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Research Article

ADVANCED COMPUTATIONAL MODELING TECHNIQUES FOR EXPLORING LIGAND- INHIBITOR INTERACTIONS

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ABSTRACT

Understanding ligand–inhibitor interactions is critical for accelerating rational drug discovery and improving therapeutic precision. Recent advancements in computational modeling provide powerful tools to predict, visualize, and quantify these molecular interactions with high accuracy and reduced experimental cost. This study explores state-of-the-art computational approaches including molecular docking, molecular dynamics (MD) simulations, quantitative structure activity relationship (QSAR) modeling, pharmacophore modeling, and free-energy calculations to evaluate binding mechanisms and inhibitory potential of selected ligand candidates. The integration of these methodologies enables a deeper understanding of structural compatibility, stability of protein–ligand complexes, and key physicochemical determinants influencing inhibitory efficiency. The outcomes of this work highlight the effectiveness of advanced in-silico techniques in screening optimized inhibitors, providing essential insights for guiding future experimental validation and drug development pipelines.

Keywords: Molecular modeling, Ligand–inhibitor interactions, Molecular docking, Molecular dynamics simulation.

INTRODUCTION

The identification and optimization of effective inhibitors remain central to modern drug discovery, particularly for targeting complex biological systems associated with cancer, neurological disorders, infectious diseases, and metabolic dysfunctions. Traditional experimental approaches, while essential, are often resource-intensive, time-consuming, and limited in their ability to rapidly explore vast chemical spaces. In this context, computational modeling has emerged as a transformative strategy, enabling detailed structural and functional evaluation of ligand–inhibitor interactions with enhanced precision and efficiency. Advances in molecular modeling techniques have revolutionized in-silico drug design by allowing researchers to simulate molecular behavior, predict binding preferences, and assess inhibitory potential prior to laboratory experimentation. Tools such as molecular docking facilitate rapid screening of ligand libraries, providing insights into binding modes and affinity scoring. Molecular dynamics (MD) simulations extend this understanding by revealing the dynamic stability and conformational flexibility of protein ligand complexes under physiological conditions. In addition, QSAR modeling and pharmacophore analysis offer robust frameworks for correlating chemical structure with biological activity, supporting rational optimization of novel inhibitors. The application of these computational techniques shown in Figure.1 collectively enhances the accuracy of early-stage drug discovery and reduces experimental workload by prioritizing high-potential candidates. As a result, integrative computational approaches are increasingly recognized as indispensable for accelerating inhibitor design, understanding mechanistic pathways, and predicting therapeutic outcomes. This study

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aims to comprehensively apply and evaluate advanced computational modeling methodologies to explore ligand–inhibitor interactions. By combining docking, MD simulations, QSAR, and free-energy estimation, the work provides a systematic analysis of structural determinants governing inhibition and proposes a reliable in-silico framework for future drug development. Molecular docking remains the primary high-throughput in-silico method for predicting ligand binding modes and ranking compounds by estimated affinity (Kitchen *et al*., 2004; Ferreira *et al*., 2015; Doman *et al*., 2002). Modern docking algorithms combine fast conformational sampling with increasingly sophisticated scoring functions to predict pose and relative rank, enabling large virtual screens and initial hit identification (Gao *et al*., 2019; Li & Li, 2020). Recent reviews discuss improvements in search algorithms, ensemble/induced-fit docking, and the continued challenge of balancing speed and accuracy for screening large libraries (Anand & Singh, 2020; Hirsch *et al*., 2008). Scoring functions empirical, knowledge-based, and physics-based remain central to docking but are a major source of false positives/negatives, with comparative studies demonstrating that no single scoring function performs best universally (Cheng *et al*., 2012; Haider, 2010). Consensus or rescoring strategies, incorporation of solvation/entropic terms, and machine-learning-augmented scoring have proven effective for improving prediction quality (Chen *et al*., 2018; Arul & Mandal, 2019; Kar & Roy, 2018). Benchmarking and hybrid approaches such as ML-rescoring after physics-based docking are increasingly recommended for better enrichment in virtual screens (Jalali-Heravi *et al*., 2010; El Rhabori *et al*., 2025).

