Supplementary Information

Synthesis of 3-(Aminomethyl)pyridine by Traceless C3-Selective Umpolung of 1-Amidopyridin-1-ium Salts

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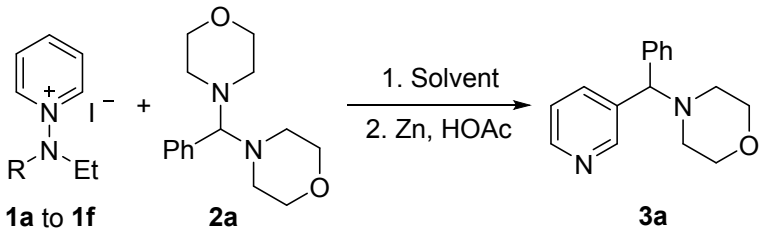
General information

Unless otherwise mentioned, all reactions were carried out under anhydrous conditions, and all commercially available reagents were used as received. 1-amidopyridin-1-ium salts[1] and aminals[2] were synthesized according to literature reports. Anhydrous solvents were obtained from a Pure Solvent purification system from Innovative Technology. Reactions were monitored by thin layer chromatography (TLC) carried out on S-2 0.25 mm E. Merck silica gel plates (60 F_{254}) and visualized by UV fluorescence (254 nm) and one of the following: phosphomolybdic acid, ninhydrin, *p*-anisaldehyde. Column chromatography was performed over Silicycle P_{60} silica gel (230–400 mesh). NMR spectra were recorded on Bruker AVANCE III 300, AVANCE III 400 and AVANCE III HD500 instruments using residual $CHCl_3$ as internal references (δ_H = 7.26 ppm and δ_C =77.16 ppm). The following abbreviations were used to designate multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), hept (heptet), m (multiplet), br (broad). High resolution mass spectra (HRMS) were recorded on a Bruker micrOTOF-QII mass spectrometer using electrospray ionization. Melting points were recorded on a WRS-1B melt point apparatus (Shanghai Shenguang Instrument Co., LTD) and were uncorrected.

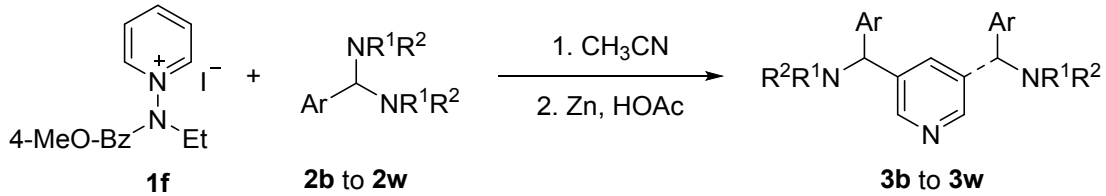
Synthesis and characterization data

General procedure for reaction conditions optimization

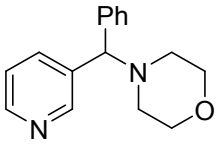


To a solution of 1-amidopyridin-1-ium iodide **1a** to **1f** (0.2 mmol) in designated solvent (1.0 mL) was added designated amount of aminal **2a**, and the mixture was stirred at designated temperature and monitored by TLC till **1a** to **1f** disappeared. The mixture was cooled to room temperature, and zinc powder (130.8 mg, 2.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using CH_2Cl_2/MeOH to give product **3a**.

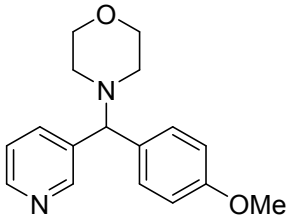
General procedure for synthesis of pyridine 3b to 3w



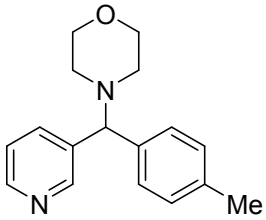
To a solution of 1-amidopyridin-1-ium iodide **1f** (76.8 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added aminal **2b** to **2w** (0.44 mmol), and the mixture was stirred in a 90 °C oil bath, and monitored by TLC till **1f** disappeared. The mixture was cooled to room temperature, and zinc powder (130.8 mg, 2.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using CH_2Cl_2/MeOH to give products **3b** to **3w**.



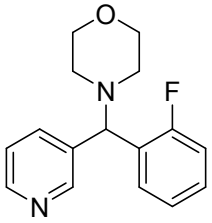
4-(phenyl(pyridine-3-yl)methyl)morpholine (**3a**): 45.6 mg (90% yield), white solid, m.p. 102 – 104 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.2 Hz, 1H), 8.41 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.72 (ddd, *J* = 7.9, 2.0 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.32 – 7.22 (m, 2H), 7.22 – 7.13 (m, 2H), 4.23 (s, 1H), 3.68 (t, *J* = 4.7 Hz, 4H), 2.36 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.8, 148.8, 141.3, 137.9, 135.5, 128.9, 128.0, 127.6, 123.7, 74.3, 67.2, 52.7. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2O$ 255.1492; Found 255.1500.



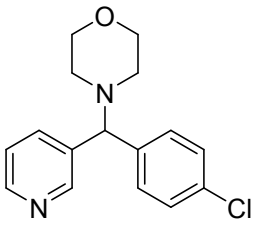
4-((4-methoxyphenyl)(pyridine-3-yl)methyl)morpholine (**3b**): 43.7 mg (77% yield), white solid, m.p. 109 – 110 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.42 (d, *J* = 3.9 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.20 (s, 1H), 3.74 (s, 3H), 3.69 (t, *J* = 4.6 Hz, 4H), 2.45 – 2.28 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 149.5, 148.5, 138.3, 135.4, 133.2, 129.1, 123.7, 114.2, 73.5, 67.1, 55.3, 52.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O_2$ 285.1598; Found 285.1604.



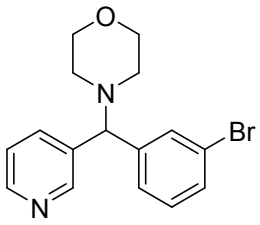
4-(pyridin-3-yl(*p*-tolyl)methyl)morpholine (**3c**): 46.8 mg (87% yield), white solid, m.p. 106 – 108 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.5 Hz, 1H), 8.42 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.74 (ddd, *J* = 7.8, 1.8 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 2H), 7.19 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.22 (s, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 2.36 (m, 4H), 2.28 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.6, 148.6, 138.2, 138.1, 137.3, 135.4, 129.6, 127.9, 123.7, 74.0, 67.1, 52.6, 21.1. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}N_2O$ 269.1648; Found 269.1653.



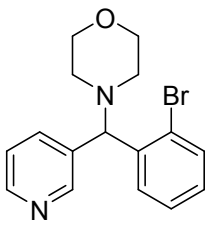
4-((2-fluorophenyl)(pyridin-3-yl)methyl)morpholine (**3d**): 49.6 mg (91% yield), white solid, m.p. 113 – 114 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.67 (d, *J* = 1.2 Hz, 1H), 8.44 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (ddd, *J* = 7.4, 1.9 Hz, 1H), 7.24 – 7.06 (m, 3H), 6.97 (ddd, *J* = 9.5, 8.0, 1.3 Hz, 1H), 4.71 (s, 1H), 3.70 (t, *J* = 4.7 Hz, 4H), 2.41 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.7 (d, ^1J(C-F) = 246.4 Hz), 149.9, 148.7, 136.8, 135.8, 128.9 (d, ^3J(C-F) = 8.4 Hz), 128.7 (d, ^3J(C-F) = 3.8 Hz), 128.0 (d, ^2J(C-F) = 12.5 Hz), 124.6 (d, ^3J(C-F) = 3.5 Hz), 123.7, 115.8 (d, ^2J(C-F) = 22.4 Hz), 67.1, 65.1 (d, ^4J(C-F) = 2.1 Hz), 52.4. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}FN_2O$ 273.1398; Found 273.1406.



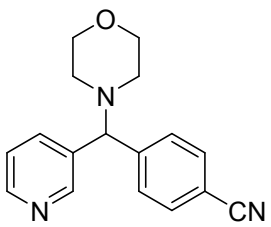
4-((4-chlorophenyl)(pyridin-3-yl)methyl)morpholine (**3e**): 46.1 mg (80% yield), white solid, m.p. 118 – 120 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1H), 8.44 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.69 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.20 (dd, *J* = 7.9, 4.9 Hz, 1H), 4.23 (s, 1 H), 3.69 (t, *J* = 4.6 Hz, 4H), 2.36 (m, *J* = 7.3 Hz, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.5, 148.9, 139.7, 137.3, 135.5, 133.3, 129.3, 129.1, 123.8, 73.5, 67.0, 52.5. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}ClN_2O$ 289.1102; Found 289.1109.



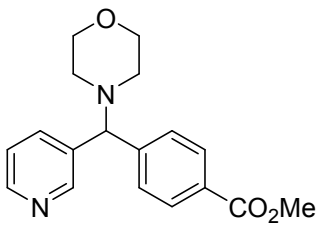
4-((3-bromophenyl)(pyridin-3-yl)methyl)morpholine (**3f**): 57.5 mg (86% yield), white solid, m.p. 127 – 128 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.7 Hz, 1H), 8.45 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.70 (ddd, *J* = 7.9, 1.7 Hz, 1H), 7.55 (dd, 1H), 7.34 (d, *J* = 1.4 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.15 (dd, *J* = 8.1, 7.5 Hz,1H), 4.21 (s, 1H), 3.70 (t, *J* = 4.6 Hz, 4H), 2.53 – 2.18 (m, *J* = 4.4 Hz, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.6, 149.0, 143.7, 137.1, 135.6, 130.8, 130.8, 130.6, 126.6, 123.8, 123.0, 73.7, 67.0, 52.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}BrN_2O$ 333.0597; Found 333.0604.



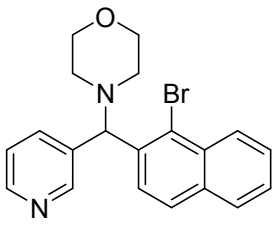
4-((2-bromophenyl)(pyridin-3-yl)methyl)morpholine (**3g**): 61.5 mg (92% yield), white solid, m.p. 132 – 133 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.7 Hz, 1H), 8.44 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.77 (ddd, *J* = 8.1, 1.7 Hz, 2H), 7.49 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.32 (ddd, *J* = 8.1, 7.2, 0.9 Hz,1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.06 (ddd, *J* = 7.8, 1.5 Hz, 1H), 4.83 (s, 1H), 3.69 (t, *J* = 4.7 Hz, 4H), 2.55 – 2.40 (m, 2H), 2.40 – 2.28 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.3, 148.8, 140.1, 136.2, 136.1, 133.4, 129.3, 128.9, 128.1, 124.6, 123.6, 71.2, 67.1, 52.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}BrN_2O$ 333.0597; Found 333.0600.



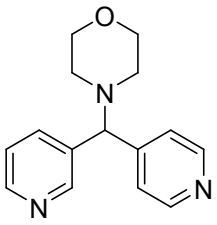
4-(morpholino(pyridin-3-yl)methyl)benzonitrile (**3h**): 47.1 mg (84% yield), white solid, m.p. 143 – 145 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.8 Hz, 1H), 8.44 (d, *J* = 4.5, 1.2 Hz, 1H), 7.67 (ddd, *J* = 7.8, 1.8 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.22 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.31 (s, 1H), 3.69 (m, 4H), 2.35 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.5, 149.2, 146.8, 136.4, 135.6, 132.8, 128.6, 123.9, 118.6, 111.5, 73.7, 66.9, 52.5. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}N_3O$ 280.1444; Found 280.1452.



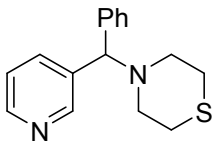
methyl 4-(morpholino(pyridin-3-yl)methyl)benzoate (**3i**): 49.5 mg (79% yield), white solid, m.p. 91 – 92 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.5 Hz, 1H), 8.44 (dd, *J* = 4.5, 1.2 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 2H), 7.71 (ddd, *J* = 8.1, 1.8, 1.5 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.31 (s, 1H), 3.86 (s, 3H), 3.70 (t, *J* = 4.6 Hz, 4H), 2.37 (m, *J* = 4.3 Hz, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.7, 149.6, 149.0, 146.4, 137.0, 135.6, 130.3, 129.5, 127.9, 123.8, 73.9, 67.0, 52.5, 52.2. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{21}N_2O_3$ 313.1547; Found 313.1554.



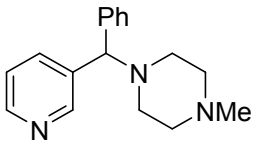
4-((1-bromonaphthalen-2-yl)(pyridin-3-yl)methyl)morpholine (**3j**): 71.2 mg (93% yield), white solid, m.p. 159 – 160 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.87 (d, *J* = 1.8 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.86 (ddd, *J* = 7.8, 1.8 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.61 – 7.44 (m, 2H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.22 (s, 1H), 3.80 – 3.60 (m, 4H), 2.60 – 2.36 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.2, 148.9, 138.2, 136.4, 135.9, 133.9, 132.6, 128.5, 128.1, 127.8, 127.7, 126.9, 125.8, 124.6, 123.6, 71.9, 67.1, 52.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{20}BrN_2O$ 383.0754; Found 383.0754.



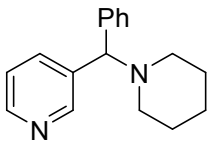
4-(pyridin-3-yl(pyridin-4-yl)methyl)morpholine (**3k**): 88.0 mg (69% yield), white solid, m.p. 90 – 92 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.59 (d, *J* = 1.5 Hz, 1H), 8.49 (d, *J* = 5.7 Hz, 2H), 8.47 – 8.38 (m, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 5.7 Hz, 2H), 7.20 (dd, *J* = 7.9, 4.8 Hz, 1H), 4.23 (s, 1H), 3.67 (t, *J* = 4.6 Hz, 4H), 2.34 (q, *J* = 4.6 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.4, 150.2, 149.6, 149.3, 135.9, 135.5, 123.8, 122.9, 73.1, 66.9, 52.3. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}N_3O$ 256.1444; Found 256.1441.



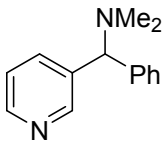
4-(phenyl(pyridin-3-yl)methyl)thiomorpholine (**3l**): 126.8 mg (94% yield), white solid, m.p. 86 – 88 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.40 –7.15 (m, 6H), 4.44 (s, 1H), 2.67 (s, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.6, 148.5, 140.8, 137.6, 135.4, 128.7, 128.0, 127.4, 123.5, 73.4, 53.5, 28.1. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2S$ 271.1264; Found 271.1267.



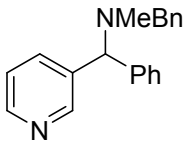
1-methyl-4-(phenyl(pyridin-3-yl)methyl)piperazine (**3m**): 119.2 mg (89% yield), white solid, m.p. 105 – 107 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.2 Hz, 1H), 8.42 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.71 (ddd, *J* = 7.9, 2.0 Hz, 1H), 7.46 – 7.32 (m, 2H), 7.33 – 7.23 (m, 2H), 7.22 – 7.09 (m, 2H), 4.27 (br s, 1H), 2.46 (s, 8H), 2.29 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.6, 148.5, 141.6, 138.2, 135.4, 128.8, 127.9, 127.4, 123.6, 73.7, 55.3, 51.7, 45.8. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}N_3$ 268.1808; Found 268.1812.



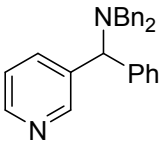
3-(phenyl(piperidin-1-yl)methyl)pyridine (**3n**): 75.1 mg (60% yield), white solid, m.p. 87 – 88 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.2 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.37 (m, 2H), 7.30 (m, 2H), 7.20 (m, 2H), 4.29 (s, 1H), 2.30 (m, 4H), 1.57 (m, 4H), 1.44 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.7, 148.3, 142.0, 138.7, 135.5, 128.6, 128.0, 127.2, 123.5, 74.2, 53.1, 26.2, 24.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{21}N_2$ 253.1699; Found 253.1701.



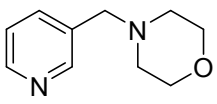
N,*N*-dimethyl-1-phenyl-1-(pyridin-3-yl)methanamine (**3o**): 58.6 mg (55% yield), white solid, m.p. 82–84 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.44 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.76 (ddd, *J* = 7.8, 2.0 Hz, 1H), 7.40 (m, 2H), 7.30 (m, 2H), 7.20 (m, 2H), 4.13 (s, 1H), 2.20 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.6, 148.5, 142.4, 138.9, 135.2, 128.8, 127.8, 127.4, 123.6, 75.4, 44.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{17}N_2$ 213.1386; Found 213.1389.



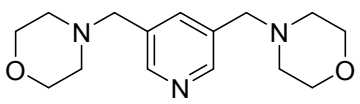
N-benzyl-*N*-methyl-1-phenyl-1-(pyridin-3-yl)methanamine (**3p**): 114.2 mg (79% yield), white solid, m.p. 119 – 121 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.73 (d, *J* = 2.2 Hz, 1H), 8.45 (dd, *J* = 4.8, 1.7 Hz, 1H), 7.84 (ddd, *J* = 7.9, 2.0 Hz, 1H), 7.58 – 7.18 (m, 11H), 4.56 (s, 1H), 3.57 (d, *J* = 13.5 Hz, 1H), 3.47 (d, *J* = 13.5 Hz, 1H), 2.10 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.8, 148.5, 141.7, 139.4, 138.4, 135.6, 128.8, 128.6, 128.4, 128.1, 127.5, 127.0, 123.6, 72.7, 59.7, 40.2. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{21}N_2$ 289.1699; Found 289.1703.



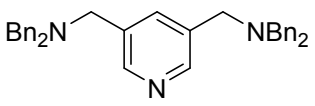
N,*N*-dibenzyl-1-phenyl-1-(pyridin-3-yl)methanamine (**3q**): 40.9 mg (22% yield), white solid, m.p. 166 – 168 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.54 (d, *J* = 2.7 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.14 (m, 16H), 5.04 (s, 1H), 3.59 (d, *J* = 14.1 Hz, 2H), 3.58 (d, *J* = 14.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.8, 148.6, 139.2, 138.9, 136.7, 136.0, 129.3, 128.7, 128.6, 128.5, 127.6, 127.2, 123.2, 65.1, 53.9. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2$ 365.2012; Found 365.2014.



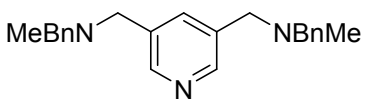
4-(pyridin-3-ylmethyl)morpholine (**3r**): 22.0 mg (25% yield), pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.5 Hz, 1H), 8.48 (dd, *J* = 4.7, 1.3 Hz, 1H), 7.66 (ddd, *J* = 7.8 Hz, 1H), 7.23 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.68 (m, 4H), 3.48 (s, 2H), 2.42 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.6, 148.8, 136.9, 133.3, 123.5, 67.0, 60.7, 53.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{15}N_2O$ 179.1179; Found 179.1182.



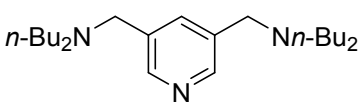
3,5-bis(morpholinomethyl)pyridine (**3r'**): 90.6 mg (65% yield), pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.1 Hz, 2H), 7.61 (dd, *J* = 2.2 Hz, 1H), 3.66 (m, 8H), 3.47 (s, 4H), 2.40 (m, 8H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.3, 137.4, 132.8, 66.8, 60.4, 53.4. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{24}N_3O_2$ 278.1863; Found 278.1866.



1,1'-(pyridine-3,5-diyl)bis(*N*,*N*-dibenzylmethanamine) (**3s**): 212.5 mg (85% yield), pale yellow solid, m.p. 146 – 148°C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (br s, 2H), 7.86 (s, 1H), 7.49 – 7.22 (m, 20H), 3.59 (s, 8H), 3.58 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.0, 139.4, 136.7, 134.9, 128.8, 128.4, 127.2, 58.2, 55.2. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{35}H_{36}N_3$ 498.2904; Found 498.2909.

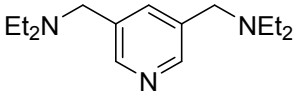


1,1'-(pyridine-3,5-diyl)bis(*N*-benzyl-*N*-methylmethanamine) (**3t**): 143.3 mg (83% yield), pale yellow solid, m.p. 121 – 124 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.1 Hz, 2H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.51 – 7.02 (m, 10H), 3.55 (s, 4H), 3.54 (s, 4H), 2.21 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.1, 138.9, 137.0, 134.3, 128.9, 128.3, 127.1, 61.9, 58.9, 42.2. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{28}N_3$ 346.2278; Found 346.2284.

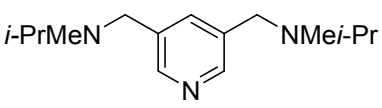


N,*N*′-(pyridine-3,5-diylbis(methylene))bis(*N*-butylbutan-1-amine) (**3u**): 57.0 mg (32% yield), pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 2.1 Hz, 2H), 7.60 (s, 1H), 3.51 (s, 4H), 2.48 – 2.23 (t, *J* = 7.2 Hz, 8H), 1.50 – 1.34 (m, 8H), 1.34 – 1.17 (m, 8H), 0.84 (t, *J* = 7.3 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.8, 137.1,

135.2, 55.9, 53.6, 29.4, 20.6, 14.2. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{44}N_3$ 362.3530; Found 362.3535.

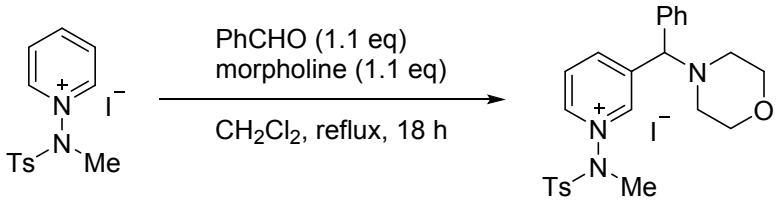


N,*N*′-(pyridine-3,5-diylbis(methylene))bis(*N*-ethylethanamine) (**3v**): 82.3 mg (66% yield), pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.37 (s, 2H), 7.64 (s, 1H), 3.54 (s, 4H), 2.48 (q, *J* = 7.1 Hz, 8H), 0.99 (t, *J* = 7.1 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.1, 137.5, 134.4, 54.7, 46.8, 11.6. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{28}N_3$ 250.2278; Found 250.2284.



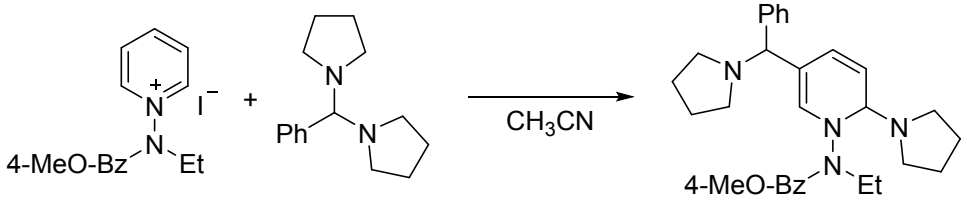
N,*N*′-(pyridine-3,5-diylbis(methylene))bis(*N*-methylpropan-2-amine) (**3w**): 75.5 mg (61% yield), pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.39 (s, 2H), 7.66 (s, 1H), 3.50 (s, 4H), 2.88 (hept, *J* = 6.6 Hz, 2H), 2.12 (s, 6H), 1.05 (d, *J* = 6.6 Hz, 12H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.1, 137.2, 134.8, 54.8, 53.4, 36.8, 17.9. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{28}N_3$ 250.2278; Found 250.2277.

Procedure for synthesis of 1-((*N*,4-dimethylphenyl)sulfonamido)-3-(morpholino(phenyl) methyl) pyridin-1-ium iodide



To a solution of 1-(*N*-methyltoluenesulfonamido)pyridin-1-ium iodide (39.4 mg, 0.1 mmol) in CH_2Cl_2 (2.0 mL) was added benzaldehyde (12.1 mg, 0.11 mmol) and morpholine (10.2 mg, 0.11 mmol). The mixture was stirred in a 50 °C oil bath for 18 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by gravity chromatography to give the titled product as yellow solid. 24.9 mg (44% yield), m.p. 142 – 143 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.85 (d, *J* = 6.5 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.19 (dd, *J* = 8.0, 6.5 Hz, 1H), 7.46 – 7.27 (m, 9H), 4.92 (s, 1H), 3.80 (s, 3H), 3.74 – 3.65 (m, 4H), 2.49 (s, 3H), 2.46 (s, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.3, 147.2, 145.9, 144.6, 143.8, 136.3, 131.3, 129.5, 129.5, 129.0, 128.9, 128.9, 126.9, 71.2, 66.9, 51.7, 40.2, 22.2. **HRMS** (ESI-TOF) *m/z*: $[M - I^-]^+$ Calcd for $C_{24}H_{28}N_3O_3S$ 438.1846; Found 438.1851.

Procedure for synthesis of *N*-ethyl-4-methoxy-*N*-(5-(phenyl(pyrrolidin-1-yl)methyl)-2-(pyrrolidin-1-yl) pyridin-1(2*H*)-yl)benzamide (4).

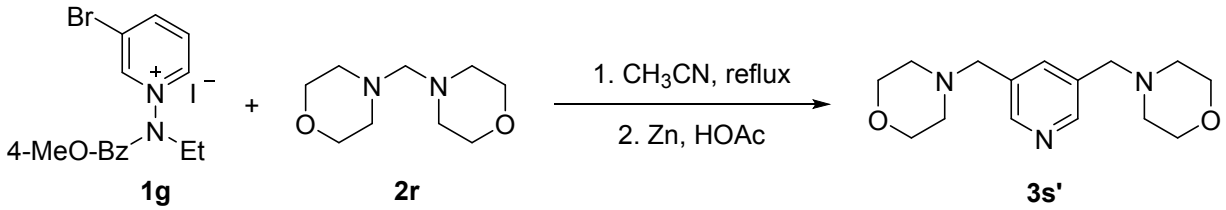


1f **2x** **4**

To a solution of **1f** (77.0 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added aminal **2x** (101.5 mg, 0.44 mmol). The mixture was stirred at room temperature for 1 h then a yellow precipitate was formed. The mixture was filtrated, washed with cold CH_3CN and dried in vacuo to give **4** as yellow powder (72.3 mg 74% yield). **^{1}H**

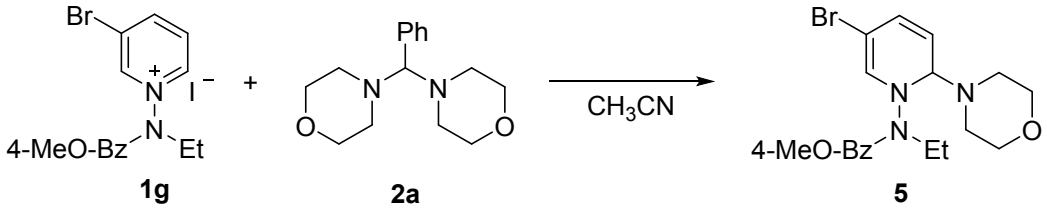
NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.37 (s, 1H), 7.21 – 7.02 (m, 5H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 11.5 Hz, 1H), 6.34 – 6.19 (m, 2H), 4.37 (s, 1H), 4.10 (dq, 1H), 4.01 (dq, 1H), 3.83 (s, 3H), 3.27 (m, 4H), 2.40 (m, 2H), 2.33 (m, 2H), 1.99 – 1.89 (m, 4H), 1.73 (d, *J* = 6.5 Hz, 4H), 1.18 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.7, 160.7, 146.1, 144.4, 143.6, 138.9, 131.8, 129.0, 127.8, 126.2, 126.1, 112.7, 112.6, 98.0, 68.1, 55.5, 53.5, 49.3, 36.4, 25.5, 23.9, 11.9. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{39}N_4O_2$ 487.3068; Found 487.3063.

Procedure for synthesis of 3,5-bis(morpholinomethyl)pyridine 3s' from 1g



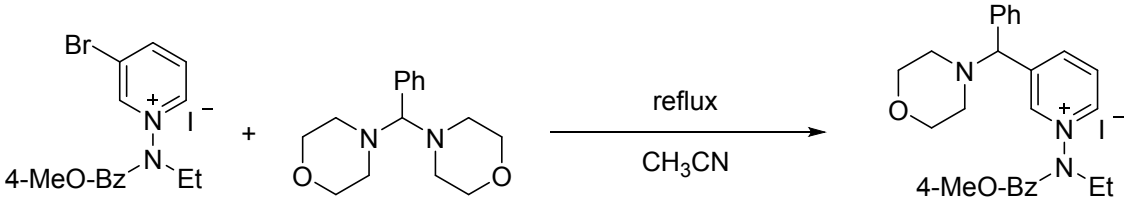
To a solution of **1g** (92.7 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added aminal **2r** (82.2 mg, 0.44 mmol), and the mixture was stirred in a 90 °C oil bath for 4 h. The mixture was cooled to room temperature, and zinc powder (65.4 mg, 1.0 mmol) and glacial acetic acid (1.0 mL) were added and stirred for 5 min. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using CH_2Cl_2/MeOH to give products **3s'** as pale yellow oil (36.6 mg, 66% yield).

Procedure for synthesis of *N*-(5-bromo-2-morpholinopyridin-1(2*H*)-yl)-*N*-ethyl-4-methoxybenzamide (5)



To a solution of **1g** (92.6 mg, 0.2 mmol) in CH_3CN (1.0 mL) was added **2a** (115.5 mg, 0.44 mmol). The mixture was stirred at room temperature for 1 h, then the solvent was removed in vacuo and the residue was purified by flash chromatography to give **5** as yellow powder (71.4 mg, 85% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.44 (s, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 10.6 Hz, 1H), 6.50 (d, *J* = 13.2 Hz, 1H), 5.59 (dd, *J* = 13.1, 10.7 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 3.78 – 3.65 (m, 4H), 3.23 – 3.12 (m, 4H), 1.22 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.9, 161.2, 147.4, 139.0, 138.5, 133.2, 126.9, 112.4, 111.2, 98.4, 66.2, 55.3, 48.5, 36.9, 11.3. **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{25}BrN_3O_3$ 422.1074; Found 422.1071.

Procedure for synthesis of 1-(*N*-ethyl-4-methoxybenzamido)-3-(morpholino(phenyl)methyl) pyridin-1-ium iodide (7').



