Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Understanding the Conformational Analysis of Gababutin Based Hybrid Peptides

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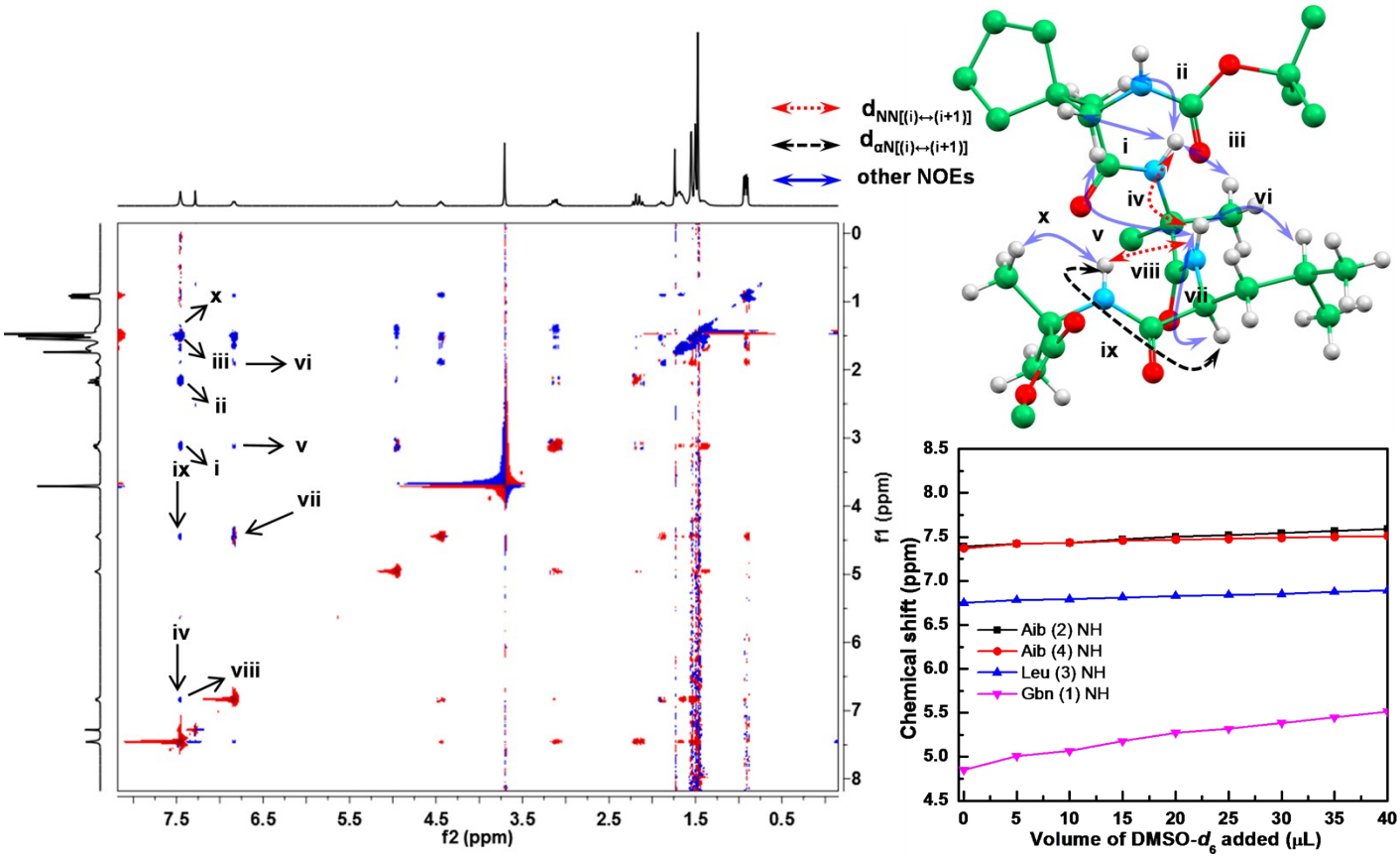


Fig. S1 ^{1}H-^{1}H ROESY spectrum of peptide **2** (400 MHz, $CDCl_3$ at 298 K, mixing time = 200 ms), showing several representative NOEs over the peptide backbone, suggesting a double turn conformations as found in the solid state structure. DMSO-d_6 solvent titrations plot for peptide **2** in $CDCl_3$ supports the presence of a hydrogen-bonded folded structure.

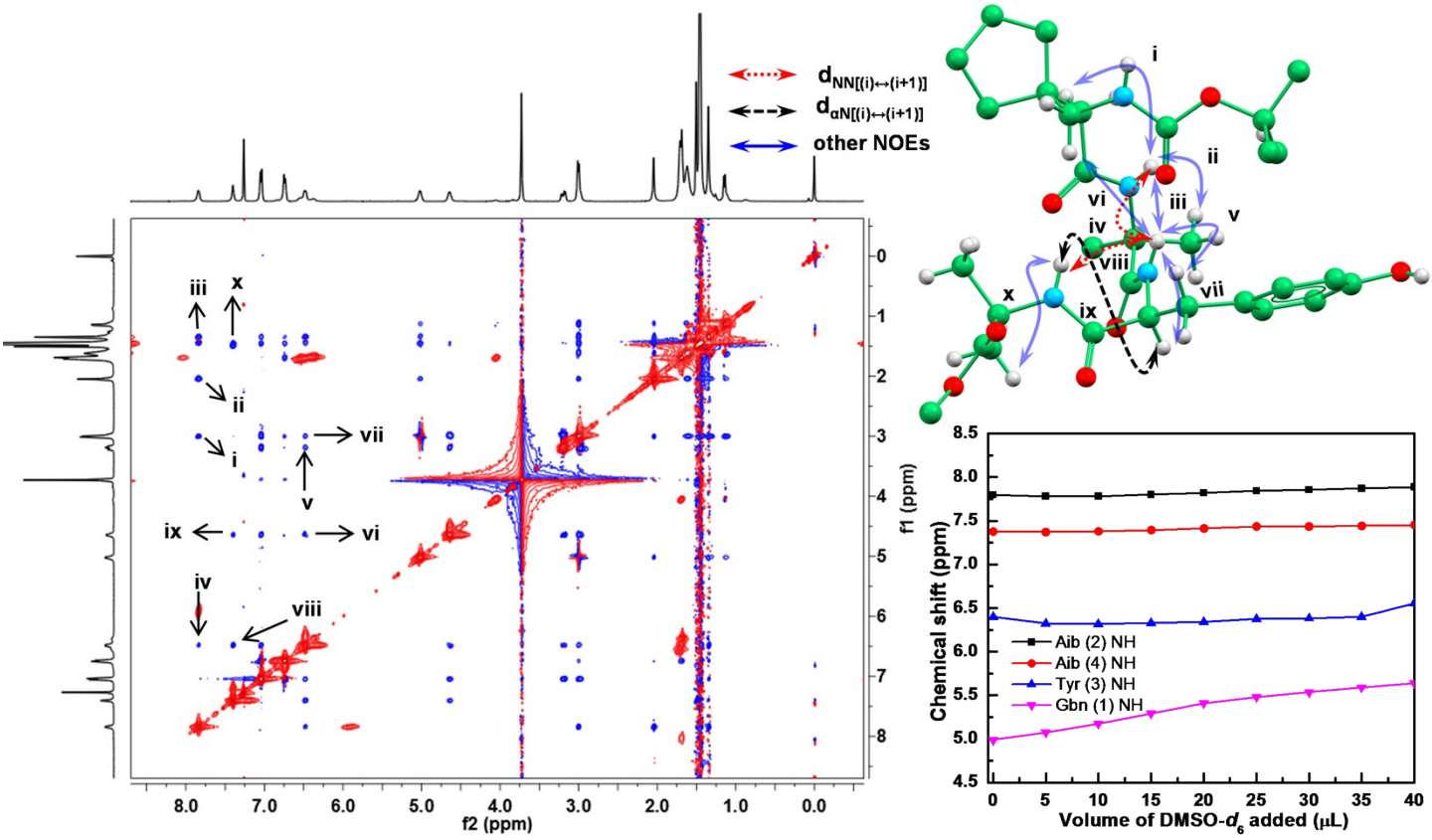


Fig. S2 ^{1}H-^{1}H ROESY spectrum of peptide **3** (400 MHz, $CDCl_3$ at 298 K, mixing time = 200 ms), showing several representative NOEs over the peptide backbone, suggesting a double turn conformations as found in the solid state structure. DMSO-d_6 solvent titrations plot for peptide **3** in $CDCl_3$ supports the presence of a hydrogen-bonded folded structure.

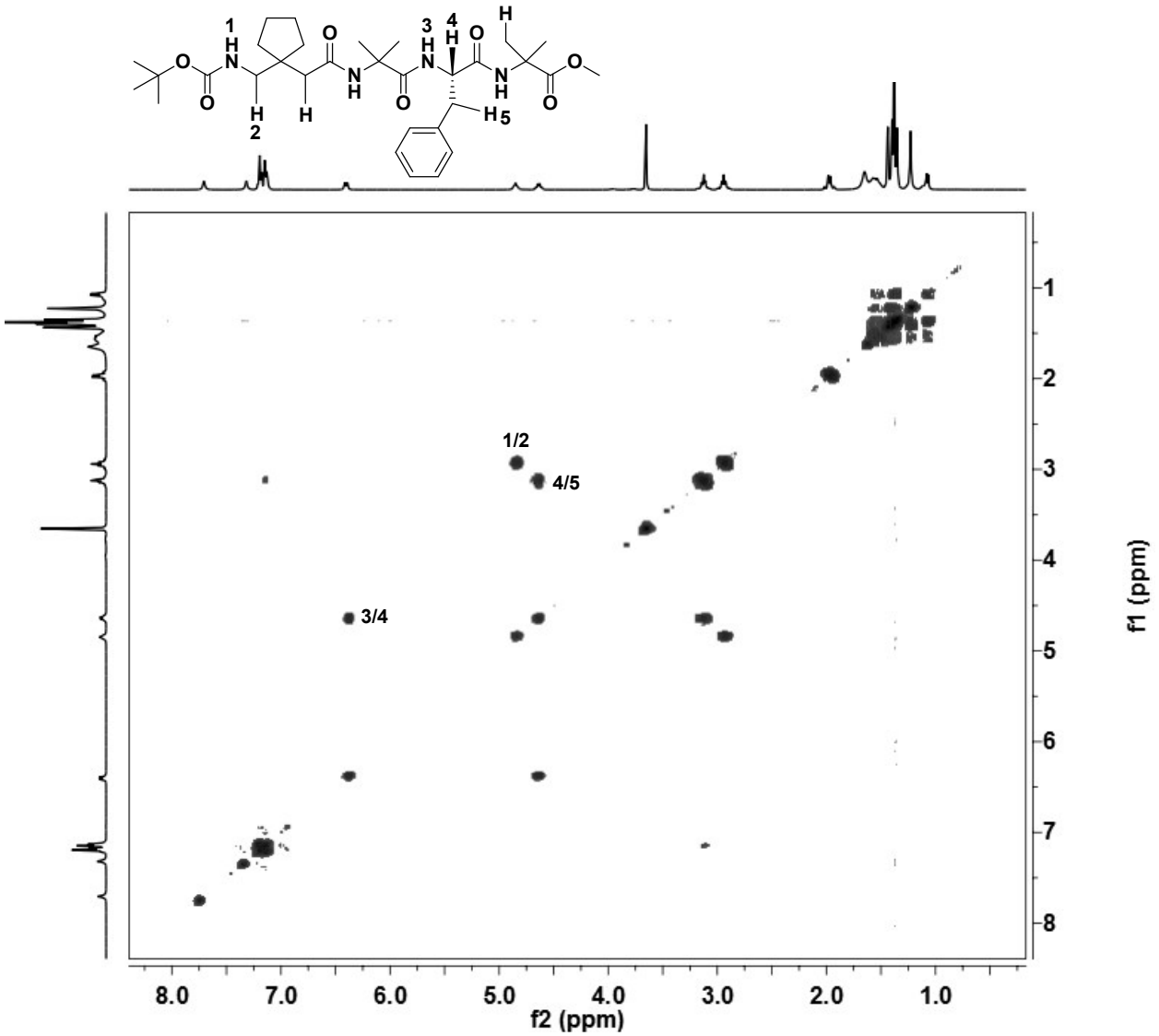


Fig. S3 ^{1}H-^{1}H COSY spectrum of peptide **1** (400 MHz, $CDCl_3$ at 298 K).

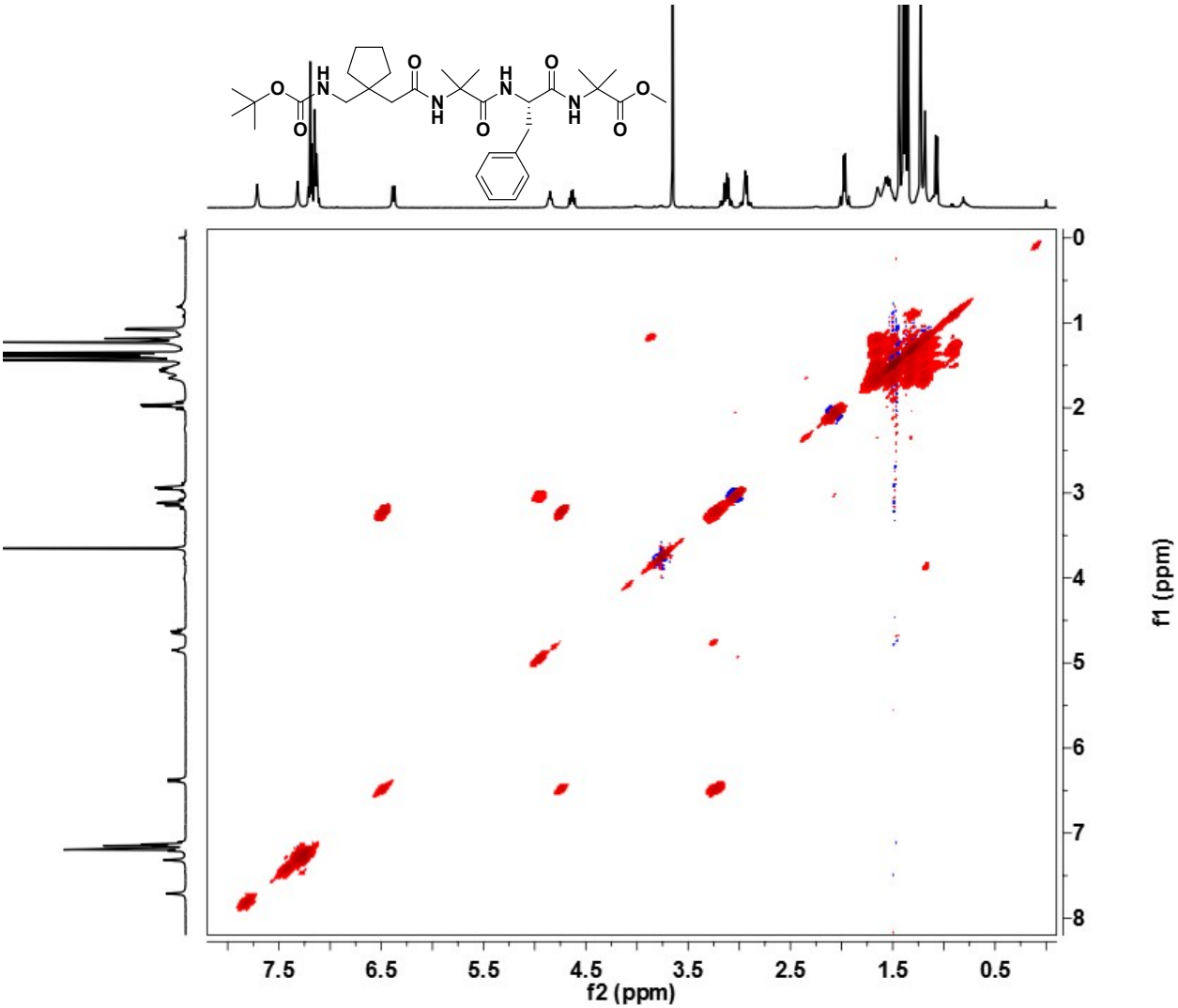


Fig. S4 ^{1}H-^{1}H TOCSY spectrum of peptide **1** (400 MHz, $CDCl_3$ at 298 K, mixing time = 80 ms).

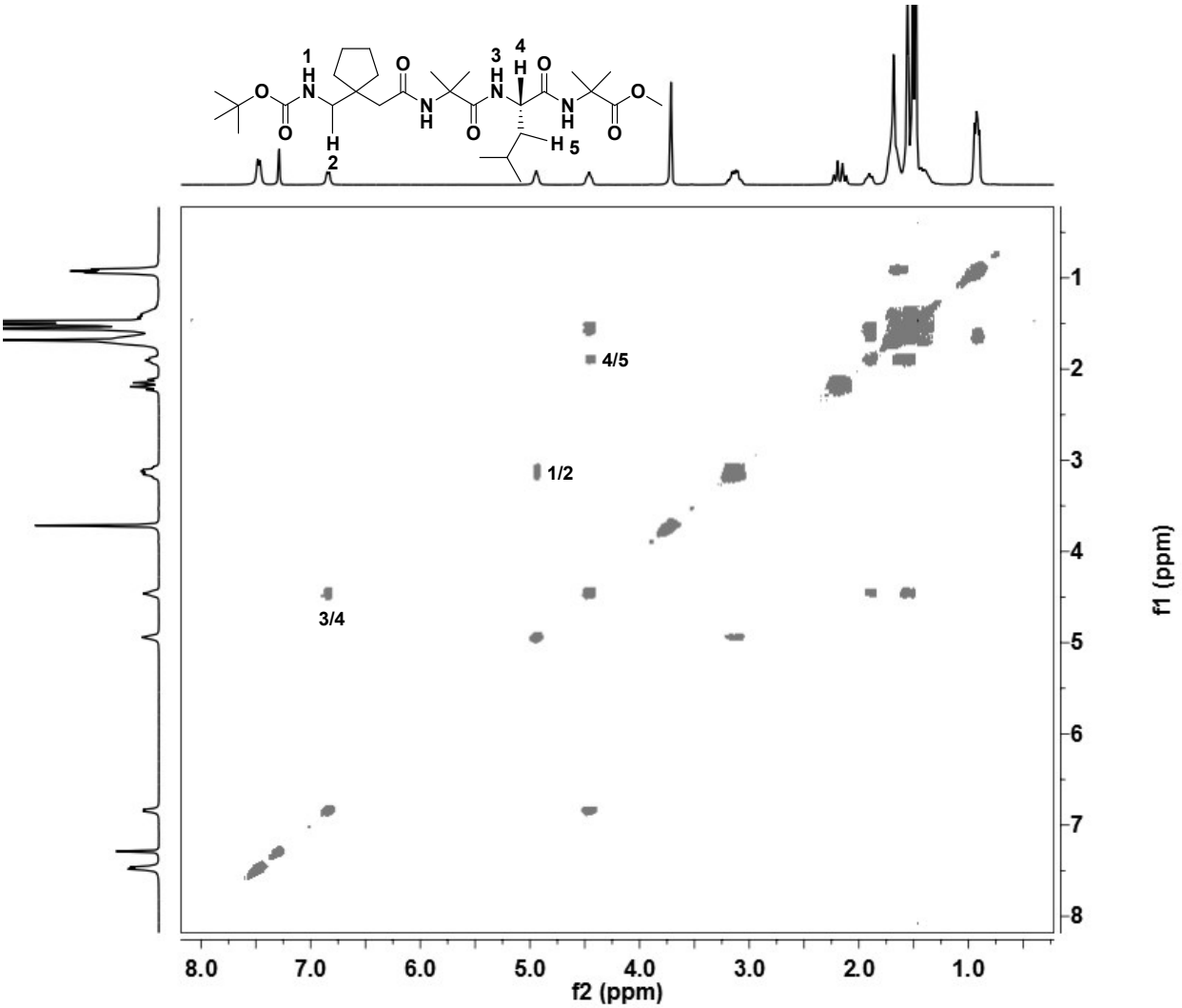


Fig. S5 ^{1}H-^{1}H COSY spectrum of peptide **2** (400 MHz, $CDCl_3$ at 298 K).

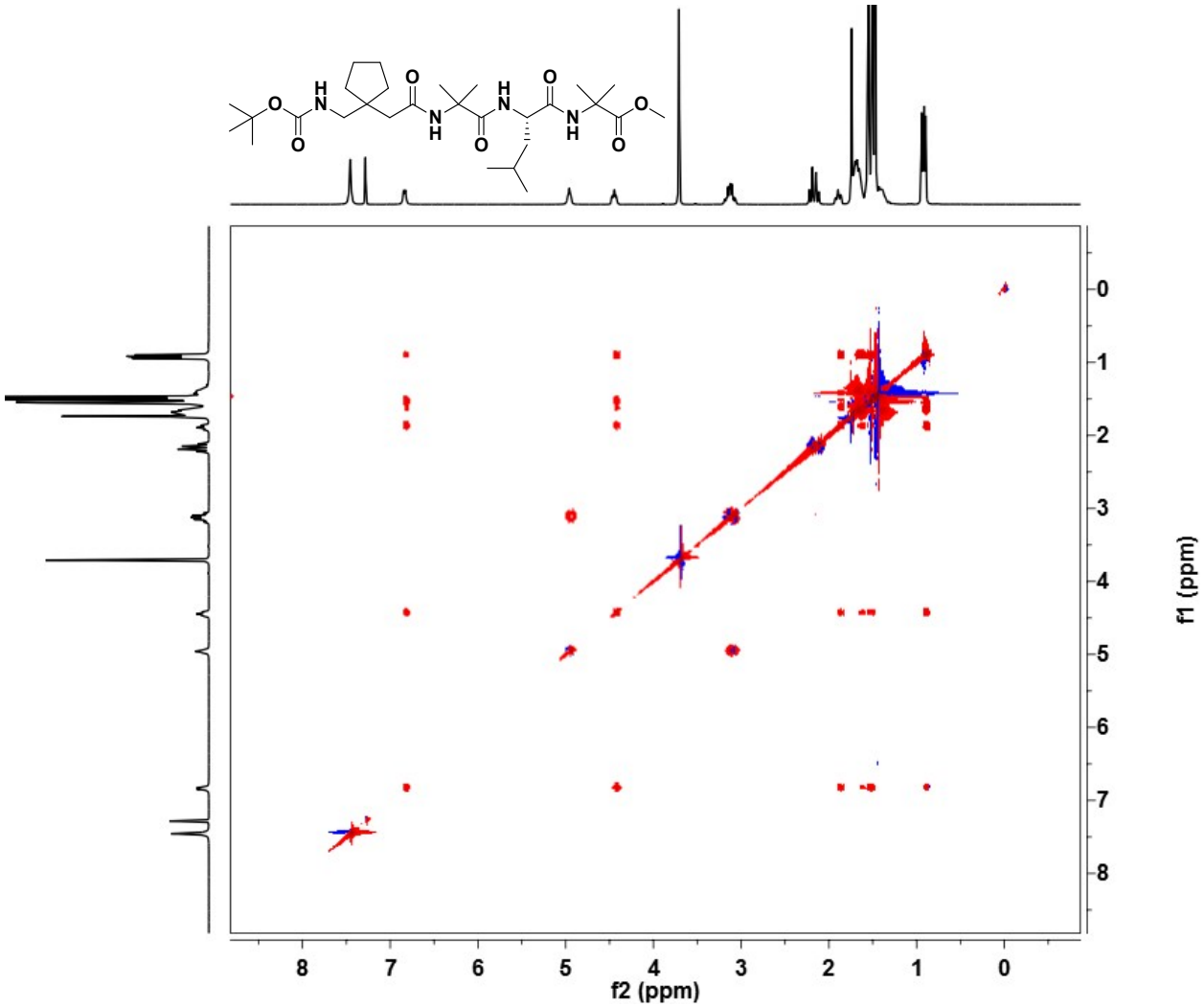


Fig. S6 ^{1}H-^{1}H TOCSY spectrum of peptide **2** (400 MHz, $CDCl_3$ at 298 K, mixing time = 80 ms).

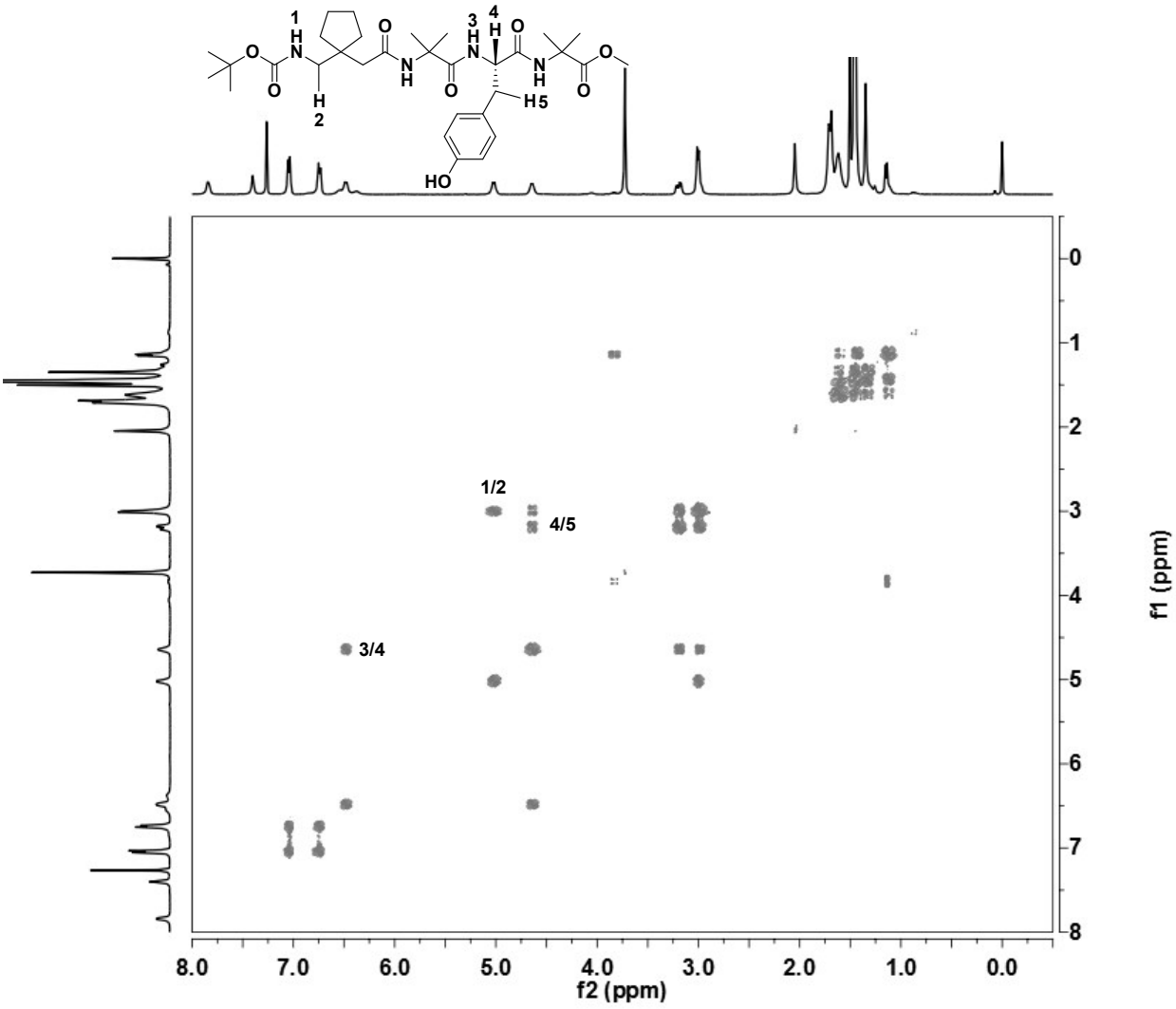


Fig. S7 ^{1}H-^{1}H COSY spectrum of peptide **3** (400 MHz, $CDCl_3$ at 298 K).

