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

One-pot synthesis of GABA amides via nucleophilic addition of amines to cyclopropenes

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Supporting Information

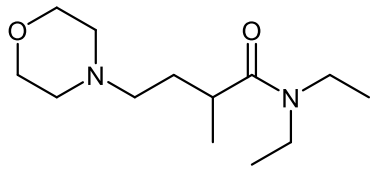
Table of Contents

General Information

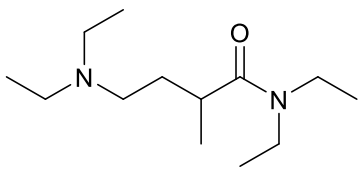
NMR spectra were recorded on a Bruker Avance DRX-500 with a dual carbon/proton cryoprobe (CPDUL). ^{13}C NMR spectra were registered with broadband decoupling. The (+) and (-) designations represent positive and negative intensities of signals in ^{13}C DEPT-135 experiments. IR spectra were recorded on a Shimadzu FT-IR 8400S instrument. HRMS was carried out on LCT Premier (Micromass Technologies) instrument; ESI TOF detection techniques were used. GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with FID detector and equipped with an AOC-20i auto-injector and an AOC-20S auto-sampler tray (150 vials); 30 m 0.25 mm 0.25 mm capillary column, SHR5XLB, polydimethylsiloxane; 5% Ph was employed. Helium (99.96%), additionally purified by passing consecutively through a CRS oxygen/moisture/hydrocarbon trap (#202839) and VICI oxygen/moisture trap (P100-1), was used as a carrier gas. Hydrogen gas was used as FID fuel; zero-grade air and zero-grade nitrogen were used as an oxidant and make-up gas, respectively, for the FID. All these gases were purified by passing through CRS #202839 traps. The following GC parameters were used for all analyses: carrier gas flow rate 2.5 mL/min; oven temperature program: 50 ^{o}C (2 min) - 20 ^{o}C/min - 230 ^{o}C (6 min), injector temperature 275 ^{o}C. Column chromatography was carried out on silica gel (Sorbent Technologies, 40-63 μm). Pre-coated silica gel plates (Sorbent Technologies Silica XG 200 μm) were used for TLC analyses. Anhydrous dichloromethane was obtained by passing degassed commercially available HPLC-grade inhibitor-free solvents consecutively through two columns filled with activated alumina and stored over molecular sieves under nitrogen. Water was purified by dual stage deionization followed by dual stage reverse osmosis. Synthesis of starting materials: *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide (**2a**), *N*,*N*-Diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**2b**) and (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**2c**) was detailed in our recent report.[1] Commercially available amines: aniline (**8i**), diethylamine (**8a**), pyrrolidine (**8c**), morpholine (**8d**), *n*-butylamine (**8j**) were dried with granulated potassium hydroxide and distilled immediately prior to use. All other reagents were purchased from commercial vendors and used as received.

(1)(a) W. M. Sherrill, R. Kim, M. Rubin, *Synthesis* **2009**, 1477. (b) R. Kim, W. M. Sherrill, M. Rubin, *Tetrahedron* **2010**, *66*, 4947.

Synthesis of GABA-amide derivatives

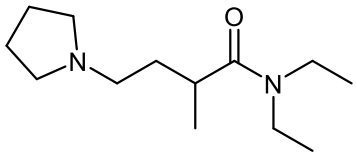


N,N-Diethyl-2-methyl-4-morpholinobutanamide **(5ad)**: (Typical procedure): Oven-dried 2 mL Weaton vial was charged with *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and morpholine (**8d**) (86 μL, 85 mg, 0.96 mmol, 1.5 equiv). The mixture was stirred at 100 ^{o}C for 1 hr, then $NaBH_4$ (25 mg, 0.65 mmol, 1.0 equiv) in dry dichloromethane (2 mL) was added, and the resulting solution was stirred overnight at r.t. The reaction mixture was partitioned between 2M aqueous NaOH (2 mL) and ethyl acetate (2 mL). The organic phase was separated, the aqueous layer was extracted with ethyl acetate (2 x 2 mL). Combined organic layers were concentrated in vacuum and diluted with 2M aqueous HCl (3 mL). The resulting solution was washed with ethyl acetate (3 x 5 mL), then basified with NaOH and extracted with ethyl acetate (3 x 5 mL). Combined organic layers were washed with brine (5 mL), dried with $MgSO_4$ and evaporated. Preparative column chromatography of residue on Silica gel doped with 0.5% of triethylamine in EtOAc afforded the titled compound as a yellow oil, R_f 0.25 (EtOAc). Yield 107 mg (0.44 mmol, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (t, *J* = 4.7 Hz, 4H), 3.45 – 3.27 (m, 4H), 2.76 – 2.72 (m, 1H), 2.42 (br. s, 2H), 2.36 (br. s, 2H), 2.30 – 2.24 (m, 2H), 1.92 – 1.88 (m, 1H), 1.55 – 1.51 (m, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 67.2 (-, 2C), 56.8 (-), 53.8 (-, 2C), 42.0 (-), 40.4 (-), 33.4 (+), 31.0 (-), 18.6 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 2930, 2854, 2806, 1659, 1643, 1614, 1445, 1427, 1379, 1359, 1257, 1116, 1070, 995, 854, 793, 773; HRMS (TOF ES): found 265.1880, calculated for $C_{13}H_{26}N_2O_2Na$ (M+Na) 265.1892 (4.5 ppm).

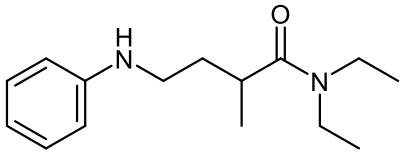


4-(Diethylamino)-N,N-diethyl-2-methylbutanamide (**5aa**): Was prepared according to Typical Procedure employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and diethylamine (**8a**) (202

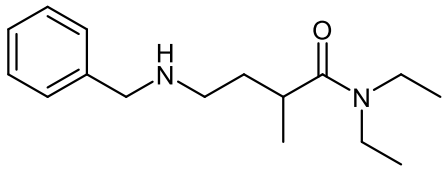
μL, 143 mg, 1.95 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.28 (CH_2Cl_2/MeOH 10:1). Yield 98 mg (0.43 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 – 3.36 (m, 2H), 3.31 – 3.20 (m, 2H), 2.71 – 2.64 (m, 1H), 2.54 – 2.43 (m, 4H), 2.43 – 2.32 (m, 2H), 1.85 – 1.81 (m, 1H), 1.50 – 1.46 (m, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 50.5 (-), 46.7 (-, 2C), 41.9 (-), 40.4 (-), 33.5 (+), 31.3 (-), 18.4 (+), 15.0 (+), 13.2 (+), 11.7 (+, 2C); FT IR (NaCl, cm^{-1}): 2968, 2932, 2799,1637, 1448, 1429, 1379, 1261, 1126, 1070; HRMS (TOF ES): found 251.2095, calculated for $C_{13}H_{28}N_2ONa$ (M+Na) 251.2099 (1.6 ppm).



N,N-Diethyl-2-methyl-4-(pyrrolidin-1-yl)butanamide (**5ac**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and pyrrolidine (**8c**) (160 μL, 139 mg, 1.95 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.30 (CH_2Cl_2/MeOH 10:1). Yield 104 mg (0.46 mmol, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 – 3.36 (m, 2H), 3.34 – 3.23 (m, 3H), 2.76 – 2.71 (m, 1H), 2.50 – 2.44 (m, 4H), 2.37 – 2.34 (m, 1H), 1.92 – 1.88 (m, 1H), 1.74 (br. s, 4H), 1.61 – 1.57 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.07 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7, 54.1 (-), 54.1 (-, 2C), 41.9 (-), 40.4 (-), 33.8 (+), 33.3 (-), 23.6 (-, 2C), 18.4 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 2968, 1786, 1634, 1464, 1433, 1379, 1261, 1221, 1128, 1097, 752, 733; HRMS (TOF ES): found 227.2117, calculated for $C_{13}H_{27}NO_2$ (M+H) 227.2123 (2.6 ppm).

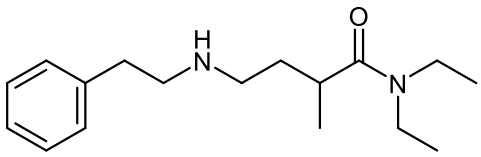


N,N-Diethyl-2-methyl-4-(phenylamino)butanamide (**5ai**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and aniline (**8i**) (118 μL, 121 mg, 1.30 mmol, 2.0 equiv). The reaction was carried out at 140 ^{o}C for 5 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.30 (CH_2Cl_2/MeOH 15:1). Yield 110 mg (0.44 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 2H), 6.67 (t, *J* = 7.3 Hz, 1H), 6.57 (d, *J* = 7.9 Hz, 2H), 3.74 (br. s, 1H), 3.42 – 3.34 (m, 2H), 3.32 – 3.24 (m, 2H), 3.15 – 3.04 (m, 2H), 2.83 – 2.74 (m, 1H), 2.17 – 2.04 (m, 1H), 1.71 – 1.63 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.14 – 1.09 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 148.4, 129.2 (+, 2C), 117.2 (+), 112.7 (+, 2C), 42.4 (-), 41.9 (-), 40.5 (-), 33.9 (+), 33.9 (-), 18.6 (+), 14.9 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3350, 2972, 1932, 1628, 1603, 1508, 1466, 1433, 1321, 1260, 750, 733, 694; HRMS (TOF ES): found 271.1773, calculated for $C_{15}H_{24}N_2ONa$ (M+Na) 271.1786 (4.8 ppm).

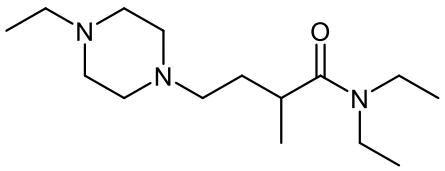


4-(Benzylamino)-N,N-diethyl-2-methylbutanamide (**5ah**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcyclo-prop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and benzylamine (**8h**) (142 μL, 139 mg, 1.30 mmol, 2.0 equiv). The reaction was carried out at 115 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.33 (CH_2Cl_2/MeOH 10:1). Yield 111 mg (0.42 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.17 (m, 5H), 3.76 – 3.69 (m, 2H), 3.36 – 3.24 (m, 4H), 2.80 – 2.71 (m, 1H), 2.64 – 2.52 (m, 2H), 2.47 (br. s, 1H), 1.93 – 1.85 (m, 1H), 1.59 – 1.51 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H), 1.06 – 1.01 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 139.9, 128.5 (+, 2C), 128.4 (+, 2C), 127.1 (+), 54.0 (-), 47.2 (-), 42.0 (-), 40.5 (-), 34.4 (-), 33.6 (+), 18.4 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3282,

2972, 2931, 1634, 1454, 1433, 1379, 1263, 1219, 1125, 1097, 733, 698; HRMS (TOF ES): found 285.1933, calculated for $C_{16}H_{26}N_2ONa$ (M+Na) 285.1943 (3.5 ppm).

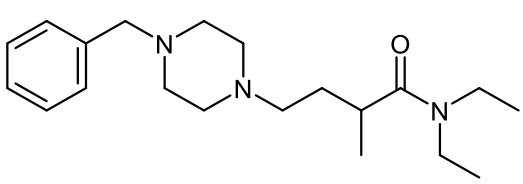


N,N-Diethyl-2-methyl-4-(phenethylamino)butanamide **(5ag)**: Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and 2-phenethylamine (**8g**) (123 μL, 118 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ^oC for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.32 (CH_2Cl_2/MeOH 15:1). Yield 135 mg (0.49 mmol, 75%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.20 – 7.18 (m, 3H), 3.41 – 3.20 (m, 4H), 2.88 (t, *J* = 6.1 Hz, 2H), 2.84 – 2.81 (m, 2H), 2.78 (br.s, 1H), 2.78 – 2.69 (m, 1H), 2.69 – 2.57 (m, 2H), 1.92 – 1.83 (m, 1H), 1.64 - 1.55 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 139.8, 128.8 (+, 2C), 128.6 (+, 2C), 126.3 (+), 51.0 (-), 47.4 (-), 42.0 (-), 40.5 (-), 36.1 (-), 34.1 (-), 33.6 (+), 18.3 (+), 15.0 (+), 13.2 (+); FT IR (NaCl, cm^{-1}): 3303, 2970, 2932, 1632, 1452, 1433, 1379, 1261, 924, 910, 738, 700; HRMS (TOF ES): found 277.2275, calculated for $C_{17}H_{29}N_2O$ (M+H) 277.2280 (1.8 ppm).

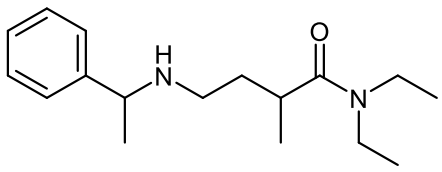


N,N-Diethyl-4-(4-ethylpiperazin-1-yl)-2-methylbutanamide (**5ae**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-ethylpiperazine (**8e**) (124 μL, 111 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ^oC for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.25 (CH_2Cl_2/MeOH 15:1). Yield 126 mg (0.47 mmol, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.48 – 3.35 (m, 2H), 3.33 – 3.19 (m, 2H),

2.71 (td, J = 13.7, 6.8 Hz, 1H), 2.37 (br. s, 8H), 2.38 (q, J = 7.1 Hz, 2H), 2.29 – 2.16 (m, 2H), 1.87 (td, J = 13.6, 8.0 Hz, 1H), 1.52 (td, J = 13.3, 7.3 Hz, 1H), 1.16 (t, J = 7.1 Hz, 3H), 1.10 – 1.04 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.8, 56.3 (-, 2C), 53.2 (-), 53.0 (-), 52.4 (-, 2C), 42.0 (-), 40.5 (-), 33.6 (+), 31.6 (-), 18.6 (+), 15.0 (+), 13.3 (+), 12.0 (+); FT IR (NaCl, cm^{-1}): 2968, 2932, 2808, 1643, 1634, 1467, 1447, 1431, 1259, 1164, 1132, 1026, 943, 781; HRMS (TOF ES): found 270.2535, calculated for $C_{15}H_{32}N_3O$ (M+H) 270.2545 (3.7 ppm).

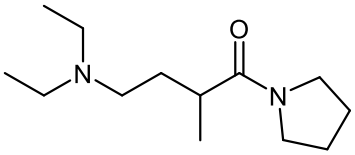


4-(4-Benzylpiperazin-1-yl)-N,N-diethyl-2-methylbutanamide (**5af**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methylcycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-benzylpiperazine (**8f**) (169 μL, 172 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.33 (CH_2Cl_2/MeOH 12:1). Yield 159 mg (0.48 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.19 (m, 5H), 3.46 (s, 2H), 3.52 – 3.36 (m, 2H), 3.34 – 3.20 (m, 2H), 2.76 – 2.68 (m, 1H), 2.45 (br. s, 8H), 2.35 – 2.22 (m, 2H), 1.88 (td, J = 13.6, 7.9 Hz, 1H), 1.53 (td, J = 13.4, 7.1 Hz, 1H), 1.17 (t, J = 7.1 Hz, 3H), 1.11 – 1.07 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 138.2, 129.3 (+, 2C), 128.3 (+, 2C), 127.2 (+), 63.2 (-), 56.3 (-, 2C), 53.2 (-), 53.1 (-, 2C), 42.0 (-), 40.5 (-), 33.7 (+), 31.4 (-), 18.6 (+), 15.1 (+), 13.3 (+); FT IR (NaCl, cm^{-1}): 2969, 2934, 2808, 1632, 1452, 1433, 1379, 1363, 1346, 1136, 1013, 924, 910, 733, 698; HRMS (TOF ES): found 332.2689, calculated for $C_{20}H_{34}N_3O$ (M+H) 332.2702 (3.9 ppm).

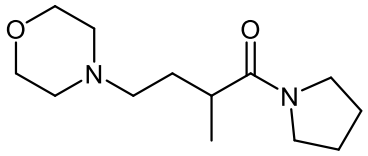


N,N-Diethyl-2-methyl-4-((1-phenylethyl)amino)-butanamide (**5ak**): Was prepared according to Typical Procedure, employing *N*,*N*-diethyl-1-methyl-

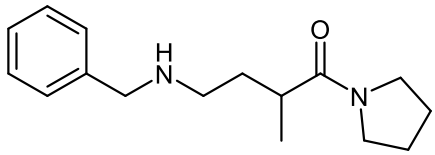
cycloprop-2-ene-1-carboxamide **(7a)** (100 mg, 0.65 mmol, 1.0 equiv) and 1-phenyl-ethylamine (**8k**) (126 μL, 118 mg, 0.98 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 3 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as inseparable mixture of diastereomers (dr 1:1); a yellow oil, R_f 0.27 (CH_2Cl_2/MeOH 15:1). Yield 117 mg (0.42 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br. s, 2H), 7.53 (t, *J* = 6.3 Hz, 4H), 7.39 – 7.31 (m, 6H), 4.18 – 4.12 (m, 2H), 3.39 – 3.18 (m, 8H), 2.88 – 2.83 (m, 1H), 2.82 – 2.72 (m, 3H), 2.66 – 2.58 (m, 2H), 2.08 – 1.91 (m, 4H), 1.76 (t, *J* = 7.2 Hz, 6H), 1.10 (t, *J* = 7.0 Hz, 6H), 1.03 – 0.98 (m, 3H), 1.00 (t, *J* = 5.8 Hz, 6H), 0.95 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 175.1, 137.4, 137.2, 129.2 (+, 2C), 129.2 (+, 2C), 129.1 (+), 129.0 (+), 127.9 (+, 2C), 127.9 (+, 2C), 58.6 (+), 58.5 (+), 43.4 (-), 42.8 (-), 42.4 (-), 42.2 (-), 40.7 (-), 40.5 (-), 34.0 (-), 33.7 (-), 29.9 (+), 29.7 (+), 21.1 (+), 20.7 (+), 17.8 (+), 17.4 (+), 14.9 (+, 2C), 13.0 (+, 2C); FT IR (NaCl, cm^{-1}): 3437, 2972, 2749, 1624, 1456, 1382, 1264, 1218, 1078, 768, 703; HRMS (TOF ES): found 277.2269, calculated for $C_{17}H_{29}N_2O$ (M+H) 277.280 (4.0 ppm).



4-(Diethylamino)-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**5ca**): Was prepared according to Typical Procedure, employing (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)-methanone **(7c)** (100 mg, 0.66 mmol, 1.0 equiv) and diethylamine (**8a**) (205 μL, 145 mg, 1.98 mmol, 3.0 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.27 (CH_2Cl_2/MeOH 10:1). Yield 97 mg (0.43 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 – 3.49 (m, 1H), 3.45 – 3.39 (m, 3H), 3.06 (q, *J* = 7.1 Hz, 4H), 2.99 – 2.89 (m, 2H), 2.72 – 2.63 (m, 1H), 2.18 – 2.09 (m, 1H), 2.02 – 1.92 (m, 2H), 1.89 – 1.83 (m, 3H), 1.38 (t, *J* = 7.2 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 49.3 (-), 46.6 (-), 46.6 (-, br., 2C), 46.1 (-), 36.1 (+), 26.9 (-), 26.2 (-), 24.3 (-), 17.8 (+), 8.9 (+, 2C); FT IR (NaCl, cm^{-1}): 3422, 2971, 1620, 1468, 1443, 1344, 1271, 1040, 733, 701; HRMS (TOF ES): found 249.1941, calculated for $C_{13}H_{26}NO_2Na$ (M+Na) 249.1943 (0.8 ppm).

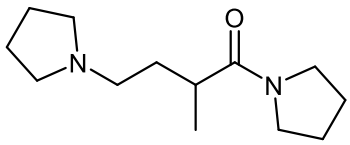


2-Methyl-4-morpholino-1-(pyrrolidin-1-yl)butan-1-one (**5cd**): Was prepared according to Typical Procedure, employing (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**7c**) (100 mg, 0.66 mmol, 1.0 equiv) and morpholine (**8d**) (86 μL, 86 mg, 0.99 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.26 (CH_2Cl_2/MeOH 20:1). Yield 108 mg (0.45 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (t, *J* = 4.5 Hz, 4H), 3.59 – 3.54 (m, 1H), 3.45 – 3.38 (m, 3H), 2.66 – 2.57 (m, 1H), 2.42 – 2.35 (m, 4H), 2.33 – 2.23 (m, 2H), 1.94 – 1.88 (m, 3H), 1.86 – 1.79 (m, 2H), 1.55 – 1.47 (m, 1H), 1.10 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 67.2 (-, 2C), 57.0 (-), 53.8 (-, 2C), 46.6 (-), 45.8 (-), 36.1 (+), 30.8 (-), 26.3 (-), 24.5 (-), 17.9 (+); FT IR (NaCl, film, cm^{-1}): 2968, 2870, 1625, 1468, 1441, 1341, 1273, 1117, 1071, 916, 867, 753, 703, 664; HRMS (TOF ES): found 257.2586, calculated for $C_{13}H_{25}N_2O_2$ (M+H) 241.1916 (0.0 ppm).

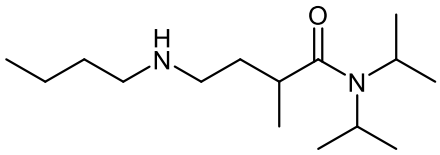


4-(Benzylamino)-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**5ch**): Was prepared according to Typical Procedure, employing (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone (**7c**) (100 mg, 0.66 mmol, 1.0 equiv) and benzylamine (**8h**) (94 μL, 92 mg, 0.86 mmol, 1.3 equiv). The reaction was carried out at 100 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.30 (CH_2Cl_2/MeOH 15:1). Yield 112 mg (0.43 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.22 (m, 4H), 7.20 – 7.16 (m, 1H), 3.76 (q, *J* = 13.2 Hz, 2H), 3.46 – 3.40 (m, 1H), 3.36 – 3.30 (m, 3H), 3.21 (br. s, 1H), 2.65 – 2.61 (m, 3H), 1.90 – 1.82 (m, 3H), 1.78 – 1.71 (m, 2H), 1.67 – 1.58 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 138.2, 128.7 (+, 2C), 128.7 (+, 2C), 127.6 (+), 53.4 (-), 46.7 (-), 46.5 (-), 46.0 (-), 36.1 (+), 33.0 (-), 26.3 (-), 24.4 (-), 17.4 (+); FT IR (NaCl, film, cm^{-1}): 3426, 2966, 2928,

2872, 1628, 1454, 1435, 1340, 743, 700; HRMS (TOF ES): found 261.1960, calculated for $C_{16}H_{25}N_2O$ (M+H) 261.1967 (2.7 ppm).

