Novel Indole-based Peroxisome Proliferator-activated Receptor Agonists: Design, SAR, Structural Biology, and Biological Activities

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Peroxisome proliferator-activated receptors gamma (PPARγ) are ligand-dependent transcription factor of the nuclear hormone receptor superfamily. PPARgamma has been shown to increase glucose uptake and metabolism in liver, adipose tissue and muscle. With the function in regulating glucose homeostasis, PPARγ is a valid drug target for treating type II diabetes.

To further understand the interaction with the hPPARγ receptor, crystals of the hPPARγ ligand-binding domain (LBD) in a complex with BPR1H036 were prepared by cocrystallization. The cocrystal structure was solved to a resolution of 2.28 Å.The binding site of the PPARγ - BPR1H036 complex structure was compared to the published structures, the most significant movement was the shift of the residues 364 and 363 (Figure 1).The X-ray diffraction data were collected using synchrotron radiations at NSRRC BL17B2 beam lines.

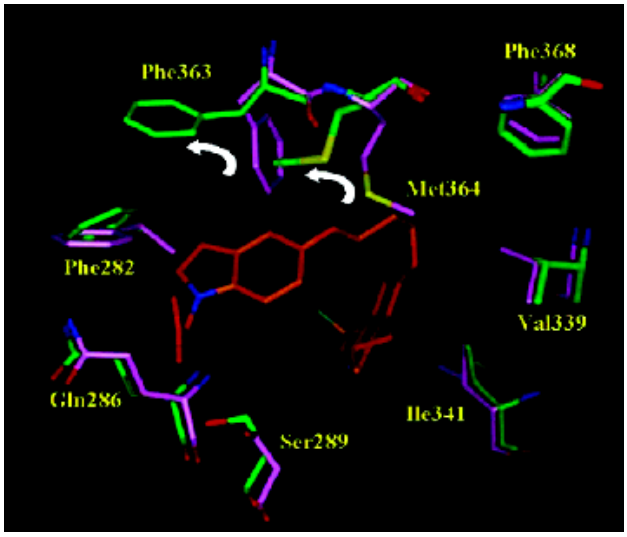

Figure 1. The shift in residues of PPARγ protein (purple before ligand binding, green after ligand binding) upon binding of ligand BPR1H036 (orange) with monomer A of PPAR*Á* protein. The arrows depict the shift of residue Met364 away from the active site to accommodate the linker group of BPR1H036 and the consequent shift of residue Phe363.
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Compound BPR1H036 with an *n*-propyl linker substituted on the 5-position of indole and an acetic acid head showed the most potent binding and functional activities at PPARγ (Figure. 2).

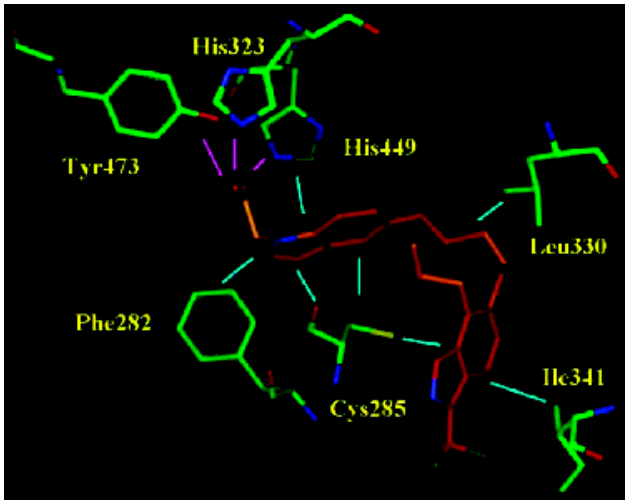

Figure 2. The structure of monomer A of PPARγ in the complex with BPR1H036 (orange) is depicted. The hydrogen bonding interactions are shown as solid lines in magenta, and the hydrophobic interactions are shown in cyan.
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Superimposition of PPARγ LBD in the complexes with BPR1H036, rosiglitazone, and GW409544 revealed differences in the protein-ligand interactions (Figure 3). The structural biology studies of BPR1H036, revealed that the indole ring contributed strong hydrophobic interactions with PPARγ and could be an important moiety for the binding to the protein.

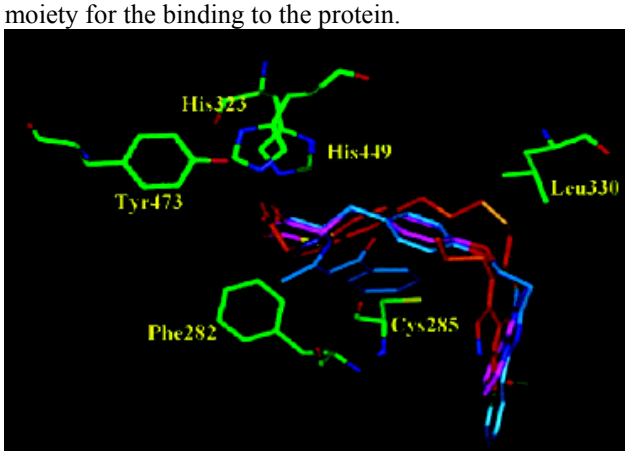

Figure 3. Superposition of the structures of BPR1H036 (orange), rosiglitazone (magenta), and GW409544 (blue) in the binding pocket of PPARγ.
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