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Identification of a Series of Oxadiazole-Substituted α-Isopropoxy Phenylpropanoic Acids with Activity on PPARα, PPARγ, and PPARδ

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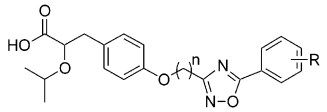
Abstract—A series of oxadiazole-substituted α-isopropoxy phenylpropanoic acids with dual agonist activity on PPARα and PPARγ is described. Several of these compounds also showed partial agonist activity on PPARδ. Resolution of one analogue showed that PPARα and PPARγ activity resided in mainly one enantiomer, whereas PPARδ activity was retained in both enantiomers.

Type 2 diabetes, or non-insulin-dependent diabetes mellitus, is the most prevalent endocrine disease in the world. An estimated 120 million people worldwide suffer from this disease.[1] Type 2 diabetes is primarily characterized by peripheral resistance to the actions of insulin, which leads to hyperglycemia. There is also a high frequency of concurrent dyslipidemia (e.g., high levels of triglycerides and low levels of HDL-c), which may contribute significantly to accelerated coronary atherosclerosis, the leading cause of death in these individuals.[2,3] Treatment of insulin resistance and dyslipidemia simultaneously would provide the great benefit for type 2 diabetic patients.

Recently, a new class of insulin-sensitizing drugs called thiazolidinediones (TZDs) has been found to provide improvements in glycemic control and hyperlipidemia in type 2 diabetics. The potency of the marketed insulin sensitizing drugs rosiglitazone[4] and pioglitazone[5] has been correlated with their activity on the orphan nuclear receptor PPARγ.[6] This correlation facilitated the discovery of the tyrosine-derived insulin sensitizer farglitazar (GI262570), whose structure was optimized by screening against PPARγ in vitro.[7] Fibrates are a class of drugs that are effective at lowering serum triglycerides and raising HDL-c.[8] Experimental evidence has indicated that PPARα is the receptor through which fibrates mediate their effects on lipid metabolism.[8,9] Therefore, PPARα/γ dual agonists may provide superior therapy to the current PPARγ-selective agonists, due to the additional lipid control afforded by the PPARα component. Although less is known about the third PPAR subtype, a selective PPARδ agonist GW501516 was recently shown to increase HDL-c and lower triglycerides.[10]

α-Alkoxy-substituted carboxylic acids have been previously disclosed as non-TZD insulin sensitizers in vivo,[11–13] but limited information on activity against the three PPAR subtypes has been reported. Here we report a series of α-isopropoxy phenylpropanoic acids containing oxadiazole tails (**1** and **2**, Fig. 1) that are potent and efficacious PPARα/γ dual agonists. Additionally,



1 n = 1
2 n = 2

Figure 1. PPAR agonists.

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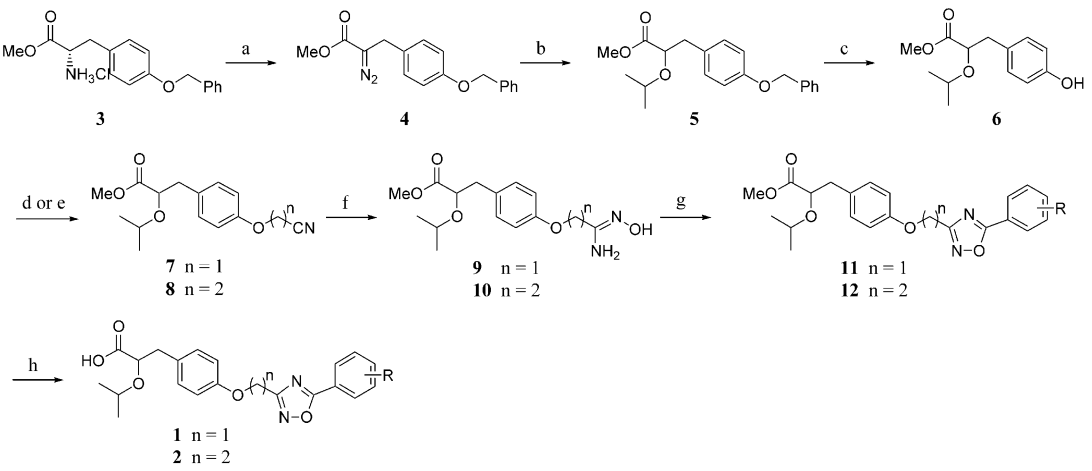

Scheme 1. Reagents: (a) (i) Na_2CO_3; (ii) isoamyl nitrite, cat. HOAc, $CHCl_3$, reflux, 30 min, 100%; (b) $Rh_2(OAc)_4$, *i*-PrOH, rt, overnight, 38%; (c) H_2, 10% Pd/C, EtOH, rt, overnight, 98%; (d) chloroacetonitrile, Cs_2CO_3, CH_3CN, rt, overnight, 79%; (e) acrylonitrile, cat. benzyltrimethyl ammonium hydroxide, MeOH, reflux, 24 h, 64%; (f) NH_2OH, H_2O/MeOH, reflux, 4 h, 71% for **9** and 17% for **10**; (g) acyl chlorides, pyridine, reflux, 2 h; or carboxylic acids, 1,1′-carbonyl diimidazole, DMF, 110 °C, 24–90%; (h) LiOH, THF/H_2O/MeOH, rt, overnight, 90–100%.

some compounds within this series also demonstrate partial agonist activity on PPARδ.

