Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A Convenient Synthesis of Difficult Medium-Sized Cyclic Peptides by Staudinger Mediated Ring-Closure

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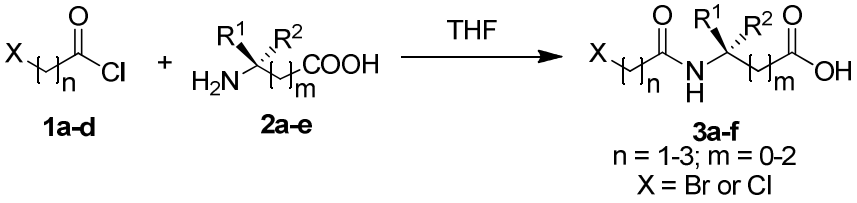
SUPPORTING INFORMATION

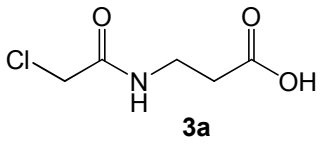
1. General Information. All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were reagent grade or HPLC grade (Fisher Solvents were dried using standard protocols kept under a dry atmosphere of nitrogen. Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, Acetone-d_6 or CD_3OD-d_4 using a 300 or 500 MHz spectrometer (with TMS as an internal standard) at ambient temperature unless otherwise stated. Chemical shifts are reported in parts per million relative to residual solvent $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.23 ppm). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, dd = doublet of doublets, quint = pentet. All ^{13}C NMR spectra were recorded with complete proton decoupling. The data have been reported in order to provide the maximum amount of information regarding coupling constants, which has necessarily led to integrals reported following a group of peaks in some instances. High-resolution and high-performance liquid chromatography mass spectral analyses were performed by the University of Florida chemistry department facility staff. Reactions were carried out in oven-dried glassware under an argon or nitrogen atmosphere unless otherwise noted. All microwave assisted reactions were carried out with a single mode cavity Discover Microwave Synthesizer (CEM Corporation, NC). The reaction mixtures were transferred into a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation (Discover mode; run time: 60 sec.; PowerMax-cooling mode). Analytical TLC was performed on E. Merck silica gel 60 F254 plates and visualized by UV and potassium permanganate staining. Flash column chromatography was performed on E. Merck silica gel 60 (40–63 mm). Yields refer to chromatographically and spectroscopically pure compounds

2. Experimental procedures

General procedure I for the preparation of compounds 3a-f



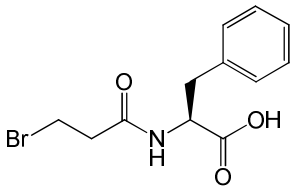
To a suspension of amino acid (**2a-e**) in dry THF (20 mL/1 mmol) at 0 °C was added halogen acyl chloride (**1a-d)** (l.5 eq.) and the resulting mixture was refluxed for 2.5 h. The reaction mixture was filtered hot and the solvent was evaporated under reduced pressure. Then diethyl ether (30 mL/1 mmol **2a-e**) was added to the residue and left in the fridge to recrystallize. The solid obtained was washed with hexanes (5 mL/1 mmol), cold diethyl ether (5 mL/1 mmol) and dried to give desired products (**3a-f**).



3a

3-(2-Chloroacetamido)propanoic acid (3a)

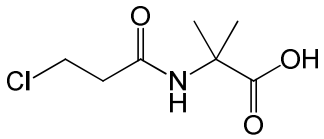
The compound was synthesized following the general procedure I from chloroacetyl chloride (4.77 mL, 60 mmol) and *β*-alanine (3.56 g, 40 mmol) in 75% yield (5.06 g, 28 mmol). White microcrystals, mp 99-100 ^{o}C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.40 (t, J = 6.8 Hz, 2H), 3.24-3.34 (m, 2H), 4.04 (s, 2H), 8.26 (br s, 1H), 12.27 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 33.5, 35.2, 42.5, 165.9, 172.8; Anal. Calcd for $C_5H_8ClNO_3$: C, 36.27; H, 4.87; N, 8.46. Found: C, 36.33; H, 4.95; N, 8.33.



3b

(S)-2-(3-Bromoropropanamido)-3-phenylpropanoic acid (3b)

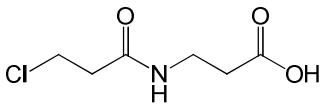
The compound was synthesized following the general procedure I from 3-bromopropyl chloride (3.63 mL, 36 mmol) and *L*-phenylalanine (4.00 g, 24 mmol) in 88% yield (6.30 g, 21 mmol). White microcrystals, mp 94-98 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.57 (dt, J = 6.5, 1.9 Hz, 2H), 2.86 (dd, J = 14.0, 9.2 Hz, 1H), 3.05 (dd, J = 13.8, 5.1 Hz, 1H), 3.69 (t, J = 6.3 Hz, 2H), 4.41-4.50 (m, 1H), 7.16-7.30 (m, 5H), 8.37 (d, J = 8.0 Hz, 1H), 12.75 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.9, 38.0, 40.7, 53.5, 126.5, 128.2, 129.2, 137.5, 168.9, 172.9; Anal. Calcd for $C_{12}H_{14}BrNO_3$: C, 48.02; H, 4.70; N, 4.67. Found: C, 47.94; H, 4.50; N, 4.91.



3c

2-(3-Chloropropanamido)-2-methylpropanoic acid (3c)

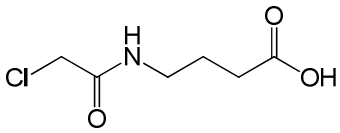
The compound was synthesized following the general procedure I from 3-chloropropyl chloride (5.6 g, 44 mmol) and 2-methylalanine (3.00 g, 29 mmol) in 73% yield (4.10 g, 21 mmol). White microcrystals, mp 167-169 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.33 (br s, 6H), 2.56 (t, J = 6.3 Hz, 2H), 3.74 (t, J = 6.5 Hz, 2H), 8.18 (br s, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 25.0, 38.0, 40.9, 54.9, 168.3, 175.4. HRMS (m/z): $[M-H]^-$ calcd for $C_7H_{11}ClNO_3$, 192.0433, found 192.0442.



3d

3-(3-Chloropropanamido)propanoic acid (3d)

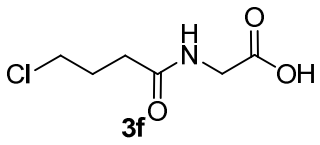
The compound was synthesized following the general procedure I from 3-chloropropyl chloride (7.48 g, 59 mmol) and 3-aminopropanoic acid (3.50 g, 39 mmol) in 56% yield (3.95 g, 22 mmol). White microcrystals, mp 116-120 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.37 (t, J = 6.9 Hz, 2H), 2.54 (t, J = 6.3 Hz, 2H), 3.25 (q, J = 6.4 Hz, 2H), 3.76 (t, J = 6.5 Hz, 2H), 8.09 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 33.9, 34.9, 38.2, 41.1, 169.0, 172.9.



3e

4-(2-Chloroacetamido)butanoic acid (3e)

The compound was synthesized following the general procedure I from chlororacetyl chloride (2.31 mL, 29 mmol) and γ-aminobutyric acid (2.00 g, 19 mmol) in 72% yield (2.51 g, 14 mmol). White microcrystals, mp 75-79 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.64 (quint, J = 7.2 Hz, 2H), 2.22 (t, J = 7.4 Hz, 2H), 3.06-3.13 (m, 2H), 4.03 (s, 2H), 8.23 (br s, 1H), 12.08 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): 24.3, 30.9, 38.3, 42.7, 165.9, 174.1; Anal. Calcd for $C_6H_{10}ClNO_3$: C, 40.13; H, 5.61; N, 7.80. Found: C, 39.78; H, 5.73; N, 7.45.

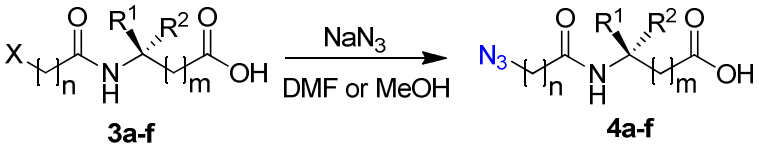


3f

2-(4-Chlorobutanamido)acetic acid (3f)

The compound was synthesized following the general procedure I from 4-chlorobutanoyl chloride (4.79 mL, 50 mmol) and glycine (2.50 g, 33 mmol) in 38% yield (2.27 g, 13 mmol). Sticky solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.93 (q, J = 6.9 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 3.64 (t, J = 6.5 Hz, 2H), 3.72 (d, J = 6.0 Hz, 2H), 8.24 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): 28.3, 32.1, 40.6, 45.0, 171.4, 171.6.

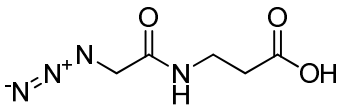
General procedure II for the preparation of compounds 4a-f



3a-f **4a-f**

n = 1-3; m = 0-2
X = Br or Cl

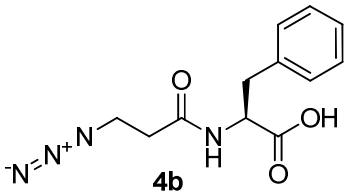
Dipeptide derivatives **3a-f** was dissolved in a minimum amount of methanol (**4a**) or DMF (**4b-f**) and then sodium azide (5 eq.) was added to the solution. The suspension was heated at 80 °C for 72 h (methanol) or 24 h (DMF). The solvent was removed under reduced pressure and brine was added to the residue until extra sodium azide was dissolved. The resulting mixture was acidified slowly with HCl to pH 5 and extracted with ethyl acetate (3 x 10 mL/1 mmol **3a-f**). The organic layers were combined, then dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure to give the desired products **4a-f.** Compounds **4b** and **4c** were recrystallized from a CH_2Cl_2:hexanes mixture.



4a

3-(2-Azidoacetamido)propanoic acid (4a)

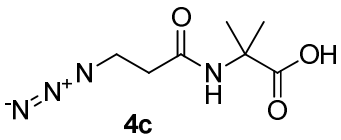
The compound was synthesized following the general procedure II from 3-(2-chloroacetamido)propanoic acid (**3a**) (2.00 g, 12.1 mmol) in 63% yield (1.31 g, 7.6 mmol). Colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.62 (t, J = 6.0 Hz, 2H), 3.53-3.60 (m, 2H), 3.99 (s, 2H), 6.87 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 33.7, 34.9, 52.8, 167.4, 176.5. HRMS (m/z): $[M-H]^-$ calcd for $C_5H_7N_4O_3$, 171.0524, found 171.0531.



4b

(S)-2-(3-Azidopropanamido)-3-phenylpropanoic acid (4b)

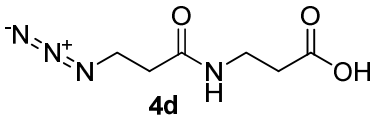
The compound was synthesized following the general procedure II from (S)-2-(3-bromoropropanamido)-3-phenylpropanoic acid (**3b**) (3.51 g, 11.7 mmol) in 54% yield (1.66 g, 6.3 mmol). White microcrystals, mp 128-129 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.37 (t, J = 6.2 Hz, 2H), 2.86 (dd, J = 13.8, 9.3 Hz, 1H), 3.06 (dd, J = 13.7, 5.0 Hz, 1H), 3.42 (t, J = 6.3 Hz, 2H), 4.41-4.49 (m, 1H), 7.17-7.31 (m, 5H), 8.35 (d, J = 8.1 Hz, 1H), 12.72 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.3, 36.8, 46.8, 53.5, 126.4, 128.1, 129.1, 137.5, 169.5, 172.9.



4c

2-(3-Azidopropanamido)-2-methylpropanoic acid (4c)

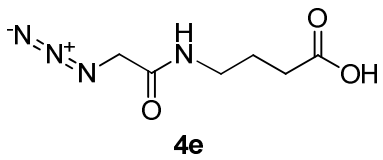
The compound was synthesized following the general procedure II from (2-(3-chloropropanamido)-2-methylpropanoic acid (**3c**) (3.00 g, 15.5 mmol) in 82% yield (2.54 g, 12.7 mmol). Yellow microcrystals, mp 145-152 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.33 (s, 6H), 2.36 (t, J = 6.5 Hz, 2H), 3.46 (t, J = 6.5 Hz, 2H), 8.17 (br s, 1H), 12.30 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 24.9, 34.4, 46.8, 54.8, 168.9, 175.4. HRMS (*m/z*): [M-H]$^-$ calcd for $C_7H_{11}N_4O_3$ 199.08371, found 199.0843.



4d

3-(3-Azidopropanamido)propanoic acid (4d)

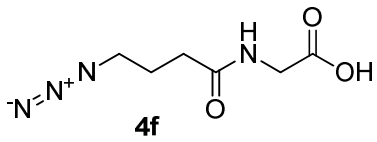
The compound was synthesized following the general procedure II from 3-(3-chloropropanamido)propanoic acid (**3d**) (2.00 g, 11.1 mmol) in 63% yield (1.31 g, 7.0 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.41 (t, J = 6.3 Hz, 2H), 2.60 (t, J = 5.8 Hz, 2H), 3.54 (q, J = 6.0 Hz, 2H), 3.60 (t, J = 6.5 Hz, 4H), 6.38 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 33.9, 35.2, 36.0, 47.5, 170.9, 176.3. HRMS (*m/z*): [M-H]$^-$ calcd for $C_6H_9N_4O_3$, 185.0680, found 185.0686.



4e

4-(2-Azidoacetamido)butanoic acid (4e)

The compound was synthesized following the general procedure II from 4-(2-chloroacetamido)butanoic acid (**3e**) (1.50 g, 8.35 mmol) in 68% yield (1.06 g, 5.68 mmol). Yellow sticky solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89 (quint, J = 6.8 Hz, 2H), 2.51 (t, J = 6.9 Hz, 2H), 3.36 (q, J = 6.6 Hz, 2H), 4.00 (s. 2H), 6.59 (br s 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2, 32.7, 38.5, 52.8, 167.3, 169.1.

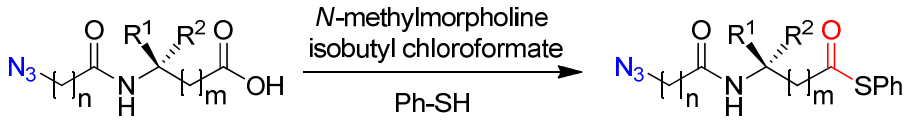


4f

2-(4-Azidobutanamido)acetic acid (4f)

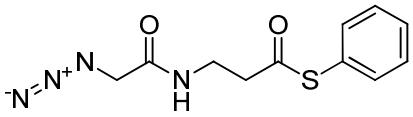
The compound was synthesized following the general procedure II from 2-(4-chlorobutanamido)acetic acid (**3f**) (2.00 g, 11.2 mmol) in 63% yield (1.31 g, 7.0 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.75 (q, J = 7.1 Hz, 2H), 2.20 (t, J = 7.4 Hz, 2H), 3.33 (t, J = 6.9 Hz, 2H), 3.73 (d, J = 6.0 Hz, 2H), 8.22 (br s, 1H), 12.52 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.5, 31.9, 40.6, 50.1, 171.4, 171.7.

General procedure III for the preparation of compounds 5a-f



4a-f **5a-f**

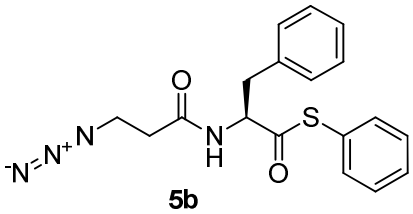
A solution of azidoprotected dipeptides **4a-e** and *N*-methylmorpholine (1 eq.) in dry THF (10 mL/1 mmol) was cooled to 0 °C under argon atmosphere. To the resulting solution, isobutyl chloroformate was added (1 eq.). After 5 min, thiophenol (1.1 eq.) was added and the mixtured was stirred for 24 h at room temperature. The solvent was evaportated under reduced pressured and the residue was taken up with ethyl acetate (30 mL/ 1 eq.). The organic layer was washed with Na_2CO_3 (3 x 15 mL/ 1 eq.), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was recrystallized from a CH_2Cl_2/hexanes mixture to give **5a-f.**



5a

S-Phenyl 3-(2-azidoacetamido)propanethioate (5a)

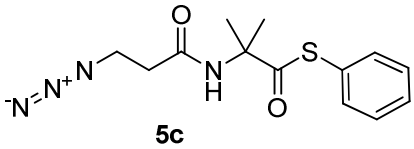
The compound was synthesized following the general procedure III from 3-(2-azidoacetamido)propanoic acid (**4a**) (0.93 g, 5.38 mmol) in 57% yield (0.81 g, 3.07 mmol). White microcrystal, mp 63-64 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.93 (t, J = 6.2 Hz, 2H), 3.55-3.65 (m, 2H), 3.96 (s, 2H), 6.79 (br s, 1H), 7.40-7.46 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.3, 42.8, 52.7, 127.1, 129.5, 129.9, 134.7, 166.9, 197.3; Anal. Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.99; H, 4.58; N, 21.20. Found: C, 50.11; H, 4.57; N, 21.24.



5b

(S)-S-Phenyl 2-(3-azidopropanamido)-3-phenylpropanethioate (5b)

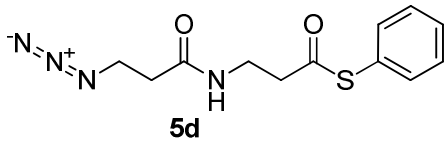
The compound was synthesized following the general procedure III from (S)-2-(3-azidopropanamido)-3-phenylpropanoic acid (**4b**) (1.41 g, 5.4 mmol) in 66% yield (1.26 g, 3.6 mmol). White microcrystals, mp 86-87 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.54-2.73 (m, 2H), 2.92 (dd, J = 13.8, 10.2 Hz, 1H), 3.15 (dd, J = 14.0, 5.0 Hz, 1H), 3.71-3.78 (m, 2H), 4.67-4.76 (m, 1H), 7.18-7.31 (m, 5H), 7.34-7.39 (m, 2H), 7.45-7.48 (m, 3H), 8.90 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.4, 36.6, 46.7, 60.6, 126.6, 127.2, 128.2, 129.1, 129.3, 129.5, 134.5, 136.9, 170.2, 198.3. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{18}H_{16}N_4O_2SNa$, 370.1043, found 370.0656.



5c

S-Phenyl 2-(3-azidopropanamido)-2-methylpropanethioate (5c)

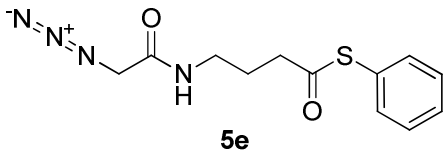
The compound was synthesized following the general procedure III from 2-(3-azidopropanamido)-2-methylpropanoic acid (**4c**) (1.75 g, 5.99 mmol) in 64% yield (1.12 g, 3.83 mmol). Yellow microcrystals, mp 55-57 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.58 (br s, 6H), 2.43 (t, J = 6.5 Hz, 2H), 3.61 (t, J = 6.3 Hz, 2H), 6.41 (br s, 1H), 7.34-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.6, 36.3, 47.3, 63.1, 127.6, 129.3, 129.5, 135.2, 169.7, 201.3. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{16}N_4O_2SNa$, 315.0886, found 315.0894.



5d

S-Phenyl 3-(3-azidopropanamido)propanethioate (5d)

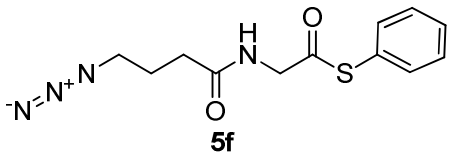
The compound was synthesized following the general procedure III from 3-(3-azidopropanamido)propanoic acid (**4d**) (0.20 g, 1.07 mmol) in 65% yield (0.19 g, 0.70 mmol). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.34 (t, J = 6.5 Hz, 2H), 2.89 (t, J = 5.9 Hz, 2H), 3.55 (q, J = 5.9 Hz, 4H), 6.21 (br s, 1H), 7.39-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 35.4, 36.0, 42.9, 47.5, 127.2, 129.5, 129.9, 134.7, 170.1, 197.9. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}N_4O_3Na$, 301.0730, found 301.0739.



5e

S-Phenyl 4-(2-azidoacetamido)butanethioate (5e)

The compound was synthesized following the general procedure III from 4-(2-azidoacetamido)butanoic acid (**4e**) (0.20 g, 1.07 mmol) in 55% yield (0.16 g, 0.59 mmol). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89 (quint, J = 7.1 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 3.27-3.33 (m, 2H), 3.89 (s, 2H), 6.58 (br s, 1H), 7.37 (s, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7, 34.0, 47.5, 51.1, 127.3, 129.5, 129.9, 134.7, 170.2, 197.9. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}N_4O_3Na$, 301.0730, found 301.0736.

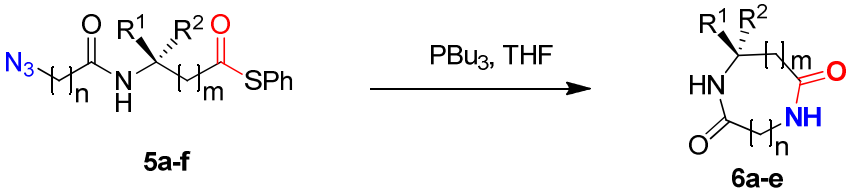


5f

S-Phenyl 2-(4-azidobutanamido)ethanethioate (5f)

The compound was synthesized following the general procedure III from 2-(4-azidobutanamido)acetic acid (**4f**) (1.50 g, 8.06 mmol) in 65% yield (1.46 g, 5.25 mmol). Pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.92 (q, J = 6.8 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 3.35 (t, J = 6.5 Hz, 2H), 4.24-4.27 (m, 2H), 6.43 (br s, 1H), 7.35-7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.8, 33.0, 49.1, 50.8, 127.3, 129.5, 130.0, 134.9, 172.4, 195.7. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}N_4O_3Na$, 301.0730, found 301.0738.

General procedure for the cyclization of azido dipeptidoyl thioesters (5e-f) to form compounds 6a-f

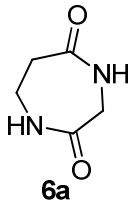


5a-f **6a-e**

General procedure IVA for the preparation of compounds 6a-c. To a solution of azido dipeptidoyl thioesters **5a-c** in dry THF (10 mL/1 mmol), PBu_3 (1.5 eq.) was added under argon atmosphere. The solution was subjected to microwave irradiation (50 °C, 50 W, 5 min). The reaction was allowed to cool to room temperature, and then diluted with CH_2Cl_2 (10 mL/1 mmol). Hexanes was added until the solution turned turbid and was then left to crystallize in the

freezer. The solid obtained was filtered off, washed with diethyl ether (2 mL/1 mmol) and dried under high vaccuum yielding pure products **6a-c.**

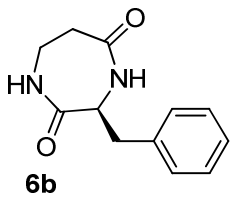
General procedure IVB for the preparation of compounds 6e-f. To a solution of thioesters **5d-f** in dry THF (100 mL/1 mmol), PBu_3 (1.5 eq.) was added dropwise under argon atmosphere. The mixture was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure and the residue was taken up with ethyl acetate and washed with an aqueous solution of Na_2CO_3. The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography using ethyl acetate:hexanes (gradient) as eluent to yield pure **6e-f.**



6a

1,4-Diazepane-2,5-dione (6a)

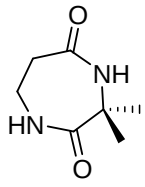
The compound was synthesized following the general procedure IVA from (*S*)-phenyl 3-(2-azidoacetamido)propanethioate (**5a**) (200.00 mg, 0.76 mmol) in 73% yield (70.43 mg, 0.55 mmol). White microcrystals, mp 247-248 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.52-2.59 (m, 2H), 3.26-3.30 (m, 2H), 3.70 (d, J = 2.7 Hz, 2H), 7.73 (br s, 1H), 7.81 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 35.5, 37.3, 45.5, 170.6, 172.4; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_5H_8N_2O_2Na$, 151.0479, found 151.0482.



6b

(S)-3-Benzyl-1,4-diazepane-2,5-dione (6b)

The compound was synthesized following the general procedure IVA from (*S*)-phenyl 2-(3-azidopropanamido)-3-phenylpropanethioate **(5b)** (200.00 mg, 0.56 mmol) in 66% yield (80.75 mg, 0.37 mmol). White microcrystals, mp 222-223 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.31-2.39 (m, 1H), 2.58-2.66 (m, 1H), 2.77 (dd, J = 8.6, 4.7 Hz, 1H), 3.03-3.12 (m, 2H), 3.61-3.67 (m, 1H), 4.52-4.58 (m, 1H), 7.19 (t, J = 4.2 Hz, 1H), 7.28 (t, J = 4.4 Hz, 2H), 7.35 (d, J = 4.5 Hz, 2H), 7.45 (br s, 1H), 7.84 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.9, 35.8, 36.1, 52.9, 126.2, 128.1, 129.4, 138.3, 171.5, 172.0; Anal. Calcd for $C_{12}H_{14}N_2O_2$: C 66.04, H 6.47, N 12.83. Found: C 65.74, H 6.61, N 12.60. HRMS (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}N_2O_2Na$, 241.0947, found 241.0955.

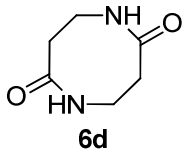


6c

3,3-Dimethyl-1,4-diazepane-2,5-dione (6c)

The compound was synthesized following the general procedure IVA from (*S*)- phenyl 2-(3-azidopropanamido)-3-phenylpropanethioate (**5c**) (0.19 g, 0.68 mmol) in 75% yield (79.61 mg, 0.51 mmol). White microcrystals, mp 253-256 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.34 (s, 6H), 2.44-2.51 (m, 2H), 3.15-3.21 (m, 2H), 7.34 (s, 1H), 7.86 (br s, 1H); ^{13}C NMR (DMSO-d_6,

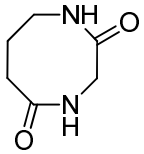
75 MHz): δ 29.3, 37.0, 37.4, 57.4, 173.7, 173.9; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_7H_{12}N_2O_2Na$, 179.0791, found 179.0792.



6d

1,5-Diazocane-2,6-dione (6d)

The compound was synthesized following the general procedure IVB from (*S*)-phenyl 4-(2-azidoacetamido)butanethioate (**5e**) (200.00 mg, 0.72 mmol) in 55% yield (56.83 mg, 0.40 mmol). White microcrystals, mp 295-300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.57 (t, J = 7 Hz, 4H), 3.38 (q, J = 4.3 Hz, 4H), 7.54 (t, J = 4.2 Hz, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 36.2, 37.4, 172.4; HRMS (*m/z*): $[M+Na]^+$ calcd for $C_6H_{10}N_2O_2Na$ 165.0634, found 165.0641.

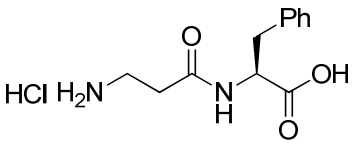


6e

1,4-Diazocane-2,5-dione (6e)

The compound was synthesized following the general procedure IVB from (*S*)-phenyl 4-(2-azidoacetamido)butanethioate (**5e**) (200.00 mg, 0.72 mmol) in 57% yield (58.23 mg, 0.41 mmol) or S-phenyl 2-(4-azidobutanamido)ethanethioate (**5f**) (0.20 g, 0.72 mmol) in 51% yield (52.57 mg, 0.37 mmol). Colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.97-2.04 (m, 2H), 2.58 (t, J = 4.8 Hz, 2H), 3.70 (t, J = 4.4 Hz, 2H), 4.11 (br s, 2H), 8.43 (br s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.1, 32.5, 42.9, 44.8, 167.1, 176.4; MS (*m/z*): $[M+H]^+$ calcd for $C_6H_{11}N_2O_2$ 143.16, found 143.0

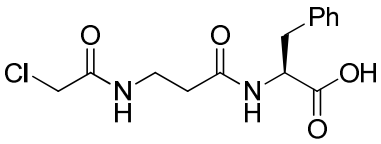
En route for the preparation of cyclic tripeptide 12



8

(*S*)-2-(3-Aminopropanamido)-3-phenylpropanoic acid hydrochloride (8)

HCl gas was passed through a solution of Boc-*β*-Ala-L-Phe (7) (336.17 mg, 1.00 mmol) in dioxane (25 mL) for 1 h. The dioxane solution was concentrated under vacuum and ether was added. The turbid solution was left to crystallize in the freezer overnight. The solid formed was filtered and washed with dry diethyl ether (5 mL), dried under high vacuum to give the corresponding *β*-Ala-L-Phe hydrochloride **8** in 88% yield (239.44 mg, 0.88 mmol). White sticky solid. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.41-2.60 (m, 2H), 2.81-3.00 (m, 3H), 3.06 (dd, J = 8.6, 5.3 Hz, 1H), 4.38-4.46 (m, 1H), 7.12-7.30 (m, 5H), 8.09 (br s, 3H), 8.57 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 32.5, 35.8, 37.3, 54.3, 127.1, 128.8, 129.7, 138.2, 170.0, 173.5.

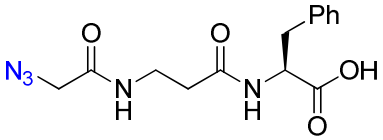


9

(*S*)-2-(3-(2-Chloroacetamido)propanamido)-3-phenylpropanoic acid (9)

The compound was prepared according to the general method I for the preparation of compounds **3a-f** from chloroacetyl chloride (0.12 mL, 1.5 mmol) and (*S*)-2-(3-aminopropanamido)-3-phenylpropanoic acid hydrochloride (**8**) (272.09 mg, 1.00 mmol) in 81% yield (5.06 g, 0.81 mmol). White microcrystals, mp 188-189 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.18-2.36 (m,

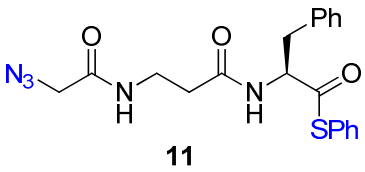
2H), 2.85 (dd, *J* = 13.7, 9.5 Hz, 1H), 3.05 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.17-3.24 (m, 2H), 4.01 (s, 2H), 4.39-4.47 (m, 1H), 7.16-7.30 (m, 5H), 8.17 (t, *J* = 5.6 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 12.72 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.6, 35.6, 36.8, 42.6, 53.4, 126.4, 128.2, 129.1, 137.6, 165.8, 170.3, 173.1. HRMS (*m/z*): $[M-H]^-$ calcd for $C_{14}H_{16}ClN_2O_4$, 311.0804, found 311.0813.



10

(*S*)-2-(3-(2-Azidoacetamido)propanamido)-3-phenylpropanoic acid (10)

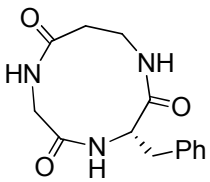
The compound was prepared according to the general method II for the preparation of compounds **4a-f** from (*S*)-2-(3-(2-chloroacetamido)propanamido)-3-phenylpropanoic acid (**9**) (624.18 mg, 2.00 mmol) in 61% yield (389.34 mg, 1.22 mmol). White microcrystals, mp 160-161 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.18-2.34 (m, 2H), 2.84 (dd, *J* = 13.8, 9.6 Hz, 1H), 3.04 (dd, *J* = 13.7, 5.0 Hz, 1H), 3.16-3.23 (m, 2H), 3.75 (s, 2H), 4.37-4.46 (m, 1H), 7.17-7.30 (m, 5H), 8.07 (t, *J* = 5.6 Hz, 1H), 8.26 (d, *J* = 8.2 Hz, 1H), 12.7 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.8, 35.2, 36.7, 50.7, 53.4, 126.4, 128.1, 129.0, 137.7, 167.2, 170.2, 173.1. HRMS (*m/z*): $[M-H]^-$ calcd for $C_{14}H_{16}N_5O_4$, 318.1208, found 318.1223.



11

(S)-S-Phenyl 2-(3-(2-azidoacetamido)propanamido)-3-phenylpropanethioate (11)

The compound was prepared according to the general method III for the preparation of compounds **5a-f** from (*S*)-2-(3-(2-azidoacetamido)propanamido)-3-phenylpropanoic acid (**10**) (500 mg, 1.57 mmol) in 51% yield (328.91 mg, 0.80 mmol). White microcrystals, mp 94-97 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.26-2.46 (m, 2H), 2.93 (dd, J = 13.7, 10.4 Hz, 1H), 3.15 (dd, J = 13.8, 4.8 Hz, 1H), 3.23-3.31 (m, 2H), 3.76 (s, 2H), 4.66-4.74 (m, 1H), 7.19-7.32 (m, 5H), 7.35-7.39 (m, 2H), 7.45-7.48 (m, 3H), 8.16 (t, J = 5.6 Hz, 1H), 8.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 34.8, 35.1, 36.6, 50.7, 60.5, 126.6, 127.3, 128.3, 129.1, 129.3, 129.4, 134.5, 137.0, 167.3, 170.9, 198.5; Anal. Calcd for $C_{20}H_{21}N_5O_3S$: C, 58.38; H, 5.14; N, 17.02. Found: C, 58.50; H, 5.26; N, 16.94.



12

(*S*)-3-Benzyl-1,4,7-triazecane-2,5,8-trione (12)

The compound was prepared according to the general method IVB for the preparation of compounds **6e-d** from (*S*)-phenyl 2-(3-(2-azidoacetamido)propanamido)-3-phenylpropanethioate (**11**) (205.57 mg, 0.50 mmol) in 48% yield (66.03 mg, 0.24 mmol). Colorless oil. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.92 (dd, J = 8.3, 6.2 Hz, 1H), 3.13 (dd, J = 8.4, 3.0 Hz, 1H), 3.41 (q, J

= 7.4 Hz, 2H), 4.15 (t, *J* = 3.9 Hz, 2H), 4.66-4.71 (m, 1H), 5.37 (dd, *J* = 3.6, 1.2 Hz, 2H), 7.34-7.37 (m, 2H), 7.42-7.48 (m, 2H), 7.49-7.52 (m, 1H), 8.13 (t, *J* = 3.0 Hz, 1H), 8.18 (d, *J* = 2.1 Hz, 1H), 8.82 (d, *J* = 4.5 Hz, 1H); ESI-MS *m/z*: 298 (M+Na).

