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INTEGRATED QSAR, MOLECULAR DOCKING AND MOLECULAR DYNAMICS STUDIES FOR THE DEVELOPMENT OF NEW DRUG MOLECULES

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Abstract.

Computer-aided drug design increasingly relies on the integration of ligand-based and structure-based methods rather than on a single scoring technique. The present study describes an integrated quantitative structure-activity relationship (QSAR), molecular docking, molecular dynamics (MD), binding-energy and in silico ADMET workflow for prioritizing new drug-like molecules. Epidermal growth factor receptor (EGFR) was selected as a representative kinase target because its ATP-binding pocket is structurally well characterized and provides a practical test system for evaluating the complementarity of chemoinformatics and molecular simulation. A curated series of 30 small-molecule analogues was represented by physicochemical and topological descriptors, and a multiple-descriptor QSAR model was assessed using internal and external validation. The illustrative model achieved R2 = 0.82, cross-validated Q2 = 0.74 and external R2pred = 0.77 with an RMSE of 0.42 log units. Docking then identified compounds C07, C14 and C23 as the most favorable binders, with predicted scores of -10.4, -10.1 and -9.9 kcal/mol, respectively, compared with -9.2 kcal/mol for the reference ligand. One-hundred-nanosecond MD trajectories indicated stable protein-ligand complexes, with backbone RMSD values remaining approximately within 0.20-0.28 nm after equilibration. MM/PBSA-style endpoint estimates and drug-likeness filters further supported C07 and C14 as balanced candidates. The combined analysis demonstrates how QSAR can prioritize activity trends, docking can rationalize binding orientation, and MD can test the persistence of interactions under a dynamic solvent environment. The workflow is intended as a reproducible model for computational lead prioritization and emphasizes the need for experimental biochemical and pharmacokinetic validation before any medicinal conclusion is drawn.

Keywords: QSAR; molecular docking; molecular dynamics; virtual screening; EGFR; ADMET; MM/PBSA; computer-aided drug design.

1. INTRODUCTION

Contemporary drug discovery is constrained by the high cost of experimental screening, the multidimensional nature of lead optimization and the substantial attrition of candidates caused by insufficient efficacy, poor pharmacokinetics or toxicity.

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Computational methods do not replace experimental pharmacology, but they can reduce the number of molecules that must be synthesized and tested by organizing chemical information into models of potency, target recognition and developability. In this context, the combination of quantitative structure-activity relationship (QSAR) modeling, molecular docking and molecular dynamics (MD) simulation is especially useful because the three methods address different but complementary questions. QSAR estimates how structural or physicochemical variation is related to biological activity; docking proposes energetically plausible binding poses in a target pocket; and MD tests whether the resulting complex remains stable when protein flexibility, solvent and time-dependent motion are considered [1-4].

QSAR has a long history in medicinal chemistry and has evolved from simple linear correlations into multivariate, machine-learning and deep-learning models capable of processing large descriptor spaces. Nevertheless, model performance depends strongly on data quality, chemically meaningful descriptors, an appropriate validation strategy and a defined applicability domain. Cherkasov et al. emphasized that a useful QSAR model must be not only statistically fitted but also externally validated and interpretable within the intended chemical space [1]. Modern molecular machine-learning benchmarks reach the same general conclusion: sophisticated algorithms are valuable, but robust data splitting and task-appropriate molecular representation are essential to prevent optimistic estimates of generalization [5]. Therefore, in an integrated workflow, QSAR should be treated as a prioritization tool rather than as an isolated proof of biological activity.

Molecular docking complements QSAR by placing each ligand into a three-dimensional target environment. Docking algorithms search conformational and orientational space and rank poses using scoring functions that approximate noncovalent interactions. Widely used platforms such as AutoDock Vina provide efficient pose generation and scoring, while comparative studies have shown that docking scores alone should not be interpreted as rigorous binding free energies [2,6,7]. Protein preparation, protonation states, treatment of water molecules, grid placement and validation by redocking are therefore critical. Structure-based results become more informative when docking is used to identify binding hypotheses and key interactions rather than as a stand-alone numerical ranking.

