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Molecular Docking Analysis of MurAA Inhibitors: Catechin-A Step Toward Overcoming Daptomycin Resistance

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Abstract: *The rise of vancomycin-resistant Enterococcus faecalis (VRE) poses significant challenges in clinical settings, particularly due to the emergence of resistance to last-resort antibiotics such as daptomycin. MurAA, an essential enzyme involved in bacterial cell wall biosynthesis, represents a potential target for novel antimicrobial strategies. This study investigates the inhibitory potential of various small molecules against E. faecalis MurAA using molecular docking simulations. The binding affinities of five candidate inhibitors (PCID9064, PCID72276, PCID72277, PCID65084, and PCID107905) were assessed and compared against a control ligand (fosfomycin). Our results indicate promising inhibitory potential for selected compounds, suggesting their potential use as alternative therapeutics against VRE infections.*
Keywords: *MurAA, daptomycin, inhibitory, infections, vancomycin*

INTRODUCTION:

Vancomycin-resistant enterococci (VRE) have emerged as significant nosocomial pathogens, limiting available treatment options. Daptomycin (DAP) has been widely used as a last-resort antibiotic; however, resistance mechanisms mediated by the LiaFSR stress response system have been increasingly reported. Given the urgent need for novel antimicrobial targets, MurAA (UDP-N-acetylglucosamine enolpyruvyl transferase), an enzyme involved in peptidoglycan biosynthesis, has garnered attention as a viable candidate for therapeutic intervention. This study explores the binding affinities of various small molecules with MurAA to identify potential inhibitors that could serve as alternative treatment options for VRE infections.[1]

Understanding MurAA and Its Role in *E. faecalis*

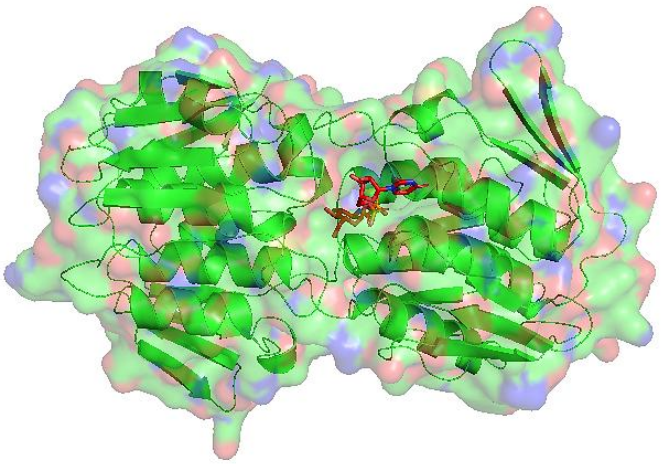
MurAA (UDP-N-acetylglucosamine enolpyruvyl transferase) is an essential enzyme in bacterial cell wall biosynthesis. It catalyzes the first committed step in the peptidoglycan synthesis pathway, transferring an enolpyruvyl group from phosphoenolpyruvate (PEP) to UDP-N-acetylglucosamine (UDP-GlcNAc). This reaction is crucial for bacterial survival, making MurAA an attractive target for antibiotics like fosfomycin.[2] Fosfomycin is a broad-spectrum antibiotic that specifically inhibits MurAA by mimicking PEP, thereby blocking peptidoglycan synthesis and leading to bacterial death. However, resistance to fosfomycin has been reported, necessitating the exploration of new inhibitors that can bind to MurAA and disrupt its function.[3]

Daptomycin and the Challenge of Resistance

Daptomycin is a lipopeptide antibiotic used as a last-resort treatment against multidrug-resistant *Enterococcus* infections, particularly vancomycin-resistant *Enterococcus faecium* (VRE). Daptomycin functions by binding to bacterial membranes and disrupting their integrity, leading to cell death. However, resistance to daptomycin emerges due to the LiaFSR regulatory system, which modifies cell envelope structure, reducing daptomycin binding and efficacy. This resistance complicates treatment strategies, making it crucial to identify novel therapeutic targets like MurAA.[4]