3. Copy of ^{1}H and ^{13}C NMR spectra

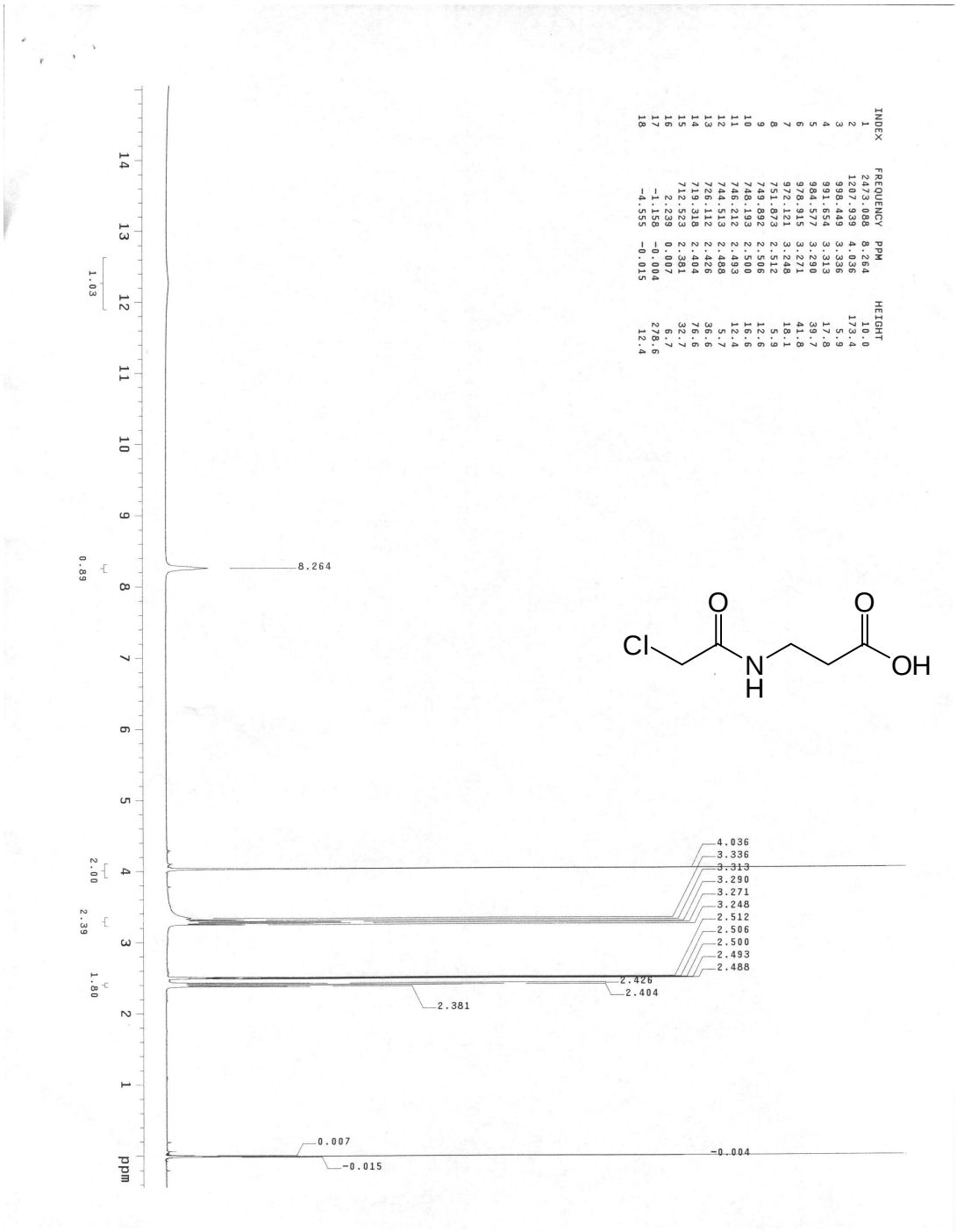


Figure S1. ^{1}H NMR spectrum of **3a**

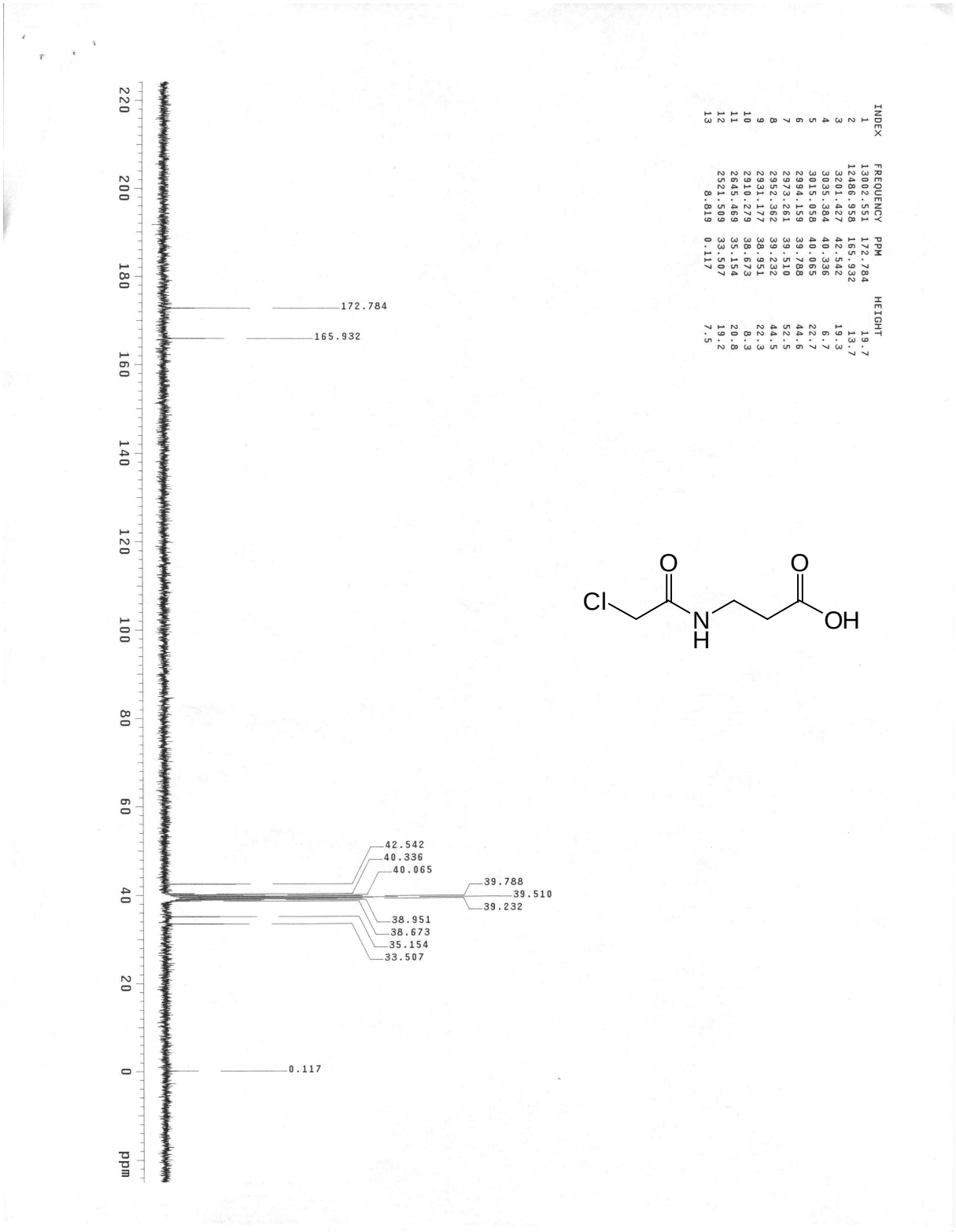


Figure S2. ^{13}C NMR spectrum of **3a**

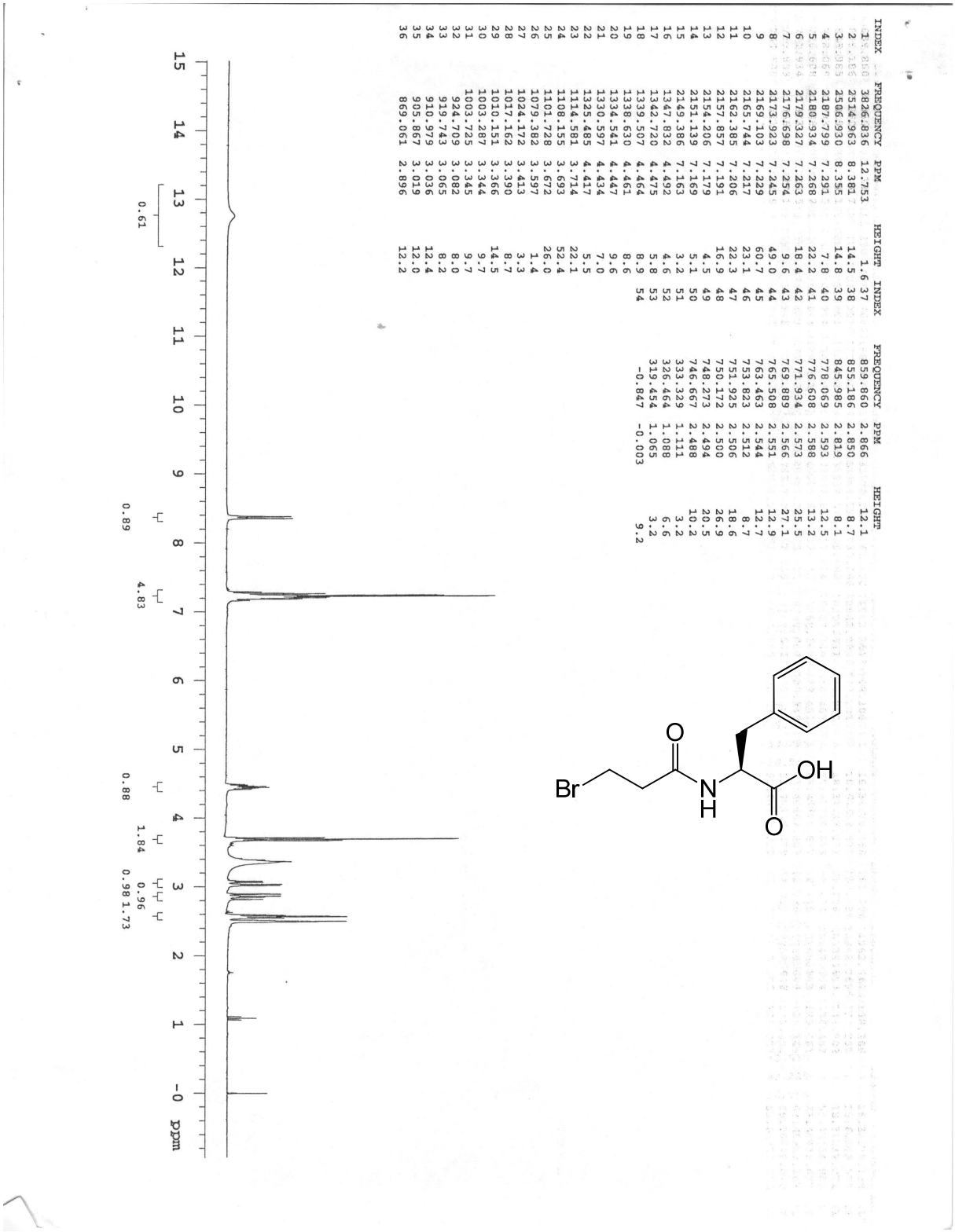


Figure S3. ^{1}H NMR spectrum of **3b**

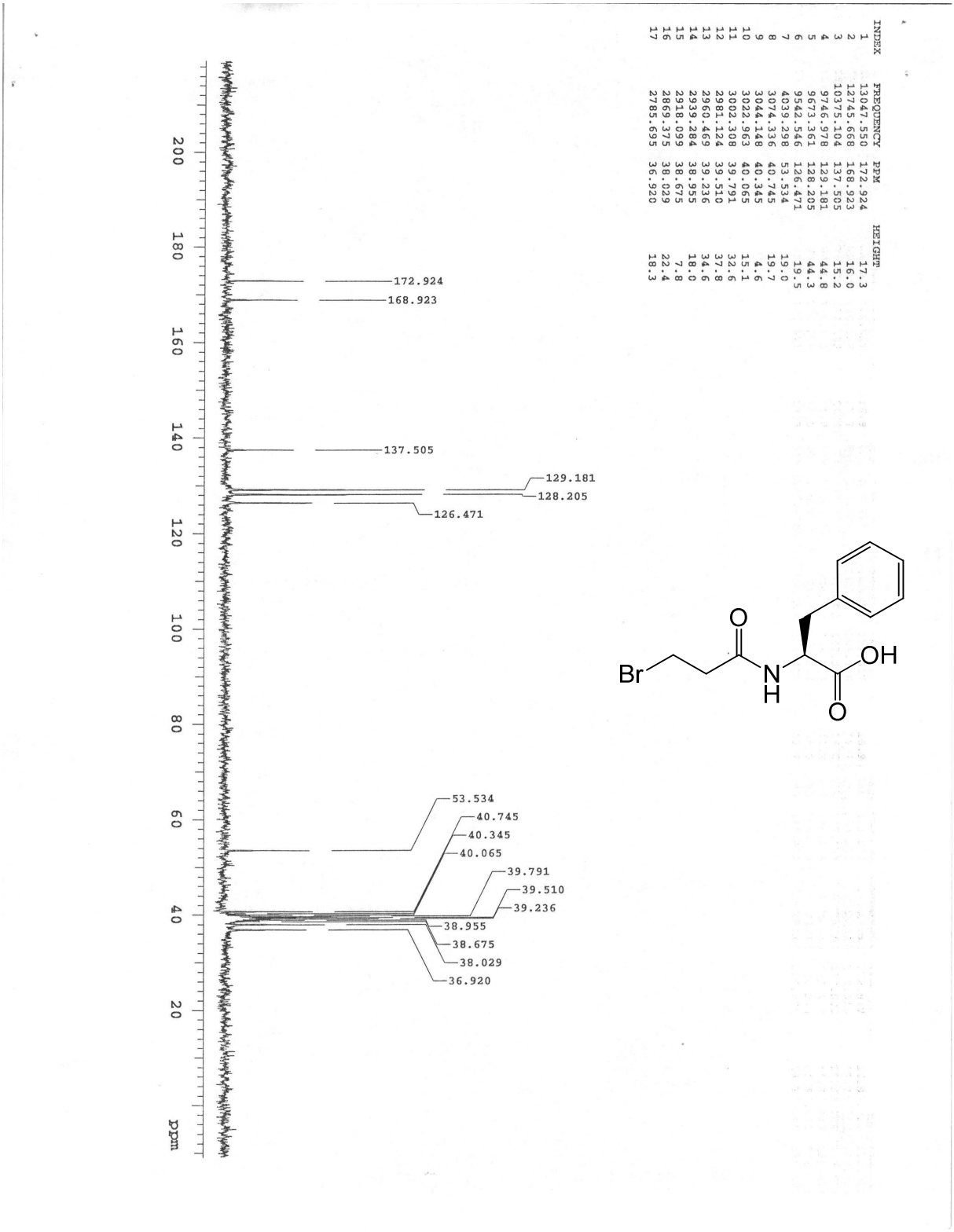


Figure S4. ^{13}C NMR spectrum of **3b**

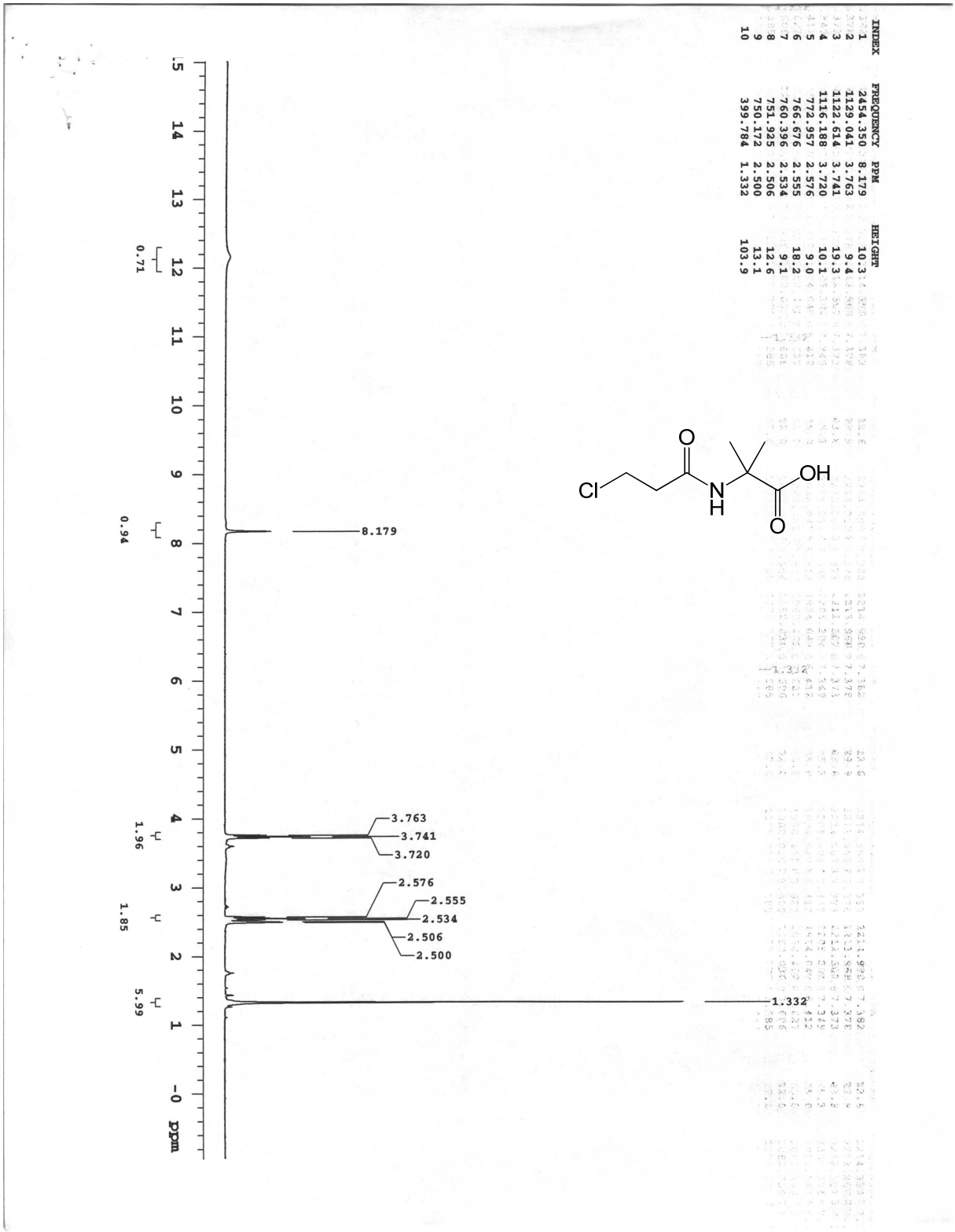


Figure S5. ^{1}H NMR spectrum of **3c**

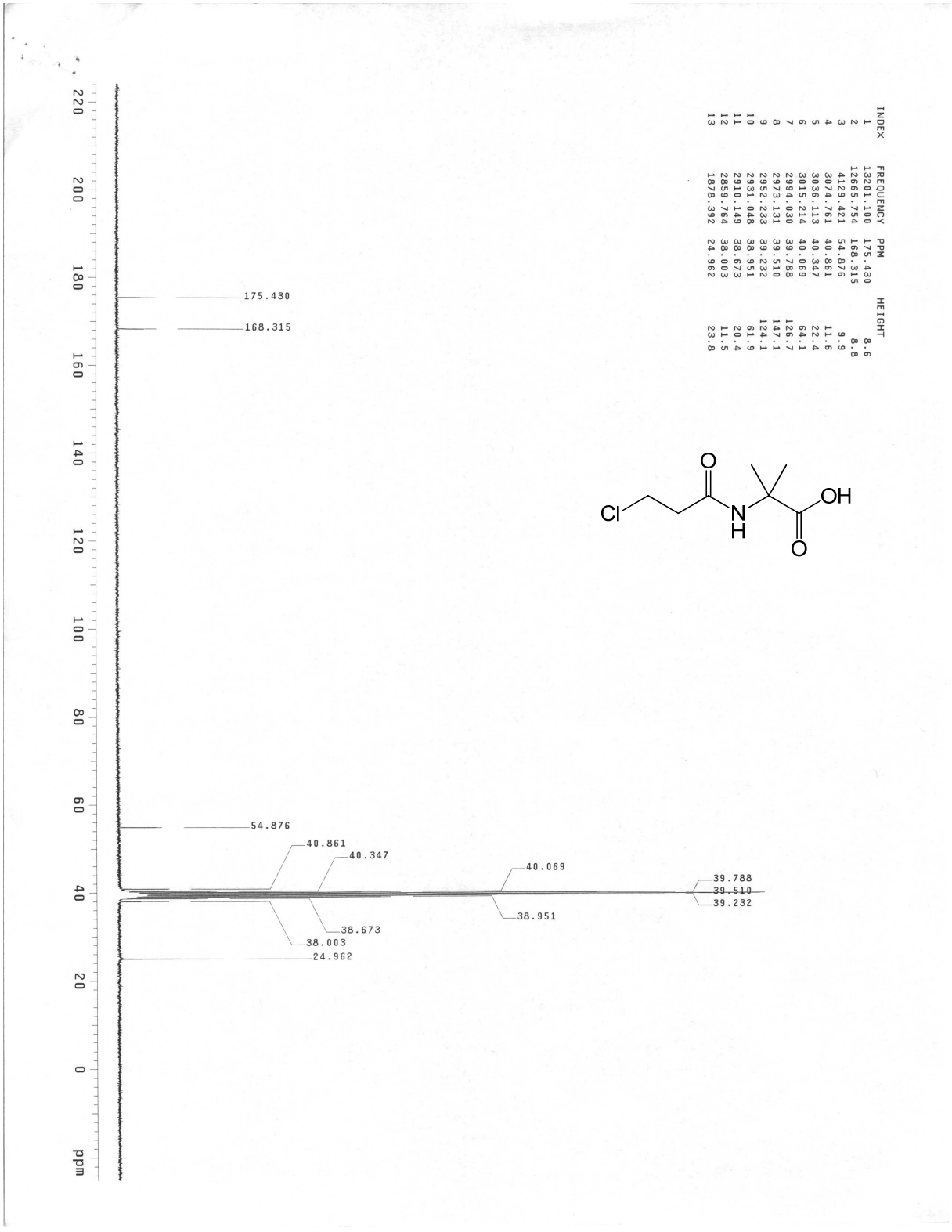


Figure S6. ^{13}C NMR spectrum of **3c**.

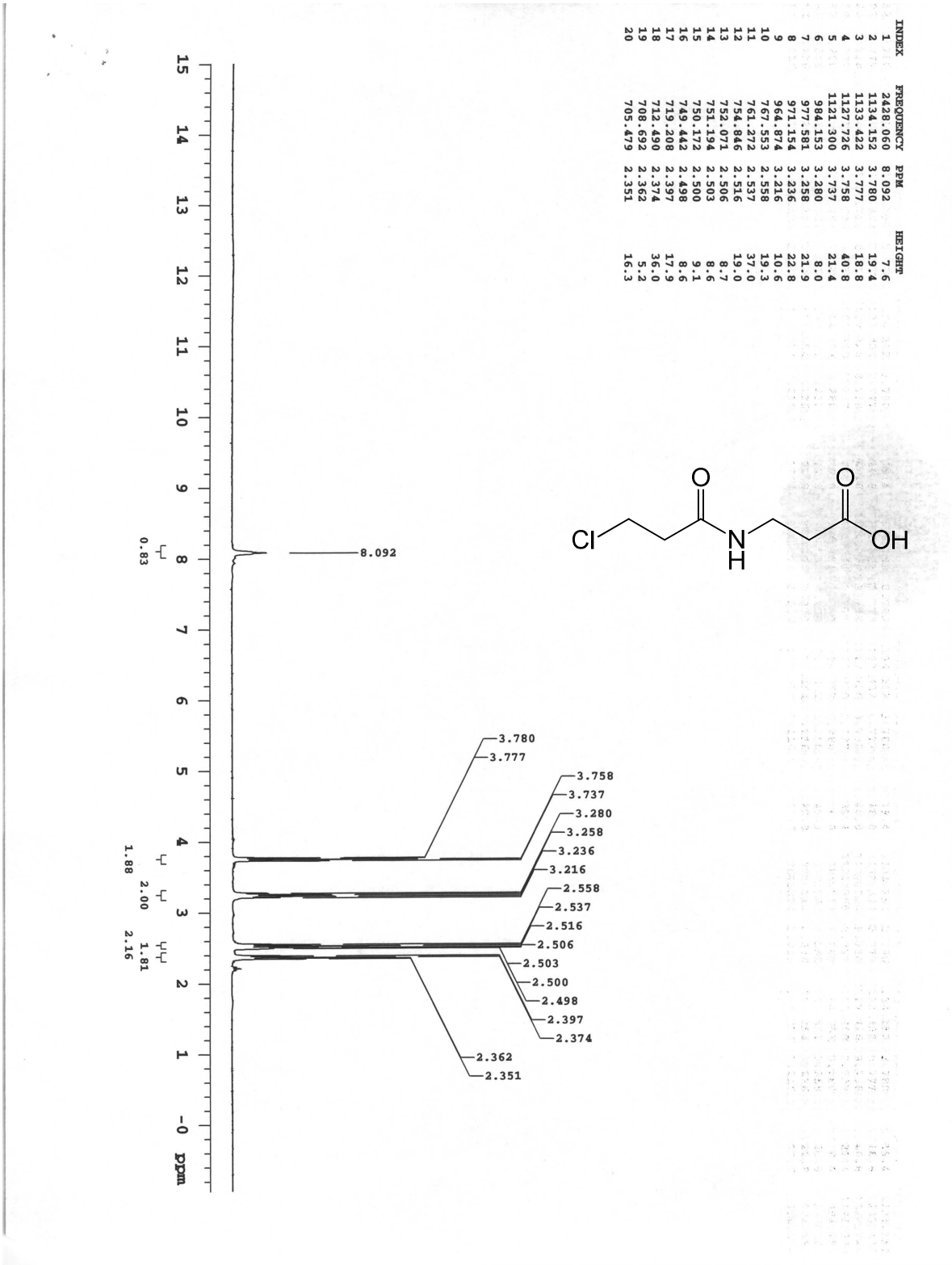


Figure S7. ^{1}H NMR spectrum of **3d**

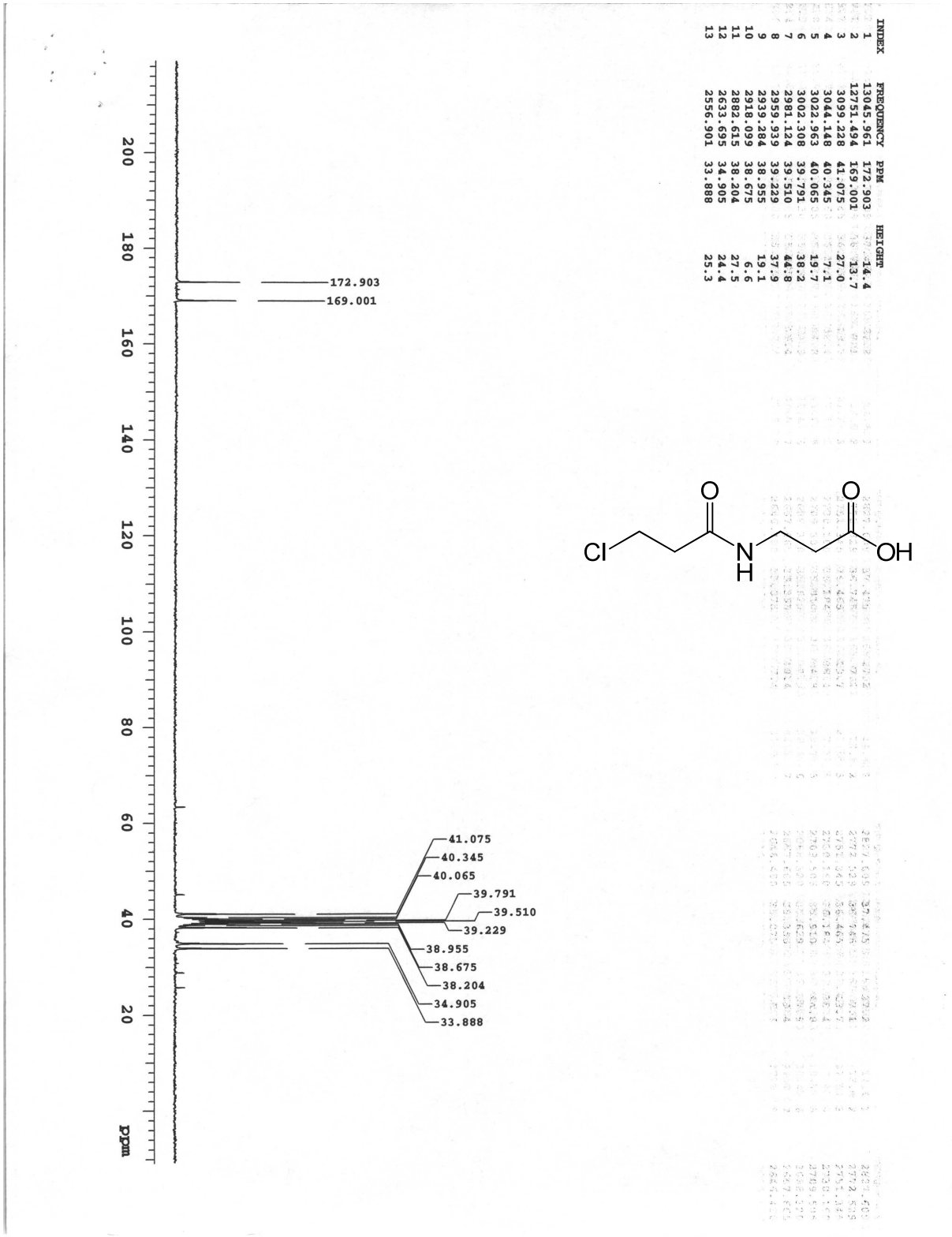


Figure S8. ^{13}C NMR spectrum of **3d**

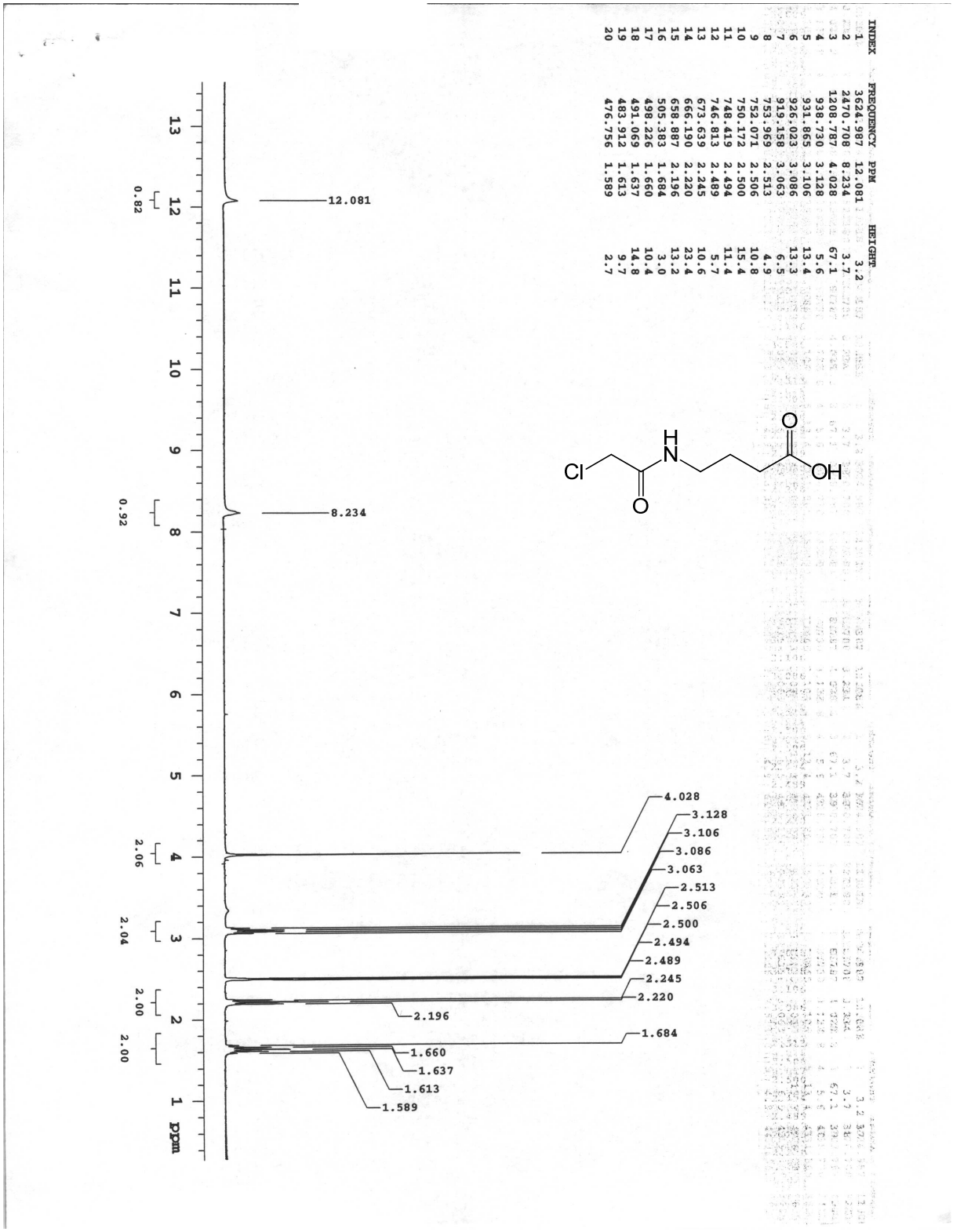


Figure S9. ^{1}H NMR spectrum of **3e**.

