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RESEARCH ARTICLE

Mechanism of Antibiotic Resistance in Multi-Drug Resistant Klebsiella sp.: Protein and Drug Interactions

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Abstract: Multi-drug resistant Klebsiella pneumoniae poses a significant global health threat due to its resistance mechanisms against multiple antibiotic classes. The SHV-1 β-lactamase enzyme, a type of serine-based β-lactamase, plays a crucial role in hydrolyzing β-lactam antibiotics, contributing to treatment failures. This study investigates the molecular interactions between tazobactam, a β-lactamase inhibitor, and through computational approaches. Molecular docking using AutoDock 4.2 revealed strong binding affinity (-9.46 kcal/mol) between tazobactam and SHV-1 β-lactamase, with key interactions involving hydrogen bonds with ARG-205, MET-A186, THR-A71, and LYS-A234 residues. Molecular dynamics simulations over 100 nanoseconds using GROMACS 2025.1 demonstrated complex stability with RMSD fluctuations ranging from 0.15-0.2 nm after initial equilibration. RMSF analysis identified flexible regions (0.1-0.2 nm) important for drug binding dynamics. The computational analysis was complemented by ADME profiling to assess drug-like properties. Results indicate that tazobactam exhibits promising binding affinity and structural stability against SHV-1 β-lactamase, supporting its therapeutic potential in combination therapy. This study provides molecular-level insights into the mechanism of β-lactamase inhibition, contributing to the understanding of structure-activity relationships essential for developing effective treatments against multidrug-resistant Klebsiella infections.

Keywords: Klebsiella pneumoniae, SHV-1 β-lactamase, tazobactam, molecular docking, antibiotic resistance.

INTRODUCTION

Antimicrobial drug resistance (AMR) and multi-drug resistance (MDR) are becoming global threats nowadays [1]. Particularly, *Klebsiella pneumoniae*, which belongs to the Enterobacteriaceae family, has recently emerged as a non-stoppable contagious organism during clinical practice. It uses several mechanisms to restrict the entry of antibiotics, like surface porin proteins (OmpK35, and OmpK36, LamB, OmpK26, PhoE, and KpnO); using an active efflux system (AcrAB-TolC); biofilm formation. All these proteins were controlled by genes such as blaSHV, blaTEM, kpnEF, PhoPQ, etc. [2,3]. This organism produces nosocomial infections and is predominantly responsible for catheter-associated urinary tract infections, pneumonia, and blood-borne infections [4]] in the intensive care patients [5]. As this is the opportunistic pathogen which has drug resistance potential and increases the treatment cost [6], the World Health Organisation recently announced it as a critical priority pathogen [7]. It indicates MDR *Kl.pnemonia* infections need quick diagnostic protocols and novel treatment methods [8].

Latest technologies have unlocked its capacity to produce sulfhydryl variable β-lactamase enzymes (SHV-I) to break down the β-lactam ring of next-generation cephalosporins and penicillin antibiotics [9]. This is due to the establishment of a covalent bond with the β-lactam antibiotic using the active site serine residue containing 238- and 240 -positioned amino acids [10]. So, new and combined β-lactamase inhibitor antibiotic therapy has been proposed to break the β-lactamase-mediated resistance [11,12]. SHV-1 β-lactamase is a type of β-lactamase enzyme class A which is enriched with α-helices arrangement and encircled by a five-stranded β-sheet. The active site Ser70 (serine) is present in the conserved SXXK motif with the 240s loop and the Ω-loop [13].

Tazobactam, a type of β-lactamase inhibitor, can make the acylation of the serine active site by initial reversible binding, which helps to make a covalent bond with serine β-lactamase. So, the acylation of the active site's serine is caused by the initial reversible binding. The combination of tazobactam and piperacillin efficiently produced synergistic activity to suppress the activity of β-lactamases [14]. But identifying a similar the active site is quite a cumbersome process in drug development. Studying the protein-drug interactions at the molecular level may help to prescribe the precision medicine. It can be possible to excel at molecular docking (MD) and molecular dynamics simulations (MDS) to understand conformational changes, structural stability, and binding mechanisms of protein-drug interactions [15] and protein-ligand interactions by high-resolution molecular dynamics [16]. Also, thermodynamics, binding kinetics and conformational dynamics are essential to learning

the drug mechanisms [17]. Hence, the current study was carried out to determine the interaction between tazobactam and SHV-1 β-lactamase with the computational biological tools.

