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

Synthesis and biological evaluation of moiramide B derivatives

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Supporting Information

Materials and methods

All air- or moisture-sensitive reactions were carried out in oven-dried glassware (75 °C) under an atmosphere of nitrogen or argon. Anhydrous dichloromethane, diethyl ether and DMF were purchased from Acros Organics and stored under nitrogen. Triethylamine was dried over potassium hydroxide prior to use. Pentane and ethyl acetate were distilled prior to use. The products were purified by automated flash chromatography using a Büchi Pure C-815 chromatography system and Teledyne Isco RediSep® Silver Normal-phase Silica Flash (30–70 µm) columns. Alternatively, columns were packed using Macherey-Nagel silica 60 (0.04–0.063 mm). For reversed-phase flash chromatography, a Büchi Reveleris® Prep chromatography system and Büchi FlashPure Select C18 (30 µm spherical) columns were used. Preparative HPLC was performed on a Büchi Reveleris® Prep chromatography system using a Phenomenex Luna® C18(2) 100 Å column (250 x 21.1 mm, 5 µm). Analytical TLC was performed on pre-coated silica gel plates (Macherey-Nagel, Polygram® SIL G(UV_{254}). Visualization was accomplished with UV light, $KMnO_4$ solution, cerium(IV)/ ammonium molybdate solution or ninhydrin solution. Melting points were determined with a MEL-TEMP II apparatus and are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with Bruker Avance II 400 [400 MHz (^{1}H), 100 MHz (^{13}C), 377 MHz (^{19}F)], Avance I 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] and Avance Neo 500 [500 MHz (^{1}H), 125 MHz (^{13}C) and 471 MHz (^{19}F)] spectrometers in CD_3OD, $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm (δ) with respect to TMS, and methanol-d_3, $CHCl_3$ or DMSO-d_5 was used as the internal standard. In the moiramide derivatives, the succinimide unit was present as a mixture of *cis* and *trans* isomers and the enol form in variable ratios. Unless otherwise stated, the chemical shifts of the major *trans* isomer are given below. Gas chromatography was performed on a Shimadzu GC-2010 (autoinjector AOC-20i, mass detector GCMS-QP2010 Plus, CI technique) with a FS-Supreme-5ms capillary column (25 m x 0.25 mm) and nitrogen as carrier gas. Optical rotations were measured with a Krüss P8000-T80 polarimeter at the sodium D line (589 nm). α_D^{20} values are given in 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded with a Finnigan MAT 95 sector field spectrometer (CI) or a Bruker Daltonics maXis 4G hr-ToF spectrometer (ESI).

General procedures

GP1: Saponification of methyl esters: To a solution of 1.0 eq. methyl ester in THF (0.08 M) were added 1.1–2.1 eq. aqueous 1 M lithium hydroxide solution. The mixture was stirred at the temperature and for the time indicated below. After removal of the solvent in vacuo, the residue was dissolved in water and acidified to pH = 2–3 using 1 M HCl. If the product precipitated as a solid, it was collected by suction filtration and dried in vacuo. Otherwise the aqueous layer was extracted three times with EtOAc and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude carboxylic acid was used in the next step without further purification.

GP2: Amide coupling: To a solution of 1.0–1.3 eq. carboxylic acid in anhydrous DMF (0.07 M) were successively added 1.0–1.3 eq. PyBOP and 3.6–4.0 eq. DMAP. After stirring at room temperature for 10 min, 1.0 eq. amine hydrochloride **2** were added at 0 °C and the mixture was stirred at the same temperature for 30 min. EtOAc was added and the mixture was washed once with 1 M HCl, three times with 5 % LiCl solution,

once with saturated $NaHCO_3$ solution and once with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography and, if necessary, preparative HPLC.

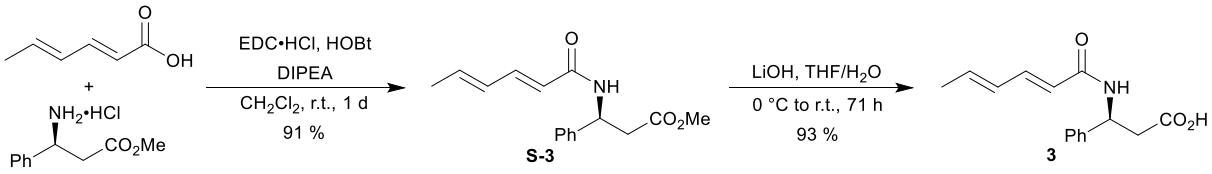
GP3: CuAAC: In a 4 mL vial 1.0 eq. alkyne **11** and 1.2 eq. azide were dissolved in *t*-BuOH/H_2O 1:1 (0.05 M). An aqueous $CuSO_4$ solution (1 M, 0.5 eq.) and an aqueous sodium ascorbate solution (1 M, 0.6 eq.) were added successively. The vial was purged with argon, sealed with a rubber septum and the mixture was stirred at room temperature overnight. After removal of the solvent in vacuo, the residue was purified by reversed-phase flash chromatography. If necessary, the product was further purified by preparative HPLC.

GP4: Sonogashira coupling: 1.0 eq. alkyne **9**, 0.1 eq. $Pd(PPh_3)_2Cl_2$, 0.2 eq. CuI and 3.5 eq. aryl iodide (if the aryl iodide was a solid) were placed in a 4 mL vial. The vial was sealed with a rubber septum and purged with argon over 5 min. Triethylamine (0.1 M) and 3.5 eq. aryl iodide (if the aryl iodide was a liquid) were added. The mixture was stirred at room temperature for 2.5 h. Then the resulting suspension was diluted with MeCN, filtered and concentrated in vacuo. The residue was purified by flash chromatography.

Synthetic procedures

(3*R*,4*S*)-3-(L-Valyl)-4-methylpyrrolidine-2,5-dione hydrochloride (2). To a solution of 1.72 g (5.49 mmol, 1.0 eq.) Boc protected amine **1**[1] in 2 mL CH_2Cl_2 were added 13.7 mL (54.9 mmol, 10 eq.) HCl (4 M in dioxane) at 0 °C. After stirring at the same temperature for 90 min, the solvent was removed in vacuo and the crude product was used in the next step without further purification. Yield: 1.36 g (5.46 mmol, 100 %); yellow foam; α_D^{20} = +14.6 (c = 1.0, MeOH); major isomer (enol): ^{1}H NMR (500 MHz, CD_3OD): δ = 4.69 (d, *J* = 3.5 Hz, 1 H), 3.40 (q, *J* = 7.3 Hz, 1 H), 2.74 (sptd, *J* = 7.0, 3.5 Hz, 1 H), 1.30 (d, *J* = 7.3 Hz, 3 H), 1.23 (d, *J* = 7.0 Hz, 3 H), 0.93 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3OD): δ = 200.1, 181.2, 173.9, 65.0, 38.6, 29.6, 19.8, 16.2, 14.8, lacks quaternary enol carbon; HRMS (CI) calcd. for $C_{10}H_{17}O_3N_2^+$ $[M–Cl]^+$: 213.1234, found: 213.1231.

Synthesis of building block 3



Methyl (*S*)-3-((2*E*,4*E*)-hexa-2,4-dienamido)-3-phenylpropanoate (S-3). To a solution of 1.00 g (8.92 mmol, 1.0 eq.) (2*E*,4*E*)-hexa-2,4-dienoic acid, 3.43 mL (ρ = 0.74 g/mL, 19.6 mmol, 2.2 eq.) DIPEA and 2.73 g (17.8 mmol, 2.0 eq.) HOBt in 30 mL CH_2Cl_2 were added 1.88 g (9.81 mmol, 1.1 eq.) EDC·HCl. After stirring at room temperature for 10 min, 1.92 g (8.92

[1] (*a*) D. J. Dixon and S. G. Davies, *Chem. Commun.*, 1996, 1797–1798; (*b*) S. G. Davies and D. J. Dixon, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2635–2644.

mmol, 1.0 eq.) (*S*)-β-phenylalanine methyl ester·HCl were added and stirring at room temperature was continued overnight. EtOAc was added and the mixture was washed with 1 M HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 1:1). Yield: 2.23 g (8.16 mmol, 91 %); pale yellow solid; m.p. 117–119 °C (from cyclohexane, EtOAc); R_f 0.44 (pentane/EtOAc 1:1); $\boldsymbol{\alpha_D^{20}}$ = –89.2 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5 H), 7.19 (dd, *J* = 15.0, 10.2 Hz, 1 H), 6.64 (d, *J* = 8.3 Hz, 1 H), 6.20–6.02 (m, 2 H), 5.79 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.4, 5.9 Hz, 1 H), 3.61 (s, 3 H), 2.97 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.86 (dd, *J* = 15.8, 6.0 Hz, 1 H), 1.83 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 165.6, 141.7, 140.5, 138.1, 129.6, 128.7, 127.5, 126.3, 121.2, 51.8, 49.4, 39.6, 18.6; HRMS (CI) calcd for $C_{16}H_{20}O_3N$ $[M+H]^+$: 274.1438, found: 274.1433.

(*S*)-3-((2*E*,4*E*)-Hexa-2,4-dienamido)-3-phenylpropanoic acid (3). According to GP1 2.20 g (8.05 mmol, 1.0 eq.) methyl ester **S-3** were reacted with 8.85 mL (8.85 mmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 71 h. Yield: 1.94 g (7.48 mmol, 93 %); colorless solid; m.p. 197–199 °C (from water); R_f 0.15 (pentane/EtOAc 1:1); $\boldsymbol{\alpha_D^{20}}$ = –114.3 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.25 (bs, 1 H), 8.49 (d, *J* = 8.4 Hz, 1 H), 7.36–7.27 (m, 4 H), 7.23 (m, 1 H), 6.97 (dd, *J* = 15.0, 10.8 Hz, 1 H), 6.21 (dd, *J* = 14.9, 10.8 Hz, 1 H), 6.08 (m, 1 H), 5.92 (d, *J* = 15.2 Hz, 1 H), 5.26 (d, *J* = 8.0 Hz, 1 H), 2.72 (dd, *J* = 15.5, 7.9 Hz, 1 H), 2.67 (dd, *J* = 15.7, 7.1 Hz, 1 H), 1.78 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 164.5, 142.6, 139.6, 136.8, 129.9, 128.3, 127.0, 126.6, 122.8, 49.5, 41.0, 18.3; HRMS (CI) calcd for $C_{15}H_{17}O_3N$ $[M]^+$: 259.1203, found: 259.1198.

Moiramide B (4). According to GP2 36.6 mg (141 µmol, 1.3 eq.) acid **3** were reacted with 27.0 mg (109 µmol, 1.0 eq.) **2**, 73.4 mg (141 µmol, 1.3 eq.) PyBOP and 53.1 mg (434 µmol, 4.0 eq.) DMAP. The crude product was purified by flash chromatography (EtOAc). Analytical data were in accordance with those previously reported.[1] Yield: 26.9 mg (59 µmol, 55 %); colourless, amorphous solid; R_f 0.49 (EtOAc); α_D^{20} = –95.4 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (bs, 1 H), 8.38 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 7.37–7.15 (m, 5 H), 6.95 (dd, *J* = 14.7, 11.1 Hz, 1 H), 6.20 (dd, *J* = 14.6, 11.3 Hz, 1 H), 6.07 (dq, *J* = 14.5, 6.4 Hz, 1 H), 5.92 (d, *J* = 15.1 Hz, 1 H), 5.27 (m, 1 H), 4.63 (dd *J* = 7.9, 5.5 Hz, 1 H), 3.92 (d, *J* = 5.3 Hz, 1 H), 2.91 (quin, *J* = 6.6 Hz, 1 H), 2.76 (dd, *J* = 14.1, 8.6 Hz, 1 H), 2.64 (dd, *J* = 14.3, 6.1 Hz, 1 H), 2.29 (m, 1 H), 1.79 (d, *J* = 6.3 Hz, 3 H), 1.07 (d, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 142.8, 139.4, 136.7, 129.9, 128.2, 126.8, 126.4, 122.9, 63.0, 57.8, 49.8, 41.9, 38.9, 28.1, 19.4, 18.2, 17.2, 14.5; HRMS (ESI) calcd. for $C_{25}H_{32}N_3O_5^+$ $[M+H]^+$ 454.2336, found 454.2332.

***N*-((*S*)-3-((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)hexanamide (5).** To a solution of 20.7 mg (45.6 µmol, 1.0 eq.) moiramide B (**4**) in 900 µL methanol were added 2 mg Pd/C (10 % Pd) at room temperature. After hydrogenation at atmospheric pressure (H_2 balloon) for 4 h, the mixture was filtered through celite and concentrated in vacuo. The residue was purified by reversed phase flash chromatography (H_2O to MeCN). Yield: 20.8 mg (45.4 mmol, 100 %); colourless, amorphous solid; α_D^{20} = –32.4 (c = 0.5, MeOH); ^{1}H NMR

(500 MHz, DMSO-d_6): δ = 11.4 (bs, 1 H), 8.2 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 8.4 Hz, 1 H), 7.33–7.15 (m, 5 H), 5.18 (m, 1 H), 4.65 (dd, *J* = 8.4 Hz, 5.3 Hz, 1 H), 3.95 (d, *J* = 5.5 Hz, 1 H), 2.92 (dd, *J* = 7.3, 5.5 Hz, 1 H), 2.71 (dd, *J* = 14.3, 8.8 Hz, 1 H), 2.58 (dd, *J* = 14.3, 5.9 Hz, 1 H), 2.31 (m, 1 H), 2.06 (m, 2 H), 1.46 (quin, *J* = 7.3 Hz, 2 H), 1.31–1.03 (m, 7 H), 0.93–0.57 (m, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 171.1, 169.9, 143.1, 128.1, 126.7, 126.3, 62.9, 57.8, 49.7, 42.0, 38.9, 35.4, 30.8, 28.2, 24.9, 21.8, 19.4, 17.2, 14.5, 13.8; HRMS (ESI) calcd. for $C_{25}H_{36}N_3O_5^+$ $[M+H]^+$ 458.2649, found 458.2646.

Nona-2,8-diynoic acid (6). A solution of 6.17 mL (ρ = 0.810 g/mL, 47.1 mmol, 1.0 eq.) octa-1,7-diyne in 188 mL anhydrous diethyl ether was cooled to 0 °C and 15.7 mL (47.1 mmol, 1.0 eq.) ethylmagnesium bromide (3 M in diethyl ether) were added dropwise. After stirring at room temperature for 4 h, an excess of CO_2 (~ 100 g dry ice) was slowly bubbled through the resulting suspension via syringe. After completion of the addition, stirring was continued for another 15 h. TLC control indicated the presence of three compounds (unconverted starting material, monoacid **6** and diacid side product). The reaction was quenched by the addition of 1 M HCl and the layers were separated. The aqueous layer was extracted with EtOAc twice and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (pentane/EtOAc 7:3 + 1 % HOAc). Yield: 1.94 g (12.9 mmol, 27 %); yellow oil; R_f 0.51 (pentane/EtOAc 7:3 + 1% HOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.98 (bs, 1 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 2.24 (td, *J* = 6.8, 2.6 Hz, 2 H), 1.96 (t, *J* = 2.7 Hz, 1 H), 1.73 (m, 2 H), 1.65 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.9, 91.9, 83.5, 72.8, 68.9, 27.3, 26.3, 18.3, 17.8; HRMS (CI) calcd for $C_9H_{11}O_2$ $[M+H]^+$: 151.0754, found: 151.0762.

Pentafluorophenyl nona-2,8-diynoate (7). To a solution of 1.00 g (6.66 mmol, 1.0 eq.) nona-2,8-diynoic acid **6** and 1.41 g (7.66 mmol, 1.15 eq.) pentafluorophenol in 26.6 mL anhydrous CH_2Cl_2 were added 1.40 g (7.32 mmol, 1.1 eq.) EDC·HCl at 0 °C. The mixture was allowed to slowly warm to room temperature and stirred for 19 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 9:1). Yield: 1.47 g (4.65 mmol, 70 %); colourless oil; R_f 0.39 (pentane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (t, *J* = 7.0 Hz, 2 H), 2.27 (td, *J* = 6.8, 2.7 Hz, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H), 1.80 (m, 2 H), 1.69 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 141.1 (dtt, $J_{C,F}$ = 253.1, 8.8, 3.7 Hz), 139.8 (dtt, $J_{C,F}$ = 254.6, 13.9, 3.7 Hz), 137.9 (dtdd, $J_{C,F}$ = 252.4, 12.5, 5.9, 2.9 Hz), 124.2 (m), 95.0, 83.3, 71.0, 69.0, 27.3, 26.1, 15.8, 17.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ = –152.0 (m, 2 F), –157.1 (t, *J* = 21.8 Hz, 1 F), –161.9 (m, 2 F); HRMS (CI) calcd. for $C_{15}H_{10}O_2F_5^+$ $[M+H]^+$: 317.0595, found: 317.0586.

Pentafluorophenyl (2*E*,4*E*)-nona-2,4-dien-8-ynoate (8). To a solution of 1.43 g (4.52 mmol, 1.0 eq.) **7** in 22.6 mL toluene 59 mg (226 µmol, 5 mol-%) triphenylphosphine were added. After stirring at 50 °C for 18 h, the solvent was removed in vacuo. The residue was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 9:1). Yield: 1.37 g (4.33 mmol, 96 %); pale yellow solid; m.p. 62–64 °C (from cyclohexane, EtOAc); R_f 0.43 (pentane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (m, 1 H), 6.42–6.26 (m, 2 H), 6.04 (d, *J* = 15.3 Hz, 1 H), 2.47 (m, 2 H), 2.36 (m, 2 H), 2.01 (t, *J* = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 149.2, 144.9, 141.3 (dtt, $J_{C,F}$ =

250.9, 8.1, 4.4 Hz), 139.4 (dtt, $J_{C,F}$ = 252.4, 13.2, 4.4 Hz), 137.9 (dtdd, $J_{C,F}$ = 250.2, 13.9, 5.9, 2.2 Hz), 129.2, 125.5 (m), 82.8, 69.4, 31.8, 17.9; ^{19}F NMR (377 MHz, $CDCl_3$): δ = –152.7 (m, 2 F), –158.5 (t, *J* = 21.8 Hz, 1 F), –162.6 (m, 2 F); HRMS (CI) calcd. for $C_{15}H_{10}O_2F_5^+$ $[M+H]^+$: 317.0595, found: 317.0622.

Methyl (*S*)-3-((2*E*,4*E*)-nona-2,4-dien-8-ynamido)-3-phenylpropanoate (9). To a solution of 757 mg (2.39 mmol, 1.0 eq.) pentafluorophenyl ester **8** in 24 mL CH_2Cl_2, 857 µL (ρ = 0.74 g/mL, 4.91 mmol, 2.05 eq.) DIPEA and 568 mg (2.63 mmol, 1.1 eq.) (*S*)-β-phenylalanine methyl ester hydrochloride were successively added at room temperature. After stirring for 6 d, EtOAc was added and the mixture was washed with 1 M HCl, saturated $NaHCO_3$ solution and brine. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by reversed phase flash chromatography (H_2O to MeCN). Yield: 641 mg (2.06 mmol, 86 %); colourless solid; m.p. 106–108 °C (from MeCN, H_2O); R_f 0.43 (pentane/EtOAc 1:1); α_D^{20} = –65.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 5 H), 7.20 (dd, *J* = 15.0, 10.6 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 6.21 (dd, *J* = 15.2, 10.8 Hz, 1 H), 6.10 (dt, *J* = 15.2, 6.2 Hz, 1 H), 5.85 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.5, 5.9 Hz, 1 H), 3.61 (s, 3 H), 2.98 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.87 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.38 (m, 2 H), 2.31 (m, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 165.3, 141.3, 140.5, 140.3, 129.4, 128.7, 127.6, 126.2, 122.5, 83.2, 69.1, 51.8, 49.4, 39.6, 31.7, 18.1; HRMS (CI) calcd. for $C_{19}H_{21}O_3N^+$ $[M+H]^+$: 312.1594, found: 312.1599.

(*S*)-3-((2*E*,4*E*)-Nona-2,4-dien-8-ynamido)-3-phenylpropanoic acid (10). According to GP1 441 mg (1.42 mmol, 1.0 eq.) methyl ester **9** were reacted with 1.56 mL (1.56 mmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 53 h. Yield: 397 mg (1.36 mmol, 94 %); colourless solid; m.p. 138–139 °C (from H_2O); R_f 0.14 (pentane/EtOAc 1:1); α_D^{20} = –98.2 (c = 1.0, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 14.9, 11.1 Hz, 1 H), 6.26 (dd, *J* = 14.9, 11.0 Hz, 1 H), 6.07 (m, 1 H), 5.97 (d, *J* = 15.0 Hz, 1 H), 5.26 (q, *J* = 7.7 Hz, 1 H), 2.80 (m, 1 H), 2.76–2.63 (m, 2 H), 2.37–2.22 (m, 4 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.7, 164.3, 142.6, 139.6, 139.2, 129.5, 128.3, 127.0, 126.5, 123.8, 83.7, 71.7, 49.5, 40.9, 31.2, 17.5; HRMS (ESI) calcd. for $C_{18}H_{20}NO_3^+$ $[M+H]^+$ 298.1438, found 298.1435.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (11). According to GP2 200 mg (673 µmol, 1.0 eq.) acid **10** was reacted with 167 mg (673 µmol, 1.0 eq.) amine **2** (673 µmol, 1.0 eq.), 350 mg (673 µmol, 1.0 eq.) PyBOP and 296 mg (2.42 mmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield: 200 mg (406 µmol, 60 %); pale reddish, amorphous solid; α_D^{20} = –77.9 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (s, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.34–7.25 (m, 4 H), 7.20 (m, 1 H), 6.95 (dd, *J* = 15.0, 10.6 Hz, 1 H), 6.25 (dd, *J* = 15.2, 10.9 Hz, 1 H), 6.06 (dt, *J* = 15.3, 6.3 Hz, 1 H), 5.97 (d, *J* = 15.3 Hz, 1 H), 5.28 (td, *J* = 8.4, 6.3 Hz, 1 H), 4.63 (dd, *J* = 8.5, 5.4 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.91 (dd, *J* = 7.5, 5.6 Hz, 1 H), 2.76 (dd, *J* = 14.3, 8.5 Hz, 1 H), 2.65 (dd, *J* = 14.4, 6.0 Hz, 1 H), 2.34–2.23 (m, 5 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.2, 142.8, 139.5, 139.1, 129.5, 128.2, 126.8, 126.4,

123.9, 83.7, 71.7, 63.0, 57.8, 49.8, 41.9, 38.9, 31.2, 28.1, 19.4, 17.5, 17.2, 14.5; HRMS (ESI) calcd. for $C_{28}H_{34}N_3O_5^+$ $[M+H]^+$: 492.2493, found: 492.2495.

(2*E*,4*E*)-7-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-hepta-2,4-dienamide (12a). According to GP3 10.0 mg (20.3 µmol, 1.0 eq.) **11** were reacted with 3.3 mg (25 µmol, 1.2 eq.) benzyl azide,[2] 10.2 µL (10.2 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 12.2 µL (12.2 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O to MeCN). Yield: 8.8 mg (14.0 µmol, 69 %); pale yellow, amorphous solid; α_D^{20} = –24.0 (c = 1.0, MeOH); NMR showed the presence of two isomers (rotamers or succinimide *cis*/*trans* isomers) which were in rapid exchange according to 1D NOESY measurements;[3] *major isomer*: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.41 (d, *J* = 8.2 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.89 (s, 1 H), 7.39–7.15 (m, 10 H), 6.93 (dd, *J* = 14.8, 11.1 Hz, 1 H), 6.18 (dd, *J* = 15.4, 11.1 Hz, 1 H), 6.07 (dt, *J* = 15.0, 6.3 Hz, 1 H), 5.93 (d, *J* = 15.1 Hz, 1 H), 5.53 (s, 2 H), 5.28 (td, *J* = 7.9, 6.4 Hz, 1 H), 4.63 (dd, *J* = 8.2, 5.3 Hz, 1 H), 3.92 (d, *J* = 5.3 Hz, 1 H), 2.91 (m, 1 H), 2.81–2.58 (m, 4 H), 2.47–2.22 (m, 4 H), 1.07 (d, *J* = 7.2 Hz, 3 H), 0.8 (d, *J* = 6.9 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.4, 180.0, 173.7, 169.8, 164.3, 146.3, 142.8, 140.5, 139.3, 136.3, 129.2, 128.7, 128.2, 128.2, 128.0, 127.6, 126.4, 123.6, 122.3, 63.0, 57.8, 52.6, 49.8, 41.9, 39.0, 31.8, 28.1, 24.5, 19.4, 17.2, 14.5; *minor isomer (selected signals)*: ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.53 (d, *J* = 7.3 Hz, 1 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 0.72 (t, *J* = 7.2 Hz, 3 H), 0.66 (t, *J* = 6.4 Hz, 3 H); HRMS (ESI) calcd. for $C_{35}H_{41}N_6O_5^+$ $[M+H]^+$: 625.3133, found: 625.3160.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3R,4S)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-7-(1-pentyl-1*H*-1,2,3-triazol-4-yl)-hepta-2,4-dienamide (12b) According to GP3 10.0 mg (20.3 µmol, 1.0 eq.) **11** were reacted with 2.8 mg (25 µmol, 1.2 eq.) pentyl azide,[4] 10.2 µL (10.2 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 12.2 µL (12.2 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O to MeCN). Yield: 9.8 mg (16.2 µmol, 80 %); pale yellow, amorphous solid; α_D^{20} = –63.1 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (s, 1 H), 8.39 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.83 (s, 1 H), 7.35–7.24 (m, 4 H), 7.21 (m, 1 H), 6.93 (dd, *J* = 15.0, 10.8 Hz, 1 H), 6.20 (dd, *J* = 15.1, 11.1 Hz, 1 H), 6.08 (dt, *J* = 15.1, 6.6 Hz, 1 H), 5.93 (d, *J* = 15.1 Hz, 1 H), 5.27 (m, 1 H), 4.63 (dd, *J* = 8.4, 5.3 Hz, 1 H), 4.27 (t, *J* = 6.9 Hz, 2 H), 3.92 (d, *J* = 5.3 Hz, 1 H), 2.91 (m, 1 H), 2.81–2.59 (m, 4 H), 2.45 (m, 2 H), 2.29 (m, 1 H), 1.76 (quin, *J* = 7.2 Hz, 2 H), 1.26 (m, 2 H), 1.17 (m, 2 H), 1.07 (d, *J* = 7.5 Hz, 3 H), 0.82 (t, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.9 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 145.9, 142.8, 140.6, 139.3, 129.1, 128.2, 126.8, 126.4, 123.5, 121.9, 63.0, 57.8, 49.8, 49.1, 41.9, 38.9, 32.0, 29.4, 28.1, 28.0, 24.5, 21.5, 19.4, 17.2, 14.5, 13.8; HRMS (ESI) calcd. for $C_{33}H_{45}N_6O_5^+$ $[M+H]^+$: 605.3446, found: 605.3451.

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[2] A. Tripolszky, K. Németh, P. T. Szabó and E. Bálint, *Molecules*, 2019, **24**, 2085.
[3] D. X. Hu, P. Grice and S. V. Ley, *J. Org. Chem.*, 2012, **77**, 5198–5202.
[4] S. Jana, S. Adhikari, M. R. Cox and S. Roy, *Chem. Commun.*, 2020, **56**, 1871–1874.

Benzyl 2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)acetate (12c). According to GP3 10.0 mg (20.3 µmol, 1.0 eq.) **11** were reacted with 4.7 mg (25 µmol, 1.2 eq.) benzyl 2-azidoacetate,[5] 10.2 µL (10.2 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 12.2 µL (12.2 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O + 0.1 % HCOOH to MeCN). Yield: 9.2 mg (13.5 µmol, 66 %); colourless, amorphous solid; α_D^{20} = –53.8 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (bs, 1 H), 8.40 (d, *J* = 8.2 Hz, 1 H), 8.10 (d, *J* = 8.5 Hz, 1 H), 7.42–7.24 (m, 9 H), 7.20 (m, 1 H), 6.94 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.23 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.09 (dt, *J* = 15.1, 6.7 Hz, 1 H), 5.95 (d, *J* = 15.3 Hz, 1 H), 5.41 (s, 2 H), 5.27 (td, *J* = 8.2, 6.3 Hz, 1 H), 5.19 (s, 2 H), 4.63 (dd, *J* = 8.4 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.91 (qd, *J* = 7.3, 5.5 Hz, 1 H), 2.80–2.72 (m, 3 H), 2.64 (dd, *J* = 14.4, 6.0 Hz, 1 H), 2.46 (m, 2 H), 2.29 (m, 1 H), 1.07 (d, *J* = 7.5 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 167.3, 164.2, 146.0, 142.8, 140.5,, 139.3, 135.4, 129.1, 128.5, 128.3, 128.2, 128.1, 126.8, 126.4, 123.6, 123.5, 66.7, 63.0, 57.8, 50.2, 49.8, 49.5, 41.9, 38.9, 32.0, 28.1, 24.4, 19.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{37}H_{43}N_6O_7^+$ $[M+H]^+$: 683.3188, found: 683.3210.

2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid (12d). According to GP3 10.0 mg (20.3 µmol, 1.0 eq.) **11** were reacted with 2.5 mg (25 µmol, 1.2 eq.) azidoacetic acid,[6] 10.2 µL (10.2 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 12.2 µL (12.2 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O + 0.1 % HCOOH to MeCN). Yield: 8.5 mg (14.3 µmol, 71 %); colourless, amorphous solid; α_D^{20} = –50.1 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.42 (d, *J* = 8.2 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.82 (s, 1 H), 7.37–7.25 (m, 4 H), 7.21 (m, 1 H) 6.94 (dd, *J* = 15.1, 10.8 Hz, 1 H), 6.23 (dd, *J* = 15.1, 10.8 Hz, 1 H), 6.10 (dt, *J* = 15.3, 6.7 Hz, 1 H), 5.95 (d, *J* = 15.3 Hz, 1 H), 5.27 (td, *J* = 8.1, 6.1 Hz, 1 H), 5.14 (s, 2 H), 4.62 (dd, *J* = 8.2, 5.5 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.91 (m, 1 H), 2.81–2.60 (m, 4 H), 2.46 (m, 2 H), 2.29 (m, 1 H), 1.07 (d, *J* = 7.0 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.4, 180.0, 173.7, 169.8, 168.7, 164.3, 145.8, 142.8, 140.6, 139.3, 129.0, 128.2, 126.8, 126.4, 123.6, 123.3, 63.0, 57.8, 50.6, 49.9, 41.9, 38.9, 32.0, 28.1, 24.5, 19.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{30}H_{37}N_6O_7^+$ $[M+H]^+$: 593.2718, found: 593.2720.

2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)acetic acid (12e). According to GP3 10.0 mg (20.3 µmol, 1.0 eq.) **11** were reacted with 5.6 mg (25 µmol, 1.2 eq.) potassium 2-(2-(2-azidoethoxy)ethoxy)acetate, 10.2 µL (10.2 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 12.2 µL (12.2 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O + 0.1 % HCOOH to MeCN).

[5] R. C. Brewster and A. N. Hulme, *Molecules*, 2021, **26**, 5461.
[6] J. Schmitz, T. Li, U. Bartz and M. Gütschow, *ACS Med. Chem. Lett.*, 2016, **7**, 211–216.

Yield: 13.8 mg (20.3 µmol, 100 %); colourless, amorphous solid; α_D^{20} = –44.6 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 12.48 (bs, 1 H), 11.35 (bs, 1 H), 8.43 (d, *J* = 8.2 Hz, 1 H), 8.13 (d, *J* = 8.1 Hz, 1 H), 7.84 (s, 1 H), 7.39–7.24 (m, 4 H), 7.20 (m, 1 H), 6.94 (dd, *J* = 15.1, 10.8 Hz, 1 H), 6.22 (dd, *J* = 14.6, 11.0 Hz, 1 H), 6.09 (dt, *J* = 15.0, 6.4 Hz, 1 H), 5.94 (d, *J* = 15.1 Hz, 1 H), 5.27 (m, 1 H), 4.62 (m, 1 H), 4.46 (t, *J* = 5.1 Hz, 2 H), 3.97 (s, 2 H), 3.92 (d, *J* = 4.9 Hz, 1 H), 3.78 (t, *J* = 5.0 Hz, 2 H), 3.62–3.49 (m, 4 H), 2.91 (m, 1 H), 2.82–2.58 (m, 4 H), 2.45 (q, *J* = 7.1 Hz, 2 H), 2.29 (m, 1 H), 1.08 (d, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 203.4, 180.0, 173.7, 171.7, 169.8, 164.3, 145.9, 142.8, 140.6, 139.4, 129.0, 128.2, 126.8, 126.4, 123.6, 122.4, 69.7, 69.5, 68.8, 67.6, 63.0, 57.8, 49.9, 49.2, 41.9, 38.9, 32.0, 28.1, 24.5, 19.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{45}N_6O_9^+$ $[M+H]^+$: 681.3243, found: 681.3247.

***tert*-Butyl (2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)carbamate (12f).** According to GP3 20.0 mg (40.6 µmol, 1.0 eq.) **11** were reacted with 13.4 mg (25 µmol, 1.2 eq.) *tert*-butyl (2-(2-(2-azidoethoxy)ethoxy)ethyl)carbamate, 20.3 µL (20.3 µmol, 0.5 eq.) $CuSO_4$ solution (1 M) and 24.4 µL (24.4 µmol, 0.6 eq.) sodium ascorbate solution (1 M). The crude product was purified by reversed phase flash chromatography (H_2O to MeCN) followed by preparative HPLC (Luna® C18(2), H_2O/MeCN 90:10 to 5:95). Yield: 11.7 mg (15.3 µmol, 38 %); pale yellow resin; α_D^{20} = –53.8 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 11.35 (bs, 1 H) 8.39 (d, *J* = 8.5 Hz, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.81 (s, 1 H), 7.34–7.24 (m, 4 H), 7.20 (m, 1 H), 6.94 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.74 (t, *J* = 5.3 Hz, 1 H), 6.22 (dd, *J* = 15.3, 10.7 Hz, 1 H), 6.09 (dt, *J* = 15.1, 6.6 Hz, 1 H), 5.94 (d, *J* = 15.3 Hz, 1 H), 5.27 (td, *J* = 8.5, 6.3 Hz, 1 H), 4.63 (dd, *J* = 8.4, 5.3 Hz, 1 H), 4.45 (t, *J* = 5.3 Hz, 2 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 3.77 (t, *J* = 5.3 Hz, 2 H), 3.49 (m, 2 H), 3.44 (m, 2 H), 3.33 (m, 2 H), 3.04 (q, *J* = 6.0 Hz, 2 H), 2.91 (dd, *J* = 7.4, 5.6 Hz, 1 H), 2.81–2.59 (m, 4 H), 2.46 (q, *J* = 7.2 Hz, 2 H), 2.29 (m, 1 H), 1.36 (s, 9 H), 1.07 (d, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.75 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 155.6, 145.8, 142.8, 140.6, 139.4, 129.0, 128.2, 126.8, 126.4, 123.5, 122.3, 77.6, 69.5, 69.4, 69.1, 68.8, 63.0, 57.8, 49.8, 49.2, 41.9, 40.4, 38.9, 32.1, 28.2, 28.1, 24.5, 19.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{39}H_{56}N_7O_9^+$ $[M+H]^+$: 766.4134, found: 766.4160.

2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethan-1-amine hydrochloride (12g). To a solution of 5.0 mg (6.5 µmol, 1.0 eq.) Boc-protected amine **12f** in 20 µL CH_2Cl_2 were added 16.3 µL (65 µmol, 10 eq.) HCl (4 M in dioxane) at 0 °C. After stirring at the same temperature for 30 min, the resulting suspension was concentrated in vacuo. The residue was dissolved in water and lyophilized. Yield: 4.5 mg (6.4 µmol, 98 %); pale yellow, amorphous solid; α_D^{20} = –55.2 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, DMSO-d$_6$): δ = 11.36 (bs, 1 H), 8.62 (bs, 1 H), 8.24 (d, *J* = 7.6 Hz, 1 H), 7.95 (bs, 3 H), 7.85 (s, 1 H), 7.34–7.24 (m, 4 H), 7.20 (m, 1 H), 6.94 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.22 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.08 (dt, *J* = 15.4, 6.9 Hz, 1 H), 5.97 (d, *J* = 15.3 Hz, 1 H), 5.25 (td, *J* = 8.4, 6.1 Hz, 1 H), 4.59 (dd, *J* = 7.9, 5.8 Hz, 1 H), 4.47 (t, *J* = 5.2 Hz, 2 H),

3.94 (d, *J* = 5.3 Hz, 1 H), 3.79 (t, *J* = 5.3 Hz, 2 H), 3.58–3.48 (m, 6 H), 2.96–2.81 (m, 4 H), 2.74 (t, *J* = 7.4 Hz, 2 H), 2.61 (m, 1 H), 2.46 (m, 2 H), 2.29 (m, 1 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.5, 180.0, 173.8, 169.9, 164.3, 145.8, 143.0, 140.5, 139.3, 129.0, 128.2, 126.8, 126.4, 123.6, 122.5, 69.5, 69.4, 68.8, 66.6, 63.2, 57.7, 50.0, 49.3, 41.9, 38.5, 32.0, 28.1, 24.5, 19.4, 17.3, 14.6; HRMS (ESI) calcd. for $C_{34}H_{48}N_7O_7^+$ $[M–Cl]^+$: 666.3610, found: 666.3615.

Methyl (*S*)-3-phenyl-3-((2*E*,4*E*)-9-phenylnona-2,4-dien-8-ynamido)propanoate (13a). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 52.6 µL (ρ = 1.823 g/mL, 470 µmol, 3.5 eq.) iodobenzene, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 6:4). Yield: 34.7 mg (90 µmol, 67 %); pale yellow, amorphous solid; R_f 0.48 (pentane/EtOAc 1:1); α_D^{20} = –49.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.17 (m, 11 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 6.23 (dd, *J* = 15.2, 10.4 Hz, 1 H), 6.15 (dt, *J* = 15.3, 6.4, 1 H), 5.85 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.4, 5.9 Hz, 1 H), 3.60 (s, 3 H), 2.97 (dd, *J* = 15.8, 5.9 Hz, 1 H), 2.85 (dd, *J* = 15.9, 5.9 Hz, 1 H), 2.53 (m, 2 H), 2.45 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.4, 141.3, 140.6, 140.5, 131.5, 129.3, 128.6, 128.2, 127.7, 127.5, 126.2, 123.6, 122.4, 88.8, 81.4, 51.8, 49.4, 39.6, 32.0, 19.1; HRMS (ESI) calcd. for $C_{25}H_{26}NO_3^+$ $[M+H]^+$: 388.1907, found: 388.1929.

Methyl (*S*)-3-((2*E*,4*E*)-9-(4-chlorophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13b). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 112 mg (470 µmol, 3.5 eq.) 1-chloro-4-iodobenzene, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 6:4). Yield: 35.3 mg (84 µmol, 62 %); pale yellow solid; m.p. 123–124 °C; R_f 0.57 (pentane/EtOAc 1:1); α_D^{20} = –48.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.14 (m, 10 H), 6.73 (d, *J* = 8.1 Hz, 1 H), 6.22 (dd, *J* = 15.2, 10.6 Hz, 1 H), 6.13 (dt, *J* = 15.3, 6.1 Hz, 1 H), 5.85 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 7.8, 5.7 Hz, 1 H), 3.60 (s, 3 H), 2.96 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.85 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.51 (m, 2 H), 2.44 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.3, 141.3, 140.5, 140.4, 133.6, 132.8, 129.4, 128.7, 128.5, 127.6, 126.2, 122.5, 122.1, 89.9, 80.4, 51.8, 49.4, 39.6, 31.9, 19.1; HRMS (ESI) calcd. for $C_{25}H_{25}NO_3Cl^+$ $[M+H]^+$: 422.1517, found: 422.1517.

