New insights into peptide Docking and Molecular Dynamics for β-lactamase inhibitor discovery.

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Introduction

Since the clinical introduction of antibiotics, antimicrobial resistance (AMR) has emerged as a global challenge. AMR has been recognized as one of the leading causes of mortality worldwide, impacting human, animal, and environmental health, thereby necessitating an integrated One Health approach. In this context, β-lactamases, enzymes capable of hydrolyzing β-lactam antibiotics, stand as the most significant mechanism of AMR. Consequently, the use and search for β-lactamase inhibitors have become an essential strategy to preserve the efficacy of these antibiotics.

Materials & Methods

Following the analysis of the β-lactamase TEM-1 (PDB ID: 1ERM) active site's chemical features, 34 five-residue peptides were formulated.

Figure 1: Lead optimization to candidate selection workflow. Created in https://BioRender.com

Peptide construction was performed using the Discovery Studio Visualizer and was subsequently optimized using Foldit Standalone. Docking was carried out with the GOLD software, using the GoldScore function. To date, the three best performing peptides (Peptides 32, 33 and 34) were selected for Molecular Dynamics (MD) studies, which were performed using the Desmond program. (Figure 1)

Results

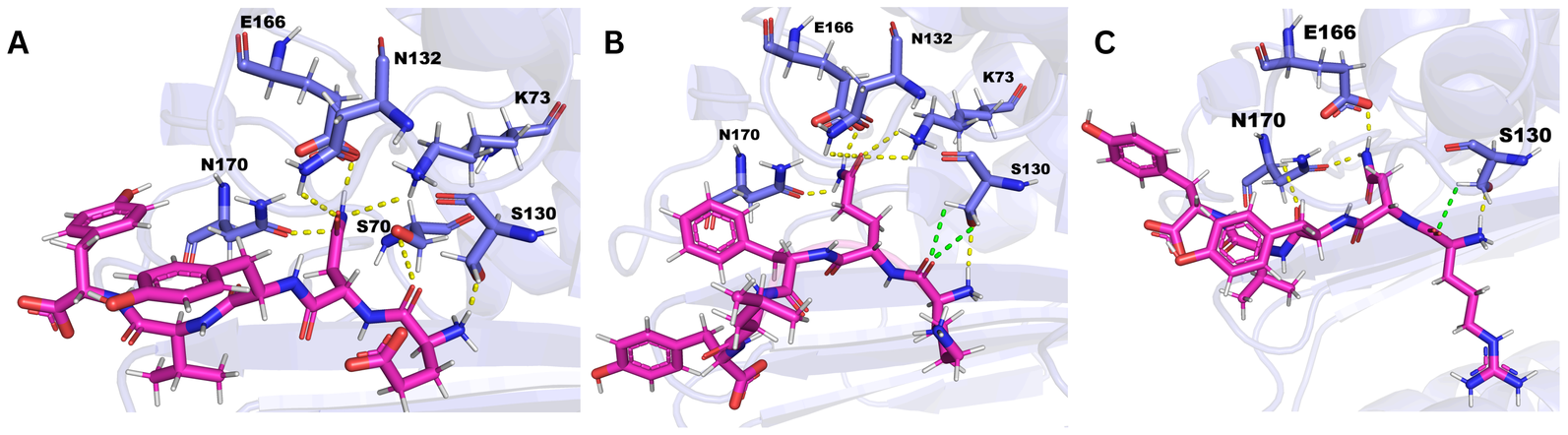

Figure 2: A) Molecular docking of TEM-1 β-lactamase with peptide 32. **B)** Molecular docking of TEM-1 β-lactamase with peptide 33. **C)** Molecular docking of TEM-1 β-lactamase with peptide 34. Interactions are represented by dashed lines: hydrogen bonds in yellow and carbon-hydrogen bonds in green. Atom colors: nitrogen in royal blue, oxygen in red, carbon in pink (peptide) and light blue (TEM-1).

Docking and MD interaction data are summarized in Table 1. Peptide 32 established hydrogen bonds with conserved residues essential for catalysis (S70, S73, S130, E166, and N170). Peptide 34 formed hydrogen bonds with the residues (S130, E166, and N170), while also forming two carbon-hydrogen bonds with S130. Furthermore, Peptide 33 interacted with (S73, S130, E166, and N170) via hydrogen bonds, including a single carbon-hydrogen bond with S130, as shown in Figure 2.

