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Design of a partial PPARδ agonist

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Abstract—Structure based ligand design was used in order to design a partial agonist for the PPARδ receptor. The maximum activation in the transactivation assay was reduced from 87% to 39%. The crystal structure of the ligand binding domain of the PPARδ receptor in complex with compound **2** was determined in order to understand the structural changes which gave rise to the decrease in maximum activation.

The peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor super-family. There are three PPAR subtypes, PPARα, PPARγ and PPARδ.[1] The use of PPARγ activators, for example, rosiglitazone and pioglitazone (glitazones), in the treatment of type 2 diabetes has been established due to their abilities to lower blood glucose and insulin levels and improve insulin sensitivity.[2,3] Similarly, PPARα activators, for example, fenofibrate and clofibrate (fibrates), have been used clinically for more than three decades for their ability to lower plasma triglycerides (TG) and moderately raise HDL-cholesterol.[4] There is no drug available targeting the third PPARδ receptor, but there is evidence that PPARδ is involved in lipid homeostasis.[5–7] The ligand binding domains of the PPARs consist of 13 α-helices and four β-strands. One of the α-helices is the C-terminal helix that contains the AF-2 transcriptional activation domain which is involved in recruitment of co-activators. The use of partial PPARγ agonists has been suggested in order to avoid adverse effects, such as oedema and body weight gain.[8] In this work, the partiality was obtained by design of compounds without direct interactions with the AF-2 helix.

The aim of this investigation was to identify partial PPARδ agonists by design of compounds with weaker or none interactions with the AF-2 helix. Our starting structure was **1** with 87% maximum activation compared to GW501516 on the hPPARδ receptor, Figure 1, Table 1.[5] Compound **1** came out of our PPAR programme, where it was derived from GW501516 utilizing the Y-shaped PPAR receptor binding pocket to design a more rigid molecule. Compound **1** was a partial agonist on the PPARα and PPARγ receptor subtypes and close to a full agonist on the PPARδ receptor subtype (Table 1).

Compound **1** was docked into the crystal structure of the ligand binding domain of the PPARδ receptor crystallized with GW2433 (1GWX).[10,11] In the predicted docking pose, the ortho-methyl group was positioned in a rather narrow binding pocket close to the AF-2 helix. The carboxylic acid in **1** was predicted to make hydrogen bond interactions with H323 on helix 5, H449 on helix 10 and Y473 on the AF-2 helix, Figure 2. The hypothesis was that introduction of a group larger than the ortho-methyl in this part of the molecule would prevent or weaken interactions between the carboxylic acid in the molecule and the AF-2 helix.

Compound **2**, containing a cyclopentyl ring instead of the methyl, was therefore synthesized[9] and tested in the transactivation assay, Figure 1, Scheme 1 and Table 1 and Figure 3.

Reduction of the commercially available 4-hydroxy-1-indanone gave the core structure of the acid half of the molecule (top line Scheme 1). The sulfur ether linker was introduced using sodium thiocyanate and bromine to give the thiocyanate adduct, which after alkylation

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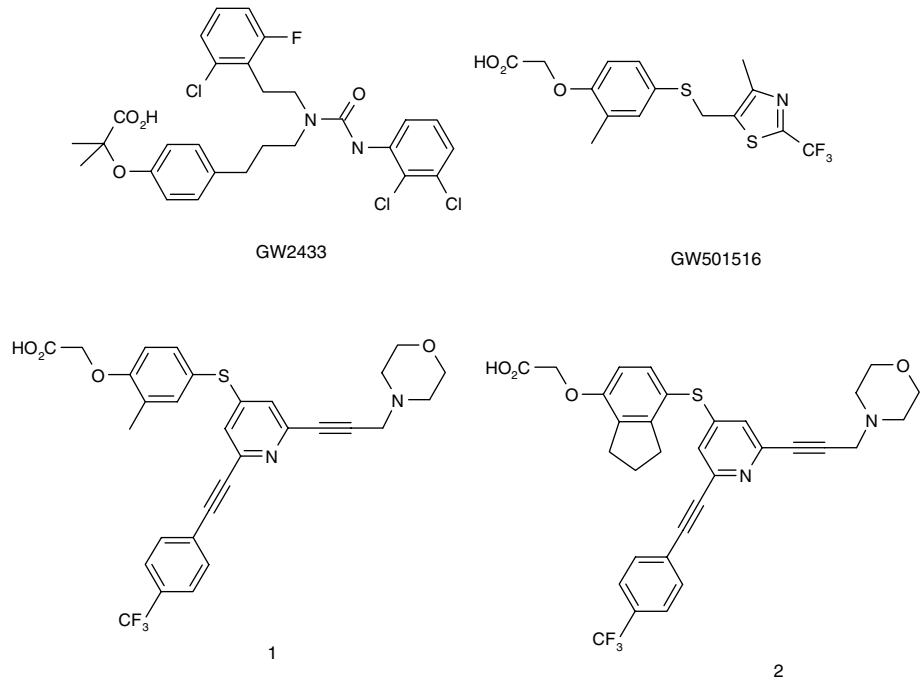


