Supporting Information For

Regiocontrolled Wacker Oxidation of Cinnamyl Azides

Angela S. Carlson, Cristian Calcanas, Ryan M. Brunner, Joseph J. Topczewski

Department of Chemistry
University of Minnesota – Twin Cities
Minneapolis, Minnesota 55455

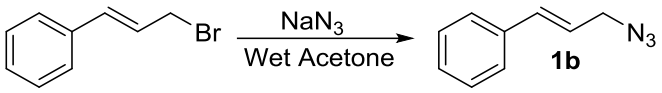
Table of Contents

Azide Precautions: Organic and inorganic azides are known to be high-energy materials and explosions have been reported with their use.[1] All of the azides reported herein were synthesized without incident; however, several precautions were taken. First, all azides synthesized herein have a C/N ratio of ≥ 3:1. Second, reactions with more than 1 mmol of azide were placed behind safety shields both in the fume hood and during rotary evaporation. Third, all waste solutions (both organic and aqueous) that could be contaminated by azide were kept segregated in specially labeled containers and were kept STRICTLY free of acid to prevent incidental formation of HN_3.

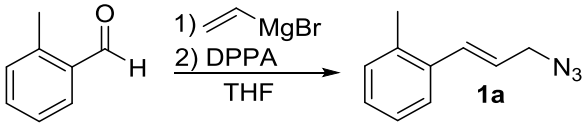
General: All reactions sensitive to air or moisture were carried out in oven-dried glassware using standard Schlenk line techniques. All reactions were mixed by magnetic stirring (100-600 rpm). All reactions conducted at elevated temperatures used aluminum block heating with an external thermocouple. Dry THF was obtained from a commercial solvent purification system using activated alumina columns and stored under a positive pressure of argon. Other reagents and solvents were purchased from commercial suppliers and were used as received. Reactions were monitored by gas chromatography or thin layer chromatography (TLC) using pre-coated plastic plates impregnated with a fluorescent indicator (254 nm). Visualization was carried out with UV light (254 nm), $KMnO_4$, or PMA stains. Column chromatography was performed using a Teledyne Isco CombiFlash R_f purification system utilizing normal phase pre-column load cartridges and gold high performance columns.

Instrumentation: All proton (^1H) NMR spectra were recorded at 400 MHz on a Bruker spectrometer. All carbon (^{13}C) NMR spectra were recorded at 101 MHz on a Bruker spectrometer. Chemical shifts are expressed in ppm and are referenced to residual solvent as an internal standard (^1H: $CHCl_3$, 7.27 ppm; ^{13}C: $CDCl_3$, 77.2 ppm). Infrared (IR) spectra were performed as a film on NaCl plates on a Nexus 670 FT-IR and are reported in cm^{-1}. Gas chromatography (GC) was performed on a Shimadzu GC-2010 Plus using a SH-Rxi-5ms 15 m column and a flame ionization detector. The GC temperature ramp was as follows: Hold at 65 ^oC (3 min), 15 ^oC/min gradient (65-225 ^oC), hold at 225 ^oC (3 min). Yields reported based on GC analysis were determined by linear regression of a 5-point calibration curve with naphthalene as the internal standard.

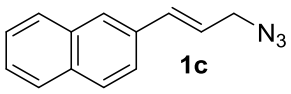
Substrate Synthesis and Characterization Data



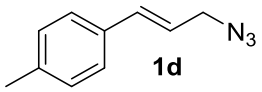
Compound 1b: To a solution of cinnamyl bromide (1.07 g, 5.45 mmol) in acetone (7 mL) at rt was added a solution of NaN_3 (1.27 g, 19.6 mmol) in H_2O (7 mL). After 18 h, the reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. This afforded compound **1b** (0.856 g, 99%) as a slightly yellow oil. Characterization data for this compound has been reported.[2] The material obtained from this method provided an identical ^{1}H NMR spectrum.



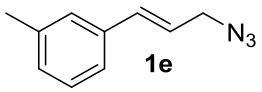
General Procedure: This procedure was adapted from prior work:[3] To a solution of 2-methylbenzaldehyde (1.0 mL, 8.6 mmol) in THF (10 mL) at 0 °C was added vinyl magnesium bromide (8.7 mL, 1.0 M in THF, 8.7 mmol). After 10 min, diphenylphosphoryl azide (2.1 mL, 10 mmol) was added and the solution was warmed to 40 °C. After 18 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-30% EtOAc in hexanes) afforded compound **1a** (1.19 g, 80%) as a yellow oil. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.



Compound 1c: A variation of the general procedure was used. Final purification by column chromatography (0-30% EtOAc in hexanes) afforded compound **1c** as a pale yellow solid in 69% yield. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.

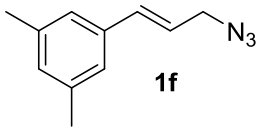


Compound 1d: A variation of the general procedure was used. Final purification by column chromatography (5% EtOAc in hexanes) afforded compound **1d** as a yellow oil in 84% yield. Characterization data for this compound has been reported.[5] The material obtained from this method provided an identical ^{1}H NMR spectrum.



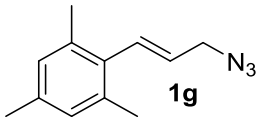
Compound 1e: A variation of the general procedure was used. Final purification by column chromatography (0-20% EtOAc in hexanes) afforded compound **1e** as a yellow oil in 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 3H), 7.15 (d, J = 6.7 Hz, 1H), 6.67 (d, J = 15.8 Hz,

1H), 6.28 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.97 (d, *J* = 6.5 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 136.1, 134.8, 129.1, 128.7, 127.5, 123.9, 122.3, 53.2, 21.5. IR (NaCl, thin film, cm^{-1}): 3033, 2920, 2098, 1604, 1488, 1441, 1348, 1232, 966, 878, 775, 692. HRMS (EI): Calculated for $C_{10}H_{11}N_3^+$, (M^+) 173.0953, found 173.0957.



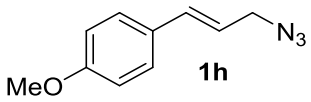
1f

Compound 1f: A variation of the general procedure was used. Final purification by column chromatography (5% EtOAc in hexanes) afforded compound **1f** as a pale green oil in 51% yield. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.



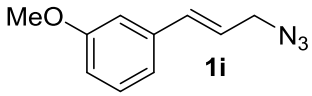
1g

Compound 1g: A variation of the general procedure was used. Final purification by column chromatography (0-10% EtOAc in hexanes) afforded compound **1g** as a slightly yellow oil in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.64 (d, *J* = 16.0 Hz, 1H), 5.78 (dt, *J* = 16.0, 6.7 Hz, 1H), 3.96 (d, *J* = 6.6 Hz, 2H), 2.31 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9, 136.0, 133.0, 133.0, 128.8, 127.3, 53.6, 21.12, 21.08. IR (NaCl, thin film, cm^{-1}): 2918, 2099, 1612, 1480, 1444, 1232, 978, 853. HRMS (EI): Calculated for $C_{12}H_{15}N_3^+$, $(M)^+$ 201.1266, found 201.1261.



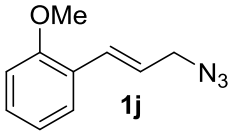
1h

Compound 1h: A variation of the general procedure was used. Final purification by column chromatography (5% EtOAc in hexanes) afforded compound **1h** as a yellow oil in 84% yield. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum



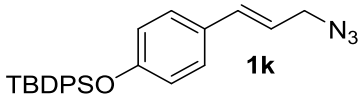
1i

Compound 1i: A variation of the general procedure was used. Final purification by column chromatography (0-15% EtOAc in hexanes) afforded compound **1i** as a yellow oil in 62% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 7.7 Hz, 1H), 7.00 – 6.89 (m, 1H), 6.85 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.64 (d, *J* = 15.7 Hz, 1H), 6.25 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.96 (d, *J* = 6.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 137.6, 134.6, 129.8, 122.9, 119.5, 114.0, 112.2, 55.4, 53.2. IR (NaCl, thin film, cm^{-1}): 3003, 2938, 2836, 2101, 1599, 1580, 1266, 1157, 1047, 970. HRMS (EI): Calculated for $C_{10}H_{11}N_3O$, (M^+) 189.0897, observed 189.0892.



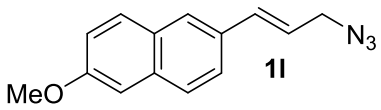
1j

Compound 1j: A variation of the general procedure was used. Final purification by column chromatography (0-10% EtOAc in hexanes) afforded compound **1j** as a yellow oil in 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.30 (td, *J* = 8.3, 1.7 Hz, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.98 (t, *J* = 8.0, 1H), 6.92 (d, *J* = 8.2 Hz, 1H) 6.31 (dt, *J* = 15.9, 6.7 Hz, 1H), 3.98 (d, *J* = 6.7 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 129.8, 129.4, 127.3, 125.2, 123.1, 120.8, 111.1, 55.6, 53.7. IR (NaCl, thin film, cm^{-1}): 3003, 2937, 2837, 2100, 1598, 1245, 752; HRMS (CI): Calculated for $C_{10}H_{15}N_4O^+$, $(M+NH_4)^+$ 207.1240, found: 207.1231.



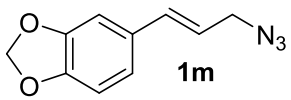
1k

Compound 1k: A variation of the general procedure was used. Final purification by column chromatography (0-10% EtOAc in hexanes) afforded compound **1k** as a yellow oil in 63% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 6.7 Hz, 4H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 4H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.54 (d, *J* = 15.7 Hz, 1H), 6.06 (dt, *J* = 15.7, 6.8 Hz, 1H), 3.89 (d, *J* = 6.7 Hz, 2H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 135.6, 134.5, 132.9, 130.1, 129.2, 128.0, 127.8, 120.2, 120.1, 53.4, 26.7, 19.6. IR (NaCl, thin film, cm^{-1}): 3072, 3032, 2932, 2858, 2099, 1604, 1509, 1258, 1114, 918. HRMS (CI): Calculated for $C_{25}H_{26}N_4SiO^+$, $(M+NH_4)^+$ 431.2262, found 431.2251.



1l

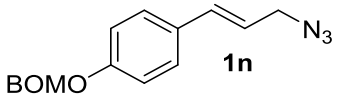
Compound 1l: A variation of the general procedure was used. Final purification by column chromatography (0-15% EtOAc in hexanes) afforded compound **1l** as a tan solid in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 3H), 7.62 – 7.55 (m, 1H), 7.20 – 7.10 (m, 2H), 6.79 (d, *J* = 15.7 Hz, 1H), 6.32 (dt, *J* = 15.7, 6.7 Hz, 1H), 4.00 (d, *J* = 6.5 Hz, 2H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 134.8, 134.5, 131.4, 129.6, 128.9, 127.2, 126.8, 124.1, 121.6, 119.2, 105.9, 55.3, 53.2. IR (NaCl, thin film, cm^{-1}): 2969, 2939, 2843, 2098, 1626, 1600, 1242, 1030, 973, 859. HRMS (CI): Calculated for $C_{14}H_{17}N_4O^+$, $(M+NH_4)^+$ 257.1397, found: 257.1385.



1m

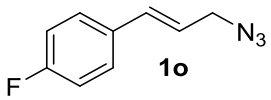
Compound 1m: A variation of the general procedure was used. Final purification by column chromatography (5% EtOAc in hexanes) afforded compound **1m** as a yellow oil in 72% yield.

Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.



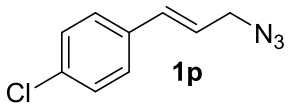
1n

Compound 1n: A variation of the general procedure was used. After 18 h (before the reaction was quenched), NaN_3 (2 equivalents) was added. After an additional 4 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compound **1n** as a yellow oil in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.29 (m, 7H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 15.7 Hz, 1H), 6.14 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.31 (s, 2H), 4.74 (s, 2H), 3.94 (d, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 137.3, 134.3, 130.1, 128.6, 128.2, 128.1, 128.0, 120.8, 116.6, 92.4, 70.2, 53.3. IR (NaCl, thin film, cm^{-1}): 3064, 3033, 2900, 2100, 1607, 1510, 1226, 1088, 1003, 845, 738, 698. HRMS (ESI): Calculated for $C_{17}H_{17}N_3NaO_2^+$, $(M+Na)^+$ 318.1213, found 318.1228.



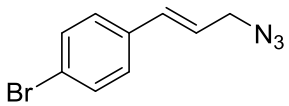
1o

Compound 1o: A variation of the general procedure was used. After 18 h (before the reaction was quenched), NaN_3 (2 equivalents) was added. After an additional 4 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-20% EtOAc in hexanes) afforded compound **1o** as a yellow oil in 80% yield. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.



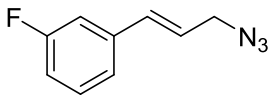
1p

Compound 1p: A variation of the general procedure was used. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compound **1p** as a yellow oil in 63% yield. Characterization data for this compound has been reported.[4] The material obtained from this method provided an identical ^{1}H NMR spectrum.

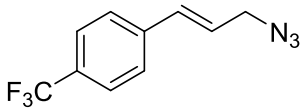


Compound 1q: A variation of the general procedure was used. After 5 min following the addition of DPPA (before the reaction was quenched), NaN_3 (1.1 equiv) was added. After an additional 48 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$),

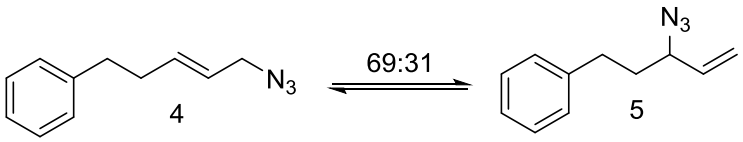
filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compound **1q** as a yellow oil in 60% yield. Characterization data for this compound has been reported except for an HRMS.[6] The material obtained from this method provided an identical ^{1}H NMR spectrum. HRMS (CI): Calculated for $C_9H_9NBr^+$, $(M-N_2+H)^+$ 209.9913, found: 209.9921.



Compound 1r: A variation of the general procedure was used. After 5 min following the addition of DPPA (before the reaction was quenched), NaN_3 (1.1 equiv) was added. After an additional 48 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compound **1r** as a yellow oil in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (td, *J* = 7.9, 6.0 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.11 (dt, *J* = 10.1, 2.1 Hz, 1H), 6.98 (tdd, *J* = 8.3, 2.6, 1.0 Hz, 1H), 6.63 (d, *J* = 15.7 Hz, 1H), 6.26 (dt, *J* = 15.8, 6.5 Hz, 1H), 3.97 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (d, J_{C-F} = 246.4 Hz), 138.5 (d, J_{C-F} = 8.1 Hz), 133.4 (d, J_{C-F} = 2.0 Hz), 130.3 (d, J_{C-F} = 8.1 Hz), 124.1, 122.7 (d, J_{C-F} = 3.0 Hz), 115.2 (d, J_{C-F} = 21.2 Hz), 113.3 (d, J_{C-F} = 22.2 Hz), 52.9. IR (NaCl, thin film, cm^{-1}): 2102, 1584, 1446, 1269, 1145. HRMS (CI): Calculated for $C_9H_9N_2F^+$, $(M-N_2+H)^+$ 150.0714, found: 150.0717.



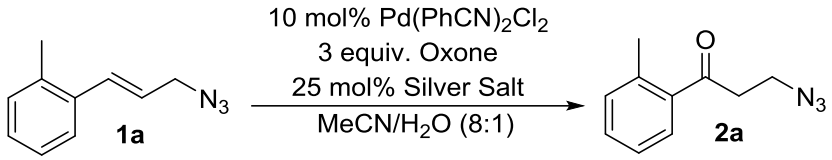
Compound 1s: A variation of the general procedure was used. After 2 h following the addition of DPPA (before the reaction was quenched), NaN_3 (1 equiv) was added. After an additional 18 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compound **1s** as a yellow oil in 53% yield. Characterization data for this compound has been reported.[7] The material obtained from this method provided an identical ^{1}H NMR spectrum.



Compounds 4 and 5: A variation of the general procedure was used. After 5 min following the addition of DPPA (before the reaction was quenched), NaN_3 (1.1 equiv) was added. After an additional 48 h, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (0-60% EtOAc in hexanes) afforded compounds **4** and **5** as a yellow oil in 70% yield. Compounds **4** and **5** were isolated as a mixture in a 69:31 ratio. ^{1}H NMR data given below is

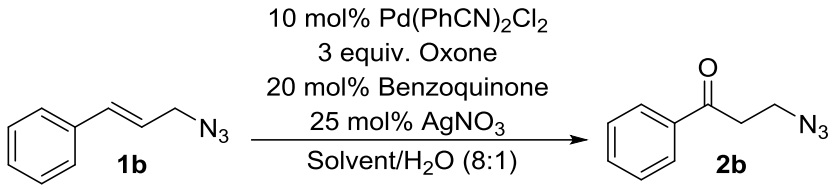
based off of idealized integrations of the resulting mixture: ^{1}H NMR (400 MHz, $CDCl_3$) **4**: δ 7.34 – 7.28 (m, 3H), 7.25 – 7.17 (m, 1H), 5.86 – 5.74 (m, 1H), 5.56 (dtt, *J* = 14.9, 6.6, 1.4 Hz, 1H), 3.71 (d, *J* = 6.7 Hz, 2H), 2.81 – 2.66 (m, 2H), 2.43 (q, *J* = 7.2 Hz, 2H); **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.25 – 7.17 (m, 2H), 5.86 – 5.74 (m, 1H), 5.33 – 5.26 (m, 2H), 3.83 (apparent q, *J* = 7.4 Hz, 1H), 2.81 – 2.66 (m, 2H), 1.97 – 1.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) (reported for the mixture of **4** and **5**): δ 141.5, 141.1, 135.9, 135.7, 128.6, 128.5, 128.5, 128.5, 126.2, 126.1, 123.7, 118.5, 64.2, 52.8, 35.9, 35.6, 34.1, 32.0. IR (NaCl, thin film, cm^{-1}): 3064, 3027, 2927, 2858, 2097, 1496, 1454, 1242. HRMS (CI): Calculated for $C_{11}H_{17}N_4^+$, $(M+NH_4)^+$ 205.1448, found: 205.1444.

General Procedures for the Optimization of the Wacker Oxidation



Silver salt screen. A stock solution of azide **1a** (149.9 mg, 0.866 mmol) and naphthalene (23.3 mg, 0.182 mmol) was prepared in MeCN (4.5 mL). Separate vials were each charged with $Pd(PhCN)_2Cl_2$ (2.0-2.3 mg, 5.2-6.0 µmol) and either KNO_3 or AgX (14-16 µmol). To each vial, MeCN (100 µL), H_2O (50 µL), and 300 µL of the stock azide solution were added. The vials were sealed under air at rt. After 15 min, Oxone (49-57 mg, 0.16-0.19 mmol) was added to each vial. After 24 h, each reaction was diluted with H_2O (1 mL) and EtOAc (1 mL). The phases were separated and the organic layer was analyzed by GC to determine the percent yield. All of the reactions were run in duplicate and the average values are reported.

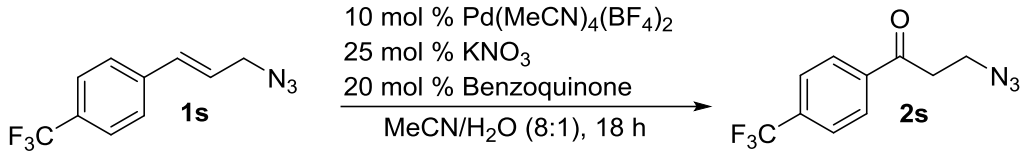
Evaluating the catalyst, additives, and procedure. Stock solutions were prepared immediately prior to use as follows: A stock solution of **1a** (116.2 mg, 0.672 mmol) and naphthalene (18.6 mg, 0.145 mmol) was prepared in MeCN (2.2 mL). A solution of $Pd(MeCN)_4(BF_4)_2$ (13.3 mg, 30.0 µmol) was prepared in 500 µL MeCN. A solution of benzoquinone (13.4 mg, 0.124 mmol) was prepared in 1100 µL MeCN. A solution of KNO_3 (11.8 mg, 0.117 mmol) was prepared in 250 µL H_2O. A solution of $AgNO_3$ (20.5 mg, 0.121 mmol) was prepared in H_2O (350 µL). The reactions were each run in separate vials and the vials were charged as follows: with either catalyst $Pd(MeCN)_4(BF_4)_2$ solution (100 µL) or $Pd(PhCN)_2Cl_2$ (2.2-2.6 mg, 5.7-6.8 µmol), MeCN (100 µL), additive solution (50 µL of $AgNO_3$ solution, KNO_3 solution, or blank H_2O), benzoquinone solution (100 µL), and solution of azide with standard (300 µL). The final volume of all reaction solutions was 450 µL (8:1 MeCN: wter). The vials were sealed under air at rt. **Procedure A:** After 15 min, Oxone (53-58 mg, 0.17-0.19 mmol) was added to each vial. After 24 h at rt, each reaction was diluted with H_2O (1 mL) and EtOAc (1 mL). The phases were separated and the organic layer was analyzed by GC to determine percent yields. **Procedure B:** Oxone (49-57 mg total, 0.16-0.19 mmol) was added in 0.5 equiv. portions. The first portion was added after 1 h. Subsequent additions were performed every 12 h. After an additional 12 hours (72 h total), each reaction was diluted with H_2O (1 mL) and EtOAc (1 mL). The phases were separated and the organic layer was analyzed by GC to determine percent yields. All of the optimization screens were run in duplicate and the average values are reported.



Solvent Screen. A stock solution of **1b** (116 mg, 0.740 mmol) and dodecane (23.3, 0.137 mmol) was prepared in 1100 µL DCM. This solution was transferred to separate vials in 100 µL portions and concentrated. The residue of azide and standard was dissolved in a respective solvent (400 µL) and H_2O (50 µL) was added. To the vial, $Pd(PhCN)_2Cl_2$ (2.2-2.9 mg, 5.7-7.8 µmol), $AgNO_3$ (2.7-4.6 mg, 16-27 µmol), and benzoquinone (1.7-3.8 mg, 16-35 µmol) were added sequentially. The vials were sealed under air at rt. After 15 min, Oxone (59.2-85.5 mg, 193-280 µmol) was added to each vial. After 18 h, each reaction was diluted with H_2O (1 mL) and EtOAc (1 mL). The phases were separated and the organic layer was analyzed by GC to determine the yield. All of the reactions were run in duplicate and the average values are reported.

entry	solvent	1b remaining (%)	2b (%)
1	MeCN	0	80
2	MeCN	0	76
3	DMF	17	7
4	DMF	24	6
5	DMA	54	20
6	DMA	40	23
7	DME	56	3
8	DME	60	2
9	^{t}BuOH	1	0
10	^{t}BuOH	1	2

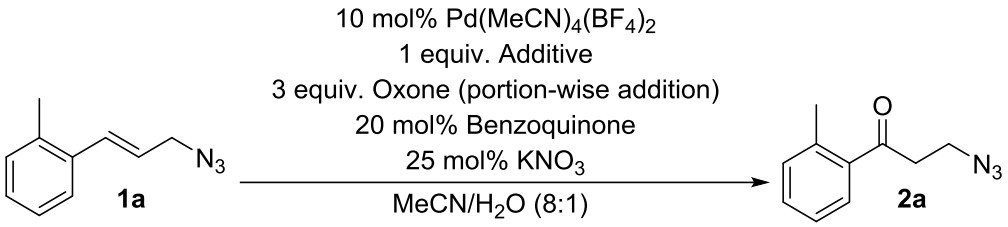
Temperature Screen – This screen was performed using the same procedure as the additive screens.[a]



entry	temperature (ºC)	1s remaining (%)	2s (%)
1	20	53	7
2	40	42	10
3	50	54	11
4	60	55	11

[a]The reported yield is uncalibrated and naphthalene was used as an internal standard. The response factor used was for compound **1s**. The yield differs from the isolated yield due to the difference in pre-catalyst and error in the calibration.

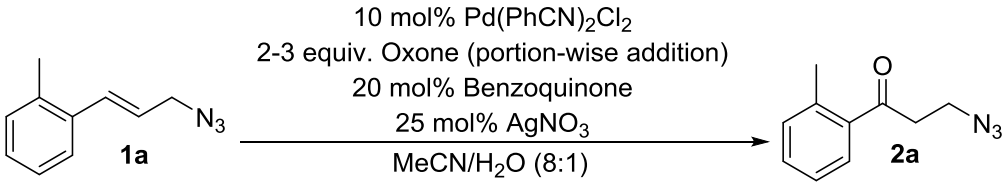
Additive Screen for Functional Group Tolerance



Additive screen. A stock solution of **1a** (184 mg, 1.07 mmol) and naphthalene (27.2 mg, 0.212 mmol) was prepared in MeCN (5.4 mL). Individual 4 mL vials were charged with 900 µL portions of this solution. One additive was added individually to each vial as follows: chromone (28.0 mg, 0.192 mmol), (2-bromoethyl)benzene (31.9 mg, 0.172 mmol), 2,6-lutidine (21.1 mg, 0.197 mmol), 4-phenyl-1-butene (30.8 mg, 0.233 mmol). Independently, a solution of $Pd(MeCN)_4(BF_4)_2$ (32.2 mg, 72.4 µmol) and benzoquinone (13.4 mg, 0.124 mmol) was prepared in 1.3 mL MeCN. A solution of KNO_3 (18.2 mg, 0.180 mmol) was prepared in 650 µL H_2O.

Separate vials were charged with 100 µL catalyst solution, 50 µL KNO_3 solution, and 300 µL of the respective additive solution containing azide and starting material. The final volume of all reaction solutions was 450 µL. The vials were sealed under air at rt. After 15 min, Oxone (35-39 mg, 0.11-0.13 mmol) was added to each vial. After 24 h, another portion of Oxone (16–19 mg, 51-63 µmol) was added. After an additional 12 h, each reaction was diluted with H_2O (1 mL) and EtOAc (1 mL). The phases were separated and the organic layer was analyzed by GC to determine percent yields. All of the other additives were tested using this general procedure. All of the additive screens were run in duplicate and the average values are reported.

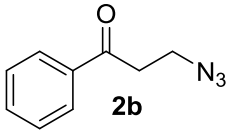
General Procedure and Characterization Data for the Substrate Scope of the Wacker Oxidation



General Procedure: On the benchtop, a 20 mL vial was charged with $Pd(PhCN)_2Cl_2$ (22.4 mg, 58.4 µmol), $AgNO_3$ (29.8 mg, 175 µmol), and benzoquinone (12.7 mg, 118 µmol). The solids were dissolved in MeCN (4 mL) and H_2O (0.5 mL). After 5 min at rt, **1a** (109 mg, 632 µmol) was added neat. Oxone (359 mg total, 1.17 mmol) was added in 0.5 equiv. portions (t = 5 min, 1 h, 12 h, 24 h). After an additional 12 h (36 h total), the reaction was poured onto acetic acid (20 mL, 0.5 M in H_2O) and brine. The resulting solution was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2a** as a yellow oil in 82% and 79% yield in duplicate trials. The average of 81% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.46 – 7.37 (m, 1H), 7.34 – 7.18 (m, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 3.18 (t, *J* = 6.4 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7, 138.7, 137.0, 132.2, 131.8, 128.7, 125.8, 46.4, 40.2, 21.5. IR (NaCl, thin film, cm^{-1}): 2930, 2105, 1685, 1456,

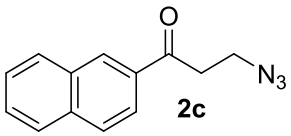
1366, 1287, 1212, 977, 757. HRMS (ESI): Calculated for $C_{10}H_{11}N_3ONa^+$, $(M+Na)^+$ 212.0794, found 212.0802.

Note: Several of the β-azido-ketone products were unstable under basic conditions. Products of azide elimination are initially formed, followed by rapid decomposition. Improved and reproducible yields were obtained when the extraction solution and column conditions were run in the presence of AcOH as a buffer. Contact time with silica gel was also minimized to prevent decomposition by reducing the amount of silica and by equilibrating the column before loading the sample.



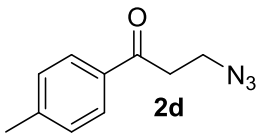
2b

Compound 2b: A variation of the general procedure was used. Five portions of Oxone were added (t = 20 min, 3 h, 12 h, 24 h, 36 h; total reaction time = 48 h). Final purification by column chromatography (10% EtOAc in hexanes) afforded ketone **2b** (81.7 mg, 77%) as a slightly yellow oil. In a duplicate experiment, the product was isolated in 75%. The average of 76% is reported. Characterization data for this compound has been reported.[6] The material obtained from this method provided an identical ^{1}H NMR spectrum.



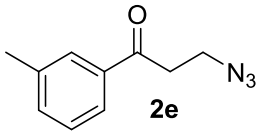
2c

Compound 2c: A variation of the general procedure was used. Six portions of Oxone were added (t = 1, 12, 24, 36, 48, 60 h; total reaction time = 72 h). Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2c** as a tan solid in 85% and 86% yield in duplicate trials. The average of 86% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.05 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.69 – 7.54 (m, 2H), 3.82 (t, *J* = 6.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 136.0, 133.9, 132.6, 130.1, 129.8, 128.9, 128.8, 128.0, 127.1, 123.8, 46.5, 37.9. IR (NaCl, thin film, cm^{-1}): 3062, 2922, 2852, 2100, 1682, 1627, 1469, 1373, 1255, 1183, 1124, 821, 751. HRMS (ESI): Calculated for $C_{13}H_{11}N_3NaO^+$, $(M+Na)^+$ 248.0794, found 248.0795.



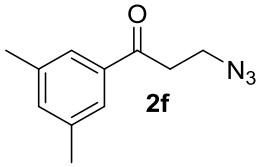
2d

Compound 2d: The General procedure was used and the product was isolated as a tan solid in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.23 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.9, 144.6, 134.1, 129.6, 128.3, 46.4, 37.7, 21.8. IR (NaCl, thin film, cm^{-1}): 2923, 2105, 1683, 1607, 1370, 1284, 1181, 807. HRMS (ESI): Calculated for $C_{10}H_{11}N_3ONa^+$, $(M+Na)^+$ 212.0794, found 212.0791.



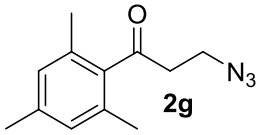
2e

Compound 2e: A variation of the general procedure was used. Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded the ketone **2e** as a yellow oil in 68% and 69% yield in duplicate trials. The average of 69% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.74 (m, 2H), 7.45 – 7.33 (m, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.24 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5, 138.7, 136.6, 134.5, 128.8, 128.7, 125.4, 46.4, 37.8, 21.5. IR (NaCl, thin film, cm^{-1}): 2920, 2101, 1684, 1586, 1368, 1256, 1163, 690, 631. HRMS (ESI): Calculated for $C_{10}H_{11}N_3ONa^+$, $(M+Na)^+$ 212.0794, found 212.0787.



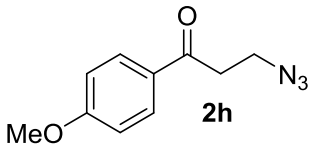
2f

Compound 2f: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 3, 6, 20 h; total reaction time = 32 h). Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2f** as a yellow oil in 84% and 89% yield in duplicate trials. The average of 87% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 2H), 7.24 (s, 1H), 3.73 (t, *J* = 6.5 Hz, 2H), 3.24 (t, *J* = 6.5 Hz, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 138.5, 136.7, 135.3, 126.0, 46.4, 37.9, 21.4. IR (NaCl, thin film, cm^{-1}): 2918, 2100, 1682, 1605, 1444, 1365, 1294, 1181, 1160, 862, 687. HRMS (ESI): Calculated for $C_{11}H_{13}N_3NaO^+$, $(M+Na)^+$ 226.0951, found 226.0957.



2g

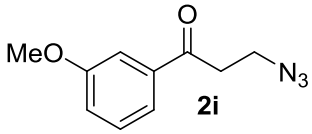
Compound 2g: A variation of the general procedure was used. Six portions of Oxone were added (t = 1, 8, 24, 36, 48, 60 h; total reaction time = 72 h). Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2g** as a yellow oil in 56% and 58% yield in duplicate trials. The average of 57% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 3.72 (t, *J* = 6.3 Hz, 2H), 2.95 (t, *J* = 6.3 Hz, 2H), 2.30 (s, 3H), 2.22 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7, 139.0, 138.9, 132.8, 128.9, 45.8, 43.8, 21.2, 19.2. IR (NaCl, thin film, cm^{-1}): 2923, 2100, 1699, 1611, 1445, 1361, 1379, 1290, 1235, 1154, 852. HRMS (ESI): Calculated for $C_{12}H_{15}N_3NaO^+$, $(M+Na)^+$ 240.1107, found 240.1110.



2h

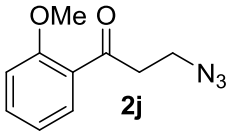
Compound 2h: A variation of the general procedure was used. Three portions of Oxone were added (at t = 1, 7, and 24 h; total reaction time = 36 h). Final purification by column

chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2h** as a tan solid in 93% and 84% yield in duplicate trials. The average of 89% is reported. Characterization data for this compound has been reported.[7] The material obtained from this method provided an identical ^{1}H NMR spectrum.



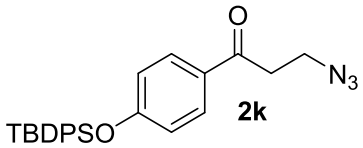
2i

Compound 2i: A variation of the general procedure was used. Two portions of Oxone (1 equiv. each) were added (t = 10 min, 1 h; total reaction time = 18 h). Final purification by column chromatography (5% EtOAc in hexanes) afforded ketone **2i** as a yellow in 61%, 84%, and 68% yield in multiple trials. The average of 71% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.7 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.14 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 3.87 (s, 3H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.24 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.1, 160.1, 137.9, 129.9, 120.8, 120.2, 112.4, 55.7, 46.4, 38.0. IR (NaCl, thin film, cm^{-1}): 3005, 2941, 2837, 2103, 1685, 1486, 1431, 1369, 1290, 1260, 1196, 1171, 1047, 875, 783. HRMS (ESI): Calculated for $C_{10}H_{11}N_3NaO_2^+$, $(M+Na)^+$ 228.0743, found 228.0752.



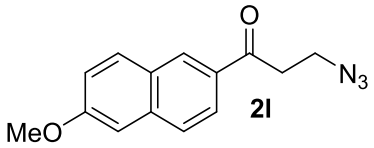
2j

Compound 2j: A variation of the general procedure was used. Two portions of Oxone (1 equiv. each) were added (t = 10 min, 4 h; total reaction time = 24 h). Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2j** as a yellow in 85% and 81% yield in duplicate trials. The average of 83% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.49 (ddd, *J* = 8.7, 7.3, 1.9 Hz, 1H), 7.09 – 6.93 (m, 2H), 3.93 (s, 3H), 3.67 (t, *J* = 6.5 Hz, 2H), 3.29 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 159.1, 134.3, 130.7, 127.3, 120.9, 111.7, 55.6, 46.6, 43.0. IR (NaCl, thin film, cm^{-1}): 2944, 2841, 2102, 1672, 1597, 1485, 1437, 1287, 1246, 1163, 1114, 1023, 759. HRMS (ESI): Calculated for $C_{10}H_{11}N_3NaO_2^+$, $(M+Na)^+$ 228.0743, found 228.0743.



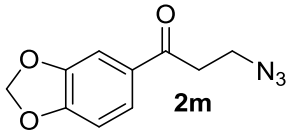
2k

Compound 2k: A variation of the general procedure was used. Two portions of Oxone (1 equiv. each) were added (t = 1, 3 h; total reaction time = 18 h). Final purification by column chromatography (5% EtOAc in hexanes) afforded ketone **2k** as a yellow in 92% and 91% yield in duplicate trials. The average of 92% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.62 (m, 6H), 7.54 – 7.22 (m, 6H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.69 (t, *J* = 6.5 Hz, 2H), 3.13 (t, *J* = 6.5 Hz, 2H), 1.14 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.8, 160.6, 135.5, 132.2, 130.4, 130.2, 130.0, 128.1, 120.0, 46.4, 37.4, 26.6, 19.6. IR (NaCl, thin film, cm^{-1}): 3072, 2932, 2894, 2859, 2105, 1679, 1598, 1509, 1428, 1272, 1168, 1114, 913, 701. HRMS (ESI): Calculated for $C_{25}H_{27}N_3NaO_2Si^+$, $(M+Na^+)$ 452.1765, found 452.1767.



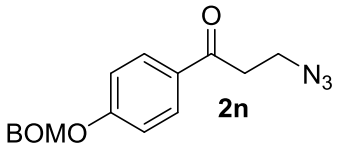
2l

Compound 2l: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 3, 5, and 20 h; total reaction time = 32 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2l** as a yellow oil in 78% and 75% yield in duplicate trials. The average of 77% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.99 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.21 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 3.95 (s, 3H), 3.78 (t, *J* = 6.5 Hz, 2H), 3.33 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 160.1, 137.6, 131.9, 131.3, 129.9, 127.9, 127.4, 124.5, 120.0, 105.9, 55.6, 46.5, 37.6. IR (NaCl, thin film, cm^{-1}): 2938, 2102, 1676, 1624, 1482, 1267, 1183, 1028, 858. HRMS (ESI): Calculated for $C_{14}H_{13}N_3NaO_2^+$, $(M+Na^+)$ 278.0900, found 278.0892.



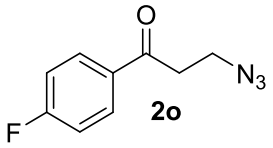
2m

Compound 2m: A variation of the general procedure was used. Five portions of Oxone were added (t = 1, 3, 6, 20, 28 h; total reaction time = 40 h). Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2m** as a tan solid in 72% and 79% yield in duplicate trials. The average of 76% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.06 (s, 2H), 3.72 (t, *J* = 6.5 Hz, 2H), 3.17 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 152.3, 148.5, 131.5, 124.6, 108.1, 108.0, 102.1, 46.5, 37.6. IR (NaCl, thin film, cm^{-1}): 2916, 2116, 1660, 1612, 1504, 1436, 1355, 1255, 1039, 936, 902, 885, 828, 786. HRMS (ESI): Calculated for $C_{10}H_9N_3NaO_3^+$, $(M+Na)^+$ 242.0536, found 242.0539.



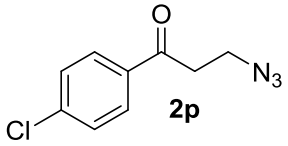
2n

Compound 2n: A variation of the general procedure was used. Three portions of Oxone were added (t = 15 min, 5 h, 7 h; total reaction time = 24 h). Final purification by column chromatography (20% EtOAc in hexanes) afforded ketone **2n** as a yellow in 71% and 68% yield in duplicate trials. The average of 70% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.9 Hz, 2H), 7.37-7.33 (m, 5H), 7.16 (d, *J* = 8.8 Hz, 2H), 5.38 (s, 2H), 4.75 (s, 2H), 3.76 (t, *J* = 6.5 Hz, 2H), 3.23 (t, *J* = 6.5 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 195.7, 161.5, 136.8, 130.4, 130.3, 128.5, 128.1, 128.0, 116.0, 91.9, 70.4, 46.3, 37.3. IR (NaCl, thin film, cm^{-1}): 3065, 3032, 2907, 2106, 1678, 1601, 1233, 1170, 1092, 984, 848, 740, 699. HRMS (ESI): Calculated for $C_{17}H_{17}N_3O_3Na^+$, $(M+Na)^+$ 334.1162, found 334.1174.



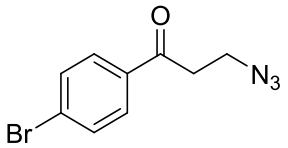
2o

Compound 2o: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 12, 24, 36 h; total reaction time = 48 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2o** as a slightly yellow oil in 76% and 74% yield in duplicate trials. The average of 75% is reported. Characterization data for this compound has been reported.[7] The material obtained from this method provided an identical ^{1}H NMR spectrum.

