World Journal of Pharmaceutical Science and Research

www.wjpsronline.com

Research Article

ISSN: 2583-6579
SJIF Impact Factor: 6.916
Year - 2026
Volume: 5; Issue: 6
Page: 1008-1017

IN SILICO DESIGN, 3D QSAR, PHARMACOPHORE MODELLING, AND MOLECULAR DOCKING STUDIES OF NOVEL ANTIDIABETIC AGENTS

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Article Received: 27 April 2026 | | Article Revised: 17 May 2026 | | Article Accepted: 07 June 2026

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DOI: https://doi.org/10.5281/zenodo.20689219

How to cite this Article: Satyendra Singh Rathore (2026) IN SILICO DESIGN, 3D QSAR, PHARMACOPHORE MODELLING, AND MOLECULAR DOCKING STUDIES OF NOVEL ANTIDIABETIC AGENTS. World Journal of Pharmaceutical Science and Research, 5(6), 1008-1017.

ABSTRACT

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency. Dipeptidyl peptidase-4 (DPP-4) inhibitors have emerged as a significant therapeutic class for T2DM management. In this study, a comprehensive Computer-Aided Drug Design (CADD) approach was utilized to design novel DPP-4 inhibitors. A dataset of 21 benzoic-acid based xanthine derivatives with known DPP-4 inhibitory activity was used to generate predictive 3D QSAR and pharmacophore models using BIOVIA Discovery Studio 2021. The best 3D QSAR hypothesis exhibited a strong correlation coefficient of 0.772, highlighting the critical importance of hydrogen bond acceptors and hydrophobic features for receptor binding. This validated model was subsequently employed for the virtual screening of a diverse drug-like database, identifying IBS189112 as a top template hit. Following rigorous hit-to-lead optimization, a novel 1,3,5-triazine derivative was theoretically designed. Molecular docking simulations with the human DPP-4 enzyme (PDB ID: 5Y7H) revealed an excellent LibDock score of 129, with robust binding interactions at key catalytic residues including PHE357, TYR547, GLN553, ARG560, and LYS554. Furthermore, in silico ADMET and Lipinski rule evaluations confirmed its highly favorable pharmacokinetic profile. The purely computational findings suggest that the designed 1,3,5-triazine derivative represents a highly promising candidate for DPP-4 inhibition, warranting future wet-lab synthesis and biological evaluation for T2DM management.

KEYWORDS: DPP-4 Inhibitors, 3D QSAR, Pharmacophore Modelling, Virtual Screening, Molecular Docking, In Silico Design.

INTRODUCTION

Diabetes Mellitus is a rapidly growing global health crisis, with an estimated 537 million people affected in 2021. Type 2 Diabetes Mellitus (T2DM) accounts for the vast majority of these cases. Among the therapeutic interventions

available, Dipeptidyl Peptidase-4 (DPP-4) inhibitors (gliptins) have garnered significant attention due to their efficacy in amplifying glucose-dependent insulin release while maintaining a weight-neutral profile and a low risk of hypoglycemia.

Despite the clinical success of marketed gliptins, there is an ongoing need to explore novel chemical scaffolds for DPP-4 inhibition with enhanced efficacy and minimized adverse effects. Computer-Aided Drug Design (CADD) provides a robust, cost-effective, and time-efficient paradigm for the discovery and optimization of novel bioactive molecules before committing to resource-intensive chemical synthesis. Techniques such as 3D Quantitative Structure-Activity Relationship (3D QSAR), pharmacophore modelling, and molecular docking facilitate a deep understanding of ligand-receptor interactions at the molecular level.

The present study focuses on in silico ligand-based and structure-based drug design approaches. Using a series of previously reported benzoic-acid based xanthine derivatives, predictive 3D QSAR and pharmacophore models were built. These models were deployed in virtual screening workflows to identify novel hits. The research outlines the rational design, structural optimization, and comprehensive computational validation of a promising novel DPP-4 inhibitor candidate.