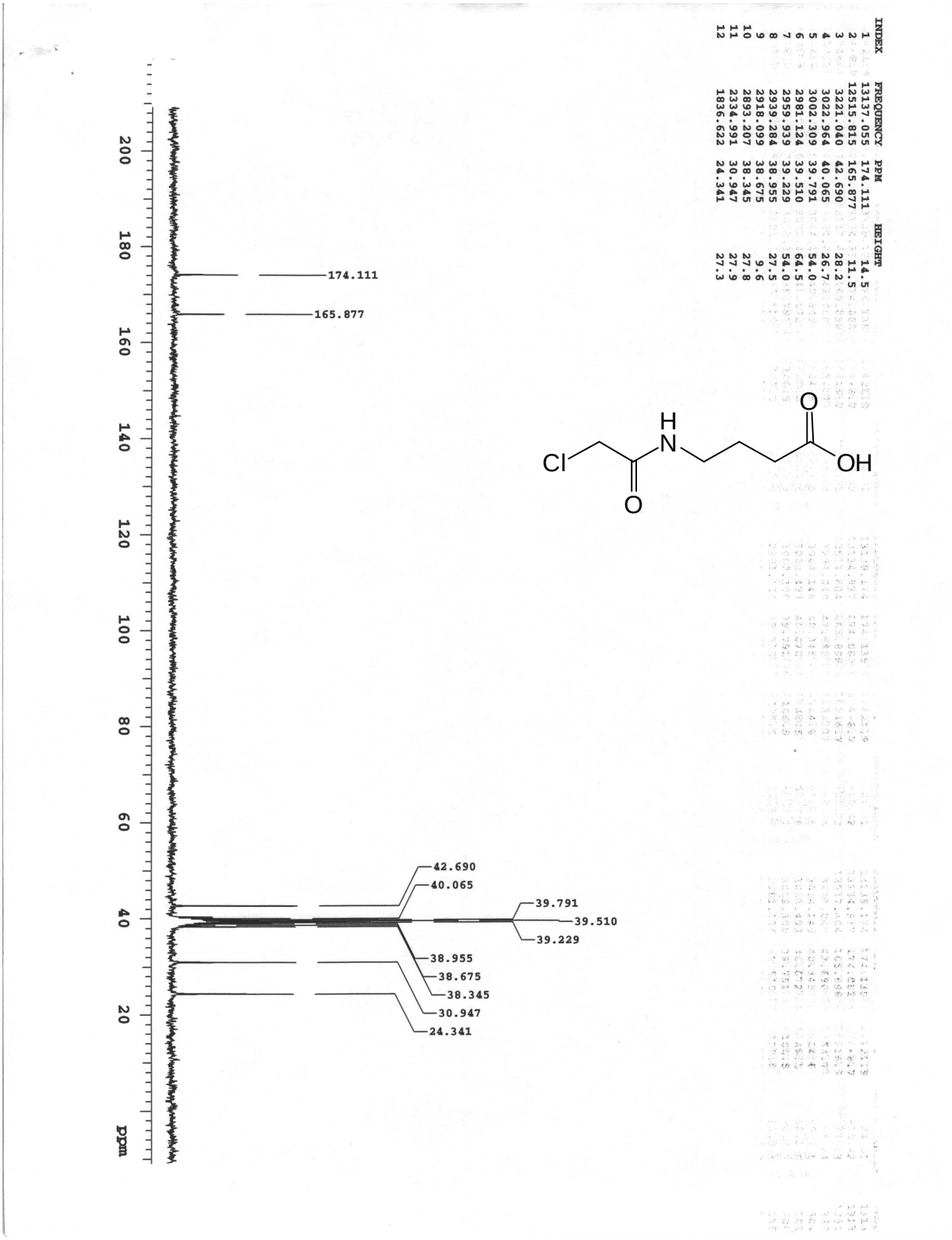


Figure S10. ^{13}C NMR spectrum of **3e**

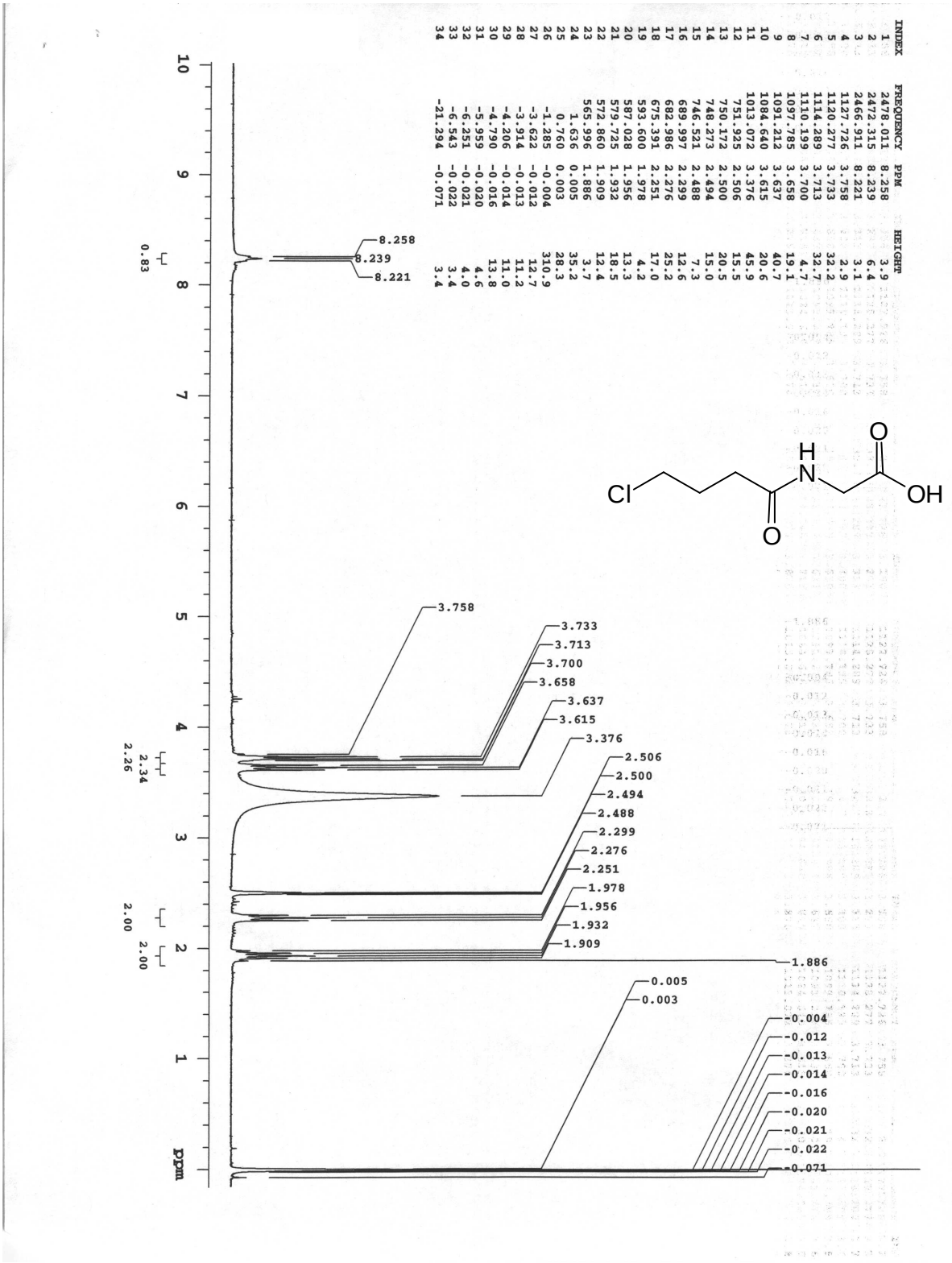


Figure S11. ^{1}H NMR spectrum of **3f**

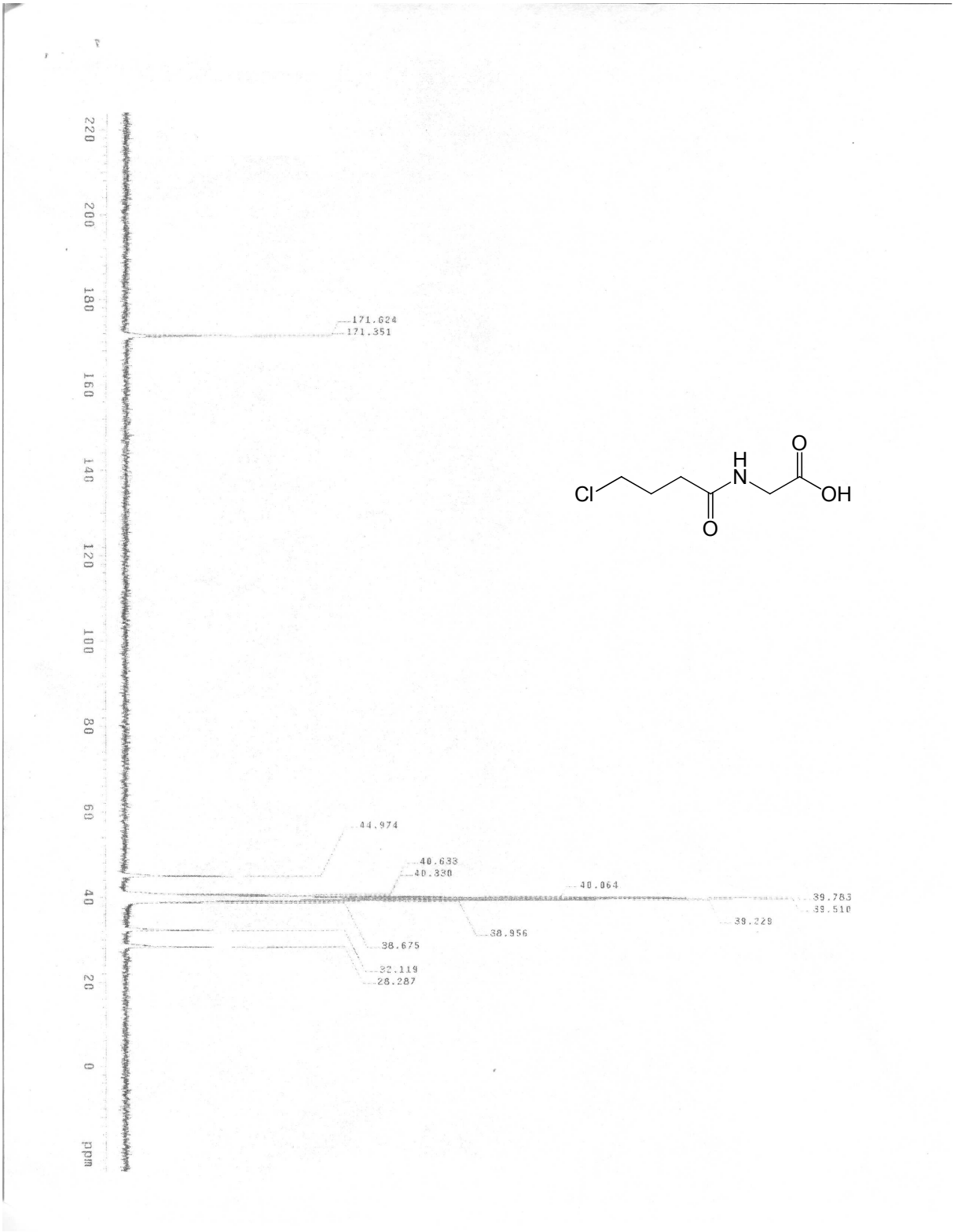


Figure S12. ^{13}C NMR spectrum of **3f**

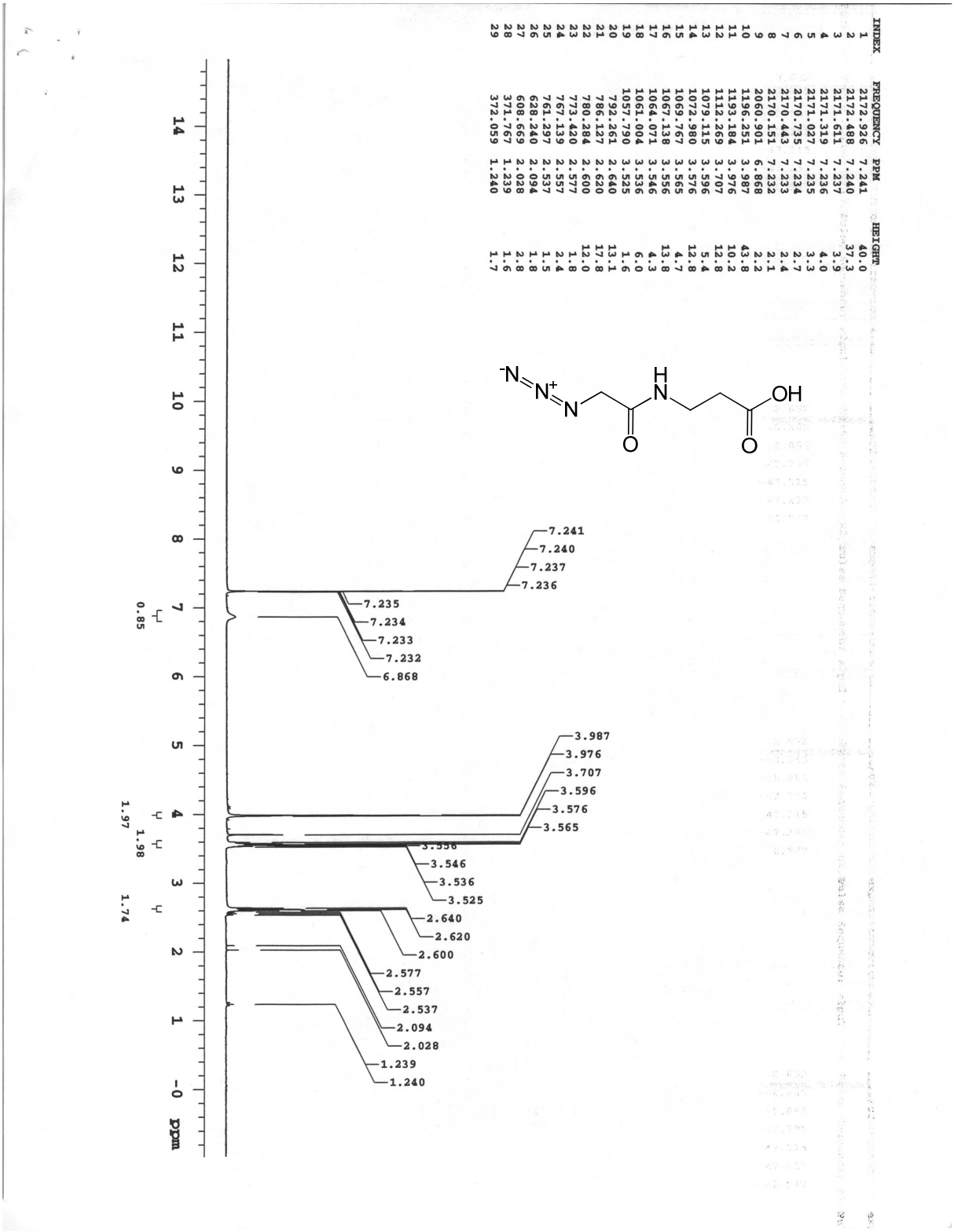


Figure S13. ^{1}H NMR spectrum of **4a**

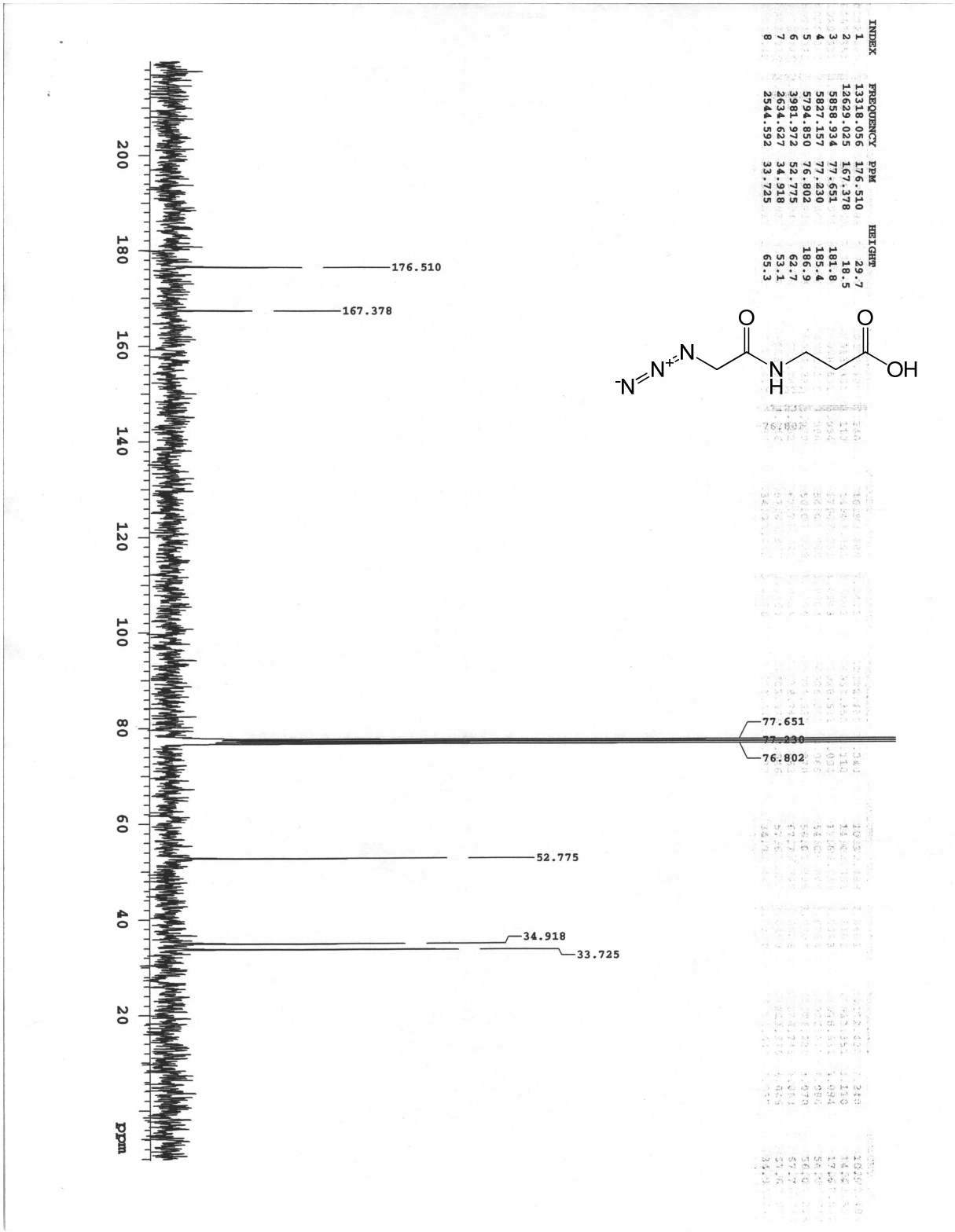


Figure S14. ^{13}C NMR spectrum of **4a**

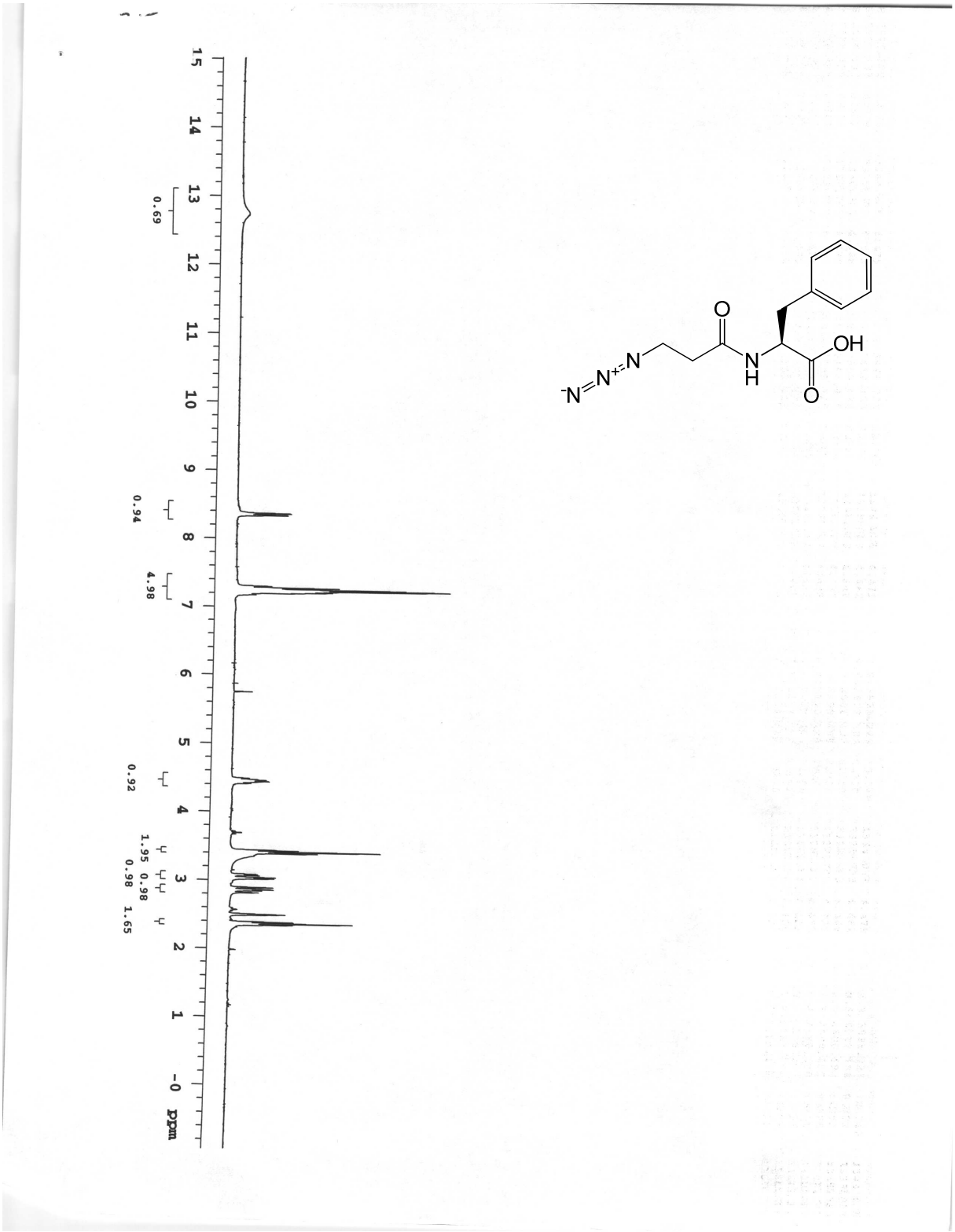


Figure S15. ^{1}H NMR spectrum of **4b**

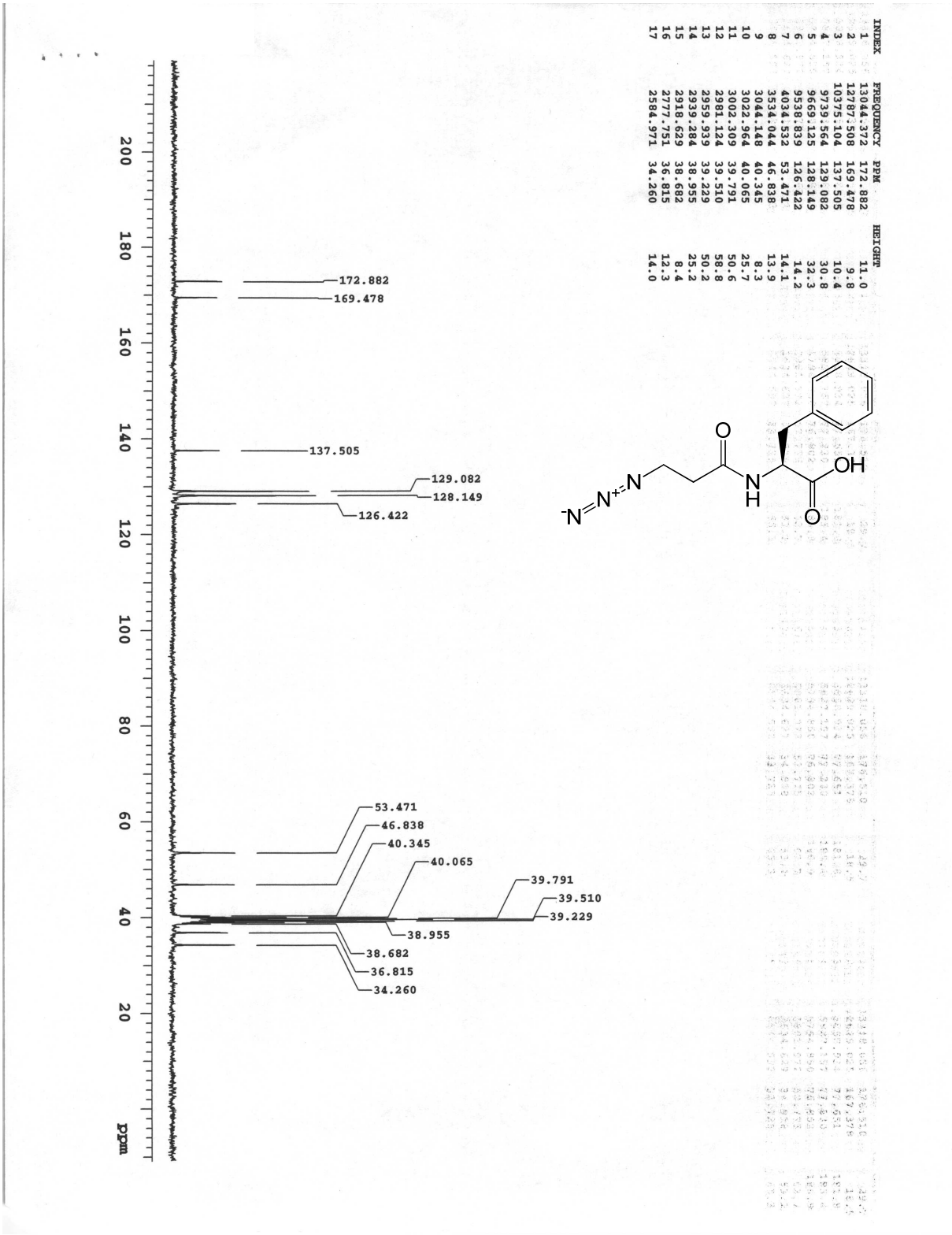


Figure S16. ^{13}C NMR spectrum of **4b**

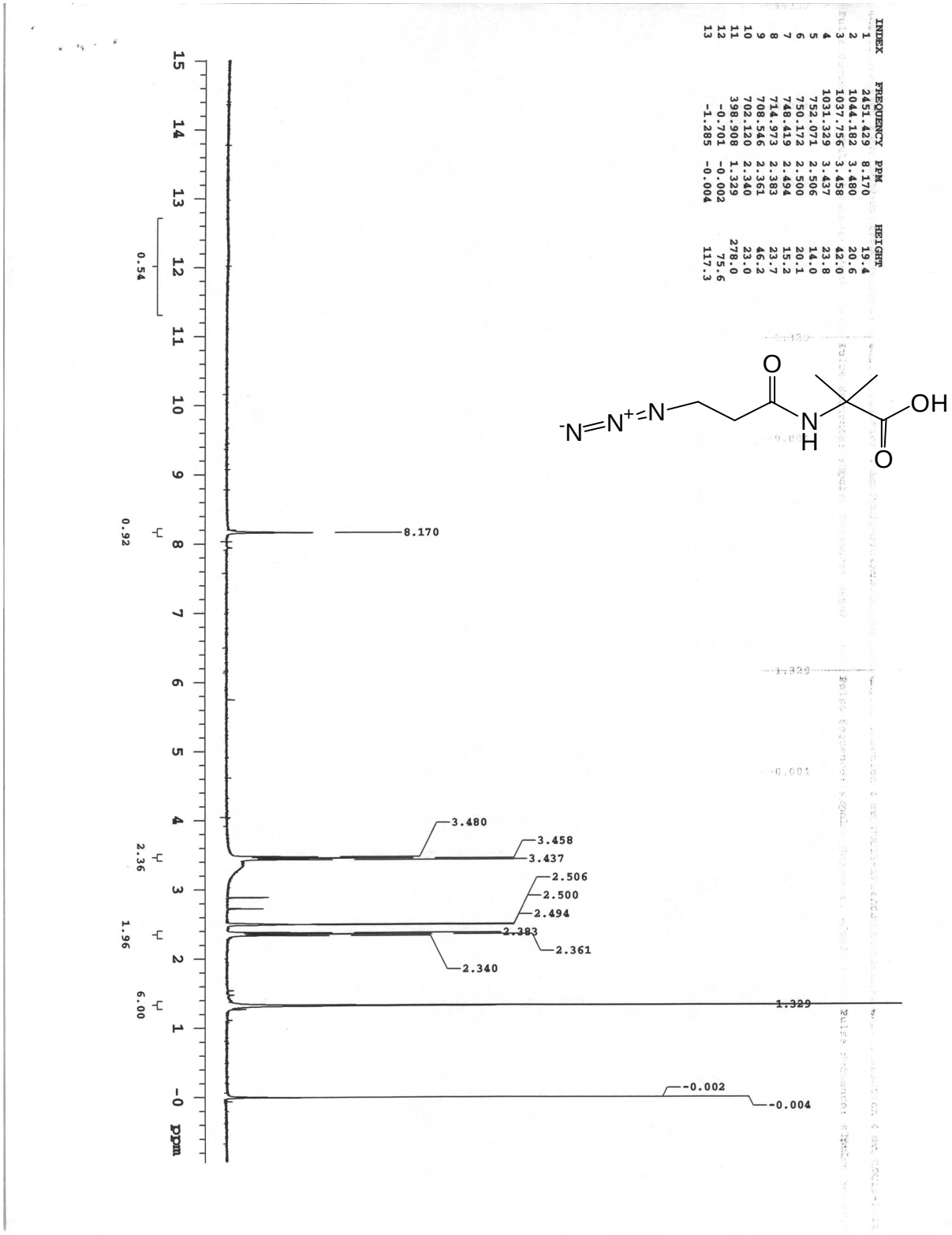


Figure S17. ^{1}H NMR spectrum of **4c**

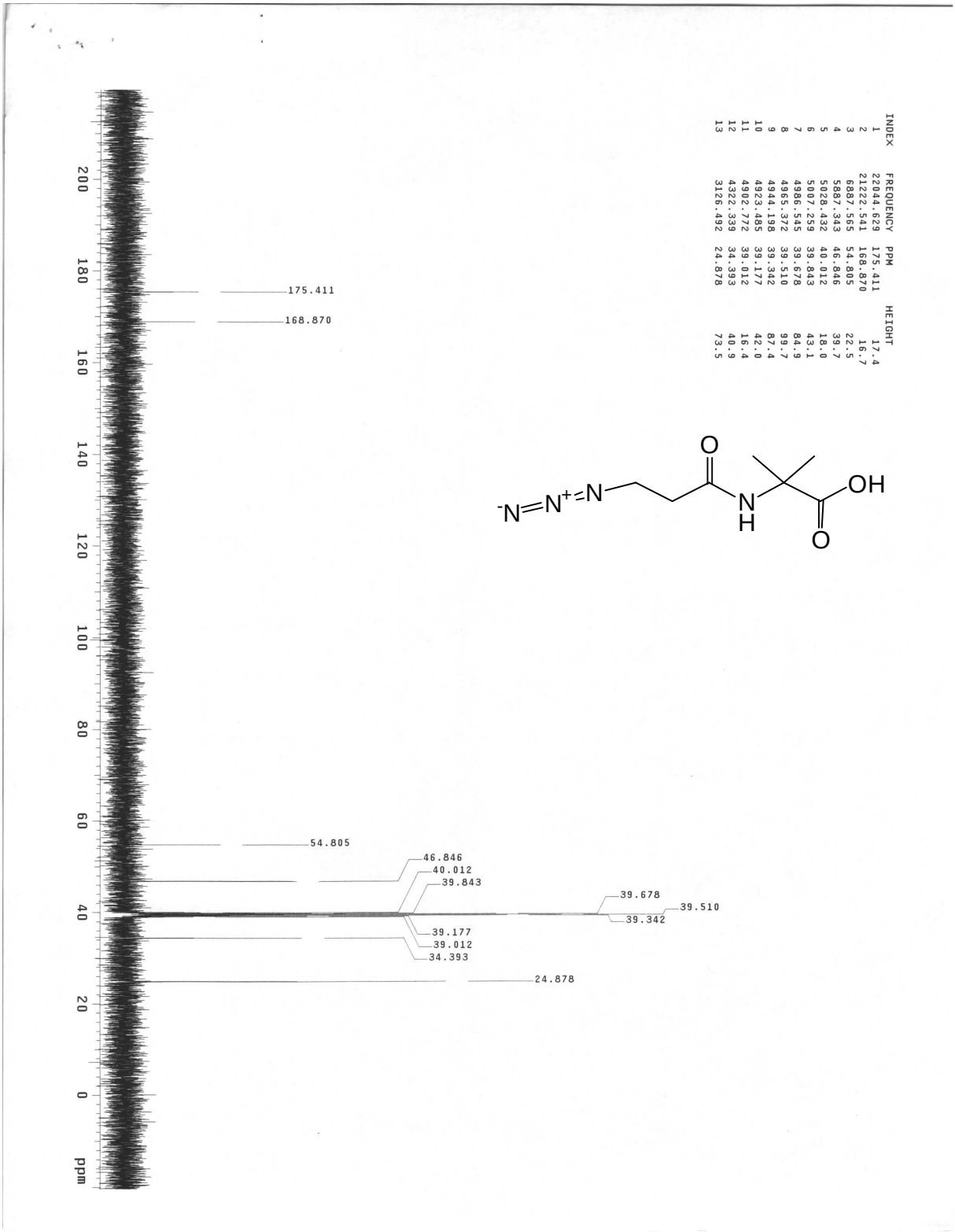


Figure S18. ^{13}C NMR spectrum of **4c**

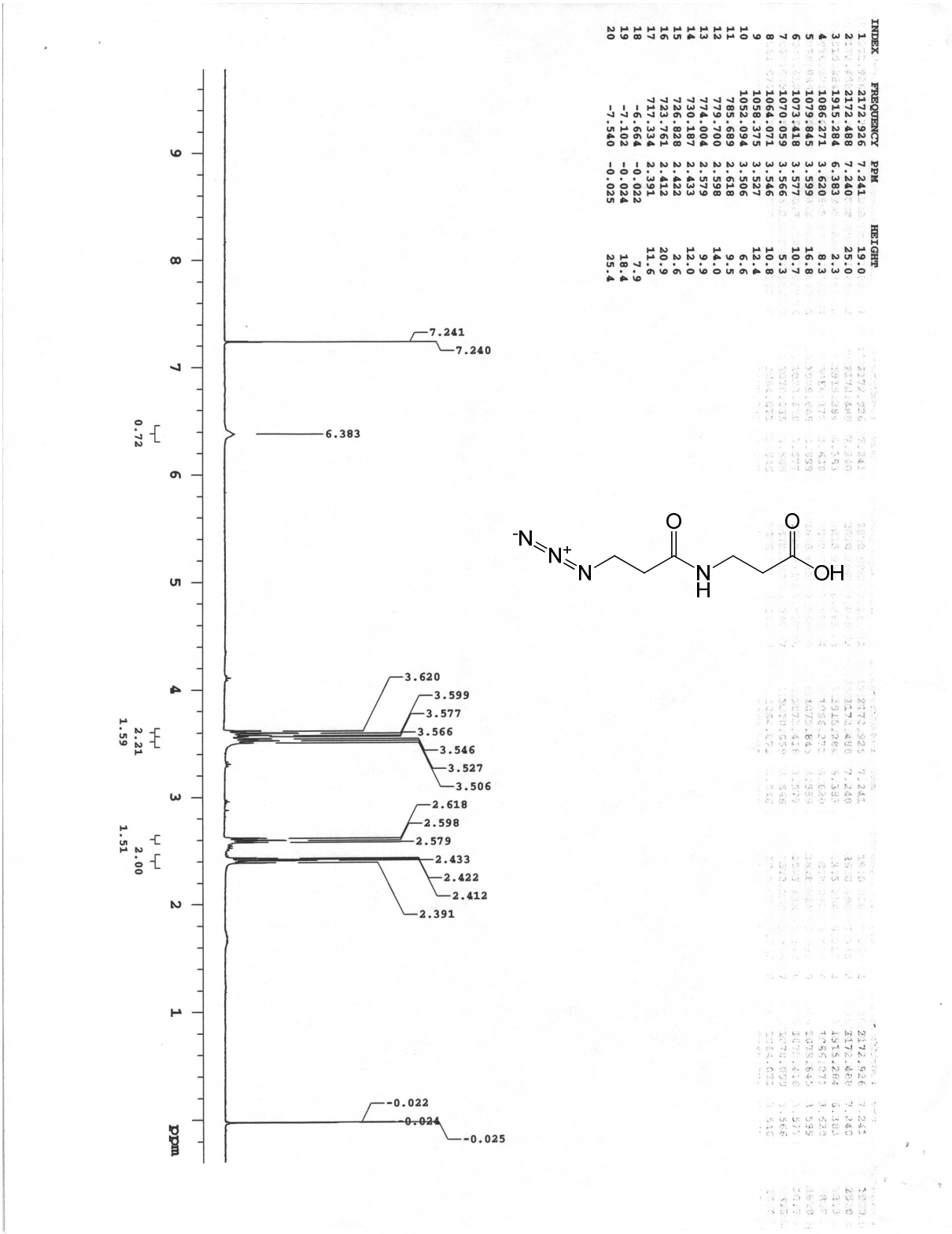


Figure S19. ^{1}H NMR spectrum of **4d**

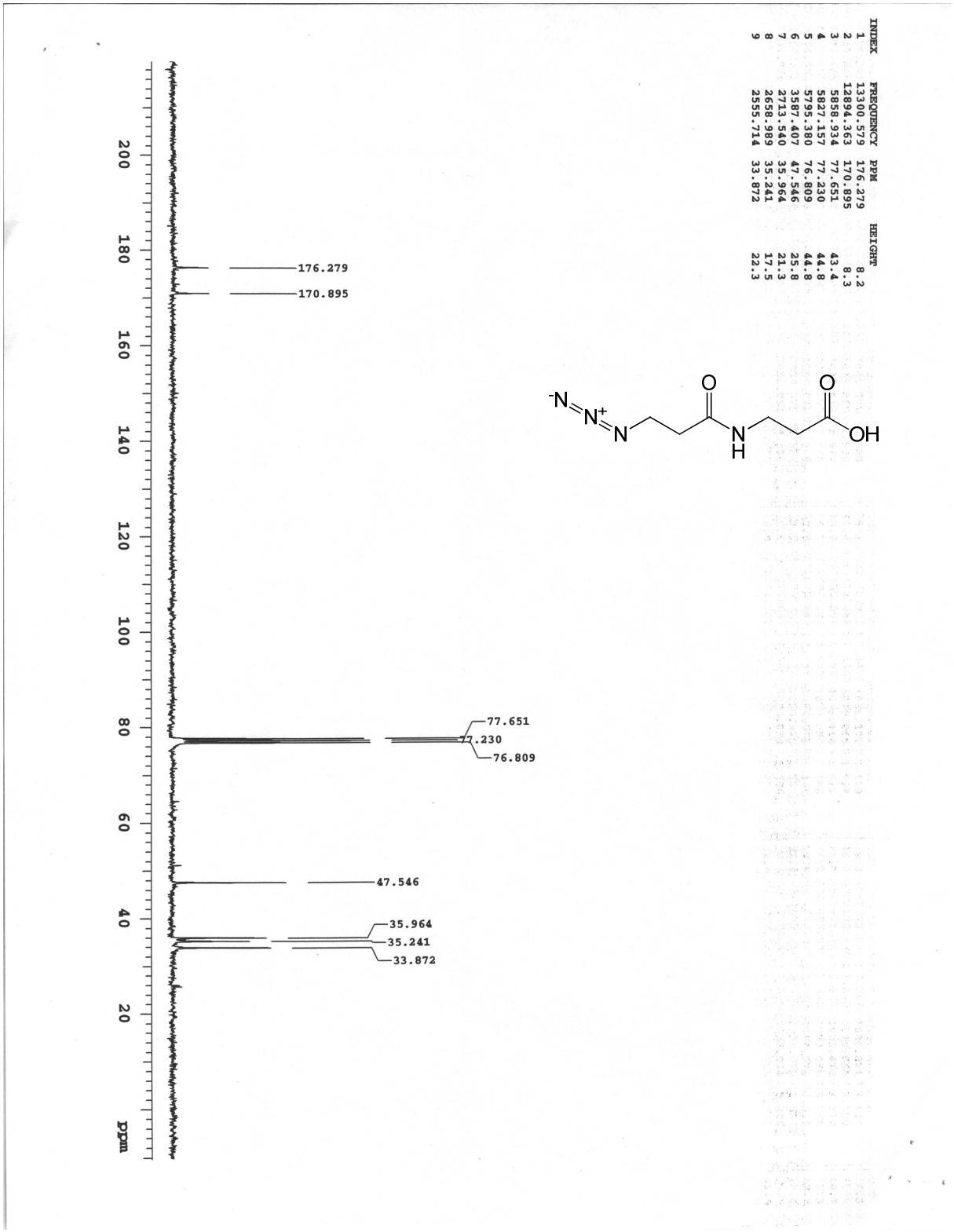


Figure S20. ^{13}C NMR spectrum of **4d**

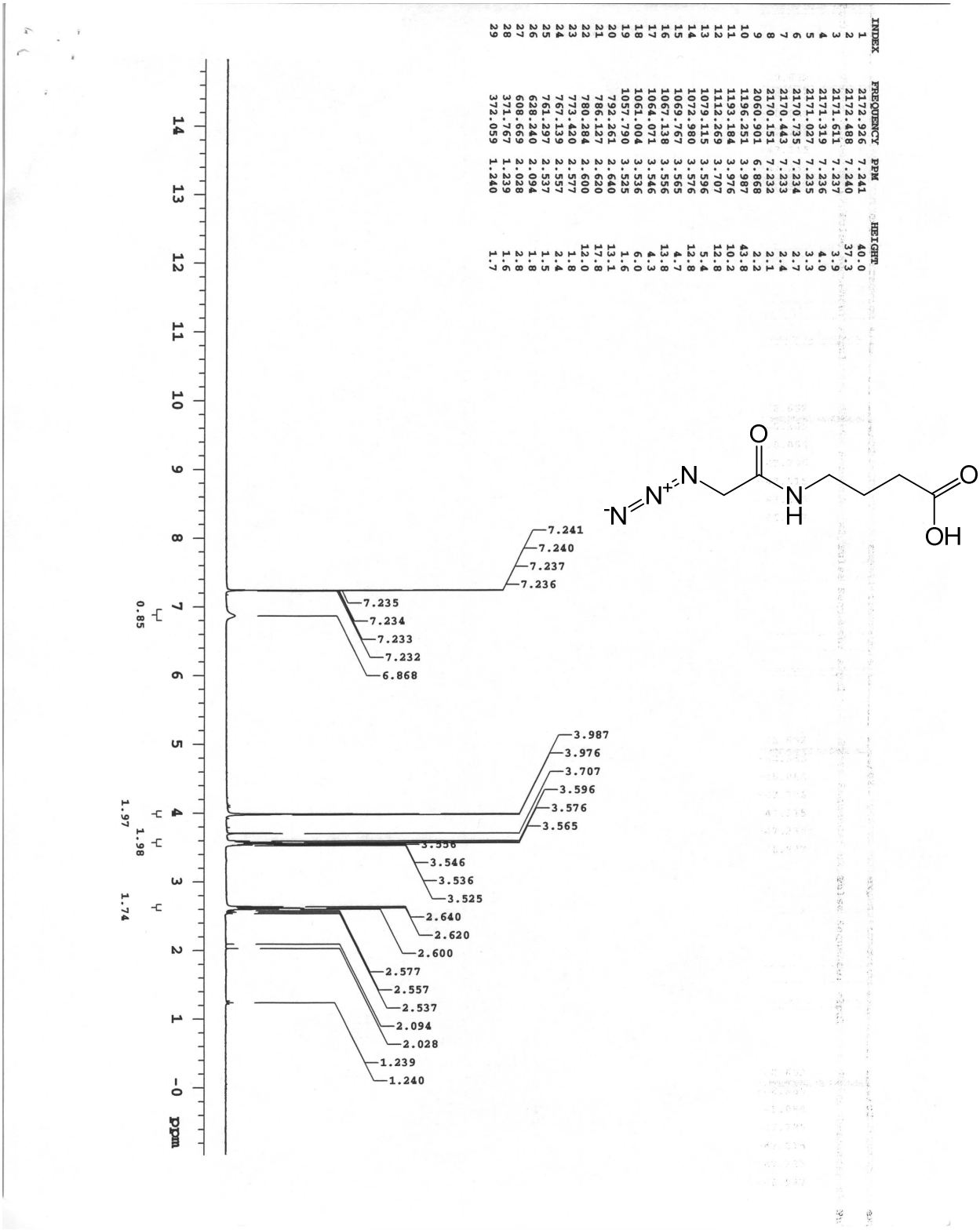


Figure S21. ^{1}H NMR spectrum of **4e**

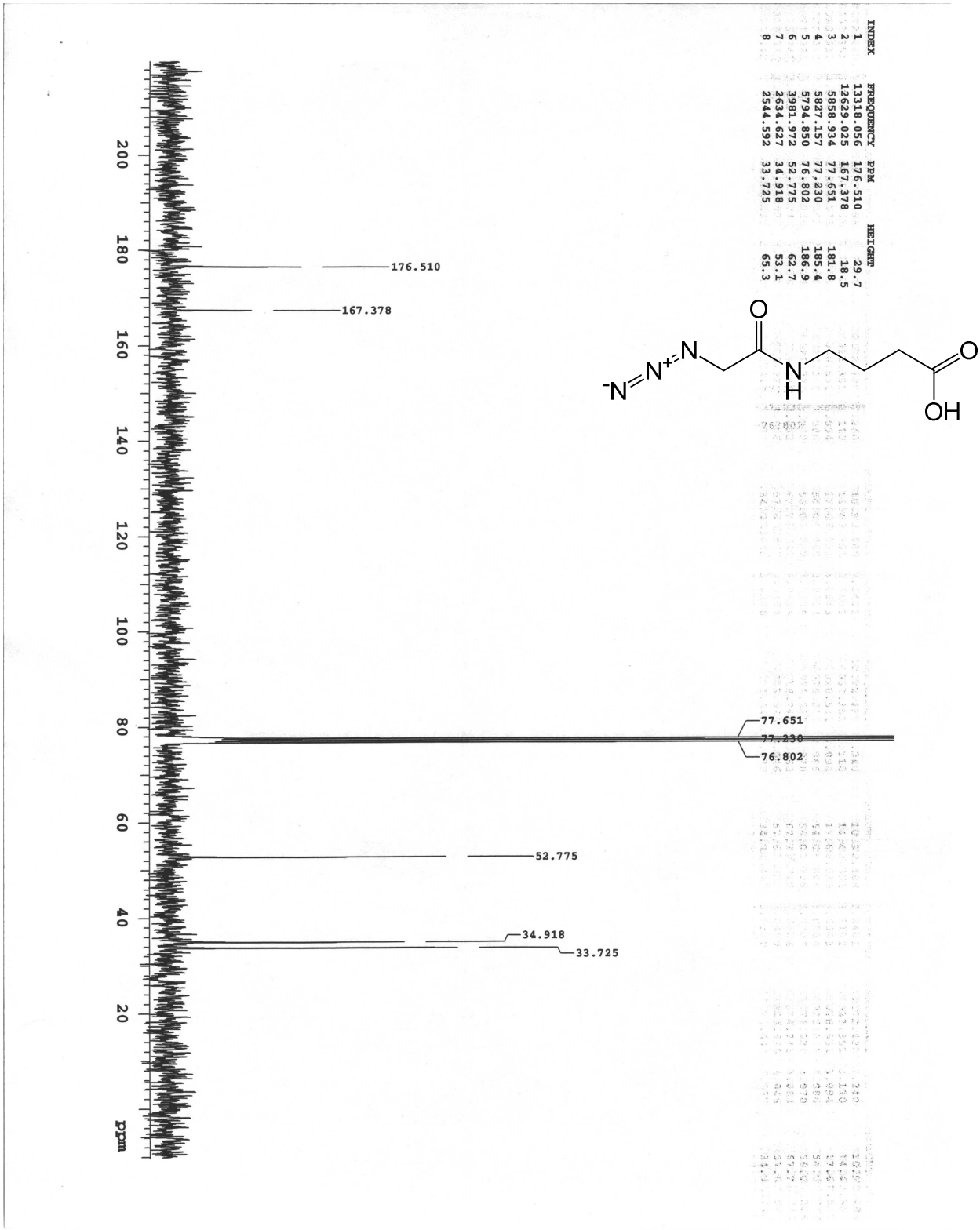


Figure S22. ^{13}C NMR spectrum of **4e**

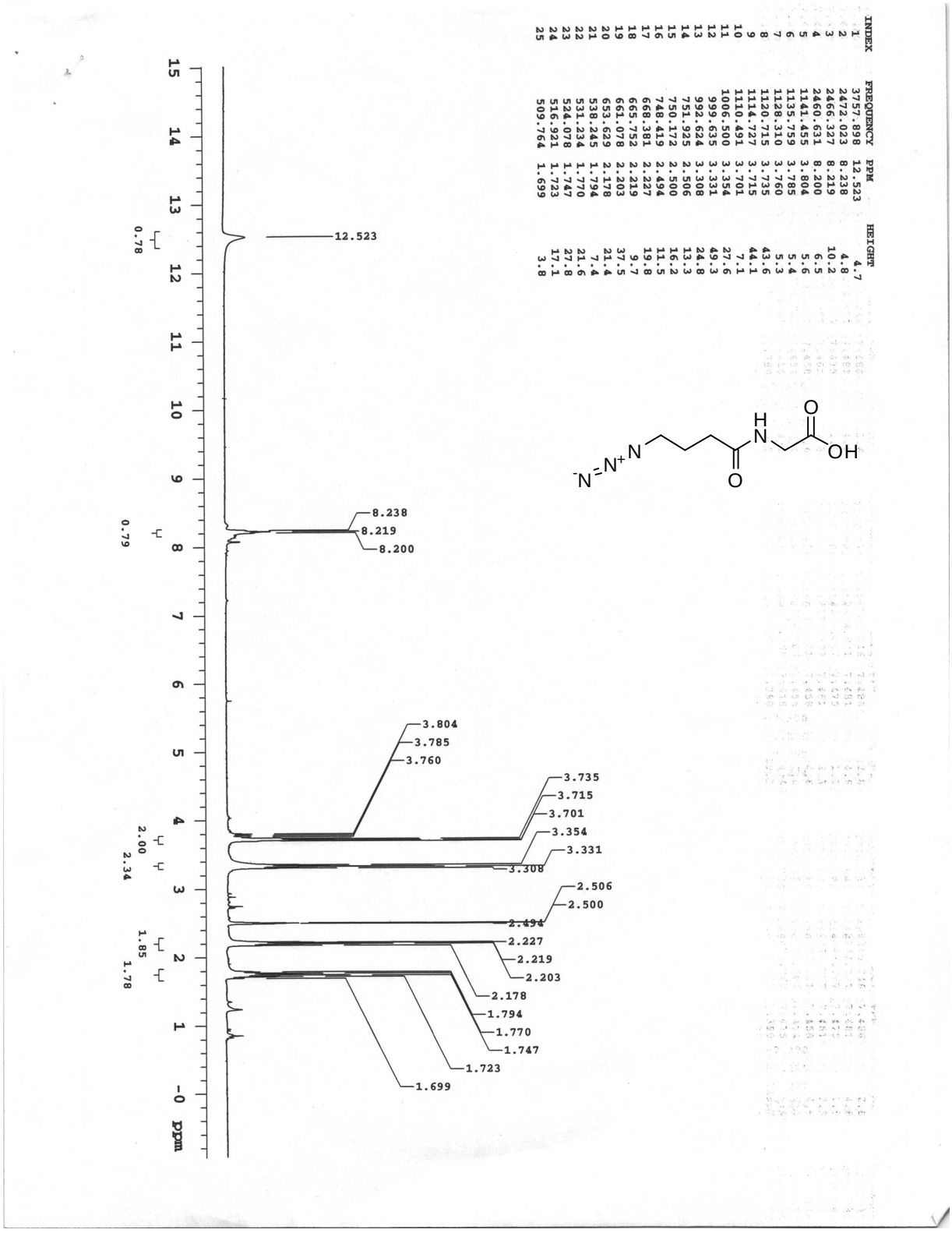


Figure S23. ^{1}H NMR spectrum of **4f**

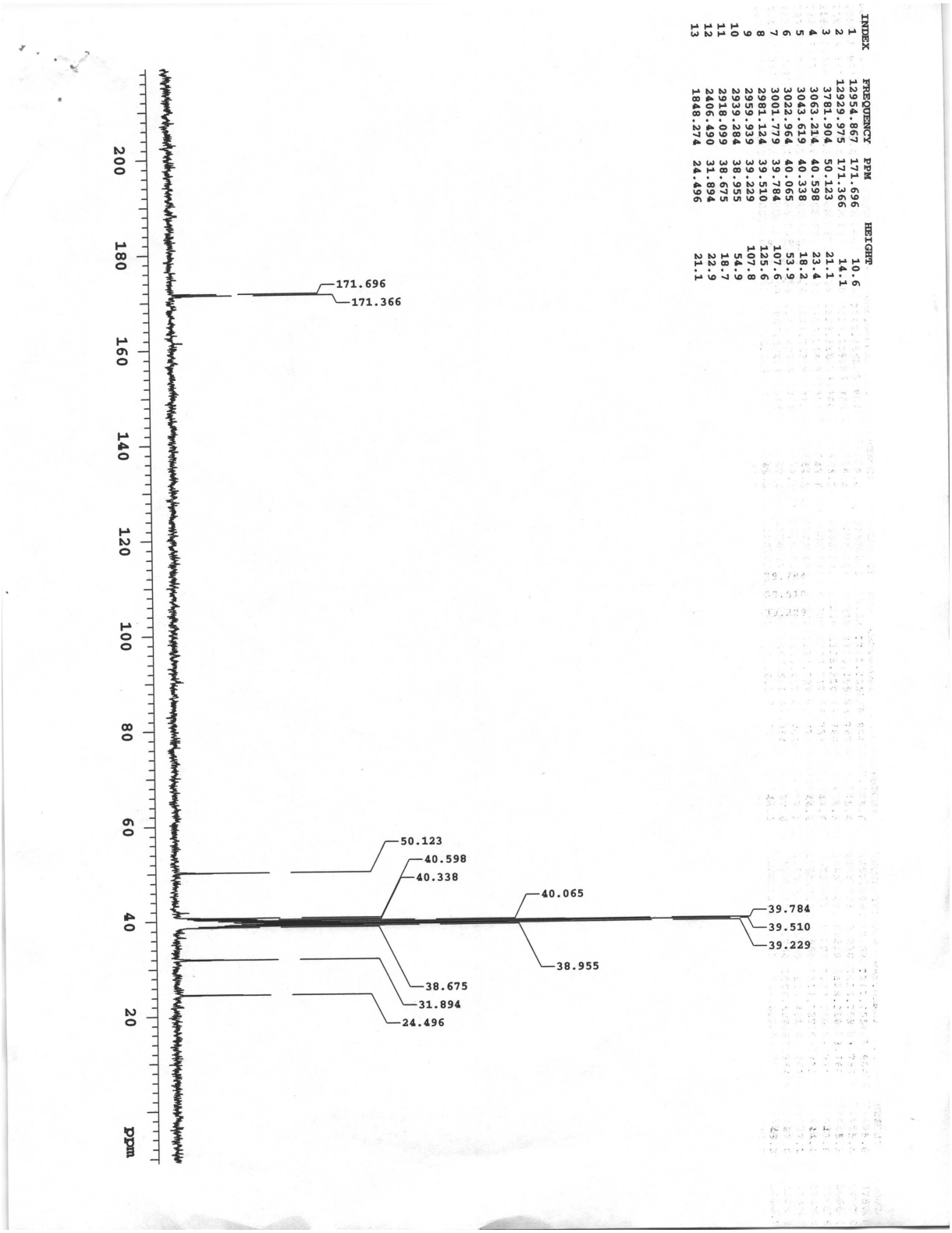


Figure S24. ^{13}C NMR spectrum of **4f**

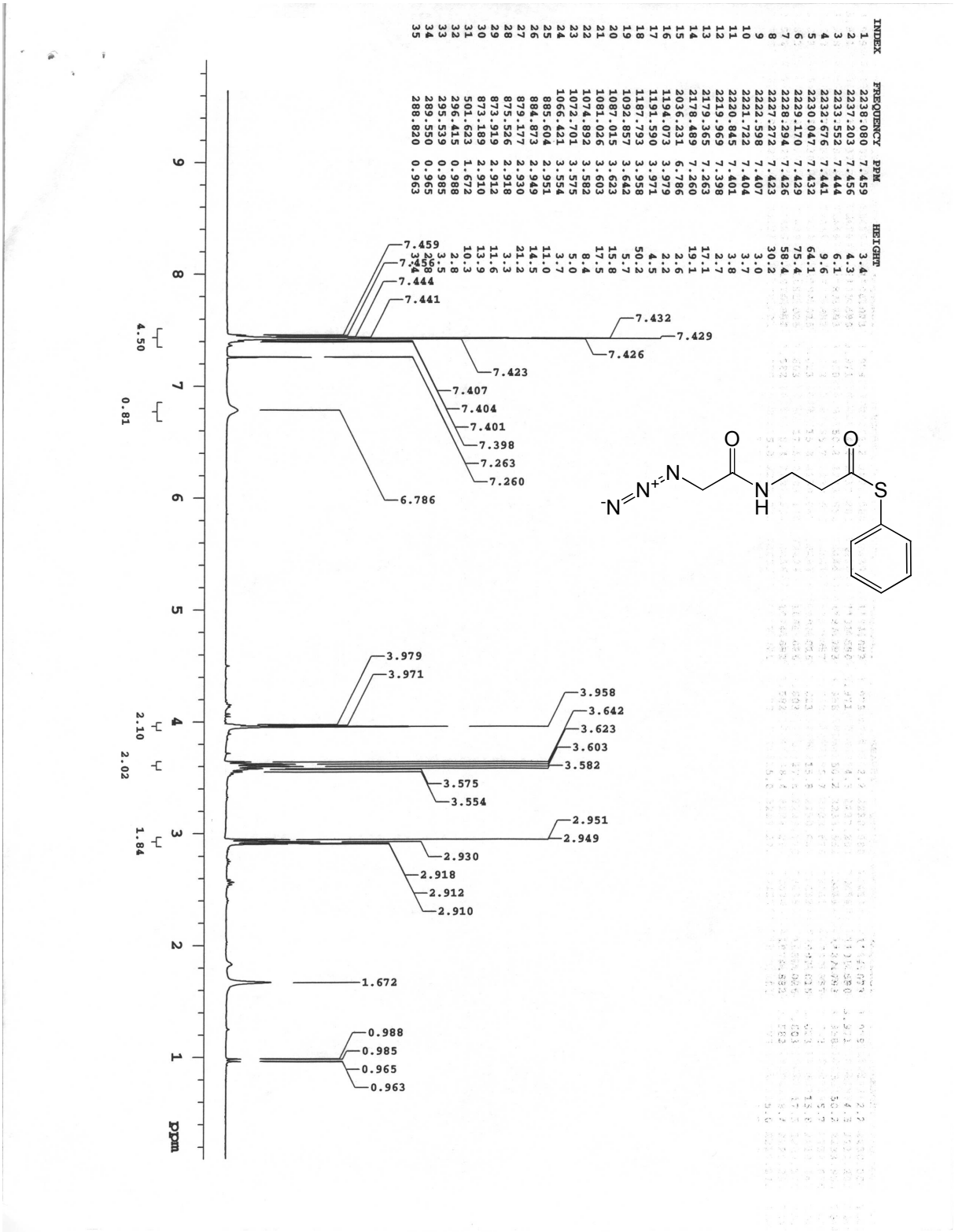


Figure S25. ^{1}H NMR spectrum of **5a**

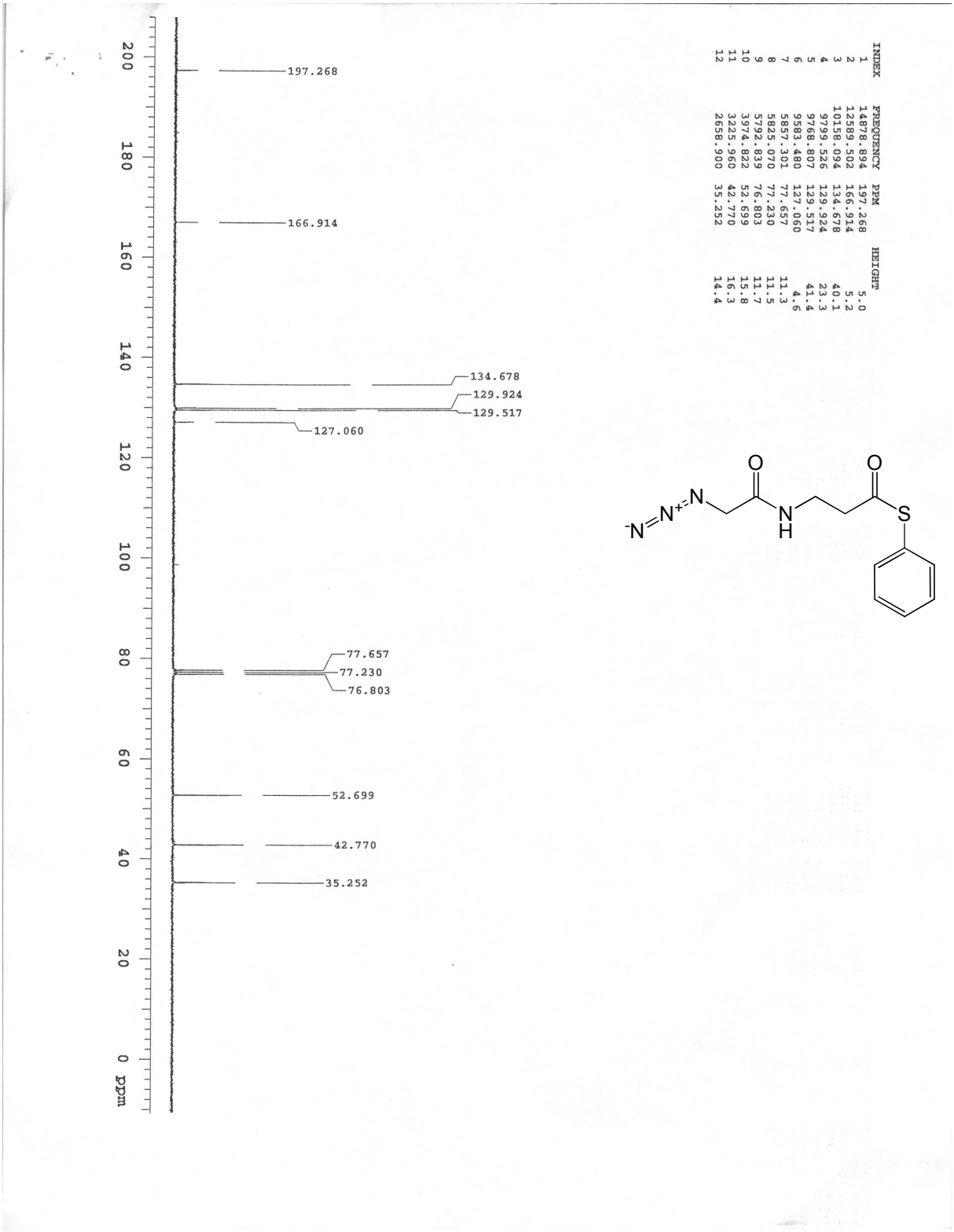


Figure S26. ^{13}C NMR spectrum of **5a**

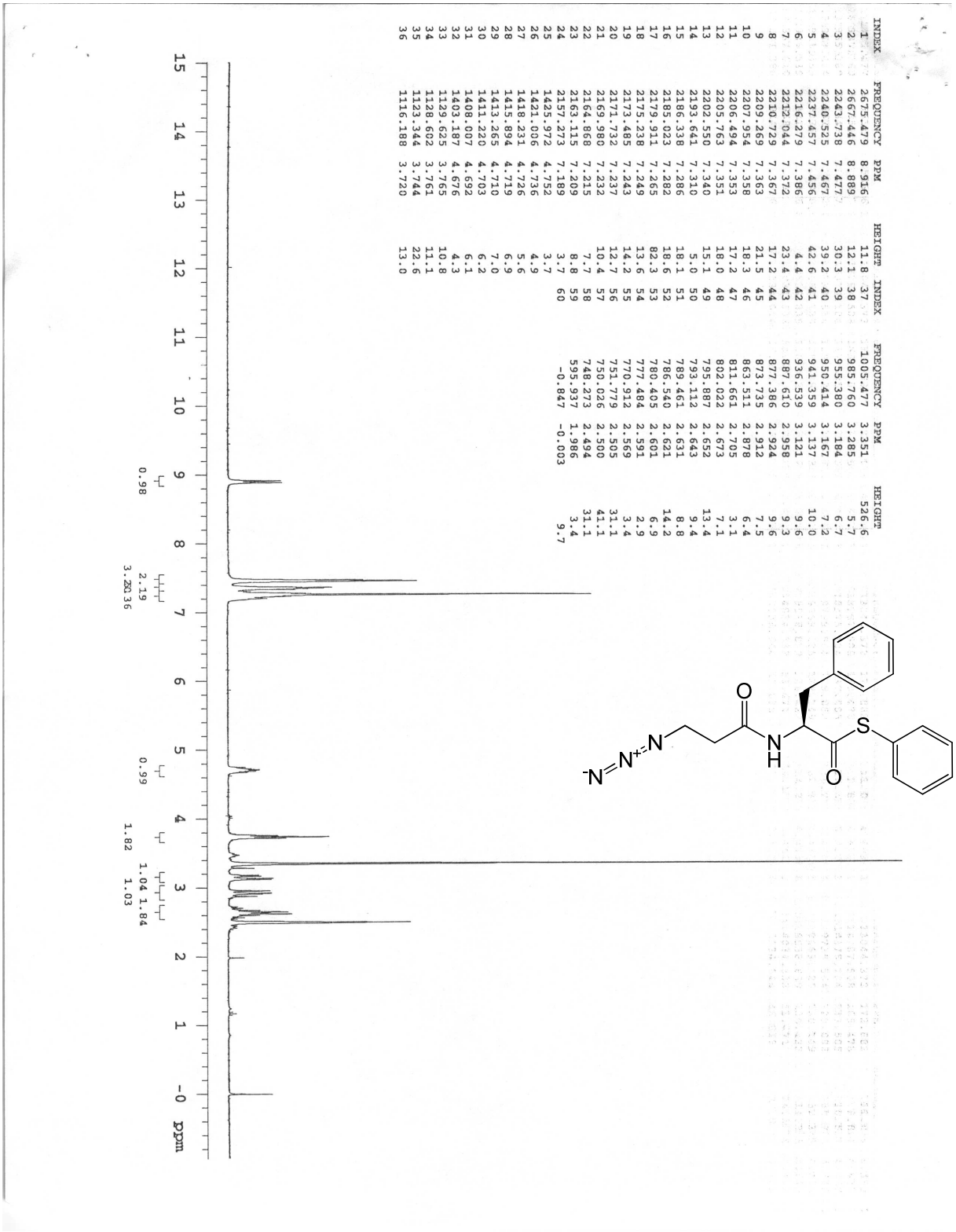


Figure S27. ^{1}H NMR spectrum of **5b**

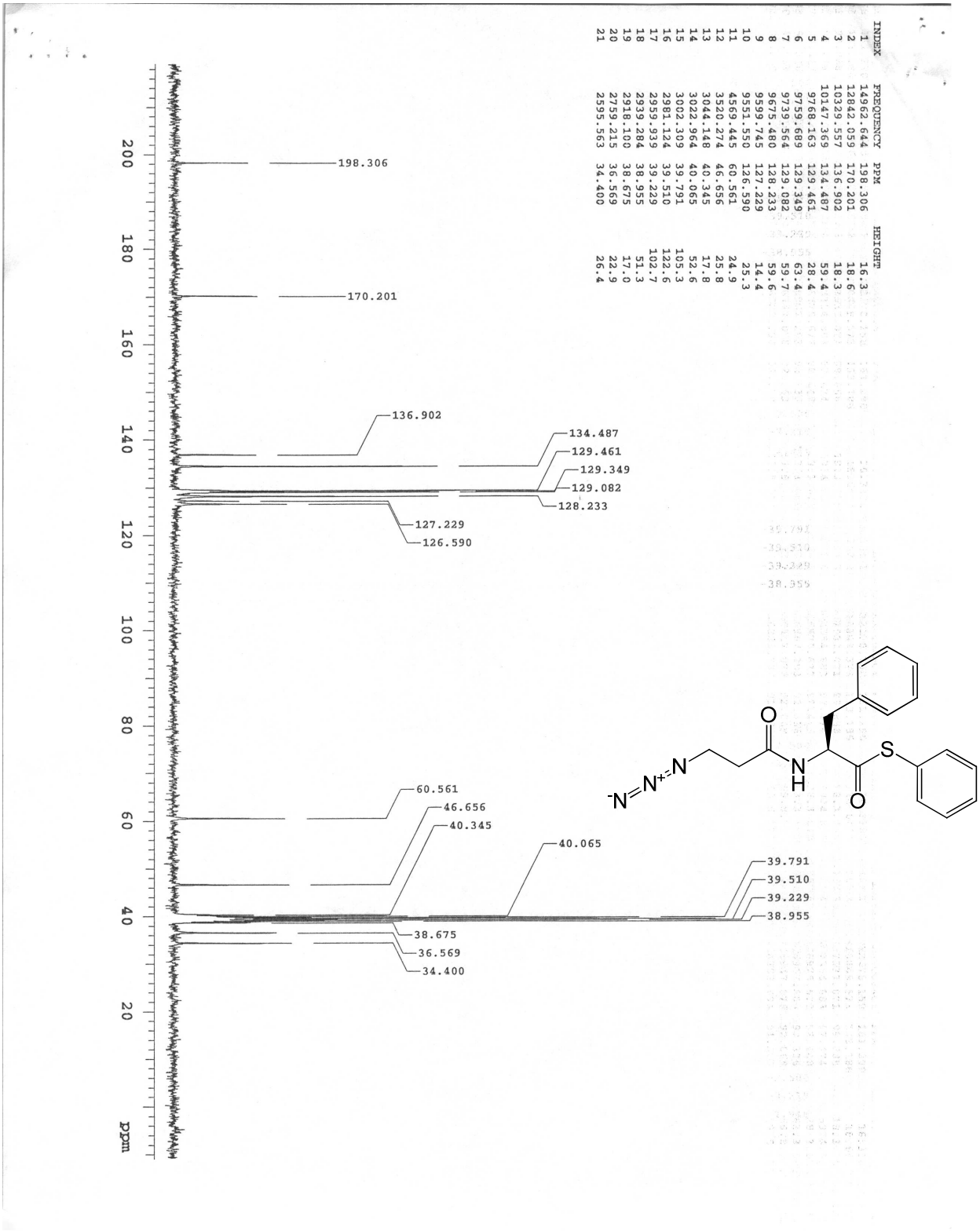


Figure S28. ^{13}C NMR spectrum of **5b**

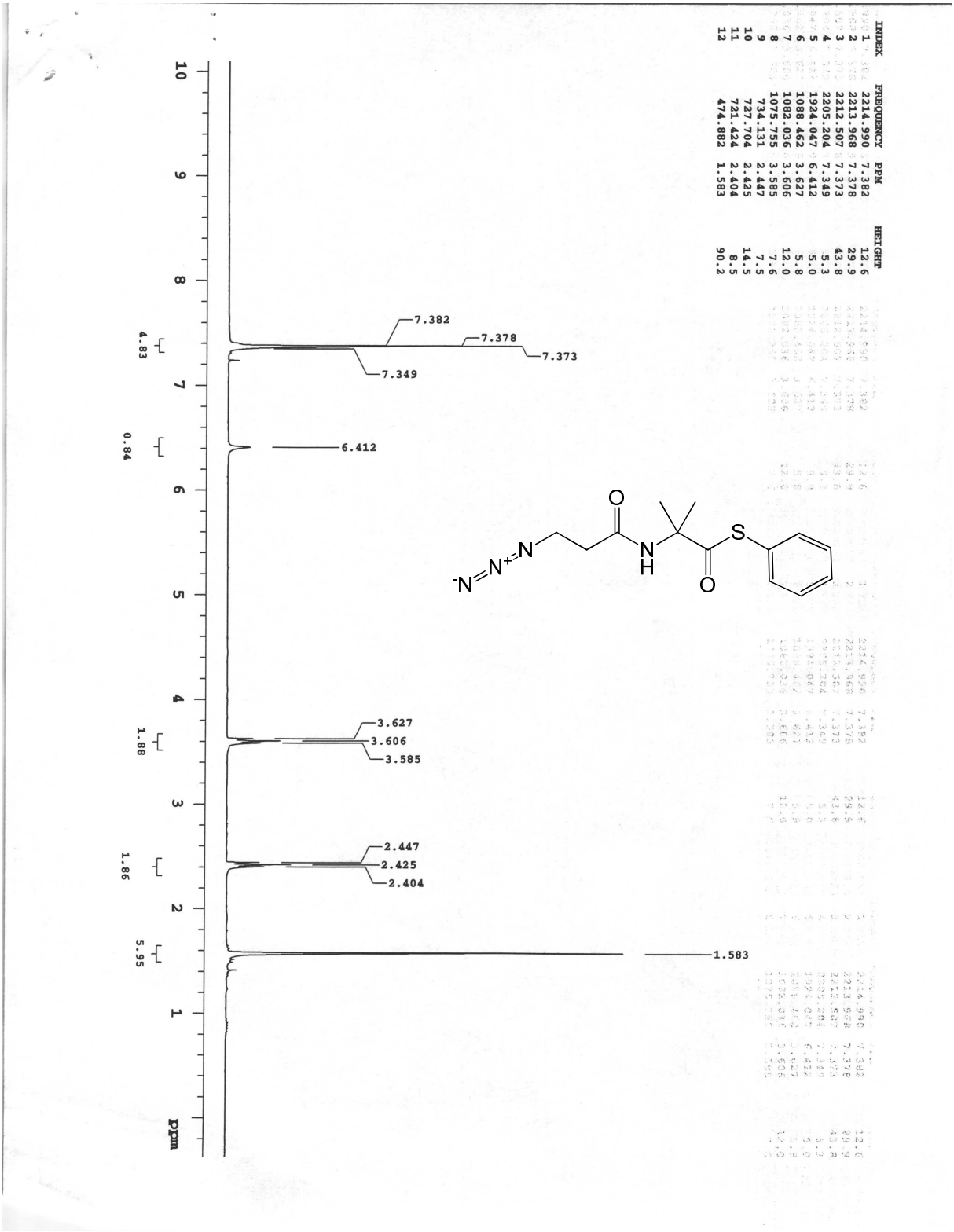


Figure S29. ^{1}H NMR spectrum of **5c**

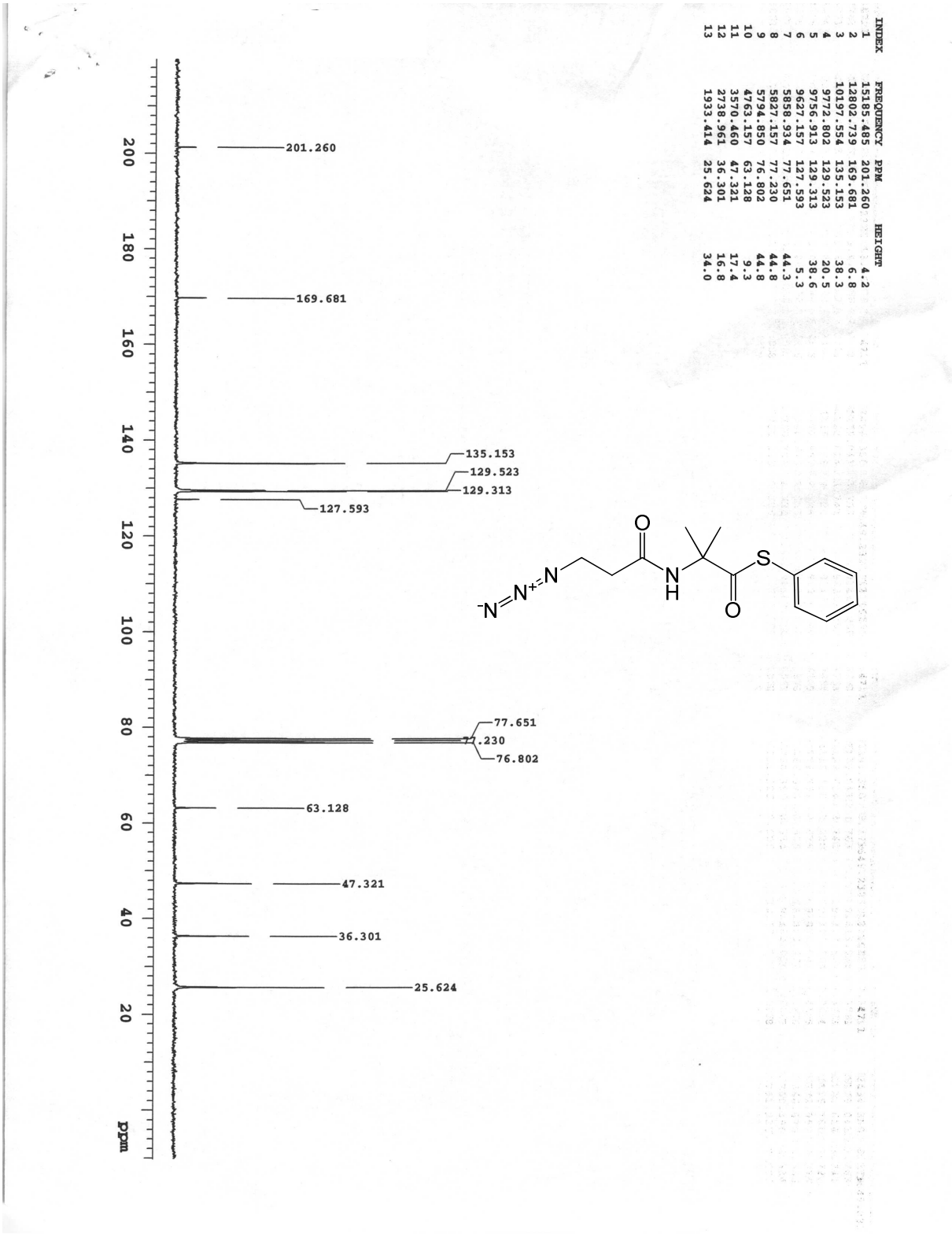


Figure S30. ^{13}C NMR spectrum of **5c**

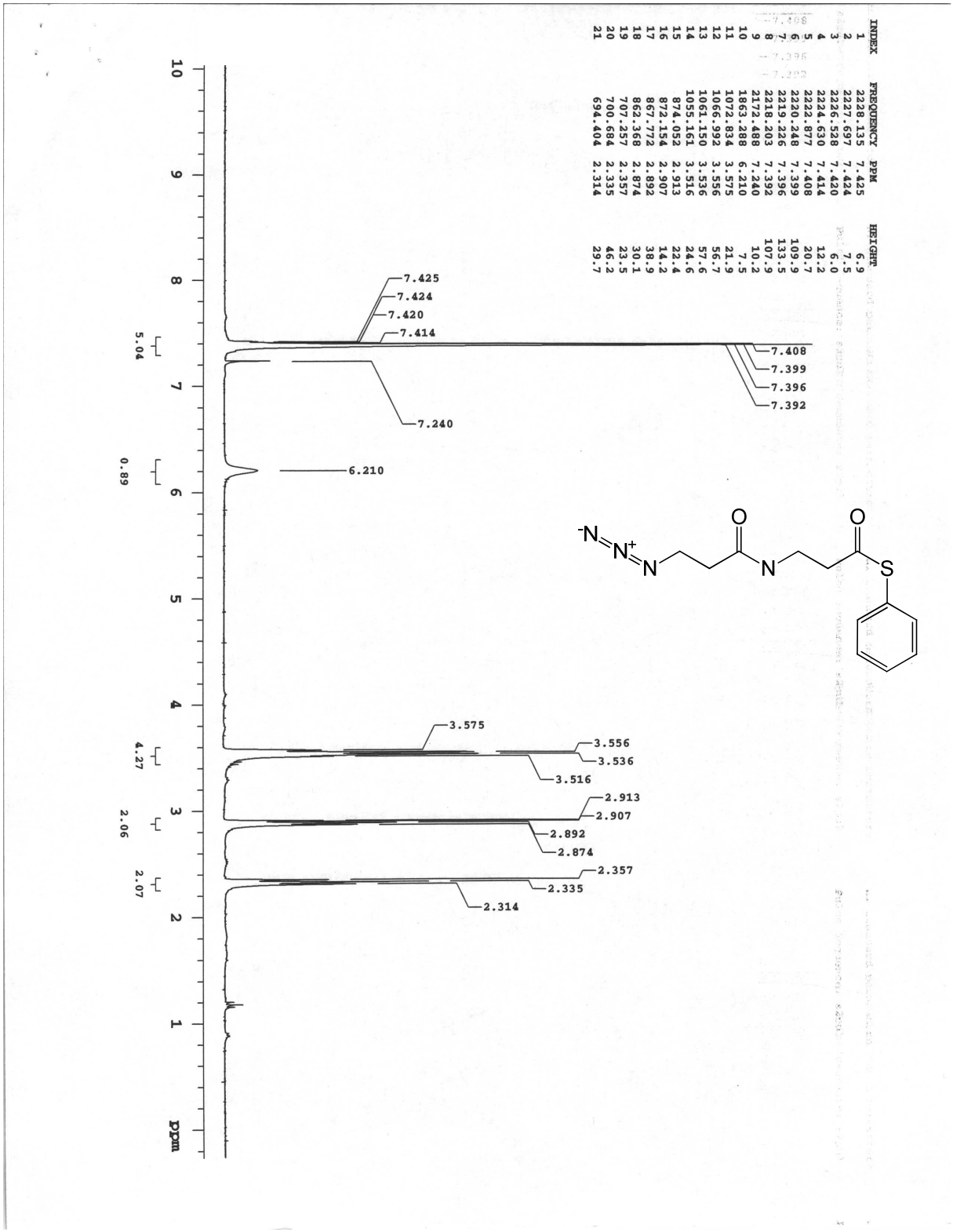


Figure S31. ^{1}H NMR spectrum of **5d**

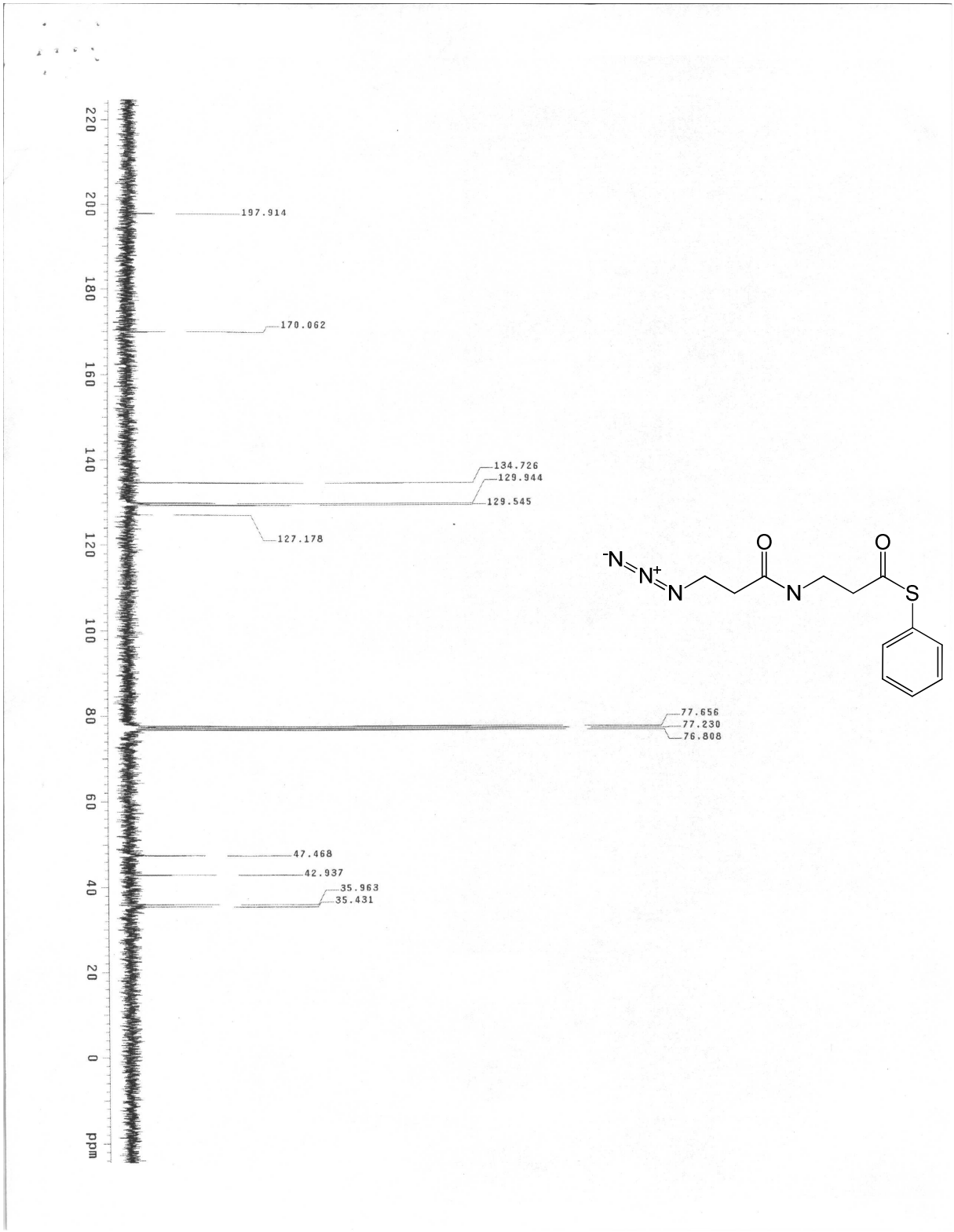


Figure S32. ^{13}C NMR spectrum of **5d**

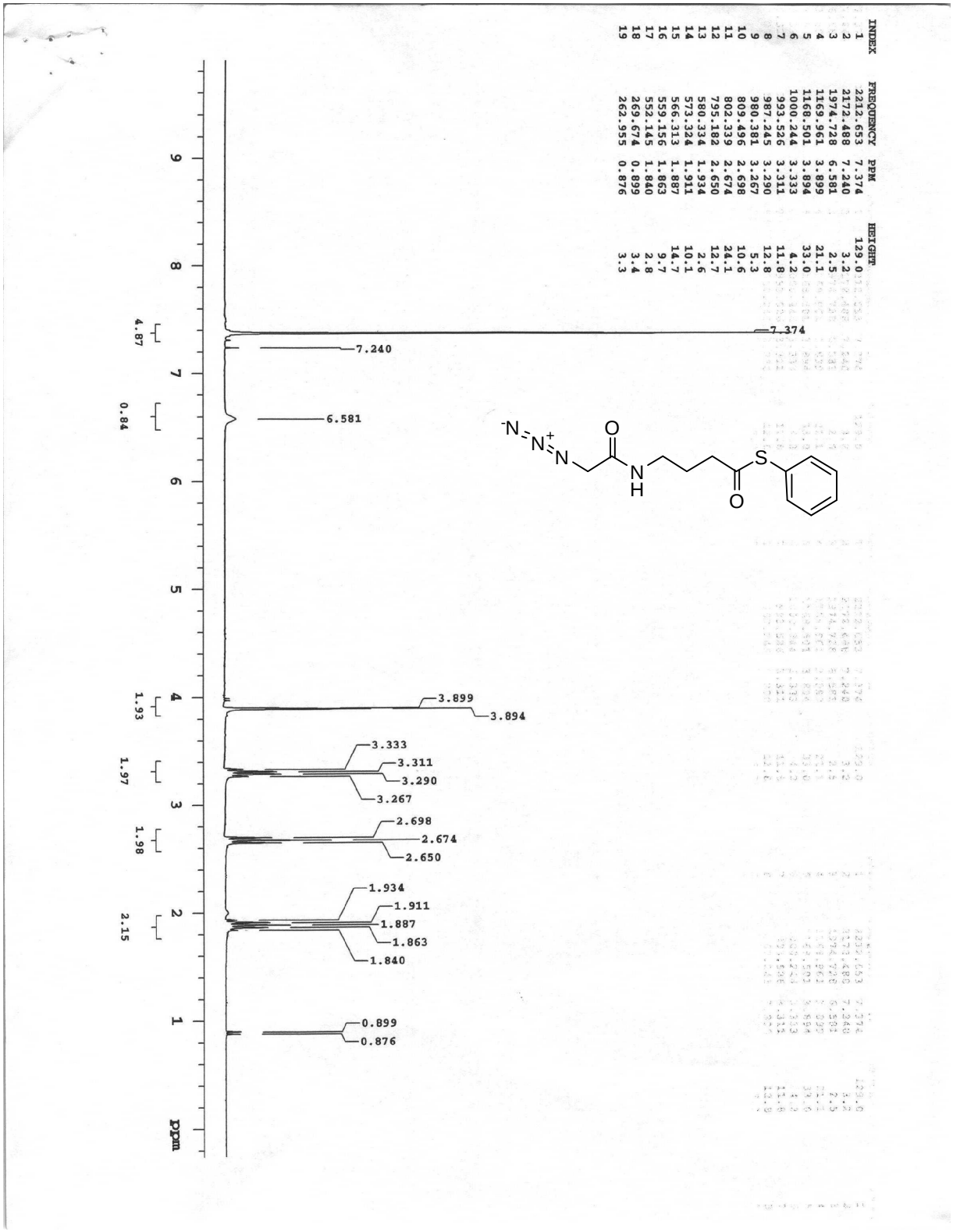


Figure S33. ^{1}H NMR spectrum of **5e**

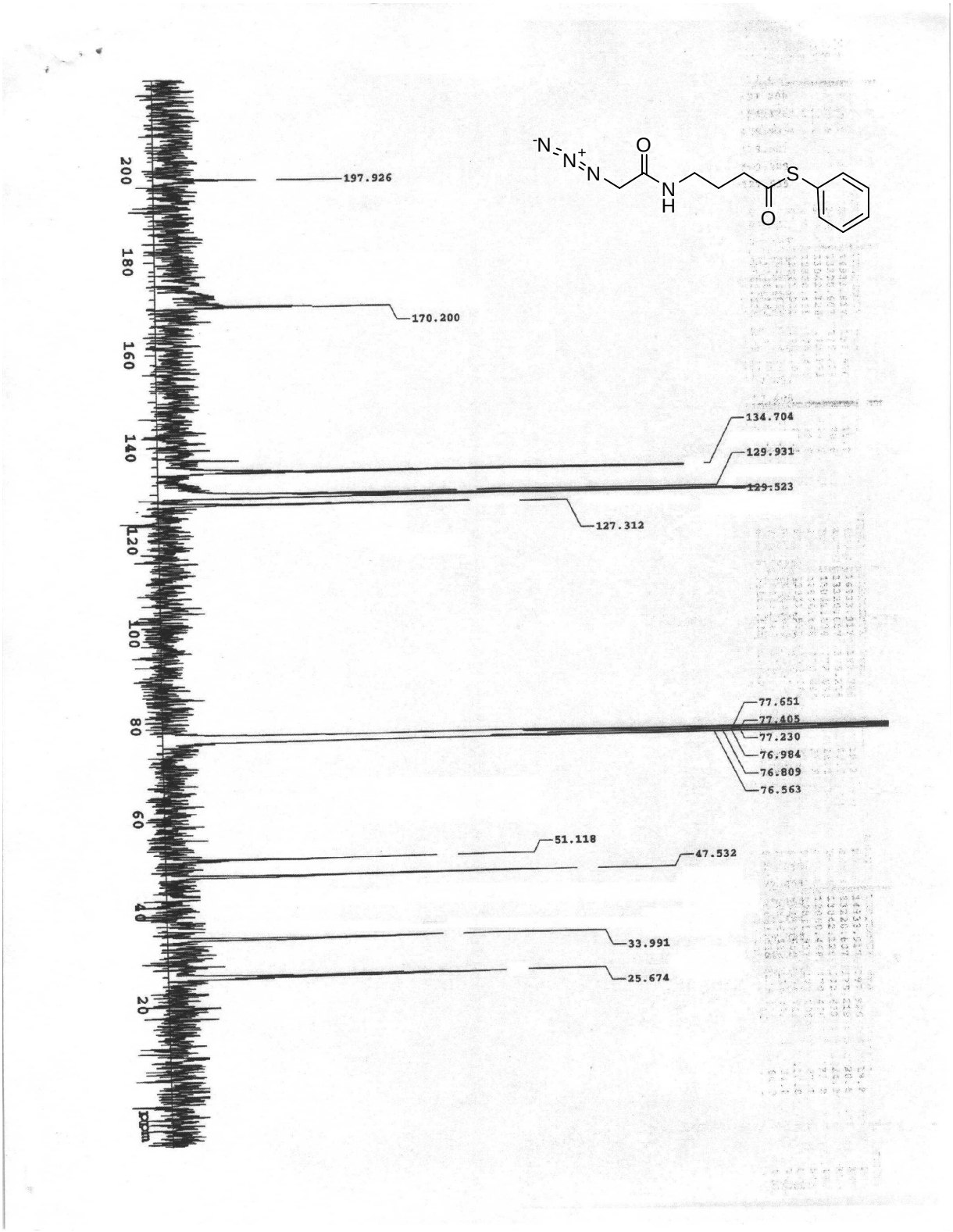


Figure S34. ^{13}C NMR spectrum of **5e**

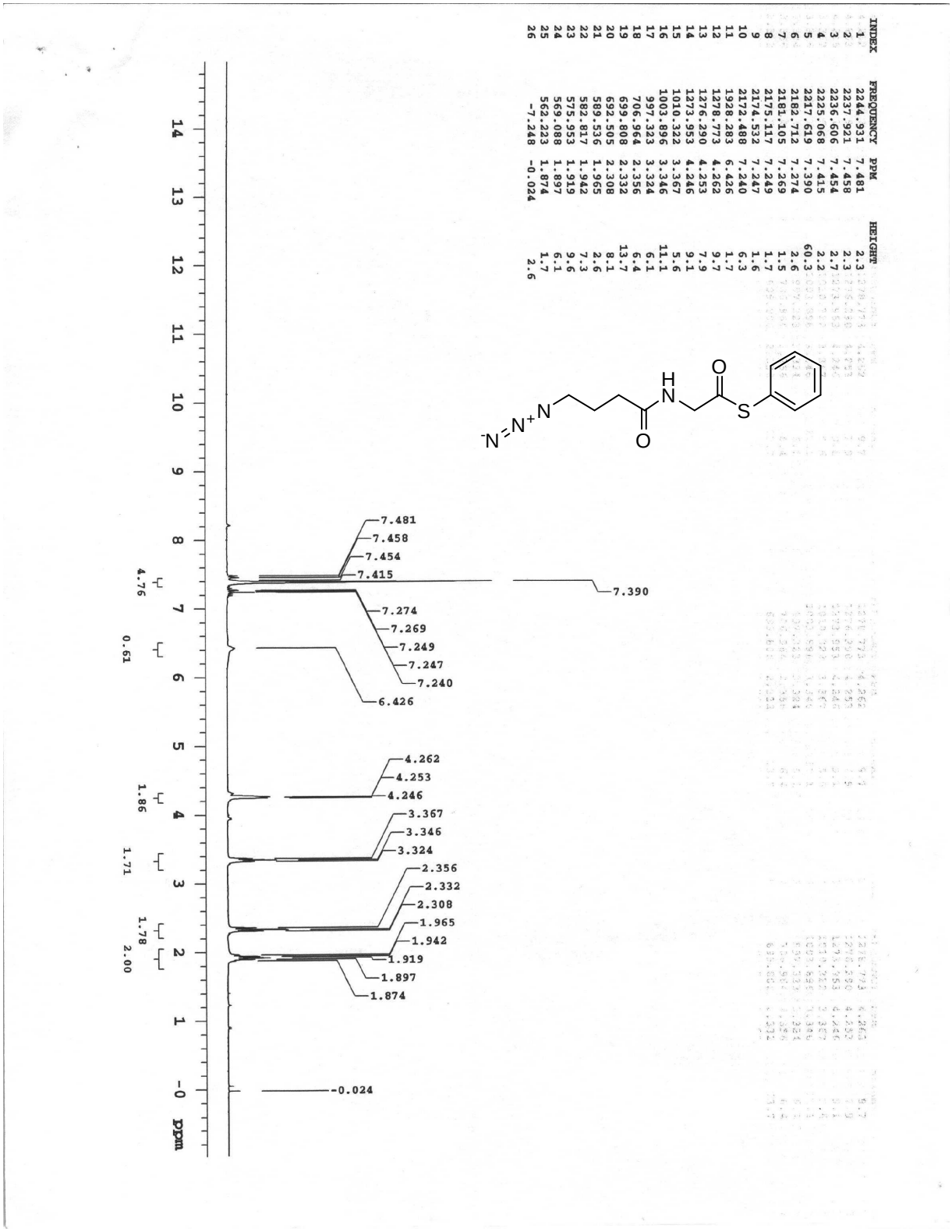


Figure S35. ^{1}H NMR spectrum of **5f**

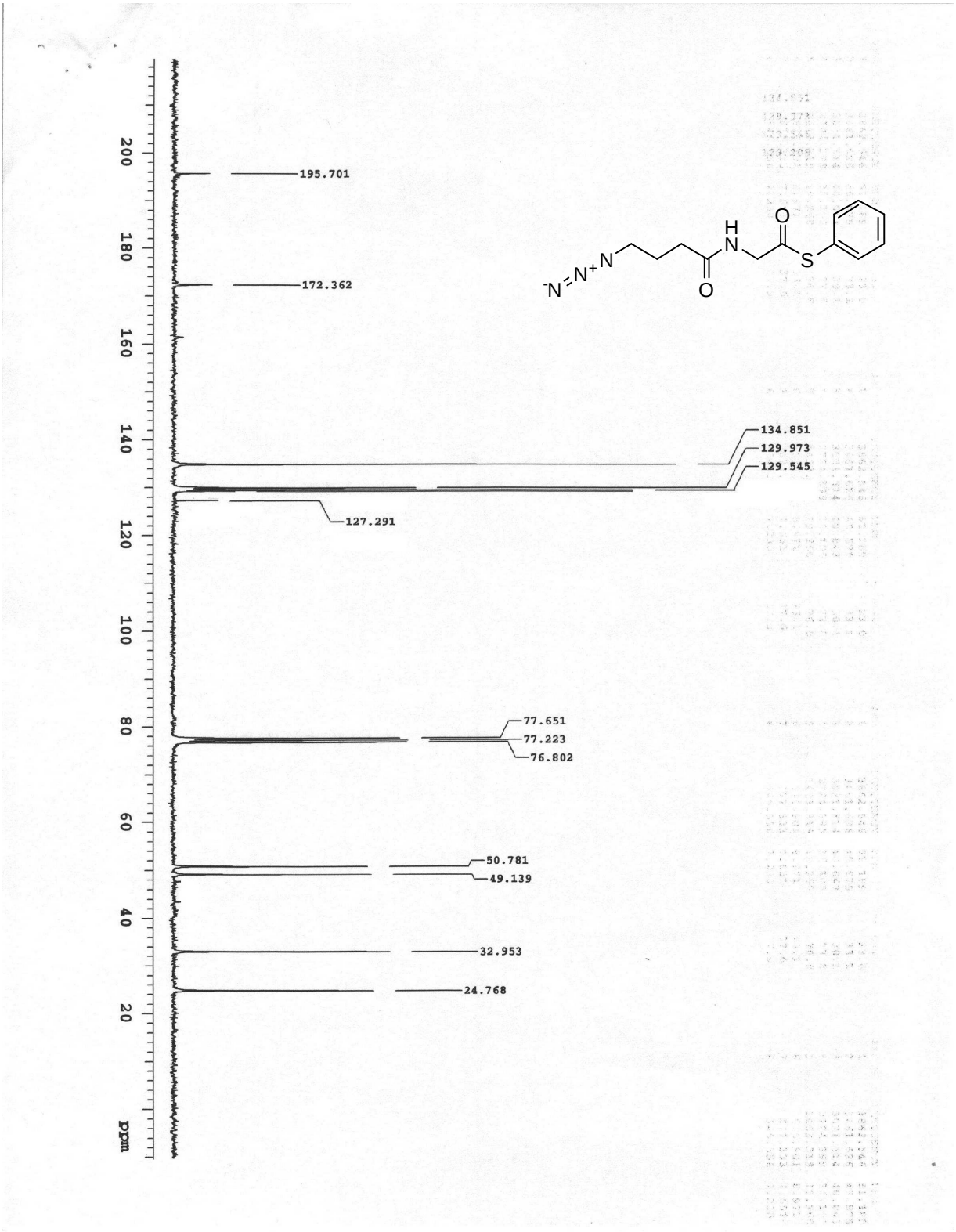


Figure S36. ^{13}C NMR spectrum of **5f**

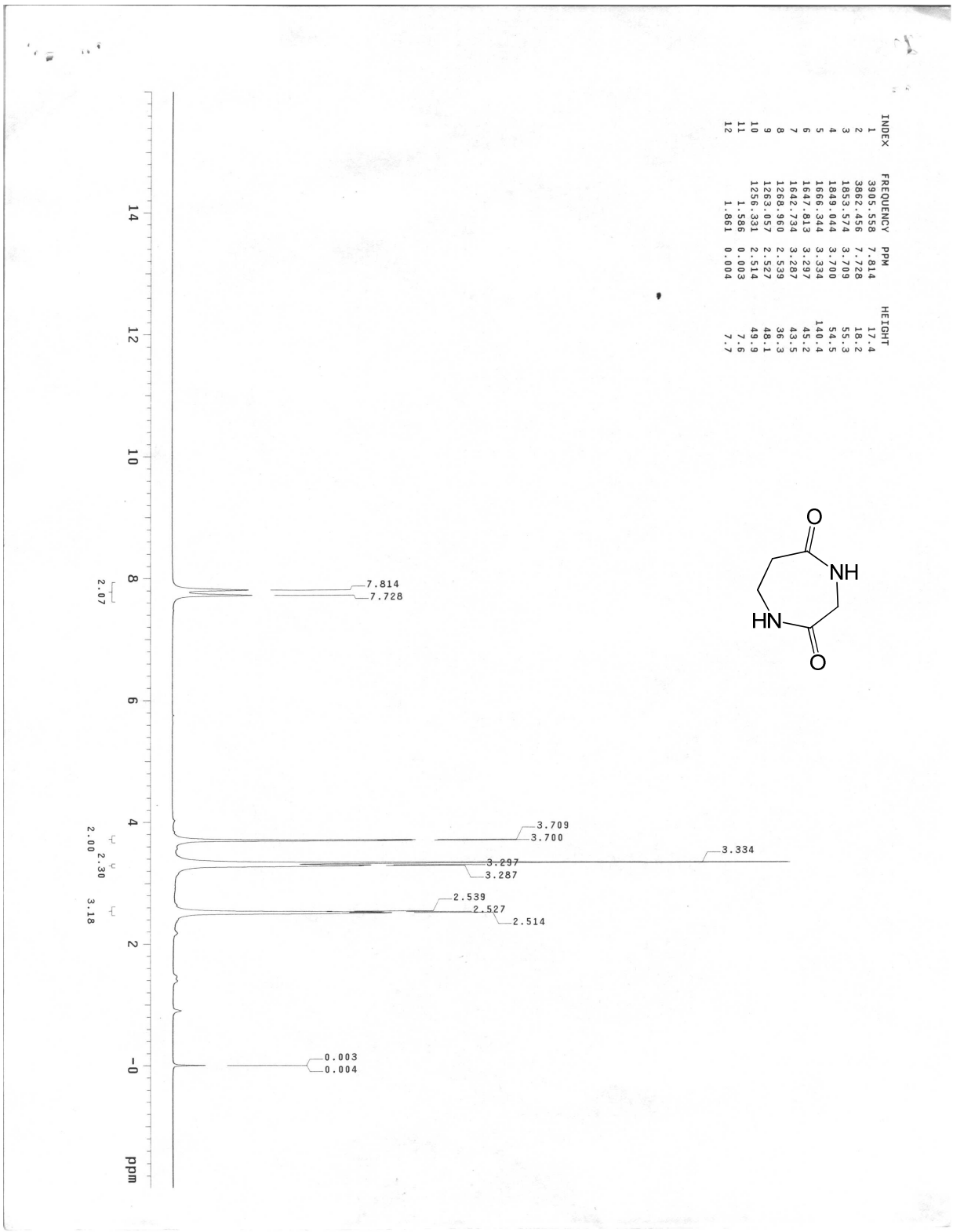


Figure S37. ^{1}H NMR spectrum of **6a**

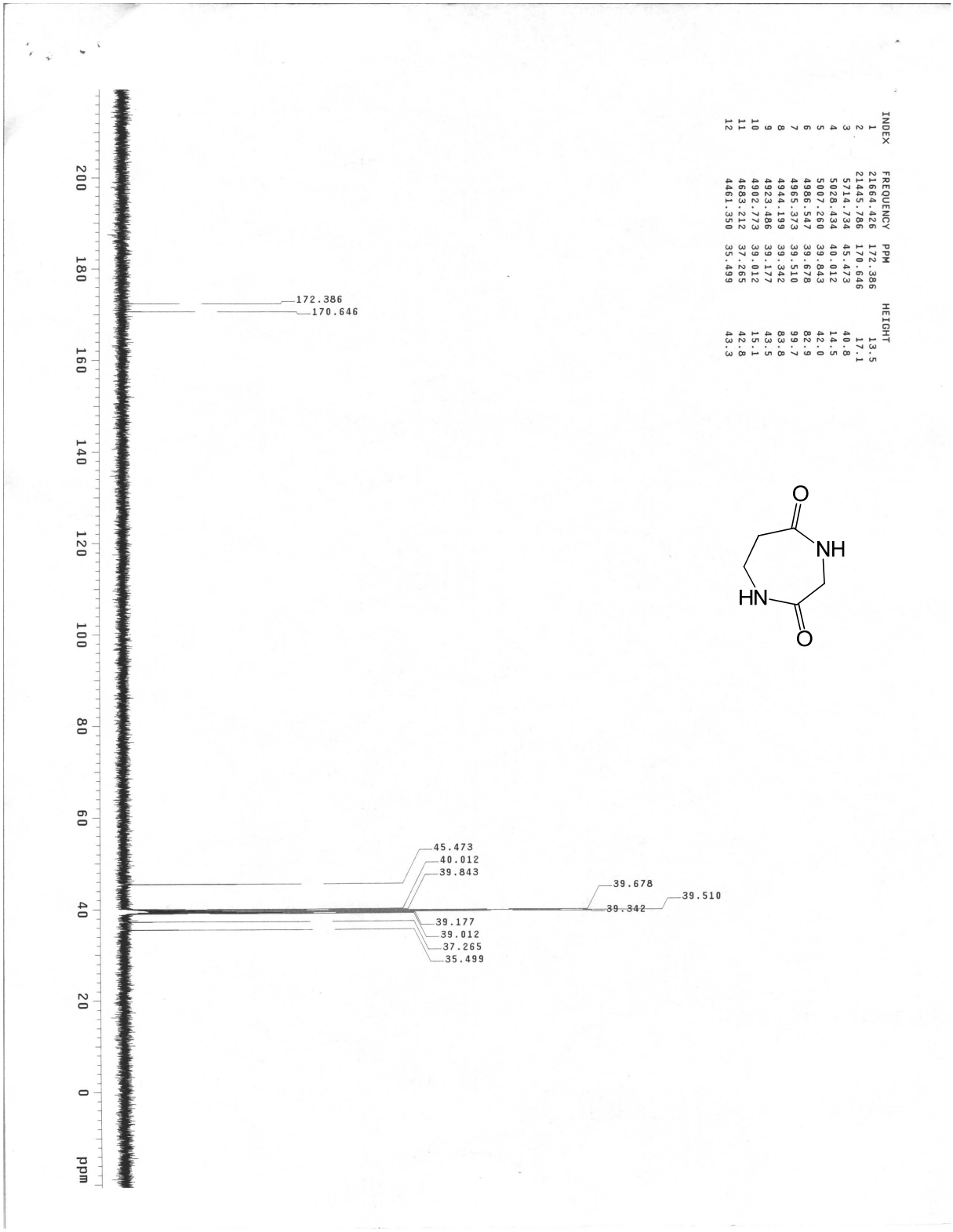


Figure S38. ^{13}C NMR spectrum of **6a**

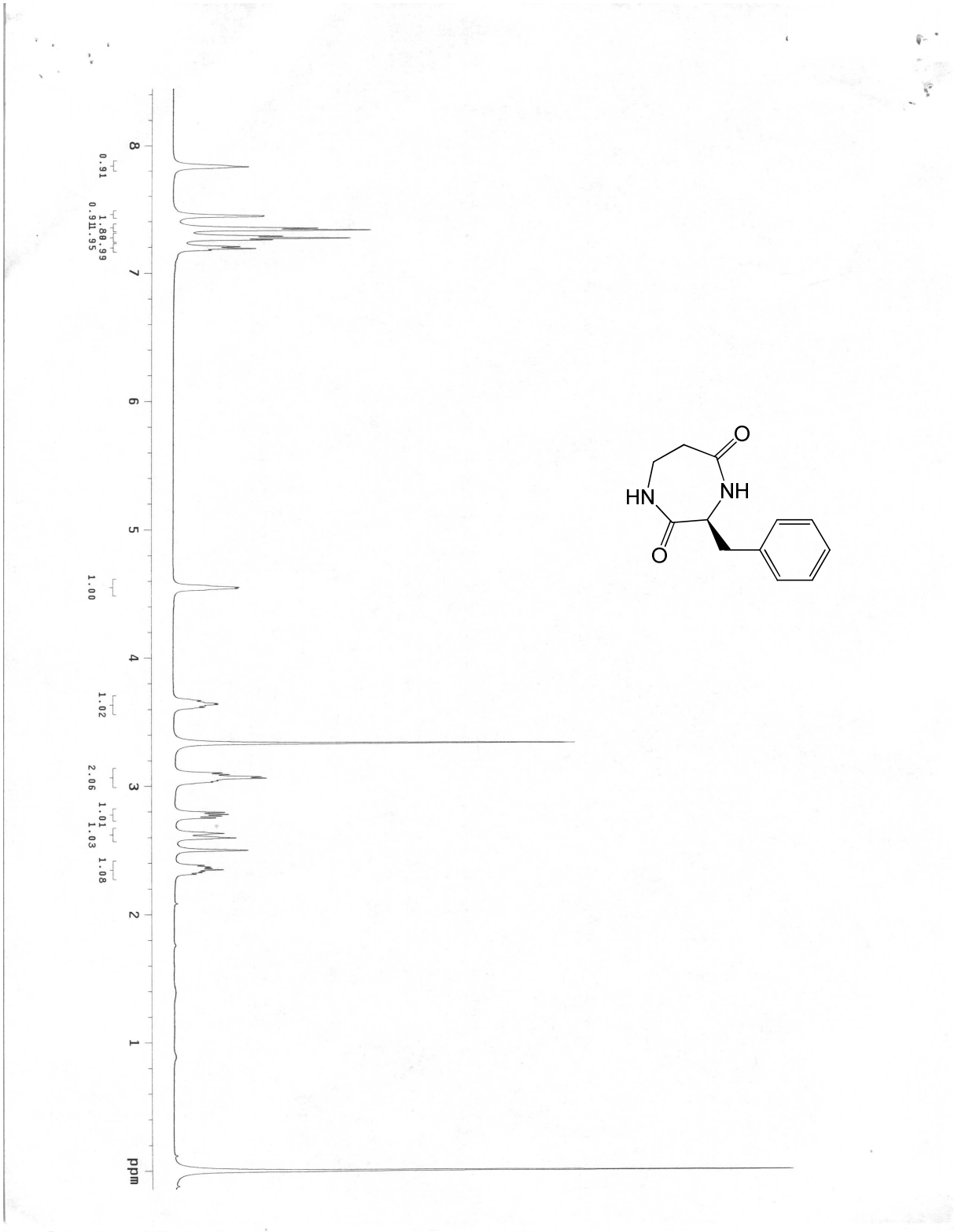


Figure S39. ^{1}H NMR spectrum of **6b**

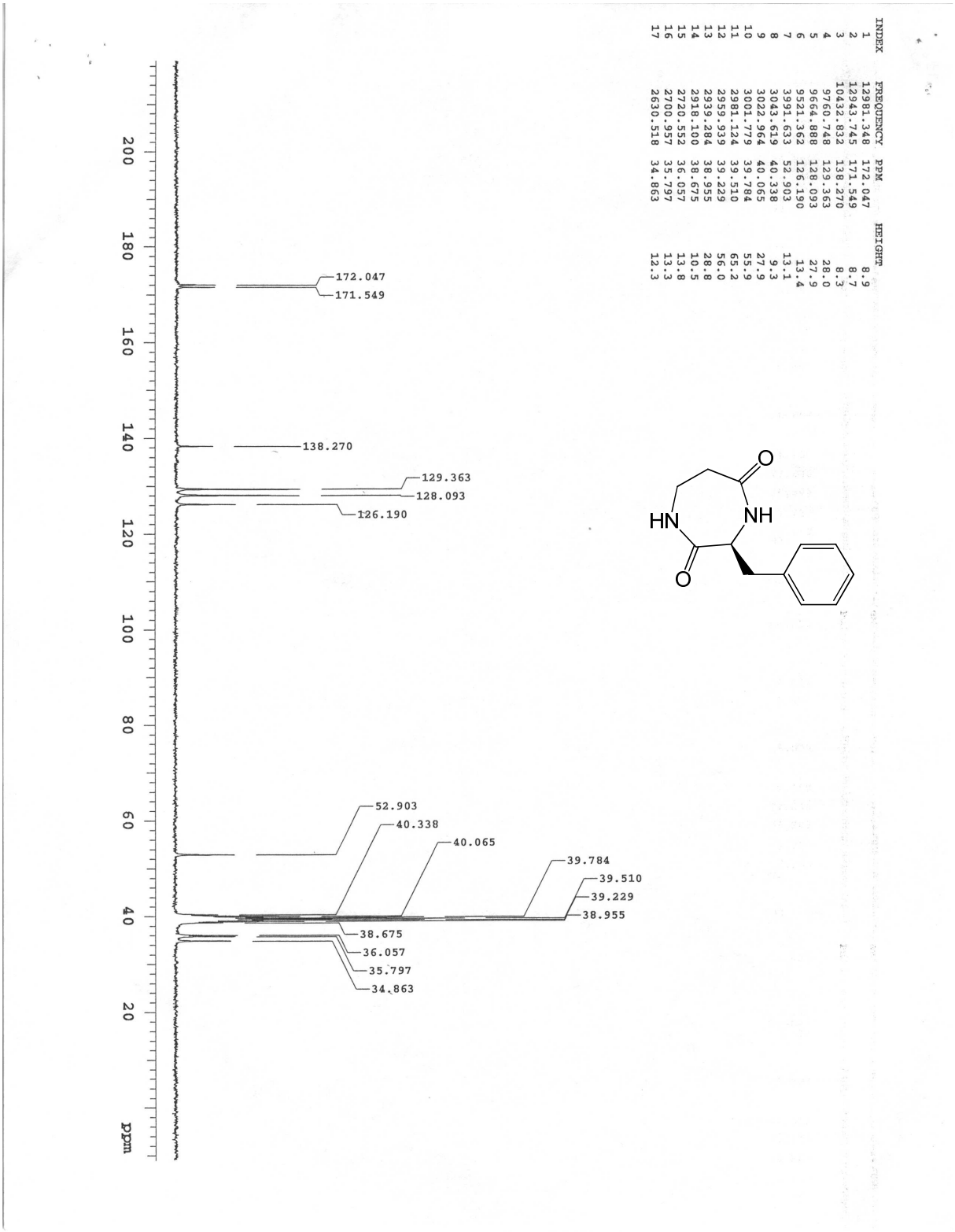


Figure S40. ^{13}C NMR spectrum of **6b**

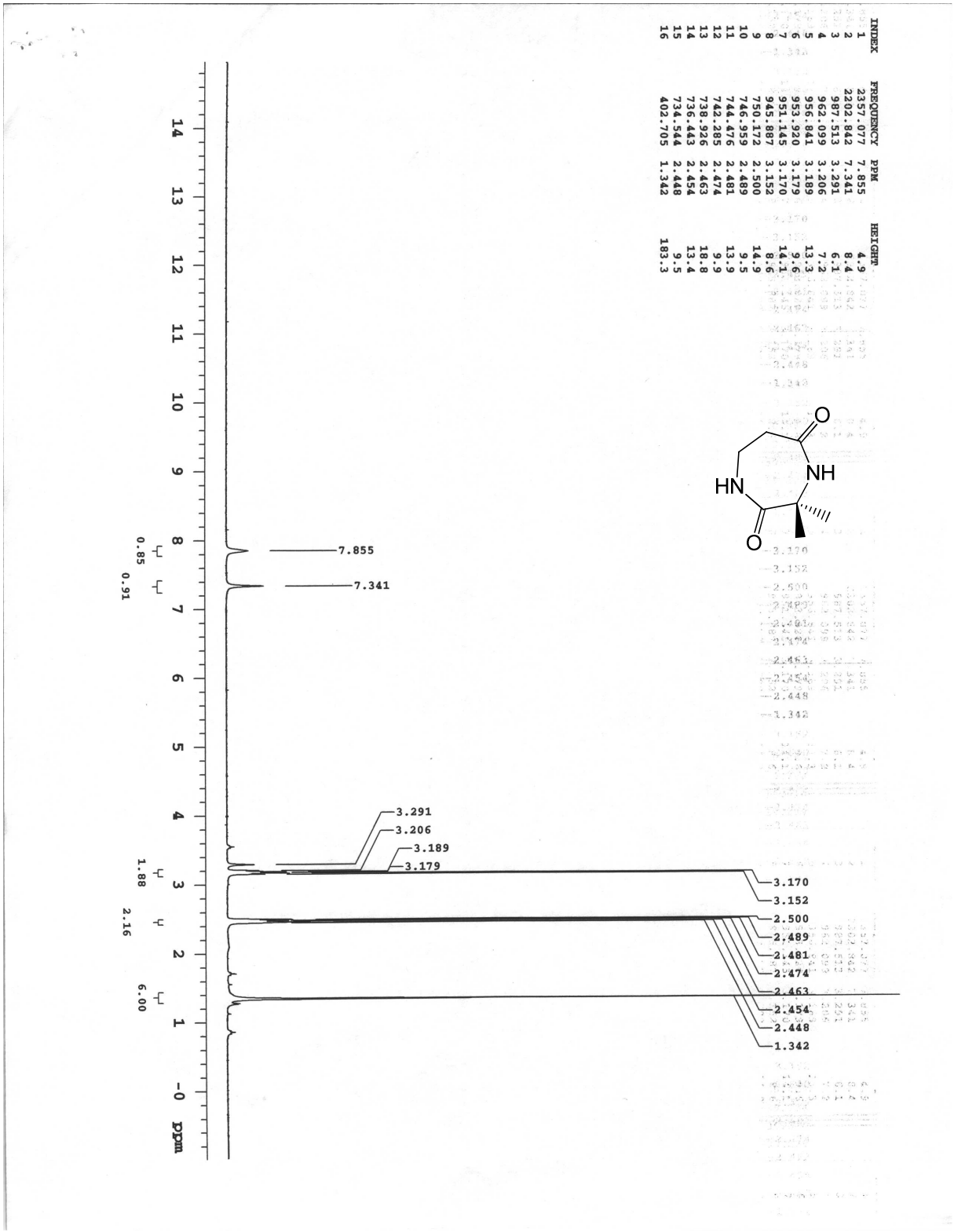


Figure S41. ^{1}H NMR spectrum of **6c**

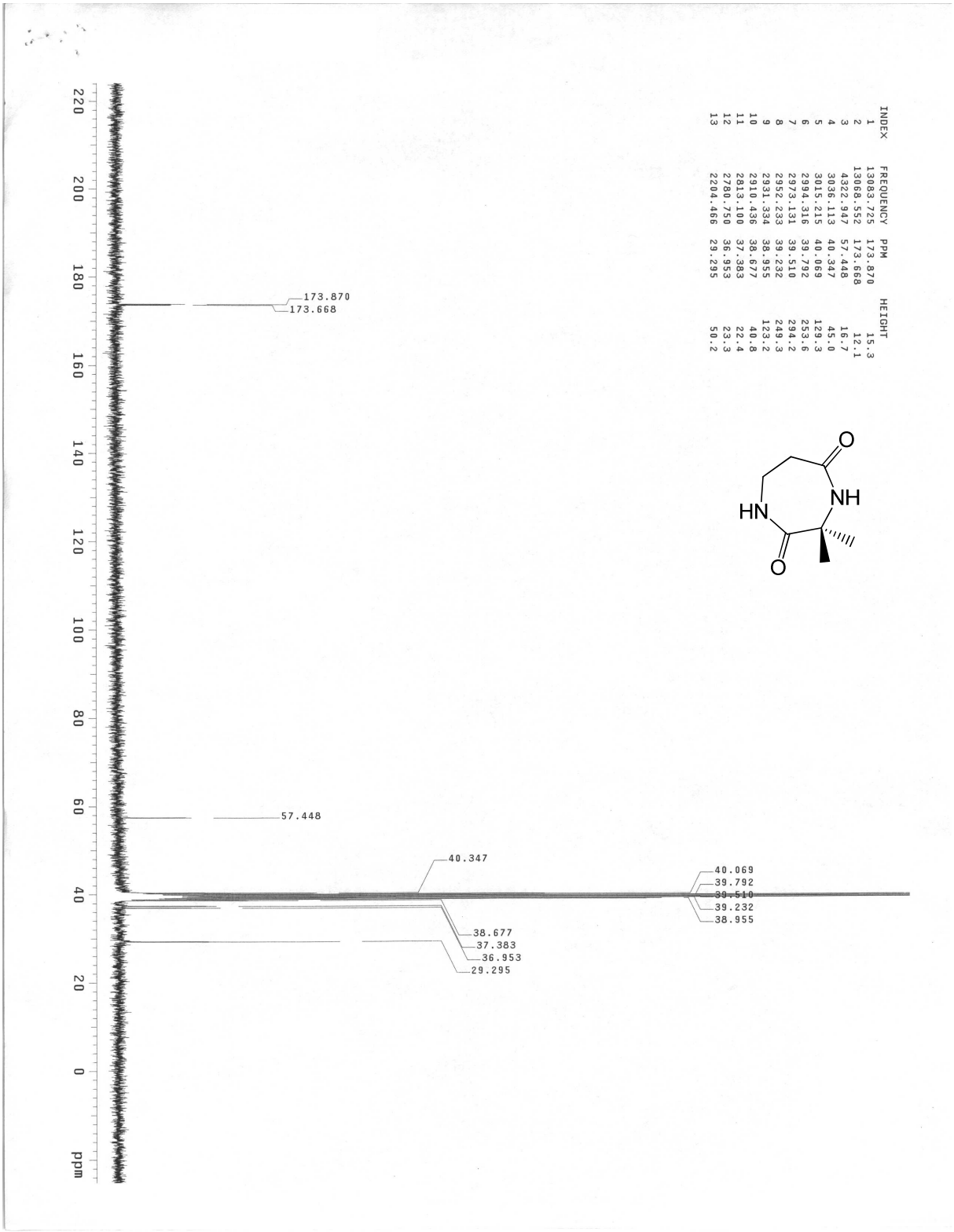


