Supporting Information for

Evaluation of the antibacterial and antibiofilm activity of novel CRAMP-vancomycin conjugates with diverse linkers

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General Remarks.

Fmoc-Gln(Trt)-OH, Fmoc-Glu(Tbu)-OH, Fmoc-Pro-OH, Fmoc-Val-OH, Fmoc-Leu-OH, Fmoc-Lys(Boc)-OH, Fmoc-Phe-OH, Fmoc-Asn(Trt)-OH, Fmoc-Ile-OH, Fmoc-Gly-OH, Rink amide resin (0.63 mmol/g), DIC, oxyma were purchased from Irish Biotech. Peptide synthesis grade DMF was purchased from Acros. TFA, TIS, DCM, piperidine, *N*-methyl morpholine, 4-methyl piperidine and DIPEA were purchased from Sigma Aldrich. Vancomycin was purchased from A K Scientific, Inc.

General protocol for the screening CRAMP and CRAMP-vancomycin conjugates for antibacterial activity.

The broth microdilution method as described by the CLSI guidelines is used to determine the minimum inhibitory concentration (MIC).[34] The following microorganisms are used for analysis (Table 1):

Table 1: Microorganisms used for screening at optimal growth temperature.

Species	Gram	Growth at (°C)
Yersinia enterocolitica ATCC9610	-	30
Salmonella Typhimurium LT2	-	37
Pseudomonas putida G1	-	30
Escherichia coli XL-1 Blue MRF'	-	37
Bacillus cereus LMG 9610	+	30
Bacillus subtilis PSB3	+	37
Micrococcus luteus ATCC4689	+	30
Staphylococcus aureus ATCC6538	+	37

The peptide and their conjugates are resuspended in PBS buffer (pH 7.4) right before the start of the experiment at a final concentration of 1 mM. Two-fold serial dilutions of the peptide are prepared in sterile microtiter plates with 96 round bottom wells. A standardized inoculum is obtained by growing the test organisms overnight in Mueller-Hinton broth and adjusting the suspensions to a turbidity equivalent to a 0.5 McFarland standard using 2xMH. This suspension is diluted 100x times in 2xMH. Each well of the microdilution tray is inoculated with an equal volume of the inoculum and the peptide solution. This results in a two-fold dilution of the peptide concentration and the inoculum, which means the MH broth is now present in a 1x concentration. After mixing, the trays are sealed off with parafilm. The microtiter plate is incubated at the bacterium's optimum growth temperature for 18 hours. The growth in the wells containing the peptides is always compared to the growth in the negative and positive controls. For a test to be considered valid, acceptable growth (≥ 2 mm button) must occur in the positive control well. The MIC is the lowest concentration that completely inhibits the growth of the inoculum.

General protocol for the screening of CRAMP and CRAMP-vancomycin conjugates for preventive antibiofilm activity.

Static peg assay for prevention of *S.* Typhimurium biofilm formation.

The device used for biofilm formation is a platform carrying 96 polystyrene pegs (Nunc no. 445497) that fits as a lid on a microtiter plate, with a peg hanging into each microtiter plate well. Two-fold serial dilutions series of the compounds in 100 µL liquid broth (Tryptic Soy Broth diluted 1/20 (TSB 1/20)) per well were prepared in the microtiter plate (2 or 3 repeats

per compound). Subsequently, 100 µL overnight culture of *S*. Typhimurium ATCC14028 (grown in Luria-Bertani medium) was added to each well of the microtiter plate, resulting in a total amount of 200 µL medium per well. The pegged lid was placed on the microtiter plate and the plate was incubated for 24h at 25 ^{o}C without shaking. During this incubation period biofilms were formed on the surface of the pegs. Devices). For quantification of biofilm formation (after 48 h), the pegs were washed once in 200 µl phosphate buffered saline (PBS). The remaining attached bacteria were stained for 30 min with 200 µl 0.1 % (w/v) crystal violet in an isopropanol/methanol/PBS solution (v/v 1:1:18). Excess stain was rinsed off by washing the pegs twice in a 96-well plate filled with 200 µl distilled water per well. After the pegs were air dried (30 min), the dye bound to the adherent cells was extracted in a microtiterplate with 30 % glacial acetic acid (200 µl). The OD_{570} of each well was measured in a microtiter plate reader (Multimode Synergy MX, Biotek), as a measure for the amount of biofilm formed on each peg and used to calculate the percentage biofilm inhibition compared to the untreated control. The IC_{50} value (concentration needed to prevent biofilm formation with 50%) and 95% confidence interval for each compound was determined from concentration gradients by using the GraphPad software of Prism.

Equipments used.

NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$, D_2O, methanol-d_4 or DMSO-d_6 as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as an internal reference. For, TLC, analytical TLC plates (Alu-gram SIL G/UV_{254}) and 70-230 mesh silica gel (E. M. Merck) were used.

Mass spectrometry.

Mass spectra (MW < 500) were recorded by using a Kratos MS50TC and a Kratos Mach III system. The ion source temperature was 150-250 °C, as required. High-resolution electron impact (EI) mass spectra were performed with a resolution of 10000. The low-resolution spectra were obtained with a HP5989A MS instrument.

ESI-MS (MW <2000): a Thermo Electron LCQ Advantage apparatus with Agilent 1100 pomp- and injection system coupled to an Xcalibur data analyzing software was used. MeOH or ACN were used as eluents.

MALDI (MW >2000): Bruker, Ultra Flex II TOF-TOF coupled to flex analysis software was used.

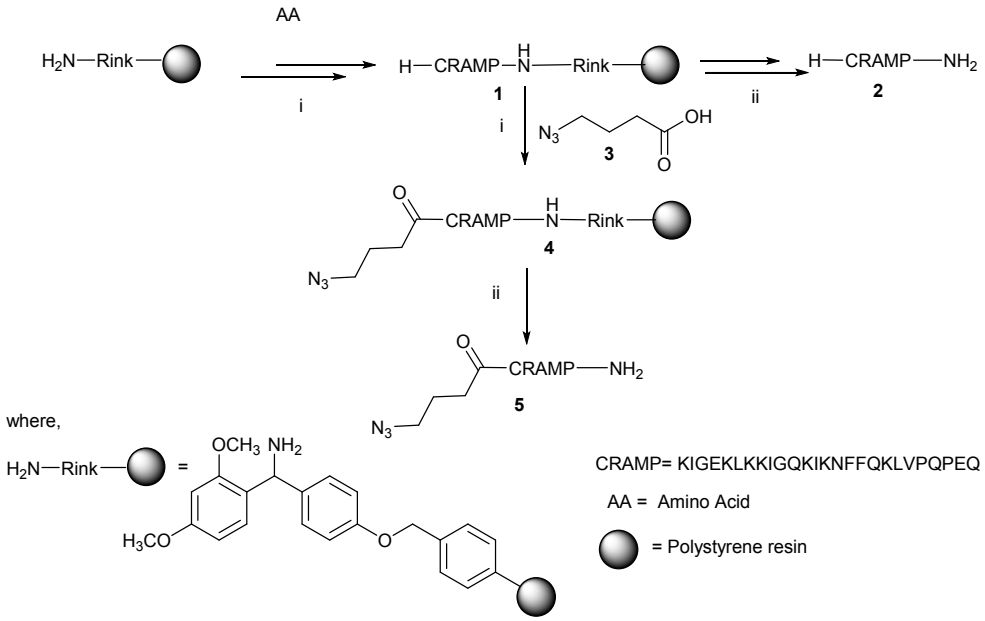
FT-ICR (MW >2000): Bruker, APEX-Qe with Data analysis software was used.

LC-MS: an Alltech Prevail RP-C18, 5 µm, 150 mm x 2.1 mm, and Phenomenex Luna RP-C18, 3µm, 150mm x 2.0 mm. System 1: Agilent 1100 degasser, binary pomp and autosampler coupled to a Thermo Electron LCQ Advantage mass spectrometer with APCI-or ESI source and Xcalibur data analysis software. System 2: Agilent 1100 degasser, quaternary pomp, auto sampler, UV-DAD detector and thermostated column module coupled to Agilent 6110 single-quadrupole MS and Agilent LC/MSD chemstation software.

RP-HPLC: a Waters Delta 600 analytical/preparative system equipped with a Waters 996 Photo Diode Array Detector was used. Preparative column size: Alltech C18 Prevail 5 µm, 150 mm x 22 mm, and Phenomenex Luna C18, 5µm, 150 mm x 22 mm.

CD-spectrometer: CD measurements were carried out on a JASCO J-810 spectropolarimeter equipped with a computer temperature cuvette holder. A 0.001 mm pathlength cuvette was used for the measurements of all peptides. The parameters selected for these measurements are; sensitivity: standard (100mdeg), data pitch: 1 nm, bandwidth: 1 nm, response: 1 sec, scanning speed: 50nm/min, measurement range: 260nm-190nm, scanning mode: continuous, accumulation: 3.

General experimental methods.



Reagents and conditions: **Condition-1** i) Oxyma, DIC, rt, 2h, deprotection: 4-methylpiperidine in DMF (20% solution); ii) TFA/TIS/DCM (95:2.5:2.5), rt, 3h.

Scheme 1: Synthesis of CRAMP 2 and 5.

General procedure for the synthesis of CRAMP 1.

1) Fmoc (Fluorenylmethyloxycarbonyl)-deprotection of the resin: Rink amide resin (1 g, 0.63 mmol/g loading capacity) was Fmoc-deprotected using a solution of 4-methyl piperidine in DMF (20% v/v, 5 mL), washed, dried and kept for swelling for 20 min in DMF/DCM (5:95, 2 mL).

2) Coupling of amino acids to pre-swollen Rink amide resin: Fmoc-protected amino acid (1.89 mmol) and oxyma (1.89 mmol) were dissolved in DMF/DCM (5:95, 5 mL) and the solution was stirred for 10 min at rt. Then DIC (1.89 mmol) was added and the solution was stirred for 2 min. The resulting mixture was added to the pre-swollen Rink amide resin (1 g, 0.63 mmol) and shaken for 2h at rt. The resulting resin was washed with DCM, DMF (until all unreacted reagents were washed away) and diethyl ether respectively and dried for 5 min *in vacuo*. Completion of the coupling was checked by DESC reagent.[1] In case the reaction was found to be incomplete, the same process was repeated (Scheme 1).

3) Fmoc-deprotection of resin linked amino acid: after completion of the reaction 4-methyl piperidine in DMF (20% v/v, 5 mL) was added and the mixture was shaken for 15 min at rt. The resulting resin was washed with DMF, DCM and diethyl ether

and dried for 5 min *in vacuo*. The same procedure was repeated for the coupling and deprotection of the other amino acids to obtain peptide **1**.

4) Final cleavage from the resin: after completion of the sequence, the cleavage of the resin linked peptide **1** was carried out upon treatment with a TFA/TIS/DCM solution (95:2.5:2:5 v/v/v, 5 mL) for 3h at rt. The cleaved and deprotected peptide **2** was precipitated with cold diethyl ether (10 mL). The precipitate was collected by centrifugation, dried and purified by preparative HPLC (0-30% ACN/H_2O with 0.1% HCOOH in 30 min, retention time = 25 min). The peptide was obtained in 30% yield and >90% purity.

Peptide characterization: an aliquot of crude peptide was analysed by ESI-MS (and LCMS (Figure 1 & 2). Calculated average mass 3065.72; Found: 3065.73

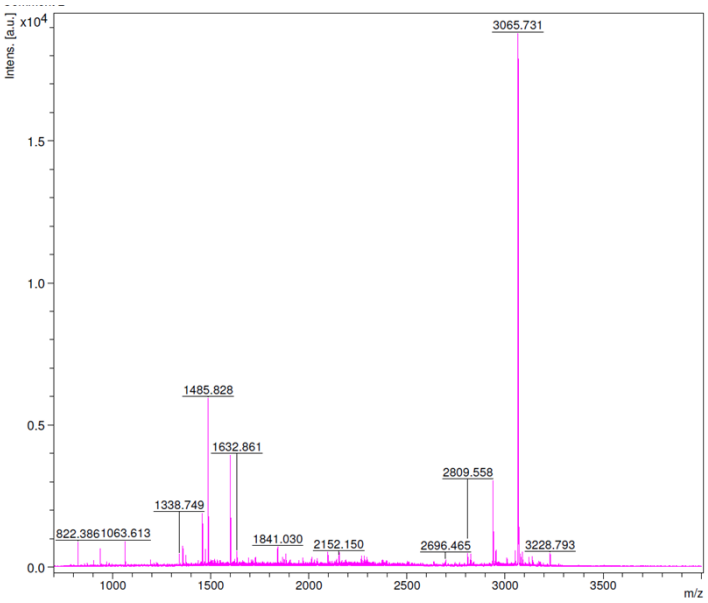


Figure 1: MALDI-TOF mass spectrum of CRAMP **2**.

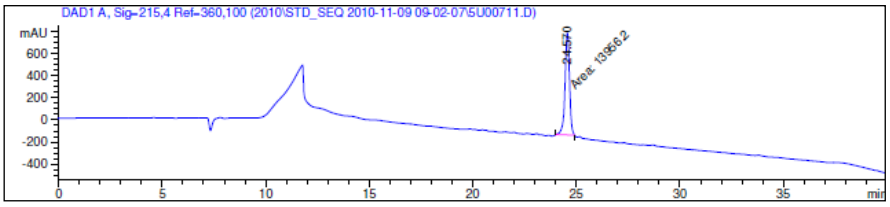


Figure 2: LCMS chromatogram of crude CRAMP **2**.

Synthesis of 4-azido butanoic acid 3.

4-Azido butanoic acid was synthesized according to a procedure described in the literature [2] and the analytical data were in accordance with the literature.[3]

Synthesis of 4 & 5.

4-Azido butanoic acid **3** (0.52 mmol) and oxyma (0.52 mmol) were dissolved in DMF/DCM (5:95, 2 mL) and the solution was stirred for 10 min at rt. DIC (0.52 mmol) was added and the mixture was stirred for 2 min. This solution was

added to pre-swollen resin linked CRAMP **1** (0.17 mmol) in DMF/DCM (5:95, 2 mL) and the mixture was shaken for 2h. After completion of the coupling the peptide **5** was cleaved from the resin with a mixture of TFA/TIS/DCM (95:2.5:2:5, 3 mL) by stirring 3h at rt. The crude compound was purified by preparative RP-HPLC (0-30% ACN/H_2O with 0.1% HCOOH in 30 min, retention time = 27 min), the acetonitrile was removed *in vacuo* and the remaining water was lyophilized yielding 55% of peptide **5** as a white powder (Scheme 1). The purified materials were analysed by ESI-MS, MALDI-TOF and LCMS. Calculated average mass 3176.85, Found: 3176.86.

Synthesis of the linkers.

Linkers **10a-n** were synthesized according to the reported procedures [4-6] using amines **7a-j** (Table 2) and acids **8a-e** (Table 3) followed by deprotection of the resulting compound **9a-n** (Scheme 2-4). Linkers **10o-s** were purchased from Sigma Aldrich and Acros and used as received (Table 4). Linkers **10t-w** were synthesized by following the reported procedures[6-9] and Scheme 5-6 using amine **7k** (Table 2) and acids **8f-h** (Table 3).

Table 2: Commercially available amines used to assemble linkers **10a-n** and **10t-w**.

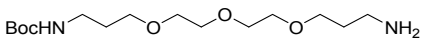
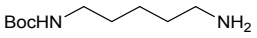
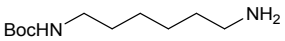
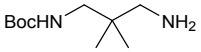
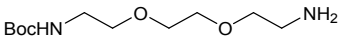
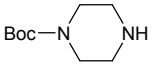
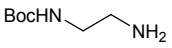
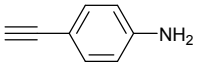
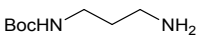
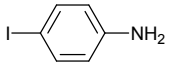
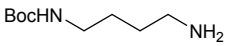
No.	Structure	No.	Structure
7a		**7g**	
7b		**7h**	
7c		**7i**	
7d		**7j**	
7e		**7k**	
7f			

Table 3: Commercially available carboxylic acids used to assemble linkers **10a**-**n** and **10t**-**w**.

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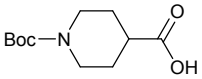
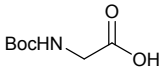
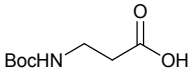
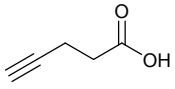
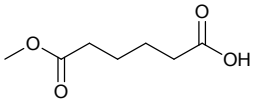
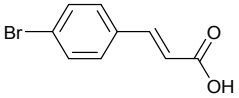
8a	
8b	
8c	
8d	
8e	
8f	

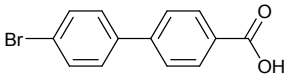
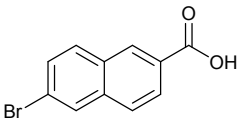
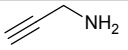
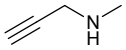
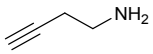
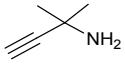
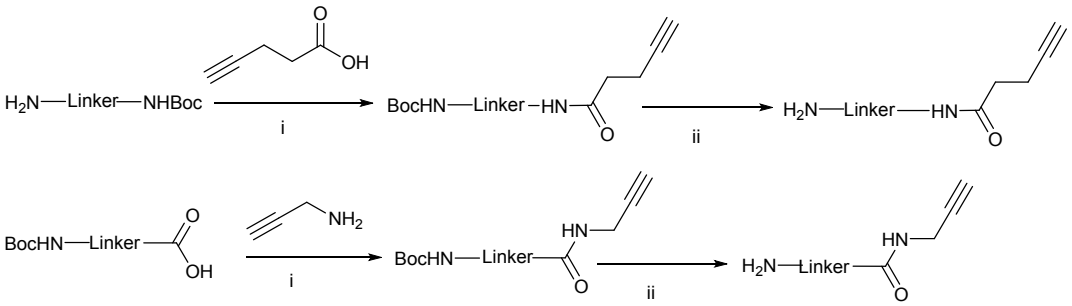
8g	
8h	

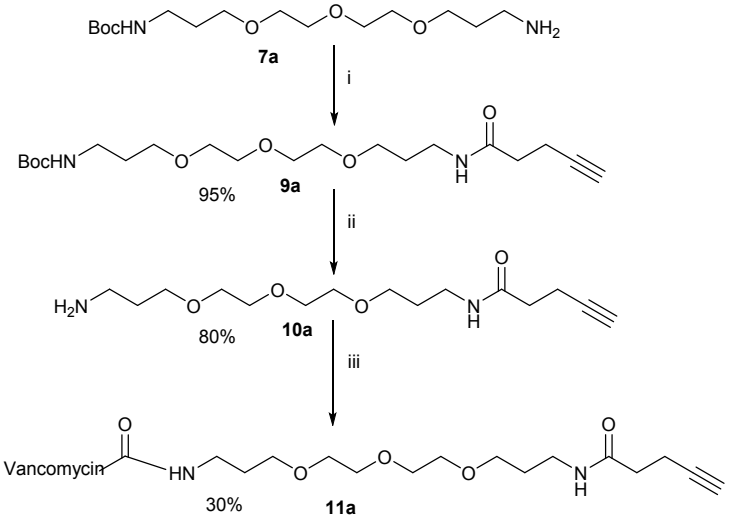
Table 4: Commercially available linkers **10o-s**.

No.	Structure	No.	Structure
10o		**10r**	
10p		**10s**	
10q			



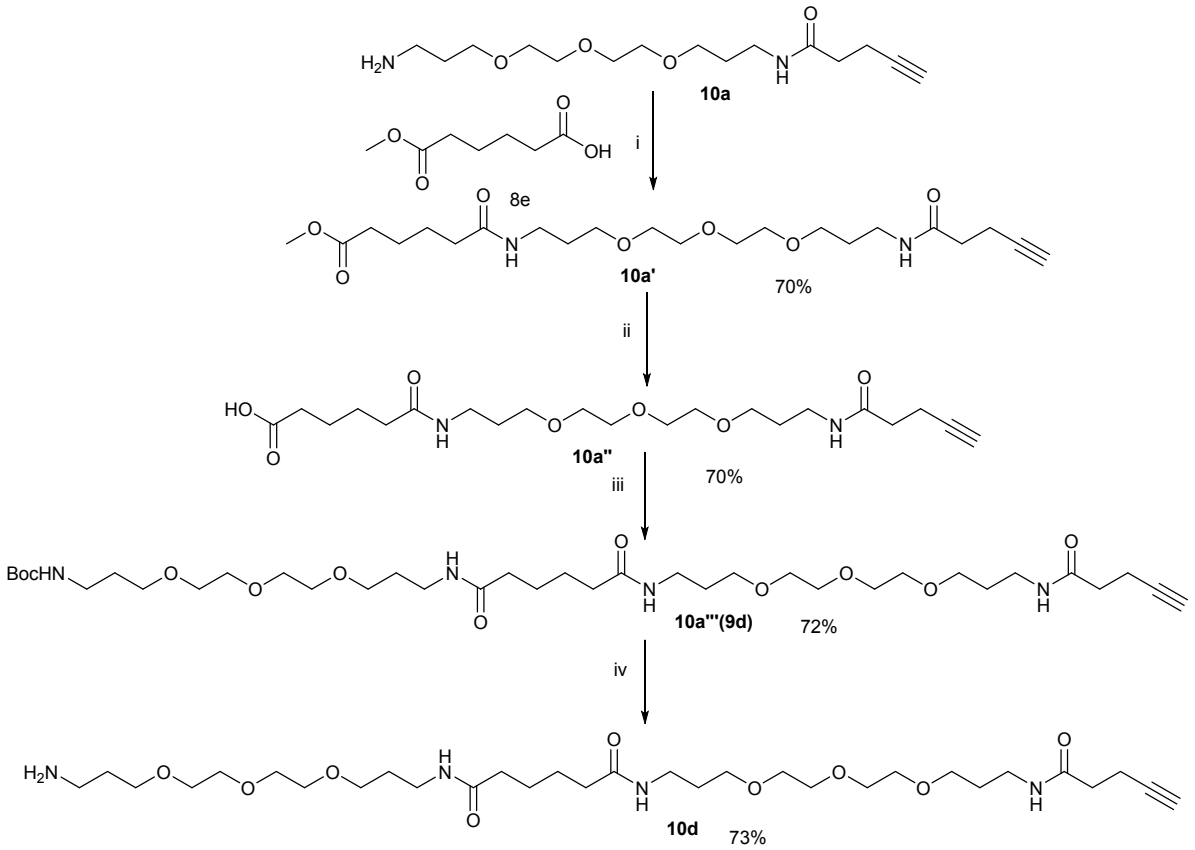
Reagents and conditions: i) HOAt, EDC.HCl, DCM, *N*-methyl morpholine, rt, 4h; ii) 4N HCl in 1,4-dioxane, DCM, 0 °C to rt, 2h.

Scheme 2: General scheme for the synthesis of aliphatic linkers 10a-m.



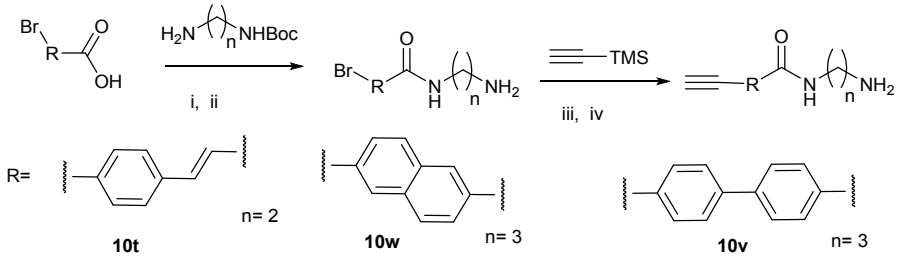
Reagents and conditions: i) 4-pentynoic acid, HOAt, EDC·HCl, DCM, *N*-methyl morpholine, rt, 4h; ii) 4N HCl in 1,4-dioxane, DCM, 0 °C to rt, 2h; iii) vancomycin, HOAt, EDC·HCl, DCM, *N*-methyl morpholine, rt, 7-8h.

Scheme 3: Synthesis of vancomycin linker **11a**.



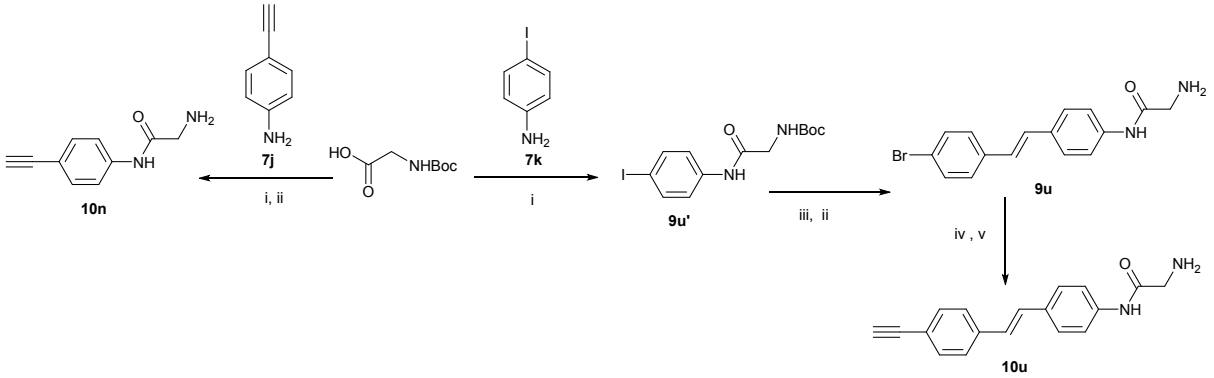
Reagents and conditions: i) HOAt, EDC·HCl, *N*-methylmorpholine, rt, 4-5h; ii) LiOH, THF/H_2O, 3-4h, rt; iii) **7a**, HOAt, EDC·HCl, *N*-methylmorpholine, rt, 4-5h; iv) 4N HCl in 1,4-dioxane, DCM, 0 °C to rt, 3-4h.

Scheme 4: Synthesis of linker **10d**.



Reagents and conditions: i) HATU, DIPEA, DMF, rt, 4h; ii) 4N HCl in 1,4-dioxane, DCM, 0 °C to rt, 2h; iii) piperidine, $Pd(PPh_3)_2Cl_2$, 85 °C, 30 min; iv) TBAF, THF, rt, 30 min.

Scheme 5: Synthesis of aromatic linker 10t, 10w & 10v.



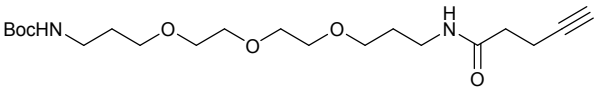
Reagents and conditions: i) Ethyl chloroformate, TEA, THF, 0°C to rt, 15h; ii) 4N HCl in 1,4-dioxane, DCM, 0 °C to rt, 2h; iii) 4-bromo-styrene, $Pd(OAc)_2$, tetrabutylammonium bromide, potassium acetate, DMF, 80 °C, 4-5h; iv) trimethylsilylacetylene, piperidine, $Pd(PPh_3)_2Cl_2$, 85 °C, 30 min; v) TBAF, THF, rt, 30 min**.**

Scheme 6: Synthesis of aromatic linker 10n & 10u.

Procedure for the synthesis of linker 9a-c and 9e-j.

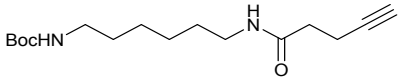
4-Pentynoic acid (130 mg, 1.2 mmol), EDC·HCl (301 mg, 1.57 mmol) and HOAt (214 mg, 1.57 mmol) were dissolved in DCM (5 mL) and stirred for 5 min. To this solution was added mono-*N*-Boc protected diamine linker **7a-j** (Table 3) and *N*-Me-morpholine (till pH 8) and stirred for 4h at rt. After completion, reaction mass was poured into water, extracted with DCM (25 mL x 2), dried over anhydrous sodium sulphate, the solvent was evaporated *in vacuo* and the crude product was purified using column chromatography (eluent: MeOH 2-5% in DCM) to obtain **9a-c** and **9e-j** in good to satisfactory yield.[4]

Spectral data of the *N*-Boc protected linkers 9a-c.



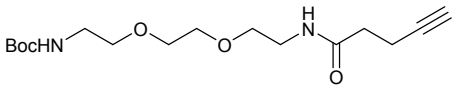
tert-Butyl 15-oxo-4,7,10-trioxa-14-azanonadec-18-ynylcarbamate (9a).

Viscous liquid, yield 95%; data of this compound were in accordance with the already published work.[4]



tert-Butyl 6-pent-4-ynamidohexylcarbamate (9b).

White semisolid, yield 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.75 (br s, 1H), 4.52 (br s, 1H), 3.26 (q, *J* = 6.4 Hz, 2H), 3.10 (d, *J* = 6.2 Hz, 2H), 2.52 (d, *J* = 6.9 Hz, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 2.00 (s, 1H), 1.58-1.50 (m, 4H), 1.44 (s, 9H), 1.33 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.01, 156.13, 83.09, 79.04, 69.22, 40.15, 39.21, 35.32, 29.95, 29.36, 28.40, 26.16, 14.95; HRMS (EI): calcd for $C_{16}H_{28}N_2O_3$: 296.2100, found: 296.2092.



tert-Butyl 2-(2-(2-pent-4-ynamidoethoxy)ethoxy)ethylcarbamate (9c).

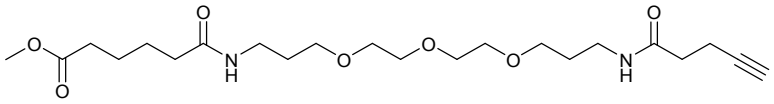
Viscous liquid, yield 90%; Data of this compound were in accordance with the already published work.[5]

Synthesis of linker 9d.

Synthesis of linker **9d** was accomplished in 3 steps:

Step 1: synthesis of 10a'.

Monomethyl adipic ester **8e** (260 mg, 1.62 mmol), EDC·HCl (311 mg, 1.62 mmol) and HOAt (221 mg, 1.62 mmol) were dissolved in CH_2Cl_2 (5 mL) and stirred for 5 min. To this solution was added **10a** (375 mg, 1.25 mmol) and *N*-methyl morpholine (till pH 8) and the resulting mixture stirred for 4h at rt. After completion, the reaction mass was poured in water, extracted with DCM (2 x 15 mL), dried over anhydrous sodium sulphate, the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (eluents: MeOH/DCM, 4/96).

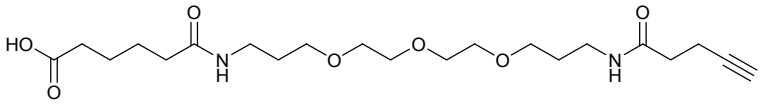


Methyl 5,21-dioxo-10,13,16-trioxa-6,20-diazahexacos-1-yn-26-oate (10a').

Viscous liquid, yield 70%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (d, *J* = 75.2 Hz, 2H), 3.67 (s, 3H), 3.66 – 3.63 (m, 4H), 3.62 – 3.55 (m, 8H), 3.37 (p, *J* = 6.3, 6.3, 6.3, 6.3 Hz, 4H), 2.52 (td, *J* = 7.1, 6.9, 2.5 Hz, 2H), 2.40-2.32 (m, 4H), 2.21 – 2.15 (m, 2H), 1.99 (t, *J* = 2.6, 2.6 Hz, 1H), 1.78 (dt, *J* = 11.9, 6.0, 6.0 Hz, 4H), 1.66 (p, *J* = 3.6, 3.6, 3.6, 3.6 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.97, 172.55, 170.92, 83.17, 79.20, 70.44, 70.06, 69.96, 69.93, 51.55, 37.86, 37.80, 35.31, 33.70, 29.04, 28.95, 25.12, 24.47, 14.90. ESI-MS: calcd for $C_{22}H_{38}N_2O_7$: 442.0, found: 443.0.

Step-2: synthesis of 10a".

10a' (155 mg, 0.35 mmol) was dissolved in THF (4 mL) and a solution of LiOH (2.25 mmol) in water (4 mL) was added dropwise and the mixture was allowed to stir at rt for 5h. After completion of the reaction, THF was removed *in vacuo* and 1N HCl solution was added till pH 5, so that a white solid precipitated. This was washed with diethyl ether, dried *in vacuo* and used for the next step without purification.

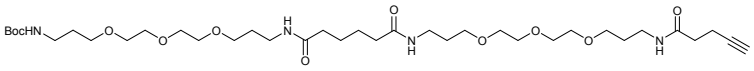


5,21-Dioxo-10,13,16-trioxa-6,20-diazahexacos-1-yn-26-oic acid (10a").

White solid, yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 2H), 3.77 – 3.47 (m, 12H), 3.42-3.32 (s, 4H), 2.53-2.23 (d, *J* = 42.5 Hz, 8H), 2.00 (s, 1H), 1.79-1.60 (d, *J* = 35.2 Hz, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.81, 173.15, 171.59, 83.10, 70.40, 70.35, 70.01, 69.96, 69.82, 69.26, 37.91, 37.83, 36.12, 35.31, 33.61, 28.89, 28.83, 24.97, 24.29, 24.23, 14.95; HRMS (EI): calcd for $C_{22}H_{36}N_2O_7$: 428.2523, found: 428.2514.

Step-3: synthesis of 10a"'or 9d.

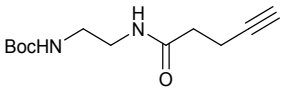
9d was synthesized from acid **10a"** and amine **7a** following the procedure applied for the synthesis of **9a-c**.



tert-Butyl 15,20,36-trioxo-4,7,10,25,28,31-hexaoxa-14,21,35-triazatetracont-39-ynylcarbamate (9d).

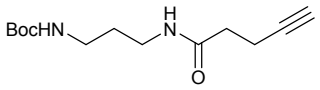
Viscous liquid, yield 72%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (br s, 1H), 6.55 (br s, 2H), 5.09 (br s, 1H), 3.63-3.54 (m, 22H), 3.51-3.33 (m, 6H), 3.31 (d, *J* = 4.7 Hz, 6H), 2.53 (t, *J* = 6.9 Hz, 2H), 2.41-2.31 (m, 4H), 2.18 (s, 4H) , 2.00 (s, 1H), 1.79-1.73 (m, 8H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.88, 171.08, 156.12, 83.26, 78.95, 70.51, 70.47, 70.19, 70.11, 70.08, 70.05, 70.00, 69.95, 69.85, 69.48, 69.11, 38.44, 37.85, 37.75, 37.72, 36.17, 35.29, 29.70, 29.01, 29.94, 28.46, 25.17, 25.14,14.93; ESI-MS: calcd for $C_{36}H_{66}N_4O_{11}$: 730.93, found: 732.1 $[M+H]^+$.

Spectral data of the *N*-Boc protected linkers 9e-j.



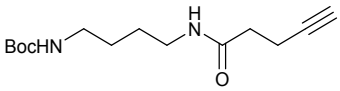
tert-Butyl 2-pent-4-ynamidoethylcarbamate (9e).

White semisolid, yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.28 (br s, 1H), 4.91 (br s, 1H), 3.39-3.27 (m, 4H), 2.55-2.51 (m, 2H), 2.50-2.37 (m, 2H), 2.00 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.65, 156.89, 82.97, 79.70, 69.28, 40.65, 40.14, 35.30, 28.38, 14.92; MS (CI): calcd for $C_{12}H_{20}N_2O_3$: 240.14, found: 241.10



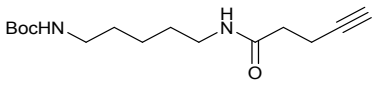
tert-Butyl 3-pent-4-ynamidopropylcarbamate (9f).

White semisolid, yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.32 (br s, 1H), 4.89 (br s, 1H), 3.30 (q, *J* = 6.2 Hz, 2H), 3.17 (q, *J* = 6.0 Hz, 2H), 2.56-2.52 (m, 2H), 2.41 (t, *J* = 6.9 Hz, 2H), 1.99 (s, 1H), 1.66-1.59 (s, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.34, 156.69, 82.99, 79.36, 69.24, 36.99, 35.92, 35.43, 30.18, 28.40, 14.98; MS (CI): calcd for $C_{13}H_{22}N_2O_3$: 254.35, found: 255.0.



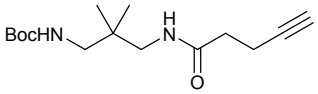
tert-Butyl 4-pent-4-ynamidobutylcarbamate (9g).

White semisolid, yield 90%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (br s, 1H), 4.61 (br s, 1H), 3.31 (t, *J* = 6.9 Hz, 2H), 3.12 (s, 2H), 2.53 (t, *J* = 5.6 Hz, 2H), 2.38 (t, *J* = 6.9 Hz, 2H), 2.02 (s, 1H), 1.53 (d, *J* = 3.2 Hz, 4H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.04, 156.14, 83.08, 79.22, 69.33, 40.09, 39.20, 35.36, 28.42, 27.66, 26.66, 14.97.δ 171.05, 156.10, 83.10, 79.23, 69.33, 40.09, 39.20, 35.36, 28.42, 27.66, 26.66, 14.97; HRMS (EI): calcd for $C_{14}H_{24}N_2O_3$: 268.1786, found: 268.1759.



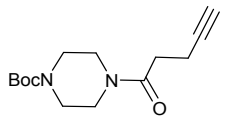
tert-Butyl 5-pent-4-ynamidopentylcarbamate (9h).

White semisolid, yield 92%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (br s, 1H), 4.55 (br s, 1H), 3.27 (q, *J* = 6.2 Hz, 2H), 3.11 (q, *J* = 6.2 Hz, 2H), 2.53 (t, *J* = 6.7 Hz, 2H), 2.38 (t, *J* = 6.7 Hz, 2H), 2.02 (s, 1H), 1.56-1.47 (m, 4H), 1.44 (s, 9H), 1.37-1.33 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.02, 156.13, 83.08, 79.12, 69.30, 40.22, 39.32, 35.36, 29.67, 29.09, 28.42, 23.86, 14.97. δ 171.03, 156.14, 83.09, 79.12, 69.30, 40.22, 39.32, 35.36, 29.67, 29.09, 28.42, 23.86, 14.96; HRMS (EI): calcd for $C_{15}H_{26}N_2O_3$: 282.1943, found: 282.1921.



tert-Butyl 2,2-dimethyl-3-pent-4-ynamidopropylcarbamate (9i).

Colorless viscous liquid, yield 87%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (br s, 1H), 5.12 (br s, 1H), 3.03 (d, *J* = 6.5 Hz, 2H), 2.88 (d, *J* = 6.9 Hz, 2H), 2.55(t, *J* = 6.6 Hz, 2H), 2.43 (t, *J* = 6.7 Hz, 2H), 1.98 (s, 1H), 1.44 (s, 9H), 0.86 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.44, 157.10, 83.15, 79.48, 69.21, 53.43, 47.30, 45.45, 36.40, 35.70, 28.38, 23.41, 15.12. δ 171.45, 157.11, 83.15, 79.49, 69.21, 53.43, 47.29, 45.45, 36.40,35.70, 28.37, 23.40, 15.11; HRMS (EI): calcd for $C_{15}H_{26}N_2O_3$: 282.1943, found: 282.1978.

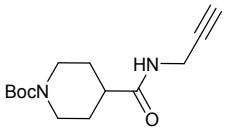


tert-Butyl 4-pent-4-ynoylpiperazine-1-carboxylate (9j).

White semisolid, yield 88%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.60 (d, *J* = 5.2 Hz, 2H), 3.45-3.39 (m, 6H), 2.57 (s, 4H), 1.98 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.53, 154.52, 83.32, 80.34, 68.86, 45.20, 41.50, 32.19, 28.36, 14.48; HRMS (EI): calcd for $C_{14}H_{22}N_2O_3$: 266.1630, found: 266.1631.

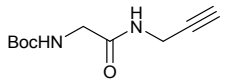
Synthesis of linker 9k-m.

9k-m were synthesized by following the procedure applied for the synthesis of **9a-c** using acid **8a-c** (Table 4) and propargylamine **10o**.



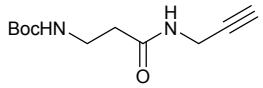
tert-Butyl 4-(prop-2-ynylcarbamoyl)piperidine-1-carboxylate (9k).

White semisolid, yield 89%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.67 (br s, 1H), 4.16-4.08 (m, 2H), 4.06 (q, *J* = 2.3 Hz, 2H), 2.74 (t, *J* = 11.8 Hz, 2H), 2.29-2.19 (m, 2H), 1.82 (d, *J* = 11.8 Hz, 2H), 1.70-1.56 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.08, 154.65, 79.68, 79.55, 71.66, 43.22, 42.98, 29.16, 28.46, 28.43.δ 174.09 154.66, 79.68, 79.55, 71.66, 42.97, 29.16, 28.46, 28.43; HRMS (EI): calcd for $C_{14}H_{22}N_2O_3$: 266.1630, found: 266.1631.



tert-Butyl 2-oxo-2-(prop-2-ynylamino)ethylcarbamate (9l).

Viscous liquid, yield 87%; data of this compound were in accordance with the already published work.[4]

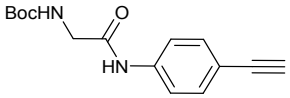


tert-Butyl 3-oxo-3-(prop-2-ynylamino)propylcarbamate (9m).

White semisolid, Yield: 87%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.97 (br s, 1H), 5.12 (br s, 1H), 4.05 (q, *J* = 2.4 Hz, 2H), 3.41 (q, *J* = 6.2 Hz, 2H), 2.42 (t, *J* = 6.0 Hz, 2H), 2.23 (s, 1H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.12, 156.18, 79.47, 79.42, 71.59, 36.50, 36.14, 29.13, 28.40.δ 171.13, 156.20, 79.47, 77.43, 71.59, 36.50, 36.13, 29.13, 28.40; m/z: calcd for $C_{11}H_{18}N_2O_3$: 226.130, found: 227.0

Synthesis of 9n.

To a solution of *N*-Boc-glycine **8b** (1.44 mmol) in THF (2 mL) at 0 °C were added triethylamine (1.44 mmol) and ethyl chloroformate (1.44 mmol) over a period of 10 min, and the reaction mixture was stirred for 30 min. After the addition of the 4-aminophenylacetylene **7j** (1.44 mmol), the mixture was stirred for an additional 1h at 0 °C. Then, the reaction mixture was warmed to rt, and stirring was kept overnight. After completion of the reaction, the solvent was evaporated *in vacuo*, the residue was dissolved in ethyl acetate (15 mL x 2) and washed with brine (15 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude product was purified by column chromatography using EA/heptane (40:60) as eluent, yielding a white solid in 65%.[6]



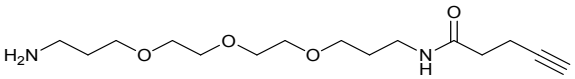
tert-Butyl 2-(4-ethynylphenylamino)-2-oxoethylcarbamate (9n).

White solid, yield 65%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (br s, 1H), 7.46 (q, *J* = 8.4 Hz, 4H), 5.24 (br s, 1H), 3.92 (d, *J* = 5.8Hz, 2H), 3.04 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, MeOD): δ 170.61, 158.59, 140.09, 133.62, 120.80, 119.18, 84.21, 80.84, 78.05, 45.08, 28.72; HRMS (EI): calcd for $C_{15}H_{18}N_2O_3$: 274.1300, found: 274.1300.

Synthesis of linkers 10a-m.

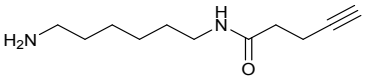
Compounds **9a-m** (0.75 mmol) were dissolved in CH_2Cl_2 (5 mL) and HCl-dioxane (4N solution, 4 mL) was added and the mixture was stirred at rt for 3-4h. The reaction was monitored by TLC (MeOH/DCM, 1:9, Rf = 0.1). After completion of the reaction, the solvents were removed *in vacuo* and the product was washed with diethyl ether and dried *in vacuo*.

Spectral data of linkers 10a-m.



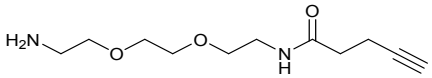
***N*-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)pent-4-ynamide (10a).**

White semisolid, yield 80%; data of this compound were in accordance with published work.[4]



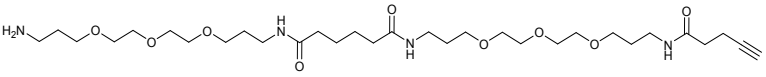
***N*-(6-Aminohexyl)pent-4-ynamide (10b).**

White semisolid, yield 78%; the compound was obtained as a hydrochloride salt; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.91 (s, 2H), 4.00 (s, 4H), 3.03 (s, 1H), 2.75 (s, 2H), 2.50 (s, 4H), 2.28 (d, *J* = 28.0 Hz, 2H), 1.53-1.36 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.48, 83.28, 70.11, 39.38, 39.07, 34.51, 28.01, 26.55, 25.34, 25.11, 14.64; HRMS (EI): calcd for $[C_{11}H_{20}N_2O+H]^+$: 197.1648, found: 197.1653.



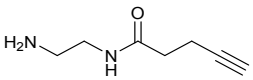
***N*-(2-(2-(2-Aminoethoxy)ethoxy)ethyl)pent-4-ynamide (10c).**

White semisolid, yield 83%; this compound was used directly for the next step without further purification.



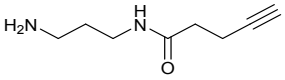
***N*^{1}-(3-(2-(2-(3-Aminopropoxy)ethoxy)ethoxy)propyl)-*N*^{6}-(15-oxo-4,7,10-trioxa-14-azanonadec-18-ynyl)adipamide (10d).**

Viscous liquid, yield 73%; ESI-MS: calculated for $C_{31}H_{58}N_4O_9$: 630.042, found: 631.5 $[M+H]^+$. This product was used directly without further purification.



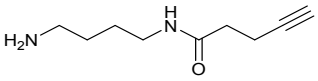
***N*-(2-Aminoethyl)pent-4-ynamide (10e).**

Viscous liquid, yield 72%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, D_2O): δ 3.24 (t, *J* = 6.0 Hz, 2H), 3.06 (t, *J* = 6.1 Hz, 2H), 2.41 (s, 4H), 2.28 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 175.68, 83.43, 70.06, 39.16, 36.75, 34.22, 14.27; HRMS (EI): calcd for $[C_7H_{12}N_2O+H]^+$: 141.1028, found: 141.1088.



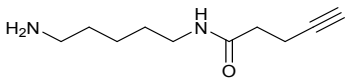
***N*-(3-Aminopropyl)pent-4-ynamide (10f).**

Viscous liquid, yield 82%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, D_2O): δ 3.24 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.44-2.30 (m, 4H), 2.29 (s, 1H), 1.85-1.76 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 175.06, 83.28, 70.16, 48.85, 36.97, 35.95, 34.39, 14.57; HRMS (EI): calcd for $[C_8H_{14}N_2O+H]^+$: 155.1178, found: 155.1182.



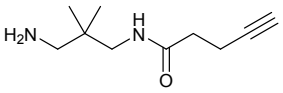
***N*-(4-Aminobutyl)pent-4-ynamide (10g).**

Viscous liquid, yield 86%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, D_2O): δ 3.16 (t, *J* = 6.6, 6.6 Hz, 2H), 2.92 (t, *J* = 7.2, 7.2 Hz, 2H), 2.44-2.32 (m, 4H), 2.92 (t, *J* = 7.2, 7.2 Hz, 1H), 1.66-1.45 (m, 4H); ^{13}C NMR (75 MHz, D_2O): δ 174.68, 83.34, 70.15, 39.11, 38.55, 34.51, 25.46, 24.15, 14.63; HRMS (EI): calcd for $[C_9H_{16}N_2O+H]^+$: 169.1335 $[M+H]^+$, found: 169.1344.



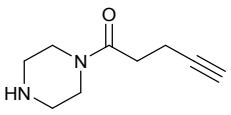
***N*-(5-Aminopentyl)pent-4-ynamide (10h).**

White semisolid, yield 80%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96 (s, 3H), 3.04 (q, *J* = 6.4, 6.4, 6.4 Hz, 2H), 2.80 – 2.67 (m, 3H), 2.43 – 2.19 (m, 4H), 1.55 (p, *J* = 7.6, 7.6, 7.5, 7.5 Hz, 2H), 1.36 (dp, *J* = 23.9, 8.2, 8.2, 7.6, 7.6 Hz, 4H); ^{13}C NMR (75 MHz, D_2O): δ 174.50, 83.29, 70.16, 38.92, 34.50, 27.79, 26.30, 22.89, 14.66; HRMS (EI): calcd for $[C_{10}H_{18}N_2O+H]^+$: 183.1491, found: 183.1499.



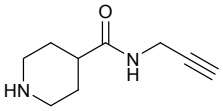
***N*-(3-Amino-2,2-dimethylpropyl)pent-4-ynamide (10i).**

White semisolid, yield 82%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, D_2O): δ 3.10 (s, 2H), 2.76 (s, 2H), 2.49-2.40 (m, 4H), 2.35 (s, 1H), 0.96 (s, 6H; ^{13}C NMR (75 MHz, D_2O): δ 175.73, 83.55, 70.44, 46.28, 45.92, 34.42, 34.39, 22.35, 14.75; HRMS (EI): calcd for $[C_{10}H_{18}N_2O+H]^+$: 183.1491, found: 183.1493.



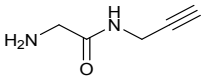
1-(Piperazin-1-yl)pent-4-yn-1-one (10j).

White semisolid, yield 85%; the compound was obtained as a hydrochloride salt. ^{1}H NMR (300 MHz, DMSO-d6): δ 9.50 (d, 3H), 3.68 (t, *J* = 5.1, 5.1 Hz, 4H), 3.07 (d, *J* = 19.8 Hz, 4H), 2.80 (s, 1H), 2.64 (dt, *J* = 14.7, 7.0, 7.0 Hz, 2H), 2.4-2.34 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 173.26, 84.25, 70.15, 43.40, 42.81, 40.72, 38.95, 31.52, 14.30; HRMS (EI): calcd for $C_9H_{14}N_2O$: 166.1106, found: 166.1100.



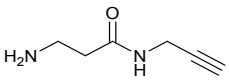
***N*-(Prop-2-ynyl)piperidine-4-carboxamide (10k).**

White semisolid, yield 85%; ^{1}H NMR (300 MHz, D_2O): δ 3.88 (d, *J* = 2.1 Hz, 2H), 3.49-3.37 (m, 2H), 2.97 (td, *J* = 12.6, 12.5, 2.7 Hz, 2H), 2.63 – 2.47 (m, 2H), 2.01-1.92 (m, 2H), 1.87 – 1.66 (m, 2H); ^{13}C NMR (75 MHz, D_2O): δ 176.00, 79.62, 71.77, 43.08, 39.53, 28.78, 24.83; HRMS (EI): calcd for $C_9H_{14}N_2O$: 166.1106, found: 166.1104.



2-Amino-*N*-(prop-2-ynyl)acetamide (10l).

White semisolid, yield 79%; ^{1}H NMR (300 MHz, D_2O): δ 3.44 (t, *J* = 6.0, 6.0 Hz, 2H), 3.07 (t, *J* = 6.0, 6.0 Hz, 2H), 2.42 (s, 4H), 2.29 (s, 1H); ^{13}C NMR (75 MHz, D_2O): δ 166.83, 79.26, 72.13, 40.48, 28.90; MS (CI): calcd for $C_5H_8N_2O$: 112.0636, found: 113.0

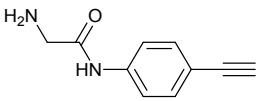


3-Amino-*N*-(prop-2-ynyl)propanamide (10m).

White semisolid, yield 88%; ^{1}H NMR (300 MHz, D_2O): δ 3.91 (d, *J* = 2.0 Hz, 2H), 3.21 (t, *J* = 6.7, 6.7 Hz, 2H), 2.62 (t, *J* = 6.7, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, D_2O): δ 171.98, 79.58, 71.88, 35.60, 31.85, 28.75; HRMS (EI): calcd for $C_6H_{10}N_2O$: 126.0793, found: 126.0797.

Synthesis of compound 10n.

Compound **9n** 100 mg (0.36 mmol) was dissolved in dioxane (0.5 mL) and H_2O (4.5 mL) in a screw capped vial and the mixture was heated at 140 ^{o}C for 3h. After completion of the reaction, the reaction mixture was cooled to rt after which the product precipitated as a light yellow solid. It was filtered through a Büchner funnel, washed with diethyl ether and dried *in vacuo* to obtain **10n**.[9]



2-Amino-*N*-(4-ethynylphenyl)acetamide (10n).

Viscous liquid, yield 95%; ^{1}H NMR (300 MHz, DMSO-d6) δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 4.07 (d, *J* = 0.9 Hz, 1H), 3.28 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 172.35, 139.35, 132.33, 118.82, 115.96, 83.55, 79.71, 45.56; HRMS (EI): calcd for $C_{10}H_{10}N_2O$: 174.0793, found: 174.0798.

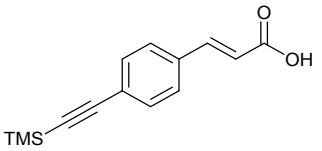
Synthesis of aromatic linker 10t-w.

Synthesis of linker 10t ((*E*)-N-(2-aminoethyl)-3-(4-ethynylphenyl)acrylamide).

Synthesis of linker **10t** was accomplished in 3 steps:

Step-1: synthesis of ((*E*)-3-(4-((trimethylsilyl)ethynyl)phenyl)acrylic acid) (9t').

In a 10 mL screw cap vial were placed **8f** (1.04 mmol), TMS acetylene (2.08 mmol), piperidine (1.10 mL, 10 equiv.), $PdCl_2(PPh_3)_2$ (0.04 mmol, 4 mol%) and a magnetic stir bar. The reaction mixture was stirred at 85 °C for 30 min. After completion of the reaction, the reaction mixture was poured in water (25 mL) and the product was extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with 1N HCl solution, brine (25 mL) and dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the crude product was subjected to column chromatography over silica gel (2-4% methanol in DCM) to afford the corresponding compound.[7]

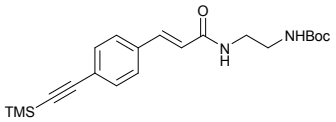


(*E*)-3-(4-((Trimethylsilyl)ethynyl)phenyl)acrylic acid (9t').

White solid, yield 78%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.48 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H,), 7.60 (d, *J* =16.0 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* =16.0 Hz, 1H), 0.23 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ167.4, 142.7, 134.7, 132.0, 128.4, 123.6, 120.4, 104.8, 96.2, -0.153; HRMS (EI): calcd for $C_{14}H_{16}O_2Si$: 244.0920, found: 244.0911.

Step-2: synthesis of (*E*)-*tert*-butyl 2-(3-(4-(trimethylsilyl)ethynyl)phenyl) acrylamido)ethylcarbamate (9t).

To a solution of compound **9t'** (1.63 mmol) in DMF (5 mL) were added HATU (1.96 mmol), **7d** (1.80 mmol) and DIPEA (2.13 mmol) and the reaction mixture was stirred at rt for 4h. After completion of the reaction, the mixture was poured into water and extracted with ethyl acetate (2 x 30 mL). The organic layer was washed with brine and concentrated *in vacuo*. The crude product was subjected to column chromatography over silica gel (2-4% methanol in DCM) to afford compound **9t**.

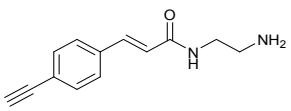


(*E*)-*tert*-Butyl 2-(3-(4-(trimethylsilyl)ethynyl)phenyl) acrylamido)ethylcarbamate (9t).

White solid, yield 82%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (t, *J* = 5.8 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H,), 7.46 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 15.6 Hz, 1H), 6.85 (t, *J* = 5.8 Hz, 1H), 6.63 (t, *J* = 15.6 Hz, 1H), 3.20 (q, *J* = 6.1 Hz, 2H), 3.02 (q, *J* = 6.1 Hz, 2H), 1.37 (s, 9H), .0.02 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): 165.0, 155.7, 137.6, 135.5, 132.2, 127.8, 123.6, 122.9, 105.0, 95.9, 77.8, 40.4, 38.8, 28.3, 0.014; HRMS (EI): calcd for $C_{21}H_{30}N_2O_3Si$: 386.2026, found: 386.2037.

