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Molecular Docking-Guided Repositioning of Non-Antibiotic Compounds as Potential Inhibitors of *Staphylococcus aureus*

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Abstract— The rapid emergence of antimicrobial resistance in Staphylococcus aureus underscores the urgent need for alternative therapeutic strategies beyond conventional antibiotics. Drug repositioning offers a time- and cost-efficient pathway by leveraging approved pharmaceuticals with established safety profiles. In this study, we investigated the potential of non-antibiotic drugs as inhibitors of S. aureus tyrosyl-tRNA synthetase (TyrRS; PDB ID: 1JIJ), a validated antibacterial target essential for protein synthesis.

A library of 34 compounds was screened using molecular docking, yielding 15 candidates with favorable binding energies and interactions within the TyrRS active site. Six compounds—meloxicam, piroxicam, quetiapine, fluoxetine, duloxetine, and atorvastatin—were prioritized for experimental validation based on binding affinity and interaction with catalytic residues. In vitro antimicrobial assays conducted at low concentrations (0.0002–0.0008 mg mL⁻¹ and 5–20 mg mL⁻¹) showed no significant inhibition. Subsequent evaluation at higher concentrations (20–50 mg mL⁻¹) revealed that piroxicam exhibited consistent, dose-dependent antibacterial activity, producing inhibition zones of 0.4–0.6 cm. Atorvastatin demonstrated selective activity at 40 mg mL⁻¹ with an inhibition zone of 0.7 cm, whereas fluoxetine and quetiapine were inactive under all tested conditions.

These results identify piroxicam and atorvastatin as promising candidates for antimicrobial repurposing and support the feasibility of targeting TyrRS with non-antibiotic drugs. This work highlights drug repositioning as a viable strategy to accelerate the discovery of novel antibacterial agents and address the escalating global burden of antimicrobial resistance.

Keywords— Drug repositioning, Non-Antibiotic Compounds, Staphylococcus aureus, molecular docking, antimicrobial resistance, Tyrosyl-tRNA synthetase (TyrRS)

I. Introduction

Drug repositioning has emerged as a valuable strategy in the pharmaceutical industry, offering a cost-effective and time-efficient alternative to the traditional drug development[1,2]. This approach includes the identification of new therapeutic uses of existing drugs already approved for other clinical indications. By building on established pharmacokinetic, safety and efficacy data, drug repositioning reduces the risks of initial development and speeds up the transition to clinical use.[3]. Drug repositioning against antibiotic-resistant bacterial pathogens has received considerable attention, because the rise of multi drug-resistant organisms is a major threat to global health and has outpaced the development of new antibiotics. In this context, the repositioning of non-antibiotic compounds with previously unknown antimicrobial activity offers a promising opportunity for the expansion of therapeutic options and the treatment of urgent clinical needs. Furthermore, this strategy facilitates the rapid introduction of therapeutic alternatives against pathogens such as *Staphylococcus aureus*, which can reduce conventional resistance mechanisms, thus contributing to the development of antimicrobial chemotherapy [4, 5].

Staphylococcus aureus (S. aureus), a highly adaptive pathogen that may become resistant to several classes of antibiotics, is one of the most important threats to antibiotic resistance.[6]. The emergence and spread of methicillin-resistant *Staphylococcus aureus* (MRSA) strains has been linked to increased morbidity, mortality and healthcare burdens worldwide. These strains are particularly challenging because they exhibit resistance to β-lactam antibiotics, which are commonly used as first-line agents for the treatment of staphylococcal infections. Moreover, their resistance often extends to multiple other antimicrobial classes, leaving clinicians with a limited number of effective therapeutic options. Consequently, S. aureus has been recognised by the World Health Organisation as a priority pathogen in the global fight against antimicrobial resistance[7]. The clinical and epidemiological challenges posed by MRSA highlight the urgent need for new antibacterial strategies that act through

non-conventional mechanisms and are less susceptible to resistance development[8]. In this respect, drug repurposing is a pragmatic solution, particularly when combined with computational tools to improve the efficiency and rationality of the discovery process[9].

