Small Molecule Ligands of Methyl-Lysine Binding Proteins

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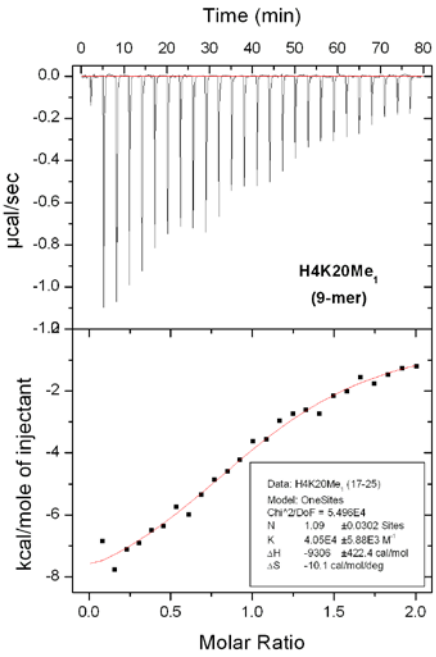
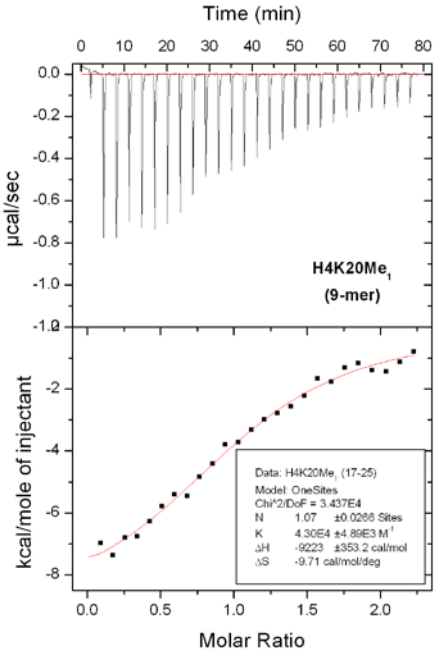
Experimental Section

Isothermal Titration Calorimetry

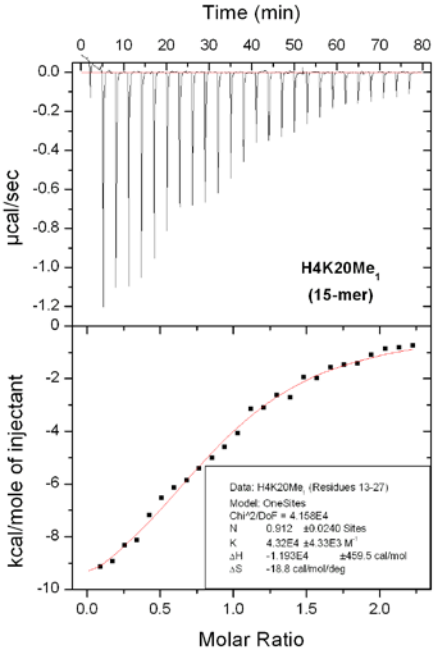
Titrations of H4K20Me$_1$ Peptides to L3MBTL1.

Residues 17-25 in duplicates:

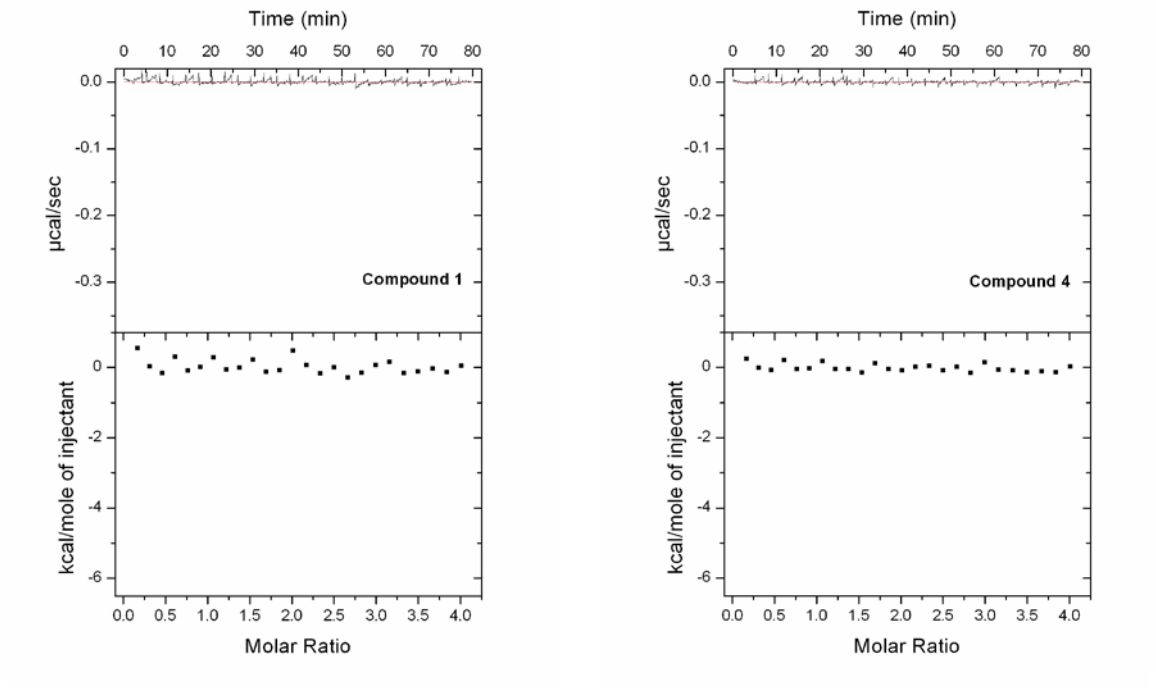




Residues 13-27:

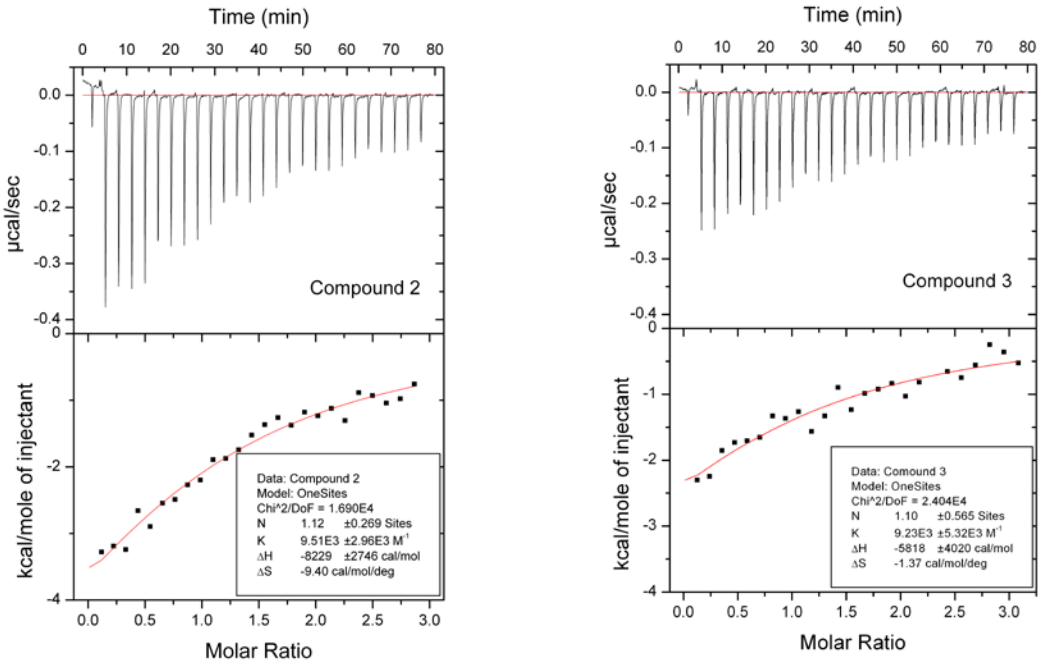


Non-Binding Compounds **1** and **4** with wt L3MBTL1.

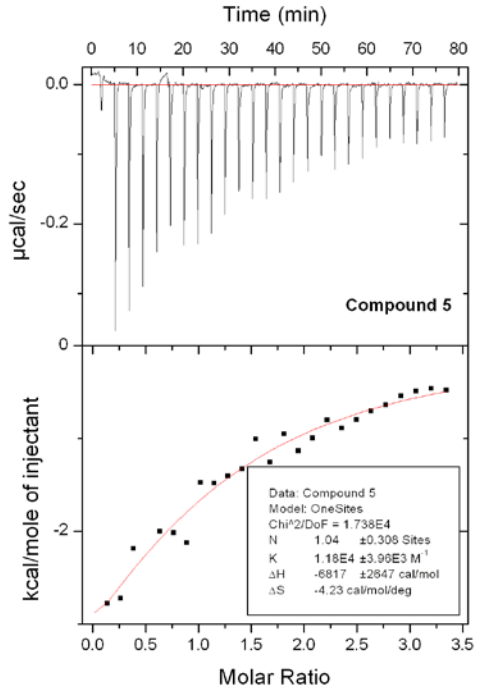


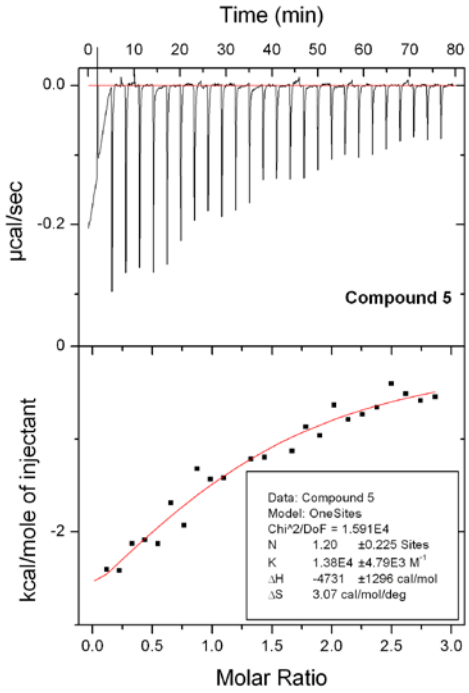
Weakly Binding Compounds **2** and **3** with wt L3MBTL1.

With the experimental setup of only 50 µM protein used, the K_d for weak interactions (mono-and dimethylamine **2** and **3**) could only be estimated.

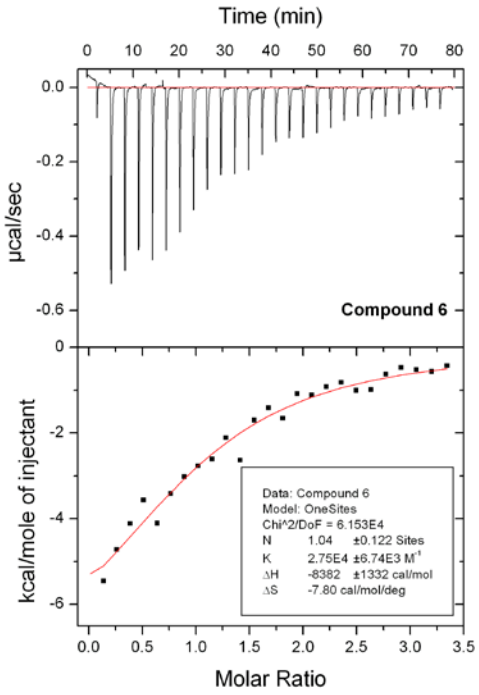


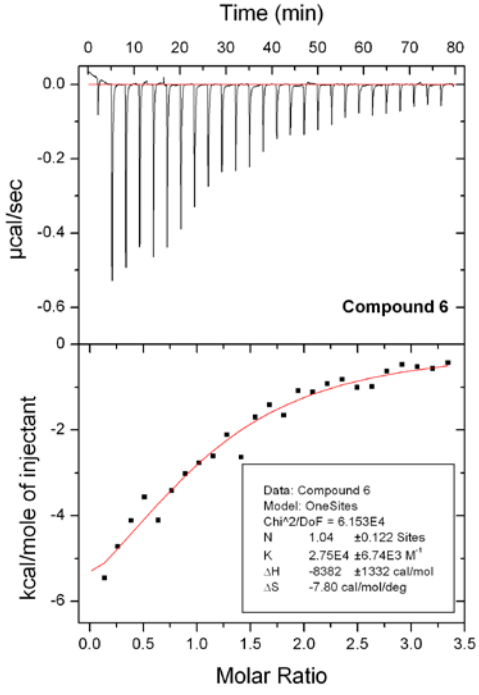
Compound **5** in duplicates with wt L3MBTL1:



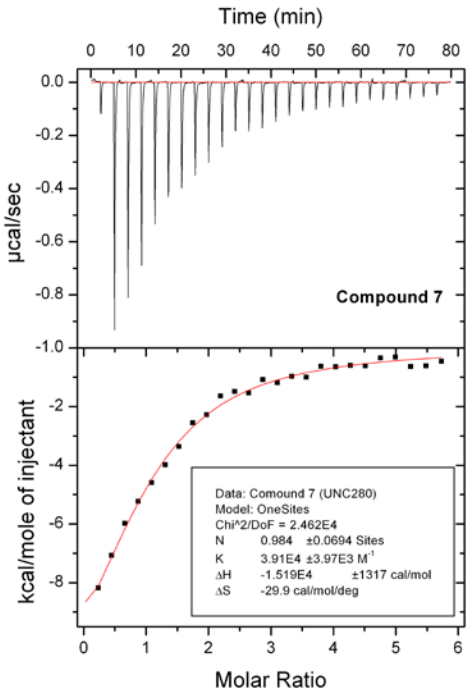


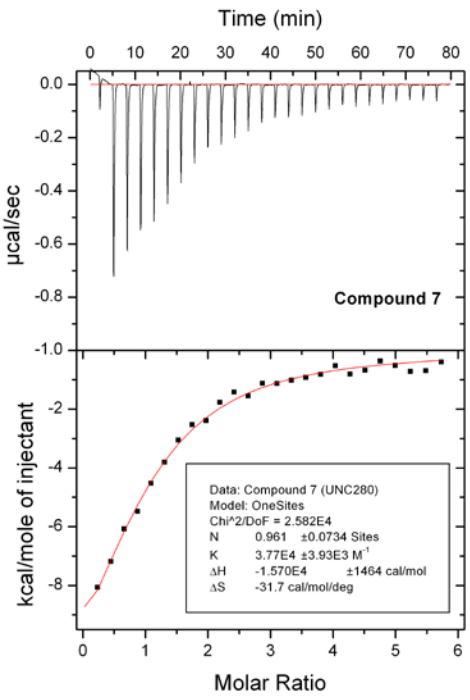
Pyrrolidine **6** in duplicates with wt L3MBTL1:



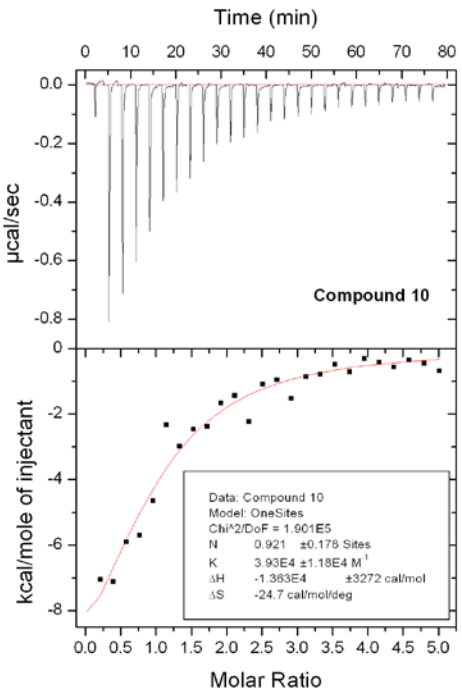


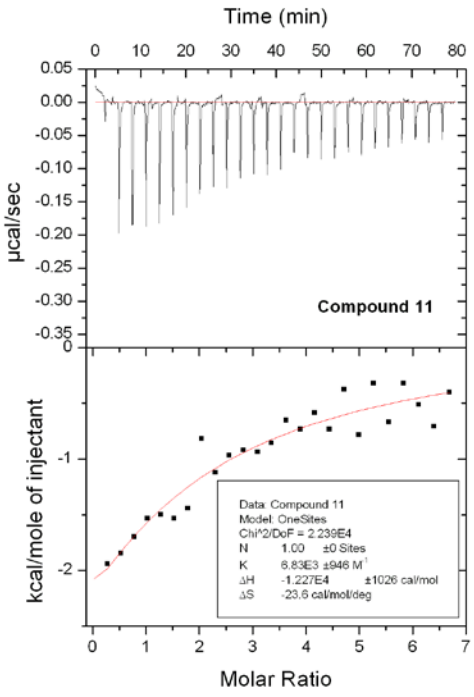
Nicotinamide **7** in duplicates with wt L3MBTL1:

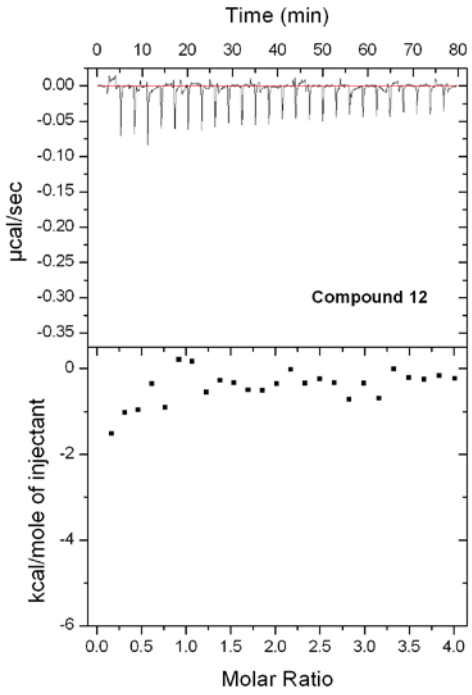


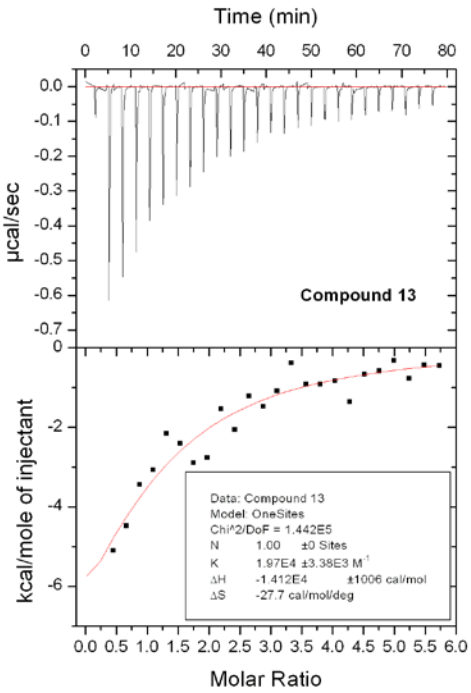


Sulfonamides **10** - **13** with wt L3MBTL1:

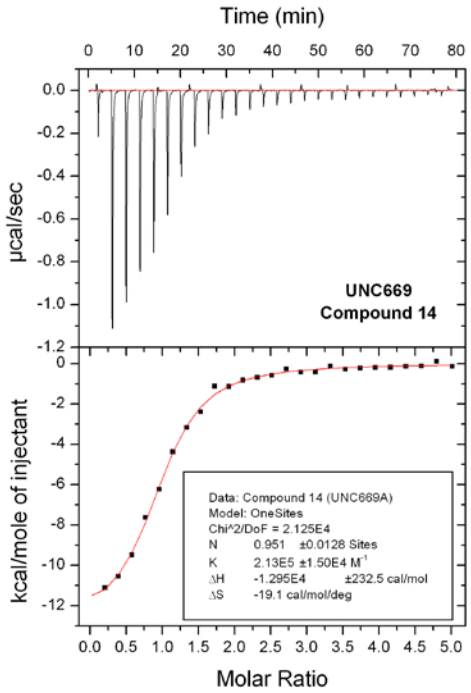


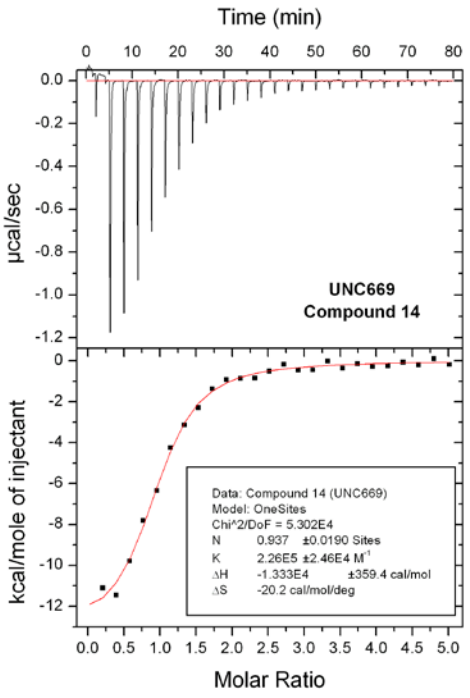




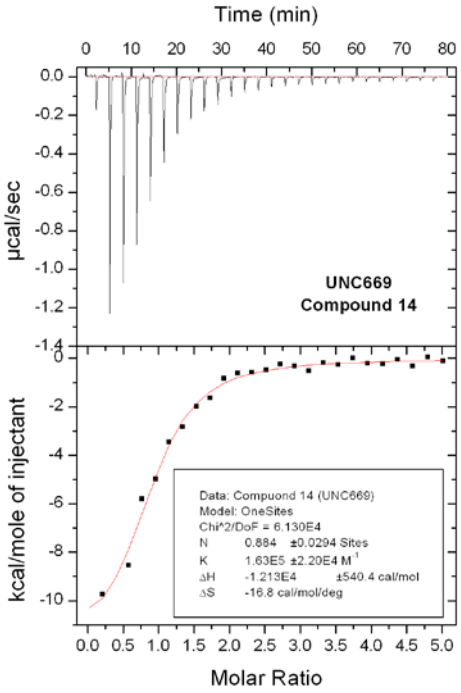


Nicotinamide **14** in triplicates with wt L3MBTL1:



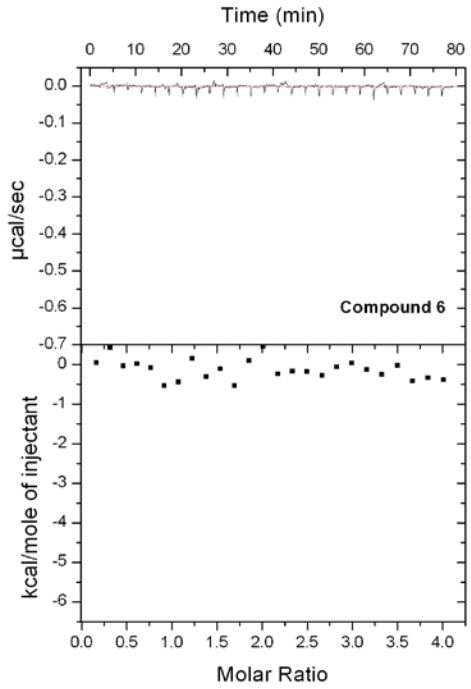


Nicotinamide **14** in triplicates with wt L3MBTL1:

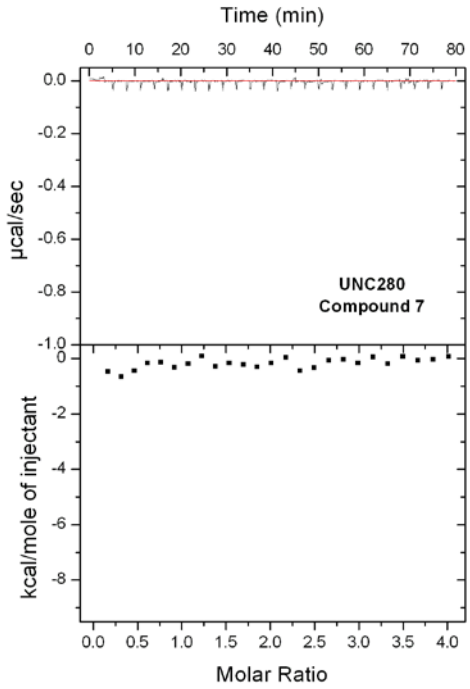


Isothermal Titration Calorimetry using D355A Mutant of L3MBTL1

Compound **6** with D355A mutant of L3MBTL1.



Nicotinaminde **UNC280** (Compound **7)** with D355A mutant of L3MBTL1:



Nicotinaminde **UNC669** (Compound **14)** with D355A mutant of L3MBTL1:

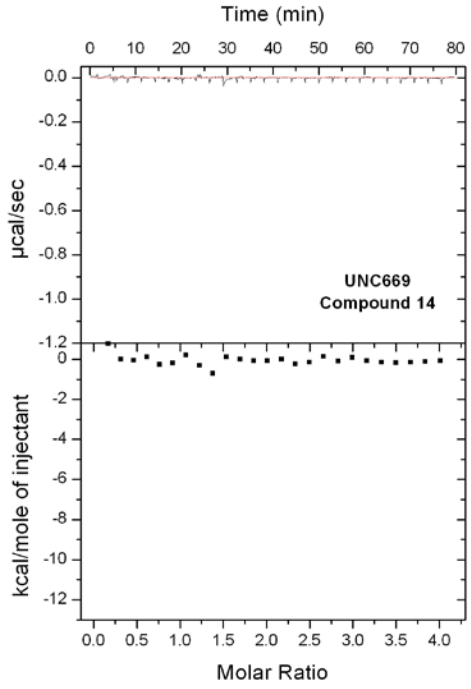
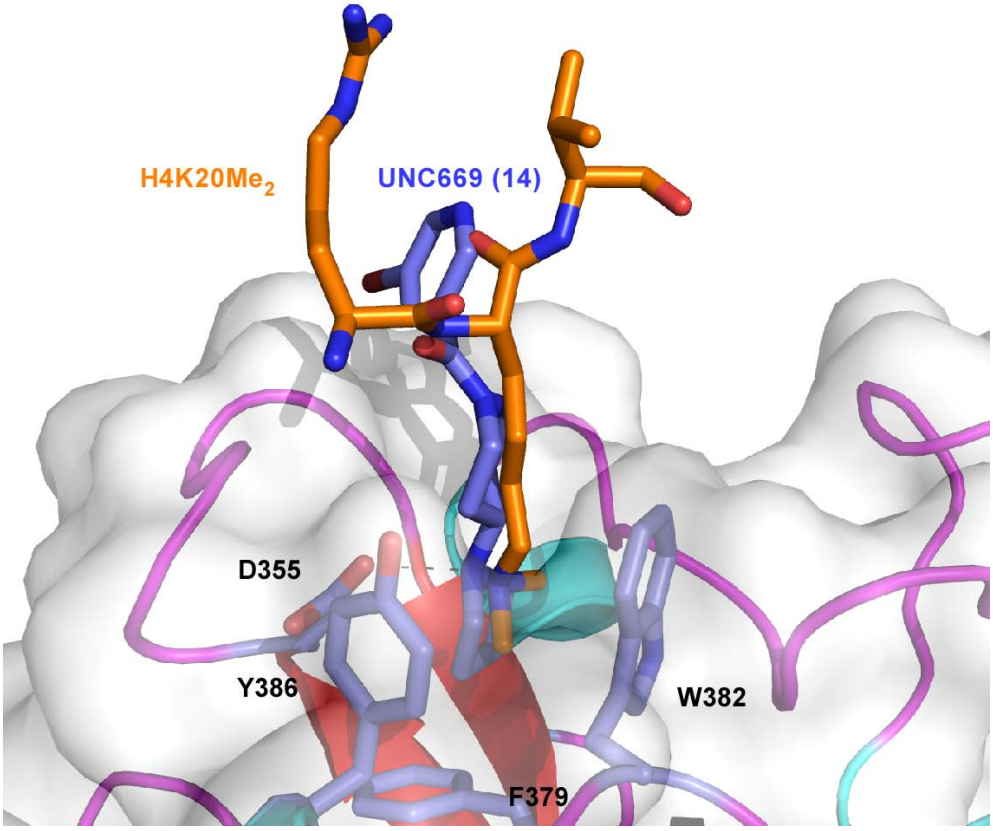


Table 1 Data collection and refinement statistics	
	3MBT/UNC669
Data collection	
Space group	$P3_2$
Unit cell dimensions	
a, *b*, *c* (Å)	106.3, 106.3, 90.1
α, β, γ (º)	90, 90, 120
Wavelength (Å)	0.97911
Resolution (Å)	50.0 – 2.55 (2.64 – 2.55)
R_{merge} (%)	11.8 (53.3)
$I/\sigma I$	9.5 (2.2)
Completeness (%)	100.0 (100.0)
Redundancy	3.0 (3.0)
Refinement	
Resolution (Å)	92.03 – 2.55
No. reflections	35,254
R_{work} / R_{free}	19.1 / 24.2
Number of atoms	
Protein (Chains A, B, C)	2534, 2509, 2525
UNC669	40
Glycerol	12
Sulfate	15
Water	38
Average *B*-factors (Å^2)	
Protein (Chains A, B, C)	39.3, 42.5, 47.6
UNC669	60.1
Glycerol	55.8
Sulfate	69.9
Water	29.3
R.m.s. deviations	
Bond lengths (Å)	0.010
Bond angles (º)	1.177

Values in parentheses are for the highest-resolution shell.

Atomic coordinates and structure factors for 3MBT/UNC669 complex have been deposited in the Protein Data Bank with accession code 3P8H.

Overlay of UNC669 and H4K20Me$_2$ when bound to L3MBTL1



Ligand Efficiencies

The ligand efficiencies were calculated using the pK_d data available from ITC experiments[1] using Discovery Studio software.

	K_d	pK_d	pK_d/Heavy Atoms	pK_d/All Atoms
H4K20Me$_1$ Peptide[1] (Residues 17-25)	24	4.62	0.054	0.024
UNC280 (**7**)	26	4.59	0.229	0.108
UNC669 (**14**)	5	5.30	0.264	0.132

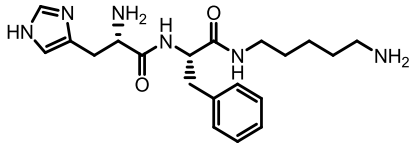
General Procedure for Chemical Synthesis

HPLC data for all compounds were acquired using an Agilent 6110 Series system with the UV detector set to 220 nm. Samples were injected (<10 μL) onto an Agilent Eclipse Plus 4.6 × 50 mm, 1.8 μM, C18 column at rt. A mobile phase of A being H_2O + 0.1% acetic acid and B being MeOH + 0.1% acetic acid was used. A linear gradient from 10% to 100% B in 5.0 min was followed by pumping 100% B for another 2 minutes with a flow rate of 1.0 mL/min. Mass spectra (MS) data were acquired in positive ion mode using an Agilent 6110 single quadrupole mass spectrometer with an electrospray ionization (ESI) source. High-resolution (negative ion) mass spectra (HRMS) were acquired using a Shimadzu LCMS-IT-TOF time-of-flight mass spectrometer. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian Mercury spectrometer at 400 MHz for proton (^{1}H NMR) and 100 MHz for carbon (^{13}C NMR); chemical shifts are reported in ppm (δ) relative to the solvent peaks.[2] Preparative HPLC was performed using an Agilent Prep 1200 series with the UV detector set to 220 nm. Samples were injected onto a Phenomenex Luna 75 × 30 mm, 5 μM, C18 column at room temperature (rt). A mobile phase of A being H_2O + 0.1% TFA and B being MeOH was used with a flow rate of 30 mL/min.

[1] Min, J.; Allali-Hassani, A.; Nady, N.; Qi, C.; Ouyang, H.; Liu, Y.; MacKenzie, F.; Vedadi, M.; Arrowsmith, C. H. *Nat. Struct. Mol. Biol.* **2007,** *14*, 1229.
[2] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem*. **1997**, *62*, 7512.

A linear gradient from 10% to 100% B in 17.0 min was followed by pumping 100% B for another 3 minutes.

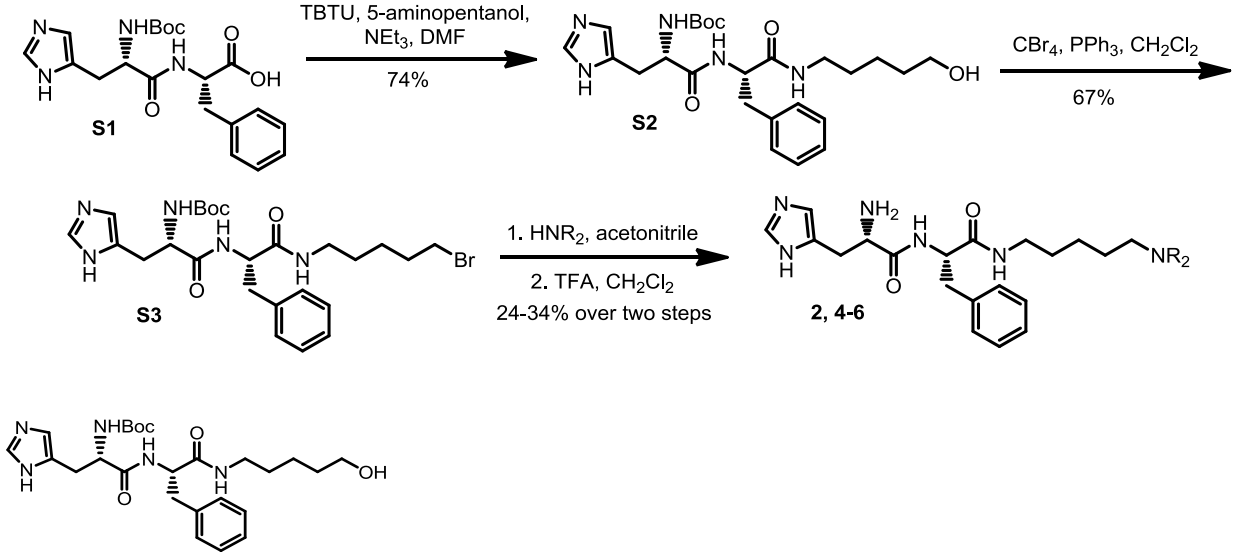
HPLC was used to establish the purity of targeted compounds. All compounds that were evaluated in biochemical and biophysical assays had > 95% purity at 220 nm using the HPLC methods described.



Compound 1: To a solution of 400 mg (0.98 mmol) of acid **S1**[3] in 5 mL of DMF was added 415 mg (1.3 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N'N'*-tetramethyluronium tetrafluoroborate (TBTU) at rt. After 10 min, 262 mg (1.3 mmol) of *N*-Boc-1,5-diaminopentane and 0.3 mL (2 mmol) of NEt_3 were added. The mixture was stirred at rt for 12 h. Then, the reaction was quenched by addition of sat. aq NH_4Cl and diluted with 25 mL of EtOAc. The phases were separated and the aqueous phase was further extracted with EtOAc (2 × 30 mL). The combined organic extracts were washed with sat. aq NaCl, dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was taken up in CH_2Cl_2 and 1 mL of TFA was added at rt. The mixture was stirred for 18 h, the solvent removed under reduced pressure and the crude mixture taken up in MeOH. After filtration, the primary amine was purified by HPLC to afford 237 mg (48%) of the TFA salt of the title compound **1** as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, J = 1.2 Hz, 1H), 7.45 (s, 1H), 7.34 – 7.20 (m, 5H), 4.58 (t, J = 7.7 Hz, 1H), 4.25 – 4.20 (m, 1H), 3.44 and 3.35 (d AB q, $\Delta\nu_{AB}$ = 32.7 Hz, J = 15.7, 5.3 Hz, 2H), 3.26 (dd, J = 13.5, 6.8 Hz, 1H), 3.13 – 2.98 (m, 3H), 2.92 – 2.85 (m, 2H), 1.67 – 1.57 (m, 2H), 1.48 – 1.39 (m, 2H), 1.32 – 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.60, 168.72, 137.77, 136.13, 130.28, 129.63, 128.38, 128.08, 119.79, 56.91, 53.09, 40.56, 40.24, 38.86, 29.63, 28.22, 27.86, 24.67. MS (ESI): 387 $[M+H]^+$; HPLC: 100%, t_R: 0.55 min. HRMS calcd. for $C_{20}H_{30}N_6O_2$ + H: 387.2509; found: 387.2521 $[M+H]^+$.

[3] Bodi, J.; Sueli-Vargha, H.; Medzihradszky-Schweiger, H.; Medzihradszky, K.; Saran, A., *ACH Models in Chemistry* **1995**, *132*, 925.