Figure 1. Graphical illustration of the structures discussed.

of the phenol was reduced to the thioether with dithioerythritol. Arylation of the thioether with tribromopyridine gave the desired 4-pyridyl product in good yield. Sonogashira cross-coupling with 4-trifluorophenylacetylene and then with *N*-propargylmorpholine gave the ester of the desired product. Basic hydrolysis of the ester gave compound **2**.

In the transactivation assay, **2** had similar potency as **1** but the maximum activation was reduced from 87% to 39%, Table 1 and Figure 3. In order to investigate if this was due to a reduced interaction between the carboxylic acid and the AF-2 helix, the ligand binding domain of the hPPARδ receptor was co-crystallized with **2**.[14] In the crystal structure a hydrogen bond is observed between the carboxylic acid in **2** and H449 in the receptor, Figure 4. However, no hydrogen bonds are observed between the ligand and H323 or Y473, Figure 4. In addition, a water molecule, Wat21, which makes a hydrogen bond both with the nitrogen atom in the pyridine ring in **2** and the backbone carbonyl in L340 in the receptor, is observed in the hydrophobic part of the binding pocket.

The crystal structures of PPARδ crystallized with GW2433 (1GWX) and PPARδ co-crystallized with **2** (2Q5G) have the same overall structure except for the AF-2 helix, Figure 5. The AF-2 helix in 2Q5G adopts

Table 1. In vitro human PPAR transactivation data for **1** and **2** and standard compounds

Compound	hPPARα EC_{50}[a] (μM)/% max[b]	hPPARγ EC_{50}[a] (μM)/% max [c]	hPPARδ EC_{50}[a] (μM)/% max[d]
1	0.1/50	5.5/28	0.05/87
2	–/<10	–/<10	0.13/39
NNC61-4655	0.01/100	2.6/96	6.4/57
Rosiglitazone	>10 / >24	0.3/100	–/<10
GW501516	3.9/68	>10/>22	0.008/100

If a plateau was not reached at the highest concentration then the maximal effect was indicted to be greater than this value and the EC_{50} was assigned to be >10 μM.

[a] Compounds were tested in at least three separate experiments in at least five concentrations ranging from 0.001 to 30 μM. EC_{50} is the concentration giving 50% of the maximal activity observed for a given compound. EC_{50} was not calculated for compounds producing transactivation lower than 10% at 30 μM. The results are expressed as means and ± SEM was less than 15%.

[b] Fold activation relative to maximum activation (100%) obtained with NNC 61-4655.[18]

[c] Rosiglitazone.

[d] GW501516.

Table 2. Diffraction data and refinement statistics for the PPARδ-compound **2** complex

Diffraction data statistics (53.73–2.70 Å)	
No. of measured reflections	41117
No. of unique reflections	16233
R-merge[a]	0.099 (0.373)
Completeness (%)	95.7 (98.6)
Mean I/σ(I)	6.3 (2.1)
Average redundancy	2.53 (2.47)
Refinement statistics (83.92–2.70 Å)	
R-factor[b] (%)	22.5 (31.2)
R-free[c] (%)	30.5 (47.0)
No. of atoms (total)	3904
Bond length rmsd from ideal (Å)	0.014
Bond angle rmsd from ideal (deg)	1.625
Average B-factor (Å^2)	41.6

Values in parentheses refer to the highest resolution shell.

[a] R-merge = $\Sigma|I-\langle I\rangle|/\Sigma I$, where the sums are overall symmetry related reflections of intensity I.

[b] R-factor = $\Sigma_{work}||F_{obs}|-k|F_{calc}||/\Sigma_{work}F_{obs}$.

[c] R-free = $\Sigma_{test}||F_{obs}|-k|F_{calc}||/\Sigma_{test}F_{obs}$, where F_{obs} and F_{calc} are observed and calculated structure factors, respectively, k is the scale factor, and the sums are overall reflections in the working set and the test set (5.1% of the data), respectively.