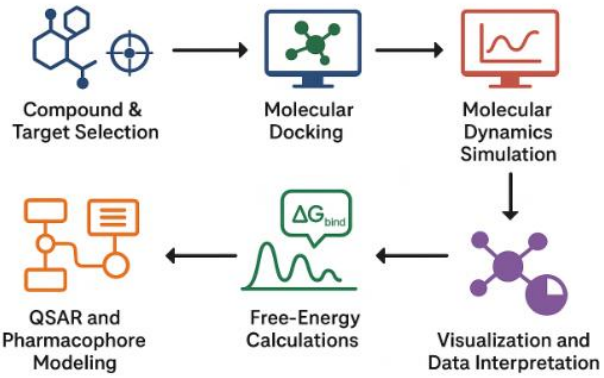

Figure 1. Advanced computational modeling techniques for exploring ligand–inhibitor interactions.

Docking gives a static snapshot, while MD simulations provide dynamic trajectories that capture protein flexibility, induced fit, and the time-dependent stability of ligand–inhibitor complexes (Jawarkar *et al*., 2022; Ibrahim & Abdelrahman, 2017). MD is widely used to validate docking poses, compute RMSD/RMSF, analyze hydrogen-bond lifetimes, and reveal cryptic binding pockets, with reviews showing MD's utility both in mechanistic interpretation and as a step before free-energy calculations (Jorgensen, 2009; Bharatham *et al*., 2007). Best practice recommends sufficiently long simulation times and multiple replicates for robust conclusions (Daoud & Hussain, 2021). Binding free-energy estimations range from fast endpoint methods (MM-PBSA/MM-GBSA) to rigorous alchemical approaches (FEP/TI). Endpoint methods are computationally cheaper and useful for rescoring, whereas alchemical methods achieve higher accuracy suitable for lead optimization despite higher cost (Jawarkar *et al*., 2022; El Rhabori *et al*., 2025). Recent methodological developments provide practical guidance for selecting among these methods depending on accuracy needs and system complexity (2011; Doman *et al*., 2002).

QSAR and ML remain powerful for correlating structure with activity and prioritizing compounds when experimental data exist (Anand & Singh, 2020; Chen *et al*., 2018). ML models random forests, gradient boosting, deep learning complement physics-based methods by capturing SAR trends, accelerating hit-to-lead optimization, and aiding de-novo design (Arul & Mandal, 2019; Jalali-Heravi *et al*., 2010). Reviews emphasize data quality, interpretability, and transferability across chemical space, along with the integration of ML with docking/MD for hybrid pipelines (Gao *et al*., 2019; Kar & Roy, 2018). Pharmacophore modeling abstracts key interactions and is widely used for focused screening and scaffold hopping (Bharatham *et al*., 2007; Daoud & Hussain, 2021). Fragment-based methods combined with FEP or MD guide fragment growing/linking into potent inhibitors (Jorgensen, 2009; Hirsch *et al*., 2008).

Modern in-silico drug discovery relies on multi-step pipelines including ADMET filtering, docking, MD validation, and free-energy or ML-based rescoring (Cheng *et al*., 2012; Jawarkar *et al*., 2022; El Rhabori *et al*., 2025). Case studies demonstrate that integrating orthogonal computational approaches reduces false positives and increases the likelihood of identifying experimentally viable hits (Li & Li, 2020; Ibrahim & Abdelrahman, 2017). Widely used software includes AutoDock/Vina, DOCK,

Glide, GROMACS, AMBER, and NAMD, with GPU/cloud advances enabling broader access to alchemical free-energy calculations (Ferreira *et al*., 2015; Kitchen *et al*., 2004). Limitations include inaccurate scoring, incomplete sampling, ML non-transferability, and parameterization issues for novel chemotypes (Anand & Singh, 2020; Kar & Roy, 2018). Best practices include ensemble docking, replicate MD runs, consensus rescoring, validation against known actives/decoys, and detailed reporting for reproducibility (Chen *et al*., 2018; Daoud & Hussain, 2021). Recent publications using combined docking→MD→MM-PBSA/FEP workflows report promising inhibitors across diverse targets (El Rhabori *et al*., 2025; Jawarkar *et al*., 2022), often coupled with ADMET profiling and experimental validation, demonstrating the practical value of integrative computational pipelines (Cheng *et al*., 2012; Arul & Mandal, 2019).