MATERIALS AND METHODS

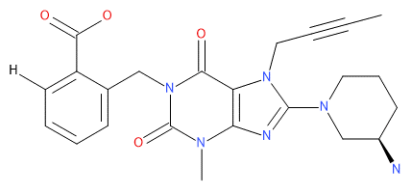
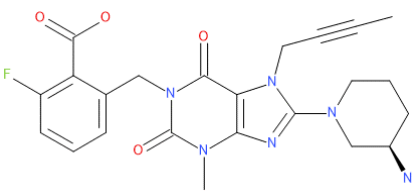
Computational Setup and Software

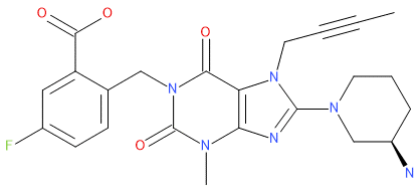
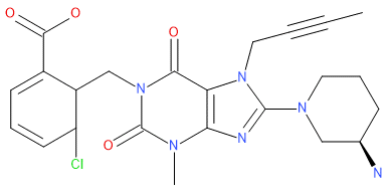
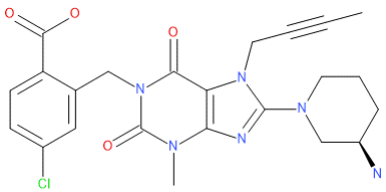
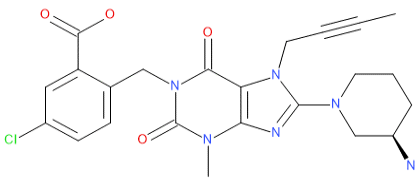
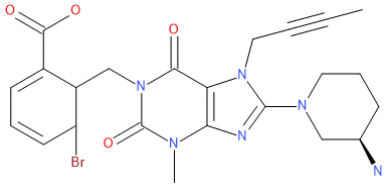
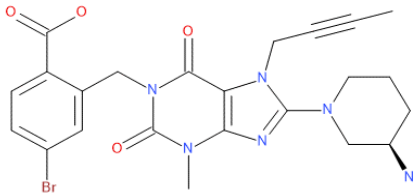
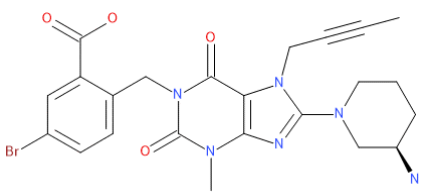
All computational experiments were performed using BIOVIA Discovery Studio 2021 (Dassault Systèmes) installed on a workstation operating Windows 10 Pro (Intel Xeon CPU, 16 GB RAM). Chemical structures were sketched using BIOVIA Draw. The SwissADME web server was used for predicting physicochemical and pharmacokinetic properties.

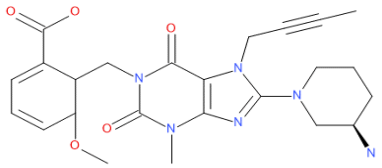
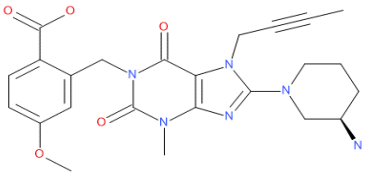
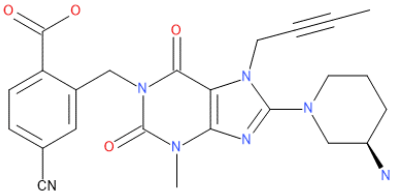
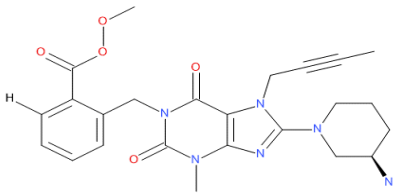
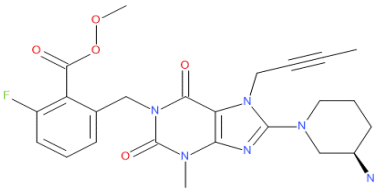
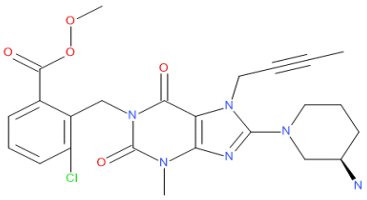
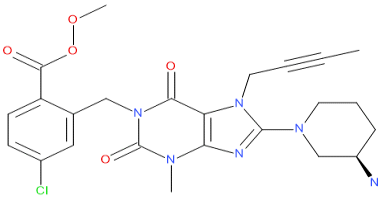
Dataset Preparation and Pharmacophore Modelling

