Synthesis and biological evaluation of dihydropyrano-[2,3-c]pyrazoles as a new class of PPARγ partial agonists

Peroxisome proliferator-activated receptor γ (PPARγ) is a well-known target for thiazolidinedione antidiabetic drugs. In this paper, we present the synthesis and biological evaluation of a series of dihydropyrano[2,3-c]pyrazole derivatives as a novel family of PPARγ partial agonists. Two analogues were found to display high affinity for PPARγ with potencies in the micro molar range. Both of these hits were selective against PPARγ, since no activity was measured when tested against PPARα, PPARδ and RXRα. In addition, a novel modelling approach based on multiple individual flexible alignments was developed for the identification of ligand binding interactions in PPARγ. In combination with cell-based transactivation experiments, the flexible alignment model provides an excellent analytical tool to evaluate and visualize the effect of ligand chemical structure with respect to receptor binding mode and biological activity.

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