Figure S42. ^{13}C NMR spectrum of **6c**

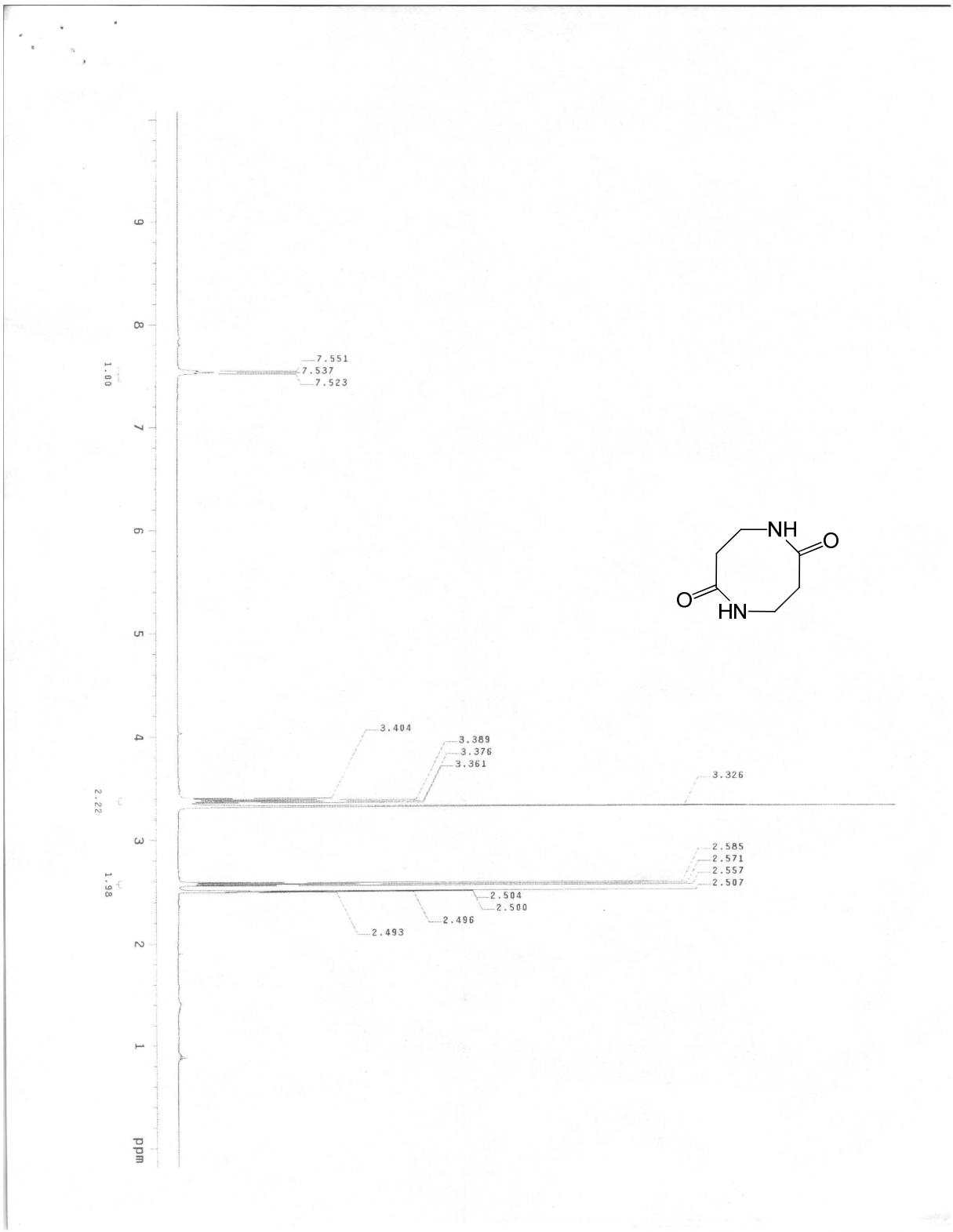


Figure S43. ^{1}H NMR spectrum of **6d**

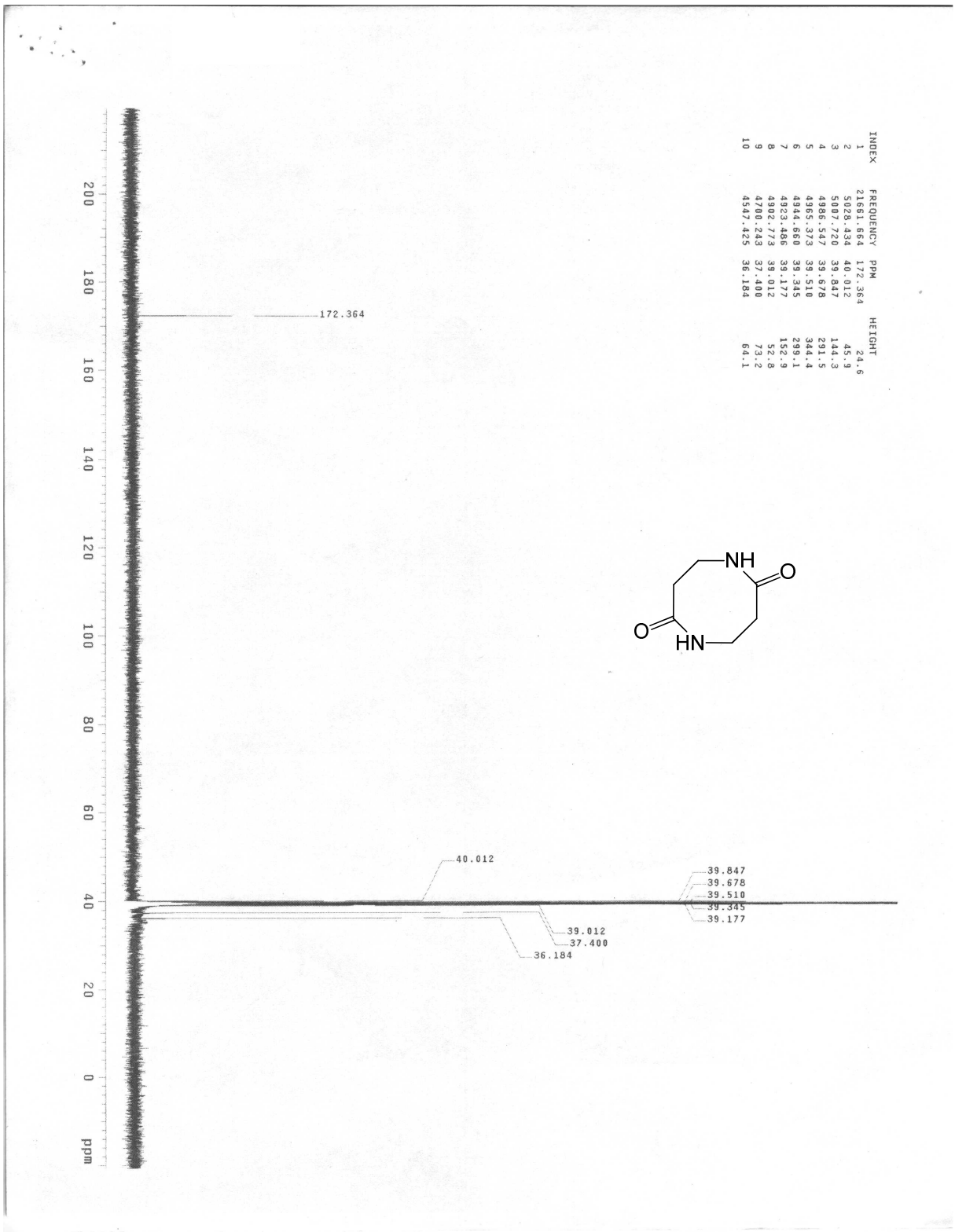


Figure S44. ^{13}C NMR spectrum of **6d**

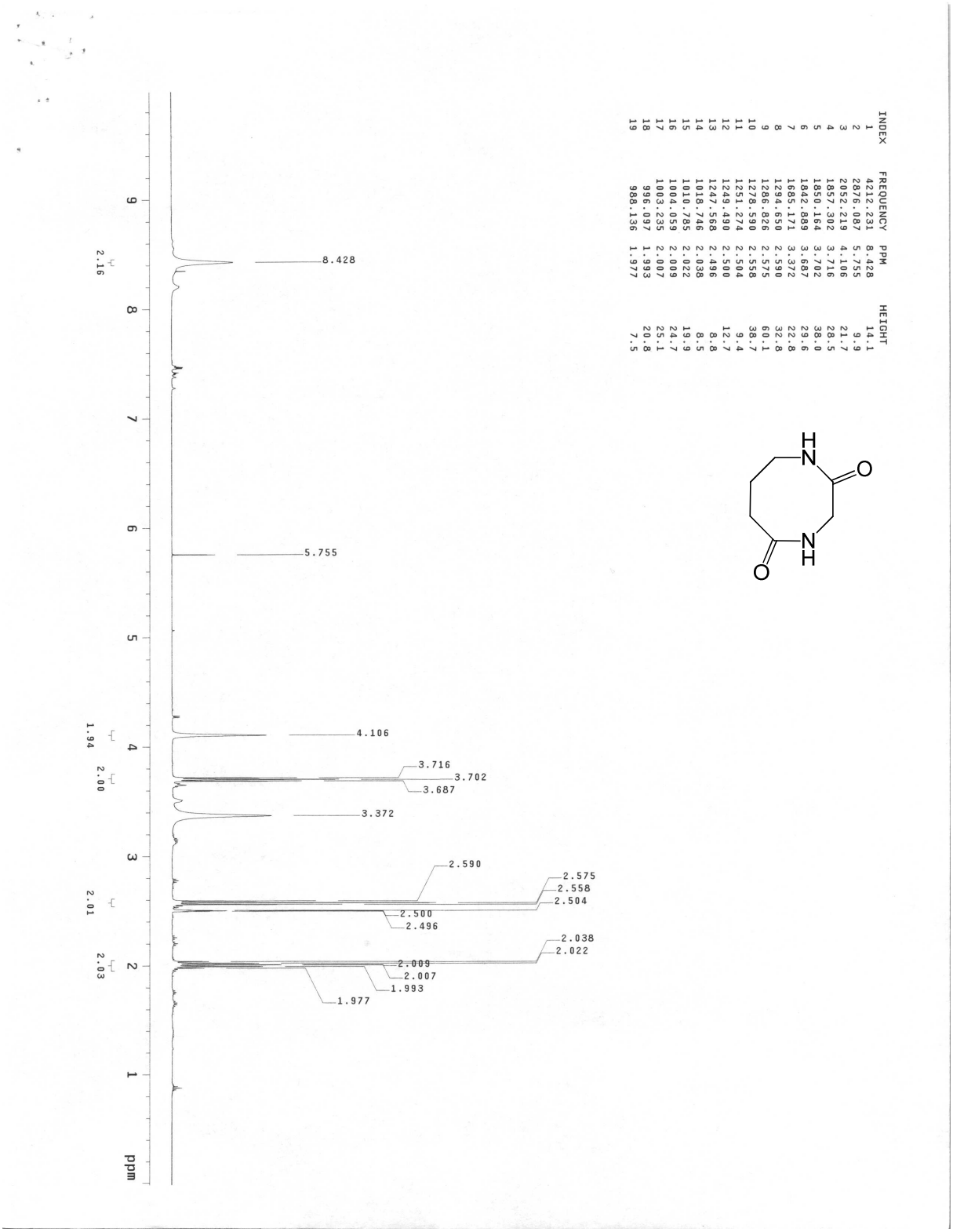


Figure S45. ^{1}H NMR spectrum of **6e**

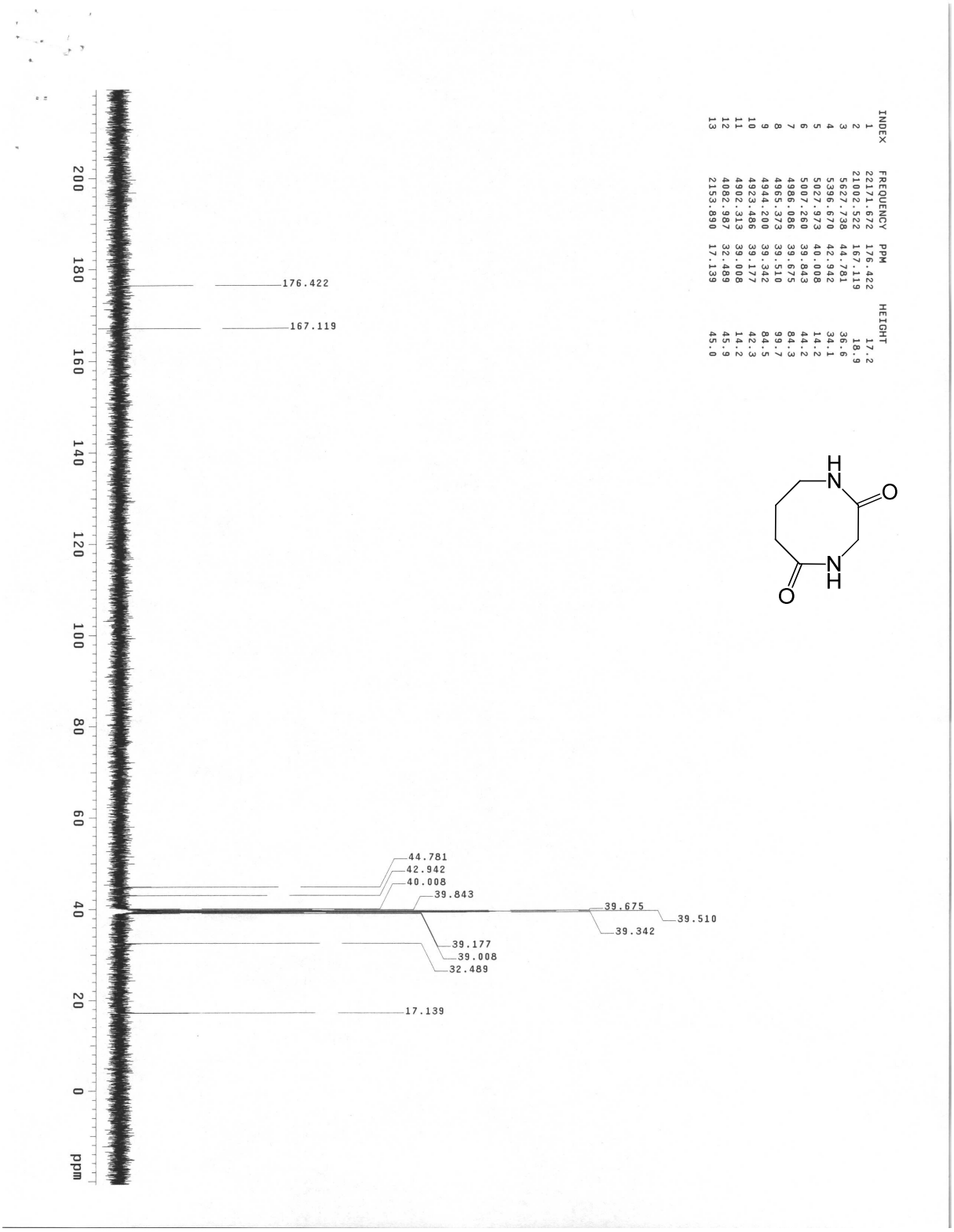


Figure S46. ^{13}C NMR spectrum of **6e**

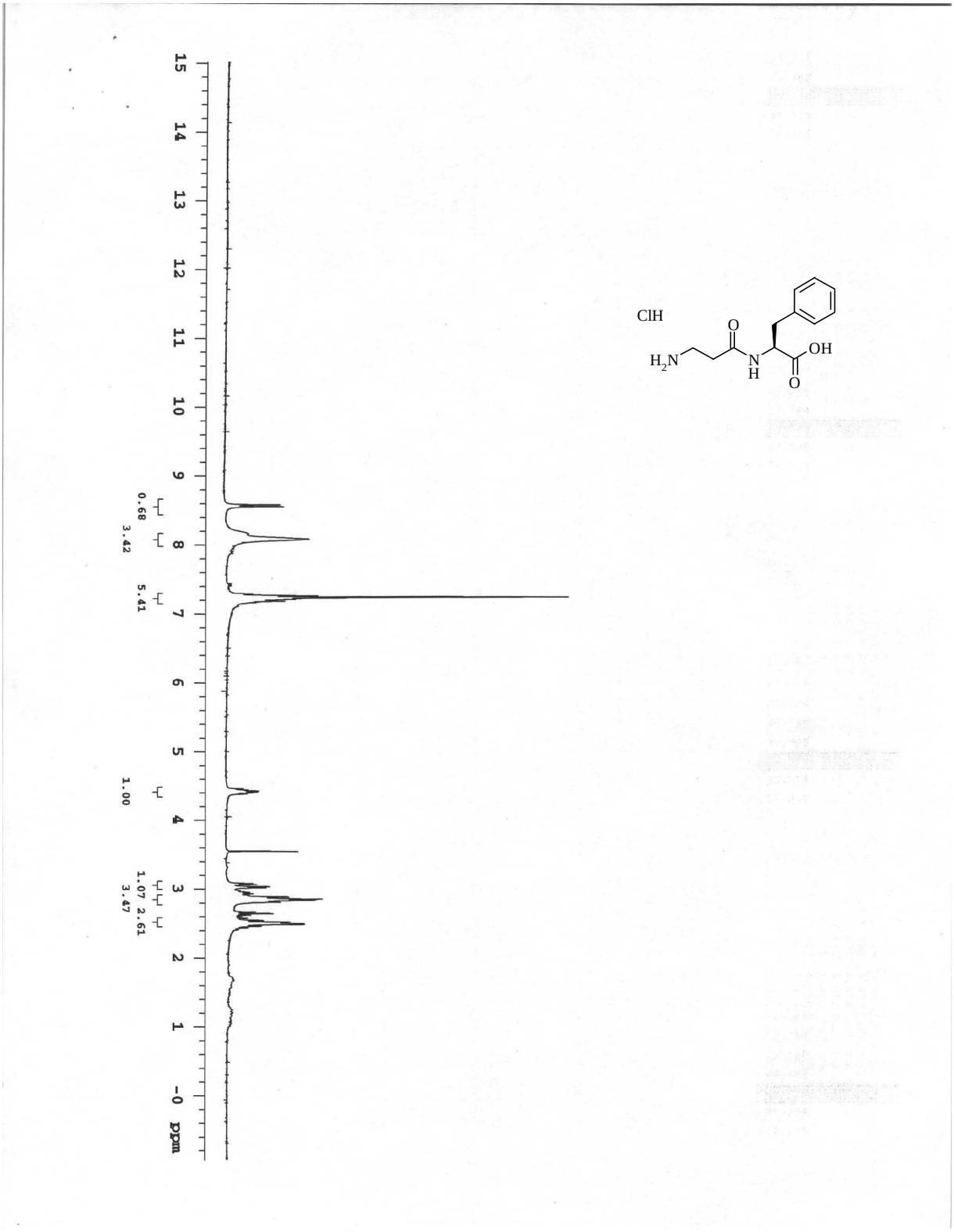


Figure S47. ^{1}H NMR spectrum of **8**

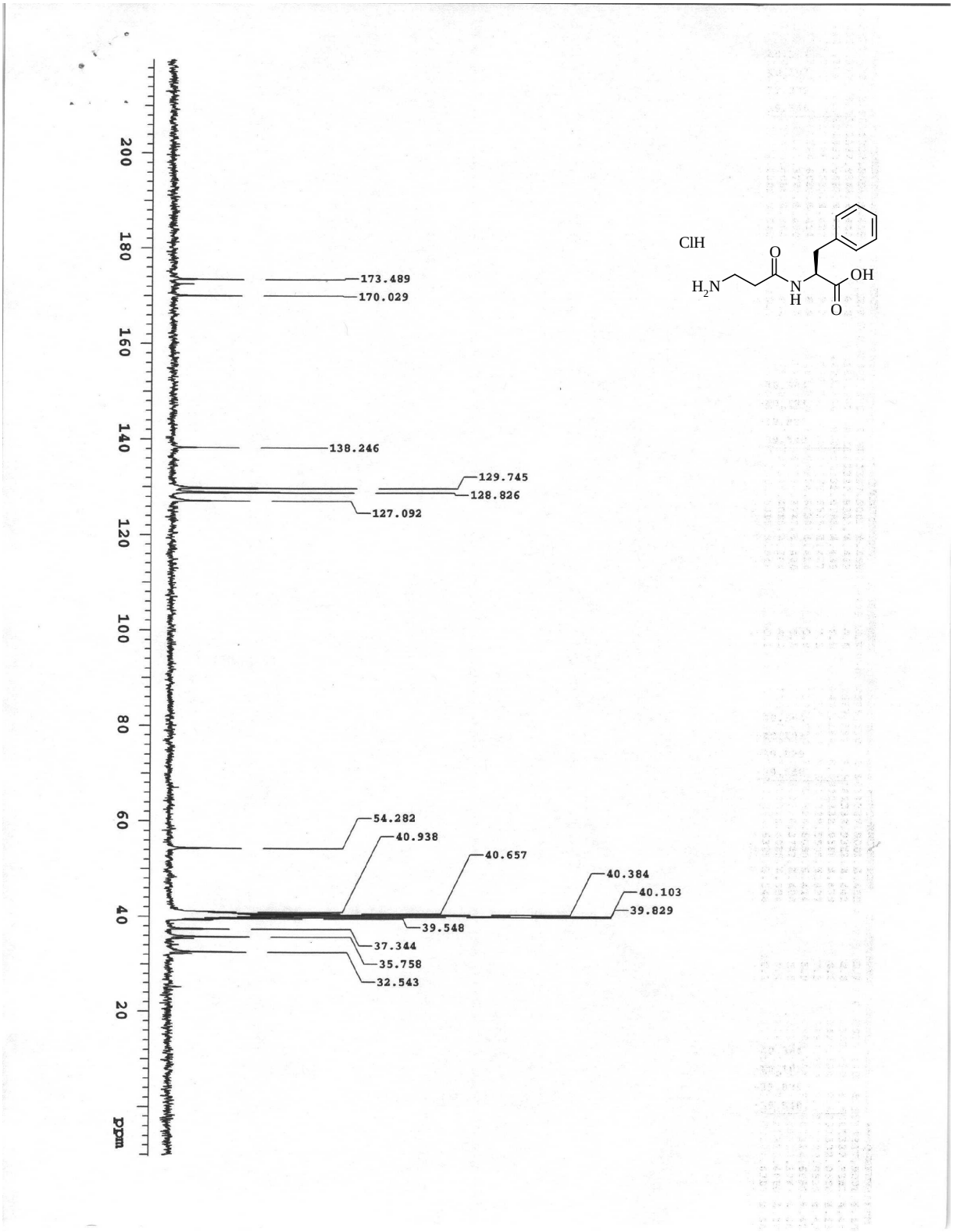


Figure S48. ^{13}C NMR spectrum of **8**

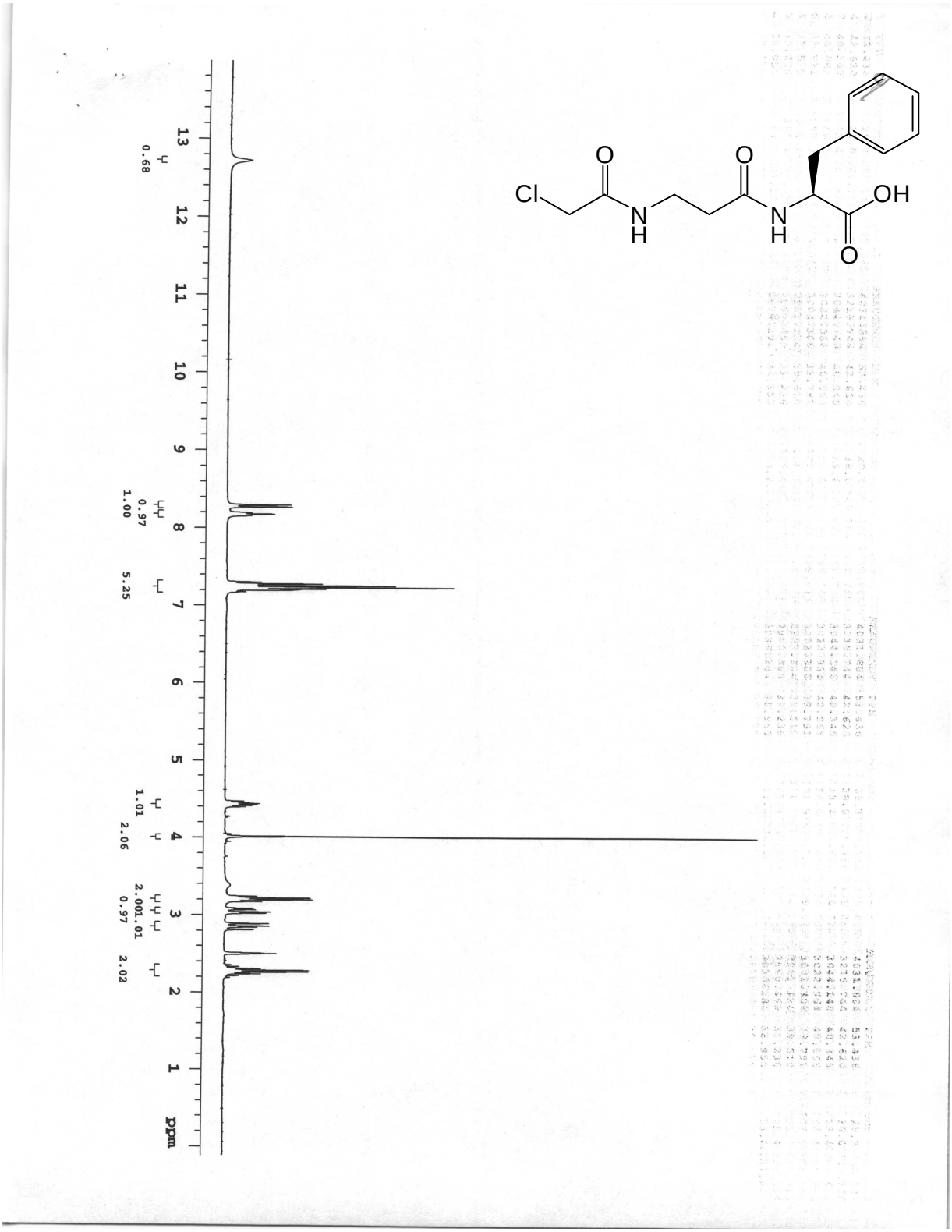


Figure S49. ^{1}H NMR spectrum of **9**

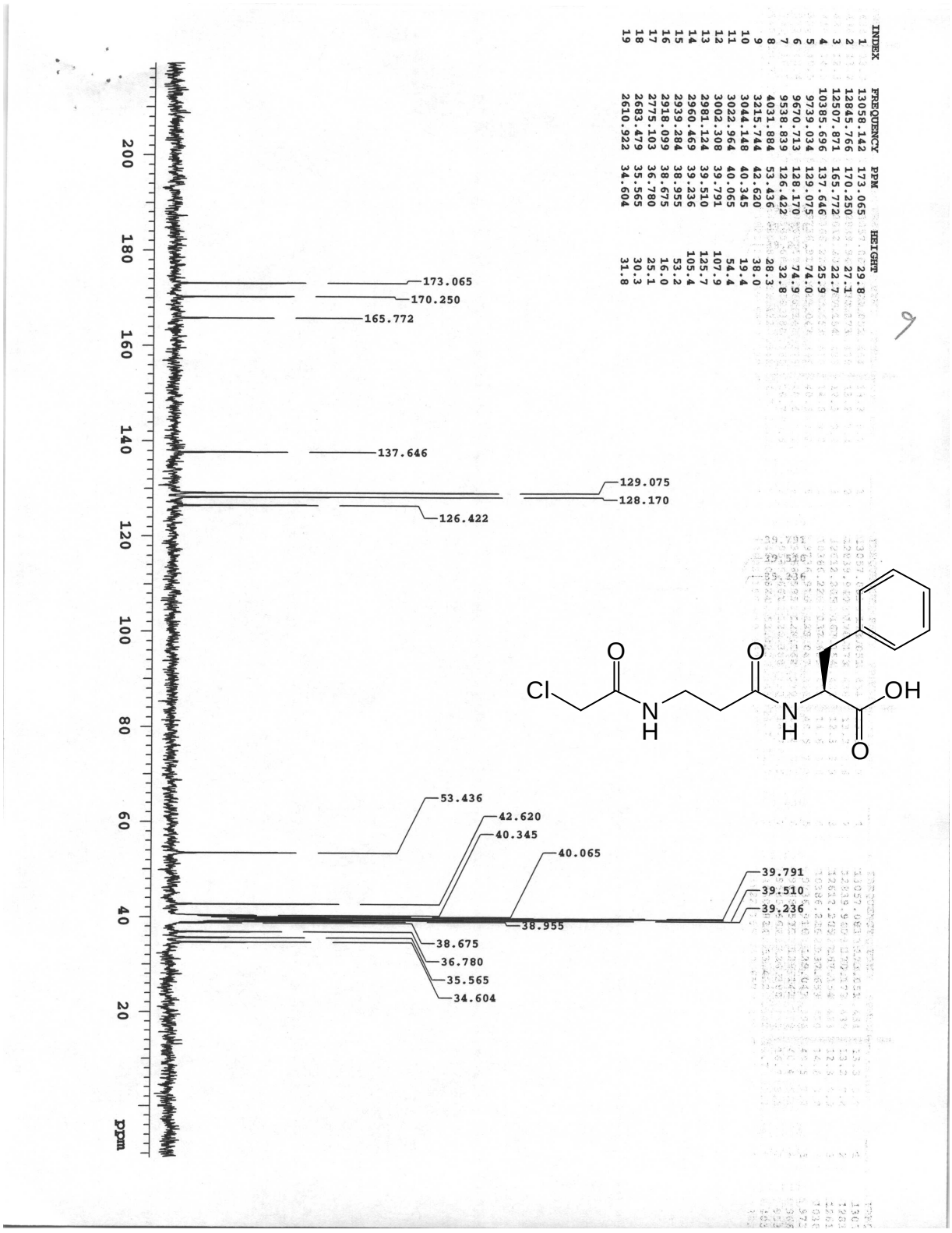


Figure S50. ^{13}C NMR spectrum of **9**

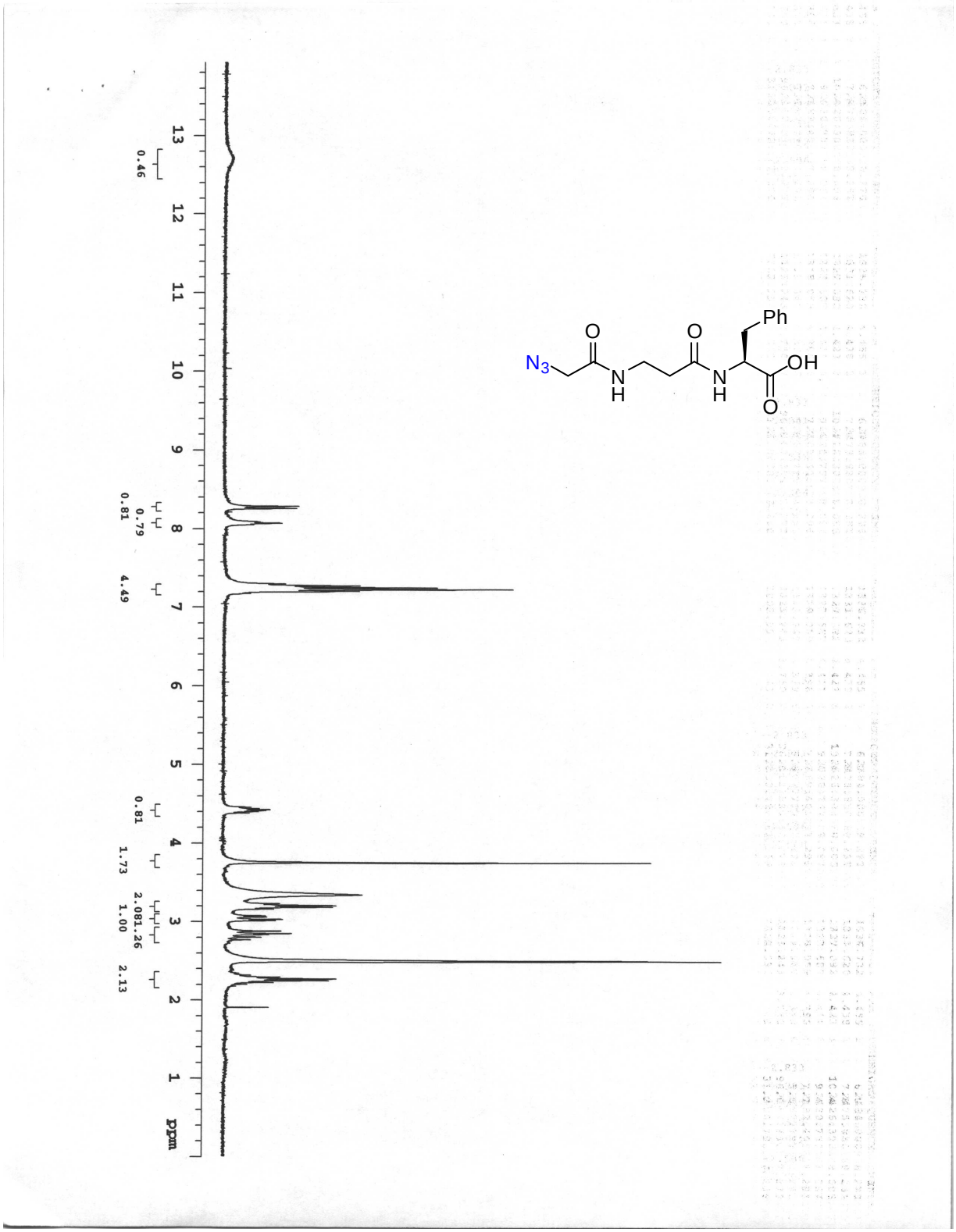


Figure S51. ^{1}H NMR spectrum of **10**

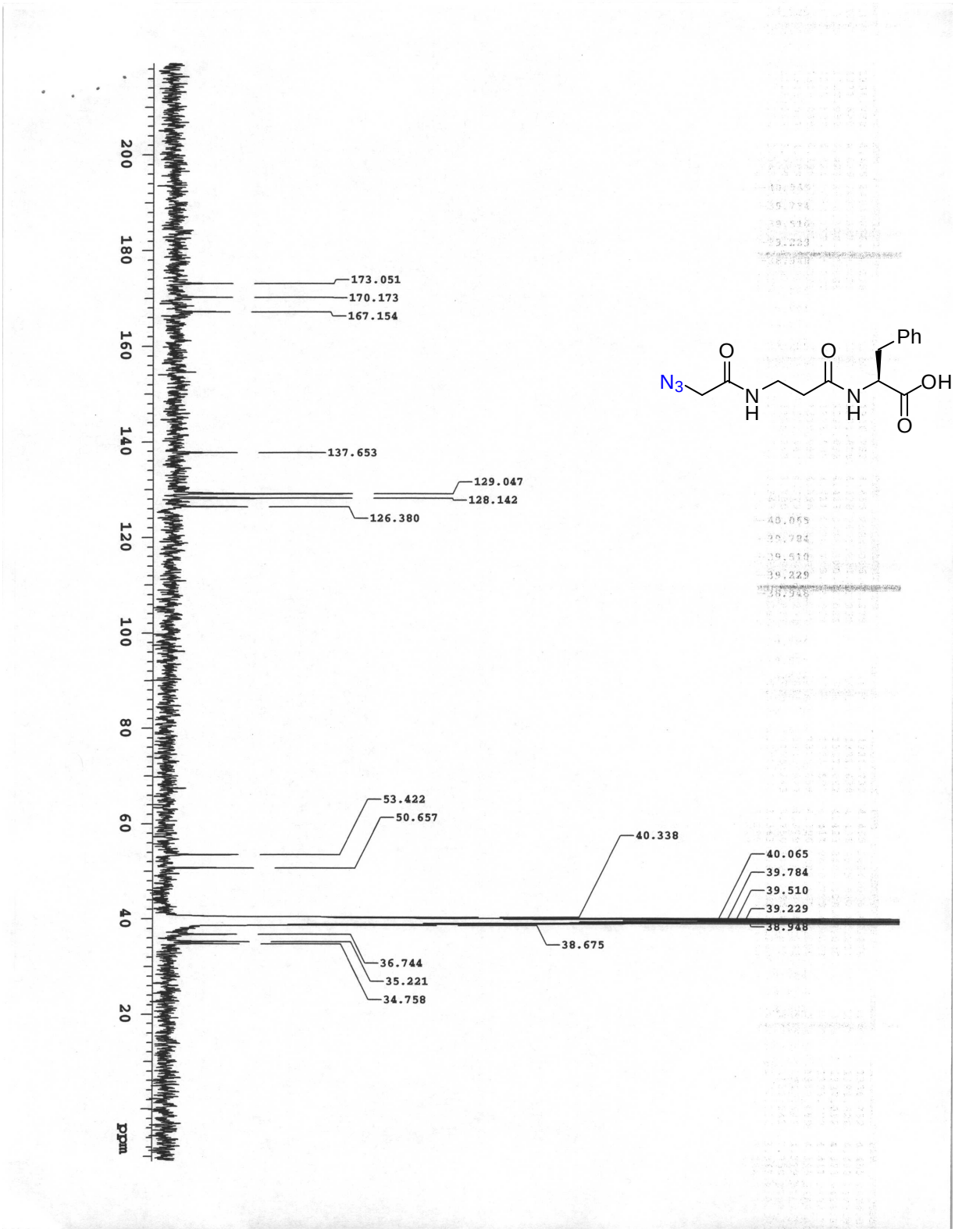


Figure S52. ^{13}C NMR spectrum of **10**

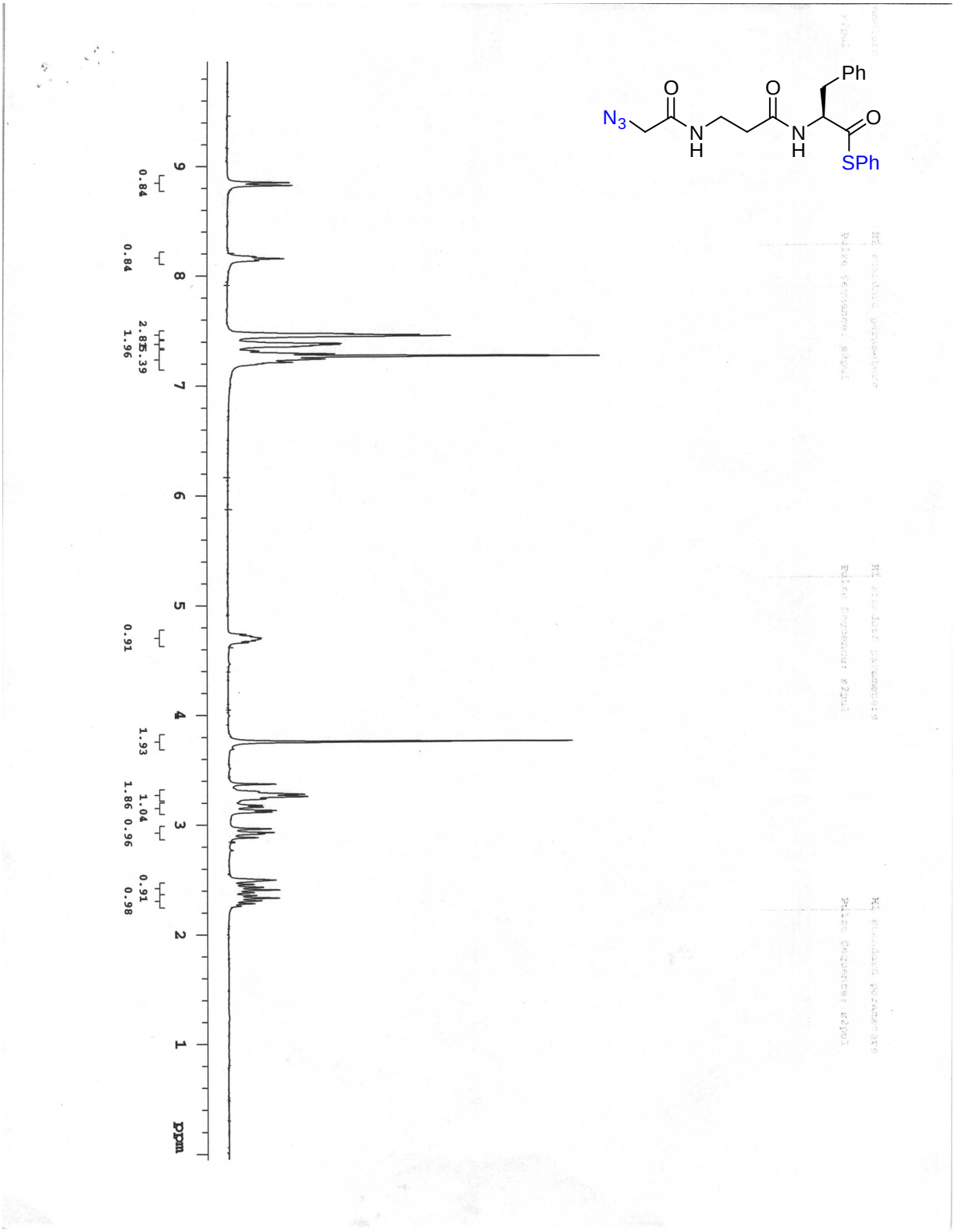


Figure S53. ^{1}H NMR spectrum of **11**

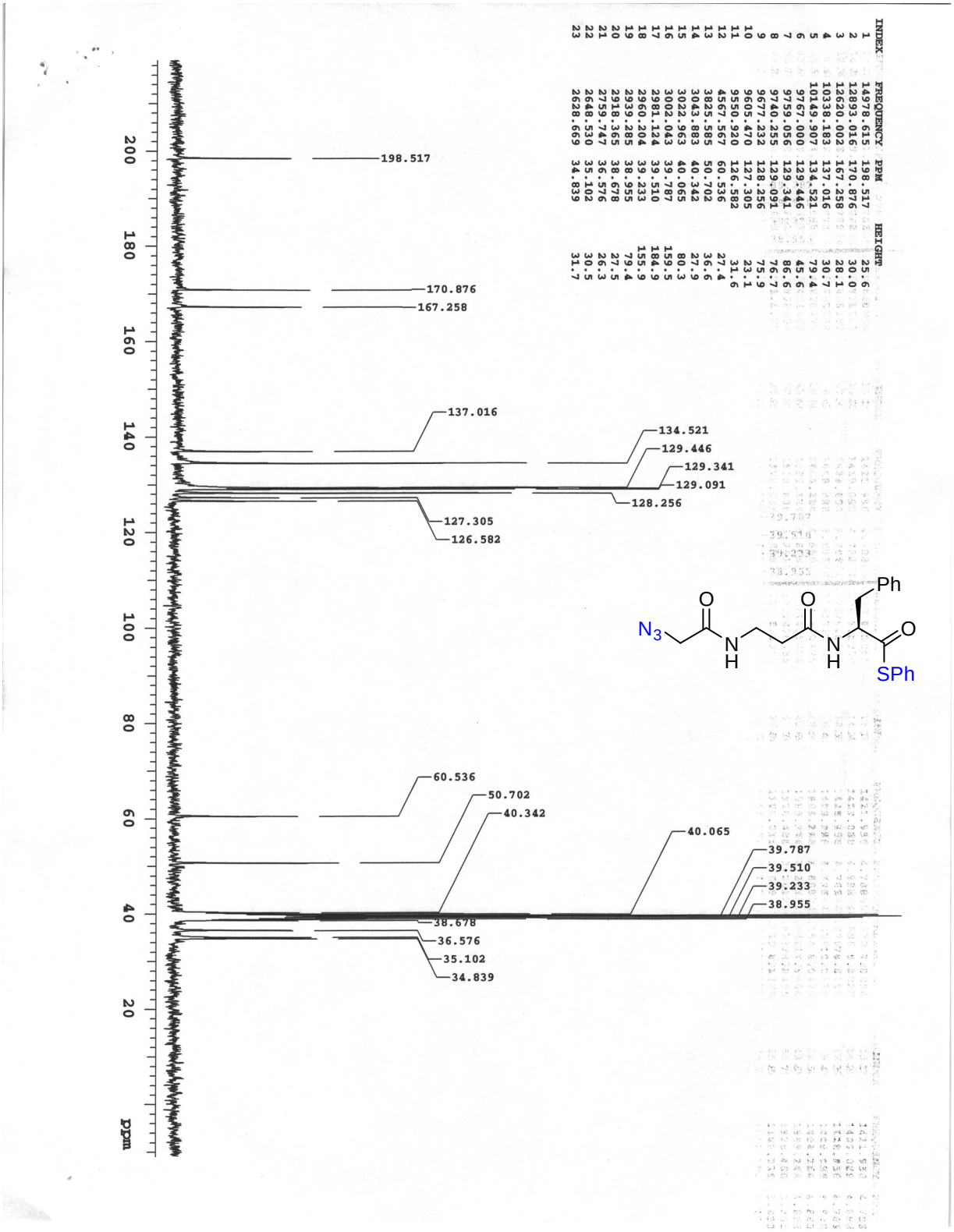


Figure S54. ^{13}C NMR spectrum of **11**

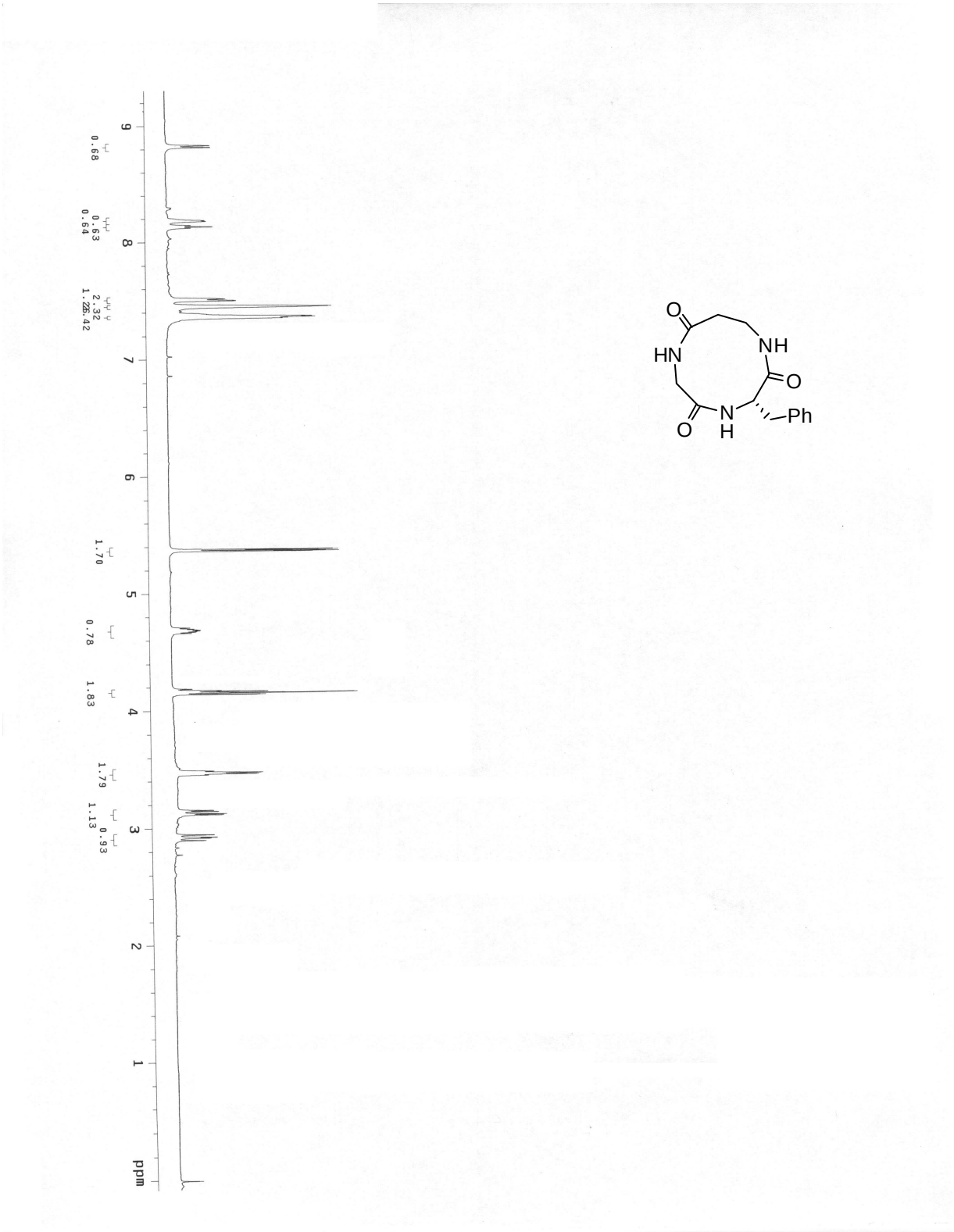


Figure S55. ^{1}H NMR spectrum of **12**

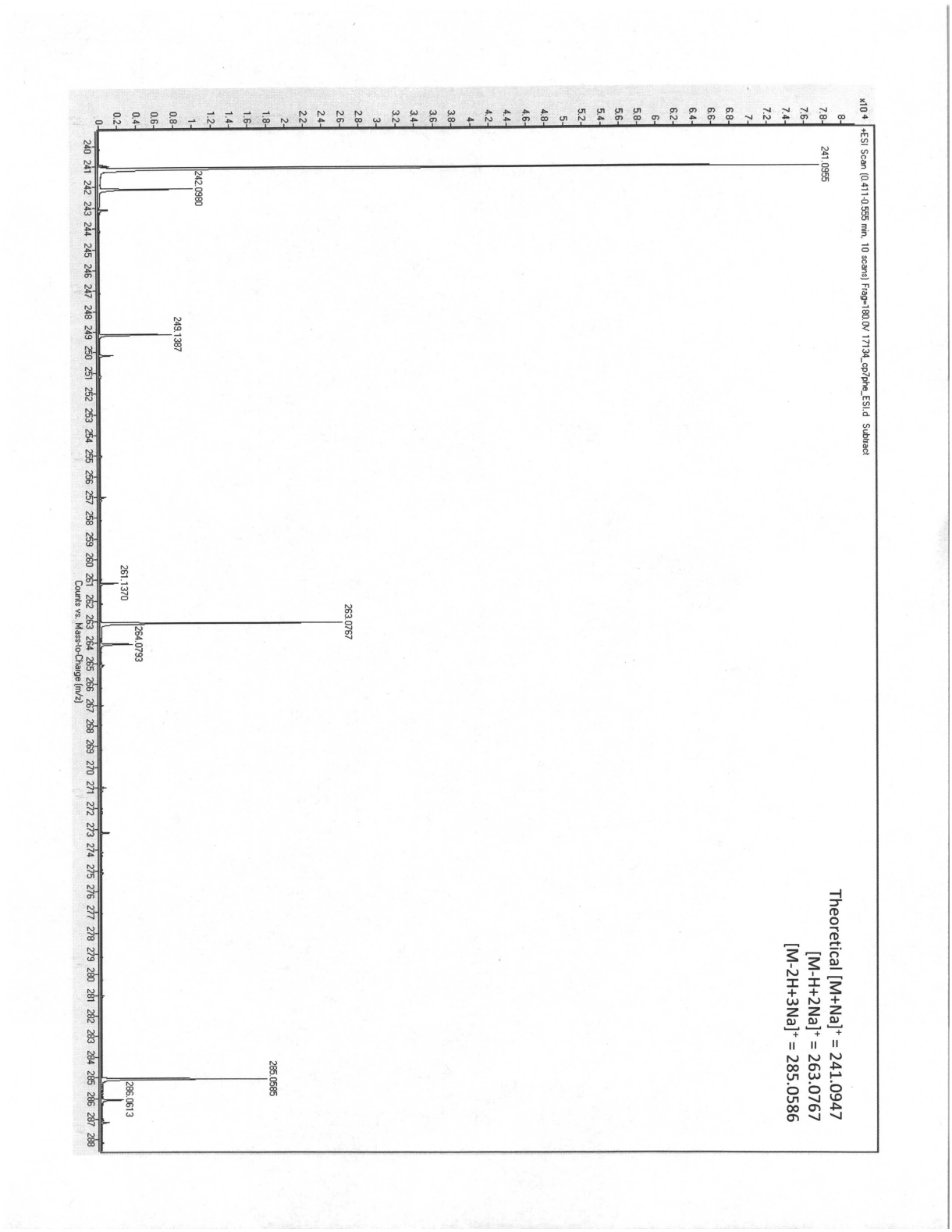


Figure S56. HRMS-ESI spectrum of **6b**

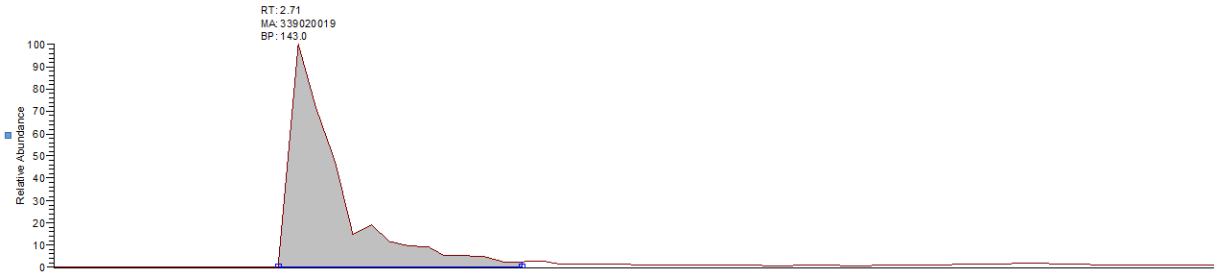


Figure S57**.** HPLC-MS chromatogram of the cyclic dipeptide **6e** was the only major compound in the sample.

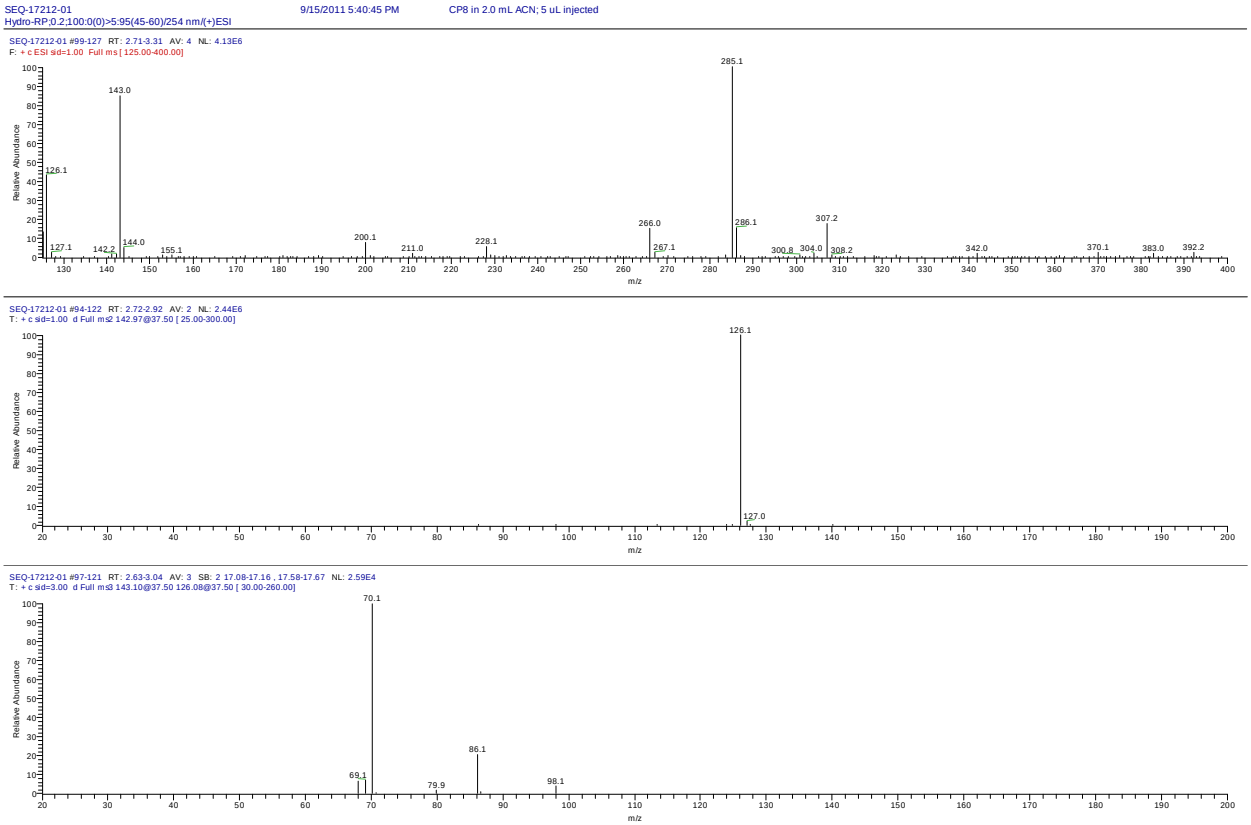


Figure S58. MS data of the cyclic dipeptide **6e** (RT 2.71 min). It produced m/z 143 [M+H]+, m/z 285 [M+H+M]+ and m/z 307 [M+Na+M]+ ions (top). The m/z 143 was dissociated to m/z 126 via loss of NH3 (middle) which was further dissociated to m/z 98 (-CO), 86 (-40 u), and 70 (-56 u) (bottom).

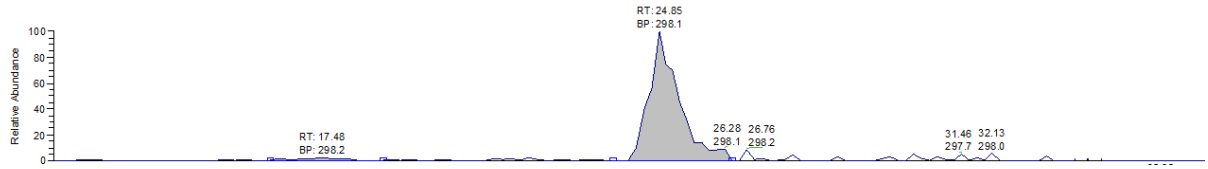


Figure S59**.** HPLC-MS chromatogram of the cyclic trieptide **12** was the only major compound in the sample.

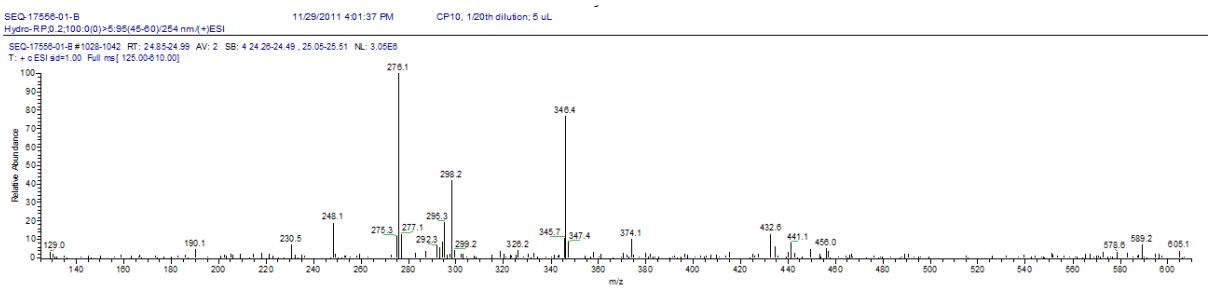


Figure S60. MS data of the cyclic tripeptide **12** (RT 24.85 min). The (+)ESI-MS m/z 276 and m/z 298 are the [M+H]+ and [M+Na]+ ions, respectively, of a MW 275 compound.

4. Computational details

4.1 Computational details for the cyclization of aza-ylides and and cartesian coordinates of stationary points

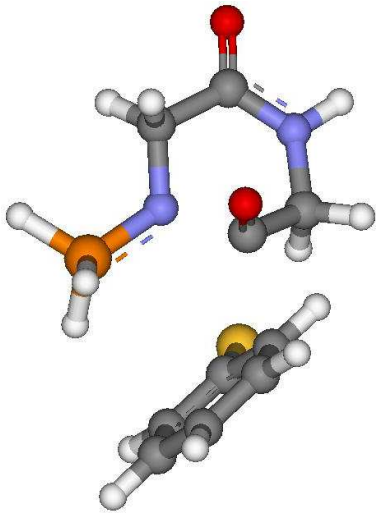
All calculations were performed with the density functional theory (DFT) using the B3LYP functional with the GAUSSIAN 03 series of programs,[1] using the Pople 6-31+G** polarized basis set. The analytical second derivatives are used to determine the nature of the stationary points and a full thermochemical analysis was performed (Table S1). Computations were performed on model compounds (PH_3 as model phosphine).

Table S1. Activation parameters