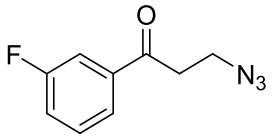


2p

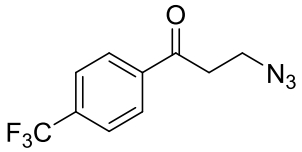
Compound 2p: A variation of the general procedure was used. Four portions of Oxone were added (t = 8, 20, 32, 44 h; total reaction time = 56 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2p** as a yellow in 53% yield. ^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.91 (d, *J*= 8.3 Hz, 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 3.75 (t, *J*= 6.3 Hz, 2H), 3.22 (t, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 140.2, 134.9, 129.6, 129.3, 46.2, 37.8. IR (NaCl, thin film, cm^{-1}): 2727, 2107, 1686, 1590, 1402, 1209, 1169, 1093. HRMS (ESI): Calculated for $C_9H_8ClN_3ONa^+$, $(M+Na)^+$ 232.0248, found 232.0247.



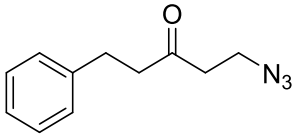
Compound 2q: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 15, 25, 39 h; total reaction time = 63 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2q** as a slightly yellow oil in 75% and 62% yield in duplicate trials. The average of 69% is reported. Characterization data for this compound has been reported.[9] The material obtained from this method provided an identical ^{1}H NMR spectrum.



Compound 2r: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 15, 25, 39 h; total reaction time = 63 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **2r** as a slightly yellow oil in 44% and 45% yield in duplicate trials. The average of 45% is reported. Characterization data for this compound has been reported.[9] The material obtained from this method provided an identical ^{1}H NMR spectrum.

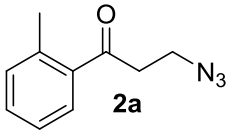


Compound 2s: A variation of the general procedure was used. Oxone (3 equiv) was added in one portion. After 18 h at 50 °C, the reaction was poured onto acetic acid (20 mL, 0.5 M in H_2O) and brine. The resulting solution was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (5% EtOAc and 1% acetic acid in hexanes) afforded ketone **2s** as a slightly yellow oil in 24% and 26% yield in duplicate trials. The average of 25% is reported. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 3.78 (t, *J* = 6.3 Hz, 2H), 3.28 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 134.9 (q, J_{C-F} = 32.8 Hz), 128.4, 127.6, 125.9 (q, J_{C-F} = 3.8 Hz), 123.5 (q, J_{C-F} = 273.4 Hz), 46.0, 38.0. ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.2. IR (NaCl, thin film, cm^{-1}): 2107, 1692, 1410, 1324, 1125, 1066. HRMS (CI): Calculated for $C_{10}H_8N_3F_3NaO^+$, $(M+Na^+)$ 266.0512, found 266.0509.



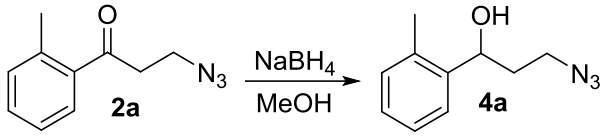
Compound 6: A variation of the general procedure was used. Four portions of Oxone were added (t = 1, 15, 20, 25 h; total reaction time = 48 h). Final purification by column chromatography (10% EtOAc and 1% acetic acid in hexanes) afforded ketone **6** as a slightly yellow oil in 53% and 56% yield in duplicate trials. The average of 54% is reported. The isolated material contained small quantities of ketone **7**, which was not readily separable. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.12 (m, 5H), 3.57 (t, *J* = 6.4 Hz, 2H), 2.95 (t, *J* = 7.5 Hz, 2H), 2.80 (t, *J* = 7.5 Hz, 2H), 2.67 (t, *J* = 6.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.0, 140.7, 128.6, 128.3, 126.3, 45.7, 44.7, 41.7, 29.6. IR (NaCl, thin film, cm^{-1}): 2926, 2099, 1716, 1496, 1373, 1284, 842. HRMS (ESI): Calculated for $C_{11}H_{13}N_3ONa^+$, $(M+Na)^+$ 226.0951, found 226.0946.

Gram Scale Reaction

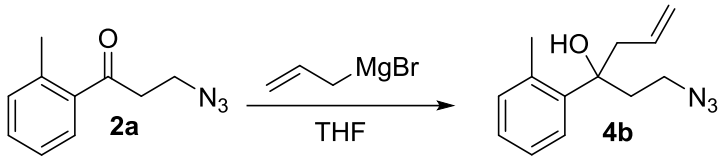


On the benchtop, to an 100 mL round-bottom flask containing $Pd(PhCN)_2Cl_2$ (217 mg, 0.558 mmol), $AgNO_3$ (250 mg, 1.47 mmol), and benzoquinone (129 mg, 1.19 mmol), was added MeCN (40 mL) and H_2O (5 mL) at rt. After 5 min, compound **1a** (1.01 g, 5.85 mmol) was added neat. Oxone (3.52 g total, 11.5 mmol) was added in 0.5 equiv. portions (t = 1, 4, 10, 30 h). After an additional 12 h (42 h total), the reaction was diluted with brine. The resulting solution was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (5% EtOAc in hexanes) afforded ketone **2a** (887 mg, 80%) as a slightly yellow oil. In a duplicate experiment, 1.01 g of azide **1a** afforded 0.841 g of ketone **2a** (76%). The average yield of 78% is reported.

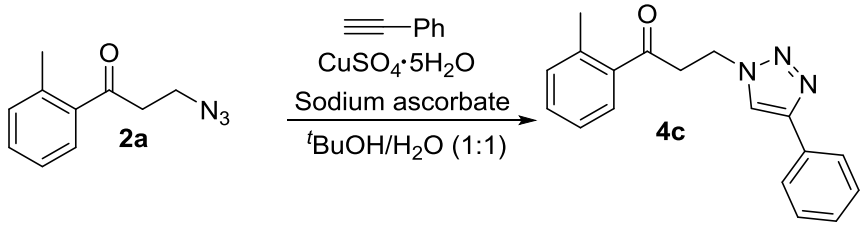
Derivatization



To a solution of compound **2a** (105 mg, 0.557 mmol) in MeOH (2 mL) in an ice bath was added $NaBH_4$ (43 mg, 1.1 mmol). After 30 min, the reaction was quenched by addition of H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford compound **4a** (104 mg, 98%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 1H), 7.38 – 7.08 (m, 3H), 5.07 (t, *J* = 6.0 Hz, 1H), 3.61 – 3.49 (m, 1H), 3.49 – 3.39 (m, 1H), 2.37 (s, 3H), 1.94 (apparent q, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 134.4, 130.6, 127.6, 126.5, 125.1, 68.0, 48.6, 36.8, 19.0. IR (NaCl, thin film, cm^{-1}): 3381, 2927, 2098, 1461, 1346, 1263, 1072, 1009, 760, 727. HRMS (ESI): Calculated for $C_{10}H_{13}N_3NaO^+$, ($M+Na^+$) 214.0951, found 214.0949.



To a solution of compound **2a** (113 mg, 0.600 mmol) in THF (2 mL) at -78 °C was added allyl magnesium bromide (0.70 mL, 0.70 mmol, 1 M in Et_2O). The solution was slowly warmed to -10 °C over 2 h and then quenched with H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Final purification by column chromatography (20% EtOAc in hexanes) afforded compound **4b** (115 mg, 83%) as a slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 1H), 7.23 – 7.13 (m, 3H), 5.57 (dddd, *J* = 17.2, 10.1, 8.7, 6.0 Hz, 1H), 5.22 – 5.11 (m, 2H), 3.34 (ddd, *J* = 12.3, 8.7, 7.0 Hz, 1H), 3.15 (ddd, *J* = 12.4, 8.9, 5.3 Hz, 1H), 2.94 (ddt, *J* = 14.0, 5.9, 1.4 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.51 (s, 3H), 2.34 (ddd, *J* = 14.1, 8.7, 5.4 Hz, 1H), 2.11 (ddd, *J* = 14.1, 8.9, 6.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 134.4, 133.2, 132.9, 127.4, 127.0, 126.2, 120.3, 76.2, 47.7, 46.2, 39.3, 22.8. IR (NaCl, thin film, cm^{-1}): 2951, 2822, 2770, 2722, 2097, 1107. HRMS (ESI): Calculated for $C_{13}H_{17}N_3NaO^+$, ($M+Na^+$) 254.1264, found 254.1270.



To a solution of compound **2a** (81.7 mg, 0.472 mmol) in ^{t}BuOH/H_2O (1:1, 2 mL) at rt was added phenyl acetylene (67 µL, 0.61 mmol), copper sulfate pentahydrate (9.0 mg, 36 µmol), and sodium ascorbate (31.5 mg, 0.159 mmol) sequentially. After 18 h, the reaction was diluted with H_2O. The resulting solution was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford compound **4c** (0.115 g, 84%) as a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.84 (d, *J* = 7.2 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.46 – 7.37 (m, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 2H), 4.84 (t, *J*

= 6.2 Hz, 2H), 3.63 (t, *J* = 6.2 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 147.6, 138.8, 136.3, 132.3, 132.2, 130.7, 128.9, 128.8, 128.1, 126.0, 125.7, 121.1, 45.1, 41.1, 21.6. IR (NaCl, thin film, cm^{-1}): 3126, 3098, 2966, 1684, 1568, 1465, 1370, 1381, 1225, 1080, 975, 757, 690. HRMS (ESI): Calculated for $C_{18}H_{17}N_3NaO^+$, ($M+Na^+$) 314.1264, found 314.1262.

References

(1) Kemsley, J. More Details on the University of Minnesota Explosion and Response. http://cenblog.org/the-safety-zone/2014/07/more-details-on-the-university-of-minnesota-explosion-and-response/ (accessed Nov 4, 2017).

(2) Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. Unsupported Copper Nanoparticles in the 1,3-Dipolar Cycloaddition of Terminal Alkynes and Azides. *Eur. J. Org. Chem.* **2010**, 1875–1884.

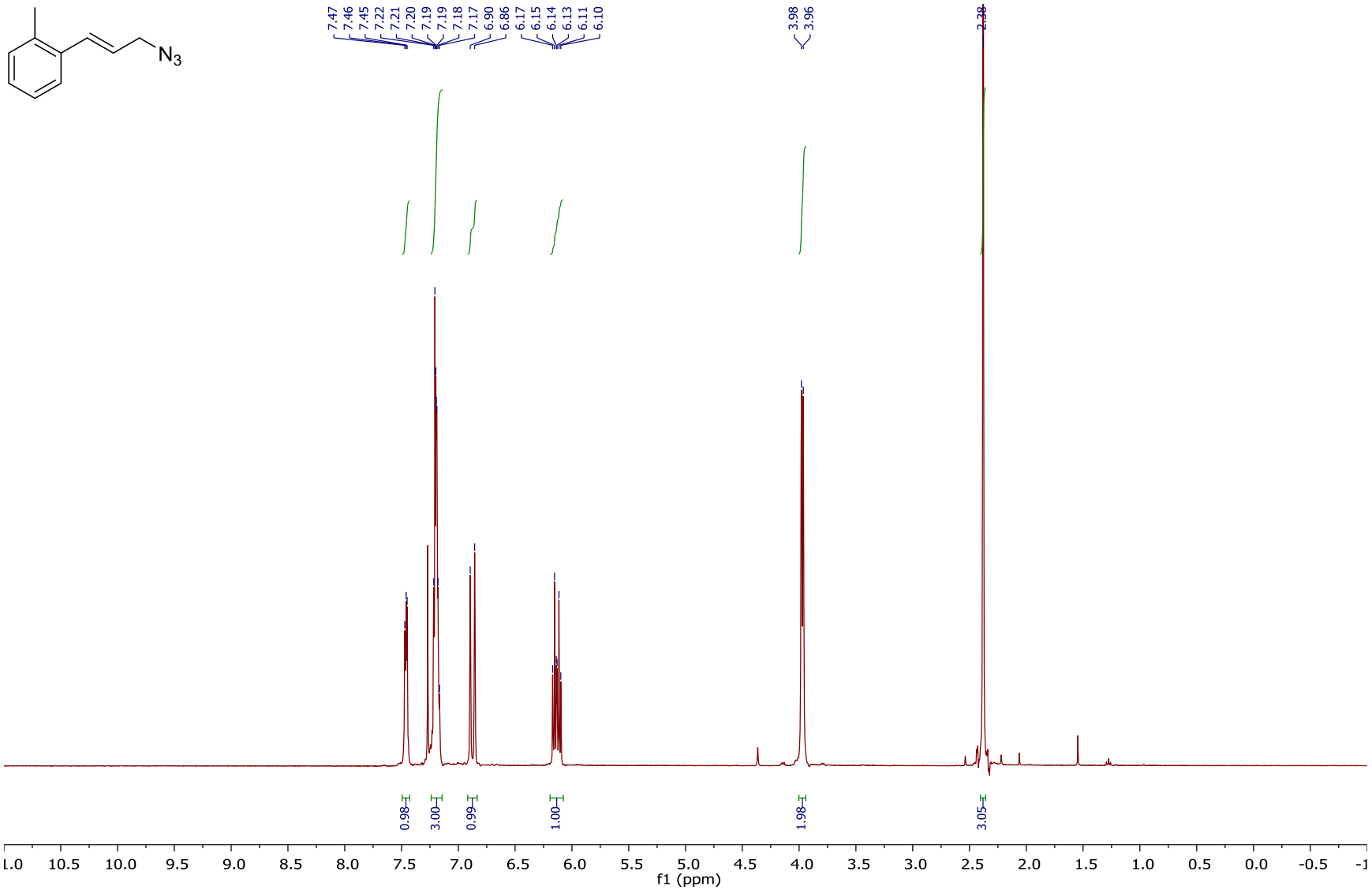
(3) Packard, M. H.; Cox, J. H.; Suding, V. P.; Topczewski, J. J. The Effect of Proximal Functionality on the Allylic Azide Equilibrium. *Eur. J. Org. Chem.* **2017**.

(4) Chen, H.; Yang, W.; Wu, W.; Jiang, H. Palladium-Catalyzed Regioselective Azidation of Allylic C–H Bonds under Atmospheric Pressure of Dioxygen. *Org. Biomol. Chem.* **2014**, *12*, 3340–3343.

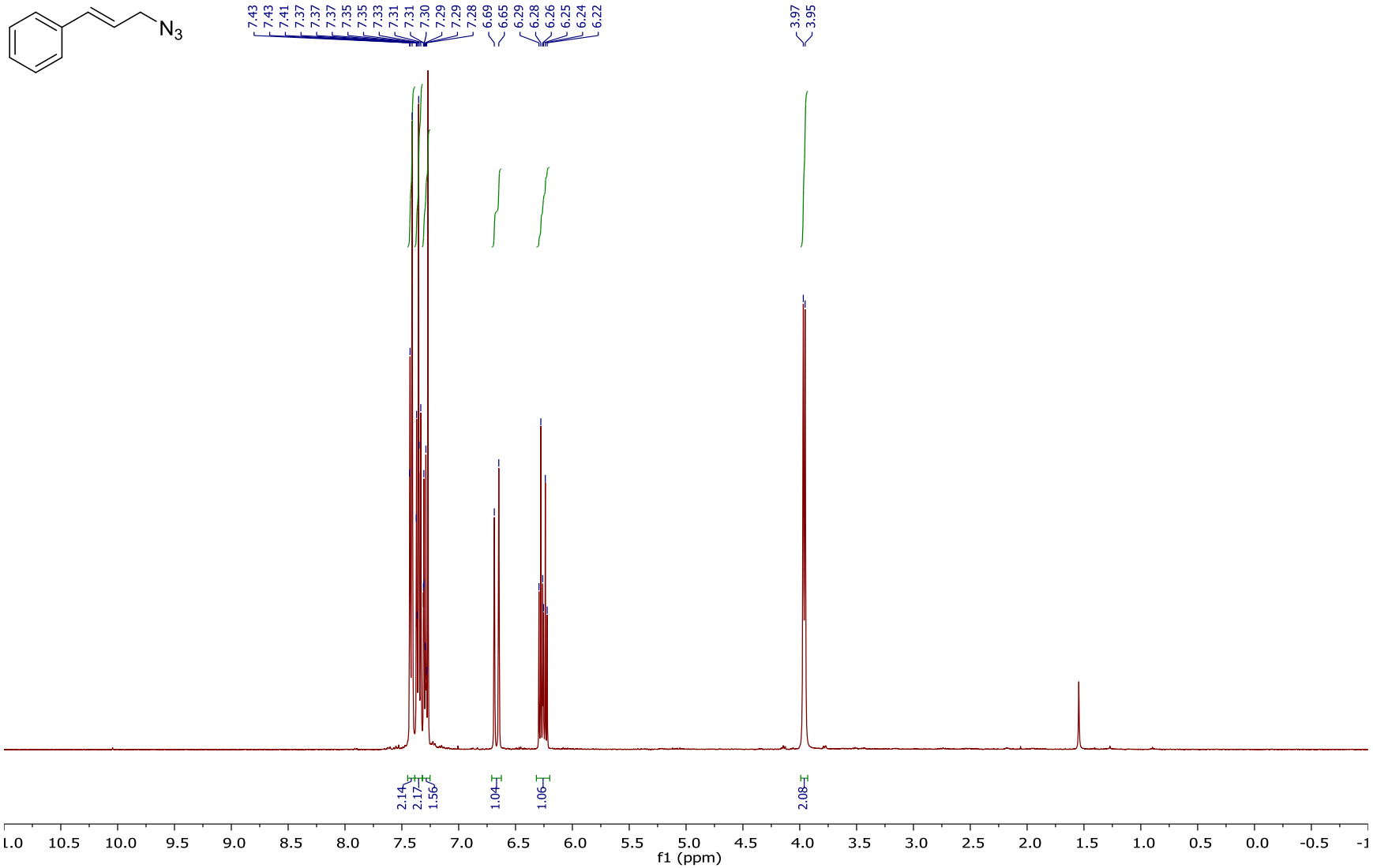
(5) Rueping, M.; Vila, C.; Uria, U. Direct Catalytic Azidation of Allylic Alcohols. *Org. Lett.* **2012**, *14*, 768–771.

(6) Singh, P. N. D.; Mandel, S. M.; Sankaranarayanan, J.; Muthukrishnan, S.; Chang, M.; Robinson, R. M.; Lahti, P. M.; Ault, B. S.; Gudmundsdóttir, A. D. Selective Formation of Triplet Alkyl Nitrenes from Photolysis of β-Azido-Propiophenone and Their Reactivity. *J. Am. Chem. Soc.* **2007**, *129*, 16263–16272.

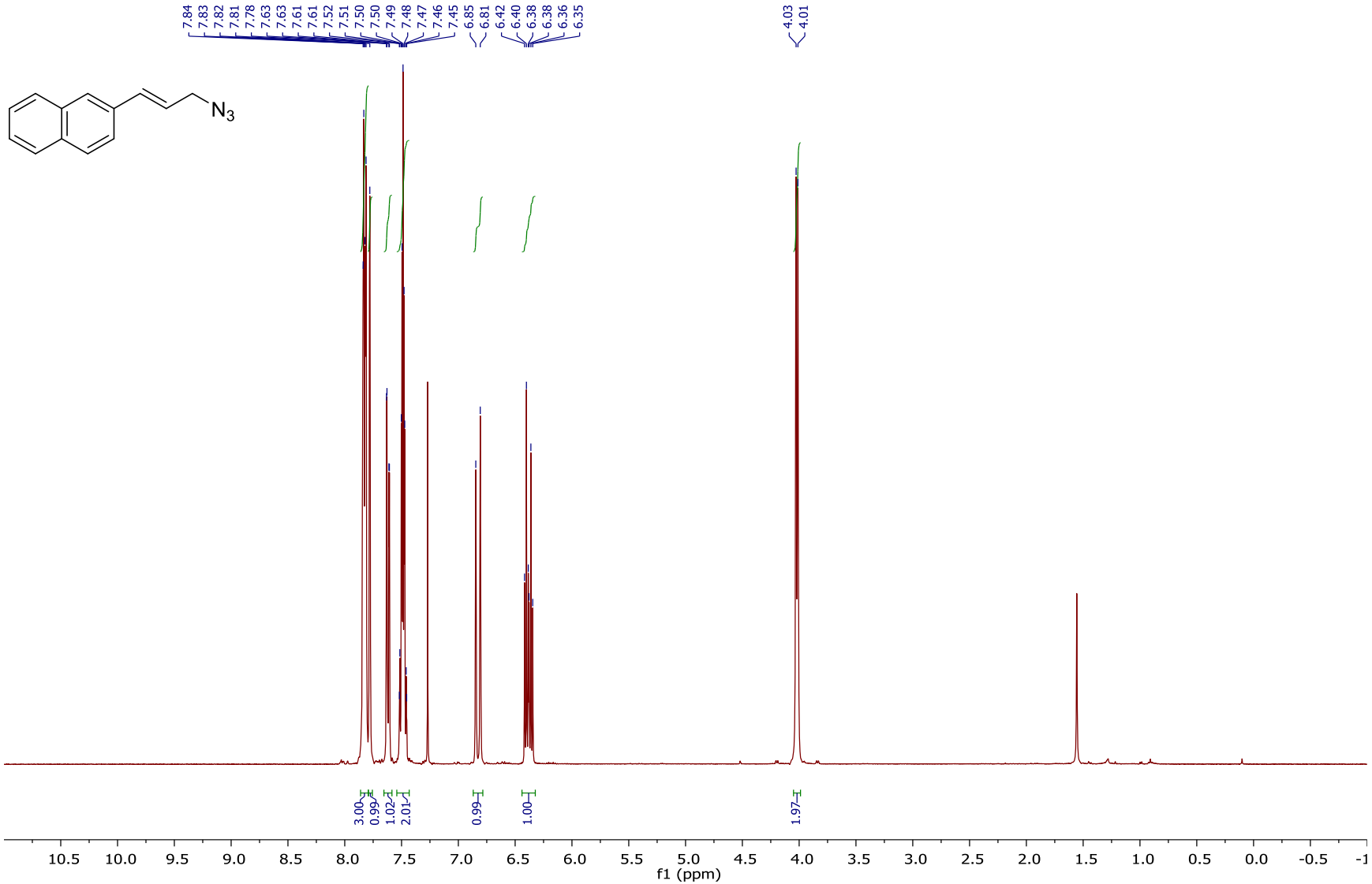
(7) Singh, P. N. D.; Muthukrishnan, S.; Murthy, R. S.; Klima, R. F.; Mandel, S. M.; Hawk, M.; Yarbrough, N.; Gudmundsdóttir, A. D. A Simple and Fast Procedure for Efficient Synthesis of β- and γ-Azidoarylketones. *Tetrahedron Lett.* **2003**, *44*, 101–103.



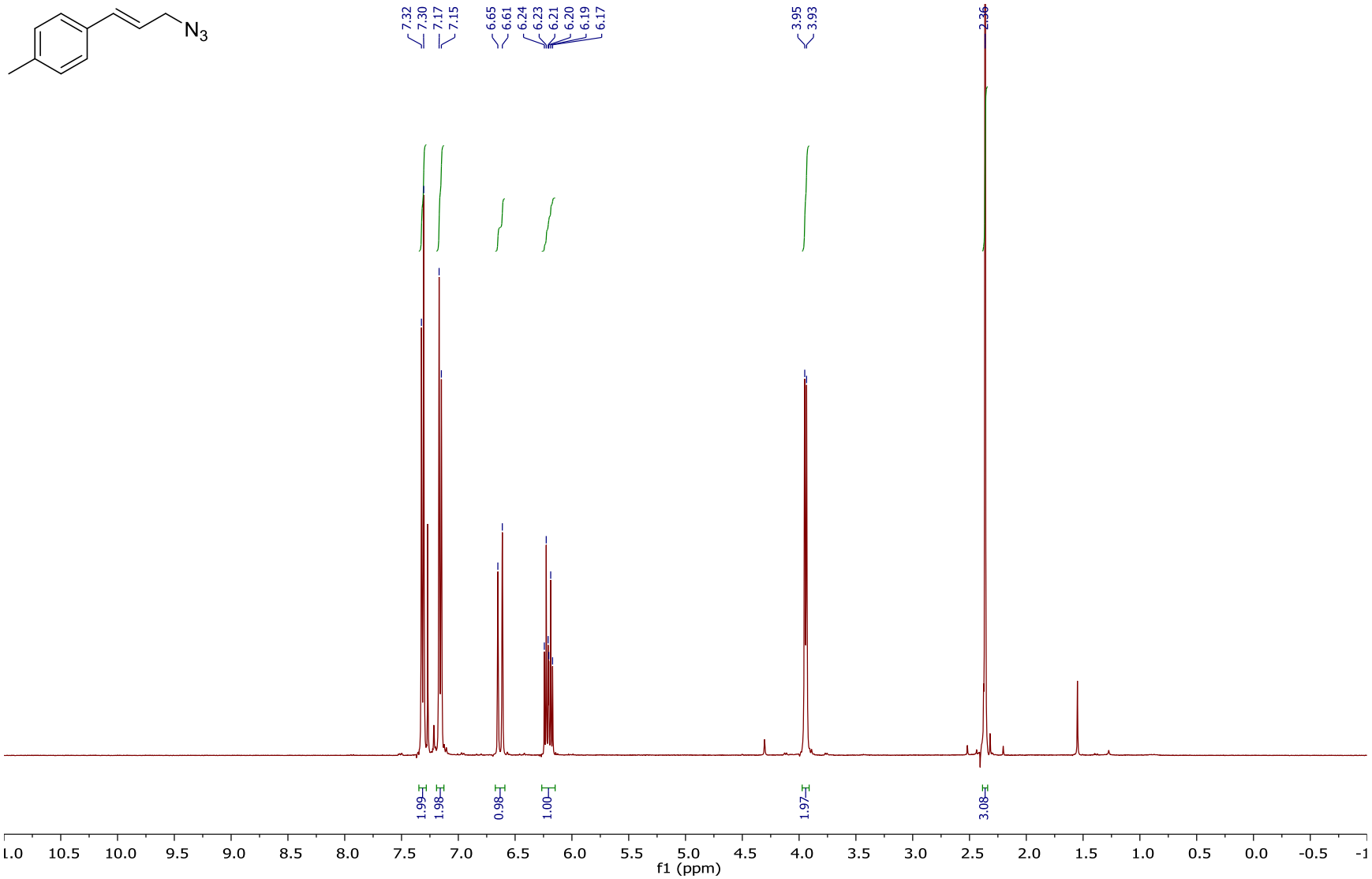
Compound 1a: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



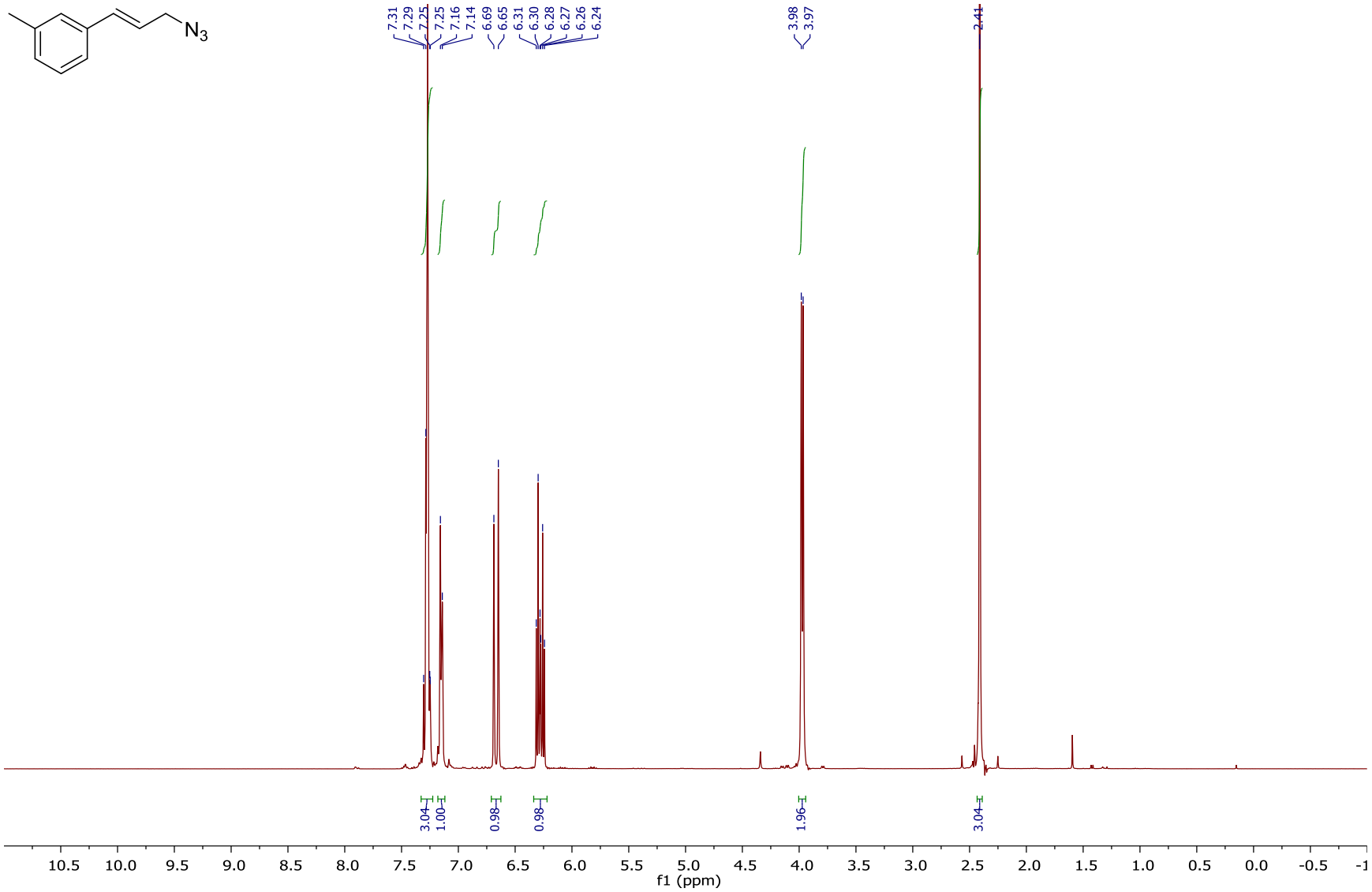
Compound 1b: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



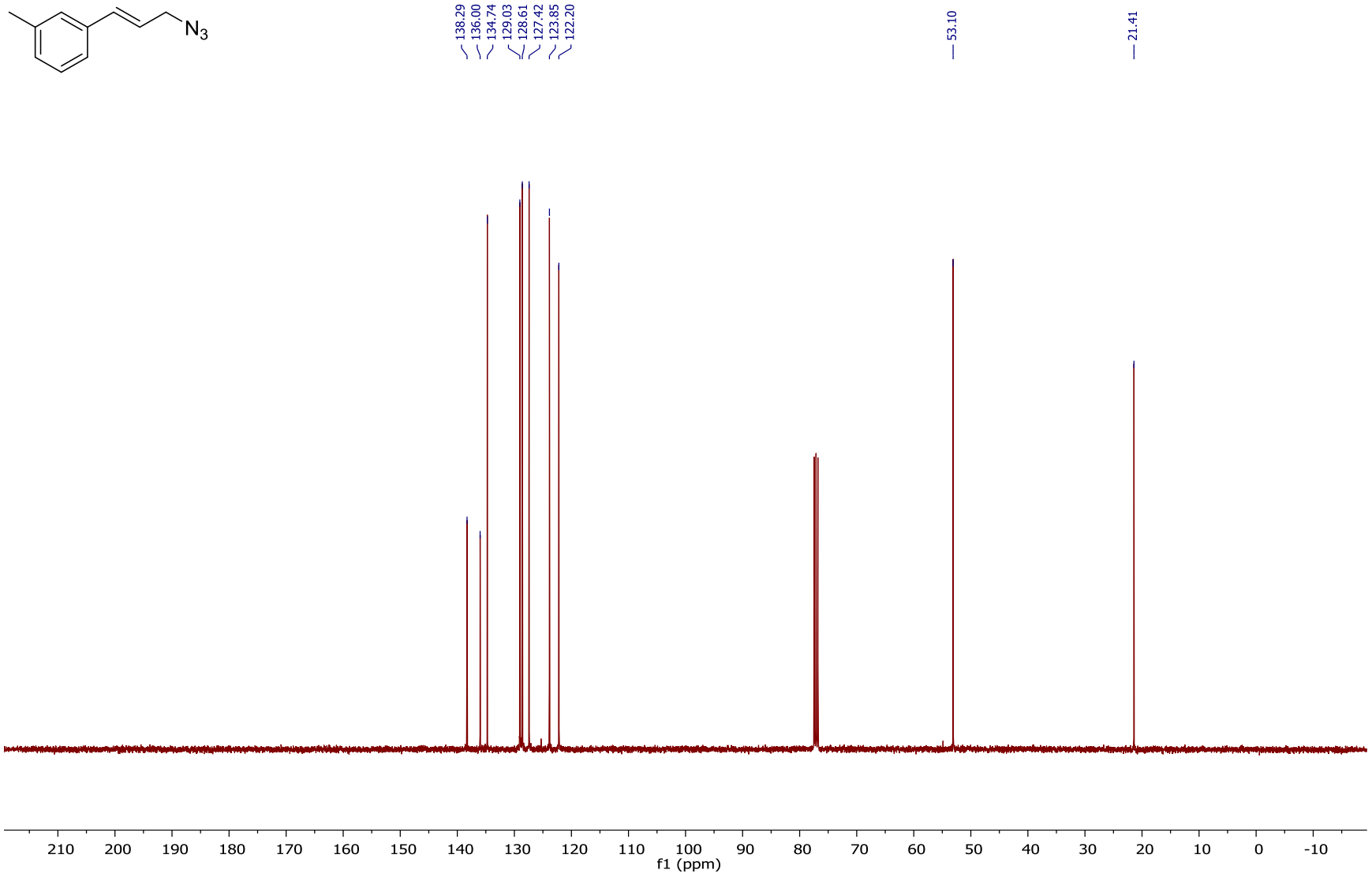
Compound 1c: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



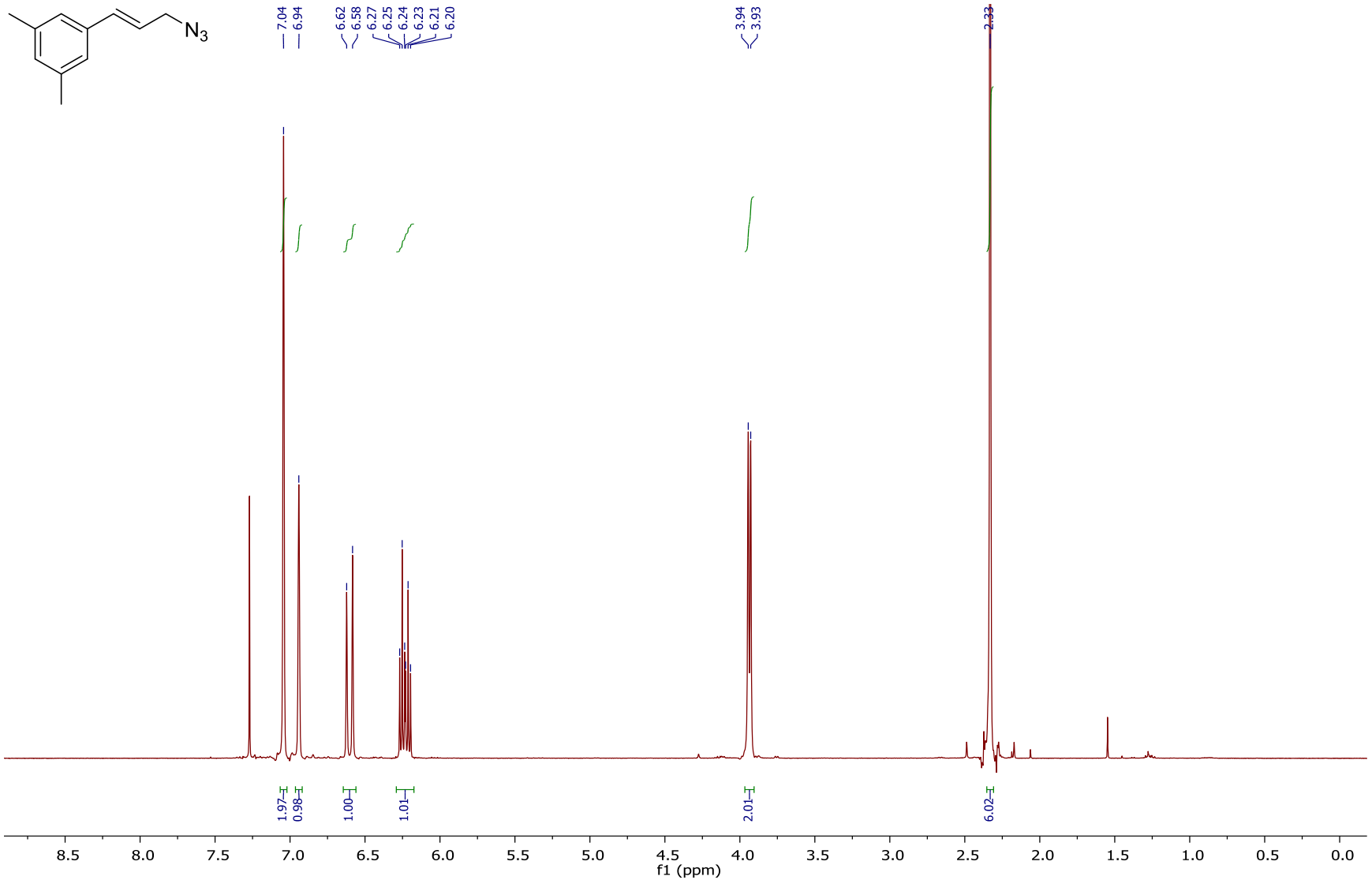
Compound 1d: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



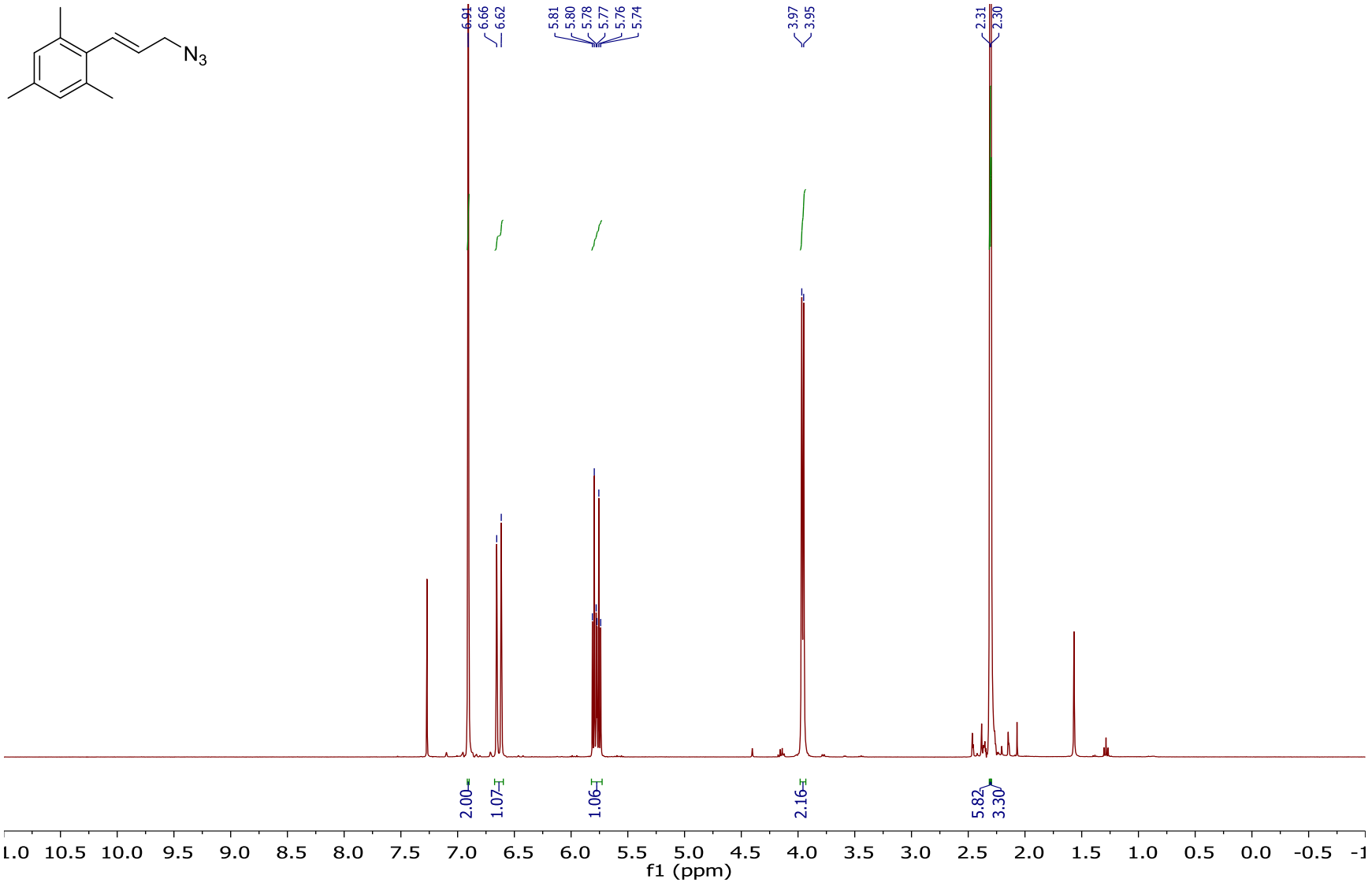
Compound 1e: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