Step-3: synthesis of (*E*)-N-(2-aminoethyl)-3-(4-ethynylphenyl) acrylamide (10t).

Compound **10t** ((*E*)-N-(2-aminoethyl)-3-(4-ethynylphenyl)acrylamide) was obtained by following the procedure applied for the synthesis of **10n**.



(*E*)-N-(2-Aminoethyl)-3-(4-ethynylphenyl)acrylamide (10t).

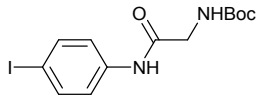
White solid, yield 62%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.31 (dd, 8.0 Hz, 8.0 Hz, 4H), 7.20 (d, *J* = 15.8, Hz, 1H), 6.46 (d, 15.8 Hz, 1H), 4.09 (s, 1H), 3.46 (s, 2H), 3.00 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.83, 137.41, 135.43, 132.18, 127.64, 123.49, 122.36, 83.24, 82.24, 41.54, 40.81; HRMS (EI): calcd for $C_{13}H_{14}N_2O$: 214.1106, found: 214.1125.

Synthesis of linker (*E*)-2-amino-*N*-(4-(4-ethynylstyryl)phenyl)acetamide (10u).

Synthesis of **10u** was accomplished in 4 steps:

Step-1: synthesis of tert-butyl 2-(4-iodophenylamino)-2-oxoethylcarbamate (9u').

9u' was synthesized from **7k** and **8b** following the procedure applied for the synthesis of **9n**.

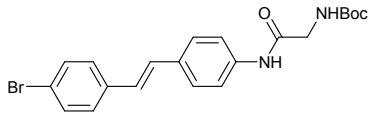


tert-Butyl 2-(4-iodophenylamino)-2-oxoethylcarbamate (9u').

White solid, yield 68%; ^{1}H NMR (300 MHz, DMSO-d6): δ 10.03 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.06 (t, *J* = 6.0, 6.0 Hz, 1H), 3.71 (d, *J* = 6.1 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, DMSO): δ 168.39, 155.89, 138.75, 137.34, 121.22, 86.51, 78.04, 43.80, 28.17; HRMS (EI): calcd for $C_{13}H_{17}N_2O_3$: 376.0283, found: 376.0276.

Step-2: synthesis of (*E*)-tert-butyl 2-(4-(4-bromostyryl)phenylamino)-2-oxoethylcarbamate (9u").

In a round-bottom 2 necked flask, **9u'** (500 mg, 1.33 mmol) was added to a mixture of tetrabutylammonium bromide (322 mg, 1.99 mmol), potassium acetate (210 mg, 2.14 mmol), palladium acetate (15 mg, 0.066 mmol) and 4-bromostyrene (268 mg, 1.46 mmol) and the mixture was stirred in DMF (12 mL) at rt under argon. The mixture was heated up to 80 ^{o}C for 4-5h and then cooled to rt. After completion of the reaction, as monitored by TLC (heptane/EA, 4:6) and mass analysis, it was cooled to rt, poured in water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with brine (50 mL) and dried over Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure and the crude product was subjected to column chromatography over silica gel(30-40% EA in heptane) to afford the compound in 62% yield.[8]

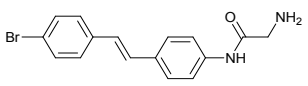


(*E*)-tert-Butyl 2-(4-(4-bromostyryl)phenylamino)-2-oxoethylcarbamate (9u").

Yellow solid, yield 62%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H), 7.64-7.51 (m, 8H), 7.18 (dd, *J* = 15.8 Hz,15.8 Hz, 2H), 7.06 (t, 5.9 Hz, 1H), 3.73 (d, *J* = 6.0 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.21, 155.90, 138.67, 136.55, 131.68, 131.53, 128.93, 128.19, 127.09, 125.67, 120.12, 119.10, 78.03, 43.78, 28.18.; HRMS (EI): calcd for $C_{21}H_{23}N_2O_3Br$: 430.0892, found: 430.0888.

Step-3: synthesis of 9u.

9u was synthesized from **9u"** by following the procedure used for the synthesis of **10a-m**.

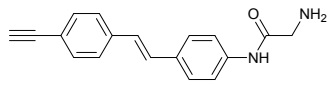


(*E*)-2-Amino-*N*-(4-(4-bromostyryl)phenyl)acetamide 9u.

White solid, yield 85%; ^{1}H NMR (300 MHz, DMSO-d_6): ^{1}H NMR (300 MHz, DMSO-d6) δ 10.98 (s, 1H), 8.33 (s, 3H), 7.69 (s, 1H), 7.64 (d, *J* = 16.5 Hz, 2H), 7.58 (s, 1H), 7.55 (s, 4H), 7.21 (q, *J* = 16.5, 16.5, 16.4 Hz, 2H), 3.83 (s, 2H).; ^{13}C NMR (75 MHz, DMSO-d_6): 164.7, 138.0, 136.4, 132.3, 131.5, 128.8, 128.2, 127.2, 126.0, 120.2, 119.1, 40.9.; MS (CI): calcd for $C_{21}H_{23}N_2O_3Br$: 330.036, found: 331.0.

Step-4: synthesis of 10u.

In a 10 mL screw cap vial were placed **9u** (1.51 mmol), TMS acetylene (3.13 mmol), piperidine (1.66 mL, 10 equiv), $PdCl_2(PPh_3)_2$ (0.06 mmol, 4 mol%) and a magnetic stir bar. The reaction mixture was stirred at 85 °C for 30 min. After completion of the reaction, the mixture was poured in water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layer was concentrated under reduced pressure yielding a yellow solid. This product was dissolved in THF (2mL) and cooled in an ice bath at 0 °C. A solution of TBAF (tetrabutylammonium fluoride) in THF (1.8 mmol, dissolved in 1 mL THF) was added dropwise and the mixture was allowed to stir at rt for 30 min. After completion of the reaction, THF was removed *in vacuo* and the solid residue obtained was dissolved in a water/ACN mixture and purified by preparative HPLC using a gradient of 35% ACN in water/HCOOH. The solvent was removed under reduced pressure and the residue was dried to obtain pure product in 40% yield. [7]



(*E*)-2-Amino-*N*-(4-(4-ethynylstyryl)phenyl)acetamide (10u).

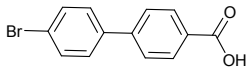
Yellow solid, yield 40%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (s, 1H), 7.66 (d, 8.0 Hz, 2H), 7.64-7.57 (m, 4H), 7.46 (d, 8.0 Hz, 2H), 7.22 (dd, *J* = 15.5 Hz, 2H), 4.23 (s, 1H), 3.45 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 164.58, 137.89, 137.59, 132.02, 131.67, 130.63, 129.08, 128.71, 128.31, 127.25, 126.40, 120.26, 118.79, 83.44, 81.22, 43.80; HRMS (EI): calcd for $C_{18}H_{16}N_2O$: 276.1263, found: 276.1262.

Synthesis of linker 10v (*N*-(3-aminopropyl)-4'-ethynylbiphenyl-4-carboxamide.

Linker **10v** was synthesized in 4 steps:

Step-1: synthesis of 8g.

8g was synthesized from methyl 4'-bromobiphenyl-4-carboxylate by following the procedure applied for the synthesis of **10a"**.

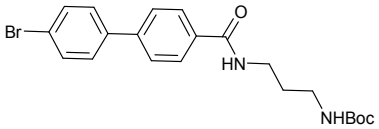


4'-Bromobiphenyl-4-carboxylic acid (8g).

White solid, yield 96%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.69 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.03, 142.86, 138.14, 131.92, 130.07, 129.98, 129.00, 126.68, 121.82; HRMS (EI): calcd for $C_{19}H_9BrO_2$: 275.9786, found: 275.9803.

Step 2: Synthesis of 9v'.

9v' was synthesized from **8g** by following the procedure applied for the synthesis of **9t**.

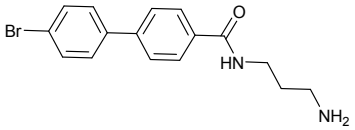


***tert*-Butyl 3-(4'-bromobiphenyl-4-ylcarboxamido)propylcarbamate (9v').**

White solid, yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 8.5 Hz, 8.5 Hz, 4H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.38 (bs, 1H), 4.92 (bs, 1H), 3.53 (dd, *J* = 6.0 Hz, 6.0 Hz, 2H), 3.27 (dd, *J* = 6.2 Hz, 6.2 Hz, 2H),1.6-1.67 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.02, 157.07, 142.78, 139.02, 133.59, 132.00, 128.74, 127.67, 126.96, 122.25, 79.62, 37.01, 36.09, 30.23, 28.40; HRMS (EI): calcd for $C_{21}H_{25}BrN_2O_3$: 432.1049, found: 432.1058.

Step-3: Synthesis of 9v.

9v was synthesized from **9v'** by following the procedure applied for the synthesis of **10a-m**.

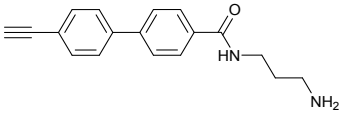


***N*-(3-Aminopropyl)-4'-bromobiphenyl-4-carboxamide (9v).**

white solid, yield 88%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.15 (bs, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.70 (m, 4H), 3.38 (m, 2H), 2.84 (m, 2H), 1.88-1.84 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.84, 141.38, 138.27, 133.29, 131.88, 128.93, 127.97, 126.40, 121.57, 36.49, 36.06, 27.13.; HRMS (EI): calcd for $C_{16}H_{17}BrN_2O$: 332.0524, found: 332.0529.

Step-4: Synthesis of 10v.

10v was synthesized from **9v** by following the procedure used for the synthesis of **10u**.



***N*-(3-Aminopropyl)-4'-ethynylbiphenyl-4-carboxamide (10v).**

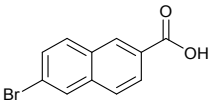
Yellow solid, yield 50%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.9 (bs, 1H), 8.5 (bs, NH, 2H), 7.9 (d, *J* = 8.4 Hz, 2H), 7.77 (t, *J* = 8.4 Hz, 4H),7.58 (d, *J* = 8.3 Hz, 2H), 4.3 (s, 1H), 3.18 (t, *J* = 6.2 Hz, 2H), 2.84 (t, *J* = 6.2 Hz, 2H), 1.84 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.87, 141.47, 139.44, 133.55, 132.30, 127.93, 127.02, 126.47, 121.28, 83.20, 81.82, 36.43, 27.63, 23.03; HRMS (EI): calcd for $C_{18}H_{18}N_2O$: 278.1419, found: 278.1430.

Synthesis of stilbene linker 10w.

Synthesis of **10w** was accomplished in 4 steps:

Step-1: synthesis of 8h.

8h was synthesized from methyl 6-bromo-2-naphthoate by following the procedure used for the synthesis of **10a"**.

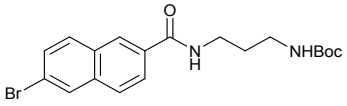


6-Bromo-2-naphthoic acid (8h).

White solid, yield 96%; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.32 (s, 1H), 8.12- 8.03(m, 2H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.15, 135.93, 131.40, 130.67, 130.45, 129.79, 129.59, 128.66, 127.39, 126.31, 121.74.; HRMS (EI): calcd for $C_{11}H_7O_2Br$: 249.9629, found: 249.9623.

Step-2: synthesis of 9w'.

9w' was synthesized from **8h** by following the procedure used for the synthesis of **9t** and **9v**.

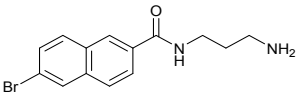


***tert*-Butyl 3-(6-bromo-2-naphthamido)propylcarbamate (9w').**

White solid, yield 85%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.03 (s,1H), 7.95 (d, *J* = 8.4 Hz,1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.61-7.53 (m, 2H), 4.93 (t, *J* = 5.7 Hz, 1H), 3.56 (q, *J* = 6.0 Hz, 6.0 Hz, 2H), 3.29 (q, *J* = 6.1 Hz, 6.1Hz, 2H), 1.79-1.71 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.12, 157.10, 135.60, 132.20, 131.10, 130.58, 130.06, 129.79, 127.52, 127.40, 124.79, 121.72, 79.68, 37.07, 36.17, 30.21, 28.41; HRMS (EI): calcd for $C_{19}H_{23}N_2O_3Br$: 406.0892, found: 406.0932.

Step-3: synthesis of 9w.

9w was synthesized from **9w'** by following the procedure applied for the synthesis of **10a-m**.

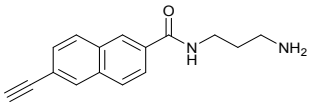


***N*-(3-Aminopropyl)-6-bromo-2-naphthamide (9w).**

White solid, yield 90%; ^{1}H NMR (300 MHz, D_2O): δ 7.80 (s, 1H), 7.67 (s,1H), 7.44-7.20 (m, 4H), 3.36 (t, *J* = 6.7 Hz, 2H), 2.98 (t, *J* = 6.7 Hz, 2H), 1.94-1.85 (m, 2H); ^{13}C NMR (75 MHz, D_2O):169.6, 134.9, 130.3, 130.0, 129.9, 129.6, 129.2, 127.3, 127.1, 123.7, 121.5, 37.1, 36.7, 26.8; HRMS (EI): calcd for $C_{14}H_{15}N_2OBr$: 306.0368, found: 306.0358.

Step-4: synthesis of 10w.

10w was synthesized from **9w** by following the procedure used for the synthesis of **10u**.



***N*-(3-Aminopropyl)-6-ethynyl-2-naphthamide (10w).**

White solid, yield 50%; ^{1}H NMR (300 MHz,DMSO-d_6): δ 8.98 (t, *J* = 5.5 Hz, 1H), 8.46 (s, 1H), 8.44 (s, 1H), 8.14 (s, 1H), 8.01-7.97 (m, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 4.35 (s, 1H), 3.35 (t, *J* = 6.5 Hz, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.48-2.47 (t, *J* = 2 Hz, 2H), 1.84-1.76 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.16, 133.54, 132.66, 131.69, 131.41, 129.30, 128.85, 127.77, 127.27, 124.99, 120.56, 83.50, 81.99, 36.72, 36.48, 27.86.; HRMS (EI): calcd for $C_{16}H_{16}N_2O$: 252.1263, found: 252.1285.

Synthesis of vancomycin-linker conjugates 11a-w.

Vancomycin·HCl **6** (75 mg, 0.051 mmol), EDC·HCl (12 mg, 0.0.067 mmol) and HOAt (9 mg, 0.067mmol) were dissolved in DMF (5 mL) and the mixture was stirred for 5 min. To this solution were added a solution of linker **10a-w** (1.2 equiv) in DMF (1 mL) and *N*-methyl morpholine (till pH 8) and the mixture was stirred for 7-8h at rt. The reaction was monitored by ESI-MS. DMF was removed *in vacuo* and the residue was purified by preparative RP-HPLC (0-40% ACN/H_2O with 0.1 % HCOOH in 40 min).

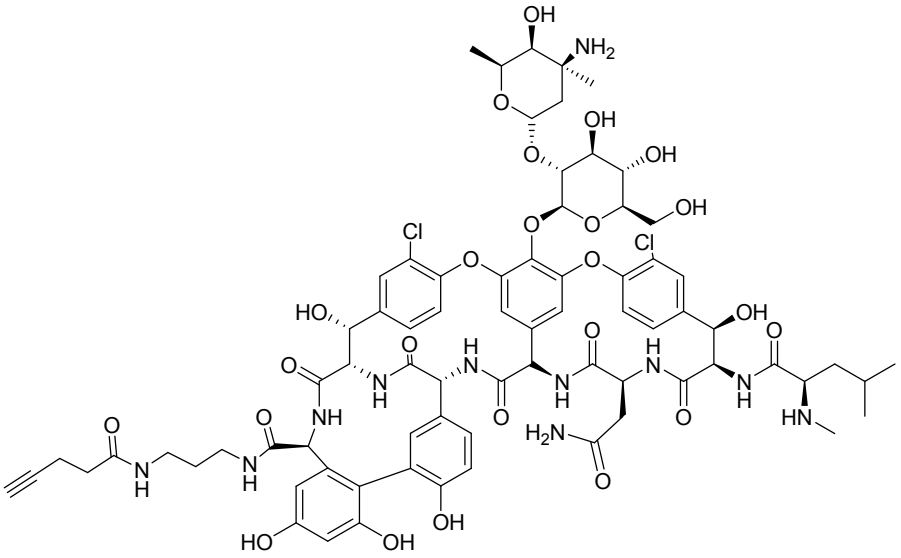
The retention time was in the range of 25-35 min. The acetonitrile was removed *in vacuo* and the remaining water was lyophilized affording compounds **11a-w** as a white powder in 40-55% yield and 95-98% purity. The compounds thus obtained were characterized by mass spectrometric analysis (ESI-MS, Table 5).

Table 5: Mass spectrometric data of compound **11a-w**.

Entry	Vancomycin -inker conjugates	Linker **10**	Calculated Average Mass	Found ESI-MS [m/z]	Mol.formula
1	**11a**	**10a**	1731.5	1731.8 $[M]^+$, 1156.0 $[2M+3H]^{3+}$	$C_{81}H_{101}Cl_2N_{11}O_{27}$
2	**11b**	**10b**	1627.5	1628.9 $[M+H]^+$,1086.5 $[2M+3H]^{3+}$	$C_{77}H_{93}Cl_2N_{11}O_{24}$
3	**11c**	**10c**	1659.5	1661.0 $[M+H]^+$, 831.5 $[M+2H]^{2+}$	$C_{77}H_{93}Cl_2N_{11}O_{26}$
4	**11d**	**10d**	2061.5	2061.82 $[M]^+$,1031.42 $[M+2H]^{2+}$	$C_{97}H_{131}Cl_2N_{13}O_{32}$
5	**11e**	**10e**	1571.5	1572.2 $[M+H]^+$, 1048.2 $[2M+3H]^{3+}$	$C_{73}H_{85}Cl_2N_{11}O_{24}$
6	**11f**	**10f**	1585.5	1586.0 $[M+H]^+$,1059.8 $[2M+3H]^{3+}$	$C_{74}H_{87}Cl_2N_{11}O_{24}$
7	**11g**	**10g**	1599.5	1600.9 $[M+H]^+$	$C_{75}H_{89}Cl_2N_{11}O_{24}$
8	**11h**	**10h**	1613.5	1614.5 $[M+H]^+$	$C_{76}H_{91}Cl_2N_{11}O_{24}$
9	**11i**	**10i**	1613.5	1614.0 $[M+H]^+$	$C_{76}H_{91}Cl_2N_{11}O_{24}$
10	**11j**	**10j**	1597.5	1598.0 $[M+H]^+$, 802.9 $[M+2H]^{2+}$	$C_{75}H_{87}Cl_2N_{11}O_{24}$
11	**11k**	**10k**	1597.5	1598.7 $[M+H]^+$	$C_{75}H_{87}Cl_2N_{11}O_{24}$
12	**11l**	**10l**	1543.5	1544.9 $[M+H]^+$	$C_{71}H_{81}Cl_2N_{11}O_{24}$
13	**11m**	**10m**	1557.5	1558.9 $[M+H]^+$	$C_{72}H_{83}Cl_2N_{11}O_{24}$
14	**11n**	**10n**	1605.5	1606.9 $[M+H]^+$	$C_{76}H_{83}Cl_2N_{11}O_{24}$
15	**11o**	**10o**	1486.5	1487.6 $[M+H]^+$	$C_{69}H_{78}Cl_2N_{10}O_{23}$
16	**11p**	**10p**	1500.5	1502.0 $[M+H]^+$	$C_{70}H_{80}Cl_2N_{10}O_{23}$
17	**11q**	**10q**	1514.5	1516.7 $[M+H]^+$	$C_{71}H_{82}Cl_2N_{10}O_{23}$
18	**11r**	**10r**	1514.5	1515.1 $[M+H]^+$	$C_{71}H_{82}Cl_2N_{10}O_{23}$
19	**11s**	**10s**	1500.5	1501.3 $[M+H]^+$	$C_{70}H_{80}Cl_2N_{10}O_{23}$
20	**11t**	**10t**	1643.53	1644.9 $[M+H]^+$	$C_{79}H_{87}Cl_2N_{11}O_{24}$
21	**11u**	**10u**	1705.54	1706.2 $[M+H]^+$	$C_{84}H_{89}Cl_2N_{11}O_{24}$
22	**11v**	**10v**	1707.56	1709.0 $[M+H]^+$	$C_{84}H_{91}Cl_2N_{11}O_{24}$
23	**11w**	**10w**	1681.54	1683.9 $[M+H]^+$	$C_{82}H_{89}Cl_2N_{11}O_{24}$

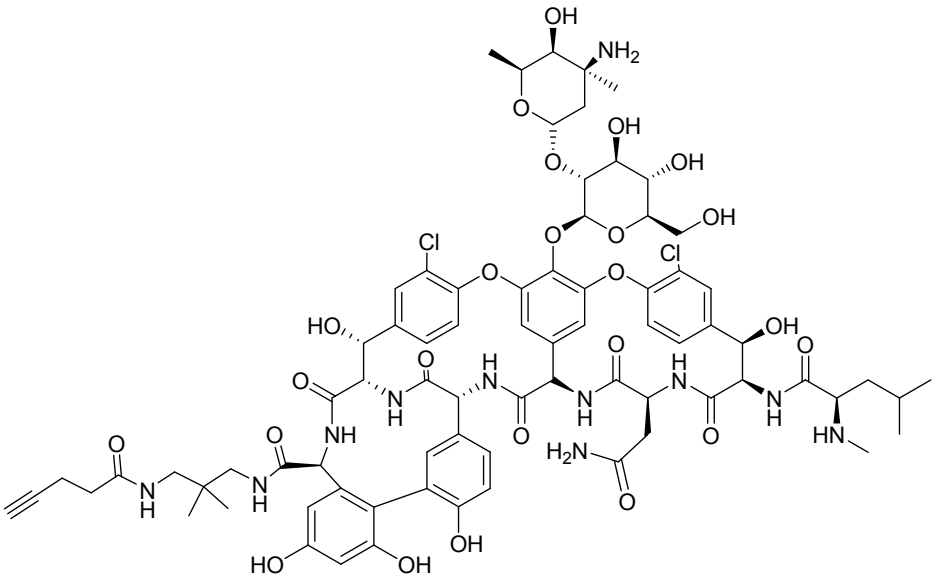
^{1}H NMR of some of the vancomycin linker conjugates are presented below.

Vancomycin –linker conjugate **11f**



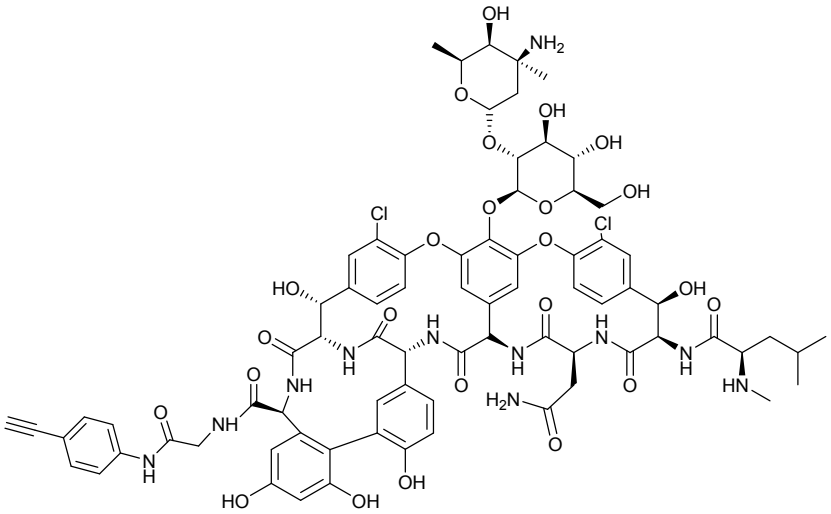
White solid, ^{1}H NMR (300 MHz, DMSO-d6) δ 8.74 (t, *J* = 6.0, 6.0 Hz, 1H), 8.53 (d, *J* = 42.8 Hz, 2H), 8.31 (s, 2H), 8.07 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.93 – 7.71 (m, 5H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.19 (m, 5H), 6.81 – 6.61 (m, 2H), 6.32 (d, *J* = 26.6 Hz, 1H), 5.74 (d, *J* = 6.7 Hz, 1H), 5.54 (s, 1H), 5.42 – 5.09 (m, 5H), 4.88 (s, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.53 – 4.16 (m, 6H), 3.79 – 3.33 (m, 13H), 3.23 (d, *J* = 34.8 Hz, 5H), 3.05 (t, *J* = 6.1, 6.1 Hz, 4H), 2.31 (s, 3H), 2.22 – 1.83 (m, 1H), 1.81 – 1.60 (m, 3H), 1.49 (s, 2H), 1.28 (s, 2H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.88 (dd, *J* = 12.9, 6.5 Hz, 6H).

Vancomycin –linker conjugate **11i**



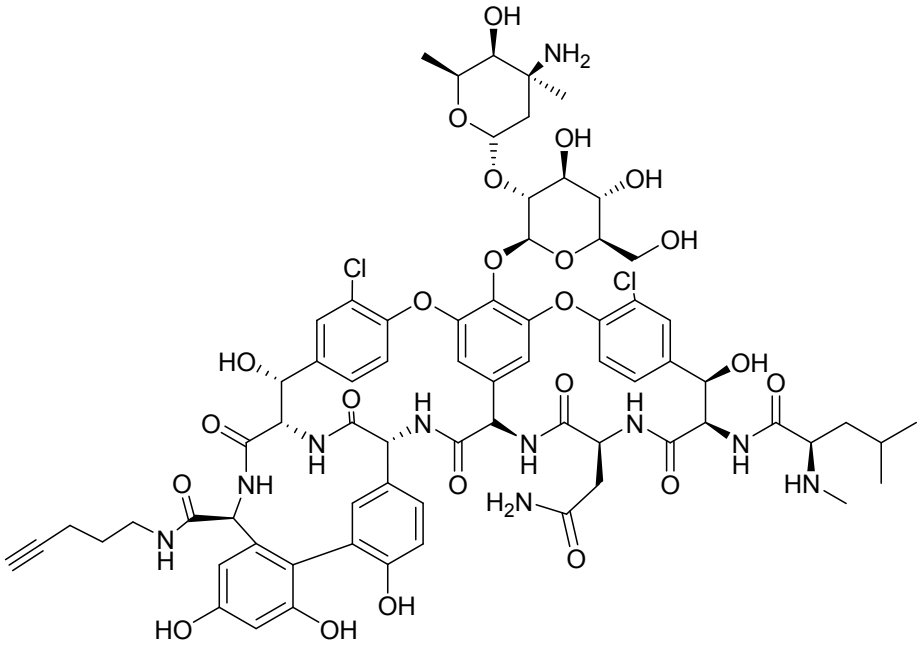
White solid, ^{1}H NMR (300 MHz, DMSO-d6) δ 8.70 – 7.76 (m, 11H), 7.62 – 7.19 (m, 8H), 6.97 – 6.64 (m, 5H), 6.38 (s, 1H), 6.19 (s, 1H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.54 (s, 1H), 5.46 – 5.09 (m, 7H), 4.78 (dd, *J* = 62.1, 6.2 Hz, 3H), 4.44-4.24 (m, 4H), 3.78 – 3.39 (m, 2H), 3.36 – 2.95 (m, 5H), 2.78-2.66 (m, 2H), 2.45 – 2.23 (m, 11H), 2.16-1.67 (m, 3H), 1.56 – 1.36 (m, 1H), 1.29 (s, 3H), 1.06 (d, *J* = 5.6 Hz, 3H), 0.88 (dd, *J* = 13.6, 6.7 Hz, 9H), 0.76 (s, 3H).

Vancomycin –linker conjugate **11n**



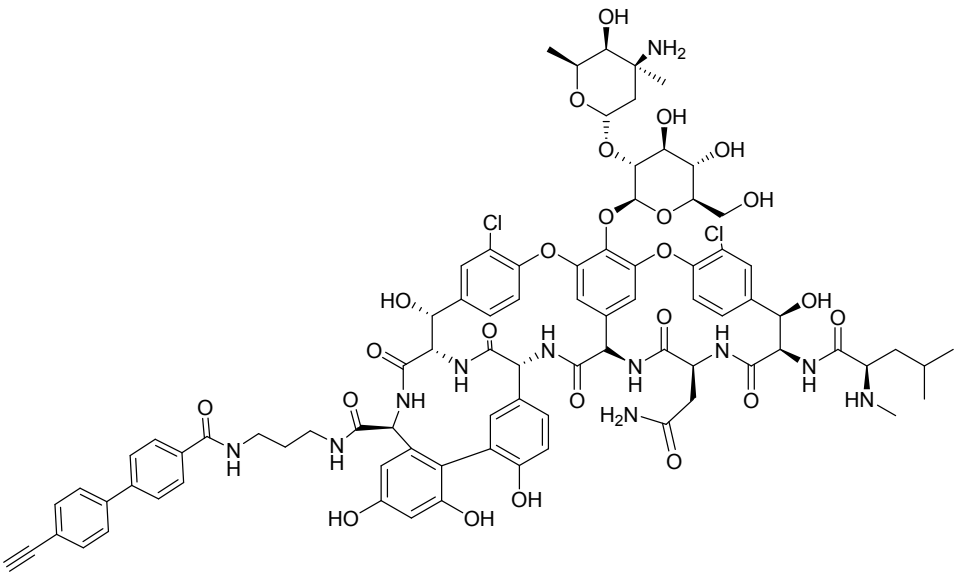
White solid, ^{1}H NMR (600 MHz, D_2O) δ 8.35 (s, 2H), 7.84 – 7.37 (m, 7H), 7.24 (d, *J* = 65.5 Hz, 2H), 6.98 (d, *J* = 57.5 Hz, 2H), 6.56-6.48 (m, 2H), 5.66 (s, 1H), 5.54 – 5.23 (m, 5H), 5.07 (s, 1H), 4.83 (s, 1H), 4.62 (s, 2H), 4.38 (s, 1H), 4.15-4.07 (m, 3H), 3.71 (s, 3H), 3.55 (d, *J* = 29.7 Hz, 2H), 3.39 (s, 1H), 3.28 (s, 3H), 2.72 (s, 3H), 2.63-2.61 (m, , 4H), 2.05-1.99 (m, 1H), 1.75 (s, 1H), 1.65 (d, *J* = 37.3 Hz, 2H), 1.38 (s, 3H), 1.13 (s, 3H), 0.87 (dd, *J* = 23.6, 6.4 Hz, 6H).

Vancomycin –linker conjugate **11r**



White solid, ^{1}H NMR (300 MHz, DMSO-d6) δ 8.60 (s, 1H), 8.42 (s, 1H), 8.32 (s, 2H), 7.99-7.78 (m, 4H), 7.49-7.24 (m, 7H), 6.88 (s, 1H), 6.72 (dt, *J* = 14.9, 7.5, 7.5 Hz, 3H), 6.37 (s, 1H), 6.23 (s, 1H), 5.76 (s, 1H), 5.75 (s, 1H), 5.54 (s, 1H), 5.32 – 5.10 (m, 5H), 4.94 – 4.80 (m, 1H), 4.68 (d, *J* = 6.2 Hz, 2H), 4.40 (dd, *J* = 21.1, 5.5 Hz, 4H), 4.22 (d, *J* = 12.9 Hz, 2H), 4.03 (dd, *J* = 14.3, 7.2 Hz, 2H), 3.68 (d, *J* = 10.9 Hz, 2H), 3.61 – 3.39 (m, 6H), 3.34 – 3.15 (m, 4H), 3.11 – 3.01 (m, 1H), 2.89 (s, 1H), 2.79 (t, *J* = 2.3, 2.3 Hz, 1H), 2.73 (s, 1H), 2.31 (s, 3H), 2.20-2.12 (m, 3H), 1.89 (s, 1H), 1.78 – 1.59 (m, 4H), 1.40 (s, 1H), 1.28 (s, 2H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.88 (dd, *J* = 13.1, 6.5 Hz, 6H).

Vancomycin conjugate **11v**



White solid, ^{1}H NMR (300 MHz, DMSO-d6) δ 8.75 (t, *J* = 5.9, 5.9 Hz, 1H), 8.60 (s, 1H), 8.47 (s, 1H), 8.31 (s, 2H), 8.22 (s, 1H), 8.08 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.92 – 7.69 (m, 6H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.56 – 7.18 (m, 5H), 6.88-6.68 (m, 3H), 6.32 (d, 1H), 5.75 (d, *J* = 8.4 Hz, 1H), 5.54 (s, 1H), 5.40 – 5.11 (m, 5H), 4.89 (s, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.45-4.29 (m, 6H), 3.76 – 3.34 (m, 5H), 3.36 – 2.98 (m, 6H), 3.07 (t, *J* = 7.3, 7.3 Hz, 1H), 2.32 (s, 3H), 2.19 – 2.09 (m, 1H), 1.75 – 1.68 (m, 3H), 1.49 – 1.38 (m, 1H), 1.29 (s, 2H), 1.06 (d, *J* = 6.1 Hz, 2H), 0.88 (dd, *J* = 13.0, 6.5 Hz, 6H).

General procedure for the synthesis of CRAMP-Vancomycin conjugates 12a-w.

The CRAMP-butyl azide derivative **5** (20 mg, 6.29 µmol) and **11a-w** (6.91 µmol) were dissolved in H_2O/DMF (9:1, 5 mL). $CuSO_4 \cdot 5H_2O$ (4.7 mg, 18.8 µmol) and sodium ascorbate (7.4 mg, 37.7 µmol) were added and the mixture was stirred at 40 °C for 15-20h. The reaction was monitored by ESI-MS and LCMS indicating the appearance of two compounds having a similar mass. After completion of the reaction, the solvent was removed *in vacuo*. The crude product was purified using preparative RP-HPLC (0-50% ACN/H_2O with 0.1% HCOOH in 50 min). The retention time was between 36-40 min. The acetonitrile was removed *in vacuo* and the remaining water was lyophilized affording the products **12a-w** and **12a'-w'** in an average yield of 30-40% (total yield of both isolated products) and 95-98% purity. The percentage of the second peak-product varied between 30 to 50% of total yield. These products were characterized by mass spectrometric analysis (MALDI-TOF and ESI-MS). Mass spectrometric data are presented in Table 6.

Table 6: Mass spectrometric data.

Entry	Vancomycin Linker	CRAMP-Vancomycin conjugates	Calculated average mass	Found mass [m/z]
1	**11a**	**12a**	4907.5	4908.63 $[M+H]^+$ FT-ICR avg mass
2	**11b**	**12b**	4803.5	4800.45 FT-ICR monoisotopic mass
3		**12b'**	4803.5	4802.45 FT-ICR monoisotopic mass
4	**11c**	**12c**	4835.5	4834.44 FT-ICR monoisotopic mass

5		**12c′**	4835.5	4834.45 FT-ICR monoisotopic mass
6	**11d**	**12d**	5237.5	5236.73 FT-ICR monoisotopic mass
7		**12d′**	5237.5	5235.71 FT-ICR monoisotopic mass
8	**11e**	**12e**	4747.5	4746.591 MALDI monoisotopic mass
9		**12e′**	4747.5	4748.14 MALDI avg mass
10	**11f**	**12f**	4761.5	4763.93 MALDI avg mass
11		**12f′**	4761.5	4762.98 MALDI avg mass
12	**11g**	**12g**	4775.5	4799.87 $[M+Na]^+$ MALDI avg mass
13		**12g′**	4775.5	4800.19 $[M+Na]^+$ MALDI avg mass
14	**11h**	**12h**	4789.5	4790.52 MALDI avg mass
15		**12h′**	4789.5	4789.57 MALDI avg mass
16	**11i**	**12i**	4789.5	4794.23 MALDI avg mass
17		**12i′**	4789.5	4791.22 MALDI avg mass
18	**11j**	**12j**	4772.5	4797.88 $[M+Na]^+$ MALDI avg mass
19		**12j′**	4772.5	4798.19 $[M+Na]^+$ MALDI avg mass
20	**11k**	**12k**	4772.5	4775.69 MALDI avg mass
21		**12k′**	4772.5	4797.08 $[M+Na]^+$ MALDI avg mass
22	**11l**	**12l**	4718.5	4722.35 MALDI avg mass
23		**12l′**	4720.5	4723.459 MALDI avg mass
24	**11m**	**12m**	4732.5	4756.72 $[M+Na]^+$ MALDI avg mass
25		**12m′**	4732.5	4736.21 MALDI avg mass
26	**11n**	**12n**	4781.5	4785.04 MALDI avg mass
27		**12n′**	4781.5	4782.03 MALDI avg mass
28	**11o**	**12o**	4661.5	4664.26 MALDI avg mass
29		**12o′**	4661.5	4667.43 MALDI avg mass
30	**11p**	**12p**	4675.5	4678.08 MALDI avg mass
31		**12p′**	4675.5	4677.61 MALDI avg mass
32	**11q**	**12q**	4689.5	4692.50 MALDI avg mass
33		**12q′**	4689.5	4692.19 MALDI avg mass
34	**11r**	**12r**	4689.5	4691.67 MALDI avg mass
35		**12r′**	4689.5	4691.923 MALDI avg mass
36	**11s**	**12s**	4675.5	4678.08 MALDI avg mass
37		**12s′**	4675.5	4676.83 MALDI avg mass
38	**11t**	**12t**	4821.5	4823.24 MALDI avg mass
39		**12t′**	4821.5	4822.67 MALDI avg mass
40	**11u**	**12u**	4882.5	4885.59 MALDI avg mass

41		**12u'**	4882.5	4884.70 MALDI avg mass
42	**11v**	**12v**	4884.5	4887.54 MALDI avg mass
43		**12v'**	4884.5	4887.74 MALDI avg mass
44	**11w**	**12w**	4858.5	4861.08 MALDI avg mass
45		**12w'**	4858.5	4861.73 MALDI avg mass

CD analysis

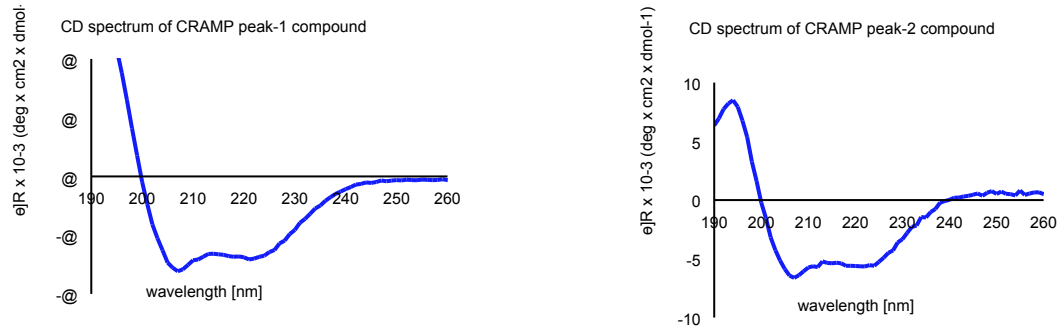


Figure 3. CD Spectrum of the compounds in TFE (Trifluoroethanol) corresponding with peak 1 and peak 2 in the LCMS chromatogram of CRAMP **2**.

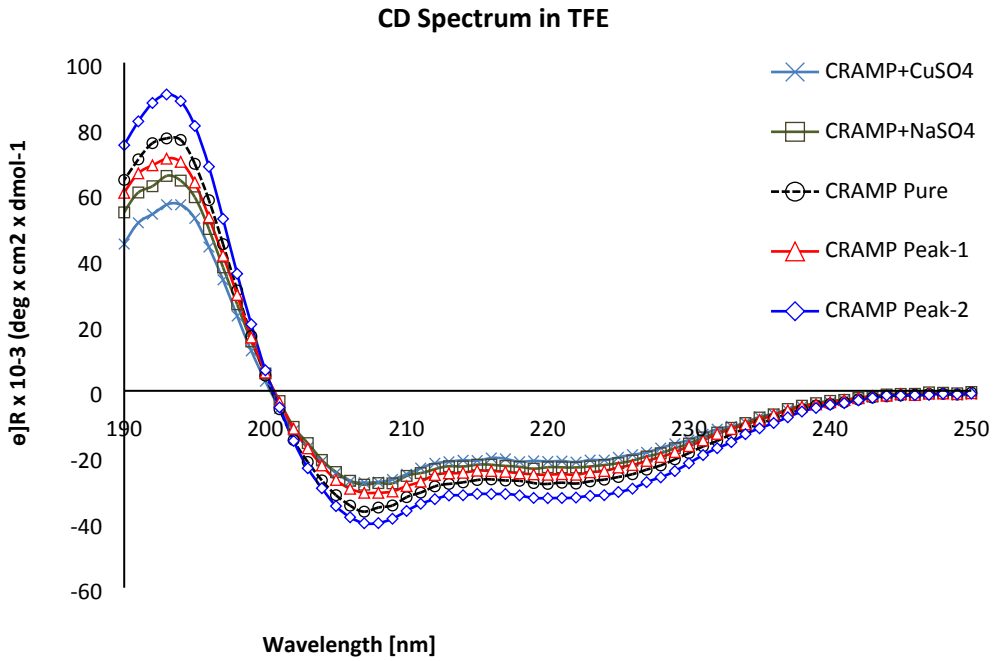


Figure 4a: CD spectra of CRAMP **2** with; i) compound isolated from peak-1 and peak-2 generated upon the treatment of CRAMP with $CuSO_4 \cdot 5H_2O$, ii) CRAMP + $CuSO_4 \cdot 5H_2O$ and iii) CRAMP + Na_2SO_4, respectively in TFE.

Conditions for sample preparation: solution of i) CRAMP (5 mg) + CuSO4·5H_2O and ii) CRAMP (5 mg) + Na_2SO_4 was prepared by stirring corresponding sulphate salts (3.0 equiv) with CRAMP at 40 °C in 1 mL water for 20h.

- For CD measurements in TFE, 10 µL of this prepared solution was diluted to 400µL with TFE.
- For CD measurements in water, 10 µL of this prepared solution was diluted to 400µL with milliQ water.

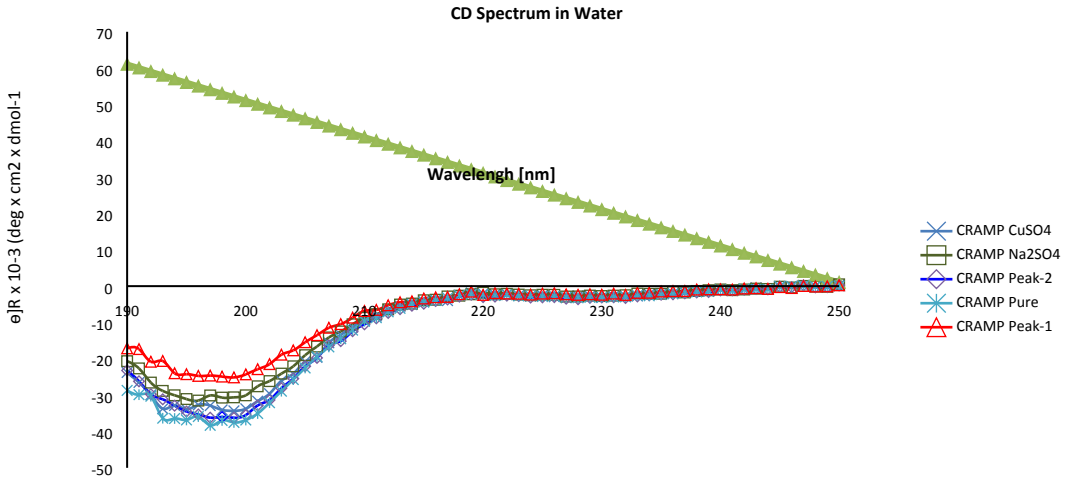


Figure 4b: CD spectra of CRAMP **2** with; i) compounds isolated from peak-1 and peak-2 generated upon the treatment of CRAMP with $CuSO_4$·5H_2O, ii) CRAMP + $CuSO_4$·5H_2O and iii) CRAMP + Na_2SO_4, respectively in water.

Determination of the enantiomeric purity of the amino acids of peptides.

Method (provided by C.A.T. GmbH & Co., Germany)

The method for the determination of the enantiomeric purity of amino acid residues in peptides involves the hydrolysis in 6N HCl/H_2O. It follows suitable derivatization of the free amino acids and gas chromatographic separation of the enantiomers on chirasil Val or cyclodextrine derivatized columns. During hydrolysis and cleavage however, racemization occurs and the amount of racemate determined represents the sum of racemate originally present in the peptide plus that generated during acidolysis. To determine the enantiomeric purity of the amino acids before hydrolysis, amino acids racemized during sample preparation are labeled by deuterion.

The peptide or amino acid derivative is hydrolysed in 6N DCl/D_2O whereby racemisation is accomplished by deuterium exchange in the α-C position. If necessary, antioxidant or scavenger is added and/or labile deuteriums are exchanged against hydrogens. The amino acids are derivatized using achiral reagents in order to get volatile derivatives. The enantiomers are gas chromatographically separated on chiral capillary using EI SIM mass spectrometry for detection. The relative amounts of D- and L enantiomers originally present in the sample (before hydrolysis) are determined by monitoring the non-deuterated molecular ions or suitable fragment ions of both enantiomers.

Sample preparation.

Fmoc and DNP protective groups are cleaved using piperidine/DCM and thiophenol/DMF respectively, if present. About 1 mg of the peptide/amino acid derivative is hydrolyzed in 6N DCl (0.3-0.5 mL) in D_2O for 8-24h at 110 °C. If necessary an antioxidant/scavenger is added. After removal of excess of reagent in speed-vac or by a stream of nitrogen, the sample is esterified with deuteron chloride-ethyl alcohol (300-500 µL, 3N) for 20 min at 110 °C. In accordance to the column specification homologue alcohols are possible. After cooling to about 50 °C the vial is opened and the reagent is evaporated

with a gentle stream of nitrogen at moderate temperature. The residue is dissolved in triflouroacetic anhydride/ethyl trifluoroacetate (1:2; 250-300 µL) or pentafluoropropionic acid anhydride/ DCM (1:9). The vial is tightly closed and heated for 10 min to 130-140 ^{o}C. After cooling to rt, the excess of reagent was removed by a stream of nitrogen. The residue is dissolved in a suitable solvent (150 µL) and injected. If histidine is to be determined, 50 µL isopropyl or butyl chloroformate are added to the sample and the vial is heated to 110 ^{o}C for 10 min, and again the excess of reagent was removed by a stream of nitrogen. The residue is dissolved in a suitable solvent (150 µL) and injected.

Chromatographic conditions.

Gas chromatograph: GC HP 6890 or equivalent

Mass spectrometer: HP 5973 or equivalent

Column: 0.28 µm chiral capillary

Detector: mass selective detector

Injector: Split injector

Injection: 0.5 µL

Carrier gas: Hydrogen

Flows: Carrier gas 1.5 mL/min, Split: 35 mL, Purge 4 mL/min

Temperatures: Injector: 190 ^{o}C

Oven 65 ^{o}C isotherm for 3 min, 4 ^{o}C/min to 190 ^{o}C

Calculation of the enantiomeric purity.

Equation:

$\%D = (Area_D/Area_D + Area_L) \times 100$

-The limit of quantitation was 0.1% of the optical antipode.

-The standard deviation was <0.1%.

The following impurity of optical antipode (enantiomer) was found in compounds corresponding to peak-1 & 2 of CRAMP **2** (Table 7).

Table 7. Enantiomeric purity of CRAMP peak-1 compound.

Amino acid	Percentage of impurities Peak 1	Percentage of impurities Peak 2
Valine	0.28% D-Enantiomer	0.21% D-Enantiomer
Isoleucine	< 0.10% D-Isoleucine 0.17% L-allo-Isoleucine < 0.10% D-allo-Isoleucine	< 0.10% D-Isoleucine 0.10% L-allo-Isoleucine < 0.10% D-allo-Isoleucine
Proline	< 0.10% D-Enantiomer	< 0.10% D-Enantiomer
Leucine	< 0.10% D-Enantiomer	< 0.10% D-Enantiomer
Aspartic acid	0.43% D-Enantiomer	0.49% D-Enantiomer
Glutamic acid	< 0.10% D-Enantiomer	< 0.10% D-Enantiomer
Phenyl alanine	0.10% D-Enantiomer	< 0.10% D-Enantiomer
Lysine	< 0.10% D-Enantiomer	< 0.10% D-Enantiomer

AFM analysis.

Protocol: First mica was freshly cleaved. Next, the peptide solutions (1mg/ml) were 2000 times diluted to a final concentration of 0.5ng/µl. 10µl of this solution was deposited on the freshly cleaved mica and allowed to incubate for 30 seconds. The surface was subsequently rinsed by 50µl Milli-Q water and blown dry with N_2.

Images were recorded with tapping mode on a multimode AFM with a nanoscope IV controller (Veeco/Digital Instruments, Santa Barbara, USA). Conditions were chosen so that the tapping was as gently as possible. Typicaly, images of one by one micrometer were recorded with 1024 by 1024 pixels. Images analysis was carried out by making use of the Scanning Probe Imaging Processor (version 6.0.2., Image Metrology A/S, Hørsholm, Denmark). Images were plane fitted and flattened using a second-order polynomial. The height and volume of particles with a height of at least 200 nm was subsequently calculated using this software.

Spectroscopic data

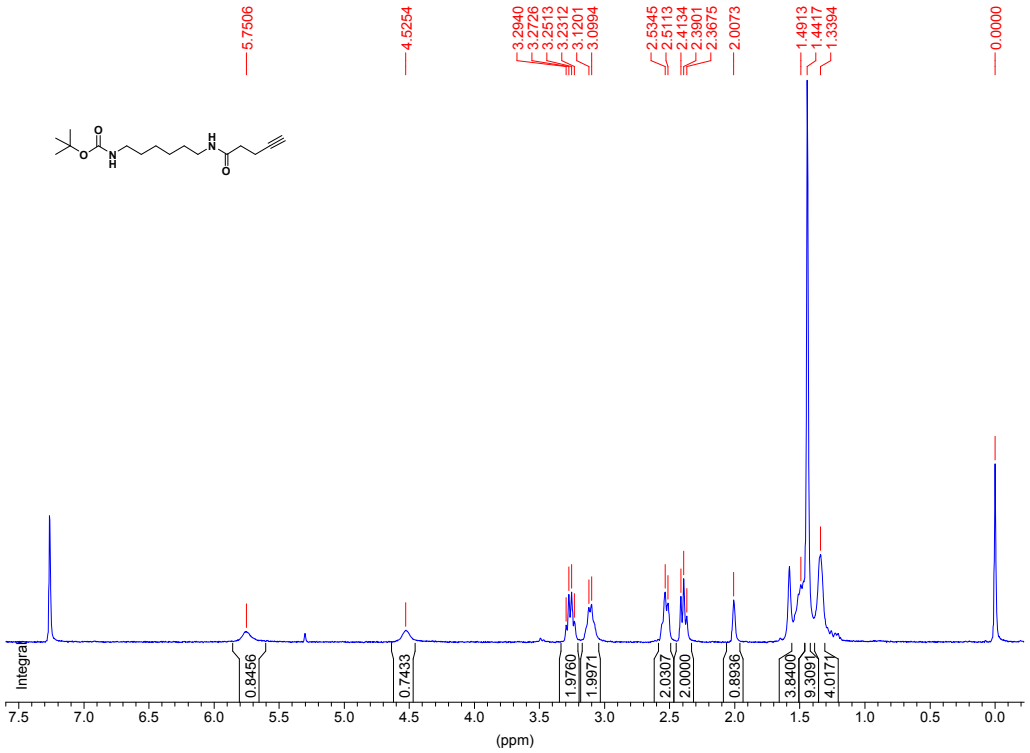


Figure 5: ^{1}H spectrum of compound **9b** (300 MHz, $CDCl_3$).

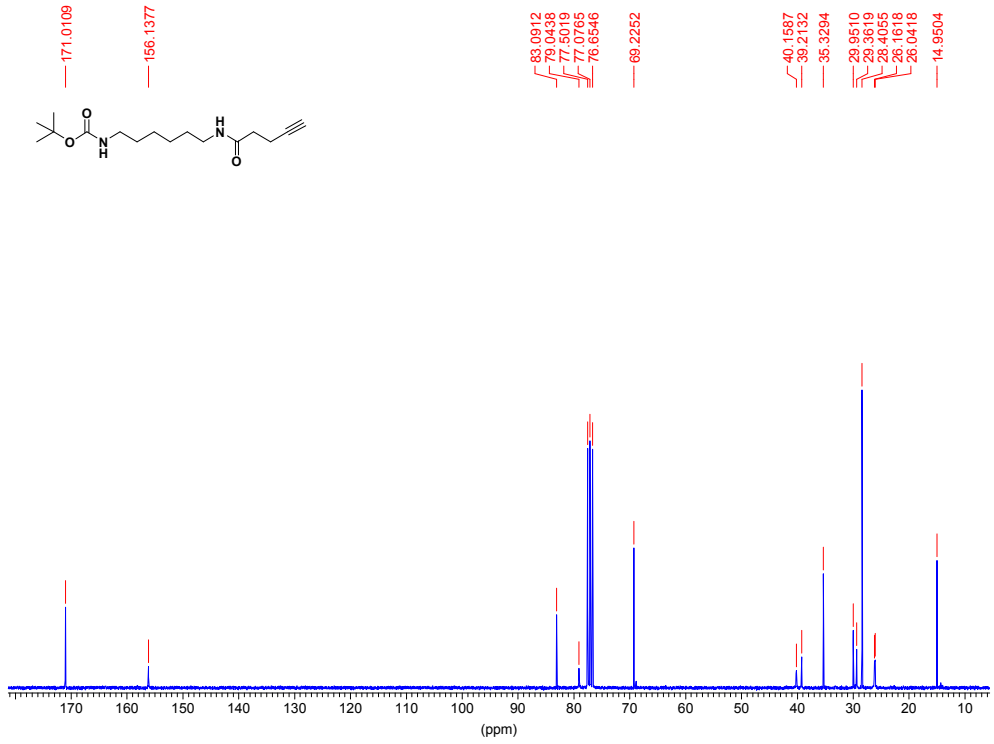


Figure 6: ^{13}C NMR spectrum of compound **9b** (300 MHz, $CDCl_3$).

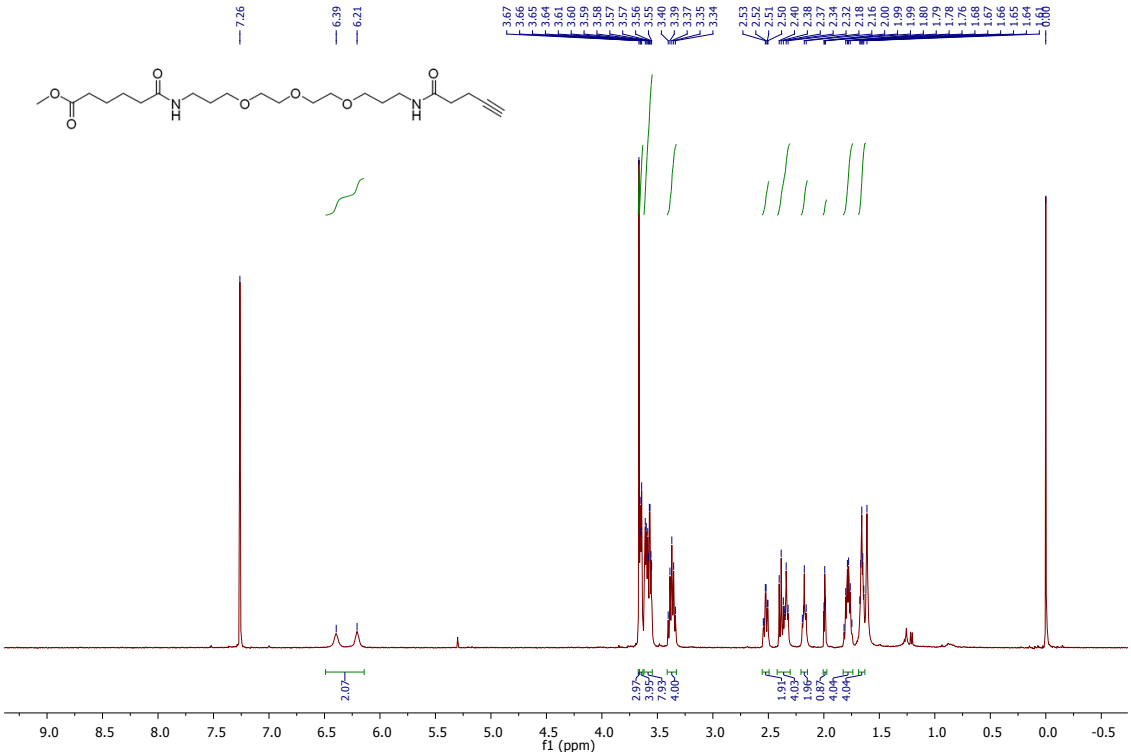


Figure 7: ^{1}H NMR spectrum of compound **10a'** (400 MHz, $CDCl_3$).

