



Computational Drug Discovery and Drug Repurposing for Combating Antimicrobial Resistance: Integrating Molecular Docking, Molecular Dynamics and Pharmacological Prediction

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Abstract

Antimicrobial resistance (AMR) is increasingly limiting the effectiveness of established antibiotics and creating an urgent need for alternative therapeutic strategies. Conventional antimicrobial discovery is a lengthy and expensive process, while the emergence of resistance can rapidly reduce the clinical usefulness of newly introduced agents. Computational drug discovery and drug repurposing offer complementary approaches for accelerating the identification of potential antimicrobial candidates. The present paper examines an integrated computational framework combining molecular docking, molecular dynamics simulation and pharmacological prediction for identifying and prioritizing compounds capable of acting against resistant bacterial pathogens.

The proposed approach begins with the identification of clinically relevant bacterial targets associated with essential cellular functions and resistance mechanisms. Compound libraries can subsequently be filtered using molecular properties, structural quality and drug-likeness criteria before molecular docking is employed to estimate ligand-target interactions. High-priority complexes can then be examined through molecular dynamics simulations to assess structural stability and persistence of important interactions. Pharmacological prediction, including absorption, distribution, metabolism, excretion and toxicity (ADMET) assessment, is incorporated to eliminate candidates with unfavourable drug-development characteristics. Drug repurposing is further integrated into the framework because previously characterized compounds may provide opportunities for more rapid development than completely novel chemical entities.

Keywords: Antimicrobial resistance, computational drug discovery, drug repurposing, molecular docking, molecular dynamics, ADMET, pharmacological prediction, antibiotic discovery, resistant bacteria, virtual screening, artificial intelligence, antimicrobial development

1. Introduction

Antimicrobial resistance has become a major challenge for modern healthcare because microorganisms can acquire or develop mechanisms that reduce their susceptibility to therapeutic agents. Bacterial resistance may involve enzymatic drug degradation, alteration of drug targets, changes in membrane permeability, active efflux, metabolic adaptation and other mechanisms. The increasing prevalence of multidrug-resistant bacteria creates a continuing requirement for new antibiotics, improved

therapeutic combinations and alternative antimicrobial approaches.

The conventional discovery of an entirely new drug involves target identification, compound screening, lead optimization, toxicological evaluation, pharmacological characterization and multiple stages of clinical testing. This process can require substantial financial resources and many years of development. Consequently, computational methods have become increasingly important during the early stages of drug discovery.