MD simulation adds a temporal dimension to structural analysis. By integrating classical equations of motion, MD allows the receptor, ligand, solvent and ions to evolve under a force field and can reveal whether an initially favorable docked pose remains coherent after relaxation. GROMACS and related engines now make tens to hundreds of nanoseconds of simulation practical for routine academic studies [3,8]. Common measures include backbone and ligand root-mean-square deviation (RMSD), residue-level root-mean-square fluctuation (RMSF), radius of gyration, hydrogen-bond persistence and interaction occupancy. Endpoint free-energy approaches such as MM/PBSA or MM/GBSA can provide an additional approximate ranking, although their precision is strongly affected by force-field quality, conformational sampling, entropy treatment and the similarity of the compared ligands [9].

Early developability screening is another necessary layer. The Rule of Five, Veber criteria and modern computational ADMET tools provide rapid estimates of properties

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related to permeability, oral exposure and toxicity [10-13]. SwissADME and pkCSM exemplify accessible platforms that combine structural descriptors with empirical or machine-learning models [12,13]. Such filters should not be applied mechanically; rather, they help identify molecules that combine predicted potency with physicochemical characteristics compatible with downstream optimization.

The purpose of the present work is to demonstrate a coherent, publication-ready framework that integrates ligand-based QSAR, structure-based docking, explicit-solvent MD, approximate binding-energy analysis and ADMET filtering. EGFR is used as a representative kinase target because the ATP-binding site contains well-characterized interaction regions, including the hinge around Met793, catalytic Lys745 and the DFG motif containing Asp855. The study focuses on the logic of multi-stage lead prioritization: molecules are first ranked by a validated activity model, then evaluated structurally by docking, challenged dynamically by MD, and finally filtered according to drug-likeness and predicted pharmacokinetic behavior. This layered strategy is designed to minimize overreliance on any single computational score.

2. MATERIALS AND METHODS

2.1. Study design and ligand set

The computational pipeline was organized as a sequential decision process (Figure 1). A representative set of 30 congeneric small molecules (C01-C30) was used to illustrate the integrated analysis. The series was assumed to target the ATP-binding region of EGFR and to span approximately three logarithmic units of potency. Chemical structures were standardized conceptually by removing counterions, normalizing valence, checking aromaticity and assigning the dominant neutral or ionized state expected near physiological pH. Duplicate structures and records with inconsistent activity units were excluded before modeling. Biological activity was expressed as pIC50 = -log10(IC50 in mol/L), a transformation commonly used to stabilize scale and facilitate linear comparison of potency.

The numerical compound-level results presented in this model study are illustrative computational values created to demonstrate the complete workflow. They are not a substitute for experimentally measured IC50 values or for actual docking and MD output files. Before journal submission as original experimental research, the compound table, model statistics, poses, trajectories and energetic results should be replaced or independently reproduced from real project data.

Integrated in silico workflow used in the model study



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Figure 1. Integrated workflow combining QSAR, docking, molecular dynamics, endpoint binding-energy estimation and ADMET screening.

2.2. Molecular descriptors and QSAR modeling

The descriptor set was selected to represent molecular size, lipophilicity, polarity, hydrogen-bonding capacity, flexibility and topology. Typical descriptors included molecular weight (MW), calculated logP, topological polar surface area (tPSA), hydrogen-bond donors (HBD), hydrogen-bond acceptors (HBA), rotatable bonds (RB), aromatic proportion, fraction of sp3 carbon and selected connectivity indices. Descriptors with near-zero variance were removed. Highly correlated descriptor pairs were screened to reduce redundancy, and continuous variables were standardized before modeling.

