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Structure-based design of indole propionic acids as novel PPARα/γ co-agonists

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Abstract—In the quest for novel PPARα/γ co-agonists as putative drugs for the treatment of type 2 diabetes and dyslipidemia, we have used a structure-based design approach to identify propionic acids with a 1,5-disubstituted indole scaffold as potent PPARα/γ activators. Compounds **13**, **24**, and **28** are examples of submicromolar dual agonists with different α/γ EC_{50} ratios that are selective against the δ-isoform. Analysis of the X-ray complex structure of PPARγ with the indole propionic acid **13** provides a rationalization for some of the observed SAR.

The peroxisome proliferator-activated receptors (PPAR) α, γ, and δ are ligand dependent nuclear transcription factors which belong to the nuclear hormone receptor super-family. They regulate the expression of a variety of genes involved in glucose and lipid homeostasis.[1,2] PPARα agonists are primarily associated with lipid modulating effects, whereas PPARγ agonists are involved in glucose homeostasis, insulin sensitivity, and lipid storage. The action of PPARδ agonists is less known but might be directed toward dyslipidemia and potentially obesity[3] as well as wound healing.[4] The research in our group focused on PPARα/γ co-agonists in order to combine the fuel storing and insulin sensitizing effect of PPARγ with the fuel burning and lipid modulating effect of PPARα. In addition, selectivity against PPARδ would be desirable to differentiate clinical effects. We followed a structure-based approach with the goal of identifying potent PPARα/γ co-agonists applicable as tailored therapy for type 2 diabetes and associated co-morbidities.

As of March 2006, in total 24 protein structures of the PPAR ligand binding domains (LBD) have been solved by X-ray crystallography and released in the Protein Data Bank[5] (PPARα, 3; PPARγ, 14; and PPARδ, 7). This vast structural information has provided considerable insight into the factors controlling receptor binding and functional activation as well as isoform selectivity.[6–9] In all three isoforms, the ligands partly fill a large, curved binding pocket with a common binding mode for PPAR agonists. The similar shapes of the binding pockets of PPARα and PPARγ are shown in Figure 1 for the complexes with the PPARα/γ co-agonist tesaglitazar **1**.[10] One can schematically analyze the protein–ligand interactions of typical PPAR agonists using the simplified topological representation shown in Scheme 1. The bifunctional acidic head group, known are so far carboxylic acids and 2,4 thiazolidinediones, is involved in up to four hydrogen bonds with the receptor. This part is crucial for PPAR activation by anchoring the flexible C-terminal transactivation helix (AF2-helix) close to the protein, thereby providing an interface together with other parts of the receptor for successful co-activator binding. The central aromatic moiety is located in a hydrophobic protein environment involving Met, Cys, Leu, and Ile residues at van der Waals distance, while the cyclic tail region is partly solvent exposed and tolerates more polar and more diverse substituents. To adapt to the curved binding site, flexible linkers connecting the three pharmacophore centers, sometimes branched to access additional subpockets, are found in known PPAR agonists.

Previous studies have capitalized on the available structural information to support lead finding and optimization. Structure-based design was used to improve potency[11] and species selectivity[12] by introducing

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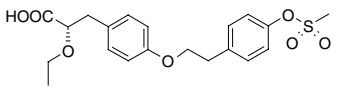

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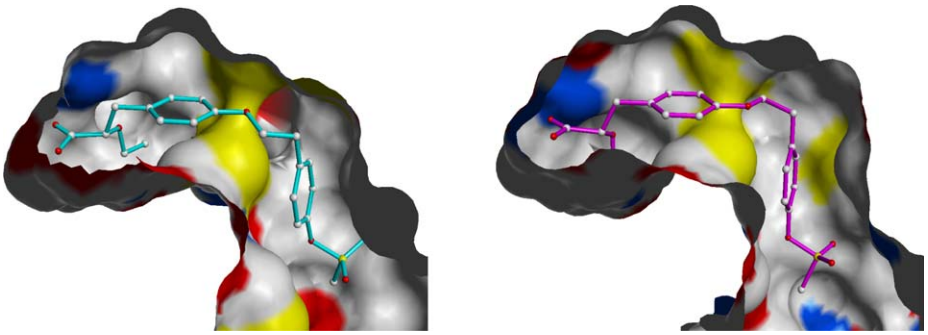
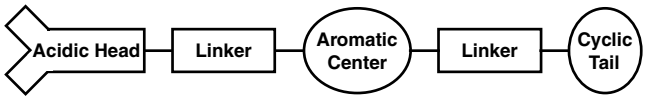