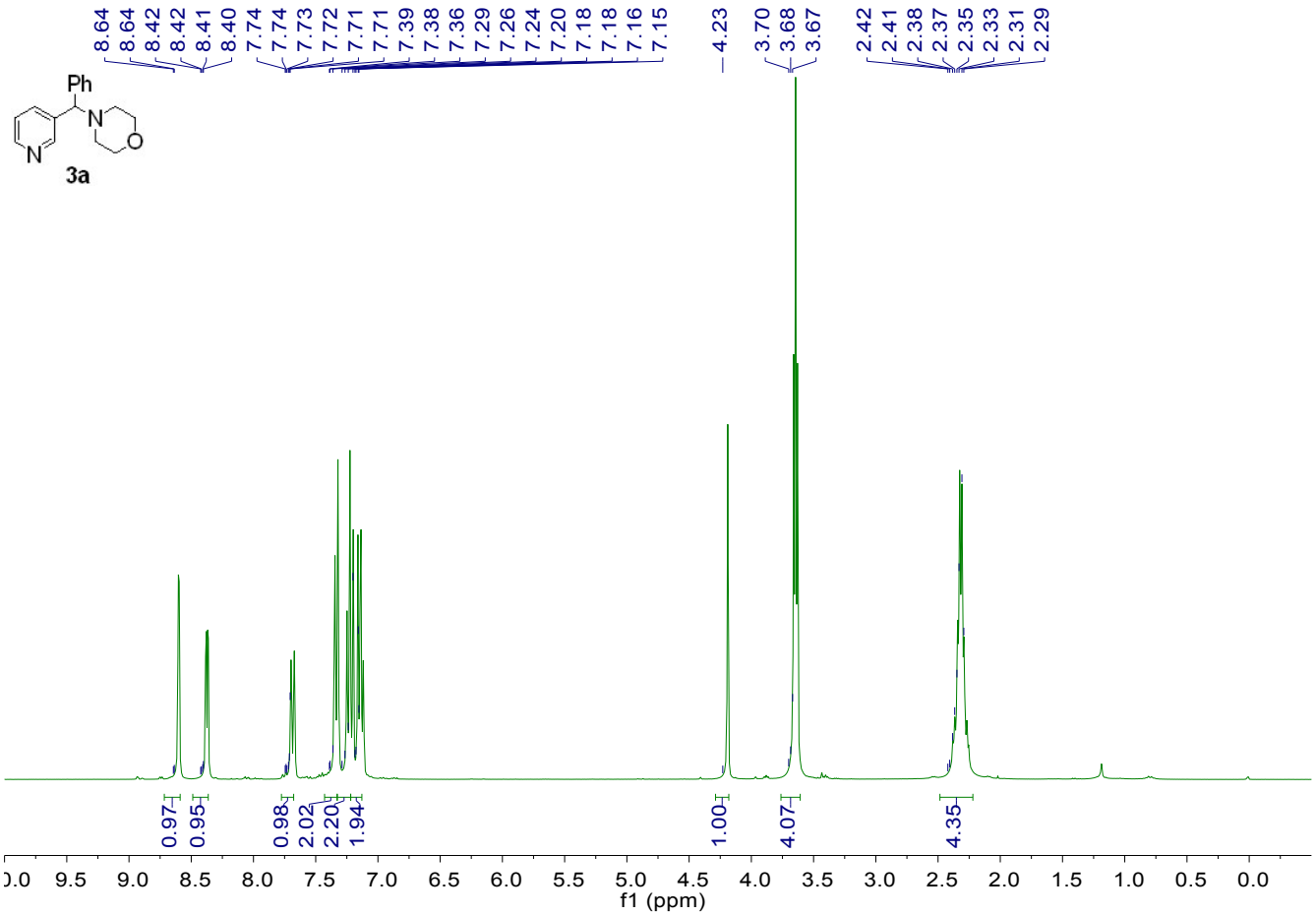
1g **2a** **7'**

A solution of **1g** (92.9 mg, 0.2 mmol) and **2a** (115.5 mg, 0.44 mmol) in CH_3CN (1.0 mL) was stirred in a 90 °C oil bath for 30 min. The solvent was removed in vacuo and the residue was purified by gravity chromatography to give **7'** as yellow foam (88.5 mg, 79% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.66 (d, *J* = 6.2 Hz, 1H), 9.56 (s, 1H), 8.74 (d, *J* = 8.1 Hz, 1H), 8.33 (dd, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.48 – 7.18 (m, 5H), 6.91 (d, *J* = 8.4 Hz, 2H), 5.01 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.77 – 3.57 (m, 4H), 2.49 (m, 2H), 2.35 (m, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.4, 162.9, 146.8, 146.5, 145.9, 137.4, 130.9, 129.9, 129.5, 128.6, 128.4, 122.4, 114.3, 77.4, 70.7, 66.7, 55.6, 51.7, 50.8, 13.4. **HRMS** (ESI-TOF) *m/z*: $[M - I^-]^+$ Calcd for $C_{26}H_{30}N_3O_3^+$ 432.2282; Found 432.2280.

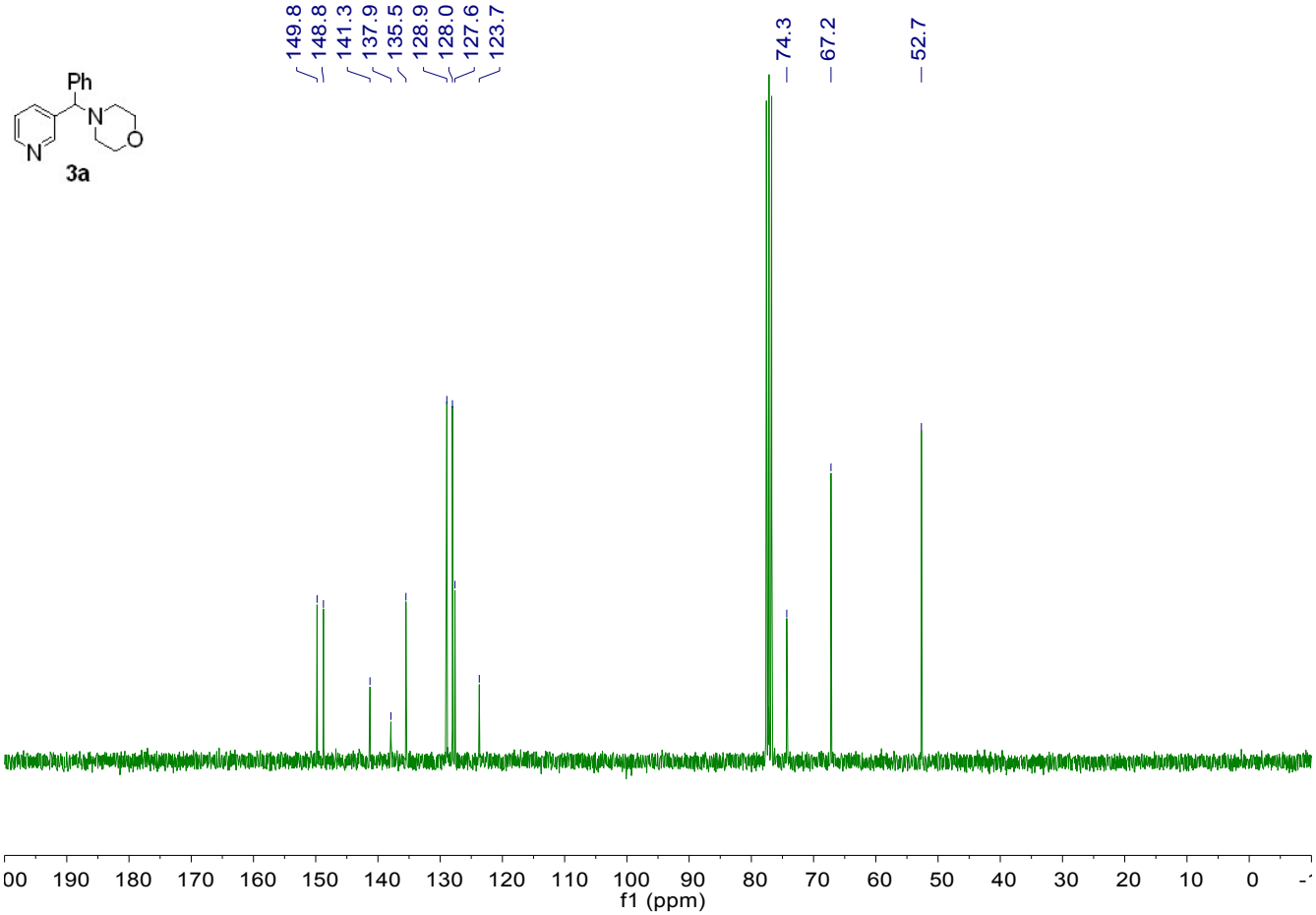
References

1. (a) C. Legault and A. B. Charette, *J. Org. Chem.*, 2003, **68**, 7119-7122; (b) M. A. de las Heras, A. Molina, J. J. Vaquero, J. L. Garcia Navio and J. Alvarez-Builla, *J. Org. Chem.*, 1993, **58**, 5862-5865.
2. (a) B. Hatano, K. Nagahashi and T. Kijima, *J. Org. Chem.*, 2008, **73**, 9188-9191; (b) Y. Zhou, Y. Xie, L. Yang, P. Xie and H. Huang, *Tetrahedron Lett.*, 2013, **54**, 2713-2716; (c) S. V. Lieberman, *J. Am. Chem. Soc.*, 1955, **77**, 1114-1116.

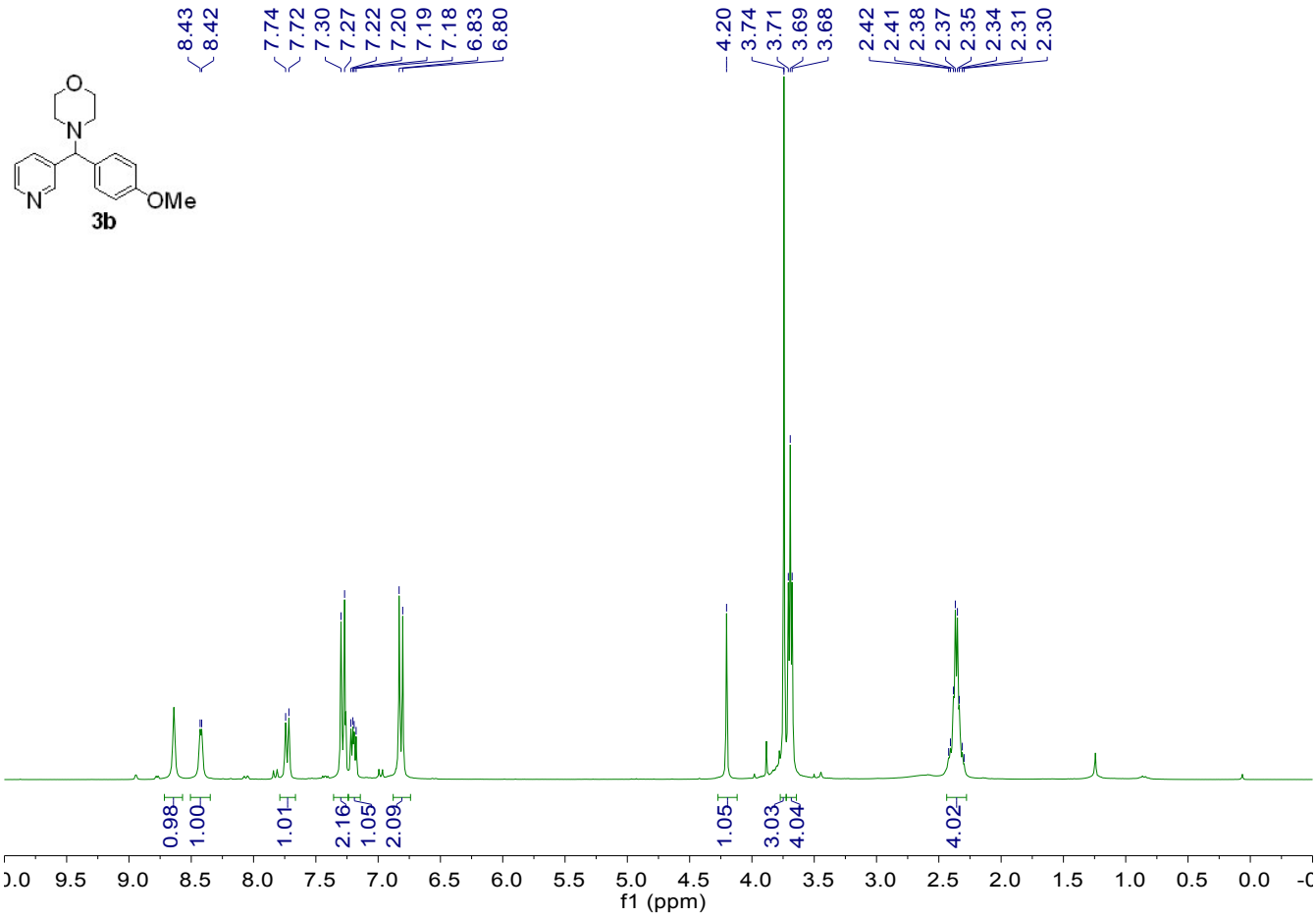
^{1}H NMR and ^{13}C NMR spectra of products



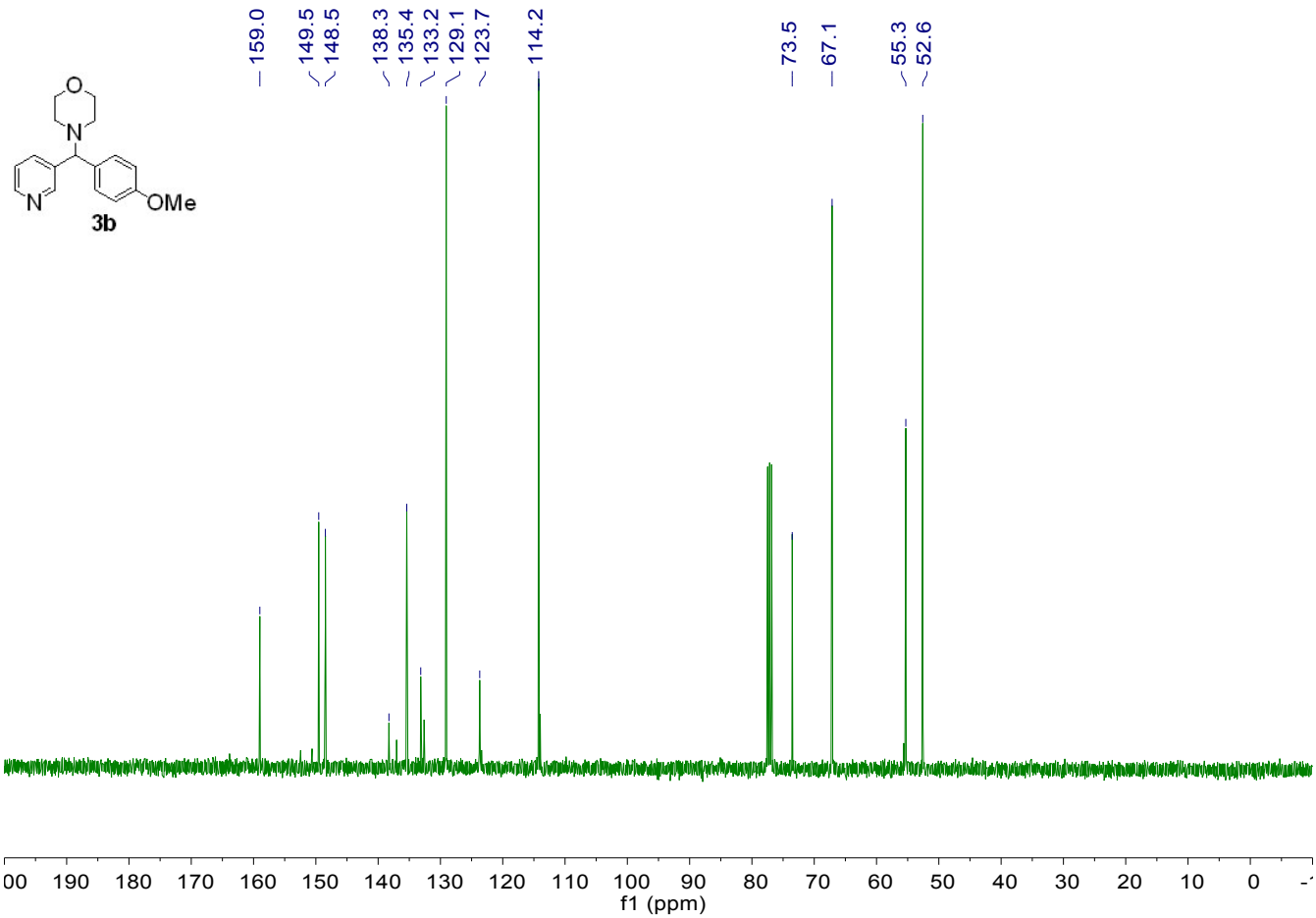
^{1}H NMR of **3a**, 300 MHz in $CDCl_3$



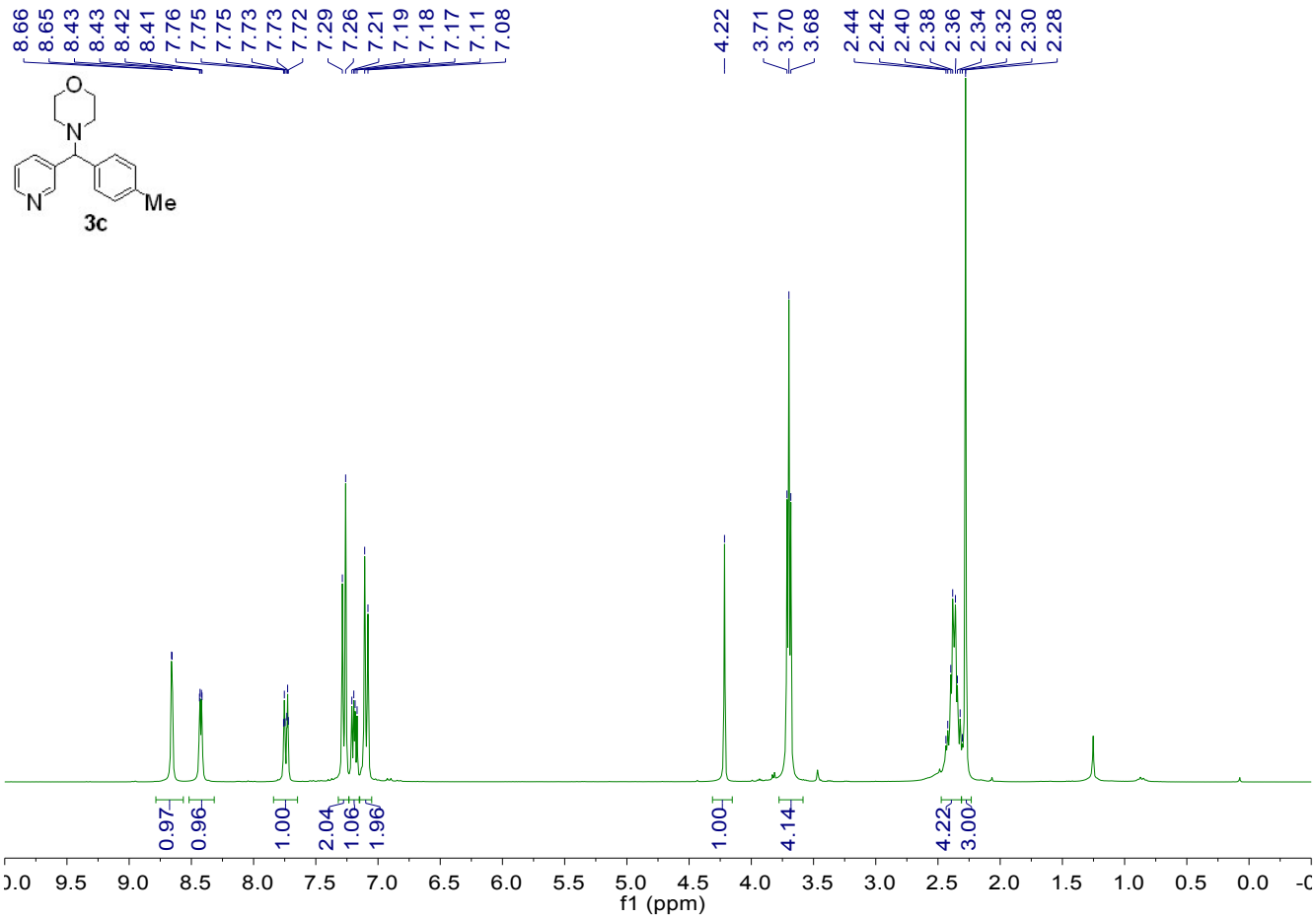
^{13}C NMR of **3a**, 75 MHz in $CDCl_3$



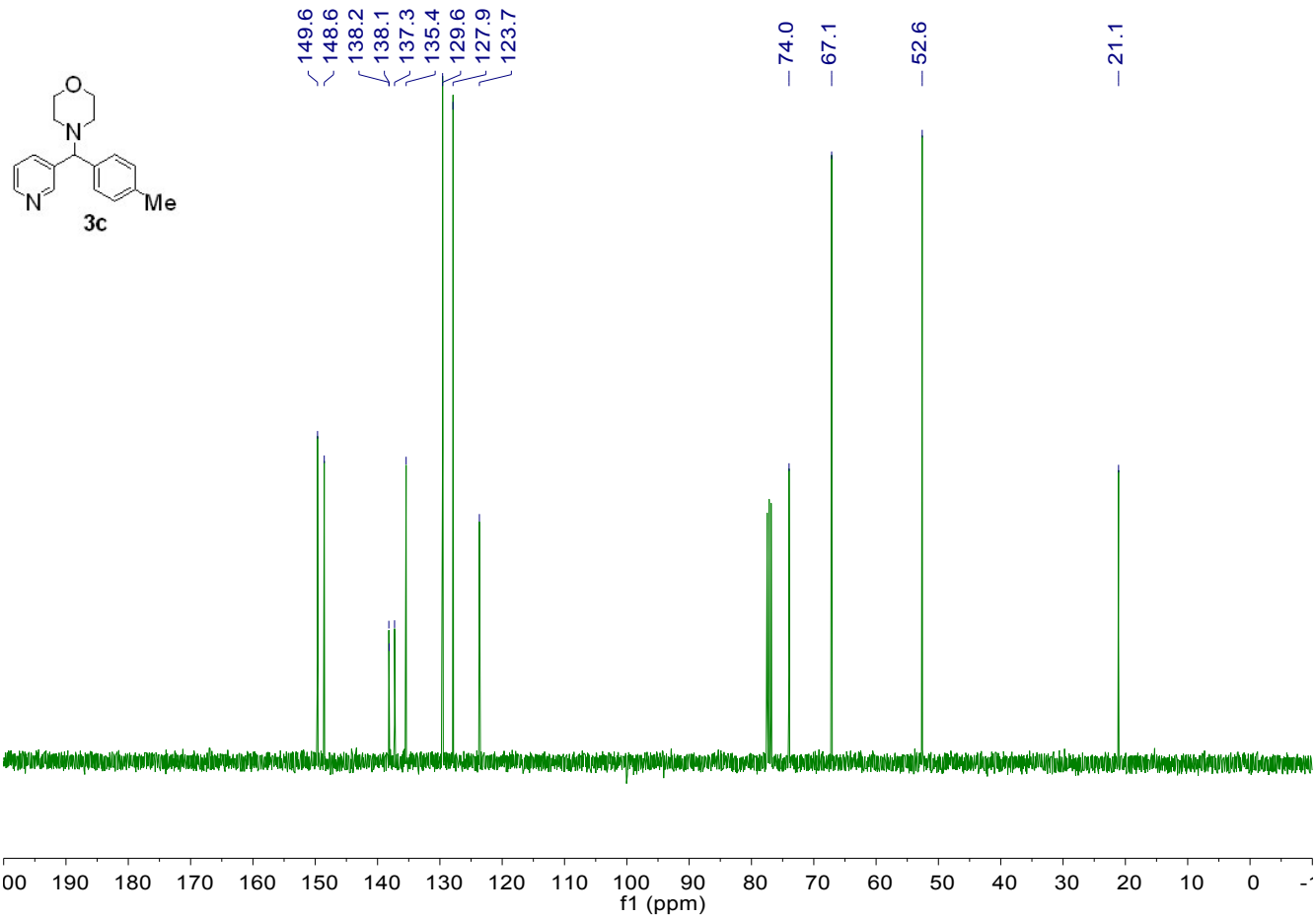
^{1}H NMR of **3b**, 300 MHz in $CDCl_3$



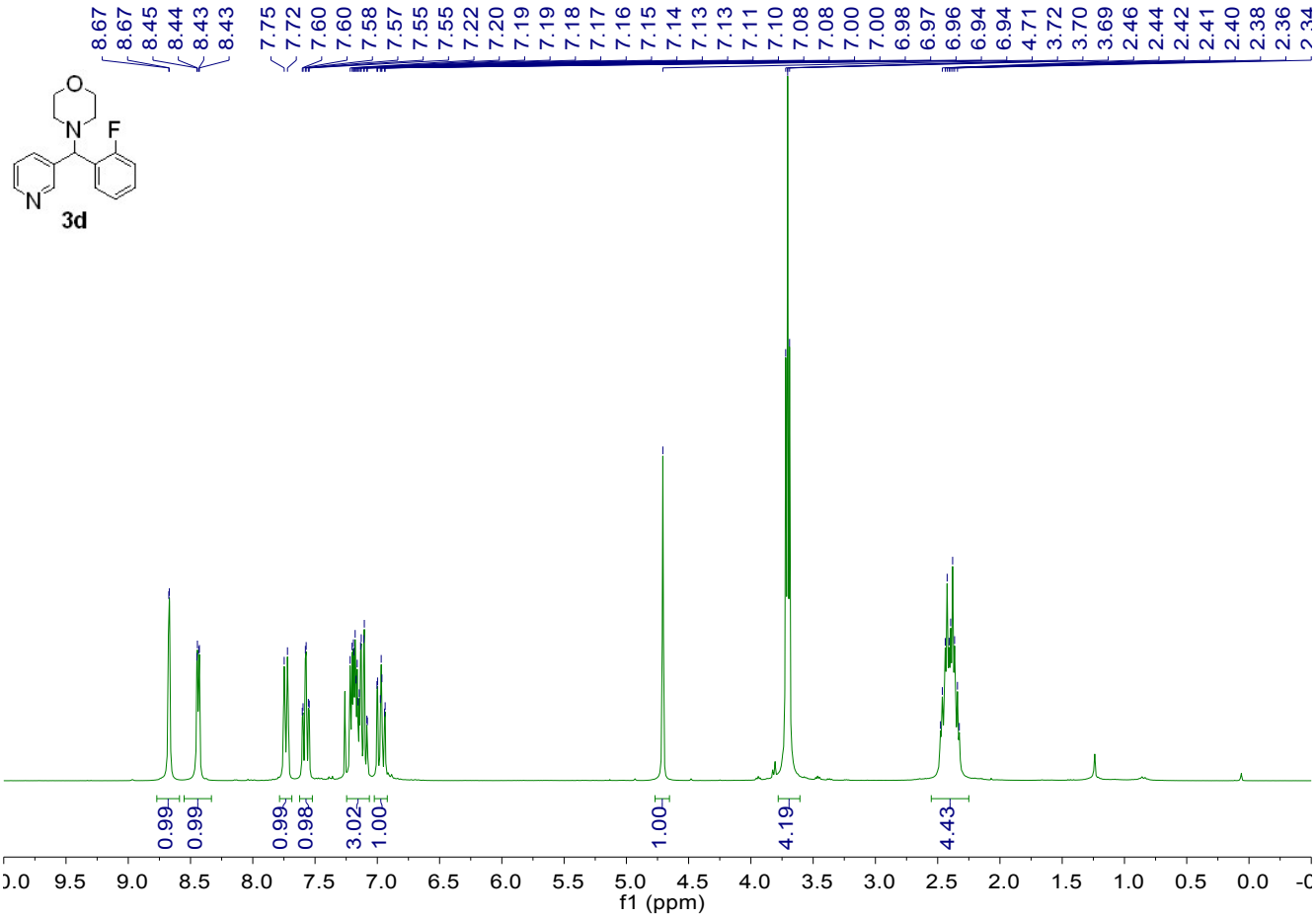
^{13}C NMR of **3b**, 100 MHz in $CDCl_3$



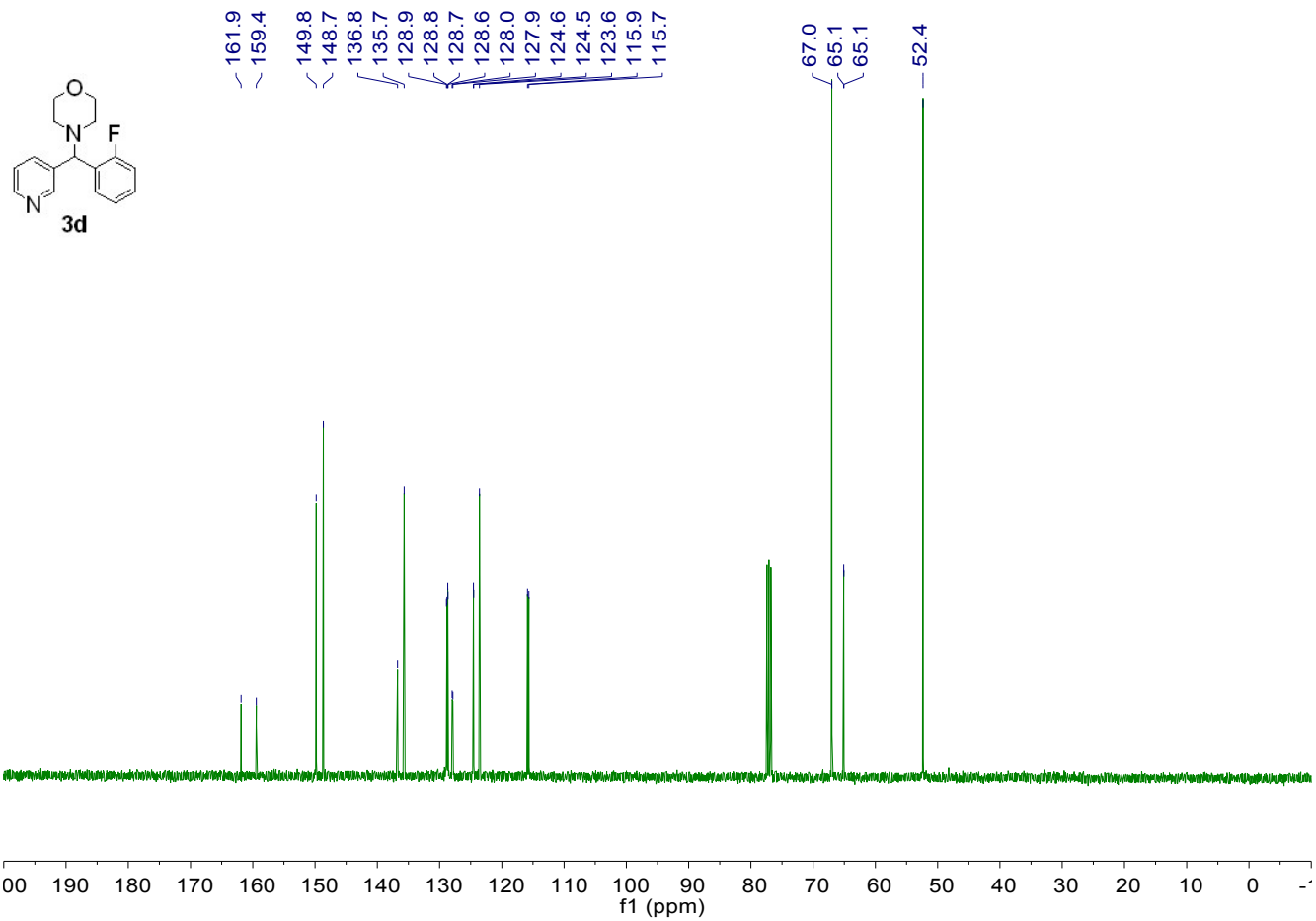
^{1}H NMR of **3c**, 300 MHz in $CDCl_3$



