

Supporting Information

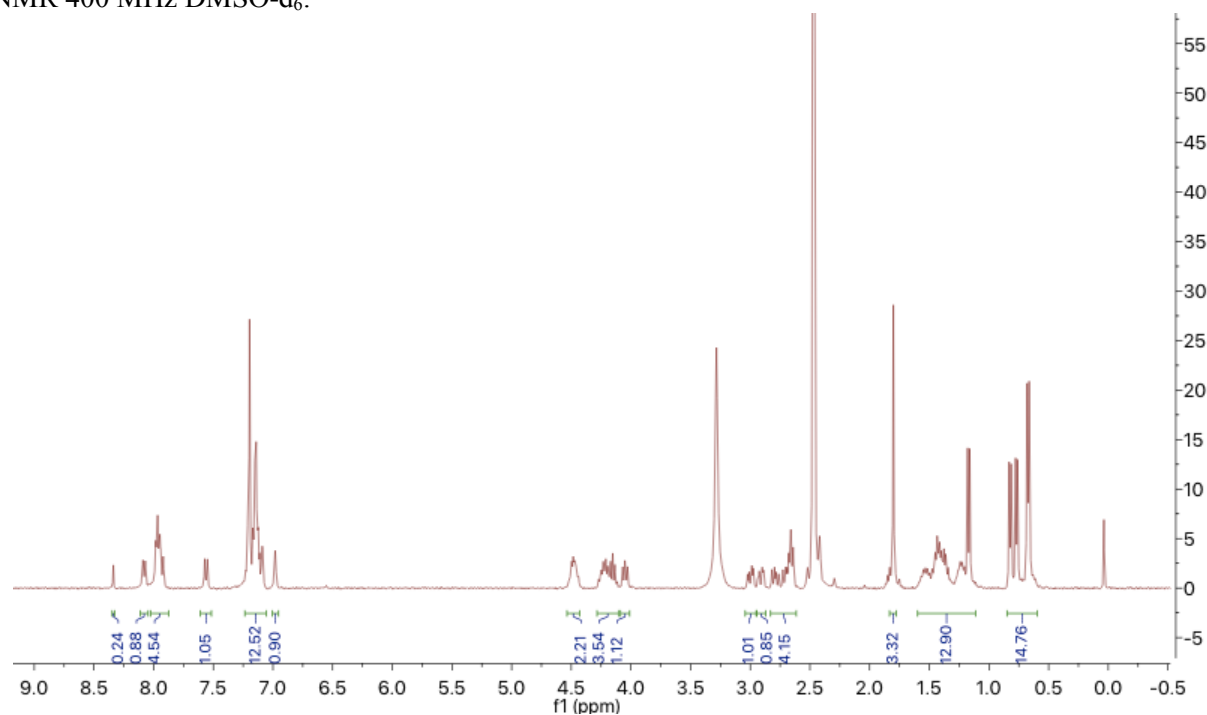
RSC Advances

N-Amino peptide scanning reveals inhibitors of A β ₁₋₄₂ aggregation

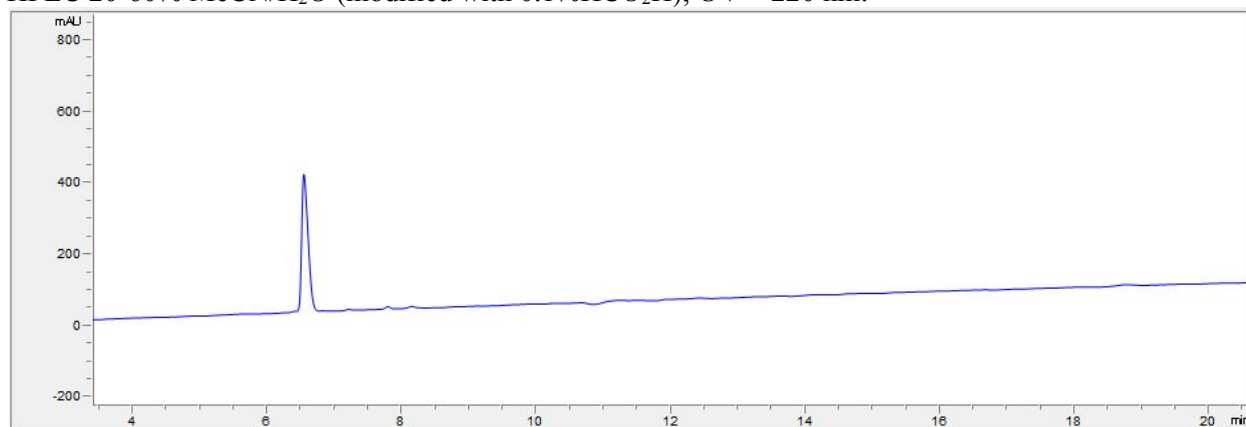
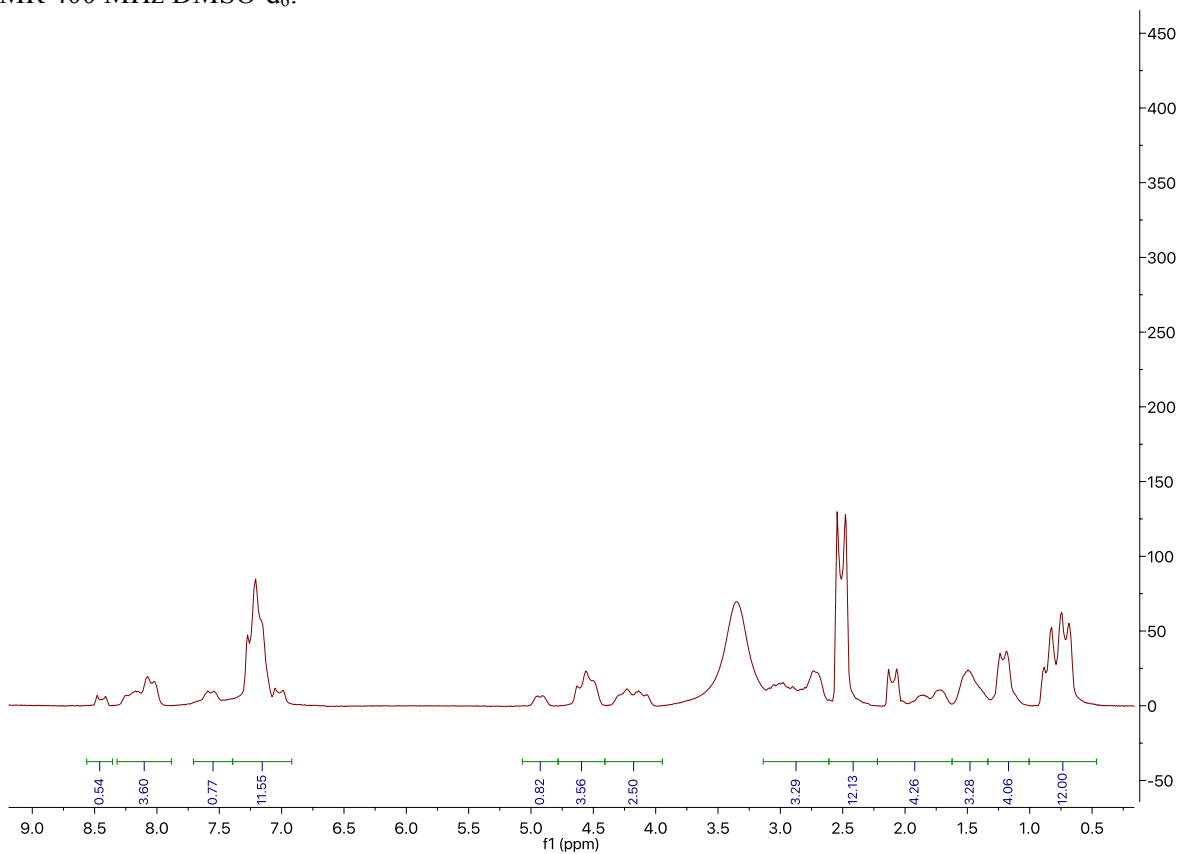
Khalilia C. Tillet[†] and Juan R. Del Valle^{‡*}

[†]*Department of Chemistry, University of South Florida, Tampa, FL 33620, USA*

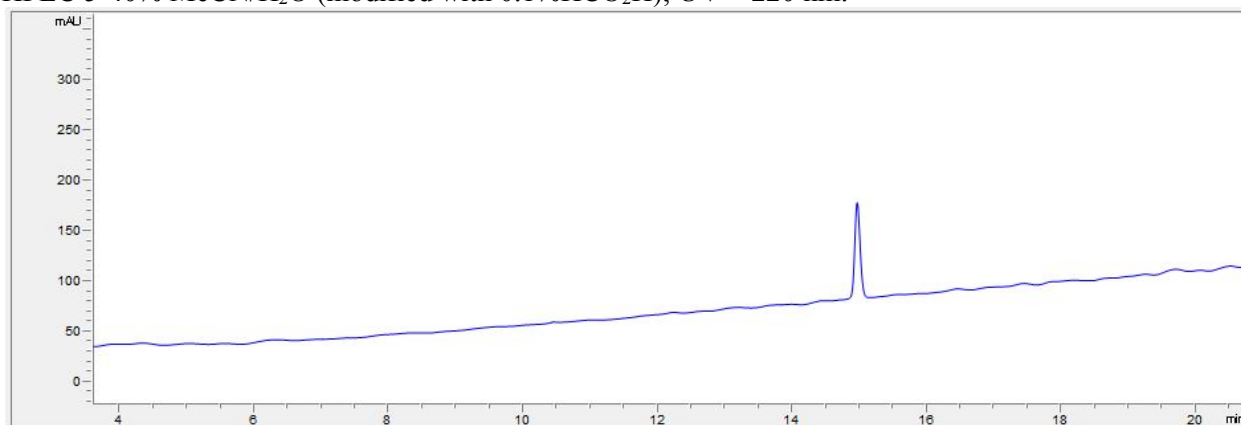
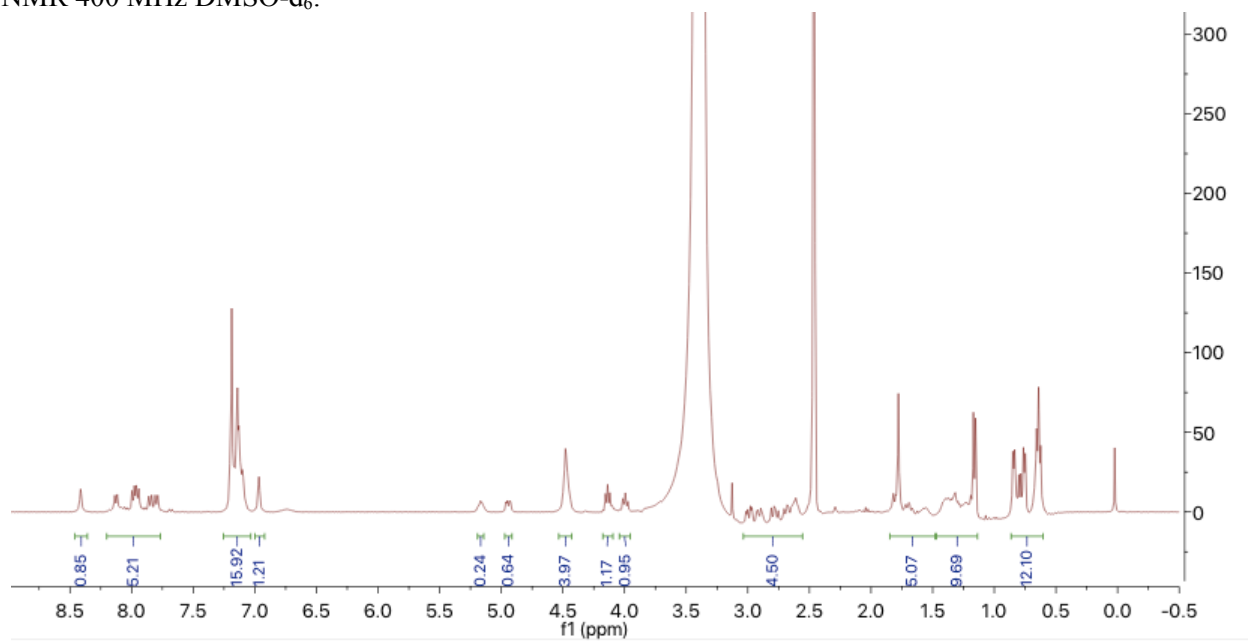
[‡] *Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, IN 46530, USA*

RP-HPLC and 1D ^1H NMR Data for Synthesized Compounds.**Ac-Lys-Leu-Val-Phe-Phe-Ala-NH₂ (3)**RP-HPLC 5-40% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm: ^1H NMR 400 MHz DMSO-d₆:

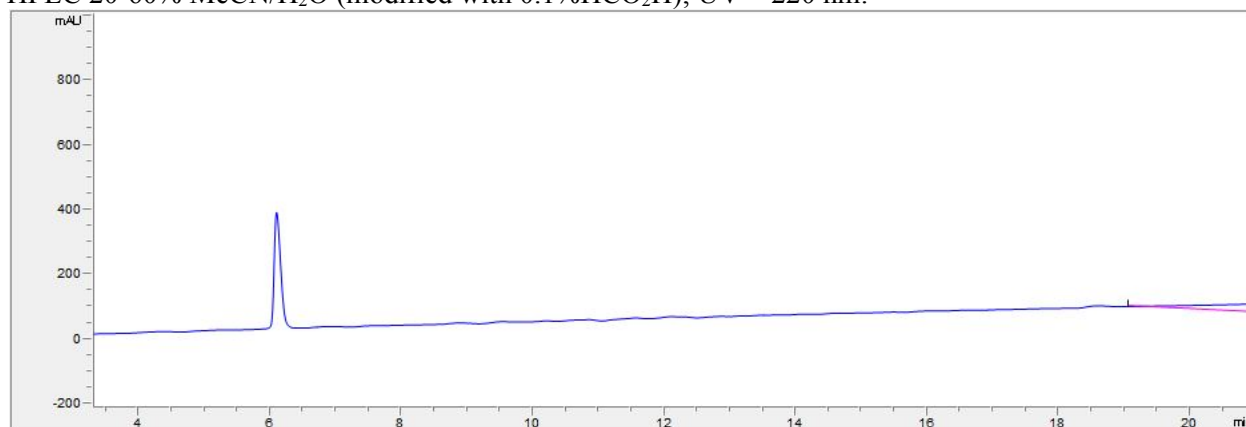
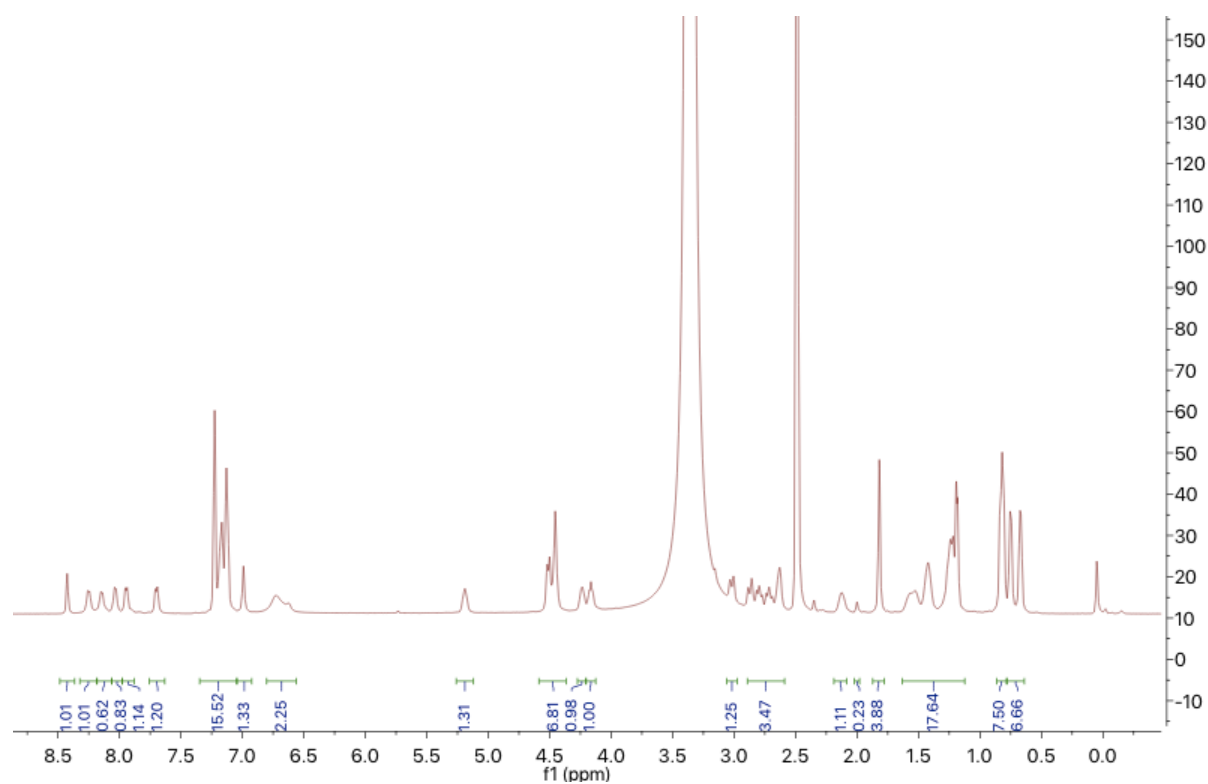
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Lys	4.23	1.48	γ 1.28, δ 1.59, ϵ 2.71
Leu	4.27	1.51	γ 1.41, δ 0.77, 0.82
Val	4.06	1.88	γ 0.70
Phe ⁴	4.47	3.03, 2.95	
Phe ⁵	4.49	2.81, 2.71	
Ala	4.20	1.18	

