# Direct Aminoalkylation of Arenes and Hetarenes via Ni-Catalyzed Negishi Cross-Coupling Reactions

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# Supporting information

Experimental procedures, analytical and spectroscopy data for final products (30 pages).

**General considerations.**

All reactions were carried out under an argon atmosphere in dried glassware. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be > 97 % pure as determined by $^{1}$H-NMR (25 °C) and capillary GC analysis.

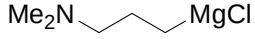
**General Procedure 1: Preparation of aminoalkylmagnesium chlorides by insertion of magnesium**.

Magnesium turnings (1.2 equiv.) and LiCl (2.0 equiv.) were placed in an argon flushed three-necked flask and dried for 10-20 min at 130 °C under vacuum (1 mbar). The flask was refilled with argon and then cooled under argon. After the addition of THF (500 mL per 1 mol of the alkyl chloride) and DIBAL-H (20% in hexane, 3 mol %), the alkyl chloride, dissolved in THF (500 mL per 1 mol) was added dropwise so that the mixture was gently boiling. Then, the reaction mixture was refluxed for another 2 h. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.3 M to 0.8 M in THF was obtained.

**General Procedure 2: Cross-coupling of the aminoalkylmagnesium chlorides with aryl electrophiles using Ni(acac)$_2$ and DPE-Phos.**

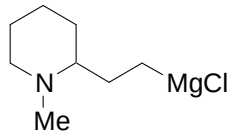
A dry Schlenk flask, equipped with a magnetic stirring bar, was charged with a solution of $ZnBr_2$ (450 mg, 2 mmol) in THF (1 mL) and *N*-methylpyrrolidone (0.3 mL). The mixture was stirred at room temperature for 15 min. The aminoalkylmagnesium chloride (1.2 mmol) was added and the mixture was stirred at room temperature for 15 min. The electrophile (1.0 mmol), DPE-Phos (27 mg, 5 mol %) and Ni(acac)$_2$ (9 mg, 2.5 mol %) dissolved in THF (1 mL) were added and the mixture was stirred at room temperature until the complete consumption of the electrophile was observed by GC analysis.
The reaction mixture was quenched with sat. aq. $K_2CO_3$ solution (20 mL), extracted with diethyl ether (3 × 20 mL). The combined organic layers were extracted with 2 N HCl (2 x 20 mL) and water (20 mL). The acidic aqueous layer was basified with sat. $K_2CO_3$ and extracted with diethyl ether (3 × 20 mL), the extract dried over anhydrous $Na_2SO_4$. After filtration, the solvent was evaporated in vacuo and purified by column chromatography, if necessary.

**Synthesis of 3-(dimethylamino)propylmagnesium chloride.**



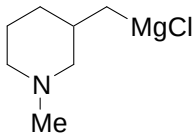

(3-Chloropropyl)dimethylamine (12.16 g, 100 mmol) was reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP 1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.80 M in THF was obtained, 82% yield.

**Synthesis of 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride.**



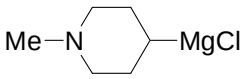

2-(2-Chloroethyl)-1-methylpiperidine (16.17 g, 100 mmol) was reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP 1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.71 M in THF was obtained, 66% yield.

**Synthesis of (1-methylpiperidin-3-yl)methylmagnesium chloride.**



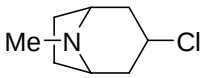

3-(Chloromethyl)-1-methylpiperidine (14.77 g, 100 mmol) was reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP 1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.50 M in THF was obtained, 77% yield.

**Synthesis of (1-methylpiperidin-4-yl)magnesium chloride.**




4-Chloro-1-methylpiperidine (13.36 g, 100 mmol) was reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP 1**. The solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.62 M in THF was obtained, 56% yield.

**Synthesis of 3-chloro-8-methyl-8-azabicyclo[3.2.1]octane.**




Solution of tropine (28.3g 200 mmol) in $CHCl_3$ (250 mL) was cooled down to -30°C. Thionyl chloride (47.6 g, 400 mmol) was added slowly and the solution was stirred at reflux temperature for 3 h and then additional 16 h at room temperature. The solution was carefully mixed with 6N NaOH, aqueous phase extracted with $CH_2Cl_2$/$Et_2O$ (1:1) and washed with sat. aq. $K_2CO_3$ solution. The $K_2CO_3$ solution was extracted with $CH_2Cl_2$ three times and the combined organic layers were dried over anhydrous $Na_2SO_4$. After removal of the solvent in vacuo, the crude product was purified by fractionated distillation in vacuo, which furnished 3-chloro-8-methyl-8-azabicyclo[3.2.1]octane (14.9 g, 93.0 mmol, 47%) as a colorless oil.

**B.p.:** 80°C (12 mbar).

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 4.18-4.06 (m, 1H), 3.18-3.16 (m, 2H), 2.31 (s, 3H), 2.07-1.90 (m, 6H), 1.58-1.51 (m, 2H).

**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 61.4, 53.3, 41.1, 38.7, 26.7.

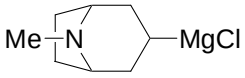
**MS** (EI, 70 eV), m/z (%): 159 (7) [$M^+$], 124 (100), 96 (11), 94 (3), 82 (8), 67 (7).

**HRMS**: calculated for $C_8H_{14}ClN$ 159.0815, found 159.0813.

**IR** (ATR): ῡ [$cm^{-1}$] = 2936 (vs), 2878 (s), 2798 (m), 1449 (m), 1336 (s), 1301 (m), 1238 (s), 1129 (w), 1042 (m), 1027 (s), 866 (m), 832 (m), 762 (s), 640 (m)

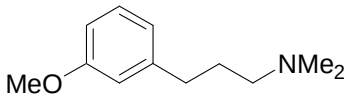
The analytical data match those from the literature[1].

**Synthesis of 8-methyl-8-azabicyclo[3.2.1]octyl-3-magnesium chloride.**




3-Chloro-8-methyl-8-azabicyclo[3.2.1]octane (15.97 g, 100 mmol) was reacted with Mg turnings (2.88 g, 120 mmol) and LiCl (8.48 g, 200 mmol) according to **TP 1**. The fresh solution was titrated prior to use at room temperature against a solution of iodine in THF. A concentration of 0.3 M in THF was obtained, 35% yield.

