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Biochemoinformatics approaches to combating bacterial resistance: advances, challenges and perspectives

Abordagem de bioquimioinformática no combate à resistência bacteriana: avanços, desafios e perspectivas

Enfoque de la bioquimioinformática en el combate a la resistencia bacteriana: avances, desafíos y perspectivasa biochemoinformatics

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ABSTRACT
Antimicrobial resistance constitutes a major global public health problem that undermines treatment efficacy and increases morbidity and mortality associated with bacterial infections. In light of this challenging scenario and the limitations of conventional therapies, the development of innovative strategies for discovering new antimicrobial agents has become essential. Within this context, this article aims to review the advances, challenges, and future perspectives of biochemoinformatics in combating bacterial resistance. The methodology consists of a narrative literature review addressing molecular mechanisms of resistance, the use of structural databases such as the Protein Data Bank (PDB), and the application of hierarchical pipelines that integrate virtual screening, molecular modeling, ADME/Tox prediction, and experimental validation. The analyzed studies indicate that biochemoinformatics accelerates drug discovery, reduces costs, and identifies promising candidates with higher potential for biological activity, including against critical pathogens such as *Klebsiella pneumoniae*. Thus, the integration of computational tools, artificial intelligence, and biological validation establishes this approach as a promising strategy for drug design against multidrug-resistant strains.

Keywords: antimicrobial resistance, biochemoinformatics, virtual screening, antimicrobial, *Klebsiella pneumoniae.*

RESUMO
A resistência antimicrobiana é um grave problema de saúde pública global, que compromete a eficácia dos tratamentos, aumentando a morbimortalidade associada às infecções bacterianas. Diante desse cenário desafiador a limitação das terapias convencionais, torna-se essencial o desenvolvimento de estratégias inovadoras para a descoberta de novos agentes antimicrobianos. Nesse contexto, este artigo objetiva revisar os avanços, desafios e perspectivas da bioquimioinformática no combate à resistência bacteriana. A metodologia consiste em uma revisão narrativa da literatura, abordando mecanismos moleculares de resistência, o uso de bases de dados estruturais como o Protein Data Bank (PDB) e a aplicação de pipelines hierárquicos que integram triagem virtual, modelagem molecular, predições ADME/Tox e validação experimental. Os estudos analisados indicam que a bioquimioinformática acelera a descoberta de fármacos, reduz custos e seleciona candidatos promissores com maior potencial de atividade biológica, inclusive frente a patógenos críticos como *Klebsiella pneumoniae*. Assim, a integração de ferramentas computacionais, inteligência artificial e validação biológica consolida essa abordagem como uma estratégia promissora para o planejamento de novos fármacos frente a cepas multirresistentes.

Palavras-chave: resistência antimicrobiana, bioquimioinformática, triagem virtual, antimicrobiano, *Klebsiella pneumoniae*

RESUMEN
La resistencia antimicrobiana constituye un grave problema de salud pública global, ya que compromete la eficacia de los tratamientos y aumenta la morbimortalidad asociada a las infecciones bacterianas. Ante este escenario desafiante y las limitaciones de las terapias convencionales, resulta esencial el desarrollo de estrategias innovadoras para el descubrimiento de nuevos agentes antimicrobianos. En este contexto, el presente artículo tiene como objetivo revisar los avances, desafíos y perspectivas de la bioquimioinformática en el combate a la resistencia bacteriana. La metodología consiste en una revisión narrativa de la literatura que aborda los mecanismos moleculares de resistencia, el uso de bases de datos estructurales como el Protein Data Bank (PDB) y la aplicación de pipelines jerárquicos que integran cribado virtual, modelado molecular, predicciones ADME/Tox y validación experimental. Los estudios analizados indican que la bioquimioinformática acelera el descubrimiento de fármacos, reduce costos y permite la selección de candidatos prometedores con mayor potencial de actividad biológica, incluso frente a patógenos críticos como *Klebsiella pneumoniae*. De este modo, la integración de herramientas computacionales, inteligencia artificial y validación biológica consolida este enfoque como una estrategia prometedora para el diseño de nuevos fármacos frente a cepas multirresistentes.

