

Supporting Information

New 2-Aryloxy-3-phenyl-propanoic Acids As Peroxisome Proliferator-Activated Receptors α/γ Dual Agonists Able to Upregulate the Mitochondrial Carnitine Shuttle System Gene Expression

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Superposition of **S-16** and PPAR γ partial agonists **25-27** into the PPAR γ -LBD (Figures 6–9)

(S)-Ethyl 2-(4-bromo-phenoxy)-3-phenylpropanoate (20a); (R)-ethyl 2-(4-bromo-phenoxy)-3-phenylpropanoate (20b); ethyl 2-(4-bromo-phenoxy)-3-phenylpropanoate (20c). 80% yield. ^1H NMR: δ = 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.19–3.24 (m, 2H, PhCH_2), 4.17 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.71–4.75 (dd, 1H, CH), 6.68–6.73 and 7.22–7.35 (m, 9H, aromatics); GC/MS, m/z (%): 350 (50) $[\text{M}+2]^+$, 348 (50) $[\text{M}]^+$, 177 (100), 135 (84).

(S)-Ethyl 2-(4-bromo-2-methyl-phenoxy)-3-phenylpropanoate (20d). 70% yield. ^1H NMR: δ = 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.18 (s, 3H, CH_3Ph), 3.25 (d, 2H, PhCH_2), 4.16 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.74 (t, 1H, CH), 6.44–6.47 and 7.13–7.30 (m, 8H, aromatics); GC/MS, m/z (%): 364 (66) $[\text{M}+2]^+$, 362 (68) $[\text{M}]^+$, 177 (96), 135 (100).

(S)-Ethyl 2-(4-bromo-3-methyl-phenoxy)-3-phenylpropanoate (20e). 71% yield. ^1H NMR: δ = 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.31 (s, 3H, CH_3Ph), 3.18–3.28 (m, 2H, PhCH_2), 4.17 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.71–4.75 (dd, 1H, CH), 6.50–6.54, 6.73–6.74 and 7.21–7.35 (m, 8H, aromatics); GC/MS, m/z (%): 364 (67) $[\text{M}+2]^+$, 362 (69) $[\text{M}]^+$, 177 (89), 135 (100).

(S)-Ethyl 2-(4-bromo-2,6-dimethyl-phenoxy)-3-phenylpropanoate (20f). 82% yield. ^1H NMR: δ = 1.06 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.20 (s, 6H, 2 CH_3Ar), 3.24 (d, 2H, PhCH_2), 4.02 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.57 (t, 1H, CH), 7.10 and 7.20–7.32 (m, 7H, aromatics); GC/MS, m/z (%): 378 (31) $[\text{M}+2]^+$, 376 (31) $[\text{M}]^+$, 177 (100), 135 (85).

Ethyl 2-(4-bromo-3,5-dimethyl-phenoxy)-3-phenylpropanoate (20g). 54% yield. ^1H NMR: δ = 1.19 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.32 (s, 6H, 2 CH_3Ar), 3.20–3.23 (m, 2H, PhCH_2), 4.17 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.71–4.76 (m, 1H, CH), 6.57 and 7.23–7.31 (m, 7H, aromatics); GC/MS, m/z (%): 378 (98) $[\text{M}+2]^+$, 376 (100) $[\text{M}]^+$, 224 (60), 135 (83).

(S)-Ethyl 2-(3-methyl-biphenyl-4-yloxy)-3-phenylpropanoate (21a). 72% yield. ^1H NMR: δ = 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.28 (s, 3H, CH_3Ph), 3.28 (d, 2H, PhCH_2), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.82 (t, 1H, CH), 6.64–6.67, 7.24–7.52 (m, 13H, aromatics); GC/MS, m/z (%): 360 (100) $[\text{M}]^+$, 184 (60), 135 (72).

(S)-Ethyl 2-(2-methyl-biphenyl-4-yloxy)-3-phenylpropanoate (21b). 75% yield. ^1H NMR: δ = 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.20 (s, 3H, CH_3Ph), 3.19–3.32 (m, 2H, PhCH_2), 4.21 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.79–4.84 (dd, 1H, CH), 6.67–6.77, 7.07–7.10 and 7.21–7.40 (m, 13H, aromatics); GC/MS, m/z (%): 360 (100) $[\text{M}]^+$, 184 (37), 135 (27).

(S)-Ethyl 2-(3,5-dimethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21c). 54% yield. ^1H NMR: δ = 1.07 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.31 (s, 6H, 2 CH_3Ar), 3.23–3.37 (m, 2H, PhCH_2), 4.04 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.62–4.67 (dd, 1H, CH), 7.21–7.55 (m, 12H, aromatics); GC/MS, m/z (%): 374 (100) $[\text{M}]^+$, 301 (10), 197 (77), 135 (56).

Ethyl 2-(2,6-dimethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21d). 60% yield. ^1H NMR: δ = 1.22 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.95 (s, 6H, 2 $\text{CH}_3\text{-Ph}$), 3.18–3.31 (m, 2H, PhCH_2), 4.15–4.28 (m, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.78–4.82 (dd, 1H, CH), 6.58, 7.07–7.10 and 7.21–7.41 (m, 12H, aromatics); GC/MS, m/z (%): 374 (100) $[\text{M}]^+$, 301 (17), 198 (83).

(S)-Ethyl 2-(2',6'-dimethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21e). 25% yield. ^1H NMR: δ = 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.99 (s, 6H, 2 CH_3Ar), 3.22–3.34 (m, 2H, PhCH_2), 4.15–4.24 (m, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.81–4.86 (dd, 1H, CH), 6.86–7.37 (m, 12H, aromatics); GC/MS, m/z (%): 374 (100) $[\text{M}]^+$, 301 (11), 198 (25), 135 (44).

(S)-Ethyl 2-(4'-methyl-biphenyl-4-yloxy)-3-phenylpropanoate (21f). 80% yield. ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.37 (s, 3H, CH_3Ph), 3.22–3.33 (m, 2H, PhCH_2), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.80–4.84 (dd, 1H, CH), 6.87–6.92 and 7.19–7.47 (m, 13H, aromatics); GC/MS, m/z (%): 360 (100) $[\text{M}]^+$, 184 (45), 135 (27).