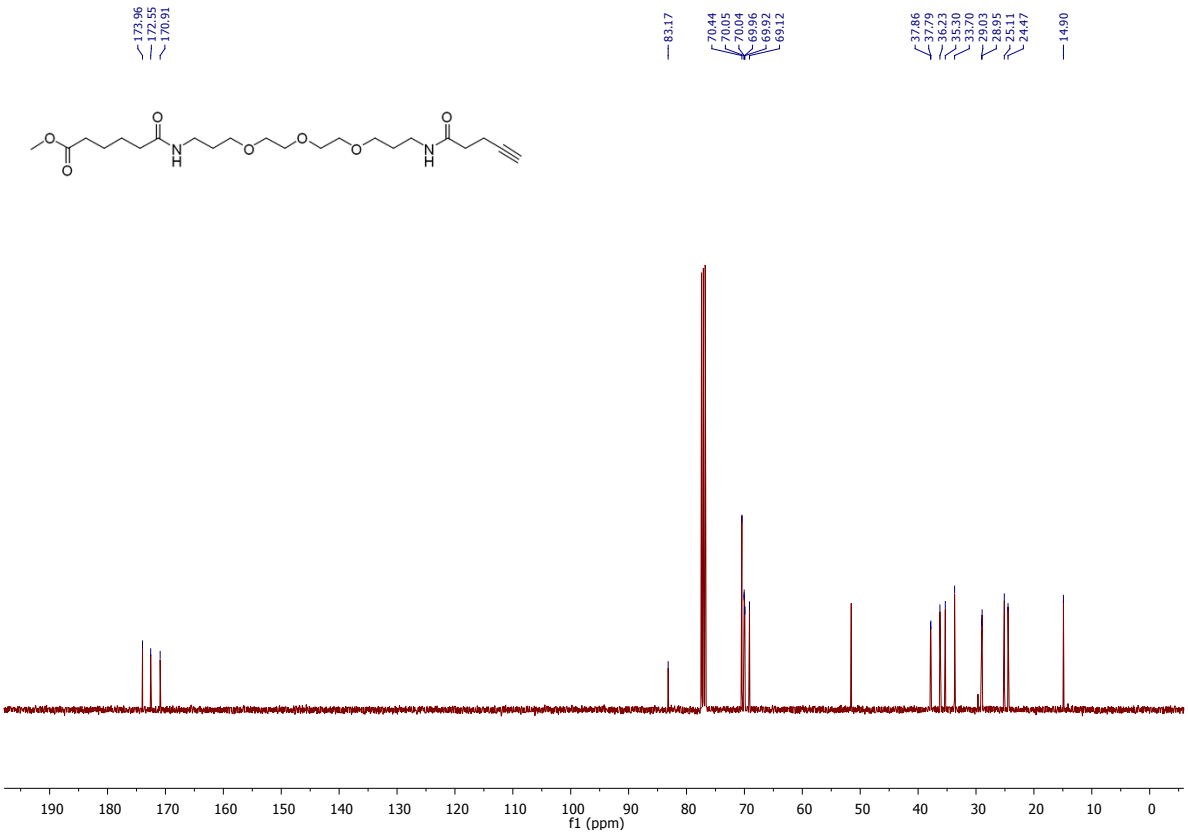


Figure 8: ^{13}C NMR spectrum of compound **10a'** (300 MHz, $CDCl_3$).

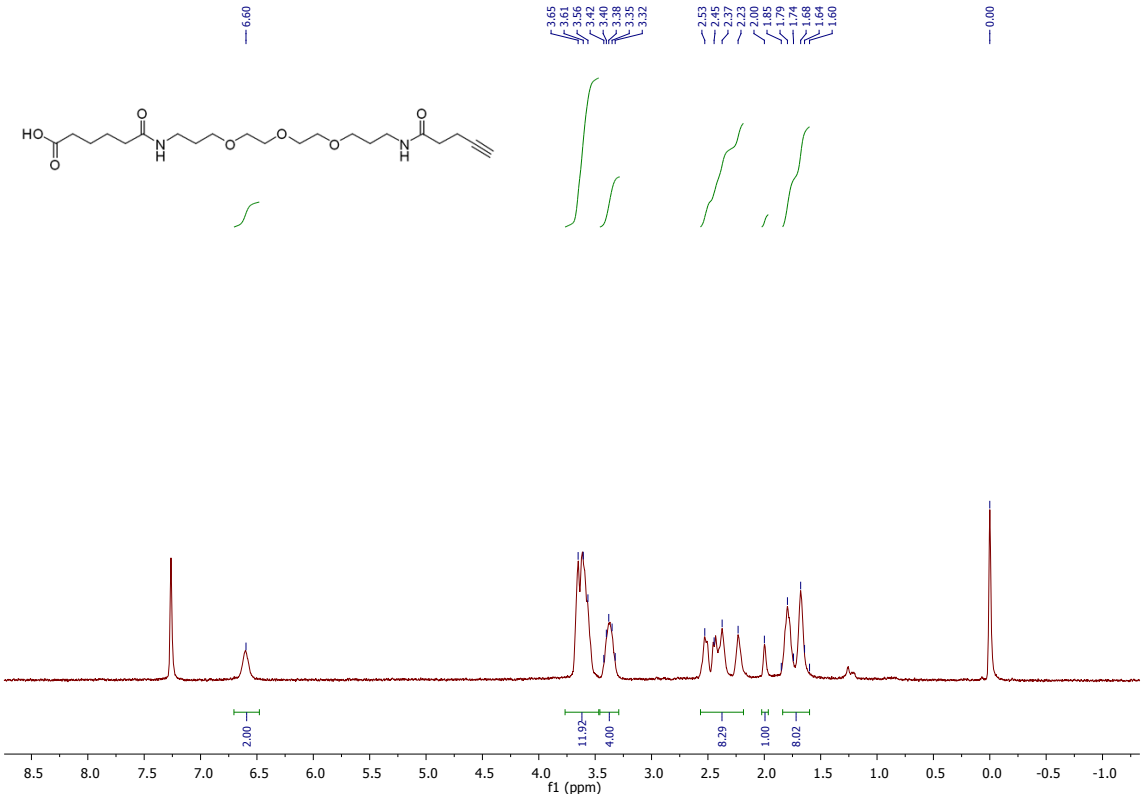


Figure 9: ^{1}H NMR spectrum of compound **10a"** (300 MHz, $CDCl_3$).

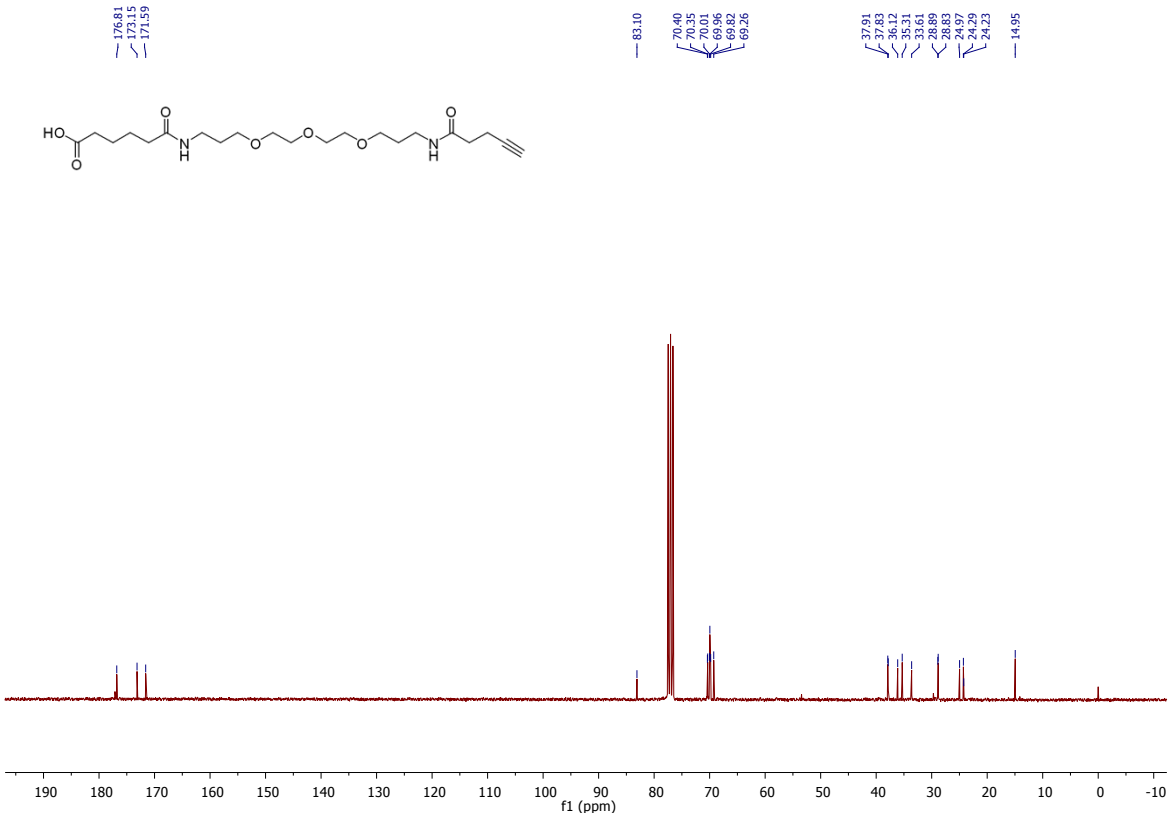


Figure 10: ^{13}C NMR spectrum of compound **10a"** (300 MHz, $CDCl_3$).

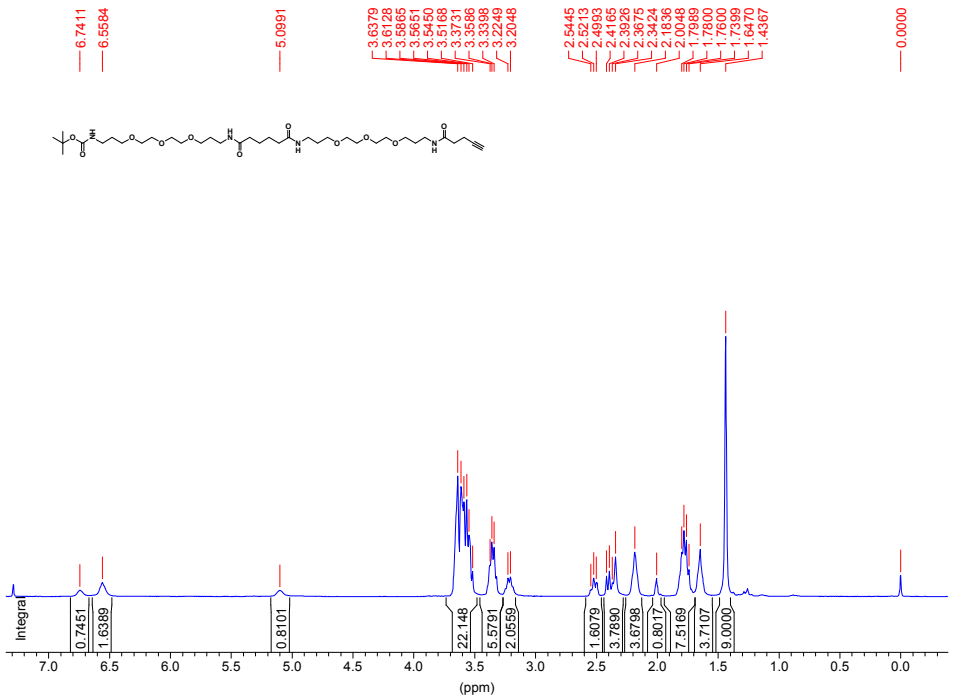


Figure 11: ^{1}H NMR spectrum of compound **9d** (300 MHz, $CDCl_3$).

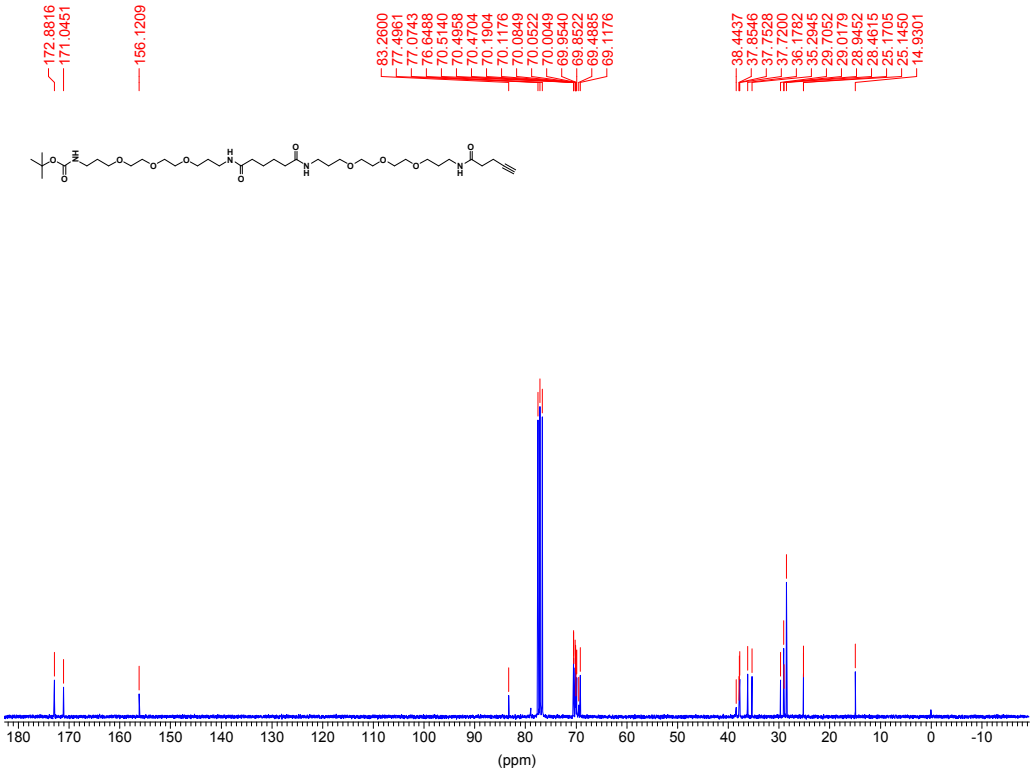


Figure 12: ^{13}C NMR spectrum of compound **9d** (300 MHz, $CDCl_3$).

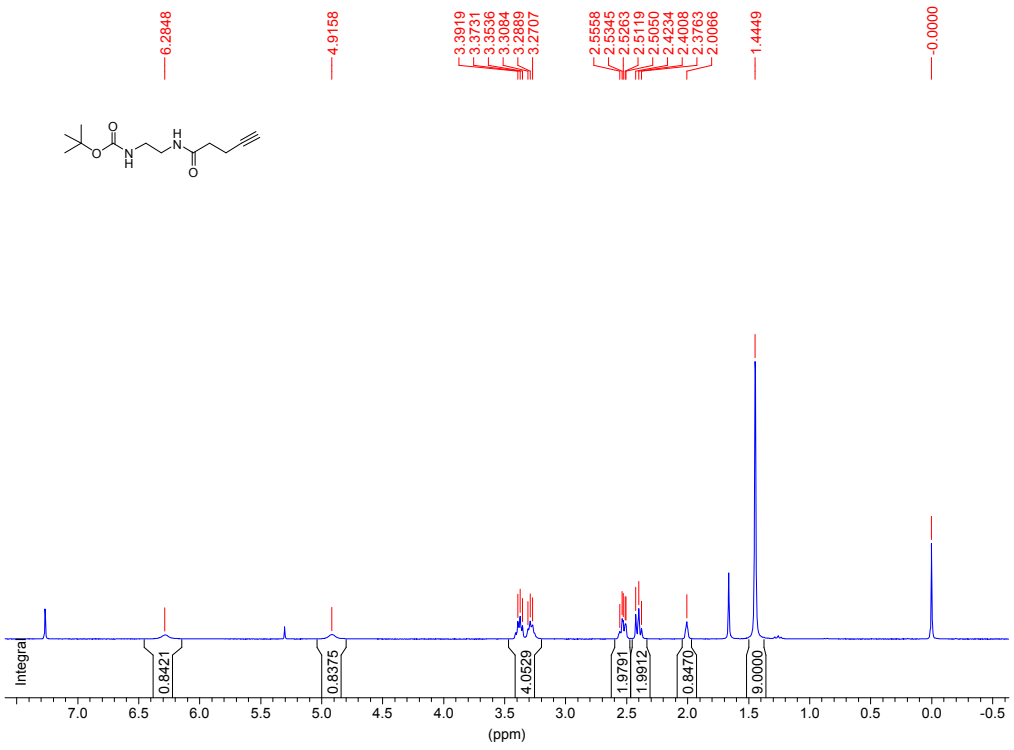


Figure 13: ^{1}H NMR spectrum of compound **9e** (300 MHz, $CDCl_3$).

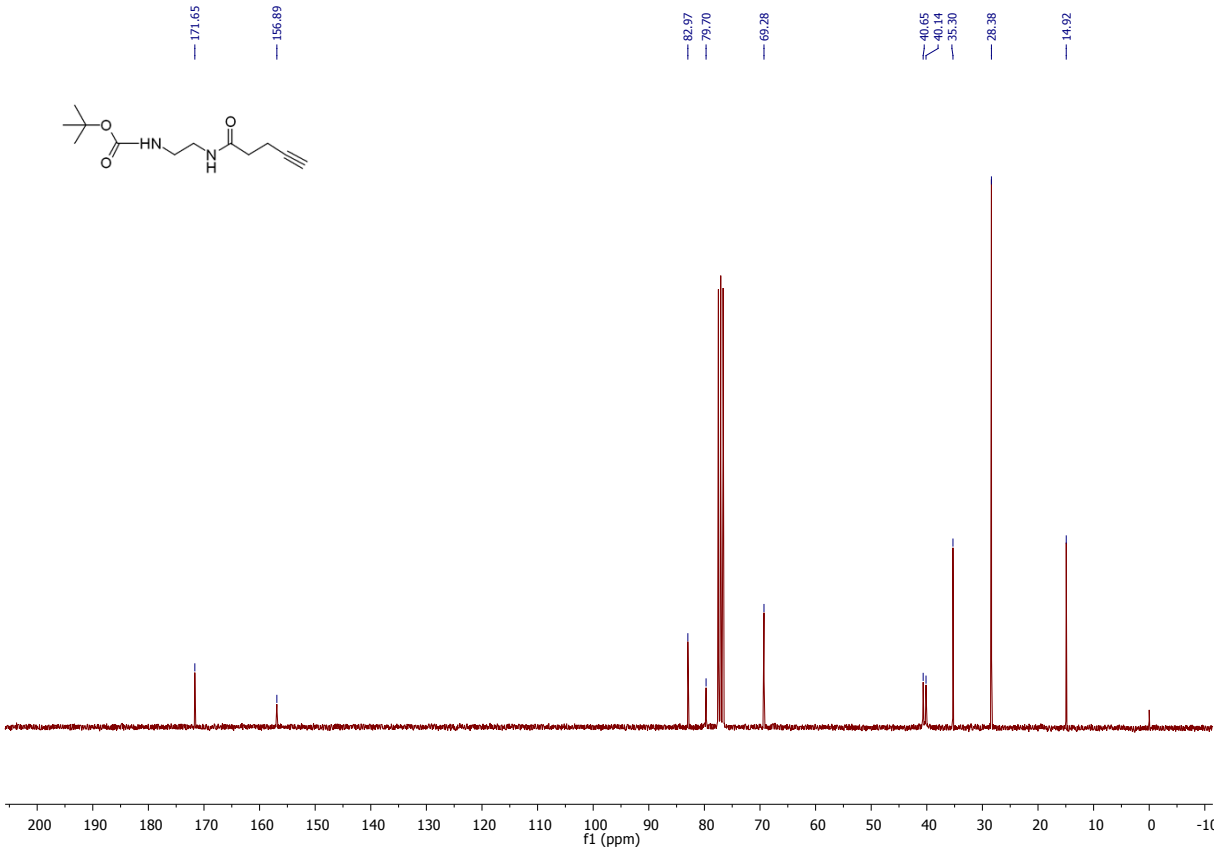


Figure 14: ^{13}C NMR spectrum of compound **9e** (300 MHz, $CDCl_3$).

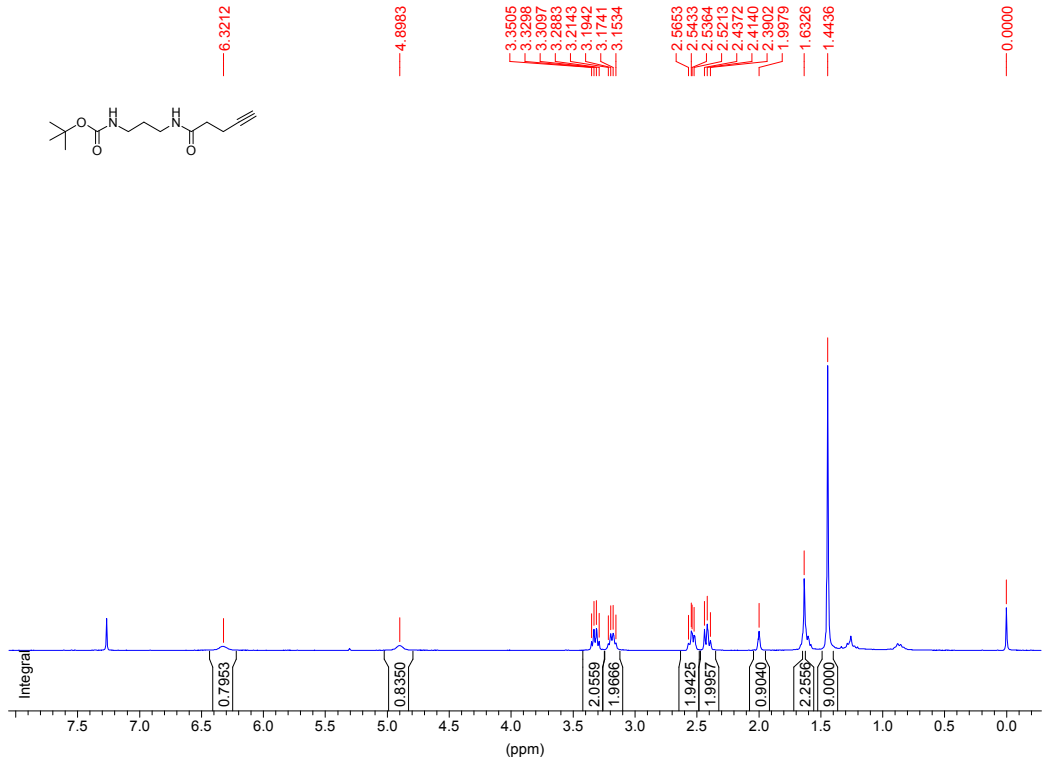


Figure 15: ^{1}H NMR spectrum of compound **9f** (300 MHz, $CDCl_3$).

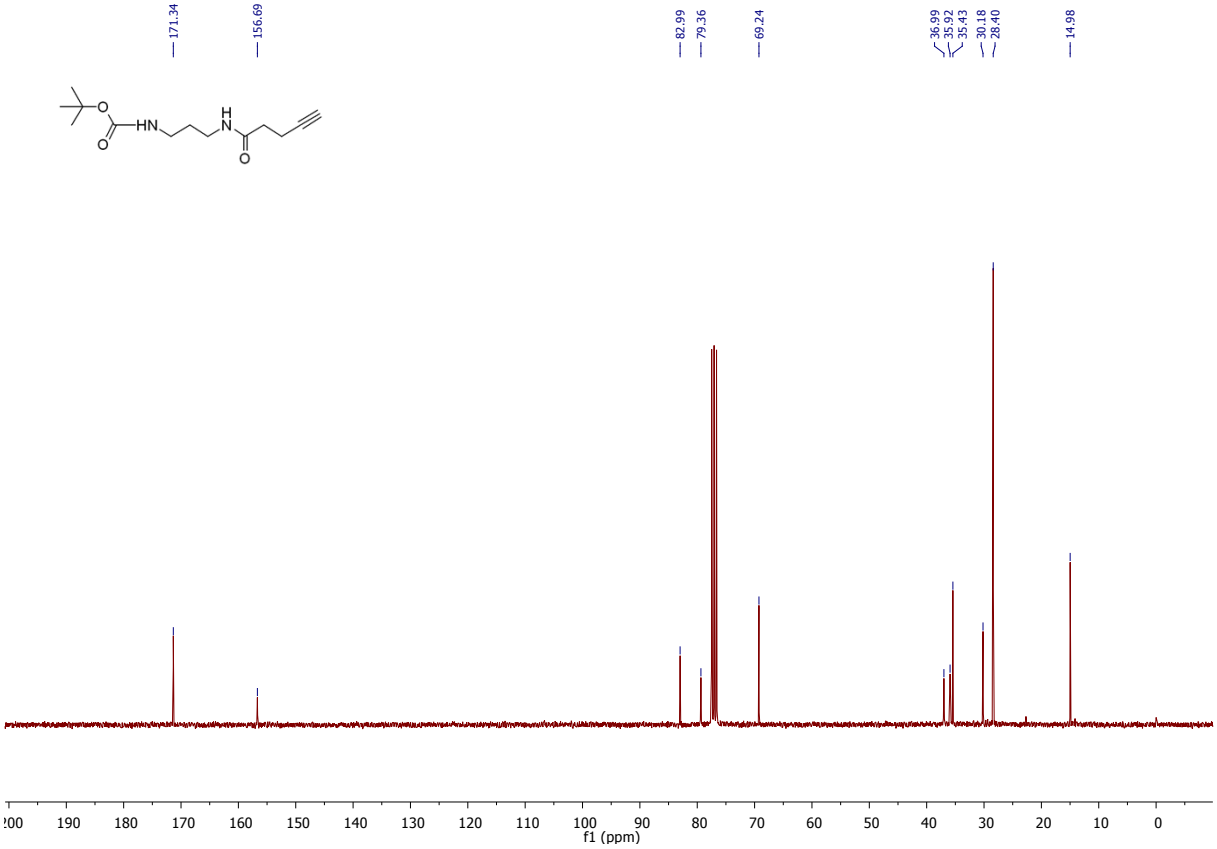


Figure 16: ^{1}H NMR spectrum of compound **9f** (300 MHz, $CDCl_3$).

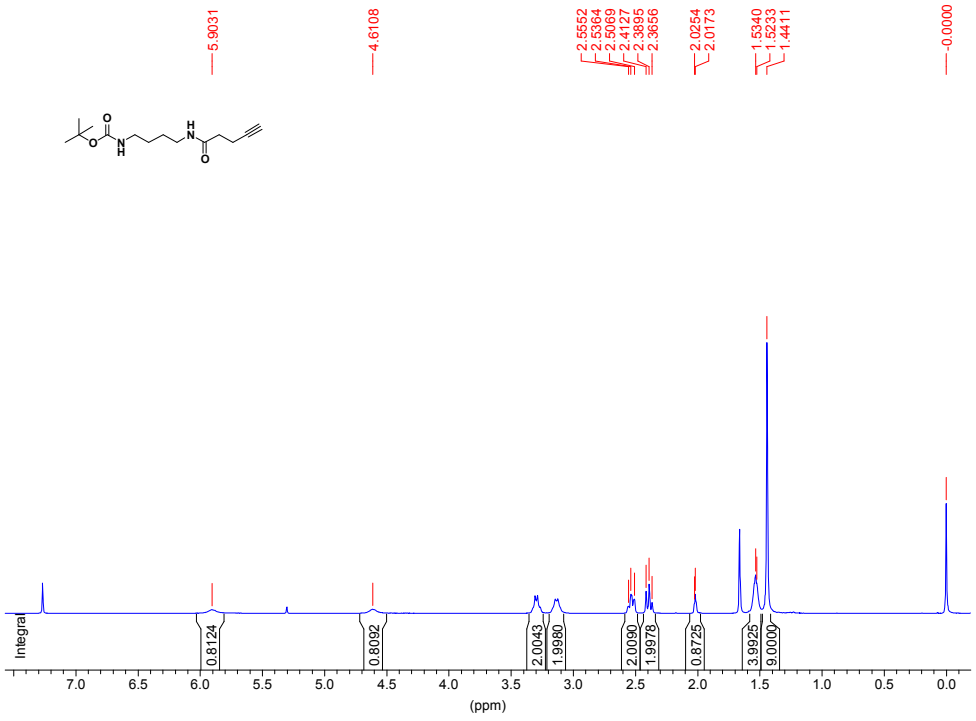


Figure 17: ^{1}H NMR spectrum of compound **9g** (300 MHz, $CDCl_3$).

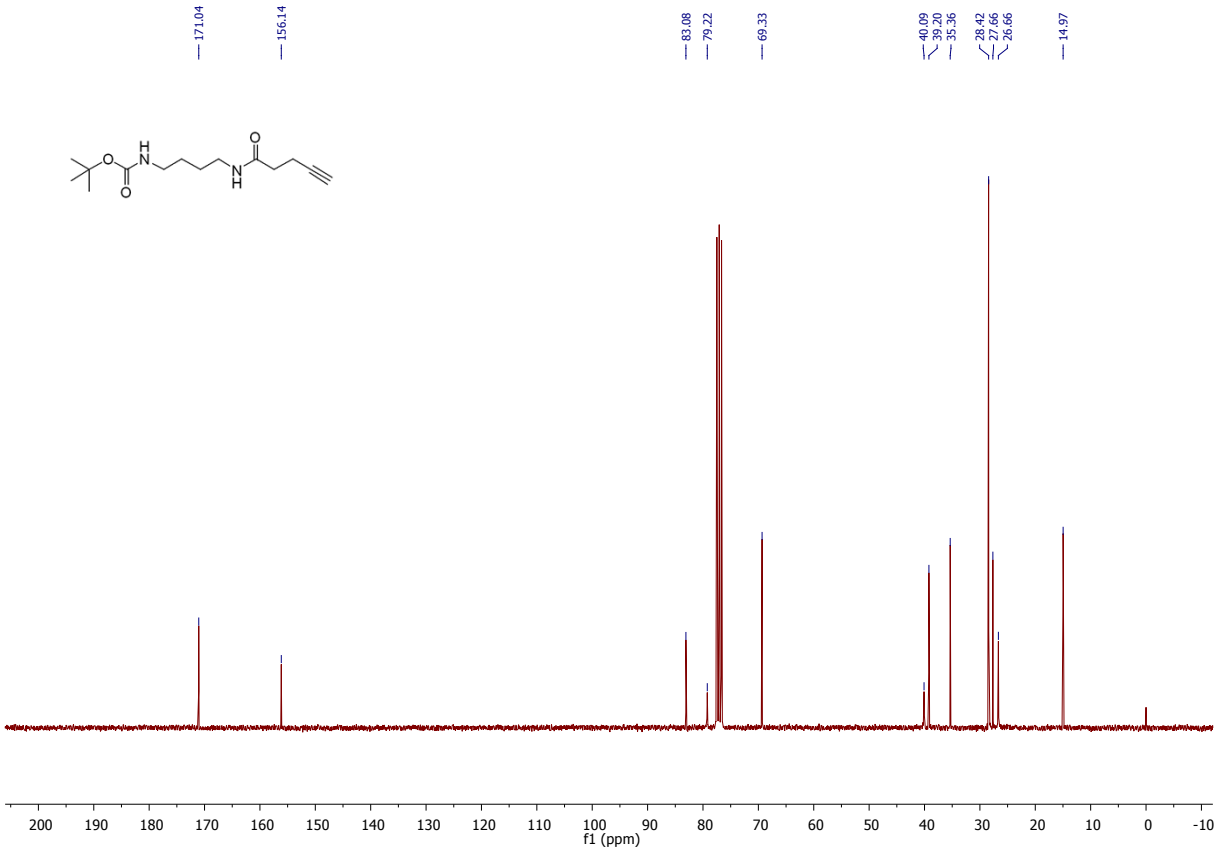


Figure 18: ^{13}C NMR spectrum of compound **9g** (300 MHz, $CDCl_3$).

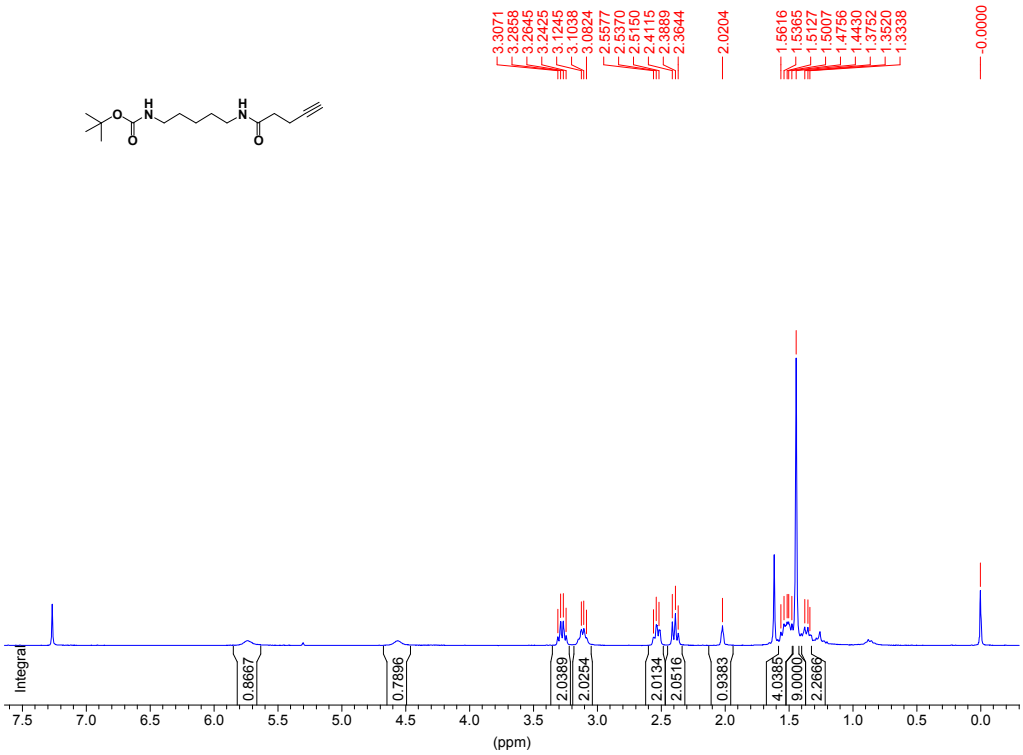


Figure 19: ^{1}H NMR spectrum of compound **9h** (300 MHz, $CDCl_3$).

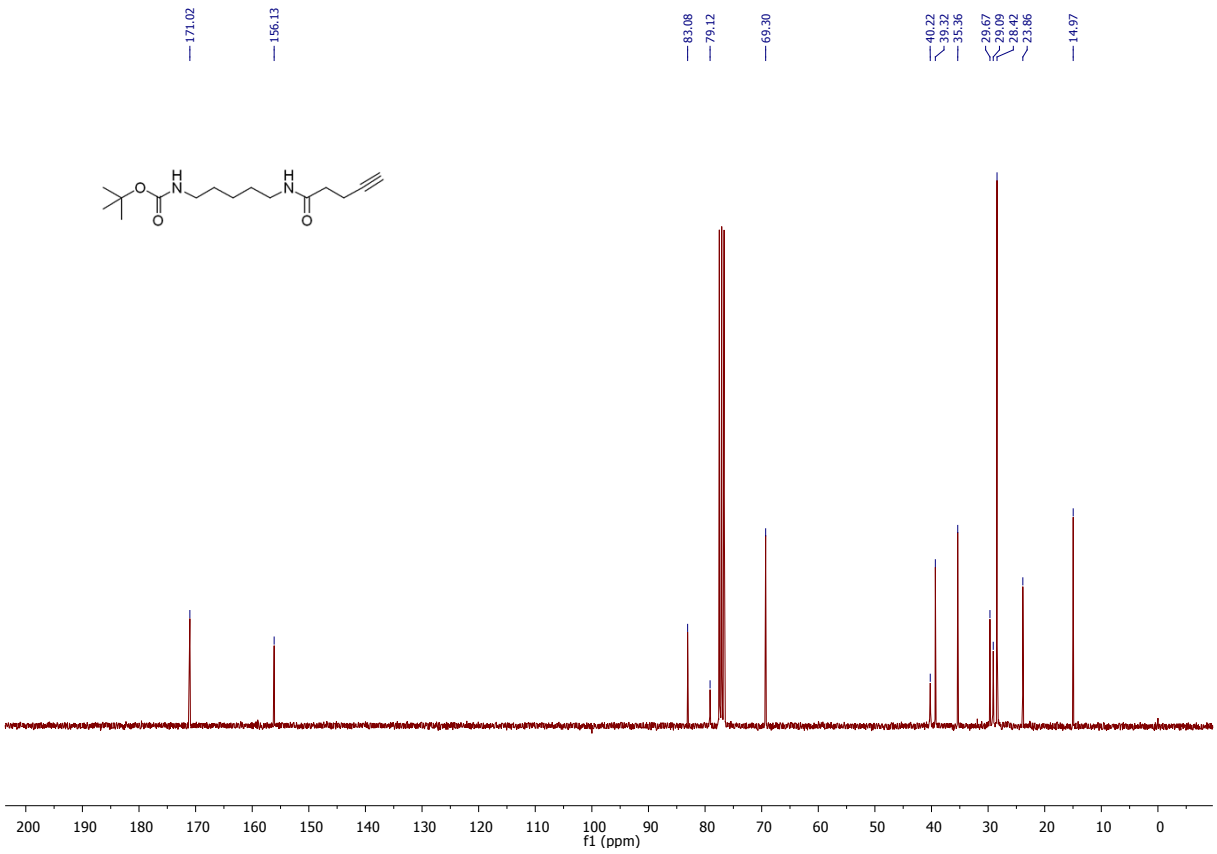


Figure 20: ^{13}C NMR spectrum of compound **9h** (300 MHz, $CDCl_3$).

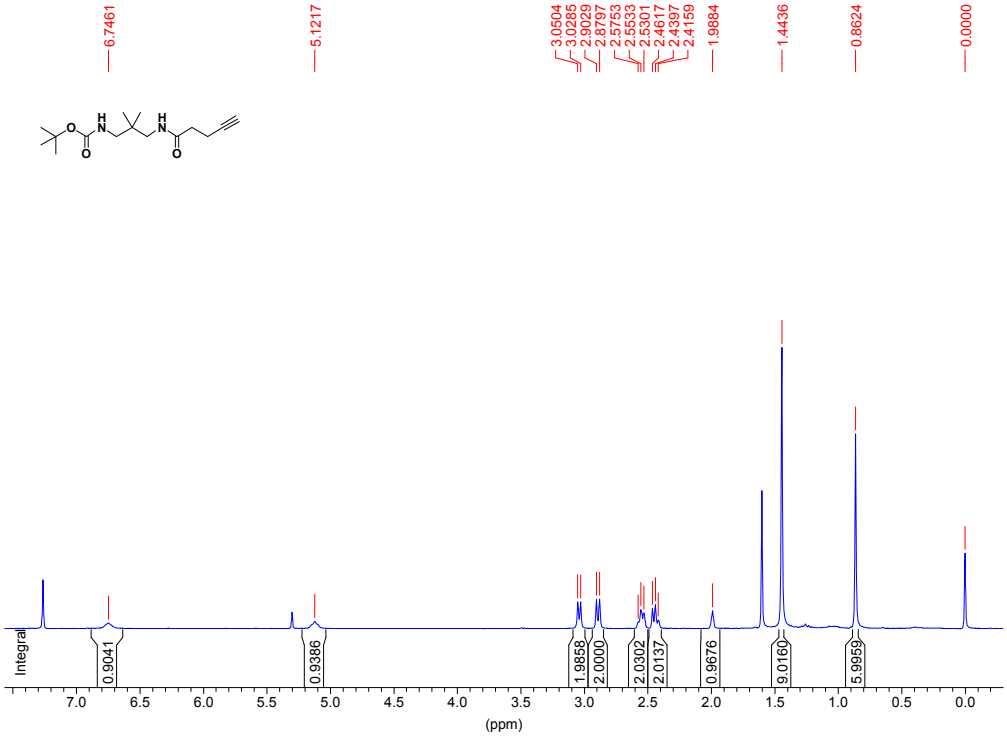


Figure 21: ^{1}H NMR spectrum of compound **9i** (300 MHz, $CDCl_3$).

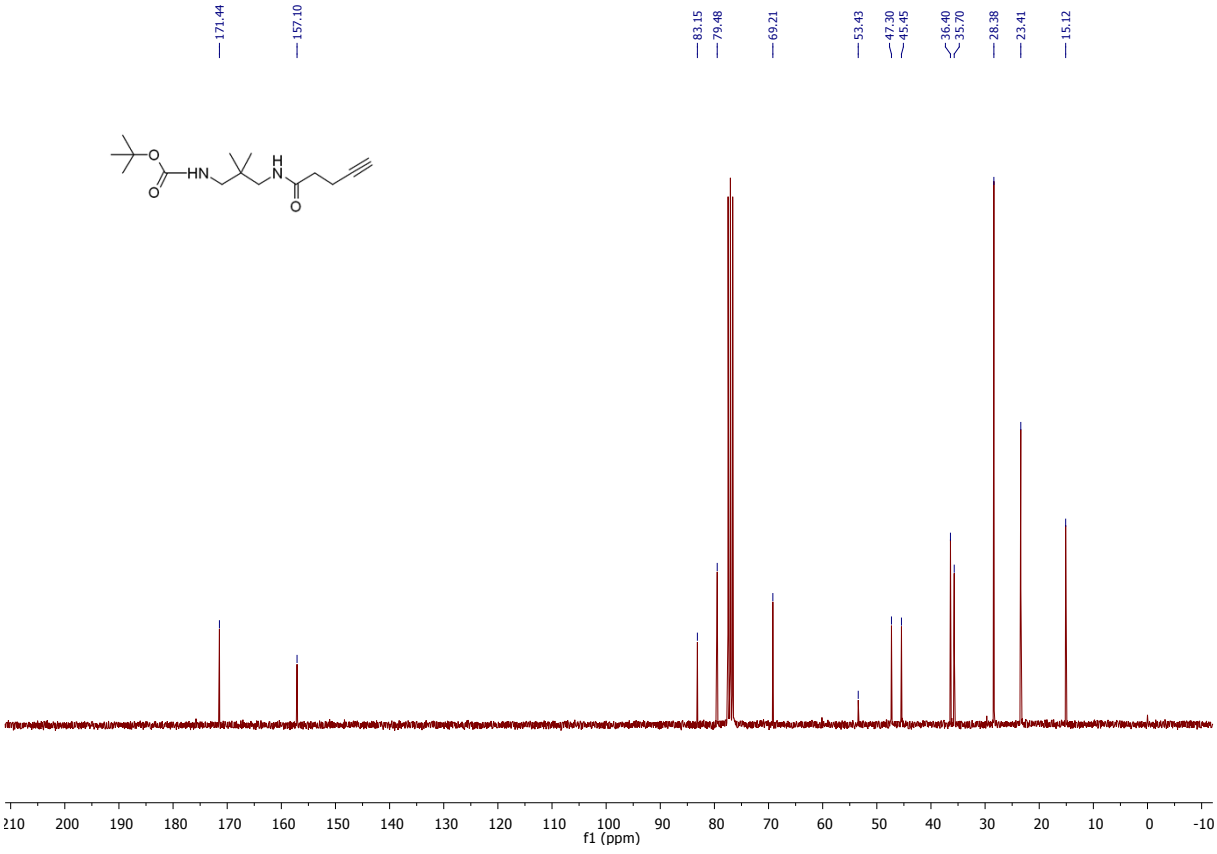


Figure 22: ^{13}C NMR spectrum of compound **9i** (300 MHz, $CDCl_3$).

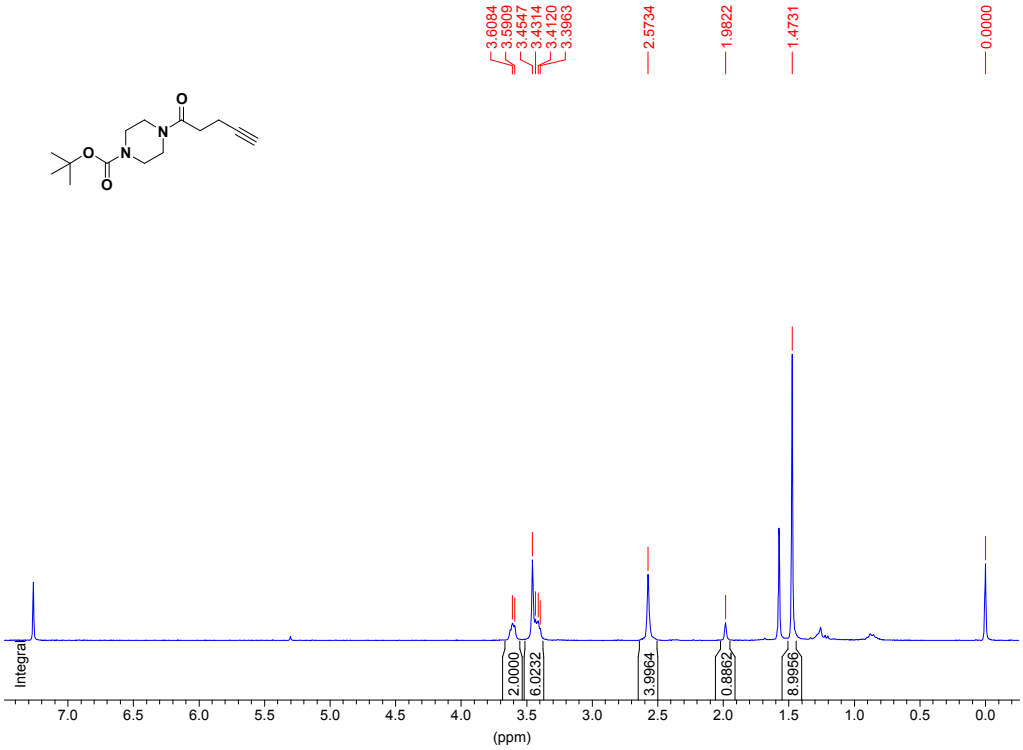


Figure 23: ^{1}H NMR spectrum of compound **9j** (300 MHz, $CDCl_3$).

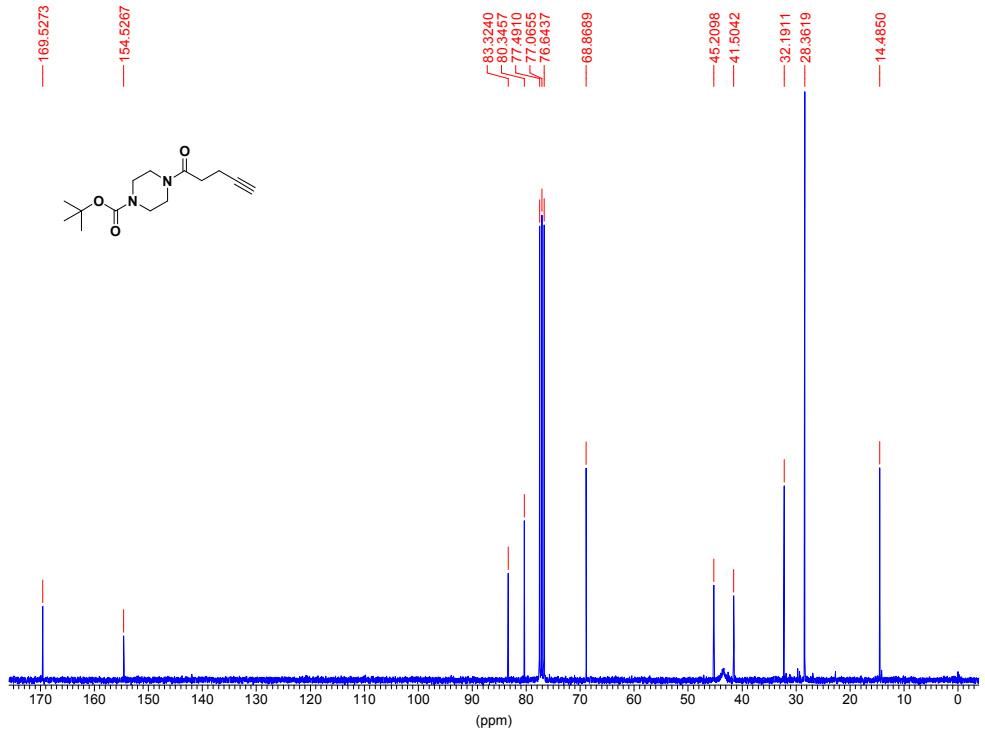


Figure 24: ^{13}C NMR spectrum of compound **9j** (300 MHz, $CDCl_3$).

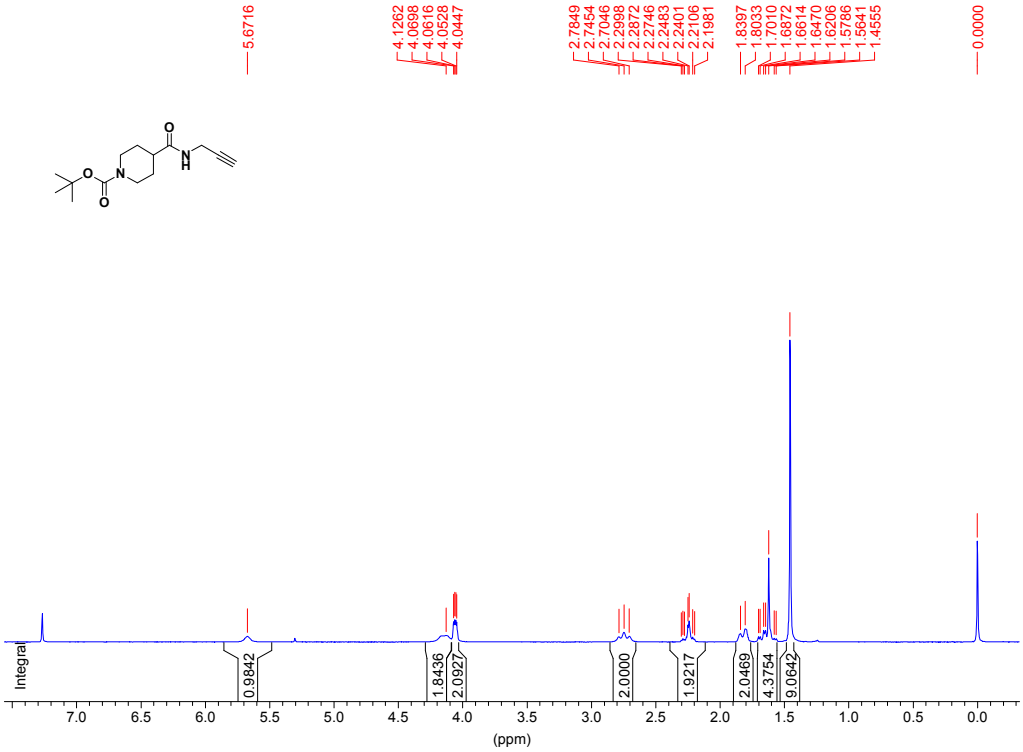


Figure 25: ^{1}H NMR spectrum of compound **9k** (300 MHz, $CDCl_3$).

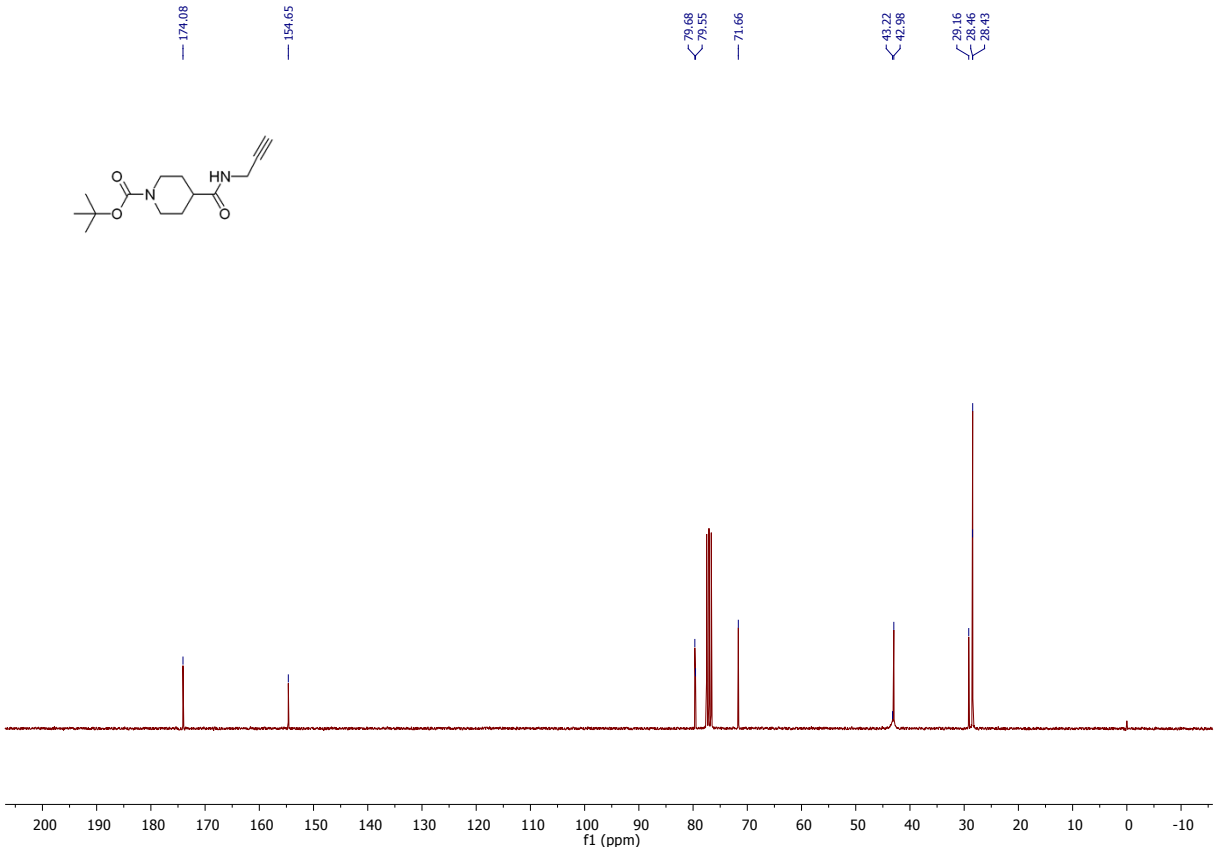


Figure 26: ^{13}C NMR spectrum of compound **9k** (300 MHz, $CDCl_3$).

