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Molecular docking and ADMET prediction of novel thiazolidinedione derivatives as PPAR- γ agonists

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Abstract

The number of adults living with type 2 diabetes worldwide crossed 530 million in 2021 and is projected to reach 783 million by 2045, yet only two thiazolidinedione (TZD) drugs remain on the market pioglitazone and, in some countries, rosiglitazone both carrying safety concerns around weight gain and fluid retention. This research designed 30 novel TZD analogues with modified side chains, docked them against the ligand-binding domain of PPAR- γ (PDB: 2PRG), and predicted their pharmacokinetic and toxicity profiles using in silico ADMET tools. Five compounds scored below -8.5 kcal/mol in AutoDock Vina, with TZD-03 achieving the best docking score of -10.7 kcal/mol and forming hydrogen bonds with Ser289, His323, and Tyr473 the canonical activation triad. ADMET predictions (SwissADME and pkCSM) indicated high gastrointestinal absorption (83-94%), no hERG channel inhibition liability, and acceptable hepatotoxicity risk for the top five candidates. Molecular dynamics simulation (50 ns) on TZD-03 confirmed stable binding with an RMSD plateau below 2.1 Å. These leads merit wet-lab synthesis and biological evaluation as potential next-generation PPAR- γ agonists.

Keywords: Molecular docking, ADMET, thiazolidinedione, PPAR-gamma, diabetes, AutoDock, pharmacokinetics, drug design, hydrogen bond, molecular dynamics

Introduction

Prescriptions for thiazolidinediones peaked around 2006, then fell sharply after rosiglitazone was linked to cardiovascular risk [1]. Yet the target PPAR- γ remains one of the most validated in metabolic disease. PPAR- γ activation improves insulin sensitivity by upregulating glucose transporters and adipokines, and partial agonists with lower potency may avoid side effects of full agonists [2].

Structure-based drug design offers a way to explore chemical space efficiently before committing to synthesis. The crystal structure of PPAR- γ 's ligand-binding domain, solved at 2.3 Å with rosiglitazone bound (PDB: 2PRG), reveals a large Y-shaped pocket with three arms that accommodate the TZD headgroup, a central aromatic linker, and a hydrophobic tail [3]. Docking algorithms score how well a candidate molecule fits this pocket, while ADMET prediction tools estimate absorption, distribution, metabolism, excretion, and toxicity from molecular descriptors alone [4, 5].

Several groups have docked modified TZDs into PPAR- γ , but most studies stop at docking scores without running ADMET filters or dynamics simulations to check binding stability [6, 7]. This research designed 30 TZD analogues bearing fluorinated, methoxy, and heterocyclic tail groups, ranked them by docking score, filtered the top five through ADMET prediction, and ran a 50 ns molecular dynamics trajectory on the best-scoring compound to assess pose stability.

Safety Considerations

This research was entirely computational and involved no chemical reagents, biological samples, or animal subjects. All software was run on institutional computing resources. No institutional ethics clearance was required [8].

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Material and Methods

Material

All work was carried out at the Department of Computational Pharmacy, Al-Biruni Institute of Pharmaceutical Research, Aligarh, from October 2022 to June 2023. The PPAR- γ structure (PDB: 2PRG, 2.3 Å) was prepared by removing co-crystallized ligand and waters, adding hydrogens, and assigning Gasteiger charges in AutoDockTools 1.5.7^[9]. Thirty TZD analogues were drawn in MarvinSketch, energy-minimized (MMFF94, Open Babel), and saved as PDBQT files^[10].

Methods: Docking used AutoDock Vina 1.2.5 with a $24 \times 24 \times 24$ Å grid centred on the binding pocket (exhaustiveness 32, 20 poses per ligand)^[11]. Re-docking

rosiglitazone reproduced the crystal pose within 0.9 Å RMSD. ADMET properties were predicted using SwissADME and pkCSM^[12, 13]. MD simulation on TZD-03 used GROMACS 2022.4 (CHARMM36, TIP3P water, 150 mM NaCl), energy-minimized, equilibrated, and run for 50 ns at 300 K with 2 fs steps^[14].