Ethyl 2-(3'-methyl-biphenyl-4-yloxy)-3-phenylpropanoate (21g). 95% yield. ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.39 (s, 3H, CH_3Ph), 3.20–3.33 (m, 2H, PhCH_2), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.80–4.85 (m, 1H, CH), 6.87–6.92, 7.10–7.12, 7.23–7.32 and 7.43–7.48 (m, 13H, aromatics); GC/MS, m/z (%): 360 (100) $[\text{M}]^+$, 184 (45), 135 (31).

(S)-Ethyl 2-(2'-methyl-biphenyl-4-yloxy)-3-phenylpropanoate (21h). 93% yield. ^1H NMR: δ = 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.24 (s, 3H, CH_3Ph), 3.22–3.33 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$),

4.81–4.85 (dd, 1H, CH), 6.86–6.89 and 7.16–7.34 (m, 13H, aromatics); GC/MS, m/z (%): 360 (100) $[M]^+$, 184 (29), 135 (38).

(S)-Ethyl 2-(2,2'-dimethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21i). 88% yield. ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.97 (s, 3H, CH_3Ph), 2.01 (s, 3H, CH_3Ph), 3.19–3.27 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.79–4.84 (dd, 1H, CH), 6.50–6.54, 6.65–6.76, 6.90–7.05 and 7.13–7.36 (m, 12H, aromatics); GC/MS, m/z (%): 374 (100) $[M]^+$, 198 (34), 135 (31).

(S)-Ethyl 2-(2'-fluoro-biphenyl-4-yloxy)-3-phenylpropanoate (21l). 49% yield. ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.20–3.33 (m, 2H, PhCH_2), 4.21 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.81–4.85 (dd, 1H, CH), 6.88–6.93 and 7.08–7.45 (m, 13H, aromatics); GC/MS, m/z (%): 364 (100) $[M]^+$, 188 (56), 135 (46).

(S)-Ethyl 2-(2'-trifluoromethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21m). 45% yield. ^1H NMR: δ = 1.18 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.21–3.33 (m, 2H, PhCH_2), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.82–4.87 (dd, 1H, CH), 6.83–6.88 and 7.18–7.72 (m, 13H, aromatics); GC/MS, m/z (%): 414 (100) $[M]^+$, 238 (77), 135 (81), 91 (43).

(S)-Ethyl 2-(2'-phenyl-biphenyl-4-yloxy)-3-phenylpropanoate (21n). 95% yield. ^1H NMR: δ = 1.15 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.16–3.28 (m, 2H, PhCH_2), 4.15 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.73–4.78 (dd, 1H, CH), 6.66–6.71, 6.97–7.02 and 7.09–7.39 (m, 18H, aromatics); GC/MS, m/z (%): 422 (100) $[M]^+$, 135 (33).

(S)-Ethyl 2-(2'-methoxy-biphenyl-4-yloxy)-3-phenylpropanoate (21o). 77% yield. ^1H NMR: δ = 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.19–3.32 (m, 2H, PhCH_2), 3.79 (s, 3H, $\text{CH}_3\text{O-Ph}$), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.79–4.83 (dd, 1H, CH), 6.85–7.02 and 7.19–7.43 (m, 13H, aromatics); GC/MS, m/z (%): 376 (100) $[M]^+$, 200 (32), 135 (28).

(S)-Ethyl 2-(2'-ethyl-biphenyl-4-yloxy)-3-phenylpropanoate (21p). 78% yield. ^1H NMR: δ = 1.07 (t, 3H, $\text{CH}_3\text{CH}_2\text{Ph}$), 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.55 (q, 2H, $\text{CH}_3\text{CH}_2\text{Ph}$), 3.23–3.34 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.81–4.85 (dd, 1H, CH), 6.84–6.89 and 7.12–7.36 (m, 13H, aromatics); GC/MS, m/z (%): 374 (100) $[M]^+$, 135 (46).

(S)-Ethyl 2-(2'-isopropyl-biphenyl-4-yloxy)-3-phenylpropanoate (21q) or (R)-ethyl 2-(2'-isopropyl-biphenyl-4-yloxy)-3-phenylpropanoate (21r). 55% yield. ^1H NMR: δ = 1.12 (d, 6H, $(\text{CH}_3)_2\text{CHPh}$), 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.02 (m, 1H, $(\text{CH}_3)_2\text{CHPh}$), 3.21–3.33 (d, 2H, PhCH_2), 4.21 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.80–4.85 (dd, 1H, CH), 6.83–6.91 and 7.12–7.37 (m, 13H, aromatics); GC/MS, m/z (%): 388 (100) $[M]^+$, 135 (46).

Ethyl 2-(2'-formyl-biphenyl-4-yloxy)-3-phenylpropanoate (22). 69% yield. ^1H NMR: δ = 1.21 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.24–3.35 (m, 2H, PhCH_2), 4.21 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.82–4.87 (dd, 1H, CH), 6.91–6.95, 7.22–7.63 and 7.97–8.00 (m, 13H, aromatics), 9.94 (s, 1H, CHO); GC/MS, m/z (%): 374 (100) $[M]^+$, 135 (40).

Ethyl 2-(2'-propenyl-biphenyl-4-yloxy)-3-phenylpropanoate (23a). 25% yield (mixture of *cis* and *trans* isomers). ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.77–1.81 (m, 3H, $\text{CH}_3\text{CH}=\text{CH}$), 3.24–3.29 (m, 2H, PhCH_2), 4.22 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.79–4.83 (m, 1H, CH), 5.65–5.71 (m, 1H, $\text{CH}_3\text{CH}=\text{CH}$), 6.14–6.31 (m, 1H, $\text{CH}_3\text{CH}=\text{CH}$), 6.82–6.89 and 7.17–7.33 (m, 13H, aromatics); GC/MS, m/z (%): 386 (42) $[M]^+$, 209 (100), first eluted; 386 (47) $[M]^+$, 209 (100), second eluted.

Ethyl 2-(2'-pent-1-enyl-biphenyl-4-yloxy)-3-phenylpropanoate (23b). 17% yield (mixture of *cis* and *trans* isomers). ^1H NMR: δ = 0.91 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.35–1.50 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 2.05–2.25 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}$), 3.24–3.29 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.80–4.84 (dd, 1H, CH), 5.52–5.61 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 6.14–6.34 (m, 1H, $\text{CH}_2\text{CH}=\text{CH}$), 6.82–6.88 and 7.18–7.34 (m, 13H, aromatics); GC/MS, m/z (%): 414 (51) $[M]^+$, 237 (60), 195 (100), first eluted; 414 (62) $[M]^+$, 237 (62), 195 (100), second eluted.

