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Research Article

Structural and mechanistic insights into *AmpC β-lactamase* from *Morganella morganii*

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ABSTRACT Antimicrobial resistance caused by β-lactamases is a global health issue. Among β-lactamases, AmpC β-lactamase plays a major role in resistance against broad-spectrum β-lactam antibiotics in Gram-negative pathogens. *Morganella morganii* is an emerging opportunistic pathogen causing urinary tract, wound, and nosocomial infections. However, structural and dynamic insights of AmpC β-lactamase enzyme remain limited. This study aimed to resolve the structural architecture of *M. morganii* AmpC and identify potential inhibitory compounds using an integrated computational workflow. The AmpC sequence (UniProt ID: P94958) was analyzed for physicochemical and immunological properties. The protein contains 379 amino acids with an estimated molecular weight of ~41.27 kDa and theoretical pI of 8.69. Antigenic profile score (score:0.449) showed possible antigenic potential. On the other hand, allergenicity analysis demonstrated the protein as non-allergenic protein. Comparative homology modeling produced a high-quality 3-dimensional protein structure for downstream analysis. Ramachandran analysis showed that more than 90% residues located in favoured regions which confirms structural reliability. The Phyre2-derived model showed optimal query coverage and structural integrity. The screening of 21 compounds identified Oncoglabrinol C as the strongest binder (binding energy = −11.44 kcal/mol, inhibition constant = 4.09 nM). The ligand formed stable hydrogen bonds with catalytic residues such as Glu80, Arg147, Arg229, Val230, and Gln234. Additionally, π–π interactions were also observed involving Tyr189 and Tyr240. Lastly, molecular dynamics simulations ran over 100ns demonstrated structural stability of the AmpC–Oncoglabrinol C complex. RMSD stabilized near 6 Å after 80 ns, while radius of gyration decreased from approx. 22.6 Å to 20.6 Å with stable Hydrogen bonding. These results confirmed increase ligand binding and highly favorable interaction energetics. These results identify Oncoglabrinol C as a potential compound for inhibitor development. This work supports structure-guided drug discovery targeting AmpC-mediated β-lactam resistance.

KEYWORDS *Morganella morganii*, *AmpC*, Antimicrobial Resistance, β-lactamase, Nosocomial

Introduction

Antibiotic resistance is one of the most serious global health challenges today (Imtiaz *et al*, 2024; Vitiello *et al*, 2024). Gram-negative bacteria are major contributors to this crisis (Puljko *et al*, 2024). Many of these pathogens produce β-lactamase enzymes that destroy β-lactam antibiotics. AmpC β-lactamase is one of the most important resistance enzymes (Hinchliffe *et al*, 2022). It hydrolyzes penicillins, cephalosporins, and several β-lactam inhibitor combinations. *Morganella morganii* is an opportunistic Gram-negative pathogen linked to urinary tract and post-surgical infections (Narendrakumar *et al*, 2022; Russo *et al*, 2024). It is commonly found as a commensal organism but can become pathogenic under clinical conditions. The spread of AmpC-producing strains increases treatment failure risks (Ting *et al*, 2024). Overexpression of AmpC reduces the effectiveness of commonly prescribed antibiotics. Current therapeutic options are becoming limited due to multi-drug resistance (Vitiello *et al*, 2024). Carbapenems are often used as last-resort drugs. However, resistance against carbapenems is also increasing. The global burden of antimicrobial resistance is expected to rise further in coming decades. The lack of detailed structural and mechanistic understanding of AmpC enzymes complicates drug development. Therefore, identifying novel inhibitors against AmpC enzymes is urgently needed for future therapeutic strategies.