Methyl (*S*)-3-((2*E*,4*E*)-9-(4-nitrophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13c). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 117 mg (470 µmol, 3.5 eq.) 1-iodo-4-nitrobenzene, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 1:1). Yield: 42.4 mg (98 µmol, 73 %); yellow resin; R_f 0.37 (pentane/EtOAc 1:1); α_D^{20} = –51.7 (c = 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J* = 8.8 Hz, 2 H), 7.49 (d, *J* = 8.8 Hz, 2 H), 7.35–7.17 (m, 6 H), 6.77 (m, 1 H), 6.24 (dd, *J* = 15.0, 10.6 Hz, 1 H), 6.12 (dt, *J* = 15.2, 6.6 Hz, 1 H), 5.87 (d, *J* = 14.9 Hz, 1 H), 5.50 (dt, *J* = 8.4, 5.9 Hz, 1 H), 3.60 (s, 3 H), 2.96 (dd, *J* = 15.8, 5.9 Hz, 1 H), 2.85 (dd, *J* = 16.0, 6.0 Hz, 1 H), 2.57 (m, 2 H), 2.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.3, 146.6, 141.1, 140.4, 139.9, 132.2, 130.7,

129.6, 128.6, 127.6, 126.2, 123.5, 122.7, 94.9, 80.0, 51.8, 49.5, 39.6, 31.6, 19.2; HRMS (ESI) calcd. for $C_{25}H_{25}O_5N_2^+$ $[M+H]^+$: 433.1758, found: 433.1765.

Methyl (*S*)-3-((2*E*,4*E*)-9-(4-methoxyphenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13d). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 110 mg (470 µmol, 3.5 eq.) 4-iodoanisole, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 6:4). Yield: 35.4 mg (85 µmol, 63 %); pale yellow, amorphous solid; R_f 0.41 (pentane/EtOAc 1:1); α_D^{20} = –49.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 8 H), 6.23 (dd, *J* = 15.2, 10.3 Hz, 1 H), 6.15 (dt, *J* = 15.2, 6.0 Hz, 1 H), 5.85 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.2, 5.9 Hz, 1 H), 3.78 (s, 3 H), 3.60 (s, 3 H), 2.97 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.85 (dd, *J* = 15.9, 6.0 Hz, 1 H), 2.50 (m, 2 H), 2.44 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.4, 159.1, 141.4, 140.8, 140.5, 132.9, 129.3, 128.7, 127.5, 126.2, 122.3, 115.8, 113.8, 87.2, 81.1, 55.2, 51.8, 49.4, 39.6, 32.2, 19.1; HRMS (ESI) calcd. for $C_{26}H_{28}NO_4^+$ $[M+H]^+$: 418.2013, found 418.2018.

Methyl (*S*)-3-((2*E*,4*E*)-9-(4-aminophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13e). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 103 mg (470 µmol, 3.5 eq.) 4-iodoaniline, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by normal phase (cyclohexane to cyclohexane/EtOAc 44:55) followed by reversed phase flash chromategraphy (H_2O to MeCN). Yield: 21.1 mg (52 µmol, 39 %); pale yellow, amorphous solid; R_f 0.45 (pentane/EtOAc 1:1); α_D^{20} = –51.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 6 H), 7.18 (d, *J* = 8.6 Hz, 2 H), 6.65 (d, *J* = 8.3 Hz, 1 H), 6.57 (d, *J* = 8.6 Hz, 2 H), 6.22 (dd, *J* = 15.4, 10.0 Hz, 1 H), 6.15 (dt, *J* = 15.0, 6.2 Hz, 1 H), 5.83 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.3, 5.9 Hz, 1 H), 3.75 (bs, 2 H), 3.61 (s, 3 H), 2.97 (dd, *J* = 15.8, 5.9 Hz, 1 H), 2.86 (dd, *J* = 15.8, 6.0 Hz, 1 H), 2.50 (m, 2 H), 2.43 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 165.4, 146.1, 141.5, 141.0, 140.5, 132.7, 129.2, 128.7, 127.6, 126.2, 122.2, 114.7, 113.1, 86.2, 81.6, 51.8, 49.4, 39.6, 32.3, 19.2; HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_3^+$ $[M+H]^+$: 403.2016, found: 403.2022.

Methyl (*S*)-3-((2*E*,4*E*)-9-(4-hydroxyphenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13f). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 103 mg (470 µmol, 3.5 eq.) 4-iodophenol, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromategraphy (cyclohexane to cyclohexane/EtOAc 3:7). Yield: 29.5 mg (73 µmol, 55 %); pale yellow resin; R_f 0.11 (pentane/EtOAc 1:1); α_D^{20} = –55.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (bs, 1 H), 7.37–7.14 (m, 8 H), 6.89 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 8.6 Hz, 2 H), 6.19 (dd, *J* = 15.3, 9.9 Hz, 1 H), 6.11 (dt, *J* = 15.2, 6.2 Hz, 1 H), 5.83 (d, *J* = 15.2 Hz, 1 H), 5.49 (dt, *J* = 8.4, 6.0 Hz, 1 H), 3.59 (s, 3 H), 2.94 (dd, *J* = 15.8, 6.2 Hz, 1 H), 2.84 (dd, *J* = 15.8, 5.7 Hz, 1 H), 2.48 (m, 2 H), 2.41 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 166.0, 156.3, 142.0, 141.5, 140.2, 133.0, 129.1, 128.7, 127.7, 126.2, 121.8, 115.5, 114.9, 86.7, 81.4, 51.9, 49.7, 39.7, 32.2, 19.1; HRMS (ESI) calcd. for $C_{25}H_{26}NO_4^+$ $[M+H]^+$: 404.1856, found: 404.1874.

Methyl (*S*)-3-((2*E*,4*E*)-9-(2-fluorophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13g). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted

with 54.8 µL (ρ = 1.903 g/mL, 470 µmol, 3.5 eq.) 1-fluoro-2-iodobenzene, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by normal phase (cyclohexane to cyclohexane/EtOAc 6:4) followed by reversed phase flash chromatography (H_2O to MeCN). Yield: 15.4 mg (38 µmol, 28 %); pale yellow resin; R_f 0.45 (pentane/EtOAc 1:1); α_D^{20} = –35.2 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.18 (m, 8 H), 7.09–6.99 (m, 2 H), 6.64 (d, *J* = 8.3 Hz, 1 H), 6.26 (dd, *J* = 15.3, 10.6 Hz, 1 H), 6.16 (dt, *J* = 15.0, 6.5 Hz, 1 H), 5.86 (d, *J* = 15.0 Hz, 1 H), 5.52 (dt, *J* = 8.3, 5.9 Hz, 1 H), 3.61 (s, 3 H), 2.98 (dd, *J* = 15.9, 5.6 Hz, 1 H), 2.87 (dd, *J* = 15.9, 5.9 Hz, 1 H), 2.57 (m, 2 H), 2.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 165.4, 162.8 (d, $J_{C,F}$ = 250.2 Hz), 141.4, 140.5, 140.4, 135.5, 129.5, 129.3 (d, $J_{C,f}$ = 8.1 Hz), 128.7, 127.6, 126.2, 123.8 (d, $J_{C,f}$ = 3.7 Hz), 122.4, 115.3 (d, $J_{C,F}$ = 20.5 Hz), 112.1 (d, $J_{C,f}$ = 16.1 Hz), 94.3 (d, $J_{C,f}$ = 3.7 Hz), 74.8, 51.8, 49.4, 39.6, 31.9, 19.3; ^{19}F NMR (377 MHz, $CDCl_3$): δ = –110.9 (s, 1 F); HRMS (ESI) calcd. for $C_{25}H_{25}NO_3F^+$ $[M+H]^+$: 406.1813, found: 406.1820.

Methyl (*S*)-3-((2*E*,4*E*)-9-(2-nitrophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13h). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 117 mg (470 µmol, 3.5 eq.) 1-iodo-2-nitrobenzene, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI. The crude product was purified by flash chromatography (cyclohexane to cyclohexane/EtOAc 1:1). Yield: 39.0 mg (90 µmol, 67 %); pale yellow resin; R_f 0.46 (pentane/EtOAc 1:1); α_D^{20} = –40.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 1 H), 7.59–7.47 (m, 2 H), 7.39 (ddd, *J* = 8.4, 6.7, 1.8 Hz, 1 H), 7.34–7.16 (m, 6 H), 6.72 (m, 1 H), 6.26 (dd, *J* = 15.4, 10.6 Hz, 1 H), 6.14 (dt, *J* = 14.9, 6.6 Hz, 1 H), 5.88 (d, *J* = 15.0 Hz, 1 H), 5.50 (dt, *J* = 8.3, 6.0 Hz, 1 H), 3.60 (s, 3 H), 2.96 (dd, *J* = 15.9, 6.0 Hz, 1 H), 2.85 (dd, *J* = 15.8, 6.0 Hz, 1 H), 2.59 (m, 2 H), 2.48 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.4, 150.0, 141.2, 140.5, 140.0, 134.8, 132.6, 129.7, 128.6, 128.1, 127.5, 126.3, 124.4, 122.6, 118.9, 97.6, 76.7, 51.8, 49.5, 39.7, 31.5, 19.5; HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_5^+$ $[M+H]^+$: 433.1758, found: 433.1782.

Methyl (*S*)-3-phenyl-3-((2*E*,4*E*)-9-(pyridin-3-yl)nona-2,4-dien-8-ynamido)propanoate (13i). According to GP4 41.8 mg (134 µmol, 1.0 eq.) alkyne **9** were reacted with 96 mg (470 µmol, 3.5 eq.) 3-iodopyridine, 9.4 mg (13 µmol, 0.1 eq.) $Pd(PPh_3)_2Cl_2$ and 5.1 mg (27 µmol, 0.2 eq.) CuI, except that the reaction was carried out at 60 °C for 2 h. The crude product was purified by normal-phase (cyclohexane/EtOAc 1:1 to 3:7) followed by reversed-phase flash chromatography (H_2O to MeCN). Yield: 25.1 mg (65 µmol, 48 %); colourless resin; R_f 0.45 (pentane/EtOAc 1:1); α_D^{20} = –47.1 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (bs, 1 H), 8.5 (bs, 1 H), 7.66 (d, *J* = 7.9 Hz, 1 H), 7.35–7.16 (m, 7 H), 6.77 (d, *J* = 8.3 Hz, 1 H), 6.24 (dd, *J* = 15.2, 10.6 Hz, 1 H), 6.12 (dt, *J* = 15.4, 6.6 Hz, 1 H), 5.86 (d, *J* = 15.0 Hz, 1 H), 5.51 (dt, *J* = 8.3, 6 Hz, 1 H), 3.60 (s, 3 H), 2.97 (dd, *J* = 15.9, 5.9 Hz, 1 H), 2.85 (dd, *J* = 15.8, 5.9 Hz, 1 H), 2.54 (m, 2 H), 2.46 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 165.3, 125.1, 147.9, 141.2, 140.5, 140.1, 138.6, 129.6, 128.7, 127.6, 126.2, 123.0, 122.6, 120.9, 92.6, 78.1, 51.8, 49.5, 39.6, 31.8, 19.1; HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_3^+$ $[M+H]^+$: 389.1860, found 389.1890.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-phenylnona-2,4-dien-8-ynamide (14a) According to GP1 34.2 mg (88.2 µmol, 1.0 eq.) methyl ester **13a** were saponified using 185 µL (185 µmol, 2.1 eq.) LiOH (1 M in water) under reflux for 2 h. According to GP2 the crude acid was reacted with 22.0 mg (88.2 µmol, 1.0 eq.) amine **2**, 45.9 mg (88.2 µmol, 1.0 eq.) PyBOP and 38.8 mg (318 µmol, 3.6 eq.) DMAP. The product was purified by normal-phase flash chromatography (cyclohexane to EtOAc). Yield: 28.0 mg (49.3 µmol, 56 %); pale yellow, amorphous solid; α_D^{20} = –70.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.09 (d, *J* = 8.5 Hz, 1 H), 7.42–7.25 (m, 9 H), 7.21 (m, 1 H), 7.00 (dd, *J* = 15.0, 10.9 Hz, 1 H), 6.31 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.14 (dt, *J* = 15.3, 6.9 Hz, 1 H), 5.99 (d, *J* = 15.1 Hz, 1 H), 5.28 (td, *J* = 8.4, 6.2 Hz, 1 H), 4.64 (dd, *J* = 8.5, 5.3 Hz, 1 H), 3.93 (d, *J* = 5.5 Hz, 1 H), 2.92 (dd, *J* = 7.3, 5.6 Hz, 1 H), 2.77 (dd, *J* = 14.3, 8.6 Hz, 1 H), 2.65 (dd, *J* = 14.3, 5.9 Hz, 1 H), 2.55 (t, *J* = 6.9 Hz, 2 H), 2.40 (q, *J* = 6.9 Hz, 2 H), 2.28 (m, 1 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.74 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 142.8, 139.6, 139.2, 131.2, 129.6, 128.5, 128.2, 128.0, 126.8, 126.4, 123.9, 123.1, 89.8, 81.1, 63.0, 57.8, 49.9, 42.0, 38.9, 31.4, 28.2, 19.4, 18.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{38}N_3O_5^+$ $[M+H]^+$: 568.2806, found: 568.2814.

(2*E*,4*E*)-9-(4-Chlorophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14b). According to GP1 35.0 mg (83.0 µmol, 1.0 eq.) methyl ester **13b** were saponified using 91 µL (91 µmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 46 h. According to GP2 the crude acid was reacted with 20.6 mg (83.0 µmol, 1.0 eq.) amine **2**, 43.2 mg (83.0 µmol, 1.0 eq.) PyBOP and 36.5 mg (299 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield: 37.4 mg (62.1 µmol, 75 %); pale yellow, amorphous solid; R_f 0.56 (EtOAc); α_D^{20} = –68.6 (c = 0.5, $CHCl_3$/MeOH 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.37 (bs, 1 H), 8.42 (d, *J* = 8.2 Hz, 1 H), 8.09 (d, *J* = 8.2 Hz, 1 H), 7.43–7.34 (m, 4 H), 7.34–7.24 (m, 4 H), 7.20 (m, 1 H), 7.00 (dd, *J* = 14.6, 11.3 Hz, 1 H), 6.30 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.13 (dt, *J* = 15.1, 6.7 Hz, 1 H), 5.99 (d, *J* = 15.3 Hz, 1 H), 5.29 (m, 1 H), 4.64 (dd, *J* = 7.7, 5.7 Hz, 1 H), 3.93 (d, *J* = 5.5 Hz, 1 H), 2.92 (dd, *J* = 7.3, 5.6 Hz, 1 H), 2.77 (dd, *J* = 13.8, 8.9 Hz, 1 H), 2.65 (dd, *J* = 14.1, 5.3 Hz, 1 H), 2.55 (t, *J* = 7.0 Hz, 2 H), 2.40 (q, *J* = 6.4 Hz, 2 H), 2.28 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 142.8, 139.5, 139.2, 132.9, 132.7, 129.7, 128.7, 128.2, 126.8, 126.4, 124.0, 122.0, 91.1, 80.0, 63.0, 57.8, 49.9, 42.0, 38.9, 31.3, 28.2, 19.4, 18.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{37}N_3O_5Cl^+$ $[M+H]^+$: 602.2416, found: 602.2431.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(4-nitrophenyl)nona-2,4-dien-8-ynamide (14c). According to GP1 41.1 mg (94.8 µmol, 1.0 eq.) methyl ester **13c** were saponified using 105 µL (105 µmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 46 h. According to GP2 the crude acid was reacted with 23.6 mg (94.8 µmol, 1.0 eq.) amine **2**, 49.5 mg (94.8 µmol, 1.0 eq.) PyBOP and 41.8 mg (342 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield:

45.1 mg (73.6 µmol, 77 %); pale yellow, amorphous solid; R_f 0.53 (EtOAc); α_D^{20} = –73.8 (c = 0.5, $CHCl_3$/MeOH 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.43 (d, *J* = 8.4 Hz, 1 H), 8.18 (d, *J* = 8.7 Hz, 2 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.62 (d, *J* = 8.7 Hz, 2 H), 7.35–7.24 (m, 4 H), 7.20 (m, 1 H), 7.01 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.32 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.15 (dt, *J* = 15.1, 6.9 Hz, 1 H), 6.00 (d, *J* = 15.3 Hz, 1 H), 5.29 (m, 1 H), 4.64 (dd, *J* = 8.2, 5.3 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.92 (m, 1 H), 2.77 (dd, *J* = 14.0, 8.9 Hz, 1 H), 2.69–2.58 (m, 3 H), 2.43 (q, *J* = 6.7 Hz, 2 H), 2.28 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.73 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 146.4, 142.8, 139.3, 139.2, 123.4, 130.0, 129.8, 128.2, 126.9, 126.4, 124.0, 123.8, 96.0, 79.8, 63.0, 57.8, 49.9, 41.9, 38.9, 31.1, 28.2, 19.4, 18.6, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{37}N_4O_7^+$ $[M+H]^+$: 613.2657, found: 613.2676.

(2*E*,4*E*)-9-(4-Methoxyphenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14d). According to GP1 33.1 mg (79.2 µmol, 1.0 eq.) methyl ester **13d** were saponified using 87 µL (87 µmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 46 h. According to GP2 the crude acid was reacted with 19.7 mg (79.2 µmol, 1.0 eq.) amine **2**, 41.3 mg (79.2 µmol, 1.0 eq.) PyBOP and 34.9 mg (285 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield: 35.1 mg (58.7 µmol, 74 %); pale yellow, amorphous solid; R_f 0.53 (EtOAc); α_D^{20} = –41.3 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.42 (d, *J* = 8.5 Hz, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.35–7.25 (m, 6 H), 7.21 (m, 1 H), 7.00 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 6.30 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.13 (dt, *J* = 15.4, 6.9 Hz, 1 H), 5.99 (d, *J* = 15.1 Hz, 1 H), 5.29 (td, *J* = 8.2, 6.1 Hz, 1 H), 4.65 (dd, *J* = 8.5, 5.3 Hz, 1 H), 3.93 (d, *J* = 5.5 Hz, 1 H), 3.75 (s, 3 H), 2.92 (m, 1 H), 2.77 (dd, *J* = 14.3, 8.6 Hz, 1 H), 2.65 (dd, *J* = 14.2, 6.0 Hz, 1 H), 2.52 (m, 2 H), 2.38 (q, *J* = 6.9 Hz, 2 H), 2.29 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 158.8, 142.8, 139.7, 139.2, 132.6, 129.6, 128.2, 126.8, 126.4, 123.9, 115.1, 114.1, 88.0, 80.9, 63.0, 57.8, 55.2, 49.9, 42.0, 38.9, 31.5, 28.2, 19.4, 18.4, 17.2, 14.5; HRMS (ESI) calcd. for $C_{35}H_{40}N_3O_6^+$ $[M+H]^+$: 598.2912, found: 598.2908.

(2*E*,4*E*)-9-(4-Aminophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14e). According to GP1 20.4 mg (50.6 µmol, 1.0 eq.) methyl ester **13e** were saponified using 55.8 µL (55.8 µmol, 1.1 eq.) LiOH (1 M in water) at room temperature for 46 h. Contrary to the general procedure, the carboxylate was used in the next step without acidification. According to GP2 the crude carboxylate was reacted with 12.6 mg (50.6 µmol, 1.0 eq.) amine **2**, 26.4 mg (50.6 µmol, 1.0 eq.) PyBOP and 22.3 mg (186 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield: 22.4 mg (38.4 µmol, 76 %); pale yellow, amorphous solid; R_f 0.46 (EtOAc); α_D^{20} = –67.6 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 7.40–7.24 (m, 4 H), 7.21 (m, 1 H), 7.11–6.89 (m, 3 H), 6.47 (d, *J* = 8.1 Hz, 2 H), 6.28 (dd, *J* = 14.6, 11.3 Hz, 1 H), 6.12 (dt, *J* = 15.1, 6.6 Hz, 1 H), 5.98 (d, *J* = 15.1 Hz, 1 H), 5.59–5.06 (m, 3 H), 4.65 (dd, *J* = 8.2, 5.3 Hz, 1 H), 3.93 (d, *J* = 5.3 Hz, 1 H), 2.92 (m, 1 H), 2.77 (dd, *J* =

14.1, 8.8 Hz, 1 H), 2.64 (dd, *J* = 14.3, 5.7 Hz, 1 H), 2.47 (t, *J* =7.0 Hz, 2 H), 2.36 (q, *J* = 6.6 Hz, 2 H), 2.29 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 148.6, 142.8, 139.9, 139.3, 132.2, 129.4, 128.2, 126.8, 126.4, 123.8, 113.6, 109.4, 85.8, 82.2, 63.0, 57.8, 49.9, 42.0, 38.9, 31.8, 28.2, 19.4, 18.6, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{39}N_4O_5^+$ $[M+H]^+$: 583.2915, found: 583.2938.

(2*E*,4*E*)-9-(4-Hydroxyphenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14f). According to GP1 29.2 mg (72.3 µmol, 1.0 eq.) methyl ester **13f** were saponified using 152 µL (152 µmol, 2.1 eq.) LiOH (1 M in water) at room temperature for 46 h. According to GP2 the crude acid was reacted with 18.0 mg (72.3 µmol, 1.0 eq.) amine **2**, 37.7 mg (72.3 µmol, 1.0 eq.) PyBOP and 31.8 mg (261 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc) followed by preparative HPLC (Luna® C18(2), H_2O + 0. 1 % HCOOH/MeCN 90:10 to 5:95). Yield: 15.1 mg (25.9 µmol, 36 %); colourless, amorphous solid; R_f 0.48 (EtOAc); α_D^{20} = –69.7 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 9.71 (s, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.5 Hz, 1 H), 7.35–7.25 (m, 4 H), 7.20 (m, 1 H), 7.17 (d, *J* = 8.5 Hz, 2 H), 6.98 (d, *J* = 15.0, 10.9 Hz, 1 H), 6.70 (d, *J* = 8.5 Hz, 2 H), 6.29 (dd, *J* = 15.0, 11.1 Hz, 1 H), 6.13 (dt, *J* = 15.1, 6.9 Hz, 1 H), 5.98 (d, *J* = 15.1 Hz, 1 H), 5.28 (td, *J* = 8.2, 6.0 Hz, 1 H), 4.64 (dd, *J* = 8.4, 5.3 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.92 (dd, *J* = 7.3, 5.6 Hz, 1 H), 2.77 (dd, *J* = 14.3, 8.6 Hz, 1 H), 2.64 (dd, *J* = 14.2, 6.0 Hz, 1 H), 2.49 (m, 2 H), 2.37 (q, *J* = 6.8 Hz, 2 H), 2.28 (m, 1 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 0.80 (d, *J* = 6.7 Hz, 3 H), 0.74 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 157.3, 142.8, 139.8, 139.3, 132.7, 129.5, 128.3, 126.9, 126.4, 123.8, 115.5, 113.4, 87.2, 81.3, 63.0, 57.8, 49.9, 42.0, 38.9, 31.6, 28.2, 19.4, 18.5, 17.2, 14.5; HRMS (ESI) calcd. for $C_{34}H_{38}N_3O_6^+$ $[M+H]^+$: 584.2755, found: 584.2776.

(2*E*,4*E*)-9-(2-Fluorophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14g). According to GP1 14.7 mg (36.3 µmol, 1.0 eq.) methyl ester **13g** were saponified using 76.2 µL (76.2 µmol, 2.1 eq.) LiOH (1 M in water) at reflux for 4 h. Contrary to the general procedure, a mixture of 360 µL THF and 300 µL methanol was used as solvent. Subsequently, according to GP2 the crude acid was reacted with 9.0 mg (36 µmol, 1.0 eq.) amine **2**, 18.8 mg (36.3 µmol, 1.0 eq.) PyBOP and 16.0 mg (161 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc) followed by preparative HPLC (Luna® C18(2), H_2O + 0.1 % HCOOH/MeCN 90:10 to 5:95). Yield: 1.6 mg (2.7 µmol, 8 %); colourless, amorphous solid; R_f 0.48 (EtOAc); α_D^{20} = –92.5 (c = 0.2, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (bs, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.07 (d, *J* = 8.5 Hz, 1 H), 7.44 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.39 (m, 1 H), 7.32–7.15 (m, 7 H), 6.98 (d, *J* = 15.0, 10.9 Hz, 1 H), 6.31 (dd, *J* = 15.1, 11.0 Hz, 1 H), 6.13 (dt, *J* = 15.4, 6.9 Hz, 1 H), 5.98 (d, *J* = 15.1 Hz, 1 H), 5.27 (td, *J* = 8.4, 6.2 Hz, 1 H), 4.64 (dd, *J* = 8.4, 5.3 Hz, 1 H), 3.92 (d, *J* = 5.5 Hz, 1 H), 2.91 (dd, *J* = 7.4, 5.6 Hz, 1 H), 2.76 (dd, *J* = 14.3, 8.6 Hz, 1 H), 2.67–2.57 (m, 3 H), 2.41 (q, *J* = 6.9 Hz, 2 H), 2.28 (m, 1 H), 1.07 (d, *J* = 7.3 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.73 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7,

169.8, 164.3, 162.0 (d, $J_{C,F}$ = 250.0 Hz), 142.8, 139.4, 139.2, 133.4, 130.1 (d, $J_{C,F}$ = 8.3 Hz), 129.7, 128.2, 126.8, 126.4, 124.6 (d, $J_{C,F}$ = 3.7 Hz), 123.9, 115.5 (d, $J_{C,F}$ = 21.1 Hz), 111.3 (d, $J_{C,F}$ = 16.5 Hz), 95.3 (d, $J_{C,F}$ = 2.8 Hz), 74.3, 63.0, 57.8, 49.9, 41.9, 38.9, 31.2, 28.1, 19.4, 18.6, 17.1, 14.5; ^{19}F NMR (471 MHz, DMSO-d_6) δ –111.3 (m, 1 F); HRMS (ESI) calcd. for $C_{34}H_{37}N_3O_5F^+$ $[M+H]^+$: 586.2712, found: 586.2719.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(2-nitrophenyl)nona-2,4-dien-8-ynamide (14h). According to GP1 38.0 mg (87.9 µmol, 1.0 eq.) methyl ester **13h** were saponified using 185 µL (185 µmol, 2.1 eq.) LiOH (1 M in water) at reflux for 1 h. According to GP2 the crude acid was reacted with 21.9 mg (87.9 µmol, 1.0 eq.) amine **2**, 45.7 mg (87.9 µmol, 1.0 eq.) PyBOP and 38.6 mg (316 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (cyclohexane to EtOAc). Yield: 33.4 mg (54.5 µmol, 62 %); pale yellow, amorphous solid; α_D^{20} = –64.3 (c = 1.0, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.36 (bs, 1 H), 8.42 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.4 Hz, 1 H), 8.03 (d, *J* = 8.2 Hz, 1 H), 7.72–7.62 (m, 2 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.38–7.25 (m, 4 H), 7.20 (m, 1 H), 6.99 (d, *J* = 15.0, 11.1 Hz, 1 H), 6.32 (dd, *J* = 14.9, 11.2 Hz, 1 H), 6.15 (dt, *J* = 15.0, 6.9 Hz, 1 H), 5.99 (d, *J* = 15.1 Hz, 1 H), 5.28 (td, *J* = 8.1, 6.4 Hz, 1 H), 4.64 (dd, *J* = 8.4, 5.3 Hz, 1 H), 3.93 (d, *J* = 5.5 Hz, 1 H), 2.92 (dd, *J* = 7.2, 5.6 Hz, 1 H), 2.77 (dd, *J* = 14.2, 8.7 Hz, 1 H), 2.68–2.56 (m, 3 H), 2.42 (q, *J* = 6.5 Hz, 2 H), 2.28 (m, 1 H), 1.08 (d, *J* = 7.5 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H), 0.73 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 149.9, 142.8, 139.3, 139.2, 134.4, 133.3, 129.7, 129.1, 128.2, 126.8, 126.4, 124.3, 124.0, 117.3, 97.9, 76.1, 63.0, 57.8, 49.9, 42.0, 38.9, 31.0, 28.2, 19.4, 18.8, 17.1, 14.5; HRMS (ESI) calcd. for $C_{34}H_{37}N_4O_7^+$ $[M+H]^+$: 613.2657, found: 613.2679.

(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(pyridin-3-yl)nona-2,4-dien-8-ynamide (14i) According to GP1 25.0 mg (64.4 µmol, 1.0 eq.) methyl ester **13i** were saponified using 135 µL (135 µmol, 2.1 eq.) LiOH (1 M in water) at reflux for 1 h. Contrary to the general procedure, a mixture of 780 µL THF and 700 µL methanol was used as solvent and the carboxylate was used in the next step without acidification. Subsequently, according to GP2 the crude carboxylate was reacted with 16.0 mg (64.4 µmol, 1.0 eq.) amine **2**, 33.5 mg (64.4 µmol, 1.0 eq.) PyBOP and 28.3 mg (232 µmol, 3.6 eq.) DMAP. The product was purified by flash chromatography (CH_2Cl_2 to CH_2Cl_2/MeOH 85:15) followed by preparative HPLC (Luna® C18(2), H_2O + 0.1 % HCOOH/MeCN 90:10 to 5:95). Yield: 2.5 mg (4.4 µmol, 7 %); colourless, amorphous solid; α_D^{20} = –74.8 (c = 0.25, $CHCl_3$/MeOH 1:1); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.35 (bs, 1 H), 8.57 (bs, H), 8.51 (bs, 1 H), 8.41 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.5 Hz, 1 H, 7.78 (dt, *J* = 7.8, 1.7 Hz, 1 H), 7.37 (dd, *J* = 7.8, 4.9 Hz, 1 H), 7.34–7.24 (m, 4 H), 7.20 (m, 1 H), 6.99 (m, 1 H), 6.32 (dd, *J* = 14.8, 11.1 Hz, 1 H), 6.15 (dt, *J* = 15.3, 6.9 Hz, 1 H), 5.99 (d, *J* = 15.3 Hz, 1 H), 5.27 (td, *J* = 8.3, 6.3 Hz, 1 H), 4.63 (dd, *J* = 8.5, 5.3 Hz, 1 H), 3.93 (d, *J* = 5.6 Hz, 1 H), 2.91 (dd, *J* = 7.3, 5.5 Hz, 1 H), 2.76 (dd, *J* = 14.3, 8.7 Hz, 1 H), 2.68–2.55 (m, 3 H), 2.42 (q, *J* = 7.0 Hz, 2 H), 2.28 (m, 1 H), 1.07 (d, *J* = 7.5 Hz, 3 H), 0.79 (d, *J* = 6.7 Hz, 3 H), 0.73 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.3, 180.0, 173.7, 169.8, 164.3, 151.6, 148.4, 142.8, 139.4, 139-2, 138.4, 129.7, 128.2, 126.8, 126.4, 124.0, 123.5, 120.1, 93.3, 78.0, 63.0, 57.8, 49.9, 45.9,

38.9, 31.2, 28.1, 19.4, 18.5, 17.1, 14.5; HRMS (ESI) calcd. for $C_{33}H_{37}N_4O_5^+$ $[M+H]^+$: 569.2758, found: 569.2765.

Biological activities of Moiramide derivatives

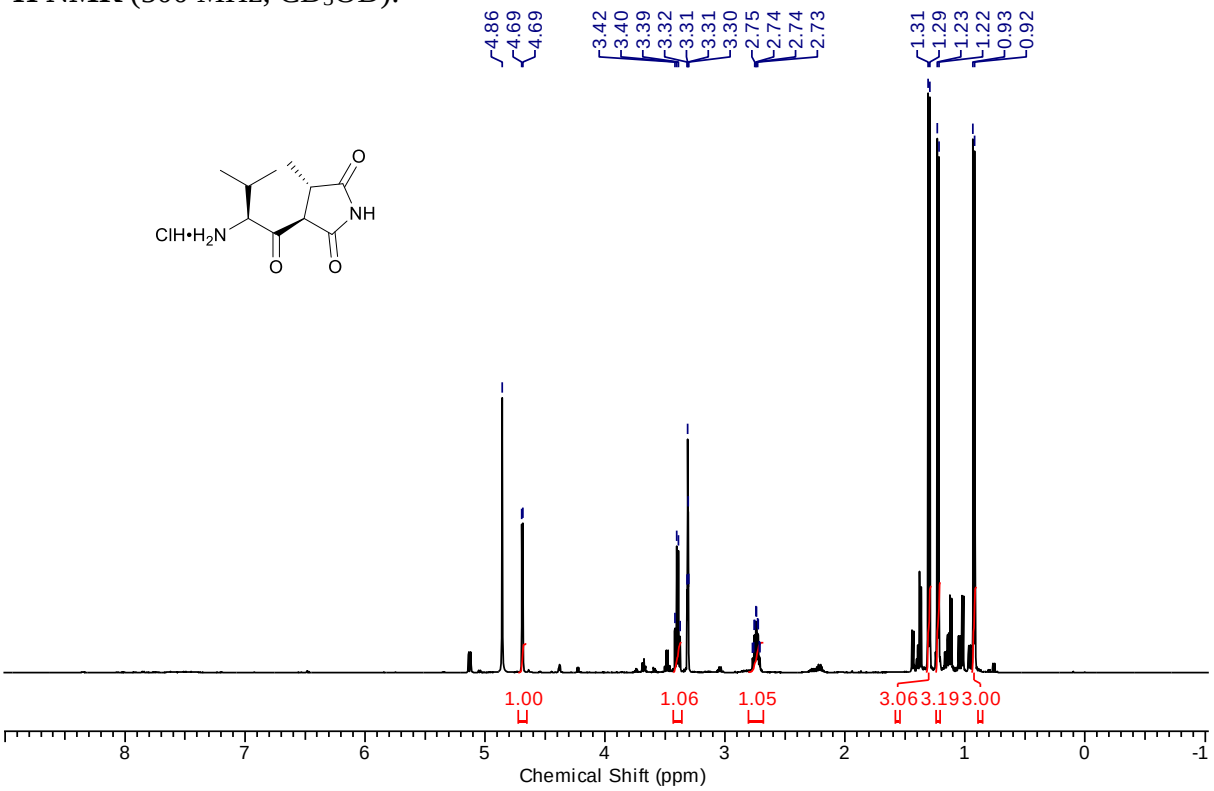
	MIC [µg/mL]													IC50 [µg/mL]
Comp.	*B. subtilis* [DSM-10]	*S. aureus* Newman	*M. smegmatis* [MC2155]	*M. tuberculosis* [H37Ra]	*C. freundii* [DSM-30039]	*E. coli WT* [BW25113]	*E. coli acrB* [JW0451-2]	*P.aeruginosa* PA14 [DSM-19882]	*A. baumannii* [DSM-30008]	*M. hiemalis* [DSM-2656]	*P. anomala* [DSM-6766]	*C. neoformans* [DSM-11959]	*C. albicans* [DSM-1665]	HepG2
4	1-2	1-2	≥64	≥64	≥64	(32*)	4	≥64	≥64	≥64	≥64	≥64	≥64	≥37
5	16	4-8	≥64	≥64	≥64	≥64	32	≥64	≥64	≥64	≥64	≥64	≥64	≥37
11	4-8	4	≥64	≥64	≥64	≥64	16-32	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12a	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12b	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12c	-64	64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12d	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12e	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12f	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
12g	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14a	2-4	1	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14b	4	2	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14c	8-16	2	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14d	16	2	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14e	8-16	1	≥64	≥64	≥64	≥64	64	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14f	4	1	≥64	≥64	≥64	≥64	32 (64*)	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14g	8	2	≥64	≥64	≥64	≥64	(64*)	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14h	8-16	2	≥64	≥64	≥64	≥64	32 (64*)	≥64	≥64	≥64	≥64	≥64	≥64	≥37
14i	≥64	8	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥64	≥37

*not fully inhibited

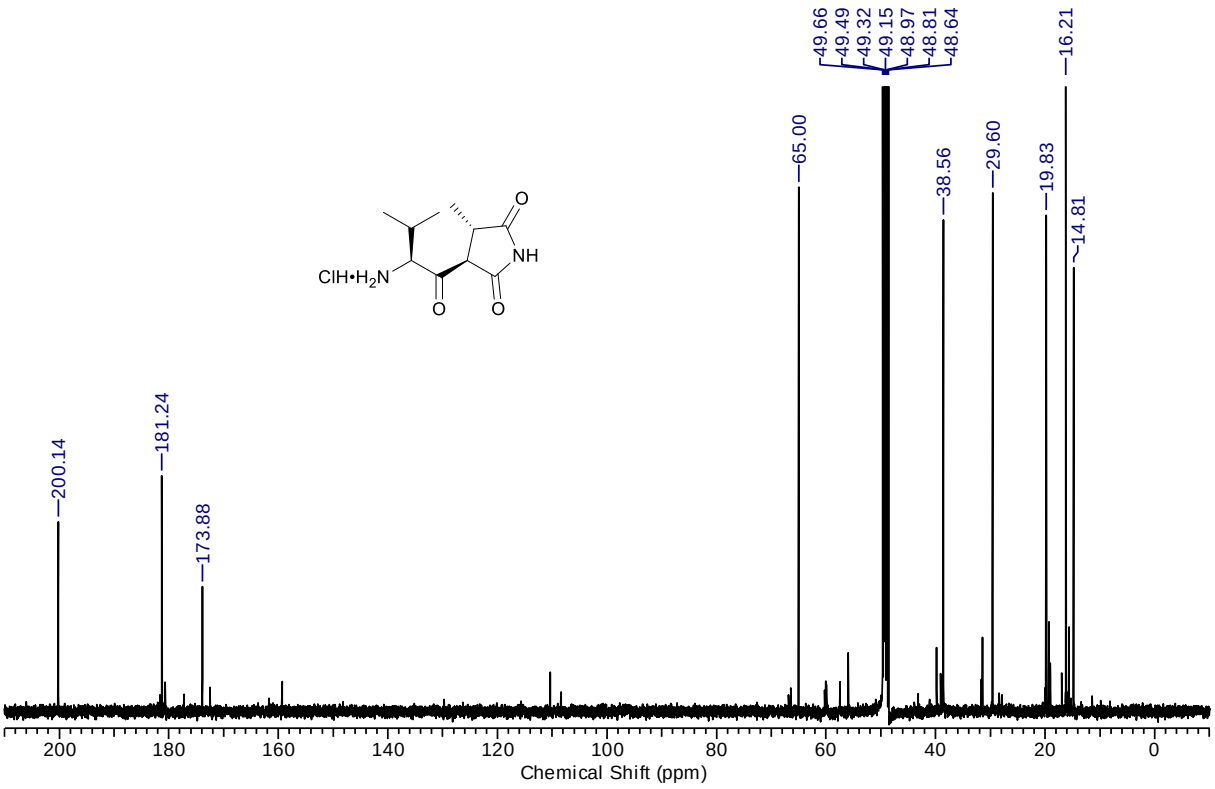
Copies of the NMR spectra and GC-MS chromatograms

(3*R*,4*S*)-3-(L-Valyl)-4-methylpyrrolidine-2,5-dione hydrochloride (2, crude product, mixture of enol, *cis* and *trans* isomers**)**

^{1}H NMR (500 MHz, CD_3OD):

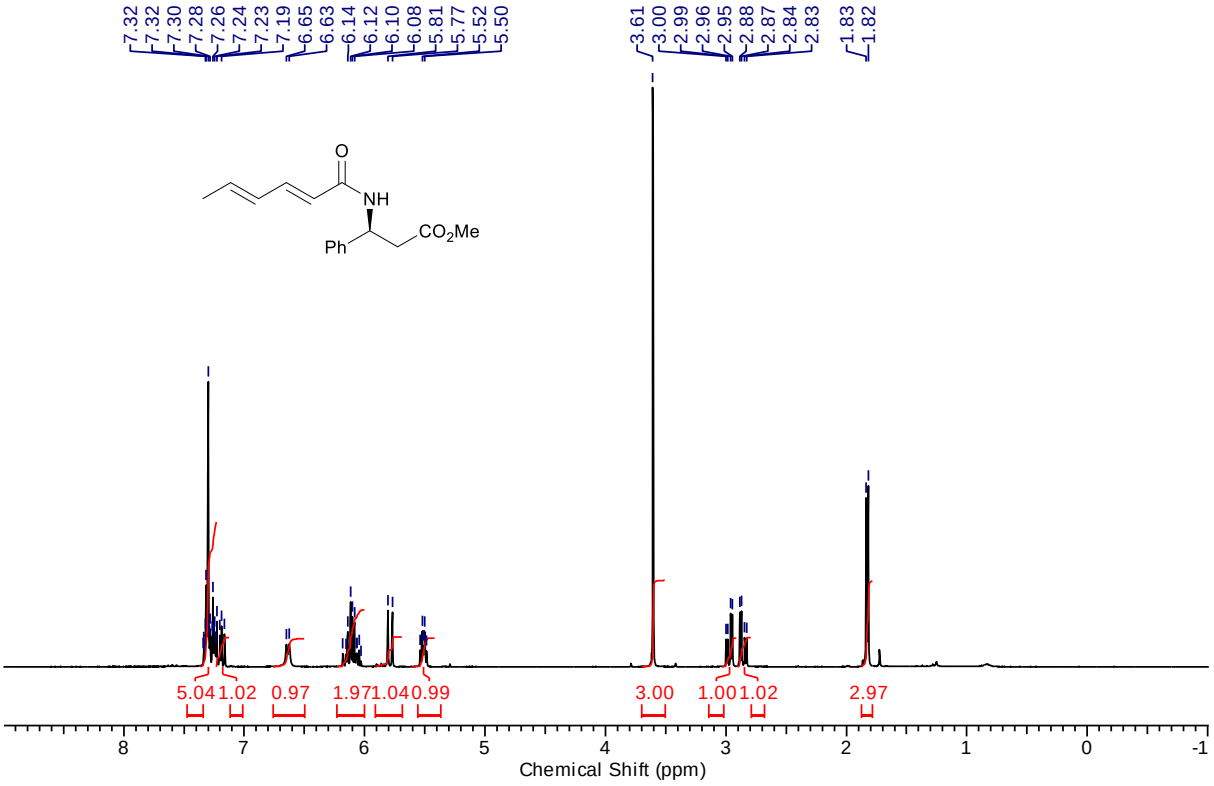


^{13}C NMR (125 MHz, CD_3OD):