Ethyl 2-(2'-styryl-biphenyl-4-yloxy)-3-phenylpropanoate (23c). 54% yield (mixture of *cis* and *trans* isomers). ^1H NMR: δ = 1.20 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 3.20–3.35 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.79–4.83 (dd, 1H, CH), 6.35–6.51 (dd, 2H, $\text{CH}_3\text{CH}=\text{CH}$), 6.82–7.39 (m, 18H, aromatics); GC/MS, m/z (%): 448 (52) $[M]^+$, 271 (100), first eluted; 448 (53) $[M]^+$, 271 (100), second eluted.

Ethyl 2-(2'-propyl-biphenyl-4-yloxy)-3-phenylpropanoate (24a). 92% yield. $^1\text{H NMR}$: δ = 0.80 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.22 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.43 (m, 2H, ($\text{CH}_3\text{CH}_2\text{CH}_2$), 2.51 (t, 2H, ($\text{CH}_3\text{CH}_2\text{CH}_2$), 3.23–3.33 (m, 2H, PhCH_2), 4.20 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.81–4.86 (dd, 1H, CH), 6.84–6.89 and 7.13–7.36 (m, 13H, aromatics); GC/MS, m/z (%): 388 (100) $[\text{M}]^+$, 135 (36).

Ethyl 2-(2'-pentyl-biphenyl-4-yloxy)-3-phenylpropanoate (24b). 86% yield. $^1\text{H NMR}$: δ = 0.79 (t, 3H, $\text{CH}_3\text{CH}_2\text{CH}_2$), 1.13–1.25 (m, 7H, $\text{CH}_3\text{CH}_2\text{O}$ and $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 1.49 (m, 2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2$), 2.52 (t, 2H, $\text{CH}_3(\text{CH}_2)_3\text{CH}_2$), 3.21–3.33 (m, 2H, PhCH_2), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.81–4.85 (dd, 1H, CH), 6.84–6.89 and 7.12–7.35 (m, 13H, aromatics); GC/MS, m/z (%): 416 (100) $[\text{M}]^+$, 135 (60).

Ethyl 2-(2'-phenethyl-biphenyl-4-yloxy)-3-phenylpropanoate (24c). 93% yield. $^1\text{H NMR}$: δ = 1.19 (t, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 2.66–2.71 and 2.82–2.87 (2 m, 4H, PhCH_2CH_2), 3.24–3.35 (m, 2H, PhCH_2CH), 4.19 (q, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.82–4.86 (dd, 1H, CH), 6.85–6.95 and 7.10–7.36 (m, 18H, aromatics); GC/MS, m/z (%): 450 (100) $[\text{M}]^+$, 181 (42).

(S)-2-(3-Methyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (2). Crystallized from *n*-hexane, 47% yield, mp: 108–112 °C. ee = 99% (methyl ester, Chiralcel OD column, *n*-hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 280 nm); $[\alpha]_{\text{D}} = -11$ (c=1, methanol); $^1\text{H NMR}$: δ = 2.27 (s, 3H, CH_3Ph), 3.27–3.40 (m, 2H, PhCH_2), 4.89–4.93 (m, 1H, CH), 6.69–6.72 and 7.22–7.52 (m, 14H, 13 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), m/z (%): 346 (100) $[\text{M}]^+$, 184 (38), 121 (74). Anal. Calcd for C₂₂H₂₀O₃: C, 79.50%; H, 6.06%. Found: C, 79.11%; H, 6.12%.

(S)-2-(2-Methyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (3). Crystallized from CHCl_3/n -hexane, 54% yield, mp: 127–129 °C. ee = 95% (methyl ester, Chiralcel OD column, *n*-hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 280 nm); $[\alpha]_{\text{D}} = -2$ (c=1, methanol); $^1\text{H NMR}$: δ = 2.21 (s, 3H, CH_3Ph), 3.25–3.37 (m, 2H, PhCH_2), 4.88–4.92 (m, 1H, CH), 6.69–6.77, 7.10–7.13 and 7.22–7.41 (m, 14H, 13 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), m/z (%): 346 (100) $[\text{M}]^+$, 184 (47), 121 (91). Anal. Calcd for C₂₂H₂₀O₃: C, 79.50%; H, 6.06%. Found: C, 79.42%; H, 6.08%.

(S)-2-(3,5-Dimethyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (4). Crystallized from *n*-hexane/ CHCl_3 , 60% yield, mp: 101–103 °C. ee = 98% (methyl ester, Chiralcel OD column, *n*-hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 280 nm); $[\alpha]_{\text{D}} = -37$ (c=1, methanol); $^1\text{H NMR}$: δ = 2.27 (s, 6H, 2 CH_3Ph), 3.30 (d, 2H, PhCH_2), 4.74 (t, 1H, CH), 7.20–7.54 (m, 13H, 12 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), m/z (%): 360 (100) $[\text{M}]^+$, 197 (85), 121 (98). Anal. Calcd for C₂₃H₂₂O₃: C, 79.74%; H, 6.40%. Found: C, 79.11%; H, 6.12%.

2-(2,6-Dimethyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (5). Crystallized from CHCl_3/n -hexane, 82% yield, mp: 173–174 °C. $^1\text{H NMR}$: δ = 1.96 (s, 6H, 2 CH_3Ph), 3.23–3.36 (m, 2H, PhCH_2), 4.87–4.91 (dd, 1H, CH), 6.60 (s, 2H, aromatics), 7.05–7.09 and 7.22–7.41 (m, 11H, 10 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), m/z (%): 360 (100) $[\text{M}]^+$, 198 (74), 121 (64). Anal. Calcd for C₂₃H₂₂O₃: C, 79.74%; H, 6.40%. Found: C, 79.99%; H, 6.35%.

(S)-2-(2',6'-Dimethyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (6). Crystallized from CHCl_3/n -hexane, 88% yield, mp: 129–132 °C. ee = 98% (methyl ester, Chiralcel OD column, *n*-hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 280 nm); $[\alpha]_{\text{D}} = -6$ (c=1, methanol); $^1\text{H NMR}$: δ = 1.99 (s, 6H, 2 CH_3Ph), 3.30–3.33 (m, 2H, PhCH_2), 4.88–4.92 (dd, 1H, CH), 6.88–7.36 (m, 13H, 12 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), m/z (%): 360 (100) $[\text{M}]^+$, 121 (89). Anal. Calcd for C₂₃H₂₂O₃: C, 79.74%; H, 6.40%. Found: C, 79.30%; H, 6.33%.