General Procedure for Preparation of Compounds **2, 4 – 6**:



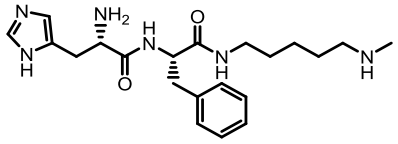
Alcohol S2: To a solution of 1.5 g (3.73 mmol) of acid **S1** in 15 mL of DMF was added 1.8 g (5.6 mmol) of TBTU and the mixture was stirred for 15 min at rt after which it became clear Then, 774 mg (7.5 mmol) of 5-aminopentanol were added in one portion along with 1 mL (7.5 mmol) of NEt_3. The solution was stirred at rt overnight. The reaction was quenched by addition of 40 mL of sat. aq $NaHCO_3$ and diluted with 60 mL of CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation.

The crude material was purified by column chromatography on silica gel (CH_2Cl_2 – 10% MeOH/CH_2Cl_2 + 1% NH_3; monitored at 220 nm) to afford 1.34 g (74%) of the title compound **S2** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (t, J = 5.2 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.26 – 7.21 (m, 2H), 7.20 – 7.14 (m, 3H), 6.83 (d, J = 7.7 Hz, 1H), 6.76 (s, 1H), 4.46 – 4.37 (m, 1H), 4.14 – 4.04 (m, 1H), 3.36 (t, J = 6.6 Hz, 2H), 3.10 – 2.92 (m, 3H), 2.86 – 2.68 (m, 3H), 1.43 – 1.28 (m, 12H), 1.27 – 1.16 (m, 3H); ^{13}C NMR (101 MHz, DMSO-d_6, two overlapping peaks) δ 170.96, 170.31, 155.05, 137.65, 134.69, 129.14, 127.99, 126.19, 78.34, 60.59, 54.55, 53.82, 38.61, 37.68, 32.19, 29.31, 28.85, 28.11, 22.83.

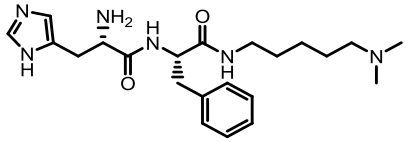
To a solution of 1.5 g (4.5 mmol) of CBr_4 in 15 mL of CH_2Cl_2 was added 1.2 g (4.5 mmol) of PPh_3 at 0 °C. The solution turned bright-yellow and after 5 min, 870 mg (1.8 mmol) of alcohol **S2** was added in 5 mL of CH_2Cl_2. The mixture was allowed to warm to rt over 3 h. Upon completion of the reaction, as judged by TLC analysis, the reaction was

quenched by addition of sat. aq $NaHCO_3$ and sat. aq $Na_2S_2O_3$. The layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (2 × 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by column chromatography on 40 g of silica (adsorbed on silica, CH_2Cl_2 – 10% MeOH/CH_2Cl_2 + 1% NH_3; monitor at 220 nm) to afford 654 mg (67%) of the bromide **S3** along with small amounts of triphenylphosphine oxide.

For the following steps, the bromide **S3** was taken up in acetonitrile and the amines were added as described below. The reactions were stirred for 16 h, then the solvent was removed by rotary evaporation. The crude mixtures were taken up in CH_2Cl_2 and 1 mL of TFA was added to remove the Boc-protecting group at rt. Upon completion of the deprotection, the solvent was removed under reduced pressure, the crude material taken up in MeOH, filtered and the crude product was purified by HPLC.

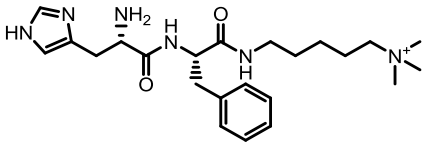


Compound 2: The general procedure was followed using 0.3 mmol of bromide **S3** in 2 mL of acetonitrile and 2 mL of $MeNH_2$ (2 M in THF). After purification, 46 mg (29%) of the TFA salt of the monomethyl peptidomimetic were obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.86 (d, *J* = 1.4 Hz, 1H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.34 – 7.21 (m, 5H), 4.58 (dd, *J* = 8.3, 7.2 Hz, 1H), 4.22 (dd, *J* = 6.6, 5.3 Hz, 1H), 3.44 and 3.35 (d AB q, $\Delta\nu_{AB}$ = 35.2 Hz *J* = 15.6, 5.2 Hz, 2H), 3.14 – 2.99 (m, 3H), 2.98 – 2.92 (m, 2H), 2.70 (s, 3H), 1.69 – 1.59 (m, 2H), 1.49 – 1.40 (m, 2H), 1.32 – 1.23 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.69, 168.63, 137.75, 136.06, 130.27, 129.64, 128.10, 127.92, 120.00, 56.93, 52.97, 50.20, 40.22, 38.84, 33.54, 29.61, 27.66, 26.75, 24.68. MS (ESI): 401 $[M+H]^+$; HPLC: 100%, t_R: 0.53 min; HRMS calcd. for $C_{21}H_{32}N_6O_2$ + H: 401.2660; found: 401.2632 $[M+H]^+$.

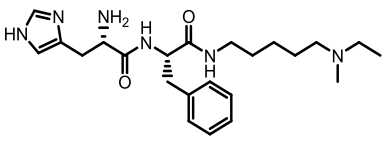


Compound 3 To a solution of 185 mg (0.46 mmol) of acid **S1** in 2 mL of DMF was added 192 mg (0.6 mmol) of TBTU and the mixture was stirred for 15 min at rt. Upon complete dissolution, 150 mg (1.2 mmol) of 5-(dimethylamino)amylamine was added and the solution was stirred at rt overnight. The reaction was quenched by addition of 10 mL of sat. aq $NaHCO_3$ and

diluted with 15 mL of EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried over Na_2SO_4 and filtered. The solvent was evaporated and the crude product was dissolved in 8 mL of CH_2Cl_2 and 1 mL of TFA was added. Upon completion of the Boc-deprotection as judged by LCMS analysis, the solvent was removed by rotary evaporation and the crude material was taken up in 1 mL of MeOH, filtered and purified by HPLC at 220 nm to afford 73 mg (30%) of the dimethyl peptidomimetic as the TFA salt as a white, waxy solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (d, *J* = 5.5 Hz, 1H), 7.43 (s, 1H), 7.35 – 7.21 (m, 5H), 4.59 (dd, *J* = 8.3, 7.2 Hz, 1H), 4.23 – 4.17 (m, 1H), 3.46 – 3.38 (m, 1H), 3.37 – 3.25 (m, 2H), 3.14 – 2.97 (m, 5H), 2.88 (s, 6H), 1.73 – 1.63 (m, 2H), 1.51 – 1.41 (m, 2H), 1.32 – 1.21 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD, two overlapping peaks) δ 173.69, 168.65, 137.73, 136.13, 130.26, 129.66, 128.13, 119.89, 58.87, 56.88, 53.01, 43.42, 40.21, 38.86, 29.63, 27.77, 25.25, 24.69; MS (ESI): 415 $[M+H]^+$; HPLC: 100%, t_R: 0.56 min; HRMS calcd. for $C_{22}H_{34}N_6O_2$ + H: 415.2816; found: 415.2802 $[M+H]^+$.

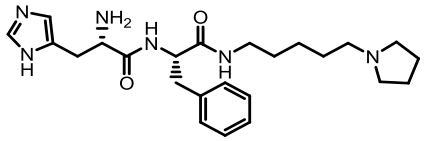


Compound 4: The general procedure was followed using 0.6 mmol of bromide **S3**, 2 mL of Me_3N (4.2 M in EtOH). The product was obtained as a light yellow solid (110 mg, 34%) after purification as the TFA salt. ^{1}H NMR (400 MHz, CD_3OD) δ 8.88 – 8.80 (d, *J* = 1 Hz, 1H), 7.44 (s, 1H), 7.35 – 7.22 (m, 5H), 4.59 (t, *J* = 7.7 Hz, 1H), 4.22 (t, *J* = 6.0 Hz, 1H), 3.43 and 3.35 (d AB q, $\Delta\nu_{AB}$ = 31.2 Hz, *J* = 15.7, 5.3 Hz, 2H), 3.34 – 3.25 (m, 3H), 3.13 (s, 9H), 3.11 – 2.99 (m, 3H), 1.81 – 1.71 (m, 2H), 1.54 – 1.45 (m, 2H), 1.31 – 1.21 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.70, 168.61, 137.77, 136.06, 130.27, 129.65, 128.10, 127.82, 120.05, 67.70, 56.92, 53.53, 52.95, 40.18, 38.85, 29.63, 27.61, 24.58, 23.57. MS (ESI): 429 $[M+H]^+$; HPLC: 100%, t_R: 0.60 min; HRMS calcd. for $C_{23}H_{37}N_6O_2^+$: 429.2978. found: 429.2982 $[M]^+$.



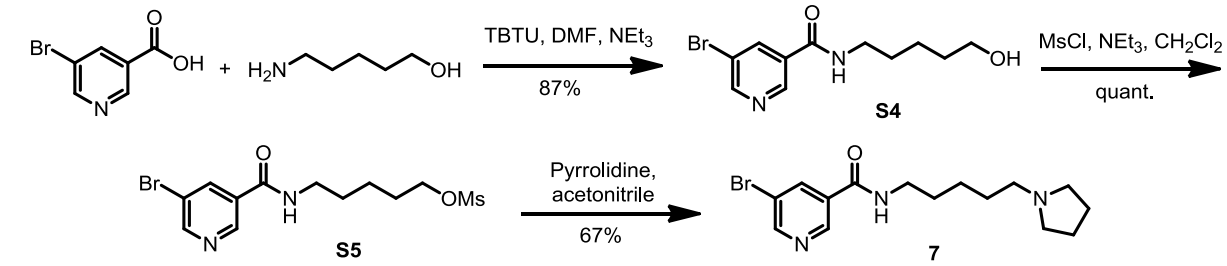
Compound 5: The general procedure was followed as for the monomethylamine **2** using 0.4 mmol of bromide **S3**, 0.2 mL (2.4 mmol) of *N*-ethylmethylamine in 2 mL of acetonitrile. The TFA salt of the product was obtained as a light yellow solid (41 mg, 24%). ^{1}H NMR (400

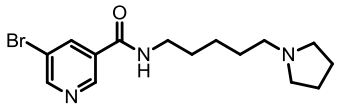
MHz, CD_3OD) δ 8.87 (d, *J* = 1.0 Hz, 1H), 7.45 (s, 1H), 7.35 – 7.20 (m, 5H), 4.59 (t, *J* = 7.7 Hz, 1H), 4.22 (dd, *J* = 6.5, 5.4 Hz, 1H), 3.44 and 3.35 (d AB q, $\Delta\nu_{AB}$ = 35.3 Hz, *J* = 15.7, 5.2 Hz, 2H), 3.30 – 3.26 (m, 1H), 3.18 – 2.98 (m, 7H), 2.84 (s, 3H), 1.76 – 1.62 (m, 2H), 1.52 – 1.41 (m, 2H), 1.33 (t, *J* = 7.3 Hz, 3H), 1.31 – 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.70, 168.61, 137.75, 136.07, 130.26, 129.65, 128.11, 127.87, 120.02, 56.90, 56.65, 52.95, 52.36, 40.21, 39.78, 38.85, 29.64, 27.64, 24.89, 24.79, 9.55; MS (ESI): 429 $[M+H]^+$; HPLC: 100%, t_R: 0.52 min; HRMS calcd. for $C_{23}H_{36}N_6O_2$ + H: 429.2978; found: 429.2990 $[M+H]^+$.



Compound 6: The general procedure was followed using 0.79 mmol of starting bromide **S3**, 0.4 mL (4.8 mmol) of pyrrolidine in 4 mL of acetonitrile. The TFA salt of the product was obtained as a light yellow solid (147 mg, 33 %). ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 7.42 (s, 1H), 7.37 – 7.21 (m, 5H), 4.58 (t, *J* = 7.7 Hz, 1H), 4.21 (t, *J* = 5.9 Hz, 1H), 3.64 (br s, 2H), 3.41 and 3.34 (d AB q, $\Delta\nu_{AB}$ = 31.1 Hz *J* = 15.7, 5.3 Hz, 2H), 3.29 – 3.23 (m, 1H), 3.18 – 2.96 (m, 7H), 2.22 – 1.95 (m, 4H), 1.75 – 1.63 (m, 2H), 1.51 – 1.40 (m, 2H), 1.33 – 1.22 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 173.71, 168.60, 137.74, 136.07, 130.26, 129.65, 128.11, 127.84, 120.03, 56.91, 56.07, 55.15, 52.94, 40.22, 38.85, 29.62, 27.63, 26.68, 24.82, 23.96; MS (ESI): 441 $[M+H]^+$; HPLC: 100%, t_R: 0.77 min; HRMS calcd. for $C_{24}H_{36}N_6O_2$ + H: 441.2973; found: 441.2962 $[M+H]^+$.

Procedure for the Preparation of Nicotinamide **7**:





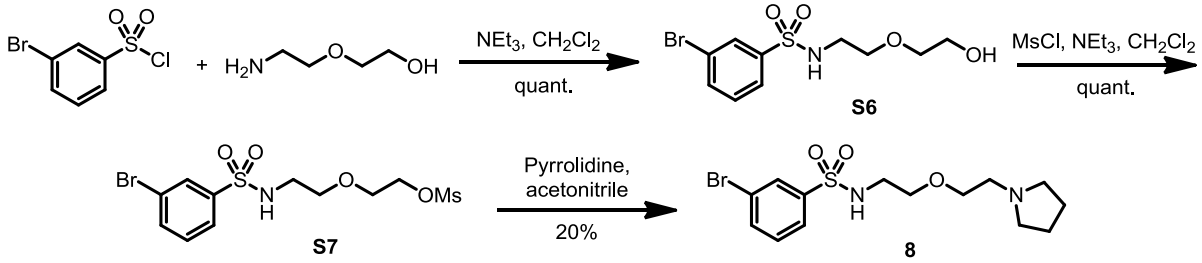
5-Bromo-*N*-(5-(pyrrolidin-1-yl)pentylnicotinamide (**UNC 280**, Compound **7**): To a solution of 5 g (24.74 mmol) of 5-bromopyridine-3-carboxylic acid in 20 mL of DMF was added 11.25 g (29.7 mmol) of *O*-(benzotriazol-1-yl)-*N,N,N'N'*-tetramethyluronium hexafluorophosphate (HBTU) and the mixture was stirred for 15 min at rt, at which point it became clear. Next, 5.11 g (49.50 mmol) of 5-aminopentanol was added followed by 6.9 mL (49.5 mmol) of NEt_3 and the mixture was stirred overnight. The reaction was quenched by addition of 60 mL of sat. aq $NaHCO_3$ and diluted with 50 mL of CH_2Cl_2, the layers were separated and the aqueous phase was further extracted with CH_2Cl_2 (6 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica (adsorbed on silica, CH_2Cl_2 – 10% MeOH/CH_2Cl_2) to afford 6.2 g (87%) of the alcohol **S4** as a white solid.

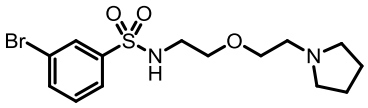
A solution of 755 mg (2.63 mmol) of alcohol **S4** in 30 mL of CH_2Cl_2 and 5 mL of THF was sonicated and stirred until the starting material was dissolved, then cooled to 0 °C. Next, 1.1 mL (7.73 mmol) of NEt_3 and 0.4 mL (5.15 mmol) of MsCl were added dropwise via syringe. The solution was stirred for 2 h at 0 °C, upon which it became slightly yellow. The reaction was quenched by addition of 20 mL of sat. aq $NaHCO_3$ and stirred vigorously for 20 min. The mixture was then diluted with 30 mL of EtOAc and 20 mL of sat. aq $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation to afford the mesylate **S5** as a yellow solid (978 mg, quant.) which was used in the following step without further purification.

To a solution of 270 mg (0.738 mmol) of mesylate **S5** in 4 mL of acetonitrile was added 0.24 mL (2.96 mmol) of pyrrolidine and the mixture was stirred for 14 h. The reaction was

quenched with sat. aq $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by HPLC to afford 224 mg (67%) of the TFA salt of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.92 (d, *J* = 1.8 Hz, 1H), 8.81 (d, *J* = 2.2 Hz, 1H), 8.40 (t, *J* = 2.0 Hz, 1H), 3.69 – 3.61 (m, 2H), 3.42 (t, *J* = 7.0 Hz, 2H), 3.22 – 3.15 (m, 2H), 3.11 – 3.02 (m, 2H), 2.22 – 2.09 (m, 2H), 2.08 – 1.95 (m, 2H), 1.84 – 1.74 (m, 2H), 1.74 – 1.65 (m, 2H), 1.52 – 1.42 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 166.41, 153.89, 147.61, 139.18, 133.26, 121.83, 56.15, 55.16, 40.51, 29.80, 26.61, 24.81, 23.95. MS (ESI): 340 and 342 $[M+H]^+$; HPLC: 100%, t_R: 2.61 min; HRMS calcd. for $C_{15}H_{22}BrN_3O$ + H: 340.1025 and 342.1004; found: 340.1036 and 342.1023 $[M+H]^+$.

Procedure for the Preparation of Sulfonamide **8**:





3-Bromo-*N*-(2-(2-(pyrrolidin-1-yl)ethoxy)ethylbenzenesulfonamide (8):

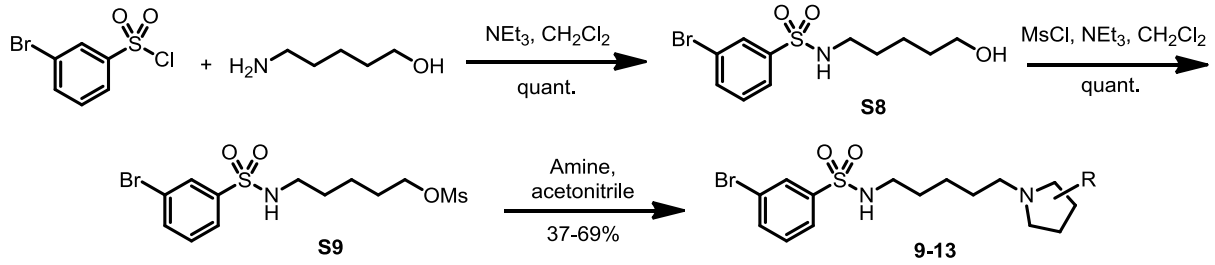
To a stirring solution of 1.89 g (18.0 mmol) of 2-aminoethoxyethanol and 2.2 mL of NEt_3 in 90 ml of CH_2Cl_2 was added 2 g (7.83 mmol) of 3-bromobenzenesulfonylchloride in 10 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to warm to rt and stirred for 14 h. Upon completion of the displacement, the reaction was quenched by addition of sat. aq $NaHCO_3$ and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were washed with sat. aq NaCl, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude product (2.9 g, quant.) was used in the next step without further purification.

