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Identification of Peroxisome Proliferator-Activated Receptors α/γ Dual Agonists for Treatment of Metabolic Disorders, Insilico Screening, and Molecular Dynamics Simulation

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Abstract : Background: TypeII Diabetes mellitus is a foremost health problem worldwide, predisposing to increased mortality and morbidity. Undesirable effects of the current medications have prompted the researcher to develop more potential drug(s) against the disease. The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptors family and take part in a vital role in the regulation of metabolic equilibrium. They can induce or repress genes associated with adipogenesis, lipid, and glucose metabolism. Aims: Investigation of PPARα/γ agonistic hits were screened by hierarchical virtual screening followed by molecular dynamics simulation and knowledge-based structure-activity relation (SAR) analysis using approved PPAR α/γ dual agonist. Methods: The PPARα/γ agonistic activity of compounds was searched by using Maestro through structure-based virtual screening and molecular dynamics (MD) simulation application. Virtual screening of nuclear-receptor ligands was done, and the binding modes with protein-ligand interactions of newer entity(s) were investigated. Further, binding energy prediction, Stability studies using molecular dynamics (MD) simulation of PPARα and γ complex was performed with the most promising hit along with the structural comparative analysis of approved PPARα/γ agonists with screened hit was done for knowledge-based SAR. Results and Discussion: The silicone chip-based approach recognized the most capable nine hits and had better predictive binding energy as compared to the reference drug compound (Tesaglitazar). In this study, the key amino acid residues of binding pockets of both targets PPARα/γ were acknowledged as essential and were found to be associated in the key interactions with the most potential dual hit (ChemDiv-3269-0443). Stability studies using molecular dynamics (MD) simulation of PPARα and γ complex was performed with the most promising hit and found root mean square deviation (RMSD) stabile around 2Å and 2.1Å, respectively. Frequency distribution data also revealed that the key residues of both proteins showed maximum contacts with a potent hit during the MD simulation of 20 nanoseconds (ns). The knowledge-based SAR studies of PPARα/γ agonists were studied using 2D structures of approved drugs like aleglitazar, tesaglitazar, etc. for successful designing and synthesis of compounds PPARγ agonistic candidates with anti-hyperlipidimic potential.

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