Differentially expressed genes (DEGs) play a major role in understanding disease mechanisms (Reza *et al*, 2022). DEG analysis helps identify genes that are upregulated or downregulated during infection or stress (Alam *et al*, 2022; Andalib *et al*, 2023). Among bacterial pathogens, DEGs analyses can highlight resistance-related pathways. These

genes may affect enzyme production, mutation response, or virulence mechanisms (Yang *et al*, 2024). Bioinformatics provides suitable tools to unveil these molecular patterns. It allows rapid analysis of genomics, transcriptomics, proteomics, and structural data (Alam *et al*, 2022). With the advent of computational biology, the analysis time and cost have been significantly reduced as compared to experimental approaches. Protein modeling can predict 3-dimensional structures in the absence of crystal structures. While molecular docking identifies potential drug candidates to enhance drug discovery (Ahmad and Raza, 2024; Heissel *et al*, 2024). On the other hand. molecular dynamics simulations undermine the protein stability in physiological environments. These tools together help predict protein behavior and ligand binding strength (Heissel *et al*, 2024). Bioinformatics also supports vaccine design and epitope prediction. It helps understand antigenicity and allergenicity properties of proteins (Agarwal *et al*, 2024; Shetty *et al*, 2024). Integrating DEG analysis with structural bioinformatics can improve drug target validation. Therefore, bioinformatics approaches are highly useful for studying resistance proteins like AmpC.

Despite extensive research, structural details of *Morganella morganii* AmpC remain limited. Many experimental structures are unavailable for this specific enzyme. This creates challenges for structure-based drug discovery. There is also limited information about natural compound inhibitors targeting this protein. Computational approaches can help bridge this knowledge gap. This study aims to build a reliable three-dimensional model of AmpC β-lactamase. The study also evaluates physicochemical and immunological properties of the protein. Another objective is to identify potential inhibitors through molecular docking analysis. The study further validates binding stability using molecular dynamics simulations. Binding free energy calculations are also performed to confirm ligand affinity. The study focuses on screening both known and natural compounds. Identifying strong binders can help guide future experimental drug development. This work also contributes to understanding structural mechanisms of antibiotic resistance. The results may support development of new therapeutic strategies against resistant pathogens. Therefore, this study is important for advancing structure-guided drug discovery against AmpC-mediated resistance.

Materials and Methods

Sequence Retrieval and Primary Analysis

The amino acid sequence of AmpC beta-lactamase from *Morganella morganii* was retrieved from the UniProt database. The UniProt accession ID used was P94958. The FASTA sequence was downloaded for further computational analysis. Primary sequence analysis was performed using the ExPASy ProtParam tool. Molecular weight, theoretical pI, and residue composition were calculated. The number of positively and negatively charged residues was determined. Protein stability parameters were also evaluated. Antigenicity was predicted using the VaxiJen v2.0 server. A threshold value of 0.4 was used for antigen prediction. Allergenicity prediction was performed using the AllerTOP v2.0 server. Default parameters were used for allergenicity analysis. T-cell epitope prediction was performed using the EpiDOCK server. The protein FASTA sequence was used as input. Binding prediction was performed for common MHC class II alleles. These analyses helped evaluate immunological and biochemical properties of the AmpC protein.

Homology Modeling and Structure Validation

Three-dimensional structure modeling was performed using comparative homology modeling methods. Multiple modeling servers were used to improve prediction accuracy. These included Phyre2, SWISS-MODEL, ModWeb, and CPHmodels-3. The AmpC FASTA sequence was submitted to each server. Generated models were downloaded for validation and comparison. Energy minimization was performed using the YASARA energy minimization server. Structural validation was performed using multiple quality assessment tools. Ramachandran plot analysis was performed using PROCHECK. Structural quality was further evaluated using Verify3D and ERRAT servers. ProSA web server was used to evaluate overall model quality. G-factor values were also calculated for stereochemical validation. The model with the best validation scores was selected. The Phyre2 model showed the best structural quality and coverage. The final structure was used for docking and simulation studies. These validation steps ensured structural reliability of the predicted AmpC model.