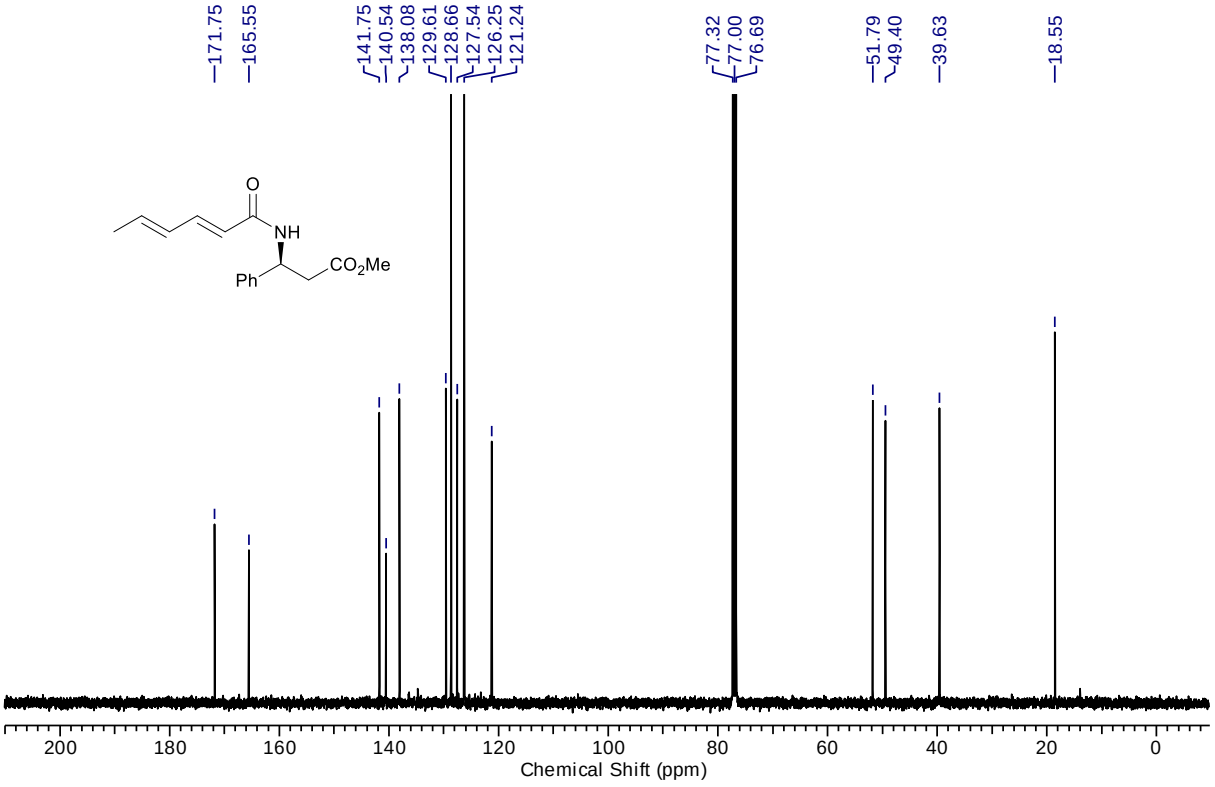


Methyl (*S*)-3-((2*E*,4 *E*)-hexa-2,4-dienamido)-3-phenylpropanoate (S-1)

^{1}H NMR (400 MHz, $CDCl_3$):

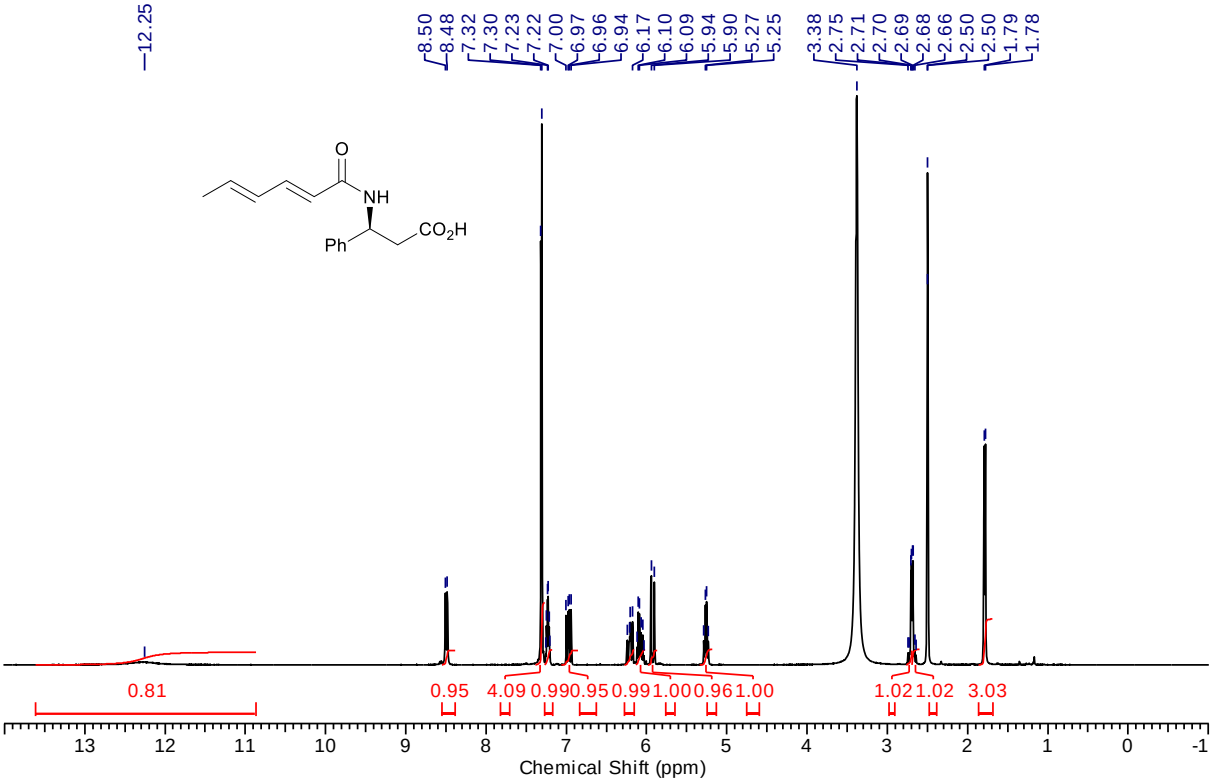


^{13}C NMR (100 MHz, $CDCl_3$):

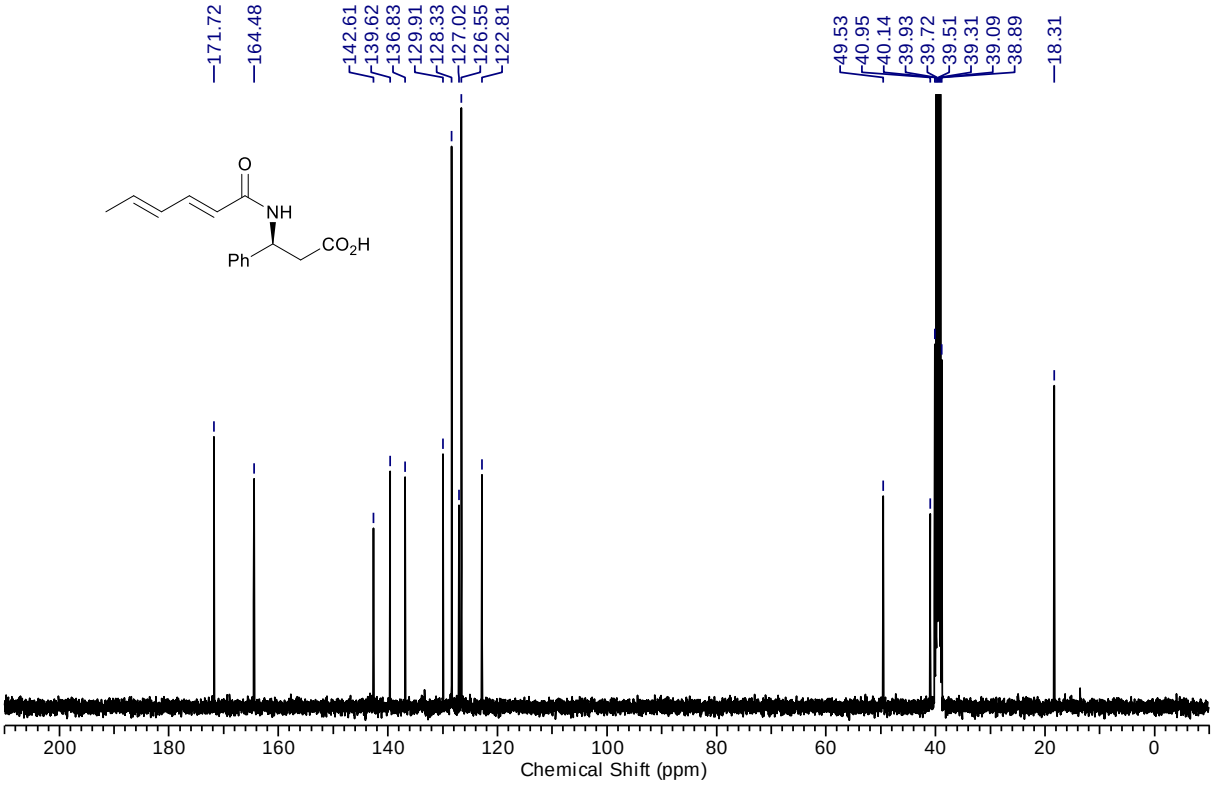


(*S*)-3-((2*E*,4*E*)-Hexa-2,4-dienamido)-3-phenylpropanoic acid (3)

^{1}H NMR (400 MHz, DMSO-d_6):

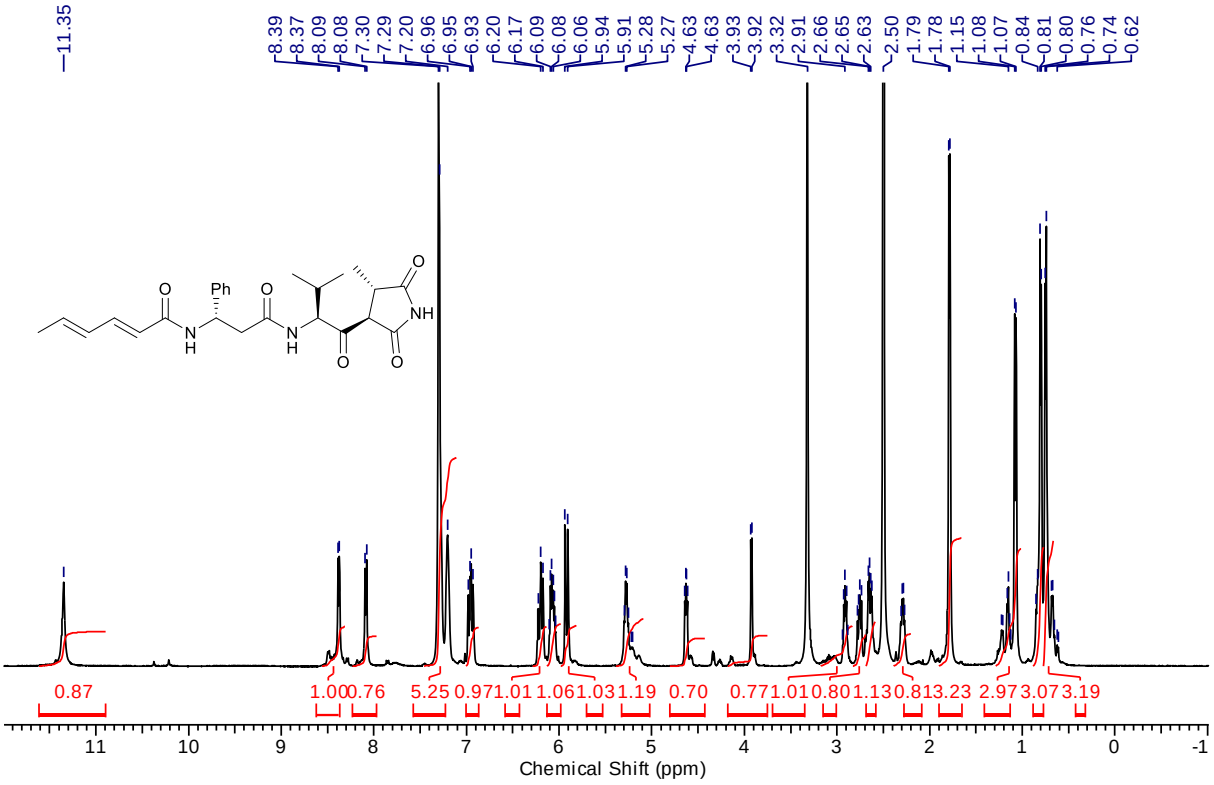


^{13}C NMR (100 MHz, DMSO-d_6):

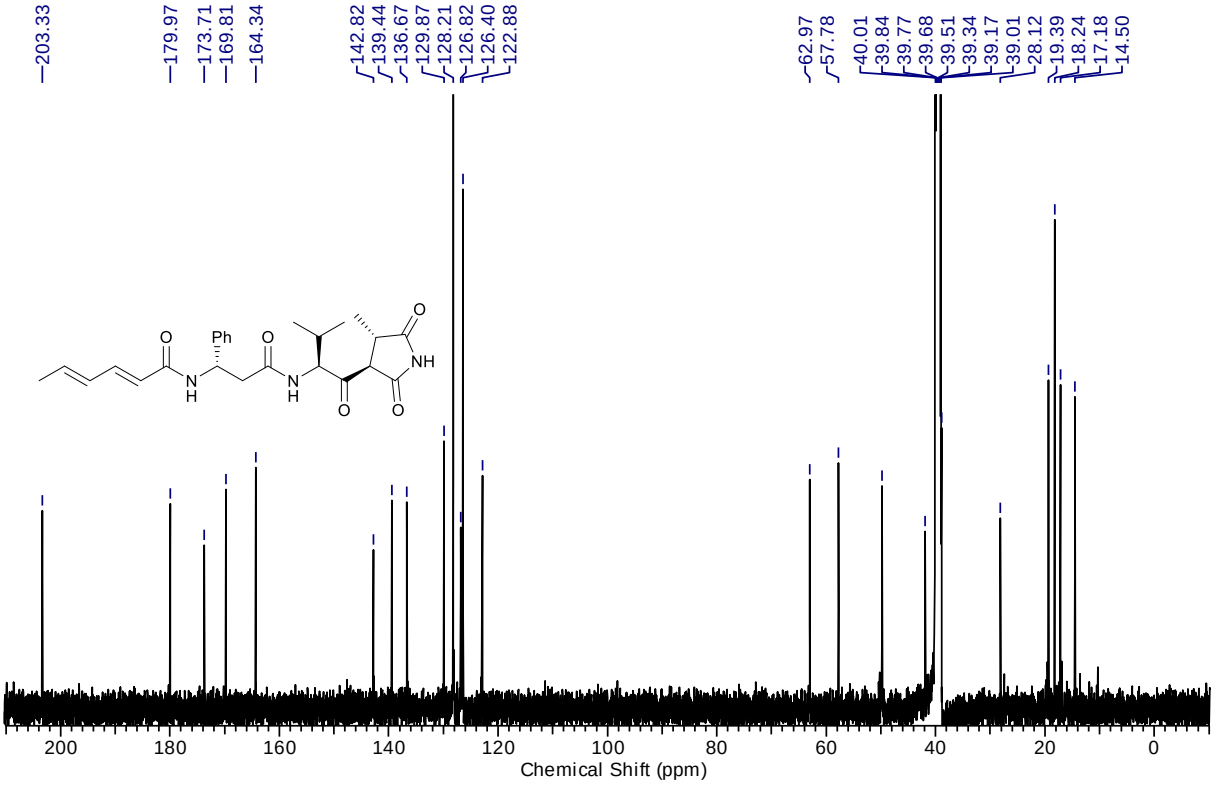


Moiramide B (4)

^{1}H NMR (500 MHz, DMSO-d_6):

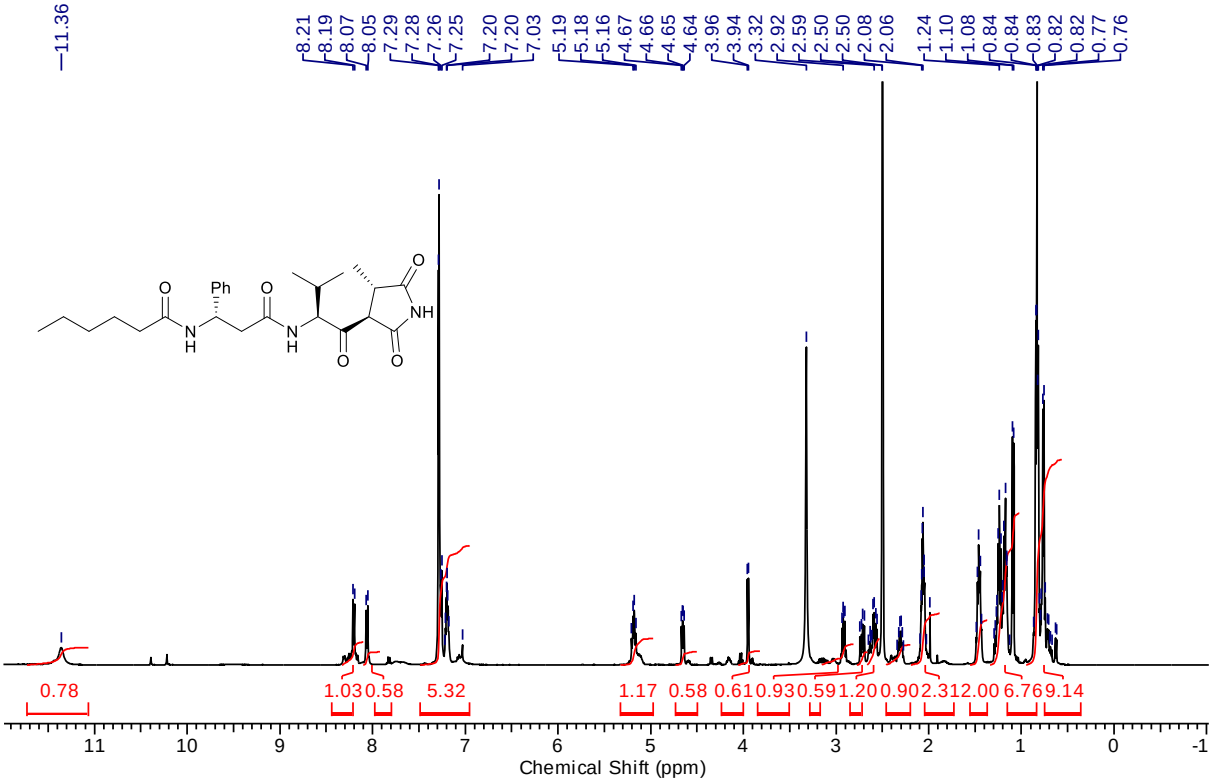


^{13}C NMR (125 MHz, DMSO-d_6):

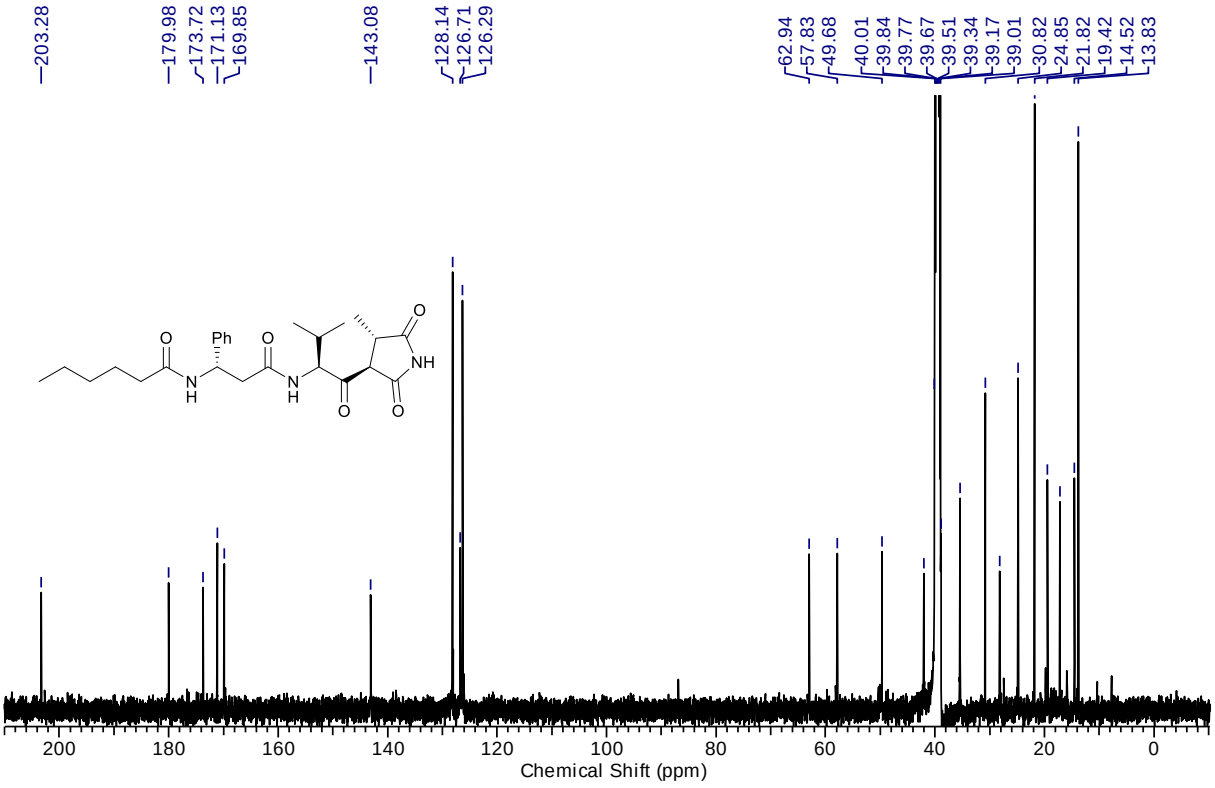


***N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)hexanamide (5)**

^{1}H NMR (500 MHz, DMSO-d_6):

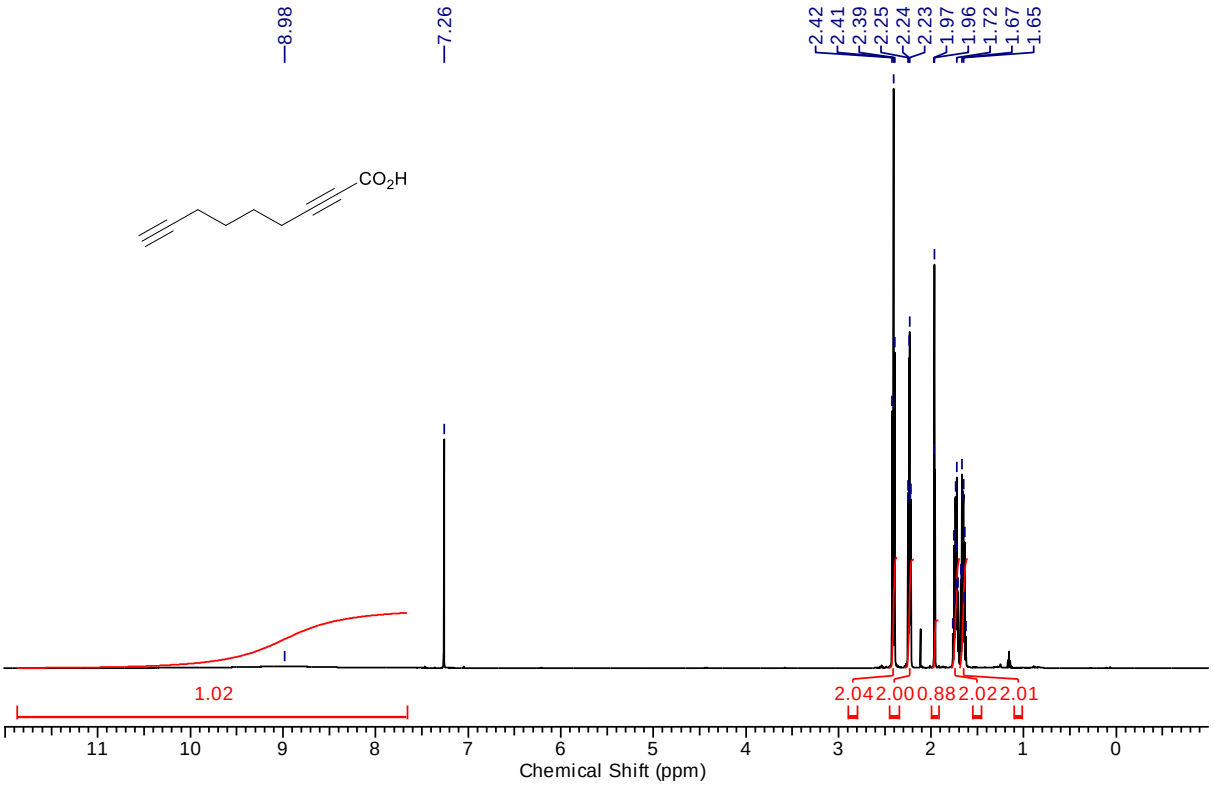


^{13}C NMR (125 MHz, DMSO-d_6):

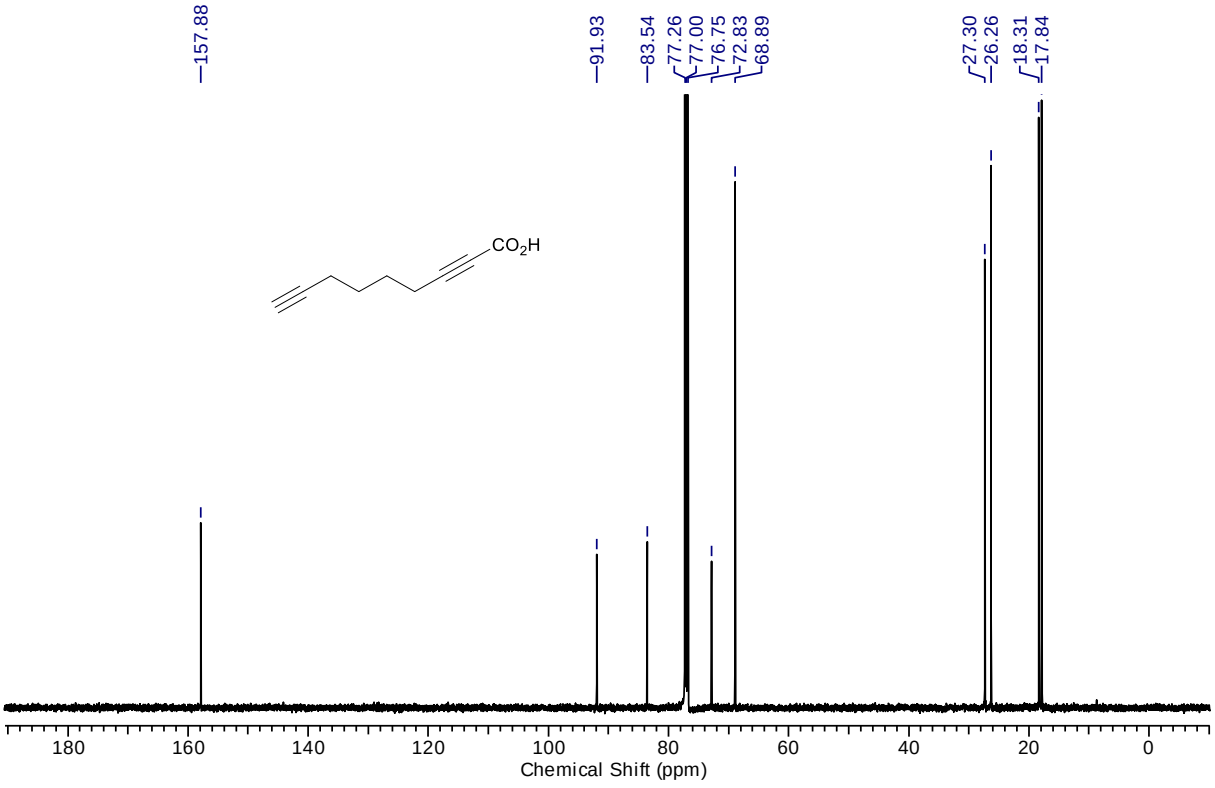


Nona-2,8-diynoic acid (6)

^{1}H NMR (500 MHz, $CDCl_3$):

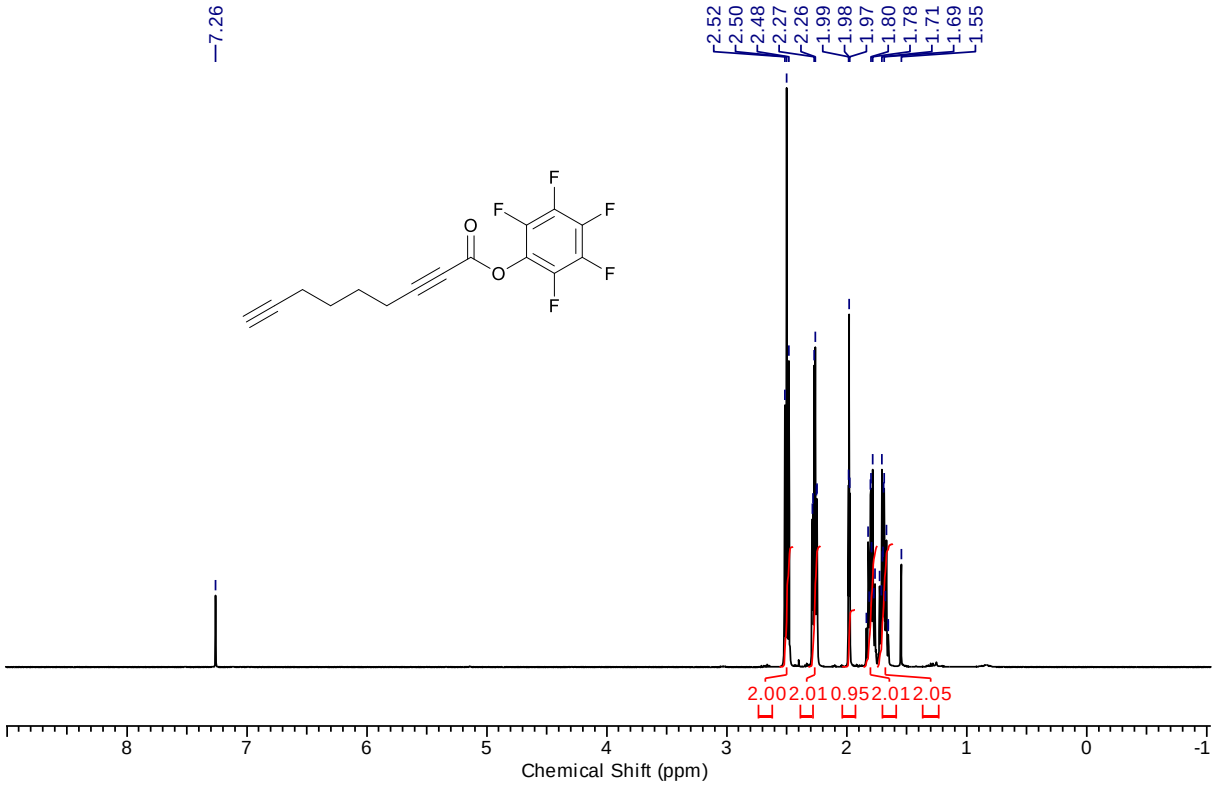


^{13}C NMR (125 MHz, $CDCl_3$):

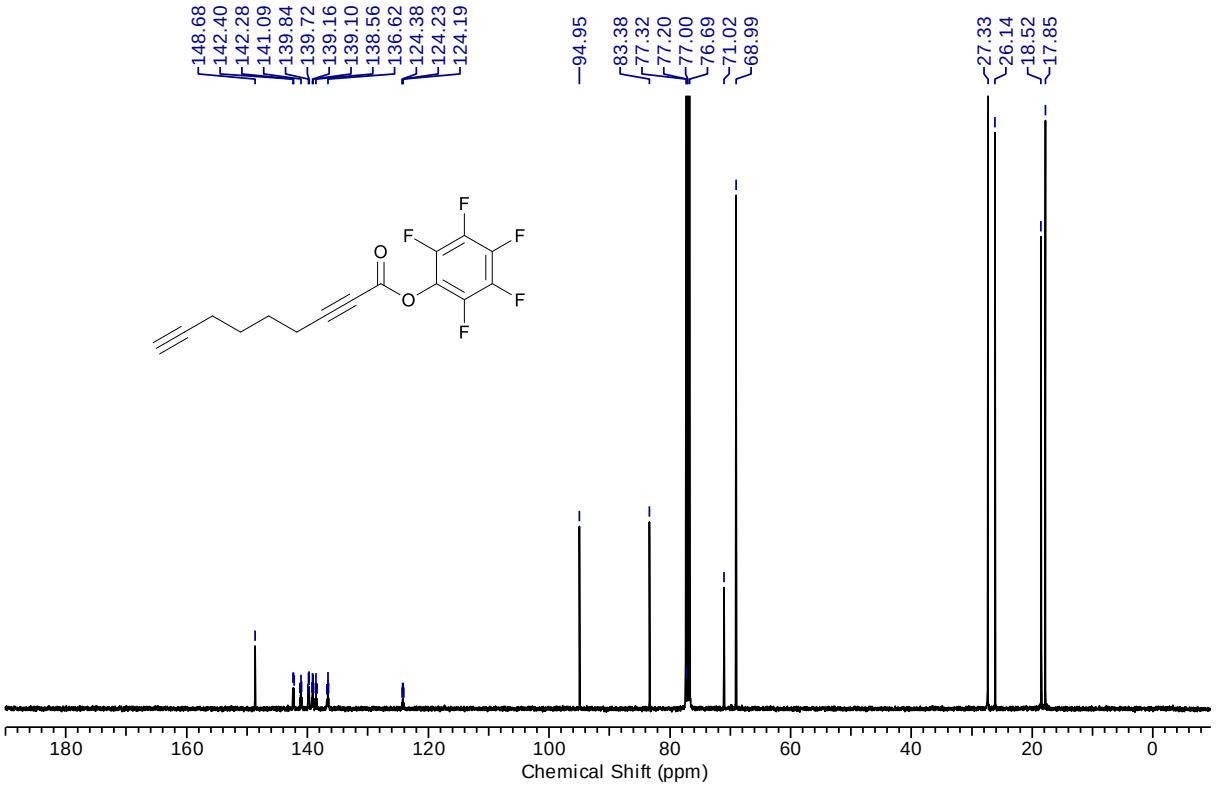


Perfluorophenyl nona-2,8-diynoate (7)

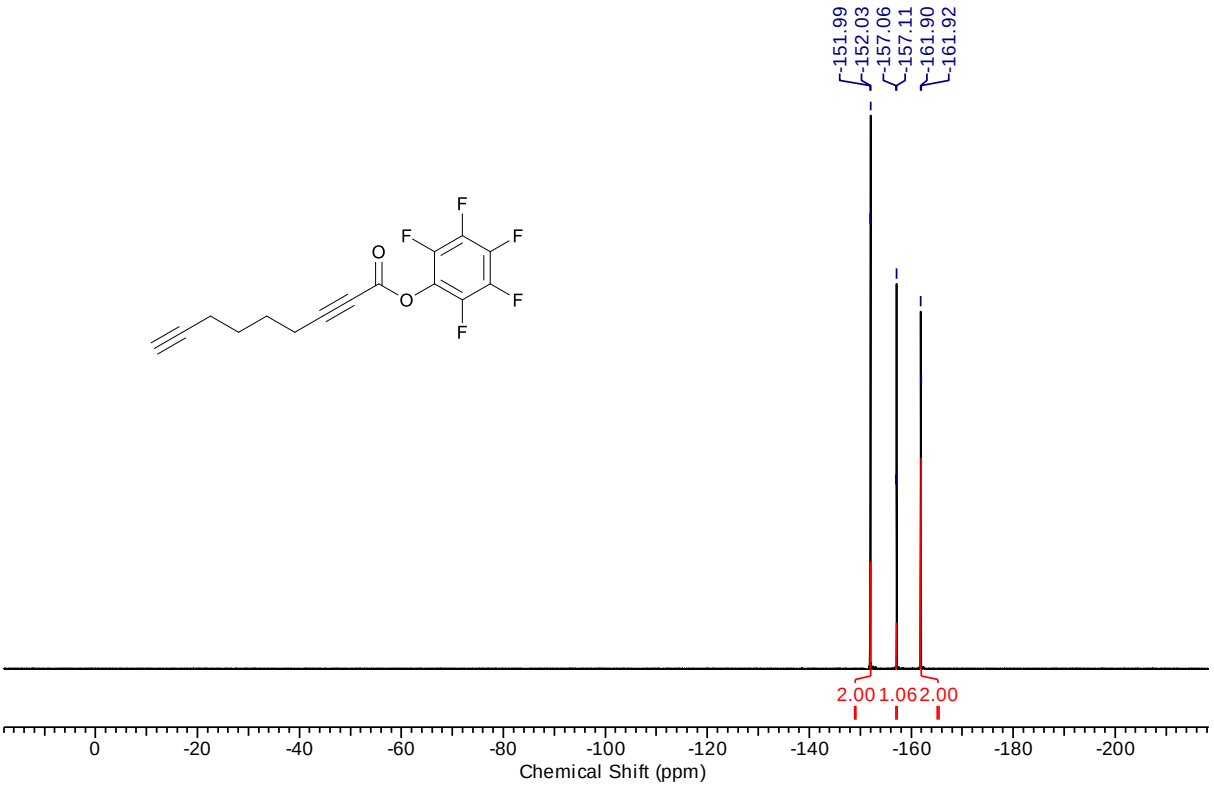
^{1}H NMR (400 MHz, $CDCl_3$):



^{13}C NMR (100 MHz, $CDCl_3$):



^{19}F NMR (377 MHz, $CDCl_3$):

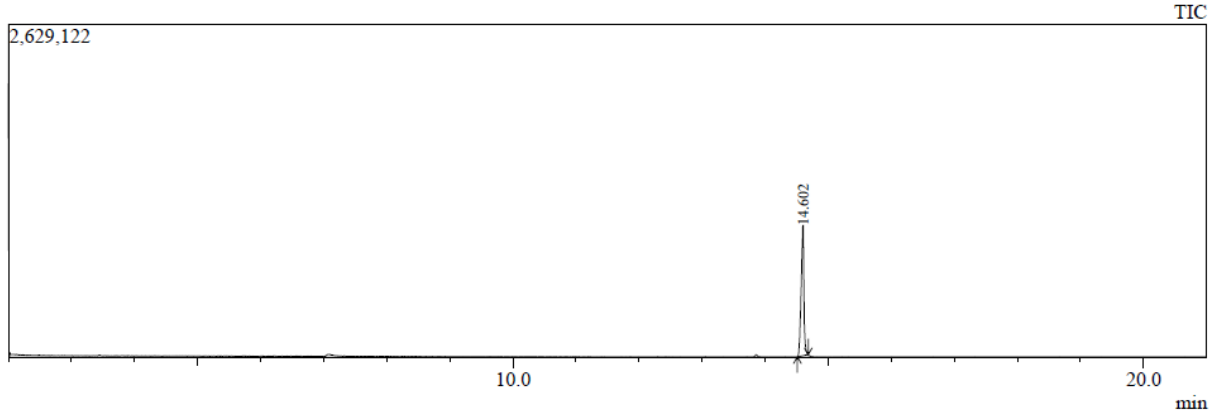


GC-MS (7)