Ac-aLys-Leu-Val-Phe-Phe-Ala-NH₂ (4)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

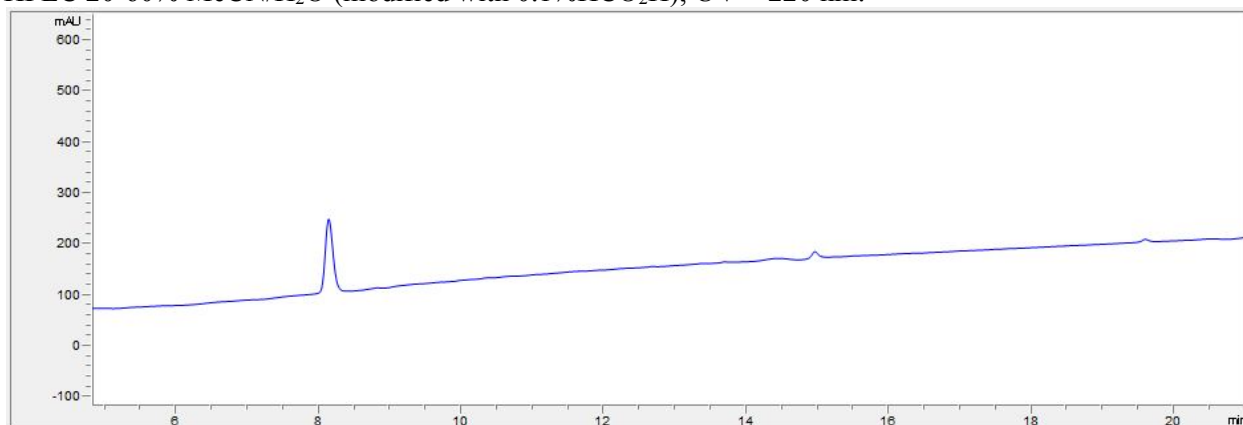
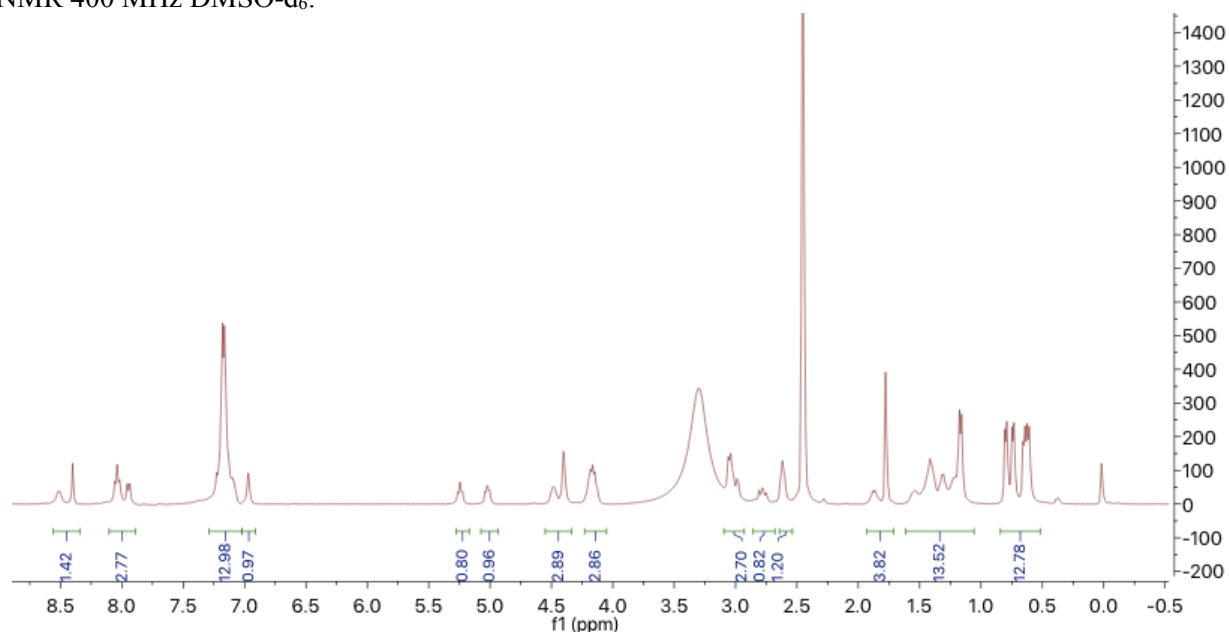
	α	β	others
Lys	4.90	1.50	γ 1.23, δ 1.70, ϵ 2.73
Leu	4.26	1.39	δ 0.78, 0.83
Val	4.06	1.84	γ 0.69
Phe ^{4/5}	4.50, 4.52	3.02, 2.92, 2.82, 2.74	
Ala	4.16	1.19	

Ac-Lys-aLeu-Val-Phe-Phe-Ala-NH₂ (5)RP-HPLC 5-40% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

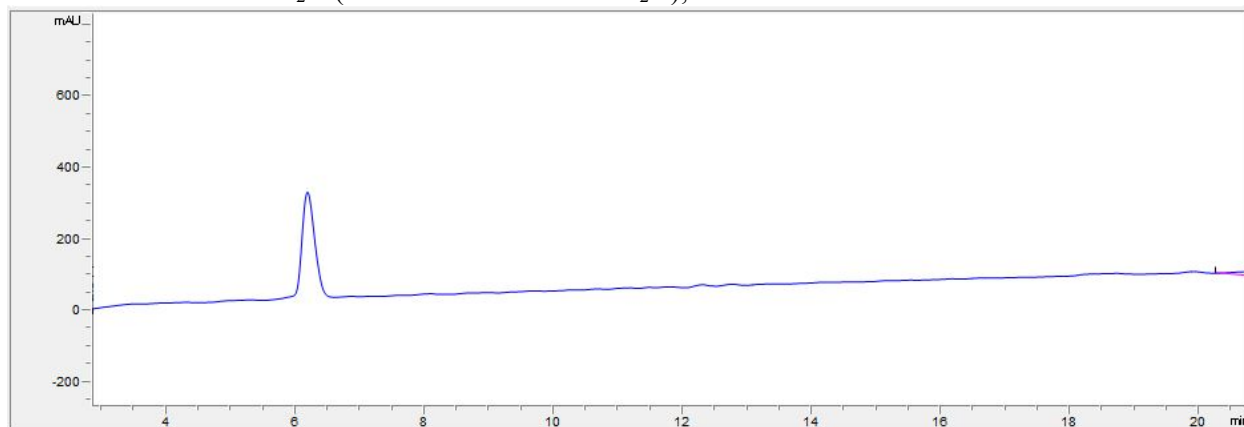
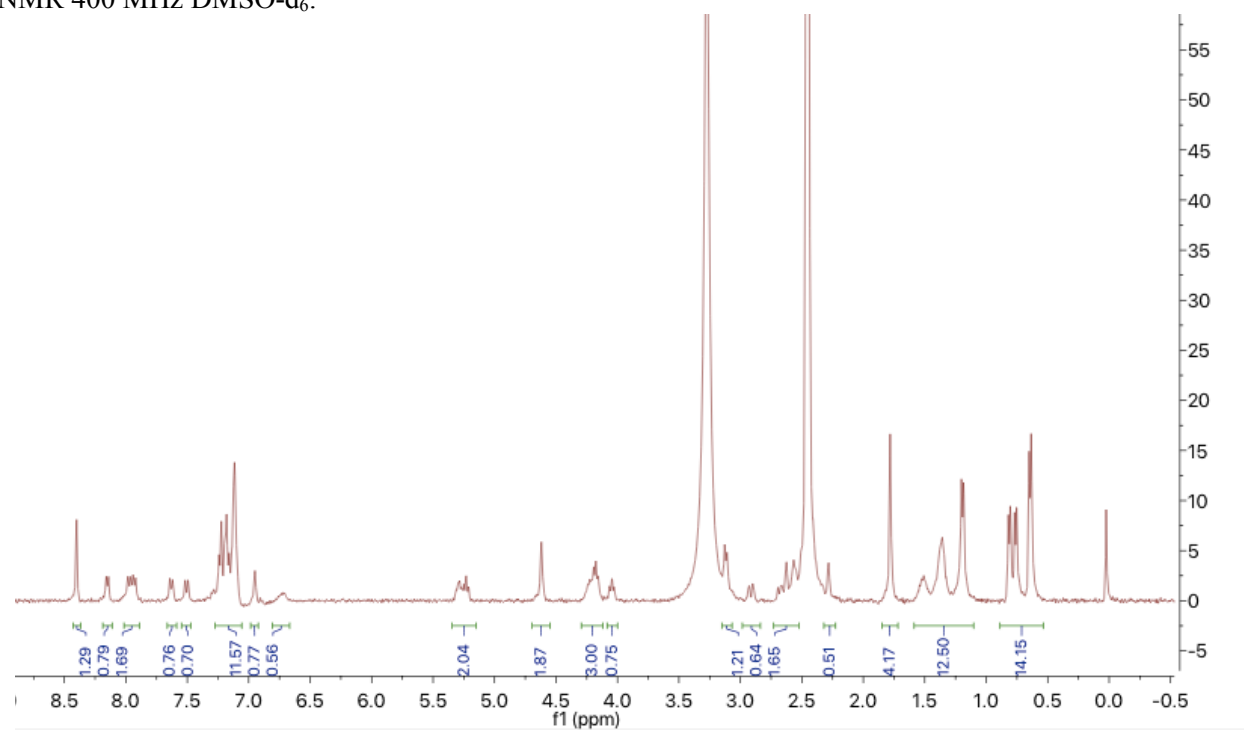
	α	β	others
Lys	5.19	1.40	γ 1.23, δ 1.71, ϵ 1.54
Leu	4.94	1.70	γ 1.32, δ 0.77, 0.84
Val	3.98	1.86	γ 0.65
Phe ^{4/5}	4.44	2.97, 2.90, 2.79, 2.69	
Ala	4.14	1.19	

Ac-Lys-Leu-aVal-Phe-Phe-Ala-NH₂ (6)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

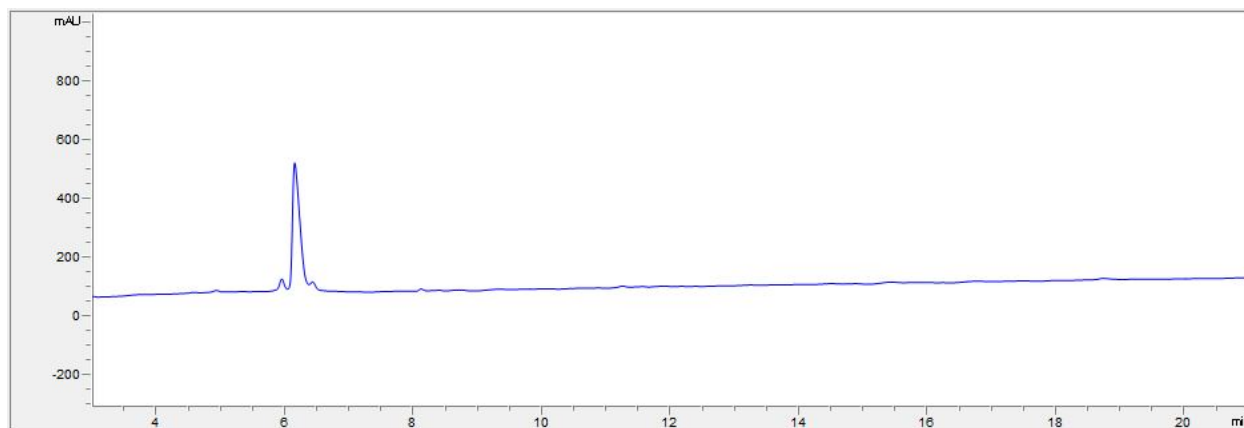
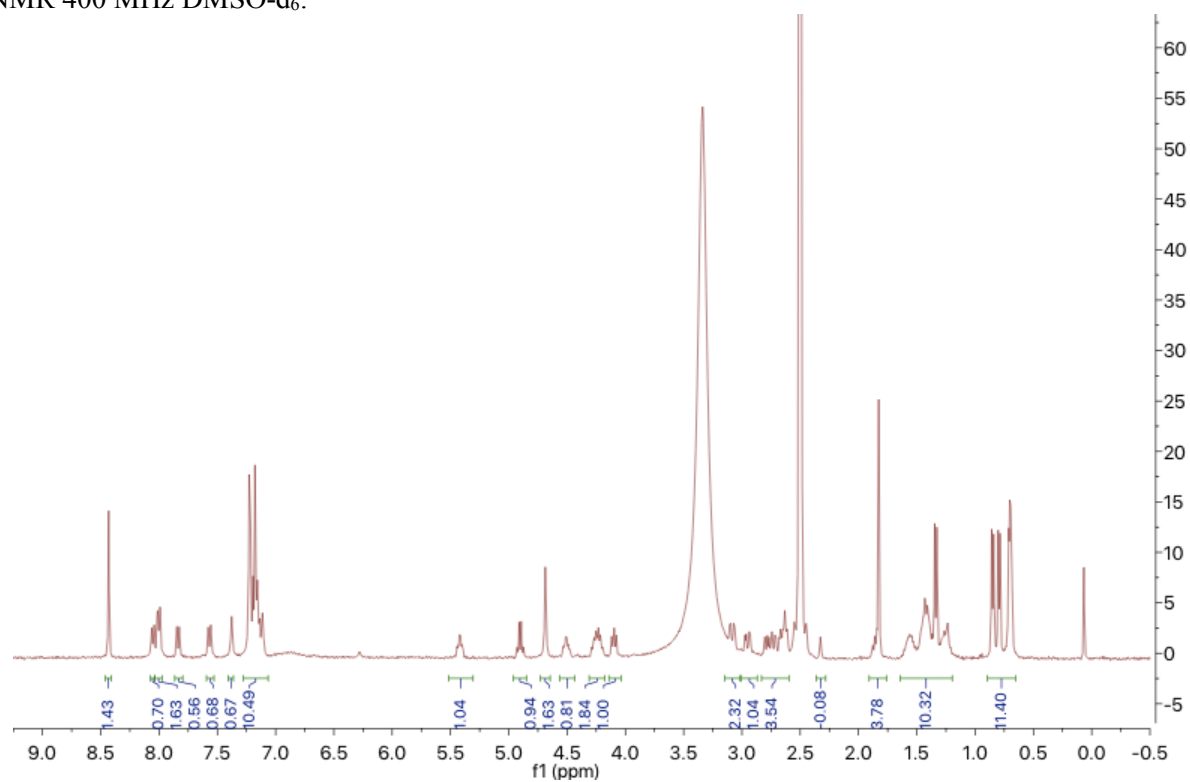
	α	β	others
Lys	4.19	1.40	γ 1.20, δ 1.53, ϵ 2.59
Leu	5.13	1.49	γ 1.22, δ 0.77, 0.82
Val	4.47	2.09	γ 0.62
Phe ⁴	4.48	2.75, 2.98	
Phe ⁵	4.41	2.60, 2.82	
Ala	4.11	1.15	