One of the most helpful computational techniques to support drug repurposing efforts is molecular docking. This technique allows for virtual simulation of small molecule interactions with specific biological targets, predicting both binding affinity and molecular orientation within the active site [10, 11]. When used for bacterial targets such as S. aureus survival essential enzymes, molecular docking allows for a rapid screening of large libraries of compounds to identify candidates with a favorable interaction profile. This approach not only speeds up the prioritization of molecules for experimental validation but also provides insight into the relationship between structure and activity that may guide future optimization. In this study, molecular docking was used to evaluate non-antibiotic drugs for their potential to inhibit tyrosyl-tRNA synthetase (TyrRS), a key enzyme in the *S. aureus* protein biosynthesis pathway[12, 13]. Analysis of protein–ligand interactions at the active site of tyrosyl-tRNA synthetase (TyrRS) provides a rational and structural framework for the identification of new inhibitory activities, thus facilitating the development of therapeutic strategies against multidrug-resistant *S. aureus* infections[14].

The selection of candidate compounds for experimental validation was based on a multi-criteria filtering strategy integrating both computational and pharmacological considerations. From the initial docking library, compounds were prioritized not only according to predicted binding affinity toward tyrosyl-tRNA synthetase but also based on the quality of ligand–protein interactions, including contacts with key catalytic and conserved residues within the active site. Additional selection criteria included structural diversity, drug-likeness, and clinical relevance, favoring compounds with established pharmacokinetic and safety profiles to maximize translational potential within a drug repurposing framework. Importantly, compounds representing different therapeutic classes were retained to explore diverse chemical scaffolds and potential mechanisms of antibacterial action.

The design of in vitro concentration ranges was guided by both exploratory and practical considerations. Initial assays were conducted at low concentrations to evaluate potential antimicrobial activity within ranges closer to reported therapeutic plasma levels, thereby assessing the feasibility of repositioning under clinically relevant conditions. The absence of significant inhibition at these levels prompted the evaluation of higher concentrations to determine whether antibacterial effects could be observed under conditions of increased compound exposure. This stepwise approach enabled the identification of dose-dependent responses while accounting for the possibility that repurposed compounds may require higher concentrations to exert antimicrobial effects due to differences in primary pharmacological targets. Furthermore, the selected concentration ranges were constrained by solubility limits and assay compatibility to ensure experimental reliability.

II. MATERIALS AND METHODS

A. *Data Collection*

A total of 34 compounds were selected for molecular docking using a drug repurposing approach targeting *S. aureus*. These compounds represent a diverse set of molecules from various pharmacological classes, specifically non-antibiotic drugs with established clinical use. These included anti-inflammatory drugs, statins, antipsychotics, antidepressants, and antipyretics (Table I). Inclusion criteria were based on known pharmacokinetic properties, safety profiles, and structural suitability for molecular docking analysis. This diverse pharmacological spectrum was intended to maximize the likelihood of identifying novel antimicrobial activity among compounds with mechanisms of action distinct from those of conventional antibiotic. Chemical structures of the selected drugs were retrieved in SDF format from the PubChem database and prepared for molecular docking using standard ligand optimization protocols.

Table I. Non-Antibiotic selected compounds

Non-Antibiotic compounds	
Anti-inflammatory - Antipyretic	**Antipsychotic**
Diclofenac	Flupentixol
Ibuprofen	Trifluoperazine
Indomethacin	Perphenazine
Meloxicam	Quetiapine
Naproxen	Thioridazine
Nimesulide	Chlorpromazine
Valdecoxib	Fluphenazine
Paracetamol	Haloperidol
Ketoprofen	Olanzapine
Metamizole	Loxapine
Etodolac	**Antidepressant**
Piroxicam	Amitriptyline
Acetylsalicylic acid	Fluoxetine
Statin	Sertraline
Atorvastatin	Duloxetine
Rosuvastatin	Bupropion
Simvastatin	Escitalopram
Lovastatin	Agomelatine

