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1,3,5-Trisubstituted aryls as highly selective PPARδ agonists

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Abstract—A series of highly potent and selective PPARδ agonists is described using the known non-selective ligand GW2433 as a structural template. Compound **1** is bioavailable, potent (10 nM), and shows no cross-activity with other PPAR subtypes up to 10 μM, making it a useful tool in studying the biological effects of selective PPARδ activation.

The peroxisome proliferator-activated receptors (PPARs) are lipid-activated transcription factors belonging to the nuclear receptor superfamily. PPARs are generally considered as sensors for natural fatty acids and other diet-derived lipid metabolites, and have been shown to be key regulators of genes involved in energy homeostasis and inflammation. To date, three major subtypes have been identified, namely PPARα, PPARγ, and PPARδ. Two successful classes of marketed drugs, the hypolipidemic fibrates and the insulin sensitizing TZDs, are believed to be acting through activation of the PPARα[1–3] and PPARγ[4–6] subtypes, respectively.

Several studies have suggested important roles of PPARδ in regulating lipid metabolism and energy homeostasis in muscle and fat (Fig. 1).[7–11] Notably, the potent PPARδ agonist GW501516 increased HDL-C (80%) and decreased elevated triglyceride and insulin levels (50%) in obese rhesus monkeys.[12] These results suggest that PPARδ agonists might be useful in the treatment of diseases associated with the metabolic syndrome, such as dyslipidemia and insulin resistance.

To date, reports on synthetic selective PPARδ agonists remain limited.[13–18] To further elucidate molecular mechanisms and pharmacological responses following PPARδ activation, we initiated medicinal chemistry efforts to identify PPARδ-selective agonists.

We report the identification of 1,3,5-substituted aryl systems, such as compound **1** (Fig. 2) as potent and selective PPARδ activators based on structure-based drug design.

A co-crystal structure of the PPARδ ligand-binding domain (LBD) and the synthetic pan-agonist GW2433 revealed that the affinity of this ligand to the PPARδ subtype most likely arose from its ability to adopt a Y-shaped fitting into the similarly shaped receptor binding pocket.[19] The shape complementarity may be especially important for subtype selectivity given the rather large binding pockets (>1000 Å^3) of all three PPAR subtypes, enabling the receptors to bind a wide range of fatty acids and their metabolites in several conformations. The function of these ligands may be seen as skeletons that enable the dynamic receptor to wrap around them and adopt an active conformation. Figure 3 shows that the virtually docked 1,3,5-substituted aromatic system **1** nicely overlays with GW2433, yet it is conformationally restrained enough to pick up subtle differences in the extensive hydrophobic side-pockets between subtypes possibly leading to enhanced ligand specificity.

Keywords: Nuclear receptors; Peroxisome proliferator-activated receptor delta; PPAR agonists; Virtual docking.
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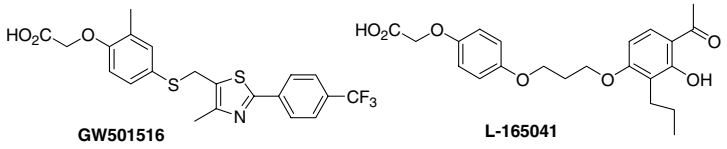


Figure 1. PPARδ agonists used in efficacy studies reported to date.

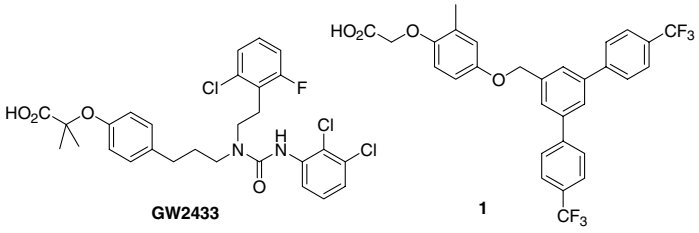


Figure 2. Pan-agonist GW2433 and novel PPARδ-selective agonist **1**.