Ac-Lys-Leu-Val-aPhe-Phe-Ala-NH₂ (7)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

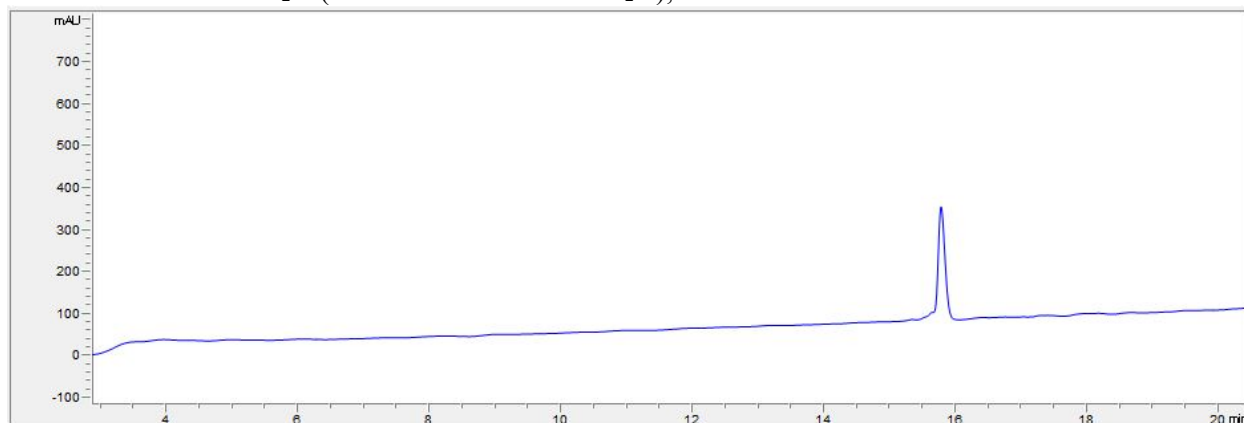
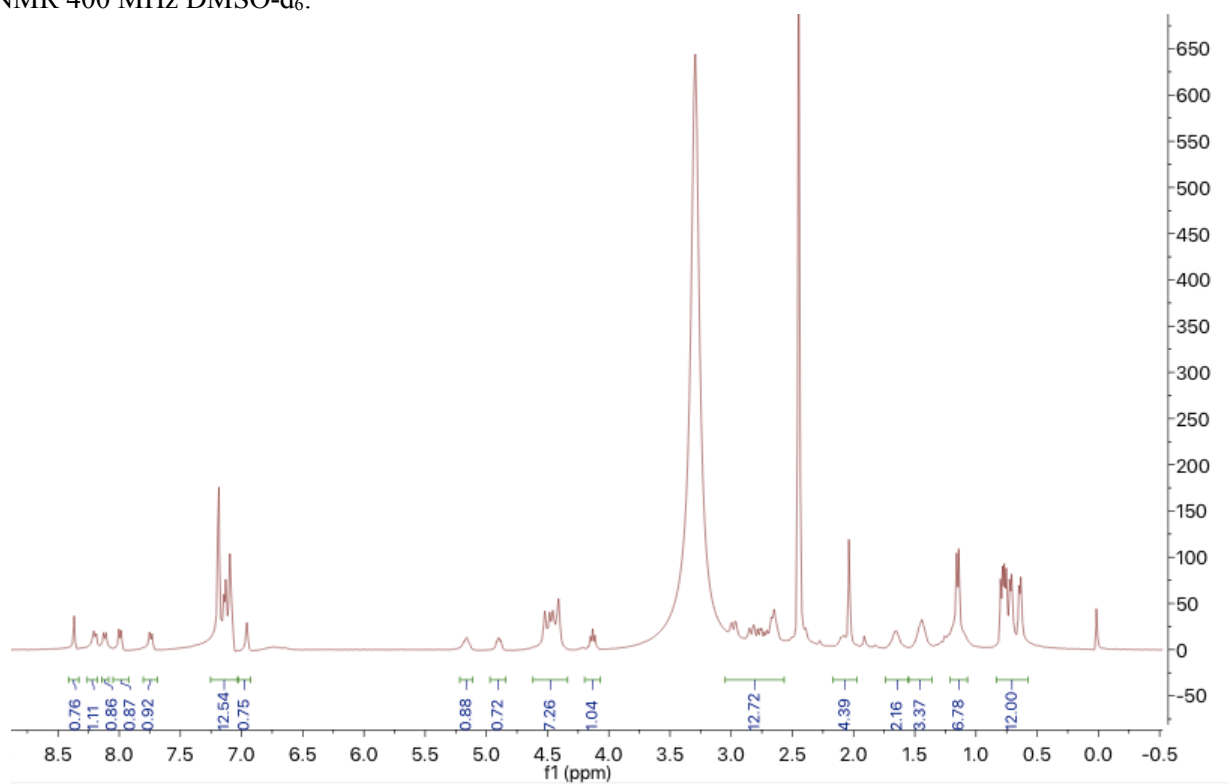
	α	β	others
Lys	4.19	1.42	γ 1.33, δ 1.55, ϵ 2.64
Leu	4.16	1.55	γ 1.32, δ 0.78, 0.81
Val	5.01	1.89	γ 0.62
Phe ⁴	5.22	3.05, 2.82	
Phe ⁵	4.47	3.02, 2.98	
Ala	4.13	1.17	

Ac-Lys-Leu-Val-Phe-aPhe-Ala-NH₂ (8)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

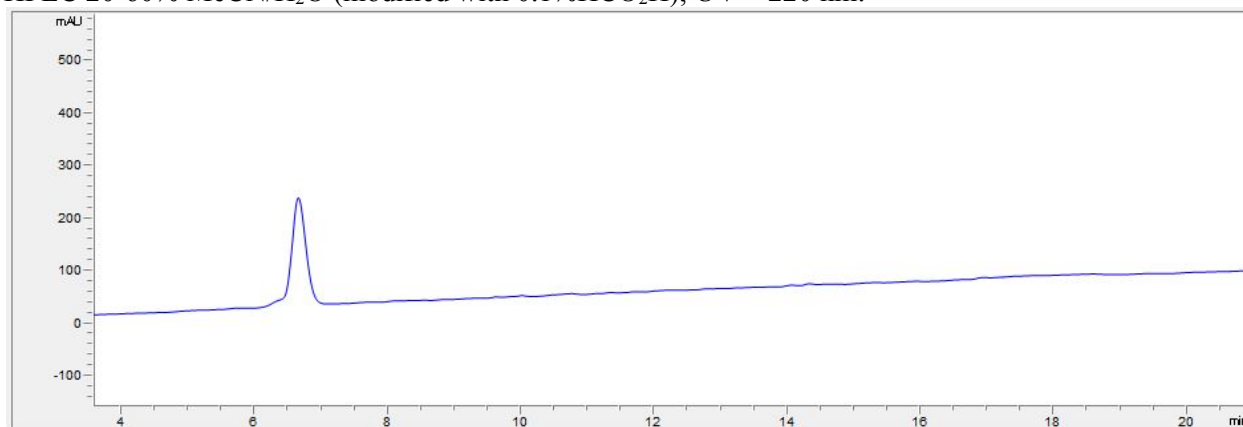
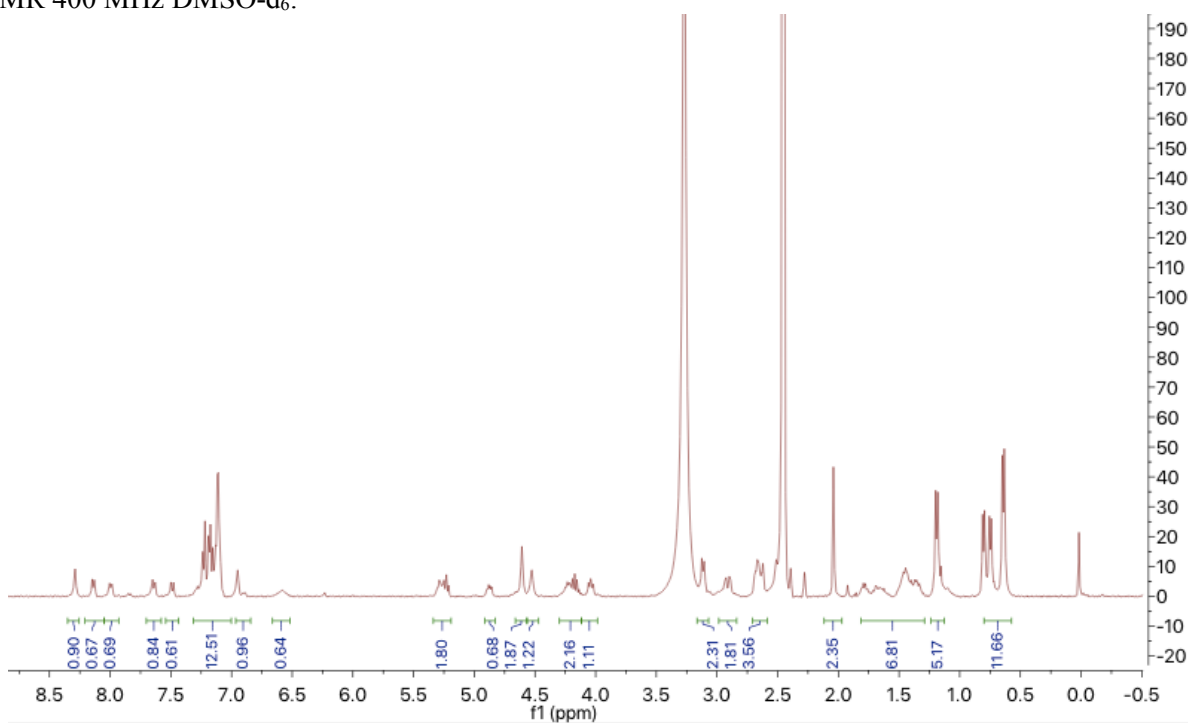
	α	β	others
Lys	4.20	1.35	γ 1.2, δ 1.50, ϵ 2.58
Leu	4.22	1.39	γ 1.37, δ 0.77, 0.80
Val	4.03	1.79	γ 0.63, 0.64
Phe ⁴	5.27	2.66, 2.89	
Phe ⁵	5.22	3.11	
Ala	4.16	1.19	

Ac-Lys-Leu-Val-Phe-Phe-aAla-NH₂ (9)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

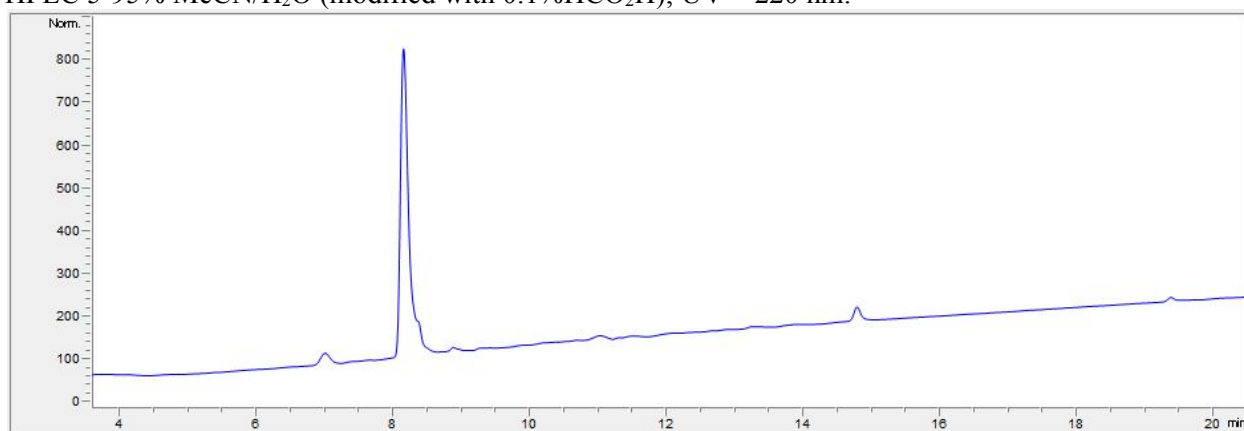
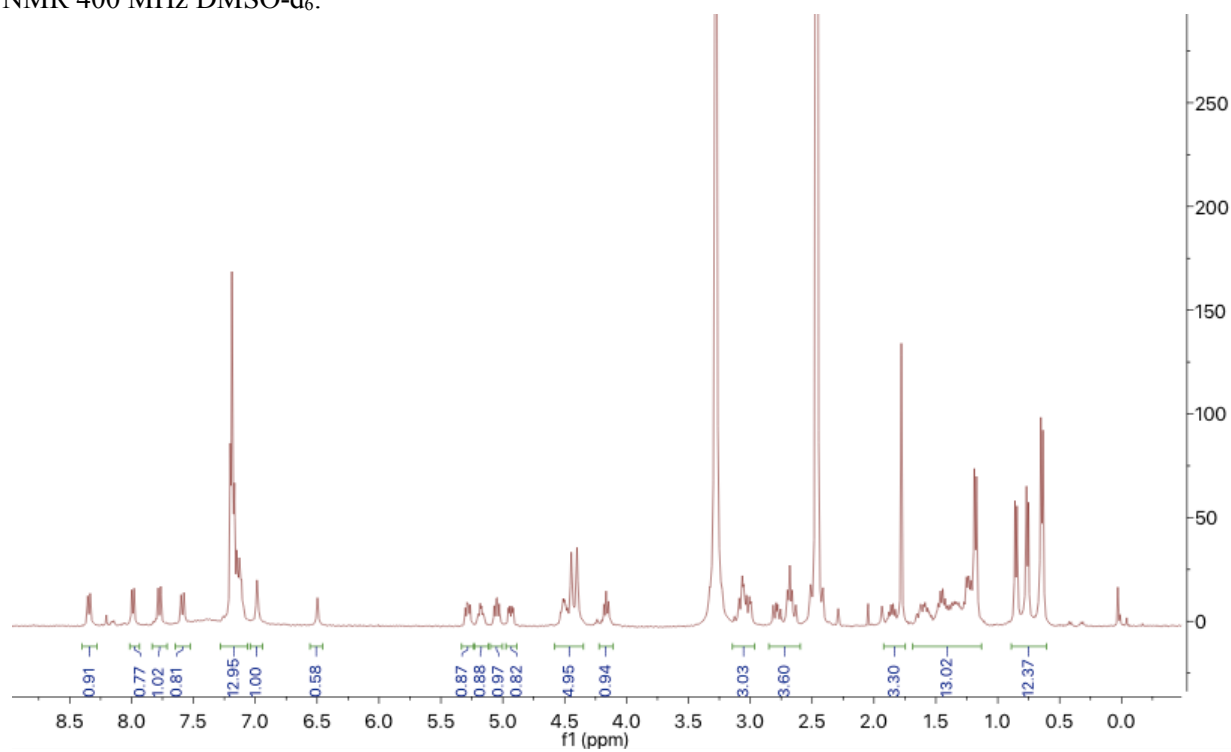
	α	β	others
Lys	4.18	1.40	γ 1.20, δ 1.53, ϵ 2.60
Leu	4.22	1.38	γ 1.81, δ 0.82, 0.75
Val	4.07	1.81	γ 0.66
Phe ⁴	4.46	2.67, 2.92	
Phe ⁵	5.38	2.74, 3.03	
Ala	4.86	1.30	

Ac-aLys-Leu-aVal-Phe-Phe-Ala-NH₂ (10)RP-HPLC 5-40% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