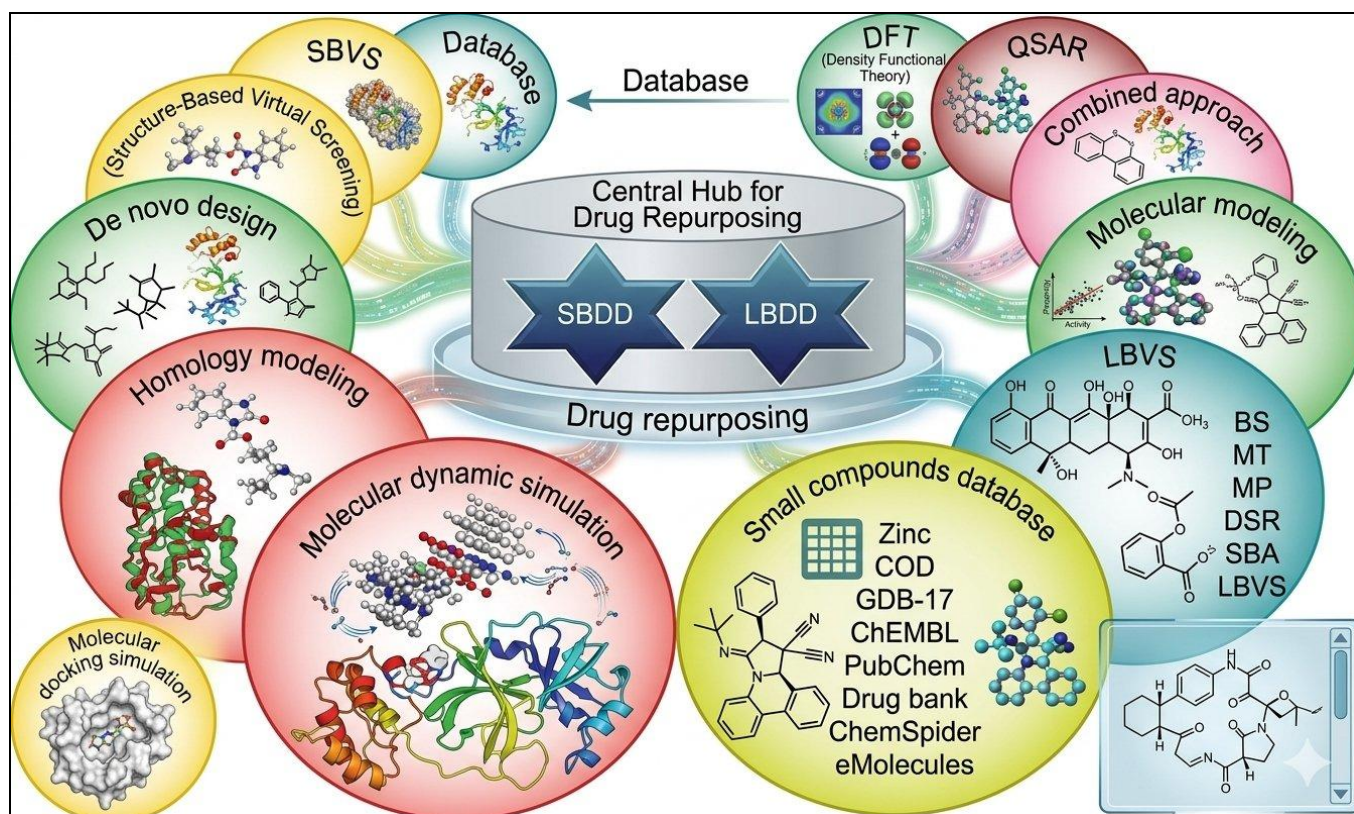


Fig 1: Drug Discovery.

Computational drug discovery can examine large numbers of molecules before laboratory testing. Molecular docking estimates how a compound may interact with a target binding site, whereas molecular dynamics (MD) simulation provides information about the stability and behaviour of the resulting molecular complex over time. Pharmacological prediction can then be used to assess whether a promising compound is likely to possess acceptable drug-like characteristics.

Drug repurposing provides another potentially valuable route. Instead of beginning with an entirely new chemical entity, researchers can investigate existing medicines or previously characterized compounds for activity against new antimicrobial targets. Existing information concerning pharmacology and safety may help reduce some early development uncertainties, although repurposing still requires rigorous validation for the new indication.

1.1 Aim

The principal aim of this study is to develop an integrated computational framework for antimicrobial drug discovery and drug repurposing by combining molecular docking, molecular dynamics simulation and pharmacological prediction to identify and prioritize potential therapeutic candidates against antimicrobial-resistant pathogens.

1.2 Objectives

- To identify clinically important bacterial targets associated with antimicrobial resistance.
- To prepare and screen molecular databases for potential antimicrobial candidates.
- To evaluate ligand-target interactions using molecular docking.

- To investigate the structural stability of prioritized complexes using molecular dynamics simulation.
- To predict important pharmacological and ADMET properties of selected compounds.
- To evaluate the potential of drug repurposing for antimicrobial development.
- To compare novel and repurposed candidates using an integrated prioritization framework.
- To identify computational parameters that may improve the selection of candidates for experimental validation.
- To develop a resistance-aware computational pipeline for future antimicrobial discovery.