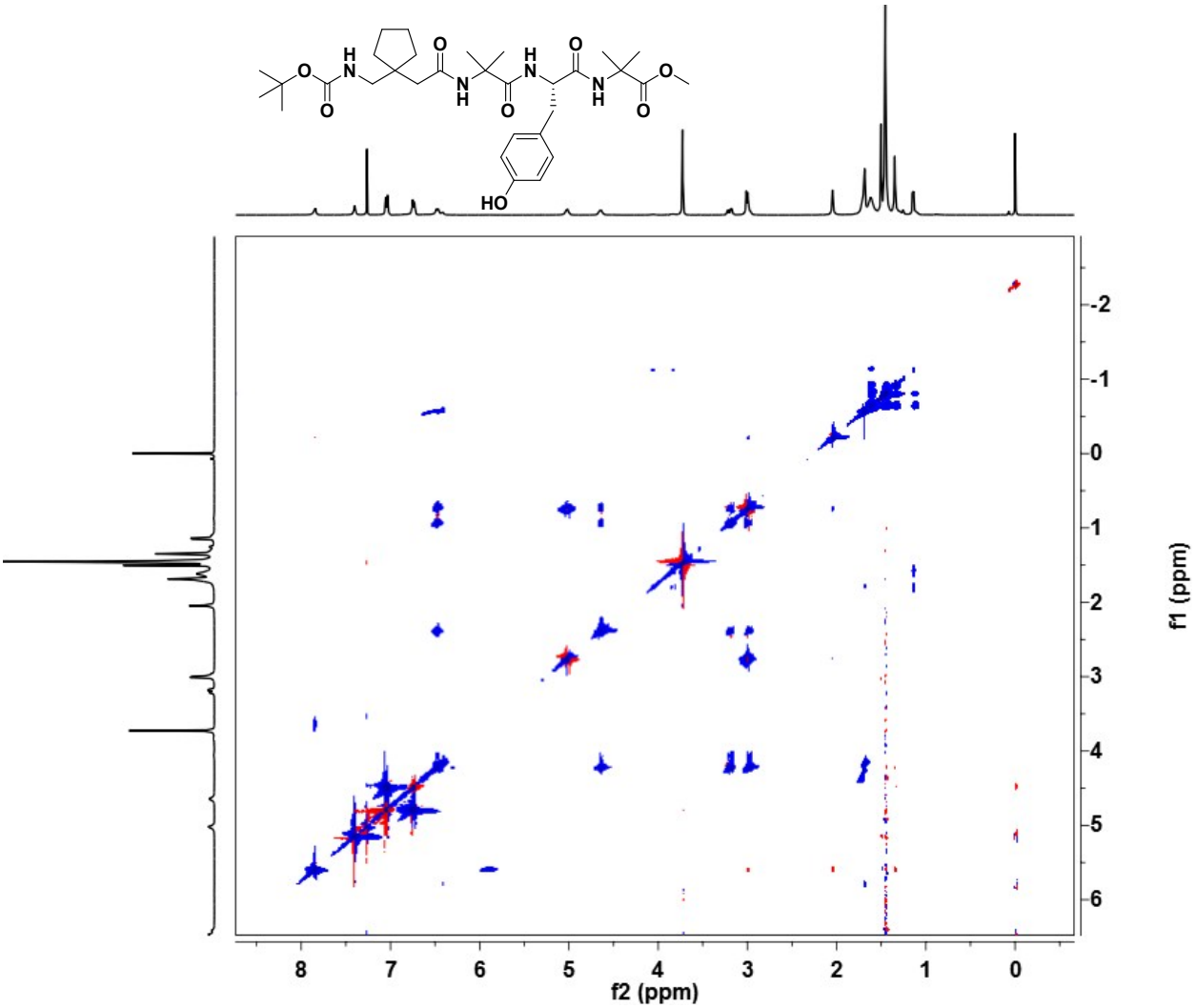


Fig. S8 ^{1}H-^{1}H TOCSY spectrum of peptide **3** (400 MHz, $CDCl_3$ at 298 K, mixing time = 80 ms).

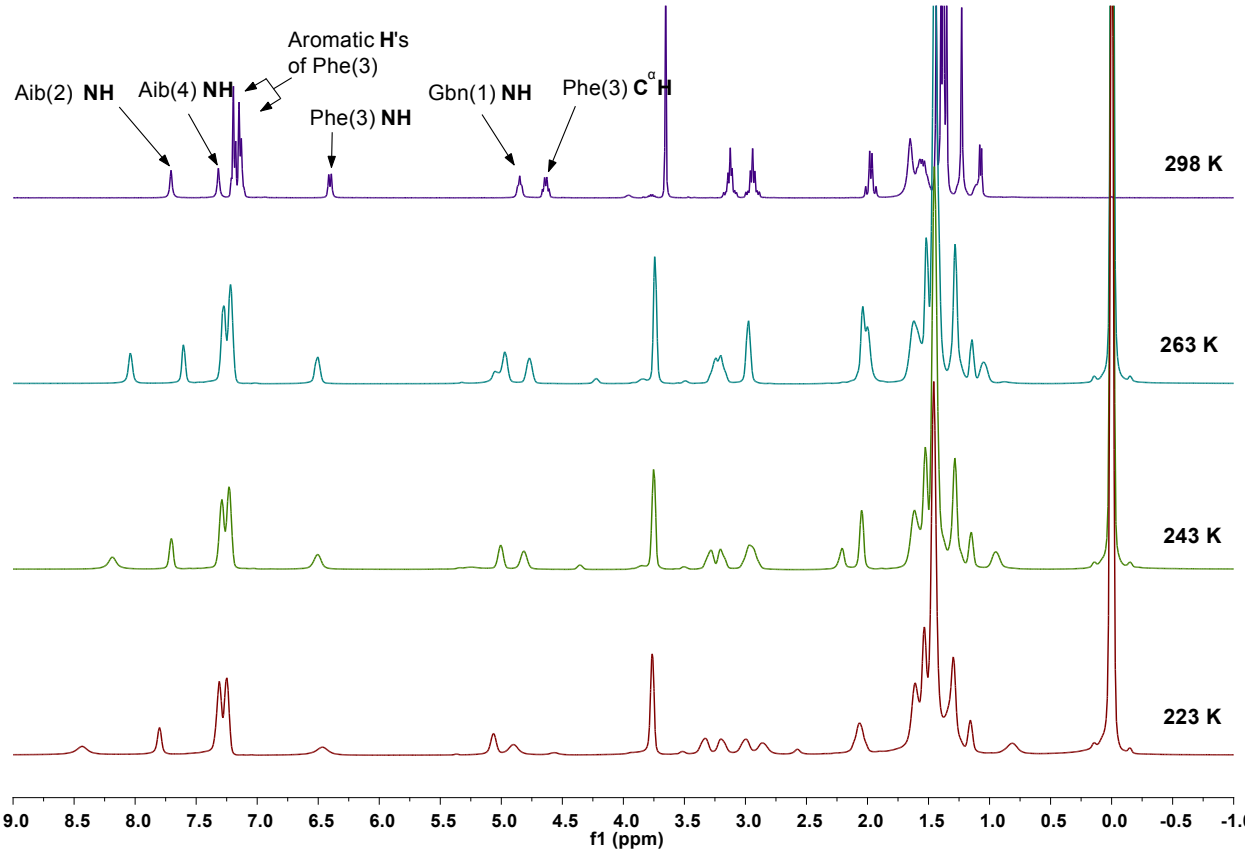


Fig. S9 Temperature dependent ^{1}H NMR spectra (400 MHz, $CDCl_3$) of peptide **1** in $CDCl_3$ illustrating peak broadening and downfield shift of NH protons upon cooling from 298 to 223 K.

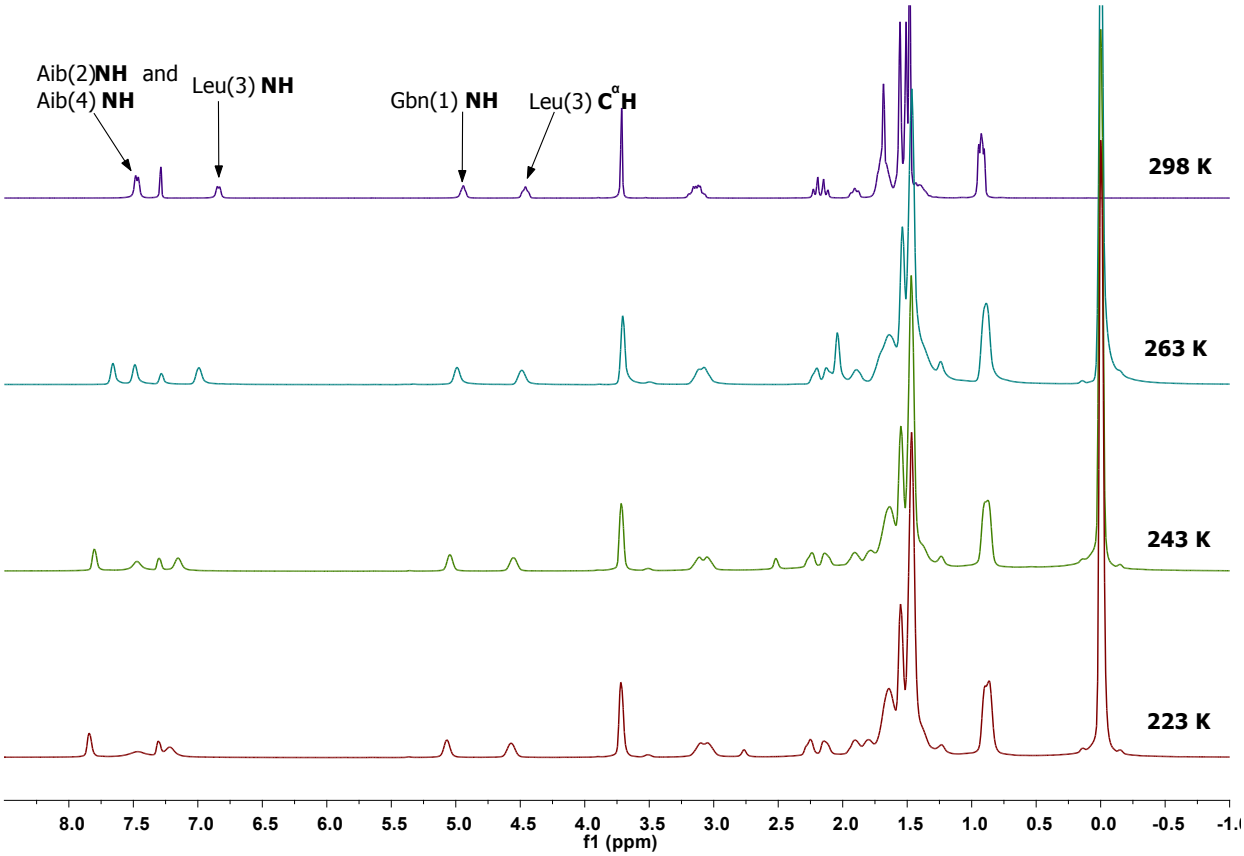


Fig. S10 Temperature dependent ^{1}H NMR spectra (400 MHz, $CDCl_3$) of peptide **2** in CDC_3 illustrating peak broadening and downfield shift of NH protons upon cooling from 298 to 223 K.

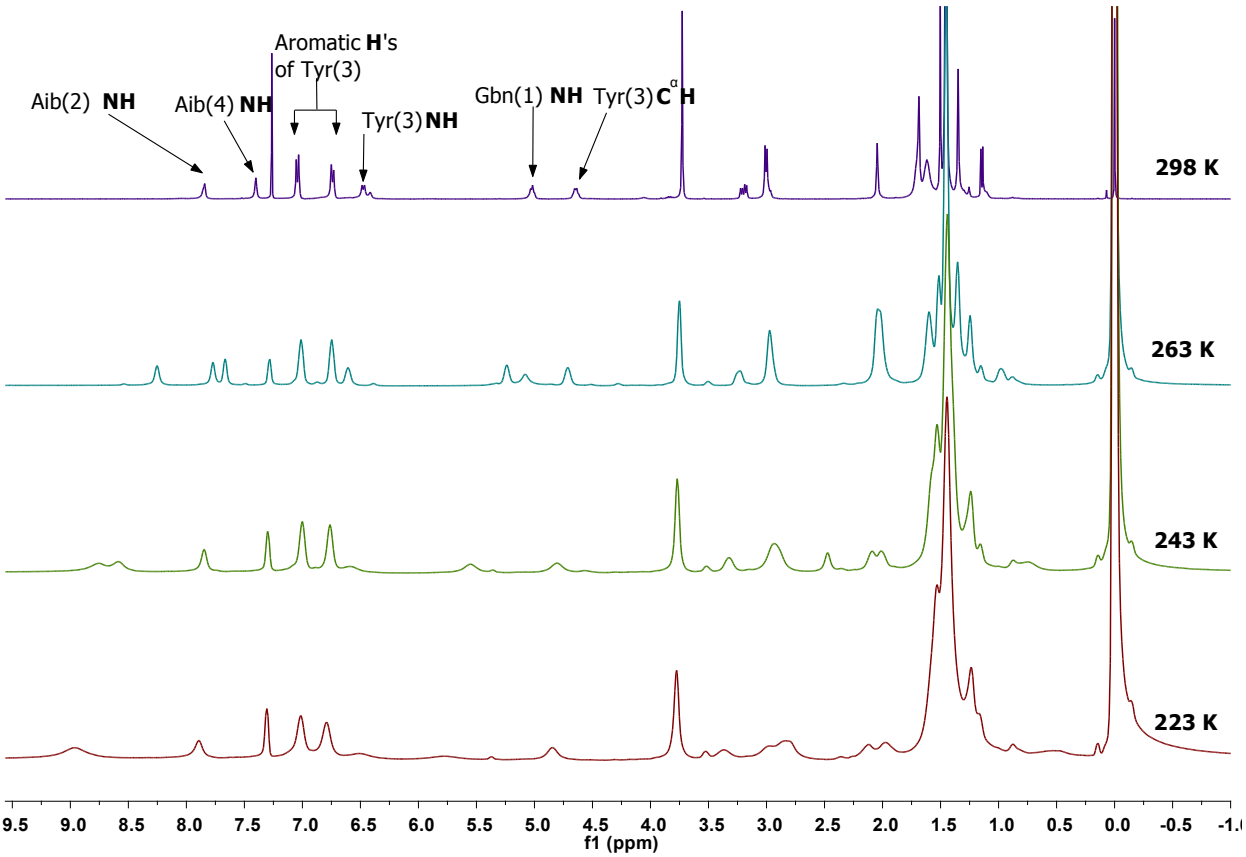


Fig. S11 Temperature dependent ^{1}H NMR spectra (400 MHz, $CDCl_3$) of peptide **3** in CDC_3 illustrating peak broadening and downfield shift of NH protons upon cooling from 298 to 223 K.

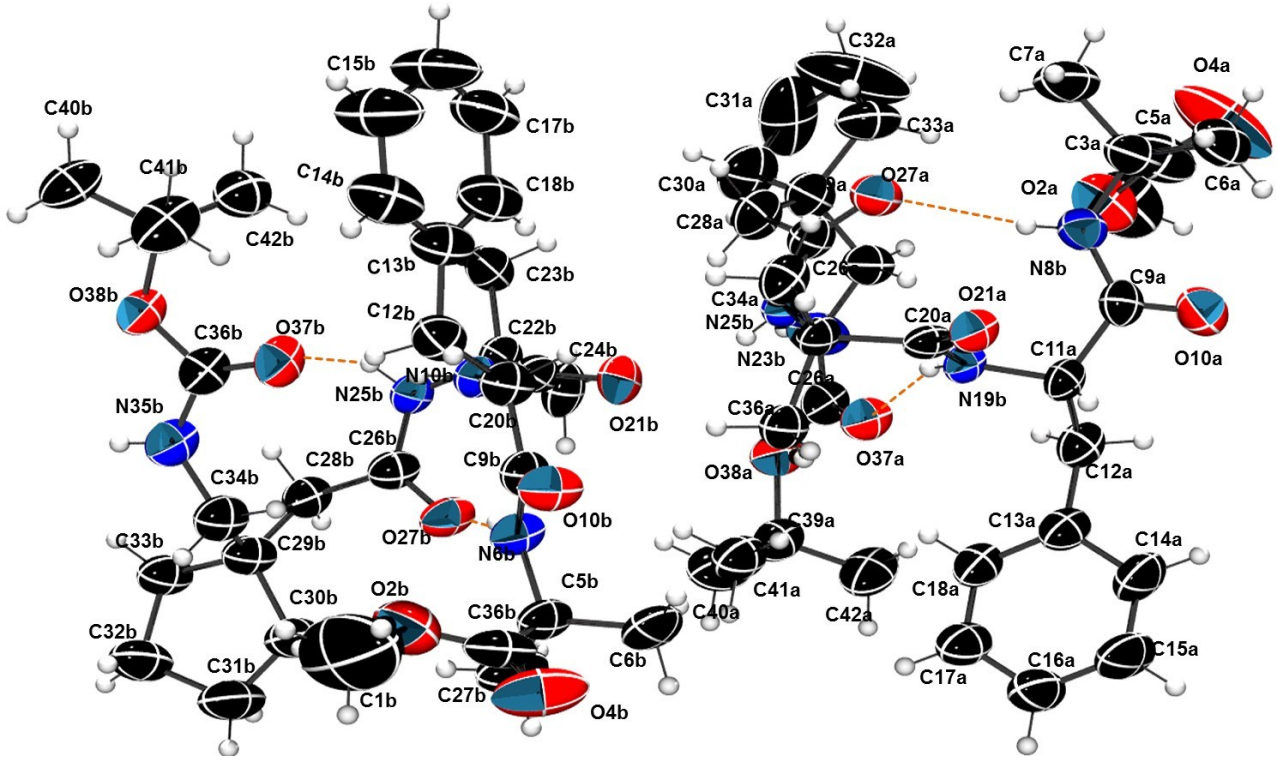


Fig. S12 ORTEP diagram of peptide **1** with atomic numbering. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms are not labeled for clarity.

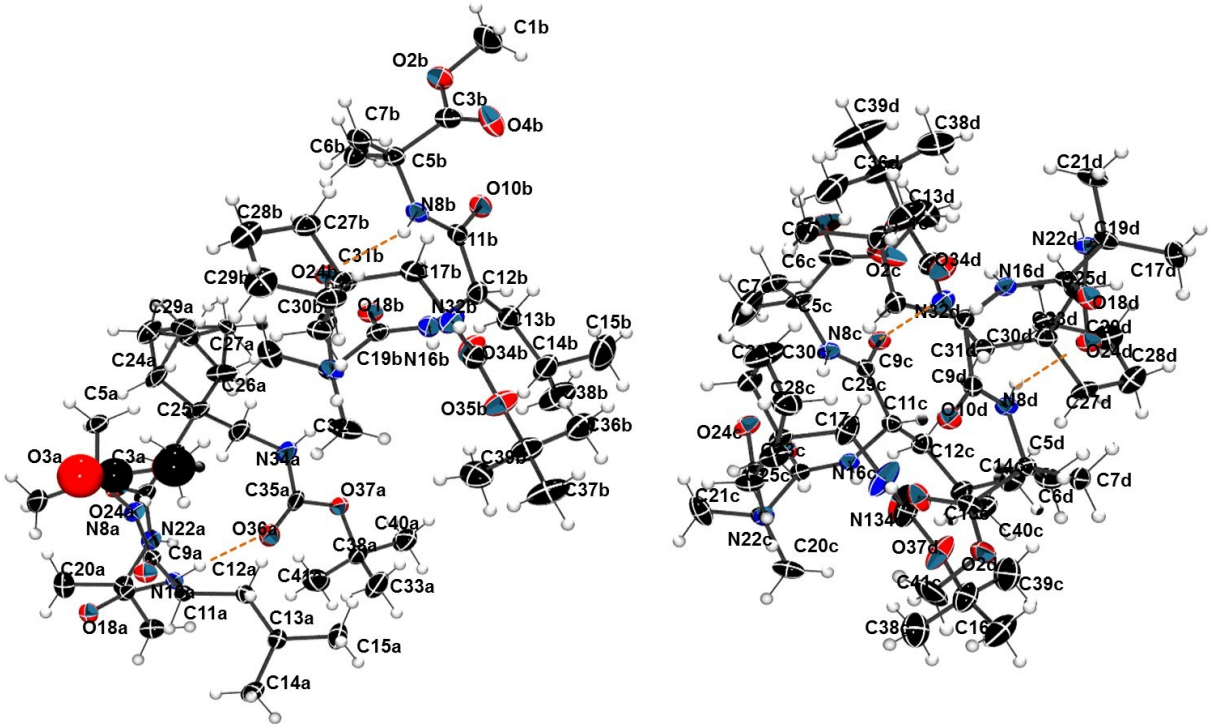


Fig. S13 ORTEP diagram of peptide **2** with atomic numbering. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms are not labeled for clarity.

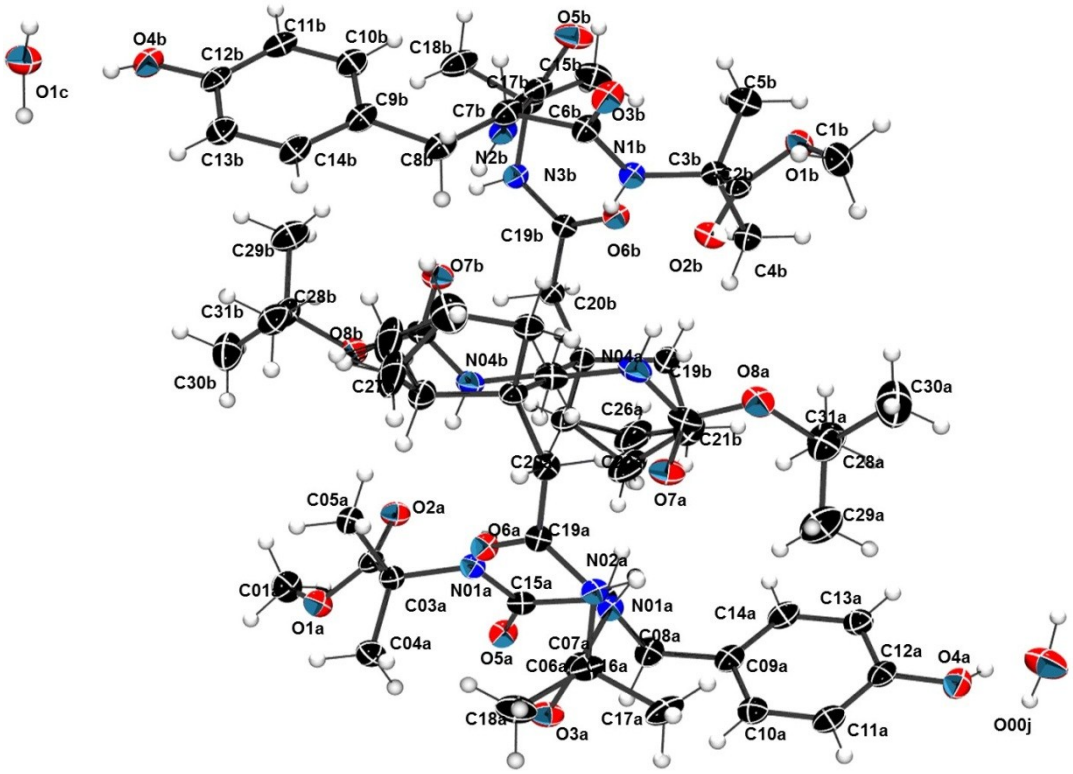


Fig. S14 ORTEP diagram of peptide **3** with atomic numbering. Thermal ellipsoids are shown at 50% probability. Hydrogen atoms are not labeled for clarity.