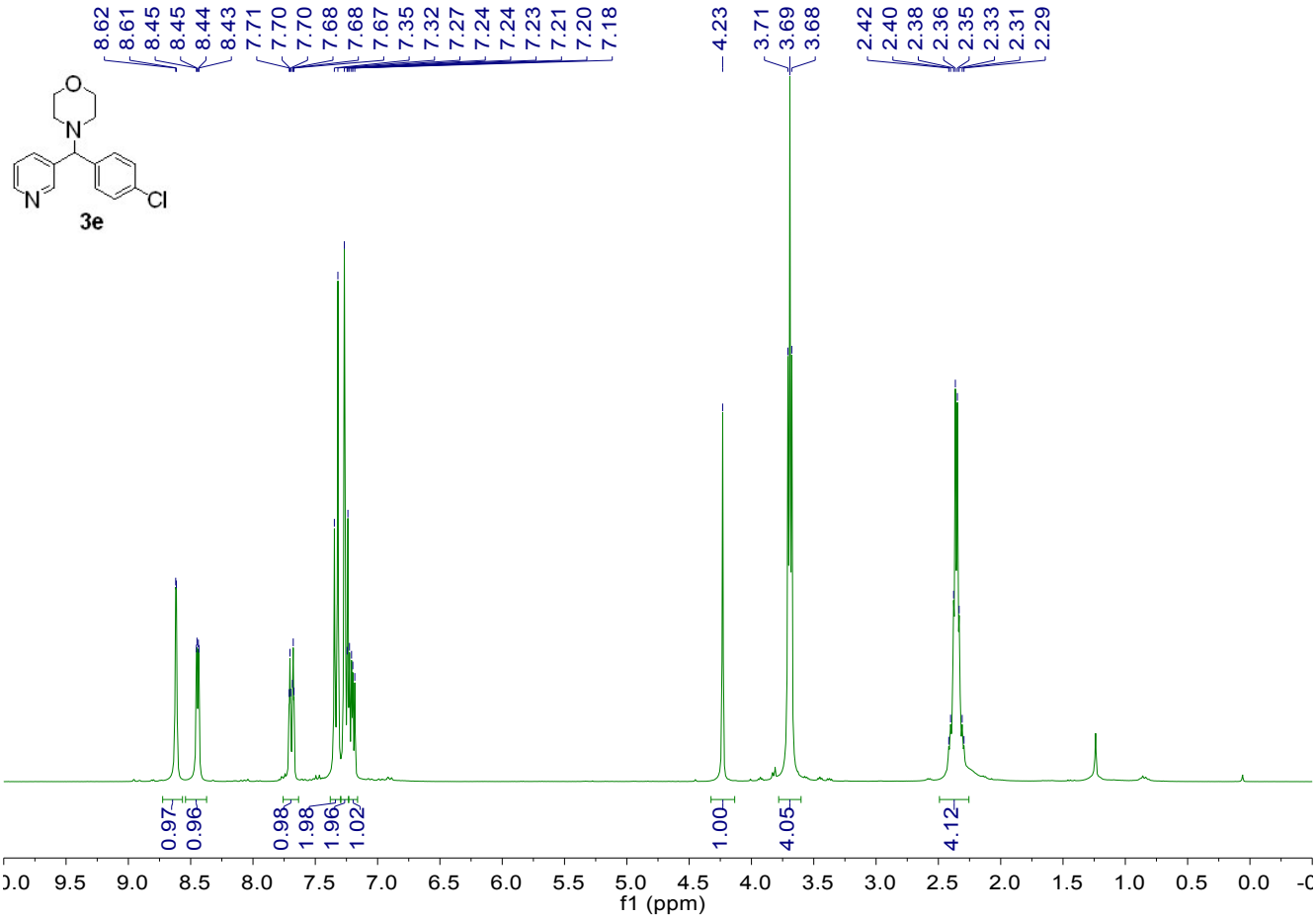
^{13}C NMR of **3c**, 100 MHz in $CDCl_3$



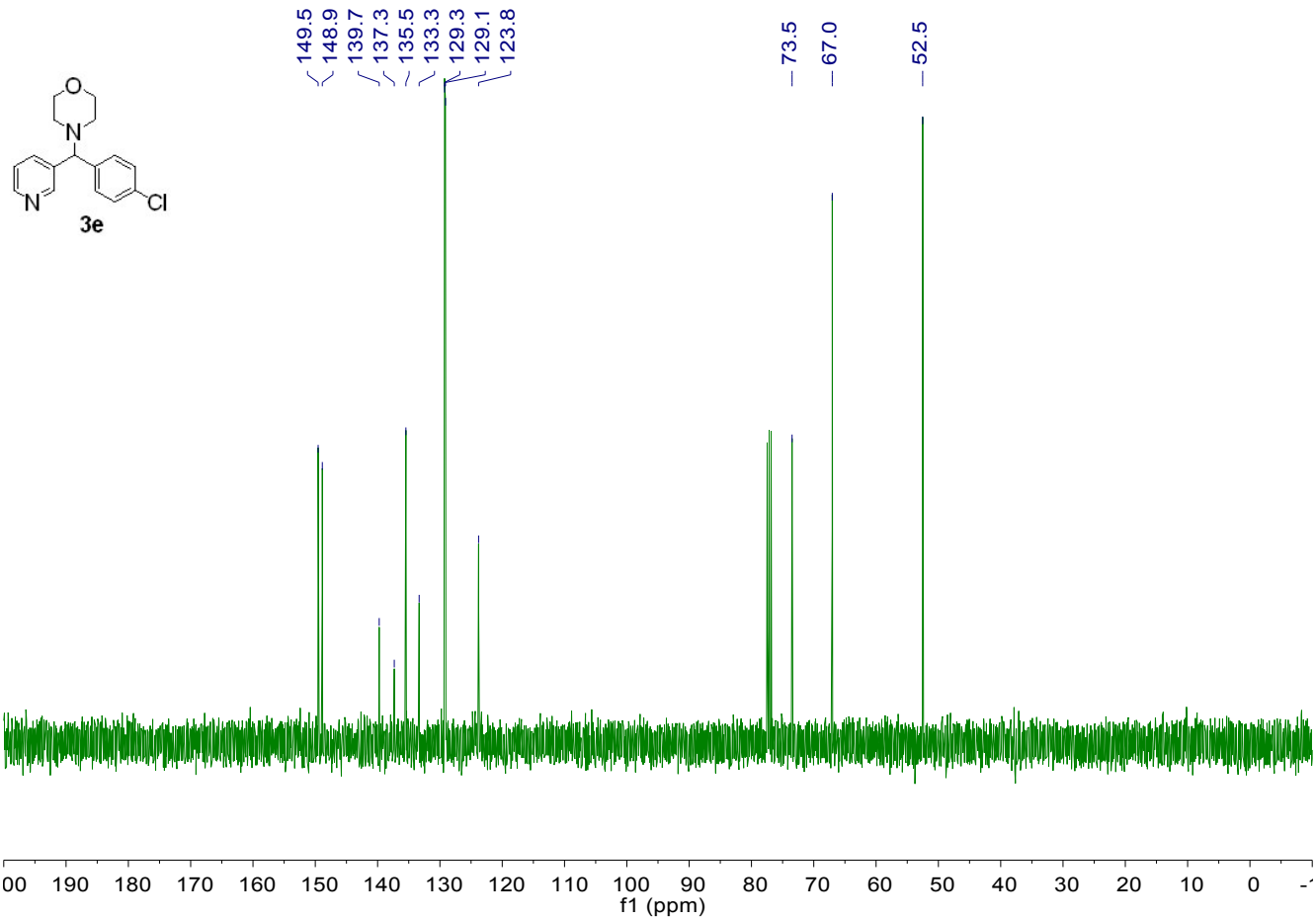
^{1}H NMR of **3d**, 300 MHz in $CDCl_3$



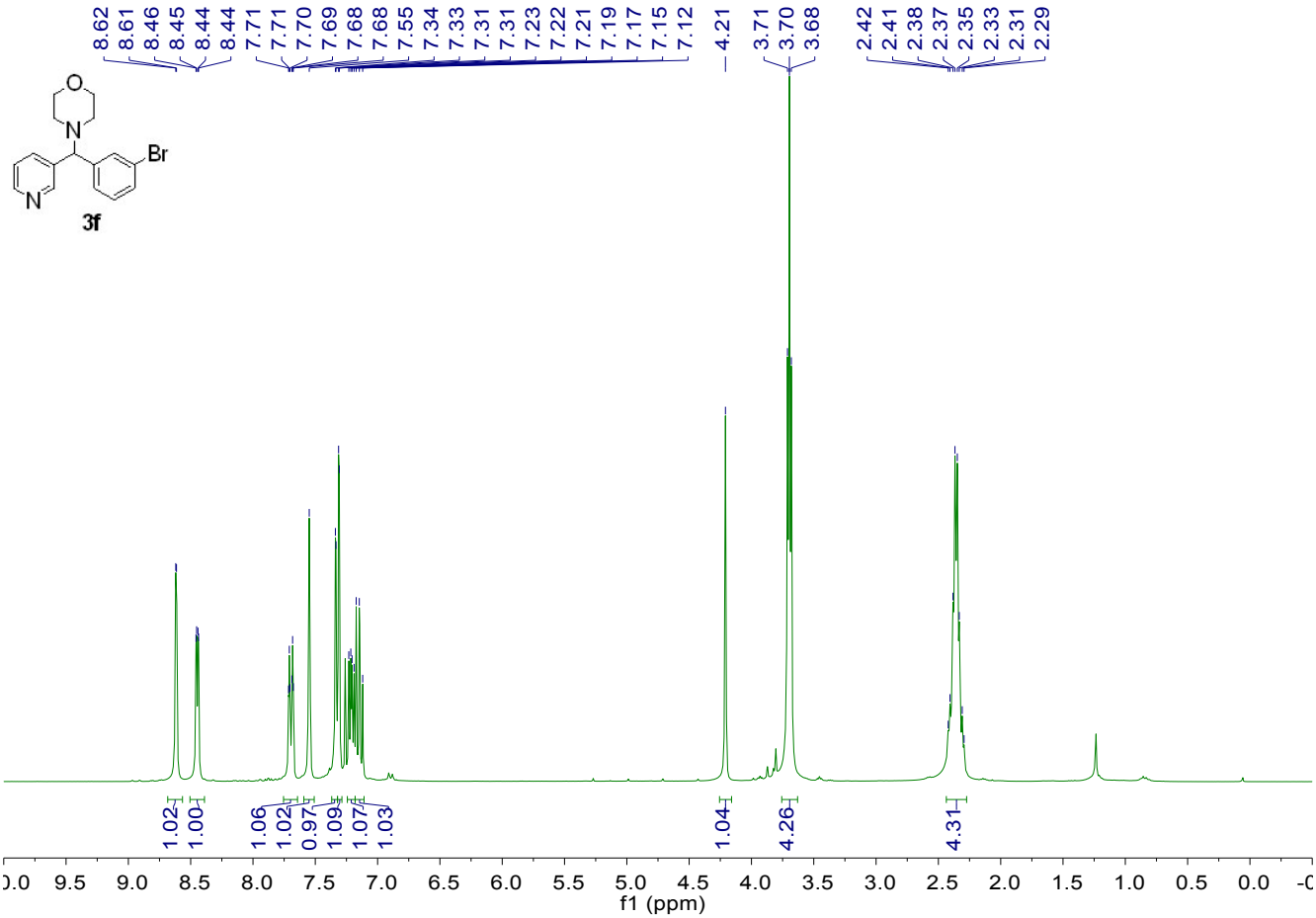
^{13}C NMR of **3d**, 100 MHz in $CDCl_3$



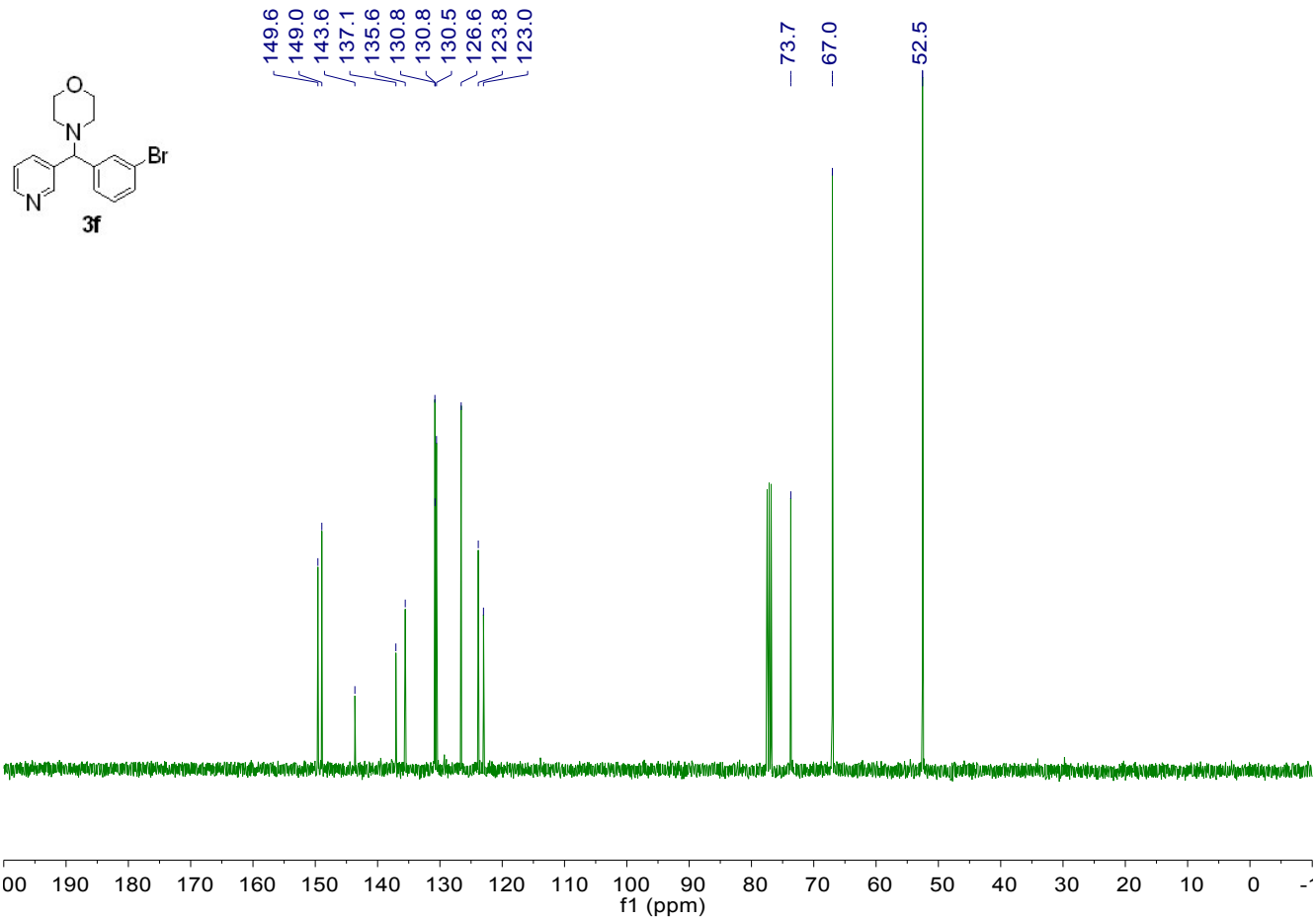
^{1}H NMR of **3e**, 300 MHz in $CDCl_3$



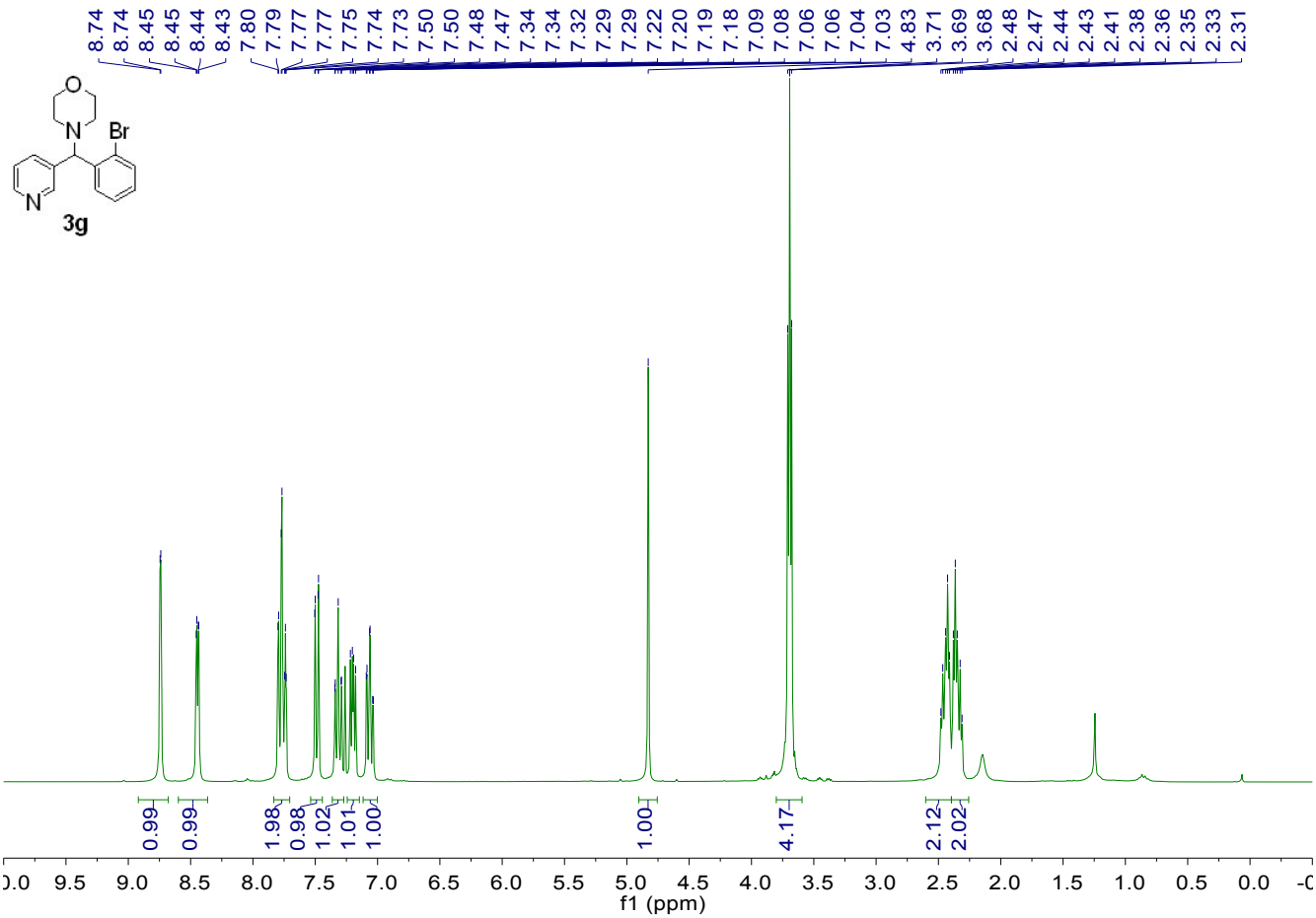
^{13}C NMR of **3e**, 100 MHz in $CDCl_3$



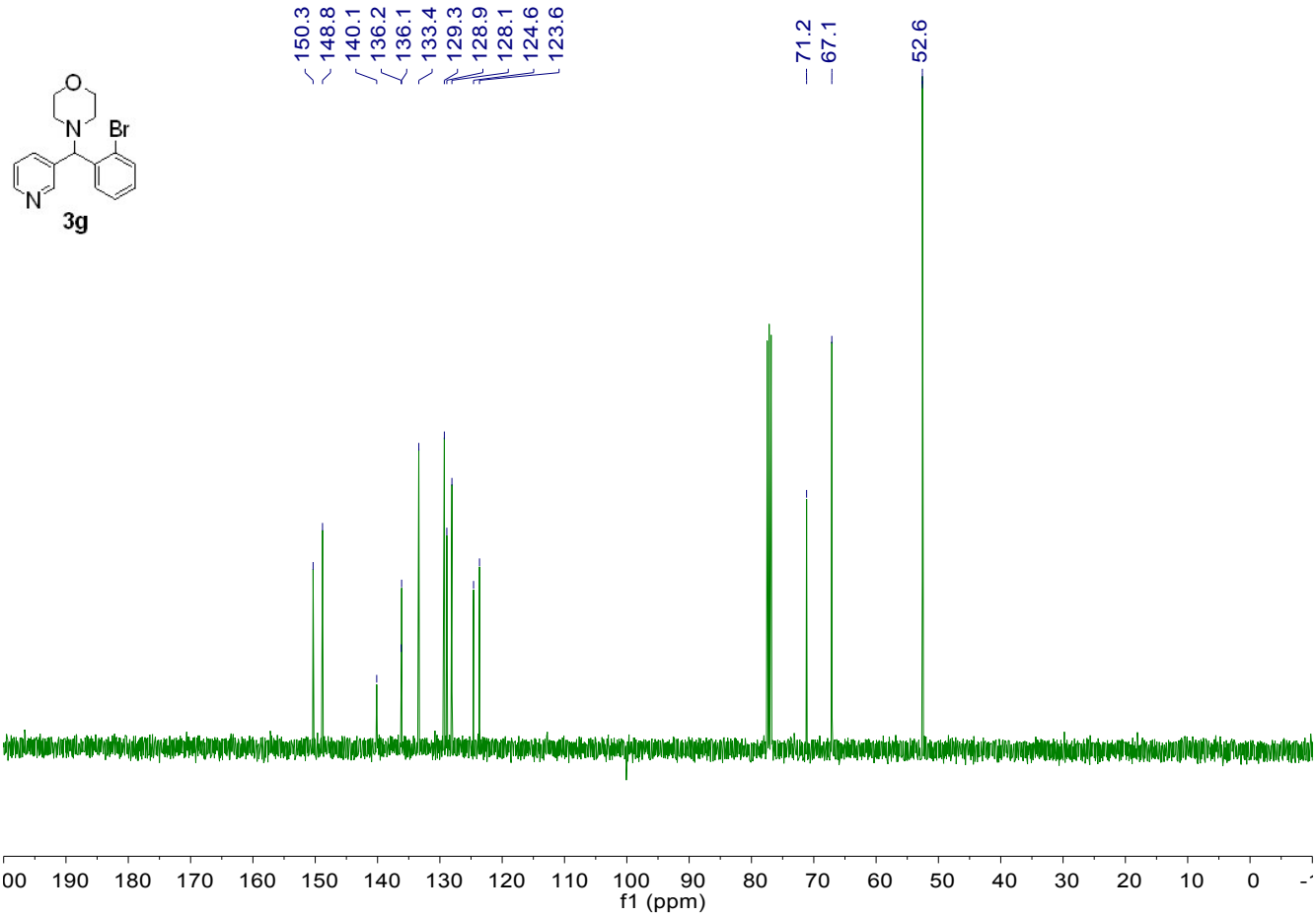
^{1}H NMR of **3f**, 300 MHz in $CDCl_3$



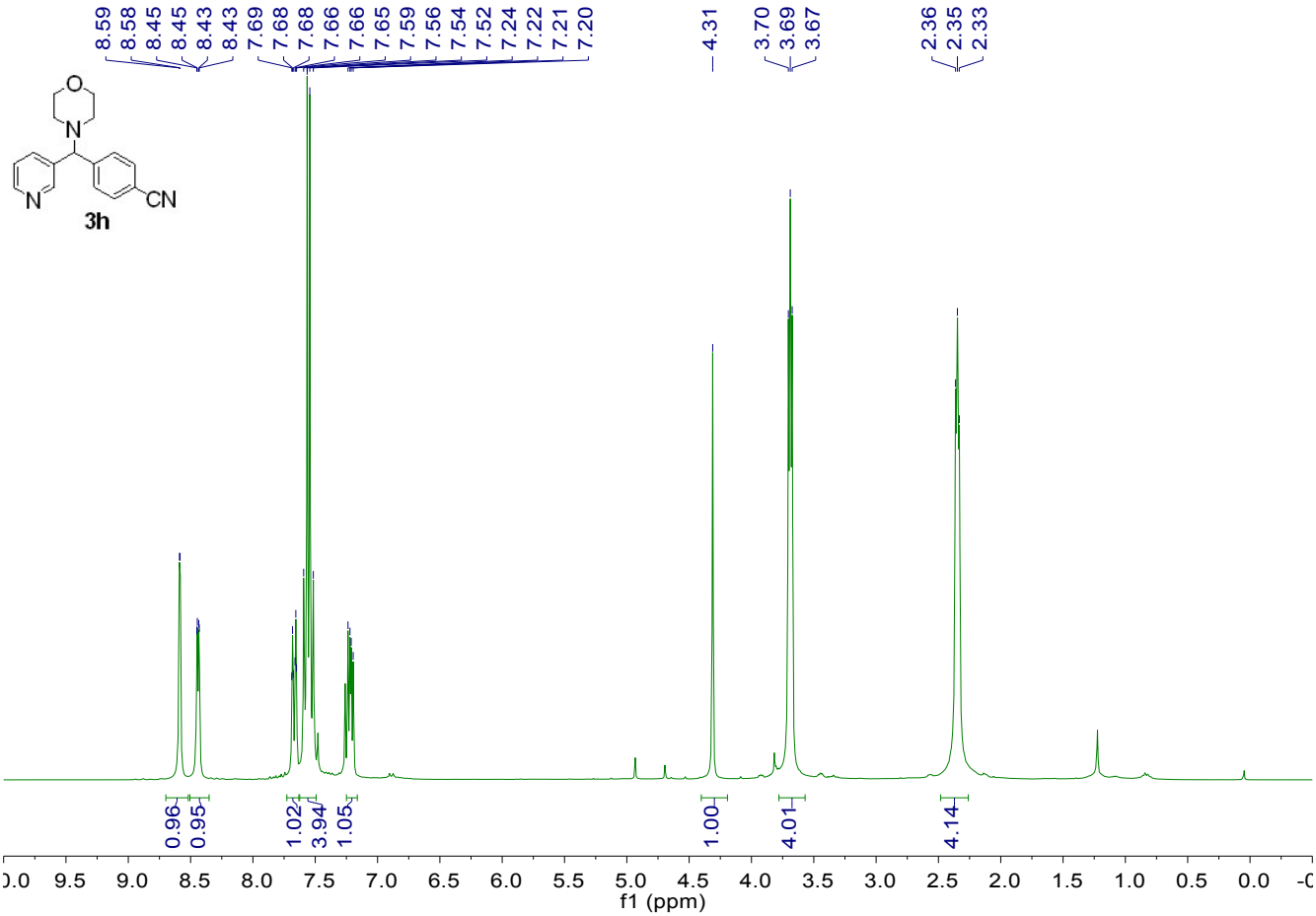
^{13}C NMR of **3f**, 100 MHz in $CDCl_3$



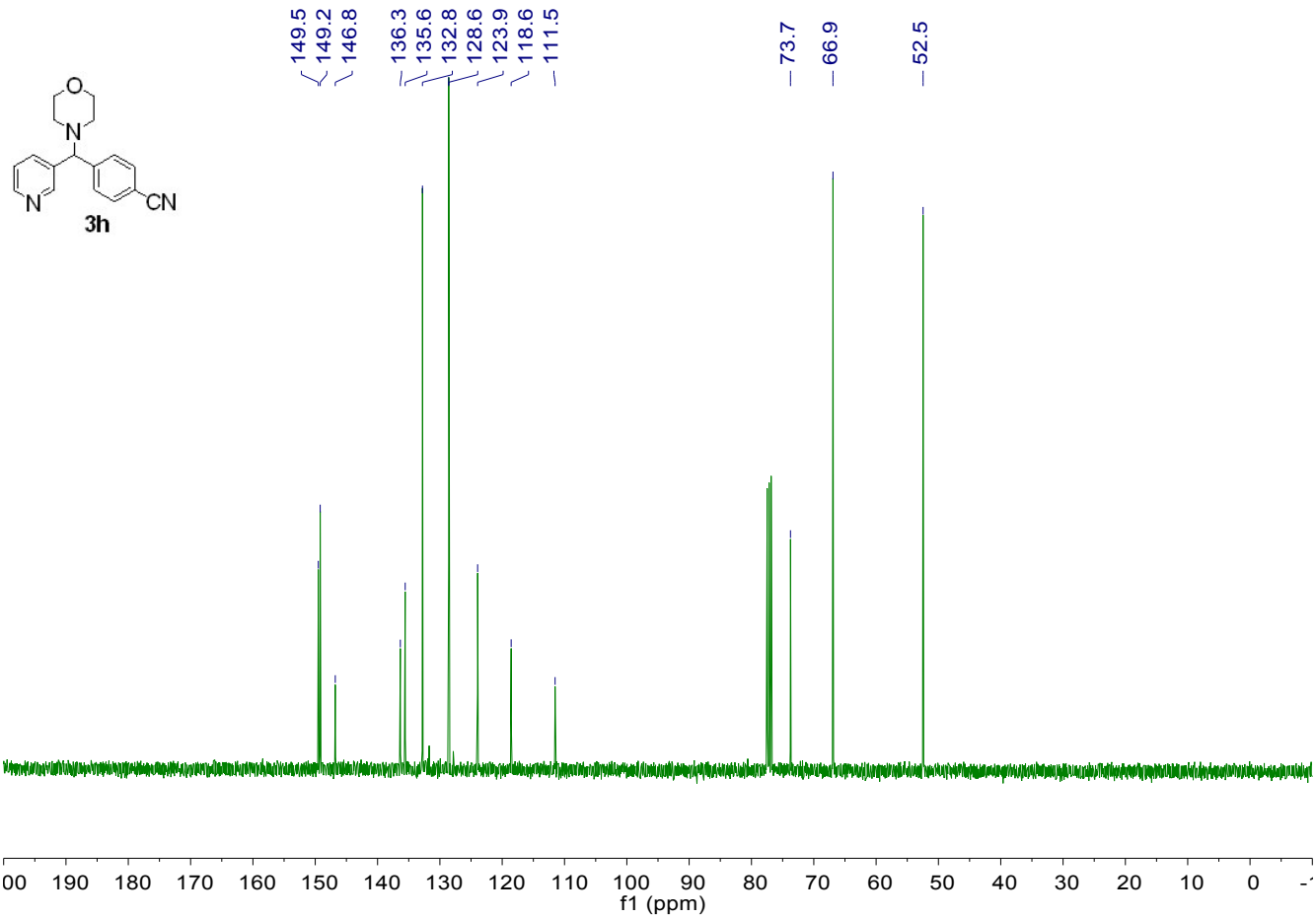
^{1}H NMR of **3g**, 300 MHz in $CDCl_3$



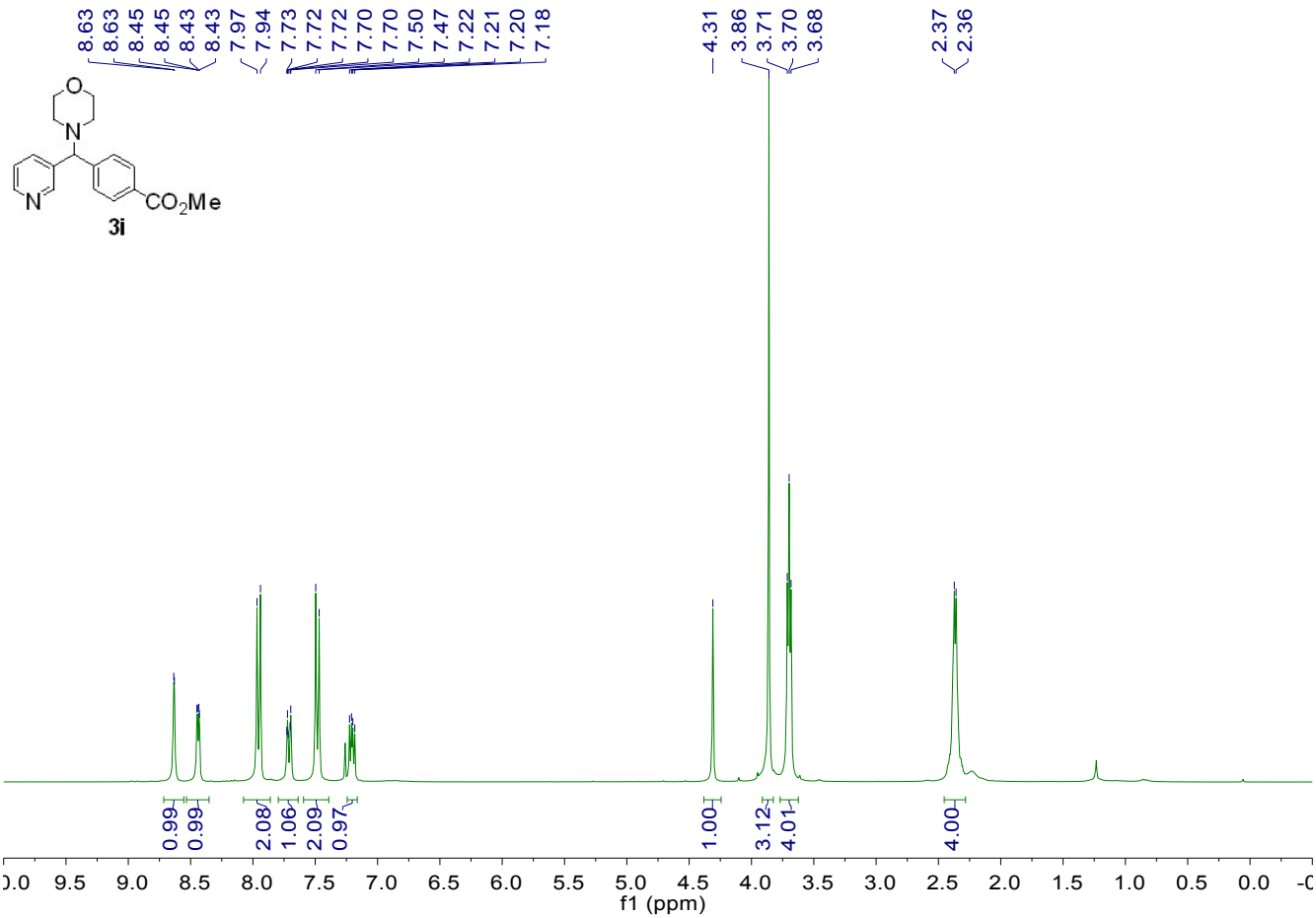
^{13}C NMR of **3g**, 100 MHz in $CDCl_3$



