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Molecular Docking Of Dual PPAR Alpha/Gama Agonist For Type 2 Diabetes Structure Based Drug Design For Selective Cyclooxygenase-2(COX 2) Inhibitor

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ABSTRACT
Type 2 Diabetes Mellitus (T2DM) is a multifactorial metabolic disorder characterized by insulin resistance, dyslipidemia, and chronic inflammation. The nuclear receptors PPAR-α and PPAR-γ regulate lipid and glucose metabolism and are prominent therapeutic targets. This study investigates Aleglitazar, a known dual PPAR-α/γ agonist, and its structural derivatives for potential multi-target activity, including COX-2 inhibition. A structure-based drug design (SBDD) approach was employed using molecular docking techniques via AutoDock Vina to simulate ligand binding within the active sites of PPAR-α, PPAR-γ, and COX-2. Five compounds, including the parent Aleglitazar and four functionalized analogues (–COONa, $–CH_3$, $–NH_2$, –OH), were computationally optimized and docked against selected target receptors (PDB IDs: 2P54 and 3CS8). Compound 2 (–COONa) exhibited the most favorable binding energy and pose stability for both PPAR isoforms. The study also explored whether COX-2 inhibitory pharmacophores could be integrated without disrupting PPAR binding. Visual analysis using PyMOL confirmed significant receptor interactions, particularly via hydrogen bonding and hydrophobic contacts. The research demonstrates the utility of in silico docking as a cost-effective and predictive tool in the early phases of drug discovery, with implications for the development of dual or triple-target agents with improved efficacy and reduced side effects.

Keywords: Dual PPAR Agonist, Aleglitazar Derivatives, Type 2 Diabetes Mellitus, COX-2 Inhibition

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a complex metabolic disorder marked by chronic hyperglycemia, insulin resistance, and progressive β-cell dysfunction (figure 1). It is the most prevalent form of diabetes worldwide, often accompanied by dyslipidemia and low-grade systemic inflammation.[1,2] Over time, these metabolic abnormalities lead to severe complications, including cardiovascular disease, nephropathy, retinopathy, and neuropathy.[3]

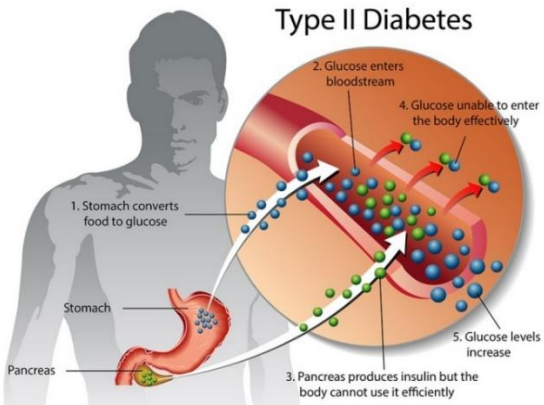


Figure 1: Type 2 Diabetes Mellitus [4]

Peroxisome proliferator-activated receptors (PPARs) play a critical role in managing glucose and lipid metabolism.[5] Among the three isoforms, PPAR-α and PPAR-γ are the most relevant in T2DM therapy. PPAR-α promotes fatty acid oxidation and improves lipid clearance, while PPAR-γ enhances insulin sensitivity and facilitates glucose uptake in adipose tissue. Dual activation of these receptors offers a synergistic approach to controlling both hyperglycemia and dyslipidemia.[6, 7] Aleglitazar, a synthetic dual PPAR-α/γ agonist, was developed with this therapeutic goal and showed promising efficacy in early clinical studies. However, its development was discontinued due to cardiovascular safety concerns.[8, 9]

