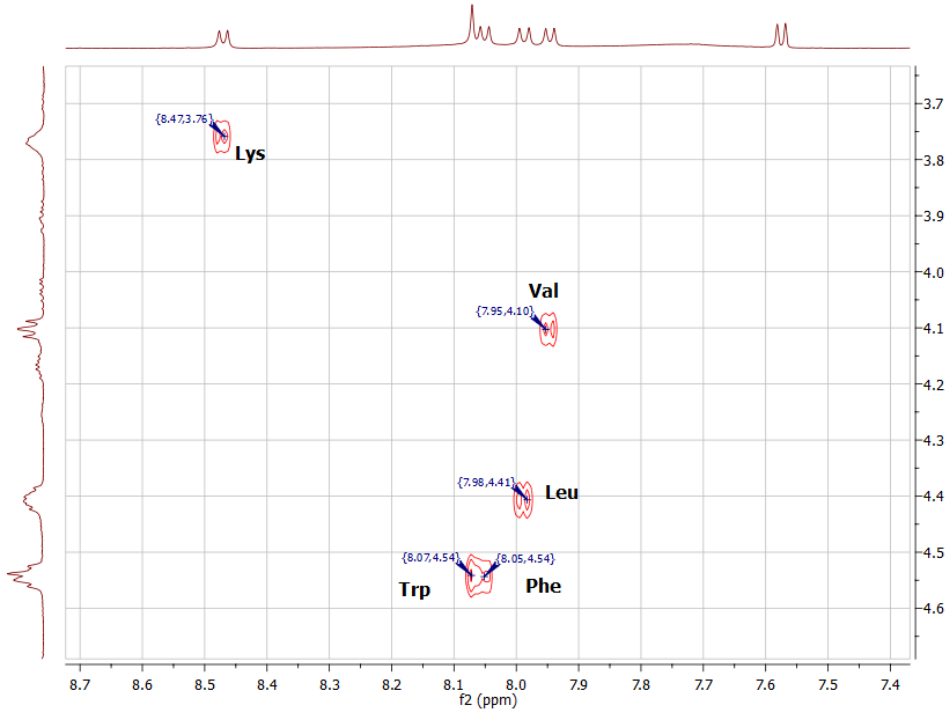
Supplementary Material

1. ^{1}H NMR data

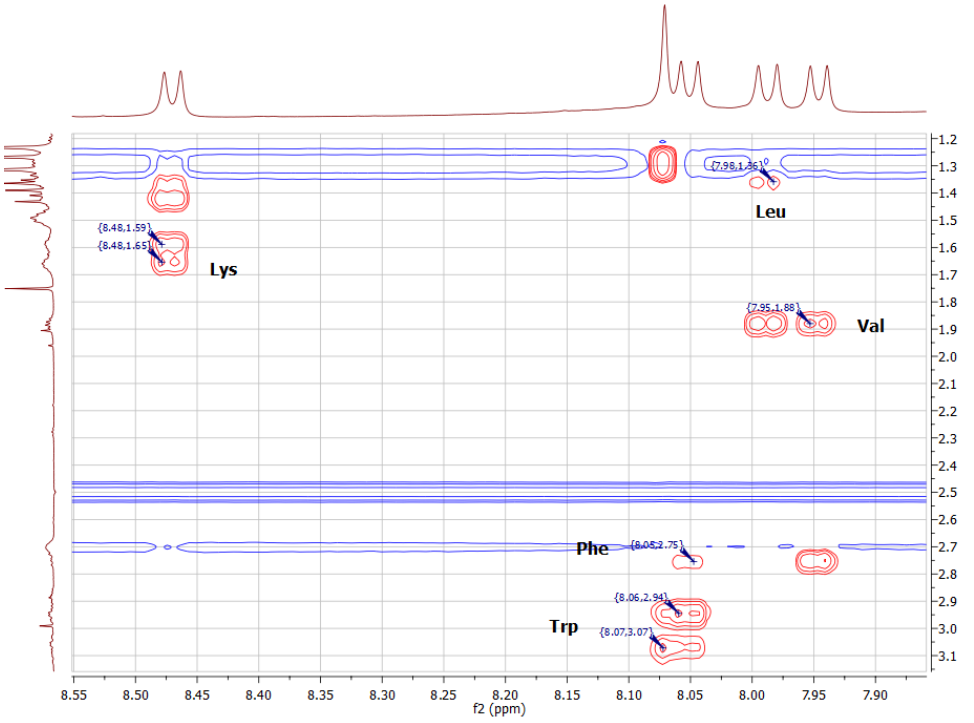
KLVFF ^{1}H NMR (500 MHz, DMSO-d6) δ 8.46 (d, 1H, NH Leu, *J* = 7.9 Hz), 8.22 (d, 1H, NH Phe2, *J* = 7.8 Hz), 7.93 – 7.90 (m, 2H, NH Val, NH Phe1), 7.28 – 7.18 (m, 10H, ArH), 4.56 (m, 1H, CαH Phe1), 4.43 (m, 1H, CαH Phe2), 4.38 (m, 1H, CαH Leu), 4.08 (m, 1H, CαH Val), 3.75 (m, 1H, CαH Lys), 3.05 (m, 1H, CαH (Phe2) C*H*H), 2.97 (m, 1H, CαH (Phe1) C*H*H), 2.92 (m, 1H, CαH (Phe2) CH*H*), 2.73 (m, 1H, CαH (Phe1) CH*H*), 2.68 (m, 2H, CαH (Lys) $CH_2CH_2CH_2CH_2$), 1.85 (m, 1H, CαH (Val) C*H*), 1.69 – 1.63 (m, 2H, CαH (Lys) $CH_2CH_2CH_2CH_2$), 1.58 (m, 1H, CαH (Leu) CH_2CH), 1.51 – 1.47 (m, 2H, CαH (Lys) $CH_2CH_2CH_2CH_2$), 1.42 – 1.34 (m, 2H, CαH (Leu) CH_2CH), 1.31 – 1.26 (m, 2H, CαH (Lys) $CH_2CH_2CH_2CH_2$), 0.88 – 0.83 (m, 6H, (Leu) 2 x CH_3), 0.72 – 0.69 (m, 6H, (Val) 2 x CH_3).