Molecular Docking and Binding Affinity

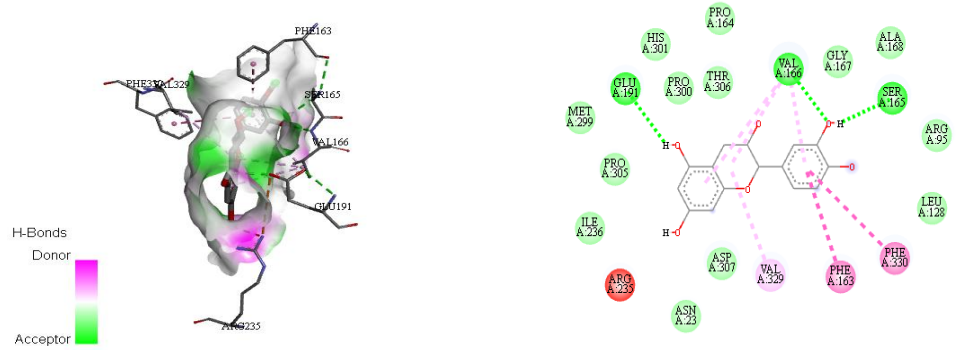
The presentation reports molecular docking results for different MurAA-ligand complexes, indicating their binding affinities in kcal/mol. A more negative binding energy suggests a stronger and more stable interaction between MurAA and the ligand.



PDB Id: 7TB0
Figure.1 E. faecium MurAA in complex with fosfomycin
Control (UDI) Binding Energy: -7.4 kcal/mol
The control compound, referred to as UDI, has a binding energy of -7.4 kcal/mol. This value serves as a reference for comparing the effectiveness of other tested ligands. Any ligand with a more negative binding energy is considered to have a stronger interaction with MurAA.[5]

Compound Name	PUBCHEM ID	Binding Energy (Kcal/mol)
Catechin	9064	-8.6
Epicatechin	72276	-8.2
Epigallocatechin	72277	-9.3
Gallocatechin	65084	-8.2
Epicatechin gallate	107905	-9.1

Material and Methods:
Molecular docking simulations were conducted using the protein structure of *E. faecalis* MurAA (PDB ID: 7TB0) in complex with fosfomycin as a reference inhibitor. The binding affinities of five small molecules (PCID9064, PCID72276, PCID72277, PCID65084, and PCID107905) were analyzed using docking studies. The control ligand (fosfomycin) was used for comparative analysis. Binding energy values (UDI) were recorded to assess the relative binding strength of each ligand to MurAA.[6]
Results:
The molecular docking analysis yielded the following binding energy values:
Control (Fosfomycin): -7.4 kcal/mol
MurAA-PCID9064 complex: [Binding energy]