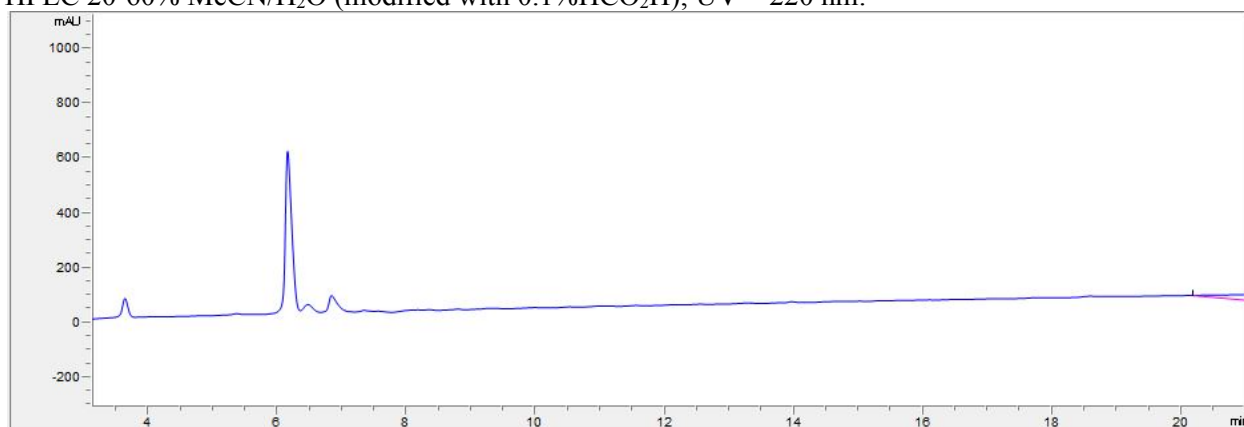
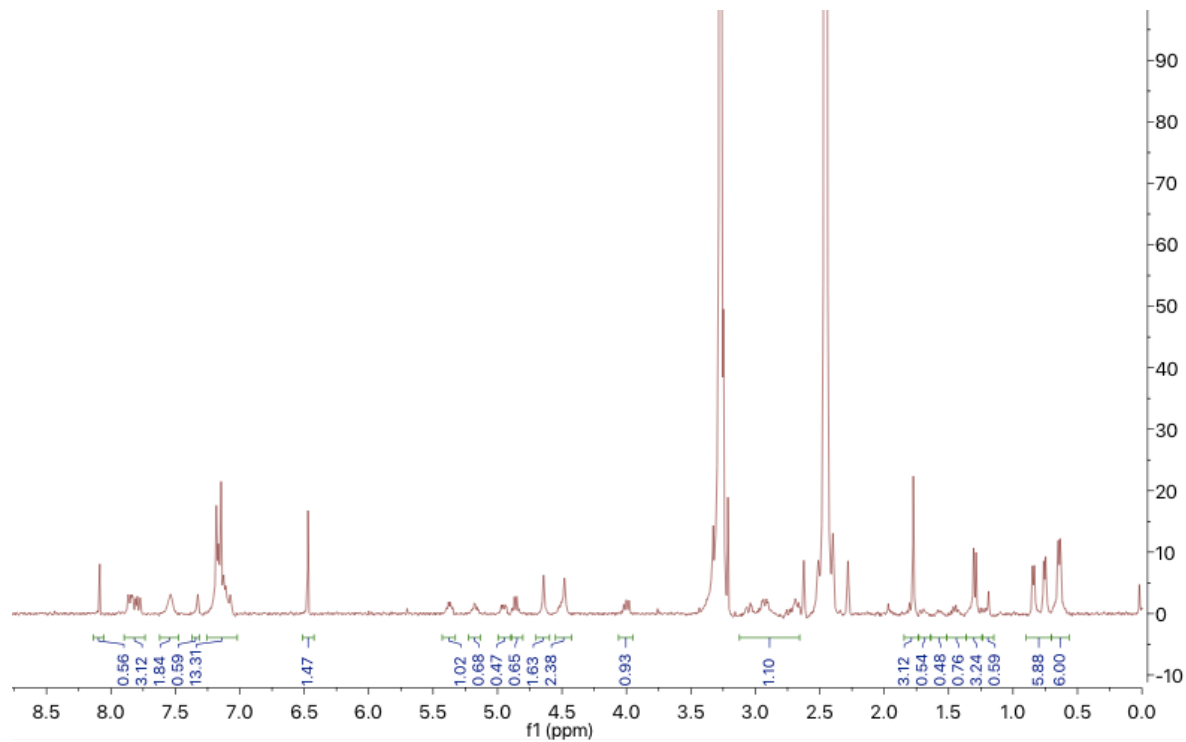
	α	β	others
Lys	4.91	1.67	γ 1.42, δ 1.12, ϵ 2.63
Leu	5.18	1.27	γ 1.21, δ 0.78, 0.81
Val	4.48	1.12	γ 0.66
Phe ^{4/5}	4.44, 4.49	2.70, 2.84, 2.76, 2.98	
Ala	4.16	1.16	

Ac-aLys-Leu-Val-Phe-aPhe-Ala-NH₂ (11)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

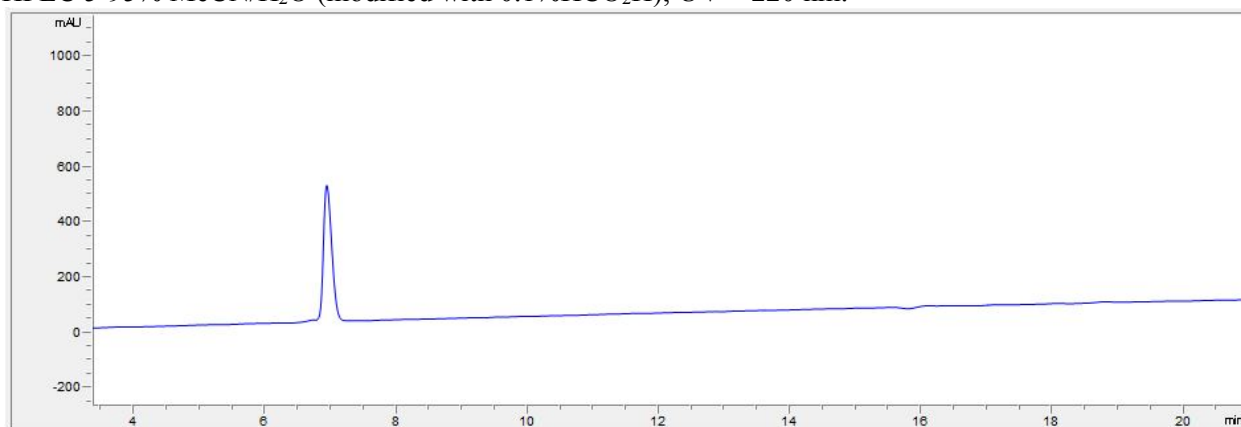
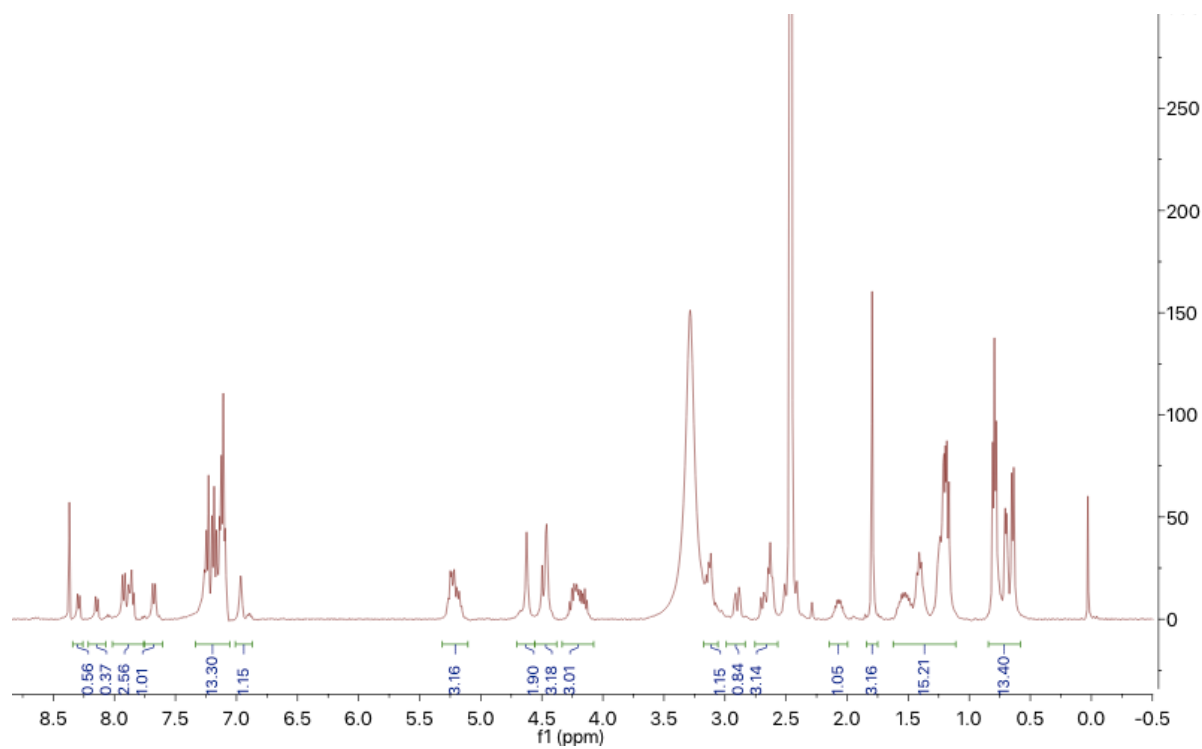
	α	β	others
Lys	4.89	1.37	γ 1.14, δ 1.65, ϵ 2.67
Leu	4.26	1.48	γ 1.21, δ 0.77, 0.83
Val	4.08	1.81	γ 0.65
Phe ⁴	5.30	2.64, 2.94	
Phe ⁵	5.24	2.74, 3.13	
Ala	4.18	1.20	

Ac-Lys-aLeu-Val-aPhe-Phe-Ala-NH₂ (12)RP-HPLC 5-95% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

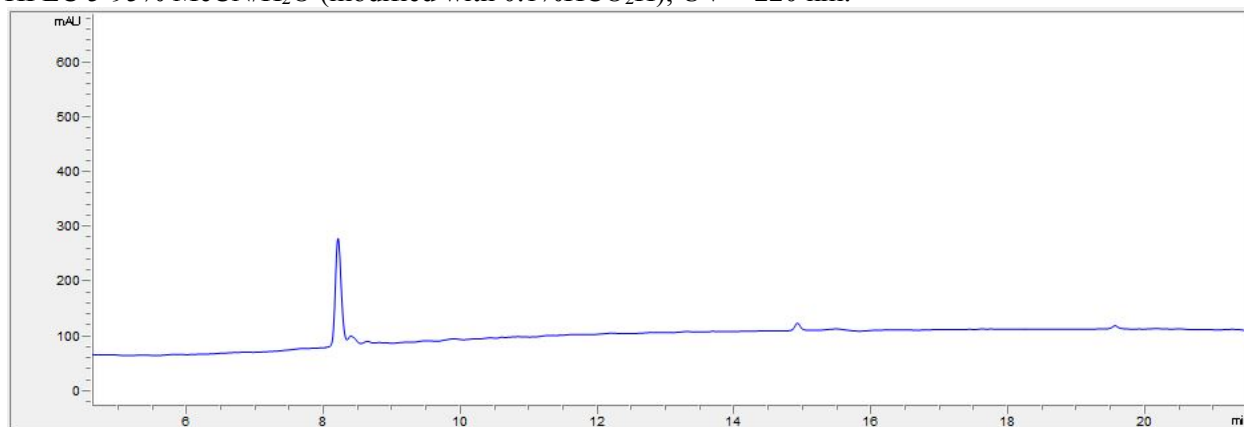
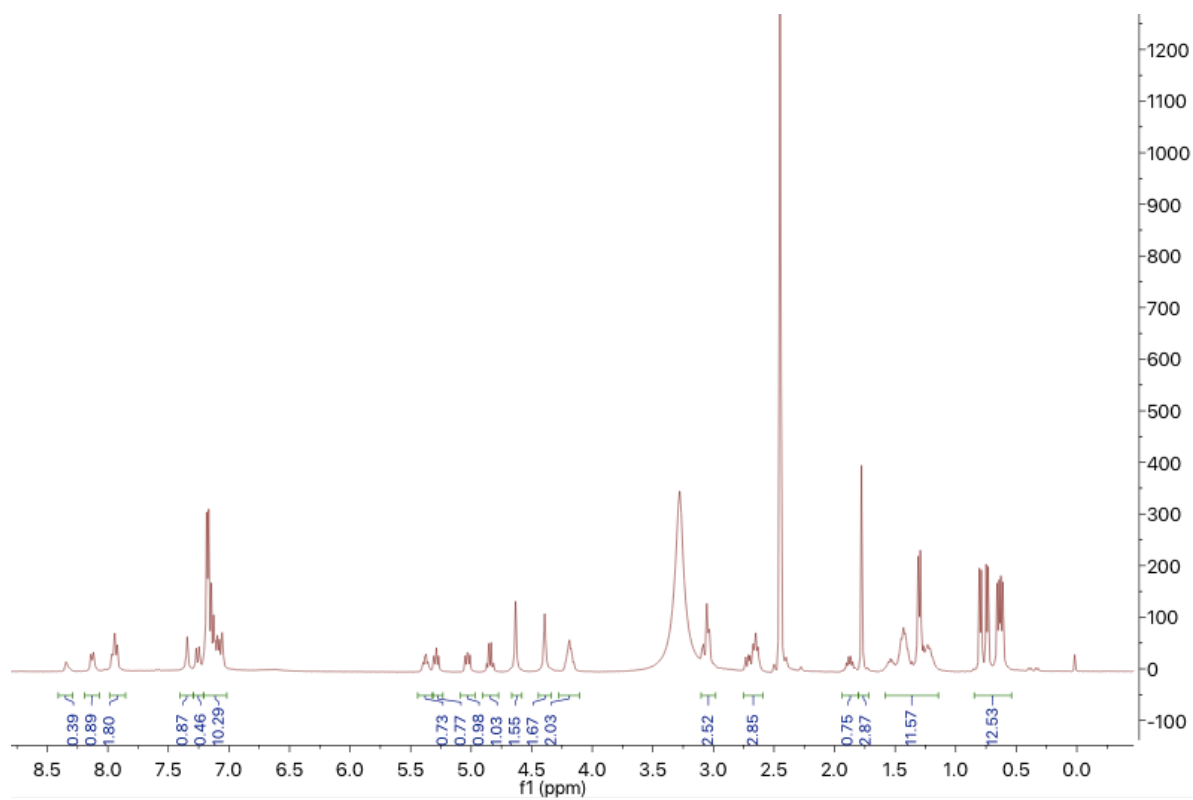
	α	β	others
Lys	5.17	1.53	γ 1.25, δ 1.37, ϵ 2.67
Leu	4.94	1.63	γ 1.23, δ 0.86, 0.76
Val	5.03	1.86	γ 0.64
Phe ⁴	4.50	2.83, 3.02	
Phe ⁵	5.28	2.79, 3.10	
Ala	4.16	1.78	

Ac-Lys-aLeu-Val-Phe-Phe-aAla-NH₂ (13)RP-HPLC 20-60% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