HRMS $[M+H]^+$ calc'd = 653.4027, $[M+H]^+$ found = 653.4023.

2. ROESY spectra for peptide 2

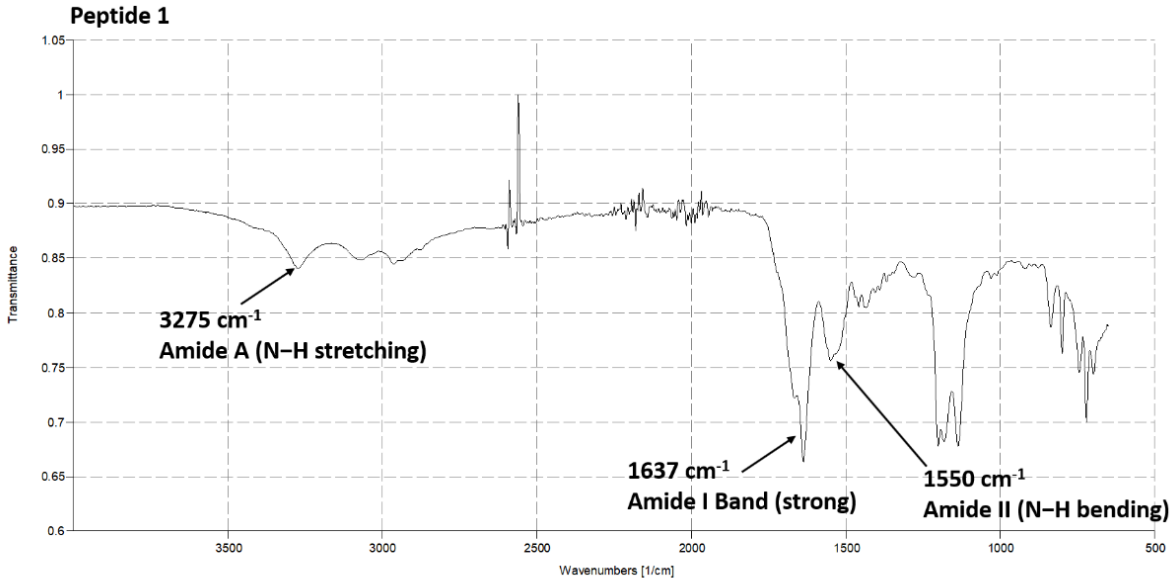


Supplementary Figure S1. Peptide **2** CαHs to NHs (*i*+1)

