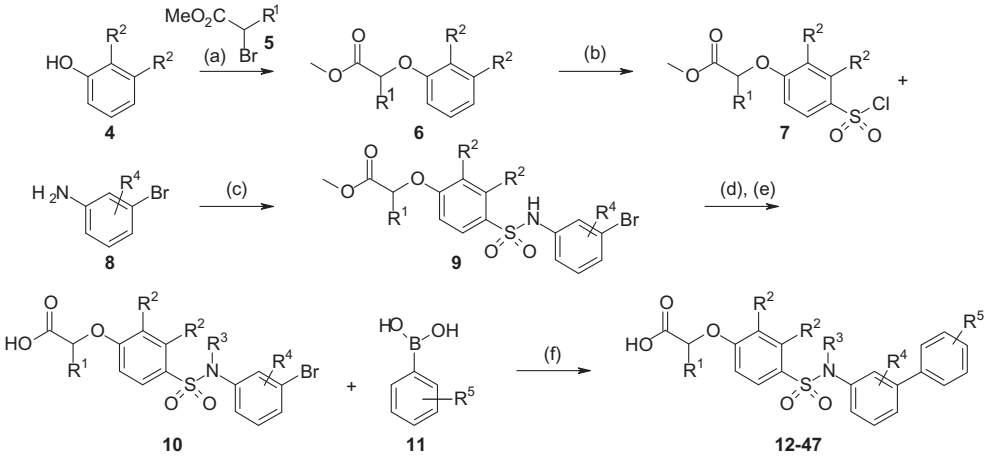


Compound	hPPAR Binding pIC$_{50}$			hPPAR δ Reporter	
	α	γ	δ	pEC$_{50}$	%Max
1	5.7	5.2[c]	8.3	8.5[c]	98
2[b]	4.8	5.3	5.9	6.8	75
3	4.7	5.1	7.3	7.6[c]	56

Figure 1. Structures and assay results for lead phenoxyacetic acids. Values are means of at least two experiments, standard deviation (SD) <0.2 unless otherwise noted. [b]Values are $n = 1$. [c]SD = 0.3.



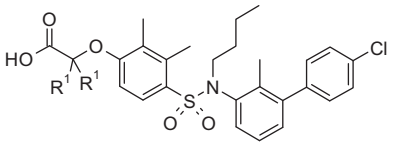
Scheme 1. Reagents and conditions: (a) K_2CO_3, DMF, microwave 170 °C, 10 min; (b) chlorosulfonic acid, 0 °C to rt, 4 h; (c) pyridine, 16 h; (d) R^3Br, K_2CO_3, DMF, microwave 170 °C, 7 min; (e) LiOH, THF/H_2O; (f) $Pd(dppf)_2Cl_2$, Cs_2CO_3, THF:H_2O (1:1), microwave 160 °C, 10 min.

the resulting sulfonyl chloride **7** was combined with the appropriate aniline **8** in pyridine to afford sulfonamide **9**. Alkylation of the sulfonamide nitrogen with an alkyl halide in DMF under microwave conditions, followed by hydrolysis of the methyl ester afforded the phenoxyacetic acid intermediate **10** which was then coupled with a variety of boronic acids **11** in parallel to produce the final products **12–47**. This synthetic strategy proved to be a highly efficient and robust method for rapid SAR identification for this series, using one synthetic sequence to explore four points of diversity simultaneously. All final compounds were purified by reversed-phase HPLC to purities of >95% (LC–MS, UV 214 nm detection). PPARδ binding affinity and subtype selectivity were then determined in an in vitro ligand displacement assay[7] and functional PPARδ activity was evaluated in a standard Gal4 chimera cell-based reporter assay.[8] The results are summarized below.

Initially the SAR at the alpha position of the phenoxyacetic acid (R^1) was investigated (Table 1). Ligand bound crystal structures have shown that PPARδ possesses a narrow lipophilic pocket adjacent to the AF-2 helix where the phenoxyacetic acid headgroup binds and participates in a key hydrogen bonding network.[9] Therefore, incorporating alkyl substituents adjacent to the carboxylic acid to disrupt stabilization of the AF-2 helix could lead to partial efficacy. A similar strategy was reported by researchers at Novo Nordisk.[10] We discovered that potency and efficacy could be modulated by changing the substituents at this position. The desmethyl analogue **12** was the most potent, but displayed the highest level of PPARδ agonist activity (85%). Lengthening the R^1 alkyl group resulted in further erosion of binding affinity and functional activity (**13–15**). Chiral separation of compound **3** generated compounds **(*S*)-3a** and **(*R*)-3b**.[11] Data from the cell-based reporter assay demonstrated a distinct difference in functional potency but similar efficacy for these two compounds, with the *R*-enantiomer (**3b**) displaying superior potency.