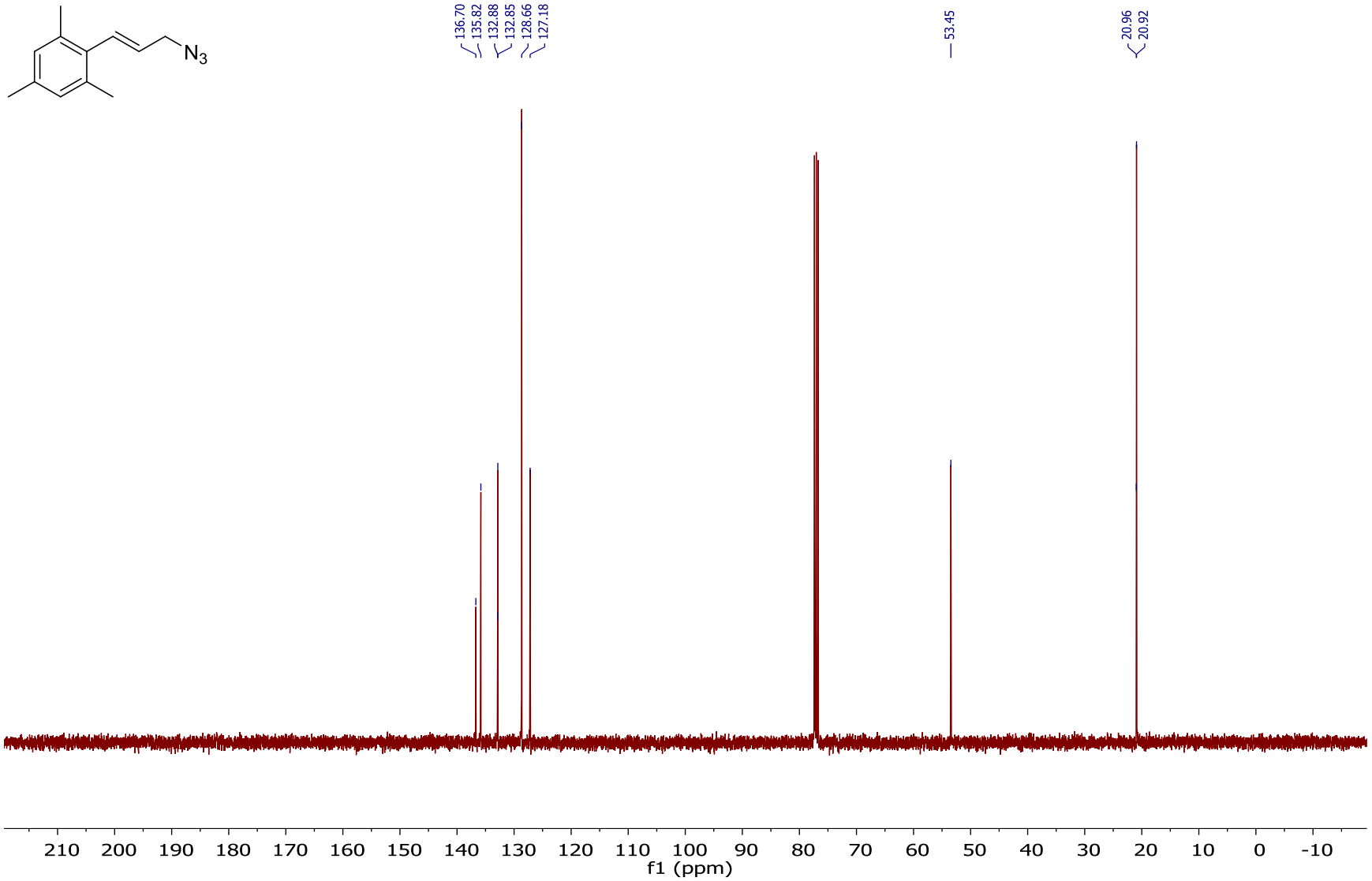
Compound 1e: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



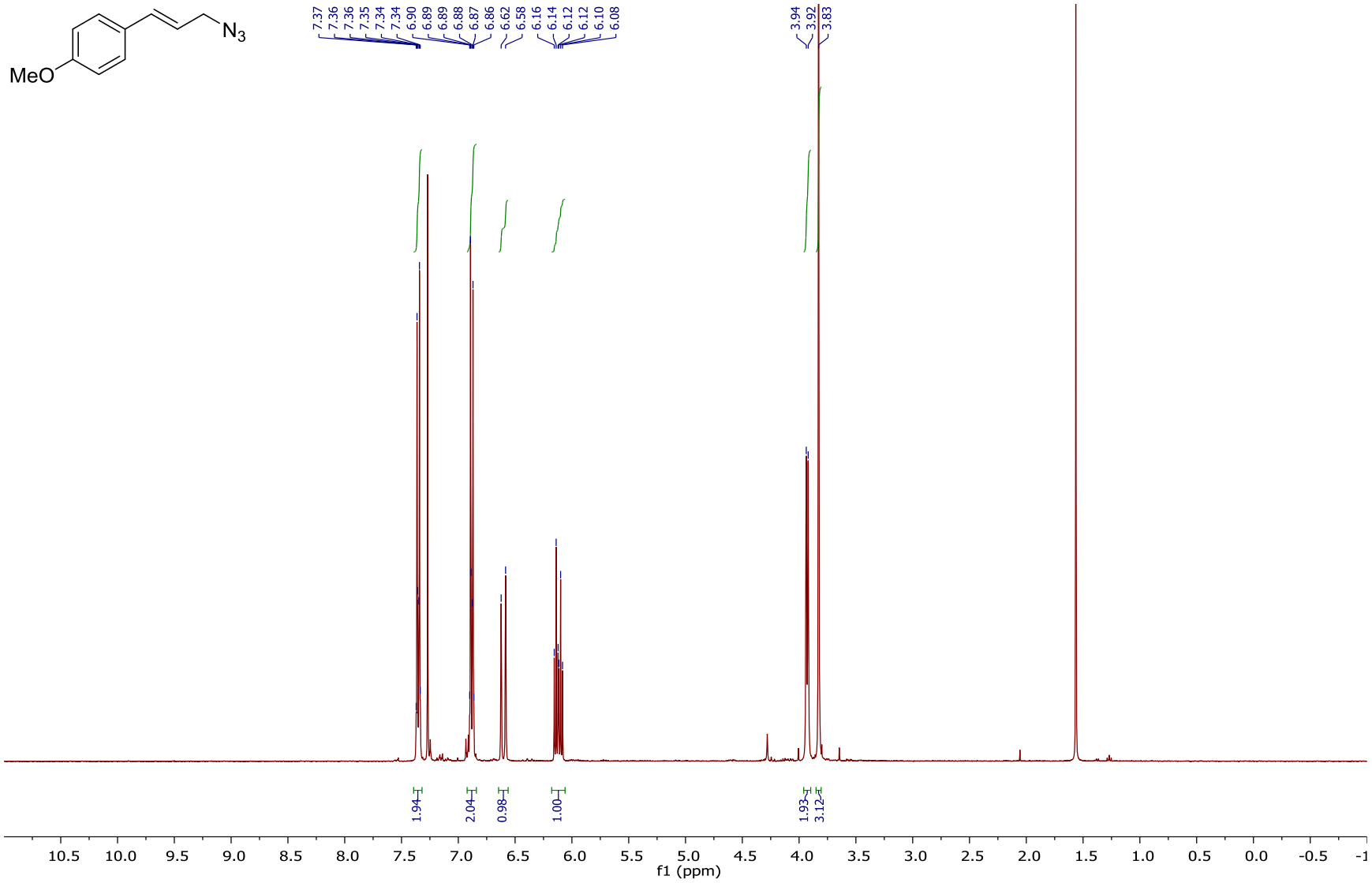
Compound 1f: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



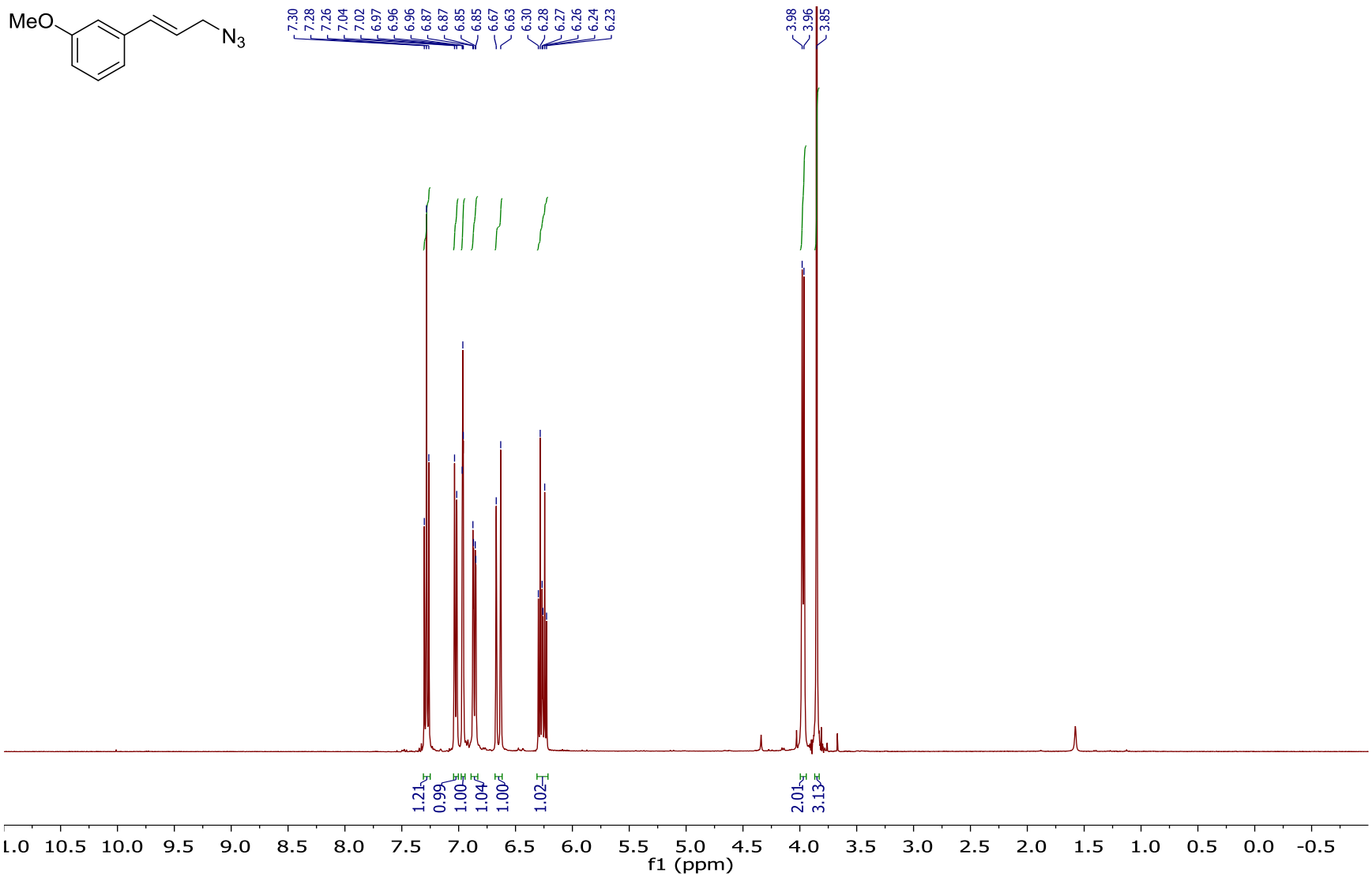
Compound 1g: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



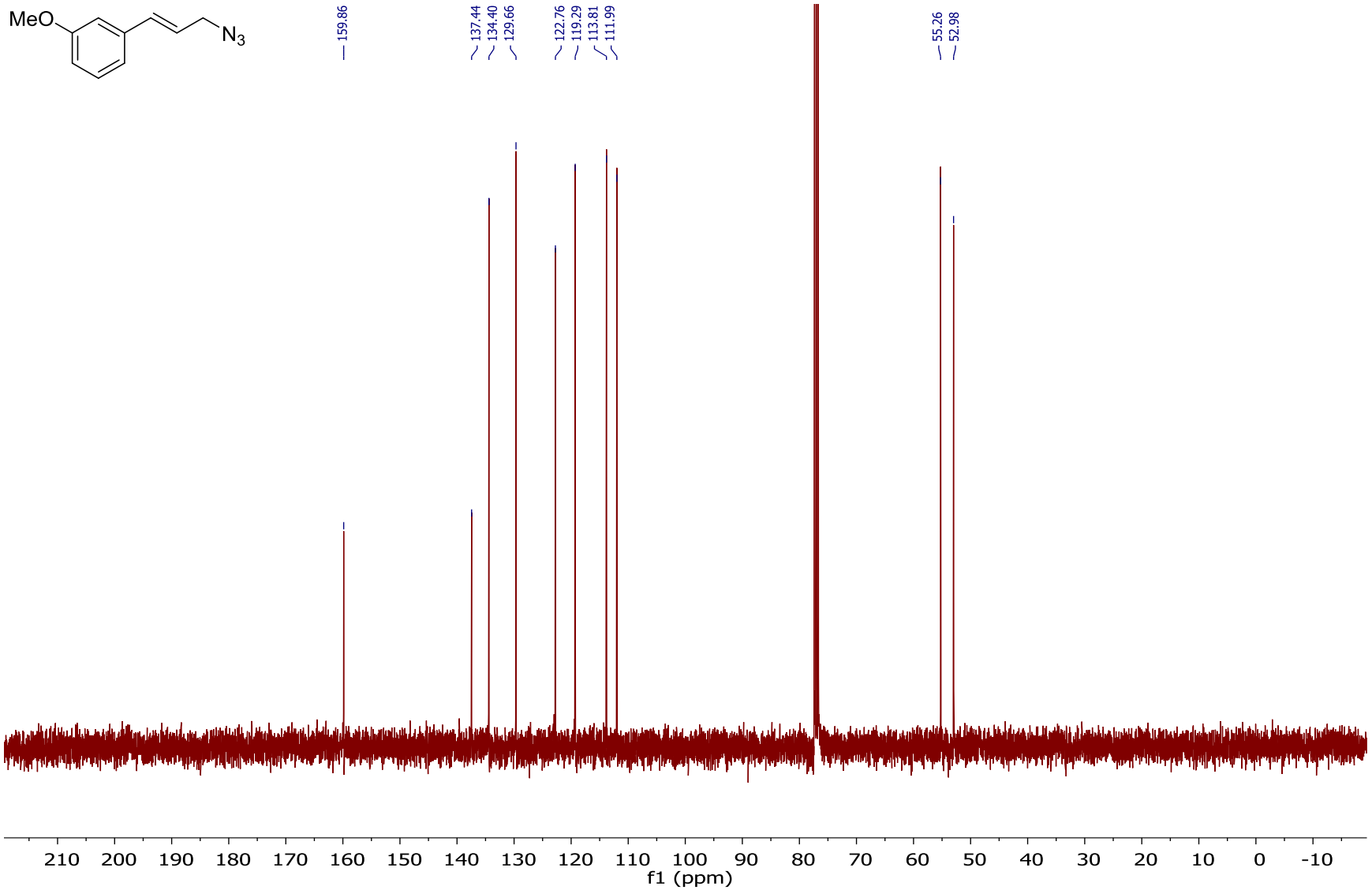
Compound 1g: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



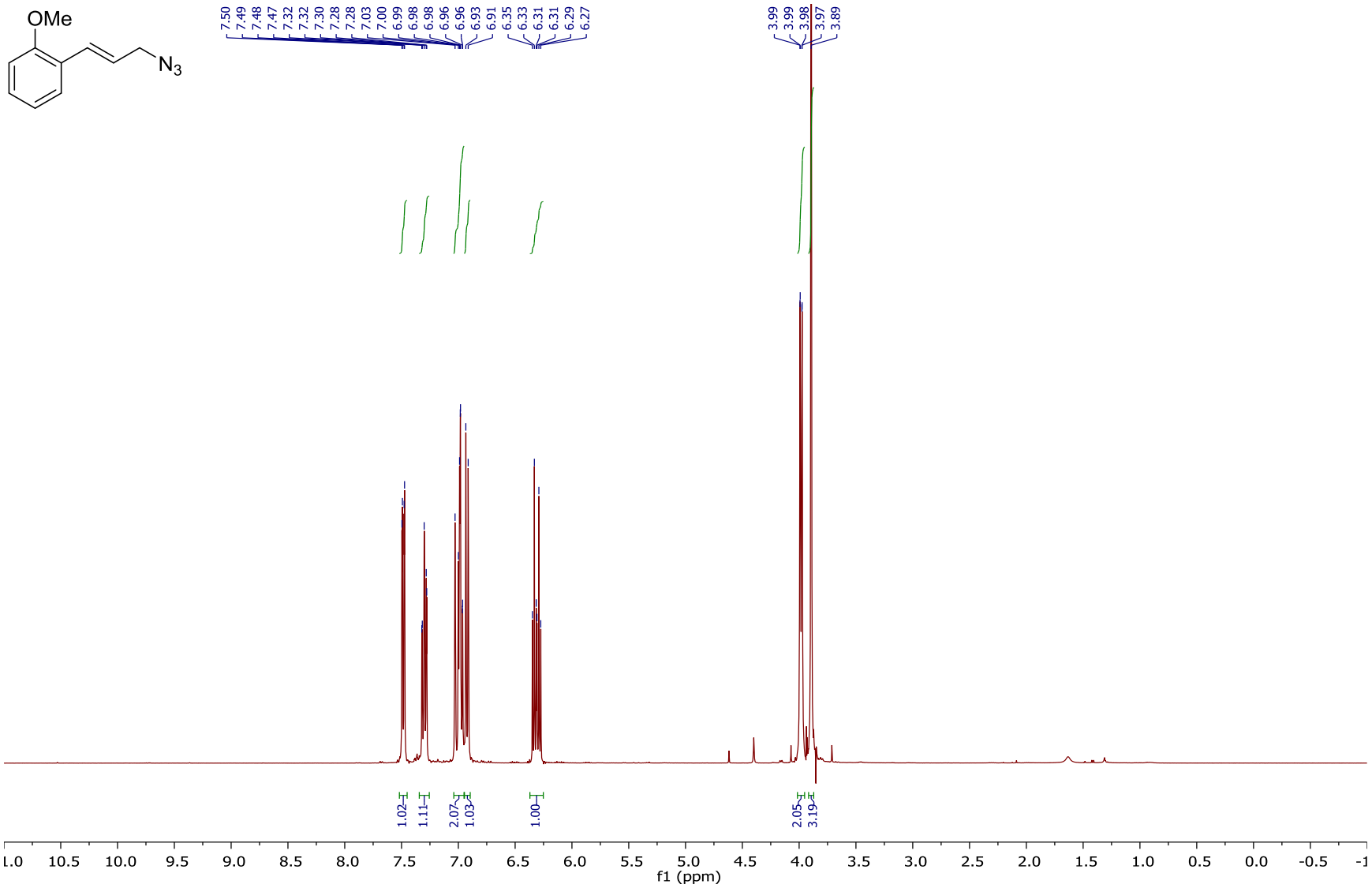
Compound 1h: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



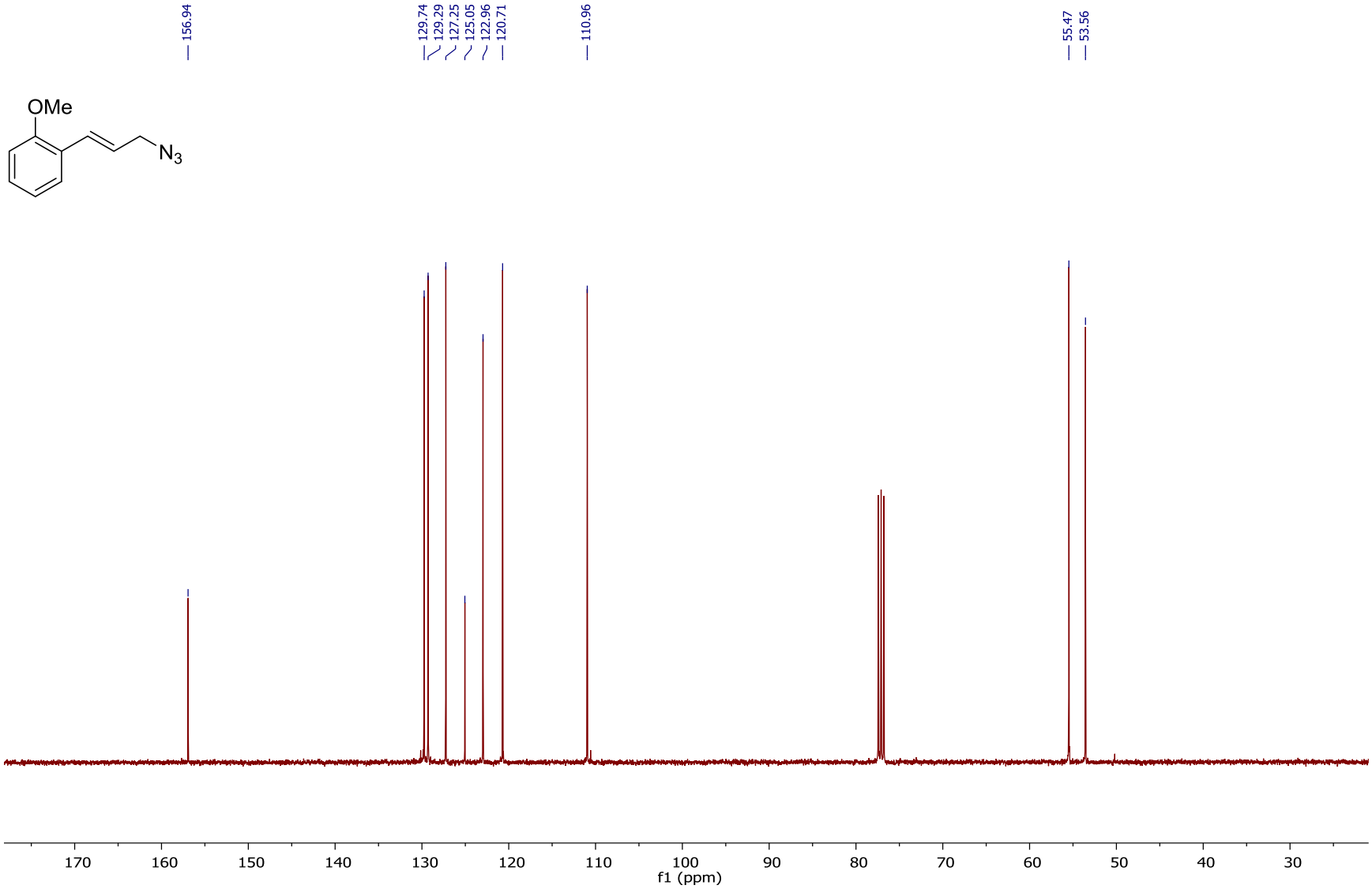
Compound 1i: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



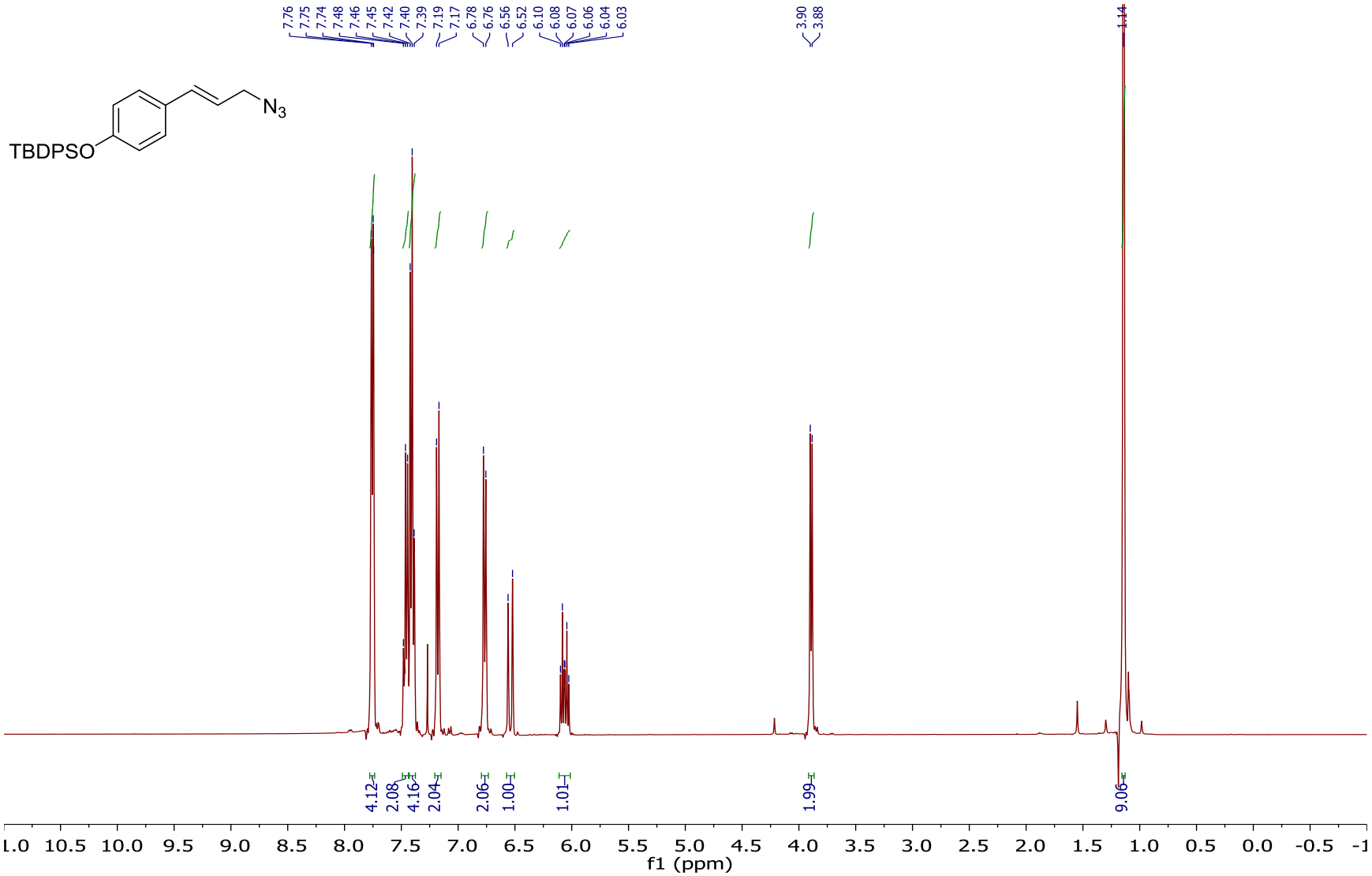
Compound 1i: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



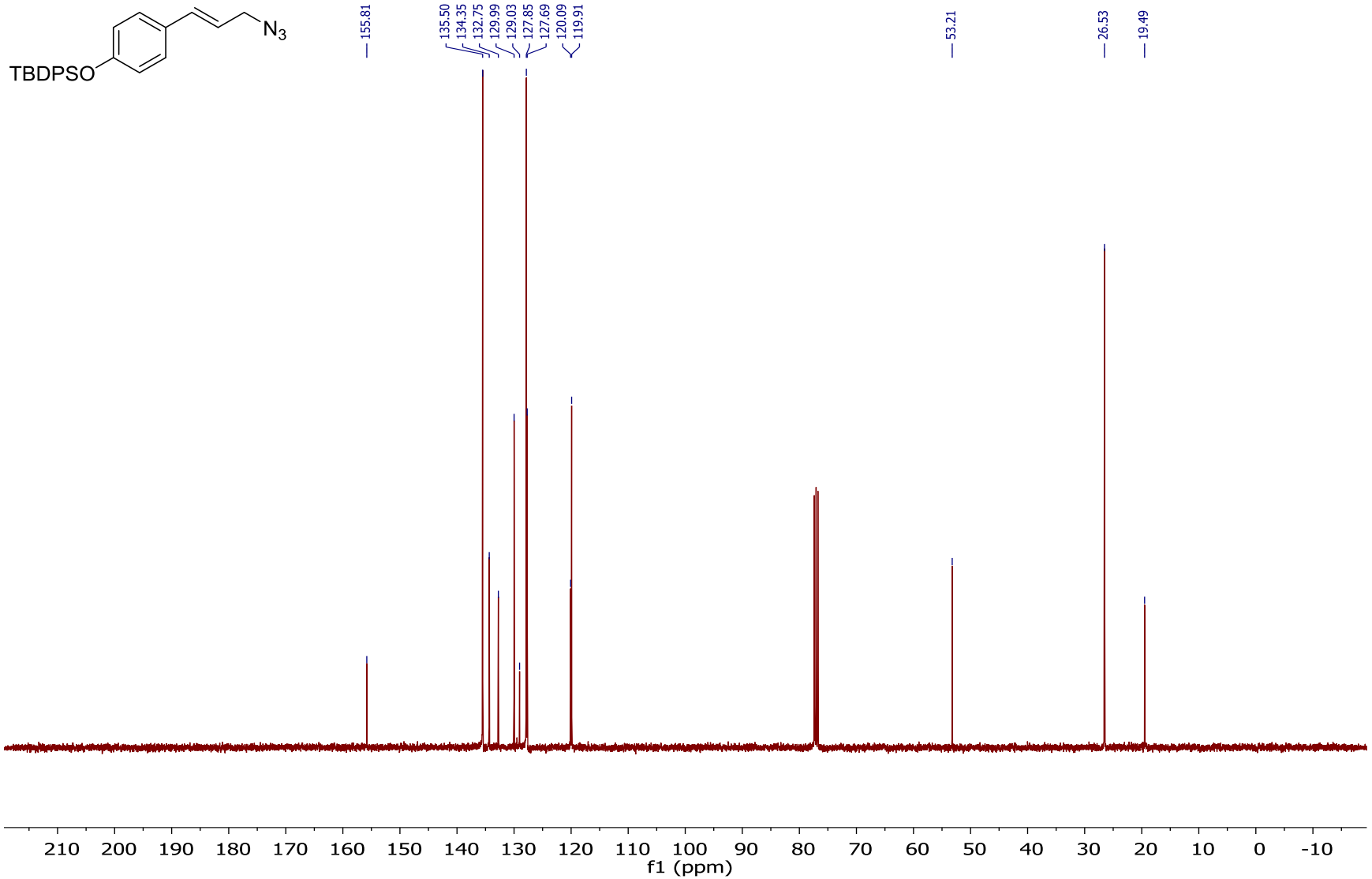
Compound 1j: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



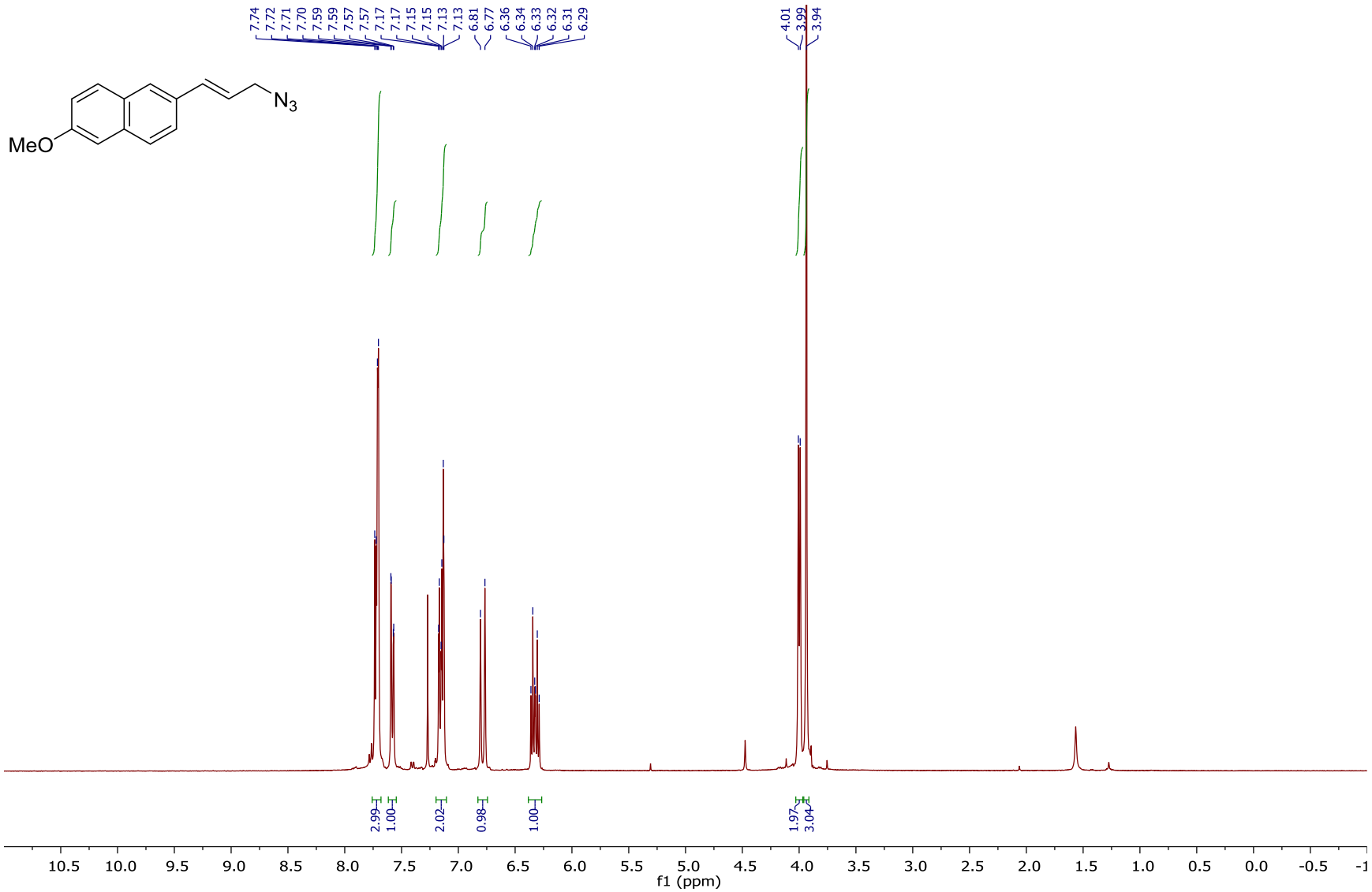
Compound 1j: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



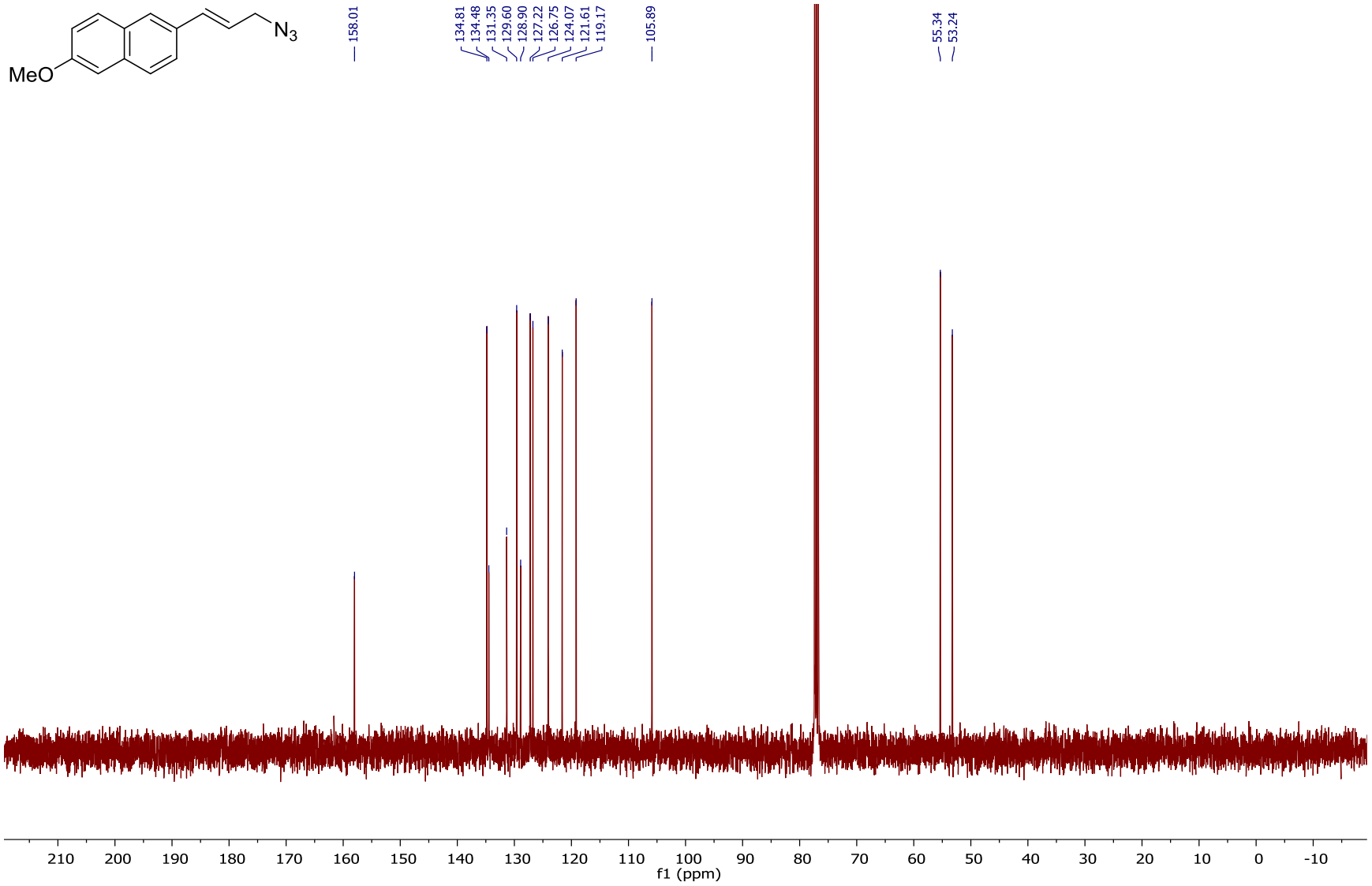
Compound 1k: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