Palabras clave: resistencia antimicrobiana, bioquimioinformática, cribado virtual, antimicrobianos, *Klebsiella pneumoniae.*

1 INTRODUCTION

Antimicrobial resistance (AMR) represents a severe global public health problem, predominantly affecting hospitalized patients but increasingly present in community settings. AMR compromises treatment efficacy and increases morbidity and mortality rates associated with infections (Oliveira et al., 2023; Ahmed et al., 2024; Melgarejo-Touchet et al., 2024; World Health Organization [WHO], 2024). Estimates indicate that such infections account for approximately 25% of deaths worldwide and 45% in less developed countries (WHO, 2024). According to projections by Fongang, Mbaveng, and Kuete (2023), by 2050 mortality attributable to antimicrobial resistance will reach 4.73 million in Asia, 4.15 million in Africa, 0.39 million in Europe, 0.392 million in Latin America, 0.317 million in North America, and 0.022 million in Oceania.

Multiple mechanisms drive this resistance, including the production of drug-inactivating enzymes and structural alterations in cell wall proteins that reduce antibiotic uptake. As a result,

healthcare systems face longer hospital stays, increased frequency and severity of infections, and a growing reliance on high-cost and sometimes more toxic drugs (Batista & Ribeiro, 2020; Antimicrobial Resistance Collaborators, 2022; Oliveira et al., 2023; Brasil, 2024).

According to the Pan American Health Organization (PAHO, 2017), bacteria belonging to the genera *Acinetobacter* and *Pseudomonas*, as well as several members of the Enterobacteriaceae family (including *Klebsiella*, *Escherichia coli*, *Serratia* and *Proteus*), rank among the most critical multidrug-resistant pathogens. These organisms pose particular risks in hospital environments and among patients requiring ventilators or catheters, as they cause severe infections such as sepsis and pneumonia (PAHO, 2017).

Among Enterobacteriaceae, *Klebsiella pneumoniae* (*K. pneumoniae*) stands out as a major virulent agent responsible for severe nosocomial infections, including pneumonia, meningitis, and urinary tract infections, particularly in immunocompromised individuals. This pathogen also contributes to community-acquired infections in Brazil and worldwide and exhibits a remarkable capacity to develop enzymatic resistance mechanisms against a wide range of antibiotics, including carbapenems. Such resistance significantly limits therapeutic options and underscores the urgent need for novel antimicrobial agents (Djahmi et al., 2014; Sousa et al., 2019; Terreni et al., 2021; Li et al., 2023). In the state of Amapá, this situation mirrors the global trend. Data from the Brazilian Health Regulatory Agency (ANVISA, 2023) on healthcare-associated infections (HAIs) and antimicrobial resistance indicate that 67% of *K. pneumoniae* strains isolated from intensive care units exhibited resistance to carbapenems.

Given this challenging scenario, overcoming obstacles in the discovery and development of new antibacterial agents has become an urgent priority (Aragón-Muriel et al., 2025; Silva et al., 2025). In this context, biochemoinformatics has emerged as a promising tool to address antimicrobial resistance (Oliveira et al., 2023). This approach employs virtual screening strategies, molecular modeling, and experimental validation through the use of structural databases, molecular docking tools, ADMET prediction, and molecular dynamics simulations. These integrated methods accelerate the identification of promising compounds while optimizing time and cost during the early stages of drug discovery (Bastos et al., 2023; Oliveira et al., 2023).

Accordingly, reviewing and discussing the advances, challenges, and perspectives of biochemoinformatics in combating antimicrobial resistance highlights its contribution to rational

drug design against multidrug-resistant strains and to the promotion of scientific innovation in healthcare.