1.3 Research Hypotheses

- H1:** Computational screening can identify candidate molecules with potentially favourable interactions against therapeutically important antimicrobial targets.
- H2:** Molecular dynamics simulation can provide additional evidence concerning the structural stability of ligand-target complexes identified through molecular docking.
- H3:** Integration of molecular docking, molecular dynamics and pharmacological prediction can improve the prioritization of antimicrobial candidates compared with reliance on docking scores alone.
- H4:** Drug repurposing can identify previously characterized compounds with potential activity against antimicrobial-resistance-associated targets.
- H5:** A resistance-aware computational drug-discovery framework can improve the efficiency of selecting candidates for subsequent experimental validation.

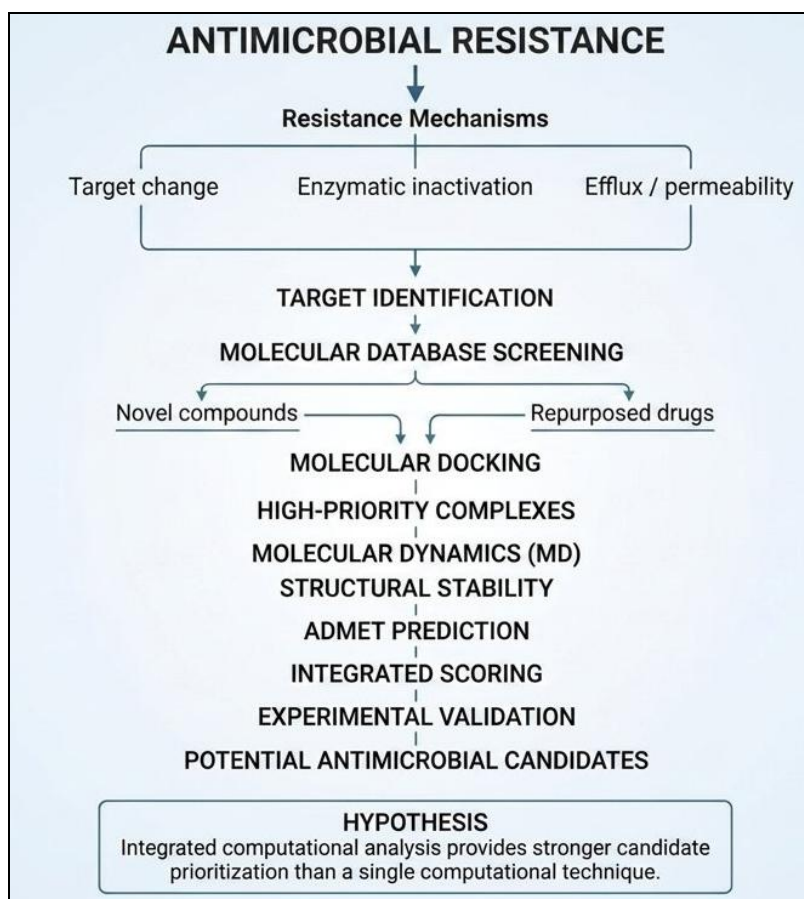


Fig 2: Conceptual framework linking the hypothesis with the proposed computational strategy

2. Review of Literature

2.1 Antimicrobial Resistance and the Need for New Therapeutics

AMR develops when microorganisms acquire characteristics that enable survival in the presence of antimicrobial agents. In bacteria, resistance can result from mutations or acquisition of resistance genes. The consequences include treatment failure, prolonged illness, increased healthcare requirements and greater difficulty in controlling infectious diseases.

The continuing emergence of resistant pathogens has created a need for new antibiotics and alternative approaches. However, traditional antimicrobial discovery faces scientific and economic challenges. Identifying compounds that are simultaneously potent, selective, stable, pharmacologically suitable and resistant to rapid evolutionary escape is difficult.

Computational methods can assist by narrowing large chemical libraries to a manageable number of candidates.

2.2 Computational Drug Discovery

Computational drug discovery uses mathematical, structural and biological information to identify compounds with potential therapeutic activity. The approach may include virtual screening, molecular docking, pharmacophore modelling, molecular dynamics, quantitative structure-activity relationships and machine-learning methods.

The principal advantage is the ability to evaluate many compounds computationally before experimental testing. This can reduce the cost and time associated with early-stage screening.