To a solution of 1.27 g (4.04 mmol) of alcohol **S6** in 40 mL of CH_2Cl_2 were added 2.2 mL (15.7 mmol) of NEt_3 and 0.6 mL (7.83 mmol) of MsCl at 0 °C and the mixture was

stirred for 2 h. The reaction was quenched by addition of 20 mL of sat. aq $NaHCO_3$ and stirred vigorously for 15 min. The mixture was diluted with 30 mL of CH_2Cl_2 and 20 mL of sat. aq $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with sat. aq NaCl and dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation to afford 1.8 g (quant.) of the mesylate **S7** as a light yellow solid which was used in the following step without further purification.

To a solution of 800 mg (1.5 mmol) of mesylate **S7** in 5 mL of acetonitrile was added 0.6 mL (7.4 mmol) of pyrrolidine and the mixture was stirred for 14 h. The reaction was quenched with sat. aq $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by HPLC to afford 111 mg (20%) of the TFA salt of the title compound as a yellowish solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.01 (t, *J* = 1.8 Hz, 1H), 7.86 – 7.79 (m, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 3.77 – 3.72 (m, 2H), 3.72 – 3.64 (m, 2H), 3.58 (t, *J* = 5.3 Hz, 2H), 3.42 – 3.37 (m, 2H), 3.17 – 3.09 (m, 4H), 2.23 – 2.10 (m, 2H), 2.10 – 1.97 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 144.04, 136.69, 132.20, 130.67, 126.70, 123.87, 71.04, 66.50, 55.55, 55.49, 43.70, 23.84; MS (ESI): 377 and 379 $[M+H]^+$; HPLC: 100%, t_R: 3.19 min.

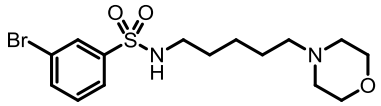
Procedure for the Preparation of Sulfonamides **9-13**:



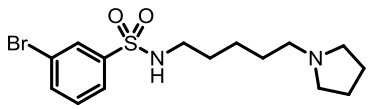
5-(3-Bromophenylsulfonamido)pentyl methanesulfonate (**S9**): To a stirring solution of 808 mg (7.83 mmol) of 5-amino-1-pentanol and 1.1 mL of NEt_3 in 35 ml of CH_2Cl_2 was added 1 g (3.91 mmol) of 3-bromobenzenesulfonylchloride in 5 mL of CH_2Cl_2 at 0 °C. The mixture was allowed to warm to rt and stirred for 14 h. Upon completion of the displacement, the reaction was quenched by addition of sat. aq $NaHCO_3$ and the layers were separated. The aqueous phase was further extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The crude

product was purified by column chromatography (adsorbed on silica, CH_2Cl_2 – 5% MeOH/CH_2Cl_2) to afford 1.3 g (quant.) of the alcohol **S8** as a white solid.

A 100 mL RB flask, charged with a magnetic stir bar, 1.3 g (4.04 mmol) of alcohol **S8** in 30 mL of CH_2Cl_2 cooled to 0 °C. Next, 2.3 mL (16.14 mmol) of NEt_3 and 0.63 mL (8.07 mmol) of MsCl were sequentially added via syringe. The solution was stirred at 0 °C for 2 h. The reaction was quenched by addition of 20 mL of $NaHCO_3$ (aq) and stirred vigorously for 15 min. The mixture was diluted with 30 mL of CH_2Cl_2 and 20 mL of sat. aq $NaHCO_3$ and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with sat. aq NaCl, dried over $MgSO_4$, filtered and the solvent was removed by rotary evaporation to afford 1.7 g (quant.) of mesylate **S9** as a light yellow solid which was used in the following steps without further purification.

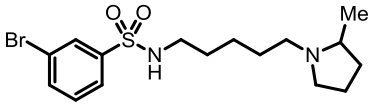


3-Bromo-*N*-(5-morpholinopentyl)benzenesulfonamide (9): To a solution of 70 mg (0.18 mmol) of mesylate **S9** in 2 mL of acetonitrile was added 31 mg (0.35 mmol) of morpholine and the mixture was stirred for 14 h. The reaction was quenched with sat. aq $NaHCO_3$ and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was purified by HPLC to afford 52 mg (59%) of the TFA salt of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (t, *J* = 1.6 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 4.14 – 4.00 (m, 2H), 3.83 – 3.67 (m, 2H), 3.55 – 3.41 (m, 2H), 3.19 – 3.03 (m, 4H), 2.90 (t, *J* = 6.6 Hz, 2H), 1.79 – 1.67 (m, 2H), 1.60 – 1.50 (m, 2H), 1.49 – 1.37 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 144.06, 136.56, 132.14, 130.68, 126.69, 123.84, 65.07, 58.36, 53.17, 43.45, 30.02, 24.37, 24.10; MS (ESI): 391 and 393 $[M+H]^+$; HPLC: 100%, t_R: 3.42 min.

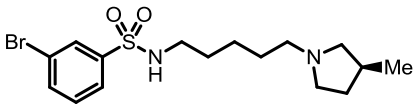


3-Bromo-*N*-(5-pyrrolidin-1-yl)pentylbenzenesulfonamide (10): The general procedure for the mesylate displacement was followed with 1.7 g (4.3 mmol) of mesylate **S9**, 1.1 mL (12.9 mmol) of pyrrolidine in 30 mL of acetonitrile. After workup, the crude product was purified by column chromatography on silica silica (adsorbed on silica, CH_2Cl_2 – 10%

MeOH/CH_2Cl_2/1% NH_3) to afford 1.1 g (69%) of the title compound. A portion was further purified by HPLC and the TFA salt of the title compound was obtained as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.00 – 7.96 (m, 1H), 7.84 – 7.76 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 3.70 – 3.58 (m, 2H), 3.20 – 3.11 (m, 2H), 3.11 – 3.00 (m, 2H), 2.89 (t, *J* = 6.6 Hz, 2H), 2.22 – 2.10 (m, 2H), 2.08 – 1.95 (m, 2H), 1.77 – 1.65 (m, 2H), 1.60 – 1.49 (m, 2H), 1.48 – 1.36 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 144.08, 136.54, 132.14, 130.68, 126.70, 123.83, 56.12, 55.16, 43.47, 30.01, 26.42, 24.42, 23.94; MS (ESI): 375 and 377 $[M+H]^+$; HPLC: 100%, t_R: 3.29 min.

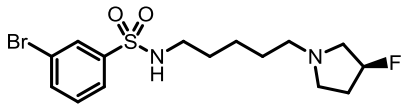


5-Bromo-*N*-(5-(2-methyl)pyrrolidin-1-yl)pentylbenzenesulfonamide (11): The general procedure for the mesylate displacement was followed using 110 mg (0.275 mmol) of mesylate **S9**, 90 mg (1.06 mmol) of 2-methylpyrrolidine in 2 mL of acetonitrile. After HPLC purification, 77 mg (56%) of the TFA salt of the title compound was obtained as a light yellow solid. By NMR analysis, two conformers are observed in a 10:1 ratio. ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 3.72 – 3.62 (m, 1H), 3.50 – 3.38 (m, 1H), 3.20 – 3.07 (m, 1H), 2.99 – 2.92 (m, 1H), 2.90 (t, *J* = 6.6 Hz, 3H), 2.38 – 2.27 (m, 1H), 2.18 – 1.95 (m, 2H), 1.82 – 1.62 (m, 3H), 1.61 – 1.49 (m, 2H), 1.49 – 1.38 (m, 5H including d at 1.43, *J* = 6.5 Hz); ^{13}C NMR (101 MHz, CD_3OD) δ 144.08, 136.55, 132.14, 130.69, 126.70, 123.83, 65.96, 54.80, 54.46, 43.48, 32.37, 30.01, 26.18, 24.54, 22.43, 16.38. MS (ESI): 389 and 391 $[M+H]^+$. HPLC: 100%, t_R: 3.41 min.

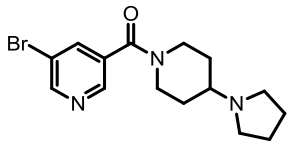


(*S*)-3-Bromo-*N*-(5-(3-methyl)pyrrolidin-1-yl)pentylbenzenesulfonamide (12): The general procedure for the mesylate displacement was followed using 120 mg (0.3 mmol) of mesylate **S9**, 70 mg (1.06 mmol) of (*S*)-3-methylpyrrolidine hydrochloride and 0.16 mL (0.9 mmol) of diisopropylethylamine in 2 mL of acetonitrile. After HPLC purification, 55 mg (37%) of the TFA salt of the title compound was obtained as a reddish-brown solid. By NMR analysis, two conformations are visible in a 1.2:1 ratio. ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (t, *J* = 1.7 Hz, 1H, both conformers), 7.80 (tdd, *J* = 8.1, 1.8, 1.0 Hz, 2H, both conformers), 7.50 (t, *J* =

7.9 Hz, 1H, both conformers), 3.75 – 3.67 (m, 2H, major), 3.67 – 3.58 (m, 2H, minor), 3.25 – 3.03 (m, 4H, both conformers), 2.89 (t, *J* = 6.6 Hz, 2H, both conformers), 2.68 – 2.52 (m, 1H, both conformers), 2.47 – 2.14 (m, 2H, both conformers), 1.79 – 1.64 (m, 3H, both conformers), 1.63 – 1.49 (m, 2H, both conformers), 1.49 – 1.38 (m, 2H, both conformers), 1.16 (d, *J* = 6.6 Hz, 2H, major), 1.14 (d, *J* = 6.8 Hz, 2H, minor); ^{13}C NMR (101 MHz, CD_3OD) δ 144.08, 136.55, 132.14, 130.68, 126.70, 123.83, 61.49 (major isomer), 61.09, 56.80, 56.51 (major isomer), 55.85, 54.78 (major isomer), 43.46, 33.54 (major isomer), 33.19, 32.77, 31.78 (major isomer), 30.01, 26.35 (major isomer), 26.26, 24.40, 18.37, 17.33 (major isomer). MS (ESI): 389 and 391 $[M+H]^+$. HPLC: 100%, t_R: 3.68 min.

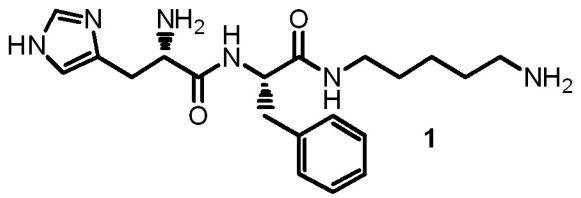


(*S*)-3-Bromo-*N*-(5-(3-fluoro)pyrrolidin-1-yl)pentylbenzenesulfonamide (13): The general procedure for the mesylate displacement was followed using 110 mg (0.275 mmol) of mesylate **S9**, 90 mg (1.06 mmol) of (*S*)-3-fluoropyrrolidine hydrochloride and 0.14 mL (0.82 mmol) of NEt_3 in 2 mL of acetonitrile. After HPLC purification, 68 mg (49%) of the TFA salt of the title compound was obtained as a yellowish solid. ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (t, *J* = 1.8 Hz, 1H), 7.84 – 7.77 (m, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 5.45 (d, *J* = 51.9 Hz, 1H), 4.01 – 3.74 (m, 2H), 3.29 – 3.14 (m, 3H), 2.90 (t, *J* = 6.6 Hz, 2H), 2.68 – 2.08 (m, 3H), 1.78 – 1.68 (m, 2H), 1.61 – 1.49 (m, 2H), 1.49 – 1.38 (m, 2H). ^{13}C NMR (101 MHz, CD_3OD) δ 144.07, 136.55, 132.14, 130.68, 126.70, 123.83, 92.77 (d, $|J_{CF}$ = 176.8 Hz|), 60.87 (d, $|J_{CF}$ = 24.0 Hz|), 56.64 – 56.26 (m), 53.50 – 53.16 (m), 43.47, 31.75 (d, $|J_{CF}$ = 17.0 Hz|), 30.01, 26.21, 24.39. MS (ESI): 393 and 395 $[M+H]^+$. HPLC: 100%, t_R: 3.353 min.



5-Bromo-*N*-(4-(pyrrolidinyl)piperidinyl)nicotinamide (**UNC669,** Compound **14**): To a solution of 80 mg (0.4 mmol) of 5-bromopyridine-3-carboxylic acid in 3 mL of DMF was added 140 mg (0.44 mmol) of TBTU and the mixture was stirred for 10 min. at rt. Then, 66 mg (0.44 mmol) of 4-(1-pyrrolidinyl)piperidine and 0.6 mL (0.44 mmol) of NEt_3 were added and the mixture was stirred for 16 h at rt. The mixture was quenched with 20 mL of sat. aq $NaHCO_3$ and diluted with 20 mL of EtOAc. The layers were separated and the aqueous phase was extracted

with EtOAc (3 × 20 mL). The combinded organic extracts were dried over Na_2SO_4, filtered and the solvent was removed by rotary evaporation. The crude product was taken up in MeOH, filtered and purified by HPLC to afford 123 mg (69%) of the TFA salt of the title compound as a off-white powder after lyophilyzation. ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (d, *J* = 2.2 Hz, 1H), 8.59 (d, *J* = 1.8 Hz, 1H), 8.12 (t, *J* = 2.0 Hz, 1H), 4.82 – 4.66 (m, 1H), 3.92 – 3.74 (m, 1H), 3.73 – 3.57 (m, 2H), 3.46 (tt, *J* = 11.8, 4.0 Hz, 1H), 3.29 – 3.09 (m, 3H), 3.07 – 2.83 (m, 1H), 2.38 – 2.09 (m, 4H), 2.08 – 1.94 (m, 2H), 1.80 – 1.59 (m, 2H); ^{13}C NMR (101 MHz, CD_3OD) δ 167.81, 152.96, 146.81, 138.95, 134.37, 121.91, 62.86, 52.83, 23.89; MS (ESI): 338 $[M+H]^+$. HPLC: 100%, t_R: 2.21 min. HRMS calcd. for $C_{15}H_{21}BrN_3O^+$: 338.0868 and 340.0848; found: 338.0868 and 340.0850 $[M+H]^+$.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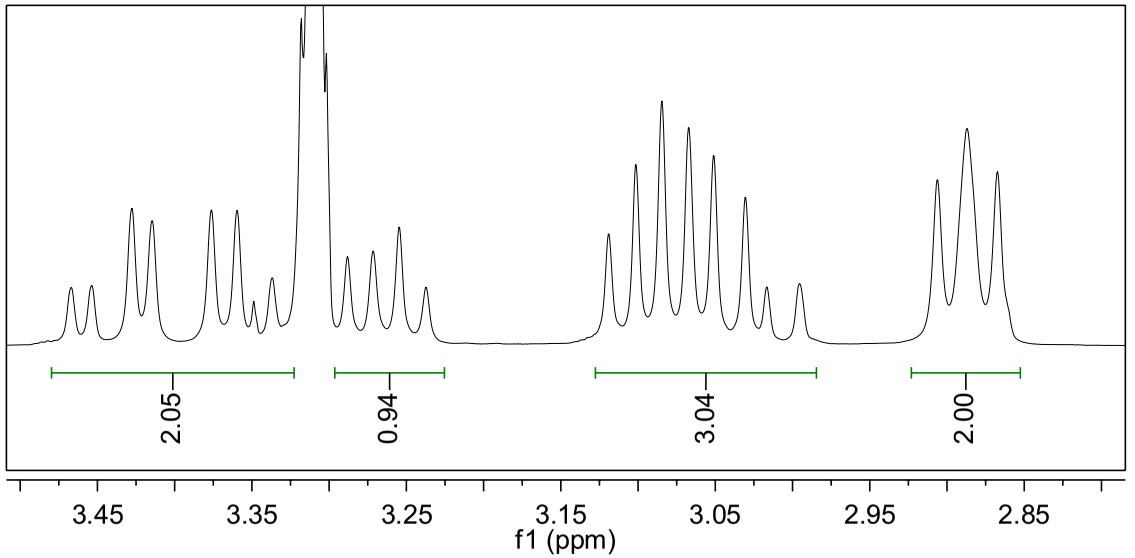
N
O
N
H
NH2
1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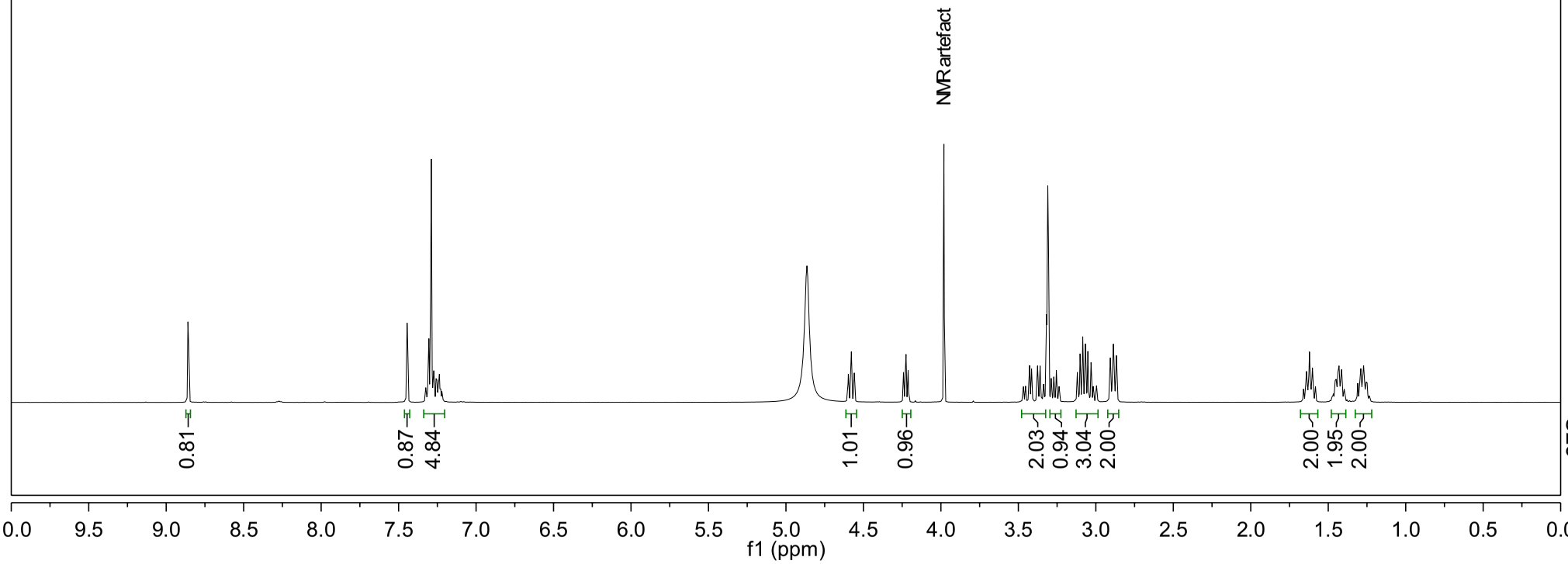
2.95
2.85
f1 (ppm)