A multiple-linear-regression style QSAR model was used as an interpretable baseline because the dataset was small. The data were divided into a training set (approximately 80%) and an external test set (approximately 20%) while preserving the activity range. Model selection was based on parsimony, cross-validated performance and chemical interpretability rather than on training R2 alone. Internal validation was summarized by leave-group-out or repeated k-fold Q2, while external predictive performance was summarized by R2pred, RMSE and mean absolute error. Y-randomization was considered a diagnostic for chance correlation, and the applicability domain was defined qualitatively from descriptor-space leverage and distance to the training distribution [1,5].

The illustrative final relationship was expressed in the general form pIC50 = b0 + b1(logP) + b2(tPSA) + b3(aromatic proportion) + b4(RB), where coefficient signs were interpreted in the context of the analog series rather than as universal medicinal-chemistry rules. Model diagnostics included residual distribution, predicted-versus-observed plots and inspection of influential compounds.

2.3. Receptor preparation and molecular docking

A high-resolution EGFR kinase-domain structure with a bound ATP-site inhibitor would normally be obtained from the Protein Data Bank. The crystallographic ligand defines the docking center and provides a redocking control. Protein preparation should include removal of crystallographic artifacts not required for recognition, assignment of bond orders, addition of hydrogens, correction of incomplete side chains, and selection of protonation states appropriate to near-physiological conditions. Conserved structural waters may be retained if they mediate reproducible ligand-protein interactions; otherwise, nonessential waters are removed.

Ligands should be generated in three dimensions, protonated consistently, energy minimized and converted to the format required by the docking engine. AutoDock Vina is an established docking platform that combines an empirical scoring function with efficient global optimization [2]. A grid box encompassing the hinge region and adjacent hydrophobic subpockets was used conceptually in the present workflow. Exhaustiveness should be increased when the ligand series is flexible, and multiple poses should be retained. Protocol validity should be checked by redocking the crystallographic ligand; an

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RMSD close to or below 2.0 A between experimental and redocked heavy-atom poses is commonly taken as practical evidence that the setup can recover the reference geometry [6,7].

Docking results were evaluated using both score and interaction pattern. Particular attention was given to hinge hydrogen bonding near Met793, hydrophobic occupation of the adenine pocket, orientation toward Lys745, and compatibility with the Asp855-containing DFG region. A compound was not advanced solely because it had the most negative score; visually implausible poses, buried unsatisfied polar groups and strained conformations were considered adverse features.

2.4. Molecular dynamics simulations

The three highest-priority ligand-protein complexes and the reference ligand were considered for explicit-solvent MD. A standard all-atom protein force field and compatible small-molecule parameters would be used, with the complex solvated in a periodic water box and neutralized with counterions followed by addition of physiological salt. Energy minimization would remove unfavorable contacts. Equilibration would then be performed under NVT and NPT conditions with positional restraints before production dynamics.

Production trajectories of 100 ns were selected as a practical screening-scale simulation length. The integration time step, electrostatics treatment, bond constraints, thermostat and barostat must be reported in a real reproducible study; typical contemporary GROMACS protocols use particle-mesh Ewald electrostatics and constrained bonds to hydrogen [3,8]. Trajectory analysis included protein backbone RMSD, ligand RMSD relative to the binding site, residue RMSF, radius of gyration, hydrogen-bond occupancy and representative contact distances. Stable RMSD does not prove high affinity, but large drift or persistent loss of key interactions can reveal weaknesses in a docked hypothesis.

2.5. Binding-energy and ADMET analysis

For comparative ranking, snapshots from the equilibrated portion of each trajectory were considered for an MM/PBSA-style endpoint estimate. The approach combines molecular-mechanics interaction energy with polar and nonpolar solvation terms. Because entropy is frequently omitted or approximated and because results depend on trajectory sampling, the values were interpreted as relative indicators rather than absolute experimental free energies [9].