B. *Ligand preparation*

Ligand preparation for molecular docking was performed using the PyRx 0.8 virtual screening tool, which incorporates the AutoDock Vina module for docking simulations. A total of 34 non-antibiotic compounds,

previously selected based on their pharmacological diversity and repurposing potential, were retrieved in PDB format from the PubChem database. The structures were imported into PyRx and subjected to energy minimization to optimize their geometries and reduce steric strain. Hydrogen atoms were added, and partial charges were assigned to ensure appropriate molecular configurations for docking. Subsequently, all ligands were converted to PDBQT format using Open Babel within PyRx, enabling compatibility with the AutoDock Vina engine. This standardized preparation ensured that all compounds were suitable for efficient and accurate virtual screening against the target protein.

C. *Protein preparation*

The crystal structure of *S. aureus* tyrosyl-tRNA synthetase (TyrRS) was retrieved from the Protein Data Bank (PDB ID: 1JIJ). The protein structure was preprocessed using PyRx, which involved conversion to macromolecule format, removal of crystallographic water molecules, addition of polar hydrogens, and assignment of Gasteiger charges. The active site region was defined based on reported literature, focusing on key amino acid residues essential for substrate binding and catalytic activity. The processed protein was subsequently saved in PDBQT format to ensure compatibility with the docking software

D. *Molecular Docking*

Molecular docking was performed using PyRx 0.8, a virtual screening platform that integrates AutoDock Vina as its docking engine. The prepared protein target and the 34 optimized ligands in PDBQT format were imported into the PyRx environment. A grid box was defined to encompass the active site of the tyrosyl-tRNA synthetase (TyrRS) enzyme, based on structurally conserved catalytic residues reported in the literature. Each compound was docked individually using the default AutoDock Vina parameters, which estimate binding affinity in terms of free energy (kcal/mol). Multiple binding poses were generated for each compound, and the pose with the lowest binding energy was selected for further analysis. The resulting docking scores were used to rank the compounds according to their predicted interaction strength with the target site. The top-ranked binding conformations were visualized using Discovery Studio Visualizer to examine ligand–protein interactions, including hydrogen bonds, hydrophobic contacts, and spatial complementarity within the active site

E. *Selection Criteria for Candidate Compounds*

Candidate selection for further analysis was based on a combination of computational and structural criteria. Compounds exhibiting the lowest (most negative) binding energy values—indicating high predicted affinity for the TyrRS active site (Tyr36, Cys37, Gly38, Ala39, Asp40, Leu70, Thr75, Asp80, Lys84, Tyr170, Gln174, Asp177, Gly193, Asp195, Gln196, and Ile200)—were prioritized. In addition to docking scores, the nature and number of interactions with key catalytic residues (such as Tyr36, Asp40, Asp80, Lys84, Tyr170, and Gln196) were evaluated to assess the likelihood of functional inhibition. Compounds were further analyzed based on their binding orientation, interaction specificity, and overall fit within the active pocket. To ensure relevance for drug repurposing, only FDA-approved non-antibiotic drugs with established safety profiles were considered for downstream *in vitro* testing. This integrative approach enabled the rational identification of the most promising candidates for potential antimicrobial repositioning against *Staphylococcus aureus.*

F. *In Vitro Antimicrobial Assay*

To evaluate the antimicrobial potential of the selected non-antibiotic compounds, *in vitro* susceptibility assays were performed using a *Staphylococcus aureus* strain reactivated in Luria-Bertani (LB) liquid medium. The bacterial culture was incubated at 30 °C under controlled conditions to ensure optimal growth. A total of 200 mL of solid LB medium was prepared, sterilized, and distributed into 10 sterile Petri dishes (20 mL per dish). Two plates were designated for bacterial growth monitoring and culture maintenance, while the remaining eight were used for antimicrobial susceptibility testing.