**[3-(3-Methoxy-phenyl)propyl]-dimethylamine** (**3a**)




3-Bromoanisole (187 mg, 1.0 mmol) was reacted with 3-(dimethylamino)propylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 ºC for 3 h, according to **TP 2**. Aqueous workup furnished [3-(3-methoxy-phenyl)-propyl]-dimethyl-amine (188 mg, 0.97 mmol, 97% yield) as a yellow oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.21-7.15 (m, 1H), 6.79-6.70 (m, 3H), 3.78 (s, 3H), 2.63-2.58 (t, J = 7.8 Hz, 2H), 2.31-2.26 (t, J = 7.3 Hz, 2H), 2.21 (s, 6H), 1.83-1.73 (m, 2H).

**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 159.9, 144.2, 129.5, 121.0, 114.4, 111.3, 59.5, 55.4, 45.7, 34.0, 29.6.

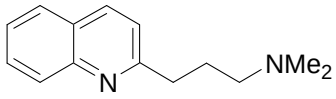
**MS** (EI, 70 eV), m/z (%): 193 (43) [$M^+$], 122 (11), 121 (8), 91 (7), 59 (4), 58 (100).

**HRMS**: calculated for $C_{12}H_{19}NO$ 193.1467, found 193.1466.

[1] S. Archer, M. R. Bell, T. R. Lewis, J. W. Schulenberg, M. J. Unser, *J. Am. Chem. Soc.* **1957,** *79*, 6337-6338.

**IR** (ATR): ῦ [$cm^{-1}$] = 3382 (vs), 3014 (m), 2942 (s), 2836 (m), 1600 (s), 1584 (s), 1486 (vs), 1466 (s), 1438 (s), 1258 (vs), 1154 (s), 1038 (s), 916 (m), 886 (w), 784 (m), 696 (m).

***N*,*N*-Dimethyl-(3-quinolin-2-yl-propyl)amine** (**3b**)




2-Chloroquinoline (164 mg, 1.0 mmol) was reacted with (3-(dimethylamino)propyl magnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 ºC for 3 h, according to **TP 2**. Aequous workup furnished *N*,*N*-dimethyl-(3-quinolin-2-yl-propyl)amine (189 mg, 0.88 mmol, 88% yield) as a brownish oil.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.97-7.92 (m, 2H), 7.66-7.63 (m, 1H), 7.60-7.54 (m, 1H), 7.38-7.33 (m, 1H), 7.19 (d, J = 8.4 Hz, 1H), 2.91 (t, J = 7.8 Hz, 2H), 2.30 (t, J = 8.0 Hz, 2H), 2.15 (s, 6H), 1.98-1.88 (m, 2H).

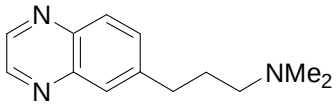
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 162.5, 148.1, 136.4, 129.5, 129.0, 127.7, 126.9, 125.9, 121.6, 59.4, 45.6, 37.1, 27.9.

**MS** (EI, 70 eV), m/z (%): 170 (6) [$M^+$], 143 (100), 128 (17), 115 (7), 72 (19), 58 (80)

**HRMS**: calculated for $C_{14}H_{18}N_2$ 214.1470, found 214.1477.

**IR** (ATR): ῦ [$cm^{-1}$] = 2940 (m), 2858 (w), 2814 (m), 2764 (m), 1618 (m), 1600 (s), 1562 (m), 1504 (s), 1462 (m), 1426 (s), 1140 (m), 1040 (m), 826 (vs), 748 (vs), 618 (m)

***N*,*N*-Dimethyl-3-(quinoxalin-6-yl)propan-1-amine** (**3c**)




6-Bromoquinoxaline (209 mg, 1.0 mmol) was reacted with (3-(dimethylamino) propylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 ºC for 1 h, according to **TP 2.** Aqueous workup furnished *N*,*N*-dimethyl-3-(quinoxalin-6-yl)propan-1-amine (211 mg, 0.98 mmol, 98% yield) as an orange-brown oil.

**$^{1}$H-NMR** ($CDCl_3$, 600 MHz, 25°C): δ [ppm] = 8.64-8.62 (m, 2H), 7.87-7.86 (m, 1H), 7.75-7.74 (m, 1H), 7.48-7.47 (m, 1H), 2.72 (t, J = 7.7 Hz, 2H), 2.17 (t, J = 7.3 Hz, 2H), 2.07 (s, 6H), 1.81-1.71 (m, 2H).

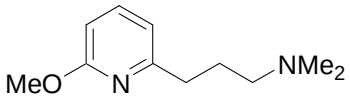
**$^{13}$C-NMR** ($CDCl_3$, 150 MHz, 25°C): δ [ppm] = 145.0, 144.3, 143.2, 141.8, 131.7, 129.3, 127.8, 59.1, 45.6, 33.7, 29.0.

**MS** (EI, 70 eV), m/z (%): 215 (6) [$M^+$], 169 (1), 142 (4), 71 (9), 58 (100).

**HRMS**: calculated for $C_{13}H_{17}N_3$ 215.1422, found 215.1422.

**IR** (ATR): ῦ [$cm^{-1}$] = 2940 (m), 2856 (m), 2814 (m), 2764 (m), 1620 (m), 1498 (s), 1452 (s), 1368 (m), 1132 (m), 1024 (vs), 958 (s), 896 (m), 864 (s), 830 (s), 664 (m)

**3-(6-Methoxypyridine-2-yl)-*N*,*N*-dimethylpropan-1-amine** (**3d**)




2-Chloro-6-methoxypyridine (144 mg, 1.0 mmol) was reacted with (3-(dimethylamino)propyl magnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 °C for 1 h, according to **TP 2**. Aqueous workup furnished 2-(3-dimethylaminopropyl)-6-methoxypyridine (164 mg, 0.85 mmol, 85% yield) as a yellow-orange oil.

**$^1$H-NMR** ($CDCl_3$, 600 MHz, 25°C): δ [ppm] = 7.37-7.34 (m, 1H), 6.61 (d, J = 7.3 Hz, 1H), 6.44 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.62 (t, J = 7.7 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.14 (s, 6H), 1.86-1.80 (m, 2H).

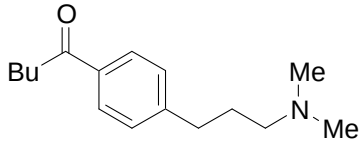
**$^{13}$C-NMR** ($CDCl_3$, 150 MHz, 25°C): δ [ppm] = 163.8, 159.8, 138.8, 115.2, 107.5, 59.5, 53.2, 45.6, 35.7, 27.4.