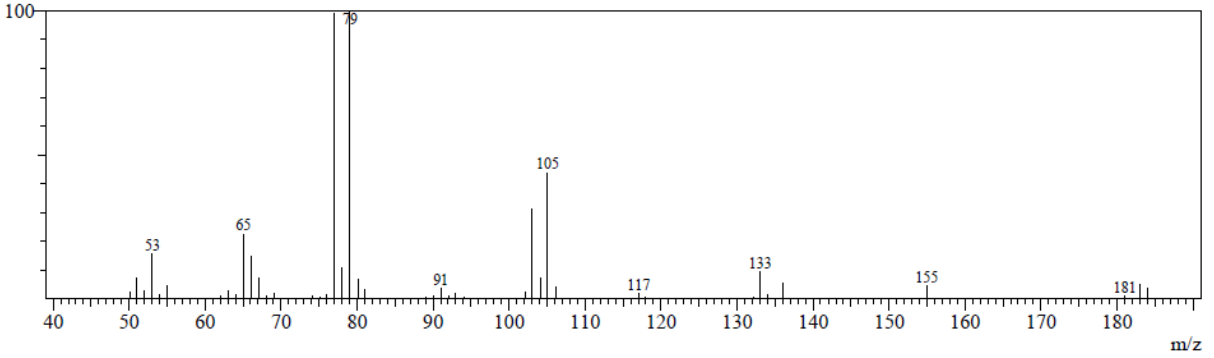
Column: FS Supreme 5ms (25 m x 0.25 mm)

Carrier gas: N_2

T_0 [2 min] = 60 °C, 10 °C/min to 200 °C [5 min], injector 250 °C

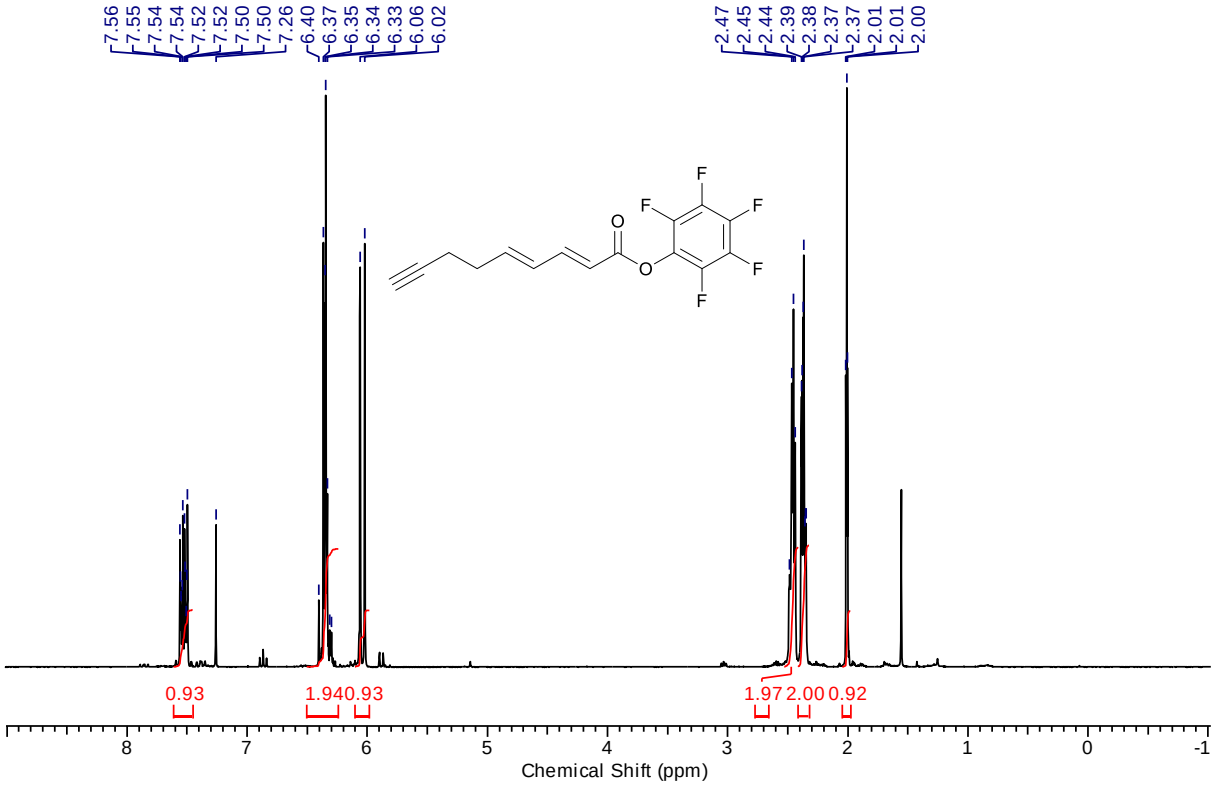


Peak#:1 R.Time:14.602(Scan#:3782)
MassPeaks:48
RawMode:Averaged 14.600-14.607(3781-3783)
BG Mode:Calc. from Peak Group 1 - Event 1

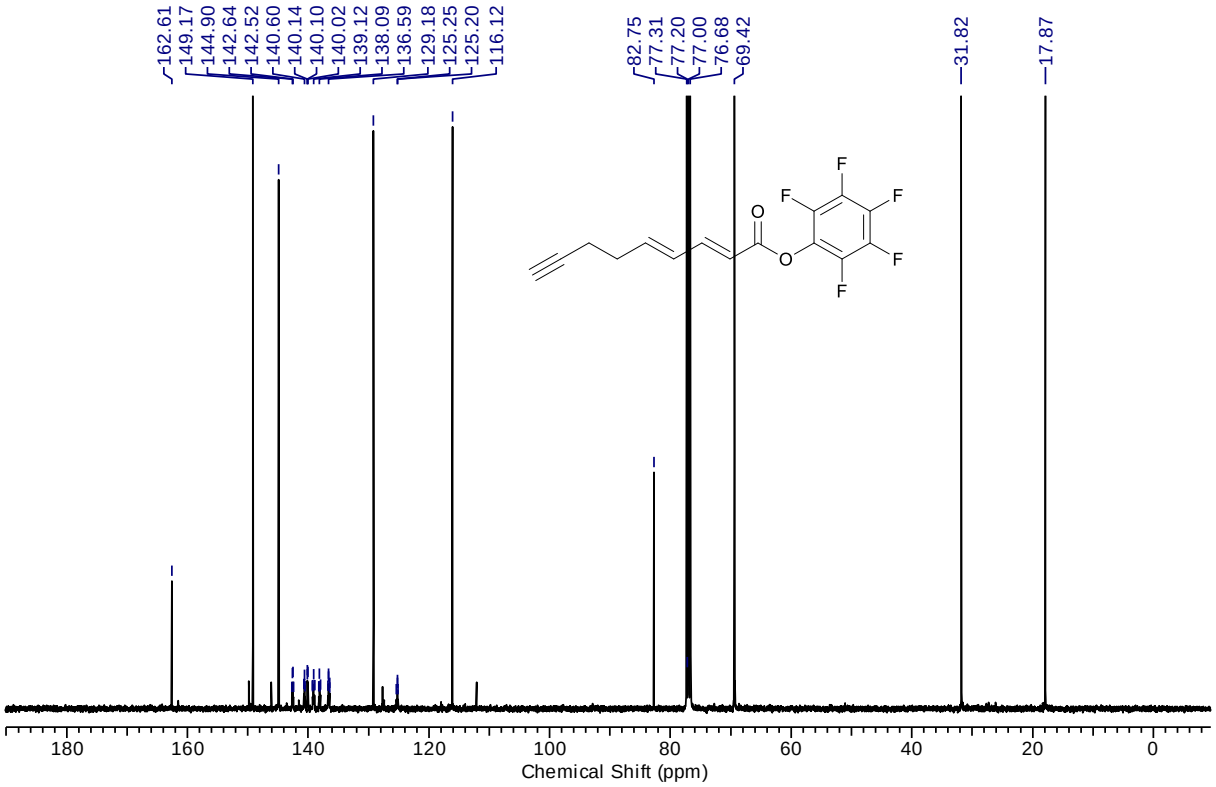


Perfluorophenyl (2*E*,4*E*)-nona-2,4-dien-8-ynoate (8)

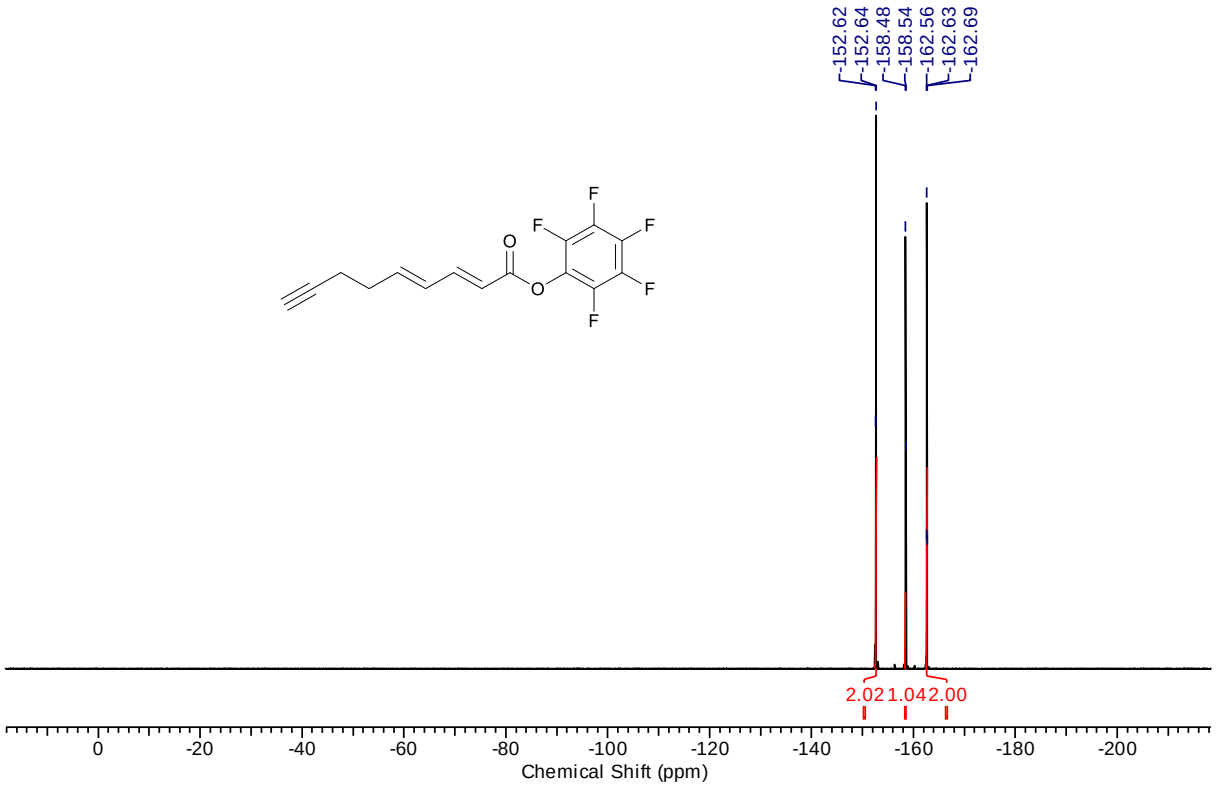
^{1}H NMR (400 MHz, $CDCl_3$):



^{13}C NMR (100 MHz, $CDCl_3$):



^{19}F NMR (377 MHz, $CDCl_3$):

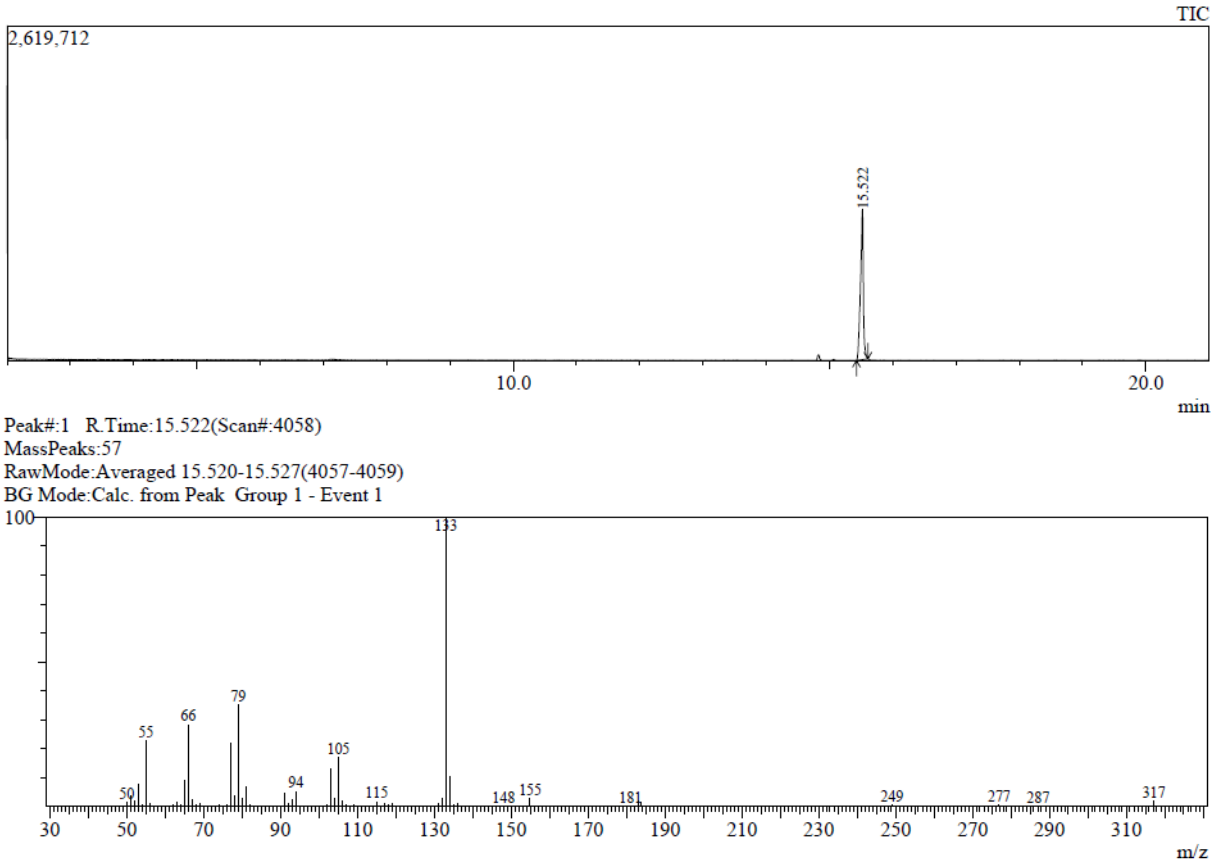


GC-MS (8)

Column: FS Supreme 5ms (25 m x 0.25 mm)

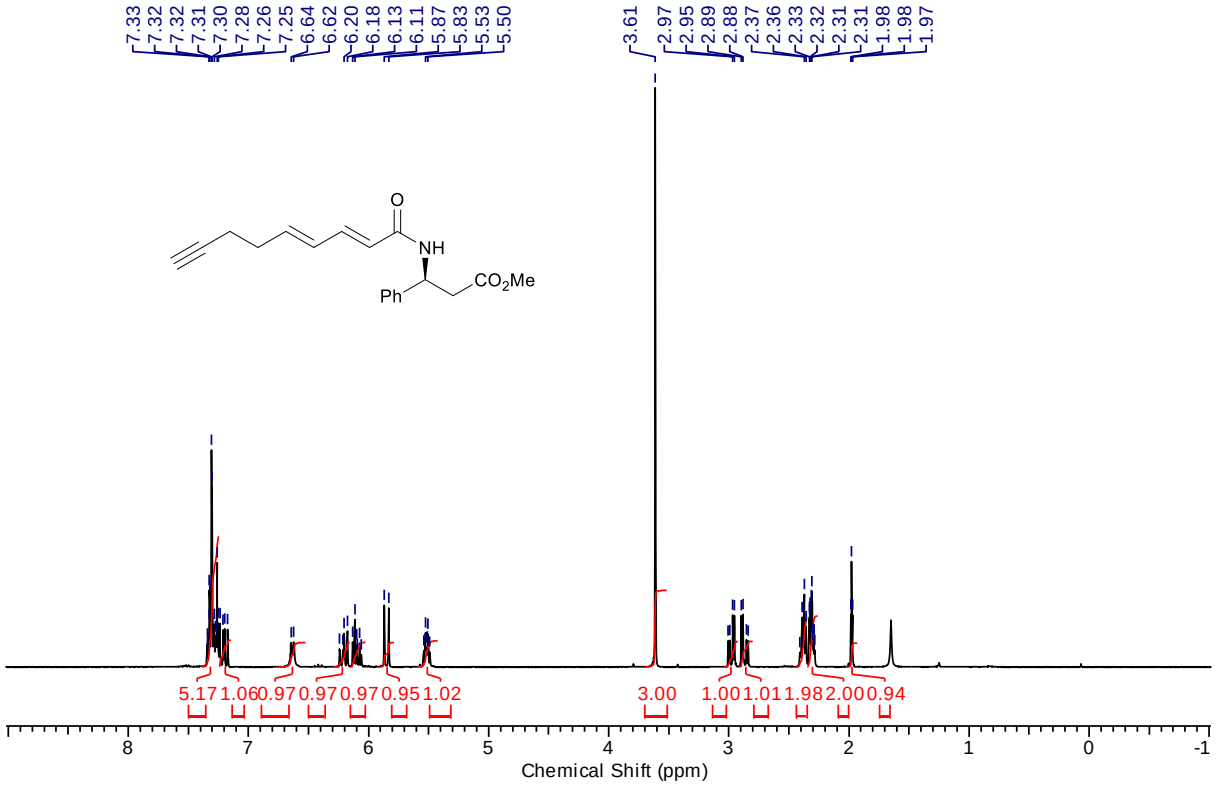
Carrier gas: N_2

T_0 [2 min] = 60 °C, 10 °C/min to 200 °C [5 min], injector 250 °C

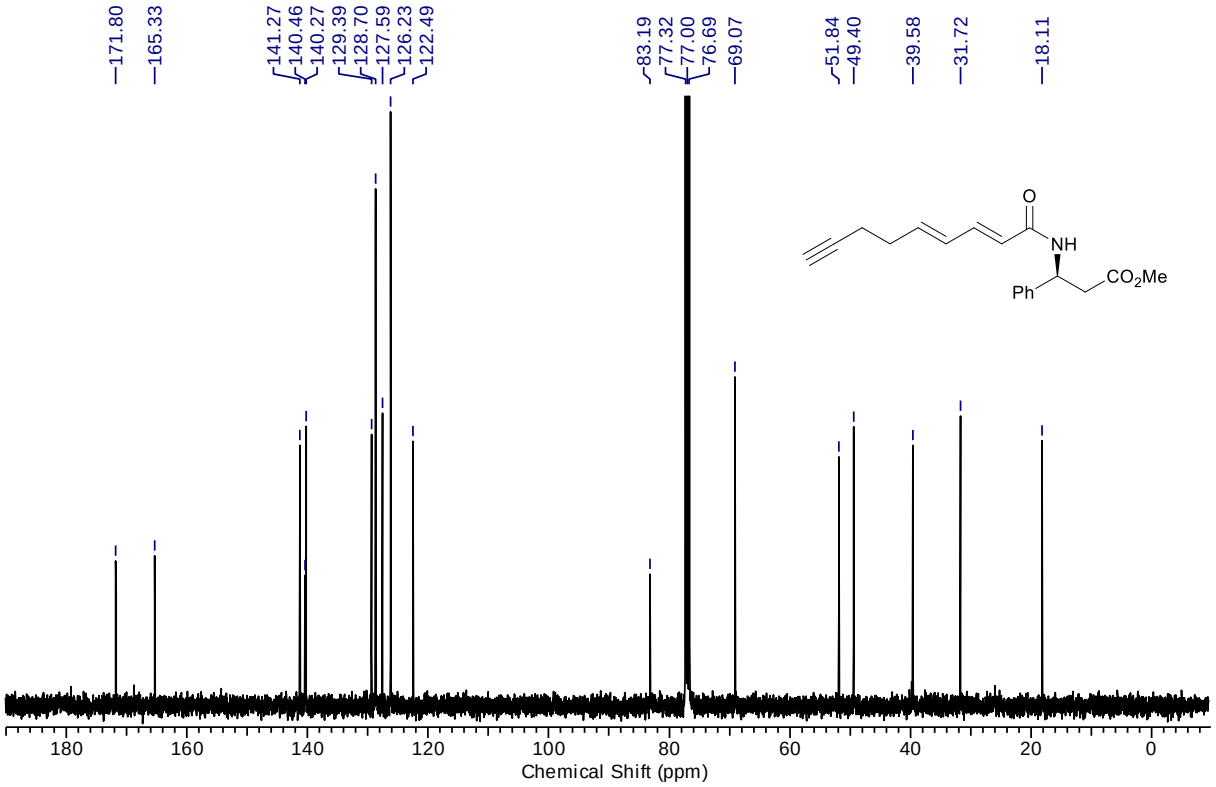


Methyl (*S*)-3-((2*E*,4*E*)-nona-2,4-dien-8-ynamido)-3-phenylpropanoate (9)

^{1}H NMR (400 MHz, $CDCl_3$):

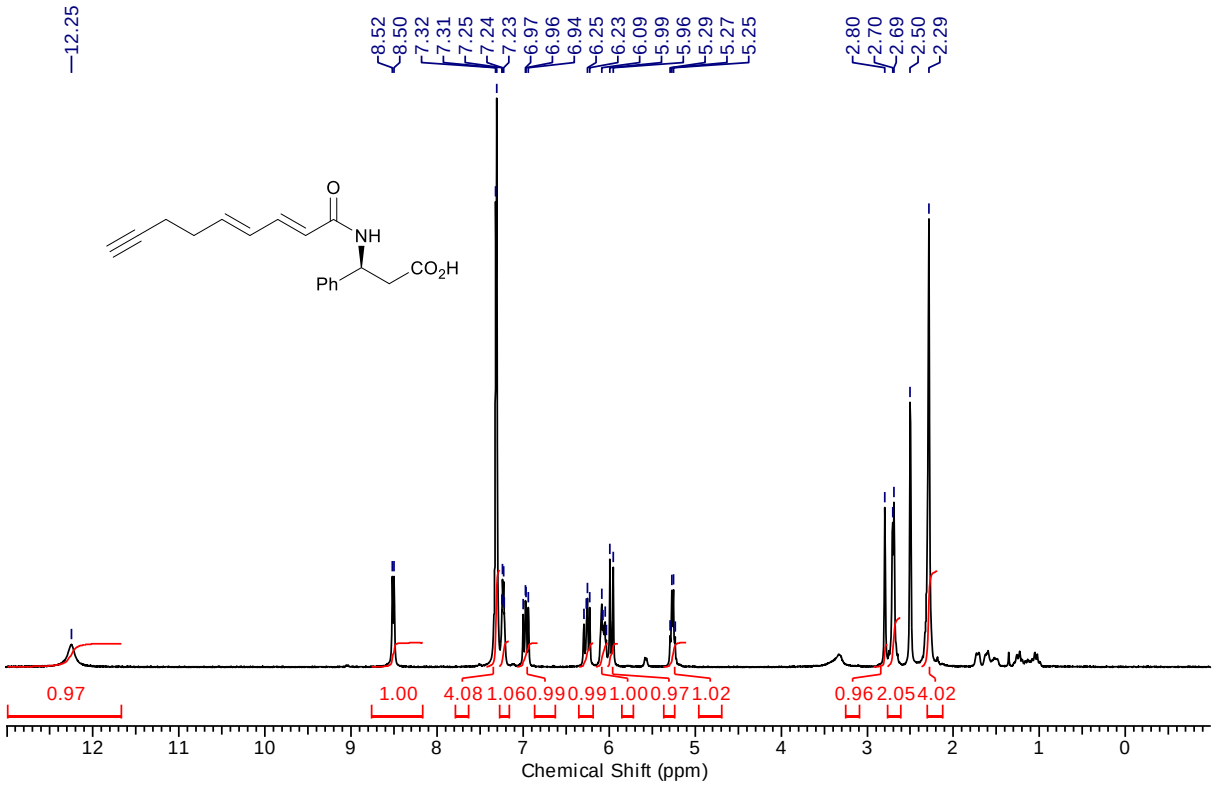


^{13}C NMR (100 MHz, $CDCl_3$):

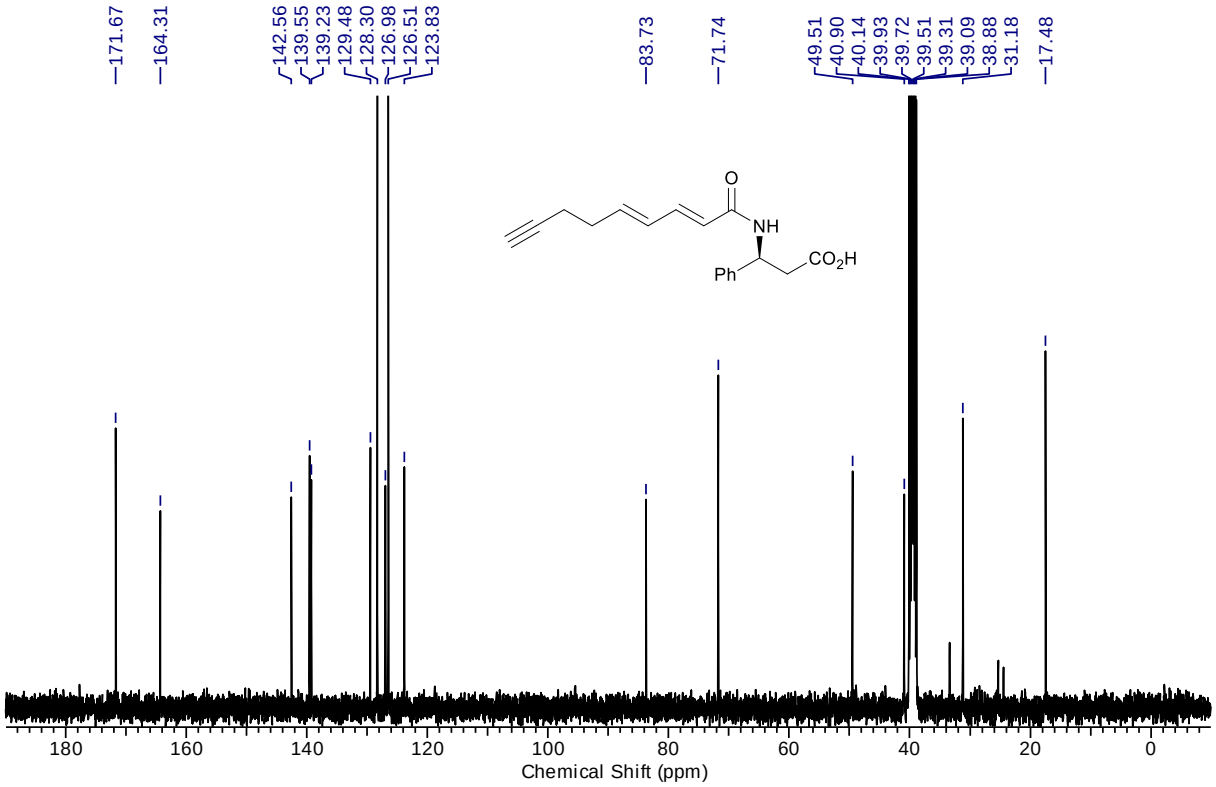


(*S*)-3-((2*E*,4*E*)-Nona-2,4-dien-8-ynamido)-3-phenylpropanoic acid (10)

^{1}H NMR (400 MHz, DMSO-d_6):

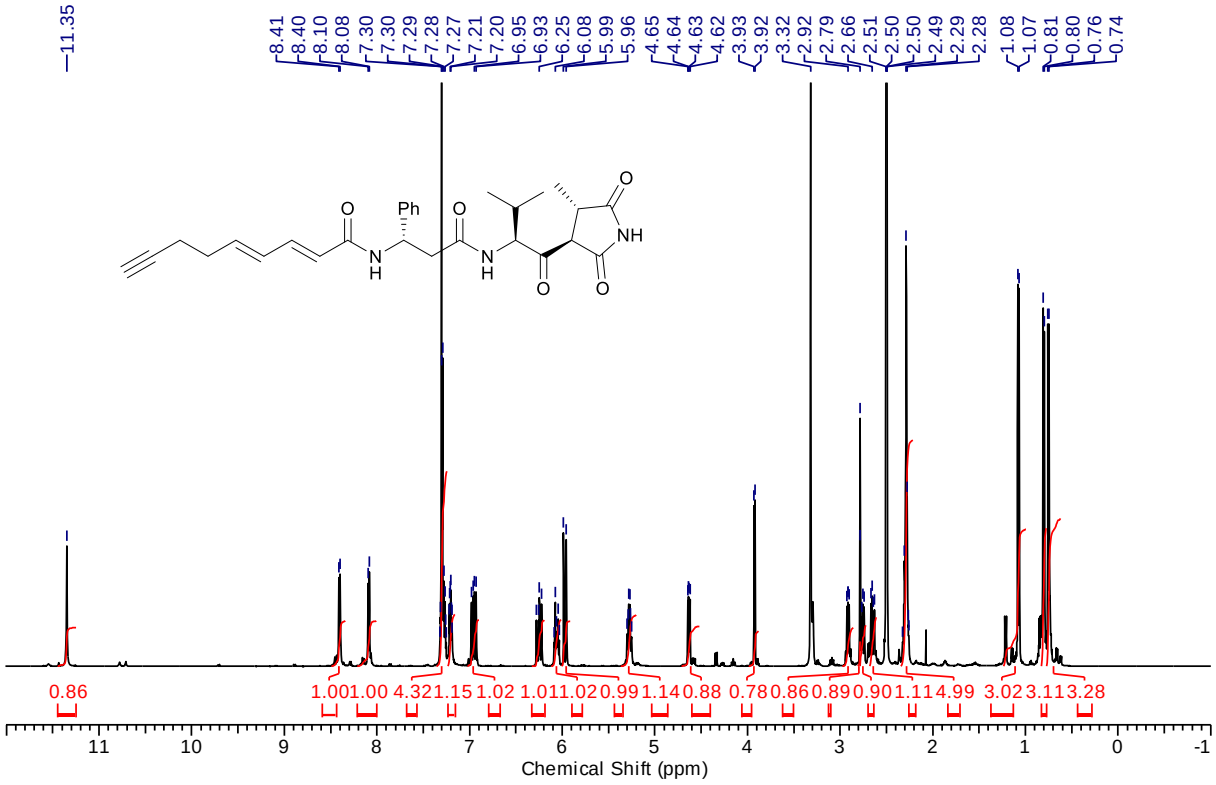


^{13}C NMR (100 MHz, DMSO-d_6):

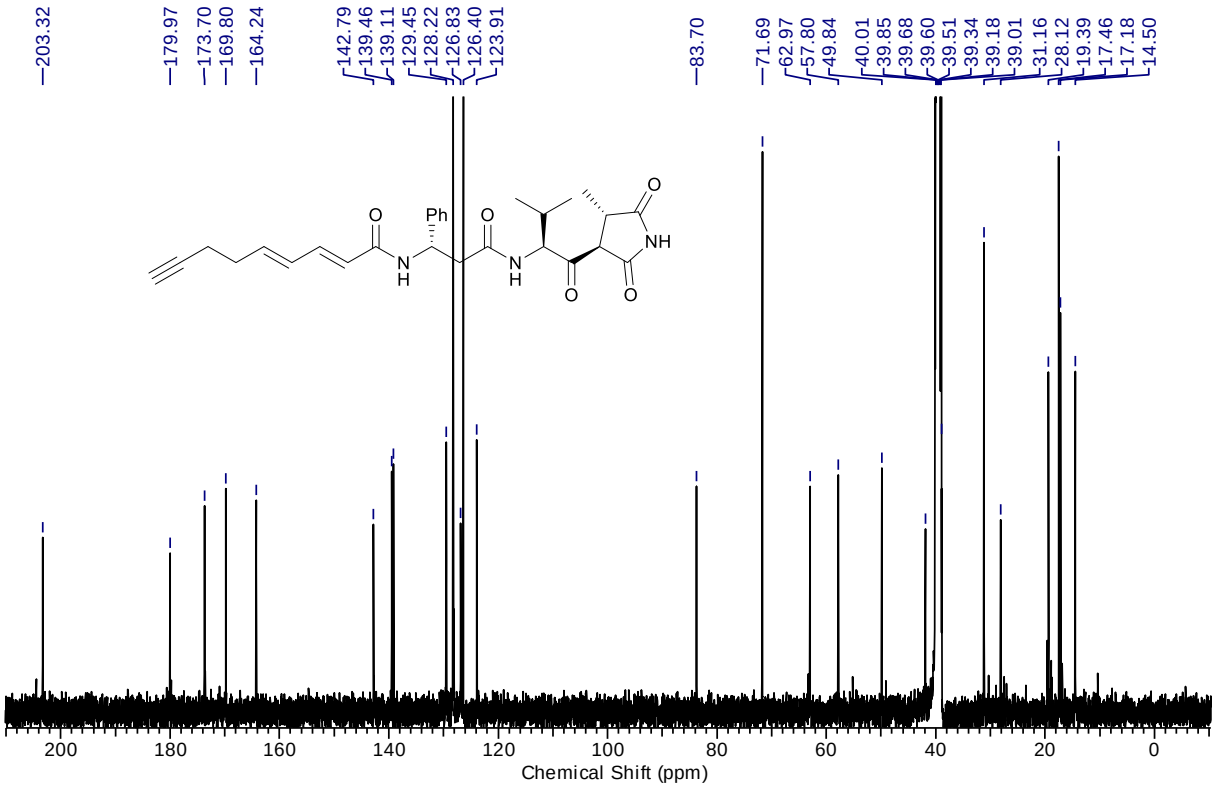


(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (11)

^{1}H NMR (500 MHz, DMSO-d_6):

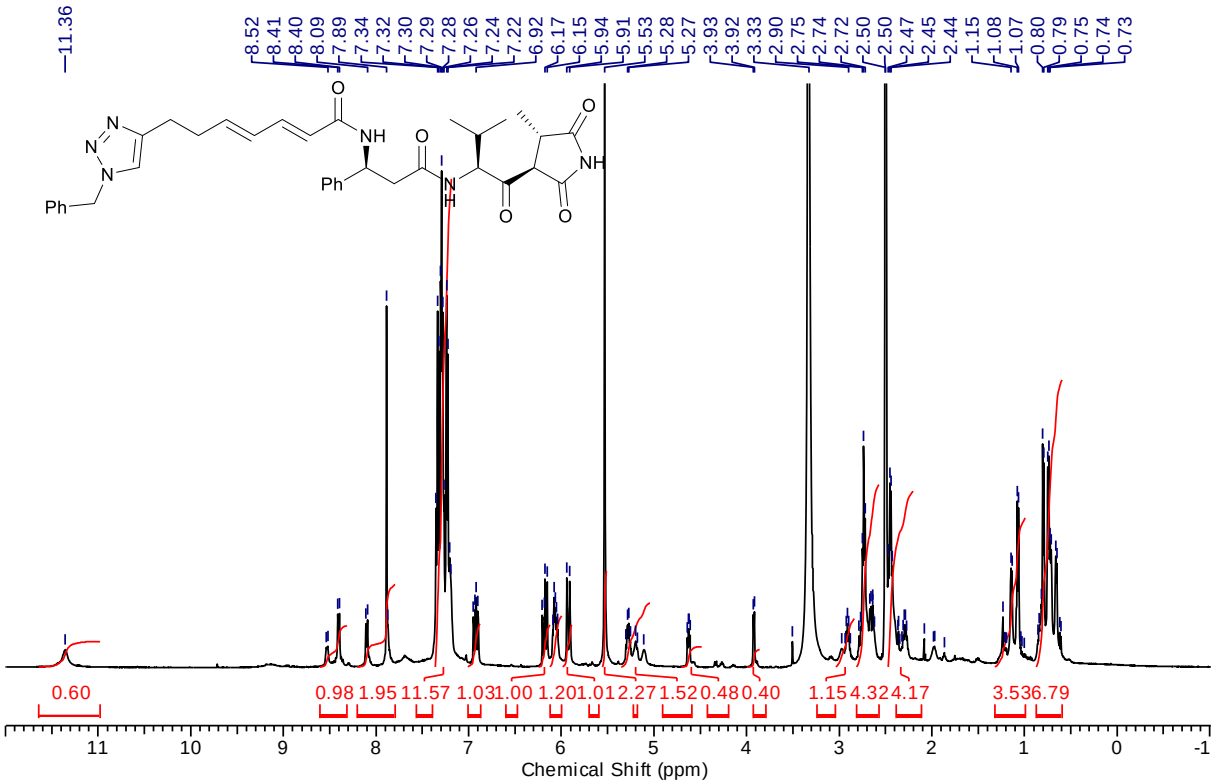


^{13}C NMR (125 MHz, DMSO-d_6):

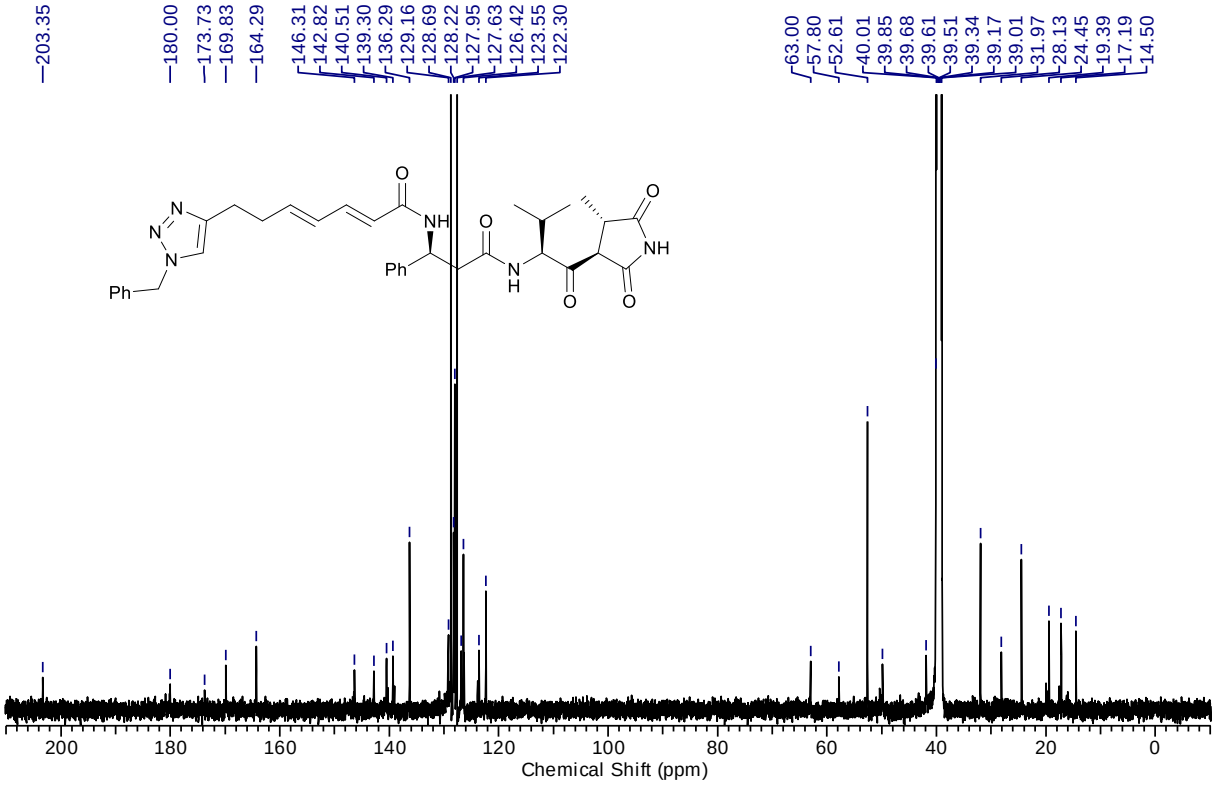


(2*E*,4*E*)-7-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)hepta-2,4-dienamide (12a)

