Electronic Supplementary Material (ESI) for RSC Advances.

Supporting Information

Design and Synthesis of Cyclic Depsipeptide Containing Triazole (CDPT) Ring

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CONTENTS:

1) General Consideration:

All chemicals were purchased from Sigma-Aldrich, India and used without further purification. Solvents were distilled prior to use. Triple distilled water was used for the reaction. The reactions were performed in air atmosphere without any specific precautions. Melting points were determined with open capillary tube on a Gallenkamp (variable heater) melting point apparatus and were uncorrected. FT-IR spectra were recorded as KBr pellets on a Bruker Tensor 27 spectrometer with Opus 5.5 software. The ^{1}H NMR spectra (400 MHz) and ^{13}C-NMR (100 MHz) of the synthesized compounds were recorded in Bruker AVANCE 400 MHz NMR spectrometer in DMSO-d_6, MeOD-d_4 and $CDCl_3$ solvent and the chemical shifts (d) were expressed in parts per million and coupling constants (*J*) in hertz. Spin multiplicities are described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass analysis was performed on quadruple-time of flight (Q-Tof) mass spectrometer (Micromass, USA) using electrospray ionization (ESI) in positive mode. TLC is performed using precoated aluminium sheets with silica gel 60 F254.

The HPLC instrumentation consists of a Waters 600E pump, a Rheodyne injector with 5 µL loop, Waters 486 tunable Absorbance (UV) detector, Waters 2996 Photodiode Array (PDA) detector and Waters In-line Degasser AF. A Waters Symmetry C_{18} (4.6x150 mm^2, 5 µL) column was used for the analysis. The UV detector was tuned at 215 nm and PDA detector was set between 190 and 400 nm. HPLC grade acetonitrile (50%): triple distilled water (50%): triflouoroacetic acid (0.1%) was used as an isocratic eluent at a flow rate of 1 mL/min. Samples were prepared by dissolving 1 mg of compound in 1 mL of HPLC grade methanol. Each sample of 10 µL was injected separately. Data acquisition and processing for HPLC studies were carried out with empower software.

2) Experimental Procedures:

(A) Synthesis of propargyl amino esters 6a & other all amino esters:[1]

(i) To a solution of Boc-Leu-OH (1.0 g, 4.33 mmol) in THF (20 ml) at 0 ^{o}C was added portion wise *N*,*N*'-Carbonyldiimidazole (CDI) (842 mg, 5.2 mmol, 1.2 equiv). After the effervescence subsided, the solution was stirred at the same temperature for 45 min to 1 h and propargyl alcohol (291 mg, 0.3 ml, 5.2 mmol, 1.2 equiv) was added and reaction mixture was stirred at room temperature for 8 h. The solvent was removed on rotavapour and residue was taken up in ethyl acetate (100 ml) and washed with saturated solution of sodium bicarbonate (10 ml x 2), 1N HCl (10 ml x 2), water (10 ml), brine and dried over anhydrous sodium sulphate and evaporated to dryness on rotavapour to afford colorless viscous oil.

(ii) Crude was taken in DCM (10 ml), cooled to 0 ^{o}C and TFA (10 ml) was added. Reaction mixture was stirred at same temperature for 2 h, evaporated the excess of solvent on rotavapour, diethylether (20 ml) was added and extract with water (20 ml x 2). Discarded the ether layer and aq. layer was basified by sat. solution of sodium bicarbonate, extract the aq. layer by 15% isopropanol : chloroform (50 ml x 3). Combined organic layer was dried over anh. sodium suphate and evaporated on rotavapour to afford pale yellow oil in 68% (500 mg) yield. In the same way other propargyl amino esters were also prepared.

(B) Synthesis of propargyl amino ester containing dipeptides 7a & all other amino ester containing dipeptide:[1]

(i) To a solution of Boc-Phe-OH (653 mg, 2.47 mmol) in THF (20 ml) at 0 ^{o}C was added portion wise *N*,*N*'-Carbonyldiimidazole (CDI) (480 mg, 2.96 mmol, 1.2 equiv). After the effervescence subsided, the solution was stirred at the same temperature for 45 min to 1 h and **6a** (500 mg, 2.96 mmol, 1.2 equiv) was added and reaction mixture was stirred at room temperature for 8 h. The solvent was removed on rotavapour and residue was taken up in ethyl acetate (100 ml) and washed with saturated solution of sodium bicarbonate (10 ml x 2), 1N HCl (10 ml x 2), water (10 ml), brine and dried over anhydrous sodium sulphate and evaporated to dryness on rotavapour to afford colorless viscous oil, which was triturated with diethylether: n-Pentane to afford white solid in 70% (1.0 g) yield.
(ii) White solid was taken in DCM (10 ml), cooled to 0 ^{o}C and TFA (10 ml) was added. Reaction mixture was stirred at same temperature for 2 h, evaporated the solvent on rotavapour to afford brown oil as TFA salt of propargyl amino ester containing dipeptide **7a** in quantitative (760 mg) yield and was used as such for the next batch. In the same way other propargyl amino esters containing dipeptides were also prepared.

(C) Synthesis of azido-alkyne containing linear depsipeptide 9a & other azido-alkyne containing linear depsipeptide:[1,2]

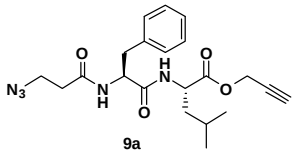
In a ice cold solution of 3-azido propionic acid **8** (230 mg, 2 mmol) in DCM, added EDC.HCl (460 mg, 2.4 mmol, 1.2 equiv), HOBt (324 mg, 2.4 mmol, 1.2 equiv) and stirred at the same temperature for 30 minutes; followed by added TFA salt of propargyl amino ester containing dipeptides **7a** (760 mg, 2.4 mmol, 1.2 equiv) and DIPEA (775 mg/1ml, 6.0 mmol, 3 equiv), stirred the reaction mixture over night at room temperature. Excess of solvent were evaporated on rotavapour, added ethyl acetate (200 ml); washed the organic layer with saturated solution of sodium bicarbonate (10 ml x 2), 1N HCl (10 ml x 2), water (10 ml), brine and dried over anhydrous sodium sulphate and evaporated to dryness on rotavapour to afford brown viscous oil, which was purified by silica gel column chromatography (mess size 60-120, eluent ethyl acetate: n-hexane 10% to 35%) to afford **9a** as white solid in 70% (578 mg) yield. In the same way other azido-alkyne containing linear depsipeptide were also prepared.

(D) Synthesis of cyclic depsipeptide containing triazole (CDPT) ring 10a & other CDPT ring:[2]

To a 250 mL round-bottomed flask charged with alkyne azide **9a** (100 mg, 0.242 mmol) in toluene (200 mL) was added DBU (109 µL, 0.726 mmol, 3 equiv). The solution was degassed with argon for thirty minutes and then heated to reflux while flushing with argon. At reflux, copper (I) bromide (7.0 mg, 0.048 mmol, 0.2 equiv) was added, and the solution was stirred at reflux under argon for 14 h. The mixture was

then cooled to rt and poured through a 2 in pad of Celite. The Celite pad was washed with MeOH (3 × 25 mL). The filtrate was concentrated in vacuo to provide blue-green oil. The product was purified via flash chromatography (5-10% MeOH in CH_2Cl_2) to afford cyclic depsipeptide **10a** (62 mg, 62% yield) as a white solid. In the same way other cyclic depsipeptides were also prepared.

3) Characterization Details of Compounds (9a-k and 10a-k):



9a

(S)-prop-2-ynyl 2-((S)-2-(3-azidopropanamido)-3-phenylpropanamido)-4-methylpentanoate(9a):

White solid compound, mp: 95-97 ^oC

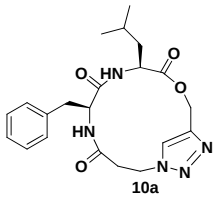
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.32-7.22 (m, 5 H), 6.45 (d, J = 7.6 Hz, 1 NH), 6.29 (d, J = 8.0 Hz, 1 NH), 4.74-4.70 (m, 3 H), 4.55 (m, 1 H), 3.59-3.56 (m, 2 H), 3.09 (t, J = 5.2 and 6.8 Hz, 2 H), 2.51 (t, J = 2.4 and 2.0 Hz, 1 H), 2.41 (t, J = 6.4 and 6.0 Hz, 2 H), 1.62-1.51 (m, 3 H), 0.90 (t, J = 5.2 Hz, 6 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.42, 170.83, 169.86, 136.28, 129.36, 128.56, 127.00, 76.69, 75.38, 54.27, 52.61, 50.89, 47.19, 40.97, 38.29, 35.52, 24.71, 22.60, 21.82ppm

IR: 3283, 3080, 2959, 2103, 1751, 1644, 1557, 1443, 1153, 701 cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_4Na$; Calculated: 436.1961, Found: 436.3251 (M + Na)

HPLC: RT 12.21min (215 nm)



10a

(6S,9S)-6-benzyl-9-isobutyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10a):

White Solid, mp: 246-248 ^oC

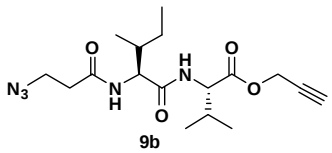
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.33 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 9.6 Hz, 1H), 7.57 (s, 1H), 7.27-7.13 (m, 5H), 5.46 (d, J = 12.4 Hz, 1H), 4.96 (d, J = 12.8 Hz, 1H), 4.60-4.56 (m, 3H), 3.92 (q, 1H), 2.77-2.56 (m, 4H), 1.55-1.46 (m, 2H), 1.23 (m, 1H), 0.87-0.76 (m, 6H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.85, 170.72, 169.26, 143.83, 137.41, 129.44, 128.64, 126.89, 124.19, 58.02, 54.09, 50.84, 46.87, 38.55, 38.40, 36.98, 24.37, 23.56, 21.85ppm

IR: 3295, 2958, 1743, 1640, 1543, 1197, 700 cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_4Na$; Calculated: 436.1961, Found: 436.6154 (M + Na)

HPLC: RT 4.91min (215 nm)



9b

(S)-prop-2-ynyl2-((2S,3R)-2-(3-azidopropanamido)-3-methylpentanamido)-3-methylbutanoate(9b):

White solid compound, mp: 97-98 ^{o}C

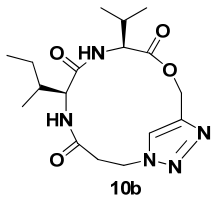
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 6.65-6.63 (m, 2 NH), 4.80 (dd, J = 2.4 Hz, 1 H), 4.68 (dd, J = 2.8 and 2.4 Hz, 1 H), 4.55 (q, J = 5.2 Hz, 1 H), 4.43 (t, J = 8.4 and 8.0 Hz, 1 H), 3.65-3.60 (m, 2 H), 2.50-2.45 (m, 3 H), 2.23-2.21 (m, 1 H), 1.86-1.85 (m, 1 H), 1.55 (m, 1 H), 1.19 (m, 1 H), 0.96-0.89 (m, 12 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.75, 170.70, 170.01, 76.68, 75.25, 57.72, 57.24, 52.38, 47.37, 37.30, 35.56, 30.87, 24.99, 18.80, 17.75, 15.16, 11.12ppm

IR: 3288, 2966, 2101, 173, 1634, 1548, 1182, 1140, 991, 684 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4Na$; Calculated: 388.1961, Found: 388.4152 (M + Na)

HPLC: RT 7.88min (215 nm) and 6.34min (244 nm)



10b

(6S,9S)-6-sec-butyl-9-isopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10b):

White Solid, mp: 250-252 ^{o}C

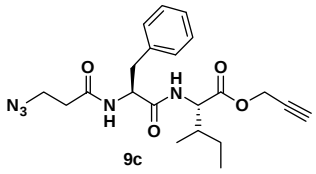
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 7.81-7.76 (m, 2 NH), 7.56 (s, 1 H), 5.36 (d, J = 12.8 Hz, 1 H), 5.16 (d, J = 12.8 Hz, 1 H), 4.66-4.60 (m, 2 H), 4.07 (t, J = 9.2 and 8.8 Hz, 1 H), 3.92 (t, 1 H), 2.68-2.58 (m, 2 H), 2.04-2.02 (m, 1 H), 1.61-1.59 (m, 1 H), 1.41-1.40 (m, 1 H), 1.07-1.03 (m, 1 H), 0.91-0.77 (m, 12 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.65, 169.64, 168.97, 143.49, 122.98, 58.23, 57.92, 57.51, 46.33, 36.44, 36.09, 28.67, 24.82, 19.43, 18.36, 15.37, 10.53ppm

IR: 3291, 2966, 1744, 1638, 1544, 1385, 1196, 1136, 734 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4$+H; Calculated: 366.2141, Found: 366.4604 (M + H)

HPLC: RT 3.86min (215 nm)



9c

(2S,3R)-prop-2-ynyl-2-((S)-2-(3-azidopropanamido)-3-phenylpropanamido)-3-methylpentanoate (9c): White solid compound, mp: 80-81 ^{o}C

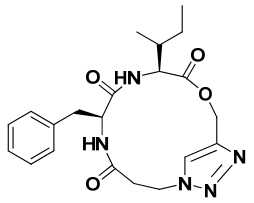
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.31-7.23 (m, 5 H), 6.43 (d, J = 7.2 Hz, 1 H), 6.30 (d, J = 8.0 Hz, 1 H), 4.77-4.65 (m, 3 H), 4.52 (q, J = 5.2 and 4.8 Hz, 1 H), 3.59 (t, J = 6.0 and 6.4 Hz, 2 H), 3.15-3.03 (m, 2 H), 2.51 (t, J = 2.4 and 2.0 Hz, 1 H), 2.43 (t, J = 6.4 and 6.0 Hz, 2 H), 1.88-1.84 (m, 1 H), 1.39-1.35 (m, 1 H), 1.11-1.08 (m, 1 H), 0.91-0.79 (m, 6 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.03, 170.45, 169.53, 136.35, 129.37, 128.63, 127.04, 76.76, 75.43, 56.64, 54.46, 52.43, 47.25, 38.43, 37.73, 35.56, 25.07, 15.32, 11.49ppm

IR: 3284, 3071, 2967, 2104, 1752, 1643, 1551, 1449, 1385, 1253, 1184, 1143, 989, 699 cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_4Na$; Calculated: 436.1961, Found: 436.5372 (M + Na)

HPLC: RT 11.71min (215 nm) and 9.15min (244 nm)



10c

(6S,9S)-6-benzyl-9-sec-butyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10c):

White Solid, mp: 256-257 ^{o}C

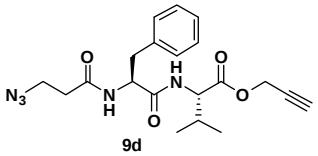
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 7.94 (d, J = 8.8 Hz, 1 NH), 7.78 (d, J = 8.4 Hz, 1 NH), 7.57 (s, 1 H), 7.29-7.15 (m, 5 H), 5.27 (q, J = 12.8 Hz, 2 H), 4.62-4.45 (m, 3 H), 3.97 (t, J = 9.6 and 9.2 Hz, 1 H), 2.89-2.75 (m, 2 H), 1.82 (m, 1 H), 1.30 (m, 1 H), 0.93-0.76 (m, 6 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.83, 169.60, 168.88, 143.47, 137.03, 128.87, 128.24, 126.51, 123.15, 57.58, 56.66, 55.18, 46.21, 37.64, 36.48, 34.46, 23.88, 15.46, 10.28ppm

IR: 3289, 3066, 2966, 1746, 1640, 1544, 1457, 1382, 1337, 1257, 1195, 1135, 1051, 1002, 745, 700 cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_4Na$; Calculated: 436.1961, Found: 436.5372 (M + Na)

HPLC: RT 4.80min (215 nm)



9d

(S)-prop-2-ynyl-2-((S)-2-(3-azidopropanamido)-3-phenylpropanamido)-3-methylbutanoate(9d):

Semi-solid white compound

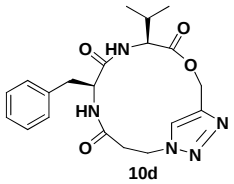
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.30-7.20 (m, 5 H), 6.74 (d, J = 7.6 Hz, 1 NH), 6.66 (d, J = 8.0 Hz, 1 NH), 4.83 (d, J = 7.2 Hz, 1 H), 4.75-4.65 (m, 2 H), 4.48 (q, J = 5.2 and 4.8 Hz, 1 H), 3.56 (t, J = 6.4 Hz, 2 H), 3.07 (d, J = 6.8 Hz, 2 H), 2.50 (t, J = 2.4 and 1.6 Hz, 1 H), 2.42 (t, J = 6.4 Hz, 2 H), 2.17-2.12 (m, 1 H), 0.89 (dd, J = 6.8 Hz, 6 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.63, 170.48, 170.10, 136.43, 129.35, 128.45, 126.87, 76.75, 75.37, 57.40, 54.41, 32.39, 47.20, 38.48, 35.34, 30.98, 18.78, 17.73ppm

IR: 3281, 3071, 2967, 2103, 1750, 1643, 1553, 1185, 1145, 699 cm^{-1}

ESI-MS: $C_{20}H_{25}N_5O_4Na$; Calculated: 422.1804, Found: 422.6348 (M + Na)

HPLC: RT 7.99min (215 nm) and 6.54min (244 nm)



10d

(6S,9S)-6-benzyl-9-isopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10d):

White Solid, mp: 258-260 ^{o}C

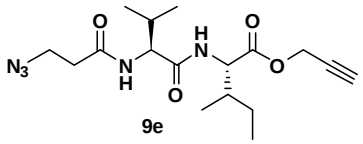
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.13 (d, J = 9.2 Hz, 1 NH), 7.90 (d, J = 8.8 Hz, 1 NH), 7.64 (s, 1 H), 7.28-7.16 (m, 5 H), 5.33 (d, J = 12.8 Hz, 1 H), 5.20 (d, J = 12.8 Hz, 1 H), 4.65-4.44 (m, 3 H), 3.89 (t, J = 9.2 and 9.6 Hz, 1 H), 2.91-2.79 (m, 2 H), 2.06-2.00 (m, 1 H), 0.89-0.76 (m, 6 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 171.49, 170.06, 169.35, 143.96, 137.66, 129.32, 128.74, 126.98, 123.67, 58.56, 58.05, 55.62, 46.64, 38.15, 36.70, 29.21, 19.84, 18.73ppm

IR: 3287, 3065, 2963, 1744, 1641, 1544, 1200, 700 cm^{-1}

ESI-MS: $C_{20}H_{25}N_5O_4Na$; Calculated: 422.1804, Found: 422.3406 (M + Na)

HPLC: RT 4.01min (215 nm)



9e

(2S,3R)-prop-2-ynyl 2-((S)-2-(3-azidopropanamido)-3-methylbutanamido)-3-methylpentanoate(9e):

White solid compound, mp: 99-100 ^{o}C

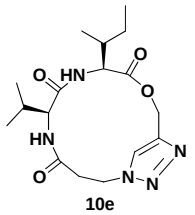
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 6.43-6.38 (m, 2 NH), 4.80 (dd, J = 3.2 and 2.4 Hz, 1 H), 4.68 (dd, J = 2.4 Hz, 1 H), 4.60 (q, J = 4.8 Hz, 1 H), 4.36 (t, J = 7.6 and 8.0 Hz, 1 H), 3.66-3.62 (m, 2 H), 2.49-2.46 (m, 3 H), 2.13-2.08 (m, 1 H), 1.97-1.93 (m, 1 H), 1.47-1.43 (m, 1 H), 1.24-1.19 (m, 1 H), 0.99-0.91 (m, 12 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.32, 170.81, 170.02, 76.73, 75.34, 58.55, 56.34, 52.48, 47.42, 37.66, 35.78, 31.31, 25.13, 19.09, 18.30, 15.44, 11.52ppm

IR: 3294, 2972, 2099, 1752, 1635, 1549, 1387, 1298, 1178, 1140, 990, 677 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4Na$; Calculated: 388.1961, Found: 388.4786 (M + Na)

HPLC: RT 7.90min (215 nm) and 6.32min (244 nm)



10e

(6S,9S)-9-sec-butyl-6-isopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10e):

White Solid, mp: 282-283 ^{o}C

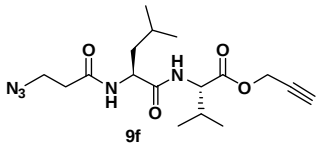
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.00 (d, J = 9.2 Hz, 1 NH), 7.83 (d, J = 8.8 Hz, 1 NH), 7.69 (s, 1 H), 5.30-5.22 (m, 2 H), 4.69-4.55 (m, 2 H), 4.06 (t, J = 9.2 and 9.6 Hz, 1 H), 3.98 (t, J = 8.4 and 9.2 Hz, 1 H), 2.68-2.67 (m, 2 H), 1.87-1.82 (m, 2 H), 1.44-1.40 (m, 1 H), 1.08-1.01 (m, 1 H), 0.88-0.72 (m, 12 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.69, 169.58, 168.97, 143.49, 122.92, 59.86, 57.52, 56.42, 46.26, 35.98, 34.27, 29.99, 23.96, 19.12, 18.78, 15.41, 10.03ppm

IR: 3285, 3228, 2965, 1748, 1650, 1536, 1176, 1050, 822 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4Na$; Calculated: 388.1961, Found: 388.4893(M + Na)

HPLC: RT 4.24min (215 nm)



9f

(S)-prop-2-ynyl-2-((S)-2-(3-azidopropanamido)-4-methylpentanamido)-3-methylbutanoate(9f):

Colorless semisolid

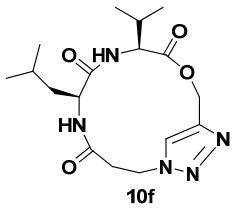
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 6.48 (d, J = 8.8 Hz, 1 NH), 6.1 (d, J = 8.0 Hz, 1 NH), 4.80 (dd, J = 2.0 and 2.4 Hz, 1 H), 4.68 (dd, J = 2.0 and 2.4 Hz, 1 H), 4.57-4.51 (m, 2 H), 3.63 (t, J = 6.4 and 7.2 Hz, 2 H), 2.49-2.43 (m, 3 H), 2.24-2.22 (m, 1 H), 1.71-1.53 (m, 3 H), 0.97-0.86 (m, 12 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.24, 170.28, 169.39, 76.69, 74.83, 56.59, 52.05, 51.38, 46.79, 40.53, 35.26, 30.67, 24.25, 22.28, 21.69, 18.34, 17.04ppm

IR: 3274, 2961, 2097, 1749, 1643, 1547, 1262, 1184, 1142, 677 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4Na$; Calculated: 388.1961, Found: 388.4725(M + Na)

HPLC: RT 7.82min (215 nm) and 6.38min (244 nm)



10f

(6S,9S)-6-isobutyl-9-isopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10f):

White Solid, mp: 244-245 ^{o}C

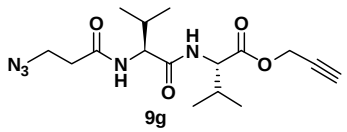
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 7.78 (d, J = 8.8 Hz, 1 NH), 7.64 (d, J = 8.8 Hz, 1 NH), 7.56 (s, 1 H), 5.32 (d, J = 12.4 Hz, 1 H), 5.22 (d, J = 12.8 Hz, 1 H), 4.66-4.57 (m, 2 H), 4.28-4.22 (m, 1 H), 3.94 (t, J = 9.6 Hz, 1 H), 2.68-2.65 (m, 1 H), 2.57-2.53 (m, 1 H), 2.02-1.96 (m, 1 H), 1.56-1.51 (m, 1 H), 1.44-1.35 (m, 2 H), 0.90-0.75 (m, 12 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 171.76, 169.69, 168.96, 143.44, 123.12, 57.72, 57.56, 52.55, 46.15, 40.88, 36.44, 28.80, 24.23, 22.46, 21.58, 19.31, 18.02ppm

IR: 3290, 2962, 1741, 1657, 1528, 1467, 1256, 996, 673 cm^{-1}

ESI-MS: $C_{17}H_{27}N_5O_4Na$; Calculated: 388.1961, Found: 388.5149(M + Na)

HPLC: RT 3.90min (215 nm)



9g

(S)-prop-2-ynyl-2-((S)-2-(3-azidopropanamido)-3-methylbutanamido)-3-methylbutanoate(9g):

White solid compound, mp: 112-113 ^{o}C

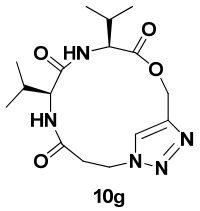
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 6.54 (d, J = 8.4 Hz, 1 NH), 6.45 (d, J = 8.4 Hz, 1 NH), 4.80 (dd, J= 2.4 Hz, 1 H), 4.68 (dd, J = 2.4 and 2.0 Hz, 1 H), 4.57 (q, J = 4.8 and 5.2 Hz, 1 H), 4.39 (t, J = 8.0 and 7.6 Hz, 1 H), 3.64 (q, J = 6.0 Hz, 2 H), 2.50-2.47 (m, 3 H), 2.24-2.23 (m, 1 H), 2.11-2.09 (m, 1 H), 0.99-0.93 (m, 12 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.66, 170.86, 170.10, 76.75, 75.35, 58.57, 57.26, 52.50, 47.44, 35.72, 31.31, 30.98, 19.11, 18.90, 18.38, 17.77ppm

