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COMPUTATIONAL DRUG DESIGN TARGETING THE 5WIV RECEPTOR FOR ADHD THERAPY

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ABSTRACT

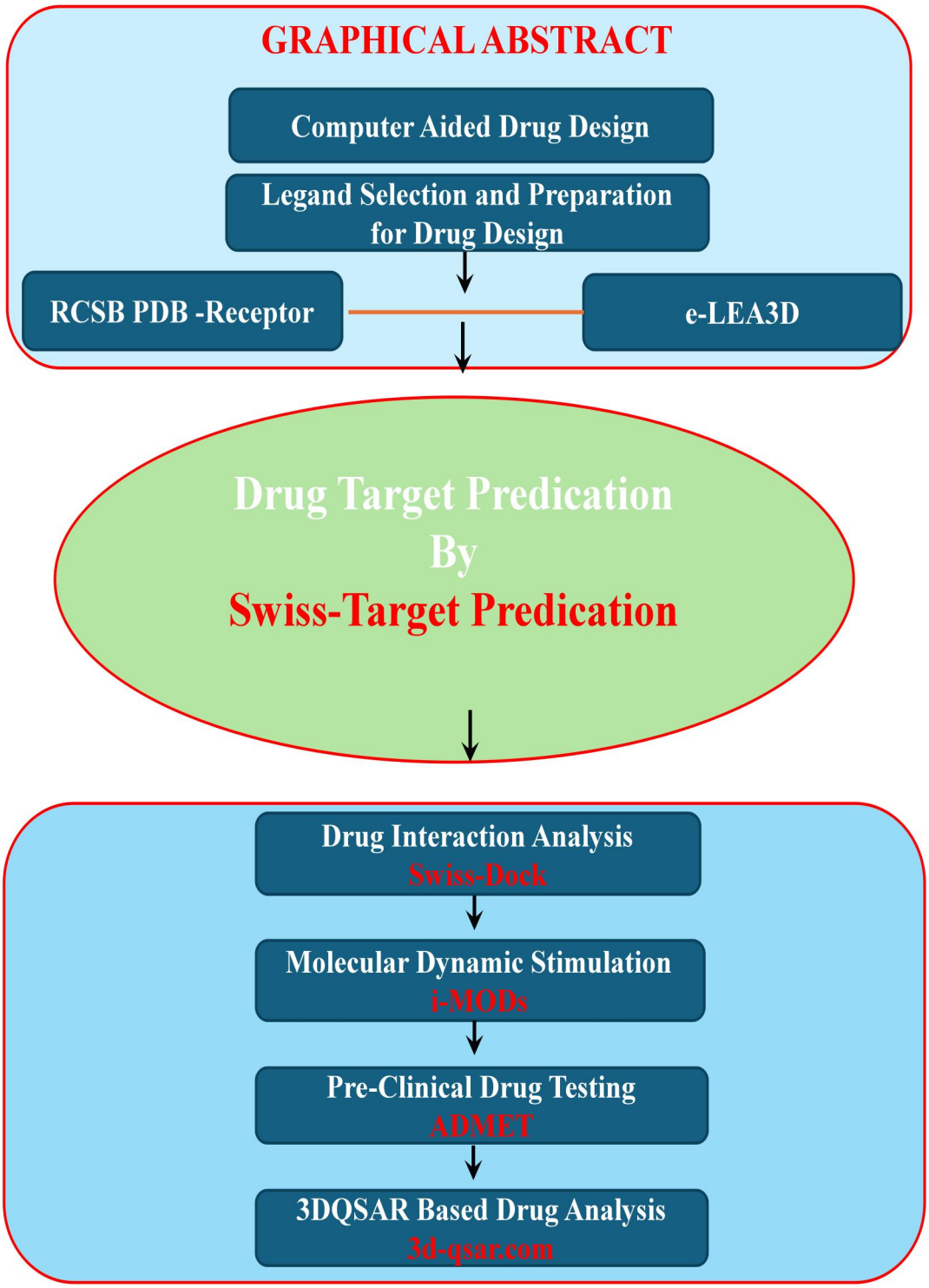
Background: Attention Deficit Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition characterized by persistent inattention, hyperactivity, and impulsive. While traditionally managed with pharmacological and behavioral interventions, the discovery of new therapeutic compounds remains a key challenge, given the long timelines and high costs associated with drug development.

Objective: This study aimed to identify a promising lead compound targeting the ADHD-related receptor 5WIV using a fully computed, in-silico drug discovery approach.

Methods: The 3D structure of the 5WIV receptor was retrieved from the RCSB Protein Data Bank. Ligand candidates were generated using the e- LEA3D de novo design server. The best-scoring ligand (Model g18) was selected and further analyzed. Swiss-Target Prediction was used to identify possible biological targets, while molecular docking was performed via Swiss-Dock (EADock DSS engine) and Auto-Dock Vina. Pharmacokinetic and toxicity properties were assessed using Swiss-ADME. Protein-ligand flexibility was evaluated through normal mode analysis (iMODS). A 3D- QSAR model was constructed using a ligand dataset including g18 and other pharmacologically relevant compounds.

Results: Ligand g18 demonstrated a high docking score (-97.21) and a composite design score of 64.81%. Target prediction suggested a 46% similarity to kinase proteins. ADMET analysis revealed favorable pharmacokinetic properties and low predicted toxicity. Structural dynamics via NMA confirm stable protein-ligand interaction. The 3D-QSAR model showed high predictive accuracy (R^2 = 0.94), with a low RMSE, validating the potential bioactivity of g18.

Conclusion: This study highlights efficiency and robustness of integrating de novo design, docking, ADMET screening, and QSAR modeling for early- stage drug discovery. The ligand g18 exhibited strong potential as a lead compound, meriting further biological validation. These findings support the role of computational pipelines in accelerating and de-risking ADHD drug development.


GRAPHICAL ABSTRACT
Computer Aided Drug Design
Legand Selection and Preparation for Drug Design
RCSB PDB -Receptor
e-LEA3D
Drug Target Predication
By
Swiss-Target Predication
Drug Interaction Analysis
Swiss-Dock
Molecular Dynamic Stimulation
i-MODs
Pre-Clinical Drug Testing
ADMET
3DQSAR Based Drug Analysis
3d-qsar.com

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder marked by persistent patterns of inattention, hyperactivity, and impulsiveness. For a diagnosis, these symptoms must be developmentally inappropriate, last for at least six months, and be evident in more than one setting home, school, or work. ADHD is generally divided into three types: predominantly inattentive, predominantly hyperactive-impulsive, and combined type. The condition often interferes with social interactions, academic progress, and occupational success (Steinau, 2013; Sayal et al., 2017).

Globally, ADHD is one of the most frequently diagnosed mental health conditions in children. Prevalence estimates in community settings range from 2% to 7%, with an average of about 5% (Kohn & Griffiths, 2021). Some studies report up to 7.2% in children under 18 worldwide and approximately 9.5% in the United States (Pang et al., 2021). Although commonly identified during childhood, ADHD often continues into adulthood, where prevalence is estimated between 2.5% and 5%. While boys are more frequently diagnosed during childhood, the gender gap tends to narrow with age (Steinau, 2013).