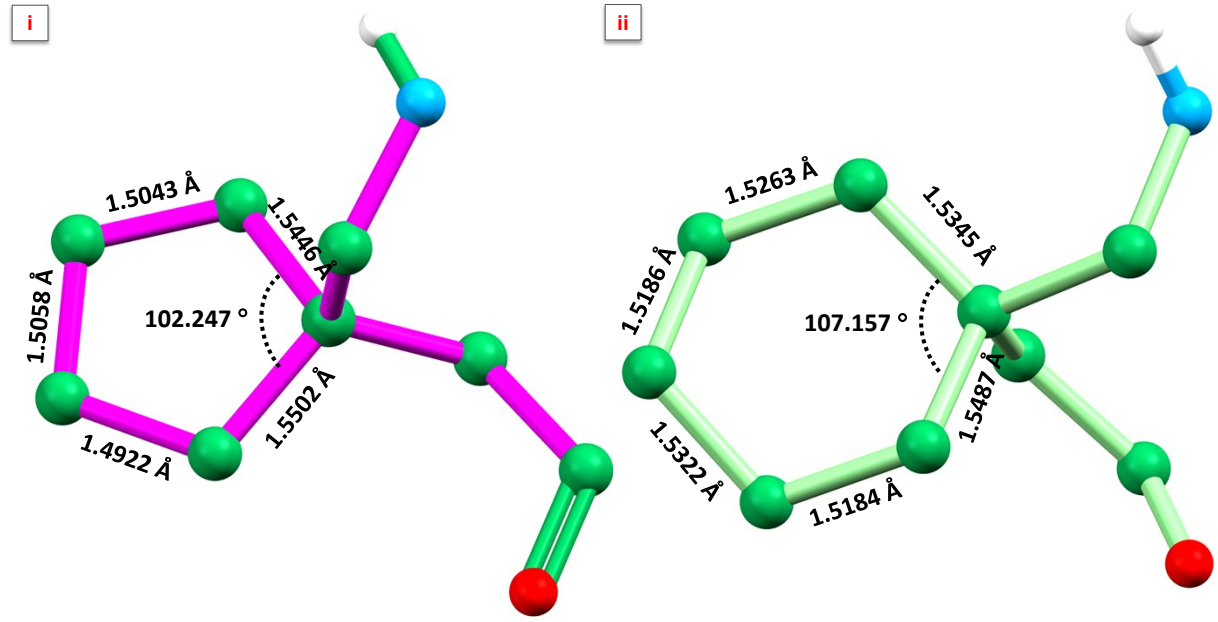


Fig. S15 Evaluation of average geometries (bond lengths and bond angles) observed for (a) Gbn in peptides **1-3** and (b) Gpn residue (of those reported peptides see ref S1) determined so far in crystal structures (number of residues Gbn = 8; Gpn = 10).

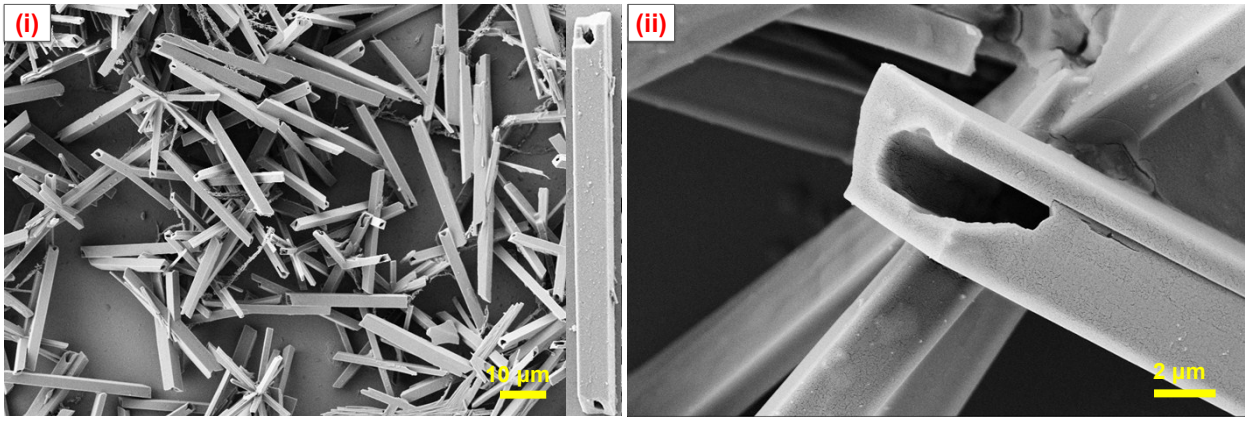


Fig. S16 FE-SEM images showing the (i) and (ii) well-defined microtubular structures of peptide **2**, inset showing a single rectangular cross-sectioned microtube entity with hollow ends.

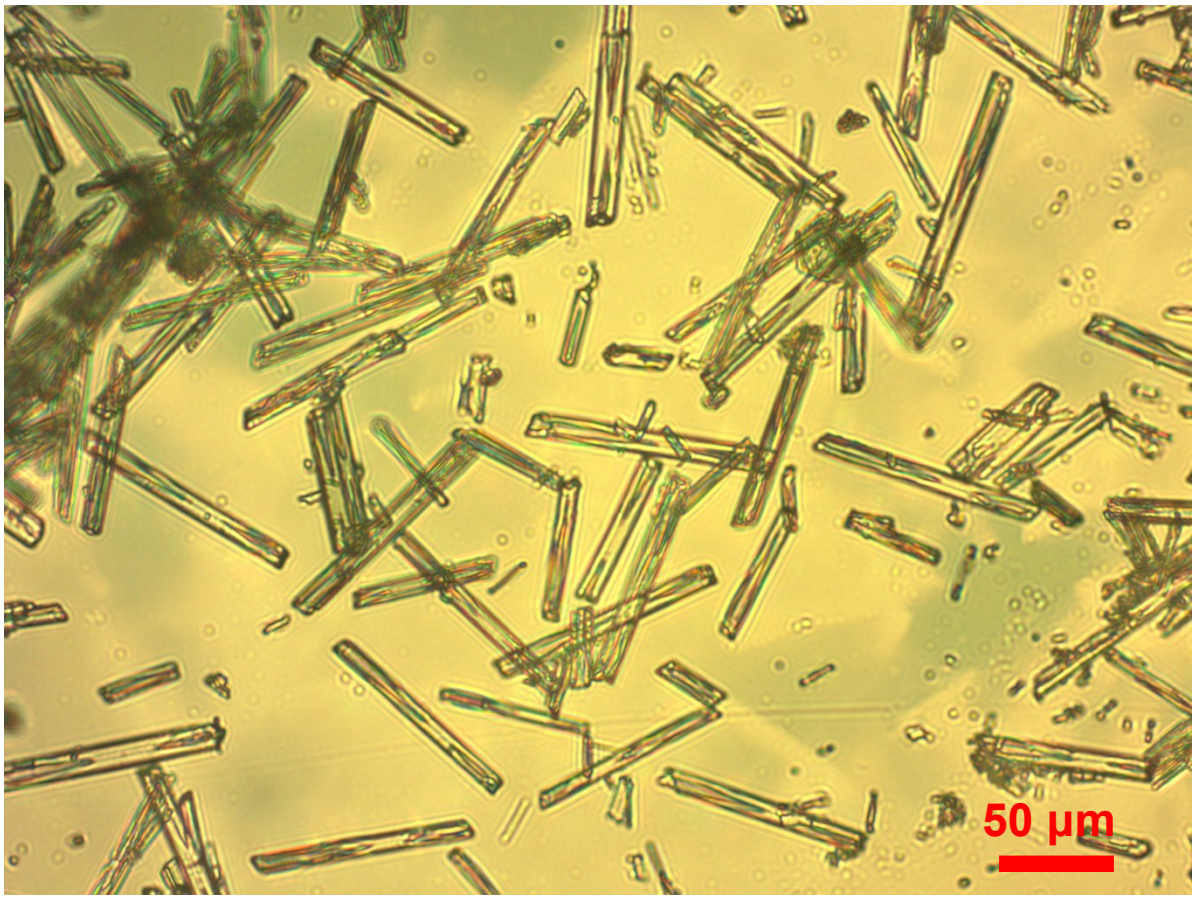


Fig. S17 Optical image showing well-defined discrete microtubular structures of peptide **2**. Image also clearly showing the rectangular cross-sectioned microtubular structures.

Table S1 Representative ^{1}H NMR NH resonances observed for peptide **1** (Chemical shift δ_{ppm})[a]

Volume of DMSO-d_6 added (μL)	Chemical shift (δ_{ppm})							
	Aib(2) NH	$\Delta\delta^b$	Aib(4) NH	$\Delta\delta^b$	Phe(3) NH	$\Delta\delta^b$	Gbn(1) NH	$\Delta\delta^b$
0	7.7456		7.3452		6.3777		4.8421	
5	7.7829		7.3793		6.4155		5.0257	
10	7.7810		7.3775		6.4138		5.0244	
15	7.8017		7.3969		6.4389		5.1327	
20	7.8197	0.1871	7.4135	0.1348	6.4595	0.1871	5.2189	0.7000
25	7.8428		7.4356		6.4917		5.3266	
30	7.8557		7.4478		6.5101		5.395	
35	7.8754		7.4673		6.5397		5.4075	
40	7.8885		7.4800		6.5648		5.5422	

[a]Chemical shifts of proton resonances in 8% DMSO-d_6/$CDCl_3$, [b]$\Delta\delta$ is the chemical shift difference for the NH protons in 8% DMSO-d_6/$CDCl_3$ and $CDCl_3$.

Table S2 Representative ^{1}H NMR NH resonances observed for peptides **2** (Chemical shift δ_{ppm})[a]

Volume of DMSO-d_6 added (μL)	Chemical shift (ppm)							
	Aib(2) NH	$\Delta\delta^b$	Aib(4) NH	$\Delta\delta^b$	Leu(3) NH	$\Delta\delta^b$	Gbn(1) NH	$\Delta\delta^b$
0	7.3922		7.3711		6.7495		4.8514	
5	7.4227		7.4227		6.7826		5.0084	
10	7.4356		7.4356		6.7919		5.0655	
15	7.4713		7.4572		6.8127		5.1780	
20	7.5061	0.1996	7.4701	0.1406	6.8304	0.1419	5.2734	0.6637
25	7.5226		7.4786		6.8408		5.3195	
30	7.5463		7.4903		6.8509		5.3859	
35	7.5679		7.5025		6.8767		5.4482	
40	7.5918		7.5117		6.8914		5.5151	

[a]Chemical shifts of proton resonances in 8% DMSO-d_6/$CDCl_3$, [b]$\Delta\delta$ is the chemical shift difference for the NH protons in 8% DMSO-d_6/$CDCl_3$ and $CDCl_3$.

Table S3 Representative ^{1}H NMR NH resonances observed for peptide **3** (Chemical shift δ_{ppm})[a]

Volume of DMSO-d_6 added (μL)	Chemical shift (ppm)							
	Aib(2) NH	$\Delta\delta^b$	Aib(4) NH	$\Delta\delta^b$	Tyr(3) NH	$\Delta\delta^b$	Gbn(1) NH	$\Delta\delta$
0	7.7951		7.3758		6.3987		4.9869	
5	7.7829		7.3749		6.323		5.0754	
10	7.781		7.3821		6.3166		5.1748	
15	7.8017		7.3957		6.3282		5.2936	
20	7.82	0.0934	7.4135	0.0782	6.3415	0.1576	5.4077	0.6517
25	7.8428		7.4338		6.3775		5.4784	
30	7.8557		7.4359		6.3849		5.5337	
35	7.8701		7.4441		6.4011		5.5889	
40	7.8885		7.454		6.5563		5.6384	

[a]Chemical shifts of proton resonances in 8% DMSO-d_6/$CDCl_3$, [b]$\Delta\delta$ is the chemical shift difference for the NH protons in 8% DMSO-d_6/$CDCl_3$ and $CDCl_3$.

Table S4 Crystal and diffraction parameters of peptides 1-3

	Peptide 1	**Peptide 2**	**Peptide 3**
Empirical formula	C_{31} H_{46} N_4 O_8	C_{28} H_{50} N_4 O_7	C_{31} H_{50} N_4 O_9
Crystal habit	Colorless needle	Colorless rectangular	Colorless rectangular
Crystalizing solvent	Methanol/Water	Methanol/Water	Methanol/Water
Space group	$P2_1$	$P2_1$	$P2_1$
a (Å)	12.0777(4)	20.81140(10)	10.958(2)
b (Å)	21.0362(6)	12.83240(10)	16.851(3)
c (Å)	14.3712(5)	23.6124(2)	18.872(4)
α (deg)	90	90	90
β (deg)	107.602(3)	100.8460(10)	101.84(3)
γ (deg)	90	90	90
Volume (Å^3)	3480.32	6193.29	3410.64
Z	2	2	4
Molecules/asymmetric unit	2	4	2
Co-crystallized solvent	None	None	Water
Molecular weight	602.72	568.38	622.75
Density (g/cm^3) (cal)	1.123	1.189	1.213
F (000)	1270	2414	1344
θ Max. (˚)	65.083	70.055	72.215
Reflections collected / unique	31697/11585	41053/19726	33156/11892
Max. and min. transmission	1.000 and 0.405	1.000 and 0.850	0.982 and 0.972
R_{int}	0.0808	0.0102	0.0224
Final R (%)/wR2 (%)	0.0828/0.2174	0.0803/0.2351	0.0363/.0964
Goodness-of-fit (S)	1.059	1.064	1.045
λ (Å)	1.54178	1.54178	1.54178
Data / restraints / parameters	11585/773/1	19726/1444/9	11892/852/7
CCDC	1542080	1542088	1542089

Table S5 Hydrogen bond parameters of peptides **1-3**

Peptide / Compound		Type of hydrogen-bond	D-H···A	H···A(Å)	D···A(Å)	∠D-H···A(°)
1	Molecule A	Intramolecular	N19A-H19A···O37A	2.18	3.00	160.0
			N8A-H8A···O27A	2.23	3.03	154.0
		Intermolecular	N25A-H25A···O21B	2.07	2.88	157.3
			N25B-H25B···O21A	2.07	2.90	161.5
	Molecule B	Intramolecular	N19B-H19B···O37B	2.02	2.86	163.5
			N8B-H8B···O27B	2.15	3.00	170.0
		Intermolecular	N25B-H25B···O21A	2.07	2.90	161.5
			N25A-H25A···O21B	2.07	2.88	157.3
2	Molecule A	Intramolecular	N16A-H16A···O36A	2.08	2.93	169.0
			N8A-H8A···O24A	2.26	3.00	144.5
		Intermolecular	N22A-H22A···O18A	2.32	3.13	155.8
			N34A-H34A···O4B	2.01	2.86	167.1
			N32B-H32B···O2A	2.15	3.00	167.1
	Molecule B	Intramolecular	N16B-H16B···O34B	1.97	2.75	149.2
			N8B-H8B···O24B	2.19	2.94	147.3
		Intermolecular	N32B-H32B···O2A	2.15	3.00	167.1
			N34B-H34B···O4B	2.10	2.86	167.1
			N22B-H22B···O18B	2.36	3.15	154.1
	Molecule C	Intramolecular	N16C-H16C···O36C	1.93	2.74	157.2
			N8C-H8C···O24C	2.33	3.01	136.1
		Intermolecular	N34C-H34C···O4D	1.96	2.81	170.0
			N22C-H22C···O18C	2.35	3.11	155.1
	Molecule D	Intramolecular	N16D-H16D···O34D	2.11	2.94	159.1
			N8D-H8D···O24D	2.20	2.96	148.8
		Intermolecular	N22D-H22D···O18D	2.35	3.13	151.0
			N34C-H34C···O4D	1.96	2.81	170.0
3	Molecule A	Intramolecular	N2A-H2A···O7A	2.00	2.72	141.2
			N1A-H1A···O6A	2.32	2.91	126.0
		Intermolecular	N4A-H4A···O2B	2.08	2.94	174.0
			N4B-H4B···O2A	2.26	3.11	172.0
			N3A-H3A···O3A	2.31	3.05	144.0
		Solvent mediated	O1C-H3···O2A	2.12	3.03	151.2
			O00J-H9···O5A	1.80	2.76	166.0
			O4A-H2···O00J	1.88	2.72	166.0
	Molecule B	Intramolecular	N2B-H2B···O7B	2.16	2.97	158.0
			N1B-H1B···O6B	2.40	3.04	132.7
		Intermolecular	N4B-H4B···O2A	2.26	3.11	172.0
			N4A-H4A···O2B	2.08	2.94	174.0
			N3B-H3B···O3B	2.12	2.92	154.4
		Solvent mediated	O1C-H10···O5B	1.77	2.72	155.0
			O00J-H8···O2B	2.28	3.28	160.0
			O4B-H1···O1C	1.78	2.67	160.2

Table S6 Backbone dihedral angles for the peptides **1-3**

Peptide / Compound	Residue	ϕ	θ_1	θ_2	ψ	ω	Type of Turn Observed
1 Molecule A	Gbn(1)	-120	65	58	-129	-170	Type I β-turn
	Aib(2)	-56			-35	-175	
	Phe(3)	-86			12	-179	
	Aib(4)	60			27	-	
1 Molecule B	Gbn(1)	-115	58	59	-139	-165	Type I β-turn
	Aib(2)	-55			-33	-174	
	Phe(3)	-86			5	174	
	Aib(4)	50			46	-	
2 Molecule A	Gbn(1)	-102	68	56	-143	-172	Type I β-turn
	Aib(2)	-48			-39	-172	
	Leu(3)	-74			-19	170	
	Aib(4)	48			45	-	
2 Molecule B	Gbn(1)	104	-65	-58	151	171	Type III′ β-turn
	Aib(2)	56			31	-179	
	Leu(3)	56			35		
	Aib(4)	-53			144	-	
2 Molecule C	Gbn(1)	111	-67	-54	138	172	Type I β-turn
	Aib(2)	52			37	176	
	Leu(3)	56			41	-178	
	Aib(4)	-41			-48	-	
2 Molecule D	Gbn(1)	-96	64	59	-153	-168	Type III′ β-turn
	Aib(2)	-55			-35	-175	
	Leu(3)	-77			-12	168	
	Aib(4)	52			-142	-	
3 Molecule A	Gbn(1)	108	-60	-57	152	167	Type III β-turn
	Aib(2)	59			28	-178	
	Tyr(3)	52			44	-166	
	Aib(4)	-59			146	-	
3 Molecule B	Gbn(1)	-102	61	60	-156	-164	Type III′ β-turn
	Aib(2)	-59			-30	-174	
	Tyr(3)	-74			-19	157	
	Aib(4)	58			-141	-	

Table S7 Average backbone dihedral angles of Gbn residues of peptides **1-3** and Gpn residues of Gpn-based hybrid peptides[1]

Peptide	Residue	ϕ	θ_1	θ_2	ψ
Boc-Gbn-Aib-Phe-Aib-OMe (**1**)	Gbn(1)	-117.5 ± 2.5	61.5 ± 3.5	57 ± 1.0	-134 ± 5.0
Boc-Gpn-Aib-Phe-Aib-OMe	Gpn	-101.0 ± 5.0	-67 ± 1.0	-57.5 ± 0.5	-159
Boc-Gbn-Aib-Leu-Aib-OMe (**2**)	Gbn(1)	107.5 ± 1.5	66 ± 1.0	56 ± 2.0	144.5 ± 6.5
Boc-Gpn-Aib-Leu-Aib-OMe	Gpn	107 ± 5.0	-65.5 ± 1.5	-56.5 ± 1.5	143.5 ± 7.5
Boc-Gbn-Aib-Tyr-Aib-OMe (**3**)	Gbn(1)	108	-60	-57	152
Boc-Gpn-Aib-Tyr-Aib-OMe	Gpn	107	-62	-57	152

Table S8 Self-assembled morphological diversity of Gpn-based hybrid peptides in various solvent mixtures[1]

	Self-assembled morphology	
Solvent system	Methanol : water	THF : water
Boc-Gpn-Aib-Phe-Aib-OMe	spherical aggregates[a]	nanorod assemblies[b]
Boc-Gpn-Aib-Leu-Aib-OMe	helical nanofibrillar structures[a]	-
Boc-Gpn-Aib-Tyr-Aib-OMe	microcrystal morphology[a]	cross-linked nanofibrillar structures[a]

[a] concentration of peptide solution c = 3.0 mmol L^{-1};[b] concentration of peptide solution c = 5.0 mmol L^{-1}

Experimental Section

General Methods and Materials:

Cyclopentanone, triethyl phosphonoacetate, nitromethane, Pd/C (10%), α-aminoisobutyric acid, L-leucine, L-phenylalanine, L-tyrosine, HOBt (1-hydroxybenzotriazole), DCC (*N*,*N*'-dicyclohexylcarbodiimide) were obtained commercially. For chemical reactions and purification of peptides purpose, methanol, dimethylformamide, ethyl acetate and toluene were dried according to literature. Reactions were monitored by thin-layer chromatography (TLC). Visualization was attained with UV light and potassium permanganate stain followed by charring on hot-plate. All intermediates and final compounds were purified and well characterized by FT-IR, ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and mass spectral studies. The concentrations

were in the range 1-10 mmol L^{-1} in $CDCl_3$ and DMSO-d_6 for ^1H and ^{13}C-NMR. The concentration for DMSO titration studies was 20 mmol L^{-1} and for 2D-NMR experiments was 30 mmol L^{-1}. For DMSO titration study, the initial concentration of the samples in $CDCl_3$ was kept to 20 mmol L^{-1}, and the total amount of DMSO-d_6 used was 8% of the total volume. Chemical shifts were expressed in parts per million (ppm, δ) relative to residual solvent protons as internal standards ($CHCl_3$: δ 7.26, DMSO: 2.50 for ^1H, $CHCl_3$: δ 77.00, DMSO: 39.50 for ^{13}C). ^1H-NMR multiplicities were designated as singlet (s), doublet (d), triplet (t), quartet (q) multiplet (m) and broad singlet (bs). ^1H NMR spectra assignments of three tetrapeptides were achieved by using a combination of 2D COSY, ROESY and TOCSY experiments. All the ROESY and TOCSY NMR experiments were recorded at 298 K with mixing time of 200 and 80 ms respectively. FT-IR spectroscopic measurements were done with KBr pellet technique and crystal material was placed in between two KBr pellets like sandwich manner and scanned between 500 cm^{-1} to 4000 cm^{-1} over 64 scans at a resolution of 4 cm^{-1} and at an interval of 1 cm^{-1}. Mass spectra were recorded on a Bruker micrOTOF-Q II by positive-mode electrospray ionization.

Synthesis of Precursor: Gababutin hydrochloride

Synthesis of ethyl 2-cyclopentylideneacetate 5:

20 mL of 5N K_2CO_3 (6.90 g, 123.35 mmol) solution was taken in round bottom flask (R.B) containing 80 mL of THF. 8.00 g (95.10 mmol) of cyclopentanone **4** was added drop wise to the stirred solution and stirred for at least 15 minutes at room temperature. The reaction mixture was cooled for 5-10 minutes under ice-water bath. 23.44 g (104.61 mmol) of triethyl phosphonoacetate was added slowly drop wise using a syringe to the stirred reaction mixture about 15-20 minutes. After 10 minutes, the reaction mixture was allowed to room temperature for 1 h. After 1 h, water (80 mL) was added to the reaction mixture and the crude product was

extracted with petroleum ether (3 × 80 mL). The combined organic phase was washed with brine (2 × 80 mL) and dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield **5**. Purification was done by silica gel column (100-200 mesh) using diethyl ether and hexane (0.4 : 9.6) as eluent. **5** was obtained as colorless oil. Yield = 13.92 g, 95%. FT-IR (KBr): $\tilde{\upsilon}$ = 2980, 2933, 2856, 1715, 1650, 1447, 1271, 1156 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (s, 1H), 4.12 (q, J = 7.08 Hz, 2H), 2.74 (t, J = 6.72 Hz, 2H), 2.41 (t, J = 6.84 Hz, 2H), 1.77-1.59 (m, 4H), 1.24 (t, J = 7.08 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 169.10, 167.03, 111.16, 59.51, 36.04, 32.71, 26.53, 25.60, 14.48 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_9H_{14}O_2Na$ 177.0891; found 177.0910.

Synthesis of ethyl 2-(1-(nitromethyl)cyclopentyl)acetate 6:

At first, a condenser (without water circulation) was set to a two-neck round bottom flask. 7.42 g (70.00 mmol) of sodium carbonate was taken and immediately purged with argon gas balloon. To this reaction mixture, 60 mL of dry DMSO was added and warmed the reaction mixture for 2 h at 100 °C. Then, a mixed solution of 10.78 g (70.00 mmol) of **5** and 6.40 g (105 mmol) of nitromethane was added slowly drop wise using a syringe about 30 minutes and heating was continued for 3 h. The reaction progress was monitor by TLC (diethyl ether : hexane 1 : 9). After completion of the reaction, it was allowed to room temperature and cooled on an ice-water bath. Then it was diluted with ice-cold water and acidified with concentrated hydrochloric acid. It was extracted with petroleum ether (3 × 50 ml) and the combined extractions was dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield **6**. Purification was done by silica gel column (100-200 mesh) using diethyl ether and hexane (1 : 9) as eluent.

6 was obtained as oil (11.12 g, 74%): FT-IR (KBr): $\tilde{\upsilon}$ = 2962, 2876, 1731, 1550, 1377, 1183 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.61 (S, 2H), 4.14 (q, J = 7.12 Hz, 2H), 2.55 (s, 2H), 1.75-

1.55 (m, 8H), 1.26 (t, J = 7.04 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.52, 81.33, 60.55, 40.80, 40.58, 36.35, 24.17, 14.30 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{10}H_{17}NO_4Na$ 238.1055; found 238.1077.

Synthesis of 2-azaspiro[4.4]nonan-3-one 7:

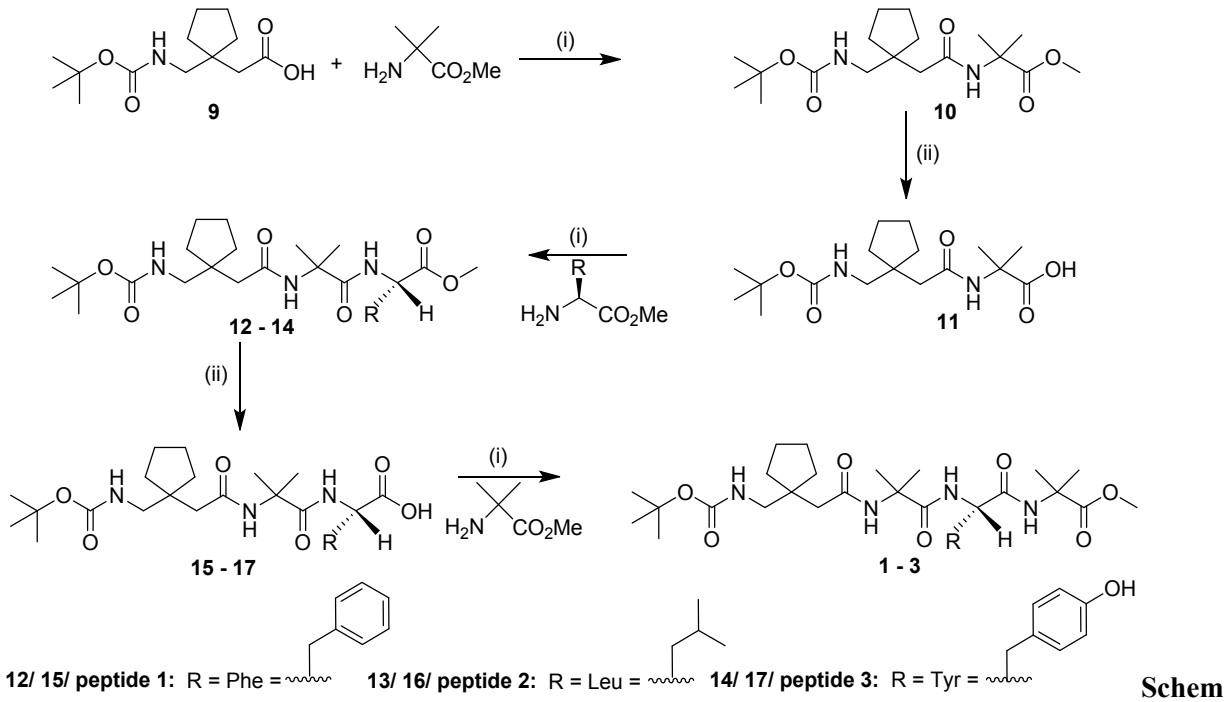
10% Pd/C (15 mol%) was taken in a round bottom flask, and the flask was purged with argon gas for 5 minutes. 8.60 g (40.00 mmol) of **6** dissolved in methanol (70 mL) was poured into the flask. The flask was evacuated and a hydrogen gas bladder was fixed to the flask. The reaction was stirred at room temperature for 48 h. After the completion of reaction, the catalyst was removed by filtration through celite. The filtrate was evaporated in vacuo to yield **7** as brownish red color oil. To this, dichloromethane was added (40 mL) and washed with 1N HCl (20 mL). The obtained dichloromethane was evaporated in vacuo to get **7** and purified by column chromatography using ethyl acetate and toluene (4 : 6) as eluent. **7** was obtained as white crystalline solid. Yield = 5.11 g, 92%. FT-IR (KBr): $\tilde{\upsilon}$ = 3417, 2952, 2867, 1680, 1486, 1251, 1064 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (bs, 1H), 3.49 (s, 2H), 2.33 (s, 2H), 1.73-1.55 (m, 8H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.97, 60.76, 41.92, 41.71, 39.21, 23.71 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_8H_{13}NONa$ 162.0895; found 162.0823.