IR: 3286, 3077, 2964, 2875, 2098, 1751, 1635, 1549, 1388, 1300, 1182, 1140, 991, 694 cm^{-1}

ESI-MS: $C_{16}H_{25}N_5O_4Na$; Calculated: 374.1804, Found: 374.5731(M + Na)

HPLC: RT 5.35min (215 nm) and 4.55min (244 nm)



10g

(6S,9S)-6,9-diisopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10g):

White Solid, mp: 264-266 ^{o}C

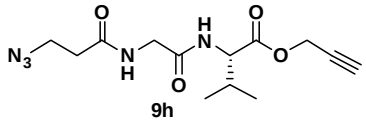
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 7.81-7.78 (m, 2 NH), 7.58 (s, 1 H), 5.36 (d, J = 12.4 Hz, 1 H), 5.17 (d, J = 12.8 Hz, 1 H), 4.66-4.57 (m, 2 H), 4.01 (t, J = 8.8 and 8.4 Hz, 1 H), 3.92 (t, J = 9.2 Hz, 1 H), 2.69-2.57 (m, 2 H), 2.05-2.00 (m, 1 H), 1.85-1.80 (m, 1 H), 0.91-0.82 (m, 12 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.68, 169.60, 169.10, 143.46, 123.04, 59.59, 57.93, 57.49, 46.33, 36.32, 30.01, 28.69, 19.44, 19.20, 18.71, 18.36ppm

IR: 3287, 2965, 1743, 1634, 1544, 1386, 1279, 1233, 1008, 693 cm^{-1}

ESI-MS: $C_{16}H_{25}N_5O_4Na$; Calculated: 374.1804, Found: 374.4485(M + Na)

HPLC: RT 3.37min (215 nm)



9h

(S)-prop-2-ynyl 2-(2-(3-azidopropanamido)acetamido)-3-methylbutanoate(9h):

Colorless oil,

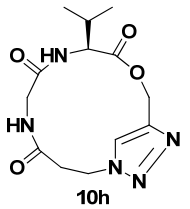
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.03 (d, J = 8.4 Hz, 1 NH), 6.92 (d, J = 4.8 Hz, 1 NH), 4.78-4.67 (m, 2 H), 4.57 (q, J = 5.2 and 4.8 Hz, 1 H), 4.11-3.99 (m, 2 H), 3.65 (t, J = 6.4 Hz, 2 H), 2.54-2.50 (m, 3 H), 2.26-2.21 (m, 1 H), 1.01-0.89 (m, 6 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.09, 171.00, 169.42, 76.81, 75.54, 57.34, 52.48, 47.33, 43.16, 35.25, 30.96, 18.85, 17.75ppm

IR: 3298, 2969, 2102, 1746, 1656, 1540, 1267, 1187, 1147, 1026, 674 cm^{-1}

ESI-MS: $C_{13}H_{19}N_5O_4Na$; Calculated: 332.1335, Found: 332.2042 (M + Na)

HPLC: RT 4.12min (215 nm) and 3.64min (244 nm)



(S)-9-isopropyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10h):

White Solid, mp: 262-264 ^{o}C

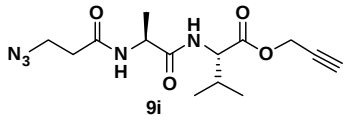
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.23-8.18 (m, 2 NH), 7.59 (s, 1 H), 5.29 (d, J = 12.8 Hz, 1 H), 5.18 (d, J = 12.4 Hz, 1 H), 4.62 (t, J = 5.2 and 6.4 Hz, 2 H), 4.10 (m, 1 H), 3.89 (q, J = 8.4 Hz, 1 H), 3.17 (dd, J = 5.2 Hz, 1 H), 2.74-2.67 (m, 1 H), 2.56-2.44 (m, 1 H), 2.00 (m, 1 H), 0.89 (t, J = 6.8 and 6.4 Hz, 6 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.42, 169.41, 169.02, 142.86, 124.28, 58.87, 57.35, 46.40, 42.12, 36.22, 28.39, 18.98, 18.58ppm

IR: 3393, 3343, 3161, 2963, 1713, 1662, 1505, 1396, 1262, 1211, 1262, 1035, 984, 649cm^{-1}

ESI-MS: $C_{13}H_{19}N_5O_4Na$; Calculated: 374.1804, Found: 332.20 (M + Na)

HPLC: RT 2.93 min (215 nm)



(S)-prop-2-ynyl 2-((S)-2-(3-azidopropanamido)propanamido)-3-methylbutanoate(9i):

Colorless oil,

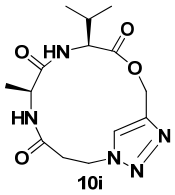
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 6.94 (d, J = 8.4 Hz, 1 NH), 6.70 (d, J = 7.2 Hz, 1 NH), 4.80 (dd, J = 2.4 Hz, 1 H), 4.71-4.65 (m, 2 H), 4.55 (q, J = 5.2 and 4.8 Hz, 1 H), 3.63 (q, J = 6.4 Hz, 2 H), 2.50-2.45 (m, 3 H), 2.25-2.20 (m, 1 H), 1.40 (d, J = 7.2 Hz, 3 H), 0.95 (q, J = 6.8 Hz, 6 H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ,172.79, 170.92, 169.97, 76.78, 75.39, 57.31, 52.46, 48.71, 47.26, 35.44, 30.92, 18.84, 18.39, 17.74ppm

IR: 3297, 2971, 2103, 1748, 1647, 1544, 1186, 994, 673 cm^{-1}

ESI-MS: $C_{14}H_{21}N_5O_4K$; Calculated: 362.1231, Found: 362.1324 (M + K)

HPLC: RT 4.49min (215 nm) and 3.92min (244 nm)



10i

(6S,9S)-9-isopropyl-6-methyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione(10i):

White Solid, mp: 258-260 ^{o}C

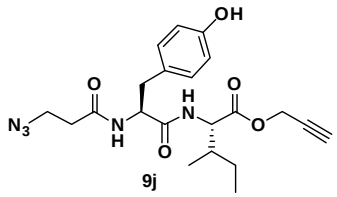
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.17-7.57 (m, 3 H), 5.32-5.08 (m, 2 H), 4.70-4.55 (m, 2 H), 4.23-4.15 (m, 1 H), 4.03-3.95 (m, 1 H), 2.74-2.33 (m, 2 H), 2.02-1.95 (m, 1 H), 1.19 (d, J = 7.2 Hz, 3 H), 0.89-0.77 (m, 6 H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 172.92, 169.96, 169.20, 143.71, 123.54, 58.19, 57.81, 50.37, 46.18, 36.33, 29.22, 19.44, 18.19, 18.02ppm

IR: 3256, 3056, 2969, 1742, 1652, 1552, 1442, 1368, 1264, 1188, 1119, 995, 777, 691cm^{-1}

ESI-MS: $C_{14}H_{21}N_5O_4Na$; Calculated: 346.1491, Found: 346.2001 (M + Na)

HPLC: RT 2.98 min (215 nm)



9j

(2S,3R)-prop-2-ynyl 2-((S)-2-(3-azidopropanamido)-3-(4-hydroxyphenyl)propanamido)-3-methyl-pentanoate (9j):

Colorless oil,

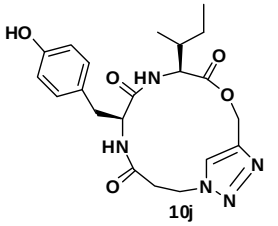
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.07 (dd, J = 8.8 & 8.4 Hz, 2H), 6.76-6.48 (m, 4H), 4.77-4.65 (m, 3H), 4.51 (q, J = 5.2 Hz, 1H), 3.58 (t, J = 6.0 & 6.4 Hz, 2H), 3.08 (d, J = 6.8 Hz, 1H), 2.99-2.97 (m, 1H), 2.51 (q, J = 2.4 Hz, 1H), 2.43 (q, J = 1.6 & 6.4 Hz, 2H), 1.87-1.85 (m, 1H), 1.40-1.37 (m, 1H), 1.124-1.11 (m, 1H), 0.90-0.88 (m, 6H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 171.34, 170.56, 170.49, 155.35, 130.44, 121.06, 115.59, 75.56, 75.52, 56.70, 54.71, 52.57, 47.20, 37.75, 37.68, 35.56, 25.05, 15.29, 11.52ppm

IR: 3410, 3299, 2964, 2923, 2104, 1746, 1718, 1699, 1647, 1548, 1517, 1220, 1198, 1145, 1020cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_5Na$; Calculated: 452.1910, Found: 452.2547 (M + Na)

HPLC: RT 4.41min (215 nm) and 7.28 min (244 nm)



10j

(6S,9S)-9-sec-butyl-6-(4-hydroxybenzyl)-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione (10j):

White Solid, mp: 268-270 ^{o}C

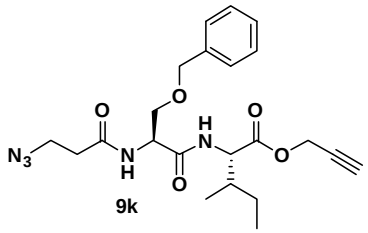
^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 9.22 (s, 1H), 7.81 (d, J = 9.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.53 (s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 6.60 (d, J = 8.4 Hz, 2H), 5.23 (d, J = 6.4 Hz, 2H), 4.58-4.49 (m, 2H), 4.35 (d, J = 6.0Hz, 1H), 3.95 (t, J = 10 and 9.6 Hz, 1H), 2.73-2.62 (m, 2H), 1.77-1.75 (m, 1H), 1.28-1.24 (m, 1H), 0.91-0.72 (m, 7H) ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 171.07, 169.68, 168.93, 156.01, 129.88, 127.08, 123.20, 115.11, 57.64, 56.71, 55.64, 46.27, 36.97, 36.53, 34.61, 23.97, 15.50, 10.35 ppm

IR: 3453, 2969, 1748, 1637, 1540, 1508, 1098, 608cm^{-1}

ESI-MS: $C_{21}H_{27}N_5O_5Na$ Calculated: 452.1910, Found: 452.2681 (M + Na)

HPLC: RT 3.16 min (215 nm)



9k

(2S,3R)-prop-2-ynyl 2-((S)-2-(3-azidopropanamido)-3-(benzyloxy)propanamido)-3-methylpentanoate (9k):

Colorless oil,

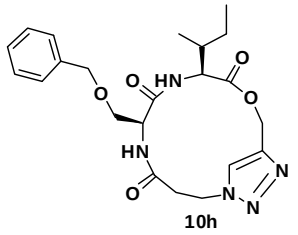
^{1}H-NMR ($CDCl_3$, 400 MHz) δ, 7.33-7.26 (m, 6H), 6.89 (d, J = 6.8 Hz, 1H), 4.77-4.55 (m, 6H), 3.89 (q, J = 4.0 Hz, 1H), 3.62-3.55 (m, 3H), 2.51-2.46 (m, 3H), 1.92-1.88 (m, 1H), 1.38-1.34 (m, 1H), 1.09-1.06 (m, 1H), 0.90-0.87 (m, 6H)ppm

^{13}C-NMR ($CDCl_3$, 100 MHz) δ, 170.70, 170.23, 170.21, 137.25, 128.44, 127.94, 127.93, 76.89, 75.46, 73.50, 69.55, 56.75, 52.44, 52.27, 47.26, 37.54, 35.49, 24.86, 15.45, 11.52ppm

IR: 3454, 2966, 2104, 1749, 1717, 1645, 1550, 1184, 1109, 1025, 698cm^{-1}

ESI-MS: $C_{22}H_{29}N_5O_5Na$ Calculated: 466.2066, Found: 466.2498 (M + Na)

HPLC: RT 17.88 min (215 nm) and 13.60 min (244 nm)



10h

(6S,9S)-6-(benzyloxymethyl)-9-sec-butyl-11-oxa-1,5,8,14,15-pentaazabicyclo[11.2.1]hexadeca-13(16),14-diene-4,7,10-trione (10k):

White Solid, mp: 226-228 ^{o}C

^{1}H-NMR (DMSO-d_6, 400 MHz) δ, 8.02 (d, J = 9.2 Hz, 1H), 7.68 (s, 1H), 7.59 (d, J = 9.6 Hz, 1H), 7.36-7.26 (m, 5H), 5.28 (m, 2H), 4.69-4.66 (m, 1H), 4.59-4.45 (m, 4H), 4.07 (t, J = 9.6 & 10 Hz, 1H), 3.65 (q, J = 4.8 Hz, 1H), 3.50-3.47 (m, 1H), 2.71-2.69 (m, 2H), 1.76-1.74 (m, 1H), 1.40-1.37 (m, 1H), 0.94-0.72 (m, 7H)ppm

^{13}C-NMR (DMSO-d_6, 100 MHz) δ, 170.10, 169.95, 169.65, 143.94, 138.25, 128.64, 127.95, 123.53, 72.73, 70.33, 58.10, 57.49, 54.47, 46.58, 36.37, 35.24, 24.17, 15.81, 10.78ppm

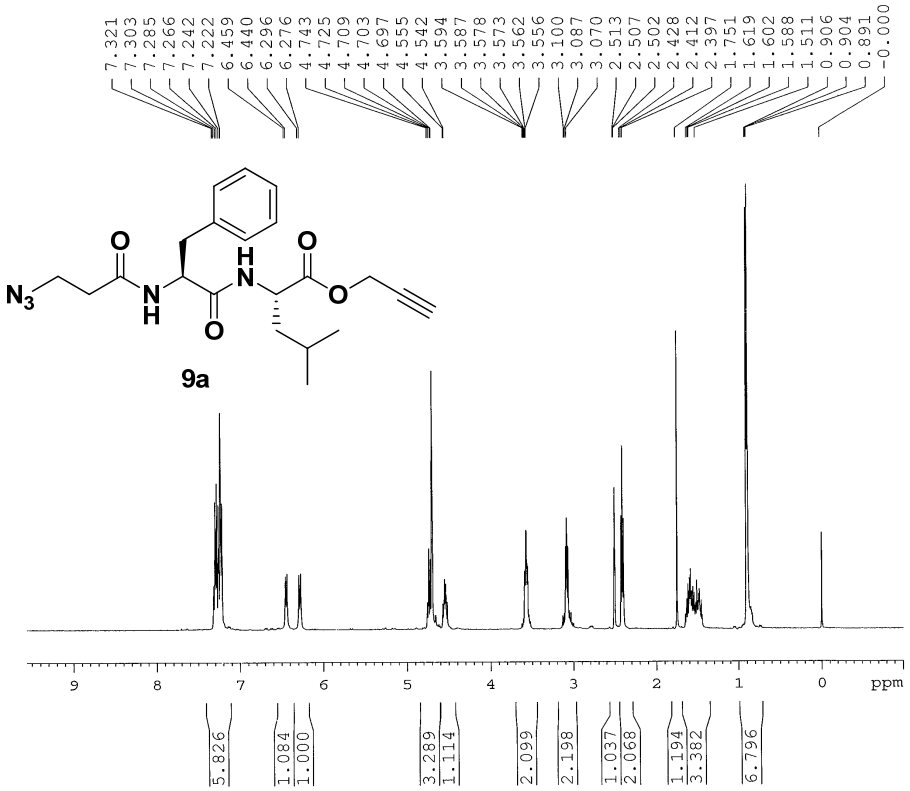
IR: 3453, 2969, 1751, 1636, 1538, 1508, 1087, 608cm^{-1}

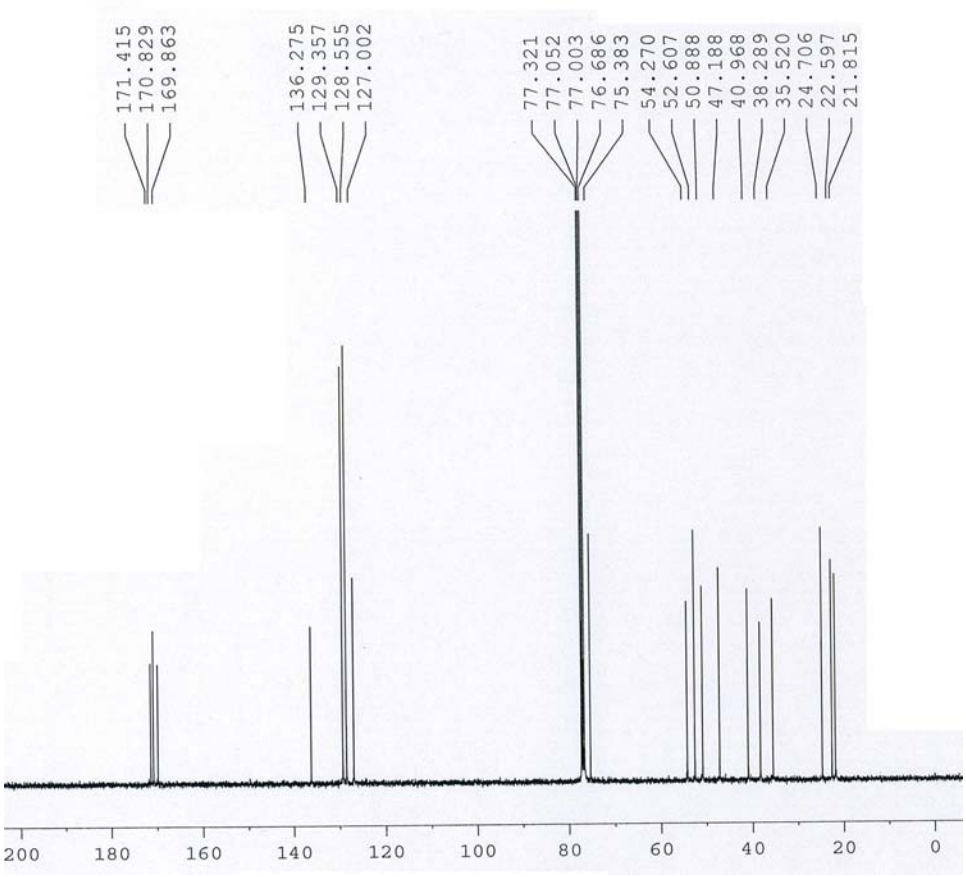
ESI-MS: $C_{22}H_{29}N_5O_5Na$ Calculated: 466.2066, Found: 466.2875 (M + Na)

HPLC: RT 6.88 min (215 nm)

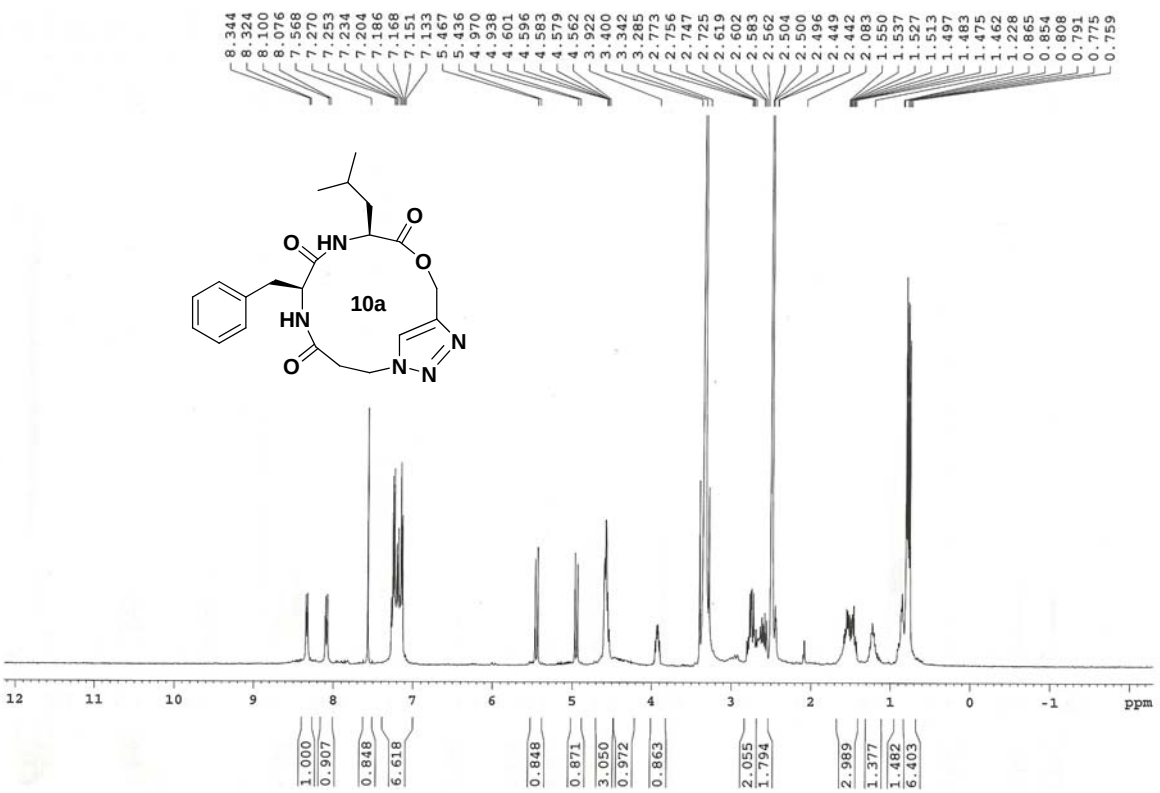
4) ^{1}H-NMR and ^{13}C-NMR Spectra of 9a-k and 10a-k