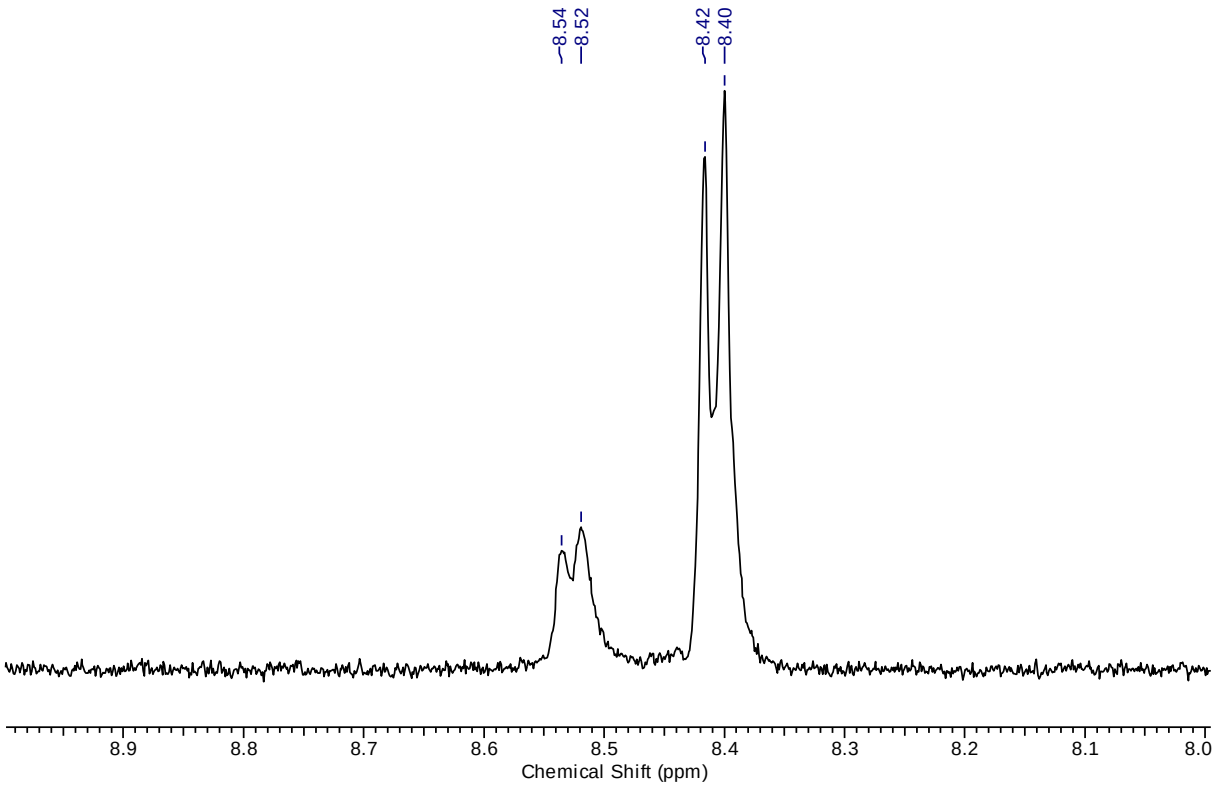
^{1}H NMR (500 MHz, DMSO-d_6):



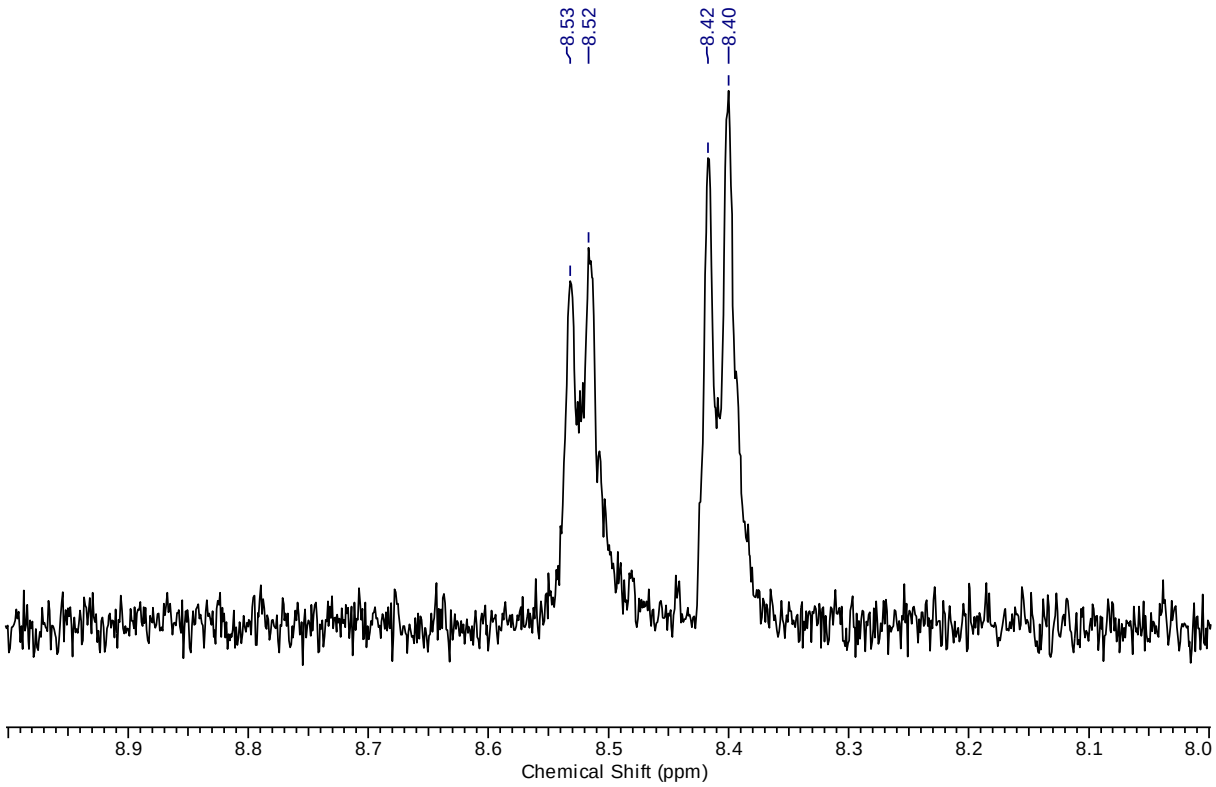
^{13}C NMR (125 MHz, DMSO-d_6):



1 D CSSF NOESY (500 MHz, DMSO-d_6, 8.41 ppm)

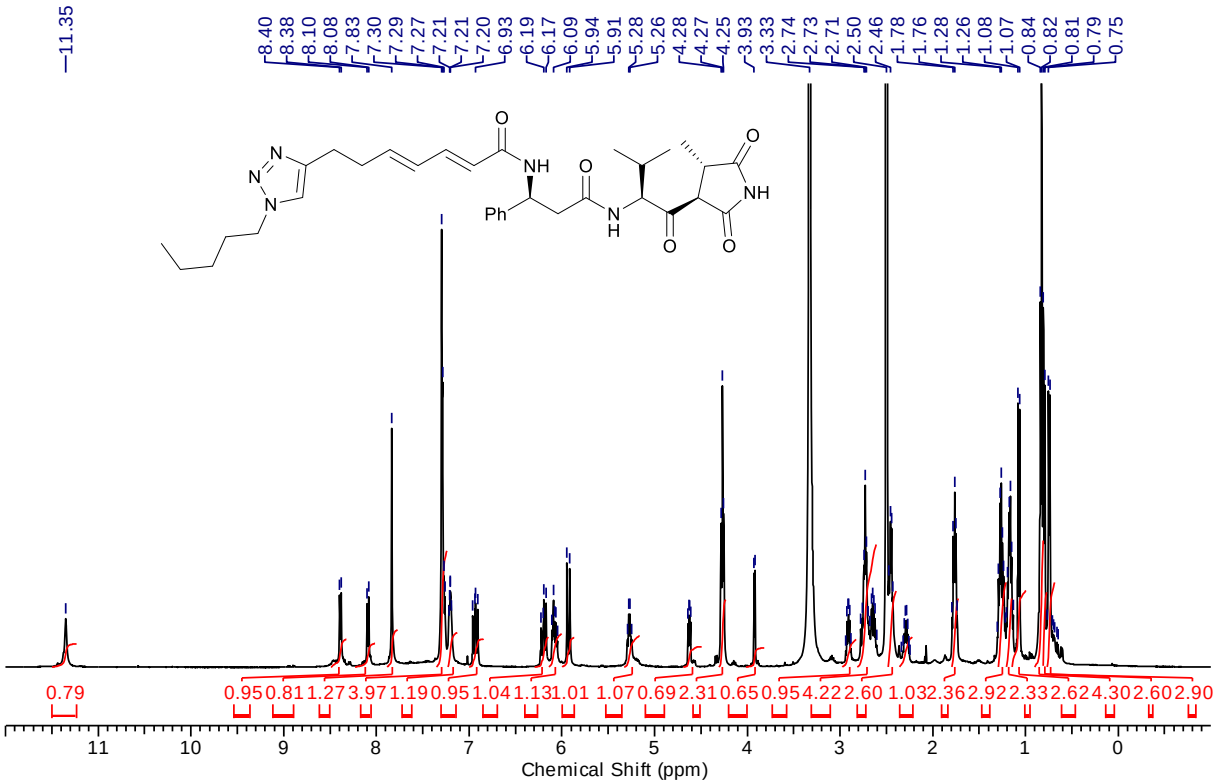


1 D CSSF NOESY (500 MHz, DMSO-d_6, 8.53 ppm)

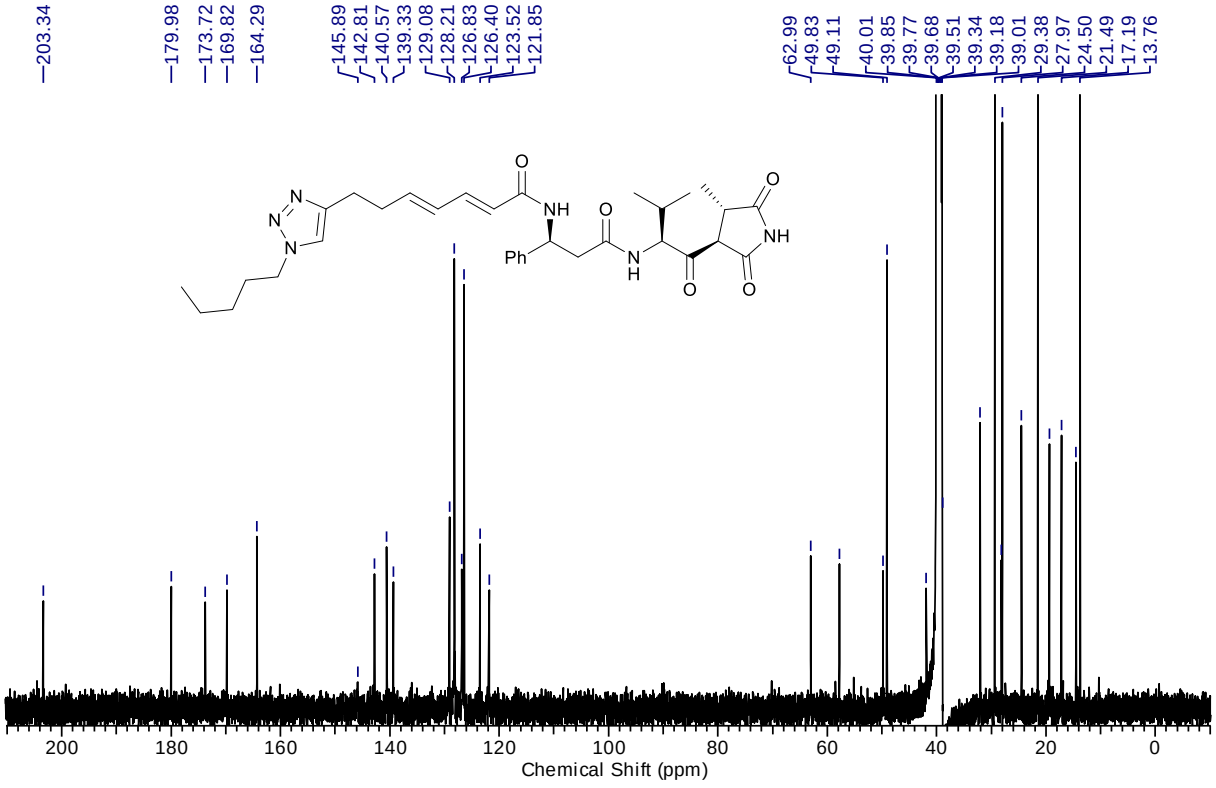


(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3R,4S)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-7-(1-pentyl-1*H*-1,2,3-triazol-4-yl)hepta-2,4-dienamide (12b)

^{1}H NMR (500 MHz, DMSO-d_6):

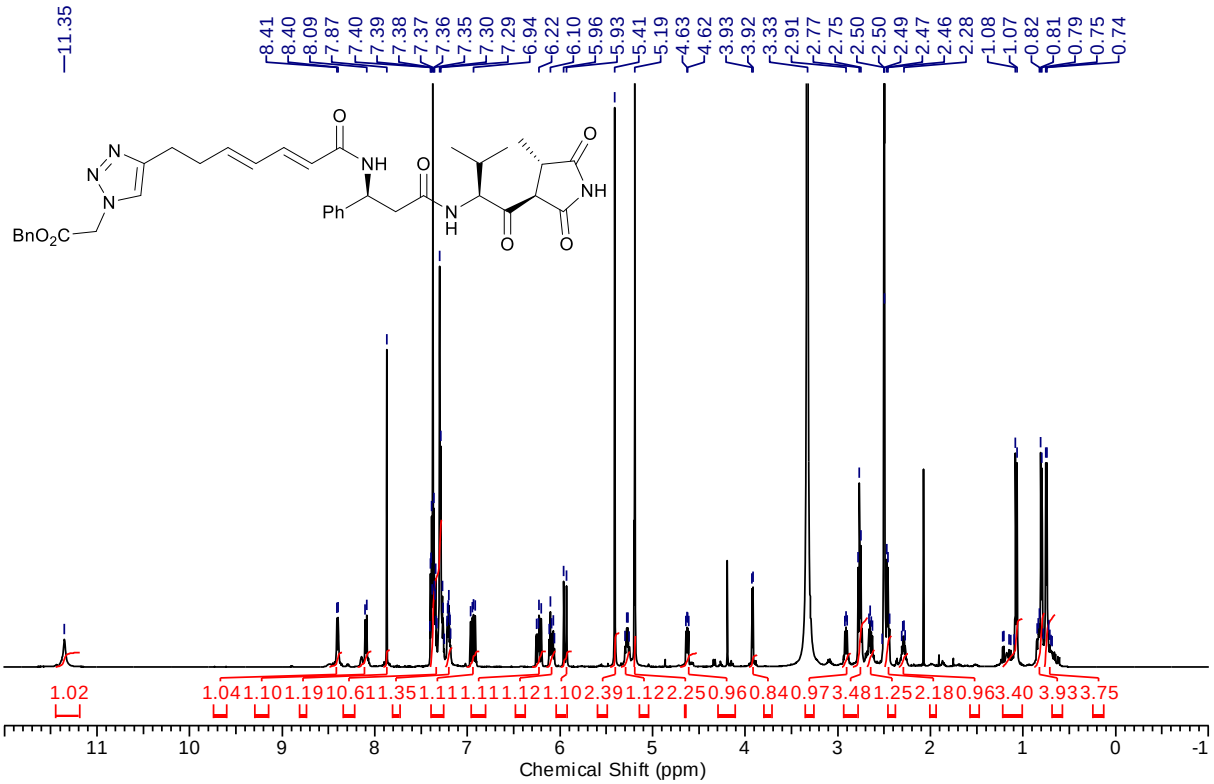


^{13}C NMR (125 MHz, DMSO-d_6):

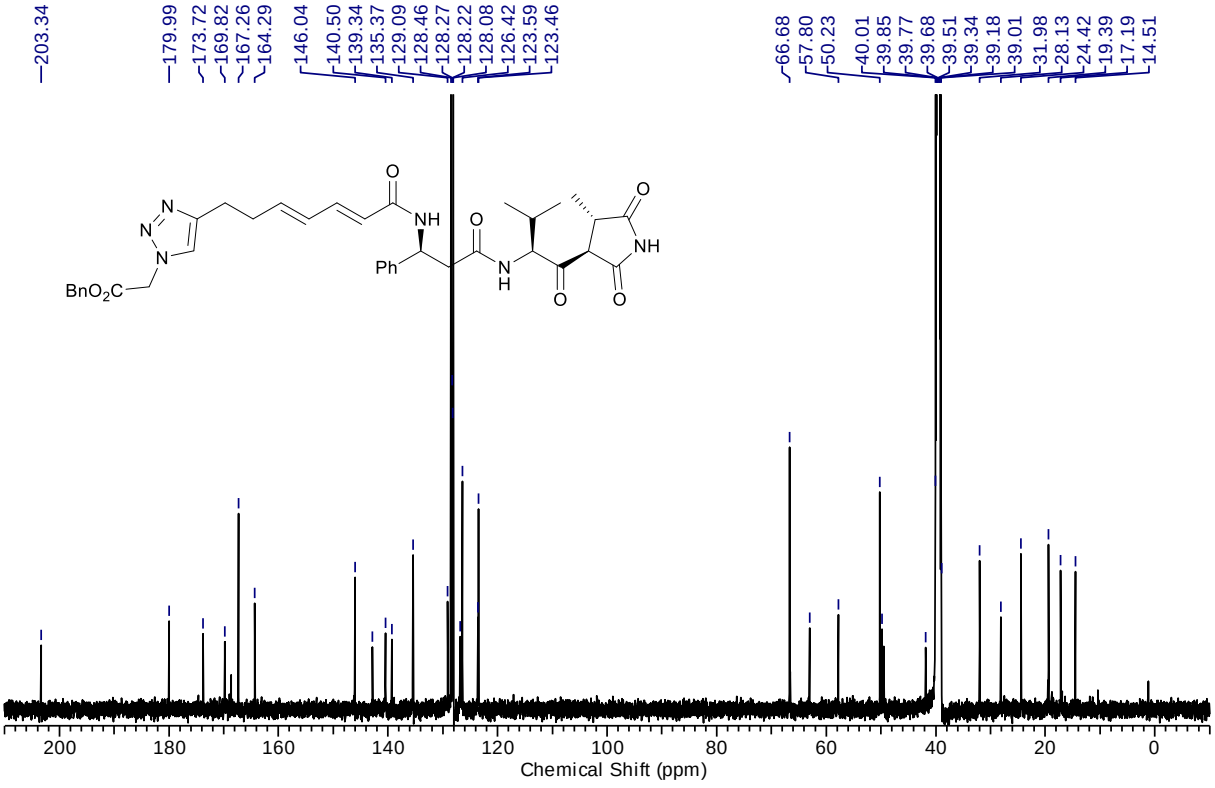


Benzyl 2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)acetate (12c)

^{1}H NMR (500 MHz, DMSO-d_6):

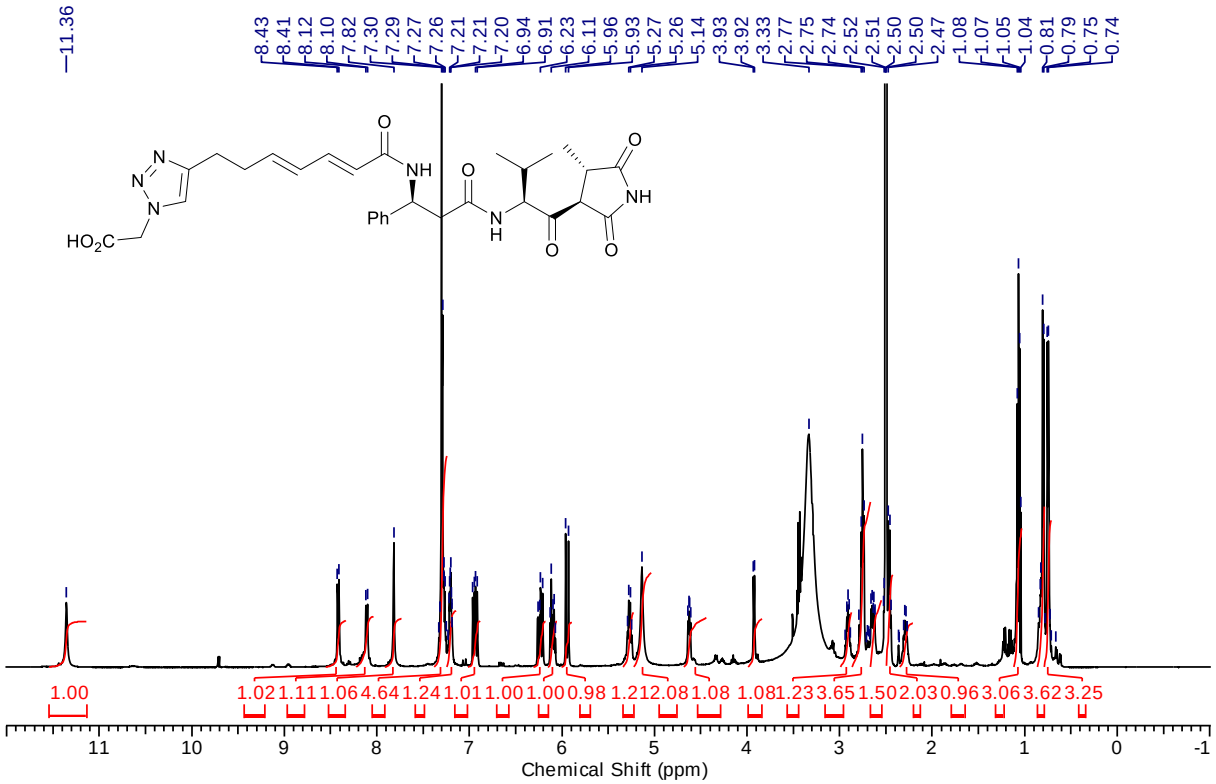


^{13}C NMR (125 MHz, DMSO-d_6):

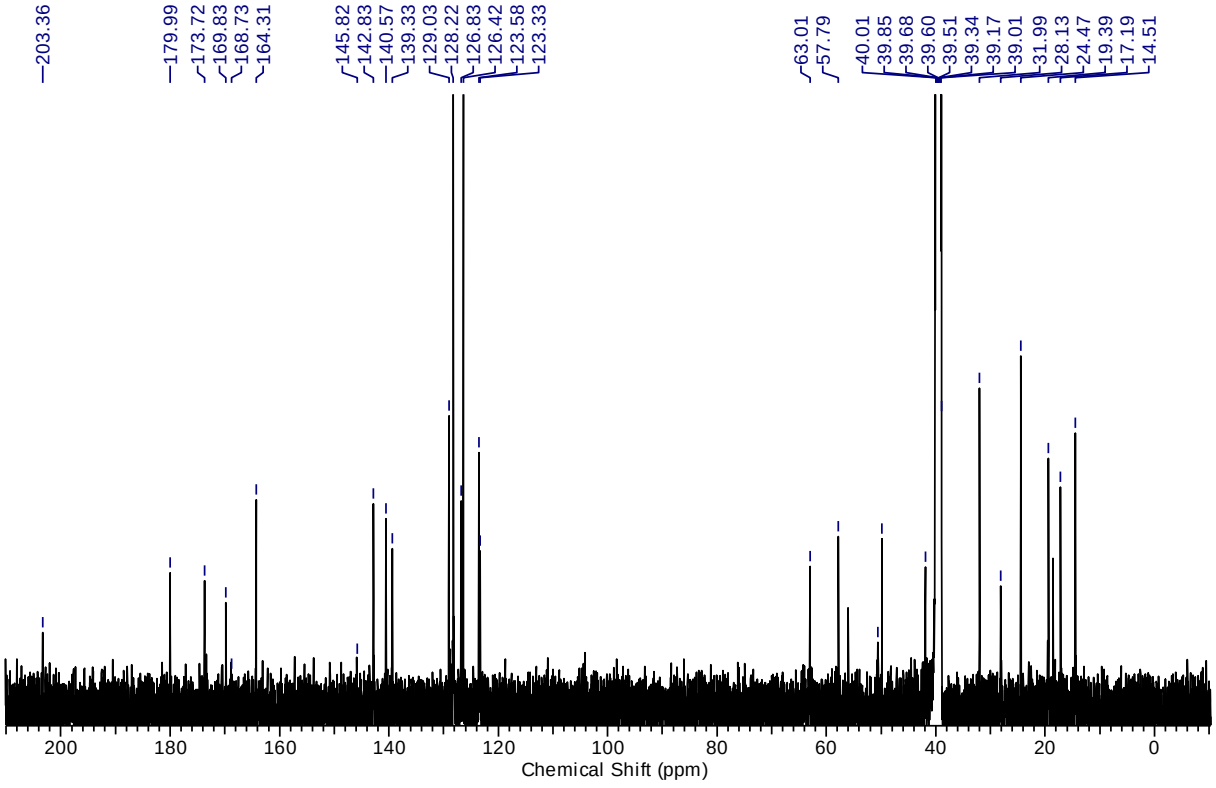


2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)acetic acid (12d)

^{1}H NMR (500 MHz, DMSO-d_6):

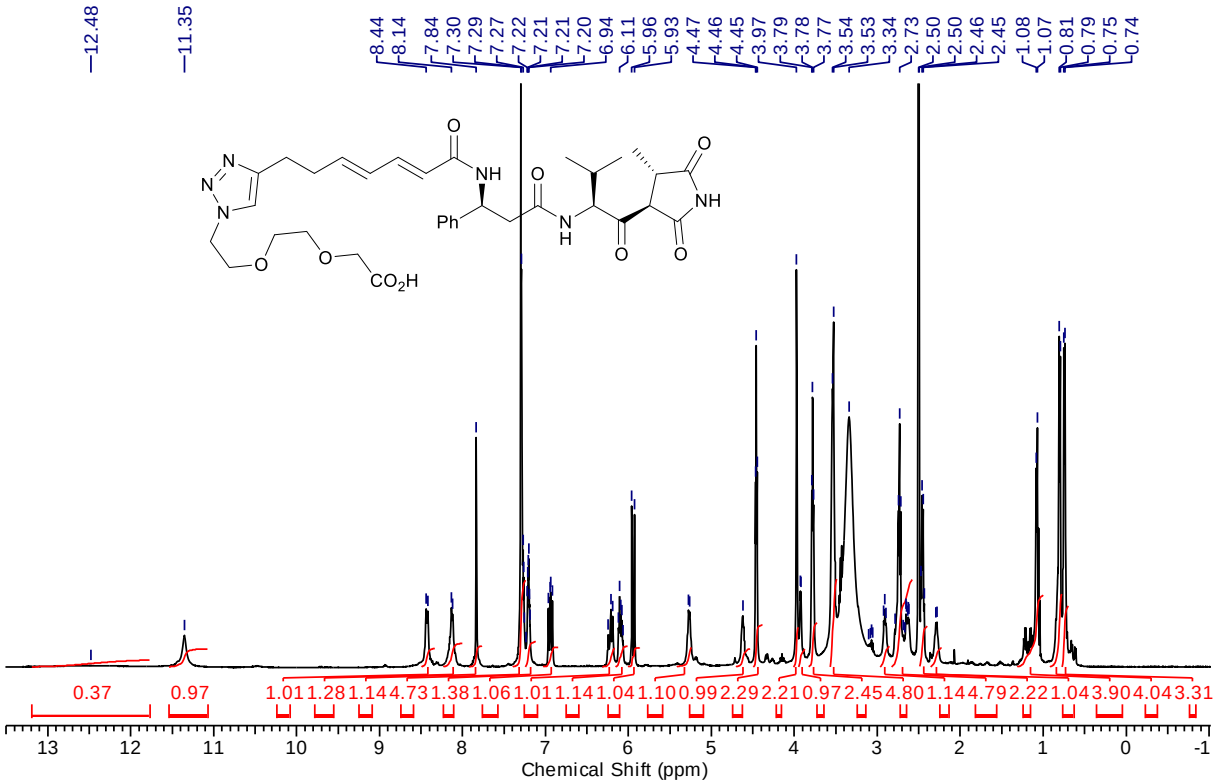


^{13}C NMR (125 MHz, DMSO-d_6):

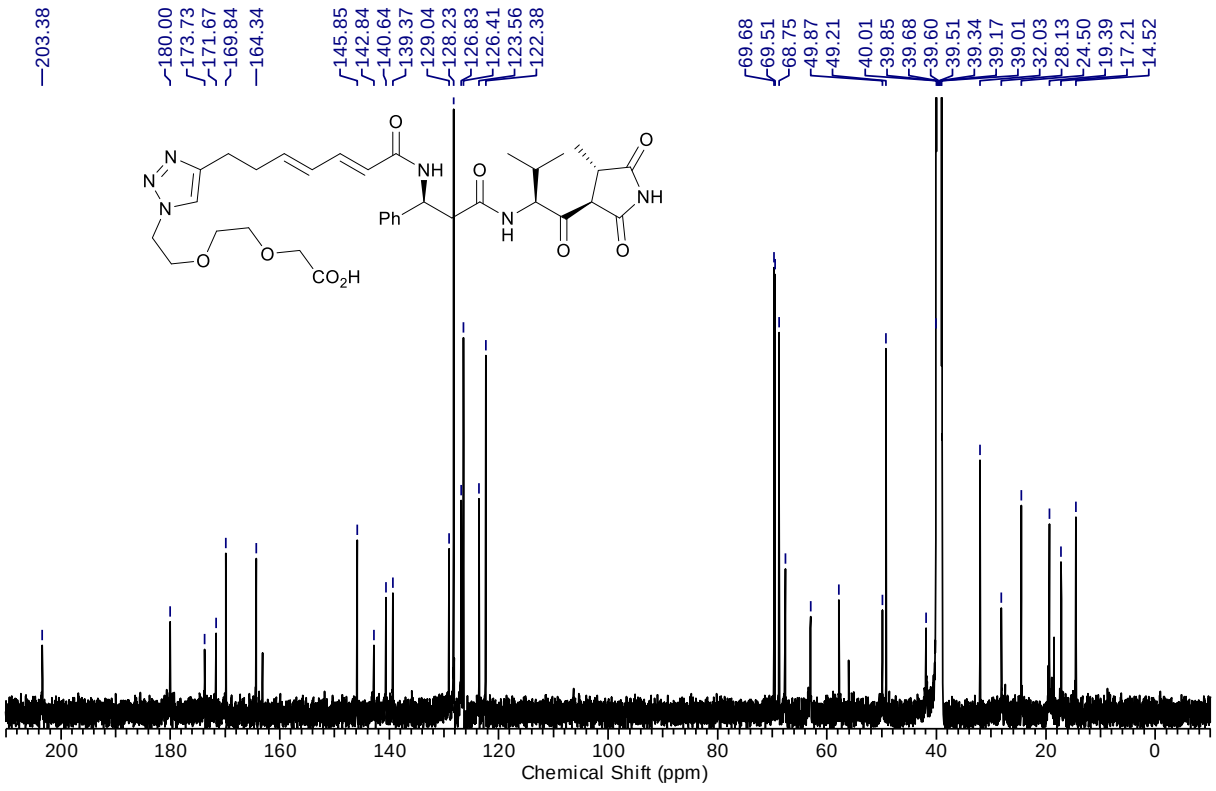


2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)acetic acid (12e)

^{1}H NMR (500 MHz, DMSO-d_6):

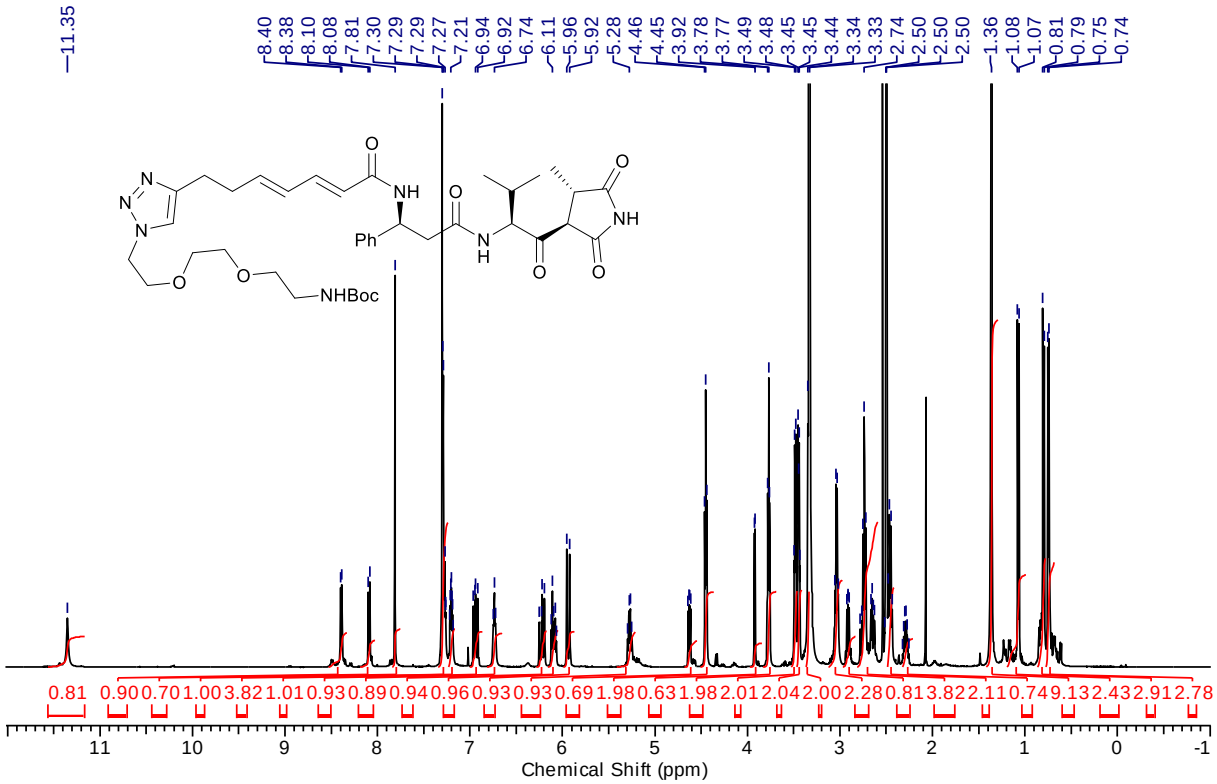


^{13}C NMR (125 MHz, DMSO-d_6):

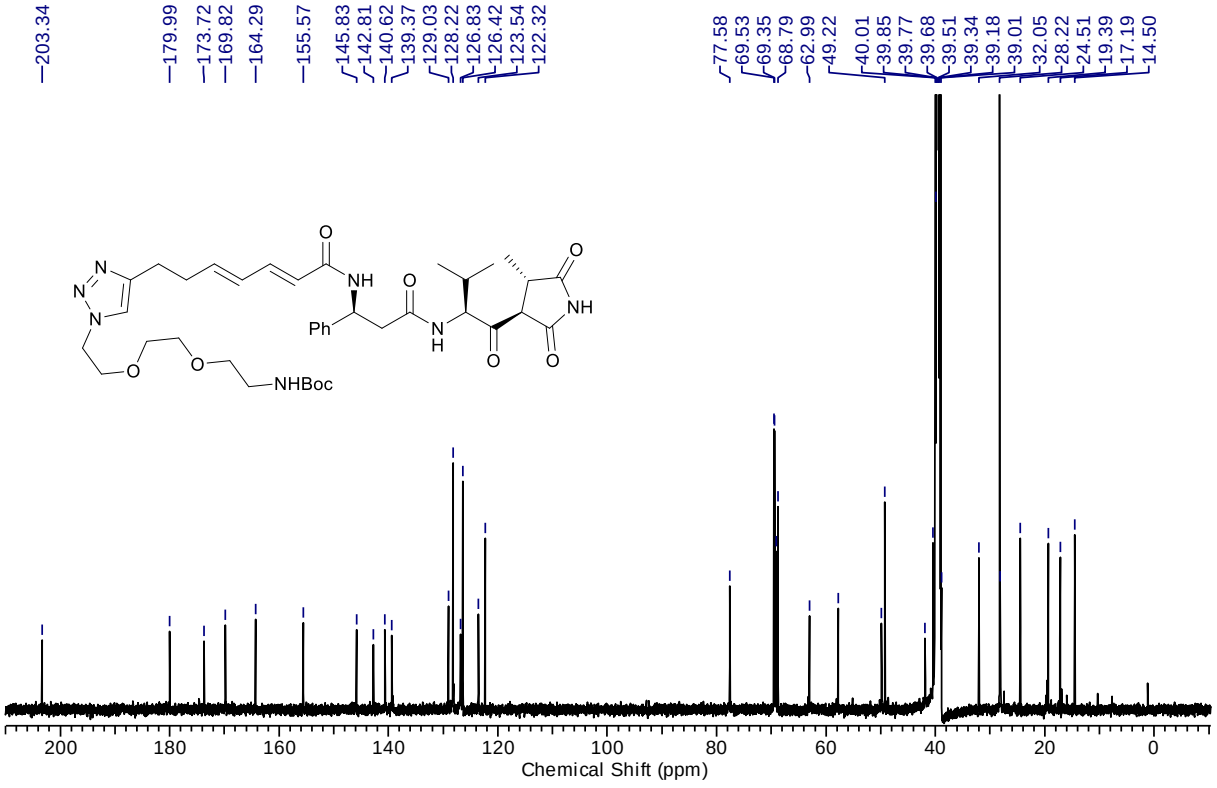


***tert*-Butyl (2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethyl)carbamate (12f)**

^{1}H NMR (500 MHz, DMSO-d_6):

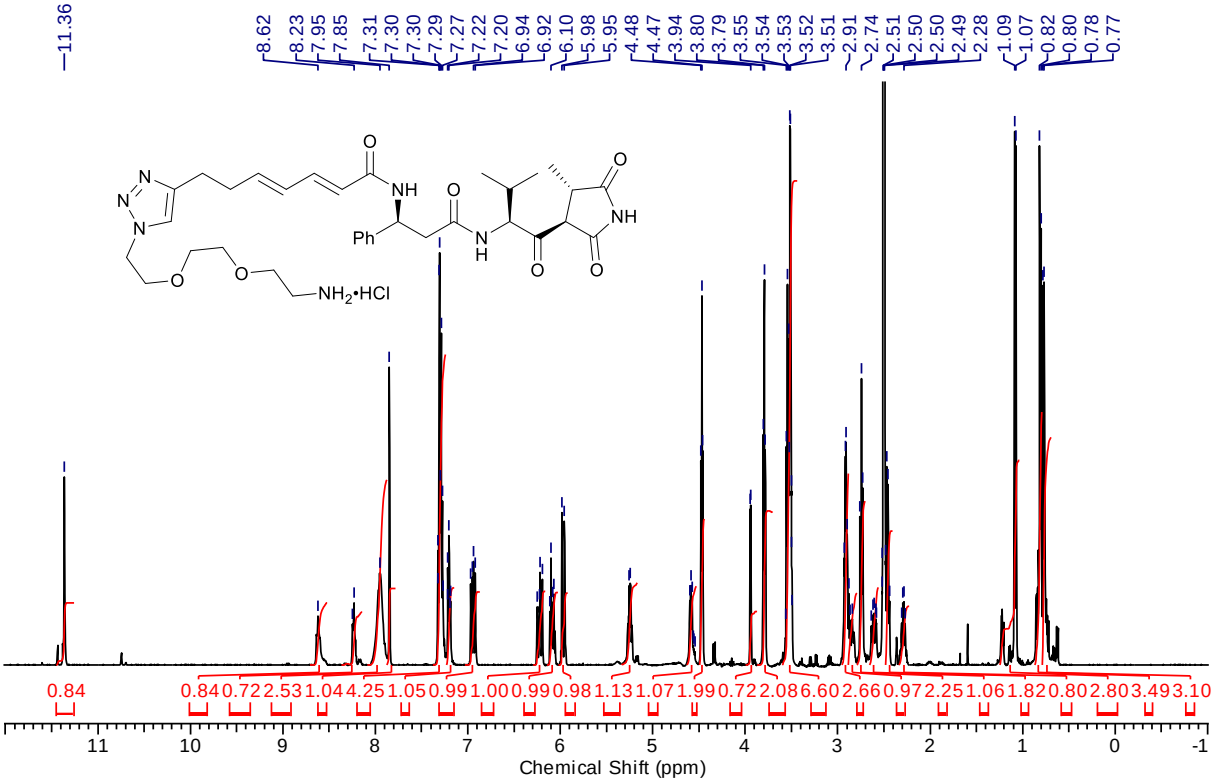


^{13}C NMR (125 MHz, DMSO-d_6):

