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MOLECULAR MODELING AND ADMET-GUIDED OPTIMIZATION OF NOVEL ANTIBACTERIAL COMPOUNDS AGAINST DRUG-RESISTANT PATHOGENS

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ABSTRACT

Antimicrobial resistance has intensified the need for antibacterial agents that combine potent target engagement with the ability to reach bacterial intracellular targets and maintain acceptable pharmacokinetic and safety profiles. This article evaluates an integrated molecular-modeling and ADMET-guided strategy for the prioritization and optimization of novel antibacterial compounds against drug-resistant pathogens. A structured narrative review of representative international literature was organized around target selection, quantitative structure-activity relationship (QSAR) modeling, molecular docking, molecular dynamics (MD), bacterial permeability and efflux considerations, and in silico absorption, distribution, metabolism, excretion and toxicity (ADMET) assessment. The synthesis shows that target affinity alone is an insufficient optimization objective, particularly for Gram-negative pathogens, where outer-membrane penetration, porin passage and active efflux can dominate whole-cell activity. Modern workflows therefore benefit from sequential filtering that combines structure-based binding models with physicochemical constraints, bacterial accumulation rules and mammalian safety prediction. Deep-learning studies further demonstrate that large chemical spaces can be searched for structurally novel antibacterial scaffolds, but explainability and experimental validation remain essential. An integrated decision framework is proposed in which molecular docking and QSAR identify potency-driving features, MD tests persistence of key interactions, and SwissADME, pkCSM, ADMETlab and toxicity models expose development liabilities before synthesis. The approach can reduce false-positive prioritization and support the selection of experimentally testable leads, although computational predictions cannot replace microbiological susceptibility, cytotoxicity, resistance-frequency and in vivo validation.

Keywords: antibacterial drug discovery; antimicrobial resistance; molecular docking; QSAR; molecular dynamics; ADMET; Gram-negative permeability; drug-resistant pathogens.

1. INTRODUCTION

Antimicrobial resistance (AMR) is a global therapeutic challenge because bacterial populations can acquire or select mechanisms that reduce the effectiveness of multiple antibiotic classes. A comprehensive global analysis estimated a substantial mortality burden associated with bacterial AMR in 2019, underscoring the clinical consequences of

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treatment failure and the need for new antibacterial options (1). At the same time, antibacterial discovery has faced unusually high attrition compared with many other therapeutic areas because a compound must satisfy two biological systems simultaneously: it must inhibit an essential bacterial process while also displaying sufficient exposure and acceptable safety in the host (2,3).

The difficulty is especially pronounced for Gram-negative bacteria. Their outer membrane, restricted porin channels and multidrug efflux pumps can keep intracellular drug concentrations below the level required for target inhibition even when biochemical affinity is strong (4,5). Accordingly, structure-based drug design that optimizes only a protein-ligand scoring function may generate compounds that bind well in silico yet show poor whole-cell activity. Empirical accumulation studies have shown that physicochemical features such as ionizable amines, amphiphilicity, rigidity and limited globularity can influence uptake into Escherichia coli, providing an additional design layer beyond conventional oral-drug rules (4).

Computational drug discovery has nevertheless become increasingly valuable for antibacterial research. QSAR and machine-learning methods can identify structural determinants of activity across large chemical series; molecular docking can suggest plausible binding modes and rank compounds within a defined target site; MD simulations can assess persistence of ligand-target contacts and conformational adaptation; and ADMET prediction can reveal liabilities related to solubility, intestinal absorption, CYP interactions, clearance, hERG risk, hepatotoxicity and mutagenicity before expensive synthesis and biological testing (6-12). The discovery of halicin using deep learning and, more recently, explainable graph-learning approaches that identified novel antibiotic structural classes illustrate the ability of computational methods to search chemical space beyond familiar antibacterial scaffolds (6,7).