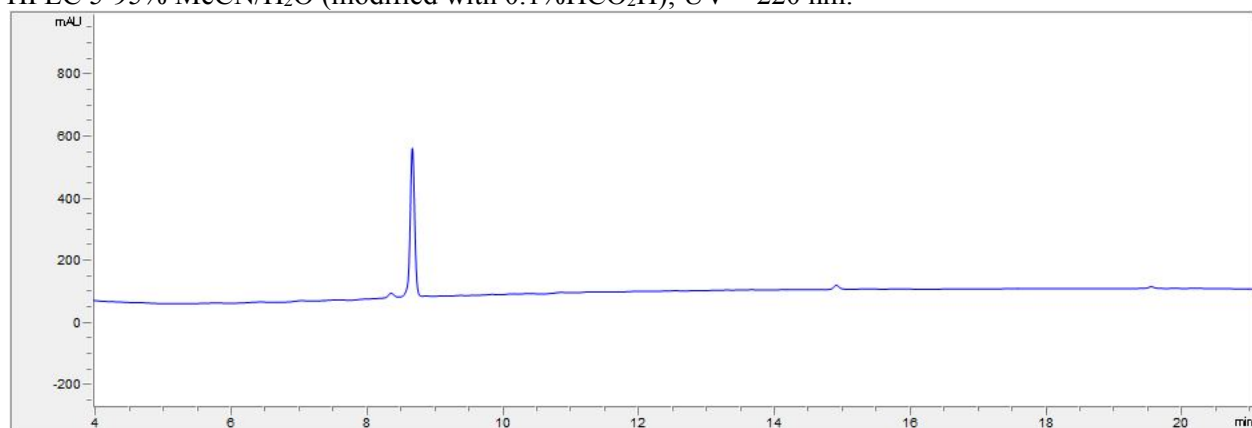
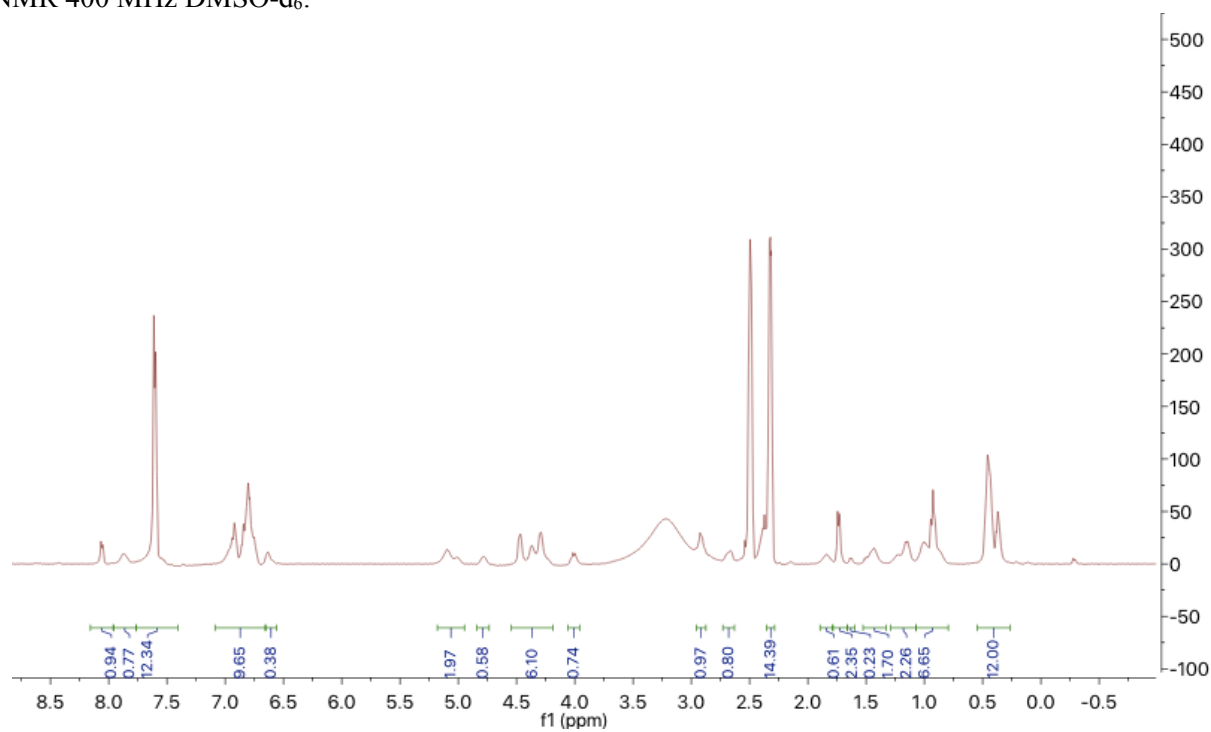
	α	β	others
Lys	4.92	1.34	γ 1.20, δ 1.71, ϵ 2.64
Leu	5.17	1.52	γ 1.39, δ 0.73, 0.83
Val	4.01	1.83	γ 0.69
Phe ⁴	4.51	2.69, 2.96	
Phe ⁵	5.38	2.78, 3.05	
Ala	4.90	1.32	

Ac-Lys-Leu-aVal-Phe-aPhe-Ala-NH₂ (14)RP-HPLC 5-95% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆

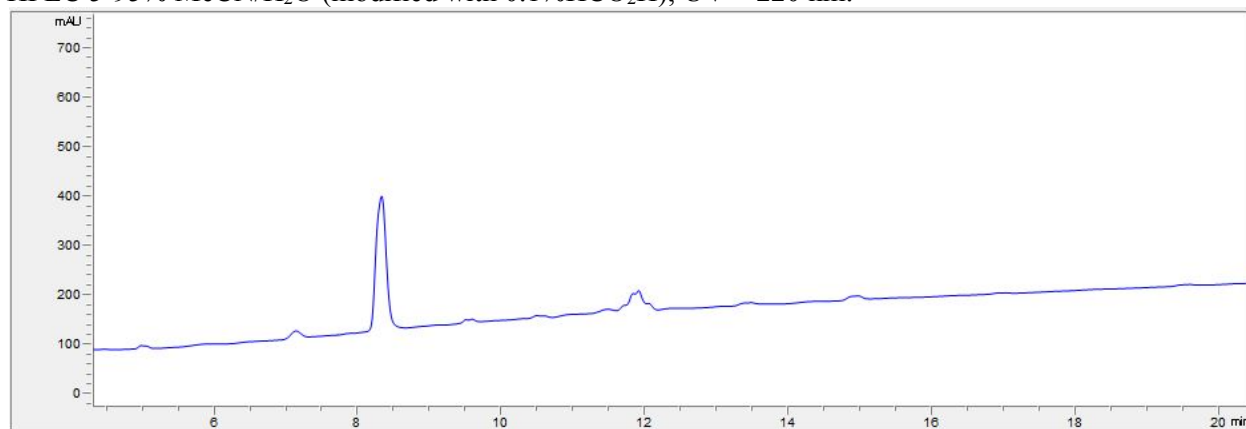
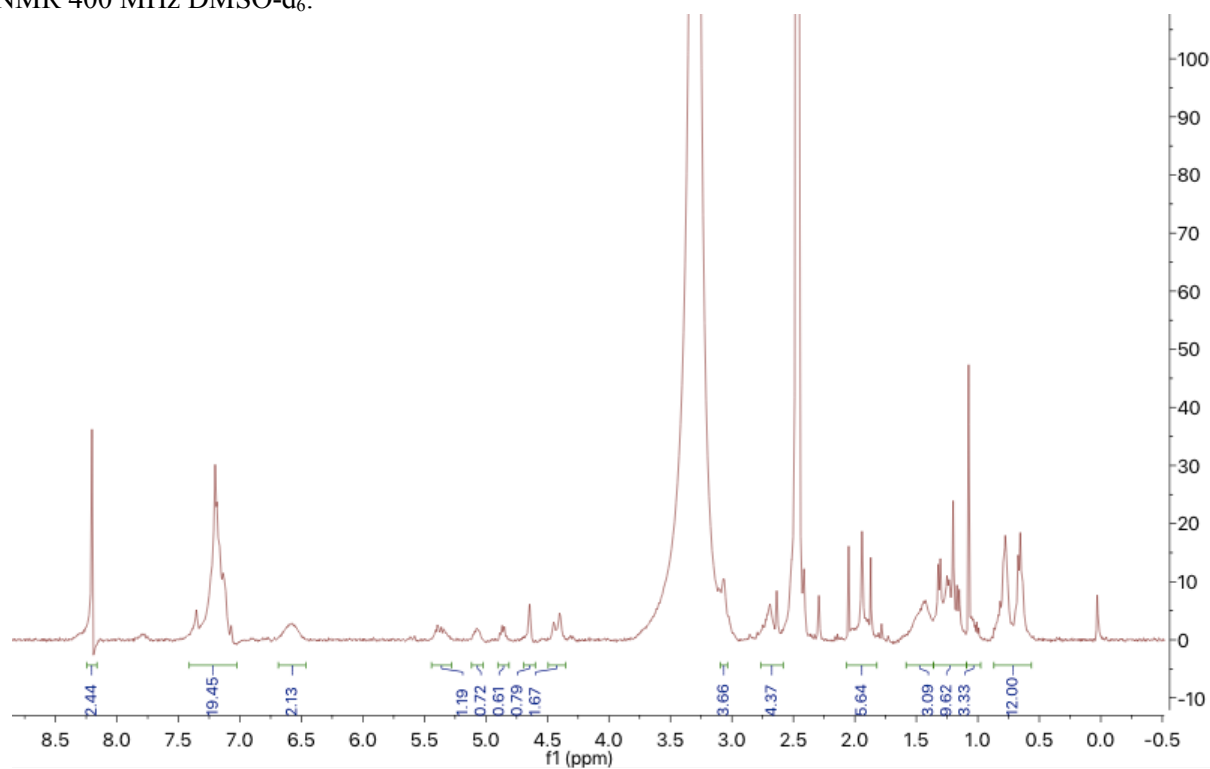
	α	β	others
Lys	4.22	1.54	γ 1.20, δ 1.41, ϵ 2.63
Leu	5.18	1.50	γ 1.24, δ 0.79
Val	4.48	2.07	γ 0.64, 0.69
Phe ⁴	5.24	3.10, 2.69	
Phe ⁵	5.22	3.14, 2.90	
Ala	4.14	1.17	

Ac-Lys-Leu-Val-aPhe-Phe-aAla-NH₂ (15)RP-HPLC 5-95% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

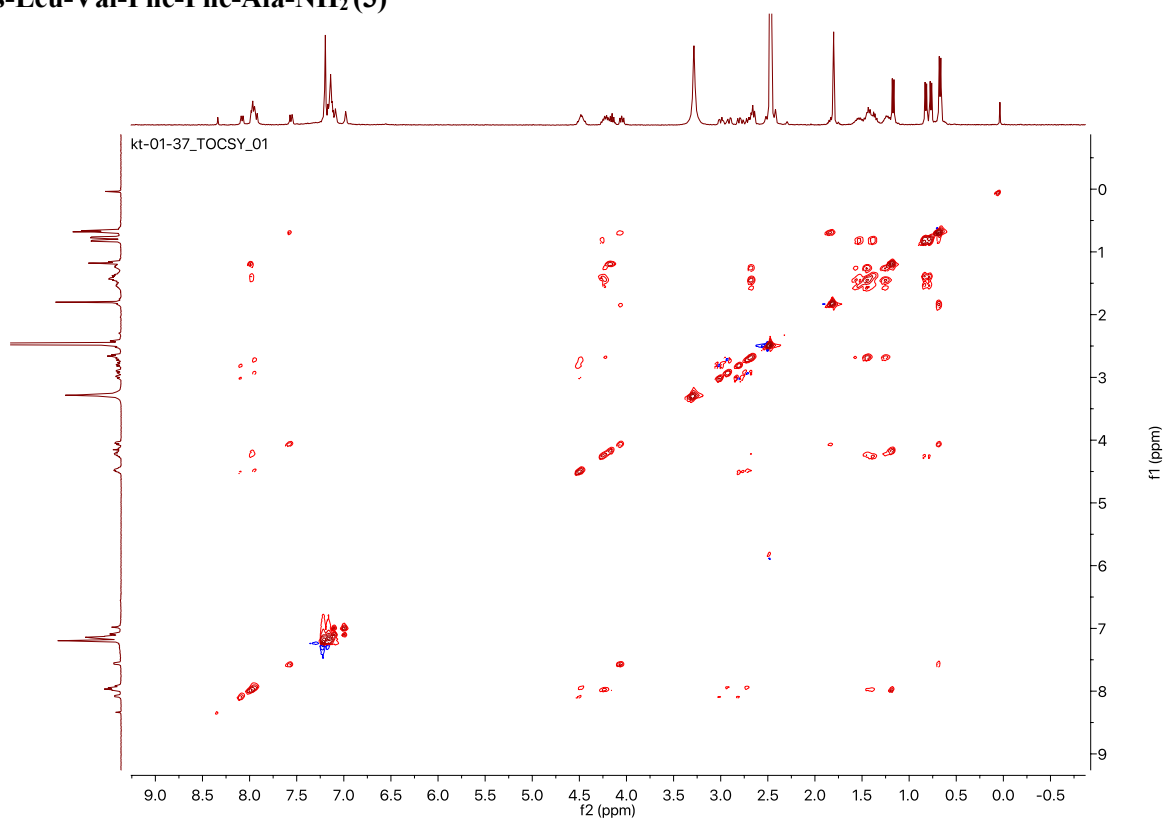
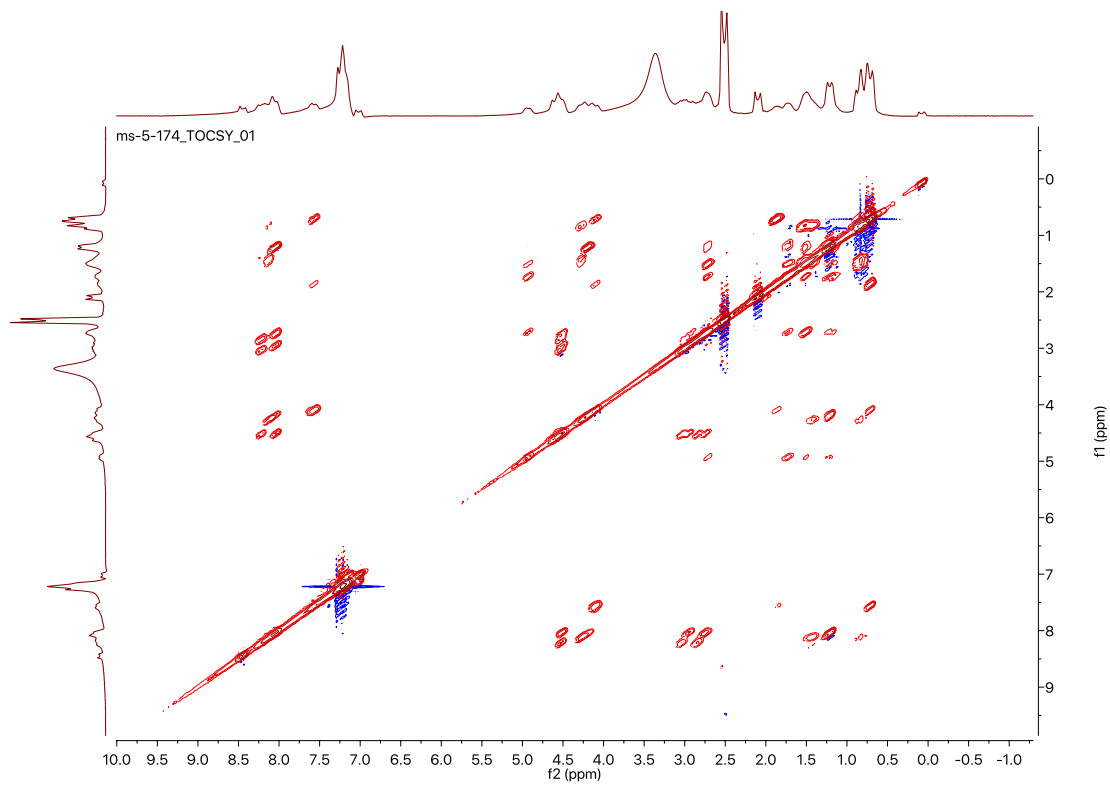
	α	β	others
Lys	4.18	1.52	γ 1.20, δ 1.42, ϵ 2.65
Leu	4.17	1.41	γ 1.29, δ 0.73, 0.78
Val	5.02	1.86	γ 0.62
Phe ⁴	5.28	3.02, 2.62	
Phe ⁵	5.37	3.04, 2.69	
Ala	4.84	1.77	

