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ORIGINAL ARTICLE

# Structural basis for telmisartan-mediated partial activation of PPAR gamma

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**Telmisartan, a selective angiotensin II type 1 receptor blocker, has recently been shown to act as a partial agonist for peroxisome proliferator-activated receptor gamma (PPARγ). To understand how telmisartan partially activates PPARγ, we determined the ternary complex structure of PPARγ, telmisartan, and a coactivator peptide from steroid receptor coactivator-1 at a resolution of 2.18 Å. Crystallographic analysis revealed that telmisartan exhibits an unexpected binding mode in which the central benzimidazole ring is engaged in a non-canonical—and suboptimal—hydrogen-bonding network around helix 12 (H12). This network differs greatly from that observed when full-agonists bind with PPARγ and prompt high-coactivator recruitment through H12 stabilized by multiple hydrogen bonds. Binding with telmisartan results in a less stable H12 that in turn leads to attenuated coactivator binding, thus explaining the mechanism of partial activation.**
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## INTRODUCTION

Angiotensin II is a physiologically active major effector of the renin–angiotensin system. Angiotensin II mediates several biological functions in the kidney, heart and blood vessels through interaction with angiotensin II type 1 receptor.[1,2] Therefore, inhibition of the renin–angiotensin system by angiotensin II type 1 receptor blockers (ARBs) may be a therapeutic target for organ protection in patients with hypertension.[3–5] Although ARBs are known to lower blood pressure, this ability depends on the specific ARB administered.[6,7] A recent meta-analysis demonstrated that telmisartan is the ARB that reduces blood pressure, the most in patients with essential hypertension.[7] Previously, we investigated the molecular basis of angiotensin II type 1 receptor inhibition by telmisartan using a molecular simulation and proposed a unique 'delta lock' structure for telmisartan that may be responsible for its high-binding affinity to angiotensin II type 1 receptor, thereby leading to its superiority over other ARBs in halting cardiovascular disease in patients with hypertension.[8]

Recently a subgroup of ARBs was reported to induce peroxisome proliferator-activated receptor-gamma (PPARγ) activity, among which telmisartan shows the strongest ability.[9,10] PPARγ is the most abundant isoform in adipose tissue and has an important role in the regulation of insulin sensitivity.[11] Thiazolidinediones, such as pioglitazone or rosiglitazone, are highly affinitive full agonists of PPARγ and are currently used to treat type-2 diabetes.[12] However, although thiazolidinediones are known to improve insulin sensitivity, glucose tolerance and lipid profile, their use has also been associated with adverse side effects such as weight gain, edema and renal-fluid retention. As a result of these clinical observations, emphasis has shifted to the development of new PPARγ ligands that retain metabolic efficacy without exerting adverse effects.

Telmisartan has recently been shown to behave like a selective PPARγ modulator,[9] a promising new type of ligand that either activates only a subset of the functions induced by cognate ligands, or acts in a cell-type-selective manner.[13] Given that this drug functions as both a strong ARB and an selective PPARγ modulator, telmisartan is expected to target cardiovascular disease and diabetes mellitus, two closely associated conditions, with improved safety profiles in hypertensive patients. Indeed, a number of clinical and experimental studies have already been conducted, which provide evidence for the beneficial effects of telmisartan in cases of type 2 diabetes, as well as metabolic syndrome and obesity.[14–20]

Although the molecular mechanism required for the selective PPARγ modulator phenotype is still unknown, partial agonism is assumed to be a typical and essential characteristic of selective PPARγ modulator.[9,13] Telmisartan exhibits this critical feature,[9] and here we describe a crystal structure of human PPARγ in complex with telmisartan that clarifies the mechanism of partial agonism.

## METHODS

### Crystallization

The human PPARγ ligand-binding domain (LBD) (225–505) was expressed in *E. coli* as an N-terminal His-tagged protein. Affinity purification was performed

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with a $Ni^{2+}$-coupled sepharose and the His-tag was removed by incubation with thrombin. Further purification was performed by ion exchange chromatography and gel filtration. The purified protein was concentrated to 16 mg ml$^{-1}$ and incubated with telmisartan (isolated and purified from Micardis tablets) and a short peptide from human steroid receptor coactivator-1 (SRC1) (residues 685–700, ERHKILHRLLQEGSPS) for 1 h at final respective concentrations of 0.5 and 1 mM. The solution was mixed with an equal volume of 0.1 M Tris–HCl (pH 7.0) and 0.8 M sodium citrate tribasic dihydrate, and crystallized using sitting drop-vapor diffusion at 293 K. Thick plate-like crystals appeared after 3–5 days.