MATERIALS AND METHODS

2.1 Protein Structure Preparation:
Using PyMOL 2.5.2, the three-dimensional structure of SHV-1 β-lactamase was extracted from Protein Data Bank (PDB Id: 1SHV) [18, 19]. Hydrogen atoms were incorporated after water molecules by the AutoDockTools package. Heteroatoms were removed [20].

2.2 Ligand Preparation:
Tazobactum (PubChem database (CID: 123630)) was optimised with the help of Gaussian 15 software and the B3LYP/6-31G(d,p). Energy minimisation was carried out to identify the most stable conformer [21].

2.3 Molecular Docking: AutoDock 4.2.6 software was utilized to perform molecular docking [22].
The binding site was identified based on known catalytic residues with a grid box centred on Ser70. The Lamarckian genetic algorithm was deployed with 100 independent runs, a population size of 150, and maximum evaluations of 2.5 × 10^6

2.4 Molecular Dynamics (MD) Simulations:
GROMACS 2025.1 with the AMBER99SB-ILDN force field was used for the MD simulation study[23]. The TIP3P water model within the dodecahedral box was used to solvate the protein-ligand complex. The system was buffered with Na+ and Cl- ions at 0.15 M concentration. Energy minimisation was done using the steepest descent algorithm followed by NVT and NPT equilibration for 100 ps each. Production runs were done for 100 ns with a 2 fs time step [24] (https://manual.gromacs.org/2025.1/)).

2.5 ADME Analysis: Absorption, Distribution, Metabolism, and Excretion (ADME) characters were examined using the SwissADME web server [25] and the pkCSM platform [26]. Lipinski's Rule of Five and Veber's criteria were used to evaluate drug-likeness.
2.6 Data Analysis: GROMACS analysis tools were used to calculate binding energies, root mean square deviation (RMSD), and root mean square fluctuation (RMSF). VMD 1.9.4. Statistical analysis was performed in R software version 4.3.2 to analyse hydrogen bonds[27].

RESULTS

3.1 Molecular Docking Analysis: The strong binding affinity between tazobactam and SHV-1 β-lactamase has the binding energy of -9.46 kcal/mol was evaluated during the molecular docking study. Similar binding energy was already proved for tazobactam with class A β-lactamases [28]. The docking pose showcased the optimal positioning of tazobactam within the active site, developing a crucial attachment with key catalytic residues. Hydrogen bond analysis determined four primary interactions: MET-A186 (2.3 Å), THR-A71 (1.9 Å), and LYS-A234 (2.2 Å) (Fig. 1a) and ARG-205 (2.1 Å) (Fig. 1b). These binding affinities explore strong electrostatic and polar contacts that stabilise the inhibitor-enzyme complex. This binding energy proves that tazobactam makes a thermodynamically stable complex with SHV-1 β-lactamase, which is essential for potential inhibition.

