UNDERSTANDING PPARα RECEPTOR ACTIVATION BY TARGETED MOLECULAR DYNAMICS

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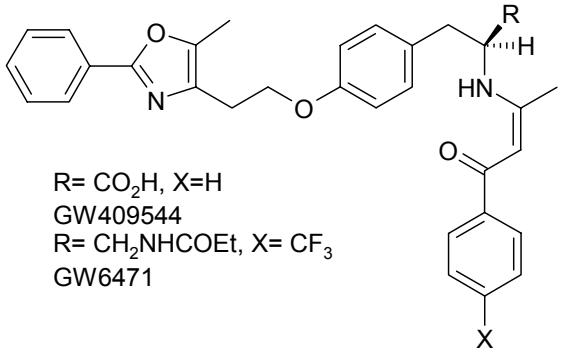
The peroxisome proliferator-activated receptor α (PPARα) regulates hepatic fatty acid metabolism and mediates the effects of fibrate lipid-lowering drugs [1]. Recently, crystal structures of the agonist- (GW409544) [2] and the antagonist- (GW6471) [3] bound PPARα Ligand Binding Domain (LBD) have been determined.



The agonist stabilizes the active conformation of LBD by direct interaction with Y464 situated on the C-terminal AF-2 helix, thus allowing the coactivator binding and gene transcription. Conversely, the antagonist disrupts the interaction between PPARa receptor and coactivator and promotes the binding of the co-repressor peptide. This indicates that antagonist induce an LBD conformation that interacts efficiently with co-repressors. The main difference between both molecules is the volume and nature of R group that prevents the proper disposition of AF-2 in the active conformation

We present in this communication a targeted molecular dynamics study of the transition between the active and inactive PPARα-LBD conformations in the presence of both the agonist and antagonist ligands. This study aims to get insights into the specific and coordinated ligand-receptor interactions that stabilize one or another conformation. The results thus obtained can be paradigmatic for the molecular mechanism of activation of other members of the nuclear receptor superfamily.

[1] Isabelle Issemann, Stephen Green. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. *Nature* **1990**, *347*, 645 – 650.
[2] Xu HE, Lambert MH, Montana VG, Plunket KD, Moore LB, Collins JL, Oplinger JA, Kliewer SA, Gampe RT Jr, McKee DD, Moore JT, Willson TM. Structural determinants of ligand binding selectivity between the peroxisome proliferator-activated receptors. *Proc Natl Acad Sci* **2001**, *98(24)*, 13919-24.
[3] H. Eric Xu, Thomas B. Stanley, Valerie G. Montana, Millard H. Lambert, Barry G. Shearer, Jeffery E. Cobb, David D. McKee, Cristin M. Galardi, Kelli D. Plunket, Robert T. Nolte, Derek J. Parks, John T. Moore, Steven A. Kliewer, Timothy M. Willson, Julie B. Stimm . Structural basis for antagonist-mediated recruitment of nuclear co-repressors by PPARα. *Nature* **2002,** *415*, 813 – 817.