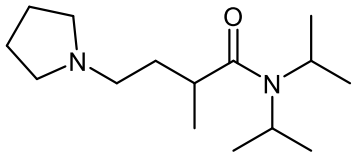


2-Methyl-1,4-di(pyrrolidin-1-yl)butan-1-one (**5cc**): Was prepared according to Typical Procedure, employing (1-methylcycloprop-2-en-1-yl)(pyrrolidin-1-yl)methanone **(7c)** (100 mg, 0.66 mmol, 1.0 equiv) and pyrrolidine (**8c**) (163 μL, 141 mg, 1.98 mmol, 3.0 equiv). The reaction was carried out at 100 ^oC for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.33 (CH_2Cl_2/MeOH 10:1). Yield 108 mg (0.48 mmol, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.55 – 3.50 (m, 1H), 3.44 – 3.36 (m, 3H), 2.63 – 3.58 (m, 1H), 2.45 (br. s, 4H), 2.41 – 2.33 (m, 2H), 1.92 – 1.87 (m, 3H), 1.84 – 1.77 (m, 2H), 1.72 (br. s, 4H), 1.60 – 1.51 (m, 1H), 1.09 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 54.2 (-), 54.1 (-, 2C), 46.5 (-), 45.7 (-), 36.2 (+), 33.1 (-), 26.3 (-), 24.5 (-), 23.6 (-, 2C), 17.6 (+); FT IR (NaCl, film, cm^{-1}): 2968, 2874, 2791, 1626, 1618, 1460, 1431, 1340, 2968, 2932, 2799,1637, 1448, 1429, 1379, 1261, 1126; HRMS (TOF ES): found 225.1962, calculated for $C_{13}H_{25}N_2O$ (M+H) 225.1967 (2.2 ppm).

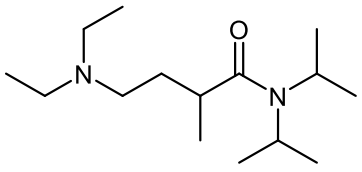


4-(Butylamino)-N,N-diisopropyl-2-methylbutan-amide (**5bj**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methyl-cycloprop-2-ene-1-carboxamide **(7b)** (100 mg, 0.55 mmol, 1.0 equiv) and butylamine (**8j**) (164 μL, 121 mg, 1.65 mmol, 3.0 equiv). The reaction was carried out at 100 ^oC for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.28 (CH_2Cl_2/MeOH 10:1). Yield 108 mg (0.42 mmol, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (br. s, 1H), 3.46 (br. s, 1H), 2.71 – 2.63 (m, 1H), 2.57 – 2.46 (m, 4H), 2.02 (br. s, 1H), 1.84 (td, J = 14.1, 7.5 Hz, 1H), 1.49 (dt, J = 13.3, 6.7 Hz, 1H), 1.40 (dt, J = 14.6, 7.2

Hz, 2H), 1.31 – 1.22 (m, 8H), 1.17 – 1.14 (t, J = 5.4 Hz, 6H), 1.04 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 49.7 (-), 47.9 (-), 47.9 (+, br.), 45.7 (+), 35.1 (+), 34.5 (-), 32.2 (-), 21.4 (+, br., 2C), 20.8 (+), 20.7 (+), 20.5 (-), 18.2 (+), 14.0 (+); FT IR (NaCl, film, cm^{-1}): 2962, 2930, 1631, 1466, 1441, 1371, 1303, 1213, 1134, 1040, 754; HRMS (TOF ES): found 257.2581, calculated for $C_{15}H_{32}N_2O$ (M+H) 255.2593 (4.7 ppm).

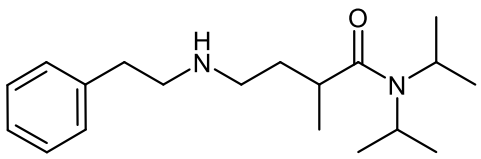


N,N-Diisopropyl-2-methyl-4-(pyrrolidin-1-yl)butanamide (**5bc**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**5b**) (100 mg, 0.55 mmol, 1.0 equiv) and pyrrolidine (**8c**) (136 μL, 118 mg, 1.65 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.31 (CH_2Cl_2/MeOH 15:1). Yield 102 mg (0.40 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (br. s, 1H), 3.44 (br. s, 1H), 2.67 (dt, J = 13.5, 6.7 Hz, 1H), 2.47 – 2.37 (m, 5H), 2.35 – 2.28 (m, 1H), 1.85 (dt, J = 17.1, 6.7 Hz, 1H), 1.69 (s, 4H), 1.50 (td, J = 14.1, 6.3 Hz, 1H), 1.29 (d, J = 6.2 Hz, 6H), 1.15 – 1.13 (m, 6H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4, 54.1 (-), 54.1 (-, 2C), 47.9 (+, br.), 45.6 (+), 35.1 (+), 33.2 (-), 23.5 (-, 2C), 21.4 (+), 21.3 (+), 20.8 (+), 20.8 (+), 18.2 (+); FT IR (NaCl, film, cm^{-1}): 2964, 2787, 1633, 1464, 1440, 1370, 1211, 1136, 1040, 752; HRMS (TOF ES): found 255.2435, calculated for $C_{15}H_{31}N_2O$ (M+H) 255.2436 (0.4 ppm).

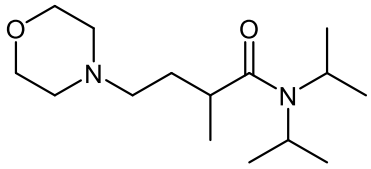


4-(Diethylamino)-N,N-diisopropyl-2-methylbutanamide (**5ba**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**7b**) (100 mg, 0.55 mmol, 1.0 equiv) and diethylamine (**8a**) (171 μL, 121 mg, 1.65 mmol, 3.0 equiv). The reaction was carried out at 100 °C for 1 hr. Reduction with $NaBH_4$, acid-base extraction followed by preparative

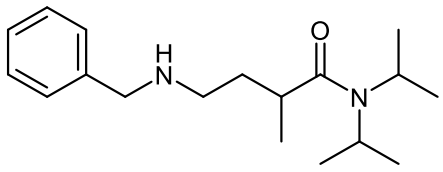
column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.26 (CH_2Cl_2/MeOH 10:1). Yield 100 mg (0.39 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 – 3.98 (br. m, 1H), 3.45 (br. s, 1H), 2.66 (dt, *J* = 13.5, 6.7 Hz, 1H), 2.57 (q, *J* = 7.0 Hz, 4H), 2.46 (t, *J* = 7.4 Hz, 2H), 1.88 (td, *J* = 14.6, 7.5 Hz, 1H), 1.49 (td, *J* = 13.4, 7.1 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 6H), 1.17 (t, *J* = 5.9 Hz, 6H), 1.07 – 1.02 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 50.3 (-), 47.9 (+, br.), 46.8 (-, 2C), 45.7 (+), 35.0 (+), 30.4 (-), 21.4 (+, br., 2C), 20.8 (+), 20.8 (+), 18.2 (+), 11.4 (+, 2C); FT IR (NaCl, film, cm^{-1}): 2967, 2932, 1636, 1630, 1466, 1439, 1372, 1211, 1134, 1038, 755; HRMS (TOF ES): found 257.2586, calculated for $C_{15}H_{33}N_2O$ (M+H) 257.2593 (2.7 ppm).



N,N-Diisopropyl-2-methyl-4-(phenethylamino)-butanamide (**5bg**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**7b**) (100 mg, 0.55 mmol, 1.0 equiv) and phenethylamine (**8g**) (104 μL, 100 mg, 0.83 mmol, 1.5 equiv). The reaction was carried out at 100 °C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.35 (CH_2Cl_2/MeOH 15:1). Yield 100 mg (0.39 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.8 Hz, 2H), 7.22 – 7.16 (m, 3H), 4.03 (br. s, 1H), 3.50 (br. s, 1H), 2.87 – 2.84 (m, 2H), 2.80 – 2.76 (m, 2H), 2.74 – 2.65 (m, 1H), 2.63 – 2.53 (m, 2H), 1.86 (td, *J* = 13.9, 7.5 Hz, 1H), 1.62 (br. s, 1H), 1.52 (dt, *J* = 13.5, 6.5 Hz, 1H), 1.36 – 1.33 (m, 6H), 1.21 – 1.16 (m, 6H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 140.2, 128.8 (+, 2C), 128.6 (+, 2C), 126.2 (+), 51.3 (-), 47.9 (+, br.), 47.8 (-), 45.8 (+), 36.5 (-), 35.0 (+), 34.6 (-), 21.5 (+, br., 2C), 20.9 (+), 20.8 (+), 18.3 (+); FT IR (NaCl, film, cm^{-1}): 2967, 1629, 1629, 1372, 1213, 1121, 1040, 755, 701; HRMS (TOF ES): found 305.2595, calculated for $C_{19}H_{33}N_2O$ (M+H) 305.2593 (0.7 ppm).

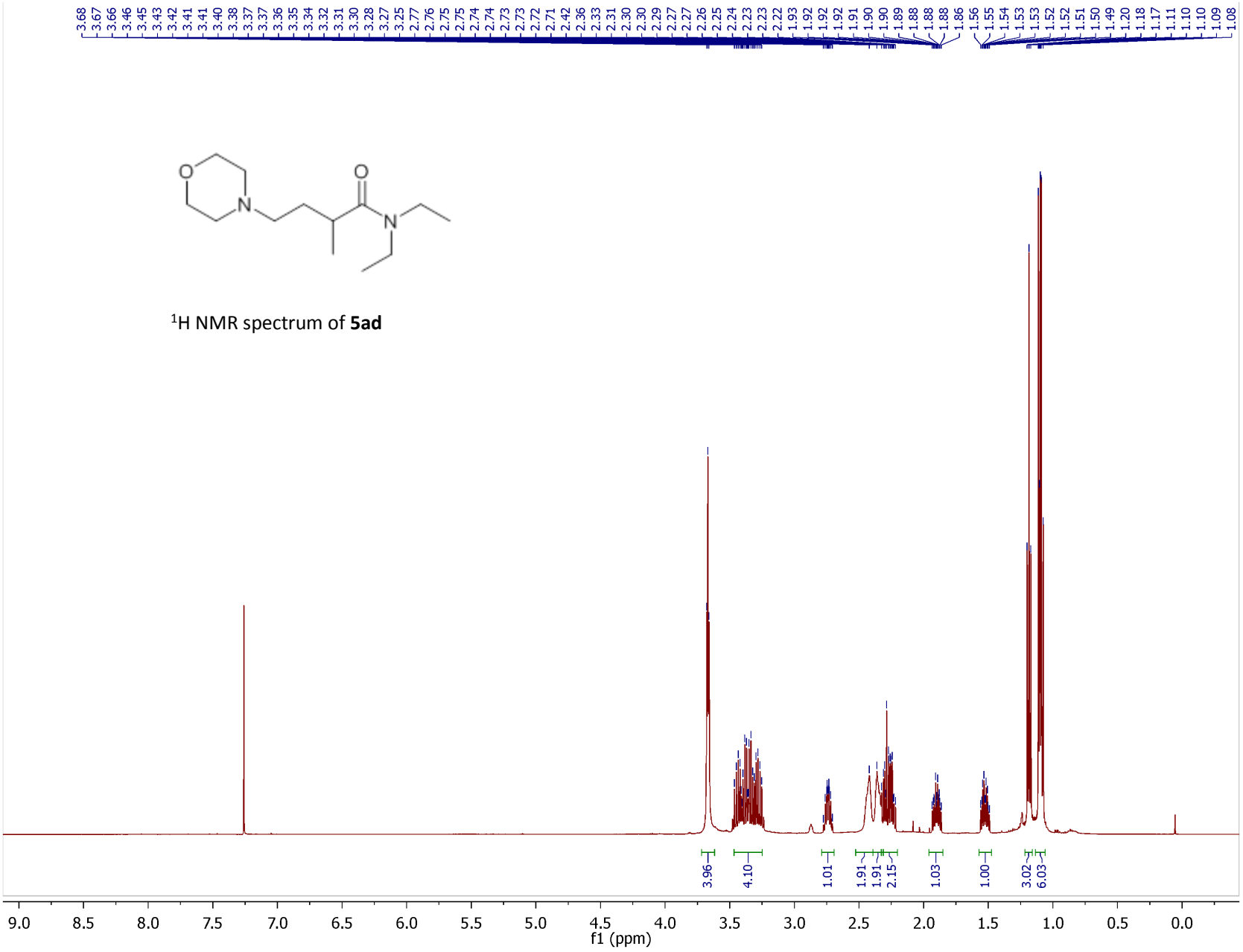


N,N-Diisopropyl-2-methyl-4-morpholinobutanamide (**5bd**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**7bd**) (100 mg, 0.55 mmol, 1.0 equiv) and morpholine (**8d**) (71 μL, 72 mg, 0.83 mmol, 1.5 equiv). The reaction was carried out at 100 ^{o}C for 1.5 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.28 (CH_2Cl_2/MeOH 20:1). Yield 98 mg (0.36 mmol, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.05 (br. s, 1H), 3.66 (t, *J* = 4.2 Hz, 4H), 3.48 (br. s, 1H), 2.74 – 2.66 (m, 1H), 2.44 – 2.41 (br. m, 2H), 2.36 – 2.31 (br. m, 2H), 2.31 – 2.21 (m, 2H), 1.89 (td, *J* = 13.5, 7.6 Hz, 1H), 1.48 (td, *J* = 13.4, 6.8 Hz, 1H), 1.33 (t, *J* = 4.3 Hz, 6H), 1.20 – 1.18 (m, 6H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 67.1 (-, 2C), 56.8 (-), 53.8 (-, 2C), 47.9 (+, br.), 45.7 (+), 34.8 (+), 30.9 (-), 21.4 (+, br., 2C), 20.9 (+), 20.9 (+), 18.5 (+); FT IR (NaCl, film, cm^{-1}): 2965, 2855, 2807, 1638, 1629, 1462, 1441, 1371, 1305, 1273, 1119, 1038, 916, 866, 752; HRMS (TOF ES): found 271.2391, calculated for $C_{15}H_{31}N_2O_2$ (M+H) 271.2386 (1.8 ppm).

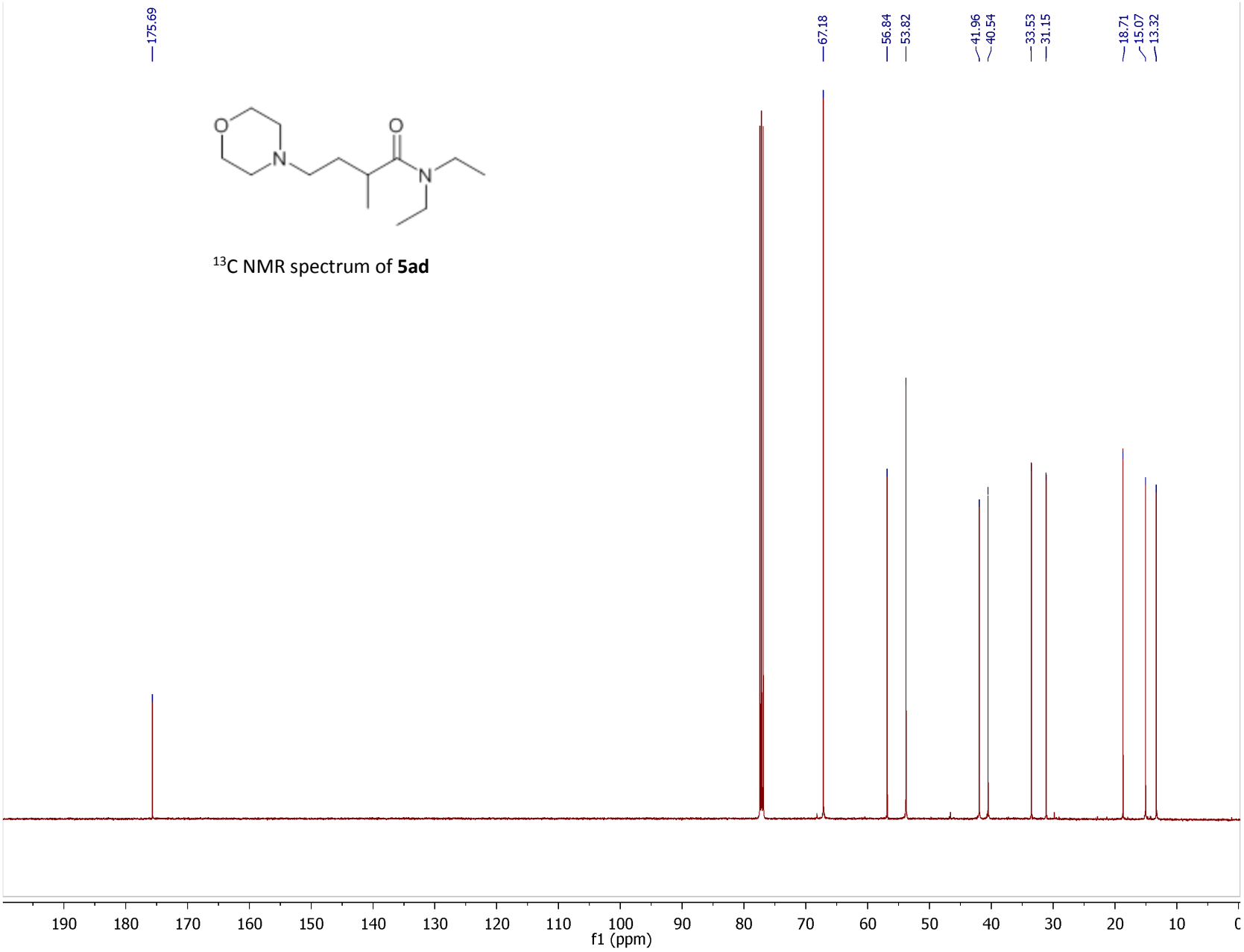


4-(Benzylamino)-N,N-diisopropyl-2-methylbutanamide (**5bh**): Was prepared according to Typical Procedure, employing *N*,*N*-diisopropyl-1-methylcycloprop-2-ene-1-carboxamide (**7b**) (100 mg, 0.55 mmol, 1.0 equiv) and benzylamine (**8h**) (78 μL, 77 mg, 0.72 mmol, 1.3 equiv). The reaction was carried out at 100 ^{o}C for 2 hrs. Reduction with $NaBH_4$, acid-base extraction followed by preparative column chromatography on Silica gel afforded the title compound as a yellow oil, R_f 0.30 (CH_2Cl_2/MeOH 15:1). Yield 109 mg (0.38 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.26 (m, 4H), 7.24 – 7.17 (m, 1H), 4.03 (br. s, 1H), 3.73 (s, 2H), 3.46 (br. s, 1H), 2.77 – 2.68 (m, 1H), 2.64 – 2.52 (m, 2H), 1.91 (dt, *J* = 14.2, 7.4 Hz, 1H), 1.84 (br.s, 1H), 1.52 (td, *J* = 13.3, 6.6 Hz, 1H), 1.33 – 1.28 (m, 6H), 1.18 – 1.14 (m, 6H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4,

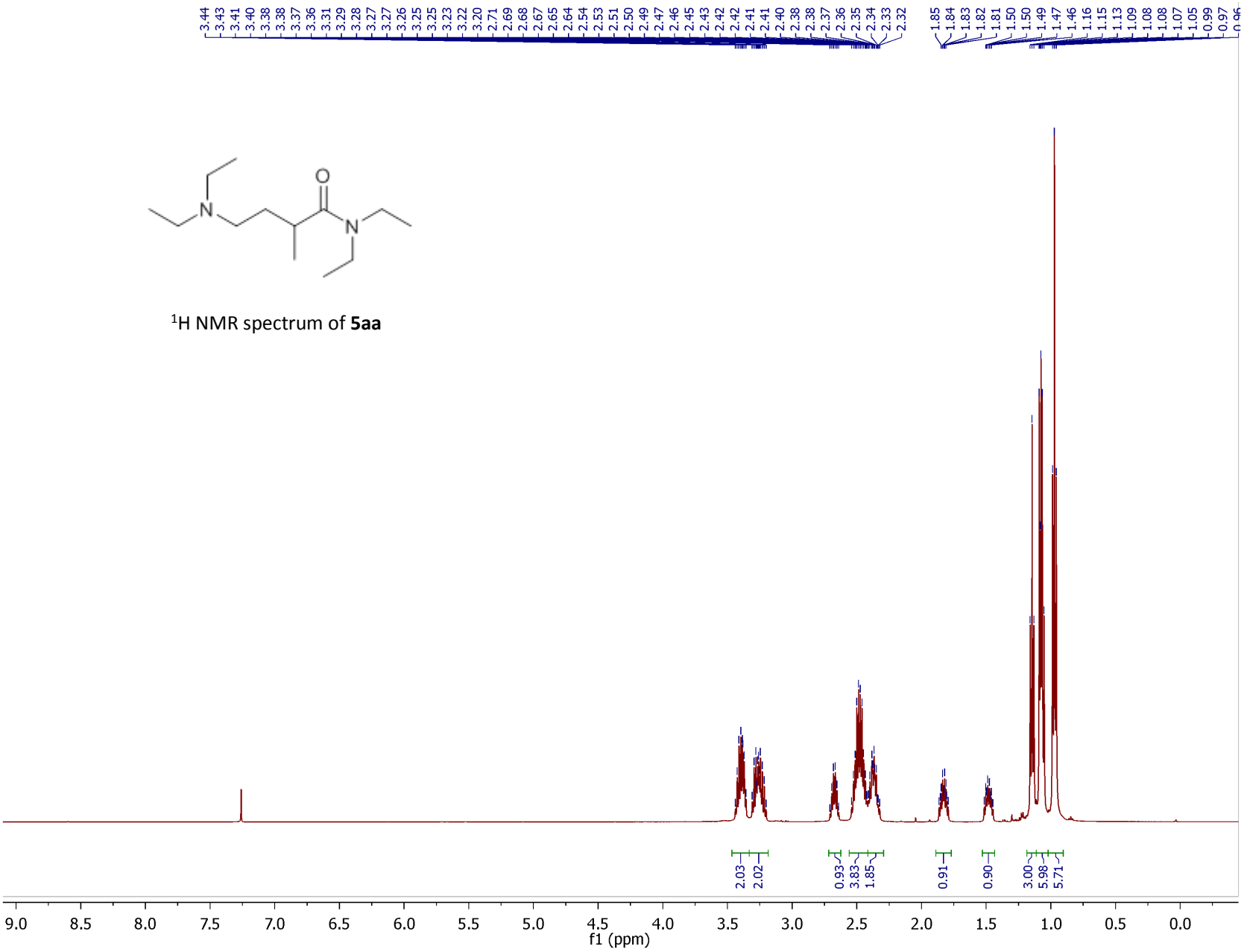
140.3, 128.4 (+, 2C), 128.2 (+, 2C), 126.9 (+), 53.99 (-), 47.8 (+, br.), 47.31 (-), 45.7 (+), 34.9 (+), 34.5 (-), 21.3 (+, br., 2C), 20.8 (+), 20.7 (+), 18.3 (+); FT IR (NaCl, film, cm^{-1}): 2965, 2930, 2872, 1634, 1439, 1370, 1327, 1304, 1211, 1119, 1040, 737, 698; HRMS (TOF ES): found 291.2430, calculated for $C_{18}H_{31}N_2O$ (M+H) 291.2436 (2.1 ppm).