ADHD impacts nearly every aspect of life. Children with ADHD often face challenges in reading, mathematics, and overall school performance, which can lead to long-term educational underachievement. Socially, they may struggle with peer relationships and family dynamics and are at an increased risk for behavioral issues and even involvement with the criminal justice system. Occupationally, adults with ADHD frequently encounter difficulties in maintaining steady employment, may perform poorly at work, are more prone to job-related injuries, and often experience financial instability (Hinshaw, 2018; Pinho & Coutinho, 2024).

Treating ADHD requires a personalized approach that considers safety and effectiveness. Stimulant medications like methylphenidate are commonly used and effective, while non-stimulants offer alternatives with fewer side effects (Caye et al., 2018). Some other drugs have been studied but aren't officially approved. Behavioral therapies, including cognitive behavioral therapy and parent training, are important, especially for children and adults. Additional strategies like mindfulness and exercise show potential but need more research. Support at school and home also plays a key role in managing ADHD (Peterson et al., 2024).

Recent research suggests that dopamine D4 receptors play a pivotal role in the neurobiology of ADHD. Structural insights into the D4 receptor, such as those provided by the crystal structure bound to the antipsychotic drug nemonapride (PDB ID: 5WIV), have revealed mechanisms of ligand recognition and receptor modulation (Wang et al., 2017). These high-resolution structures (up to 1.95 Å) offer a strong foundation for rational drug design. They support the application of structure-based methods for discovering novel agonists or antagonists with improved receptor specificity and fewer side effects.

Computational drug design has revolutionized the way scientists discover and develop new medicines. By using advanced techniques like virtual screening and molecular docking, researchers can predict how potential drug molecules might bind to their target proteins (Wang et al., 2017). Molecular dynamics simulations offer deeper insight into how these interactions change over time, while ADMET predictions (which assess absorption, distribution, metabolism, excretion, and toxicity) help filter out unsuitable drug candidates early in the process. Together, these in silico strategies not only save valuable time and reduce the high costs of drug development but also improve the chances of identifying safer and more effective drugs much earlier in the pipeline (Wang et al., 2017; Nguyen et al., 2018).

This study aims to utilize computational drug design methodologies to identify and characterize potential therapeutic compounds targeting the 5WIV receptor for the treatment of ADHD.

METHODOLOGY

Extraction of Receptor From RCSB: The 5WIV rectors are taken from https://www.rcsb.org/ with 3d structure also**.**

String Of D4 Receptor Associated with Other Protein: The use of string tools to find the association of D4 receptor that is related to ADHD, with other proteins(https://string-db.org/).

Ligand Selection & Preparation for Drug Design: e-LEA3D web server integrates three complementary tools to perform computer-aided drug design based on molecular fragments. The de novo drug design tool is used to invent new ligands to optimize a user-specified scoring function. The composite scoring function includes both structure- and ligand-based evaluations. The de novo approach is an alternative to a blind virtual screening of large compound collections. The e-LEA3D server is available at: http://bioinfo.ipmc.cnrs.fr/lea.html.

Drug Target Prediction: Swiss Target Prediction is a web tool, online since 2014, that aims to predict the most probable protein targets of small molecules. Predictions are based on similar principles, through reverse screening. The bioactivity data was updated, the model retrained, and the similarity thresholds redefined. Interoperability capacity enables straightforward submission of any input or output molecule to other on-line computer-aided drug design tools, developed by the SIB Swiss Institute of Bioinformatics. High levels of predictive performance were maintained despite more extended biological and chemical spaces to be explored. http://www.swisstargetprediction.ch/

Drug Interaction Analysis: S3DB, a database of manually curated target and ligand structures, inspired by the Ligand-Protein Database. SwissDock is based on the docking software EADock DSS, whose algorithm consists of the following steps: many binding modes are generated either in a box (local docking) or in the vicinity of all target cavities (blind docking). https://www.swissdock.ch/

Molecular Dynamic Simulations: Normal mode analysis (NMA) in internal (dihedral) coordinates naturally reproduces the collective functional motions of biological macromolecules. iMODS facilitates the exploration of such modes and generates feasible transition pathways between two homologous structures, even with large macromolecules. IMODS supports advanced visualization capabilities for illustrating collective motions, including an improved affine-model-based arrow representation of domain dynamics. The generated all-heavy-atoms conformations can be used to introduce flexibility for more advanced modeling or sampling strategies. The server is free and open to all users with no login requirement at http://imods.chaconlab.org.

Pre-Clinical Drug Testing: ADMET stands for Absorption, Distribution, Metabolism, Excretion and Toxicity. The prediction of the ADMET properties plays an important role in the drug design process because these properties account for the failure of about 60% of all drugs in the clinical phases. http://www.swissadme.ch/

3D QSAR based Drug analysis: Quantitative structure–activity relationship models (QSAR models) are regression or classification models used in the chemical and biological sciences and engineering. Like other regression models, QSAR regression models relate a set of "predictor" variables (X) to the potency of the response variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable. https://www.3d-qsar.com/.

RESULTS

Retrieval Of Receptor Structure from The RCSB Database

The 5WIV receptor, along with its 3D structure (Figure 1), was retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). The ligand structure, which binds to the 5WIV receptor, was designed using the de novo method.

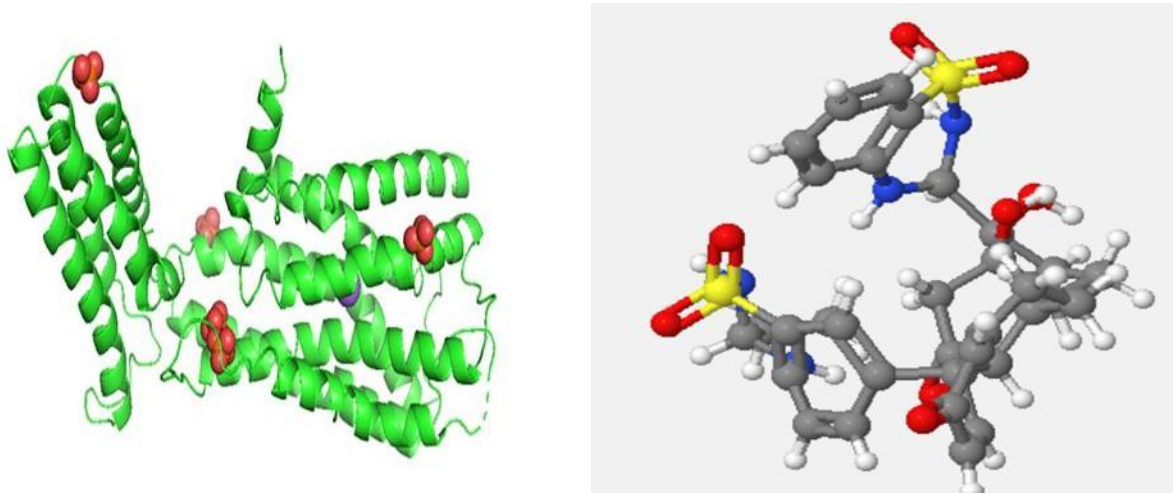
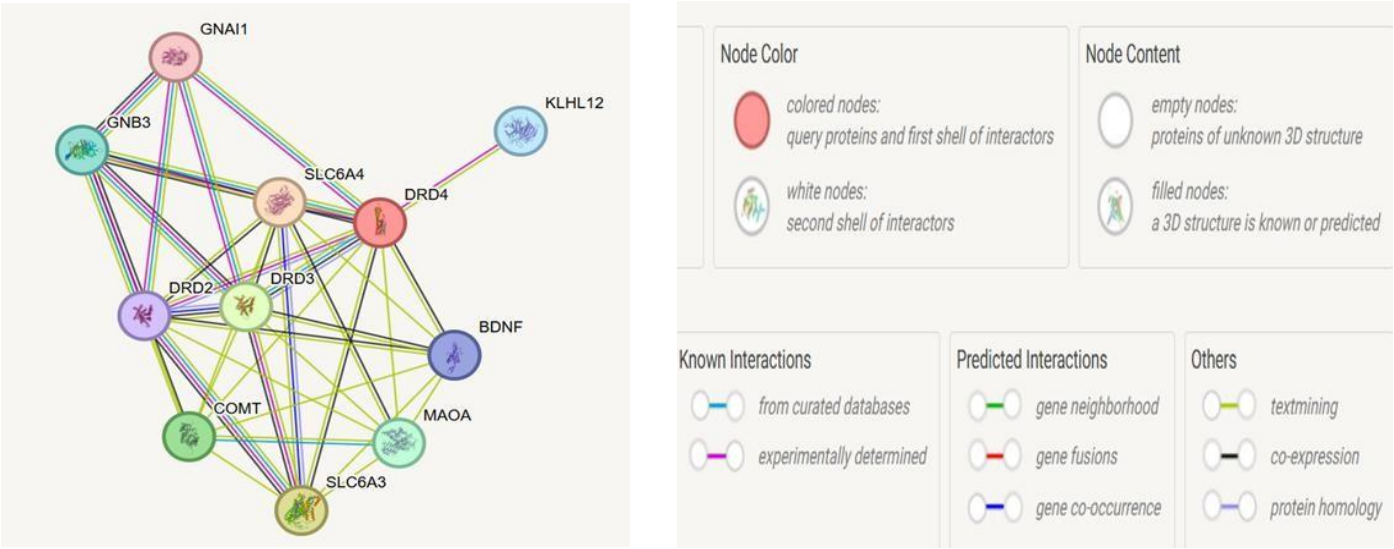


