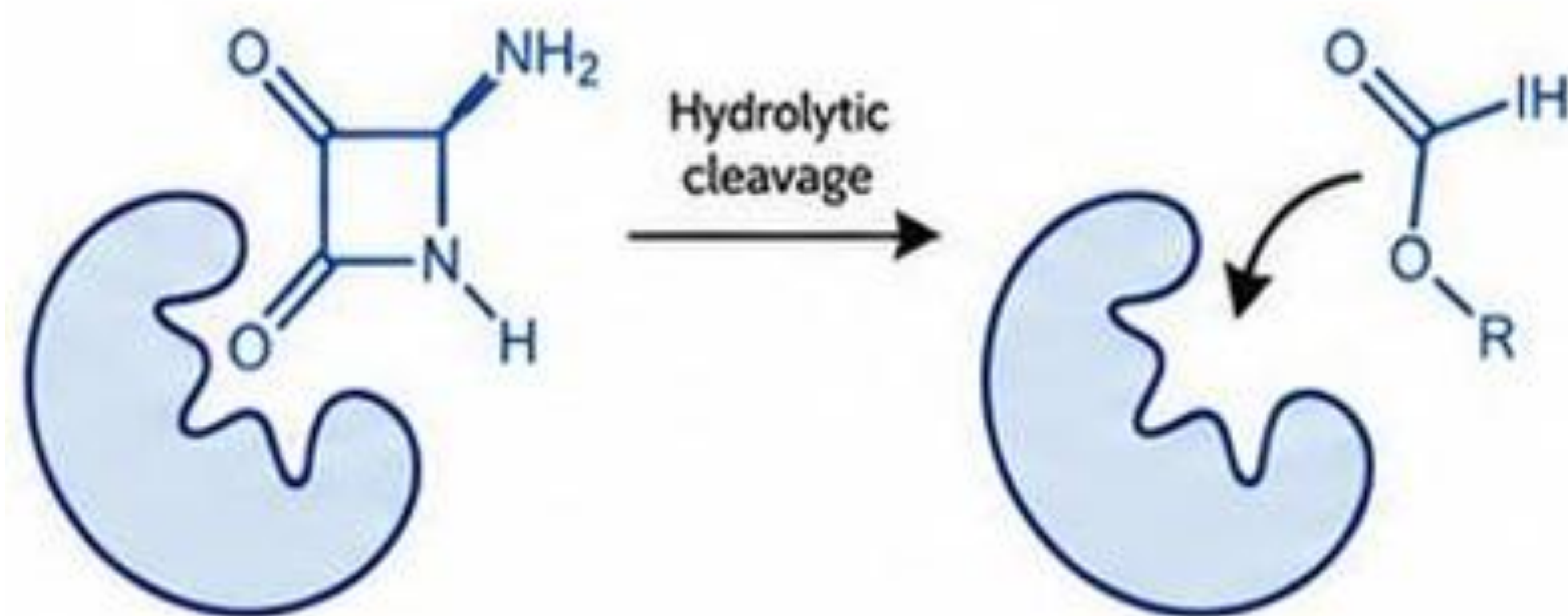


Omoyele O. Alli^{1,2}, Gbolahan O. Oduselu^{2,3}, Toluwalope D. Ilori^{2,4}, Sukuralahi A. Ibrahim^{1,2} & Olayinka A. Bankole¹
¹Olabisi Onabanjo University, ²Drug Discovery Innovation Hub (DDIH), ³WACCBIP, University of Ghana, ⁴Federal University of Agriculture, Abeokuta, Ogun State, Nigeria.

THE PROBLEM

Antimicrobial resistance (AMR) is a global health crisis causing approximately 1.27 million deaths annually. KPC-2 (Klebsiella pneumonia carbapenemase-2) is a prominent class A β -lactamase that hydrolyses nearly all β -lactam antibiotics, including carbapenems, rendering them ineffective.



HYPOTHESIS

Engaging evolutionary conserved residues distant from the highly variable active site can inhibit KPC-2 through allosteric or stable binding, overcoming common drug resistance mutations.