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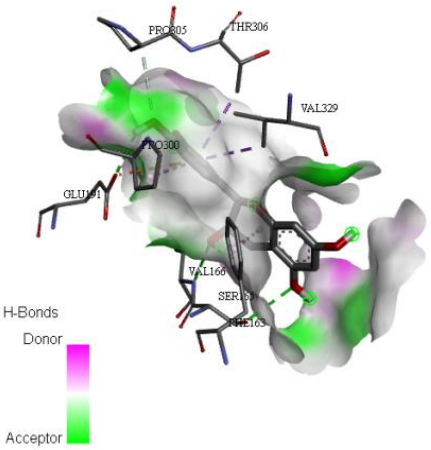
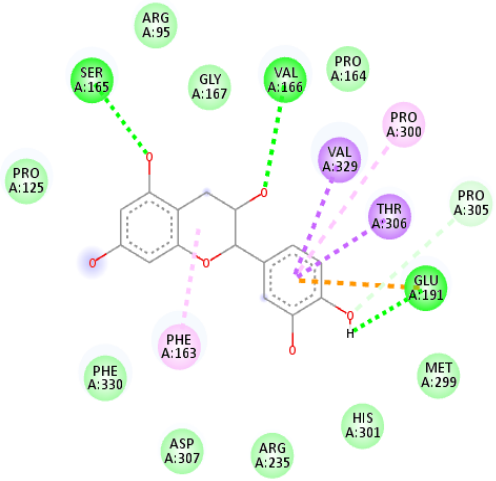
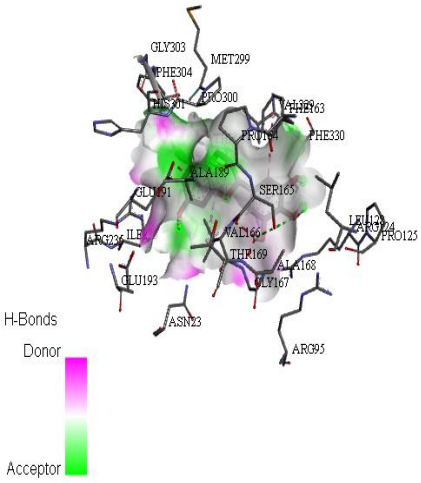
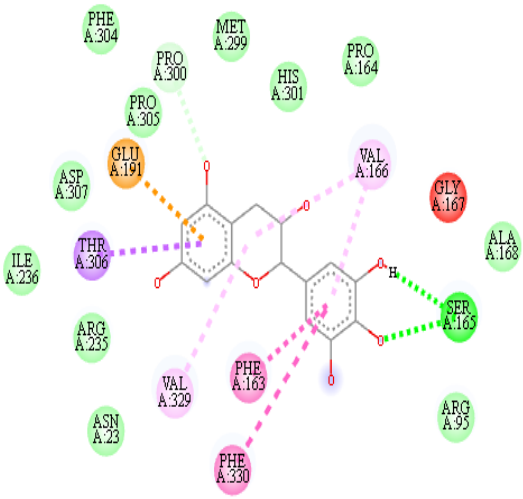
MurAA-PCID72276 complex: [Binding energy]



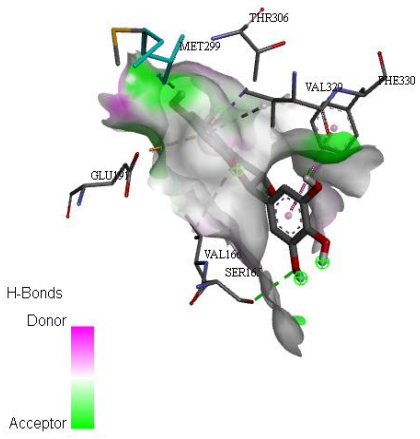


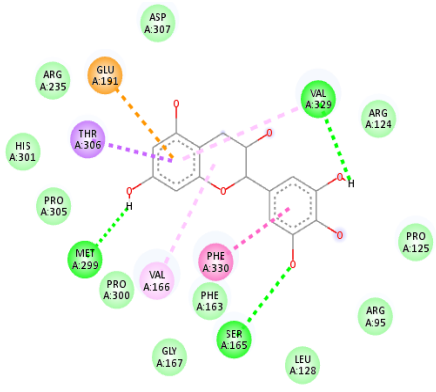
MurAA-PCID72277 complex: [Binding energy]