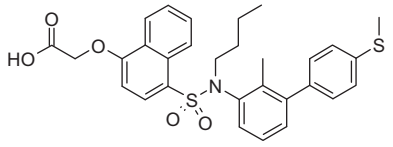
Efforts to crystallize PPARδ in complex with partial agonists such as **3** were unsuccessful. However, crystals were obtained with more agonistic compounds such as **48** (hPPARδ binding pIC$_{50}$ = 7.5, $n = 3$, hPPARδ pEC$_{50}$ = 8.1, 90%max).[12]

Table 1
hPPAR binding and functional potency: alpha position (R^1) variations[a]



Compound	R^1, R^1	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
12	H, H	5.2[b]	5.6[b]	7.9	8.7	85
3	Me, H	4.7	5.1	7.3	7.6[b]	56
13	Et, H	4.8	5.3	7.2[c]	6.9[d]	51
14	Pr, H	5.0	5.5	6.8	<5.0	––
15	Bu, H	5.0	5.4	6.8[c]	<5.0	––
3a	*S*-Me, H	4.8	5.2	6.2[c]	6.5	57
3b	*R*-Me, H	4.7	5.2	7.6[c]	7.9	59

[a] Values are means of at least two experiments, standard deviation <0.2 unless otherwise noted.
[b] SD = 0.3.
[c] SD = 0.4.
[d] SD = 0.5.



48

The crystal structure shows that **48** binds similarly to previous agonists such as **1**, and makes similar interactions with the key acid-binding residues (Fig. 2). The *R*- and *S*-methyl compounds **3a** and **3b** were overlaid into PPARδ using the crystal structure of **48** as a template. In these overlays, the *S*-methyl group of **3a** lies 2.1 Å from Thr289, whereas the *R*-methyl group of **3b** lies 2.9 Å from Leu469 in the AF2 helix.[13] This repulsion is more severe in **3a** than **3b**, consistent with their potencies, and would force either the compound or the AF2 helix to shift slightly in each case, possibly attenuating the interactions that hold the AF2 helix in the active position. This could in turn increase the mobility of the AF2 helix, while reducing the level of activation and the degree of agonism. This mobility might also explain why we were unable to crystallize other, less agonistic, partial agonists.

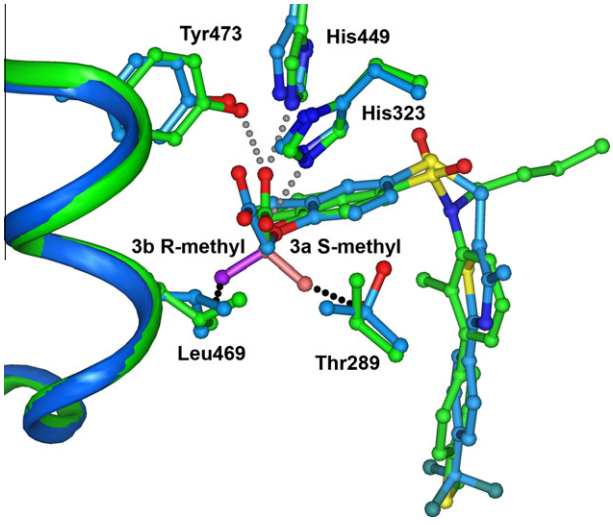
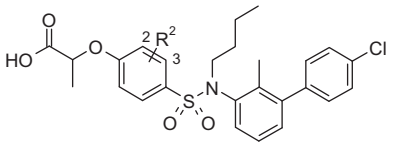


Figure 2. Crystal structure of **48** complexed with PPARδ (green carbons) overlaid onto structure of **1** (blue carbons) and the *S*- and *R*-methyl groups of **3a** (pink) and **3b** (purple), showing the AF2 helix (ribbon representation) and key side-chains (numbered by homology with PPARγ). Hydrogen bonds with the acid headgroup shown with gray dots, and repulsive interactions with Thr289 and Leu469 shown with black dots. Nitrogen, oxygen, sulfur and fluorine shown in blue, red, yellow and gray, respectively.