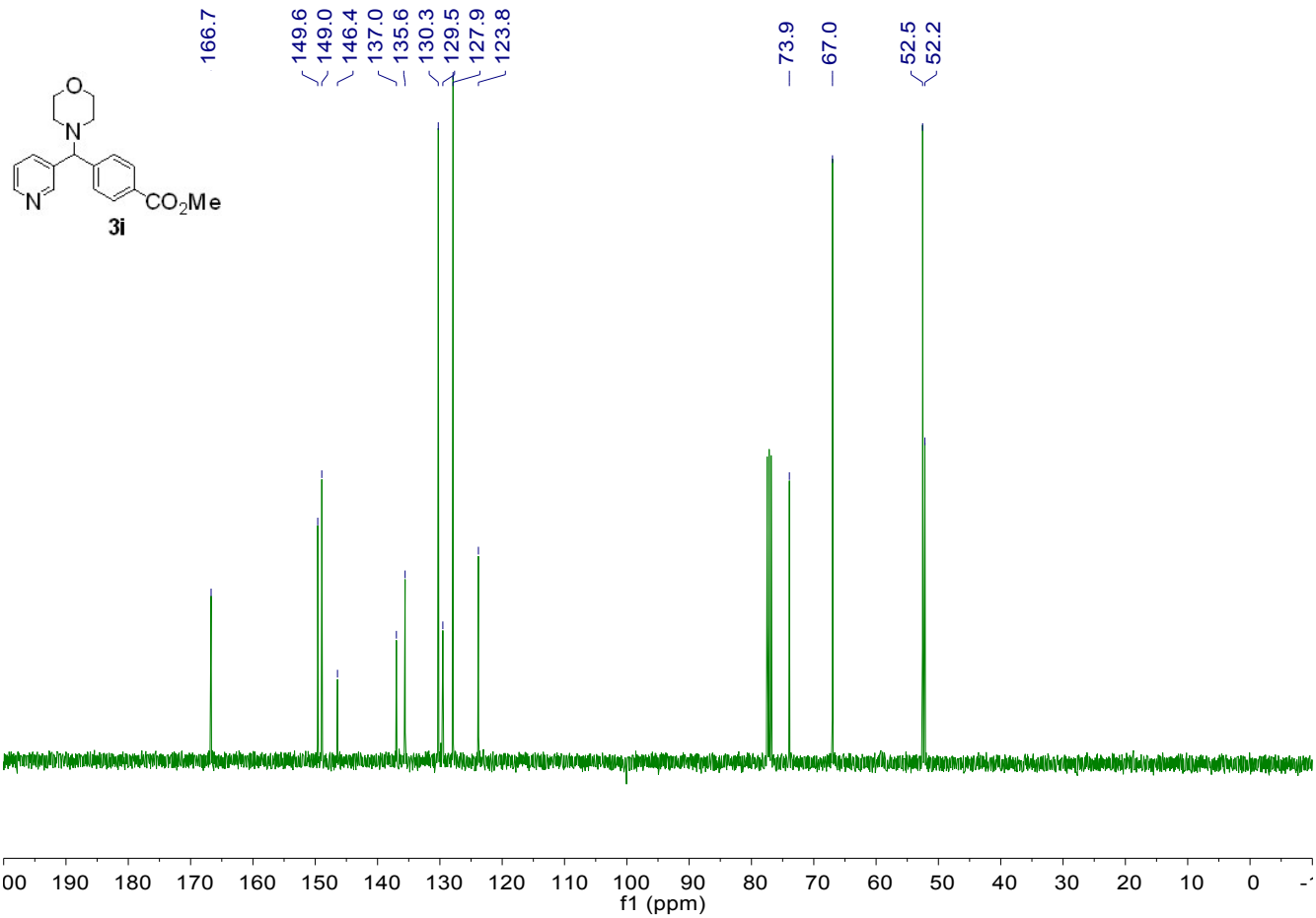
^{1}H NMR of **3h**, 300 MHz in $CDCl_3$



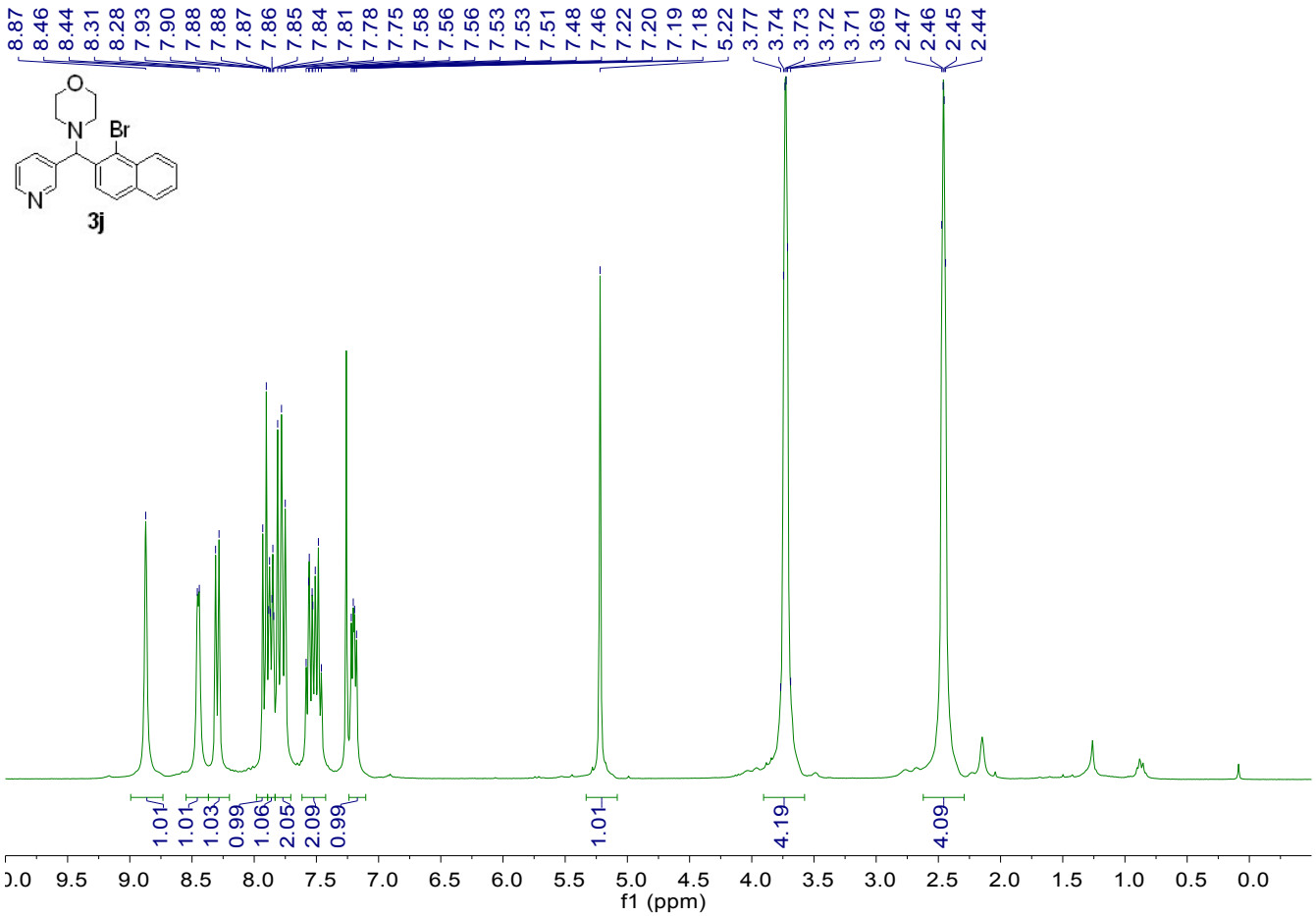
^{13}C NMR of **3h**, 100 MHz in $CDCl_3$



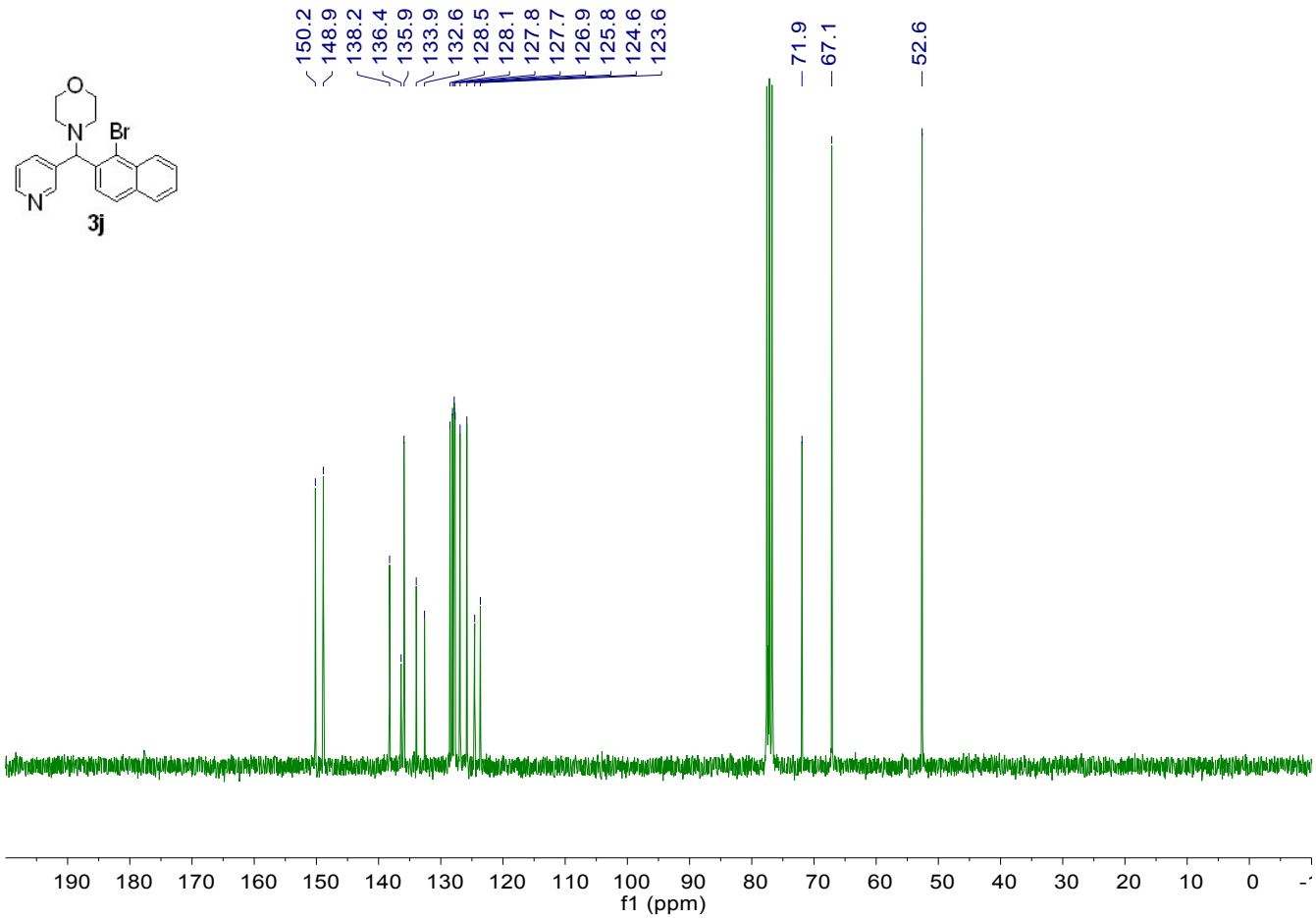
^{1}H NMR of **3i**, 300 MHz in $CDCl_3$



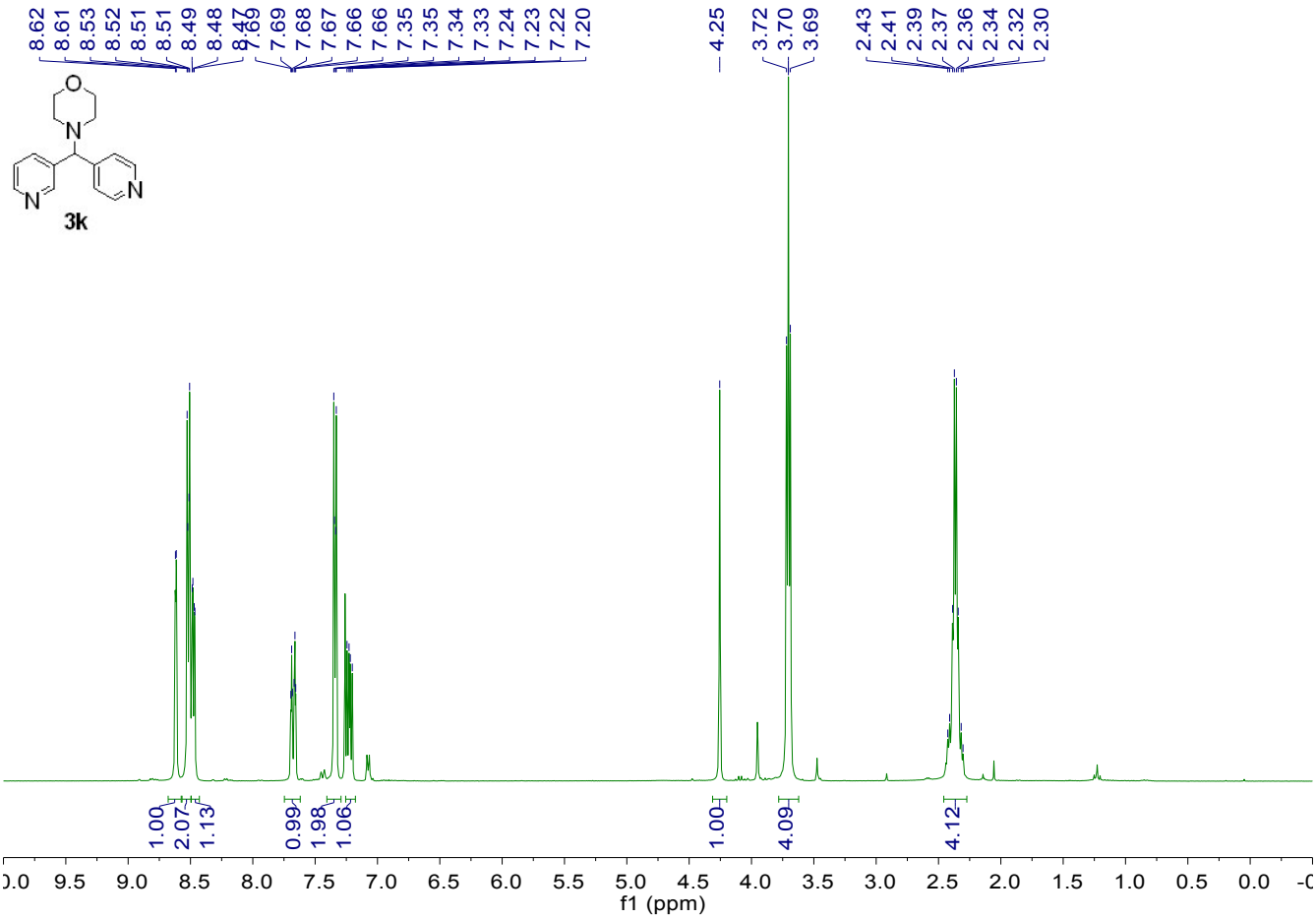
^{13}C NMR of **3i**, 100 MHz in $CDCl_3$



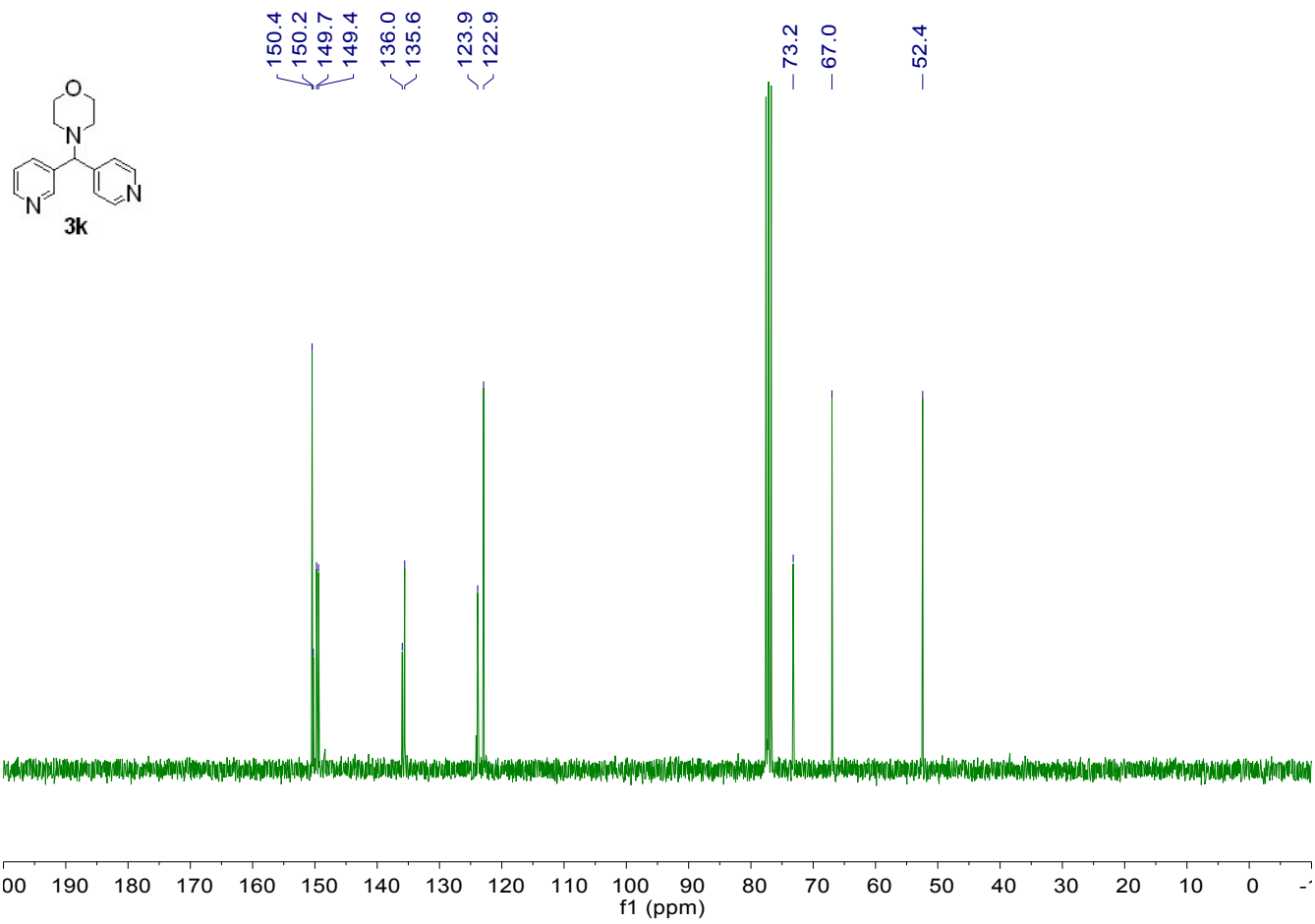
^{1}H NMR of **3j**, 300 MHz in $CDCl_3$



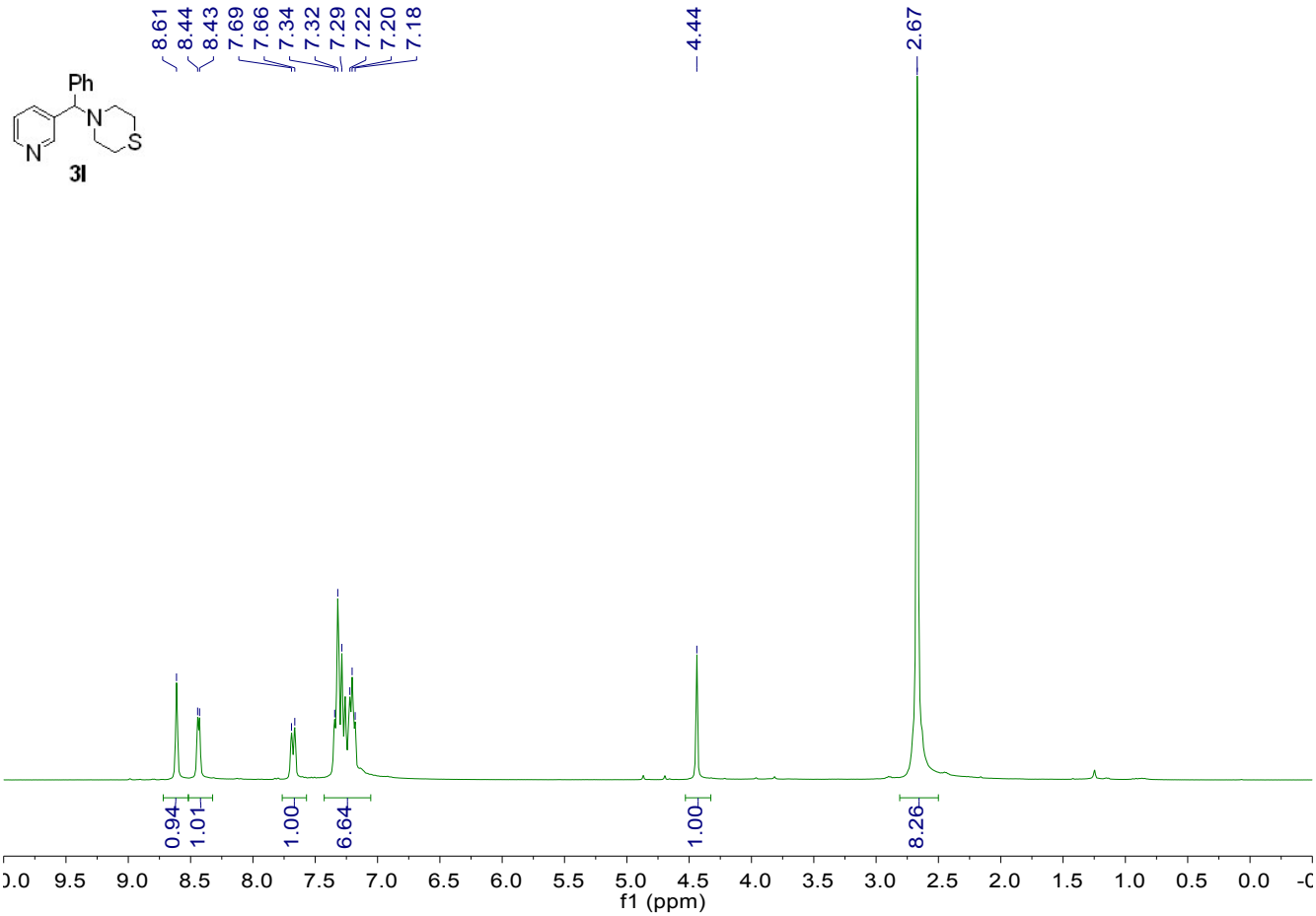
^{13}C NMR of **3j**, 75 MHz in $CDCl_3$



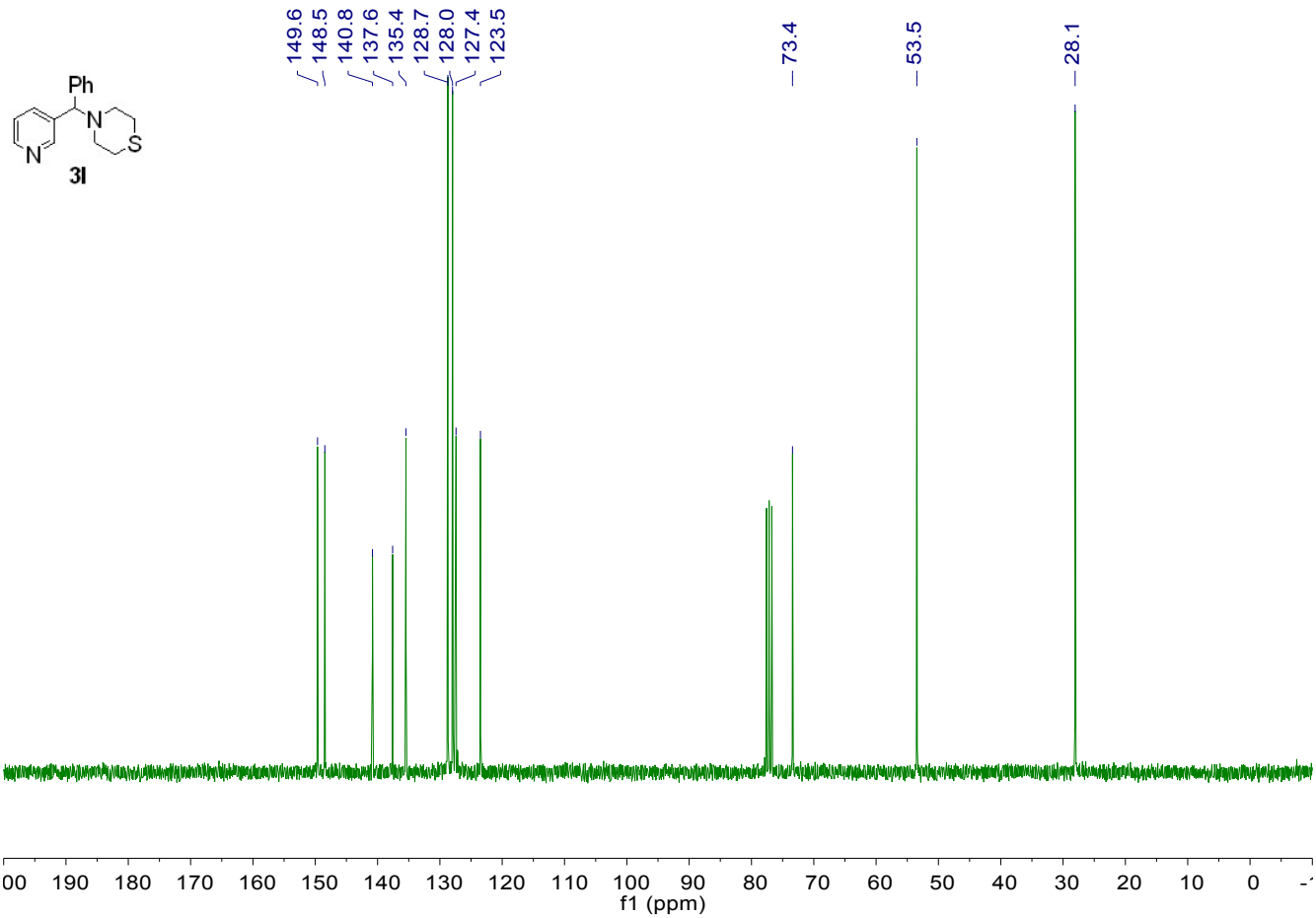
^{1}H NMR of **3k**, 300 MHz in $CDCl_3$



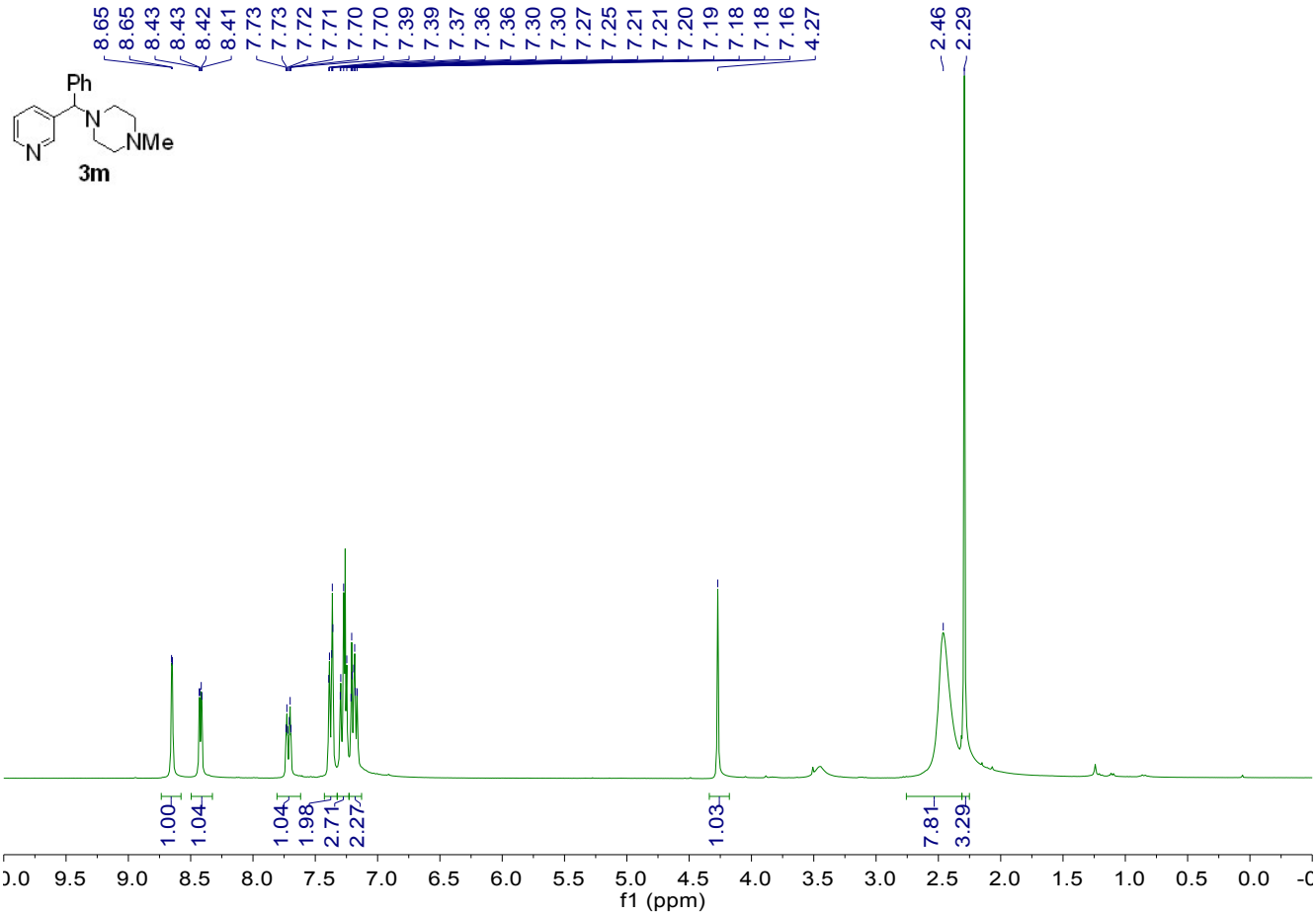
^{13}C NMR of **3k**, 75 MHz in $CDCl_3$