As previous studies have indicated no significant inhibitory activity at lower (0.0002–0.0008 mg/mL) and intermediate (5–20 mg/mL) concentrations, a high-concentration strategy was employed to evaluate the efficacy of the compounds identified by molecular docking. Stock solutions were prepared by dissolving 50 mg of each selected drug in 5 mL of 99% dimethyl sulfoxide (DMSO), yielding a final concentration of 10 mg/mL. Four working concentrations were subsequently generated by serial dilution.

The stock solution was prepared by dissolving 50 mg of each selected drug in 5 mL of 99% dimethyl sulfoxide (DMSO), resulting in a final concentration of 10 mg/mL. Four working concentrations were then prepared by sequential dilution as follows:

- 20 mg/mL (400 µL stock + 9.6 mL distilled water)
- 30 mg/mL (600 µL stock + 9.4 mL distilled water)
- 40 mg/mL (800 µL stock + 9.2 mL distilled water)
- 50 mg/mL (1000 µL stock + 9.0 mL distilled water)"

Uniform bacterial seeding was achieved by spreading 100 µL of the *S. aureus* suspension over the surface of each LB agar plate. Sterile Sensi-discs were then placed on the inoculated plates, and each disc was loaded with 20 µL of a prepared drug concentration. Two Petri dishes were used per drug, allowing the simultaneous evaluation of two concentrations per plate, with replicates included to ensure statistical reliability (Figure 1). Sulfamethoxazole, a known

anti-*S. aureus* agent, was employed as a positive control, while 99% DMSO served as a negative control to confirm that the solvent itself lacked antimicrobial activity.

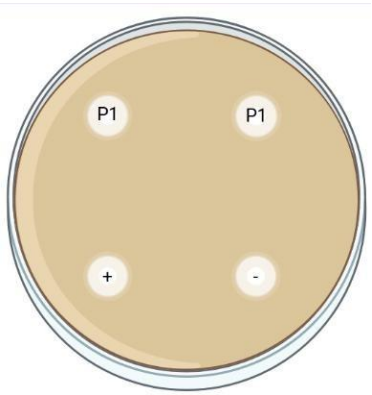


Figure 1. Schematic representation of the antimicrobial assay used to evaluate non-antibiotic drugs against *Staphylococcus aureus*.

Following disc application, plates were incubated at 30 °C for eight days to allow sufficient bacterial growth and the potential formation of inhibition zones. This extended incubation period ensured complete bacterial development and facilitated clear visualization of any antimicrobial effects. At the end of the incubation, inhibition zones were measured using digital calipers, and diameters were recorded in millimeters. All results were documented and compared across concentrations and compounds, allowing correlation of the observed antimicrobial activity with predicted binding affinities from molecular docking simulations

III. Results

Preliminary computational screening was conducted using molecular docking simulations in PyRx 0.8, with ligand–receptor interactions visually inspected in Discovery Studio Visualizer. A total of fifty non-antibiotic drugs from diverse pharmacological classes were screened against Staphylococcus aureus tyrosyl-tRNA synthetase (TyrRS; PDB ID: 1JIJ), a validated antimicrobial target involved in bacterial protein synthesis. Based on binding energy values and favourable interaction profiles with key residues within the active site, fifteen compounds were identified as initial hits. Of these, six drugs—Meloxicam, Piroxicam, Quetiapine, Fluoxetine, Duloxetine, and Atorvastatin—were prioritized for further analysis due to their optimal docking scores and structural complementarity within the active pocket (Figure 2).

Due to availability and feasibility constraints, four compounds (Piroxicam, Atorvastatin, Fluoxetine, and Quetiapine) were selected for experimental validation using in vitro susceptibility assays. Based on previously reported lack of activity at lower concentrations (0.0002–0.0008 mg/mL) and intermediate ranges (5–20 mg/mL), the current study employed high-concentration conditions (20, 30, 40, and 50 mg/mL) in an agar disc diffusion assay to evaluate antimicrobial activity.