Investigations of substitution of the phenoxyacetic phenyl acid ring at the R^2 position revealed that replacement of the 2,3-dimethyl substituents in compound **3** with a fused cyclohexyl ring (**16**) provided an analogue which retained potency and partial efficacy (hPPARδ pIC_{50} = 7.8, pEC_{50} = 7.8, 62%). All other substitutions, both electron-donating (**18**, **20**, **22**) and electron-withdrawing (**17**, **19**, **21**) resulted in less potent compounds (Table 2).

Several alkyl variants at the sulfonamide nitrogen (R^3) were prepared to explore steric effects on potency and efficacy. Addition as well as removal of a methylene unit from the linear butyl chain led to a decrease in potency (**23 and 24**). Compounds with heteroatom substituted linear chains four atoms in length (**27 and 28**), as well as small cycloalkyl-substitutions (**25** and **26**) were active, but

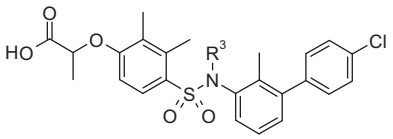
Table 2
hPPAR binding and functional potency: R^2 position variations[a]



Compound	R^2	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
16	Cyclohexyl	4.8	5.1	7.8[c]	7.8	62
3	2,3-diMe	4.7	5.1	7.3	7.6[b]	56
17	2,3-diCl	5.0	5.4	7.1	7.2	70
18	2-OMe, 3-Cl	4.8	5.2	6.8	6.5	70
19	2-F, 3-Cl	4.9	5.2	6.6	6.4[b]	81
20	2-F, 3-OMe	4.8	5.3	6.3	6.3	53
21	2,3-diF	5.0	5.5	6.2	6.5	73
22	2,3-diOMe	<4.6	5.4[c]	5.3	<5.0	

[a] Values are means of at least two experiments, standard deviation <0.2 unless otherwise noted.
[b] SD = 0.3.
[c] SD = 0.4.

Table 3
hPPAR binding and functional potency: R^3 position variations[a]



Compound	R^3	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
3	*n*-Butyl	4.7	5.1	7.3	7.6[b]	56
23	*n*-Propyl	4.7	5.1	6.9	7.1[b]	55
24	*n*-Pentyl	4.8	5.3	6.1	6.4	50
25	Cyclobutylmethyl	4.9	5.2	6.0	6.3[b]	59
26	Cyclopropylmethyl	4.8	5.1	6.1	6.1	53
27	2-OMe-ethyl	<4.7	4.9	6.3	6.3	48
28	CF_3propyl	4.7	5.3	5.9	5.7	56

[a] Values are means of at least two experiments, standard deviation <0.2 unless otherwise noted.
[b] SD = 0.3.

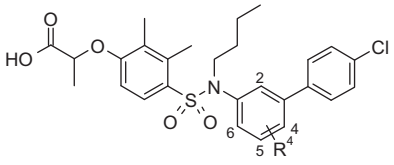
none were as potent as the parent butyl group in compound **3** (Table 3).

Substitution of the *N*-phenyl sulfonamide ring was also explored (Table 4). In general, substitutions made at the C4 (**32** and **33**) and/or C6 (**36–38**) position of the aryl ring led to decreased binding affinity and reduction in functional efficacy with substitution at C6 (**34 and 35**) being more detrimental. These substitutions may have steric effects on the adjacent *para*-chloro phenyl ring or sulfonamide group that induce conformational changes that are unfavorable to positive binding interactions. Substitution at C5 was acceptable as evidenced by the CF_3 analogue **31** which maintained potent binding affinity. Substitution at C2 was well tolerated. For example, the 2-chloro and 2-methoxy analogues **29** and **30** retained excellent potency and partial efficacy comparable to the original 2-methyl compound **3**. The 2-chloro compound **29** was the most potent partial agonist analogue (hPPARδ binding pIC_{50} = 8.1, hPPARδ pEC_{50} = 8.0, 53%max) in this set.

