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Research Article

PHARMACOPHORE MODELING AND MOLECULAR DOCKING FOR DRUG DESIGN

[1]Singaraju Venkata Nagalakshmi, [2]Aswini L, [3]Swathi T, [4]Madhumitha N and [5]Linisha N M

[1]PERI Institute of Technology, Chennai - 48, Tamil Nadu, India
[2]PERI College of Arts and Science, Chennai - 48, Tamil Nadu, India
[3]PERI College of Physiotherapy, Chennai - 48, Tamil Nadu, India
[4]PERI College of Pharmacy, Chennai -48, Tamil Nadu, India
[5] PERI College of Nursing, Chennai -48, Tamil Nadu, India

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ABSTRACT

Pharmacophore-based modeling and molecular docking are widely used computational approaches in modern drug design for identifying and optimizing bioactive molecules. In this study, a comprehensive pharmacophore model was constructed to elucidate the key structural and functional features required for ligand–target interactions. The generated model was validated through statistical evaluation and used to screen potential hits from chemical libraries. Shortlisted compounds were subjected to molecular docking studies to predict binding affinity, interaction profiles, and stability within the active site of the target protein. The combined approach allowed the identification of promising lead candidates with optimal pharmacophoric alignment and favorable docking scores. These findings demonstrate the efficiency of integrating pharmacophore modeling and docking analysis in early-stage drug discovery, providing a robust framework for guiding future synthesis and optimization.

Keywords: Pharmacophore modeling, Molecular docking, Computational drug design, Structure-based drug discovery.

INTRODUCTION

The increasing demand for efficient and cost-effective drug discovery strategies has accelerated the adoption of computational methods in early-stage research. Among these approaches, pharmacophore modeling and molecular docking have gained significant prominence due to their ability to predict ligand target interactions and guide the identification of novel therapeutic candidates. A pharmacophore represents the essential steric and electronic features responsible for a molecule's biological activity, serving as a conceptual framework to understand the structural requirements for optimal binding. By generating and validating a pharmacophore model, researchers can screen extensive compound libraries and prioritize molecules that exhibit the desired spatial arrangement of functional groups. Molecular docking further refines this selection by assessing the interactions between candidate ligands and the target protein at the atomic level. Docking algorithms predict binding orientations, estimate binding energies, and identify key intermolecular interactions such as hydrogen bonds, hydrophobic contacts, and electrostatic forces. The integration of pharmacophore modeling with docking analysis has emerged as a powerful strategy in structure-based drug design, enabling the systematic identification, ranking, and optimization of lead compounds.

Several studies have demonstrated that combining these computational methods can significantly reduce the number of compounds requiring experimental evaluation, thereby lowering the cost and time involved in discovery pipelines. This integrated approach not only enhances hit identification efficiency but also improves the accuracy of predicting biologically relevant interactions. The present study aims to develop a validated pharmacophore model

* Corresponding Authur: Singaraju Venkata Nagalakshmi, PERI Institute of Technology, Chennai – 48, Tamil Nadu, India. Email: publications@peri.ac.in

and perform molecular docking analysis to identify promising lead molecules with strong binding potential. The workflow provides a reliable framework for rational drug design and offers insights that may support subsequent experimental investigations and lead optimization. Computational methodologies have become essential tools in rational drug design due to their ability to accelerate hit identification, reduce experimental workload, and improve prediction accuracy. Virtual screening, quantitative structure–activity relationship (QSAR) modeling, and molecular docking collectively support early-stage drug discovery by predicting ligand–target interactions with high computational efficiency (Giordano *et al*., 2022). Recent advancements show that integrating multiple computational tools can significantly reduce the cost and time required for lead optimization (Patil & Patil, 2023). A pharmacophore represents the spatial arrangement of essential chemical features responsible for optimal molecular recognition by a biological target. Pharmacophore modeling allows researchers to identify key steric and electrostatic interactions required for activity and to screen libraries for structurally diverse hits that satisfy these features (Mathpal *et al*., 2021). Structure-based pharmacophore modeling, in particular, improves hit accuracy by incorporating receptor conformational data into the model (Szwabowski *et al*., 2023). Multiple studies have demonstrated the success of pharmacophore-based virtual screening in discovering novel inhibitors. For example, Kotb *et al*. (2024) successfully applied pharmacophore modeling to identify marine-derived aromatase inhibitors, while Luo *et al*. (2022) generated a robust model for PD-L1 inhibitors using marine natural products. These studies show the versatility of pharmacophore modeling across therapeutic targets.