### Data collection and structure determination

For data collection, crystals were transferred into cryoprotectant solution containing 30% (v/v) glycerol and flash frozen at 100 K. Data were collected at the Photon Factory AR-NE3A beamline (Tsukuba, Japan) and processed with HKL2000.[21] The structure of human PPARγ LBD was solved by molecular replacement using MOLREP[22,23] against an existing in-house structure of the human PPARγ LBD. Crystals belonged to the orthorhombic space group $P2_12_12$, with cell axes of a=132.9 Å, b=53.5 Å and c=53.9 Å. Data were refined by REFMAC software,[24,25] which carried out rigid body and restrained refinement. An electron density difference map was used to place the ligand in real space refinement. Manual rebuilding of protein was done with Coot.[26,27] The final structure consisted of the LBD except the region between residues 263 and 272, the coactivator peptide (residues 686–696), and 47 water molecules. Data collection and refinement statistics are given in Supplementary Table 1. The coordinates for the complexes described here have been deposited in the Protein Data Bank (PDB ID: 3VN2).

## RESULTS AND DISCUSSION

### Structure of the PPARγ complexed with telmisartan

To understand how telmisartan activates PPARγ, we crystallized the complex formed by the PPARγ LBD and telmisartan using a method similar to that previously employed on complexes formed between the LBD and other agonists (data not shown). Although we obtained plate-like crystals that belonged to space group *C*2 from the solution containing PPARγ and telmisartan and found lattices similar to those found when PPARγ LBD formed complexes with other agonists,[28–30] we did not observe telmisartan in the determined structure.

To stabilize the formation of the complex and to make new interfaces for crystal packing, a short peptide derived from the PPARγ activator SRC1 was designed based on the ternary complex structure of PPARγ.[29] As expected, when the peptide was added to the mixture containing PPARγ and telmisartan, an apparently new crystal precipitated from the solution, and its structure was subsequently analyzed by X-ray diffraction. The SRC1 peptide provided an interface with adjacent molecules in the crystal, and telmisartan was observed in the Fo-Fc electron density difference map after both rigid body and first restrained refinement.

Finally, we determined the crystal structure of PPARγ with telmisartan and the SRC1 peptide at a resolution of 2.18 Å. The overall fold was almost identical to previously determined apo and complex structures,[28–30] and comprised of 12 helices (H1-H12) and a small β-sheet region of four strands (Figure 1a). We superposed Cα atoms from the structure of PPARγ with telmisartan onto those from the structure with rosiglitazone (PDB ID: 2PRG),[29] 2-BABA (PDB ID: 1WM0)[30] and the apo structure (PDB ID: 1PRG),[29] and calculated root mean square deviations. The root mean square deviations were 0.64 Å for rosiglitazone, 0.69 Å for 2-BABA and 0.93 Å for the apo structure.

### Binding mode of telmisartan in the PPARγ

The ligand-binding site of the PPARγ LBD is a large, Y-shaped cavity with a volume around 1400 Å$^3$ and consists of three branches (Figure 1a).[31] Branch I, surrounded by H3, H5, H11 and H12, shows mainly hydrophilic character and provides an activation function-2 surface. The hydrophilic head group of rosiglitazone occupies this branch and forms a hydrogen-bonding network with key residues Ser289, His323, Tyr327, His449 and Tyr473.[29] Branch II is a hydrophobic cavity, formed by H2′, H3, H6, H7 and the β-sheet region. Branch III consists of hydrophobic and hydrophilic residues of H2, H3 and the β-sheet region. Some compounds such as farglitazar induce the slide of Phe363 side chain, resulting in the additional region (branch I'), perpendicular to branch I between H3 and H7.[28]

To our knowledge, three binding modes of telmisartan with PPARγ have been proposed by docking simulations. In the first mode, two

