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Discovery of a Novel Selective PPARγ Ligand with Partial Agonist Binding Properties by Integrated in Silico/in Vitro Work Flow

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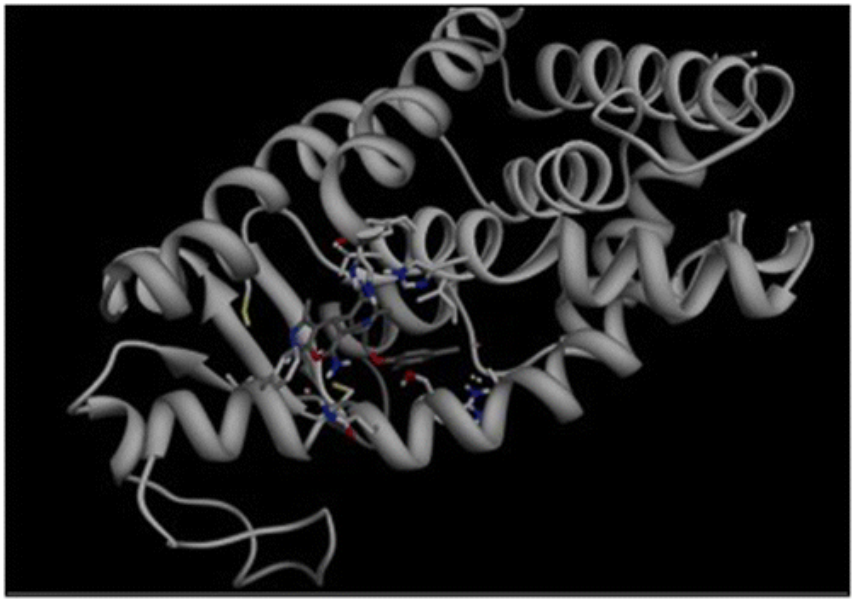
Abstract



Full agonists to the peroxisome proliferator-activated receptor (PPAR)γ, such as Rosiglitazone, have been associated with a series of undesired side effects, such as weight gain, fluid retention, cardiac hypertrophy, and hepatotoxicity. Nevertheless, PPARγ is involved in the expression of genes that control glucose and lipid metabolism and is an important target for drugs against type 2 diabetes, dyslipidemia, atherosclerosis, and cardiovascular disease. In an effort to identify novel PPARγ ligands with an improved pharmacological profile, emphasis has shifted to selective ligands with partial agonist binding properties. Toward this end we applied an integrated in silico/in vitro workflow, based on pharmacophore- and structure-based virtual screening of the ZINC library, coupled with competitive binding and transactivation assays, and adipocyte differentiation and gene expression studies. Hit compound 9 was identified as the most potent ligand (IC50 = 0.3 μM) and a relatively poor inducer of adipocyte differentiation. The binding mode of compound 9 was confirmed by molecular dynamics simulation, and the calculated free energy of binding was −8.4 kcal/mol. A novel functional group, the carbonitrile group, was identified to be a key substituent in the ligand–protein interactions. Further studies on the transcriptional regulation properties of compound 9 revealed a gene regulatory profile that was to a large extent unique, however functionally closer to that of a partial agonist.

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