In addition to metabolic dysregulation, inflammation significantly contributes to the progression of T2DM. Cyclooxygenase-2 (COX-2), an inducible enzyme involved in prostaglandin synthesis, is implicated in vascular inflammation and insulin resistance. Selective COX-2 inhibitors like celecoxib reduce inflammation but carry long-term cardiovascular risks.[10] Integrating COX-2 inhibitory functionality with dual PPAR agonism may provide a more comprehensive therapeutic approach. Integrating COX-2 inhibitory functionality into dual PPAR agonists such as Aleglitazar represents a novel strategy to create multifunctional agents that can simultaneously address hyperglycemia, dyslipidemia, and inflammation.[11, 12].This approach aligns with the growing field of multi-target drug design, wherein a single molecular entity is engineered to engage multiple biological targets to achieve a synergistic therapeutic effect. Such compounds have the potential to simplify polypharmacy, improve patient compliance, and mitigate the risk of drug-drug interactions.[13]

EXPERIMENTAL WORK

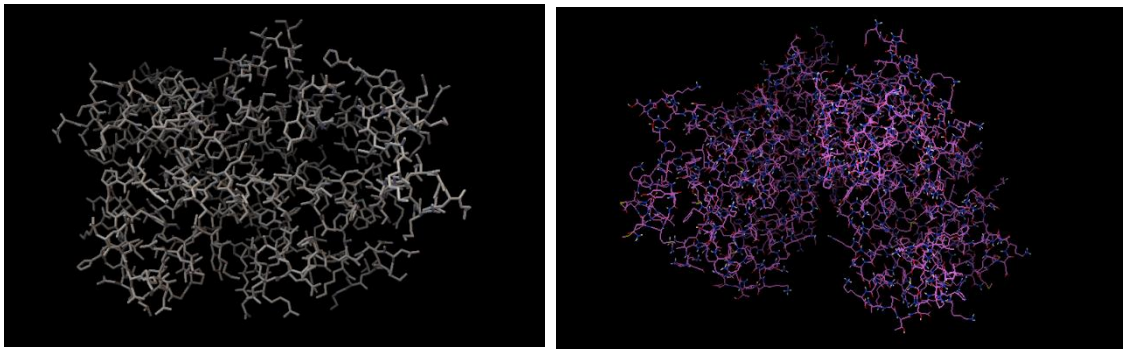
Structure-based drug design (SBDD) was employed in this study using a systematic computational workflow to evaluate Aleglitazar and its derivatives as potential dual PPAR-α/γ agonists. The workflow involved ten primary stages ranging from target selection to post-docking visualization. Each step was executed using validated cheminformatics tools to ensure accuracy and reproducibility.

1. Target Selection and Retrieval

Two relevant protein targets PPAR-α and PPAR-γ were selected based on their significance in T2DM treatment. The crystal structures of these receptors were retrieved from the RCSB Protein Data Bank in .pdb format. Specifically, PPAR-α was sourced from PDB ID: 2P54, and PPAR-γ from PDB ID: 3CS8. These structures were chosen for their high resolution and completeness of the ligand-binding domains.

2. Target Protein Preparation

Using AutoDock Tools (ADT), both protein structures underwent preprocessing. This included removing water molecules, deleting co-crystallized ligands and ions, and retaining only the chain containing the ligand-binding domain. Polar hydrogen atoms were added, and Kollman charges were assigned to ensure proper simulation of electrostatic interactions. The final protein structures were saved in .pdbqt format, suitable for docking in AutoDock Vina (figure 2).



(a) PPAR-α **(b) PPAR-γ**

Figure 2: Prepared protein structures for (a) PPAR-α (b) PPAR-γ

3. Ligand Design and Selection

Five compounds were prepared: Aleglitazar (Compound 1) and four derivatives (Compounds 2–5) featuring –COONa, $–CH_3$, $–NH_2$, and –OH substitutions (figure 3). These were drawn in ChemDraw, converted into 3D using Chem3D, and saved in .mol format for further processing.