Molecular Docking Analysis

Molecular docking analysis was performed to identify potential inhibitors of AmpC protein. A total of 21 known and natural compounds were selected for screening. Ligand structures were obtained from PubChem and literature sources. Ligand structures were converted into PDBQT format. Protein preparation was performed using AutoDock Tools. Polar hydrogens and Kollman charges were added to the protein structure. Grid box parameters were defined around the active site region. AutoDock 4.2 software was used for docking simulations. The Lamarckian Genetic Algorithm was used for conformational search. Docking parameters were set based on standard AutoDock protocols. Each ligand was docked using multiple docking runs. Binding energy and inhibition constant values were recorded. Docked complexes were analyzed using Discovery Studio Visualizer. Ligand interactions with catalytic residues were evaluated. The best ligand was selected based on binding affinity and interaction pattern.

Molecular Dynamics Simulation and Binding Energy Analysis

Molecular dynamics simulation was performed using the YASARA simulation package. The AMBER14 force field was used for protein simulation. Ligand parameters were generated using GAFF2 and AM1BCC methods. The simulation system was solvated using TIP3P water molecules. Sodium and chloride ions were added to neutralize the system. Simulation was performed at physiological pH and temperature conditions. Energy minimization was performed before simulation production run. The simulation was performed for 100 nanoseconds. NPT ensemble conditions were maintained during simulation. RMSD,

RMSF, and radius of gyration were calculated. Hydrogen bond formation was monitored during simulation. Trajectory stability was analyzed over simulation time. Binding free energy was calculated using MM/PBSA and MM/GBSA methods. Energy calculations were performed using multiple simulation snapshots. These analyses confirmed stability and binding strength of the protein–ligand complex.

Results

Sequence Features and Immunoinformatic Analysis

The AmpC beta-lactamase sequence of *Morganella morganii* was retrieved from the UniProt database. The protein consisted of 379 amino acids. The predicted molecular weight was approximately 41.27 kDa. The theoretical isoelectric point was calculated as 8.69. The protein showed slightly higher positively charged residues than negative residues. These features suggested a stable and functional enzyme structure. Antigenicity prediction using VaxiJen showed a score of 0.4498. This value suggested probable antigenic potential of the protein. Allergenicity analysis predicted the protein as non-allergenic. T-cell epitope prediction showed multiple strong binders to MHC class II alleles. Several epitopes interacted with more than 75% of tested MHC alleles (Table 1). The immunological properties suggested possible vaccine-related relevance. The biochemical parameters confirmed stability and functional enzyme characteristics. These findings supported further structural modeling and docking analysis.

Homology Modeling and Structural Validation

Comparative homology modeling was performed using four independent servers. These included Phyre2, SWISS-MODEL, ModWeb, and CPHmodels (Fig. 1). All predicted models showed good structural alignment. Among them, the Phyre2 model showed the best coverage and quality. The final model showed approximately 90% residues in favored regions. This result confirmed good stereochemical stability. Ramachandran plot results (Fig. 1). Structural validation parameters are summarized in Table 2. ERRAT and Verify3D results also supported structural quality. ProSA analysis confirmed acceptable overall model energy profile. The modeled structure was further optimized using energy minimization. The final minimized energy reached approximately −10,208 kJ/mol. The predicted structure contained dominant random coil regions. Alpha helices and beta sheets contributed smaller structural portions. The final validated structure was selected for docking analysis.

Table 1: Predicted immunological and biochemical characteristics of AmpC beta-lactamase, including antigenicity score, allergenicity prediction, and MHC class II epitope binding frequency.