Synthesis of 2-(1-(aminomethyl)cyclopentyl)acetic acid hydrochloride 8:

4.50 g (32.35 mmol) of **7** was dissolved in a mixture of 1,4-dioxane (15 mL) : 6N HCl (45 mL). The reaction mixture was refluxed for 6 h. After 6h, the reaction mixture was cooled to room temperature. It was diluted with water and washed with dichloromethane (2 × 30 mL) to recover unreacted **7** lactam. The aqueous phase evaporated in vacuo and acetone was added to the residue. After few minutes **8** was crystallize out. Yield = 4.36 g, 70% . FT-IR (KBr): $\tilde{\upsilon}$ = 3408, 3170, 2955, 1713, 1613, 1524, 1203, 1175 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.28 (bs,

1H), 8.09 (bs, 3H), 2.90 (s, 2H), 2.42 (s, 2H), 1.61-1.44 (m, 8H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.06, 45.03, 43.01, 38.89, 35.11, 23.88 ppm. HRMS (ESI-TOF) *m/z*: $(M + H)^+$ calcd for $C_8H_{16}NO_2$ 158.1176; found 158.1150.

Synthesis of Peptides



Scheme S1. Chemical structures and synthetic scheme of peptides. Reagents and conditions: (i) DCC, HOBt, DMF; (ii) 2N NaOH, MeOH.

Boc-Gbn-OH 9: 4.0 g (20.71 mmol) of Gababutin hydrochloride **8** was added to a mixture of 1,4-dioxane : water (2:1 35 mL) and neutralized with 1M NaOH (30 mL). This mixture was stirred and cooled in an ice-water bath (the pH should be above 8). After 15 minutes, 4.98 g (22.78 mmol) of di-*tert*-butylpyrocarbonate was added and stirred overnight at room temperature. The solution was concentrated under vacuo to about 10-15 mL and it was cooled for 5 minutes in an ice-water bath. The cooled solution was covered with a layer of ethyl acetate (about 30 mL) and acidified with 1M $KHSO_4$ to pH 2-3. It was extracted with ethyl acetate (3 ×

30 mL). The extracted ethyl acetate was dried over anhydrous Na_2SO_4 and evaporated in vacuo to yield **9** as white solid.

Yield = 5.06 g, 95%. FT-IR (KBr): $\tilde{\upsilon}$ = 3385, 2962, 1724, 1666, 1542, 1255 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 6.78 (m, 1H, NH of Gbn), 2.96 (d, J = 5.48 Hz, 2H, $C^{\gamma}Hs$ of Gbn), 2.19 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.55-1.49 (m, 4H), 1.45-1.40 (m, 4H), 1.36 (m, 9H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.51, 156.42, 77.68, 46.82, 45.42, 41.54, 34.41, 28.36, 24.45 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{13}H_{23}NO_4Na$ 280.1525; found 280.1602.

General Procedure for Methyl ester Hydrolysis:

Terminally protected dipeptide or tripeptide in methanol (20 mL/g) was taken in a round bottom flask (R.B) and 2N NaOH was added drop wise. The progress of hydrolysis was monitored by thin layer chromatography (TLC). The reaction was allowed for overnight. After completion of the reaction, 15 mL of distilled water was added to the reaction mixture and methanol was removed under vacuum. The aqueous part was washed with diethyl ether (2 × 30 mL). Then aqueous part was cooled under ice-water bath for 15 minutes and then pH was adjusted to 2-3 by drop wise addition of 1M HCl. It was extracted with ethyl acetate (3 × 50 ml). The extracted ethyl acetate was dried over anhydrous Na_2SO_4 and evaporated under vacuum to yield corresponding carboxylic acid which was used for the next step without purification.

General Procedure for Peptide Coupling:

Boc-protected compound (1.0 equiv) was dissolved in dry-DMF (4 mL/g) and stirred on an ice-water bath. Methyl ester protected amino acid was isolated from its corresponding methyl ester hydrochloride (2.0 equiv) by neutralization and subsequently extracted twice with ethyl acetate (2 × 30 mL). The collected ethyl acetate extracts was dried over anhydrous Na_2SO_4 and concentrated to 6-8 mL. It was then added to the pre-cooled reaction mixture followed by

addition of (1.0 equiv) HOBt, (1.1 equiv) dicyclohexylcarbodiimide (DCC). The reaction mixture was allowed to come to room temperature and stirred for 2 days for dipeptide or 3 days for tripeptides or 4 days for tetrapeptides synthesis. After completion of the reaction, ethyl acetate (40 mL) was added to the reaction mixture and dicyclohexylurea or diisopropylurea was filtered off. The organic layer was washed with 1M HCl (3 × 50 mL), brine (2 × 50 mL), 1M sodium carbonate (3 × 50 mL) and brine (2 × 50 mL) and dried over anhydrous Na_2SO_4 and evaporated in a vacuum. The purification was done by using silica gel column (100-200 mesh).

Boc-Gbn(1)-Aib(2)-OMe 10:

10 obtained as white solid. Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene (2 : 8) as eluent. Yield = 5.61 g, 90%. FT-IR (KBr): $\tilde{\upsilon}$ = 3301, 3258, 2933, 1744, 1687, 1645, 1558, 1364, 1285, 1150 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1H, NH of Aib(2)), 5.07 (t, J = 6.48 Hz, 1H, NH of Gbn(1)), 3.71 (s, 3H, OC$\underline{H}_3$), 3.14 (d, J = 7.04 Hz, 2H, C$^{\gamma}$Hs of Gbn), 2.11 (s, 2H, C$^{\alpha}$Hs of Gbn), 1.72-1.66 (m, 4H), 1.52 (s, 6H), 1.44 (s, 9H), 1.40-1.30 (m, 3H), 1.15-1.03 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 75.27, 171.07, 157.37, 79.76, 56.11, 52.47, 49.28, 47.15, 46.83, 43.28, 36.04, 34.08, 28.51, 25.74, 25.08, 23.98 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{18}H_{32}N_2O_5Na$ 379.2209; found 379.2252.

Boc-Gbn(1)-Aib(2)-OH 11:

11 was obtained as white solid. Yield = 4.37 g, 91%. FT-IR (KBr): $\tilde{\upsilon}$ = 3373, 3254, 2980, 1713, 1684, 1623, 1578, 1366, 1253, 1167 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.16 (s, 1H, NH of Aib(2)), 6.80-6.73 (m, 1H, NH of Gbn(1)), 2.92 (d, J = 4.92 Hz, 2H, C$^{\gamma}$Hs of Gbn), 2.01 (s, 2H, C$^{\alpha}$Hs of Gbn), 1.56-1.40 (m, 7H), 1.40-1.34 (m, 11H), 1.30 (s, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.75, 170.54, 156.50, 77.87, 54.75, 46.70, 46.47, 42.74, 34.65, 28.38,

25.00, 24.07 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{17}H_{30}N_2O_5Na$ 365.2052; found 365.2093.

Boc-Gbn(1)-Aib(2)-Phe(3)-OMe 12:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 4:6 as eluent. **12** was obtained as white solid. Yield = 1.64 g, 86%. $[\alpha]_D^{25}$ -1.60 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3424, 3317, 2972, 1760, 1717, 1662, 1508, 1365, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H, NH of Aib (2)), 7.32-7.12 (m, 6H, NH and aromatic protons of Phe (3)), 5.14-5.04 (m, 1H, NH of Gbn (1)), 4.88-4.80 (m, 1H, $C^{\alpha}H$ of Phe), 3.70 (s, 3H, OCH_3), 3.20-3.04 (m, 4H), 2.12 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.74-1.58 (m, 3H), 1.53-1.47 (m, 7H), 1.45-1.33 (m, 14H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.44, 172.22, 171.83, 157.34, 136.32, 129.48, 128.51, 127.00, 79.82, 57.37, 53.56, 52.30, 47.08, 46.80, 43.85, 38.00, 36.03, 35.95, 28.48, 25.25, 25.20, 23.98 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{27}H_{41}N_3O_6Na$ 526.2893; found 526.2961.

Boc-Gbn(1)-Aib(2)-Leu(3)-OMe 13:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 4:6 as eluent. **13** was obtained as white solid. Yield = 1.51 g, 85%. $[\alpha]_D^{25}$ -0.40 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3431, 3310, 2960, 1742, 1688, 1670, 1552, 1364, 1174 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.38 (m, 2H, NH of Leu (3) and Aib(2)), 5.10-4.96 (bs, 1H, NH of Gbn (1)), 4.63-4.52 (m, 1H, $C^{\alpha}H$ of Leu), 3.70 (s, 3H, OCH_3), 3.11 (d, *J* = 5.68 Hz, 2H, $C^{\gamma}Hs$ of Gbn), 2.15 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.72-1.64 (m, 4H), 1.63-1.60 (m, 5H), 1.58-1.52 (m, 8H), 1.44 (s, 9H), 0.92 (d, *J* = 4.92 Hz, 6H, $C^{\delta}Hs$ of Leu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.72, 173.71, 171.99, 157.37, 80.00, 57.62, 52.27, 51.08, 47.11, 46.88, 43.87, 41.50, 36.11, 36.00,

28.50, 25.54, 25.19, 24.92, 24.05, 23.63, 23.00, 22.02 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{24}H_{43}N_3O_6Na$ 492.3050; found 492.3118.

Boc-Gbn(1)-Aib(2)-Tyr(3)-OMe 14:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 5:5 as eluent. **14** was obtained as white solid. Yield = 1.60 g, 81%. $[\alpha]_D^{25}$ -0.08 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3303, 2963, 1746, 1686, 1640, 1517, 1366, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (bs, 1H, NH of Tyr(3)), 7.03 (d, *J* = 7.36 Hz, 2H, ring protons of Tyr), 6.90 (s, 1H, NH of Aib(2)), 6.70 (d, *J* = 7.72 Hz, 2H, ring protons of Tyr), 5.15 (bs, 1H, NH of Gbn(1)), 4.74-4.64 (m, 1H, $C^{\alpha}H$ of Tyr), 3.69 (s, 3H, OCH_3), 3.15-2.98 (m, 2H, $C^{\beta}Hs$ of Tyr), 2.95-2.81 (m, 2H, $C^{\alpha}Hs$ of Gbn), 2.08 (s, 2H, $C^{\gamma}Hs$ of Gbn), 1.67-1.51 (m, 5H), 1.48-1.37 (m, 12H), 1.36-1.06 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.53, 172.07, 171.88, 157.53, 155.53, 130.32, 115.63, 79.99, 57.53, 55.34, 52.28, 46.89, 46.64, 43.21, 36.93, 35.99, 35.56, 31.29, 28.47, 24.03, 23.93, 19.00, 17.97 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{28}H_{43}N_3O_7K$ 558.2582; found 558.2444.

Boc-Gbn(1)-Aib(2)-Phe(3)-OH 15:

15 was obtained as white solid. Yield = 1.04 g, 90%. $[\alpha]_D^{25}$ +3.67 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3414, 3310, 2977, 1720, 1694, 1658, 1517, 1365, 1172 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 1H, NH of Aib (2)), 7.54 (d, *J* = 7.36 Hz, 1H, NH of Phe(3)), 7.28-7.16 (m, 5H, aromatic protons of Phe), 6.86-6.72 (m, 1H, NH of Gbn (1)), 4.46-4.38 (m, 1H, $C^{\alpha}H$ of Phe), 3.08-2.87 (m, 4H), 2.05 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.55-1.50 (m, 4H), 1.43-1.35 (m, 14H), 1.28-1.24 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.94, 172.96, 171.13, 156.46, 137.56, 129.37, 128.21, 126.52, 77.87, 56.04, 53.46, 46.58, 46.22, 43.04, 36.75, 34.90, 34.77, 28.38,

25.12, 24.87, 24.08, 24.03 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{26}H_{39}N_3O_6Na$ 512.2737; found 512.2808.

Boc-Gbn(1)-Aib(2)-Leu(3)-OH 16:

16 was obtained as white solid. Yield = 1.01 g, 95%. $[\alpha]_D^{25}$ −1.00 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3383, 2959, 1718, 1691, 1659, 1535, 1171 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.82 (s, 1H, NH of Aib (2)), 7.64 (d, *J* = 7.8 Hz, 1H, NH of Leu(3)), 6.86-6.75 (m, 1H, NH of Gbn (1)), 4.27-4.16 (m, 1H, $C^{\alpha}H$ of Leu), 2.92 (d, *J* = 4.24 Hz, 2H, $C^{\gamma}Hs$ of Gbn), 2.17-2.01 (m, 2H, $C^{\alpha}Hs$ of Gbn), 1.65-1.48 (m, 7H), 1.41-1.34 (m, 14H), 1.32-1.26 (m, 6H), 0.85-0.78 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.39, 174.14, 170.98, 156.48, 77.88, 55.94, 50.32, 46.14, 42.82, 35.14, 34.98, 28.41, 25.80, 24.44, 24.10, 23.90, 23.13, 21.38 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{23}H_{41}N_3O_6Na$ 478.2893; found 478.2953.

Boc-Gbn(1)-Aib(2)-Tyr(3)-OH 17:

17 was obtained as white solid. Yield = 1.04 g, 90%. $[\alpha]_D^{25}$ +0.07 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3331, 2975, 1719, 1689, 1660, 1518, 1366, 1250, 1170 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.25 (bs, 1H, COO<u>H</u>), 7.93 (s, 1H, NH of Aib(2)), 7.37 (d, *J* = 7.12 Hz, 1H, NH of Tyr (3)), 6.94 (d, *J* = 7.8 Hz, 2H, ring protons of Tyr), 6.80-6.72 (m, 1H, NH of Gbn (1)), 6.61 (d, *J* = 7.72 Hz, 2H, ring protons of Tyr), 4.33-4.26 (m, 1H, $C^{\alpha}H$ of Tyr), 2.93-2.83 (m, 4H), 2.05 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.55-1.48 (m, 5H), 1.43-1.34 (m, 13H), 1.29-1.24 (m, 6H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 173.79, 173.09, 171.15, 156.49, 155.98, 130.38, 127.56, 115.00, 77.90, 56.09, 53.86, 46.58, 46.26, 43.14, 36.07, 34.89, 34.81, 28.40, 25.11, 25.02, 24.09, 24.04, 21.24 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{26}H_{39}N_3O_7Na$ 528.2686; found 528.2765.

Boc-Gbn(1)-Aib(2)-Phe(3)Aib(4)-OMe 1:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 5:5 as eluent. Peptide **1** obtained as white solid. Yield = 0.673 g, 80%. $[\alpha]_D^{25}$ −0.16 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3314, 2980, 1743, 1699, 1651, 1533, 1366, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.8 (s, 1H, NH of Aib(2)), 7.4 (s, 1H, NH of Aib(4)), 7.30-7.15 (m, 5H, aromatic protons of Phe (3)), 6.44 (d, *J* = 8.28 Hz, 1H, NH of Phe), 4.94-4.87 (m, 1H, NH of Gbn(1)), 4.74-4.67 (m, 1H, $C^{\alpha}H$ of Phe), 3.71 (s, 3H, OCH_3), 3.26-3.13 (m, 2H, $C^{\beta}Hs$ of Phe), 3.02-2.97 (m, 2H, $C^{\gamma}Hs$ of Gbn), 2.07-1.99 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.72-1.55 (m, 5H), 1.52-1.49 (m, 3H), 1.47-1.40 (m, 16H), 1.32-1.26 (m, 4H), 1.17-1.10 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.16, 173.94, 172.11, 170.53, 157.52, 137.48, 129.58, 128.63, 126.81, 80.31, 57.01, 56.25, 53.47, 52.42, 47.16, 46.73, 42.97, 36.56, 36.11, 35.81, 28.47, 26.09, 25.34, 24.69, 24.25, 24.00, 23.82 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{31}H_{48}N_4O_7Na$ 611.3421; found 611.3391.

Boc-Gbn(1)-Aib(2)-Leu(3)Aib(4)-OMe 2:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 6:5 as eluent. Peptide **2** obtained as white solid. Yield = 0.707 g, 83%. $[\alpha]_D^{25}$ −4.10 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3313, 2958, 1737, 1699, 1652, 1532, 1365, 1279, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1H, NH of Aib(2)), 7.43 (s, 1H, NH of Aib(4)), 6.81 (d, *J* = 7.32 Hz, 1H, NH of Leu(3)), 4.96-4.86 (m, 1H, NH of Gbn(1)), 4.48-4.39 (m, 1H, $C^{\alpha}H$ of Leu), 3.68 (s, 3H, OCH_3), 3.18-3.03 (m, 2H, $C^{\gamma}Hs$ of Gbn), 2.22-2.07 (m, 2H, $C^{\alpha}Hs$ of Gbn), 1.93-1.83 (m, 1H), 1.71-1.59 (m, 8H), 1.56-1.43 (m, 22H), 1.41-1.31 (m, 1H), 0.95-0.85 (m, 6H, $C^{\delta}Hs$ of Leu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.25, 174.23, 172.18, 171.83, 157.36, 80.24, 57.18, 56.16, 52.40, 51.77, 47.05, 42.91, 39.71, 36.22, 36.00, 28.51, 26.50, 25.52, 25.16, 24.65, 24.39, 24.00,

23.76, 23.46, 21.34 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{28}H_{50}N_4O_7Na$ 577.3577; found 577.3657.

Boc-Gbn(1)-Aib(2)-Tyr(3)Aib(4)-OMe 3:

Purification was done by silica gel column (100-200 mesh) using ethyl acetate and toluene 7:3 as eluent. Peptide **3** obtained as white solid. Yield = 0.653 g, 78%. $[\alpha]_D^{25}$ −3.80 (*c* 1, MeOH). FT-IR (KBr): $\tilde{\upsilon}$ = 3314, 2980, 1743, 1699, 1651, 1533, 1271, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1H, NH of Aib(2)), 7.34 (s, 1H, NH of Aib(4)), 7.08 (d, *J* = 7.4 Hz, 2H, ring protons of Tyr (3)), 6.73 (d, *J* = 7.4 Hz, 2H, ring protons of Tyr), 6.38 (d, *J* = 7.8 Hz, 1H, NH of Tyr), 5.04 (bs, 1H, OH of Tyr) 4.90 (t, J = 5.84 Hz, 1H, NH of Gbn (1)), 4.67-4.60 (m, 1H, $C^{\alpha}H$ of Tyr), 3.72 (s, 3H, OCH_3), 3.24-3.19 (m, 1H, $C^{\beta}H$ of Tyr), 3.08-2.94 (m, 3H), 2.03 (s, 2H, $C^{\alpha}Hs$ of Gbn), 1.68-1.60 (m, 3H), 1.50-1.48 (m, 6H), 1.48-1.42 (m, 16H), 1.36-1.32 (m, 3H), 1.15-1.12 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.31, 174.12, 172.34, 170.74, 157.61, 155.28, 130.76, 128.57, 115.71, 80.34, 57.11, 56.34, 53.68, 52.48, 47.19, 46.78, 43.19, 36.19, 35.78, 28.51, 26.33, 25.37, 24.66, 24.25, 24.10, 23.92, 23.62 ppm. HRMS (ESI-TOF) *m/z*: $(M + Na)^+$ calcd for $C_{31}H_{48}N_4O_8Na$ 627.3370; found 627.3456.

X-ray Crystallography

Crystallographic data for peptides **1-3** were collected on a Rigaku FRX microfocus rotating anode (3kW) at the copper Kα edge equipped with a Dectris Pilatus 200K hybrid detector. Data for peptides **2** and **3** was processed with the CrystalClear suite version 2.1b25. Data for peptide **1** was processed with CrysAlisPro version 1.171. All structures were solved with SHELXT and refined using SHELXL 2014 version.[S2] Full-matrix least-squares refinement were performed on F^2 for all unique reflections, minimizing $w(Fo^2 - Fc^2)^3$, with anisotropic displacement parameters for non-hydrogen atoms. All H atoms found in difference electron-density maps were refined

freely, all the other were treated as riding on their parent C or N atoms. Data statistics are reported in the Table S4 and cif files. Crystallographic data of peptides **1**-**3** have been deposited with the CCDC: CCDC 1542080 (peptide **1**), CCDC 1542088 (peptide **2**), and CCDC 1542089 (peptide **3**).

Field emission scanning electron microscopic (FE-SEM) study

Peptide sample preparation in MeOH : water and THF : water

Peptide solutions were prepared by mixing of 1.76 mg of peptide **1**, 1.66 mg of peptide **2** and 1.8 mg of peptide **3** respectively in 0.5 mL of methanol/tetrahydrofuran in individual vials. Peptides were completely dissolved by shaking. Chilled (~8 °C) distilled water (Milli-Q water) was added to 0.5 mL of peptide solutions (a white turbidity was formed immediate after water addition) to set the final peptide concentration to 3 mmol L^{-1} and allowed to stand at room temperature for 30 minutes and used for SEM and AFM analysis. A 100 μL of prepared self-assembled peptide aggregate solutions was drop cast on clean and dried glass slides and then kept in refrigerator for 3 hours. The glass slides with samples were allowed to dry in air at room temperature and coated with gold followed by SEM measurements. Field emission scanning electron microscopic study was performed on Carl Zeiss Microscope (model-Supra 55).

Atomic Force Microscopic (AFM) study

The above prepared self-assembled peptide aggregates were also used for tapping-mode AFM analysis. A 50 μL dilute dispersed solution of self-assembled peptide aggregate was drop-casted on mica and kept in refrigerator for 3 hours. These mica cover slips with samples were dried by slow evaporation in air at room temperature. Finally, images were obtained using a scanning probe microscope AIST-NT instrument (model no.: smart SPM-1000).

^{1}H and ^{13}C NMR spectral data

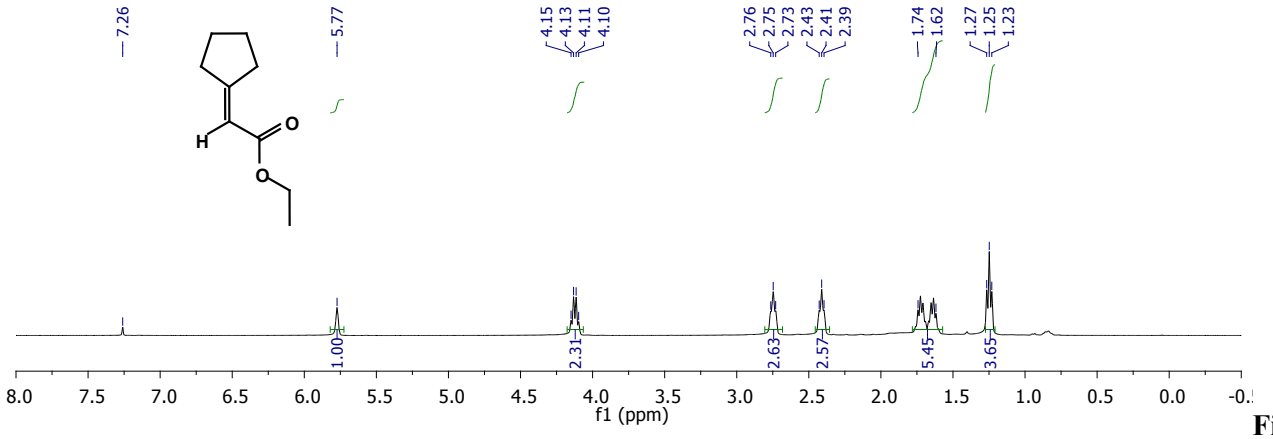


Fig. S18 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of compound **5**.