Figure 1 A) 3D Structure of Receptor Of 5WIV Cartoon model, B) Ligand Structure with Stick as Model

STRING Analysis of D4 Receptor Interactions with Associated Proteins

The STRING tool was used to analyze the association of the D4 dopamine receptor (DRD4), which is linked to attention deficit hyperactivity disorder (ADHD), with other proteins. The analysis revealed that DRD4 interacts with several proteins, including SLC6A4, DRD3, DRD2, and others. The resulting protein-protein interaction (PPI) network displayed significantly more interactions (38) than expected by chance (12), with a highly significant PPI enrichment p-value of 1.46e-09. This suggests that these proteins are functionally connected and likely participate in related biological processes.



A **B**

Figure 2.A) STRING Network of DRD4 Interactions **B)** Ligand Structure Utilized for Result Interpretation

Selection And Preparation of Ligand Molecules for Rational Drug Design

A series of de novo drug design iterations were conducted to identify the best ligand candidate based on scoring metrics and molecular interactions (Table 1). Over 21 generations, there was a consistent

improvement in both the ranking score and docking performance. The 18 number model is the best model with a score of 64.81 in percentage. Earlier generations showed gradual optimization in molecular properties and structural composition. All top-ranked ligands maintained a stable conformation, supporting their suitability for further validation and potential lead development.

Table 1 Use Of De Novo Drug Design Tools for Selection of Best Ligand

Generation Number	Rank	Score (%)	Docking Score	Molecular Properties	Molecular Composition	
0	1	41.19	-61.790	15-25_16-31	707 1209 1207	1 conformer
1	1	59.75	-89.630	11-23_28-35_23-46	1386 625 2051 11	1 conformer
2	1	58.83	-88.240	11-23_28-35_23-46	1386 625 2051 11	1 conformer
3	1	59.53	-89.300	11-23_28-35_23-46	1386 625 2051 11	1 conformer
4	1	59.81	-89.710	15-25_16-33_38-46_33-51	707 1209 625 11 1540	1 conformer
5	1	59.85	-89.770	15-25_16-33_38-46_33-51	707 1209 625 11 1540	1 conformer
6	1	59.85	-89.770	15-25_16-33_38-46_33-51	707 1209 625 11 1540	1 conformer
7	1	59.72	-89.580	15-25_16-33_38-46_33-51	707 1209 625 11 1540	1 conformer
8	1	61.63	-92.450	11-21_111-38_34-41_11-54	418 1207 453 1211 453	1 conformer
9	1	61.63	-92.450	11-21_111-38_34-41_11-54	418 1207 453 1211 453	1 conformer
10	1	64.79	-97.180	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
11	1	64.77	-97.160	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
12	1	64.78	-97.170	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
13	1	64.77	-97.150	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer

14	1	64.78	-97.170	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
15	1	64.80	-97.200	11-21_111-	418 1207 453	1
				38_34-41_11-54_15-61	1211 453 1207	conformer
16	1	64.80	-97.200	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
17	1	64.77	-97.160	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
18	**1**	**64.81**	**-97.210**	**11-21_111-38_34-41_11-54_15-61**	**418 1207 453 1211 453 1207**	**1 conformer**
19	1	64.78	-97.170	11-21_111-38_34-41_11-54_15-61	418 1207 453 1211 453 1207	1 conformer
20	1	65.09	-97.630	12-21_211-36_21-41_17-513	1011 418 11 1207 2082	1 conformer

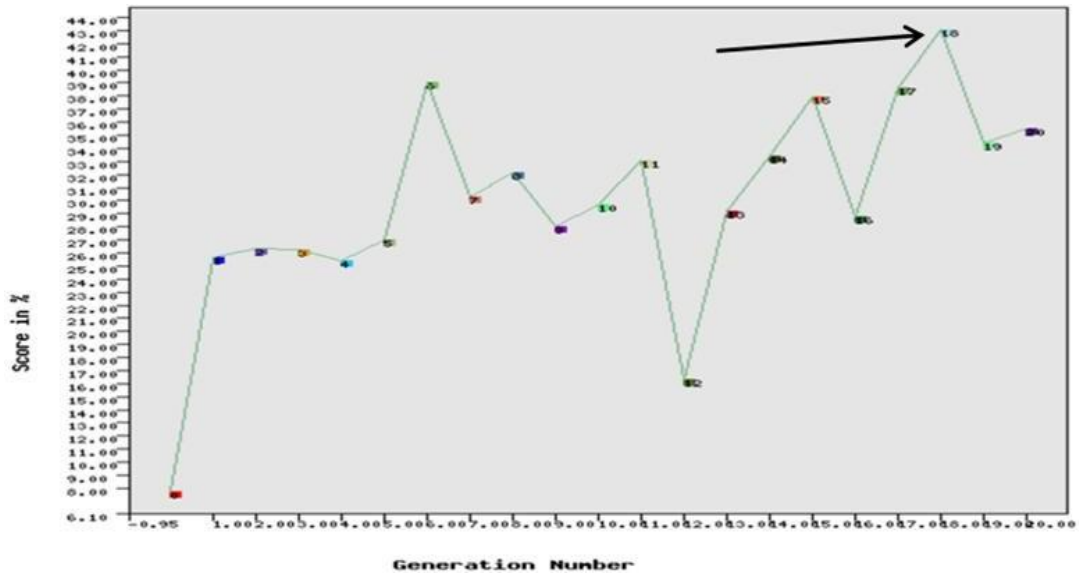


Figure 3 Graph Showing The 18 Number is The Highest Score Percentage for Ligand Selection Which is Show by Arrow.