**MS** (EI, 70 eV), m/z (%): 195 (8) [$M+H^+$], 136 (6), 124 (13), 123 (100), 72 (26), 58 (56).

**HRMS**: calculated for $C_{11}H_{19}N_2O^+$ 195.1492, found 195.1517.

**IR** (ATR): ῦ [$cm^{-1}$] = 2946 (m), 2856 (w), 2814 (w), 2764 (w), 1598 (s), 1578 (vs), 1462 (vs), 1440 (s), 1412 (s), 1288 (s), 1262 (m), 1150 (m), 1030 (s), 986 (m), 798 (s), 738 (m)

**1-[4-(3-Dimethylamino-propyl)-phenyl]-pentan-1-one** (**3e**)




1-(4-Bromo-phenyl)-pentan-1-one (241 mg, 1.0 mmol) was reacted with (3-(dimethylamino) propylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 °C for 1 h, according to **TP 2**. Aqueous workup furnished 1-[4-(3-dimethylamino-propyl)-phenyl]-pentan-1-one (223 mg, 0.90 mmol, 90% yield) as a yellow-orange oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.84 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 2.90 (t, J = 7.5 Hz, 2H), 2.66 (t, J = 7.7 Hz, 2H), 2.25 (t, J = 7.5 Hz, 2H), 2.18 (s, 6H), 1.81-1.81 (m, 2H), 1.73-1.63 (m, 2H), 1.43-1.31 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H).

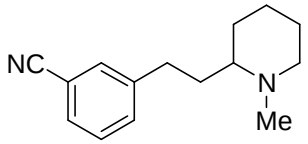
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 200.3, 148.1, 135.2, 128.8, 128.4, 59.2, 45.7, 38.4, 33.8, 29.3, 26.8, 22.7, 14.2.

**MS** (EI, 70 eV), m/z (%): 247 (3) [$M^+$], 145 (3), 115 (2), 91 (1), 58 (100).

**HRMS**: calculated for $C_{16}H_{25}NO$ 247.1936, found 247.1913.

**IR** (ATR): ῡ [$cm^{-1}$] = 2936 (m), 2860 (m), 2814 (w), 2764 (m), 1680 (vs), 1606 (s), 1460 (m), 1412 (m), 1266 (m), 1214 (m), 1180 (s), 1012 (m), 968 (m), 846 (m)

**3-(2-(1-Methylpiperidin-2-yl)ethyl)benzonitrile** (**3f**)




3-Bromobenzonitrile (182 mg, 1.0 mmol) was reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 °C for 0.5 h, according to **TP 2**. Aqueous workup furnished 3-(2-(1-methylpiperidin-2-yl)ethyl)benzonitrile (220 mg, 0.96 mmol, 96 % yield) as a yellow-orange oil.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.35-7.33 (m, 2H), 7.31-7.30 (m, 1H), 7.28-7.25 (m, 1H), 2.75-2.58 (m, 2H), 2.54-2.43 (m, 1H), 2.15 (s, 3H), 2.01-1.12 (m, 10H.

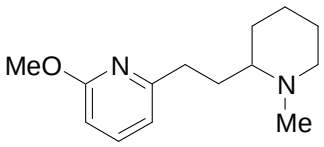
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 144.4, 133.1, 131.9, 129.6, 129.3, 119.1, 112.5, 63.2, 57.3, 43.0, 34.6, 30.8, 30.7, 25.9, 24.6.

**MS** (EI, 70 eV), m/z (%): 228 (2) [$M^+$], 171 (1), 115 (3), 98 (100), 70 (7).

**HRMS:** calculated for $C_{15}H_{20}N_2$ 228.1626, found 228.1623.

**IR** (ATR): ῡ [$cm^{-1}$] = 2932 (s), 2854 (m), 2776 (m), 2228 (m), 1442 (m), 1376 (m), 1264 (m), 1124 (m), 1032 (m), 886 (w), 796 (s), 690 (vs)

**2-Methoxy-6-(2-(1-methylpiperidin-2-yl)ethyl)pyridine** (**3g**)




2-Chloro-6-methoxy-pyridine (144 mg, 1.0 mmol) was reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 °C for 0.5 h, according to **TP 2**. Aqueous workup furnished 2-methoxy-6-(2-(1-methylpiperidin-2-yl)ethyl)pyridine (219 mg, 0.94 mmol, 94 % yield) as a yellow-orange oil.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.37-7.30 (m, 1H), 6.59 (dd, J = 7.3 Hz, 2.9 Hz, 1H), 6.42 (dd, J = 8.2 Hz, 2.9 Hz, 1H), 3.80 (s, 3H), 2.77-2.64 (m, 2H), 2.60-2.49 (m, 1H), 2.19 (s, 3H), 2.02-1.92 (m, 2H), 1.86-1.62 (m, 4H), 1.49-1.48 (m, 2H), 1.34-1.13 (m, 2H).

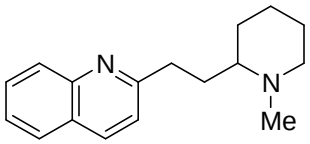
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 163.8, 160.4, 138.7, 115.1, 107.5, 63.5, 57.4, 53.2, 43.2, 33.4, 32.5, 30.9, 26.1, 24.6.

**MS** (EI, 70 eV), m/z (%): 234 (1) [$M^+$], 136 (2), 122 (83), 112 (60), 98 (100), 70 (7).

**HRMS**: calculated for $C_{14}H_{22}N_2O$ 234.1732, found 234.1710.

**IR** (ATR): ῡ [$cm^{-1}$] = 2932 (m), 2854 (m), 2776 (m), 1598 (s), 1578 (vs), 1464 (vs), 1440 (s), 1412 (s), 1286 (s), 1264 (s), 1146 (m), 1030 (vs), 798 (s), 732 (m)

**2-(2-(1-Methylpiperidin-2-yl)ethyl)quinoline** (**3h**)




2-Chloroquinoline (164 mg, 1.0 mmol) was reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 ºC for 1 h, according to **TP 2**. Aqueous workup furnished 2-(2-(1-methylpiperidin-2-yl)ethyl)quinoline (241 mg, 0.95 mmol, 95% yield) as an orange-brown oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.99-7.94 (m, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.62-7.56 (m, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 3.05-2.95 (m, 1H), 2.91-2.75 (m, 2H), 2.23 (s, 3H), 2.13-1.79 (m, 4H), 1.75-1.64 (m, 2H), 1.56-1.48 (m, 2H), 1.42-1.12 (m, 2H).