Figure 1. Chemical structure of tesaglitazar **1** (top) and its binding mode in the PPARα (ligand in cyan, left) and PPARγ (ligand in magenta, right) ligand binding domain as determined by X-ray crystallography.[8,10] The solvent-accessible surfaces of the two proteins are colored by atom types (O, red; N, blue; S, yellow; and C, white). The front parts of both binding sites are removed for the sake of clarity.



Scheme 1. Simplified topology of typical synthetic PPAR agonists. The linkers are sometimes branched to access additional subpockets in the receptor.

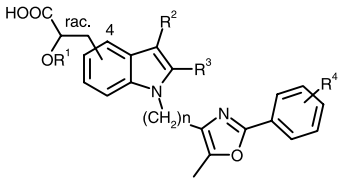
small structural changes, and docking studies were performed to identify novel substituents of isoxazolyl-serine-based PPAR ligands.[13] In addition, several receptor-based 3D-QSAR studies exist to rationalize the structure–activity relationship of specific PPAR agonist classes.[14–16] In this letter, we report the successful replacement of an entire scaffold giving access to a novel class of PPARα/γ co-agonists using structure-based modeling.

In our design approach, we focused on novel aromatic scaffolds that replace the central phenyl ring present in a large number of synthetic PPAR agonists.[17] We retained the α-alkoxy-substituted propionic acid head group which is a potent binding motif for the AF2-helix interface and which occurs in clinically advanced PPARα/γ co-agonists such as tesaglitazar **1** or naveglitazar.[18] From the binding mode of tesaglitazar **1** (Fig. 1), we deduced several design constraints that needed to be fulfilled by a novel aromatic core. First, the hydrophobic protein environment in the central region suggests aromatic systems with little polarity; hence, the sum of oxygen and nitrogen atoms was requested to be smaller than three. Second, due to the planar exit vector of the core phenyl-oxygen linkage seen in Figure 1 we focused on bicyclic annulated ring systems as planar replacements. In both PPARα and PPARγ, enough space seems to be available to accommodate a larger ring system, and some, but relatively few, agonists are published containing a bicyclic ring system in the central aromatic region.[17,19] Finally, the modeled ring systems had to make good interactions[20] with both PPARα and PPARγ isoforms taking into account the known flexibility of certain side chains, such as, for example, Met364 (PPARγ) or Met355 (PPARα).[19] The cyclic motifs considered were taken from an in-house database of ring fragments derived from the World Drug Index (WDI).[21] This database contains the ring systems and substituent attachment points frequently occurring in the WDI, subsequently modified by chemists by removing 'unwanted' structures. After filtering the database according to our three design constraints, several core structures remained. From this subset, the indole propionic acid scaffold was selected for chemical derivatization because of straightforward synthetic accessibility and favorable drug-like properties. We combined this moiety through different carbon chain linkers with a 5-methyl-2-phenyl-oxazole tail known to be a potent fragment for PPAR binding.[17,22,23] It should also be noted that PPAR agonists involving the indole substructure have been reported previously, however, in a different structural context.[19,24–26]

The preparation of compounds listed in Table 1 was accomplished in analogy to example **7** depicted in Scheme 2. 5-Formylindole **2** was subjected to a *Wittig* reaction involving (1,2-diethoxy-2-oxoethyl)-triphenylphosphonium chloride to afford acrylic ester **3** as a 95:5-mixture of *Z*- and *E*-isomers which was hydrogenated on Pd/C to give the racemic propionic ester derivative **4** in high yield (78% overall). Following the method of Goto et al.[27] butane-2,3-dione mono-oxime was reacted with 2-chlorobenzaldehyde furnishing the oxazole *N*-oxide **5** which was subsequently treated with $POCl_3$ providing the chloromethyl oxazole **6**. Coupling of compounds **4** and **6** was most conveniently accomplished with powdered KOH in DMSO,[28] conditions which concomitantly led to in situ hydrolysis of the ester group providing the indole propionic acid derivative **7** in racemic form[29] in modest yield (31%). The yields of the coupling and hydrolysis steps for the other derivatives were in the range of 4–80%.

