Supplementary Information

Artificial N-*ortho*-Nitrobenzylated Benzanilide Amino Acid Derivative Enables Control of Conformation and Membrane Permeability of Cyclic Peptides

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Supporting figures

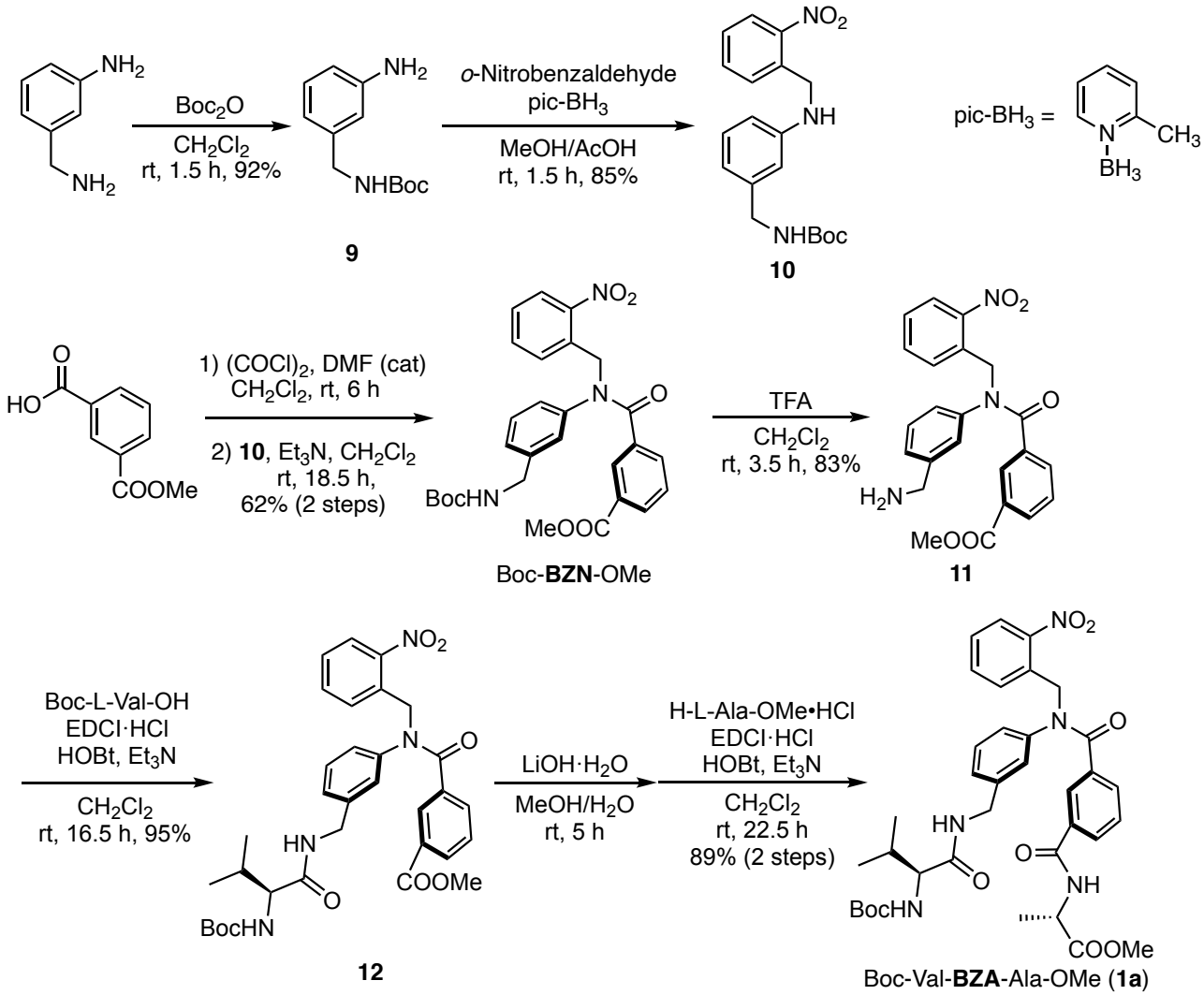


Figure S1. Synthesis of Boc-**BZN**-OMe and **1a**.

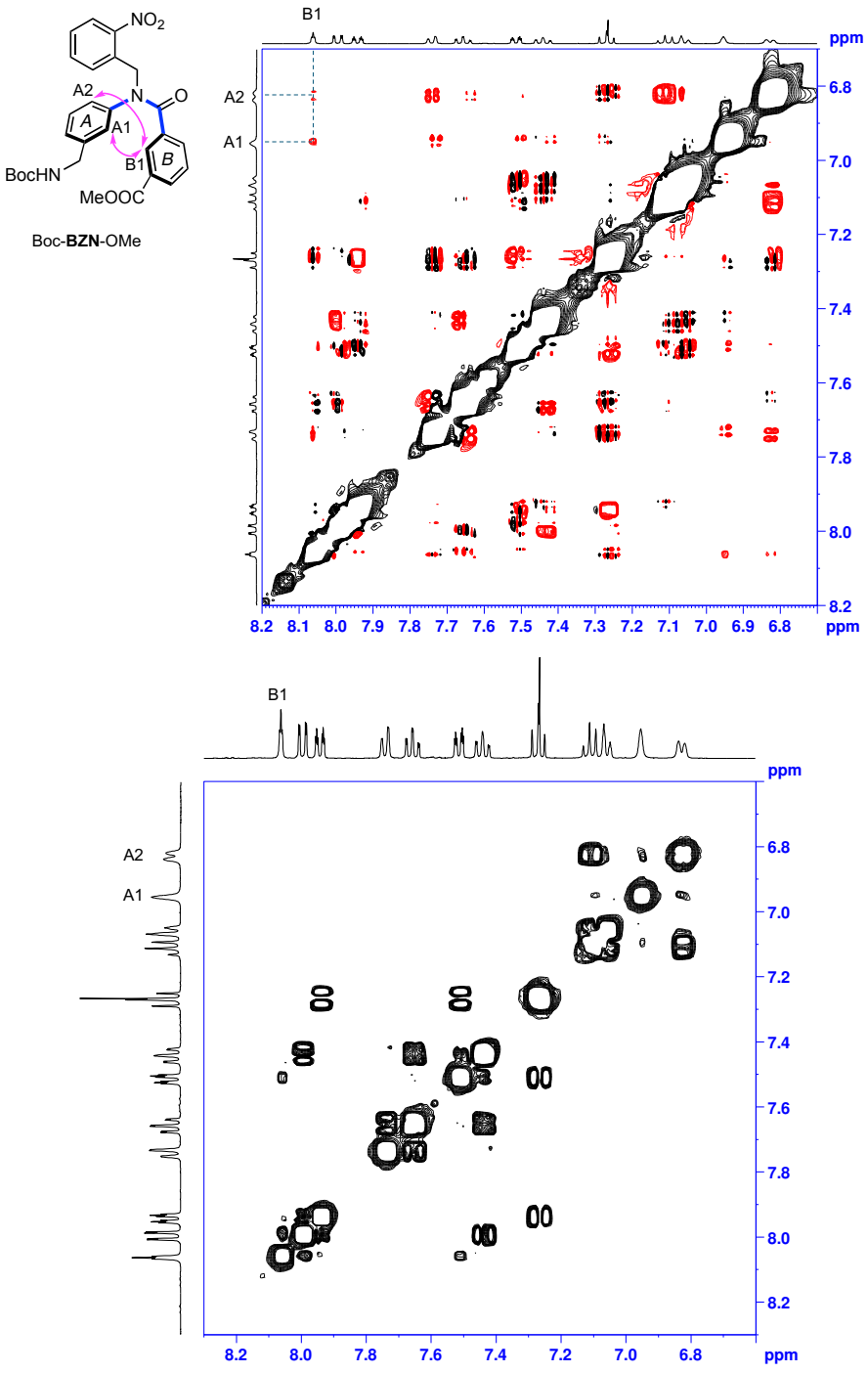


Figure S2. (a) NOESY and COSY spectra of Boc-**BZN**-OMe in $CDCl_3$ at 23°C.

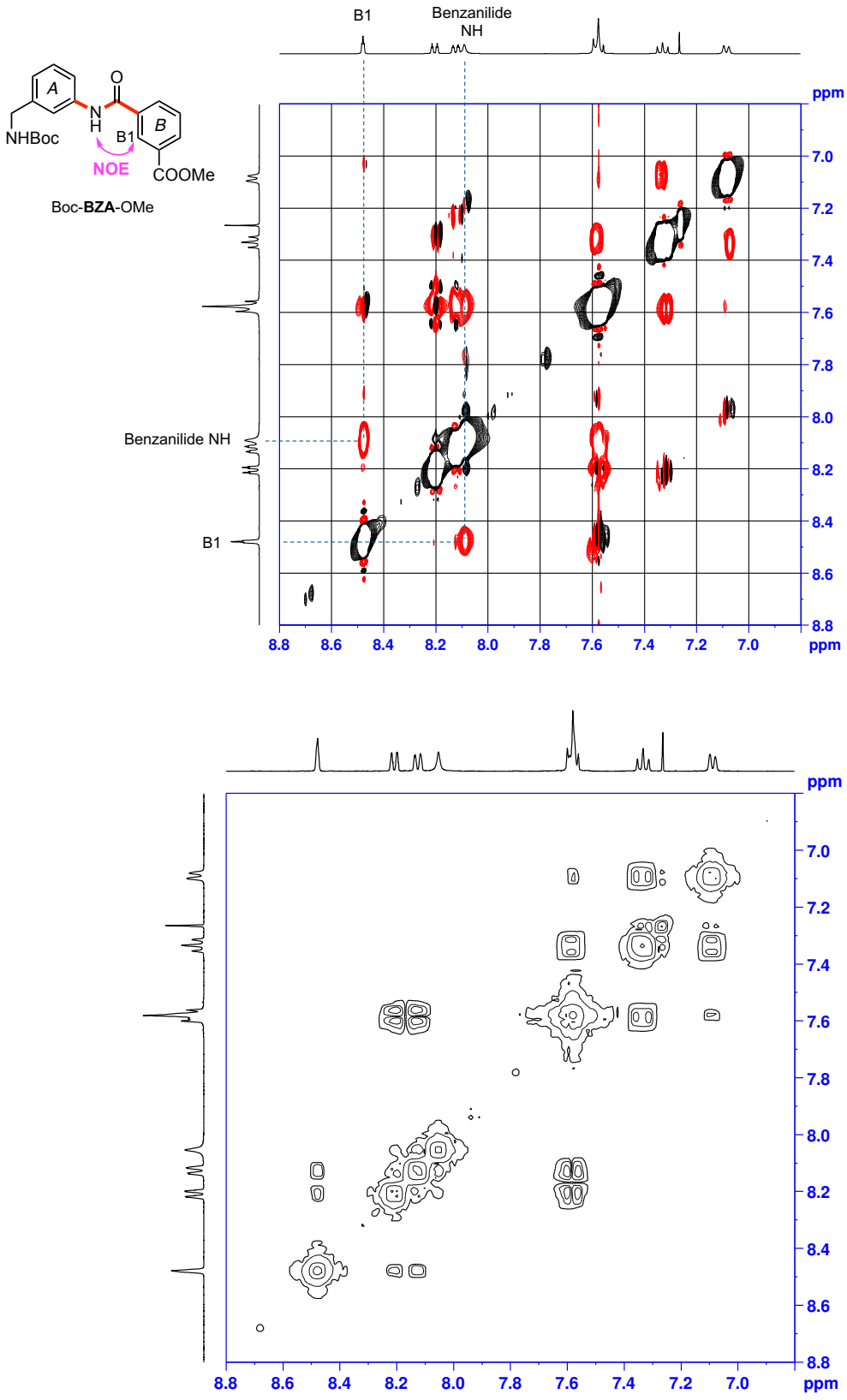


Figure S3. NOESY and COSY spectra of Boc-**BZA**-OMe in $CDCl_3$ at 23°C.

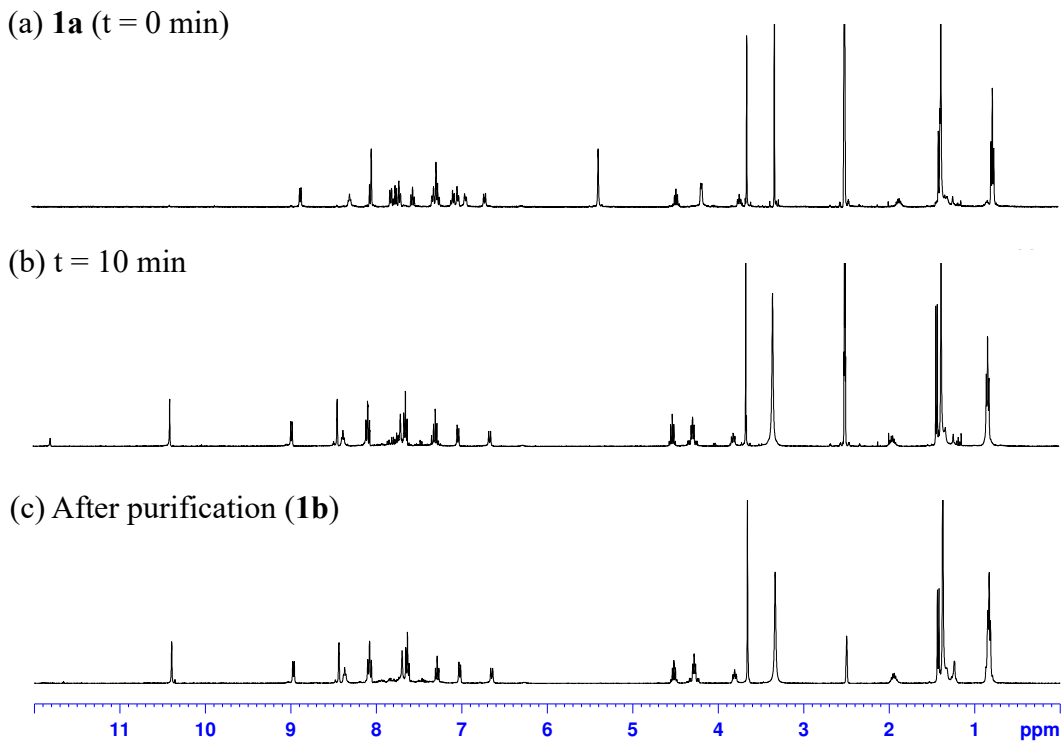
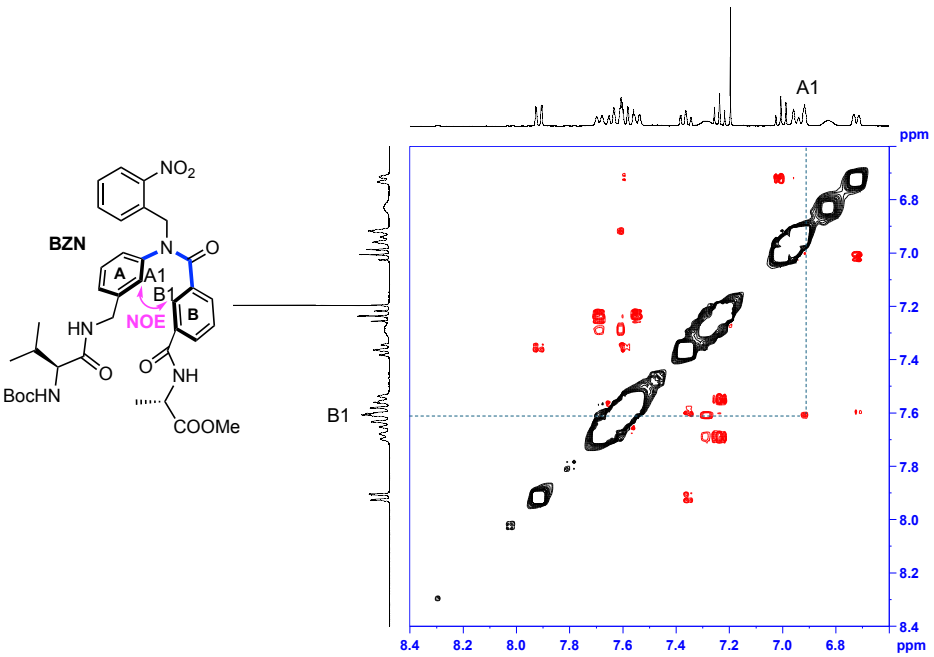


Figure S4. (a)-(c) Photoreaction of **1a** monitored by ^{1}H-NMR in DMSO-d_6 at 23 °C.

1a



1b

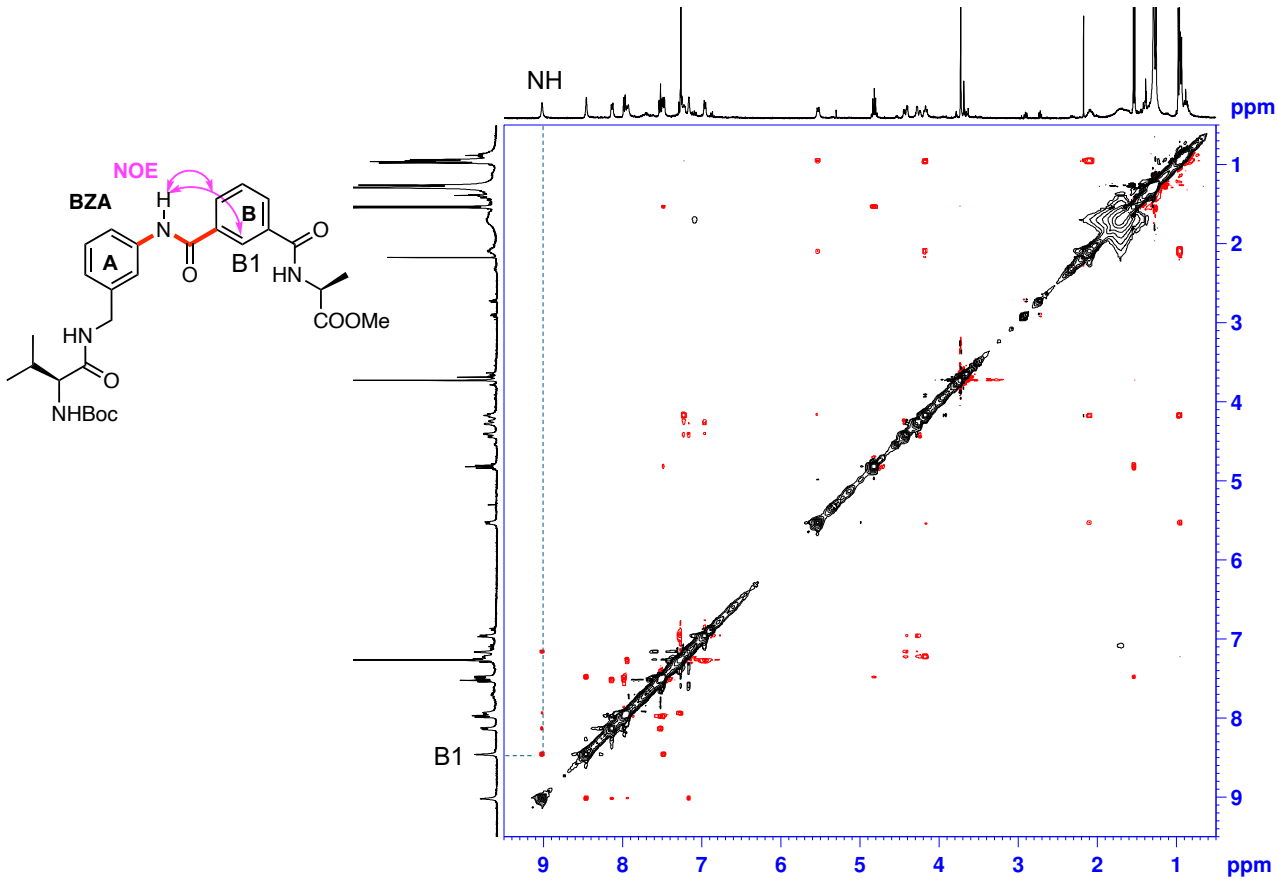


Figure S5. NOESY spectra of **1a** and **1b** in $CDCl_3$ at 23°C.

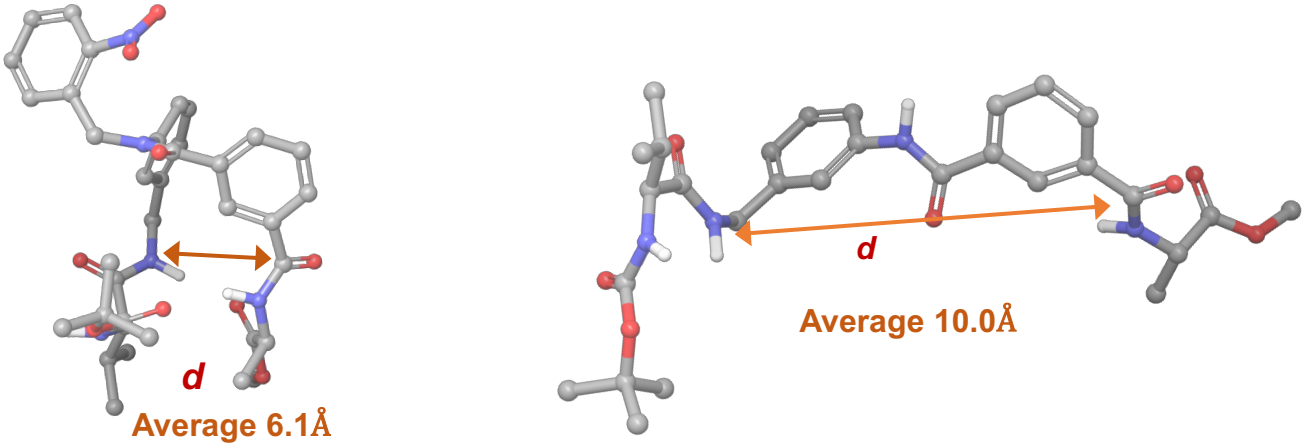


Figure S6. Centroid structures of the largest cluster obtained from REST simulation (OPLS3e, $CHCl_3$, 30 ns, 8 replicas).

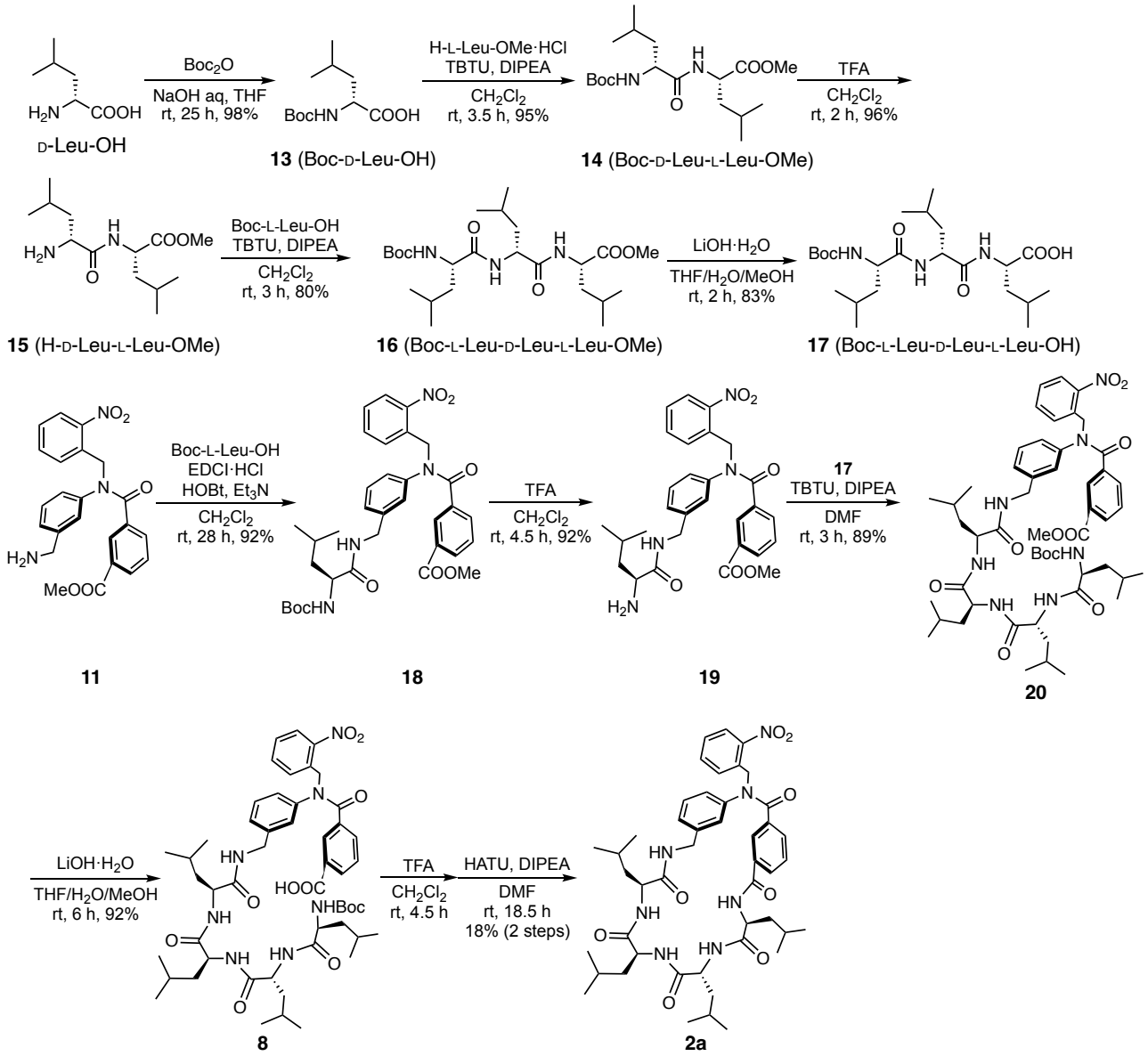


Figure S7. Synthesis of cyclic peptide **2a**.

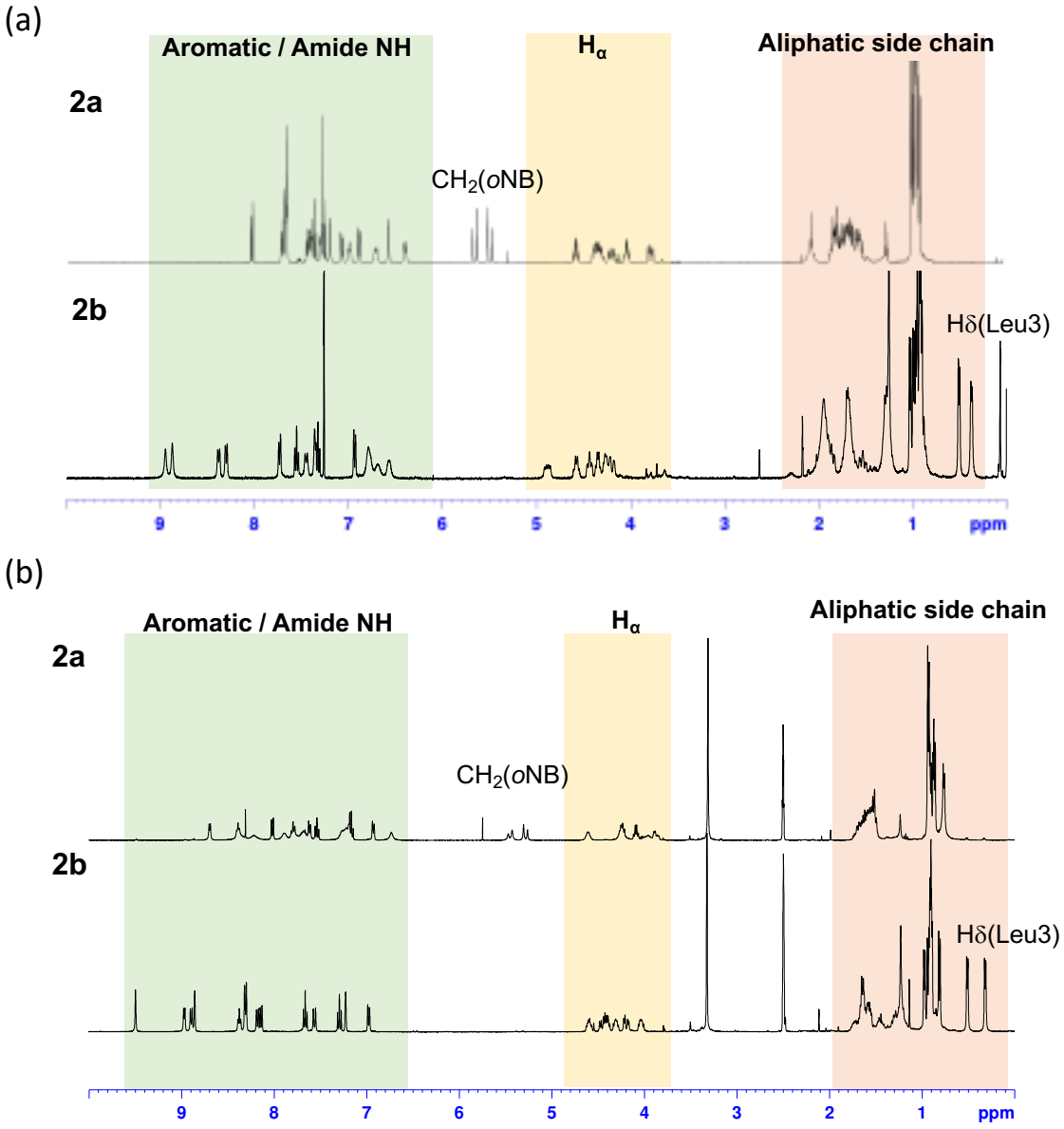


Figure S8. ^{1}H-NMR of **2a** and **2b** (a) in $CDCl_3$ and (b) in DMSO-d_6 at 23°C.

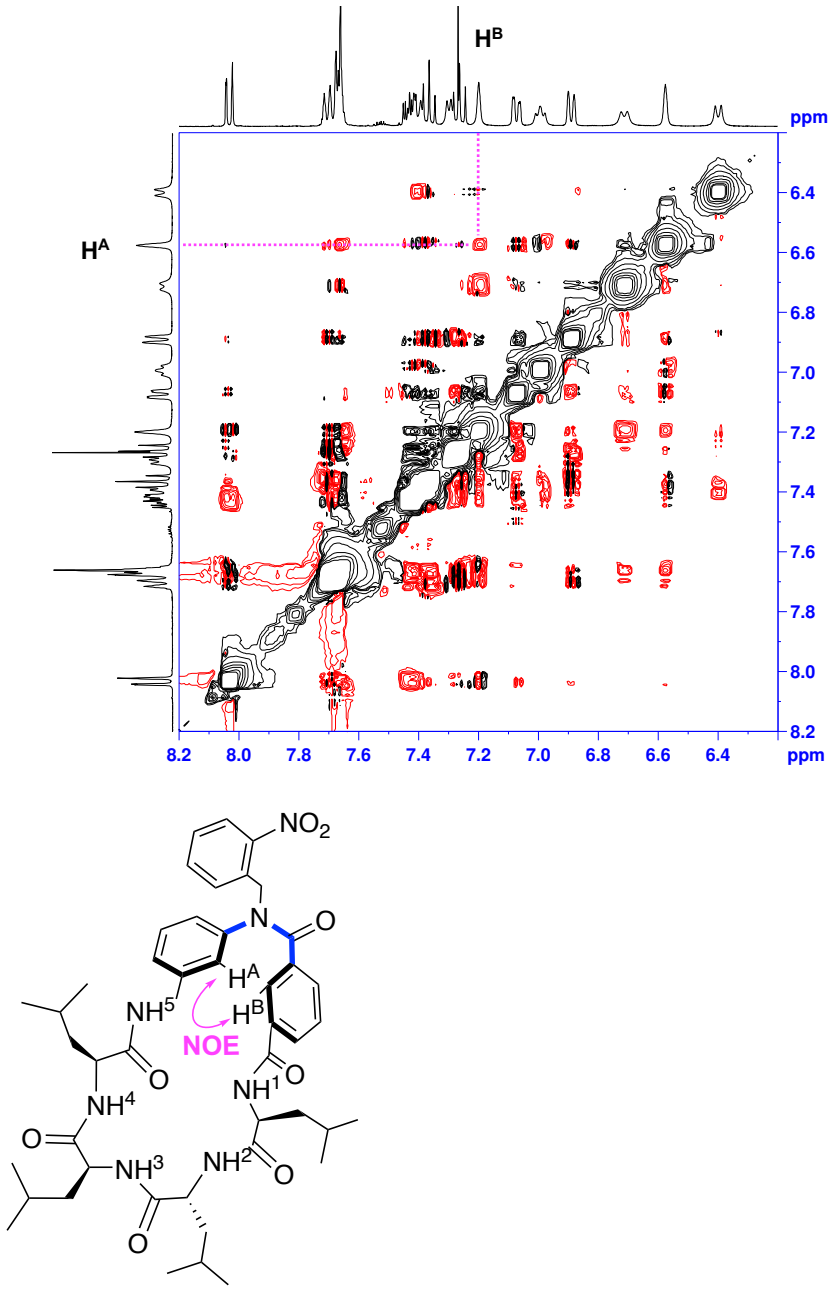


Figure S9. NOESY spectra of **2a** in $CDCl_3$ at 23°C.

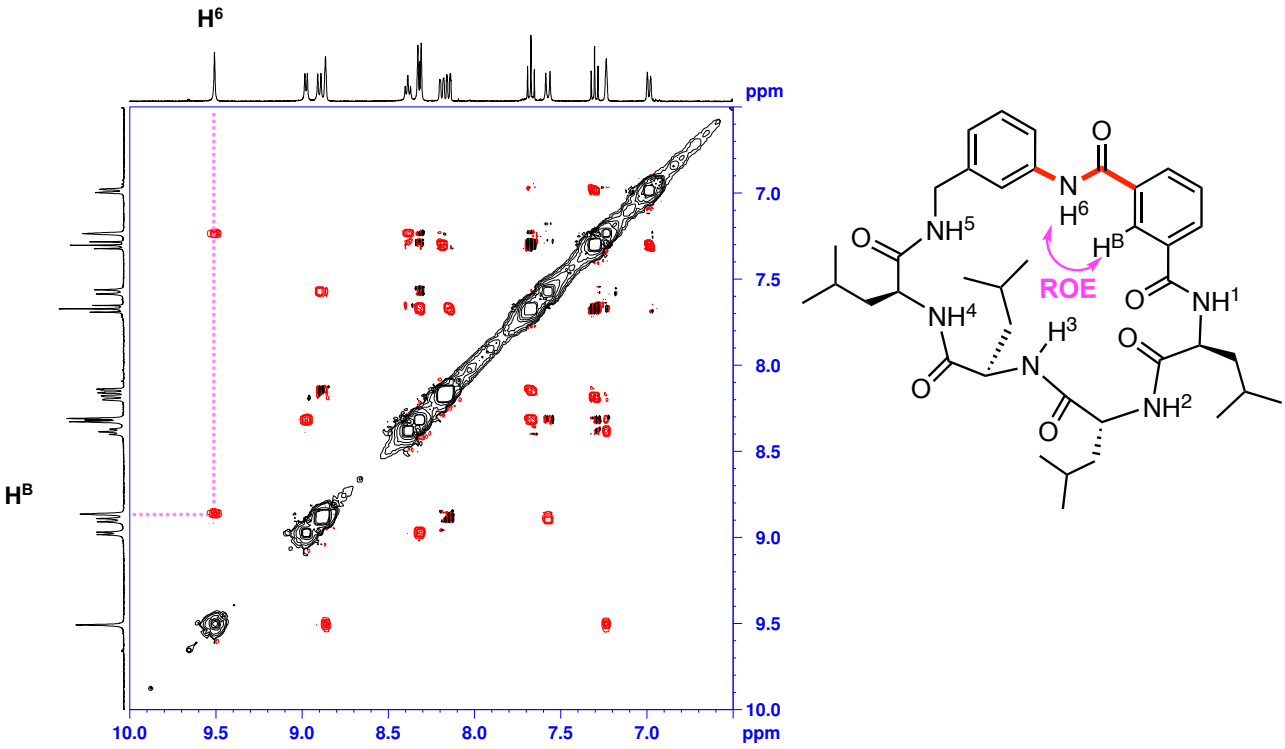
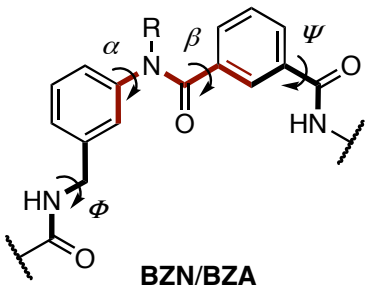
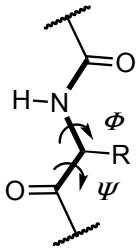


Figure S10. ROESY spectra of **2b** in DMSO-d_6 at 23°C.

(a)



BZN/BZA



α-amino acid

	BZN / BZA				Leu1		Leu2(L/D)		Leu3(L/D)		Leu4/Ala4	
	Φ	Ψ	α	β	Φ	Ψ	Φ	Ψ	Φ	Ψ	Φ	Ψ
2a	-107	-138	92	-56	-97	159	110	-123	-88	-27	-89	160
2b	145	-116	122	54	-102	110	64	50	-113	142	-101	45
3a	-75	110	97	-59	-23	137	79	-63	172	-29	-180	173
3b	-123	-36	-131	-107	-97	25	107	50	-107	133	-61	-40
4a	101	55	-84	-83	-101	-79	-109	131	58	169	-65	143
5a	79	-89	-95	105	-79	54	90	42	87	-48	-65	141
5b	131	-98	112	91	-52	-25	130	164	106	-157	-113	138

(b)

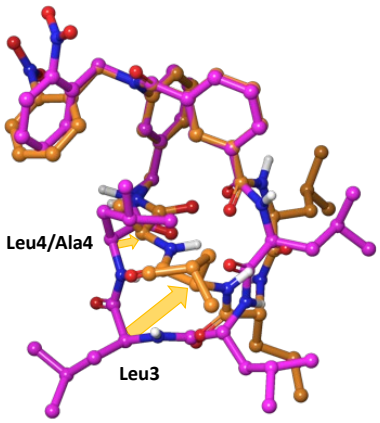
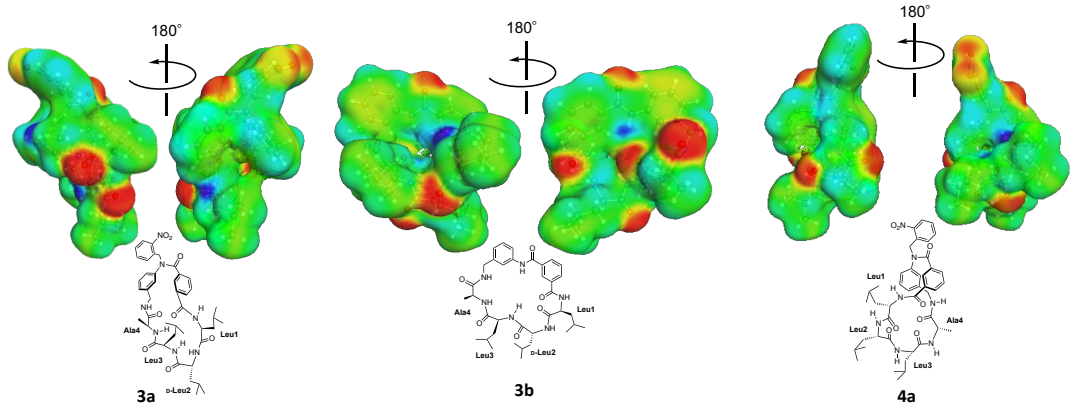


Figure S11. (a) Main-chain torsion angles of cyclic peptides. Values for D-amino acids are shown in red. (b) Superimposed structures of **2a** (magenta carbon) and **3a** (orange carbon). Benzanilide carbons were used for superimposition.

(a)



(b)

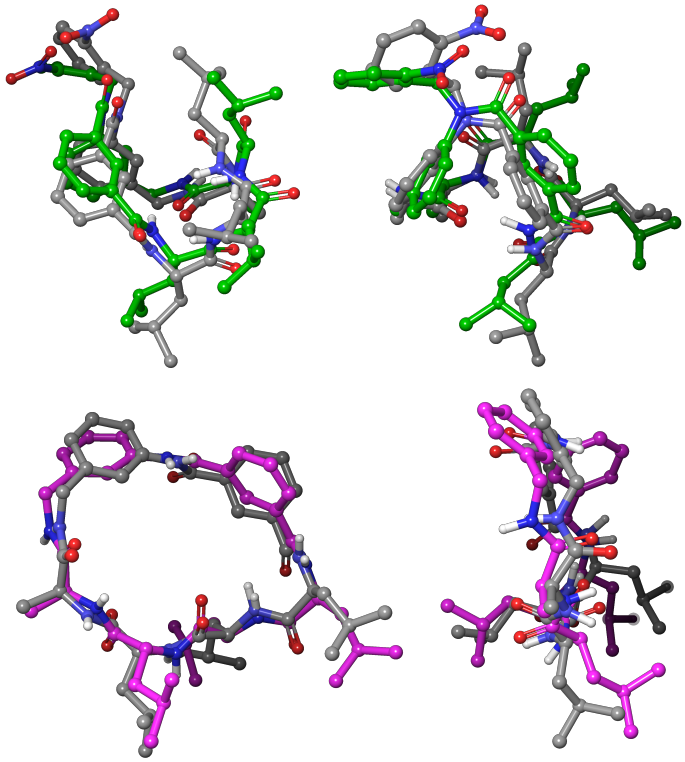


Figure S12. (a) COSMO surface of **3a**, **3b**, and **4a**. (b) Superposition of NMR structure and optimized structure at the level of BP86/def-TZVP using the COSMO solvation. **5a** (NMR structure: gray carbon, DFT-optimized structure: green carbon) and **5b** (NMR structure: gray carbon, optimized structure: magenta carbon).

Experimental section

General Methods of Synthesis and Photoreaction

Unless stated otherwise, commercial grade reagents were used without further purification. Open column chromatography was carried out using Kanto chemical silica gel (silica gel 60 N (100-210 μm)). ^{1}H-NMR (400 MHz) spectra and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker Avance 400 NMR spectrometer running Topspin. The spectra were recorded at 24 °C, unless otherwise noted. ^{1}H NMR and ^{13}C{^{1}H} NMR chemical shifts (δ) are given in parts per million (ppm) and coupling constants are given in hertz (Hz). s = singlet, brs = broad singlet, d = doublet, t = triplet, m = multiplet. ^{1}H-NMR spectra are reported relative to residual solvent signals ($CDCl_3$: 7.26 ppm, DMSO-d_6: 2.50 ppm). Data for ^{13}C{^{1}H} NMR spectra are reported in terms of chemical shift (ppm) relative to residual solvent peak ($CDCl_3$: 77.16 ppm, DMSO-d_6: 39.52 ppm). Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05. The combustion analysis was carried out in the microanalytical laboratory of the University of Tokyo. All the melting points were measured with a Yanaco Micro Melting Point Apparatus without correction. HPLC data were obtained with the following conditions: HPLC Column: Cosmosil 5C18-AR-II, Waters, 10 mm × 250 mm, Water / Acetonitrile = 10: 90 – 30: 70, flow rate 2.0 mL/min, UV detection at 250 nm. Photoreaction was carried out using PR160L-390nm (Kessil®, 40 W). Photoirradiation was performed at 390 nm.

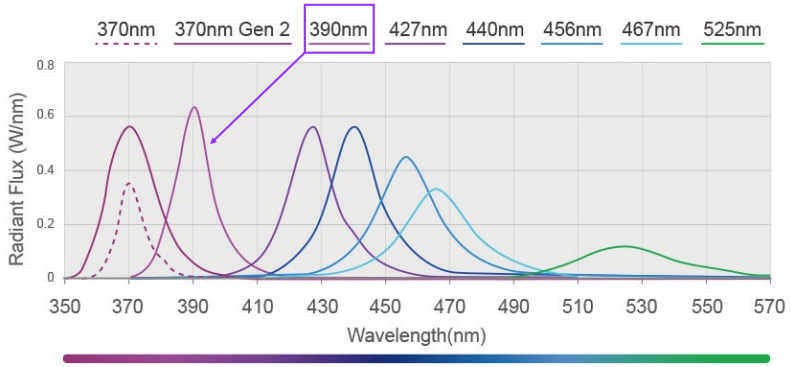
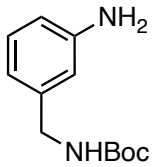


Figure S13. Spectra of PR160-390nm.

(The figure was taken from https://kessil.com/products/science_PR160L.php)

Experimental Section of Synthesis

Compound 9



To a solution of 3-aminobenzylamine (996.3 mg, 8.15 mmol) in anhydrous CH_2Cl_2 (30 mL), di-tert-butyl dicarbonate (2.25 mL, 9.79 mmol) was added dropwise at 0°C and the solution was warmed to room temperature. After stirring for 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The crude product was column-chromatographed (n-hexane: AcOEt = 3: 2) to afford **9** (1.6618 g, 7.48 mmol, 92%) as brown oil.

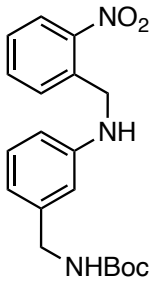
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.10 (1H, dd, J = 8.0, 8.0 Hz), 6.65 (1H, d, J = 7.6 Hz), 6.60-6.56 (2H, m), 4.83 (1H, brs), 4.21 (2H, d, J = 6.4 Hz), 3.67 (2H, brs), 1.46 (9H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 146.8, 140.2, 129.6, 117.6, 114.2, 79.5, 44.8, 28.5.

Anal. Calcd. for $C_{12}H_{18}NO_5$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.57; H, 8.24; N, 12.43.

HRMS (ESI-TOF, [M+Na$^+$]): Calcd. for $C_{12}H_{18}N_2NaO_5^+$, 245.1261. Found: 245.1285.

Compound 10



To a solution of **9** (1.5634 g, 7.03 mmol) and 2-nitrobenzaldehyde (1.0628 g, 7.03 mmol) in anhydrous MeOH / acetic acid (10: 1, 17.5 mL), α-picoline-borane (756.7 mg, 7.07 mmol) was added at room temperature. After stirring for 1.5 h, the reaction mixture was

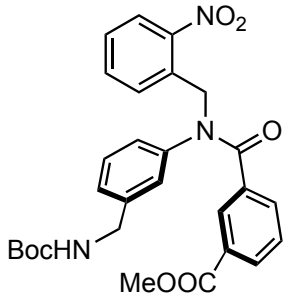
concentrated and 1M HCl solution was added to the residue. The solution was neutralized by saturated aqueous solution of $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated. To eliminate α-picoline-borane, the crude was dissolved in CH_2Cl_2 (5 mL) and 1 M HCl solution (20 mL) was added to the solution. The solution was neutralized by Na_2CO_3 (2.5 g) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was column-chromatographed (n-hexane: Acetone: Et_3N = 3:1: a little) to afford **10** and a small amount of byproducts, but they were not be separated (total 2.1471 g).

^{1}H NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.07 (1H, dd, *J* = 8.0, 1.2 Hz), 7.65 (1H, dd, *J* = 8.0, 1.2 Hz), 7.57 (1H, ddd, *J* =7.6, 7.6, 1.2 Hz), 7.43 (1H, ddd, *J* = 8.0, 8.0, 1.2 Hz), 7.10 (1H, dd, *J* = 8.0, 8.0 Hz), 6.63 (1H, d, *J* =7.8 Hz), 6.52 (1H, s), 6.45 (1H, dd, *J* = 8.0, 2.0 Hz), 4.77 (1H, brs), 4.73 (2H, d, *J* = 8.4 Hz), 4.37 (1H, t, *J* = 6.0 Hz), 4.21 (2H, d, *J* = 5.6 Hz), 1.45 (9H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 156.0, 148.3, 147.8, 140.3, 135.6, 133.8, 129.9, 129.7, 128.1, 125.3, 117.1, 112.1, 111.8, 79.5, 62.5, 45.8, 44.8, 28.5.

HRMS (ESI-TOF, [M+Na$^+$]): Calcd. for $C_{19}H_{23}N_3NaO_4^+$, 380.1581. Found: 380.1602.

Boc-BZN-OMe



To a solution of monomethyl isophthalate (725.4 mg, 4.03 mmol) in anhydrous CH_2Cl_2 (20 mL) and anhydrous DMF (2 drops), a solution of oxalyl chloride (700 μL, 8.15 mmol) in CH_2Cl_2 (15 mL) was added dropwise for 15 min at 0°C. The reaction mixture was stirred at room temperature for 6 h and the reaction mixture was concentrated.

To a solution of **10** (1.4014 g, 3.92 mmol) in anhydrous CH_2Cl_2 (20 mL), Et_3N (1100 μL, 7.91 mmol) and a solution of the above crude acid chloride in anhydrous CH_2Cl_2 (15

mL) was added at 0℃, and the mixture was warmed to room temperature and stirred 18.5 h at rt. Then the reaction mixture was filtered through Celite, washed with AcOEt, and concentrated. The residue was dissolved in AcOEt. The organic solution was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: AcOEt = 5: 2) to afford Boc-**BZN**-OMe (1.2709 g, 2.45 mmol, 62%) as light-yellow fluffy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.06 (1H, d, *J* = 0.8 Hz), 7.80 (1H, dd, *J* = 8.4, 1.2 Hz), 7.94 (1H, ddd, *J* = 7.6, 1.2, 1.2 Hz), 7.74 (1H, dd, *J* = 8.0, 0.8 Hz), 7.66 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.51 (1H, ddd, *J* = 7.6, 1.2, 1.2 Hz), 7.44 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.27 (1H, dd, *J* = 8.0 Hz), 7.11 (1H, dd, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 6.95 (1H, brs), 6.83 (1H, brd, *J* = 7.6 Hz), 5.54 (2H, s), 4.75 (1H, brs), 4.16 (2H, d, *J* = 5.6 Hz), 3.88 (3H, s), 1.44 (9H, s).

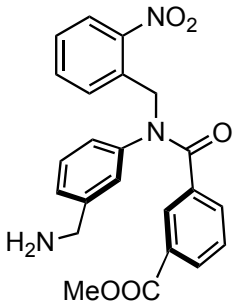
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 166.2, 148.7, 143.2, 140.9, 135.6, 133.8, 133.1, 132.7, 131.2, 130.3, 130.1, 129.7, 129.5, 128.4, 128.2, 126.6, 126.5, 126.3, 125.2, 52.4, 51.2, 44.2, 31.7, 31.0, 28.5, 22.8.

Anal. Calcd. for $C_{28}H_{29}N_3O_7$: C, 64.73; H, 5.63; N, 8.09. Found: C, 64.66; H, 5.92; N, 7.83.

Mp: 48-49.5℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{28}H_{29}N_3NaO_7^+$, 542.1898. Found: 542.1892.

Compound 11



To a solution of Boc-**BZN**-OMe (651.1 mg, 1.25 mmol) in anhydrous CH_2Cl_2 (15 mL), trifluoroacetic acid (1 mL) was added at 0℃ and the solution was warmed to room temperature and stirred for 3.5 h. Saturated aqueous solution of $NaHCO_3$ (12 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2. The organic

layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 19: 1 - 14: 1 - 9: 1) to afford **11** (434.7 mg, 1.04 mmol, 83%) as yellow amorphous.

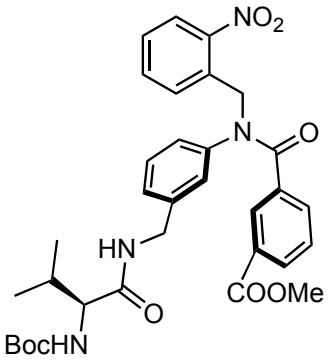
^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.07 (1H, ddd, *J* = 2.0, 2.0, 0.8 Hz), 7.97 (1H, dd, *J* = 8.4, 1.2 Hz), 7.92 (1H, dddd, *J* = 8.0, 1.6, 1.6, 0.4 Hz), 7.74 (1H, dd, *J* = 8.0, 1.2 Hz), 7.64 (1H, ddd, *J* = 7.6, 7.6, 1.6 Hz), 7.51 (1H, dddd, *J* = 8.0, 2.0, 2.0, 0.4 Hz), 7.42 (1H, ddd, *J* = 8.4, 7.6, 1.6 Hz), 7.24 (1H, ddd, *J* = 8.0, 8.0, 0.4 Hz), 7.11-7.05 (2H, m), 6.99-6.99 (1H, m), 6.80 (1H, ddd, *J* = 7.6, 2.0, 2.0 Hz), 5.54 (2H, s), 3.84 (3H, s), 3.70 (2H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 165.9, 148.3, 144.9, 142.8, 135.6, 133.5, 132.8, 132.5, 130.8, 130.0, 129.8, 129.3, 128.1, 127.9, 125.9, 125.7, 125.6, 124.8, 52.1, 52.1, 50.9, 45.6.

Anal. Calcd. for $C_{23}H_{21}N_3O_5 \cdot 0.6\ H_2O$: C, 64.21; H, 5.20; N, 9.77. Found: C, 64.08; H, 5.42; N, 9.54.

HRMS (ESI-TOF, [M+H$^+$]): Calcd. for $C_{23}H_{22}N_3O_5^+$, 420.1554. Found: 420.1570.