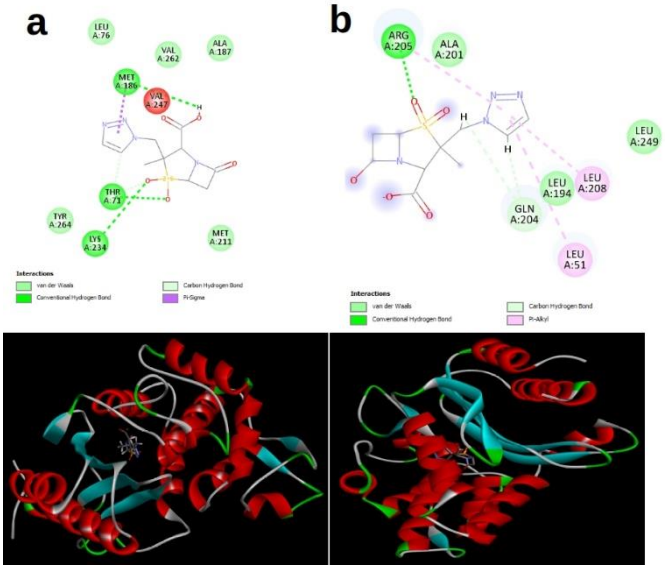

Fig. 1. Binding affinity of the tazobactam with SHV-1 β-lactamase (a). interaction with MET-A186 (2.3 Å), THR-A71 (1.9 Å), and LYS-A234 (2.2 Å); (b). ARG-205 (2.1 Å)

In the present study, the main affinity with ARG-205 is very crucial due to substrate binding and catalysis in class A β-lactamases [29]. This proves the importance of the hydrogen bonding pattern with certain residue interactions to make the stable inhibitor-enzyme complex. The binding of tazobactam with THR-A71 at the catalytic serine (Ser70) indicates that this could stop the nucleophilic attack which is necessary for β-lactam hydrolysis [13].

The molecular-level interaction of tazobactam with SHV-1 β-lactamase yields significant insights. Fragmentation of tazobactam causes inactivation of SHV-1 β-lactamase. Pagan- Pagan-Rodríguez et al. has demonstrated that fragmentation of tazobactam happens when it attached to the active site Ser70 in this enzyme and revealed that the Ser→Gly substitution at amino acid position 130 is not crucial for enzyme inactivation [30]. Further, this study was in agreement with the research of Bellini et al. [31], who demonstrated tazobactam's interaction with β-lactamase OKP-B-6 of *Klebsiella quasipneumoniae*.

3.2 Molecular Dynamics Simulation: The 100-nanosecond MD simulation offered insights into the dynamic activity of the tazobactam-SHV-1 complex. RMSD analysis proved the initial fluctuations during the first 10 ns, followed by stabilisation with values ranging from 0.15-0.2 nm (Fig. 2).

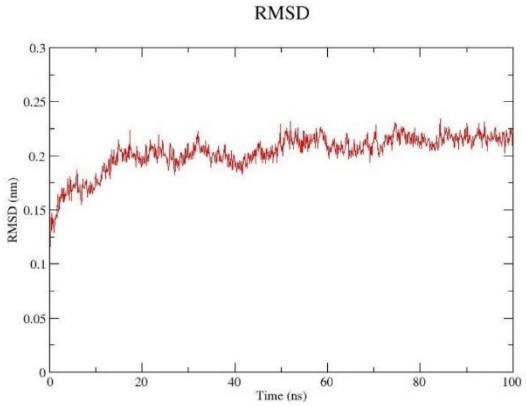

Fig. 2. Tazobactam – SHV-I complex determination in RMSD during molecular dynamic simulation analysis

During RMSD analysis, stabilisation after first equilibration confirms the stable formations of inhibitor-enzyme formation. In this study, MDS result confirms the stability of tazobactam-SHVI complex for over longer period of time. This supports the hypothesis that β-lactamase inhibitors bind with antibiotic in irreversible mode [32]. Also, the RMSD values of 0.15 to 2nm is relatively low indicates that tazobactam binding doesn't induce major alteration in protein structure. The protein backbone RMSD demonstrated excellent stability throughout the simulation, indicating that tazobactam binding does not impact confirmational changes overall protein structure. This makes the inhibitor more effective in SHV-I.

In RMSF analysis, most regions showing fluctuations between 0.1-0.2nm, confirms residue specific flexibility patterns. Notable flexibility at Ω-loop (residues 164-179) and the 240s loop are known for substrate binding and catalysis (Fig. 3). The above result was consistent the work done by Egorov et al. [33]. It is known that these loop regions change shape when they bind to a substrate and when they catalyse a reaction.