In Table 1, we summarize the binding affinity and functional transactivation data of all compounds investigated in this study. As the IC_{50} binding values are experimentally more robust than the functional data they are

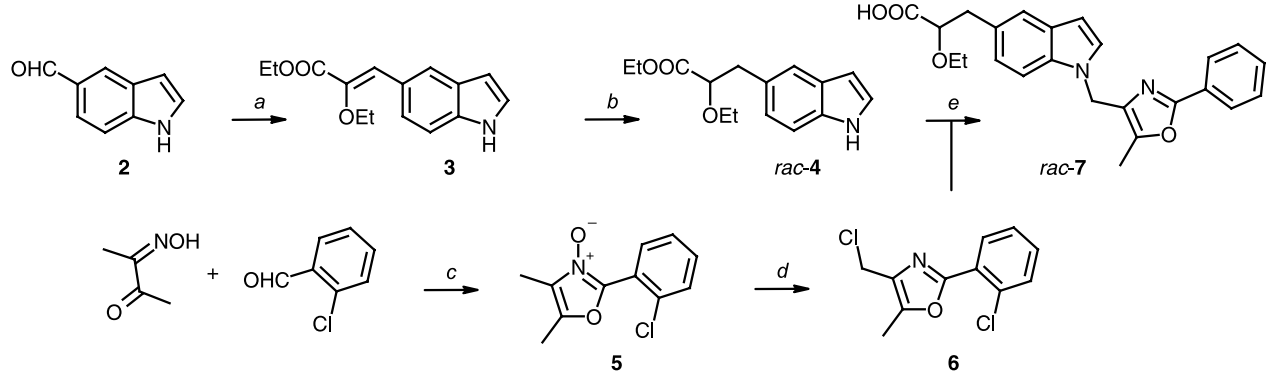
Table 1. Binding affinities and functional transactivation data of indole propionic acids on human PPAR[a]