Compound 12



To a solution of **11** (202.1 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (5 mL), N-(tert-butoxycarbonyl)-L-valine (105.2 mg, 0.48 mmol), EDCI·HCl (124.6 mg, 0.65 mmol) and HOBt (89.4 mg, 0.66 mmol) were added at room temperature and the solution was cooled to 0°C. Et_3N (200 μL, 1.43 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 16.5 h, the reaction mixture was concentrated and dissolved in CH_2Cl_2. The organic solution was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: Acetone = 5: 2) to afford **12** (282.1

mg, 0.46 mmol, 95%) as ivory solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.00 (1H, dd, *J* = 1.6, 1.6 Hz), 7.96 (1H, dd, *J* = 8.4, 1.2 Hz), 7.92 (1H, ddd, *J* = 8.0, 1.2, 1.2 Hz), 7.75 (1H, ddd, *J* = 8.0, 1.2 Hz), 7.65 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.56 (1H, ddd, *J* = 8.0, 1.6, 1.6 Hz), 7.43 (1H, ddd, *J* = 8.0, 1.6, 1.6 Hz), 7.27 (1H, dd, *J* = 8.0, 8.0 Hz), 7.09 (1H, s), 7.04 (1H, d, *J* = 4.8 Hz), 6.81 (1H, brt), 6.76-6.73 (1H, m), 5.52 (2H, s), 5.32 (1H, d, *J* = 8.8 Hz), 4.30 (2H, s), 3.98 (1H, dd, *J* = 8.8, 8.8 Hz), 3.88 (3H, s), 2.13-2.08 (1H, m), 1.41 (9H, s), 0.91 (6H, dd, *J* = 6.8, 6.8 Hz).

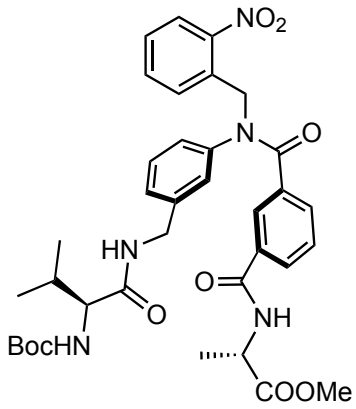
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 171.8, 169.6, 166.3, 156.0, 148.6, 143.0, 140.1, 135.5, 133.7, 133.2, 132.4, 131.0, 130.2, 129.8, 129.7, 129.7, 128.4, 128.2, 127.0, 126.6, 125.0, 79.8, 52.4, 50.9, 42.9, 31.6, 30.9, 28.3, 22.6, 17.8.

Anal. Calcd. for $C_{33}H_{38}N_4O_8 \cdot 0.4H_2O$: C, 63.33; H, 6.25; N, 8.95. Found: C, 63.12; H, 6.32; N, 8.78.

Mp: 73.5-75.0 ℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{33}H_{38}N_4NaO_8^+$, 641.2582. Found: 641.2597.

Compound 1a



To a solution of **12** (262.3 mg, 0.42 mmol) in MeOH / distilled water = 3 : 1 (4 mL), Lithium hydroxide monohydrate (36.0 mg, 0.86 mmol) was added at room temperature. After stirring for 5 h, the reaction mixture was neutralized by 5% $KHSO_4$ solution (300 μL) and evaporated, then the residue was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford carboxylic acid (Boc-Val-**BZN**-OH, 253.9 mg) as ivory solid. The crude product was used in the next step without further purification.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{32}H_{35}N_4O_8^-$, 603.2460. Found: 603.2489.

To a solution of carboxylic acid (Boc-Val-**BZN**-OH, 240.8 mg, 0.40 mmol) and L-Alanine methyl ester hydrochloride (58.7 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (5 mL), EDCI·HCl (101.3 mg, 0.53 mmol) and HOBt (68.7 mg, 0.51 mmol) were added at room temperature and the solution was cooled to 0℃. Et_3N (110 μL, 0.79 mmol) was added to the solution and the solution was warmed to room temperature. After stirring for 22.5 h, the reaction mixture was concentrated and dissolved in CH_2Cl_2. The organic solution was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: Acetone = 4: 3) to afford **1a** (246.5 mg, 0.36 mmol, 90%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 7.91 (1H, dd, *J* = 8.4, 1.2 Hz), 7.68 (1H, d, *J* = 8.0 Hz), 7.64 (1H, d, *J* = 7.2 Hz), 7.59-7.53 (3H, m), 7.36 (1H, ddd, *J* = 8.0, 8.0, 1.6 Hz), 7.27 (1H, brd, *J* = 8.4 Hz), 7.23 (1H, dd, *J* = 7.6, 7.6 Hz), 7.00 (1H, dd, *J* = 8.4, 8.4 Hz), 6.94 (1H, d, *J* = 7.6, Hz), 6.91 (1H, s), 6.80 (1H, brs), 6.71 (1H, d, *J* = 8.0 Hz), 5.54 (1H, d, *J* = 16.4 Hz), 5.34 (1H, d, *J* = 16.8 Hz), 5.17 (1H, d, *J* = 8.8 Hz), 4.71 (1H, q, *J* = 7.6 Hz), 4.47 (1H, dd, *J* = 14.8, 6.8 Hz), 3.98 (1H, brd, *J* = 15.2, 3.6 Hz), 3.80 (1H, dd, *J* = 8.4, 8.4 Hz), 3.71 (3H, s), 1.97-1.90 (1H, m), 1.40 (3H, d, *J* = 7.2 Hz), 1.380 (9H, s), 0.87 (3H, d, *J* = 6.8 Hz), 0.85 (3H, d, *J* = 6.8 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.5, 172.1, 169.8, 166.3, 156.2, 148.7, 143.2, 140.0, 135.6, 133.7, 133.1, 132.6, 132.1, 129.7, 129.7, 128.9, 128.5, 128.4, 127.5, 127.4, 127.1, 126.6, 125.2, 80.2, 60.2, 53.9, 52.7, 50.9, 48.6, 42.9, 31.9, 31.1, 31.0, 29.8, 29.4, 28.5, 19.4, 18.4, 17.7.

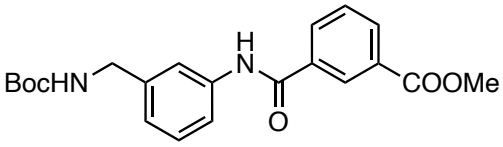
Anal. Calcd. for $C_{36}H_{43}N_5O_9 \cdot 0.1$AcOEt: C, 62.58; H, 6.32; N, 10.03. Found: C, 62.75; H, 6.70; N, 9.68.

Mp: 104.2-105.0℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{36}H_{43}N_5NaO_9^+$, 712.2953. Found: 712.2972.

Photoreaction of Boc-BZN-OMe

Boc-BZA-OMe



In an NMR tube, the solution of Boc-**BZN**-OMe (31.4 mg, 0.060 mmol) in $CDCl_3$ was photo-irradiated with UV light (390 nm). After 30 min, the solution was concentrated and the residue was dissolved in AcOEt. The solution was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated to afford Boc-**BZA**-OMe **(**15.6 mg, 0.041 mmol, 68%) as white solid.

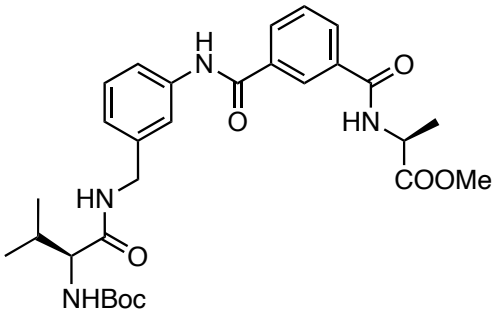
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.48 (1H, dd, *J* = 1.6, 1.6 Hz), 8.20 (1H, ddd, *J* = 7.6, 1.6, 1.6 Hz), 8.12 (1H, ddd, *J* = 8.0, 1.6, 1.6 Hz), 8.09 (1H, s), 7.59 (3H, m), 7.33 (1H, dd, *J* = 8.4, 8.4 Hz), 7.08 (1H, d, *J* = 7.6 Hz), 4.95 (1H, brs), 4.31 (2H, d, *J* = 6.0 Hz), 3.95 (3H, s), 1.46 (9H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.4, 164.8, 138.1, 135.3, 132.9, 132.2, 130.8, 129.5, 129.3, 127.7, 124.0, 119.5, 52.6, 28.6.

Mp: 119.5-120.0℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd for $C_{21}H_{24}N_2NaO_5^+$, 407.1577. Found: 407.1554.

Compound 1b



In an NMR tube, the solution of **1a** (20.0 mg, 0.0029 mmol) in $CDCl_3$ was photo-irradiated with UV light (390 nm). After 20 min, the solution was concentrated. The residue was purified by column chromatography (n-hexane: Acetone = 3: 2) to afford **1b** (14.1 mg, 0.025 mmol, 88%) as brown solid.

The same procedure applies to the reaction in MeOD and in DMSO-d_6, and **1b** was obtained in 97% and 92% yields, respectively.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 9.10 (1H, s), 8.40 (1H, s), 8.06 (1H, d, *J* = 7.2 Hz),

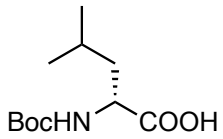
7.90 (2H, d, *J* = 7.6 Hz), 7.52 (1H, d, *J* = 6.4 Hz), 7.42 (1H, dd, *J* = 8.0, 8.0 Hz), 7.31 (1H, brs), 7.18 (1H, dd, *J* = 8.0 Hz), 7.02 (1H, s), 6.86 (1H, d, *J* = 7.2 Hz), 5.55 (1H, d, *J* = 8.8 Hz), 4.74 (1H, q, *J* = 7.2 Hz), 4.33 (1H, dd, *J* = 15.2, 5.6 Hz), 4.15-4.12 (2H, m), 3.63 (3H, s), 2.02-1.97 (1H, m), 1.45 (3H, d, *J* = 7.2 Hz), 1.19 (9H, s), 0.88 (6H, dd, *J* = 7.6, 7.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 173.7, 166.6, 165.7, 156.7, 139.0, 137.9, 135.6, 133.5, 131.6, 130.8, 129.4, 129.2, 125.5, 123.9, 120.0, 119.0, 80.2, 60.0, 53.9, 52.7, 49.0, 44.0, 31.2, 29.8, 29.4, 28.3, 19.5, 18.3, 18.1.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd for $C_{29}H_{38}N_4NaO_7^+$, 577.2633. Found: 577.2644.

Synthesis of 2a

Compound 13



To a solution of D-Leucine (635.0 mg, 4.84 mmol) in 1 M NaOH solution (10 mL), Di-*tert*-butyl dicarbonate (1274.7 mg, 5.84 mmol) dissolved in anhydrous THF (20 mL) was added at 0℃ and the solution was warmed to room temperature. After stirring for 25 h, the reaction mixture was evaporated to remove THF and washed with Et_2O. The aqueous layer was acidified with 5% $KHSO_4$ solution to pH 3 at 0℃ and the solution was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford **13** (1.0972 g, 4.74 mmol, 98%) as colorless oil.

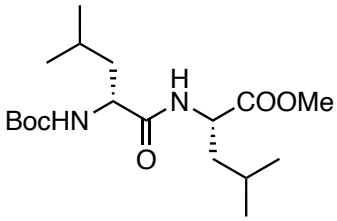
^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 12.40 (1H, brs), 7.04 (1H, d, *J* = 8.4 Hz), 3.92-3.86 (1H, m), 1.64-1.59 (1H, m), 1.540-1.47 (1H, m), 1.44-1.40 (1H, m), 1.37 (9H, s), 0.85 (6H, dd, *J* = 12, 6.4 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 174.7, 155.6, 77.9, 51.8, 28.2, 24.4, 22.9, 21.2.

Anal. Calcd. for $C_{11}H_{21}NO_4 \cdot 0.3H_2O$: C, 55.82; H, 9.20; N, 5.92. Found: C, 55.76; H, 9.34; N, 5.94.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{11}H_{20}NO_4^-$, 230.1398. Found: 230.1401.

Compound 14



To a solution of **13** (1053.3 mg, 4.55 mmol) and L-leucine methyl ester hydrochloride (863.5 mg, 4.75mmol) in anhydrous CH_2Cl_2 (50 mL), TBTU (1666.5 mg, 5.19 mmol) was added at room temperature and the solution was cooled to 0℃. DIPEA (3.17 mL, 18.2 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3.5 h, the reaction mixture was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: AcOEt = 1: 1) to afford **14** (1553.8 mg, 4.33 mmol, 95%) as white powder.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.68 (1H, brs), 4.95 (1H, d, J = 7.6 Hz), 4.62-4.57 (1H, m), 4.15 (1H, brs), 3.72 (3H, s), 1.71-1.46 (6H, m), 1.45 (9H, s), 0.95-0.93 (12H, m).

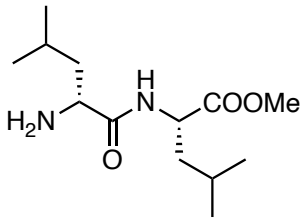
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 172.5, 155.8, 80.2, 52.3, 50.7, 41.5, 41.1, 28.4, 24.9, 24.9, 23.0, 22.9, 21.9.

Anal. Calcd. for $C_{18}H_{34}N_2O_5$: C, 60.31; H, 9.56: N, 7.81. Found: C, 60.30; H, 9.53; N, 7.83.

Mp: 116.0-117.2℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{18}H_{34}N_2NaO_5^+$, 381.2360. Found: 381.2387.

Compound 15



To a solution of **14** (1492.8 mg, 4.16 mmol) in anhydrous CH_2Cl_2 (20 mL), trifluoroacetic acid (5 mL) was added at 0℃ and the solution was warmed to room temperature. After stirring for 2 h, saturated aqueous solution of $NaHCO_3$ (50 mL) was added to the solution and the reaction mixture was extracted with CH_2Cl_2. The organic

layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography ($CHCl_3$: MeOH = 24:1 - 19: 1 - 9: 1) to afford **15** (1029.4 mg, 3.98 mmol, 96%) as colorless oil.

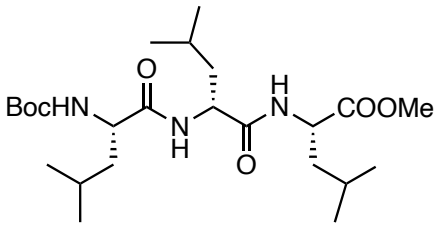
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 (1H, brd, *J* = 8.4 Hz), 4.60 (1H, ddd, *J* = 8.0, 0.8 Hz), 3.73 (3H, s), 3.40 (1H, dd, *J* = 10, 7.6 Hz), 1.74-1.56 (5H, m), 1.48 (2H, brs), 1.40-1.36 (1H, m), 0.97-0.92 (12H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 175.6, 173.7, 53.5, 52.3, 50.5, 44.0, 41.7, 25.1, 25.0, 23.5, 23.0, 22.0, 21.4.

Anal. Calcd. for $C_{13}H_{26}N_2O_3 \cdot 0.2H_2O$: C, 59.60; H, 10.16; N, 10.69. Found: C, 59.60; H, 10.06; N, 10.58.

HRMS (ESI-TOF, $[M+H]^+$): Calcd. for $C_{13}H_{27}N_2O_3^+$, 259.2016. Found: 259.2015.

Compound 16



To a solution of **15** (1023.6 mg, 3.96 mmol) and N-(tert-butoxycarbonyl)-L-leucine (922.3 mg, 3.99 mmol) in anhydrous CH_2Cl_2 (50 mL), TBTU (1401.3 mg, 4.36 mmol) was added at room temperature and the solution was cooled to 0℃. DIPEA (2.76 mL, 15.8 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3 h, the reaction mixture was washed with saturated aqueous solution of NH_4Cl, dried over anhydrous Na_2SO_4 and concentrated. To eliminate TBTU, the crude product was dissolved in AcOEt and the organic solution was washed with 1 M HCl solution, distilled water and brine, dried over anhydrous Na_2SO_4 and concentrated to afford **16** (1497.5 mg, 3.18 mmol, 80%) as white powder.

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 6.85 (1H, brd, *J* = 5.2 Hz), 6.59 (1H, brd, *J* = 7.6 Hz), 4.96 (1H, brd, *J* = 6.0 Hz), 4.55 (1H, ddd, *J* = 8.8, 8.8, 5.2 Hz), 4.50 (1H, ddd, *J* = 8.8, 8.8, 5.2 Hz), 4.08-4.07 (1H, m), 3.70 (3H, s), 1.73-1.48 (9H, m), 1.44 (9H, s), 0.96-0.91 (18H, m).

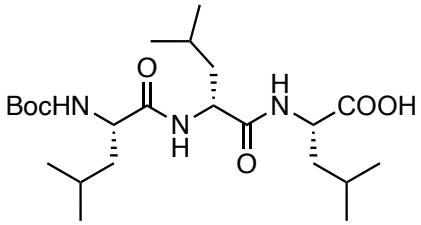
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 173.0, 172.0, 155.7, 80.1, 53.6, 52.2, 51.5, 50.8, 41.2, 40.6, 28.4, 24.9, 24.8, 23.1, 23.0, 22.8, 21.9, 21.9.

Anal. Calcd. for $C_{24}H_{45}N_3O_6$: C, 61.12; H, 9.46: N, 8.77. Found: C, 60.80; H, 9.46; N, 8.77.

Mp: 149.4-150.8℃ (recrystallized from n-hexane / CH_2Cl_2, white needles).

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{24}H_{45}N_3NaO_6^+$, 494.3201. Found: 494.3193.

Compound 17



To a solution of **16** (210.1 mg, 0.45 mmol) in MeOH / THF / distilled water = 3 : 2 : 1 (6 mL), lithium hydroxide monohydrate (37.8 mg, 0.90 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford **17** (168.8 mg, 0.37 mmol, 83%) as white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 12.56 (1H, brs), 8.00 (2H, d, J = 7.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 6.91 (1H, d, J = 7.6 Hz), 4.31 (1H, dd, J = 8.4, 8.4 Hz), 4.21 (1H, dd, J = 8.4, 8.4 Hz), 1.60-1.41 (9H, m), 1.37 (9H, s), 0.88-0.80 (18H, m).

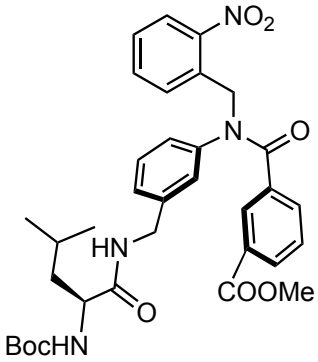
$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 173.8, 172.3, 171.8, 155.3, 78.1, 53.2, 50.7, 50.1, 41.2, 40.6, 28.2, 24.3, 24.2, 24.1, 23.1, 22.9, 22.8, 21.7, 21.4, 21.3.

Anal. Calcd. for $C_{23}H_{43}N_3O_6 \cdot 0.4H_2O \cdot 0.3DMSO$: C, 58.06; H, 9.41; N, 8.61. Found: C, 57.80; H, 9.08; N, 8.59.

Mp: 189.0-190.2℃ (recrystallized from n-hexane / CH_2Cl_2, white crystals).

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{23}H_{42}N_3O_6^-$, 456.3079. Found: 456.3090.

Compound 18



To a solution of **11** (428.3 mg, 1.02 mmol) in anhydrous CH_2Cl_2 (13 mL), N-(*tert*-butoxycarbonyl)-L-leucine (236.3 mg, 1.02 mmol), EDCI·HCl (236.5 mg, 1.23 mmol) and HOBt (167.5 mg, 1.24 mmol) were added at room temperature and the solution was cooled to 0°C. Et_3N (300 μL, 2.08 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 28 h, the reaction mixture was concentrated and dissolved in CH_2Cl_2. The organic solution was washed with brine and saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: Acetone = 5: 2) to afford **18** (579.8 mg, 0.94 mmol, 92%) as colorless powder.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.00 (1H, brs), 7.96 (1H, dd, *J* = 8.4, 1.2 Hz), 7.93 (1H, ddd, *J* = 7.6, 1.6, 1.2 Hz), 7.76 (1H, dd, *J* = 8.0, 1.2 Hz), 7.66 (1H, ddd, *J* = 7.6, 1.6, 1.6 Hz), 7.56 (1H, brd, *J* = 7.6 Hz), 7.44 (1H, ddd, *J* = 8.0, 1.2, 1,2 Hz), 7.29 (1H, dd, *J* = 8.0, 8.0 Hz), 7.07-7.03 (3H, m), 6.72-6.69 (1H, m), 6.58 (1H, brd, *J* = 5.6, 5.6 Hz), 5.54 (2H, s), 5.06 (1H, brs), 4.42 (1H, brdd, *J* = 14.8, 8.4 Hz), 4.23-4.12 (2H, m), 3.83 (3H, s), 1.76-1.66 (2H, m), 1.52-1.48 (1H, m), 1.42 (9H, s), 0.96-0.93 (6H, m).

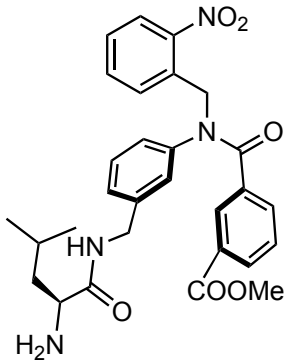
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm): 172.8, 169.6, 166.3, 155.8, 148.6, 143.0, 140.2, 135.5, 133.7, 133.1, 132.4, 131.0, 130.2, 129.8, 129.7, 129.6, 128.4, 128.2, 126.8, 126.7, 126.4, 125.0, 80.0, 53.2, 52.4, 50.9, 42.8, 41.3, 28.3, 24.8, 23.0, 21.9.

Anal. Calcd. for $C_{34}H_{40}N_4O_8 \cdot 0.4H_2O$: C, 63.82; H, 6.43; N, 8.76. Found: C, 63.55; H, 6.30; N, 8.66.

Mp: 82.0-83.0°C.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{34}H_{40}N_4NaO_8^+$, 655.2738. Found: 655.2767.

Compound 19



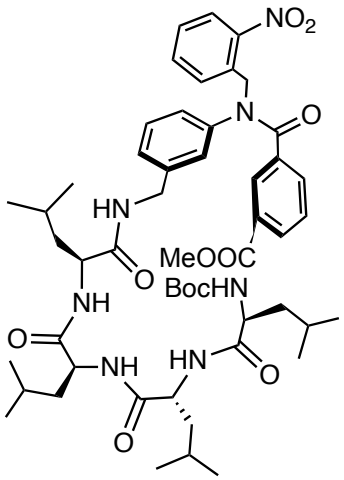
To a solution of **18** (316.9 mg, 0.51 mmol) in anhydrous CH_2Cl_2 (5 mL), trifluoroacetic acid (400 μL) was added at 0℃ and the solution was stirred at room temperature. After 3.5 h, TLC showed that the reaction was not yet finished, so trifluoroacetic acid (400 μL) was added to the reaction mixture. After stirring for 1 h, saturated aqueous solution of $NaHCO_3$ (10 mL) was added to the reaction mixture and the solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford **19** (249.9 mg, 92.0 mmol, 92%) as yellow fluffy solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.07 (1H, dd, *J* = 1.6, 1.6 Hz), 7.96 (1H, dd, *J* = 8.0, 1.2 Hz), 7.93 (1H, ddd, *J* = 8.0, 1.2, 1.2 Hz), 7.74 (1H, dd, *J* = 8.0, 1.2 Hz), 7.65 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.65-7.63 (1H, m), 7.51 (1H, ddd, *J* = 7.6, 1.6, 1.6 Hz), 7.42 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.26 (1H, ddd, *J* = 7.6, 7.6, 0.4 Hz), 7.09 (1H, dd, *J* = 7.8, 7.8 Hz), 7.05-7.03 (1H, m), 7.00-6.99 (1H, m), 6.84-6.81 (1H, m), 5.53 (2H, s), 4.29-4.27 (2H, m), 3.85 (3H, s), 3.36 (1H, dd, J = 10, 4.0 Hz), 1.77-1.65 (2H, m), 1.35-1.24 (1H, m), 0.95 (3H, d, *J* = 6.4 Hz), 0.92 (3H, d, *J* = 6.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 175.6, 169.5, 166.0, 148.4, 142.9, 140.5, 135.4, 133.6, 132.9, 132.4, 130.9, 130.0, 129.8, 129.5, 129.4, 128.2, 128.0, 126.5, 126.2, 126.2, 124.9, 53.3, 52.1, 50.9, 43.9, 42.2, 24.7, 23.3, 21.2.

HRMS (ESI-TOF, $[M+H]^+$): Calcd. for $C_{29}H_{33}N_4O_6^+$, 533.2395. Found: 533.2409.

Compound 20



To a solution of **19** (170.7 mg, 0.32 mmol) and **17** (166.5 mg, 0.36 mmol) in anhydrous DMF (5 mL), TBTU (124.6 mg, 0.39 mmol) was added at room temperature and the solution was cooled to 0°C. DIPEA (223 μL, 1.28 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3 h, water was added to the reaction mixture at 0°C and the solution was extracted with n-hexane: AcOEt (3: 1). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: Acetone = 2: 1 + Et_3N (3%)) to afford **20** (275.9 mg, 0.28 mmol, 89%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.15 (1H, s), 8.00 (1H, dd, *J* = 8.0, 1.2 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.71 (1H, d, *J* = 7.6 Hz), 7.65 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.50 (1H, d, *J* = 8.0 Hz), 7.42 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz), 7.44-7.39 (2H, m), 7.33 (1H, brs), 7.26 (1H, dd, *J* = 8.0, 8.0 Hz), 7.23 (1H, brs), 7.01-7.02 (3H, m), 6.73 (1H, brd, *J* = 7.6 Hz), 5.60 (1H, brs), 5.60-5.54 (2H, m), 4.51-4.46 (1H, m), 4.39 (1H, dd, *J* = 15.6, 6.4 Hz), 4.31 (1H, brs), 4.20 (1H, dd, *J* = 15.2, 4.8 Hz), 4.18 (1H, brs), 4.06-4.01 (1H, m), 3.88 (3H, s), 1.74-1.42 (12H, m), 1.39 (9H, s), 0.93-0.83 (24H, m).

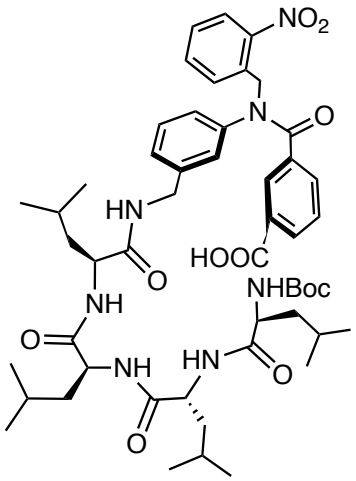
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): (some peaks of Leu side chain were overlapped) δ (ppm) 174.0, 172.8, 172.7, 169.8, 166.3, 156.4, 148.5, 143.0, 140.3, 135.7, 133.7, 133.1, 132.8, 131.0, 130.2, 130.0, 129.4, 128.2, 128.1, 126.7, 126.2, 125.1, 80.4, 53.6, 52.6, 52.3, 51.5, 42.8, 40.4, 40.0, 39.2, 28.3, 25.0, 24.9, 24.8, 23.13, 23.05, 22.9, 22.8, 22.7.

Anal. Calcd. for $C_{52}H_{73}N_7O_{11}$: C, 64.24; H, 7.64; N, 10.09. Found: C, 63.86; H, 7.64; N, 10.20.

Mp: 158.0-159.0℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{52}H_{73}N_7NaO_{11}^+$, 994.5260. Found: 994.5280.

Compound 8



To a solution of **20** (59.5 mg, 0.061 mmol) in MeOH (1 mL), lithium hydroxide monohydrate (6.9 mg, 0.16 mmol) was added at room temperature. Distilled water (1 mL) and THF (2 mL) was added to the solution and stirred at room temperature. After stirring for 3 h, the reaction mixture was acidified by 2.5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. TLC showed that the starting material did not disappear, so the reaction was performed again. The crude product was dissolved in MeOH (1 mL) and Lithium hydroxide monohydrate (13.4 mg, 0.32 mmol) and distilled water / THF (1: 1, 8 mL) was added to the solution at room temperature. After stirring for 3 h, the reaction mixture was acidified by 2.5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford **8** (53.6 mg, 0.056 mmol, 92%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 7.99 (1H, d, *J* = 8.0 Hz), 7.94 (1H, d, *J* = 8.0 Hz), 7.87 (1H, brs), 7.79 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 7.6 Hz), 7.64 (2H, dd, *J* = 7.6, 7.6 Hz), 7.42 (1H, dd, *J* = 8.0, 8.0 Hz), 7.38 (1H, brs), 7.36 (1H, dd, *J* = 8.0, 8.0 Hz), 7.29-7.21 (3H, m), 7.07 (1H, d, *J* = 7.6 Hz), 7.01 (1H, dd, *J* = 7.6, 7.6 Hz), 6.66 (1H, d, *J* = 7.6 Hz), 5.54 (3H, s), 4.58-4.39 (3H, m), 4.32 (1H, brs), 4.12 (1H, m), 1.71-1.51 (12H, m), 1.40 (9H, s), 0.90-0.85 (24H, m).

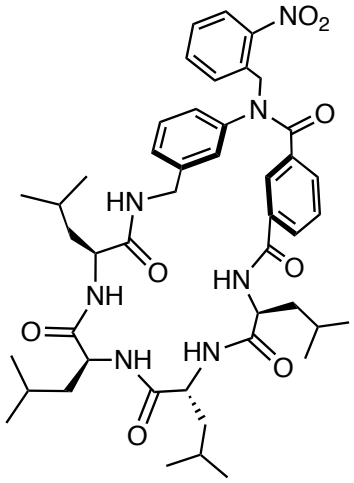
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 174.0, 173.1, 172.7, 172.4, 169.6, 156.3, 148.6, 143.3, 140.2, 135.1, 133.8, 133.7, 132.7, 131.5, 130.8, 129.7, 129.5, 128.5, 128.3, 127.5, 126.8, 125.1, 80.4, 53.5, 53.0, 52.4, 51.9, 51.4, 43.2, 40.7, 40.6, 40.3, 29.8, 28.4, 24.92, 24.88, 24.82, 23.1, 23.0, 22.9, 21.9. (some peaks of Leu side chain were overlapped)

Anal. Calcd. for $C_{51}H_{71}N_7O_{11}\cdot 0.2CHCl_3$: C, 62.62; H, 7.31; N, 9.98. Found: C, 62.60; H, 7.37; N, 9.82.

Mp: 175.2-176.8℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{51}H_{71}N_7NaO_{11}^+$, 980.5104. Found: 994.5100.

Compound 2a



To a solution of **8** (132.5 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (2 mL), trifluoroacetic acid (200 μL, excess) was added at 0℃ and the solution was stirred at room temperature. After 4 h, the reaction was not yet finished, so trifluoroacetic acid (200 μL) was added at 0℃ to the reaction mixture. After stirring 1 h at room temperature, saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture and the solution was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to afford crude amine (152.4 mg). To a solution of the crude product in anhydrous DMF (140 mL, 1.0 mM), HATU (159.8 mg, 0.42 mmol) was added at room temperature and the solution was cooled to 0℃. DIPEA (146 μL, 0.84 mmol) was added to the solution and the solution was warmed to room temperature. After stirring for 18.5 h, water was added to the reaction mixture at 0℃ and the solution was extracted with n-

hexane / AcOEt (3: 1). The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane: AcOEt: Acetone = 3: 1: 1, Hexane: AcOEt: Acetone = 5: 1: 1, $CHCl_3$: MeOH = 99: 1 - 49: 1 - 19: 1, CH_2Cl_2: MeOH = 20: 0 - 19: 1) to afford **2a** (21.4 mg, 0.025 mmol, 18%) as white solid.

^{1}H-NMR (400 MHz, $CDCl_3$) : δ (ppm) 8.03 (1H, d, *J* = 7.6 Hz), 7.71 (1H, d, *J* = 7.6 Hz), 7.68-7.66 (3H, m), 7.45-7.41 (1H, m), 7.40 (1H, brd, *J* = 8.8 Hz), 7.37 (1H, dd, *J* = 8.0 Hz), 7.30 (1H, brd, *J* = 5.2 Hz), 7.26 (1H, dd, J = 8.0, 8.0 Hz), 7.20 (1H, s), 7.07 (1H, dd, *J* = 8.0, 1.2 Hz), 6.99 (1H, brt, *J* = 6.4 Hz), 6.89 (1H, d, *J* = 8.0 Hz), 6.71 (1H, d. *J* = 8.0 Hz), 6.58 (1H, s), 6.40 (1H, brd, *J* = 8.0 Hz), 5.65 (1H, d, *J* = 17.0 Hz), 5.49 (1H, d, *J* = 17.0 Hz), 4.57 (1H, dt, *J* = 8.4, 6.8 Hz), 4.40-4.28 (2H, m), 4.19 (1H, dd, *J* = 16.0, 7.2 Hz), 4.03 (1H, dt, *J* = 7.2, 5.6 Hz), 3.77 (1H, dd, *J* = 16.0, 5.2 Hz), 1.86-1.49 (12H, m), 0.99-0.89 (24H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.6, 172.8, 172.1, 169.6, 169.5, 148.4, 143.1, 140.1, 135.4, 134.0, 133.9, 132.8, 132.4, 130.1, 129.7, 129.1, 128.8, 128.3, 127.4, 127.0, 125.3, 124.9, 124.1, 53.9, 53.1, 52.0, 51.1, 50.9, 42.5, 40.4, 39.6, 39.5, 39.3, 25.3, 25.0, 24.92, 24.90, 23.3, 23.1, 22.9, 22.5, 22.3. (some peaks of Leu side chain were overlapped)

HPLC (250 nm): t_R 9.05 min, 95%.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{46}H_{61}N_7NaO_8^+$, 862.4474. Found: 862.4497.

Compound 2b

In an NMR tube, the solution of **2a** (8.5 mg, 0.010 mmol) in DMSO-d_6 was photo-irradiated with UV light (390 nm). After 10 min, the solution was divided by column chromatography (n-hexane: AcOEt = 3: 1). DMSO was still remained, so the product dissolved in the solution (n-hexane: AcOEt = 4: 1), washed with water and brine, dried over Na_2SO_4 and concentrated to afford **2b** (6.9 mg, 0.010 mmol, 97%) as white solid.

^{1}H-NMR (400 MHz, DMSO-d_6) : δ (ppm) 9.50 (1H, s), 8.97 (1H, d, *J* = 6.4 Hz), 8.89 (1H, d, *J* = 7.6 Hz), 8.86 (1H, s), 8.38 (1H, t, *J* = 6.4 Hz), 8.31 (1H, d, *J* = 7.6 Hz), 8.31 (1H, d, *J* = 7.6 Hz), 8.18 (1H, d, *J* = 8.4 Hz), 8.14 (1H, d, *J* = 7.6 Hz), 7.66 (1H, dd, *J* = 8.0, 8.0 Hz), 7.57 (1H, d, *J* = 9.6 Hz), 7.30 (1H, dd, *J* = 8.0, 8.0 Hz), 7.23 (1H, s), 6.98

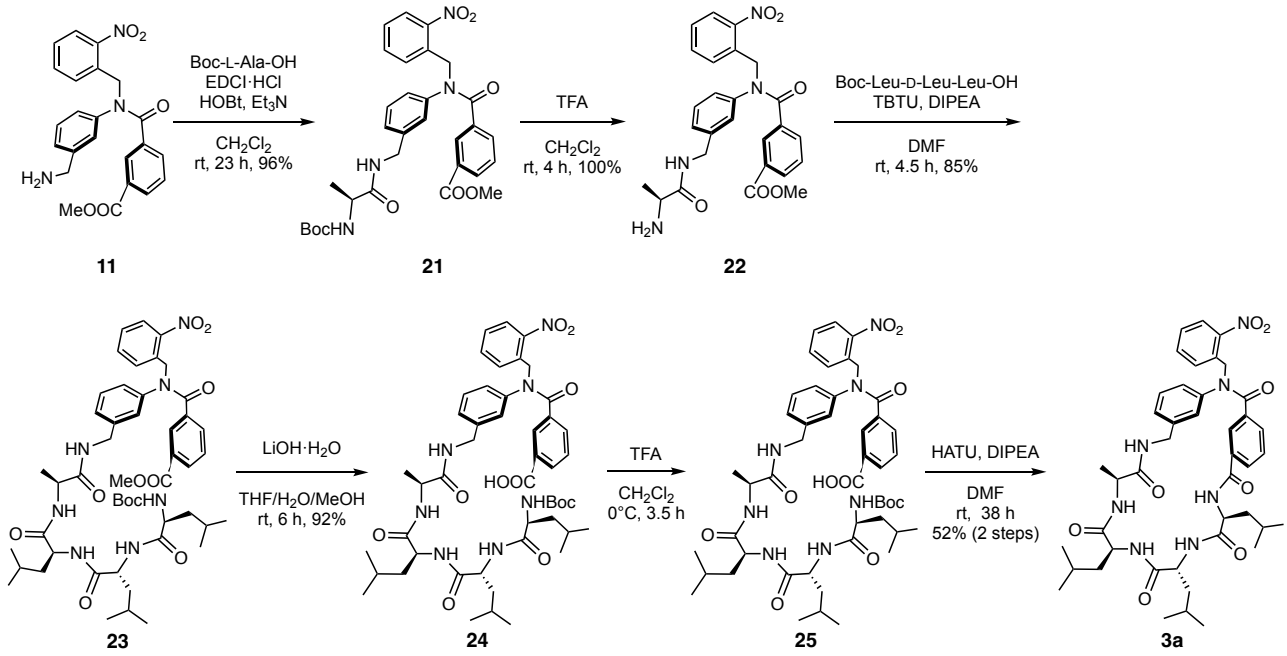
(1H, d, *J* = 8.0 Hz), 4.63-4.57 (1H, m), 4.45 (1H, dd, *J* = 16.4, 6.8 Hz), 4.43-4.37 (1H, m), 4.34-4.28 (1H, m), 4.20 (1H, dd, *J* = 16.4, 5.6 Hz), 4.06-4.01 (1H, m), 1.68-1.54 (12H, m), 0.98-0.89 (15H, m), 0.81 (3H, d, *J* = 6.4 Hz), 0.51 (3H, d, *J* = 5.6 Hz), 0.32 (3H, d, *J* = 5.6 Hz).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.0, 172.9, 171.9, 171.6, 167.4, 139.4, 138.8, 135.6, 133.5, 131.7, 129.6, 129.5, 128.4, 127.0, 122.0, 117.9, 117.2, 54.7, 54.2, 52.8, 51.2, 42.5, 40.7, 40.6, 40.1, 39.6, 29.8, 25.4, 25.2, 25.2, 24.3, 23.3, 23.0, 22.9, 22.5.

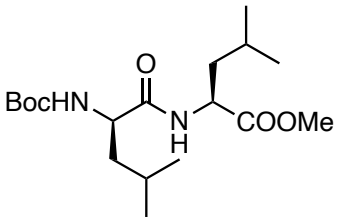
HPLC (250 nm): t_R 7.94 min, 99%.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{46}H_{61}N_7NaO_8^+$, 862.4474. Found: 862.4497.

Synthesis of 3a/ 3b



Boc-D-Leu-L-Leu-OMe



To a solution of Boc-D-Leu-OH (2.0012 g, 8.15 mmol) and L-leucine methyl ester hydrochloride (1.4803 g, 8.15 mmol) in anhydrous CH_2Cl_2 (15 mL), TBTU (2.8807 g, 8.97 mmol) was added at room temperature and the solution was cooled to 0°C. DIPEA (5.68 mL, 32.6 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3.5 h under Ar atmosphere, the reaction mixture was washed with 5% $KHSO_4$, saturated aqueous solution of Na_2CO_3, and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane / AcOEt = 4: 1) to afford Boc-D-Leu-L-Leu-OMe (2.3244 g, 6.48 mmol, 80%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.68 (1H, brs), 4.95 (1H, d, J = 7.2 Hz), 4.60-4.54 (1H, m), 4.13 (1H, brs), 3.69 (3H, s), 1.68-1.46 (6H, m), 1.42 (9H, s), 0.92-0.90 (12H, m).

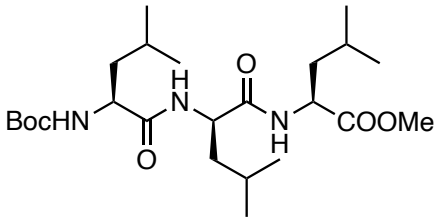
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 172.5, 155.8, 80.2, 53.1, 52.3, 50.7, 41.5, 41.1, 28.4, 24.89, 24.86, 23.0, 22.9, 22.0, 21.9.

Anal. Calcd. for $C_{18}H_{34}N_2O_5$: N, 7.81; C, 60.31; H, 9.56. Found: N, 7.75; C, 60.23; H, 9.47.

Mp: 116.0-117.2℃.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{18}H_{34}N_2O_5Na^+$, 381.2360. Found: 381.2374.

Boc- L-Leu-D-Leu-L-Leu-OMe



TFA (4 mL) was added to a solution of Boc-D-Leu-L-Leu-OMe (1.0676 g, 2.98 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0℃. The mixture was stirred for 30 min at 0℃, then warm to room temperature and was stirred another 1.5 h. The solvent was evaporated. 10% aqueous solution of Na_2CO_3 was added to the residue to adjust the pH to about 9, and the whole was extracted with EtOAc (20 mL x 3) and dried over Na_2SO_4. Evaporation of solvent gave the crude amine as white solid.

To a solution of crude amine and Boc-L-Leu-OH (0.743 g, 2.98 mmol) in anhydrous DMF (10 mL), TBTU (1.0526 g, 3.28 mmol) was added at room temperature and the solution was cooled to 0℃. DIPEA (2.08 mL, 11.94 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 4 h under Ar atmosphere, the reaction mixture was washed with 5% $KHSO_4$, saturated aqueous solution of $NaHCO_3$, and brine. The solid then was filtered and washed by AcOEt to afford Boc- L-Leu-D-Leu-L-Leu-OMe (1.1786 g, 2.50 mmol, 84%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 4.46-4.42 (2H, m), 4.02 (1H, t, J = 7.6 Hz), 3.70 (3H, s), 1.68-1.60 (7H, m), 1.52 (2H, t, J = 7.2 Hz), 1.44 (9H, s), 0.97-0.90 (18H, s).

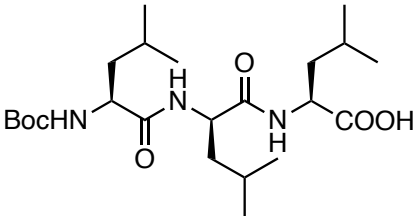
$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD): δ (ppm) 175.8, 174.6, 174.3, 157.9, 80.6, 55.0, 52.9, 52.6, 52.2, 41.9, 41.8, 41.4, 28.8, 25.9, 23.6, 23.2, 22.2, 21.9, 21.6.

Anal. Calcd. for $C_{24}H_{45}N_3O_6$: N, 8.91; C, 61.12; H, 9.62. Found: N, 8.88; C, 61.36; H, 9.32.

Mp: 150-151ºC.

HRMS (ESI$^+$, [M+Na]$^+$): Calcd. For $C_{24}H_{45}N_3O_6Na^+$: 494.3201, Found: 494.3220.

Boc- L-Leu-D-Leu-L-Leu-OH



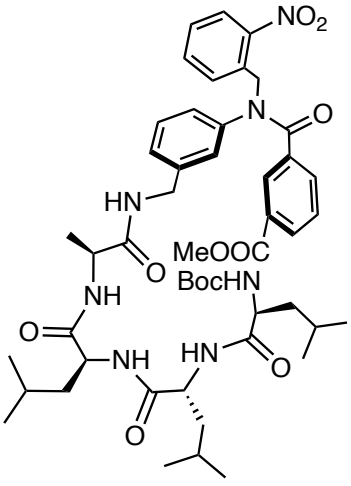
To a solution of Boc- L-Leu-D-Leu-L-Leu-OMe (1.1786 g, 2.5 mmol) in MeOH (10 mL), THF (6 mL), distilled water (3 mL), lithium hydroxide monohydrate (209.8 mg, 5.0 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3, extracted by AcOEt, washed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The solid was dried to afford crude carboxylic acid (1.8770 g, 100%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 12.56 (1H, brs), 8.00 (2H, d, J = 7.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 6.91 (1H, d, J = 7.6 Hz), 4.31 (1H, dd, J = 8.4, 8.4 Hz), 4.21 (1H, dd, J = 8.4, 8.4 Hz), 1.60-1.41 (18H, m), 1.37 (9H, s), 0.88-0.80 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.8, 172.3, 171.8, 155.3, 78.1, 53.2, 50.7, 50.1, 41.2, 40.6, 28.2, 24.3, 24.2, 24.1, 23.1, 22.9, 22.8, 21.7, 21.4, 21.3.

HRMS (ESI-TOF, [M-H]$^-$): Calcd. for $C_{23}H_{42}N_3O_6^-$, 456.3079. Found: 456.3090.

Compound 23



To a solution of **21** (351.4 mg, 0.595 mmol) in anhydrous CH_2Cl_2 (2 mL), trifluoroacetic acid (2 mL) was added at 0℃ and the solution was warmed to room temperature. After stirring for 2.5 h, saturated aqueous solution of Na_2CO_3 was added to the reaction mixture and adjust the pH to 9. The solution was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The free amine **22** (348.7 mg, 100%) was obtained as yellow amorphous.

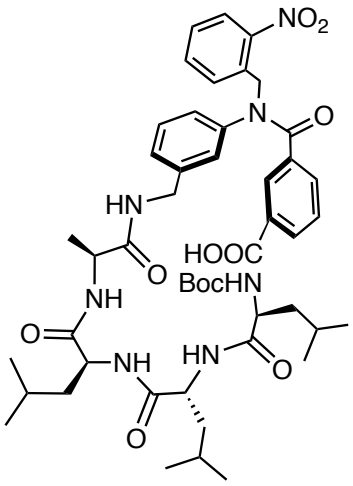
To a solution of **22** (348.7 mg) and Boc- L-Leu-D-Leu-L-Leu-OH (272.3 mg, 0.595 mmol) in anhydrous DMF (8 mL), TBTU (211.3 mg, 0.658 mmol) and DIPEA (0.415 mL, 2.38 mmol) were added at 0℃, and the reaction mixture was stirred at rt for 4.5 h under Ar atmosphere. The mixture was wash with 5%$KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. Extracted the mixture with AcOEt, dried with $NaSO_4$, evaporated and dried in vacuum. Column chromatography (n-hexane: AcOEt=3:1-1:2) gave **23** (469.8 mg, 0.505 mmol, 85%) as white amorphous.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.07 (1H, s), 7.98 (1H, d, *J* = 8.0 Hz), 7.91 (1H, d, *J* = 8.0 Hz), 7.73 (1H, d, *J* = 7.2 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 7.53 (1H, d, *J* = 8.0 Hz), 7.41 (1H, t, *J* = 7.6 Hz), 7.34 (1H, d, *J* = 7.6 Hz), 7.28-7.24 (1H, m), 7.19 (1H, s), 7.13 (1H, d, *J* = 6.4 Hz), 7.04 (3H, d, *J* = 4.8 Hz), 6.78 (1H, d, *J* = 7.2 Hz), 6.72 (1H, d, *J* = 2.8 Hz), 5.57 (1H, d, *J* = 16.8 Hz), 5.50 (1H, d, *J* = 16.8 Hz), 5.42 (1H, d, *J* = 6.4 Hz), 4.49-4.42 (1H, m), 4.37-4.05 (6H, m), 3.87 (3H, s), 1.77-1.42 (11H, m), 1.36 (9H, s), 0.93-0.86 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.1, 172.9, 172.6, 172.5, 169.9, 166.5, 148.6, 140.2, 135.7, 133.8, 133.3, 132.8, 131.1, 130.3, 130.0, 129.6, 128.3, 128.3, 127.0, 126.5, 80.5, 60.5, 53.4, 52.6, 52.5, 51.5, 48.9, 43.0, 40.5, 40.3, 39.2, 38.7, 28.4, 25.1, 24.9, 24.9, 23.2, 22.9, 22.1, 21.4, 21.17, 17.3, 14.3.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{49}H_{67}N_7O_{11}Na^+$: 952.4791. Found: 952.4817.

Compound 24



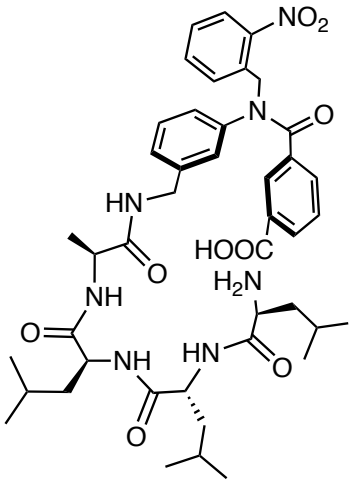
To a solution of **23** (382.8 mg, 0.412 mmol) in MeOH / THF / distilled water = 6 mL: 4 mL: 2 mL, lithium hydroxide monohydrate (138.4 mg, 3.30 mmol) was added at room temperature. After stirring for 21 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford **24** (402.8 mg, 100%) as white amorphous.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 (1H, d, *J* =8.0 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.84 (1H, d, *J* = 7.6 Hz), 7.78 (1H, s), 7.74 (1H, d, *J* = 8.0 Hz), 7.66-7.62 (2H, m), 7.44-7.36 (4H, m), 7.07-6.99 (3H, m), 6.66 (1H, d, *J* = 8.0 Hz), 5.57-5.47 (2H, m), 4.53-4.20 (6H, m), 4.11 (1H, q, *J* = 7.2 Hz), 1.69-1.44 (9H, m), 1.39 (9H, s), 1.33-1.23 (5H, m), 0.92-0.85 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 174.9, 174.0, 173.1, 172.6, 172.3, 171.2, 169.5, 169.1, 156.2, 148.6, 143.2, 140.1, 135.0, 133.9, 133.7, 132.5, 131.4, 130.7, 129.8, 129.6, 129.2, 128.6, 128.3, 127.6, 127.5, 127.2, 125.1, 80.4, 60.4, 53.2, 52.6, 52.1, 51.2, 49.0, 43.2, 40.9, 40.1, 38.6, 28.3, 24.8, 24.8, 22.9, 22.8, 22.0, 21.8, 21.5, 21.0, 20.7, 17.8, 14.2.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{48}H_{64}N_7O_{11}^-$, 914.4669. Found: 914.4696.

Compound 25



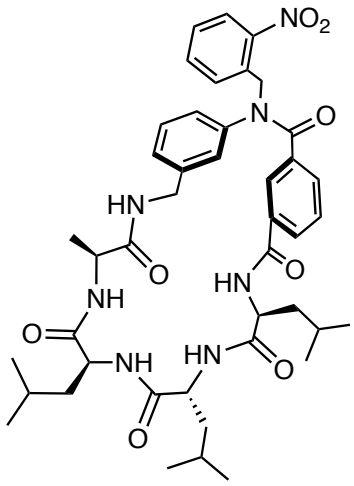
To a solution of **24** (367.3 mg, 0.401 mmol) in TFA (4 mL) and CH_2Cl_2 (1 mL) at 0℃. The mixture was stirred for 3.5 h at 0℃. The solvent was then evaporated. 10% aqueous solution of Na_2CO_3 was added to the residue to adjust the pH to about 9, and the whole was extracted with AcOEt and dried over Na_2SO_4. Evaporation of solvent gave crude **25** (0.8306 g, 100%) as yellow amorphous.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 8.02 (1H, s), 7.99 (1H, dd, *J* = 1.6, 4.4 Hz), 7.87 (1H, dt, *J* = 1.2, 7.6 Hz), 7.75 (1H, d, *J* = 7.2 Hz), 7.69 (1H, td, *J* = 1.2, 4.0 Hz), 7.49 (1H, t, *J* = 8.0 Hz), 7.38 (1H, d, *J* = 7.6Hz), 7.23-7.18 (2H, m), 7.06-7.01 (2H, m), 6.81 (1H, 6.8 Hz), 5.53 (1H, d, *J* = 16.4 Hz), 5.47 (1H, d, *J* = 16.4 Hz), 4.37-4.18 (6H, m), 1.69-1.31 (9H, m), 1.24 (3H, t, *J* = 7.2 Hz), 0.95-0.87 (18H, m)

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 178.4, 175.9, 174.8, 174.6, 173.9, 173.0, 163.3, 162.9, 141.5, 136.4, 133.3, 131.7, 130.9, 130.2, 129.4, 128.4, 127.2, 125.8, 119.5, 116.6, 61.5, 54.0, 53.9, 53.6, 50.7, 45.1, 43.2, 41.1, 40.9, 38.9, 25.91, 25.86, 25.82, 23.6, 23.3, 23.1, 22.6, 22.3, 21.3,20.9, 17.8, 14.4.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{43}H_{56}N_7O_9^-$, 814.4145. Found: 814.4132.

Compound 3a



To a solution of **25** (0.3272 mg, 0.401 mmol) in anhydrous DMF (30 mL), the solution was cooled to 0℃ and then HATU (168 mg, 0.444mmol) was added. DIPEA (280 μL, 1.61 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 38 h under Ar atmosphere, the reaction mixture was added with AcOEt and washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane/ AcOEt = 1: 1- 1:3) to afford **3a** (165.9 mg, 0.208 mmol, 52%) as orange amorphous.