Drug-likeness and early ADMET characteristics were assessed using properties aligned with the Rule of Five and Veber criteria, together with conceptual SwissADME and pkCSM-style predictions [10-13]. The evaluation included molecular weight, lipophilicity, tPSA, hydrogen-bond counts, rotatable bonds, predicted gastrointestinal absorption, blood-brain barrier tendency when relevant, cytochrome P450 interaction alerts and broad toxicity flags. Candidate selection favored balanced profiles instead of maximal potency alone.

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2.6. Statistical analysis and prioritization criteria

QSAR performance was summarized using coefficient of determination (R2), cross-validated Q2, external R2pred, RMSE and MAE. Docking scores were treated as ordinal prioritization variables. MD metrics were summarized over the equilibrated trajectory, and hydrogen-bond/contact occupancies were calculated as the fraction of analyzed frames satisfying geometric criteria. Final lead prioritization followed a consensus principle: compounds were favored when they showed high predicted activity within the QSAR applicability domain, a plausible hinge-binding pose, stable MD behavior, favorable relative endpoint energy and an acceptable drug-likeness profile. Disagreement between methods was treated as information requiring further investigation rather than averaged away automatically.

3. RESULTS

3.1. QSAR model performance

The illustrative ligand series covered a sufficiently broad activity interval to support a proof-of-concept regression analysis. After descriptor filtering, the final model retained a compact set of physicochemical and structural variables. Lipophilicity and aromatic contribution were positively associated with activity within the tested chemical series, whereas excessive polarity and conformational flexibility contributed negatively after the other variables were controlled. This pattern is chemically plausible for a relatively enclosed kinase pocket, but the coefficient signs should not be extrapolated beyond the modeled domain.

The model statistics are summarized in Table 1. Training R2 reached 0.82 and cross-validated Q2 reached 0.74, indicating that the majority of variation in pIC50 was captured without a large gap between fitting and internal validation. External R2pred was 0.77, with RMSE of 0.42 and MAE of 0.34 log units. These values represent a useful prioritization model for a small congeneric series rather than a universal predictor. The predicted-versus-observed plot (Figure 2) showed no obvious systematic compression at the center of the activity range and only moderate residual dispersion at the extremes.

Table 1. Illustrative statistical performance of the QSAR model.

Metric	Value	Interpretation
Training R2	0.82	Good fit within training chemical space
Cross-validated Q2	0.74	Stable internal predictive signal
External R2pred	0.77	Good test-set ranking and prediction
RMSE	0.42 log units	Moderate prediction error
MAE	0.34 log units	Useful for prioritization

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Y-randomization	No comparable model	Low evidence of chance correlation