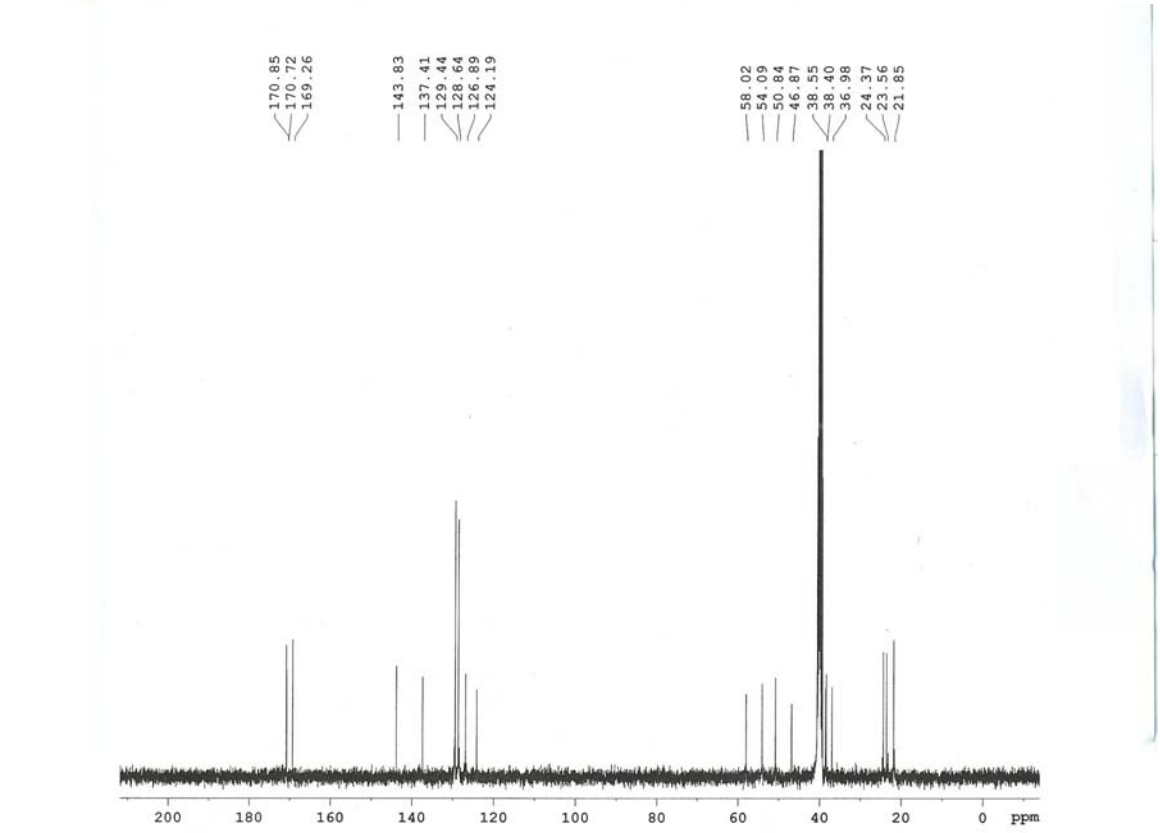
^{1}H & ^{13}C-NMR of 9a in $CDCl_3$



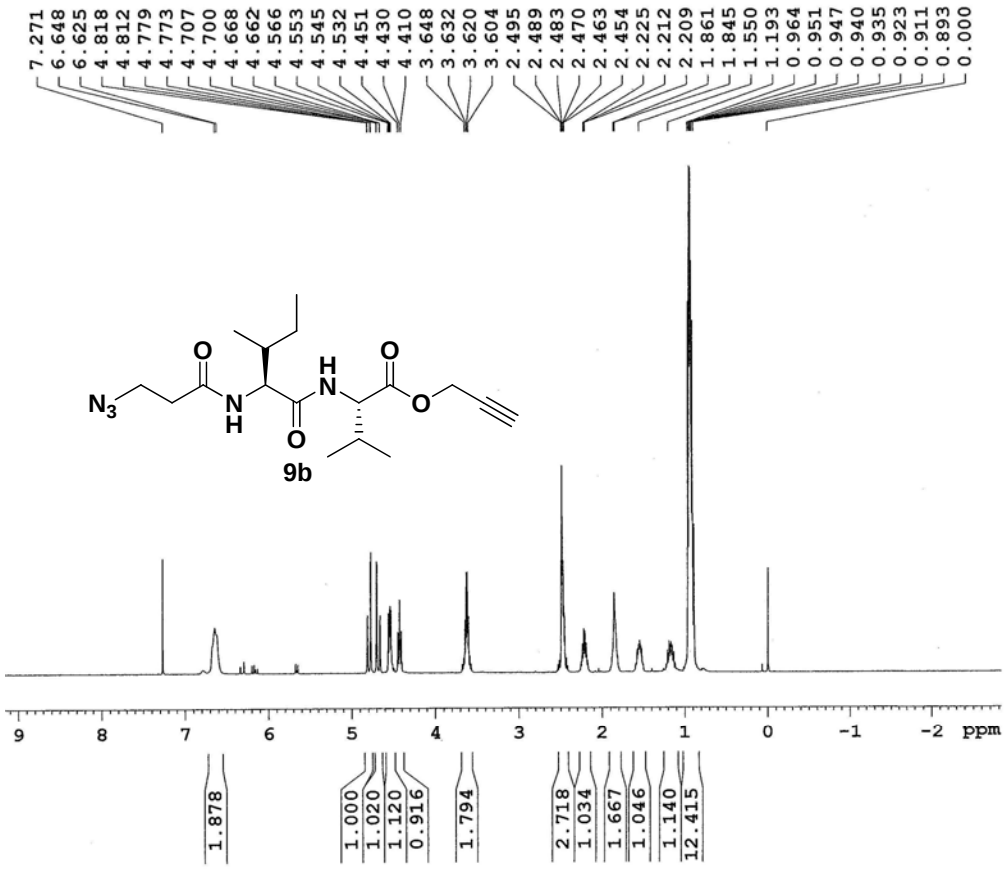


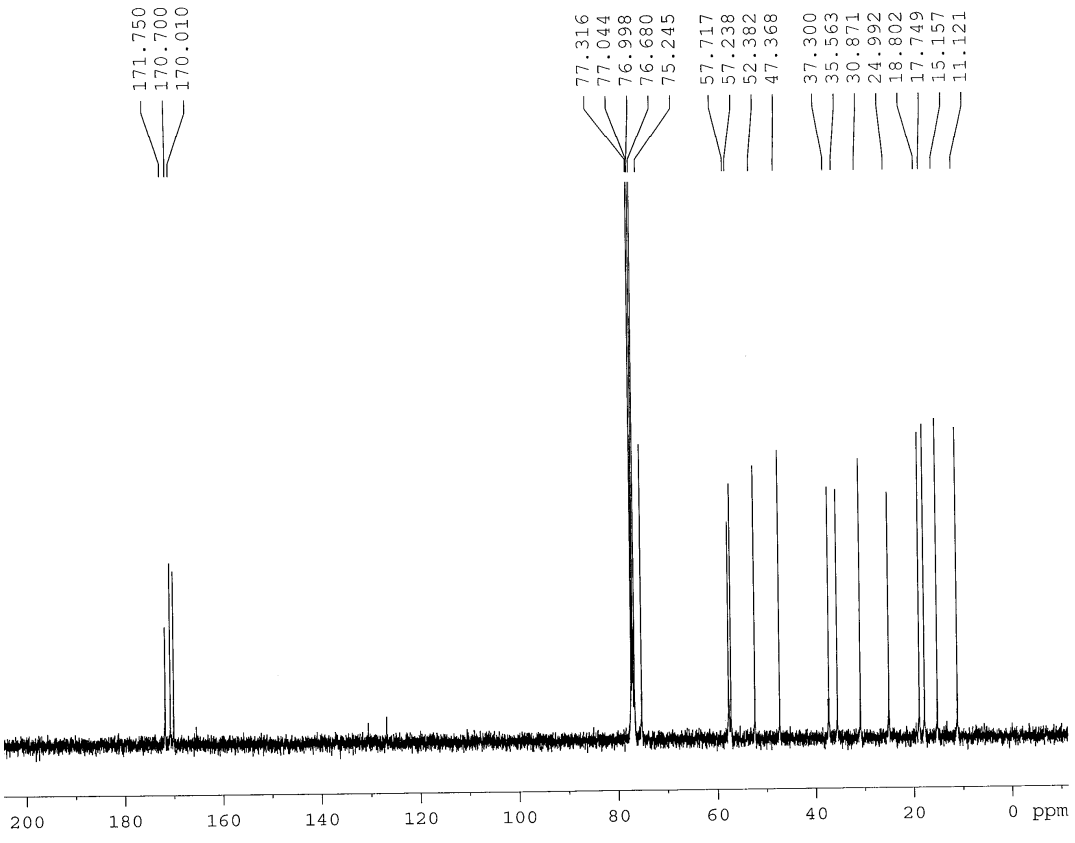
^{1}H & ^{13}C-NMR of 10a in DMSO-d6



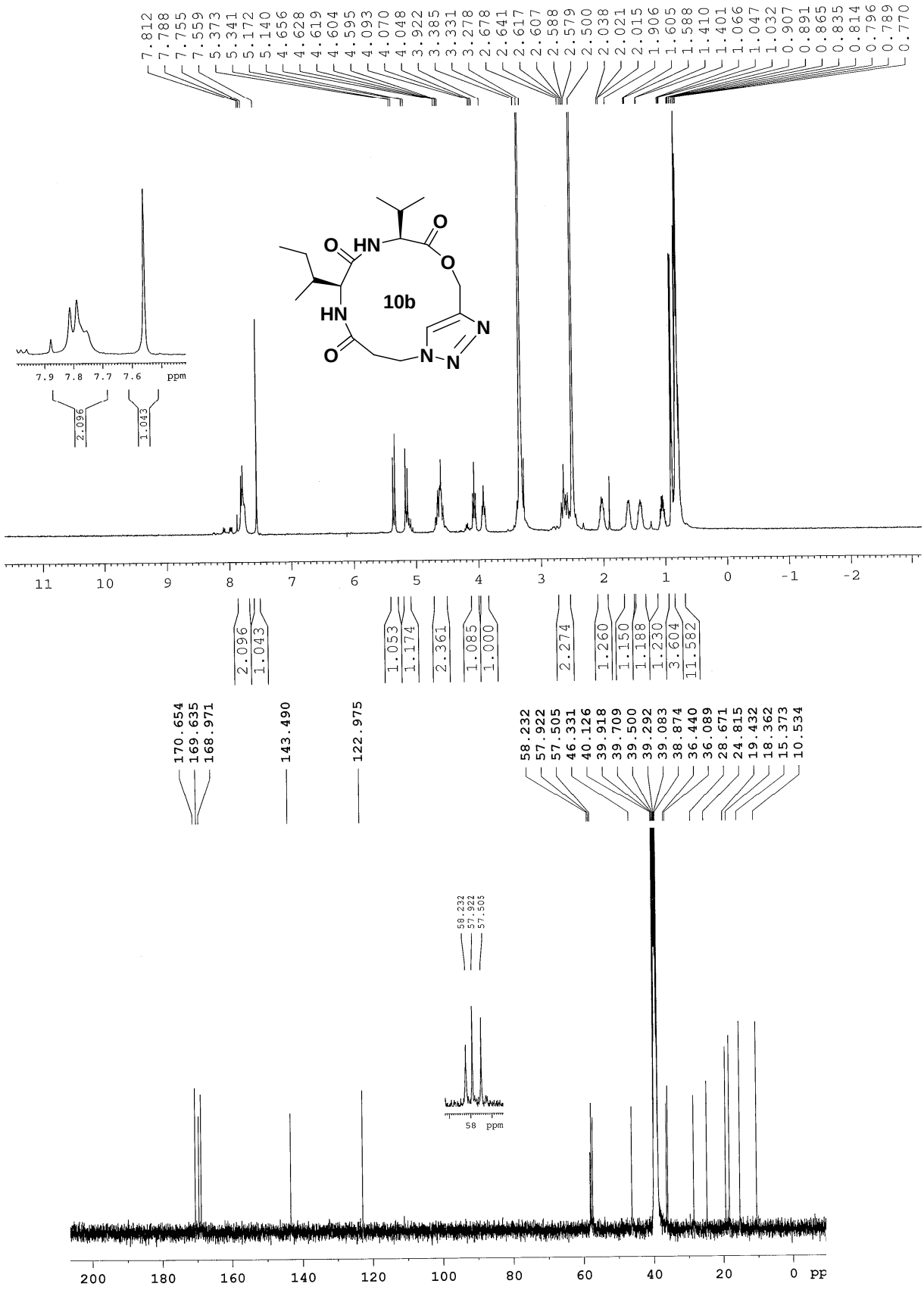


^{1}H & ^{13}C NMR of 9b in $CDCl_3$

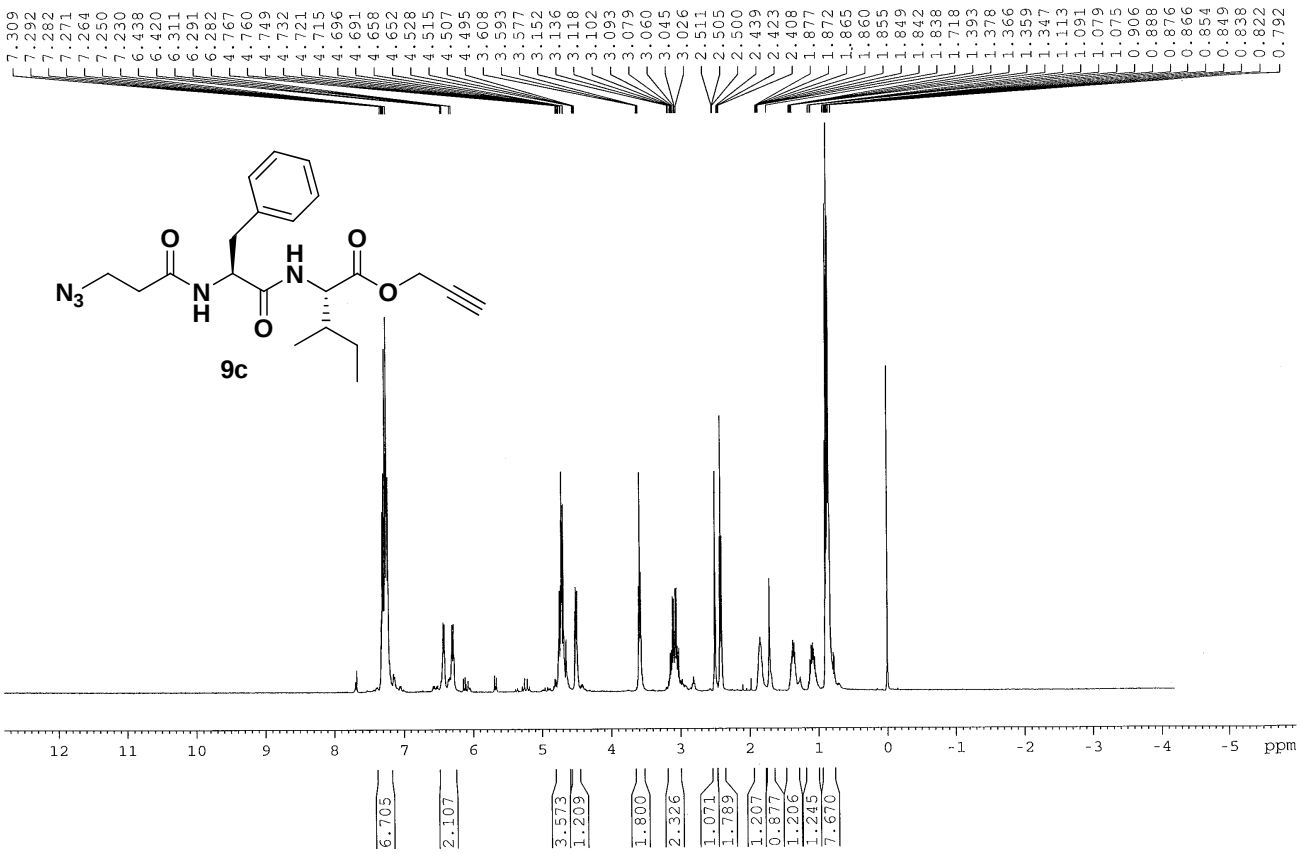


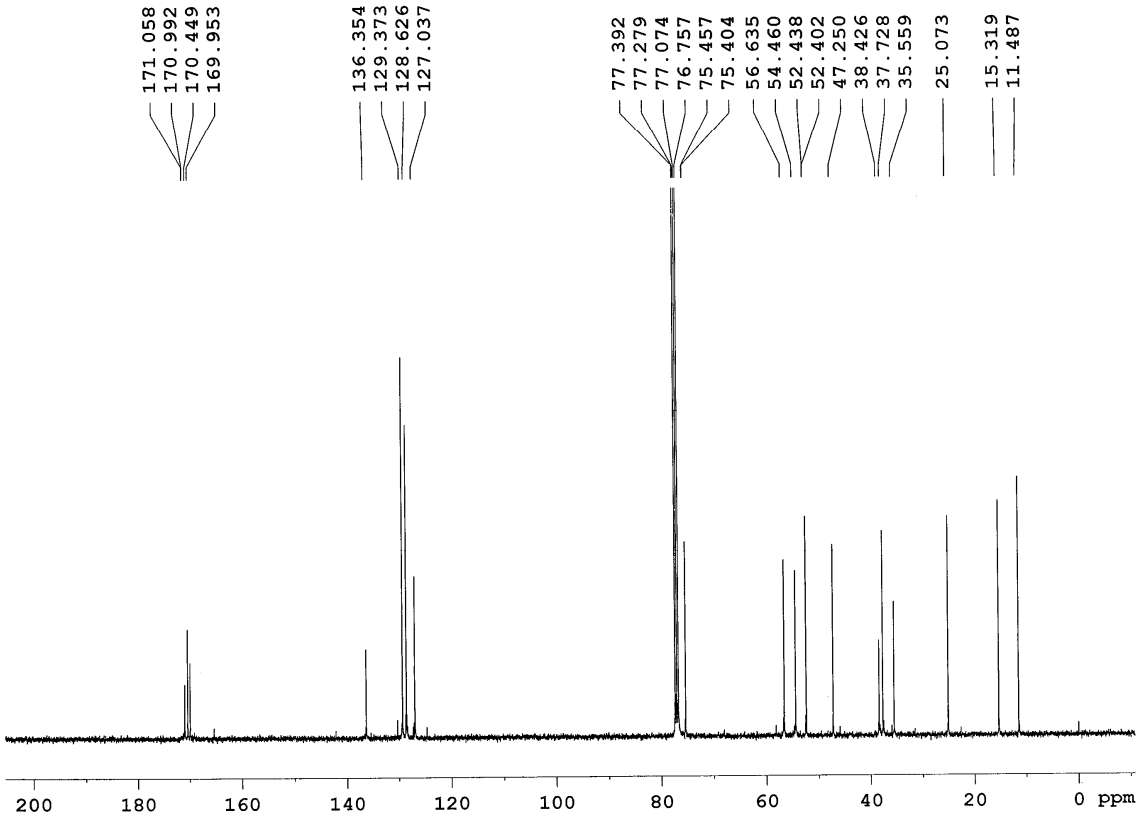


^{1}H & ^{13}C NMR of 10b in DMSO-d_6

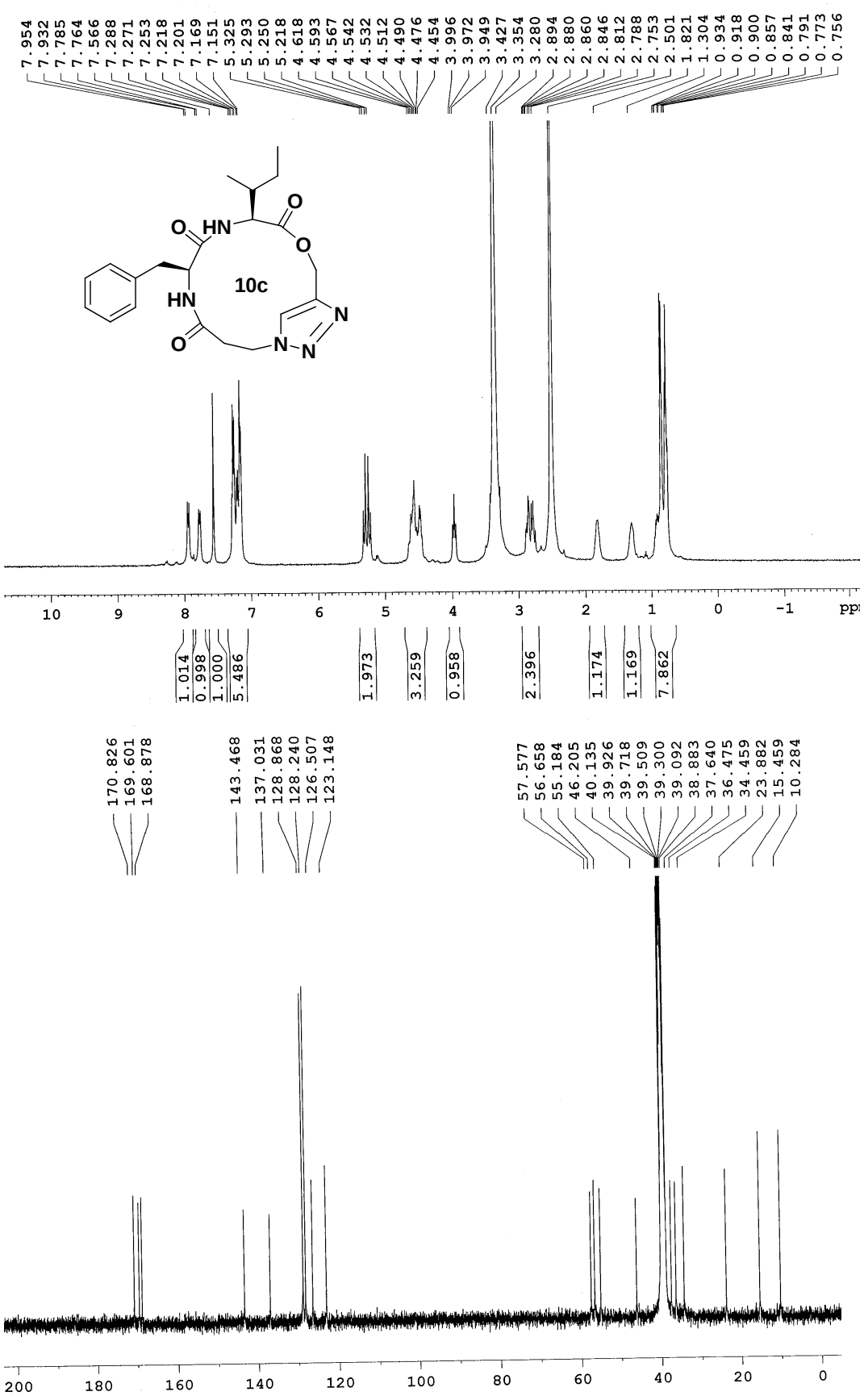


^{1}H & ^{13}C NMR of 9c in $CDCl_3$





^{1}H & ^{13}C NMR of 10c in DMSO-d_6



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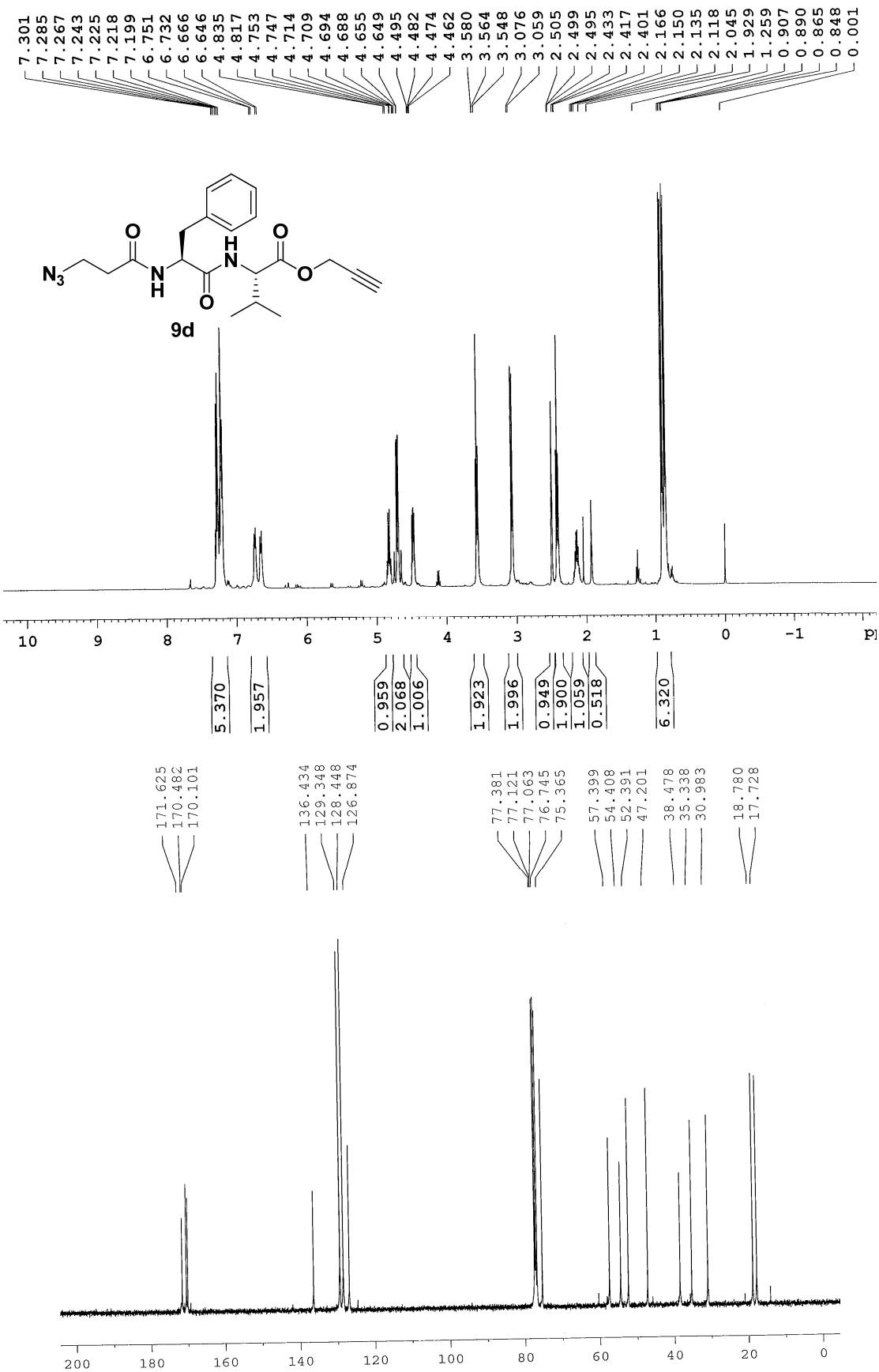
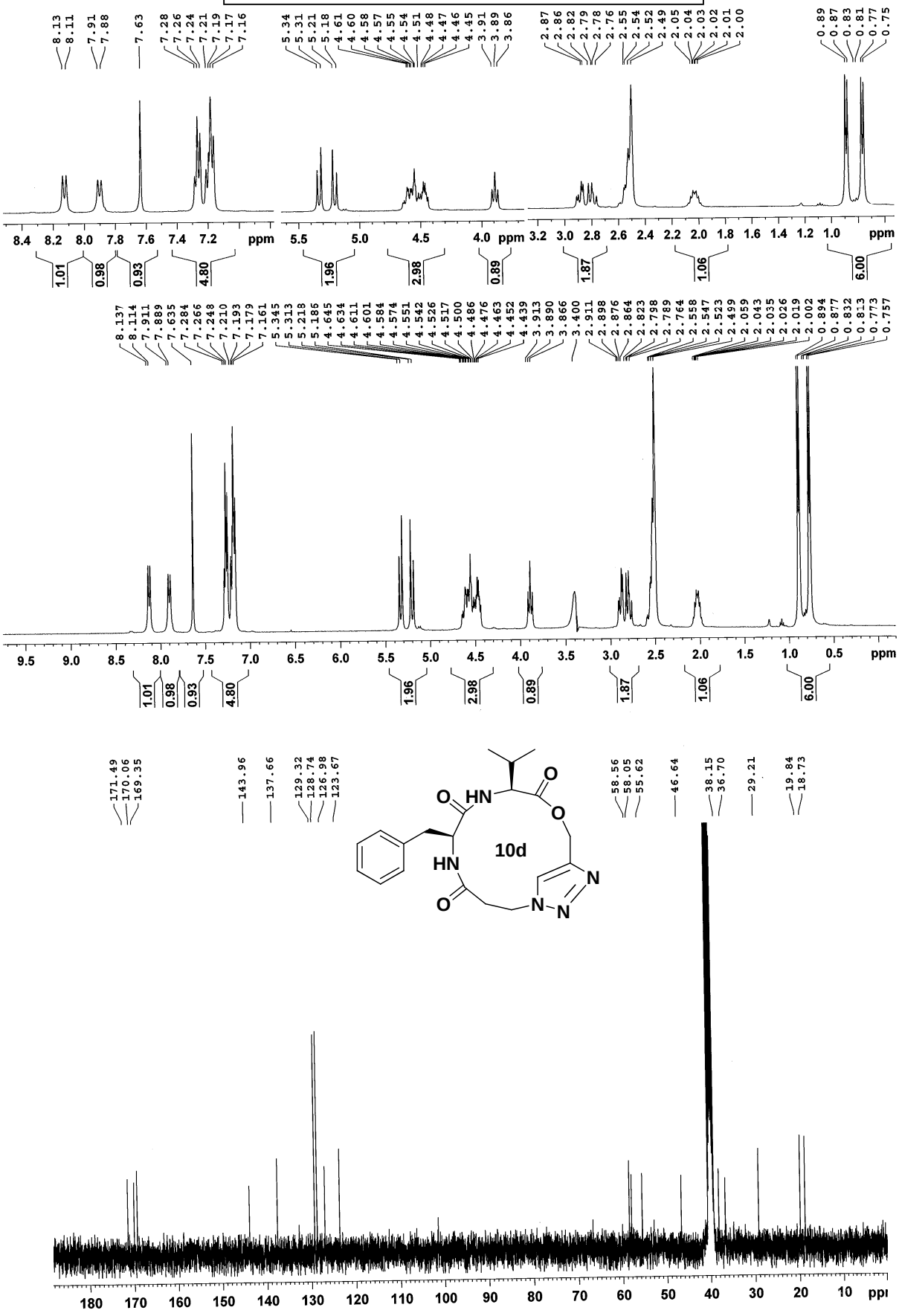
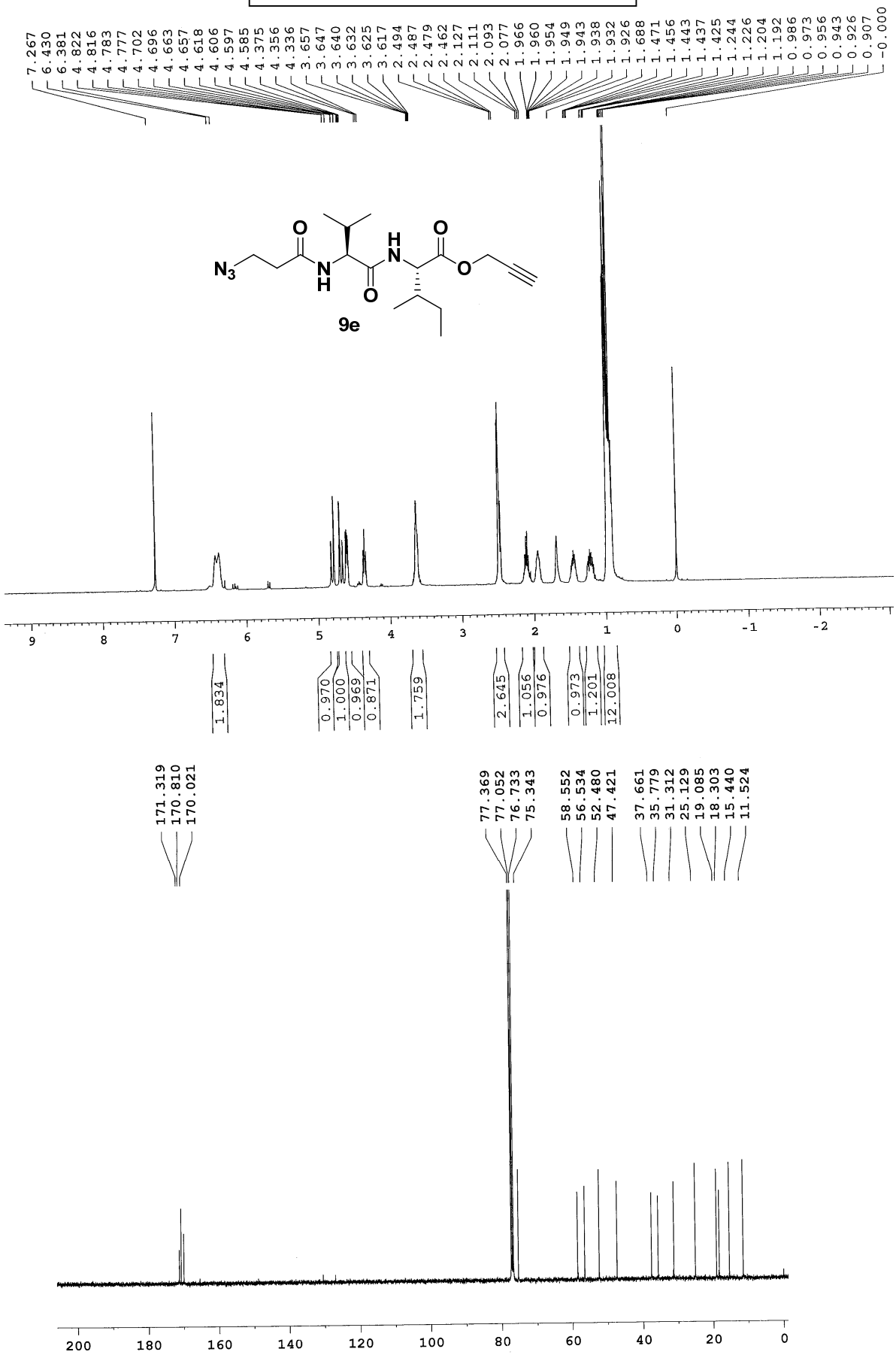


