

## Supplementary Information

### On the relative biomembrane fusogenicities of the tumor-selective liposomes of RGDK- and CGKRRK- lipopeptides

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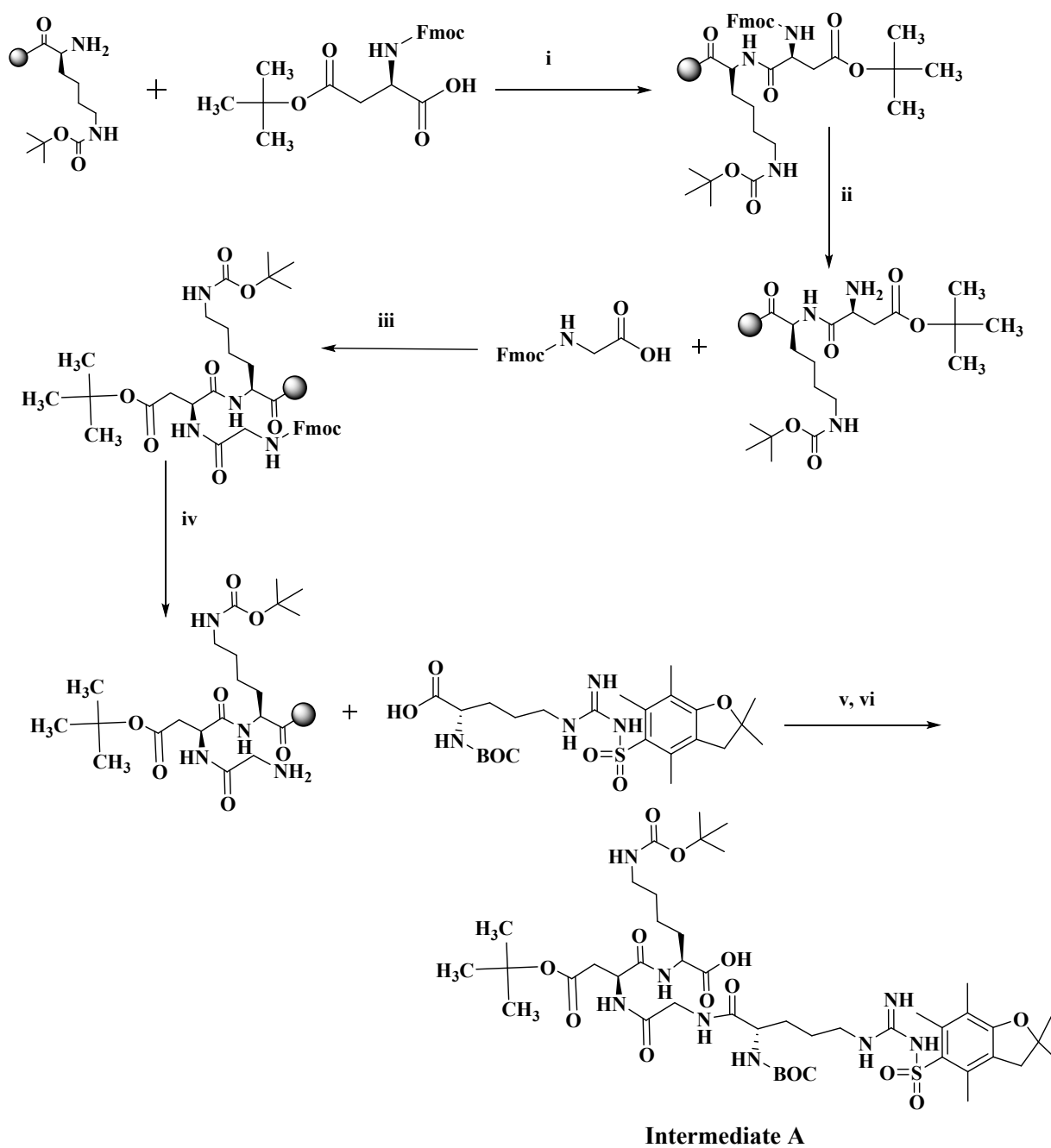
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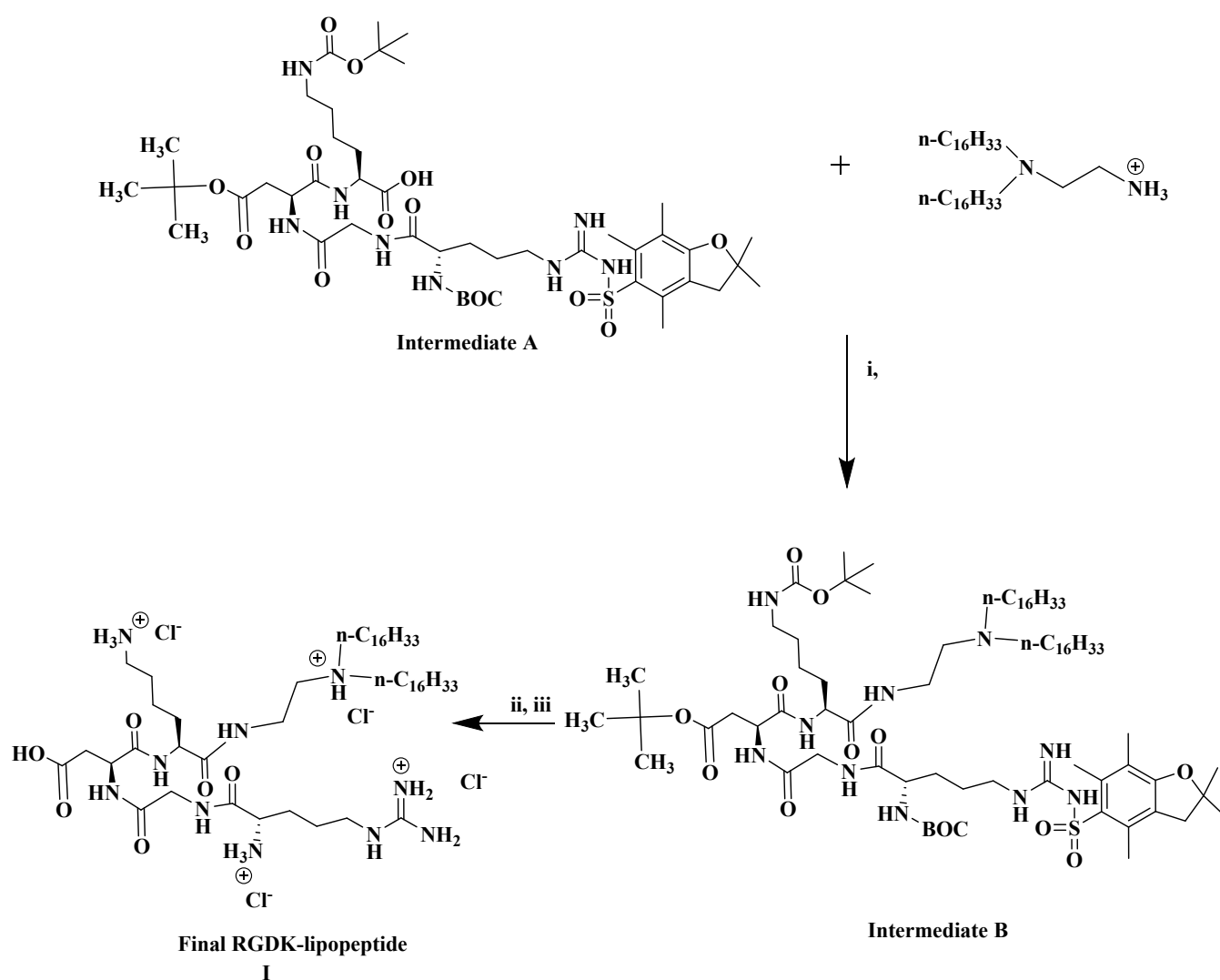
**Part A.**