The objective of this article is to synthesize current principles for molecular modeling and ADMET-guided optimization of antibacterial compounds against drug-resistant pathogens. The work is presented in IMRAD format as a structured review and computational design framework. It does not report newly generated wet-laboratory or docking data; instead, it integrates evidence from established methodological papers and antibacterial case studies to define a practical, resistance-aware sequence for target validation, virtual screening, binding-mode analysis, bacterial accumulation optimization, host ADMET evaluation and experimental confirmation.

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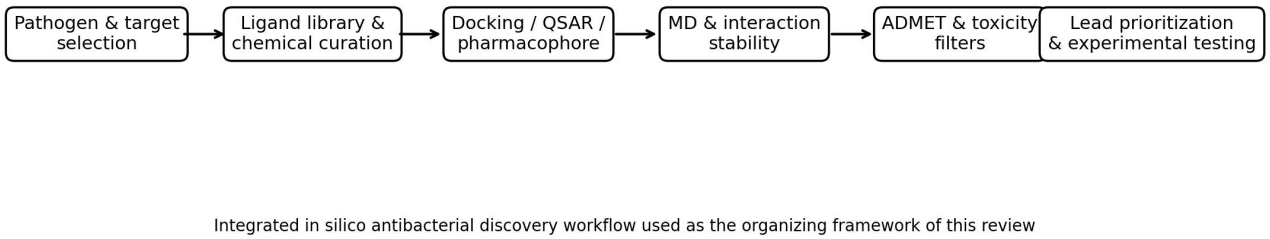


Figure 1. Integrated molecular-modeling and ADMET-guided workflow for antibacterial lead discovery and optimization.

2. MATERIALS AND METHODS

2.1. Review design and evidence selection. A structured narrative review was performed using representative peer-reviewed international literature that addressed antibacterial discovery, AMR, bacterial permeability and efflux, molecular docking, QSAR, molecular dynamics, machine-learning-enabled antibacterial discovery, and in silico ADMET/toxicity prediction. Fifteen core references were selected to anchor the framework, with emphasis on widely cited methodological papers and illustrative antibacterial studies. The synthesis was organized around the sequence of decisions typically encountered from target selection to lead prioritization.

2.2. Target-selection framework. Candidate bacterial targets were considered suitable when they met three general requirements: biological relevance to bacterial survival or virulence, structural or ligandability information sufficient for rational design, and a plausible therapeutic window relative to human homologues. Established antibacterial discovery literature indicates that target essentiality alone does not guarantee success because cellular penetration and resistance mechanisms can dominate whole-cell efficacy (2,3). Therefore, target selection was treated as the first filter rather than the final determinant of lead quality.

2.3. Molecular modeling and QSAR layer. Docking was conceptualized using the capabilities represented by AutoDock Vina 1.2.0, which supports batch docking, multiple scoring options and flexible workflow scripting (8). Docking scores were interpreted comparatively rather than as experimental binding free energies. QSAR modeling followed accepted principles of chemical data curation, descriptor relevance, validation and applicability-domain awareness (9). For compound series with measured antibacterial activity, QSAR is most informative when internal and external validation are separated and when mechanistic interpretation accompanies predictive performance.

2.4. Molecular dynamics layer. MD was included as a post-docking refinement step rather than a universal first-pass screen. The rationale is that explicit-solvent simulations can reveal whether key interactions remain stable after the protein-ligand complex is released from a static docking pose. GROMACS represents a widely used open-source platform for

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such simulations (13). Typical analyses include protein and ligand RMSD, residue-level fluctuations, hydrogen-bond persistence, contact occupancy and, when justified, end-point or alchemical free-energy estimates. These observables are supportive, not substitutes for measured MIC or biochemical inhibition.

2.5. ADMET and safety layer. Drug-likeness and pharmacokinetic prediction were organized around complementary tools rather than a single model. SwissADME provides physicochemical, lipophilicity, pharmacokinetic and medicinal-chemistry descriptors (10). pkCSM applies graph-based signatures to multiple ADMET endpoints (11), while ADMETlab 2.0 expands the number of predicted properties and provides an integrated web environment (12). ProTox-II was included as a toxicity-oriented layer capable of predicting acute toxicity classes and several organ- or mechanism-related toxicological endpoints (14). Divergent predictions were treated as uncertainty signals requiring experimental clarification.