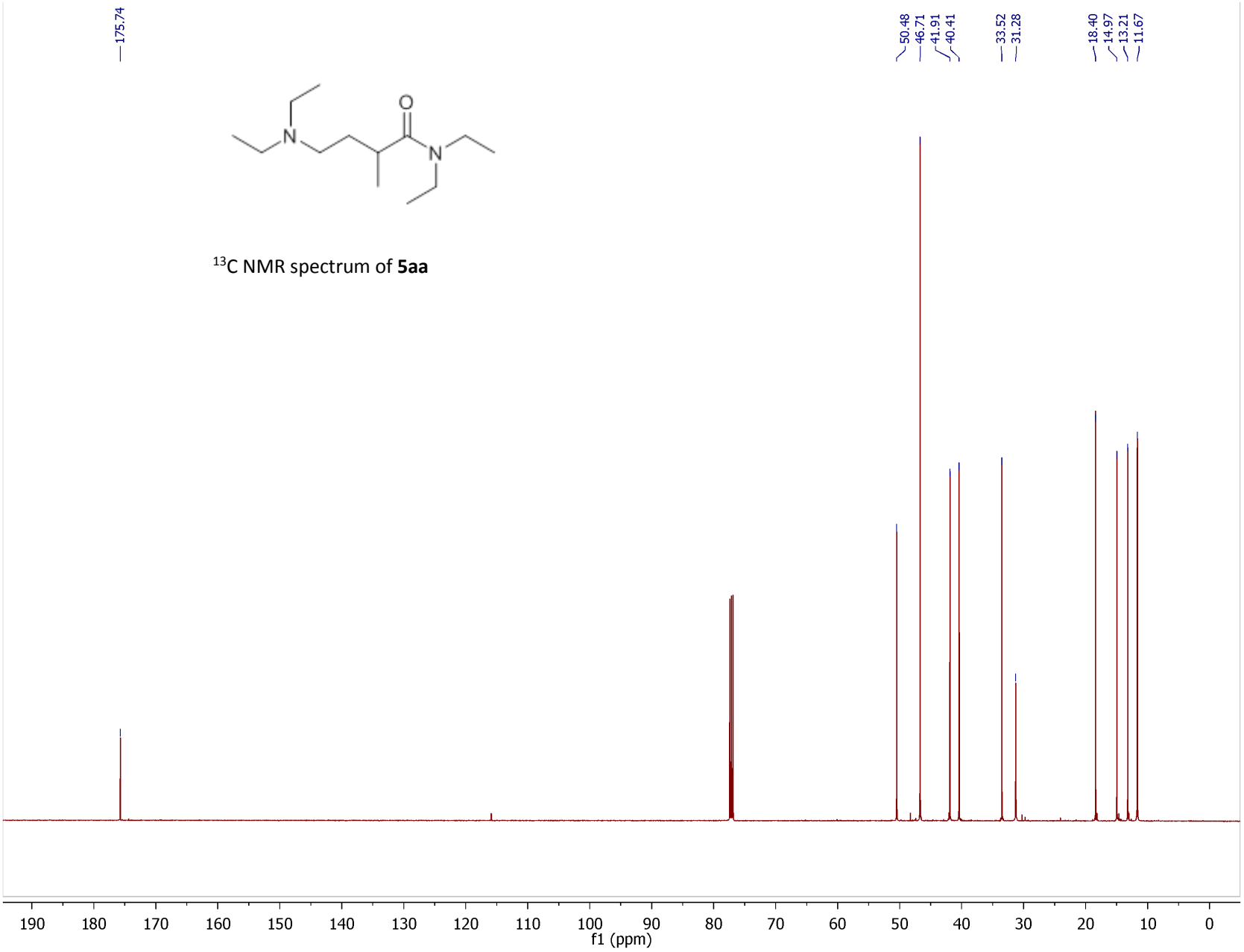
^{1}H NMR spectrum of **5ad**



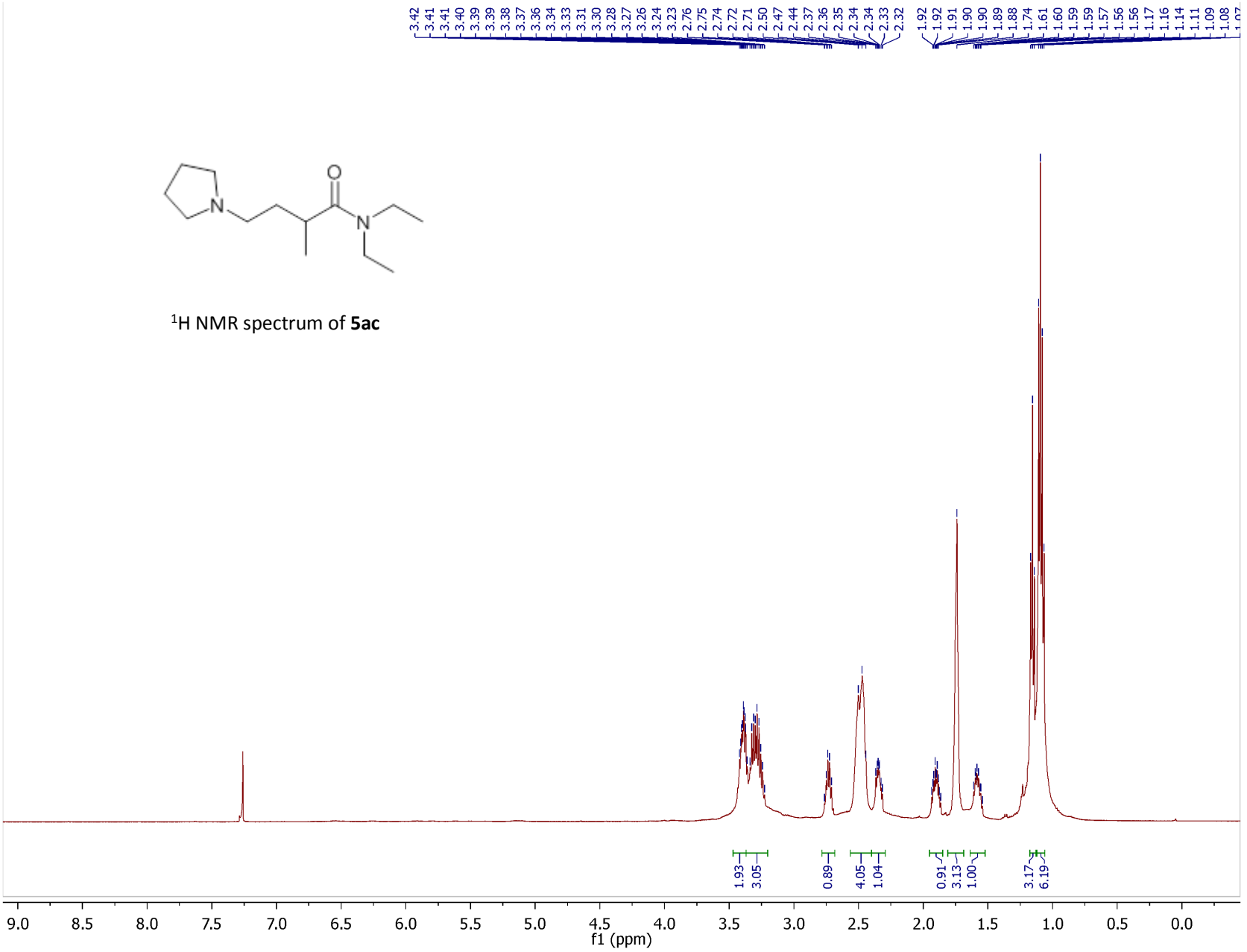
^{13}C NMR spectrum of **5ad**



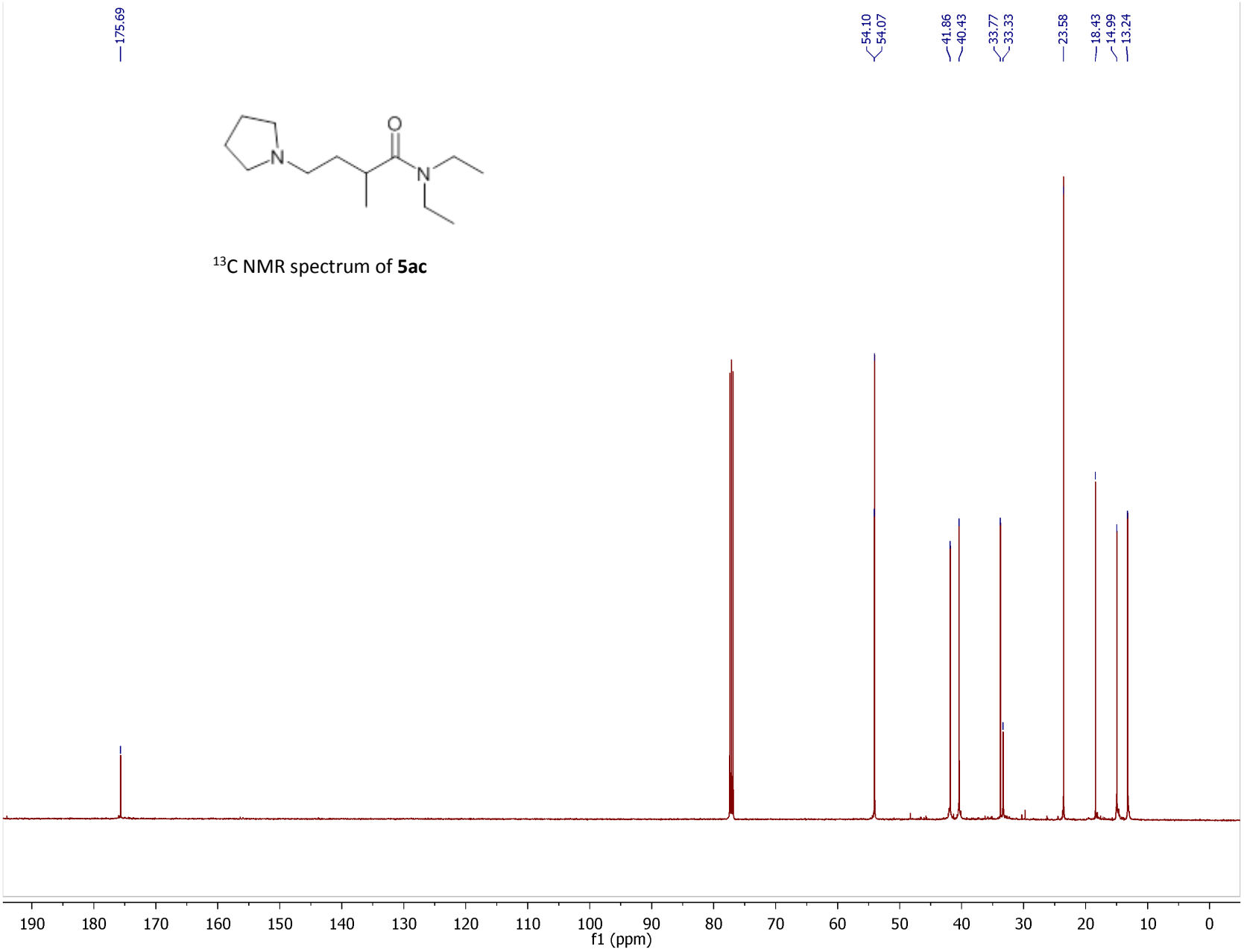
^{1}H NMR spectrum of **5aa**



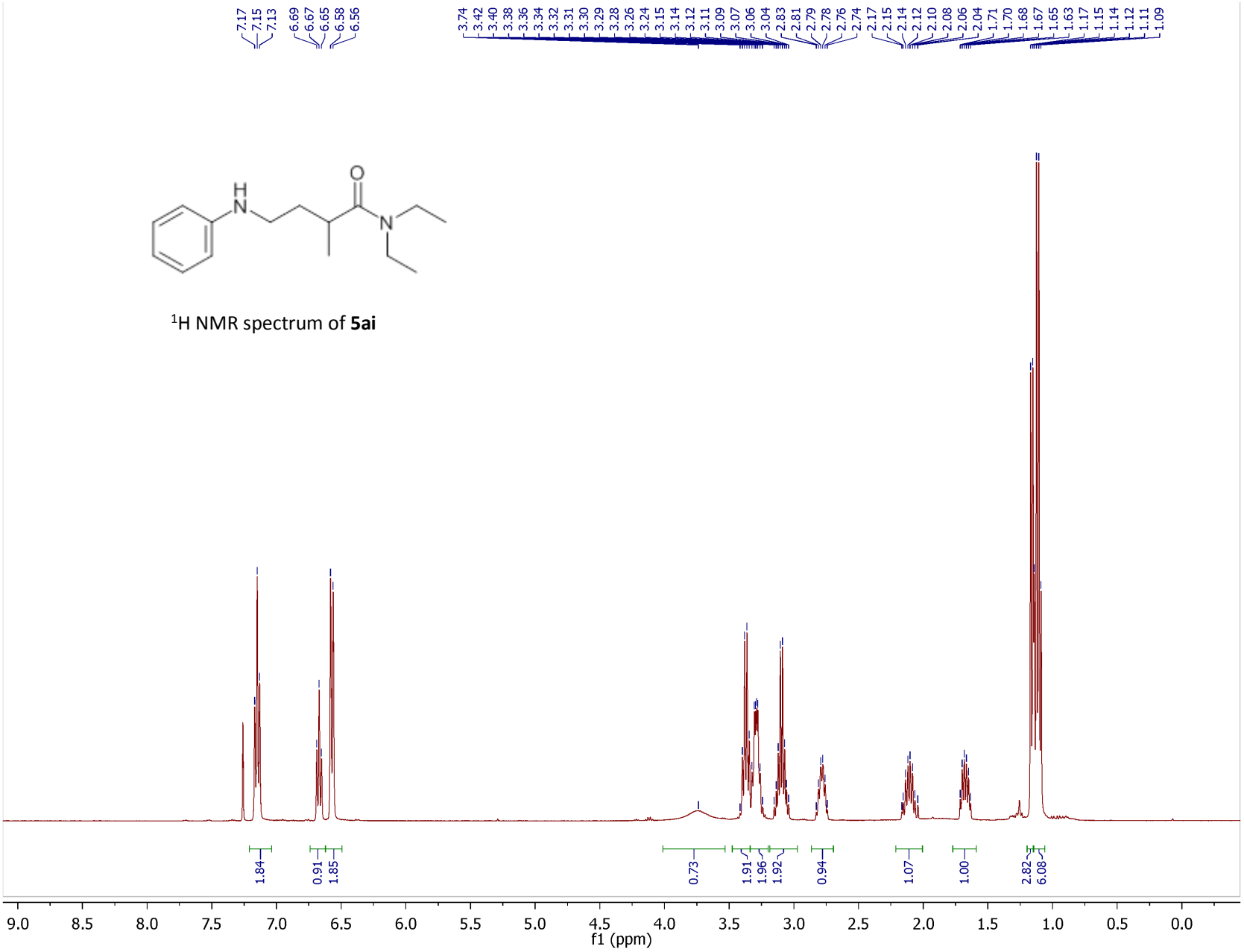
^{13}C NMR spectrum of **5aa**



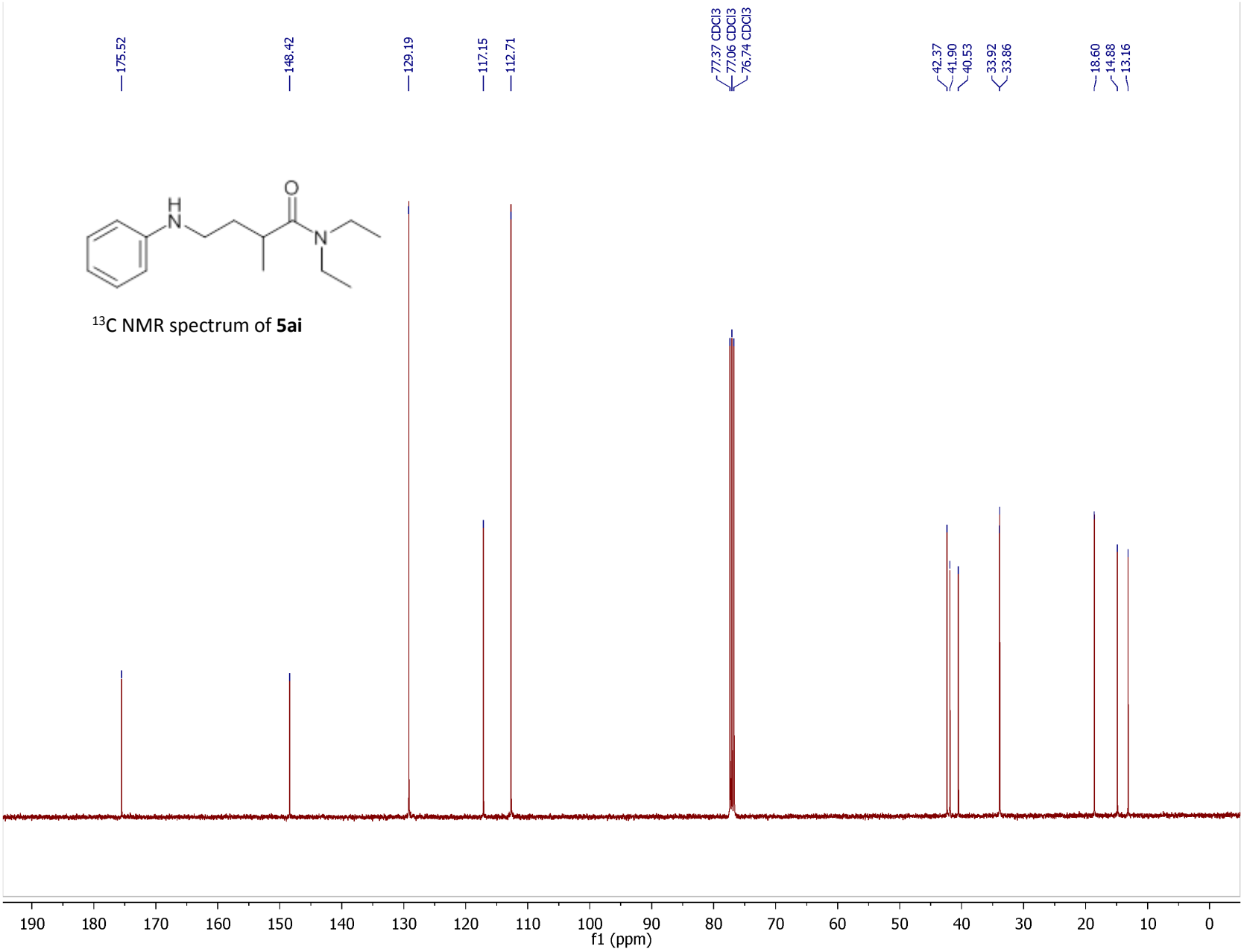
^{1}H NMR spectrum of **5ac**



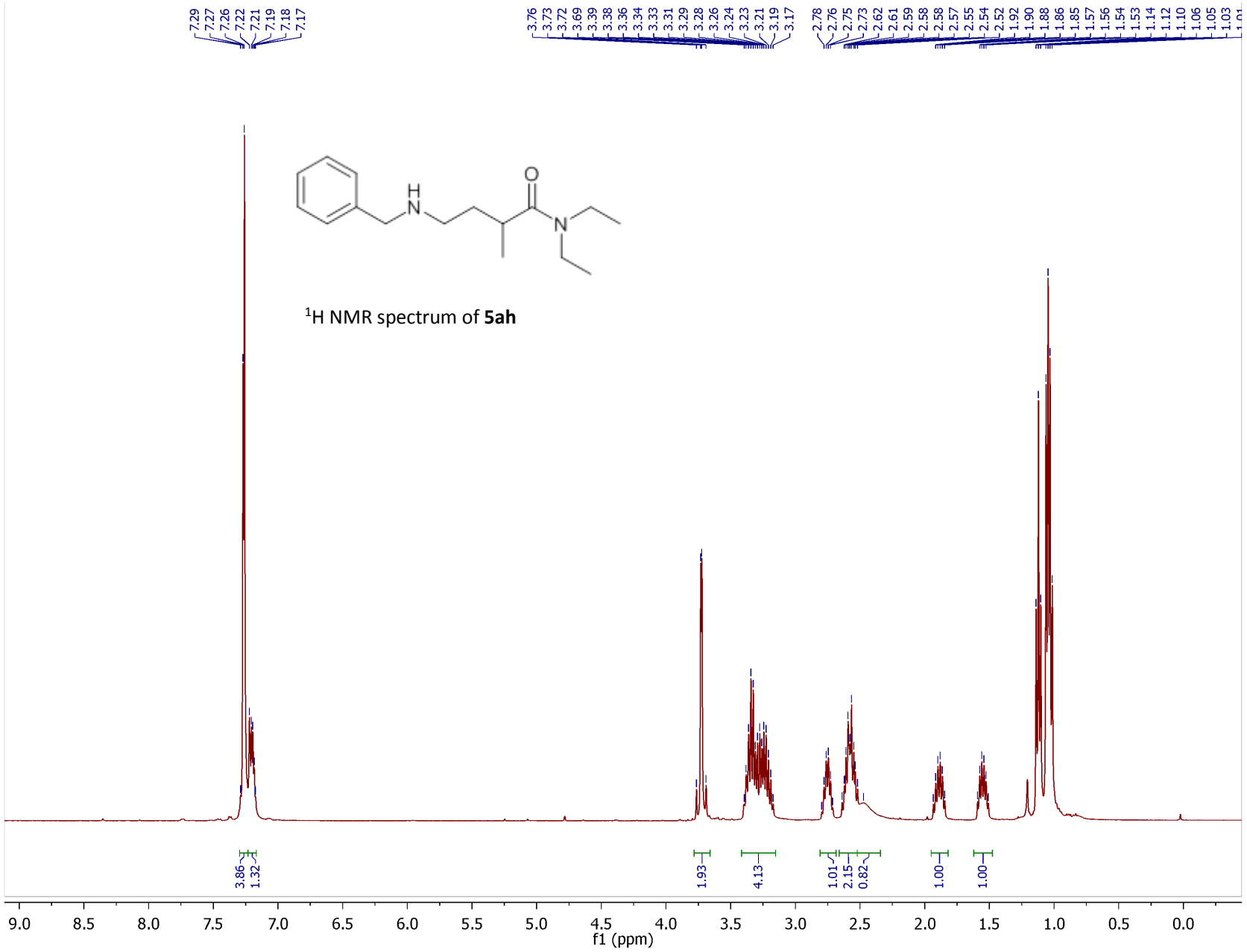
^{13}C NMR spectrum of **5ac**