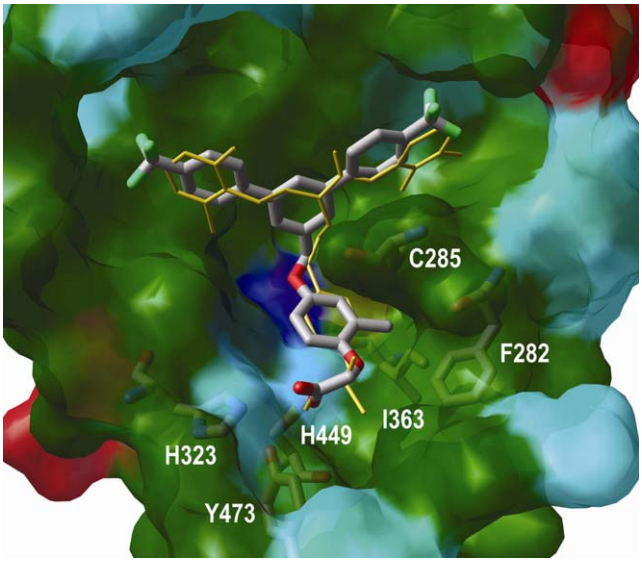


Figure 3. Overlay of compound **1** (gray) docked into the PPARδ binding pocket cocrystallized with GW2433 (yellow).

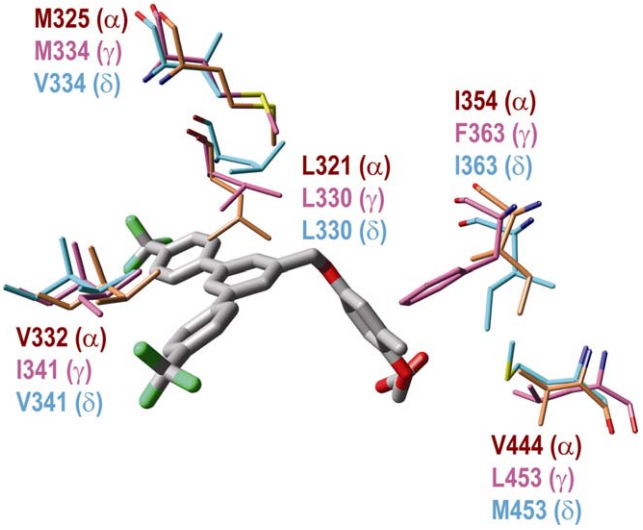


Figure 4. Residues of interest involved in predicting PPARδ selectivity of compound **1**. Brown, PPARα; pink, PPARγ; blue, PPARδ.

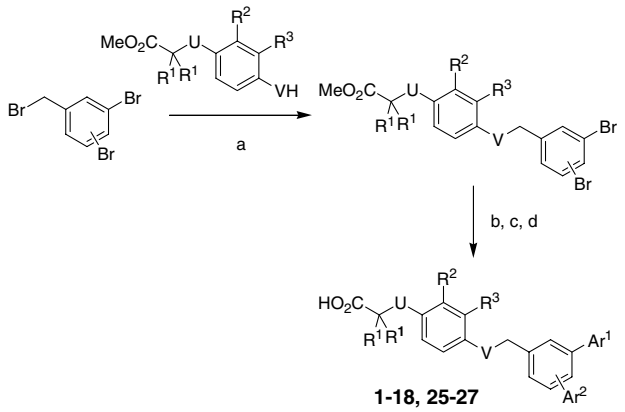
Any other substitution pattern on the core aromatic ring leads to a significant change in angles between the side-arms of the ligand and inevitable clashes with the surface of the receptor binding pocket.

It is well established that the side-arm bearing the carboxylate head group is crucial for activation of the receptor via formation of a network of hydrogen bonds with the triad H323, H449, and Y473. Based on comparisons of structural features between the subtypes,[13,20] we omitted any large substitution α to the carboxylate, but added a key *ortho*-methyl substituent in the phenyl ring to interact with a small hydrophobic pocket composed of F282, C285, and I363.

The large and extremely dynamic binding pockets of the three PPAR receptors[21] make predictions on selectivity based on certain receptor side chain residues difficult. Nevertheless, to name a few obvious differences (Fig. 4), M453 [V444 (PPARα) or L453 (PPARγ)] seems to hinder the PPARδ pocket to accommodate bulkier substituents close to the carboxylate. Likewise, the bulkier F363 in PPARγ [I354 (PPARα) or I363 (PPARδ)] may prevent *ortho*-substituted headgroup phenyls to bind with high efficiency.

