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Engineering α-Helical Antimicrobial Peptides as Nanoscale Tools to Combat Multidrug-Resistant Bacteria

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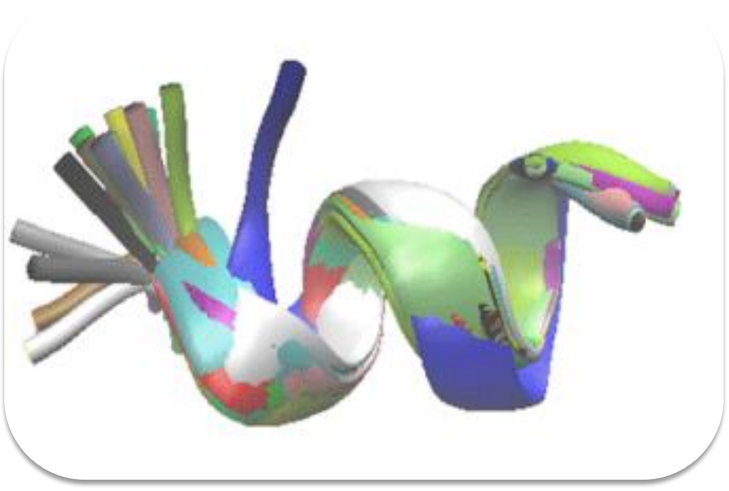
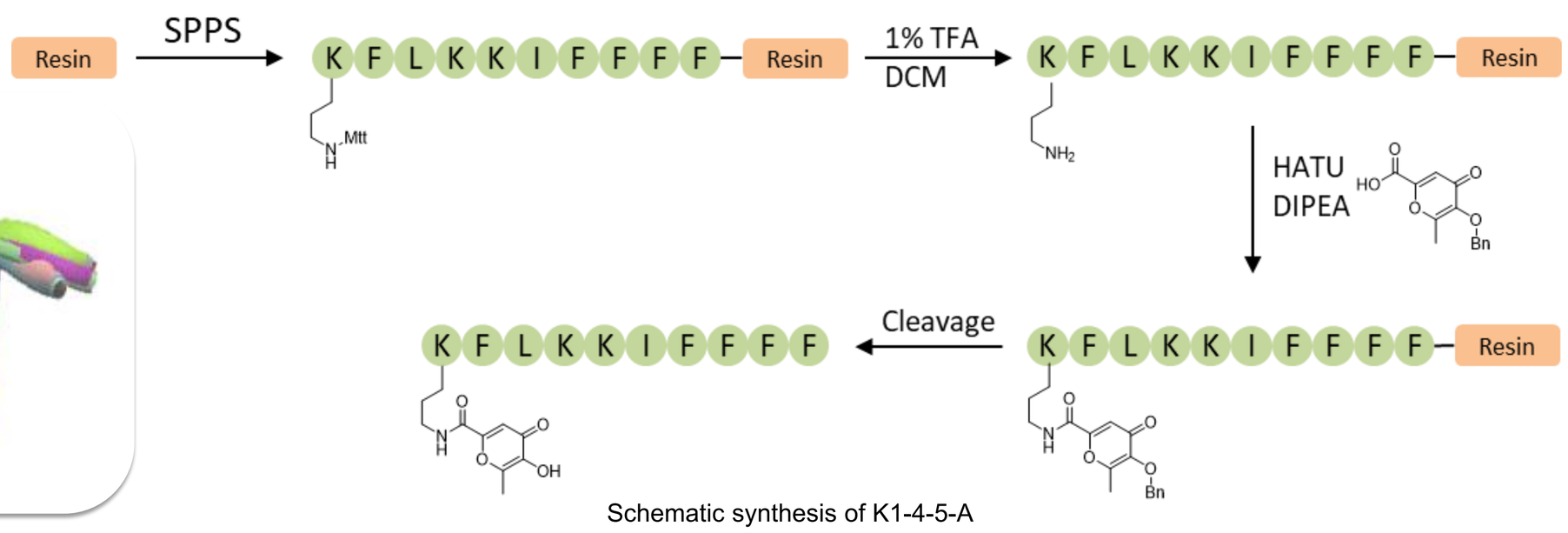
INTRODUCTION & AIM

Multidrug-resistant bacteria represent a critical global health threat. α-Helical antimicrobial peptides (AMPs) act by disrupting bacterial membranes and are less prone to resistance. In this study, we designed new α-helical AMPs using the MMFs method and enhanced their activity with metal-chelating agents such as allomaltol.