(S)-2-(4'-Methyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (7). Crystallized from CHCl_3/n -hexane, 97% yield, mp: 138–139 °C. ee = 99% (methyl ester, Chiralcel OD column, *n*-hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 280 nm); $[\alpha]_{\text{D}} = +2$ (c=1, methanol); $^1\text{H NMR}$: δ = 2.38 (s, 3H, CH_3Ph), 3.25–3.37 (m, 2H, PhCH_2), 4.87–4.91 (dd, 1H, CH), 6.88–6.93 and 7.19–7.47 (m, 14H, 13 aromatics + COOH, D₂O exchanged); GC/MS (methyl

ester), m/z (%): 346 (100) $[M]^+$, 184 (53), 121 (85). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50%; H, 6.06%. Found: C, 80.02%; H, 6.17%.

2-(3'-Methyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (8). Crystallized from $CHCl_3/n$ -hexane, 56% yield, mp: 145–146 °C. 1H NMR: δ = 2.39 (s, 3H, CH_3Ph), 3.25–3.35 (m, 2H, $PhCH_2$), 4.89–4.93 (dd, 1H, CH), 6.88–6.93, 7.12–7.14, 7.22–7.34 and 7.45–7.60 (m, 14H, 13 aromatics + COOH, D_2O exchanged); GC/MS (methyl ester), m/z (%): 346 (100) $[M]^+$, 184 (46), 121 (76). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50%; H, 6.06%. Found: C, 79.39%; H, 6.02%.

(S)-2-(2'-Methyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (9). Crystallized from $CHCl_3/n$ -hexane, 23% yield, mp: 93–95 °C. ee = 99% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 280 nm); $[\alpha]_D = -3$ (c=1, methanol); 1H NMR: δ = 2.23 (s, 3H, CH_3Ph), 3.25–3.32 (m, 2H, $PhCH_2$), 4.88–4.92 (m, 1H, CH), 6.86–6.91 and 7.14–7.35 (m, 14H, 13 aromatics + COOH, D_2O exchanged); GC/MS (methyl ester), m/z (%): 346 (100) $[M]^+$, 184 (20), 121 (51). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50%; H, 6.06%. Found: C, 79.91%; H, 6.09%.

(S)-Sodium 2-(2,2'-dimethyl-biphenyl-4-yloxy)-3-phenylpropanoate (10). Crystallized from $CHCl_3/n$ -hexane, 99% yield. ee = 75% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 254 nm); $[\alpha]_D = -8$ (c=1, methanol); 1H NMR (CD_3OD): δ = 1.86 and 1.95 (2 s, 6H, 2 CH_3Ph), 2.89–3.13 (m, 2H, $PhCH_2$), 4.25–4.29 (dd, 1H, CH), 6.55–7.31 (m, 12H, aromatics); GC/MS (methyl ester), m/z (%): 360 (39) $[M]^+$, 121 (100). Anal. Calcd for $C_{23}H_{21}O_3Na$: C, 74.99%; H, 5.75%. Found: C, 72.06%; H, 5.56%.

(S)-2-(2'-Fluoro-biphenyl-4-yloxy)-3-phenylpropanoic acid (11). Crystallized from $CHCl_3/n$ -hexane, 77% yield, mp: 117–119 °C. ee = 85% (Chiralcel AD column, n -hexane/isopropanol/TFA 95:5:0.05 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 280 nm); $[\alpha]_D = -1$ (c=1, methanol); 1H NMR: δ = 3.25–3.37 (m, 2H, $PhCH_2$), 4.89–4.93 (dd, 1H, CH), 6.90–6.95 and 7.08–7.46 (m, 14H, 13 aromatics + COOH, D_2O exchanged); GC/MS (methyl ester), m/z (%): 350 (100) $[M]^+$, 188 (54), 121 (82). Anal. Calcd for $C_{21}H_{17}FO_3$: C, 74.99%; H, 5.09%. Found: C, 74.13%; H, 5.22%.

(S)-Sodium 2-(2'-trifluoromethyl-biphenyl-4-yloxy)-3-phenylpropanoate (12). Washed with $CHCl_3$, 62% yield. ee = 88% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 254 nm); $[\alpha]_D = -6$ (c=1, methanol); 1H NMR (CD_3OD): δ = 2.91–3.14 (m, 2H, $PhCH_2$), 4.29–4.34 (dd, 1H, CH), 6.75–6.78, 7.05–7.16, 7.21–7.31 and 7.49–7.77 (m, 13H, aromatics); GC/MS (methyl ester), m/z (%): 400 (24) $[M]^+$, 121 (100). Anal. Calcd for $C_{22}H_{16}F_3O_3Na$: C, 64.71%; H, 3.95%. Found: C, 62.57%; H, 3.87%.

(S)-Sodium 2-(2'-phenyl-biphenyl-4-yloxy)-3-phenylpropanoate (13). Crystallized from methanol/ $CHCl_3$, 32% yield. ee = 94% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 254 nm); $[\alpha]_D = -5$ (c=1, methanol); 1H NMR (CD_3OD): δ = 3.06–3.21 (m, 2H, $PhCH_2$), 4.50–4.54 (dd, 1H, CH), 6.64–6.69, 6.89–6.94 and 7.05–7.36 (m, 18H, aromatics); GC/MS (methyl ester), m/z (%): 408 (44) $[M]^+$, 121 (100). Anal. Calcd for $C_{27}H_{21}O_3Na$: C, 77.87%; H, 5.08%. Found: C, 73.67%; H, 4.74%.

(S)-Sodium 2-(2'-methoxy-biphenyl-4-yloxy)-3-phenylpropanoate (14). Washed with $CHCl_3$, 95% yield. ee = 83% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 254 nm); $[\alpha]_D = -5$ (c=1, methanol); 1H NMR ($DMSO-d_6$): δ = 2.92–3.13 (m, 2H, $PhCH_2$), 3.70 (s, 3H, OCH_3), 4.25–4.29 (dd, 1H, CH), 6.71–6.74, 6.92–7.03 and 7.12–7.30 (m, 13H, aromatics); GC/MS (methyl ester), m/z (%): 362 (51) $[M]^+$, 121 (100). Anal. Calcd for $C_{22}H_{19}O_4Na$: C, 71.34%; H, 5.17%. Found: C, 68.63%; H, 5.21%.