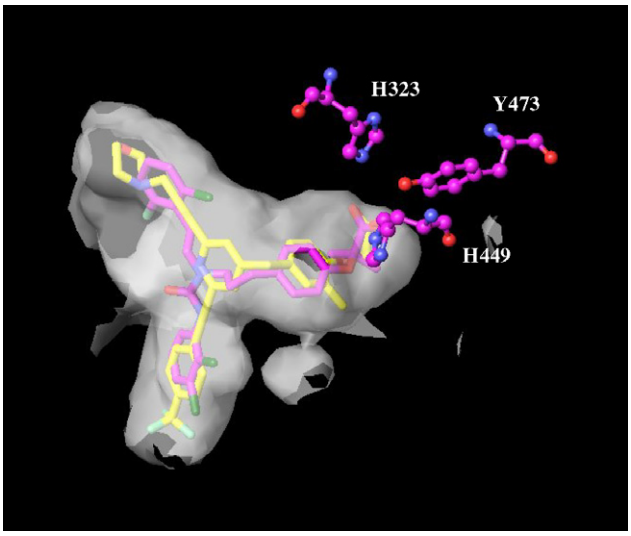


Figure 2. Compound **1** (yellow) docked into the crystal structure of the ligand binding domain of the PPARδ receptor crystallized with GW2433 (magenta). H323, H449 and Y473 are shown in ball-and-stick representation. The white surface shows the binding pocket 5 Å from GW2433.

a position in which interactions between Y473 and the ligand are absent. H323 and H449 are more or less in the same position as in 1GWX, Figure 6. The distance between the Cα carbons in H323 and H449 is 9.7 Å in 1GWX and 9.5 Å in 2Q5G. In GWX the distances between the Cα carbons in H323 and Y473 and between H449 and Y473 are 9.7 and 10.4 Å, respectively. In 2Q5G the same were longer, 14.4 and 20.9 Å, respectively. When the positions of the two ligands were compared, compound **2** in 2Q5G was moved away from the AF-2 helix compared to GW2433 in 1GWX, Figure 6. As a consequence of this a hydrogen bond interaction could still be formed between **2** and H449 but not to H323 and Y473. Compound **2** was also docked into the crystal structure of 2Q5G. The rmsd between the crystal structure and the predicted docking pose was 1.2 Å.

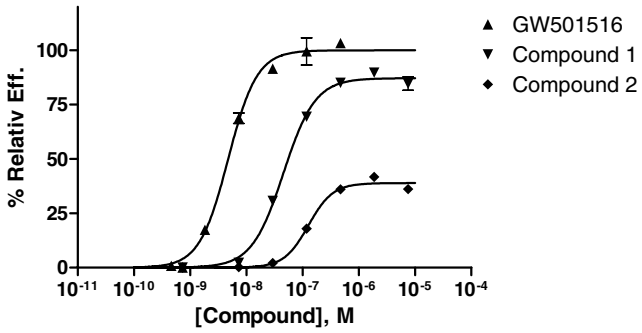


Figure 3. In vitro human PPARδ transactivation data for **1**, **2** and GW501516.

