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Insights into the PPARγ phosphorylation and its inhibition mechanism

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Peroxisome proliferator-activated receptor gamma Ligand Binding Domain (PPARγ-LBD) represents a key target for the treatment of type II diabetes and metabolic syndrome. This receptor is the target of thiazolidinediones, a class of antidiabetic drugs, which improve insulin sensitization and regulate glycemia in type 2 diabetes. Unfortunately, despite the beneficial effects of synthetic drugs, their use is associated with serious undesirable side effects1,2 related to their agonism. By contrast, a promising activation-independent mechanism that involves the inhibition of cyclin-dependent kinase 5 (Cdk5)-mediated PPARγ phosphorylation (CMPF) has been related to the insulin-sensitizing effects induced by these drugs3,4. For this reason, the search for new inhibitors of CMPF represents an opportunity for the development of an improved generation of anti-diabetic drugs acting through this nuclear receptor. Thus, with the aim to identify novel drug-like inhibitors of CMPF capable of interacting with PPARγ but that lack agonist properties we adopted a multi-disciplinary approach, including protein-protein docking, X-ray, NMR, HDX, MD simulations and site-directed mutagenesis to investigate conformational changes in PPARγ that impair the ability of Cdk5 to interact with this nuclear receptor and hence inhibit its phosphorylation.

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