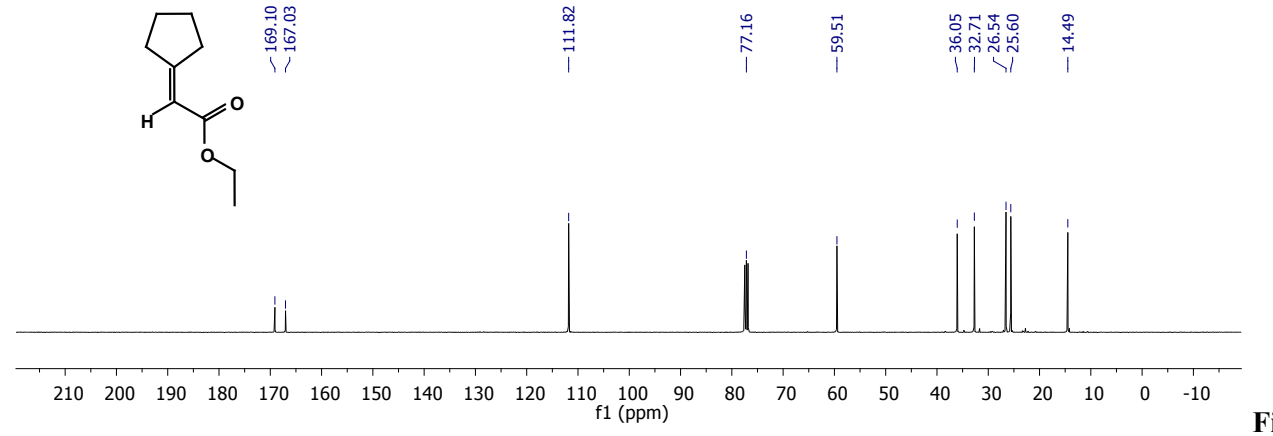


Fig. S19 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of compound **5.**

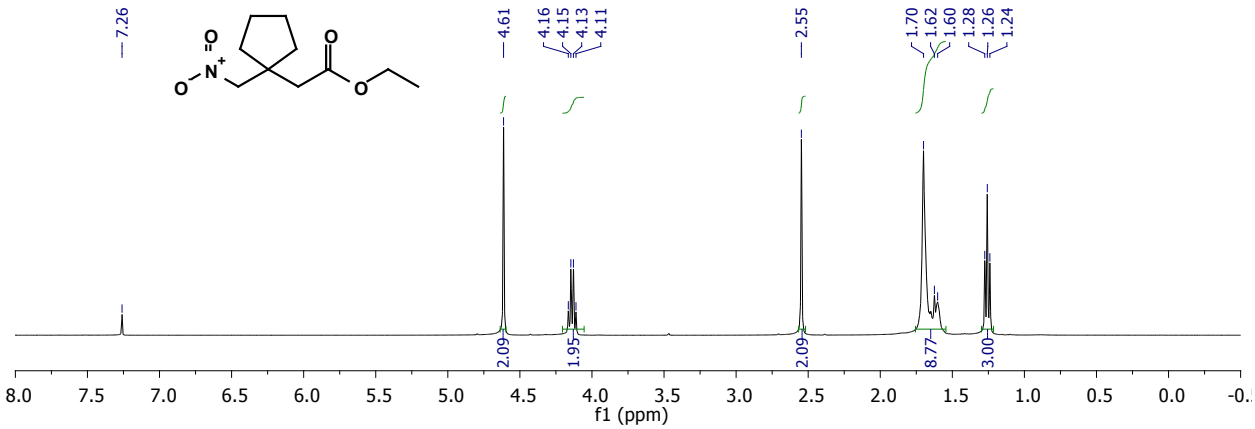


Fig. S20 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of compound **6**.

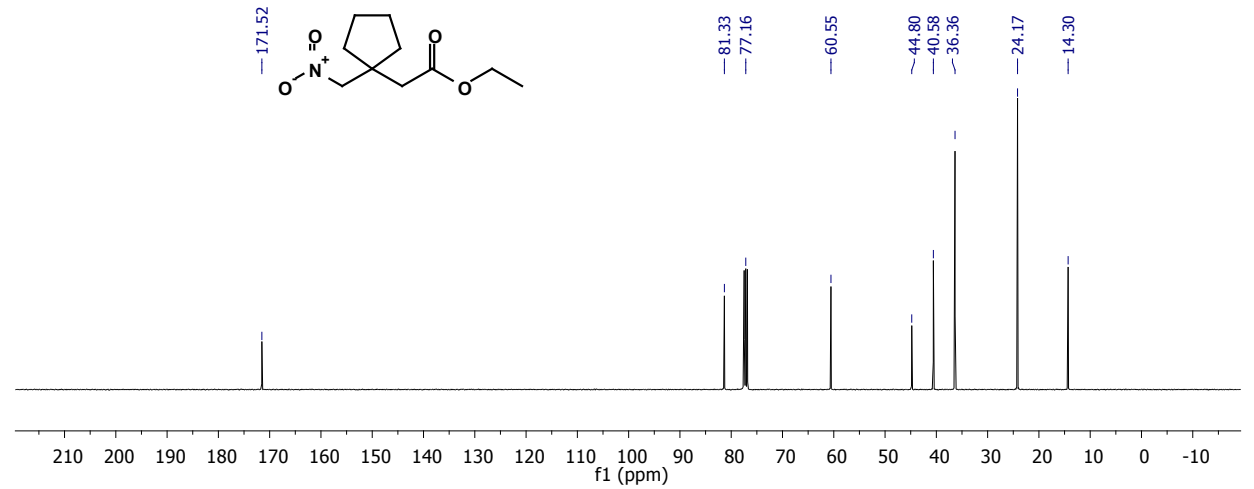


Fig. S21 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of compound **6**.

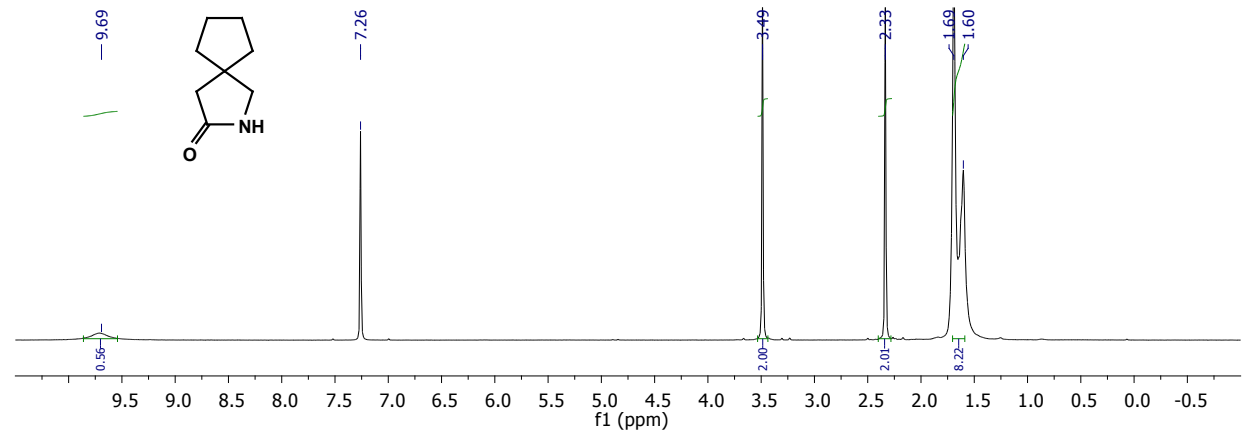


Fig. S22 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of compound **7**.

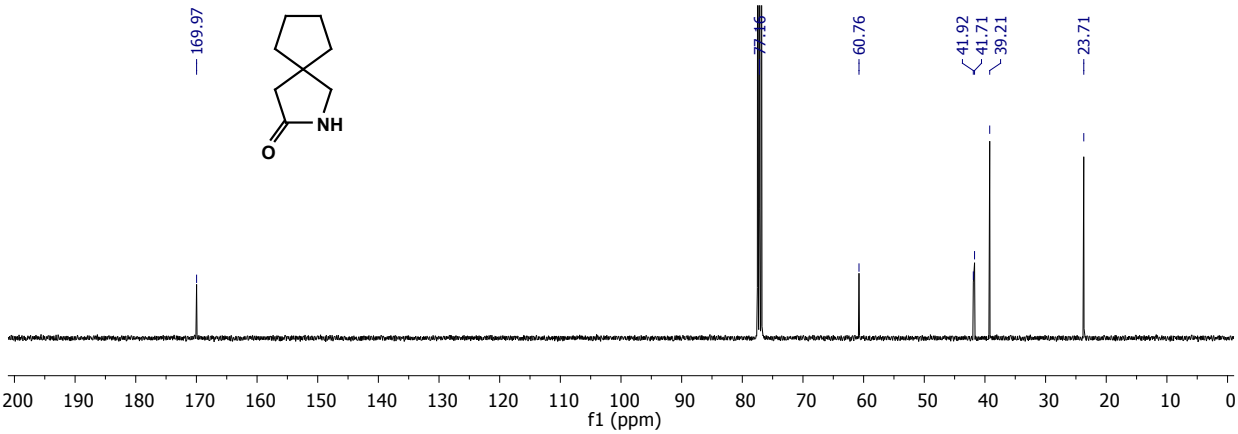


Fig. S23 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of compound **7**.

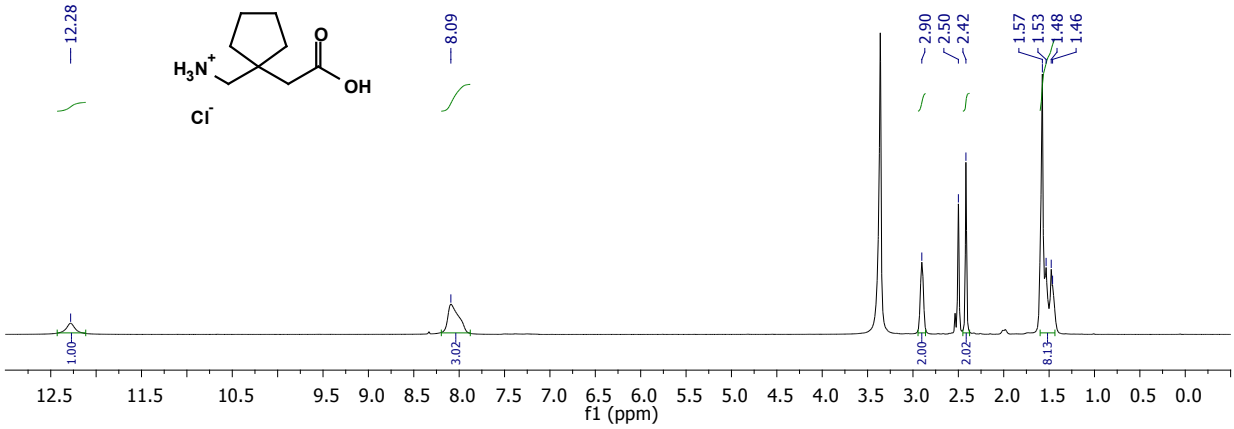


Fig. S24 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of compound **8**.

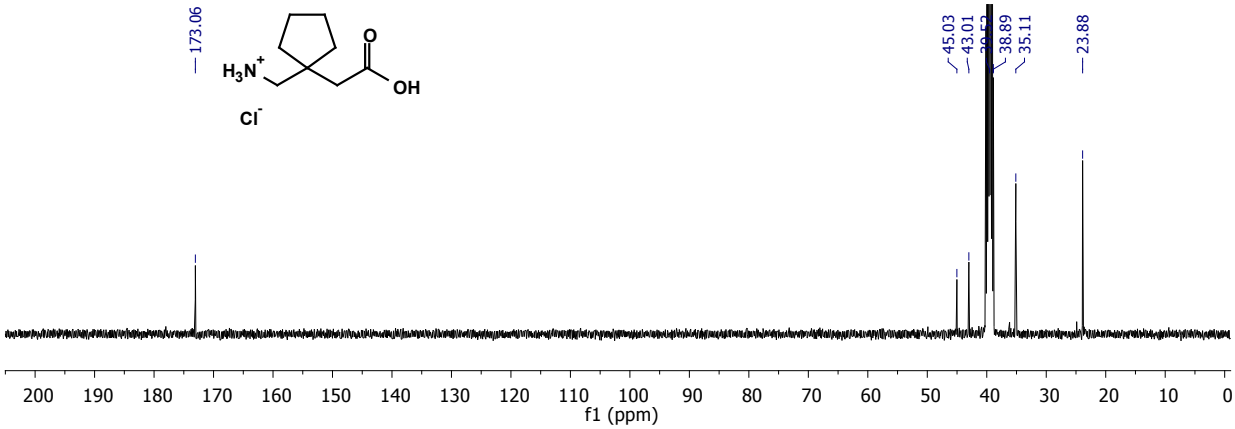


Fig. S25 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of compound **8**.

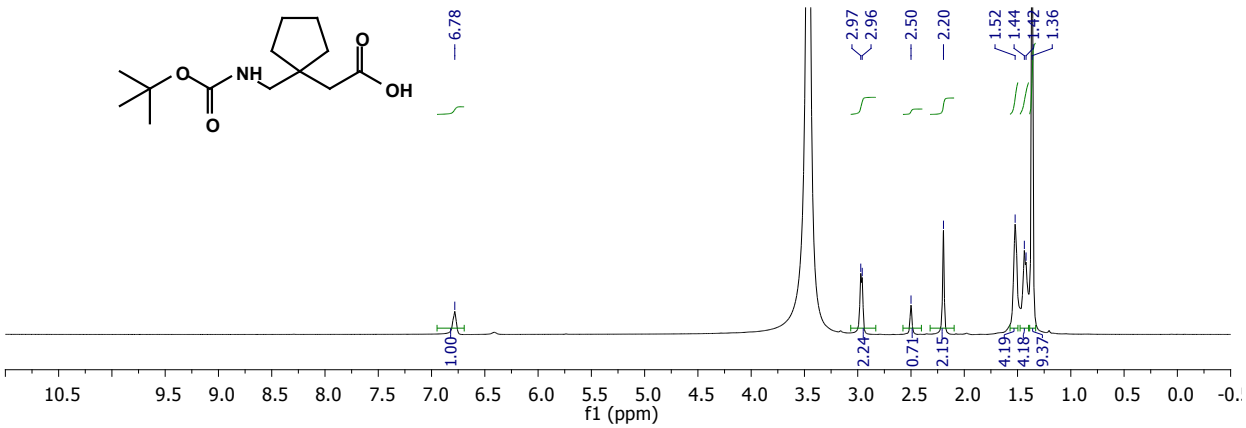


Fig. S26 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of Boc-Gbn(1)-OH **9**.

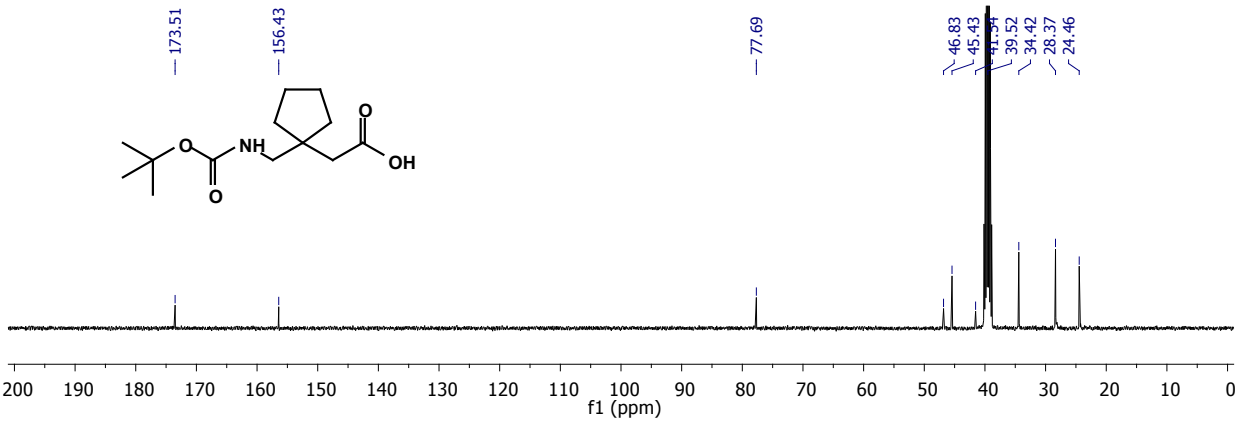


Fig. S27 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of Boc-Gbn(1)-OH **9**.

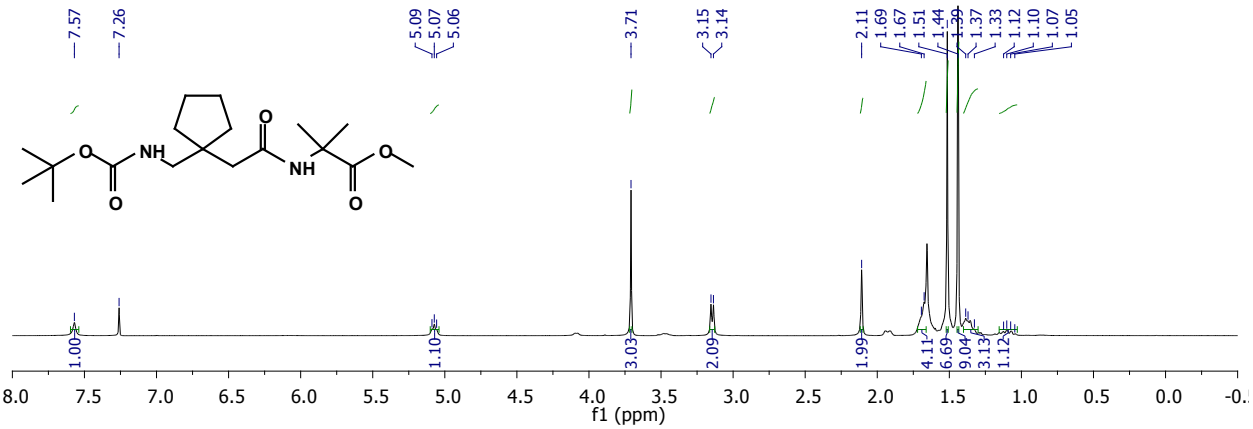


Fig. S28 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-OMe **10**.

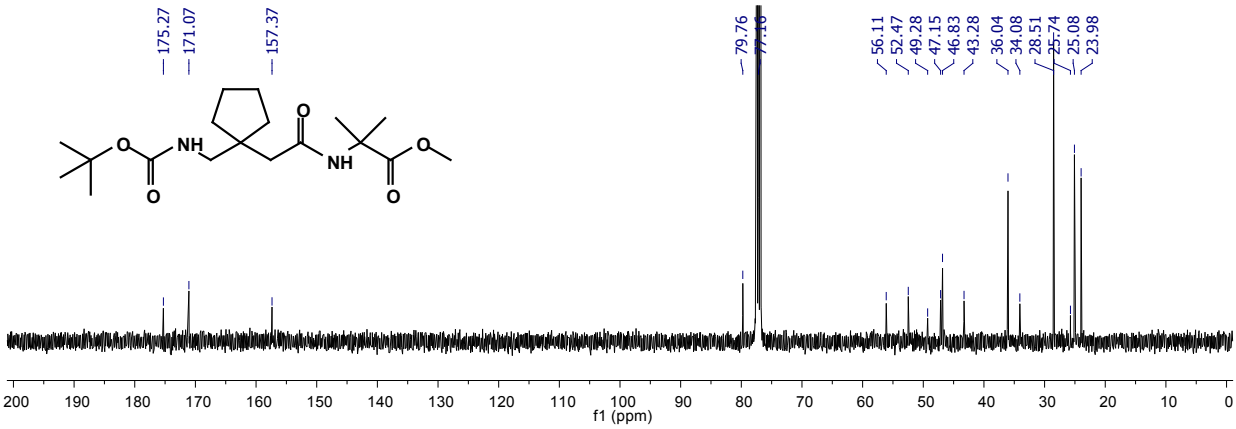


Fig. S29 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-OMe **10**.

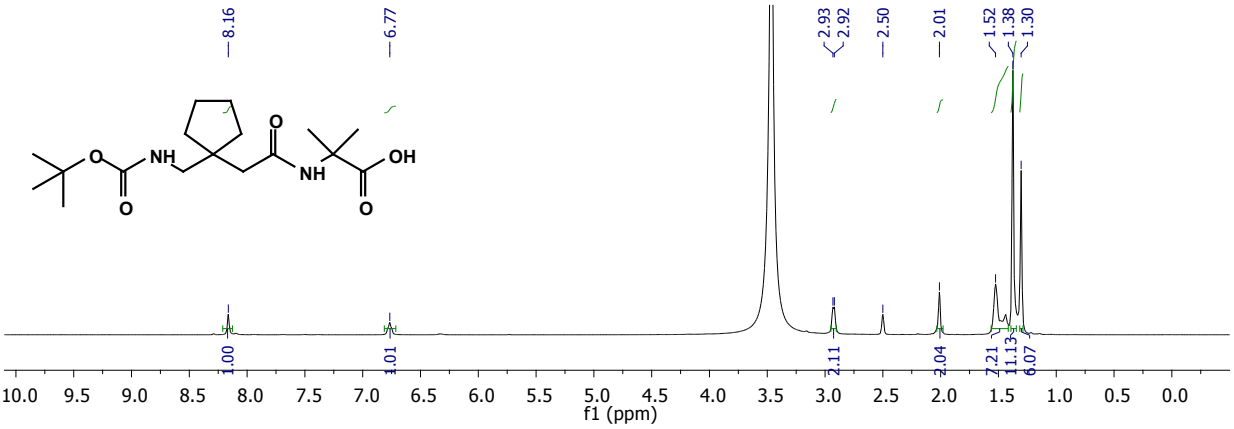


Fig. S30 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-OH **11**.

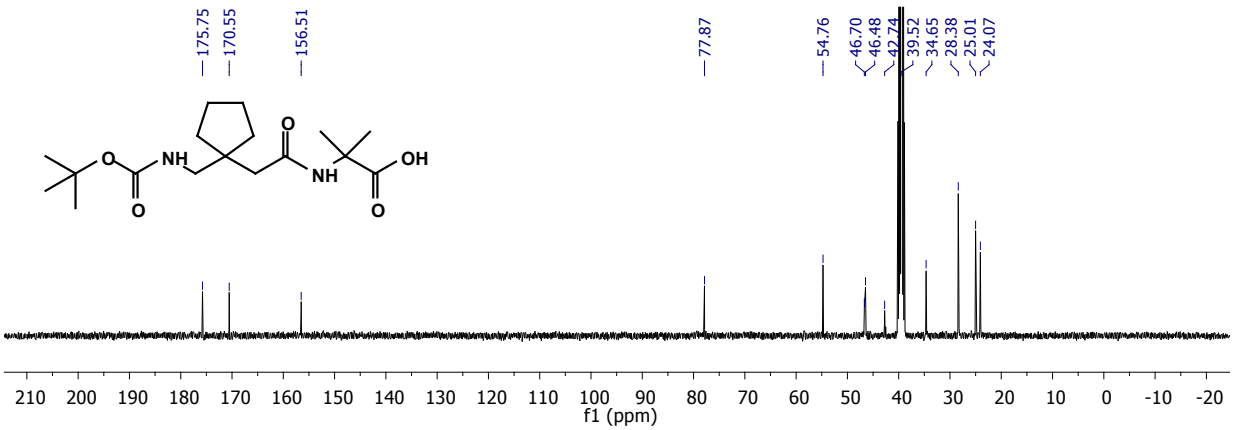


Fig. S31 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-OH **11**.

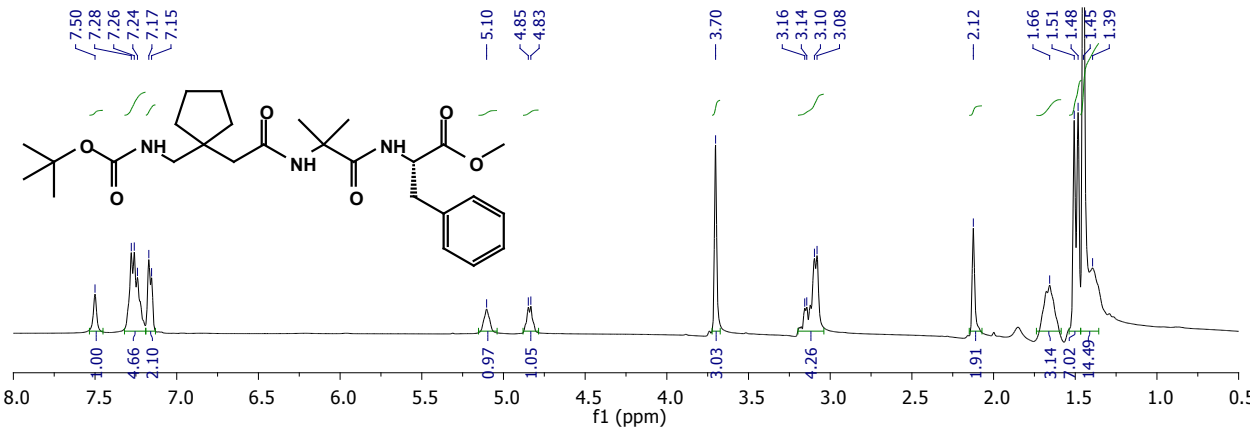


Fig. S32 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Phe(3)-OMe **12**.

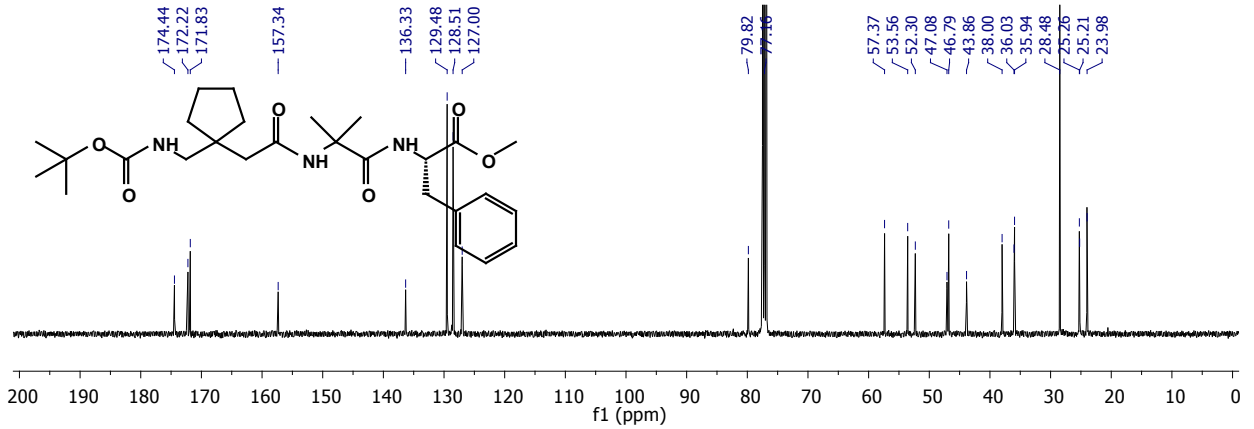


Fig. S33 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Phe(3)-OMe **12**.