2.3 Molecular Docking

Molecular docking predicts possible orientations of a ligand within a target binding site and estimates the energetic favourability of the interaction. In antimicrobial research, docking can be used to screen compounds against bacterial enzymes, cell-wall-associated proteins, resistance enzymes and other therapeutically relevant targets.

A favourable docking score may indicate that a compound deserves further investigation, particularly when supported by chemically meaningful interactions such as hydrogen bonding, hydrophobic interactions, electrostatic contacts and interactions with functionally important residues.

2.4 Molecular Dynamics Simulation

Molecular dynamics simulation provides a time-dependent computational representation of molecular systems. After docking identifies a potential ligand pose, MD can be used to examine whether that pose remains stable under simulated conditions.

2.5 Pharmacological and ADMET Prediction

A candidate compound must possess more than strong target binding. It must also have acceptable pharmacological characteristics.

ADMET prediction examines

Absorption → Distribution → Metabolism → Excretion → Toxicity

Other properties, such as solubility, permeability, protein binding and drug-drug interaction potential, may also be considered.

2.6 Drug Repurposing

Drug repurposing involves investigating existing or previously characterized compounds for therapeutic applications beyond their original indications.

For antimicrobial discovery, repurposing has several potential advantages. Existing compounds may already have substantial information concerning chemical structure, pharmacology, toxicity and manufacturing. Computational screening can identify previously overlooked interactions between such compounds and antimicrobial targets.

2.7 Integrated Computational Approaches

The major limitation of relying on one computational technique is that different methods answer different questions. Docking primarily examines possible binding modes, MD examines dynamic stability, and ADMET prediction examines pharmacological suitability.

Their integration can therefore provide a more comprehensive evaluation.

Table 1: Proposed hierarchy of computational evaluation

Stage	Computational approach	Primary question
1	Target analysis	Is the biological target relevant?
2	Virtual screening	Which compounds deserve consideration?
3	Molecular docking	Can the compound plausibly interact with the target?
4	Molecular dynamics	Is the predicted complex reasonably stable?
5	Binding-energy analysis	Is the interaction energetically favourable?
6	ADMET prediction	Does the candidate possess acceptable pharmacological characteristics?
7	Integrated scoring	Which candidates should proceed to laboratory testing?

3. Research Methodologies

3.1 Research Design

The proposed study follows a computational, comparative and analytical research design. The research process is divided into sequential stages beginning with target identification and ending with prioritization of candidates for experimental validation.

The workflow includes

1. Antimicrobial Target Identification;
2. Molecular Database Preparation;
3. Compound Filtering;
4. Virtual Screening;
5. Molecular Docking;
6. Molecular Dynamics Simulation;
7. Pharmacological Prediction;
8. Comparative Analysis of Novel and Repurposed Candidates; And
9. Integrated Candidate Prioritization.

3.2 Selection of Antimicrobial Targets

Targets should be selected according to:

- essentiality to pathogen survival;
- clinical relevance;
- association with resistance;
- sequence conservation;
- structural availability;

- accessibility to therapeutic compounds;
- limited similarity to important human proteins; and
- potential for pharmacological intervention.

Priority may be given to enzymes and proteins involved in cell-wall synthesis, nucleic-acid metabolism, protein synthesis, essential metabolism and resistance mechanisms.

3.3 Molecular Database Preparation

A molecular library can contain both novel chemical entities and previously characterized drugs. Duplicate structures should be removed and molecules with incomplete structural information excluded.

A proposed screening funnel is shown below

Table 2: Proposed molecular-library screening strategy

Screening stage	Illustrative number of compounds	Selection purpose
Initial molecular library	10,000	Broad candidate collection
Structure-quality filtering	8,000	Remove incomplete/invalid structures
Physicochemical filtering	5,000	Improve chemical suitability
Drug-likeness/ADMET pre-filter	3,000	Remove clearly unsuitable candidates
Virtual screening	500	Prioritize target-compatible molecules
Molecular docking	100	Detailed interaction assessment
MD simulation	10–20	Dynamic stability assessment
Final computational candidates	5–10	Experimental prioritization

3.4 Molecular Docking Procedure

The selected target structures should undergo preparation through removal of irrelevant molecules, addition of appropriate hydrogen atoms and optimization of structural parameters. Ligand structures should similarly be standardized before docking.