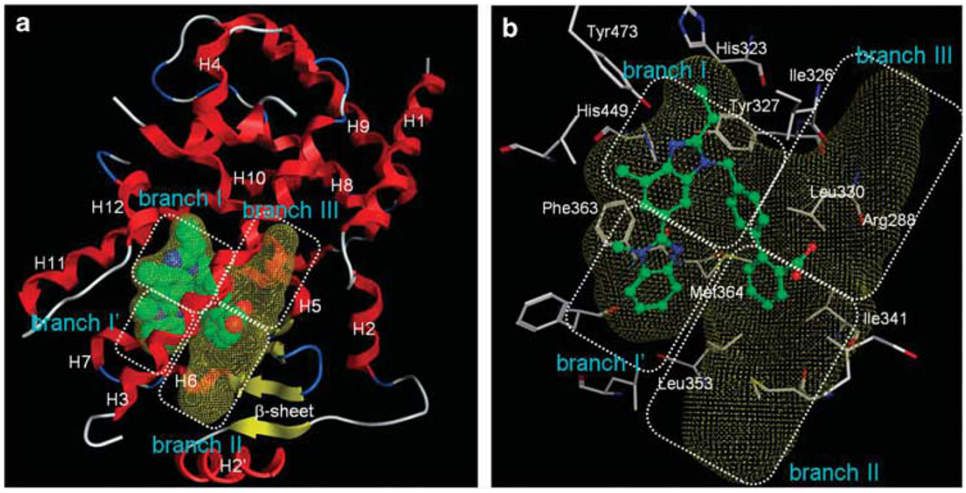


**Figure 1** Complex structure of PPARγ with telmisartan. (**a**) The overall complex structure. The ligand-binding cavity composed of four branches is shown in yellow dots. (**b**) The ligand-binding pocket of PPARγ in the presence of telmisartan. Important residues involved in the ligand-protein interaction are indicated in white.

benzimidazole rings occupy branch II, the central benzene ring and the propyl group fill branch III, and branch I is nearly empty.[9,32,33] In the second mode, the biphenyl moiety and the central benzimidazole ring occupy branches II and III, respectively, and the distal benzimidazole ring points into branch I but makes no hydrogen bonds.[34] In the third mode, the biphenyl moiety and the central benzimidazole ring fill branch I' and I, respectively, whereas the distal benzimidazole ring occupies branch II. This mode also predicts no hydrogen-bonding interaction around H12.[35]

The binding mode observed in the crystal structure we have determined adopts a U-shaped conformation around Cys285 and is distinct from these three predicted modes (Figure 1b). The central benzimidazole ring from telmisartan occupies branch I, and its N3′ nitrogen forms a hydrogen bond with H12-residue Tyr473. The His323 side chain is pushed out from the position it occupies in other complex structures, and the propyl moiety fills the newly formed region. This interaction is characteristic of telmisartan and is not observed for any other complex structure deposited in PDB except one.[36]

Substitution of this propyl moiety for a shorter alkyl chain has been found to attenuate activity,[37] indicating the importance of this interaction related with the flip of His323. The benzene ring of the central benzimidazole ring is involved in T-shaped π-stacking interaction with His449, the distal benzimidazole group fills branch I' with π–π stacking interaction with Phe363 in H9, and the 1′-methyl group contacts Phe282 via Van der Waals interaction. This interaction explains the decrease in activity caused by deletion of the 1′-methyl group.[37] The biphenyl moiety exists in branch II and III, and exhibits hydrophobic interaction with Ile326, Leu330, Ile341, Leu353 and Met364, from H5 to H7. Although the carboxylate group forms hydrogen bonds with Ser342 and Arg288 in the previous docking model,[34] in our crystal structure it does not make hydrogen bonds with any residues in branch II. This dispensability of carboxylate is consistent with the previous SAR analysis of telmisartan.[37]

### Molecular basis of PPARγ partial activation mechanism through unique binding mode of telmisartan

Previous structural studies of PPARγ suggested that the activation mechanism of full agonists and partial agonists are different from each other. Full-agonistic activity is thought to result from several factors that stabilize H12 in the proper position, prompt coactivator peptide binding, and are observed in the structure of all complexes comprised of PPARγ. These include multiple intermolecular hydrogen bonds between carboxylic acid, or its bioisostere, and amino-acid residues Ser289, His323, His449 and Tyr473, as well as intramolecular hydrogen bonds among these four residues and Tyr327.[38] In addition, a certain level of occupation in branches II or III is required to increase affinity.