(S)-Sodium 2-(2'-ethyl-biphenyl-4-yloxy)-3-phenylpropanoate (15). Washed with $CHCl_3$, 80% yield. ee = 95% (methyl ester, Chiralcel OD column, n -hexane/isopropanol 95:5 as the mobile phase, flow rate: 1.0 mL min^{-1} , detection: 254 nm); $[\alpha]_D = -8$ (c=1, methanol); 1H NMR (CD_3OD): δ = 1.01 (t, 3H, CH_3CH_2), 2.53 (q, 2H, CH_3CH_2), 3.11–3.26 (m, 2H, $PhCH_2$), 4.57–4.60 (dd, 1H, CH), 6.85–6.89 and 7.04–7.38 (m, 13H, aromatics); GC/MS (methyl ester), m/z (%): 360 (47) $[M]^+$, 121 (100). Anal. Calcd for $C_{23}H_{21}O_3Na$: C, 74.99%; H, 5.75%. Found: C, 73.68%; H, 5.75%.

(R)-Sodium 2-(2'-isopropyl-biphenyl-4-yloxy)-3-phenylpropanoate (R-16). Washed with diethyl ether, 95% yield. ee = 96% (Chiralcel OD column, *n*-hexane/isopropanol/TFA 90:10:0.05 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 254 nm); [α]_D = +3 (c=1, methanol); ¹H NMR (CD₃OD): δ = 1.09 (d, 6H, (CH₃)₂CHPh), 3.02 (m, 1H, (CH₃)₂CHPh), 3.11–3.26 (d, 2H, PhCH₂), 4.56–4.60 (dd, 1H, CH), 6.85–6.88 and 7.03–7.38 (m, 13H, aromatics); GC/MS, *m/z* (%): 374 (100) [M]⁺, 121 (59). Anal. Calcd for C₂₄H₂₃O₃Na: C, 75.38%; H, 6.06%. Found: C, 73.97 %; H, 5.97%.

(S)-Sodium 2-(2'-isopropyl-biphenyl-4-yloxy)-3-phenylpropanoate (S-16). Washed with *n*-hexane, 95% yield. ee = 94% (Chiralcel OD column, *n*-hexane/isopropanol/TFA 90:10:0.05 as the mobile phase, flow rate: 1.0 mL min⁻¹, detection: 254 nm); [α]_D = -3 (c=1, methanol). Anal. Calcd for C₂₄H₂₃O₃Na: C, 75.38%; H, 6.06%. Found: C, 76.54%; H, 5.68%.

2-(2'-Propyl-biphenyl-4-yloxy)-3-phenylpropanoic acid (17). Washed with *n*-hexane, 89% yield, mp: 88–90 °C. ¹H NMR (DMSO-*d*₆): δ = 0.72 (t, 3H, CH₃CH₂CH₂), 1.37 (m, 2H, (CH₃CH₂CH₂), 2.42 (t, 2H, (CH₃CH₂CH₂), 3.09–3.24 (m, 2H, PhCH₂), 4.93–4.98 (dd, 1H, CH), 6.85–6.88 and 7.06–7.35 (m, 14H, 13 aromatics + COOH, D₂O exchanged); GC/MS (methyl ester), *m/z* (%): 374 (100) [M]⁺, 121 (63). Anal. Calcd for C₂₄H₂₄O₃: C, 79.97%; H, 6.71%. Found: C, 79.19%; H, 7.01%.

Sodium 2-(2'-pentyl-biphenyl-4-yloxy)-3-phenylpropanoate (18). Washed with *n*-hexane, 95% yield. ¹H NMR (CD₃OD): δ = 0.77 (t, 3H, CH₃CH₂CH₂), 1.14–1.43 (m, 6H, CH₃CH₂CH₂CH₂), 2.52 (t, 2H, CH₃(CH₂)₃CH₂), 3.10–3.26 (m, 2H, PhCH₂), 4.58–4.61 (dd, 1H, CH), 6.86–6.88 and 7.06–7.38 (m, 13H, aromatics); ESI-MS, *m/z* (%): 387 (31) [M-23]⁻, 239 (100), 147 (23). Anal. Calcd for C₂₆H₂₇O₃Na: C, 76.08%; H, 6.63%. Found: C, 73.27%; H, 6.29%.

Sodium 2-(2'-phenethyl-biphenyl-4-yloxy)-3-phenylpropanoate (19). Washed with *n*-hexane and CHCl₃, 98% yield. ¹H NMR (CD₃OD): δ = 2.62 and 2.81 (2 t, 4H, PhCH₂CH₂), 3.11–3.38 (m, 2H, PhCH₂CH), 4.57–4.61 (dd, 1H, CH), 6.85–7.39 (m, 18H, aromatics); GC/MS (methyl ester), *m/z* (%): 436 (99) [M]⁺, 121 (100). Anal. Calcd for C₂₉H₂₅O₃Na: C, 78.36%; H, 5.67%. Found: C, 76.04 %; H, 5.63%.

Table 1. Statistics of Crystallographic Data and Refinement

	PPAR γ / <i>S-16</i>	PPAR γ / <i>R-16</i>
wavelength (Å)	0.873	0.873
temperature (K)	100	100
space group	C121	C121
no. of mol in the A.U.	2	2
cell axes (Å)	93.01; 62.12; 118.98	92.77; 61.27; 118.28
beta angle (°)	102.42	102.15
resolution range (Å)	24.00-2.50 (2.64-2.50)	24.00-2.50 (2.64-2.50)
R _{merge} (%)	6.5 (44.9)	8.7 (54.0)
Multiplicity	3.8 (3.8)	3.7 (3.8)
I/ σ (I)	12.4 (3.0)	9.7 (2.3)
Completeness (%)	100.0 (100.0)	99.1 (98.8)
R _{factor} (%)	26.5	24.2
R _{free} (%)	33.5	29.8
no. of unique reflections	23188	22426
rmsd bond lengths	0.009	0.008
rmsd bond angles	1.31	1.27
solvent molecules	134	140