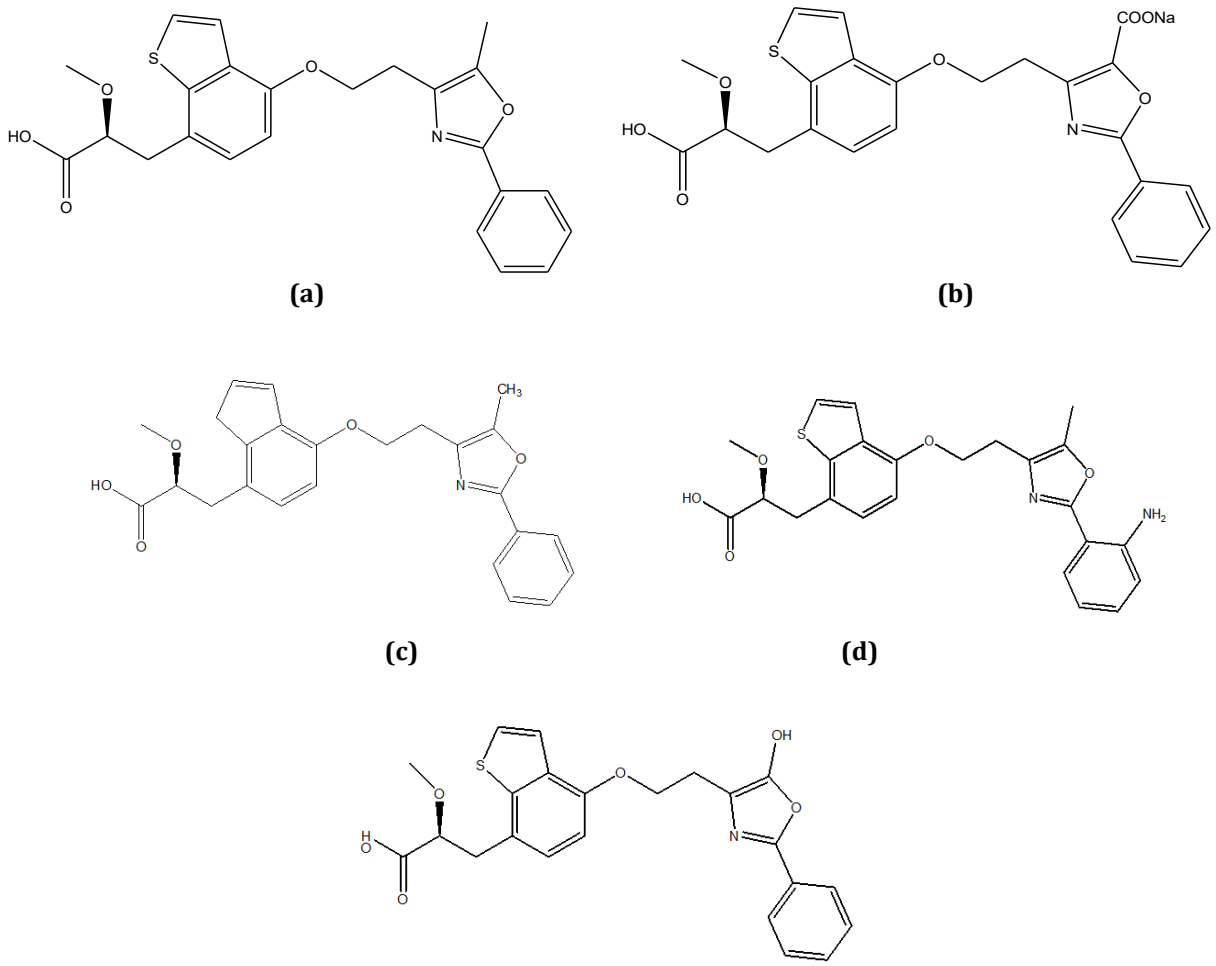


Figure 3: (a) Compound 1, (b) Compound 2, (c) Compound 3, (d) Compound 4, (e) Compound 5

4. Energy Minimization of Ligands

Energy minimization was performed using Open Babel with the MMFF94 force field. This step ensured that all ligand conformations were in their lowest energy state, improving docking accuracy. The minimized ligands were saved in .pdbqt format.

5. Molecular Docking Protocol

Docking was carried out using AutoDock Vina. Each ligand was docked into both PPAR-α and PPAR-γ using a fixed grid box around the ligand-binding site. Docking simulations generated nine binding modes per ligand, with the best pose selected based on lowest binding energy.