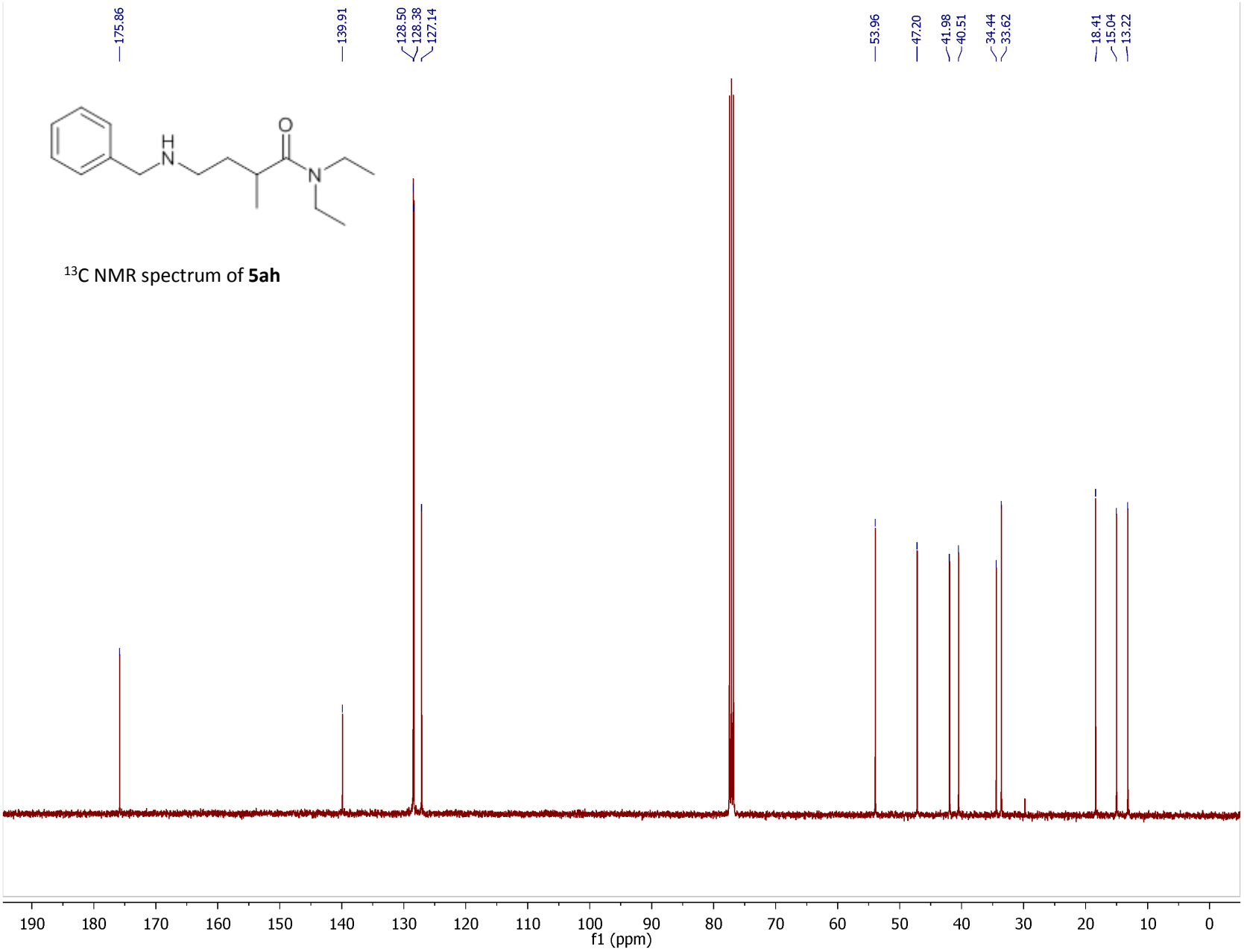
^{1}H NMR spectrum of **5ai**



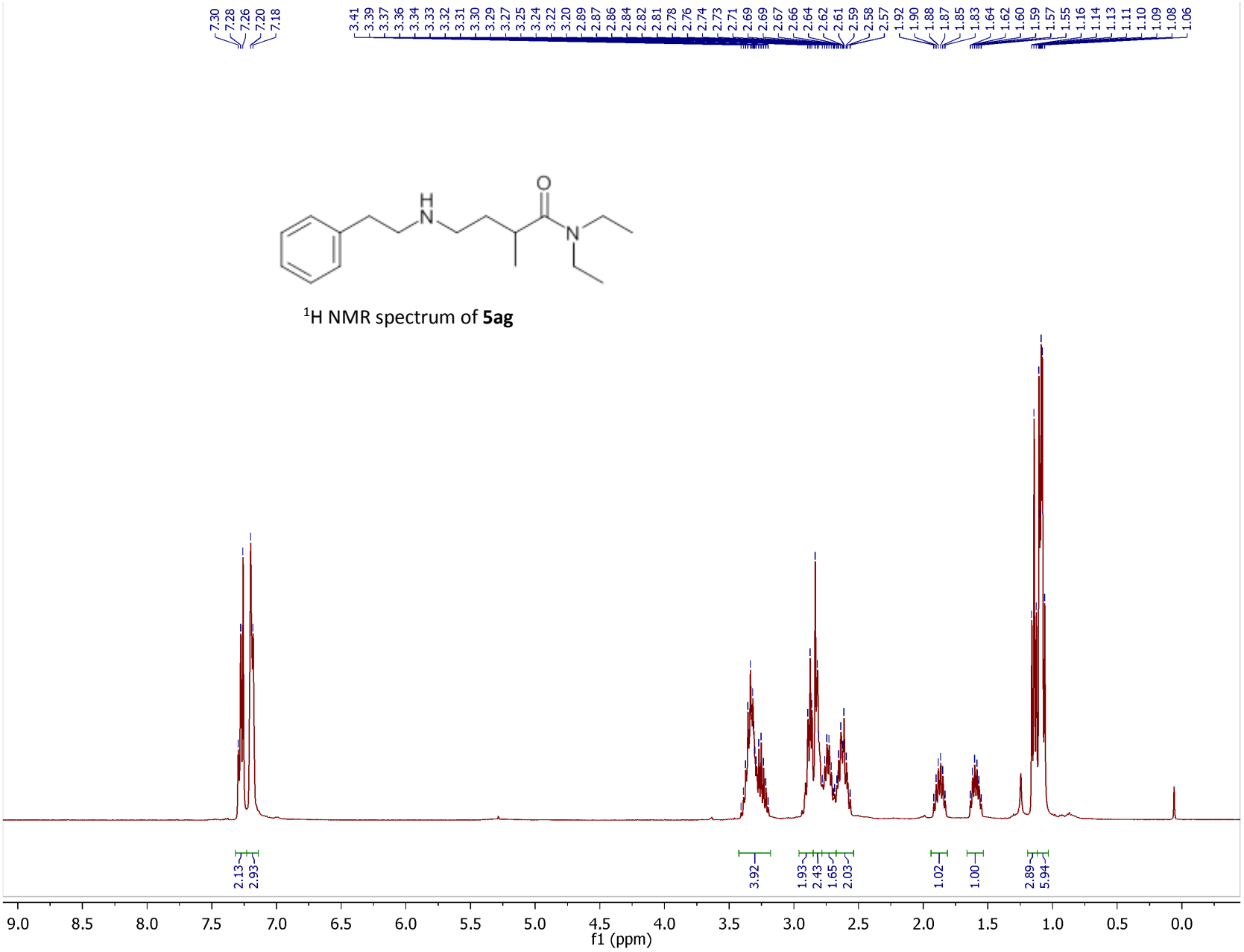
^{13}C NMR spectrum of **5ai**



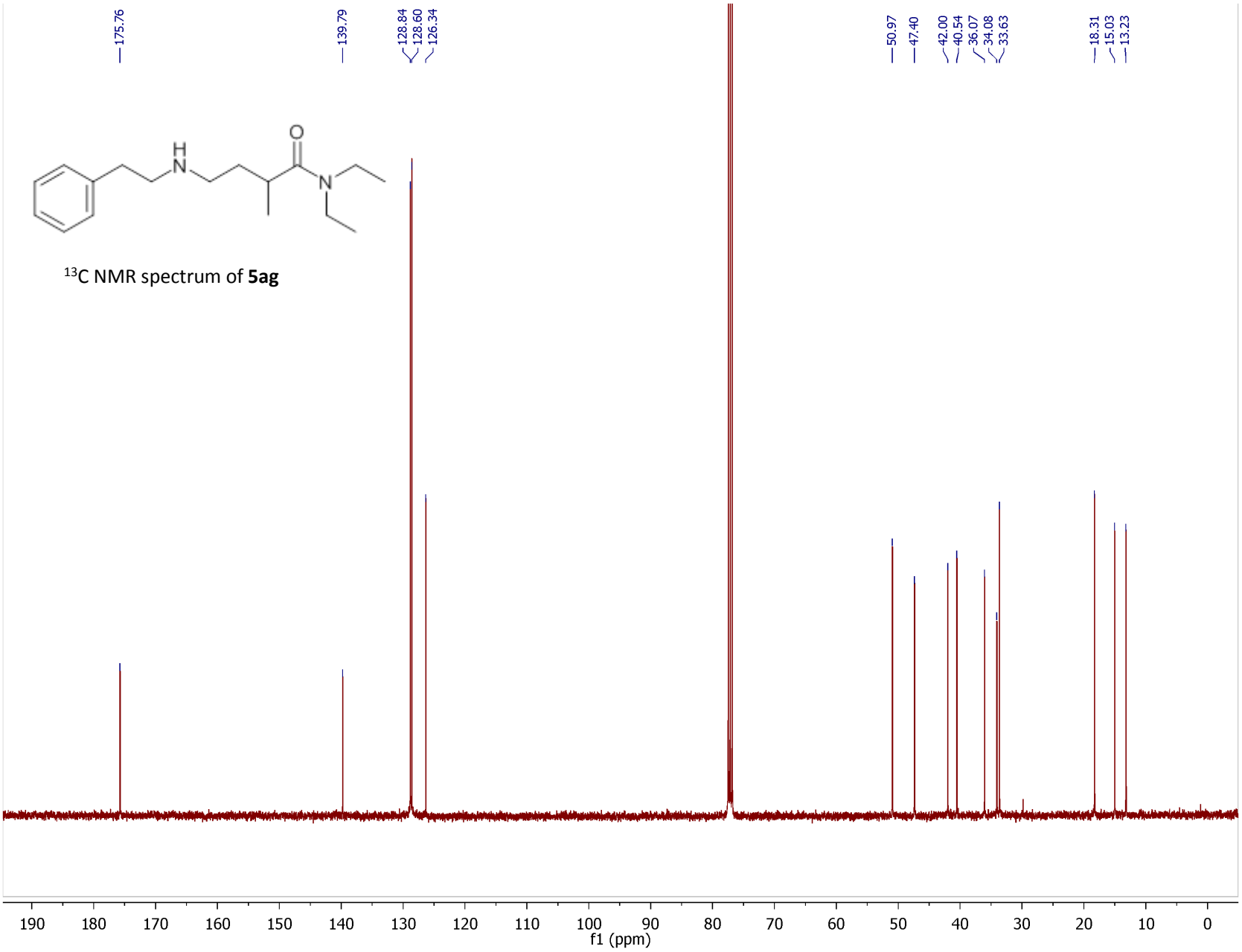
^{1}H NMR spectrum of **5ah**



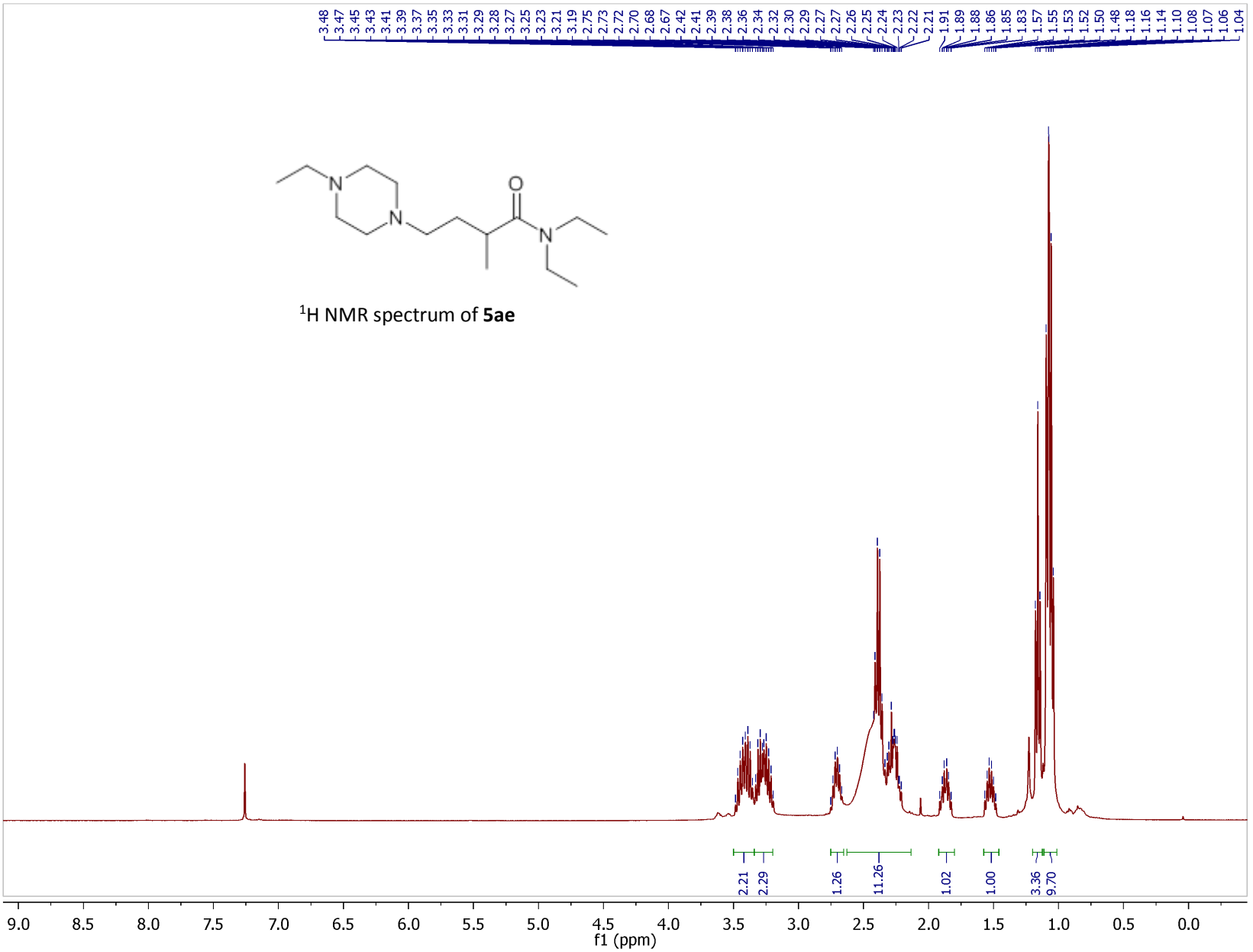
^{13}C NMR spectrum of **5ah**



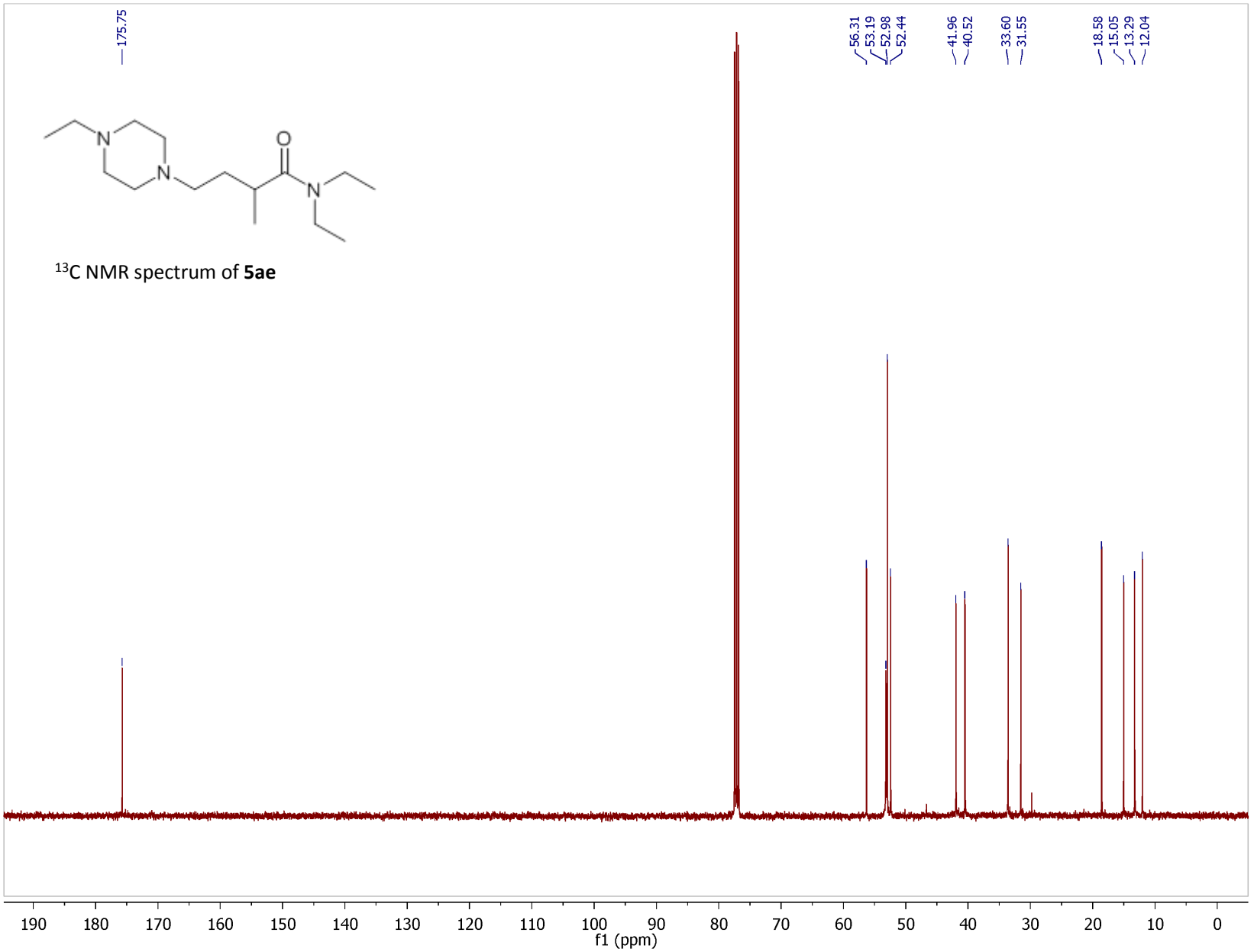
^{1}H NMR spectrum of **5ag**



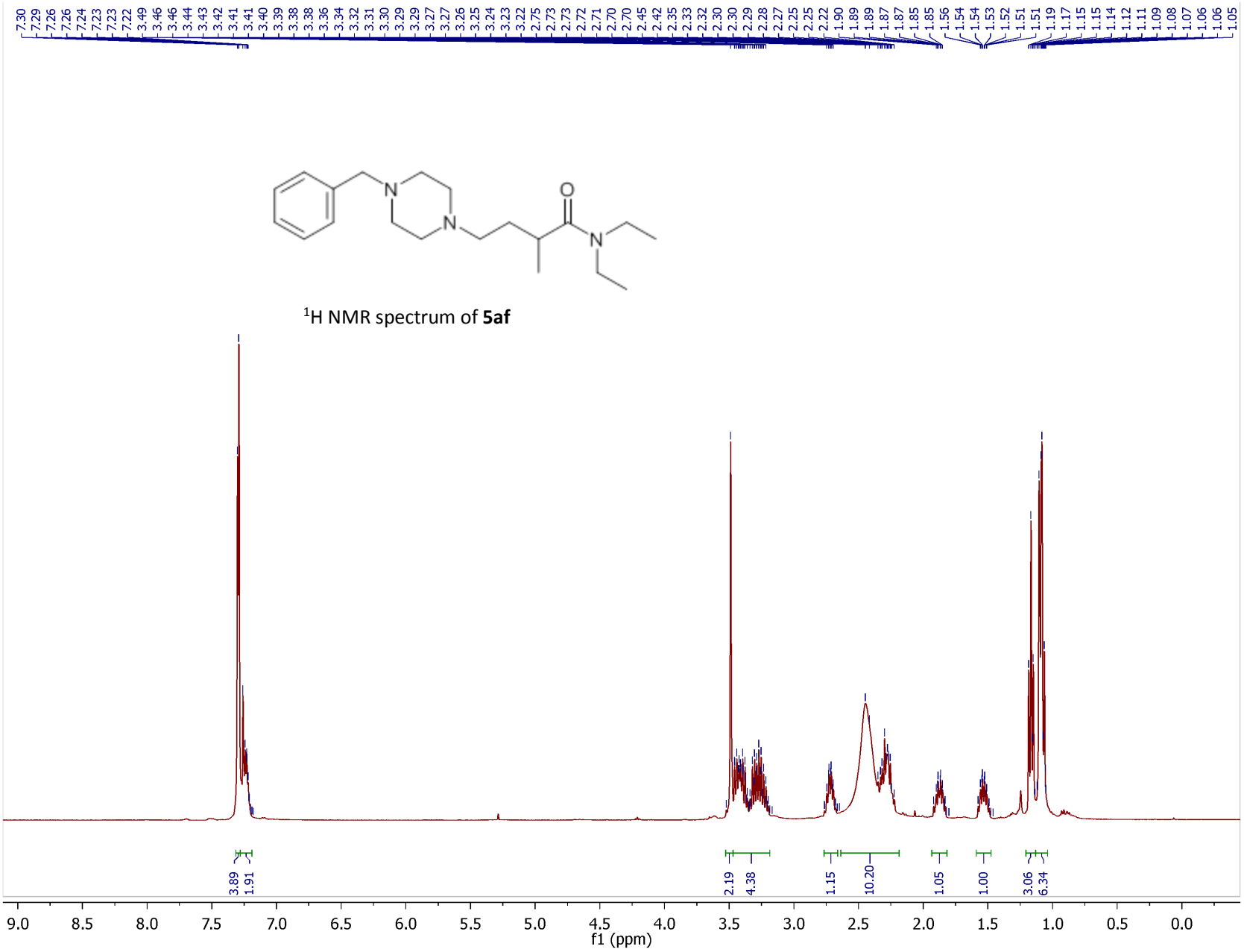
^{13}C NMR spectrum of **5ag**