NMRartefact
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0.96
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0.94
3.04
2.00
2.00
1.95
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
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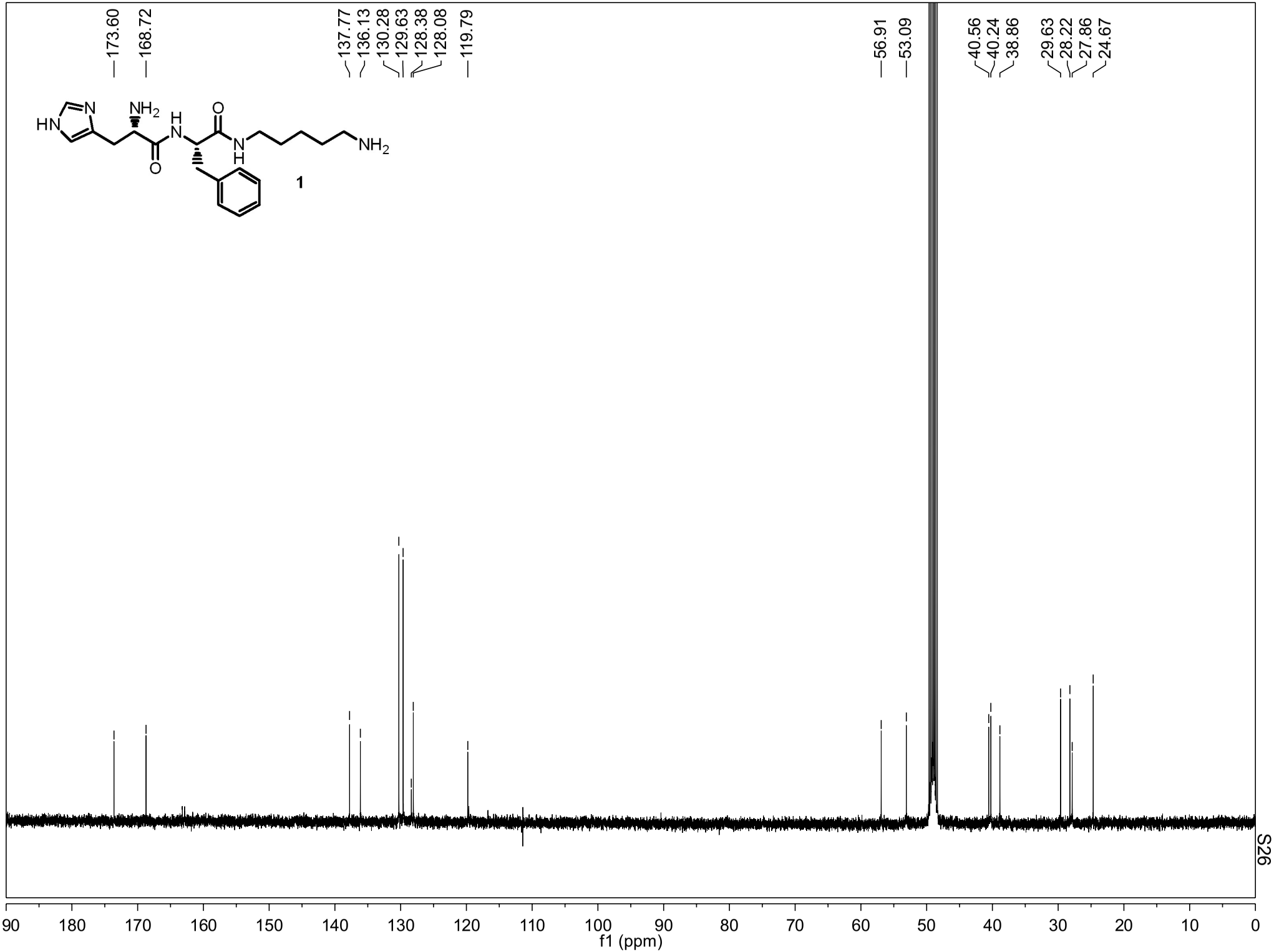
0.0
f1 (ppm)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129.63
128.38
128.08
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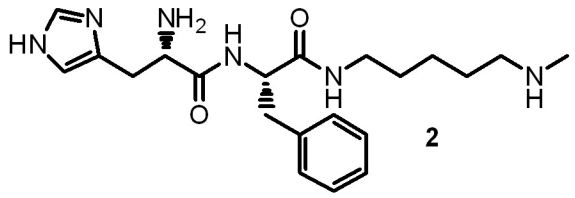
29.63
28.22
27.86
24.67
1
f1 (ppm)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N
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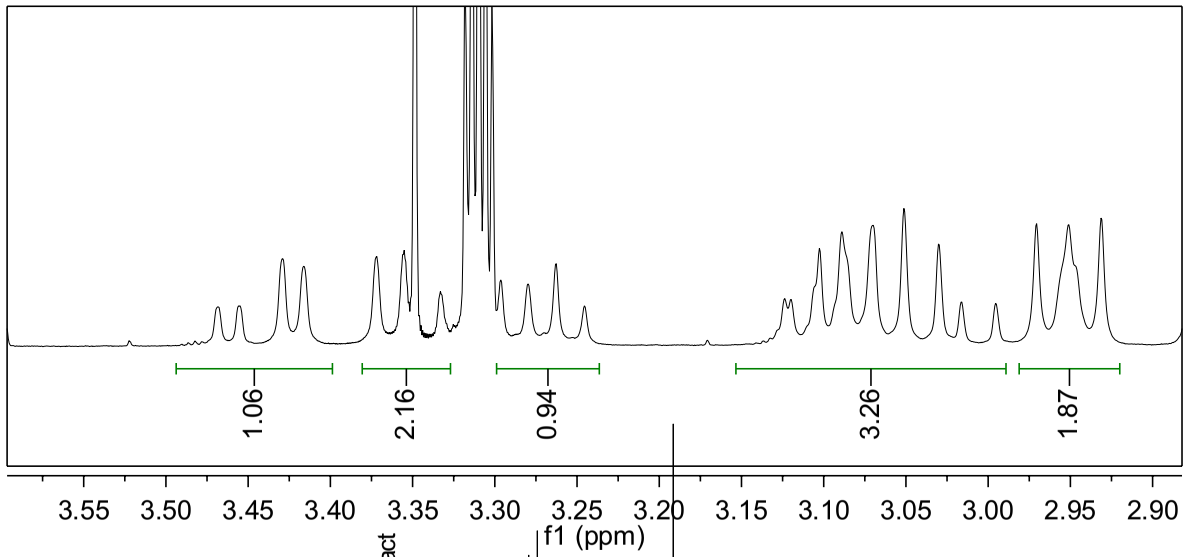
N
H
N
H
2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2.16
0.94
3.26
1.87
3.55 3.50 3.45 3.40 3.35 3.30 3.25 3.20 3.15 3.10 3.05 3.00 2.95 2.90
f1 (ppm)

NMR artefact
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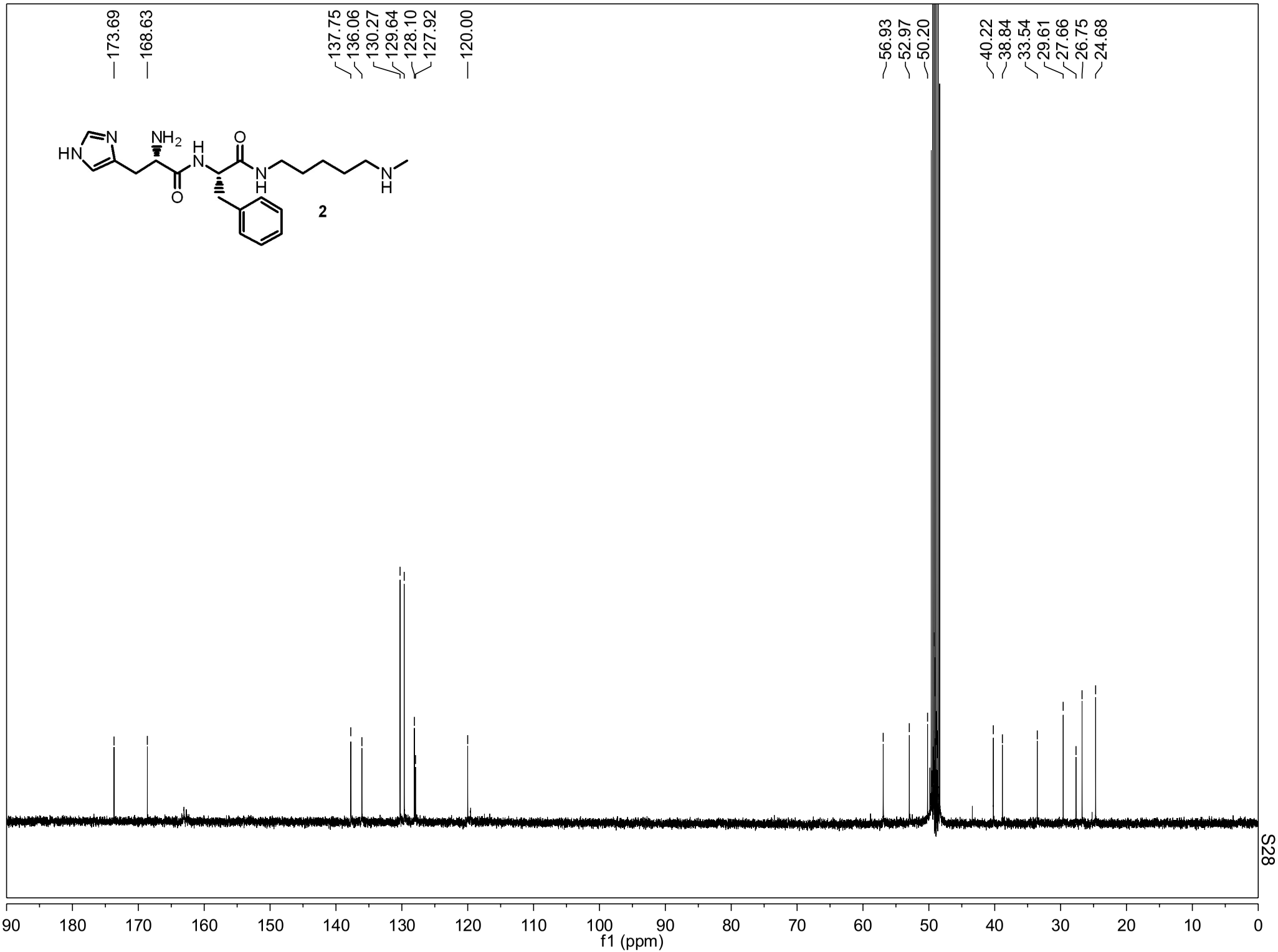
0.89
4.92
1.06
0.98
1.06
2.16
0.94
3.26
1.87
2.77
2.02
2.00
2.04
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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128.10
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56.93
52.97
50.20
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33.54
29.61
27.66
26.75
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NH2
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H
N
O
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H
N
H
2
S28
90
180
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120
110
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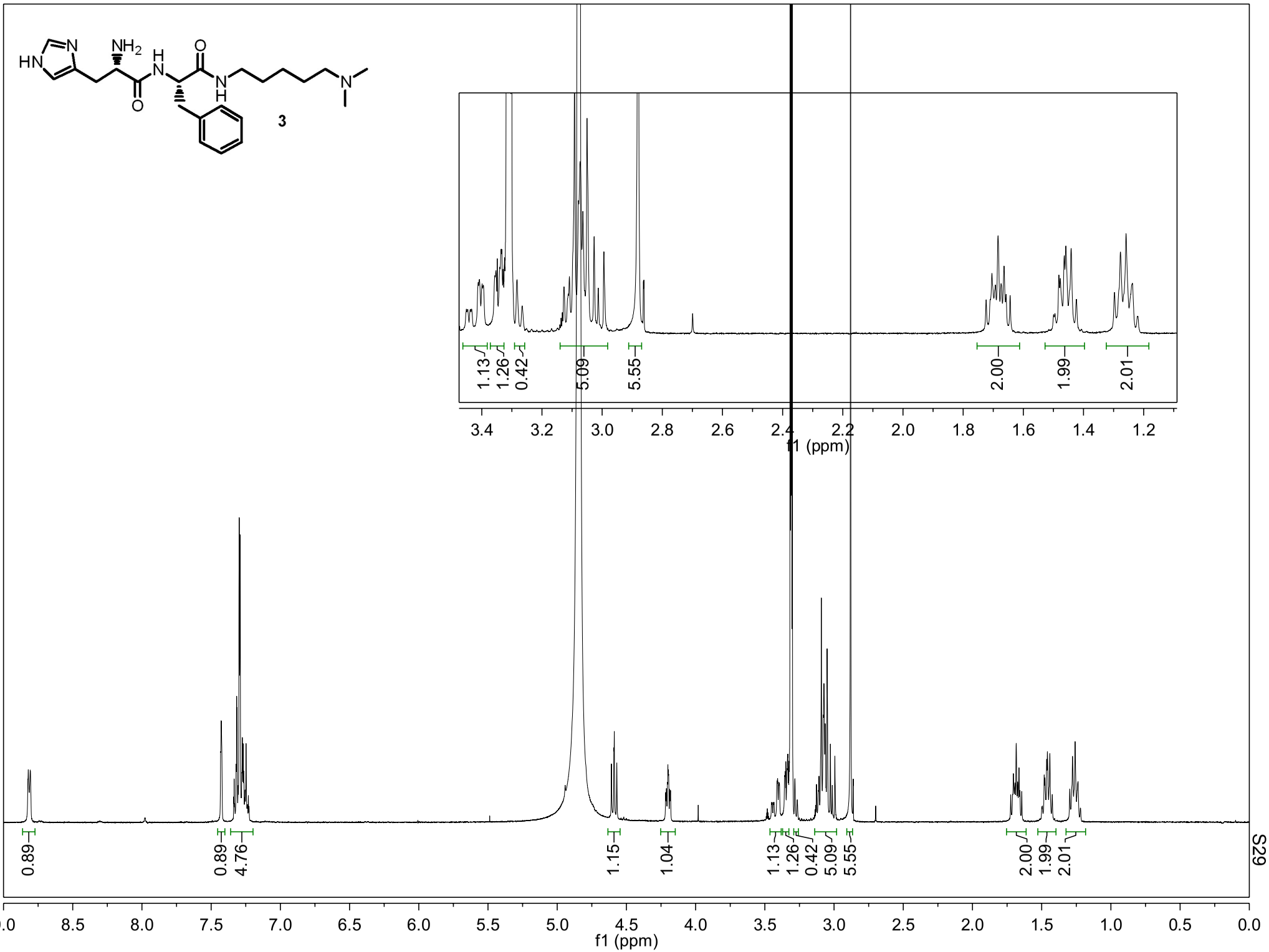
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