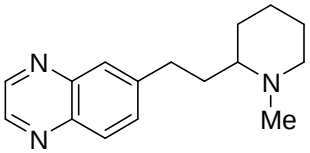
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 163.1, 148.1, 136.4, 129.5, 129.1, 127.7, 126.9, 125.8, 121.5, 63.6, 57.4, 43.3, 35.0, 33.0, 30.9, 26.1, 24.6.

**MS** (EI, 70 eV), m/z (%): 253 (1) [M-$H^+$], 168 (3), 155 (3), 143 (100), 112 (58), 98 (45), 70 (3).

**HRMS:** calculated for $C_{17}H_{21}N_2^+$ 253.1699, found 253.1701.

**IR** (ATR): ῡ [$cm^{-1}$] = 2930 (s), 2854 (m), 2776 (m), 1618 (m), 1600 (s), 1502 (s), 1442 (m), 1426 (m), 1374 (m), 1138 (m), 1118 (m), 1032 (m), 824 (vs), 756 (s), 618 (m)

**6-[2-(1-Methyl-piperidin-2-yl)-ethyl]-quinoxaline** (**3i**)




6-Bromoquinoxaline (209 mg, 1.0 mmol) was reacted with 2-(1-methylpiperidin-2-yl)ethylmagnesium chloride (0.8 M in THF, 1.5 mL, 1.2 mmol) at 25 ºC for 3 h, according to **TP 2**. Aqueous workup and purification by flash chromatography ($CH_2Cl_2$ /methanol, 10:1) furnished 6-[2-(1-methyl-piperidin-2-yl)-ethyl]-quinoxaline (232 mg, 0.91 mmol, 91 % yield) as an orange-brown oil.

**$^1$H-NMR** ($CDCl_3$, 600 MHz, 25°C): δ [ppm] = 8.74-8.72 (m, 2H), 7.96 (d, J = 8.6 Hz, 1H), 7.83 (s, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.20 (t, J = 8.4 Hz, 1H), 2.94-2.89 (m, 1H), 2.85-2.83 (m, 1H), 2.79-2.74 (m, 1H), 2.27 (s, 3H), 2.10-2.06 (m, 1H), 1.99-1.94 (m, 2H), 1.86-1.81 (m, 1H), 1.71-1.69 (m, 2H), 1.56-1.55 (m, 2H), 1.46-1.40 (m, 1H), 1.27-1.17 (m, 1H).

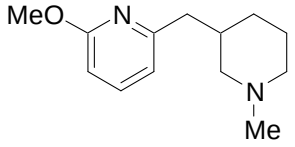
**$^{13}$C-NMR** ($CDCl_3$, 150 MHz, 25°C): δ [ppm] = 145.4, 145.1, 144.4, 143.3, 141.9, 131.7, 129.4, 127.7, 63.4, 57.2, 42.9, 34,2. 31,4. 30.6, 25.7, 24.4.

**MS** (EI, 70 eV), m/z (%): 255 (2) [$M^+$], 157 (1), 142 (4), 111 (5), 98 (100), 70 (6).

**HRMS**: calculated for $C_{16}H_{21}N_3$ 255.1735, found 255.1733.

**IR** (ATR): ῡ [$cm^{-1}$] = 2930 (vs), 2854 (m), 2776 (s), 1620 (w), 1498 (m), 1450 (m), 1366 (m), 1266 (w), 1132 (m), 1024 (m), 890 (m), 864 (m), 826 (w), 730 (w).

**2-Methoxy-6-(1-methyl-piperidin-3-ylmethyl)-pyridine** (**3j**)




2-Chloro-6-methoxypyridine (144 mg, 1.0 mmol) was reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (0.5 M in THF, 2.4 mL, 1.2 mmol) at 25 ºC for 20 h, according to **TP 2**. Aqueous workup furnished furnished 2-methoxy-6-(1-methyl-piperidin-3-ylmethyl)-pyridine (198 mg, 0.90 mmol, 90% yield) as a yellow-orange oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.38-7.33 (m, 1H), 6.58 (d, J = 7.1 Hz, 1H), 6.45 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 2.68 (d, J = 11.0 Hz, 2H), 2.49 (d, J = 7.1 Hz, 2H), 2.14 (s, 3H), 2.12-2.00 (m, 1H), 1.83-1.75 (m, 1H), 1.64-1.42 (m, 4H), 0.93-0.80 (m, 1H).

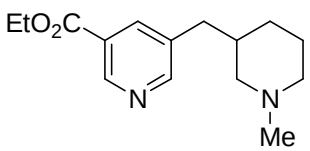
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 163.8, 158.5, 138.6, 116.0, 107.7, 62.3, 56.5, 53.3, 46.9, 43.1, 36.7, 30.6, 25.7.

**MS** (EI, 70 eV), m/z (%): 219 (8) [M-$H^+$], 123 (100), 98 (26), 70 (2), 58 (2), 43 (4).

**HRMS**: calculated for $C_{13}H_{20}N_2O$ 220.1576, found 220.1613.

**IR** (ATR): ῡ [$cm^{-1}$] = 2932 (m), 2848 (w), 2774 (m), 1598 (s), 1578 (s), 1464 (vs), 1438 (s), 1414 (s), 1302 (s), 1262 (s), 1146 (m), 1032 (s), 798 (s), 780 (s), 746 (m)

**5-(1-Methyl-piperidin-3-ylmethyl)-nicotinic acid ethyl ester** (**3k**)




5-Bromopyridine-3-carboxylic acid ethyl ester (230 mg, 1.0 mmol) was reacted with (1-methylpiperidin-3-yl)methylmagnesium chloride (0.5 M in THF, 2.4 mL, 1.2 mmol) at 25 ºC

for 20 h, according to **TP 2**. Aqueous workup and purification by flash chromatography ($CH_2Cl_2$ /methanol, 20:1) furnished 5-(1-methyl-piperidin-3-ylmethyl)-nicotinic acid ethyl ester (204 mg, 0.78 mmol, 78% yield) as a yellow-orange oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 8.91 (s, 1H), 8.42 (s, 1H), 7.94 (s, 1H), 4.26 (q, J = 7.3 Hz, 2H), 2.70-2.61 (m, 2H), 2.45 (d, J = 7.1 Hz, 2H), 2.13 (s, 3H), 1.88-1.81 (m, 2H), 1.66-1.45 (m, 4H), 1.27 (t, J = 7.3 Hz, 3H), 0.89-0.78 (m, 1H).