Finally, R^5 substitutions on the right-hand side phenyl ring were investigated (Table 5). Substitution at the *para*-position of the aromatic ring was most preferred, with electron-withdrawing groups exhibiting modest improvement in potency as compared to electron-donating groups (**3**, **42** vs **43–45**). Chloro-substituted analogues **3**, **39**, and **41** further illustrate substitution at the *para*-position as optimal.

Using the aforementioned SAR data, compounds **46** and **47** were subsequently designed, prepared and evaluated. The in vitro data for these compounds is shown in Table 6. As expected, both compounds showed increased hPPARδ potency (pEC_{50} = 8.6), yet still retained the desired partial agonist profile.

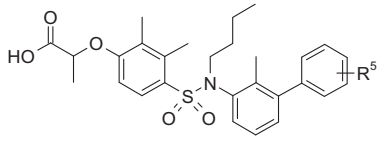
Table 4
hPPAR binding and functional potency: R^4 position variations[a]



Compound	R^4	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
3	2-Me	4.7	5.1	7.3	7.6[c]	56
29	2-Cl	4.9	5.3	8.1[e]	8.0	53
30	2-OMe	4.9	5.1	7.6[d]	7.7	66
31	5-CF3	4.9	5.3	7.2	7.0	69
32	4-F	4.7	5.7	6.7	7.4	48
33	4-Me	4.7[b]	5.5	6.4[e]	6.9	41
34	6-OCF3	4.9	5.0	5.5[d]	6.0	30
35	6-Me	5.0[d]	5.2	5.8	6.1	36
36	4,6-diF	5.0	5.8	5.5	5.9	27
37	4-F, 6-Me	5.0	5.1	5.3	5.5	25
38	2,4,6-triMe	4.7[b]	5.1	5.0	<5.0	

[a] Values are means of at least two experiments, standard deviation <0.2 unless otherwise noted.
[b] Values are $n = 1$.
[c] SD = 0.3.
[d] SD = 0.4.
[e] SD = 0.5.

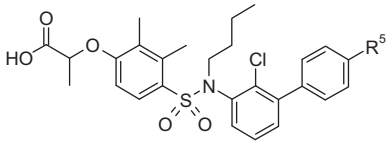
Table 5
hPPAR binding and functional potency: R^5 position variations[a]



Compound	R^5	hPPAR binding pIC_{50}			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
3	4-Cl	4.7	5.1	7.3	7.6[c]	56
39	3-Cl	5.1	5.4	6.2	6.3	42
40	3,4-diCl	4.7	5.3	6.9	6.9	47
41	2-Cl	4.9	5.3	5.8	5.7[b]	34[b]
42	4-CF_3	4.8	5.2	7.8	8.2[c]	64
43	4-OCF_3	5.0	5.3	7.1	7.4[d]	49
44	4-Me	4.8	5.3	7.1	7.5	59
45	4-OMe	4.8	5.2	7.0	7.4	56

[a] Values are means of at least two experiments, standard deviation <0.2 unless otherwise noted.
[b] Values are $n = 1$.
[c] SD = 0.3.
[d] SD = 0.4.

Table 6
hPPAR binding and functional potency for compounds **46** and **47**



Compound	R^5	hPPAR binding pIC_{50}[a]			hPPARδ reporter	
		α	γ	δ	pEC_{50}	%Max
46	OCF_3	5.0	5.2	7.8	8.6	51
47	CF_3	5.1	5.2	8.2[c]	8.6[b]	59

[a] Values are means of at least six experiments, standard deviation <0.2 unless otherwise noted.
[b] SD = 0.3.
[c] SD = 0.4.