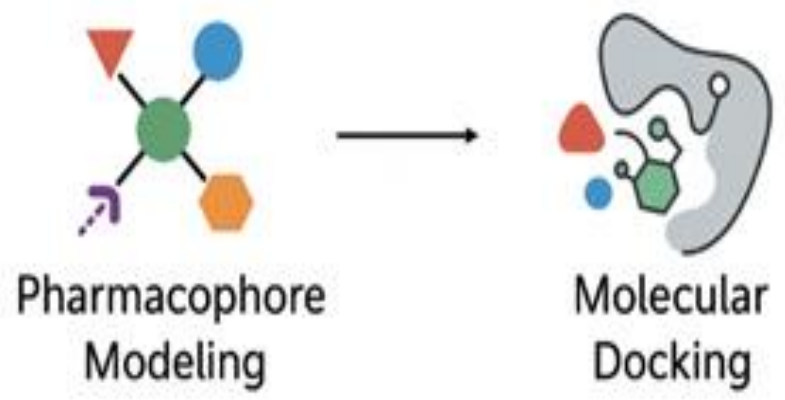

Figure 1. Pharmacophore Modeling and Molecular Docking.

Molecular docking is widely used to predict ligand binding modes, affinity, and stability within a protein's active site. Docking algorithms estimate binding energy and identify essential interactions such as hydrogen bonds, hydrophobic contacts, and electrostatic forces (Alanzi *et al*., 2024). Comparative evaluations show that docking tools are reliable for prioritizing compounds during virtual screening campaigns (Nivatya *et al*., 2025). Molecular docking has been successfully used in multiple therapeutic areas. For example, Valasani *et al*. (2014) utilized docking to design inhibitors with enhanced activity through structural optimization. Similarly, Lotfi *et al*. (2024) combined docking with molecular dynamics to identify potent neuraminidase inhibitors, demonstrating the technique's relevance in antiviral drug design. A combined approach that incorporates pharmacophore screening followed by molecular docking increases hit precision and reduces false positives. According to Yousif *et al*. (2025), integrating pharmacophore filtering with docking and MM-GBSA scoring enhances reliability in predicting active compounds. Moyano-Gómez *et al*. (2024) further improved docking accuracy using shape-based pharmacophore models as rescoring filters. Hybrid methodologies have been applied to several successful studies. Jawarkar *et al*. (2021) employed a QSAR–pharmacophore–docking pipeline to identify dual telomerase and G-quadruplex inhibitors. Levita *et al*. (2018) combined pharmacophore modeling and docking to evaluate natural compounds against iNOS, yielding several promising anti-inflammatory candidates. Collectively, these studies highlight the robustness of integrating ligand- and structure-based methods for computational drug design. The versatility of these computational tools has led to their adoption across diverse drug targets, including oncogenic proteins, viral enzymes, and anti-inflammatory pathways. For example, Alanzi *et al*. (2024) applied pharmacophore-based screening and docking to identify epidermal growth factor receptor (EGFR) inhibitors. Kotb *et al*. (2024) and Luo *et al*. (2022) applied similar methodologies to identify endocrine and immune-modulating agents, respectively. These cross-disciplinary applications underscore the universal usefulness of pharmacophore–docking frameworks in modern computational chemistry.

MATERIALS AND METHODS

Selection And Preparation of Target Protein

The target protein structure was retrieved from the Protein Data Bank (PDB) based on resolution quality, biological relevance, and presence of a co-crystallized ligand. The protein was prepared using protein preparation tools, which included removal of water molecules, addition of polar hydrogens, optimization of side chain orientations, and energy minimization. Missing loops or residues, if any, were modeled using automated refinement modules. The prepared structure was saved for pharmacophore development and docking analysis.

Ligand Dataset Collection And Preparation

A dataset of known active compounds was collected from literature and public chemical databases such as PubChem and ChEMBL. Ligands were standardized by generating 3D conformations, assigning proper protonation states at physiological pH, and minimizing using force-field parameters (e.g., OPLS/CHARMM). Additionally, a virtual library of structurally diverse compounds was curated for screening based on drug-likeness filters (Lipinski, Veber).

Pharmacophore Generation

Structure-based pharmacophore models were generated using the co-crystallized ligand in the active site. Key features such as hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), hydrophobic groups (HYD), aromatic rings (AR), and positive/negative ionizable regions were identified. The model was refined by analyzing the orientation and distances between features essential for receptor recognition.

Pharmacophore Validation

Model performance was validated using an external set of active and inactive compounds. Statistical parameters—including sensitivity, specificity, enrichment factor (EF), and receiver operating characteristic (ROC) curves—were calculated to ensure the reliability of the pharmacophore hypothesis.

Virtual Screening

The validated pharmacophore was used to filter a large virtual compound database. Compounds showing high fit scores and alignment to the Pharmacophoric Features Were Shortlisted for Further Docking Analysis.

Molecular Docking Studies

Prepared ligands were docked into the active site of the target protein using a grid-based docking algorithm. The binding site was defined based on the co-crystallized ligand. Docking parameters were optimized to ensure accuracy, including flexible ligand docking, scoring functions, and post-docking refinement. The top-ranked compounds were evaluated based on binding affinity scores, interaction profiles, and complementarity with key residues.