The general preparation of these PPAR agonists of series **1** and **2** is depicted in Scheme 1. The synthesis starts with commercially available *O*-benzyl protected tyrosine methyl ester HCl salt **3**. Diazotization of the corresponding free amine following the procedure developed by Takamura[14] provided diazo compound **4** in quantitative yield. Rhodium-catalyzed insertion of isopropanol to **4** provided α-isopropoxy methyl ester **5** in relatively low yield along with the α,β-unsaturated propenoic acid as the major side product via elimination. The propensity for byproduct formation varied with the alcohol and reaction conditions. After exploring a number of different reaction conditions, we found that three equivalents of isopropanol in toluene at room temperature provided the highest yield of **5**. Debenzylation of **5** by catalytic hydrogenolysis afforded phenol **6**, which upon alkylation with chloroacetonitrile and Cs_2CO_3 in acetonitrile provided nitrile **7**. Michael addition of **6** to acrylonitrile catalyzed by benzyltrimethyl ammonium hydroxide provided nitrile **8**. Addition of hydroxylamine to nitriles **7** and **8** provided advanced intermediates amide oximes **9** and **10**, respectively. Oxadiazole formation via treatment with acid chlorides in pyridine at reflux or with 1,1′-carbonyl diimidazole (CDI) in DMF using more readily available carboxylic acids as reported by Deegan[15] provided oxadiazoles **11** and **12**, which upon saponification furnished target molecules **1** and **2**, respectively.

The target compounds **1a**–**o** and **2a**–**h** were initially synthesized in racemic form and were evaluated for their binding affinity and functional potency against the three human PPAR subtypes. The details of both the binding[7,16] and the cell-based functional assays[6,7] have been previously reported. In general, compound affinities for the three PPAR subtypes correlated well with their potency of activation in the functional assay (data not shown). The latter was used to establish the structure–activity relationship (SAR) and is depicted in Table 1.

All of the analogues tested profile as potent PPARα and PPARγ dual agonists, with several analogues also displaying submicromolar PPARδ partial agonist activity (e.g., **1m** and **2e**). The substituents on the oxadiazole tail affect the PPARα and PPARγ potency. The number of carbon atoms (one for **1** and two for **2**) between the oxadiazole tail and the central phenoxy moiety also affects the potency. In general, compounds with a two-carbon linker (e.g., **2a**, **2b**, **2c**, and **2h**) are more potent against PPARγ but less potent against PPARα than their one-carbon linker analogues (**1a**, **1b**, **1c**, and **1n**,

Table 1. Transient transfection[a] data of PPAR agonists **1** and **2**

Compd	R	EC_{50} (nM) hPPARα	EC_{50} (nM) hPPARγ	EC_{50} (nM) hPPARδ
1a	H	160	79	10,000
1b	3-F	79	100	7900[b]
1c	4-F	160	200	7900[b]
1d	2-Me	40	100	1600[b]
1e	3-Me	79	50	1600[b]
1f	4-Me	25	16	2500[b]
1g	4-Cl	13	20	500[b]
1h	4-Br	40	32	790[b]
1i	4-CF_3	32	25	500[b]
1j	4-CF_3O	20	63	7900[b]
1k	4-*i*-Pr	13	4	7900[b]
1l	4-*t*-Bu	40	3	5000[b]
1m	3,5-di-F	40	100	160[b]
1n	3,5-di-CF_3	6	32	320[b]
1o	Cyclohexyl[d]	240	230	—[c]
2a	H	2000	13	—[c]
2b	3-F	500	2	4000[b]
2c	4-F	790	40	—[c]
2d	4-Cl	400	25	—[c]
2e	3-Cl	320	4	100[b]
2f	3-CF_3	200	6	500[b]
2g	2-CF_3	400	160	2500
2h	3,5-di-CF_3	50	4	—[c]

[a,b]Compounds were assayed for agonist activity on PPAR-GAL4 chimeric receptors in transiently transfected CV-1 cells as described;[6,7,17] EC_{50} = the concentration of test compound that gave 50% of the maximal reporter activity.
[b]Compound with percent activation 40–70%.
[c]Compounds with percent activation <40%.
[d]Cyclohexyl directly attached to oxadiazole. All data ±15% (n = 3).