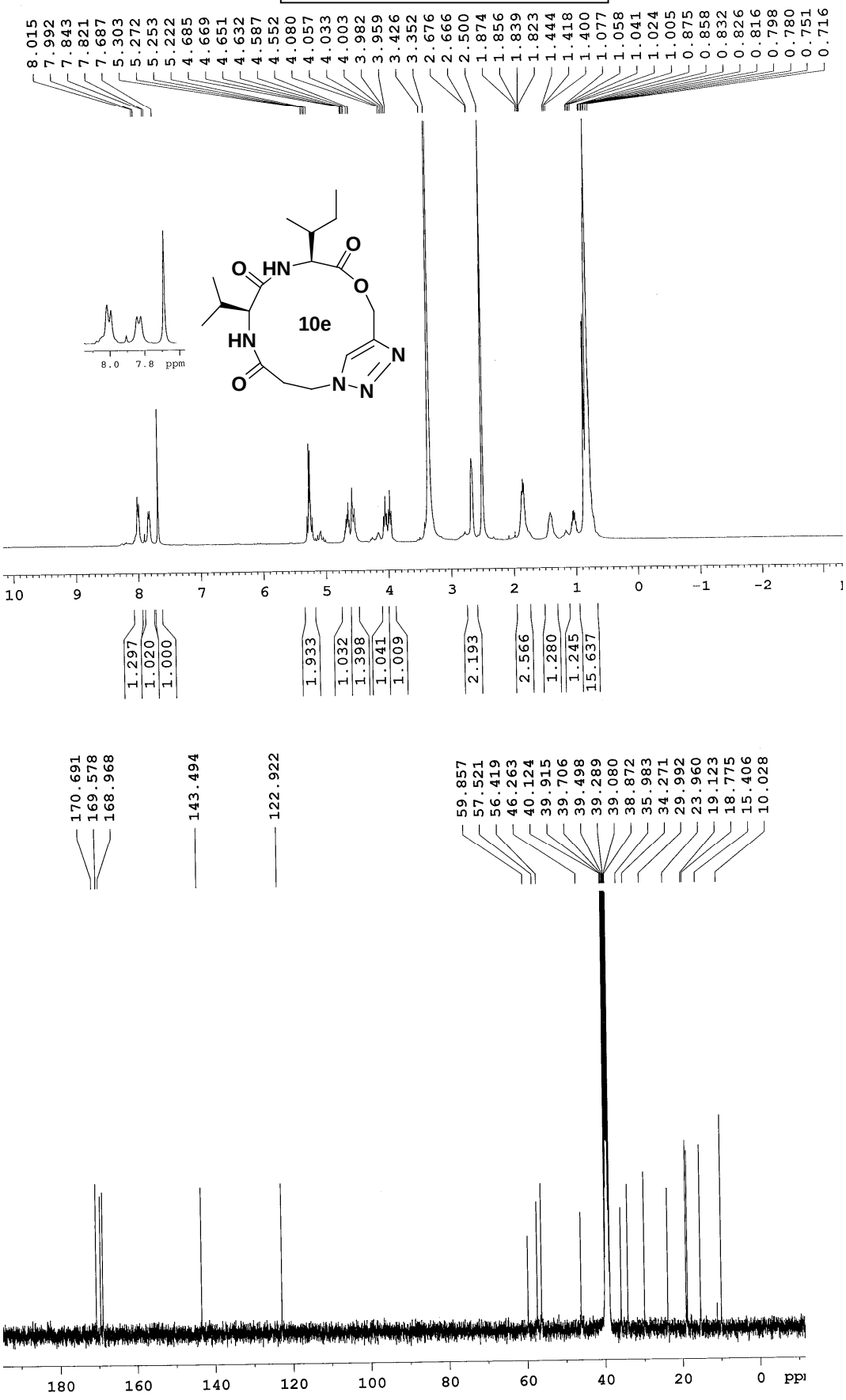
^{1}H & ^{13}C NMR of 10d in DMSO-d_6



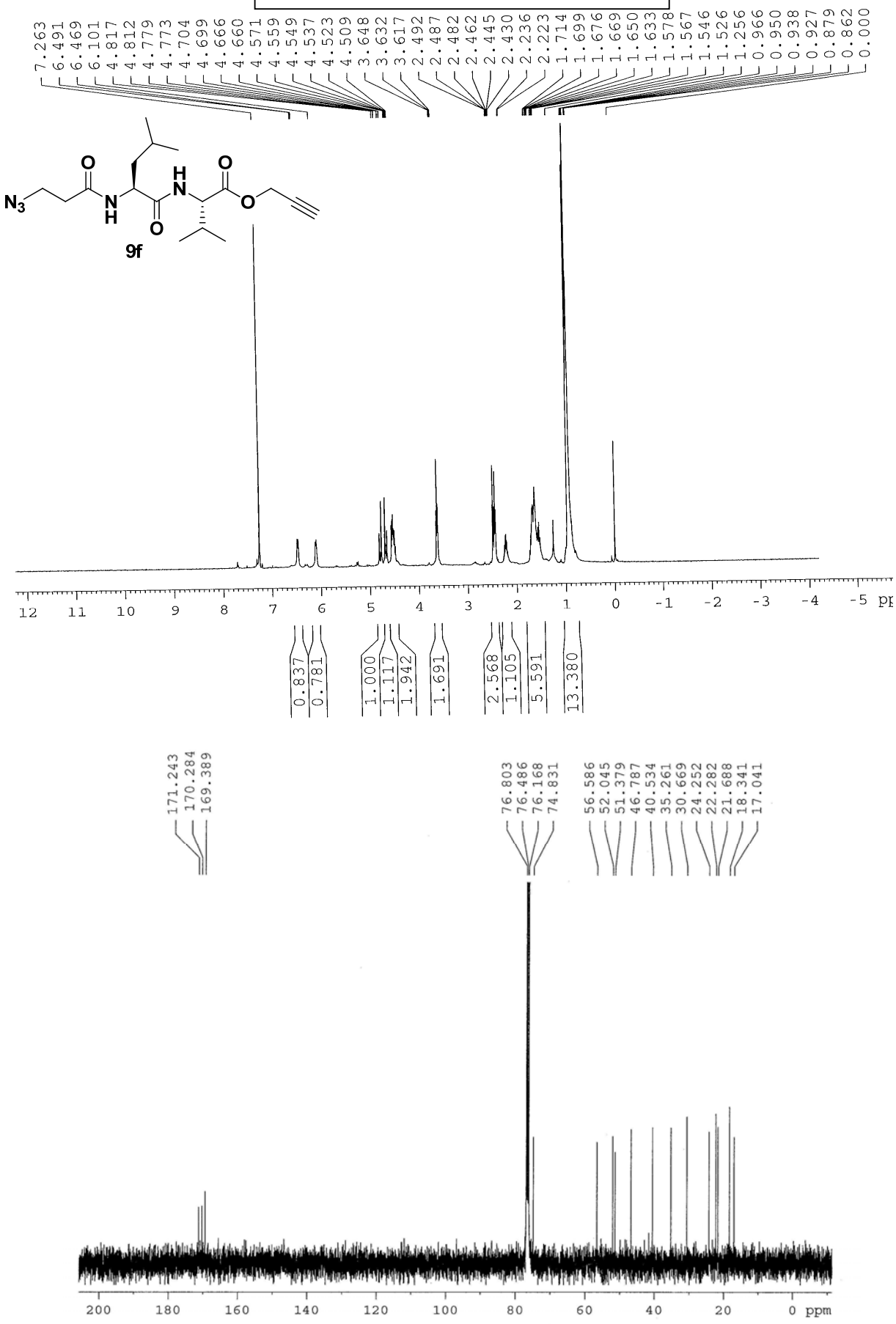
^{1}H & ^{13}C NMR of 9e in $CDCl_3$



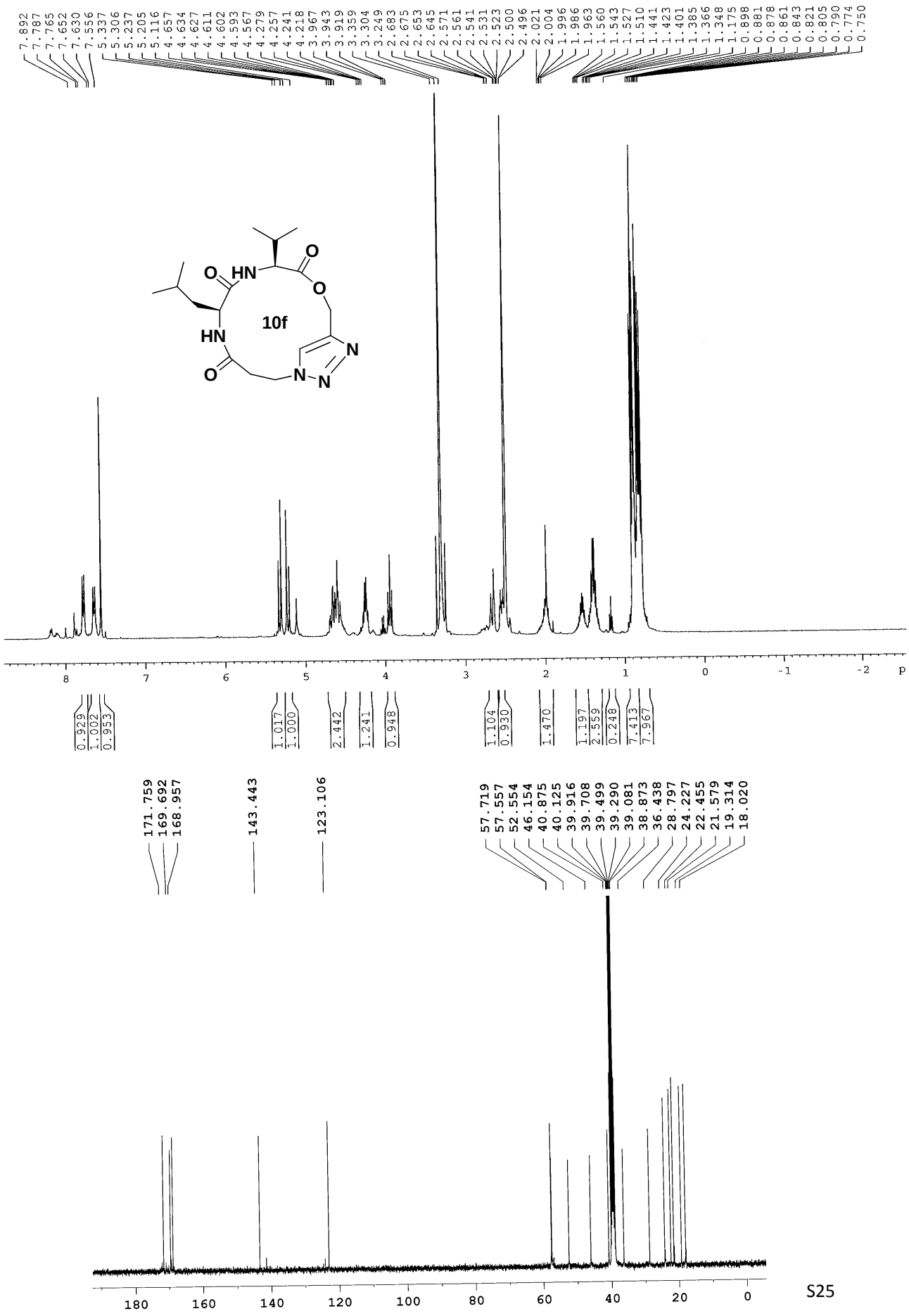
^{1}H & ^{13}C NMR of 10e in DMSO-d_6



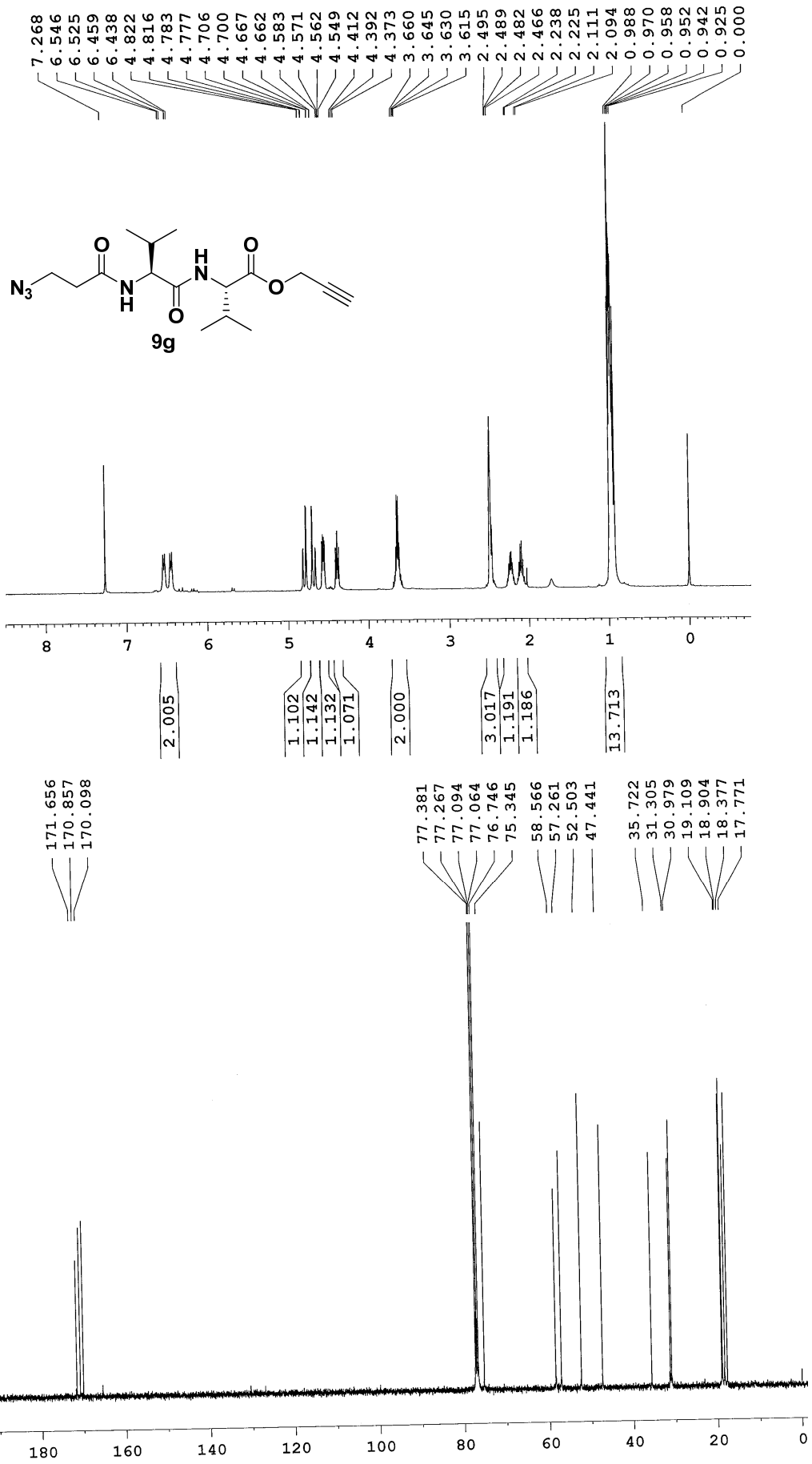
^{1}H & ^{13}C NMR of 9f in $CDCl_3$



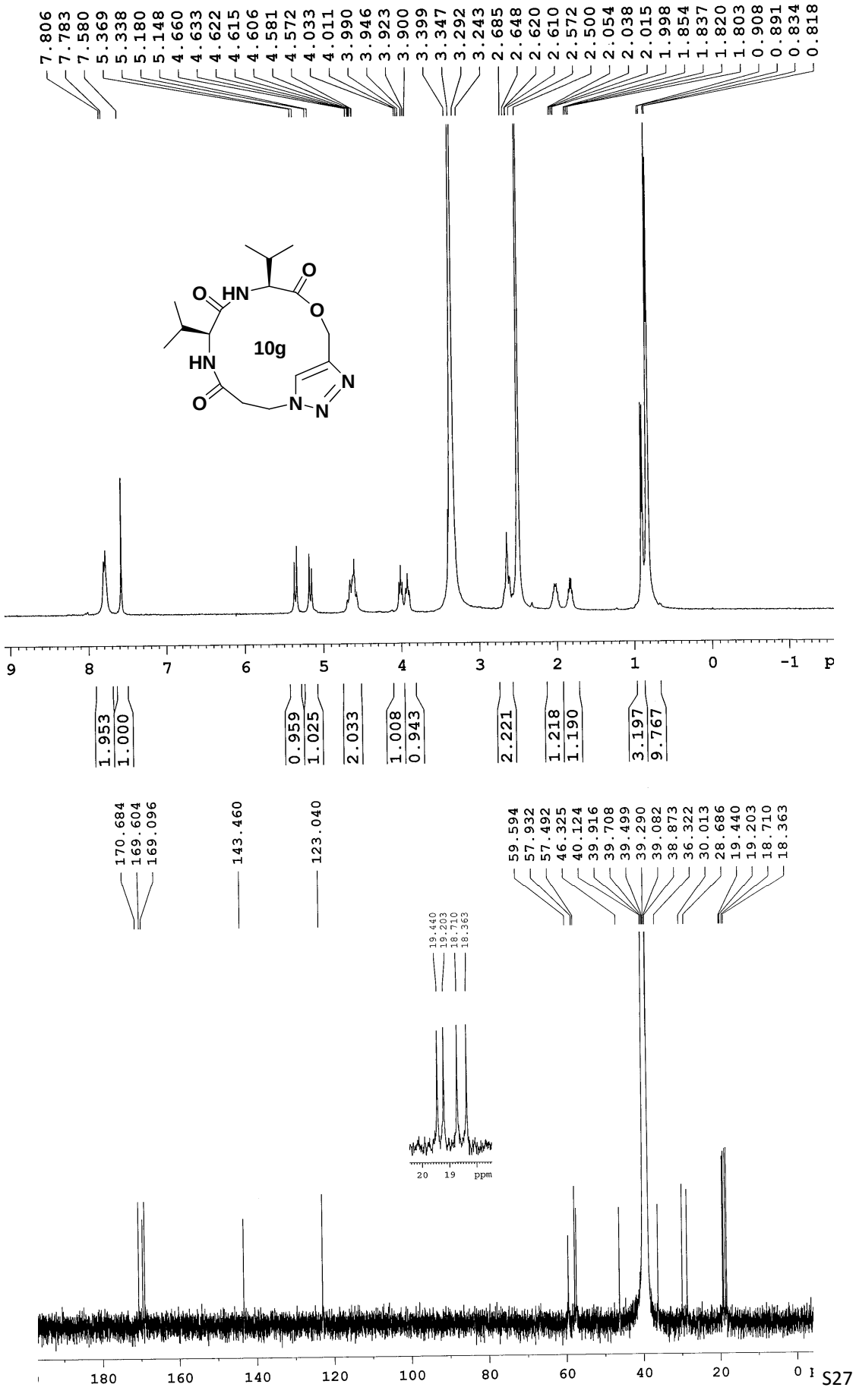
^{1}H & ^{13}C NMR of 10f in DMSO-d_6



^{1}H & ^{13}C NMR of 9g in $CDCl_3$



^{1}H & ^{13}C NMR of 10g in DMSO-d_6



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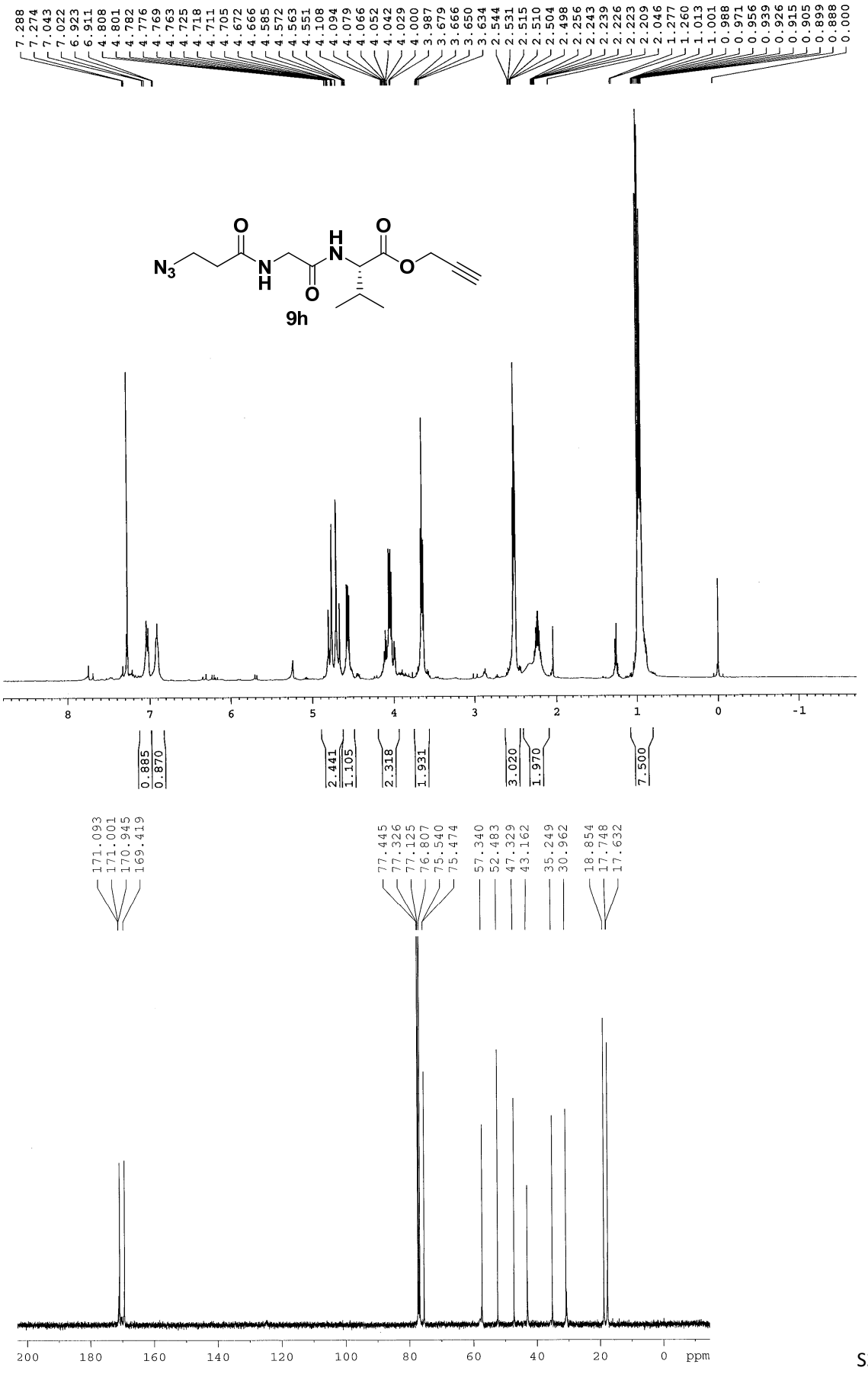

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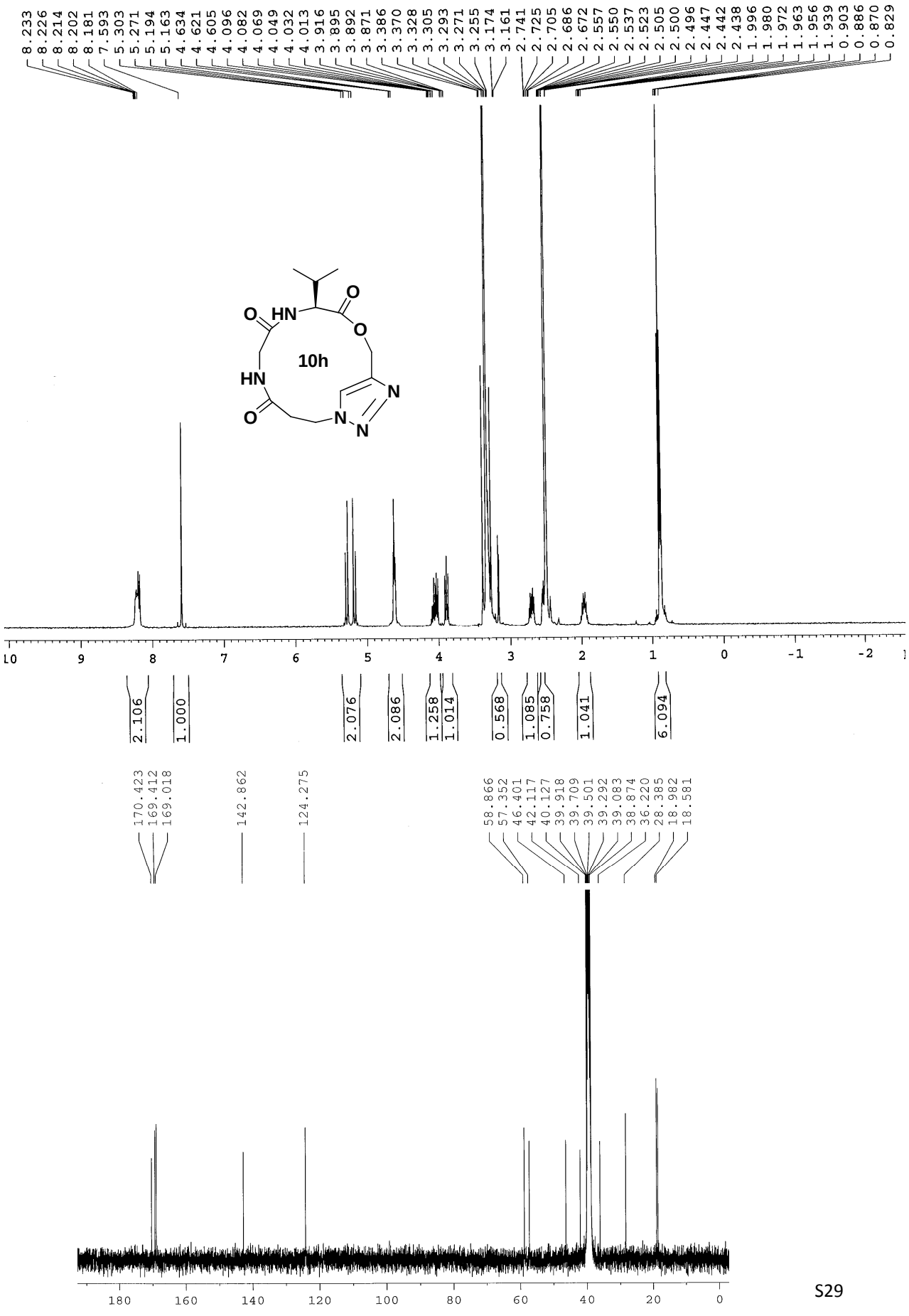
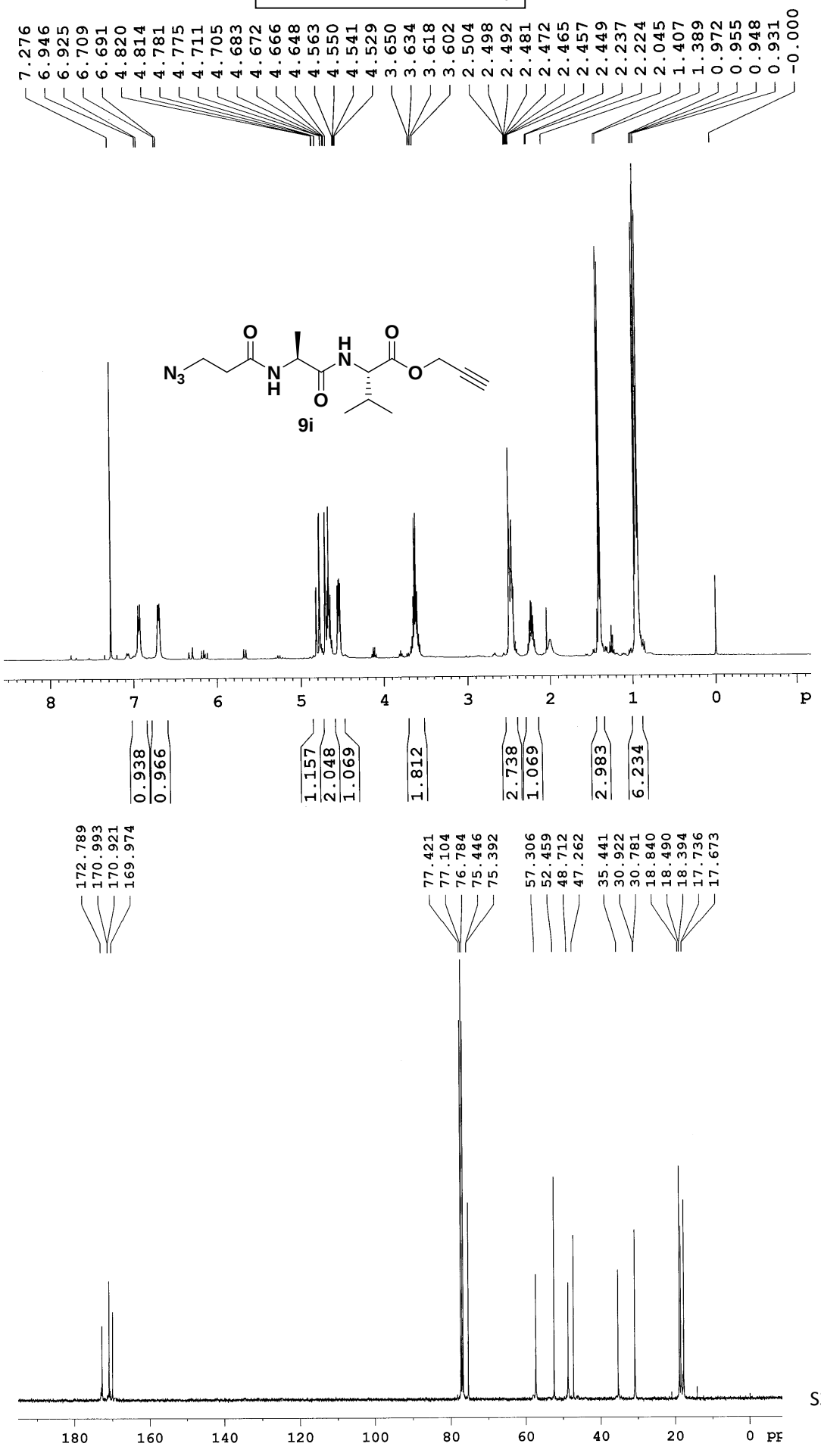
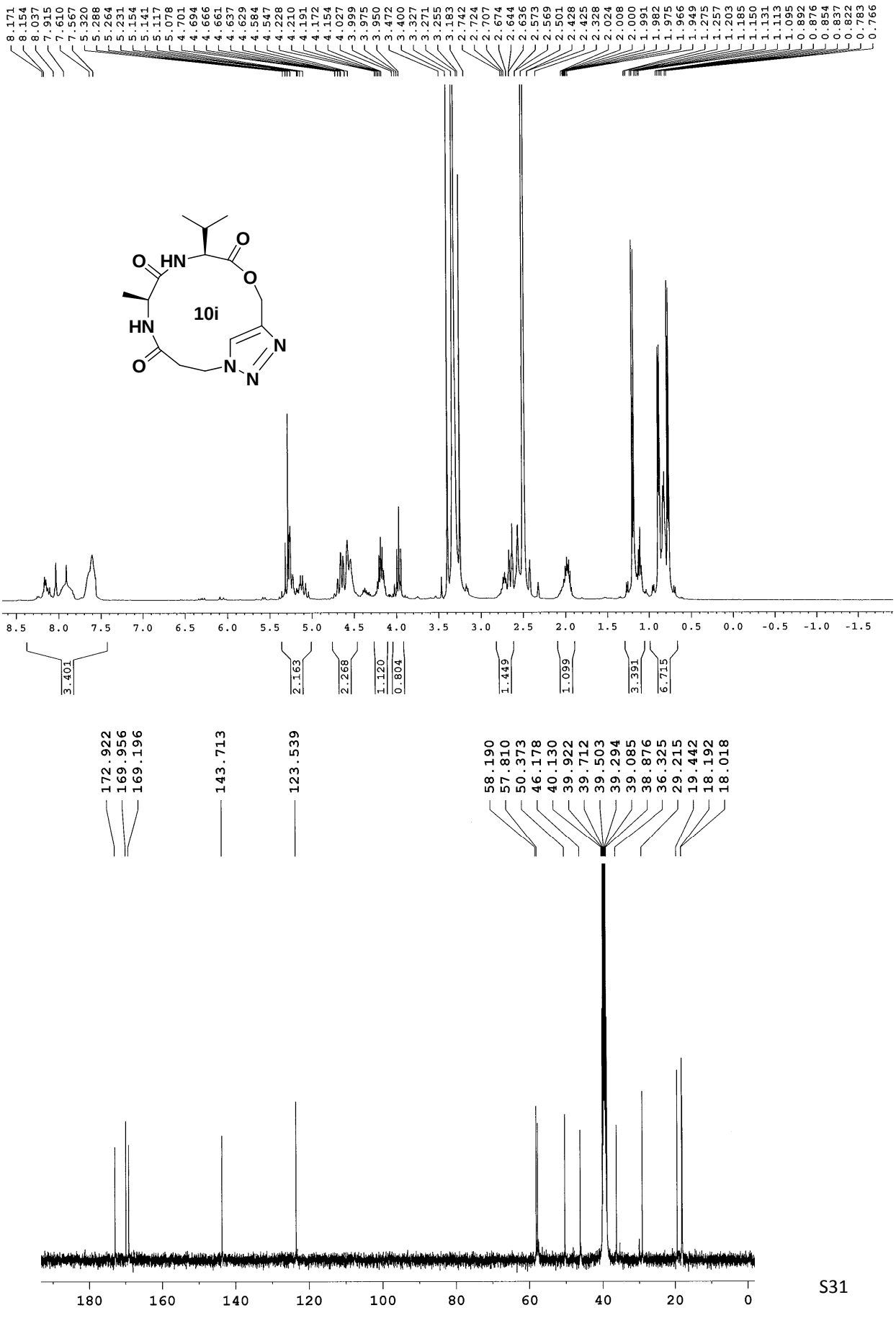