Protein UniProt ID	Epitope	Epitope	DP	DQ	DR	Total	%
P94958	13	LLAFSAPGF	2	4	12	18	78.26
P94958	51	VSVKGKPYY	2	5	11	18	78.26

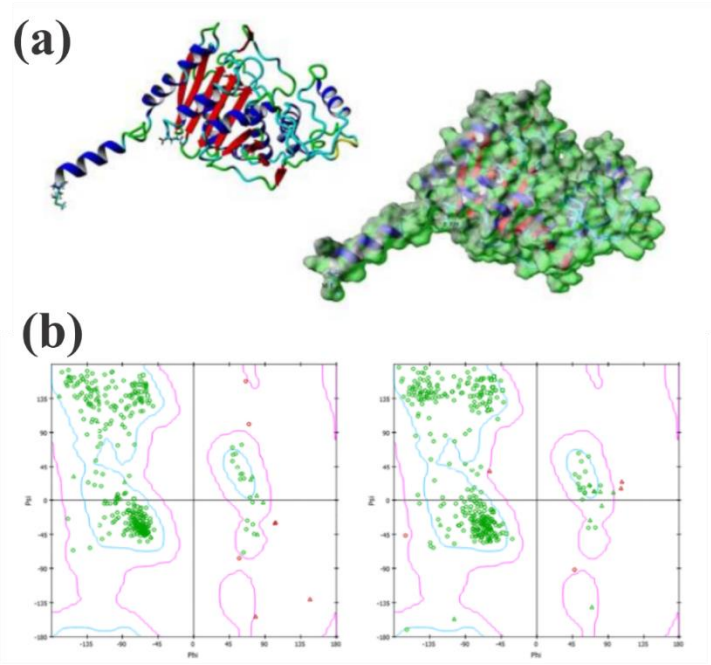

Fig 1: (a) Three-dimensional modeled structure of AmpC beta-lactamase generated using the Phyre2 server. Cartoon and surface representations are shown. (b) Ramachandran plot showing stereochemical quality of the modeled AmpC structure. Most residues are located in favored regions.

Table 2: Structural validation results of homology models generated from multiple servers using Ramachandran plot, ERRAT, Verify3D, and ProSA analysis.

Models	PROCHECK								ERAT	Verify-3D	ProSA	Template Used
	Number of non-glycine and non-proline residues				**No. of proline/glycine and end residues**	**Residues Coverage**	**Bad Contacts**	**G-factor**	**Quality Factor (%)**	**3D-ID Score >0 (%)**		
	Most Favoured Regions [A,B,L]	**Additional Allowed Regions [a,b,l,p]**	**Generously Allowed Regions [-a,-b,-l,-p]**	**Disallowed Regions**								
CPHmodel 3.0	138 (86.5%)	16 (10.1%)	4 (2.5%)	1 (0.6%)	15	174	0	0.07	71.72	17.82	-2.48	1C3B
ModBase	282 (93.7%)	19 (6.3%)	0 (0.0%)	0 (0.0%)	57	358	0	0.26	93.28	93.85	-9.07	2FFY
Swiss Model	276 (92.9%)	20 (6.7%)	0 (0.0%)	1 (0.3%)	49	346	0	0.29	90.77	93.64	-9.15	6G0T
Phyre2	289 (88.1%)	30 (9.1%)	3 (0.9%)	6 (1.8%)	51	379	0	0.16	86.25	82.85	-8.53	2HDS

Molecular Docking Analysis and Binding Interaction

Molecular docking analysis was performed using AutoDock 4.2. A total of 21 compounds were screened against the AmpC protein. Binding energies and inhibition constants were calculated. Oncoglabrinol C showed the strongest binding affinity. The binding energy was calculated as −11.44 kcal/mol. The inhibition constant was calculated as 4.09 nM. The ligand formed strong hydrogen bonds with key residues. These included Glu80, Arg147, Arg229, Val230, and Gln234. Pi–pi interactions were observed with Tyr189 and Tyr240 residues. Additional hydrophobic interactions stabilized ligand binding as shown in the docking complex (Fig. 2). Interaction profiles confirmed stable active site binding. These results suggested strong inhibitory potential of Oncoglabrinol C.