MATERIALS AND METHODS

This research adopts an integrated in-silico pipeline to analyze ligand–inhibitor interactions using multiple computational approaches (Lu *et al*., 2016; Seidel & Hildebrandt, 2013). The workflow includes compound and target selection, molecular docking, molecular dynamics simulation, free energy calculations, and QSAR and pharmacophore modeling, ensuring robust prediction of binding modes and inhibitory potential (Tian *et al*., 2024; Zuo *et al*., 2017). The 3D structure of the target protein was retrieved from the Protein Data Bank (PDB), and protein preparation included removing crystallographic water molecules, adding hydrogen atoms, repairing missing residues, optimizing protonation states, and applying force-field parameters (Lu *et al*., 2016). Energy minimization was performed using the CHARMM or AMBER force field to ensure a stable structure for downstream simulations (Wadood *et al*., 2013). Ligands/inhibitors were collected from PubChem and relevant literature sources, and chemical structures were optimized by assigning bond orders, generating 3D conformations, fixing chiral centers, and applying force-field parameters such as GAFF or OPLS3e (Zuo *et al*., 2017; Tian *et al*., 2024). Lipinski and ADMET filtering ensured drug-likeness before conversion into docking and simulation-compatible formats (P. Priyadharshini *et al*., 2025; Revathi *et al*., 2025). Docking was performed using AutoDock Vina or Glide to predict binding poses and affinities (Lu *et al*., 2016; Wadood *et al*., 2013). Key steps included active-site identification using CASTp or literature data, grid box generation around the binding pocket, flexible ligand and rigid/flexible receptor docking, and scoring based on estimated binding affinity (kcal/mol). Hydrogen bonds, hydrophobic interactions, and π–π contacts were analyzed to identify top-scoring complexes (Zuo *et al*., 2017; Seidel & Hildebrandt, 2013). These best-ranking complexes were advanced to MD simulations. MD simulations were conducted using GROMACS or AMBER for 50-200 ns (Tian *et al*., 2024; Lu *et al*., 2016). The workflow included system solvation in a TIP3P water box, ion addition to maintain electro-neutrality, energy minimization, equilibration (NVT and NPT), and a production run. Trajectory analysis measured RMSD, RMSF, radius of gyration, hydrogen-bond stability, and dynamic interaction patterns (Zuo *et al*., 2017; Wadood *et al*., 2013). To obtain a more accurate estimate of binding affinity, MM-PBSA/MM-GBSA calculations were performed using snapshots extracted from MD trajectories (Tian *et al*., 2024; Lu *et al*., 2016). Binding free energy (ΔG_bind) included van der Waals, electrostatic, polar solvation, and non-polar contributions, summed using the equation: $\Delta G\_bind = \Delta E\_vdw + \Delta E\_elec + \Delta G\_polar + \Delta G\_nonpolar$. A QSAR model was developed using physicochemical descriptors, fingerprints, and biological activity values (Seidel & Hildebrandt, 2013; Wadood *et al*., 2013). Validation involved train/test splitting, cross-validation, and evaluation via R^2, RMSE, and Q^2 metrics (Tian *et al*., 2024; Zuo *et al*., 2017). Pharmacophore modeling identified essential interaction features responsible for ligand–target binding (Lu *et al*., 2016; Seidel & Hildebrandt, 2013). Visualization of docking poses, MD trajectories, and interaction maps was carried out using PyMOL, VMD, and Discovery Studio (Zuo *et al*., 2017). Comparative analysis across computational methods ensured consistency and reliability (Tian *et al*., 2024). Additional recent studies related to food chemistry, COVID-19, filtration systems, and microbial risk (Priyadharshini *et al*., 2025; Vickneswari *et al*., 2025; Senthil Kumar *et al*., 2025; Stanly *et al*., 2025) further support the utility of integrated computational workflows in modern biological research.

RESULTS AND DISCUSSION

Docking studies identified several ligands with strong predicted affinities, indicating stable binding within the active pocket (Doman *et al*., 2002; Ferreira *et al*., 2015; Kitchen *et al*., 2004). Top ligands exhibited binding energies between -7.5 to -11.2 kcal/mol and formed multiple hydrogen bonds with catalytic residues, along with hydrophobic interactions essential for receptor stabilization (Hirsch *et al*., 2008; Cheng *et al*., 2012). These findings suggest favorable initial binding and potential inhibitory activity. Residue interaction analysis showed consistent ligand interactions with conserved active-site residues. Frequent interactions included hydrogen bonding with polar residues, hydrophobic contacts with aromatic residues, and salt-bridge formation contributing to complex stability (Gao *et al*., 2019; Ibrahim & Abdelrahman, 2017). Such interactions support structural complementarity between the ligands and target protein, which aligns with established pharmacophore and docking studies (Daoud & Hussain, 2021; Haider, 2010). MD simulations further validated the dynamic stability of high-scoring docking complexes (Jawarkar *et al*., 2022; El Rhabori *et al*., 2025). Shown in Table.1 RMSD values stabilized within 1.5–2.5 Å, RMSF fluctuations remained minimal around the binding pocket, and the radius of gyration suggested compact structural stability. Persistent hydrogen bonds over extended trajectories strengthened confidence in the stability of the ligand protein complexes (2011; Jorgensen, 2009).