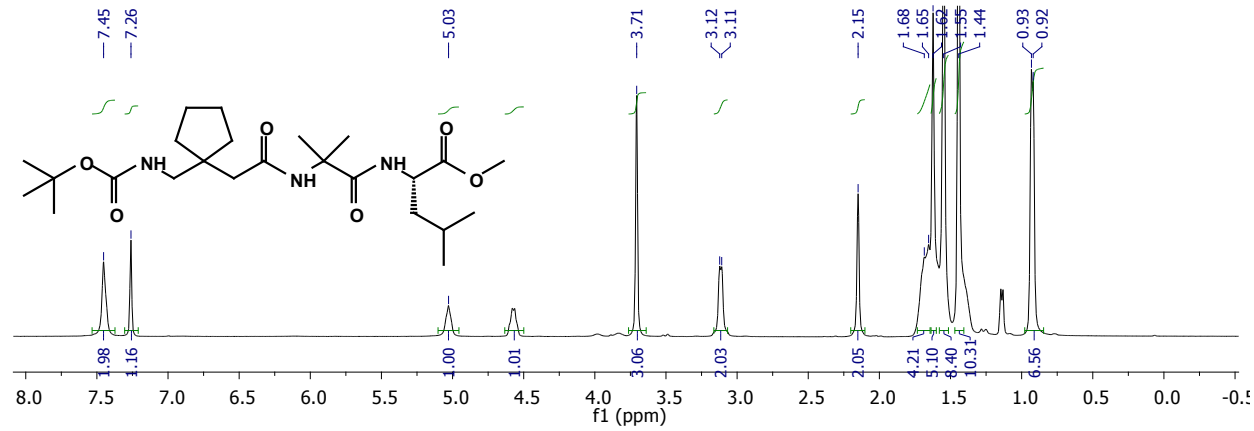


Fig. S34 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Leu(3)-OMe **13**.

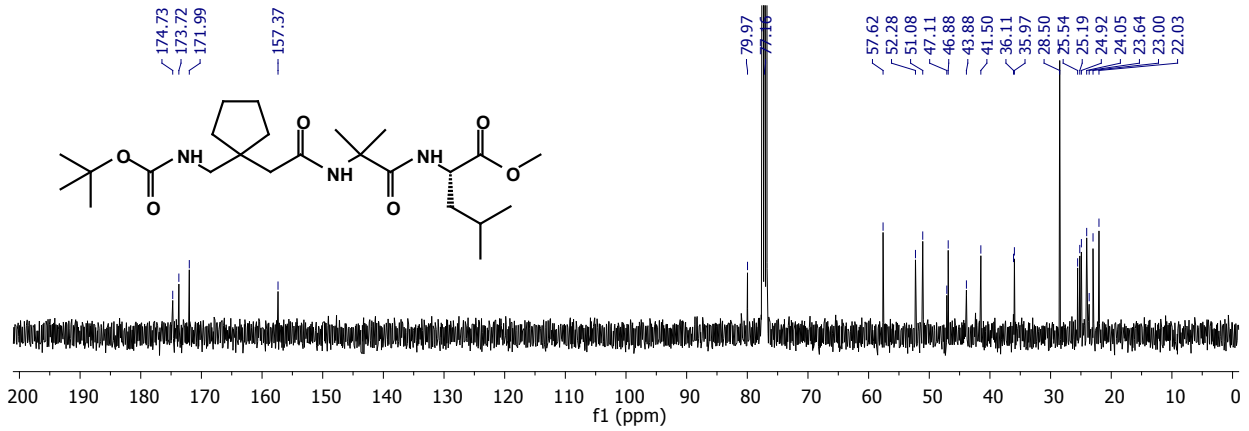


Fig. S35 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Leu(3)-OMe **13**.

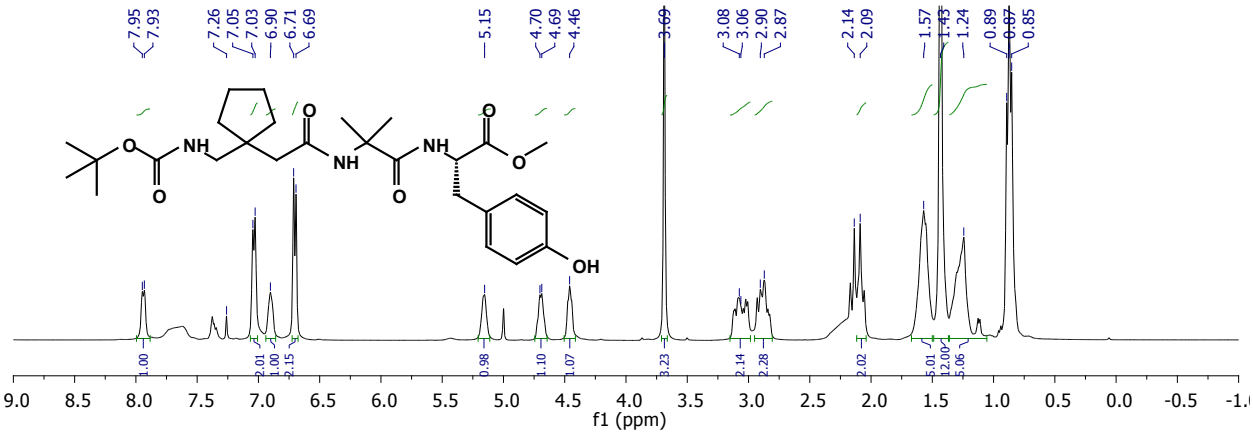


Fig. S36 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Tyr(3)-OMe **14**.

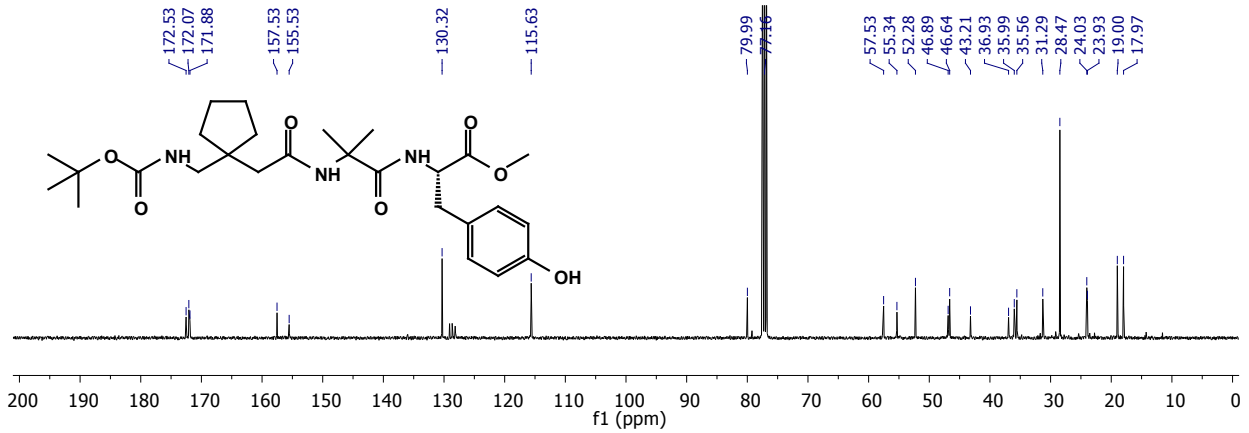


Fig. S37 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Tyr(3)-OMe **14**.

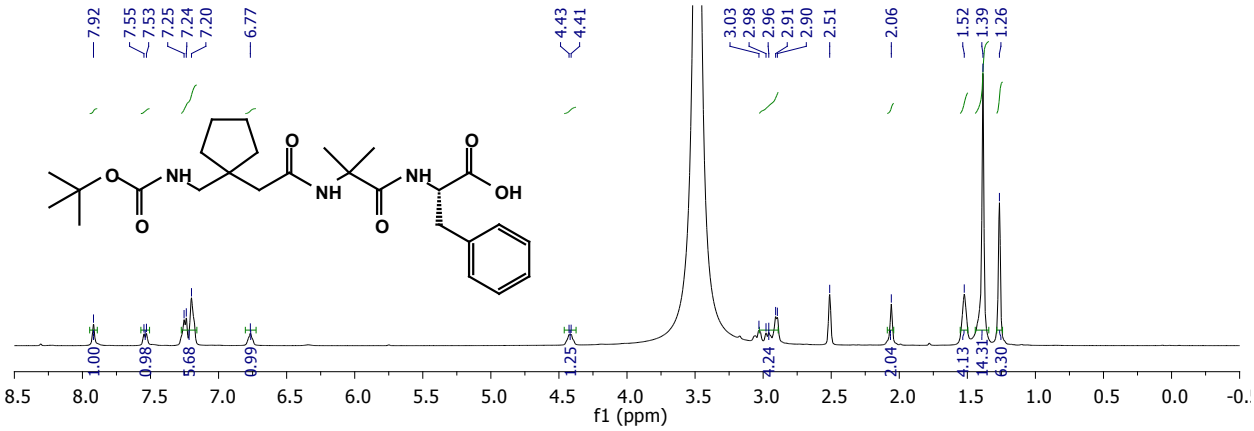


Fig. S38 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Phe(3)-OH **15**.

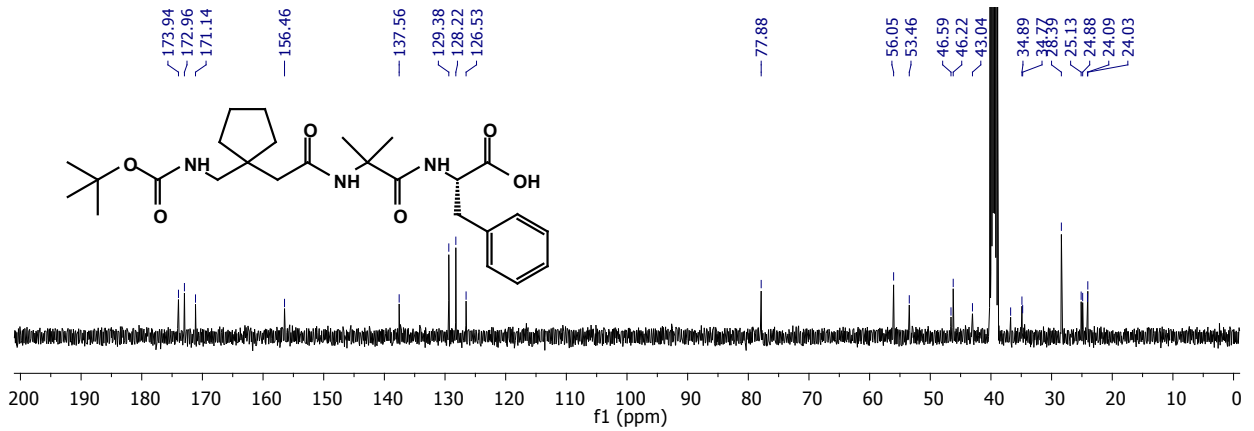


Fig. S39 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Phe(3)-OH **15**.

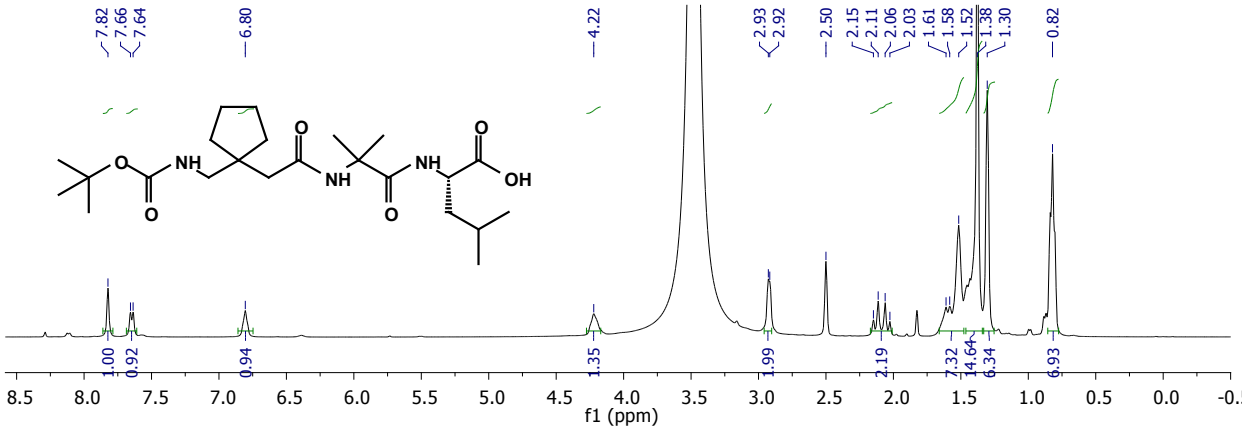


Fig. S40 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Leu(3)-OH **16**.

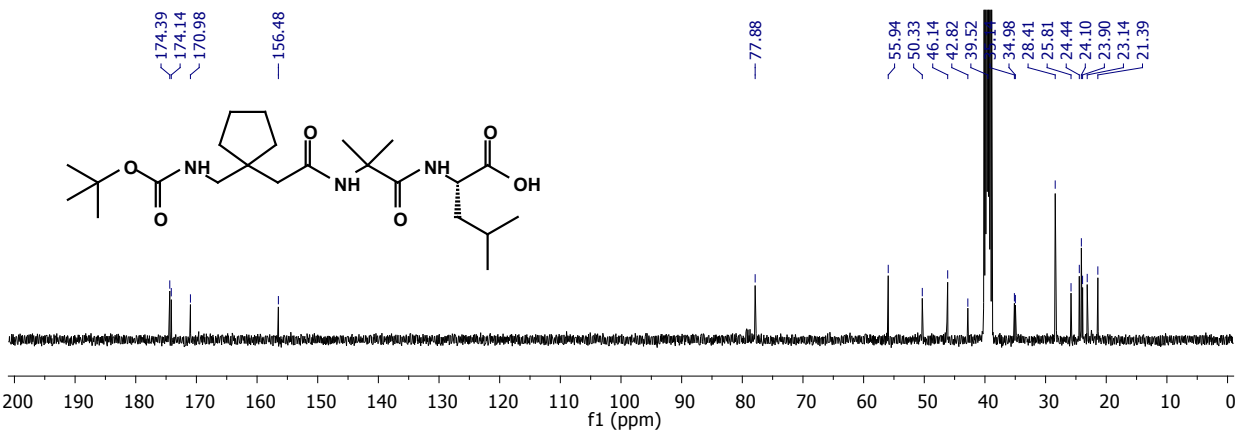


Fig. S41 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Leu(3)-OH **16**.

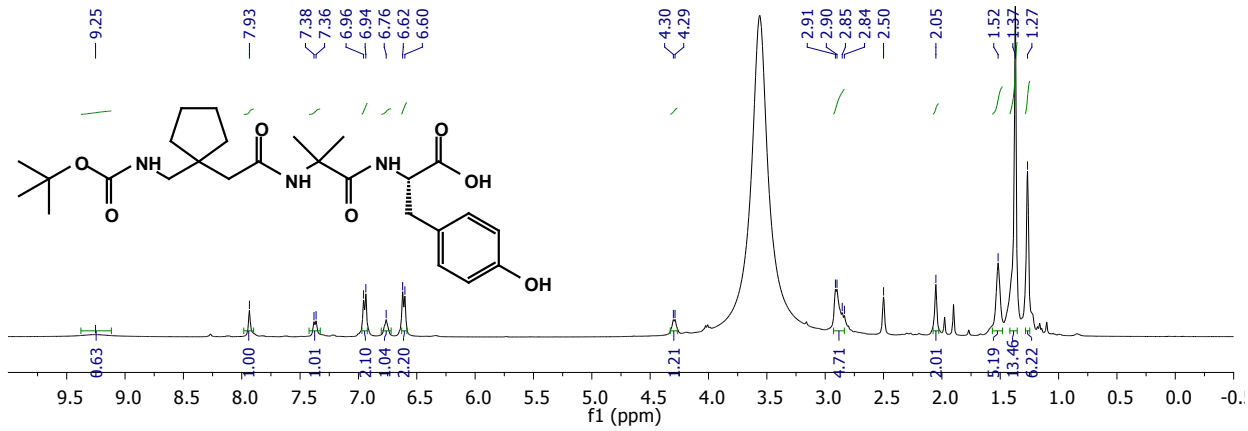


Fig. S42 ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Tyr(3)-OH **17**.

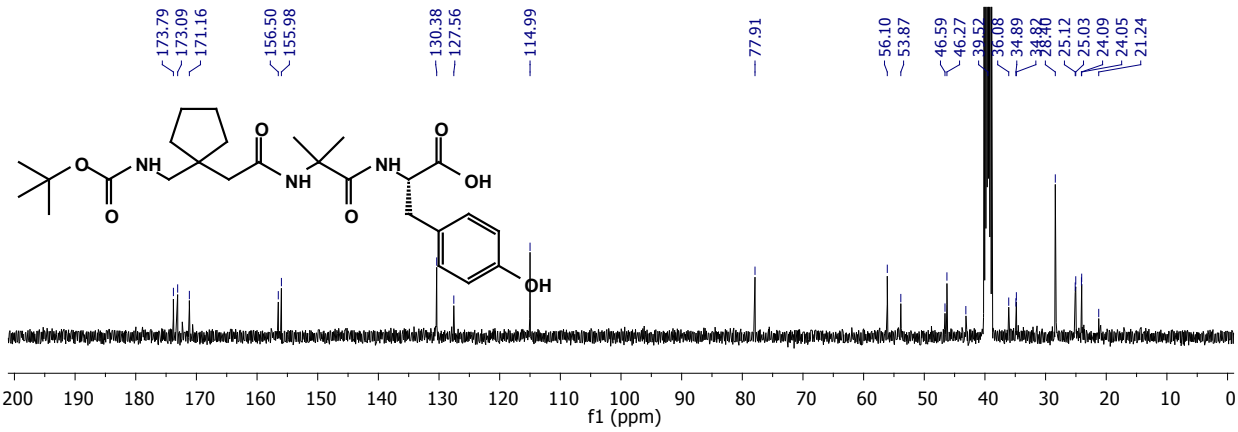


Fig. S43 ^{13}C-NMR spectrum (100 MHz, DMSO-d_6) of Boc-Gbn(1)-Aib(2)-Tyr(3)-OH **17**.

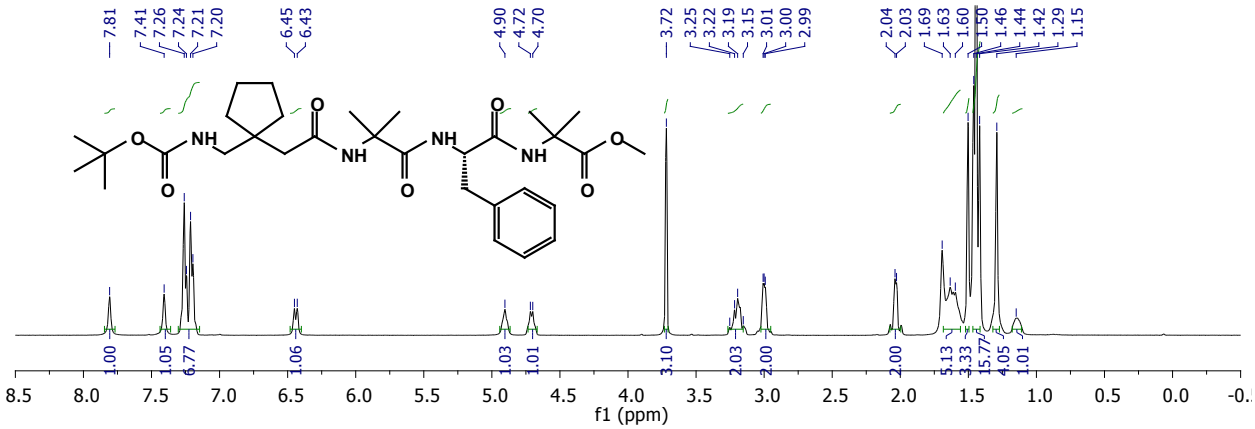


Fig. S44 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Phe(3)-Aib(4)-OMe **1**.

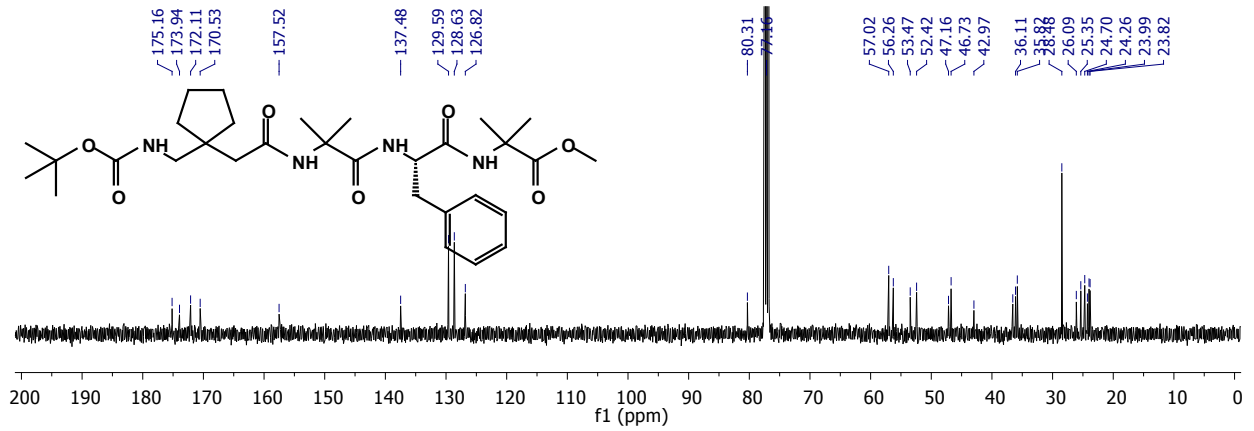


Fig. S45 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Phe(3)-Aib(4)-OMe **1**.

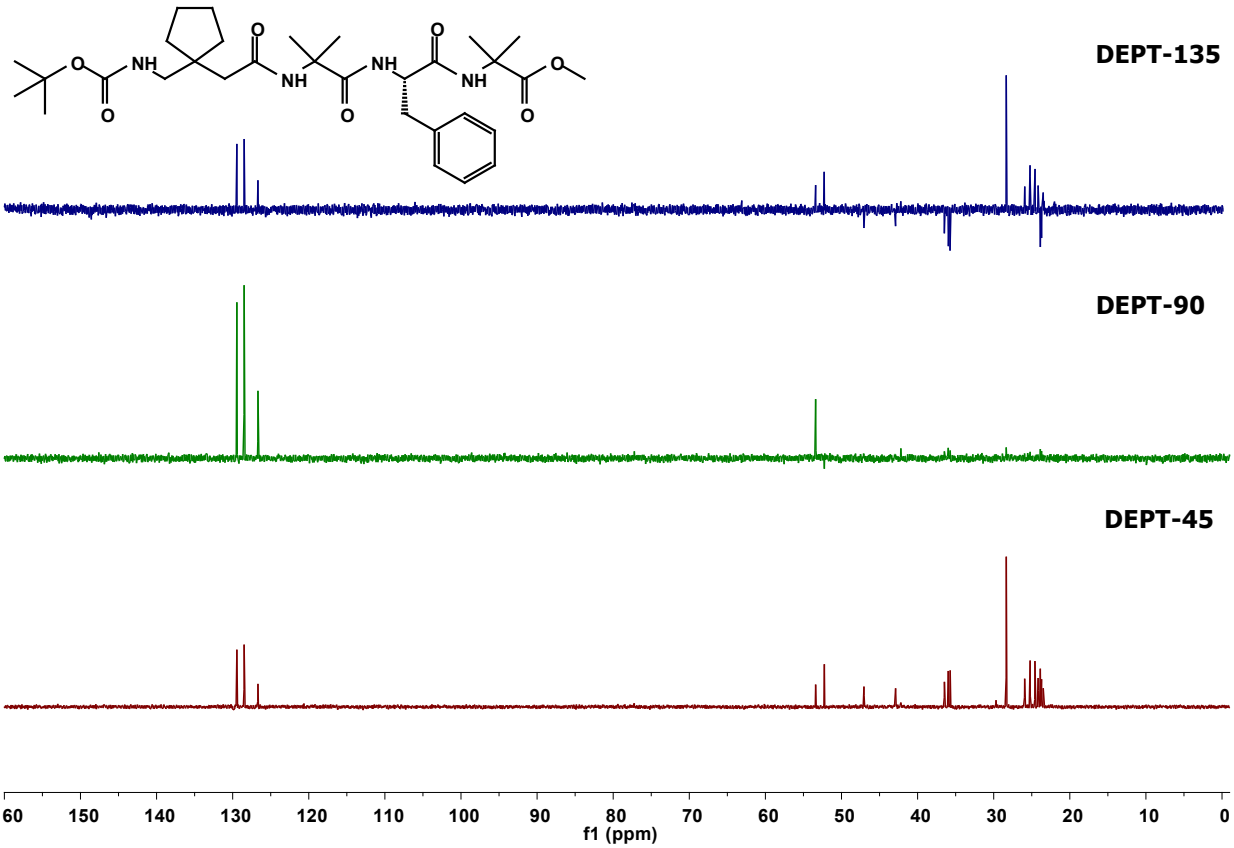


Fig. S46 ^{13}C-DEPT NMR stacked spectra (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Phe(3)-Aib-OMe **1**.