Compound	Side chain[b]	R^1	R^2	R^3	R^4	*n*	IC_{50}			Ratio γ/α	EC_{50} (% effect)[c]		
							α	γ	δ		α	γ	δ
7	C-5	Et	H	H	H	1	0.368	0.178	> 10	0.5	0.84 (50)	0.28 (93)	8.4 (6)
8	C-4	Et	H	H	H	1	0.125	1.5	3.5	12	—	—	—
9[d]	C-4	Et	H	H	H	2	—	> 10	—	—	—	—	—
10	C-4	Et	H	H	H	3	0.756	0.274	—	0.4	0.19 (71)	0.09 (76)	2.4 (8)
11	C-5	Et	H	H	2-F	1	0.735	0.196	—	0.3	1.0 (52)	0.80 (94)	> 10 (11)
12	C-5	Et	H	H	2-Me	1	0.125	0.316	—	2.5	0.83 (77)	0.99 (92)	6.5 (8)
13	C-5	Et	H	H	2-Cl	1	0.073	0.251	—	3.4	0.81 (80)	0.76 (82)	4.6 (12)
14	C-5	Et	H	H	2-OMe	1	0.181	0.742	—	4.1	1.0 (107)	1.1 (69)	> 10 (11)
15	C-5	Et	H	H	2-O*i*-Pr	1	0.209	5.4	—	26	—	—	—
16	C-5	Et	H	H	3-Cl	1	0.396	0.024	—	0.1	0.13 (75)	0.06 (125)	2.4 (19)
17	C-5	Et	H	H	4-F	1	0.121	0.377	—	3.1	0.63 (105)	0.77 (83)	> 10 (9)
18	C-5	Et	H	H	4-CF_3	1	0.070	0.321	—	4.6	0.17 (132)	0.47 (92)	1.7 (31)
19	C-5	Et	H	H	4-Et	1	0.166	0.027	—	0.2	0.07 (56)	0.19 (113)	2.5 (13)
20	C-5	Et	H	H	4-*i*-Pr	1	0.117	0.013	—	0.1	0.41 (68)	0.12 (123)	2.5 (10)
21	C-5	Et	H	H	4-*t*-Bu	1	0.173	0.015	—	0.1	0.73 (63)	0.18 (131)	> 10 (9)
22	C-5	Et	H	H	3,5-di-Me	1	0.181	0.038	—	0.2	0.02 (87)	0.04 (126)	2.5 (12)
23	C-5	Et	H	H	3,5-di-Cl	1	0.419	0.071	—	0.2	0.03 (96)	0.07 (104)	1.4 (30)
24	C-5	Et	H	H	3,5-di-OMe	1	0.253	0.025	—	0.1	0.09 (133)	0.01 (139)	2.4 (12)
25	C-5	Et	H	H	3-Me, 4-F	1	0.149	0.135	—	0.9	0.05 (87)	0.14 (121)	2.4 (10)
26	C-5	Me	H	H	H	1	0.363	0.318	—	0.9	0.35 (73)	1.1 (62)	> 10 (5)
27	C-5	Pr	H	H	4-CF_3	1	0.040	0.399	0.259	10	0.51 (118)	2.0 (42)	1.6 (12)
28	C-5	*i*-Pr	H	H	4-CF_3	1	0.061	0.139	0.892	2.3	0.02 (134)	0.16 (82)	2.2 (16)
29	C-5	Et	Me	H	4-CF_3	1	0.218	0.223	—	1.0	0.17 (295)	0.06 (113)	6.0 (10)
30	C-5	Et	H	Me	4-CF_3	1	0.352	8.0	0.372	23	—	—	—

[a] PPARα, γ, and δ radioligand binding and functional transactivation (luciferase transcriptional reporter gene) assays were performed as described in Binggeli et al.[30] All IC_{50} and EC_{50} values are in μM. The variability of the IC_{50} determinations was on average ±10%.
[b] Position of the propionic acid side chain at the indole ring.
[c] See Ref. 31.
[d] The oxazole building block was prepared according to Binggeli et al.[30]

better suited for a quantitative comparison of receptor specificities. The first derivative prepared, **7**, showed already submicromolar affinity to the α- and γ-receptors and high selectivity against PPARδ. Various modifications were explored including the position of the propionic acid side chain attached to the indole scaffold, the linker length between indole and oxazole ring, the influence of the substituents R^1, R^2, and R^3, and the nature and position of R^4 located at the terminal phenyl ring. The binding affinity of indoles substituted at the 4-position with the propionic acid residue strongly depends on the linker length (n = 1–3). With a methylene linker



Scheme 2. Reagents and conditions: (a) $Ph_3P^+CH(OEt)COOEt\ Cl^-$, tetramethylguanidine, CH_2Cl_2, 40 °C, 40 h, 95%; (b) H_2 (1 atm), Pd/C (10%), EtOH, 22 °C, 2 h, 82%; (c) AcOH/HCl(g), 0 °C, 99%; (d) $POCl_3$, $CHCl_3$, reflux, 55%; (e) KOH (powdered), DMSO, 22 °C, 16 h, 31%.

($n = 1$) a higher affinity toward the α-receptor was observed, whereas a propyl linker ($n = 3$) induced stronger γ-activity (cf. **8** vs **10**). Compound **9** containing an ethylene linker ($n = 2$) was virtually inactive at the γ-receptor. In the 5-substituted series only compound **7** with $n = 1$ was active, whereas increasing the linker length to $n = 2$ and 3 substantially reduced or even abolished the activity at the γ-receptor (data not shown). A series of 6-substituted indole derivatives with $n = 1$–3 were also prepared but did not display any affinity toward the γ-receptor (data not shown).