2 METHODOLOGY

This study constitutes a narrative literature review with a qualitative and descriptive approach, focusing on the application of biochemoinformatics to address bacterial resistance. The authors conducted the literature search in the PubMed, Scopus, SciELO, ScienceDirect, and Google Scholar databases, as well as in institutional documents from the World Health Organization, the Pan American Health Organization, and the Brazilian Health Regulatory Agency (ANVISA).

The search employed descriptors in both Portuguese and English related to antimicrobial resistance and computational tools. The review included full-text publications in Portuguese, English, and Spanish, predominantly published between 2018 and 2025, that directly addressed the application of computational methods in the context of bacterial resistance. The authors excluded duplicate studies and publications that did not align with the study objectives. The authors conducted the analysis of the selected articles using a descriptive and interpretative approach, with a narrative synthesis of the main findings.

3 THEORETICAL FRAMEWORK

3.1 MOLECULAR MECHANISMS OF RESISTANCE AND THE USE OF DATABASES SUCH AS THE PROTEIN DATA BANK (PDB)

The discovery of antibiotics revolutionized medicine; however, their indiscriminate use and the selective pressure exerted on bacteria have accelerated the evolution of resistance mechanisms. The main drivers of antimicrobial resistance include the inappropriate or excessive use of antibiotics, low-quality medications, inadequate sanitation, and natural selection. Inappropriate antibiotic use encompasses, among other factors, incomplete treatment, improper prescription, and self-medication. Microorganisms employ remarkably diverse resistance mechanisms, including antibiotic inactivation through neutralization, active extrusion from the

cell, and structural modifications of the bacterial envelope (Bharadwaj et al., 2022; Ahmed et al., 2024).

To evade the effects of antibiotics, microorganisms have developed resistance strategies that complicate disease treatment. The principal bacterial resistance mechanisms include alterations in membrane permeability, whereby specific channels responsible for the uptake of certain substances are modified, leading to resistance to specific drugs in Gram-negative bacilli; efflux pumps that actively expel antimicrobials from the intracellular to the extracellular environment; modification of the drug target site, which prevents antibiotic binding; and enzymatic mechanisms. In addition, bacteria may develop acquired resistance through the uptake of new resistance genes or DNA from other bacteria via horizontal gene transfer (Gluglieri, 2020; Bharadwaj et al., 2022; Dalmolin et al., 2022; Fontenele et al., 2023; Ahmed et al., 2024).

3.1.1 Enzymatic inactivation of antibiotics by β-Lactamases and carbapenemases

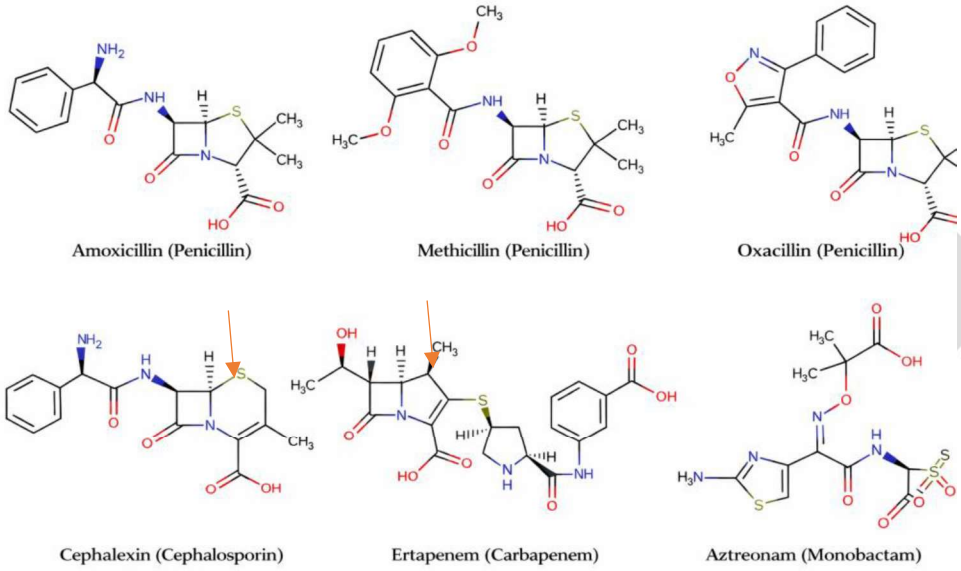
β-Lactamases are bacterial enzymes that inactivate antibiotics by hydrolyzing the β-lactam ring, thereby preventing the drug from interacting with its target receptors, the penicillin-binding proteins (PBPs) of the bacterial cell wall (Silva & Aquino, 2018; Gluglieri, 2020). β-Lactamases vary according to substrate specificity and producing microorganism and are classified into four molecular classes (A, B, C, and D) based on the Ambler classification, which relies on structural criteria (Gluglieri, 2020; Dalmolin, 2022). Figure 1 illustrates the structure of the β-lactam ring and the cleavage site catalyzed by carbapenemases, thereby facilitating the understanding of the mechanism underlying the inactivation of β-lactam antibiotics.