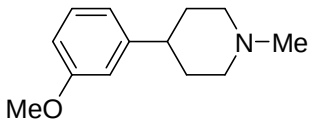
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = .5, 154.0, 148.8, 137.3, 135.4, 126.1, 61.5, 61.4, 56.0, 46.4, 37.7, 37.5, 29.9, 24.9, 14.4.

**MS** (EI, 70 eV), m/z (%): 262 (44) [$M^+$], 233 (11), 217 (13), 111 (14), 97 (100), 71 (17), 58 (32), 43 (26).

**HRMS**: calculated for $C_{15}H_{22}N_2O_2$ 262.1681, found 262.1670.

**IR** (ATR): ῡ [$cm^{-1}$] = 2932 (m), 2850 (w), 2776 (w), 1720 (vs), 1446 (m), 1368 (m), 1288 (vs), 1206 (s), 1178 (m), 1160 (m), 1104 (s), 1024 (s), 864 (w), 764 (s), 710 (m), 676 (w).

**4-(3-Methoxy-phenyl)-1-methyl-piperidine** (**3l**)




1-Bromo-3-methoxybenzene (187 mg, 1.0 mmol) was reacted with (1-methylpiperidin-4-yl)magnesium chloride (0.6 M in THF, 2.0 mL, 1.2 mmol) at 25 ºC for 6 h, according to **TP 2**. Aequous workup furnished 4-(3-methoxy-phenyl)-1-methyl-piperidine (189 mg, 0.92 mmol, 92% yield) as a yellow oil.

**$^1$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.23-7.18 (m, 1H), 6.82-6.71 (m, 3H), 3.79 (s, 3H), 2.94-2.87 (m, 2H), 2.55-2.43 (m, 1H), 2.24 (s, 3H), 2.03-1.92 (m, 2H), 1.90-1.82 (m, 4H)

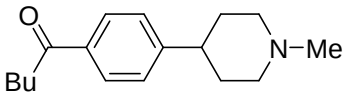
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 160.2, 144.3, 129.8, 121.1, 114.7, 111.2, 59.4, 55.2, 45.7, 42.9, 32.3.

**MS** (EI, 70 eV), m/z (%): 205 (4) [$M^+$], 134 (13), 121 (9), 97 (100), 83 (29), 70 (69), 58 (22), 43 (47)

**HRMS**: calculated for $C_{13}H_{19}NO$ 205,1467, found 205.1474.

**IR** (ATR): ῡ [$cm^{-1}$] = 3371 (vs), 3006 (m), 2910 (s), 1633 (m), 1559 (s), 1479 (vs), 1495 (s), 1233 (s), 1201 (m), 1152 (s), 1070 (s), 1011 (m), 905 (w), 856 (m), 784 (m), 696 (m).

**1-[4-(1-Methyl-piperidin-4-yl)-phenyl]-pentan-1-one** (**3m**)




1-(4-Bromo-phenyl)-pentan-1-one (241 mg, 1.0 mmol) was reacted with (1-methylpiperidin-4-yl)magnesium chloride (0.6 M in THF, 2.0 mL, 1.2 mmol) at 25 ºC for 2 h, according to **TP 2**. Aqueous workup furnished 1-[4-(1-methyl-piperidin-4-yl)-phenyl]-pentan-1-one (218 mg, 0.84 mmol, 84% yield) as an orange solid.

**Mp**.: 37 - 38 °C.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.80 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.2 Hz, 2H), 2.89-2.81 (m, 4H), 2.49-2.38 (m, 1H), 2.22 (s, 3H), 2.00-1.91 (m, 2H), 1.75-1.68 (m, 4H), 1.66 (m, 2H), 1.37-1.24 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H).

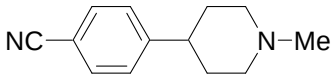
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 200.3, 151.9, 135.4, 128.5, 127.2, 56.3, 46.6, 42.3, 38.4, 33.4, 26.8, 22.7, 14.1.

**MS** (EI, 70 eV), m/z (%): 259 (90) [$M^+$], 258 (100), 202 (4), 97 (15), 83 (5), 70 (13), 43 (3).

**HRMS**: calculated for $C_{17}H_{25}NO$ 259.1936, found 260.1947.

**IR** (ATR): ῦ [$cm^{-1}$] = 2934 (m), 2872 (m), 2778 (m), 1678 (vs), 1606 (s), 1464 (m), 1444 (m), 1378 (m), 1278 (m), 1212 (m), 1182 (m), 1134 (m), 992 (m), 976 (m), 844 (m), 764 (m)

**4-(1-Methyl-piperidin-4-yl)-benzonitrile** (**3n**)




4-Cyanophenyl triflate (251 mg, 1.0 mmol) was reacted with (1-methylpiperidin-4-yl)magnesium chloride (0.6 M in THF, 2.0 mL, 1.2 mmol) at 25 ºC for 8 h, according to **TP2**. Aqueous workup furnished 4-(1-methyl-piperidin-4-yl)-benzonitrile (189 mg, 0.95 mmol, 95 % yield) as a yellow-orange solid.

**Mp**.: 70-72°C.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.51 (d, J = 8.2 Hz, 2H), 7.26 (d, J = 8.2 Hz, 2H), 2.93-2.90 (m, 2H), 2.53-2.42 (m, 1H), 2.25 (s, 3H), 2.03-1.95 (m, 2H), 1.77-1.64 (m, 4H).

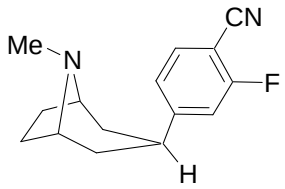
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 152.0, 132.5, 127.9, 119.2, 110.2, 56.2, 46.6, 42.4, 33.3.