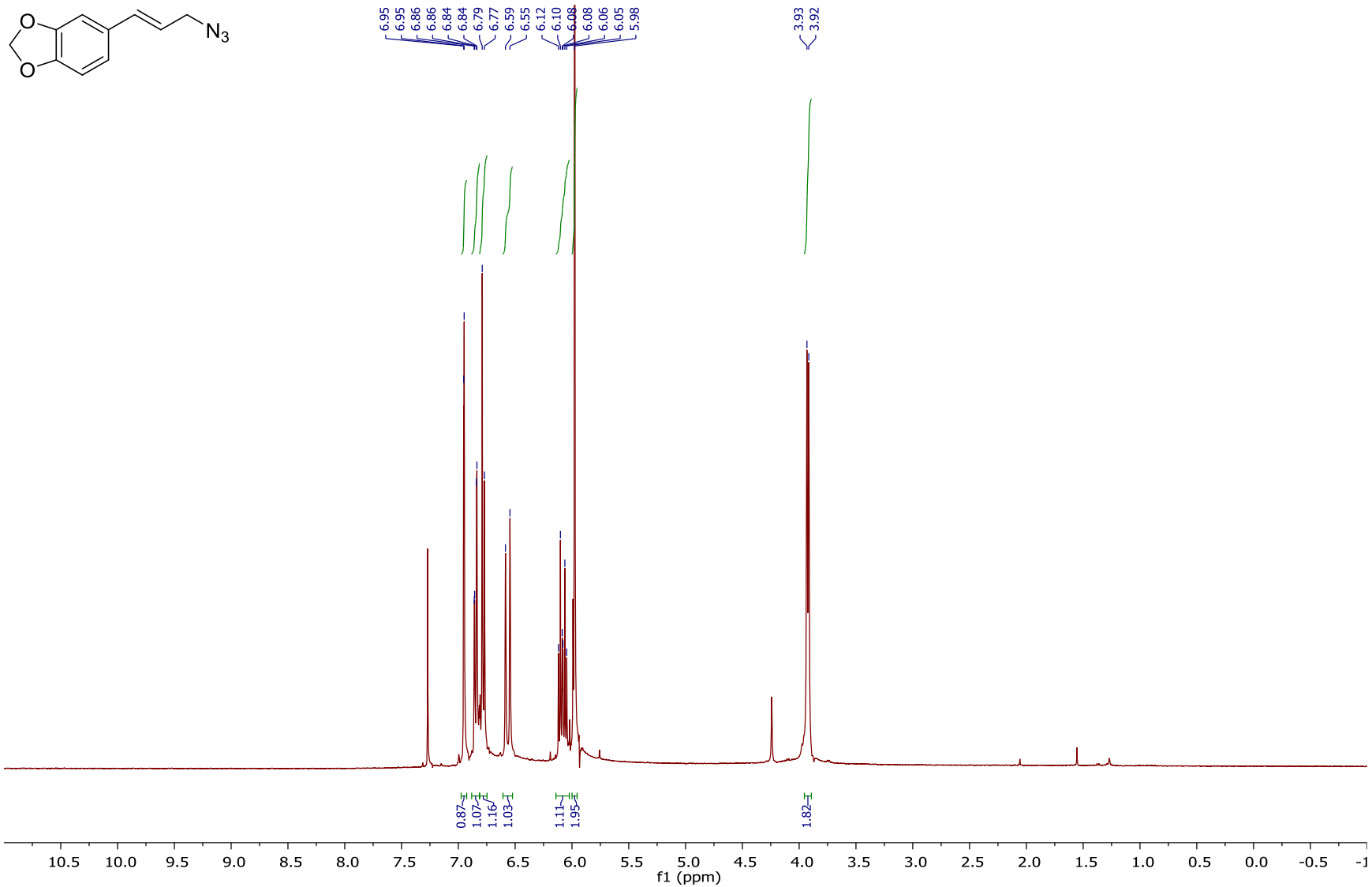
Compound 1k: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



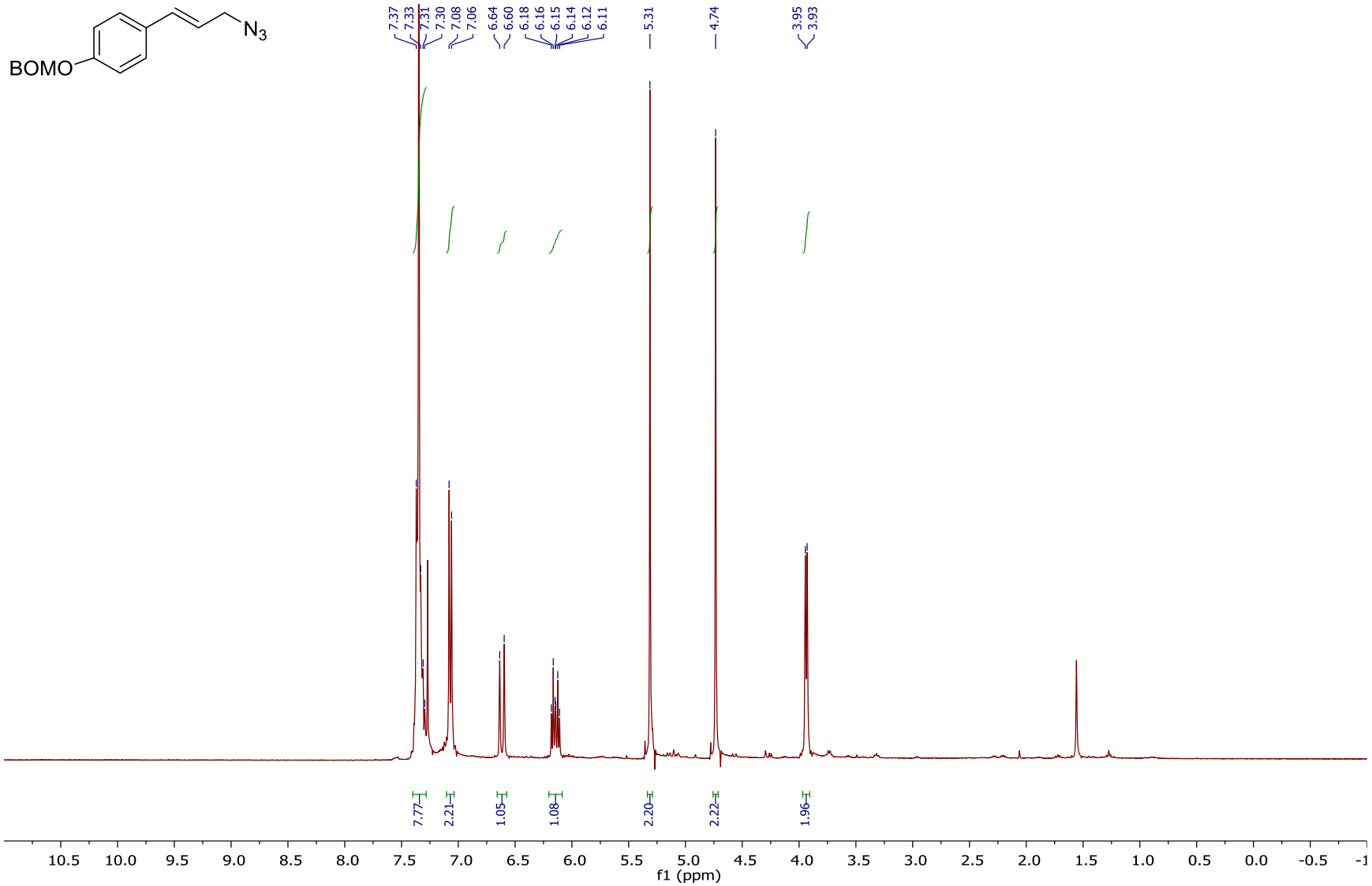
Compound 1l: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



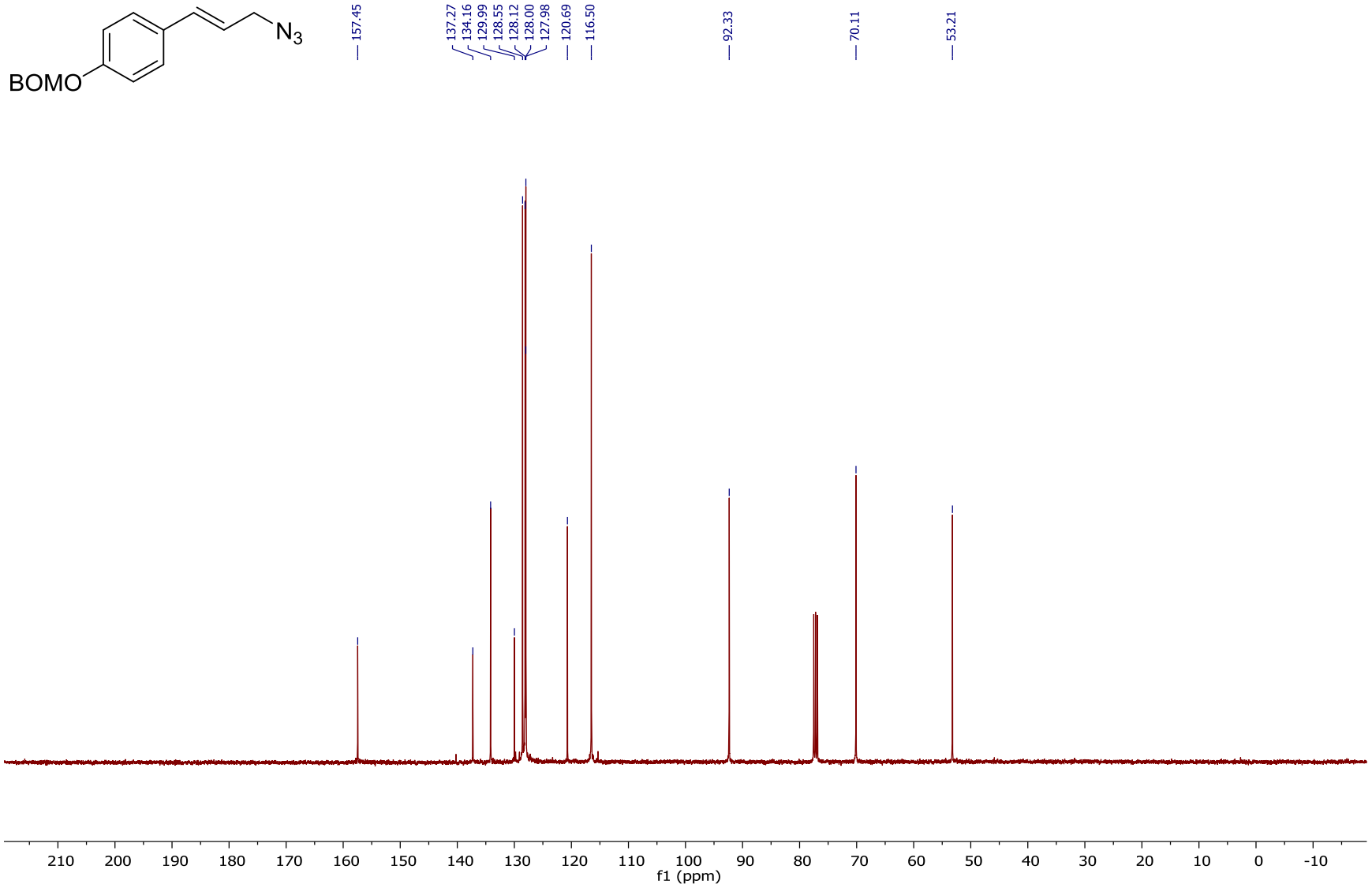
Compound 1l: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



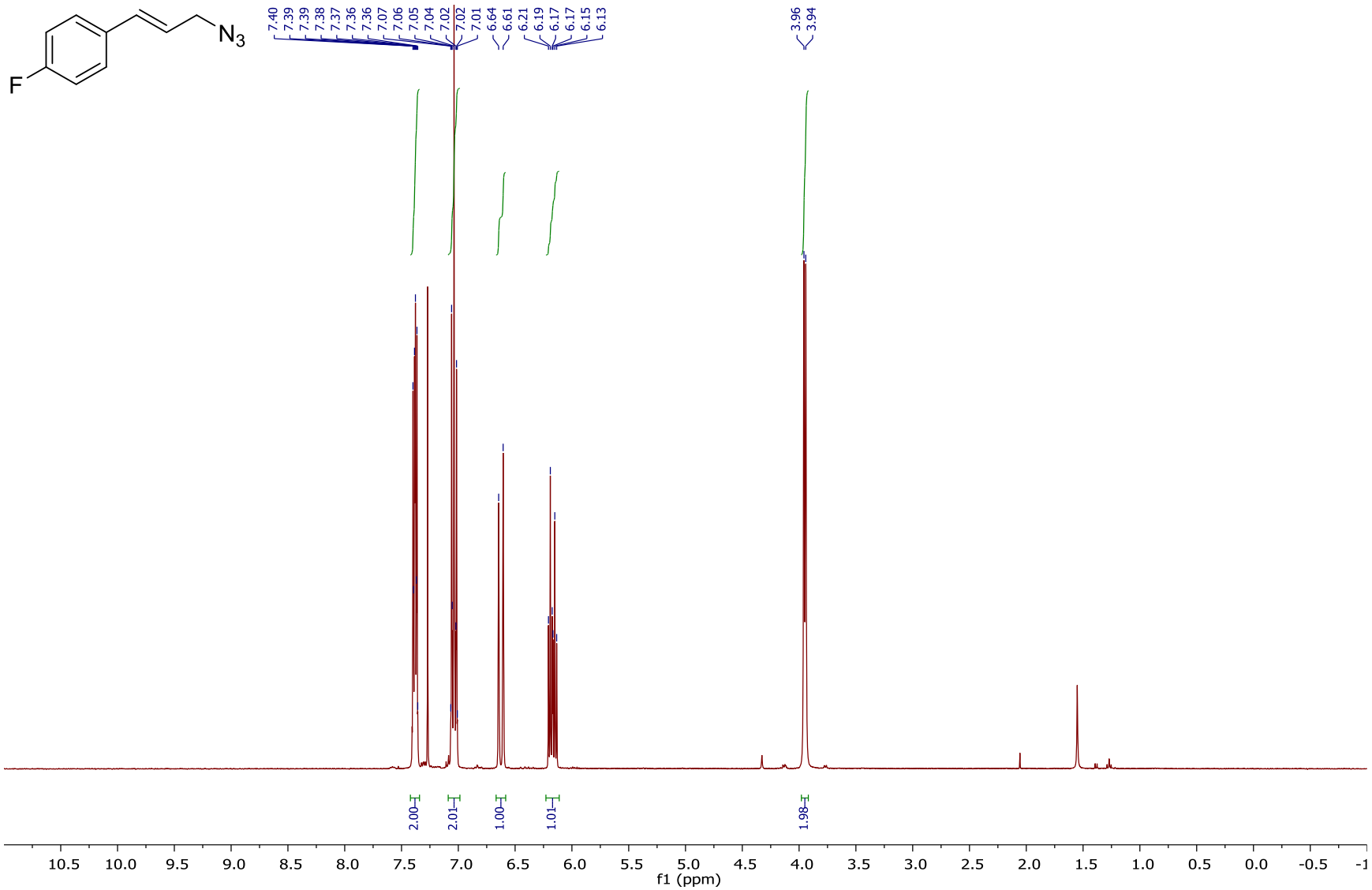
Compound 1m: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



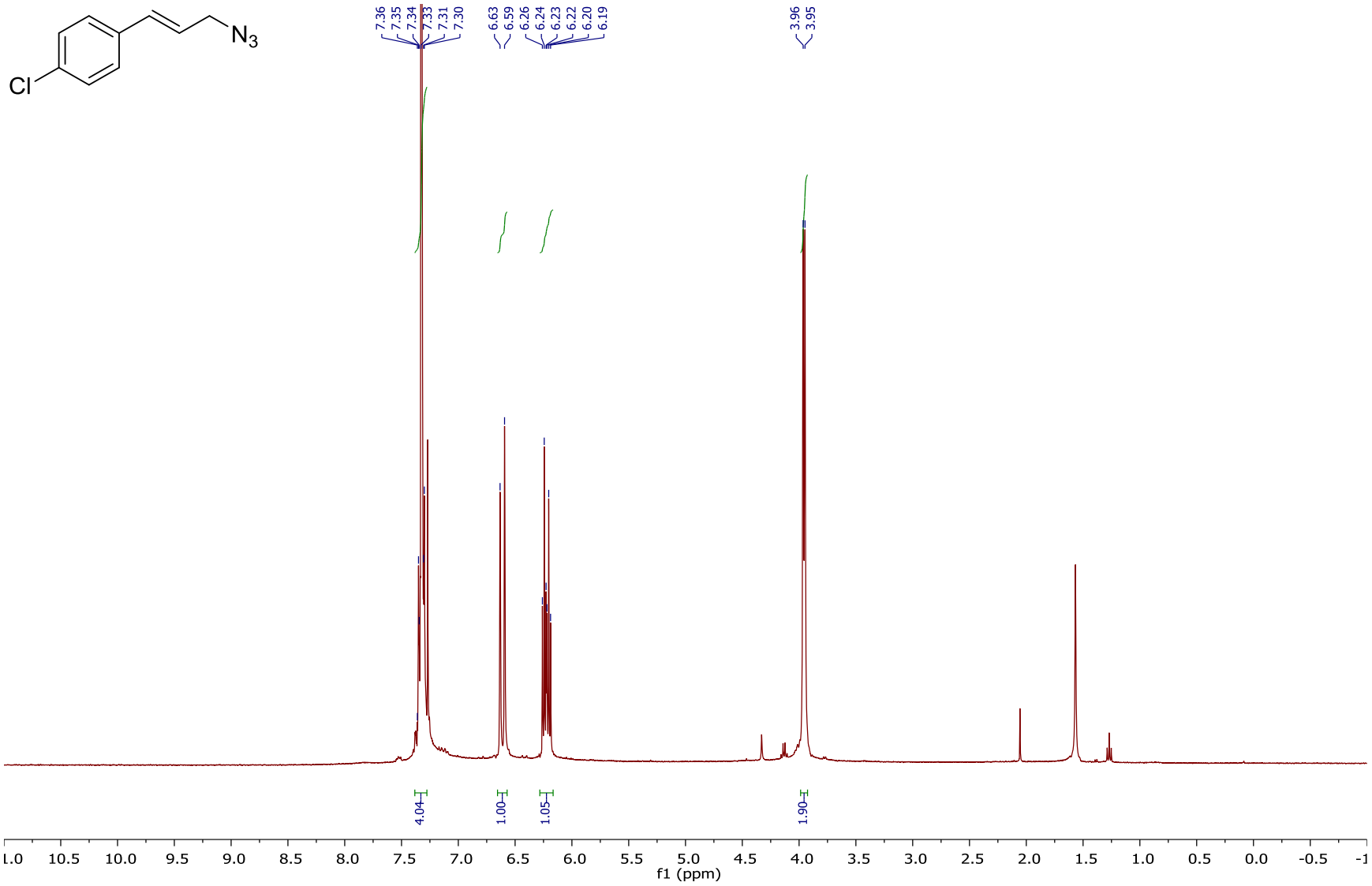
Compound 1n: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



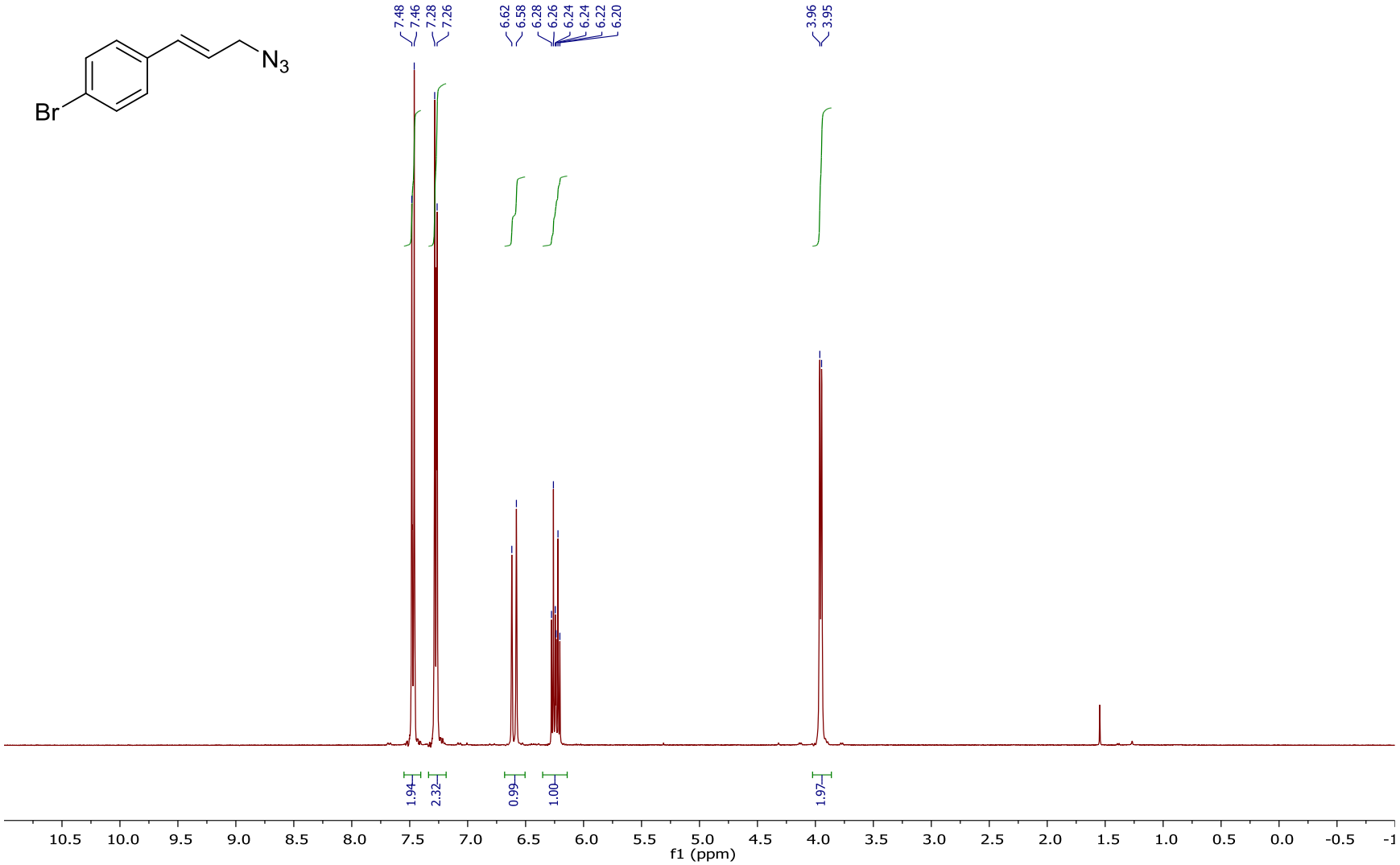
Compound 1n: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



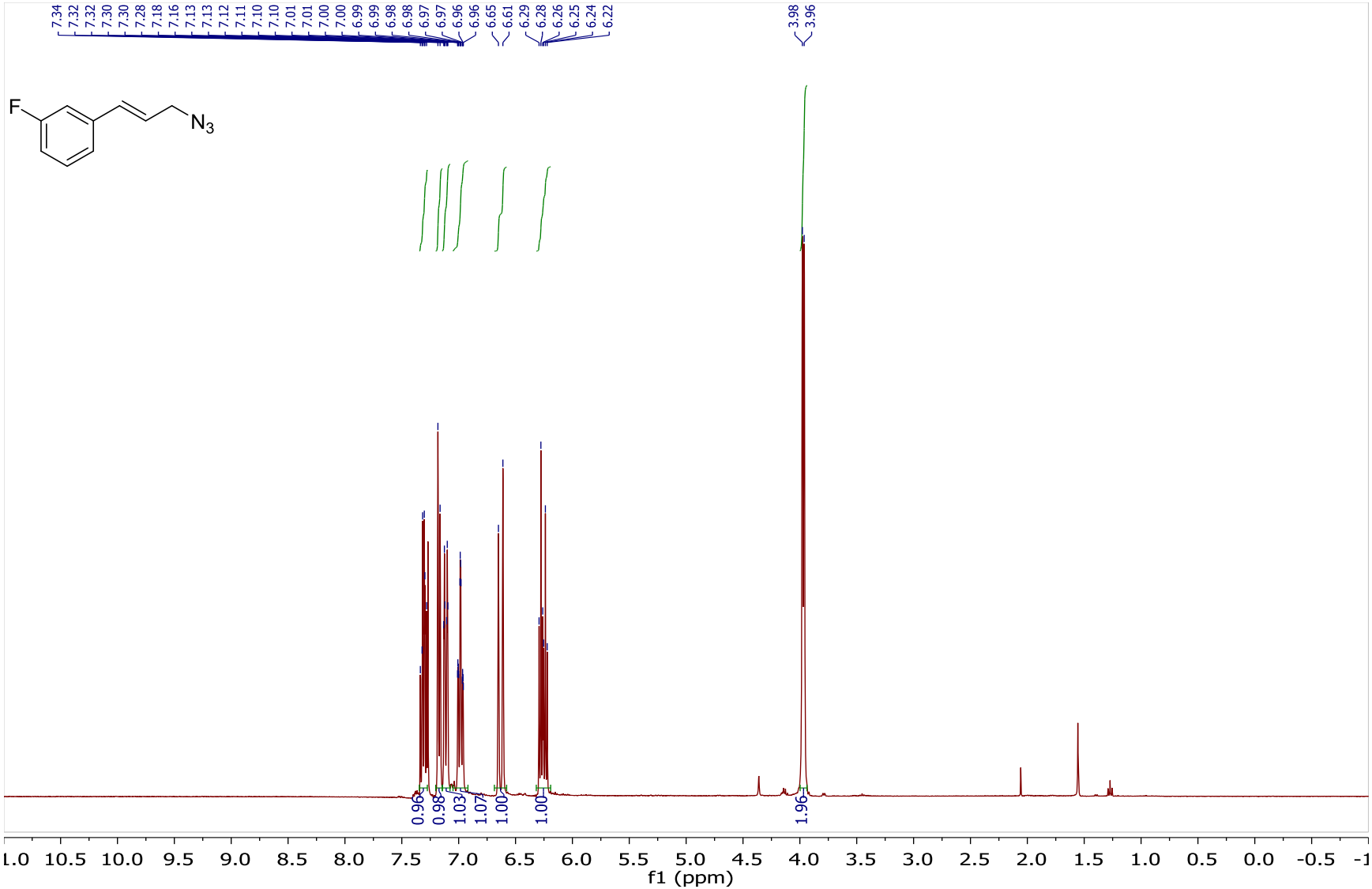
Compound 1o: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



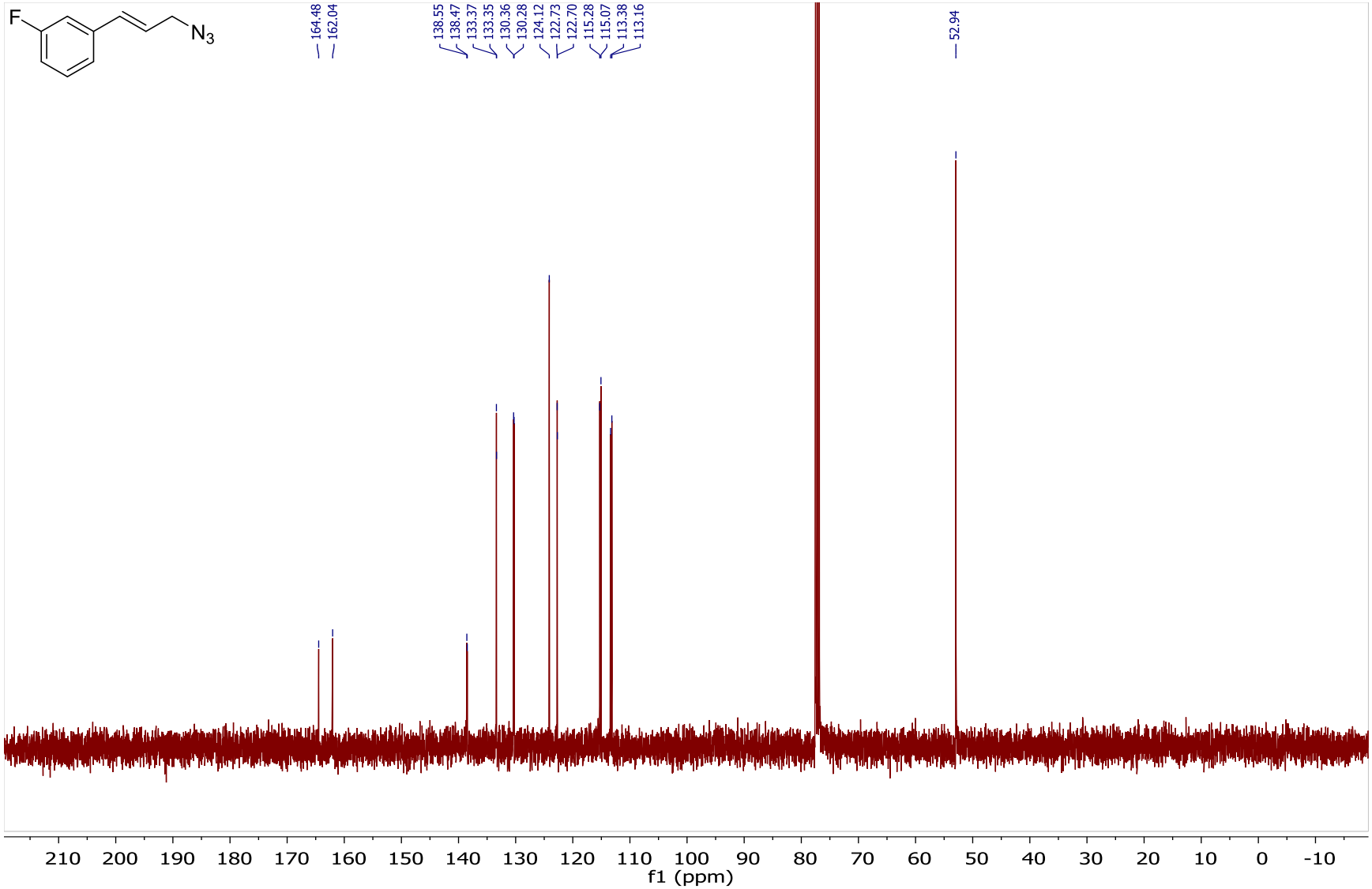
Compound 1p: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



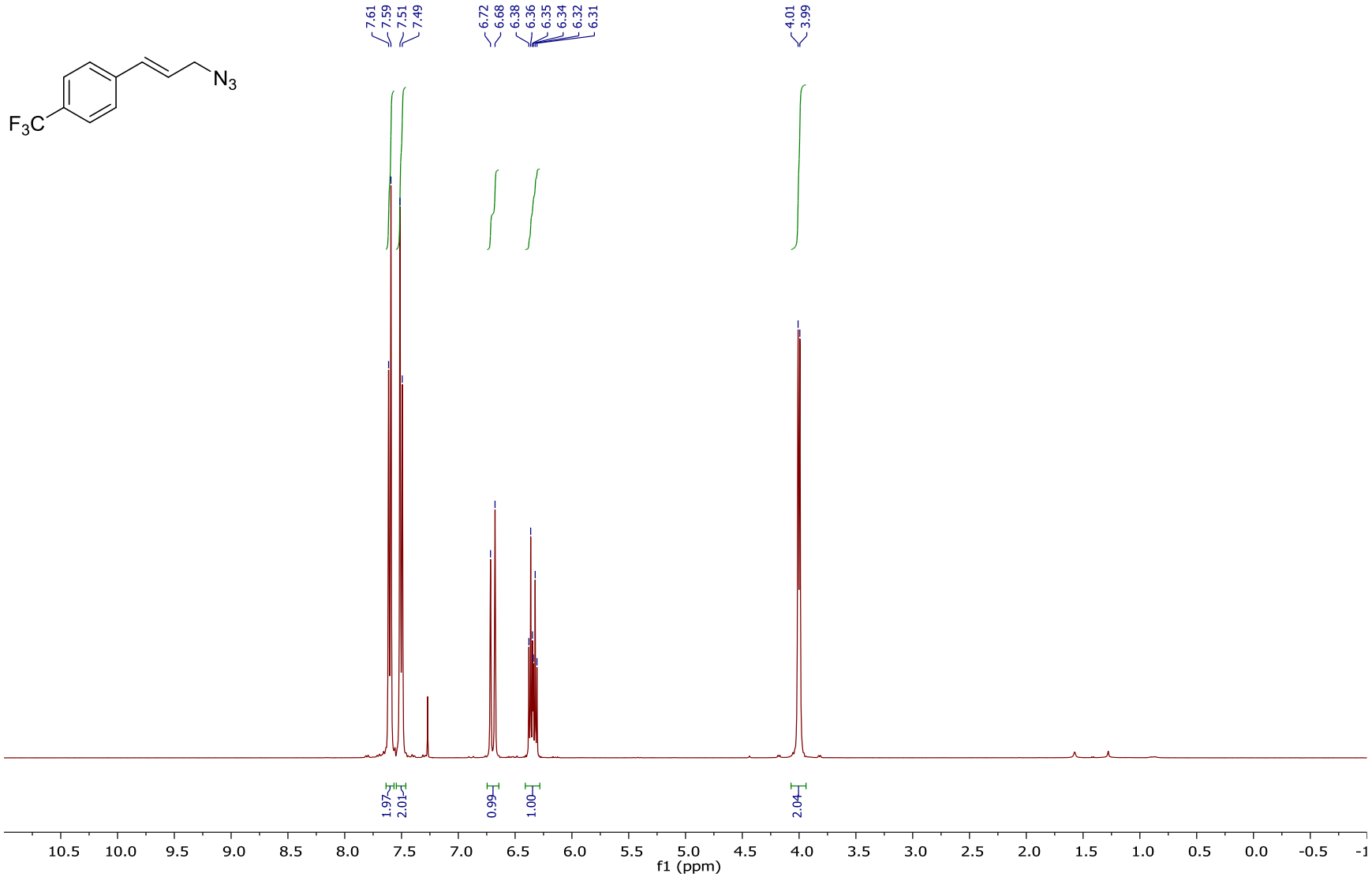
Compound 1q: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



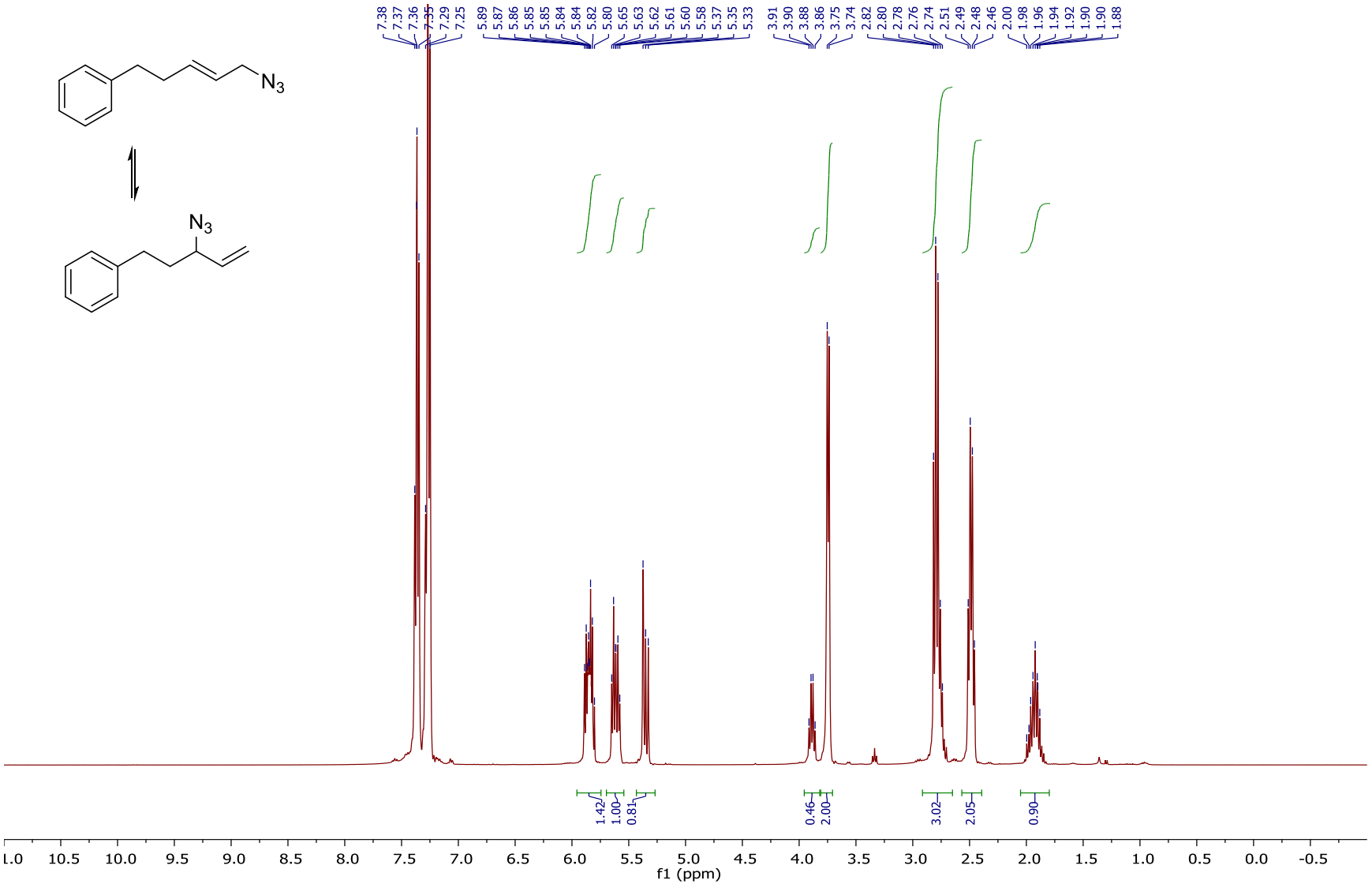
Compound 1r: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



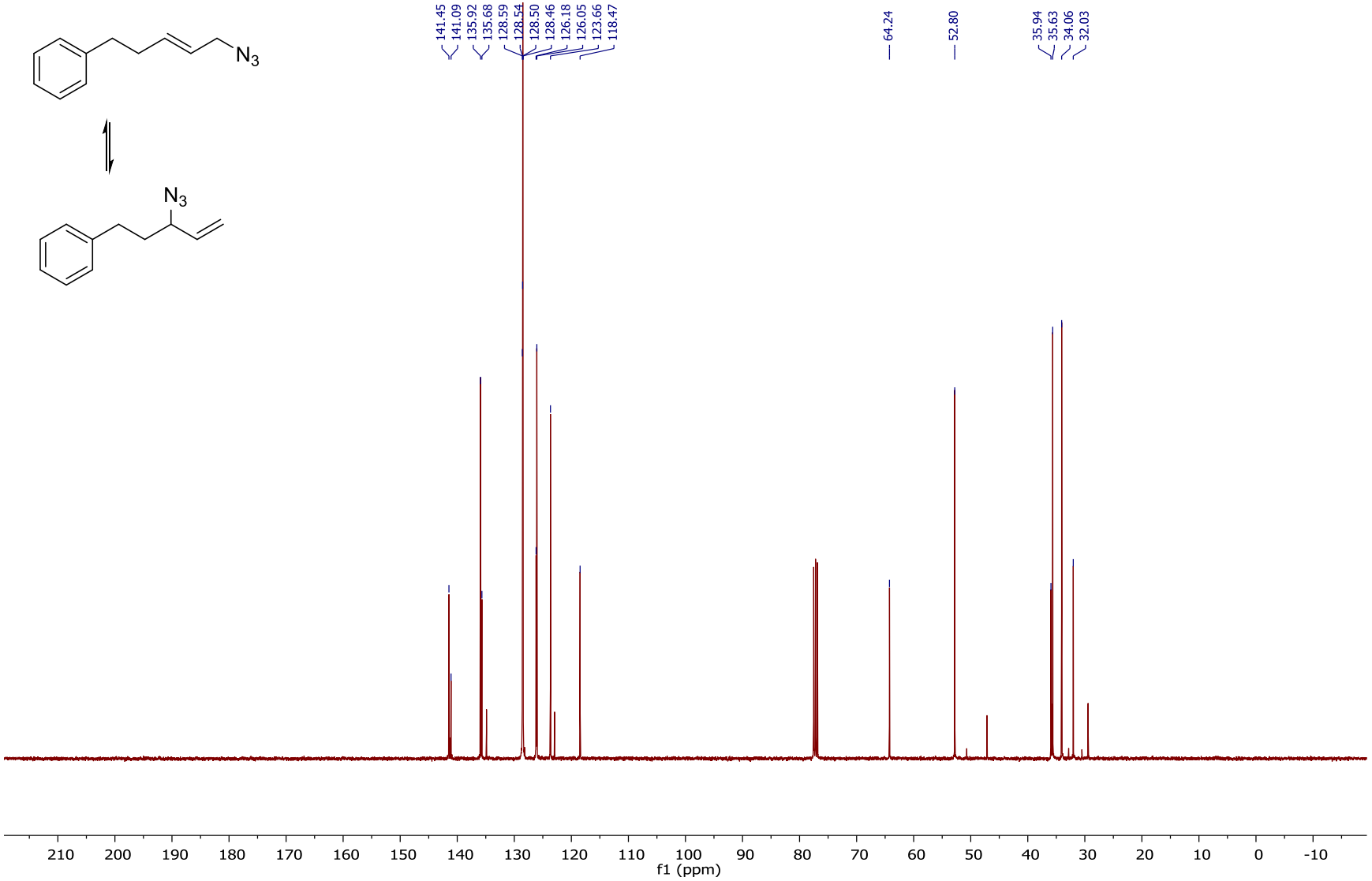
Compound 1r: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