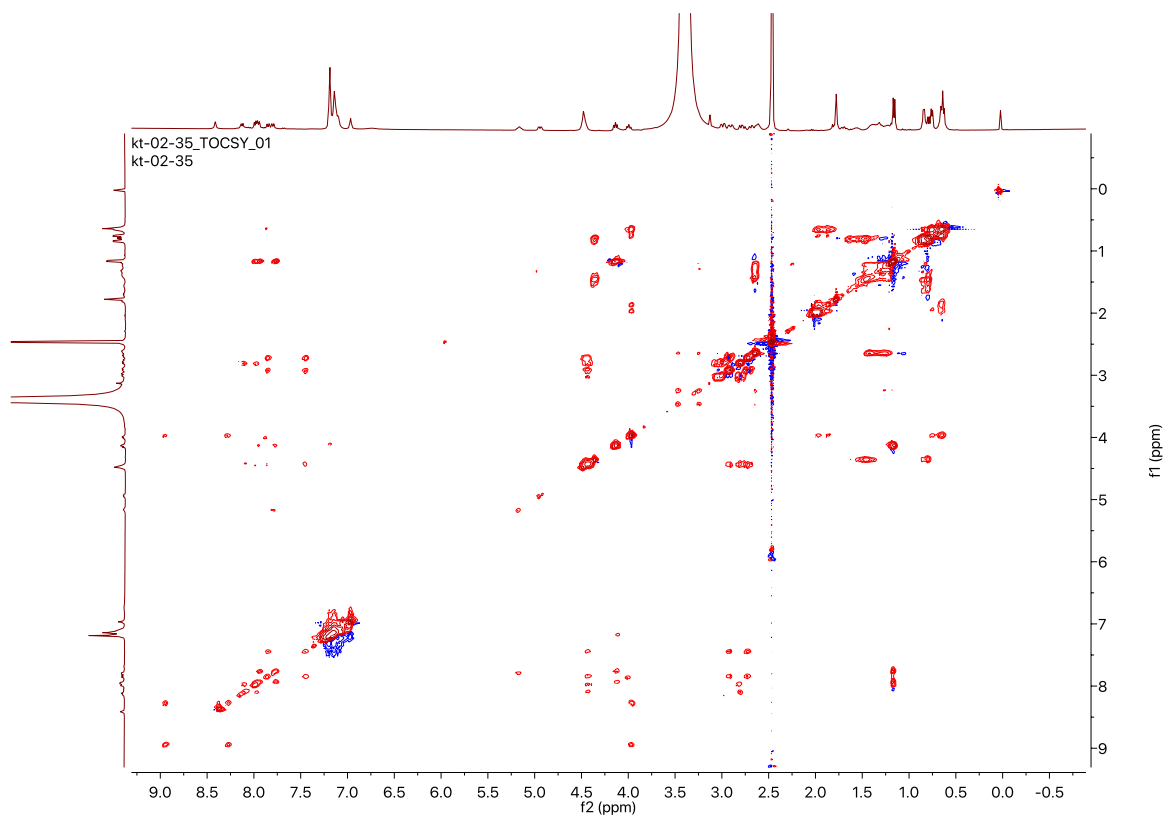
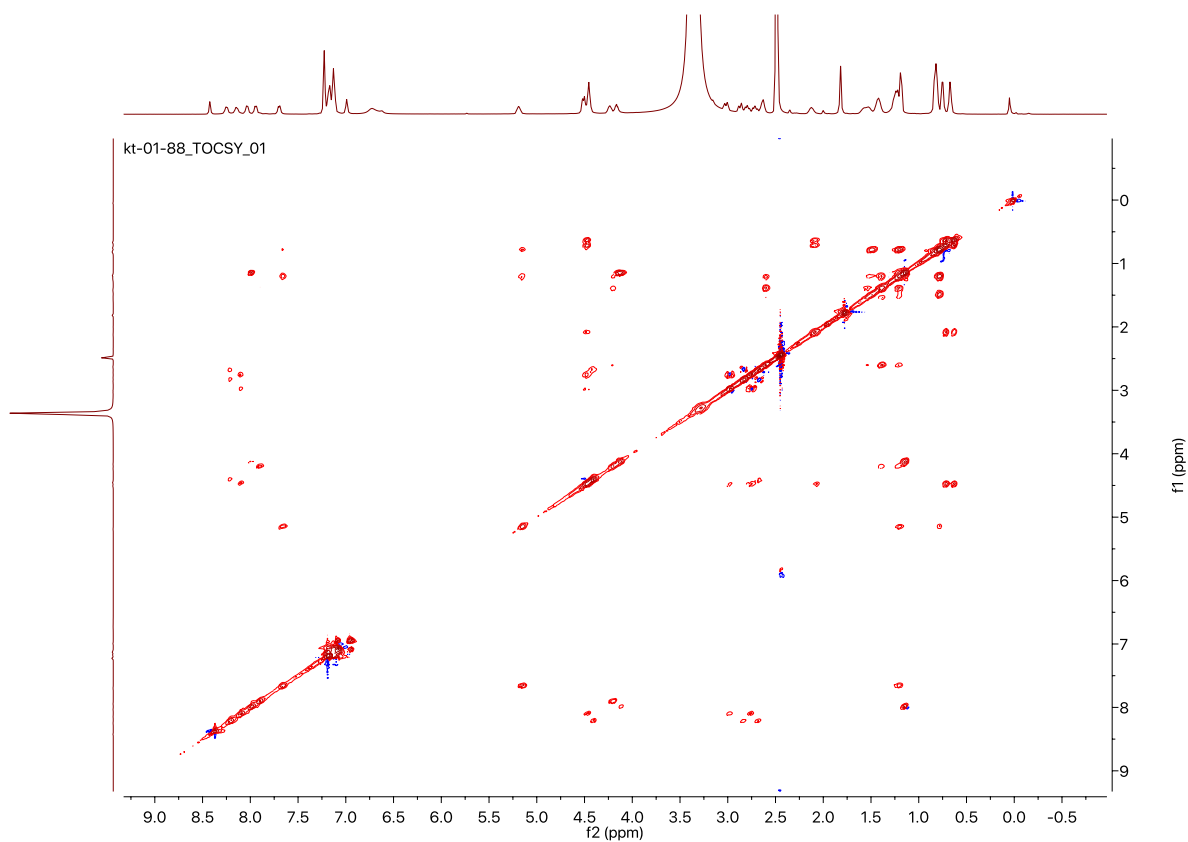
Ac-aLys-Leu-aVal-Phe-aPhe-Ala-NH₂ (16)RP-HPLC 5-95% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

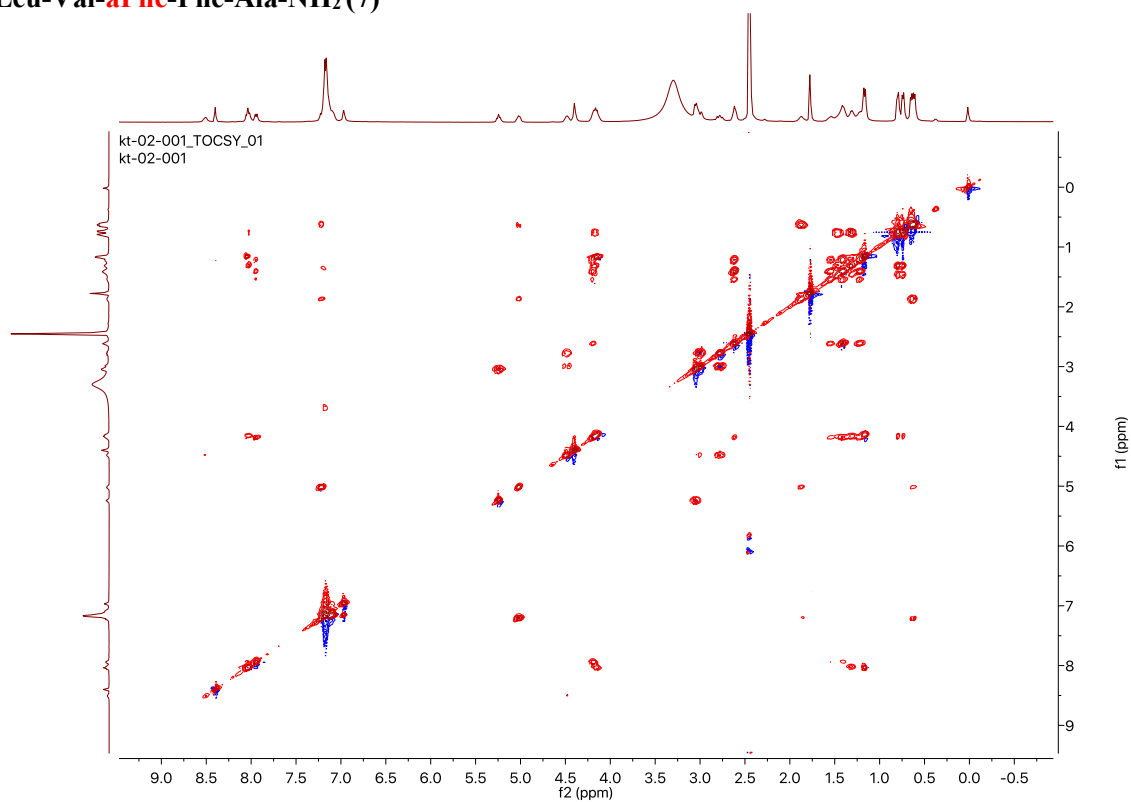
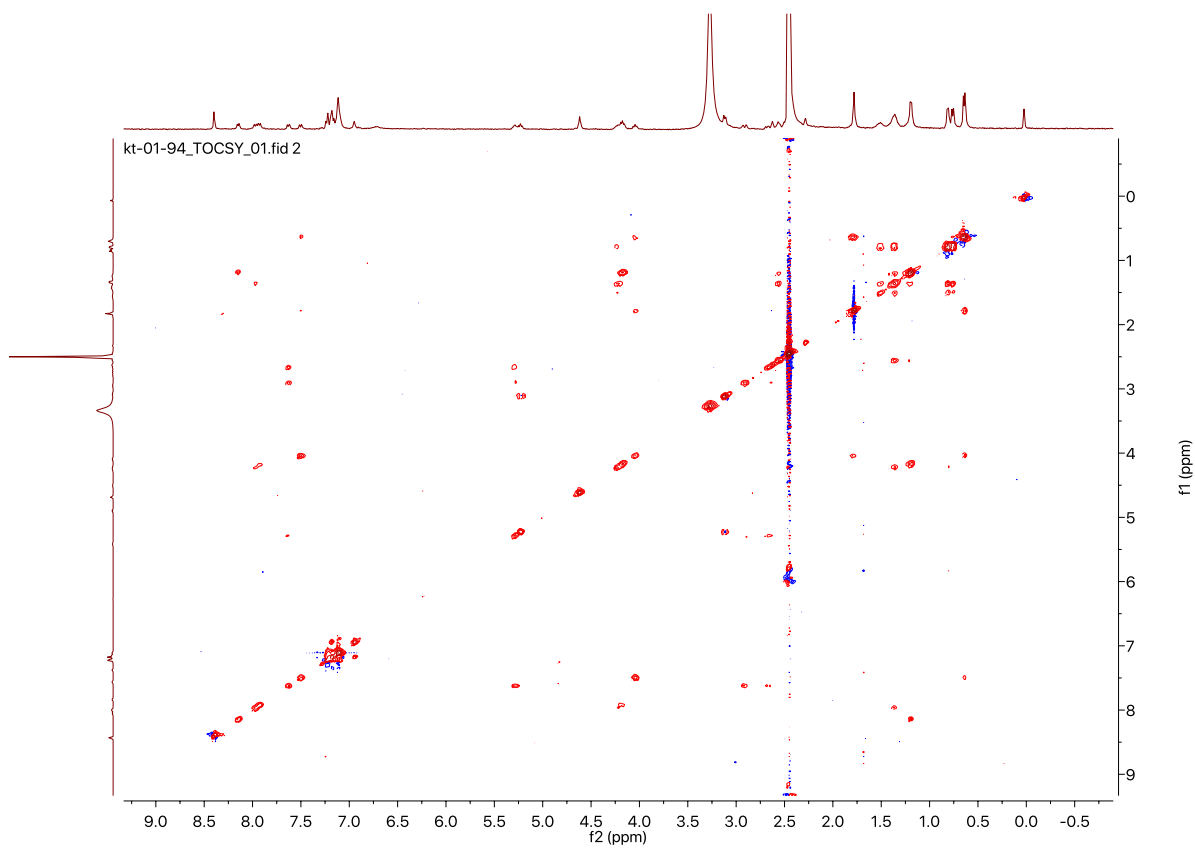
	α	β	others
Lys	4.70	1.37	γ 0.90, δ 1.10, ϵ 2.32
Leu	4.93	1.14	γ 0.99, δ 0.41
Val	4.21	1.86	γ 0.35
Phe ^{4/5}	5.01	2.86, 2.81	
	5.03	2.58, 2.31	
Ala	3.93	0.88	