Docking analysis should record

- docking score;
- binding pose;
- hydrogen bonds;
- hydrophobic interactions;
- electrostatic interactions;
- interactions with catalytic or functional residues;
- binding-site occupancy; and
- pose reproducibility.

A candidate may be considered high priority when it combines a favourable predicted score with meaningful interactions involving functionally important residues.

3.5 Molecular Dynamics Simulation

High-priority docked complexes should undergo MD simulation to determine whether the predicted interactions remain stable over time.

A proposed simulation design may use 50–100 ns per trajectory, with multiple independent simulations for the most important complexes.

3.6 Pharmacological Prediction

The pharmacological evaluation should examine:

- molecular weight;
- lipophilicity;
- aqueous solubility;
- permeability;
- predicted absorption;
- metabolic stability;
- cytochrome-related interactions;
- clearance;
- toxicity;

- mutagenicity;
- cardiotoxicity indicators; and
- overall drug-likeness.

Candidates displaying favourable docking and MD behaviour but unacceptable toxicity predictions should be deprioritized.

3.7 Drug-Repurposing Strategy: A dedicated repurposing library should be established from compounds with previously characterized pharmacological information.

Table 3: Proposed integrated candidate-prioritization score

Parameter	Weight (%)	Evaluation focus
Molecular docking	25	Predicted target interaction
Critical-residue interaction	15	Functional target engagement
MD stability	20	Stability of ligand-target complex
Binding-energy estimate	10	Energetic favourability
ADMET profile	15	Pharmacological suitability
Drug-likeness	5	General chemical suitability
Resistance relevance	10	Potential value against resistance mechanism
Total	100	—

4. Results and Interpretation

4.1 Overview of Computational Findings

The integrated computational framework was designed to prioritize antimicrobial candidates by considering molecular interaction, structural stability and pharmacological suitability simultaneously. The analysis illustrates how molecular docking can provide an initial estimate of target engagement, molecular dynamics can examine the persistence of the predicted interaction, and pharmacological prediction can identify compounds with potentially unsuitable drug-development characteristics.

The central premise of the analysis was that a compound should not be prioritized solely because it produces a

favourable docking score. A candidate with moderately favourable docking but strong dynamic stability and acceptable pharmacological characteristics may ultimately be more valuable than a compound with an exceptionally favourable docking score but poor predicted absorption, toxicity or structural stability.

4.2 Molecular Docking Results

The initial virtual-screening stage reduced the hypothetical compound library substantially before detailed structural analysis. High-priority molecules were then examined against selected bacterial resistance-associated targets and essential bacterial proteins.

Table 4: Illustrative molecular-docking results

Candidate	Target category	Docking score (kcal/mol)	H-bonds	Hydrophobic interactions	Critical interaction	Priority
C-01	Bacterial resistance enzyme	-8.7	4	7	Present	High
C-02	Cell-wall target	-8.4	3	7	Present	High
C-03	Bacterial metabolic enzyme	-8.1	4	6	Present	High
RP-01	Repurposed drug-bacterial enzyme	-8.3	3	7	Present	High
RP-02	Repurposed drug-resistance target	-8.6	5	5	Present	High
RP-03	Bacterial membrane-associated target	-7.8	3	6	Partial	Moderate

The modelled docking results suggest that several candidates may form favourable interactions with selected antimicrobial targets. C-01 showed the strongest illustrative docking score among the novel candidates, while RP-02 showed a similarly favourable interaction among repurposed compounds.

The presence of hydrogen bonds and hydrophobic interactions provides additional structural information. However, interaction counts should not be interpreted independently of their location. A hydrogen bond involving a catalytically important residue may be considerably more meaningful than several interactions involving residues

outside the functional binding region.