6. Post-Docking Visualization and Structural Analysis

The docking outputs were visualized and analyzed using PyMOL. This enabled identification of hydrogen bonds, hydrophobic interactions, and binding orientations. The binding affinities and root mean square deviation (RMSD) values were also assessed to determine pose stability and receptor compatibility.

RESULTS AND DISCUSSION

1. Energy Minimization of Ligands

The final total energy values obtained for each compound after minimization are summarized in Table 1. The energy is reported in kcal/mol and reflects the molecular stability post-optimization. These minimized structures were subsequently used as input for the docking experiments with both PPAR-α and PPAR-γ.

Table 1: Final Energy Values (kcal/mol) After Energy Minimization of Ligands Using Open Babel (MMFF94 Force Field)

Compound ID	Ligand Name	Substitution Group	Final Energy (kcal/mol)
Compound 1	Aleglitazar	None	–96.82
Compound 2	Sodium salt derivative	–COONa	–101.46
Compound 3	Methyl derivative	$-CH_3$	–94.73
Compound 4	Amino derivative	$-NH_2$	–98.65
Compound 5	Hydroxyl derivative	–OH	–100.17

2. Docking Studies Data

2.1 Docking Studies Data for PPAR Alpha

2.1.1 Docking Studies Data of Compound 1 (Aleglitazar) with PPAR-Alpha

Table 2 provides a comprehensive summary of the docking output for Aleglitazar with PPAR-Alpha.

Table 2: Binding Affinity and RMSD Values for Compound 1 (Aleglitazar) Docked with PPAR-Alpha

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.0	0.000	0.000
2	–5.9	4.593	11.007
3	–5.9	2.813	9.958
4	–5.9	9.405	15.644
5	–5.8	3.635	10.881
6	–5.8	3.070	10.050
7	–5.8	4.018	7.154
8	–5.6	4.263	7.598
9	–5.5	3.791	9.469

2.1.2 Docking Studies Data of Compound 2 (–COONa Sodium Derivative of Aleglitazar) with PPAR-Alpha

Table 3 provides a comprehensive summary of the docking output for Compound 2 with PPAR-Alpha.

Table 3: Docking Affinity and RMSD for Compound 2 (COONa Derivative) with PPAR-Alpha

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.5	0.000	0.000
2	–6.3	2.671	9.103
3	–6.2	3.904	10.312
4	–6.2	2.121	8.659
5	–6.1	4.230	9.842
6	–6.1	4.541	10.481
7	–6.0	3.116	8.937
8	–5.9	5.302	11.403
9	–5.9	6.214	12.174

2.1.3 Docking Studies Data of Compound 3 ($-CH_3$ Methyl Derivative of Aleglitazar) with PPAR-Alpha

Table 4 provides a comprehensive summary of the docking output for Compound 3 with PPAR-Alpha.

Table 4: Docking Affinity and RMSD Values of Compound 3 (Methyl Derivative) with PPAR-Alpha

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.2	0.000	0.000
2	–6.1	1.876	7.942
3	–6.1	2.603	8.518
4	–6.0	2.214	7.634
5	–6.0	3.137	8.219
6	–5.9	3.725	9.214
7	–5.9	4.489	9.632
8	–5.8	5.003	10.458
9	–5.7	5.644	11.123

2.1.4 Docking Studies Data of Compound 4 (–NH_2 Amino Derivative of Aleglitazar) with PPAR-Alpha

Table 5 provides a comprehensive summary of the docking output for Compound 4 with PPAR-Alpha.

Table 5: Docking Affinity and RMSD Values for Compound 4 (Amino Derivative) with PPAR-Alpha

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–5.8	0.000	0.000
2	–5.7	1.904	6.883
3	–5.6	2.256	7.472
4	–5.5	2.987	8.135
5	–5.5	3.146	8.429
6	–5.4	3.501	8.897
7	–5.3	4.128	9.234
8	–5.2	4.851	10.156
9	–5.2	5.089	10.611

2.1.5 Docking Studies Data of Compound 5 (Hydroxyl Derivative –OH of Aleglitazar) with PPAR-Alpha

Table 6 provides a comprehensive summary of the docking output for Compound 5 with PPAR-Alpha.