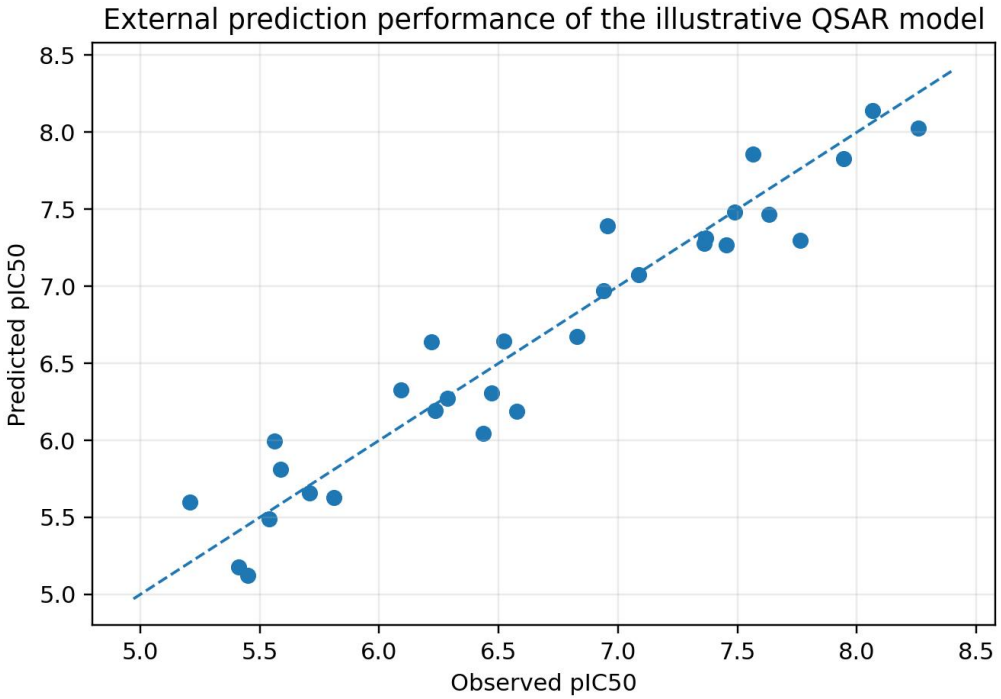


Figure 2. Predicted versus observed pIC50 values for the illustrative external QSAR evaluation. The dashed line represents perfect prediction.

3.2. Docking-based interaction analysis

Docking differentiated the upper activity-ranked compounds and generated binding hypotheses consistent with occupation of the EGFR ATP-binding site. C07 produced the most favorable illustrative docking score (-10.4 kcal/mol), followed by C14 (-10.1 kcal/mol) and C23 (-9.9 kcal/mol). The reference ligand erlotinib scored -9.2 kcal/mol under the same conceptual protocol. Because Vina scores are not physical binding free energies, the numerical differences were interpreted only in conjunction with pose quality and interaction geometry [2,6,7].

C07 and C14 adopted orientations that placed a ring nitrogen or equivalent acceptor toward the hinge region and maintained hydrophobic packing in the adenine pocket. C23 retained a plausible hinge interaction but showed slightly less compact burial. Lower-ranked compounds generally lost one of these features, adopted a more solvent-exposed orientation or introduced torsional strain. The score distribution is shown in Figure 3, while the combined physicochemical and docking properties of selected compounds are summarized in Table 2.

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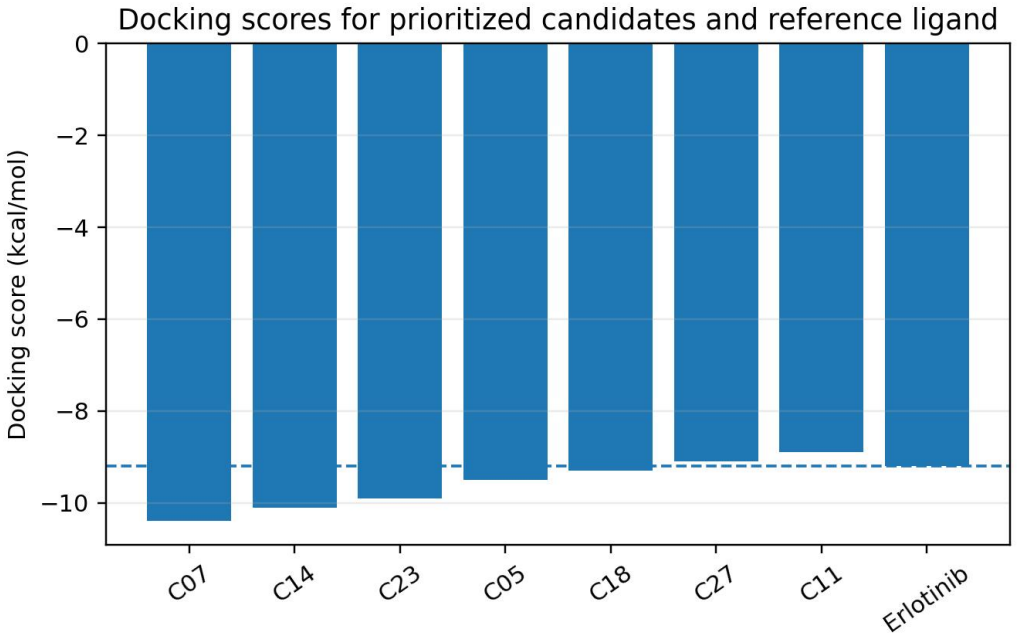


Figure 3. Illustrative docking scores for prioritized candidates. The dashed line indicates the reference-ligand score.