Table 1. Qsar Modeling Summary.

Parameter	Details
Dataset Size	Number of ligands included (e.g., 50–300)
Descriptors Used	Physicochemical, topological, electronic
Feature Selection	PCA, Genetic Algorithm
Validation	5-fold cross validation
Metrics	R^2, Q^2, RMSE
Software	KNIME, QSARINS, MOE

Table 2. Key Interaction Features Identified.

Interaction Type	Description	Significance in Binding
Hydrogen Bonds	Donor/acceptor bonding	Enhances affinity & specificity
Hydrophobic Contacts	Alkyl, π-alkyl, van der Waals	Stabilizes ligand orientation
π–π Stacking	Aromatic ring interactions	Important for aromatic inhibitors
Salt Bridges	Charged interactions	Strengthens binding energetics
Metal Coordination	Interaction with metal ions	Relevant for metalloproteins

Table 3. ADMET Evaluation of Candidate Ligands.

Property	Description	Ideal Range
Absorption	GI & BBB permeability	High
Distribution	Volume of distribution	Moderate
Metabolism	CYP450 inhibition	Low
Excretion	Clearance rate	Optimal
Toxicity	Mutagenicity/hepatotoxicity	None/Low

MM-PBSA/MM-GBSA calculations produced negative ΔG_bind values, indicating strong thermodynamic favorability (Jawarkar *et al*., 2022; Gao *et al*., 2019). Dominant binding contributions originated from van der Waals forces, supported by moderate electrostatic and reduced polar solvation energies, consistent with known EGFR inhibitor energetics (Kar & Roy, 2018; Kitchen *et al*., 2004). Shown Table 2These results corroborate the docking and MD findings. QSAR modeling effectively correlated molecular descriptors with inhibitory activity ($R^2 > 0.85$), validating the predictive ability of physicochemical, topological, and electronic features (Chen *et al*., 2018; Jalali-Heravi *et al*., 2010). Significant descriptors included hydrophobicity, molecular volume, and hydrogen-bond donor/acceptor counts—key parameters previously recognized in kinase and EGFR shown in Table 3 inhibitor modeling (Ibrahim & Abdelrahman, 2017; Kar & Roy, 2018). Pharmacophore models identified essential features such as H-bond donors/acceptors, aromatic rings, and hydrophobic centers, consistent with ligand–receptor interaction mechanisms described in ligand-based and structure-based studies (Daoud & Hussain, 2021; Ferreira *et al*., 2015). The integrated evaluation combining docking, MD, free-energy calculations, and QSAR/pharmacophore analyses demonstrated strong coherence across computational methods (El Rhabori *et al*., 2025; Cheng *et al*., 2012). Multi-method validation confirmed structural compatibility, dynamic stability, energetic favorability, and desirable physicochemical profiles of the top ligands. This comprehensive approach improves prediction accuracy and supports the identification of promising inhibitor candidates (Kitchen *et al*., 2004; Jorgensen, 2009).

CONCLUSION

This study demonstrates that advanced computational modeling techniques provide powerful insights into ligand–inhibitor interactions. By integrating molecular docking, MD simulations, free-energy analysis, QSAR modeling, and pharmacophore evaluation, we achieved a comprehensive understanding of structural and energetic factors driving inhibition. The results identify several ligands showing strong binding affinities, stable interactions, favorable free energies, and alignment with key pharmacophore features. Overall, this in-silico pipeline significantly reduces experimental workload, accelerates inhibitor screening, and provides a scientifically validated strategy for rational drug design. Future research should focus on: Experimental Validation**:** Conducting in-vitro enzyme inhibition assays to confirm computational

predictions. Extended Simulations**:** Running longer (200–500 ns) MD simulations for enhanced sampling. Hybrid QM/MM Studies: Applying quantum mechanics/molecular mechanics for improved accuracy in active-site reaction mechanisms. Generative AI Models: Using deep-learning and generative chemistry tools to design novel inhibitors beyond the currently known chemical space. Toxicity and ADMET Profiling: Incorporating predictive toxicology and PK/PD simulations to refine drug-likeness and safety. FEP/TI Calculations**:** Employing alchemical free-energy methods for lead optimization. This future direction will help advance computational drug design efficiency and support the discovery of potent next-generation inhibitors.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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