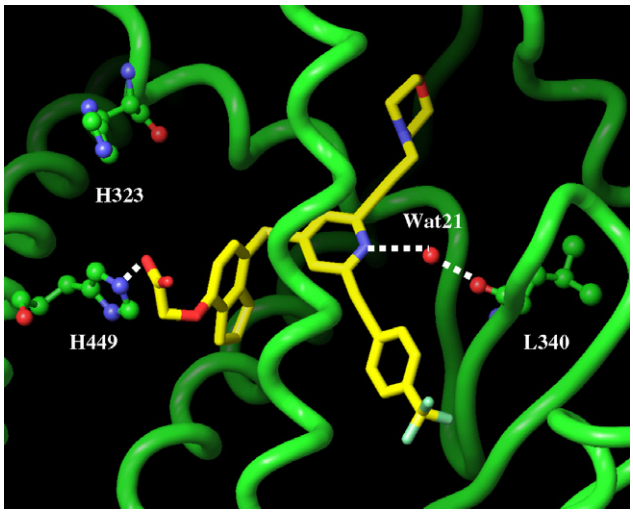
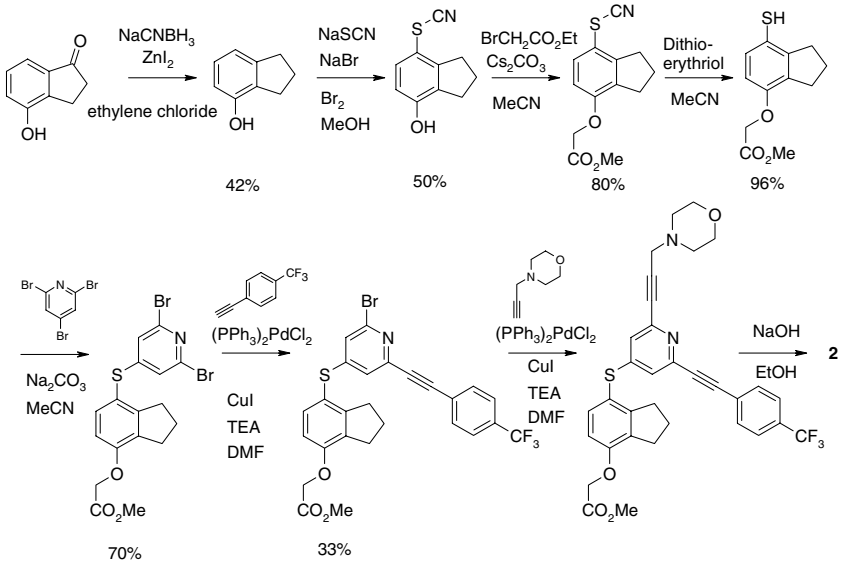


Figure 4. The crystal structure of the ligand binding domain of the PPARδ receptor (green) co-crystallized with **2** (yellow). H323, L340 and H449 are shown in ball-and-stick representation. The water molecule Wat21 makes a hydrogen bond to the nitrogen atom in the pyridine ring in **2** and to the backbone oxygen in L340. A hydrogen bond is observed between the carboxylic acid in **2** and H449.



Scheme 1. Synthesis of compound **2**.[9]

Figure 5. The crystal structure between PPARδ and GW2433 (1GWX, magenta) superimposed with the crystal structure of the ligand binding domain of the PPARδ receptor (green) co-crystallized with **2** (yellow). To demonstrate the relative position of the AF-2 helix, the ribbon from P467 to K474 in PPARδ co-crystallized with **2** is coloured yellow.

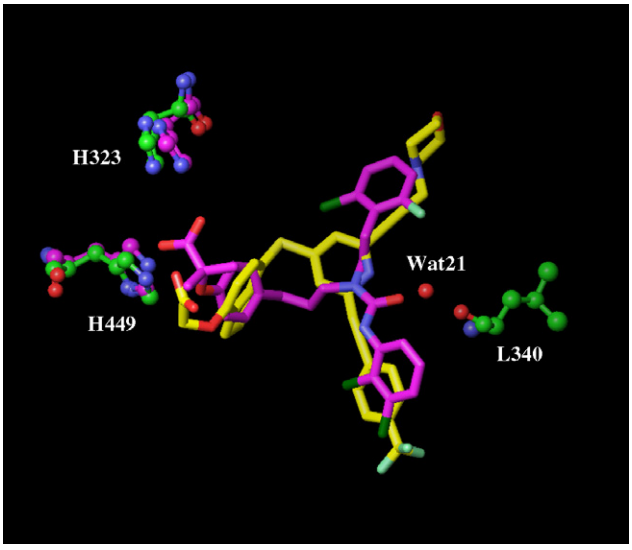


Figure 6. GW2433 in the crystal structures of PPARδ crystallized with GW2433 (1GWX, magenta) superimposed with the crystal structure of the ligand binding domain of the PPARδ receptor (green) co-crystallized with **2** (yellow). H323, L340 and H449 are shown in ball-and-stick representation.

In conclusion, a selective, partial PPARδ agonist was designed by introducing a bulky substituent close to the carboxylic acid. X-ray crystallographic data confirmed the impaired interaction to the AF-2 domain explaining the partial PPARδ efficacy. The data therefore give guidance to the design of other partial PPARδ agonists.