Among the tested compounds, Piroxicam exhibited consistent antimicrobial activity across all concentrations, with inhibition zone diameters increasing from 0.4 cm at 20 mg/mL to 0.6 cm at 50 mg/mL, indicating a clear dose-dependent effect. Atorvastatin showed a unique response, with a measurable inhibition zone of 0.7 cm observed only at 40 mg/mL, while no activity was detected at 20, 30, or 50 mg/mL. Fluoxetine and Quetiapine, despite their favorable computational profiles, did not exhibit inhibitory effects at any concentration tested. Positive controls using Sulfamethoxazole produced inhibition zones ranging from 1.5 to 2.7 cm, confirming the reliability of the experimental setup, whereas DMSO controls showed no antimicrobial activity.

IV. DISCUSSION

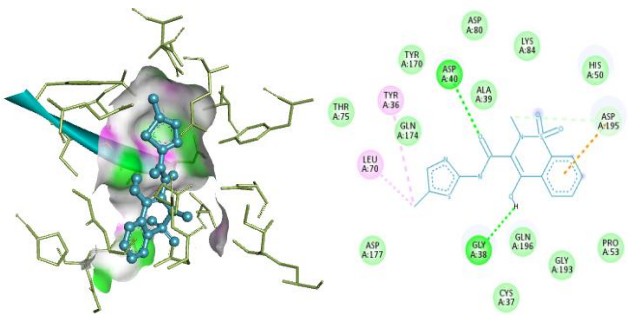
The findings of this study support the feasibility of drug repurposing as an effective and sustainable strategy for identifying alternative antimicrobial agents against *S. aureus*[15, 16]. Consistent with recent literature, the integration of virtual screening and experimental assays enables rapid prioritization of bioactive molecules from established pharmacopoeias. Previous studies have shown that non-antibiotic drugs, including antihistamines, NSAIDs, and statins, can target essential bacterial enzymes and pathways, providing further rationale for repositioning strategies against resistant pathogens.[17-20].

The computational phase of this study focused on the tyrosyl-tRNA synthetase enzyme (TyrRS), which catalyzes the aminoacylation of tRNA Tyr, a critical step in bacterial protein synthesis. Docking simulations indicated that the most promising compounds formed stable interactions with key catalytic residues, including Asp40, Asp80, Tyr170, Asp177, Gly193, Asp195, and Gln196. These results provided a structural rationale for subsequent biological validation.

Experimental validation confirmed the antimicrobial potential of Piroxicam, which exhibited a dose-dependent inhibitory response consistent with its docking-predicted interactions, including conventional hydrogen bonds, van der Waals forces, Pi-alkyl, and Pi–Pi T-shaped contacts at the enzyme's active site. These results suggest that Piroxicam may directly interfere with TyrRS enzymatic activity, thereby impairing bacterial protein synthesis[21].

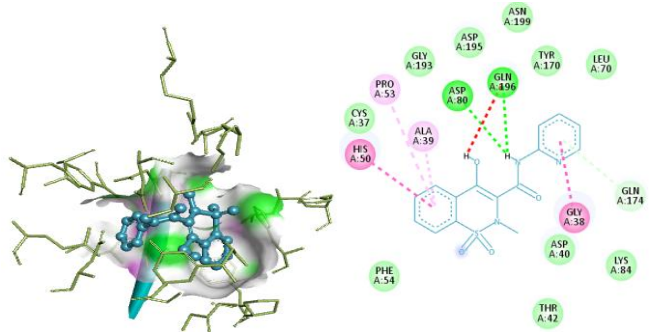
Atorvastatin, which exhibited inhibitory activity only at 40 mg/mL, displayed a more complex profile. The absence of activity at both lower and higher concentrations suggests a potential concentration threshold required for optimal target engagement. Such non-linear responses may arise from physicochemical factors, including solubility, membrane permeability, or conformational changes in the target protein at higher concentrations. This observation is consistent with the idea that some repositioned drugs may act within narrow therapeutic windows that must be experimentally determined[22]