2.6. Resistance-aware medicinal chemistry. The framework explicitly incorporated bacterial accumulation and efflux. For Gram-negative pathogens, candidate compounds should be evaluated not only for host ADMET but also for the physicochemical properties that influence bacterial entry. Richter and colleagues showed that accumulation in E. coli can be improved by features distinct from conventional eukaryotic drug-likeness rules (4). Therefore, antibacterial optimization was modeled as a multi-objective process balancing target potency, bacterial exposure, resistance liability, mammalian safety and developability.

Table 1. Representative antibacterial targets and modeling considerations in resistant pathogens.

Target	Representative resistance context	Biological function	Modeling implication
DNA gyrase / topoisomerase IV	Fluoroquinolone-resistant Gram-positive and Gram-negative bacteria	Catalytic/topological DNA control	Conserved active sites enable structure-based design; resistance mutations require cross-variant analysis.
PBP2a	Methicillin-resistant Staphylococcus aureus	Peptidoglycan cross-linking	Allosteric and active-site states should be considered; whole-cell activity depends on cell-wall access.
FabI / enoyl-ACP reductase	Selected staphylococci and other bacteria	Fatty-acid biosynthesis	Useful for target-focused design, but species dependence and bypass mechanisms must be

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Target	Representative resistance context	Biological function	Modeling implication
			considered.
LpxC	Gram-negative pathogens	Lipid A biosynthesis	Attractive Gram-negative target; optimization must address outer-membrane penetration and efflux.
DHFR / folate pathway	Multiple bacterial species	Nucleotide precursor synthesis	Strong structural precedent; selectivity versus human DHFR and resistance mutations are key.
Ribosome / macrolide-binding region	Resistant respiratory and Gram-positive pathogens	Protein synthesis	Large binding site and resistance methylation/efflux make scaffold-level optimization important.

3. RESULTS

3.1. Molecular modeling is most effective when it is positioned as a sequence of orthogonal filters. Across the reviewed literature, the major recurring theme is that no single computational score adequately predicts antibacterial success. Docking can enrich for target-compatible molecules, but whole-cell antibacterial activity requires bacterial exposure; ADMET models can identify host pharmacokinetic and safety risks, but they do not directly measure accumulation inside bacteria. The resulting evidence supports an integrated sequence in which target affinity, bacterial entry, interaction stability, host exposure and toxicity are evaluated as separate but connected dimensions.

3.2. Gram-negative permeability is a major source of false-positive virtual hits. Richter et al. experimentally measured accumulation for a chemically diverse set of small molecules and identified features associated with improved entry into E. coli, including the presence of an amine, amphiphilicity, rigidity and low globularity (4). This finding helps explain why conventional screening collections optimized around generic drug-like properties can perform poorly in Gram-negative antibacterial campaigns. Masi et al. further described how porin influx and active efflux jointly regulate intracellular antibiotic concentrations (5). Together, these studies indicate that antibacterial medicinal chemistry should incorporate pathogen-specific exposure rules alongside conventional ADMET predictions.

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3.3. Machine learning expands chemical-space exploration but does not remove the need for mechanistic validation. Stokes et al. demonstrated a deep-learning approach that identified halicin, a structurally unusual antibacterial relative to standard antibiotic classes (6). Wong et al. subsequently used explainable graph neural networks to screen more than twelve million compounds and identify structural rationales associated with antibacterial activity and low cytotoxicity, leading to a distinct class active against MRSA and vancomycin-resistant enterococci (7). These studies support computational expansion beyond close analogues, but they also show that predicted activity must be followed by experimental susceptibility, cytotoxicity, mechanism and resistance testing.