^a The values in parentheses refer to the outer shell

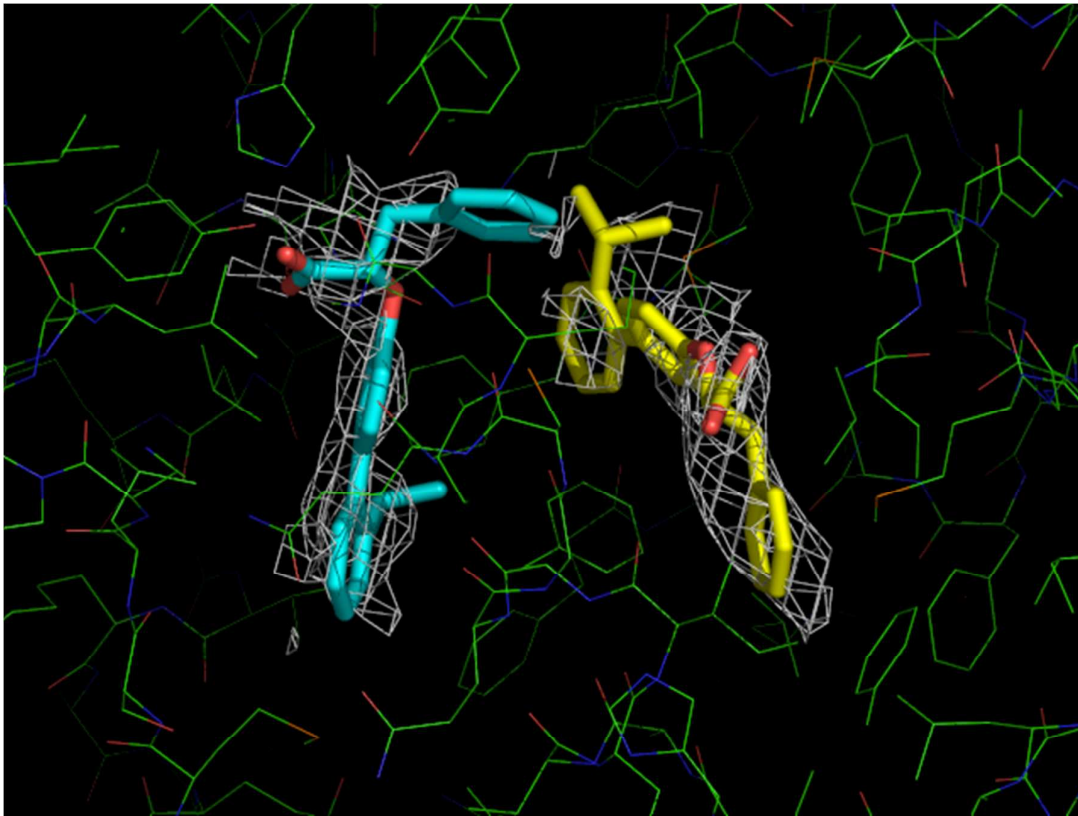


Figure 1. $2Fo - Fc$ simulated annealing omit map with the atoms of the ligand omitted from the model. The map is contoured at 1σ .

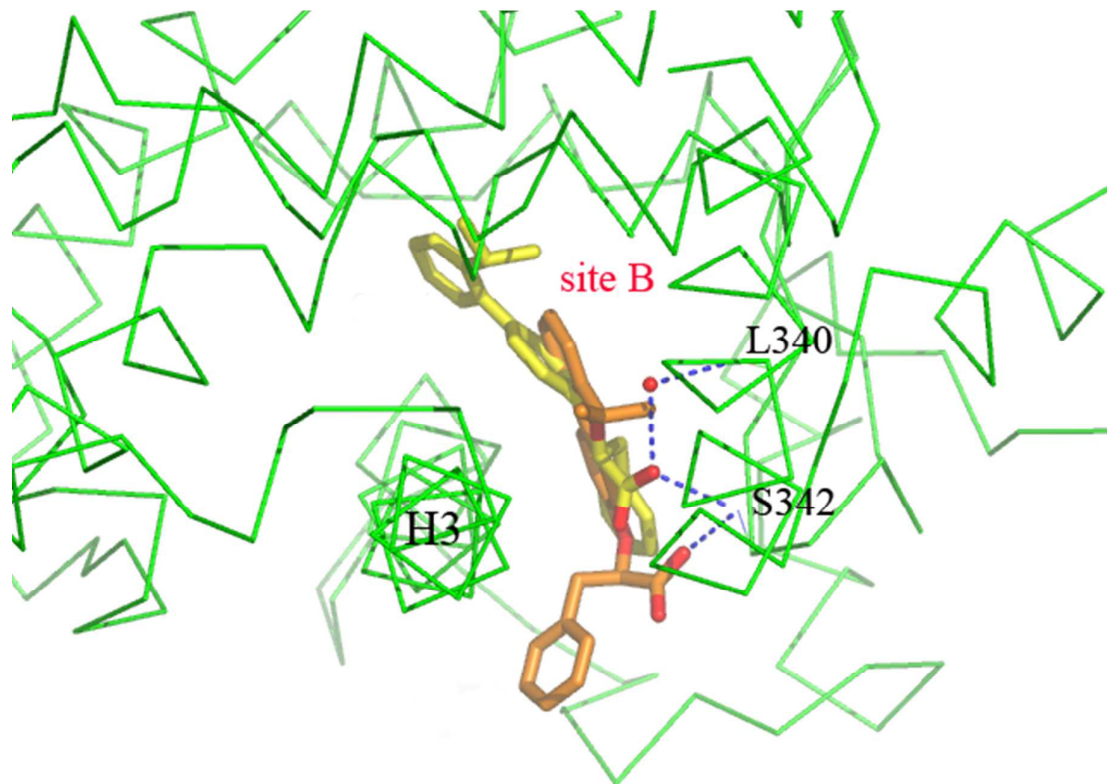


Figure 2. Superposition of *R*-16 (orange) and Mol B of *S*-16 (yellow) into the LBD of PPAR γ .

