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Integrated in silico evaluation of potential NDM-1 inhibitors through molecular docking, molecular dynamics, and MM/GBSA free energy analysis

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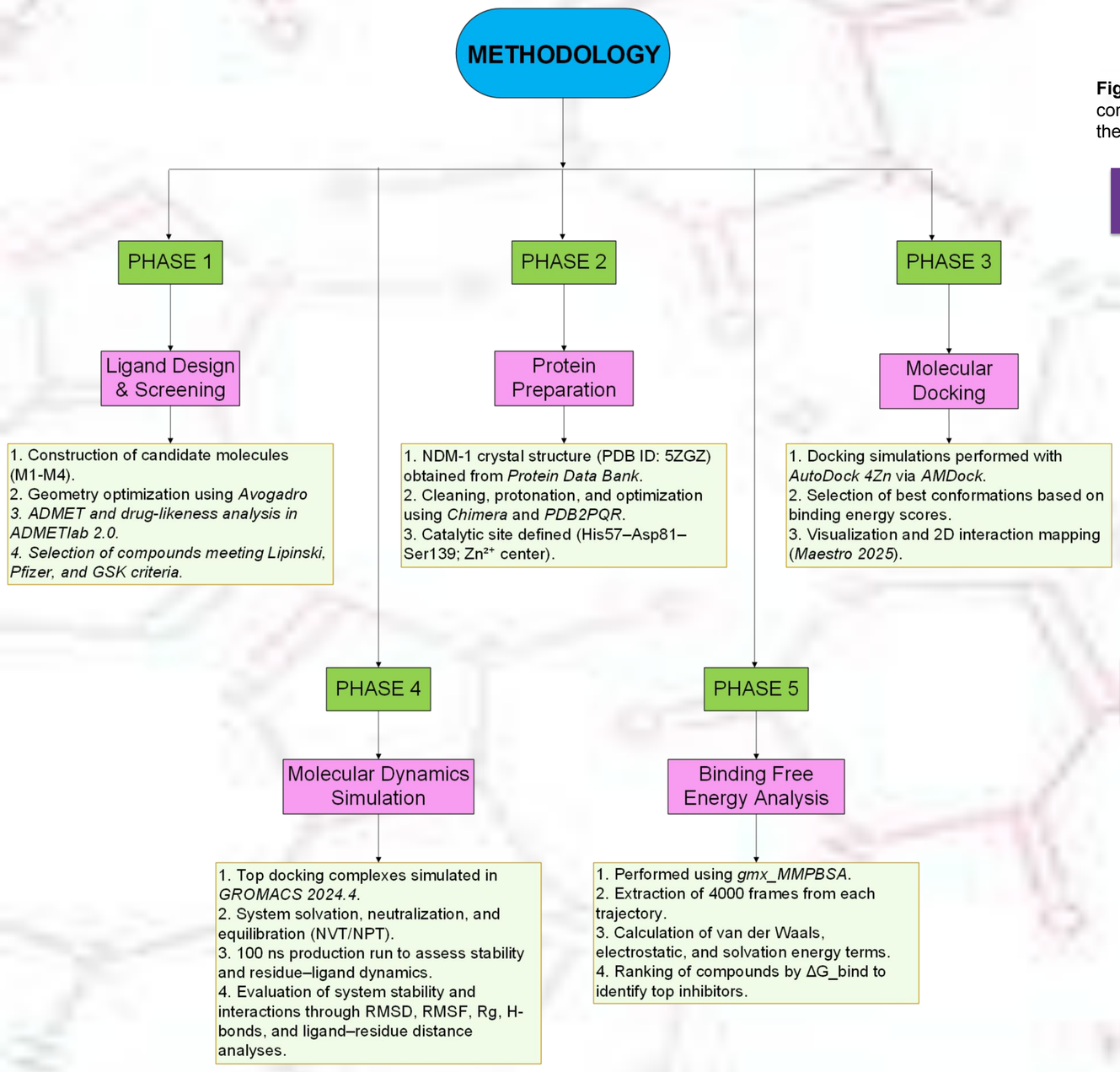
INTRODUCTION & AIM

Antibiotic resistance remains one of the most pressing global health challenges. Among the mechanisms contributing to this crisis, New Delhi Metallo-β-lactamase-1 (NDM-1) stands out for its ability to hydrolyze a broad spectrum of β-lactam antibiotics, including carbapenems, which are often used as last-resort treatments (Wu et al., 2019; Valencia & Galvis, 2024). The rapid dissemination of *blaNDM* genes, facilitated by mobile genetic elements, has severely limited therapeutic options, and to date, no clinically approved inhibitors are available (Yang et al., 2020; Haque et al., 2024a).

In this context, in silico approaches have become essential for identifying compounds capable of targeting the Zn^{2+}-dependent catalytic site of NDM-1. Molecular docking and molecular dynamics (MD) simulations allow for the assessment of ligand–protein affinity, stability, and persistence of key interactions (Kuzmanic et al., 2020; Yan et al., 2025), while MM/GBSA calculations provide a reliable estimation of binding free energy (Genheden & Ryde, 2015; Valdés-Tresanco et al., 2021).

This study applied a computational protocol to identify and characterize novel chemical scaffolds with inhibitory potential against NDM-1. Four candidate compounds (M1, M2, P3, and P4) were optimized and evaluated through molecular docking, 100 ns molecular dynamics simulations, and binding free energy estimations. The results revealed stable interactions with key catalytic residues, suggesting that these molecules could serve as promising structural frameworks for the rational design of potent and selective NDM-1 inhibitors to combat multidrug-resistant bacteria.