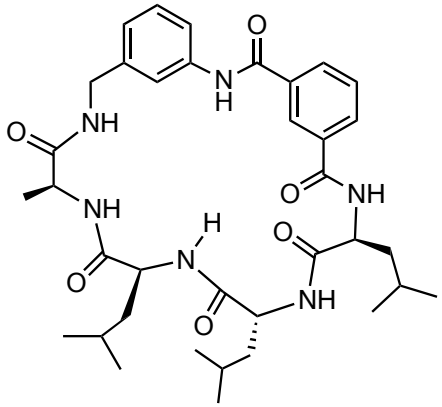
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.69 (1H, d, J = 6.0 Hz), 8.38 (1H, s), 8.30 (1H, s), 8.14 (1H, s), 8.02 (2H, d, J = 8.0 Hz), 7.84 (1H, s, J = 7.2 Hz), 7.76 (2H, t, J = 7.2 Hz), 7.63 (1H, d, J = 7.6 Hz), 7.54 (1H, t, J = 7.6 Hz), 7.31-7.19 (4H, m), 6.97 (1H, d, J = 7.2 Hz), 6.70 (1H, s), 5.36 (2H, s), 4.66 (1H, d, J = 6.0 Hz), 4.29 (1H, brs), 4.09-3.98 (4H, m), 1.64-1.45 (11H, m), 1.21 (3H, d, J = 7.6 Hz), 0.95-0.76 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 178.9, 172.3, 172.0, 171.6, 169.8, 165.3, 162.3, 148.2, 142.4, 140.4, 135.8, 134.1, 133.8, 131.9, 130.5, 129.0, 127.5, 127.2, 126.6, 125.6, 124.74, 124.67, 59.7, 52.6, 51.4, 50.3, 48.7, 40.9, 38.2, 35.7, 30.7, 24.4, 24.2, 24.0, 23.2, 22.7, 22.5, 22.1, 21.8, 20.9, 20.7, 17.9, 14.0.

HPLC (250 nm): t_R 12.08 min, 95% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{43}H_{55}N_7O_8Na^+$: 820.4004. Found: 820.4027.

Compound 3b



In an NMR tube, the solution of **3a** (28.2 mg, 0.035 mmol) in DMSO-d_6 was photo-irradiated with UV light (390 nm). After 20 min, the solvent was evaporated and the crude compound was column-chromatographed ($CHCl_3$: MeOH = 40:1) to afford **3b** (15.2 mg, 0.023 mmol, 66%) as yellow oil.

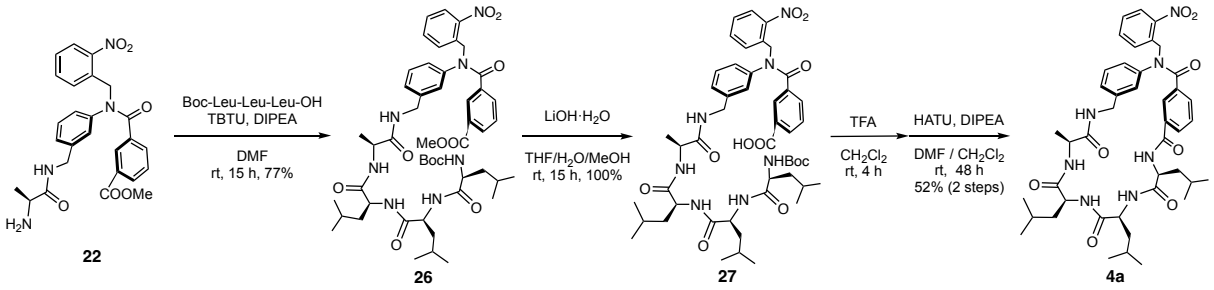
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.61 (1H, s), 8.93 (1H, d, J = 5.6 Hz), 8.90 (1H, d, J = 8.0 Hz), 8.81 (1H, s), 8.40-8.35 (1H, m), 8.29 (1H, d, J = 8.0 Hz), 8.17 (1H, d, J = 9.6 Hz), 8.13 (1H, d, J = 8.0 Hz), 8.74 (1H, d, J = 9.6 Hz), 7.66 (1H, t, J = 7.6 Hz), 7.30 (1H, t, J = 7.6 Hz), 7.21 (1H, s), 6.98 (1H, d, J = 8.0 Hz), 4.59-4.54 (1H, m), 4.49-4.39 (2H, m), 4.32 (1H, t, J = 7.2 Hz), 4.20 (1H, dd, J = 16.4, 5.6 Hz), 4.14-4.08 (1H, m), 1.69-1.56 (7H, m), 1.33-1.23 (5H, m), 0.97 (3H, d, J = 6.0 Hz), 0.92-0.90 (7H, m), 0.82 (3H, d, J = 6.4 Hz), 0.54 (3H, d, J = 6.0 Hz), 0.40 (3H, d, J = 6.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.2, 172.6, 171.5, 171.4, 165.8, 163.7, 139.8, 138.7, 134.0, 132.6, 131.4, 130.3, 128.8, 128.7, 127.0, 121.9, 117.5, 117.1, 53.4, 51.9, 50.1, 49.3, 41.2, 40.8, 24.4, 24.3, 23.4, 23.3, 22.8, 22.4, 22.2, 21.7, 20.5, 17.9.

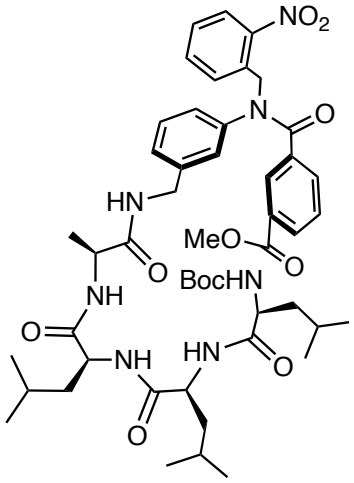
HPLC (250 nm): t_R 8.99 min, 93% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{36}H_{50}N_6O_6Na^+$, 685.3684. Found: 685.3699.

Synthesis of 4a/ 4b



Compound 26



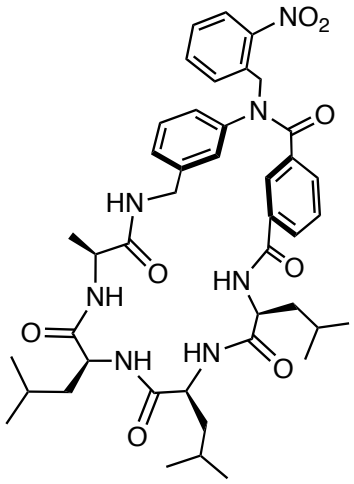
To a solution of **22** (292.3 mg, 0.596 mmol) and Boc-L-Leu-L-Leu-L-Leu-OH (281.1 mg, 0.596 mmol) in anhydrous DMF (2 mL), CH_2Cl_2 (4 mL), TBTU (211.2 mg, 0.658 mmol) and DIPEA (0.416 mL, 2.388 mmol) were added at 0°C, and the reaction mixture was stirred at rt for 15 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in AcOEt. The mixture was washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4 and evaporated. Column chromatography (n-hexane: AcOEt=2:1-1:3) gave **26** (0.4246 g, 0.456 mmol, 77%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 8.16 (1H, t, J = 5.6 Hz), 8.05-7.99 (2H, m), 7.99-7.91 (4H, m), 7.87 (1H, dt, J = 8.4, 0.8 Hz), 7.75-7.66 (2H, m), 7.56-7.46 (2H, m), 7.32 (1H, t, J = 7.6 Hz), 7.24 (1H, s), 7.11-7.06 (2H, m), 6.88-6.86 (1H, m), 5.52 (2H, s), 4.41-4.26 (5H, m), 4.04 (1H, t, J = 7.6 Hz), 3.87 (3H, s), 1.71-1.48 (9H, m), 1.45 (9H, s), 1.35 (3H, d, J = 7.6 Hz), 0.96-0.88 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 174.9, 171.9, 170.6, 167.6, 163.2, 158.2,

157.1, 150.3, 147.2, 144.0, 141.9, 137.3, 134.6, 134.2, 133.1, 131.9, 131.3, 131.2, 130.9, 130.4, 129.7, 129.4, 128.0, 127.5, 125.9, 80.8, 53.9, 53.4, 52.8, 52.1, 50.8, 43.9, 43.8, 43.2, 41.8, 41.4, 41.2, 40.4, 38.9, 37.4, 28.8, 25.9, 25.8, 23.6, 23.4, 22.1, 21.8, 19.4, 18.1. HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{49}H_{67}N_7O_{11}Na^+$: 952.4791. Found: 952.4783.

Compound 4a



To a solution of **26** (0.3259 g, 0.35 mmol) in MeOH / THF / distilled water = 3 : 2 : 1 (6 mL), lithium hydroxide monohydrate (88.1 mg, 2.10 mmol) was added at room temperature. After stirring for 15 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the crude carboxylic acid **27** (0.3206 g, 0.35 mmol, 100%) as yellow amorphous.

To a solution of crude acid (0.3206 g, 0.35 mmol) in anhydrous CH_2Cl_2 (2 mL), trifluoroacetic acid (3 mL) was added at 0℃ and the solution was stirred at room temperature for 4 h. $CHCl_3$ was added to the reaction mixture and the mixture was evaporated for 4 times. The crude peptide (0.2856 g, 0.35 mmol, 100%) was obtained as brown amorphous.

To a solution of the crude peptide (0.2856 g, 0.35 mmol) in anhydrous DMF (5 mL) and CH_2Cl_2 (3 mL), the solution was cooled to 0℃ and then HATU (147.2 mg, 0.39 mmol) was added. DIPEA (244 μL, 1.40 mmol) was added to the solution and the solution was stirred at room temperature for 48 h under Ar atmosphere. AcOEt was added to the reaction mixture and the mixture was washed with 5% aqueous solutions of $KHSO_4$ and

$NaHCO_3$, and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane / AcOEt = 1: 3) to afford **4a** (145.4 mg, 0.182 mmol, 52%) as yellow solid.

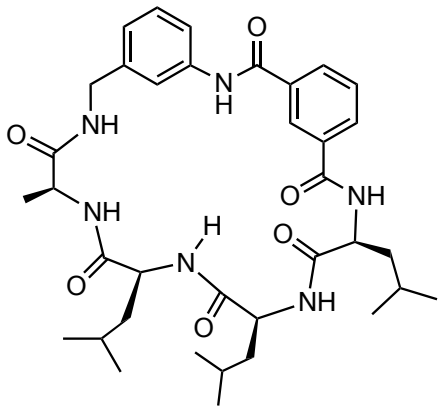
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.48 (1H, d, J = 7.2 Hz), 8.14 (1H, d, J = 5.6 Hz), 8.02 (1H, d, J = 8.0 Hz), 7.95 (1H, s), 7.88 (2H, brs), 7.81 (1H, d, J = 7.6 Hz), 7.75-7.66 (3H, m), 7.60 (1H, d, J = 7.6 Hz), 7.53 (1H, t, J = 8.0 Hz), 7.38 (1H, t, J = 7.6 Hz), 7.11-7.03 (3H, m), 6.91 (1H, d, J = 7.2 Hz), 5.48-5.26 (2H, m), 4.37 (1H, brs), 4.27-4.23 (2H, m), 4.08-3.99 (3H, m), 1.69-1.43 (9H, m), 1.28 (3H, d, J = 7.2 Hz), 0.92-0.83 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 172.4, 172.3, 171.9, 171.9, 170.3, 169.6, 166.1, 162.3, 148.2, 142.3, 140.6, 135.8, 133.8, 133.3, 131.8, 131.2, 128.7, 128.6, 128.5, 127.9, 127.3, 125.8, 125.6, 125.0, 124.7, 59.7, 52.8, 52.2, 51.1, 50.5, 49.1, 35.7, 30.7, 24.4, 24.3, 24.1, 23.2, 22.8, 22.8, 21.6, 21.5, 21.3, 21.0, 20.7, 16.8, 14.0.

HPLC (250 nm): t_R 15.90 min, 90% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{43}H_{55}N_7O_8Na^+$, 820.4004. Found: 820.4014.

Compound 4b



In an NMR tube, the solution of **4a** (23.7 mg, 0.030 mmol) in DMSO-d_6 was photo-irradiated with UV light (390 nm). After 20 min, the solvent was evaporated and the crude was column-chromatographed ($CHCl_3$: MeOH= 40:1) to afford **4b** (15.9 mg, 0.024 mmol, 81%) as yellow oil.

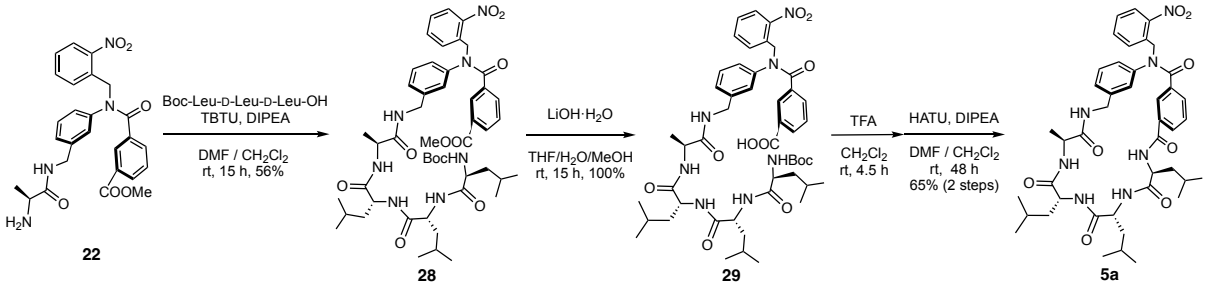
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.75 (1H, s), 8.75-8.71 (2H, m), 8.44 (1H, t, J = 6.4 Hz), 8.21-8.12 (4H, m), 8.06 (1H, d, J = 7.6 Hz), 8.67 (2H, t, J = 7.6 Hz), 7.51 (1H, d, J = 7.6 Hz), 7.30 (1H, t, J = 8.0 Hz), 7.23 (1H, s), 4.57 (1H, dd, J = 12.0, 7.6 Hz), 4.40-

4.15 (4H, m), 4.08 (1H, dd, *J* = 10.8, 4.8 Hz), 1.74-1.51 (8H, m), 1.40-1.17 (4H, m), 0.96-0.78 (12H, m), 0.59 (6H, dd, *J* = 15.2, 6.0 Hz).

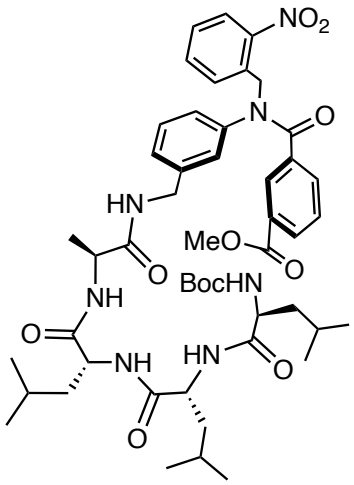
$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 173.0, 172.1, 171.6, 171.3, 166.5, 163.9, 139.7, 138.9, 134.0, 133.7, 131.1, 130.5, 128.9, 128.6, 126.8, 122.0, 117.5, 117.1, 53.7, 51.1, 50.8, 49.1, 41.3, 40.6, 24.4, 24.2, 23.7, 23.3, 22.7, 22.4, 21.8, 21.8, 21.0, 17.8.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{36}H_{50}N_6O_6Na^+$, 685.3684. Found: 685.3710.

Synthesis of 5a/ 5b



Compound 28



To a solution of **22** (216.8 mg, 0.442 mmol) and Boc-Leu-D-Leu-D-Leu-OH (202.1 mg, 0.442 mmol) in anhydrous DMF (2 mL), CH_2Cl_2 (4 mL), TBTU (156.2 mg, 0.486 mmol) and DIPEA (0.308 mL, 1.77 mmol) were added at 0°C, and the reaction mixture was stirred at rt for 15 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in AcOEt. The mixture was washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4 and evaporated. Column chromatography (n-hexane: AcOEt=2:1-1:2) gave **28** (0.2294 g,

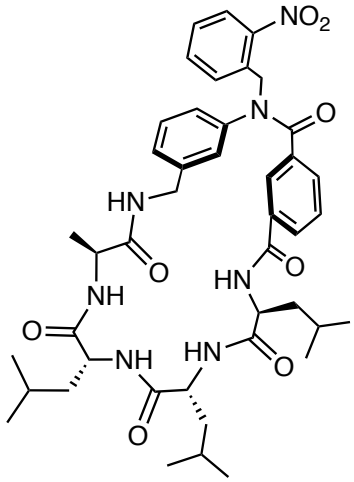
0.247 mmol, 56%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 8.06 (1H, t, *J* = 1.6 Hz), 7.99 (1H, dd, *J* = 8.4, 1.2 Hz), 7.92 (1H, dt, *J* = 8.0, 1.6 Hz), 7.75-7.68 (2H, m), 7.55 (1H, dt, *J* = 8.0, 1.2 Hz), 7.50 (1H, td, *J* = 7.6, 1.6 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.21 (1H, s), 7.13-7.06 (2H, m), 6.91-6.89 (1H, m), 5.51 (2H, s), 4.34-4.22 (5H, m), 4.41-3.99 (1H, m), 3.88 (3H, s), 1.73-1.45 (9H, m), 1.41 (9H, s), 1.32 (3H, d, *J* = 7.2 Hz), 0.97-0.83 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 174.7, 174.4, 171.9, 167.5, 150.2, 144.0, 142.0, 137.3, 134.7, 133.1, 132.0, 131.3, 131.1, 130.9, 130.4, 129.7, 129.4, 127.9, 127.5, 127.4, 126.0, 58.3, 55.0, 54.0, 53.2, 52.9, 50.8, 43.3, 42.0, 41.1, 40.9, 38.9, 28.8, 26.0, 25.9, 25.9, 23.6, 23.4, 23.2, 22.4, 22.1, 21.6, 18.4, 18.1.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{49}H_{67}N_7O_{11}Na^+$, 952.4791. Found: 952.4762.

Compound 5a



To a solution of **28** (213.4 mg, 0.23 mmol) in MeOH / THF / distilled water = 3: 2: 1 (6 mL), lithium hydroxide monohydrate (77.1 mg, 1.84 mmol) was added at room temperature and the mixture was stirred for 15 h. The reaction mixture was acidified to pH 3 with 5% aqueous solution of $KHSO_4$ and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford the crude carboxylic acid **29** (211.1 mg, 0.23 mmol, 100%) as yellow amorphous.

To a solution of the crude carboxylic acid **29** (0.2111 g, 0.23 mmol) in anhydrous CH_2Cl_2 (2 mL), trifluoroacetic acid (3 mL) was added at 0℃ and the solution was warmed to

room temperature. After stirring for 4.5 h, $CHCl_3$ was added to the reaction mixture and evaporated for 4 times. The crude peptide (0.1877 g, 0.23 mmol, 100%) was obtained as brown amorphous.

To a solution of the crude peptide (187.7 mg, 0.23 mmol) in anhydrous DMF (5 mL), CH_2Cl_2 (3 mL) the solution was cooled to 0℃ and then HATU (97.1 mg, 0.25 mmol) was added. DIPEA (161 μL, 0.92 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 48 h under Ar atmosphere, the reaction mixture was added with AcOEt and washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane / AcOEt = 1: 3) to afford **5a** (119.1 mg, 0.149 mmol, 65%) as yellow solid.

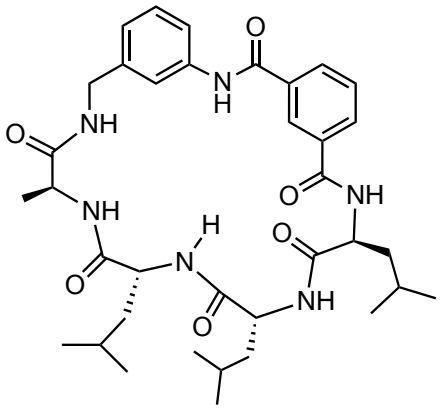
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.90 (1H, d, J = 5.6 Hz), 8.44 (1H, d, J = 6.4 Hz), 8.12 (1H, d, J = 7.2 Hz), 8.06-8.02 (2H, m), 7.93 (1H, s), 7.84-7.80 (2H, m), 7.61 (1H, d, J = 8.0 Hz), 7.56 (1H, t, J = 8.0 Hz), 7.33-7.29 (2H, m), 7.22-7.16 (3H, m), 6.894 (1H, d, J = 7.6 Hz), 6.51 (1H, s), 5.52 (1H, d, J = 16.8 Hz), 5.32 (1H, d, J = 16.8 Hz), 4.33 (1H, dd, J = 12.8, 7.2 Hz), 4.20-4.00 (4H, m), 3.79 (1H, dd, J = 16.8, 5.6 Hz), 1.88-1.51 (9H, m), 1.18 (3H, d, J = 7.6 Hz), 0.96-0.83 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.4, 172.6, 172.0, 171.7, 170.3, 169.8, 167.0, 162.3, 148.1, 142.3, 139.8, 135.6, 133.9, 133.5, 131.9, 130.2, 129.0, 128.7, 128.1, 127.1, 126.6, 124.8, 124.2, 59.7, 53.2, 52.1, 49.8, 47.9, 41.1, 35.7, 30.7, 24.5, 24.4, 24.2, 23.2, 22.9, 22.4, 22.3, 21.2, 21.0, 20.8, 18.2, 14.0.

HPLC (250 nm): t_R 19.95 min, 90% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{43}H_{55}N_7O_8Na^+$, 820.4004. Found: 820.4033.

5b



In an NMR tube, the solution of **5a** (20.3 mg, 0.025 mmol) in DMSO-d_6 was irradiated with UV light (390 nm). After 20 min, evaporate the solution and the crude compound was column-chromatographed ($CHCl_3$: MeOH= 40:1) to afford **5b** (13.0 mg, 0.020 mmol, 77 %) as yellow oil.

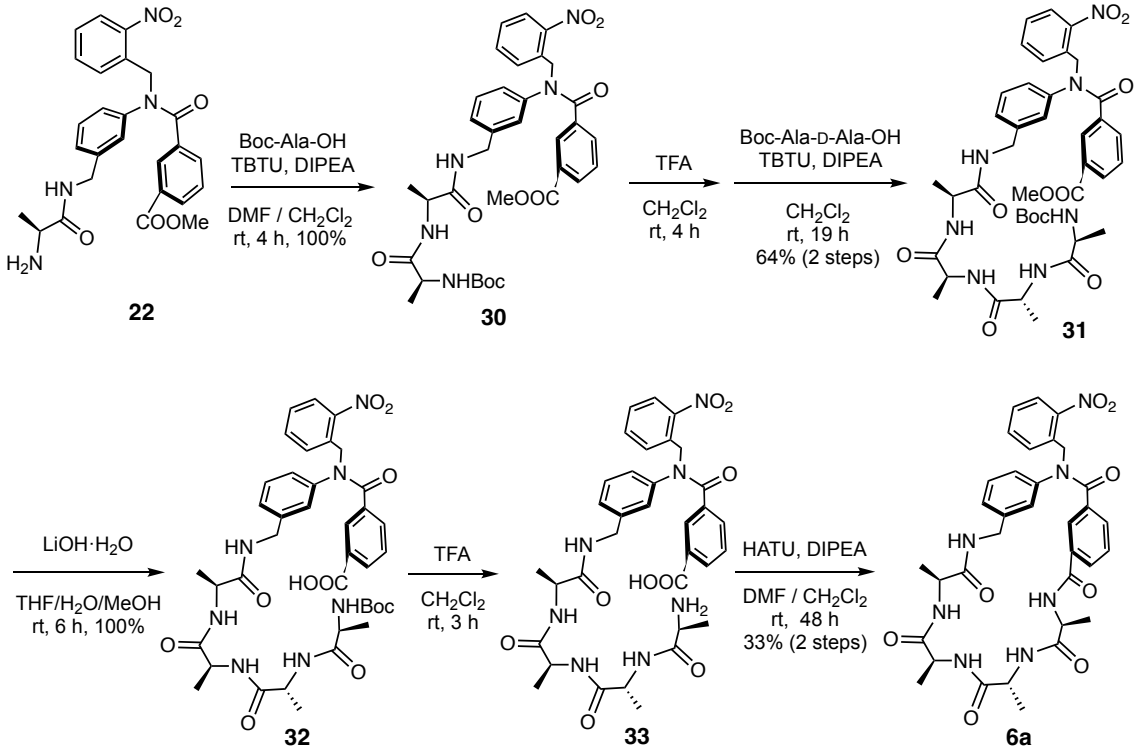
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.27 (1H, s), 8.84 (1H, d, J = 7.2 Hz), 8.39-8.36 (2H, m), 8.21 (1H, dd, J = 8.0, 3.2 Hz), 8.14 (2H, t, J = 7.2 Hz), 8.00-7.97 (2H, m), 7.75 (1H, d, J = 6.4 Hz), 7.61 (1H, t, J = 7.6 Hz), 7.29 (1H, t, J = 8.0 Hz), 7.22 (1H, s), 6.98 (1H, d, J = 8.0 Hz), 4.76 (1H, dd, J = 15.2, 8.8 Hz), 4.49-4.37 (3H, m), 4.28-4.21 (1H, m), 3.86 (1H, dd, J = 15.2, 3.6 Hz), 1.73-1.28 (9H, m), 1.22 (3H, d, J = 7.2 Hz), 0.98-0.74 (18H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 171.9, 171.6, 171.6, 171.4, 167.1, 165.0, 139.9, 139.3, 134.9, 134.3, 130.5, 130.0, 128.6, 127.5, 122.6, 118.2, 117.5, 67.4, 53.0, 52.5, 50.8, 47.6, 29.8, 28.3, 25.2, 24.4, 24.2, 23.9, 23.2, 23.0, 22.6, 22.4, 22.0, 21.4, 18.3, 13.9.

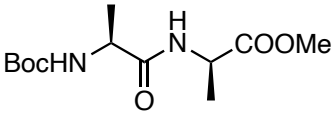
HPLC (250 nm): t_R 9.93 min, 93% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{36}H_{50}N_6O_6Na^+$, 685.3684. Found: 685.3697.

Synthesis of 6a/ 6b



Boc-Ala-D-Ala-OMe



To a solution of H-D-Ala-OMe (349.1 mg, 2.50 mmol) and Boc-Ala-OH (473.1 mg, 2.50 mmol) in anhydrous DMF (2 mL), CH_2Cl_2 (5 mL), TBTU (882.2 mg, 2.75 mmol) and DIPEA (1.742 mL, 10.00 mmol) were added at 0°C, and the reaction mixture was stirred at rt for 3 h under Ar atmosphere. The solvent was evaporated and the residue was diluted with AcOEt. The mixture was washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4 and evaporated. Column chromatography (n-hexane: Acetone=1:1-1:2) gave Boc-Ala-D-Ala-OMe (0.5855 g, 2.13 mmol, 85%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.76 (1H, s), 5.01 (1H, s), 4.19 (1H, s), 3.73 (3H, s), 1.79 (1H, s), 1.44 (9H, s), 1.40 (3H, d, J = 7.2 Hz), 1.35 (3H, d, J = 7.2 Hz).

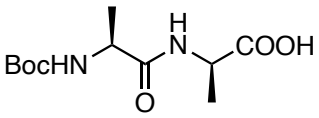
^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 173.4, 172.3, 155.7, 80.4, 52.6, 50.1, 48.1, 28.4, 18.4, 18.2, 14.3.

Anal. Calcd. for $C_{12}H_{22}N_2O_5$: N: 10.21, C: 52.54, H: 8.08. Found: N: 10.28, C: 52.84, H: 7.77.

Mp: 64-65°C.

HRMS (ESI^+, $[M+Na]^+$): Calcd. For $C_{12}H_{22}N_2O_5Na^+$: 297.1421, Found: 297.1417.

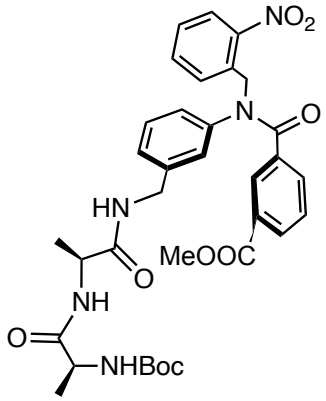
Boc-Ala-D-Ala-OH



To a solution of Boc-Ala-D-Ala-OMe (269.3 mg, 0.98 mmol) in MeOH / THF / distilled water = 3: 2: 1 (6 mL), lithium hydroxide monohydrate (118.1 mg, 2.81 mmol) was added at room temperature. After stirring for 14 h, the reaction mixture was acidified to pH 3 with 5% aqueous solution of $KHSO_4$ and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford crude Boc-Ala-D-Ala-OH (202.1 mg, 0.78 mmol, 80%) as white amorphous.

HRMS (ESI^-, $[M-H]^-$): Calcd. For $C_{11}H_{19}N_2O_5^-$: 259.1299, Found: 259.1310.

Compound 30



To a solution of **22** (225.6 mg, 0.46 mmol) and Boc-Ala-OH (87.1 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (5 mL), anhydrous DMF (1 mL), TBTU (162.2 mg, 0.51 mmol) and DIPEA (0.320 mL, 1.84 mmol) were added at 0℃, and the reaction mixture was stirred at rt for 4 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in AcOEt. The mixture was washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4

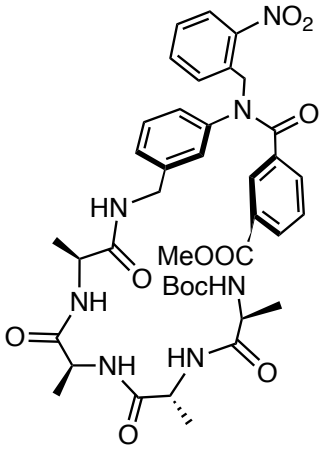
and evaporated. Column chromatography ($CHCl_3$: MeOH=9: 1) gave **30** (376.8 mg, 0.57 mmol, 100 %) as white amorphous.

^{1}H NMR (400 MHz, MeOD): δ (ppm) 8.06 (1H, s), 8.01-7.99 (3H, m), 7.95-7.92 (1H, m), 7.76-7.69 (2H, m), 7.57 (1H, d, *J* = 8.0 Hz), 7.51 (1H, t, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.6 Hz), 7.21 (1H, s), 7.14-7.07 (2H, m), 6.93 (1H, d, *J* = 7.2 Hz), 5.55 (1H, d, *J* = 16.4 Hz), 5.49 (1H, d, *J* = 16.4 Hz), 4.32-4.29 (2H, m), 4.22 (1H, d, *J* = 15.6 Hz), 4.03 (1H, d, *J* = 7.2 Hz), 3.88 (3H, s), 1.40 (9H, s), 1.33 (6H, m).

^{13}C{^{1}H} NMR (100 MHz, MeOD): δ (ppm) 175.8, 174.9, 171.9, 167.5, 164.8, 158.1, 150.2, 144.0, 141.8, 137.3, 134.7, 134.1, 133.1, 131.9, 131.3, 131.1, 130.8, 130.4, 129.6, 129.4, 128.0, 127.5, 125.9, 80.8, 79.5, 52.8, 52.1, 50.5, 43.2, 38.9, 36.9, 31.6, 28.7, 18.0.

HRMS (ESI$^+$, [M+Na]$^+$): Calcd. For $C_{34}H_{39}N_5O_9Na^+$: 684.2640, Found: 684.2655.

Compound 31



To a solution of **30** (0.3511 g, 0.53 mmol) in anhydrous CH_2Cl_2 (2 mL), trifluoroacetic acid (3.5 mL) was added at 0°C and the solution was stirred at room temperature for 4 h. $CHCl_3$ was added to the reaction mixture and the solvent was evaporated for 4 times. The crude amine was obtained as yellow amorphous, and was used in the next step without further purification.

To a solution of crude amine (297.6 mg, 0.53 mmol) and Boc-Ala-D-Ala-OH (194.3 g, 0.53 mmol) in anhydrous CH_2Cl_2 (3 mL), TBTU (187.2 mg, 0.58 mmol) and DIPEA (0.370 mL, 2.12 mmol) were added at 0°C, and the reaction mixture was stirred at rt for 19 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in

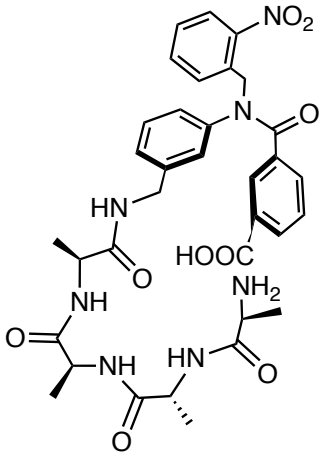
AcOEt. The mixture was washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine. The mixture was dried with Na_2SO_4 and evaporated. Column chromatography ($CHCl_3$: MeOH=50: 1- 20: 1) gave **31** (273.9 mg, 0.34 mmol, 64% in two steps) as white yellow solid.

^{1}H NMR (400 MHz, MeOD): δ (ppm) 9.07 (1H, s), 8.99 (1H, d, *J* = 8.0 Hz), 7.93 (1H, d, *J* = 8.0 Hz), 7.75-7.67 (2H, m), 7.55 (1H, d, *J* = 8.0 Hz), 7.49 (1H, td, *J* = 8.0, 1.2 Hz), 7.31 (1H, t, *J* = 8.0 Hz), 7.26 (1H, s), 7.10-7.05 (2H, m), 6.88 (1H, d, *J* = 6.8 Hz), 5.56 (1H, d, *J* = 16.4 Hz), 5.48 (1H, d, *J* = 16.4 Hz), 4.39 (1H, d, *J* = 15.6 Hz), 4.32-4.26 (1H, m), 4.21-4.17 (1H, m), 4.14-4.07 (2H, m), 4.02 (1H, dd, *J* = 14.4, 7.2 Hz), 3.87 (3H, s), 1.43-1.41 (12H, m), 1.32 (3H, d, *J* = 7.2 Hz), 1.27 (3H, d, *J* = 7.2 Hz), 1.23 (3H, d, *J* = 7.2 Hz).

^{13}C{^{1}H} NMR (100 MHz, MeOD): δ (ppm) 174.7, 174.5, 173.6, 173.6, 171.6, 170.6, 166.1, 148.8, 142.6, 140.5, 135.9, 133.3, 132.8, 130.5, 129.9, 129.6, 129.5, 128.9, 127.9, 126.5, 126.0, 125.8, 124.5, 60.1, 51.4, 50.9, 50.4, 50.2, 49.5, 41.8, 37.5, 35.5, 27.3, 19.4, 16.9, 16.4, 16.2, 16.0, 15.6, 13.1.

HRMS (ESI$^+$, [M+Na]$^+$): Calcd. For $C_{40}H_{49}N_7O_{11}Na^+$: 826.3382, Found: 826.3409.

Compound 33



To a solution of **31** (273.9 mg, 0.34 mmol) in MeOH / THF / distilled water = 3: 2: 1 (6 mL), lithium hydroxide monohydrate (110.2 mg, 2.63 mmol) was added at room temperature. After stirring for 14 h, the reaction mixture was acidified to pH 3 with 5% aqueous solution of $KHSO_4$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford crude acid **32**

(268.9 mg, 0.34 mmol, 100%) as white solid.

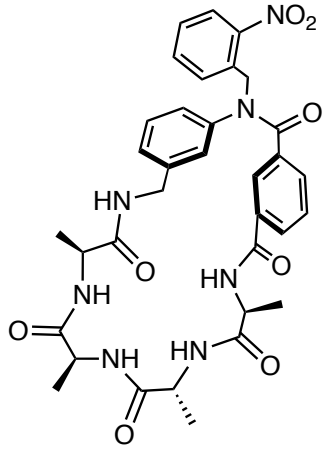
To a solution of the crude acid **32** (268.9 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (1.5 mL), trifluoroacetic acid (3 mL) was added at 0°C and the solution was stirred at room temperature for 3 h under Ar atmosphere. $CHCl_3$ was added to the reaction mixture and the solvent was evaporated for 4 times. The crude peptide **33** (257.7 mg, 0.37 mmol, 100%) was obtained as brown solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.05-8.04 (1H, m), 7.99-7.90 (2H, m), 7.75-7.67 (2H, m), 7.58-7.55 (1H, m), 7.49 (1H, t, J= 7.6 Hz), 7.35-7.31 (1H, m), 7.21 (1H, s), 7.13-7.04 (2H, m), 6.90 (1H, d, J= 8.0 Hz), 5.54 (1H, d, J= 16.4 Hz), 5.49 (1H, d, J= 16.4 Hz), 4.40-4.23 (5H, m), 3.95 (2H, d, J= 6.8 Hz), 1.51 (3H, dd, J= 3.6, 2.0 Hz), 1.41-1.32 (9H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.9, 174.8, 174.5, 172.2, 171.5, 168.7, 160.5, 150.3, 144.0, 141.6, 137.2, 134.7, 134.0, 133.1, 132.2, 131.9, 131.3, 131.0, 130.4, 129.7, 129.3, 128.1, 127.4, 125.9, 52.1, 51.2, 50.7, 50.4, 43.2, 38.9, 17.8, 17.4, 17.0, 14.0.

HRMS (ESI$^-$, [M-H]$^-$): Calcd. For $C_{34}H_{38}N_7O_9^-$: 688.2736, Found: 688.2751.

Compound 6a



To a solution of **33** (315.9 mg, 0.46 mmol) in anhydrous DMF (6 mL), CH_2Cl_2 (2 mL) the solution was cooled to 0°C and then HATU (192.1 mg, 0.50 mmol) was added. DIPEA (320 μL, 0.50 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 48 h under Ar atmosphere, the reaction mixture was added with AcOEt and washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of

$NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography ($CHCl_3$ / MeOH = 30: 1- 10:1) to afford **6a** (100.0 mg, 0.15 mmol, 33%) as white solid.

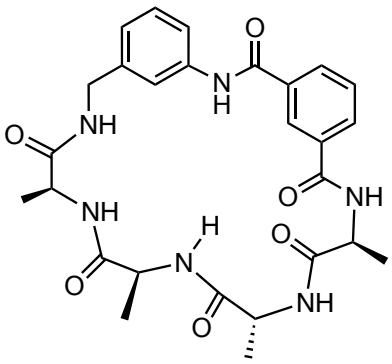
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.57 (1H, d, J = 5.6 Hz), 8.41 (1H, s), 8.36 (1H, s), 8.12 (1H, s), 8.03 (2H, d, J = 4.8 Hz), 7.92 (1H, s), 7.84-7.71 (4H, m), 7.63 (1H, d, J = 7.6 Hz), 7.55 (1H, t, J = 8.0 Hz), 7.33 (1H, d, J = 7.2 Hz), 7.27-7.18 (2H, m), 7.07 (1H, s), 5.36 (2H, s), 4.57-3.91 (6H, m), 1.34-1.18 (12H, m).

^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ (ppm) 174.4, 173.5, 170.5, 166.1, 163.5, 156.7, 148.8, 142.6, 140.4, 135.9, 133.3, 132.7, 131.7, 130.5, 129.9, 129.7, 129.4, 129.0, 128.2, 128.0, 126.9, 126.1, 124.5, 79.39, 78.1, 51.4, 50.7, 49.2, 41.9, 37.5, 35.5, 30.3, 27.3, 16.6.

HPLC (250 nm): t_R 3.54 min, 90% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{34}H_{37}N_7O_8Na^+$, 694.2596. Found: 694.2620.

Compound 6b



In an NMR tube, the solution of **6a** (14.6 mg, 0.0217 mmol) in DMSO-d_6 was photo-irradiated with UV light (390 nm). After 30 min, the solution was evaporated and the crude compound was column-chromatographed ($CHCl_3$: MeOH= 30:1- 9:1) to afford **6b** (9.4 mg, 0.0175 mmol, 81%) as white solid.

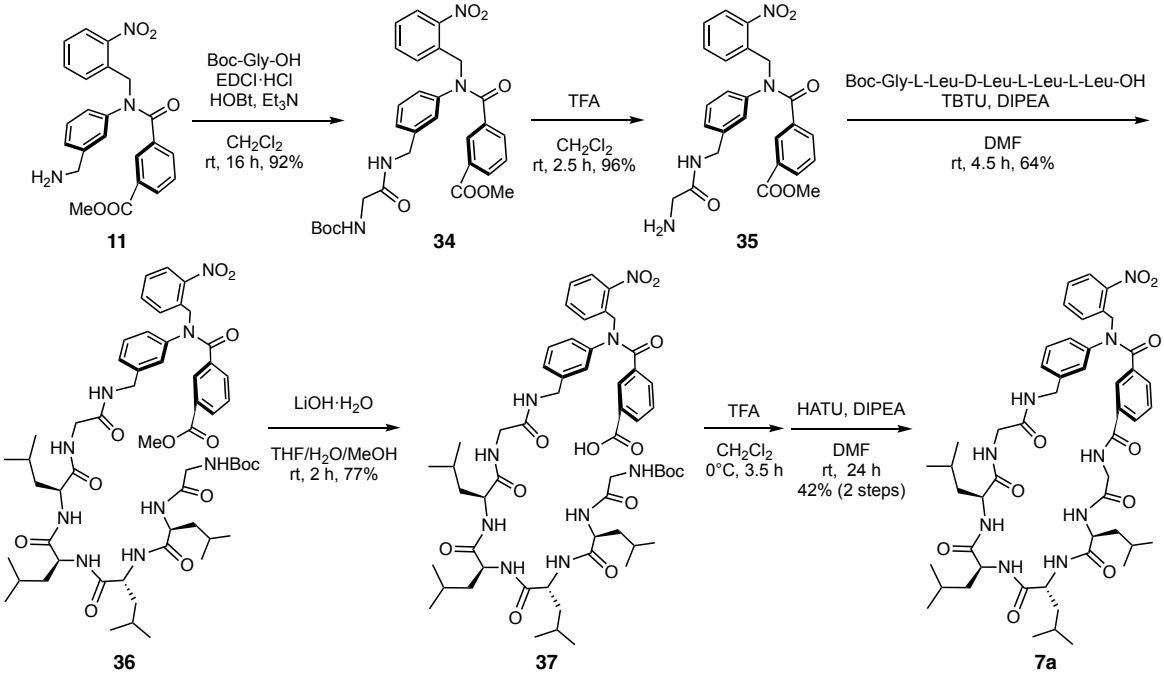
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 9.98 (1H, s), 8.96 (1H, d, J = 5.6 Hz), 8.72 (1H, s), 8.28 (1H, t, J = 6.4 Hz), 8.22 (2H, t, J = 8.0 Hz), 8.15 (1H, d, J = 8.0 Hz), 8.09 (2H, td, J = 8.4, 1.2 Hz), 7.95 (1H, s), 7.85 (1H, d, J = 8.8 Hz), 7.30 (1H, t, J = 8.0 Hz), 7.23 (1H, s), 7.00 (1H, d, J = 8.0 Hz), 4.47 (1H, t, J = 8.4 Hz), 4.40-4.23 (4H, m), 4.10 (1H, t, J = 7.2 Hz), 1.37-1.13 (12H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 172.8, 172.7, 171.8, 171.5, 165.6, 164.1, 139.9, 139.0, 134.4, 132.8, 131.7, 131.2, 128.5, 127.3, 127.1, 125.5, 122.3, 117.6, 50.2, 49.2, 47.7, 35.8, 30.8, 29.0, 27.8, 25.3, 23.2, 22.4, 18.3, 18.1, 17.4, 16.8.

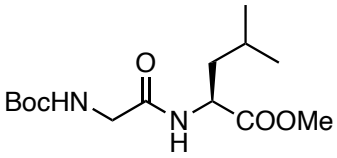
HPLC (250 nm): t_R 2.85 min, 94% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{27}H_{32}N_6O_6Na^+$, 559.2276. Found: 559.2266.

Synthesis of 7a/ 7b



Boc-Gly-L-Leu-OMe



To a solution of L-leucine methyl ester hydrochloride (622.2 mg, 3.425 mmol) and N-(tert-butoxycarbonyl)-glycine (600.0 mg, 3.425 mmol) in anhydrous CH_2Cl_2 (15 mL) and DMF (5 mL), HATU (1.4324 g, 3.7675 mmol) was added at room temperature and the solution was cooled to 0°C. DIPEA (2.39 mL, 13.7 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3 h under Ar atmosphere, the reaction mixture was added with AcOEt and washed with 5% $KHSO_4$, Na_2CO_3, brine,

dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane / AcOEt = 1: 1) to afford Boc-Gly-L-Leu-OMe (1.0126 g, 3.349 mmol, 98%) as yellow oil.

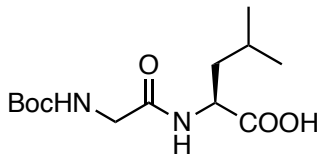
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.68 (1H, brs), 5.32 (1H, brs), 4.63-4.58 (1H, m), 3.82-3.78 (2H, m), 3.70 (3H, s), 1.61-1.58 (2H, m) 1.55-1.51 (1H, m), 1.43 (9H, s), 0.91 (6H, dd, J = 10.0, 5.6 Hz).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 171.3, 160.5, 156.2, 60.5, 52.4, 50.7, 44.4, 41.6, 28.4, 24.9, 22.9, 22.0, 21.2, 14.3.

Anal. Calcd. for $C_{14}H_{26}N_2O_5$: N, 9.26; C, 55.61; H, 8.67. Found: N, 9.27; C, 55.77; H, 8.59.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{14}H_{26}N_2O_5Na^+$, 325.1734. Found: 325.1744.

Boc-Gly-L-Leu-OH



To a solution of Boc-Gly-L-Leu-OMe (854.0 mg, 2.8243 mmol) in MeOH / THF / distilled water = 3: 2: 1 (12 mL), lithium hydroxide monohydrate (237.1 mg, 5.65 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford Boc-Gly-L-Leu-OH (680.8 mg, 2.361 mmol, 84%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 4.92 (2H, brs), 4.46 (1H, t, J = 6.8 Hz), 3.74 (2H, brs), 1.74-1.67 (1H, m), 1.65-1.60 (2H, m), 1.44 (9H, s), 0.94 (6H, dd, J = 8.4, 6.4 Hz).

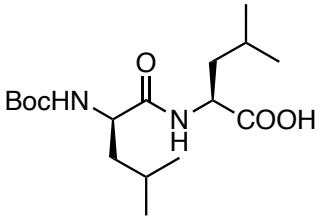
^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 175.8, 172.2, 158.2, 80.7, 51.8, 44.4, 41.7, 28.7, 25.8, 23.4, 21.9.

Anal. Calcd. for $C_{13}H_{23}N_2O_5$: N, 9.72; C, 54.15; H, 8.39. Found: N, 9.59; C, 54.16; H, 8.28.

Mp: 136.7-137.2°C

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{13}H_{23}N_2O_5^-$, 287.1612. Found: 287.1634.

Boc-D-Leu-L-Leu-OH



To a solution of Boc-D-Leu-L-Leu-OMe (1.6566 g, 4.62 mmol) in MeOH / THF / distilled water = 3 : 2 : 1 (24 mL), Lithium hydroxide monohydrate (0.3882 mg, 9.25 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford Boc-D-Leu-L-Leu-OH (1.5682 g, 4.55 mmol, 98%) as white amorphous.

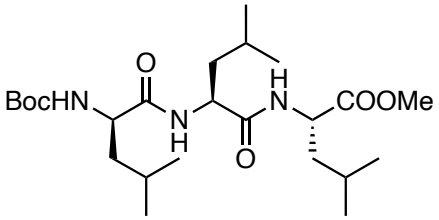
^1H NMR (400 MHz, $CDCl_3$, 50 °C): δ (ppm) 6.90 (1H, brs), 5.19 (1H, brs), 4.62 (1H, d, *J* = 4.0 Hz), 4.31 (1H, brs), 1.78-1.45 (6H, m), 1.44 (1H, s), 0.97-0.94 (12H, m).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 175.5, 173.0, 171.4, 156.3, 80.7, 60.6, 52.8, 50.9, 42.1, 41.7, 28.4, 24.9, 24.9, 23.0, 22.9, 22.2, 21.2, 14.3.

Anal. Calcd. for $C_{17}H_{32}N_2O_5$: N, 8.13; C, 59.28; H, 9.36. Found: N, 8.18; C, 59.33; H, 9.53.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{17}H_{31}N_2O_5^-$, 343.2238. Found: 343.2259.

Boc-D-Leu-L-Leu-L-Leu-OMe



To a solution of Boc-D-Leu-L-Leu-OH (1.5466 g, 4.49 mmol) and L-leucine methyl ester hydrochloride (0.8156 g, 4.49 mmol) in anhydrous CH_2Cl_2 (45 mL), TBTU (1.59 g, 4.94 mmol) was added at room temperature and the solution was cooled to 0°C. DIPEA (3.13 mL, 17.97 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 3.5 h under Ar atmosphere, the reaction mixture was washed with 5% $KHSO_4$, saturated aqueous solution of Na_2CO_3, and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-

hexane / AcOEt = 4: 1) to afford Boc-D-Leu-L-Leu-L-Leu-OMe (2.0320 g, 4.31 mmol, 96%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) (a mixture of rotamers) 6.90 (1H, s), 6.83 (1H, s), 5.50-5.41 (0.3H, brm), 5.07 (0.7 H, brs), 4.54-4.49 (2H, m), 4.11 (1H, brs), 3.68 (2.7H, s), 3.65 (0.3H, s), 1.70-1.44 (9H, m), 1.40 (9H, s), 0.91-0.87 (18H, m).

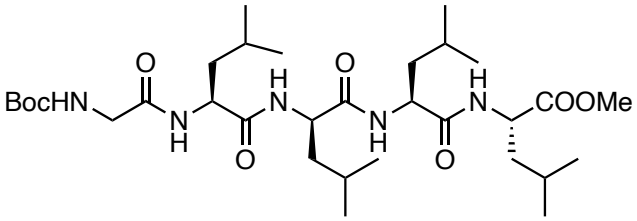
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.1, 172.9, 171.8, 155.6, 80.2, 53.5, 52.3, 52.2, 51.6, 50.9, 50.9, 41.6, 41.2, 40.7, 28.4, 24.9, 24.8, 24.7, 23.0, 23.0, 22.9, 22.1, 21.9, 21.7.

Anal. Calcd. for $C_{24}H_{45}N_3O_6$: N, 8.91; C, 61.12; H, 9.62. Found: N, 8.91; C, 61.11; H, 9.36.

Mp: 172.2-173.3°C.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{24}H_{45}N_3O_6Na^+$: 494.3201. Found: 494.3191.

Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OMe



TFA (5 mL) was added to a solution of Boc-D-Leu-L-Leu-L-Leu-OMe (1.17 g, 2.48 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0°C. The mixture was stirred for 30 min at 0°C, then warm to room temperature and was stirred another 1.5 h. The solvent was evaporated. 10% aqueous solution of Na_2CO_3 was added to the residue to adjust the pH to about 9, and the whole was extracted with EtOAc (20 mL × 3) and dried over Na_2SO_4. Evaporation of solvent gave the crude amine as white solid.

To a solution of crude amine (0.8421 g, 2.27 mmol) and Boc-Gly-L-Leu-OH (0.6501 g, 2.25 mmol) in anhydrous DMF (10 ml), TBTU (0.8012 g, 2.50 mmol) was added at room temperature and the solution was cooled to 0°C. DIPEA (1.58 mL, 9.07 mmol) was added to the solution and the solution was warmed to room temperature. After stirring 4 h under Ar atmosphere, the reaction mixture was washed with 5% $KHSO_4$, saturated aqueous solution of $NaHCO_3$, and brine. The solid then was filtered and washed by Et_2O to afford Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OMe (1.4964 g, 2.33 mmol, 94%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 4.46-4.39 (2H, m), 4.35-4.32 (1H, m), 4.26 (1H, t, J = 7.6 Hz), 3.72 (2H, s), 3.70 (3H, s), 1.80-1.55 (12H, m), 1.45 (9H, s), 0.98-0.90 (24H, m).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 175.1, 175.0, 174.9, 174.7, 172.7, 80.8, 54.0, 53.7, 53.2, 52.2, 49.9, 44.9, 41.5, 41.3, 41.0, 28.7, 26.0, 25.9, 23.6, 23.3, 23.2.

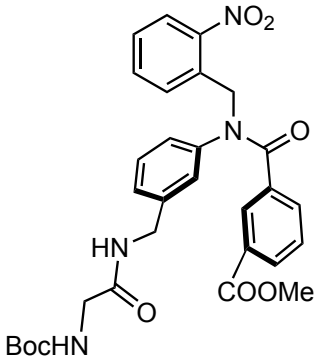
Mp: 230.2-231.5ºC.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{32}H_{59}N_5O_8Na^+$, 664.4256. Found: 664.4256.

Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OH

To a solution of Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OMe (1.1051 g, 1.72 mmol) in MeOH / THF / distilled water = 3: 2: 1 (12 mL), lithium hydroxide monohydrate (144 mg, 3.43 mmol) was added at room temperature. After stirring for 2 h, the reaction mixture was acidified by 5% $KHSO_4$ solution to pH 3 and the white solid precipitated. The white solid was filtered and washed by brine and Et_2O. The solid was dried to afford Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OH (0.9683 g, 1.54 mmol, 90%) as white solid.

Compound 34



To a solution of **11** (895.9 mg, 2.14 mmol) and Boc-Gly-OH (375.1 mg, 2.14 mmol) in anhydrous CH_2Cl_2 (15 mL) , EDCI·HCl (575.2 mg, 3.00 mmol), HOBt (404.3 mg, 2.99 mmol) and NEt_3 (0.89 mL, 6.43 mmol) were added at 0°C, and the reaction mixture was stirred for 30 min at 0ºC then stirred at rt for another 15.5 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in AcOEt. The mixture was washed with 5% $KHSO_4$, aqueous solution of Na_2CO_3 and brine. The mixture was dried with

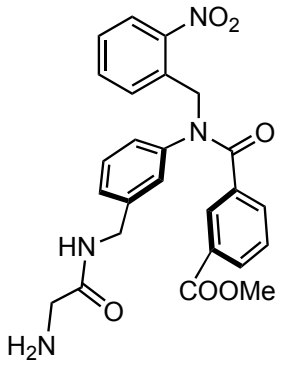
Na_2SO_4 and evaporated. Column chromatography (n-hexane: AcOEt=1:2- 1:3) gave **34** (1.1311 g, 1.96 mmol, 92%) as white amorphous.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95-7.89 (3H, m), 7.76 (1H, dd, *J* = 9.4, 1.2 Hz), 7.65 (1H, td, *J* = 7.2, 1.2 Hz), 7.57 (1H, dt, *J* = 12.0, 1.6 Hz), 7.42 (1H, td, *J* = 8.0, 1.2 Hz), 7.30-7.26 (1H, m), 7.06 (1H, s), 7.05-7.02 (2H, m), 6.70-6.68 (1H, m), 5.55 (2H, t, *J* = 5.2 Hz), 5.53 (2H, s), 5.35 (1H, brs), 4.31 (2H, d, *J* = 6.0 Hz), 3.86 (3H, s), 3.81 (2H, d, *J* = 6.0 Hz), 1.42 (9H, s).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.2, 169.6, 169.4, 166.4, 156.1, 148.7, 143.0, 140.0, 135.5, 133.7, 133.2, 132.3, 130.9, 130.2, 130.0, 129.7, 128.4, 128.2, 127.1, 127.0, 126.8, 124.9, 80.2, 75.4, 60.4, 52.4, 50.5, 44.3, 42.9, 30.9, 28.3, 28.1, 21.0, 14.2.