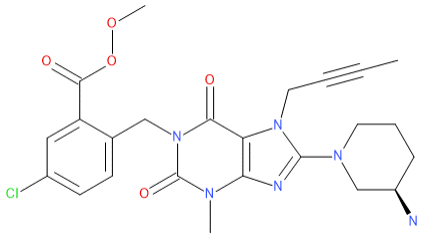
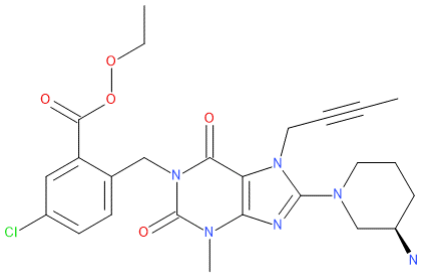
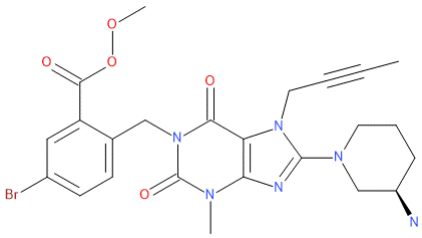
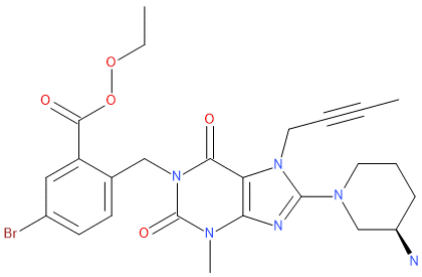
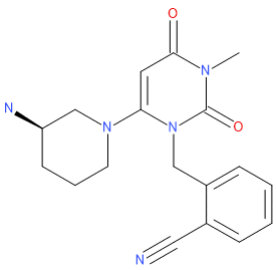
A dataset of 21 benzoic-acid based xanthine derivatives with reported in vitro DPP-4 inhibitory activity (IC50 values ranging from 0.10 nM to 85.48 nM) was selected from the literature. The structures were minimized and aligned. Ligand-based pharmacophore generation was executed to extract common chemical features essential for receptor binding.

Table 1: Literature Dataset Compounds and Inhibitory Activity.

S. No.	Compounds	DPP-4 IC50 (nM)	Structures
1	2a	1.98	
2	2b	10.21 (Moderate Active)	

3	2c	2.35	
4	2d	3.9	
5	2e	0.18	
6	2f	0.10 (Most Active)	
7	2g	1.05	
8	2h	0.72	
9	2i	0.22	

10	2j	5.99	
11	2k	0.44	
12	2l	2.43	
13	3a	2.91	
14	3b	5.06	
15	3c	50.9	
16	3d	5.61	

17	3e	20.48	
18	3f	74.43	
19	3h	22.09	
20	3i	85.48 (Least Active)	
21	3j	4.46	

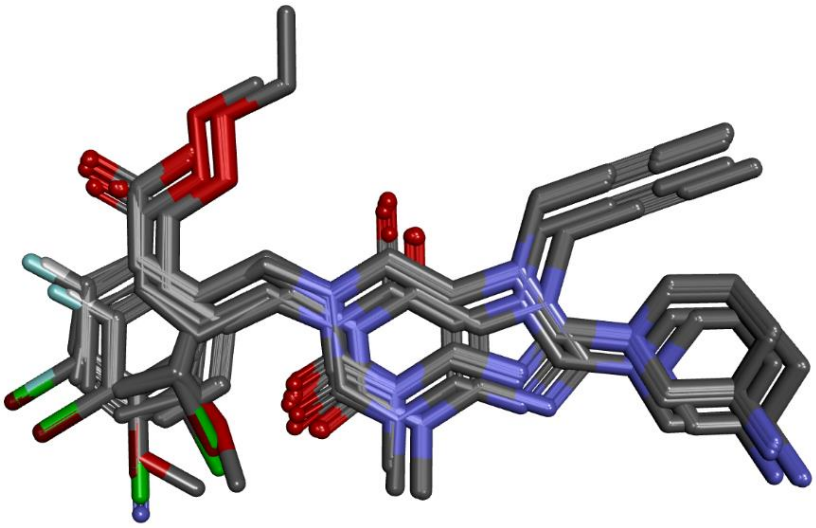


Figure 1: All literature dataset compounds superimposed in BIOVIA Discovery Studio.

3D QSAR Generation

The HYPOGEN algorithm was applied to correlate the 3D spatial arrangement of the extracted features with biological activity. Models were validated using training and test set compounds. The best hypothesis was chosen based on the Cost Function Analysis and Correlation Coefficient.