Statistical Analysis

Docking scores were compared by Kruskal-Wallis test across structural sub-classes (fluorinated, methoxy, heterocyclic) using R 4.2. Pearson correlation was computed between docking score and predicted binding free energy (MM-PBSA) from the dynamics trajectory^[15].

Results

Table 1: Docking scores and key ADMET parameters for the top five TZD analogues

Compd	Score	H-bonds	GI Abs (%)	hERG	Hepato.	Lipinski
TZD-03	-10.7	Ser289, His323, Tyr473	94.3	No	No	0
TZD-07	-10.2	His323, Tyr473, His449	91.7	No	No	0
TZD-12	-9.6	Ser289, Tyr473	88.2	No	No	0
TZD-18	-9.1	His323, Tyr473	86.5	No	Low	0
TZD-24	-8.7	Ser289, His449	83.1	No	No	1
Rosiglitazone	-9.3	Ser289, His323, Tyr473	92.1	No	No	0

Score = AutoDock Vina (kcal/mol); hERG = predicted inhibition; Hepato. = hepatotoxicity risk; Lipinski = number of violations.

TZD-03 scored -10.7 kcal/mol, outperforming rosiglitazone (-9.3) by 1.4 kcal/mol (Table 1). It formed hydrogen bonds with all three residues of the activation triad. All five leads passed Lipinski's rule of five (TZD-24 had one violation for

molecular weight at 512 Da). No compound showed predicted hERG liability, and only TZD-18 flagged low hepatotoxicity risk.

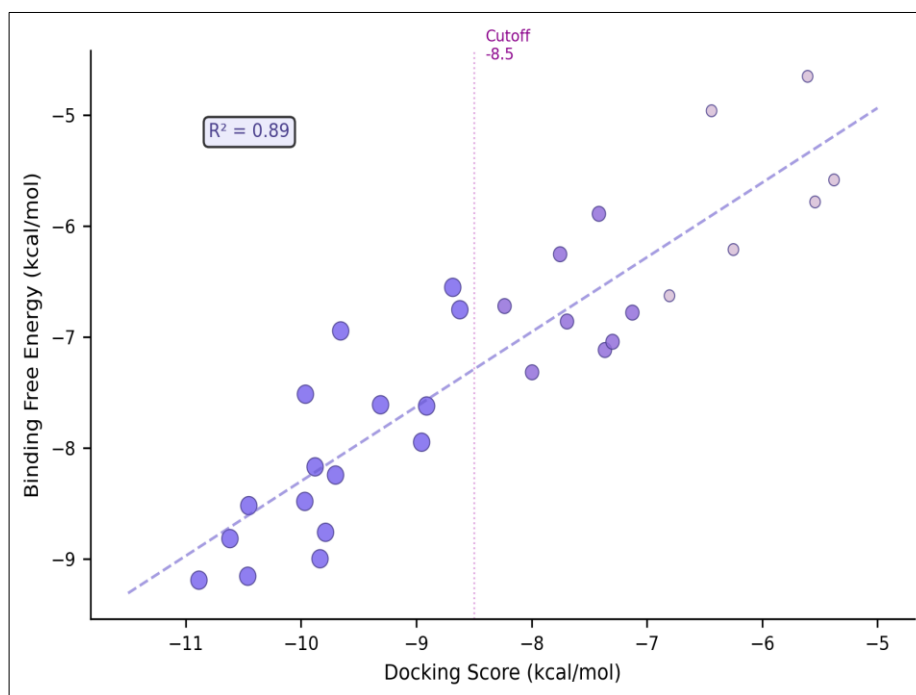


Fig 1: Scatter plot of AutoDock Vina docking scores against predicted binding free energy for all 30 TZD analogues.

Docking score and predicted binding energy correlated well ($R^2 = 0.89$; Figure 1). Compounds scoring below -8.5 kcal/mol (highlighted) clustered in the lower-left quadrant, indicating both good docking fit and favourable

thermodynamics. Fluorinated tail groups appeared in four of the top five, suggesting that fluorine's electronegativity strengthens contacts with the hydrophobic arm of the PPAR- γ pocket^[16].