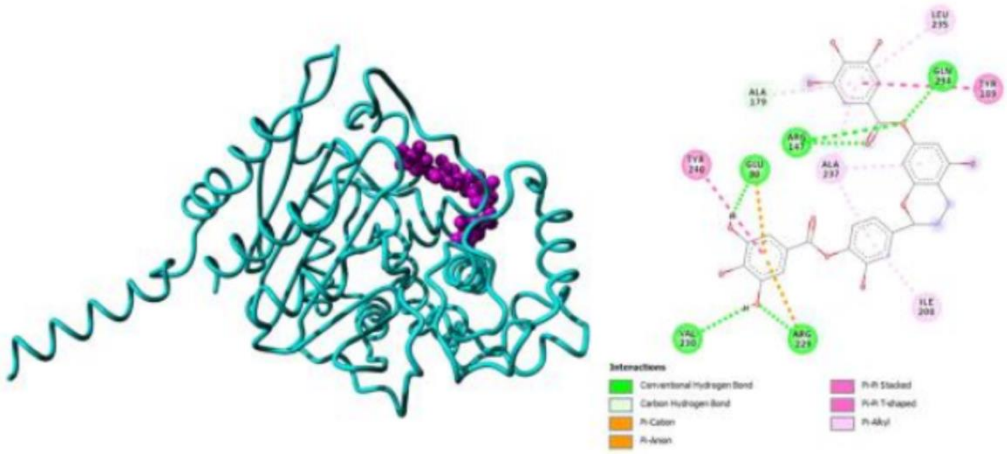

Fig 2: Docked complex of AmpC beta-lactamase with Oncoglabrinol C showing binding orientation and interaction residues within the catalytic pocket.

Molecular Dynamics Simulation Stability Analysis

Molecular dynamics simulation was performed for 100 ns. Simulation was conducted under physiological temperature and pressure. The AmpC–Oncoglabrinol C complex remained structurally stable. RMSD values initially fluctuated during early simulation. RMSD stabilized around 6 Å after approximately 80 ns. These results indicated conformational stabilization of the complex. Radius of gyration decreased from 22.6 Å to approximately 20.6 Å. This indicated increased compactness of the protein structure. Hydrogen bond analysis showed stable bond formation during simulation. Total hydrogen bonds ranged between 240 and 295 within the solute. Solute–solvent hydrogen bonds ranged between 590 and 680 (Fig. 3). RMSF analysis identified flexible residues near binding regions.

These results supported stable ligand binding and protein stability.

During the simulation run, residues 162, 230, and 299 exhibit somewhat elevated RMS fluctuation (RMSF). These residues might function as the ligand molecule's binding partners. Fig. 4 shows various screenshots of the MD simulation results. The protein's tail is prolonged in its initial conformation (shown in red) and rounded near the primary structural domain in its final conformation (shown in yellow). The ball representation shows the representative ligand, in this case OncoglabrinolC. The protein-ligand binding energy graph indicates that the ligand is firmly bound to the protein's active site.