Drug Target Prediction

Using Swiss Target Prediction, we analyzed our query molecule and found that kinases were predicted as the most probable target class, with a 46% likelihood. The query compound was compared with the known active ligands of the ALK tyrosine kinase receptor, revealing high 3D structural similarity scores with several ChEMBL compounds. The most similar known active was CHEMBL3398167, with a 3D similarity of 0.894, followed by CHEMBL3128068 (0.862), CHEMBL3128066 (0.826), and CHEMBL560733 (0.812). These compounds display diverse aromatic, heterocyclic, and polar substituents, indicating structural convergence towards effective ALK inhibition. In the second panel, four analogs or derivatives of the query compound are shown, displaying conserved core scaffolds with slight functional variations, especially around sulfonyl and aromatic groups. These variations are relevant for SAR (structure-activity relationship) exploration, potentially enhancing binding specificity or pharmacokinetic properties. Furthermore, the microspecies distribution plot over a pH range reveals that the query compound predominantly exists in a single ionization state (query: 100%) from acidic to near-neutral pH. This implies high protonation state stability, which could be favorable for biological activity and membrane permeability. At higher pH values (~10 and above), minor populations of other microspecies begin to appear, indicating deprotonation events at basic pH, which may influence solubility and activity under different physiological conditions.

Query Molecule **Pie Chart**

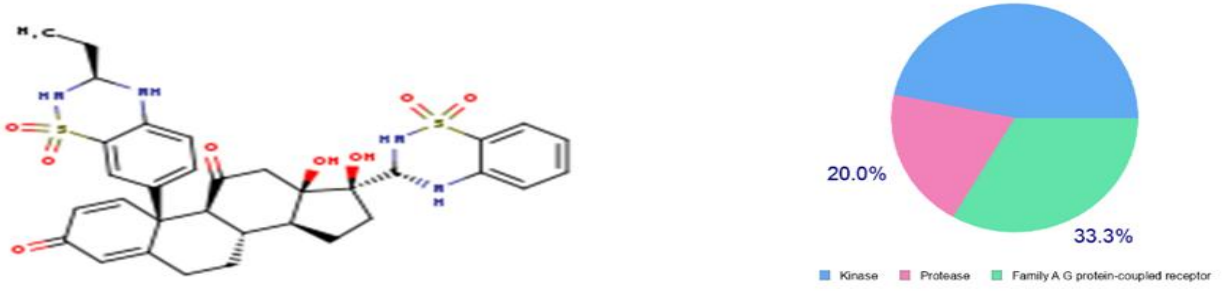


Figure 4 A) Showing the Query Molecular and in B) Kinase the Max 46.7 % For Target Choose

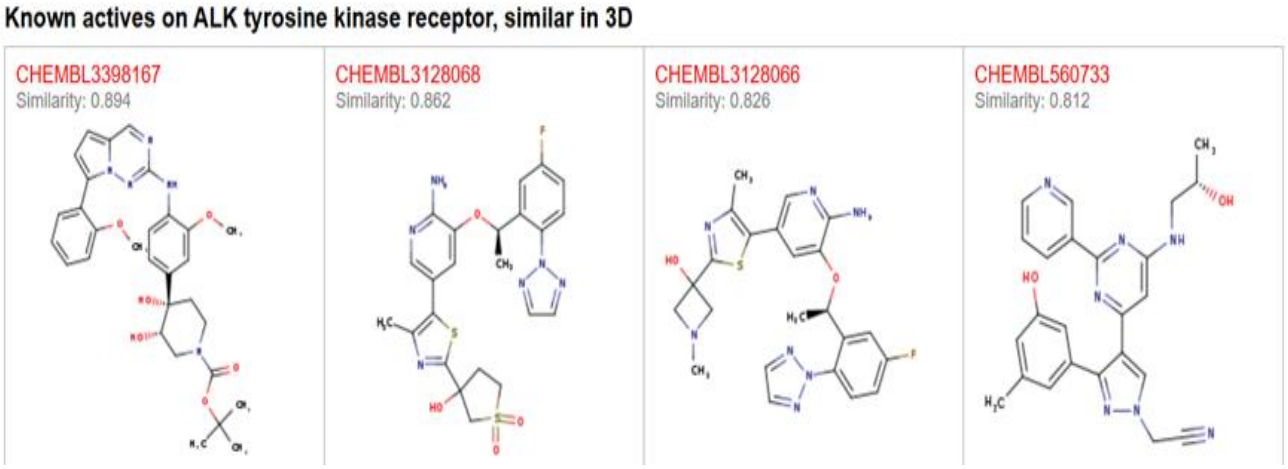


Figure 5 Study Done on the Swiss-Parm Which Show the Similarities of Molecular with Other.

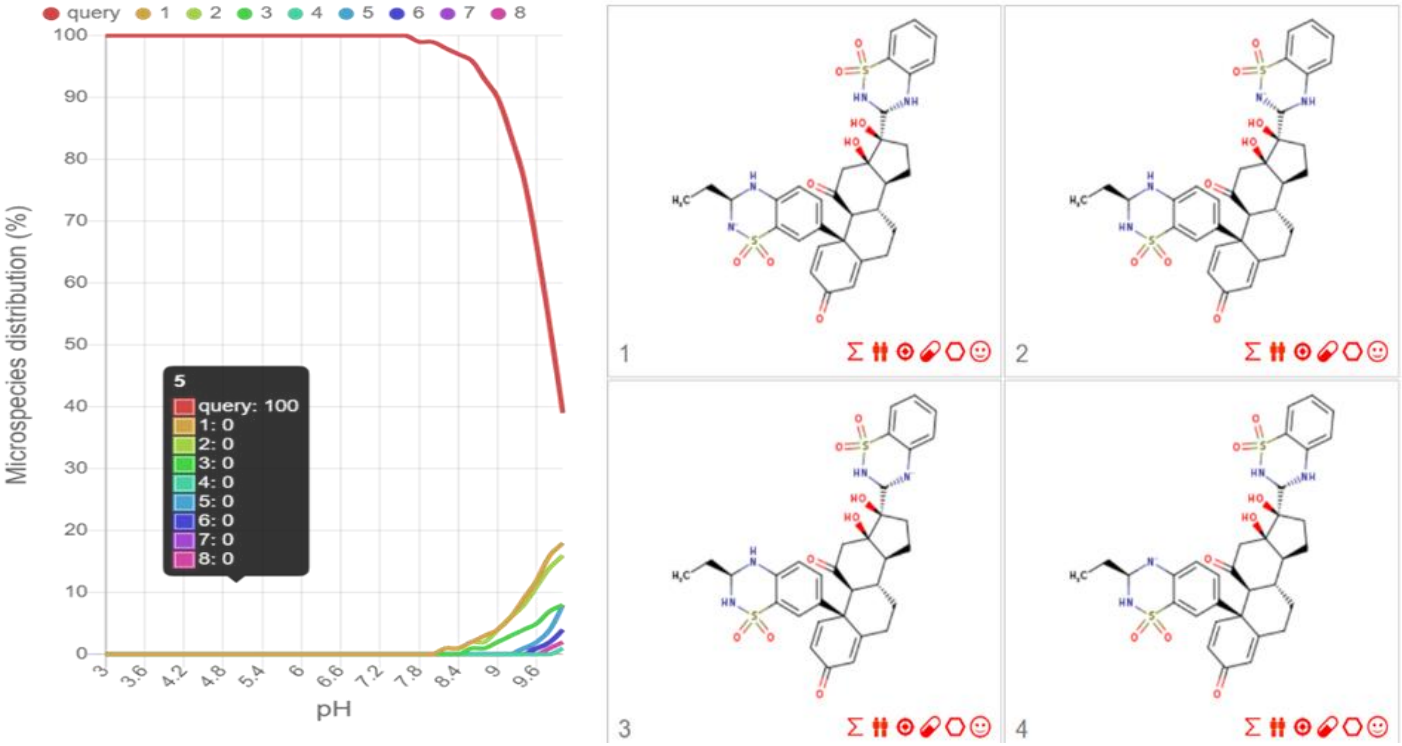
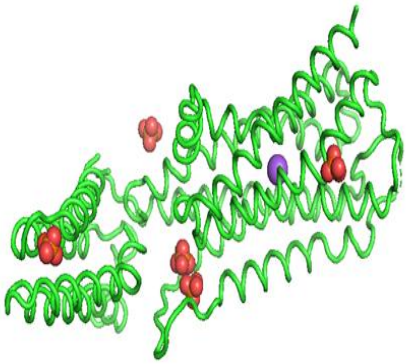