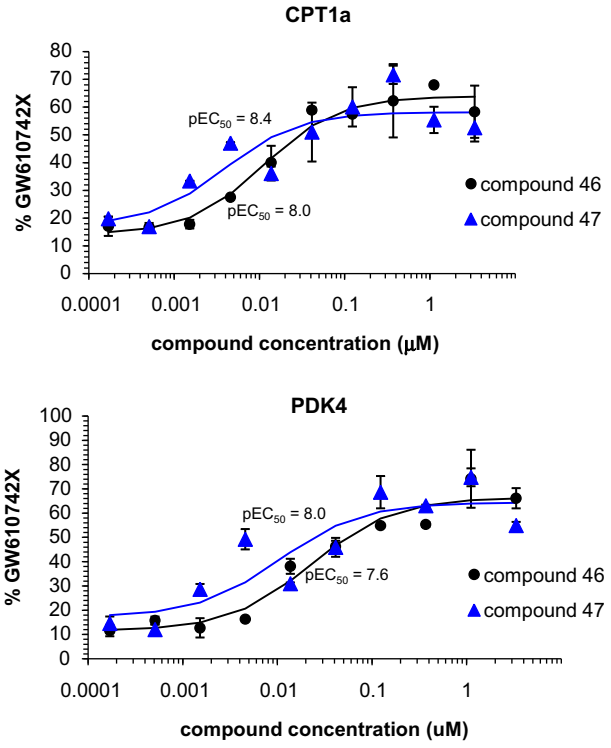


Figure 3. Expression of PPARd target genes for compounds **46** (pEC_{50} = 8.0, 7.6) and **47** (pEC_{50} = 8.4, 8.0) against CPT1a and PDK4 respectively. Each curve is expressed as a percent of the full agonist GW610742X[3] at 10 nM.

Compounds **46** and **47** were studied for their effects on the expression of the PPARδ-regulated genes CPT1a and PDK4 in human skeletal muscle cells as previously described.[14] The target gene CPT1a is an important regulator of fatty acid β-oxidation in skeletal muscle cells, and PDK4 plays a key role in skeletal muscle metabolism by contributing to the regulation of glucose metabolism. Both analogues **46** and **47** profiled as exceptionally potent partial agonists, inducing endogenous PPARδ target gene expression consistent with their profiles in the cell-based reporter assay (Fig. 3).

Table 7
In vitro and in vivo mouse DMPK results for compounds **46** and **47**

Compound	Cl_{int} (mL/min/mg)[a]	AUC_{0-inf}[b] (ng h/mL)	$T_{1/2}$[b] (h)
46	0.028	5870	5.4
47	0.018	2475	4.3

[a] Intrinsic clearance in human liver microsomes.
[b] In vivo mouse DMPK parameters: $n = 2$, two male CD rats dosed at 10 mg/kg po, vehicle formulation 0.5%HPMC/0.1% Tween 80.

Compounds **46** and **47** also had good physicochemical properties (aqueous solubility = 140 μM, artificial membrane permeability = 250 nm/s) and no significant activity against the common cytochrome P450 (CYP450) isoforms (1A2, 2C19, 2D6, 3A4 pIC_{50} <5.5) except 2C9 (pIC_{50} = 6.1). In vitro studies using human liver microsomes showed that both compounds had low clearance (0.028 and 0.018 mL/min/mg, respectively). In oral mouse pharmacokinetic (PK) studies, both compounds showed good oral exposure and half-life (Table 7). Collectively, this data provided an excellent basis for further in vivo testing of these compounds for efficacy.

Compounds **46** and **47** were therefore chosen for in vivo evaluation based on their partial induction of PPARδ-responsive genes in human muscle cell cultures and favorable PK profile.[15] At the 100 mg/kg dose, both compounds decreased body weight gain (Fig. 4), and at the 30 and 100 mg/kg dose, both compounds showed a significant improvement in glucose sensitivity by OGTT in a dose-dependent manner in the obese, insulin-resistant ob/ob mouse (Fig. 5).[16] These effects were similar to those induced by