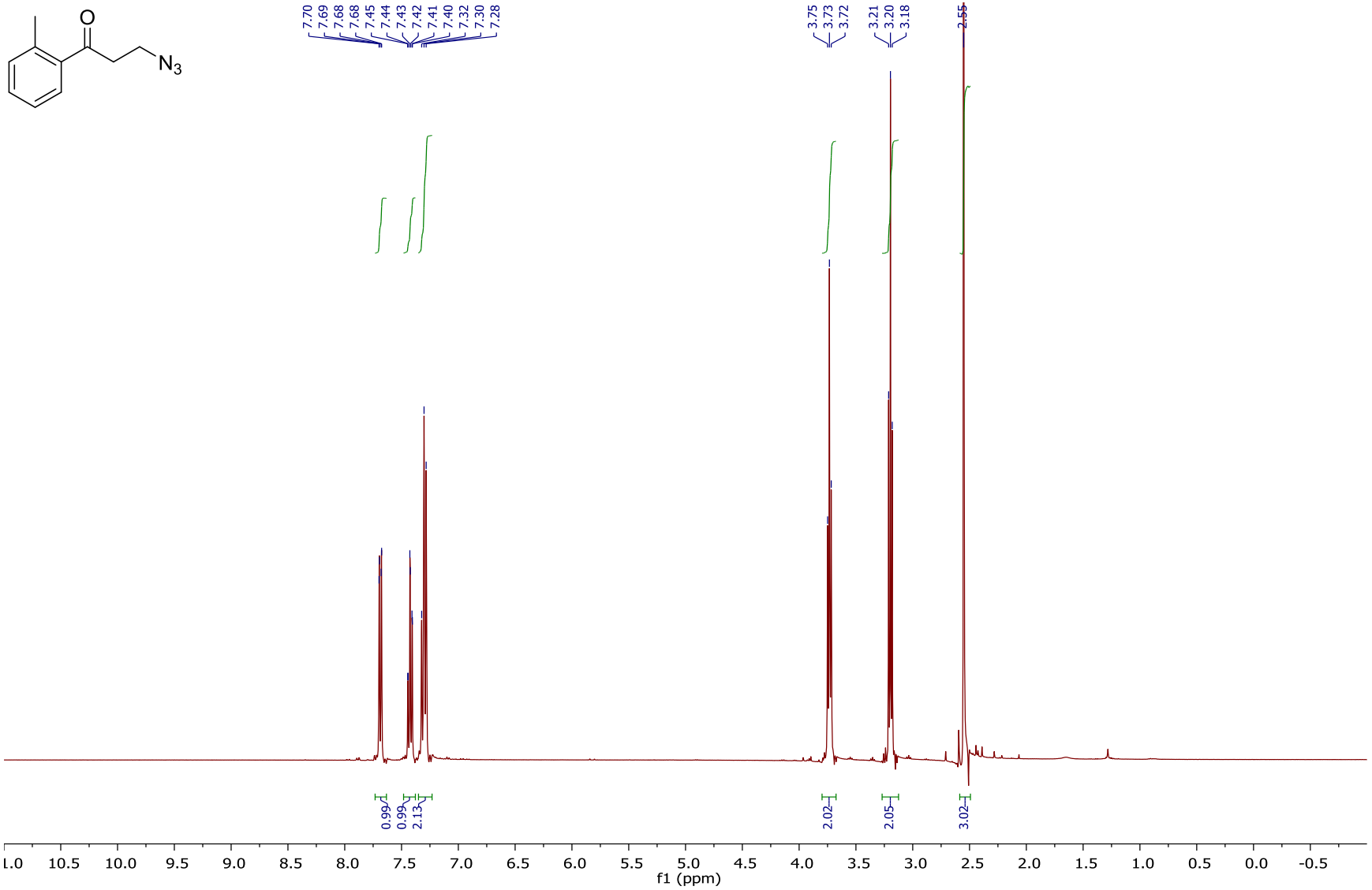
Compound 1s: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



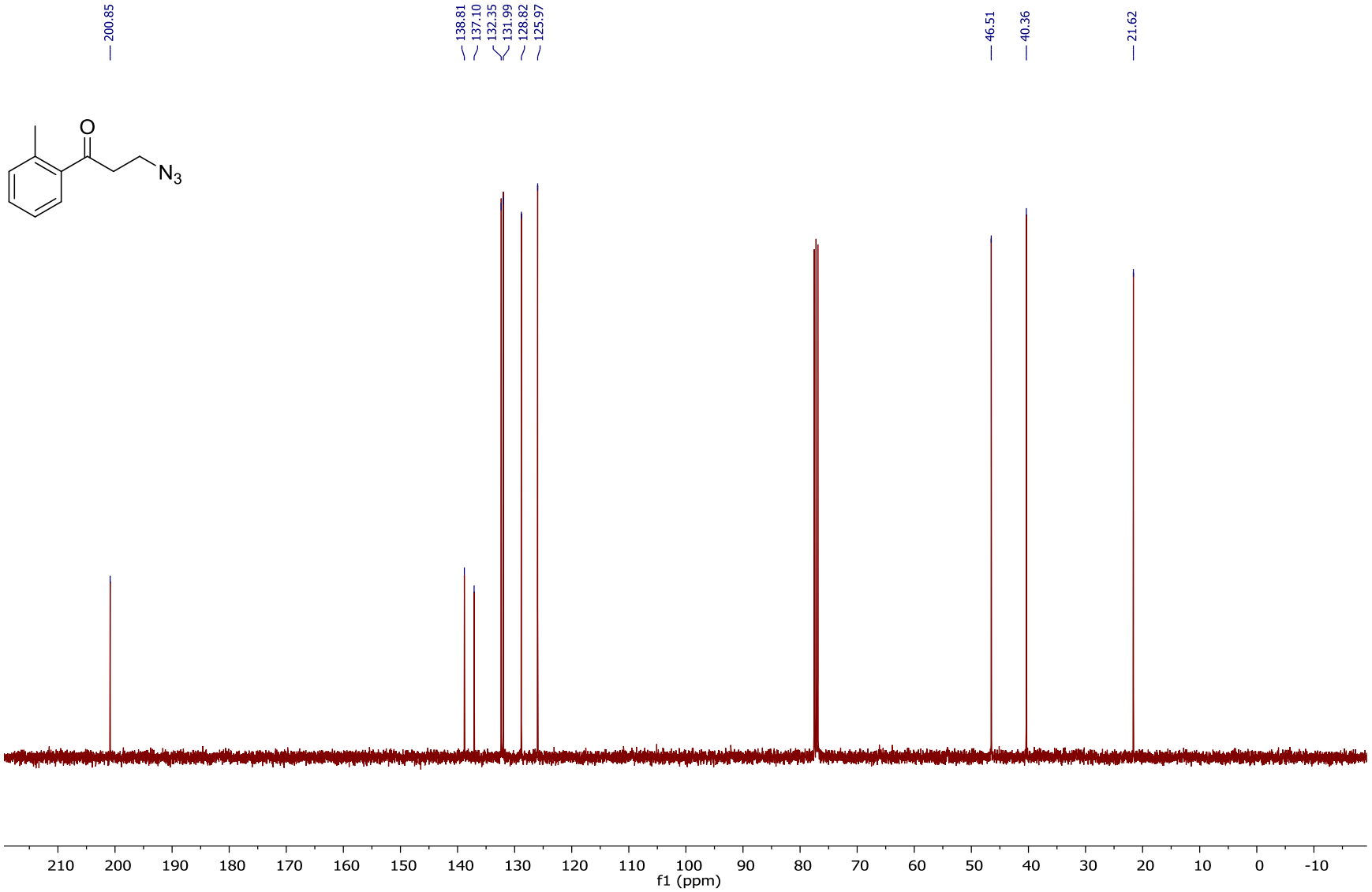
Compounds 4 and 5: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



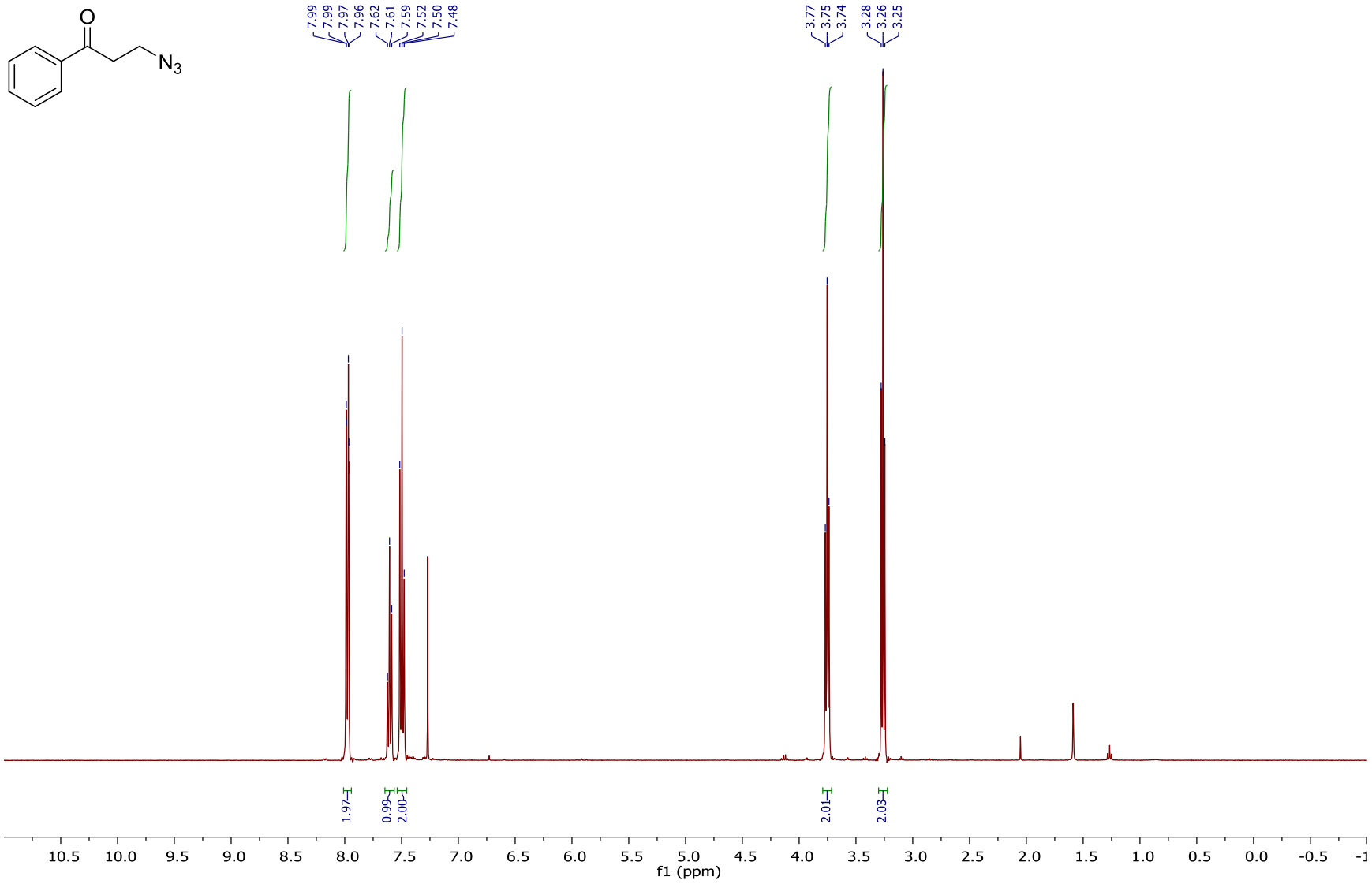
Compounds 4 and 5: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



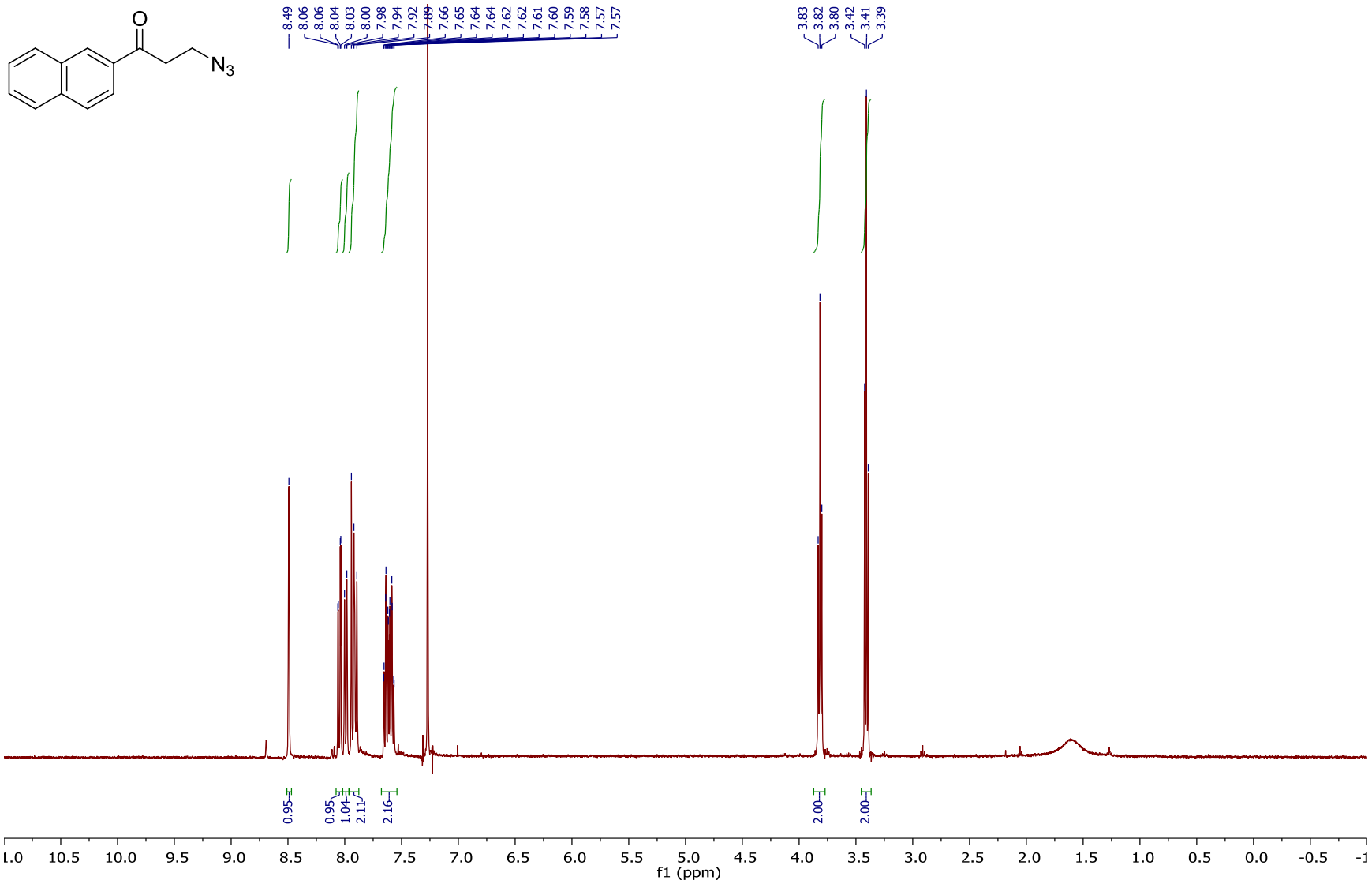
Compound 2a: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



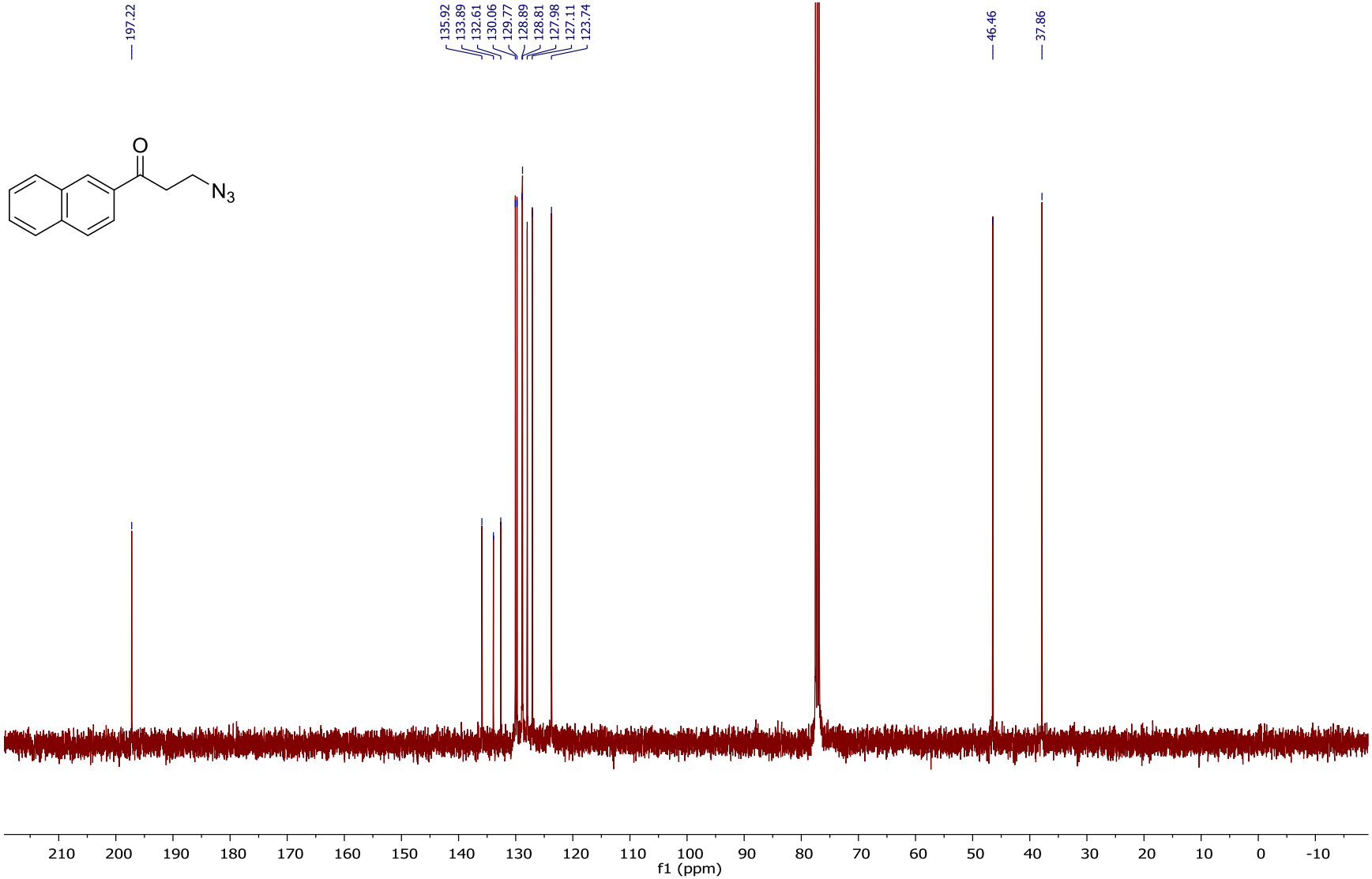
Compound 2a: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



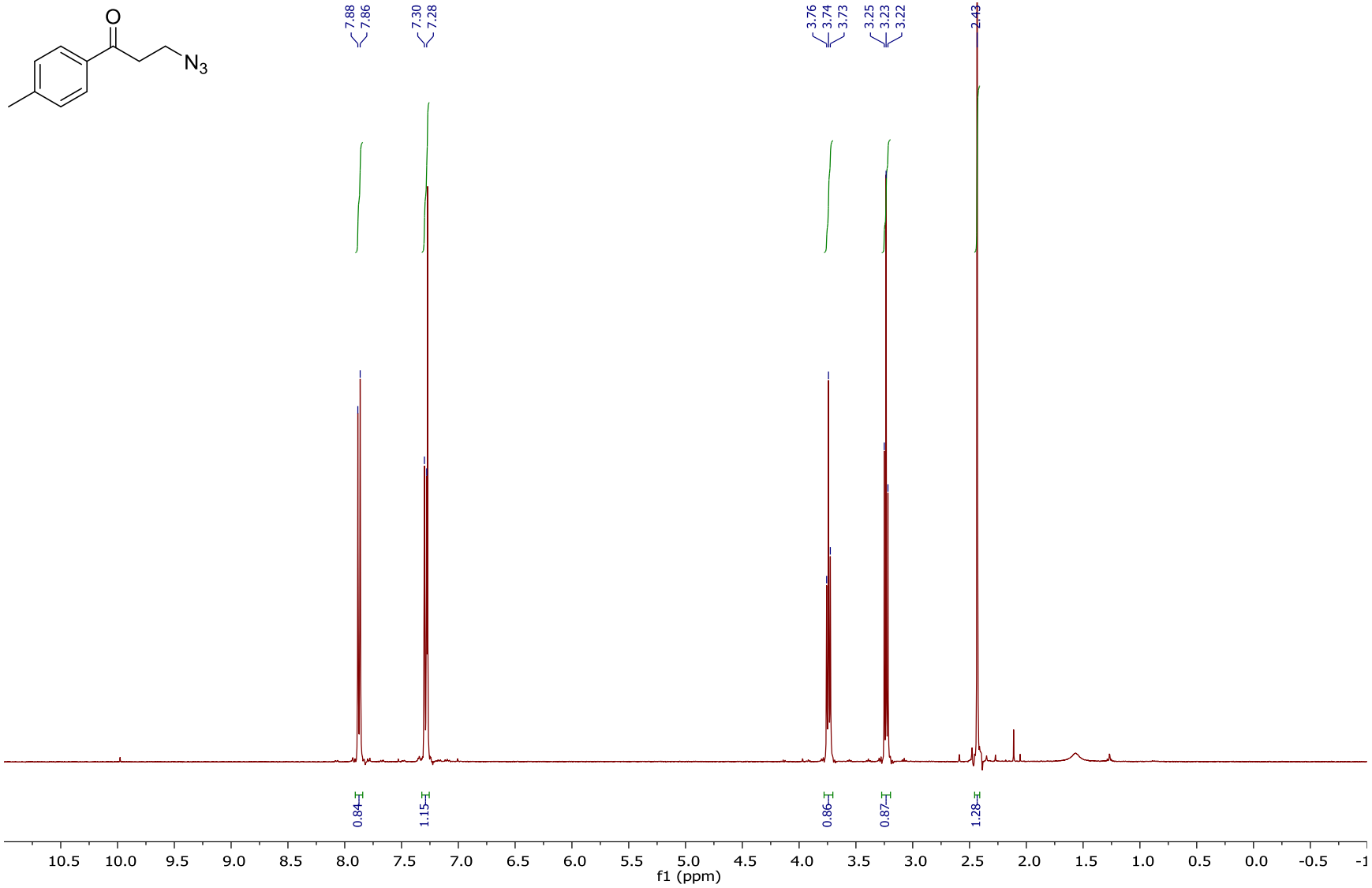
Compound 2b: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



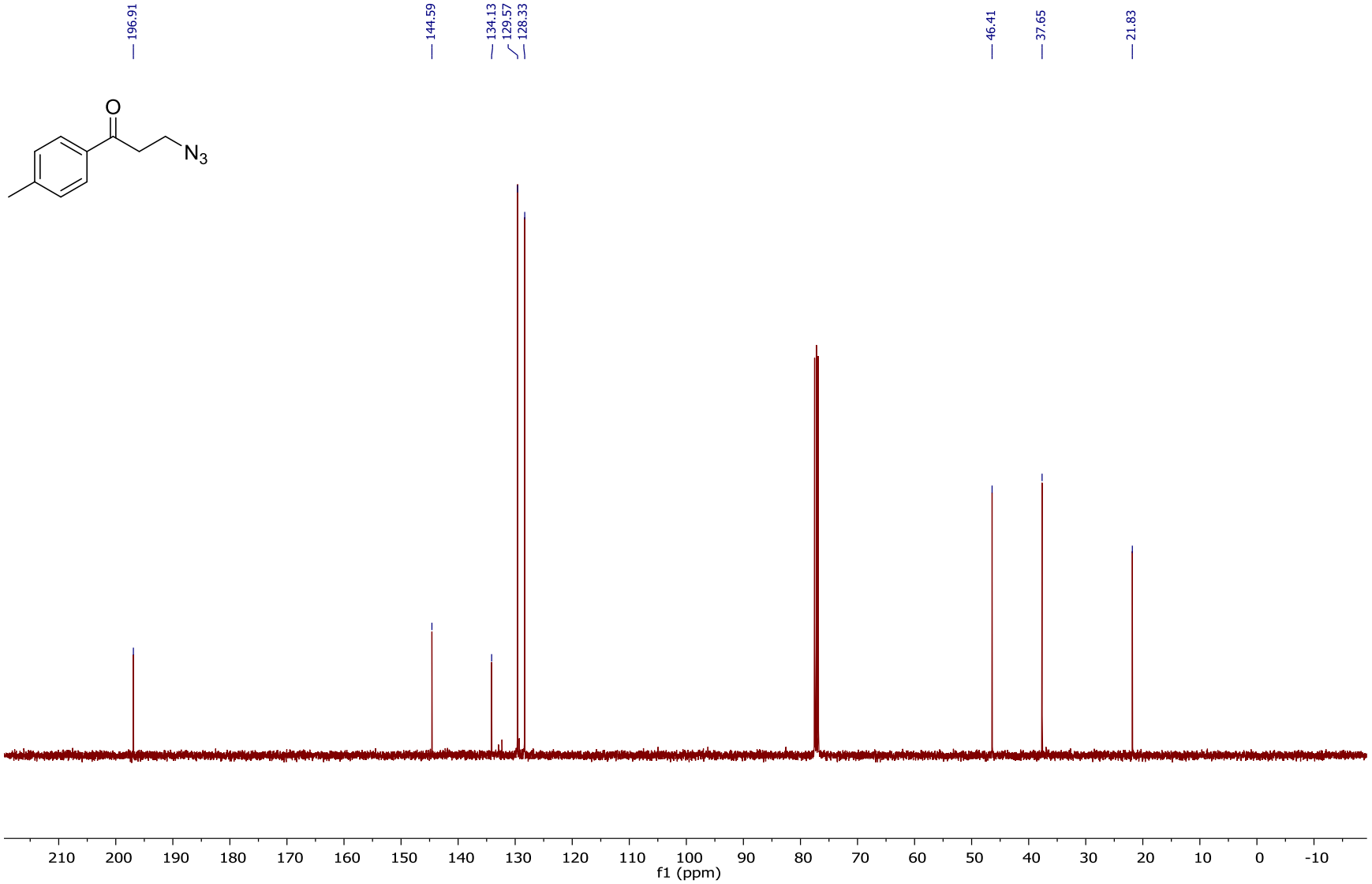
Compound 2c: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



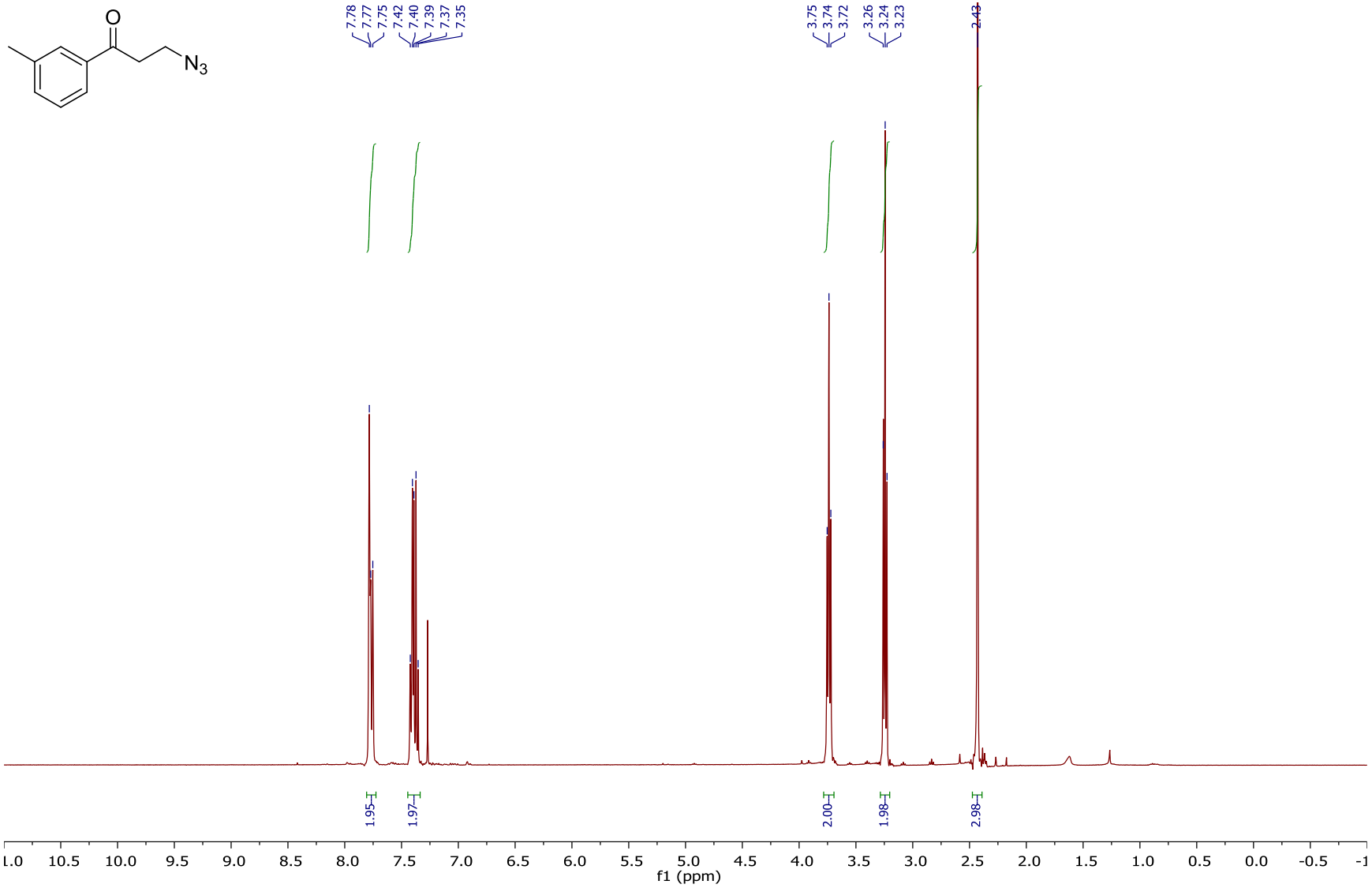
Compound 2c: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



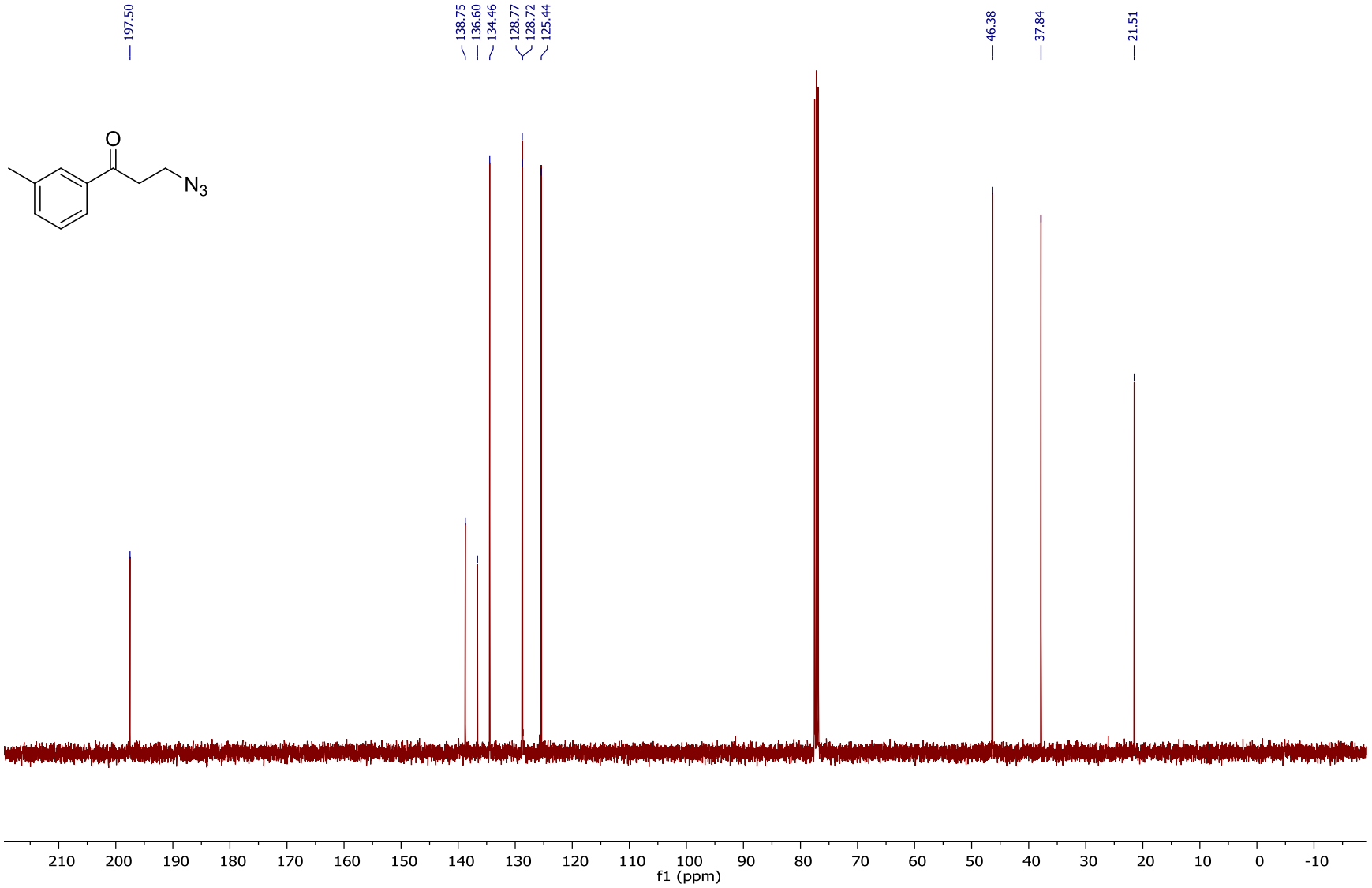
Compound 2d: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



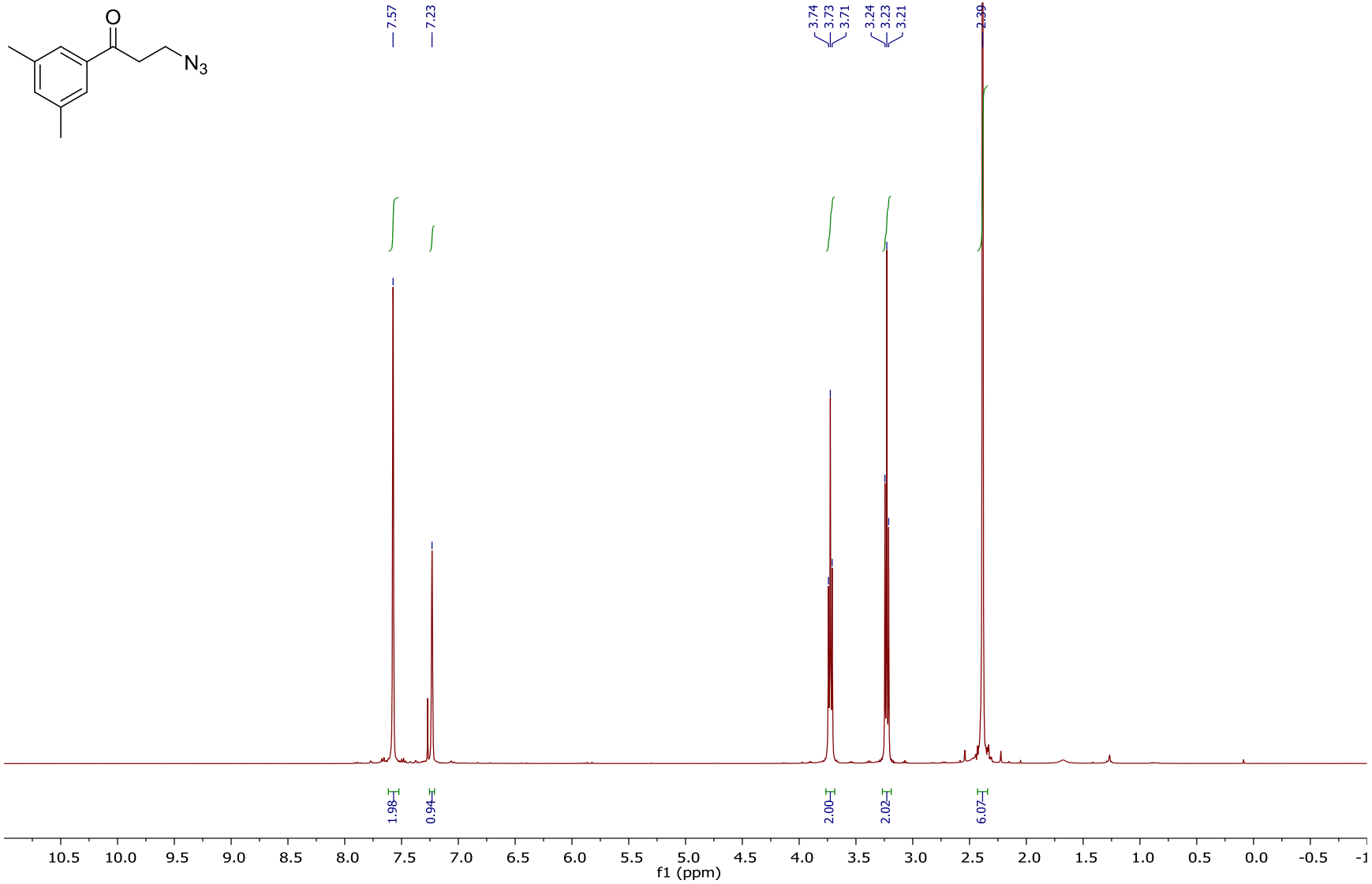
Compound 2d: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