Among β-lactamases are penicillinases, cephalosporinases, and carbapenemases, with carbapenemases predominantly found in Gram-negative bacteria, particularly Enterobacteriaceae. These enzymes degrade essential chemical structures of penicillins, monobactams, and cephalosporins, rendering these antibiotics ineffective and severely limiting therapeutic options in clinical practice (Batista & Ribeiro, 2020; Gluglieri, 2020). Class A carbapenemases are serine carbapenemases, as they possess a serine residue as the primary catalytic component located within the active site. Representative Class A carbapenemases include *Klebsiella pneumoniae* carbapenemase (KPC), non-metalloenzyme carbapenemase (NMC), imipenem-hydrolyzing carbapenemase (IMI), *Serratia marcescens* enzyme (SME), and

Guiana extended spectrum (GES) β-lactamases. Currently, KPC is the most clinically and epidemiologically significant carbapenemase worldwide, including in Brazil (Gluglieri, 2020).

Within this context, β-lactam–resistant *K. pneumoniae* strains harboring this enzyme became known as *Klebsiella pneumoniae* carbapenemase (KPC I) strains. Researchers first identified KPC-producing strains resistant to all classes of β-lactam antibiotics in 1996 through the Intensive Care Antimicrobial Resistance Epidemiology (ICARE) surveillance project in North Carolina, United States. This scenario is particularly concerning because *K. pneumoniae* accounts for approximately 3% to 8% of hospital-acquired pneumonias worldwide, especially among mechanically ventilated patients (Batista & Ribeiro, 2020; Selim et al., 2023).

Figure 1. Representative chemical structure of β-lactam antibiotics, highlighting the β-lactam ring, the site susceptible to hydrolysis catalyzed by β-lactamases and carbapenemases



Source: Adapted from Oliveira *et al* (2023)