HRMS (ESI$^+$, [M+Na]$^+$): Calcd. For $C_{30}H_{32}N_6O_8Na^+$: 599.2112, Found: 599.2096.

Compound 35



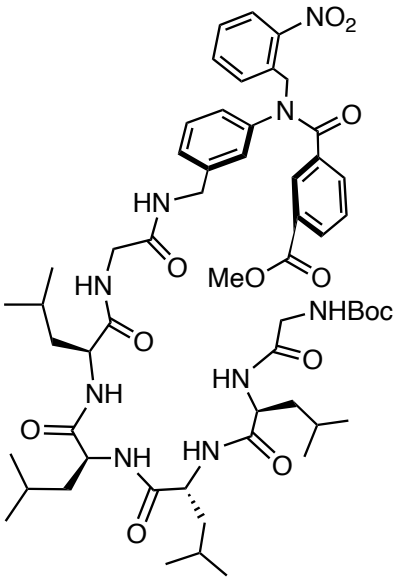
To a solution of **34** (1.0031 g, 1.734 mmol) in anhydrous CH_2Cl_2 (5 mL), trifluoroacetic acid (3 mL) was added at 0°C and the solution was warmed to room temperature. After stirring for 2.5 h, saturated aqueous solution of Na_2CO_3 (15 mL) was added to the reaction mixture and the solution was extracted with AcOEt. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The compound **35** (0.7934 g, 1.67 mmol, 96%) was obtained as yellow amorphous.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 (1H, t, *J* = 1.6 Hz), 7.98 (1H, dd, *J* = 8.0, 0.8 Hz), 7.95 (1H, dt, *J* = 8.0, 1.6 Hz), 7.76 (1H, dd, *J* = 8.0, 0.4 Hz), 7.67 (1H, td, *J* = 7.6, 1.2 Hz), 7.53 (1H, dt, *J* = 7.6, 1.6 Hz), 7.45 (2H, td, *J* = 8.0, 1.2 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 7.11 (1H, t, *J* = 7.6 Hz), 7.07 (1H, dt, *J* = 8.0, 1.6 Hz), 6.98 (1H, s), 6.82 (1H, dt, *J* = 7.6, 1.6 Hz), 5.56 (2H, s), 4.33 (2H, d, *J* = 6.0 Hz), 3.88 (3H, s), 3.36 (2H, s).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.8, 169.8, 166.3, 148.7, 143.2, 140.5, 135.7, 133.8, 133.2, 132.6, 131.1, 130.3, 130.1, 129.8, 129.8, 128.4, 128.2, 126.9, 126.6, 126.5, 125.1, 60.5, 52.4, 50.9, 44.8, 42.4, 21.2, 14.3.

HRMS (ESI^+, $[M+H]^+$): Calcd. For $C_{25}H_{25}N_4O_6^+$: 477.1769, Found: 477.1772.

Compound 36



To a solution of **35** (621.0 mg, 1.30 mmol) and Boc-Gly-L-Leu-D-Leu-L-Leu-L-Leu-OH (821.3 mg, 1.31 mmol) in anhydrous DMF (10 mL), TBTU (460.1 mg, 1.43 mmol) and DIPEA (0.91 mL, 5.22 mmol) were added at 0°C, and the reaction mixture was stirred at rt for 4.5 h under Ar atmosphere. The solvent was evaporated and the residue was dissolved in AcOEt. The mixture was washed with 5% $KHSO_4$, aqueous solution of Na_2CO_3 and brine. The mixture was dried with Na_2SO_4 and evaporated. Column chromatography (n-hexane: AcOEt= 2: 1-1.5: 1) gave **36** (900.6 mg, 0.83 mmol, 64%) as yellow amorphous.

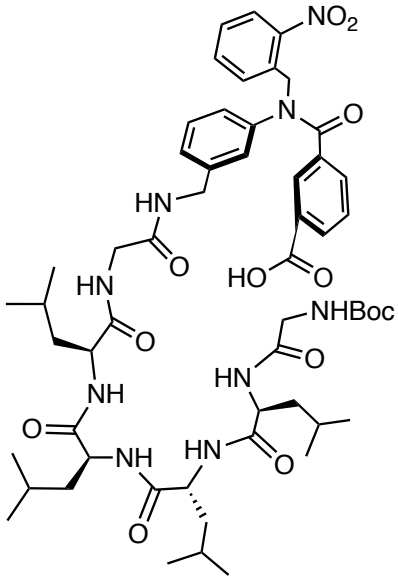
^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 8.18 (1H, d, J = 7.2 Hz), 8.14-8.09 (2H, m), 8.03-7.99 (3H, m), 7.95-7.92 (1H, m), 7.87 (1H, dt, J = 8.0, 1.2 Hz), 7.81 (1H, d, J = 7.6 Hz), 7.77-7.66 (2H, m), 7.56-7.52 (1H, m), 7.49 (1H, d, J = 7.6 Hz), 7.34 (1H, t, J = 8.0 Hz), 7.22 (1H, s), 7.09 (1H, t, J = 7.6 Hz), 7.00 (2H, d, J = 7.2 Hz), 6.89 (1H, t, J = 5.6 Hz), 5.39 (2H, s), 4.33-4.12 (6H, m), 3.83 (3H, s), 3.72-3.60 (2H, m), 3.54 (2H, d, J = 5.6 Hz), 1.62-1.43 (12H, m), 1.36 (9H, s), 0.88-0.74 (24H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.3, 172.24, 172.19, 169.2, 169.0, 168.5, 165.5, 162.3, 155.7, 148.1, 142.4, 140.6, 136.1, 133.8, 132.7, 131.8, 130.2, 129.3, 129.3, 128.8, 128.5, 128.2, 126.2, 125.9, 125.5, 124.7, 78.1, 52.2, 51.6, 51.4, 51.2, 50.5, 43.3, 42.1, 41.4, 41.1, 40.3, 40.1, 39.9, 39.7, 39.5, 39.3, 39.1, 38.9, 38.2, 38.0, 35.7, 30.7, 29.8, 29.6, 28.3, 28.1, 24.2, 24.09, 24.06, 24.00, 23.2, 23.03, 22.95, 22.85, 22.73, 21.71, 21.6, 21.5, 21.1, 13.9, 10.8.

Anal. Calcd. for $C_{56}H_{79}N_9O_{13}$: N, 11.60; C, 61.92; H, 7.33. Found: N, 11.90; C, 61.58; H, 7.40.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{56}H_{79}N_9O_{13}Na^+$, 1108.5690. Found: 1108.5698.

Compound 37



To a solution of **36** (1.1051 g, 1.72 mmol) in MeOH / THF / distilled water = 16 mL: 4 mL: 4 mL, lithium hydroxide monohydrate (188.3 mg, 4.48 mmol) was added at room temperature. The mixture was stirred for 2 h. The reaction mixture was acidified to pH 3 with 5% aqueous solution of $KHSO_4$ and the whole was extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to afford **37** (455.6 mg, 0.42 mmol, 77%) as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.19-8.08 (3H, m), 8.03-7.98 (3H, m), 7.95-7.91 (1H, m), 7.86-7.80 (2H, m), 7.76-7.71 (2H, m), 7.55-7.51 (1H, m), 7.46 (1H, d, J = 7.6

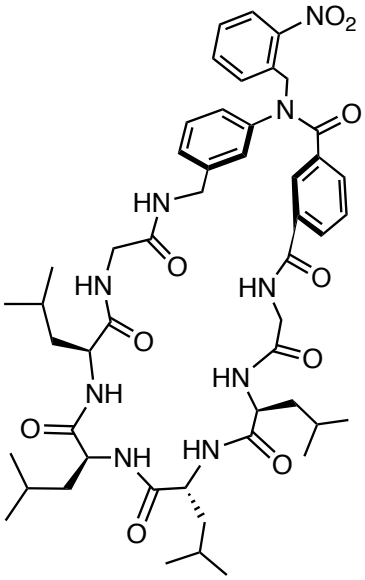
Hz), 7.31 (1H, t, *J* = 7.6 Hz), 7.21 (1H, s), 7.09 (1H, t, J= 8.0 Hz), 7.01-6.98 (2H, m), 6.87 (1H, t, *J* = 5.6 Hz), 5.39 (2H, s), 4.33-4.14 (6H, m), 3.72-3.55 (2H, m), 3.52 (2H, d, *J* = 10.8 Hz), 1.62-1.42 (12H, m), 1.36 (9H, s), 0.88-0.80 (24H, m).

$^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 172.31, 172.25, 169.23, 169.17, 168.5, 166.5, 148.1, 140.6, 135.9, 133.8, 131.9, 130.5, 130.4, 129.3, 128.8, 128.5, 128.0, 125.9, 124.7, 51.2, 38.2, 28.1, 24.18, 24.12, 24.08, 24.03, 23.1, 23.0, 22.9, 22.8, 21.7, 21.6, 21.5, 21.1.

Anal. Calcd. for $C_{55}H_{77}N_9O_{13}$: N, 11.76; C, 61.61; H, 7.24. Found: N, 11.52; C, 61.34; H, 7.38.

HRMS (ESI-TOF, $[M-H]^-$): Calcd. for $C_{55}H_{76}N_9O_{13}^-$, 1070.5568. Found: 1070.5563.

Compound 7a



To a solution of **37** (95.0 mg, 0.089 mmol) in TFA (3 mL) at 0℃. The mixture was stirred for 2 h at 0℃. The solvent was then evaporated. 10% aqueous solution of Na_2CO_3 was added to the residue to adjust the pH to 9, and the whole was extracted with EtOAc (20 mL x 3) and dried over Na_2SO_4. Evaporation of solvent gave the crude amine (95.4 mg, 0.089 mmol, 100%) as yellow amorphous.

To a solution of crude amine (83.6 mg, 0.086 mmol) in anhydrous DMF (15 mL), the solution was cooled to 0℃ and then HATU (36.0 mg, 0.098 mmol) was added. DIPEA (64 μL, 0.37 mmol) was added to the solution and the solution was warmed to room

temperature. After stirring 24 h under Ar atmosphere, the reaction mixture was added with AcOEt and washed with 5% aqueous solution of $KHSO_4$, saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by column chromatography (n-hexane / AcOEt = 1: 1) to afford **7a** (34.7 mg, 0.036 mmol, 42%) as yellow solid.

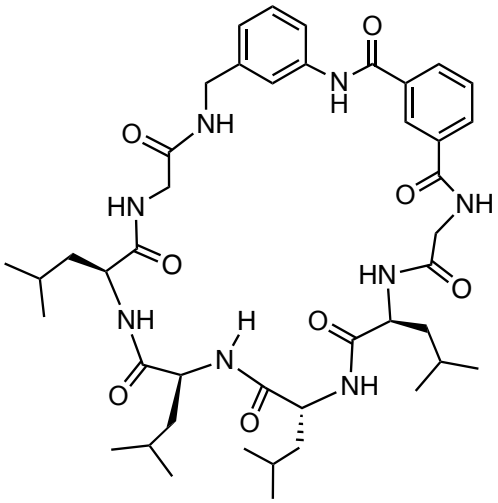
^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 7.99 (1H, d, *J* = 8.0 Hz), 7.88-7.87 (3H, m), 7.72 (1H, s), 7.60 (1H, d, *J* = 8.0 Hz), 7.54-7.50 (1H, m), 7.37 (1H, t, *J* = 4.0 Hz), 7.21 (1H, s), 7.12 (1H, t, *J* = 7.6 Hz), 7.06 (1H, d, *J* = 8.0 Hz), 6.96 (1H, d, *J* = 8.0 Hz), 5.57 (1H, d, *J* = 16.4 Hz), 5.46 (1H, d, *J* = 16.4 Hz), 4.49-4.43 (2H, m), 4.38 (1H, d, *J* = 15.2 Hz), 4.12-4.06 (3H, m), 3.98 (1H, t, *J* = 15.2 Hz), 3.87 (1H, d, *J* = 16.8 Hz), 3.64-3.57 (1H, m), 1.90 (1H, t, *J* = 10.4 Hz), 1.80-1.55 (11H, m), 1.00-0.90 (22H, m), 0.74 (3H, d, *J* = 6.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 176.6, 176.0, 175.7, 172.0, 171.5, 171.1, 169.1, 150.2, 144.3, 141.8, 137.3, 135.0, 134.2, 133.3, 133.0, 131.1, 130.4, 130.1, 129.64, 129.56, 128.9, 128.2, 127.8, 127.6, 125.9, 55.0, 54.6, 53.7, 52.9, 52.0, 49.7, 49.4, 49.2, 49.0, 48.8, 48.6, 48.4, 44.2, 43.6, 43.3, 42.3, 40.5, 39.8, 26.2, 26.1, 26.00, 25.98, 23.6, 23.3, 23.0, 22.3, 22.2, 21.3, 21.0.

Mp: 157.6-158.8 ºC.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{50}H_{67}N_9O_{10}Na^+$: 976.4903. Found: 976.4903.

7b



In an NMR tube, a solution of **7a** (20.0 mg, 0.0210 mmol) in DMSO-d_6 was photo-

irradiated with UV light (390 nm). After 20 min, the solution was evaporated and the crude was purified by column chromatography (n-hexane: AcOEt = 1:2-1:3, then $CHCl_3$: MeOH= 19:1) to afford **7b** (12.1 mg, 0.01477 mmol, 70%) as white solid.

^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 8.62 (1H, s), 8.12 (1H, d, *J* = 8.4 Hz), 8.02 (1H, d, *J* = 8.0 Hz), 7.75 (1H, d, *J* = 9.2 Hz), 7.64 (1H, t, *J* = 8.0 Hz), 7.33 (1H, t, *J* = 8.0 Hz), 7.14-7.10 (2H, m), 4.75 (1H, d, *J* = 16.0 Hz), 4.49-4.45 (1H, m), 4.30 (1H, d, *J* = 16.0 Hz), 4.25-4.16 (3H, m), 4.02 (2H, q, *J* = 14.4 Hz), 3.91 (1H, dd, *J* = 10.8, 4.0 Hz), 1.84-1.38 (12H, m), 0.97-0.88 (20H, m), 0.78 (3H, d, *J* = 6.4 Hz), 0.60 (3H, d, *J* = 6.0 Hz).

^{13}C{^{1}H} NMR (100 MHz, CD_3OD): δ (ppm) 182.9, 178.6, 172.2, 171.7, 169.7, 168.5, 165.0, 160.5, 153.4, 139.9, 139.2, 135.4, 134.2, 132.6, 128.7, 128.4, 125.9, 119.1, 116.4, 69.7, 68.2, 66.3, 62.7, 58.2, 56.5, 56.0, 51.1, 47.1, 46.5, 42.4, 41.0, 36.9, 28.9, 27.9, 25.6, 24.2, 24.1, 23.2, 23.00, 22.94, 21.8, 21.5, 21.1.

HPLC (250 nm): t_R 9.87 min, 98% purity.

HRMS (ESI-TOF, $[M+Na]^+$): Calcd. for $C_{43}H_{62}N_8O_8Na^+$, 841.4583. Found: 841.4594.

NMR spectroscopy

NMR measurements

Two-dimensional NMR spectra of **2a**, **2b**, **3a**, **3b**, **4a**, **5a**, and **5b** were recorded at 5-25 mM in DMSO-d_6 on a Bruker Avance III HD 800 or Avance III 500 spectrometer equipped with a cryogenic probe. NMR spectra were recorded at 298 K, except for **2a** spectra, which were recorded at 318 K. Two-dimensional TOCSY experiments were performed using standard pulse sequences and phase cycling (mlevetgp) with a mixing time of 60 ms, and 1,024-2,048 × 512 complex points were recorded. ROESY spectra were recorded using the previously reported pulse program and parameters (roesyadjsphpr) with a mixing time of 250 ms, and 2,048 × 1,024 complex points were recorded. Two-dimensional DQF-COSY experiments were performed using standard pulse sequences and phase cycling (cosydfetgp.2), and 8,192-16,384 × 256 complex points were recorded. Two-dimensional ^{1}H-^{13}C HSQC experiments were performed using standard pulse sequences and phase cycling (hsqcetgpsp), and 1,024 × 512 complex points were recorded for the ^{1}H and ^{13}C dimensions, respectively. Two-dimensional ^{1}H-^{13}C HMBC experiments were performed using standard pulse sequences and phase cycling (hmbcgplpndqf), and 2,048 × 2,048 complex points were recorded for the ^{1}H and ^{13}C dimensions, respectively. The inter-scan delays were set to 1.0 s in all two-dimensional experiments. All of the spectra were processed and analyzed by the Topspin 4.1 software (Bruker). Chemical shifts of ^{1}H NMR, HMBC, HSQC, ROESY, and TOCSY spectra are reported in p.p.m relative to 4,4-dimethyl-4-silapentane-1-sulfonic acid as external standards. Assignment of ^{1}H NMR was assisted by HMBC and HSQC spectrum as previously described.[1]

NMR structure calculations

The structures of **2a**, **2b**, **3a**, **3b**, **4a**, **5a**, and **5b** were calculated by a simulated annealing protocol with the software XPLOR-NIH [2] using the distance restraints defined from the intensities of signals in their respective 2D ROESY NMR spectra. Topologies and parameters for the **BZN** and **BZA** were manually generated using bonds, angles, and charge values generated by CHARMM-GUI Ligand Reader and Modeler.[3] The numbers of NOE distance restraints used for calculations were 84, 62, 68, 60, 82, 73, and 63 for **2a**, **2b**, **3a**, **3b**, **4a**, **5a**, and **5b**, respectively. The NOEs were classified as strong, medium, and weak, and only the upper distance limits were set to allow greater conformational freedom. From 100 calculations, we selected the 10 lowest energy structures with no violations of the distance restraints >0.5 Å. NOE and J values used for the calculations are summarized in Supplementary Tables. Ring current shifts were

calculated based on the Johnson-Bovey equation.[4] In the calculation, aromatic rings in **BZN** and **BZA** residues were treated as phenylalanine rings.

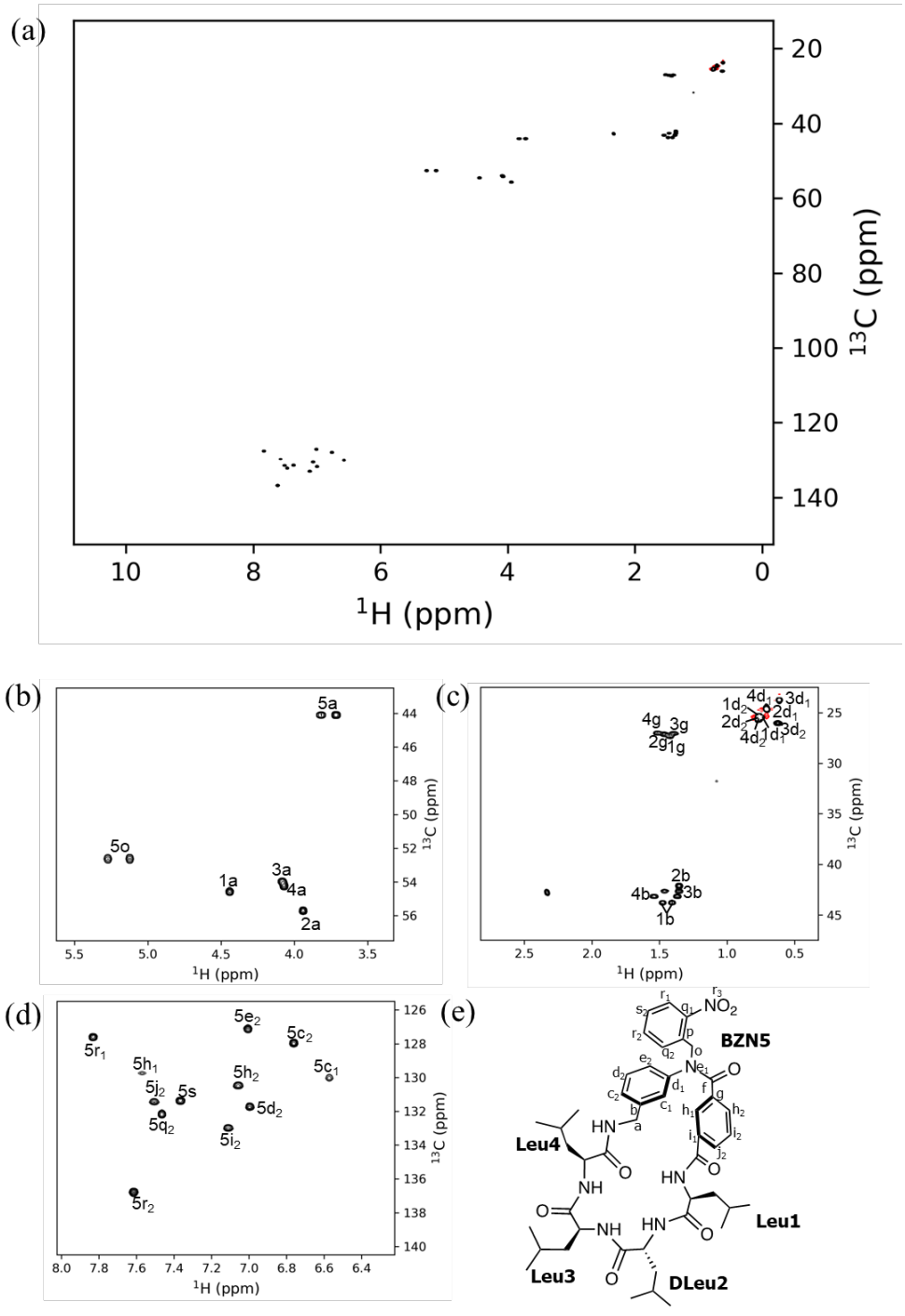


Figure S14. (a–d) ^{1}H-^{13}C HSQC spectrum of **2a** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **2a**. The resonance assignments are shown in (b-d) and summarized in Table S1.

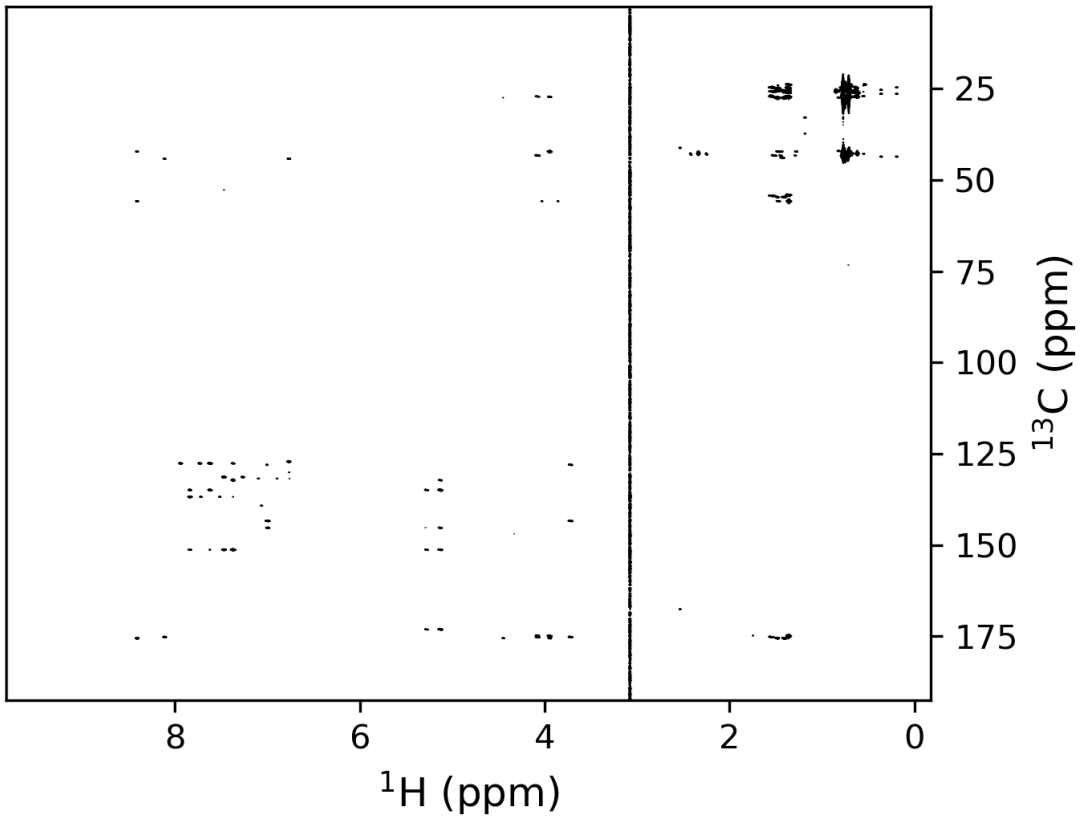


Figure S15. ^{1}H-^{13}C HMBC spectrum of **2a** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S1.

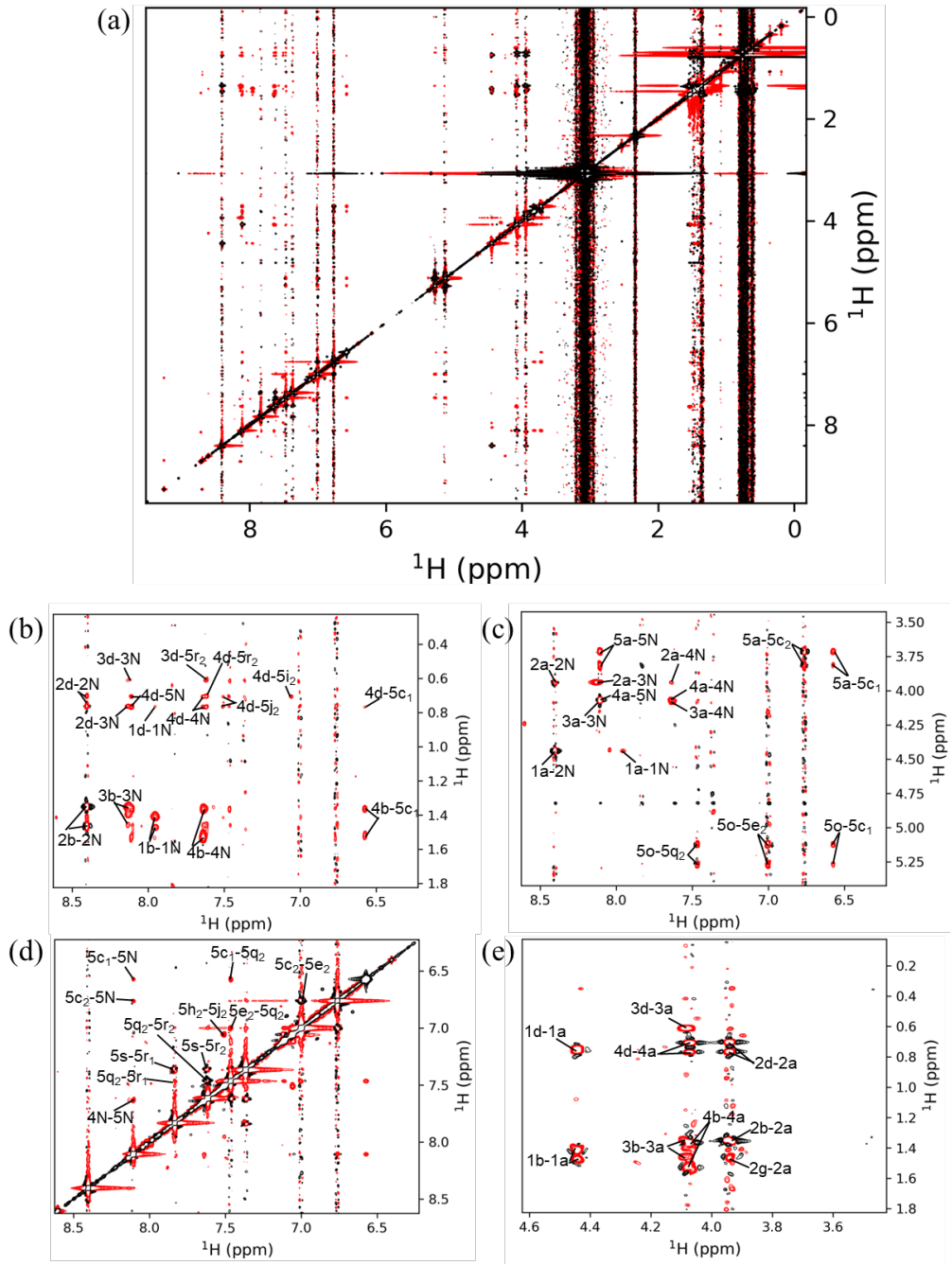


Figure S16. ROESY spectrum of **2a** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S8.

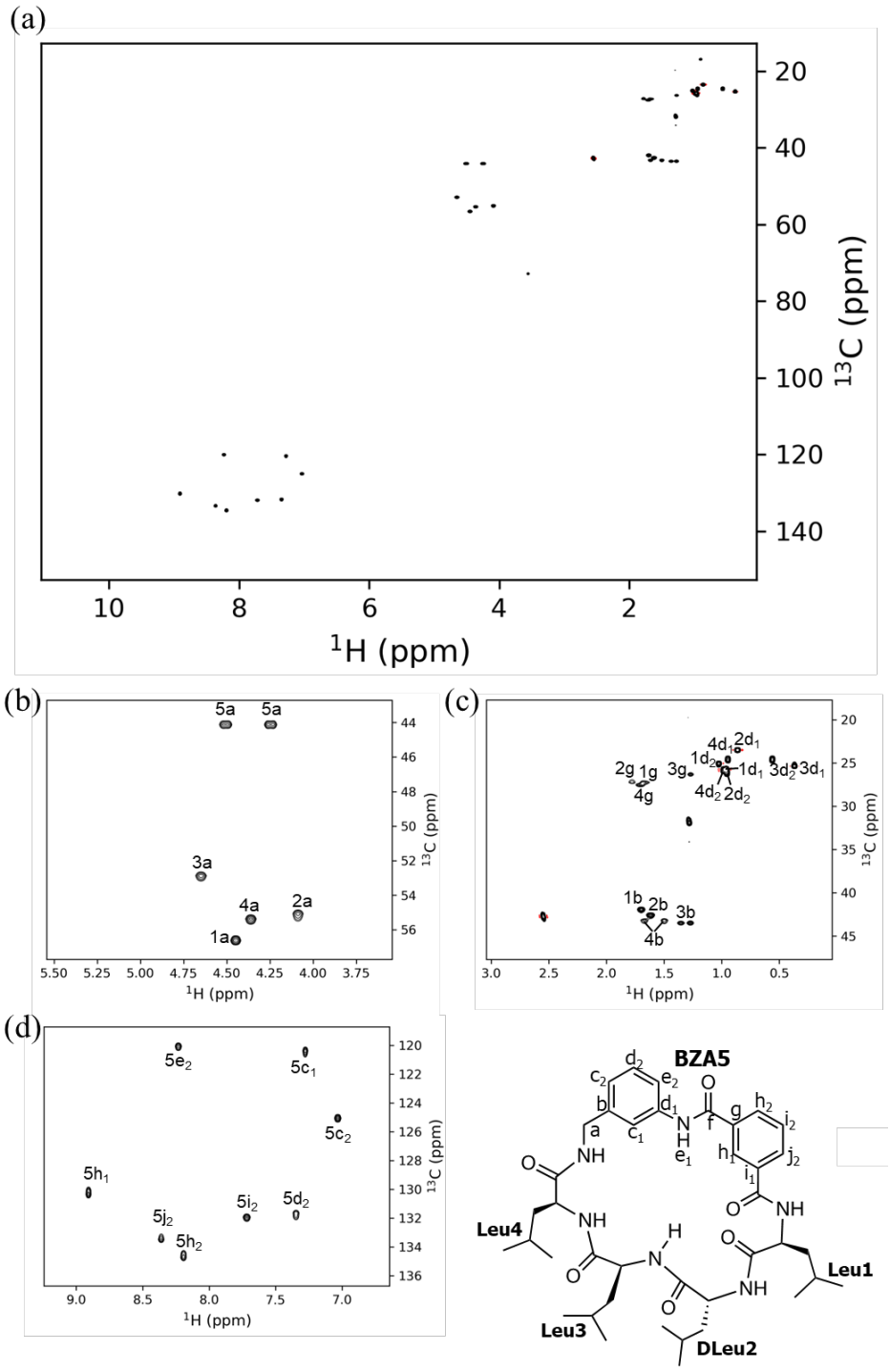


Figure S17. (a–d) ^{1}H-^{13}C HSQC spectrum of **2b** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **2b**. The resonance assignments are shown in (b-d) and summarized in Table S2.

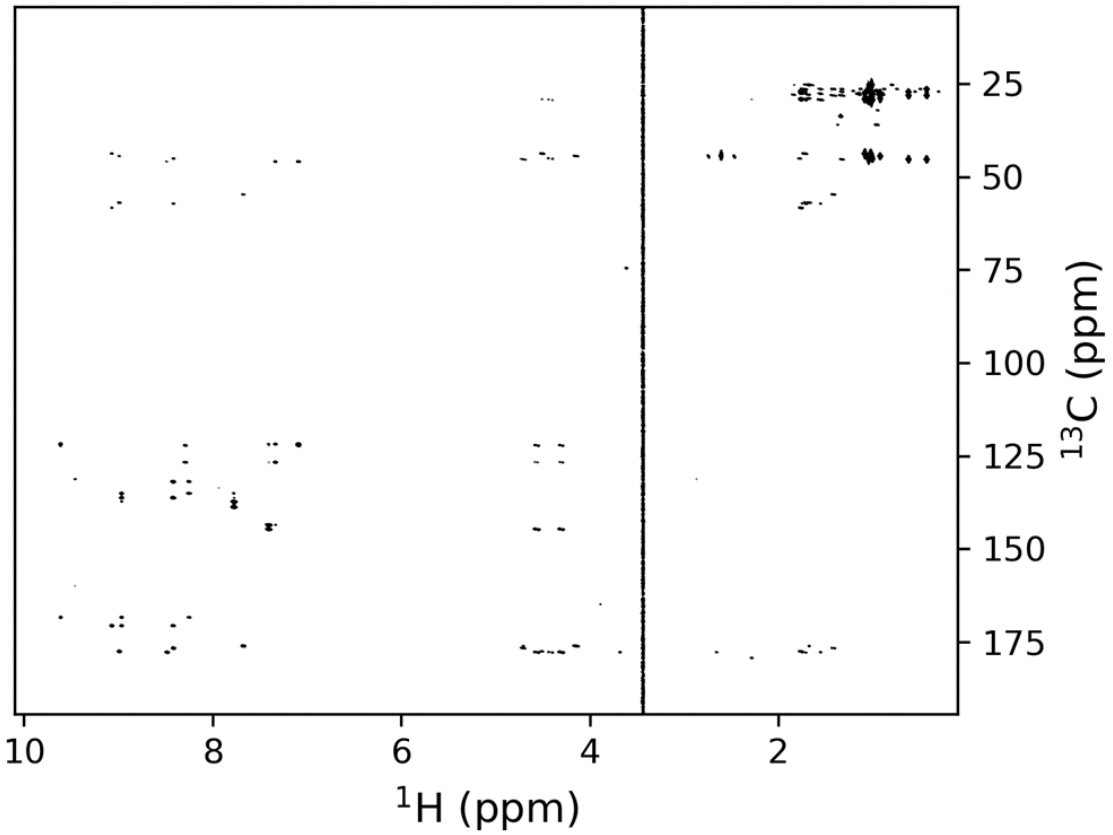


Figure S18. (a–d) ^{1}H-^{13}C HMBC spectrum of **2b** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S2.

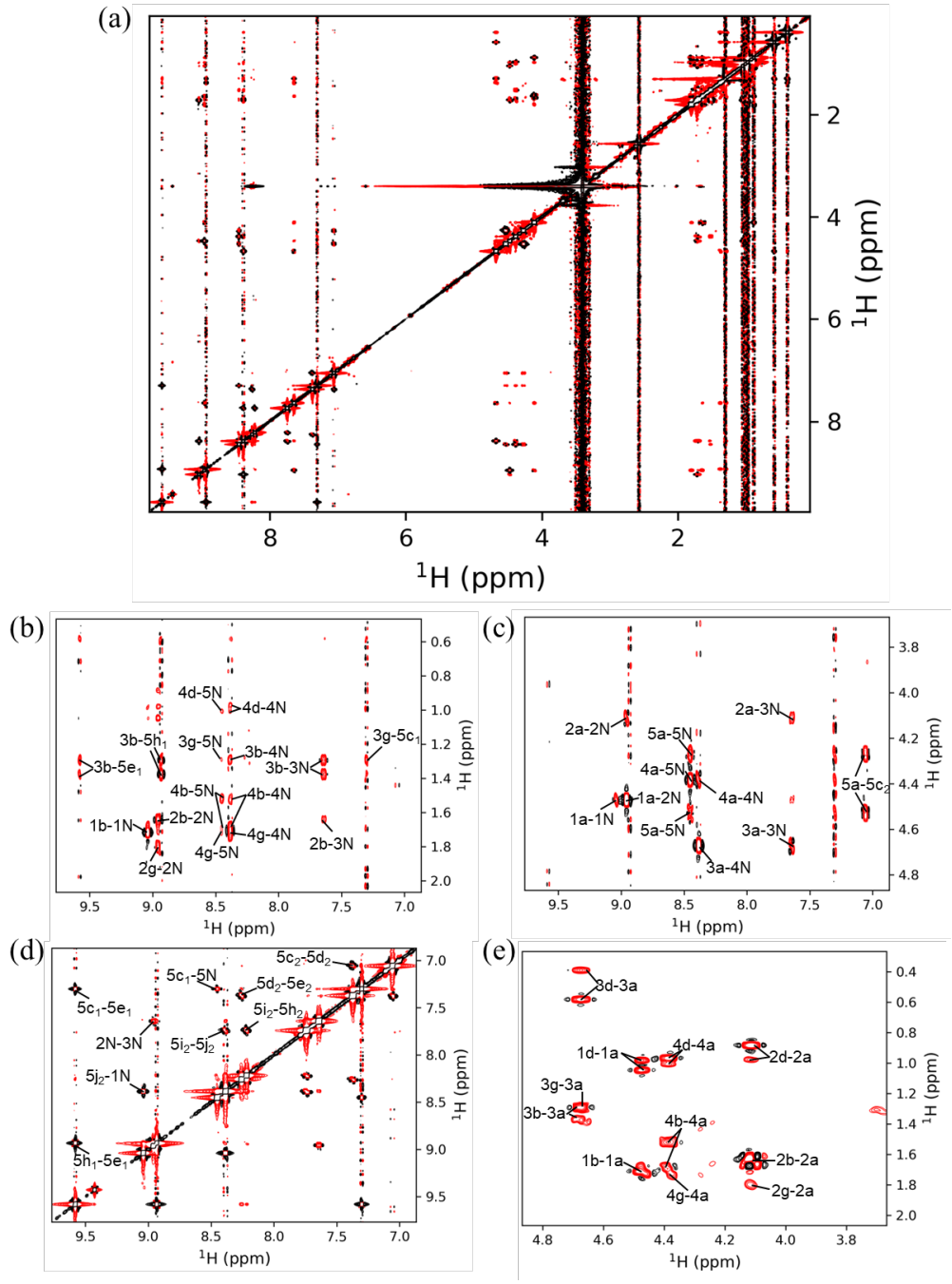


Figure S19. ROESY spectrum of **2b** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S9.

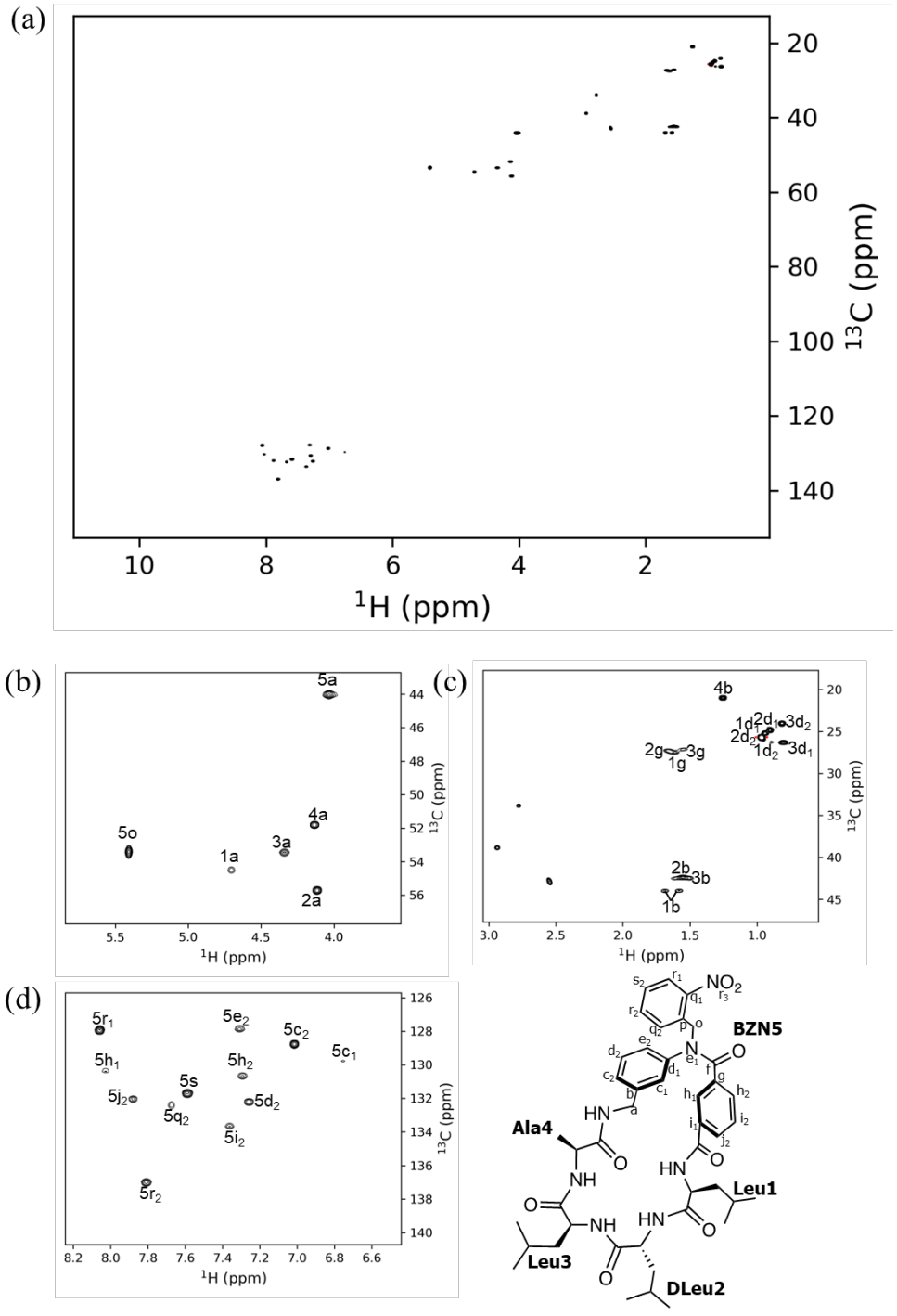


Figure S20. (a–d) ^{1}H-^{13}C HSQC spectrum of **3a** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **3a**. The resonance assignments are shown in (b-d) and summarized in Table S3.

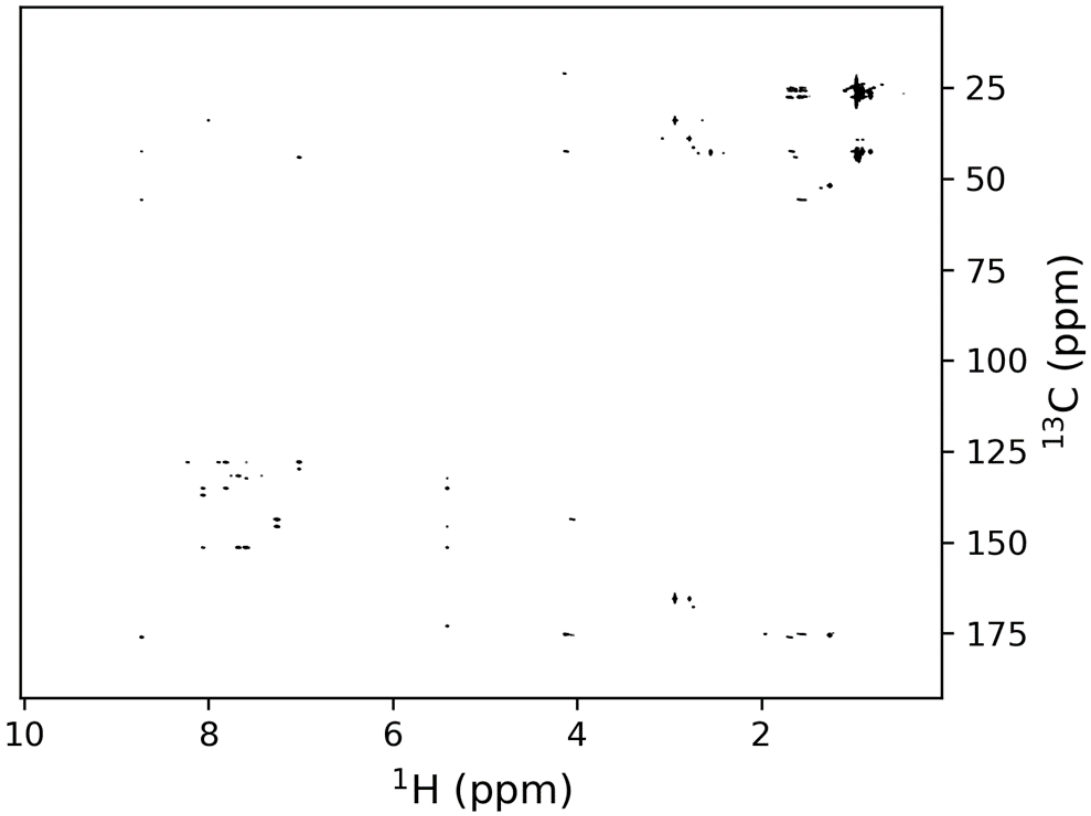


Figure S21. ^{1}H-^{13}C HMBC spectrum of **3a** recorded in DMSO-d_6. The resonance assignments are summarized in Table S3.

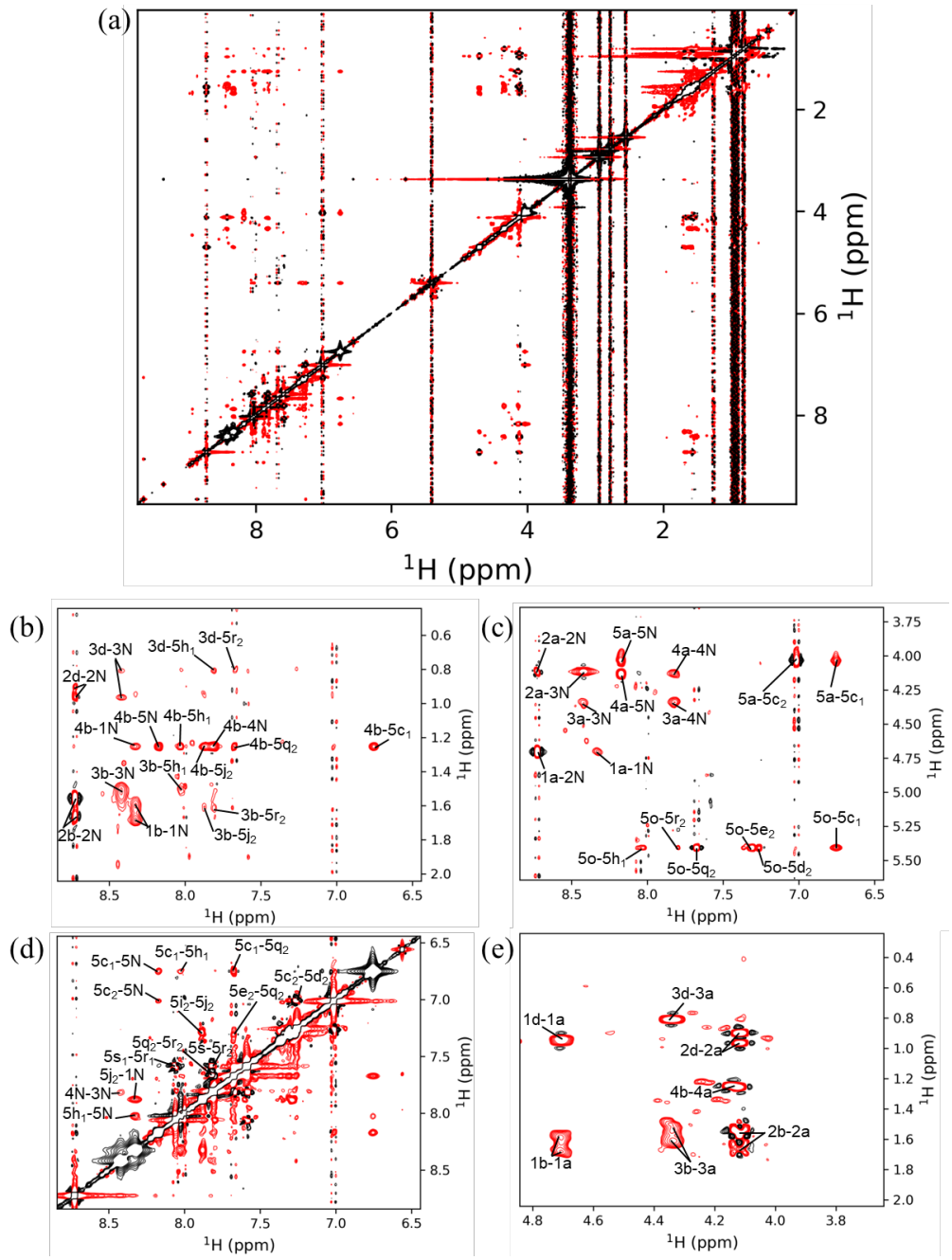


Figure S22. ROESY spectrum of **3a** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S10.

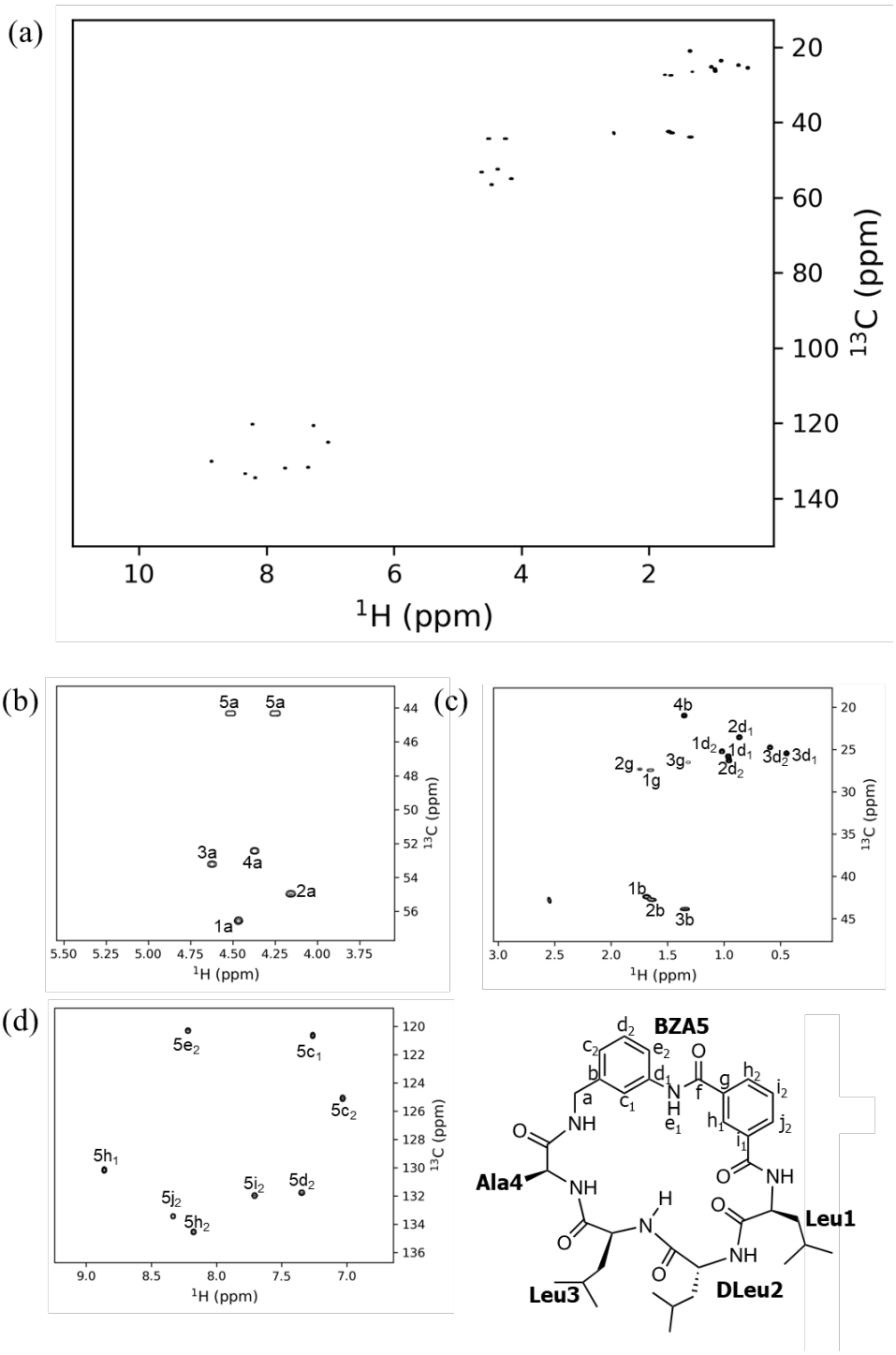


Figure S23. (a–d) ^{1}H-^{13}C HSQC spectrum of **3b** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **3b**. The resonance assignments are shown in (b-d) and summarized in Table S4.