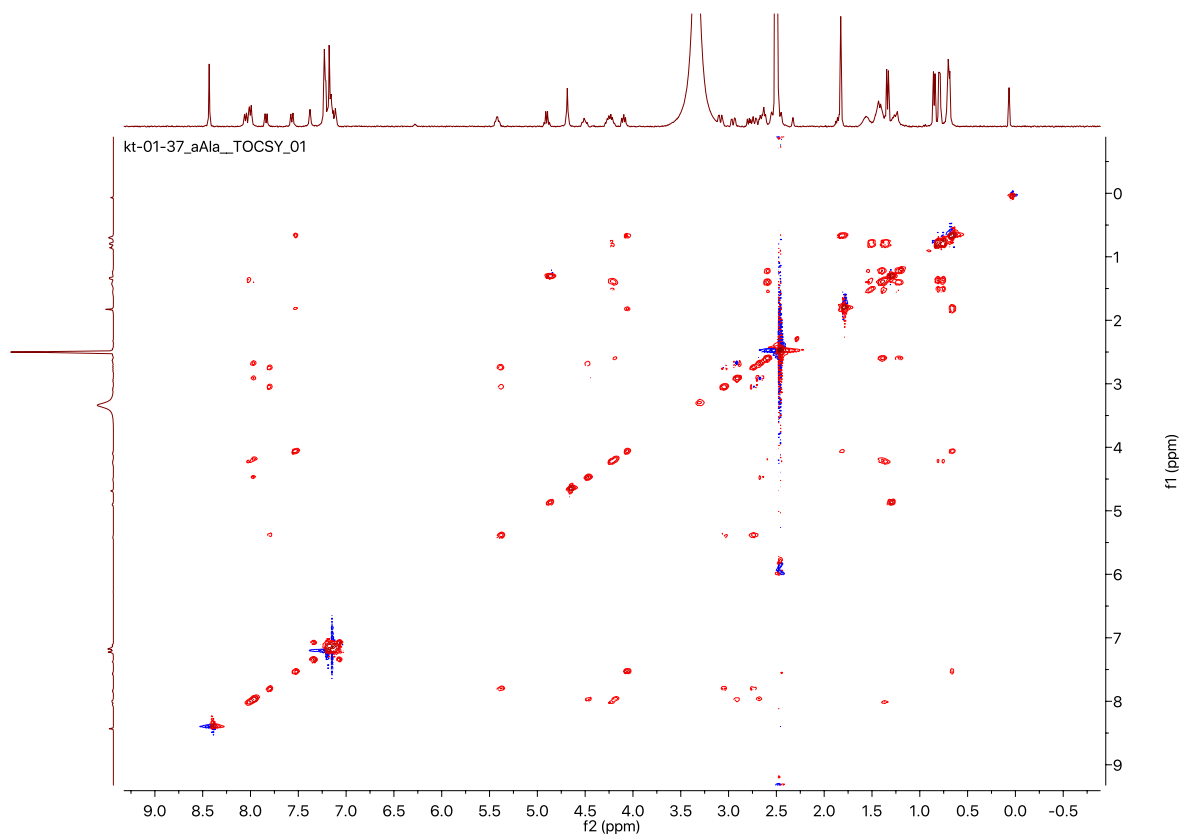
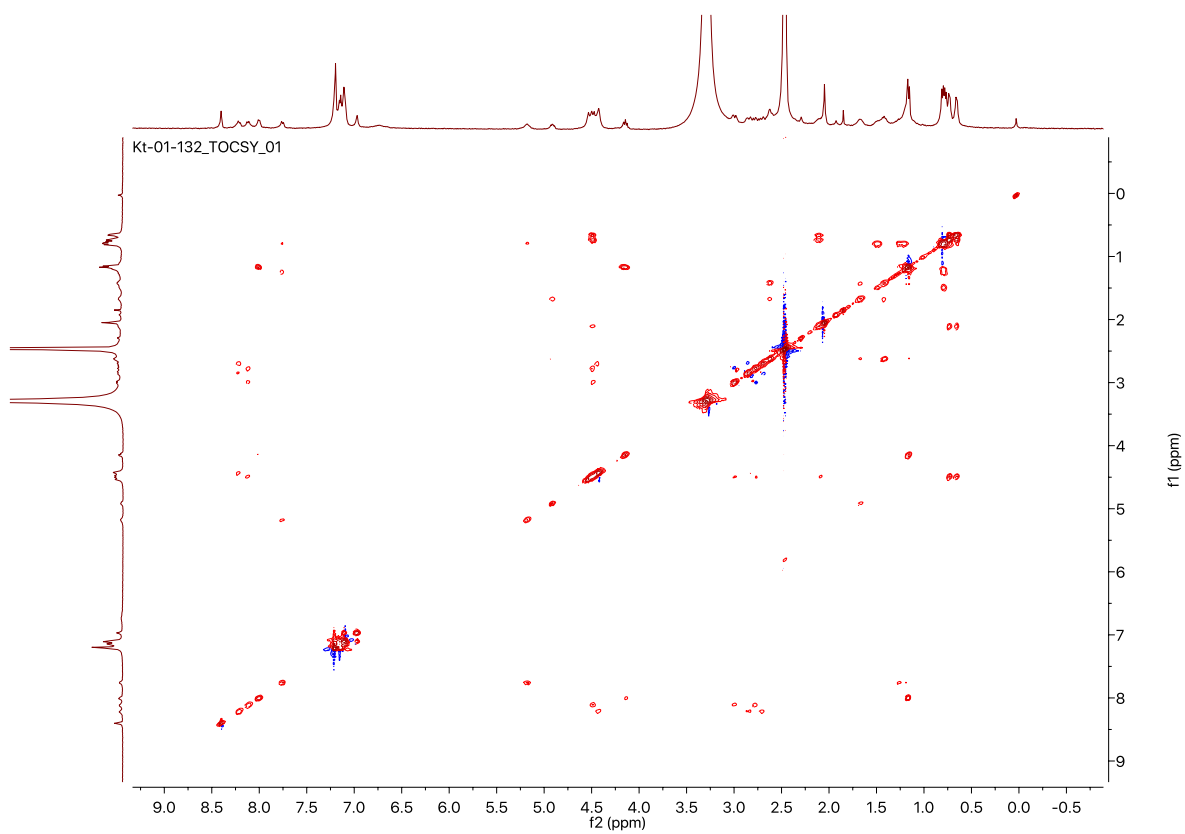
Ac-Lys-aLeu-Val-aPhe-Phe-aAla-NH₂ (17)RP-HPLC 5-95% MeCN/H₂O (modified with 0.1% HCO₂H); UV = 220 nm:¹H NMR 400 MHz DMSO-d₆:

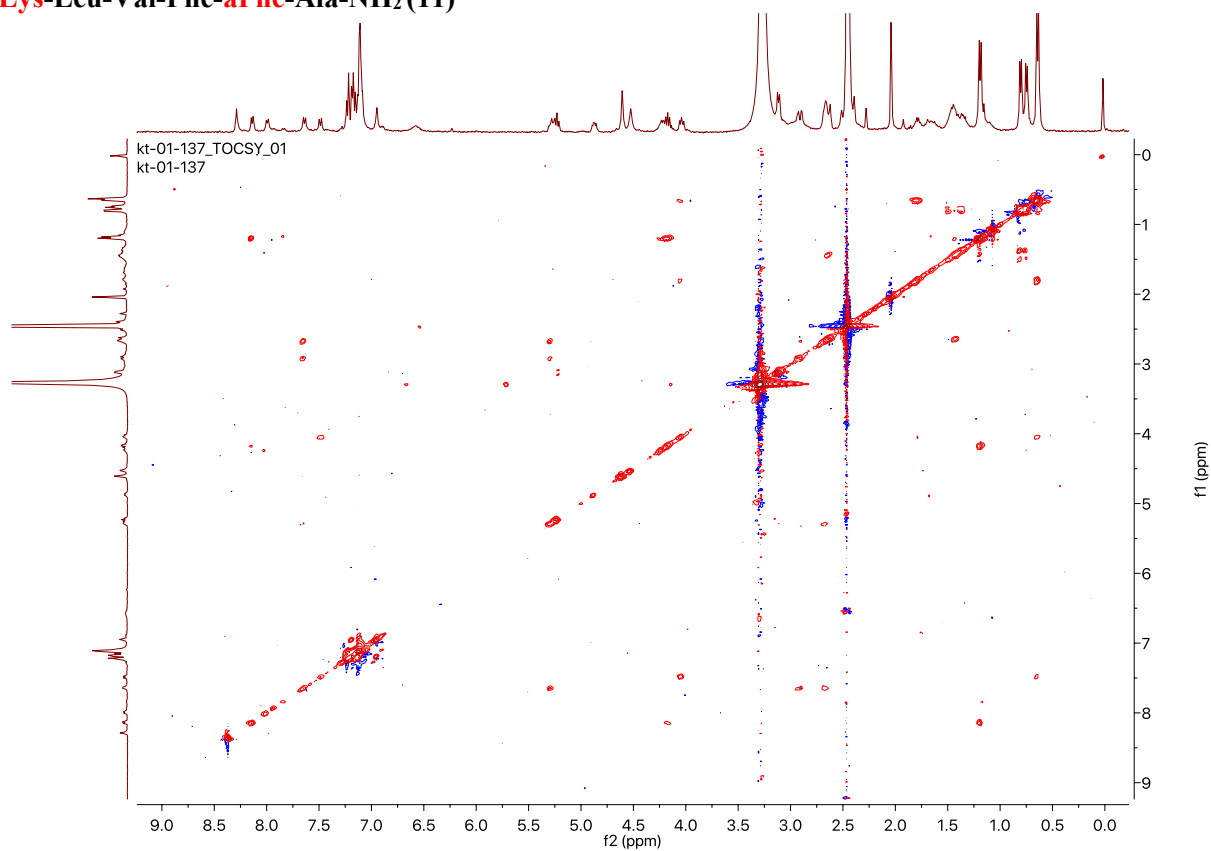
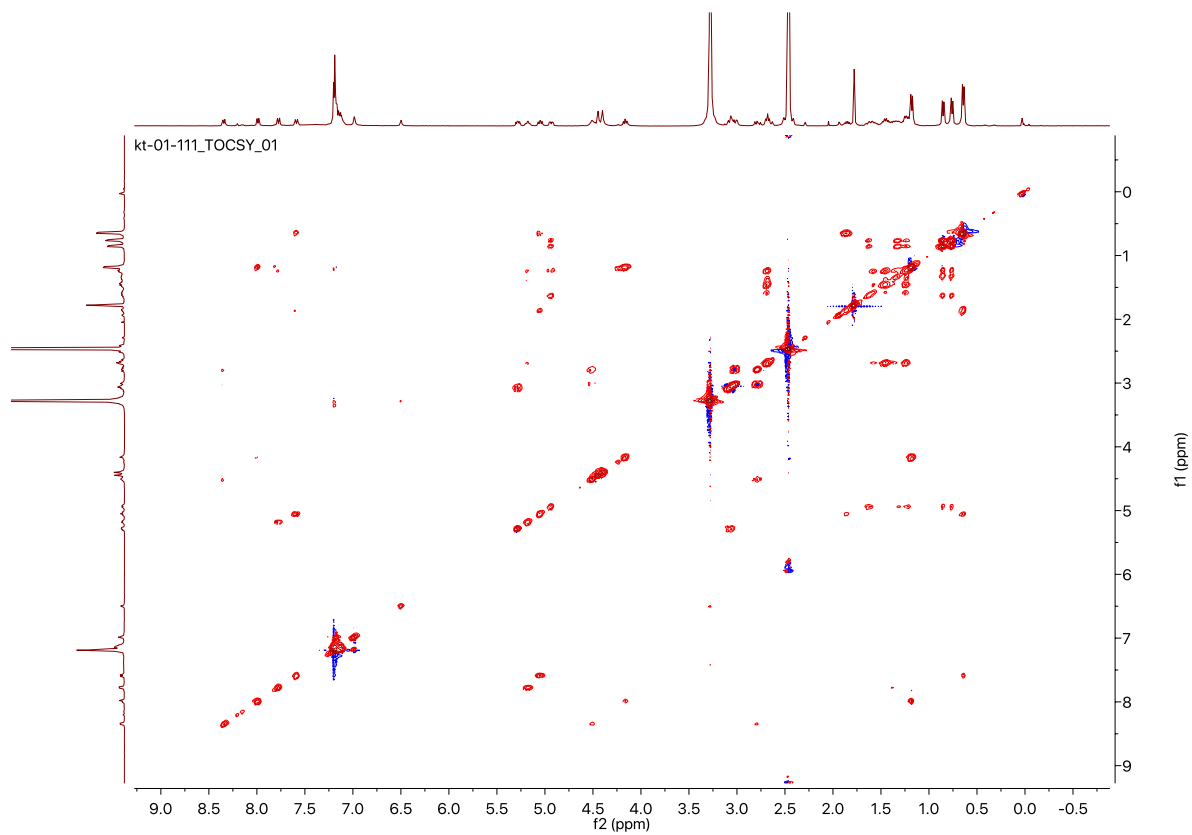
	α	β	others
Lys	5.17	1.52-1.11	ϵ 2.64
Leu	4.95	1.52-1.11	γ 0.76, 0.85
Val	5.04	2.23-1.72	γ 0.66
Phe(1)	5.34	3.08, 2.73	
Phe(2)	5.39	2.84, 2.67	
Ala	4.87	1.32	

TOCSY NMR Spectra for Synthesized Compounds (400 MHz, DMSO-d₆).**Ac-Lys-Leu-Val-Phe-Phe-Ala-NH₂ (3)****Ac-aLys-Leu-Val-Phe-Phe-Ala-NH₂ (4)**

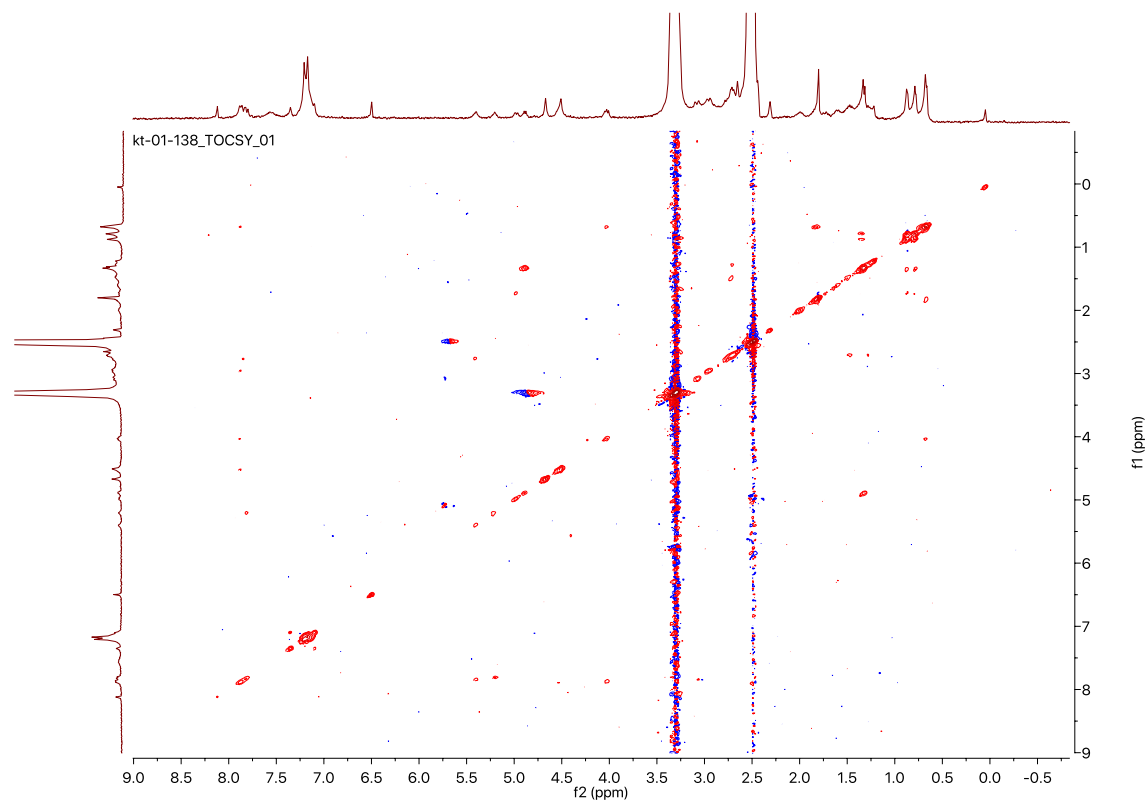
Ac-Lys-aLeu-Val-Phe-Phe-Ala-NH₂ (5)**Ac-Lys-Leu-aVal-Phe-Phe-Ala-NH₂ (6)**

Ac-Lys-Leu-Val-aPhe-Phe-Ala-NH₂ (7)**Ac-Lys-Leu-Val-Phe-aPhe-Ala-NH₂ (8)**

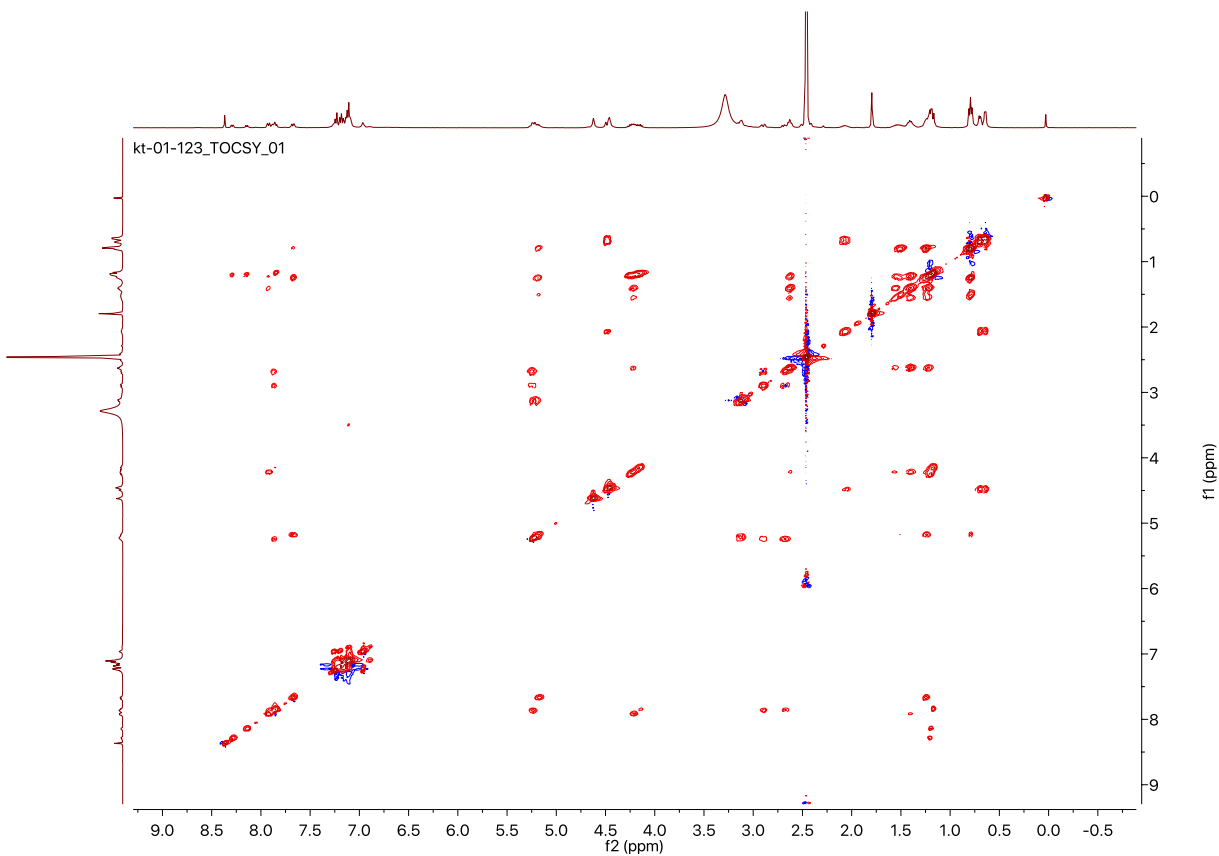
Ac-Lys-Leu-Val-Phe-Phe-aAla-NH₂ (9)**Ac-aLys-Leu-aVal-Phe-Phe-Ala-NH₂ (10)**