respectively). Most of the compounds listed in Table 1 have an oxadiazole tail substituted with an aromatic group. Compounds with non-aromatic group-substituted oxadiazole tails are much less potent (**1o**). For compounds with a one-carbon linker (**1**), the phenyl derivative **1a** was fairly potent (~100 nM) at both PPARα and PPARγ. While substitution of the phenyl ring with a fluorine did not improve the potency (**1b** and **1c**), substitution with a larger methyl group especially at the 4-position was found to improve potency for both PPARα and PPARγ (**1f**). Substitution at the 4-position with the sterically more demanding isopropyl group provided **1k** as one of the most potent PPARα/γ dual agonists with $EC_{50}=13$ nM at PPARα and $EC_{50}=4$ nM at PPARγ. The 4-*t*-Bu compound **1l** is also a potent PPARα/γ dual agonist with ~15-fold selectivity for PPARγ versus PPARα. Interestingly, substitution with trifluoromethyl groups at both 3- and 5- positions provided a potent PPARα/γ dual agonist **1n** with ~5- fold selectivity for PPARα over PPARγ. Clearly, the selectivity between PPARα and PPARγ can be fine-tuned in this series by changing the substituents on the oxadiazole tail. The selectivity between PPARα and PPARγ may be critical in order to achieve the optimal in vivo PPARα/γ dual agonist profile.

In contrast to the one-carbon linker compounds **1** that are approximately equipotent at PPARα and PPARγ, compounds with a two-carbon linker (**2**) are often >10-fold more potent at PPARγ than at PPARα. Substitution at both 3- and 5-positions with trifluoromethyl groups provided the most potent PPARα and PPARγ analogue **2h** in the two-carbon linker series with $EC_{50}=50$ nM at PPARα and $EC_{50}=4$ nM at PPARγ.

Certain compounds in both one-carbon (**1**) and two-carbon (**2**) linker series also showed partial agonist activity at PPARδ in the cell-based functional assay. These compounds stimulated transcription by only 40–70% as compared to the positive control GW501516.[10] Most of the compounds showed weak ($EC_{50}>1$ μM) potency at PPARδ. However, substitution on the phenyl ring with electron-withdrawing groups both in one-carbon series **1** and in two-carbon series **2** increased the potency (**1g–i**, **1 m–n**, **2e–f**). The most potent PPARδ compound **2e** has an EC_{50} of 100 nM in the functional assay. The in vivo pharmacological significance of the observed in vitro partial agonist activity on PPARδ is unknown.

Table 2. Different PPAR activity of **1n** enantiomers in transient transfection assay[a]

Compounds	R	EC_{50} (nM) hPPARα	EC_{50} (nM) hPPARγ	EC_{50} (nM) hPPARδ
(±)-**1n**	3,5-di-CF3	6	32	320[b]
(−)-**1n**[c]	3,5-di-CF3	4	32	630[b]
(+)-**1n**[d]	3,5-di-CF3	2500	630	790[b]

[a,b]See footnotes to Table 1. All data ±15% ($n=3$).
[c](−)-1n: $[\alpha]_D^{23}$ −18.8 (*c* 0.43, MeOH).
[d](+)-1n: $[\alpha]_D^{23}$ 19.5 (*c* 0.43, MeOH).

In order to determine whether PPAR activity resides in one or both enantiomers, the racemic methyl ester of **1n** was resolved by chiral HPLC to afford the enantiomerically pure methyl esters, which upon saponification with LiOH in THF and H_2O provided enantiomerically pure carboxylic acids (+)-**1n** and (−)-**1n**. No racemization was observed during saponification based on chiral HPLC analysis. The (−)-enantiomer [$[\alpha]_D^{23}$ −18.8 (*c* 0.43, MeOH)] is 500-fold more potent on PPARα and 12-fold more potent on PPARγ than its (+)-antipode [$[\alpha]_D^{23}$ 19.5 (*c* 0.43, MeOH)] (Table 2). Interestingly, there was little difference in the PPARδ activity of the two enantiomers. Thus, different levels of enantioselectivity was observed on each of the three PPAR subtypes. The (−)-enantiomer presumably has an (*S*)-configuration based on the cocrystal structures of PPARγ with related compounds.[18]

In summary, we have identified a series of oxadiazole-substituted α-isopropoxy phenylpropanoic acids with dual agonist activity on PPARα and PPARγ. Several of these compounds also showed partial agonist activity on PPARδ. These oxadiazole-based PPAR agonists may provide lead compounds to develop new anti-hyperglycemic agents with an improved lipid-lowering capability over currently available PPARγ agonists.

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