	Absolute energies (Hartree)					
	reagents			**TS**		
sequences	H	G	S	H	G	S
N3-Gly-Gly-SPh	-1.388,128006	-1.388,195938	142,975000	-1.388,109144	-1.388,169891	127,855000
N3-Gly-B-Ala-SPh	-1.427,424585	-1.427,496243	150,816000	-1.427,393015	-1.427,456292	133,178000
N3-B-Ala-Gly-SPh	-1.427,409830	-1.427,479665	146,979000	-1.427,393041	-1.427,456311	133,162000
N3-B-Ala-Aib-SPh	-1.505,986936	-1.506,061810	157,585000	-1.505,960884	-1.506,029625	144,677000
N3-B-Ala-Phe-SPh	-1.697,670034	-1.697,755638	180,170000	-1.697,652826	-1.697,731519	165,624000
N3-B-Ala-B-Ala-SPh	-1.466,701683	-1.466,773122	150,355000	-1.466,672020	-1.466,738071	139,016000

	activation parameters			kcal		
sequences	ΔH‡	ΔG‡	TΔS‡	ΔH‡	ΔG‡	TΔS‡
N3-Gly-Gly-SPh	0,01886	0,02605	-0,00719	11,8	16,3	-4,5
N3-Gly-B-Ala-SPh	0,03157	0,03995	-0,00838	19,8	25,1	-5,3
N3-B-Ala-Gly-SPh	0,01679	0,02335	-0,00657	10,5	14,7	-4,1
N3-B-Ala-Aib-SPh	0,02605	0,03219	-0,00613	16,3	20,2	-3,8
N3-B-Ala-Phe-SPh	0,01721	0,02412	-0,00691	10,8	15,1	-4,3
N3-B-Ala-B-Ala-SPh	0,02966	0,03505	-0,00539	18,6	22,0	-3,4

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-Gly-Gly-SPh (6-membered ring)



29

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.527477
O	1.066202	0.000000	2.139070
N	-1.202581	0.061268	2.163652
C	-2.542196	0.029058	1.582322
C	-2.569062	0.641935	0.178003
O	-2.281842	1.811733	-0.054747
N	-1.285478	-0.477282	-0.534087
P	-1.473435	-0.639510	-2.135258
S	-4.167801	-0.140936	-0.719511
C	-4.731748	1.192798	-1.766415
C	-4.906447	2.500472	-1.286690
C	-5.397523	3.494442	-2.136490
C	-5.740040	3.197093	-3.459199
C	-5.580674	1.893055	-3.936057
C	-5.069081	0.898094	-3.098735
H	-2.019959	0.445884	-2.856592
H	-2.236873	-1.747814	-2.521369
H	-0.224424	-0.850060	-2.760956
H	0.836125	-0.633581	-0.311847
H	0.217093	1.035842	-0.300511
H	-1.124636	0.104390	3.172194
H	-2.931944	-0.994276	1.545638
H	-4.647010	2.739033	-0.262745
H	-5.520914	4.504999	-1.757029

```
 H    -6.131524     3.973257    -4.110458
 H    -5.850404     1.647542    -4.959666
 H    -4.950758    -0.115913    -3.471807
 H    -3.207155     0.634138     2.207450
------
E(B3LYP/6-31+G**)= -1388.34371254 Hartree
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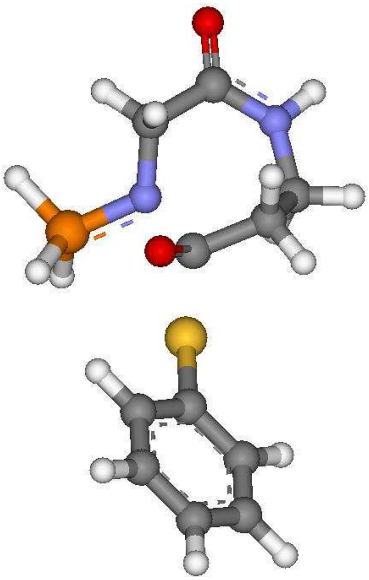
Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-Gly-βAla-SPh (7-membered ring)



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  32

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 C     0.000000     0.000000     1.530226
 O     1.073669     0.000000     2.134046
 N    -1.189255     0.045861     2.192812
 C    -2.572031     0.055428     1.695138
 C    -2.817281     0.982718     0.502342
 C    -2.560718     0.408733    -0.898332
 O    -2.320315     1.147084    -1.849214
 N    -1.128252    -0.739148    -0.579023