**Reagents:** i. Fmoc-Asp(OtBu)-OH, DMF, HBTU, DIPEA, 3 h; ii. 20% piperidine DMF (1:4) (v/v), 30 min; iii. Fmoc-Gly-OH, DMF, HBTU, DIPEA, 3 h. iv. 20% piperidine DMF (1:4) (v/v), 30 min; v. Boc-Arg(Pbf)-OH, HBTU, DIPEA, DMF, 3 h; vi. 0.25% TFA/DCM, 3 h, 0 °C, DCM.

**Figure S1A.** Scheme for synthesis of protected RGDK-peptide.

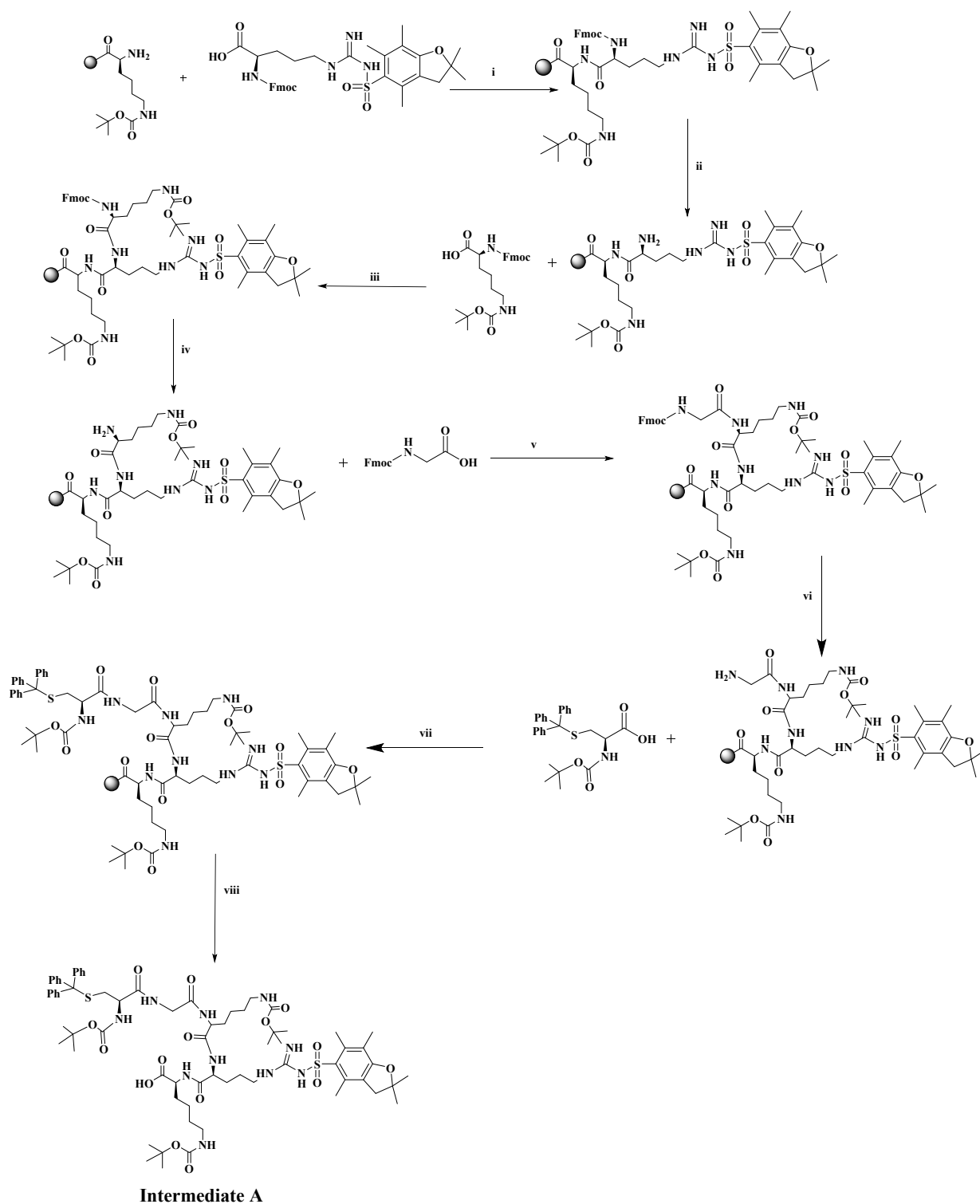
## Part B



**Reagents:** i.  $N^1, N^1$ -dihexadecylethane-1,2-diamine, EDCI, HOBT, dry DCM, DIPEA, 0 °C-RT, 24 h; ii. TFA-TIS (95:5) TFA, 12 h, RT; iii. Amberlite IR 400 Cl<sup>-</sup> ion exchange resin, MeOH.