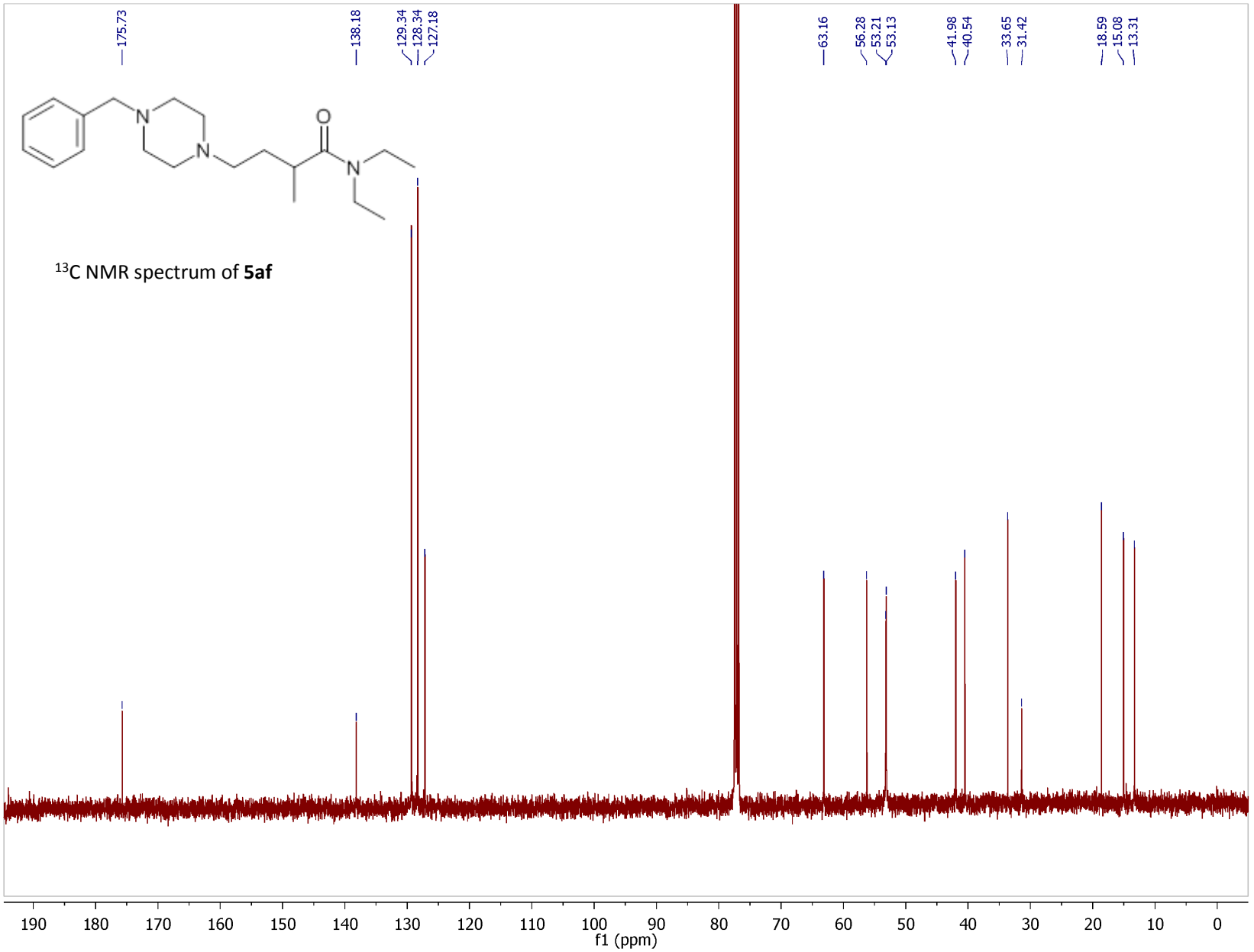
^{1}H NMR spectrum of **5ae**



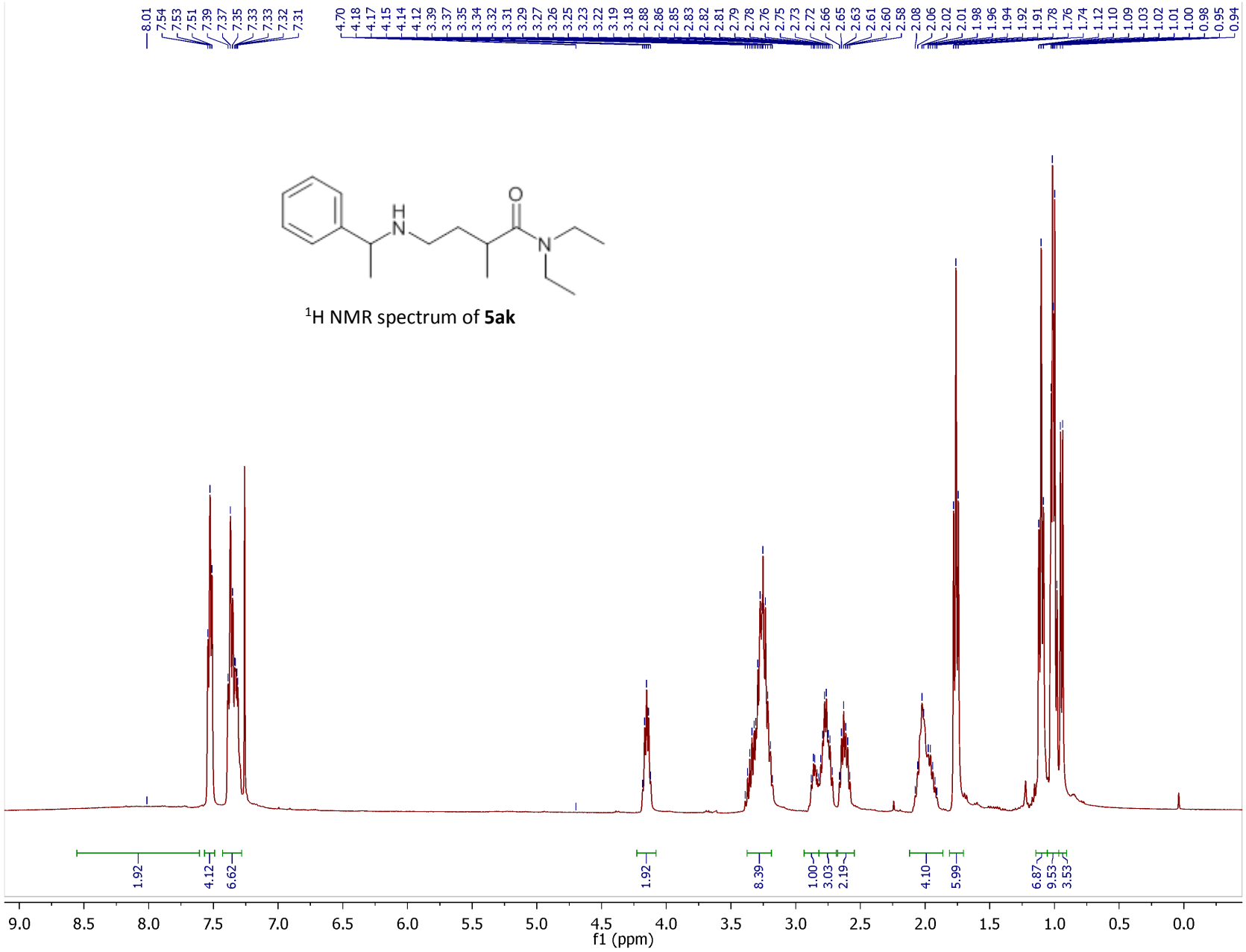
^{13}C NMR spectrum of **5ae**



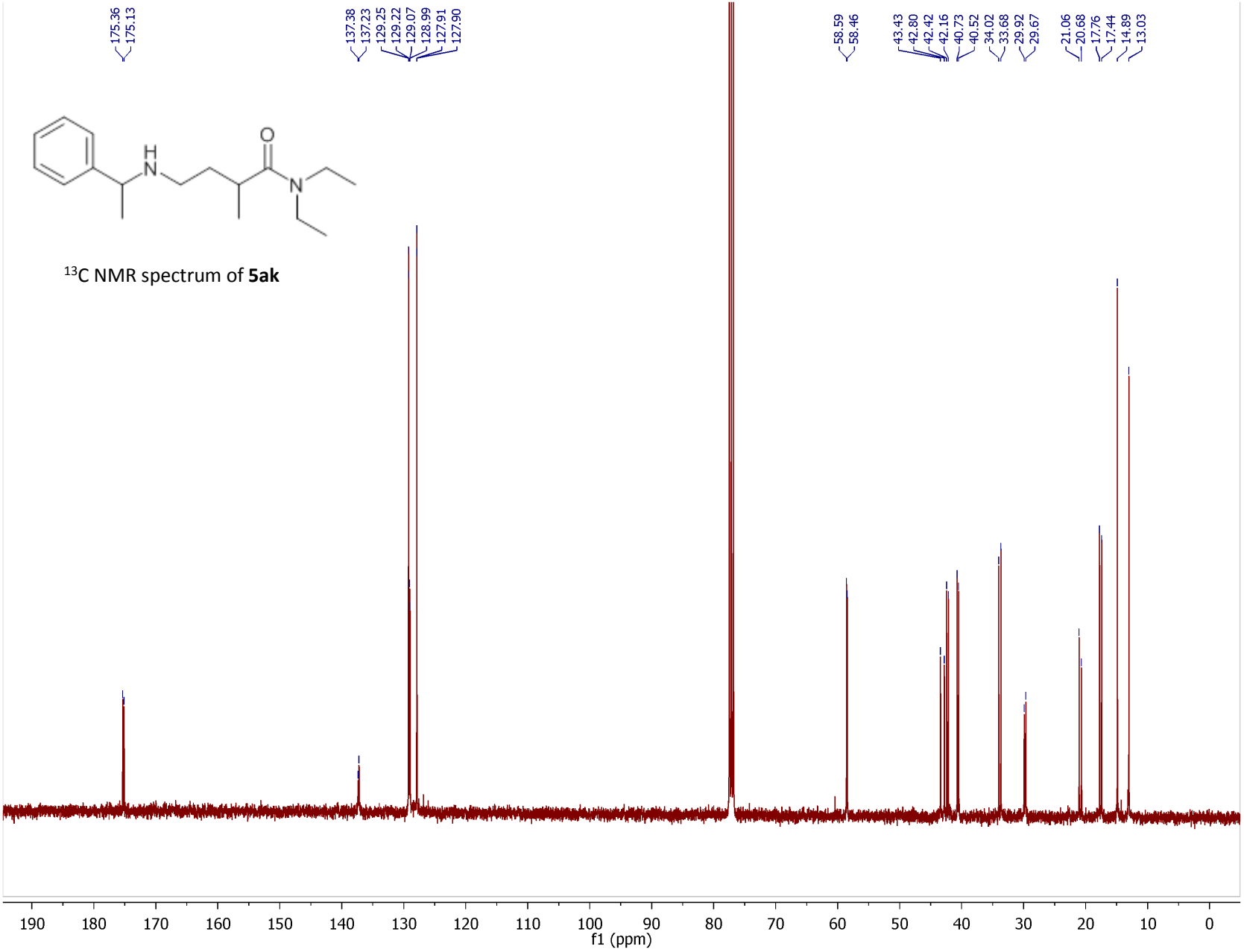
^{1}H NMR spectrum of **5af**



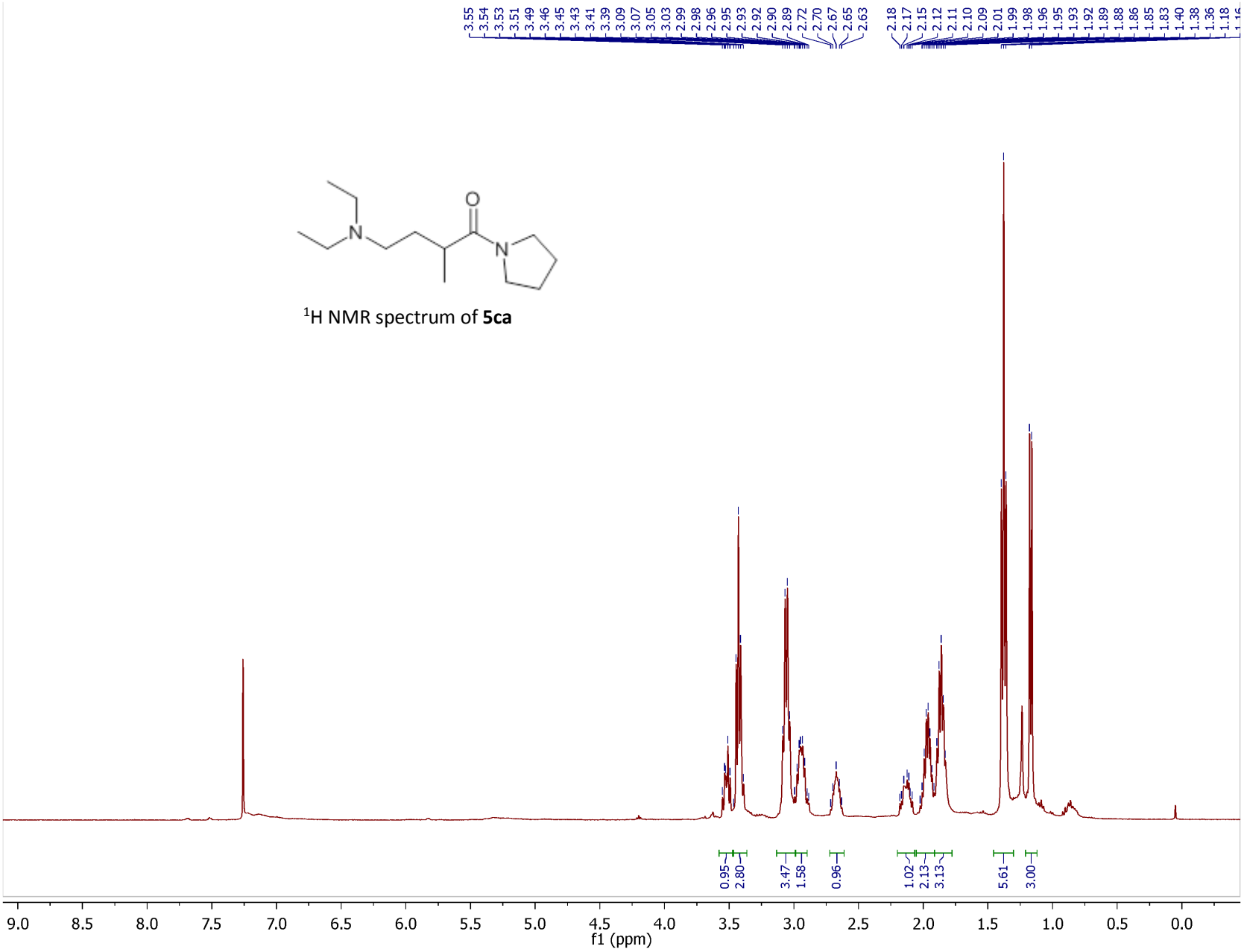
^{13}C NMR spectrum of **5af**



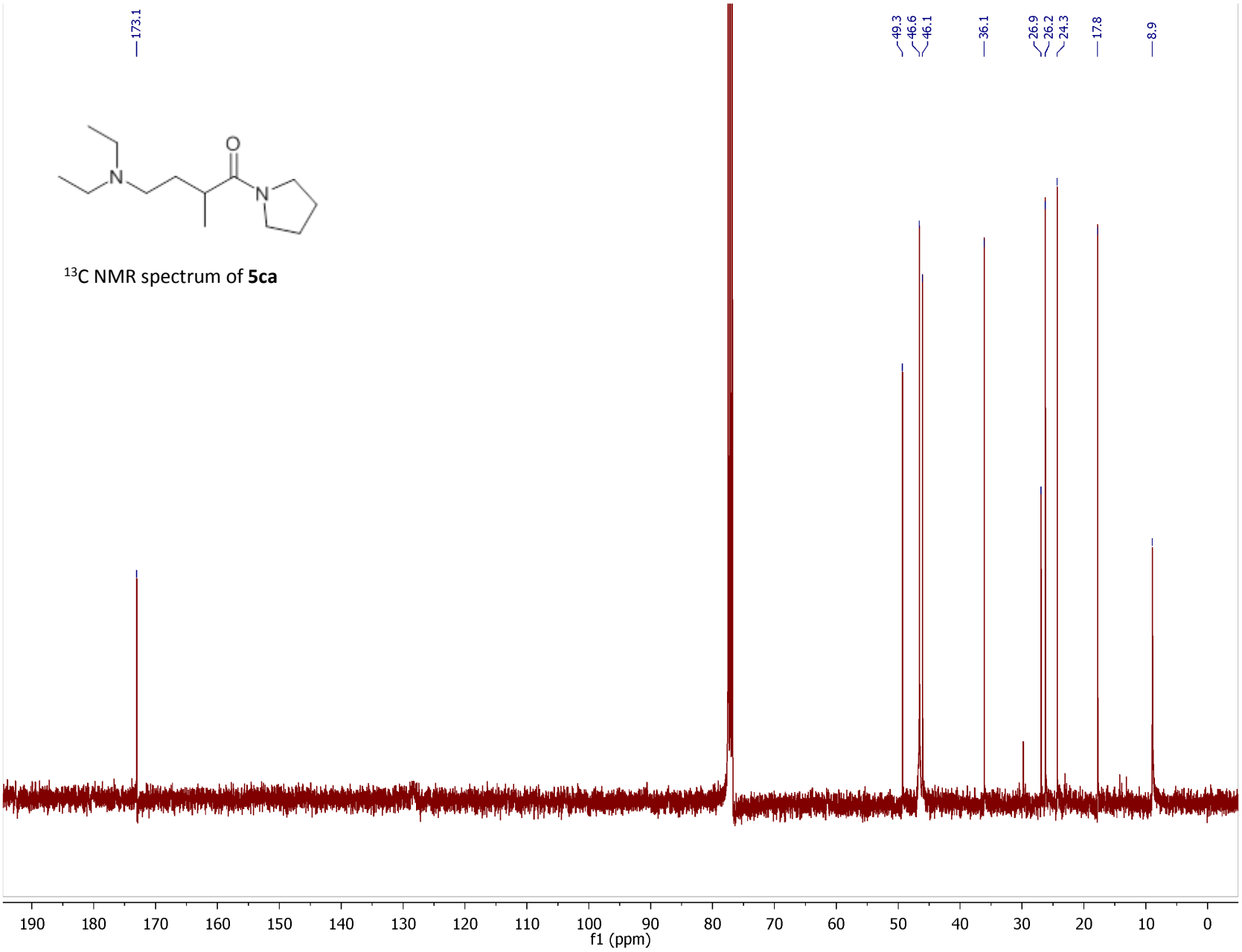
^{1}H NMR spectrum of **5ak**



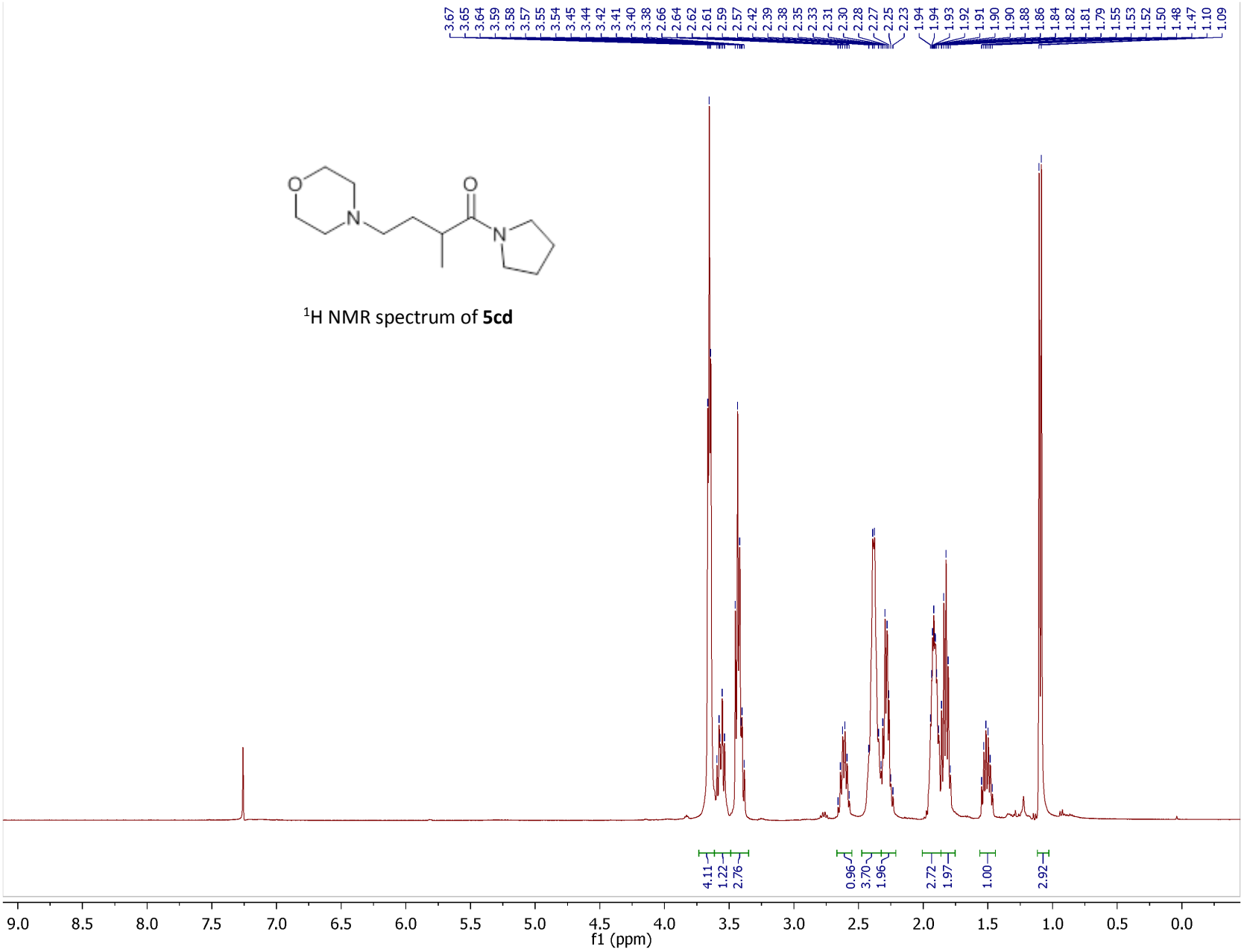
^{13}C NMR spectrum of **5ak**