3.4. ADMET-guided optimization reduces late-stage attrition by moving host-safety considerations earlier. SwissADME, pkCSM and ADMETlab provide overlapping but nonidentical predictions for absorption, solubility, permeability, metabolism, distribution and toxicity-related endpoints (10-12). Their strongest use in antibacterial lead optimization is comparative prioritization within a chemical series rather than absolute acceptance or rejection. A compound with high target affinity but poor predicted solubility, severe CYP liability or toxicity alerts may be deprioritized or redesigned before synthesis. Conversely, a moderately potent compound with balanced bacterial accumulation and host ADMET can represent a better lead-development starting point than the top-scoring docking hit.

3.5. MD contributes most when it is used to answer a focused structural question. After docking, MD can determine whether a ligand remains in a plausible binding mode, whether key hydrogen bonds or ionic contacts persist, and whether resistance-associated substitutions destabilize the complex. However, longer or more elaborate simulations do not automatically produce better biological predictions. The reviewed methodological literature therefore supports using MD as a mechanistic refinement step, with simulation design tied to specific hypotheses such as conformational stability, water-mediated interactions or variant sensitivity (13).

Table 2. Computational components and their role in antibacterial lead prioritization.

Component	Primary output	Main value	Key limitation
QSAR / ML	Activity-driving structural features; ranking within chemical series	Rapid learning from measured data	Dataset bias, activity heterogeneity, limited extrapolation
Molecular docking	Plausible binding poses; comparative scoring	Fast structure-based triage	Scoring error; static receptor; poor direct relation to MIC
Molecular dynamics	Pose persistence; flexibility; interaction occupancy	Dynamic structural validation	Force-field and sampling limitations; computational cost

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Component	Primary output	Main value	Key limitation
SwissADME	Physicochemical and pharmacokinetic descriptors	Fast drug-likeness and PK triage	Not bacteria-specific; endpoint models have domains of applicability
pkCSM / ADMETlab	Multi-endpoint ADMET predictions	Early exposure and toxicity-risk assessment	Model disagreement and training-set bias
ProTox-II	Toxicity class and mechanistic toxicity alerts	Prioritizes safer chemical space	Prediction is screening-level, not a substitute for toxicology assays
Bacterial accumulation rules	Likelihood of entry/retention in Gram-negative cells	Addresses antibacterial-specific exposure	Species, porin and efflux dependence

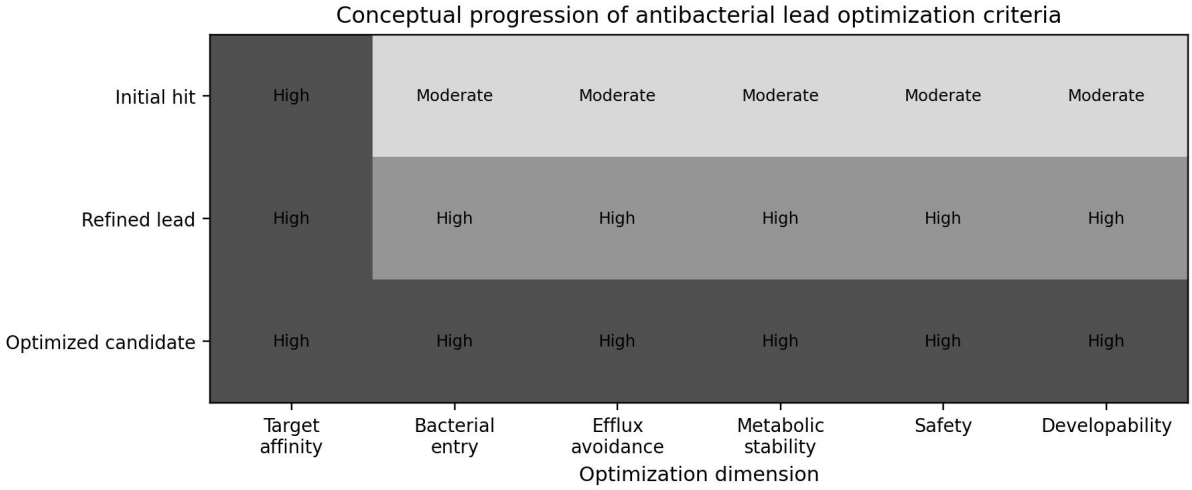


Figure 2. Conceptual multi-objective progression from an initial antibacterial hit toward an optimized candidate. Values are schematic and not experimental measurements.