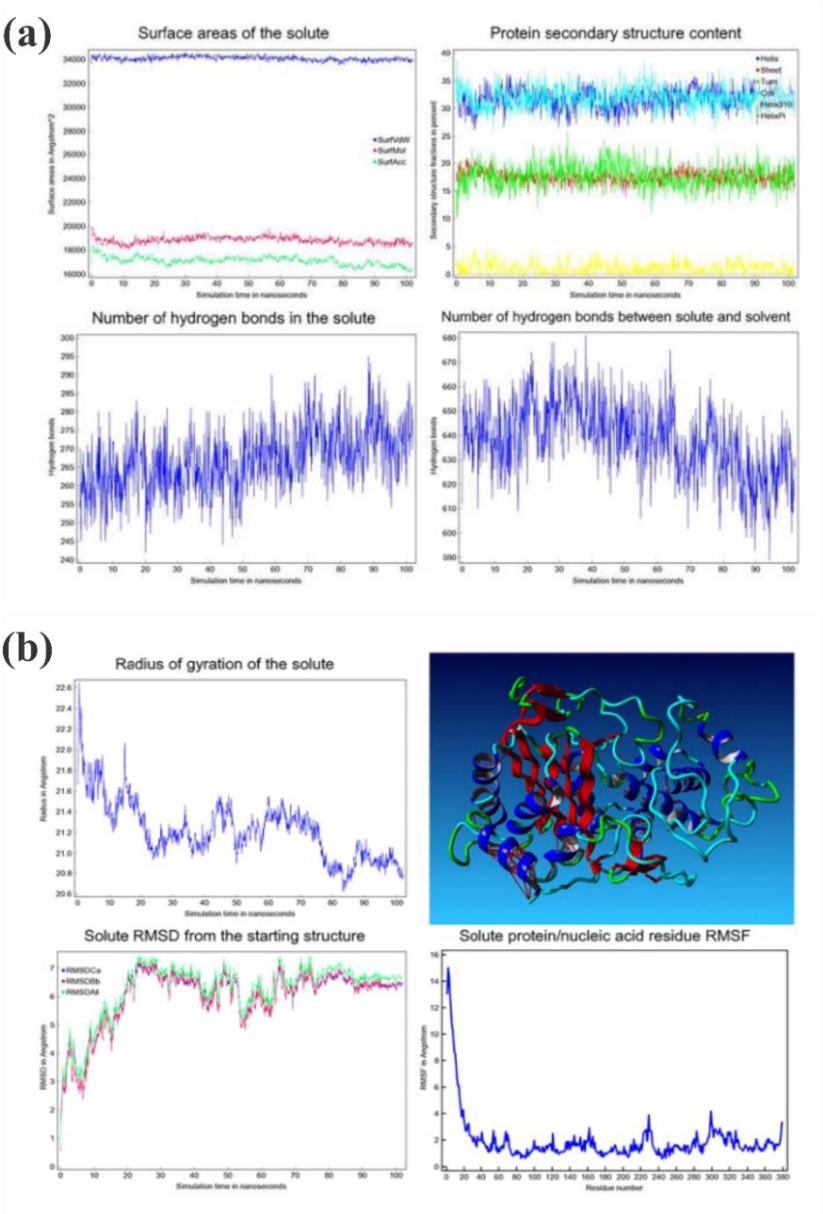

Fig 3: (a) Simulation analysis plots showing surface area, secondary structure content, and hydrogen bond formation of the protein–ligand complex during simulation. (b) Radius of gyration, RMSD, RMSF, and DCCM plots showing structural compactness, stability, and residue fluctuations during simulation.