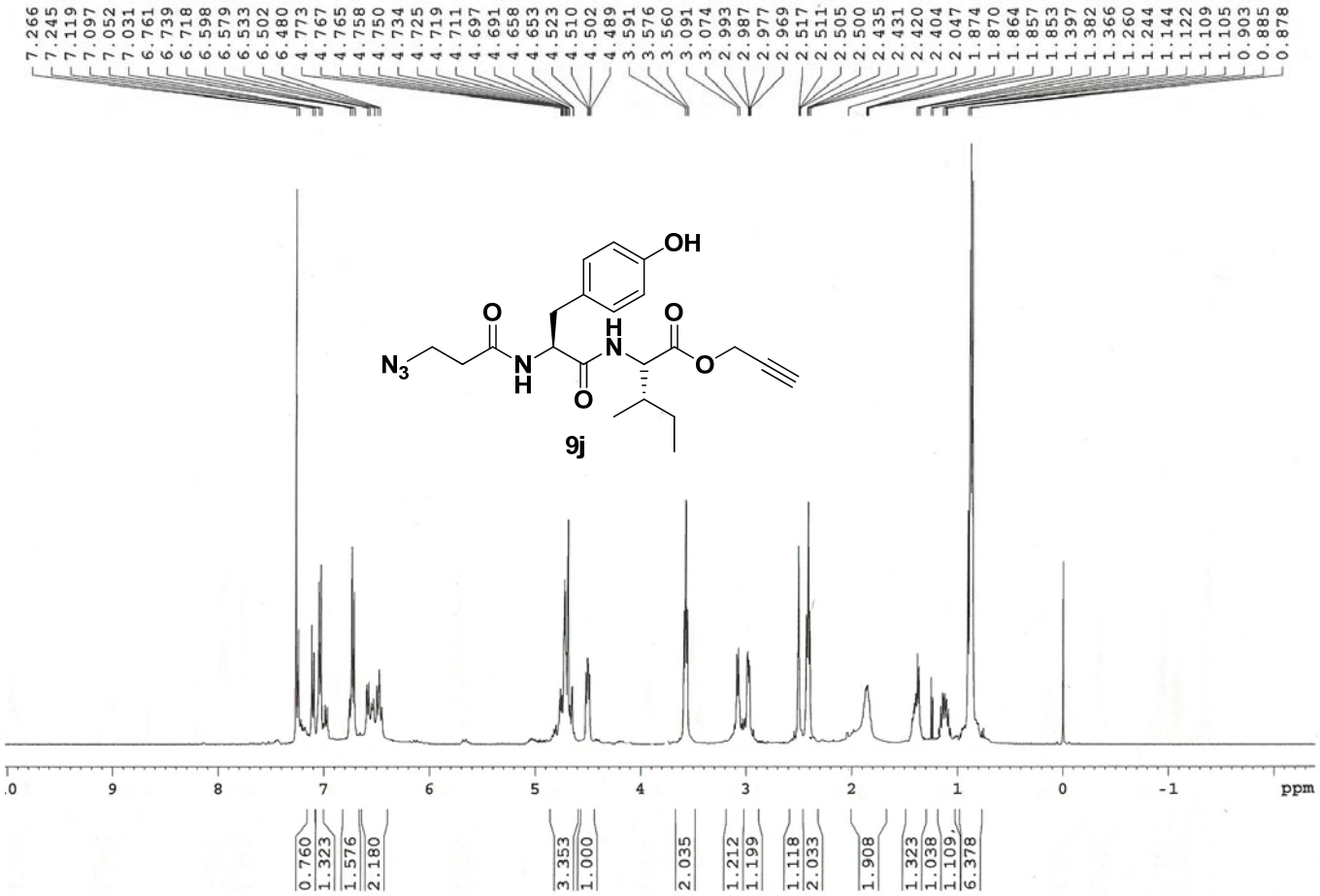
^{1}H & ^{13}C NMR of 9i in $CDCl_3$

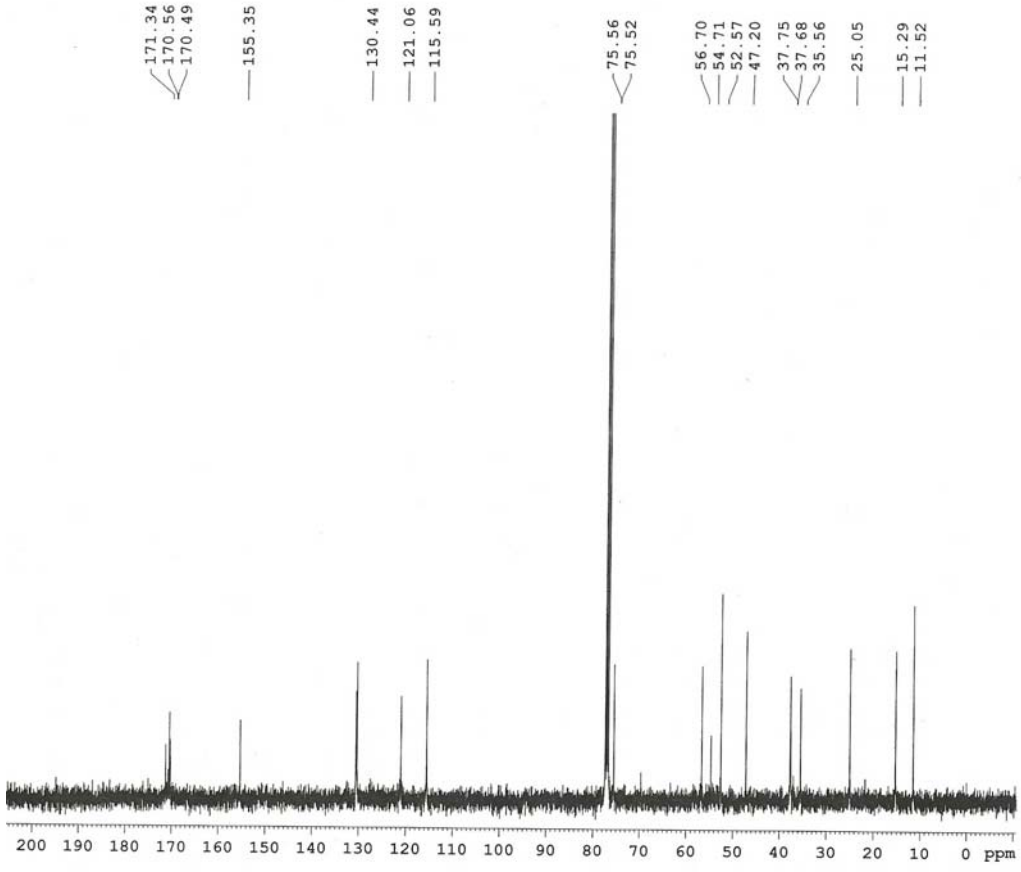


^{1}H & ^{13}C NMR of 10i in DMSO-d_6

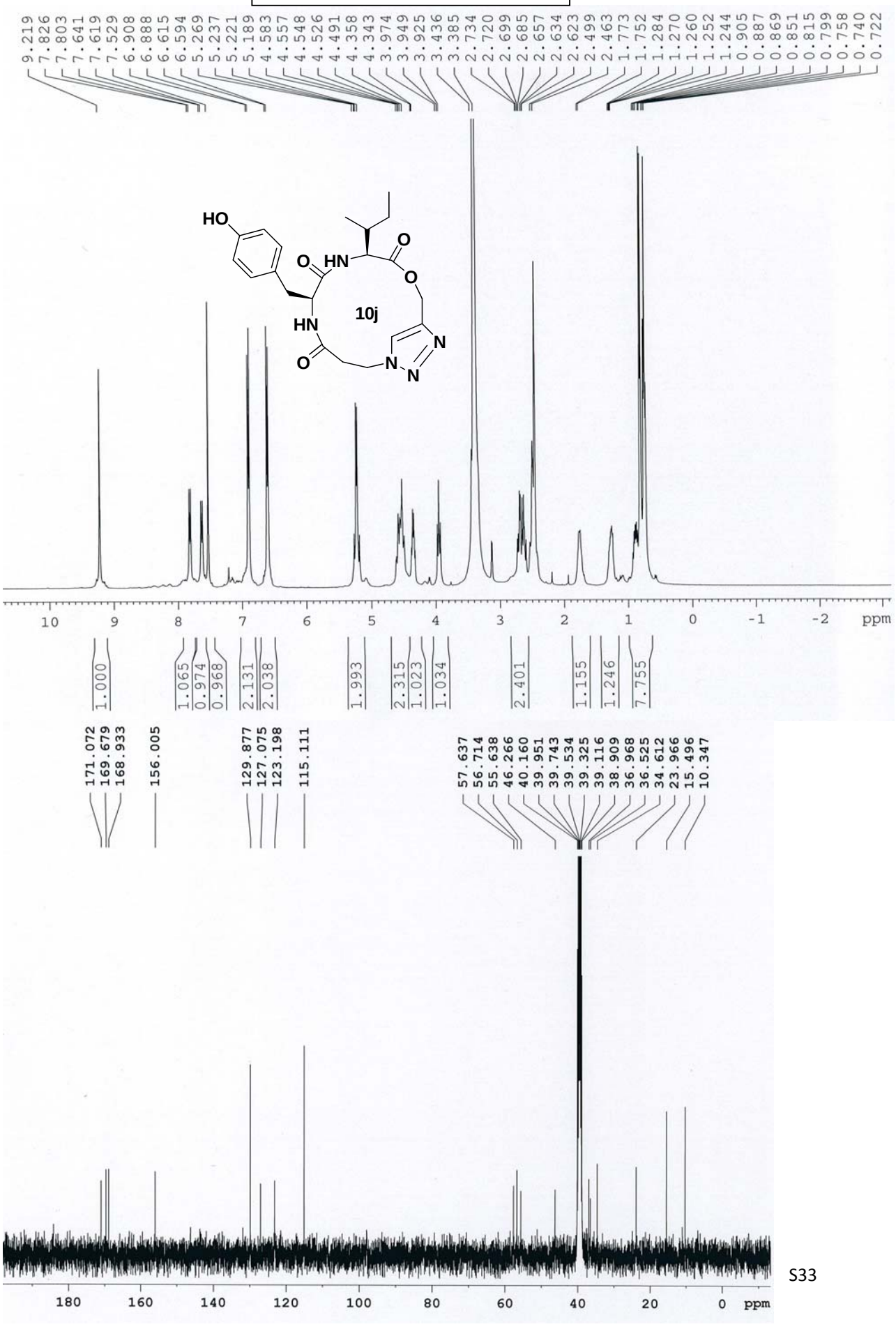


^{1}H & ^{13}C NMR of 9j in $CDCl_3$

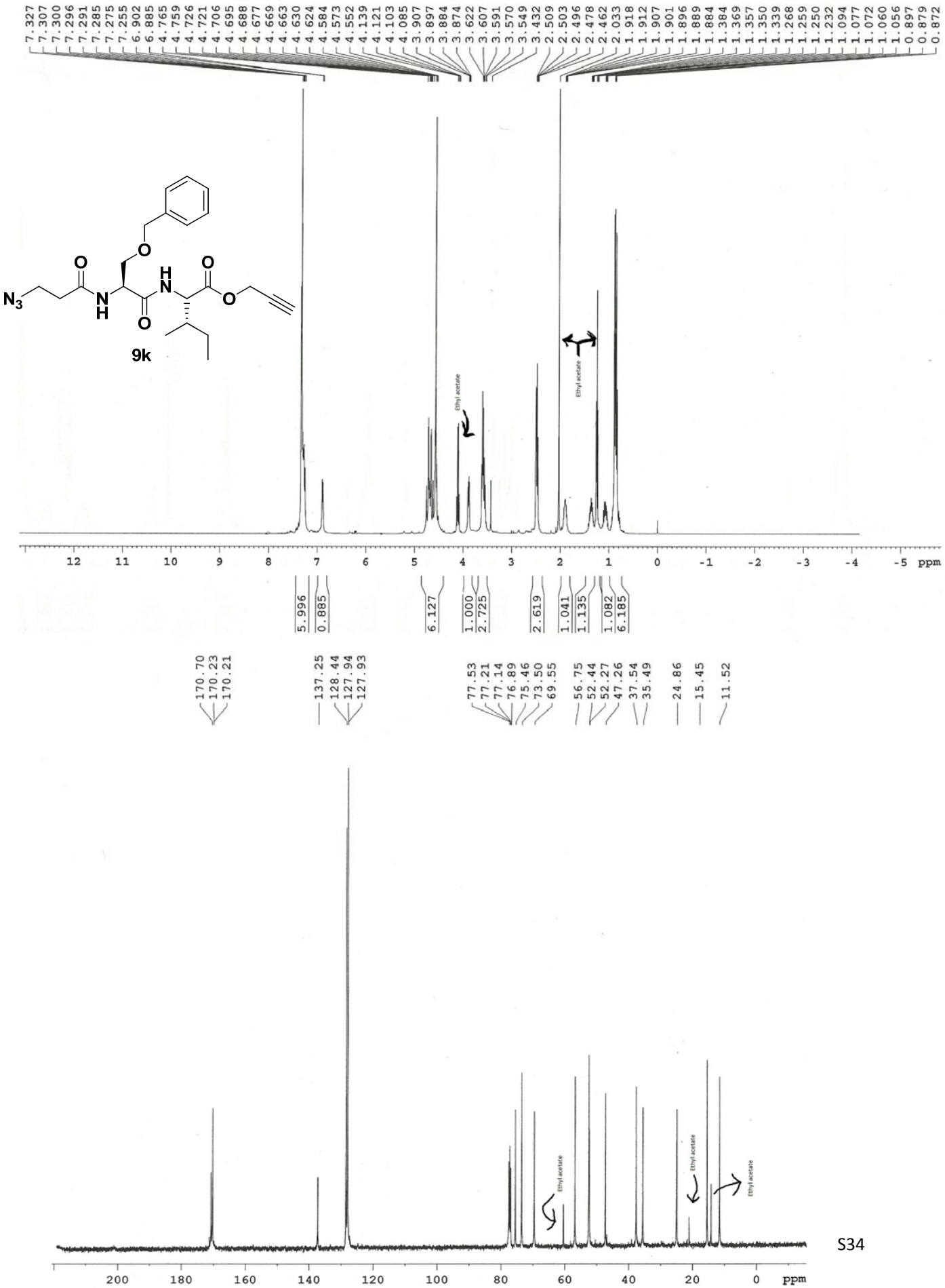




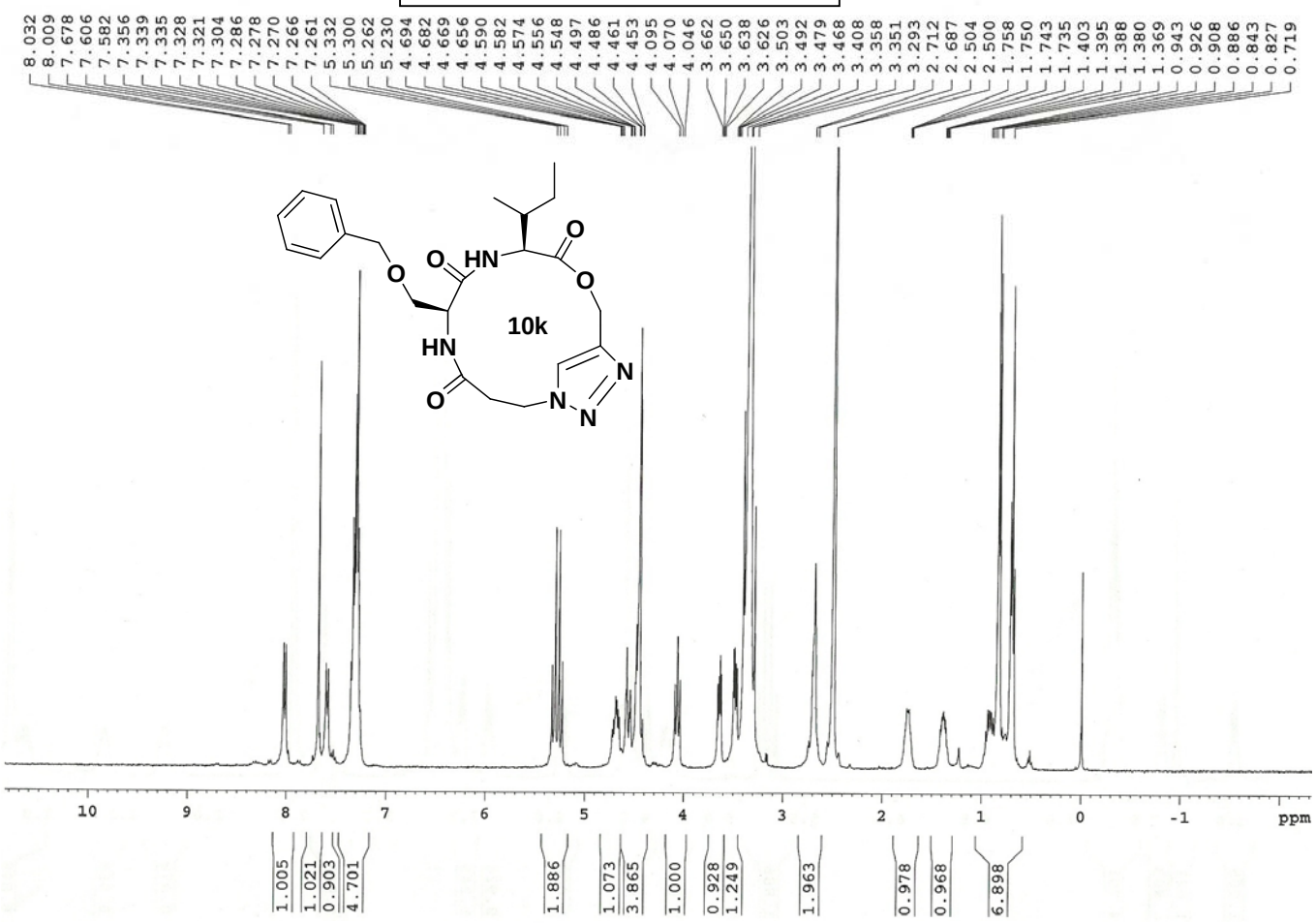
^{1}H & ^{13}C NMR of 10j in DMSO-d_6

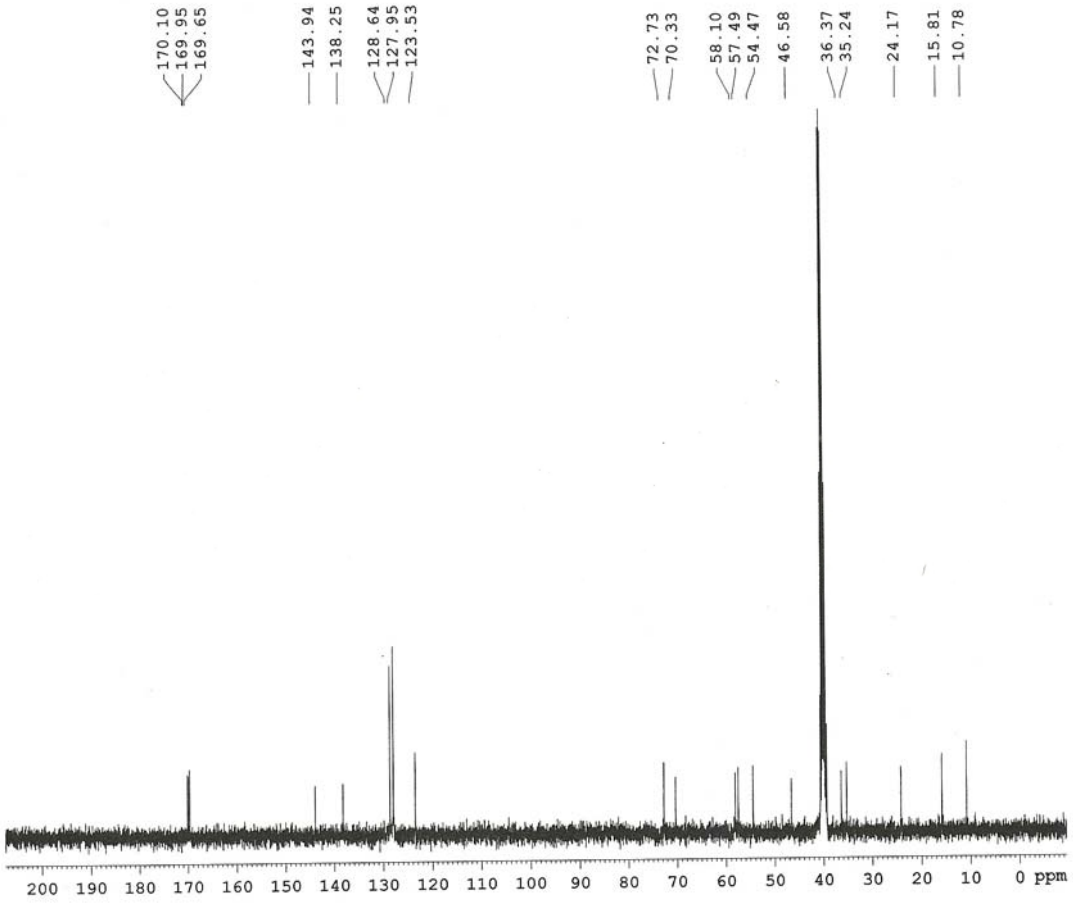


^{1}H & ^{13}C NMR of 9k in $CDCl_3$

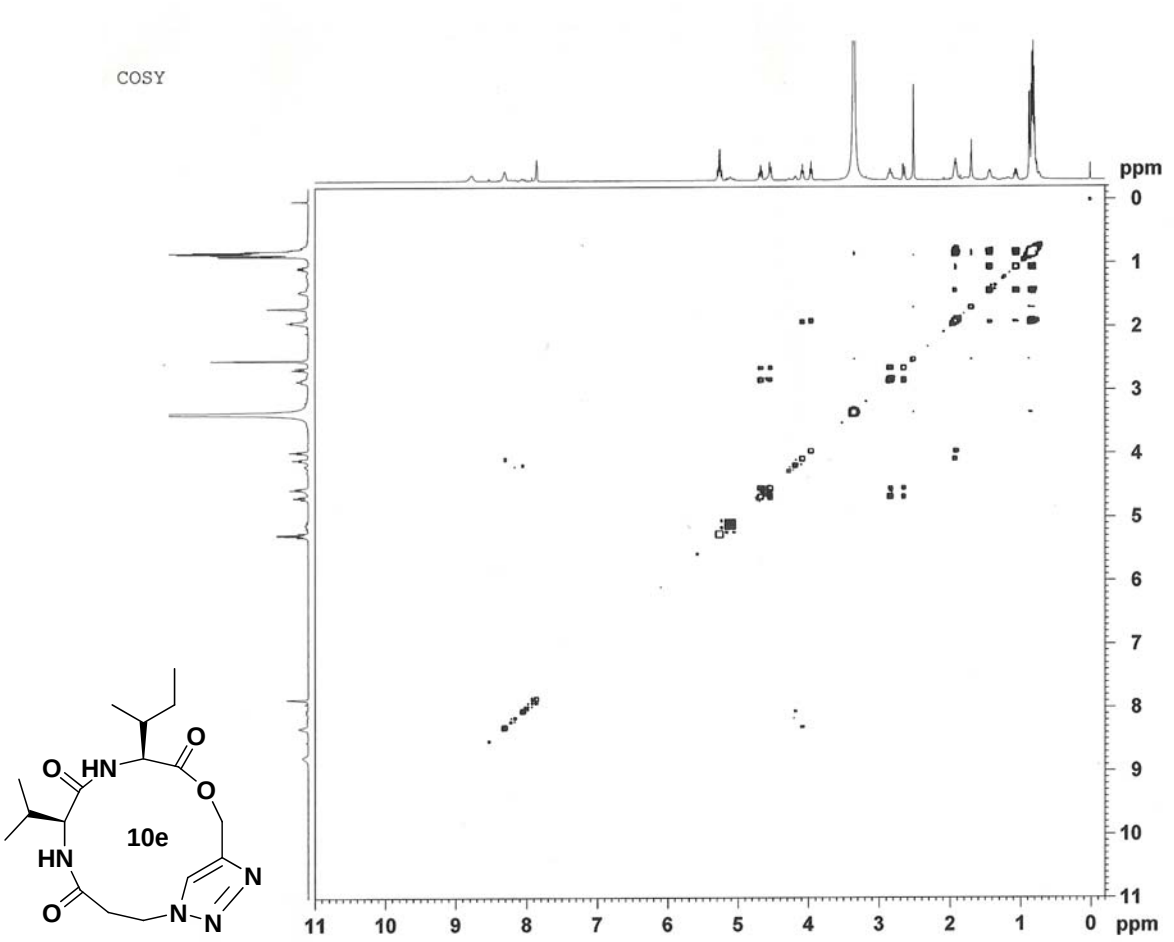