3.1.2 Other resistance modification mechanisms

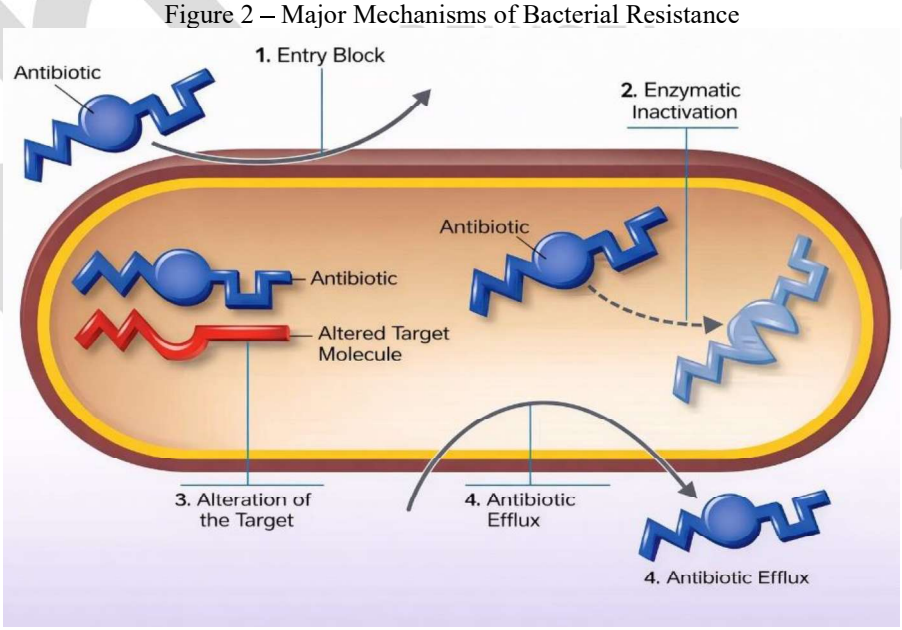
Additional resistance mechanisms involve alterations in metabolic pathways, modification of binding sites such as ribosomes that reduce antimicrobial efficacy, and increased activity of efflux pumps that remove antibiotics from bacterial cells before they reach concentrations sufficient to cause damage. In addition, bacteria can form biofilms, which are

surface-adherent microbial communities that create a physical barrier limiting antibiotic penetration and providing additional protection to bacterial cells (Uruén et al., 2021).

Moreover, bacteria acquire resistance through genetic dissemination mechanisms, whereby resistance genes are obtained from bacteria of the same species or from different species and even genera through horizontal gene transfer. This process is facilitated by mobile genetic elements such as plasmids, transposons, and integrons (Partridge et al., 2018; Ahmed et al., 2024).

This genetic mobility enables the rapid spread of multidrug resistance (MDR) among microbial populations, allowing multiple strategies to counteract antimicrobials used in medical treatment and thereby establishing antimicrobial resistance as a global public health problem (Partridge et al., 2018; Achong-Sánchez et al., 2024; World Health Organization [WHO], 2024). The main resistance mechanisms are illustrated in Figure 2.

Figure 2 – Major Mechanisms of Bacterial Resistance



Source: Silva et al., 2022

3.1.3 Use of the Protein Data Bank (PDB) for obtaining three-dimensional models of bacterial molecular targets

In the context of the escalating crisis of bacterial resistance, the use of bio-cheminformatics tools has emerged as a promising strategy that enables faster approaches to the discovery of new drugs. Within this framework, the use of accurate three-dimensional (3D) models of bacterial molecular targets is essential.

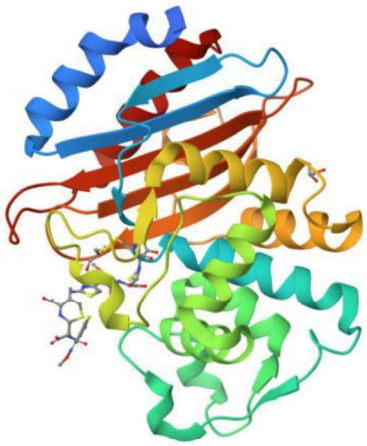
The Protein Data Bank (PDB), established in the 1970s, represents the first open-access digital data resource in the biological sciences. The database currently contains approximately 200,000 experimentally determined 3D structures obtained through X-ray crystallography, nuclear magnetic resonance spectroscopy, and electron microscopy. These accessible data allow researchers to elucidate molecular function, understand how molecules interact, determine how they catalyze chemical reactions, and clarify how they operate within cells. The PDB also serves as a valuable resource for students and educators, as it facilitates teaching and learning in structural biology (Goodsell et al., 2019; Méndez-Lucio et al., 2021).