**Figure S1B.** Scheme for synthesis of RGDK-lipopeptide (I).

**Part A.**

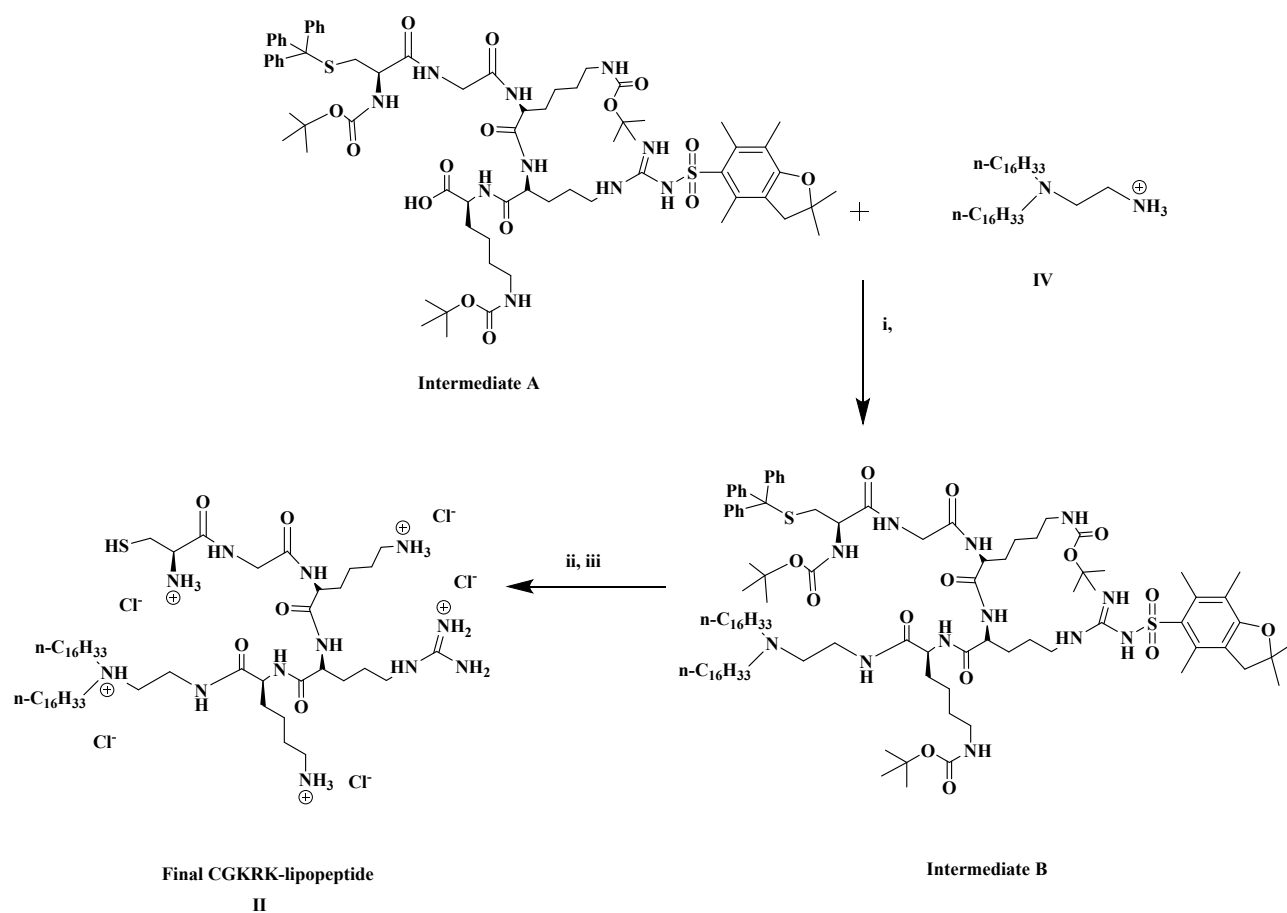


**Reagents:** i. DMF, HBTU, DIPEA, 3 h. ii. 20% PIPERIDINE iii. DMF, HBTU, DIPEA, 3 h. iv. 20% PIPERIDINE, v. HBTU, DIPEA, DMF, 3 h. vi. 20% PIPERIDINE in DMF, vii. DMF, HBTU, DIPEA, 3h, viii. 0.5% TFA/DCM, 3 h, 0 °C, DCM.

**Figure S2A.** Scheme for synthesis of protected CGKRRK-peptide.

Part

B.



**Reagents:** i.  $N^1, N^1$ -dihexadecylethane-1,2-diamine, EDCI, HOBt, dry DCM, DIPEA, 0 °C-RT, 24 h; ii. TFA-TIS (95:5), 12 h, RT; iii. Amberlite IR 400 Cl<sup>-</sup> ion exchange resin, MeOH.

**Figure S2B.** Scheme for synthesis of final CGKRK-lipopeptide (II).

AC-WR-RGDK-PEP2  
AC-WR-rgdk-pep2 8 (0.202)

TOF MS ES+  
4.76e3

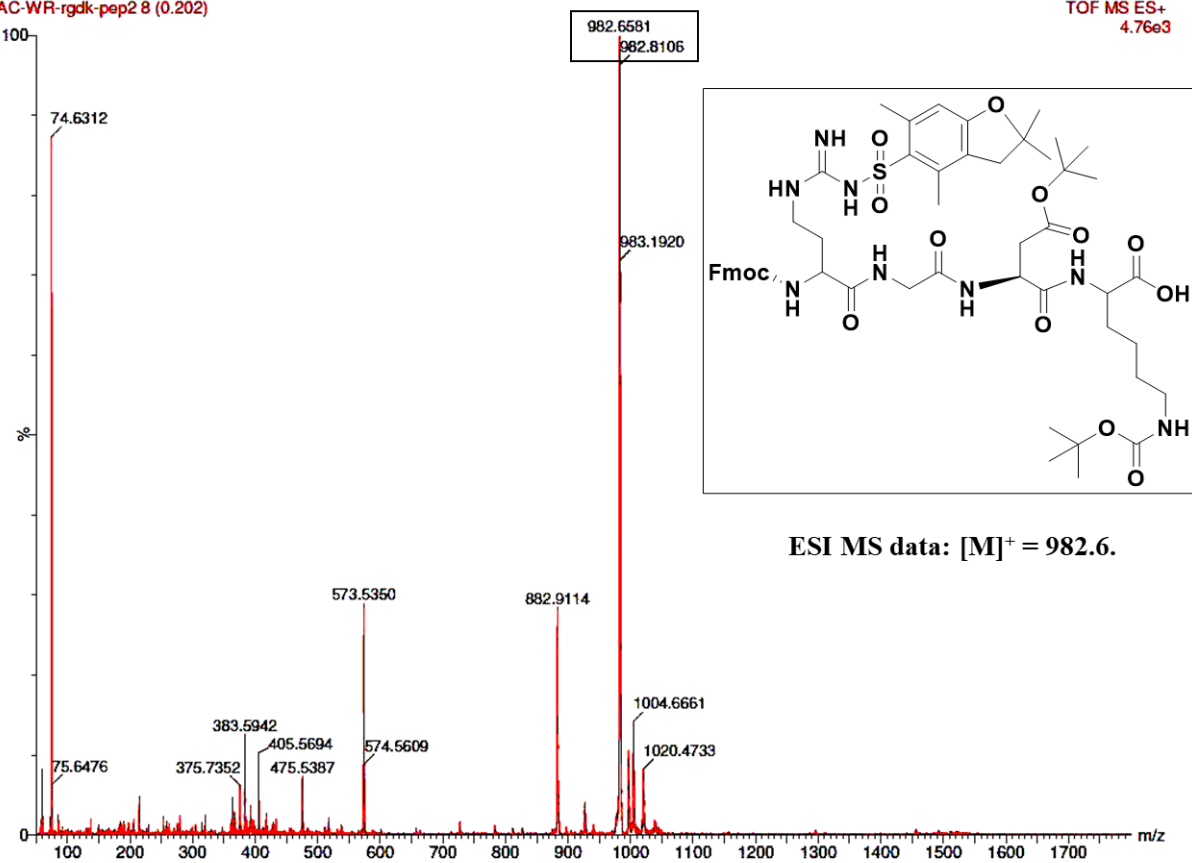


Figure S3. ESI-MS spectra of protected RGDK-peptide (Intermediate A. Figure S1A).