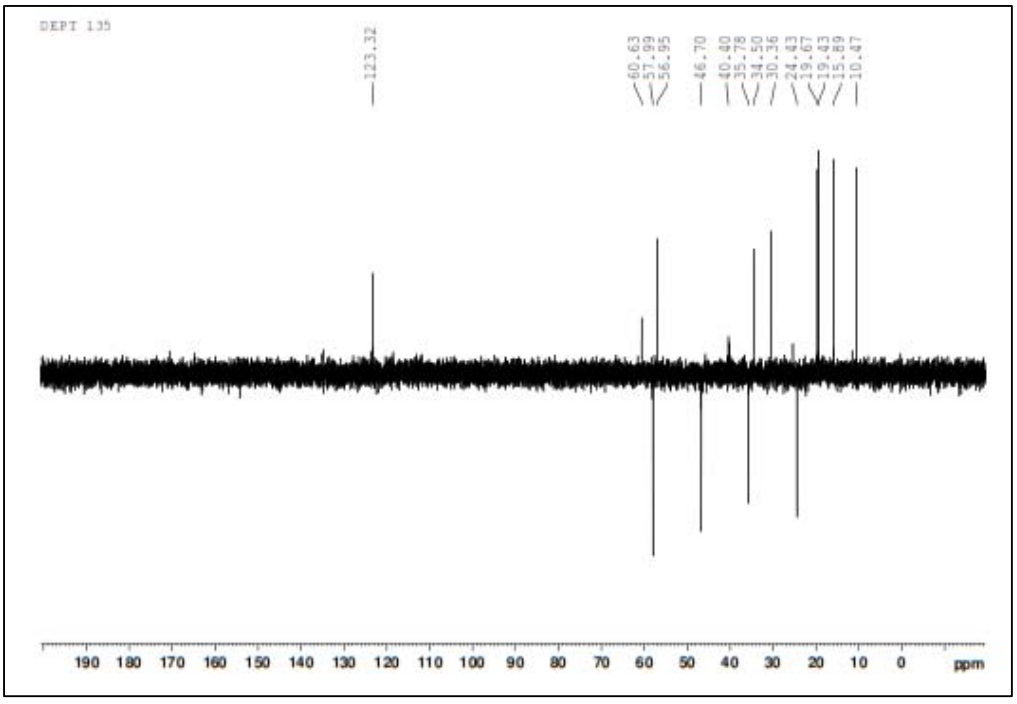
^{1}H & ^{13}C NMR of 10k in DMSO-d_6

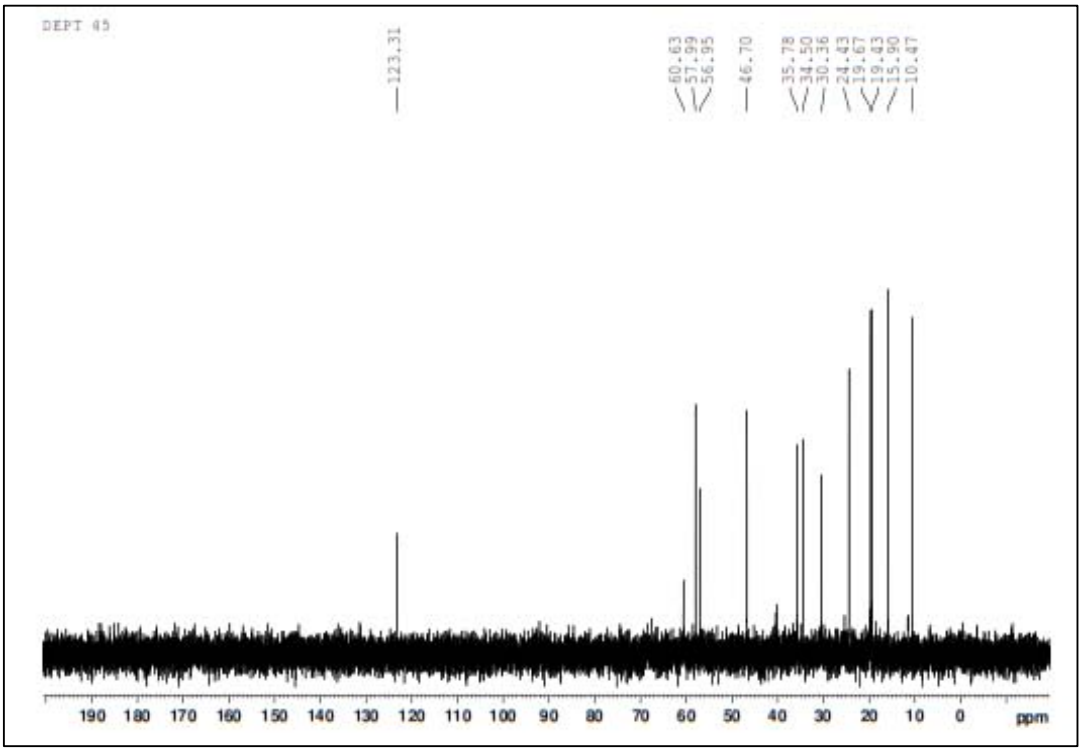




5) COSY, DEPT, TOCSY and HSQC spectra of 10e



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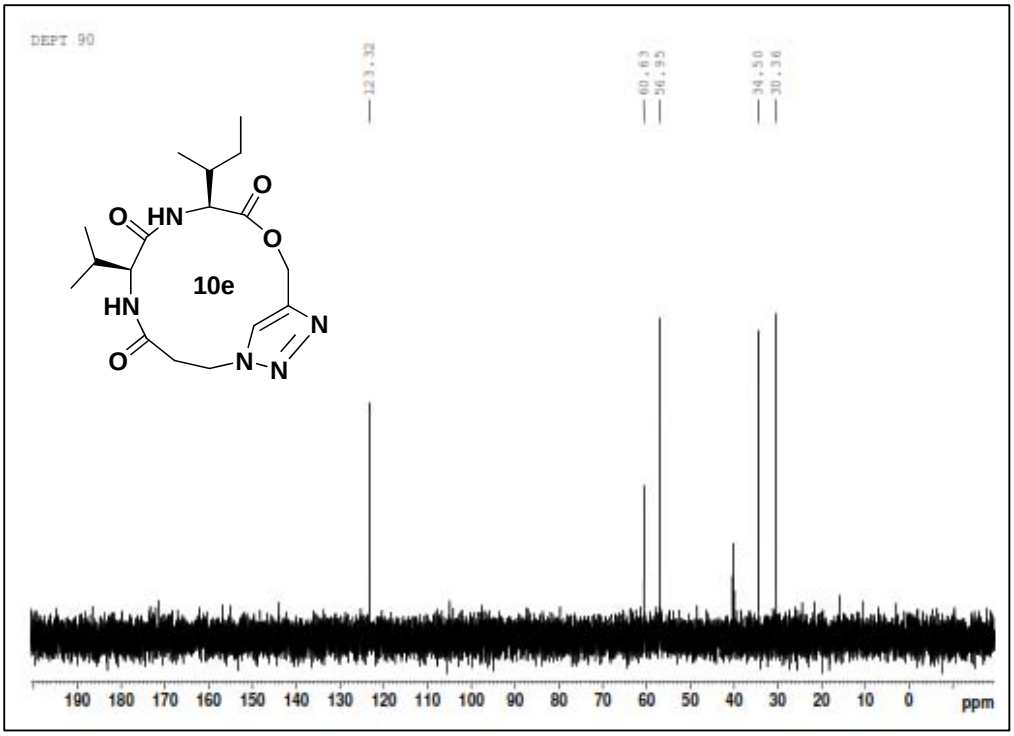
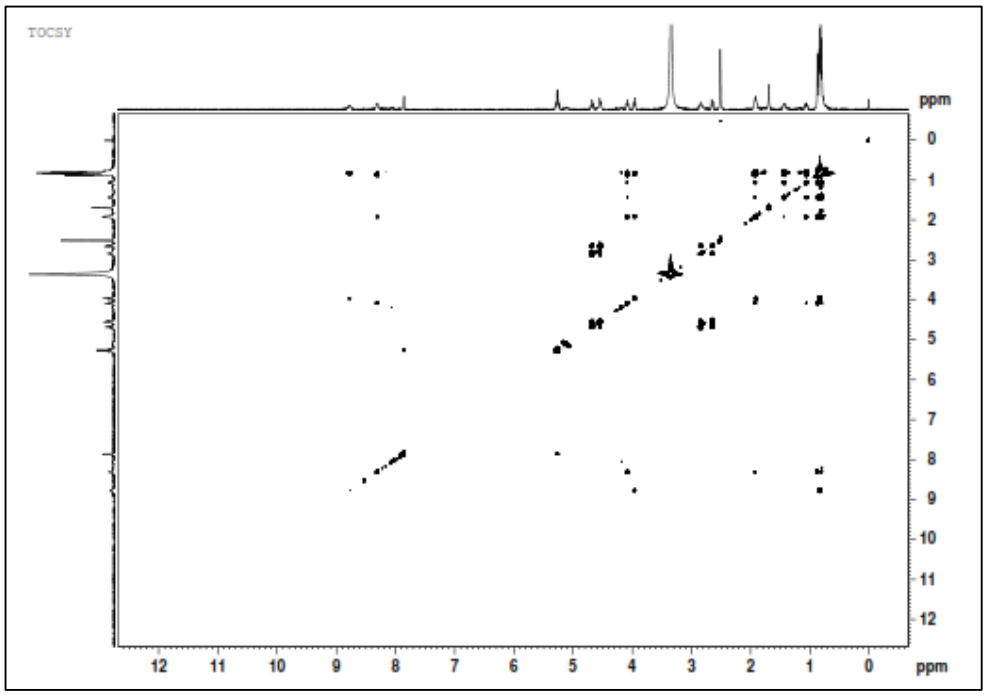
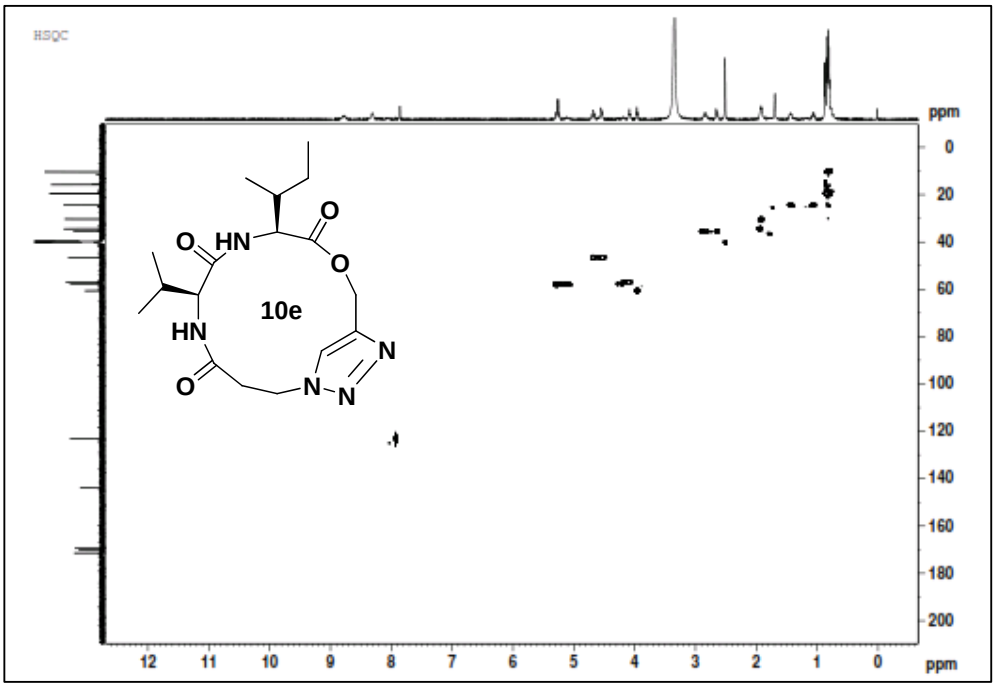
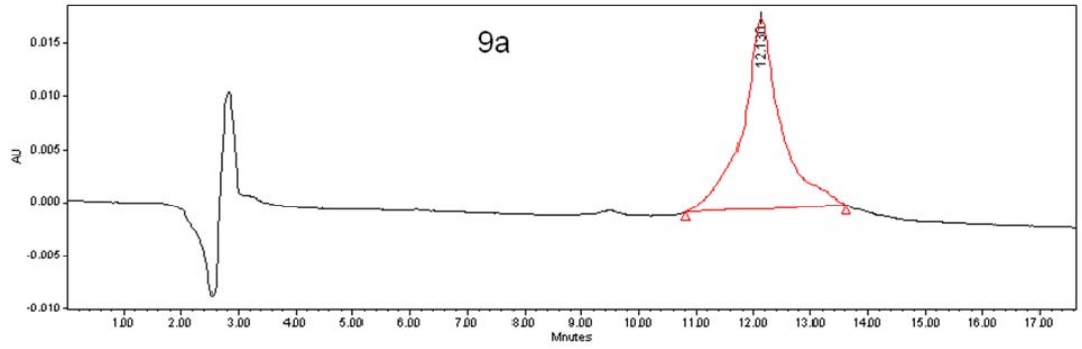
123.31
60.63
57.99
56.95
46.70
35.78
34.50
30.36
24.43
19.67
19.43
15.90
10.47
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