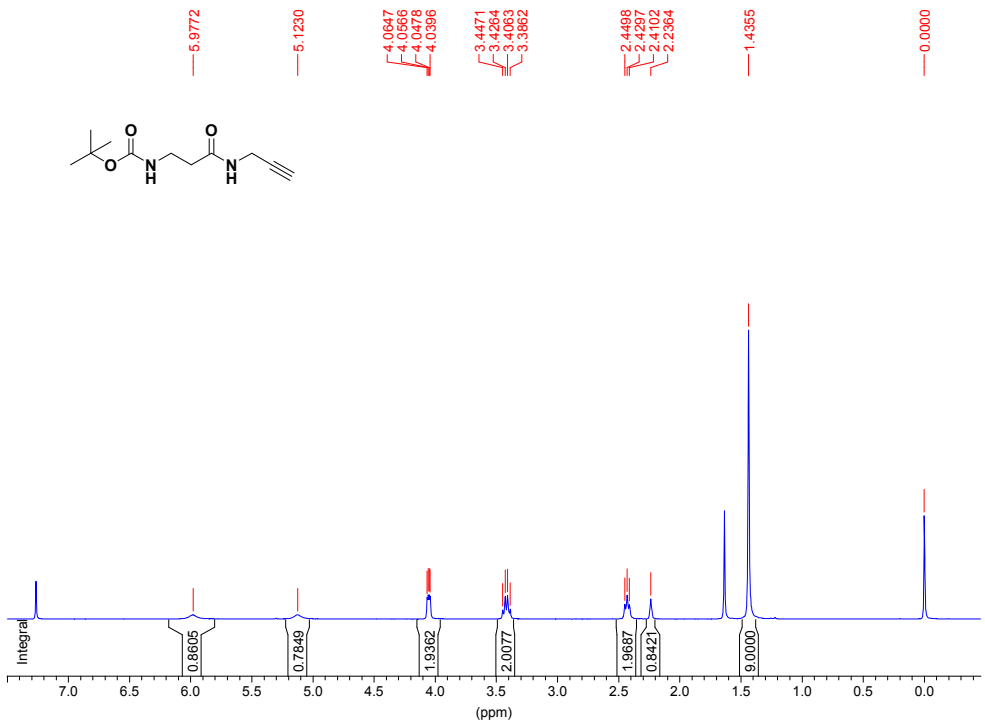


Figure 27: ^{1}H NMR spectrum of compound **9m** (300 MHz, $CDCl_3$).

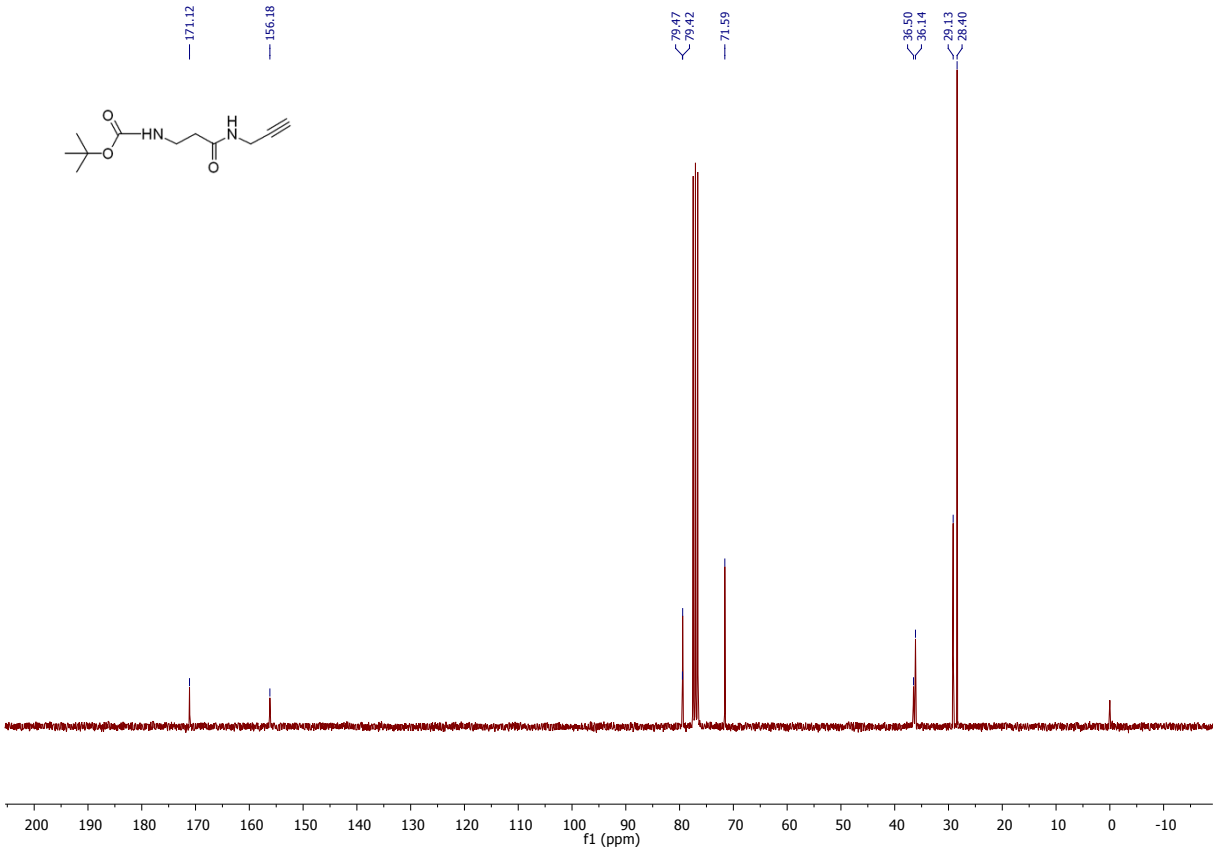


Figure 28: ^{13}C NMR spectrum of compound **9m** (300 MHz, $CDCl_3$).

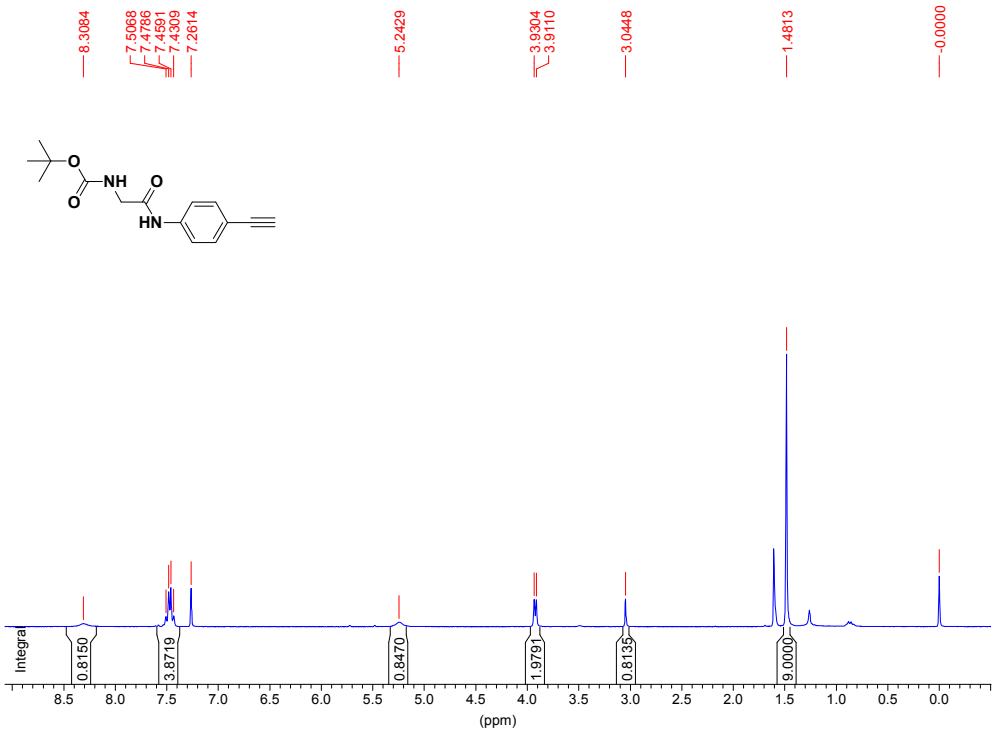


Figure 29: ^{1}H NMR spectrum of compound **9n** (300 MHz, $CDCl_3$).

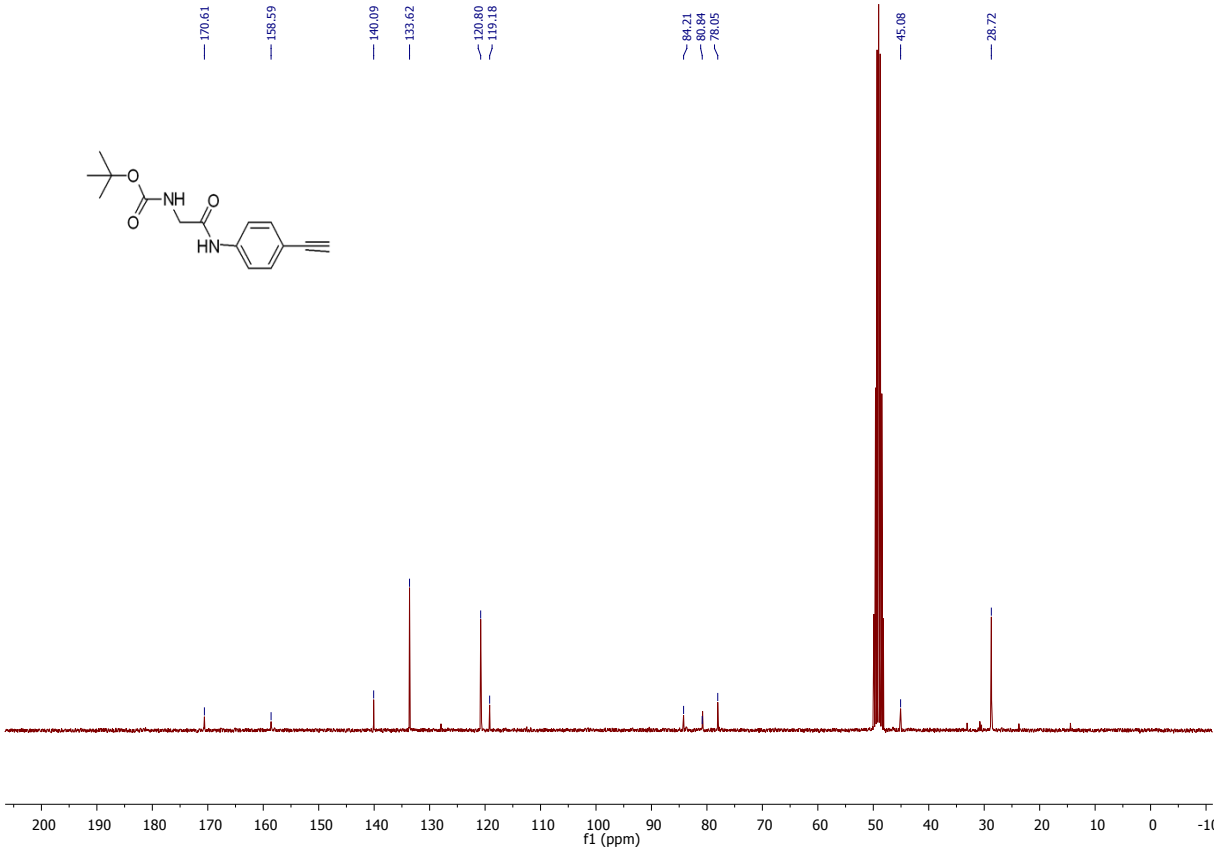


Figure 30: ^{13}C NMR spectrum of compound **9n** (300 MHz, MeOD).

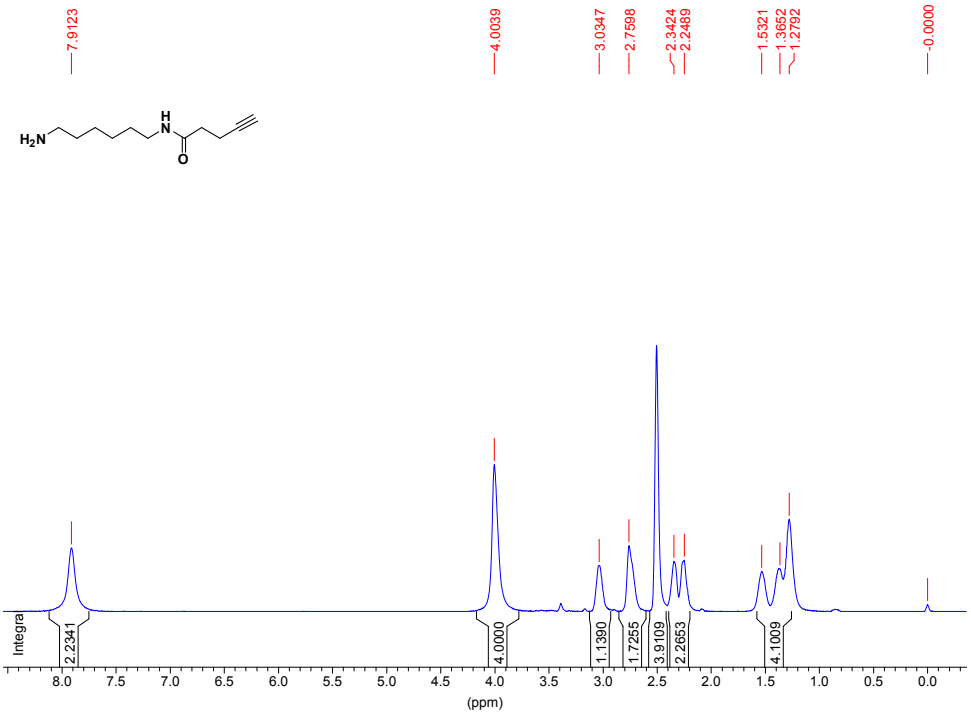


Figure 31: ^{1}H NMR spectrum of compound **10b** (300 MHz, DMSO-d_6).

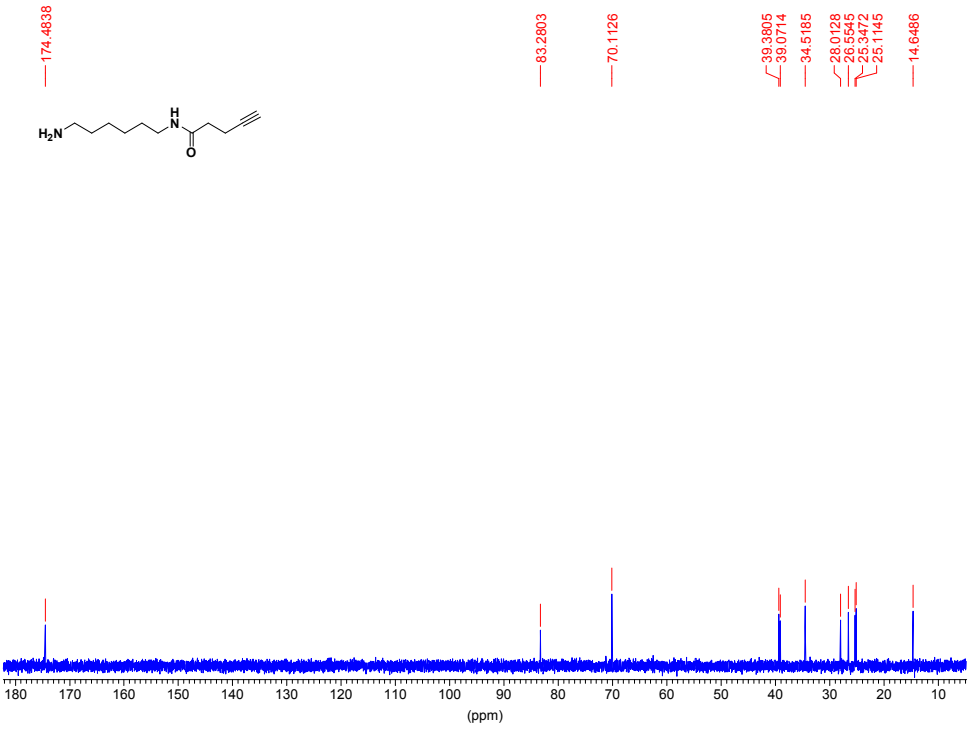


Figure 32: ^{13}C NMR spectrum of compound **10b** (300 MHz, DMSO-d_6).

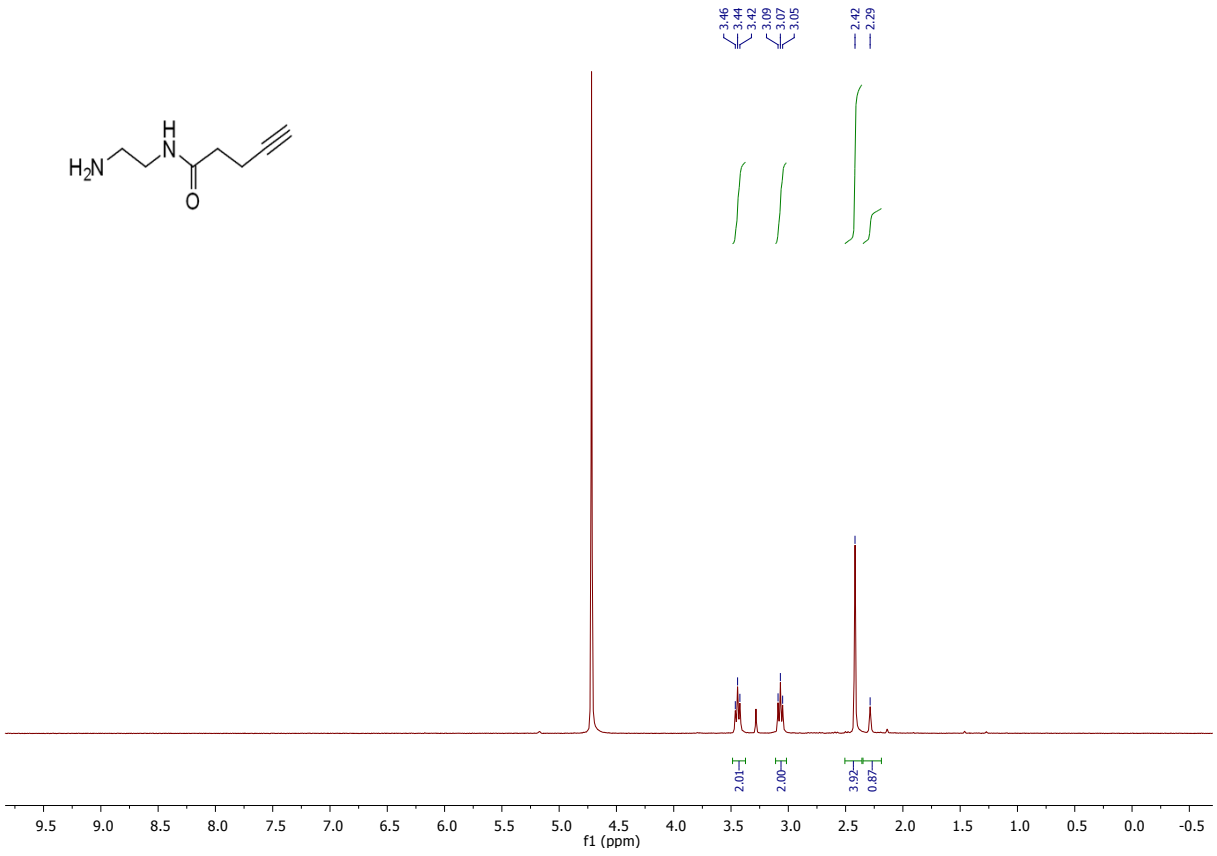


Figure 33: ^{1}H NMR spectrum of compound **10e** (300 MHz, D_2O).

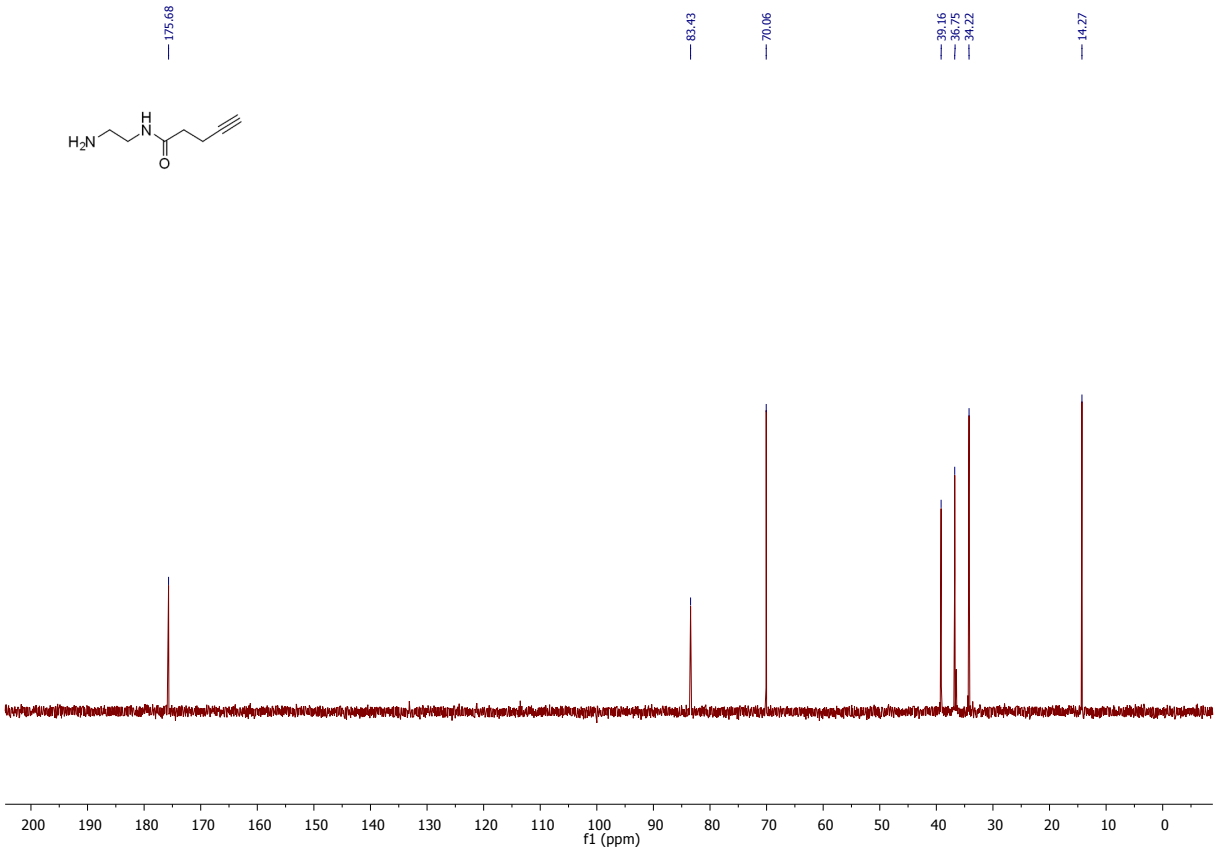


Figure 34: ^{13}C NMR spectrum of compound **10e** (300 MHz, D_2O).

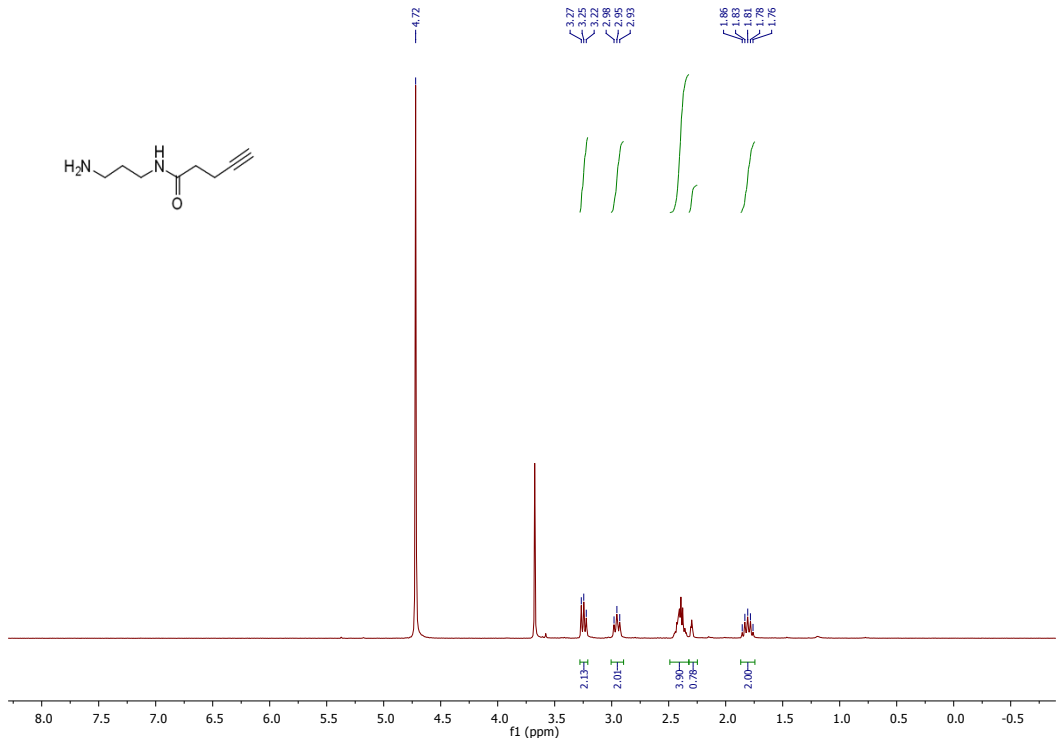


Figure 35: ^{1}H NMR spectrum of compound **10f** (300 MHz, D_2O).

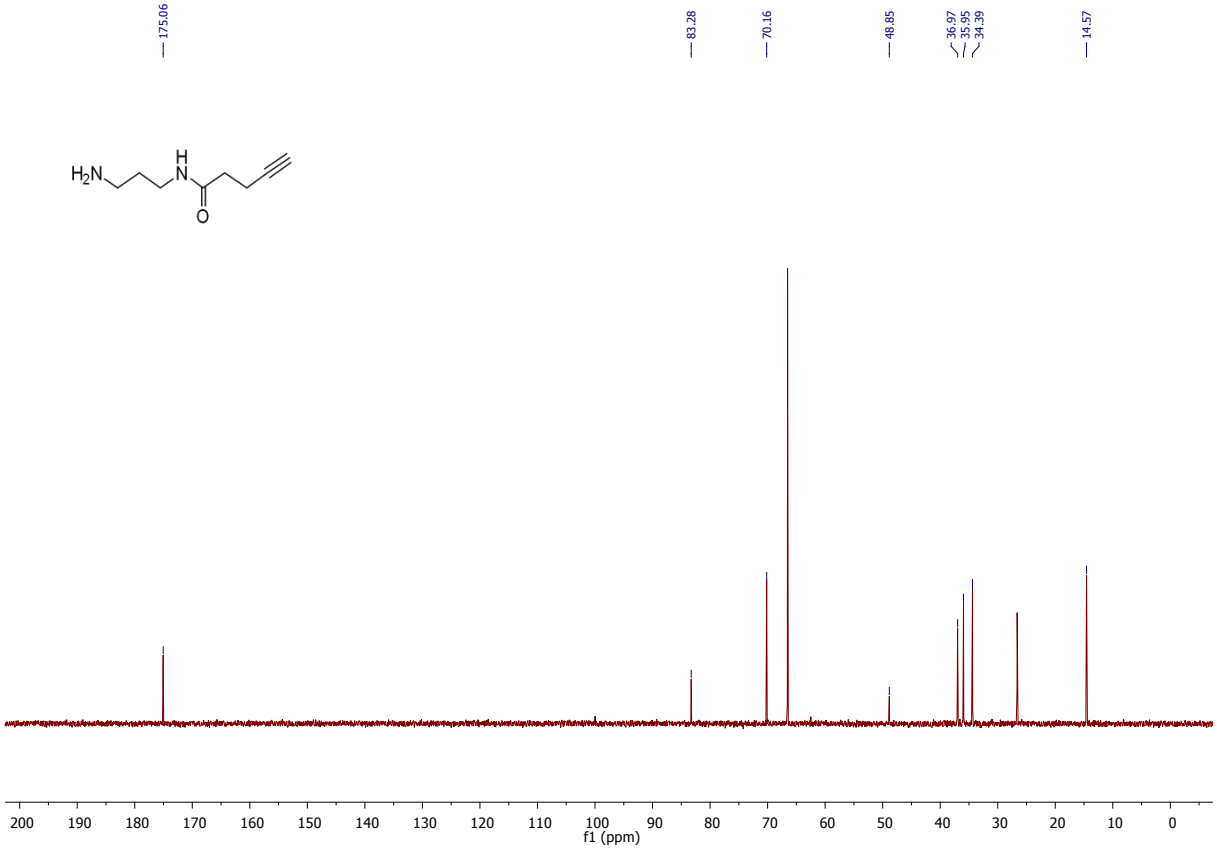


Figure 36: ^{13}C NMR spectrum of compound **10f** (300 MHz, D_2O).

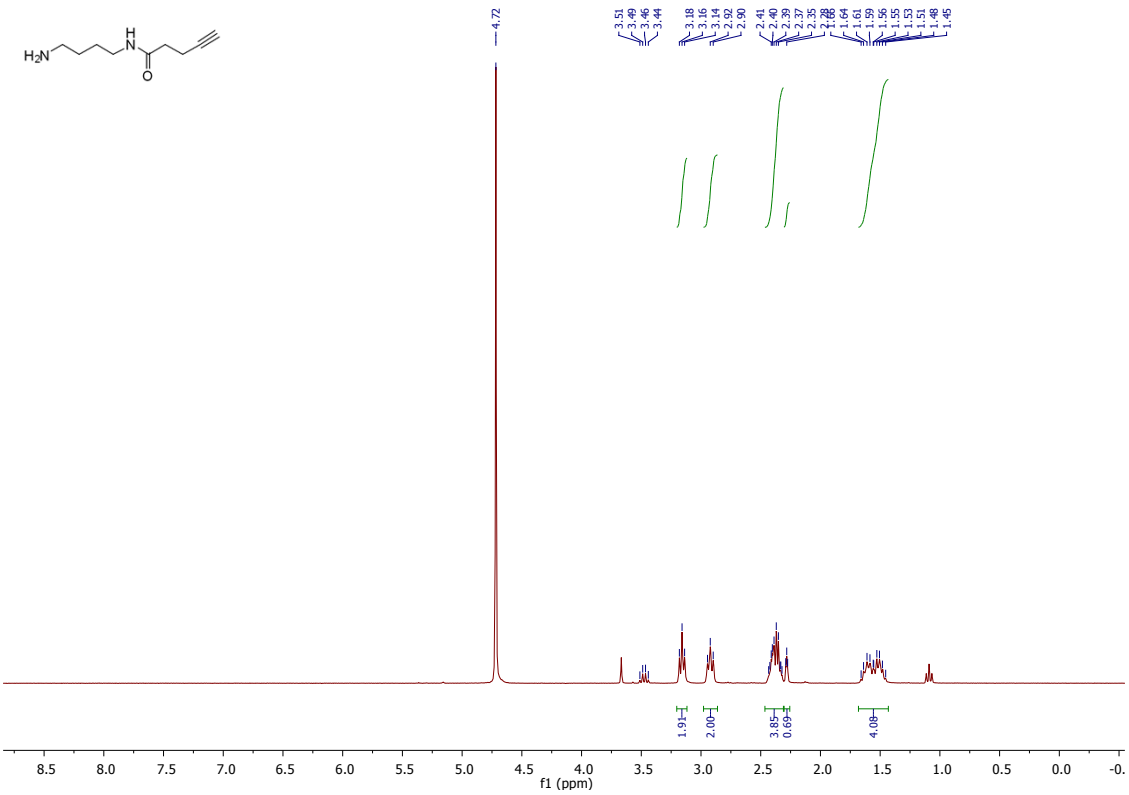


Figure 37: ^{1}H NMR spectrum of compound **10g** (300 MHz, D_2O).

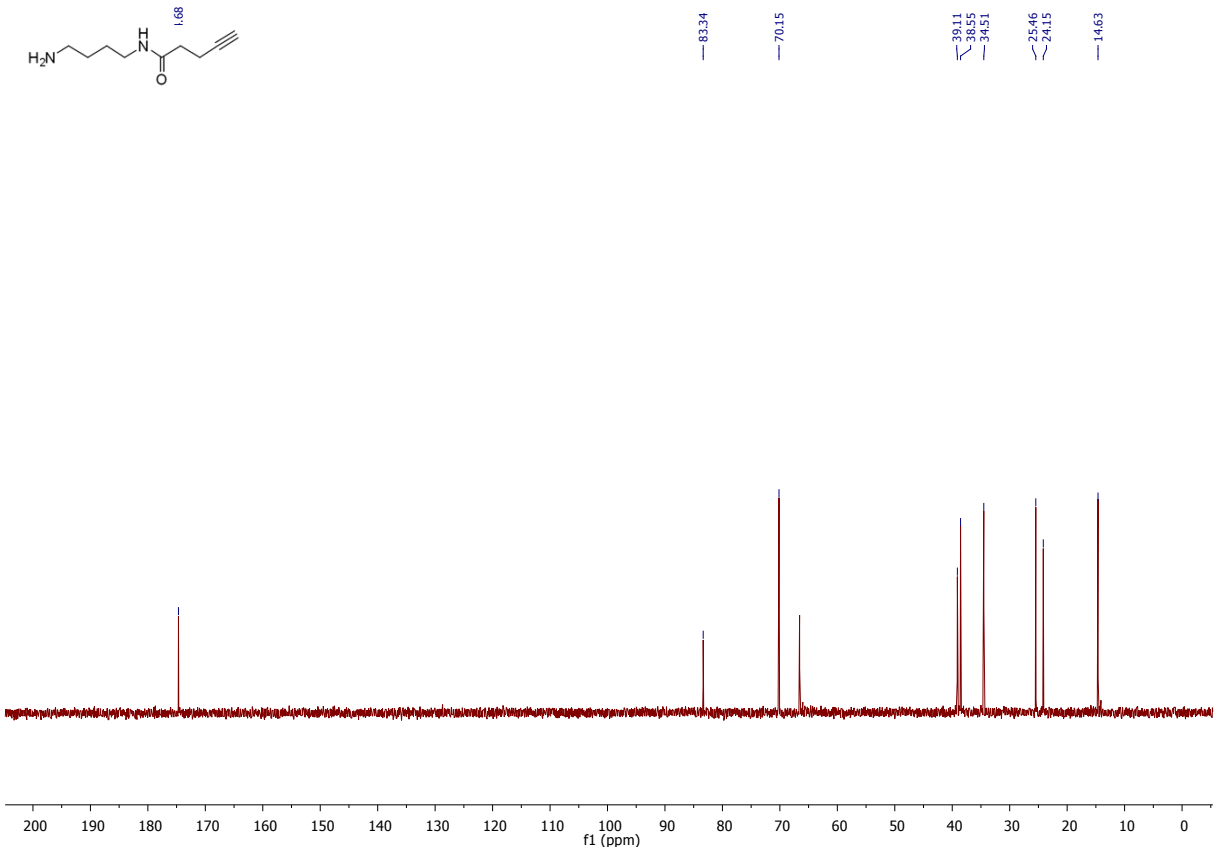


Figure 38: ^{13}C NMR spectrum of compound **10g** (300 MHz, D_2O).

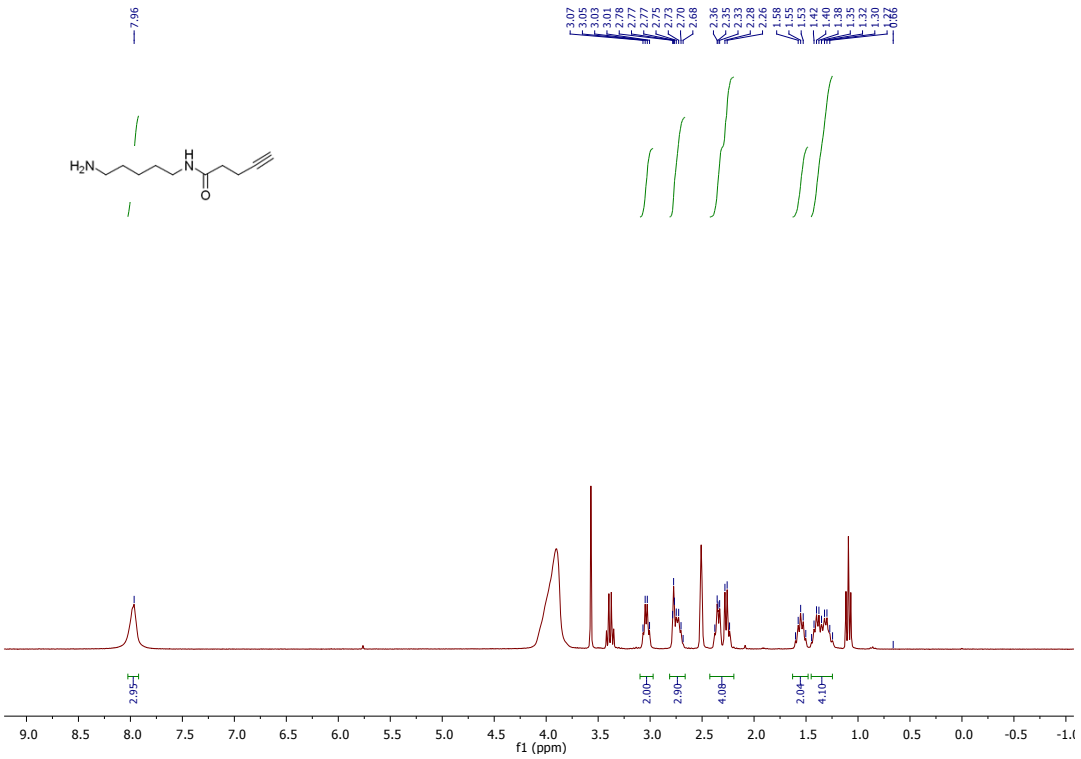


Figure 39: ^{1}H NMR spectrum of compound **10h** (300 MHz, DMSO-d_6).

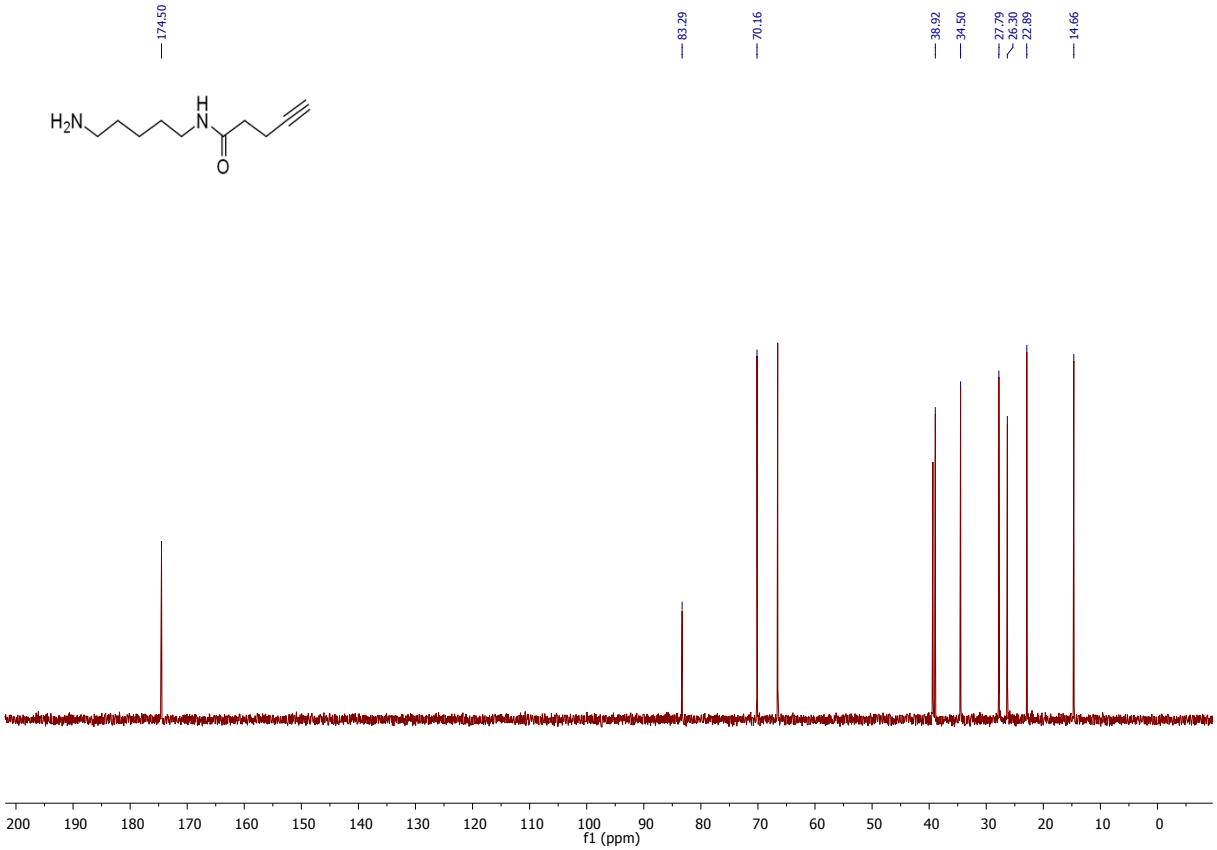


Figure 40: ^{13}C NMR spectrum of compound **10h** (300 MHz, D2O).

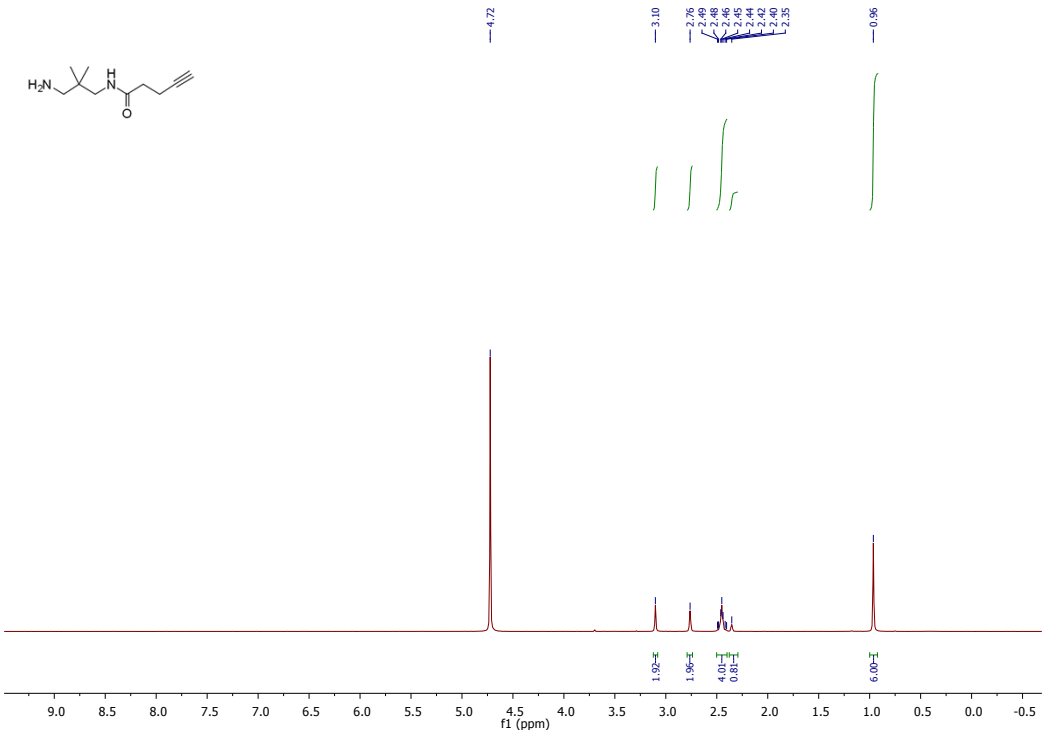


Figure 41: ^{1}H NMR spectrum of compound **10i** (300 MHz, D_2O).

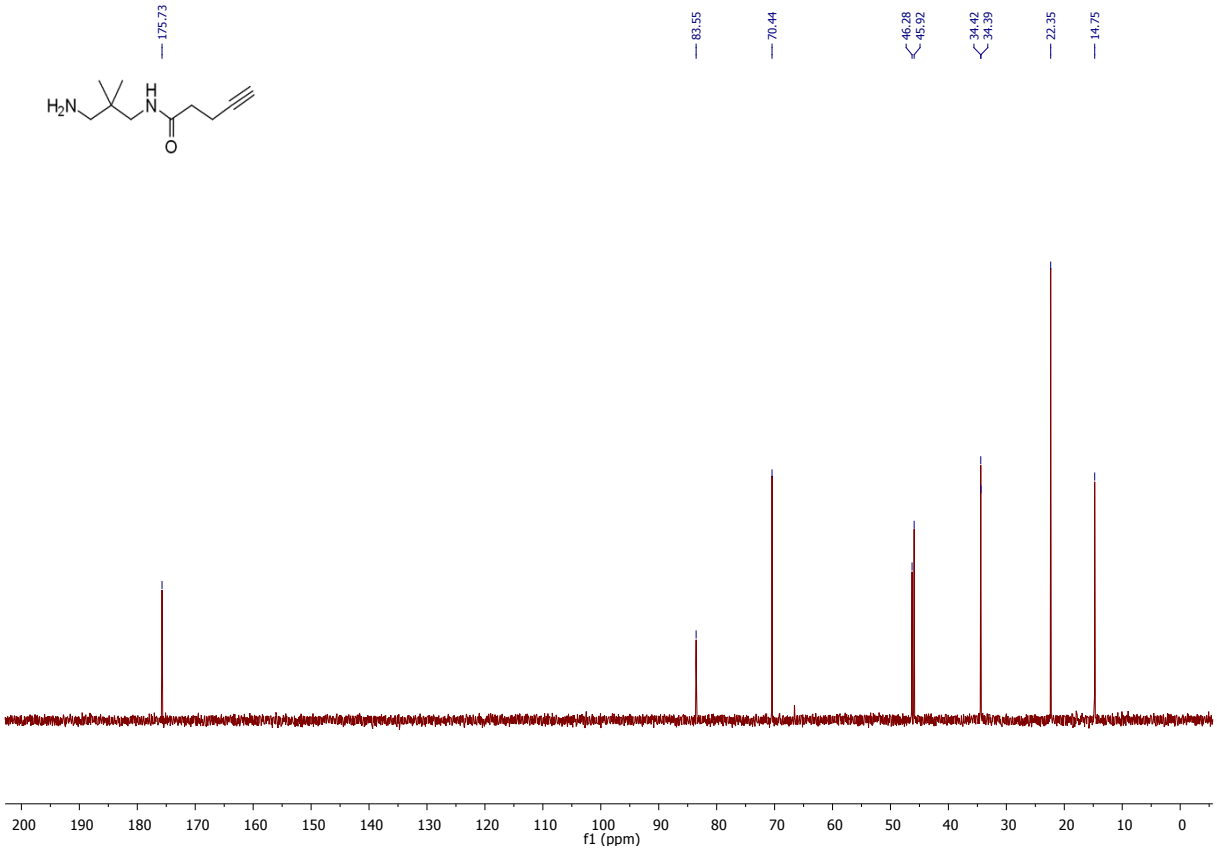


Figure 42: ^{13}C NMR spectrum of compound **10i** (300 MHz, D_2O).

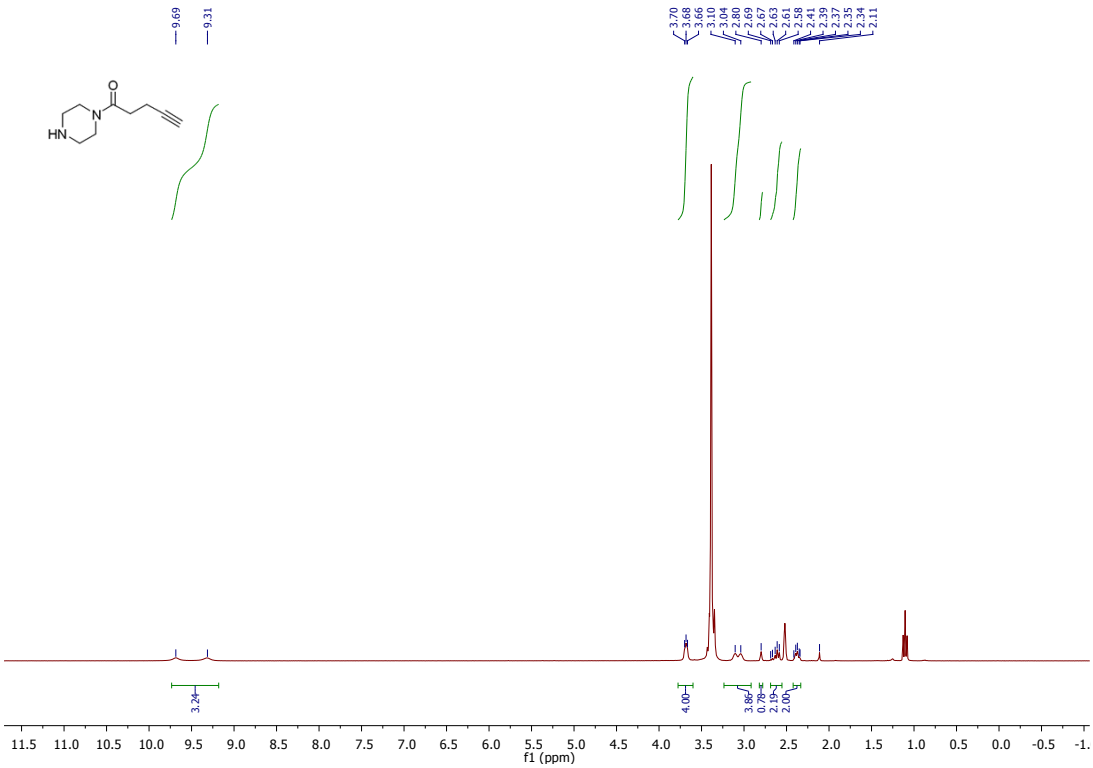


Figure 43: ^{1}H NMR spectrum of compound **10j** (300 MHz, D_2O).

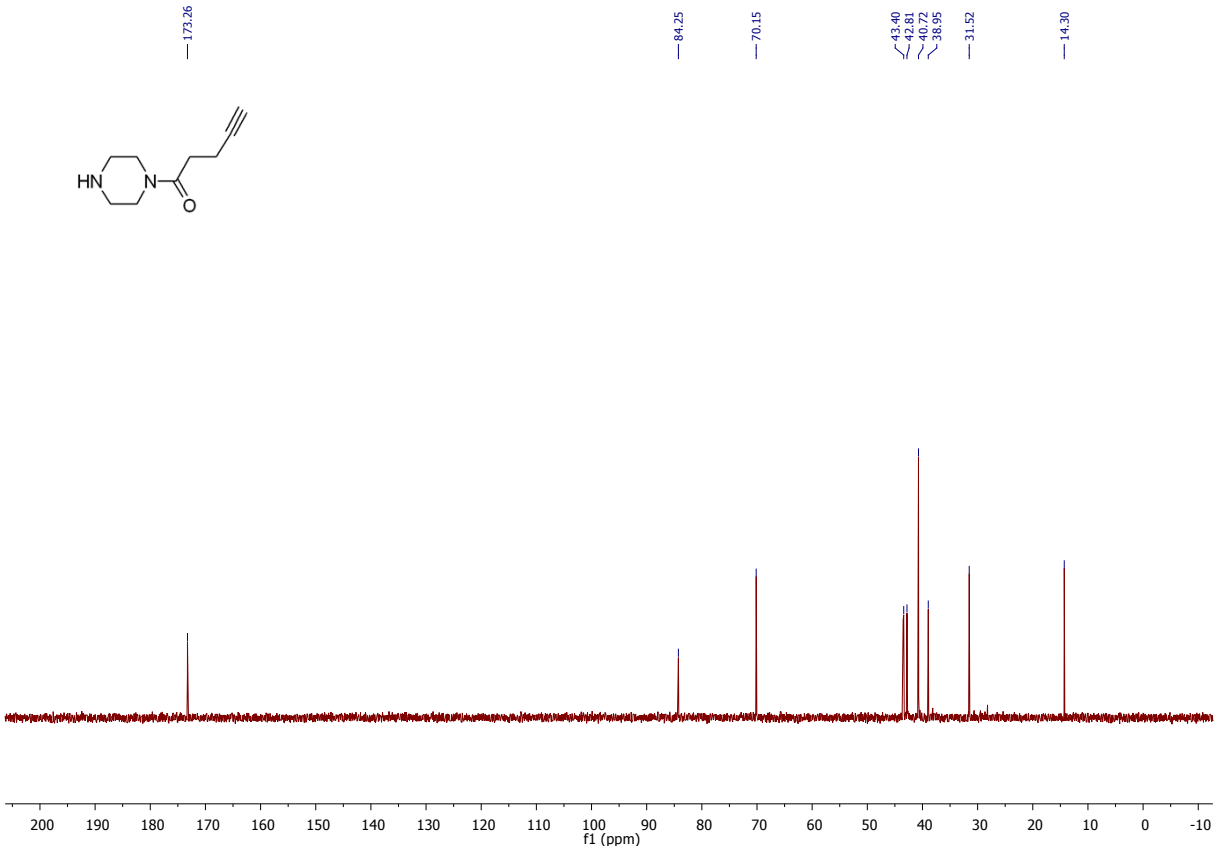


Figure 44: ^{13}C NMR spectrum of compound **10j** (300 MHz, D_2O).

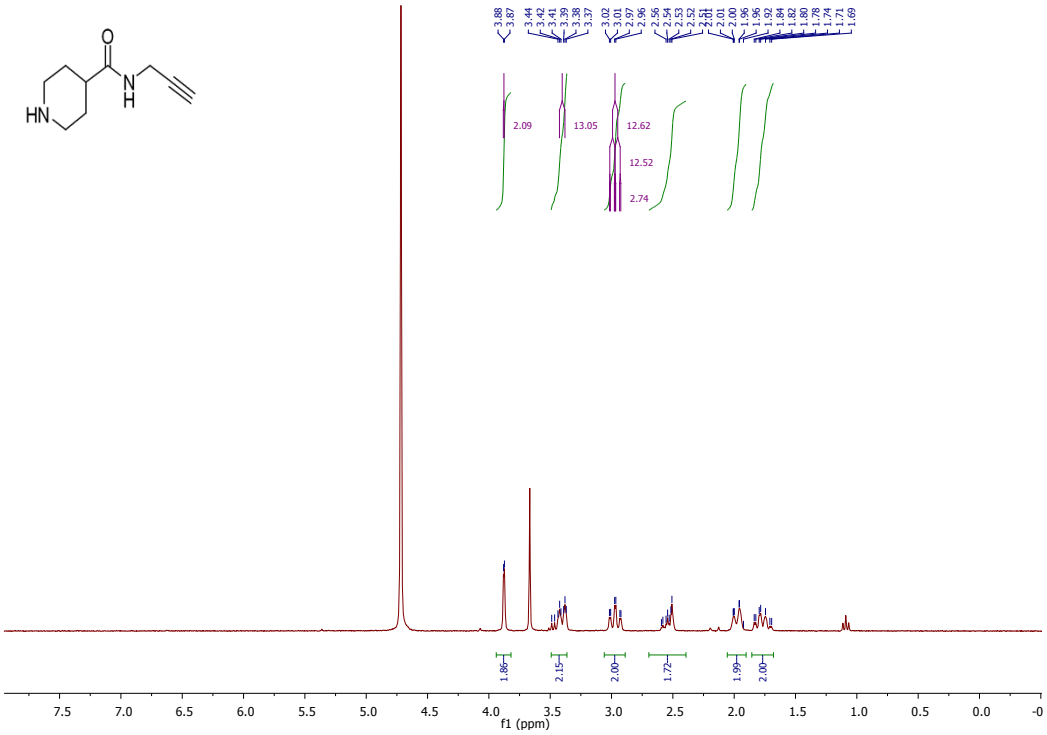


Figure 45: ^{1}H NMR spectrum of compound **10k** (300 MHz, D_2O).