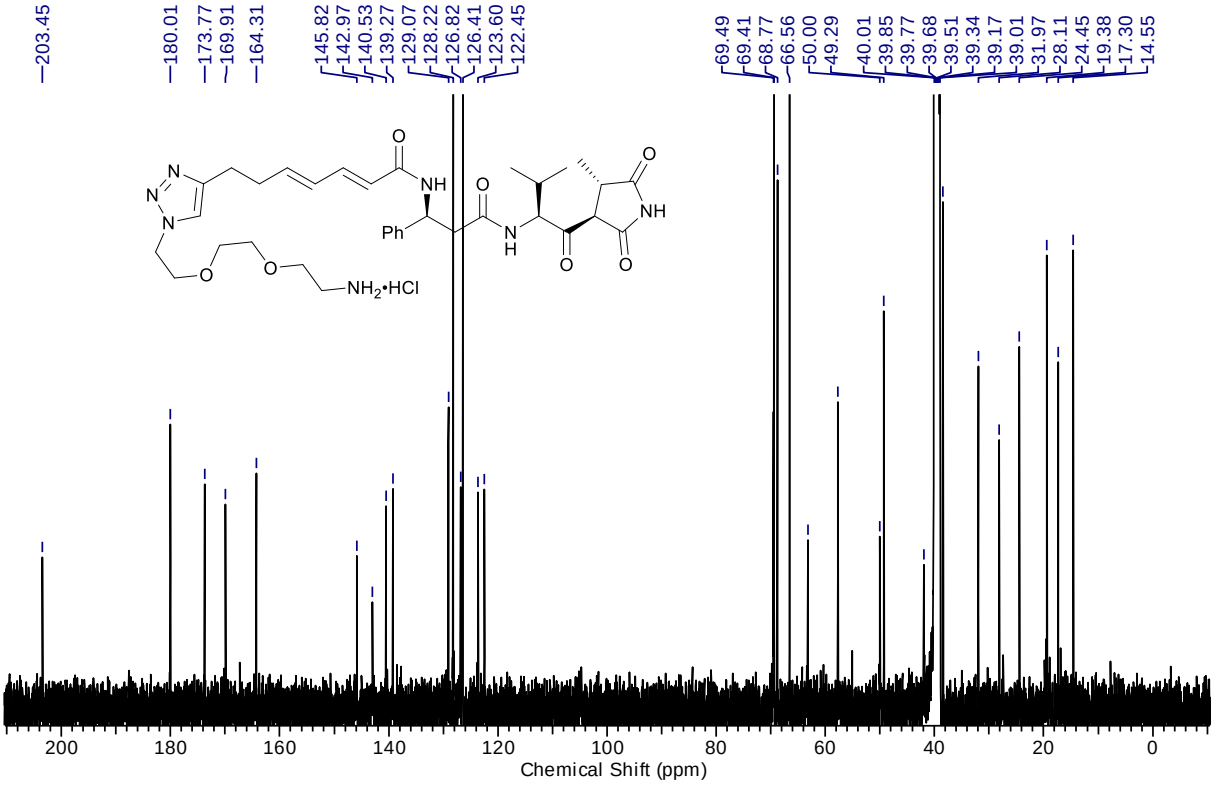


2-(2-(2-(4-((3*E*,5*E*)-7-(((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)amino)-7-oxohepta-3,5-dien-1-yl)-1*H*-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethan-1-amine hydrochloride (12g)

^{1}H NMR (500 MHz, DMSO-d_6):

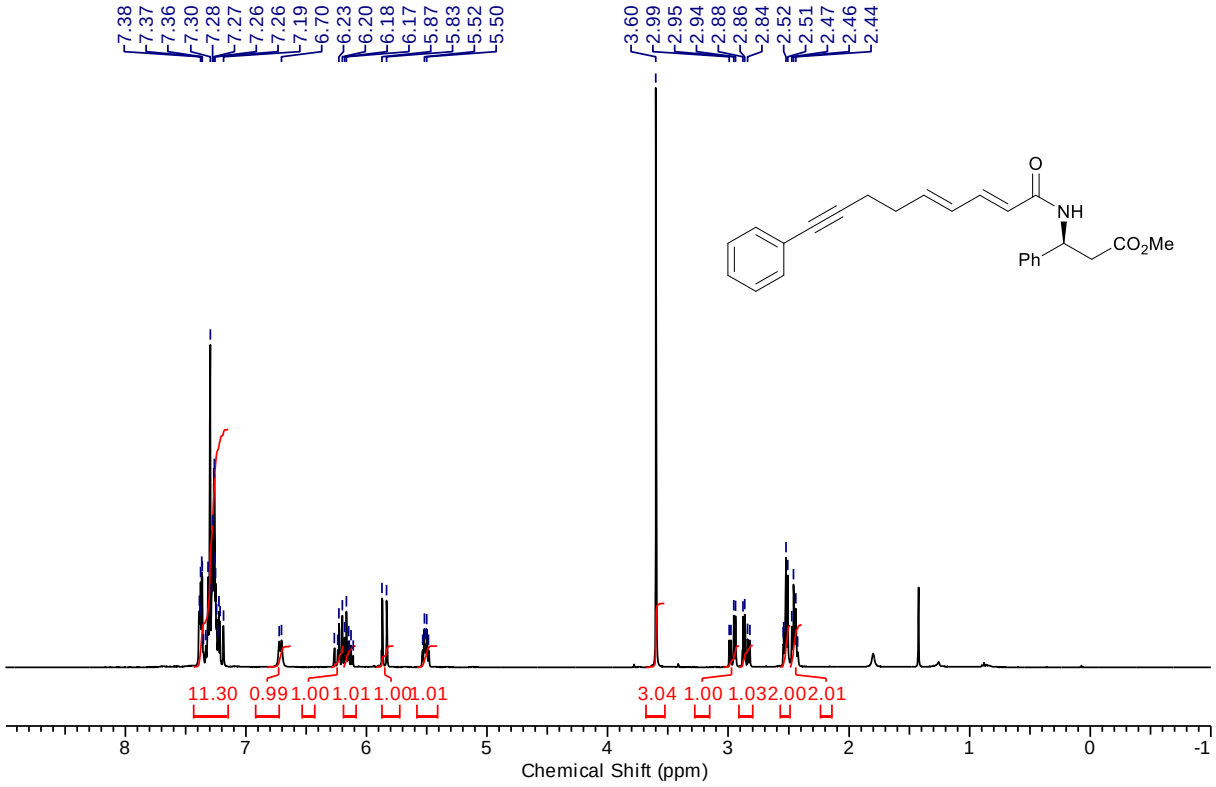


^{13}C NMR (125 MHz, DMSO-d_6):

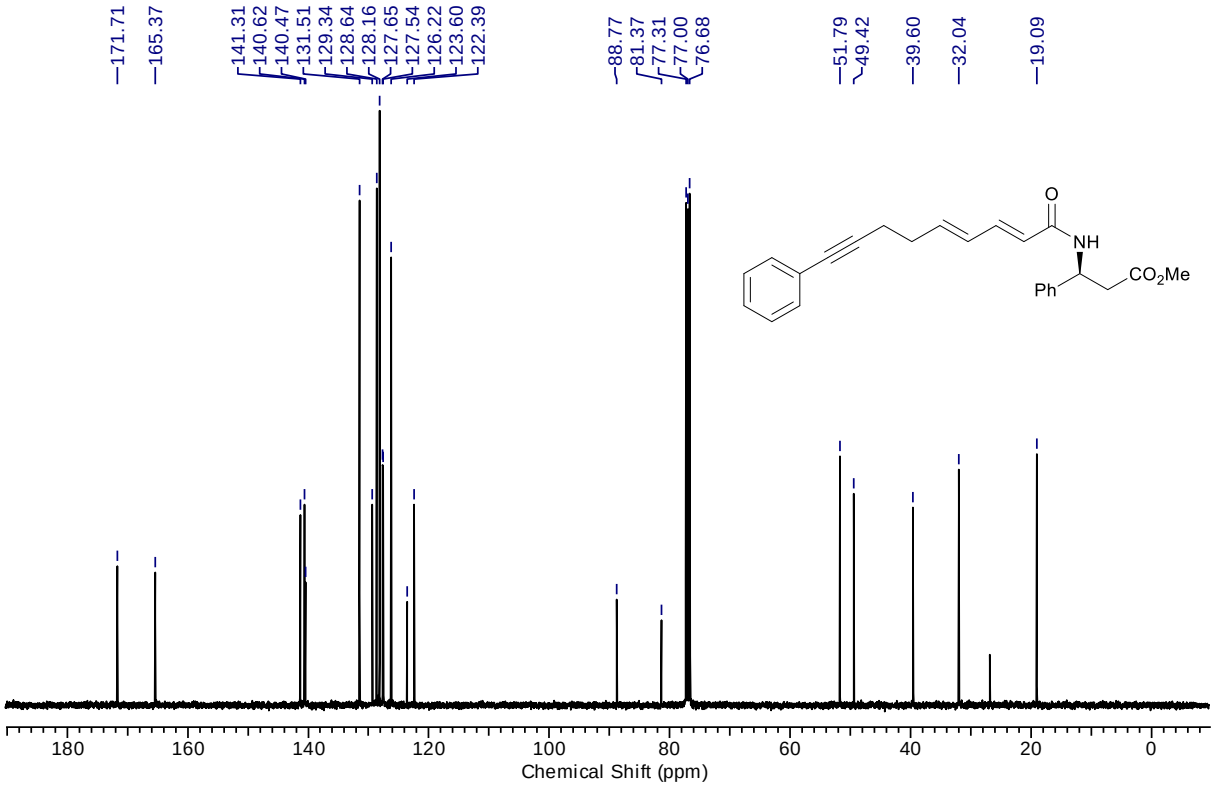


Methyl (*S*)-3-phenyl-3-((2*E*,4*E*)-9-phenylnona-2,4-dien-8-ynamido)propanoate (13a)

^{1}H NMR (400 MHz, $CDCl_3$):

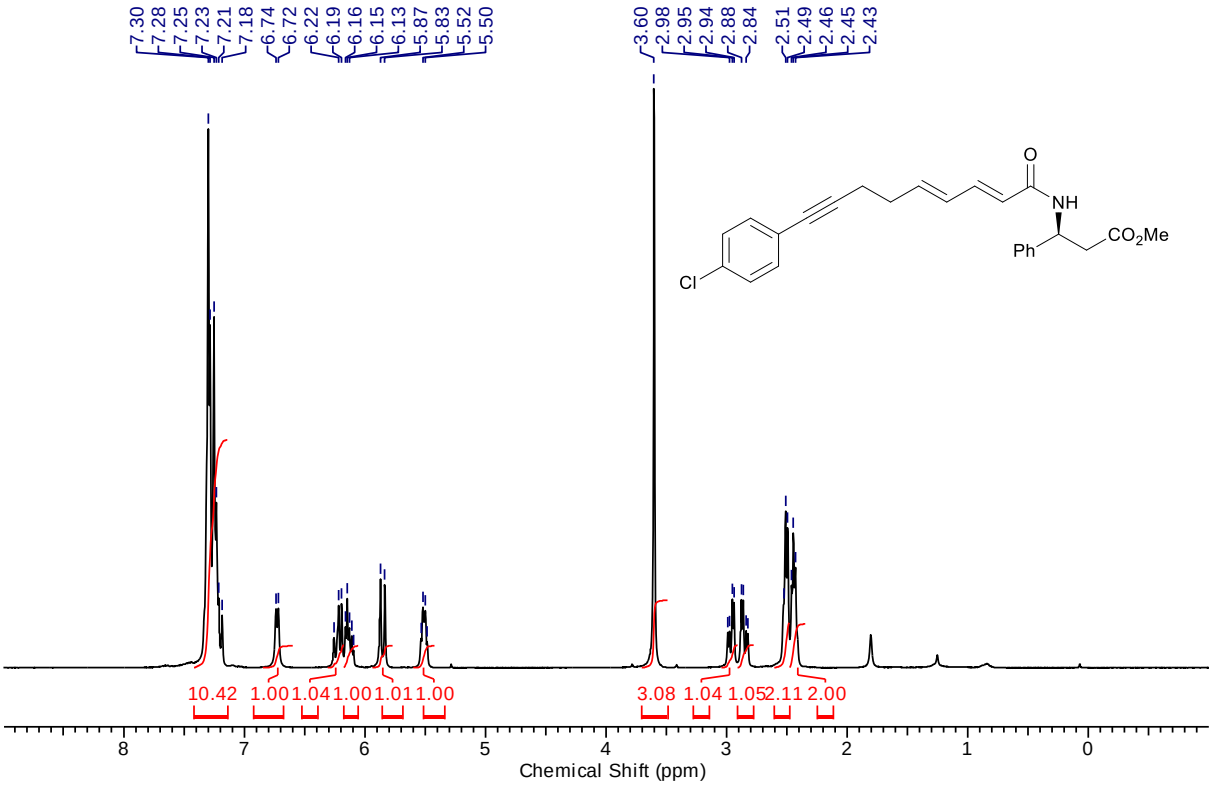


^{13}C NMR (100 MHz, $CDCl_3$):

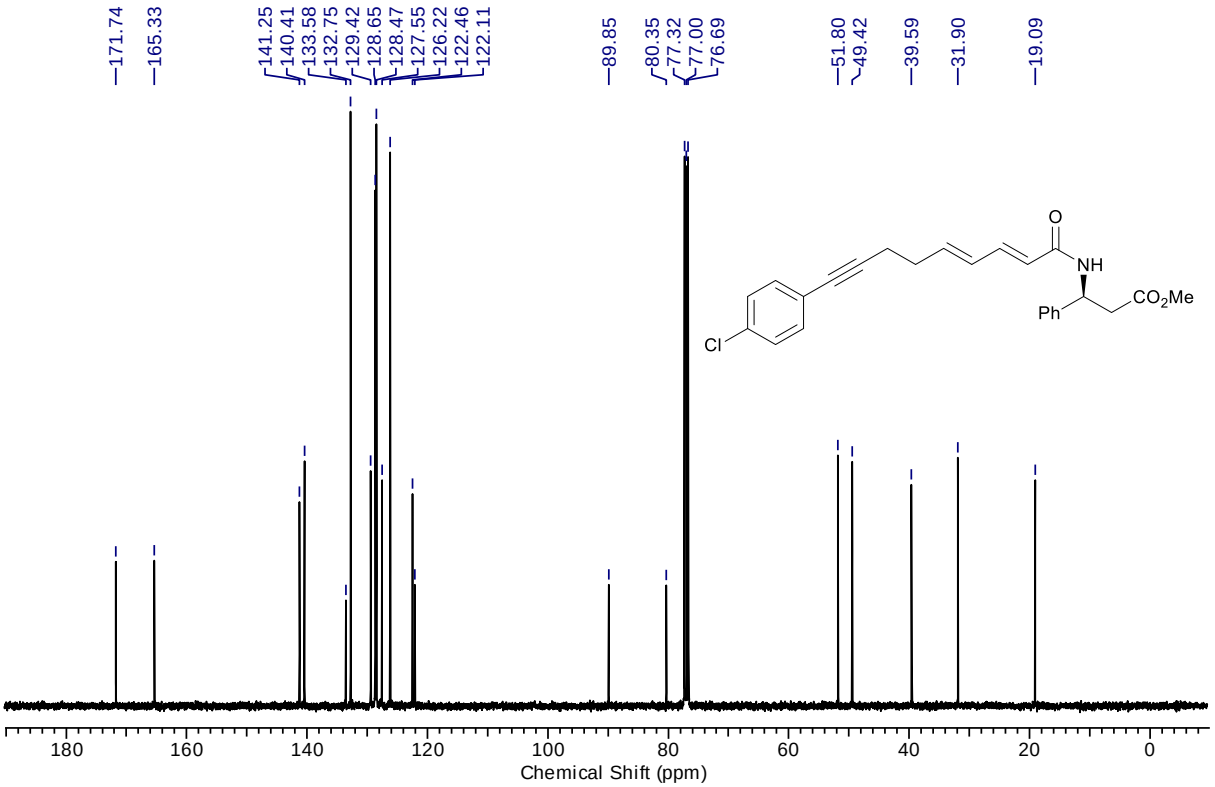


Methyl (*S*)-3-((2*E*,4*E*)-9-(4-chlorophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13b)

^{1}H NMR (400 MHz, $CDCl_3$):

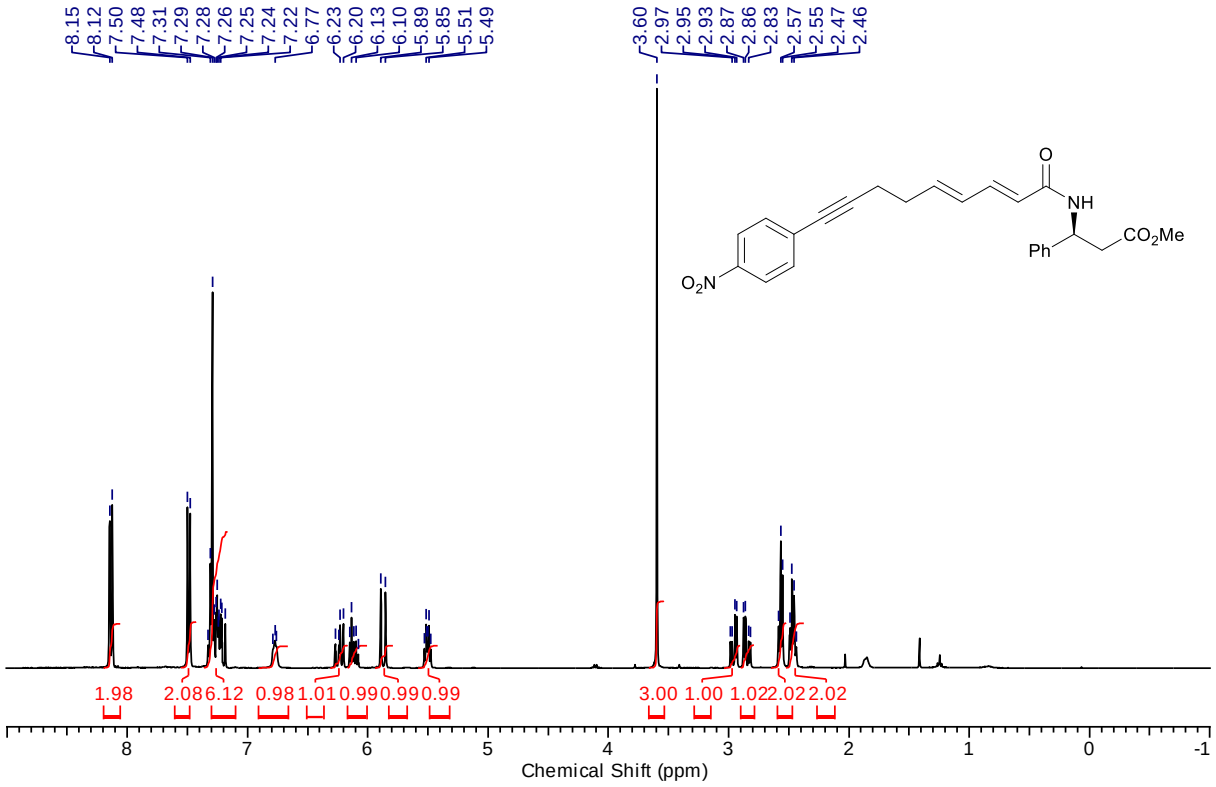


^{13}C NMR (100 MHz, $CDCl_3$):

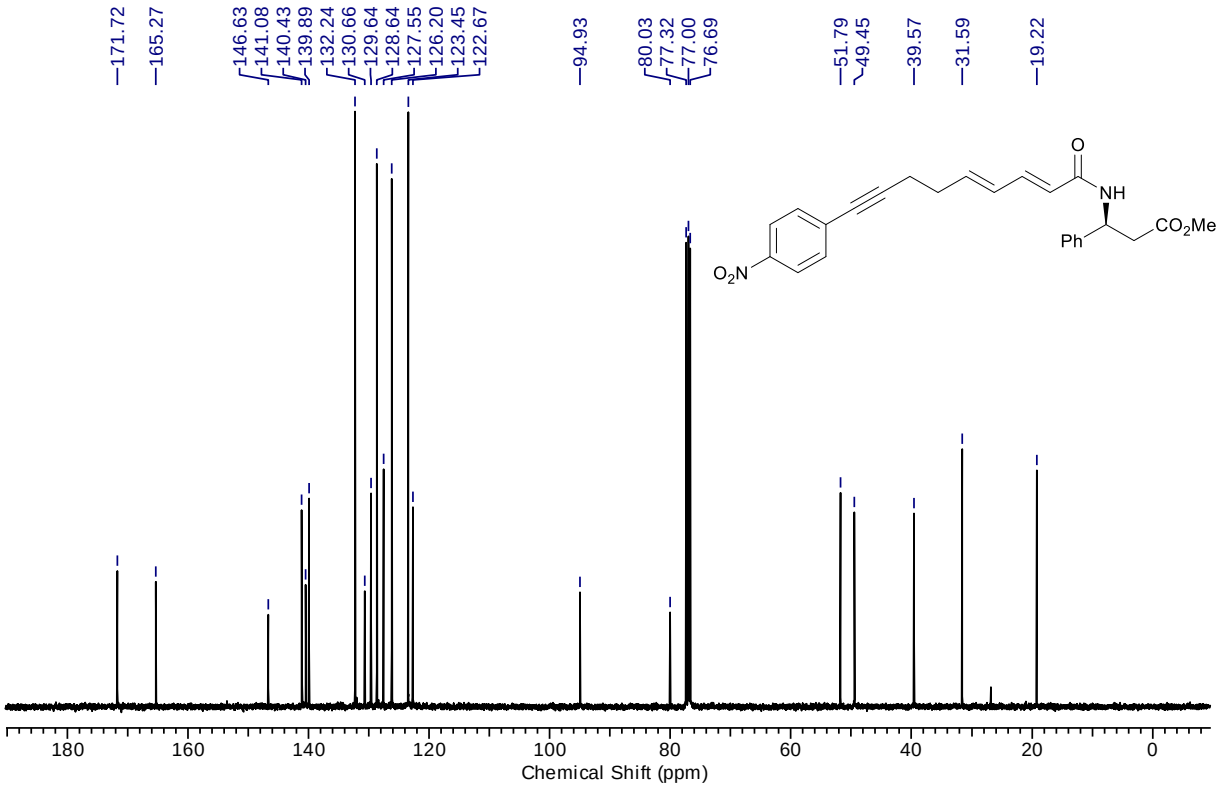


Methyl (*S*)-3-((2*E*,4*E*)-9-(4-nitrophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13c)

^{1}H NMR (400 MHz, $CDCl_3$):

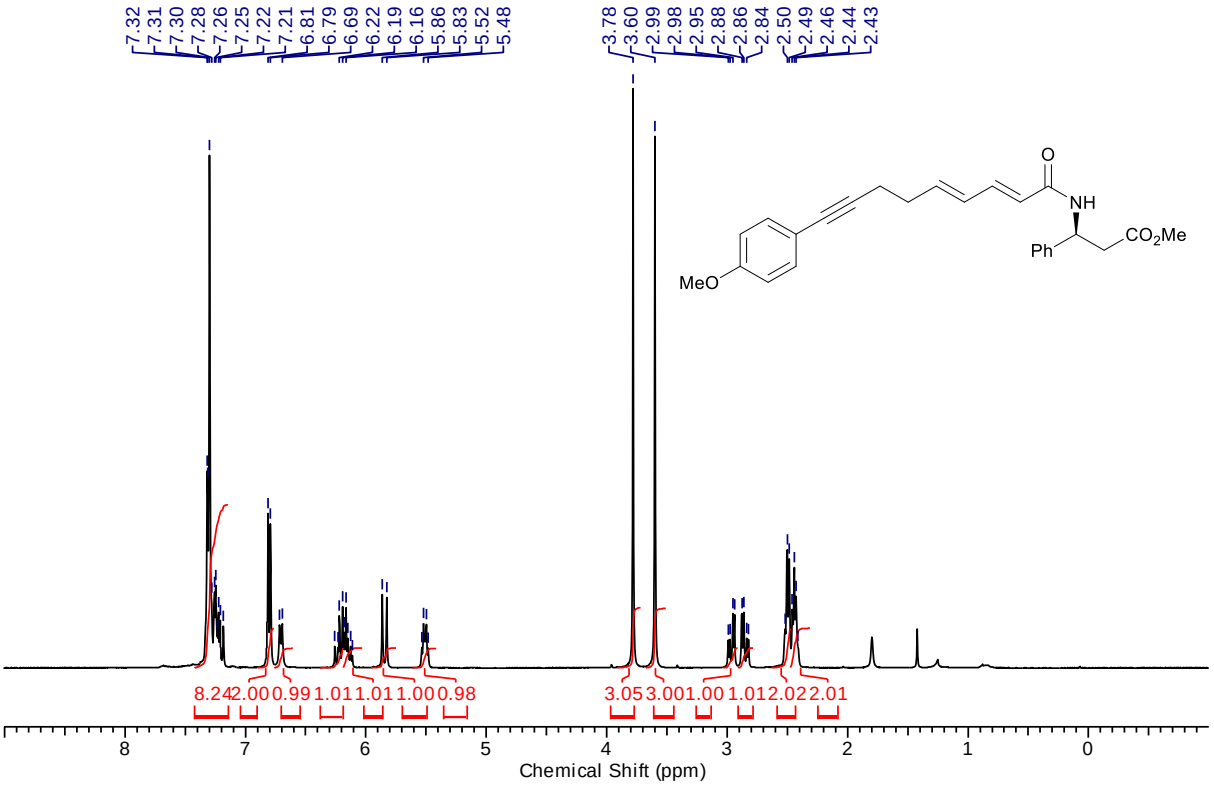


^{13}C NMR (100 MHz, $CDCl_3$):

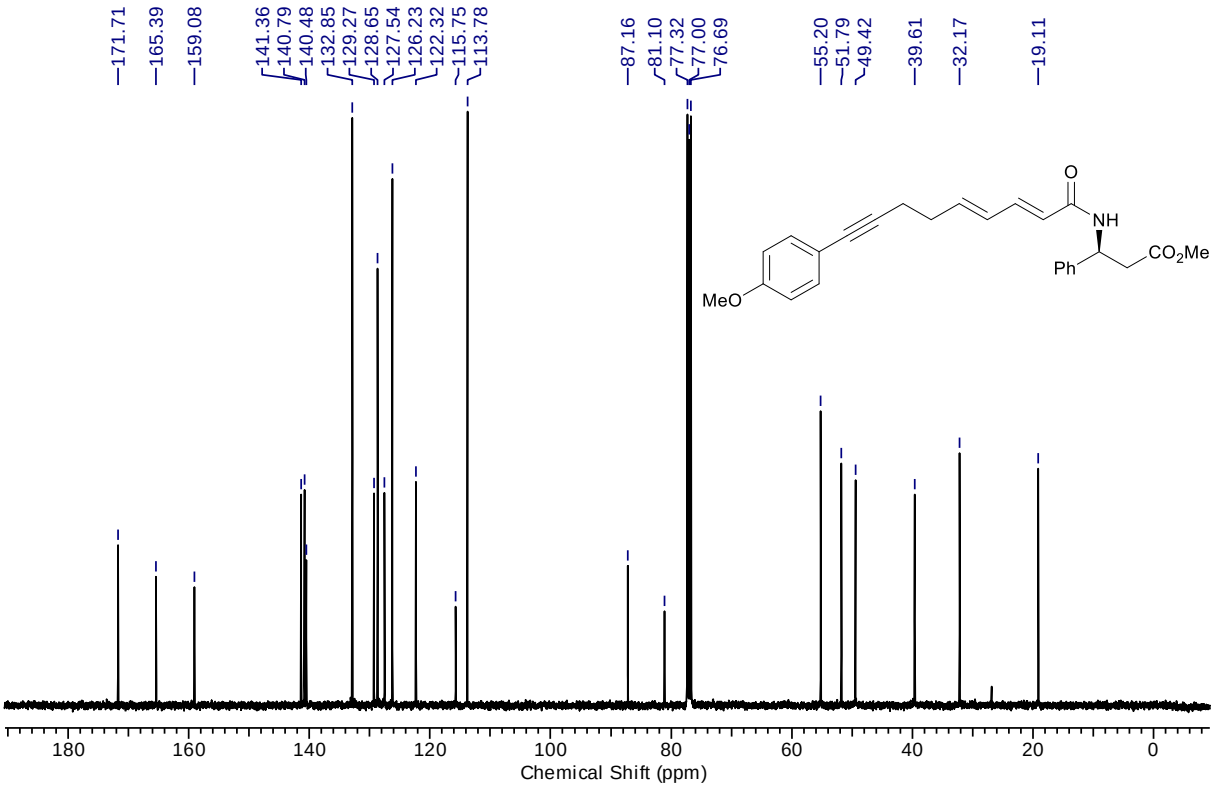


Methyl (*S*)-3-((2*E*,4*E*)-9-(4-methoxyphenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13d)

^{1}H NMR (400 MHz, $CDCl_3$):

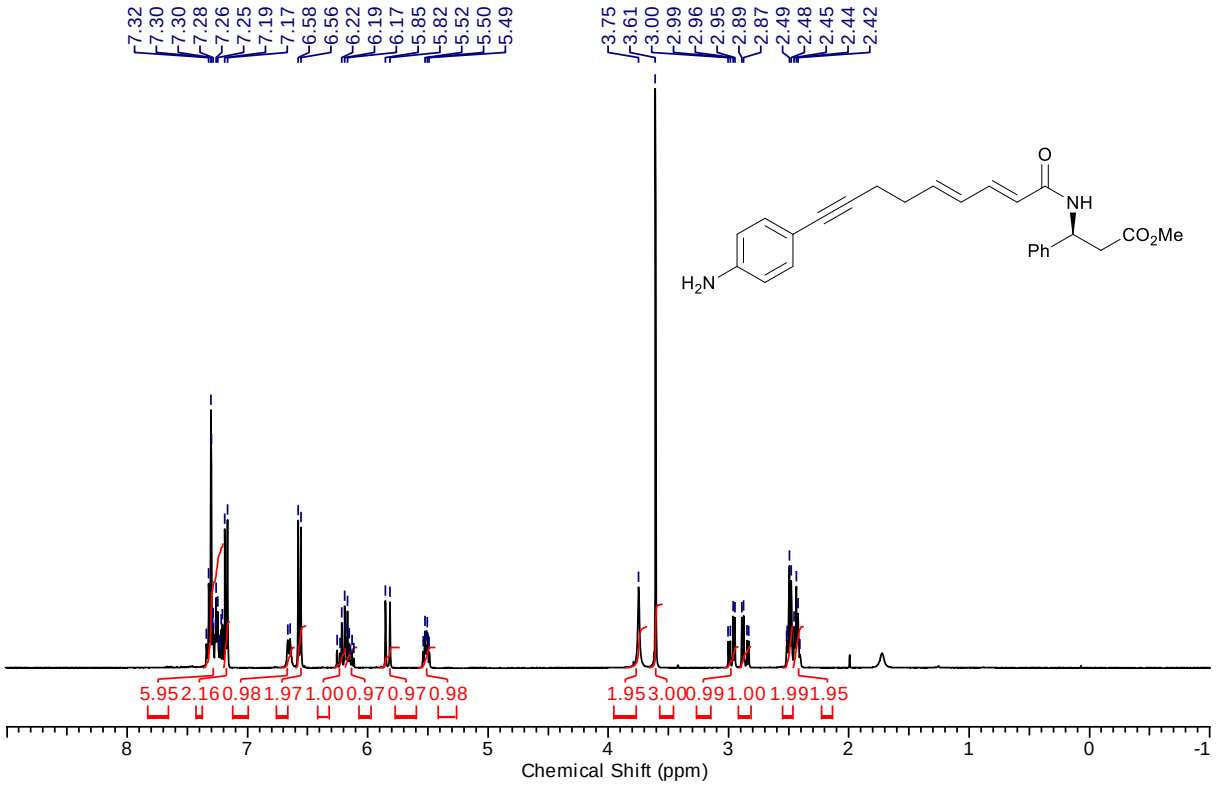


^{13}C NMR (100 MHz, $CDCl_3$):

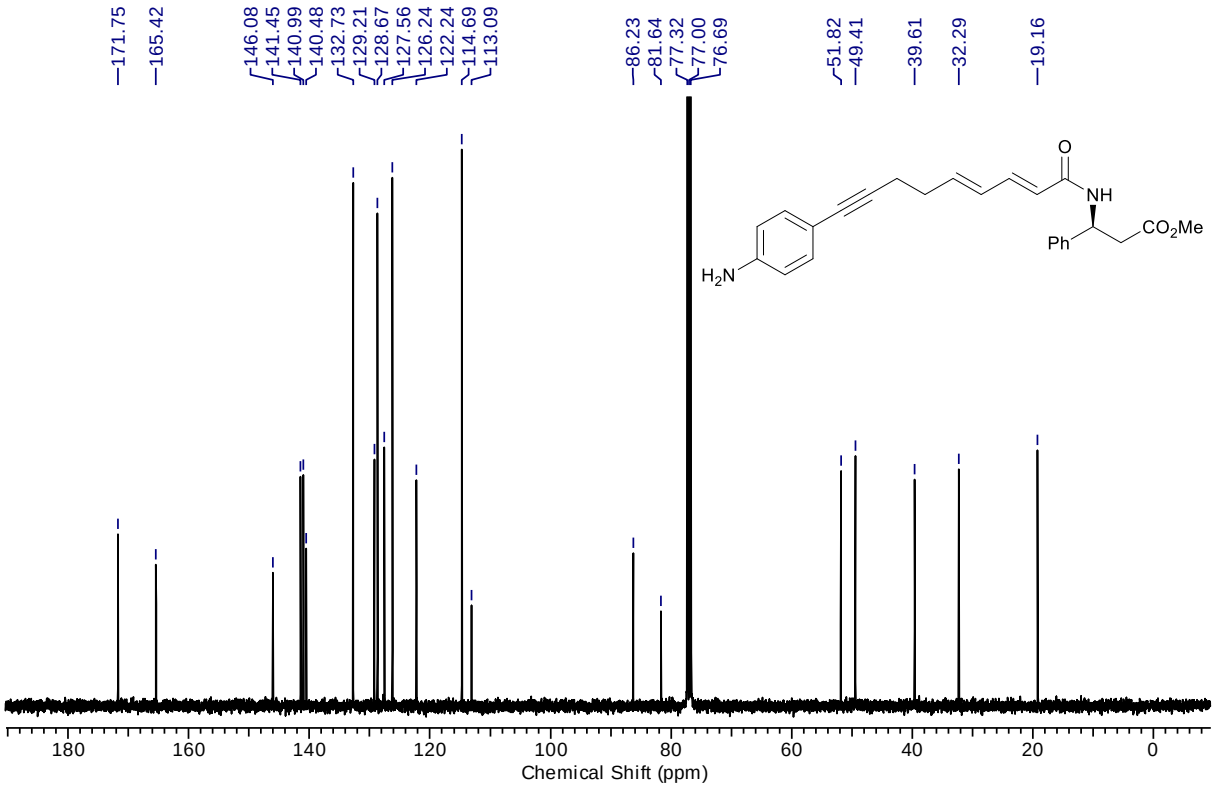


Methyl (*S*)-3-((2*E*,4*E*)-9-(4-aminophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13e)

^{1}H NMR (400 MHz, $CDCl_3$):

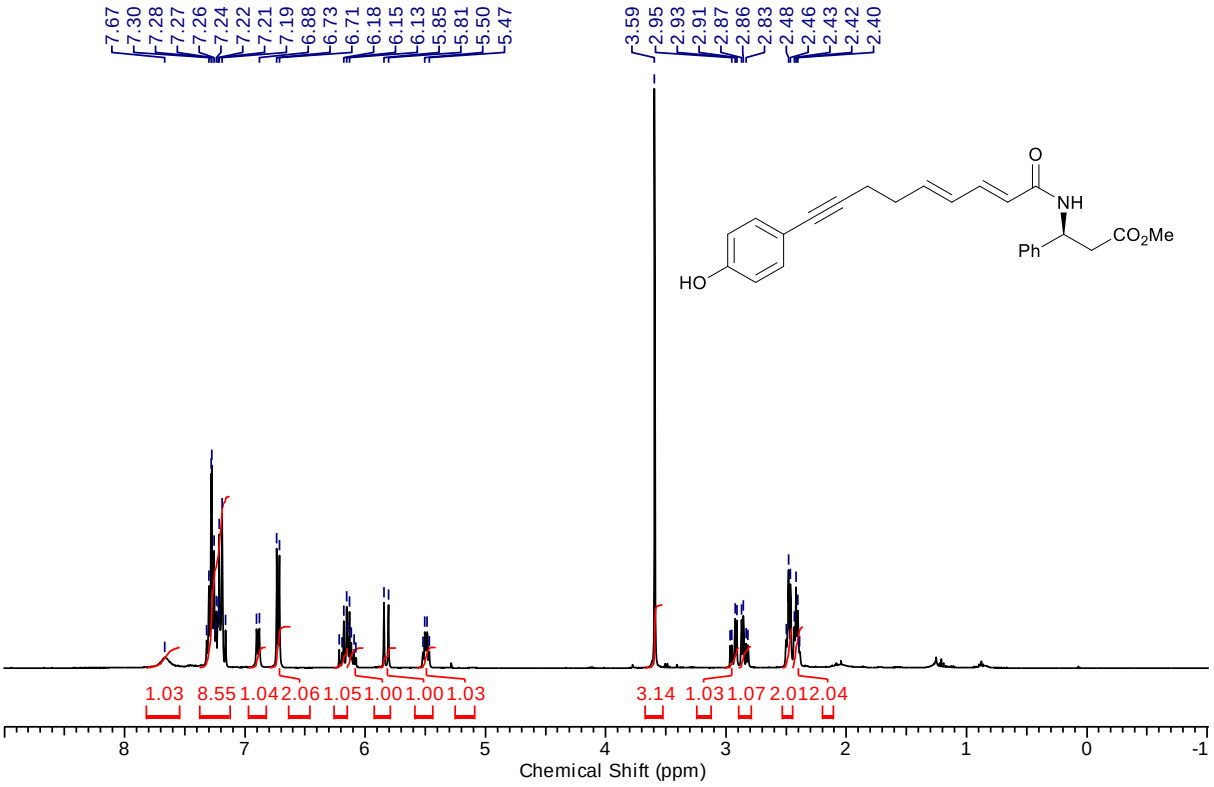


^{13}C NMR (100 MHz, $CDCl_3$):

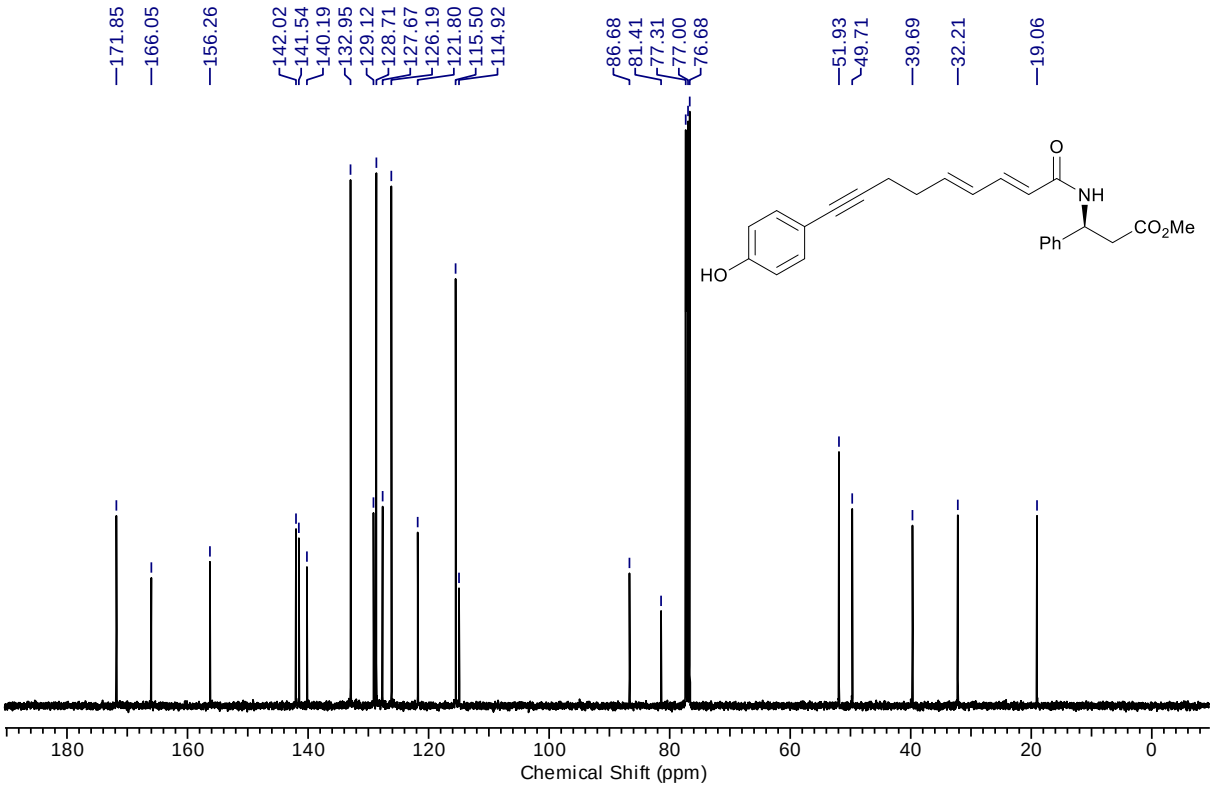


Methyl (*S*)-3-((2*E*,4*E*)-9-(4-hydroxyphenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13f)