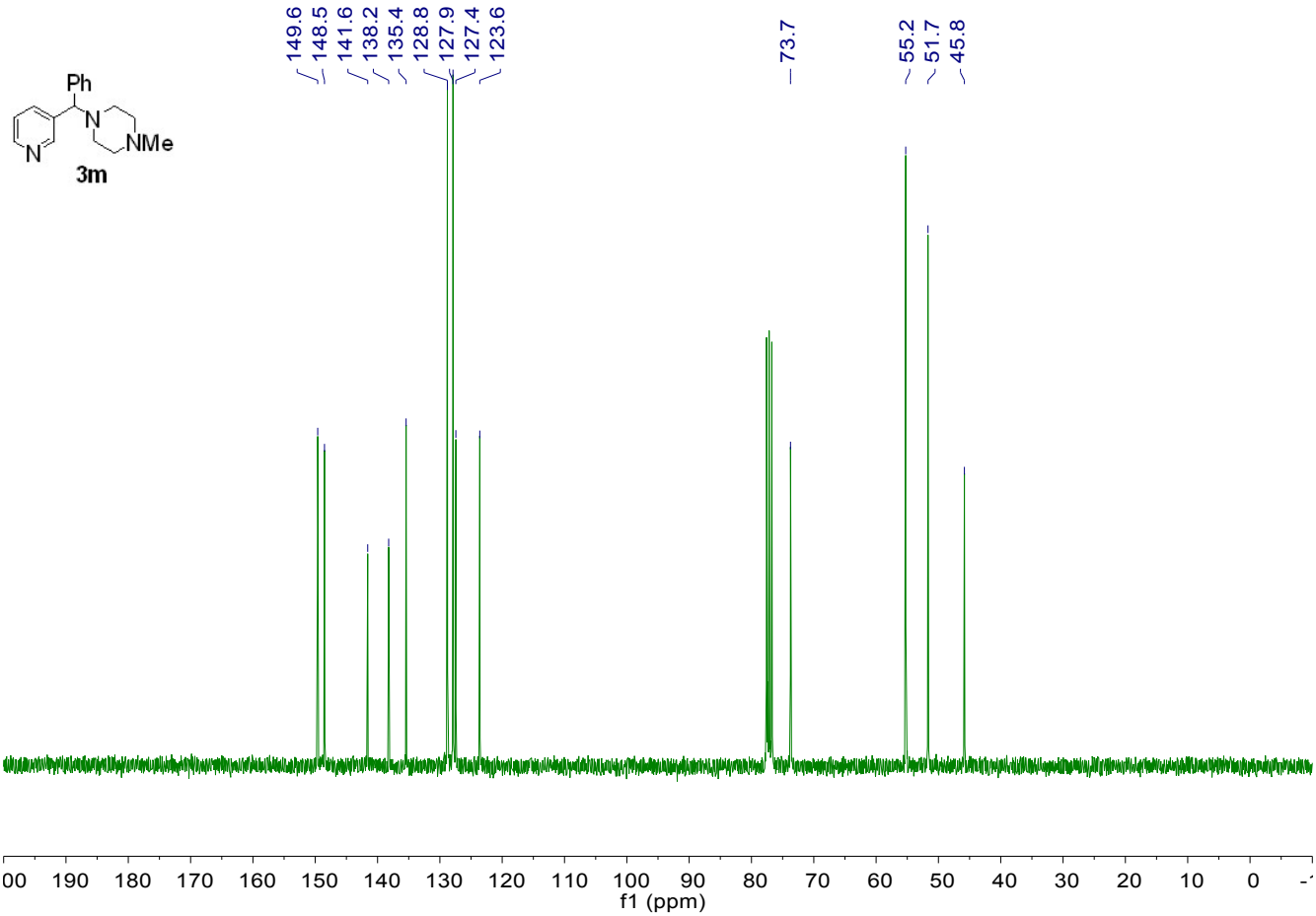
^{1}H NMR of **3l**, 300 MHz in $CDCl_3$



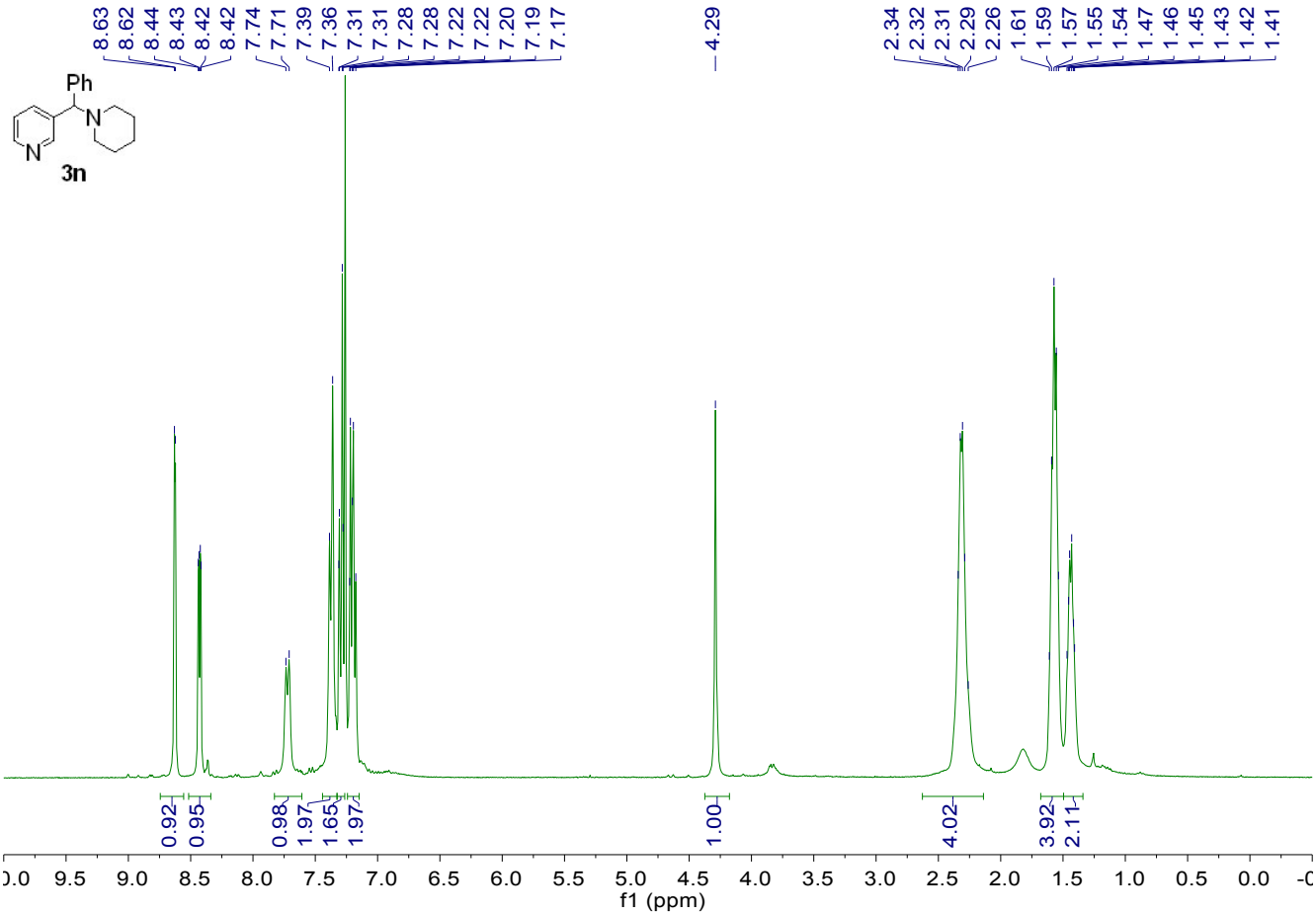
^{13}C NMR of **3l**, 75 MHz in $CDCl_3$



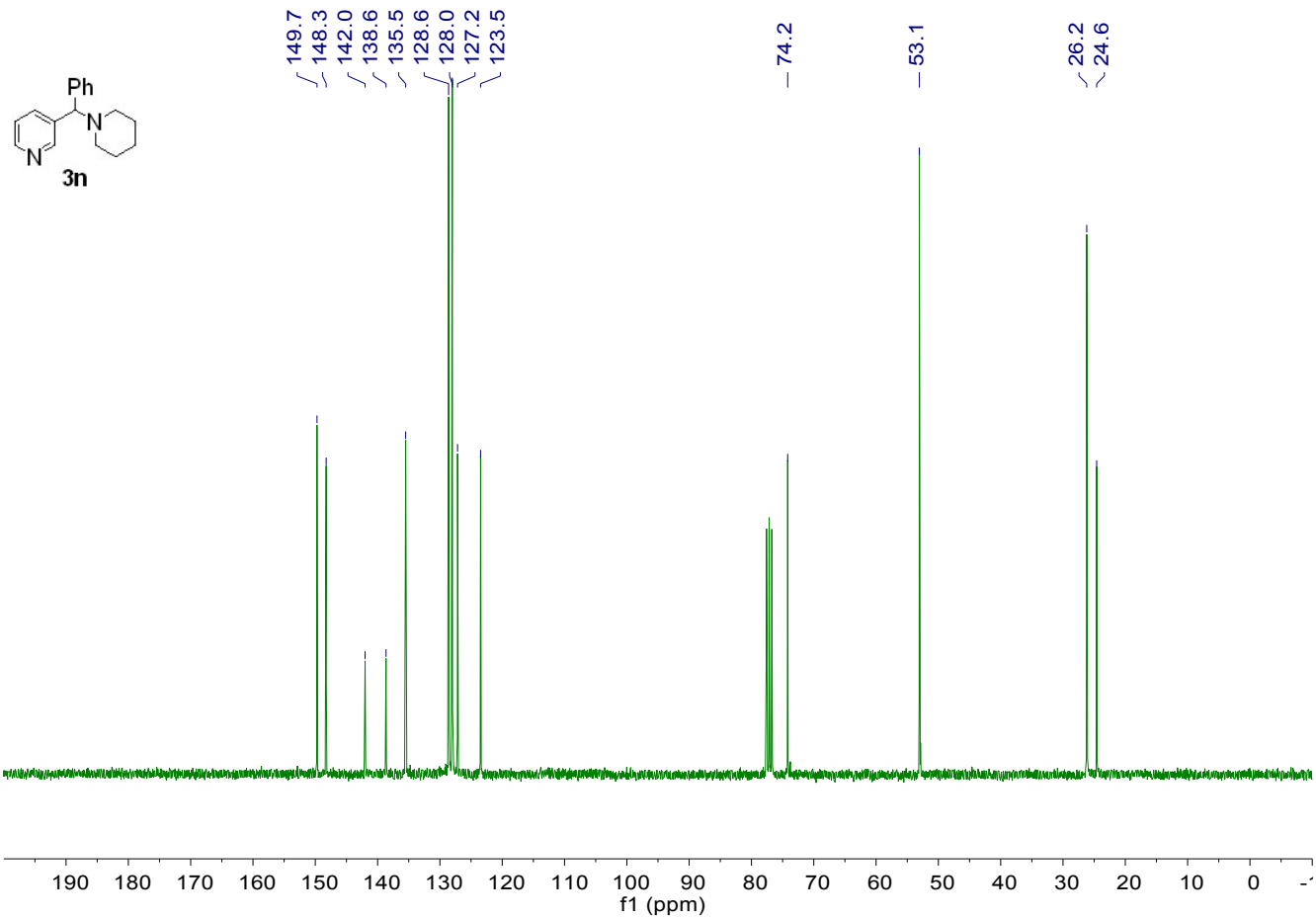
^{1}H NMR of **3m**, 300 MHz in $CDCl_3$



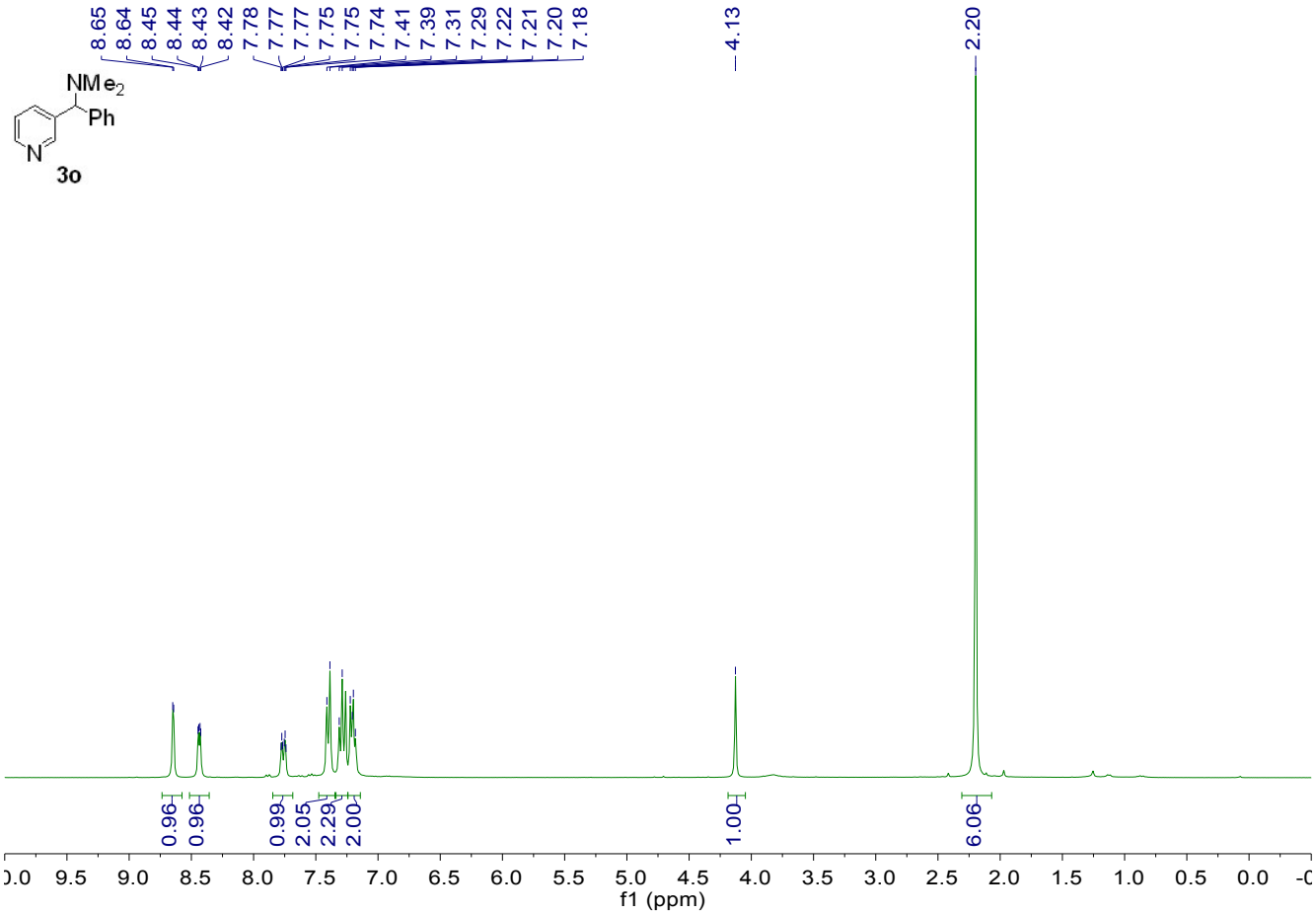
^{13}C NMR of **3m**, 75 MHz in $CDCl_3$



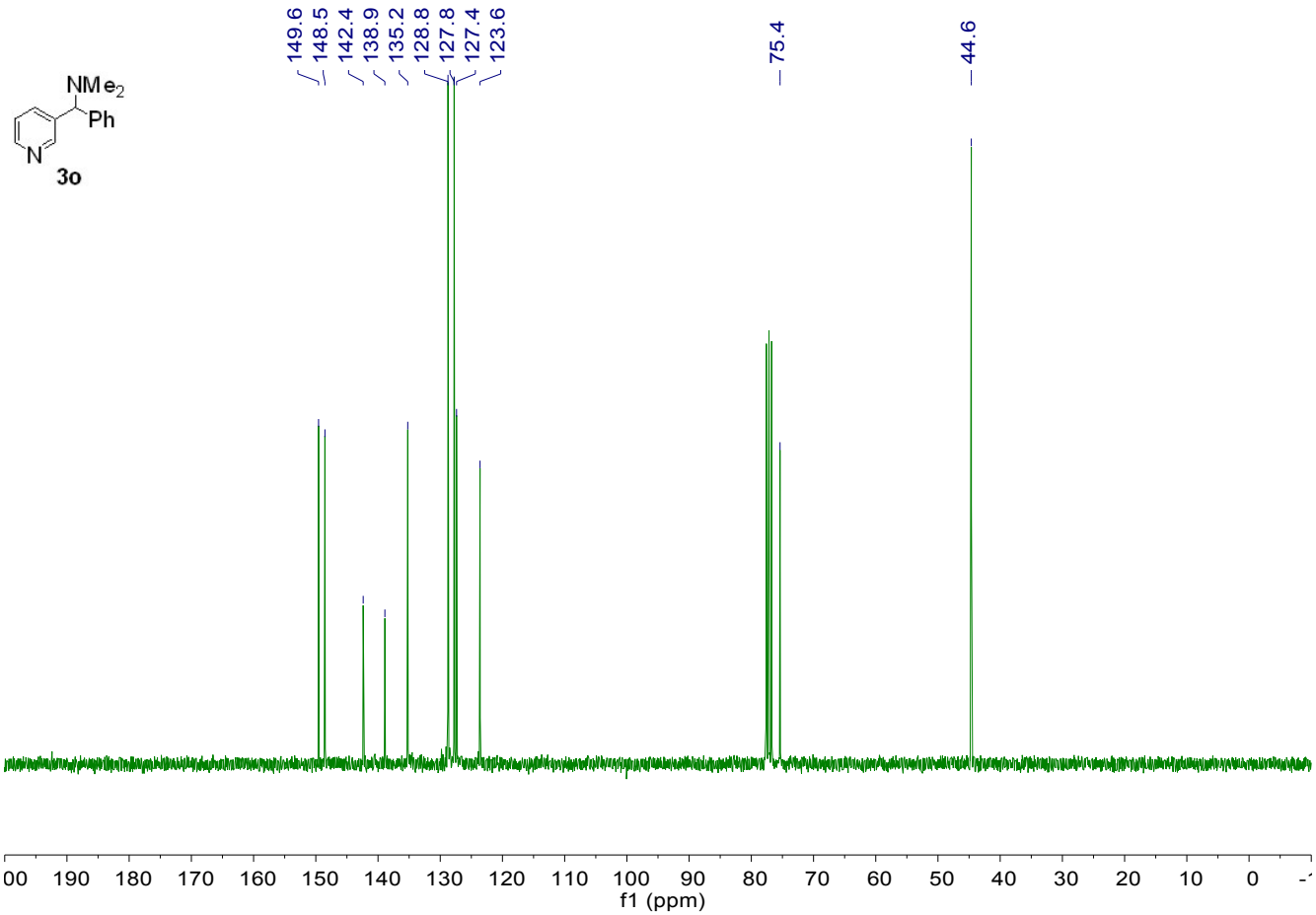
^{1}H NMR of **3n**, 300 MHz in $CDCl_3$



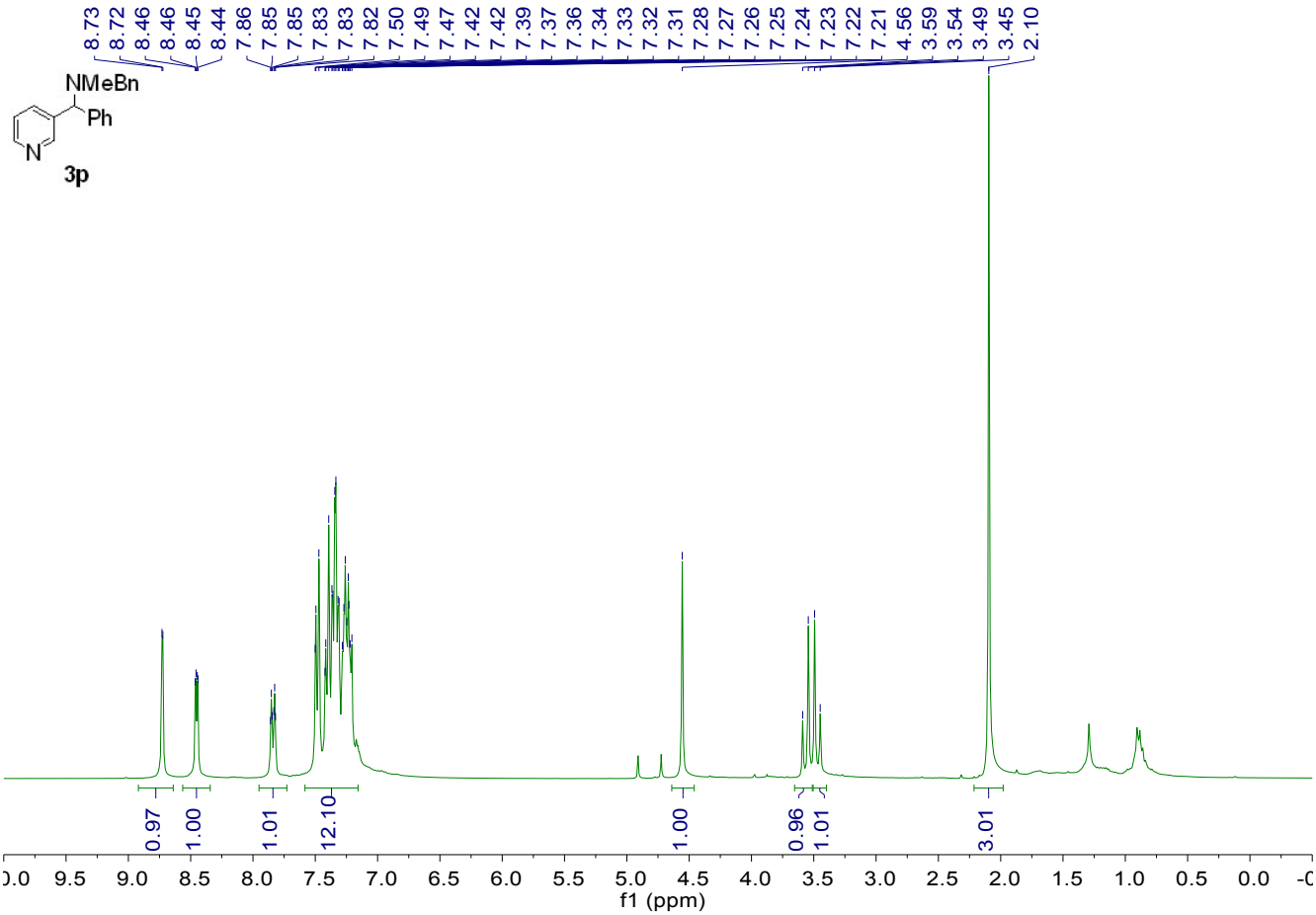
^{13}C NMR of **3n**, 75 MHz in $CDCl_3$



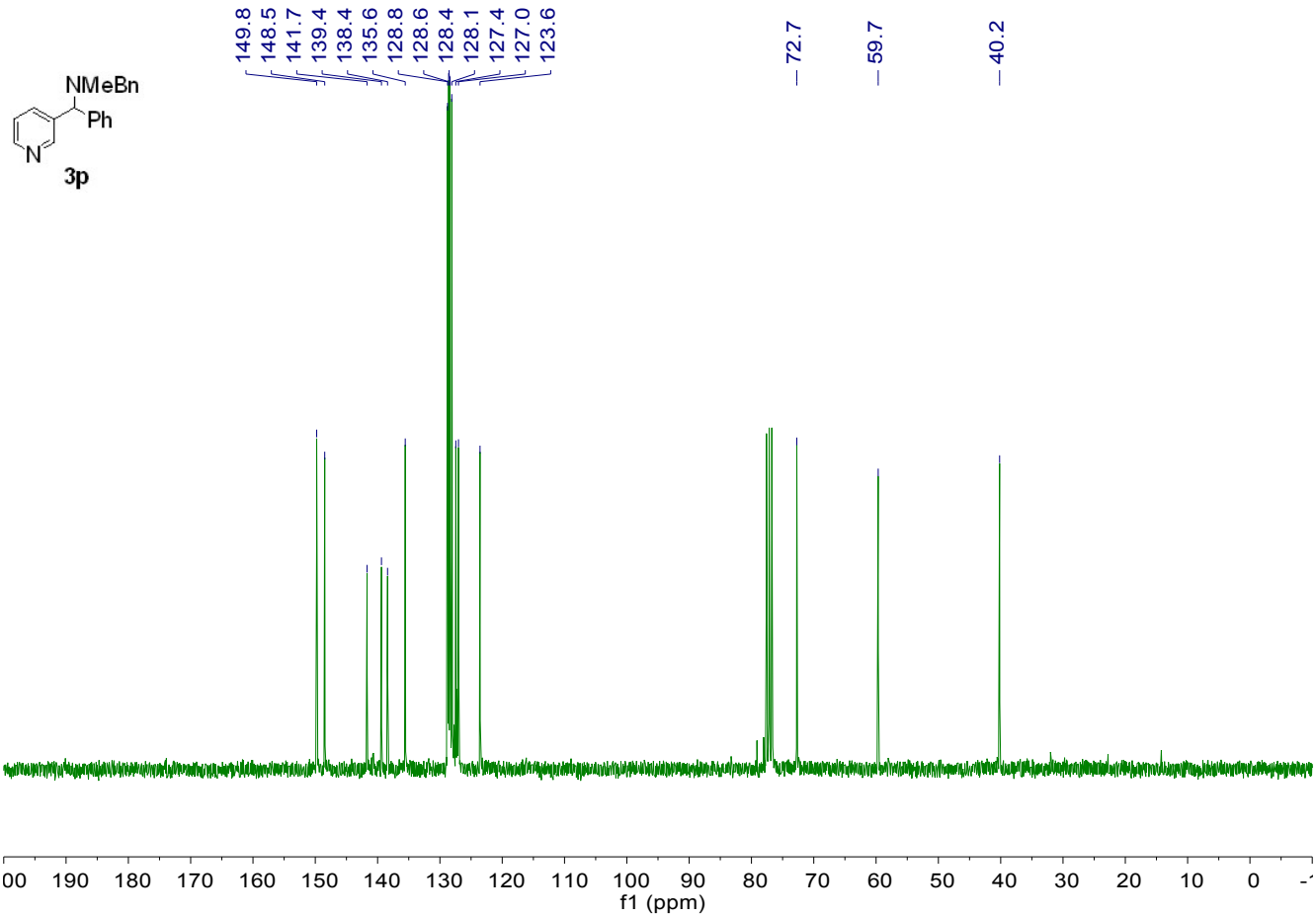
^{1}H NMR of **3o**, 300 MHz in $CDCl_3$



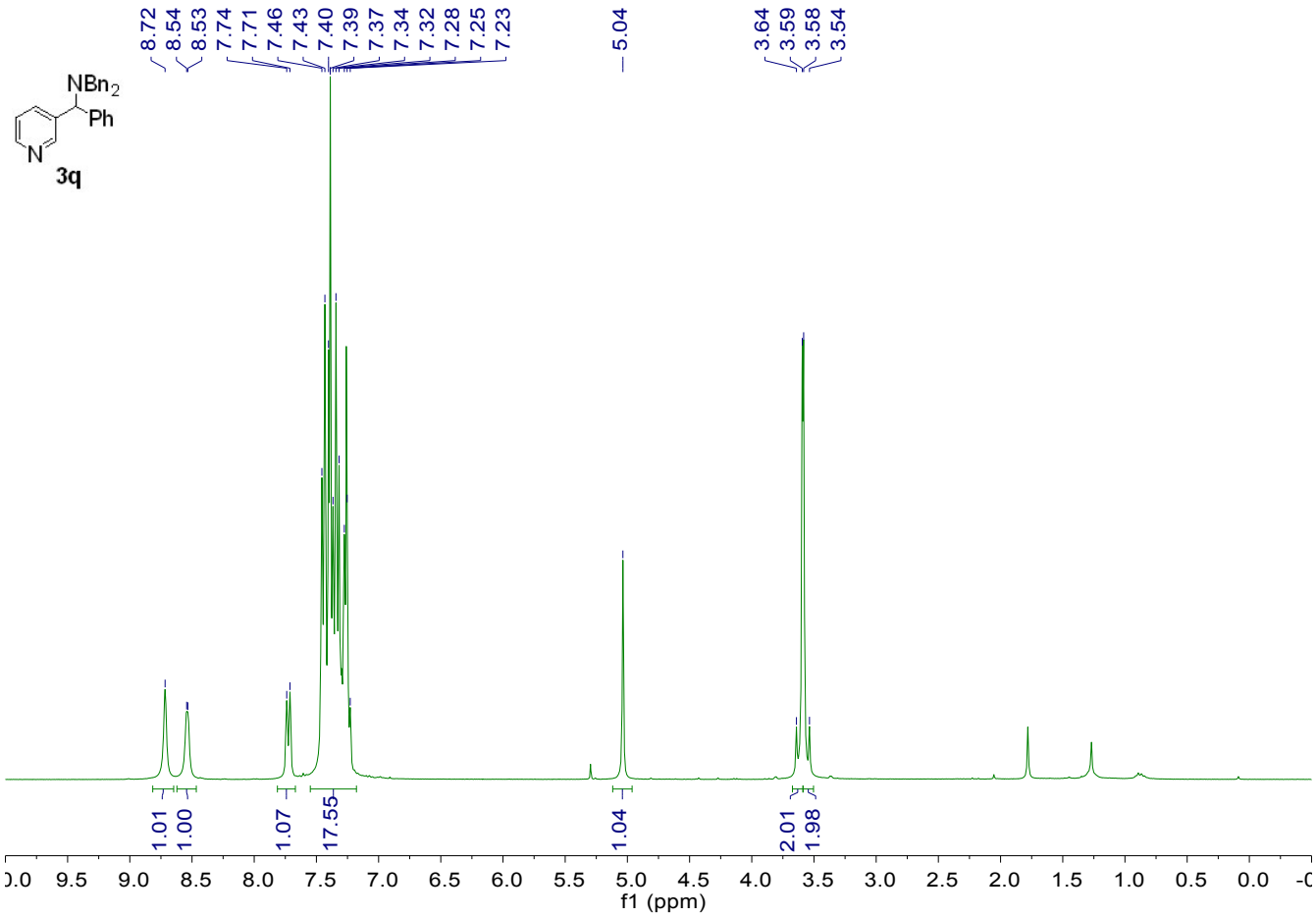
^{13}C NMR of **3o**, 75 MHz in $CDCl_3$