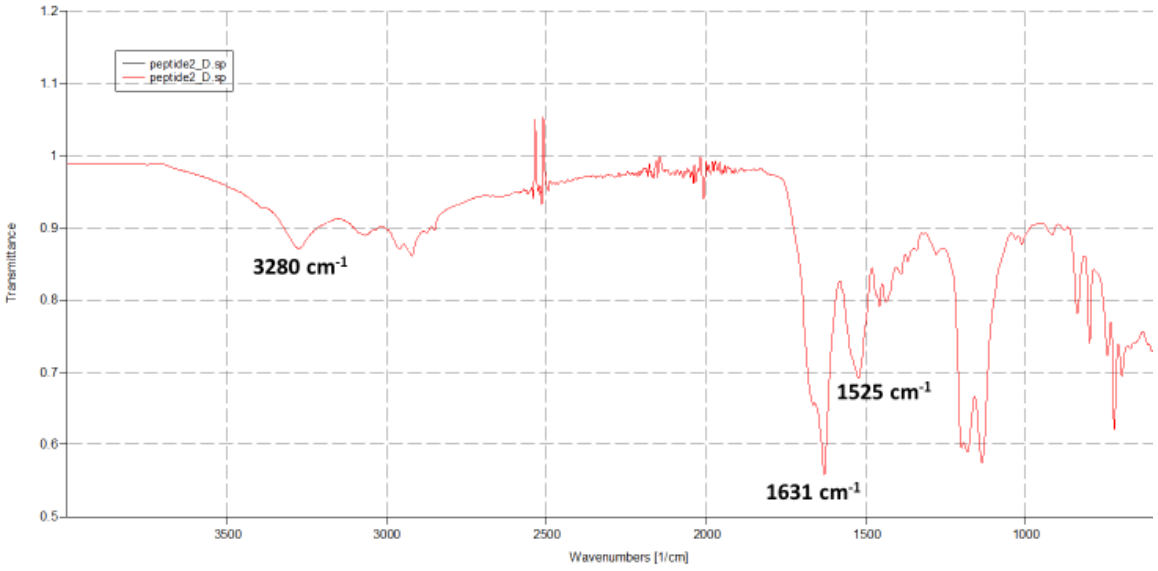


Supplementary Figure S2. Peptide **2** CβHs to NHs (*i*+1)

3. IR spectra for peptides 1 and 2



Supplementary Figure S3. IR spectrum for peptide **1**, indicative of parallel β-strand structure.



Supplementary Figure S4. IR spectrum for peptide **2**, indicative of antiparallel β-strand structure.

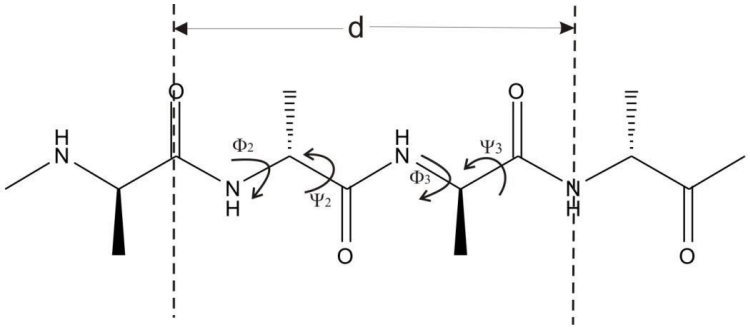
4. Computational molecular modelling

Supplementary Table S1. Backbone dihedral angles and $^{3}J_{NHC\alpha H}$ coupling constants for peptide **2**, indicating a β-strand geometry for residues 1-5, with the exception of the Aib residue.