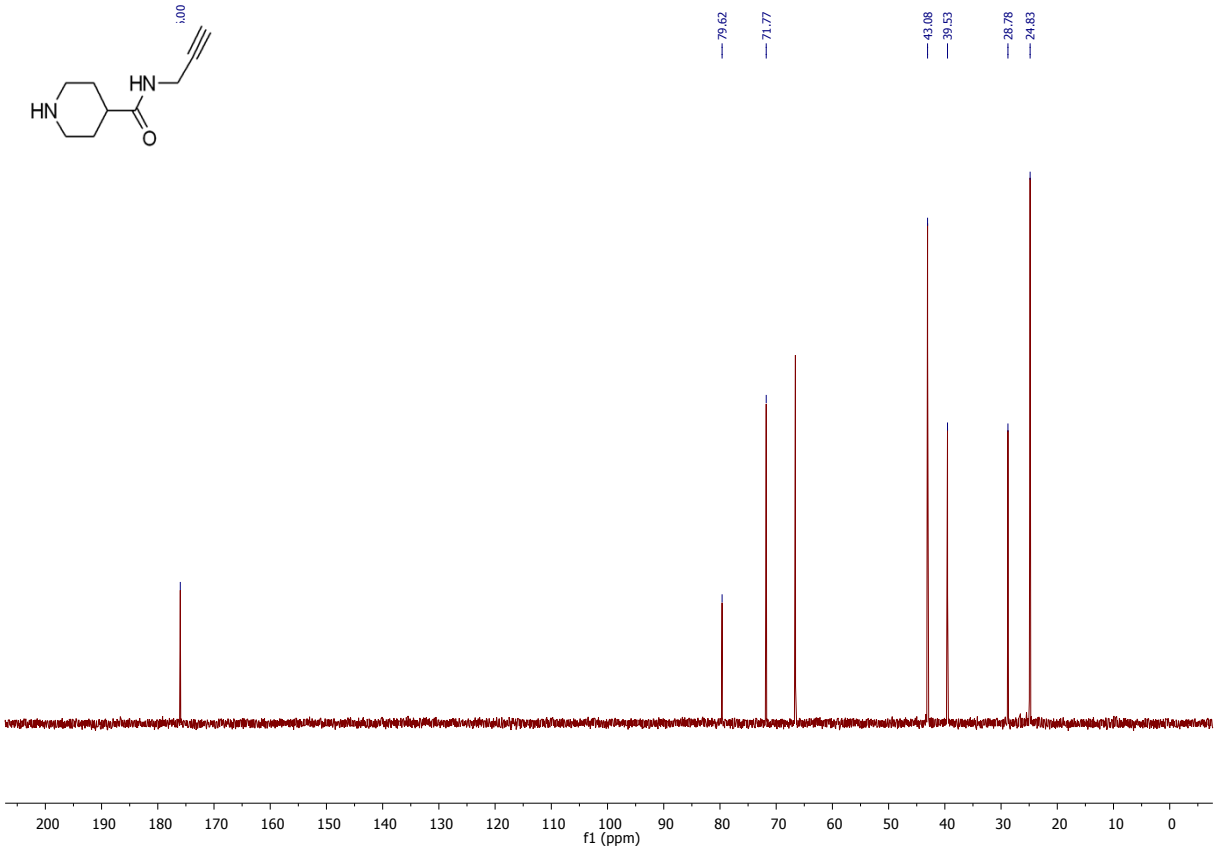


Figure 46: ^{13}C NMR spectrum of compound **10k** (300 MHz, D_2O).

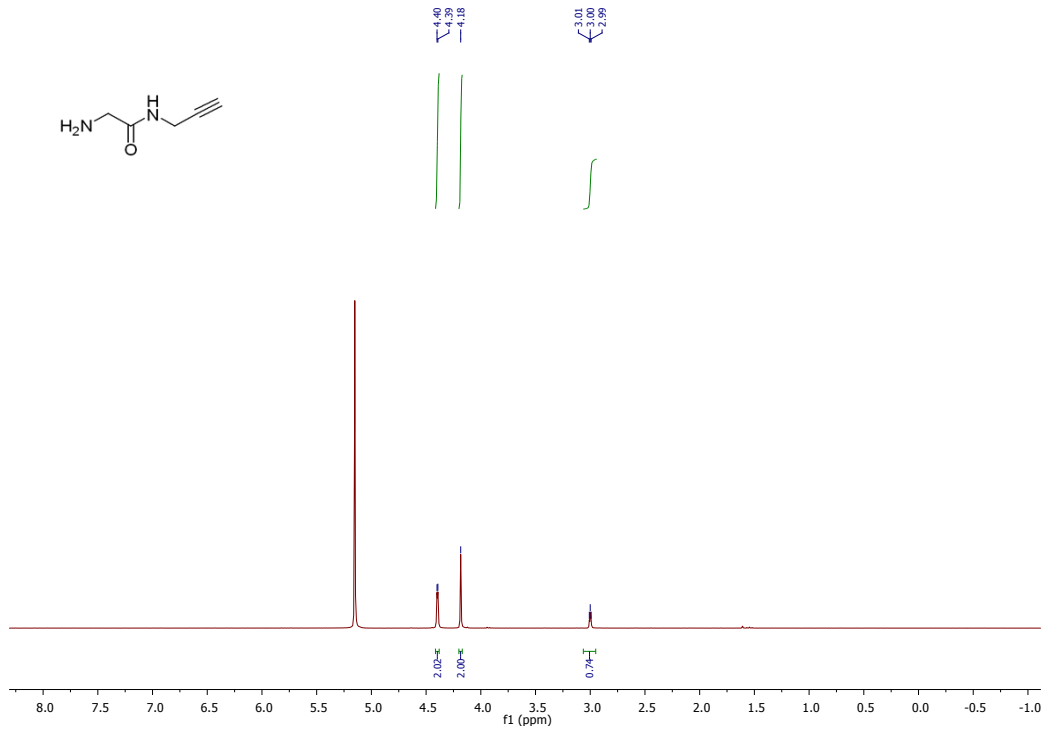


Figure 47: ^{1}H NMR spectrum of compound **10l** (300 MHz, D_2O).

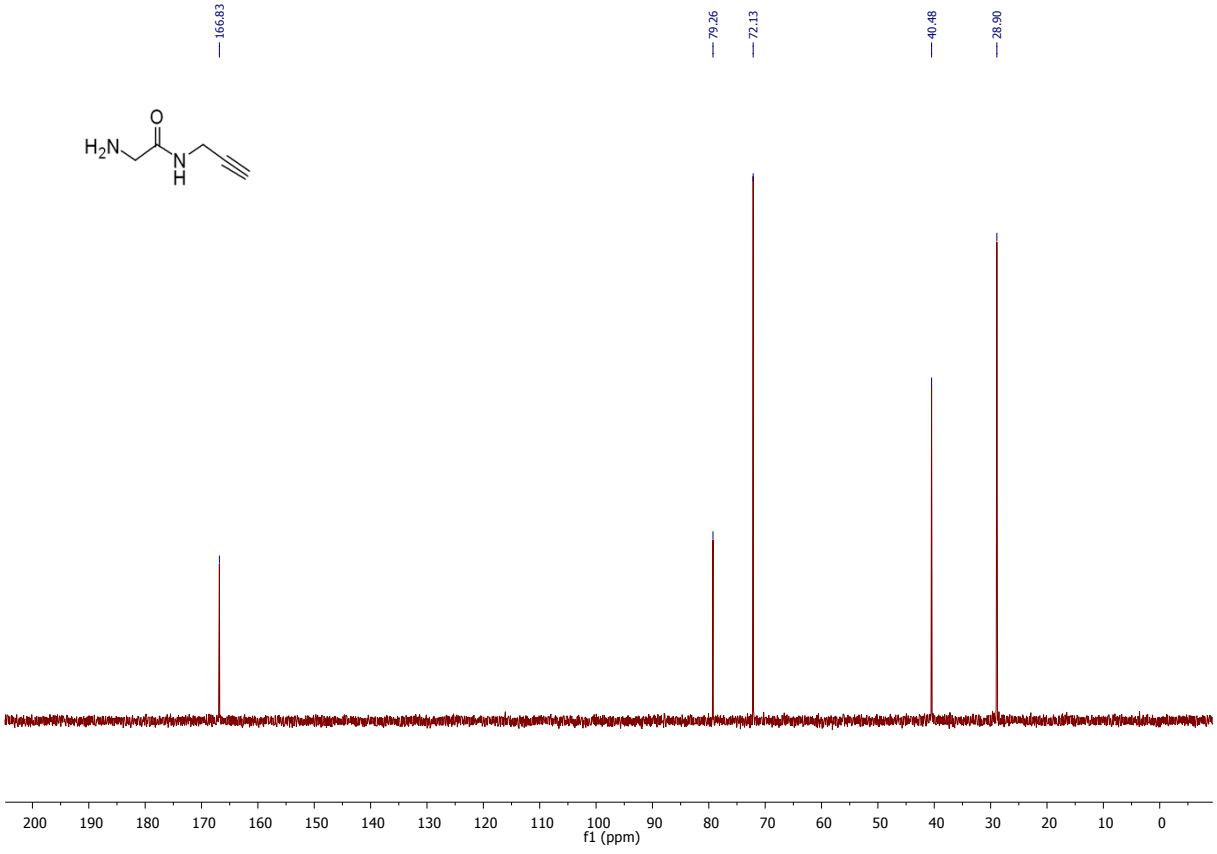


Figure 48: ^{13}C NMR spectrum of compound **10l** (300 MHz, D_2O).

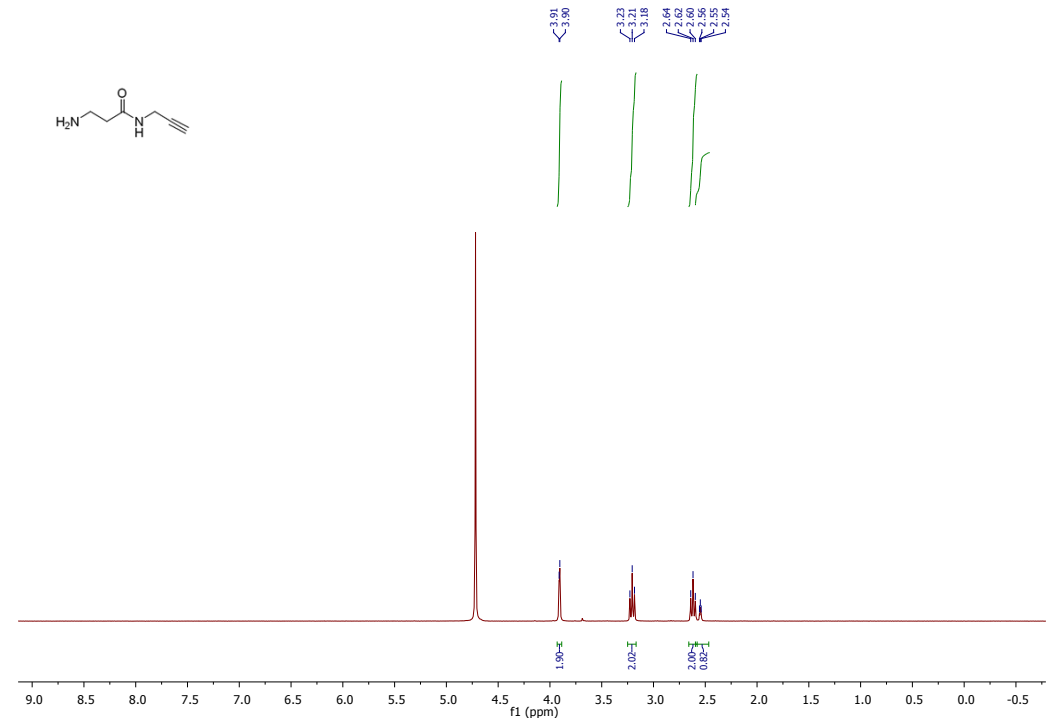


Figure 49: ^{1}H NMR spectrum of compound **10m** (300 MHz, D_2O).

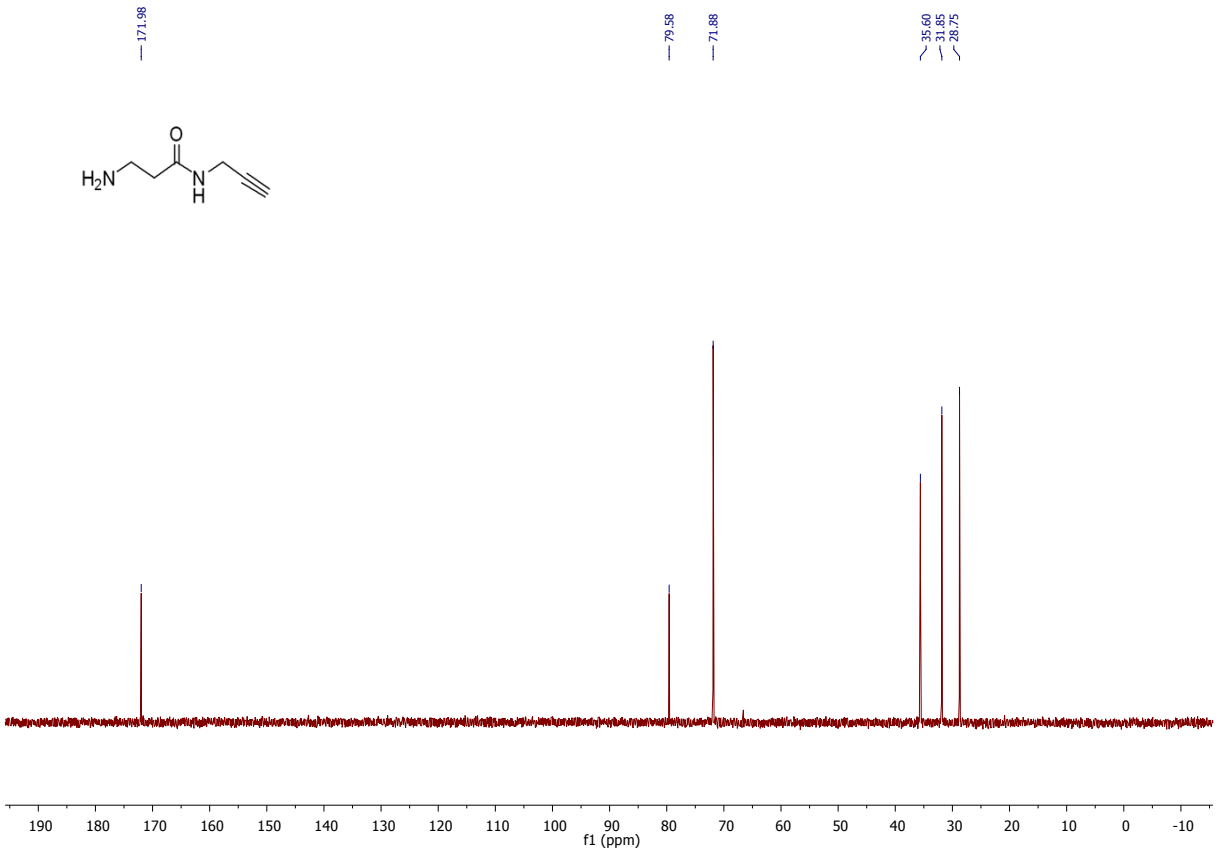


Figure 50: ^{13}C NMR spectrum of compound **10m** (300 MHz, D_2O).

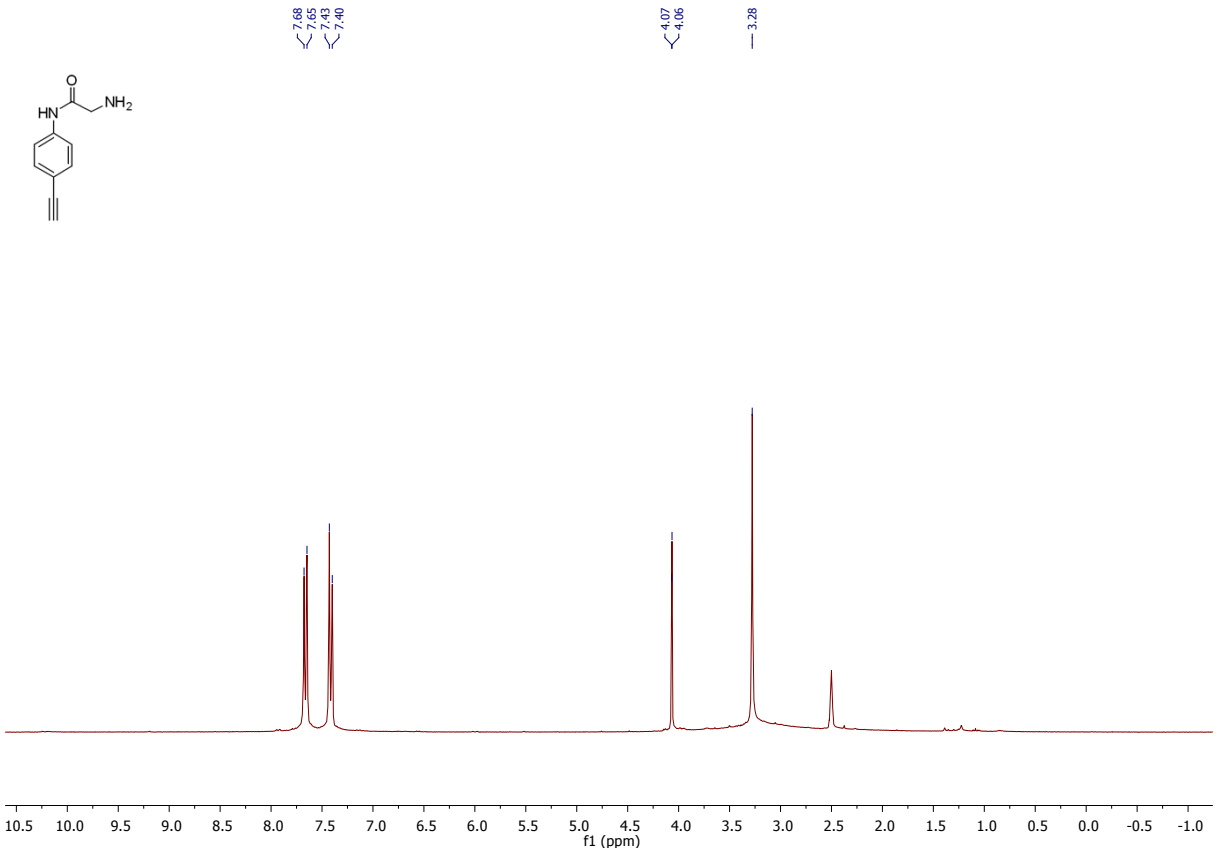


Figure 51: ^{1}H NMR spectrum of compound **10n** (300 MHz, DMSO-d_6).

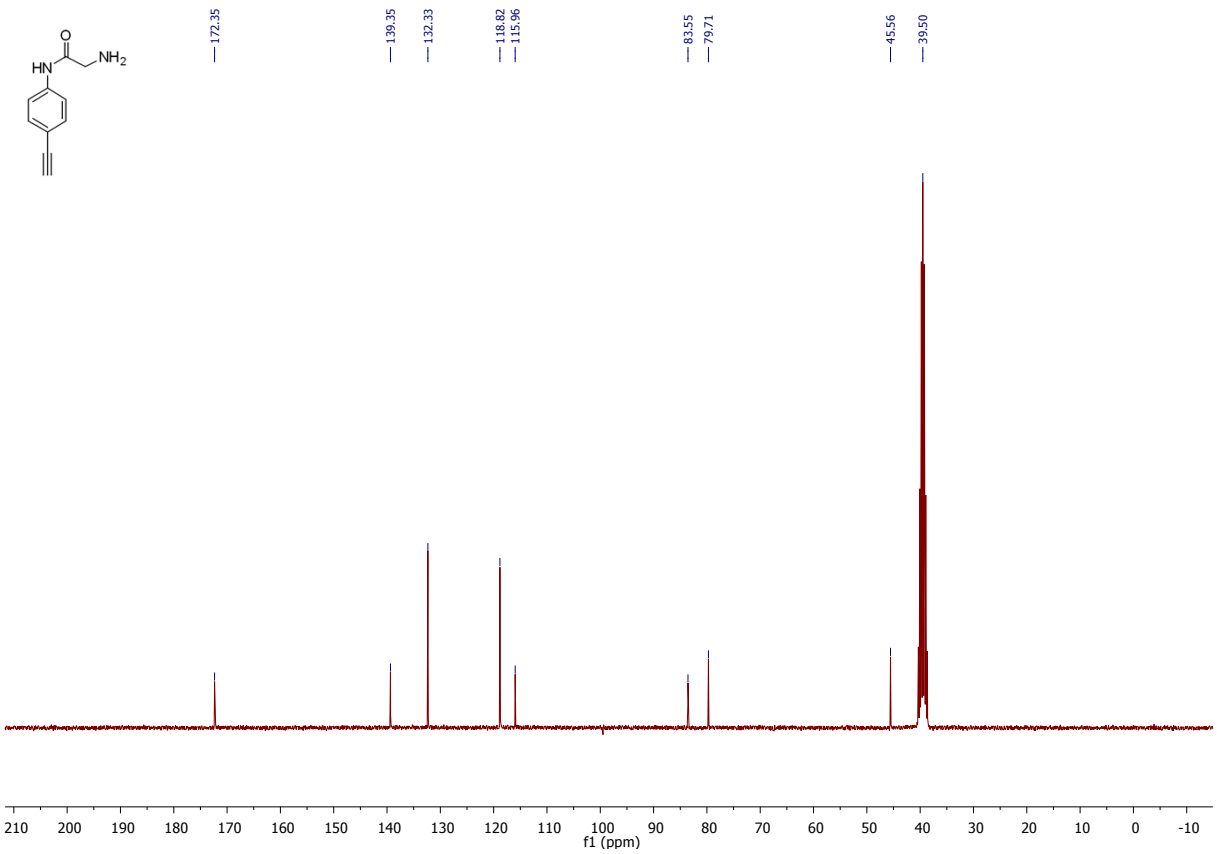


Figure 52: ^{13}C NMR spectrum of compound **10n** (300 MHz, DMSO-d_6).

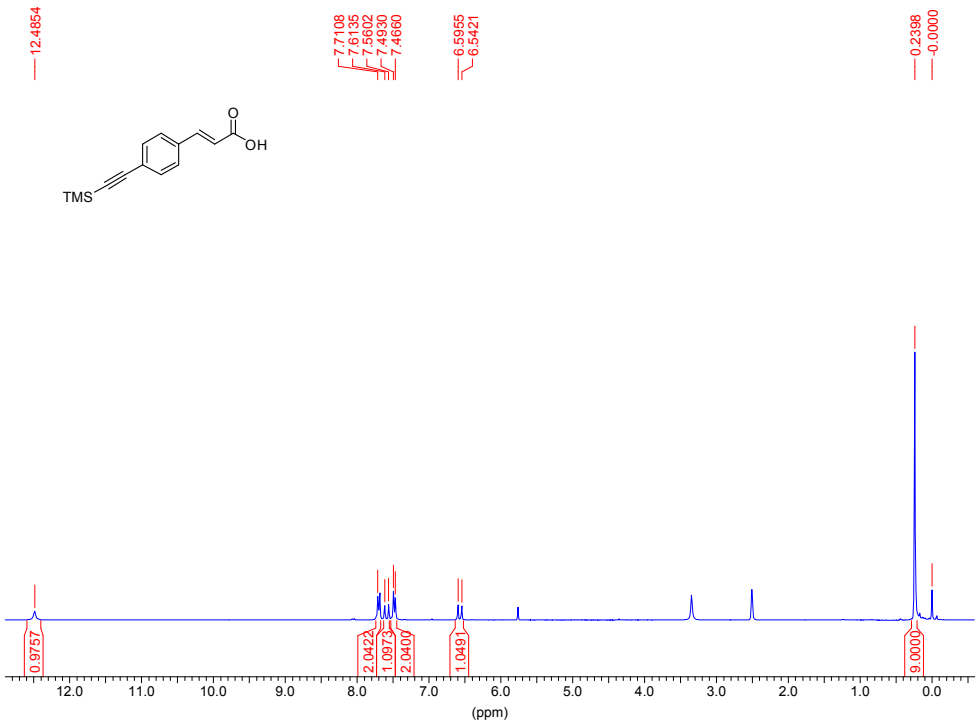


Figure 53: ^{1}H NMR spectrum of compound **9t'** (300 MHz, DMSO-d_6).

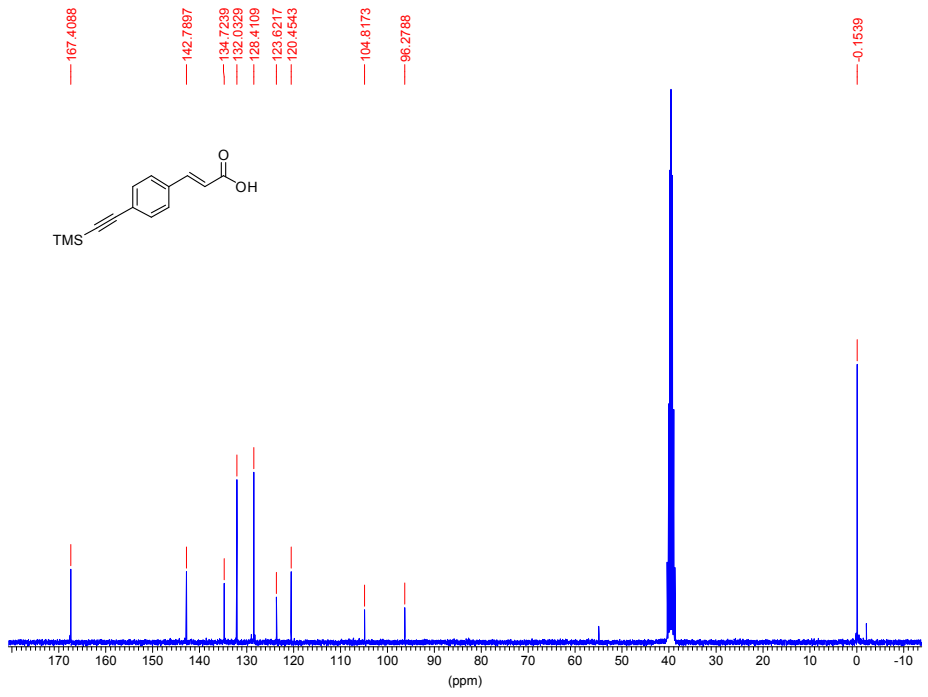


Figure 54: ^{13}C NMR spectrum of compound **9t'** (300 MHz, DMSO-d_6).

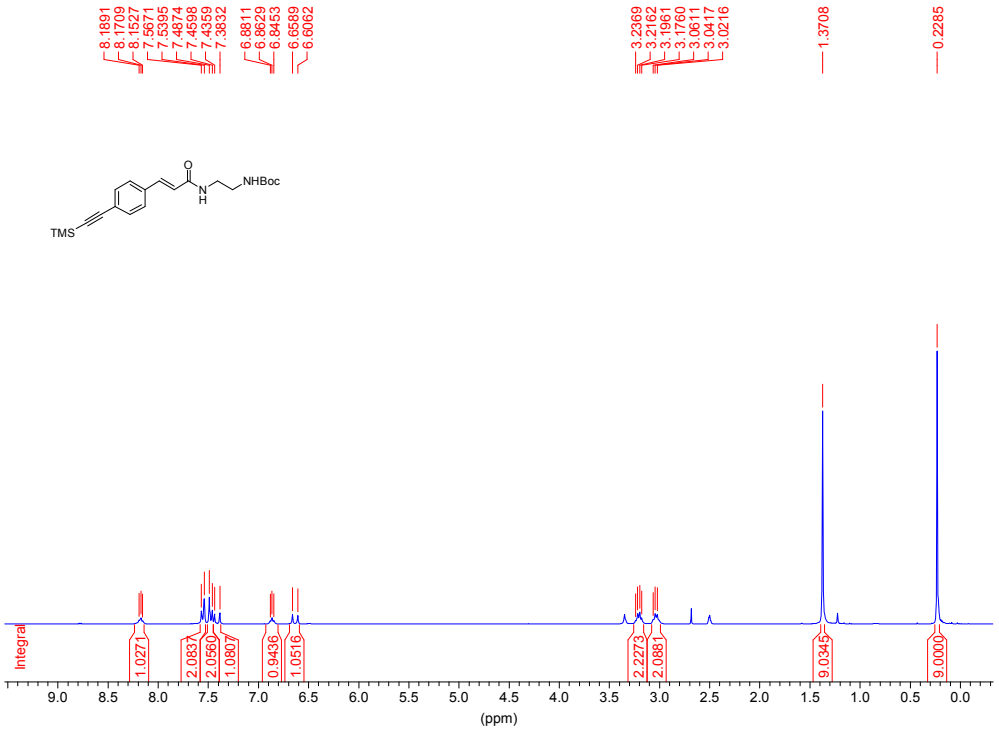


Figure 55: ^{1}H NMR spectrum of compound **9t** (300 MHz, DMSO-d_6).

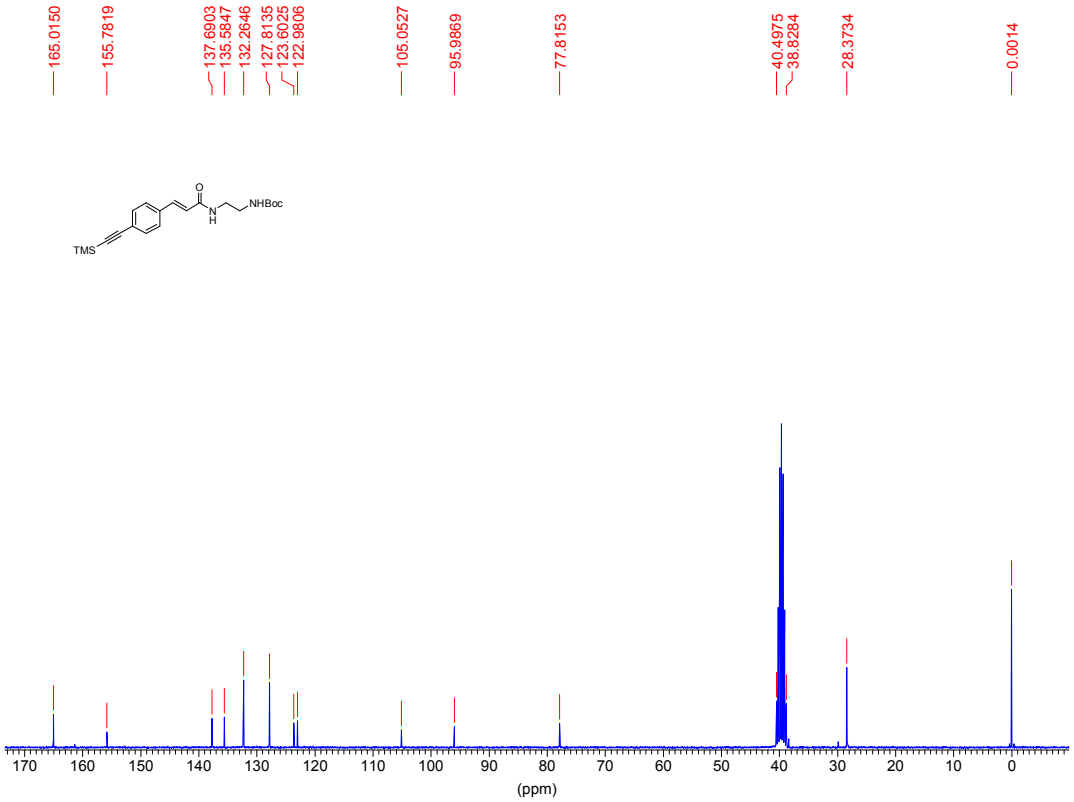


Figure 56: ^{13}C NMR spectrum of compound **9t** (300 MHz, DMSO-d_6).

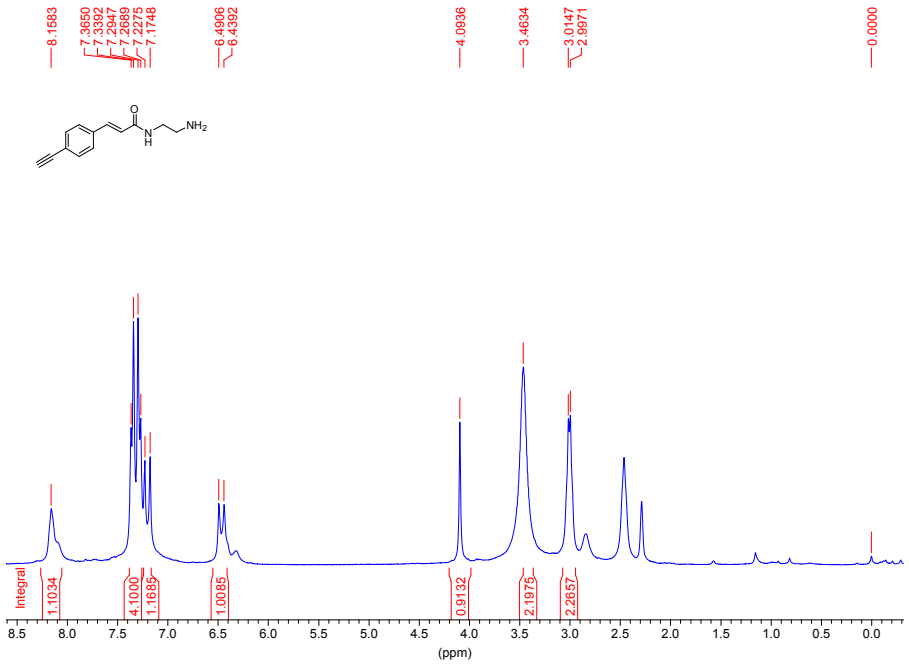


Figure 57: ^{1}H NMR spectrum of compound **10t** (300 MHz, DMSO-d_6).

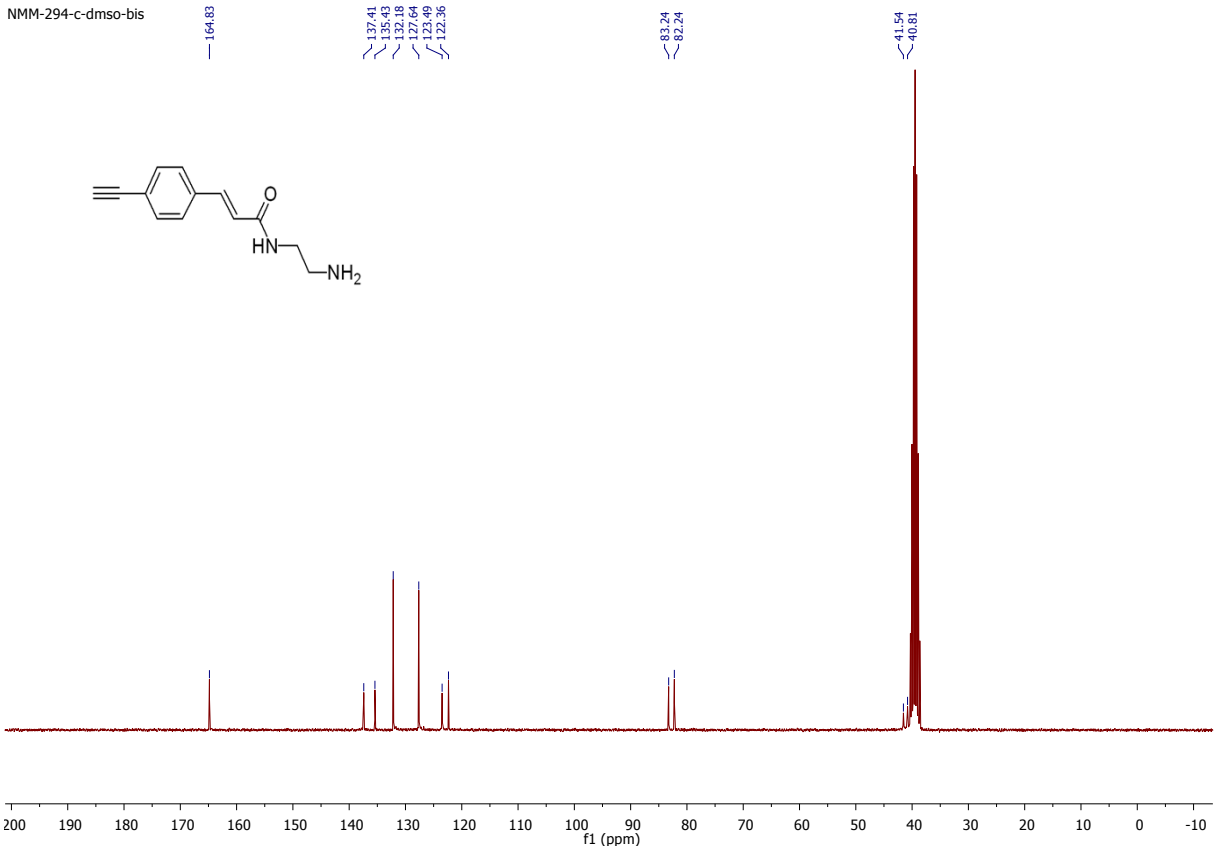


Figure 58: ^{13}C NMR spectrum of compound **10t** (300 MHz, DMSO-d_6).

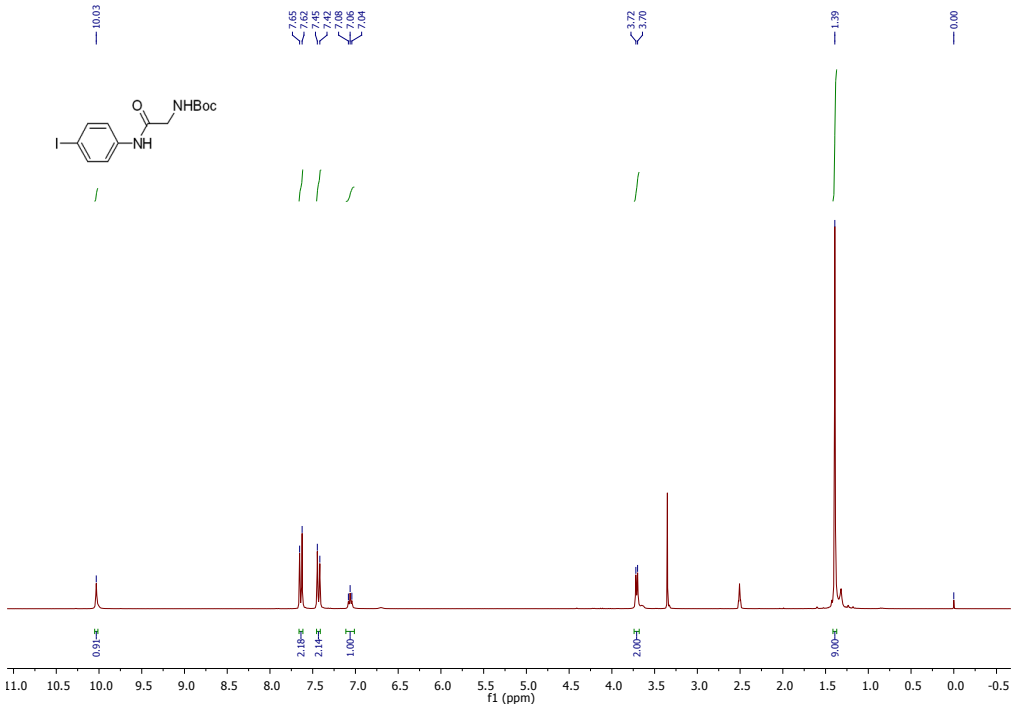


Figure 59: ^{1}H NMR spectrum of compound **9u'** (300 MHz, DMSO-d_6).

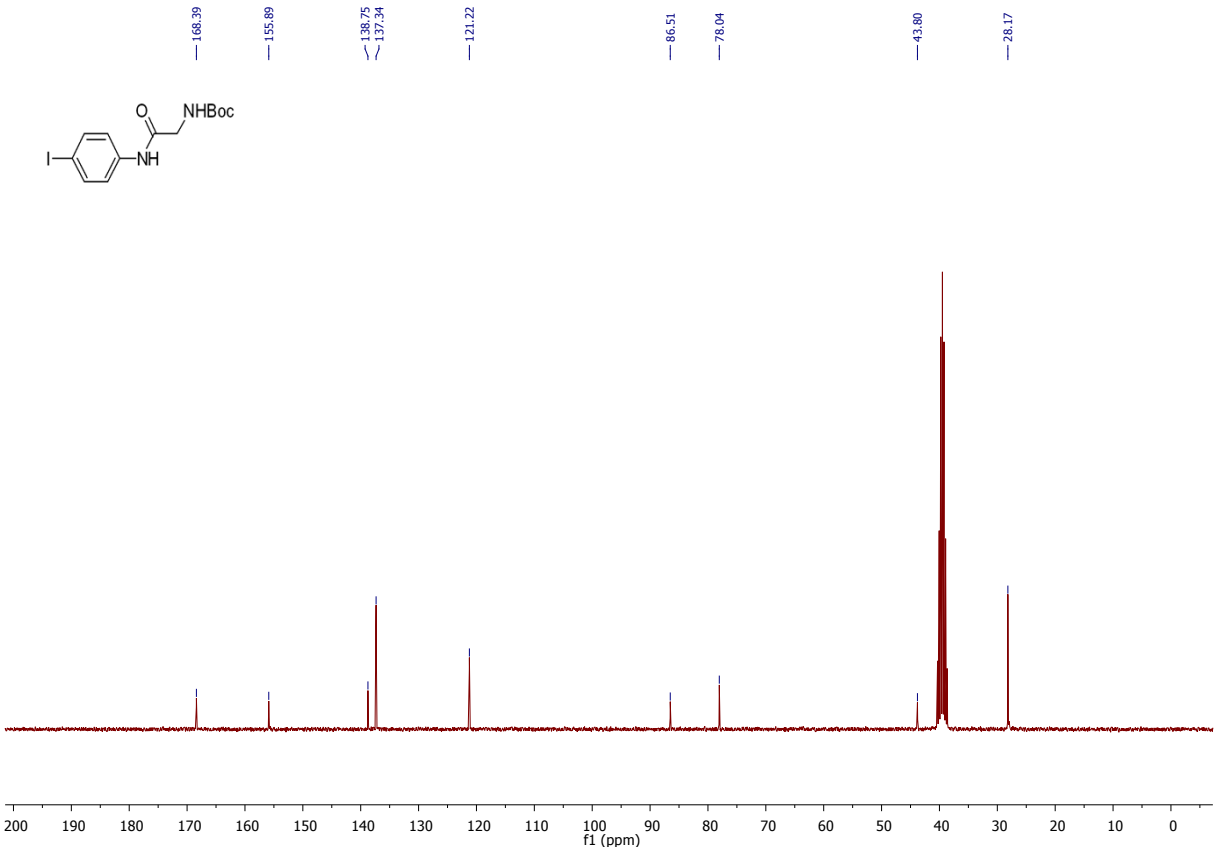


Figure 60: ^{13}C NMR spectrum of compound **9u'** (300 MHz, DMSO-d_6).

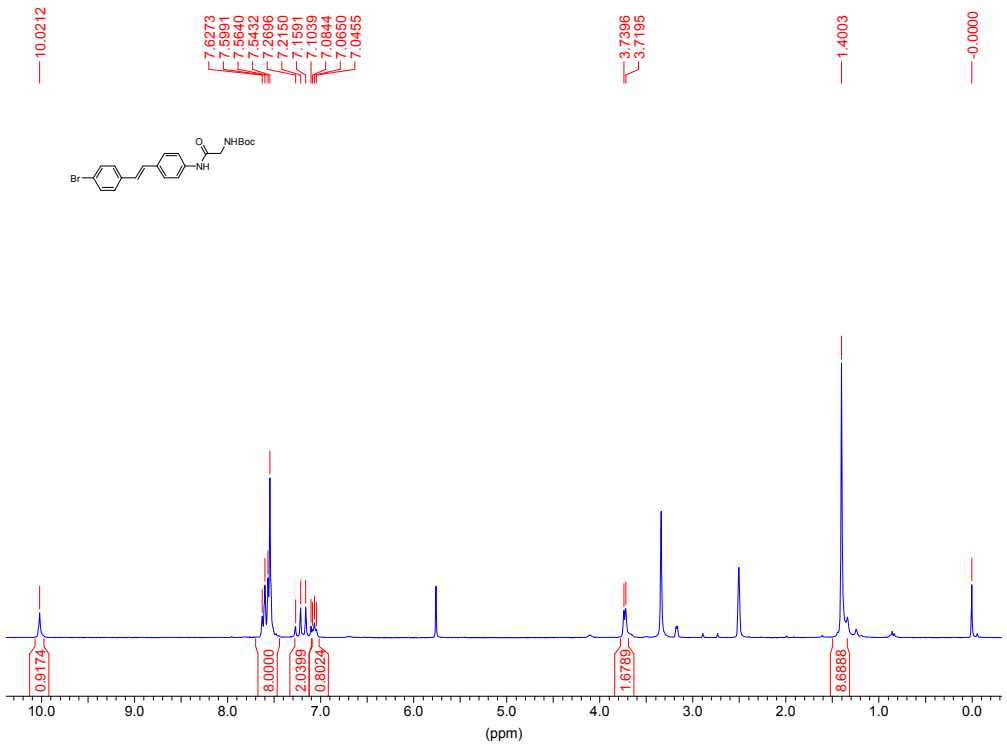


Figure 61: ^{1}H NMR spectrum of compound **9u”** (300 MHz, DMSO-d_6).

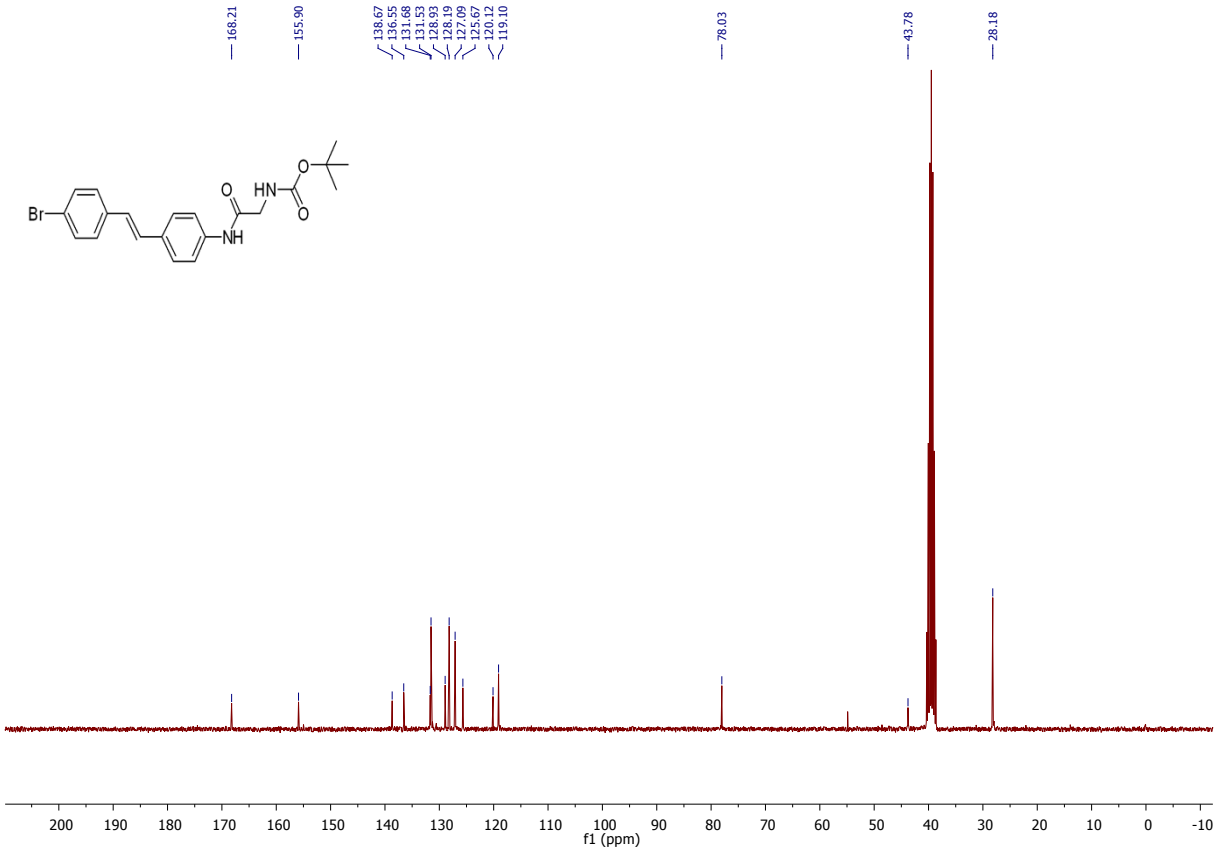


Figure 62: ^{13}C NMR spectrum of compound **9u”** (300 MHz, DMSO-d_6).

9u

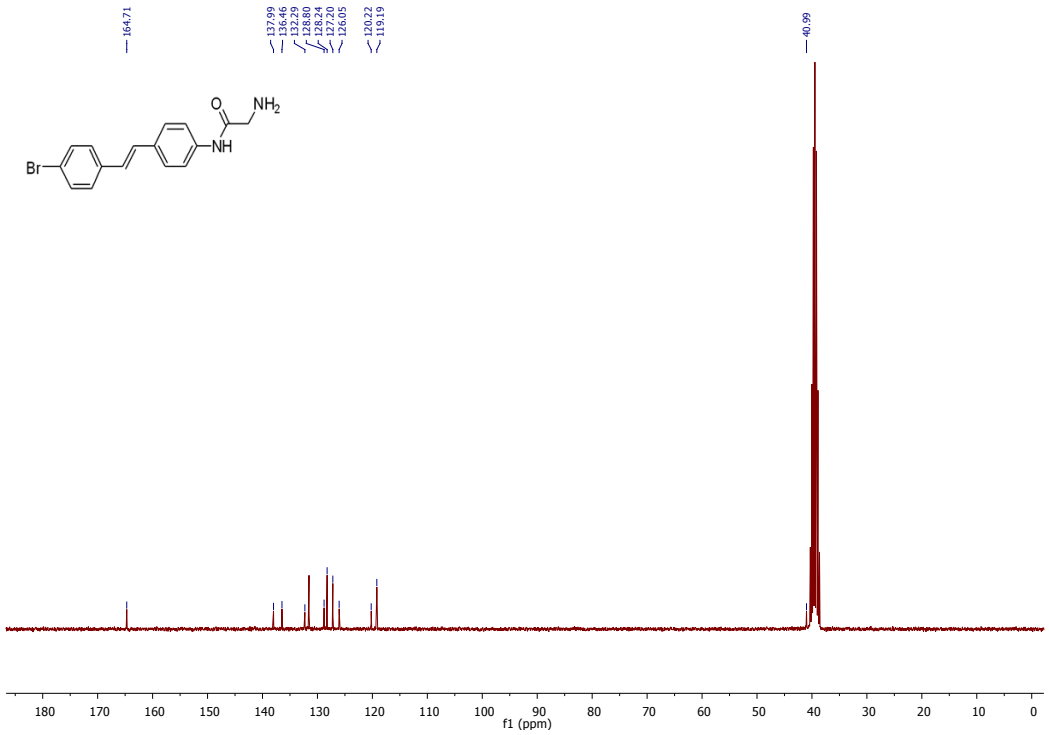


Figure 63: ^{1}H NMR spectrum of compound **9u** (300 MHz, DMSO-d_6).

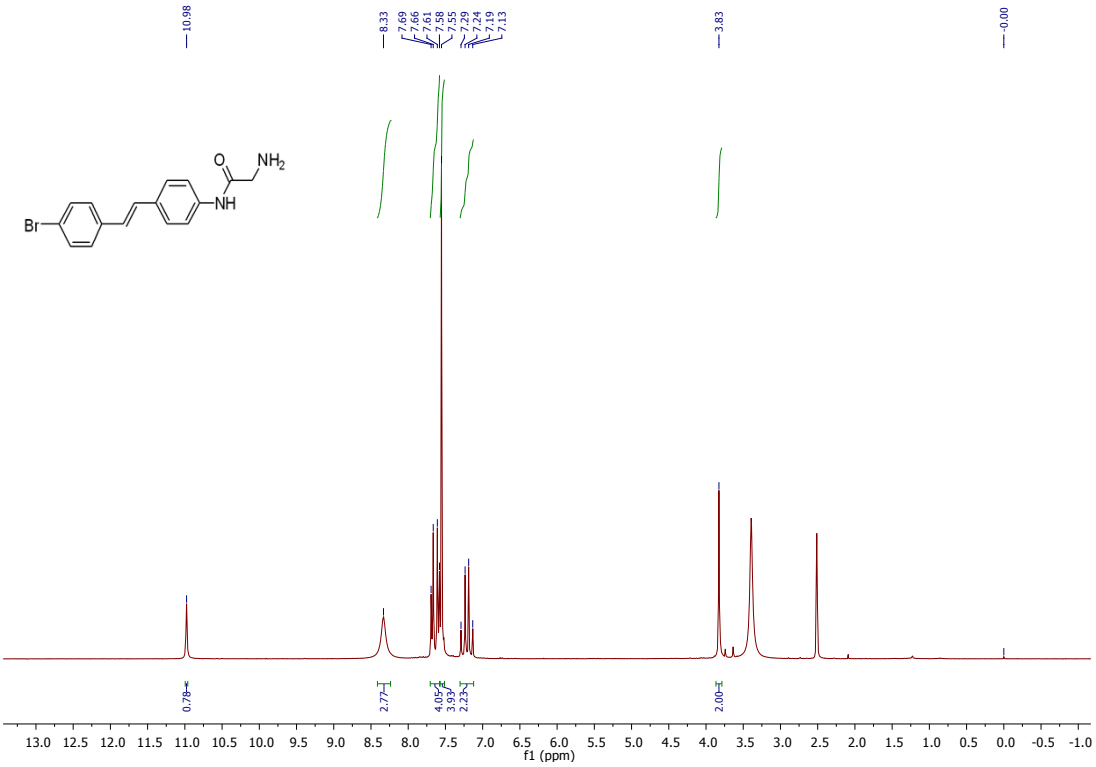


Figure 64: ^{13}C NMR spectrum of compound **9u** (300 MHz, DMSO-d_6).