3
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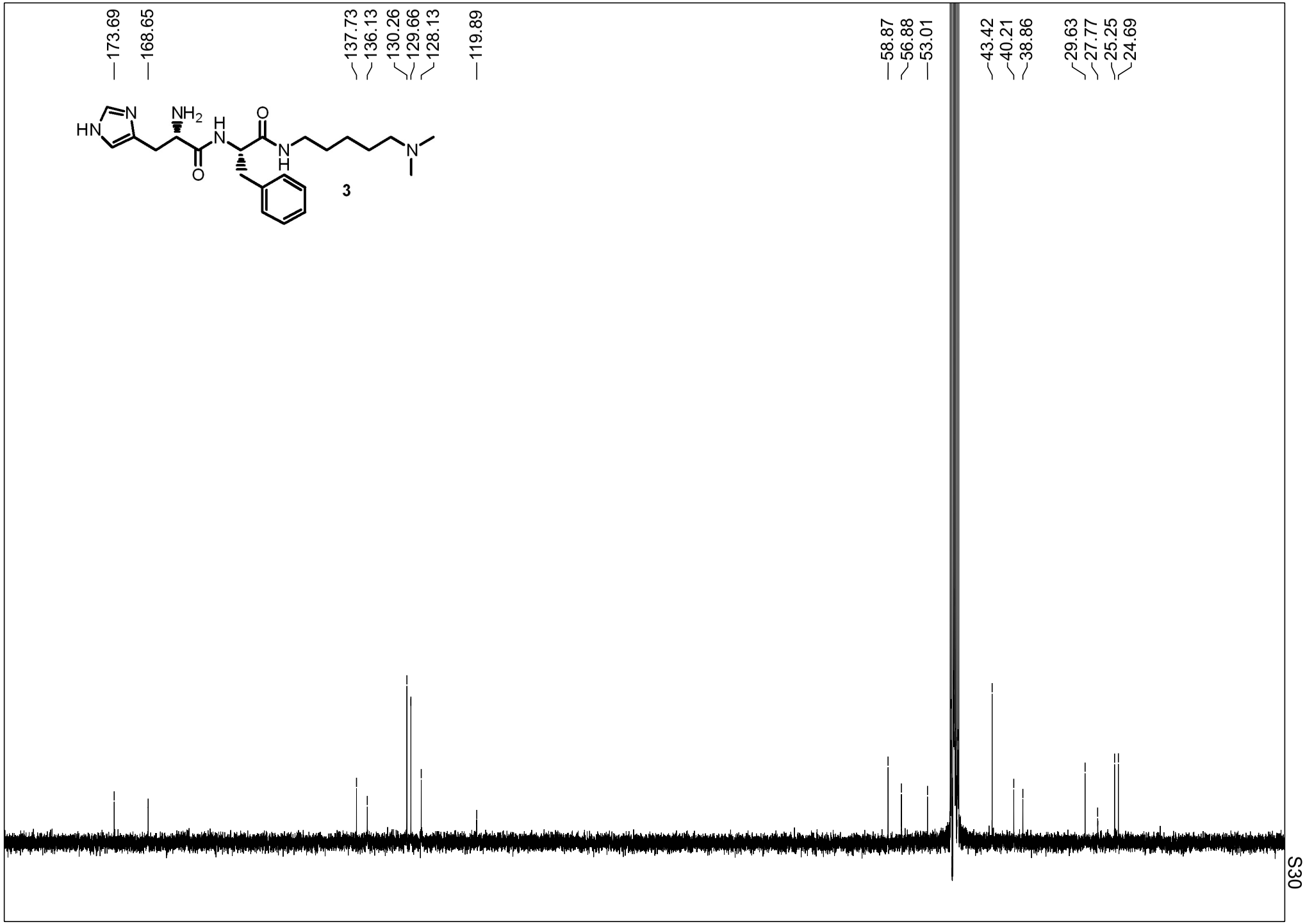
1.26
0.42
5.09
5.55
2.00
1.99
2.01
f1 (ppm)
0.89
0.89
4.76
1.15
1.04
1.13
1.26
0.42
5.09
5.55
2.00
1.99
2.01
f1 (ppm)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129.66
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53.01
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40.21
38.86
29.63
27.77
25.25
24.69
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NH2
H
N
O
O
N
H
N
3
190
180
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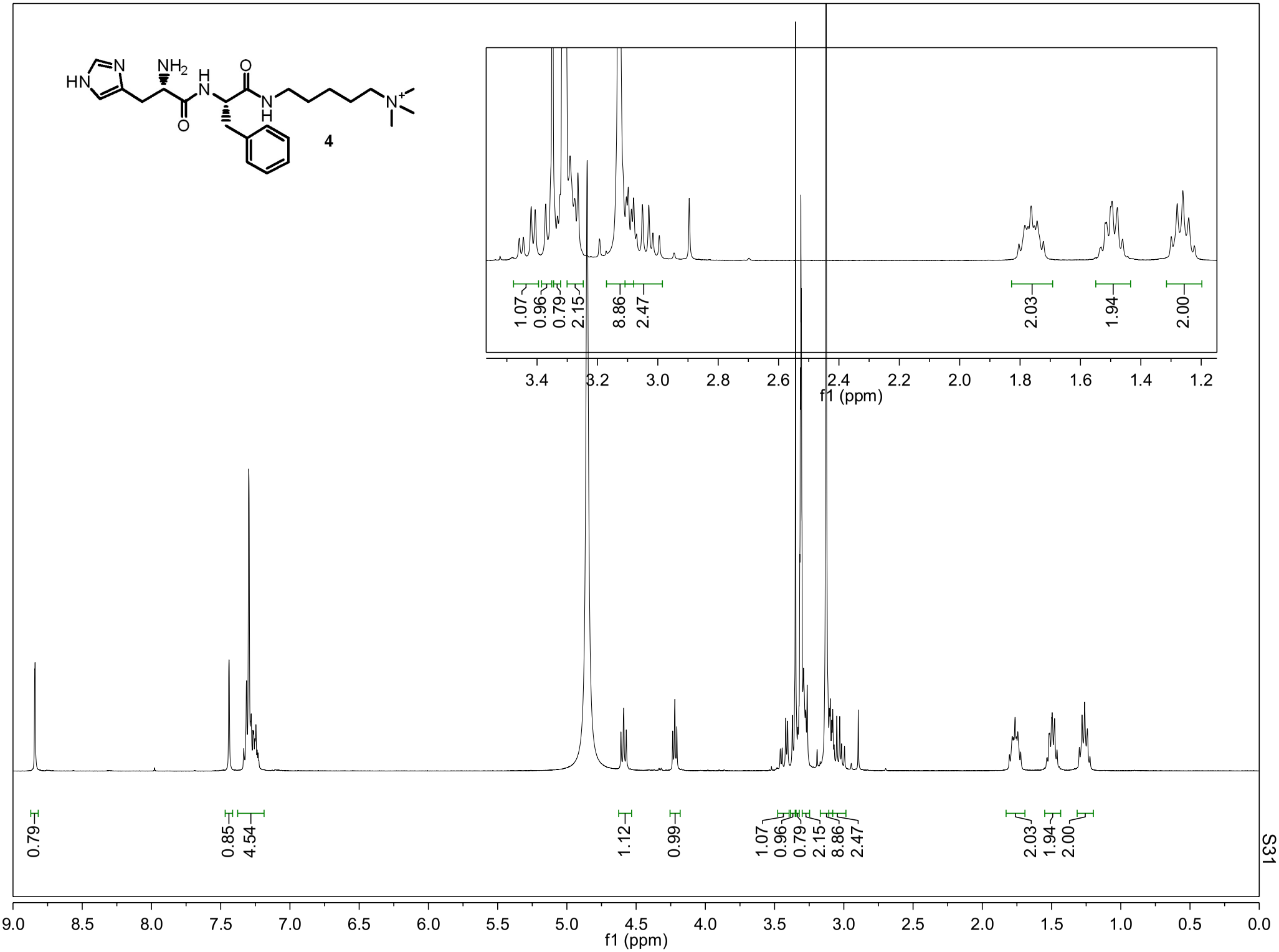
50
40
30
20
10
0
f1 (ppm)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2.00
f1 (ppm)
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0.85
4.54
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0.79
2.15
8.86
2.47
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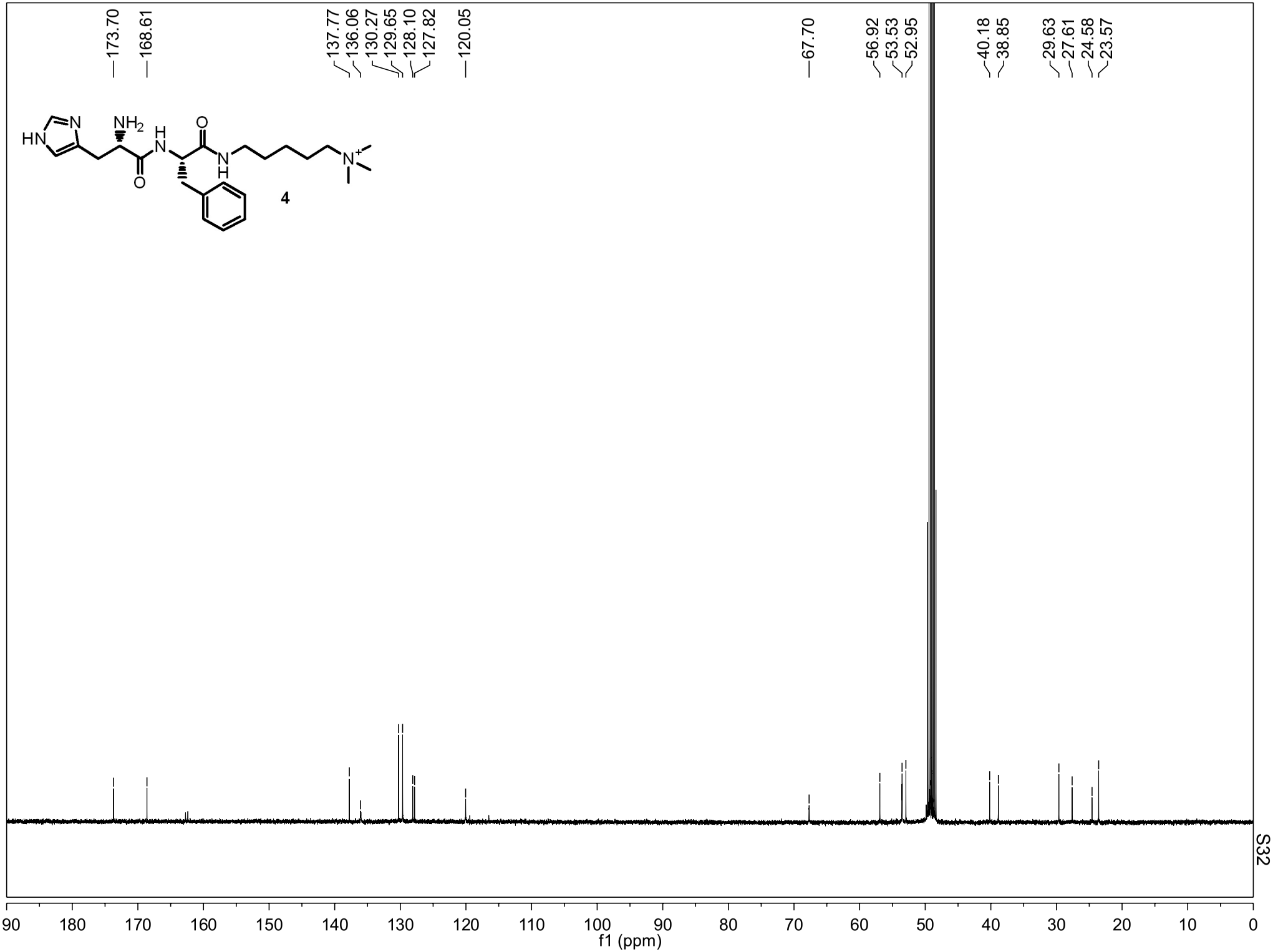
1.94
2.00
f1 (ppm)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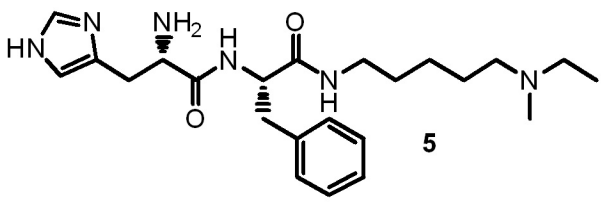
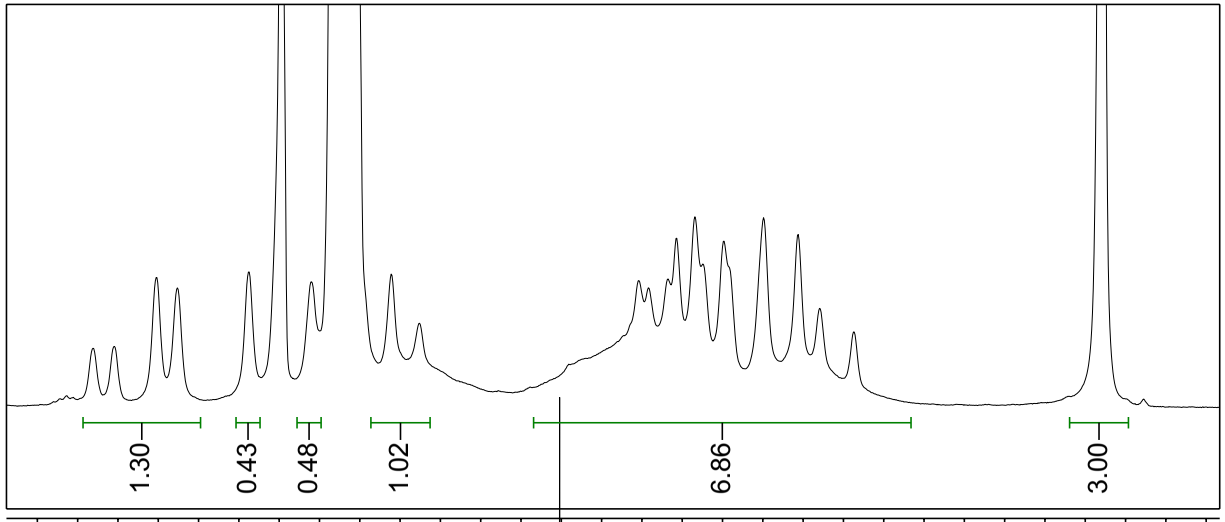
29.63
27.61
24.58
23.57
4
f1 (ppm)



5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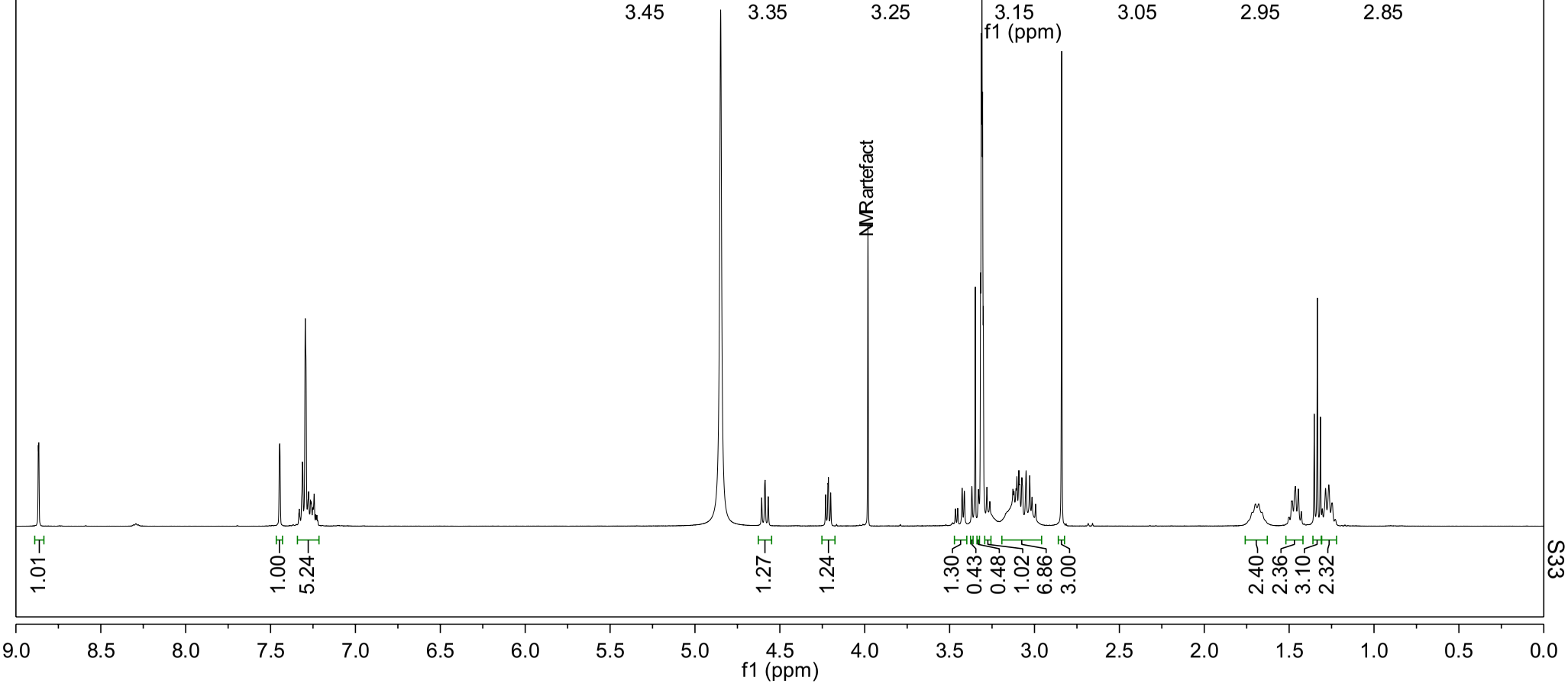
3.15
3.05
2.95
2.85
f1 (ppm)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0.48
1.02
6.86
3.00
2.40
2.36
3.10
2.32
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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2.5
2.0
1.5
1.0
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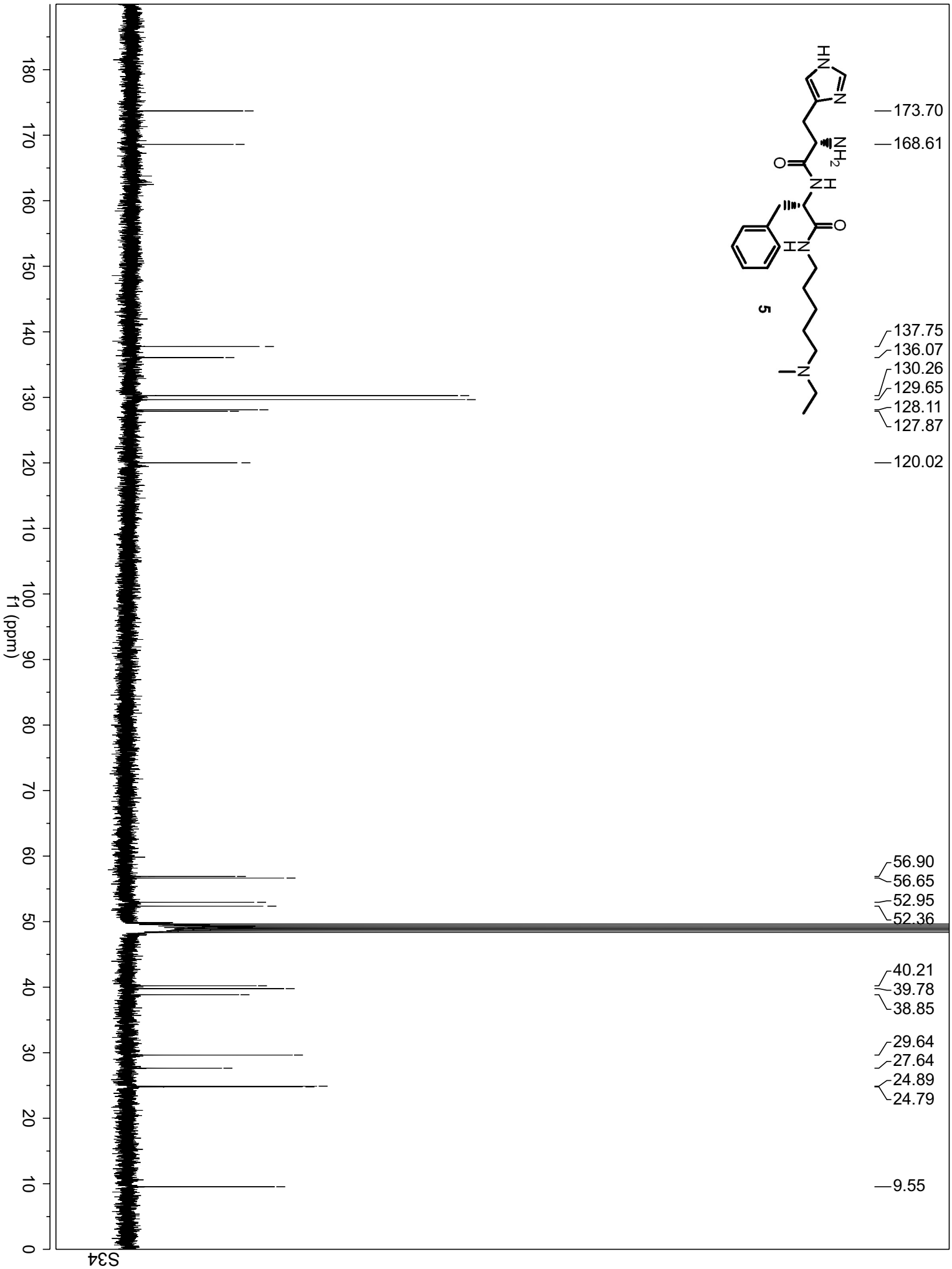
0.0
f1 (ppm)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140
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160
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180
173.70
168.61
137.75
136.07
130.26
129.65
128.11
127.87
120.02
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40.21
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27.64
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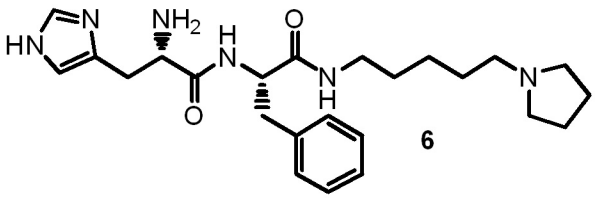
24.79
9.55
5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N
H
N
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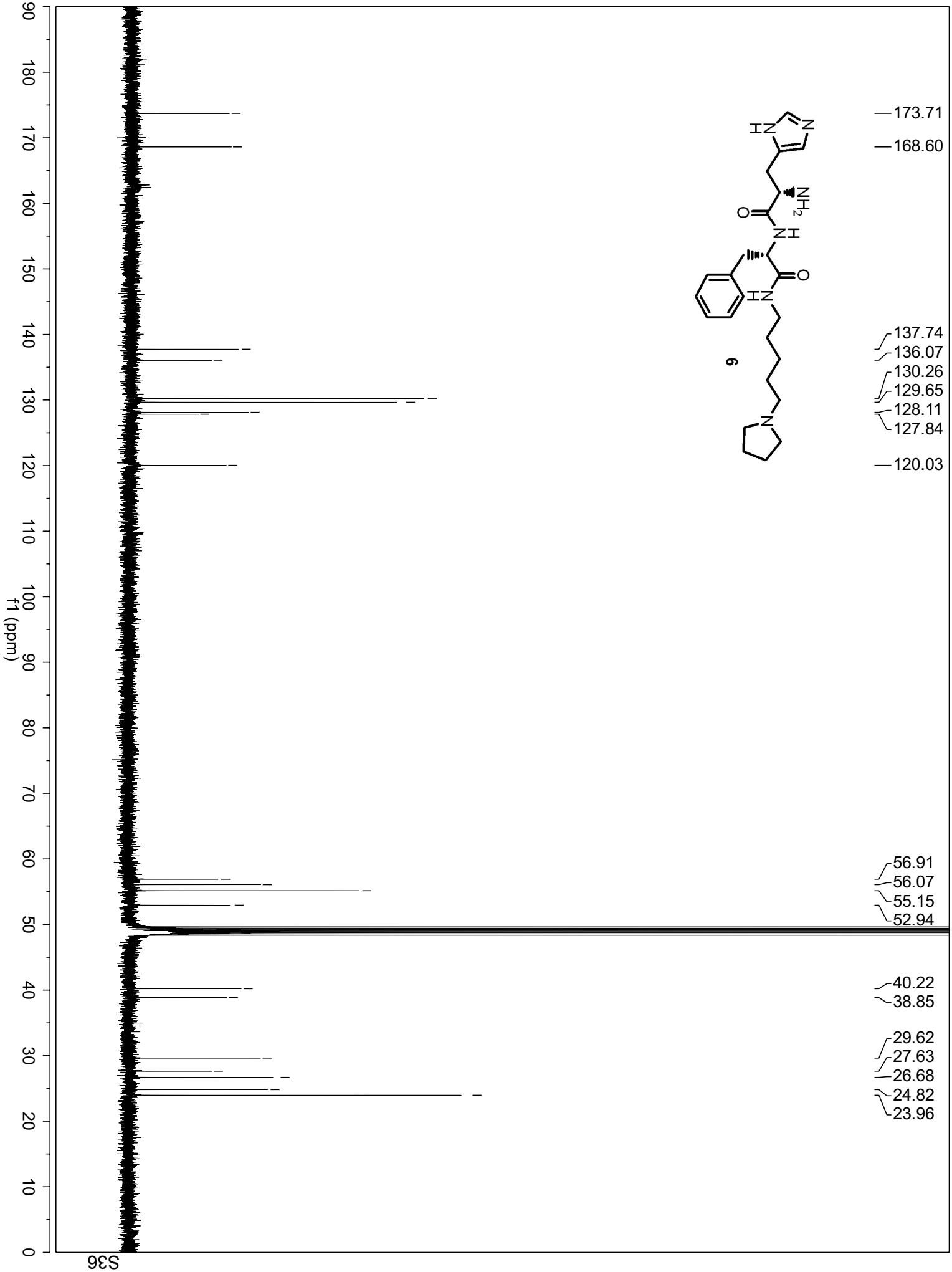
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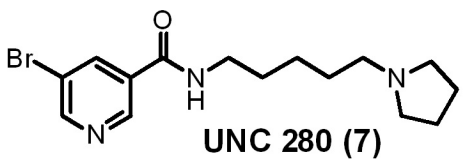
27.63
26.68
24.82
23.96
6
f1 (ppm)