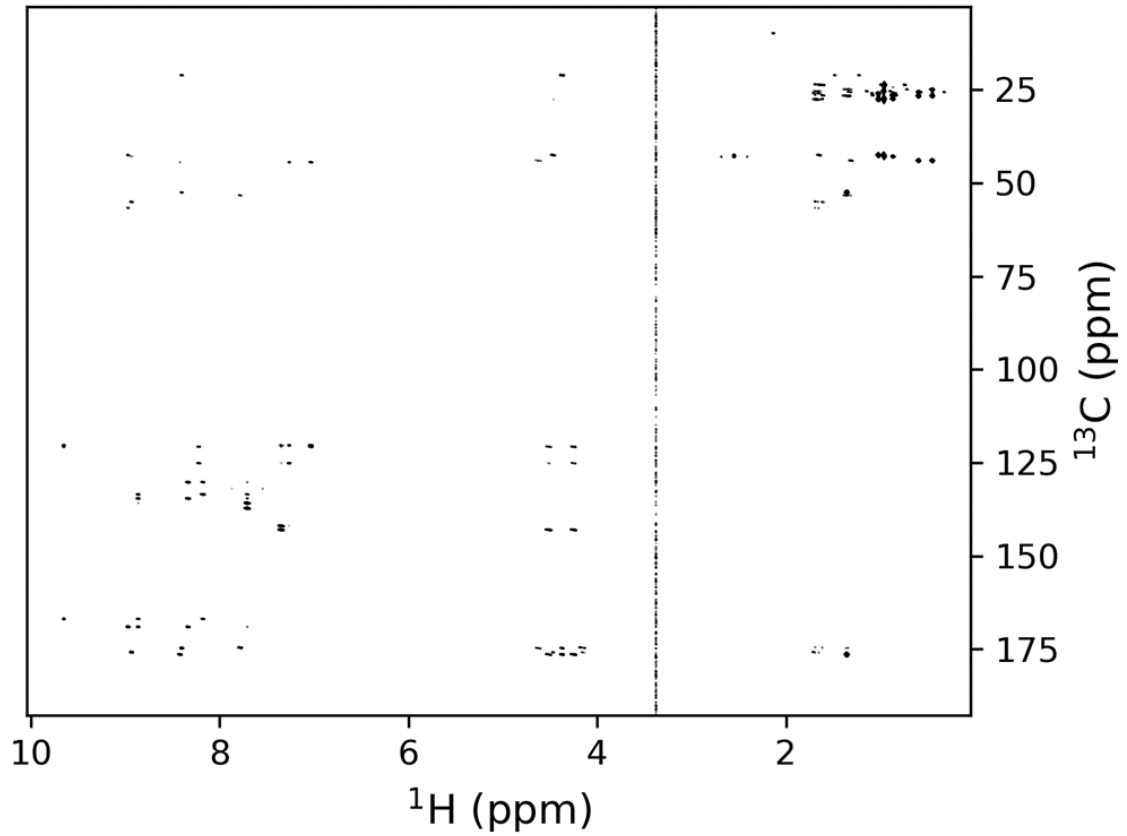


Figure S24. ^{1}H-^{13}C HMBC spectrum of **3b** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S4.

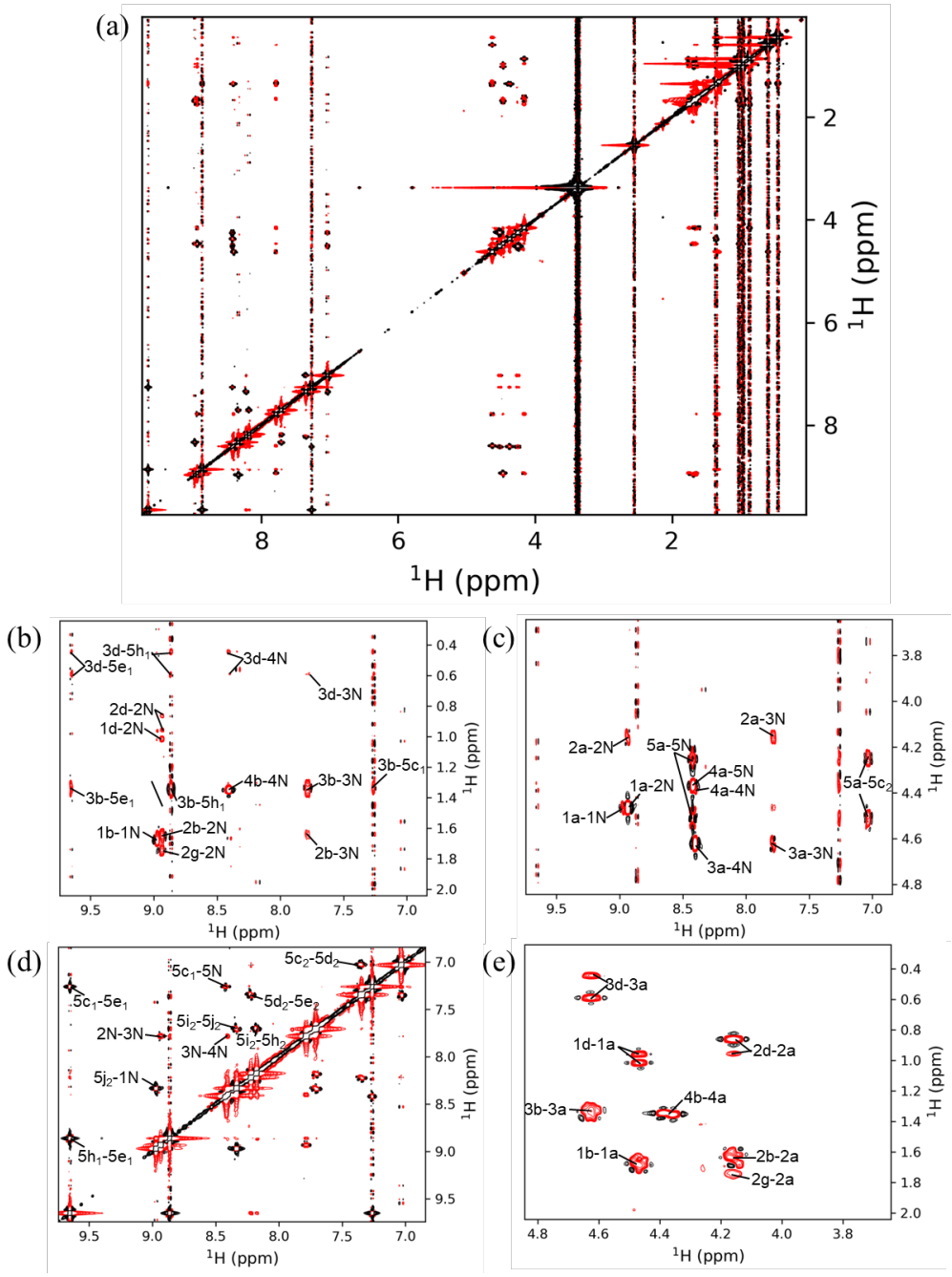


Figure S25. ROESY spectrum of **3b** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S11.

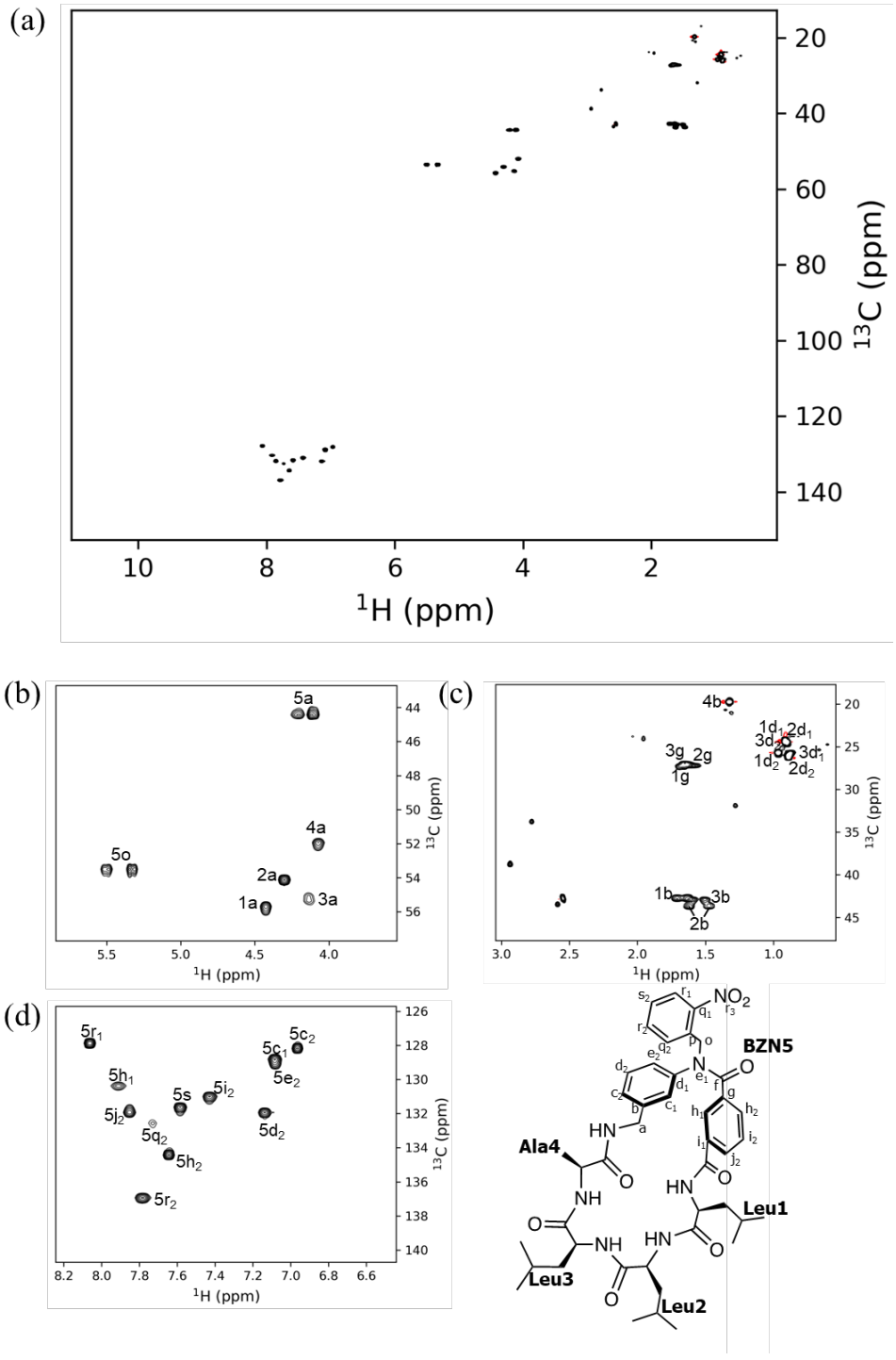


Figure S26. (a–d) ^{1}H-^{13}C HSQC spectrum of **4a** recorded in DMSO-d_6. *N*-methyl, methyl, and H_α/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **4a**. The resonance assignments are shown in (b-d) and summarized in Table S5.

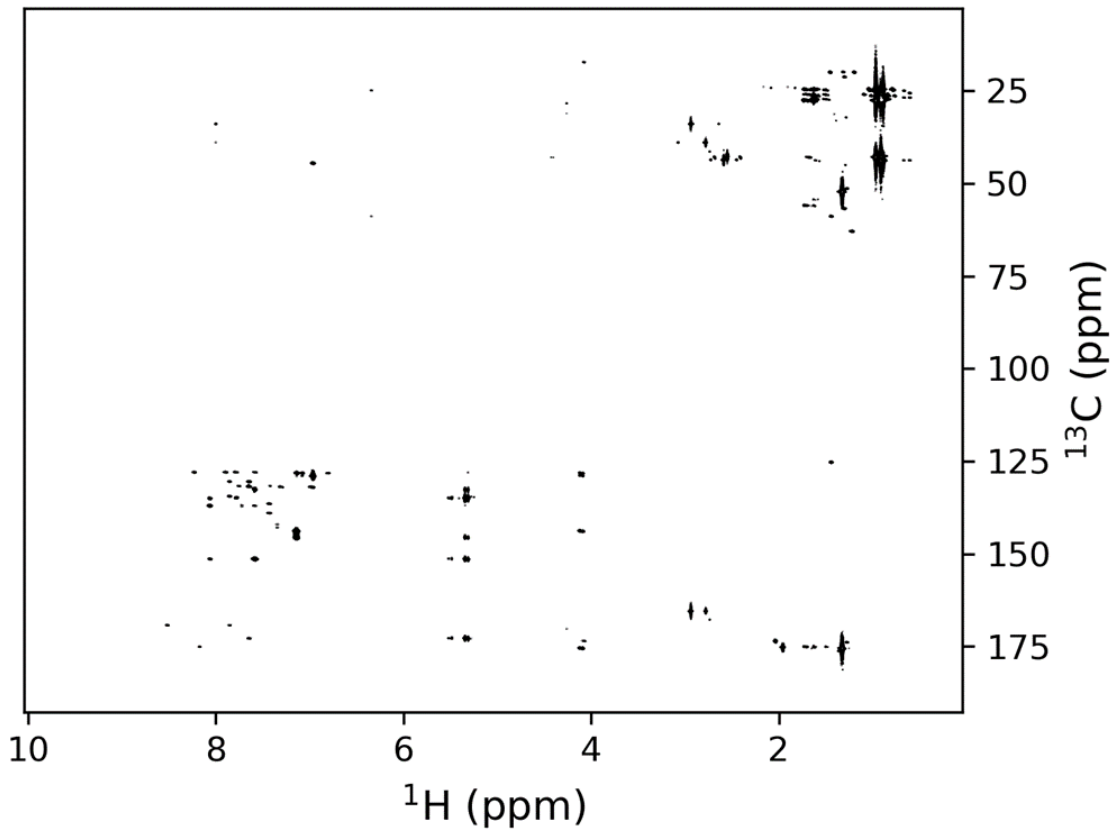


Figure S27. ^{1}H-^{13}C HMBC spectrum of **4a** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S5.

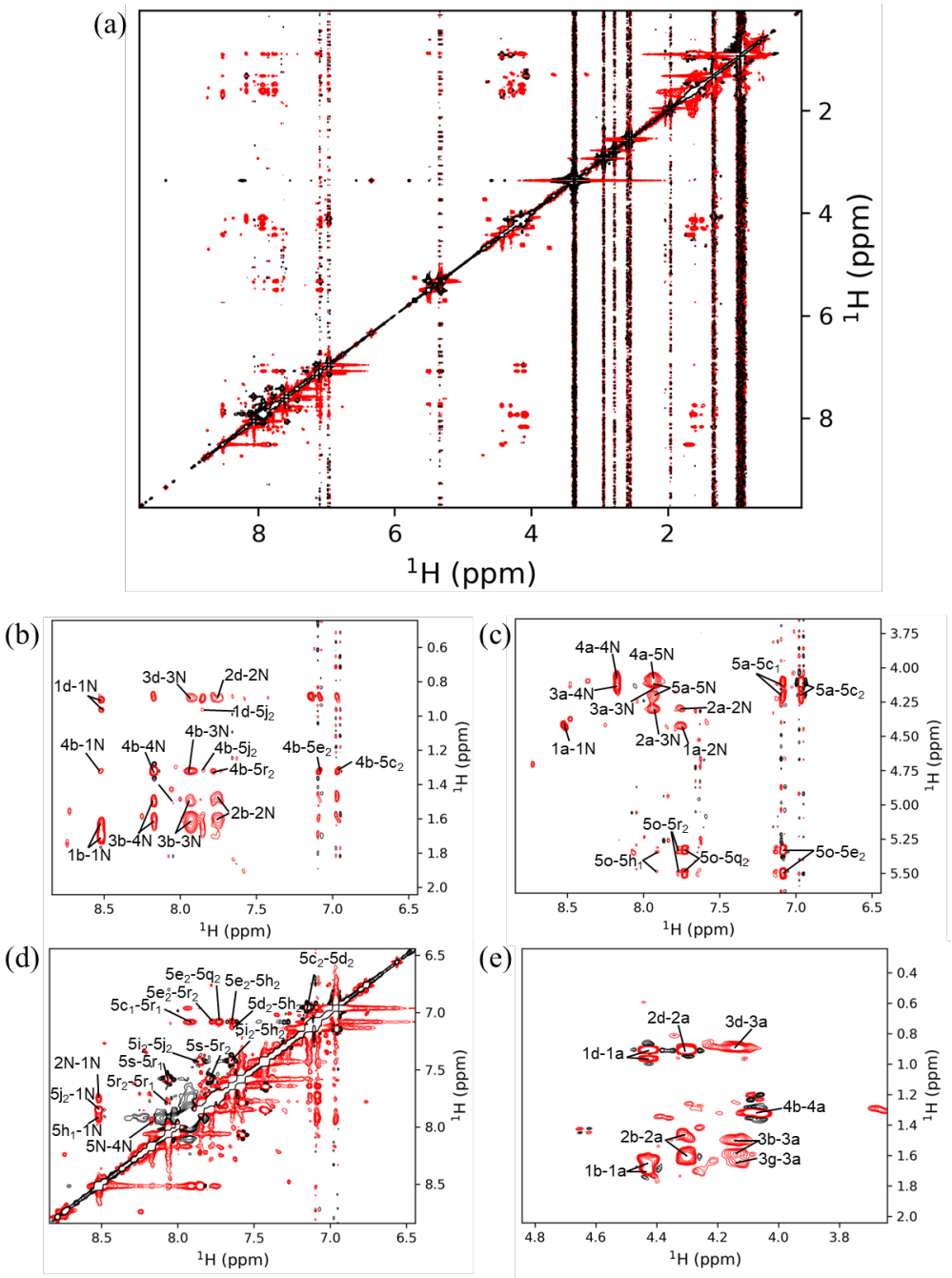


Figure S28. ROESY spectrum of **4a** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S12.

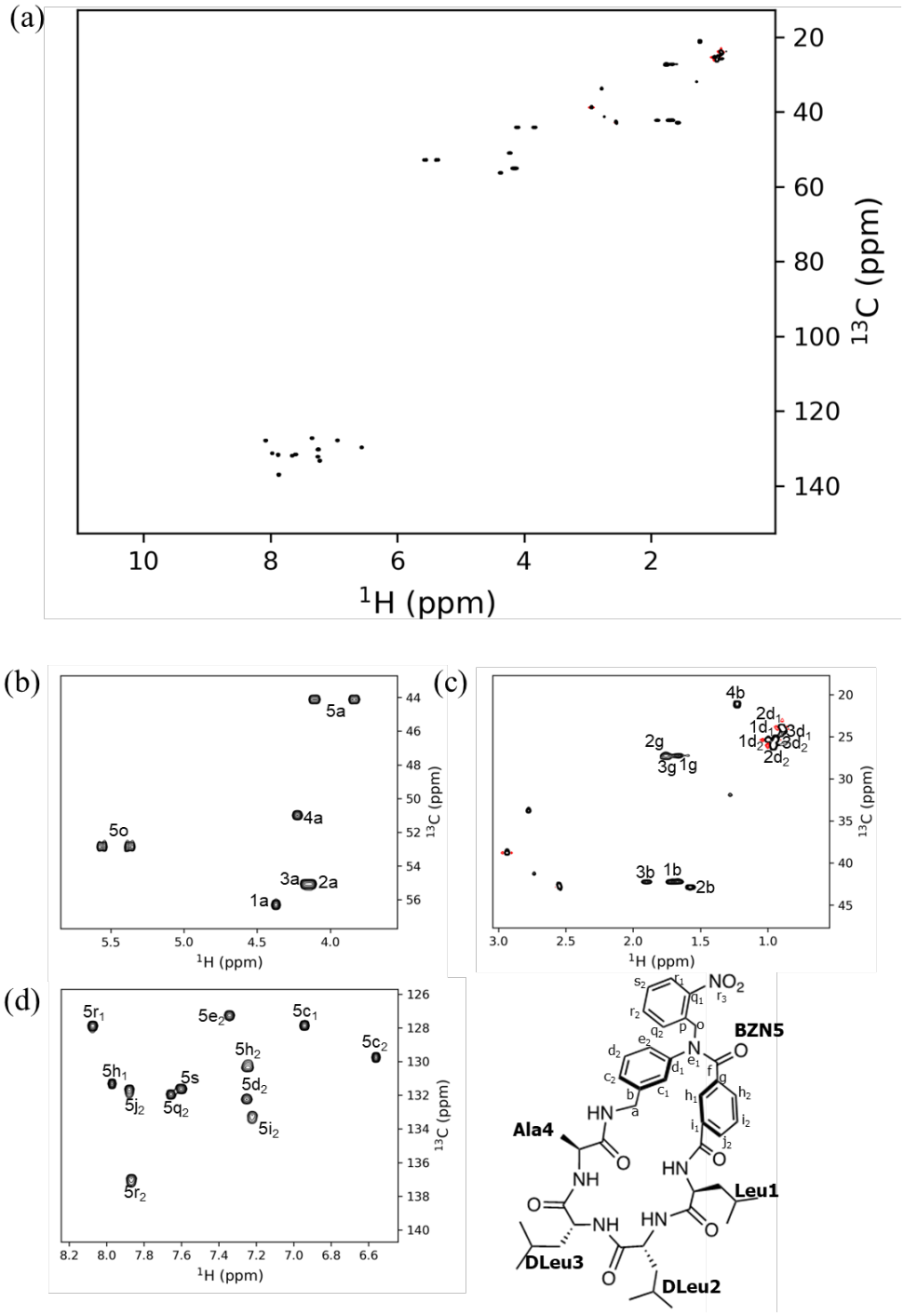


Figure S29. (a–d) ^{1}H-^{13}C HSQC spectrum of **5a** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **5a**. The resonance assignments are shown in (b-d) and summarized in Table S6.

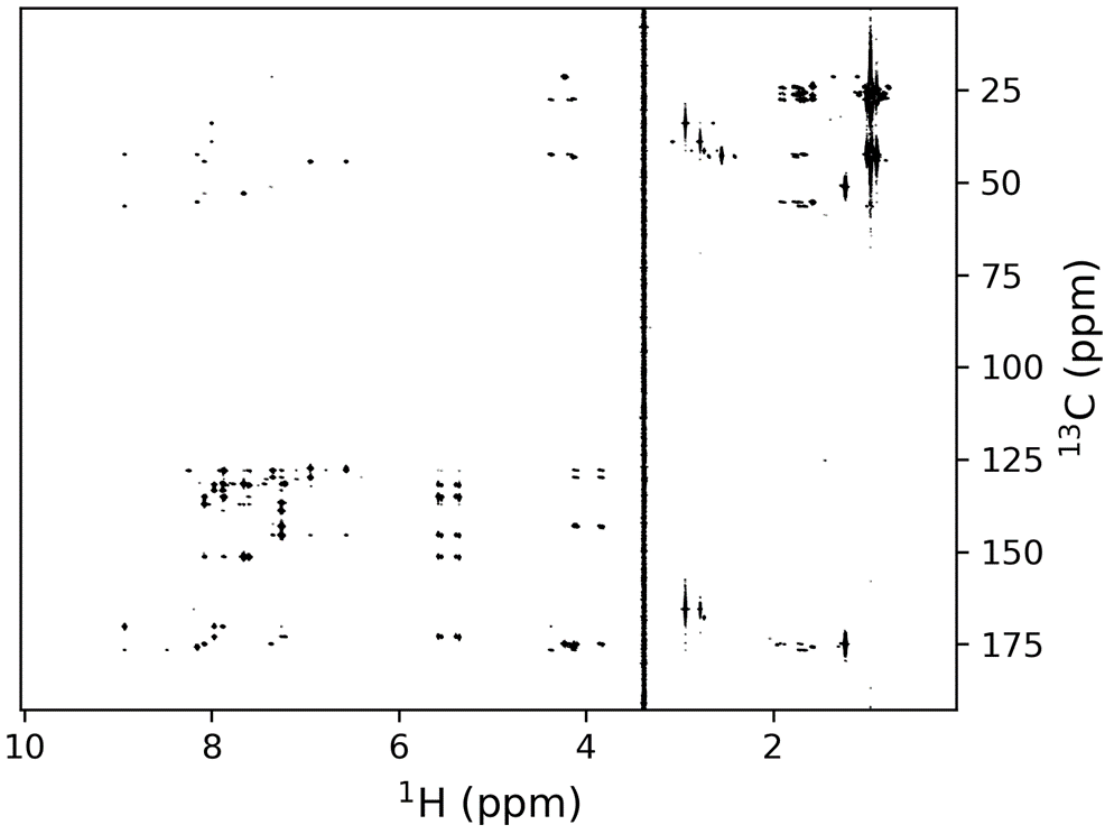


Figure S30. (a–d) ^{1}H-^{13}C HMBC spectrum of **5a** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S6.

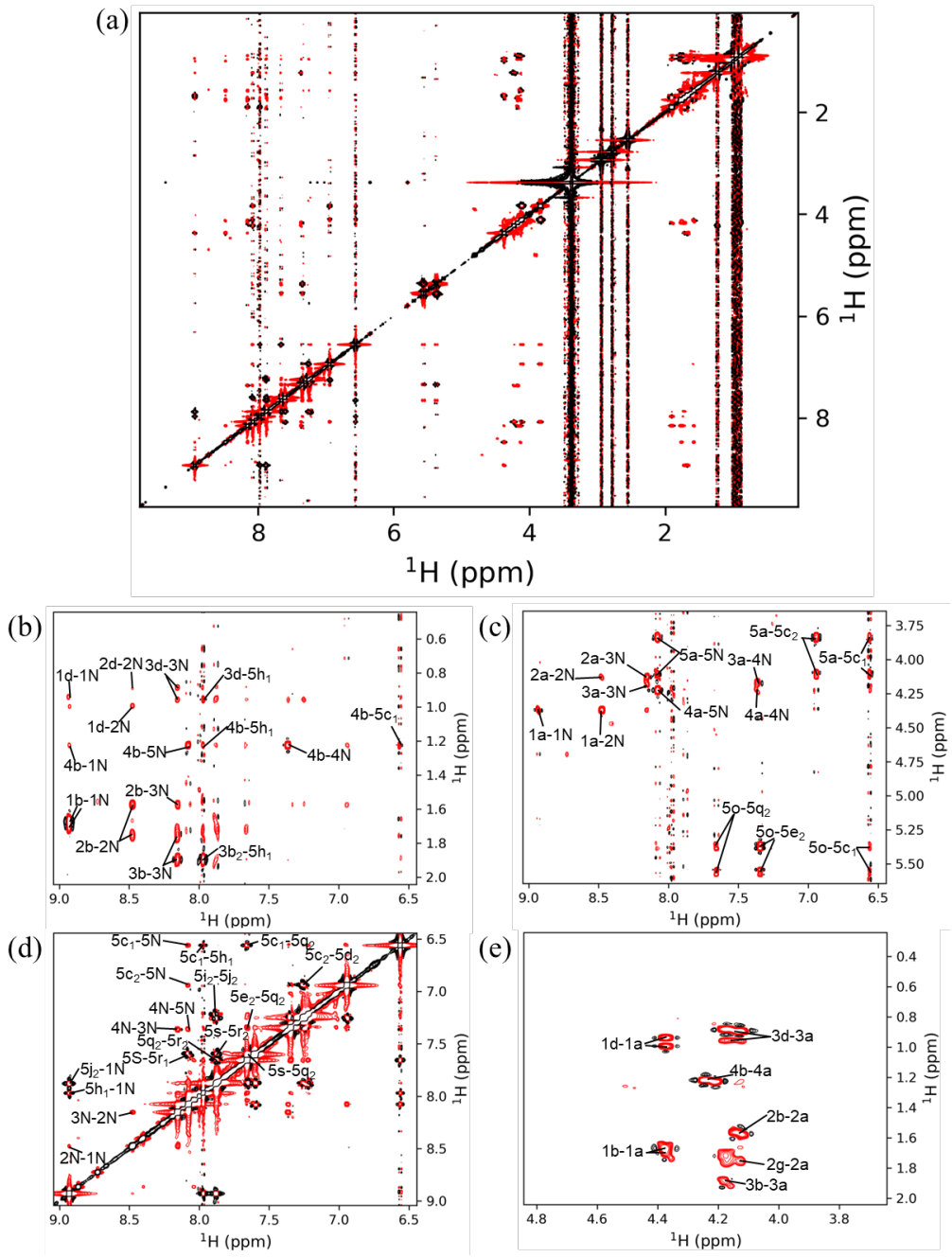


Figure S31. ROESY spectrum of **5a** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S13.

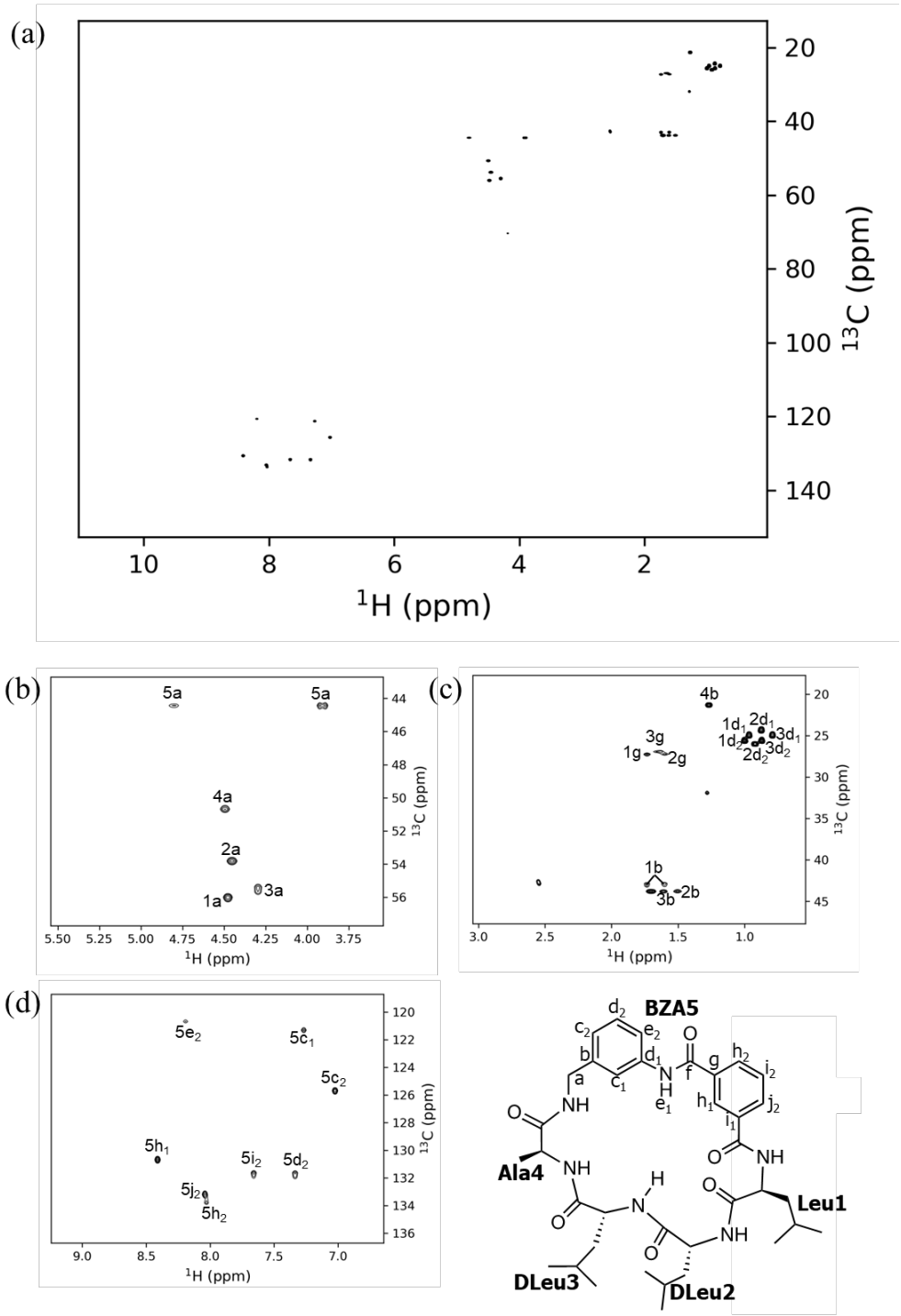


Figure S32. (a–d) ^{1}H-^{13}C HSQC spectrum of **5b** recorded in DMSO-*d*$_6$. *N*-methyl, methyl, and H$_\alpha$/*N*-methylene regions are enlarged in (b), (c), and (d) respectively. (e) Chemical structure of **5b**. The resonance assignments are shown in (b-d) and summarized in Table S7.

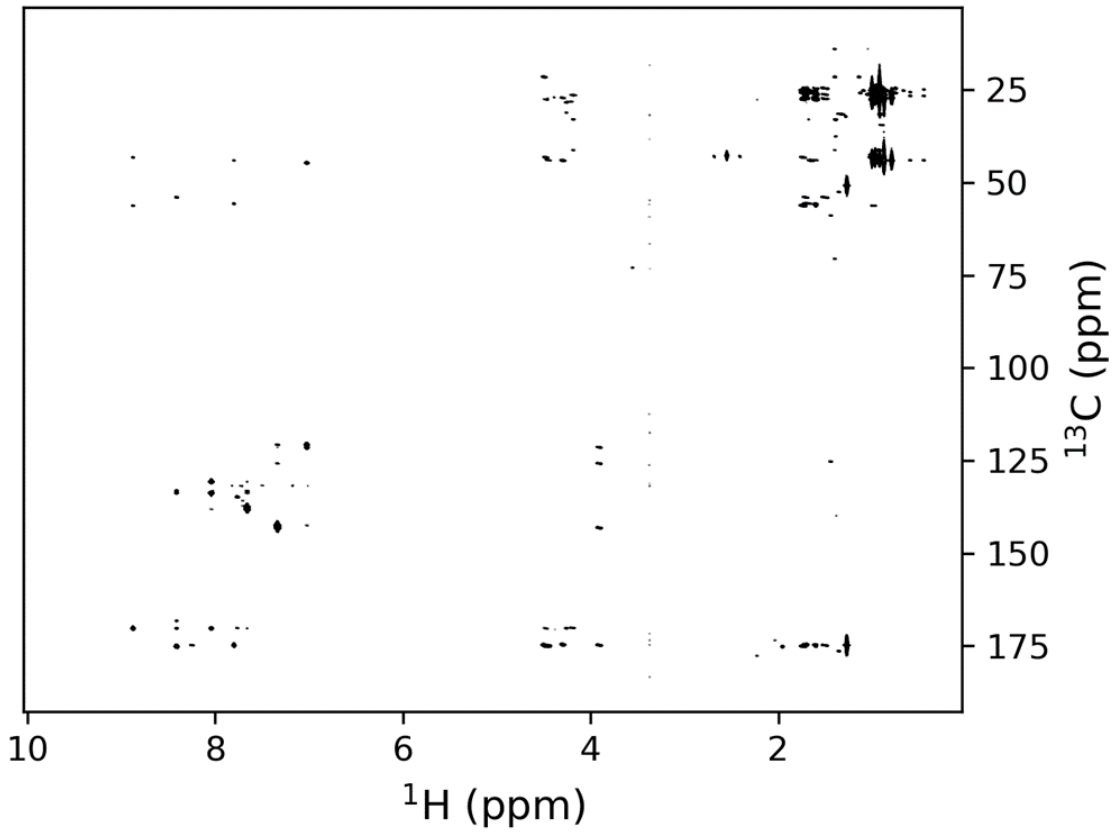


Figure S33. (a–d) ^{1}H-^{13}C HMBC spectrum of **5b** recorded in DMSO-*d*$_6$. The resonance assignments are summarized in Table S7.

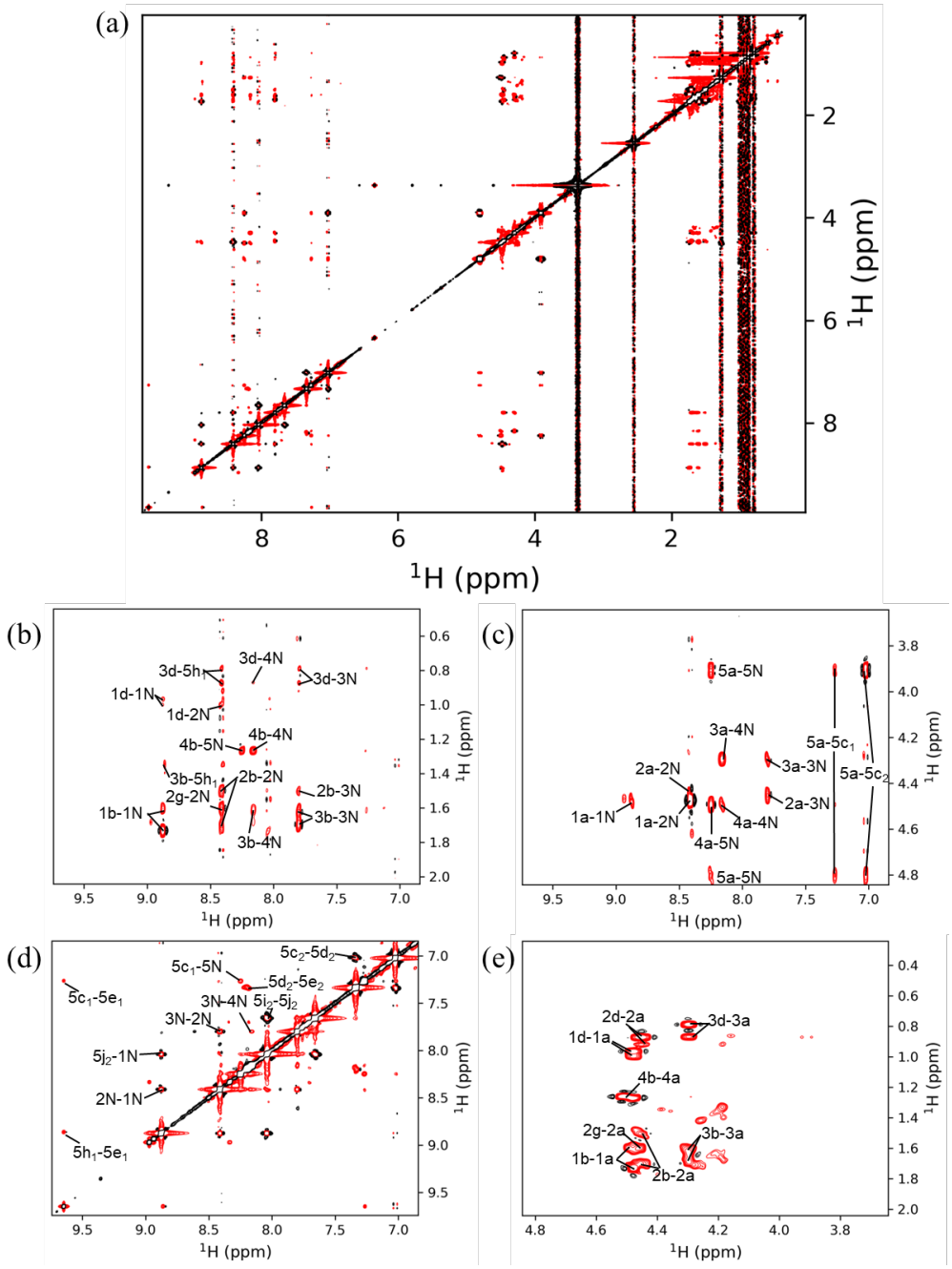


Figure S34. ROESY spectrum of **5b** recorded in DMSO-d_6. Upfield aliphatic–amide/aromatic, downfield aliphatic–amide/aromatic, amide/aromatic–amide/aromatic, downfield aliphatic–downfield aliphatic regions are enlarged in (b), (c), (d), and (e) respectively. The resonance assignments are shown in (b-e), and the observed NOEs are summarized in Table S14.

Table S1. Chemical shifts of 2a in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)	Residue number	Atom	Chemical shift (ppm)
1	C	175.5	3	CD2	26.1
1	CA	54.7	3	HN	8.13
1	CB	43.9	3	HA	4.09
1	CG	27.5	3	HB1	1.36
1	CD1	25.6	3	HB2	1.46
1	CD2	25.5	3	HG	1.4
1	HN	7.95	3	HD1	0.61
1	HA	4.44	3	HD2	0.62
1	HB1	1.41	4	C	175.2
1	HB2	1.48	4	CA	54.3
1	HG	1.43	4	CB	43.3
1	HD1	0.75	4	CG	27.1
1	HD2	0.77	4	CD1	24.7
2	C	174.9	4	CD2	25.8
2	CA	55.8	4	HN	7.64
2	CB	42.2	4	HA	4.07
2	CG	27.3	4	HB1	1.37
2	CD1	24.9	4	HB2	1.54
2	CD2	25.5	4	HG	1.52
2	HN	8.4	4	HD1	0.71
2	HA	3.94	4	HD2	0.77
2	HB1	1.36	5	CA	44.2
2	HB2	1.36	5	CB	143.4
2	HG	1.47	5	CC1	130.1
2	HD1	0.71	5	CC2	128
2	HD2	0.77	5	CD1	145.3
3	C	174.8	5	CD2	131.8
3	CA	54.1	5	CE2	127.1
3	CB	42.8	5	CF	173.1
3	CG	27.2	5	CH1	129.8
3	CD1	23.9	5	CH2	130.5

Residue number	Atom	Chemical shift (ppm)
5	CI2	133
5	CJ2	131.5
5	CO	52.7
5	CP	151.3
5	CQ1	134.9
5	CQ2	132.2
5	CR1	127.6
5	CR2	136.8
5	CS	131.4
5	HN	8.11
5	HA1	3.72
5	HA2	3.82
5	HC1	6.57
5	HC2	6.76
5	HD2	7
5	HE2	7
5	HH2	7.11
5	HI2	7.06
5	HJ2	7.51
5	HO1	5.13
5	HO2	5.27
5	HQ2	7.47
5	HR1	7.83
5	HR2	7.62

Table S2. Chemical shifts of 2b in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)
1	C	175.9
1	CA	56.8
1	CB	42.2
1	CG	27.5
1	CD1	25.9
1	CD2	25.4
1	HN	9.01
1	HA	4.45
1	HB1	1.69
1	HB2	1.69
1	HG	1.66
1	HD1	0.96
1	HD2	1.03
2	C	174.5
2	CA	55.4
2	CB	42.9
2	CG	27.4
2	CD1	23.8
2	CD2	26.4
2	HN	8.93
2	HA	4.09
2	HB1	1.62
2	HB2	1.62
2	HG	1.78
2	HD1	0.86
2	HD2	0.96
3	C	175
3	CA	53.2
3	CB	43.7
3	CG	26.6
3	CD1	25.6
3	CD2	24.9
3	HN	7.61
3	HA	4.65
3	HB1	1.27
3	HB2	1.36
3	HG	1.27
3	HD1	0.37
3	HD2	0.56
4	C	176.2
4	CA	55.6
4	CB	43.5
4	CG	27.8
4	CD1	24.9
4	CD2	26.1
4	HN	8.36
4	HA	4.36
4	HB1	1.5
4	HB2	1.67
4	HG	1.71
4	HD1	0.95
4	HD2#	0.99
5	C	169
5	CA	44.4
5	CB	143.1
5	CC1	120.6
5	CC2	125.1
5	CD1	141.9
5	CD2	131.8
5	CE2	120.2

Residue number	Atom	Chemical shift (ppm)
5	CF	166.8
5	CG	135.7
5	CH1	130.3
5	CH2	134.7
5	CI1	137.2
5	CI2	132
5	CJ2	133.5
5	HN	8.43
5	HA1	4.25
5	HA2	4.51
5	HC1	7.27
5	HC2	7.03
5	HD2	7.35
5	HE1	9.56
5	HE2	8.23
5	HH1	8.91
5	HH2	8.19
5	HI2	7.72
5	HJ2	8.36

Table S3. Chemical shifts of 3a in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)	Residue number	Atom	Chemical shift (ppm)
1	C	176.1	3	HN	8.42
1	CA	54.6	3	HA	4.34
1	CB	44.1	3	HB1	1.51
1	CG	27.6	3	HB2	1.62
1	CD1	25.3	3	HG	1.56
1	CD2	26	3	HD1	0.81
1	HN	8.33	3	HD2	0.89
1	HA	4.7	4	C	175.5
1	HB1	1.58	4	CA	52
1	HB2	1.69	4	CB	21.1
1	HG	1.63	4	HN	7.82
1	HD1	0.94	4	HA	4.13
1	HD2	0.96	4	HB	1.26
2	CA	55.8	5	CA	44.2
2	CB	42.5	5	CB	143.7
2	CG	27.4	5	CC1	129.8
2	CD1	25	5	CC2	128.8
2	CD2	25.7	5	CD1	145.7
2	HN	8.73	5	CD2	132.2
2	HA	4.12	5	CE2	127.9
2	HB1	1.56	5	CF	173
2	HB2	1.67	5	CG	137.3
2	HG	1.67	5	CH1	130.4
2	HD1	0.9	5	CH2	133.7
2	HD2	0.97	5	CI1	138.9
3	CA	53.5	5	CI2	130.7
3	CB	42.5	5	CJ2	132.1
3	CG	27.3	5	CO	53.5
3	CD1	26.4	5	CP	135.1
3	CD2	24.2	5	CQ1	151.4

Residue number	Atom	Chemical shift (ppm)
5	CQ2	132.4
5	CR1	128
5	CR2	137
5	CS	131.7
5	HN	8.17
5	HA1	4.04
5	HA2	4.04
5	HC1	6.75
5	HC2	7.01
5	HD2	7.26
5	HE2	7.31
5	HH1	8.03
5	HH2	7.36
5	HI1	7.3
5	HI2	7.29
5	HJ2	7.88
5	HO1	5.41
5	HO2	5.41
5	HQ2	7.67
5	HR1	8.06
5	HR2	7.81
5	HS	7.59

Table S4. Chemical shifts of 3b in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)
1	C	175.8
1	CA	56.6
1	CB	42.5
1	CG	27.6
1	CD1	25.9
1	CD2	25.3
1	HN	8.97
1	HA	4.47
1	HB1	1.69
1	HB2	1.69
1	HG	1.65
1	HD1	0.96
1	HD2	1.02
2	C	174.6
2	CA	55.1
2	CB	42.9
2	CG	27.5
2	CD1	23.7
2	CD2	26.5
2	HN	8.94
2	HA	4.16
2	HB1	1.64
2	HB2	1.64
2	HG	1.75
2	HD1	0.87
2	HD2	0.96
3	C	174.7
3	CA	53.3
3	CB	44
3	CG	26.7
3	CD1	25.6
3	CD2	24.9
3	HN	7.79
3	HA	4.62
3	HB1	1.34
3	HB2	1.34
3	HG	1.32
3	HD1	0.45
3	HD2	0.6
4	C	176.4
4	CA	52.5
4	CB	21.1
4	HN	8.4
4	HA	4.37
4	HB	1.35
5	C	169
5	CA	44.4
5	CB	143
5	CC1	120.7
5	CC2	125.1
5	CD1	142
5	CD2	131.8
5	CE2	120.3
5	CF	166.9
5	CG	135.8
5	CH1	130.2
5	CH2	134.6
5	CI1	137.3
5	CI2	132
5	CJ2	133.5

Residue number	Atom	Chemical shift (ppm)
5	HN	8.42
5	HA1	4.25
5	HA2	4.52
5	HC1	7.26
5	HC2	7.03
5	HD2	7.35
5	HE1	9.65
5	HE2	8.22
5	HH1	8.86
5	HH2	8.18
5	HI2	7.71
5	HJ2	8.33

Table S5. Chemical shifts of 4a in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)
1	CA	56
1	CB	43
1	CG	27.7
1	CD1	24.7
1	CD2	26.1
1	HN	8.52
1	HA	4.43
1	HB1	1.63
1	HB2	1.71
1	HG	1.68
1	HD1	0.91
1	HD2	0.97
2	CA	54.4
2	CB	43.9
2	CG	27.5
2	CD1	24.5
2	CD2	26.5
2	HN	7.76
2	HA	4.3
2	HB1	1.47
2	HB2	1.62
2	HG	1.58
2	HD1	0.9
2	HD2	0.9
3	C	175.1
3	CA	55.5
3	CB	43.2
3	CG	27.2
3	CD1	24.8
3	CD2	26
3	HN	7.93
3	HA	4.14
3	HB1	1.5
3	HB2	1.6
3	HG	1.67
3	HD1	0.89
3	HD2	0.89
4	C	175.5
4	CA	52.2
4	CB	20
4	HN	8.17
4	HA	4.07
4	HB	1.33
5	C	169.2
5	CA	44.6
5	CB	143.9
5	CC1	129
5	CC2	128.2
5	CD1	145.6
5	CD2	132
5	CE2	129.1
5	CF	172.7
5	CH1	130.5
5	CH2	134.5
5	CI2	131.1
5	CJ2	131.9
5	CO	53.8
5	CP	135
5	CQ1	151.4
5	CQ2	132.6

Residue number	Atom	Chemical shift (ppm)
5	CR1	128
5	CR2	137
5	CS	131.7
5	HN	7.94
5	HA1	4.11
5	HA2	4.2
5	HC1	7.08
5	HC2	6.96
5	HD2	7.14
5	HE2	7.08
5	HH1	7.91
5	HH2	7.65
5	HI2	7.43
5	HJ2	7.85
5	HO1	5.33
5	HO2	5.5
5	HQ2	7.73
5	HR1	8.06
5	HR2	7.78
5	HS	7.58

Table S6. Chemical shifts of 5a in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)
1	C	176.6
1	CA	56.5
1	CB	42.4
1	CG	27.6
1	CD1	25.5
1	CD2	25.6
1	HN	8.93
1	HA	4.37
1	HB1	1.66
1	HB2	1.71
1	HG	1.67
1	HD1	0.94
1	HD2	1
2	C	175.8
2	CA	55.3
2	CB	43.1
2	CG	27.4
2	CD1	24
2	CD2	26.4
2	HN	8.48
2	HA	4.13
2	HB1	1.58
2	HB2	1.58
2	HG	1.76
2	HD1	0.9
2	HD2	0.96
3	C	174.9
3	CA	55.3
3	CB	42.5
3	CG	27.7
3	CD1	24.5
3	CD2	26.1
3	HN	8.16
3	HA	4.17
3	HB1	1.72
3	HB2	1.9
3	HG	1.76
3	HD1	0.89
3	HD2	0.96
4	C	174.9
4	CA	51.2
4	CB	21.4
4	HN	7.36
4	HA	4.23
4	HB	1.23
5	C	170.2
5	CA	44.4
5	CB	143
5	CC1	129.8
5	CC2	127.9
5	CD1	145.4
5	CD2	132.3
5	CE2	127.4
5	CF	173
5	CG	136.7
5	CH1	131.4
5	CH2	133.3
5	CI1	138.8
5	CI2	130.4
5	CJ2	131.7

Residue number	Atom	Chemical shift (ppm)
5	CO	53.1
5	CP	135.1
5	CQ1	151.3
5	CQ2	131.9
5	CR1	128
5	CR2	137.1
5	CS	131.6
5	HN	8.08
5	HA1	3.84
5	HA2	4.11
5	HC1	6.56
5	HC2	6.94
5	HD2	7.25
5	HE2	7.35
5	HH1	7.97
5	HH2	7.22
5	HI2	7.25
5	HJ2	7.88
5	HO1	5.37
5	HO2	5.56
5	HQ2	7.66
5	HR1	8.08
5	HR2	7.87
5	HS	7.6

Table S7. Chemical shifts of 5b in DMSO-d_6.