In contrast, the complexes comprised of PPARγ and partial-agonists lack this hydrogen-bond network, or else it is suboptimal. This produces an unstable or unfavorable conformation for coactivator binding. Instead, partial-agonists display hydrophobic interaction in branch II or III, leading to the stabilization of H3 and the β-sheet region rather than H12.[38] A hydrogen bond with Ser342 at the border of two branches is observed for some partial agonists to reinforce this hydrophobic interaction. This H12-independent activation mechanism is characteristic of partial agonists.

The partial activation mechanism of telmisartan can be explained by the attenuation of the hydrogen-bonding network around H12, derived from the unique biding mode described here (Figures 2a–c). Telmisartan induces only one intermolecular hydrogen bond (Tyr473), whereas full agonists rosiglitazone and farglitazar form three (Ser289, His323 and Tyr473)[29] and four (Ser289, His323, His449 and Tyr473) bonds, respectively.[28] Further, the propyl group pushes His323 out from the position it occupies in full-agonist complexes. These factors give rise to the non-canonical hydrogen-bonding network around H12, which hinders recruitment of coactivator peptides. In fact, partial agonism by telmisartan is only weakly correlated with H12 stabilization. PPARγ activation was selectively reduced by a

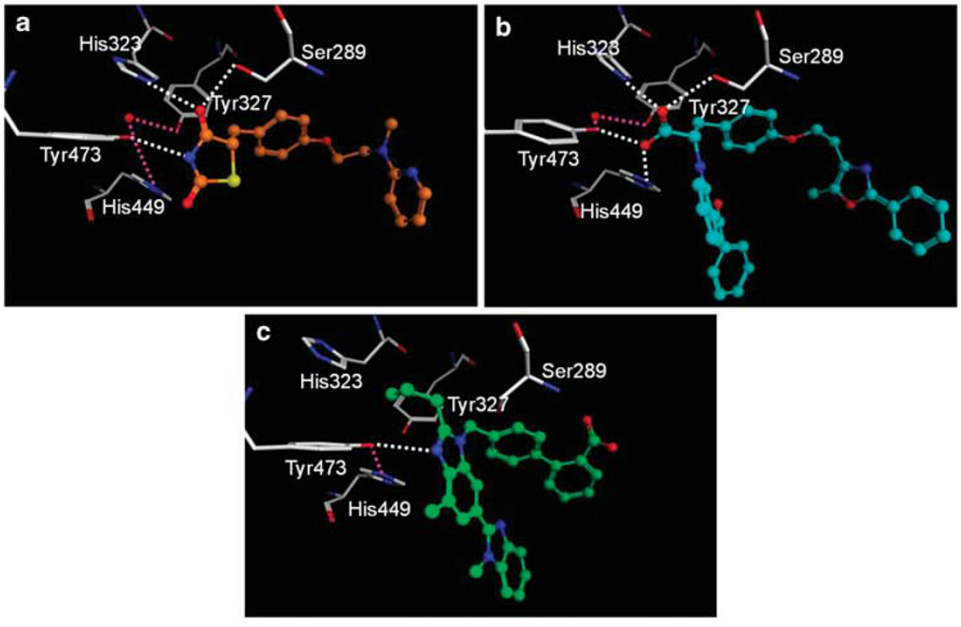


**Figure 2** Comparison of the hydrogen-bonding network around H12 among complex structures. White dotted line: intermolecular hydrogen bonds between ligands and PPARγ. Purple dotted line: hydrogen bonds observed in PPARγ water molecules. Rosiglitazone is colored orange (**a**), farglitazar is cyan (**b**) and telmisartan is green (**c**).