PIPELINE

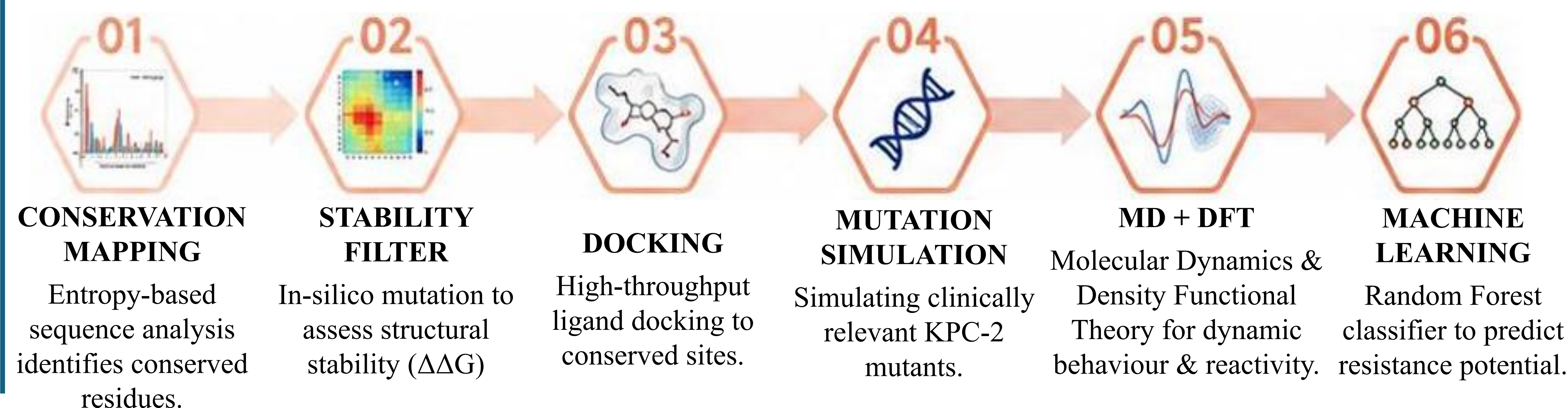
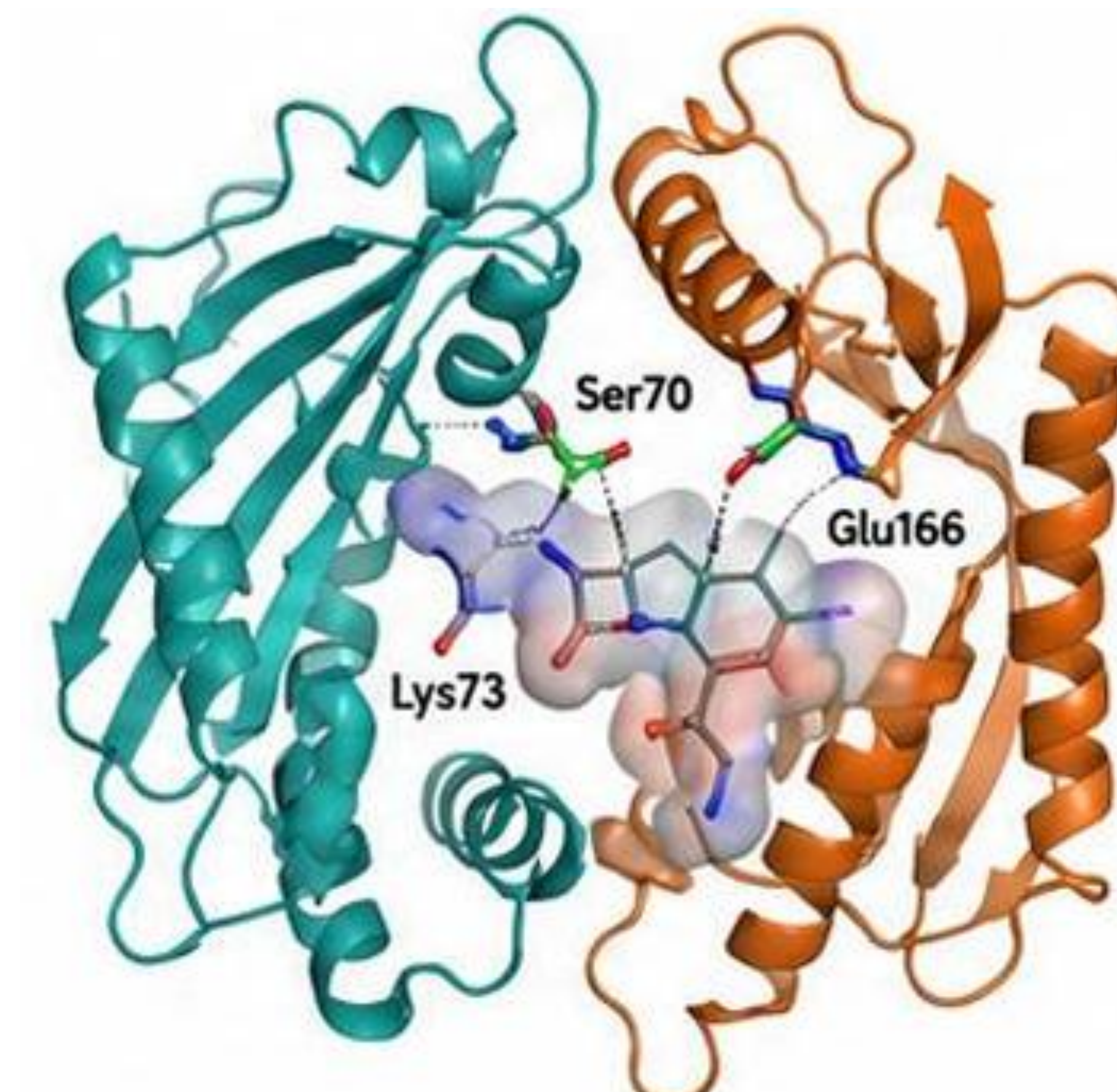