Acknowledgments

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9. Experimental procedure for the synthesis of **2**: A solution of 4-hydroxy-1-indanone (10.74 g, 72.46 mmol), $NaCNBH_3$ (13.66 g, 217.4 mmol) and zinc(II)iodide (69.1 g, 217.4 mmol) in ethylenechloride (200 mL) was stirred at reflux for 2 h. The cooled reaction mixture was filtered through silica gel and the filtrate was evaporated. The residue was purified by column chromatography using methylene chloride as eluent to give 4-hydroxyindane in 4.1 g (42%) yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04 (t, 2H), 6.83 (d, 1H), 6.61 (d, 1H), 4.58 (br. s, 1H), 2.93 (t, 2H), 2.85 (t, 2H), 2.1 (m, 2H).
To a solution of 4-hydroxyindane (5.2 g, 38.8 mmol) in dry methanol (50 ml) were added sodium thiocyanate (10.0 g, 124 mmol) and sodium bromide (4.0 g, 38.8 mmol). Bromine (2.2 mL, 43 mmol) was added to the reaction mixture over 15 min and the reaction mixture was stirred overnight at room temperature. Brine (50 mL) and ethyl acetate (100 mL) were added to the mixture, the mixture was shaken and the organic phase was isolated. The aqueous phase was extracted with additional ethyl acetate (2× 100 mL), and the combined organic phases were washed with brine (50 mL). The combined organic phases were dried and evaporated. The residue was suspended in methylene chloride (100 mL) and filtered. The filtrate was evaporated and the residue was purified by column chromatography using methylene chloride as eluent to give 7-thiocyanato-indan-4-ol in 3.7 g (50%) yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.27 (d, 1H), 6.66 (d, 1H), 5.52 (br.s, 1H), 3.09 (t, 2H), 2.91 (t, 2H), 2.17 (m, 2H).

To a solution of 7-thiocyanato-indan-4-ol (3.7 g, 19.5 mmol) and caesium carbonate (19 g, 58 mmol) in dry acetonitrile was added methyl bromoacetate (2.0 mL, 21 mmol). The reaction mixture was stirred for 1 h at room temperature, filtered and the filtrate was evaporated. The residue was purified by column chromatography using methylene chloride as eluent to give (7-thiocyanato-indan-4-yloxy)-acetic acid methyl ester in 4.1 g (80%) yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.33 (d, 1H), 6.57 (d, 1H), 4.67 (s, 2H), 3.79 (s, 3H), 3.08 (t, 2H), 3.01 (t, 2H), 2.16 (m, 2H).

(7-Thiocyanato-indan-4-yloxy)-acetic acid methyl ester (4.1 g, 15.6 mmol) and 1,4-dithioerythritol (3.1 g, 20 mmol) were refluxed for 3 h in a mixture of water (10 mL) and acetonitrile (75 mL). The reaction mixture was evaporated and the residue was purified by column chromatography using methylene chloride as eluent to give (7-mercapto-indan-4-yloxy)-acetic acid methyl ester in 3.55 g (96%) yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.05 (d, 1H), 6.47 (d, 1H), 4.62 (s, 2H), 3.79 (s, 3H), 3.16 (s, 1H), 2.98 (t, 2H), 2.89 (t, 2H), 2.11 (m, 2H).

A mixture of (7-mercapto-indan-4-yloxy)-acetic acid methyl ester (5.0 g, 21 mmol), tribromopyridine (6.6 g, 21 mmol) and sodium carbonate (2.7 g, 25 mmol) in acetonitrile (100 mL) was stirred at 80 °C for 5 h. The reaction mixture was evaporated and the residue was extracted with methylene chloride (3× 50 mL). Ethyl acetate (30 mL) was added and the mixture was heated to reflux. After cooling to room temperature crystals of [7-(2,6-dibromo-pyridin-4-ylsulfanyl)-indan-4-yloxy]-acetic acid methyl ester were collected by filtration in 7 g (70%) yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29 (d, 1H), 6.94 (s, 2H), 6.63 (d, 1H), 4.73 (s, 2H), 3.83 (s, 3H), 3.05 (t, 2H), 2.86 (t, 2H), 2.10 (m, 2H), 1.54 (br. s, 1H).

Triethylamine (10 mL) and DMF (10 mL) were added under nitrogen to a mixture of [7-(2,6-dibromo-pyridin-4-ylsulfanyl)-indan-4-yloxy]-acetic acid methyl ester (3.0 g, 6.3 mmol), 4-trifluorophenylacetylene (0.8 g, 4.8 mmol), CuI (72 mg, 0.38 mmol) and bis(triphenylphosphine)palladium chloride (356 mg, 0.5 mmol). The reaction mixture was heated in a microwave oven at 110 °C for 1 h. The reaction mixture was evaporated and the residue was extracted with citric acid solution (5%, 50 mL) and methylene chloride (50 mL). The aqueous layer was further extracted with methylene chloride (2× 15 mL). The combined organic phases were dried and evaporated. The residue was purified by HPLC to give {7-[2-bromo-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid methyl ester in 900 mg (33%) yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, 2H), 7.41 (d, 2H), 7.12 (d, 1H), 6.85 (s, 1H), 6.75 (s, 1H), 6.45 (d, 1H), 4.54 (s, 2H), 6.63 (s, 3H), 2.86 (t, 2H), 2.68 (t, 2H), 1.90 (m, 2H).