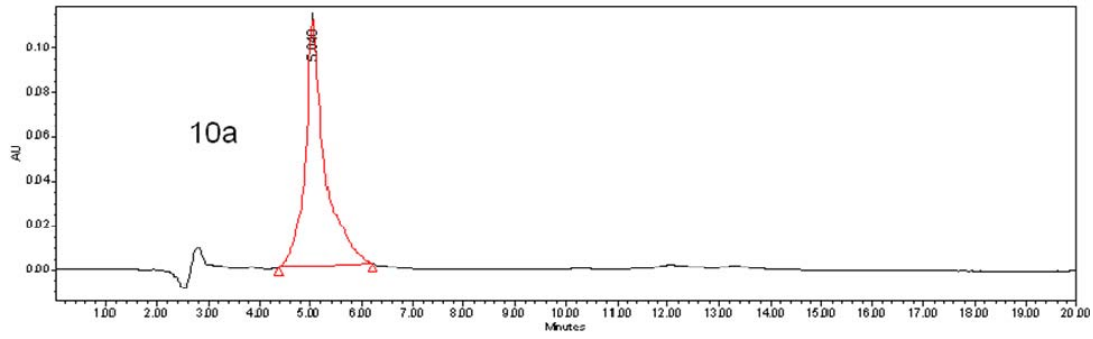

DEPT 90
123.32
60.63
56.95
34.50
30.36
O
HN
O
O
10e
HN
O
N
N
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

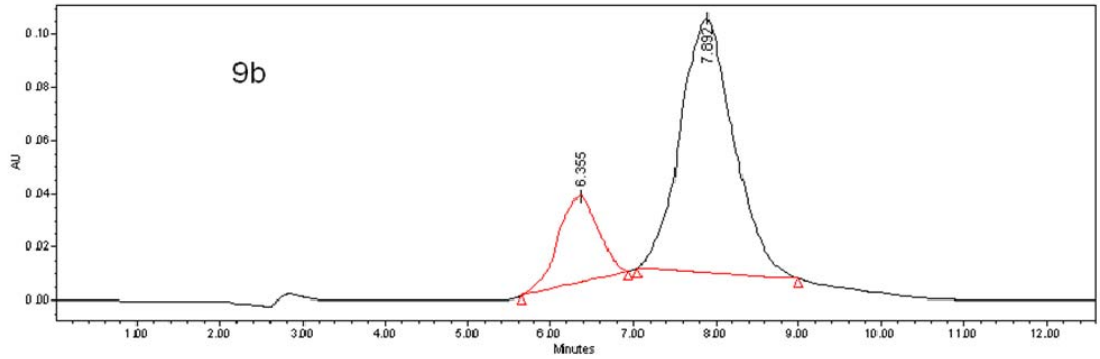

TOCSY
ppm
0
1
2
3
4
5
6
7
8
9
10
11
12
12 11 10 9 8 7 6 5 4 3 2 1 0
ppm

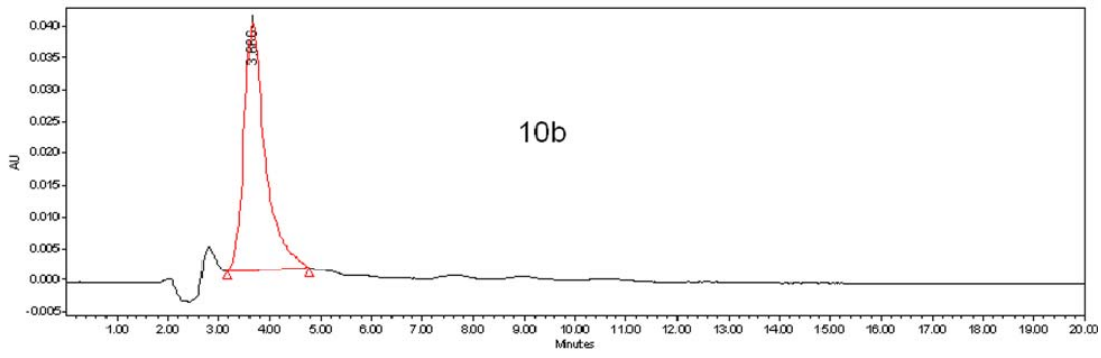

HSQC
ppm
0
20
40
60
80
100
120
140
160
180
200
12 11 10 9 8 7 6 5 4 3 2 1 0
ppm
O
HN
O
O
10e
HN
N
O
N
N

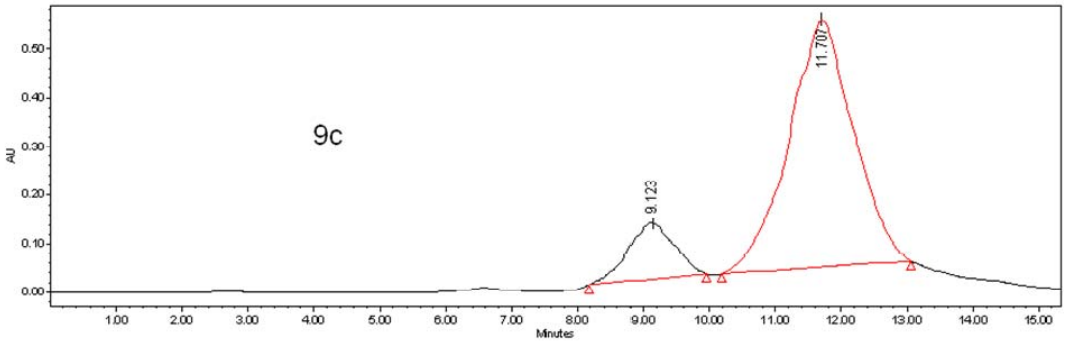
6) HPLC Purity Data of 9a-k and 10a-k







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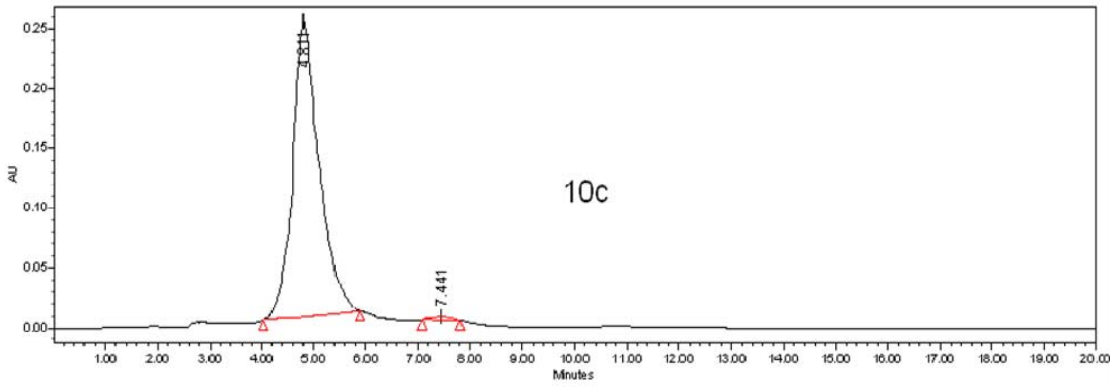
11.707
AU
Minutes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4.811
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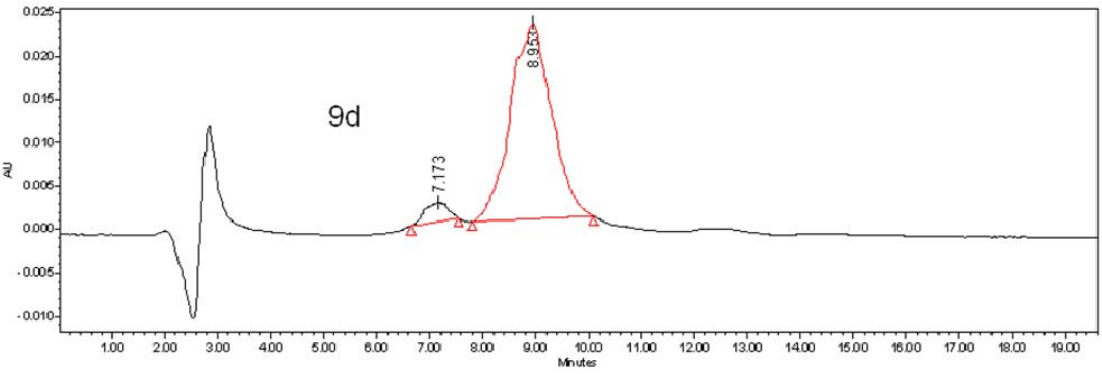
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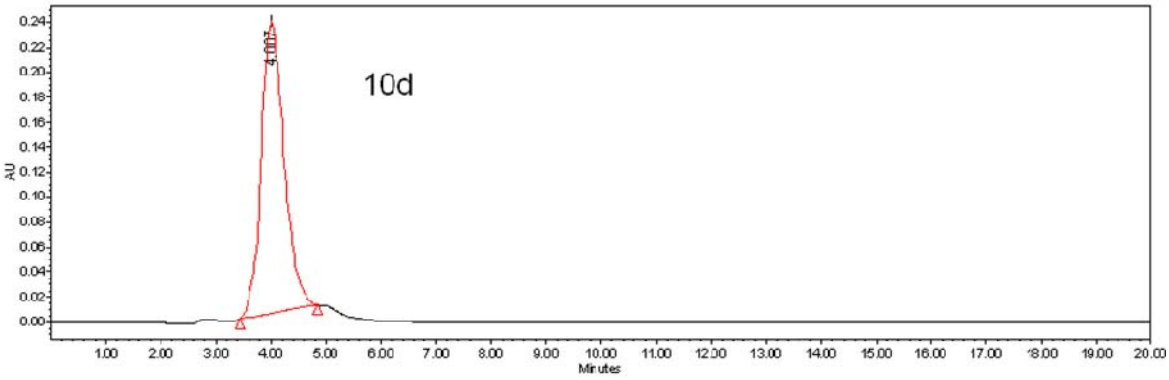
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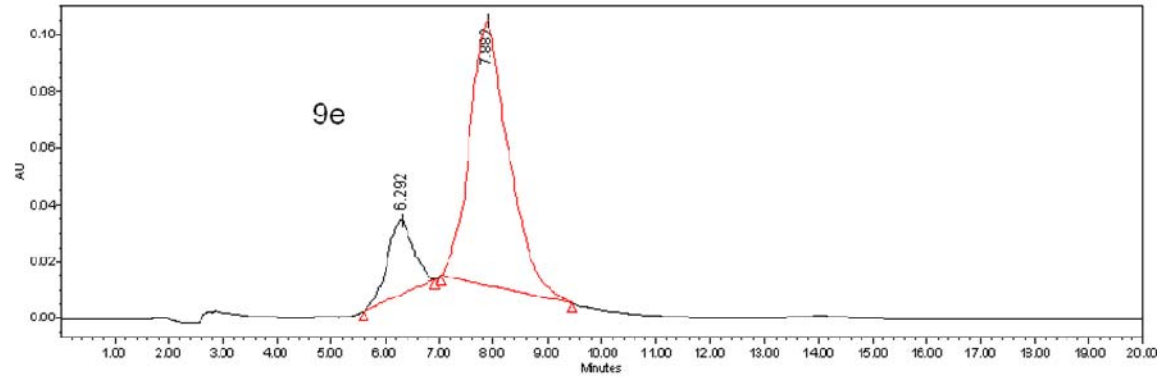
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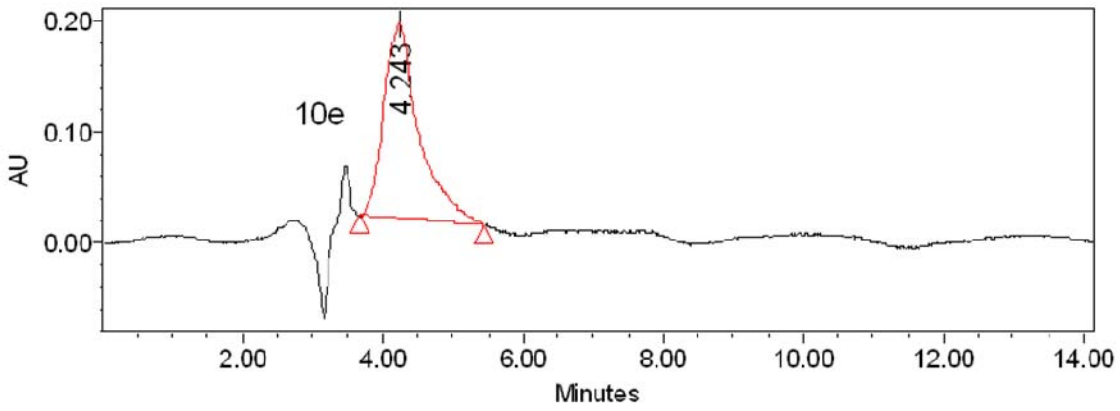
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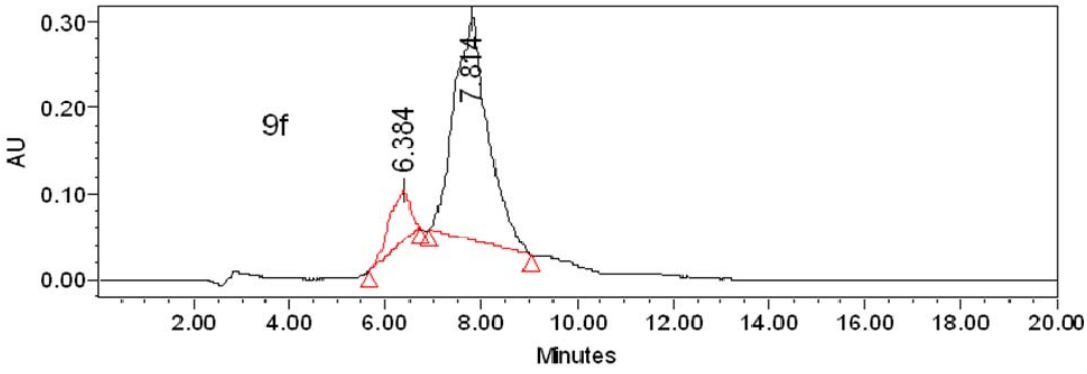
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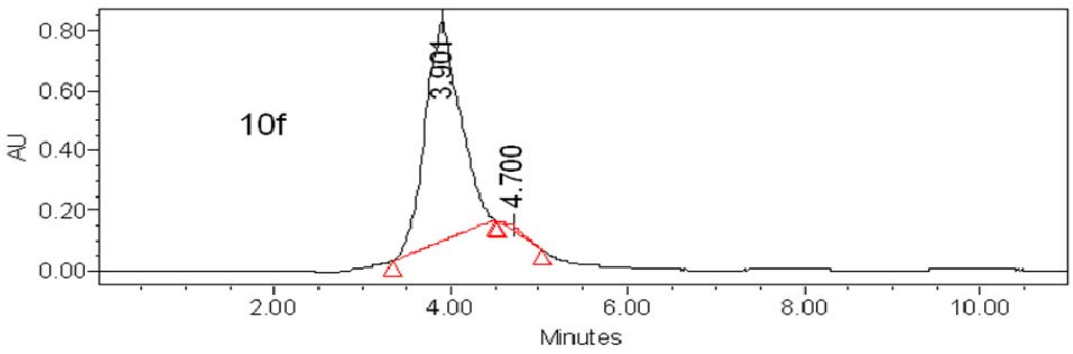
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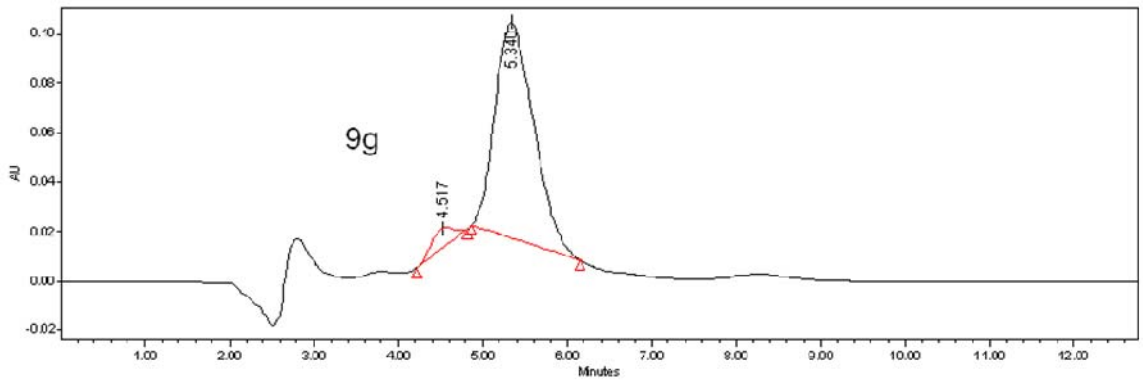
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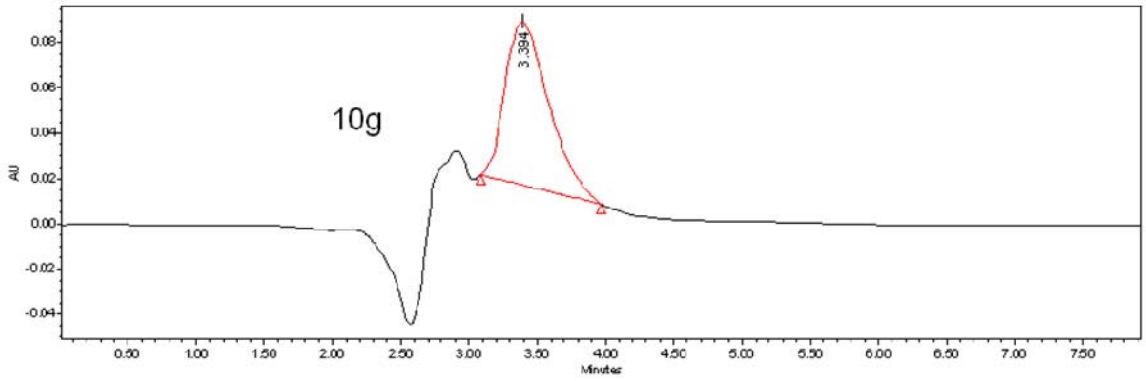
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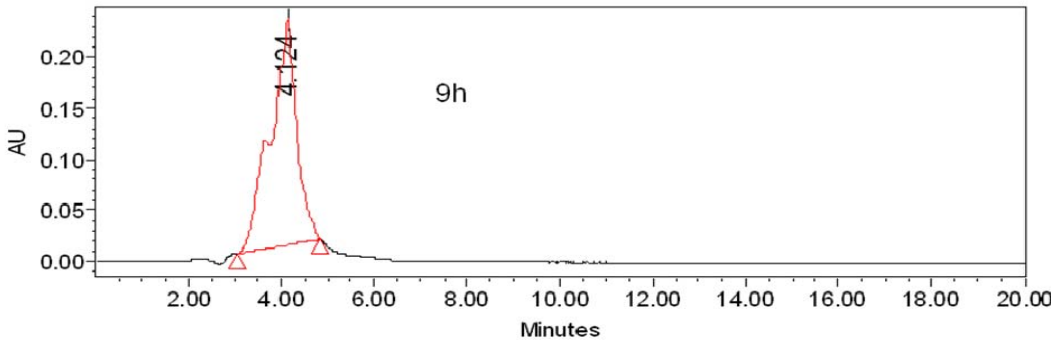
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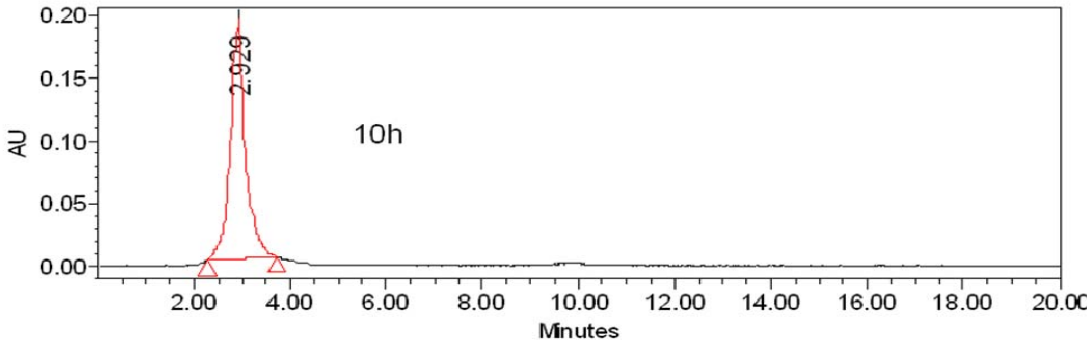
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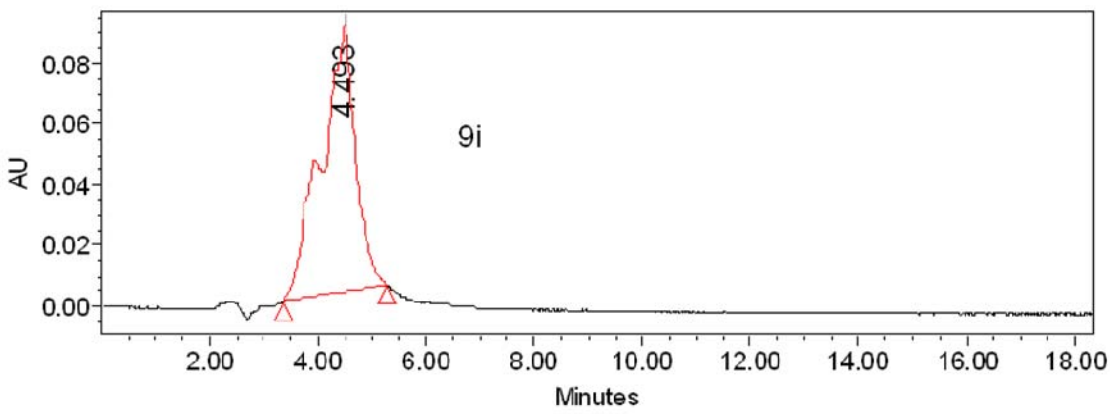
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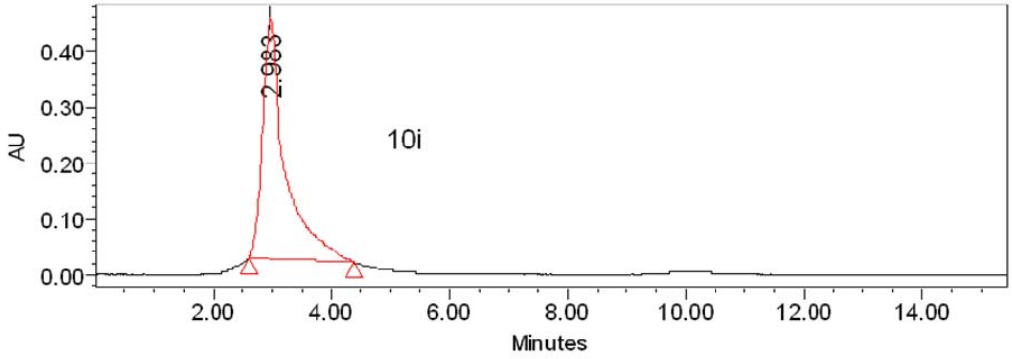
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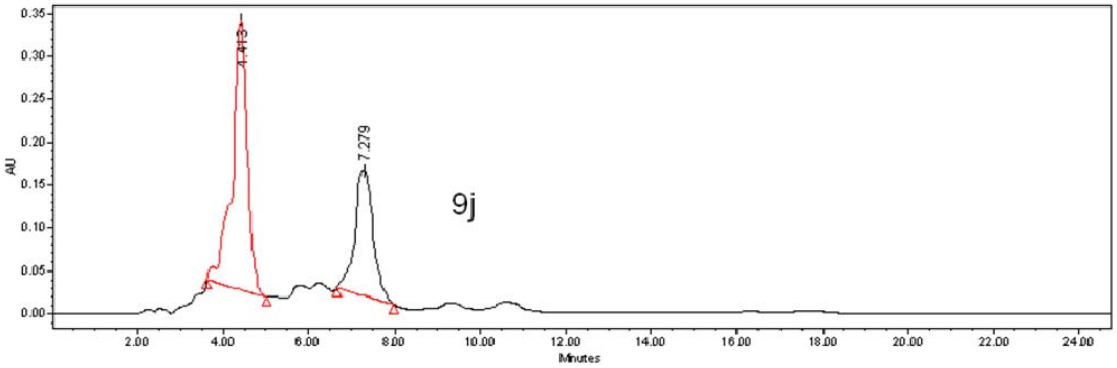
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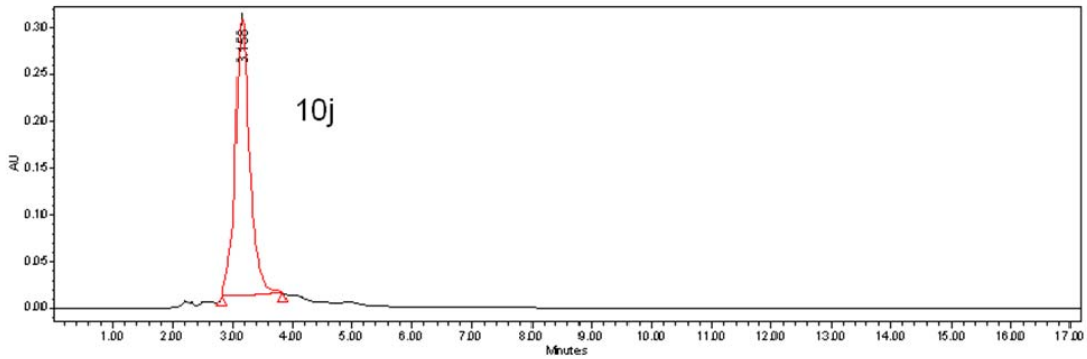
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0.20
0.15
0.10
0.05
0.00
1.00
2.00
3.00
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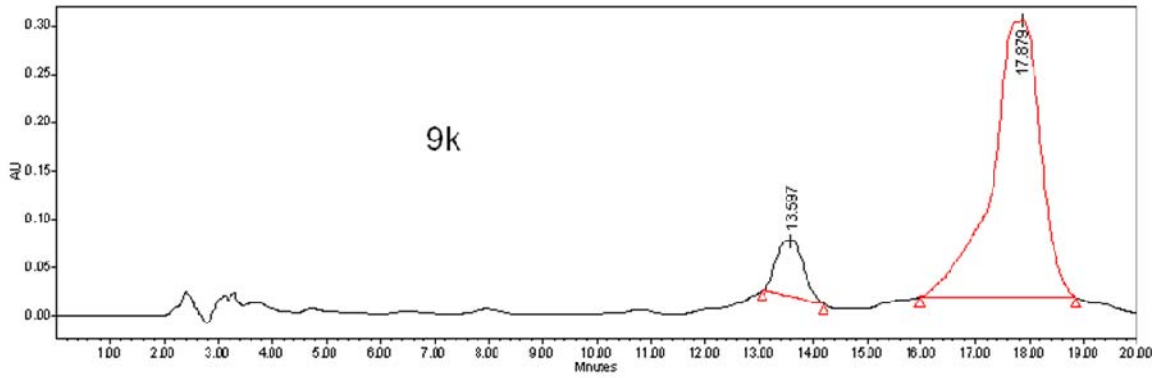
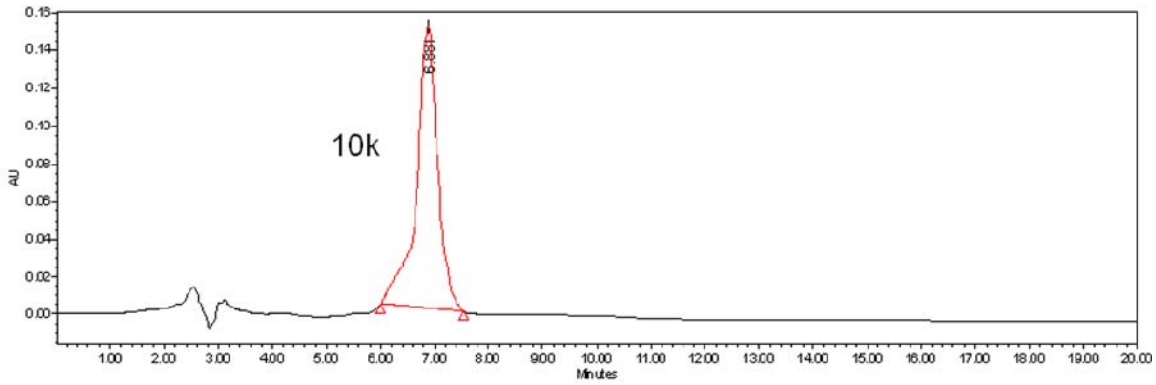
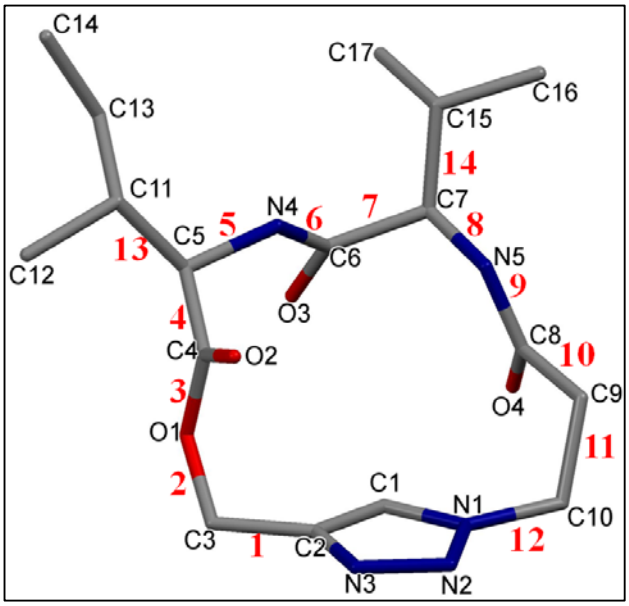
Minutes