Table 6: Docking Affinity and RMSD Values for Compound 5 (Hydroxyl Derivative) with PPAR-Alpha

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.0	0.000	0.000
2	–5.9	1.758	6.487
3	–5.8	2.106	6.912
4	–5.7	2.709	7.334
5	–5.6	3.004	7.927
6	–5.4	3.517	8.516
7	–5.3	4.002	9.205
8	–5.2	4.538	9.788
9	–5.1	5.097	10.215

2.1.6 Comparative Analysis of Compound 1 to Compound 5 with PPAR-Alpha

Table 7 provides a comprehensive summary of the docking output for Compound 1 to Compound 5 with PPAR-Alpha.

Table 7: Comparative Docking Results of Compounds 1–5 with PPAR-Alpha (Mode 1 Data)

Compound	Derivative Type	Best Binding Energy (kcal/mol)	RMSD (Å)	Best Binding Mode	Pose Stability Remarks
Compound 1	Parent (Aleglitazar)	–6.0	0.000	Mode 1	Stable alignment, moderate interaction profile
Compound 2	–COONa (Sodium derivative)	–6.5	0.000	Mode 1	Most stable pose, enhanced polar fit
Compound 3	$-CH_3$ (Methyl derivative)	–6.2	0.000	Mode 1	Lower polar interaction, hydrophobic fit
Compound 4	$-NH_2$ (Amino derivative)	–5.8	0.000	Mode 1	Moderate polar bonding, slightly shallower pose
Compound 5	–OH (Hydroxyl derivative)	–6.0	0.000	Mode 1	Weak polar binding, limited spatial engagement

Table 7 and figure 4 represents the comparative docking performance for the five ligands. The best binding energies observed (all in Mode 1) range from –5.8 to –6.5 kcal/mol, and all Mode 1 poses demonstrated RMSD values of 0.000 Å, indicating direct extraction from the docked position and no deviation from the reference alignment.