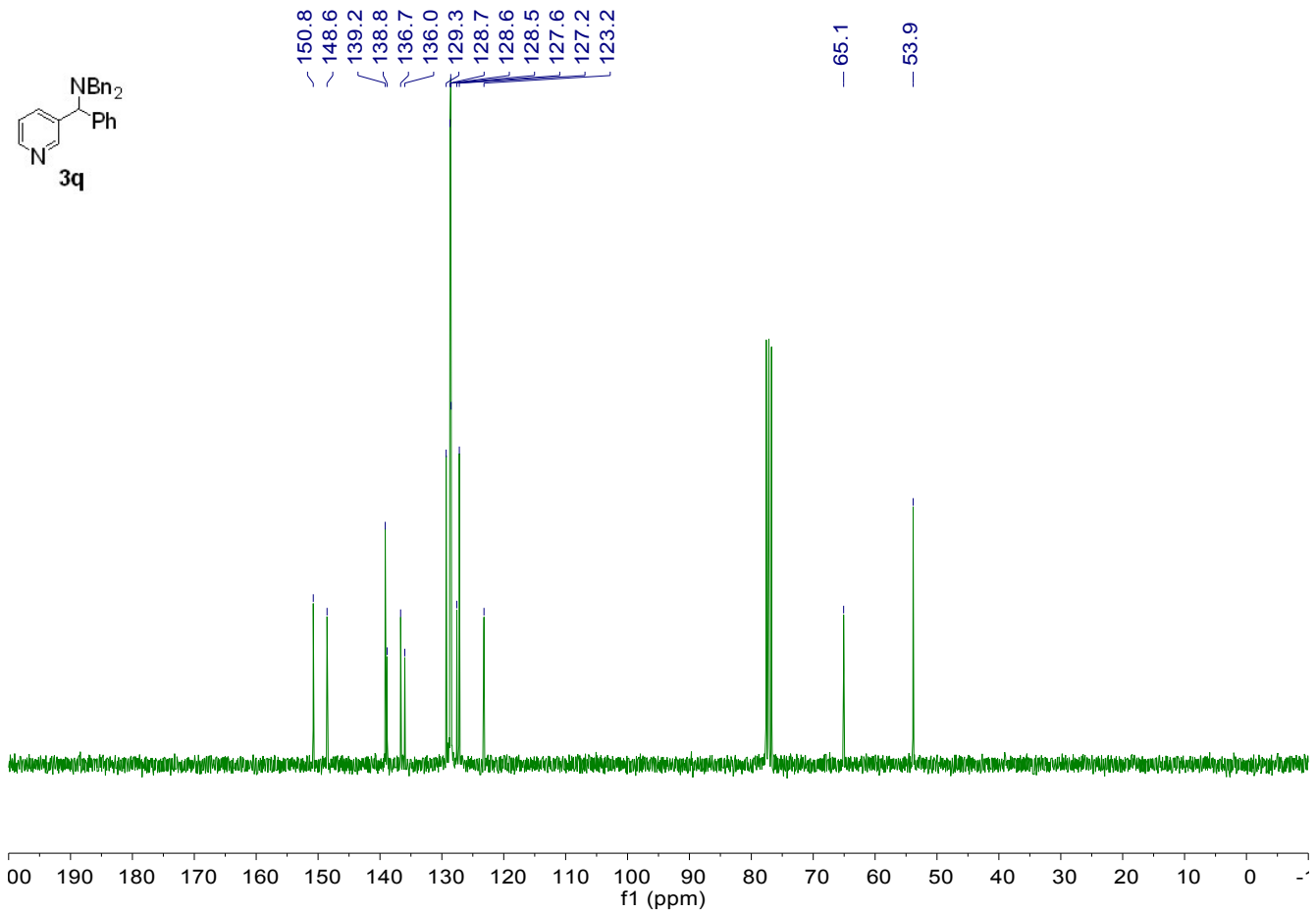
^{1}H NMR of **3p**, 300 MHz in $CDCl_3$



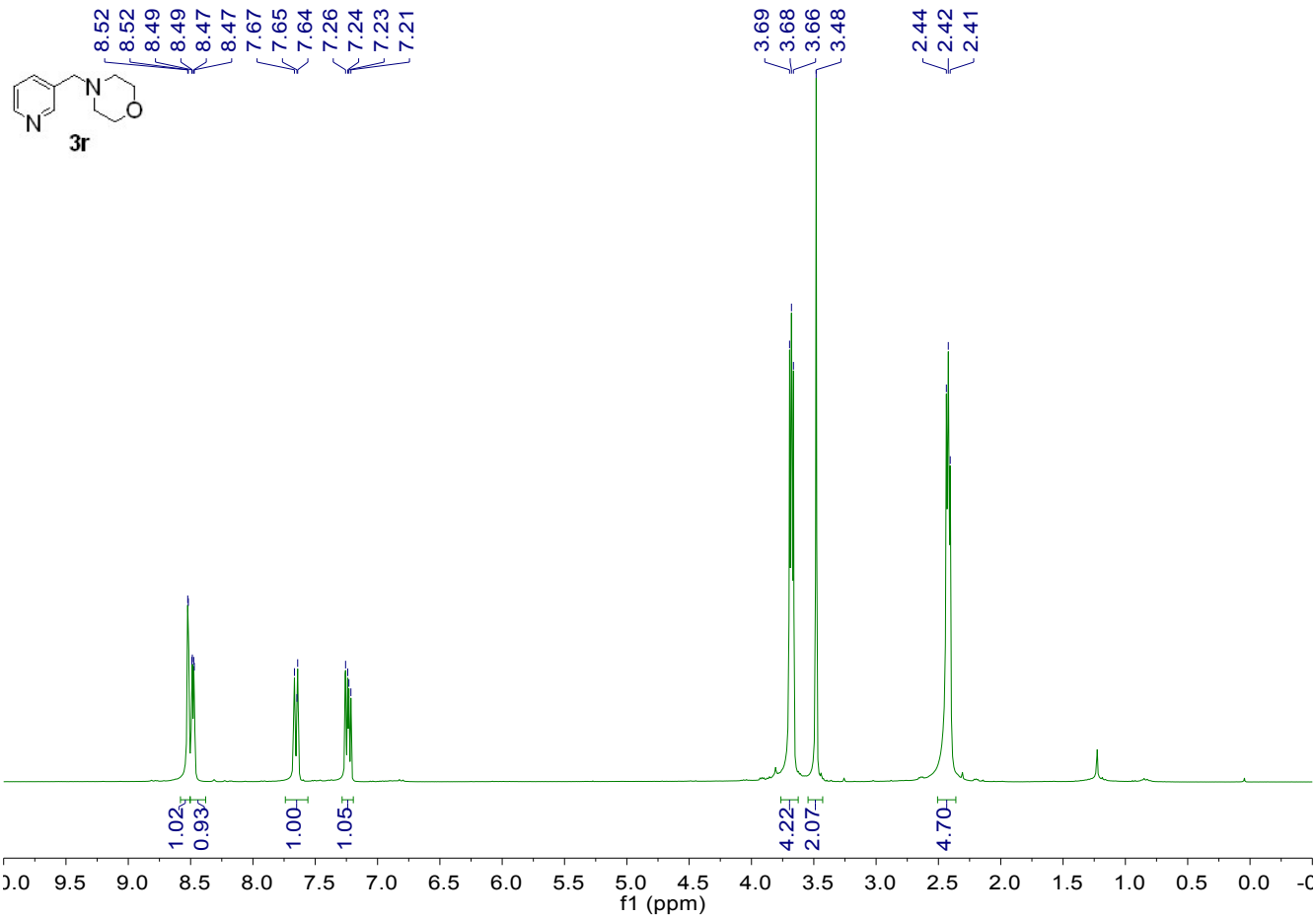
^{13}C NMR of **3p**, 75 MHz in $CDCl_3$



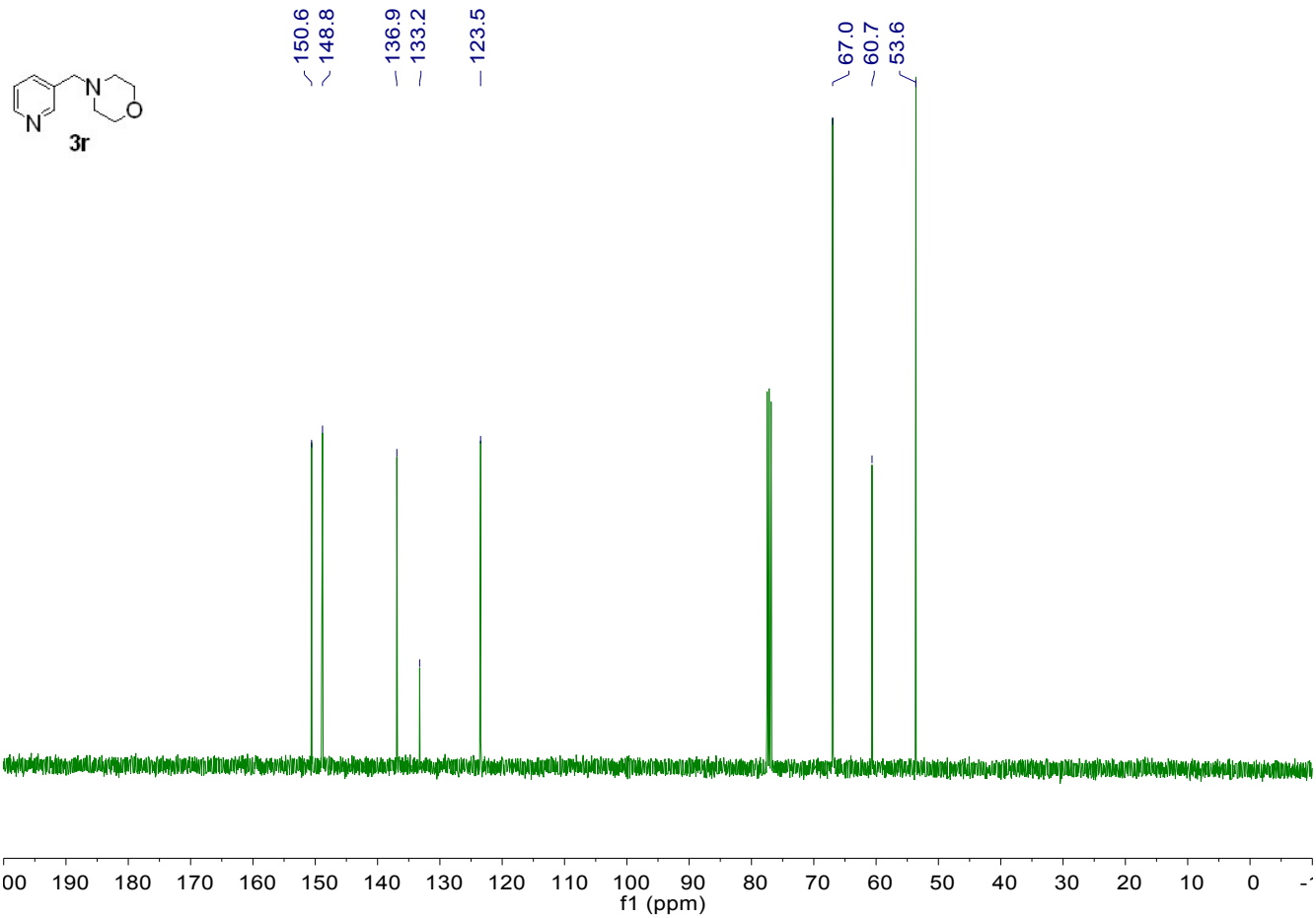
^{1}H NMR of **3q**, 300 MHz in $CDCl_3$



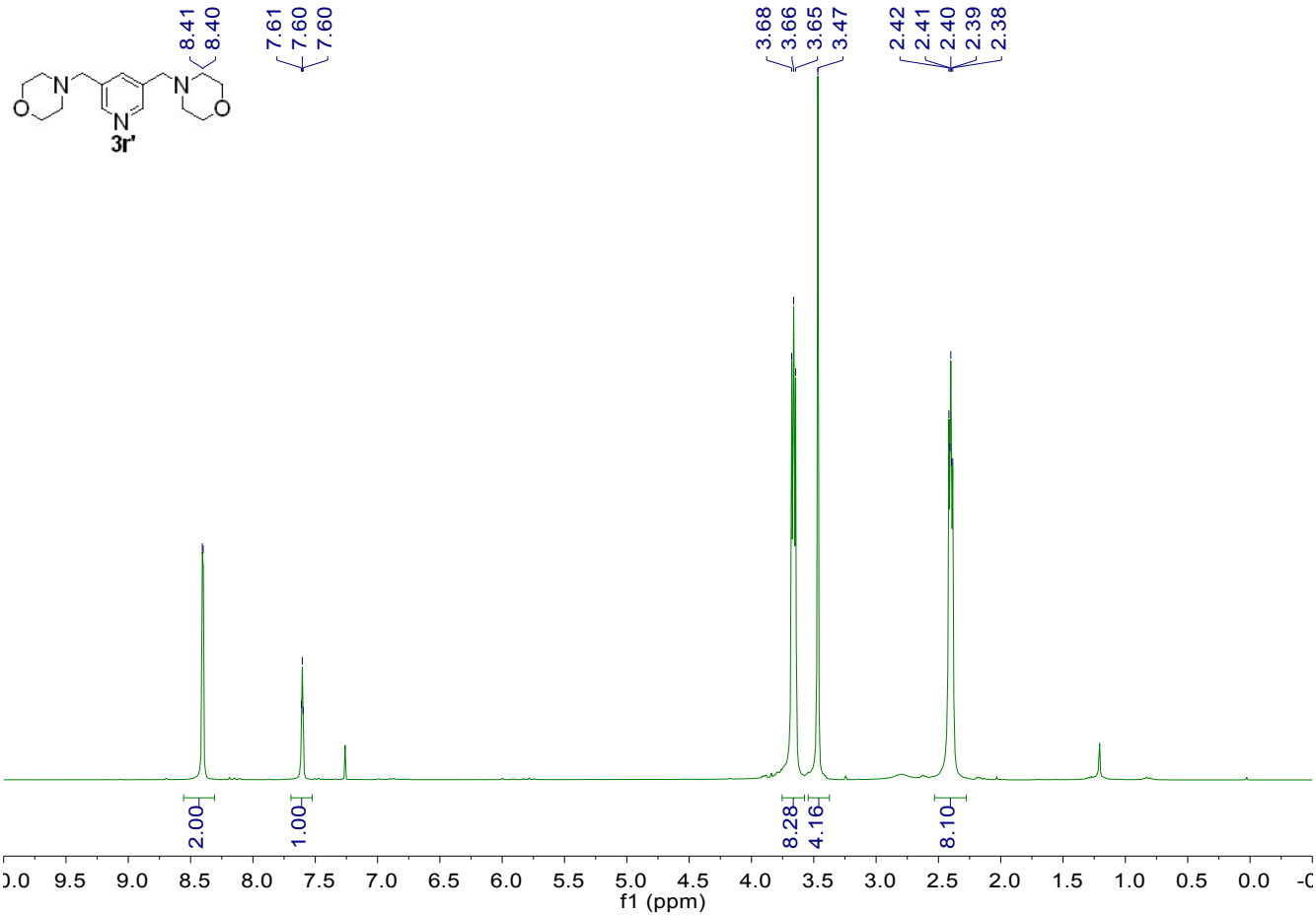
^{13}C NMR of **3q**, 75 MHz in $CDCl_3$



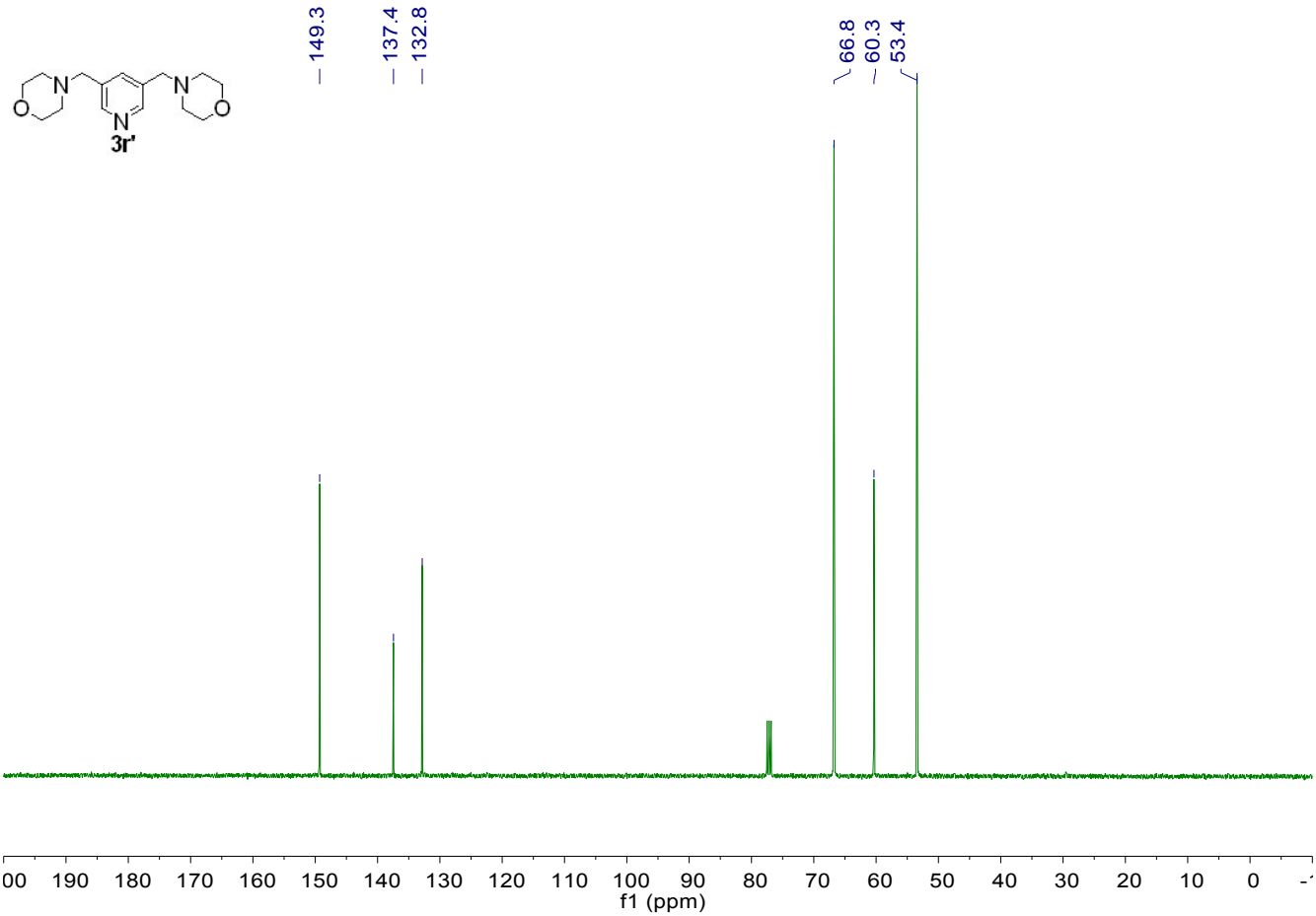
^{1}H NMR of **3r**, 300 MHz in $CDCl_3$



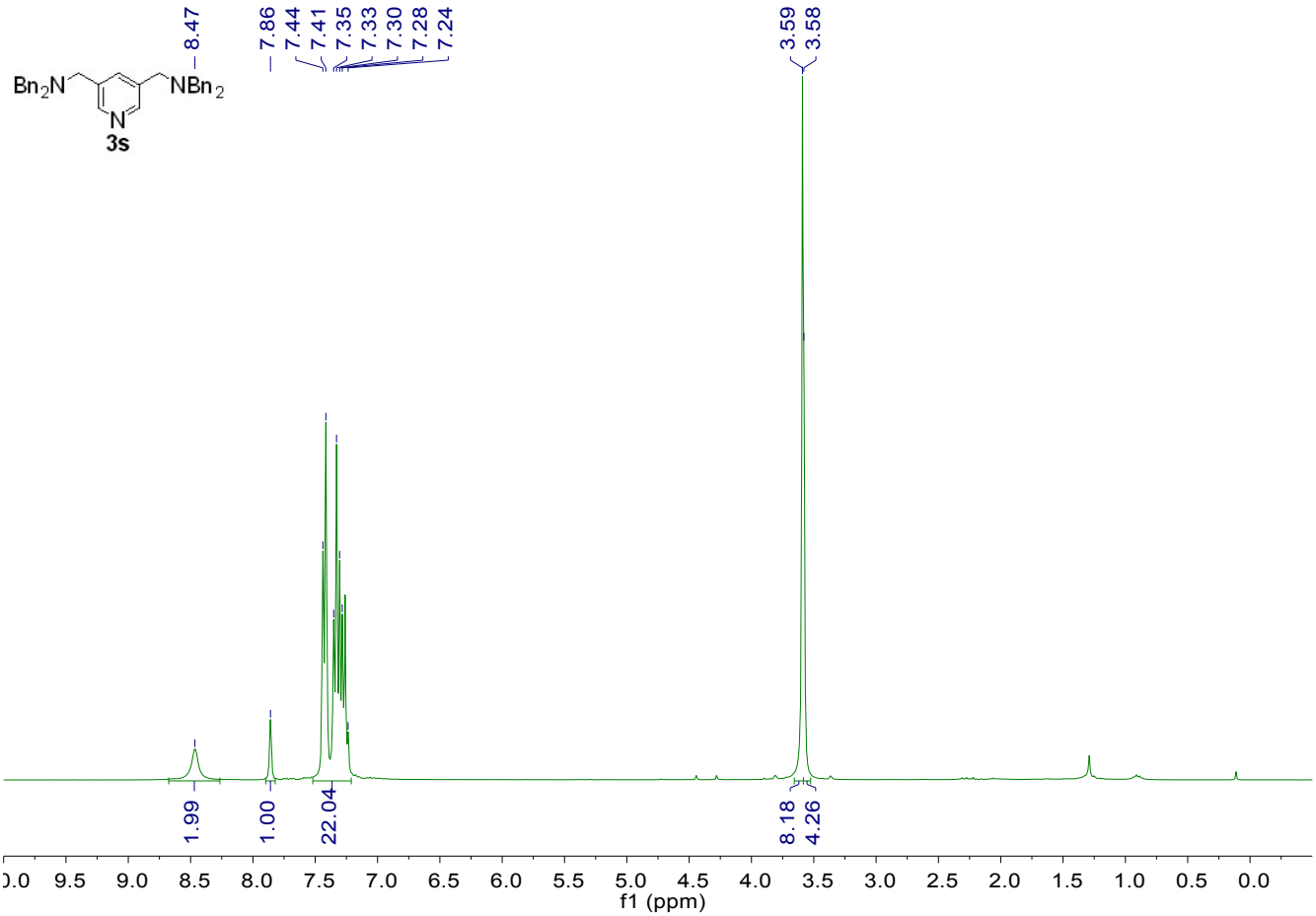
^{13}C NMR of **3r**, 100 MHz in $CDCl_3$



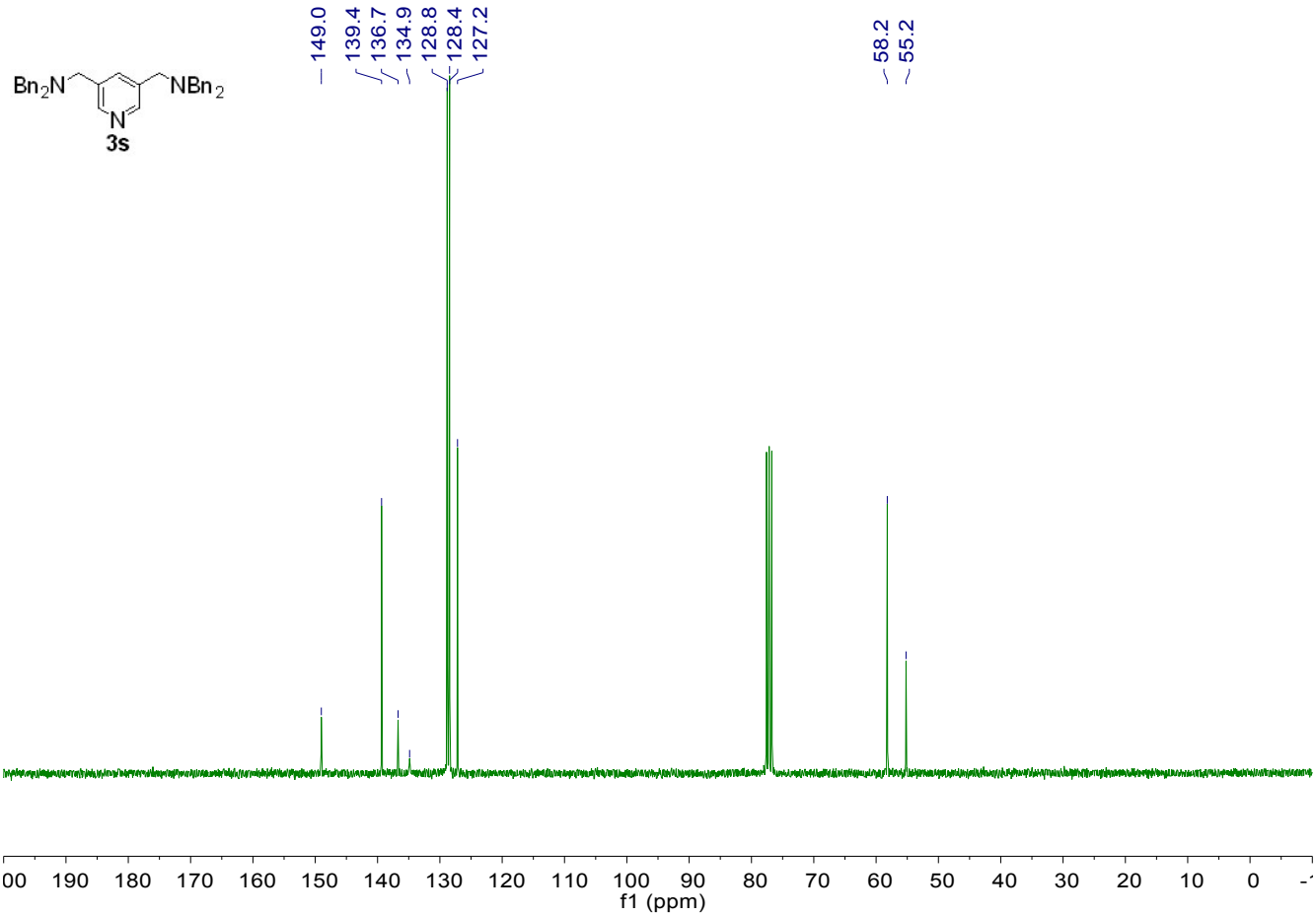
^{1}H NMR of **3r'**, 300 MHz in $CDCl_3$



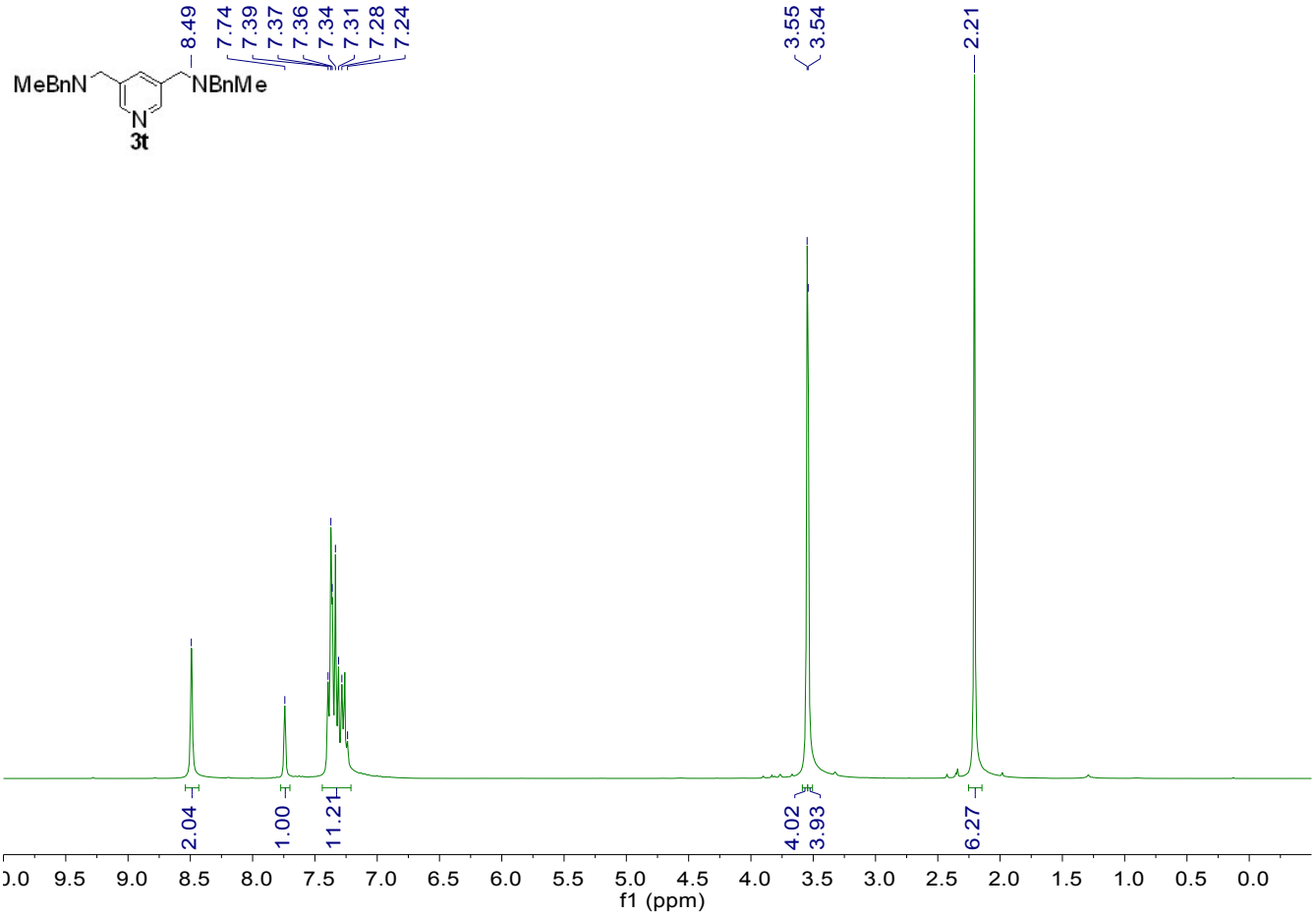
^{13}C NMR of **3r'**, 100 MHz in $CDCl_3$



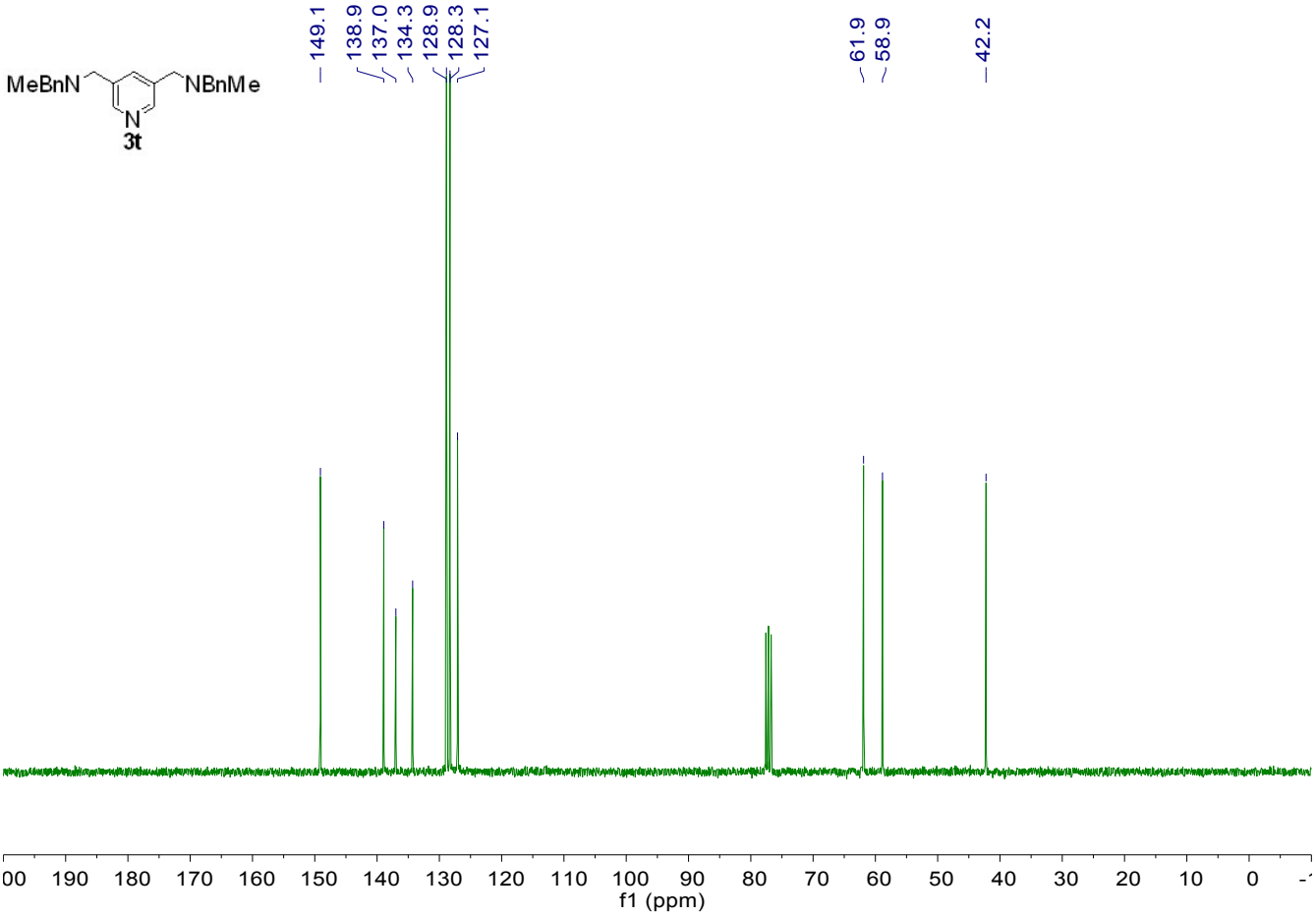
^{1}H NMR of **3s**, 300 MHz in $CDCl_3$