 P    -0.890480    -1.654851    -1.895371
 H    -1.441907    -2.942605    -1.856760
 H    -1.303434    -1.118603    -3.132852
 H     0.491810    -1.887257    -2.072930
 H     0.972960    -0.415154    -0.280340
```
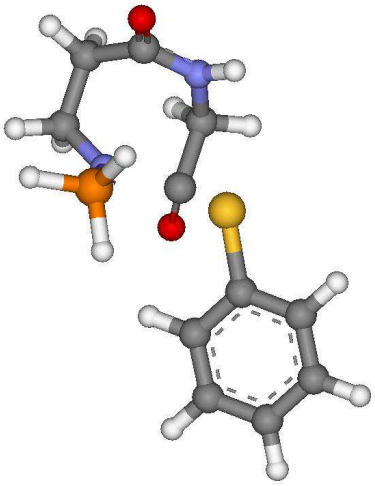

H	-0.012081	1.044592	-0.348957
H	-1.066056	0.038141	3.197590
H	-3.178976	0.405409	2.535458
H	-2.907543	-0.958890	1.454240
H	-2.218250	1.895917	0.595627
H	-3.867583	1.294115	0.494844
S	-3.790389	-1.139411	-1.240030
C	-5.006985	-0.409518	-2.328318
C	-6.358921	-0.455405	-1.949117
C	-7.346521	0.056804	-2.794086
C	-6.993969	0.635867	-4.016769
C	-5.648267	0.693248	-4.391905
C	-4.657075	0.165465	-3.560653
H	-6.630417	-0.895412	-0.994136
H	-8.389271	0.009193	-2.492228
H	-7.761252	1.038933	-4.671704
H	-5.366257	1.145488	-5.338864
H	-3.615072	0.220423	-3.851736

E(B3LYP/6-31+G**)= -1427.65765139 Hartree

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-*β*Ala-Gly-SPh (7-membered ring)



32

C	0.000000	0.000000	0.000000
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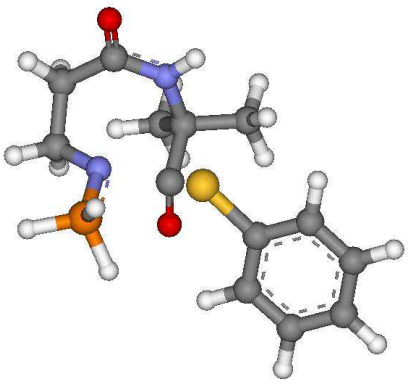
C	1.413779	0.000000	2.142895

O	1.863689	-0.967982	2.755230
N	2.160511	1.133276	1.949270
C	1.859096	2.157487	0.973171
C	2.125979	1.799794	-0.509460
O	1.690711	2.504711	-1.401313
N	1.340014	0.084398	-0.580251
P	2.210657	-1.207522	-0.988409
H	2.879968	-1.105240	-2.217000
H	1.325829	-2.295118	-1.189178
H	3.175721	-1.757857	-0.117785
H	-0.553087	0.866406	-0.379159
H	-0.532439	-0.887749	-0.364815
H	-0.483925	-0.896362	1.957097
H	-0.553163	0.866432	1.945893
H	3.115283	1.059348	2.280859
H	0.809765	2.458574	1.041940
H	2.463174	3.042628	1.188263
S	4.020381	1.145078	-0.615168
C	4.573700	1.780882	-2.187316
C	3.801113	1.686143	-3.356275
C	4.311574	2.156179	-4.569623
C	5.593992	2.707103	-4.636065
C	6.365323	2.800274	-3.473261
C	5.856760	2.349542	-2.253641
H	2.795753	1.284996	-3.313374
H	3.700041	2.090281	-5.465422
H	5.987161	3.065339	-5.583160
H	7.361118	3.233372	-3.511061
H	6.450082	2.438090	-1.348479

E(B3LYP/6-31+G**)= -1427.65788122 Hartree

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-*β*Ala-Aib-SPh (7-membered ring)

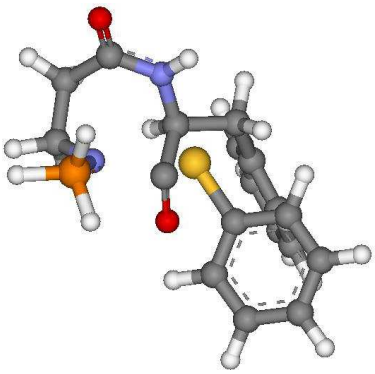


38

C	-2.912189	1.215281	0.735446
C	-3.816311	0.109360	0.128308
C	-3.130234	-0.820018	-0.874706
O	-3.620876	-0.980103	-1.992130
N	-1.998662	-1.515318	-0.525286
C	-1.106153	-1.408036	0.627540
C	-0.316519	-0.044082	0.683301
O	0.188009	0.338454	1.727948
N	-1.611067	1.241002	0.061016
P	-0.871040	2.628092	-0.297337
H	0.308735	2.939149	0.409079
H	-0.546082	2.881041	-1.640511
H	-1.728604	3.707395	0.026082
H	-2.761954	1.059200	1.811294
H	-3.430627	2.178017	0.638167
H	-4.634708	0.555976	-0.439033
H	-4.269309	-0.495967	0.921785
H	-1.624250	-2.013928	-1.324225
C	-1.825824	-1.651272	1.972532
C	-0.057615	-2.532209	0.476087