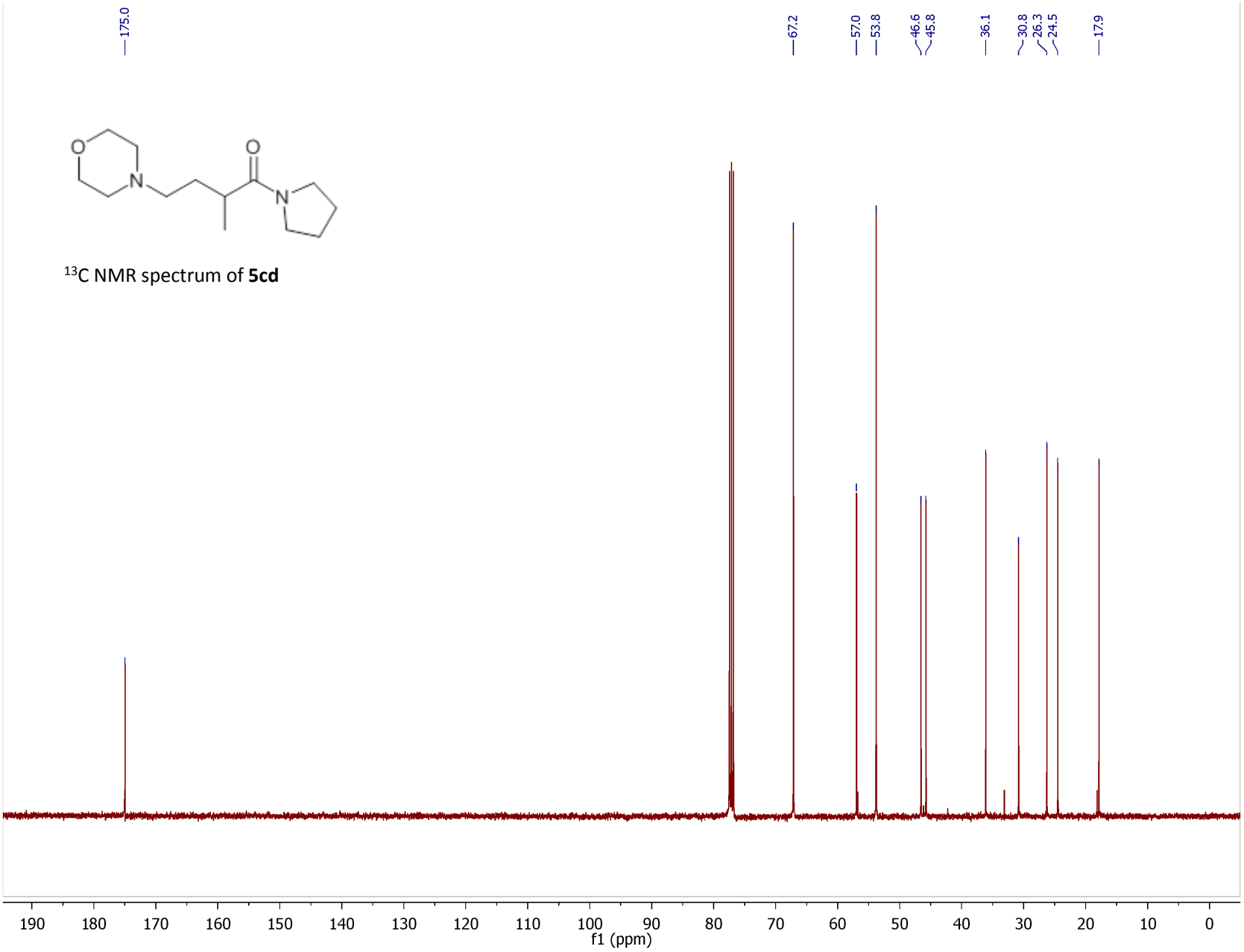
^{1}H NMR spectrum of **5ca**



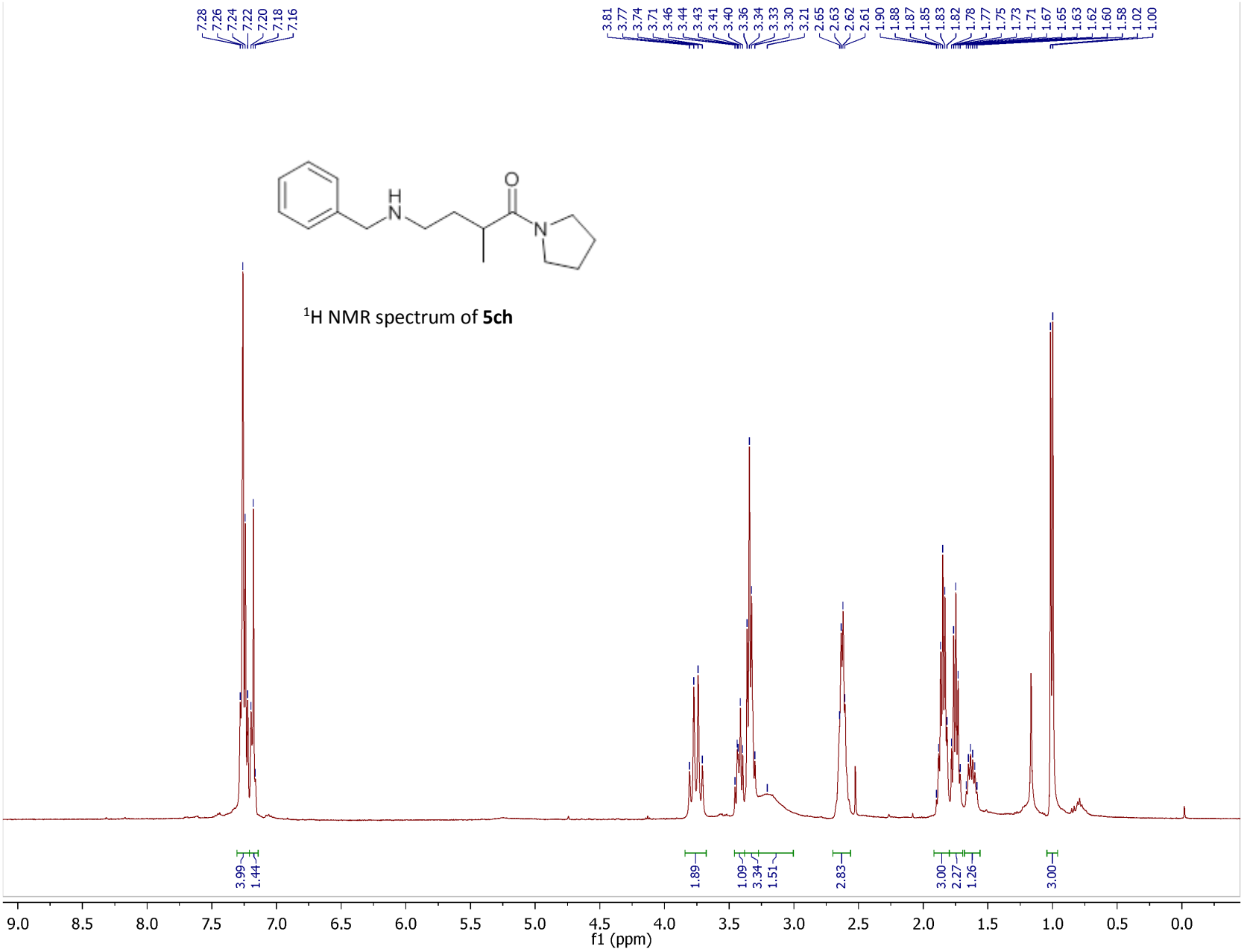
^{13}C NMR spectrum of **5ca**



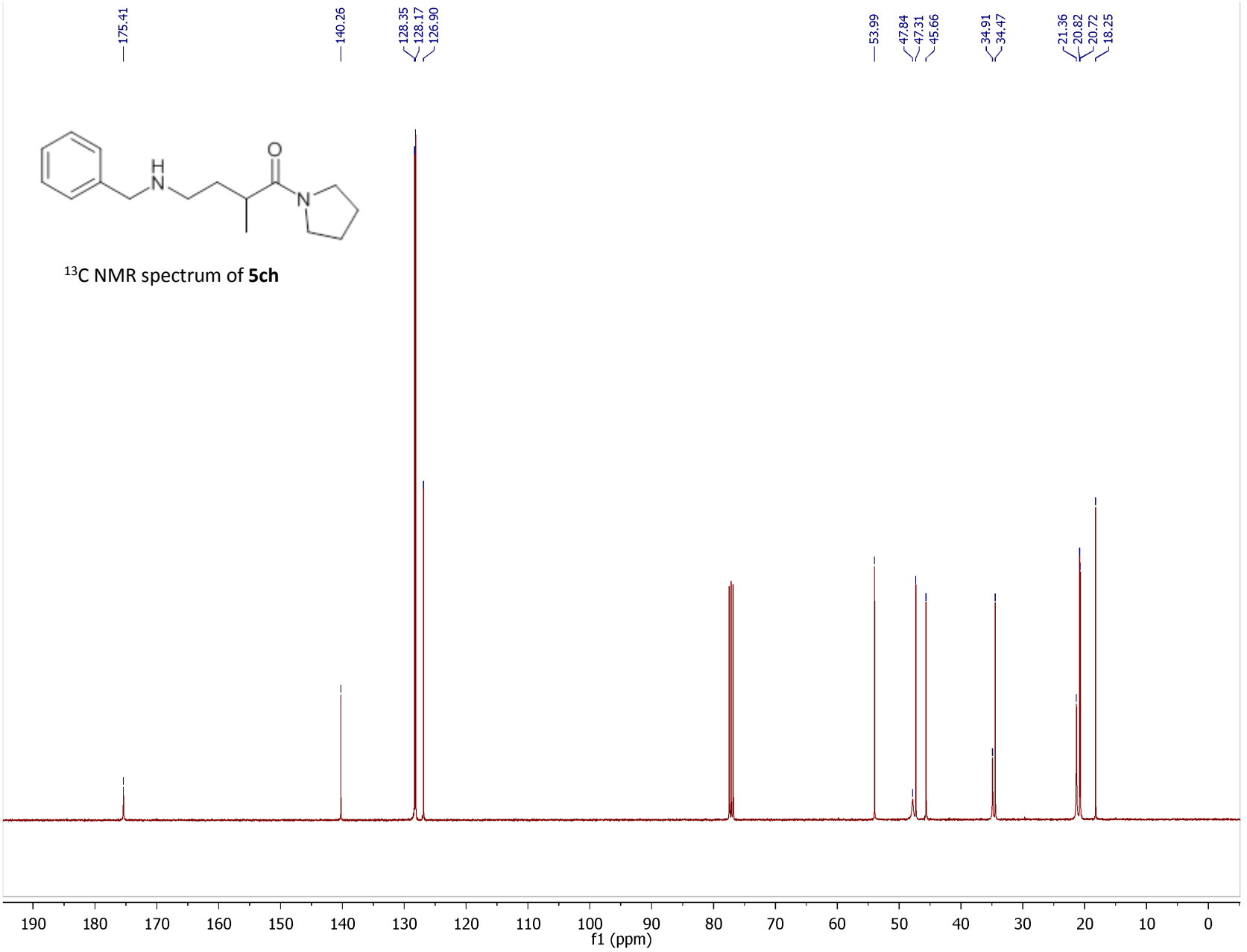
^{1}H NMR spectrum of **5cd**



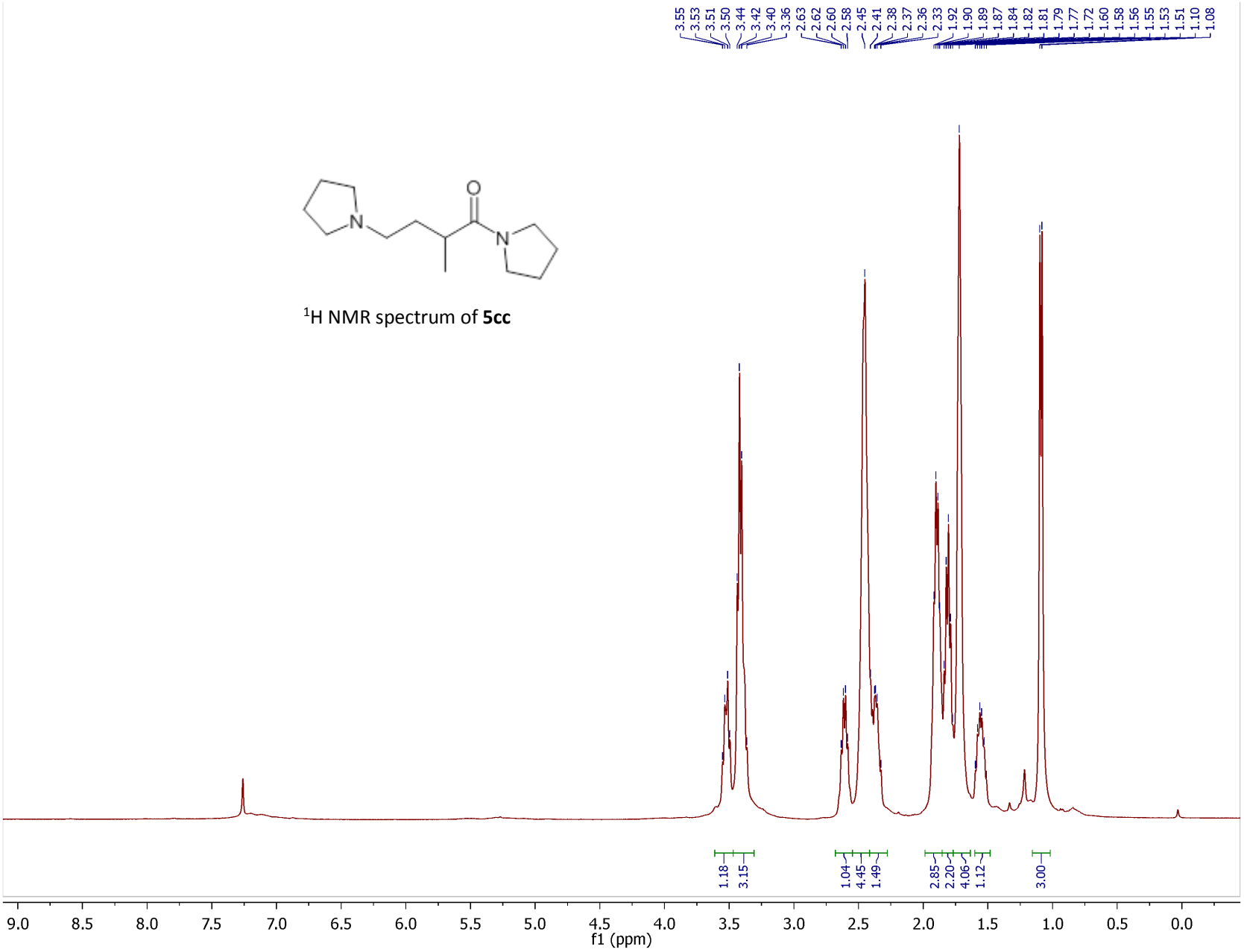
^{13}C NMR spectrum of **5cd**



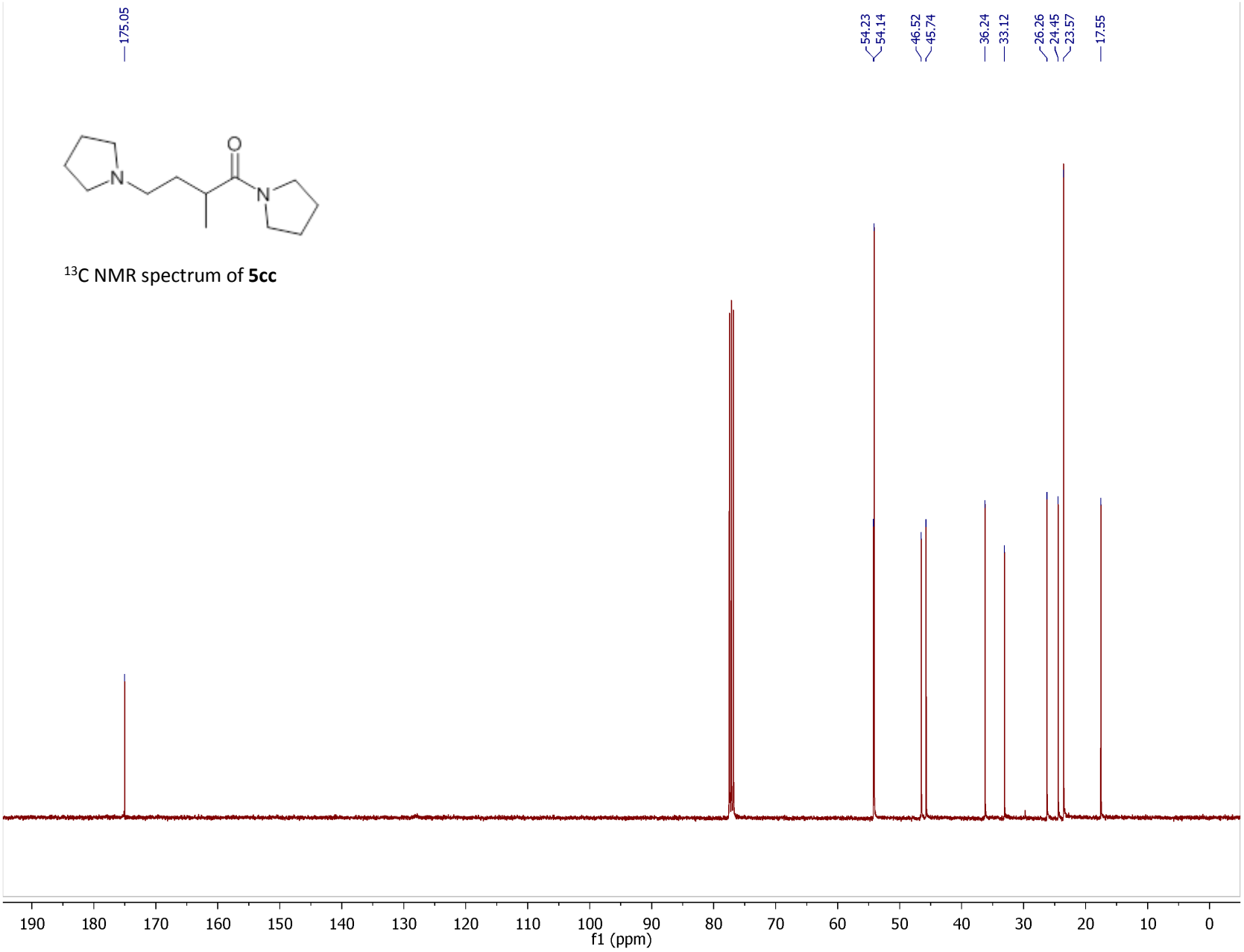
^{1}H NMR spectrum of **5ch**



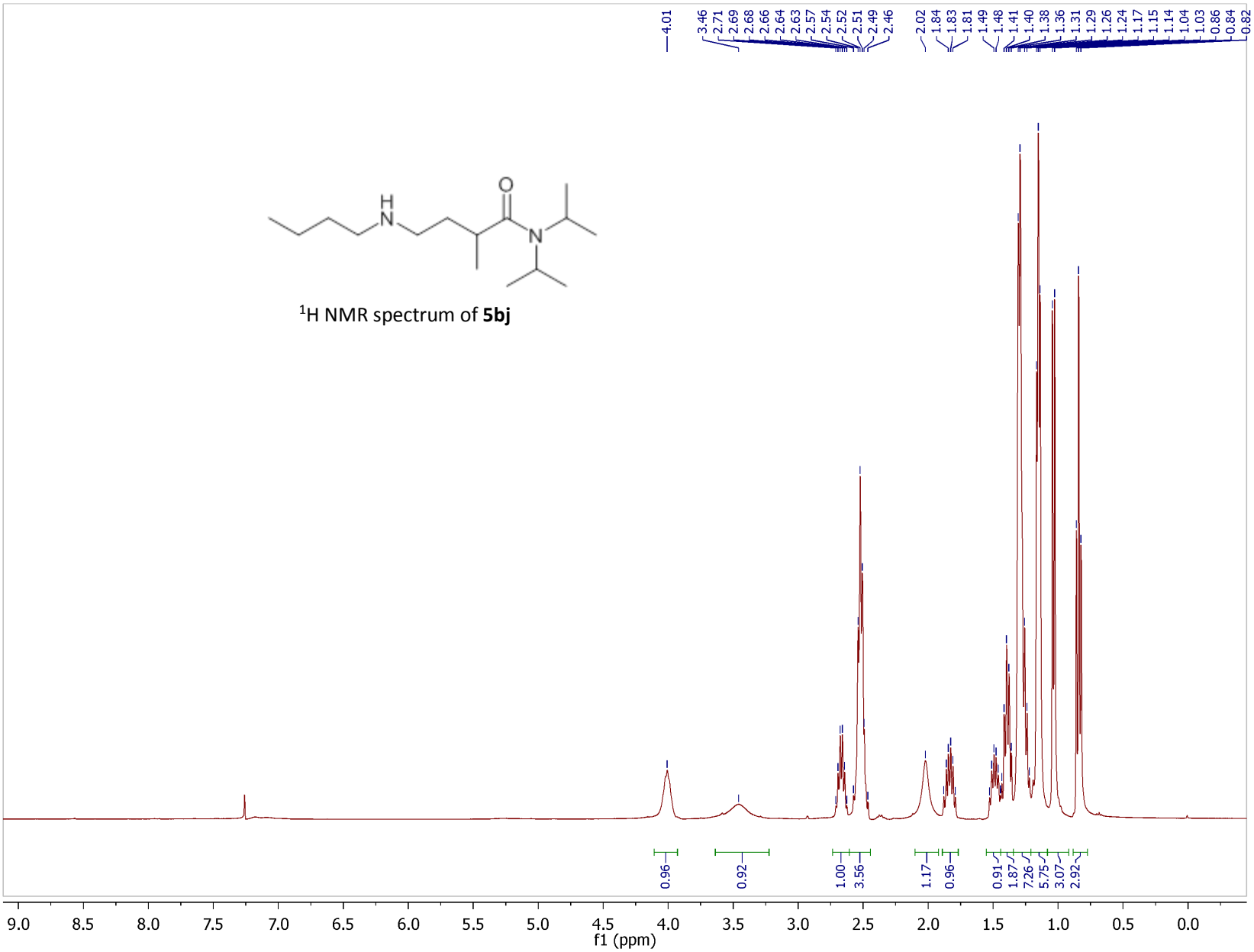
^{13}C NMR spectrum of **5ch**