Virtual Screening and Molecular Docking

The validated 3D QSAR hypothesis was employed as a 3D query to virtually screen a drug-like diverse database. Hits were filtered based on Lipinski's Rule of Five and ADMET descriptors. Molecular docking was performed using the LibDock module. The 3D crystal structure of the human DPP-4 enzyme (PDB ID: 5Y7H, resolution 3.0 Å) was retrieved from the RCSB Protein Data Bank. The protein was prepared, minimized, and a binding pocket sphere (Radius: 7.59 Å) was generated.

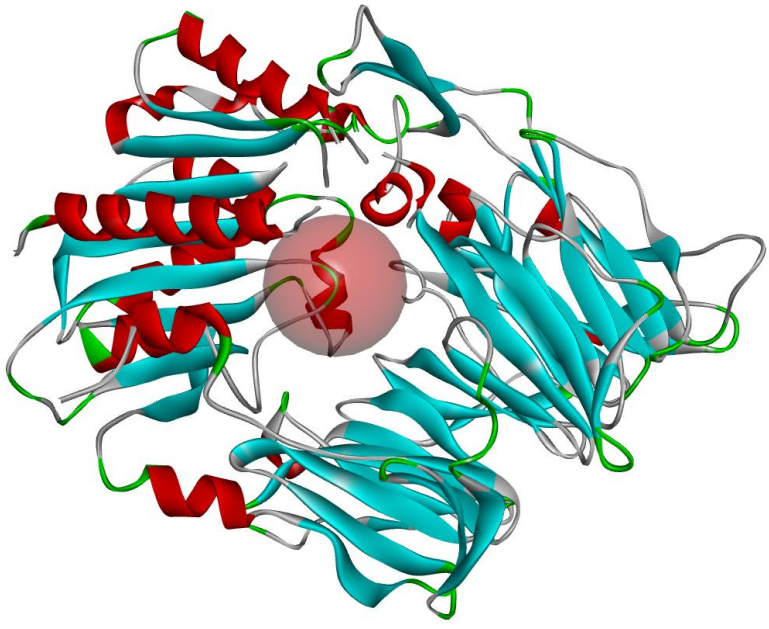


Figure 2: Human DPP4 enzyme PDB ID - 5Y7H and its binding pocket sphere.

RESULTS AND DISCUSSION

Pharmacophore and 3D QSAR Analysis

Feature mapping of the 21 active compounds revealed that hydrogen bond acceptors and hydrophobic regions are paramount for DPP-4 inhibition. The generated 3D QSAR model (Hypothesis-1) consisted of four features: two Hydrogen Bond Acceptors and two Hydrophobic features.

Table 2: 3D QSAR Hypothesis 1 Results.

Parameter	Value
Maximum Fit	6.94693
Total Cost	179.986
RMS	2.52908
Correlation	0.772547

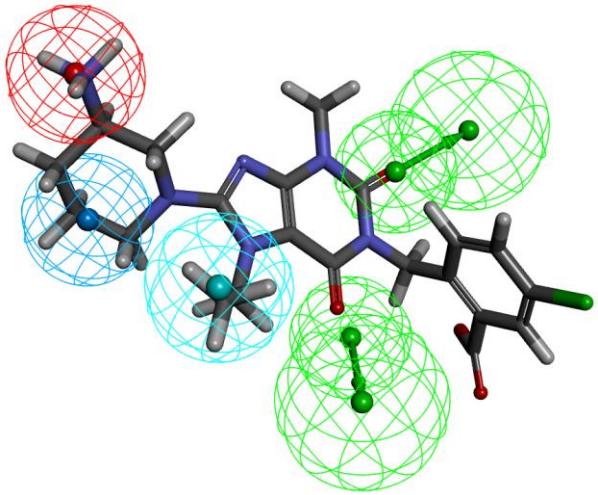


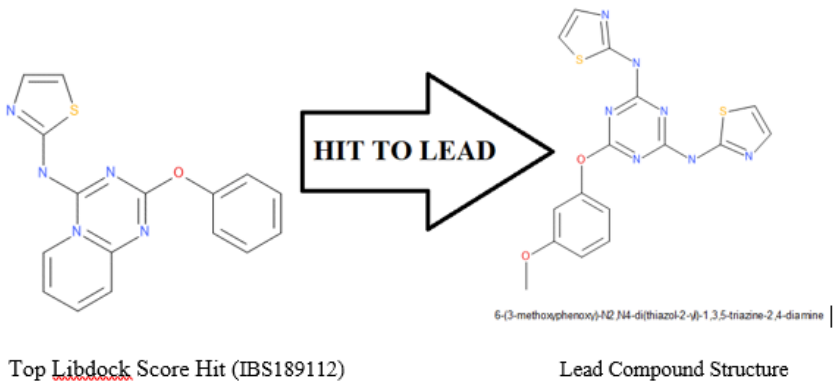
Figure 3: 3D QSAR hypothesis 1 with four-point features aligned with the most active compound (2f).