By substituting the ortho position of the terminal phenyl group, the binding affinities for PPARγ varying from R^4 = 2-F to 2-O*i*-Pr (cf. **11**–**15**) continually decrease from 0.196 to 5.4 μM, whereas for PPARα the lowest IC_{50} of 0.073 μM was observed in between (**13**, R^4 = 2-Cl substituent). The ratio between PPARγ and α binding affinity is very sensitive to the size of the substituent, steadily increasing with bulkier groups (cf. **11**–**15**). Interestingly, inverse selectivity is observed for the para position at R^4 (cf. **17**–**21**) showing the lowest PPARγ IC_{50}, 0.013 μM, for compound **20**, R^4 = 4-*i*-Pr substituent. Mono- or di-substitution at the meta position(s) did in general increase the affinity for the γ-receptor (cf. **7** vs **16** and **22**–**24**). A smaller alkyl substituent at R^1 such as a methyl group (cf. **26** vs **7**) or larger ones such as propyl or isopropyl did hardly alter the affinity toward any receptor (cf. **18** with **27** and **28**). Finally, a methyl group attached to the indole core was tolerated at 2- but not at 3-position (cf. **29** and **30**). The results in Table 1 nicely illustrate how the PPARα/γ binding selectivity can be fine-tuned with rather small substituent variations at the terminal phenyl group.

The functional activity data in Table 1 reveal that the majority of the investigated indole carboxylic acids behave as full agonists for both the PPARα and γ receptors. They are up to two orders of magnitude less potent on the PPARδ receptor, with EC_{50} values higher than 1 μM. Even at micromolar concentrations they activate this receptor only weakly or not at all (% effect <35%). As examples **13**, **24**, and **28** show, the degree of functional activation of the PPARα and γ receptors can be optimized toward the desired direction with small modifications, e.g. at R^4.

To further understand the SAR of the indole propionic acids, we cocrystallized the ternary complex of the human PPARγ receptor ligand binding domain with compound **13** and a receptor coactivator SRC-1 fragment.[32] The structure was solved to a resolution of 2.1 Å and showed clear electron density for the bound ligand in the form of its (*S*) enantiomer.[33] Some residues, 262–274, which are part of a flexible loop at the entrance of the binding site, showed no electron density and were not included in the model. The overall structure of this complex is very similar to previously published PPARγ complex structures with the AF2-helix in the agonist-type conformation. Within the ligand binding site shown in Figure 2, the four typical strong hydrogen bonds between the ligand carboxylate and the residues Ser289 (2.63 Å), His323 (2.73 Å), His449 (2.61 Å), and Tyr473 (2.56 Å) can be identified.

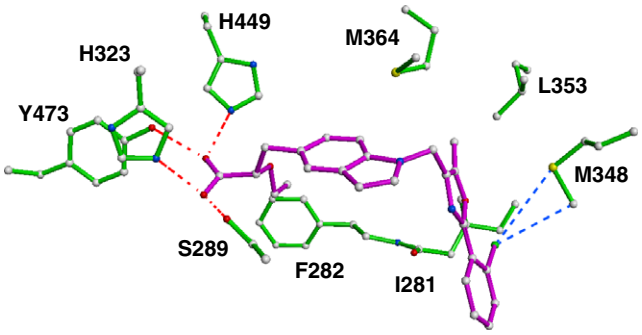


Figure 2. X-ray complex crystal structure of the PPARγ ligand binding domain with compound **13** (*S*) enantiomer. Key residues involved in protein–ligand hydrogen bonds (dashed, red) and van der Waals contacts are displayed. The blue dashed lines indicate short distances between the chlorine substituent and atoms of Met348, which is replaced in PPARα by the smaller Ile side chain (see text).