**MS** (EI, 70 eV), m/z (%): 200 (87) [$M^+$], 199 (100), 128 (4), 115 (7), 97 (12), 83 (12), 70 (27), 42 (19).

**HRMS**: calculated for $C_{13}H_{16}N_2$ 200.1313, found 200.1289.

**IR** (ATR): ῡ [$cm^{-1}$] = 2940 (s), 2834 (m), 2786 (s), 2738 (m), 2222 (s), 1606 (m), 1508 (m), 1468 (m), 1446 (s), 1416 (m), 1378 (m), 1276 (s), 1128 (m), 1080 (m), 1064 (m), 994 (s), 836 (vs), 768 (s)

***exo*-2-Fluoro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)benzonitrile** (**3o**)




4-Bromo-2-fluorobenzonitrile (200 mg, 1.0 mmol) was reacted with 8-methyl-8-aza-bicyclo[3.2.1]octyl-3-magnesium chloride (0.3 M in THF, 4.0 mL, 1.2 mmol) at 25 ºC for 30 h, according to **TP2**. Aqueous workup and purification by flash chromatography ($CH_2Cl_2$ /methanol, 20:1) furnished *exo*-2-fluoro-4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)benzonitrile (190 mg, 0.78 mmol, 78% yield) as an orange-red oil.

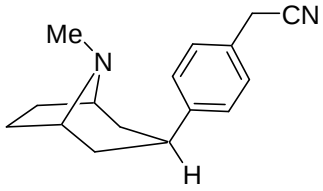
**$^1$H-NMR** ($CDCl_3$, 600 MHz, 25°C): δ [ppm] = 7.40-7.37 (m, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.98 (d, 1H, J = 10.4 Hz, 1H), 3.14-3.10 (m, 2H), 2.82-2.76 (m, 1H), 2.18 (s, 3H), 2.10-1.97 (m, 4H), 1.55-1.50 (m, 4H).

**$^{13}$C-NMR** ($CDCl_3$, 150 MHz, 25°C): δ [ppm] = 163.4, 155.3, 133.4, 124.0, 115.3, 114.3, 98.9, 61.5, 40.7, 38.8, 35.3, 26.1.

**MS** (EI, 70 eV), m/z (%): 244 (51) [$M^+$], 215 (38), 201 (8), 134 (8), 96 (32), 83 (100), 57 (6), 42 (37).
HRMS: calculated for $C_{15}H_{17}FN_2$ 244.1376, found 244.1375.

**IR** (ATR): ῡ [$cm^{-1}$] = 2958 (s), 2920 (vs), 2848 (m), 2228 (m), 1618 (vs), 1566 (m), 1502 (s), 1450 (s), 1430 (s), 1352 (m), 1256 (m), 1110 (s), 968 (m), 816 (s), 764 (s).

***exo*-[4-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-phenyl]acetonitrile** (**3p**)




(4-Bromo-phenyl)acetonitrile (196 mg, 1.0 mmol) was reacted with 8-methyl-8-aza-bicyclo[3.2.1]octyl-3-magnesium chloride (0.3 M in THF, 4.0 mL, 1.2 mmol) at 25 ºC for 72 h, according to **TP2**. Aqueous workup and purification by flash chromatography ($CH_2Cl_2$

/methanol, 20:1) furnished *exo*-[4-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-phenyl]acetonitrile (220 mg, 0.92 mmol, 92% yield) as a foamy solid.

**Mp**.: 105 - 106°C.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.09 (d, J = 8.4 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 3.48 (s, 2H), 3.27-3.25 (m, 2H), 2.72-2.62 (m, 1H), 2.32 (s, 3H), 2.14-1.98 (m, 2H), 1.67-1.64 (m, 2H), 1.50-1.45 (m, 4H).

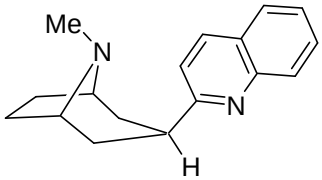
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 144.2, 131.1, 128.3, 128.2, 118.3, 63.5, 39.8, 37.8, 33.7, 25.5, 23.3.

**MS** (EI, 70 eV), m/z (%): 241 (100) [$M+H^+$], 235 (1), 102 (26), 51 (1).

**HRMS**: calculated for $C_{16}H_{21}N_2^+$ 241.1699, found 241.1691.

**IR** (ATR): ῡ [$cm^{-1}$] = 2934 (s), 2910 (s), 2798 (m), 2244 (w), 1512 (s), 1418 (s), 1354 (s), 1122 (s), 1052 (s), 1036 (s), 848 (vs), 800 (s), 786 (s), 768 (vs), 706 (m), 630 (m).

***exo*-2-(8-Methyl-8-aza-bicyclo[3.2.1]oct-3-yl)quinoline** (**3q**)




Trifluoromethanesulfonic acid quinolin-2-yl ester (277 mg, 1.0 mmol) was reacted with 8-methyl-8-aza-bicyclo[3.2.1]octyl-3-magnesium chloride (0.3 M in THF, 4.0 mL, 1.2 mmol) at 25 ºC for 72 h, according to **TP2**. Aqueous workup and purification by flash chromatography ($CH_2Cl_2$ /methanol, 20:1) furnished *exo*-2-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-quinoline (202 mg, 0.80 mmol, 80% yield) as an orange-brown oil.

**$^{1}$H-NMR** ($CDCl_3$, 300 MHz, 25°C): δ [ppm] = 7.95 (t, J = 9.0 Hz, 2H), 7.64 (d, J = 7.9 Hz, 1H), 7.58-7.53 (m, 1H), 7.38-7.33 (m, 2H), 3.22-3.11 (m, 3H), 2.28 (s, 3H), 2.11-1.99 (m, 4H), 1.73-1.68 (m, 4H).

