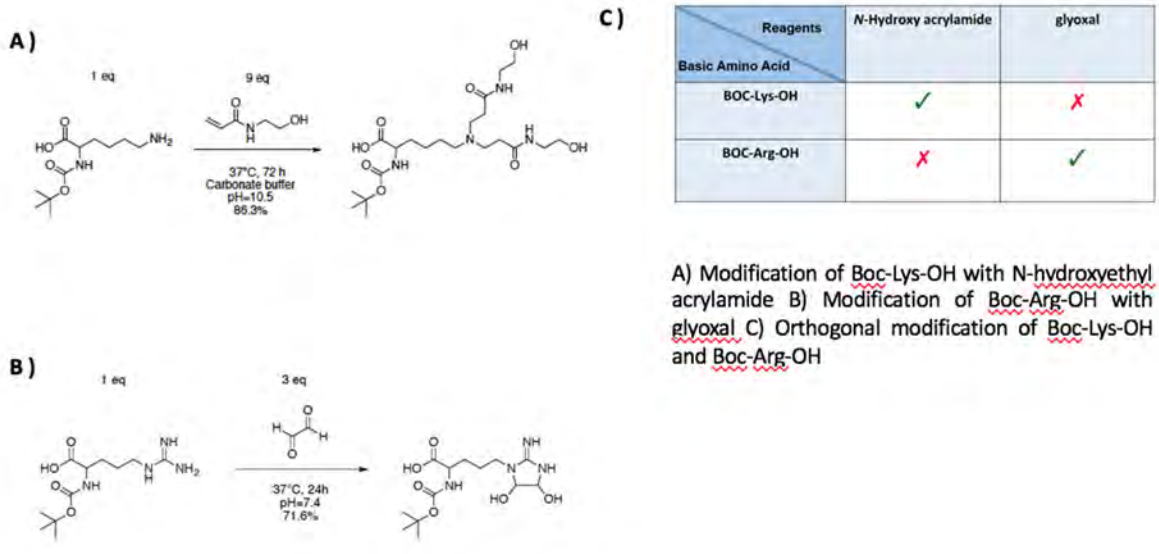
Optimal band-width antimicrobial peptides

Shadi Kordbacheh[1]*, skordbacheh@g.ucla.edu, Andrea M. Kasko*[2]*.* (1) Bioengineering, University of California, Los Angeles (UCLA), Los Angeles, California, United States (2) 410 Westwood Plaza, Department of Bioengineering, Los Angeles, California, United States

We were inspired by the defensive behavior of bacteria to engineer novel antibiotics featuring tunable functionality. This tunability will allow for an adjustable bandwidth of antimicrobial activity against multiple species within a specific set of environmental conditions. Moreover, we want to produce antibiotics able to inhibit pathogenic bacteria without harming host cells or beneficial commensal bacteria. We are interested in antimicrobial peptides (AMPs) as antibiotics, since they target generic features common to the outer membrane of many pathogenic species. Therefore, the development of resistance is significantly inhibited compared to that of conventional antibiotics. To engineer new antimicrobials, we have leveraged recently developed sequence design rules, using both positive charge and hydrophobicity as necessary conditions for antimicrobial activity. To tune the antimicrobial activity of α−helical AMPs, we have modified functional groups on the side chain of specific basic amino acids. By incorporating electron withdrawing and/or hydrophobic compounds on the side chains of arginine and lysine residues, the pK_a at which these residues become positively charged can be controlled. Therefore, by incorporating different masking groups in different locations, we can adjust the activity of the antimicrobial peptides by turning them on at specific and tunable pH values. Boc-Lys-OH and Boc-Arg-OH were orthogonally modified using *N*-hydroxyethyl acrylamide and glyoxal, respectively. The short peptide H-GKGRG-OH was modified by *N*-hydroxyethyl acrylamide and glyoxal to confirm the orthogonal modification of Lysine and Arginine.



A) Modification of Boc-Lys-OH with N-hydroxyethyl acrylamide B) Modification of Boc-Arg-OH with glyoxal C) Orthogonal modification of Boc-Lys-OH and Boc-Arg-OH

A) Modification of Boc-Lys-OH with *N*-hydroxyethyl acrylamide B) Modification of Boc-Arg-OH with glyoxal C) Orthogonal modification of Boc-Lys-OH and Boc-Arg-OH