Moreover, immediate access to these structures through the PDB enables virtual screening for the rapid identification of potential drug candidates. Molecular docking studies allow researchers to determine how small molecules bind to target proteins, while molecular dynamics simulations and interaction analyses support the rational design of more effective drugs (Méndez-Lucio et al., 2021). According to Goodsell and colleagues (2021), between 2010 and 2016 the PDB supported the discovery of approximately 90% of the 210 new drugs approved by the United States Food and Drug Administration (FDA). The PDB contains a substantial number of structures of essential proteins from priority pathogens, such as Klebsiella pneumoniae, Pseudomonas aeruginosa, and Mycobacterium tuberculosis. Researchers widely use these structures for the structural investigation of enzymes associated with antibiotic inactivation, including β-lactamases.

Accordingly, the use of three-dimensional models derived from the Protein Data Bank (PDB) plays a central role in elucidating resistance mechanisms mediated by enzymes such as KPC (Figure 3), in the development of therapeutic strategies based on enzyme inhibition, and across multiple research and educational domains in structural biology. These domains include

the discovery of new biomaterials, pharmaceuticals, and diagnostic tools (Goodsell et al., 2019; Burley, 2021; Berman et al., 2025).

Figure 3. Three-dimensional representation of Klebsiella pneumoniae carbapenemase (PDB ID: 5UJ3) in complex with a ligand, obtained from the Protein Data Bank (PDB) and used solely for illustrative purposes.



Source: RCSB Protein Data Bank.

3.2 APPLICATION OF HIERARCHICAL PIPELINES IN THE IDENTIFICATION OF BIOACTIVE COMPOUNDS WITH POTENTIAL ANTIMICROBIAL ACTIVITY

Conventional antimicrobial drug development faces significant challenges, including high costs and long research timelines from initial screening to clinical validation. Consequently, faster discovery strategies have gained increasing relevance, particularly those that combine virtual screening, artificial intelligence, and experimental assays in an organized sequence known as hierarchical pipelines (Askr et al., 2022; Oliveira et al., 2023b; Mulat et al., 2025). These pipelines consist of structured workflows with multiple levels of filtering and prioritization, based on *in silico* computational analyses that select organic molecules with potential antibiotic activity against relevant therapeutic targets (Oliveira et al., 2023b).

This approach integrates virtual screening, molecular modeling, and experimental validation, starting from large molecular datasets that are progressively reduced using increasingly specific criteria. Initially, researchers apply fast and low-cost computational methods, such as database screening and the prediction of pharmacokinetic and toxicological properties. More advanced techniques, including molecular docking and molecular dynamics

simulations, are subsequently employed, resulting in a limited number of candidates with genuine antibacterial potential for *in vitro* and *in vivo* validation (Piccirillo and Amaral, 2018; Bastos et al., 2023; Oliveira et al., 2023a; Oliveira et al., 2023b). However, virtual screening presents inherent challenges related to ligand–receptor interactions, including metabolic stability and ligand toxicity, which require the combined use of multiple computational tools (Piccirillo and Amaral, 2018).

In this context, hierarchical pipelines for identifying bioactive compounds with antimicrobial potential represent a central strategy to address antimicrobial resistance. This approach integrates chemical diversity, including natural and synthetic compounds, with computational prediction and biological validation. As a result, it reduces costs, improves hit identification, and directs experimental efforts toward candidates with a higher probability of success. The methodological framework adopted by the Applied Computational Chemistry Research Group at the Federal University of Amapá (UNIFAP) is based on an integrated bio-cheminformatics pipeline that combines virtual screening, molecular modeling, pharmacokinetic and toxicological predictions, and structural and dynamic analyses to identify promising bioactive compounds for subsequent experimental validation (Figure 4).

Initially, compounds are rationally selected from public and/or private chemical databases, including natural, synthetic, and semisynthetic molecules organized into virtual libraries (Step 1; Figure 4). These compounds undergo hierarchical virtual screening to reduce chemical space and prioritize candidates with greater pharmacological potential.