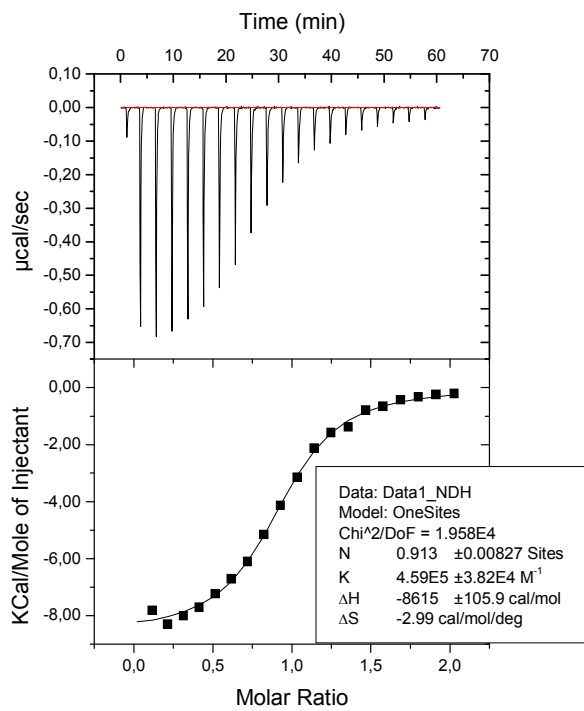


Figure 3. Titration of PPAR γ (50 μ M) with **1** (500 μ M).

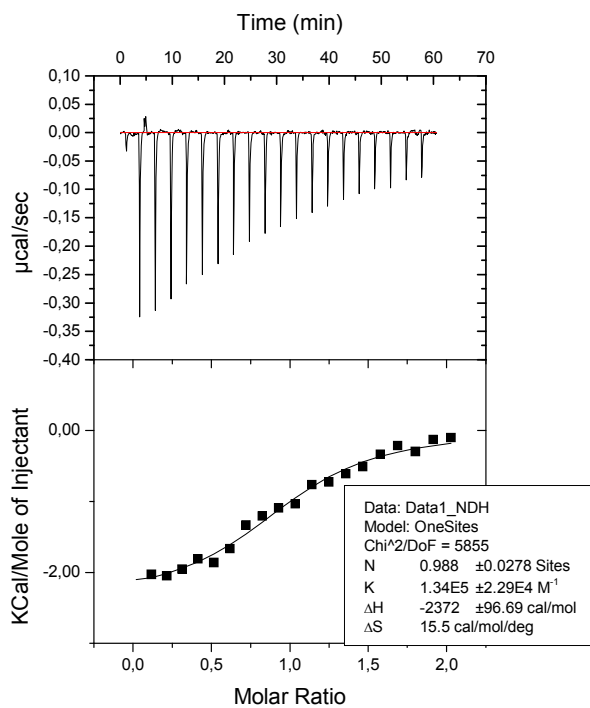


Figure 4. Titration of PPAR γ (60 μM) with **R-16** (600 μM).

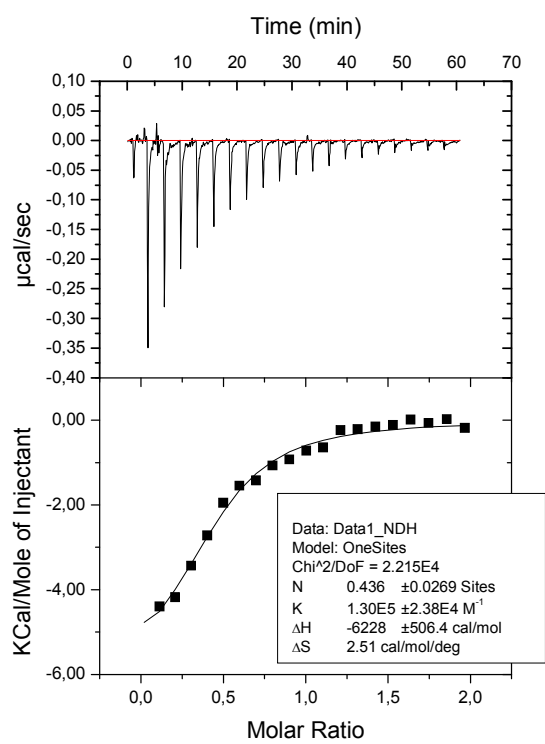


Figure 5. Reverse titration of *R-16* (60 μM) with PPARγ (547 μM).

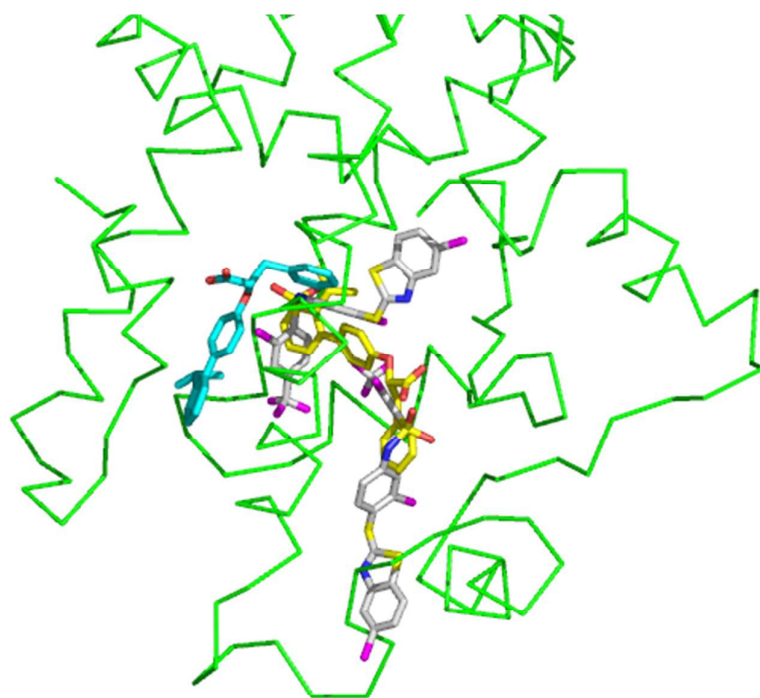


Figure 6. Superposition of **S-16** (Mol A cyan; Mol B yellow) and **25** (white) into the PPAR γ -LBD.