Pep	Seq	Protein-residue interactions		RMSD
		Docking	Molecular Dynamics	
32	ENYVY	S70;S130;K73;E166; N132	S130;N132;Y105;E239; A237;E171	2,4 Å
33	KQFLY	S130;K73;E166;N170 N132	R237;N132;Y105;E239	4,5 Å
34	RNYVY	S130;E166;N170	N132;E166;A237;E239; S235;N170	2,8 Å

Table 1: TEM-1 residues interacting with peptides (Docking/MD) and protein-ligand RMSD (20–120 ns) as a measure of conformational stability.

Regarding MD studies, Peptides 32 and 34 remained stable within the active site, corroborating their inhibitory potential. Notably, Peptide 34 showed superior performance, maintaining robust and constant water-bridge interactions with conserved residues E166, N170, and N132 (Figure 3). Conversely, Peptide 33 failed to sustain stable interactions and left the active site.

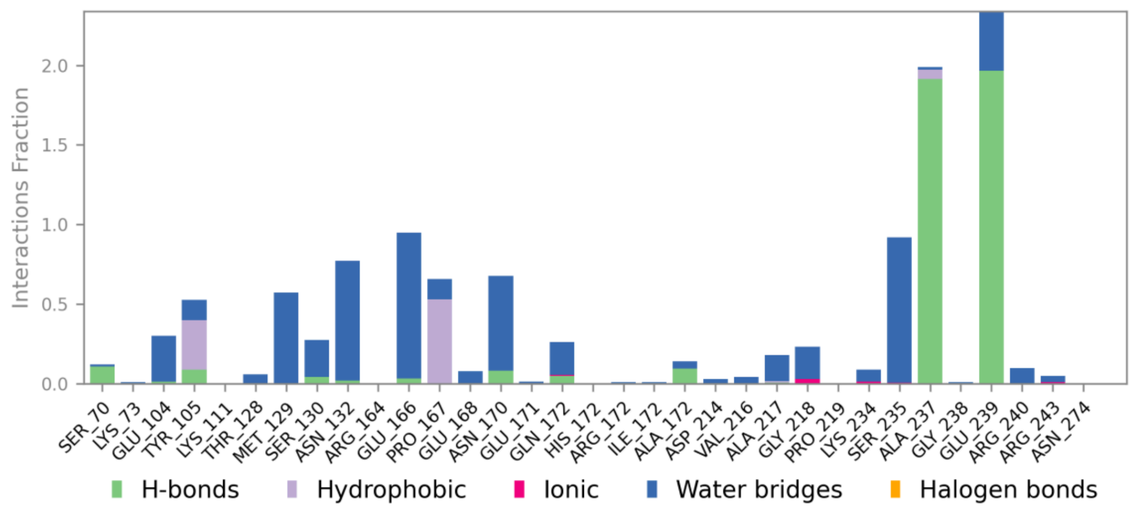

Figure 3: Interactions of peptide 34 with TEM-1 residues during the MD simulation. Molecular interactions between the protein and the ligand are classified into four fundamental categories: hydrogen bonds, hydrophobic interactions, ionic interactions, and water bridges. The quantitative analysis of these interactions is presented via stacked bar histograms, with values normalized relative to the total trajectory time. In this context, a contact fraction of 0.7 indicates that the interaction persisted for 70% of the simulation time. Notably, values exceeding 1 (100% of the simulation time) may occur, as certain residues can establish multiple simultaneous contacts of the same physicochemical nature with the ligand structure.

Conclusion

Based on these results, these peptides, which are promising as β-lactamase inhibitors, will subsequently be synthesized for minimum inhibitory concentration (MIC) assays to confirm in vitro the results obtained in silico. Moving forward, the peptides will be investigated against other β-lactamases such as KPC and CTX-M.

Related Literature

Bellucci MC, et al. Dual antibiotic approach: synthesis and antibacterial activity of antibiotic–antimicrobial peptide conjugates. Antibiotics. 2024;13(8):783.
Bush K, Bradford PA. Interplay between β-lactamases and new β-lactamase inhibitors. Nat Rev Microbiol. 2019;17(5):295–306.
Murray CJL, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet. 2022;399(10325):629–655.