

## DOCTORAL THESIS

### Stereo-selective binding of enantiomeric ligands in PPAR[gamma]: a molecular modeling study

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**Stereo-Selective Binding of Enantiomeric Ligands in PPAR $\gamma$ :**  
*A Molecular Modeling Study*

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A thesis submitted in partial fulfillment of the requirements  
for the degree of  
Doctor of Philosophy

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## Abstract

Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), the most investigated nuclear receptor (NR) among the three subtypes of PPARs (PPAR $\alpha$ , PPAR $\gamma$  and PPAR $\beta/\delta$ ), is a ligand-dependent transcription factor that directs gene expression related to adipogenesis and lipid storage. Numerous natural and synthetic molecules have been suggested as PPAR $\gamma$  ligands and classified as full agonist, partial agonist, antagonist and SPPARM depending on their activities. Literatures have reported that ginsenosides Rg3, Rh2 and their end metabolite protopanaxadiol (PPD) have the ability to enhance the insulin secretion and increase PPAR $\gamma$  expression and adipogenesis *in vitro*. However, the recent fluorescence polarization and total internal reflection fluorescence (FR-TIRF) binding-affinity assay demonstrated that the binding affinities of PPD-type ginsenosides increase with the number of sugar moieties on C-3, among the studied ginsenosides, and the bare bone PPD enantiomers exhibit hardly any binding to PPAR $\gamma$ . Since the relevant X-ray crystal structures and/or NMR data are unavailable, the binding modes of PPD-type ginsenosides in PPAR $\gamma$  were investigated by molecular modeling and Essential dynamics analysis (EDA) and reported in this thesis. The docking results indicate that ginsenoside Rg3 bind to PPAR $\gamma$  in a similar manner to that of full agonists. Further molecular dynamics (MD) results indicate that the binding of 20(S)-Rg3 is more probable than that of the 20(R)-enantiomer which agrees with the angiogenesis assay result. Bindings of Rh2 enantiomers are similar to those of Rg3 enantiomers but no stereo-selectivity is found to 20(R/S)-Rh2. However, the bindings of 20(R/S)-PPD in the protein are much weaker relative to those of Rg3 and Rh2 indicating that the sugar on Carbon-3 play an important role in the binding of PPD-type ginsenosides in PPAR $\gamma$ . The binding modes of synthetic halofenic acid (HA)

enantiomers in PPAR $\gamma$  were also investigated by using the same method. The results demonstrate that both the enantiomers have the capability to bind to PPAR $\gamma$  with different orientations in principle and double ligand-binding of HA in the protein is also possible. As a recent experiment reported, 20(R/S)-Rg3 have the capability to activate pregnane X receptor (PXR) stereo-selectively, which is another member of the NR superfamily. The investigation of the binding modes of 20(R/S)-Rg3 in PXR by molecular modeling indicates that the binding of 20(S)-Rg3 enantiomer in PXR is more probable which agrees well with biological experiments.

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