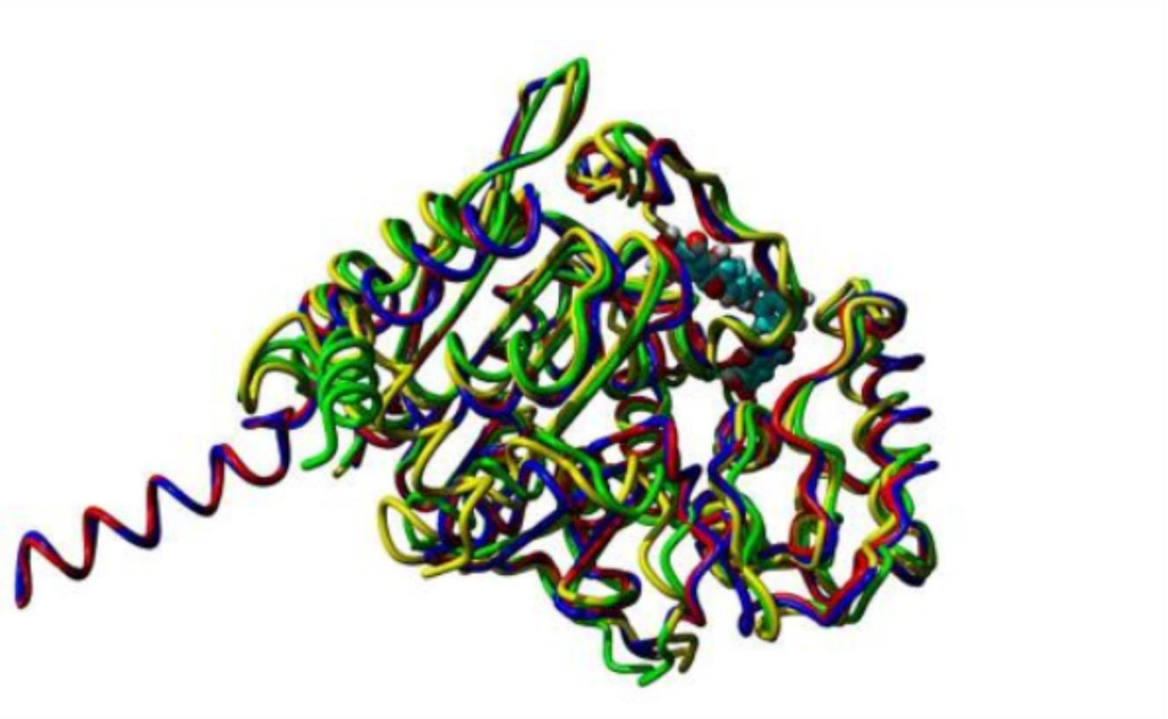

Fig 4: Six distinct ampC protein snapshots taken during the MD simulation manufacturing run. The protein's initial conformation is shown by red, its average simulated conformation by green, its energy-minimized conformation by blue, and its final conformation by yellow. Oncoglabrinol C is depicted using a ball model.

Binding Free Energy and Interaction Stability

Binding free energy calculations were performed using MM/PBSA and MM/GBSA methods. Energy calculations were performed across simulation trajectories. Binding energy remained stable during simulation time. These results confirmed strong ligand–protein interaction stability. Potential energy of receptor and complex remained similar. This indicated minimal destabilizing effect of ligand binding. Solvation energy profiles also remained stable during simulation. Binding energy trends are shown in Fig. 5. The ligand maintained strong interaction throughout simulation duration. These results confirmed docking predictions. Stable energy profiles suggested strong inhibitory potential. The ligand showed favorable energetic contribution at binding site. These findings supported selection of Oncoglabrinol C as lead inhibitor. Energy stability supported long-term binding potential. Overall results confirmed structural and functional stability of the complex.

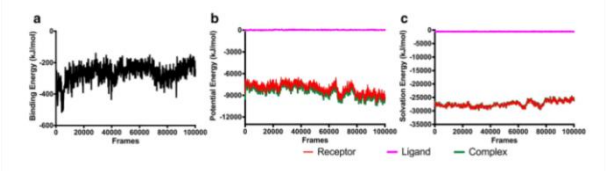

Fig 5: Binding energy, potential energy, and solvation energy plots obtained from MM/PBSA and MM/GBSA calculations during simulation.

Discussion

The present study provides structural and functional insights into AmpC beta-lactamase from *Morganella morganii.* AmpC enzymes are major contributors to β-lactam antibiotic resistance in Gram-negative bacteria (Zhanel *et al*, 2022). Increased AmpC expression is linked with treatment failure in clinical infections (Ram *et al*, 2021). The physicochemical analysis confirmed that the AmpC protein is structurally stable. The predicted molecular weight and pI values support its enzymatic functionality. The antigenicity prediction suggested that the protein may trigger immune recognition. The non-allergenic prediction indicates low allergenic risk for therapeutic targeting. The strong MHC class II epitope binding suggests immunological relevance. These findings are consistent with previous reports on bacterial resistance proteins (Sommer *et al*, 2019; Pinto *et al*, 2020; Zheng *et al*, 2022). Stable biochemical properties support its role as an active resistance enzyme. The sequence characteristics support efficient catalytic activity in bacterial cells. The presence of multiple immune-interacting epitopes may influence host–pathogen interaction (Aikawa *et al*, 2023). These features support the biological relevance of AmpC in infection persistence. The immunological predictions may support future vaccine-related exploration.