METHOD



RESULTS & DISCUSSION

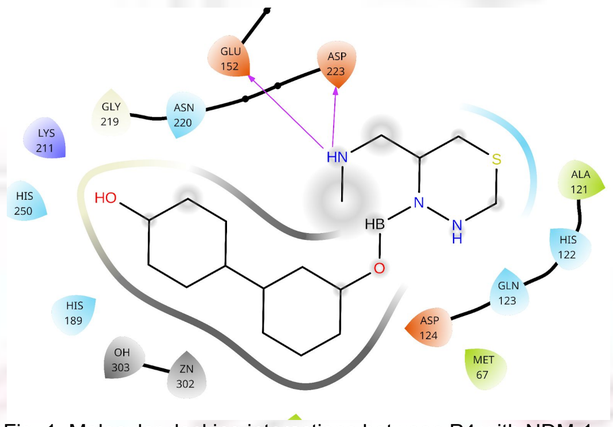


Fig. 1. Molecular docking interactions between P4 with NDM-1.

During the 100 ns simulation, the NDM-1–P4 complex maintained high structural stability. The protein backbone fluctuated within 0.1–0.3 nm, while the ligand remained stably positioned in the active pocket with an average RMSD of ~0.25 nm. This steady trajectory indicates that P4 sustains consistent non-covalent interactions throughout the simulation, confirming a robust and adaptable binding mode.

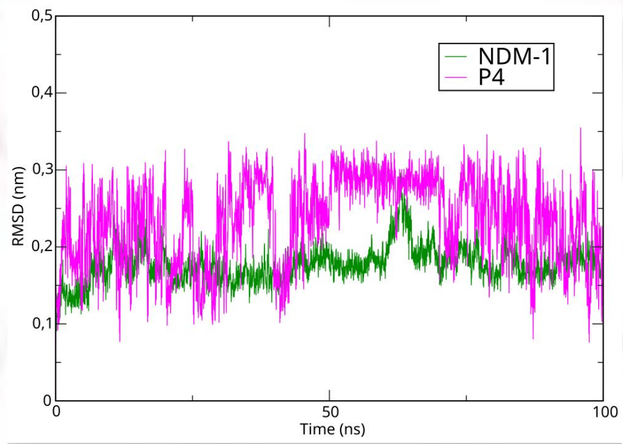


Fig. 2. RMSD plot of the NDM-1–P4 complex showing stable binding over 100 ns.

The compound P4 exhibited the strongest binding affinity toward the catalytic pocket of NDM-1, with a docking score of –9.60 kcal/mol. The ligand formed two key hydrogen bonds with Glu152 and Asp223 at distances of 1.6 Å and 1.85 Å, respectively, stabilizing its orientation near the Zn^{2+} catalytic center. These interactions suggest an optimal geometric complementarity and a strong electrostatic fit within the active site.

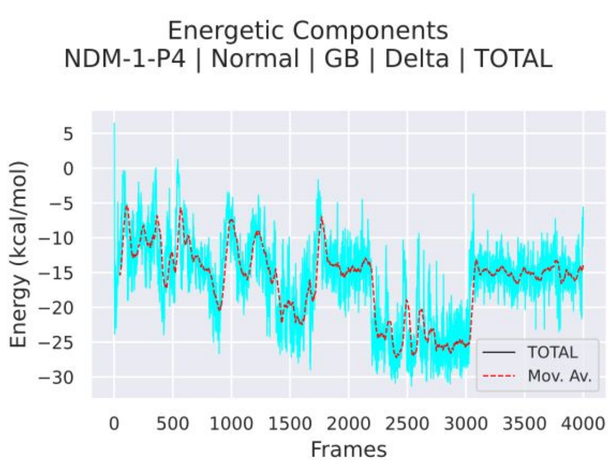


Fig. 3. Binding free energy (ΔG) profile of the NDM-1–P4 complex showing stable energetic convergence throughout the 100 ns simulation.

The MM/GBSA analysis revealed a mean ΔG_bind = –16.72 kcal/mol, the lowest among all complexes, indicating the strongest thermodynamic affinity. The Van der Waals and electrostatic contributions (ΔG_gas = –192.42 kcal/mol) were dominant, efficiently compensating for solvation penalties. The stability of ΔG_bind along the simulation confirms the persistent interaction of P4 with catalytic residues, reinforcing its potential as a promising NDM-1 inhibitor.

CONCLUSION

This study integrated advanced computational tools —molecular docking, molecular dynamics, and MM/GBSA— to explore the interaction of designed compounds with the NDM-1 enzyme, a critical target in bacterial resistance. Among the evaluated ligands, P4 stood out for exhibiting the highest structural stability, persistent interactions with key residues, and the most favorable binding free energy (–16.72 kcal/mol), highlighting its strong potential as an NDM-1 inhibitor. The combination of structural, dynamic, and energetic analyses confirms that P4 remains stable within the catalytic pocket, maintaining a sustained network of non-covalent interactions. These findings reinforce the effectiveness of the *in silico* approach for prioritizing candidates in early stages of drug design and pave the way for future experimental validations to confirm its inhibitory activity.

FUTURE WORK / REFERENCES

Future studies will focus on the *in vitro* validation of compound P4 to confirm its inhibitory potential against NDM-1. Structure-based optimization will also be explored to enhance its pharmacokinetic profile and binding affinity. Extending this computational workflow to other metallo-β-lactamases could accelerate the discovery of broad-spectrum inhibitors to combat antimicrobial resistance.

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