Next, the selected molecules are evaluated using pharmacokinetic and toxicological predictions (ADME/Tox) through established platforms such as BIOVIA Discovery Studio, Derek Nexus, and tools provided by the Swiss Institute of Bioinformatics (SIB). This step estimates parameters related to absorption, distribution, metabolism, excretion, and potential toxicological risks, allowing the early exclusion of unfavorable compounds (Step 2; Figure 4).

Molecular docking is then performed using the DockThor software to analyze ligand binding modes, conformational orientations, and interaction affinities with selected biological targets. The best poses are selected based on energetic and geometric criteria, as well as relevant intermolecular interactions (Step 3; Figure 4).

The most promising protein–ligand complexes are subsequently subjected to molecular dynamics simulations using the GROMACS package to evaluate system stability over time and the dynamic behavior of interactions under near-physiological conditions (Step 4; Figure 4).

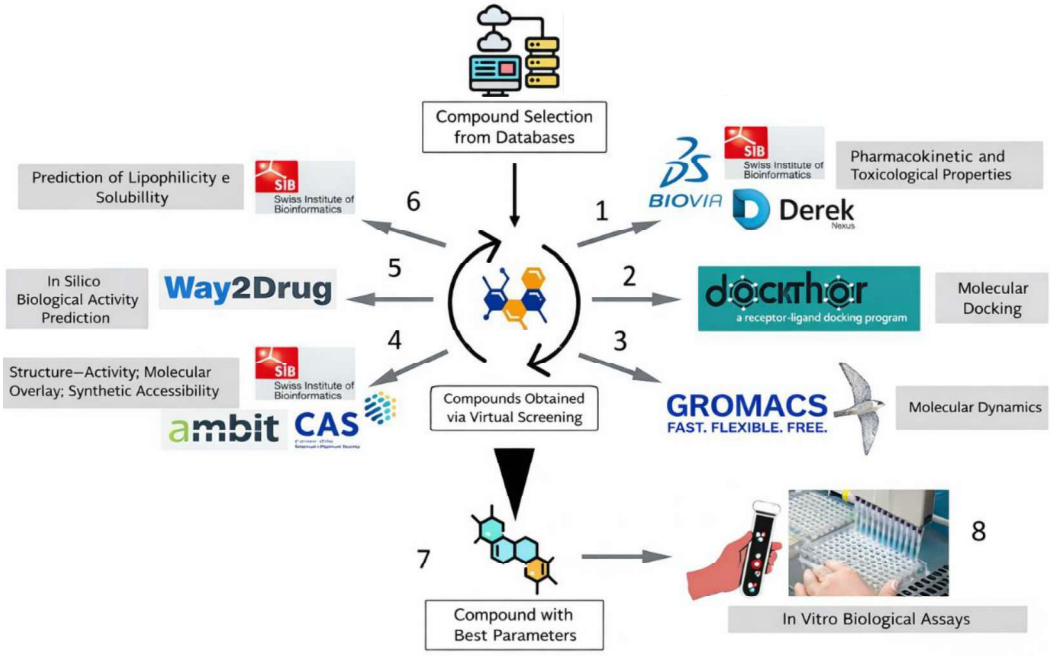
In parallel, molecular overlap analyses, structure–activity relationship (SAR) studies, and synthetic accessibility predictions are conducted using tools such as AMBIT and SwissADME modules. These analyses assess the feasibility of synthesis and structural optimization of the candidate compounds (Step 5; Figure 4).

Physicochemical properties, particularly lipophilicity (LogP) and aqueous solubility (LogS), are also evaluated using servers from the Swiss Institute of Bioinformatics to ensure that prioritized compounds display drug-like characteristics and suitable bioavailability (Step 6; Figure 4).