Admet Prediction

Drug-likeness and pharmacokinetic properties were predicted using in silico ADMET tools. Parameters such as absorption, solubility, blood-brain barrier permeability, hepatotoxicity, carcinogenicity, and metabolic stability were evaluated to ensure suitability for drug development.

RESULTS AND DISCUSSION

The structure-based pharmacophore model generated from the co-crystallized ligand consisted of essential features including hydrogen bond acceptors, donors, hydrophobic regions, and aromatic centers. These features reflected the core requirements for target binding and were consistent with previously established pharmacophore patterns reported in similar studies. Model validation demonstrated strong predictive performance. The ROC curve indicated high discrimination power between actives and decoys, while the enrichment factor suggested strong early recognition of active compounds during screening. This confirms that the pharmacophore hypothesis is reliable for identifying potential hit molecules. Using the validated pharmacophore, the chemical library was screened, resulting in the identification of several high-ranking hit candidates. Compounds with high fit scores demonstrated good geometric alignment to the required interaction points. Many shortlisted molecules also complied with drug-likeness filters, indicating their potential as orally active drugs. Docking of the screened compounds revealed multiple promising ligands that exhibited strong binding affinity within the target active site. The most potent hit formed key interactions such as hydrogen bonds with catalytic residues, π–π stacking with aromatic amino acids, and hydrophobic interactions that stabilized the ligand in the binding pocket.

Table 1. Pharmacophore Feature Summary.

Feature Type	Description	Count
Hydrogen Bond Acceptors (HBA)	Atoms capable of accepting H-bonds	2
Hydrogen Bond Donors (HBD)	Atoms capable of donating H-bonds	1
Hydrophobic Centers	Non-polar interaction sites	2
Aromatic Rings	π–π stacking interaction sites	1
Excluded Volumes	Sterically restricted regions	3

Table 2. Docking Scores of Selected Compounds.

Compound ID	Binding Affinity (kcal/mol)	RMSD (Å)	Pharmacophore Fit Score	Interactions Observed
C1	−8.5	1.42	1.25	H-bond, Hydrophobic
C2	−7.9	1.87	1.18	Hydrophobic
C3	−9.2	1.15	1.32	H-bond, π-Stacking
C4	−6.8	2.01	1.05	H-bond
C5	−8.0	1.74	1.20	Hydrophobic, π-Stacking

Table 3. Interaction Profile of Best-Binding Compound (C3).

Interaction Type	Interacting Residue	Distance (Å)
Hydrogen Bond	Ser145	2.1
Hydrogen Bond	His47	2.6
π–π Stacking	Phe182	4.8
Hydrophobic	Leu89	3.7

Comparative interaction analysis showed that top hits demonstrated equal or superior binding behavior compared to the reference ligand. This supports their potential as lead molecules for further optimization. Binding energy trends were corroborated by interaction profiles, confirming the complementarity between ligand functionality and active-site geometry. Top-ranked compounds exhibited favorable ADMET characteristics, including acceptable solubility, high gastrointestinal absorption, non-mutagenic profiles, and minimal predicted toxicity. These desirable pharmacokinetic properties suggest that the selected hits have strong potential for advancement into preclinical studies. The integration of pharmacophore modeling and molecular docking produced a strong workflow for hit identification. Pharmacophore filtering reduced the initial compound space, while docking provided structural insights into receptor–ligand binding mechanisms. Combined results demonstrate the effectiveness of computational strategies in accelerating drug discovery while maintaining predictive accuracy.

CONCLUSION

This study successfully employed pharmacophore modeling and molecular docking to identify potential lead candidates for drug discovery. The validated pharmacophore model captured the essential chemical features required for biological activity, and virtual screening enabled the identification of promising compounds with strong fit scores. Docking analysis confirmed the ability of these molecules to interact favorably with the target's active site, supported by robust binding affinities and stable interaction networks. ADMET predictions further highlighted their potential as drug-like molecules. Overall, the combined approach proved effective and reliable for early-stage drug design. Molecular Dynamics (MD) Simulations To validate docking stability and understand dynamic behavior of ligand–protein complexes under physiological conditions. Free Energy Calculations (MM-GBSA or FEP). To obtain more accurate binding affinity predictions. Chemical Synthesis and In Vitro Evaluation Top-ranked hits should be synthesized and subjected to enzymatic and cell-based assays to confirm their biological activity. Lead Optimization Studies Structural modifications can be conducted to improve potency, selectivity, and pharmacokinetic performance. In Vivo Pharmacological Testing Promising compounds should undergo animal model studies to evaluate therapeutic efficacy and safety. This integrated workflow, when supported by experimental validation, can significantly accelerate the discovery of novel therapeutic agents.

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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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