Residue number	Atom	Chemical shift (ppm)	Residue number	Atom	Chemical shift (ppm)
1	C	175.1	3	CD1	25.3
1	CA	56.3	3	CD2	26
1	CB	43.2	3	HN	7.8
1	CG	27.6	3	HA	4.3
1	CD1	25.3	3	HB1	1.61
1	CD2	25.9	3	HB2	1.7
1	HN	8.88	3	HG	1.65
1	HA	4.48	3	HD1	0.79
1	HB1	1.6	3	HD2	0.88
1	HB2	1.73	4	C	174.8
1	HG	1.73	4	CA	50.9
1	HD1	0.97	4	CB	21.6
1	HD2	1	4	HN	8.16
2	C	174.8	4	HA	4.49
2	CA	54	4	HB	1.27
2	CB	44	5	C	170.3
2	CG	27.4	5	CA	44.7
2	CD1	24.6	5	CB	143.1
2	CD2	26.4	5	CC1	121.4
2	HN	8.41	5	CC2	125.8
2	HA	4.45	5	CD1	142.5
2	HB1	1.51	5	CD2	131.8
2	HB2	1.71	5	CE2	120.7
2	HG	1.6	5	CF	168.2
2	HD1	0.88	5	CG	137.5
2	HD2	0.91	5	CH1	130.8
3	C	174.6	5	CH2	133.8
3	CA	55.7	5	CI1	138.1
3	CB	44.1	5	CI2	131.8
3	CG	27.2	5	CJ2	133.2

Residue number	Atom	Chemical shift (ppm)
5	HN	8.25
5	HA1	3.91
5	HA2	4.8
5	HC1	7.27
5	HC2	7.02
5	HD2	7.34
5	HE1	10.3
5	HE2	8.2
5	HH1	8.41
5	HH2	8.03
5	HI2	7.66
5	HJ2	8.04

Table S8. NOE summary of 2a in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HA	2	HN	1.8-2.7
2	HB	2	HN	1.8-2.7
4	HA	5	HN	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HQ2	5	HR2	1.8-2.7
5	HS	5	HR2	1.8-2.7
1	HB1	1	HA	1.8-3.5
1	HD1	1	HA	1.8-3.5
1	HD2	1	HA	1.8-3.5
2	HA	3	HN	1.8-3.5
2	HB#	2	HA	1.8-3.5
2	HD1	2	HA	1.8-3.5
2	HD2	2	HA	1.8-3.5
2	HG	2	HN	1.8-3.5
3	HD1	3	HA	1.8-3.5
3	HD2	3	HA	1.8-3.5
4	HB1	4	HA	1.8-3.5
4	HD1	4	HA	1.8-3.5
4	HG	4	HN	1.8-3.5
4	HG	4	HA	1.8-3.5
5	HA1	5	HN	1.8-3.5
5	HA1	5	HC2	1.8-3.5
5	HC1	5	HQ2	1.8-3.5
5	HO1	5	HE2	1.8-3.5
5	HO2	5	HE2	1.8-3.5
1	HA	1	HN	1.8-5.0
1	HB1	1	HN	1.8-5.0
1	HB2	1	HN	1.8-5.0
1	HB2	1	HA	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HD1	1	HN	1.8-5.0
1	HD2	1	HN	1.8-5.0
2	HA	2	HN	1.8-5.0
2	HA	4	HN	1.8-5.0
2	HD1	2	HN	1.8-5.0
2	HD2	2	HN	1.8-5.0
2	HD2	3	HN	1.8-5.0
2	HG	2	HA	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HA	4	HN	1.8-5.0
3	HB1	3	HN	1.8-5.0
3	HB1	3	HA	1.8-5.0
3	HB2	3	HN	1.8-5.0
3	HB2	3	HA	1.8-5.0
3	HD2	3	HN	1.8-5.0
3	HD2	5	HR2	1.8-5.0
3	HG	3	HN	1.8-5.0
3	HG	3	HA	1.8-5.0
4	HA	4	HN	1.8-5.0
4	HB1	4	HN	1.8-5.0
4	HB1	5	HC1	1.8-5.0
4	HB2	4	HN	1.8-5.0
4	HB2	4	HA	1.8-5.0
4	HD1	5	HN	1.8-5.0
4	HD1	4	HN	1.8-5.0
4	HD1	5	HC1	1.8-5.0
4	HD1	5	HI2	1.8-5.0
4	HD1	5	HJ2	1.8-5.0
4	HD1	5	HR2	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
4	HD2	5	HN	1.8-5.0
4	HD2	4	HN	1.8-5.0
4	HD2	5	HC1	1.8-5.0
4	HD2	5	HI2	1.8-5.0
4	HD2	5	HJ2	1.8-5.0
4	HD2	4	HA	1.8-5.0
4	HG	5	HC1	1.8-5.0
4	HN	3	HN	1.8-5.0
5	HA1	5	HC1	1.8-5.0
5	HA2	5	HN	1.8-5.0
5	HA2	5	HC1	1.8-5.0
5	HA2	5	HC2	1.8-5.0
5	HC1	5	HN	1.8-5.0
5	HC1	5	HH1	1.8-5.0
5	HC2	5	HN	1.8-5.0
5	HE2	5	HQ2	1.8-5.0
5	HH1	1	HN	1.8-5.0
5	HI2	5	HJ2	1.8-5.0
5	HJ2	1	HN	1.8-5.0
5	HO1	5	HQ2	1.8-5.0
5	HO1	5	HC1	1.8-5.0
5	HO2	5	HQ2	1.8-5.0
5	HO2	5	HC1	1.8-5.0
5	HQ2	5	HR1	1.8-5.0
5	HR2	5	HR1	1.8-5.0
5	HS	5	HR1	1.8-5.0

Table S9. NOE summary of 2b in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HA	2	HN	1.8-2.7
1	HB#	1	HN	1.8-2.7
3	HA	4	HN	1.8-2.7
4	HA	5	HN	1.8-2.7
5	HA1	5	HA2	1.8-2.7
5	HC1	5	HE1	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HH1	5	HE1	1.8-2.7
5	HJ2	1	HN	1.8-2.7
1	HB#	1	HA	1.8-3.5
1	HD1	1	HA	1.8-3.5
1	HD2	1	HA	1.8-3.5
2	HB#	2	HN	1.8-3.5
2	HD1	2	HA	1.8-3.5
3	HB1	5	HH1	1.8-3.5
3	HB1	3	HA	1.8-3.5
3	HB2	5	HH1	1.8-3.5
3	HD2	3	HA	1.8-3.5
3	HG	3	HA	1.8-3.5
4	HD1	4	HA	1.8-3.5
5	HC1	5	HN	1.8-3.5
5	HD2	5	HE2	1.8-3.5
5	HI2	5	HJ2	1.8-3.5
5	HI2	5	HH2	1.8-3.5
1	HA	1	HN	1.8-5.0
2	HA	2	HN	1.8-5.0
2	HA	3	HN	1.8-5.0
2	HB#	3	HN	1.8-5.0
2	HB#	2	HA	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
2	HD2	2	HA	1.8-5.0
2	HG	2	HN	1.8-5.0
2	HG	2	HA	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HB1	3	HN	1.8-5.0
3	HB1	4	HN	1.8-5.0
3	HB1	5	HE1	1.8-5.0
3	HB2	3	HN	1.8-5.0
3	HB2	5	HE1	1.8-5.0
3	HB2	3	HA	1.8-5.0
3	HD1	3	HA	1.8-5.0
3	HG	5	HC1	1.8-5.0
3	HG	5	HN	1.8-5.0
3	HN	2	HN	1.8-5.0
4	HA	4	HN	1.8-5.0
4	HB1	4	HN	1.8-5.0
4	HB1	5	HN	1.8-5.0
4	HB1	4	HA	1.8-5.0
4	HB2	4	HN	1.8-5.0
4	HB2	5	HN	1.8-5.0
4	HB2	4	HA	1.8-5.0
4	HD1	4	HN	1.8-5.0
4	HD1	5	HN	1.8-5.0
4	HD2	4	HN	1.8-5.0
4	HD2	5	HN	1.8-5.0
4	HD2	4	HA	1.8-5.0
4	HG	4	HN	1.8-5.0
4	HG	5	HN	1.8-5.0
4	HG	4	HA	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
5	HA1	5	HN	1.8-5.0
5	HA1	5	HC2	1.8-5.0
5	HA2	5	HN	1.8-5.0
5	HA2	5	HC2	1.8-5.0

Table S10. NOE summary of 3a in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HA	2	HN	1.8-2.7
2	HB1	2	HN	1.8-2.7
2	HD1	2	HA	1.8-2.7
3	HD1	3	HA	1.8-2.7
4	HB	4	HA	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HQ2	5	HR2	1.8-2.7
5	HS	5	HR2	1.8-2.7
1	HD1	1	HA	1.8-3.5
1	HD2	1	HA	1.8-3.5
2	HA	2	HN	1.8-3.5
2	HA	3	HN	1.8-3.5
2	HB1	2	HA	1.8-3.5
2	HB2	2	HN	1.8-3.5
2	HD2	2	HA	1.8-3.5
2	HG	2	HA	1.8-3.5
4	HA	5	HN	1.8-3.5
5	HA#	5	HN	1.8-3.5
5	HA#	5	HC2	1.8-3.5
5	HI2	5	HH2	1.8-3.5
5	HO#	5	HQ2	1.8-3.5
5	HO#	5	HE2	1.8-3.5
5	HS	5	HR1	1.8-3.5
1	HA	1	HN	1.8-5.0
1	HB1	1	HN	1.8-5.0
1	HB1	1	HA	1.8-5.0
1	HB2	1	HN	1.8-5.0
1	HB2	1	HA	1.8-5.0
1	HG	1	HA	1.8-5.0
2	HB2	2	HA	1.8-5.0
2	HD1	2	HN	1.8-5.0
2	HD2	2	HN	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HA	4	HN	1.8-5.0
3	HB1	3	HN	1.8-5.0
3	HB1	3	HA	1.8-5.0
3	HB1	5	HH1	1.8-5.0
3	HB2	3	HN	1.8-5.0
3	HB2	3	HA	1.8-5.0
3	HB2	5	HJ2	1.8-5.0
3	HB2	4	HN	1.8-5.0
3	HD1	3	HN	1.8-5.0
3	HD1	5	HH1	1.8-5.0
3	HD1	4	HN	1.8-5.0
3	HD1	5	HQ2	1.8-5.0
3	HD2	3	HN	1.8-5.0
3	HG	3	HA	1.8-5.0
4	HA	4	HN	1.8-5.0
4	HB	4	HN	1.8-5.0
4	HB	1	HN	1.8-5.0
4	HB	5	HN	1.8-5.0
4	HB	5	HH1	1.8-5.0
4	HB	5	HJ2	1.8-5.0
4	HB	5	HQ2	1.8-5.0
4	HB	5	HC1	1.8-5.0
4	HN	3	HN	1.8-5.0
5	HA#	5	HC1	1.8-5.0
5	HC1	5	HN	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
5	HC1	5	HH1	1.8-5.0
5	HC1	5	HQ2	1.8-5.0
5	HC2	5	HN	1.8-5.0
5	HE2	5	HQ2	1.8-5.0
5	HH1	1	HN	1.8-5.0
5	HJ2	1	HN	1.8-5.0
5	HO#	5	HD2	1.8-5.0
5	HO#	5	HH1	1.8-5.0
5	HO#	5	HR2	1.8-5.0
5	HO#	5	HC1	1.8-5.0

Table S11. NOE summary of 3b in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HA	2	HN	1.8-2.7
1	HB#	1	HN	1.8-2.7
1	HN	5	HJ2	1.8-2.7
3	HA	4	HN	1.8-2.7
4	HB	4	HN	1.8-2.7
4	HN	4	HA	1.8-2.7
5	HA1	5	HA2	1.8-2.7
5	HC1	5	HE1	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HE1	5	HH1	1.8-2.7
5	HJ2	5	HI2	1.8-2.7
1	HD2	1	HA	1.8-3.5
2	HD1	2	HA	1.8-3.5
3	HA	3	HD2	1.8-3.5
3	HB#	5	HH1	1.8-3.5
4	HA	4	HB	1.8-3.5
4	HA	5	HN	1.8-3.5
5	HC1	5	HN	1.8-3.5
5	HD2	5	HE2	1.8-3.5
5	HH2	5	HI2	1.8-3.5
1	HA	1	HN	1.8-5.0
1	HA	3	HN	1.8-5.0
1	HA	1	HB#	1.8-5.0
1	HD1	1	HA	1.8-5.0
1	HD2	2	HN	1.8-5.0
2	HA	3	HN	1.8-5.0
2	HA	2	HN	1.8-5.0
2	HA	2	HG	1.8-5.0
2	HA	2	HB#	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
2	HB#	2	HN	1.8-5.0
2	HB#	3	HN	1.8-5.0
2	HD1	2	HN	1.8-5.0
2	HD2	2	HN	1.8-5.0
2	HD2	2	HA	1.8-5.0
2	HG	2	HN	1.8-5.0
2	HN	3	HN	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HA	3	HD1	1.8-5.0
3	HA	3	HG	1.8-5.0
3	HB#	3	HN	1.8-5.0
3	HB#	3	HA	1.8-5.0
3	HB#	5	HC1	1.8-5.0
3	HB#	5	HE1	1.8-5.0
3	HD1	4	HN	1.8-5.0
3	HD1	3	HN	1.8-5.0
3	HD1	5	HH1	1.8-5.0
3	HD1	5	HE1	1.8-5.0
3	HD2	4	HN	1.8-5.0
3	HD2	3	HN	1.8-5.0
3	HD2	5	HH1	1.8-5.0
3	HD2	5	HE1	1.8-5.0
3	HN	4	HN	1.8-5.0
5	HA1	5	HC2	1.8-5.0
5	HA2	5	HN	1.8-5.0
5	HA2	5	HC2	1.8-5.0
5	HC1	5	HA2	1.8-5.0
5	HC1	4	HA	1.8-5.0
5	HC1	5	HA1	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
5	HE1	5	HE2	1.8-5.0
5	HE1	5	HH2	1.8-5.0

Table S12. NOE summary of 4a in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HD1	1	HA	1.8-2.7
2	HD2	2	HA	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HI2	5	HH2	1.8-2.7
5	HI2	5	HJ2	1.8-2.7
5	HS	5	HR2	1.8-2.7
1	HB2	1	HA	1.8-3.5
1	HB2	1	HN	1.8-3.5
1	HG	1	HN	1.8-3.5
2	HD1	2	HA	1.8-3.5
3	HD1	3	HA	1.8-3.5
4	HB	4	HN	1.8-3.5
4	HB	4	HA	1.8-3.5
5	HA1	5	HC2	1.8-3.5
5	HJ2	1	HN	1.8-3.5
5	HO1	5	HO2	1.8-3.5
5	HS	5	HR1	1.8-3.5
1	HA	1	HN	1.8-5.0
1	HA	2	HN	1.8-5.0
1	HB1	1	HA	1.8-5.0
1	HB1	1	HN	1.8-5.0
1	HD1	1	HN	1.8-5.0
1	HD1	5	HJ2	1.8-5.0
1	HD2	1	HA	1.8-5.0
1	HD2	1	HN	1.8-5.0
1	HD2	5	HJ2	1.8-5.0
1	HG	1	HA	1.8-5.0
2	HA	2	HN	1.8-5.0
2	HA	3	HN	1.8-5.0
2	HB1	2	HA	1.8-5.0
2	HB1	2	HN	1.8-5.0
2	HB2	2	HA	1.8-5.0
2	HB2	2	HN	1.8-5.0
2	HD1	2	HN	1.8-5.0
2	HG	2	HA	1.8-5.0
2	HN	1	HN	1.8-5.0
3	HA	4	HN	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HB1	3	HN	1.8-5.0
3	HB1	3	HA	1.8-5.0
3	HB1	4	HN	1.8-5.0
3	HB2	3	HA	1.8-5.0
3	HB2	4	HN	1.8-5.0
3	HB2	3	HN	1.8-5.0
3	HD1	3	HN	1.8-5.0
3	HD1	5	HD2	1.8-5.0
3	HD1	4	HN	1.8-5.0
3	HD1	5	HE2	1.8-5.0
3	HD1	5	HC2	1.8-5.0
3	HD2	3	HA	1.8-5.0
3	HG	3	HA	1.8-5.0
3	HN	3	HG	1.8-5.0
4	HA	4	HN	1.8-5.0
4	HA	5	HN	1.8-5.0
4	HB	3	HN	1.8-5.0
4	HB	5	HC2	1.8-5.0
4	HB	5	HE2	1.8-5.0
4	HB	5	HR2	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
4	HB	5	HJ2	1.8-5.0
4	HB	1	HN	1.8-5.0
5	HA1	5	HN	1.8-5.0
5	HA1	5	HC1	1.8-5.0
5	HA2	5	HN	1.8-5.0
5	HA2	5	HC1	1.8-5.0
5	HA2	5	HC2	1.8-5.0
5	HC1	5	HR2	1.8-5.0
5	HC1	5	HH1	1.8-5.0
5	HC2	5	HN	1.8-5.0
5	HD2	5	HH2	1.8-5.0
5	HE2	5	HH2	1.8-5.0
5	HE2	5	HQ2	1.8-5.0
5	HE2	5	HO1	1.8-5.0
5	HE2	5	HO2	1.8-5.0
5	HH1	1	HN	1.8-5.0
5	HN	4	HN	1.8-5.0
5	HO1	5	HQ2	1.8-5.0
5	HO1	5	HR2	1.8-5.0
5	HO1	5	HH1	1.8-5.0
5	HO2	5	HR2	1.8-5.0
5	HO2	5	HH1	1.8-5.0
5	HO2	5	HQ2	1.8-5.0
5	HR2	5	HR1	1.8-5.0

Table S13. NOE summary of 5a in DMSO-d_6.

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
3	HB2	5	HH1	1.8-2.7
5	HA1	5	HA2	1.8-2.7
5	HC2	5	HD2	1.8-2.7
5	HH1	1	HN	1.8-2.7
5	HJ2	1	HN	1.8-2.7
5	HQ2	5	HR2	1.8-2.7
5	HS	5	HR2	1.8-2.7
5	HS	5	HR1	1.8-2.7
1	HA	1	HN	1.8-3.5
1	HA	2	HN	1.8-3.5
1	HB1	1	HN	1.8-3.5
1	HB2	1	HN	1.8-3.5
1	HD1	1	HA	1.8-3.5
1	HD2	1	HA	1.8-3.5
1	HG	1	HN	1.8-3.5
2	HB#	2	HA	1.8-3.5
2	HD1	2	HA	1.8-3.5
3	HB2	3	HN	1.8-3.5
3	HD1	3	HA	1.8-3.5
4	HA	5	HN	1.8-3.5
4	HB	4	HA	1.8-3.5
4	HB	4	HN	1.8-3.5
5	HC1	5	HH1	1.8-3.5
5	HC1	5	HQ2	1.8-3.5
5	HI2	5	HJ2	1.8-3.5
1	HB1	1	HA	1.8-5.0
1	HB2	1	HA	1.8-5.0
1	HD1	1	HN	1.8-5.0
1	HD2	2	HN	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
2	HA	2	HN	1.8-5.0
2	HA	3	HN	1.8-5.0
2	HB#	3	HN	1.8-5.0
2	HB#	2	HN	1.8-5.0
2	HD1	2	HN	1.8-5.0
2	HD2	2	HA	1.8-5.0
2	HD2	2	HN	1.8-5.0
2	HG	2	HA	1.8-5.0
2	HG	2	HN	1.8-5.0
2	HN	1	HN	1.8-5.0
3	HA	3	HN	1.8-5.0
3	HA	4	HN	1.8-5.0
3	HB1	3	HN	1.8-5.0
3	HB2	3	HA	1.8-5.0
3	HD1	3	HN	1.8-5.0
3	HD1	5	HQ2	1.8-5.0
3	HD2	3	HA	1.8-5.0
3	HD2	5	HH1	1.8-5.0
3	HD2	3	HN	1.8-5.0
3	HD2	5	HQ2	1.8-5.0
3	HN	2	HN	1.8-5.0
4	HA	4	HN	1.8-5.0
4	HB	5	HC1	1.8-5.0
4	HB	5	HN	1.8-5.0
4	HB	1	HN	1.8-5.0
4	HN	3	HN	1.8-5.0
4	HN	5	HN	1.8-5.0
5	HA1	5	HN	1.8-5.0
5	HA1	5	HC2	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
5	HA1	5	HC1	1.8-5.0
5	HA2	5	HN	1.8-5.0
5	HA2	5	HC2	1.8-5.0
5	HA2	5	HC1	1.8-5.0
5	HC1	5	HN	1.8-5.0
5	HC2	5	HN	1.8-5.0
5	HE2	5	HQ2	1.8-5.0
5	HH2	5	HQ2	1.8-5.0
5	HO1	5	HQ2	1.8-5.0
5	HO1	5	HE2	1.8-5.0
5	HO1	5	HC1	1.8-5.0
5	HO1	5	HO2	1.8-5.0
5	HO2	5	HQ2	1.8-5.0
5	HO2	5	HE2	1.8-5.0
5	HO2	5	HC1	1.8-5.0

Table S14. NOE summary of 5b in DMSO-d_6.

F1		F2			F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)	Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
1	HN	2	HN	1.8-2.7	2	HB1	3	HN	1.8-5.0
1	HN	5	HJ2	1.8-2.7	2	HB1	2	HA	1.8-5.0
2	HN	1	HA	1.8-2.7	2	HB2	2	HN	1.8-5.0
5	HA1	5	HA2	1.8-2.7	2	HB2	2	HA	1.8-5.0
5	HC1	5	HE1	1.8-2.7	2	HG	2	HN	1.8-5.0
5	HC2	5	HD2	1.8-2.7	2	HG	2	HA	1.8-5.0
5	HE1	5	HH1	1.8-2.7	3	HA	3	HN	1.8-5.0
5	HI2	5	HJ2	1.8-2.7	3	HB1	4	HN	1.8-5.0
1	HB2	1	HN	1.8-3.5	3	HB1	3	HN	1.8-5.0
1	HB2	1	HA	1.8-3.5	3	HB1	3	HA	1.8-5.0
1	HD1	1	HA	1.8-3.5	3	HB2	4	HN	1.8-5.0
1	HG	1	HN	1.8-3.5	3	HB2	3	HA	1.8-5.0
2	HD2	2	HA	1.8-3.5	3	HD1	3	HN	1.8-5.0
2	HN	3	HN	1.8-3.5	3	HD1	5	HH1	1.8-5.0
3	HA	4	HN	1.8-3.5	3	HD1	4	HN	1.8-5.0
3	HB2	3	HN	1.8-3.5	3	HD2	3	HN	1.8-5.0
3	HD1	3	HA	1.8-3.5	3	HD2	5	HH1	1.8-5.0
4	HA	5	HN	1.8-3.5	3	HD2	3	HA	1.8-5.0
4	HB	4	HA	1.8-3.5	3	HD2	4	HN	1.8-5.0
1	HA	1	HN	1.8-5.0	3	HG	3	HN	1.8-5.0
1	HB1	1	HN	1.8-5.0	3	HN	4	HN	1.8-5.0
1	HB1	1	HA	1.8-5.0	4	HA	4	HN	1.8-5.0
1	HD1	1	HN	1.8-5.0	4	HB	4	HN	1.8-5.0
1	HD2	1	HN	1.8-5.0	4	HB	5	HN	1.8-5.0
1	HD2	1	HA	1.8-5.0	5	HA1	5	HN	1.8-5.0
1	HD2	2	HN	1.8-5.0	5	HA1	5	HC2	1.8-5.0
2	HA	3	HN	1.8-5.0	5	HA1	5	HC1	1.8-5.0
2	HA	2	HN	1.8-5.0	5	HA2	5	HN	1.8-5.0
2	HB1	2	HN	1.8-5.0	5	HA2	5	HC1	1.8-5.0

F1		F2		
Res. No.	Atom name	Res. No.	Atom name	Distance (Å)
5	HA2	5	HC2	1.8-5.0
5	HC1	5	HN	1.8-5.0
5	HD2	5	HE2	1.8-5.0
5	HE1	5	HE2	1.8-5.0
5	HE1	5	HJ2	1.8-5.0

Table S15. $^{3}J_{HNCH}$ coupling values of 2a

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	14.6	-150	-90
2	D-Leu	6.7	50	110
3	Leu	14.2	-150	-90
4	Leu	10	-150	-90

Table S16. $^{3}J_{HNCH}$ coupling values of 2b

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	6.5	-108	-48
2	D-Leu	7.5	55	115
3	Leu	10.1	-150	-90
4	Leu	7.5	-115	-55

Table S17. $^{3}J_{HNCH}$ coupling values of 3a

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	(broadening)		
2	D-Leu	5.8	42	102
3	Leu	6.4	-107	-47
4	Ala	(broadening)		

Table S18. $^{3}J_{HNCH}$ coupling values of 3b

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	5.9	-104	-44
2	D-Leu	7.9	58	118
3	Leu	9.7	-138	-78
4	Ala	7	-51	-111

Table S19. $^{3}J_{HNCH}$ coupling values of 4a

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	7.8	-117	-57
2	Leu	12	-150	-90
3	Leu		(broadening)	
4	Ala	6.7	-110	-50

Table S20. $^{3}J_{HNCH}$ coupling values of 5a

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	5	-96	-36
2	D-Leu	7	51	111
3	D-Leu	7.4	54	114
4	Ala	7.9	-118	-58

Table S21. $^{3}J_{HNCH}$ coupling values of 5b

Res. No.	Res. name	J (Hz)	ϕ_{min}(°)	ϕ_{max}(°)
1	Leu	6.9	-111	-51
2	D-Leu	9.0	69	129
3	Leu	6.3	46	106
4	Leu	8.6	-125	-65

Measurement of physiochemical properties

Solubility assay: The solubility test was performed using 0.1 M phosphate buffer (pH 6.4). Solutions of the compounds were prepared by diluting 10 mM DMSO stock solution 2 μL:165 μL in test fluid and mixed at 37 °C for 4 h by rotation at 1000 rpm. The mixed solution was loaded into a 96-well MultiScreen Filter Plate (product number MSSLBPC10, PCF for use in aqueous solubility assay, polycarbonate membrane 0.4 μm; Millipore, Bedford, Massachusetts), and filtration was performed by centrifugation. The filtrates were analyzed by high-performance liquid chromatography (HPLC)-UV (245 nm) or liquid chromatography tandem mass spectrometry (LC-MS/MS). The solubility was determined by comparing the peak area of the filtrate with that of a 100 μM standard solution. When the peak area of the filtrate was larger than that of the standard solution, the concentration was described as >100 μM. Two technical replicates were performed.

LC-MS/MS (LC: Nexera X2 (LC-30AD), MS/MS: LCMS8060 (Shimadzu)) data were obtained under the following conditions: A (0.1% formic acid /acetonitrile), B (0.1% formic acid /water). LC-MS/MS Column：CAPCELLPAK C18 MGIII 3 μm 2.0 mmID × 35 mm (Osaka Soda), 50°C, flow rate 1.0 mL/min. In some experiments, the LC-MS/MS analysis was conducted by QTRAP5500+ and LC30AD (Shimadzu). Data was obtained under the following conditions: A (0.1% formic acid /acetonitrile), B (0.1% formic acid /water). Column: InertSustain C18HP 3 μm 2.1 mmID × 100 mm (GL Sciences), Duration time is 4 min, flow rate 1.0 mL/min.

PAMPA: In order to determine the passive membrane diffusion rates, PAMPA assay was performed with a Corning Gentest Pre-coated PAMPA Plate System. The acceptor plate was prepared by adding 200 μL of 0.1 M phosphate buffer (pH 7.4) supplemented with 5% DMSO to each well, and then 300 μL of a solution of 1 μM test compounds in 0.1 M phosphate buffer (pH 6.4) with 5% DMSO was added to the donor wells. The acceptor plate was then placed on top of the donor plate and incubated at 37 °C for 4 h without agitation. After the incubation, the plates were separated and the solutions from each well of both the acceptor plate and the donor plate were transferred to 96-well plates and mixed with acetonitrile. The final concentrations of compounds in the donor and acceptor wells, as well as the concentrations of the initial donor solutions, were analyzed using LC–MS/MS. The permeability of the compounds was calculated as described previously.[5,6] Antipyrine (100 or 1 μM), metoprolol (500 or 1 μM), and sulfasalazine (500 or 1 μM) were used as reference compounds. The permeabilities of antipyrine, metoprolol, and sulfasalazine were 15.4 ± 2.7, 1.9 ± 0.5, and 0.055 ± 0.0058 × 10^{-6} cm/s, respectively. Two technical replicates were performed.

Human plasma stability assay: Loss of the parent compound over time was evaluated by LC–MS/MS. After 3 min of preincubation of human plasma (Sigma-Aldrich), 100 μM test compound was added to it (final concentration: 1 μM); the amount at time zero was used as a reference.
The mixture was incubated at 37 °C for 60 min with rotation at 1000 rpm. An aliquot of 25 μL of the incubation mixture was added to 250 μL of chilled acetonitrile/internal standard (IS, methyltestosterone 1 μM). After centrifugation at 15000 × g for 10 min at 4 °C, the supernatants were analyzed by LC–MS/MS. Human plasma stability was calculated as the percent unchanged residual compound (%) from the peak area ratio of the 60-minute sample, taking the peak area ratio of the 0-minute sample as 100%. Two technical replicates were performed.

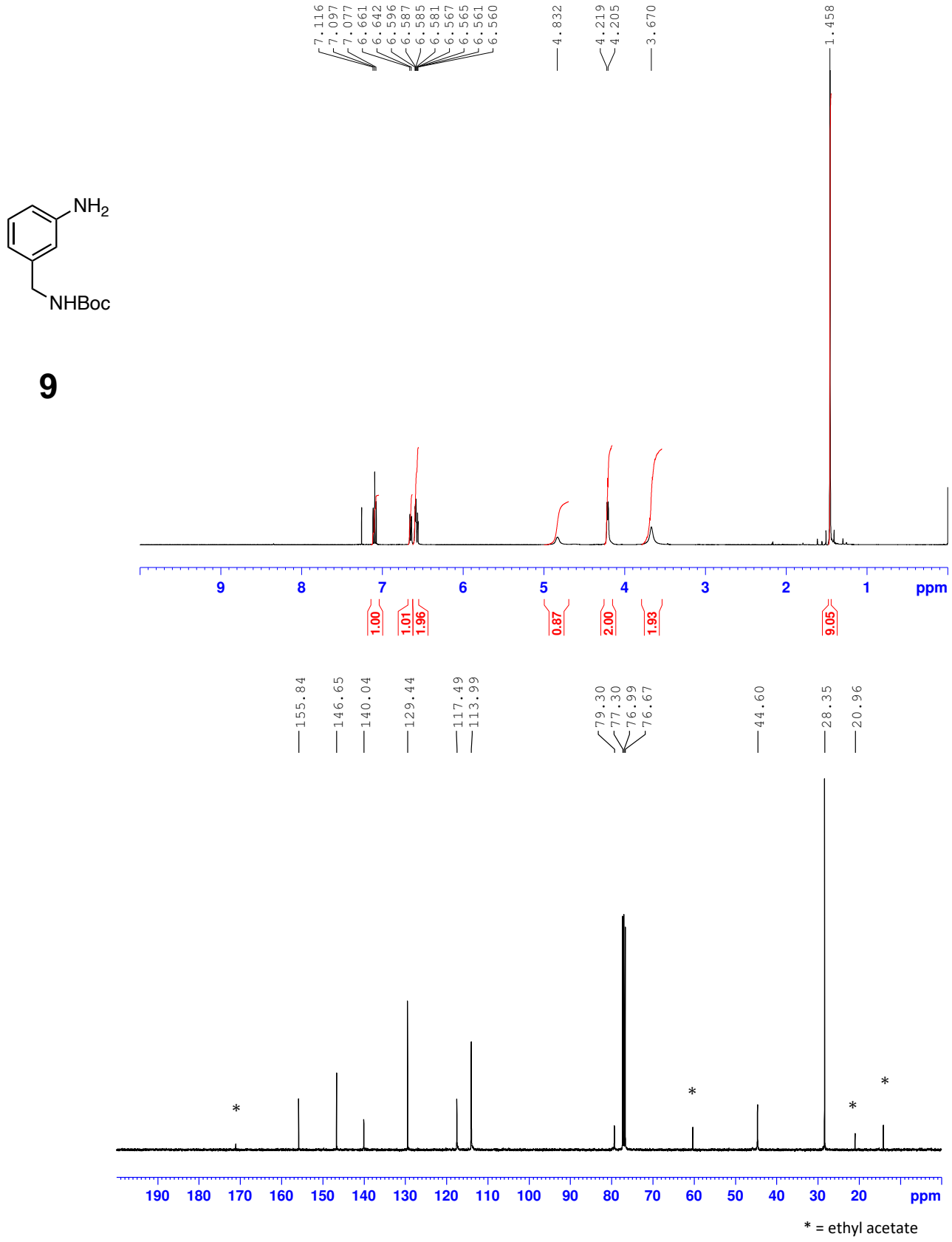
Photostability assay: Loss of the parent compound over time was evaluated by LC–MS/MS. Photostability was calculated as the remaining rate (%) after 0.5 h /1 h of static placement in a transparent Eppendorf tube under a fluorescent ceiling light. Two technical replicates were performed.

REST simulation

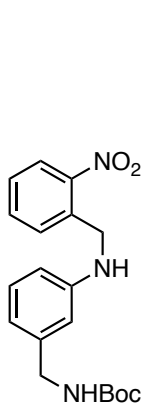
Replica exchange with solute tempering (REST) simulation was performed on Desmond (Maestro version 19-2). A custom solvent box was created for chloroform. The system initially contained solvents in cubic boxes with at least 10Å gap between the solute and the periodic boundaries.
1a and **1b**: 30 ns in $CHCl_3$, eight replicas at different temperatures (T = 300 - 651.5 or 695.1 K) were used in the simulation, and the centroid structures of the largest cluster are shown.

^{1}H and ^{13}C{^{1}H} NMR spectra

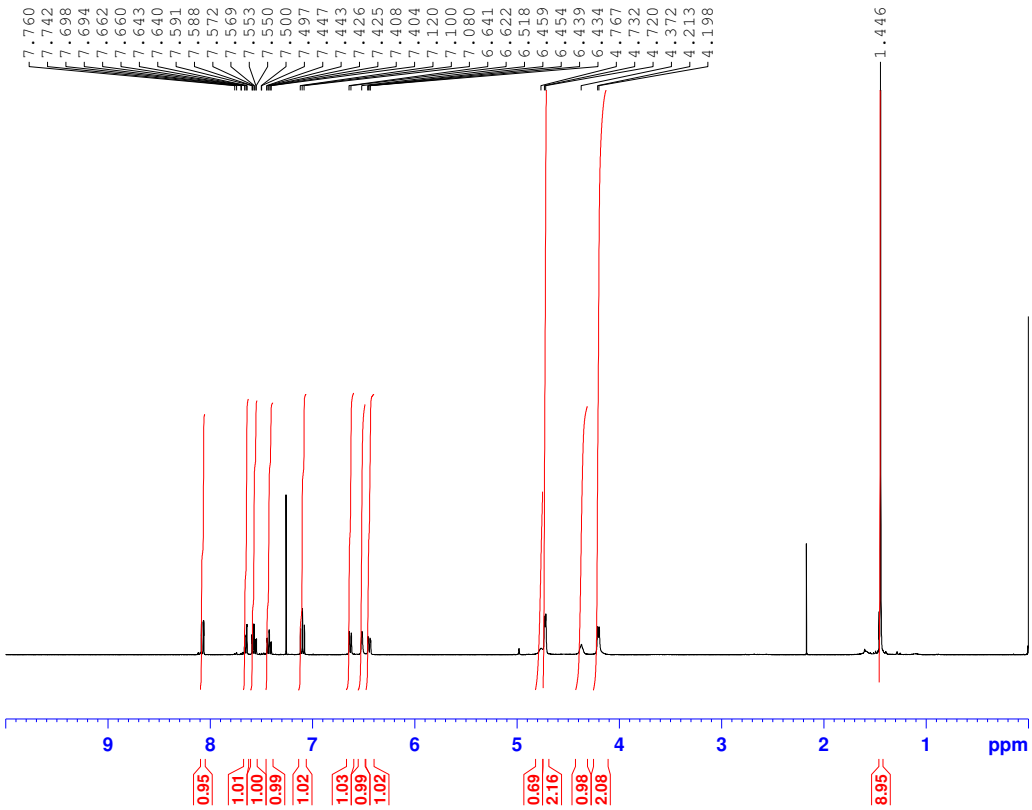
9 ($CDCl_3$, 24 °C)

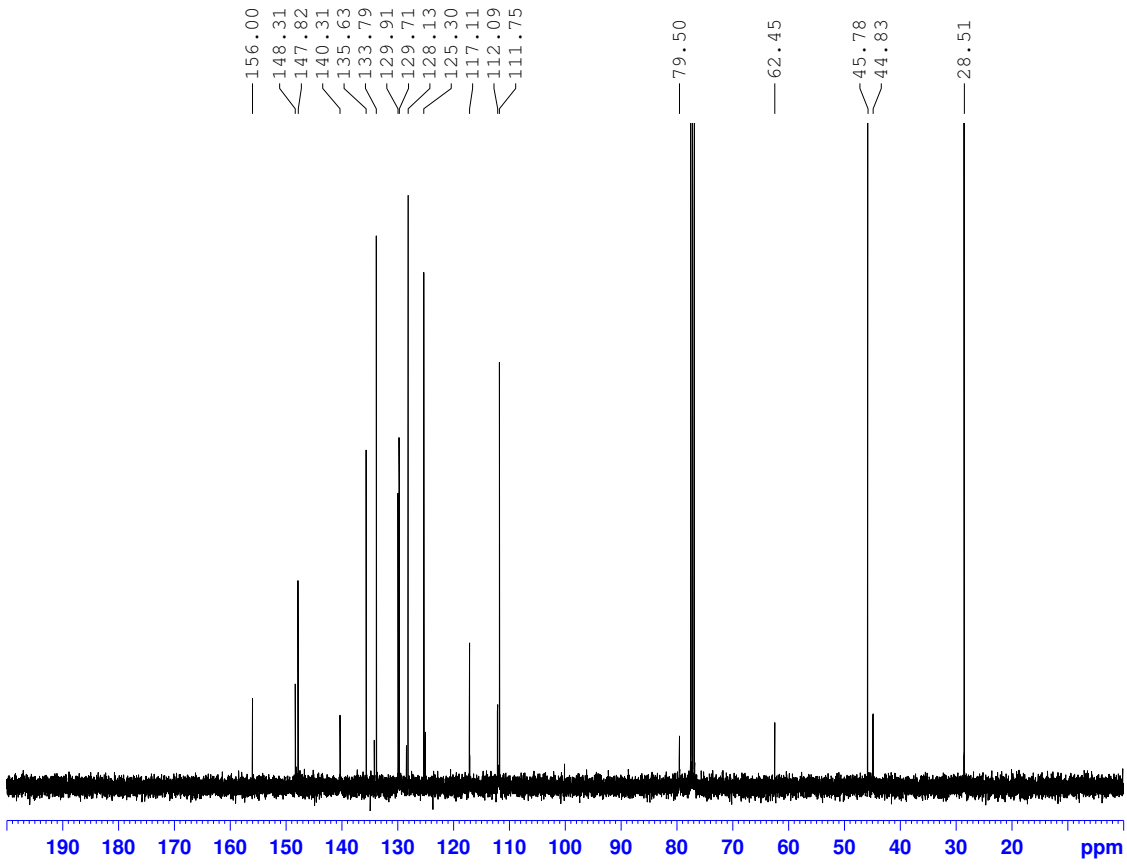


10 ($CDCl_3$, 24 °C)

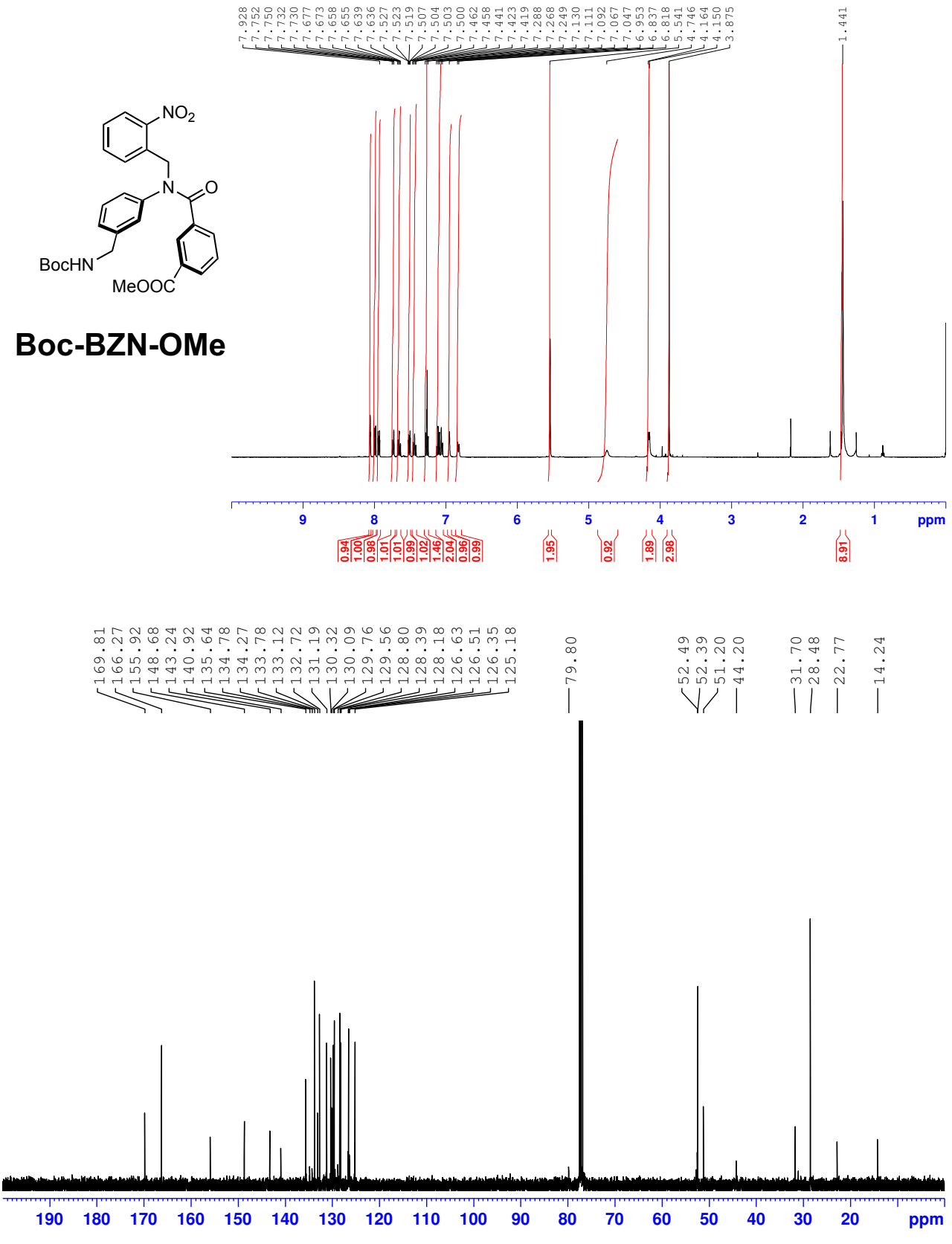


10

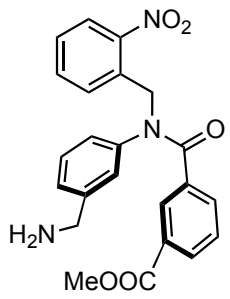




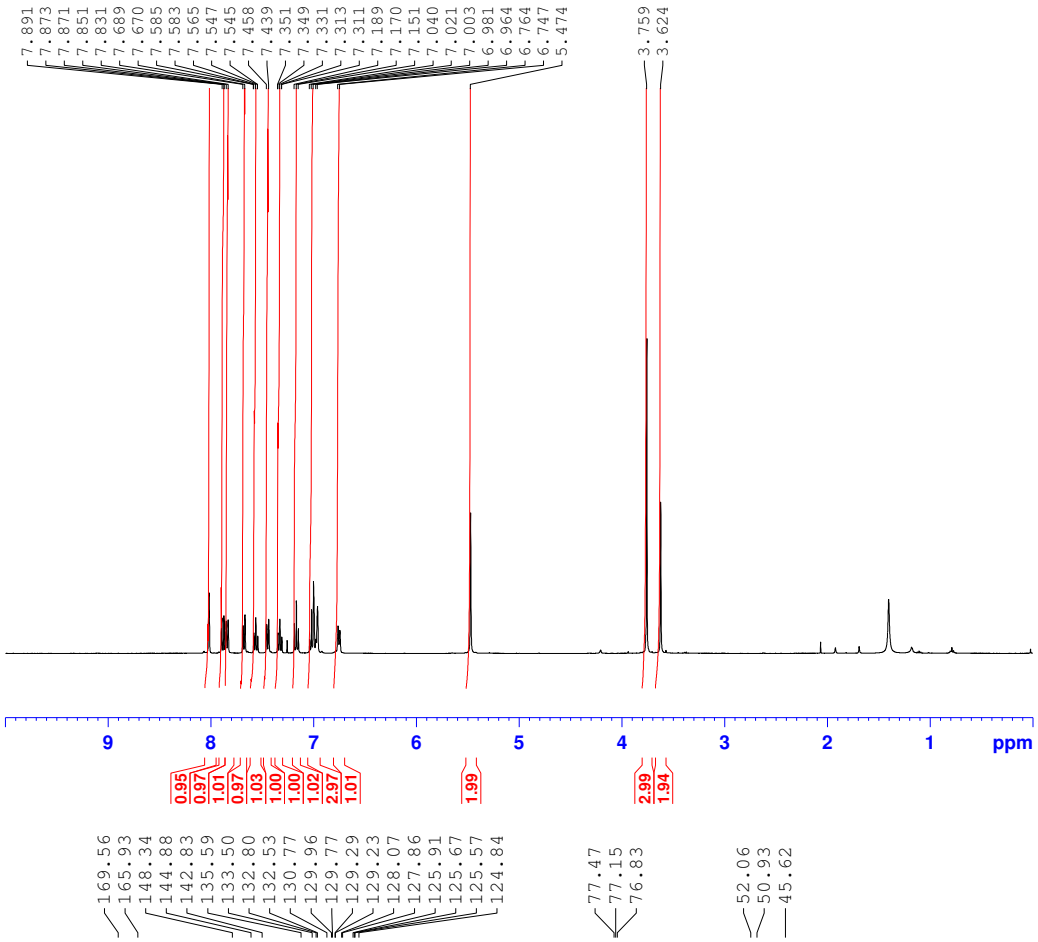
Boc-BZN-OMe ($CDCl_3$, 24 °C)

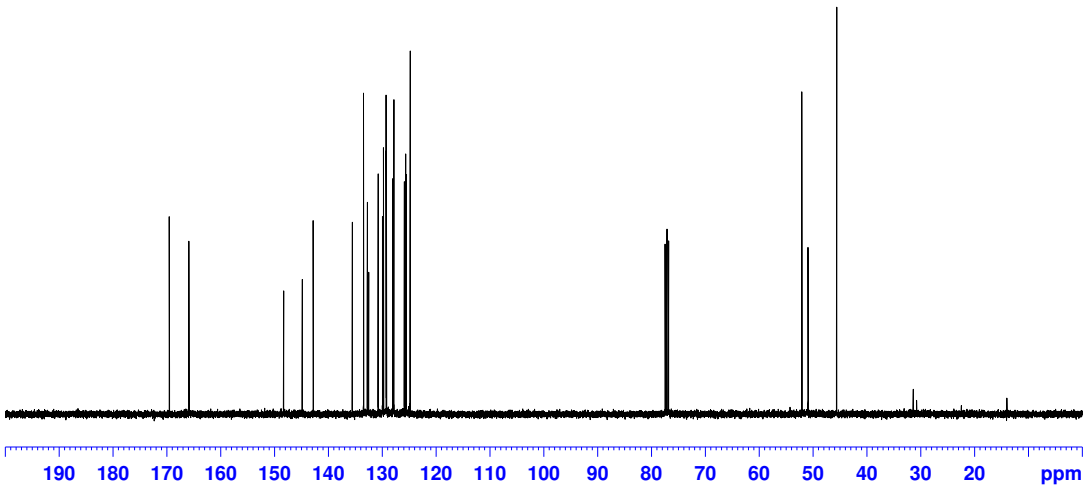


11 ($CDCl_3$, 24 °C)

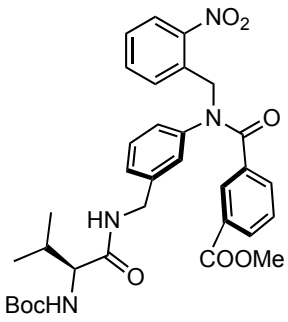


11

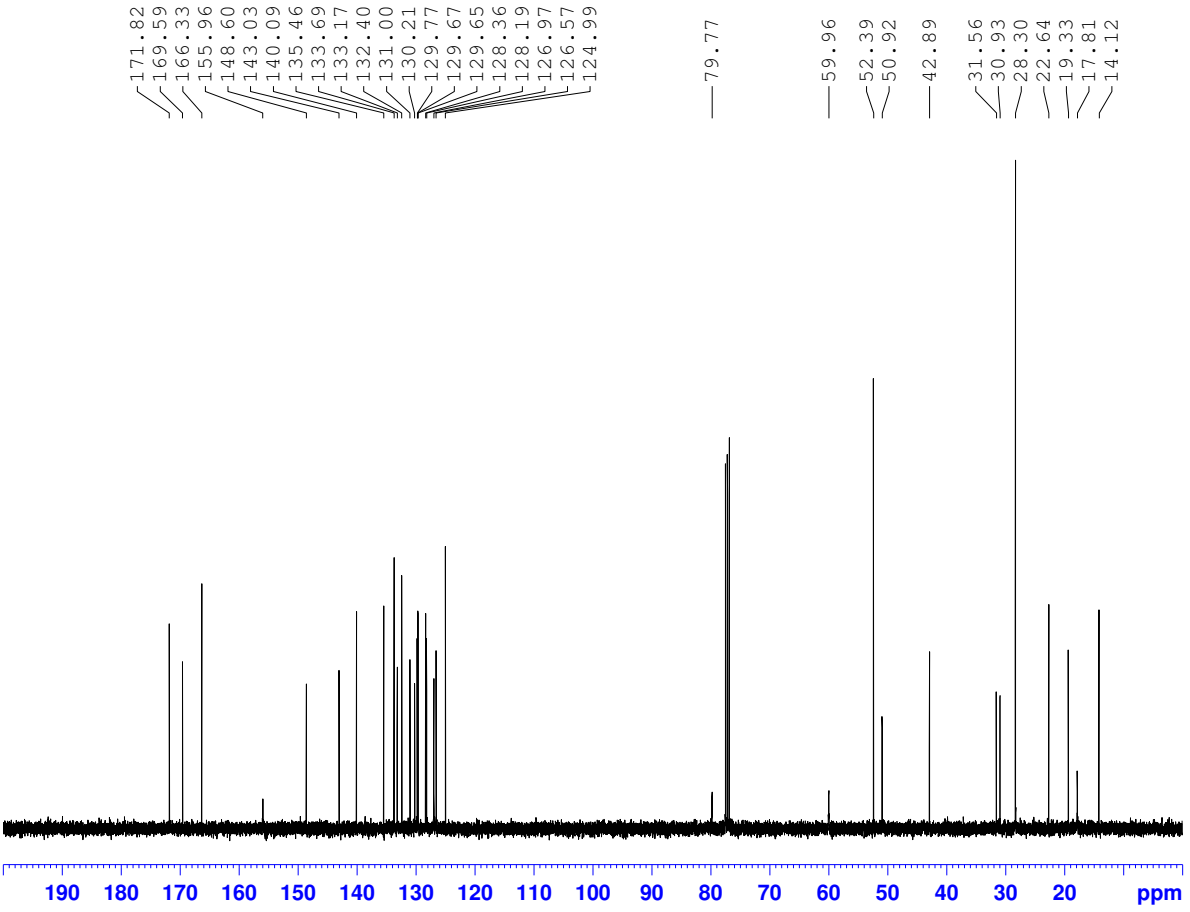




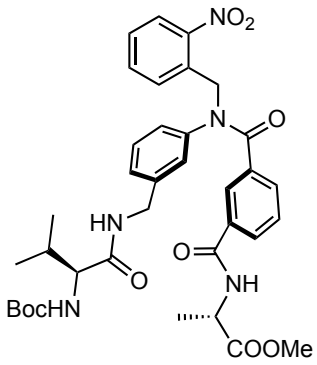
12 ($CDCl_3$, 24 °C)