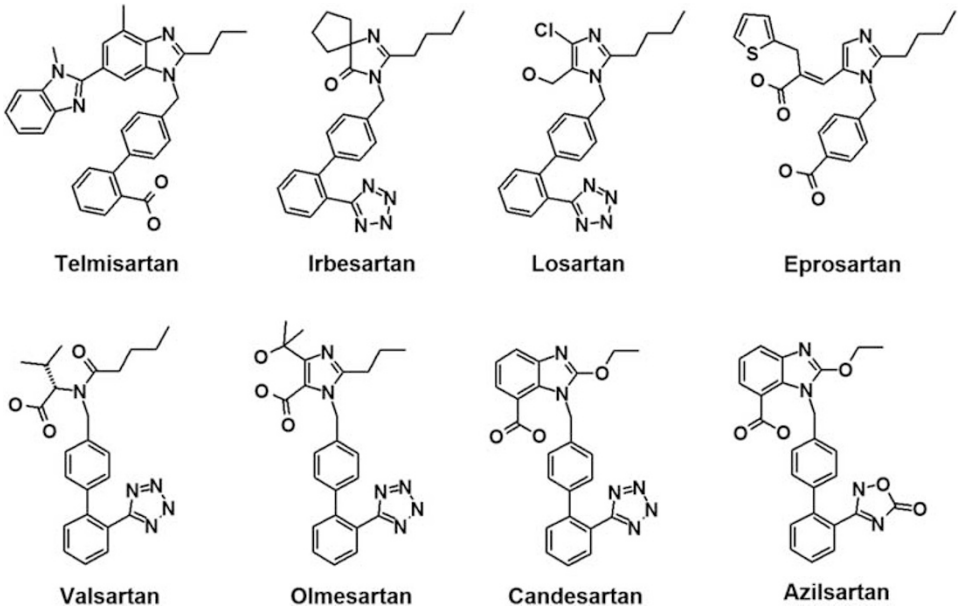


**Figure 3** Chemical structures of representative ARBs.

mutation at Tyr473 when complexed with full agonists troglitazone and pioglitazone, but not with telmisartan.[39]

Although the binding mode of telmisartan is distinct from that of rosiglitazone, the interaction between the SRC1-derived peptide and PPARγ in the ternary complex with telmisartan is almost identical to that with rosiglitazone, in which the 'LXXLL' motif in SRC1 that is essential for the interaction is packed between Lys301 and Glu471 on PPARγ.[29] This strongly suggests that the partial agonism observed with telmisartan does not arise from the stabilization of a suboptimal conformation for coactivator binding, but rather from the reduced population of optimal conformations in dynamic behavior that are difficult to detect in the crystal structures. Previous structural analysis of PPARγ with partial agonists has also revealed that the binding modes of coactivator-derived peptides are virtually identical to that seen for PPARγ with rosiglitazone.[30,40] Although some partial agonists including telmisartan are known to exhibit selectivity for coactivators, the reason behind this selectivity cannot be determined by observing complex structures. It is possible that selectivity is generated through subtle differences in dynamics.

**Structural insight into the interaction of PPARγ with other ARBs**

Telmisartan is the most potent activator of PPARγ among ARBs, followed by irbesartan and losartan. Valsartan, candesartan, olmesartan and eprosartan produce minimal activation.[9,10] Reports show that telmisartan is the only ARB that activates PPARγ at concentrations lower than can be achieved in plasma with conventional oral dosing (1–5 $\mu mol\,l^{-1}$).[9] To determine the structure responsible for the lower efficiency exhibited by other ARBs, we examined whether or not these can bind to the ligand-binding cavity of PPARγ with the assumption that the common structure of ARBs, consisting of a biphenyl moiety bearing a carboxylic or tetrazole group and an imidazole ring with an alkyl chain, occupies the same position as that of telmisartan (see Figure 3 for the structures of ARBs).

Results showed that these other ARBs did not bind well to the ligand-binding cavity, and further indicate that this was because of structural differences between the benzene ring of the central benzimidazole ring of telmisartan and the corresponding parts of other ARBs. This benzene ring is packed in a hydrophobic environment between His449 and Cys285, which is a narrow region that can accommodate only planar groups. As a result, this region seems to be unable to accommodate bulky groups that are present on valsartan, olmesartan and eprosartan. This hydrophobic region is also unfavorable to highly-hydrophilic groups such as a carboxylic acid that is involved in valsartan, olmesartan, eprosartan, candersatan, and EXP3174, the major active metabolite of losartan. Further, this ring interacts with His449 via T-shaped π-stacking, whereas most other ARBs do not. Although candesartan and azilsartan are exceptions, they also fail to exhibit the same binding mode as that of telmisartan because of a steric clash between biphenyl and carboxylic groups. These structural investigations allow an assessment of PPARγ activating properties of other ARBs.

In conclusion, we determined the ternary complex structure of PPARγ, telmisartan and an SRC1 peptide. Telmisartan exhibits an unexpected and unique binding mode that is distinct from previously predicted models. Partial agonism by telmisartan can be ascribed to the suboptimal hydrogen-bonding network around H12, which is induced by the characteristic structure of telmisartan, specifically the central propyl benzimidazole group. This group is also a structural determinant that discriminates telmisartan from weak ARBs. Ours is the first report that elucidates the partial activation mechanism of PPARγ by ARB at the atomic level.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)