Ac-aLys-Leu-Val-Phe-aPhe-Ala-NH₂ (11)**Ac-Lys-aLeu-Val-aPhe-Phe-Ala-NH₂ (12)**

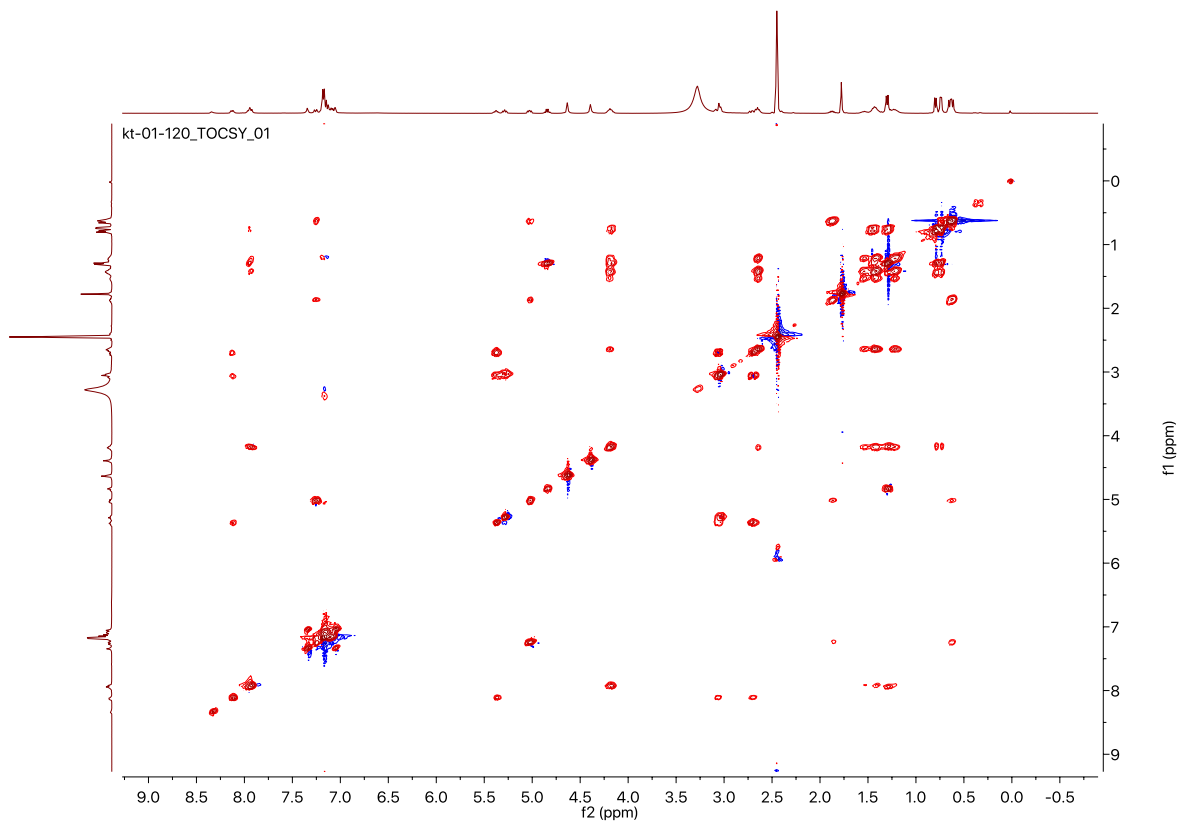
Ac-Lys-aLeu-Val-Phe-Phe-aAla-NH₂ (13)



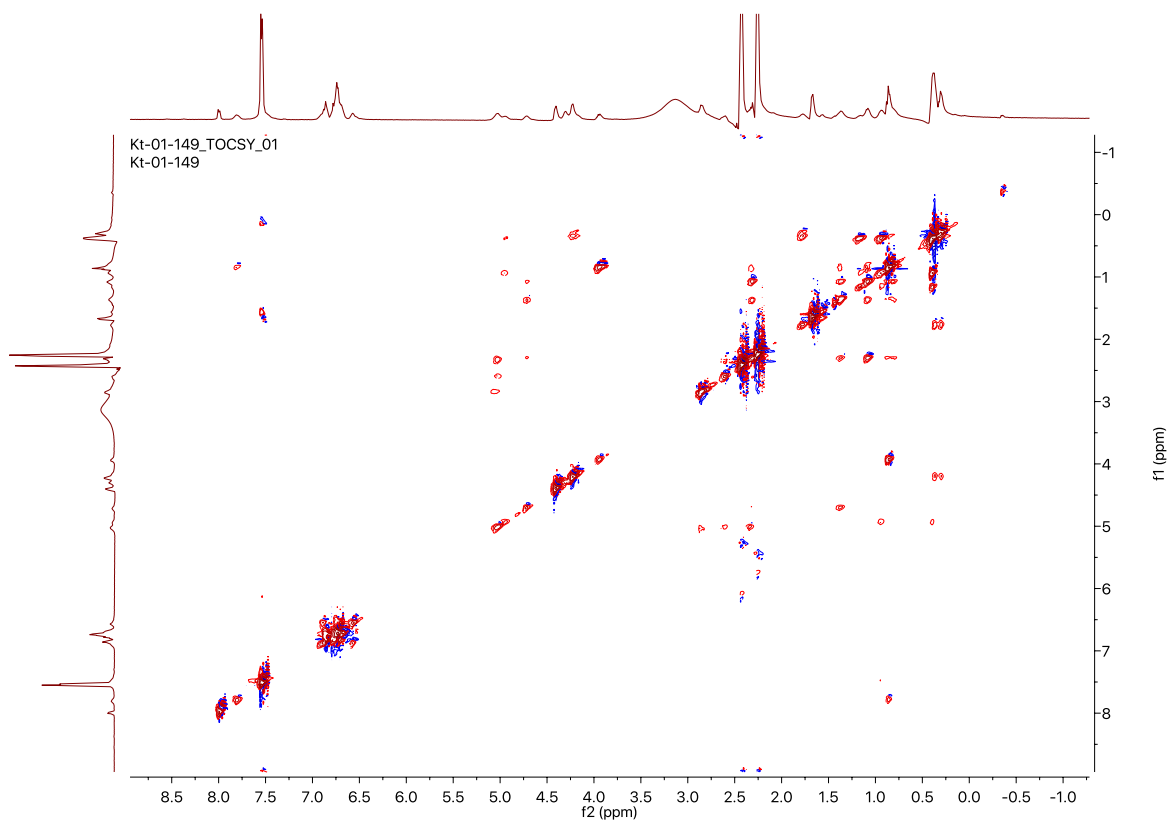
Ac-Lys-Leu-aVal-Phe-aPhe-Ala-NH₂ (14)



Ac-Lys-Leu-Val-aPhe-Phe-aAla-NH₂ (15)



Ac-aLys-Leu-aVal-Phe-aPhe-Ala-NH₂ (16)



Ac-Lys-**aLeu**-Val-**aPhe**-Phe-**aAla**-NH₂ (17)

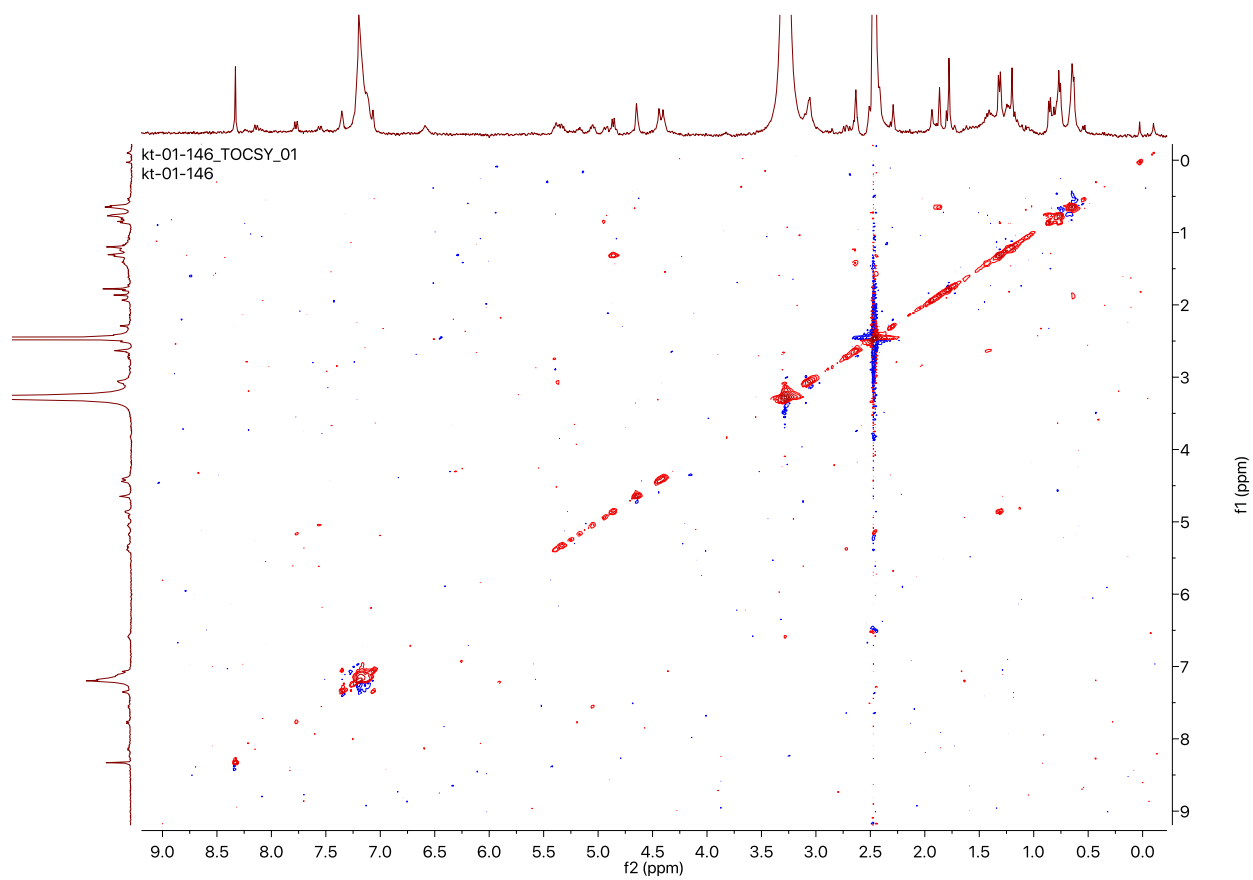


Table S1. Yields and HRMS (ESI-TOF) data for synthesized compounds.

peptide	sequence	isolated yield (%)	HRMS [M+H] ⁺ _{calc}	HRMS [M+H] ⁺ _{obs}
4	Ac- aLys -Leu-Val-Phe-Phe-Ala-NH ₂	11	779.4694	779.4697
5	Ac-Lys- aLeu -Val-Phe-Phe-Ala-NH ₂	4	779.4694	779.4714
6	Ac-Lys-Leu- aVal -Phe-Phe-Ala-NH ₂	18	779.4694	779.4711
7	Ac-Lys-Leu-Val- aPhe -Phe-Ala-NH ₂	8	779.4694	779.4680
8	Ac-Lys-Leu-Val-Phe- aPhe -Ala-NH ₂	6	779.4694	779.4687
9	Ac-Lys-Leu-Val-Phe-Phe- aAla -NH ₂	13	779.4694	779.4690
10	Ac- aLys -Leu- aVal -Phe-Phe-Ala-NH ₂	25	794.4803	794.4800
11	Ac- aLys -Leu-Val-Phe- aPhe -Ala-NH ₂	8	794.4803	794.4802
12	Ac-Lys- aLeu -Val- aPhe -Phe-Ala-NH ₂	8	794.4803	794.4811
13	Ac-Lys- aLeu -Val-Phe-Phe- aAla -NH ₂	5	794.4803	794.4802
14	Ac-Lys-Leu- aVal -Phe- aPhe -Ala-NH ₂	13	794.4803	794.4794
15	Ac-Lys-Leu-Val- aPhe -Phe- aAla -NH ₂	26	794.4803	794.4810
16	Ac- aLys -Leu- aVal -Phe- aPhe -Ala-NH ₂	15	809.4912	809.4920
17	Ac-Lys- aLeu -Val- aPhe -Phe- aAla -NH ₂	1	809.4912	809.4912

Figure S1. Effects of 1.0 equiv. of inhibitors **5**, **14**, and **15** on A β_{42} aggregation monitored by ThT fluorescence assay in repeat experiments. Error bars correspond to the standard deviation between two experiments run under identical conditions in the same plate.

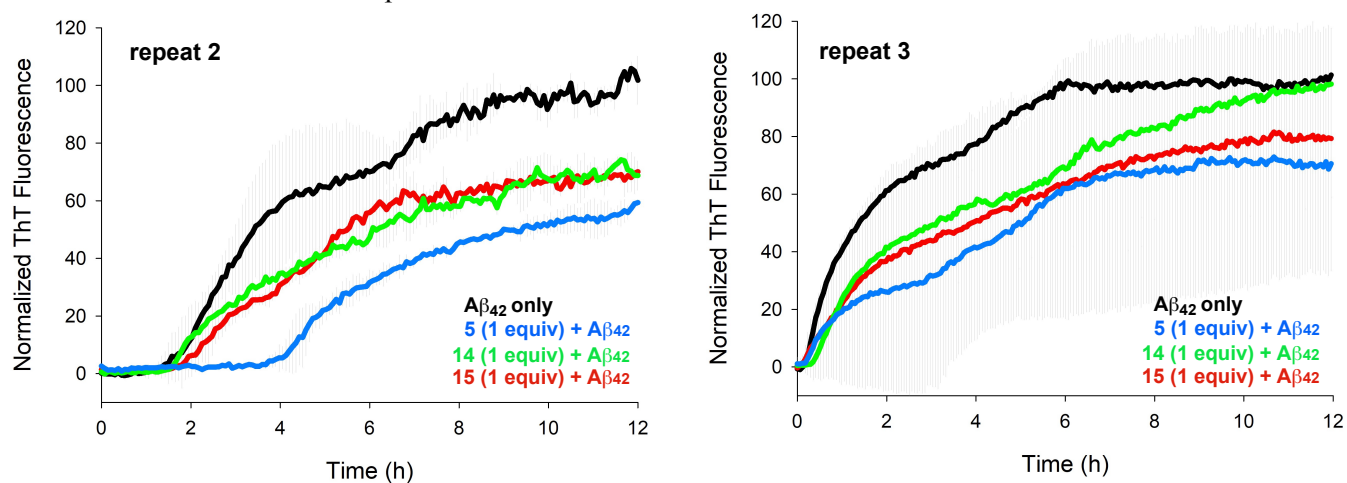


Figure S2. Circular dichroism spectra for inhibitors **5**, **14**, and **15** alone and in the presence of A β ₄₂ for 18h.