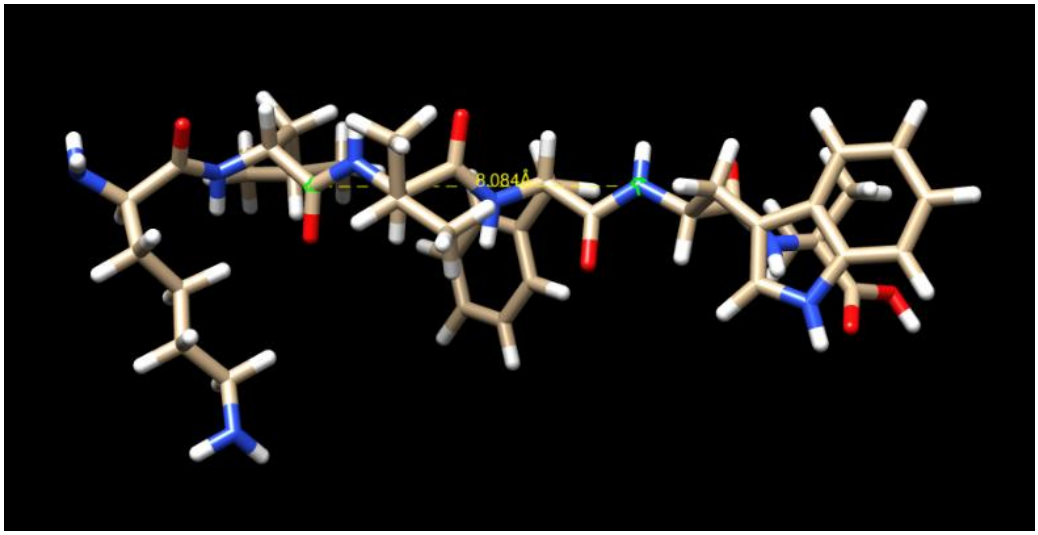
peptide 2				
D-amino acid residue	**ϕ**	**Ψ**	**Ω**	**$^{3}J_{NHC\alpha H}$ NMR coupling constants (Hz)**
Lys	**-**	**-143**	**-168**	
Leu	**96**	**-148**	**-178**	**8.0**
Val	**130**	**-134**	**179**	**9.1**
Phe	**129**	**-145**	**-171**	**8.1**
Trp	**117**	**-153**	**-176**	**8.2**
Aib	**178**	**175**	**179**	

Supplementary Table S2. Peptide **2**: Distances between CαH (*i*) to NH (*i*+1), $C\beta H_2$ (*i*) to NH (*i*+1), and NH (*i*) to NH (*i*+1), characteristic of a β-strand. **[1]**

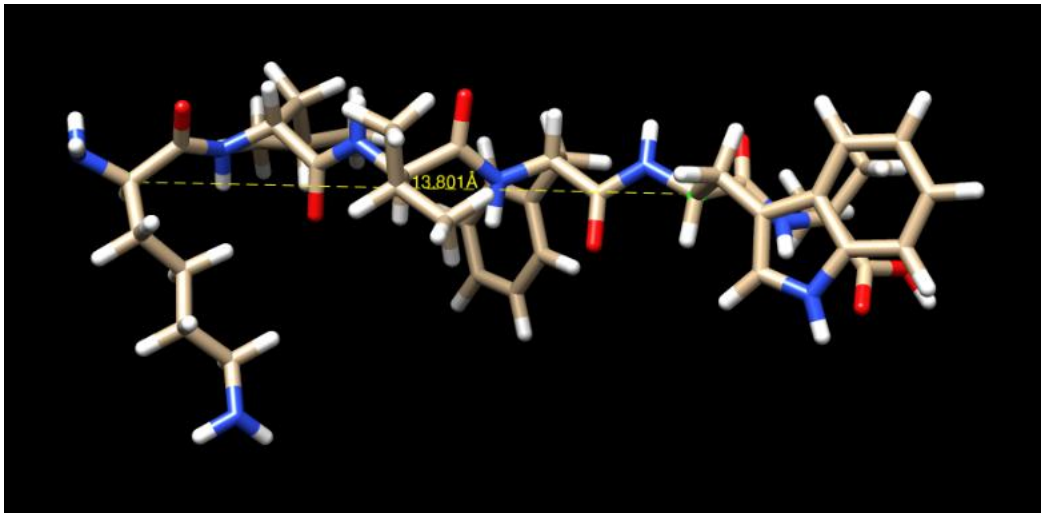
	Ideal β-strand distances (Å)	**peptide 2 (Å)**
CαH (*i*) to NH (*i*+1)	**2.2**	**2.3**
$C\beta H_2$ (*i*) to NH (*i*+1)	**3.2 - 4.5**	**2.7 - 4.2**
NH (*i*) to NH (*i*+1)	**4.3**	**4.3 – 4.4**