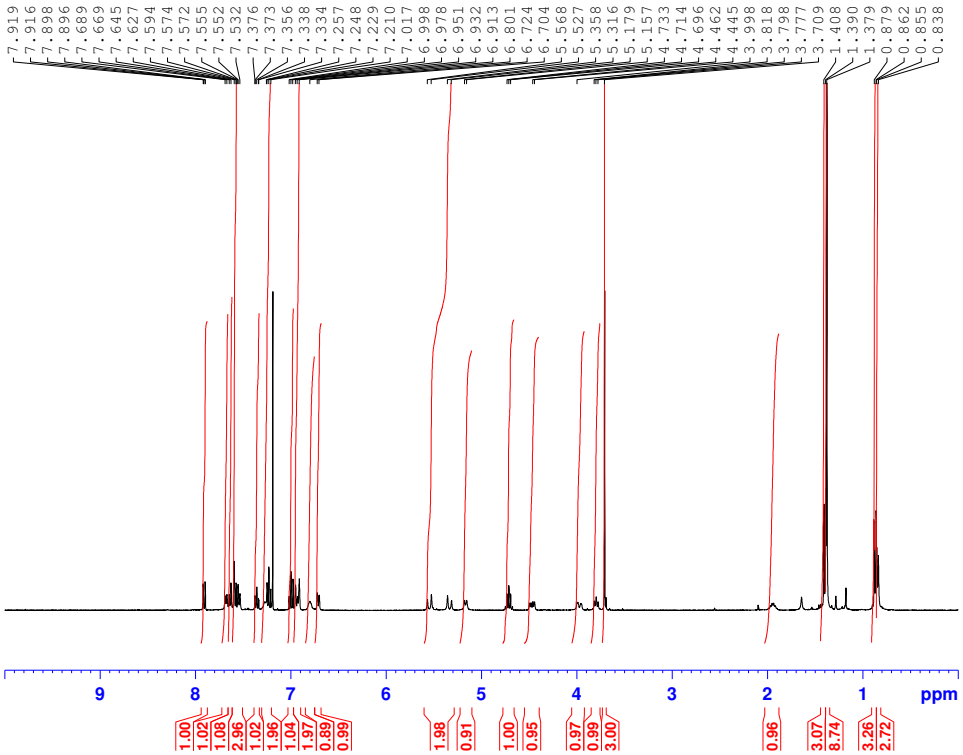
12

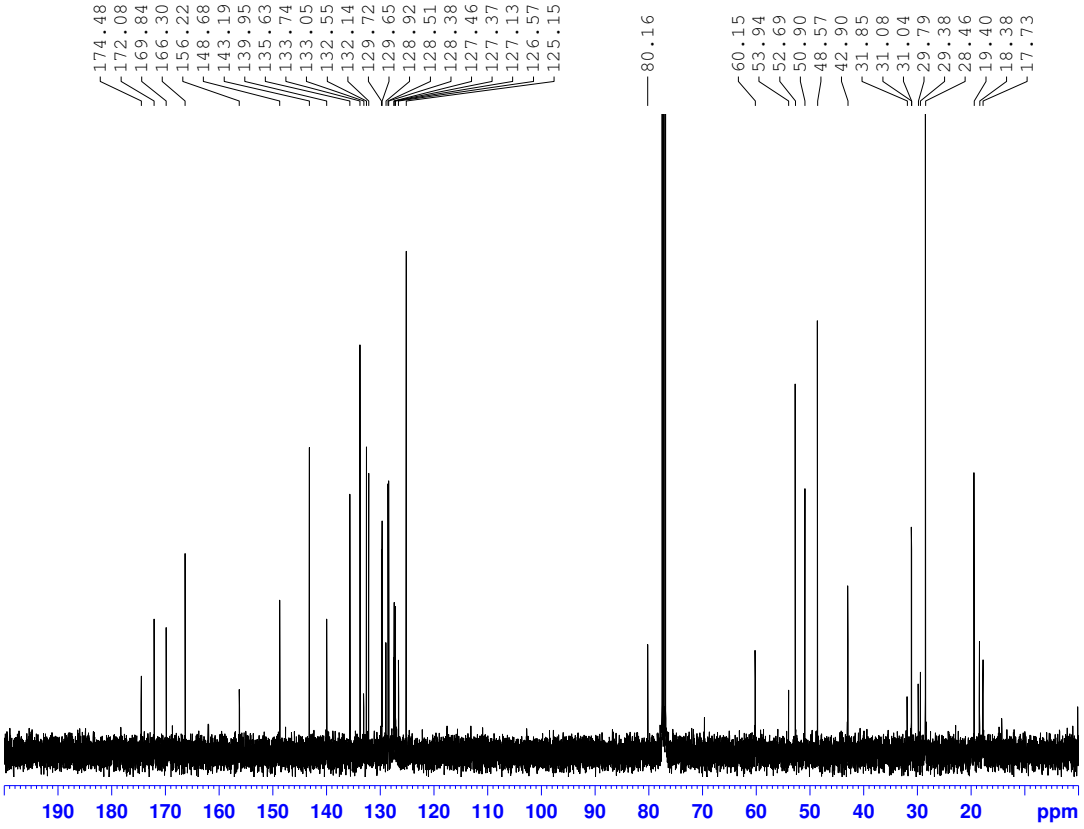


1a ($CDCl_3$, 24 °C)

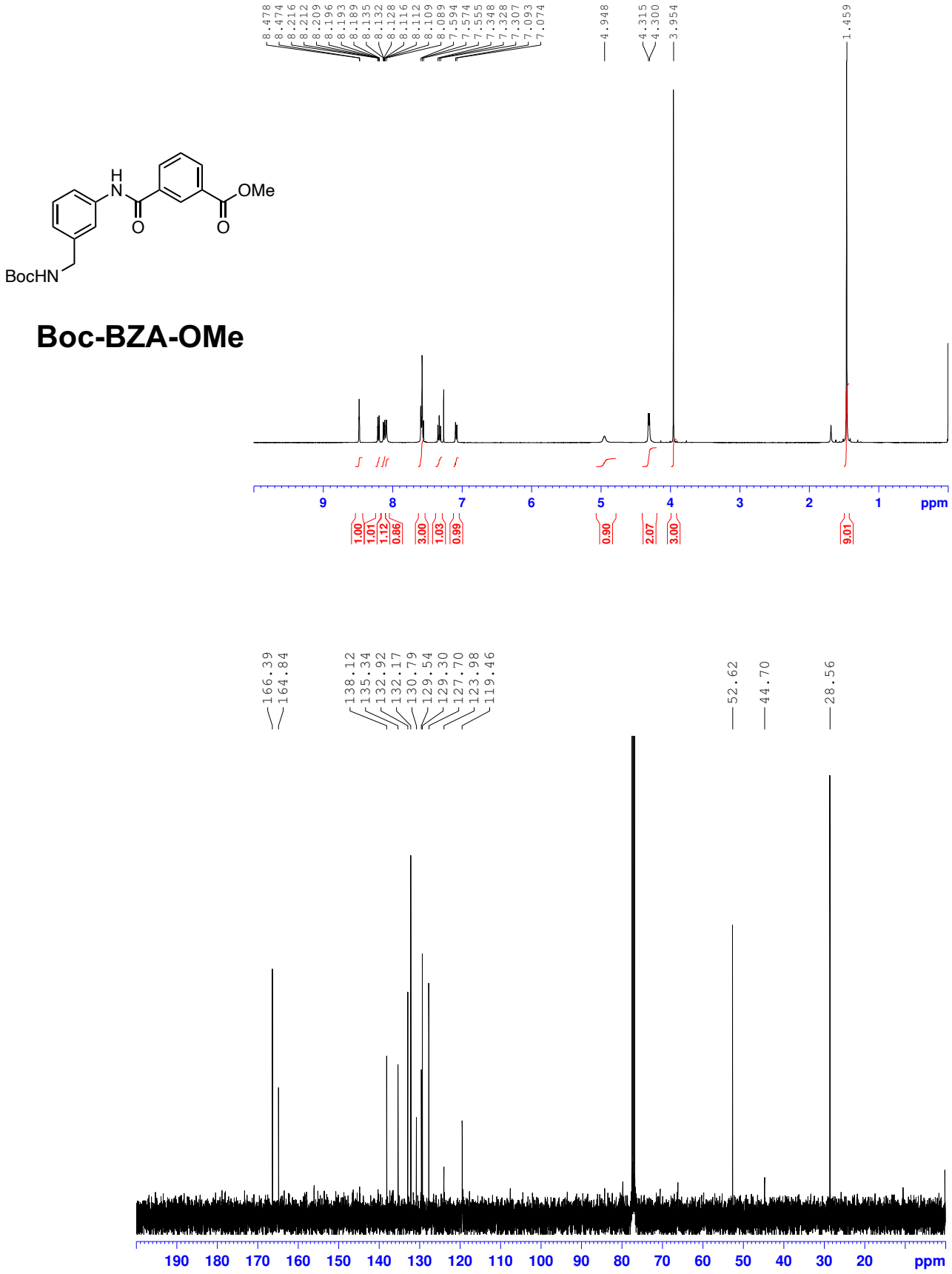


1a

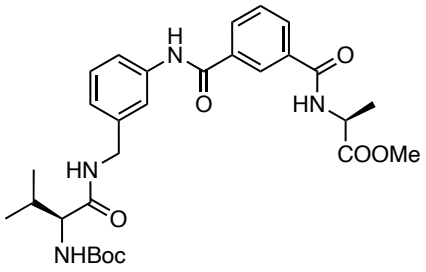




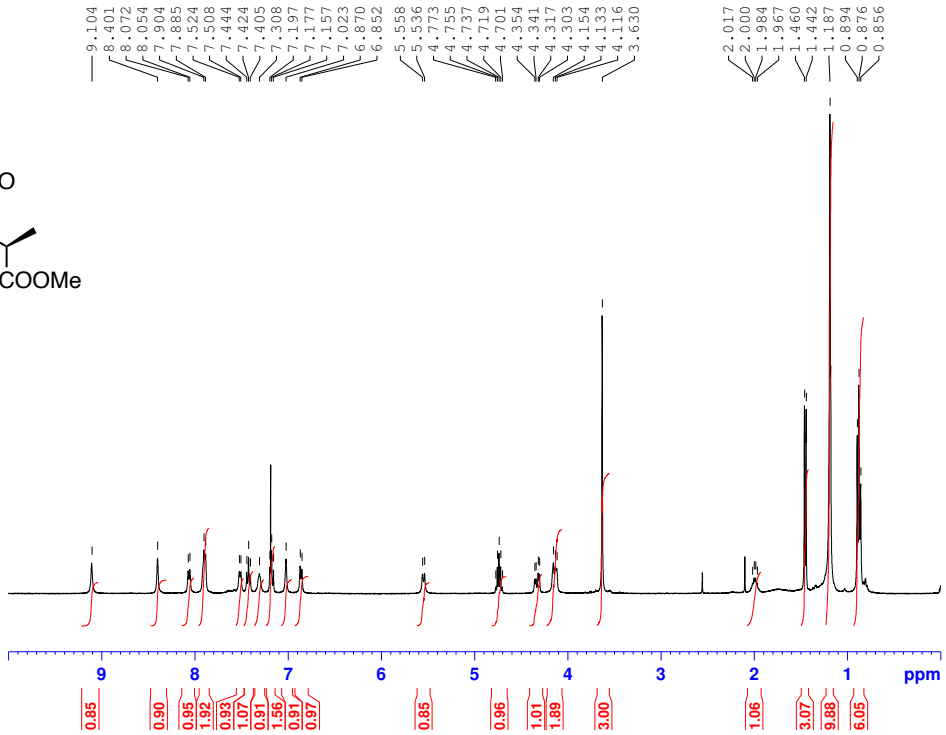
Boc-BZA-OMe ($CDCl_3$, 24 °C)

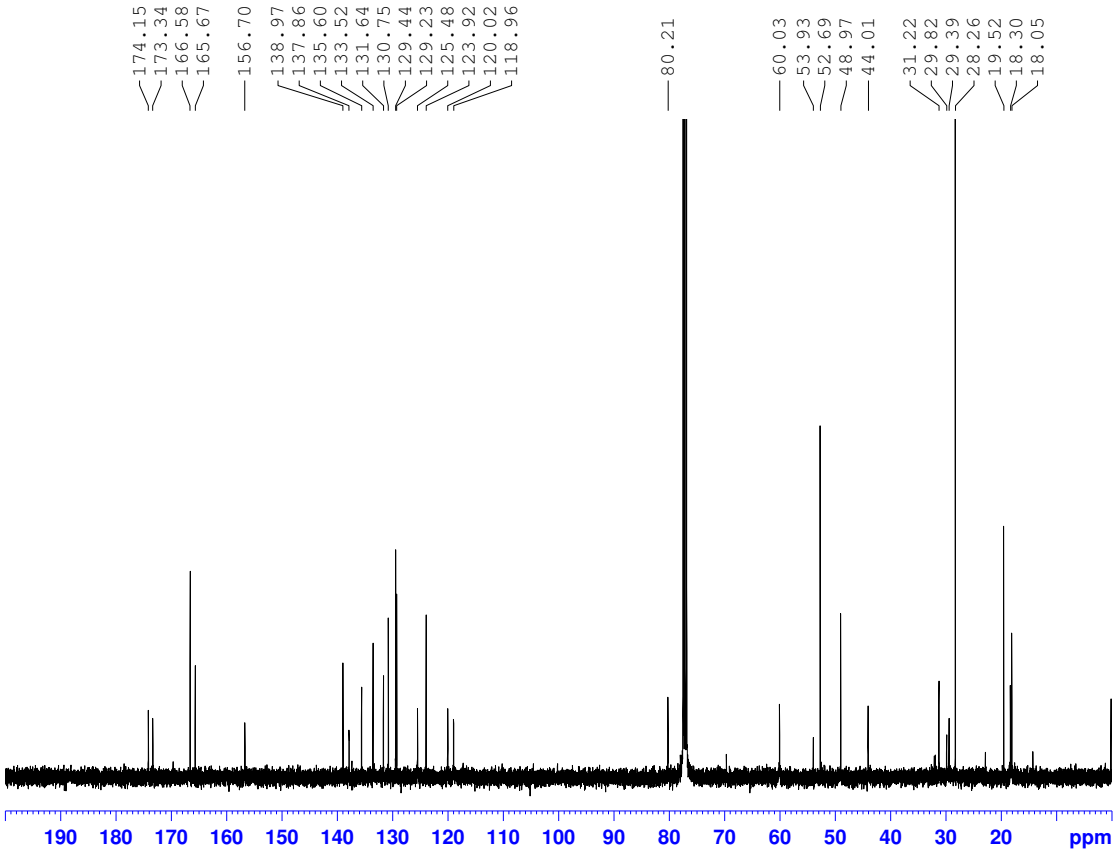


1b ($CDCl_3$, 24 °C)

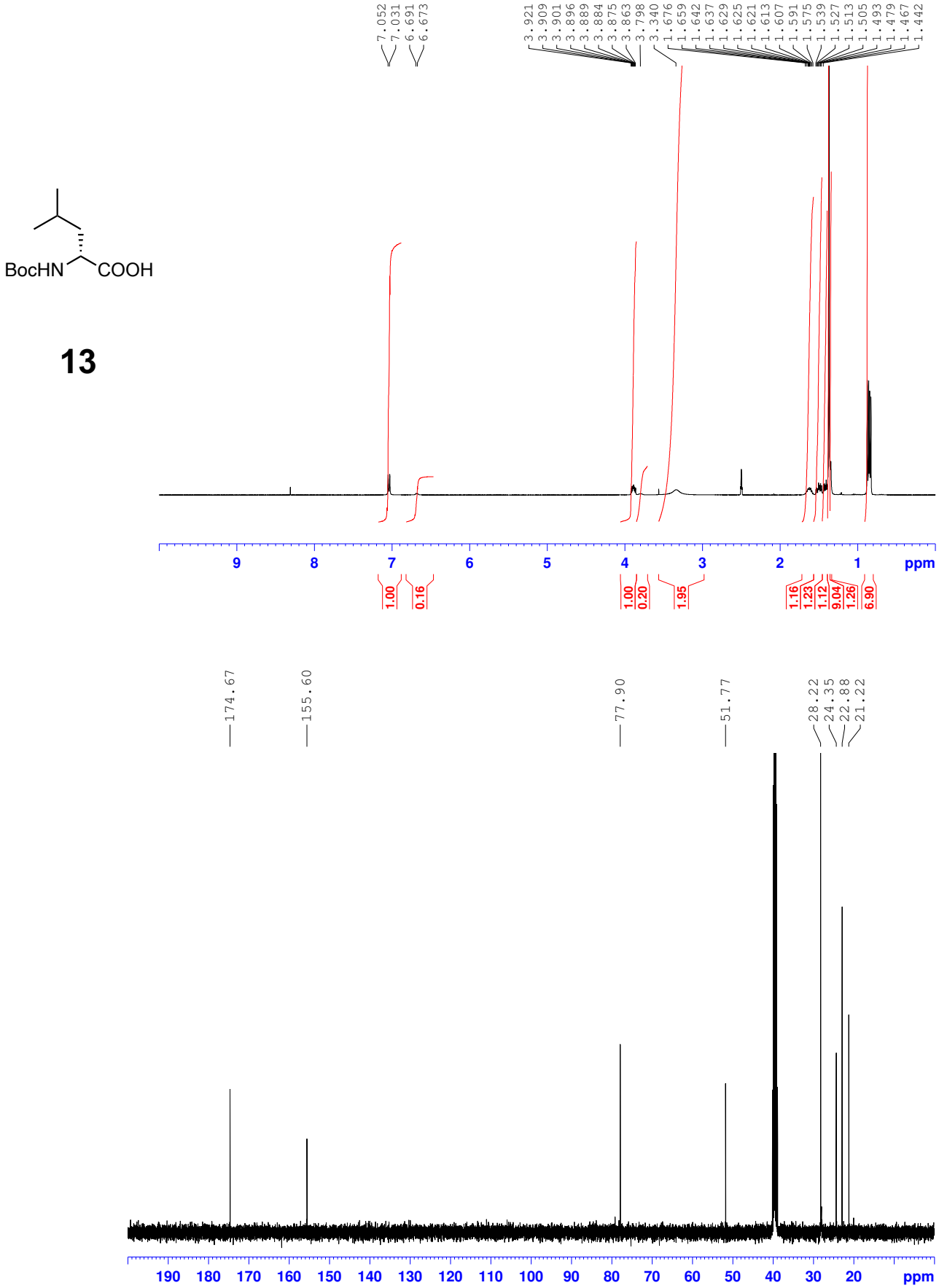


1b

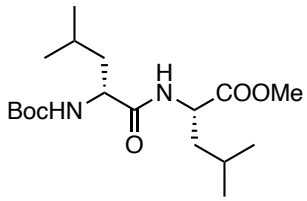




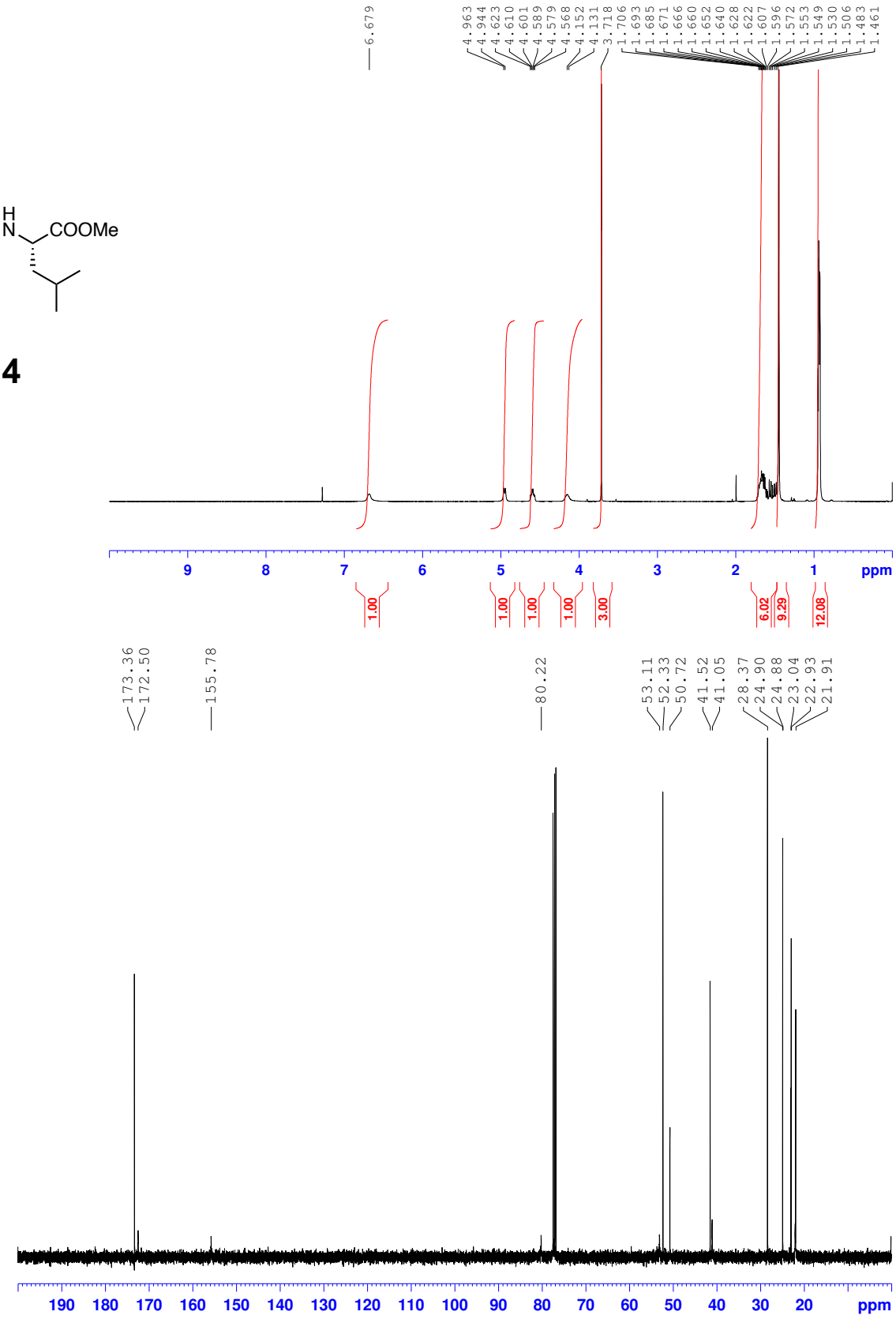
13 (DMSO-d_6, 24 °C)



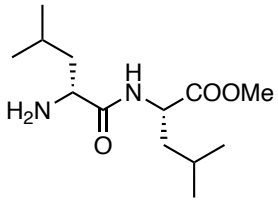
14 ($CDCl_3$, 24 °C)



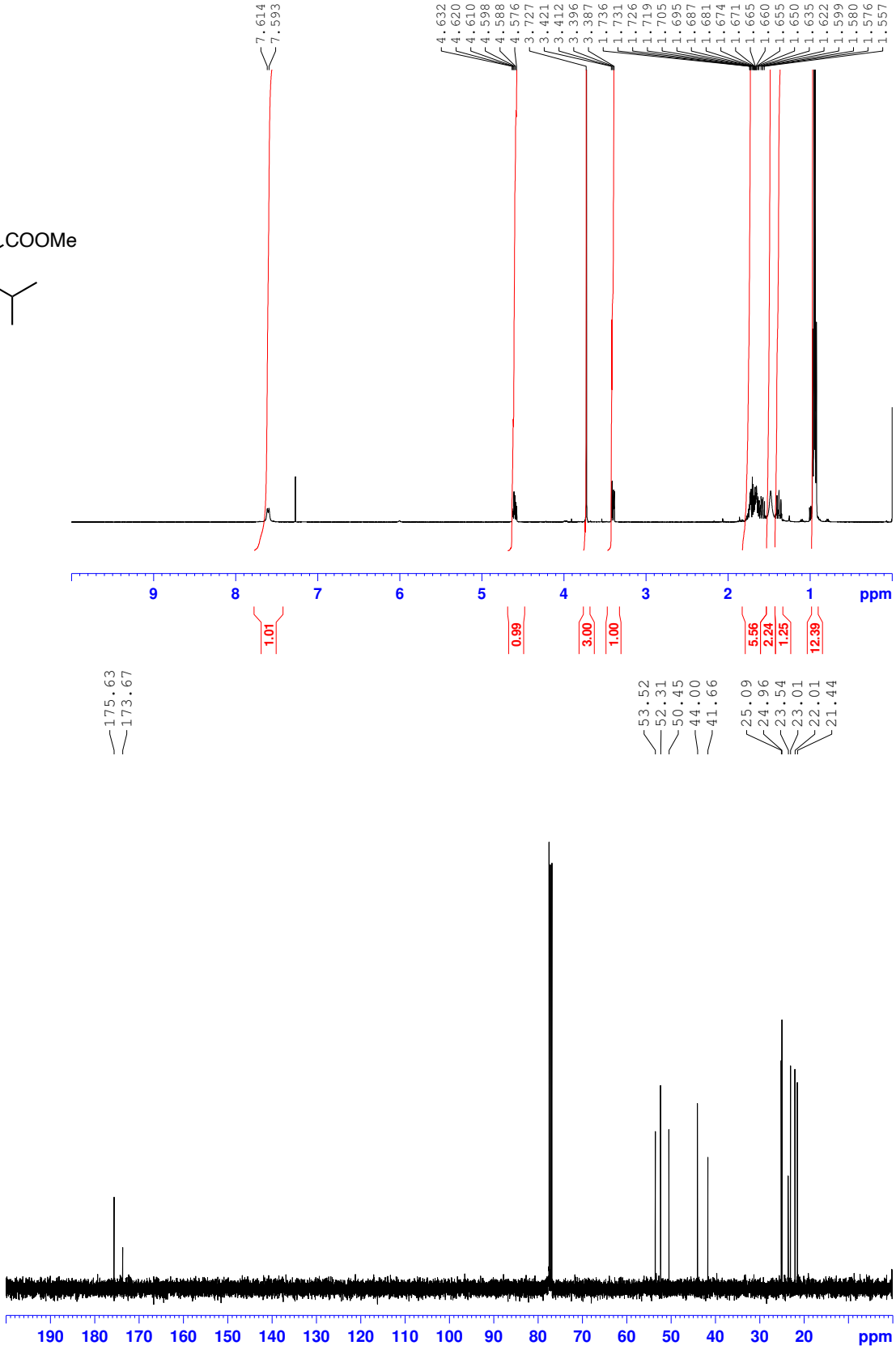
14



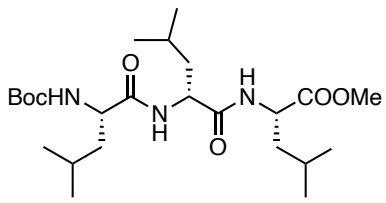
15 ($CDCl_3$, 24 °C)



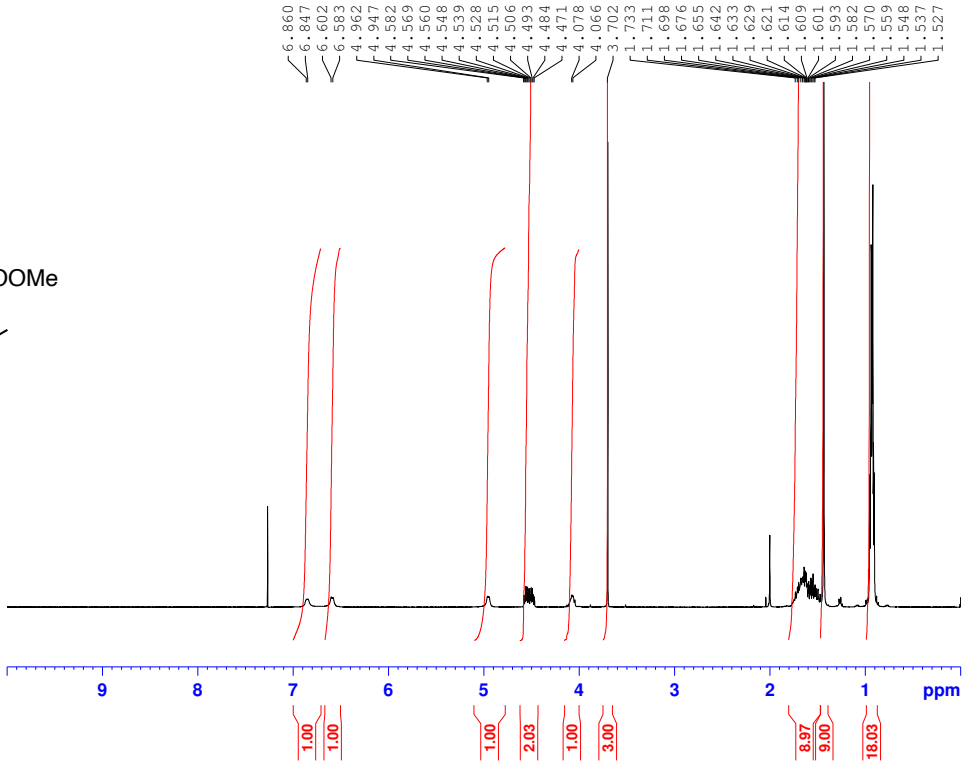
15

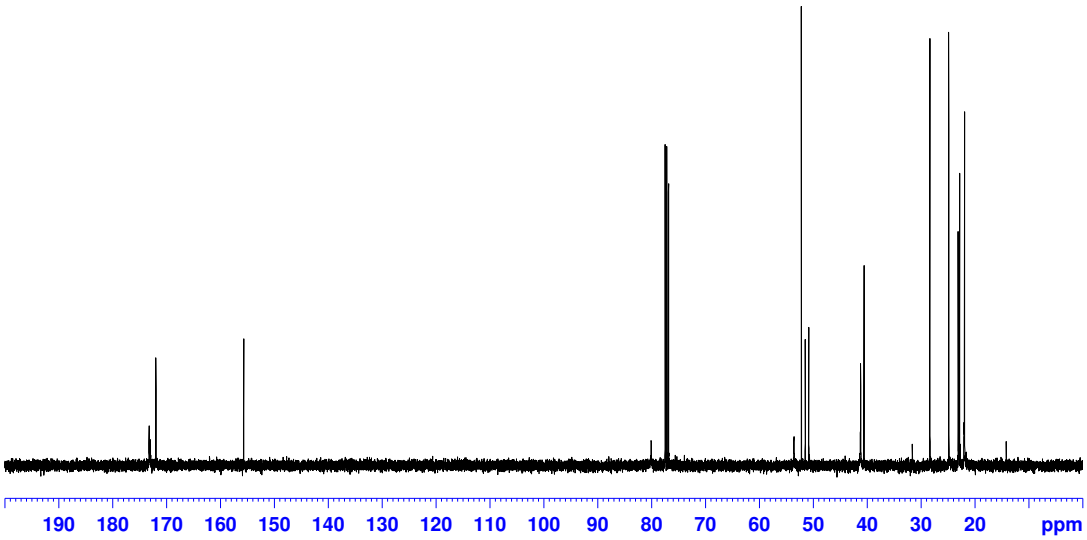


16 ($CDCl_3$, 24 °C)

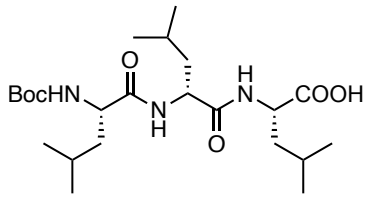


16

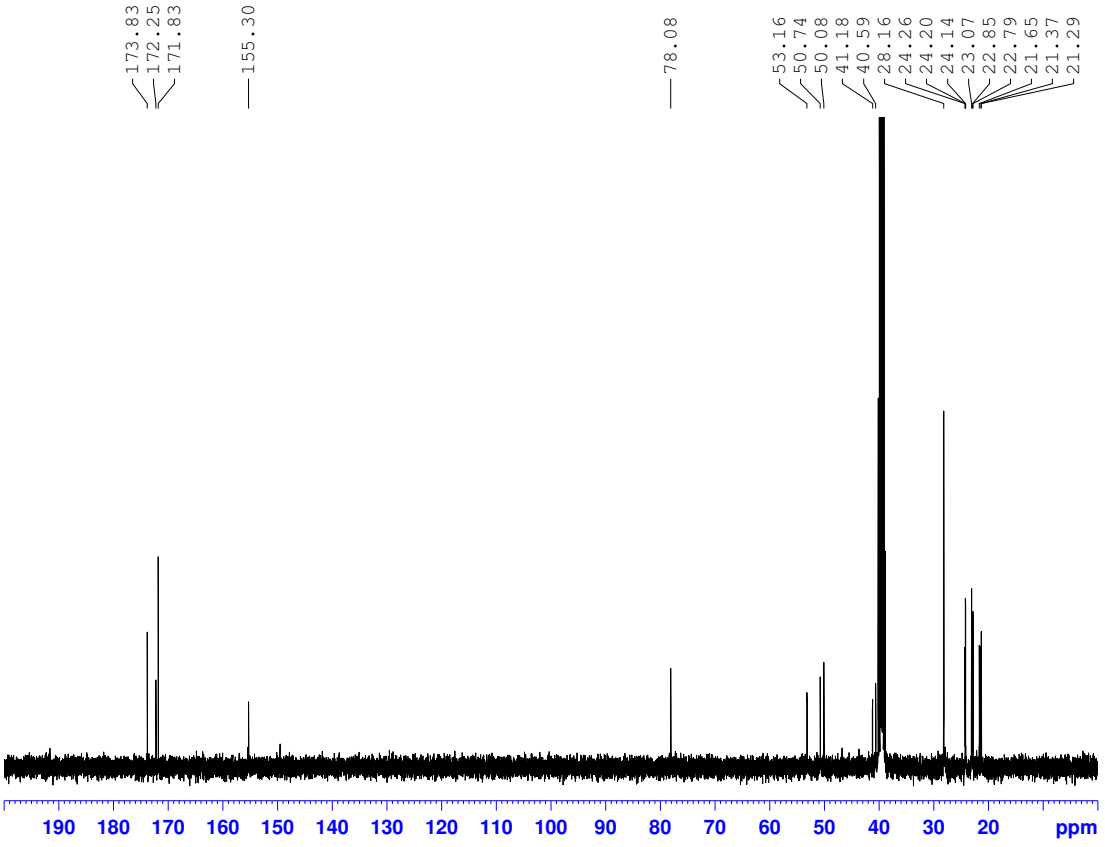




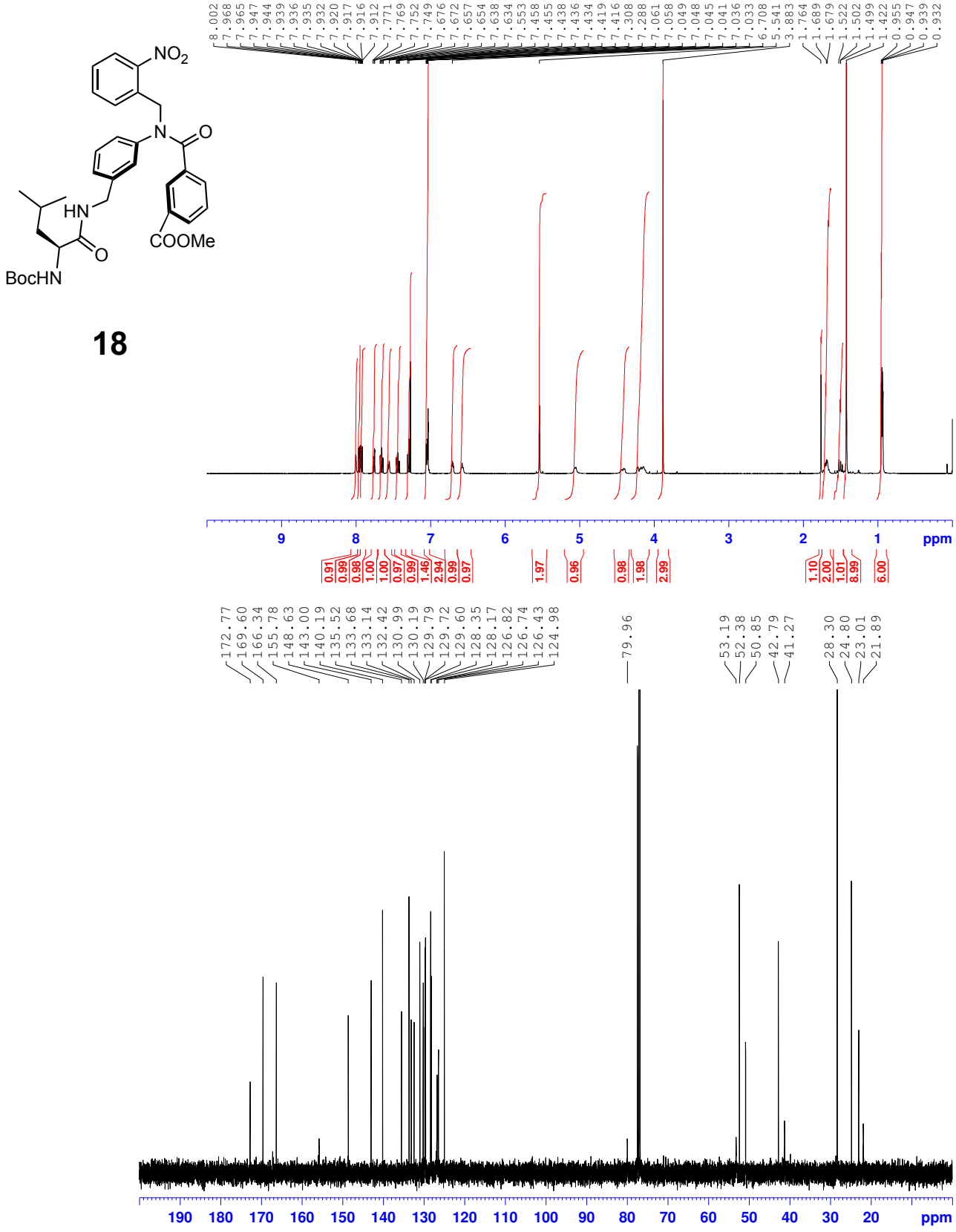
17 (DMSO-d_6, 24 °C)



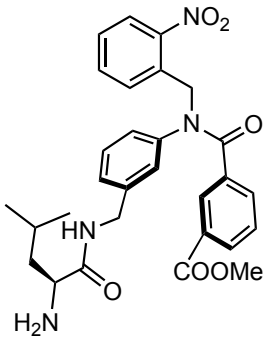
17



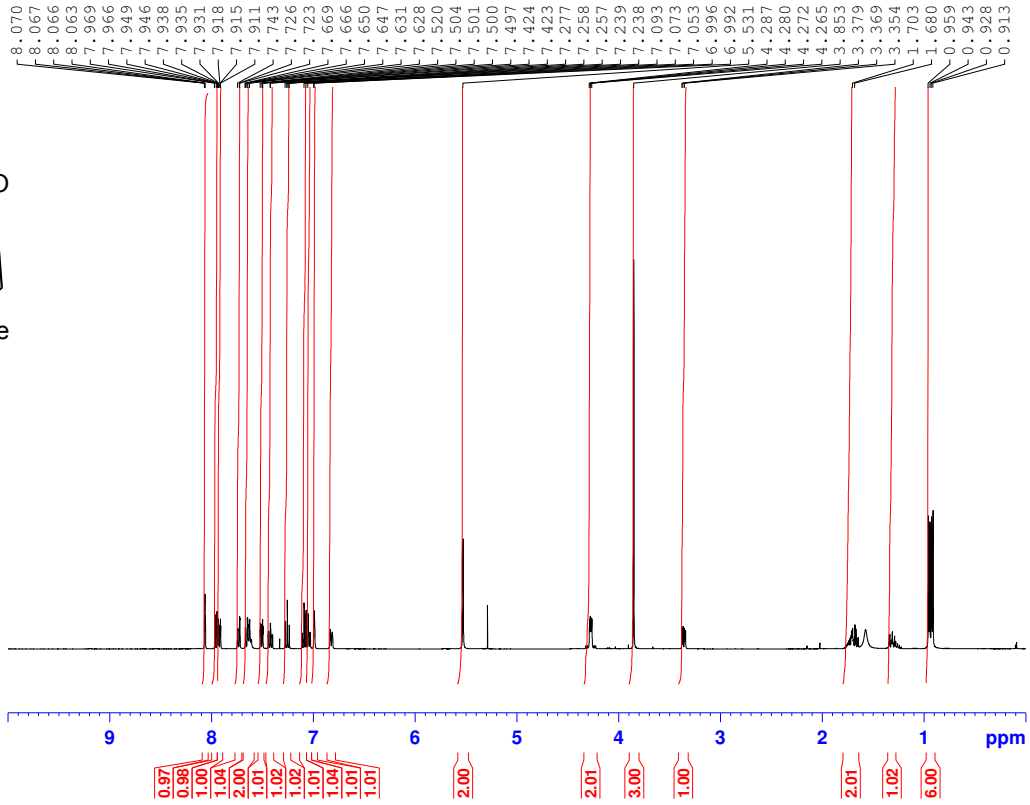
18 ($CDCl_3$, 24 °C)

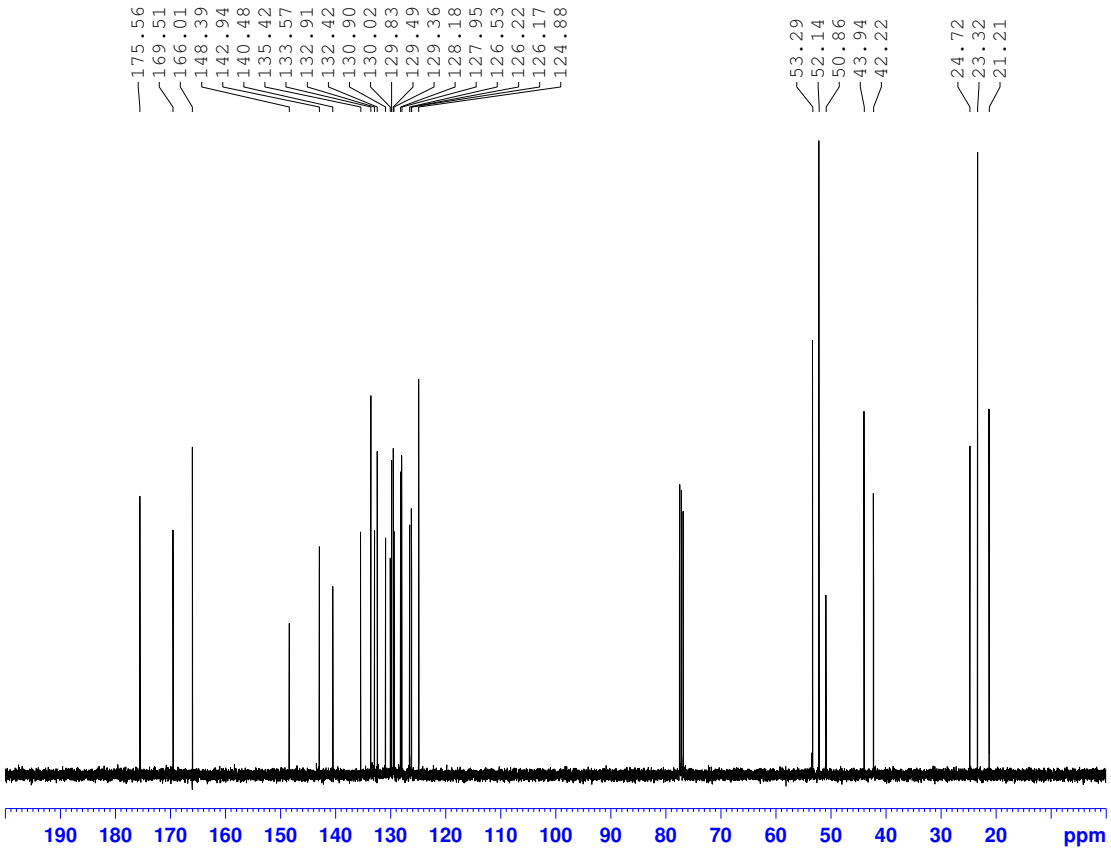

NO2
N
O
HN
O
COOMe
BocHN
18
8.002
7.968
7.965
7.947
7.944
7.939
7.936
7.935
7.932
7.920
7.917
7.916
7.912
7.771
7.769
7.752
7.749
7.676
7.672
7.657
7.654
7.638
7.634
7.553
7.458
7.455
7.438
7.436
7.434
7.419
7.416
7.308
7.288
7.061
7.058
7.049
7.048
7.045
7.041
7.036
7.033
6.708
5.541
3.883
1.764
1.689
1.679
1.522
1.502
1.499
1.422
0.955
0.947
0.939
0.932
9
8
7
6
5
4
3
2
1
ppm
0.91
0.99
0.98
1.00
1.00
0.97
0.99
1.46
2.94
0.99
0.97
1.97
0.96
0.98
1.98
2.99
1.10
2.00
1.01
8.99
6.00
172.77
169.60
166.34
155.78
148.63
143.00
140.19
135.52
133.68
133.14
132.42
130.99
130.19
129.79
129.72
129.60
128.35
128.17
126.82
126.74
126.43
124.98
79.96
53.19
52.38
50.85
42.79
41.27
28.30
24.80
23.01
21.89
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

19 ($CDCl_3$, 24 °C)

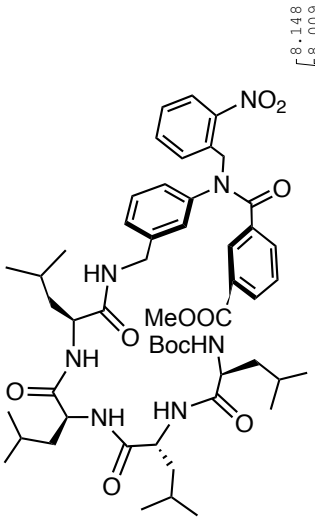


19

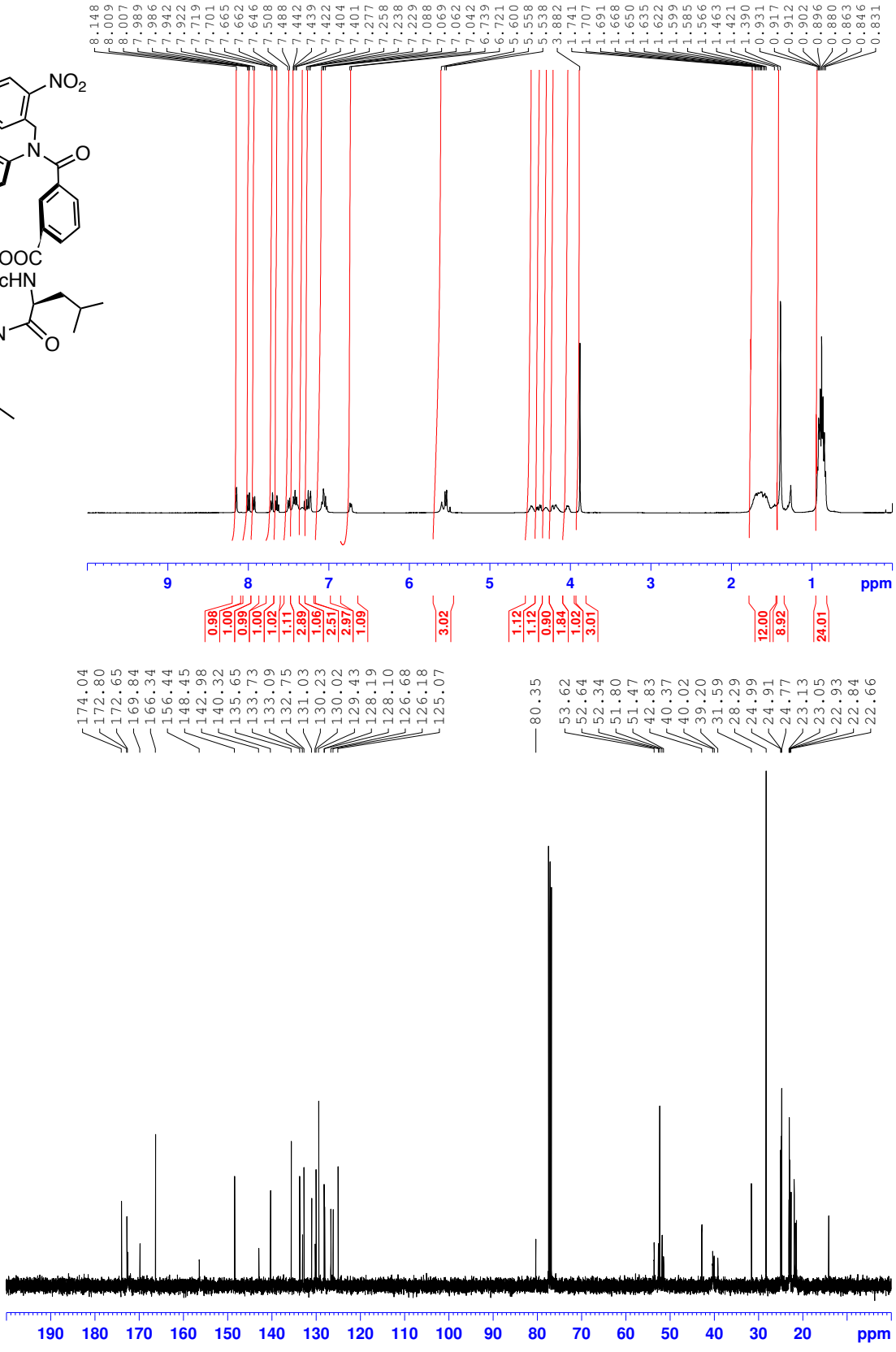




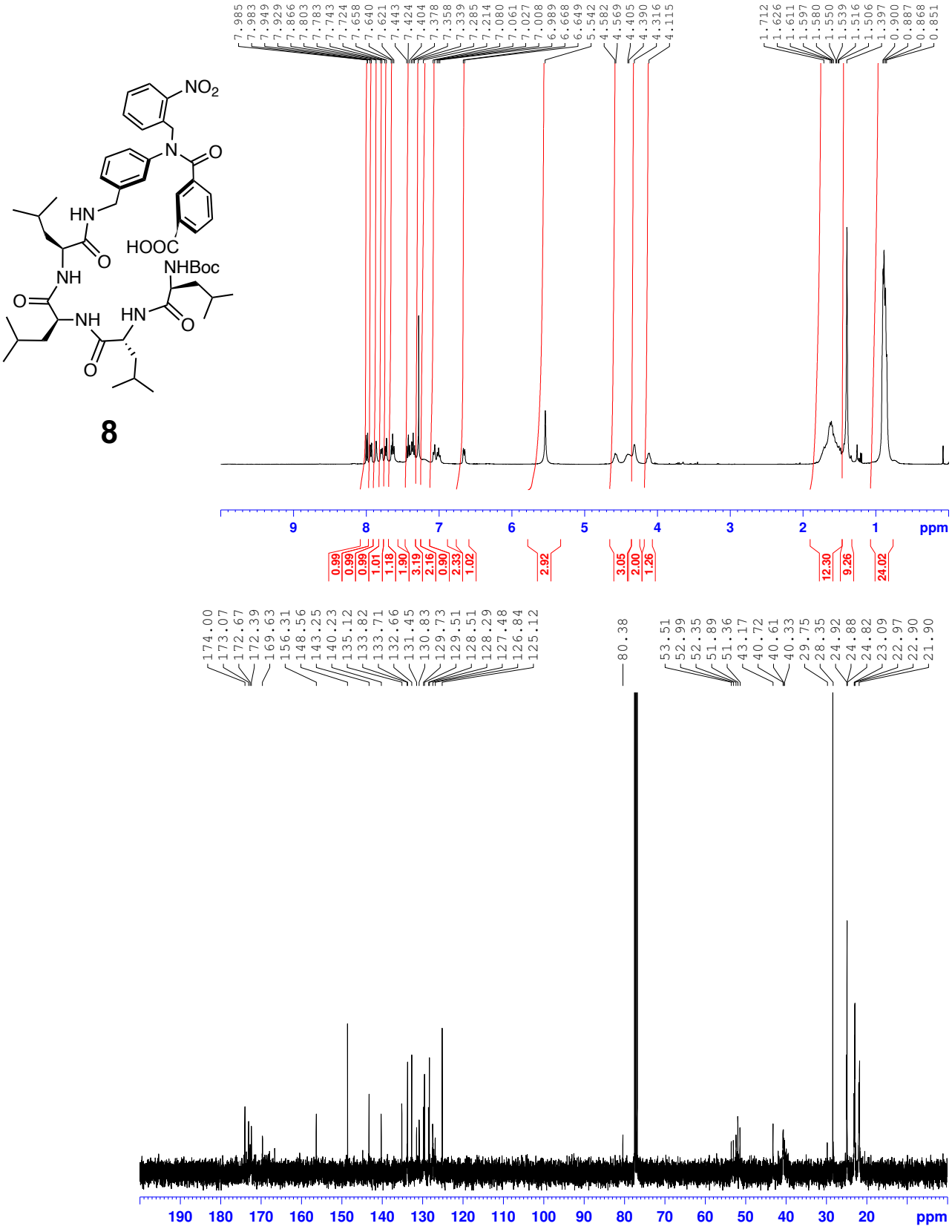
20 ($CDCl_3$, 24 °C)