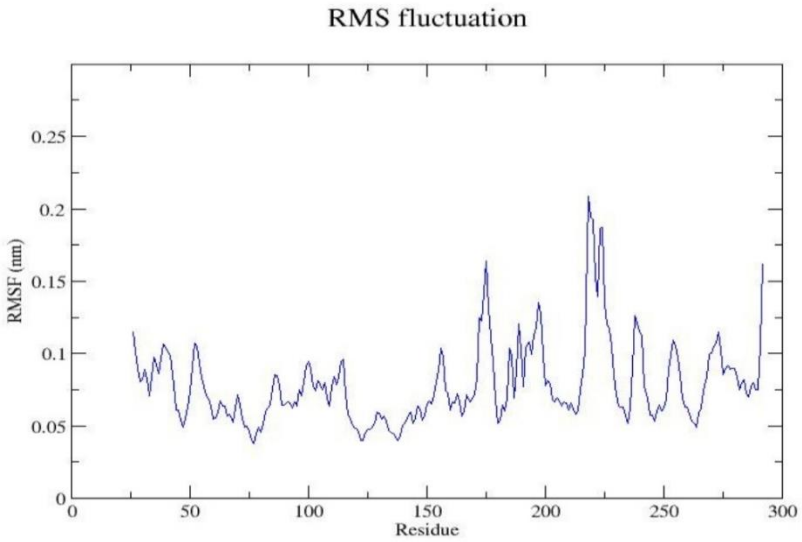

Fig. 3. Flexibility pattern analysis in RSMF analysis during molecular dynamic simulation analysis

It further confirms tazobactam does not induce protein to get rigid [34]. The active site residues showed minimal fluctuations, suggesting stable binding of the inhibitor.

3.3 Hydrogen Bond Dynamics:

In the entire simulation study, the number of hydrogen bonds between tazobactam and SHV-1 β-lactamase fluctuated between 2-5, with an average of 3.2 bonds per frame. The most persistent interactions involved ARG-205 and THR-A71, maintaining contact for >80% of the simulation time (Fig. 4).

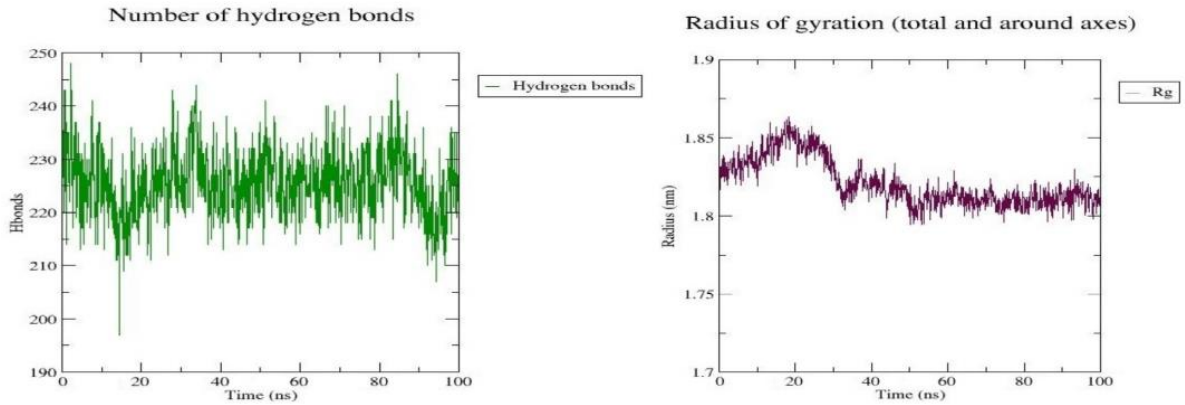

Fig. 4. Hydrogen bonds between tazobactam and SHV-1 β-lactamase

The binding kinetics of tazobactam was studied via the H2 bond dynamics. The interactions with the residues ARG-205 and THR-A71 is most essential for the recognition and binding of the inhibitor. This is the best perfect character of the effective inhibitor binding [35]. The change in the H2 bond counts (2-5) shows the dynamic nature of protein-ligand interactions are always changing and that unique binding conformations that affect the overall binding affinity [36].