Meloxicam



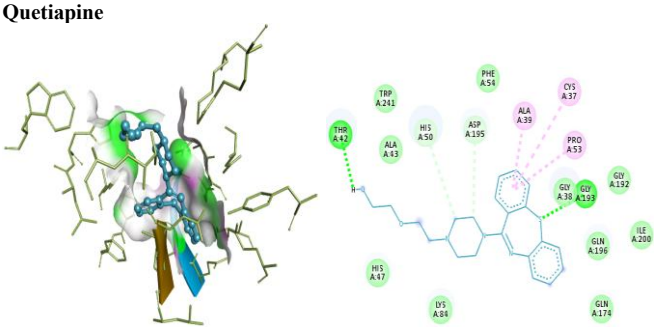
Binding Affinity (kcal/mol)	Conventional Hydrogen Bond	Carbon Hydrogen Bond	van der Waals	Alkyl	Pi-Anion
-8.7	GLY-38 ASP-40	ASP-195	CYS-37, ALA-39 HIS-50, PRO-53 THR-75, ASP-80 LYS-84, TYR-170 GLN-174, ASP-177 GLY-193, GLN196	TYR-36 LEU-70	ASP-195

Piroxicam



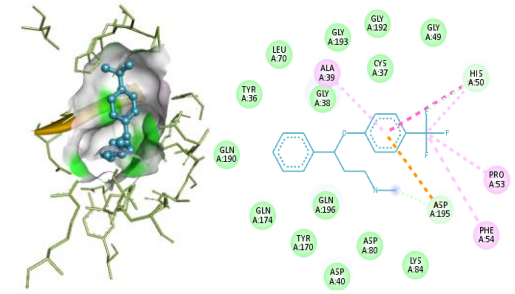
Binding Affinity (kcal/mol)	Conventional Hydrogen Bond	Pi-Donor Hydrogen Bond	van der Waals	Pi-Alkyl	Pi-Pi T-shaped
-8.0	ASP-80 GLN-196	GLN-174	CYS-37, ASP-40 THR-42, PHE-54 LEU-70, LYS-84 TYR-170, GLY193 ASP-195, ASN-199	ALA-39 PRO-53	GLY-38 HIS-50

Quetiapine



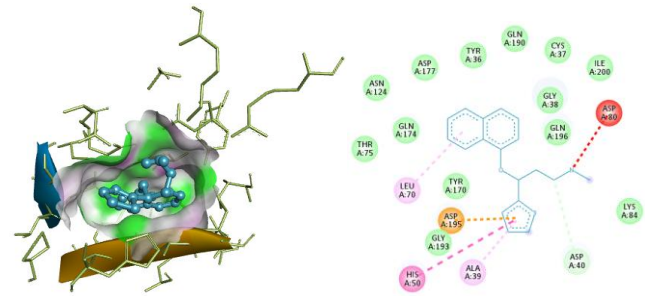
Binding Affinity (kcal/mol)	Conventional Hydrogen Bond	Carbon Hydrogen Bond	van der Waals	Pi-Alkyl
-8.1	THR-42 GLY-193	HIS-50 ASP-195	GLY-38, ALA-43 HIS-47, PHE-54 LYS-84, GLN-174 GLY192, GLN-174 ILE-200, TPR241	CYS-37 ALA-39 PRO-53

Fluoxetine



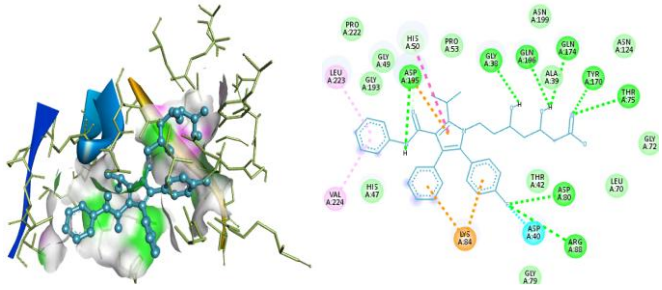
Binding Affinity (kcal/mol)	Carbon Hydrogen Bond	van der Waals	Alkyl	Pi-Alkyl	Pi-Pi T-shaped	Pi-Anion
-8.0	HIS-50 ASP-195	TYR-36, CYS-37 GLY-38, ASP-40 GLY-49, LEU-70 ASP-80, LYS-84 TYR-170, GLN-174 GLN-190, GLN-196	HIS-50 PRO-53 PHE-54	ALA-39	HIS-50	ASP-195

