Using Modelling and Docking to Search for the Natural Ligand of COUPTFII

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Abstract: The structure of the apo form of the ligand binding domain (LBD) of the nuclear receptor COUPTFII ((Chick ovalbumin upstream Promoter) was published in 2008 along with evidence that 9-cis retinoic acid (9cRA) was able to activate the protein but not at physiological levels. Here we describe the search for the endogenous ligand of COUPTFII starting with "open pocket" models based on the ligand bound forms of RXR and RAR using the program Modeller. Structural definitions of a subset of available endogenous potential ligands were extracted from the ZINC database and UCSF's Dock 6.8 was used to search for compounds that would dock to our models with a lower energy score than 9cRA on the same models. Of the over 28000 compounds searched less than 1% (131) were found to bind in the pocket of at least 2 of our models more tightly (lower grid energy score) than 9cRA. Structural comparisons between the successful candidates and the model structures as well as the results of binding and activity assays are presented.