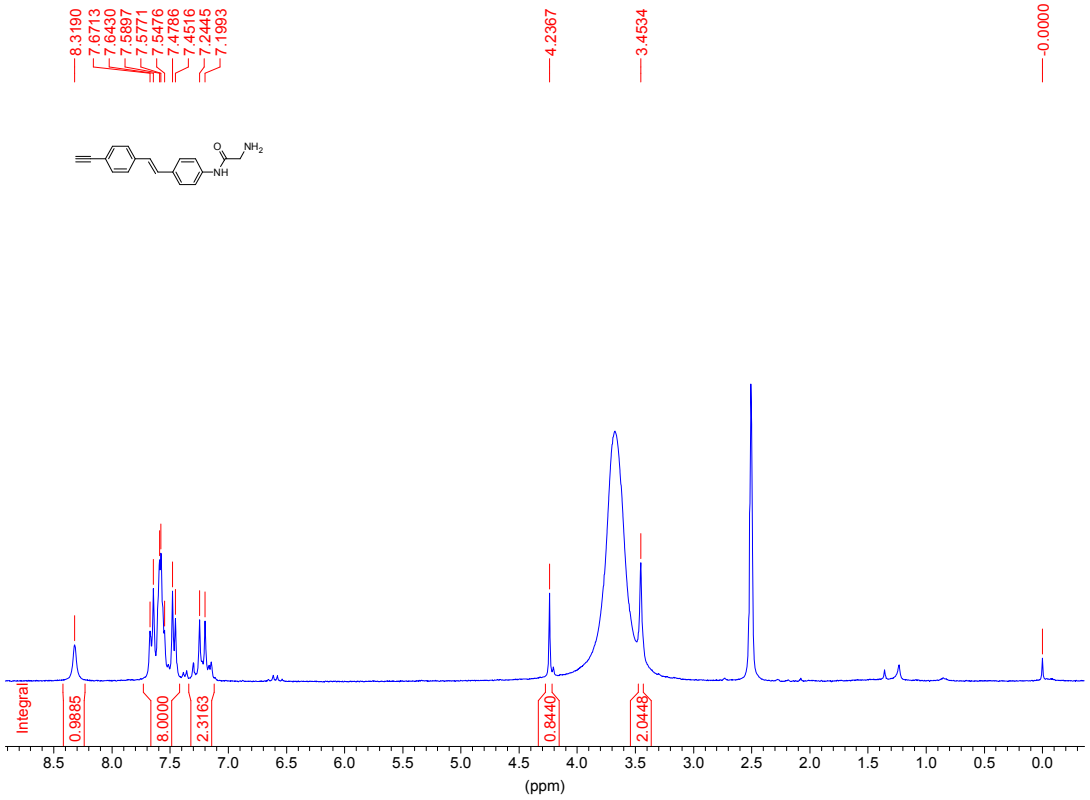


Figure 65: ^{1}H NMR spectrum of compound **10u** (300 MHz, DMSO-d_6).

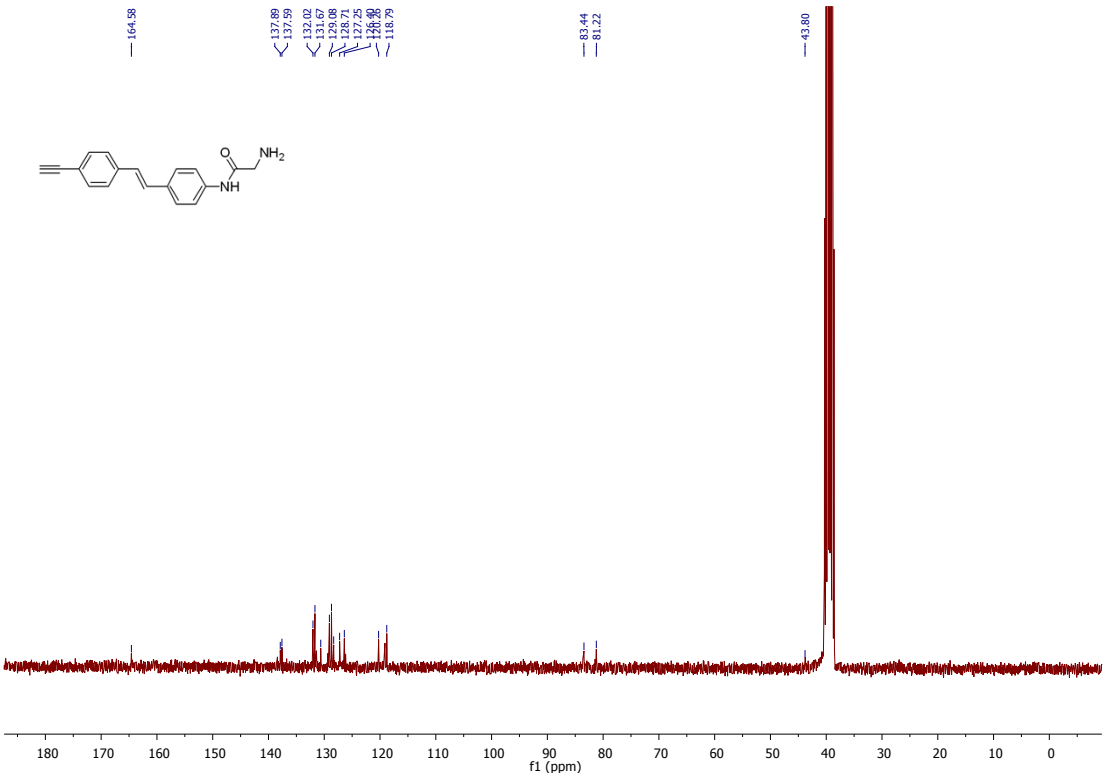


Figure 66: ^{13}C NMR spectrum of compound **10u** (300 MHz, DMSO-d_6).

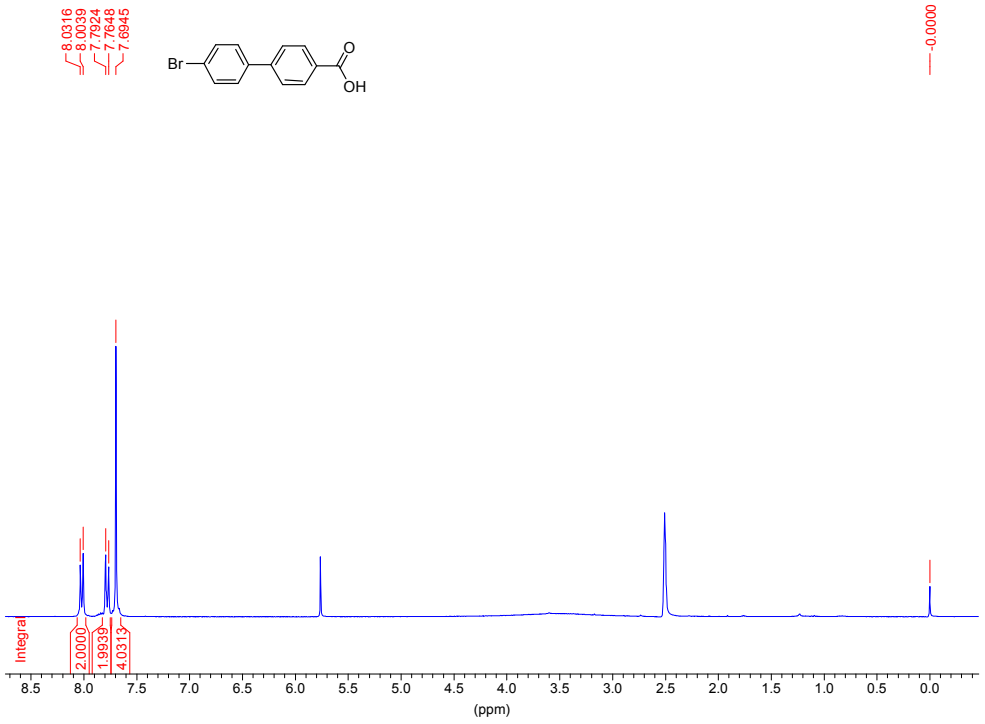


Figure 67: ^{1}H NMR spectrum of compound **8g** (300 MHz, DMSO-d_6).

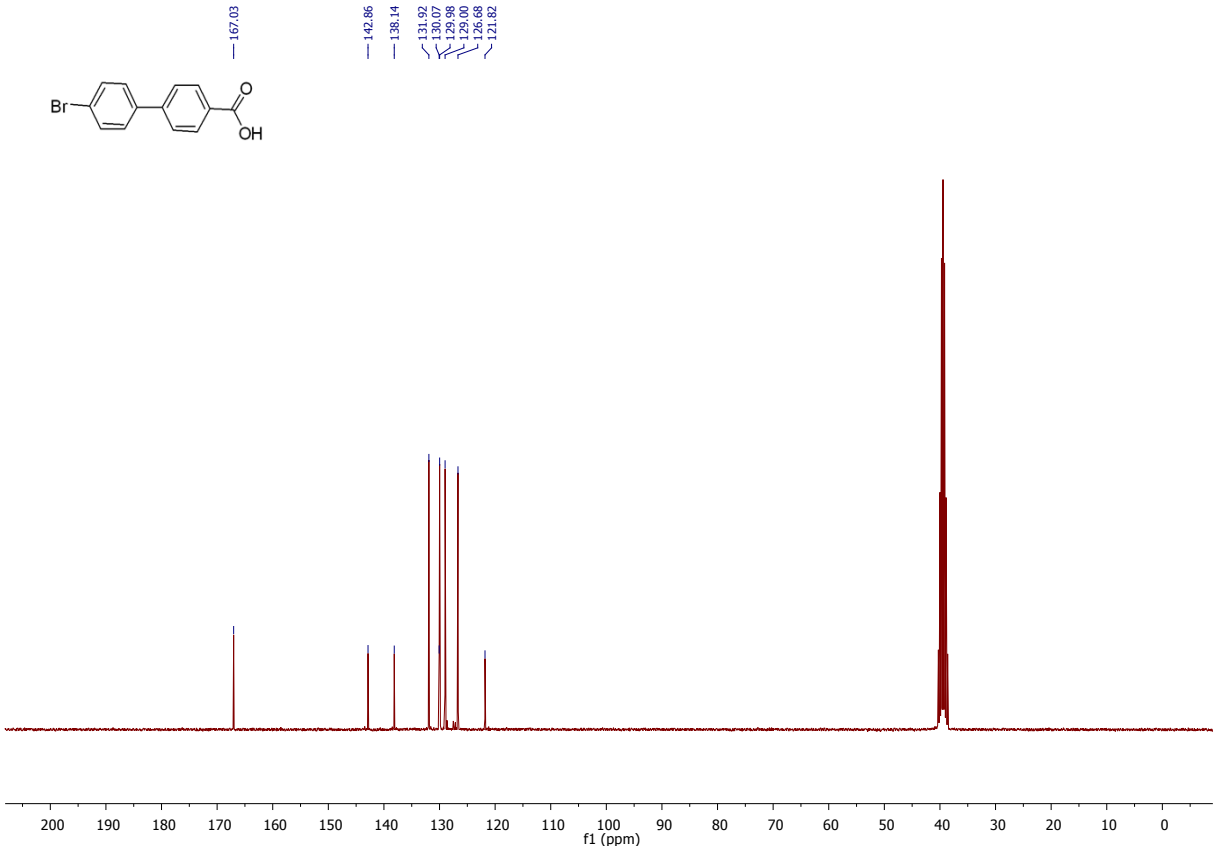


Figure 68: ^{13}C NMR spectrum of compound **8g** (300 MHz, DMSO-d_6).

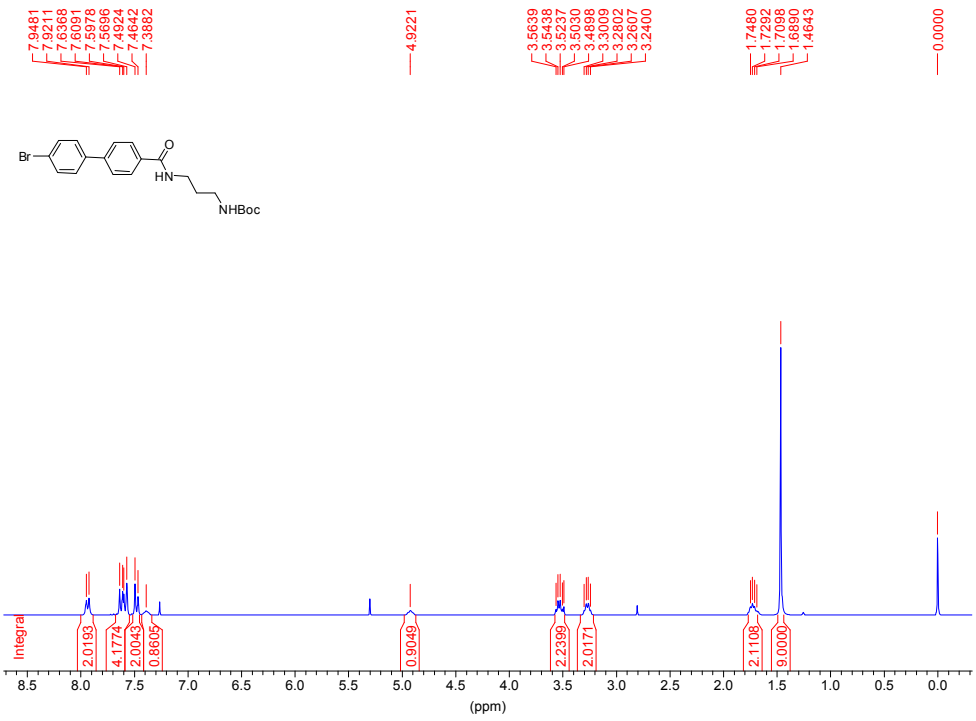


Figure 69: ^{1}H NMR spectrum of compound **9v'** (300 MHz, $CDCl_3$).

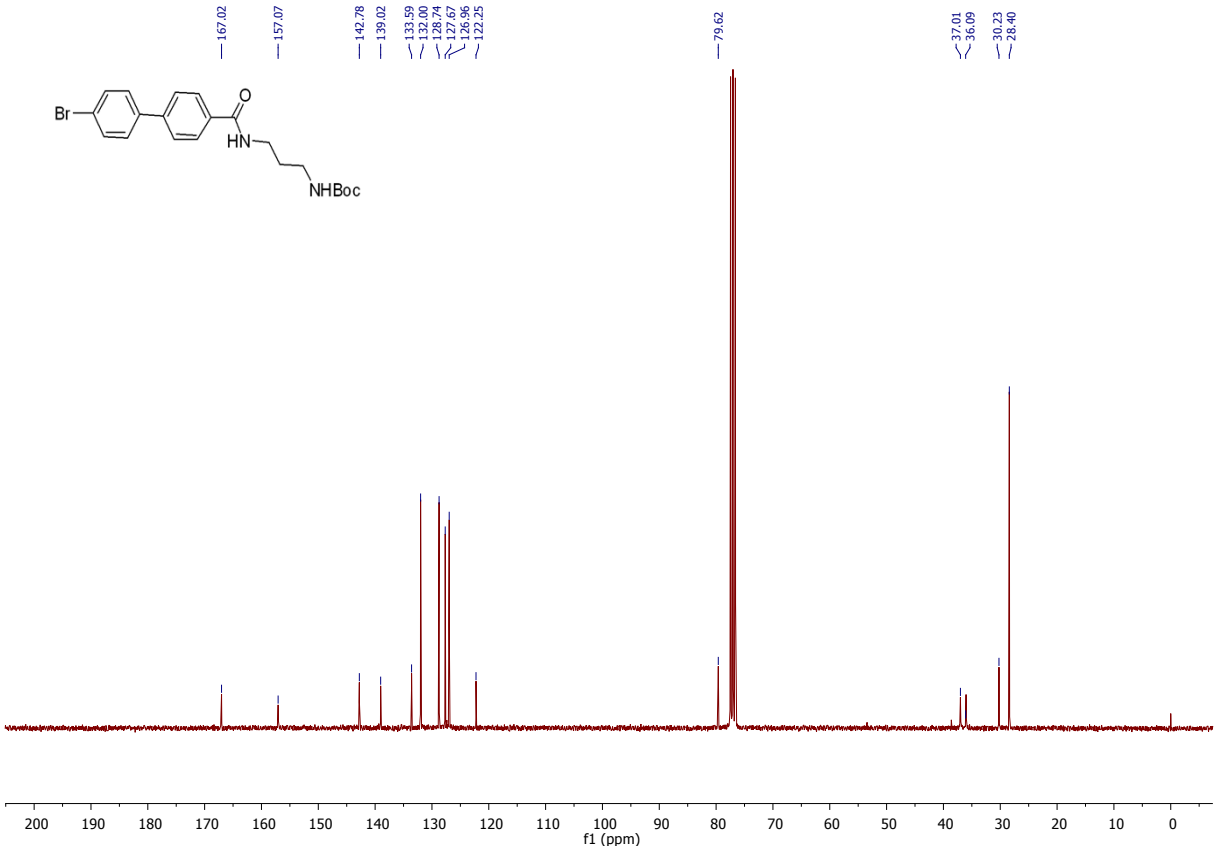


Figure 70: ^{13}C NMR spectrum of compound **9v'** (300 MHz, $CDCl_3$).

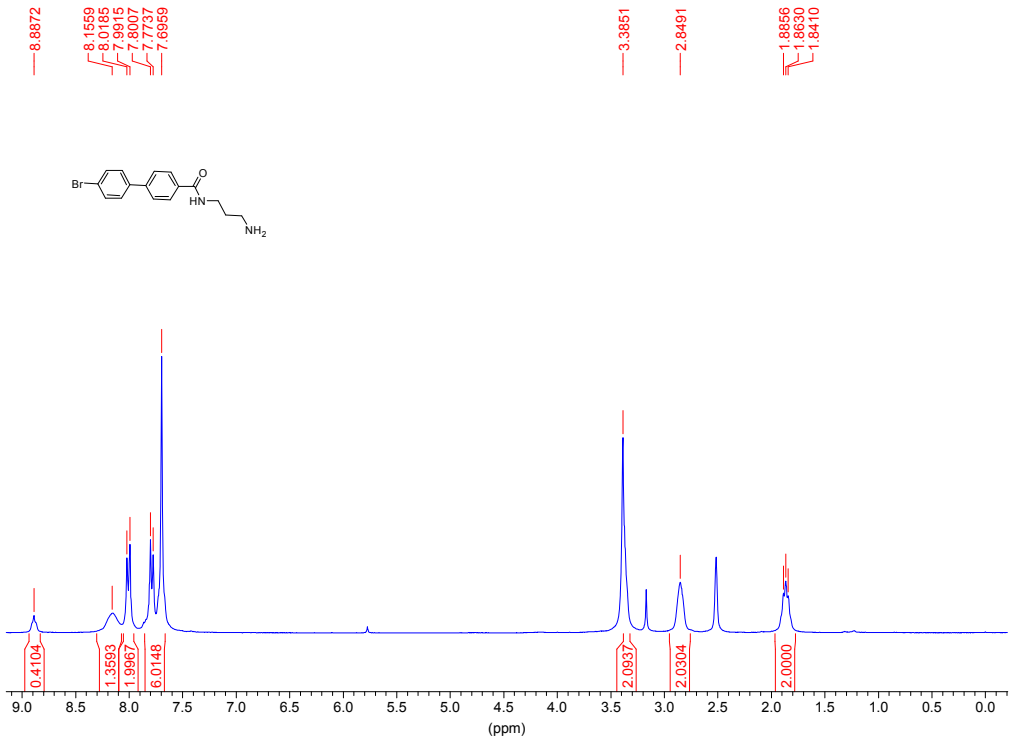


Figure 71: ^{1}H NMR spectrum of compound **9v** (300 MHz, DMSO-d_6).

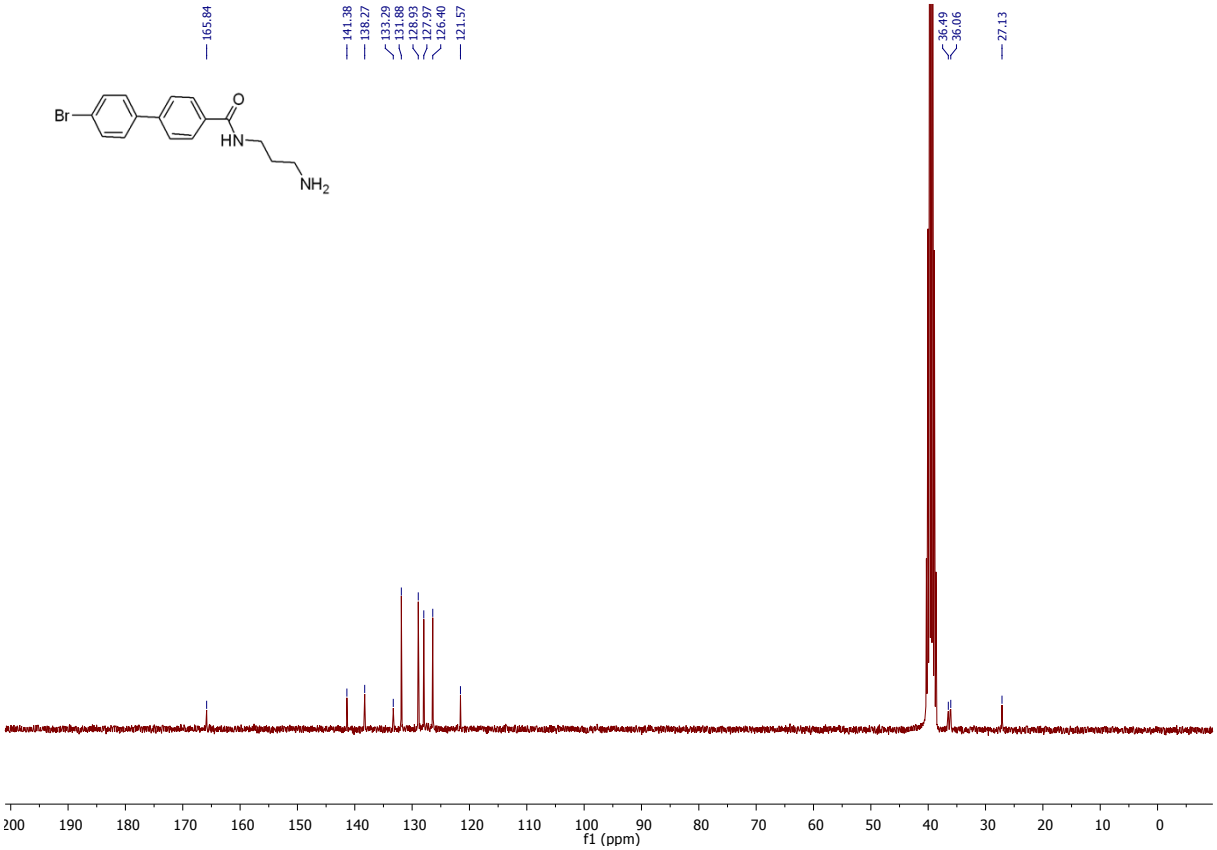


Figure 72: ^{13}C NMR spectrum of compound **9v** (300 MHz, DMSO-d_6).

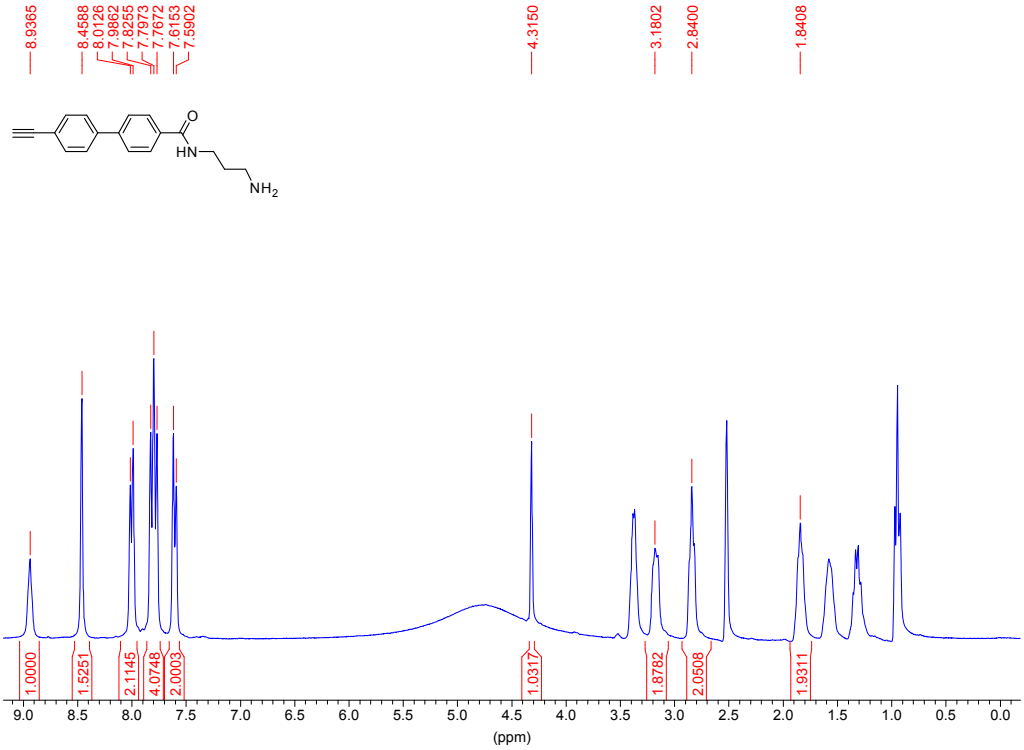


Figure 73: ^{1}H NMR spectrum of compound **10v** (300 MHz, DMSO-d_6).

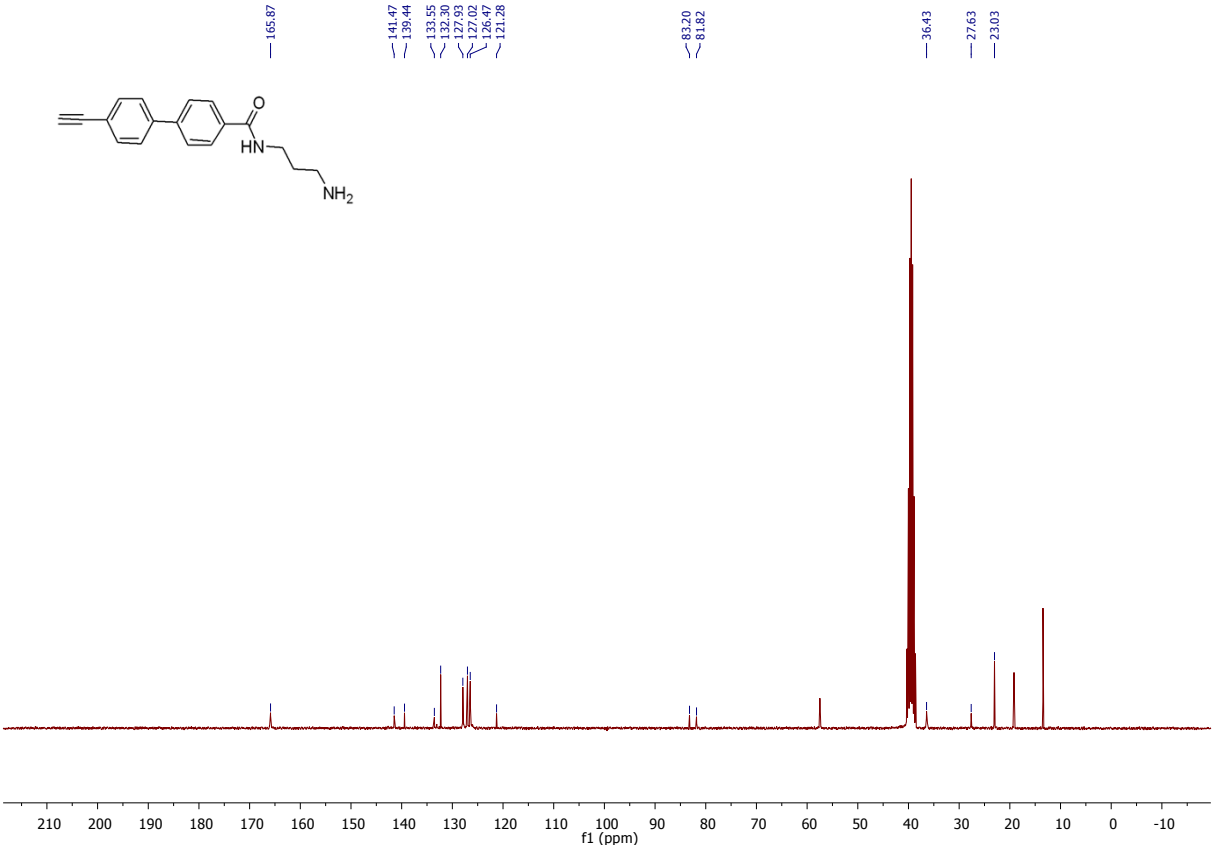


Figure 74: ^{13}C NMR spectrum of compound **10v** (300 MHz, DMSO-d_6).

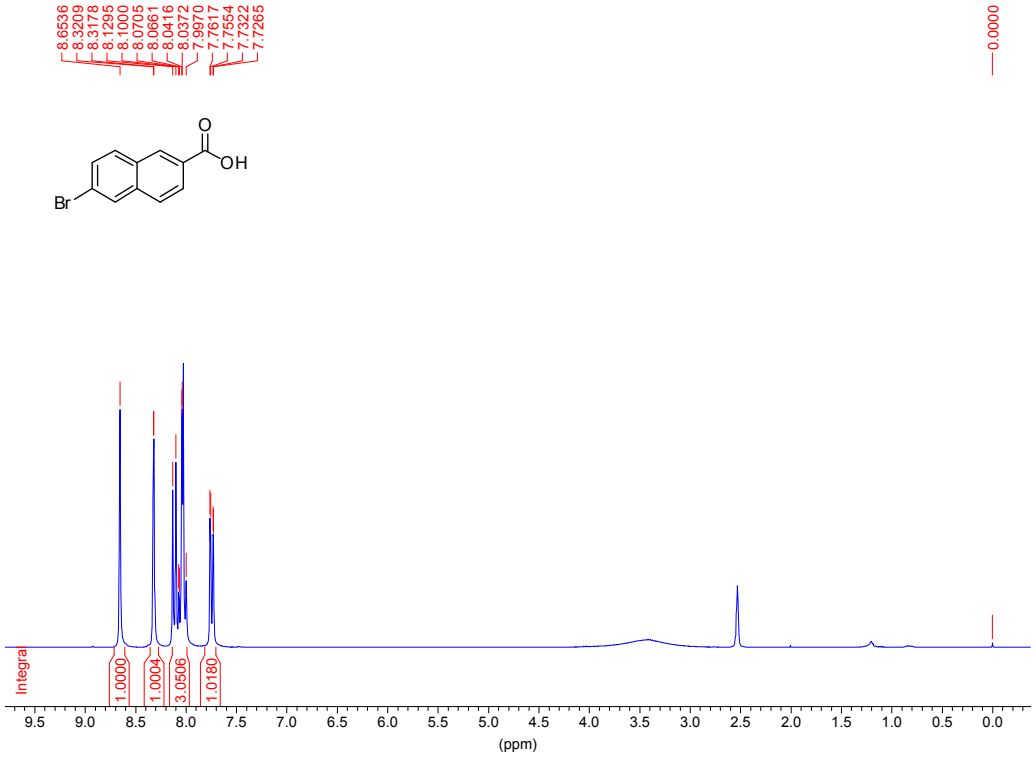


Figure 75: ^{1}H NMR spectrum of compound **8h** (300 MHz, DMSO-d_6).

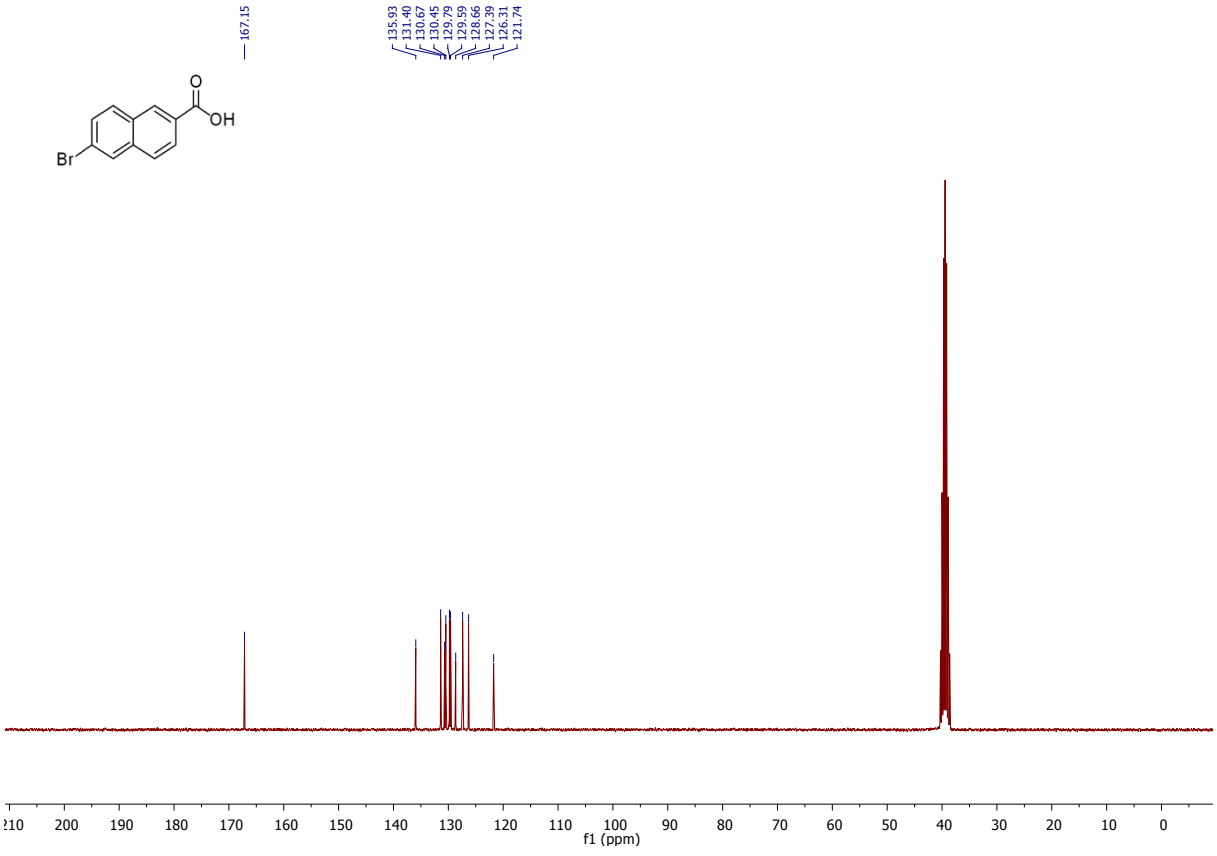


Figure 76: ^{13}C NMR spectrum of compound **8h** (300 MHz, DMSO-d_6).

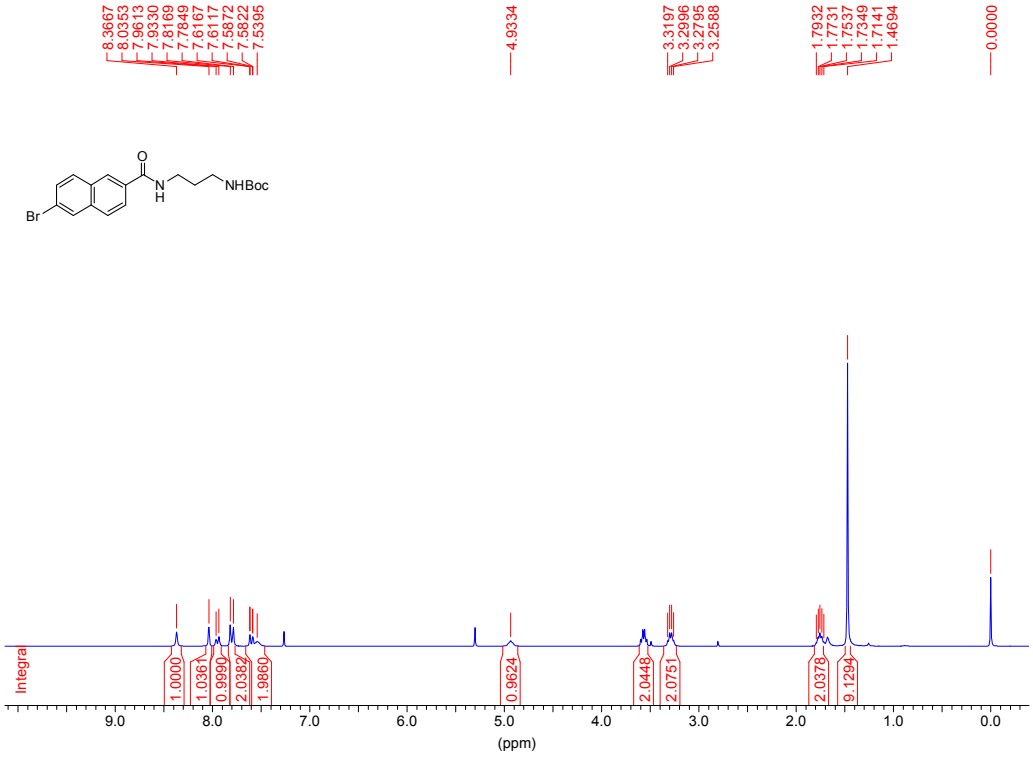


Figure 77: ^{1}H NMR spectrum of compound **9w'** (300 MHz, $CDCl_3$).

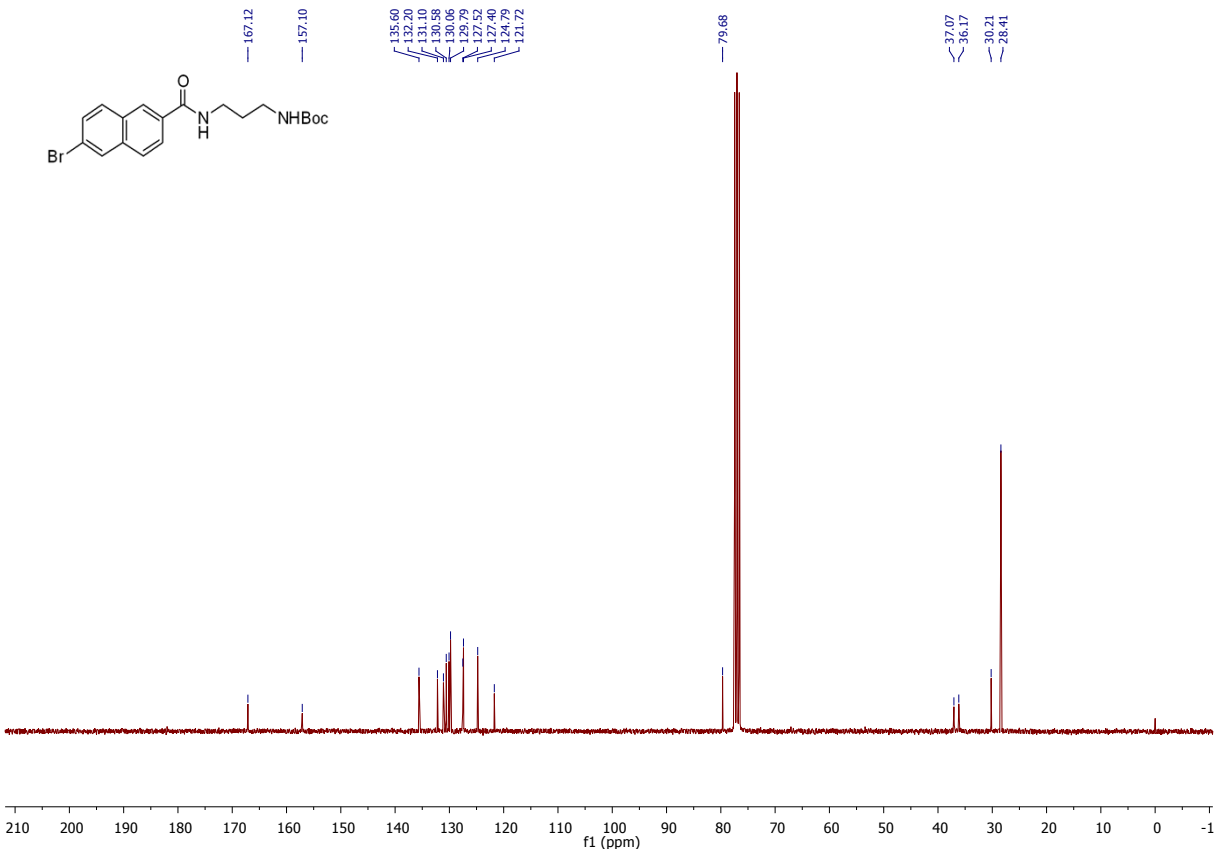


Figure 78: ^{13}C NMR spectrum of compound **9w'** (300 MHz, $CDCl_3$).

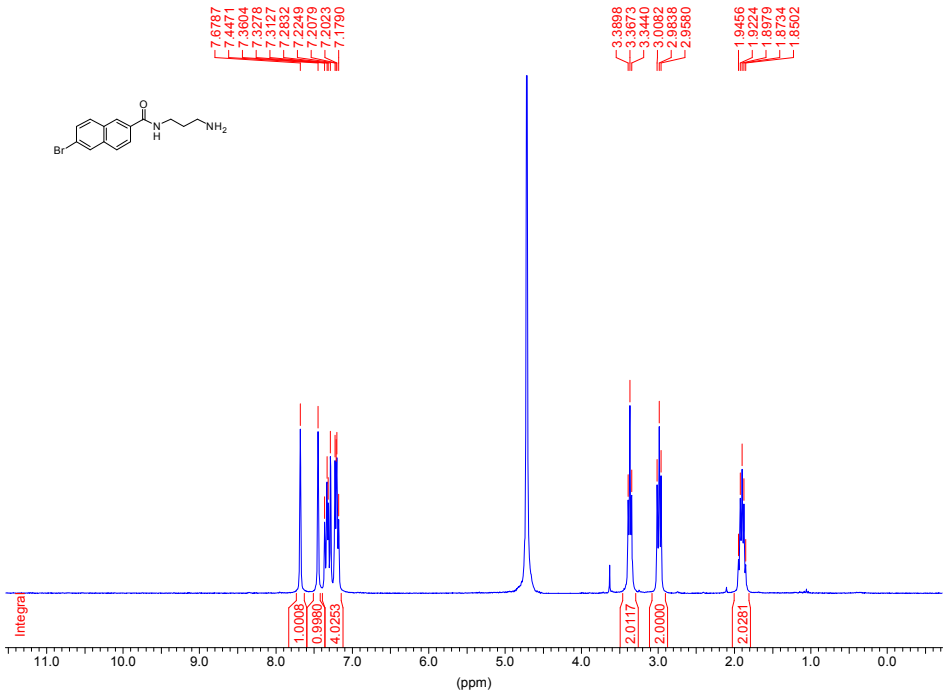


Figure 79: ^{1}H NMR spectrum of compound **9w** (300 MHz, D_2O).

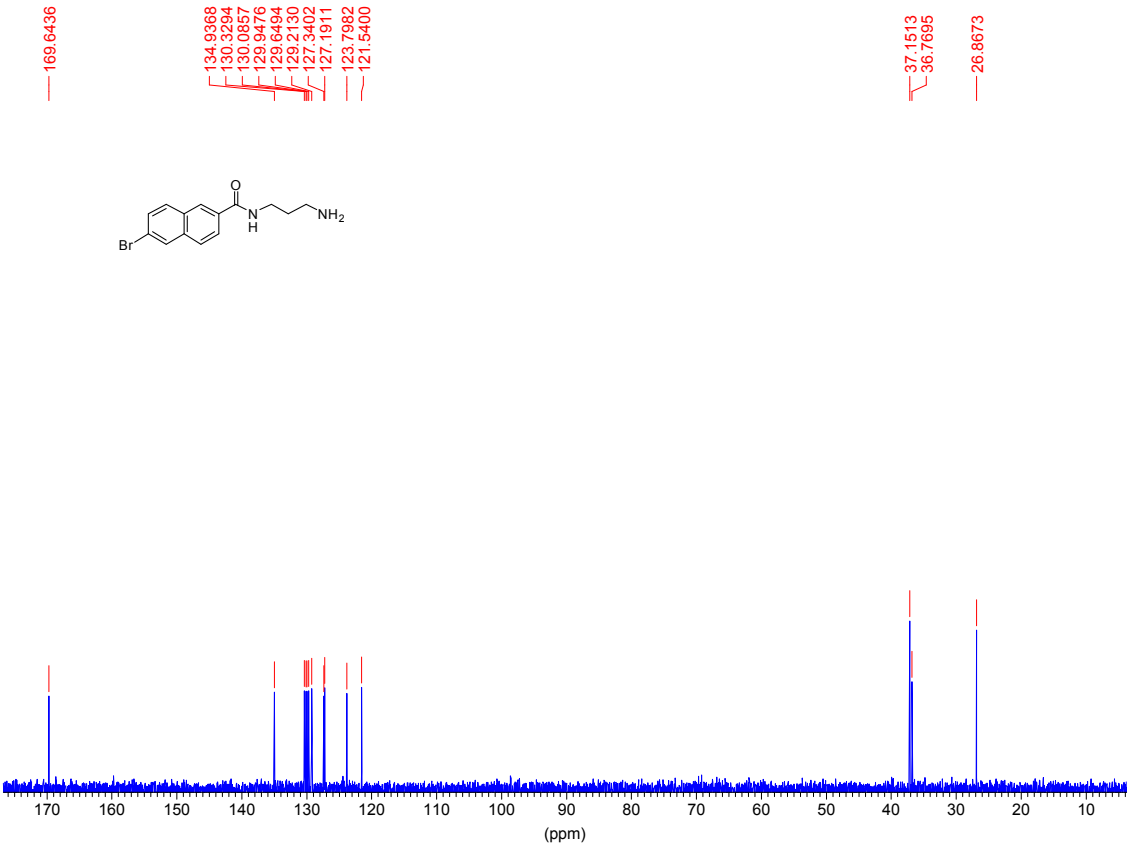


Figure 80: ^{13}C NMR spectrum of compound **9w** (300 MHz, D_2O).

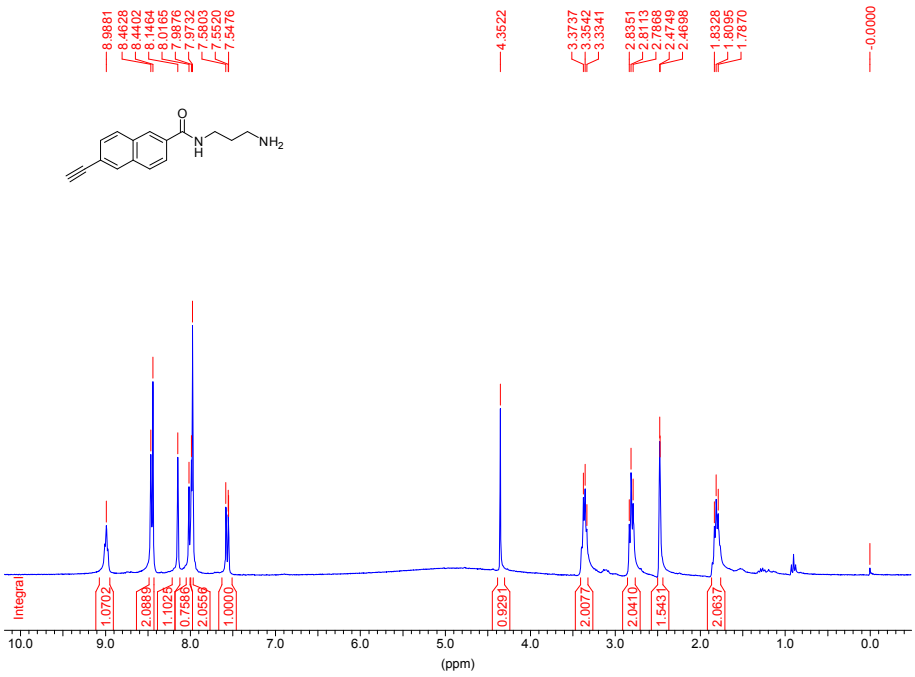


Figure 81: ^{1}H NMR spectrum of compound **10w** (300 MHz, DMSO-d_6).

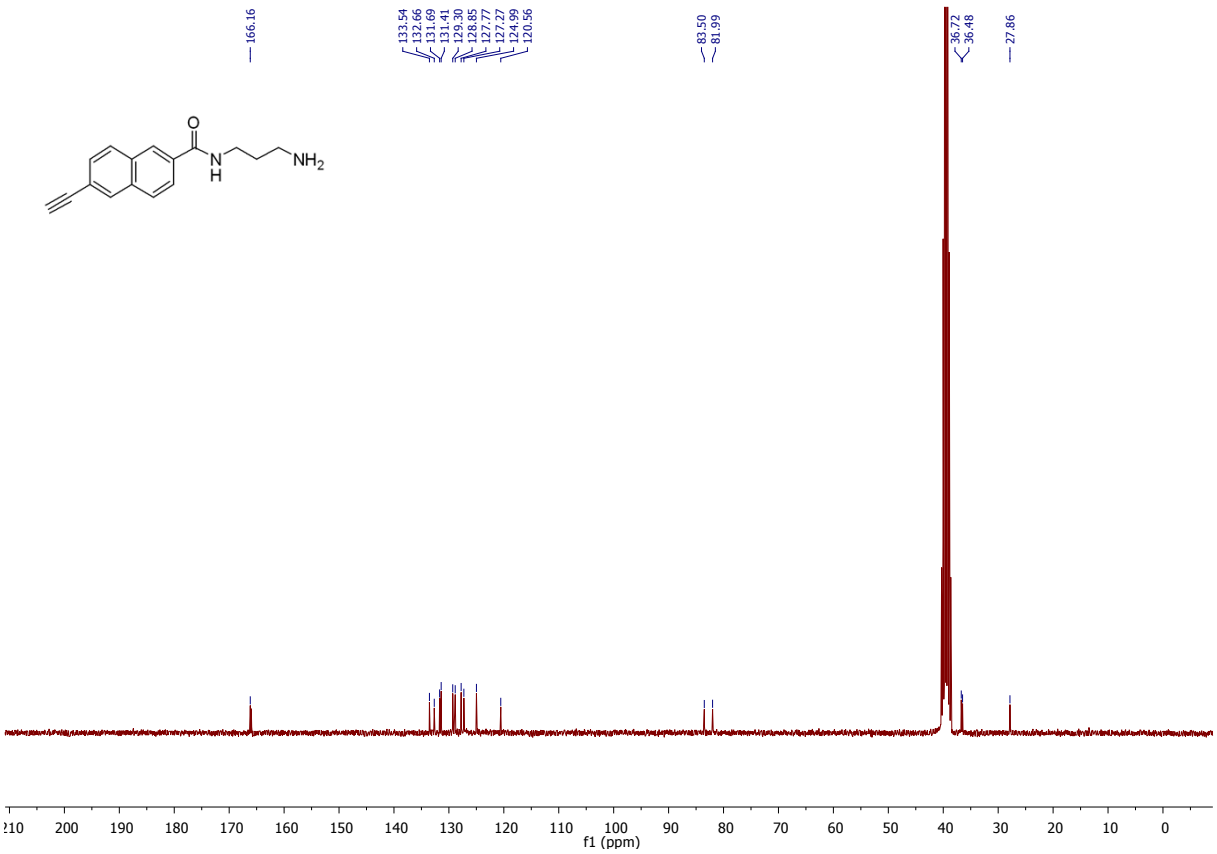


Figure 82: ^{13}C NMR spectrum of compound **10w** (300 MHz, DMSO-d_6).

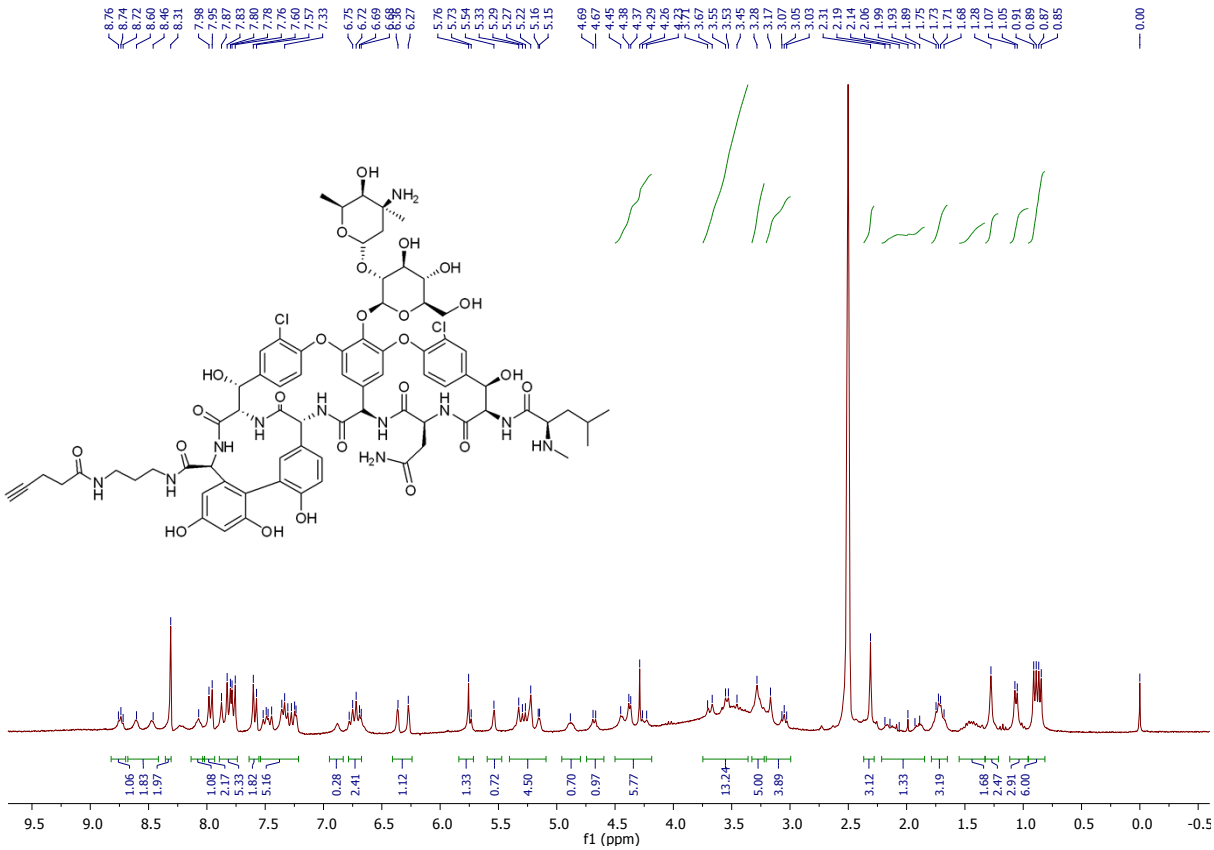


Figure 83: ^{1}H NMR spectrum of compound **11f** (300 MHz, DMSO-d6).

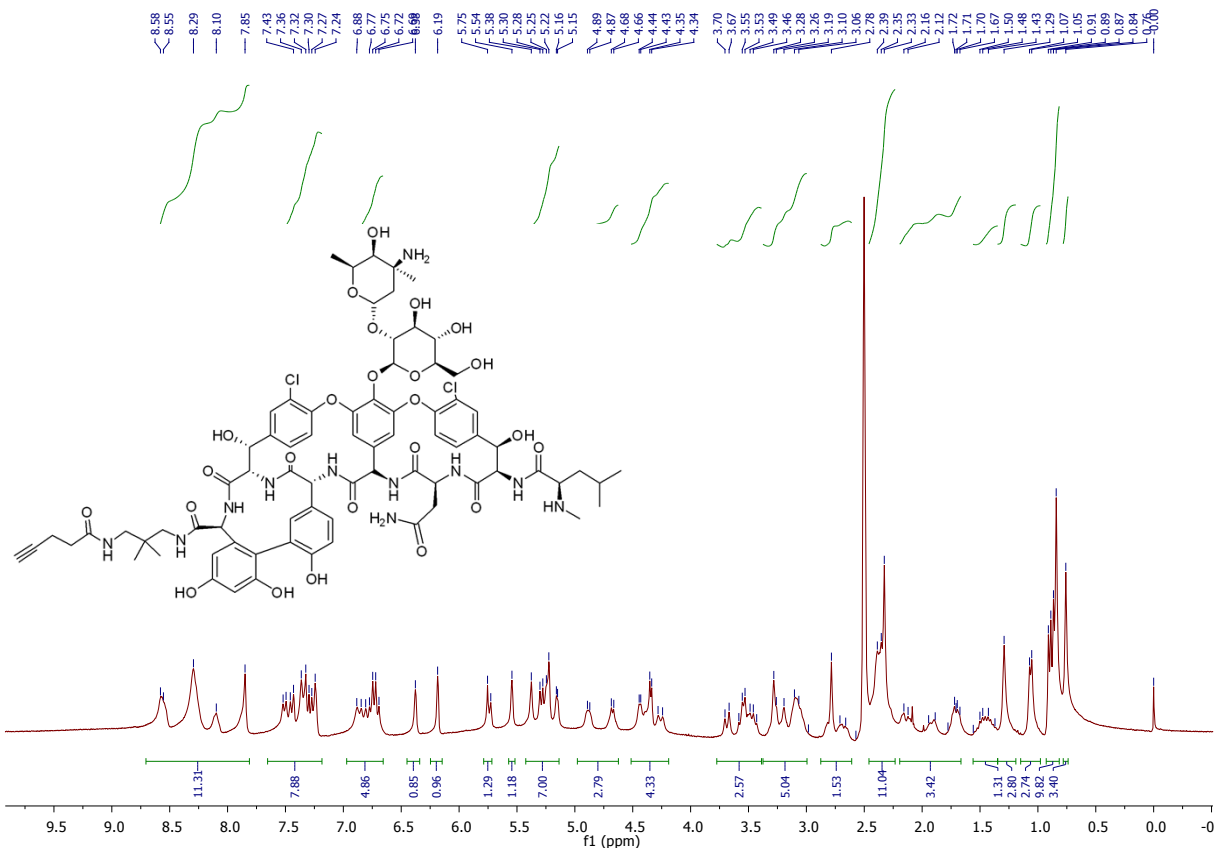


Figure 84: ^{1}H NMR spectrum of compound **11i** (300 MHz, DMSO-d6).