Duloxetine



Binding Affinity (kcal/mol)	Carbon Hydrogen Bond	van der Waals	Pi-Alkyl	Pi-Pi T-shaped	Pi-Anion
-7.8	ASP-40	TYR-36, CYS-37 GLY-38, THR-75 LYS-84, TYR-170, GLN-174, ASP-177 GLY-193, GLN-196 ILE-200	ALA-39 LEU-70	HIS-50	ASP-195

Atorvastatin



Binding Affinity (kcal/mol)	Conventional Hydrogen Bond	Carbon Hydrogen Bond	van der Waals	Pi-Alkyl	Pi-Pi T-cshaped	Pi-Anion	Halogen
-8,9	GLY-38 THR-75 ASP-80 ARG-88 TYR-170 GLN-174 ASP-195 GLN-196	HIS-50	ALA-39 THR-42 HIS-47 GLY-49 PRO-53 LEU-70 GLY-72 GLY-79 ASN-124 GLY193 ASN-199 PRO-22	LEU-223 VAL-224	HIS-50	LYS-84 HIS-50	ASP-40

Figure 2. Prioritized drugs based on docking scores and structural complementarity within the active pocket

In contrast, Fluoxetine and Quetiapine, despite favourable docking scores, did not exhibit antimicrobial activity under the tested conditions. This discrepancy highlights a limitation of molecular docking: although it predicts binding affinity and spatial complementarity, it does not account for critical biological factors such as cell wall penetration, efflux mechanisms, or compound stability in biological matrices [23, 24]. These negative outcomes underscore the importance of integrating *in silico* predictions with rigorous *in vitro* assessments to distinguish true hits from computational false positives

Finally, the study's use of high-concentration dosing, following earlier failures at subtherapeutic levels, emphasizes the importance of concentration optimization in antimicrobial screening. Although the effective concentrations reported here may exceed typical clinical dosing limits, they provide a valuable starting point for subsequent optimization efforts, including the design of analogs or formulation strategies aimed at enhancing activity while minimizing toxicity.

V. CONCLUSIONS

This study demonstrates the utility of a molecular docking-guided drug repositioning approach for identifying non-antibiotic compounds with potential antimicrobial activity against *Staphylococcus aureus*. Through virtual screening of 34 FDA-approved drugs, tyrosyl-tRNA synthetase (TyrRS) was successfully targeted as a key bacterial enzyme involved in protein synthesis. Computational analyses identified several promising candidates based on their binding affinities and interactions with catalytically relevant residues.

Subsequent *in vitro* validation confirmed the antimicrobial activity of Piroxicam, which exhibited consistent, dose-dependent inhibition of *S. aureus* growth across all tested concentrations. Atorvastatin displayed selective activity at a specific concentration, indicating a narrow therapeutic range that may be optimized through further investigation. In contrast, Fluoxetine and Quetiapine showed no biological activity, despite favorable docking profiles, underscoring the importance of integrating computational predictions with experimental validation for accurate compound selection.

Collectively, these findings support the feasibility of repurposing non-antibiotic drugs as a complementary strategy for antimicrobial development, particularly in the context of rising antibiotic resistance. Molecular docking serves as a cost-effective and rapid first-line screening tool for prioritizing candidate molecules, while in vitro assays remain essential for validating biological relevance. Future studies should focus on elucidating specific mechanisms of action, evaluating cytotoxicity profiles, and assessing potential synergistic effects with existing antibiotics to advance these findings toward clinical application

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