Virtual Screening and Hit-to-Lead Optimization

Screening the drug-like diverse database using Hypothesis-1 returned 3,225 hits. Application of rigorous Lipinski and ADMET filters isolated a top-ranking hit, IBS189112, which served as the structural template. Scaffold hopping and rational structural optimization generated a novel lead compound.

Table 3: Top LibDock Score Hit Virtually Screened from Database

Hit Name	LibDock Score	Fit Value	Lipinski Filter	ADMET Filter
IBS189112	129.014	6.59	Pass	Pass



Top Libdock Score Hit (IBS189112) Lead Compound Structure

Docking Interactions

Docking of the optimized lead compound into the active site of human DPP-4 (PDB ID: 5Y7H) yielded an impressive LibDock score of 129, theoretically surpassing reference molecules. Interaction diagrams revealed that the compound successfully established critical non-covalent interactions with active site residues.

Table 4: Lead Compound LibDock Score and Amino Acid Interactions.

Compound Name	LibDock Score	Amino Acid Interactions
6-(3-methoxyphenoxy)-N2,N4-di(thiazol-2-yl)-1,3,5-triazine-2,4-diamine	129	TYR547, PHE357, GLN553, ARG560, LYS554

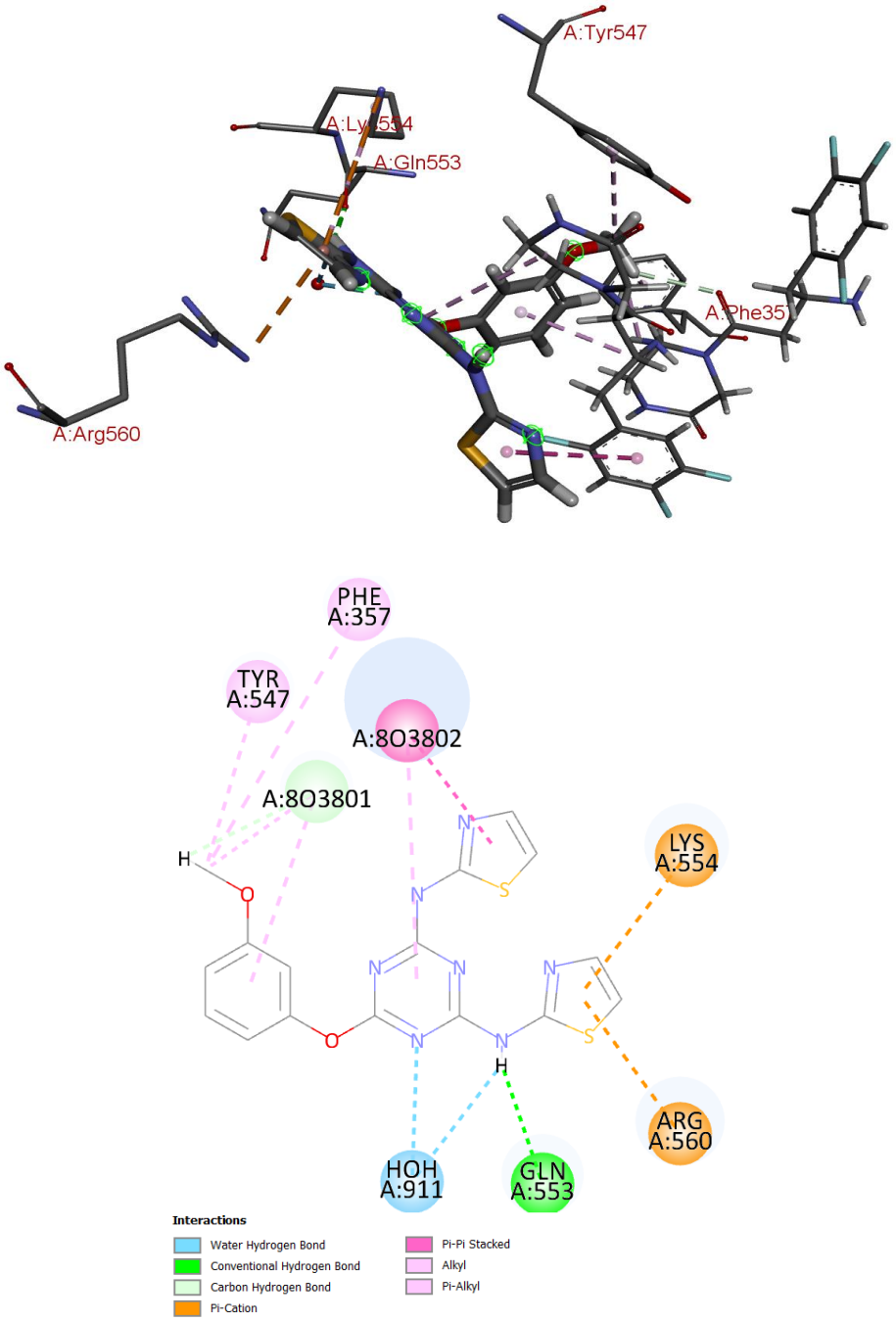


Figure 4: 3D and 2D ligand-protein interactions of the lead compound in DPP-4 active site (PDB: 5Y7H).

In Silico ADMET Profiling

Calculations indicated a molecular weight of 399.45, ALogP of 4.147, and zero violations of Lipinski's rule of five. Toxicity prediction models (TOPKAT Ames Mutagenicity) confirmed the compound is non-mutagenic.