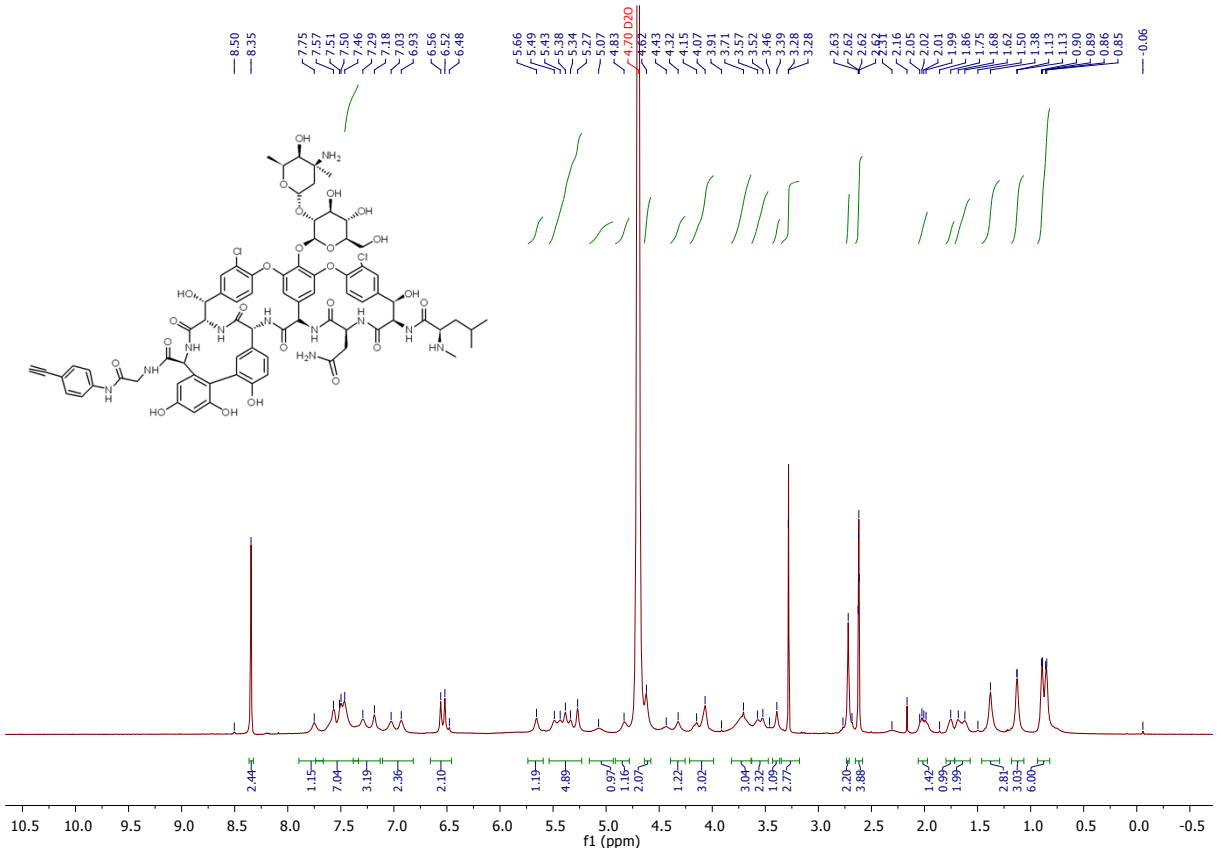


Figure 85: ^{1}H NMR spectrum of compound **11n** (600 MHz, D_2O).

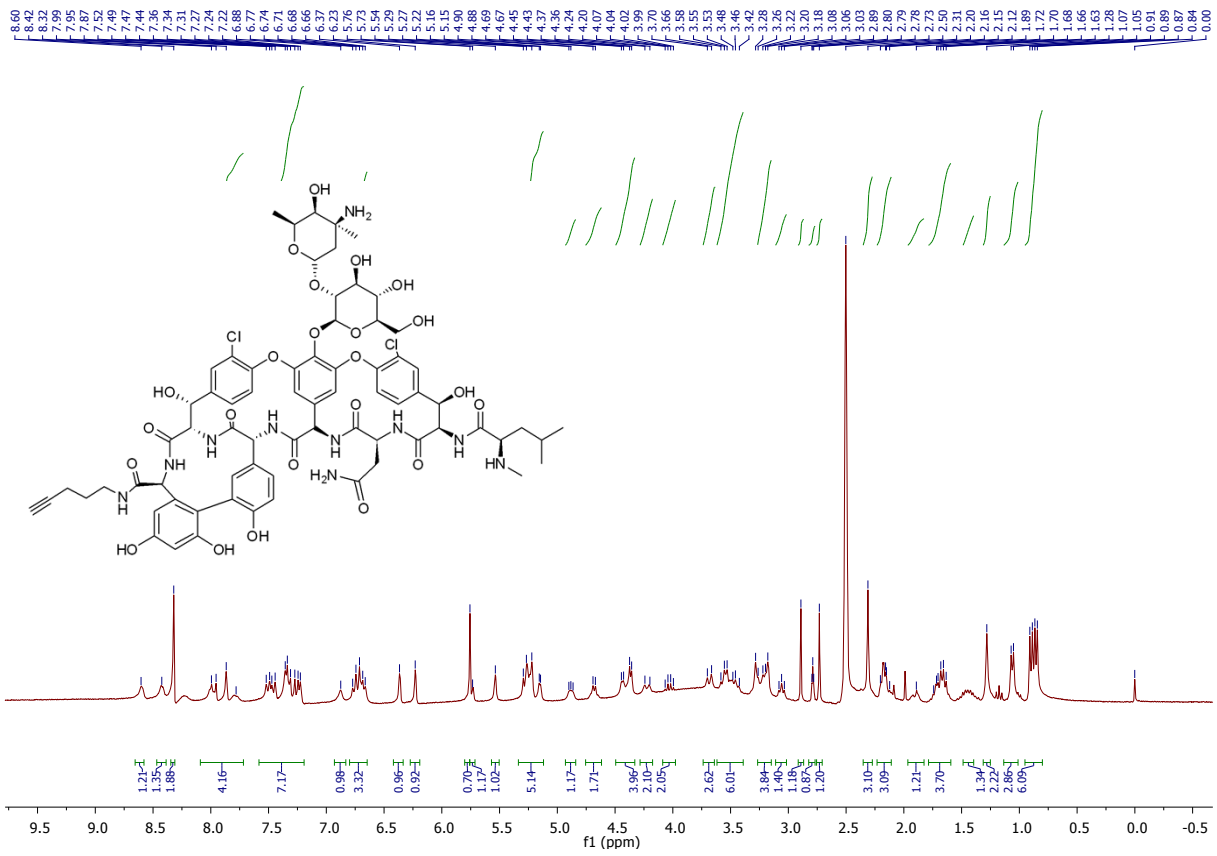


Figure 86: ^{1}H NMR spectrum of compound **11r** (300 MHz, DMSO-d6).

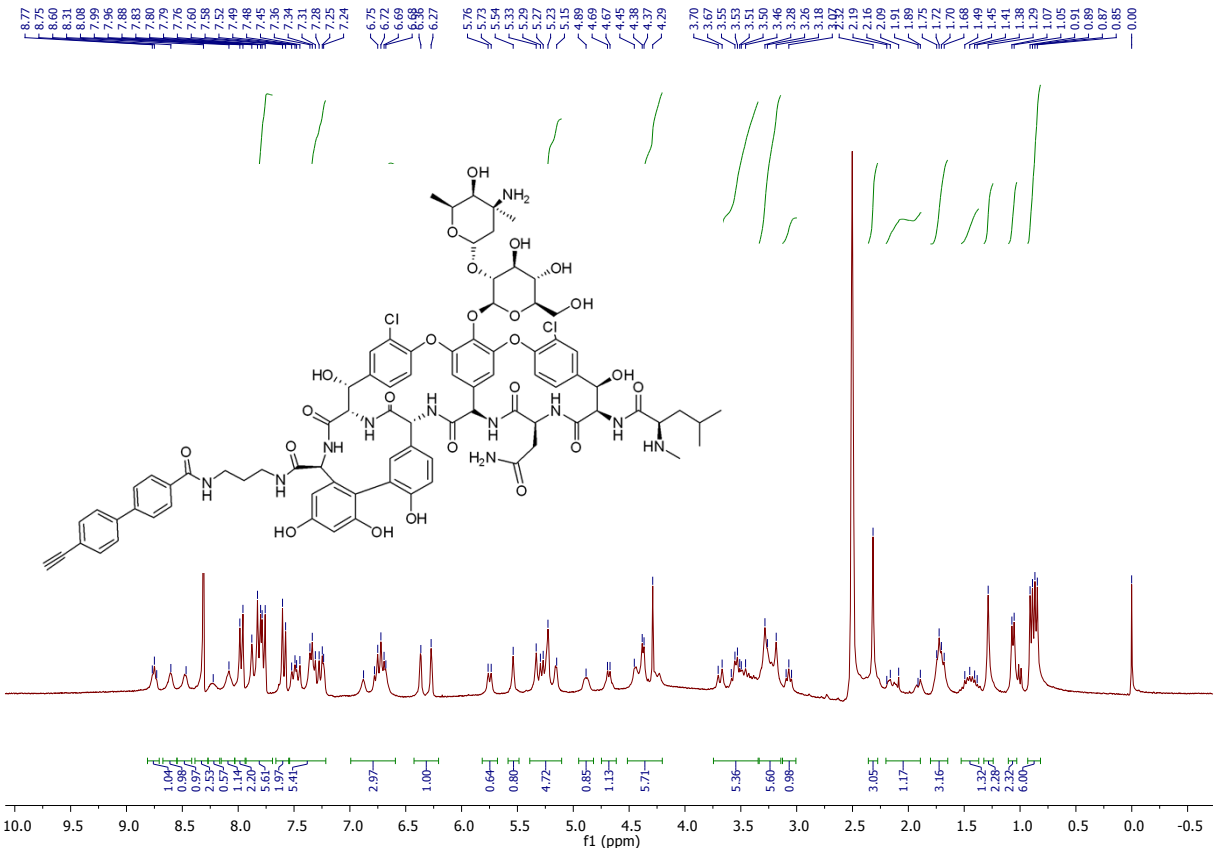


Figure 87: ^{1}H NMR spectrum of compound **11v** (300 MHz, DMSO-d6).

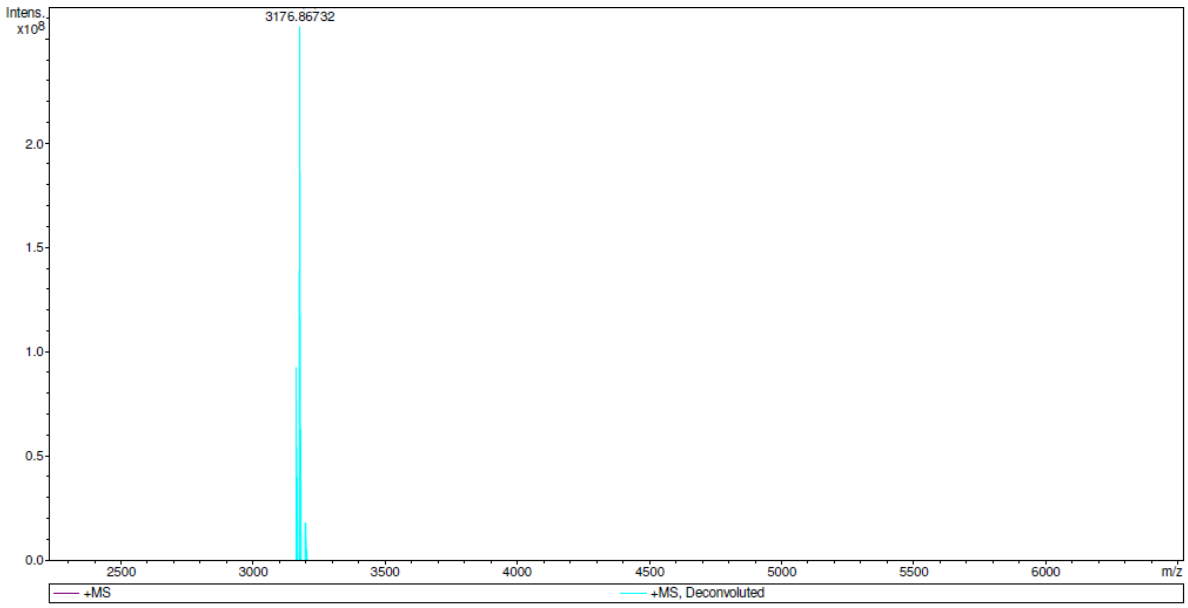


Figure 88: Mass spectrum (MALDI-TOF) of CRAMP azide **5**.

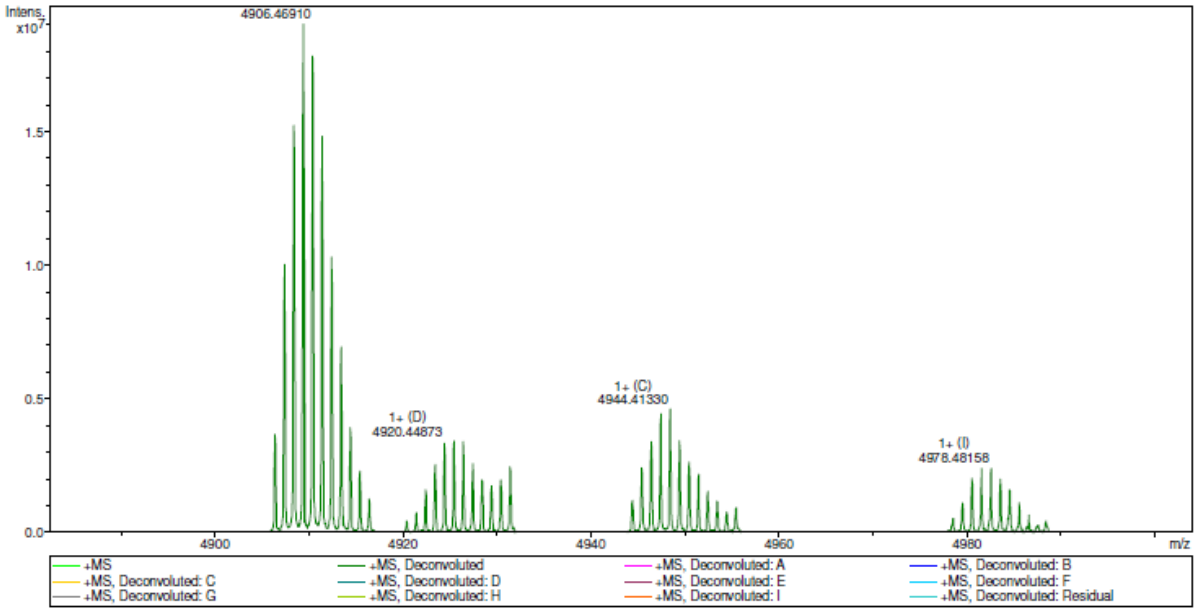


Figure 89: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12a**.

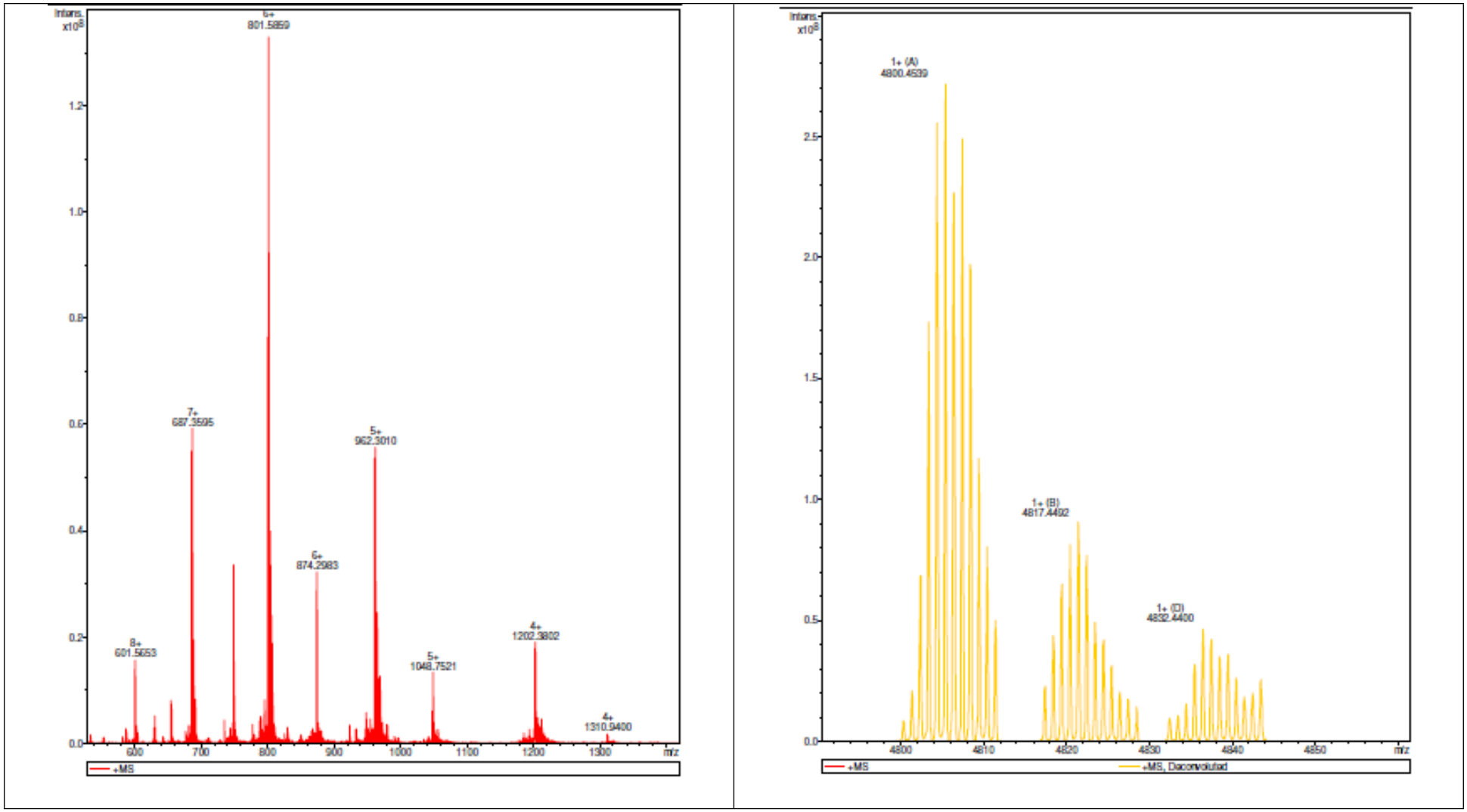


Figure 90: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12b**.

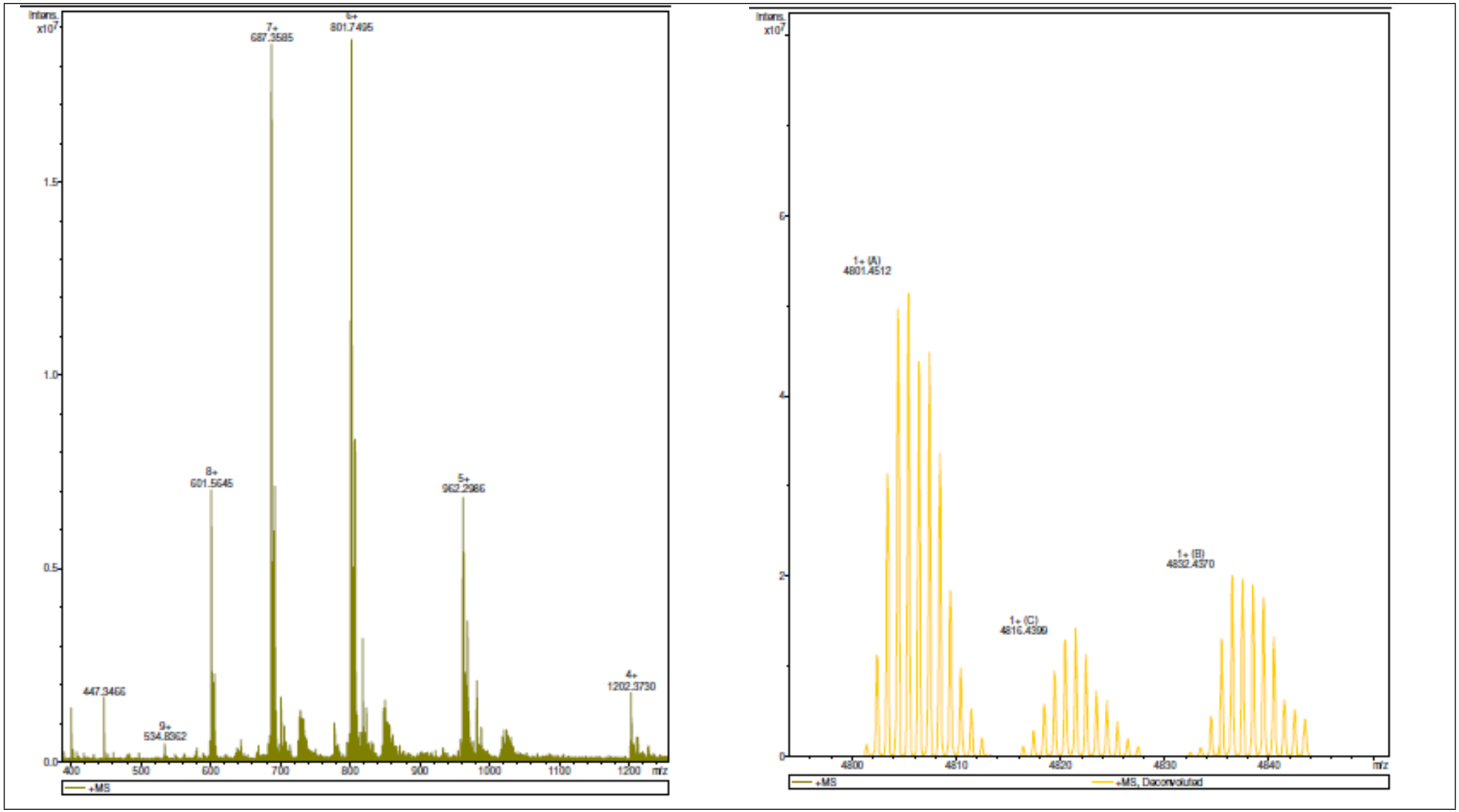


Figure 91: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12b'**.

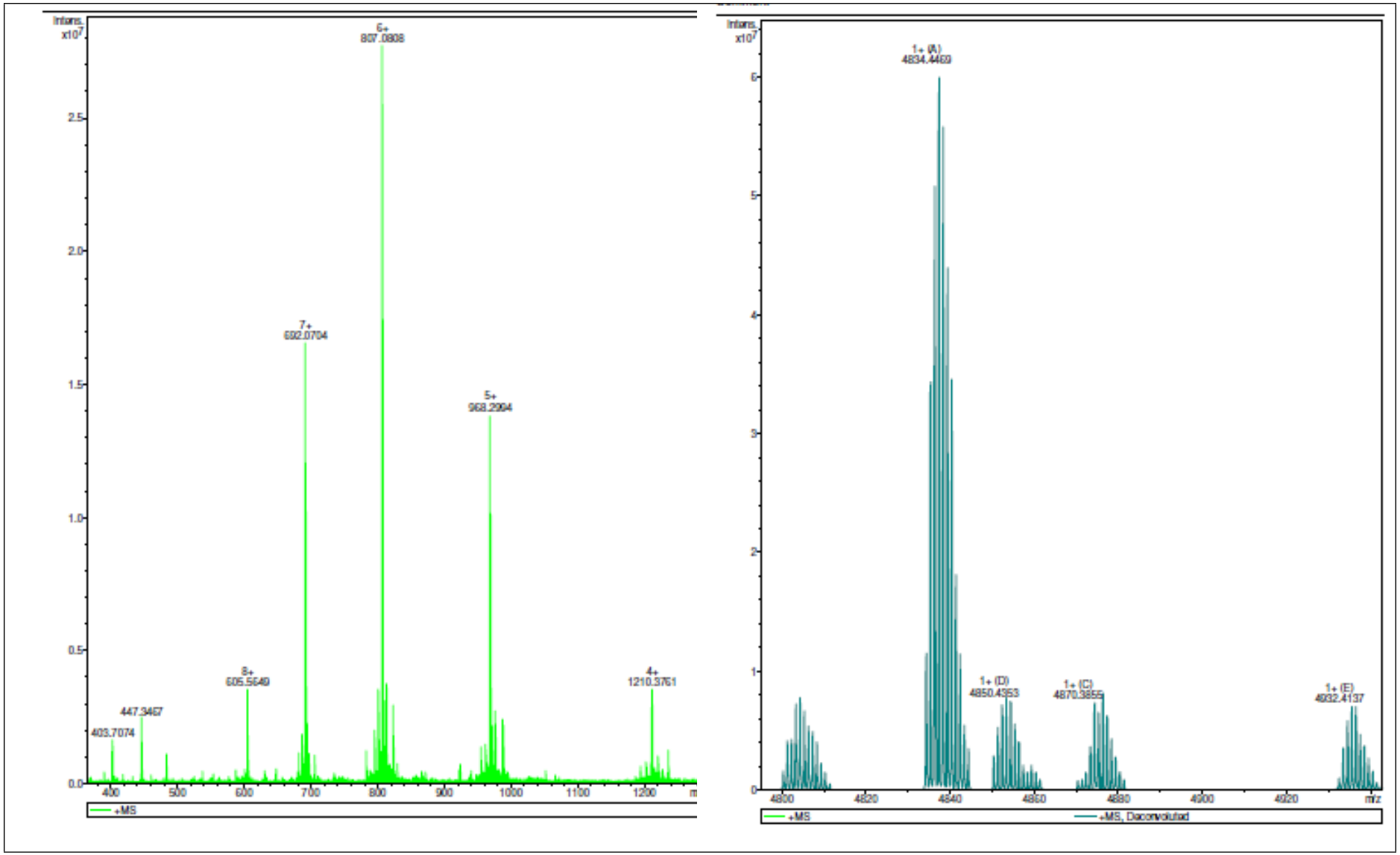


Figure 92: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12c**.

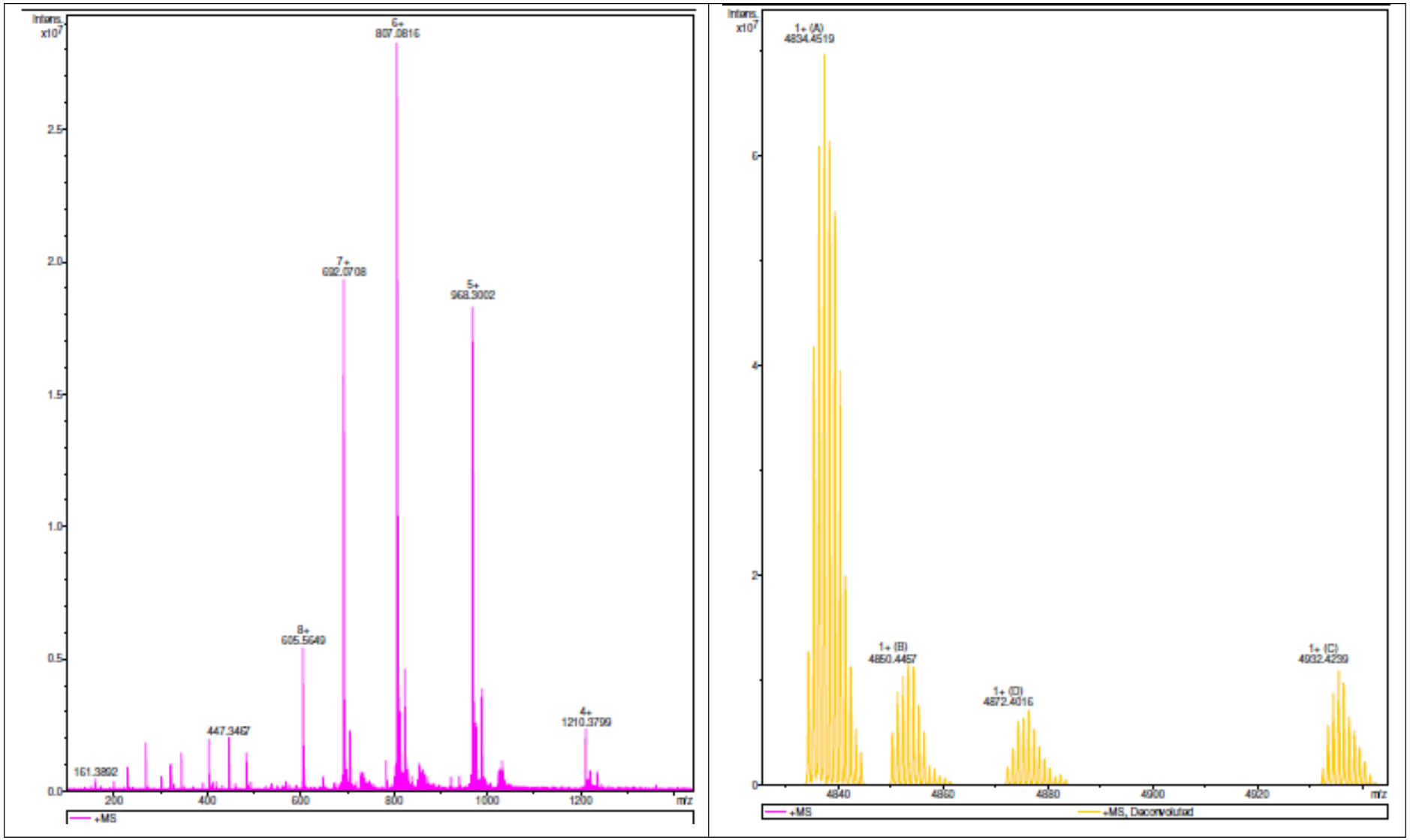


Figure 93: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12c'**.

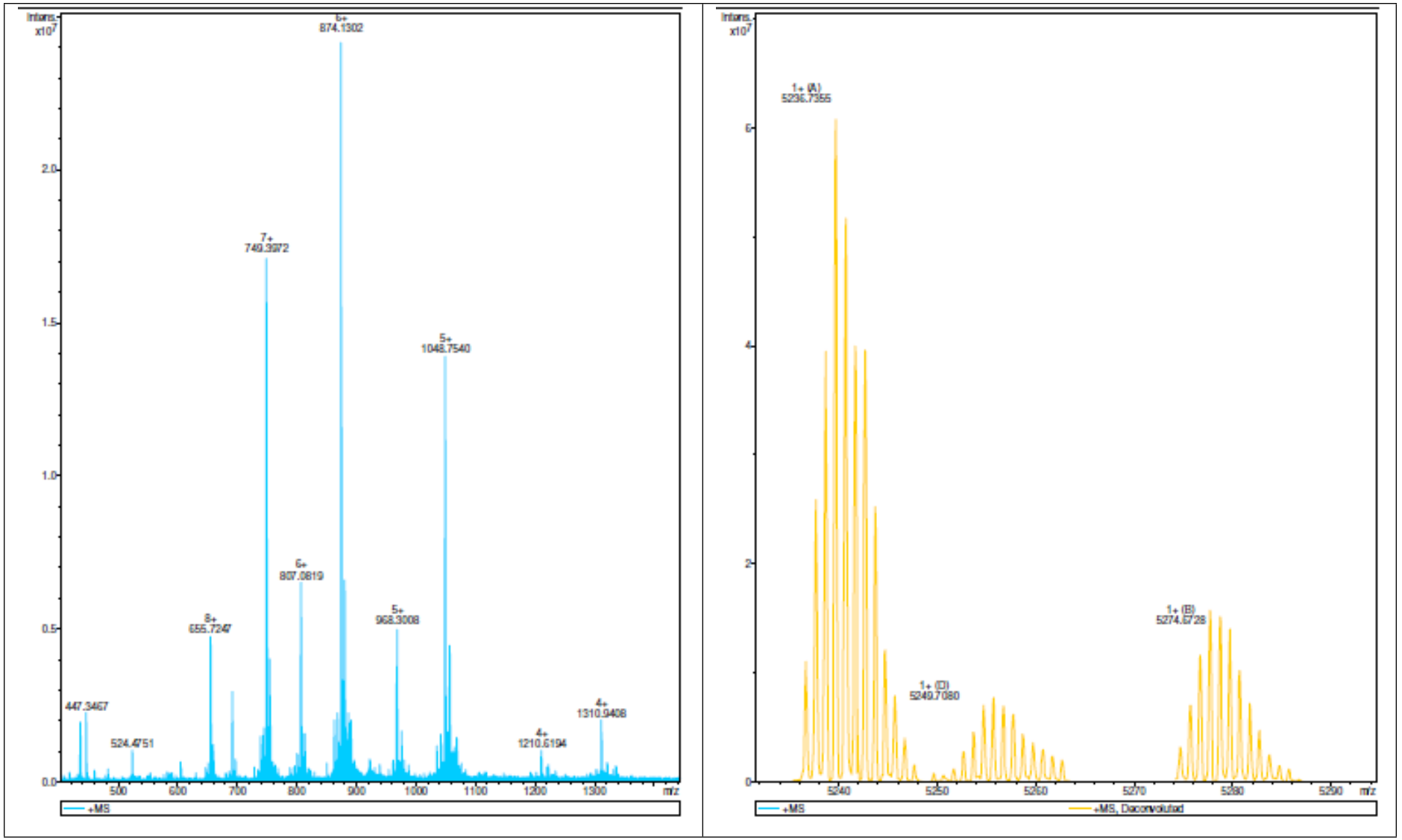


Figure 94: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12d**.

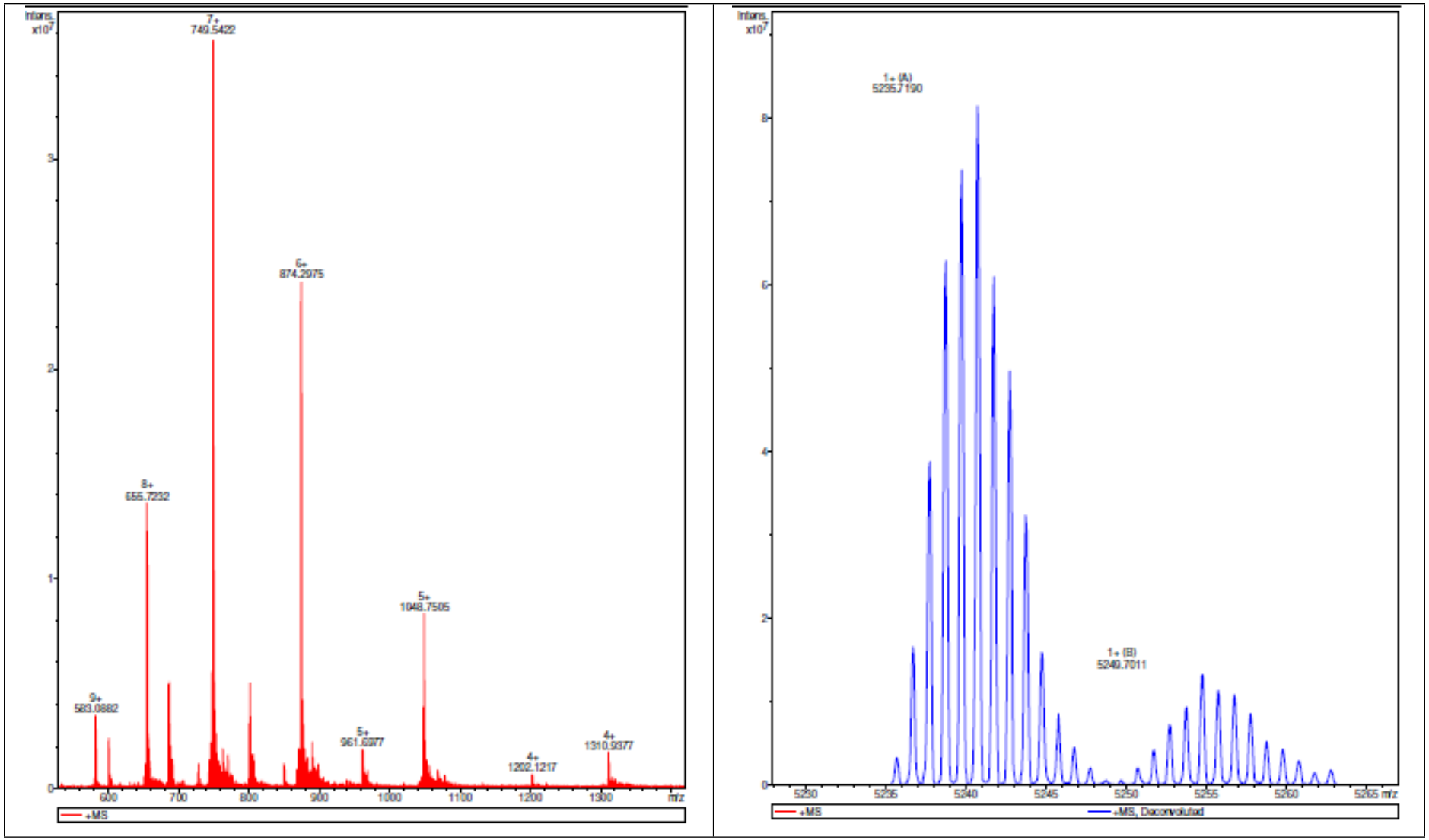


Figure 95: Mass spectrum (FT-ICR) of CRAMP-vancomycin conjugate **12d'**.

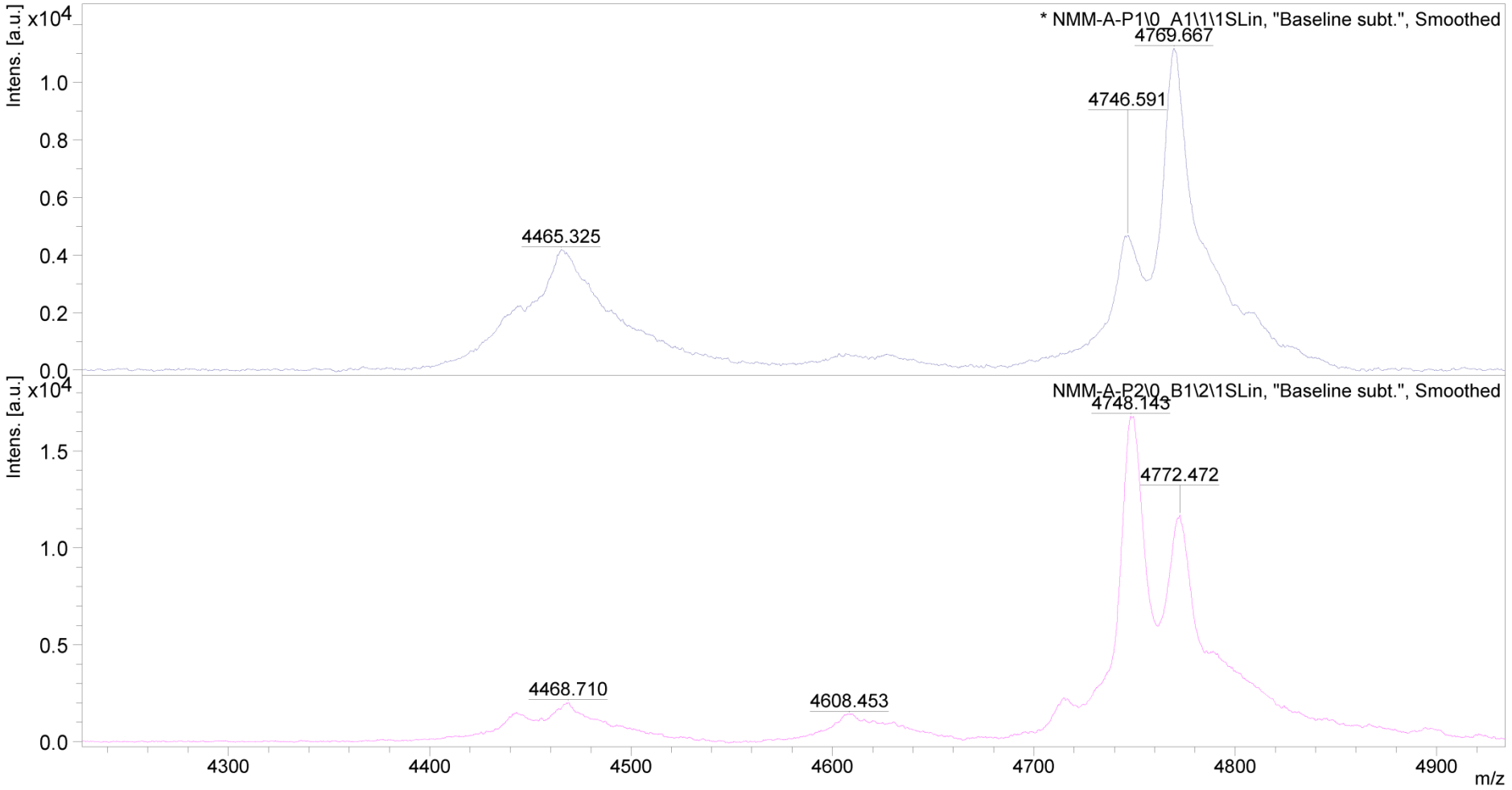


Figure 96: Mass spectra (MALDI-TOF) of CRAMP-vancomycin conjugates **12e** & **12e'**.

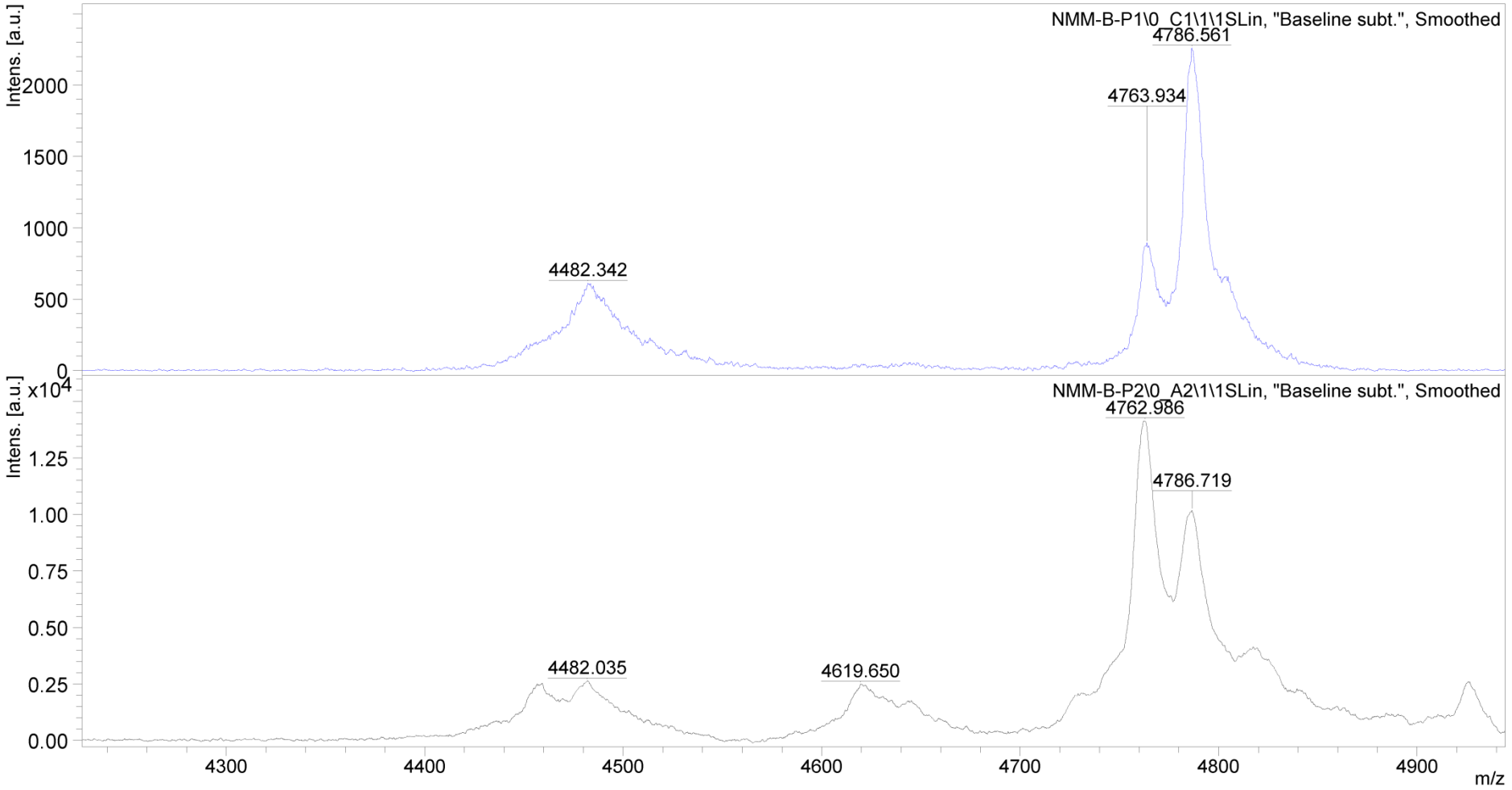


Figure 97: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12f** & **12f'**.

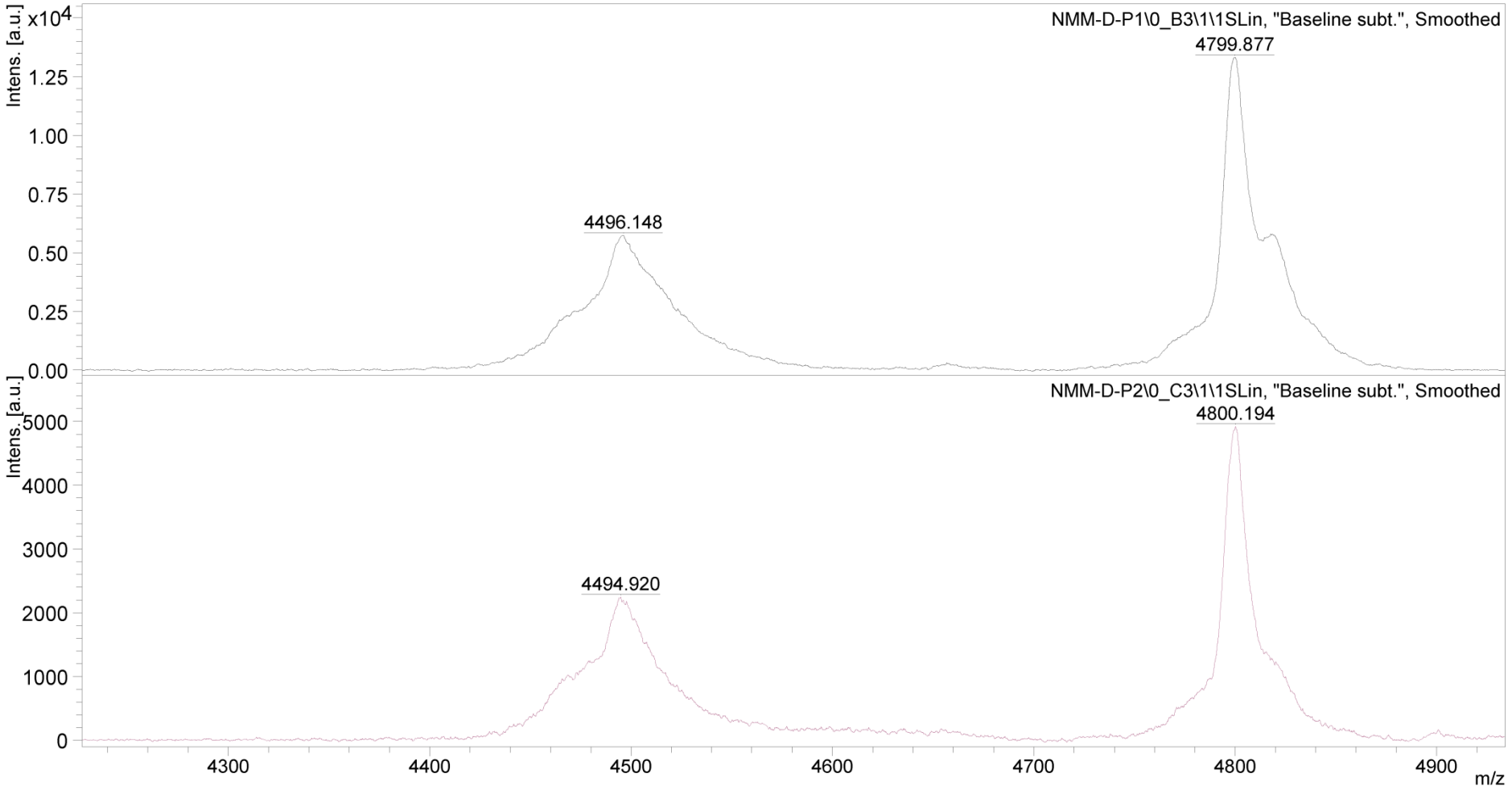


Figure 98: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12g** & **12g'.**

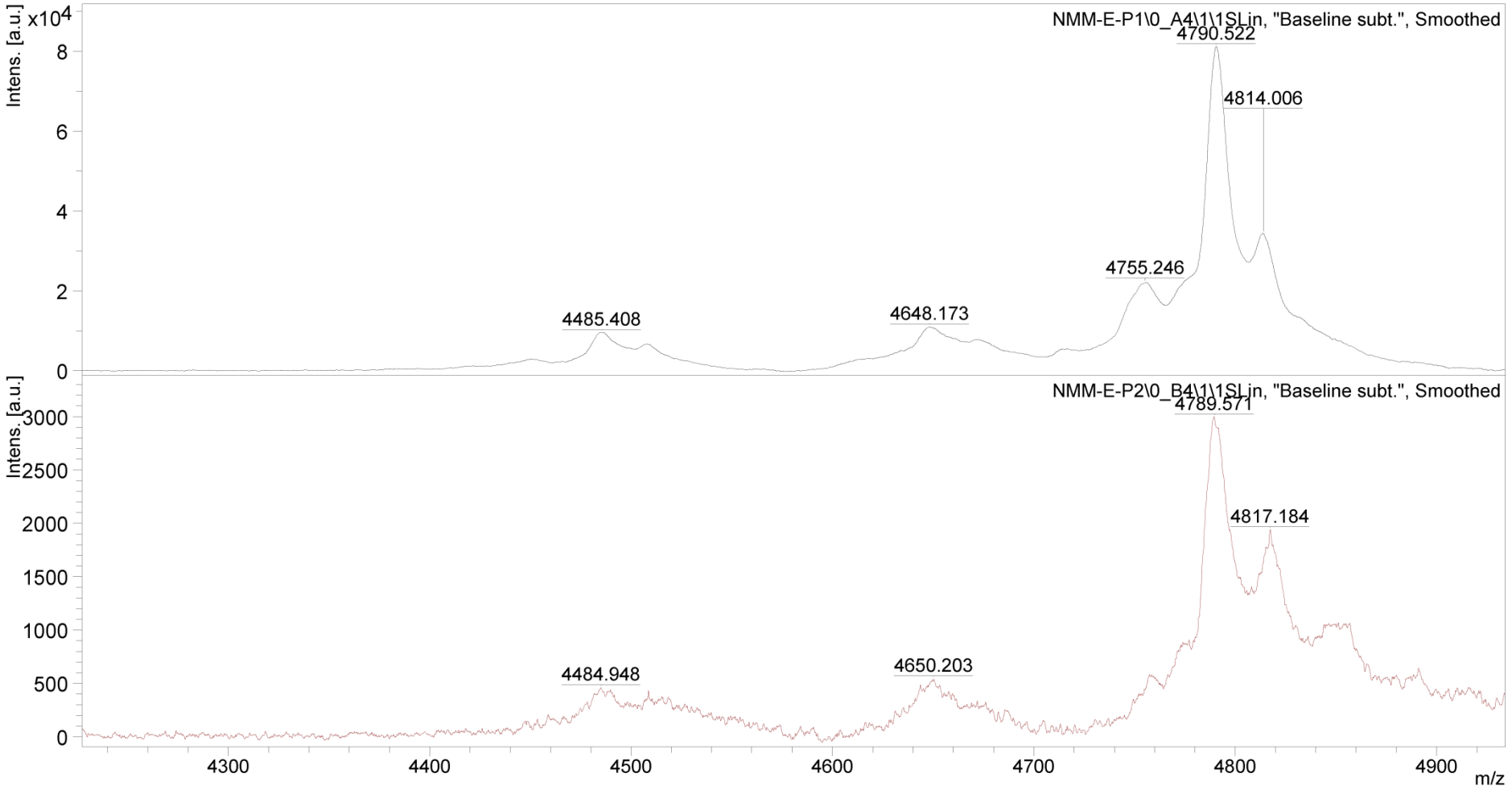


Figure 99: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12h** & **12h'.**

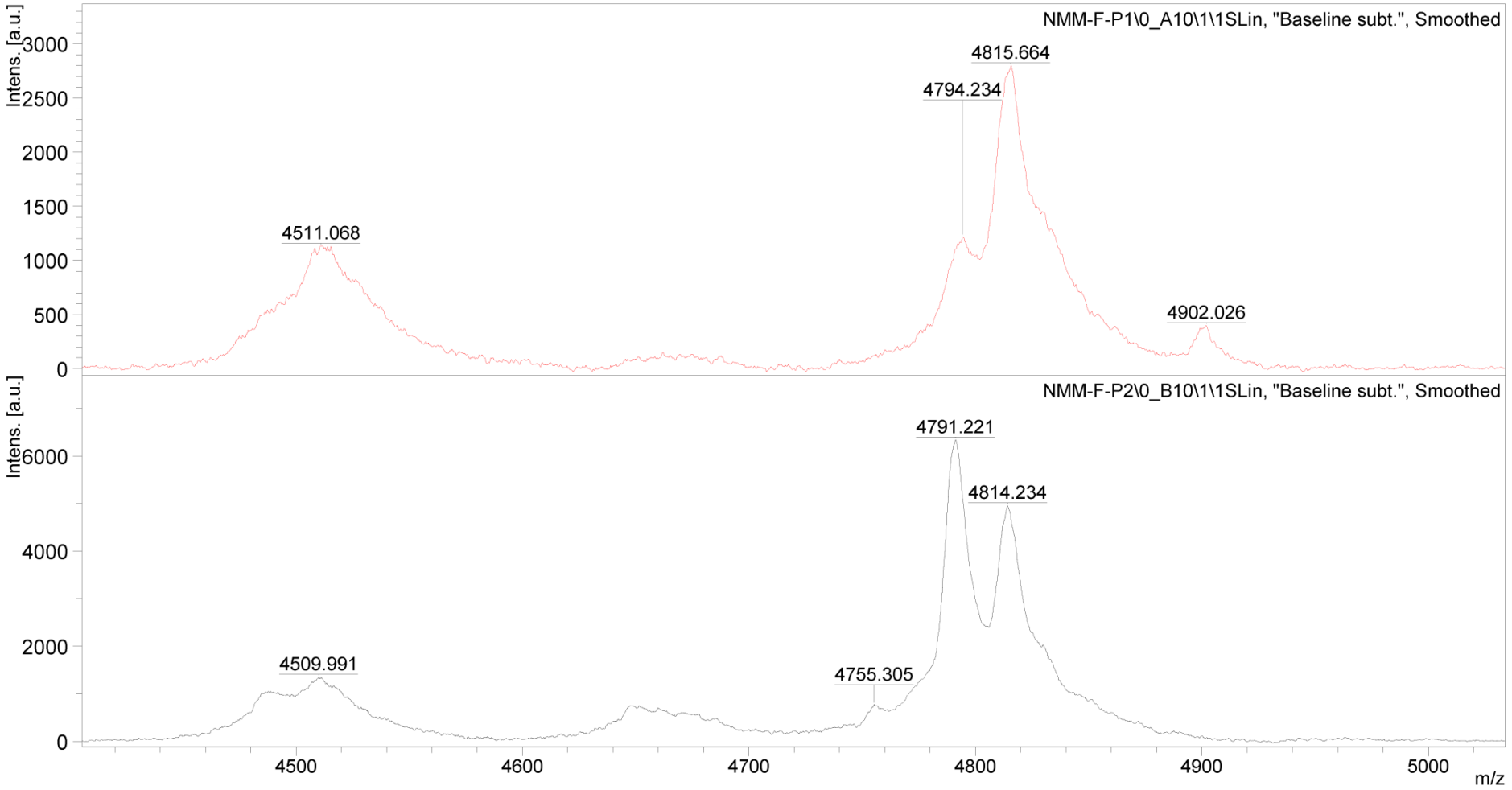


Figure 100: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12i** & **12i'.**