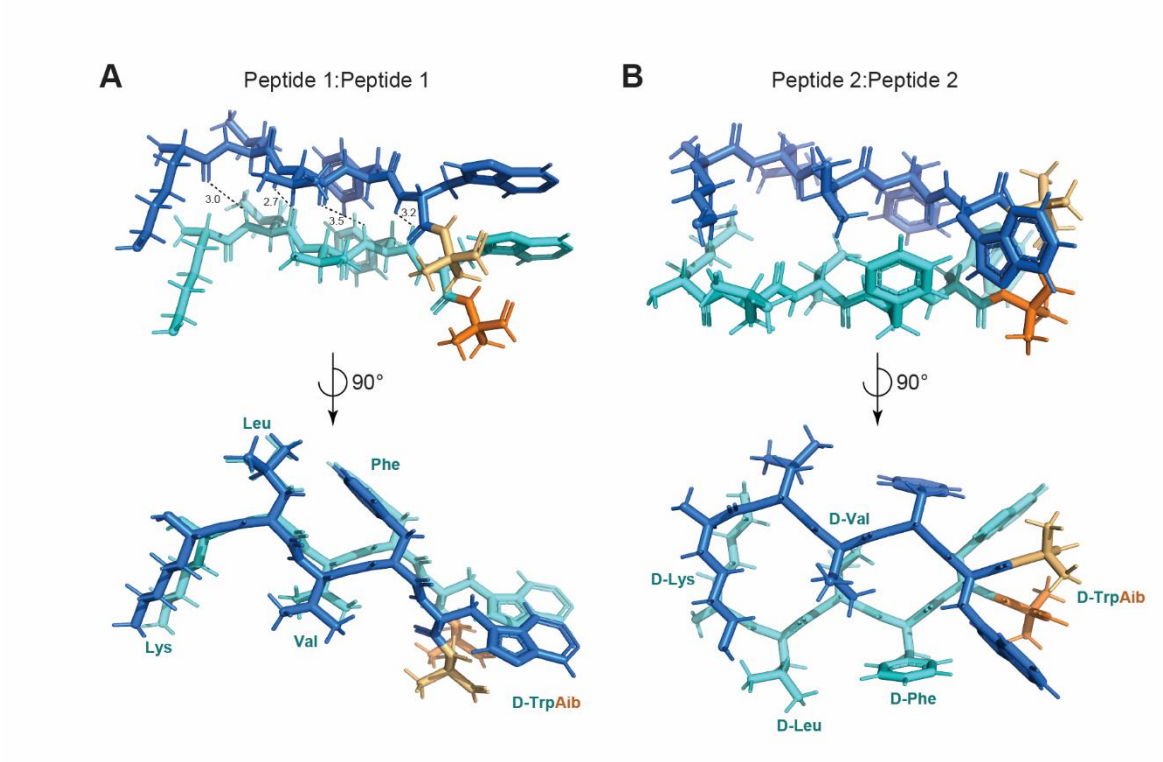
Supplementary Figure S5. Ideal peptide β-strand backbone with torsional angles Φ, Ψ, and optimal distance d = 8.0 Å. [2]



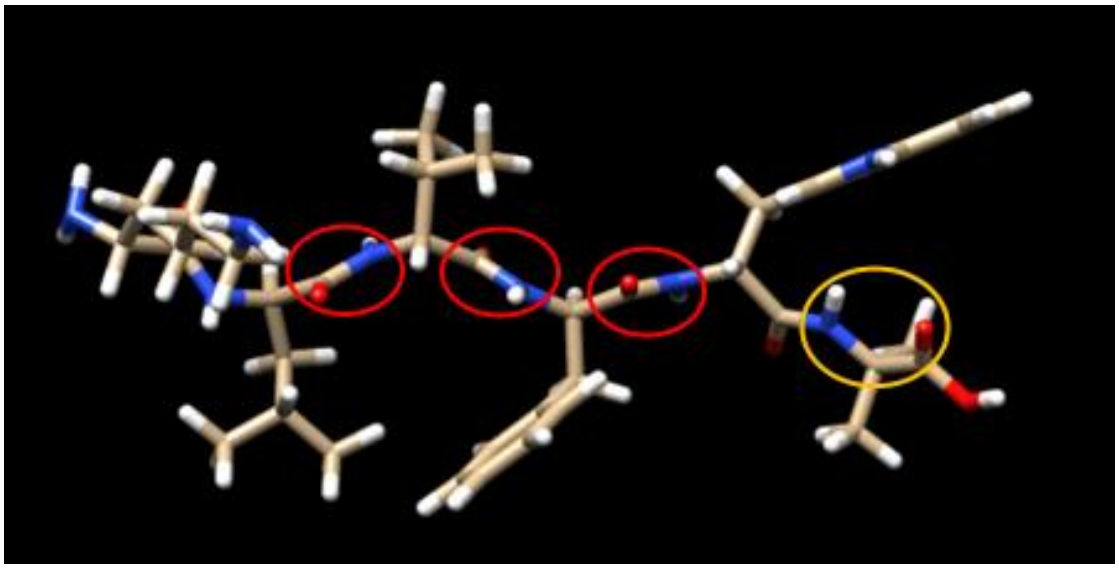
Supplementary Figure S6. Model of peptide **2**, showing optimal distance of 8.0 Å for region specified in Supplementary Figure S5.