Interestingly, V334 [M325 (PPARα) or M334 (PPARγ)] does not directly flank the ligand-binding pocket, but allows rotation of L330 to accommodate a trifluoromethyl-substituted phenyl-arm of the designed ligand specifically in the PPARδ subtype. Replacing the core phenyl group with a double bond significantly alters the position of the two side arms in the pocket, leading to lower potency and lack of PPAR subtype selectivity.[22]

The general synthesis of target molecules **1**–**18**, **25**–**30** is depicted in Scheme 1. For the 1,3,5-substituted phenyl analogs **1**–**18**, we started with a Williamson-type displacement of the commercially available 3,5-dibromobenzyl bromide with the head group phenol

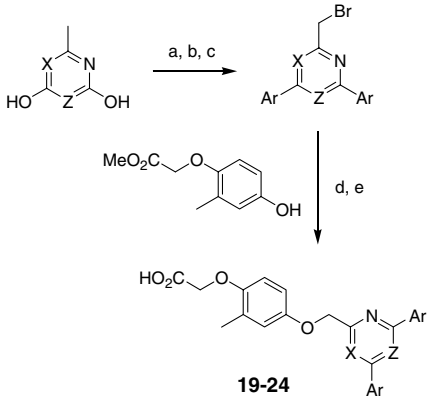


Scheme 1. Reagents and conditions: (a) Cs_2CO_3, CH_3CN, rt, 18 h (95%); (b) $Ar^1B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, H_2O/EtOH/dioxane, MW (170 °C, 6 min); (c) $Ar^2B(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, H_2O/EtOH/dioxane, MW (170 °C, 6 min) (70% over two steps); (d) LiOH, H_2O/dioxane, rt, 5 h (>95%).

(or thiophenol) of choice. The synthesis of head groups used in this study has been described.[13,14,23] The phenyl dibromide intermediates were then coupled with an excess of the appropriate aryl boronic acid under Suzuki conditions, followed by saponification of the intermediate esters to the corresponding carboxylic acids to give symmetrical analogs **1**–**13**.

Alternatively, by using one equivalent of aryl boronic acid, the mono-arylated intermediate could be isolated. This intermediate was then reacted with a different aryl boronic acid to yield non-symmetrical analogs **14**–**18** after the final saponification step. Notably, the reaction times of the Suzuki couplings used in the above reaction sequences were kept under 10 min by subjecting the reaction mixtures to microwave irradiation. 1,3,4-Substituted phenyl analogs **25**–**37** were prepared using a similar route, starting with 3,4-dibromobenzyl bromide.

Scheme 2 shows the synthetic route to pyrimidine analogs **19**–**24**. 4,6-Dihydroxy-2-methylpyrimidine was treated with $POCl_3$ to give the bis-chlorinated species.[24]



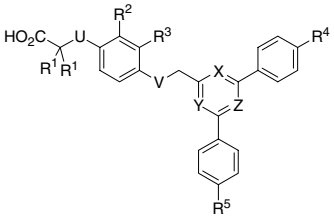
Scheme 2. Reagents and conditions: (a) $POCl_3$, 95 °C, 18 h (90%); (b) $ArB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$, H_2O/EtOH/dioxane, MW (170 °C, 6 min) (80%); (c) NBS, AIBN, CCl_4, 75 °C, 24 h (65%); (d) Cs_2CO_3, CH_3CN, rt, 18 h (95%); (e) LiOH, H_2O/dioxane, rt, 5 h (>95%).

Suzuki coupling with excess aryl boronic acids gave a bisarylated intermediate, which was selectively brominated at the methyl position using NBS. Nucleophilic substitution of the bromide with the appropriate head group phenol and subsequent hydrolysis of the ester intermediate yields 4,6-arylated pyrimidines **19**–**21**. 2,4-Arylated pyrimidines **22**–**24** were prepared in a similar fashion, starting from 2,4-dichloro-6-methylpyrimidine.

