Title:

Computational exploration of PPARα agonists: integrating ligand- and structure-based modeling for targeted drug discovery

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Abstract:

Type 2 diabetes mellitus (T2DM) is a major public health issue, characterized by hyperglycemia due to insulin resistance and/or insufficient insulin production. Uncontrolled T2DM can lead to severe complications, such as nephropathy, retinopathy, and cardiovascular disease (1,2). Among potential therapeutic agents, peroxisome proliferator-activated receptor alpha (PPARα) agonists emerge promising in T2DM management due to their ability to improve lipid profiles and enhance glycemic control. Particularly, PPARα agonists exhibit both lipid-lowering and glucose-modulating effects, making them valuable, especially for patients with coexisting dyslipidemia (1). Emerging evidence suggests that combining PPARα agonists with established T2DM treatments like biguanides or gliptins may provide synergistic benefits (3, 4).

In this study, we have developed new ligand-based (Q)SAR models and employed existing ones in our platform ProtoPRED, combined with structure-based docking with our platform DockTox, in order to search for potential PPARα agonists with favorable pharmacokinetic and toxicological properties. To achieve this,natural compound databases, including NPASS andNuBBE, were screened , yielding candidate compounds with optimal binding interaction profiles and toxicology predictions. Our findings demonstrate the efficacy of an integrative computational approach for identifying novel PPARα agonists, offering promising groundwork for future research in T2DM adjunctive therapies.

Keywords: Molecular modeling; (Q)SAR; Type II Diabetes Mellitus; Drug Discovery; PPARα.

References:

1. Artasensi A, Pedretti A, Vistoli G, Fumagalli L. Type 2 Diabetes Mellitus: A Review of Multi-Target Drugs. Molecules [Internet]. 2020 Apr 1 [cited 2024 May 13];25(8). Available from: /pmc/articles/PMC7221535/

2. Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: a review on recent drug based therapeutics. Biomedicine & Pharmacotherapy. 2020 Nov 1;131:110708.

3. Alnuaimi S, Reljic T, Abdulla FS, Memon H, Al-Ali S, Smith T, et al. PPAR agonists as add-on treatment with metformin in management of type 2 diabetes: a systematic review and meta-analysis. Scientific Reports 2024 14:1 [Internet]. 2024 Apr 16 [cited 2024 May 13];14(1):1–13. Available from: https://www.nature.com/articles/s41598-024-59390-z

4. Santana-Oliveira DA, Fernandes-Da-silva A, Miranda CS, Martins FF, Mandarim-De-lacerda CA, Souza-Mello V. A PPAR-alpha agonist and DPP-4 inhibitor mitigate adipocyte dysfunction in obese mice. J Mol Endocrinol [Internet]. 2022 May 1 [cited 2024 May 13];68(4):225–41. Available from: https://pubmed.ncbi.nlm.nih.gov/35302950/