Supplementary Figure S7. Model of **2**, showing length of peptide as 13.8 Å. An ideal β-strand is approx. 13.2 Å to 14.5 Å between (*i*) and (*i*+4) residues. [3]

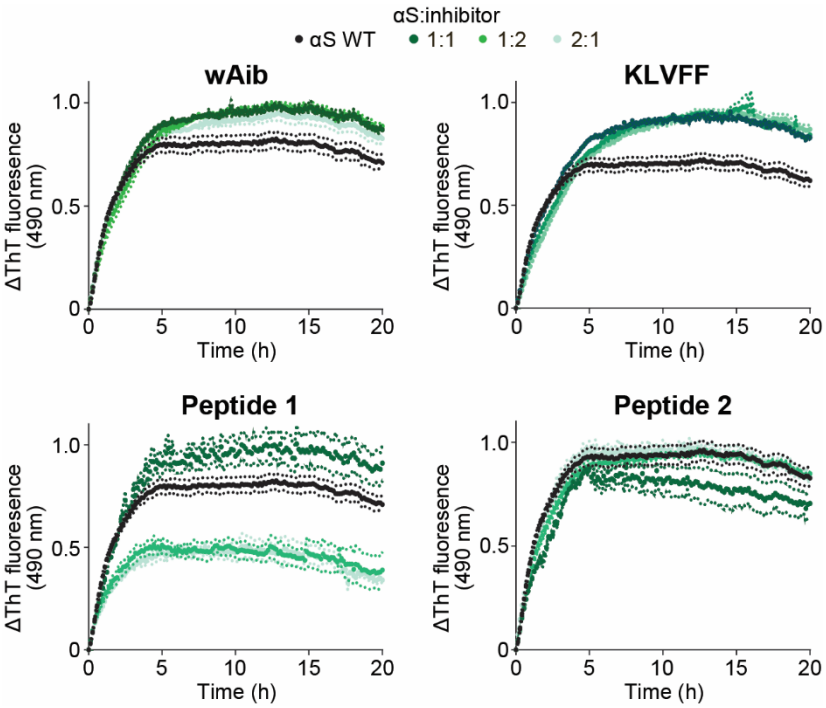


Supplementary Figure S8. A. Peptide **1** is prone to self-association via intermolecular H-bonding. **B.** Peptide **2** does not self-aggregate.



Supplementary Figure S9. Model of peptide **2** from above. Residues 1-5 are in a β-strand geometry, with backbone carbonyls and amide hydrogens positioned as such (red circles). In contrast, those associated with the Aib residue adopt a dissimilar orientation (yellow circle).