The EC_{50} values for compounds **1**–**24** were derived from in vitro transactivation assays against the human PPAR subtypes and are listed in Table 1.[25] Percent efficacies for PPARδ activation are reported relative to GW501516 (100%). Compound **2** displays micromolar activities with moderate activities for both PPARγ and PPARδ. Extending the side arms of compound **2** further into the pocket by *para*-substitution led to an up to 10-fold improvement in PPARδ activity together with a marginal ability to activate PPARα. We found that hydrophobic substituents with electron-withdrawing properties such as trifluoromethyl groups (e.g., compound **3**) were optimal (CF_3, OCF_3 > halo, alkyl, and phenyl; cf. compounds **1**, **12**, **15**, **17**, and **18**). Notably, *meta*- or *ortho*-substitutions on both phenyl rings resulted in a dramatic decrease of activity (data not shown). Alternatively, the addition of a methyl substituent in the head group phenyl ring *ortho* to the substituent bearing the carboxylate (**5**) led to a substantial increase of efficacy for PPARδ activation, but was still able to bind to PPARγ with low efficacy (30%). After combining both features in a single molecule (compound **1**), the effects of the substituents in compounds **3** and **5** proved to be synergistic. Compound **1** showed excellent potency (10 nM) and selectivity (>1000×) for PPARδ, as predicted in our in silico modeling studies above. The selectivity was also maintained on the murine receptors (data not shown).

It is evident that incorporation of a 'fibrate-type' geminal dimethyl substitution α to the carboxylate (compound **4**) is rather beneficial for PPARδ activation; but analogs showing this type of substitution consistently seem to dial in activation of the PPARα subtype as well. Methyl substitution of the head group phenyl ring *meta* (compound **6**) instead of *ortho* (compound **1**) to the carboxylate substituent does not allow favorable interaction of the ligand with the small hydrophobic side-pocket composed of F282, C285, and I363, and shows a significant decrease in activity. Early analogs **2–6** are the only exception in displaying subtype cross-activity to the otherwise completely PPAR-δ selective compound series. When the head group was switched to a literature known phenylacetic acid[16,17,26] such as in compounds **8** and **9**, the now shortened distance between carboxylate and phenyl ring forces the chloride substituent to be preferably in *meta*-position to fit into this side-pocket. Phenylacetic acid analogs in general displayed lower efficacies compared to the phenoxyacetic acid analogs. An oxomethylene linker proved to be optimal in the phenoxyacetic acid series. A slightly longer thiomethylene linker (compound **7**) is tolerated, which is in accordance with previous studies that the connection of head to tail in PPAR ligands is usually flexible and can vary in its length.

Table 1. In vitro activities for compounds **1**–**19** in cell-based transactivation assays of PPARα, PPARγ, and PPARδ