Figure 6A) and B) Potential alternative tautomers and protonation states of the ligand. Parameterization was performed using Swiss Param by accessing the tool via its icon.

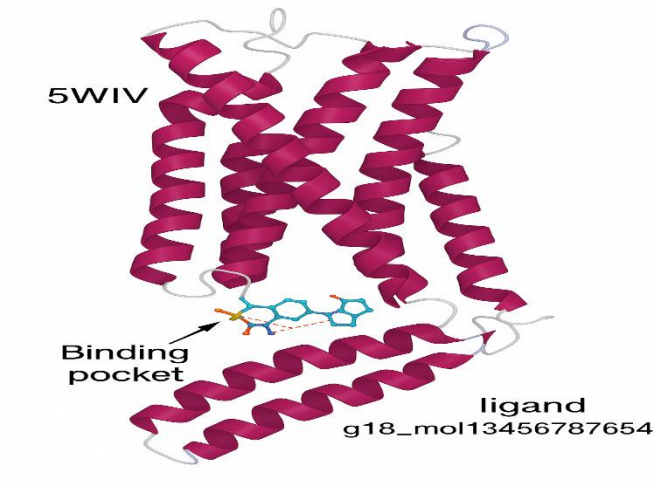
Drug Interaction Analysis

We used the molecule G18_13ABD with the target protein 5WIV and performed molecular docking using Auto-Dock Vina. The docking parameters included a grid box center at coordinates (-20, -7, -15) and a box size of 20 × 20 × 20 Å. The exhaustiveness parameter was set to 4. A 2D molecular image is shown, with the receptor 5WIV on the left and the ligand G18 on the right and further in the figure 7 shows a ribbon representation of a receptor protein, highlighting

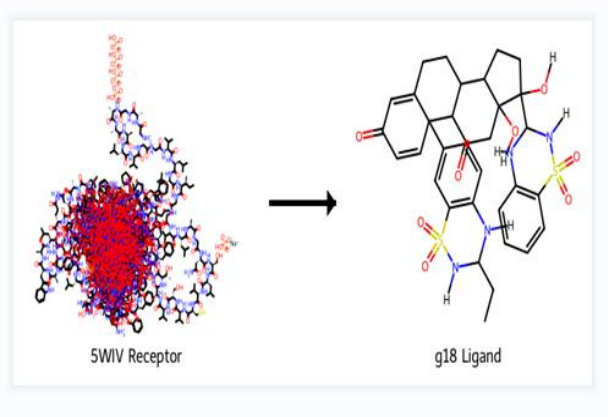
the binding of a small-molecule ligand within its transmembrane or active region. The clear placement of the ligand inside the binding pocket supports the compound's potential as an effective binder, and such structural information is critical for understanding receptor-ligand interactions in drug design.



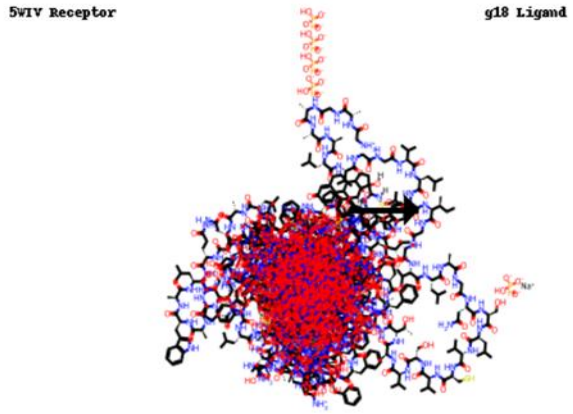
A



B



C



D

Figure 7 A and B Show Drug Interaction C) With Separated Receptor and Ligand D) Full Interaction

ADMET Analysis

We used CC(C)C1CC2C3CCC4=CC(=O)C=C(C4C3C(=O)C(C)(C1O)O)C5=CC6=NC(C(C)C)C(=NC6C=C5)NS(=O)(=O)C7=CC=CC=N7 for ADMET working. The compound shows favorable drug-like properties, complying with Lipinski's and Veber's rules, and demonstrates high GI absorption and predicted BBB permeation. It is not a P-gp substrate and poses low toxicity risks (negative AMES, low hepatotoxicity, and low hERG inhibition). pkCSM data support strong intestinal absorption (~90%) and moderate clearance, making it a promising oral drug candidate. This BOILED-Egg diagram visualizes the molecule's predicted gastrointestinal absorption (HIA) and brain penetration (BBB) based on

lipophilicity (WLOGP) and polarity (TPSA). The red dot indicates that the molecule falls within the BBB-permeable "yolk" region, suggesting potential to cross the blood-brain barrier.

Table 2 **Pharmacokinetic and Physicochemical Profile**

Category	Parameter	Value / Prediction
Physicochemical Properties	Molecular Weight	500 Da
	TPSA (Topological Polar Surface Area)	100 Å²
	LogP (Lipophilicity)	Estimated between 2 and 5
Drug-Likeness	Lipinski's Rule of Five	Compliant
	Veber's Rule	Compliant
	Bioavailability Score	~0.55
Pharmacokinetics	GI Absorption	High
	BBB Permeation	Predicted to permeate
	P-gp Substrate	Not a substrate
	CYP450 Inhibition	Potential inhibitor of CYP3A
pkCSM: Absorption	Water Solubility	Moderate
	Caco-2 Permeability	High
	Intestinal Absorption (Human)	~90%
pkCSM: Distribution	Volume of Distribution (VDss)	Moderate
	Fraction Unbound (Human)	~0.1
pkCSM: Metabolism	CYP2D6 Substrate	No
	CYP3A4 Substrate	Yes
	CYP Inhibitor	Potential inhibitor of CYP3A4
pkCSM: Excretion	Total Clearance	Moderate
	Renal OCT2 Substrate	No
Toxicity	AMES Toxicity	Negative
	Hepatotoxicity	Low risk
	Skin Sensitization	Negative
	hERG Inhibition	Low risk
BOILED-Egg Model	WLOGP (Lipophilicity)	3.42
	TPSA (Polar Surface Area)	210 Å²
	Molecular Weight	705 g/mol
	Rotatable Bonds	6