5. αS aggregation assays

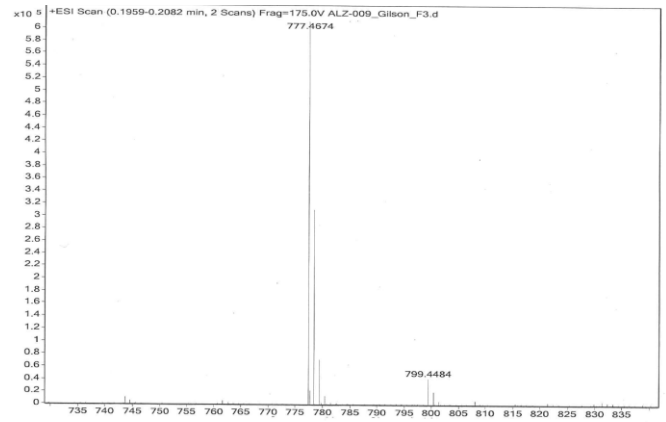


Supplementary Figure S10: Designed peptide inhibitors confer $A\beta_{42}$ specificity and do not prevent αS fibril aggregation. ThT fluorescence assay monitoring fibril formation of αS WT in the absence (50 μM, 5% w/w seed, black) and presence of either wAib, KLVFF, peptides **1** and **2** at various molar ratios. Data reported is presented as mean ± SEM (n = 3).

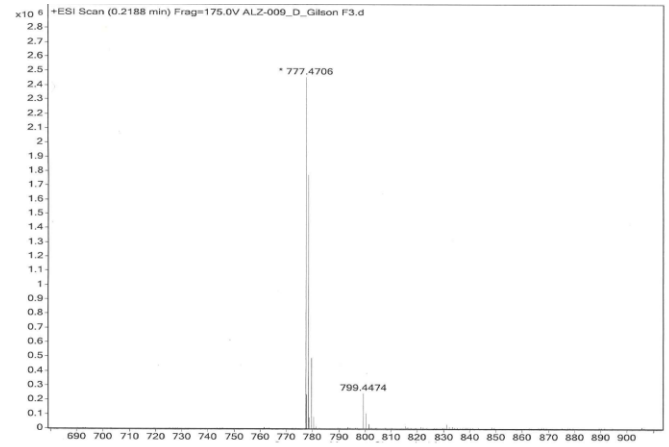
Supplementary Table S3. Elongation rates of $A\beta_{42}$ fibrils in the absence and presence of peptide inhibitors. The data is reported as mean ± SEM (n = 3).

Molar ratio ($A\beta_{42}$:Inhibitor)	**Elongation Rate (ΔThT fluorescence.h^{-1})**			
	wAib	**KLVFF**	**Peptide 1**	**Peptide 2**
$A\beta_{42}$	0.250 ± 0.013			
1:1	0.214 ± 0.009	0.197 ± 0.031	0.176 ± 0.007	0.098 ± 0.018
1:2	0.195 ± 0.009	0.179 ± 0.023	0.139 ± 0.008	0.0360 ± 0.006
1:10	0.177 ± 0.010	0.127 ± 0.027	0.069 ± 0.007	**-0.025 ± 0.007**
1:20	0.115 ± 0.014	0.124 ± 0.059	0.054 ± 0.004	**-0.0257 ± 0.017**

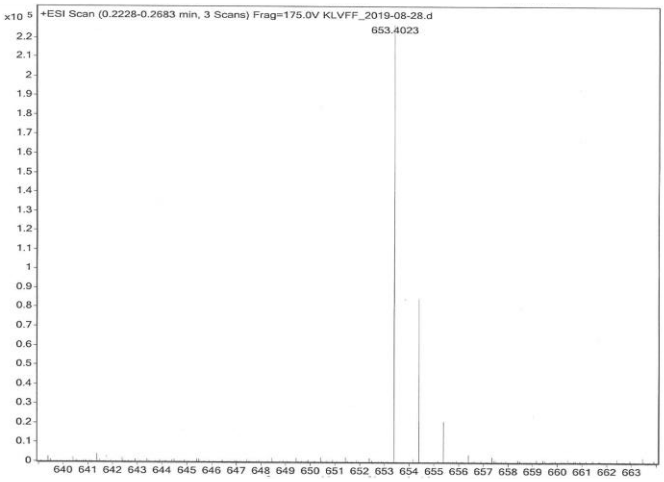
6. HRMS



Supplementary Figure S11. HRMS for peptide **1.**



Supplementary Figure S12. HRMS for peptide **2.**



Supplementary Figure S13. HRMS for KLVFF.

7. References

1 Wüthrich, K. (1986) NMR of proteins and nucleic acids. Wiley

2 Gillespie, P., Cicariello, J. and Olson, G. L. (1997) Conformational analysis of dipeptide mimetics Peptide Science. **43**, 191-217

3 Loughlin, W. A., Tyndall, J. D. A., Glenn, M. P. and Fairlie, D. P. (2004) Beta-strand mimetics. Chemical Reviews. **104**, 6085-6117