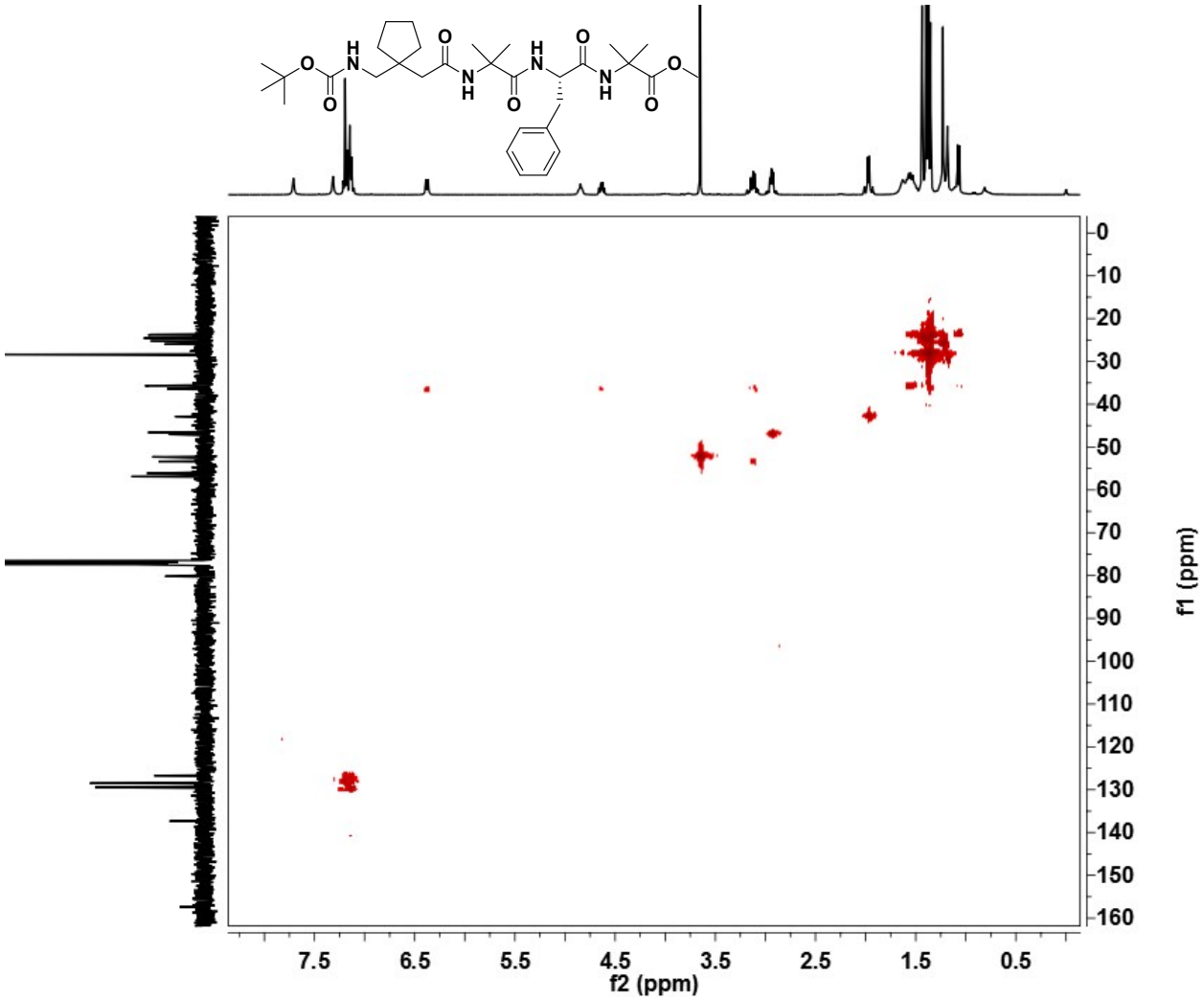


Fig. S47 ^{1}H-^{13}C COSY spectrum of Boc-Gbn(1)-Aib(2)-Phe(3)-Aib-OMe **1** ($CDCl_3$ at 298 K).

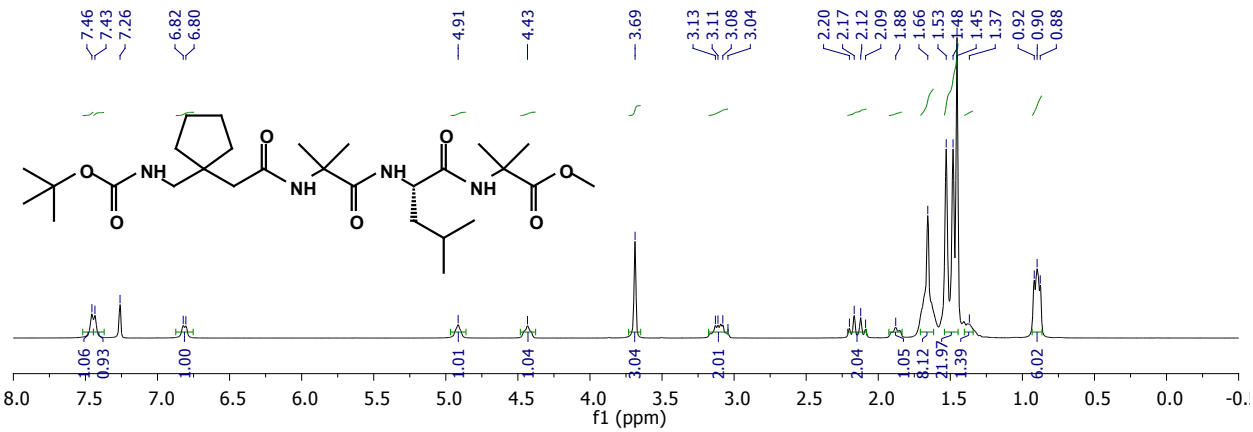


Fig. S48 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Leu(3)-Aib(4)-OMe **2**.

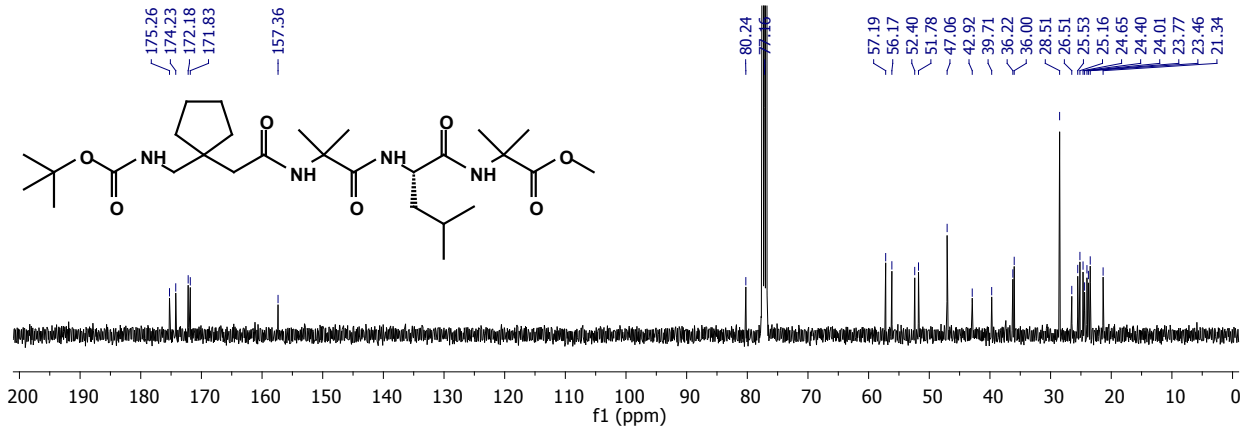


Fig. S49 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Leu(3)-Aib(4)-OMe **2**.

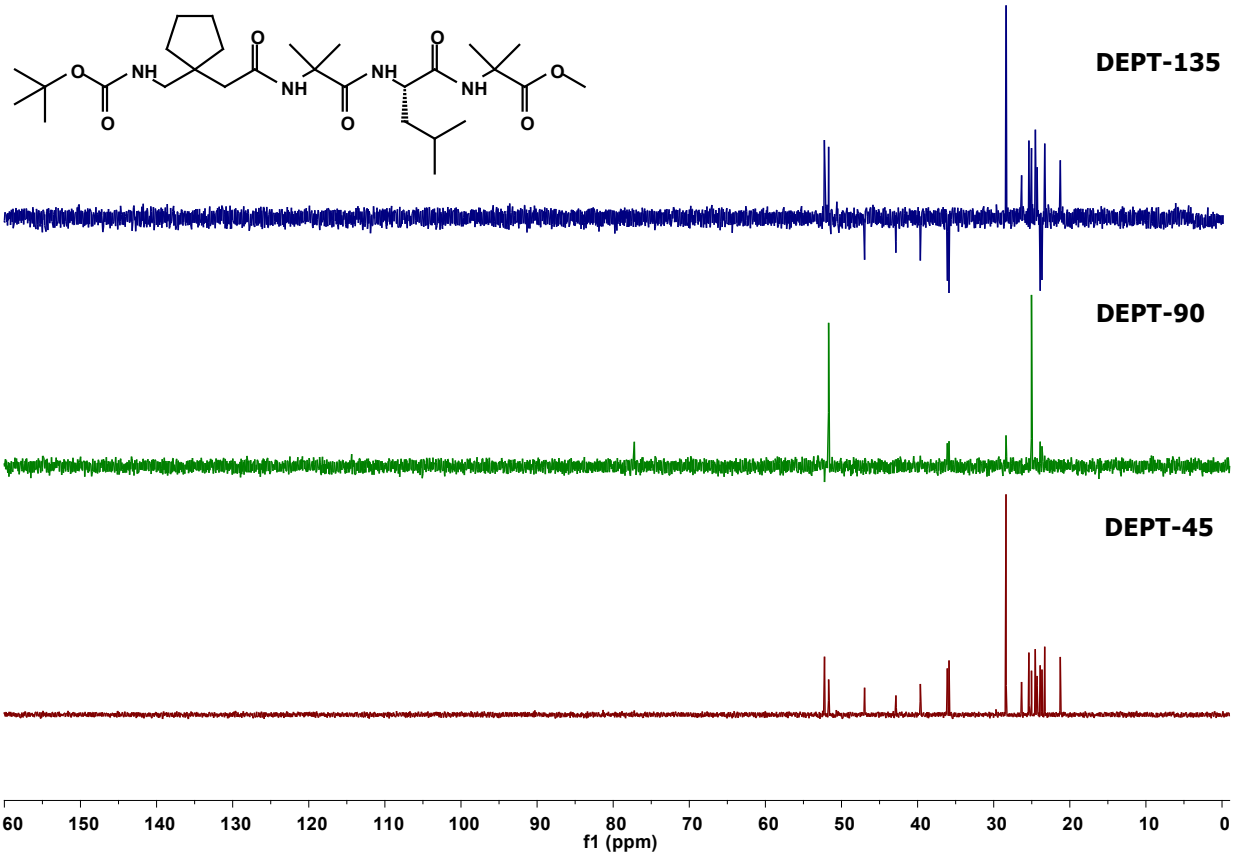


Fig. S50 ^{13}C-DEPT NMR stacked spectra (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Leu(3)-Aib-OMe **2**.

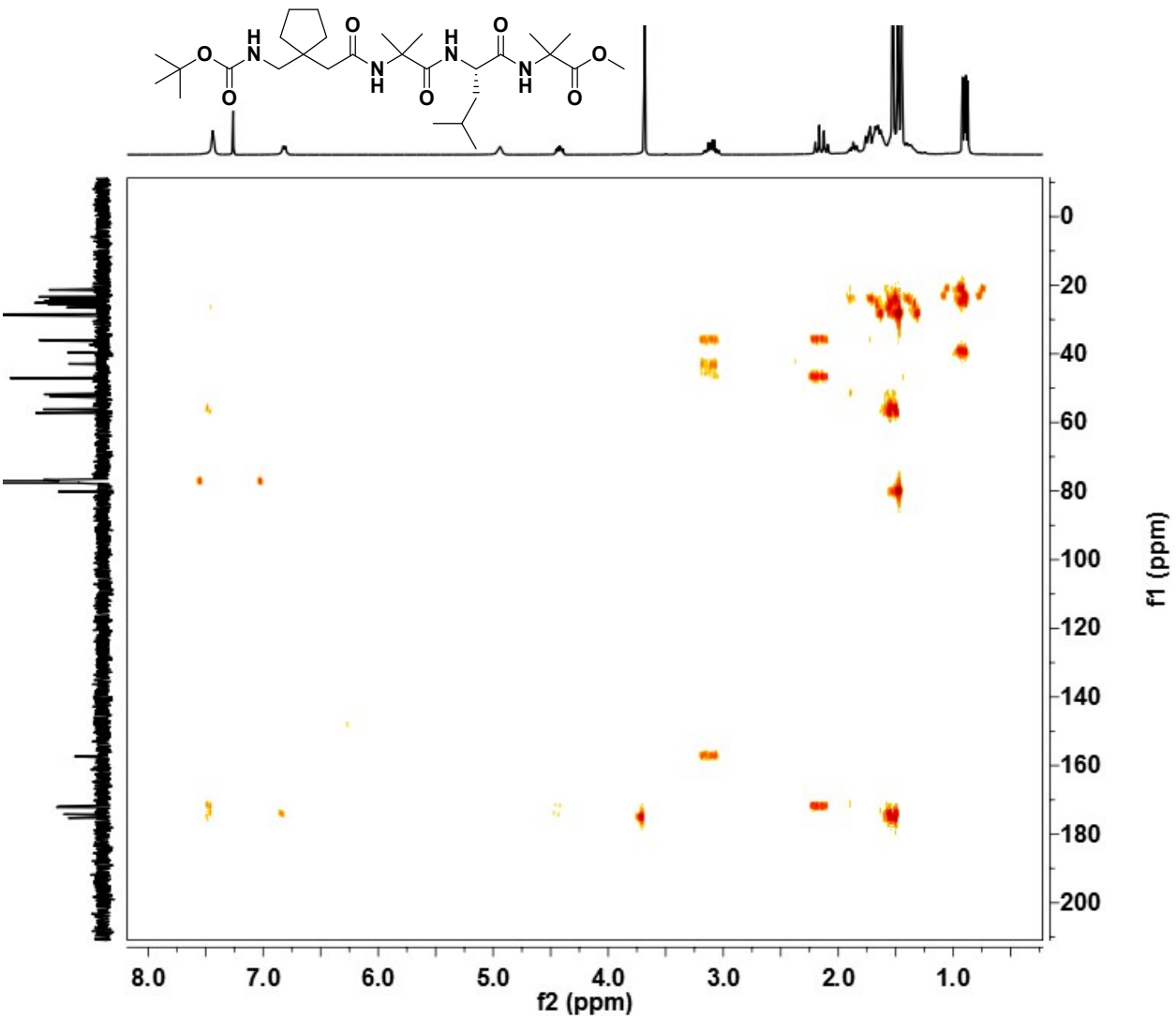


Fig. S51 ^{1}H-^{13}C COSY spectrum of Boc-Gbn(1)-Aib(2)-Leu(3)-Aib-OMe **2** ($CDCl_3$ at 298 K).

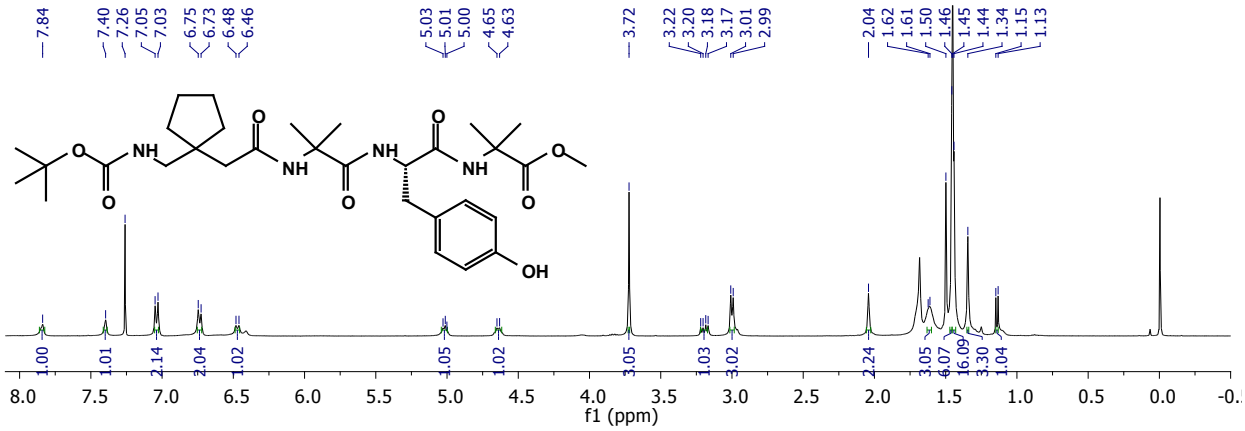


Fig. S52 ^{1}H-NMR spectrum (400 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Tyr(3)-Aib(4)-OMe **3**.

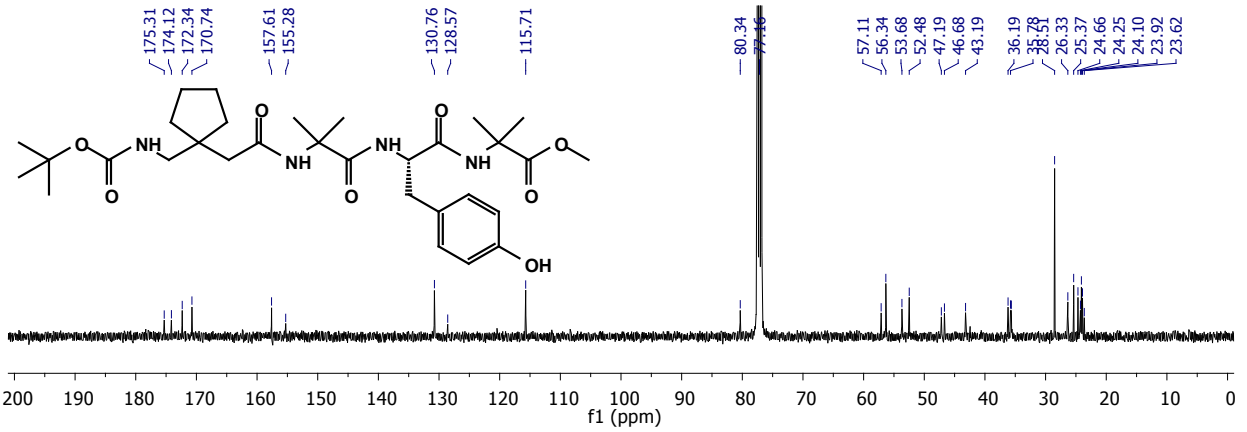


Fig. S53 ^{13}C-NMR spectrum (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Tyr(3)-Aib(4)-OMe **3**.

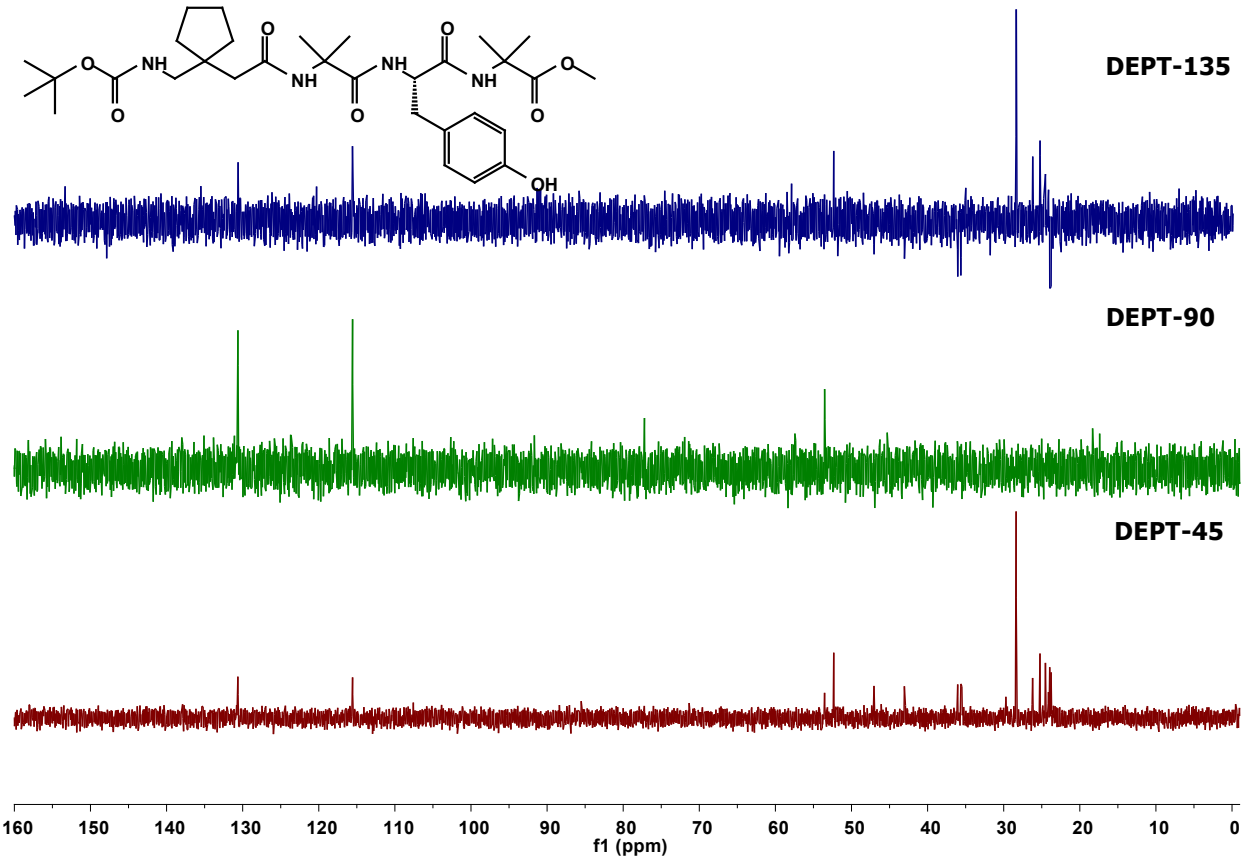


Fig. S54 ^{13}C-DEPT NMR stacked spectra (100 MHz, $CDCl_3$) of Boc-Gbn(1)-Aib(2)-Tyr(3)-Aib-OMe **3**.

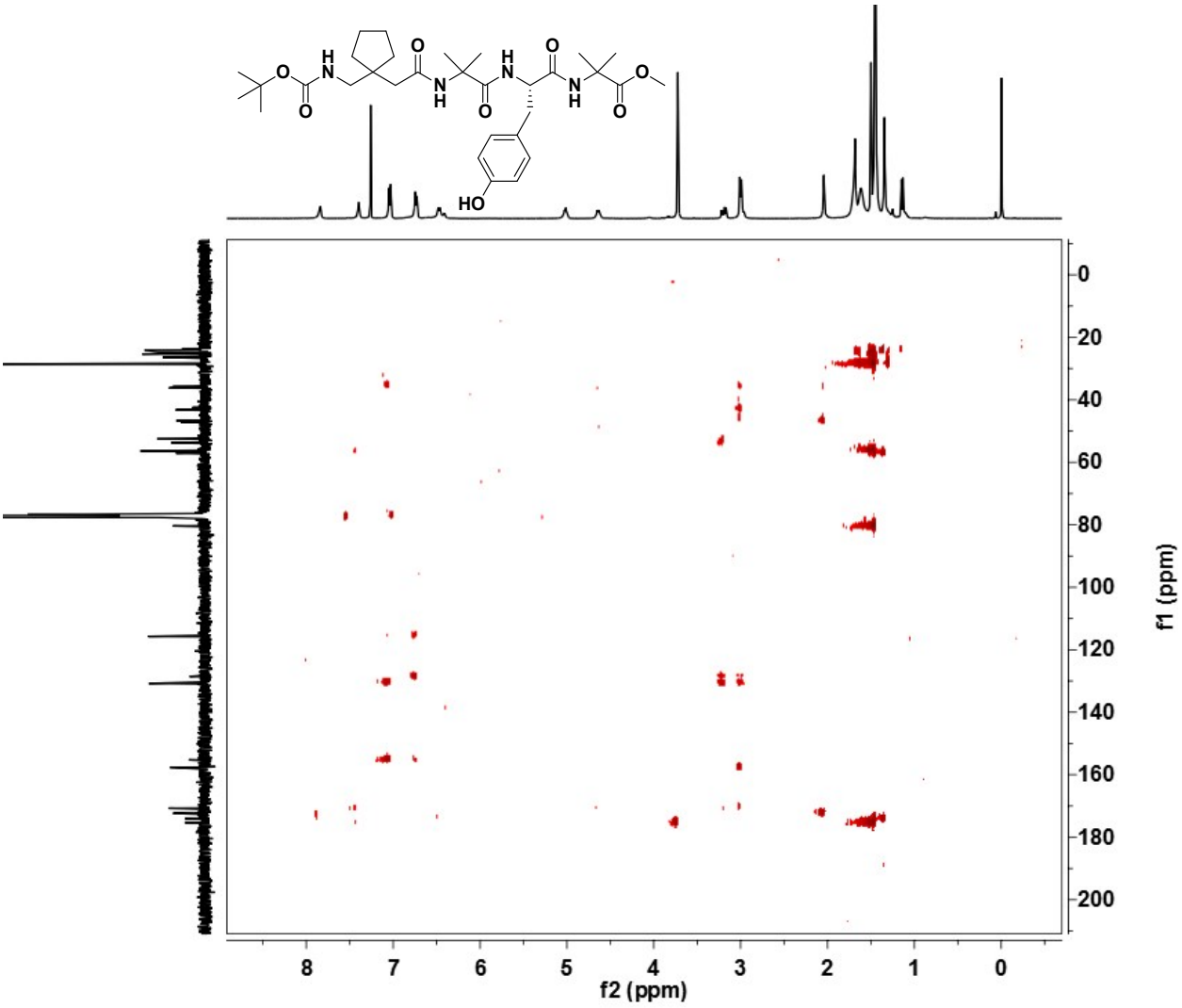


Fig. S55 ^{1}H-^{13}C COSY spectrum of Boc-Gbn(1)-Aib(2)-Tyr(3)-Aib-OMe **3** ($CDCl_3$ at 298 K).

Mass spectral data

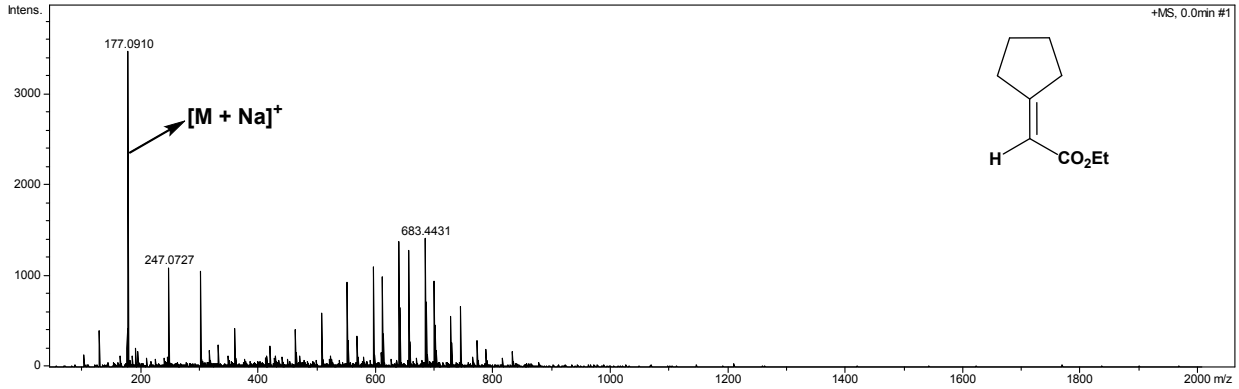


Fig. S56 HRMS spectrum of compound **5**.