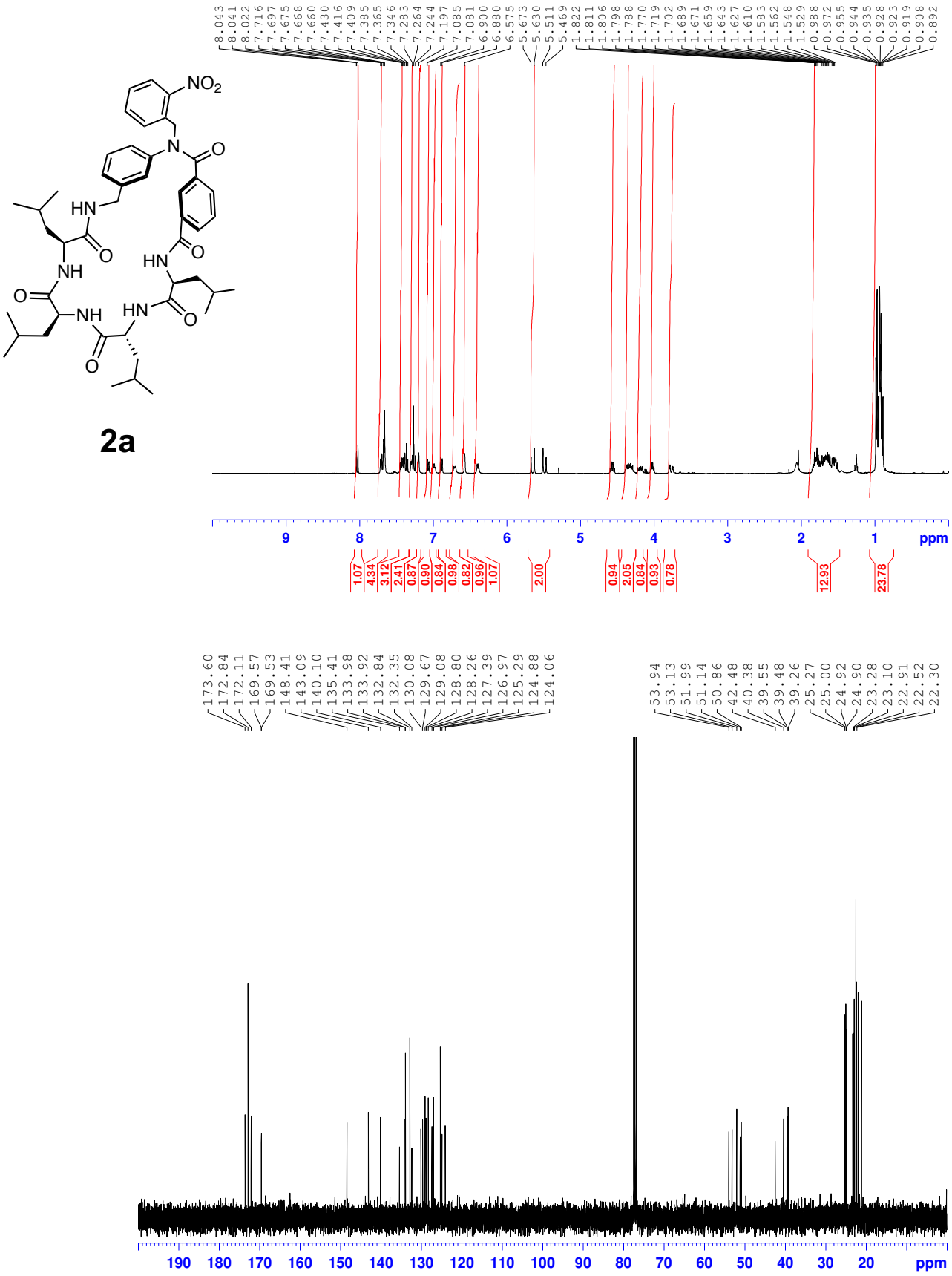
20



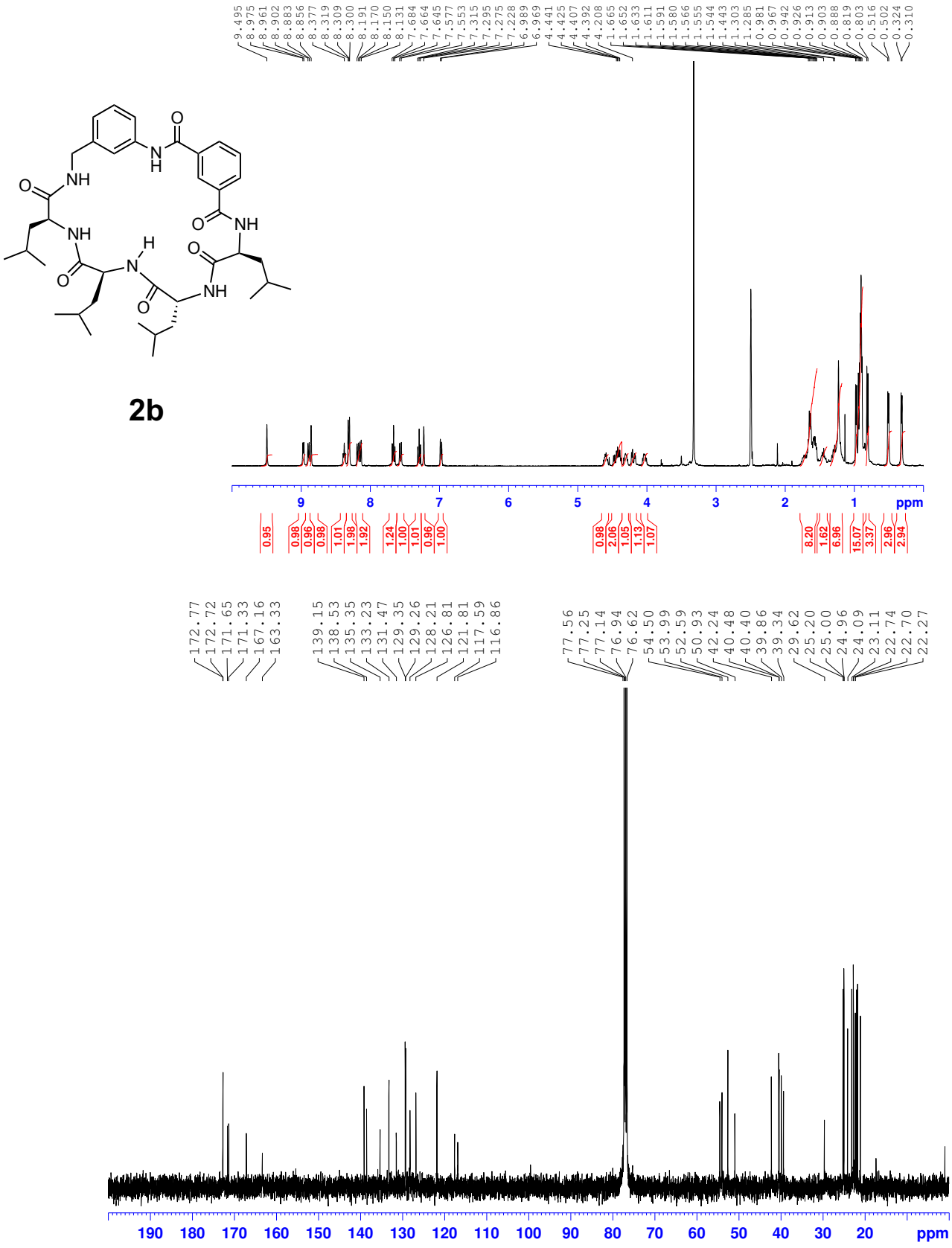
8 ($CDCl_3$, 24 °C)


NO2
N
O
HN
HOOC
NH
NHBoc
O
NH
HN
O
O
8
7.985
7.983
7.949
7.929
7.866
7.803
7.783
7.743
7.724
7.658
7.640
7.621
7.443
7.424
7.404
7.378
7.358
7.339
7.285
7.214
7.080
7.061
7.027
7.008
6.989
6.668
6.649
5.542
4.582
4.569
4.405
4.390
4.316
4.115
1.712
1.626
1.611
1.597
1.580
1.550
1.539
1.516
1.506
1.397
0.900
0.887
0.868
0.851
9 8 7 6 5 4 3 2 1 ppm
0.99 0.99 0.99 1.01 1.18 1.90 3.19 2.16 0.90 2.33 1.02
2.92
3.05 2.00 1.26
12.30 9.26 24.02
174.00
173.07
172.67
172.39
169.63
156.31
148.56
143.25
140.23
135.12
133.82
133.71
132.66
131.45
130.83
129.73
129.51
128.51
128.29
127.48
126.84
125.12
80.38
53.51
52.99
52.35
51.89
51.36
43.17
40.72
40.61
40.33
29.75
28.35
24.92
24.88
24.82
23.09
22.97
22.90
21.90
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

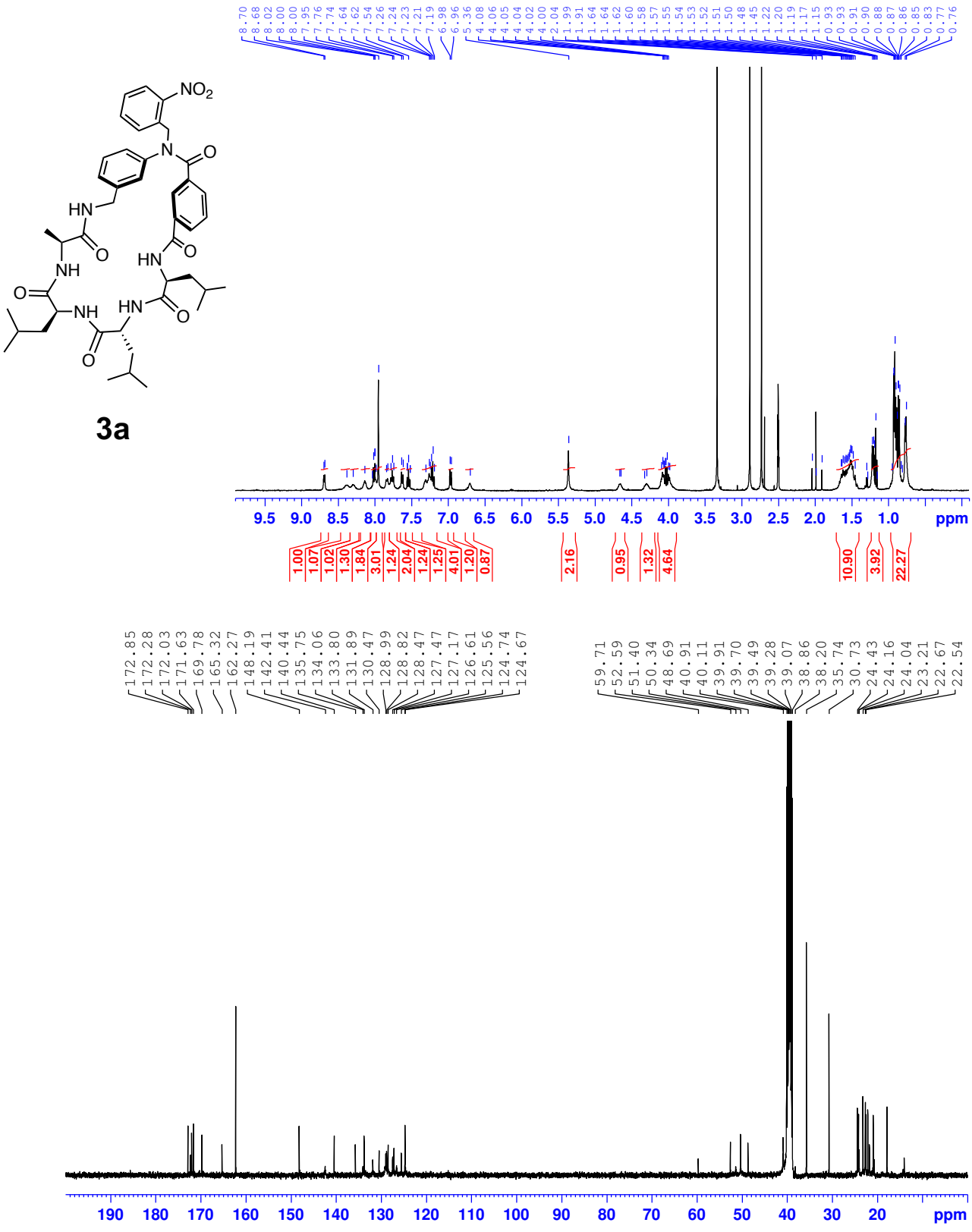
2a ($CDCl_3$, 24 °C)


NO2
N
O
HN
NH
HN
NH
HN
O
2a
8.043
8.041
8.022
7.716
7.697
7.675
7.668
7.660
7.430
7.416
7.409
7.385
7.365
7.346
7.283
7.264
7.244
7.197
7.085
7.081
6.900
6.880
6.575
5.673
5.630
5.511
5.469
1.822
1.811
1.806
1.798
1.788
1.770
1.719
1.702
1.689
1.671
1.659
1.643
1.627
1.610
1.583
1.562
1.548
1.529
0.988
0.972
0.955
0.944
0.935
0.928
0.923
0.919
0.908
0.892
9
8
7
6
5
4
3
2
1
ppm
1.07
4.34
3.12
2.41
0.87
0.90
0.84
0.98
0.82
0.96
1.07
2.00
0.94
2.05
0.84
0.93
0.78
12.93
23.78
173.60
172.84
172.11
169.57
169.53
148.41
143.09
140.10
135.41
133.98
133.92
132.84
132.35
130.08
129.67
129.08
128.80
128.26
127.39
126.97
125.29
124.88
124.06
53.94
53.13
51.99
51.14
50.86
42.48
40.38
39.55
39.48
39.26
25.27
25.00
24.92
24.90
23.28
23.10
22.91
22.52
22.30
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

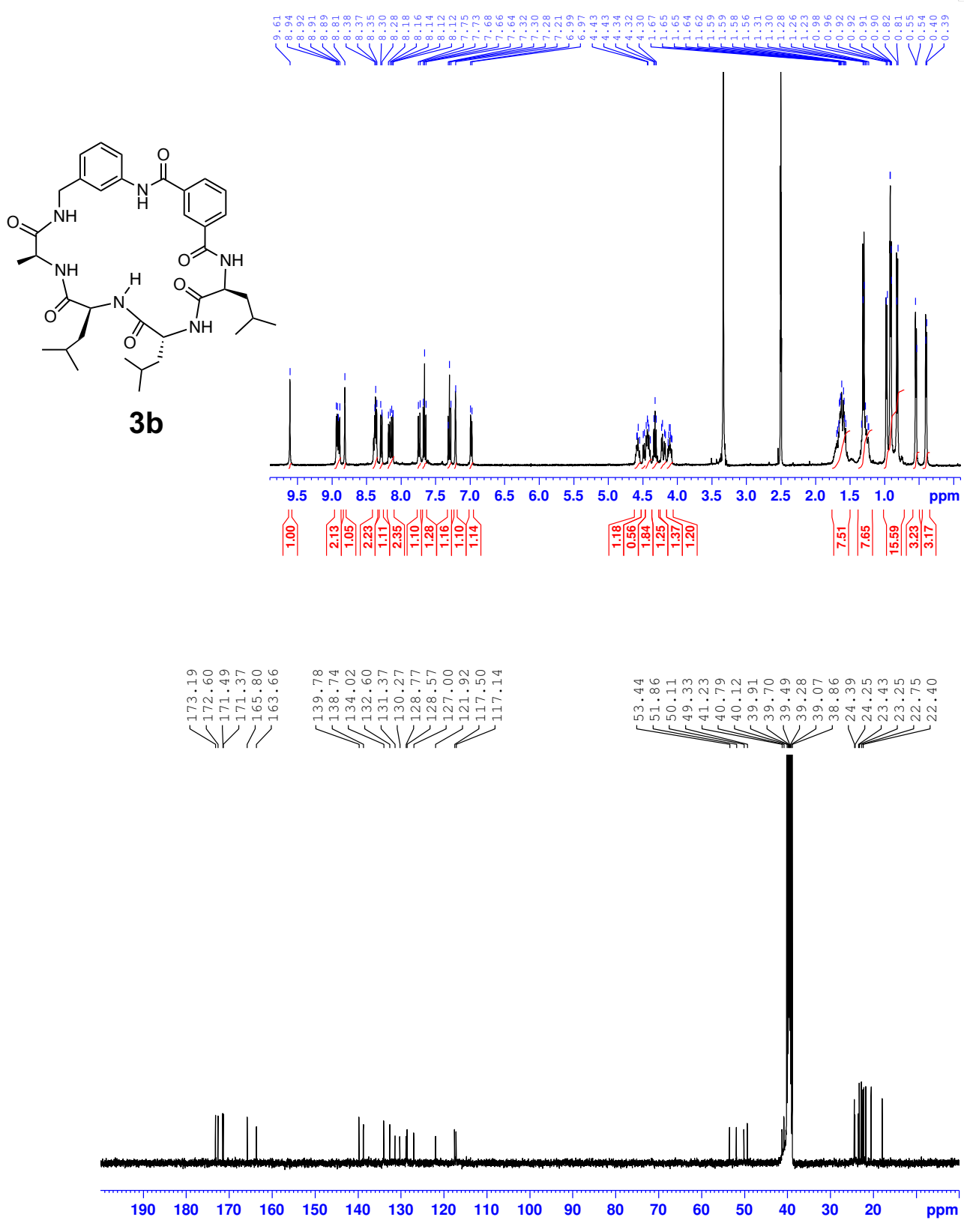
2b (^{1}H-NMR: DMSO-d_6, 24 °C, ^{13}C-NMR: $CDCl_3$, 24 °C)



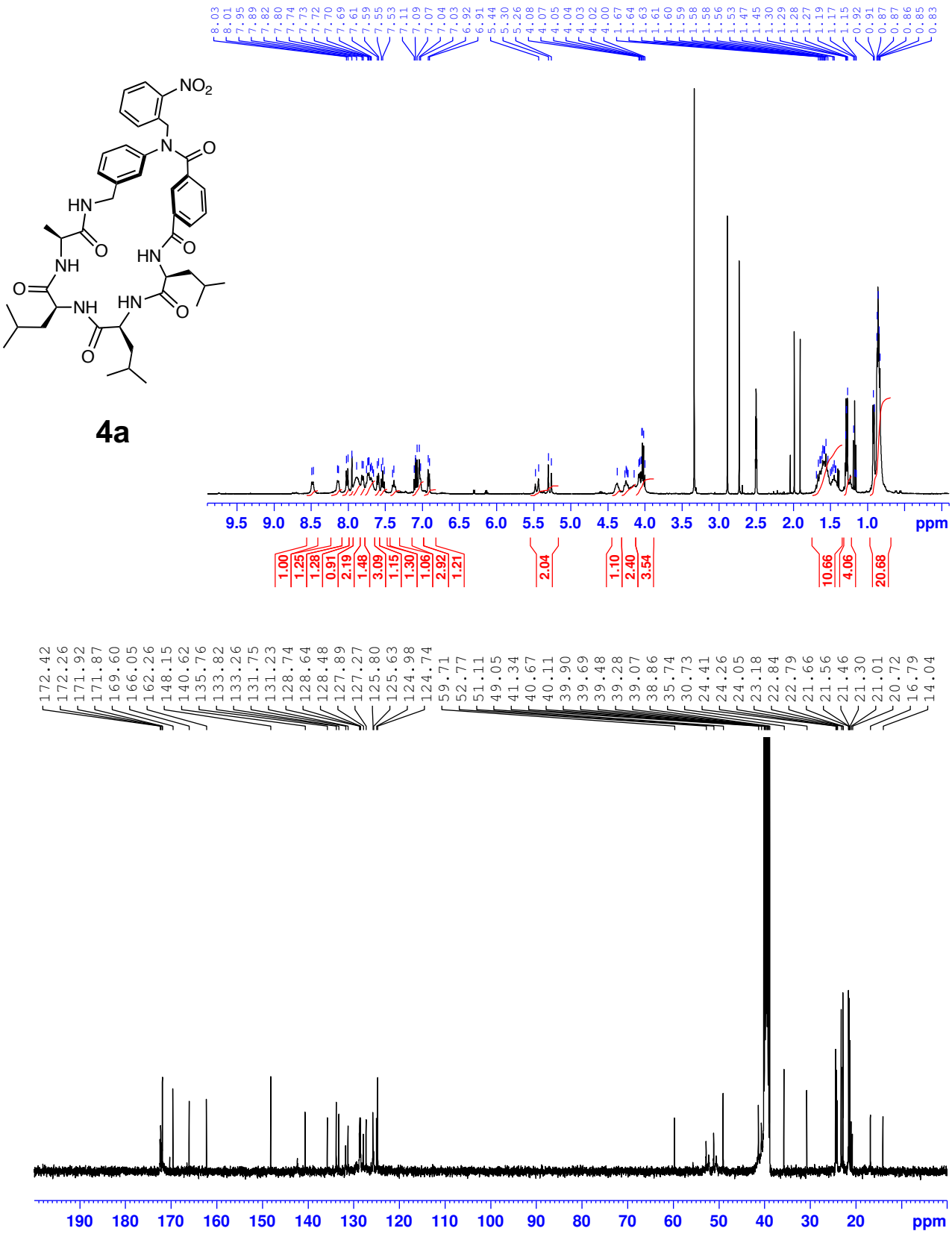
3a (DMSO-d_6, 24 °C)



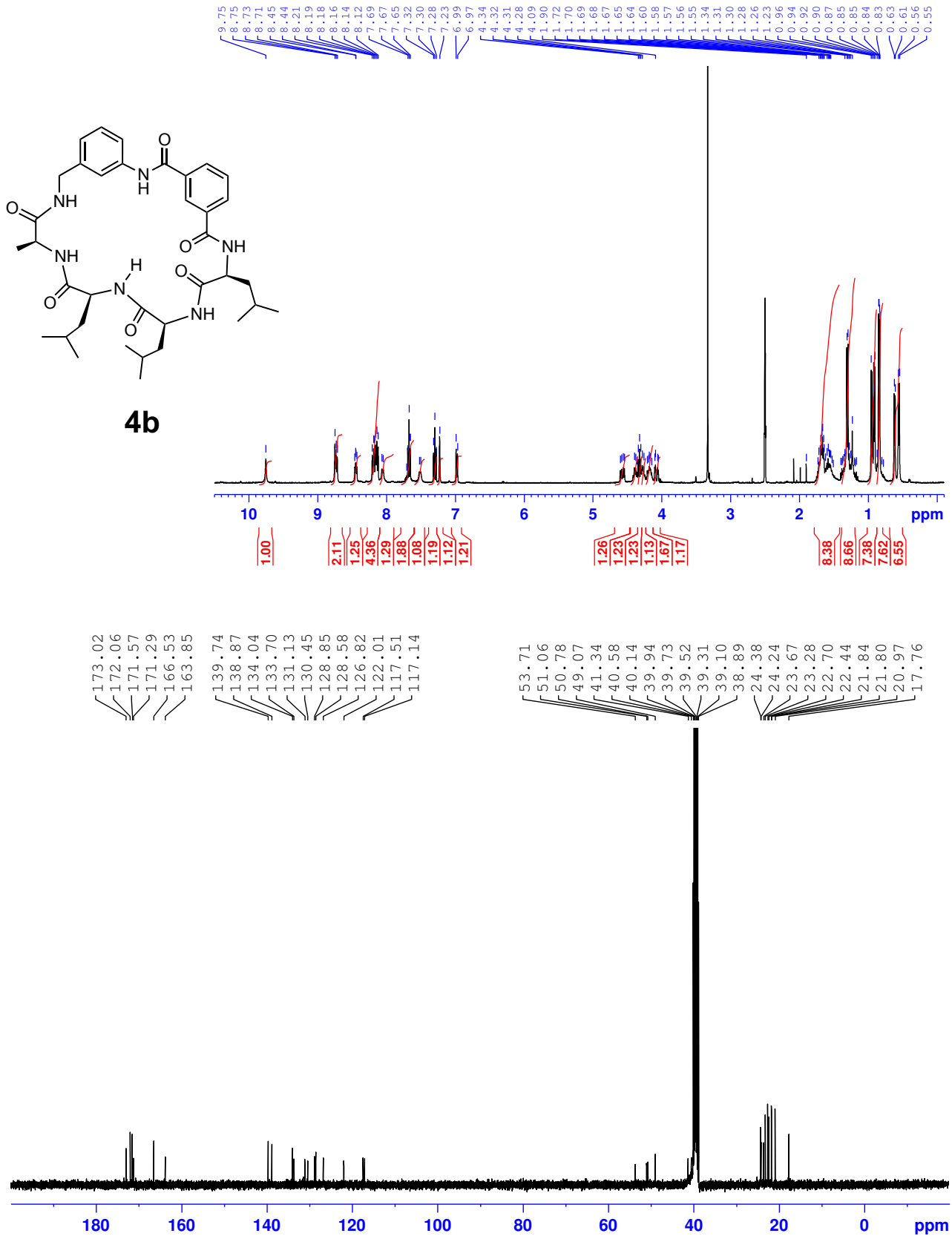
3b (DMSO-d_6, 24 °C)



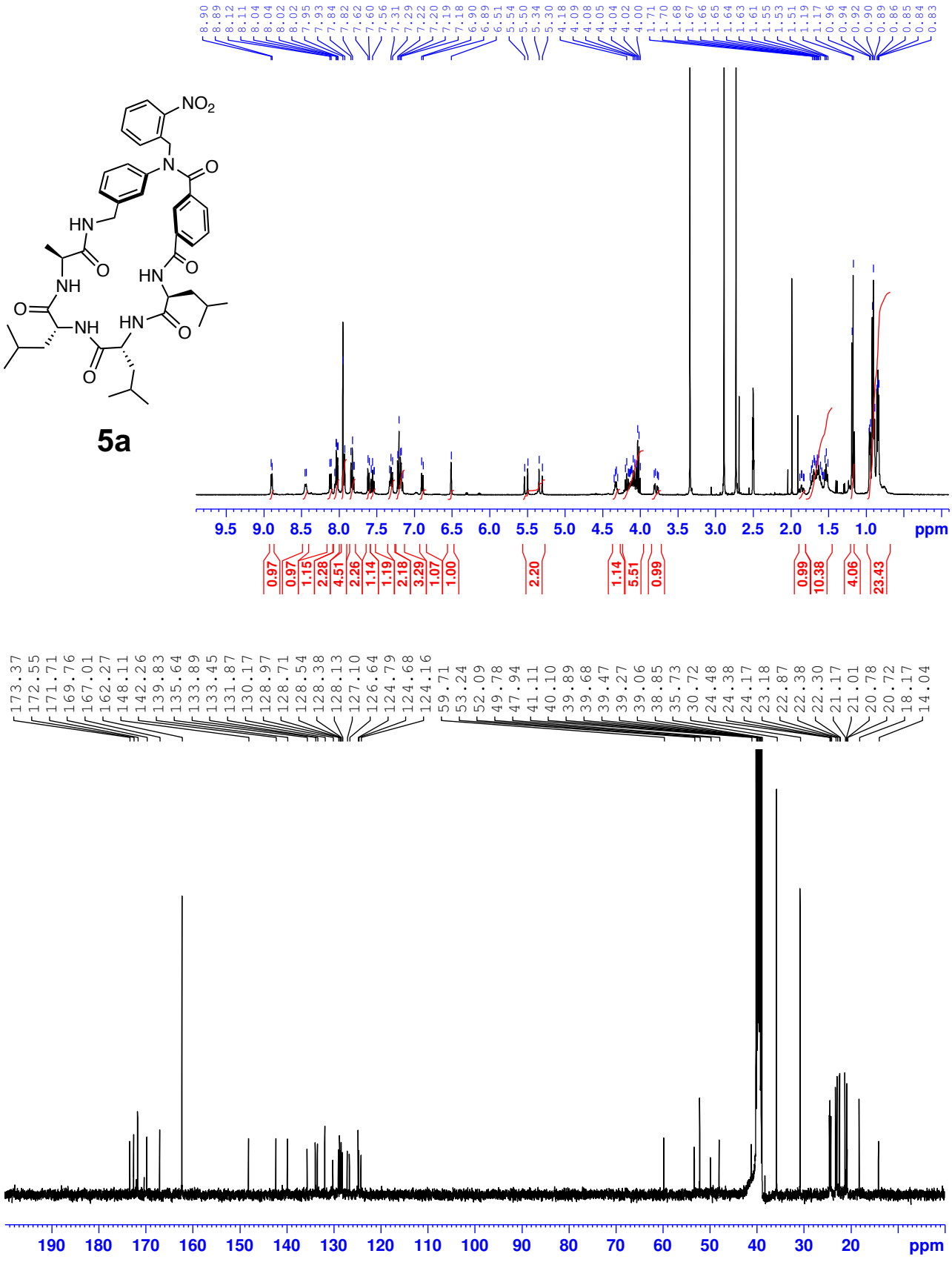
4a (DMSO-d_6, 24 °C)



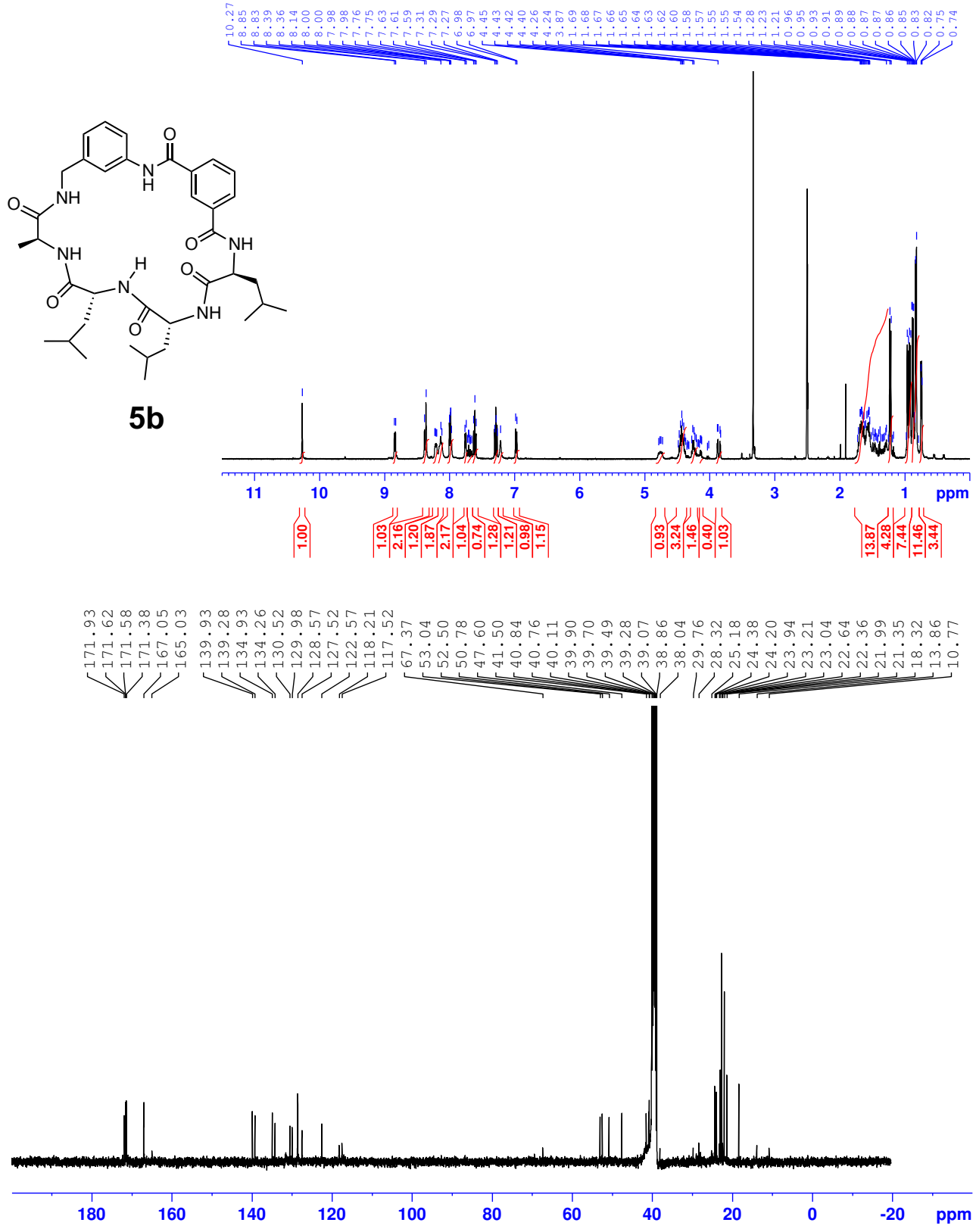
4b (DMSO-d_6, 24 °C)



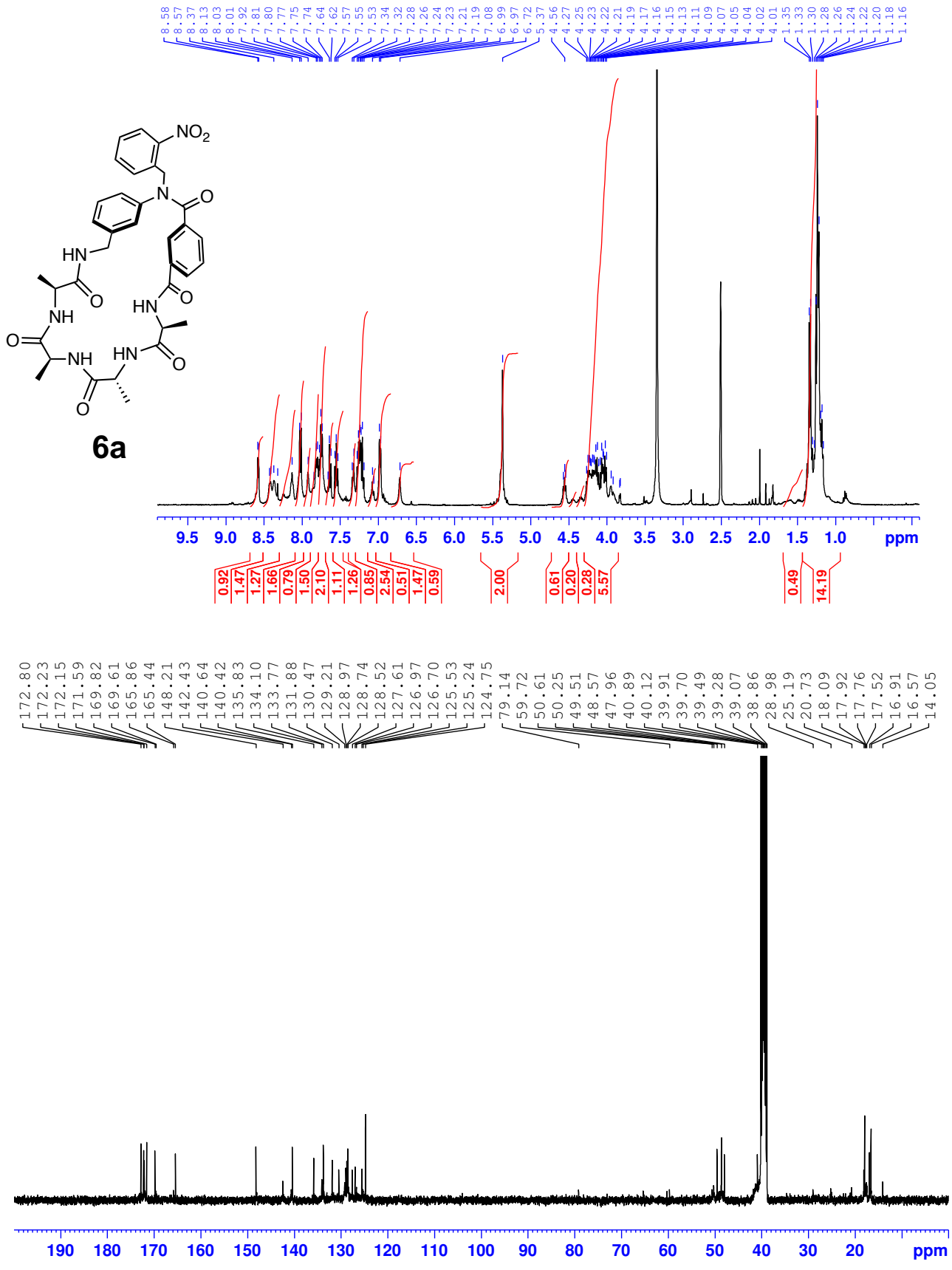
5a (DMSO-d_6, 24 °C)



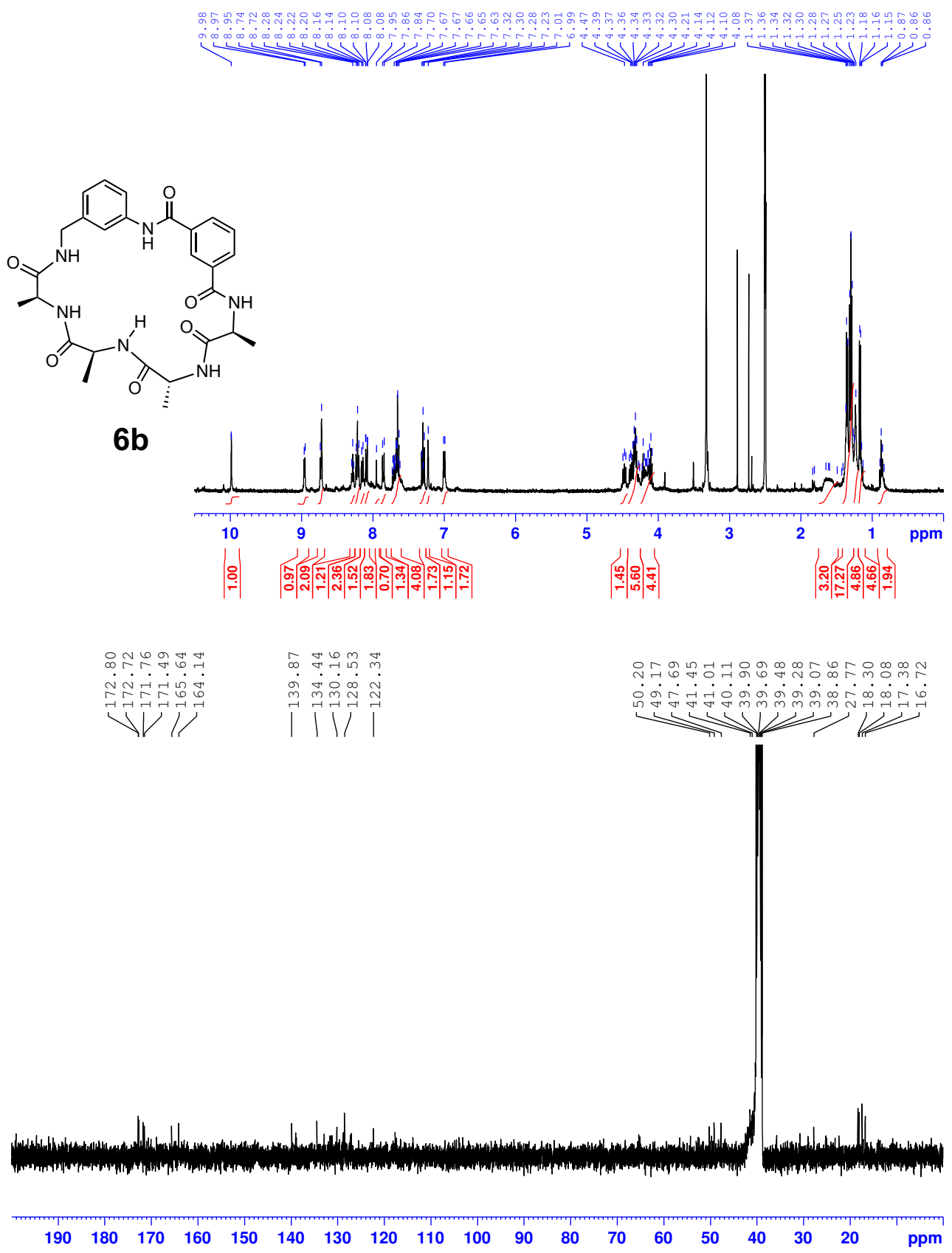
5b (DMSO-d_6, 24 °C)



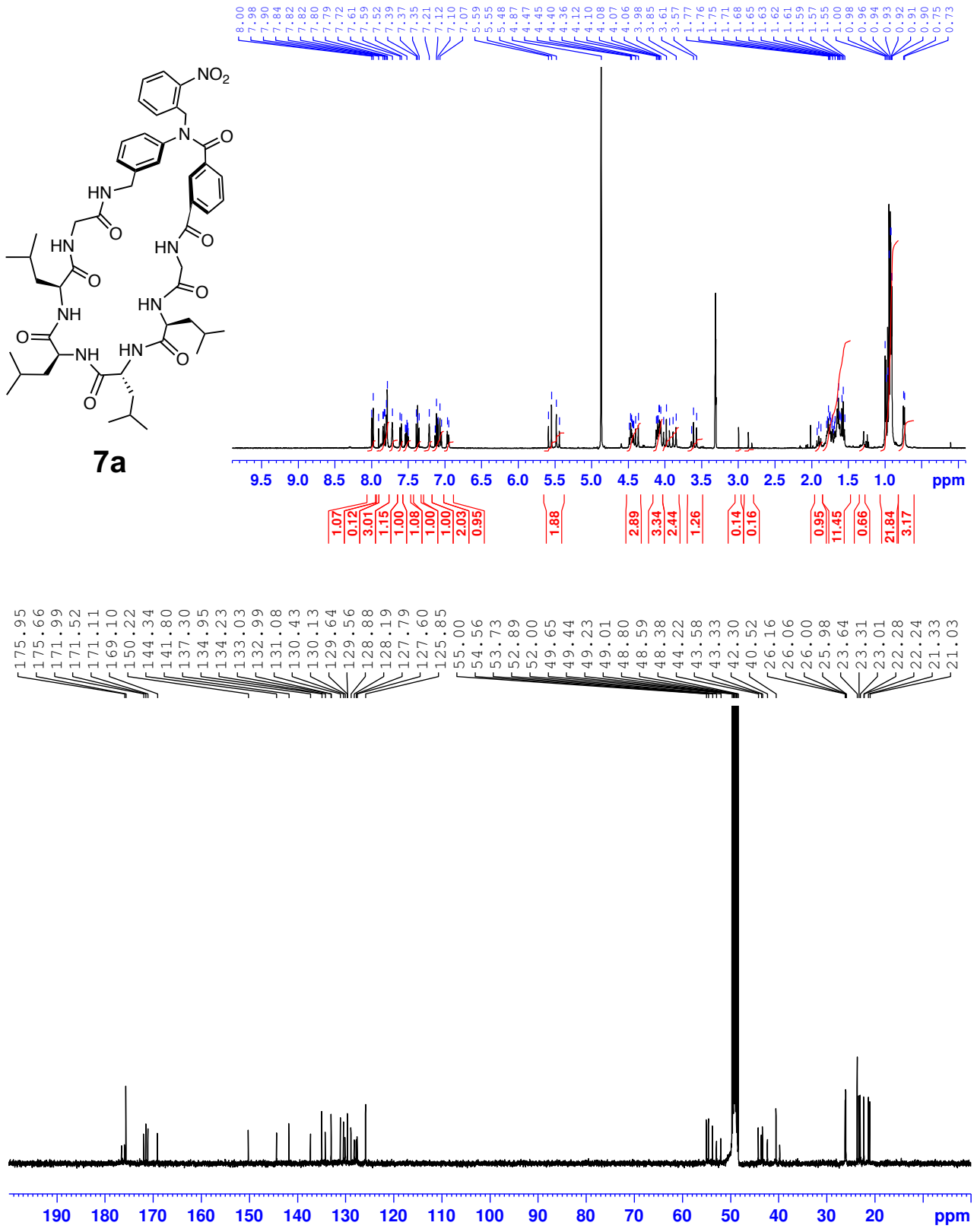
6a (DMSO-d_6, 24 °C)



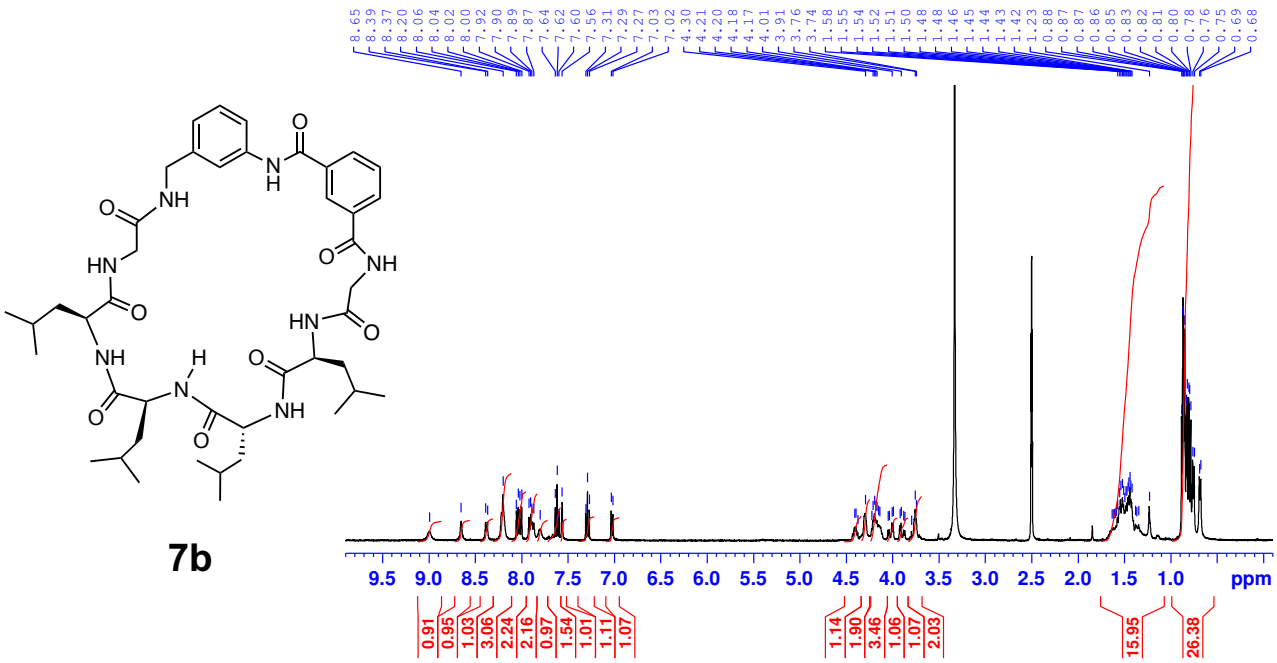
6b (DMSO-d_6, 24 °C)



7a (MeOD, 24°C)


7a
8.00 7.98 7.90 7.84 7.82 7.82 7.80 7.79 7.72 7.61 7.59 7.52 7.39 7.37 7.35 7.21 7.12 7.10 7.07 5.59 5.55 5.48 4.87 4.47 4.45 4.40 4.36 4.12 4.10 4.08 4.07 4.06 3.98 3.85 3.61 3.57 1.77 1.76 1.75 1.71 1.68 1.65 1.63 1.62 1.61 1.59 1.57 1.55 1.00 0.98 0.96 0.94 0.93 0.92 0.91 0.90 0.75 0.73
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.07 0.12 3.01 1.15 1.00 1.08 1.00 1.00 2.03 0.95 1.88 2.89 3.34 2.44 1.26 0.14 0.16 0.95 11.45 0.66 21.84 3.17
175.95 175.66 171.99 171.52 171.11 169.10 150.22 144.34 141.80 137.30 134.95 134.23 133.03 132.99 131.08 130.43 130.13 129.64 129.56 128.88 128.19 127.79 127.60 125.85 55.00 54.56 53.73 52.89 52.00 49.65 49.44 49.23 49.01 48.80 48.59 48.38 44.22 43.58 43.33 42.30 40.52 26.16 26.06 26.00 25.98 23.64 23.31 23.01 22.28 22.24 21.33 21.03
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

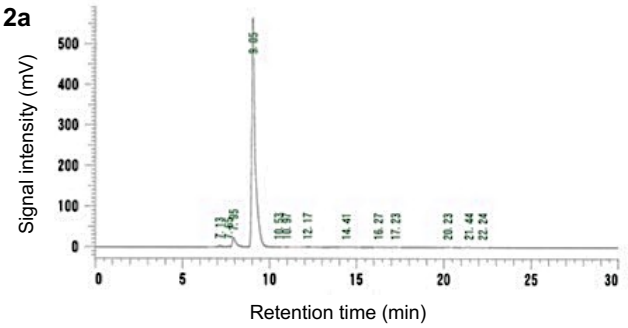
7b (DMSO-d_6, 24 °C)



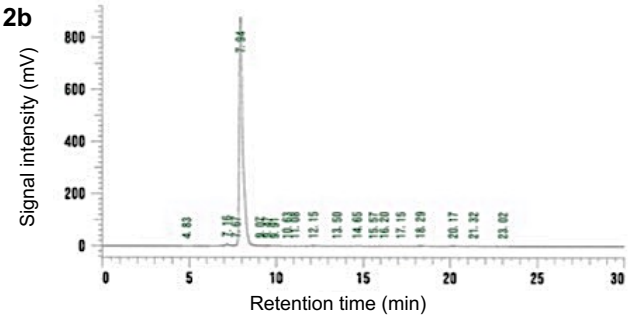
7b

HPLC charts

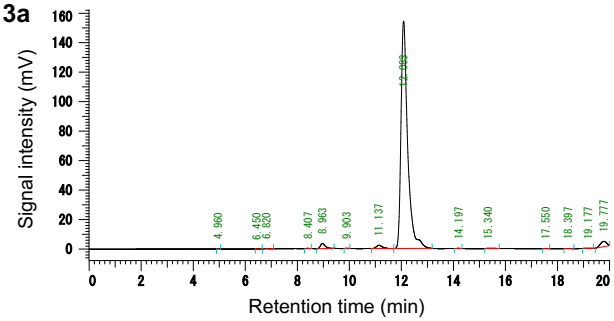
2a



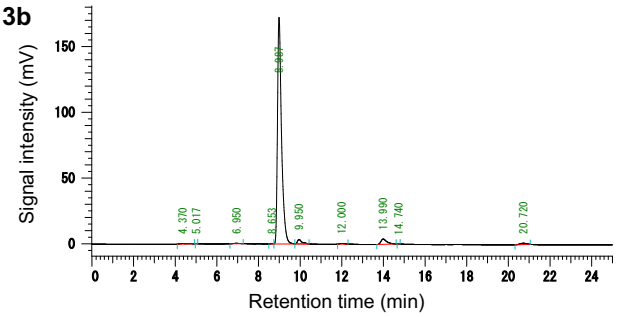
2b



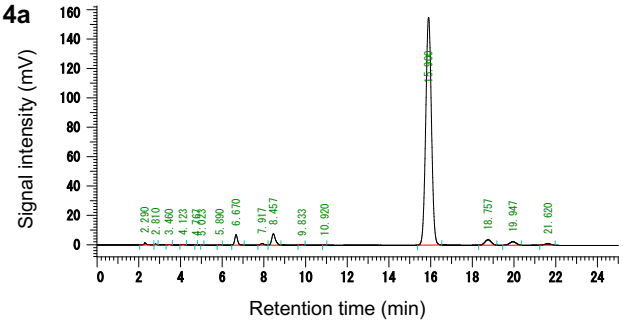
3a



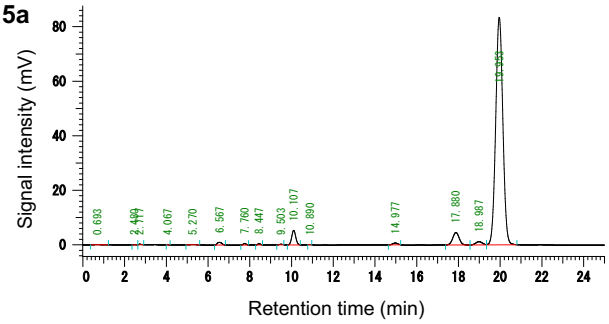
3b



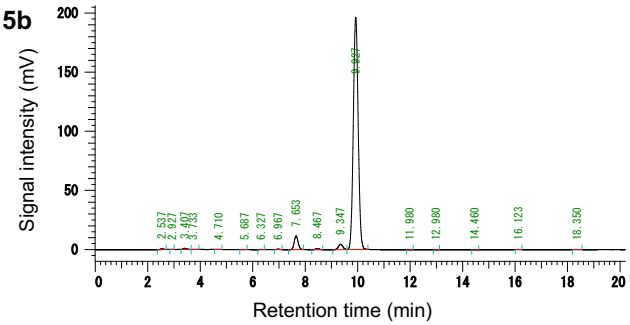
4a



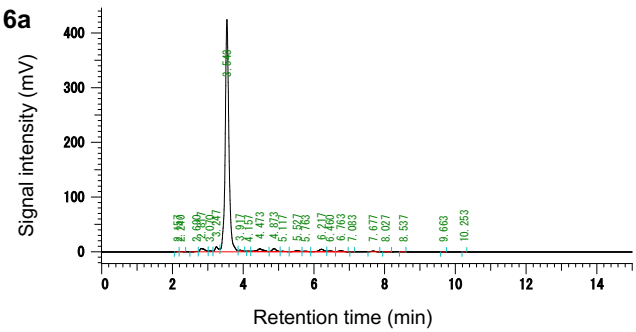
5a



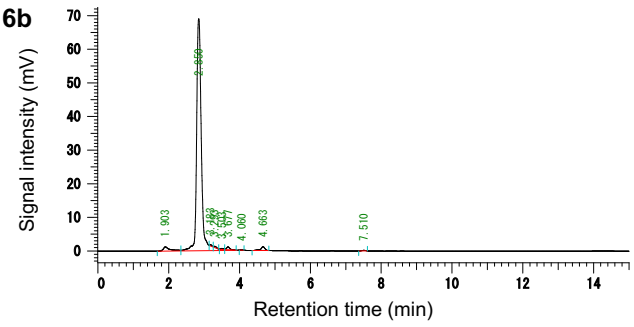
5b



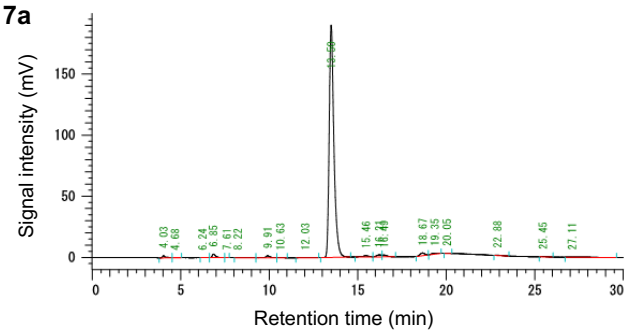
6a



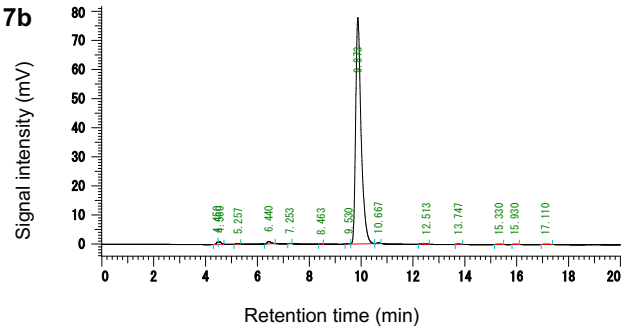
6b


Signal intensity (mV)
Retention time (min)
1. 903
4. 060
4. 663
7. 510

7a


Signal intensity (mV)
Retention time (min)
4. 03
4. 68
6. 24
6. 85
7. 61
8. 22
9. 91
10. 63
12. 03
15. 46
18. 67
19. 35
20. 05
22. 88
25. 45
27. 11

7b


Signal intensity (mV)
Retention time (min)
5. 257
6. 440
7. 253
8. 463
9. 530
10. 667
12. 513
13. 747
15. 330
15. 930
17. 110

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