H	-0.555831	-3.503578	0.555988
H	0.453778	-2.474847	-0.487905
H	0.692693	-2.455866	1.266334
H	-1.087270	-1.666274	2.776340
H	-2.561464	-0.890580	2.225188
H	-2.332305	-2.620204	1.930739
S	0.718045	0.250057	-1.006032
C	2.419996	0.073774	-0.480798
C	3.251127	-0.797820	-1.204930
C	4.602058	-0.924675	-0.873357
C	5.135331	-0.196905	0.194764
C	4.309554	0.664373	0.923171
C	2.961662	0.811485	0.584615
H	2.835646	-1.371162	-2.028525
H	5.234180	-1.597903	-1.445962
H	6.184631	-0.299642	0.456463
H	4.715414	1.231795	1.756373
H	2.325926	1.472951	1.160419

E(B3LYP/6-31+G**)= -1506.28401397 Hartree

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-*β*Ala-Phe-SPh (7-membered ring)



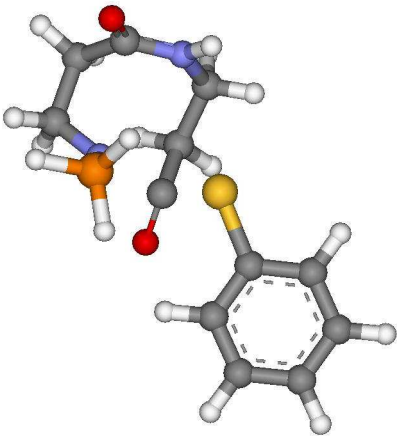
45

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.561633
C	1.412714	0.000000	2.144422
O	1.832789	-0.945108	2.810196
N	2.188211	1.106332	1.909522
C	1.937260	2.115789	0.895515
C	2.254608	1.639840	-0.554286
O	1.934887	2.296872	-1.525635
N	1.352604	-0.013691	-0.554536
P	2.053898	-1.301321	-1.205284
H	2.662797	-1.095734	-2.454247
H	1.054994	-2.265581	-1.484418
H	3.011043	-2.048044	-0.486263
H	-0.494992	0.899948	-0.383388
H	-0.588081	-0.851261	-0.366131
H	-0.481453	-0.897168	1.954994
H	-0.555313	0.865555	1.942683
H	3.145721	1.001560	2.228338
H	0.870377	2.358721	0.898193
C	2.720411	3.410831	1.239059
C	2.168544	4.682268	0.626595
C	1.065094	5.321928	1.212673
C	0.543732	6.498792	0.669793
C	1.127502	7.060920	-0.469422
C	2.231561	6.437040	-1.056761
C	2.746826	5.257758	-0.512649
H	3.769311	3.273792	0.954483
H	0.613921	4.899969	2.108850
H	2.693463	3.502278	2.330923
H	-0.309823	6.979600	1.140077

H	0.727503	7.978041	-0.892839
H	2.691945	6.865595	-1.942699
H	3.594658	4.771542	-0.985787
S	4.095308	0.781283	-0.538072
C	4.927651	1.626781	-1.871862
C	6.201778	2.167198	-1.626565
C	6.915551	2.786669	-2.654596
C	6.359773	2.891179	-3.933749
C	5.087891	2.365892	-4.178008
C	4.374808	1.728272	-3.158861
H	6.628894	2.097080	-0.630534
H	7.902509	3.193738	-2.452391
H	6.912811	3.378317	-4.731795
H	4.645490	2.448225	-5.167103
H	3.383062	1.339172	-3.354232

E(B3LYP/6-31+G**)= -1698.03267142 Hartree

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-*β*Ala-*β*Ala-SPh (8-membered ring)



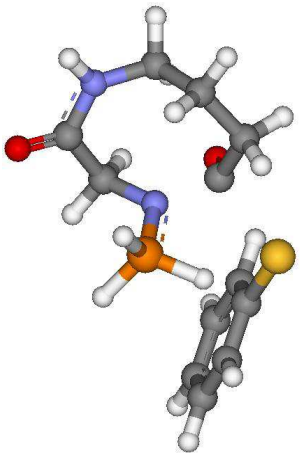
35

C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.563200
C	1.442048	0.000000	2.036596
O	2.076300	-1.054306	2.151589
N	2.037927	1.207544	2.233533
C	1.510215	2.560952	2.028760
C	0.813286	2.903164	0.694805
C	1.392962	2.466731	-0.658365
O	0.895558	2.868103	-1.697814

N	1.213493	0.592215	-0.567214
P	2.369584	-0.303232	-1.237612
H	3.555312	-0.601924	-0.536465
H	2.821369	0.156840	-2.485008
H	1.844920	-1.584604	-1.523558
H	-0.863621	0.560874	-0.377107
H	-0.123107	-1.032707	-0.348324