Table 3. Resistance-aware optimization decisions for antibacterial medicinal chemistry.

Observed problem	Likely computational/biological explanation	Optimization response
High docking score, weak whole-cell activity	Insufficient penetration, rapid efflux, target access problem	Measure/estimate accumulation; reduce

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Observed problem	Likely computational/biological explanation	Optimization response
		globularity/flexibility; assess ionization and porin compatibility
Potent activity, rapid resistance emergence	Single-step target mutation or narrow mechanism	Test resistance frequency; dock to common variants; consider dual-target or multi-mechanistic strategies
Good bacterial potency, poor mammalian safety	Off-target pharmacology or reactive/toxic chemotype	Remove toxicophores; compare ProTox-II/pkCSM alerts; add cytotoxicity assays early
Low solubility / unstable exposure	Excess lipophilicity, crystal lattice, metabolic liability	Tune cLogP/pKa; reduce planarity; evaluate metabolic soft spots and formulation options
Strong in vitro target affinity, unstable MD pose	Scoring artifact or induced-fit mismatch	Re-dock with alternative receptor states; inspect water networks; redesign interaction anchors
Broad-spectrum ambition with poor Gram-negative activity	Outer membrane and efflux barriers	Apply Gram-negative accumulation rules; assess efflux susceptibility and periplasmic exposure

4. DISCUSSION

The central implication of this synthesis is that antibacterial lead optimization should not be treated as a conventional affinity-maximization problem. Drug-resistant pathogens impose additional design constraints because resistance mechanisms operate at several levels: modification of the molecular target, reduced uptake, enzymatic drug inactivation, increased efflux, pathway bypass and phenotypic tolerance. Consequently, a compound can fail despite excellent target affinity. An effective computational program therefore needs to distinguish between target-level potency and cell-level exposure, and it must incorporate host ADMET considerations early enough that optimization does not create a molecule that is microbiologically potent but clinically undevelopable (2-5).

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The complementary relationship between QSAR and structure-based modeling is particularly important. QSAR can discover statistical relationships between molecular descriptors and measured activity, including nonobvious combinations of lipophilicity, topology, charge and substructure. Docking, in contrast, can provide a mechanistic hypothesis for target engagement. When both approaches identify the same chemical features as favorable, confidence in the design rationale increases. However, QSAR models should be interpreted within their applicability domain, and docking poses should be stress-tested through alternative receptor conformations, decoy controls, known ligands or MD. The best practice is convergence of evidence rather than reliance on a single high score (8,9).

ADMET optimization in antibacterial research also requires an important distinction between host pharmacokinetics and bacterial pharmacokinetics. SwissADME, pkCSM and ADMETlab estimate properties relevant to systemic exposure in humans, but the molecule must additionally cross the bacterial envelope and avoid bacterial efflux. This creates a two-compartment design problem. For Gram-negative targets, improvements in human membrane permeability or lipophilicity do not necessarily improve bacterial entry and can even increase nonspecific toxicity. The accumulation rules derived from E. coli studies therefore provide an antibacterial-specific counterweight to generic drug-likeness heuristics (4,10-12).

Deep learning offers a route to explore chemical spaces that are too large for conventional docking. The halicin and explainable-antibiotic studies demonstrate that model-guided selection can uncover structurally distinct antibacterial candidates (6,7). Yet these successes also highlight a methodological requirement: activity prediction should be linked to cytotoxicity filters, chemical novelty, interpretability and experimental confirmation. Explainable models are especially attractive because they can connect predicted activity to identifiable substructures that medicinal chemists can modify. In future workflows, graph neural networks, generative chemistry, structure prediction and active learning may be combined with microbiological feedback loops so that each experimental cycle retrains the computational model.