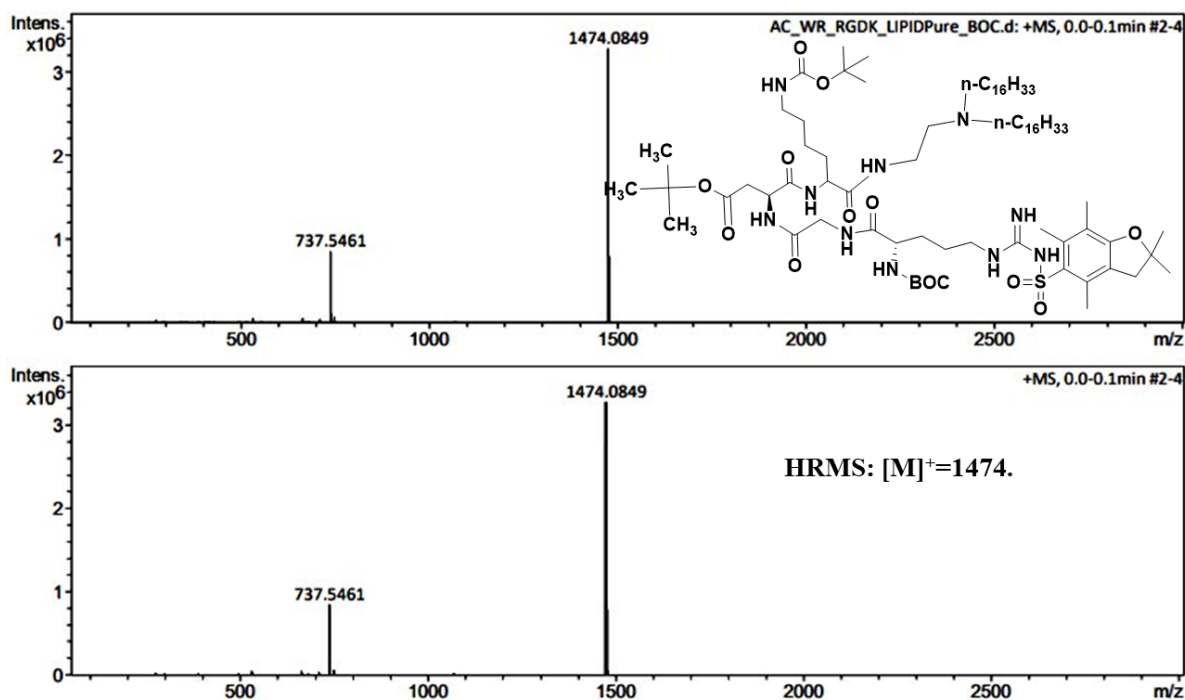


Figure S4. HRMS spectra of protected RGDK-lipopeptide (Intermediate B, Figure S1B).

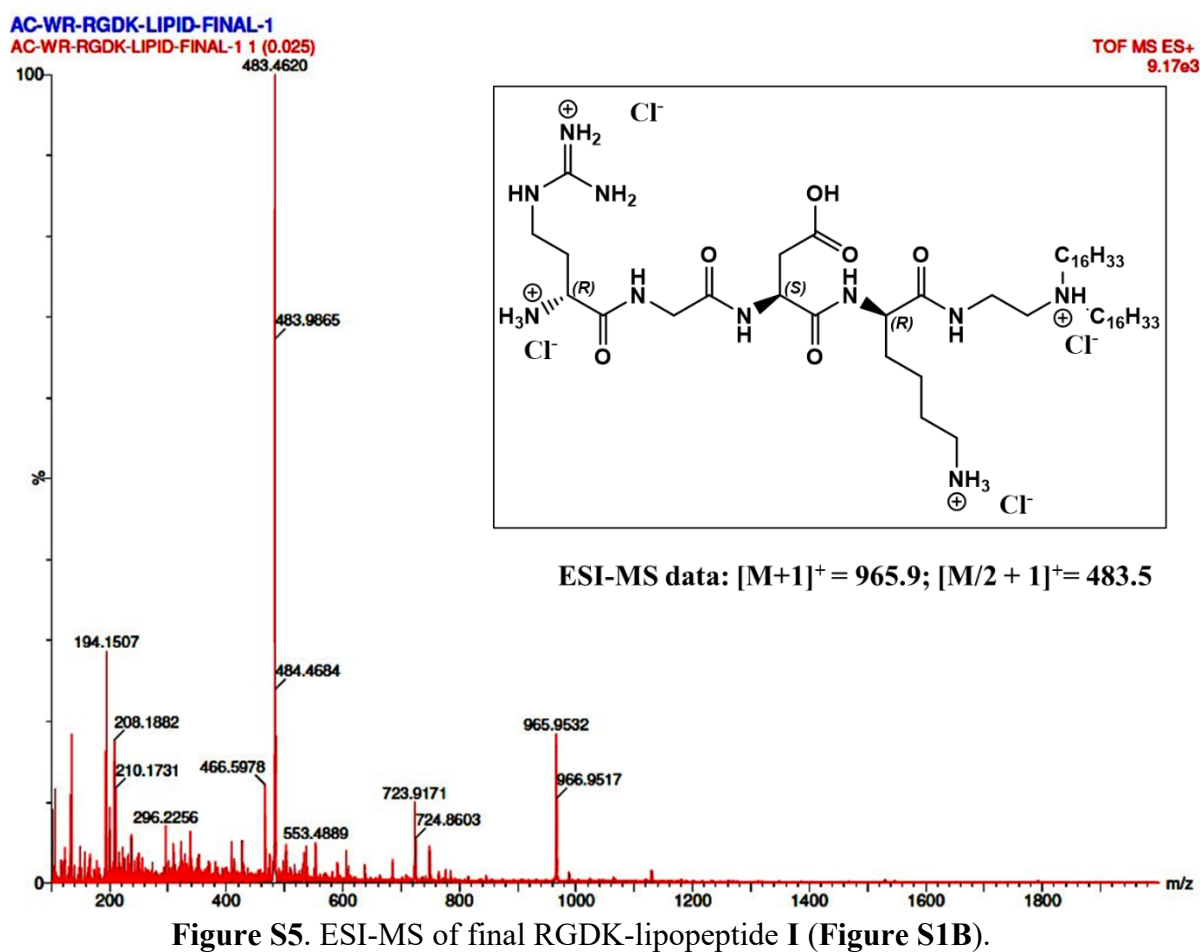
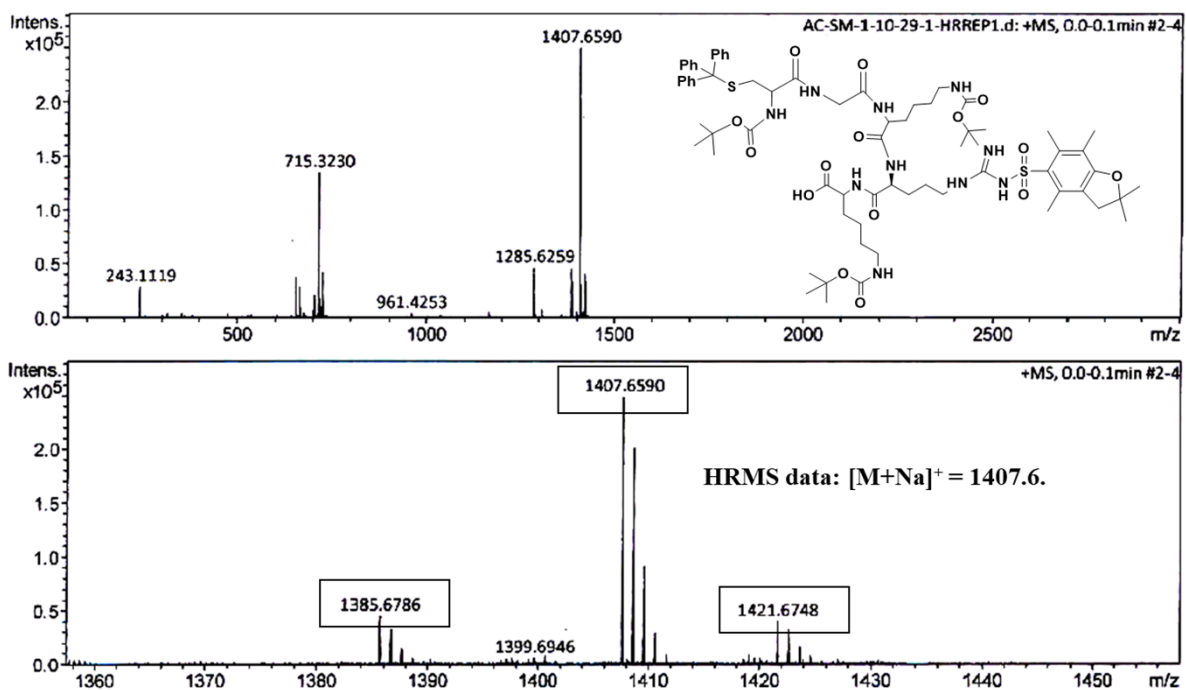