Figure 1: KPC-2 β -lactamase structure with docked meropenem-like ligand and highlighted catalytic triad (Ser70, Glu166, Lys73).

OUTCOME

The integrated pipeline successfully differentiated between conserved and variable residues. Conserved sites showed lower entropy and critical roles in stability. Ligands targeting conserved regions maintained stable binding across KPC-2 mutants, while those in variable regions exhibited significant pose shifts and reduced efficacy.

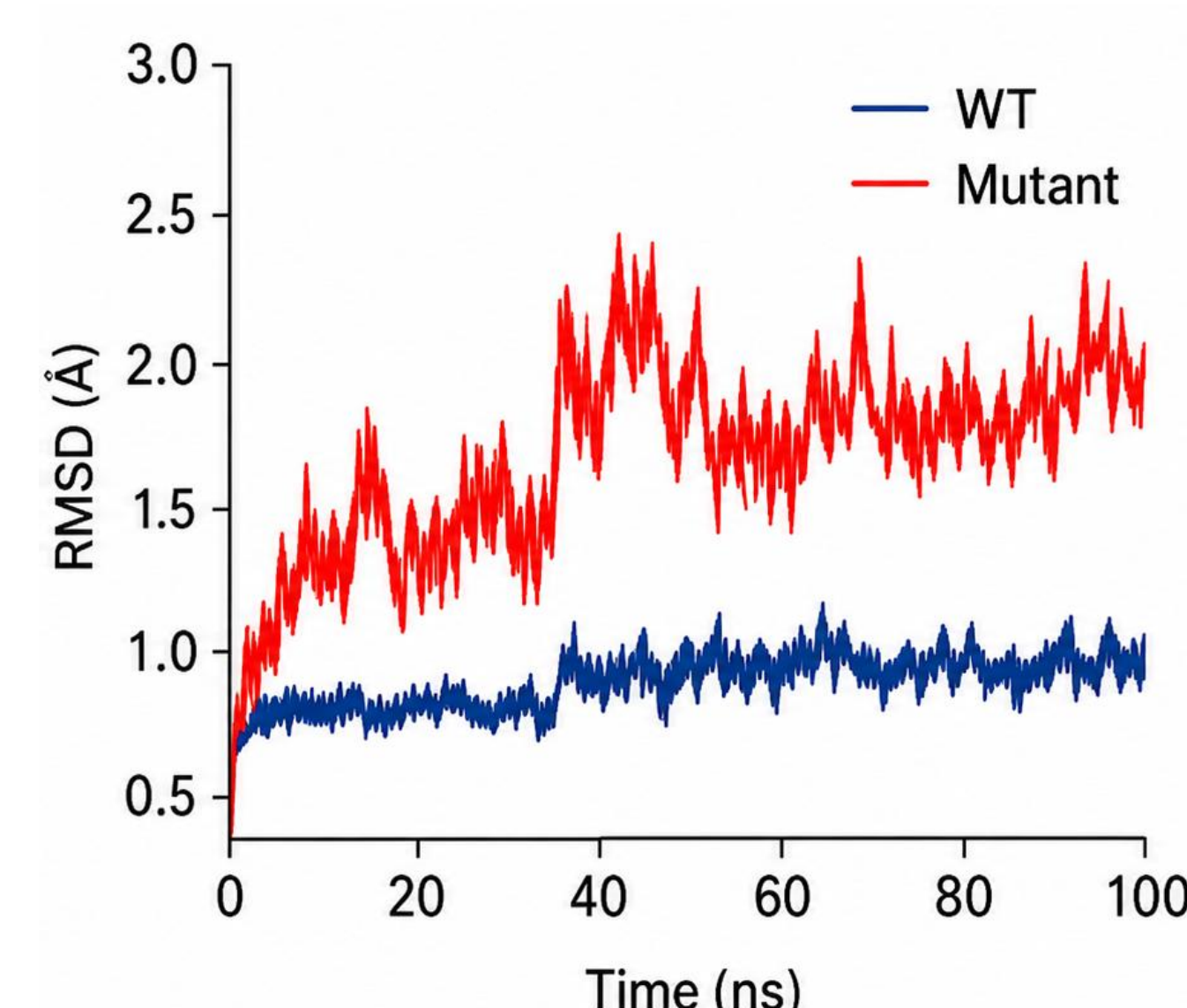


Figure 2: MD RMSD of WT vs Mutant KPC-2 complexes.