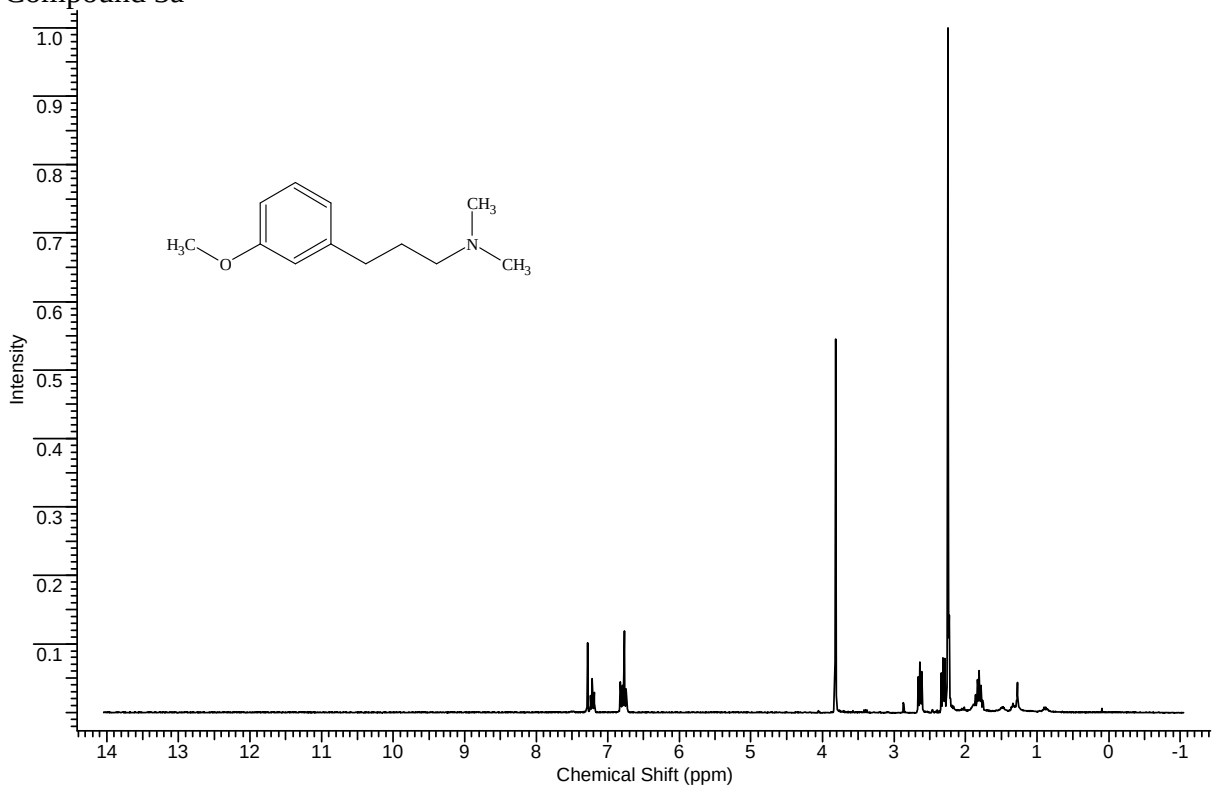
**$^{13}$C-NMR** ($CDCl_3$, 75 MHz, 25°C): δ [ppm] = 165.4, 147.9, 136.7, 129., 129.1, 127.6, 127.2, 126.0, 119.8, 61.8, 40.6, 38.5, 37.6, 36.2.

**MS** (EI, 70 eV), m/z (%): 252 (87) [$M^+$], 167 (61), 157 (100), 143 (42), 130 (20), 96 (31), 83 (62).

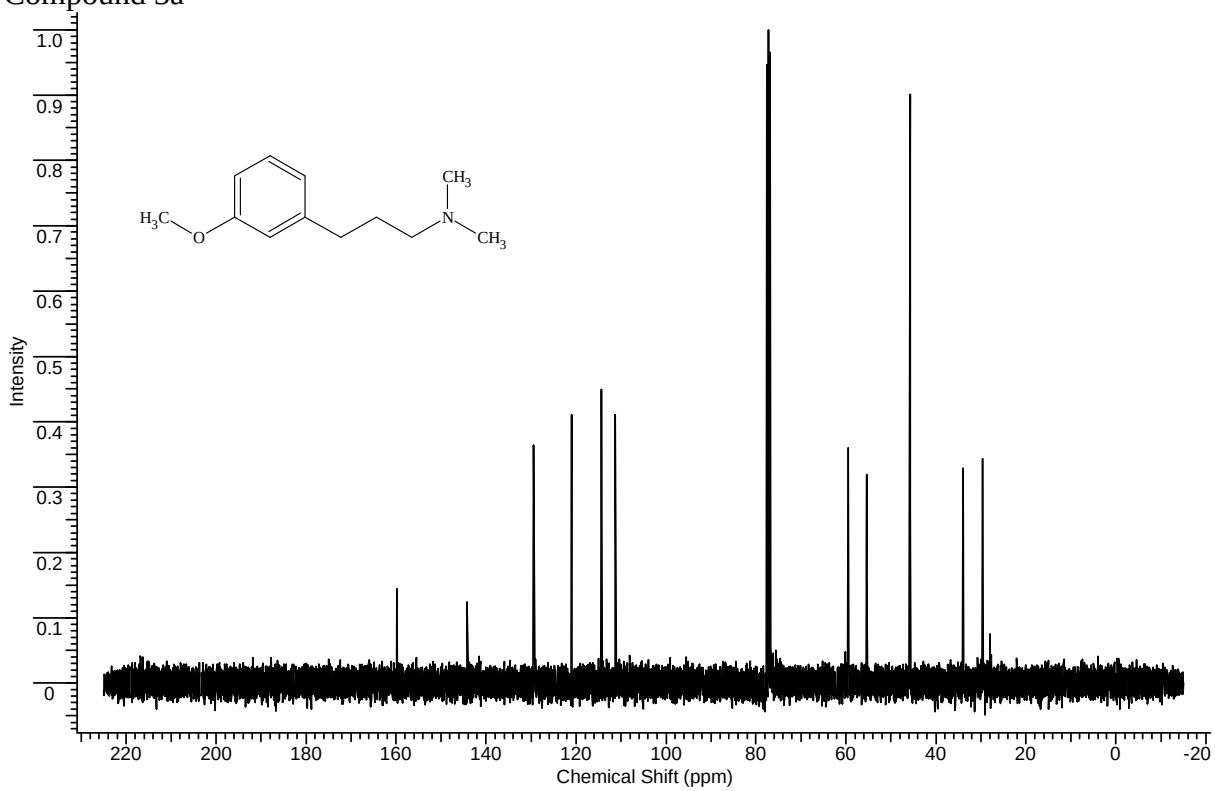
**HRMS**: calculated for $C_{17}H_{20}N_2$ 252.1626, found 252.1610.

IR (ATR): ῡ [$cm^{-1}$] = 2958 (vs), 2796 (m), 2672 (m), 2572 (s), 2548 (s), 2494 (m), 1600 (s), 1562 (m), 1502 (s), 1476 (s), 1454 (s), 1426 (s), 1396 (m), 1032 (s), 842 (m), 816 (s), 766 (s).