Figure S5. ESI-MS of final RGDK-lipopeptide I (Figure S1B).



**Figure S6.** HRMS spectra of protected CGKRK-peptide (**Intermediate A, Figure S2A.**).



AC-WR-CGKRK-LIPID-P  
AC-WR-CGKRK-LIPID-P 8 (0.202)

TOF MS ES+  
1.85e3

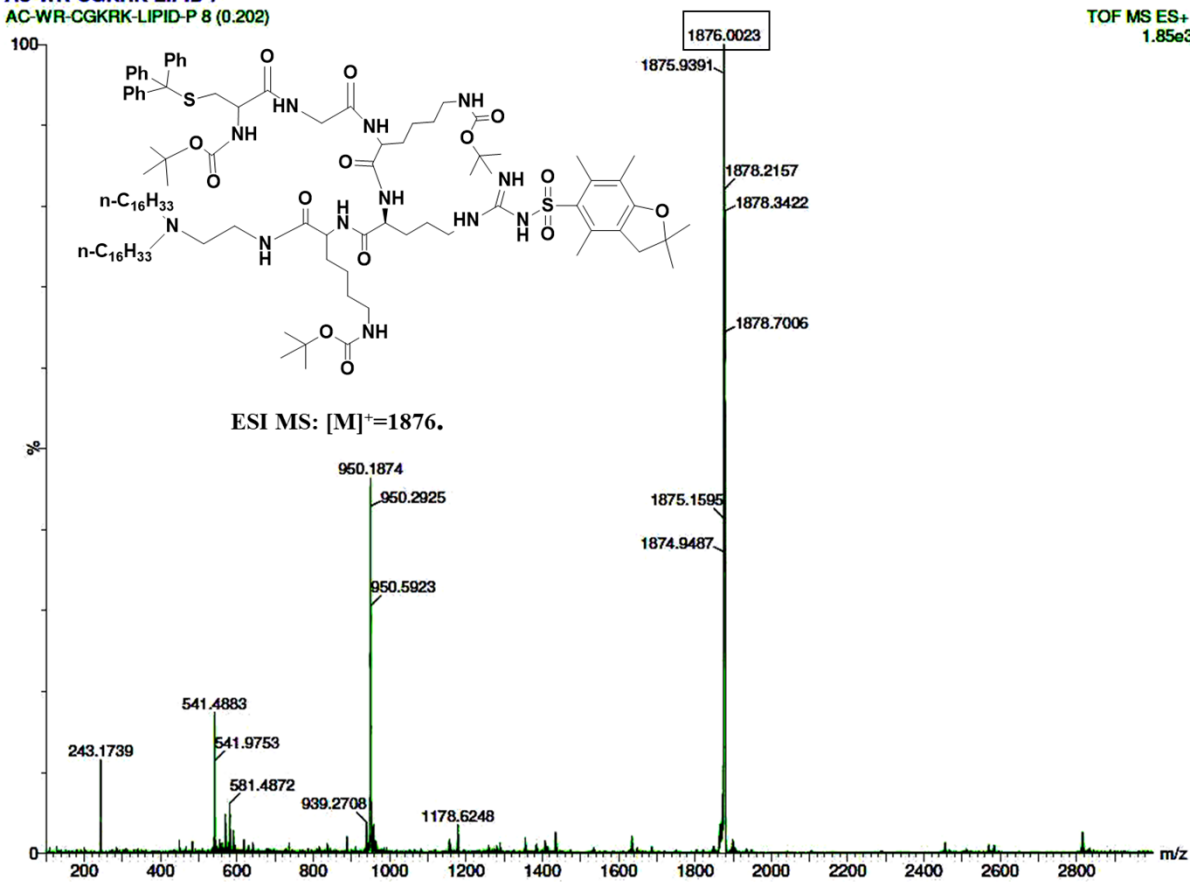
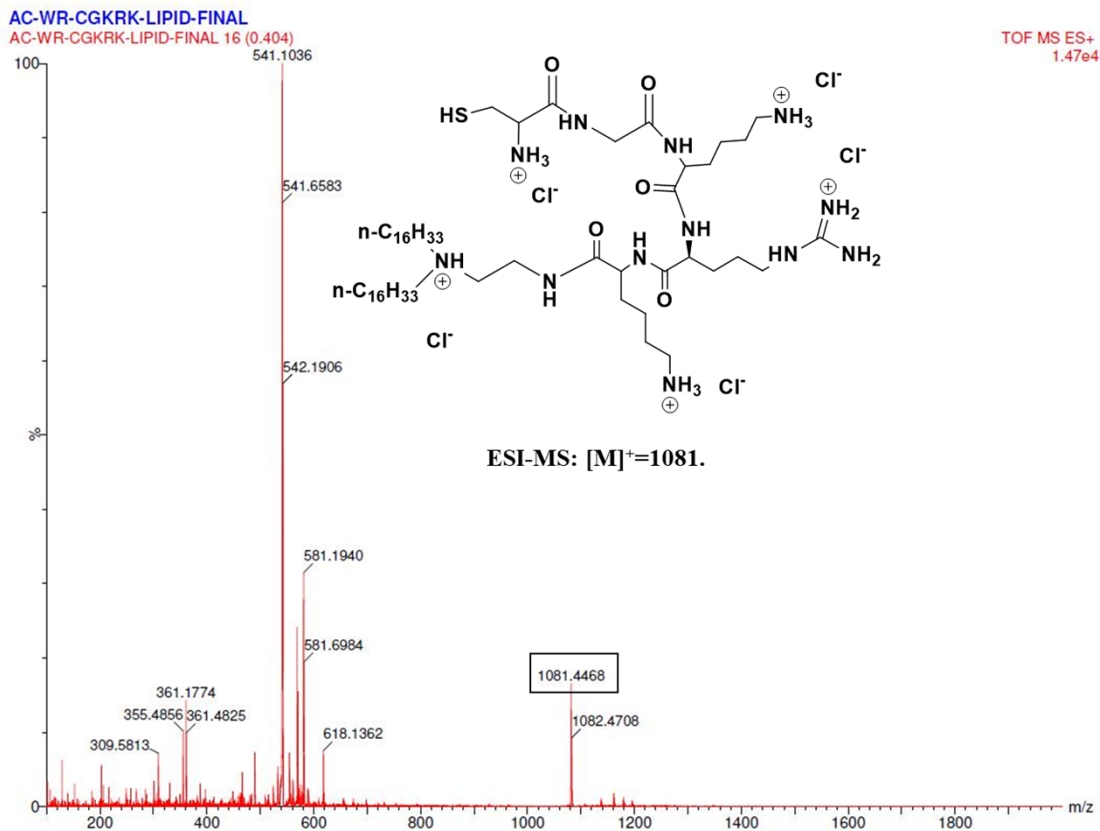