9k
AU
Minutes
13.537
17.879


10k
AU
Minutes
6.881

7) Crystallographic Characterization and Theoretical Calculations of 10e

Table S1: List of selected torsions [(°), denoted with the red number, measured in Mercury 3.0]. The values in italics are the corresponding torsions in the optimized geometry for the isolated molecule at MP2/6-311G**.



1	2	3	4	5	6	7	8	9	10	11	12	13	14
-38.3(2)	-67.7(2)	174.2(2)	-110.7(2	**91.4(2)**	-170.8(2)	**72.7(2)**	84.9(2)	179.4(2)	139.7(2)	-66.5(2)	66.2(2)	-179.0(2	175.9(2)
-36.2	*-67.0*	*167.8*	*-120.5*	***132.2***	*-172.2*	***41.2***	*75.8*	*173.0*	*151.2*	*-69.3*	*77.4*	*173.7*	*172.3*

Torsion **1**: C1/C2/C3/O1; Torsion **2**: C2/C3/O1/C4; Torsion **3**: C3/O1/C4/C5; Torsion **4**: O1/C4/C5/N4; Torsion **5**: C4/C5/N4/C6; Torsion **6**: C5/N4/C6/C7; Torsion **7**: N4/C6/C7/N5; Torsion **8**: C6/C7/N5/C8; Torsion **9**: C7/N5/C8/C9; Torsion **10**: N5/C8/C9/C10; Torsion **11**: C8/C9/C10/N1; Torsion **12**: C9/C10/N1/C1; Torsion **13**: C4/C5/C11/C13; Torsion **14**: C6/C7/C15/C16.

The values of the Torsion **5** and **7** represent a significant change in geometry in the solid state and gas phase.

Table S2: Lattice energy calculation (kcal/mol) partitioned into Coulombic, polarization, dispersion and repulsion contribution with PIXEL method in CLP program package.

	E_{Coul}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
10e	-36.6	-16.2	-41.4	46.7	-47.6

Table S3: List of intra- and intermolecular interactions along with PIXEL interaction energy (kcal/mol), partitioned into Coulombic, polarization, dispersion and repulsion contribution

	D-H···A	D···A (Å)	X···A (Å)	∠D-X···A (°)	Symmetry	Centroid Distance (Å)	E_{Cou}	E_{Pol}	E_{Disp}	E_{Rep}	E_{Tot}
	C1-H1···O1	3.182(7)	2.53	118	x, y, z						
I	**N4-H4···O4**	2.856(5)	1.88	158	x-1/2, -y+3/2, -z	5.603	**-27.9**	**-11.8**	**-18.5**	**32.1**	**-26.2**
	N5-H5···O3	2.742(5)	1.72	171							
	C15-H15···O4	3.511(6)	2.46	164							
	C11-H11···O4	3.289(7)	2.55	125							
	C16-H16A···O3	3.454(7)	2.63	132							
	C16-H16C···O2	3.498(7)	2.51	151							
	C7-H7···O2	3.585(7)	2.64	146							
II	**C3-H3B···N2**	3.500(8)	2.43	169	-x+1, y-1/2, -z+1/2	9.815	**-6.1**	**-2.2**	**-4.7**	**4.8**	**-8.2**
	C10-H10B···N3	3.465(7)	2.64	133							
III	**C14-H14B···π (C1)**	3.798(7)	2.82	150	-x+3/2, -y+1, z-1/2	10.109	**-0.7**	**-0.8**	**-5.8**	**4.4**	**-2.9**

Crystal growth, Data collection and Theoretical calculations:

Crystals of **10e** was obtained from slow evaporation of DMSO solution at room temperature. The obtained colourless single crystal of **10e** was found to have thin plate morphology. Single-crystal X-ray diffraction data was collected on a Bruker D8 venture diffractometer equipped with CMOS detector using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) at 150(2) K. Cell refinement and data reduction were performed using the program SAINT.[3] The data were scaled and absorption correction was performed using SADABS.[4] The structure was solved by direct methods using SHELXS-97[5] and refined by full-matrix least-squares methods based on F^2 using SHELXL-97[5] present in the program suite WinGX.[6] All non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were then positioned geometrically and refined using a riding model with $U_{iso}(H) = 1.2U_{eq}[C(sp^2)]$ and $U_{iso}(H) = 1.5U_{eq}C(sp^3)$. *ORTEP* diagram of the compound was generated using ORTEP-32.[7] Geometrical calculations were performed using PARST[8] and PLATON.[9] Overlay and the packing diagrams of all the structures were generated from Mercury 3.0.[10]

The molecular structures of **10e** was fully optimized at MP2/6-311G** using TURBOMOLE[11] with crystallographic coordinates as the starting geometry. Selected torsion angles in the optimized structure were compared with that of in the solid state [**Table S1**]. The lattice energy of **10e** was calculated with PIXELC module in the CLP computer program package [version 10.2.2012]. For this purpose hydrogen atoms were moved to their neutron value and an accurate electron density of the molecules was obtained at MP2/6-31G** with Gaussian 09. The total lattice energy was partitioned into their coulombic, polarization, dispersion and repulsion contributions. These results are listed in **Table S2**. The interaction energy of selected molecular pairs, extracted from the crystal packing along with the involved

intermolecular interactions, were listed in **Table S3** with the total energies being partitioned into their coulombic, polarization, dispersion and repulsion contributions.

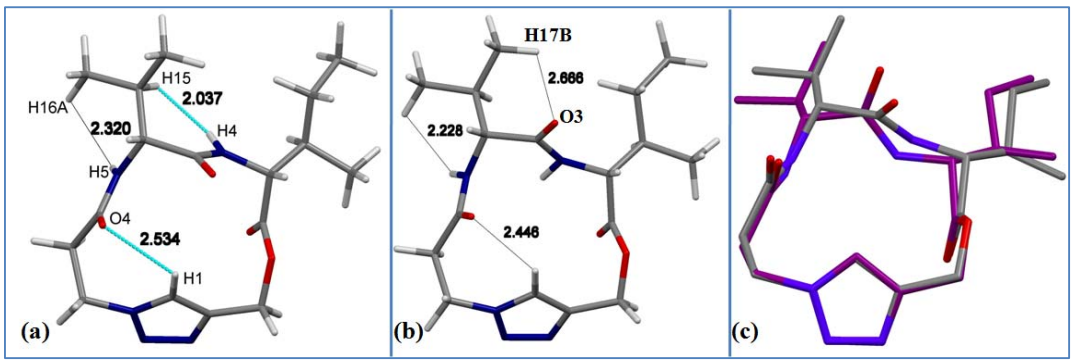


Figure S1: **(a)** Solid state molecular conformation of **10e**, showing the presence of intramolecular weak C-H...O=C hydrogen bond along with short H...H contacts. **(b)** Optimized molecular structure of **10e** at MP2/6-311G**, showing the presence of intramolecular weak C-H...O=C hydrogen bonds along with H...H contact. **(c)** Molecular overlay of the two structures. Hydrogen atoms are omitted for clarity.

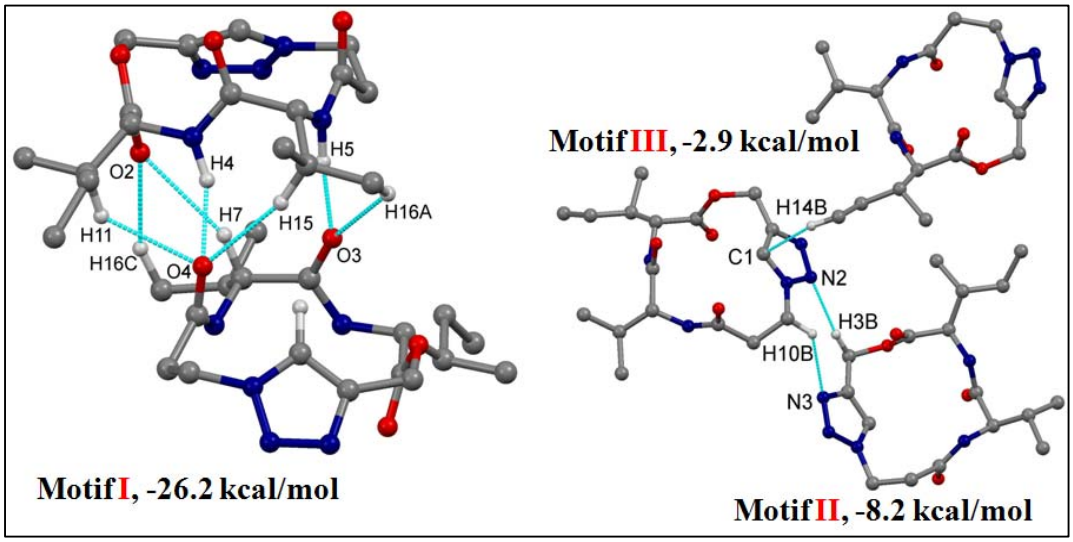


Figure S2: Molecular motifs along with their interaction energy (from **Table S3**) extracted from crystal packing of **10e.** Hydrogen atoms not participating in the intermolecular interactions are omitted for clarity.

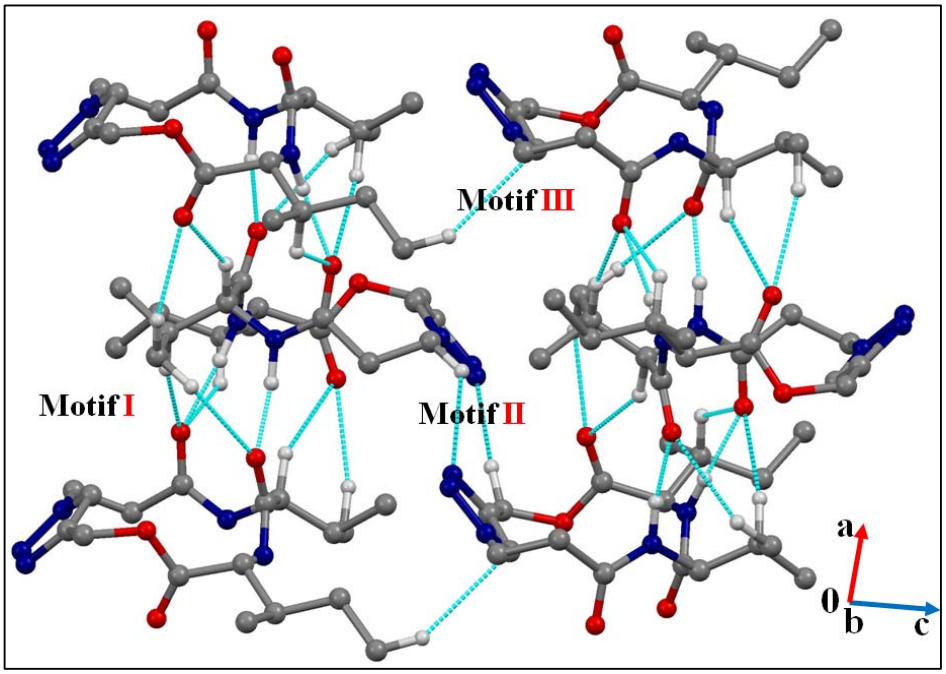


Figure S3 (a): Packing view down the *ac* plane in **10e**, displaying the network of strong N-H···O=C, weak C-H···O=C, C-H···N and C-H···π hydrogen bonds. Hydrogen atoms not participating in the intermolecular interactions are omitted for clarity.

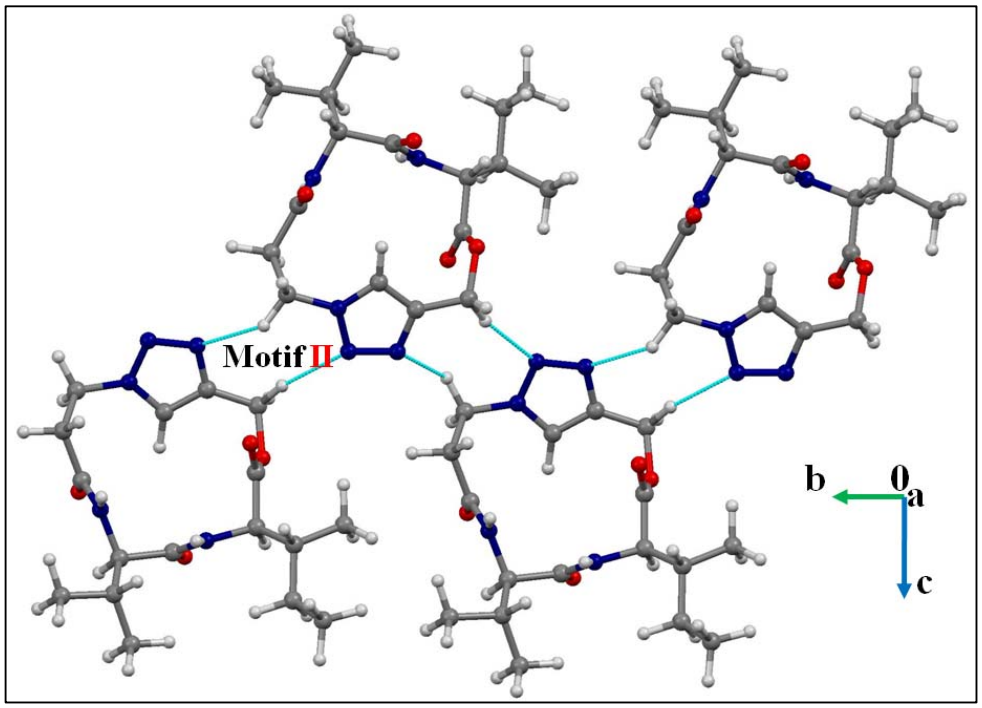


Figure S3 (b): Formation of molecular layer down the crystallographic *bc* plane *via* weak C-H···N hydrogen bonds in **10e**.

The compound **10e** crystallizes in the non-centrosymmetric orthorhombic space group $P2_12_12_1$ with Z = 4. The molecular conformation of 10e in the solid state was found to be stabilized by the presence of an intramolecular weak Fig S1(b) (involving H1 with O4) along with the N-H···H-C (sp^3) contacts (involve acidic H4 and H5 with H15 and H16A respectively) [Fig S1(a)]. The optimization of solid state molecular structure at MP2/6-311G** leads to the significant change in the torsions 3-8 and 10, with the greatest variation of 40.8° and 31.5° observed in case of torsion **4** and **7** respectively [Table 1, Fig S1(b) and S1(c)]. This variation leads to the generation of a C(sp^3)-H···O=C (involving H17B with O3) in place of a N4-H4···H15-C15(sp^3) contact in the solid state. The interactions, namely the weak C(sp^2)-H···O=C (involving H1 with O4) hydrogen bond and N5-H5···H16A-C16(sp^3) contact, are found to be present in both the solid state and optimized gas phase geometry [Fig S1(b)].

In the crystal packing of the compound, the most stabilized motif **I** [I. E = -26.2kcal/mol, with major contribution from coulombic interactions, **Fig. S2**] involves the utilization of a strong N-H···O=C (involves H4 and H5 with O4 and O3 respectively) along with weak C(sp^3)-H···O=C (involves H7 and H16C with O2, H11 and H15 with O4 and H16A with O3). The motif **I** is involved in the formation of a molecular chain utilizing 2_1 screw axis parallel to the crystallographic *a*-axis. Such a chain is linked *via* the weak C (sp^3)-H···N (motif **II**, I.E = -8.2 kcal/cal, with major contribution from coulombic and dispersion), utilizing 2_1 screw axis along the *b*- axis, and C (sp^3)-H···π hydrogen bonds (motif **II**, I.E = -2.9 kcal/cal, with major contribution from dispersion energy) utilizing 2_1 screw axis along the *c*- axis, [**Table S3**, **Fig. S2** and **S3 (a)**].

Lattice energy calculation of **10e** by PIXEL method reveal that the presence of such significant number of strong and weak interactions in the crystal packing contributes towards the cohesive energy of the compound (-47.6 kcal/mol). The major contribution towards the total lattice energy comes from the dispersion and coulombic energy term (**Table S2**).

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