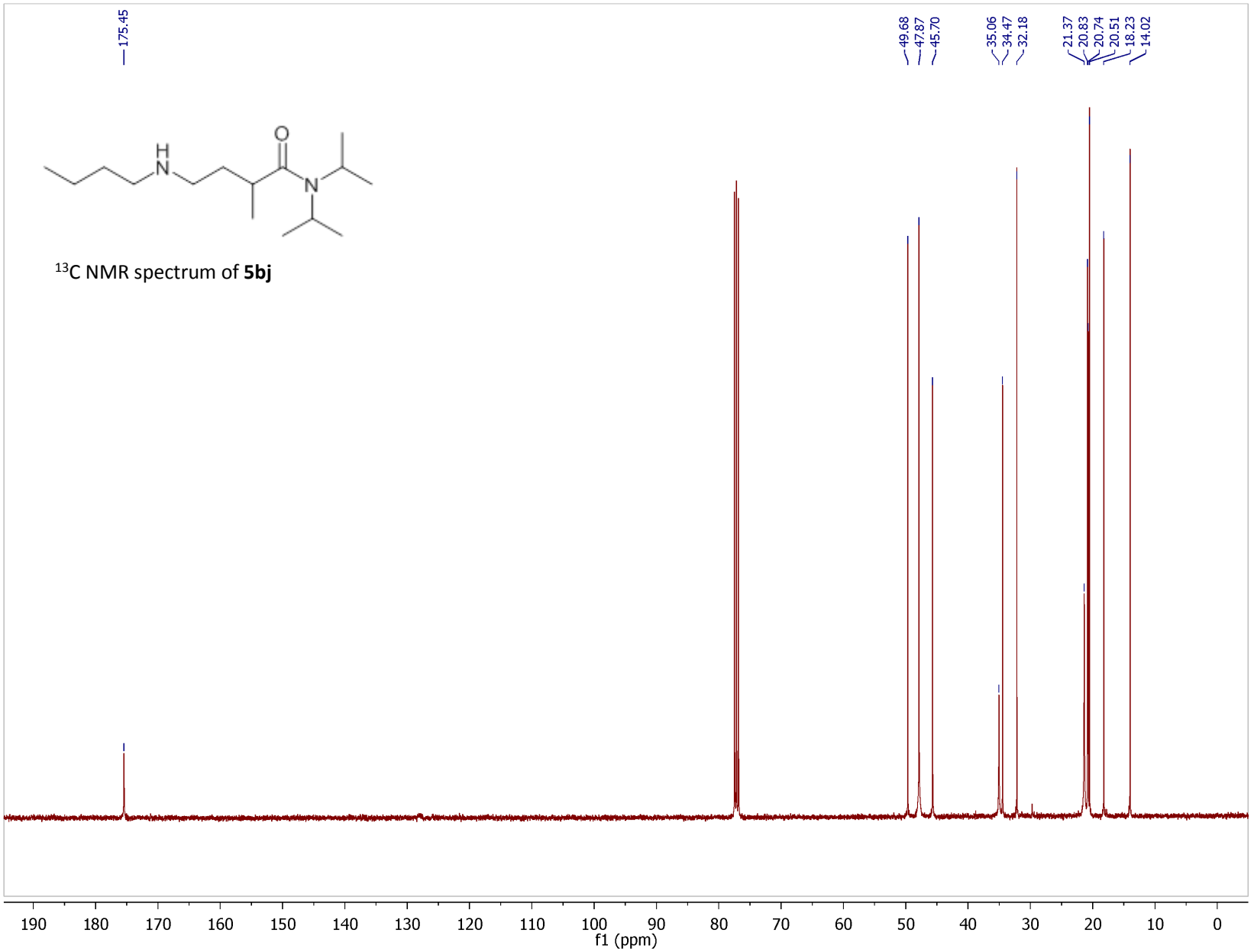
^{1}H NMR spectrum of **5cc**



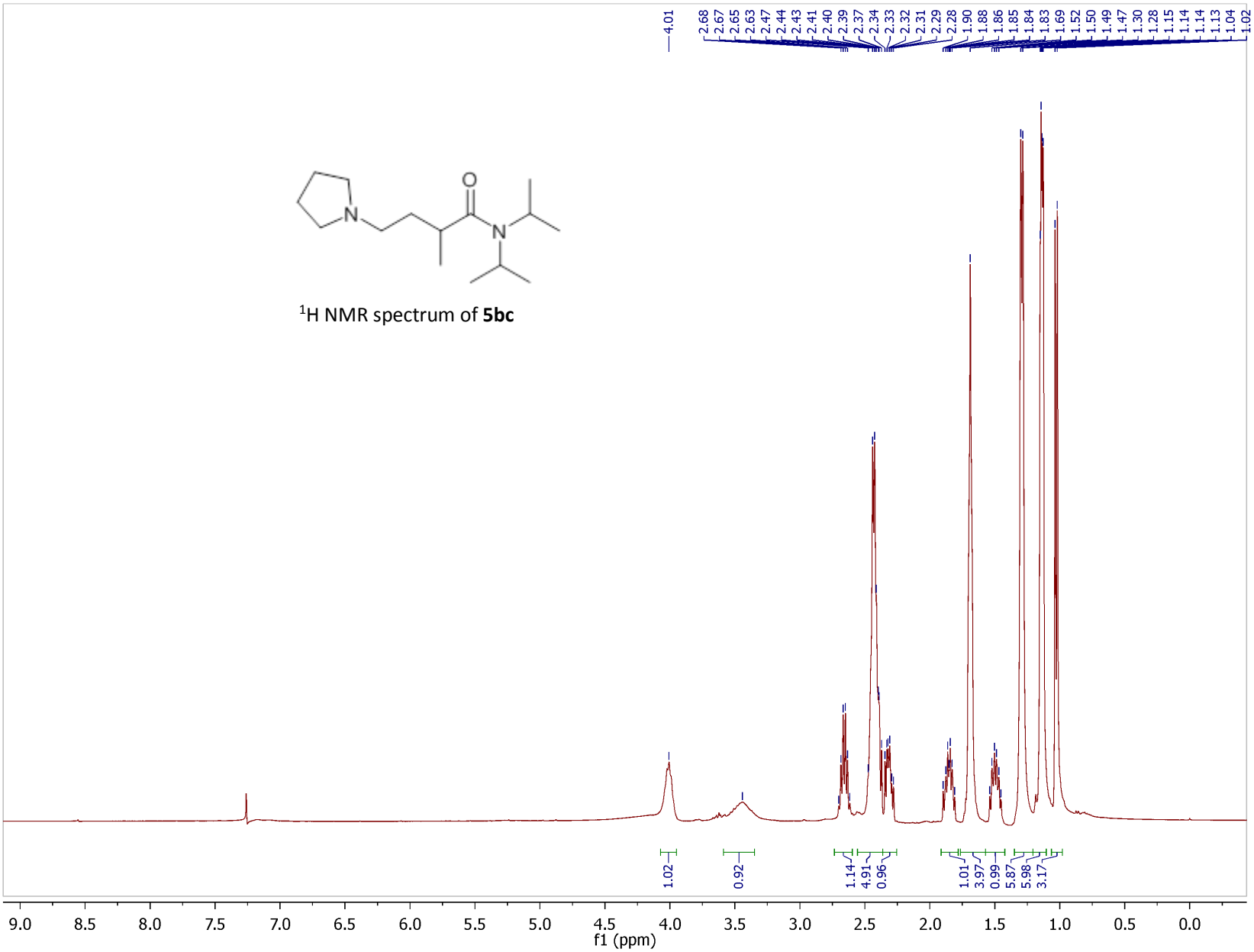
^{13}C NMR spectrum of **5cc**



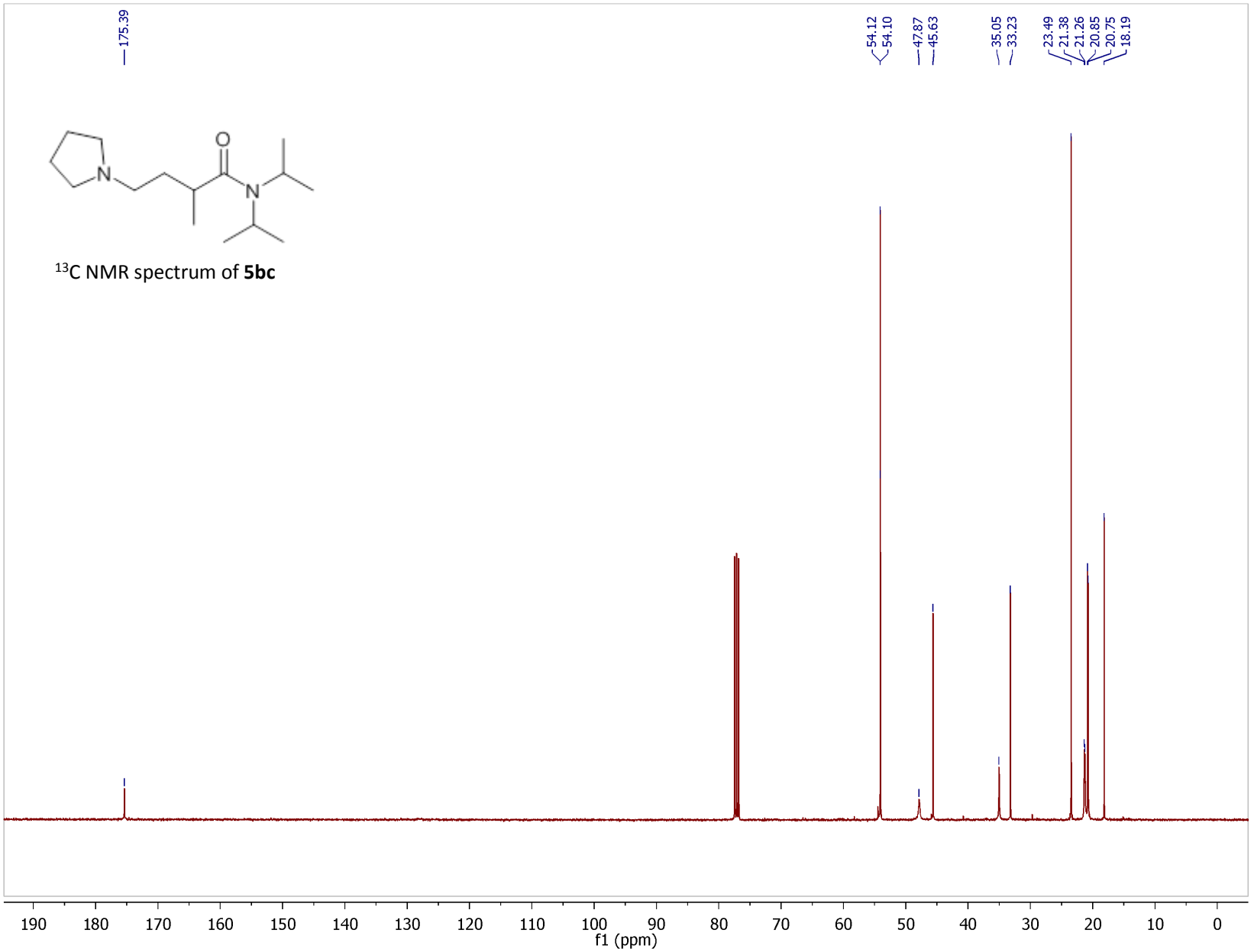
^{1}H NMR spectrum of **5bj**



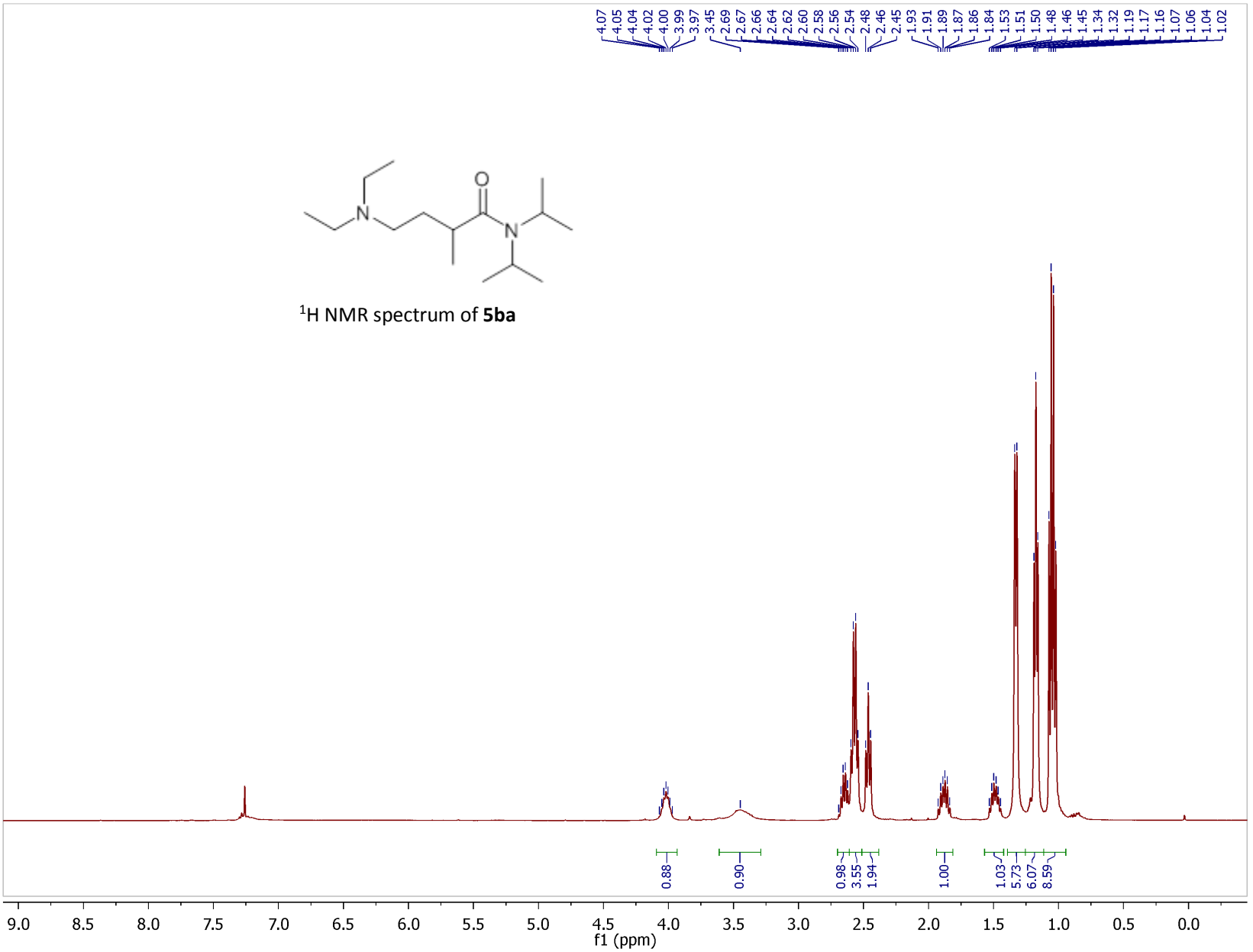
^{13}C NMR spectrum of **5bj**



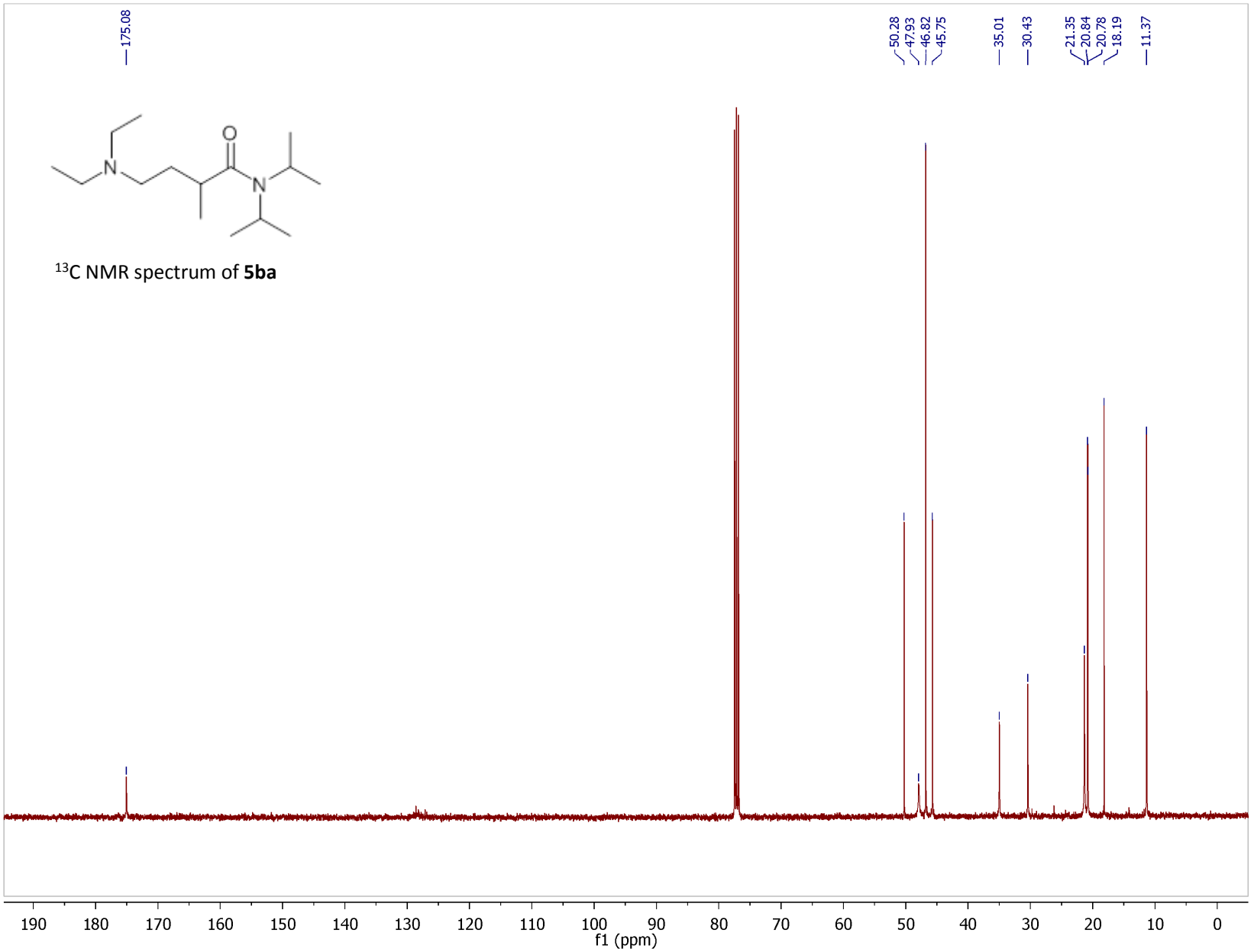
^{1}H NMR spectrum of **5bc**



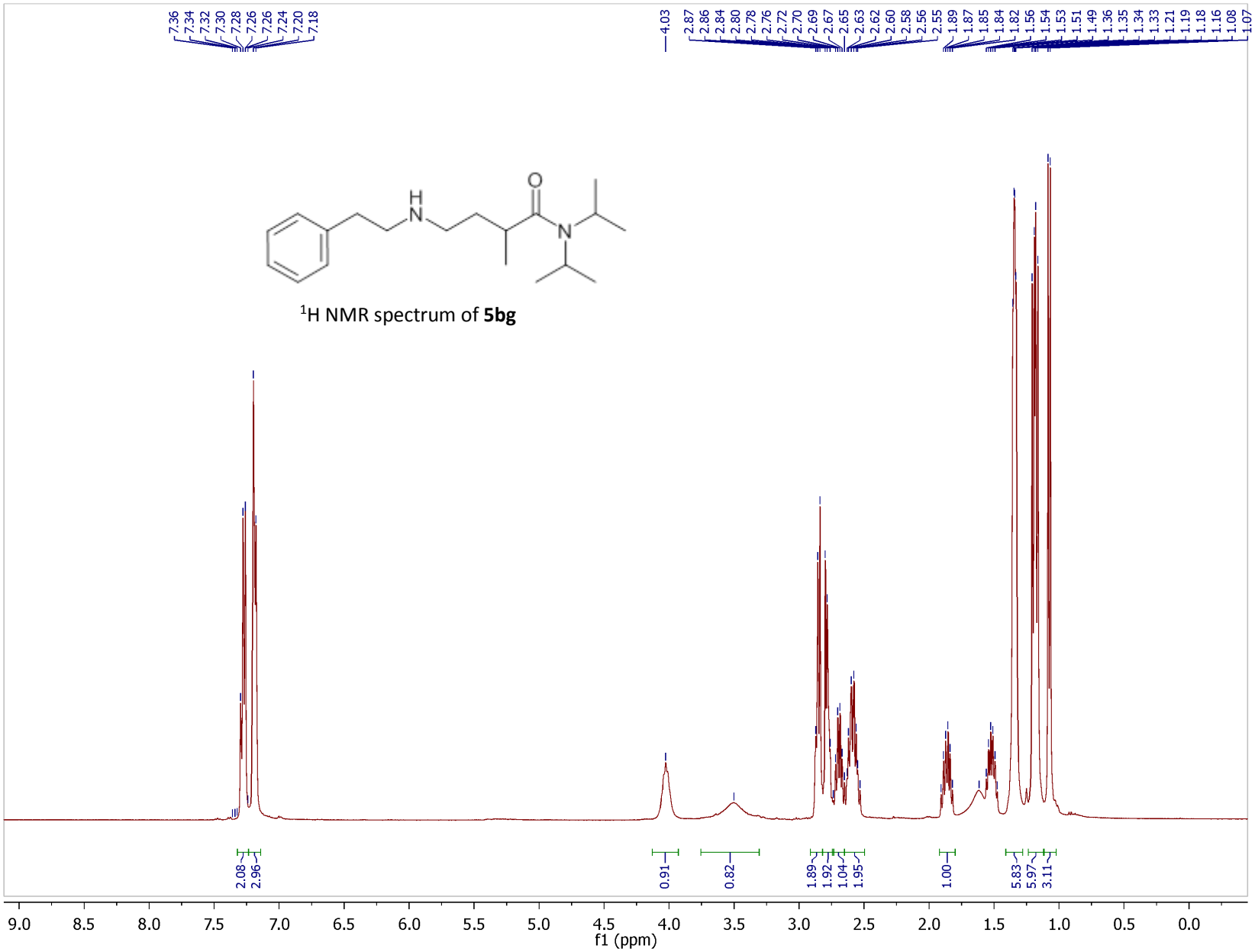
^{13}C NMR spectrum of **5bc**