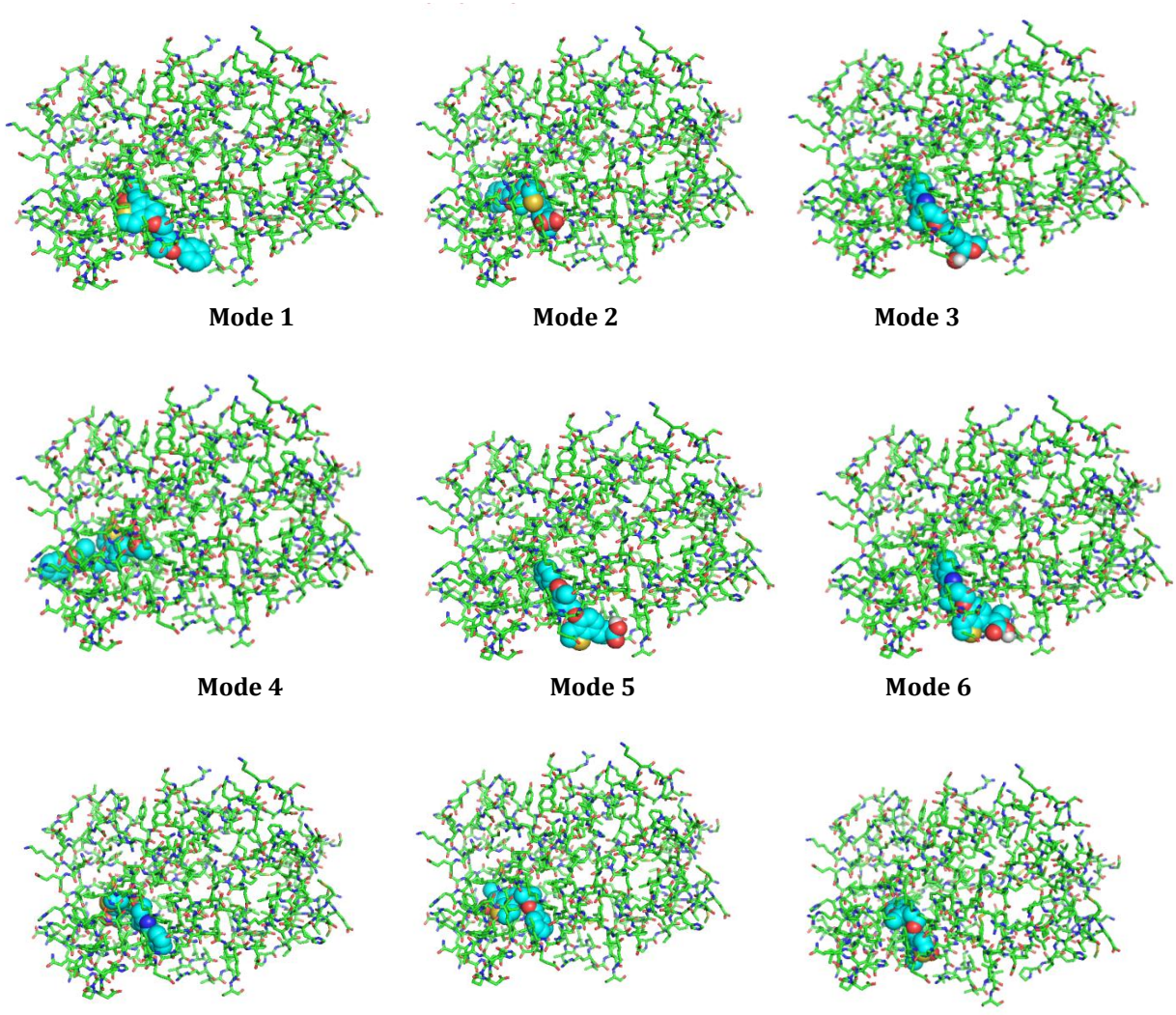


Figure 4: All 1-9 Docking Modes of Compound 2 with PPAR-Alpha

Compound 2 emerged with the strongest binding affinity (–6.5 kcal/mol), followed by Compound 3 (–6.2 kcal/mol) and Compounds 1 and 5 (both –6.0 kcal/mol). Compound 4 showed the weakest binding at –5.8 kcal/mol.

2.2 Docking Studies for PPAR-Gamma

2.2.1 Docking Studies Data of Compound 1 (Aleglitazar) with PPAR-Gamma

Table 8 provides a comprehensive summary of the docking output for Compound 1 with PPAR-Gamma

Table 8: Docking Affinity and RMSD Values for Compound 1 (Aleglitazar) with PPAR-Gamma

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.3	0.000	0.000
2	–6.2	2.511	7.842
3	–6.2	3.224	8.615
4	–6.1	4.105	9.407
5	–6.0	4.639	9.936
6	–6.0	3.751	9.157
7	–5.9	5.032	10.318
8	–5.8	5.984	11.406
9	–5.7	6.417	11.989

2.2.2 Docking Studies Data of Compound 2 (–COONa Derivative of Aleglitazar) with PPAR-Gamma

Table 9 provides a comprehensive summary of the docking output for Compound 2 with PPAR-Gamma

Table 9: Docking Affinity and RMSD Values for Compound 2 (–COONa Derivative of Aleglitazar) with PPAR-Gamma

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–7.3	0.000	0.000
2	–7.2	1.925	6.882
3	–7.1	2.618	7.764
4	–7.1	3.462	8.496
5	–6.9	4.007	9.064
6	–6.9	3.717	8.713
7	–6.8	5.093	10.472
8	–6.7	5.623	11.095
9	–6.6	6.185	11.879

2.2.3 Docking Studies Data of Compound 3 (Methyl Derivative of Aleglitazar) with PPAR-Gamma

Table 10 provides a comprehensive summary of the docking output for Compound 3 with PPAR-Gamma

Table 10: Docking Affinity and RMSD Values for Compound 3 (Methyl Derivative) with PPAR-Gamma

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.6	0.000	0.000
2	–6.5	2.102	6.384
3	–6.4	2.781	6.943
4	–6.3	3.213	7.512
5	–6.2	3.659	8.101
6	–6.1	4.088	8.722
7	–6.0	4.512	9.203
8	–5.9	4.931	9.718
9	–5.8	5.347	10.164