Br
O
N
H
N
N

UNC 280 (7)

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0.79
0.78
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1.96
1.98
1.94
1.94
1.94
2.01
1.99
2.00
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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3.5
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1.0
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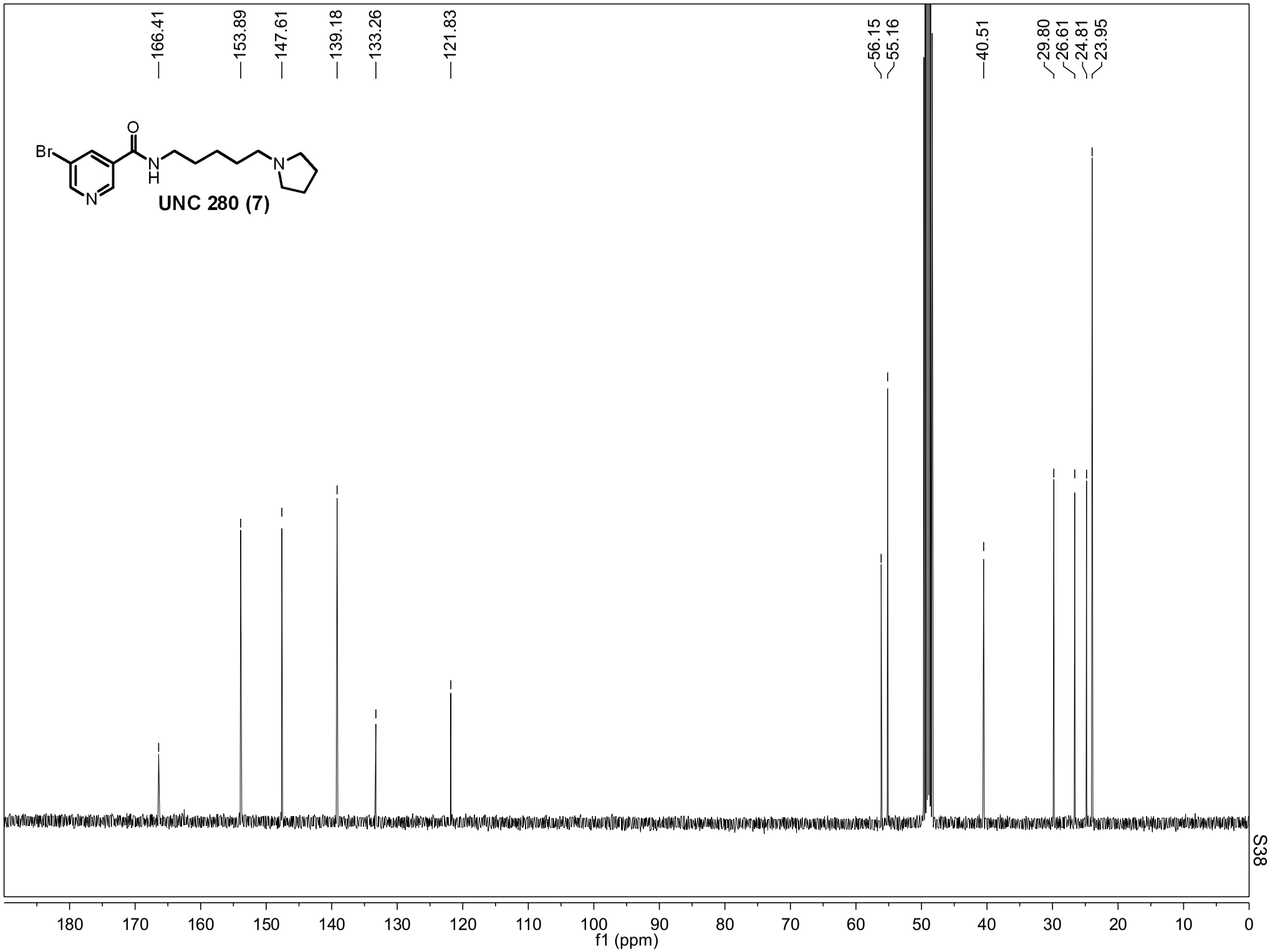
f1 (ppm)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Br
O
N
H
N
N
UNC 280 (7)
180
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160
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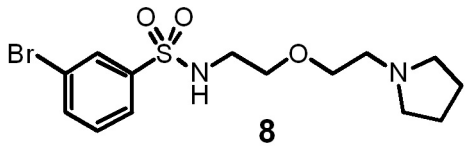
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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S
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H
O
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8

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3.86
1.95
1.92
10.0
9.5
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
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1.5
1.0
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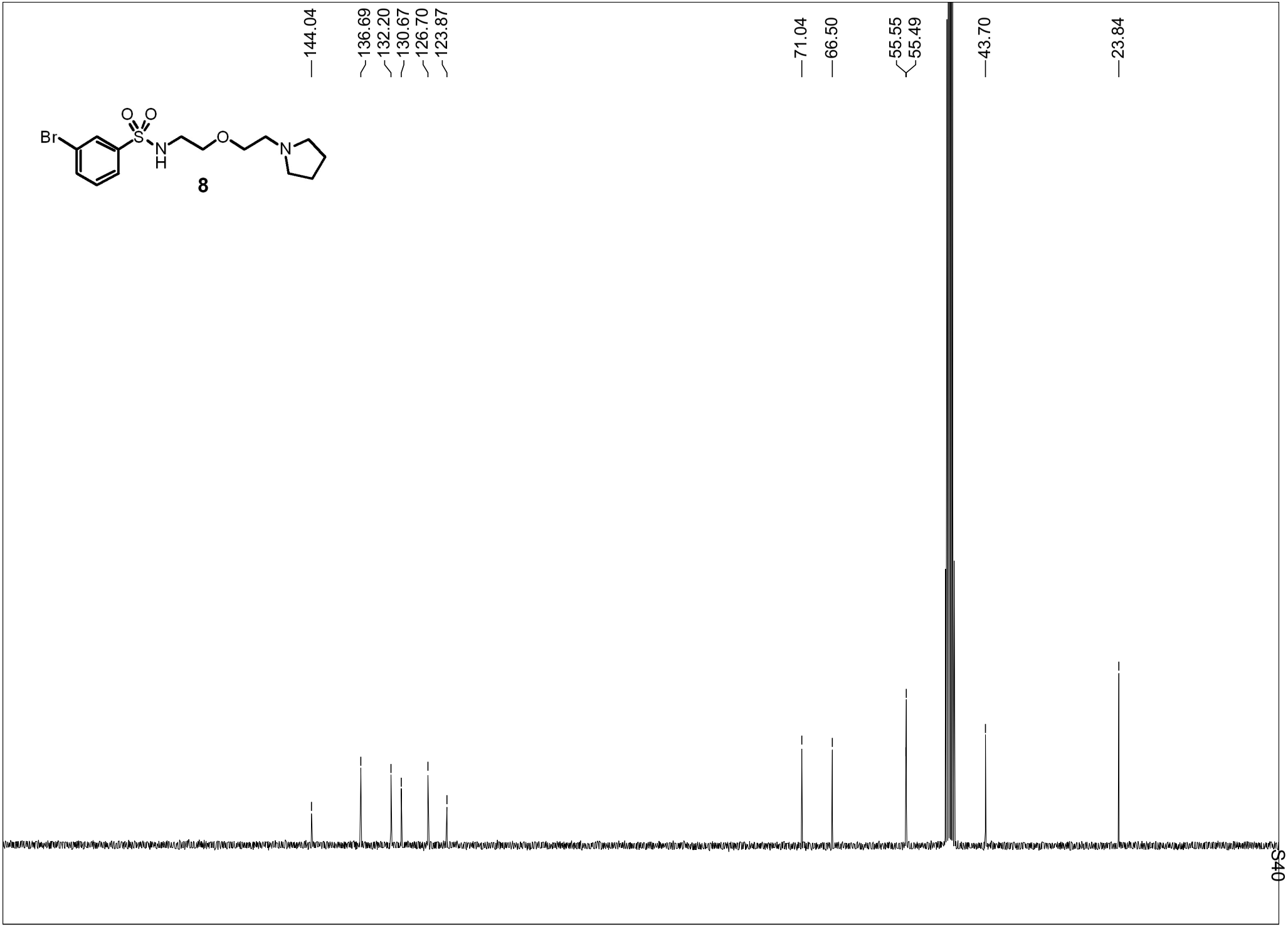
0.0
f1 (ppm)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123.87
71.04
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43.70
23.84
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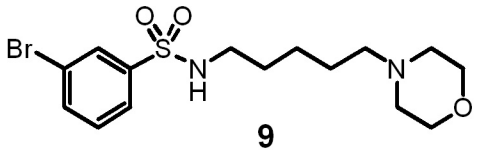
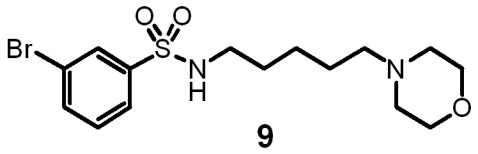
O
S
N
H
O
N
8
f1 (ppm)



9



9

144.06
136.56
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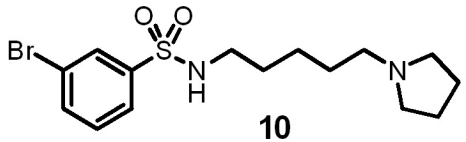
130.68
126.69
123.84
65.07
58.36
53.17
43.45
30.02
24.37
24.10

f1 (ppm)


Br
O
O
S
N
H
N

10

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2.01
2.03
2.03
1.98
2.06
2.09
2.06
9.0
8.5
8.0
7.5
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6.5
6.0
5.5
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3.0
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1.5
1.0
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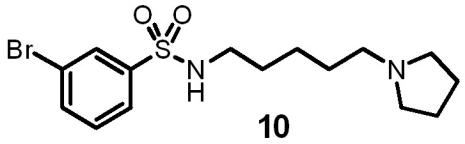
f1 (ppm)



10

144.08
136.54
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126.70
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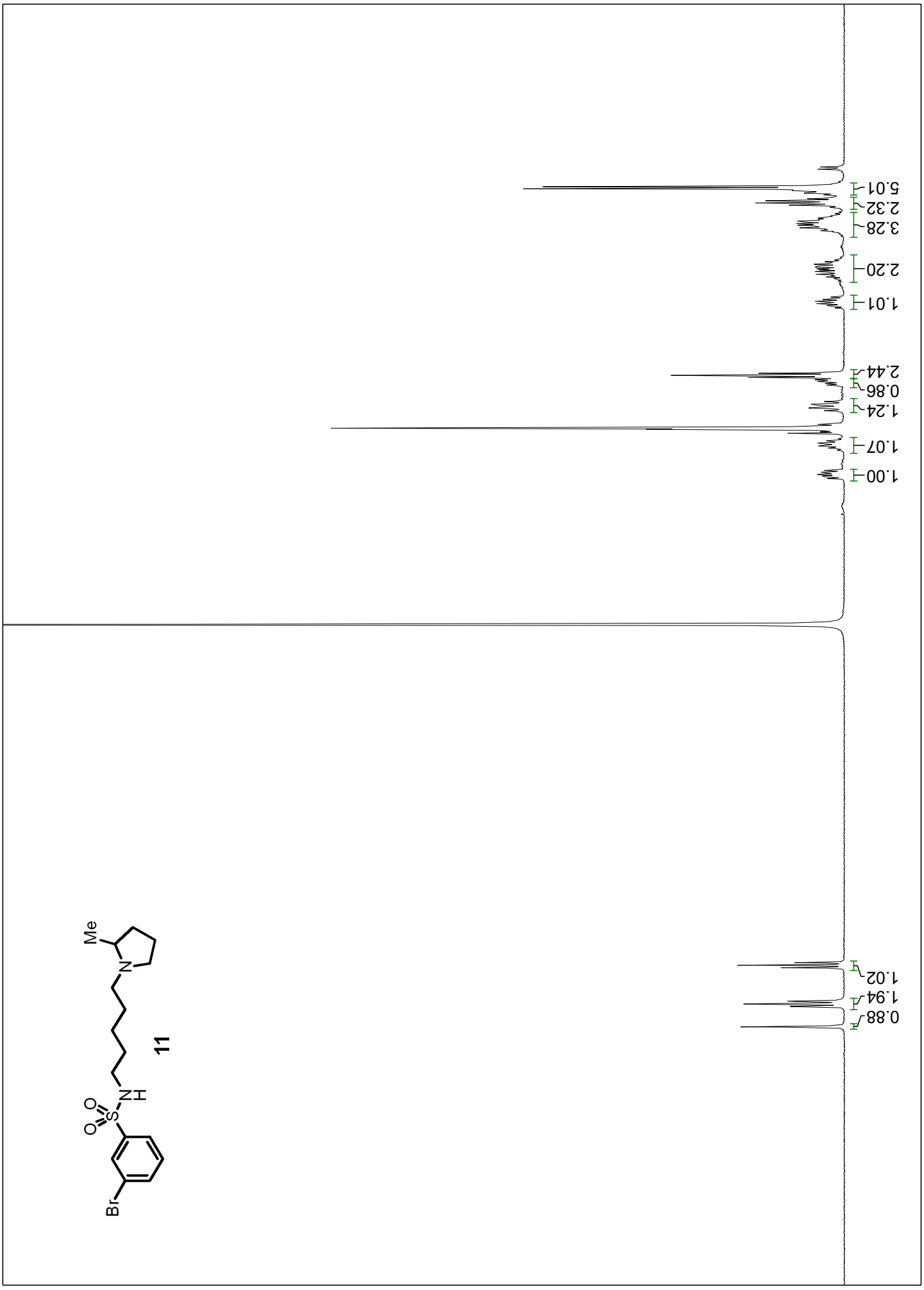
56.12
55.16
43.47
30.01
26.42
24.42
23.94