3.4 ADME Properties:

ADME properties help to understand a compound's drug-likeness property. In this study, a molecular weight of 300.29 Da with the LogP (-1.23) and polar surface area value of 112.73 Ų was observed for tazobactam during ADME analysis (Fig. 5). The above characters were fulfilling the criteria of Lipinski's principle. This predicts the molecule's water solubility and moderate permeability, for which it can be used in the intravenous (IV) solution. As per ADME analysis, tazobactam reached the drug-likeness standards, indicating the human body can easily absorb this molecule with enhanced stability [37]. Further, the moderate permeability predictions confirm that the tazobactam can be distributed equally in tissue compartments [38]. Hence, it is a more suitable candidate for clinical application as a β-lactamase inhibitor.

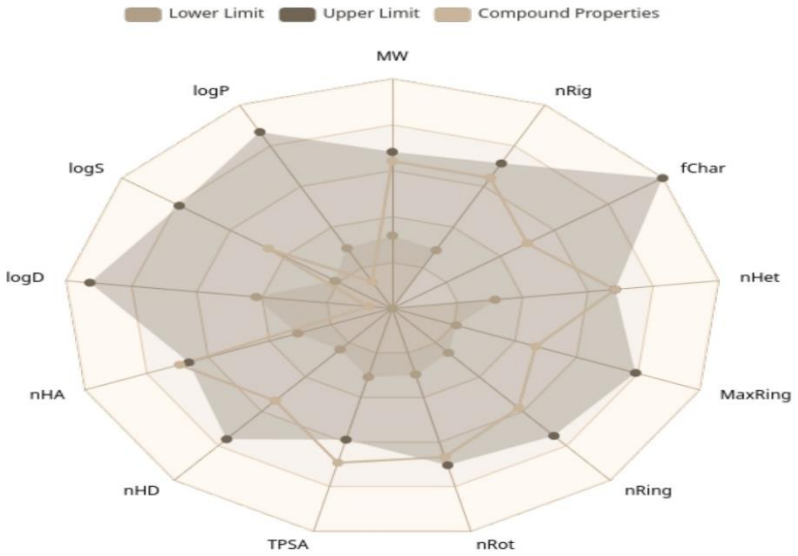

Fig.5. Pharmacokinetic analysis

Crucial binding affinity areas will be helpful to understand mutational areas to clearly identify the resistance mechanisms [39,40,41]. In this way, the current study offered a detailed key finding on structural insights that paved the way to comprehend the resistance mechanisms to formulate the potential and novel β-lactamase inhibitors [42]. The current study suggests the future drug development requires the cross-checking the computation predictions and experimental validation of participating binding modes and drug kinetic parameters.

CONCLUSION

The efficacy of tazobactam's role as a β-lactamase inhibitor was demonstrated in this study. The compound's binding affinity (-9.45 kcal/mol) and stability with ARG-205, MET-A186, THR-A71, and LYS-A234 residues were confirmed. RMSD values in MD were recorded as 0.15-0.2 over 100 nanoseconds. The H2 dynamic pattern was elucidated for ARG-205 and THR-A71, and tazobactam's ADME properties were also explored. The above screened characters confirm that tazobactam can be the potential β-lactamase inhibitor against multi-drug resistant *Klebsiella penumoniae*. Additionally, the present study findings offered a novel route for the development of generation β-lactamase inhibitors to combat the emanating resistance mechanisms.

Data availability statement
Not applicable

Ethics statement
Not applicable

Author contributions
B. Arihanth Kumaran – conceived the idea and experimentations; Selvankumar – project guide, conceived idea, drafting, editing and proofing; Sankarganesh P – drafting, editing and proofing

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