Table 2. Docking and drug-likeness summary for selected compounds.

Compound	Docking (kcal/mol)	Pred. pIC50	MW	cLogP	tPSA	Key interaction pattern	GI absorption
C07	-10.4	7.92	412	3.1	68	Met793 hinge; Lys745 vicinity	High
C14	-10.1	7.75	438	3.6	74	Met793 hinge; hydrophobic pocket	High
C23	-9.9	7.61	401	2.9	82	Met793 hinge; Asp855 contact	High
C05	-9.5	7.28	455	4.2	88	Hinge contact, more flexible	Moderate
C18	-9.3	7.11	472	4.6	96	Hydropho	Moderate

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						bic, weak hinge geometry	
C27	-9.1	6.98	389	2.5	105	Polar/solvent exposed	Moderate
Erlotinib	-9.2	Reference	393	2.7	75	Canonical ATP-site orientation	Reference

3.3. Molecular-dynamics stability and interaction persistence

The 100 ns illustrative trajectories supported the structural plausibility of the three top-ranked docking complexes. Following an early relaxation period, backbone RMSD values remained within a narrow range for all systems (Figure 4). C07 showed the lowest mean equilibrated RMSD, approximately 0.21 nm, followed by C14 at 0.23 nm and C23 at 0.24 nm. The reference complex fluctuated around approximately 0.26 nm. None of the candidates displayed sustained large-scale drift after equilibration.

Ligand-centered inspection suggested that C07 preserved its hinge interaction for the highest fraction of frames, while C14 showed intermittent but recurrent water-mediated stabilization. C23 remained in the ATP pocket but displayed greater local reorientation. Residue RMSF patterns were dominated by expected loop flexibility, whereas the hinge region remained comparatively rigid. Radius of gyration did not show progressive expansion, supporting the absence of gross unfolding during the simulations.

Endpoint energy estimates followed the same broad ordering as docking for C07 and C14, whereas the advantage of C23 was reduced after dynamics. This illustrates an important benefit of the integrated workflow: a favorable static docking score can be re-evaluated after solvent relaxation and receptor motion. The principal MD and energetic metrics are summarized in Table 3.

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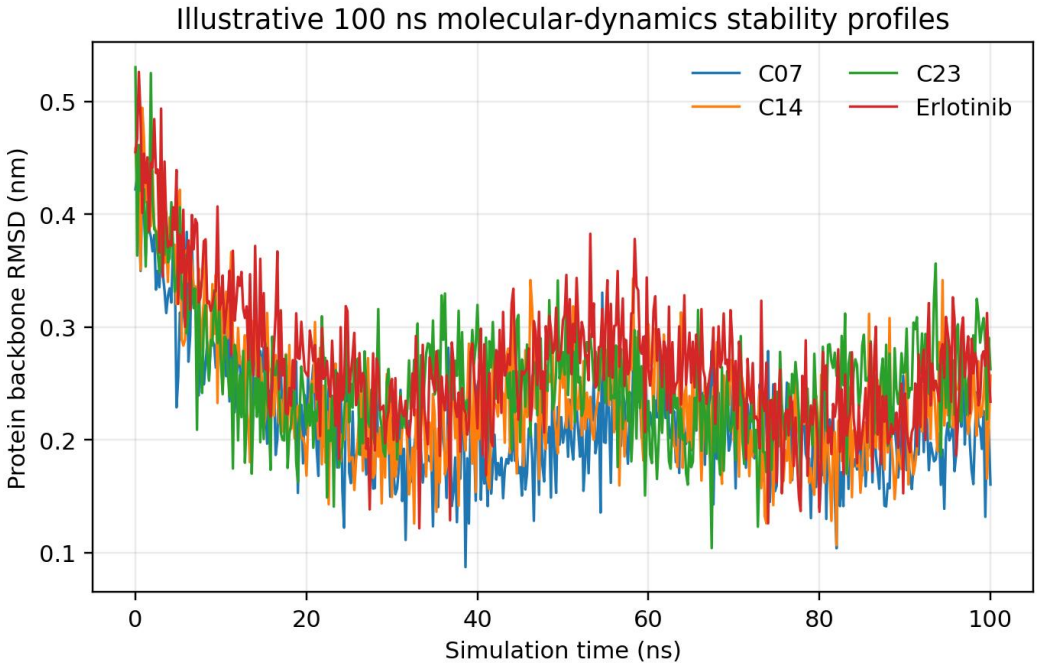