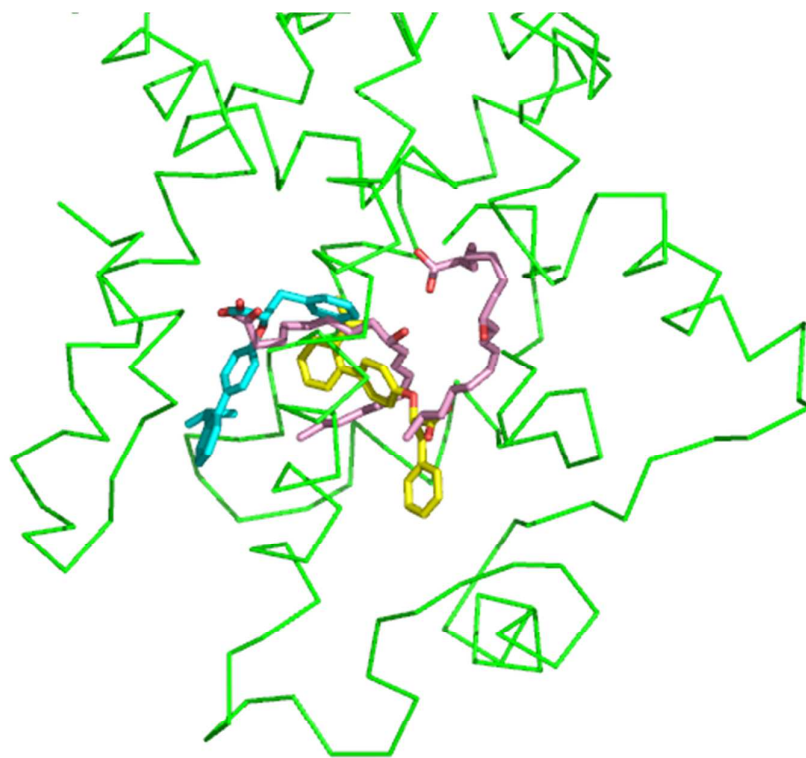


Figure 7. Superposition of **S-16** (Mol A cyan; Mol B yellow) and **26** (light pink) into the PPAR γ -LBD.

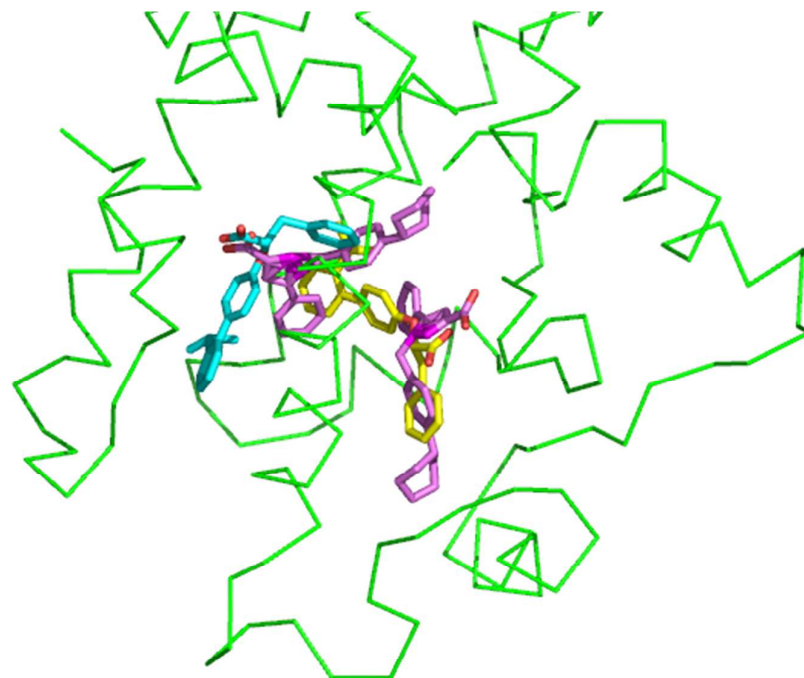


Figure 8. Superposition of *S-16* (Mol A cyan; Mol B yellow) and **27** (magenta) into the PPAR γ -LBD.

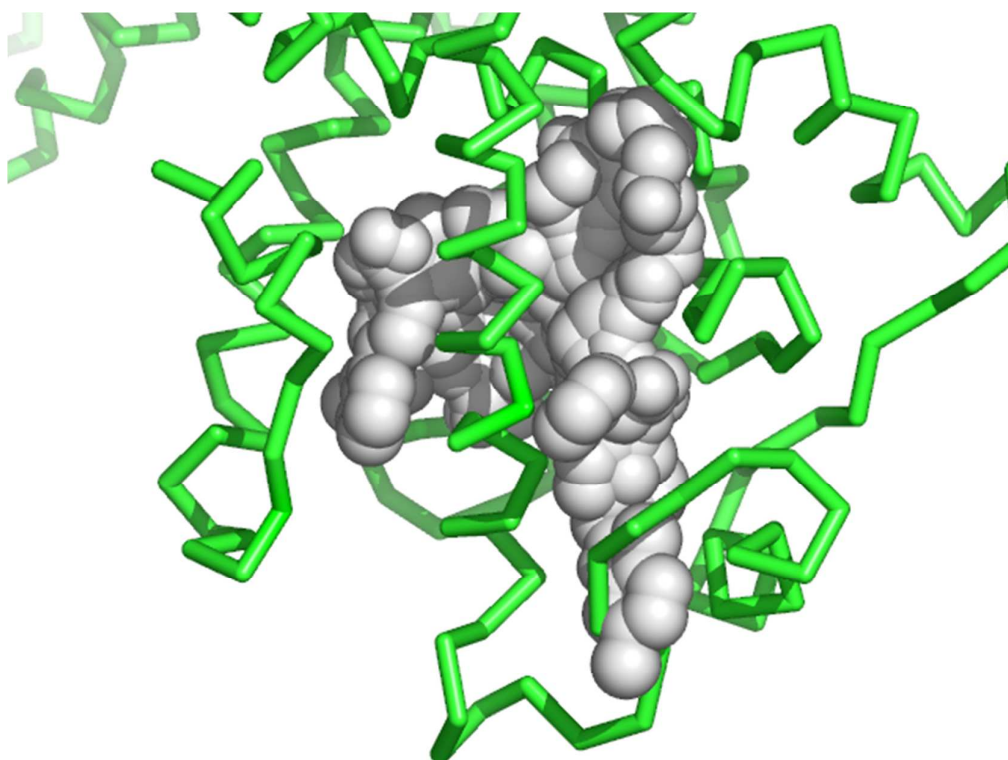


Figure 9. Superposition of the two molecules of *S*-16, 25, 26 and 27 into the PPAR γ -LBD (vdW surface).