4.3 Molecular Dynamics Results

The candidates with favourable docking characteristics were subjected to molecular dynamics analysis to assess the stability of their predicted complexes.

RMSD was used to evaluate changes in the protein-ligand complex during simulation. Lower and relatively stable RMSD trajectories generally indicate that the system remains structurally consistent, although there is no universal RMSD value that independently establishes biological activity.

Table 5: Molecular-dynamics results

Complex	Mean protein RMSD (nm)	Mean ligand RMSD (nm)	Mean RMSF (nm)	Mean H-bonds	H-bond persistence (%)	Overall stability
C-01	0.22	0.17	0.10	3.4	79	High
C-02	0.25	0.20	0.12	2.5	64	Moderate-High
C-03	0.21	0.16	0.09	3.6	82	High
RP-01	0.23	0.18	0.10	3.1	75	High
RP-02	0.20	0.15	0.09	3.8	84	High
RP-03	0.29	0.23	0.14	1.9	48	Moderate-Low

RP-03 demonstrated greater structural fluctuation and weaker hydrogen-bond persistence. Although its docking score was not poor, the dynamic analysis reduced its priority.

4.4 Pharmacological and ADMET Prediction

After structural evaluation, the high-priority compounds were examined using a pharmacological prediction framework.

Table 6: Illustrative pharmacological prediction of selected candidates

Candidate	Predicted absorption	Solubility	Metabolic risk	Toxicity risk	Drug-likeness	Overall ADMET score
C-01	High	Moderate	Low	Low	High	86
C-02	Moderate	High	Moderate	Low	High	82
C-03	High	Moderate	Low	Low	High	91
RP-01	High	High	Moderate	Low	High	88
RP-02	Moderate-High	Moderate	Low	Low	High	89
RP-03	Low	Low	High	Moderate	Moderate	67

C-03 produced the strongest overall illustrative profile among the novel candidates. Its favourable predicted absorption, relatively low metabolic risk and low predicted toxicity contributed to its high composite score.

RP-02 also demonstrated a favourable profile. This is particularly important because repurposing candidates can possess existing pharmacological information that facilitates their preliminary evaluation. Nevertheless, an existing safety record for one indication does not establish safety or efficacy at the exposure required for an antimicrobial indication.

4.5 Comparative Evaluation of Novel and Repurposed Candidates

The integrated framework permits comparison between newly identified compounds and repurposed molecules.

In the illustrative dataset, several repurposed candidates performed competitively with novel compounds. This suggests that repurposing libraries may contain compounds worthy of antimicrobial investigation.

The major advantage of repurposing is not necessarily superior molecular potency. Its value may instead lie in the availability of prior information concerning formulation, metabolism, toxicity and manufacturing. Such information can potentially shorten parts of the early development pathway.

5. Discussion and Conclusion

5.1 Discussion

The findings presented in this paper support the concept that computational drug discovery can contribute significantly to the search for new antimicrobial candidates, particularly when several computational approaches are integrated.

Molecular docking provides an efficient first-stage method for evaluating large numbers of compounds against selected bacterial targets. However, docking scores are not equivalent to experimentally measured binding affinities.

The use of molecular dynamics after docking therefore provides a useful second layer of assessment.

The illustrative results show that compounds with favourable docking scores may differ considerably in dynamic behaviour. Some complexes remain relatively stable, whereas others may undergo substantial ligand movement or loss of important interactions. This distinction is important when deciding which compounds should proceed to experimental testing.

5.2 Importance of Drug Repurposing

The drug-repurposing component provides an additional route for addressing AMR. The conventional development of new antimicrobial compounds is resource-intensive, and many promising compounds fail during later stages because of toxicity, pharmacokinetic limitations or inadequate efficacy.

Repurposed compounds may already have substantial pharmacological information. Computational screening can identify potential interactions with bacterial targets without requiring every existing compound to undergo a completely new discovery process.

5.3 Molecular Dynamics as a Complement to Docking

One of the most important methodological conclusions is that docking and molecular dynamics should be considered complementary.