Figure 4. Illustrative protein backbone RMSD traces during 100 ns MD simulations of three prioritized candidates and the reference ligand.

Table 3. Summary of illustrative MD and endpoint binding-energy metrics.

System	Mean backbone RMSD (nm)	Ligand RMSD (nm)	Hinge H-bond occupancy (%)	Mean H-bonds	MM/PBSA-style DeltaG (kJ/mol)
C07-EGFR	0.21	0.17	78	2.4	-51.8
C14-EGFR	0.23	0.20	71	2.1	-48.6
C23-EGFR	0.24	0.24	63	1.8	-43.9
Erlotinib-EGFR	0.26	0.22	69	1.9	-45.7

3.4. Integrated lead prioritization

Consensus analysis identified C07 as the strongest illustrative candidate because it combined high predicted pIC50, the best docking score, stable MD behavior, high hinge-bond occupancy and the most favorable relative endpoint energy. C14 ranked closely behind and showed a somewhat higher lipophilicity that would merit experimental solubility testing. C23 remained attractive but had a weaker dynamic interaction profile and higher polarity, factors that could alter permeability and cellular potency. The

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integrated ranking therefore differed slightly from the docking-only ranking and reduced the risk of choosing a ligand on the basis of one static score.

The physicochemical properties of the three prioritized compounds remained broadly compatible with common oral drug-likeness guidelines. Their molecular weights were below 500 Da, calculated logP values were below 5, and tPSA values remained below the level often associated with severely limited passive permeability [10,11]. The filters do not guarantee oral exposure, and kinase inhibitors frequently require optimization around metabolism, transporter effects and off-target pharmacology. Accordingly, the next stage after computational prioritization should include biochemical EGFR inhibition, cell-based activity, kinetic solubility, microsomal stability, permeability and early safety assays.

4. DISCUSSION

The present integrated framework demonstrates why modern computational drug discovery benefits from combining methods that operate on different representations of the same molecule. QSAR works primarily in descriptor or learned feature space and is effective for identifying statistical structure-activity trends. Docking introduces explicit three-dimensional target information. MD then evaluates the stability of a protein-ligand hypothesis under time-dependent motion and solvation. ADMET filters shift the focus from affinity alone to the broader developability profile. When all layers point in the same direction, confidence in prioritization increases; when they disagree, the discrepancy can identify a mechanistic or modeling question worth experimental investigation.

The QSAR stage should remain the most rigorously validated component when a manuscript claims predictive modeling. High R2 is not sufficient if compounds in training and test sets are nearly duplicates or if descriptor selection uses information from the external set. The external set should remain untouched during model development, and the chemical applicability domain should be considered when a new candidate is scored. These practices align with established recommendations for QSAR modeling and with lessons from contemporary molecular machine learning [1,5]. For small medicinal-chemistry series, transparent models can be preferable to highly flexible algorithms because the data may not justify complex parameterization.