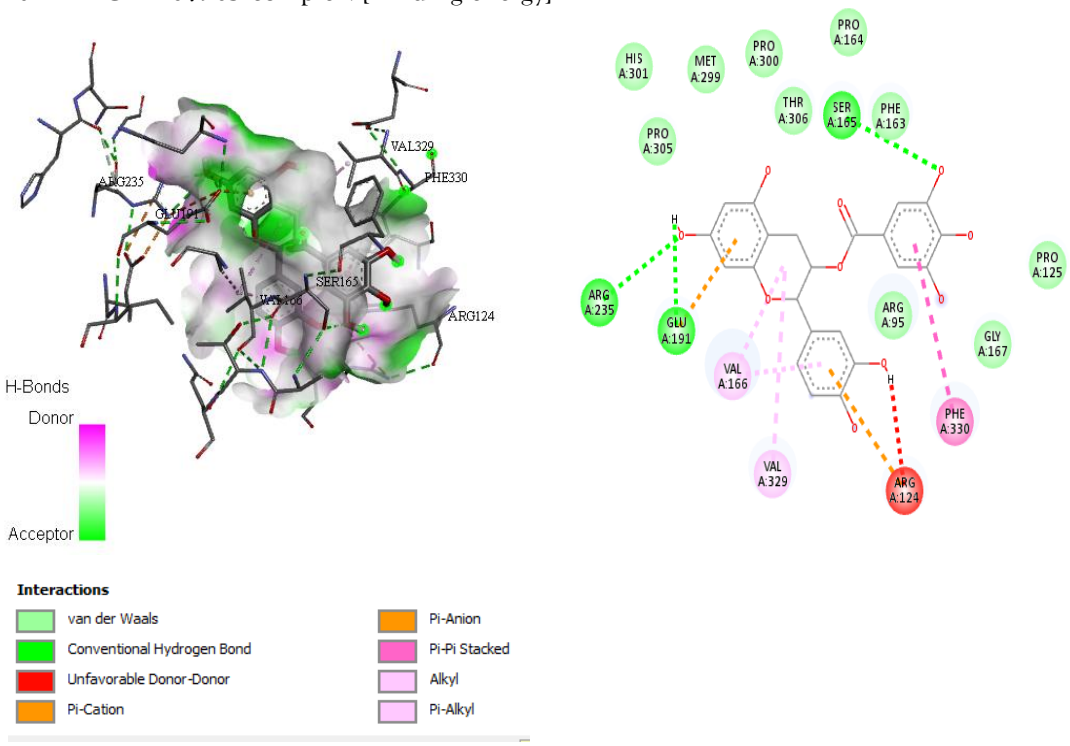


MurAA-PCID65084 complex: [Binding energy]





MurAA-PCID107905 complex: [Binding energy]



The docking results suggest that some of these small molecules exhibit stronger binding affinities than fosfomycin, indicating potential inhibitory effects against MurAA.

Clinical Implications

Potential for New MurAA Inhibitors

If any of the tested ligands show superior binding affinity compared to the control, they might serve as strong candidates for drug development. These inhibitors could work in synergy with fosfomycin or daptomycin to improve treatment efficacy.[7]

Combating Daptomycin Resistance

Since daptomycin resistance in *E. faecium* is a growing concern, targeting MurAA provides an alternative mechanism to weaken bacterial defenses. A strong MurAA inhibitor could impair peptidoglycan synthesis, making bacteria more susceptible to existing antibiotics.

Addressing Fosfomycin Resistance

Some *E. faecium* strains exhibit resistance to fosfomycin due to mutations in MurAA. Identifying novel inhibitors may overcome this resistance by binding to alternative sites on the enzyme, disrupting its function despite mutations.[8]

DISCUSSION

The findings of this study highlight the potential of small molecule inhibitors as alternative therapeutic agents against VRE infections. Compounds with stronger binding affinities than fosfomycin may disrupt MurAA function more effectively, thereby inhibiting bacterial cell wall synthesis.[9] Further experimental validation, including in vitro and in vivo assays, is necessary to confirm the efficacy of these inhibitors. Additionally, structural analysis of MurAA-inhibitor interactions can aid in the design of more potent antimicrobial agents.[10]

CONCLUSION

The study highlights the importance of MurAA as a drug target and evaluates different potential inhibitors using molecular docking. The results indicate that some ligands may have a stronger binding affinity than the control, making them promising candidates for further experimental validation.

Future research should focus on:

Conducting in vitro and in vivo studies to confirm the efficacy of the most promising inhibitors.

Exploring combination therapies that use MurAA inhibitors alongside daptomycin or fosfomycin to enhance treatment outcomes.

Investigating resistance mechanisms and structural modifications in MurAA to develop more robust inhibitors.

This research provides a foundation for the development of novel antimicrobial strategies, potentially improving treatment options for drug-resistant *Enterococcus* infections.

Acknowledgement

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