2.2.4 Docking Studies Data of Compound 4 (Amino Derivative of Aleglitazar) with PPAR-Gamma

Table 11 provides a comprehensive summary of the docking output for Compound 4 with PPAR-Gamma

Table 11: Docking Affinity and RMSD Values for Compound 4 (Amino Derivative) with PPAR-Gamma

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.9	0.000	0.000
2	–6.8	2.034	5.998
3	–6.7	2.789	6.523
4	–6.6	3.213	6.994
5	–6.5	3.698	7.412
6	–6.4	4.211	7.996
7	–6.3	4.564	8.414
8	–6.1	5.017	9.009
9	–6.0	5.448	9.457

2.2.5 Docking Studies Data of Compound 5 (Hydroxyl Derivative of Aleglitazar) with PPAR-Gamma

Table 12 provides a comprehensive summary of the docking output for Compound 5 with PPAR-Gamma

Table 12: Docking Affinity and RMSD Values for Compound 5 (Hydroxyl Derivative) with PPAR-Gamma

Docking Mode	Binding Energy (kcal/mol)	RMSD Lower Bound (Å)	RMSD Upper Bound (Å)
1	–6.8	0.000	0.000
2	–6.6	2.172	5.487
3	–6.5	2.694	5.912
4	–6.4	3.143	6.303
5	–6.3	3.546	6.899
6	–6.1	4.113	7.485
7	–6.0	4.543	7.992
8	–5.9	5.027	8.347
9	–5.9	5.416	8.733

2.2.6 Comparative Analysis of Compound 1 to Compound 5 with PPAR-Gamma

Table 13 provides a comprehensive summary of the docking output for Compound 1 to Compound 5 with PPAR-Gamma.

Table 13: Comparative Docking Summary of Compounds 1–5 with PPAR-Gamma (Best Pose – Mode 1)

Compound	Functional Group	Best Binding Energy (kcal/mol)	RMSD (Å)	Binding Mode	Positional Stability Remarks
Compound 1	Parent (Aleglitazar)	–6.3	0.000	Mode 1	Stable conformation; moderate polar–hydrophobic fit
Compound 2	–COONa Derivative	–7.3	0.000	Mode 1	Deep ionic engagement; strongest polar anchoring
Compound 3	$-CH_3$ Derivative	–6.6	0.000	Mode 1	Hydrophobic strengthening; stable but moderate fit
Compound 4	$-NH_2$ Derivative	–6.9	0.000	Mode 1	Polar interaction enhanced; good but not deepest fit
Compound 5	–OH Derivative	–6.8	0.000	Mode 1	Surface-bound H-bonding; slightly shallower alignment