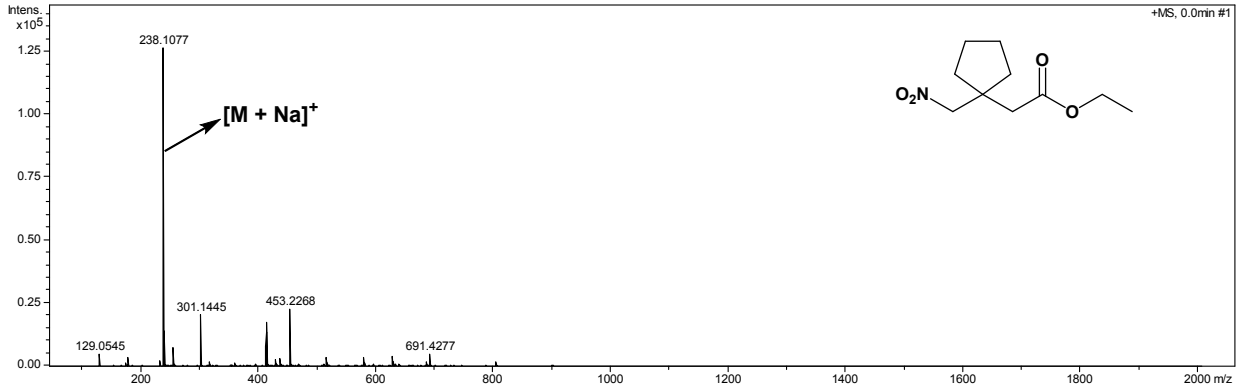


Fig. S57 HRMS spectrum of compound **6**.

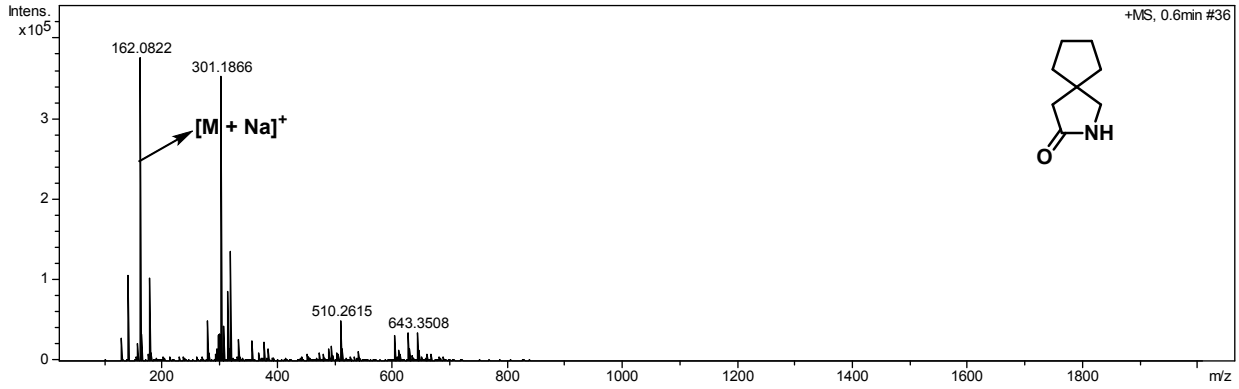


Fig. S58 HRMS spectrum of compound **7**.

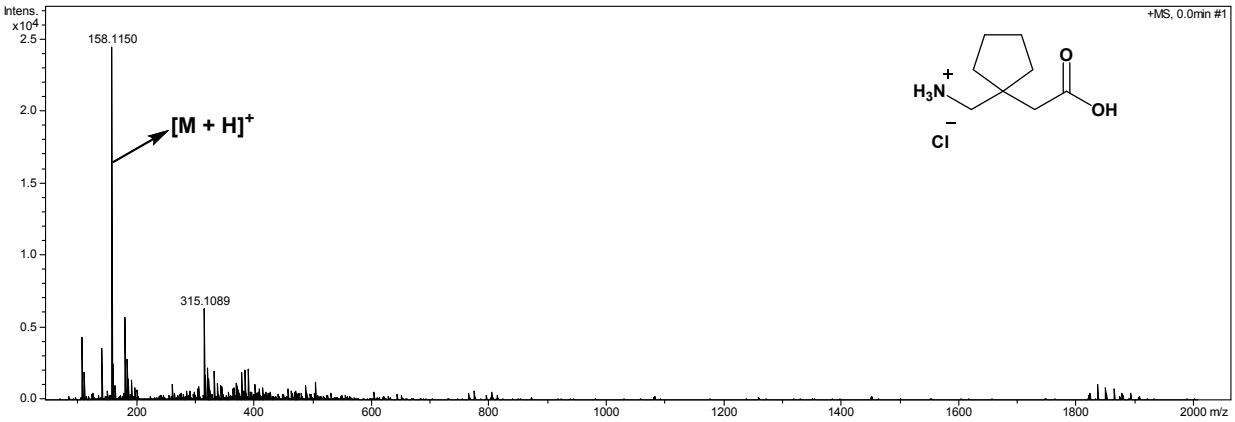


Fig. S59 HRMS spectrum of compound **8**.

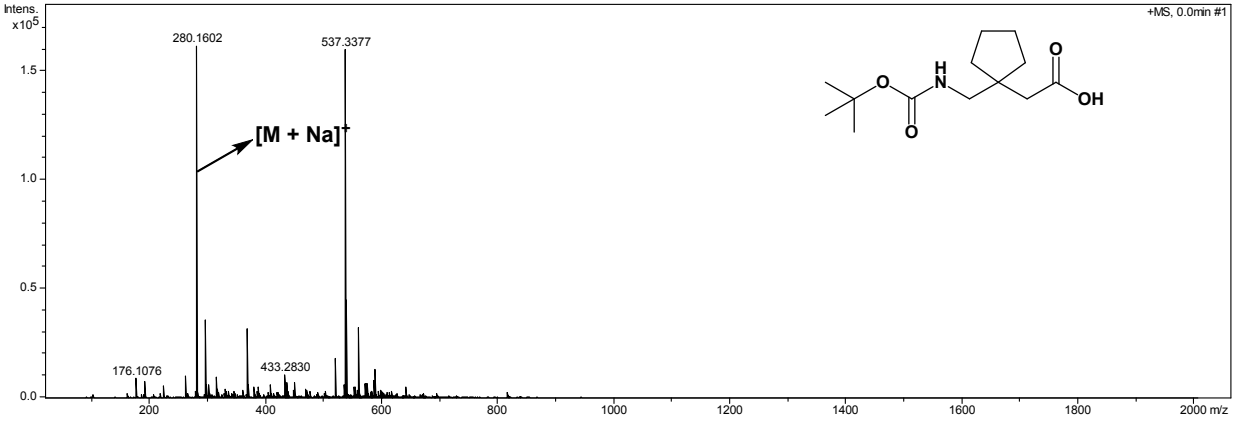


Fig. S60 HRMS spectrum of Boc-Gbn(1)-OH **9**.

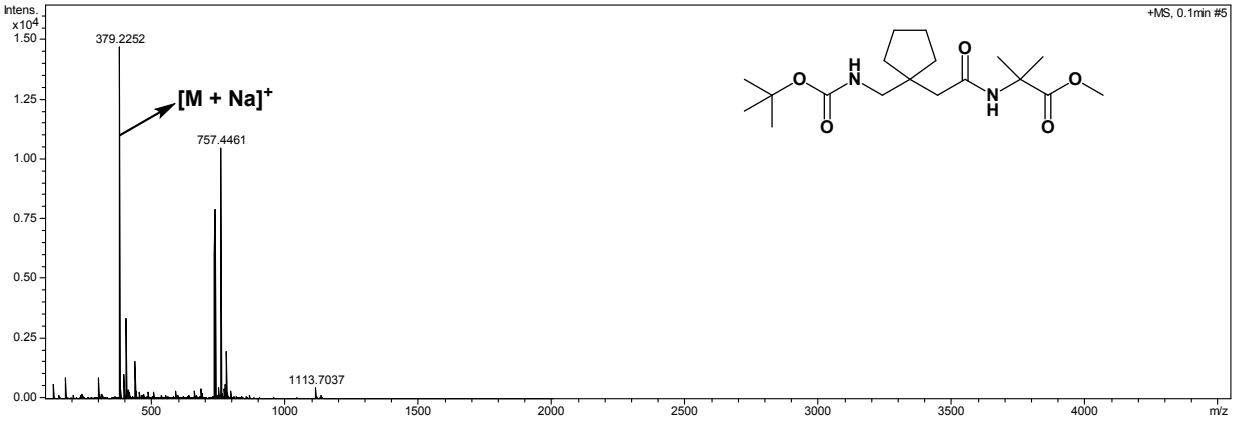


Fig. S61 HRMS spectrum of Boc-Gbn(1)-Aib(2)-OMe **10**.

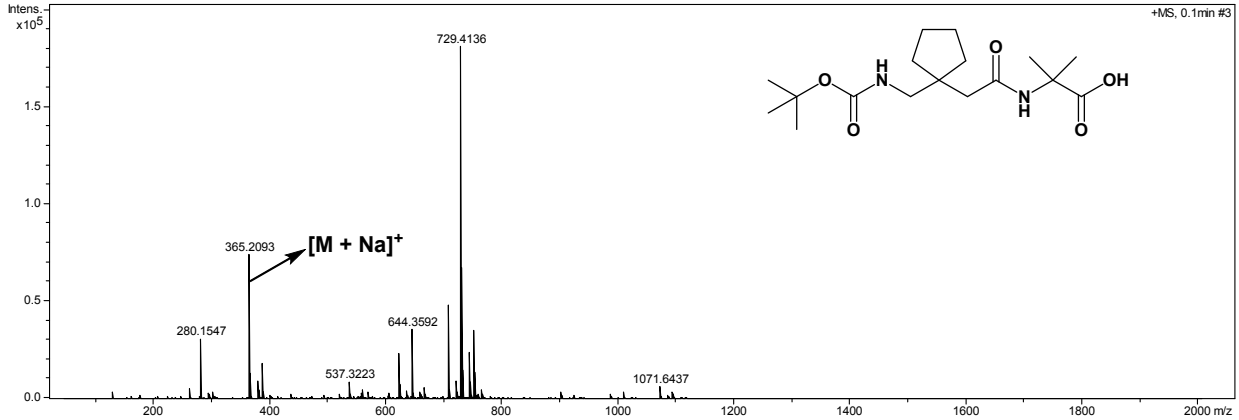


Fig. S62 HRMS spectrum of Boc-Gbn(1)-Aib(2)-OH **11**.

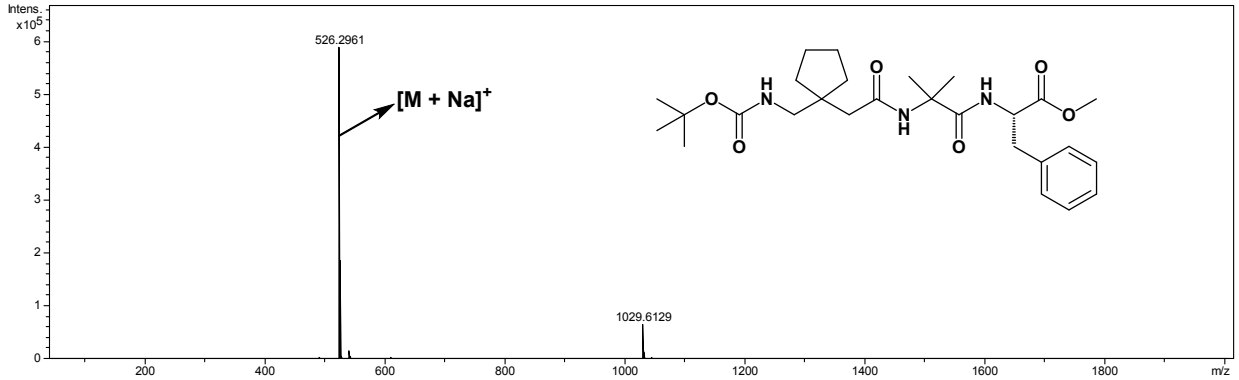


Fig. S63 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Phe(3)-OMe **12**.

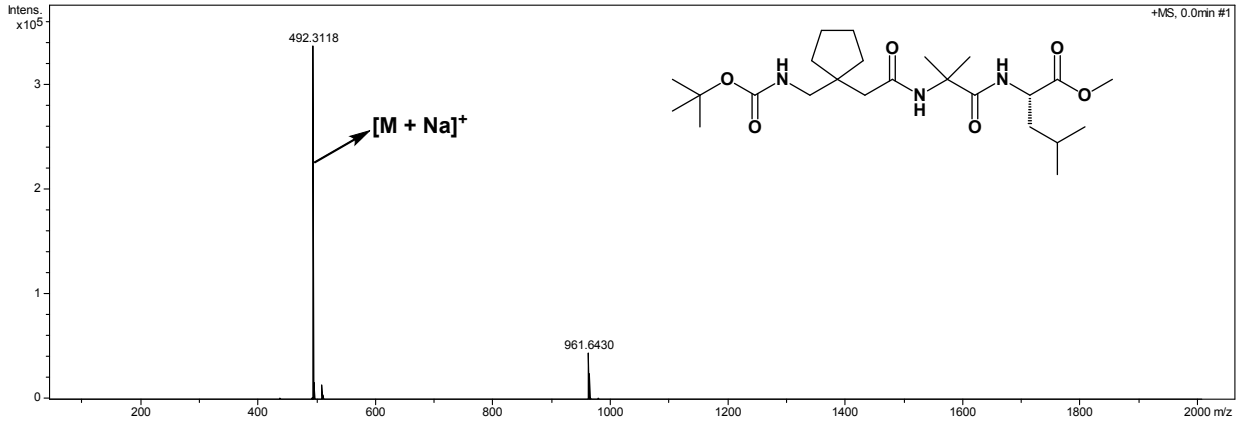


Fig. S64 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Leu(3)-OMe **13**.

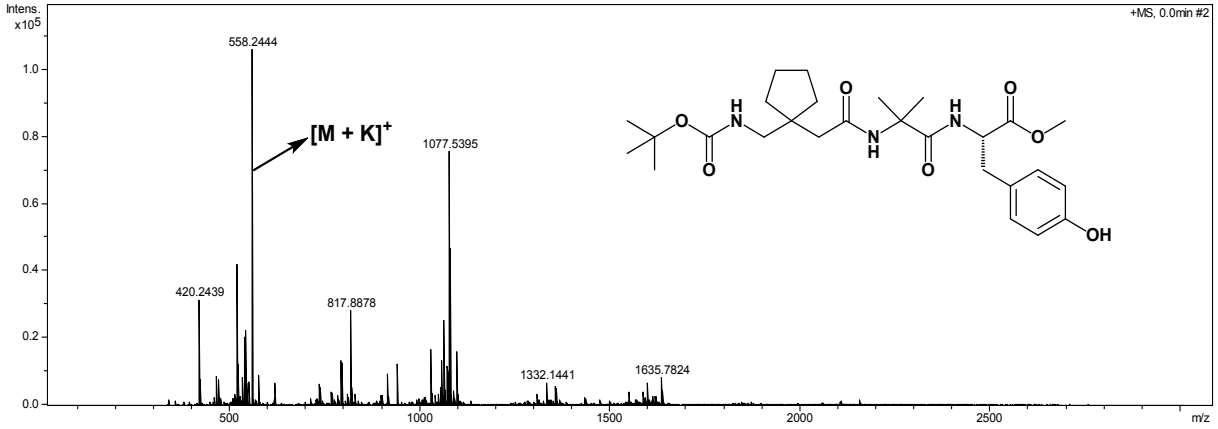


Fig. S65 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Tyr(3)-OMe **14**.

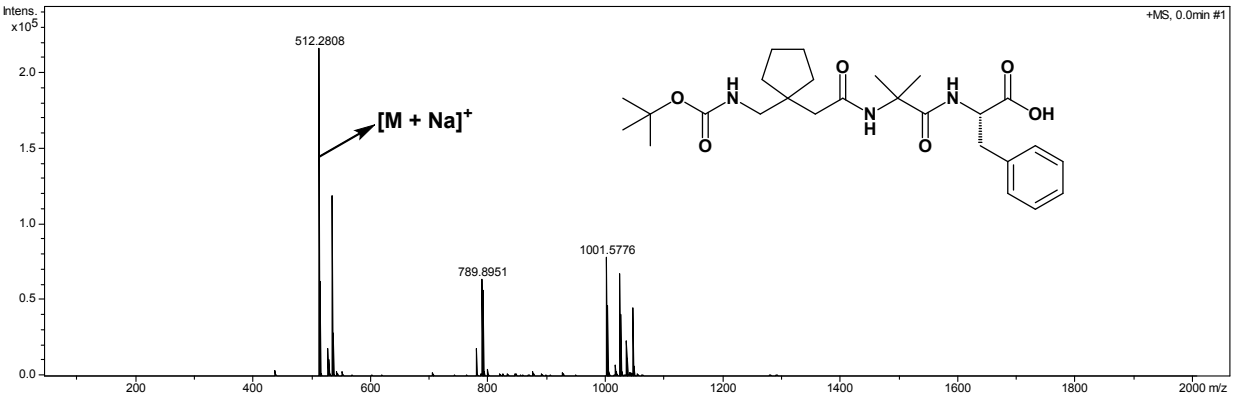


Fig. S66 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Phe(3)-OH **15**.

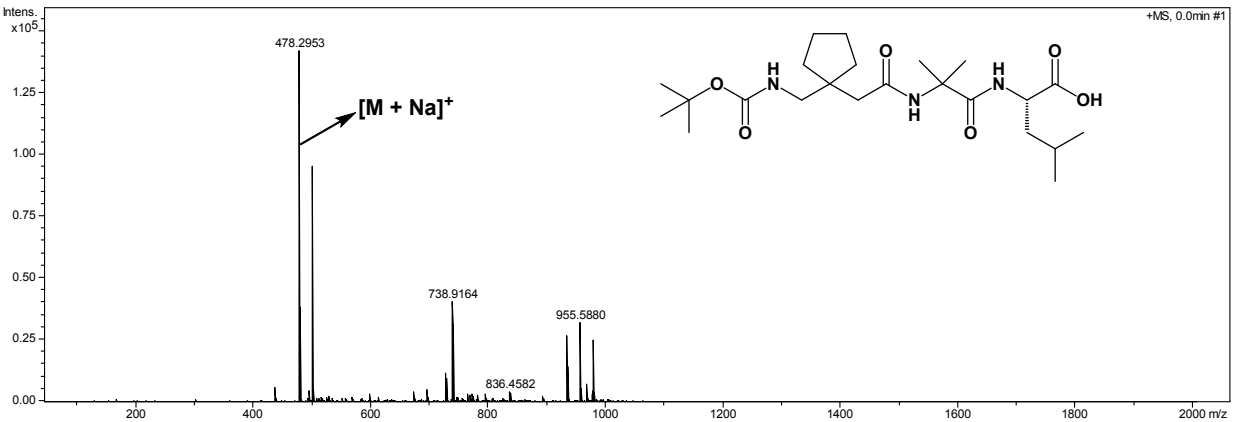


Fig. S67 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Leu(3)-OH **16**.

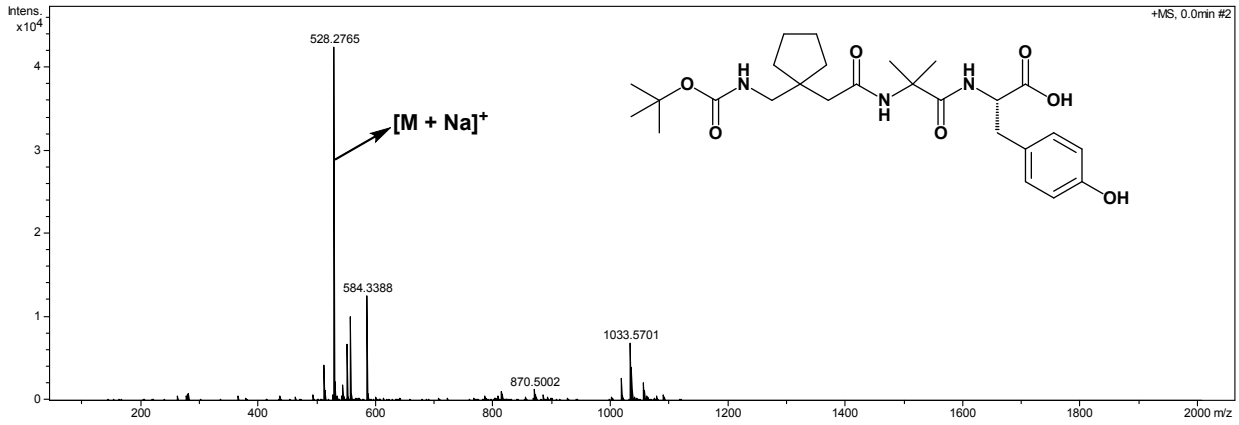


Fig. S68 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Tyr(3)-OH **17**.

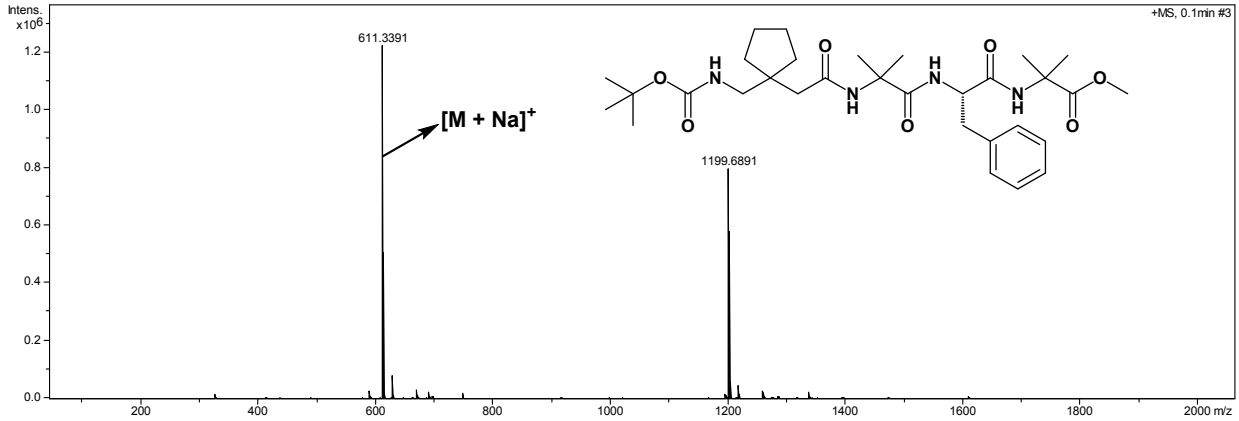


Fig. S69 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Phe(3)-Aib(4)-OMe **1**.

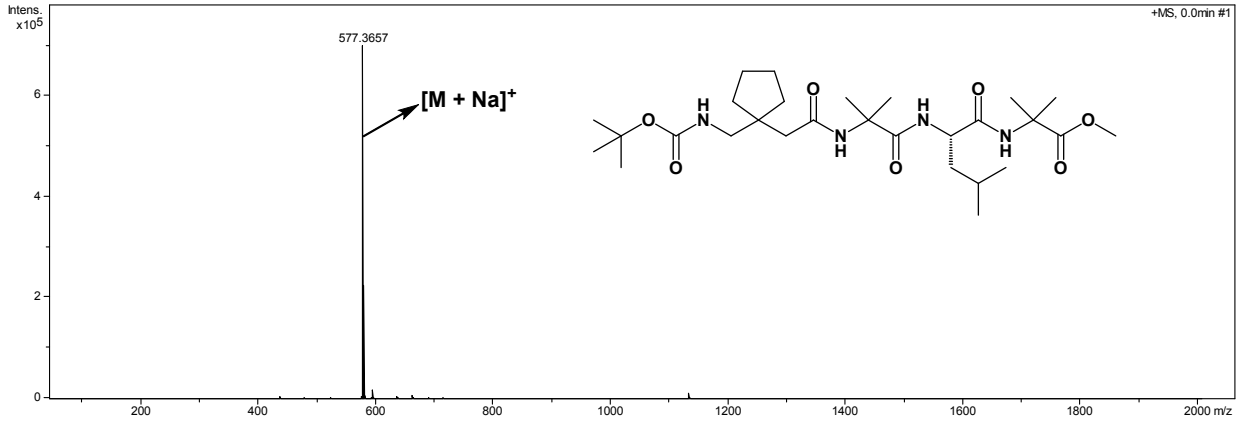


Fig. S70 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Leu(3)-Aib(4)-OMe **2**.

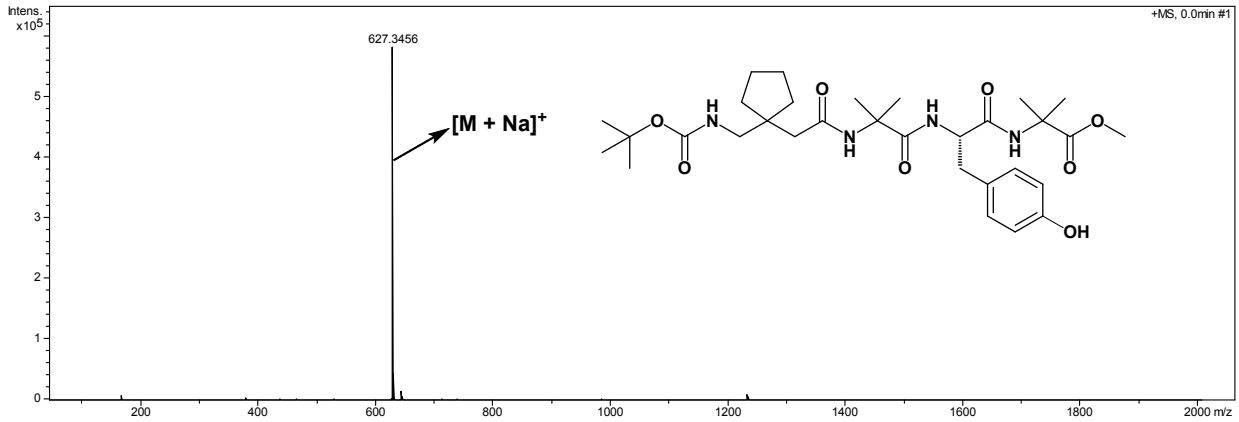


Fig. S71 HRMS spectrum of Boc-Gbn(1)-Aib(2)-Tyr(3)-Aib(4)-OMe **3**.

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S1. M. Konda, B. Kauffmann, D. B. Rasale and A. K. Das, *Org. Biomol. Chem.*, 2016, **14**, 4089.

S2. G. M. Sheldrick, *Acta Cryst. A*., 2015, **71**, 3.