Figure S7. ESI-MS spectra of protected CGKRK-lipopeptide (Intermediate B, Figure S2B).

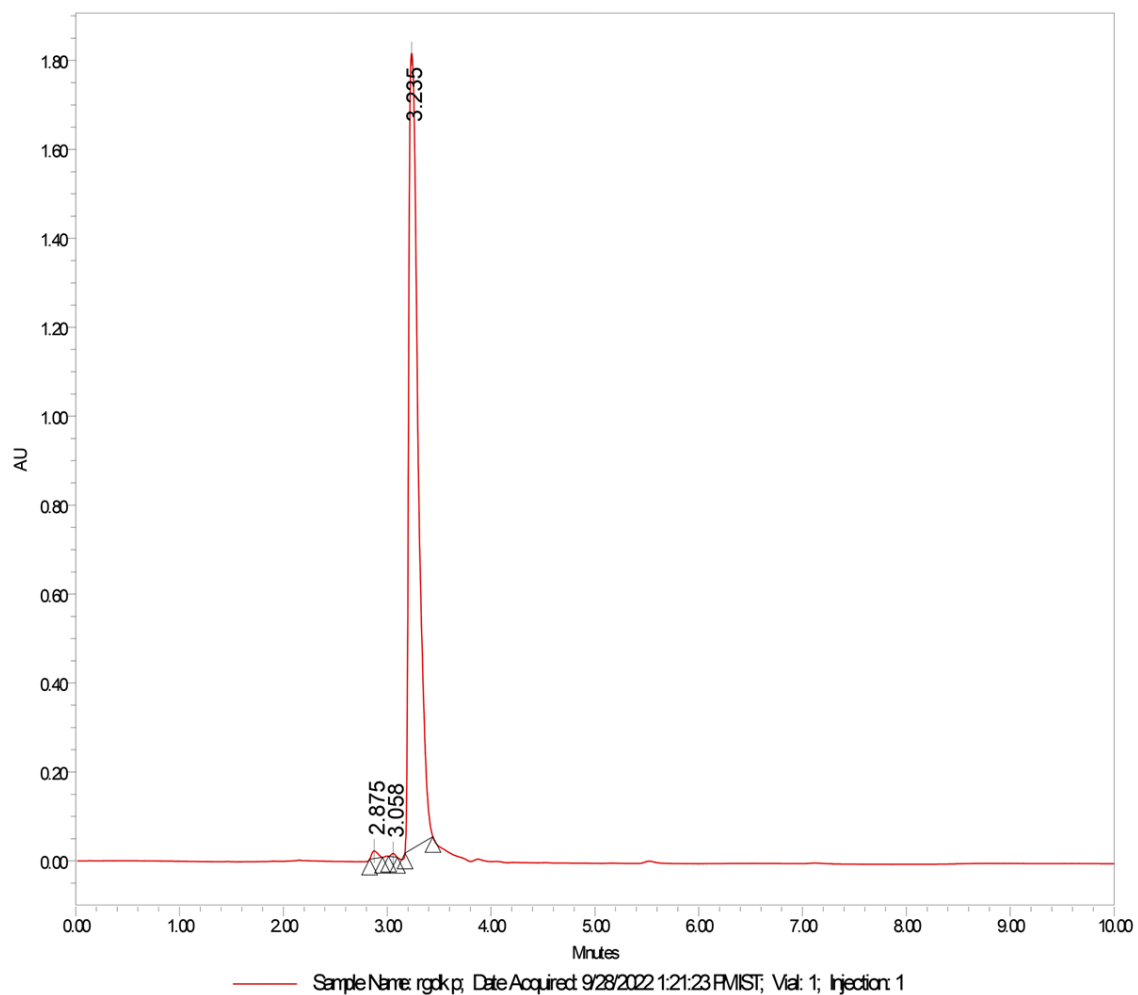


**Figure S8.** ESI-MS spectra of final CGKRK-lipopeptide (**Figure S2B**).

# HPLC

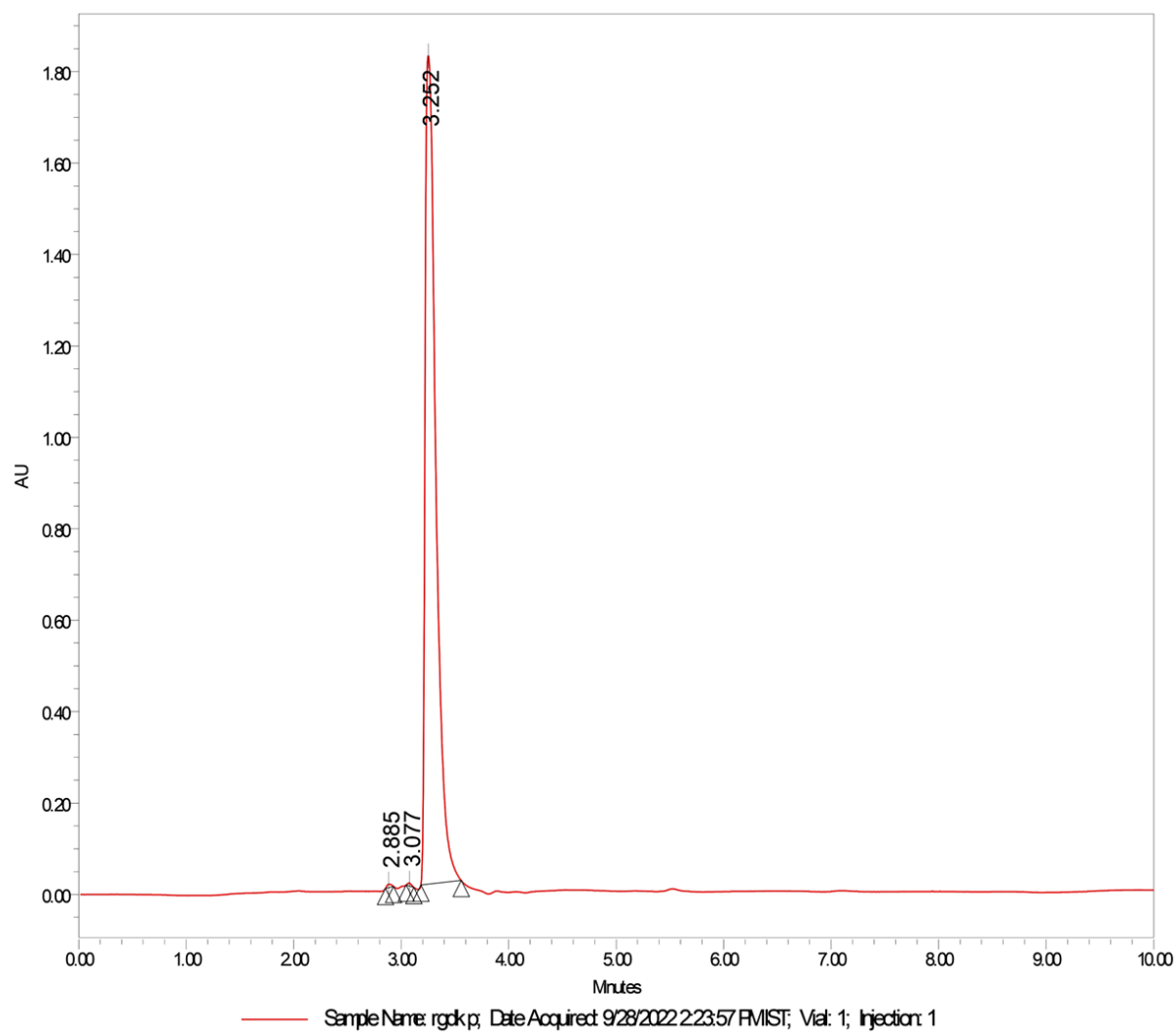