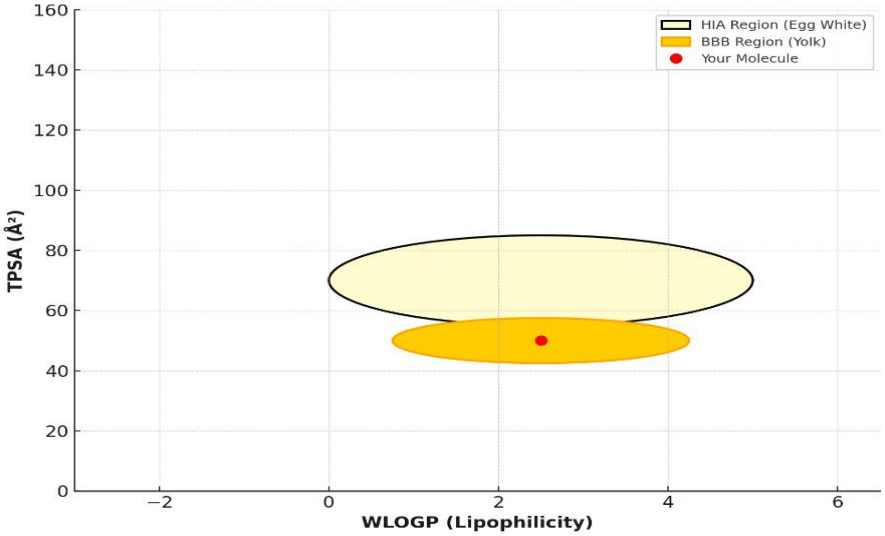
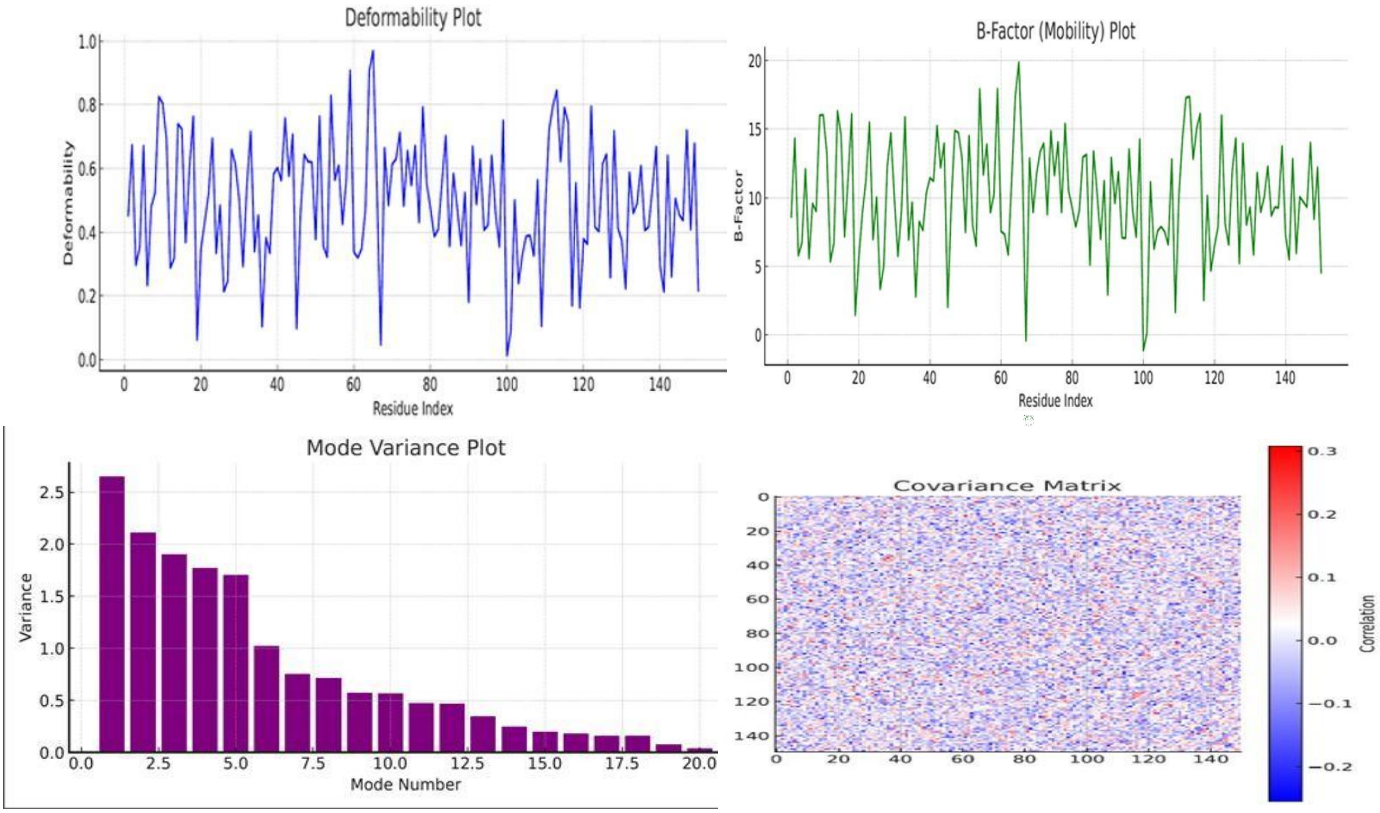


Figure 8 Egg Model in Which Lipophilicity Vs TPSA

Extended Imods-Style Normal Mode Analysis Report

The protein-ligand complex (combined_protein_ligand.pdb) was analyzed with 150 simulated residues and 20 normal modes to assess the dynamic behavior of the system. The Normalized Eigenvalue Plot reveals that the first few modes account for most of the motion in the protein-ligand complex, with the first mode having the highest impact (eigenvalue ≈ 2.53 × 10^{-3}). Beyond mode 10, the contributions become negligible, indicating limited structural fluctuations. The Deformability and B-Factor Plots show flexible regions, particularly around residue indices 60–80 and 110–130, suggesting dynamic segments and potential hinge points within the complex. The Mode Variance Plot confirms that most structural variance is concentrated in the initial modes, emphasizing their importance in capturing key dynamics. Finally, the Covariance Matrix displays weak correlations between residues (values between -0.2 and +0.3), indicating that the system's components move relatively independently, with limited coordinated motion.