Table 5: Molecular Properties and Toxicity Prediction of Lead Compound.

Property	Value
Molecular Weight	399.45 g/mol
ALogP	4.1471
Rotatable Bonds	7
Hydrogen Bond Acceptors	7
Hydrogen Bond Donors	2
TOPKAT Ames Mutagenicity	Non-Mutagenic

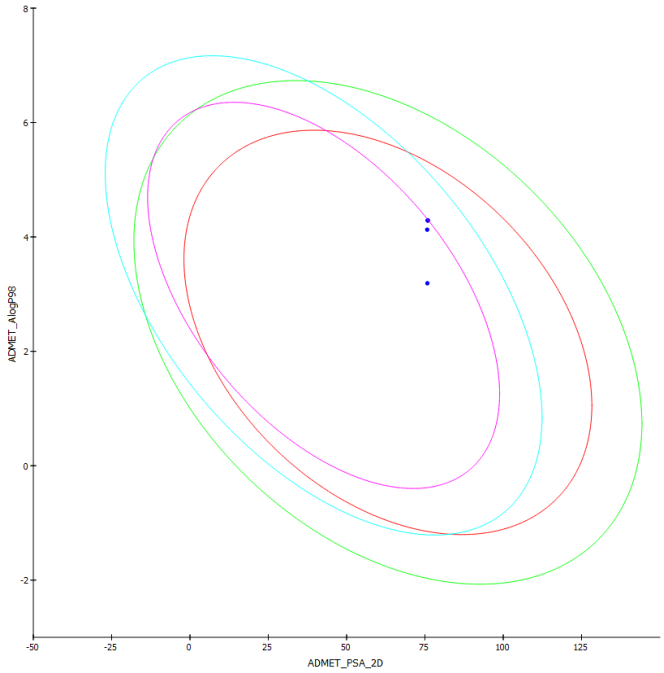


Figure 5: ADMET plot.

CONCLUSION

The purely computational approach employed in this study successfully led to the in silico design of a novel potential DPP-4 inhibitor. The 3D QSAR pharmacophore modeling emphasized the criticality of hydrophobic and hydrogen bond acceptor features. The virtually screened and rationally optimized lead compound exhibited superior theoretical binding affinity (LibDock Score: 129) and interacted selectively with key catalytic residues of the DPP-4 enzyme (PHE357, TYR547, GLN553). Furthermore, favorable ADMET characteristics position this designed 1,3,5-triazine derivative as a highly promising candidate. These computational findings provide a strong rationale for future wet-lab synthesis and subsequent in vivo pharmacological evaluation.

ACKNOWLEDGEMENT

The authors express their sincere gratitude to the management, Principal, and Director of Sri Aurobindo Institute of Pharmacy, Indore (M.P.), for providing the necessary infrastructural and laboratory facilities, as well as access to the BIOVIA Discovery Studio software, which were instrumental in the successful completion of this research work.

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