## RGDK- lipopeptide I

Mobile phase: 100% Methanol:



**Figure S9 A.** HPLC profiles of final RGDK-lipopeptide I (Figure 1) in 100% Methanol.

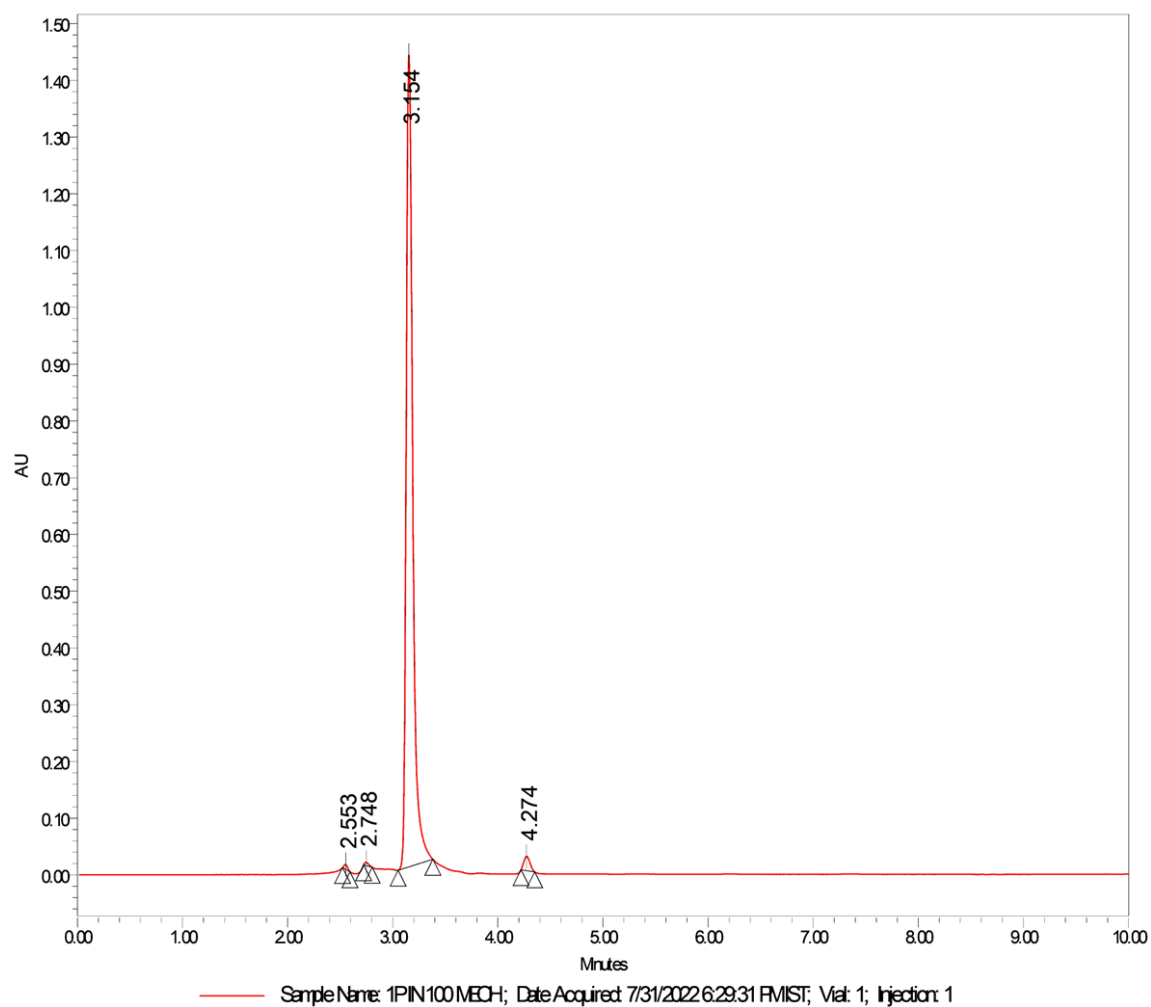
Mobile phase: 95:5 (v/v) Methanol:H<sub>2</sub>O