^{1}H NMR (400 MHz, $CDCl_3$):

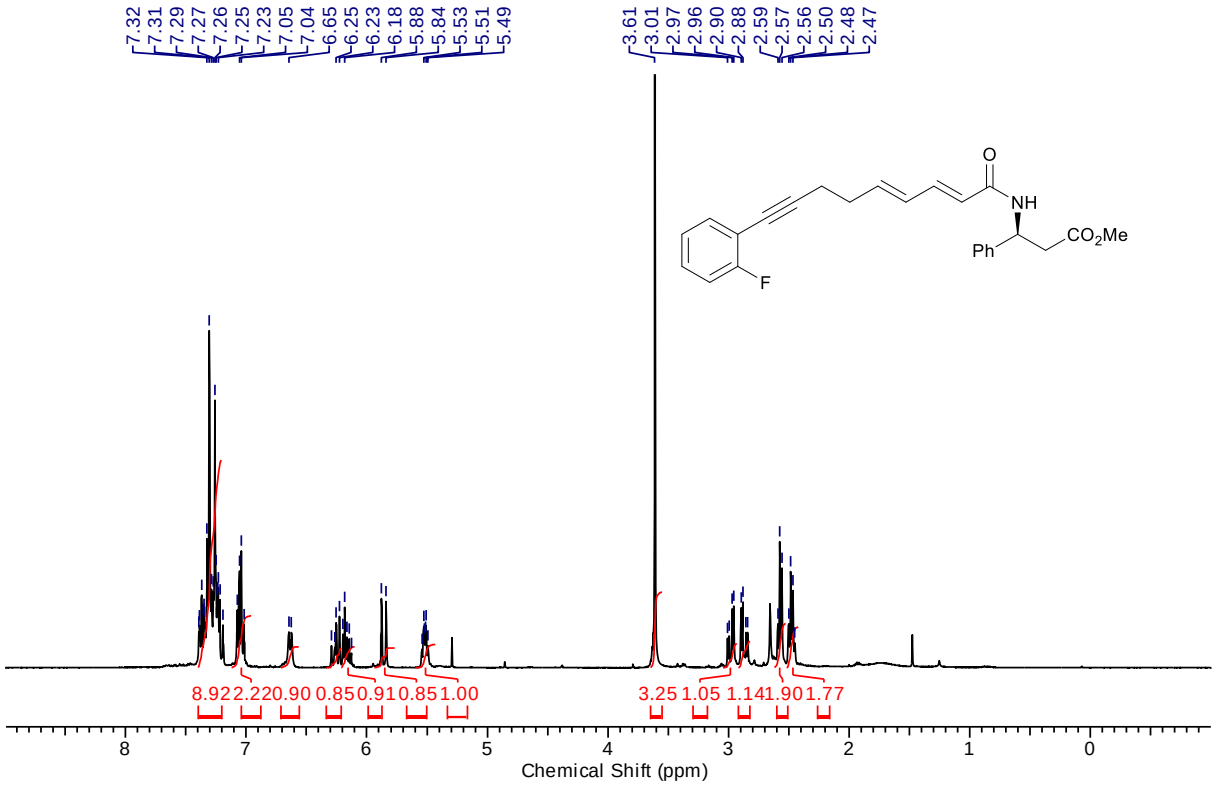


^{13}C NMR (100 MHz, $CDCl_3$):

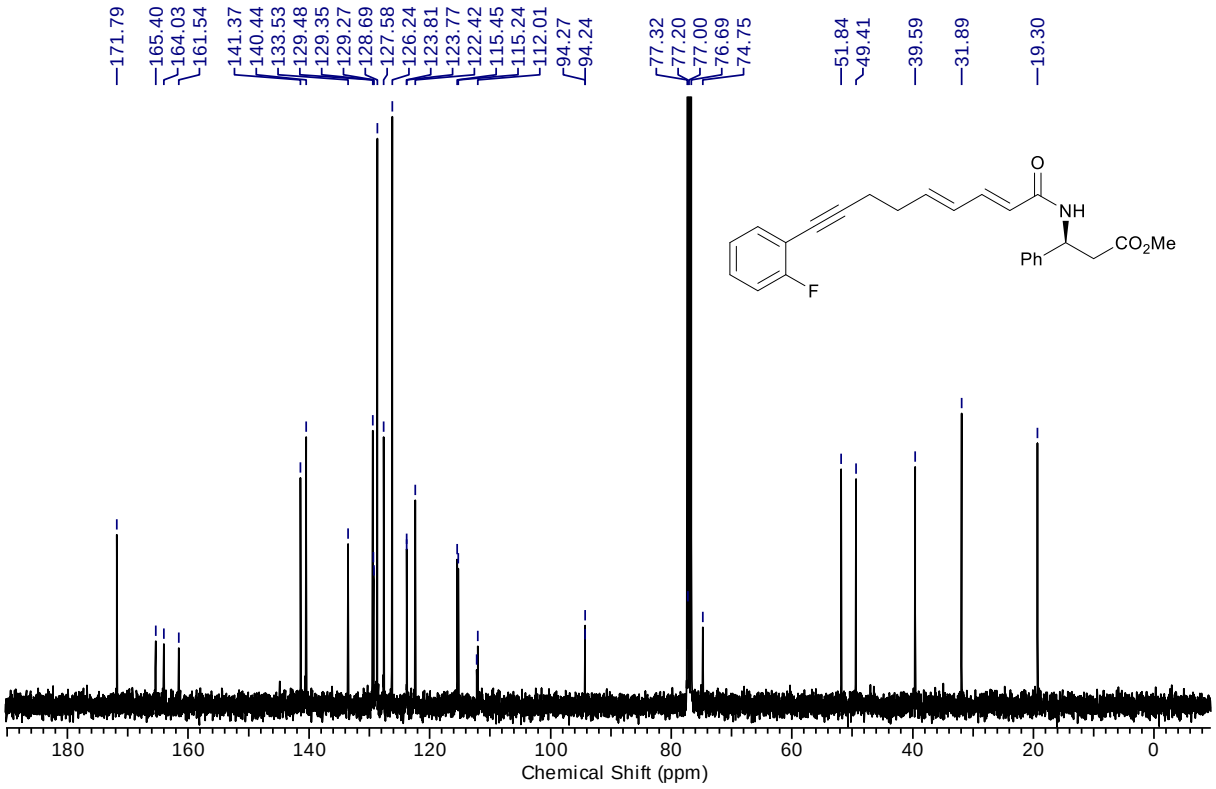


Methyl (*S*)-3-((2*E*,4*E*)-9-(2-fluorophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13g)

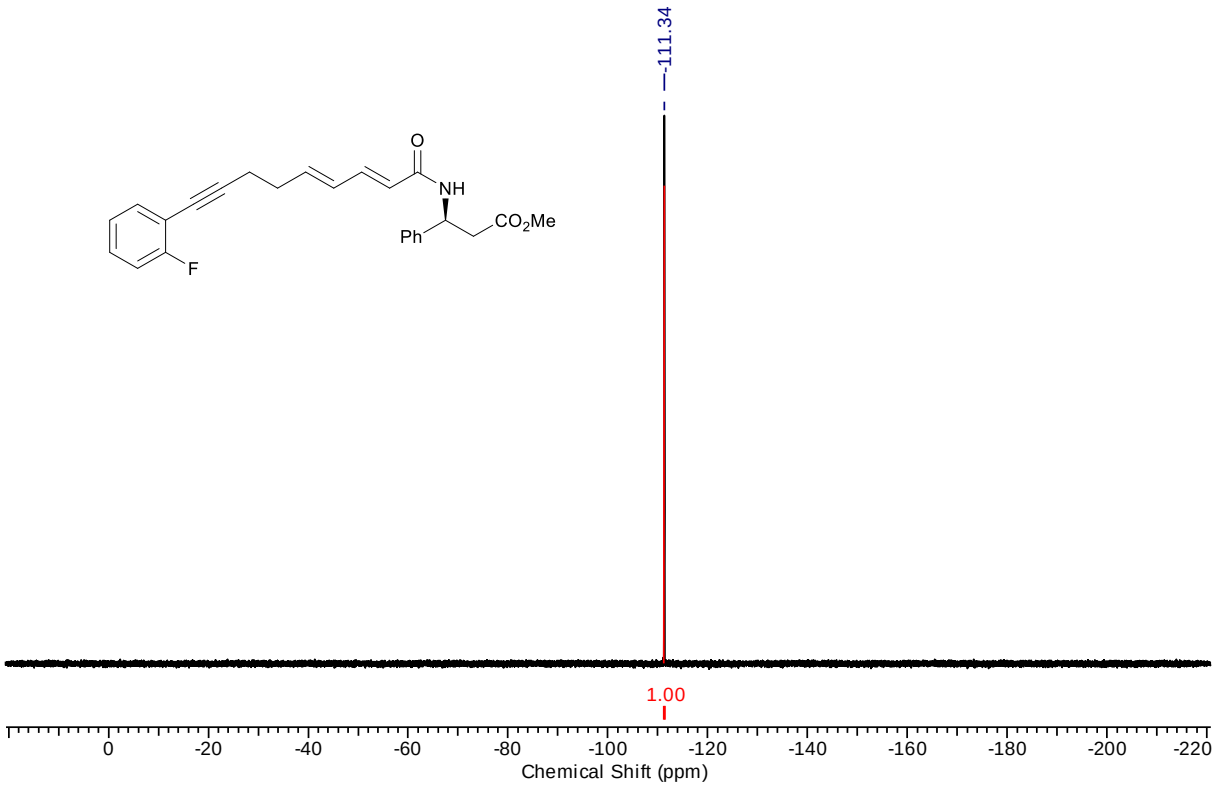
^{1}H NMR (400 MHz, $CDCl_3$):



^{13}C NMR (100 MHz, $CDCl_3$):

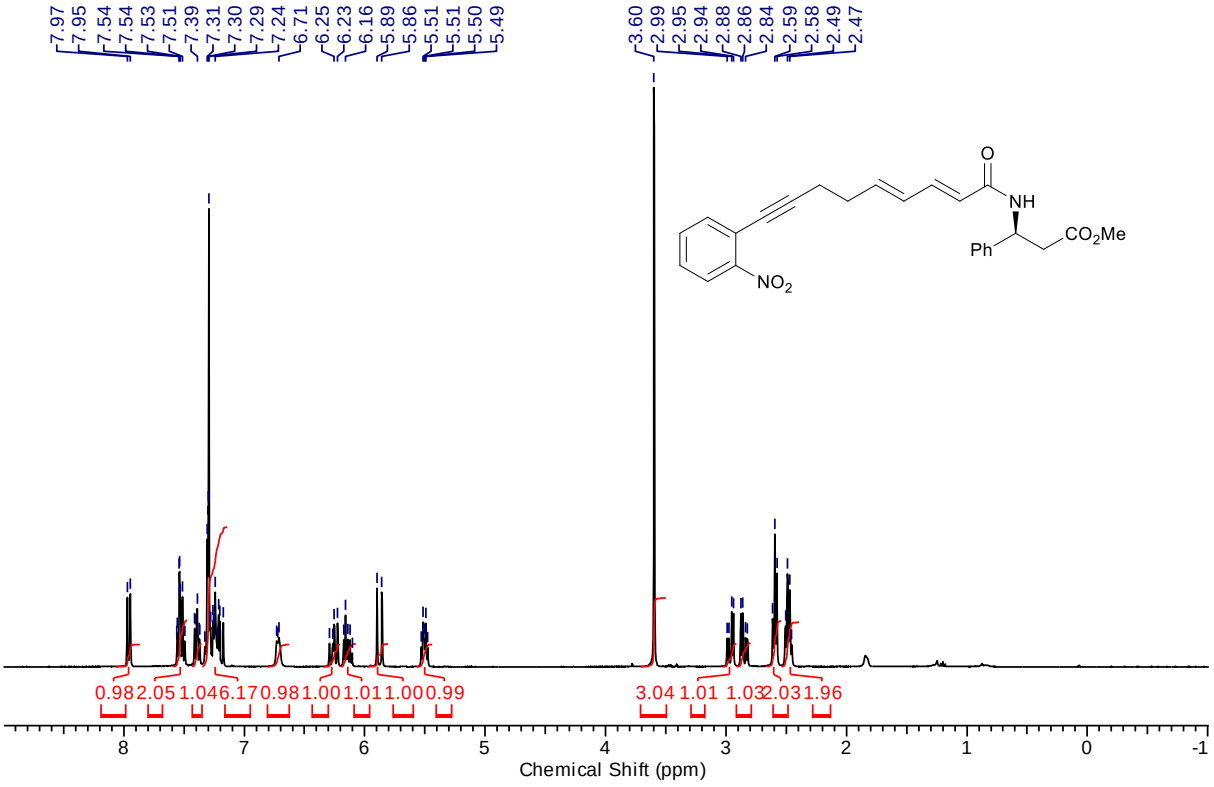


^{19}F NMR (377 MHz, $CDCl_3$):

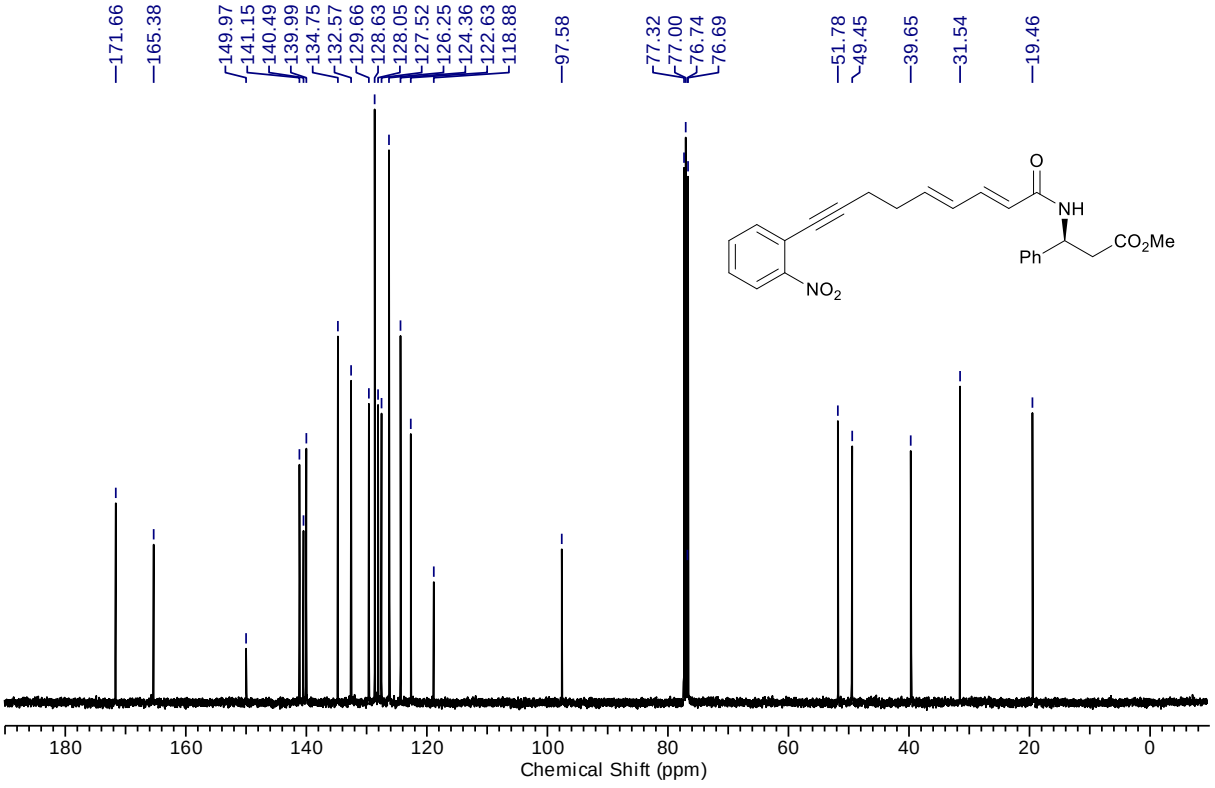


Methyl (*S*)-3-((2*E*,4*E*)-9-(2-nitrophenyl)nona-2,4-dien-8-ynamido)-3-phenylpropanoate (13h)

^{1}H NMR (400 MHz, $CDCl_3$):

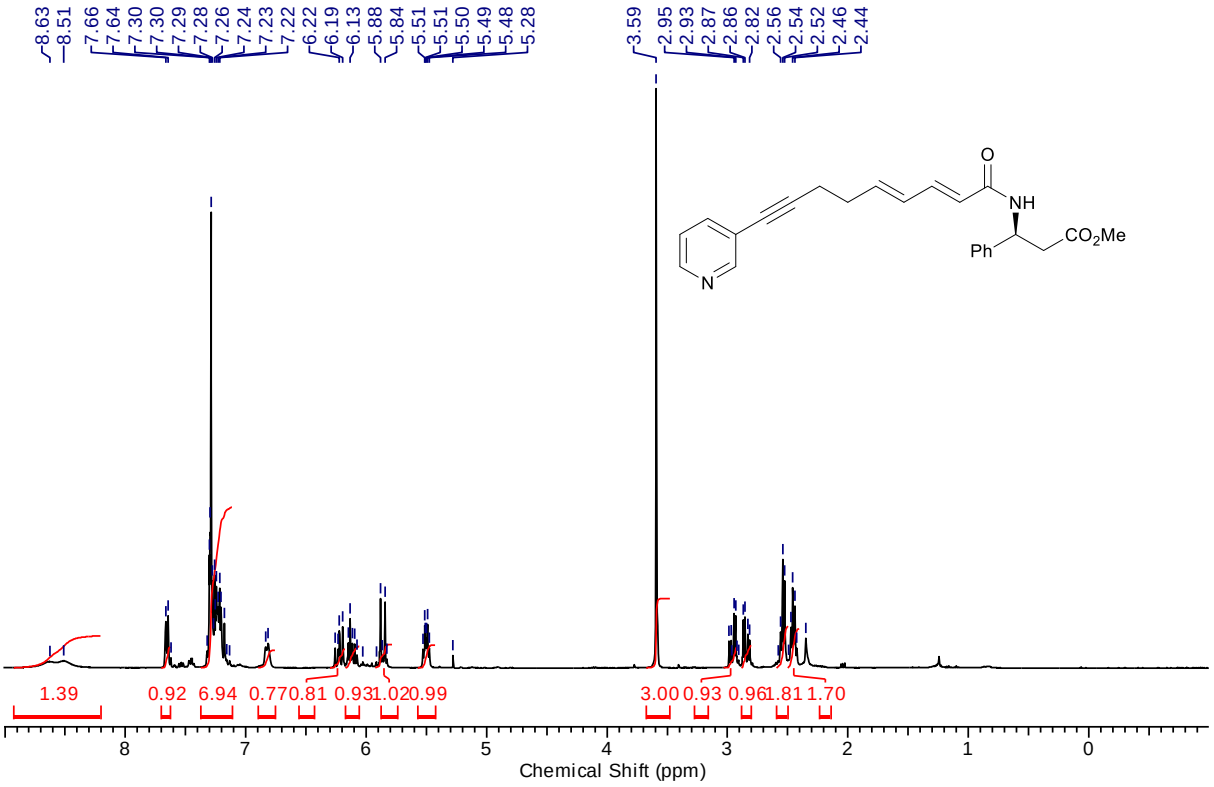


^{13}C NMR (100 MHz, $CDCl_3$):

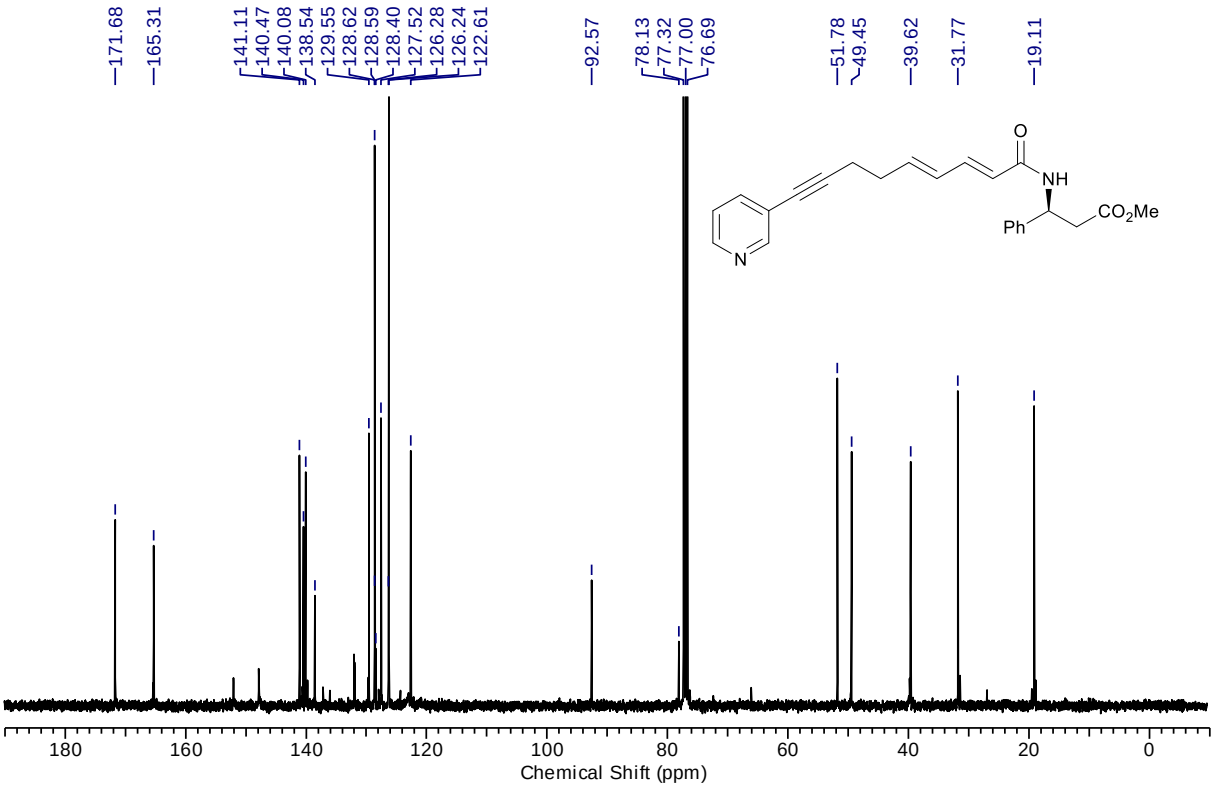


Methyl (*S*)-3-phenyl-3-((2*E*,4*E*)-9-(pyridin-3-yl)nona-2,4-dien-8-ynamido)propanoate (13i)

^{1}H NMR (400 MHz, $CDCl_3$):

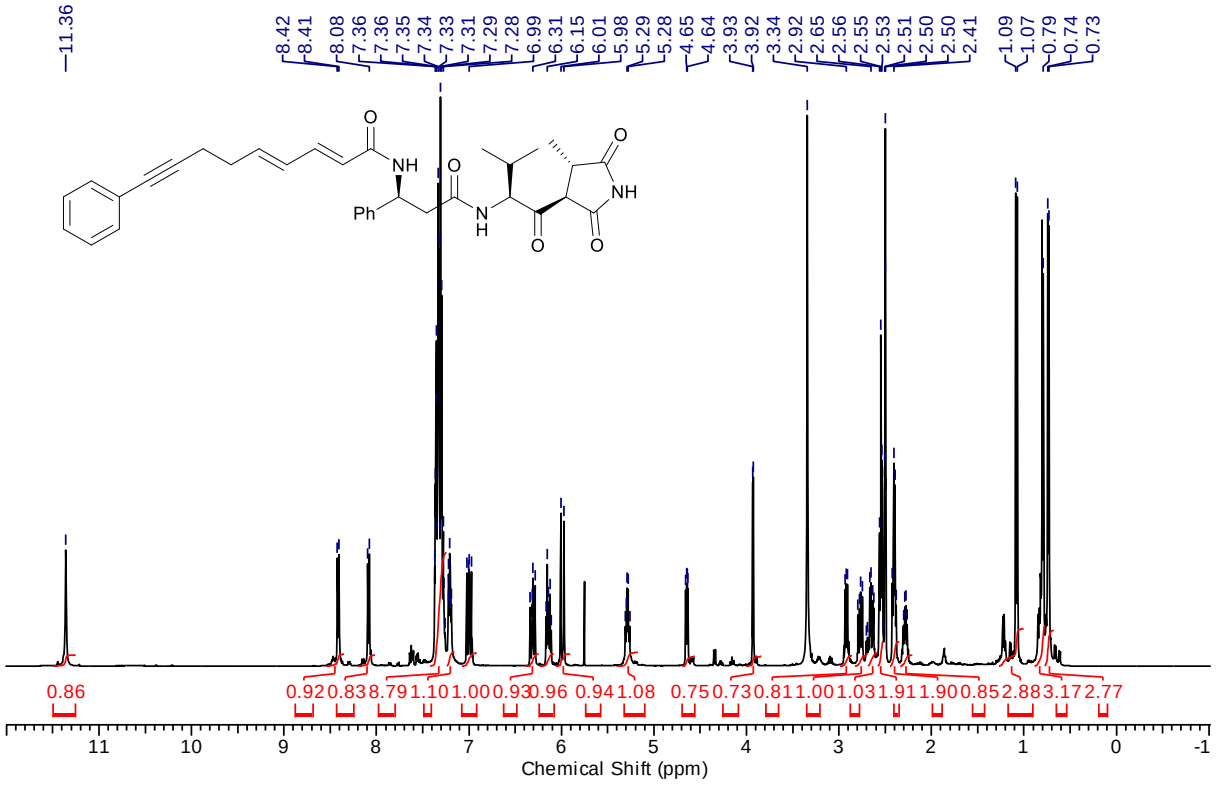


^{13}C NMR (100 MHz, $CDCl_3$):

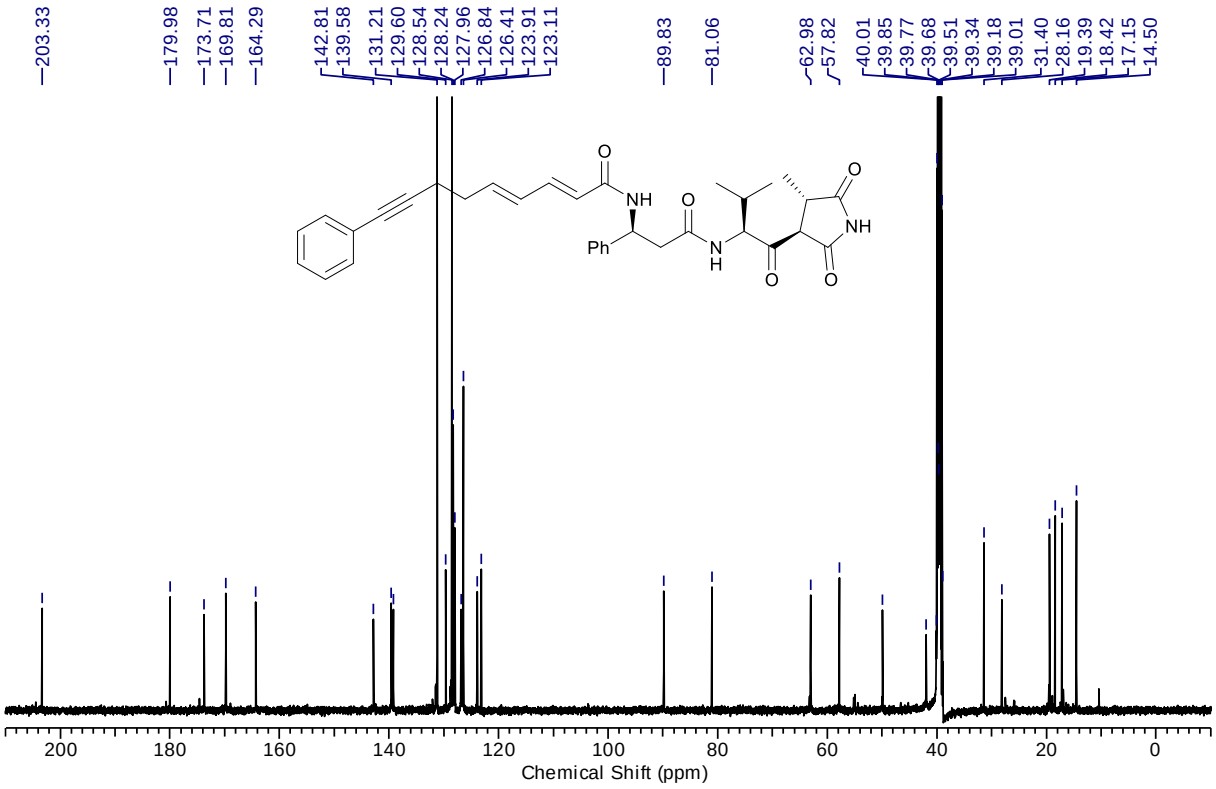


(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-phenylnona-2,4-dien-8-ynamide (14a)

^{1}H NMR (500 MHz, DMSO-d_6):

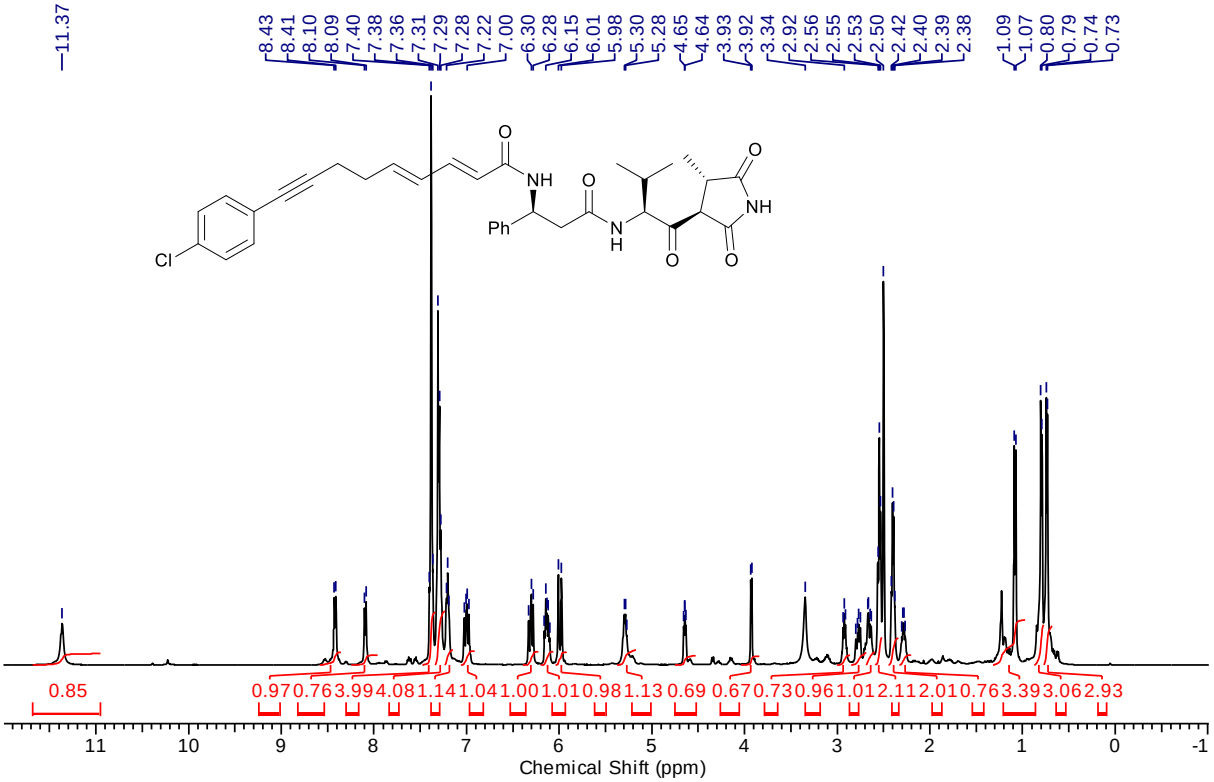


^{13}C NMR (125 MHz, DMSO-d_6):

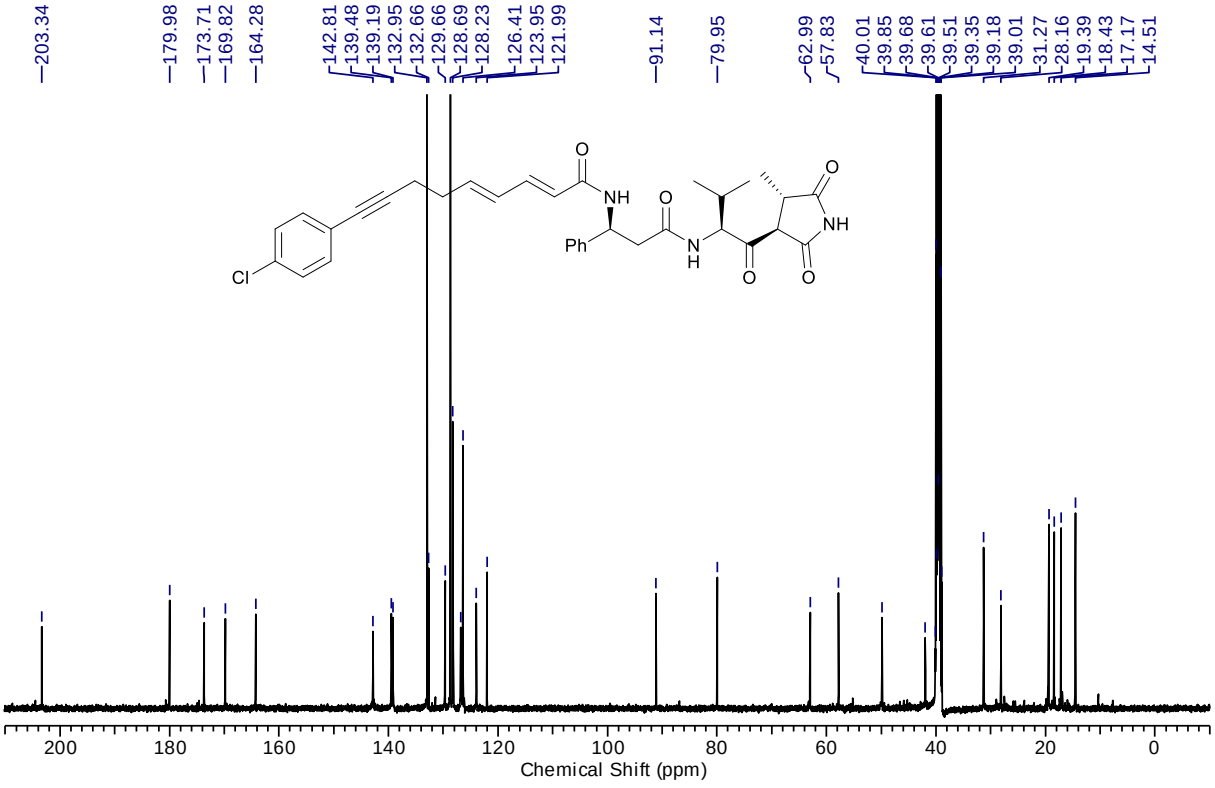


(2*E*,4*E*)-9-(4-Chlorophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14b)

^{1}H NMR (500 MHz, DMSO-d_6):

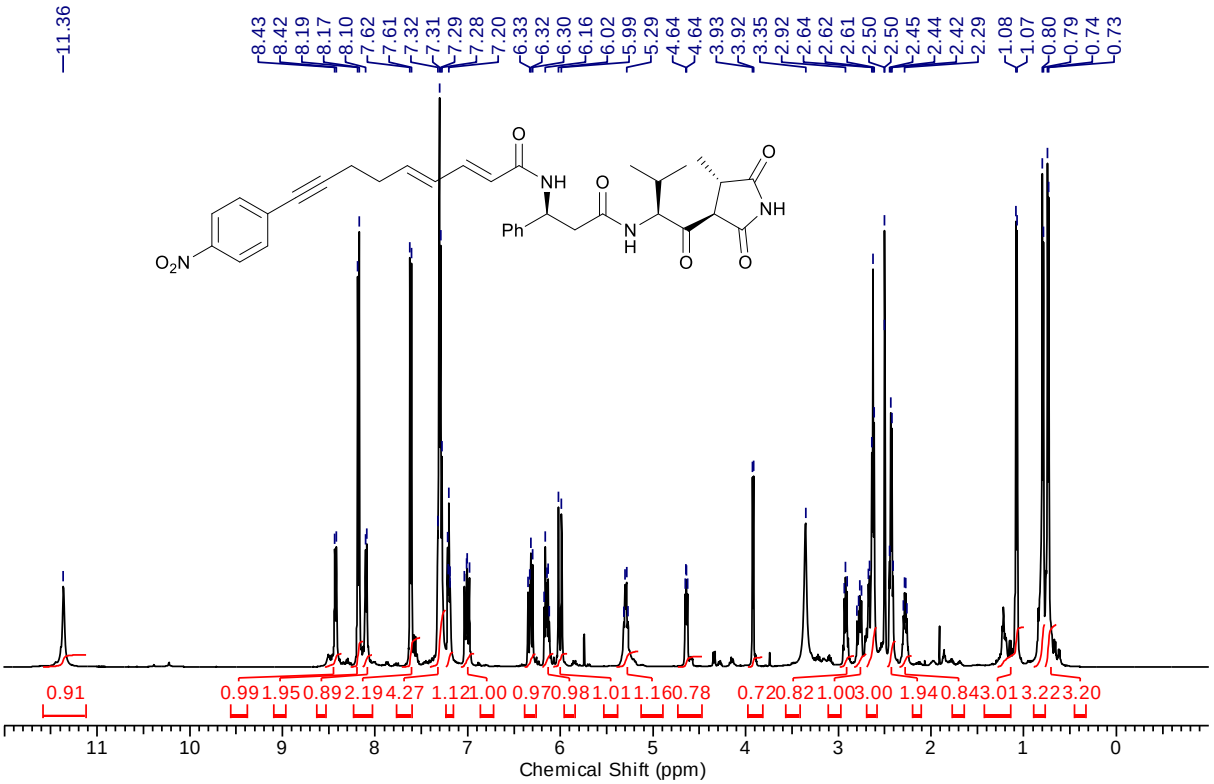


^{13}C NMR (125 MHz, DMSO-d_6):