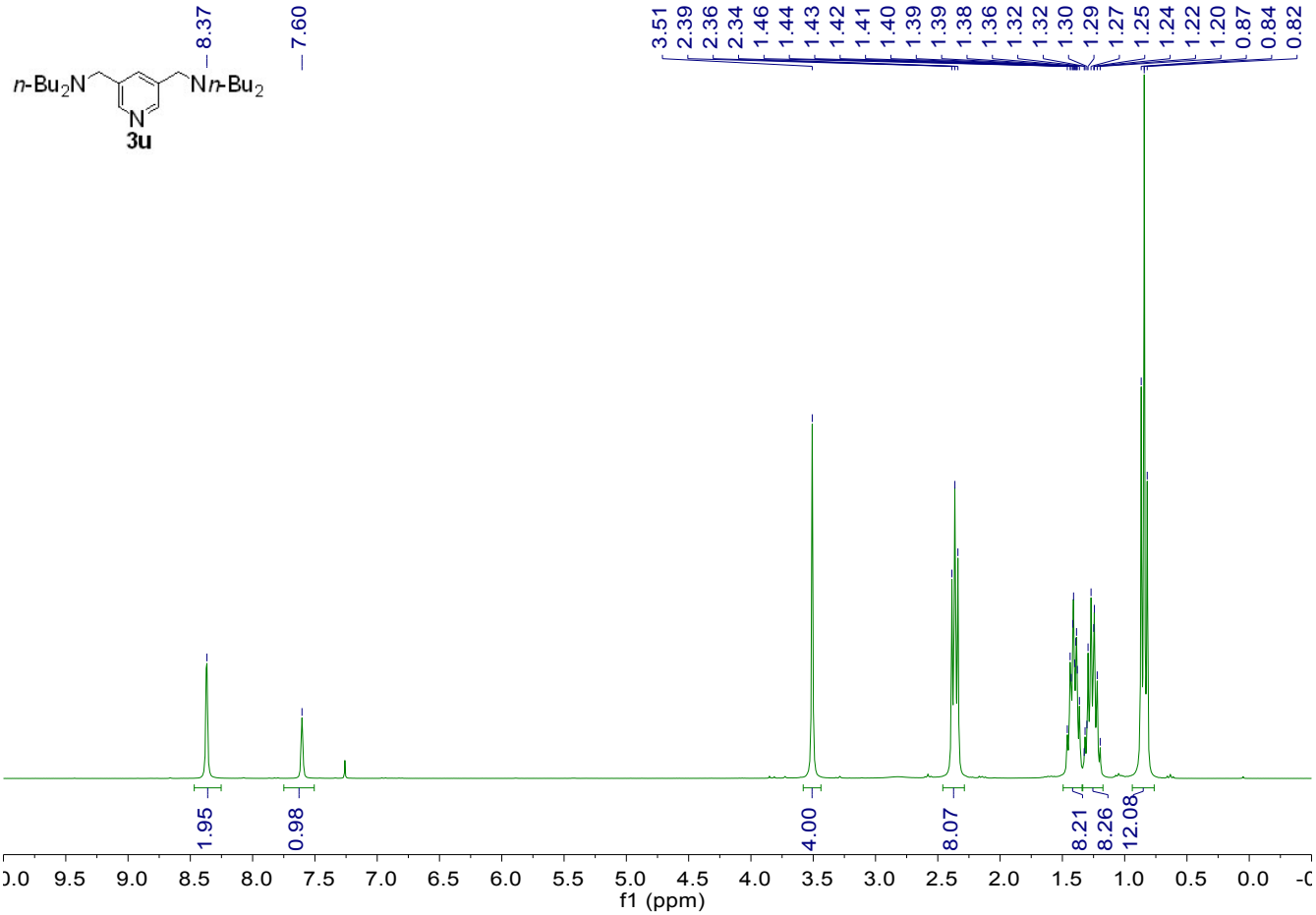
^{13}C NMR of **3s**, 75 MHz in $CDCl_3$



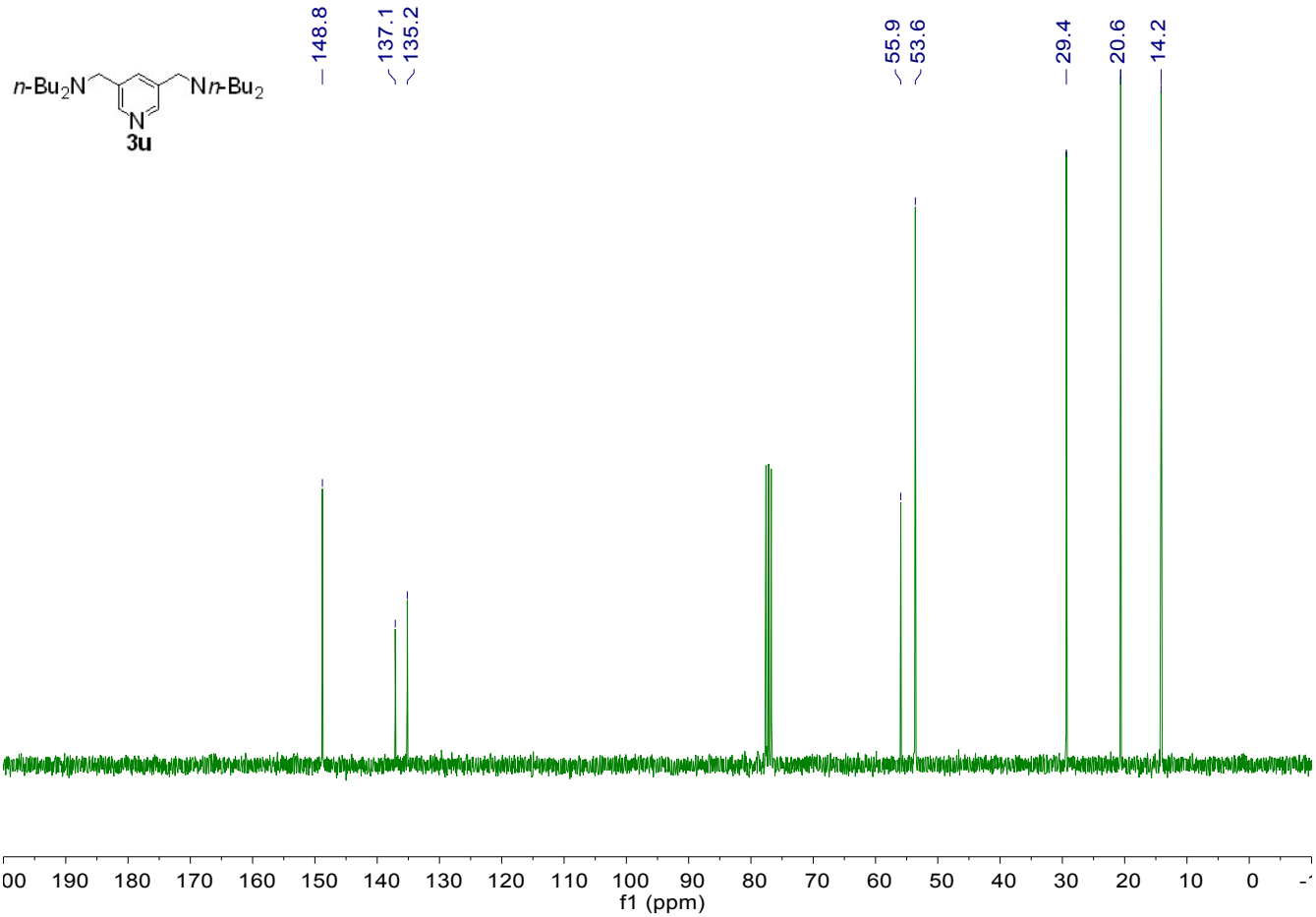
^{1}H NMR of **3t**, 300 MHz in $CDCl_3$



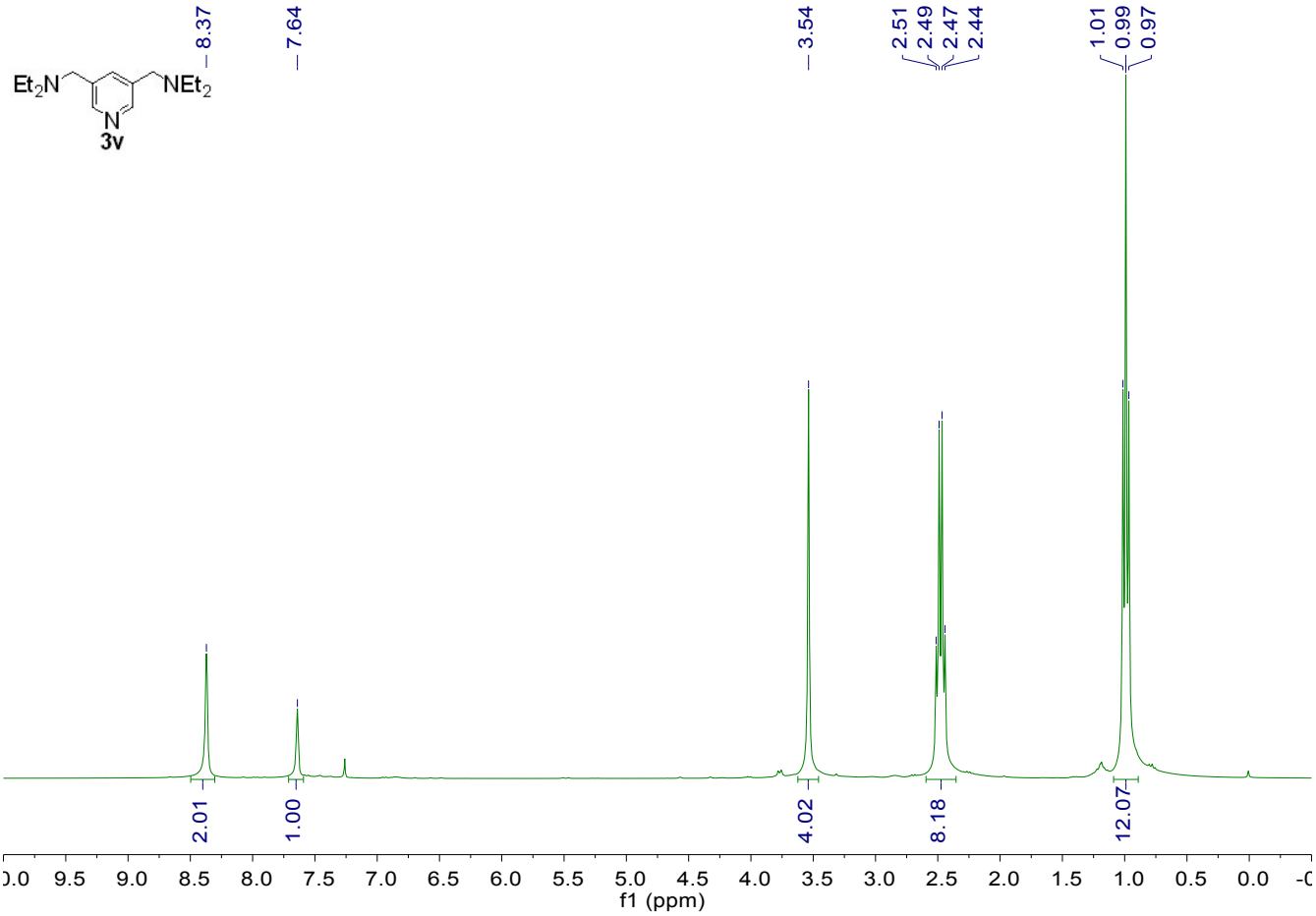
^{13}C NMR of **3t**, 75 MHz in $CDCl_3$



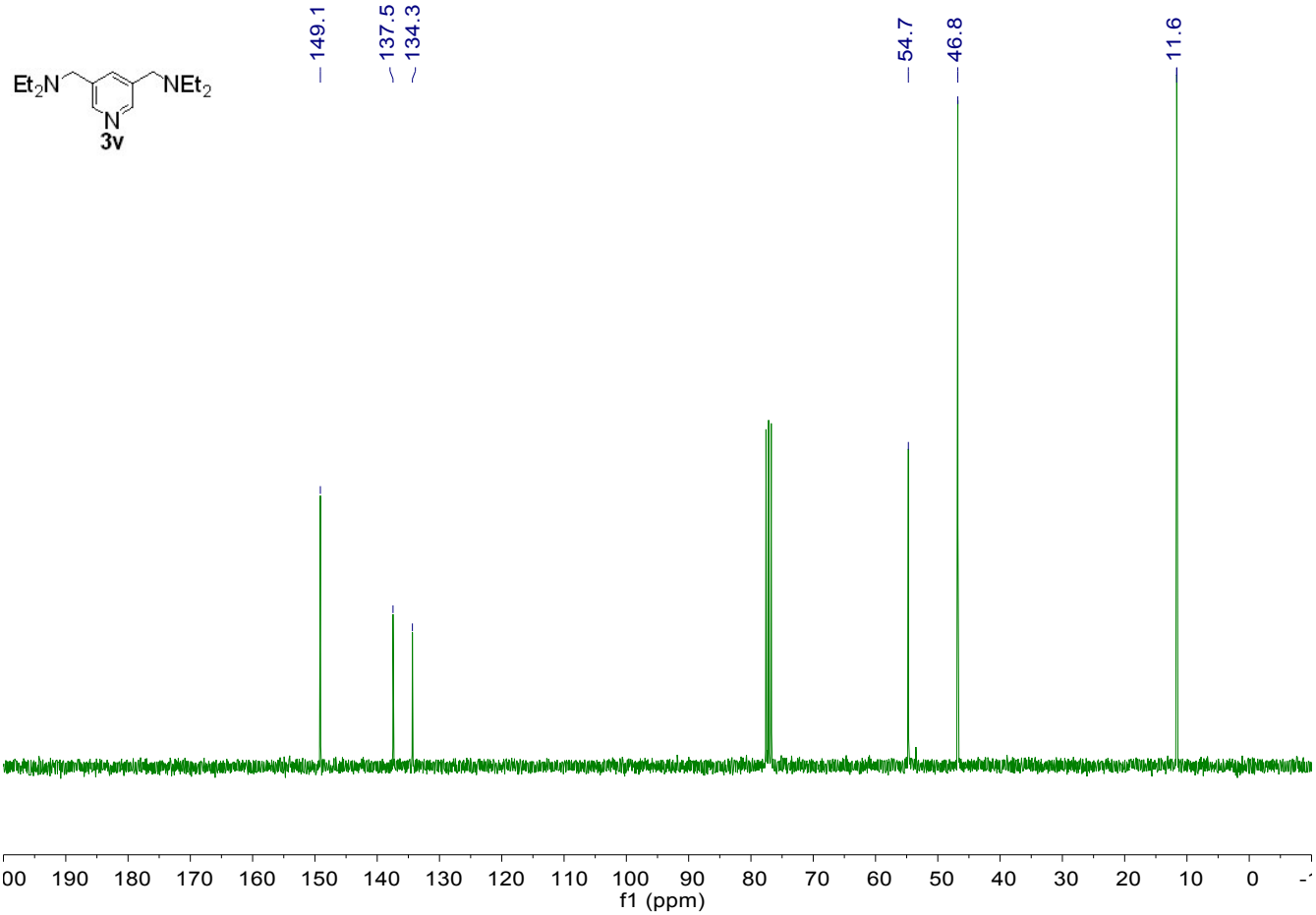
^{1}H NMR of **3u**, 300 MHz in $CDCl_3$



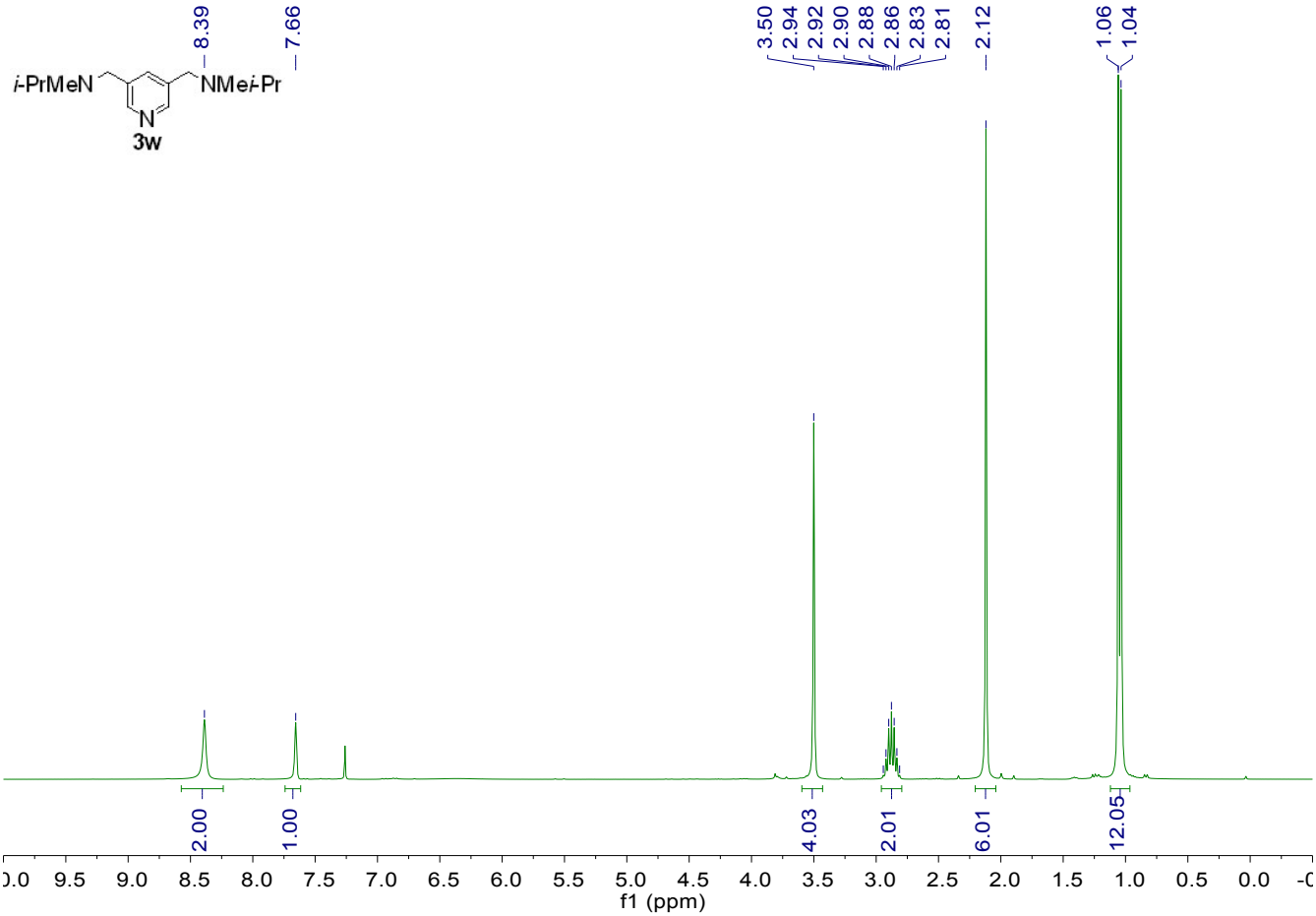
^{13}C NMR of **3u**, 75 MHz in $CDCl_3$



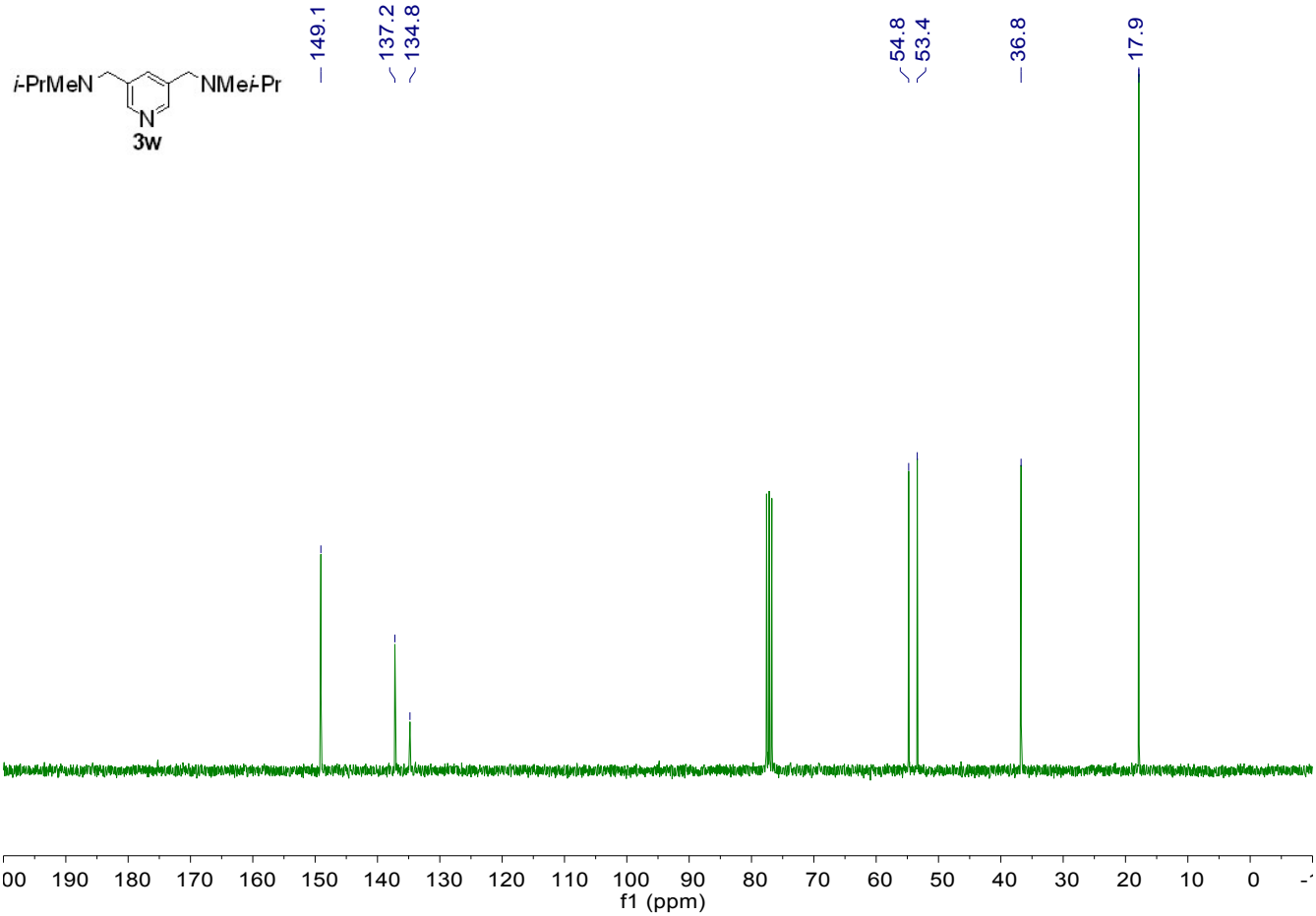
^{1}H NMR of **3v**, 300 MHz in $CDCl_3$



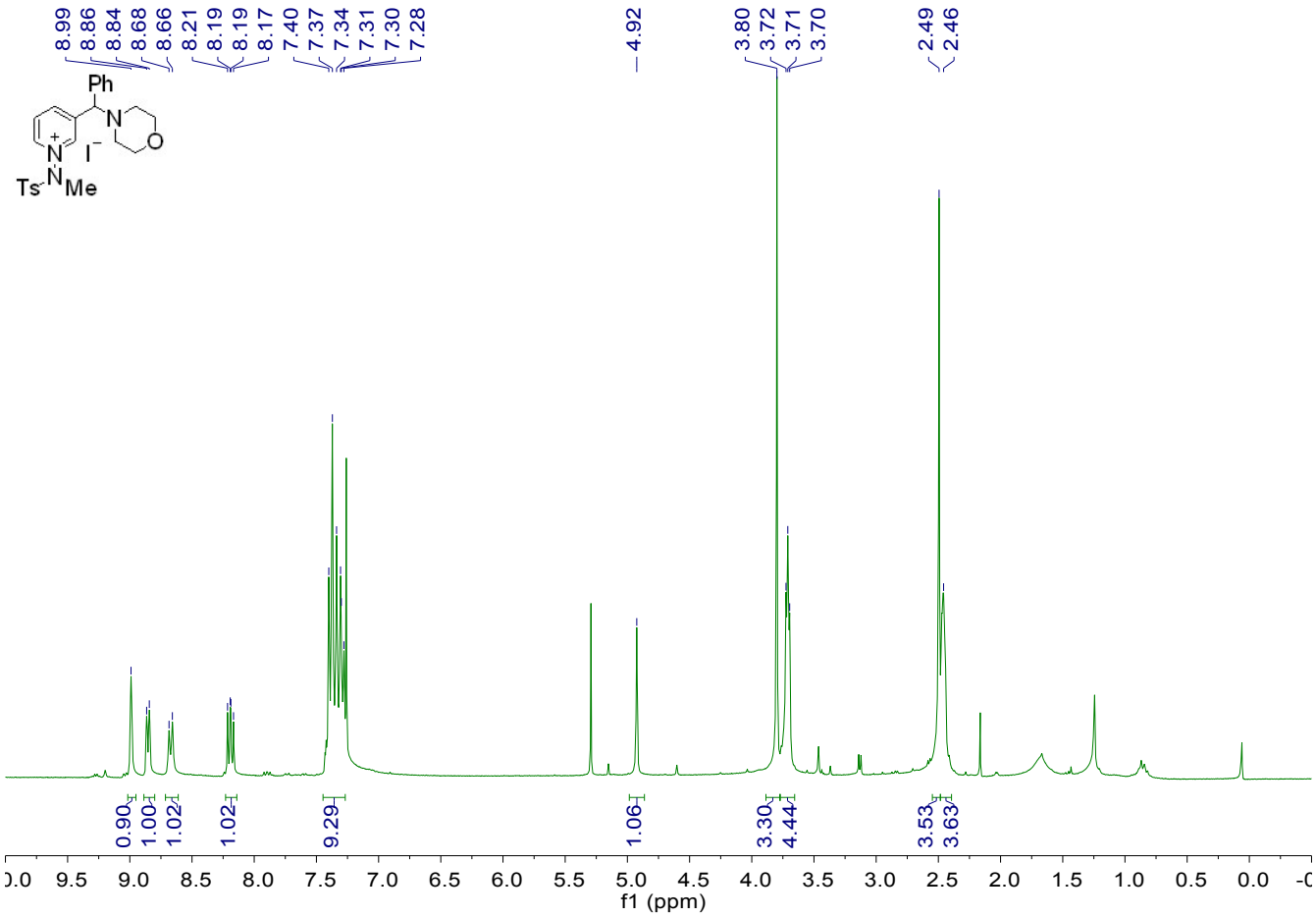
^{13}C NMR of **3v**, 75 MHz in $CDCl_3$



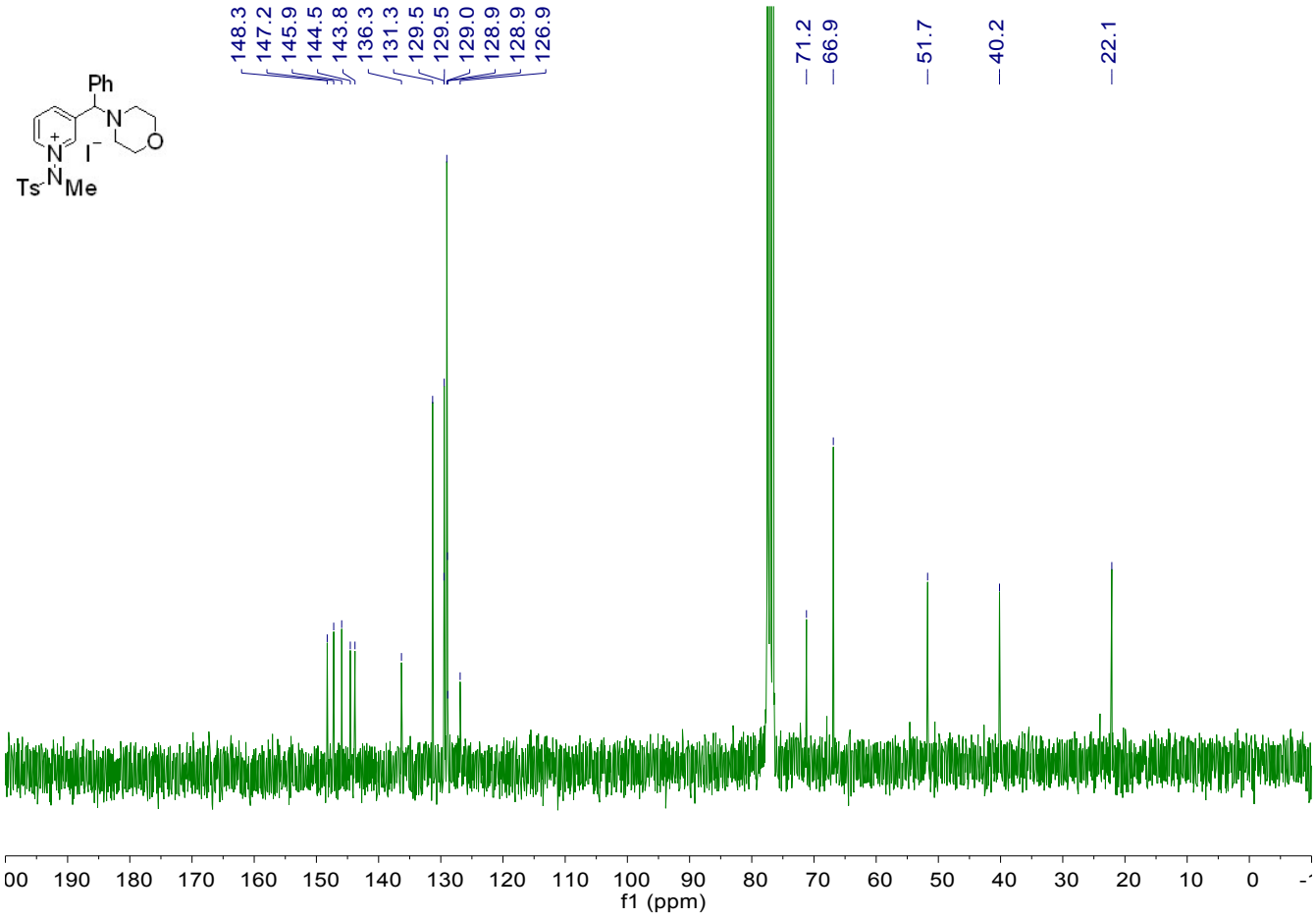
^{1}H NMR of **3w**, 300 MHz in $CDCl_3$