**Figure S9 B.** HPLC profiles of final RGDK-lipopeptide **I** (Figure 1) in 95:5 (v/v) Methanol:H<sub>2</sub>O.

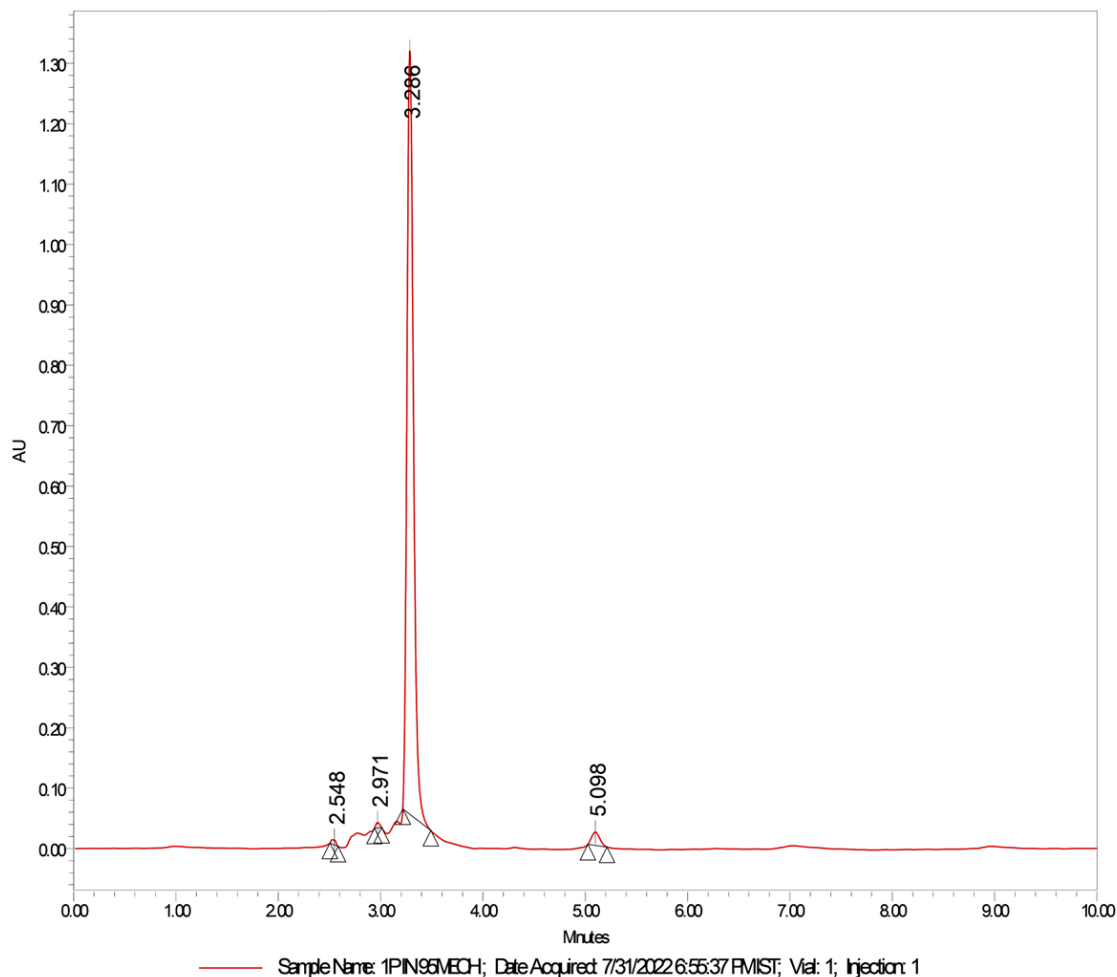
## CGKRRK-lipopeptide

Mobile phase: 100% Methanol



**Figure S10A.** HPLC profiles of final CGKRRK-lipopeptide **II** (Figure 1) in pure Methanol.

**Mobile phase: 95:5 (v/v) Methanol:H<sub>2</sub>O**



**Figure S10 B.** HPLC profiles of final CGKRR-lipo peptide **II** (Figure 1) in 95:5 (v/v) Methanol:H<sub>2</sub>O

**HPLC Conditions:**

**System:** Waters 1525

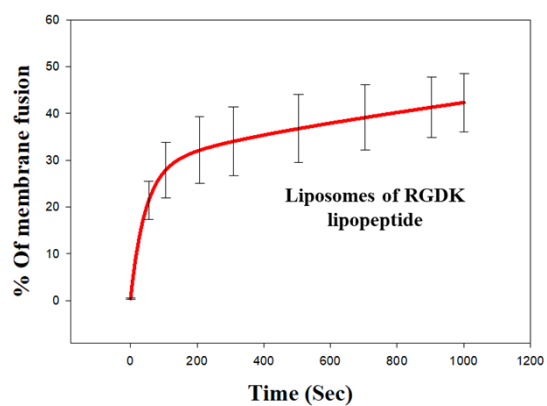
**Column:** Cosmosil C18 (4.6 ID x 250 mm)

**Mobile Phases:** Pure methanol and 95:5 (v/v) Methanol:Water

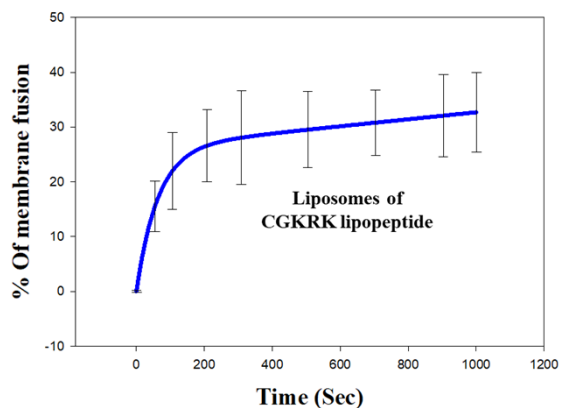
**Flow Rate:** 1.0 mL/min

**Detection:** UV at 210 nm

**A.**



**B.**



**Figure S11.** Biomembrane fusogenicities of both the liposomes of RGDK-lipopeptide (**A**) and CGKRR-lipopeptide (**B**) with model biomembranes containing error bars (based on percent of membrane fusion values observed in two repeat experiments for each time points shown).