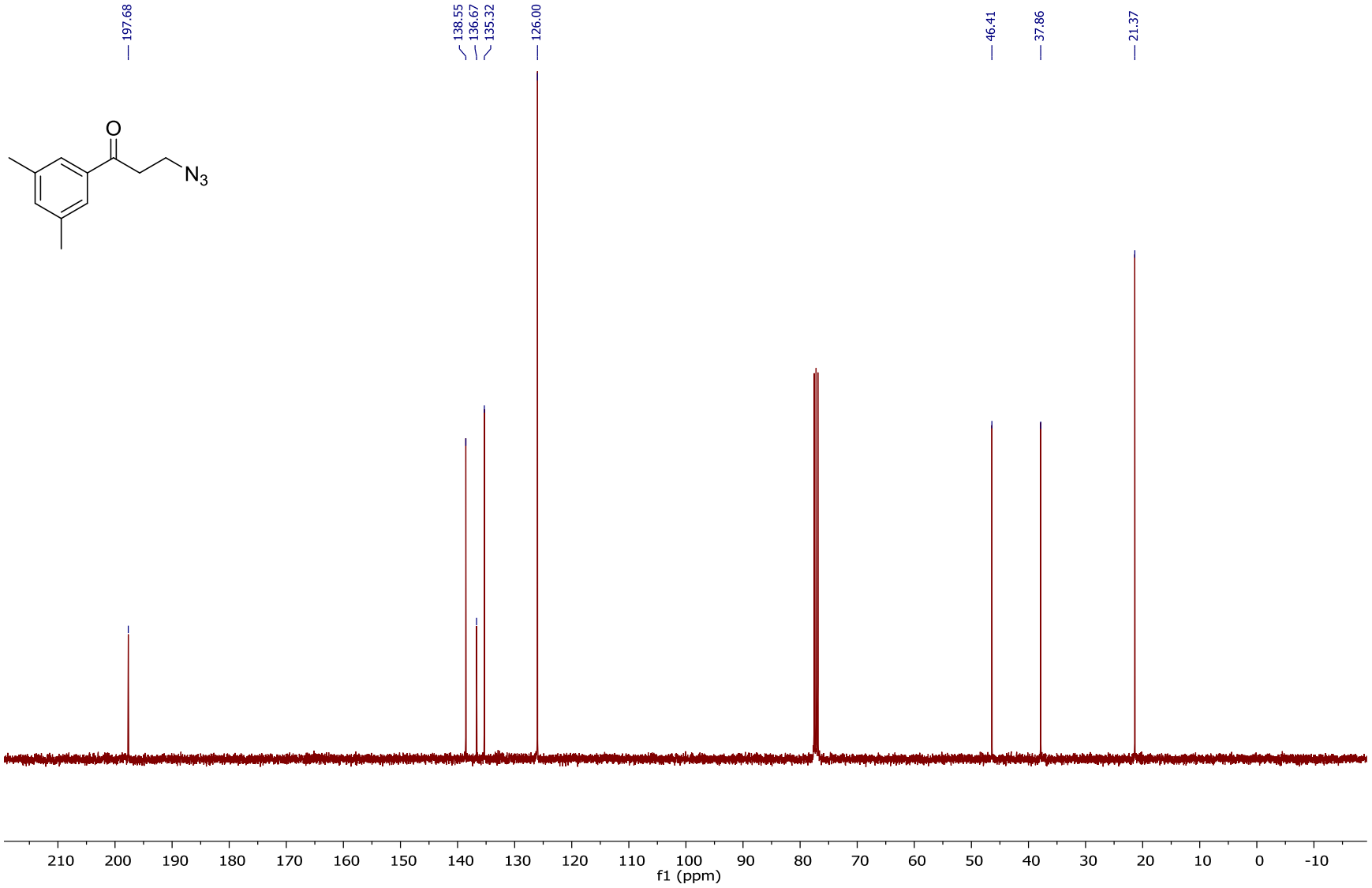
Compound 2e: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



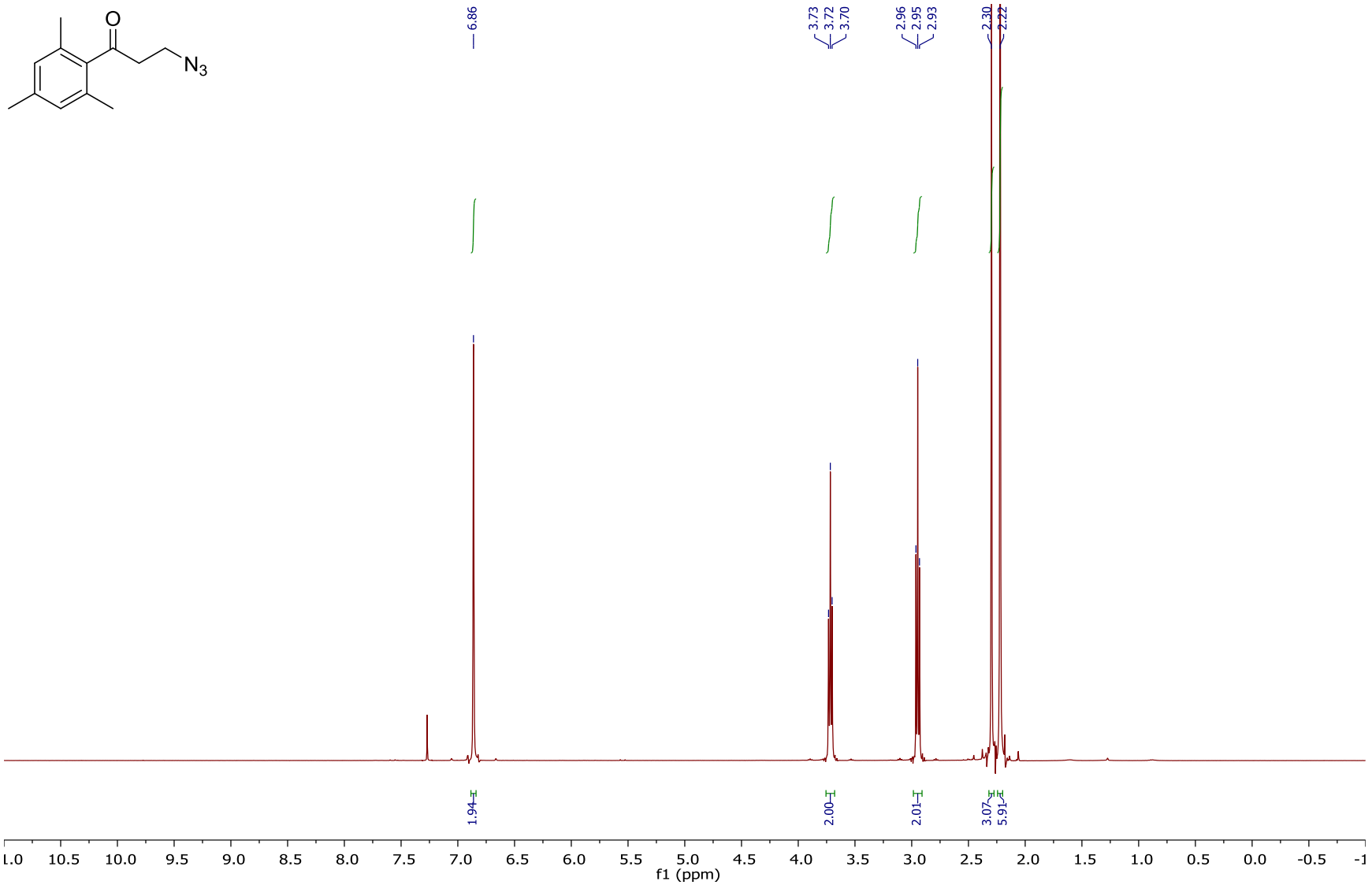
Compound 2e: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



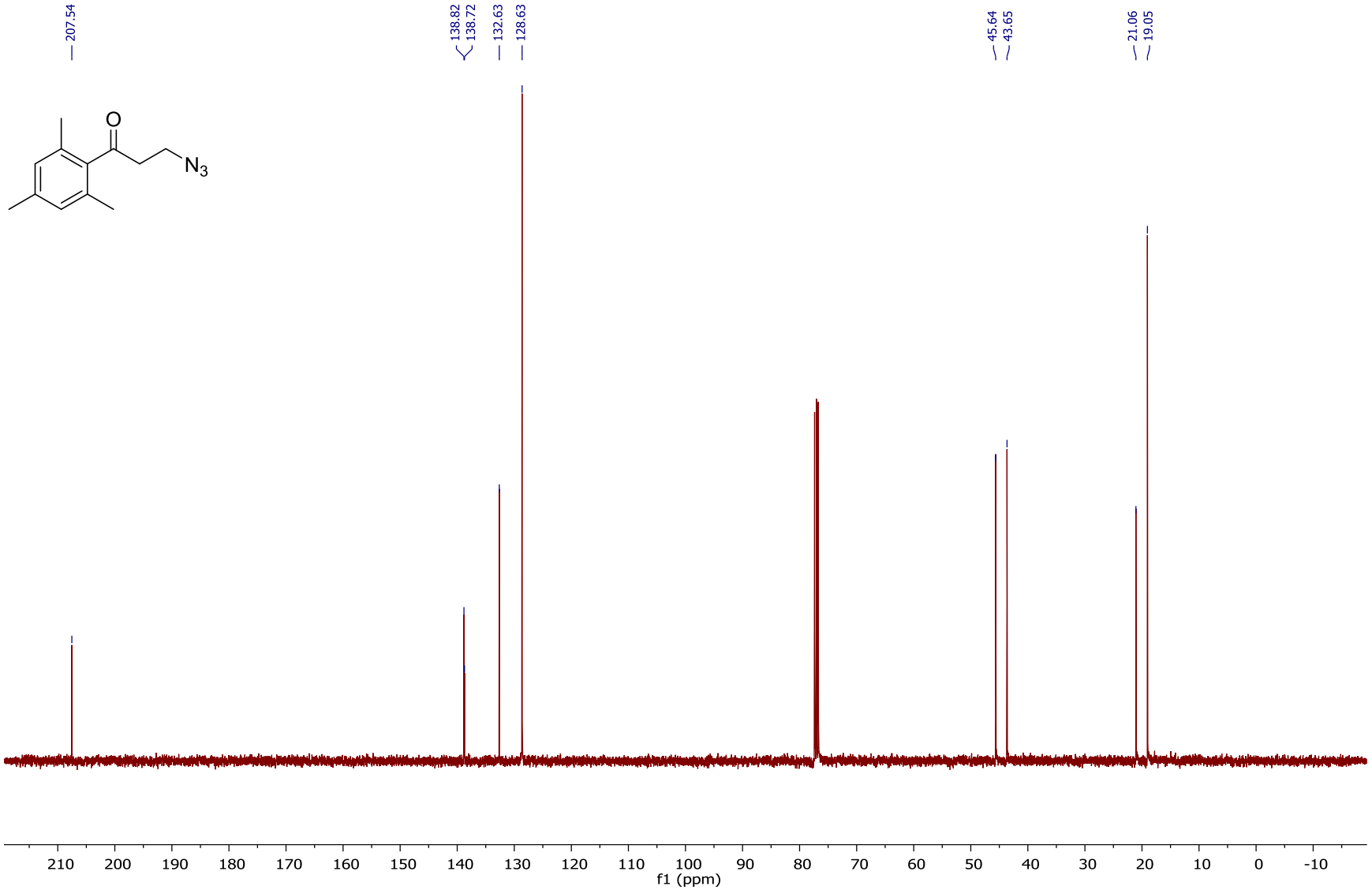
Compound 2f: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



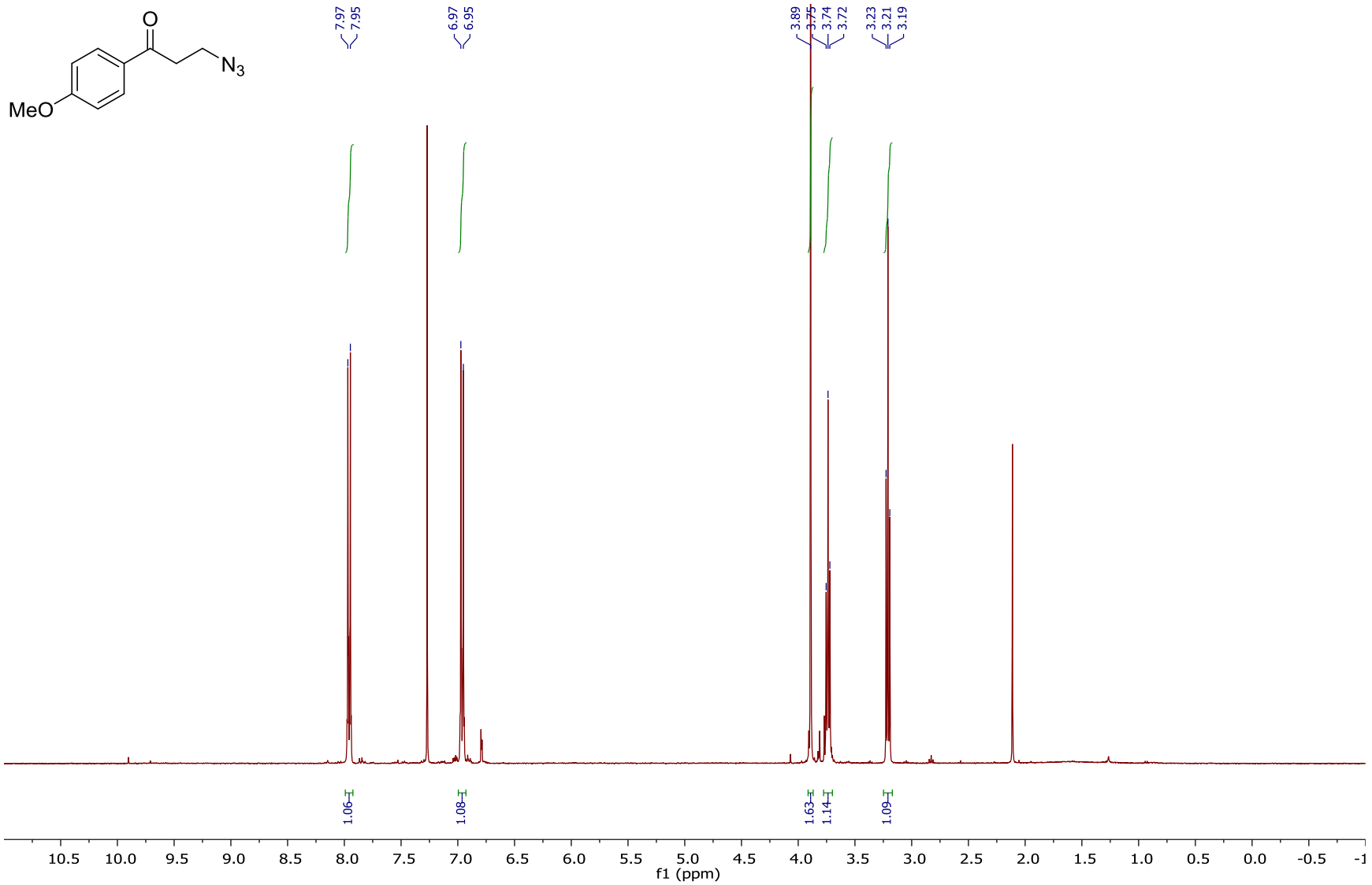
Compound 2f: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



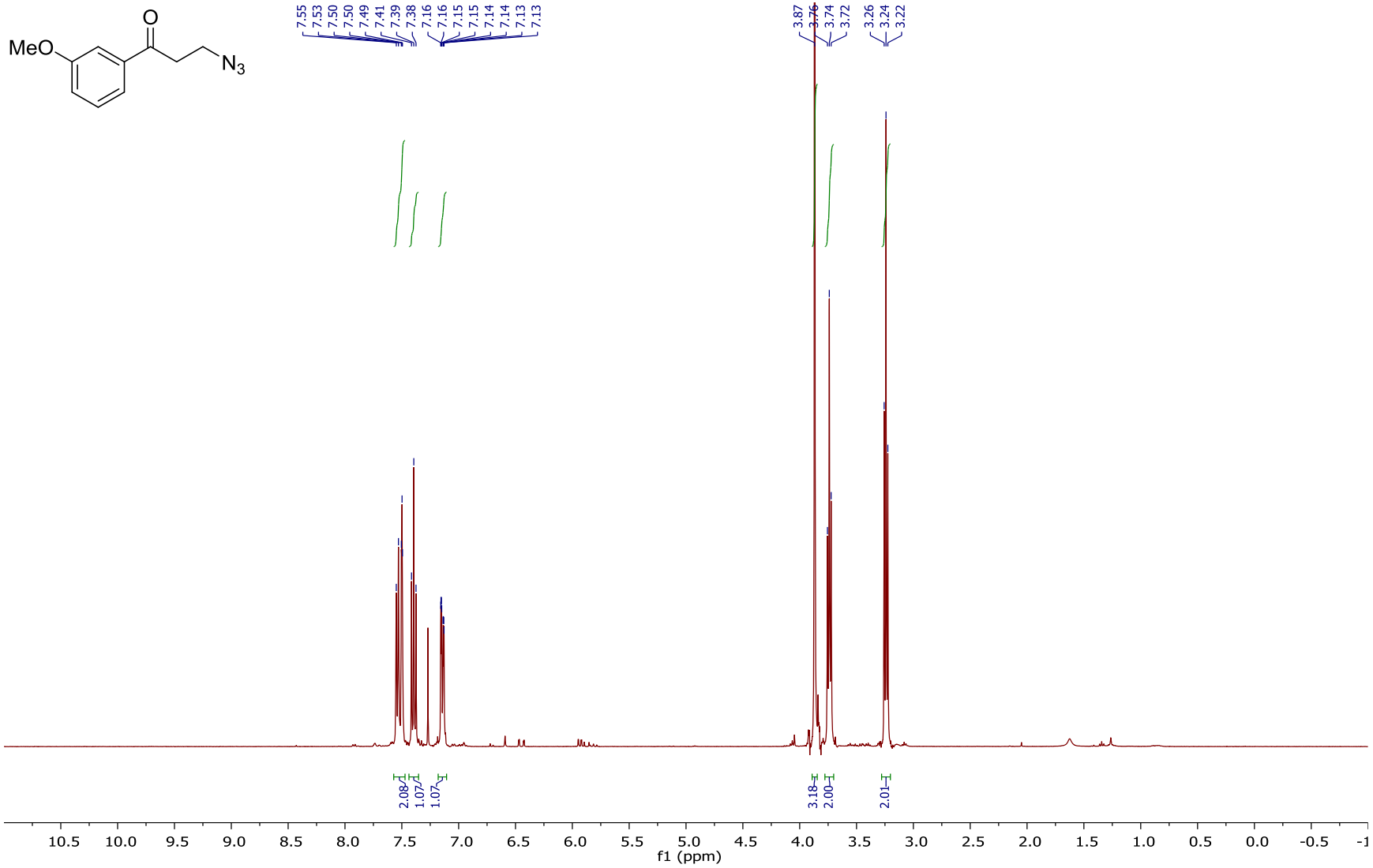
Compound 2g: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



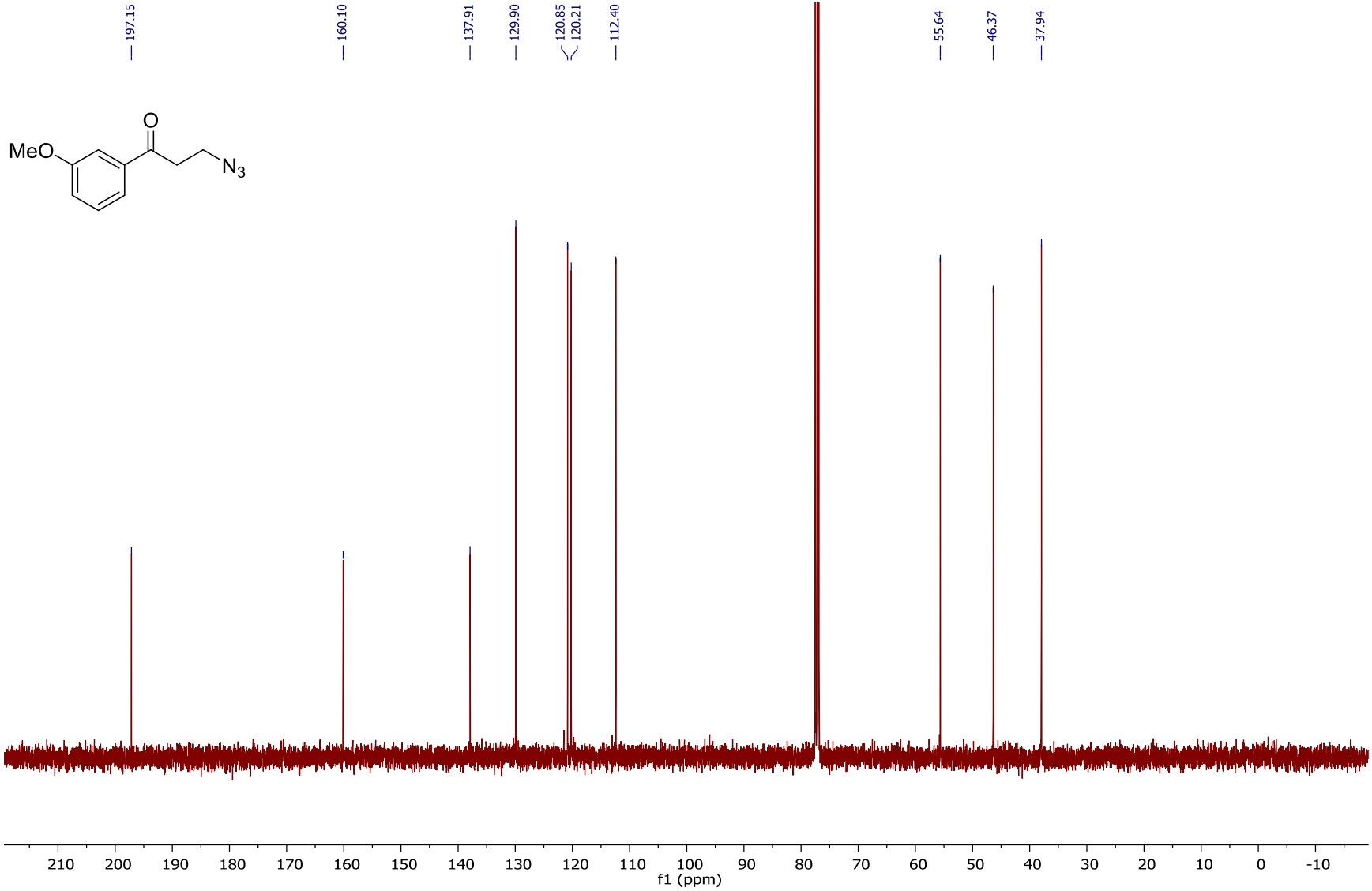
Compound 2g: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



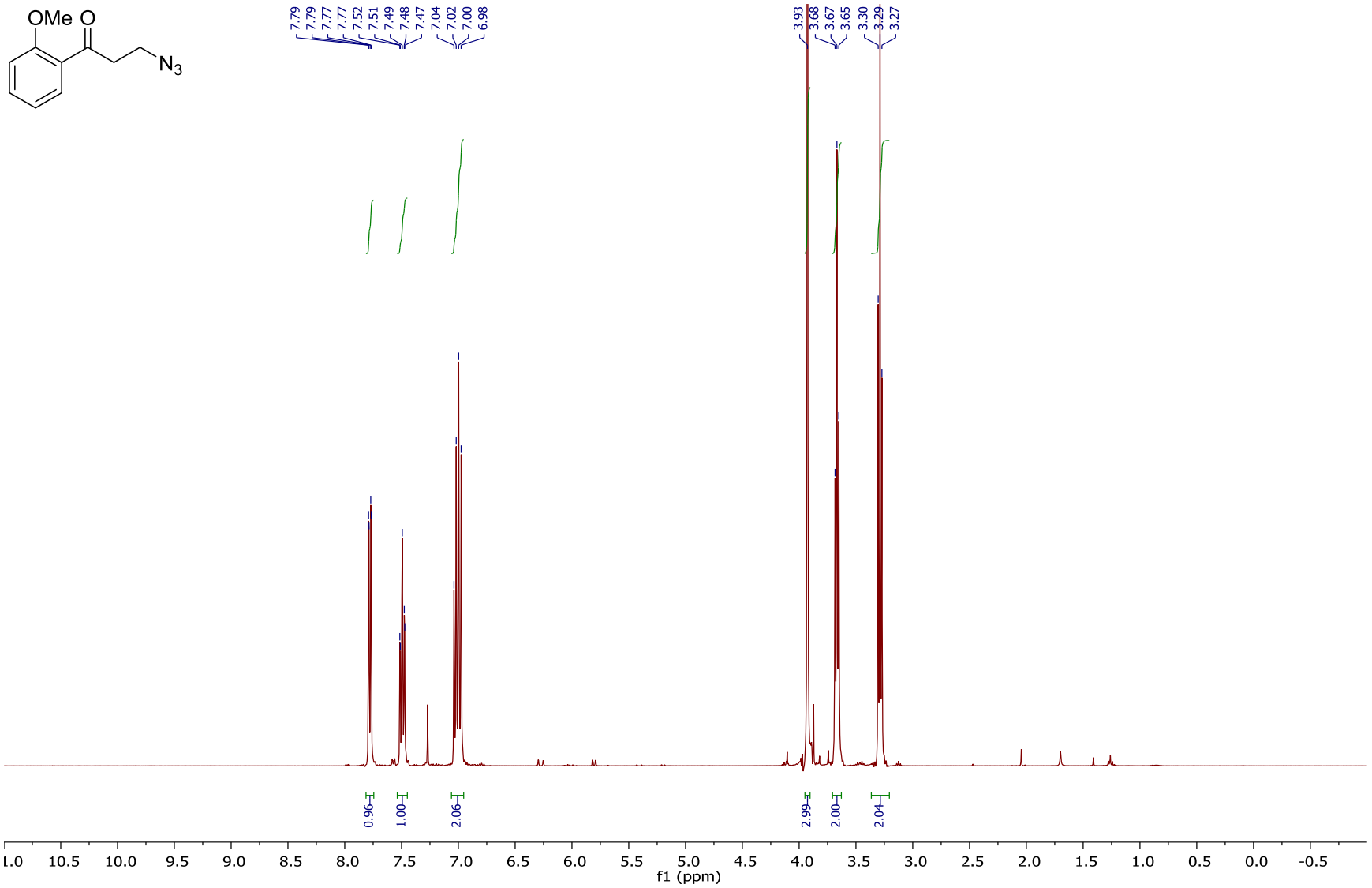
Compound 2h: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



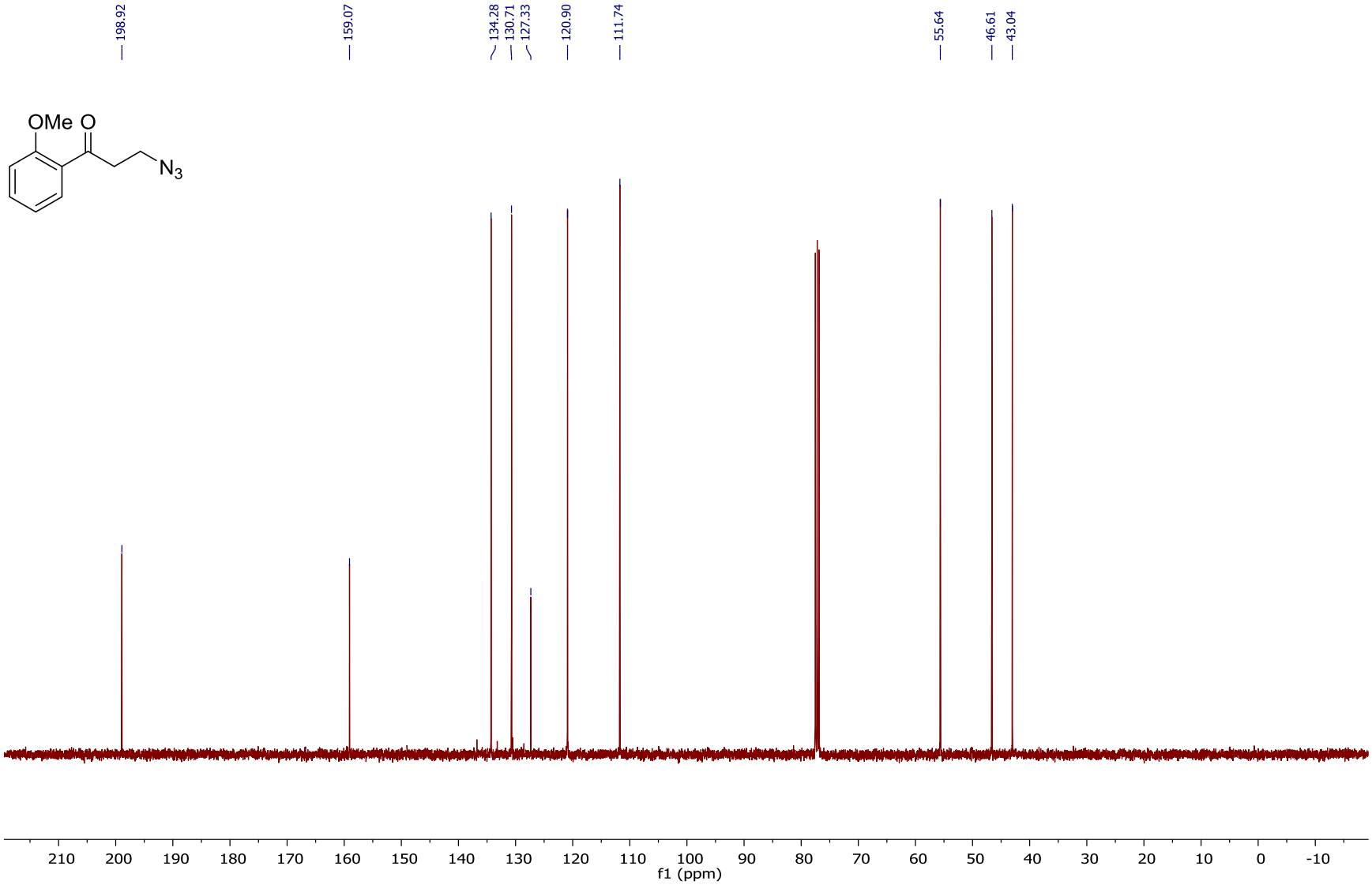
Compound 2i: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



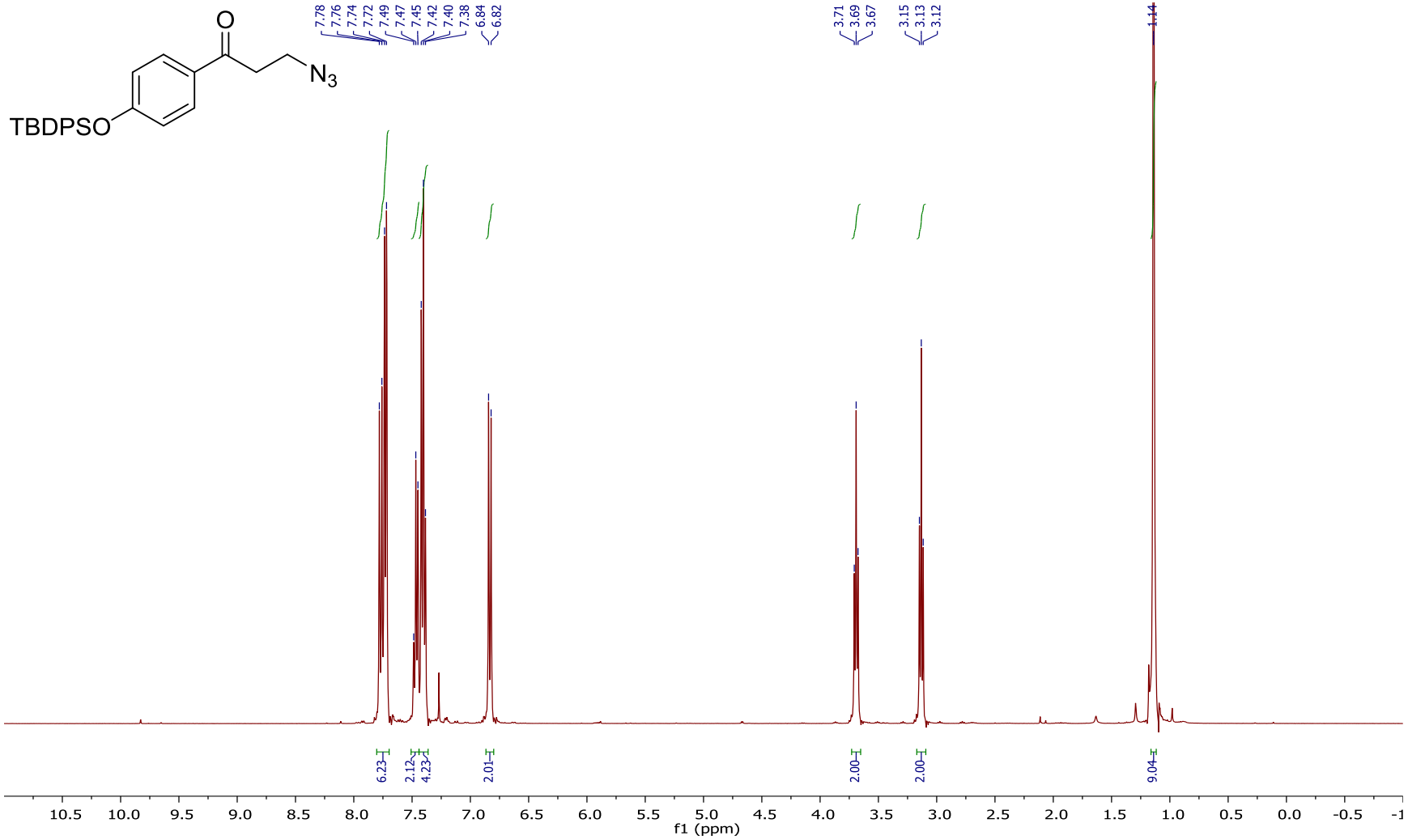
Compound 2i: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



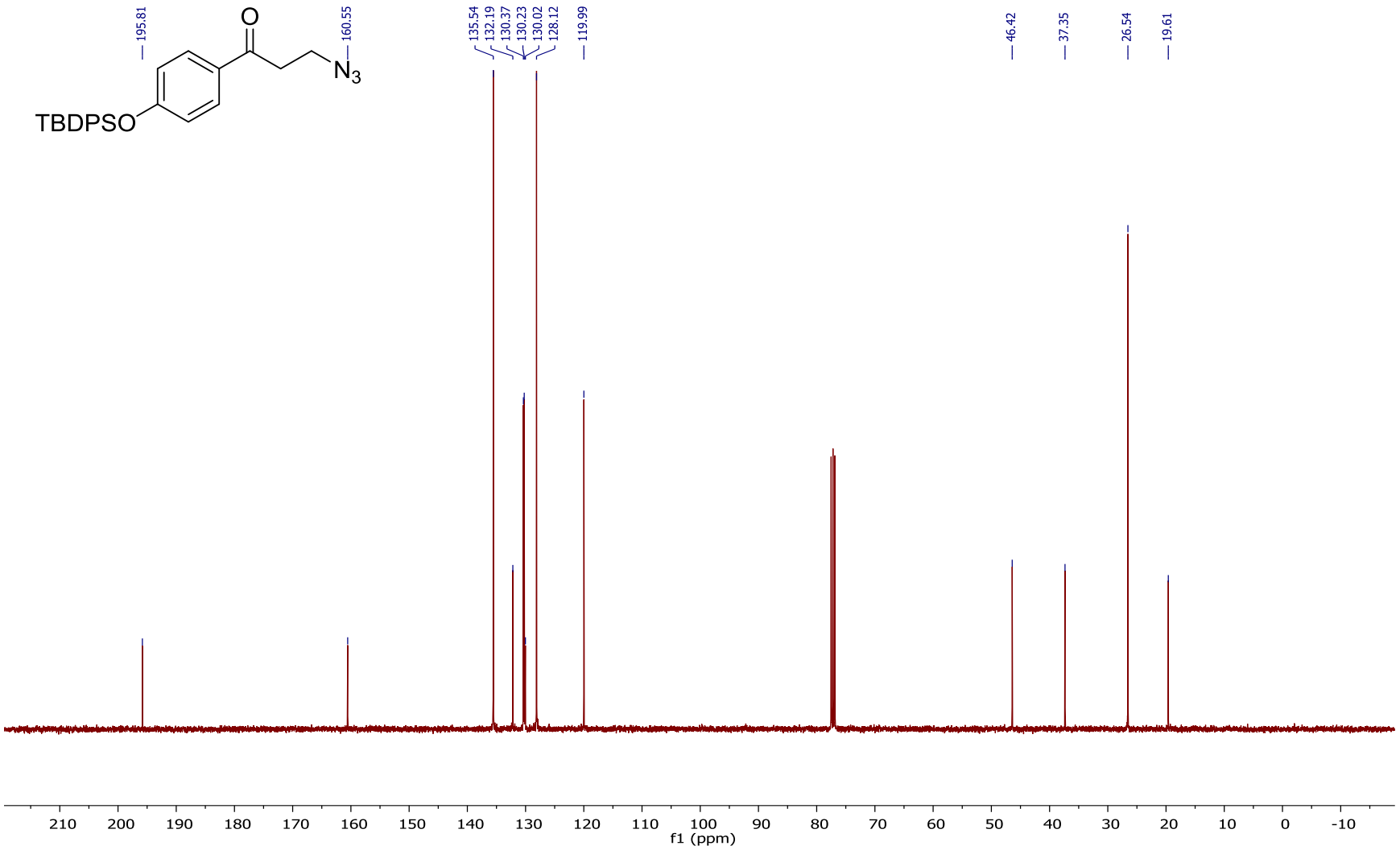
Compound 2j: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



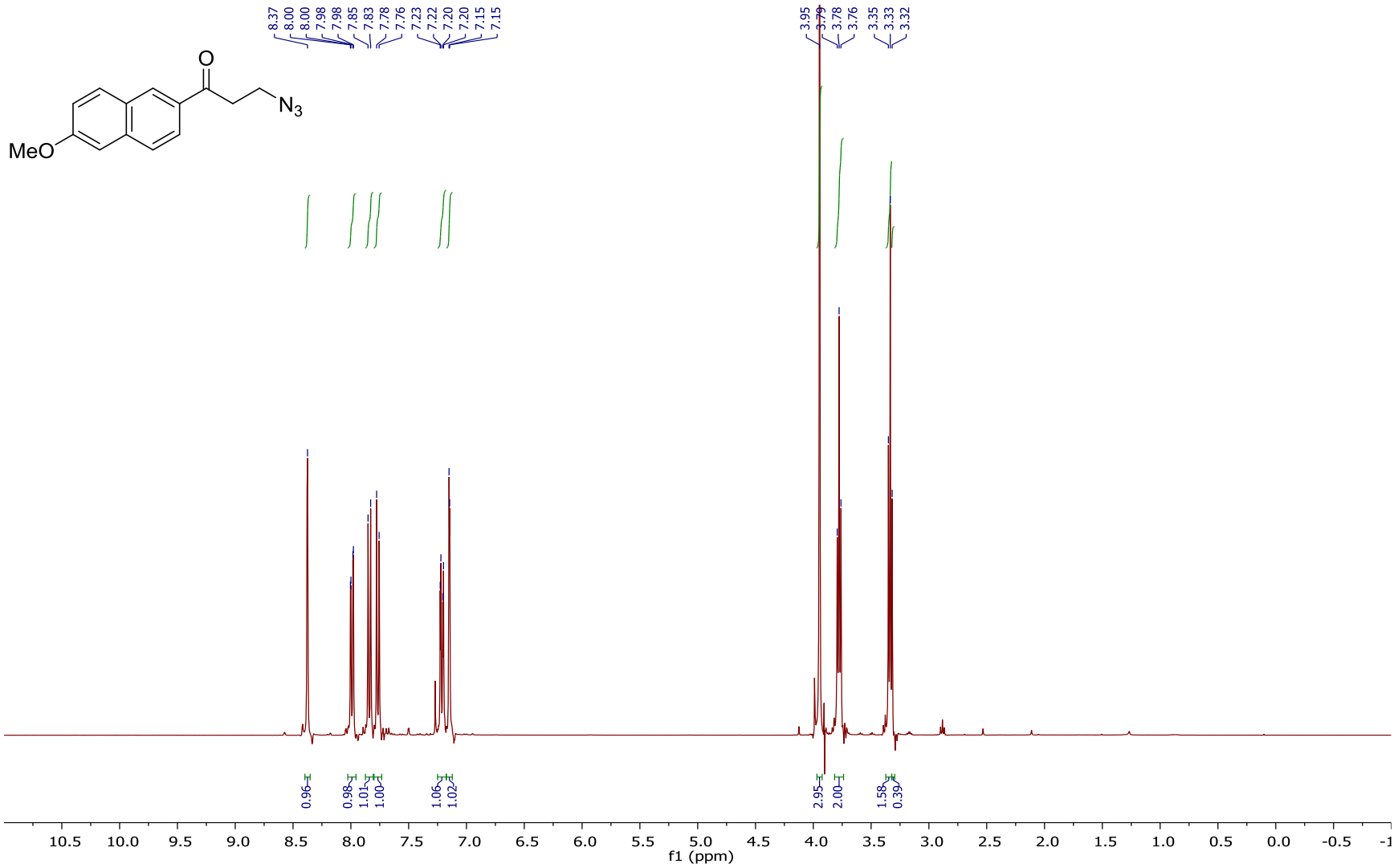
Compound 2j: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