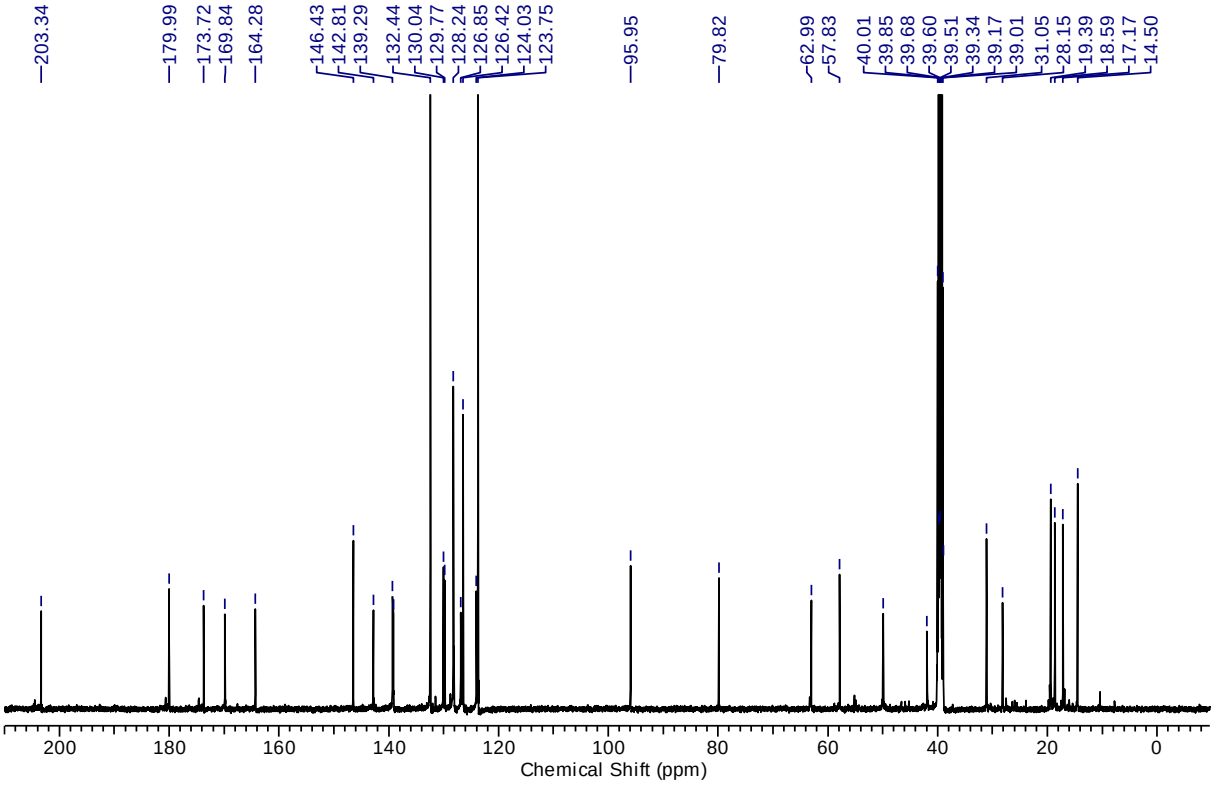


(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(4-nitrophenyl)nona-2,4-dien-8-ynamide (14c)

^{1}H NMR (500 MHz, DMSO-d_6):

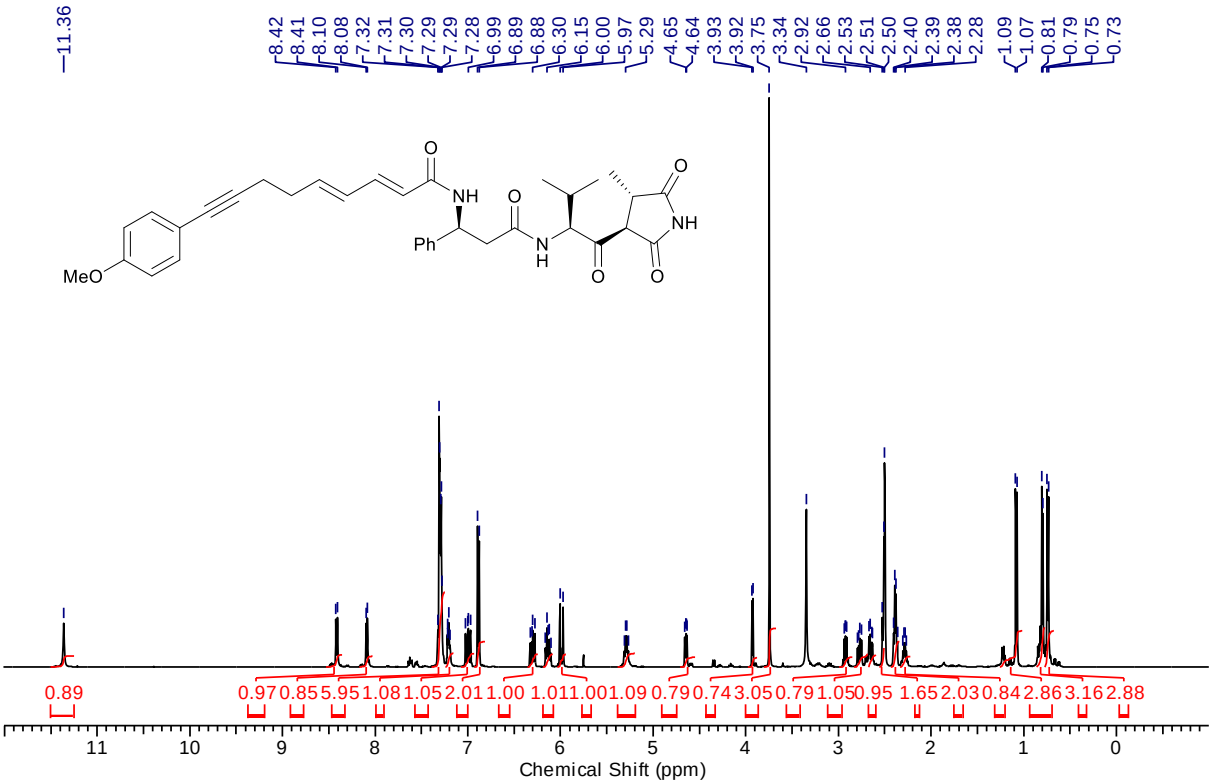


^{13}C NMR (125 MHz, DMSO-d_6):

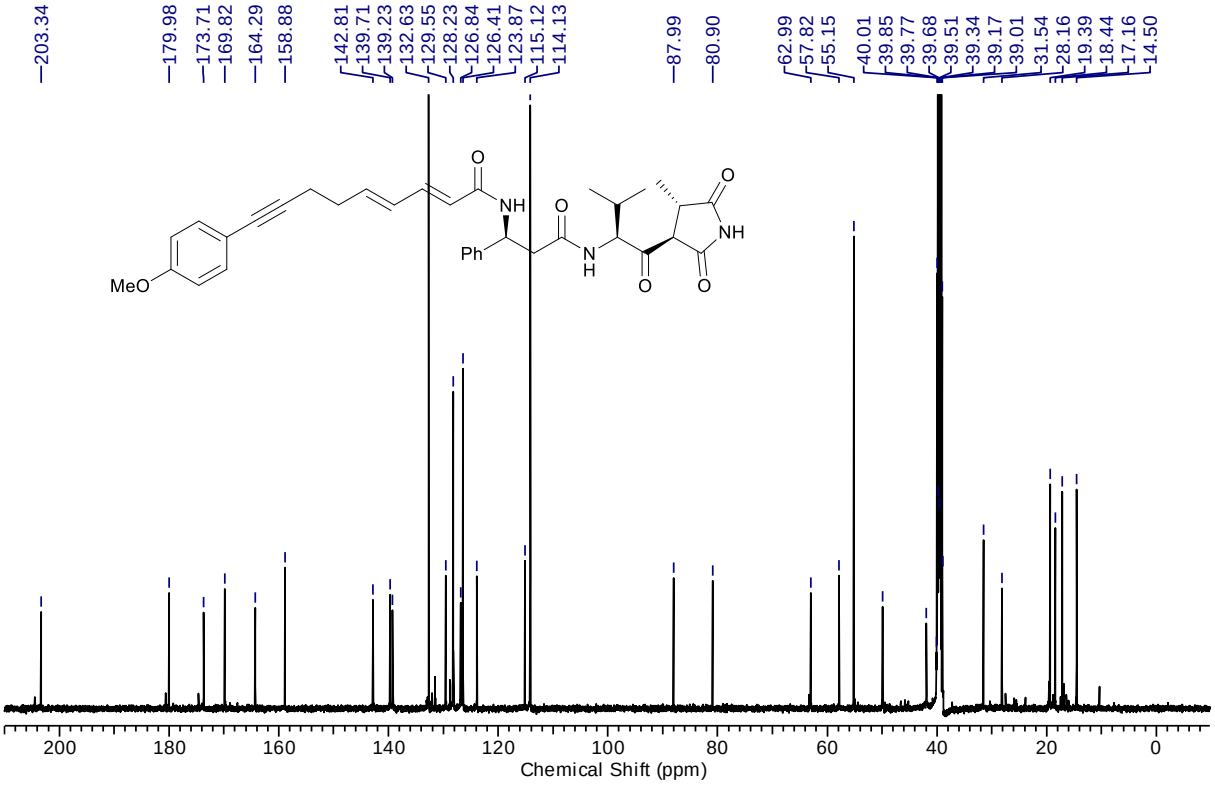


(2*E*,4*E*)-9-(4-Methoxyphenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14d)

^{1}H NMR (500 MHz, DMSO-d_6):

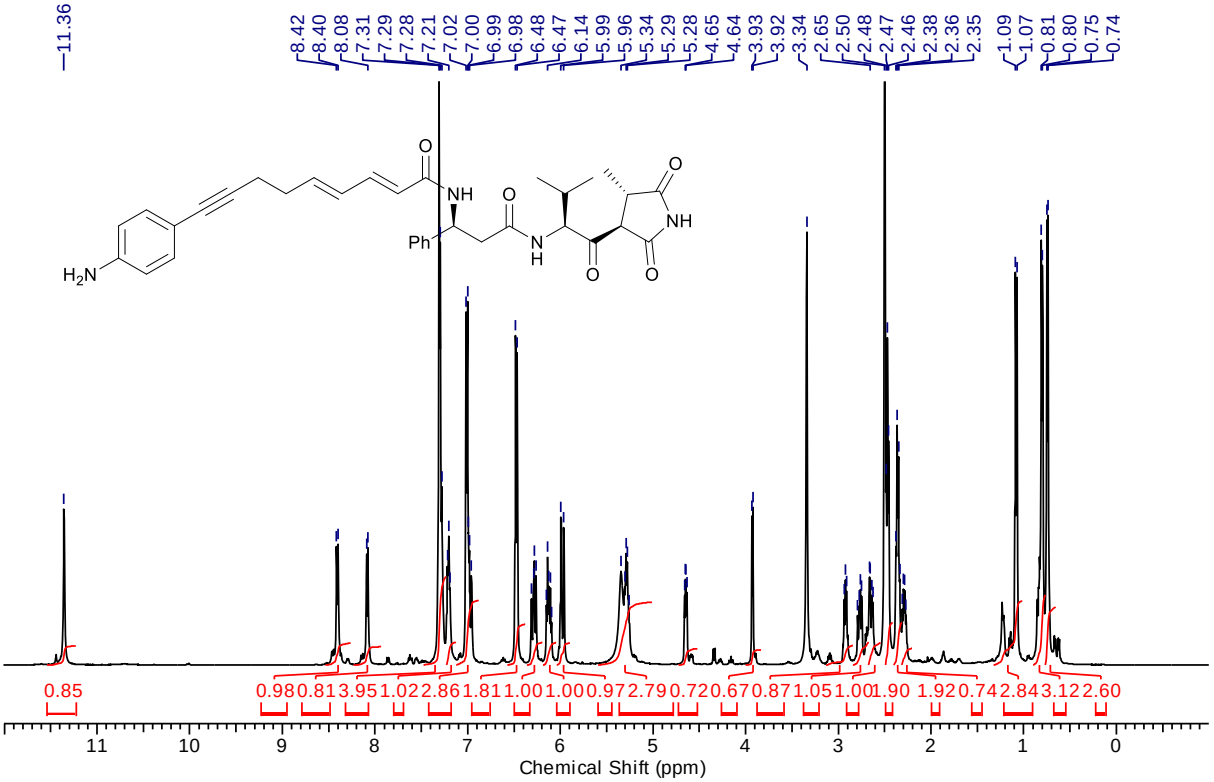


^{13}C NMR (125 MHz, DMSO-d_6):

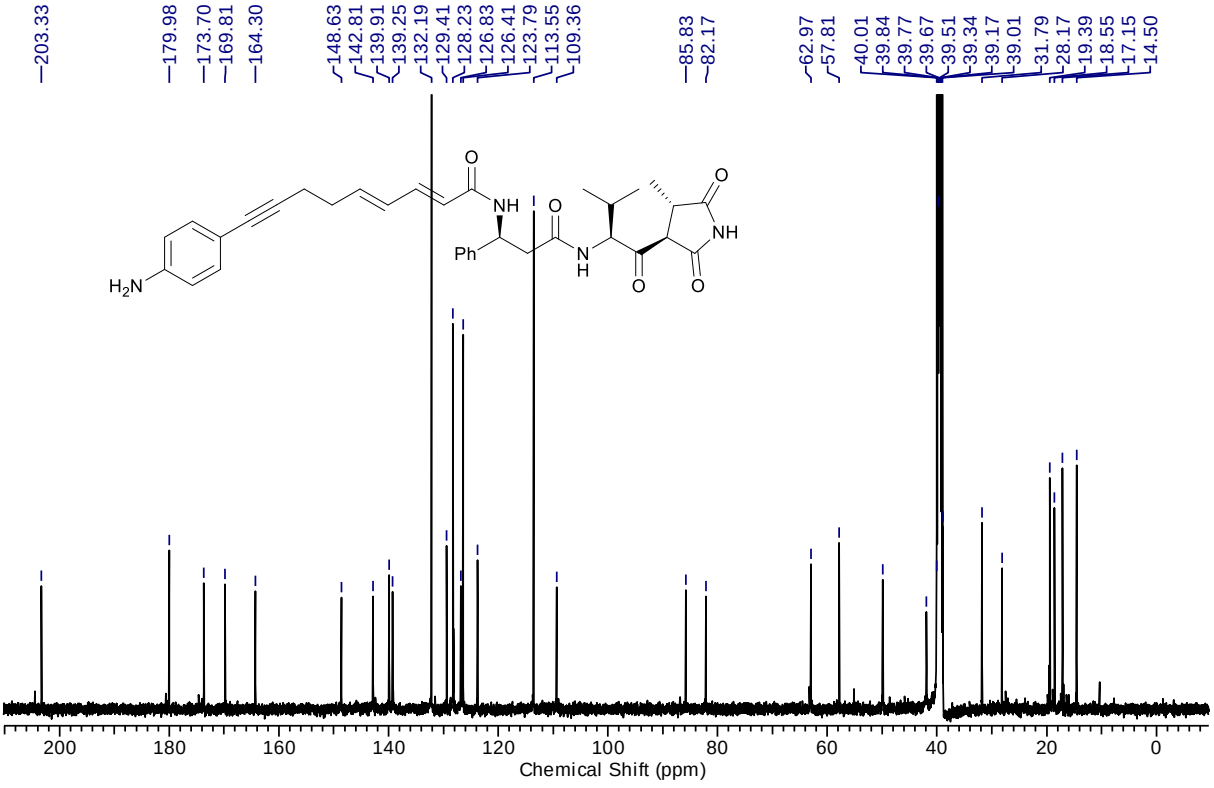


(2*E*,4*E*)-9-(4-Aminophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14e)

^{1}H NMR (500 MHz, DMSO-d_6):

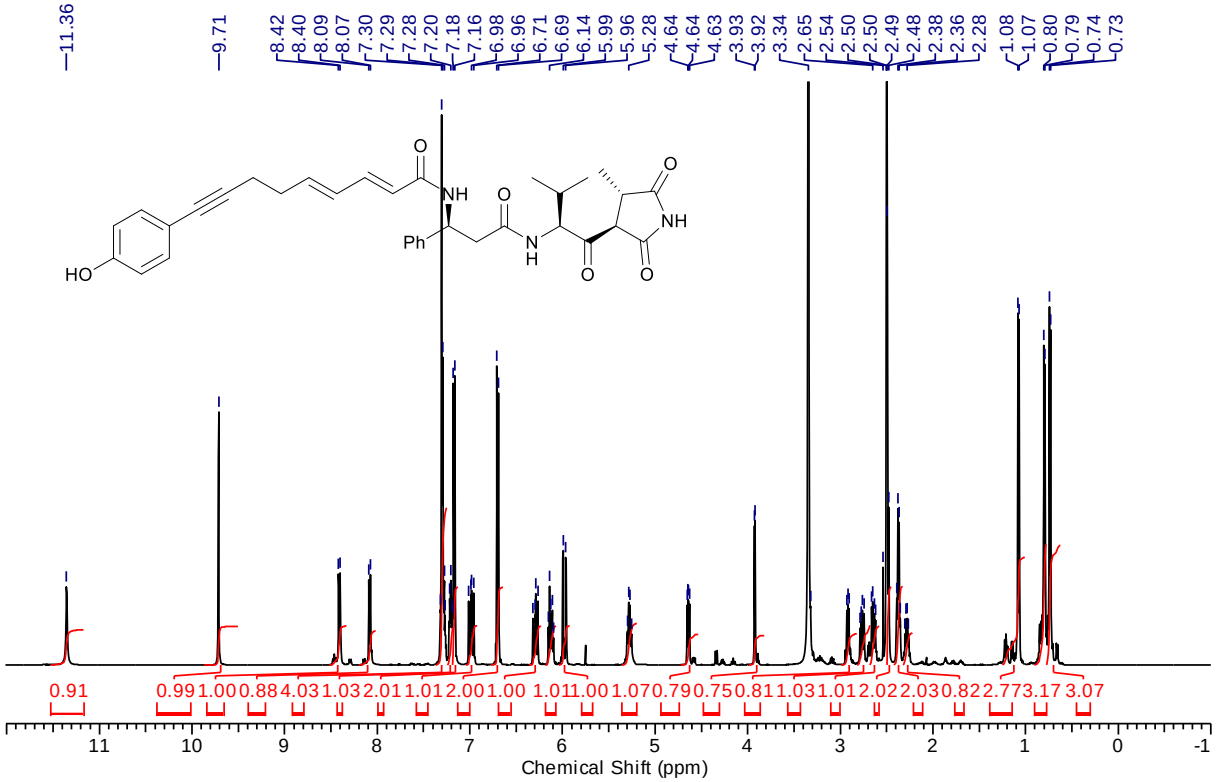


^{13}C NMR (125 MHz, DMSO-d_6):

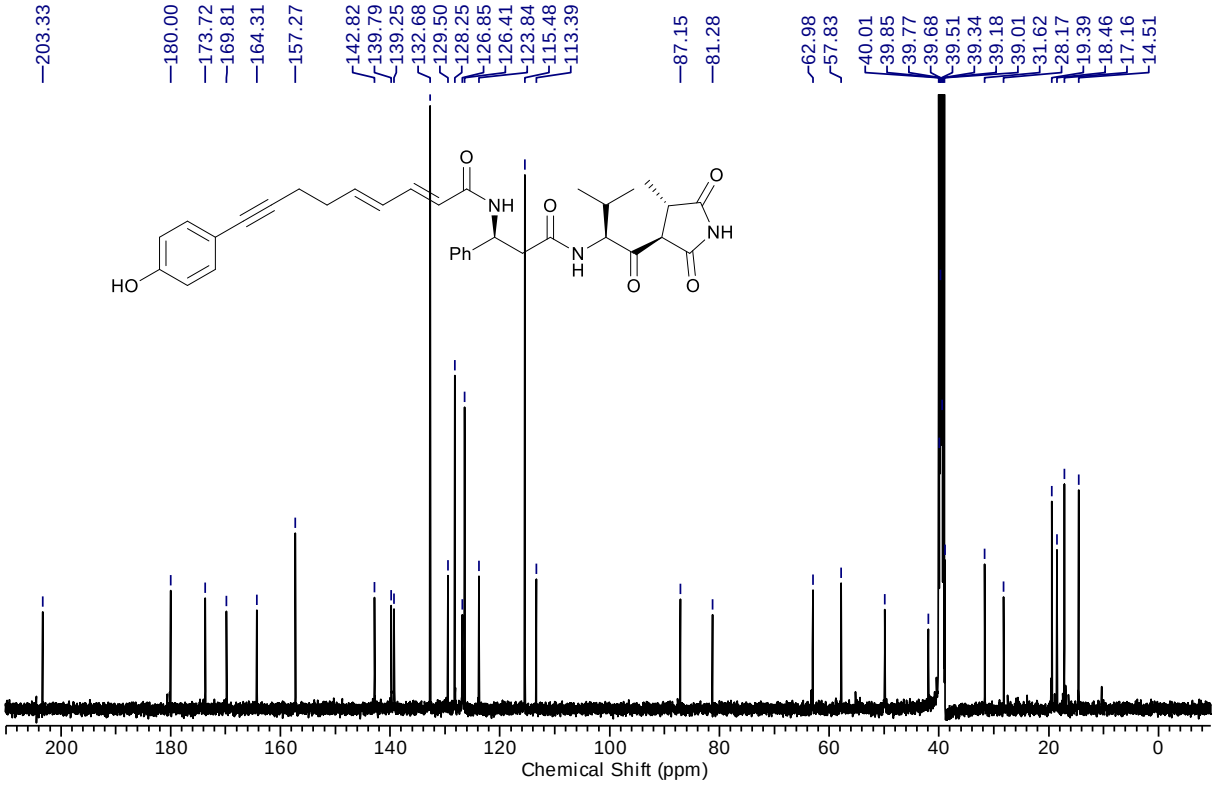


(2*E*,4*E*)-9-(4-Hydroxyphenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14f)

^{1}H NMR (500 MHz, DMSO-d_6):

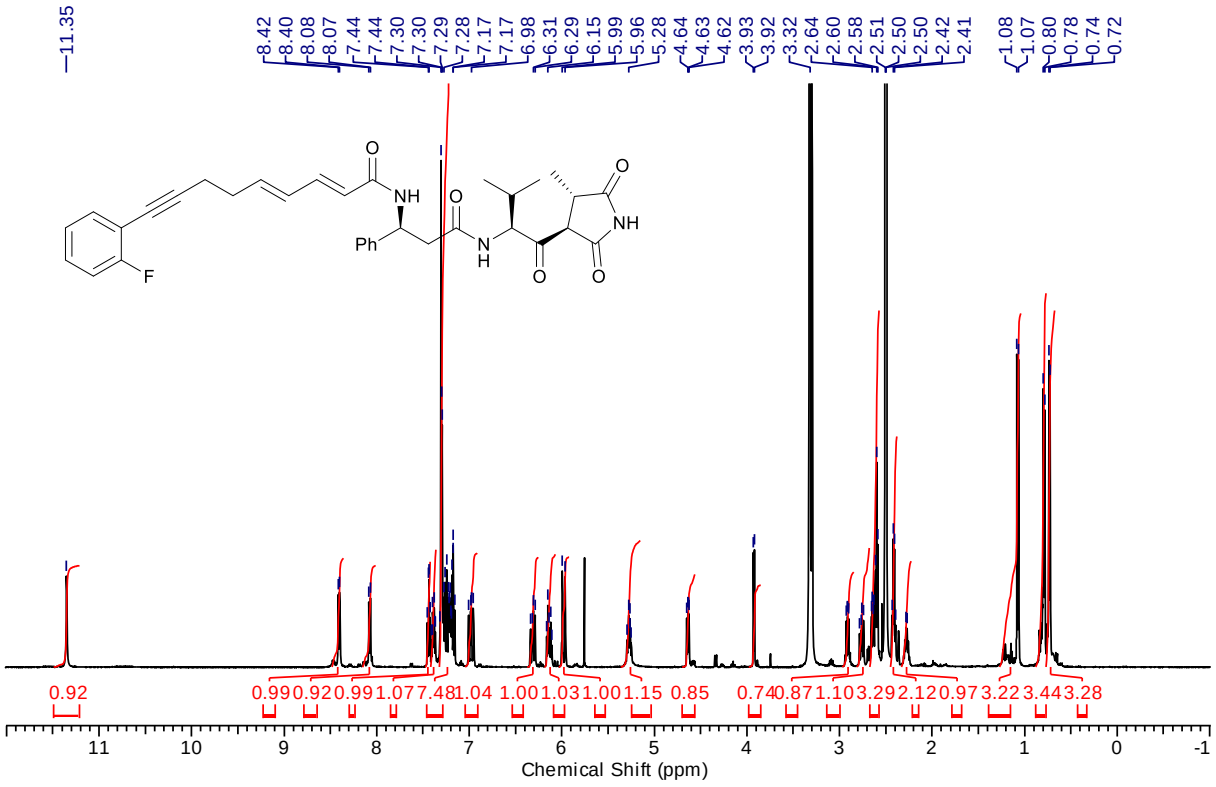


^{13}C NMR (125 MHz, DMSO-d_6):

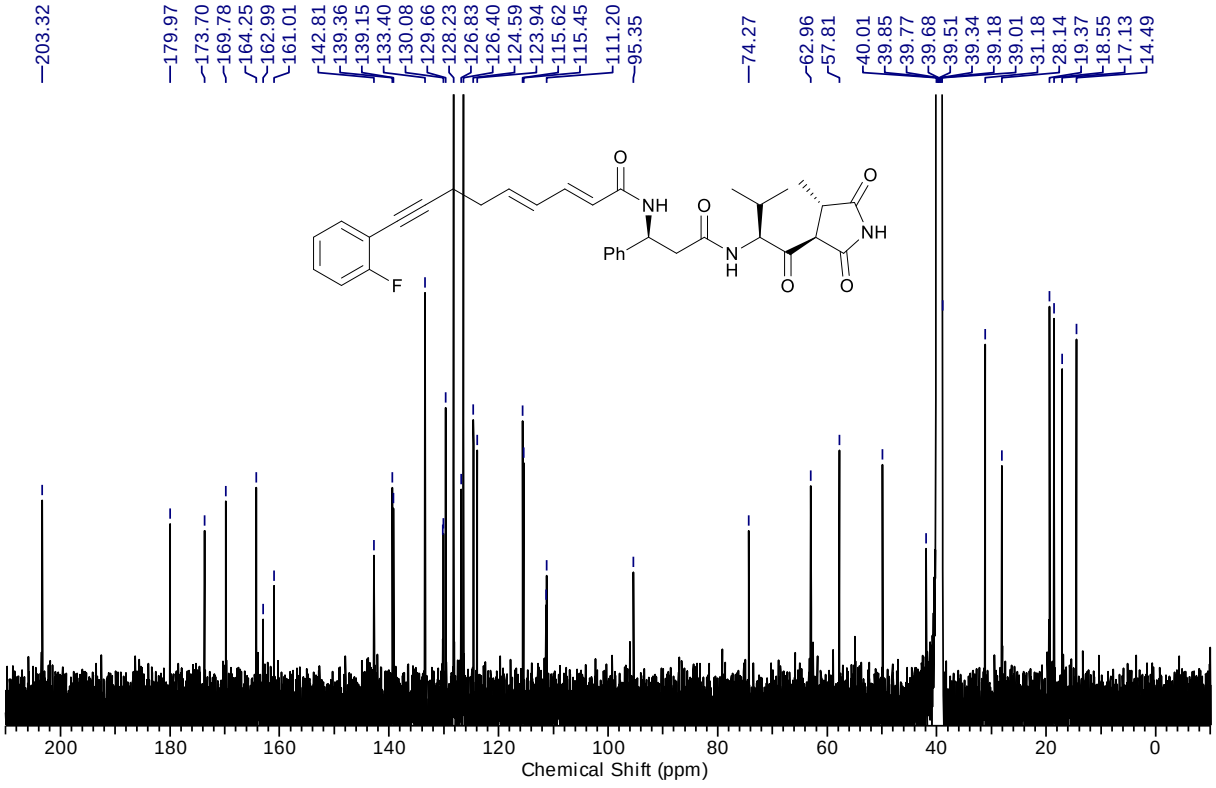


(2*E*,4*E*)-9-(2-Fluorophenyl)-*N*-((*S*)-3-(((*S*)-3-methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)nona-2,4-dien-8-ynamide (14g)

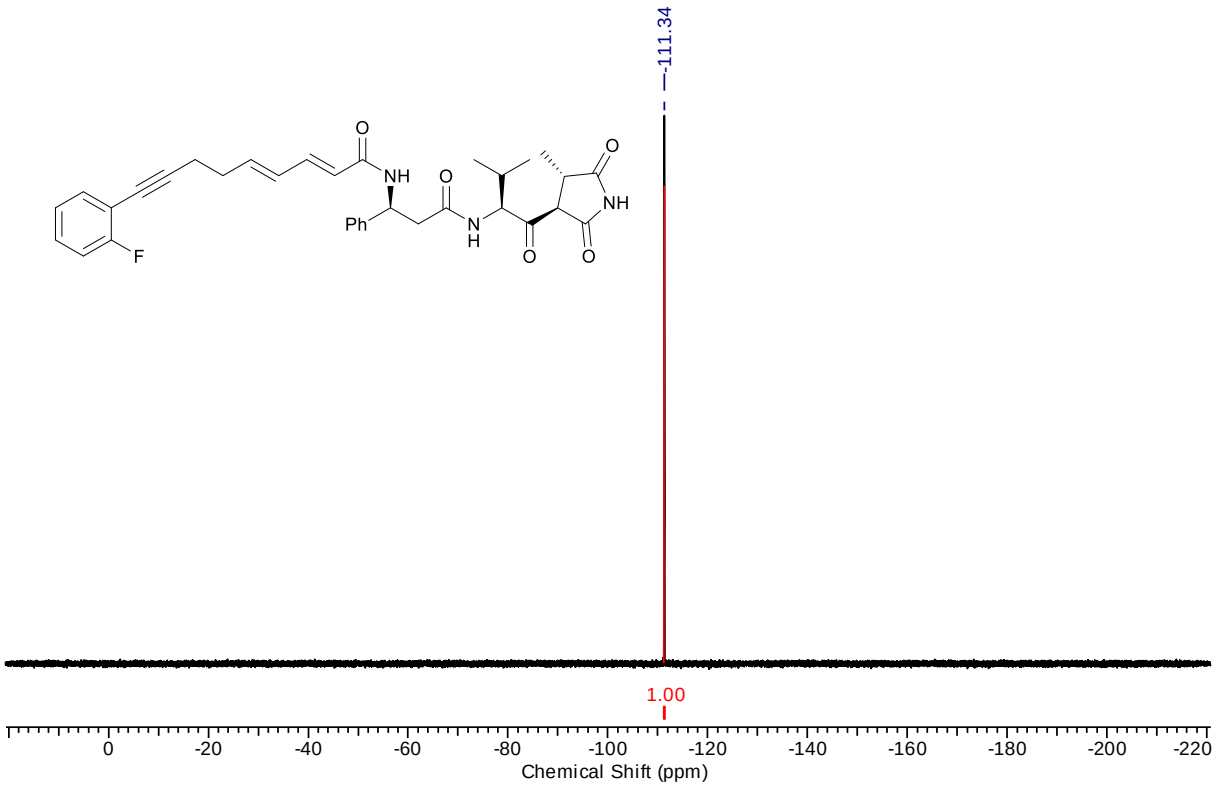
^{1}H NMR (500 MHz, DMSO-d_6):



^{13}C NMR (125 MHz, DMSO-d_6):

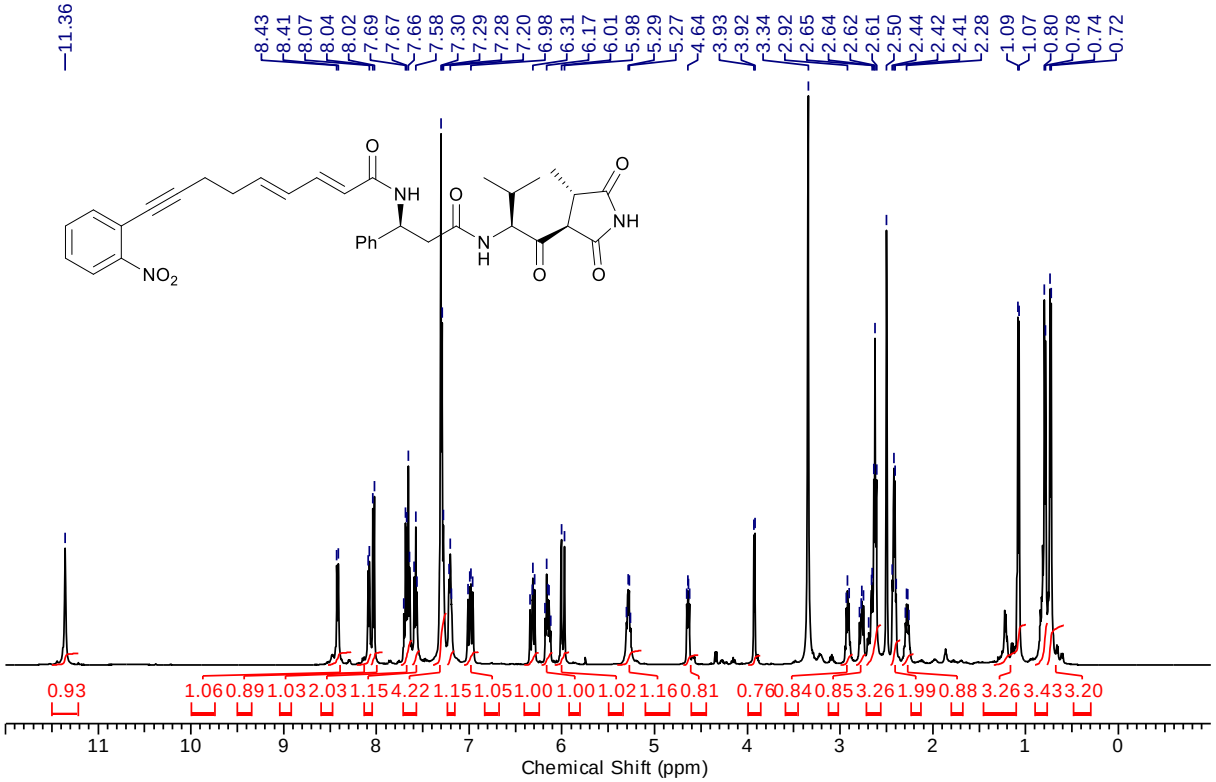


^{19}F NMR (471 MHz, DMSO-d_6):

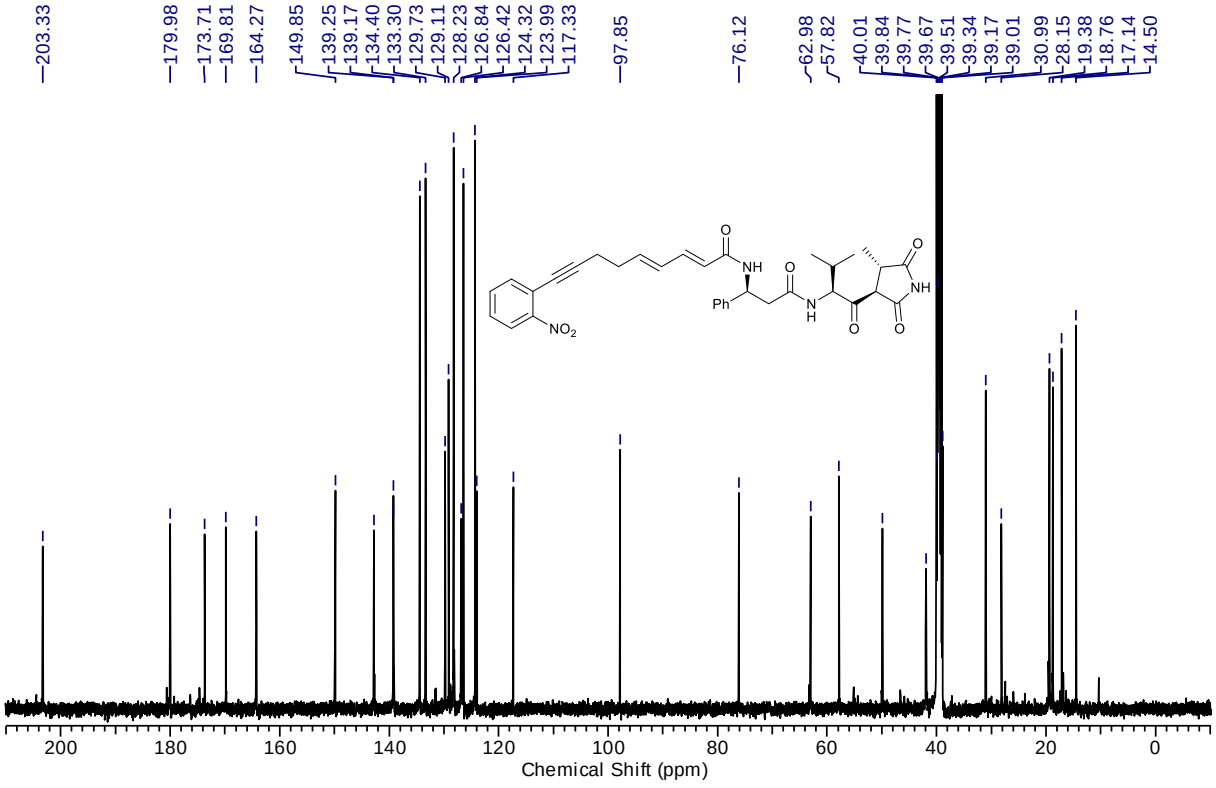


(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(2-nitrophenyl)nona-2,4-dien-8-ynamide (14h)

^{1}H NMR (500 MHz, DMSO-d_6):

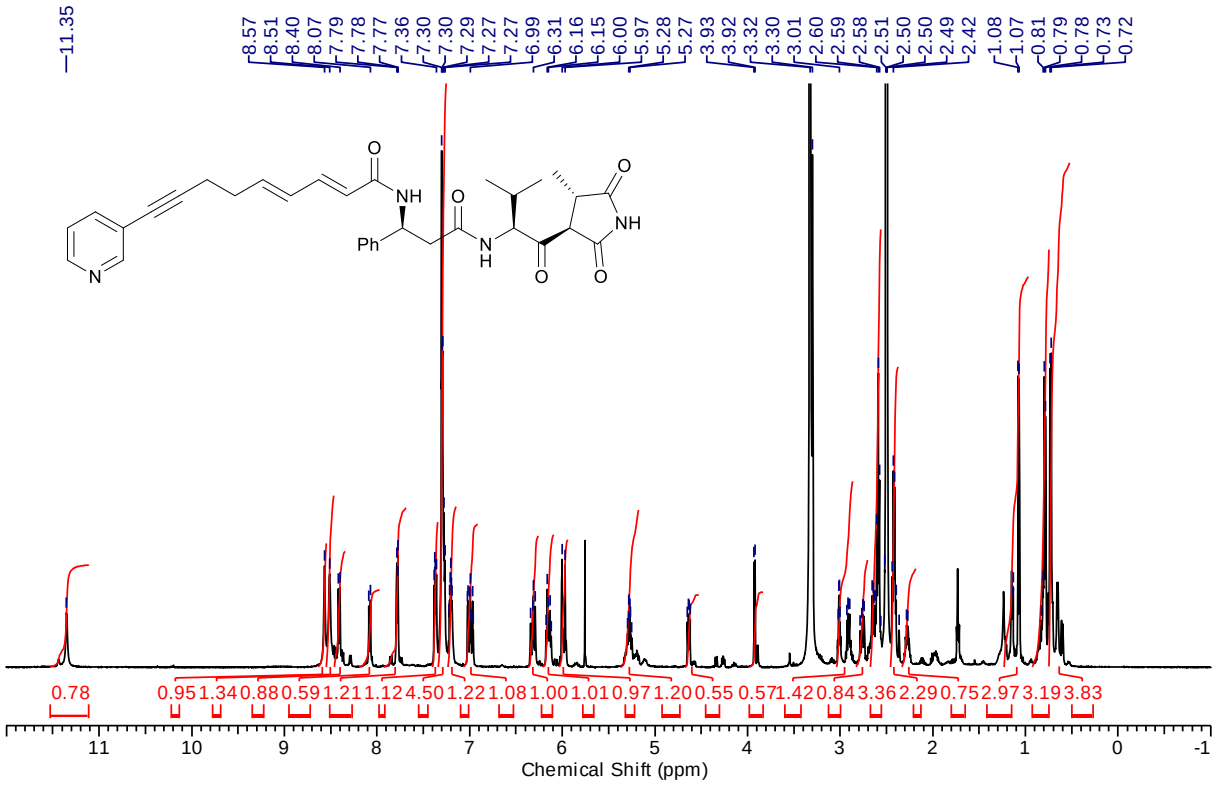


^{13}C NMR (125 MHz, DMSO-d_6):



(2*E*,4*E*)-*N*-((*S*)-3-(((*S*)-3-Methyl-1-((3*R*,4*S*)-4-methyl-2,5-dioxopyrrolidin-3-yl)-1-oxobutan-2-yl)amino)-3-oxo-1-phenylpropyl)-9-(pyridin-3-yl)nona-2,4-dien-8-ynamide (14i)

^{1}H NMR (500 MHz, DMSO-d_6):



^{13}C NMR (125 MHz, DMSO-d_6):