f1 (ppm)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1.02
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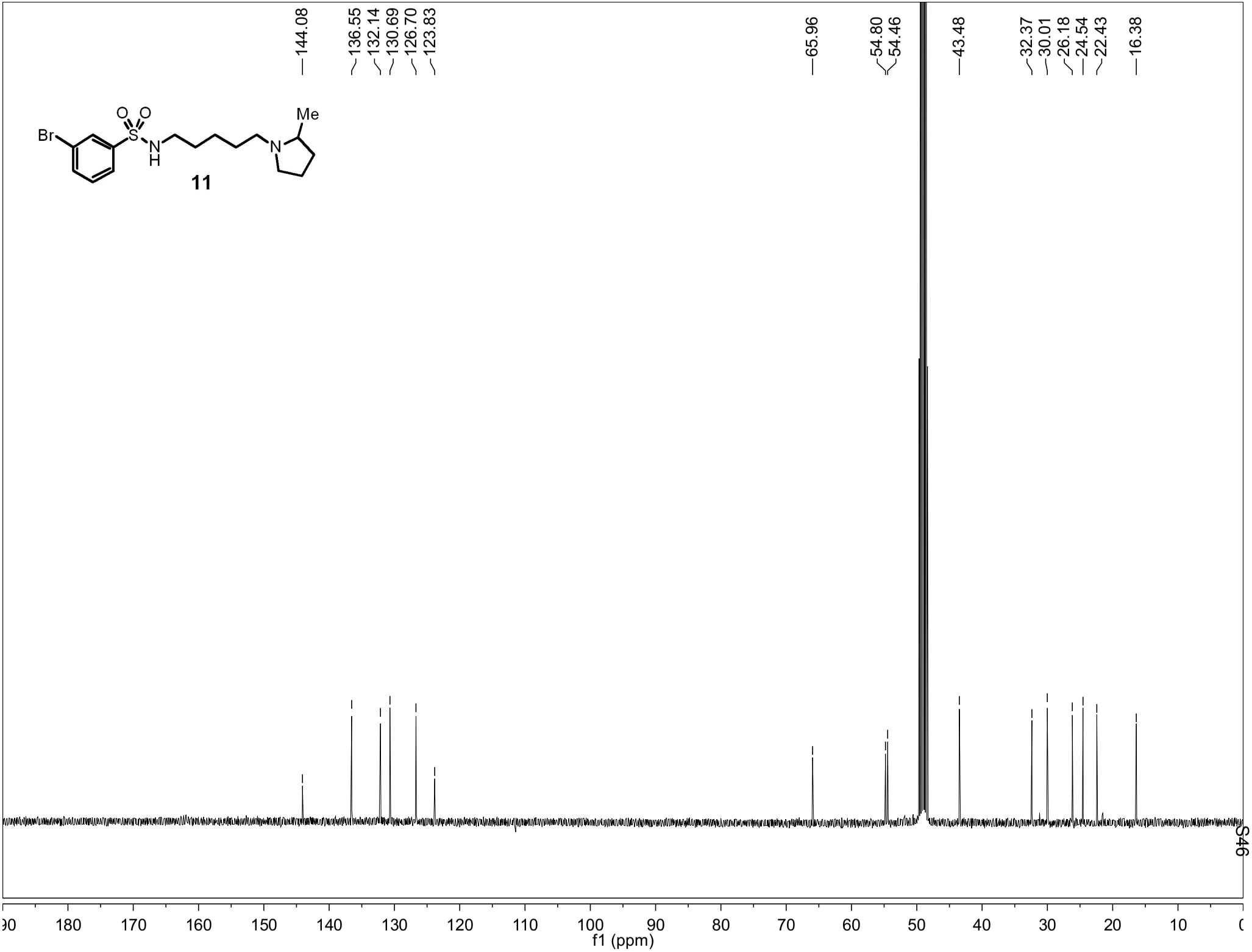
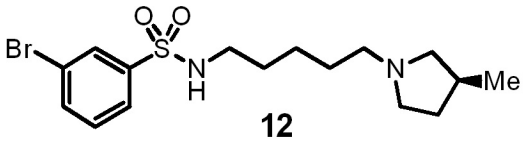
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
f1 (ppm)

Me
N
H
N
O
O
S
Br

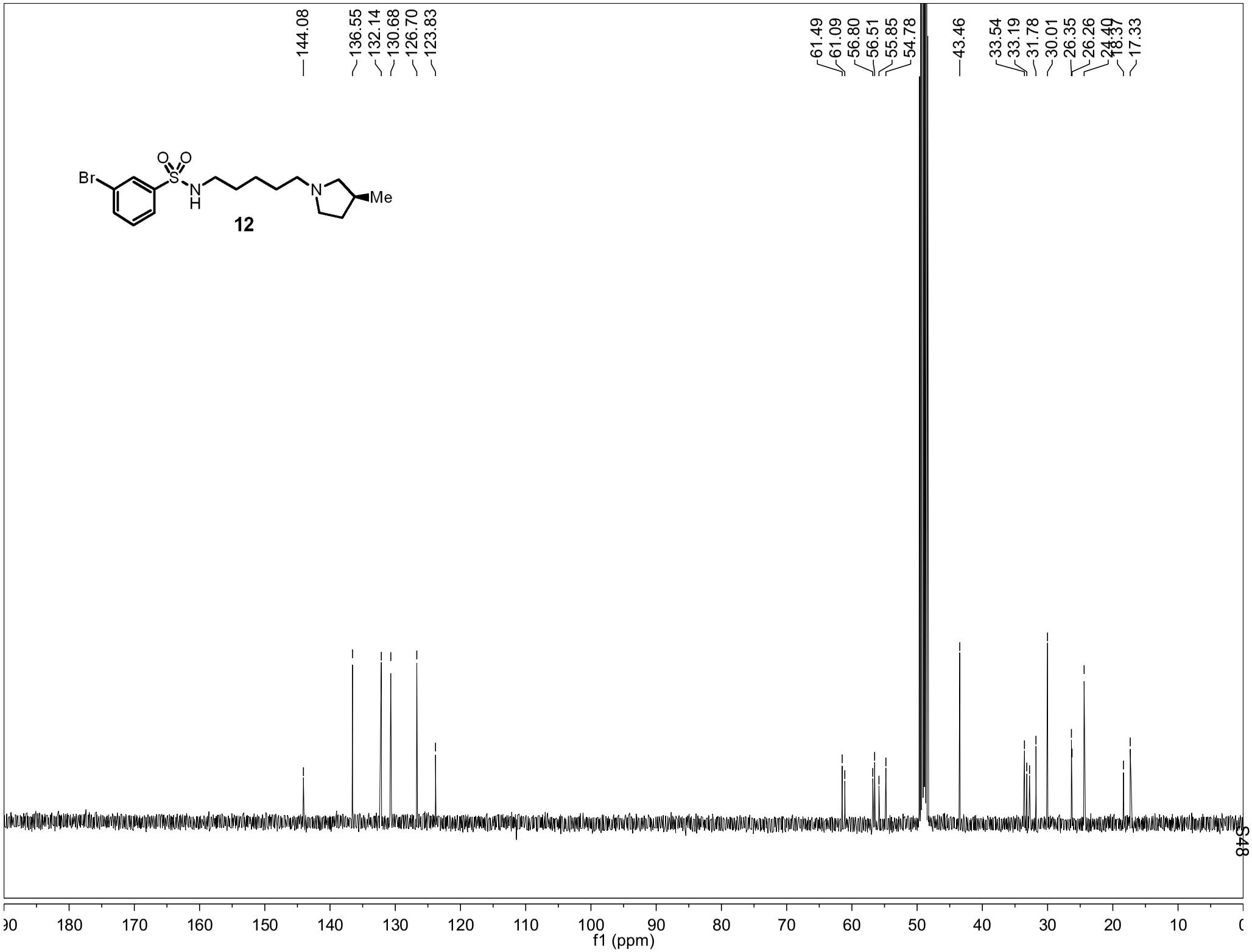
11

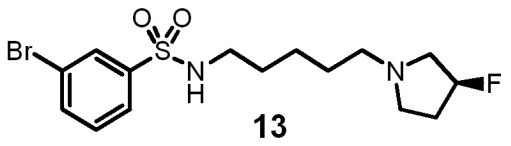

144.08
136.55
132.14
130.69
126.70
123.83
65.96
54.80
54.46
43.48
32.37
30.01
26.18
24.54
22.43
16.38
Br
O
O
S
N
H
N
Me
11
f1 (ppm)
S46


Br
O
O
S
N
H
N
Me

12

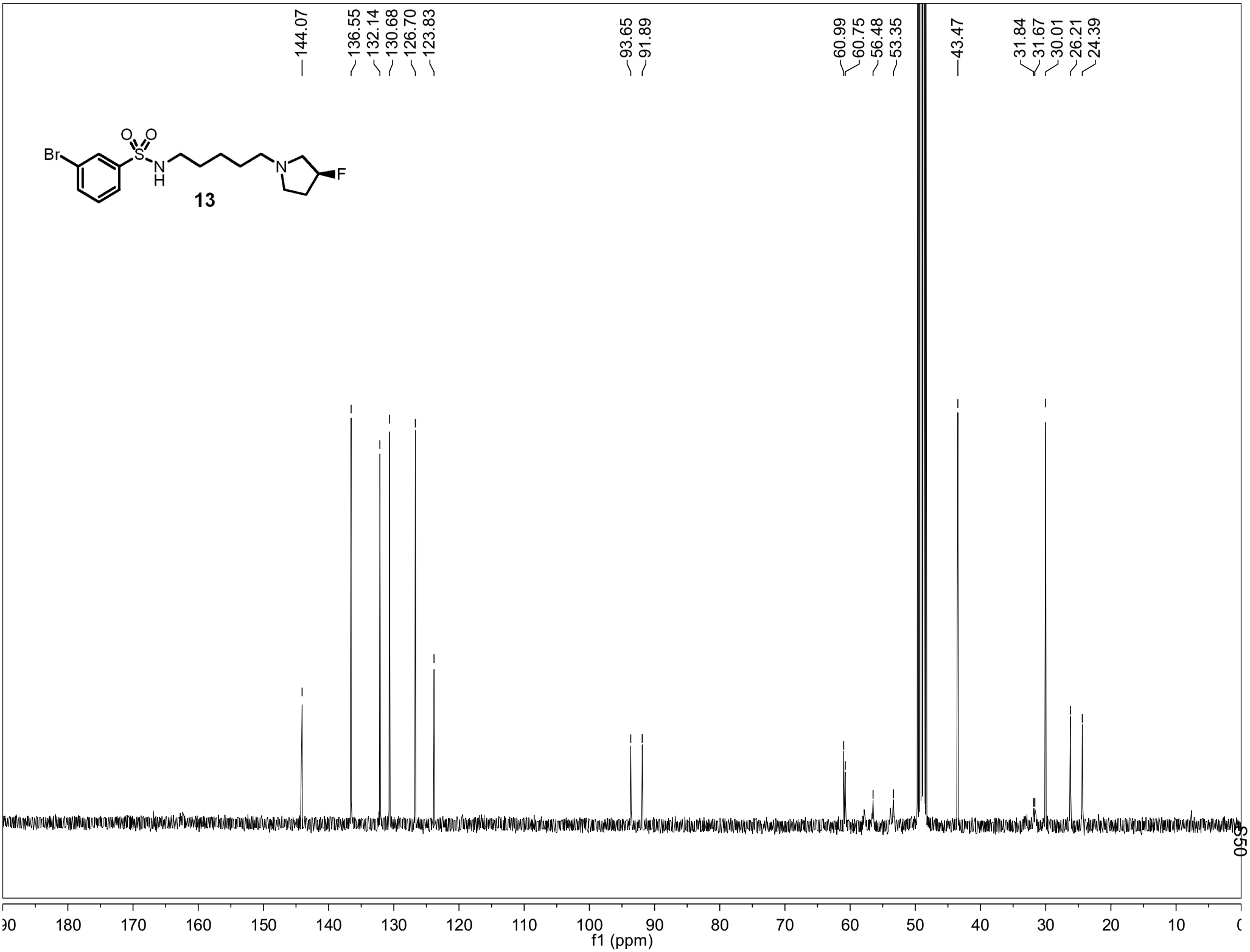
1.56
3.36
1.88
2.25
1.61
7.12
3.79
2.42
1.51
1.15
1.49
5.34
4.97
4.06
3.00
2.35
f1 (ppm)

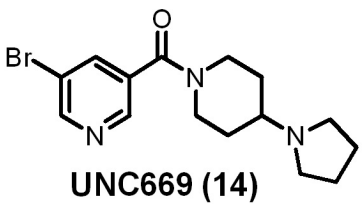

144.08
136.55
132.14
130.68
126.70
123.83
61.49
61.09
56.80
56.51
55.85
54.78
43.46
33.54
33.19
31.78
30.01
26.35
26.26
24.40
18.37
17.33
Br
O
O
S
N
H
N
Me
12
f1 (ppm)


Br
O
O
S
N
H
N
F

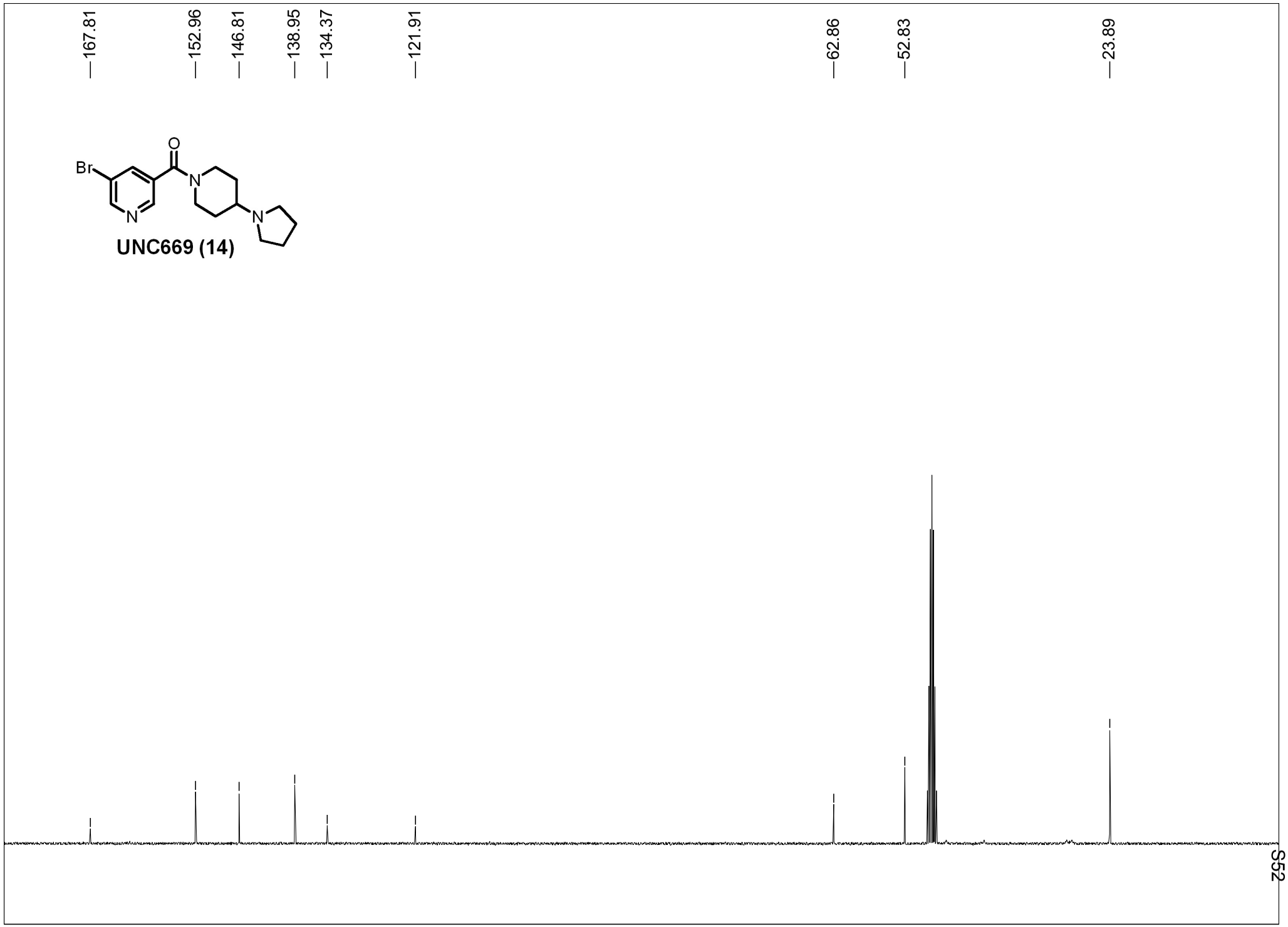
13

3.98
0.80
1.70
0.95
1.24
2.37
2.83
2.00
2.93
2.00
2.03
2.03
f1 (ppm)


144.07
136.55
132.14
130.68
126.70
123.83
93.65
91.89
60.99
60.75
56.48
53.35
43.47
31.84
31.67
30.01
26.21
24.39
Br
O
O
S
N
H
N
F
13
S50
f1 (ppm)



UNC669 (14)


167.81
152.96
146.81
138.95
134.37
121.91
62.86
52.83
23.89
Br
O
N
N
N
UNC669 (14)
f1 (ppm)