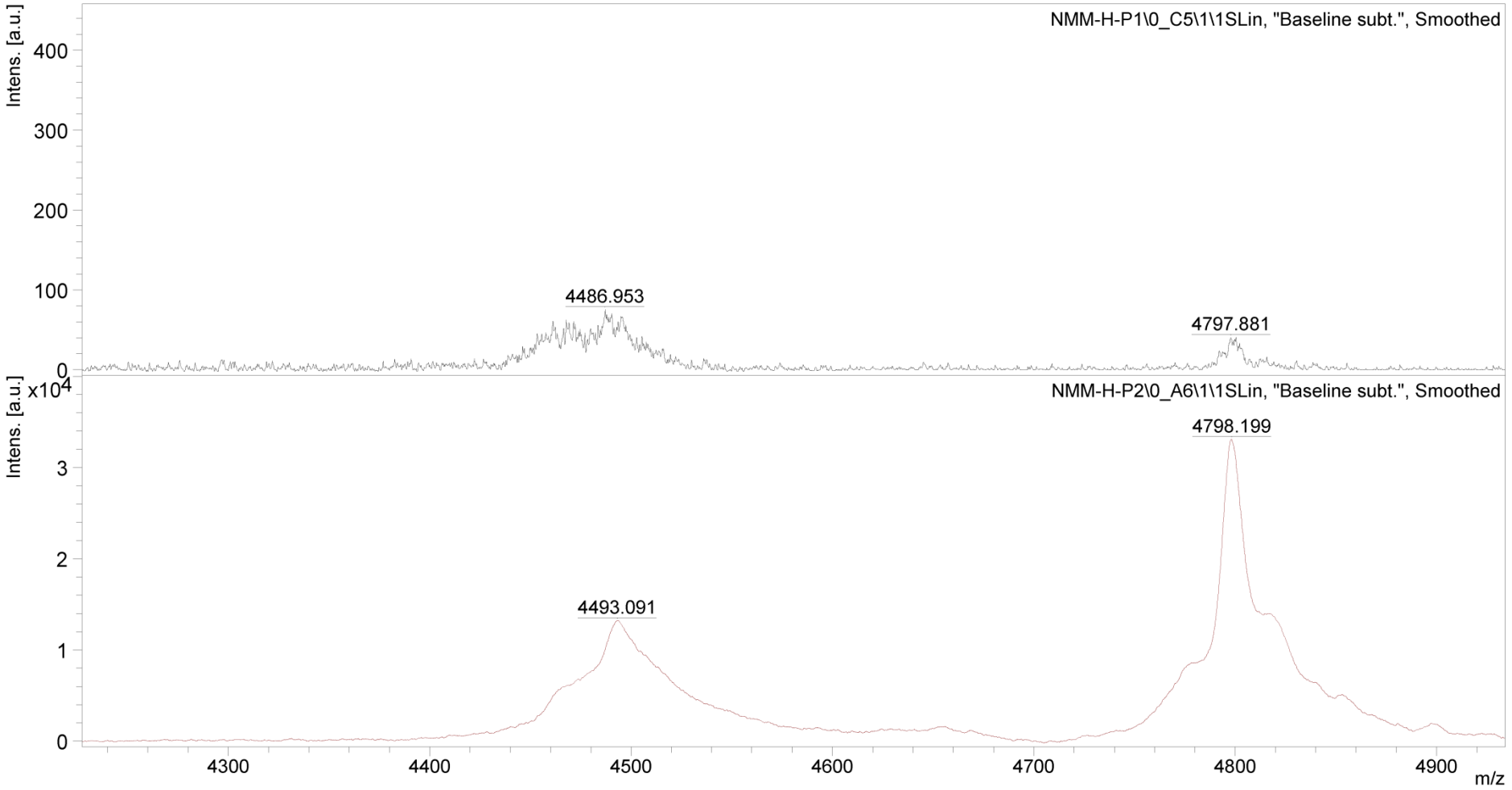


Figure 101: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12j** & **12j'.**

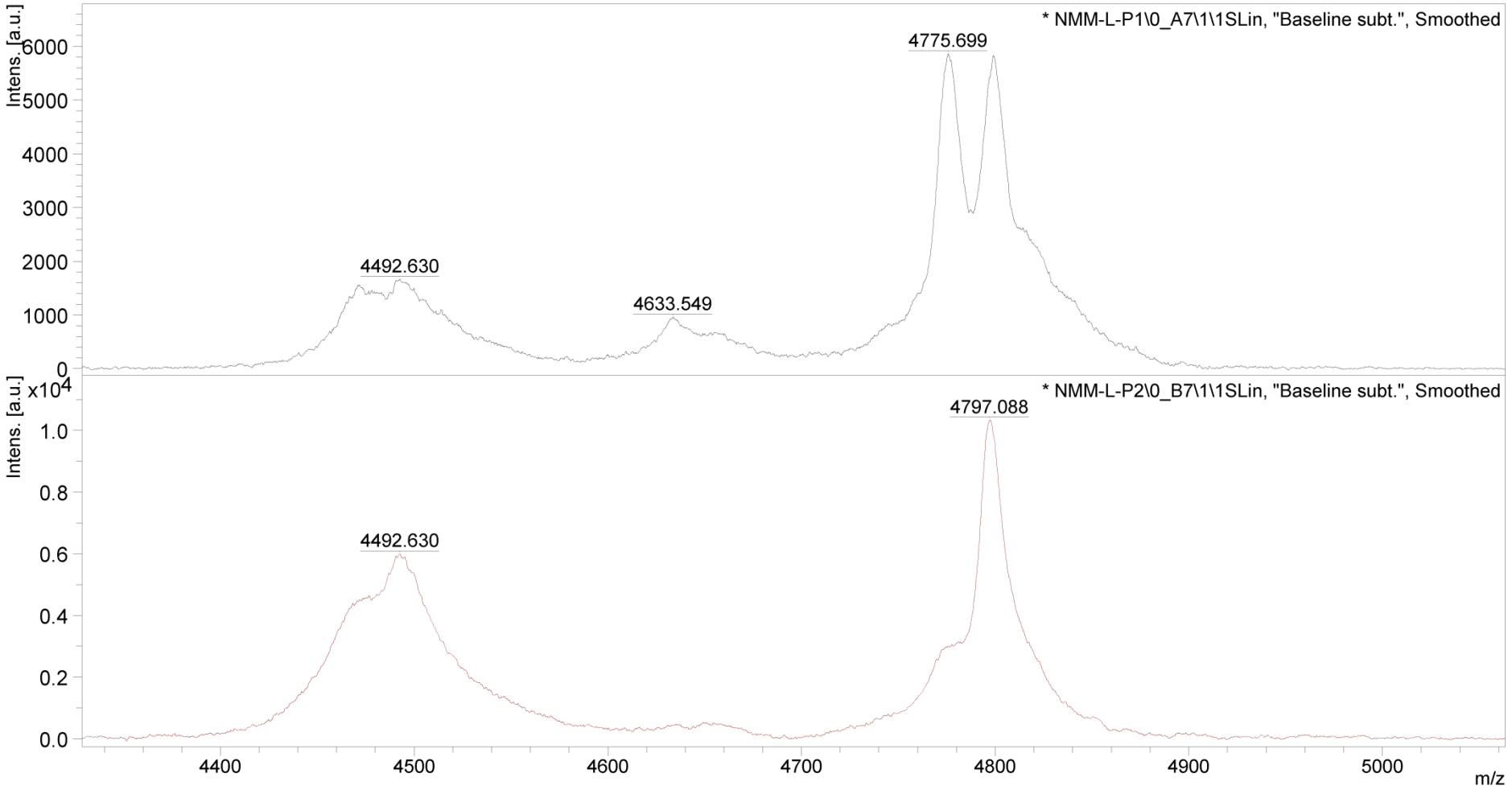


Figure 102: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12k** & **12k'.**

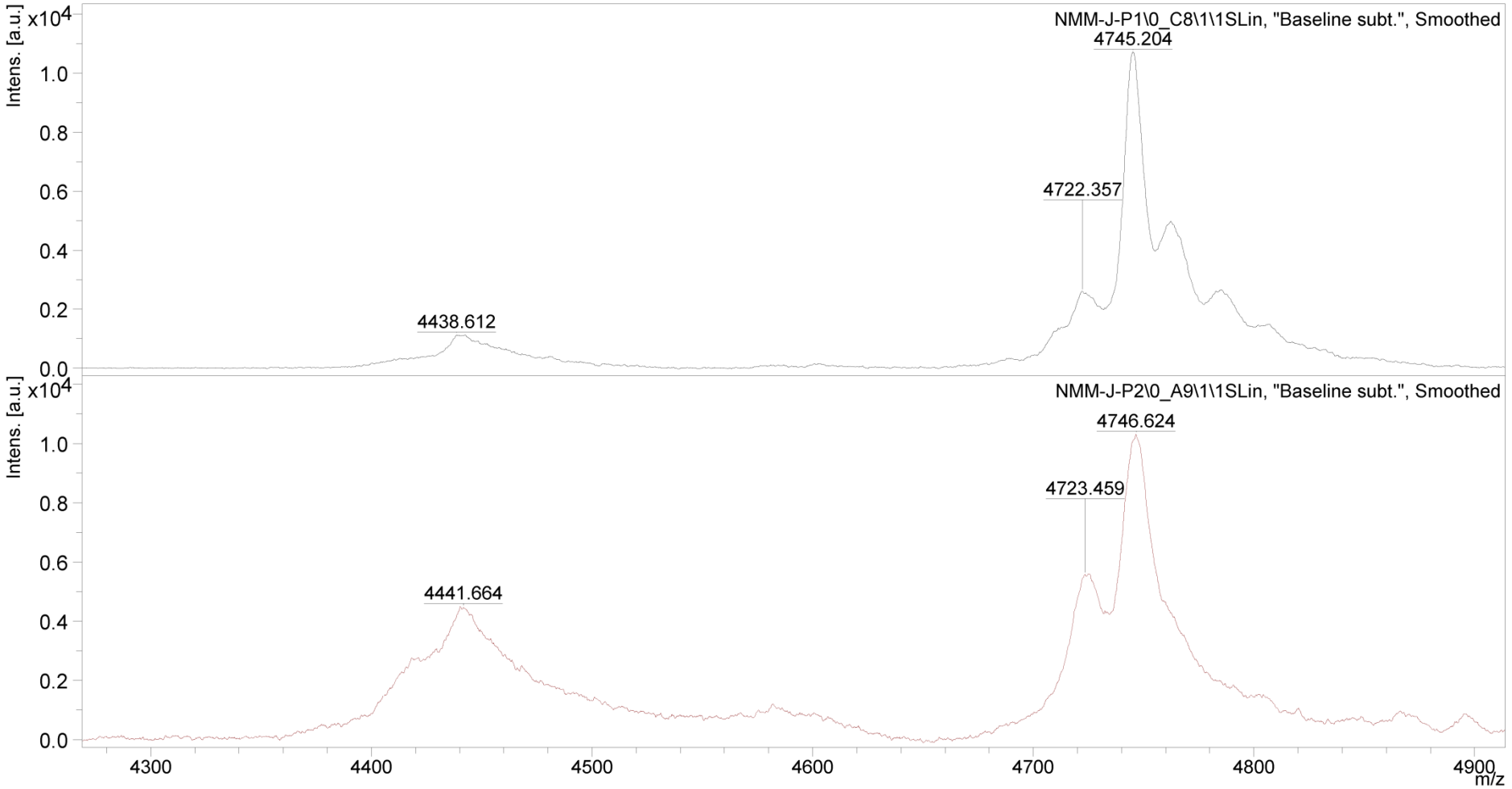


Figure 103: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12l** & **12l'**

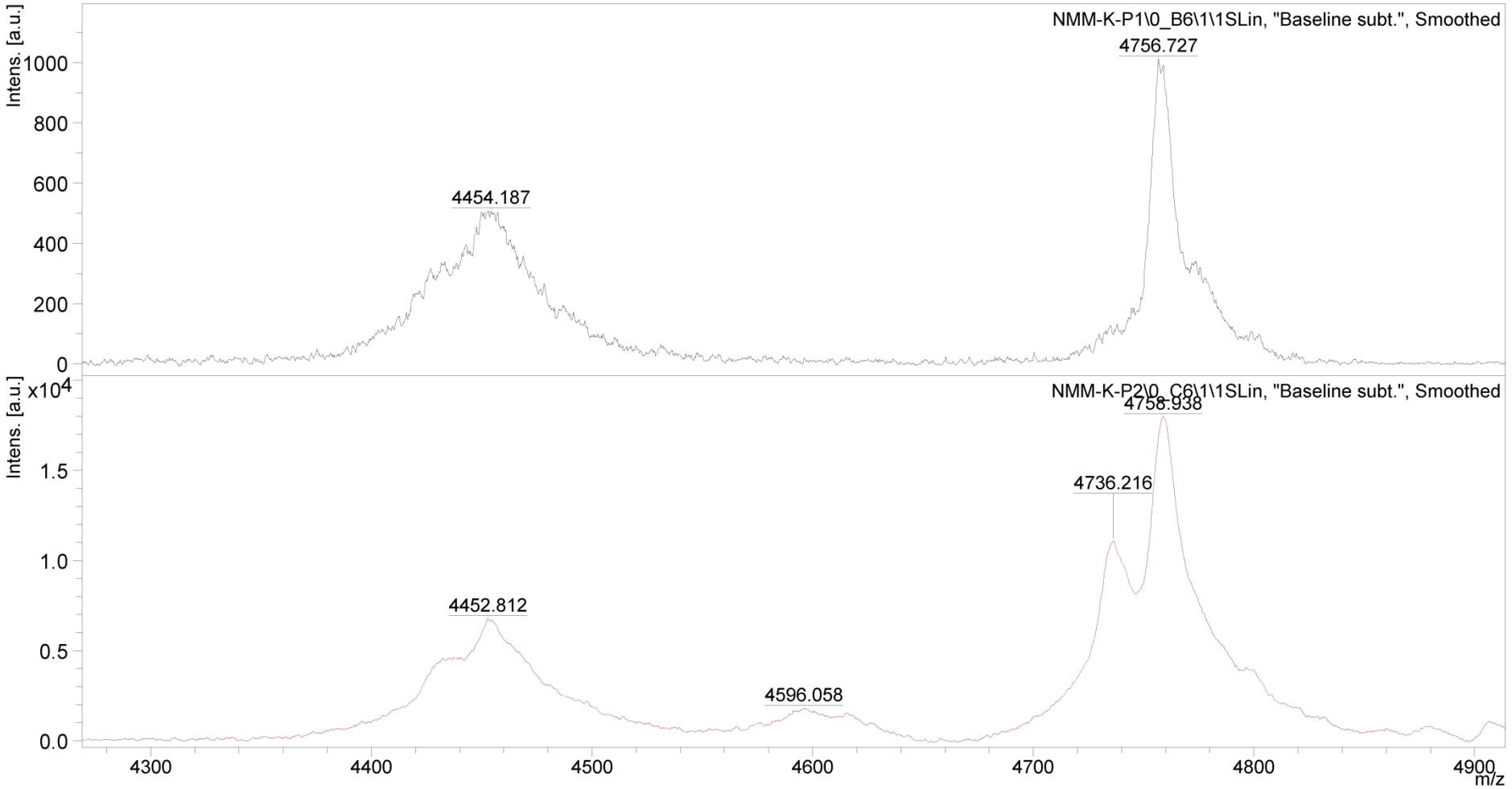


Figure 104: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12m** & **12m'**

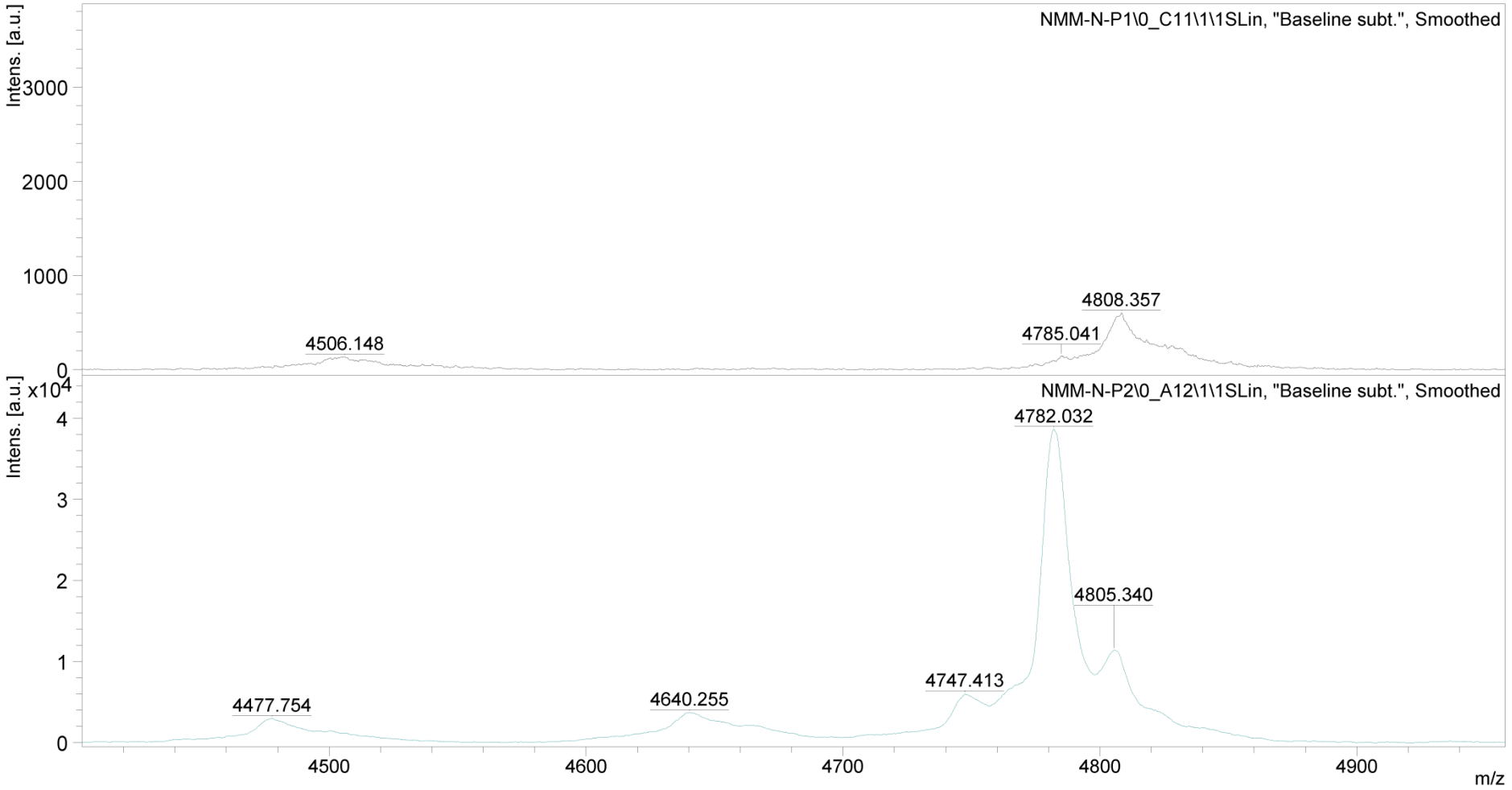


Figure 105: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12n** & **12n'.**

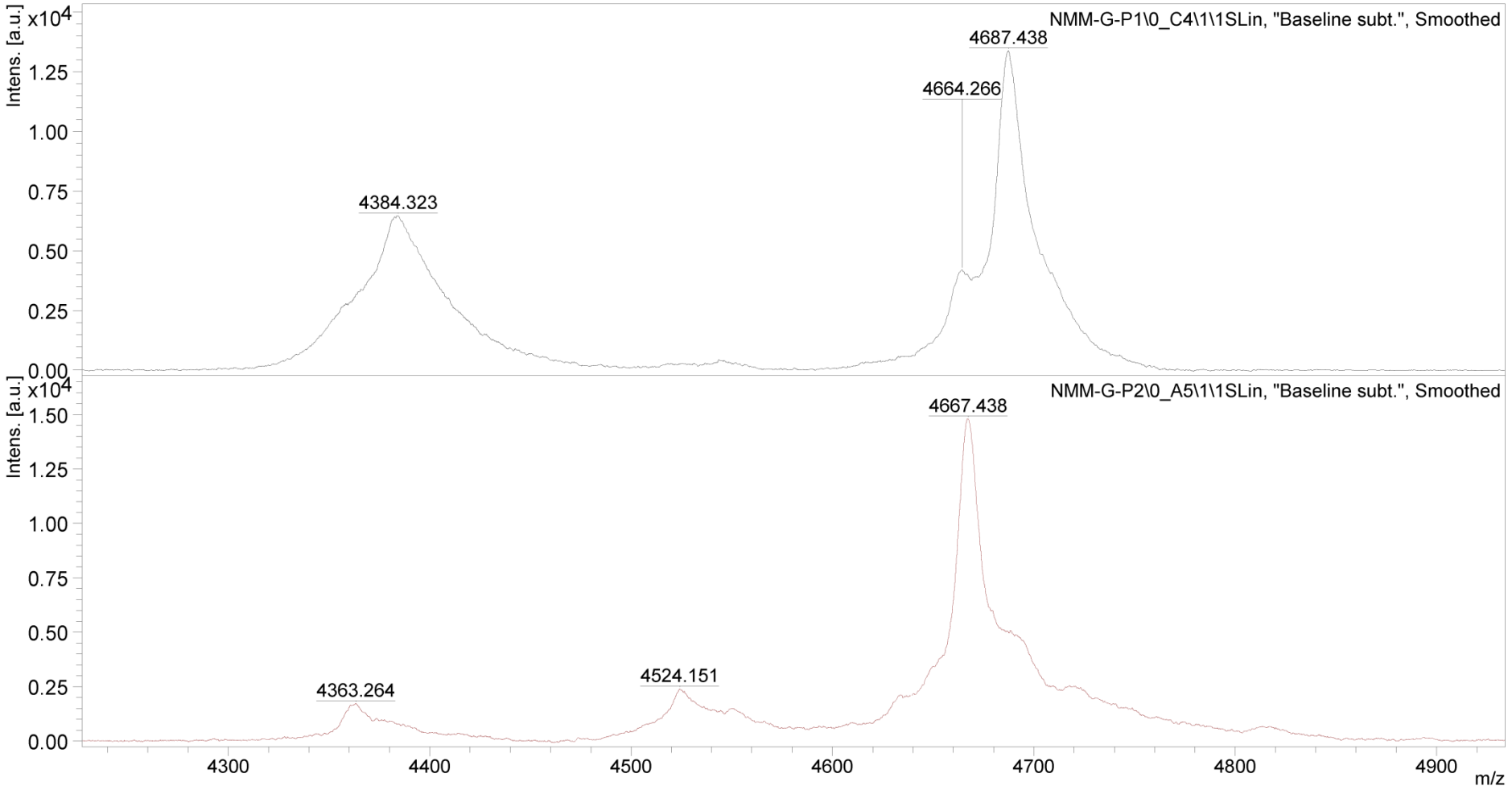


Figure 106: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12o** & **12o'.**

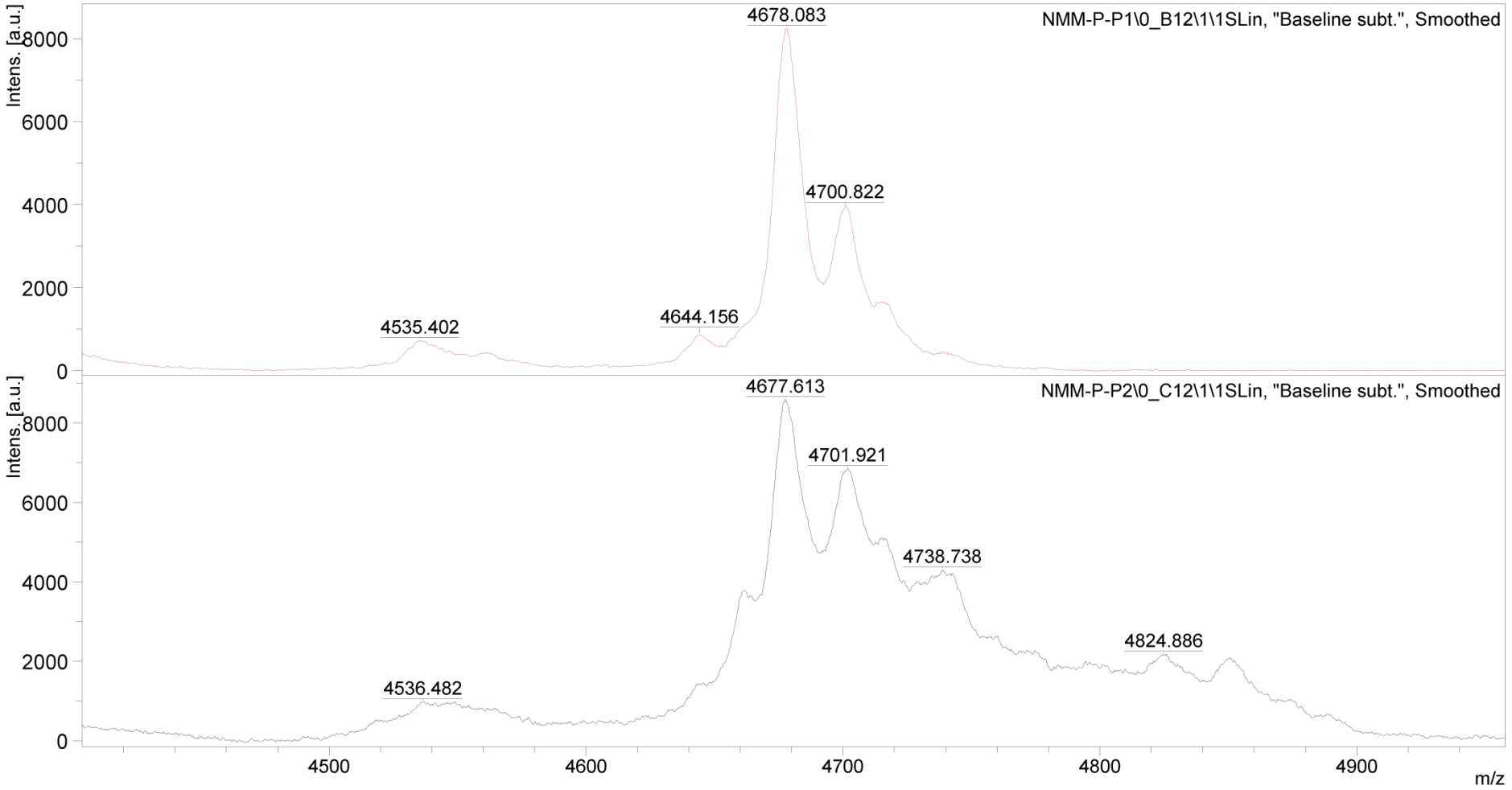


Figure 107: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12p** & **12p'.**

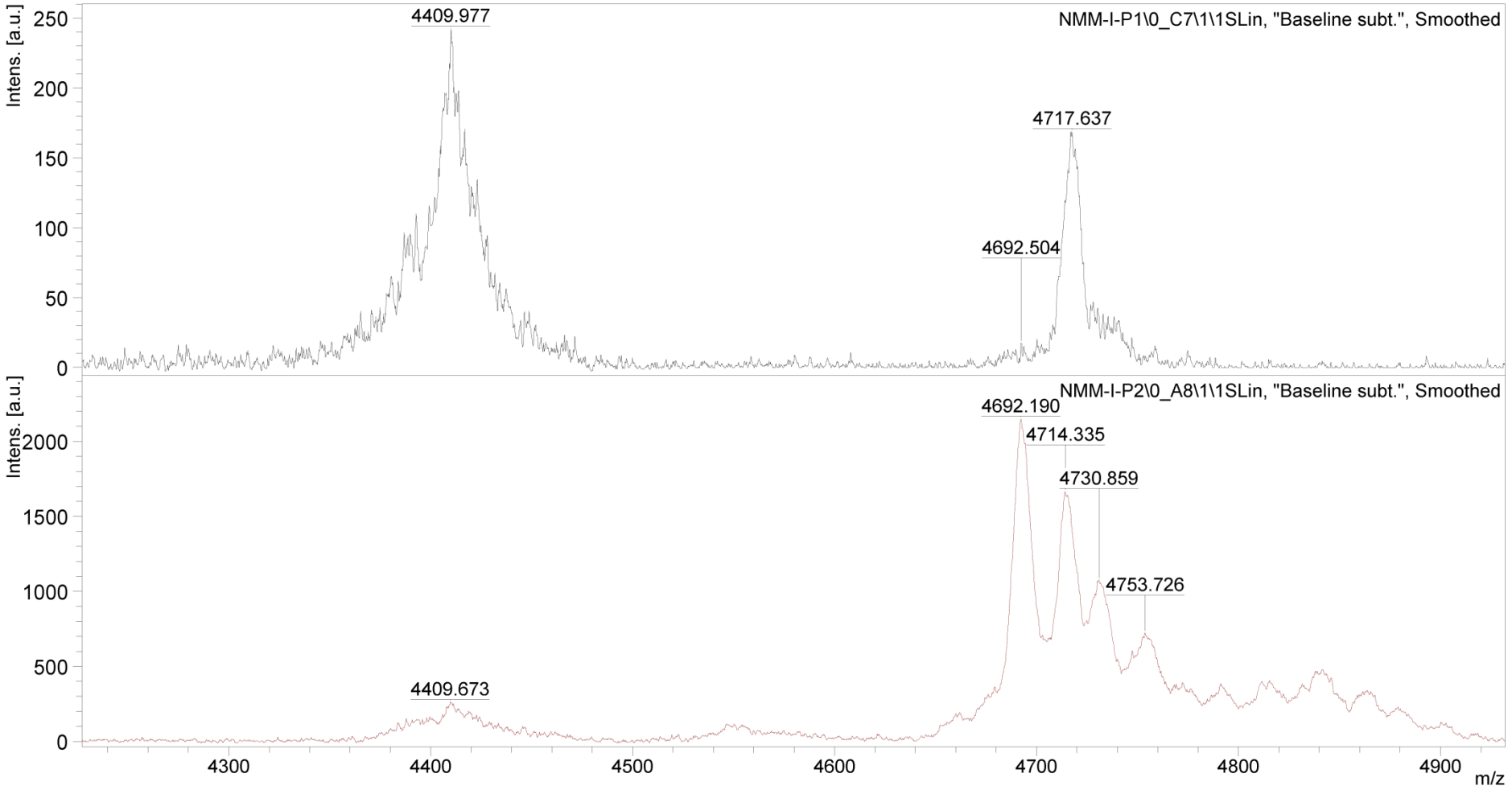


Figure 108: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12q** & **12q'.**

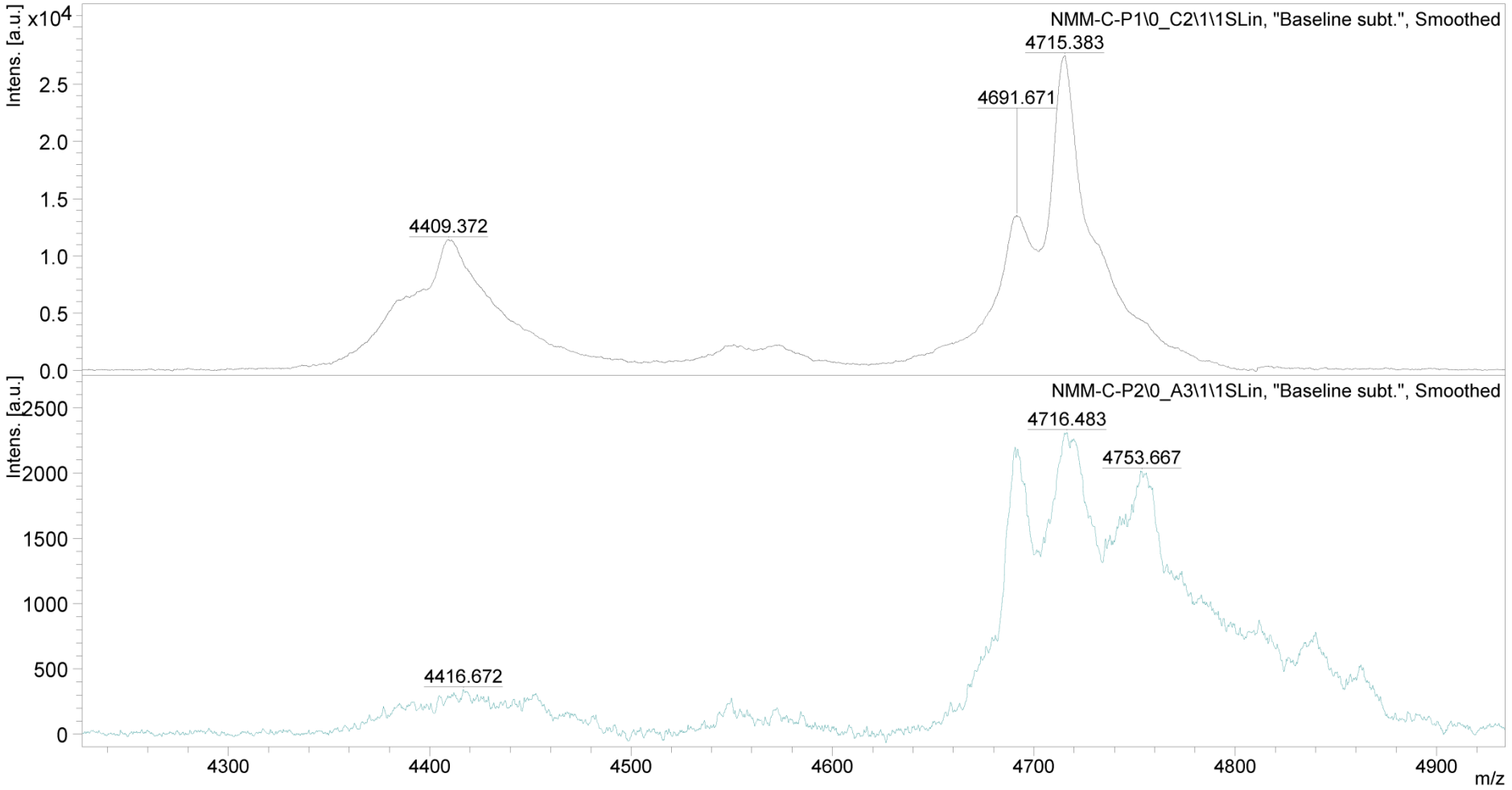


Figure 109: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12r** & **12r'.**

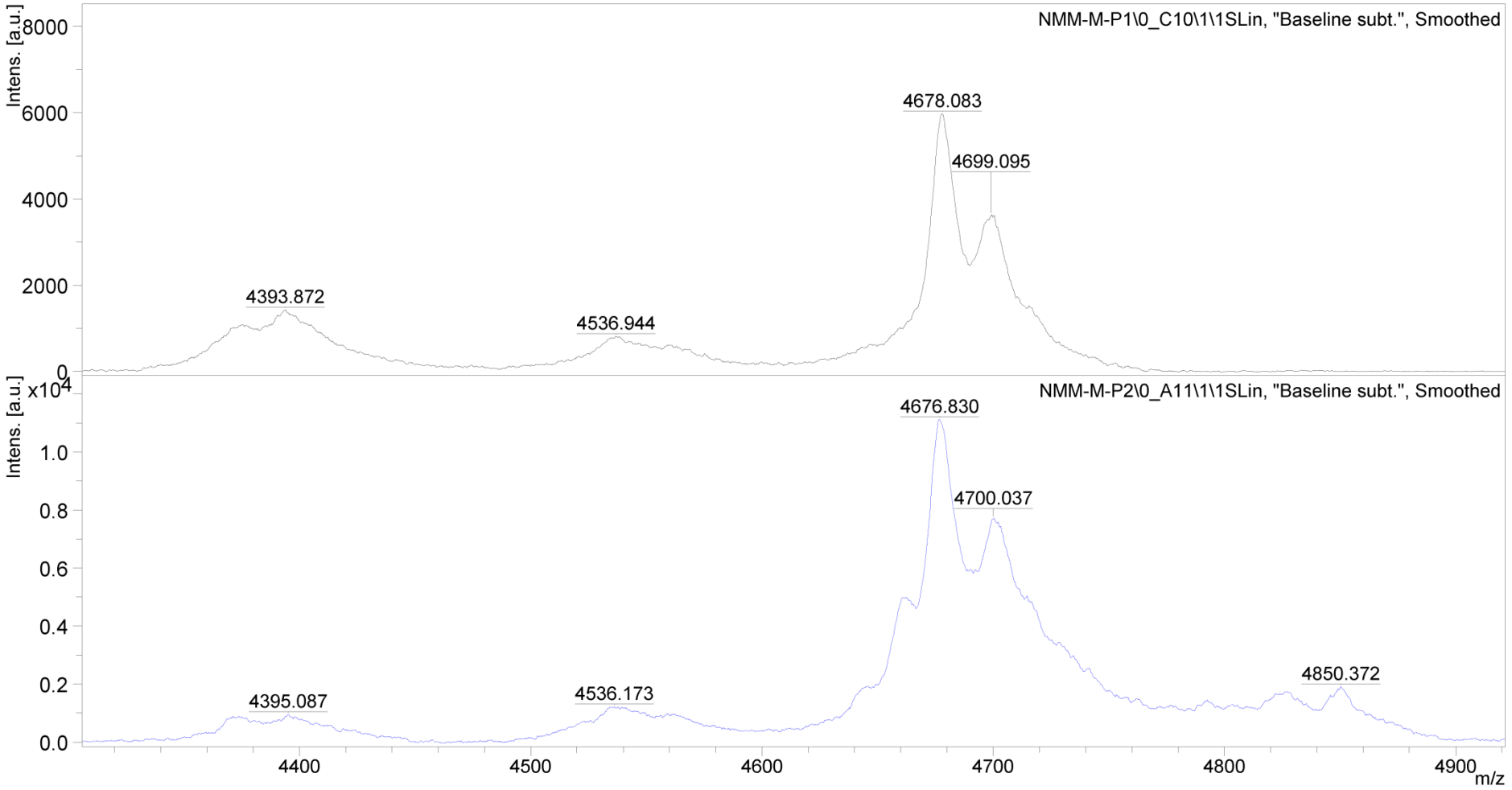


Figure 110: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12s** & **12s'.**

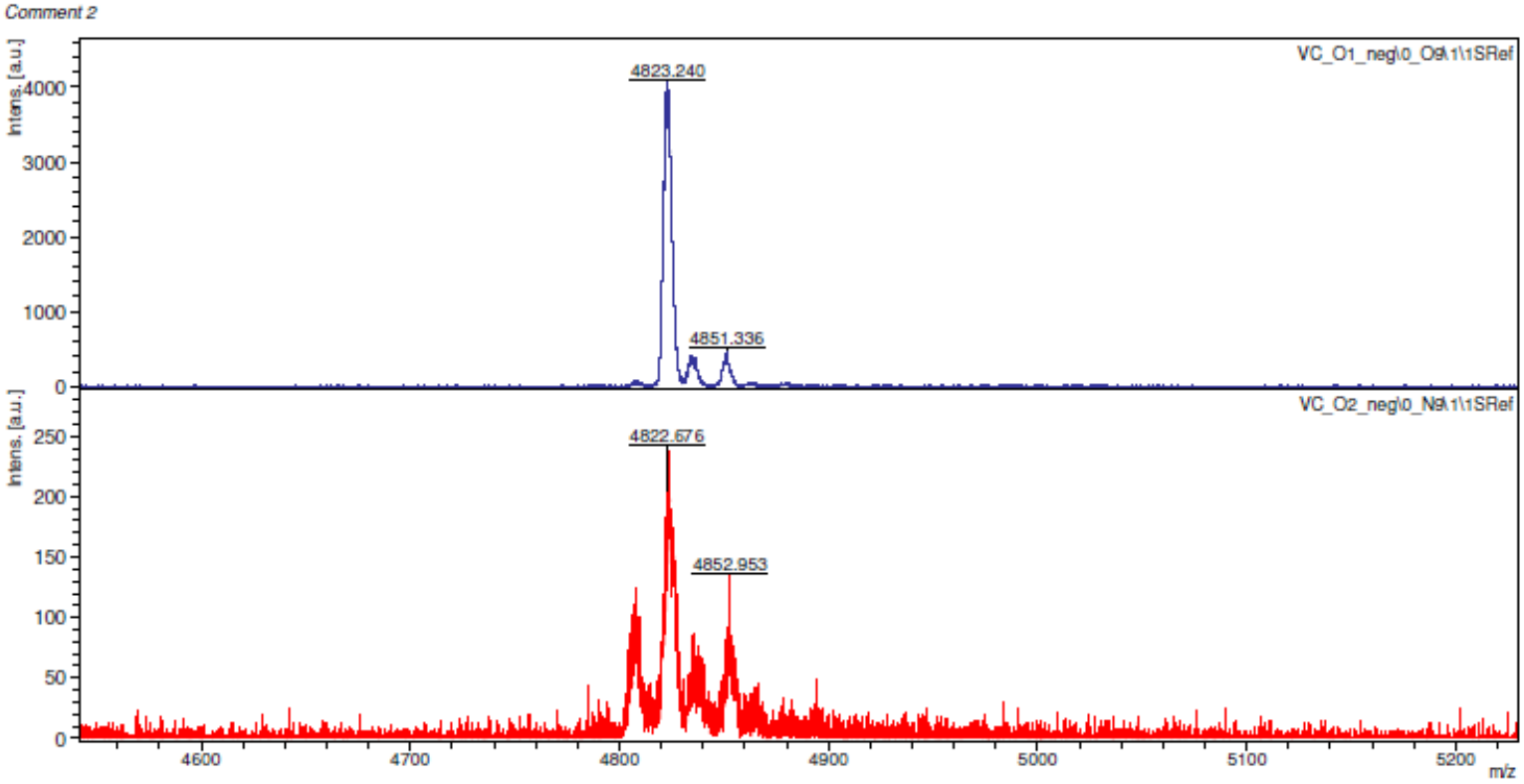


Figure 111: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12t** & **12t'.**

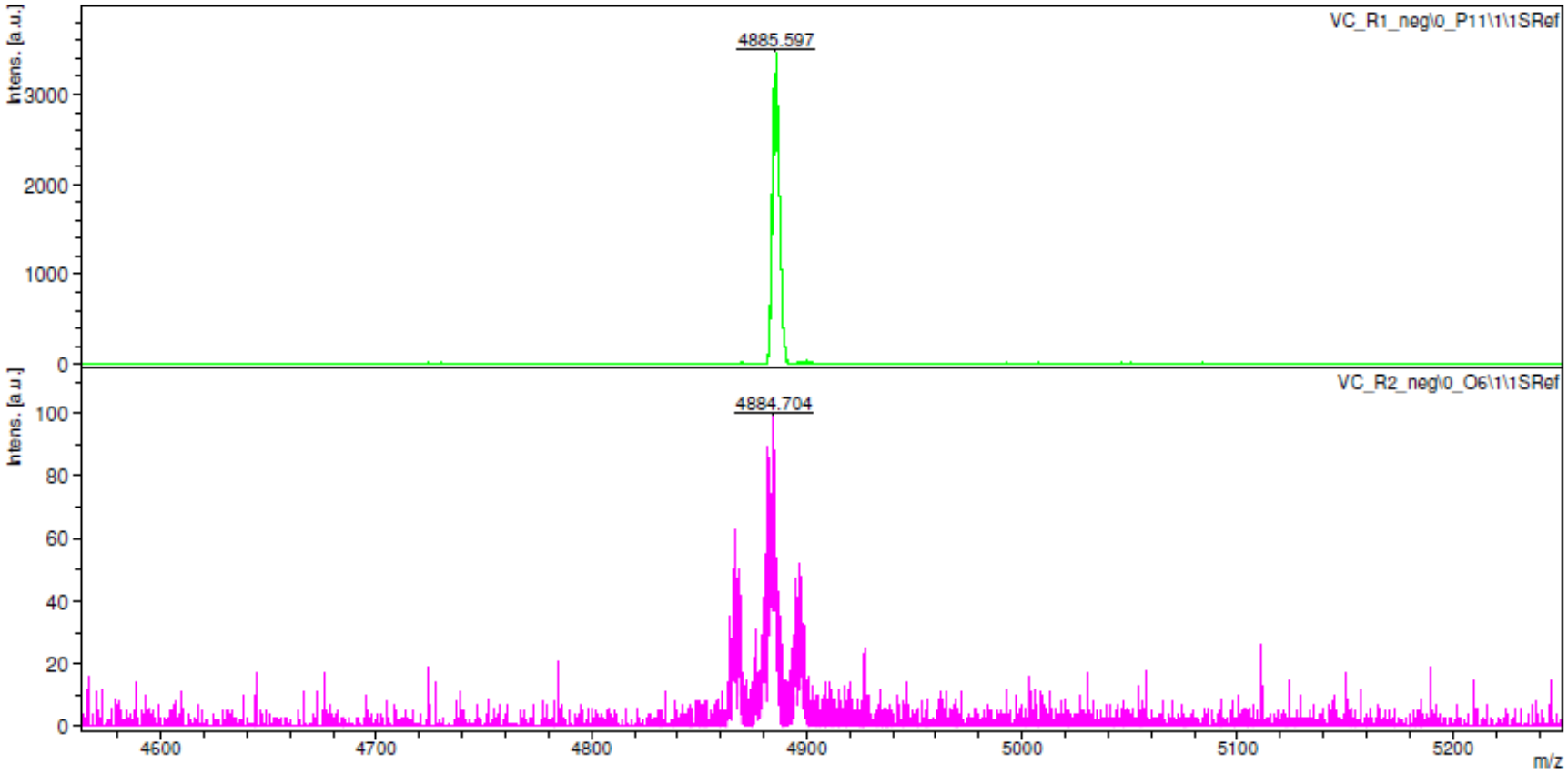


Figure 112: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12u** & **12u'.**

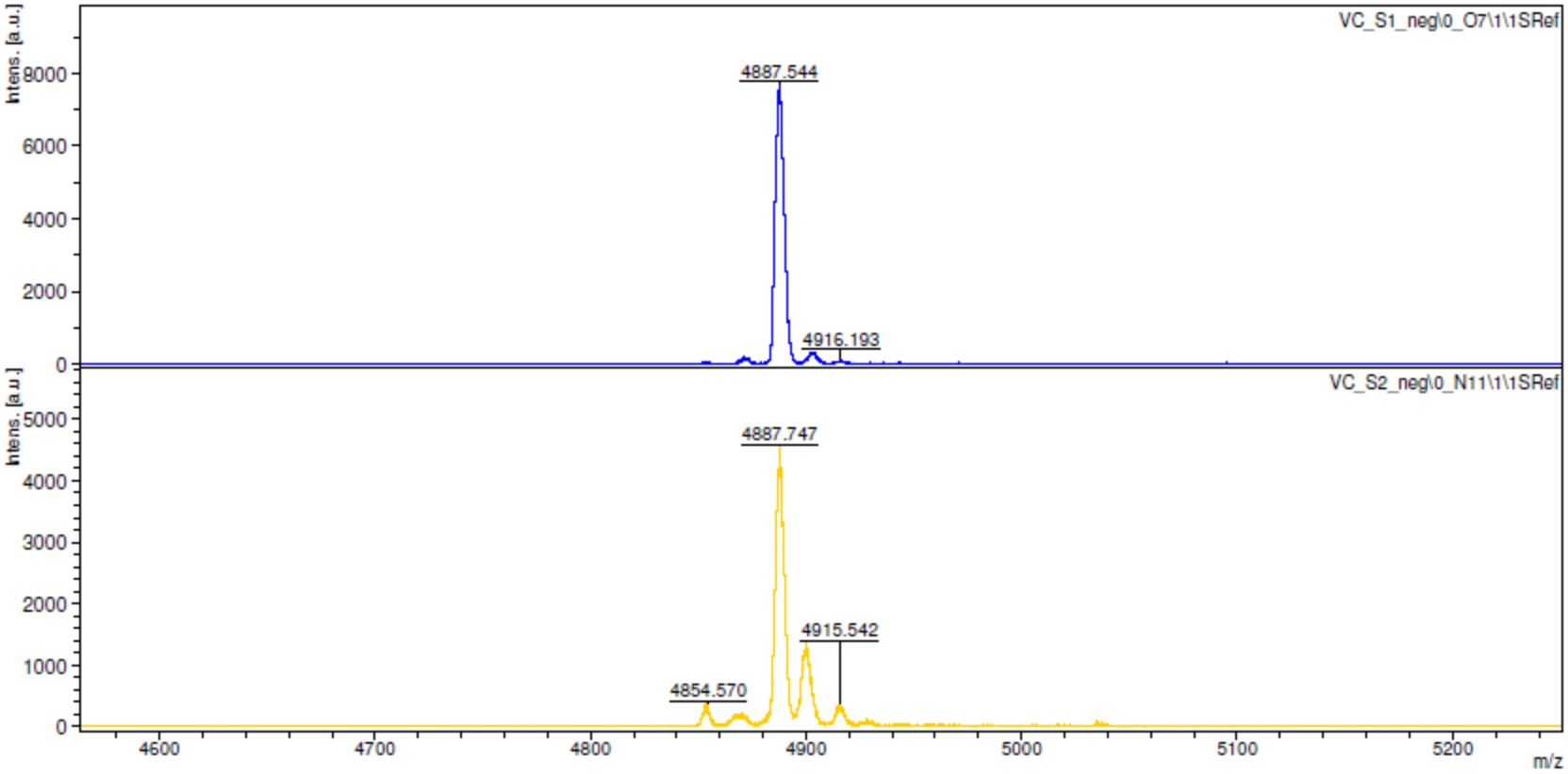


Figure 113: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12v** & **12v'.**

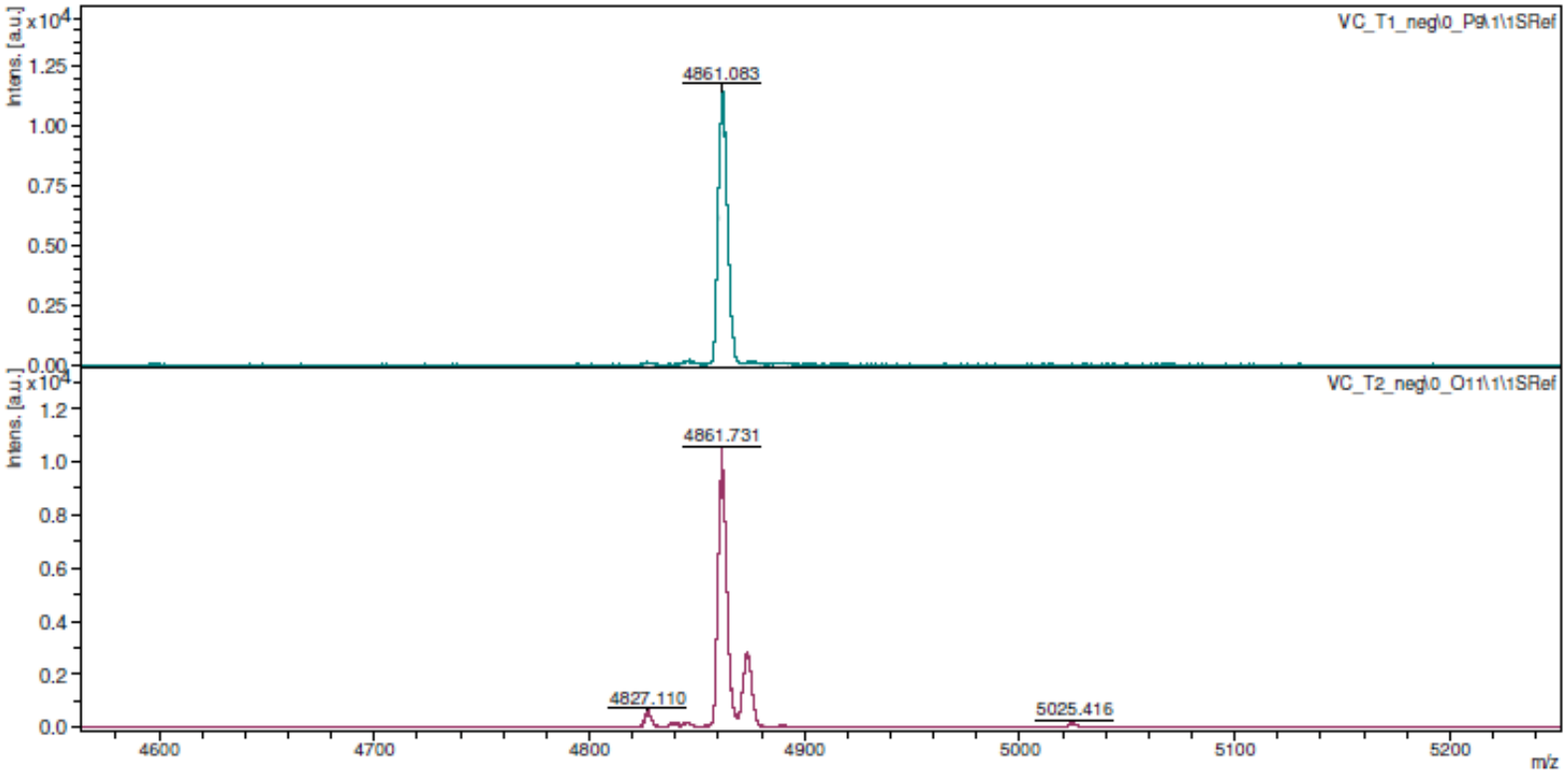


Figure 114: Mass spectrum (MALDI-TOF) of CRAMP-vancomycin conjugates **12w** & **12w'.**

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