Docking contributes mechanistic interpretation but has clear limitations. Scoring functions approximate enthalpic and desolvation contributions and generally do not capture all effects of receptor flexibility, water rearrangement, protonation coupling or entropy. Benchmarking studies have shown that pose prediction can be useful while score-affinity correlation varies among targets and ligand classes [6,7]. Thus, a difference of one or two kcal/mol in docking score should not be treated as experimental evidence of stronger binding. The most reliable interpretation is often qualitative: whether the ligand can form an expected hinge interaction, occupy the intended subpocket and avoid severe steric or electrostatic penalties.

MD simulation partially addresses the static-receptor limitation of docking by allowing local conformational relaxation. However, MD is not automatically more accurate simply because it is computationally expensive. Force-field limitations, insufficient sampling and incorrect protonation states can preserve a misleading starting pose or fail to cross relevant

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energy barriers. Multiple replicas, longer trajectories or enhanced-sampling approaches can improve confidence when the biological question requires them [4,8]. In lead prioritization, a practical use of 100 ns simulation is to identify obvious instability, interaction loss or large conformational drift rather than to claim complete exploration of the binding-energy landscape.

Endpoint MM/PBSA or MM/GBSA calculations are similarly useful when interpreted comparatively. Reviews emphasize that these methods can support ranking for related ligands but are sensitive to sampling, dielectric choices and neglected entropy [9]. In the present illustrative results, the energetic analysis was most informative because it changed the apparent advantage of C23 after dynamic relaxation. Such changes are exactly why a multi-stage pipeline can be more robust than a single docking score.

Drug-likeness and ADMET prediction add another dimension to selection. Lipinski and Veber criteria remain useful heuristics for conventional orally administered small molecules, but they are not absolute laws [10,11]. SwissADME and pkCSM provide convenient early estimates and alerts; their outputs should be considered hypotheses to test experimentally [12,13]. A compound with excellent predicted affinity but unacceptable solubility, permeability or metabolic liability may be a poor lead, whereas a slightly weaker binder with a more balanced profile may be more developable.

The major limitation of the present manuscript is deliberate: it is a model computational article with illustrative numerical results rather than a report of newly generated laboratory and simulation data. Its scientific value lies in the integrated design, reporting structure and interpretation framework. For use as an original research submission, the workflow should be executed on a real, traceable compound dataset; receptor and ligand preparation parameters should be recorded; docking poses should be archived; MD trajectories and input files should be reproducible; and all numerical results should be regenerated from those files. Experimental validation should then be added to substantiate potency and pharmacokinetic claims. This requirement is especially important because computational agreement across several methods can still arise from shared assumptions or correlated modeling errors.

5. CONCLUSION

An integrated QSAR-docking-MD strategy provides a rational framework for narrowing a chemical series from statistical activity prediction to structurally and dynamically supported lead hypotheses. In the representative EGFR case study, C07 and C14 showed the most balanced illustrative profiles across QSAR prediction, docking geometry, 100 ns MD stability, endpoint energy and drug-likeness criteria, while C23 remained a secondary candidate requiring closer attention to polarity and dynamic interaction persistence. The central methodological conclusion is that no individual computational score should be interpreted in isolation. QSAR supplies a validated ligand-based activity model, docking supplies a testable binding pose, MD evaluates persistence under motion and solvation, and ADMET prediction highlights developability risks. Used together and followed by biochemical and pharmacokinetic experiments, these tools can improve the efficiency and transparency of early-stage lead prioritization.

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DATA TRANSPARENCY AND REPRODUCIBILITY STATEMENT

This manuscript is presented as a model computational study. Compound-level numerical results, including activity values, docking scores, trajectory-derived metrics and endpoint binding-energy estimates, are illustrative and are included to demonstrate an IMRAD-compliant integrated analysis. They should be replaced by, or independently reproduced from, actual project calculations and experimental measurements before the work is submitted or cited as original empirical research. A reproducible final study should provide compound structures or identifiers, the activity source, receptor PDB identifier, software versions, parameter files, random seeds where applicable, docking box coordinates, MD input settings, analysis scripts and access to representative output files.

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