Reliable structural modeling is essential when experimental structures are unavailable (Huang *et al*, 2024). The homology model generated in this study showed strong stereochemical quality. Approximately 90% residues were present in favored Ramachandran regions. This indicates strong backbone conformational stability. The ProSA and ERRAT results confirmed acceptable structural quality. The

Phyre2 model showed the best structural coverage and quality. This suggests high confidence in predicted protein folding. The dominance of random coils suggests structural flexibility in some regions. Flexible regions often support substrate binding and enzyme activity. Energy minimization further improved structural stability of the model. The final minimized structure showed removal of steric clashes. These findings indicate that the model is suitable for docking analysis. The validated structure provides a reliable platform for inhibitor screening. Structural validation ensures reliability of downstream simulation studies (Dyla *et al*, 2022; Sun *et al*, 2024).

Molecular docking results identified Oncoglabrinol C as the strongest binder. The binding energy of −11.44 kcal/mol indicates strong binding affinity. The low inhibition constant suggests high inhibitory potential. Hydrogen bonding with catalytic residues supports stable active site binding. Interactions with Glu80, Arg147, and Arg229 indicate catalytic pocket targeting. Hydrophobic and pi interactions further stabilize ligand binding. These interactions increase ligand residence time in the binding pocket. Similar interaction patterns have been reported in effective β-lactamase inhibitors. The presence of multiple interaction types increases binding stability (Dyla *et al*, 2022). These findings support Oncoglabrinol C as a potential inhibitor candidate. The docking results suggest strong competitive inhibition potential. The ligand orientation suggests optimal catalytic site blocking. Docking results provide strong support for further simulation validation. Natural compounds are important sources of novel drug scaffolds (Reza *et al*, 2022; Heissel *et al*, 2024; Sun *et al*, 2024).

Molecular dynamics simulations confirmed structural stability of the complex. RMSD stabilization after 80 ns suggests conformational equilibrium. Stable RMSD indicates stable protein backbone structure. The decrease in radius of gyration indicates increased protein compactness. Increased compactness often reflects stable ligand binding. Hydrogen bond stability further confirms strong protein–ligand interaction. Stable solute and solvent hydrogen bonding suggests stable hydration shell. RMSF analysis showed flexibility in specific residues. Flexible residues may support ligand accommodation and enzyme activity (Singh *et al*, 2016; Pazhang *et al*, 2018). Stable secondary structure content suggests minimal structural disruption (Timofeev *et al*, 2018). These findings confirm stable binding during physiological conditions (Robert *et al*, 2023). Simulation results validate docking predictions. Long simulation duration increases confidence in binding stability. Stable MD profiles support long-term inhibitor binding potential (Lee *et al*, 2024).

Binding free energy analysis confirmed strong interaction stability. MM/PBSA and MM/GBSA results showed stable energy trends. Stable binding energy indicates strong ligand retention. Similar receptor and complex potential energy suggest structural compatibility. Stable solvation energy supports stable ligand environment. These results indicate thermodynamically favorable binding. Strong binding stability supports drug candidate potential. Energy stability across simulation frames increases prediction reliability. The ligand showed consistent energetic contribution at binding site. These findings support selection of Oncoglabrinol C as lead compound. Stable energy profiles support potential experimental validation (Jaganathan and Kumaradhas, 2024). These findings support structure-guided drug discovery approaches. Natural compound-based inhibitors may reduce resistance development risk. The study provides a strong computational foundation for drug design. Overall, the study supports Oncoglabrinol C as a promising AmpC inhibitor candidate.

Declaration of Competing Interest

The authors declare that they have no competing or conflict of interests.

Author Contributions

MOS: Conceptualization, Methodology, formal analysis, Writing—original draft preparation, Writing—review and editing. This author has read and agreed to the published version of the manuscript.

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