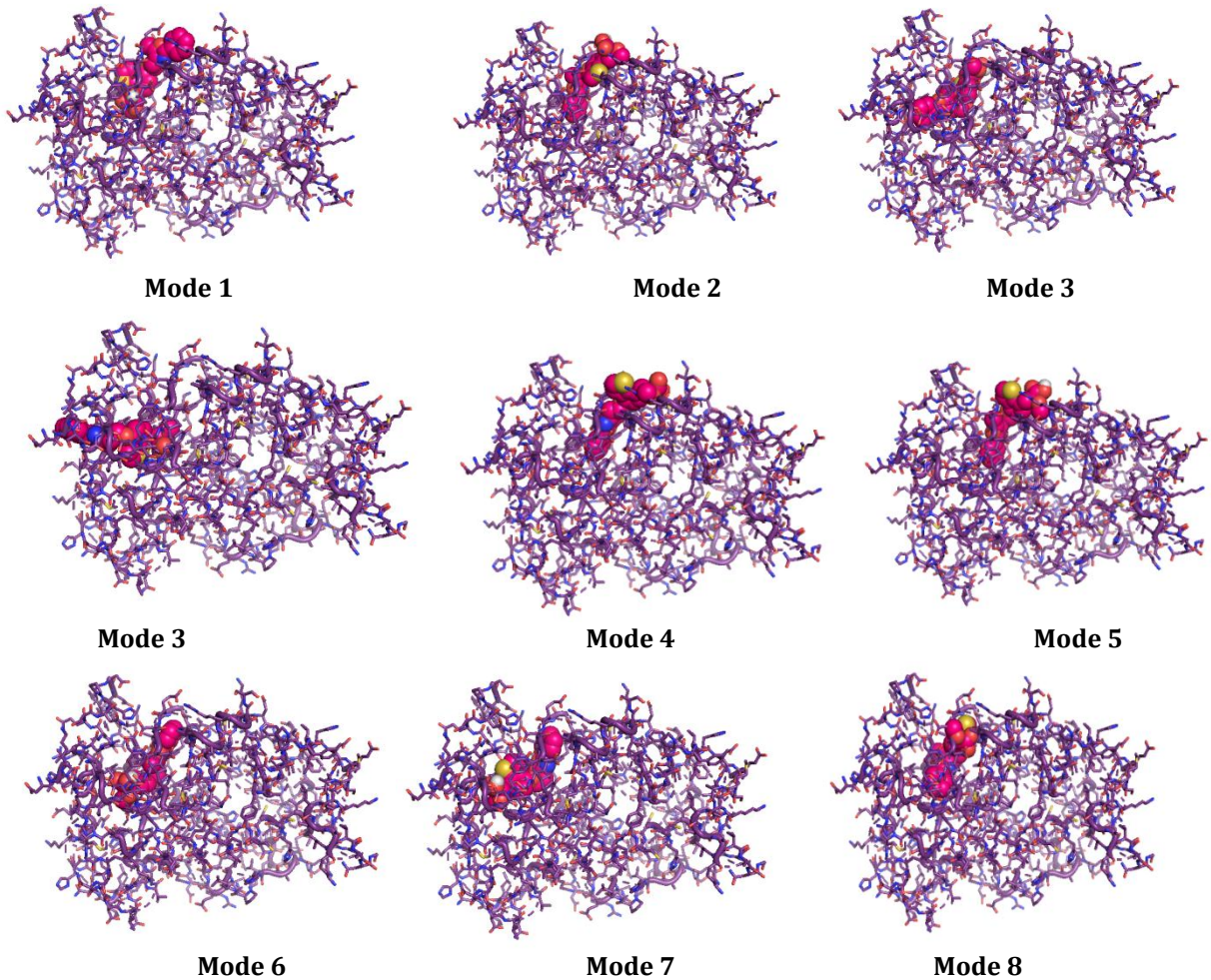


Figure 5: All 1-9 Docking Modes of Compound 2 with PPAR-Alpha

Table 13 and figure 5 summarizes the most favorable docking pose (Mode 1) of each compound with PPAR-gamma based on binding energy and RMSD values. Compound 2 consistently displays the most favorable interaction characteristics, showing the deepest polar engagement and strongest electrostatic interaction profile, making it the most promising ligand in the series

SUMMARY AND CONCLUSION

This study employed a structure-based drug design (SBDD) approach to evaluate Aleglitazar and four of its derivatives for dual activation of PPAR-α and PPAR-γ, key targets in type 2 diabetes management. Among the tested compounds, the sodium carboxylate derivative (Compound 2) exhibited the most favorable binding

energies (–6.5 kcal/mol for PPAR-α, –7.3 kcal/mol for PPAR-γ), surpassing the parent compound and other derivatives. Molecular docking confirmed strong electrostatic and hydrogen bond interactions, particularly with polar residues, aided by the –COONa group. Other derivatives showed moderate or weak binding due to limited polar interactions or unfavorable geometry. RMSD analysis validated pose stability across docking modes, with Compound 2 consistently maintaining optimal alignment. The study confirms that introducing ionizable functional groups significantly improves receptor binding affinity. Compound 2 stands out as a potential dual PPAR modulator and a promising lead for future antidiabetic drug development. This computational framework offers a robust basis for further optimization.

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CONFLICT OF INTEREST

There is no conflict of interest.

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