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In silico optimization of pyrimidine-thiazolidinedione hybrids targeting PPAR-γ: Design, docking, MM-GBSA, ADMET, and MD simulation

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ABSTRACT Type 2 diabetes mellitus (T2DM) is a significant global health issue that can cause severe complications such as ketoacidosis, neuropathy, kidney failure, stroke, and heart disease if left untreated. To develop safer, more effective treatments, new pyrimidine-based thiazolidinedione analogues were designed and evaluated as potential peroxisome proliferator-activated receptors (PPAR)-γ agonists using *in silico* techniques. Molecular docking was performed against three PPAR-γ crystal structures (PDB IDs: 4Y29, 2HWQ, 2G0G) using Food And Drug Administration-approved agonists (Pioglitazone, Rivoglitazone, and Ciglitazone) as references. The derivatives RP111, RP10, and RP179 showed the highest affinities for 4Y29 (−10.406 kcal/mol), 2HWQ (−9.659 kcal/mol), and 2G0G (−11.043 kcal/mol), respectively. The binding affinities of the designed derivatives were higher than those of the reference drugs used in the study. Molecular mechanics, generalized born surface area binding energy, and absorption, distribution, metabolism, excretion, and toxicity predictions demonstrated encouraging outcomes. In addition, 100 ns molecular dynamics simulation of RP179 (ligand exhibiting most favorable docking score), confirmed complex stability and key interactions, supporting docking results. Overall, the findings suggest that RP179 is a strong candidate for development as PPAR-γ agonist for managing T2DM.

KEY WORDS Diabetes, Molecular docking, Molecular dynamics, Pyrimidine, Thiazolidinedione.

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