Resistance-aware design should begin before a candidate becomes optimized. Computational screening against common target variants can identify substitutions that weaken binding, whereas network or multi-target analysis can reveal alternative mechanisms. Experimental resistance-frequency measurements and serial-passage studies remain essential, but modeling can prioritize which mutations to test and whether a scaffold is vulnerable to single-site escape. In parallel, efflux and permeability models should be used to avoid producing compounds whose apparent spectrum is limited primarily by exposure rather than target conservation.

Several limitations constrain the conclusions of this review. First, the literature is heterogeneous in pathogen, assay format, target, modeling method and validation depth, so direct numerical comparison across studies is inappropriate. Second, in silico ADMET platforms are trained on chemical datasets that may underrepresent antibacterial chemotypes, particularly highly polar or ionizable molecules. Third, docking and MD remain approximations and cannot reproduce the full complexity of the bacterial cell envelope, transporter competition or intracellular sequestration. Finally, no computational

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workflow can establish antibacterial efficacy or safety without experimental confirmation. These limitations support the use of modeling as a prioritization and hypothesis-generation system rather than as a replacement for microbiology and pharmacology.

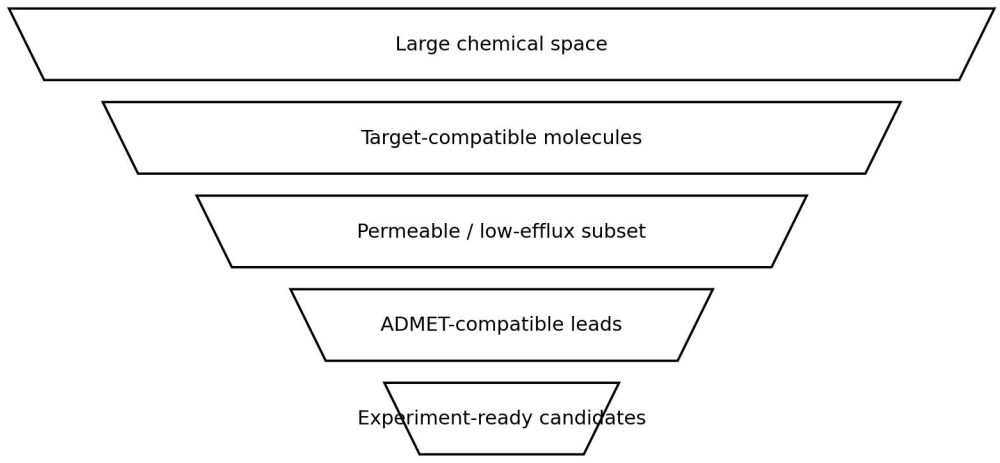


Figure 3. Resistance-aware decision funnel for reducing chemically attractive but biologically nonviable antibacterial hits.

5. CONCLUSION

Molecular modeling and ADMET-guided optimization provide a rational framework for discovering antibacterial compounds against drug-resistant pathogens when they are integrated with pathogen-specific exposure and resistance considerations. QSAR and machine learning can identify activity-driving chemical patterns and explore large chemical spaces; molecular docking can propose target-binding modes; MD can test structural persistence; and ADMET prediction can expose host pharmacokinetic and toxicity liabilities before extensive synthesis. For Gram-negative pathogens, these methods must be complemented by bacterial accumulation and efflux considerations because target affinity alone does not predict intracellular exposure. The most defensible computational workflow is therefore multi-objective and sequential: validate the target, rank chemically diverse hits, test binding hypotheses, evaluate bacterial access, refine dynamic interactions, screen host ADMET and toxicity, and then advance a small set of candidates to microbiological and pharmacological validation. Such integration can reduce wasted synthesis and improve lead quality, but predicted scores should remain clearly separated from experimentally measured antibacterial efficacy.

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