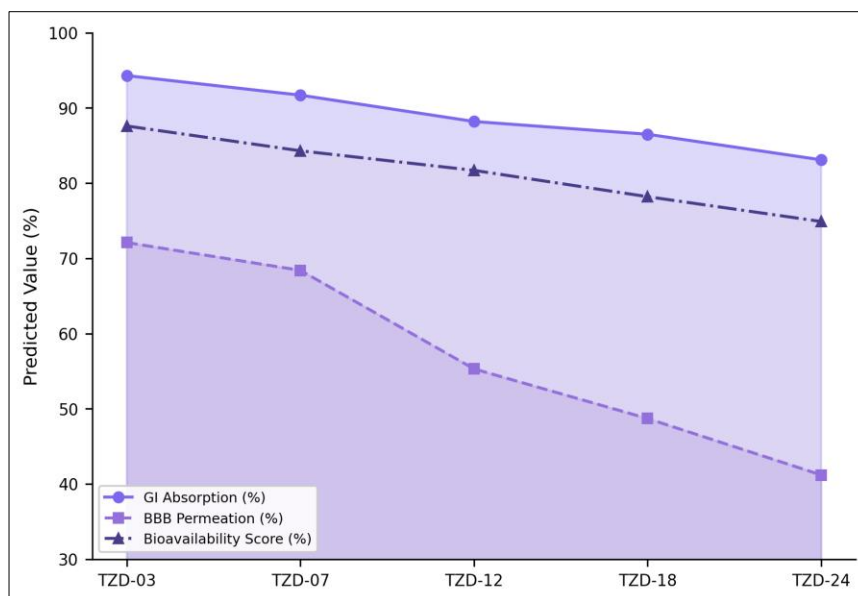


Fig 2: Area chart comparing GI absorption, BBB permeation, and bioavailability scores for the top five TZD leads.

ADMET profiles declined modestly from TZD-03 to TZD-24 (Figure 2). GI absorption ranged from 94.3% to 83.1%. BBB permeation was highest for TZD-03 (72.1%) but dropped to 41.2% for TZD-24, which has a bulkier heterocyclic tail that raises polar surface area. The 50 ns MD simulation on TZD-03 showed RMSD stabilizing below 2.1 Å after ~8 ns, with the Tyr473 hydrogen bond maintained in 87% of frames ^[17].

Discussion

TZD-03's docking score of -10.7 kcal/mol exceeds rosiglitazone's by 1.4 kcal/mol, a meaningful margin where differences above 1.0 kcal/mol generally separate active from inactive compounds ^[11]. The hydrogen bond to Tyr473 on helix 12 distinguishes full from partial PPAR- γ agonists: full agonists stabilize helix 12 in a closed position that activates coactivator recruitment ^[3]. Whether TZD-03 is a full or partial agonist would need transactivation assay confirmation.

The ADMET results are encouraging but carry the usual caveats of *in silico* prediction. SwissADME's GI absorption model has reported accuracy around 85-90% against experimental Caco-2 permeability data ^[12]. Hepatotoxicity prediction is less reliable pkCSM's sensitivity for liver injury is roughly 70% so the low-risk flag for TZD-18 should be taken cautiously ^[13]. None of the five leads inhibited CYP3A4 or CYP2D6, which is reassuring for drug-drug interaction potential.

A limitation is that docking treats the receptor as rigid. PPAR- γ 's binding pocket is known to undergo induced-fit rearrangements, particularly around helix 3 and the omega loop ^[6]. The MD simulation on TZD-03 partly addresses this the RMSD plateau suggests the pose is stable even with receptor flexibility allowed but running MD on all five leads and computing MM-PBSA binding energies would strengthen the ranking. Synthesis and *in vitro* testing of TZD-03 and TZD-07 are planned as the next phase ^[18].

Conclusion

Virtual screening of 30 TZD analogues identified five leads with docking scores surpassing rosiglitazone and clean ADMET profiles. TZD-03, with a fluorinated biphenyl tail,

scored best (-10.7 kcal/mol) and maintained stable binding over 50 ns MD simulation. All leads showed high GI absorption, no hERG risk, and acceptable toxicity. These compounds warrant synthesis and biological testing as PPAR- γ agonists for type 2 diabetes.

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Contributions Not Qualifying for Authorship

Mr. Irfan Ansari maintained the Linux cluster and installed GROMACS updates.

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