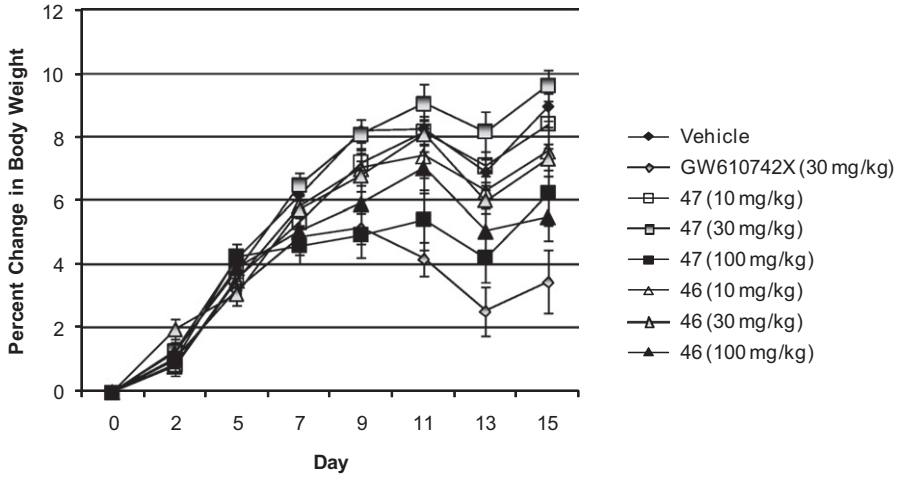


Figure 4. Effects of compounds **46** and **47** on body weight. Vehicle formulation 0.5% HPMC/0.1% Tween80 (n = 8/dose group).

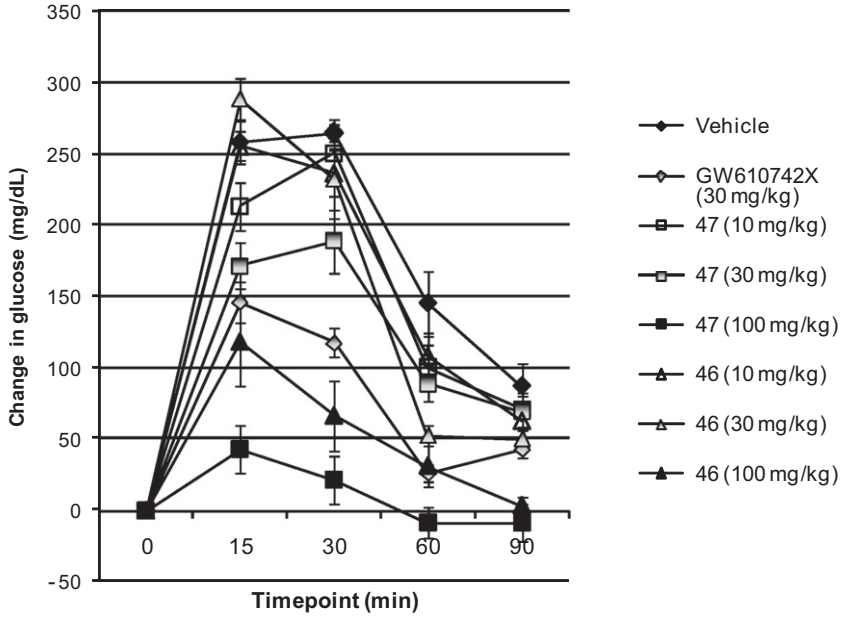


Figure 5. Effects of compounds **46** and **47** in oral glucose tolerance test (OGTT). Vehicle formulation 0.5% HPMC/0.1% Tween80 (n = 8/dose group).

the full agonist GW610742X. These data suggest that PPARδ partial agonists such as **46** and **47** (pEC_{50} = 8.6, 51% and 59%max, respectively) can deliver anti-diabetic efficacy in mice.

In summary, a series of phenoxyacetic acids as subtype selective and potent hPPARδ partial agonists has been developed. Systematic structural modifications of this template at five positions of diversity were achieved through one primary solution-phase synthesis which resulted in the rapid identification of key structure–activity relationships (SAR), and the discovery of two potent exemplars. Compounds **46** and **47** were further evaluated in vivo, and at both the 30 and 100 mg/kg dose, both compounds decreased body weight gain and significantly improved insulin sensitivity by OGTT in the obese, insulin-resistant ob/ob mouse suggesting that PPARδ partial agonists can deliver anti-diabetic efficacy in mice.

Acknowledgments

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Supplementary data

Supplementary data (synthetic procedures and characterization data for compounds **46** and **47**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.02.077.

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12. The crystal structure of **48** was solved at 2.4 Å resolution, R = 20.0%, R_{free} = 23.6%, PDB code 3PEQ.
13. Distances reported are the average distances from the residues in the crystal structure of **48** bound to PPARd which has two subunits. Compounds **3a** and **3b** were overlaid into both subunits, with the (*S*)-methyl of **3a** lying 2.01 and 2.26 Å from Thr289 in the two subunits, and with the (*R*)-methyl of 3b lying 2.78 and 2.93 Å from Leu469 in the two subunits.
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