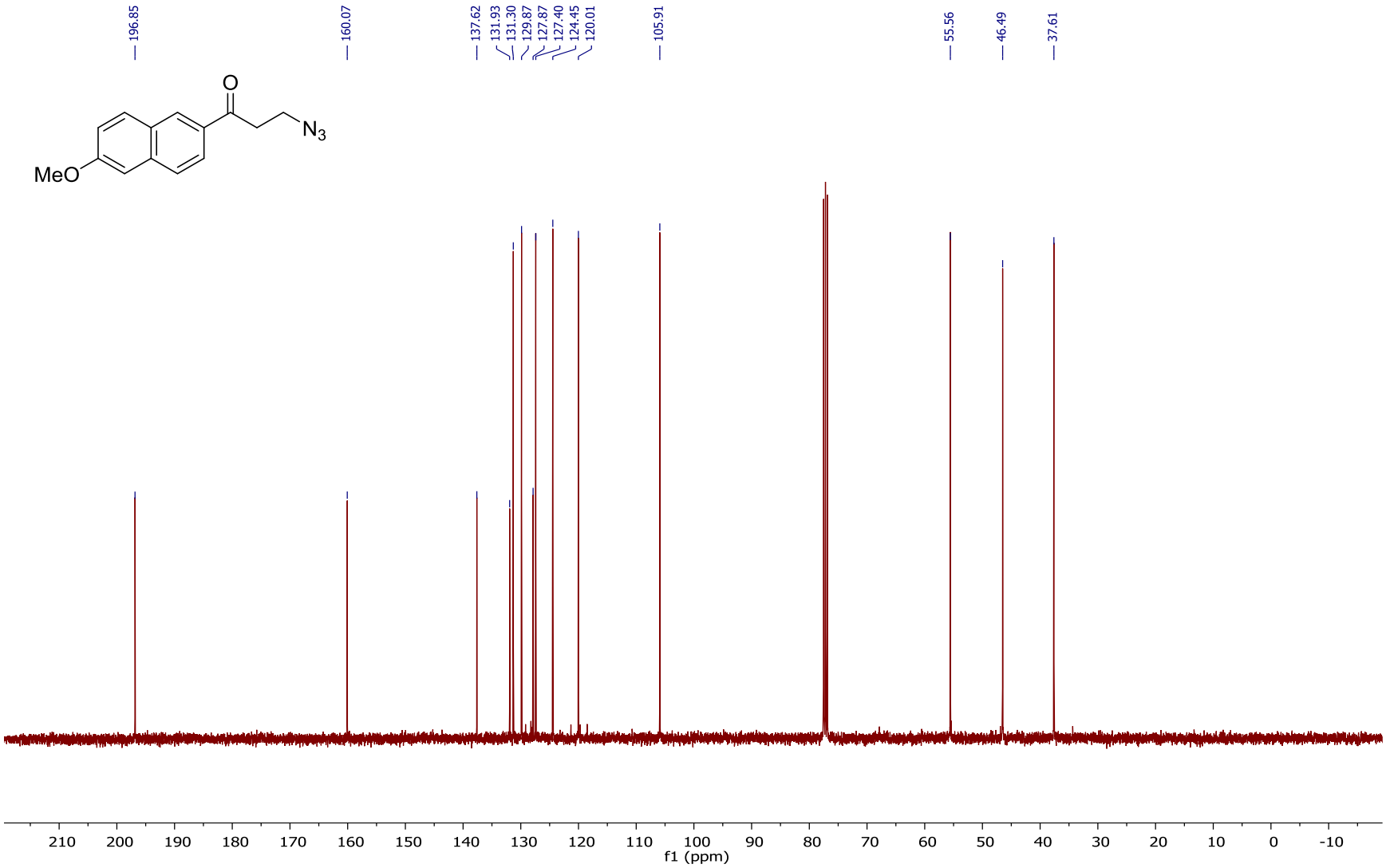
Compound 2k: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



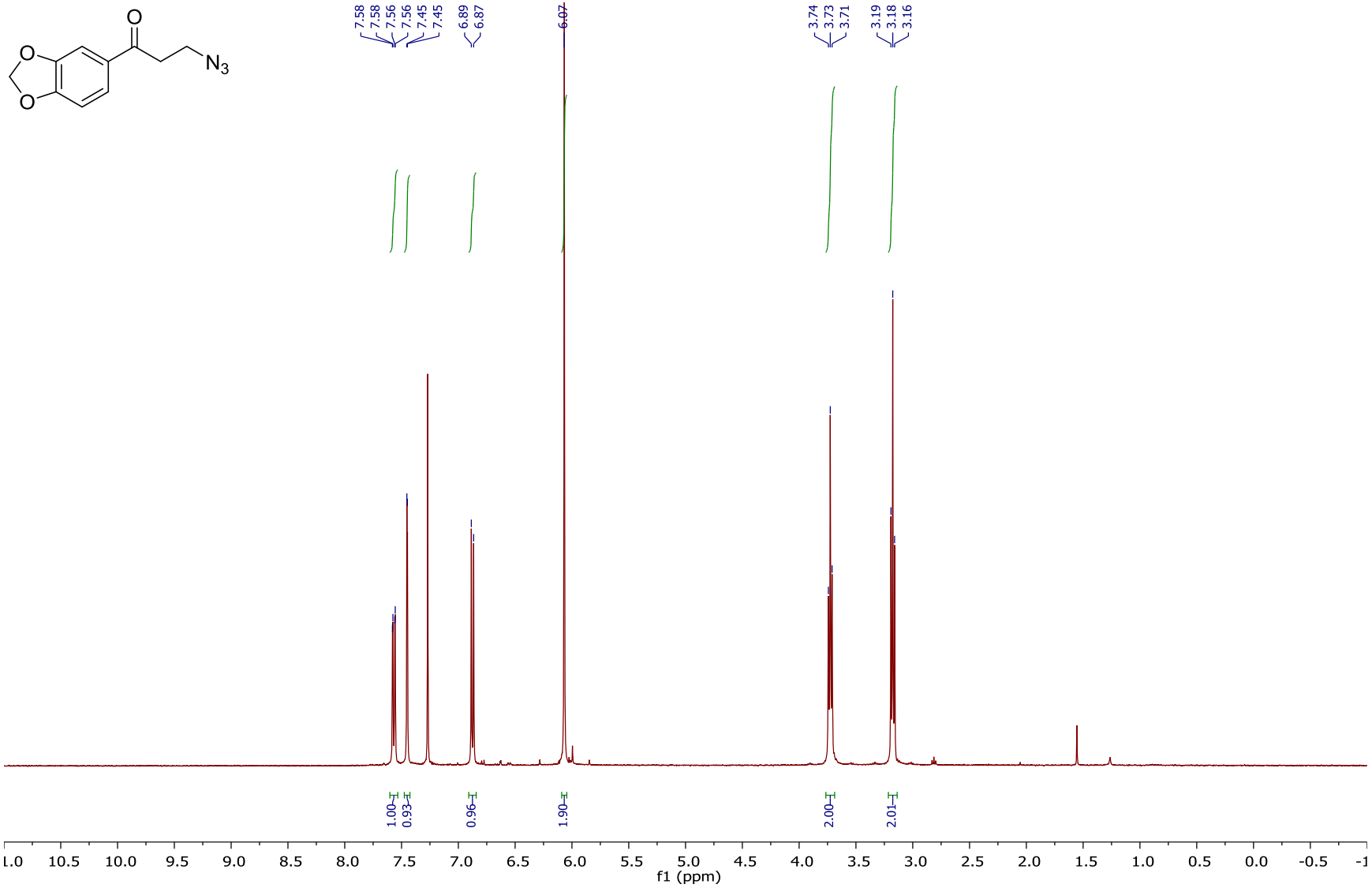
Compound 2k: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



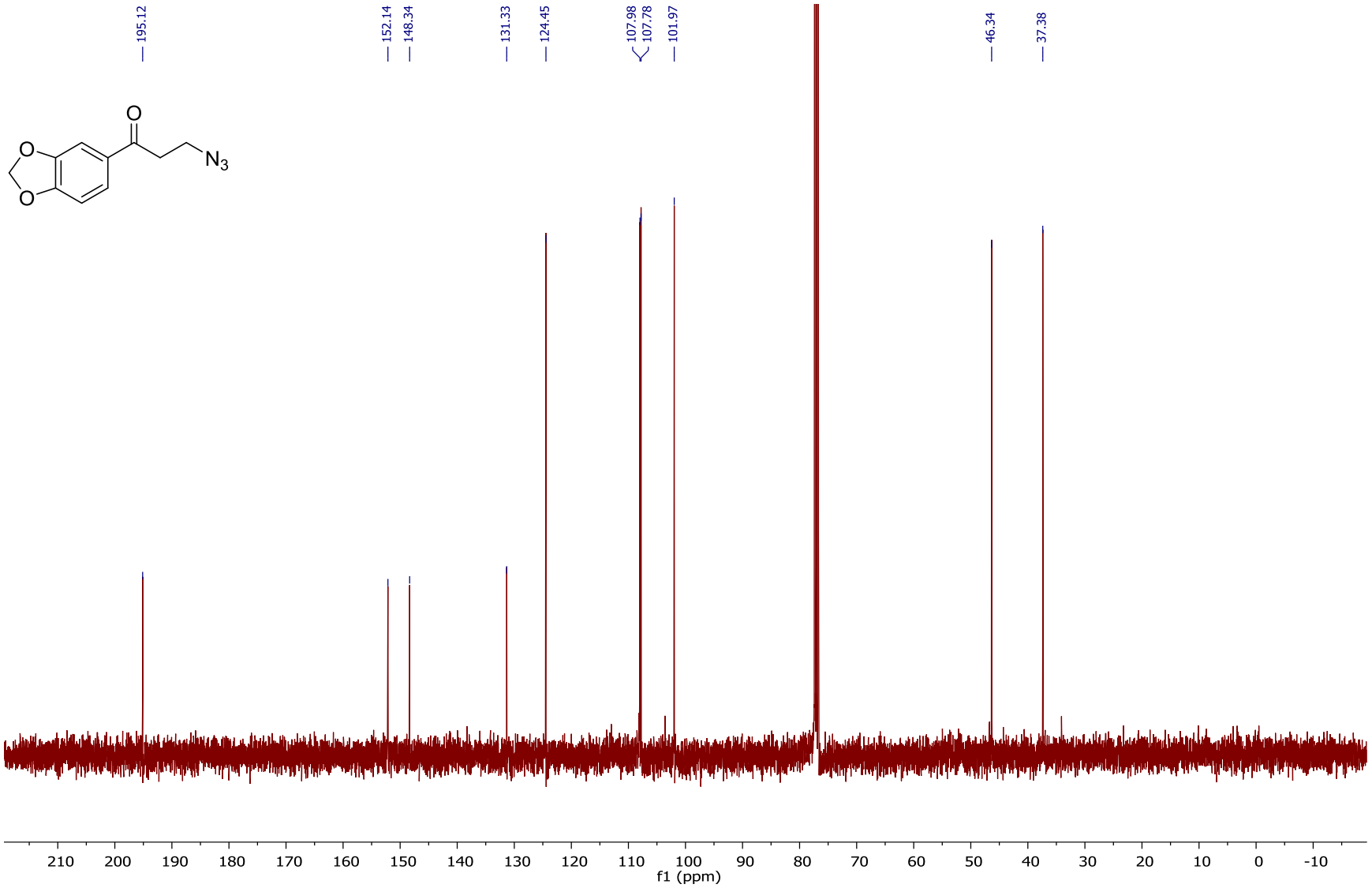
Compound 2l: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



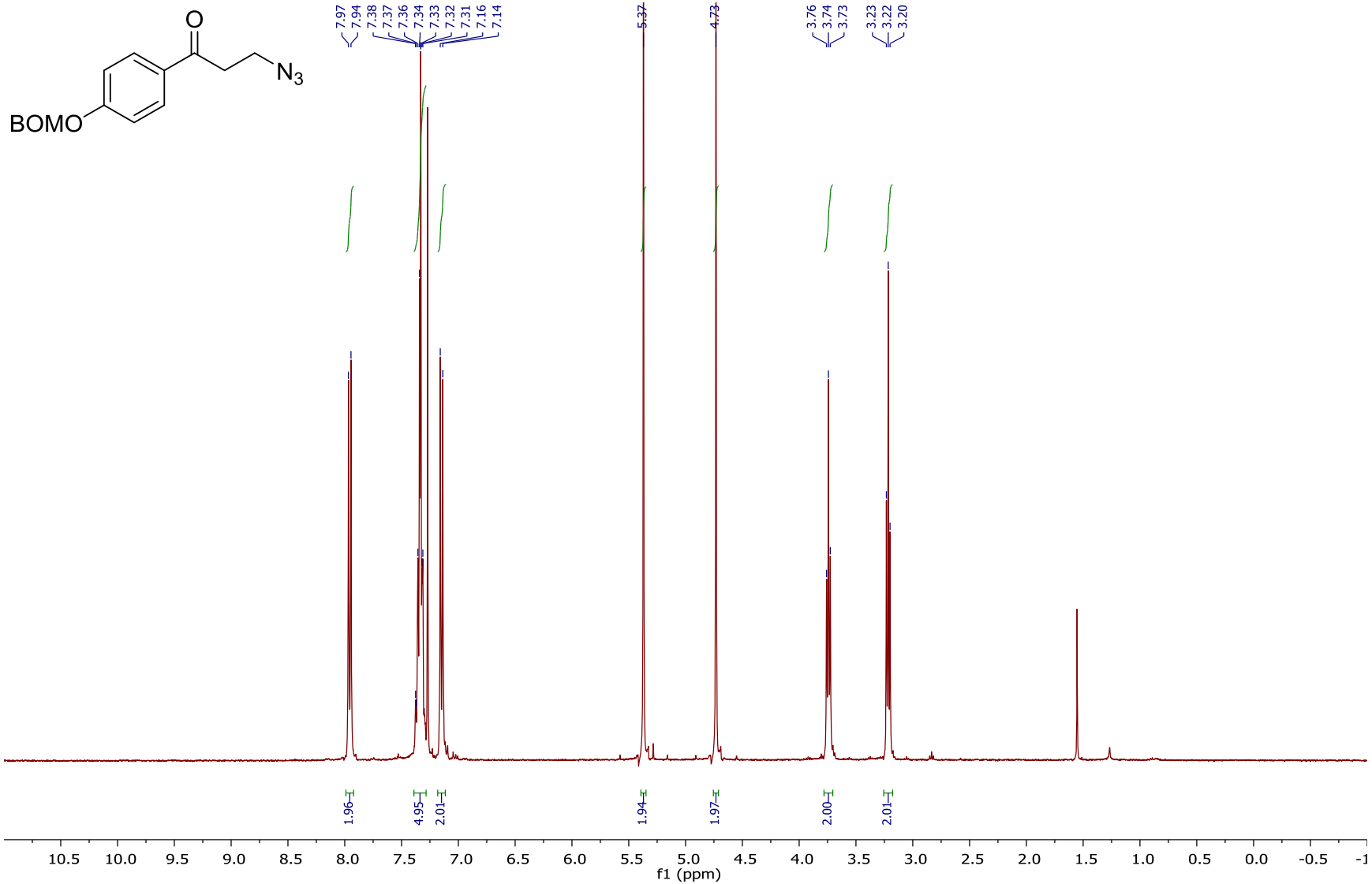
Compound 2l: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



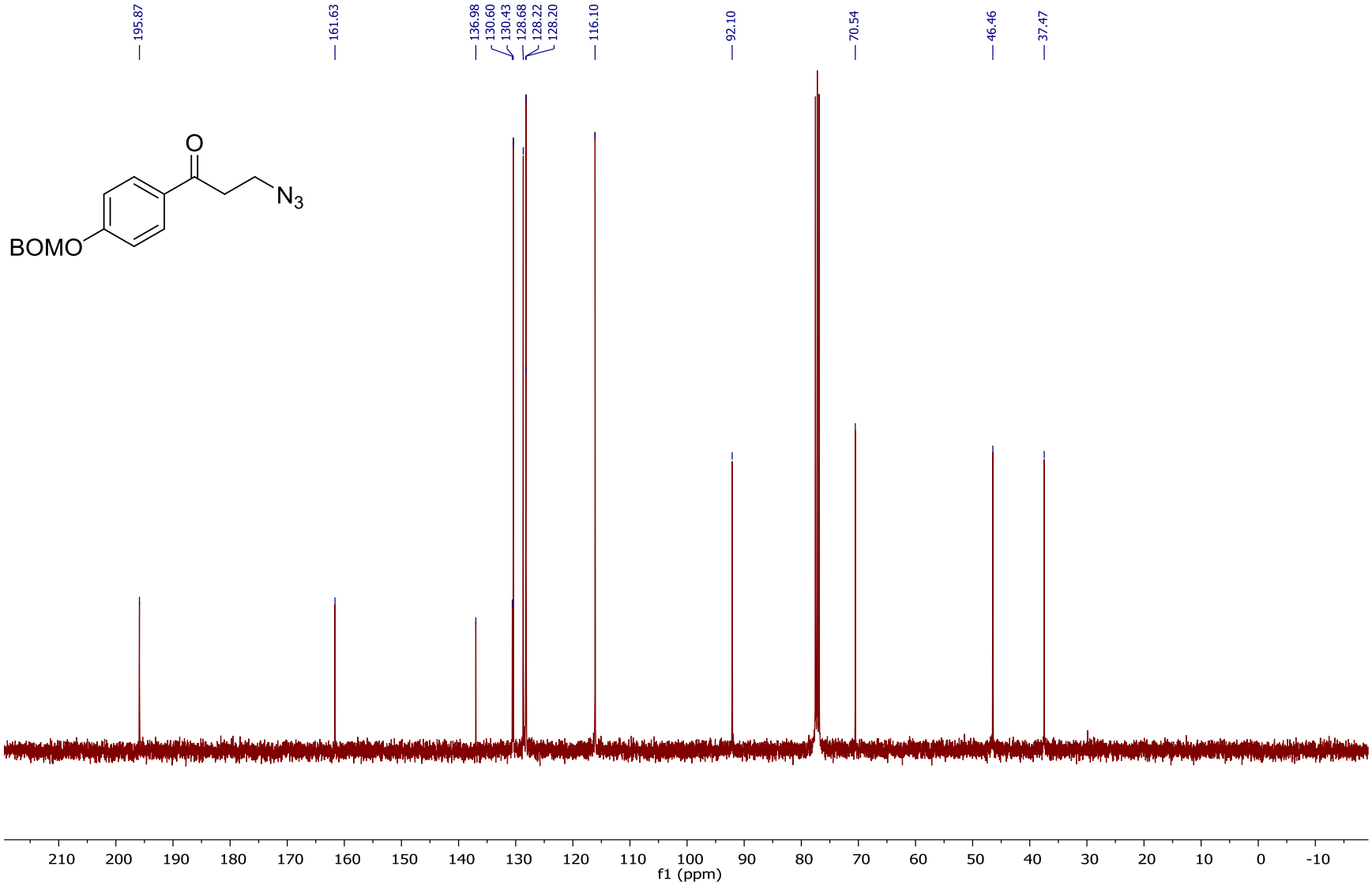
Compound 2m: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



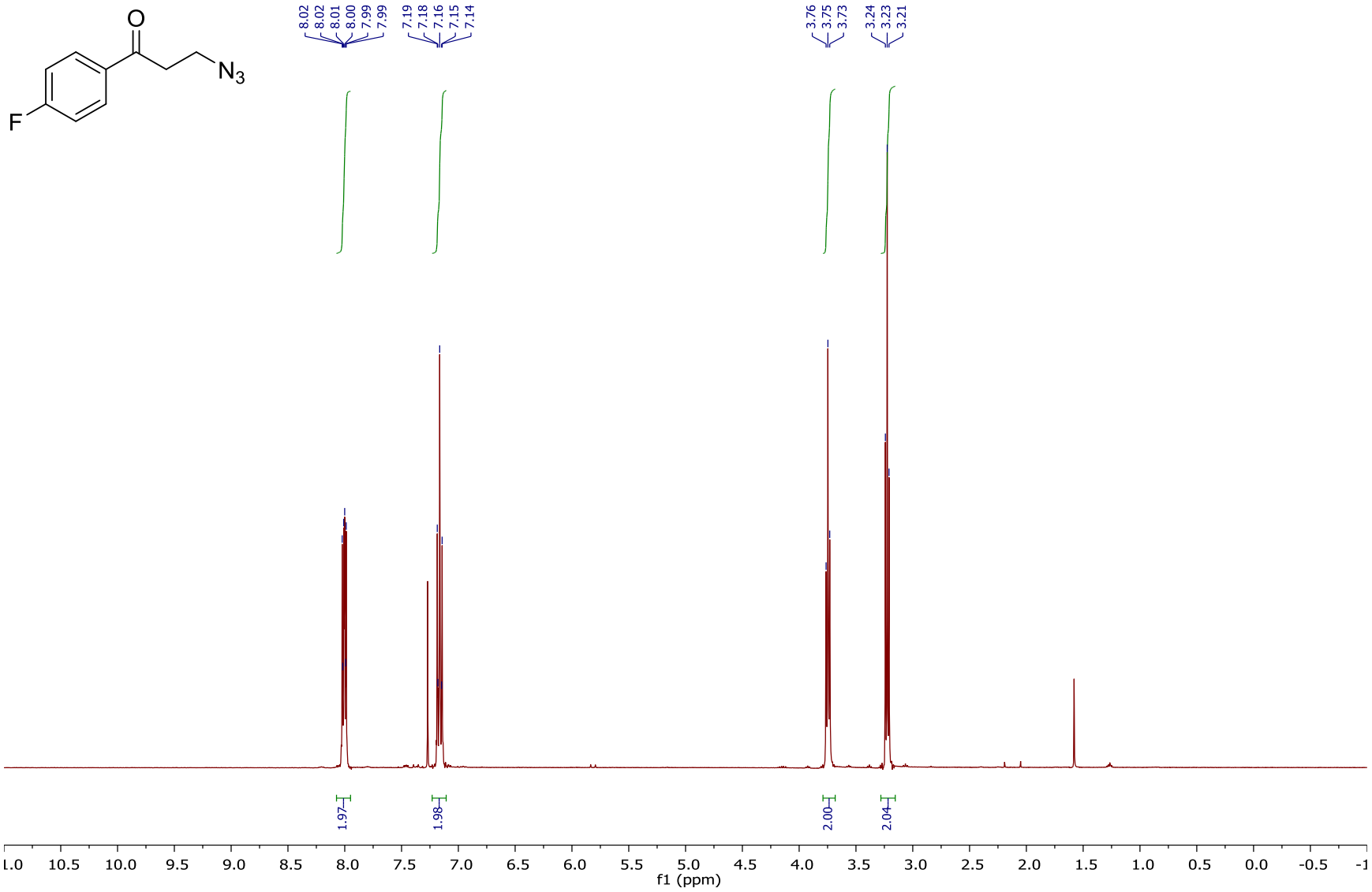
Compound 2m: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



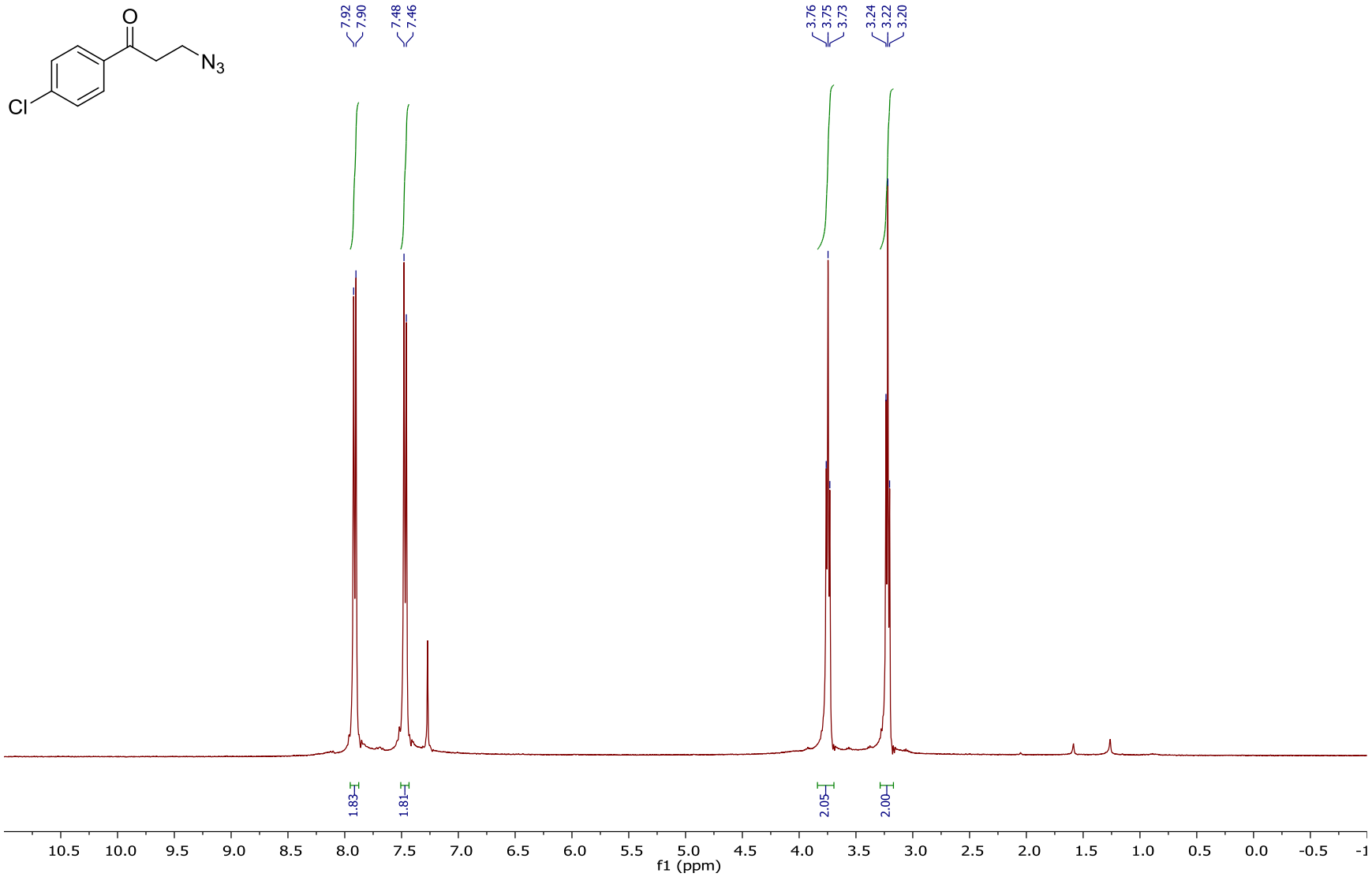
Compound 2n: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



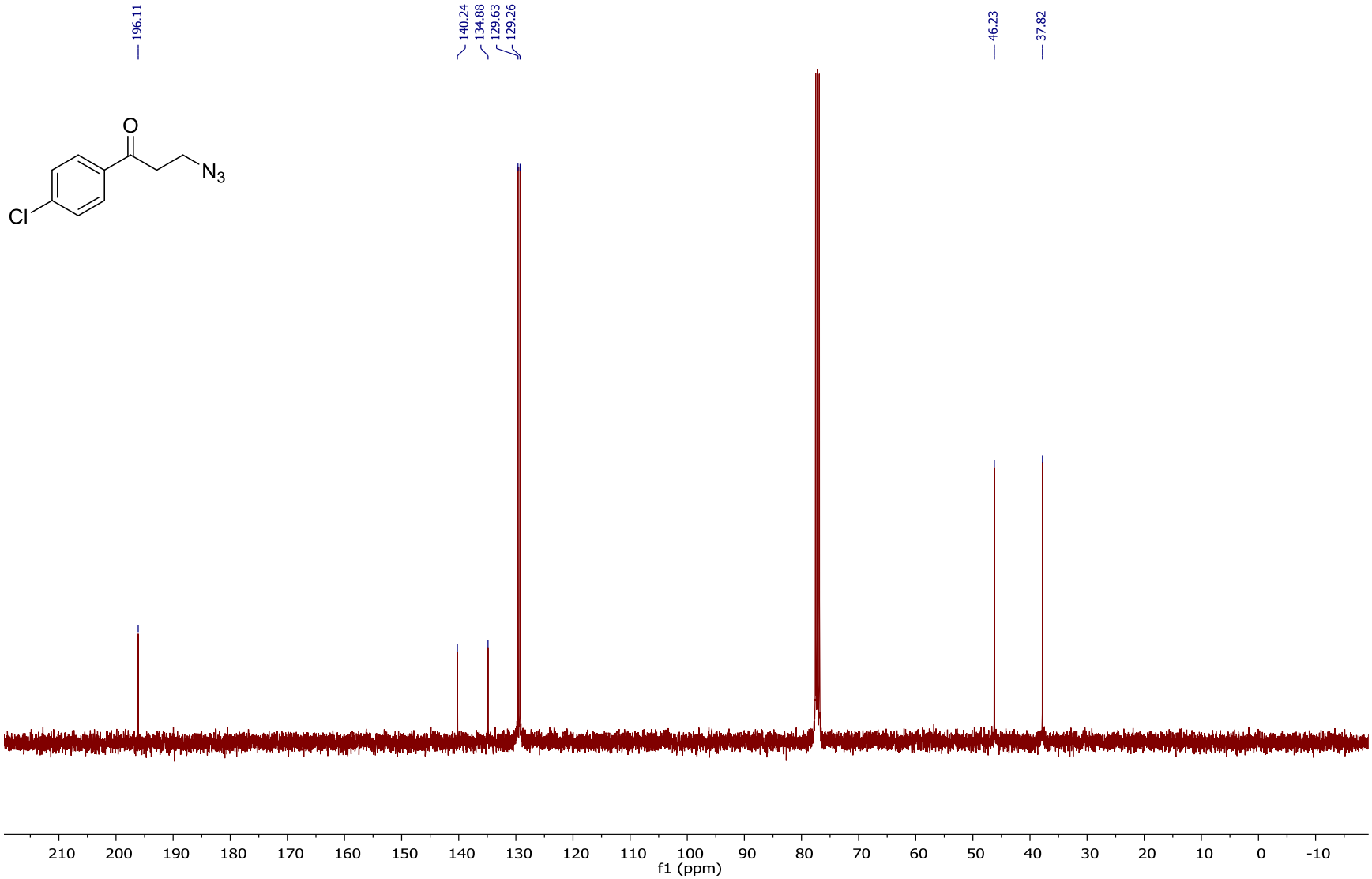
Compound 2n: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



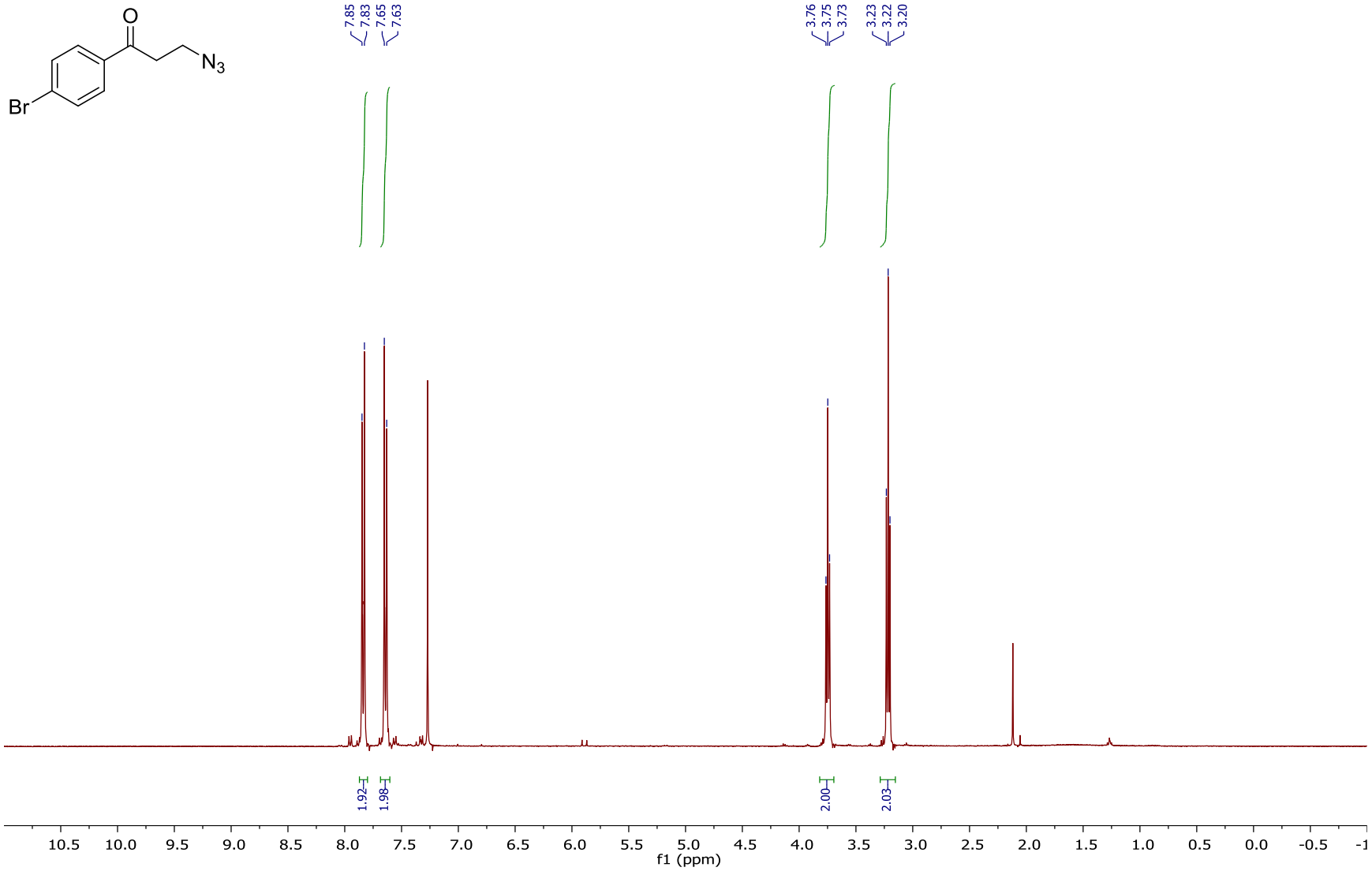
Compound 2o: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



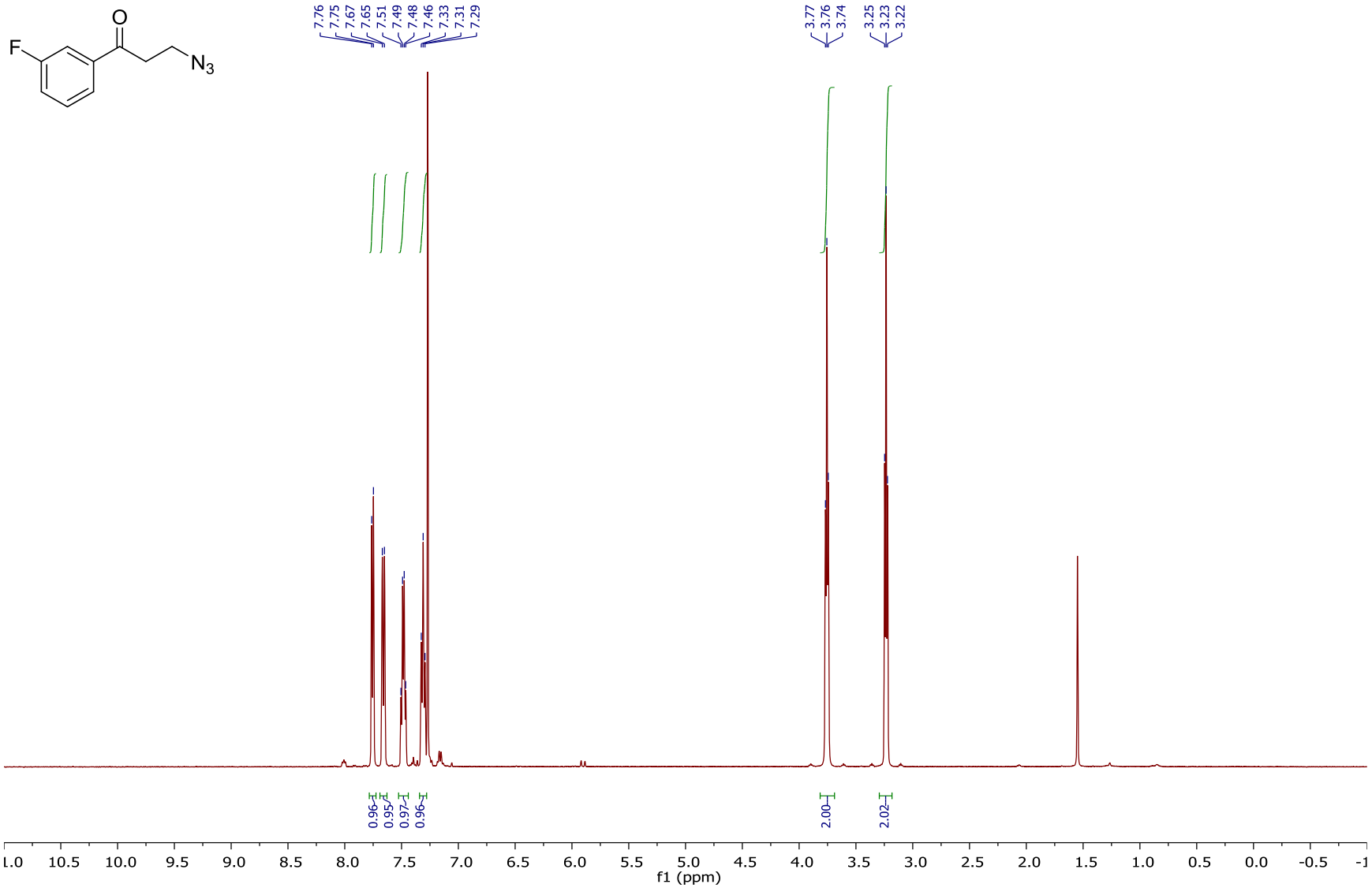
Compound 2p: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



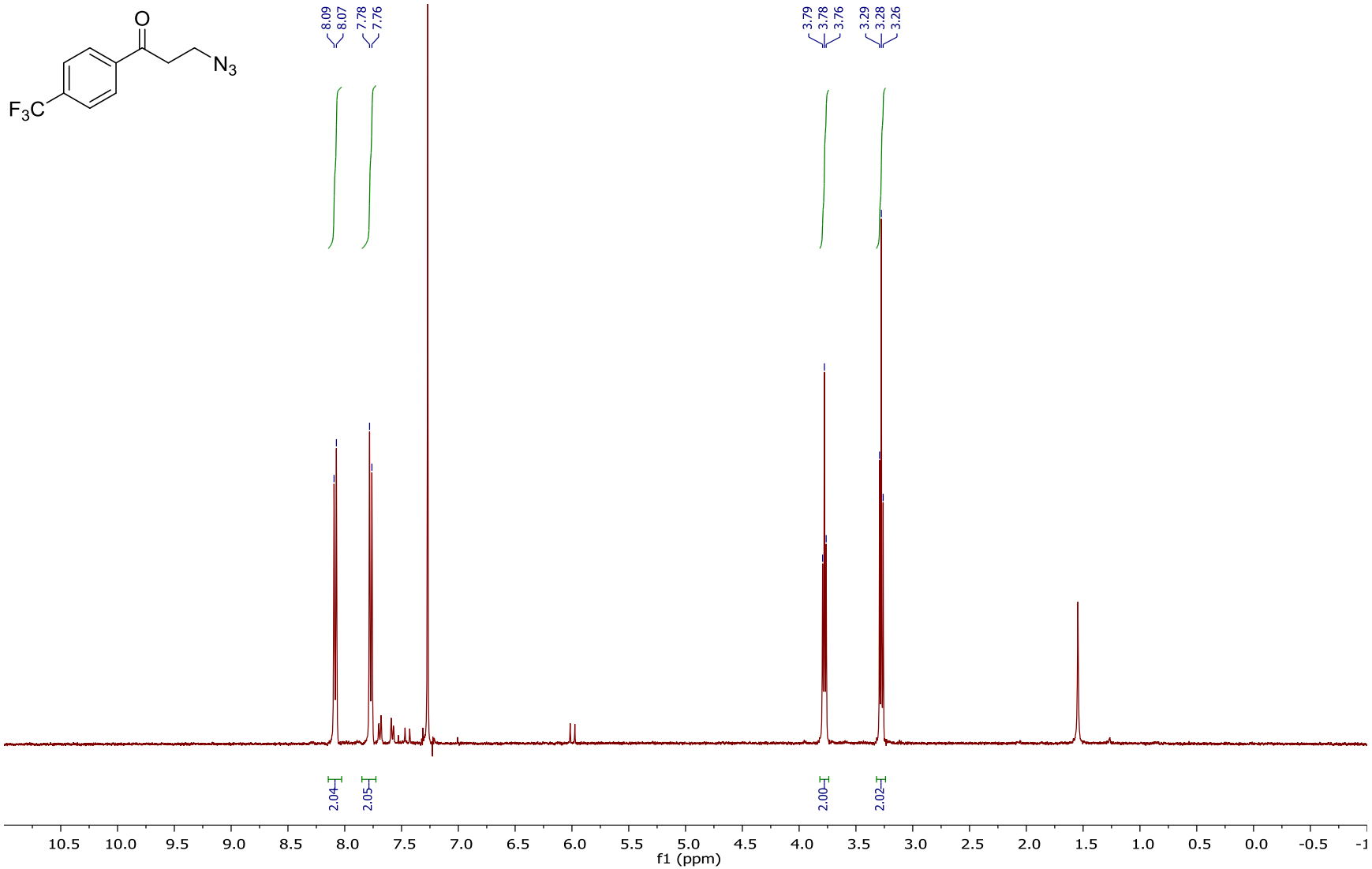
Compound 2p: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