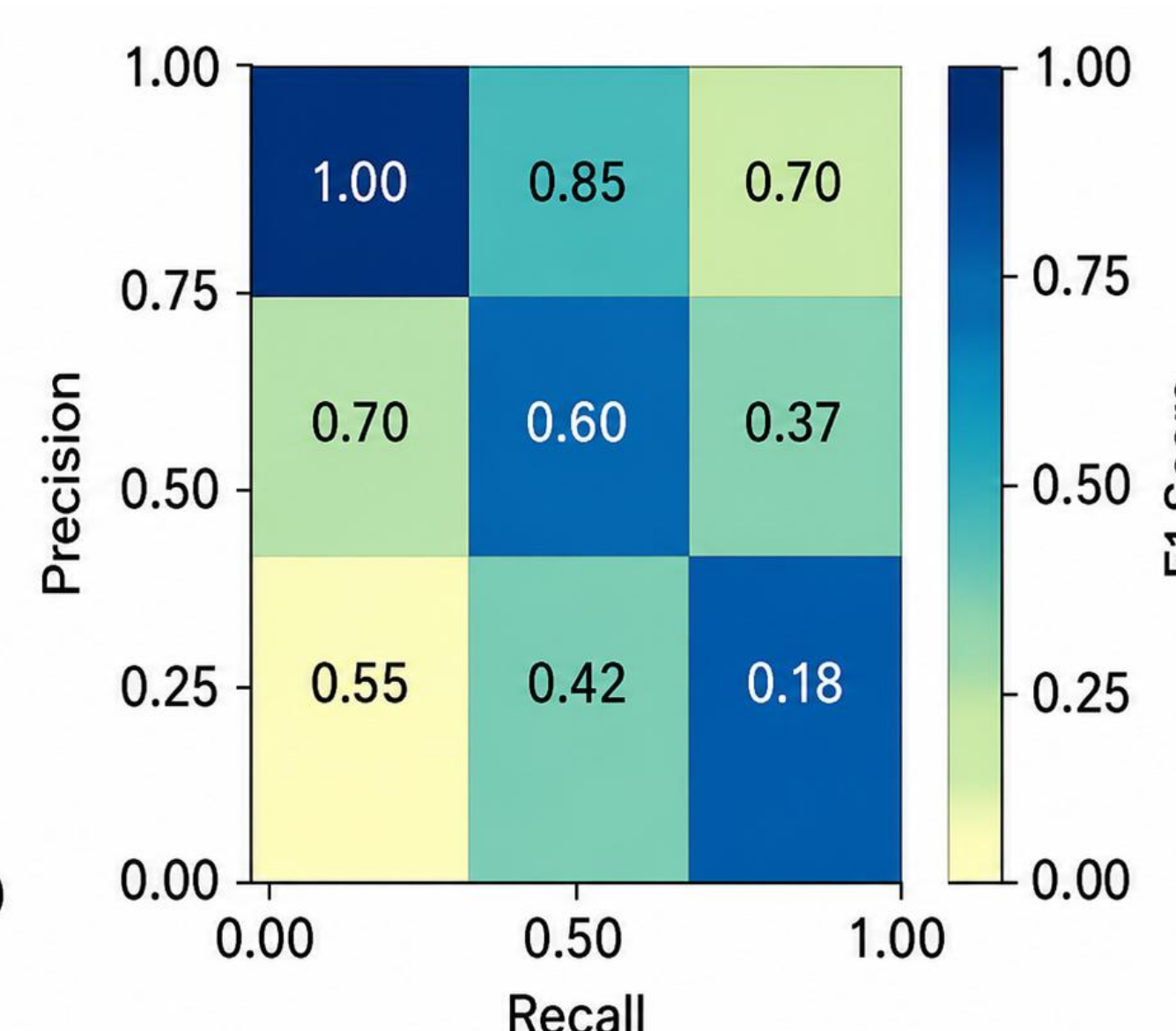


Figure 3: Random Forest classification performance.

84%

RF classification accuracy

3,214

Homologous sequences analysed

100 ns

MD simulation per complex



Keywords: AMR • KPC-2 • MD Simulation • Evolution-Guided Drug Design

CONCLUSION

Our evolution-aware approach integrates computational tools to identify robust binding sites on KPC-2. This framework facilitates the design of novel antimicrobial agents that are less susceptible to common resistance mutations, contributing to sustainable antibiotic development.