Compound	U	V	R^1	R^2	R^3	X	Y	Z	R^4	R^5	α (μM)	γ (μM)	δ (μM)	δ % eff
2	O	O	H	H	H	CH	CH	CH	H	H	>10	1.2	0.97	45
3	O	O	H	H	H	CH	CH	CH	CF_3	CF_3	1.64	>10	0.11	100
4	O	O	Me	H	H	CH	CH	CH	CF_3	CF_3	0.73	0.37	0.05	94
5	O	O	H	Me	H	CH	CH	CH	H	H	>10	0.74[a]	0.56	70
1	O	O	H	Me	H	CH	CH	CH	CF_3	CF_3	>10	>10	0.01	90
6	O	O	H	H	Me	CH	CH	CH	CF_3	CF_3	3.33	>10	0.07	79
7	O	S	H	Me	H	CH	CH	CH	CF_3	CF_3	>10	>10	0.03	83
8	Bond	O	H	H	Cl	CH	CH	CH	CF_3	CF_3	>10	>10	0.54	39
9	Bond	S	H	H	Cl	CH	CH	CH	CF_3	CF_3	>10	>10	0.16	54
10	O	O	H	Me	H	CH	CH	CH	OMe	OMe	>10	>10	0.35	94
11	O	O	H	Me	H	CH	CH	CH	NMe_2	NMe_2	>10	>10	0.49	74
12	O	O	H	Me	H	CH	CH	CH	Cl	Cl	>10	>10	0.11	80
13	O	O	H	Me	H	CH	CH	CH	OCF_3	OCF_3	>10	>10	0.03	81
14	O	O	H	Me	H	CH	CH	CH	CF_3	*m*-CF_3	>10	>10	0.56	56
15	O	O	H	Me	H	CH	CH	CH	CF_3	OCF_3	>10	>10	0.06	87
16	O	O	H	Me	H	CH	CH	CH	CF_3	OMe	>10	>10	0.07	93
17	O	O	H	Me	H	CH	CH	CH	CF_3	Me	>10	>10	0.07	78
18	O	O	H	Me	H	CH	CH	CH	CF_3	Ph	>10	>10	0.06	75
19	O	O	H	Me	H	N	N	CH	OMe	OMe	>10	>10	0.11	72
20	O	O	H	Me	H	N	N	CH	OCF_3	OCF_3	>10	>10	0.09	89
21	O	O	H	Me	H	N	N	CH	CF_3	CF_3	>10	>10	0.04	78
22	O	O	H	Me	H	CH	N	N	OMe	OMe	>10	>10	0.21	80
23	O	O	H	Me	H	CH	N	N	OCF_3	OCF_3	>10	>10	0.04	83
24	O	O	H	Me	H	CH	N	N	CF_3	CF_3	>10	>10	0.03	90
L-165041[b]											10	5.5	0.53	—
GW2433[b]											0.17	2.5	0.19	—
GW501516											1.23	>10	0.004	100

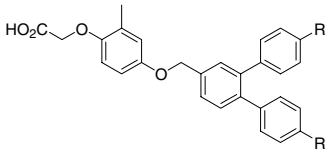
[a] 30% efficacy (standard: rosiglitazone).
[b] Reported values.[27]

The SAR results on analogs **10**–**13** underline the predominantly hydrophobic character of the receptor binding pocket. Attempts to desymmetrize the ligand (compounds **14**–**18**) did not result in significantly improved activity profile. The 50-fold drop in potency together with a substantial decrease in efficacy seen for compound **14** emphasizes that *para*-substitution of the tail phenyls is required for efficient receptor activation. Upon substituting the core phenyl ring with pyrimidines as in compounds **19**–**24** a similar SAR was observed, which opens the door to explore other heterocyclic replacements.

To verify our postulation that a 1,3,5-substitution pattern around the center six-membered aryl ring is required, we synthesized a series of 1,3,4-substituted analogs **25**–**27**. All compounds displaying this substitution pattern were inactive in the in vitro transactivation assays for all three PPAR subtypes (Table 2).

In summary, despite the extremely dynamic nature of the side-chain residues surrounding the PPAR ligand-binding pocket, subtype selectivity was achieved by designing a conformationally restrained ligand. Based on our docking results, the PPARδ subtype in its activated state is able to accommodate a rigid Y-shaped aromatic system displaying roughly 120 degree side-arm angles (e.g., **1**) without having to undergo a series of non-productive conformational changes.

Table 2. In vitro activities for compounds **25**–**27**



Compound	X	R	α (μM)	γ (μM)	δ (μM)
25	CH	OMe	>10	>10	>10
26	CH	OCF_3	>10	>10	>10
27	N	CF_3	>10	>10	>10

The experimental data were in excellent correlation with our in silico predictions. We were able to identify a series of highly potent and efficacious PPARδ agonists (compound **1** with $EC_{50} = 10$ nM) that are structurally distinct from GW501516 with an improved selectivity

profile. At concentrations up to 10 μM most analogs reported did not show any activation of other PPAR subtypes or other nuclear receptors. An in vitro metabolic stability assessment of compounds **1** and **23** gave no metabolic liabilities after incubation with mouse, rat or human liver microsomes. Additionally, compounds **1** and **23** had favorable pharmacokinetic properties ($F > 50\%$, $C_{max} > 4$ μM, $t_{1/2} \sim 3$–6 h) when dosed orally at 10 mpk as a 0.5% CMC suspension in mice. We believe that the compounds described will be highly valuable tools to dissect pharmacological effects of selective PPARδ activation in animal models.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.02.079.

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