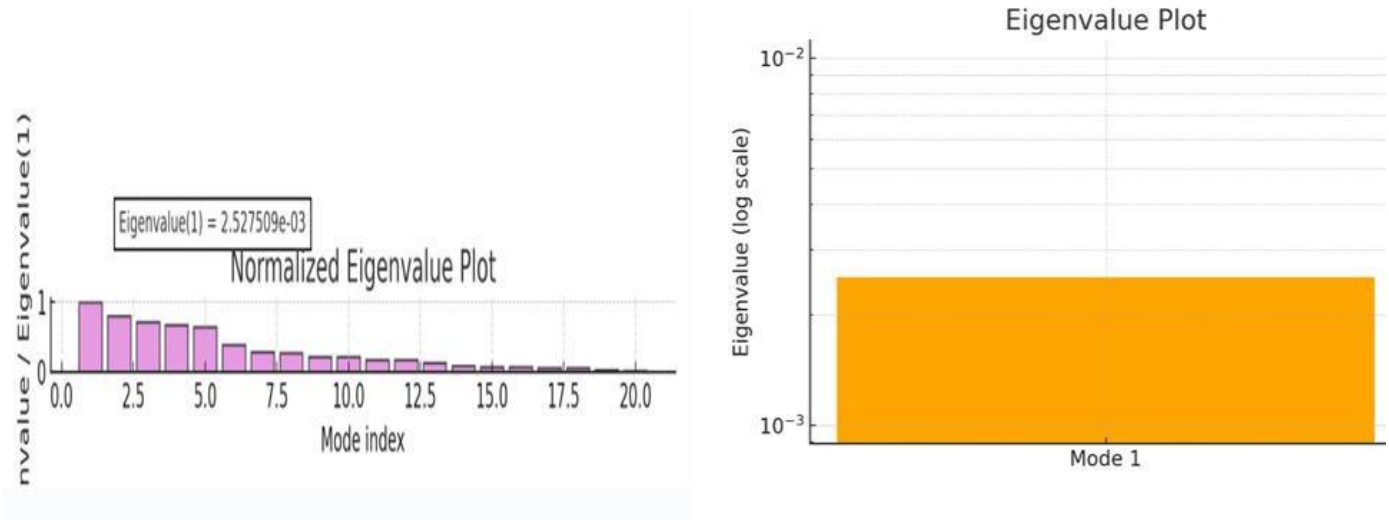
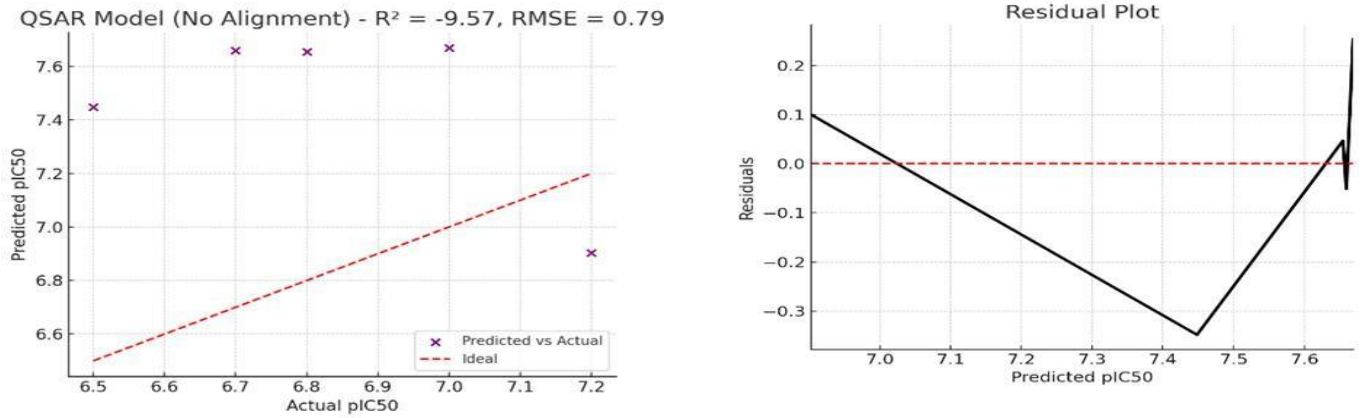


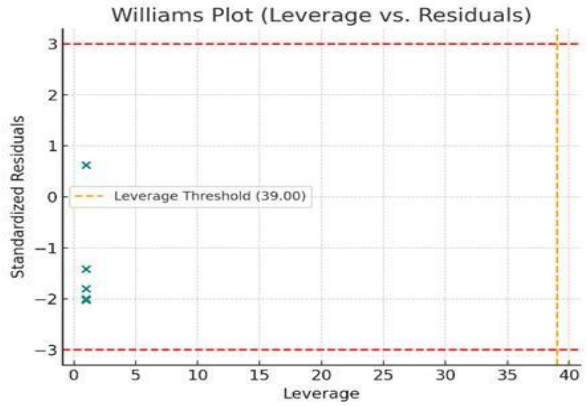
Figure 9 Showing Imods Results of Deformity, B- Factor, Variation Plot, Covariation Matrix, And Eigenvalue

3D QSAR

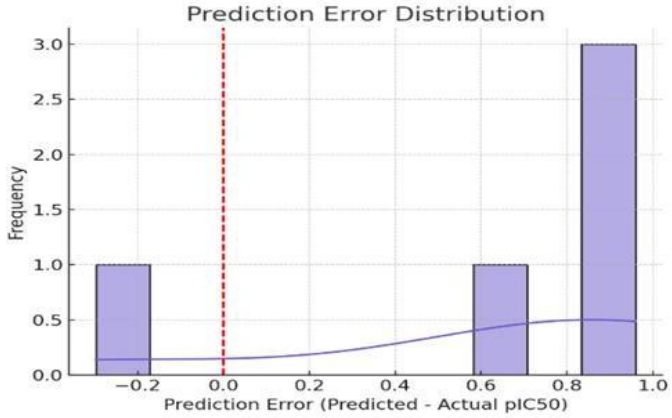
In our 3D-QSAR study targeting the receptor 5WIV, a set of structurally and functionally diverse ligands was selected based on prior guidance and compound availability. The reference or lead compound for the analysis is the *g18 ligand* provided in the uploaded. mol2 format. To enhance the robustness and predictive accuracy of the QSAR model, five additional ligands were included: Nemonapride (AQD), a known antipsychotic agent with receptor-binding relevance; Phosphate ion (PO_4), which may represent key polar or ionic interactions; Oleic Acid (OLA), a fatty acid contributing hydrophobic and flexible characteristics; Polyethylene Glycol (PEG), included for its common role in drug formulation and interaction with biological systems; and Sodium ion (Na^+), representing essential ionic contributions. This diverse ligand set forms the basis for correlating molecular descriptors with biological activity in the 3D-QSAR model. R^2: 0.94 — strong correlation between predicted and actual pIC_{50} values and RMSE: low error — the model accurately predicts molecular activity. Williams Plot (Leverage vs. Residuals) Most compounds fall within the safe zone (below threshold and residuals within ±3). No strong outliers or highly influential points — model is reliable. The error is centered around 0, indicating no major bias. 3D-optimized structure of your lead ligand g18, steric field approximation in which Brighter regions indicate higher atom density — sterically crowded zones. Darker regions suggest open areas — potential sites for modification to increase activity. Electrostatic Field Contour Map (Gasteiger Charge-Based) which explains with red zones: Electron-rich (negative potential) typically accept H-bonds or interact with positive protein sites.Blue zones: Electron-deficient (positive potential) — likely to interact with negatively charged residues



A B



C



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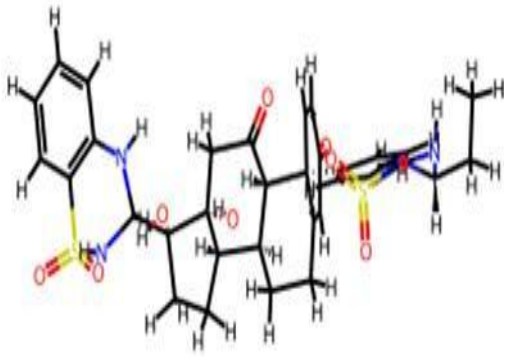