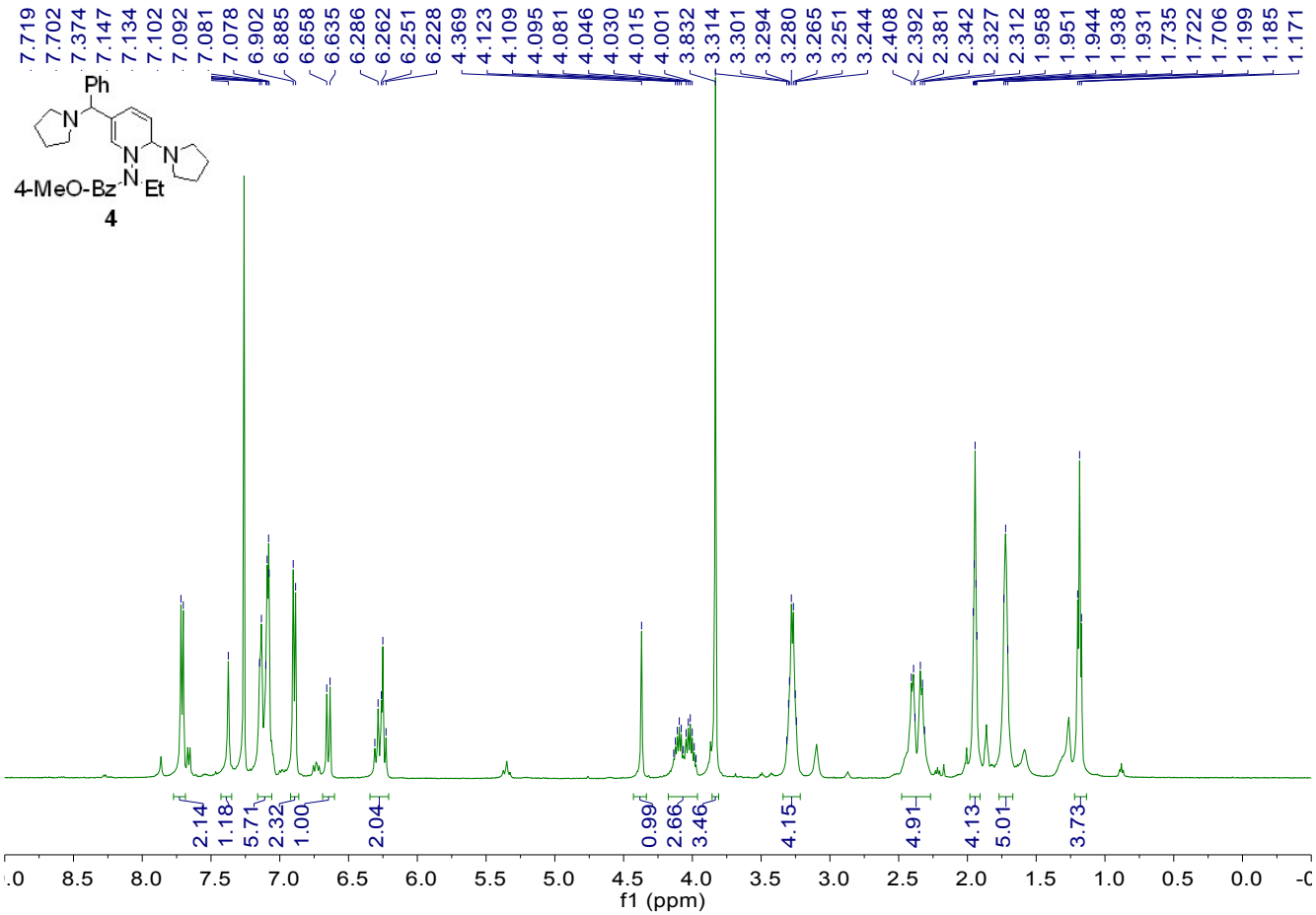
^{13}C NMR of **3w**, 75 MHz in $CDCl_3$



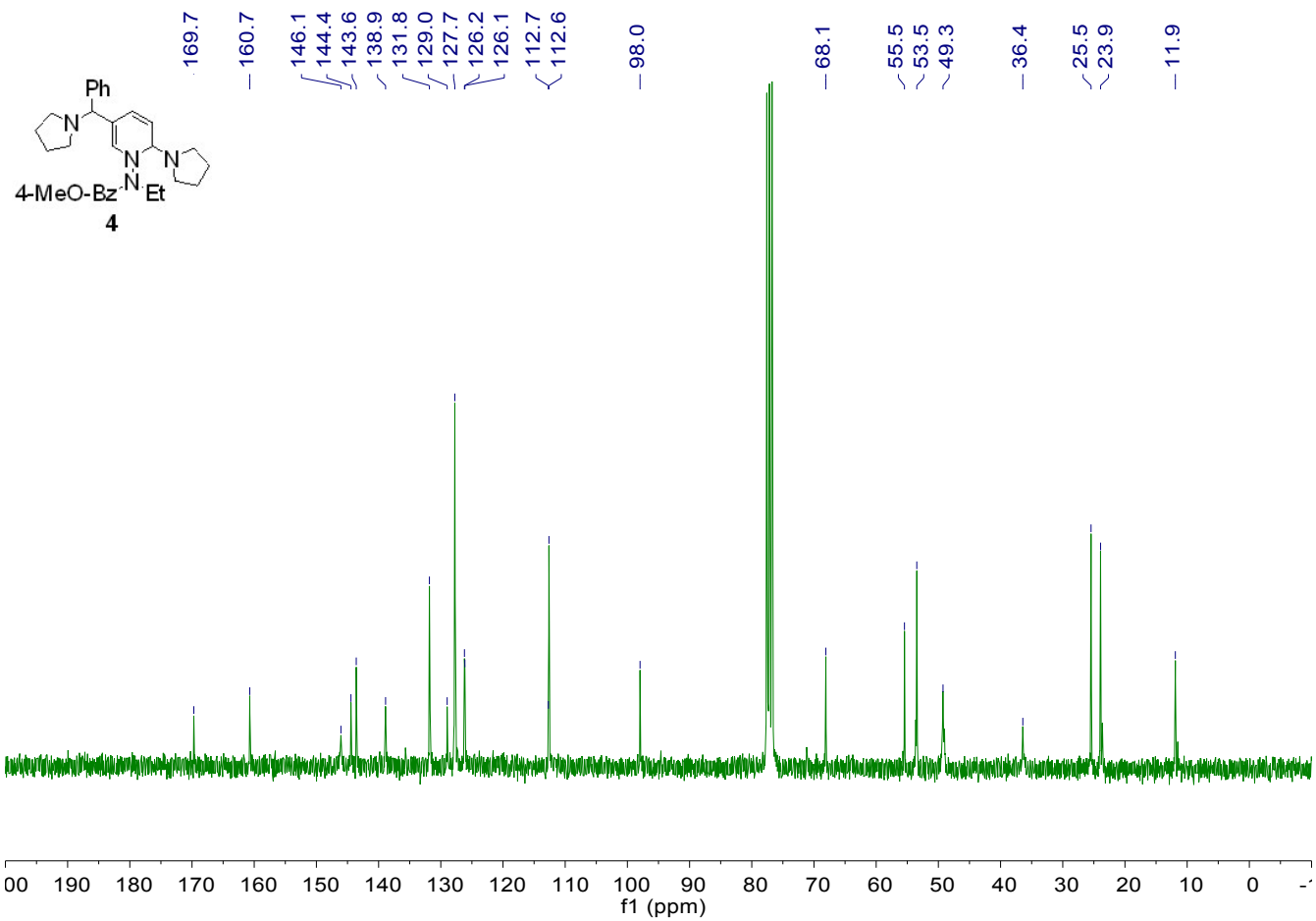
^{1}H NMR, 300 MHz in $CDCl_3$



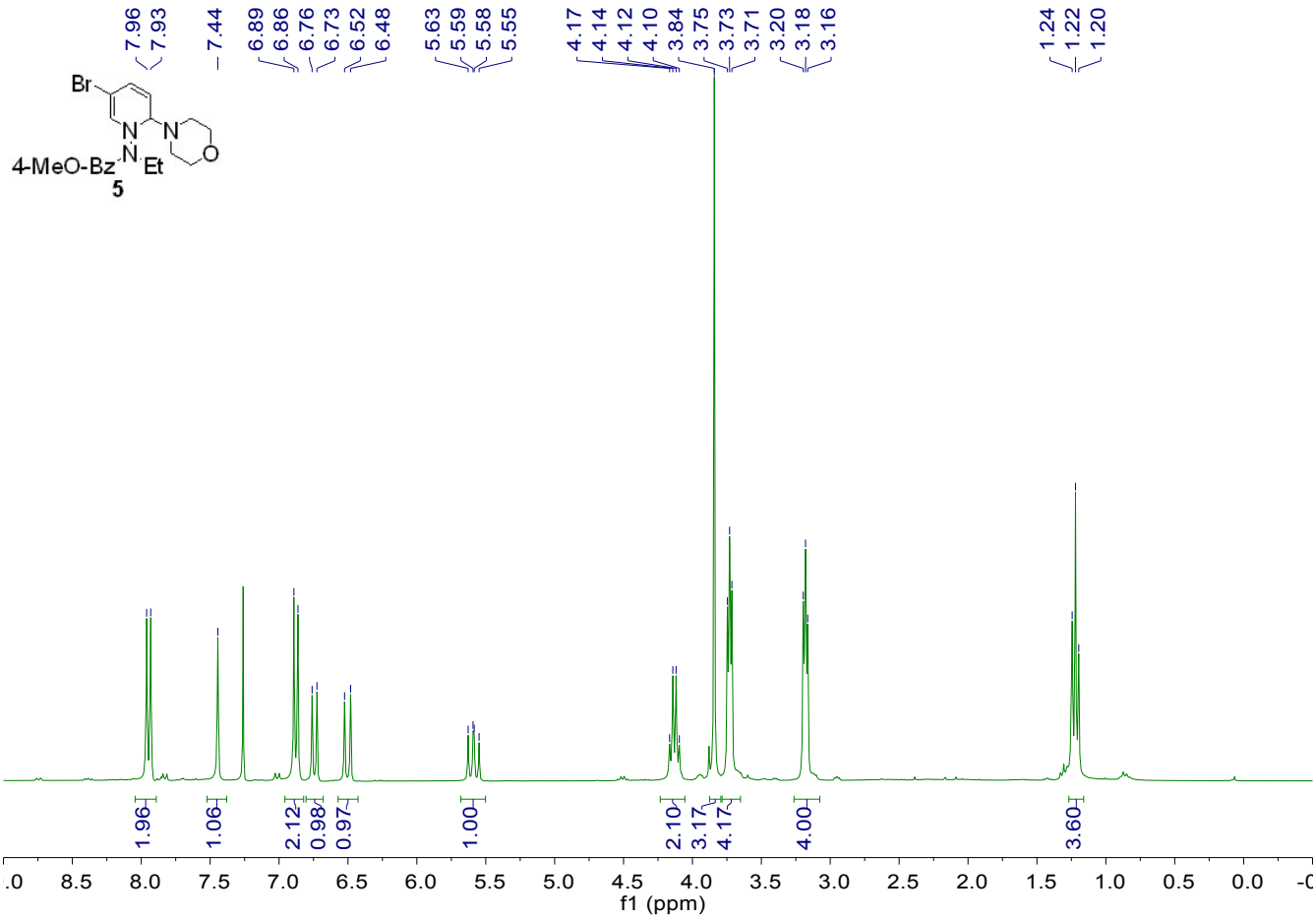
^{13}C NMR, 75 MHz in $CDCl_3$



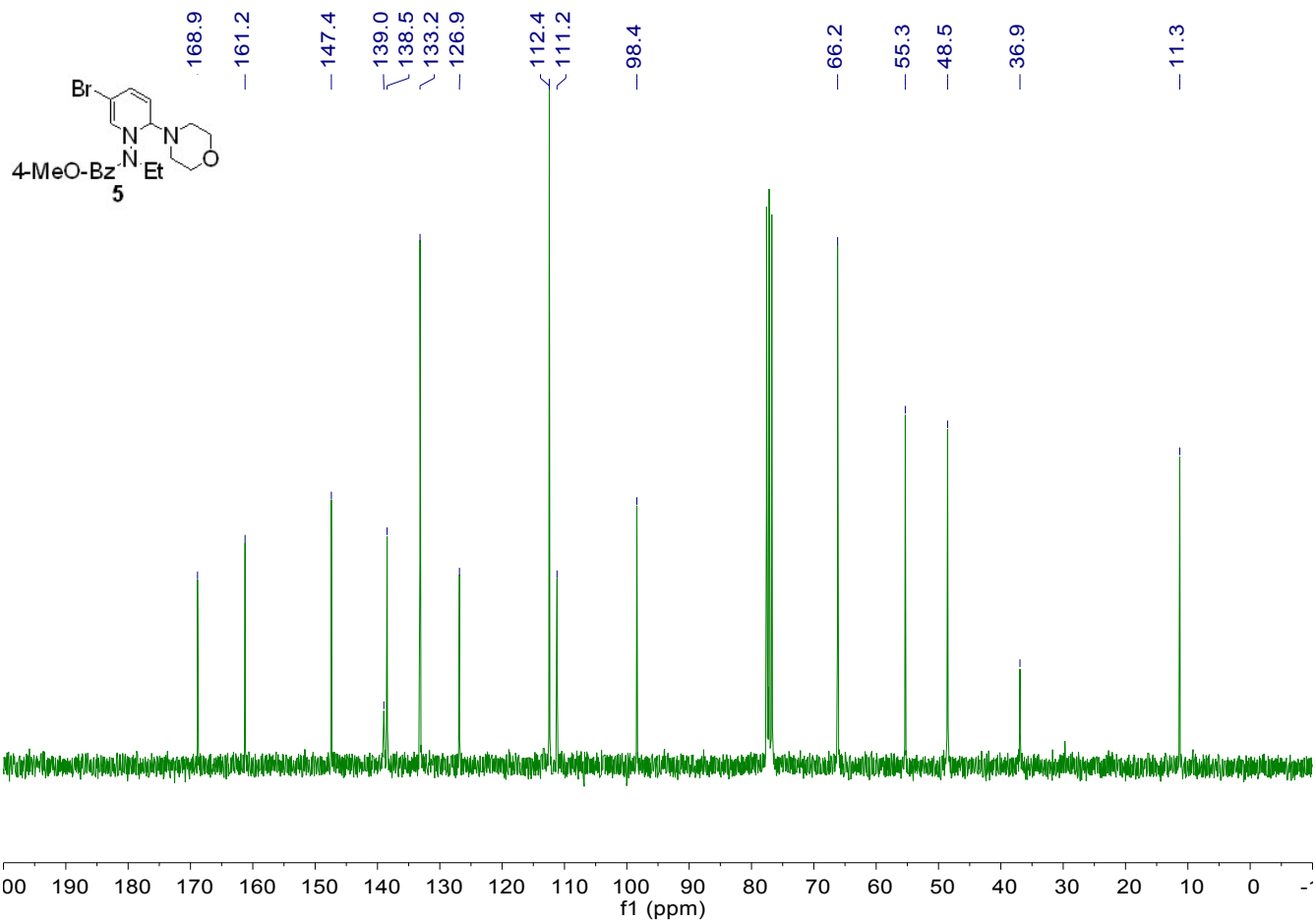
^{1}H NMR of **4**, 500 MHz in $CDCl_3$



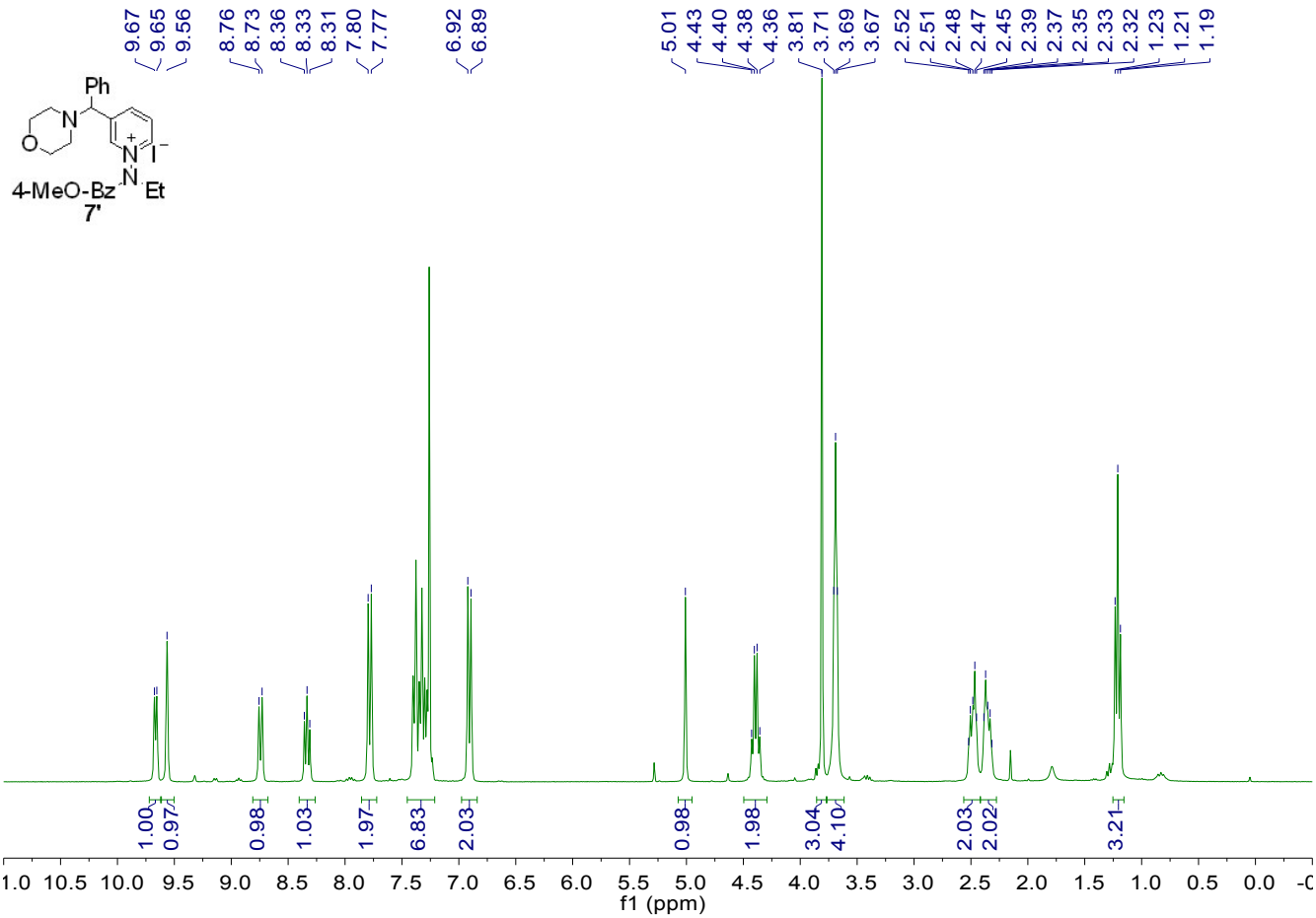
^{13}C NMR of **4**, 75 MHz in $CDCl_3$



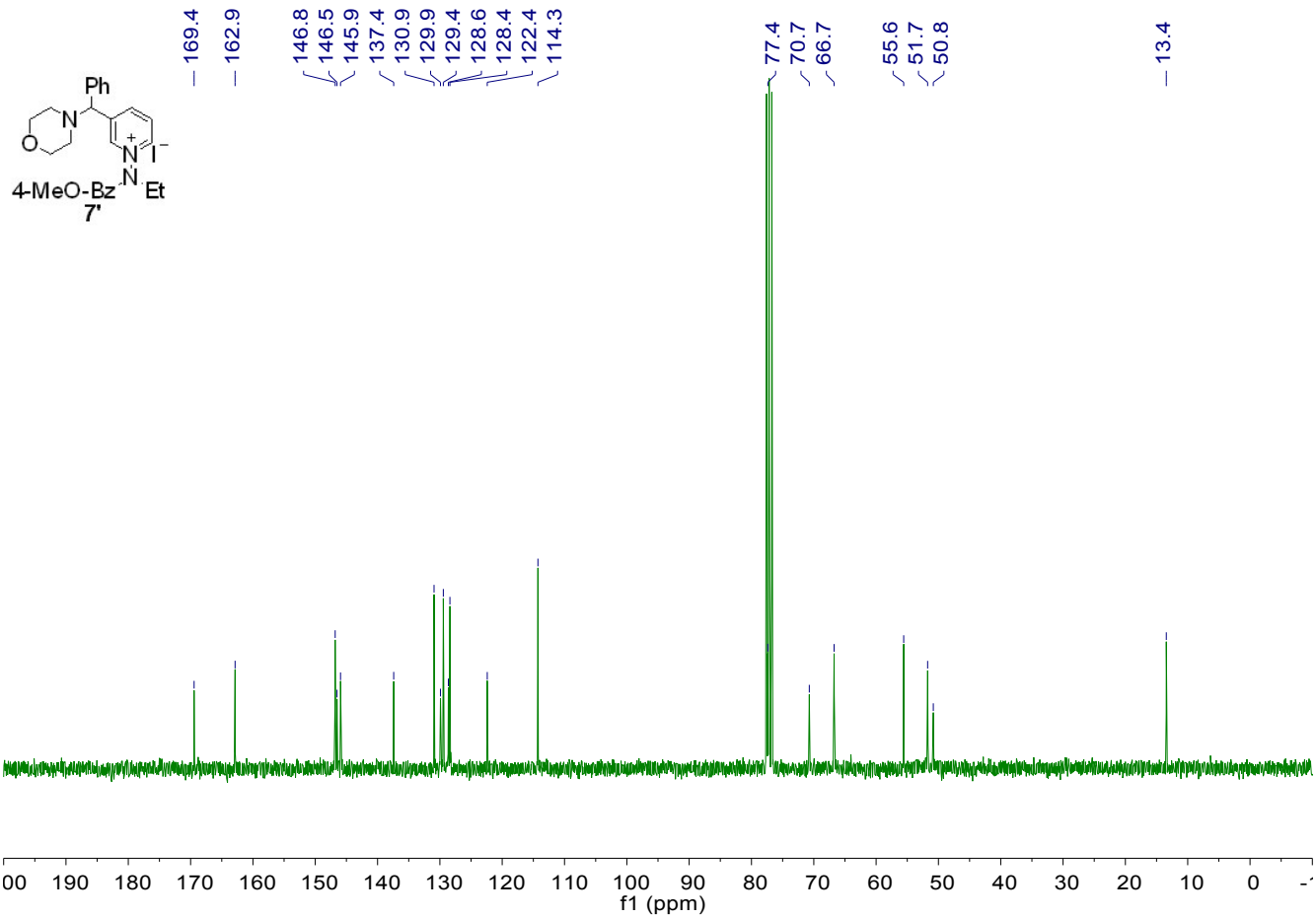
^{1}H NMR of **5**, 300 MHz in $CDCl_3$



^{13}C NMR of **5**, 75 MHz in $CDCl_3$



^{1}H NMR of **7'**, 300 MHz in $CDCl_3$



^{13}C NMR of **7'**, 75 MHz in $CDCl_3$

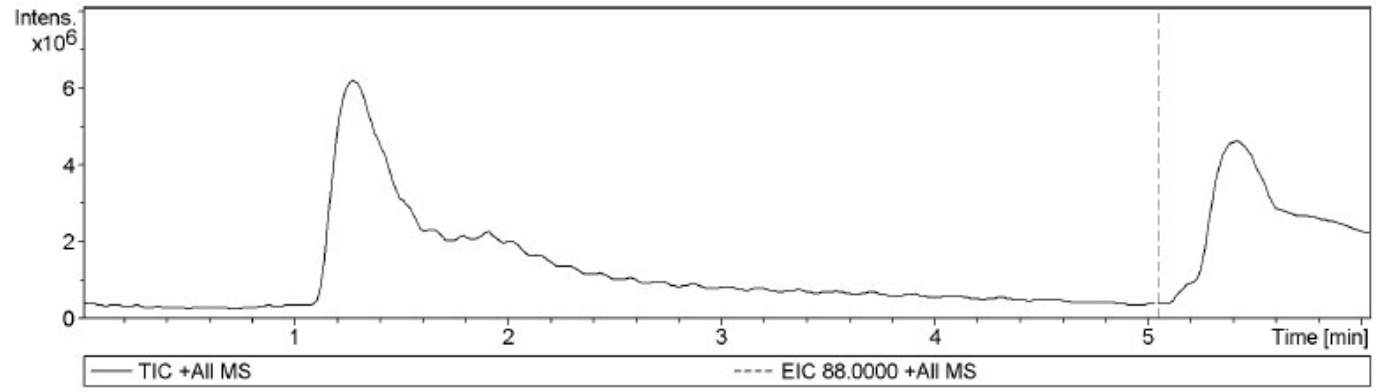
HPLC-HRMS spectrum of reaction mixture

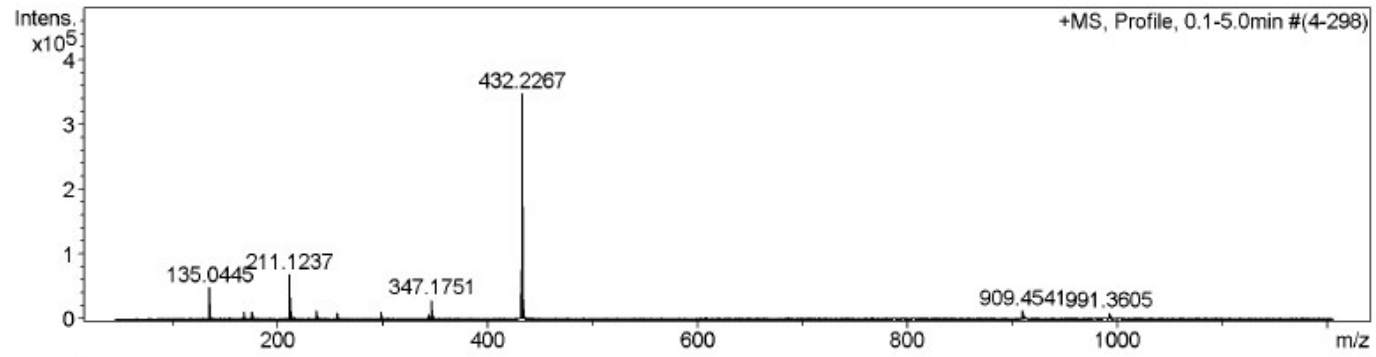
(experiment entry 8, Table 2 in main text)

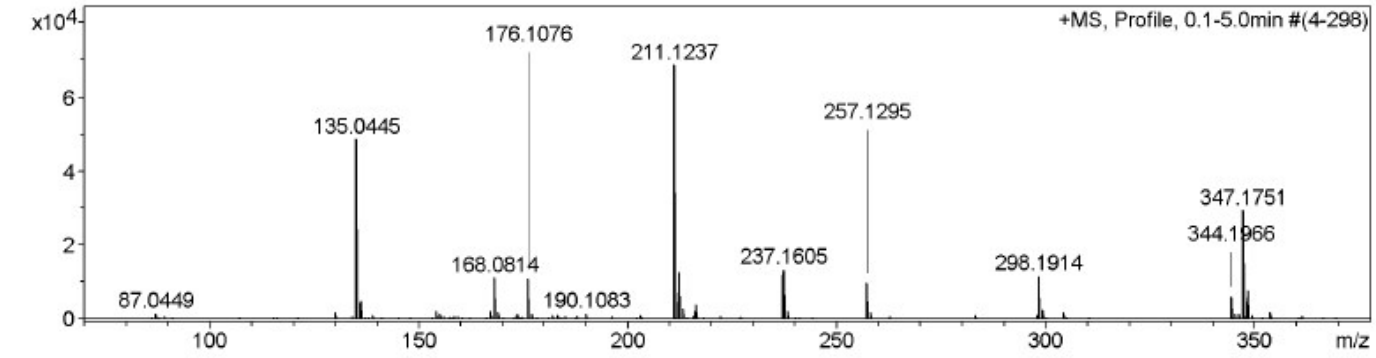
Generic Display Report

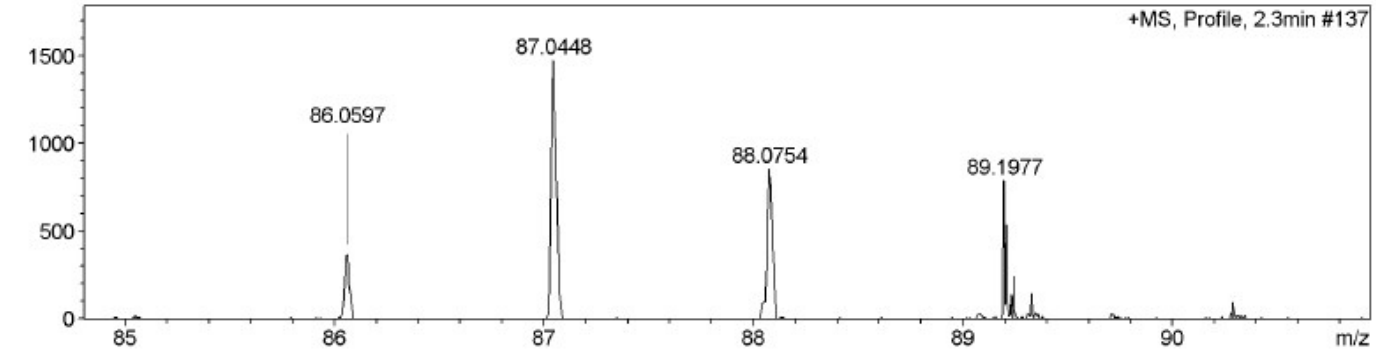
Analysis Info

Analysis Name	D:\Data\tps\tps-xvi-107_41_01_9694.d	Acquisition Date	1/5/2017 6:49:29 PM
Method	LC-MS3-HR-low.m	Operator	NPS-LAB, CIAC
Sample Name	tps-xvi-107	Instrument	micrOTOF-Q II
Comment			









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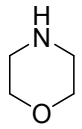
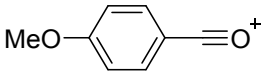
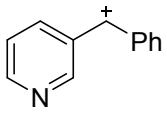
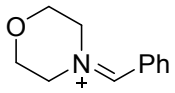
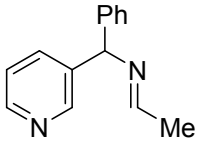
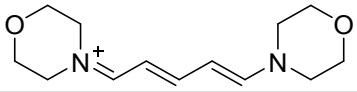
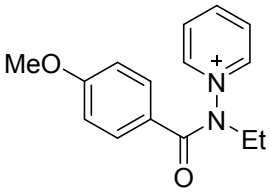
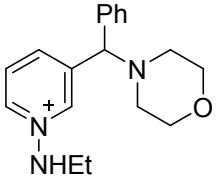
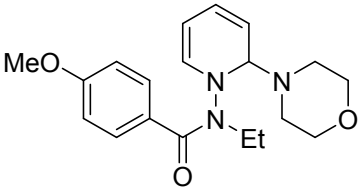
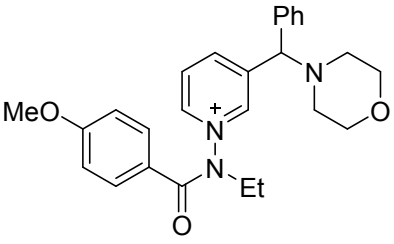
Peak Assignment

Observed	Calculated	Cation	Formula	Assigned Structure
88.0754	88.0757	$[M + H]^+$	$C_4H_{10}NO^+$	
135.0445	135.0441	M^+	$C_8H_7O_2^+$	
168.0814	168.0808	M^+	$C_{12}H_{10}N^+$	
176.1076	176.1070	M^+	$C_{11}H_{14}NO^+$	
211.1237	211.1230	$[M + H]^+$	$C_{14}H_{15}N_2^+$	
237.1605	237.1598	M^+	$C_{13}H_{21}N_2O_2^+$	
257.1295	257.1285	M^+	$C_{15}H_{17}N_2O_2^+$	
298.1914	298.1914	M^+	$C_{18}H_{24}N_3O^+$	
344.1966	344.1969	$[M + H]^+$	$C_{19}H_{26}N_3O_3^+$	
347.1751				unknown
432.2267	432.2282	M^+	$C_{26}H_{30}N_3O_3^+$	

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