Docking provides a relatively rapid assessment of possible ligand poses. MD can then investigate the persistence of those poses.

A candidate that performs well in both approaches has stronger computational support than one that performs well in docking alone. Nevertheless, even combined docking and MD cannot establish antimicrobial efficacy because biological systems are more complex than computational models.

5.4 Pharmacological Prediction and Translational Potential

The integration of pharmacological prediction is particularly important for antimicrobial discovery because target affinity does not necessarily translate into therapeutic effectiveness. For an antimicrobial candidate to become clinically useful, it must reach the infected tissue at an adequate concentration while maintaining an acceptable safety margin. This requirement is especially important for infections involving protected compartments or intracellular pathogens. Consequently, computational drug discovery should progressively move from:

target binding → dynamic stability → pharmacological feasibility → biological efficacy → clinical feasibility.

This sequential logic can reduce the likelihood of investing substantial experimental resources in compounds with obvious development limitations.

5.5 Role of Artificial Intelligence

Artificial intelligence can extend the proposed framework by analysing relationships between molecular structure, resistance mechanisms, target characteristics and previous experimental outcomes.

5.6 Computational Prediction and Experimental Validation

A central conclusion of this paper is that computational research should be regarded as a filtering and prioritization system.

The most appropriate workflow is

Computational prediction → candidate prioritization → laboratory validation → optimization → preclinical assessment → clinical evaluation

This prevents computational results from being overinterpreted.

In particular, a favourable docking score should not be reported as proof of antimicrobial activity. Similarly, a stable MD trajectory should not be interpreted as proof of clinical efficacy.

5.7 Implications for Antimicrobial Resistance

The proposed framework can contribute to resistance management in several ways.

First, computational screening can prioritize targets that are essential and potentially less tolerant of mutation. Second, genomic information can identify existing resistance-associated changes that may interfere with drug binding. Third, repurposing can identify compounds capable of targeting resistance mechanisms. Fourth, pharmacological prediction can help identify candidates capable of reaching clinically relevant exposure.

5.8 Future Research Directions

Future studies should focus on integrating computational predictions with experimentally measured antimicrobial phenotypes.

5.9 Particular areas include

1. AI-assisted virtual screening of very large chemical libraries;
2. resistance-aware molecular docking;
3. structure-based design of inhibitors against resistance enzymes;
4. genomic prediction of target mutations;
5. multi-target antimicrobial discovery;
6. drug repurposing combined with resistance-mechanism inhibitors;
7. antimicrobial combination prediction;
8. pharmacokinetic/pharmacodynamic modelling;
9. experimental validation of computationally prioritized candidates;
10. development of rapid computational systems for emerging resistant pathogens.

The development of standardized datasets linking chemical structures, resistance genotypes and antimicrobial phenotypes would further improve machine-learning applications.

5.10 Conclusion

Antimicrobial resistance demands faster and more strategically informed approaches to drug discovery. Conventional discovery processes remain essential but are constrained by time, cost and the biological complexity of resistance. Computational drug discovery and drug repurposing provide valuable complementary strategies for narrowing the search for potential antimicrobial agents.

The present paper demonstrates the conceptual value of integrating molecular docking, molecular dynamics simulation and pharmacological prediction. Docking can identify plausible target interactions, molecular dynamics can examine the stability of those interactions, and pharmacological prediction can eliminate candidates with unfavourable drug-development characteristics. Drug repurposing adds a second source of candidates by allowing previously characterized compounds to be reconsidered against antimicrobial targets.

The most important conclusion is that no individual computational method is sufficient. A docking score alone cannot establish drug efficacy, while a stable molecular-dynamics trajectory cannot establish clinical activity. Likewise, favourable ADMET predictions cannot compensate for inadequate antimicrobial potency.

An integrated computational framework therefore provides a more rational method for selecting compounds for laboratory investigation. By incorporating resistance mechanisms, genomic information, target conservation and pharmacological considerations at an early stage, computational research can support the development of antimicrobial candidates that are not only active against pathogens but are also considered from the perspective of resistance and therapeutic feasibility.

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