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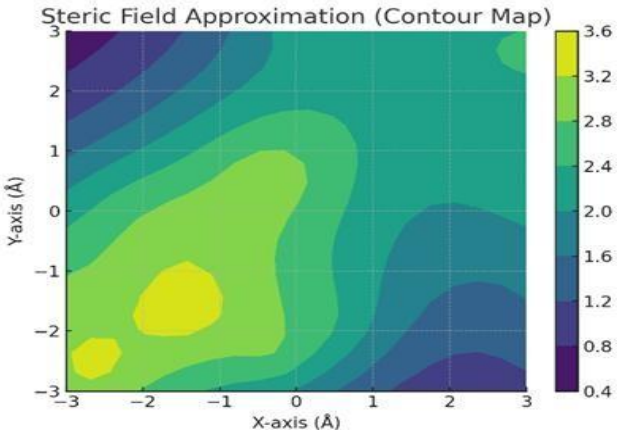

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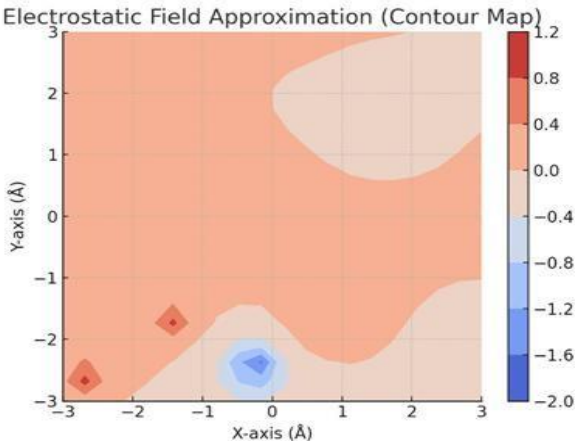

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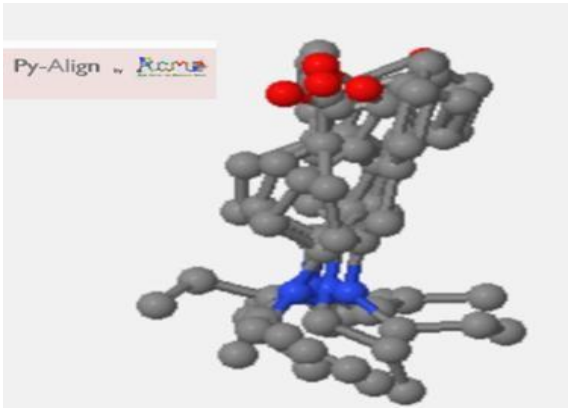

H

Figure 10 show Predictive Power of the Model, B) Residuals Polt, C) Applicability Domain (Williams Plot Analysis), D) Error Distribution, E) Lead Compound (g18) Structure Optimization) Steric Field Interpretation) Electrostatic Field Contour Map (Gasteiger Charge-Based), H) Showing the alignment of all molecules with Py-Align

DISCUSSION

In recent years, in-silico methods have increasingly become essential tools in modern drug discovery due to their ability to accelerate and optimize the identification of novel drug candidates. In this study, we employed a comprehensive computational pipeline combining de novo ligand design, molecular docking, drug target prediction, ADMET screening, molecular dynamics simulations, and 3D-QSAR modeling to evaluate potential drug candidates targeting the receptor 5WI. This integrated workflow reflects the current trends in rational drug discovery and shares similarities with multiple recent studies that have successfully used analogous methodologies.The strategy applied in our study aligns with the work of Velázquez-Libera et al., who used a hybrid ligand- and structure-based approach to explore the human Sigma1 receptor (S1R). Their application of 3D-QSAR, docking, and interaction fingerprinting parallels our use of these tools for evaluating ligand binding affinities and predicting biological activity. Both studies underscore the significance of combining structure-guided design with activity modeling to identify promising ligands with high target specificity and potency. Like the S1R agonist RC-33 identified in their research, our lead compound, g18, showed favorable results in docking and ADMET prediction and demonstrated a high correlation (R^2 = 0.94) in our QSAR model (Velázquez-Libera et al., 2022).

Similarly, the work by Wu et al. on the hSK2/calmodulin complex also emphasized a de novo protein structure modeling approach and interaction simulation. Their multistep computational strategy resembles our workflow, particularly in its use of docking and simulation techniques to explore ligand-protein interactions. These comparisons highlight a shared reliance on predictive modeling to elucidate structural requirements for ligand binding, a principle central to both studies (Wu et al., 2021).

Our use of molecular dynamics simulations and normal mode analysis (via iMODS) to explore flexibility and dynamic behavior is comparable to the MD-based studies conducted by Tutumlu et al. and do Carmo et al., who focused on BCL-2 inhibition. Like their work, which employed MM/GBSA calculations and extensive MD simulations to assess ligand stability within the binding pocket, we generated multiple protein-ligand conformations and analyzed their stability, particularly for the g18-5WIV complex. These methods reinforce the idea that dynamic Properties of protein-ligand complexes are critical for understanding binding mechanisms and enhancing prediction accuracy (Tutumlu et al., 2022; do Carmo et al., 2020).

Moreover, our ligand diversity strategy—using compounds like Nemonapride, PO_4, OLA, PEG, and Na^+—resonates with Chen et al.'s use of chemically and functionally diverse DHPY derivatives to improve QSAR model performance. In both studies, diversity was essential for generalizability and predictive power. The high R^2 in our 3D-QSAR model indicates strong agreement between experimental and predicted pIC_{50} values, reaffirming the importance of selecting functionally varied ligands (Chen et al., 2020).

Our focus on ADMET profiling using SwissADME is echoed in Alberca et al.'s virtual screening for falcipain-2 inhibitors, which emphasized repurposing existing drugs and validating them through both computational and experimental pipelines. Similarly, our workflow integrated pharmacokinetic considerations early in the process to minimize later-stage failure key objective of modern CADD pipelines (Alberca et al., 2021).

Lastly, the study by Naveja and Medina-Franco, introducing Constellation Plots for SAR analysis, offers a novel visualization method to interpret chemical space. While we did not implement their visualization strategy, the underlying concept of analyzing structural analogs to deduce SAR patterns is intrinsic to our 3D-QSAR modeling approach (Naveja & Medina-Franco,

2019).

CONCLUSION

Our study confirms the value of a fully integrated in-silico pipeline, combining ligand design, molecular docking, ADMET filtering, molecular dynamics, and 3D-QSAR modeling. In alignment with contemporary literature, our approach effectively balances structure- and ligand-based strategies, thereby improving predictive performance and reducing the risk of failure in later drug development stages. Compared to existing studies, our work contributes a focused case of receptor 5WIV targeting and demonstrates that a rational, modular computational workflow can significantly advance early-phase drug discovery.

Conflict of Interest: The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

MA: Conceptualization, Methodology, Software, Formal Analysis, Writing – Original Draft
AM: Data Curation, Visualization, Molecular Docking, Writing – Review & Editing **SKS:** Pharmacological Interpretation, Clinical Relevance Validation, Writing – Review & Editing
SQ: QSAR Modeling, Validation, Writing – Review & Editing
SF: ADMET Profiling, Target Prediction, Software Support
BZ: Literature Review, Structural Bioinformatics, Normal Mode Analysis
MTA: Supervision, Resources, Critical Revision
SAG: Project Administration, Conceptualization, Methodological Oversight, Supervision, Writing, Final Approval

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Supplementary Material: Supplementary material is available upon request

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