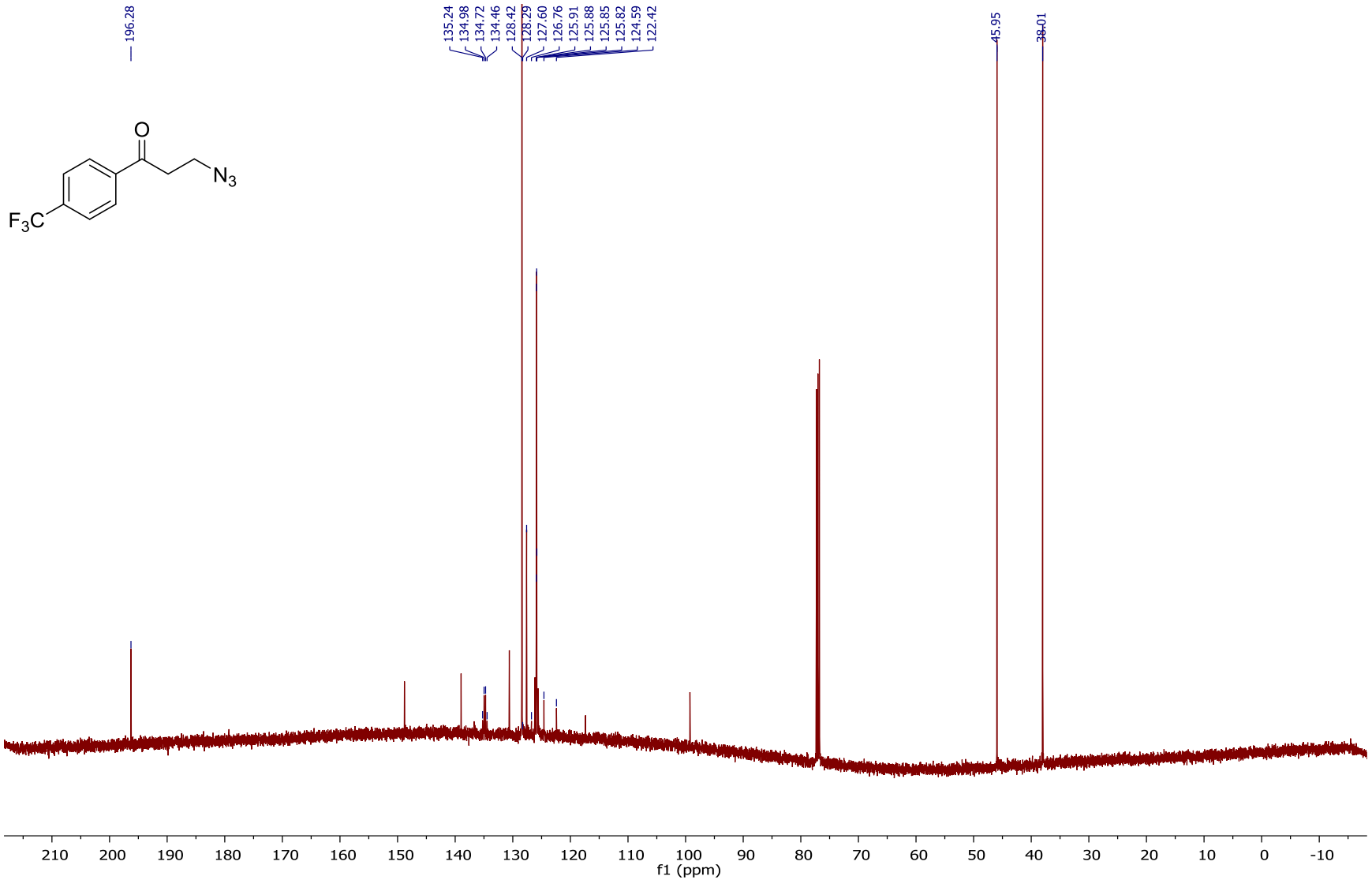
Compound 2q: 500 MHz ^{1}H NMR spectrum in $CDCl_3$



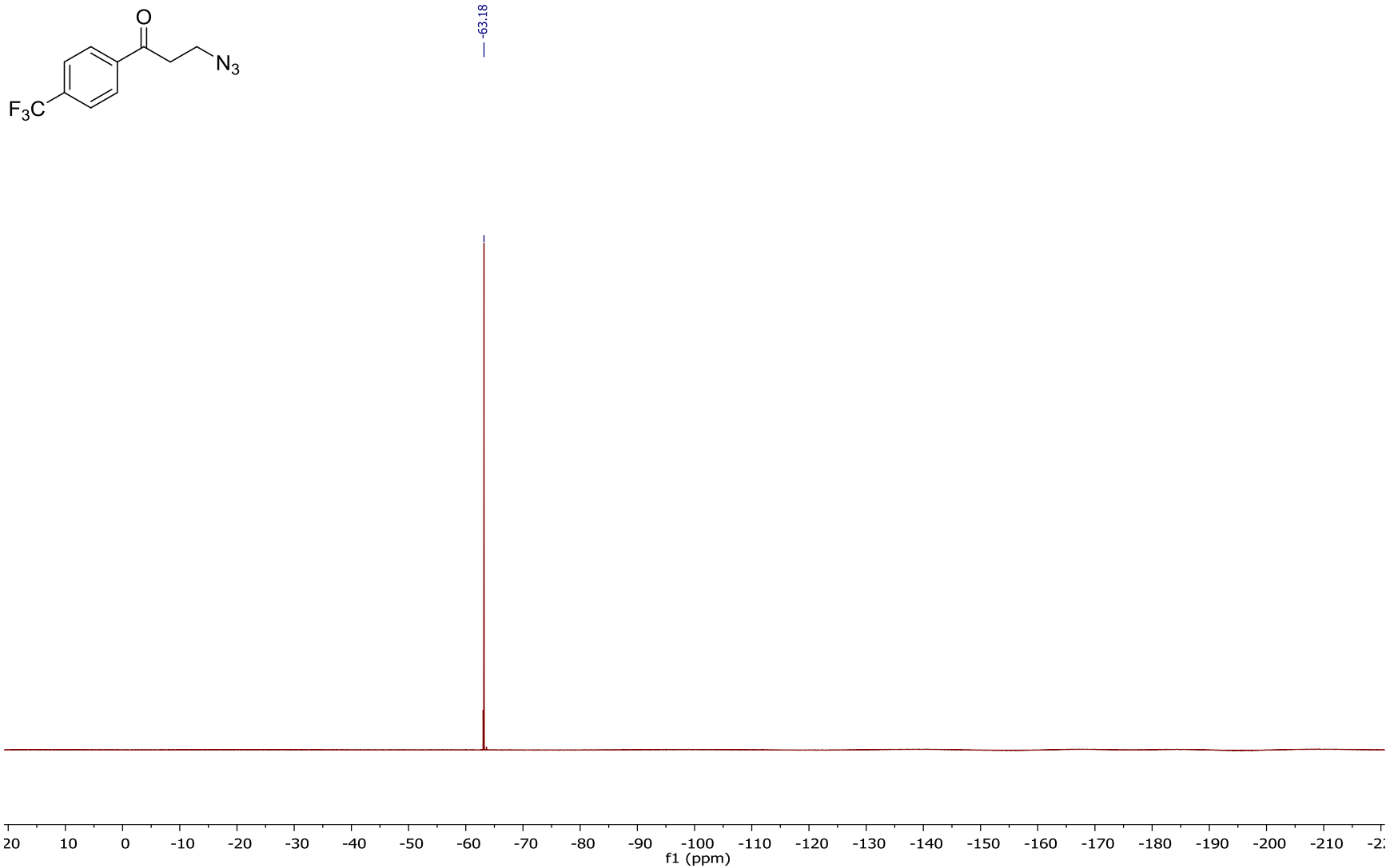
Compound 2r: 500 MHz ^{1}H NMR spectrum in $CDCl_3$



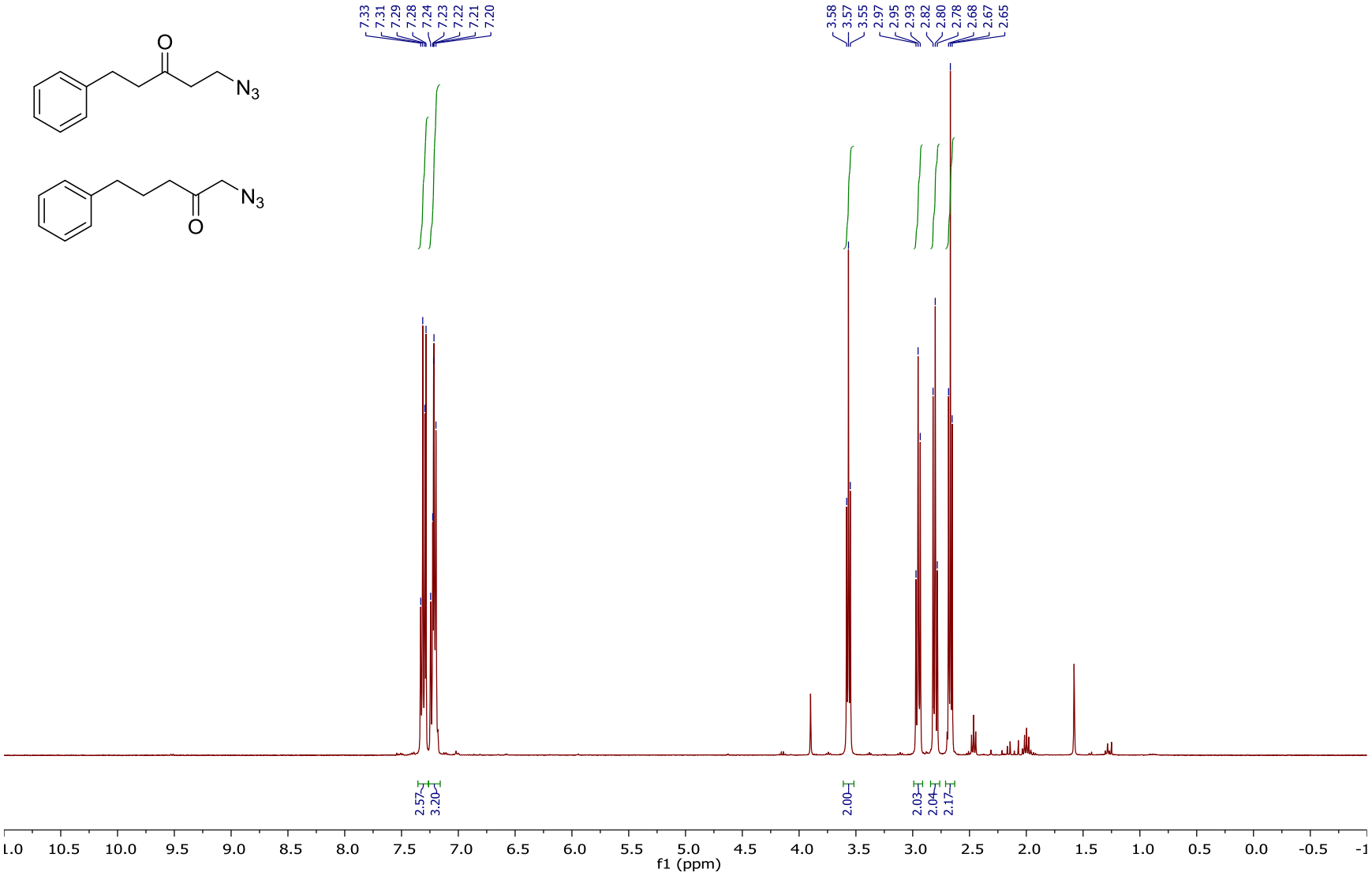
Compound 2s: 500 MHz ^{1}H NMR spectrum in $CDCl_3$



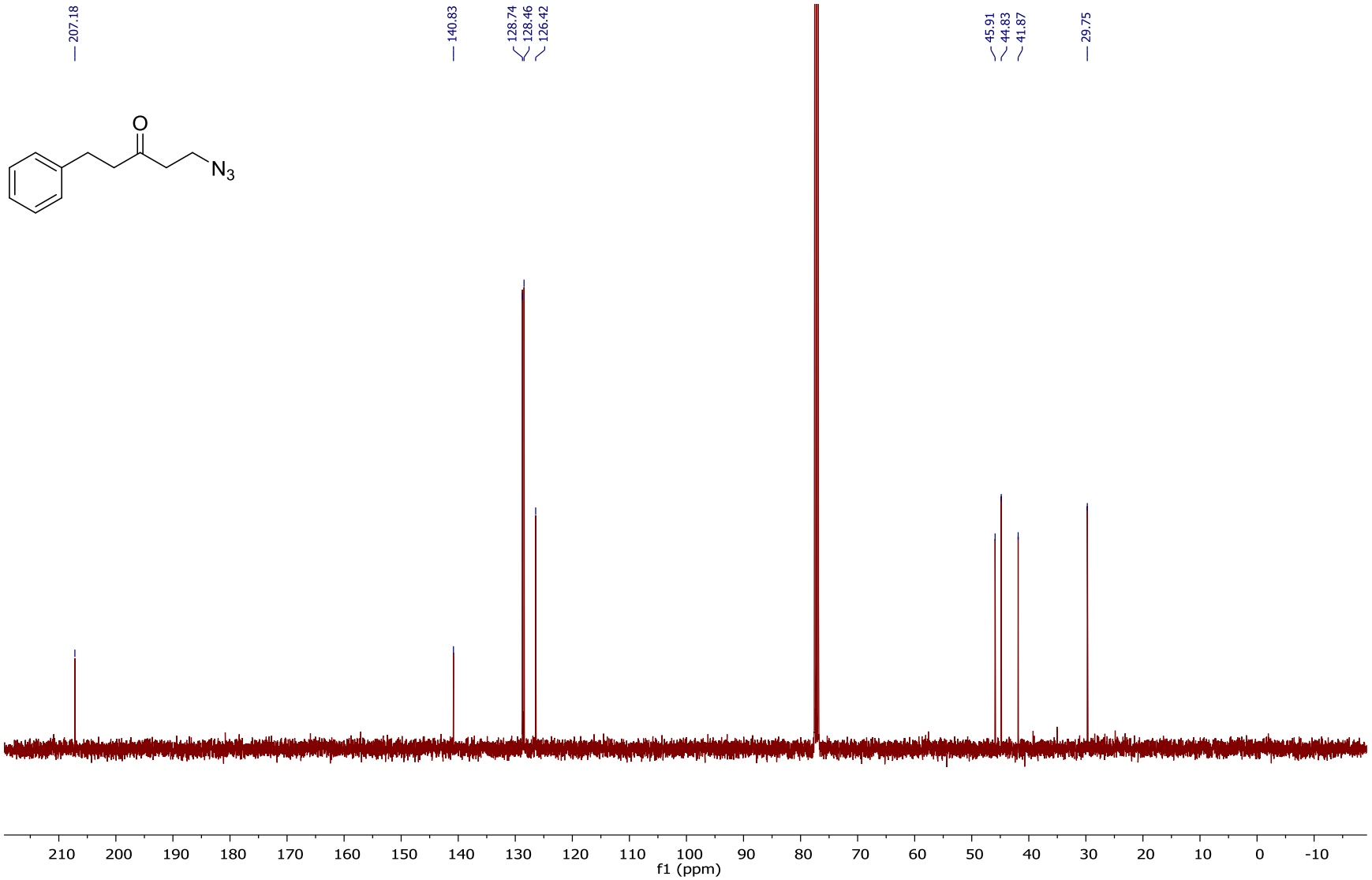
Compound 2s: 126 MHz ^{13}C NMR spectrum in $CDCl_3$



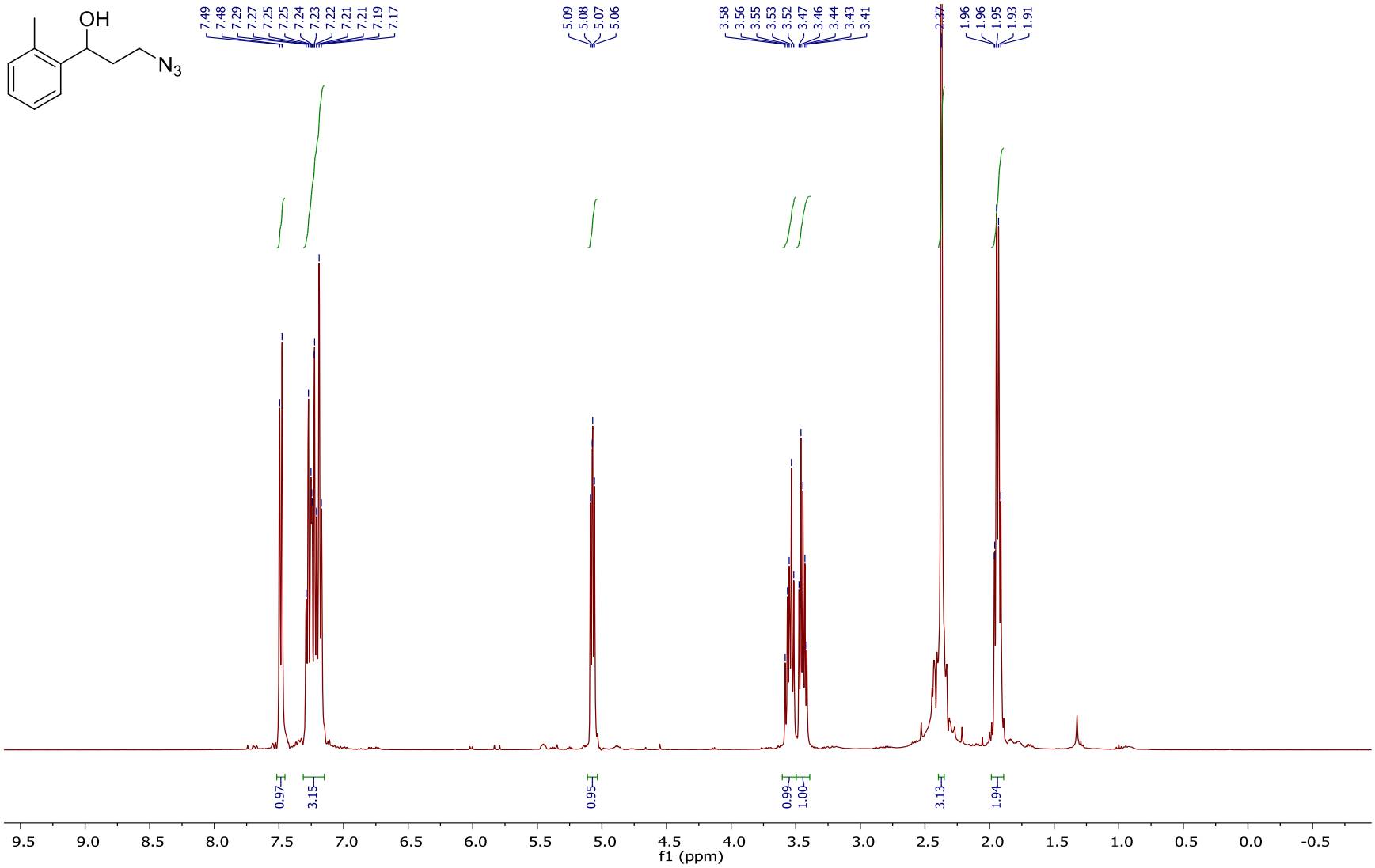
Compound 2s: 470 MHz ^{19}F NMR spectrum in $CDCl_3$



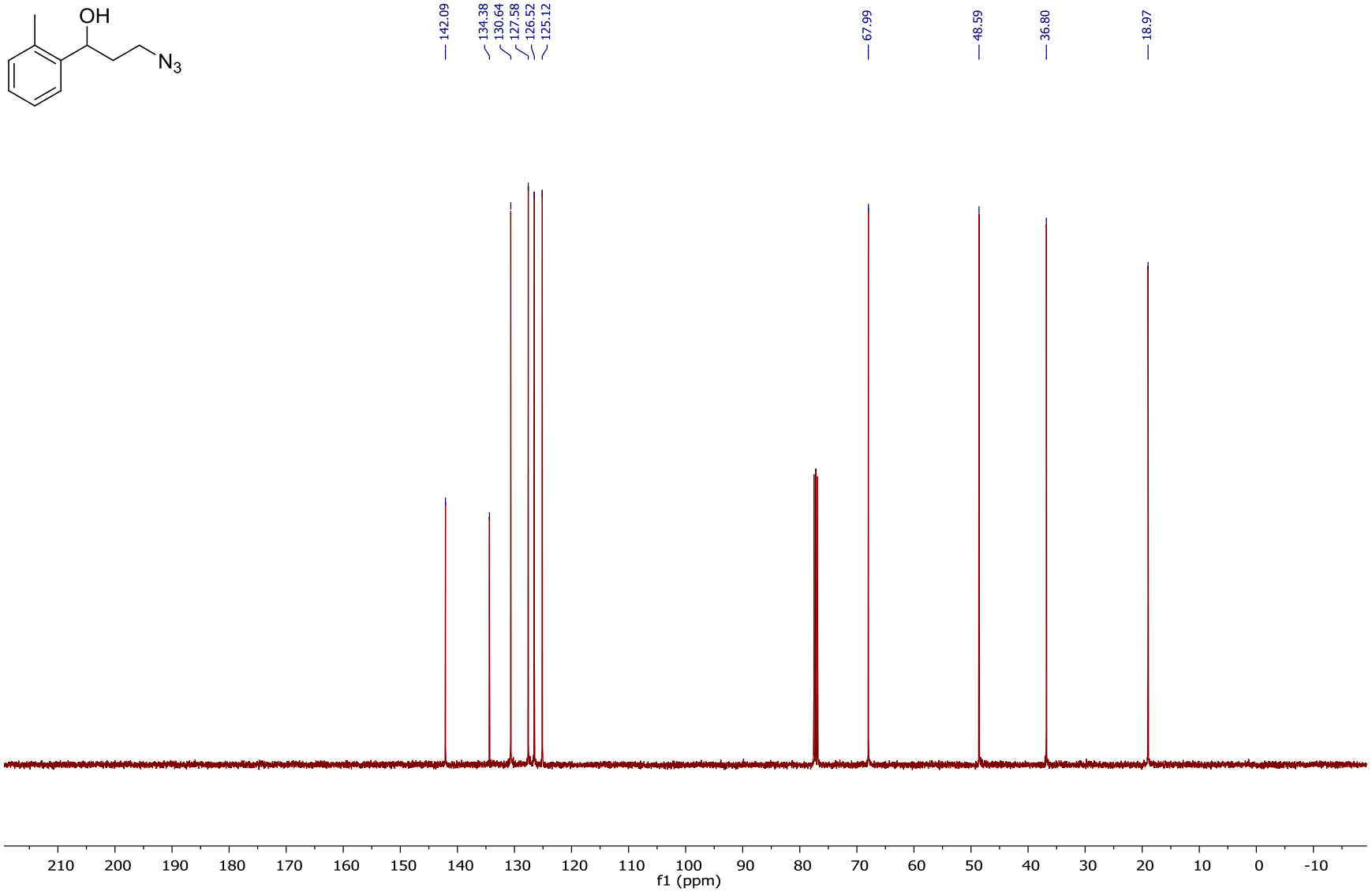
Compound 6: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



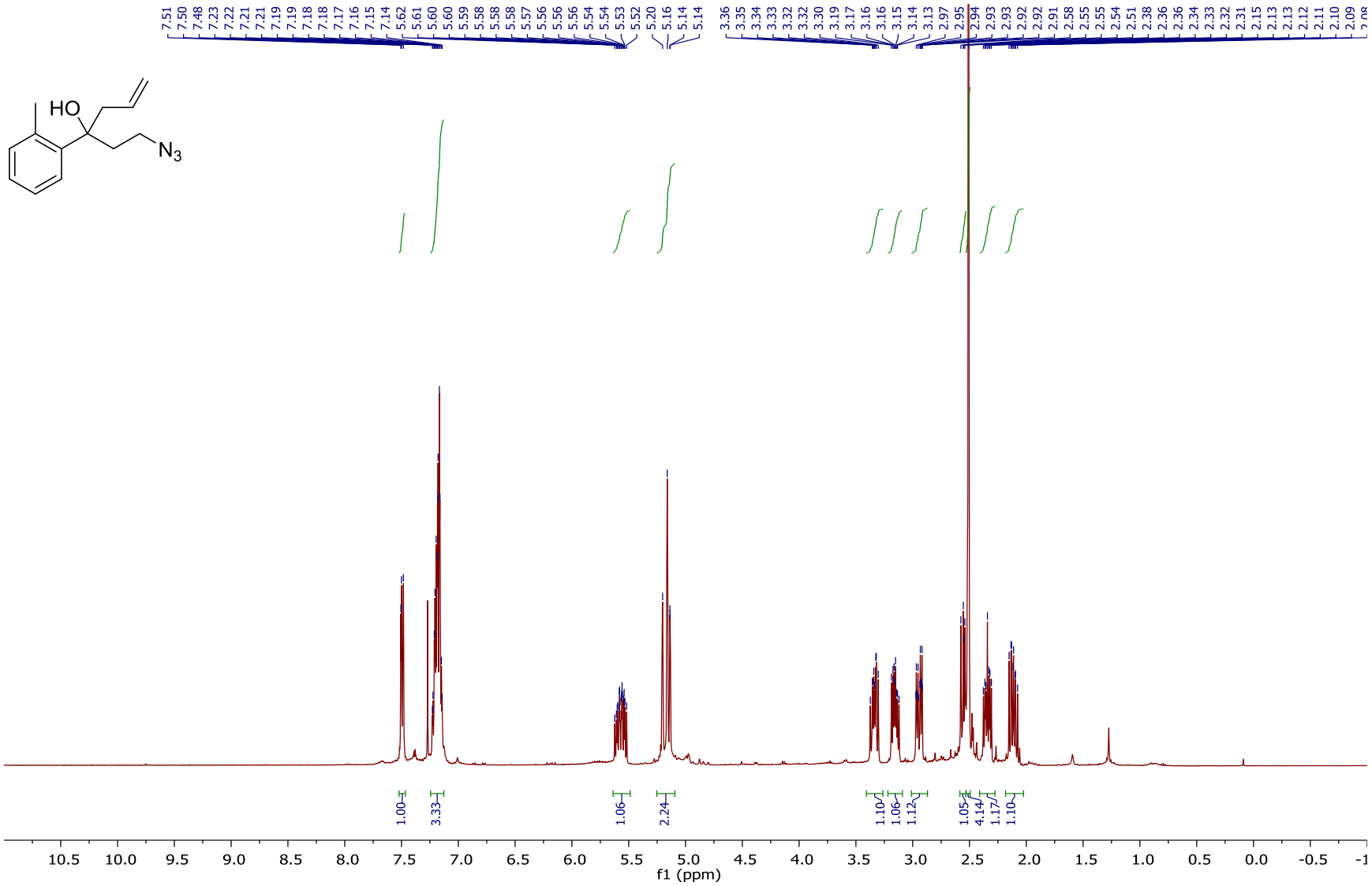
Compound 6: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



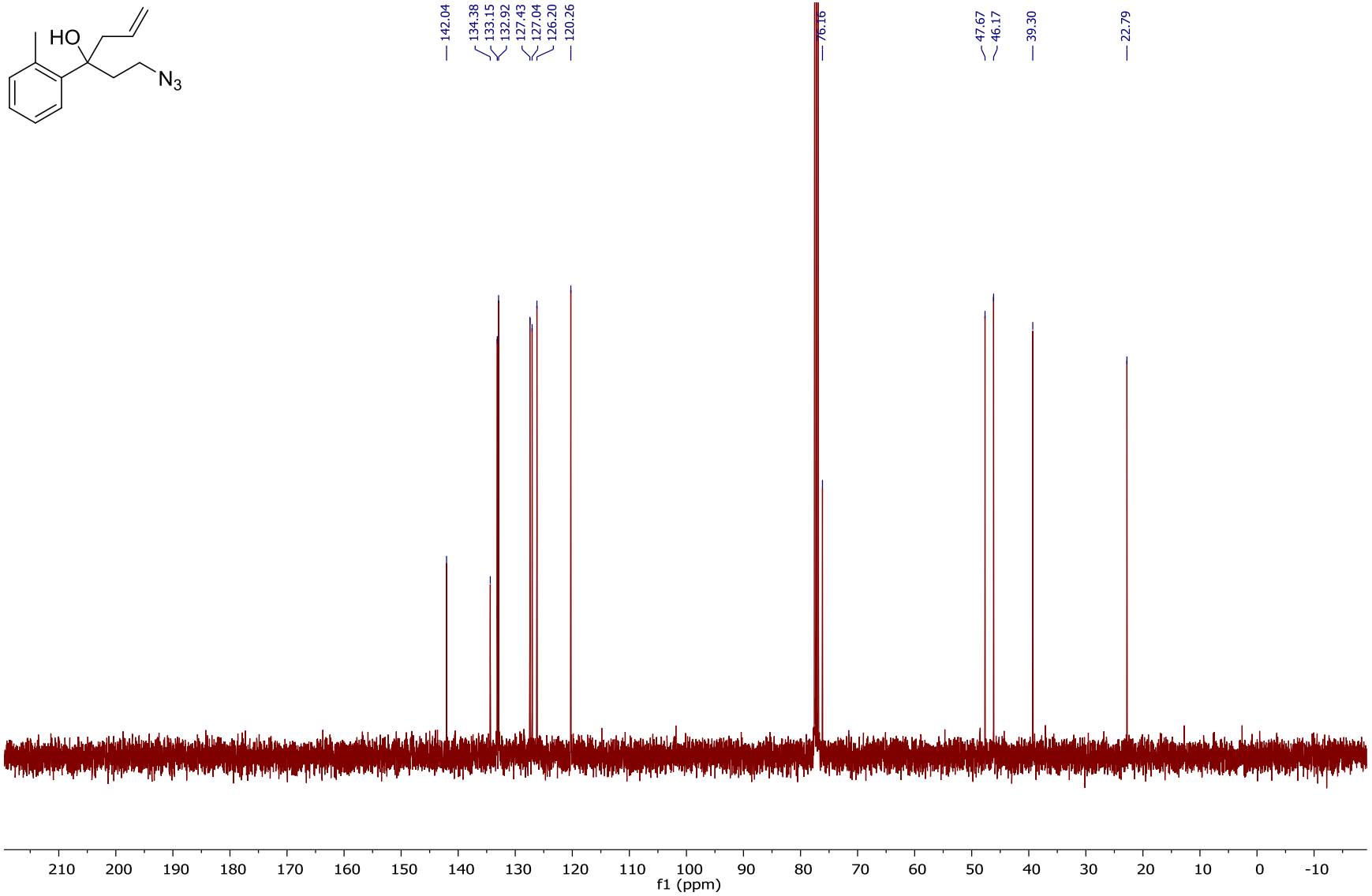
Compound 9: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



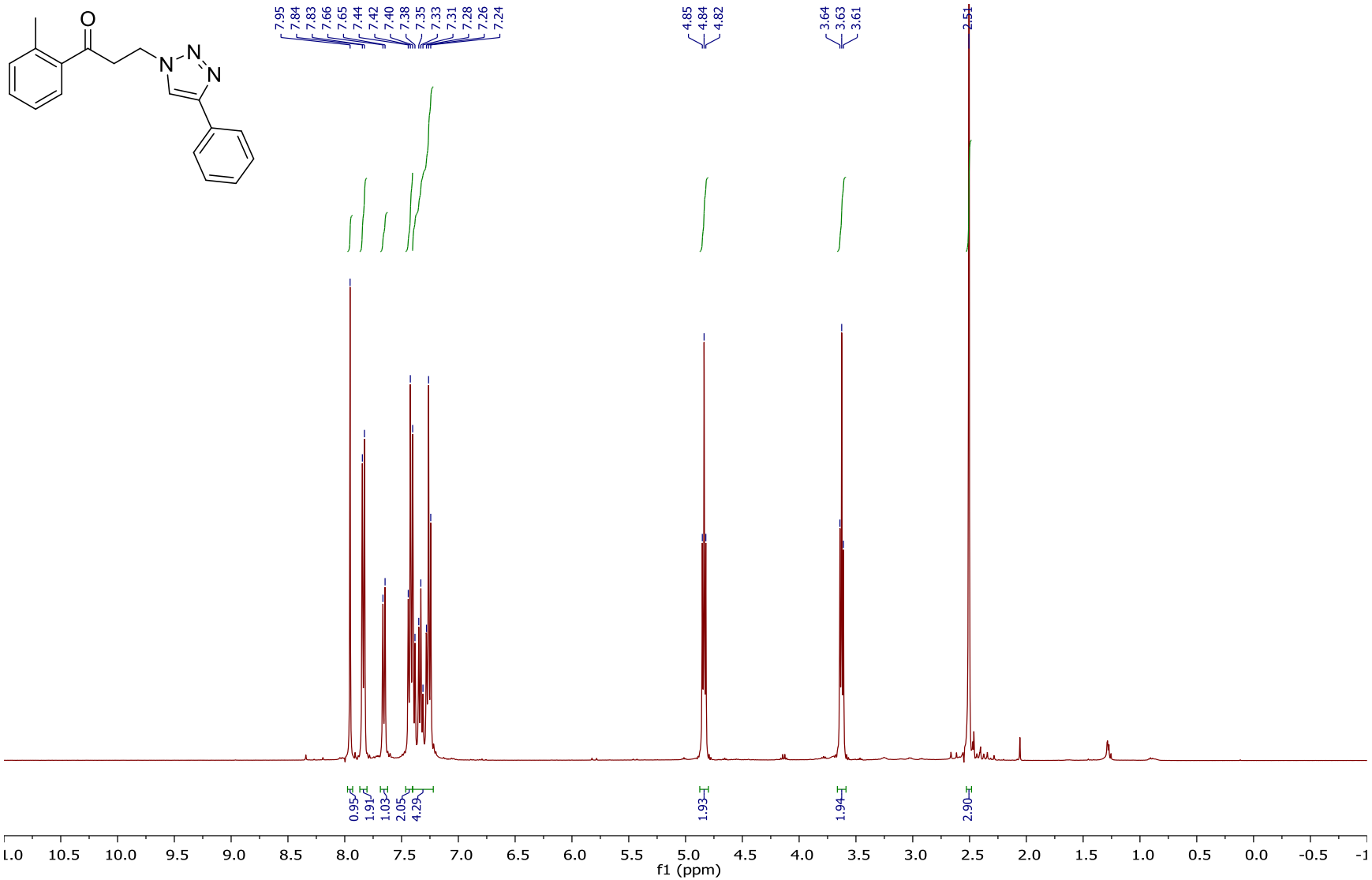
Compound 9: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



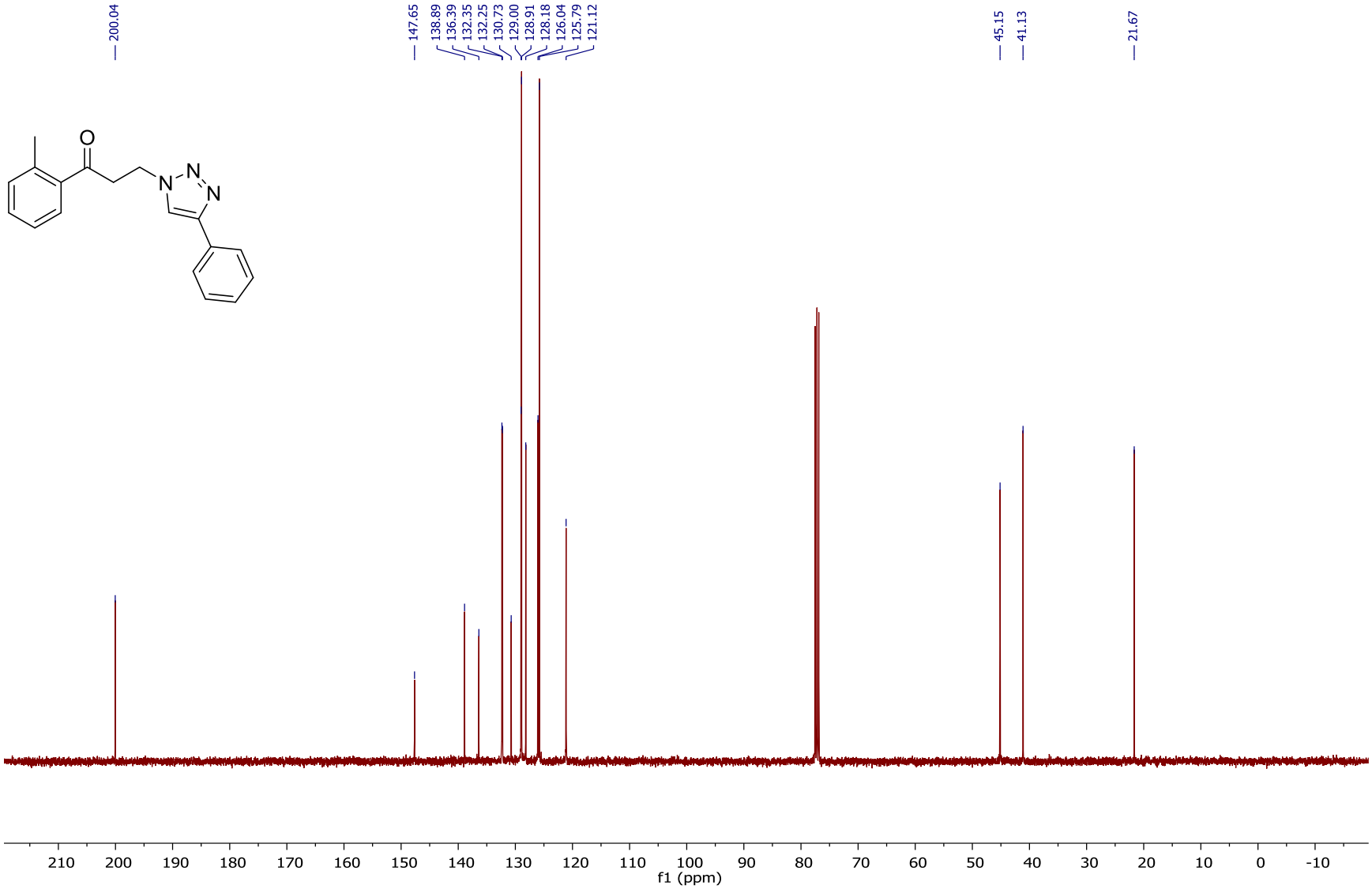
Compound 10: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



Compound 10: 101 MHz ^{13}C NMR spectrum in $CDCl_3$



Compound 11: 400 MHz ^{1}H NMR spectrum in $CDCl_3$



Compound 11: 400 MHz ^{1}H NMR spectrum in $CDCl_3$