METHODS

Peptides were designed via MMF-based dihedral angle calculations to predict stable α-helical conformations. They were synthesized using Fmoc solid-phase peptide synthesis and characterized by FT-IR, HPLC, and ESI+ MS. Antibacterial activity was evaluated by broth microdilution assays against *S. aureus, E. coli*, and *K. pneumoniae*.



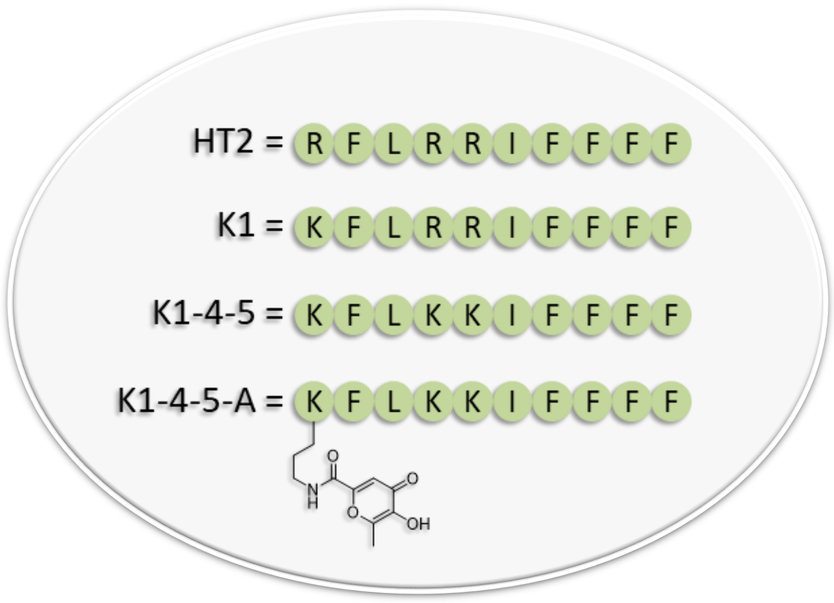
Schematic synthesis of K1-4-5-A

RESULTS & DISCUSSION

HT2, the reference peptide, exhibited strong activity against *Staphylococcus aureus* (MIC 18.75 μM), moderate effects against *Escherichia coli* (75 μM), and limited activity against *Klebsiella pneumoniae* (150 μM). Structural analogues designed with MMFs showed different outcomes: K1 (Arg1→Lys) lost activity completely, confirming the essential role of Arg1; K1-4-5 (Arg1/4/5→Lys) retained partial antimicrobial effects. The co-administration of peptides with allomaltol significantly enhanced activity, lowering MIC values to 37.5 μM for *S. aureus* and *E. coli*, suggesting a clear synergistic effect between membrane disruption and metal ion chelation. Most notably, the covalently modified derivative K1-4-5-A, carrying a maltol-like chelating group, restored potent and selective activity against *S. aureus* (MIC 18.75 μM), comparable to HT2. These findings support the dual-action strategy as a way to boost potency and reduce resistance risk.

Compounds	*S. aureus*	*K. pneumoniae*	*E. coli*
HT2	18.75 μM	150 μM	75 μM
K1	300 μM	300 μM	300 μM
K1-4-5	300 μM	150 μM	75 μM
Allomaltol	300 μM	300 μM	300 μM
K1-allomaltol 1:1	75 μM	300 μM	150 μM
K1-allomaltol 1:2	75 μM	300 μM	150 μM
K1-4-5	300 μM	150 μM	75 μM
K1-4-5-allomaltol 1:1	37.5 μM	75 μM	37.5 μM
K1-4-5-allomaltol 1:2	37.5 μM	75 μM	37.5 μM
K 1-4-5-A	18.75 μM	300 μM	75 μM

Minimum inhibitory concentrations (MICs, expressed in μM) of the tested compounds and their combinations against three bacterial strains.



CONCLUSION

This work shows that MMF-guided peptide design is a powerful strategy for creating stable and effective α-helical AMPs. The dual mechanism of action (membrane disruption combined with metal chelation) enhances antimicrobial activity and selectivity against resistant bacteria. These results highlight a promising nanoscale approach for next-generation antimicrobial therapeutics, paving the way for further *in vivo* studies and clinical translation.

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