Several hydrophobic residues, some of which are shown in Figure 2, interact with the ligand through van der Waals interactions. The polar nitrogen atom of the phenyloxazole tail is solvent exposed. Comparing the binding modes of tesaglitazar **1** (Fig. 1, right) with compound **13** (Fig. 2) in PPARγ reveals that the *N*-methylene-substituted indole 5-propionic acid represents an excellent bioisosteric replacement of the known tyrosine-based scaffold, comprising similar ligand overlap and tail exit vector, respectively.

Based on the X-ray structure of **13**, we can now rationalize the strong dependence of the ratio between PPARα and γ binding affinity upon ortho substitution of the terminal phenyl group (Table 1). As illustrated in Figure 2, relatively short contacts between Met348 and the Cl atom are observed (Cl...S: 4.16 Å; Cl...C: 3.85) in PPARγ and apparently some energy penalty for the deformation of the protein has to be paid for this substituent as the smaller F-atom shows tighter binding. This hypothesis is also supported by the slight positional shift of the terminal methyl group of Met348, by 0.4 Å, away from the ligand relative to other PPARγ X-ray structures. As revealed by another X-ray complex structure (data not shown), additionally increasing the size of the ortho substituent at R^4 to 2-OMe leads to a flipping of the terminal phenyl group in PPARγ with the ortho substituent pointing now toward the solvent-exposed side. In PPARα, the Met348 residue is replaced by the smaller Ile side chain, which apparently is more tolerant toward bigger substituents. The inverse sensitivity of the PPARγ/α IC_{50} ratio observed for the para position at R^4 (Table 1) is less clear from the X-ray structure information, as this part of the ligand is in contact with the flexible loop 262–274, which is disordered in the crystallized complex.

In summary, we have identified a novel series of indole-based PPARα/γ co-agonists, which are selective against the δ isoform, through a scaffold selection process involving protein structure analysis and molecular modeling. Optimizing the substituents on this scaffold including known potent PPAR fragments led to balanced PPARα/γ co-agonists. Small aromatic substitutions at the terminal phenyl group strongly affect the relative

PPARα/γ binding and functional activation in vitro, thereby providing a class of molecules with the opportunity to potentially fine-tune the insulin sensitizing and lipid-lowering effects. The enantioselective synthesis and in vivo studies with pure (*S*) antipodes will be reported separately.

Acknowledgments

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29. Racemates are described only. Selected compounds have been prepared in optically pure form and it has been confirmed that essentially all PPAR activity is residing in the (*S*) enantiomers. Synthesis and in vivo activity of further developed optically pure compounds will be reported separately.
30. Binggeli, A.; Wirz, B.; Grether, U.; Hilpert, H.; Humm, R.; Iding, H.; Kuhn, B.; Maerki, H.-P.; Meyer, M.; Mohr, P. U.S. Patent 2,004,053,979, 2004.
31. Effects are reported in relation to reference compounds whose activity was set to 100%: 2-(*S*)-2-(2-Benzoyl-phenylamino)-3-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-phenyl}-propionic acid (Farglitazar, GW 262570) (PPAR alpha); 5-{4-[2-(5-methyl-2-phenyl-oxazol-4-yl)-ethoxy]-benzo[*b*]thiophen-7-ylmethyl}-thiazolidine-2,4-dione (Edaglitazone) (PPAR gamma); and {2-methyl-4-[4-methyl-2(4-trifluoromethyl-phenyl)-thiazol-5-ylmethylsulfanyl]-phenoxy}-acetic acid (GW 501516) (PPAR delta).
32. Co-crystals of PPARγ-LBD with **13** were obtained using an identical protocol as described in Burgermeister, E. et al. *Mol. Endocrinol.* **2006**, *20*, 809. Data have been collected in-house on a rotating anode (λ = 1.5418 Å) to a maximum resolution of 2.1 Å. Crystals belong to the orthorhombic space group $P2_12_12_1$ with cell axes a = 54.3, b = 68.3, and c = 87.9 Å. For structure determination, the data have been refined against an existing in-house PPARγ-LBD structure. Difference electron density was used to place the ligand by real space refinement.
33. The coordinates of the PPARγ-compound **13** structure were deposited to the Protein Data Bank (PDBid: 2gtk).