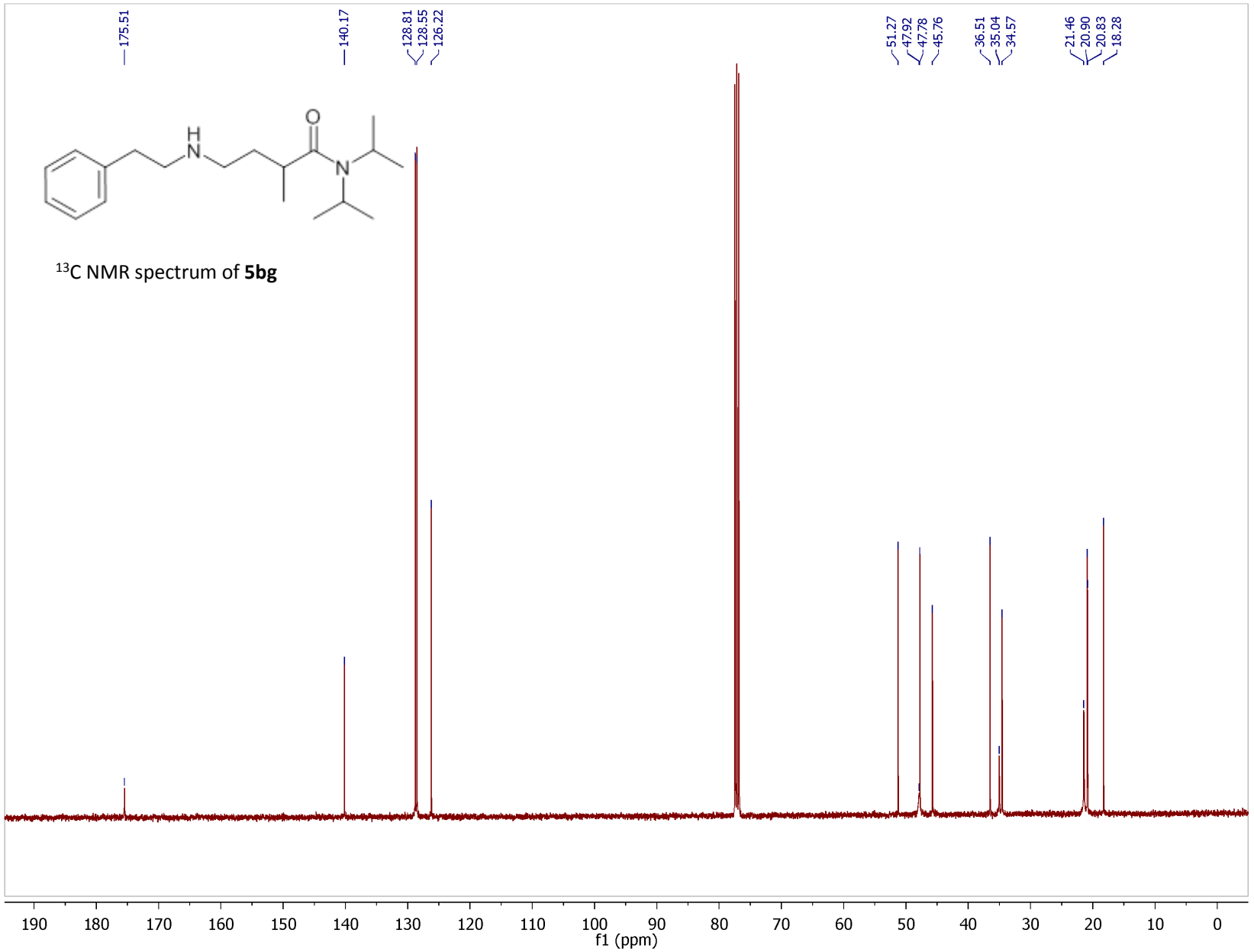
^{1}H NMR spectrum of **5ba**



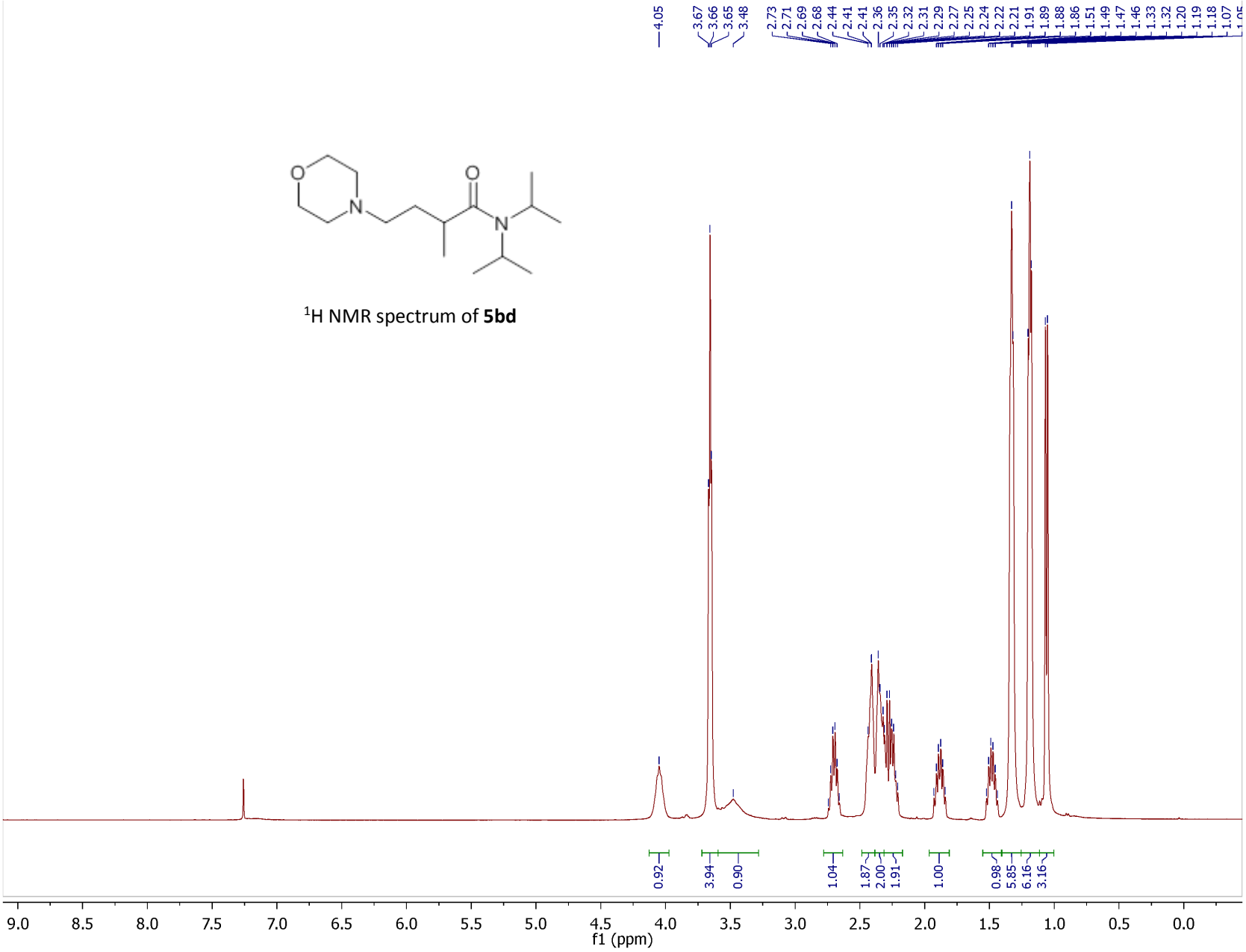
^{13}C NMR spectrum of **5ba**



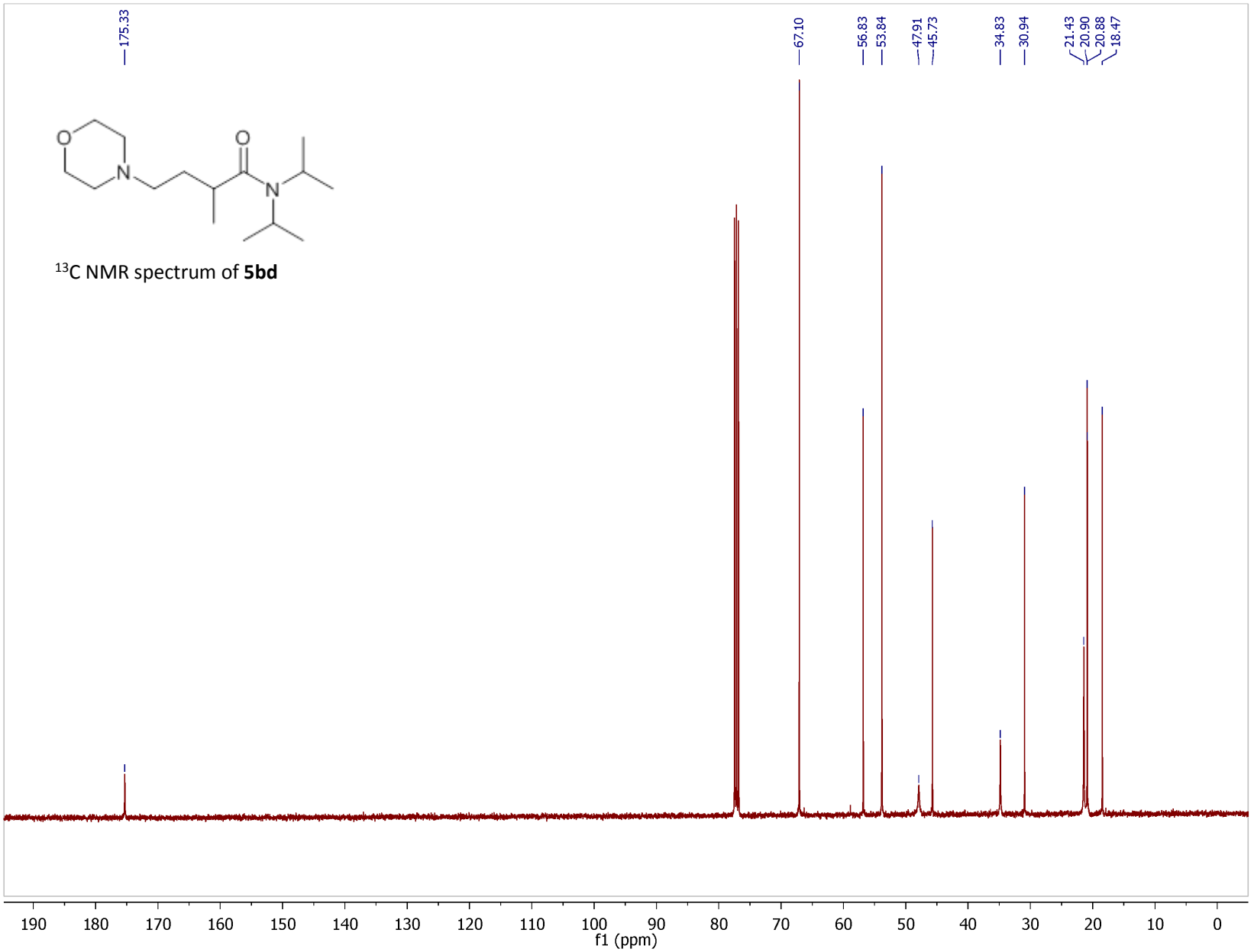
^{1}H NMR spectrum of **5bg**



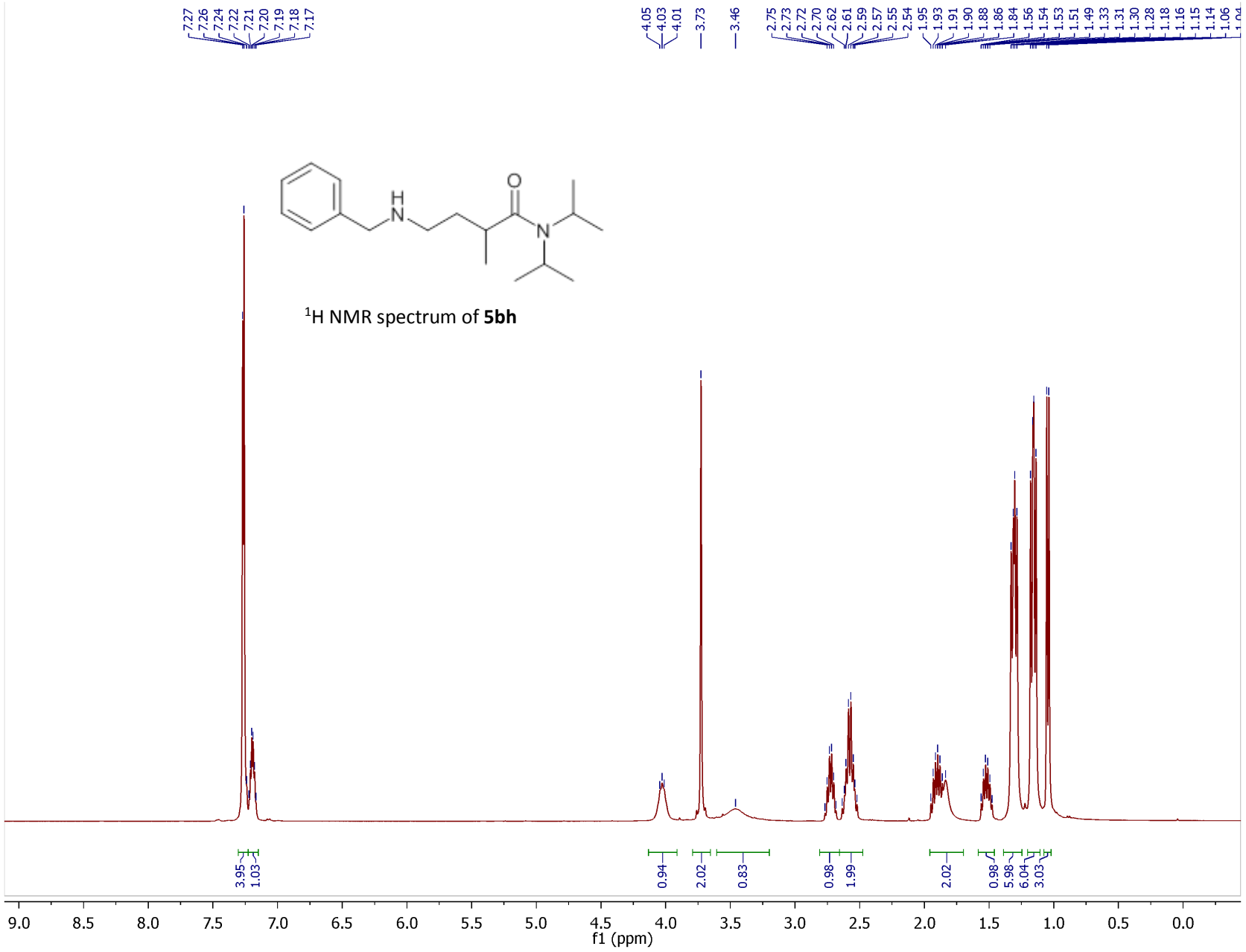
^{13}C NMR spectrum of **5bg**



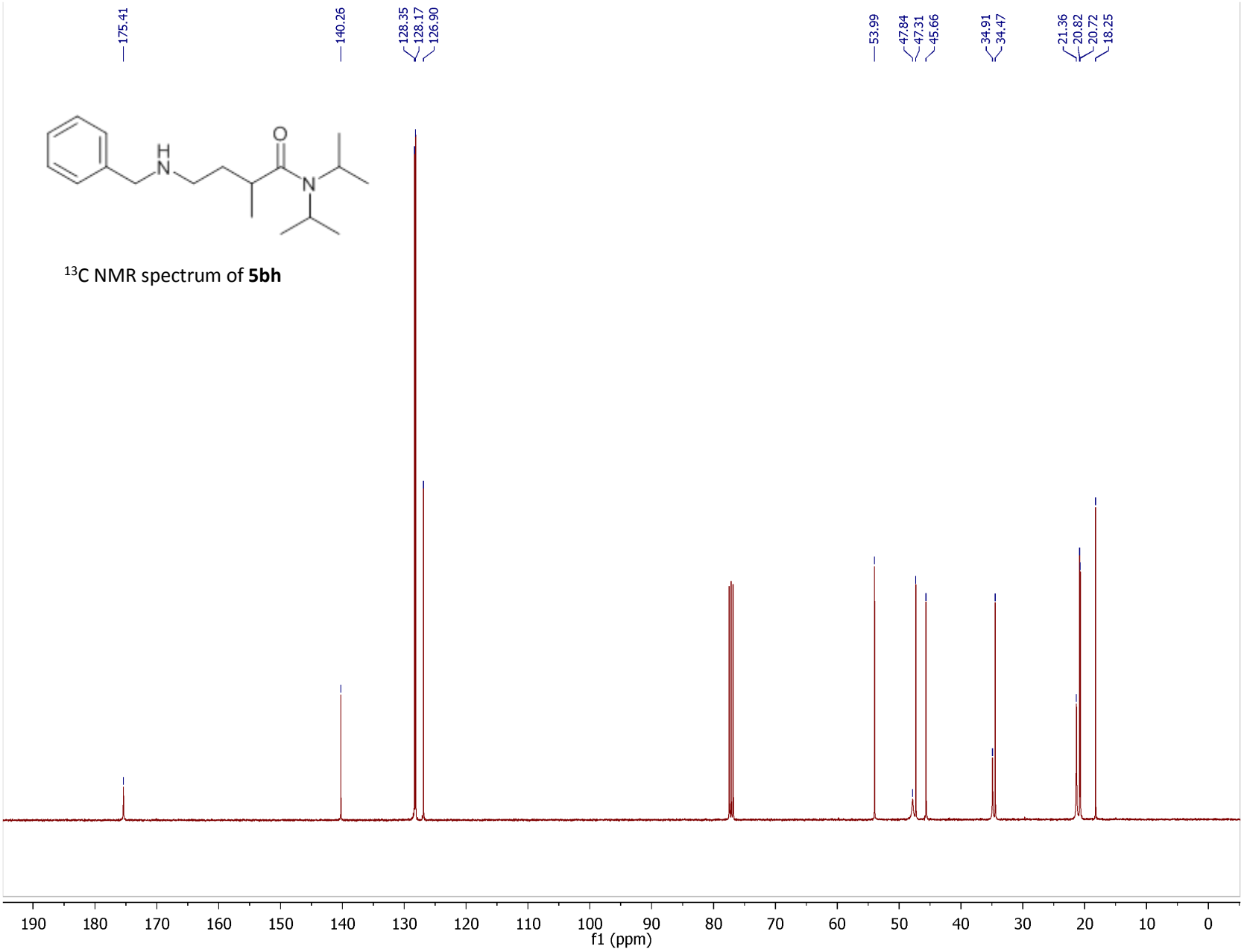
^{1}H NMR spectrum of **5bd**



^{13}C NMR spectrum of **5bd**



^{1}H NMR spectrum of **5bh**



^{13}C NMR spectrum of **5bh**