Triethylamine (5 mL) and DMF (5 mL) were added under nitrogen to a mixture of {7-[2-bromo-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid methyl ester (150 mg, 0.27 mmol), *N*-propargylmorpholine (66 mg, 0.53 mmol), CuI (3 mg, 0.016 mmol) and bis(triphenylphosphine)palladium chloride (14 mg, 0.02 mmol). The reaction mixture was heated in a microwave oven at 110 °C for 1 h. The reaction mixture was evaporated and the residue was purified by HPLC to give {7-[2-(3-morpholin-4-yl-prop-1-ynyl)-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid methyl ester in 40 mg yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H), 7.60 (d, 2H), 7.33 (d, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 6.64 (d, 1H), 4.73 (s, 2H), 3.83 (s, 3H), 3.75 (m, 4H), 3.50 (s, 2H), 3.05 (t,2H), 2.87 (t, 2H), 2.62 (m, 4H), 2.10 (m, 2H), 1.62 (br.s, 1H).

A solution of {7-[2-(3-morpholin-4-yl-prop-1-ynyl)-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid methyl ester (40 mg, 0.066 mmol) in ethanol (10 mL) and 1N NaOH (5 mL) were stirred at room temperature for 30 min. To the reaction mixture was added 1N HCl(5 mL) and the mixture was extracted with ethyl acetate (3× 20 mL). The organic phase was washed with water, dried and evaporated to give {7-[2-(3-morpholin-4-yl-prop-1-ynyl)-6-(4-trifluoromethyl-phenylethynyl)-pyridin-4-ylsulfanyl]-indan-4-yloxy}-acetic acid (**2**) in 35 mg yield. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H), 7.60 (d, 2H), 7.26 (m, 4H), 6.69 (d, 1H), 6.57 (s, 1H), 4.70 (s, 2H), 3.82 (m, 4H), 3.65 (s, 2H), 3.6 (br.s, 2H), 3.05 (t, 2H), 2.87 (t, 2H), 2.82 (m, 4H), 2.08 (m, 2H).

10. Glide docking. The structure manipulations were performed in Maestro version 7.5 (Maestro 7.0, Schrödinger, LLC, New York, NY, 1999–2005). Glide calculations were performed with Impact version 4.0.[12,13] **1** was built in Maestro version 7.5, a formal charge of −1 was assigned and the molecule was minimized with the OPLS_2005 force field. Compound **1** was docked with Glide version 4.0 using the SP mode and the van der Waals radii of the ligand atoms were scaled by 0.8.
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14. The crystal structure was determined by ActiveSight, San Diego.
    Crystals were grown at 277 K using the hanging drop vapour diffusion technique mixing 1 μl of 6 mg/ml PPARδ, 1mM **2**, 0.5% (w/v) heptyl-β-D-glucopyranoside, 20 mM Hepes, pH 7.5, 40 mM imidazole, 40 mM NaCl, 2 mM Tris(2-carboxyethyl)phosphine hydrochloride, and 500 mM ammonium acetate with 1 μl mother liquor (2 M NaCl, 10% (w/v) PEG6000) leaving it to equilibrate over 300 μl mother liquor. Diffraction data were collected at 95 K on crystals cryocooled in mother liquor containing 15% (w/v) xylitol at ALS, beamline 5.0.3, using an ADSC Quantum 4R detector. The crystals belong to space group C2 (a = 112.6 Å, b = 65.6Å, c = 101.2 Å, β = 124.1°). Auto indexing, data reduction and scaling of the data were performed with d*TREK.[15] The structure was determined using the molecular replacement technique implemented in the program Phaser[16] with PDB entry 2GWX[11] as search model. Introduction of the ligand and alternating cycles of manual rebuilding and positional refinement using REFMAC5[17] gave a final model with R-factor = 22.5% (R-free = 30.5%). The statistics for diffraction data and refinement are summarized in Table 2. Coordinates and structure factors have been deposited in the PDB (Accession code 2Q5G).
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