H	-0.552913	0.856753	1.956846
H	-0.475192	-0.908877	1.939512
H	3.025755	1.133832	2.442791
H	0.809489	2.814437	2.836354
H	2.372211	3.220163	2.145820
H	-0.232959	2.582952	0.693943
H	0.783542	3.997587	0.633861
S	3.412646	2.432671	-0.552286
C	3.891409	3.548992	-1.860616
C	3.444588	3.393339	-3.182671
C	3.882174	4.273114	-4.176468
C	4.779978	5.299936	-3.871504
C	5.232029	5.453510	-2.557158
C	4.783467	4.590790	-1.554852
H	5.122837	4.719325	-0.531324
H	5.926909	6.250796	-2.307641
H	5.122982	5.975504	-4.650009
H	3.520393	4.150829	-5.193814
H	2.737224	2.610243	-3.426264

E(B3LYP/6-31+G**)= -1466.96681296 Hartree

Cartesian coordinates for the TS associated with the cyclization of the aza-ylide thioester derived from azido-Gly-GABA-SPh (8-membered ring)



35

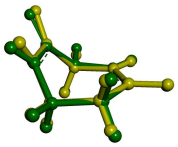
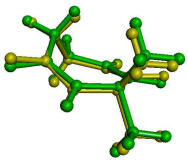
C	0.000000	0.000000	0.000000
C	0.000000	0.000000	1.531642
O	1.064314	0.000000	2.156103
N	-1.204978	0.029873	2.169371
C	-2.538754	0.234314	1.592434
C	-2.839606	1.714636	1.219754
C	-2.935677	2.052480	-0.289188
C	-1.986236	1.246492	-1.189077
O	-2.277555	0.100397	-1.537040
N	-0.478109	1.273649	-0.560891
P	0.495757	2.577787	-0.562659
H	0.661299	3.266677	0.664057
H	-0.126225	3.424386	-1.525594
H	1.820431	2.240899	-0.906960
H	1.027865	-0.206563	-0.313001
H	-0.651911	-0.770100	-0.423115
H	-1.114753	0.107181	3.175615
H	-2.662007	-0.414858	0.722795
H	-3.248082	-0.113811	2.347675
H	-2.064382	2.333043	1.686650
H	-3.785081	2.021091	1.682855
H	-2.780578	3.129609	-0.415997
H	-3.935692	1.828446	-0.672648
S	-1.802000	2.663226	-2.904751
C	-0.640066	1.764127	-3.908608
C	-0.901046	0.436674	-4.297698
C	0.021365	-0.260676	-5.081402
C	1.205591	0.351744	-5.505695
C	1.465154	1.675178	-5.137114
C	0.554381	2.373990	-4.339220
H	0.751145	3.410023	-4.074025
H	2.374274	2.167468	-5.473090
H	1.912785	-0.192633	-6.125144
H	-0.193068	-1.286117	-5.371053
H	-1.819160	-0.038767	-3.972995

E(B3LYP/6-31+G**)= -1466.96642431 Hartree

4.2 Conformational analysis of compounds 6a, 6c, 6d and 6e

A series of conformers were generated using Marvin Suite (ChemAxon Kft, Hungary)[2] and each conformer was optimized using HyperChem.[3] For both **6a** and **6c**, the most stable conformer was envelop-like. A similarity analysis between the predicted conformers for **6a** and **6c** and the Xray results show in each case high levels of overlay similarity (Table S2).

Table S2. Similarity analysis between ball and stick model of both Xray crystal structure (yellow) and theoretical conformer (green)

Entry	3D Superimpose	Overlay Similarity (%)
6a		93.7
6c		98.5

5. References

1. Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

2. Marvin Sketch 5.8.0, ChemAxon Kft, Hungary, 2012.

3. Hyperchem 8.0.6, Hypercube Inc.: Gainesville, FL, 2008.