By integrating all computational parameters—including binding affinity, dynamic stability, ADME/Tox profiles, synthetic accessibility, and physicochemical properties—the pipeline enables the selection of compounds with the most favorable overall profiles. These compounds are classified as potential hits or leads (Step 7; Figure 4).

Finally, prioritized compounds are submitted to *in vitro* biological assays, which are essential for validating *in silico* predictions and confirming the pharmacological activity observed computationally. This final step consolidates the integrated methodological approach proposed by the research group (Figure 4; Step 8).

Figure 4 – Example of a schematic workflow of hierarchical virtual screening stages



Source: Prepared by the authors.

3.3 REPRESENTATIVE STUDIES APPLYING BIOCHEMOINFORMATICS

Research conducted by the Applied Computational Chemistry Research Group (http://dgp.cnpq.br/dgp/espelhogrupo/10685), affiliated with the Molecular Modeling and Computational Chemistry Laboratory at the Federal University of Amapá (www2.unifap.br/lmqc), provides representative evidence of the application of biochemoinformatics pipelines to combat bacterial resistance through the rational discovery of novel antimicrobial agents.

Within this framework, Oliveira et al. (2023) performed a hierarchical virtual screening of polyoxygenated dibenzofurans against methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The study began with a pivot molecule with experimentally validated activity, followed by the construction of a pharmacophore model and large-scale screening of chemical structure databases. Subsequent steps included similarity analysis, ADME/Tox prediction, antibacterial activity prediction, molecular docking against essential targets, molecular dynamics simulations, and free energy calculations. This integrated workflow led to the selection of three hit compounds exhibiting favorable binding affinity, conformational stability, and synthetic accessibility, supporting their progression to experimental validation.

Collectively, studies from this research group demonstrate the consolidation of biochemoinformatics pipelines as a rational strategy for discovering new antimicrobial agents. Starting from template compounds, natural products, and metal complexes, these approaches integrate virtual screening, structural similarity analysis, ADME/Tox-based refinement, evaluation of synthetic accessibility, and advancement toward synthesis and biological validation within collaborative research networks. These efforts enabled the identification of promising candidates against critical drug-resistant pathogens, including *Staphylococcus aureus*, *Mycobacterium abscessus*, and multidrug-resistant Gram-negative bacteria such as *Klebsiella pneumoniae*. Together, these findings reinforce the translational character of the laboratory and highlight the role of biochemoinformatics as a strategic funnel for accelerating antimicrobial drug discovery (Bastos et al., 2021; Moraes-Neto et al., 2022; Aragón-Muriel et al., 2025; Silva et al., 2025).

4 FINAL CONSIDERATIONS AND PERSPECTIVES

Hierarchical virtual screening integrated with biochemoinformatics approaches has become established as an effective and cost-efficient strategy to accelerate the discovery of new antibiotics in the face of advancing bacterial resistance. By integrating structural, chemical, and biological data, biochemoinformatics enables the selection of compounds with potential biological and therapeutic activity, functioning as a rational funnel for lead identification. The practical relevance of this approach is exemplified by the identification of halicin, a small synthetic molecule initially investigated as an antidiabetic agent and later repurposed as an antibiotic through deep learning–based computational screening. Prioritized in silico from large chemical libraries, halicin underwent experimental validation and demonstrated broad-spectrum bactericidal activity, including against multidrug-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA).

Regarding future perspectives, the integration of metabolomic data stands out as a promising avenue for more accurate target identification, alongside the increasing use of artificial intelligence and machine learning to predict resistance profiles and automate screening stages. In parallel, strengthening regional epidemiological surveillance and expanding collaborative open-data platforms represent essential measures to support more context-sensitive and

responsive pipelines tailored to local demands. Finally, experimental validation remains indispensable for confirming computational findings and translating prioritized candidates into tangible therapeutic solutions, thereby consolidating biochemoinformatics as an applied tool in the fight against antimicrobial resistance, particularly in regions such as the state of Amapá.

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