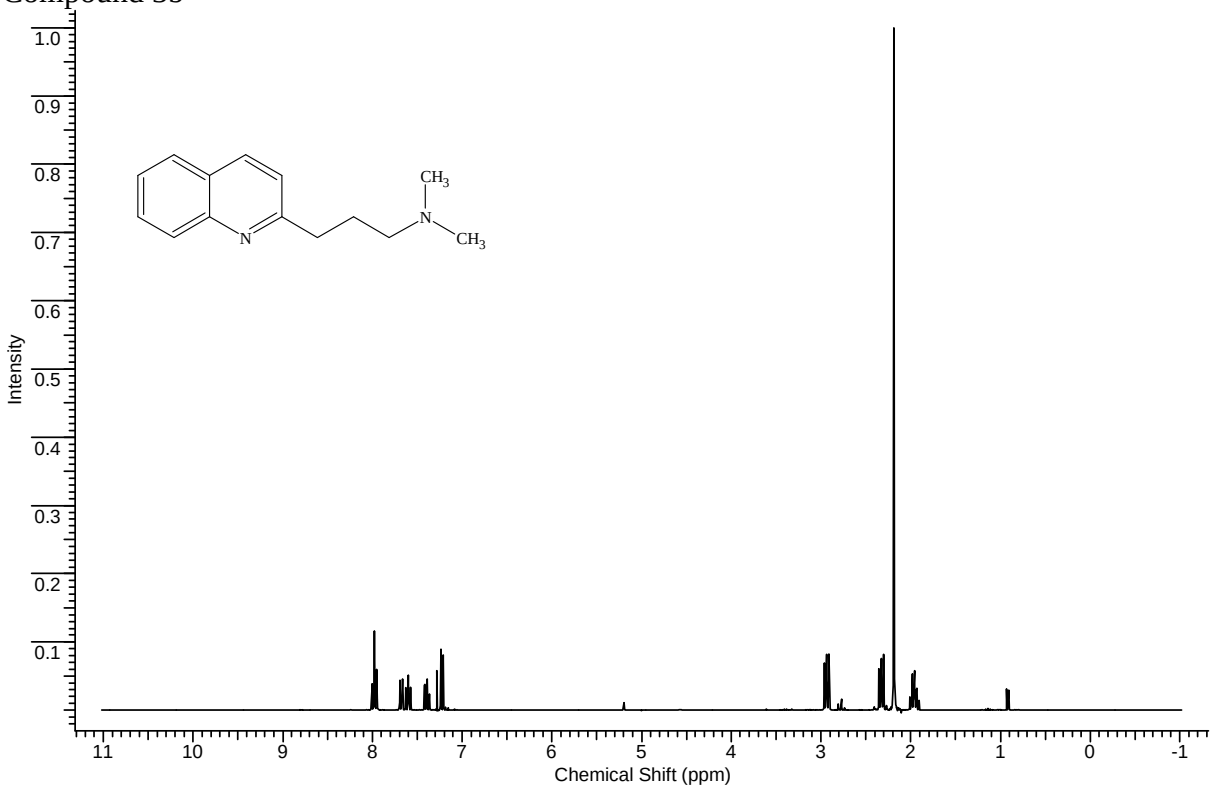
Compound 3a



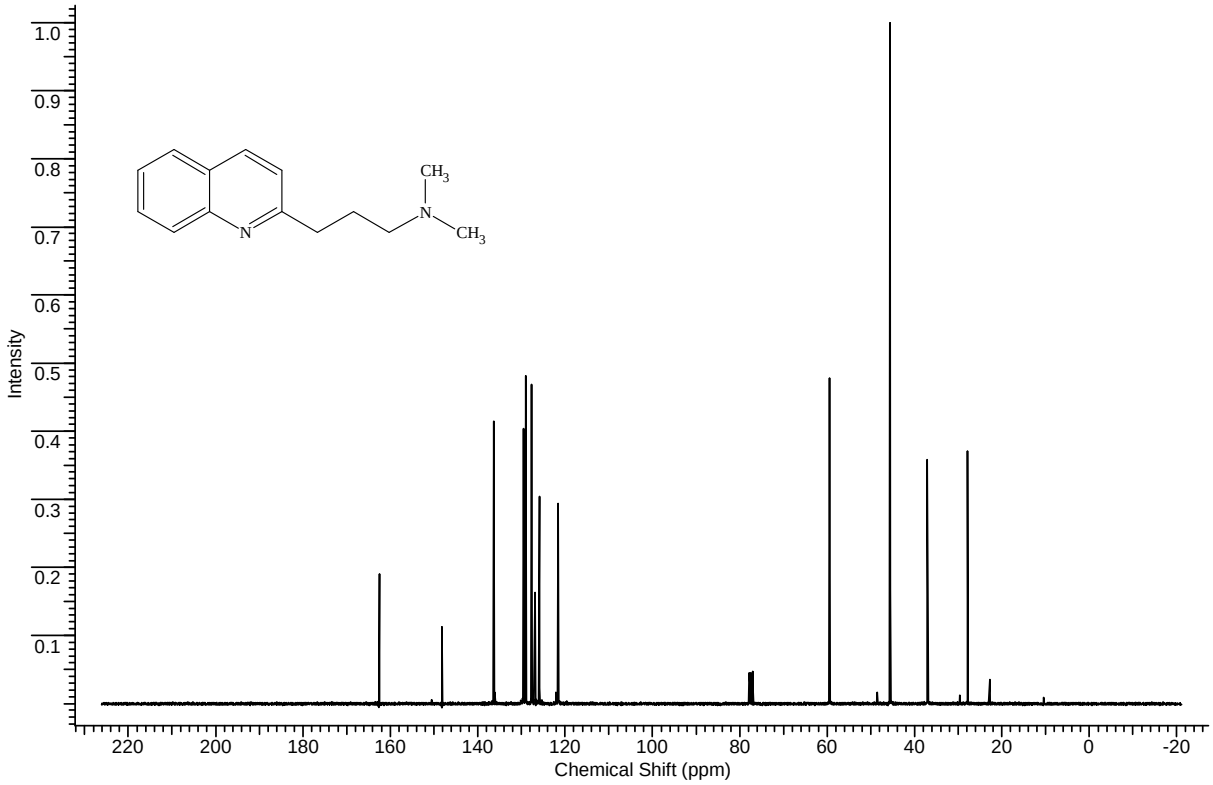

Compound 3a



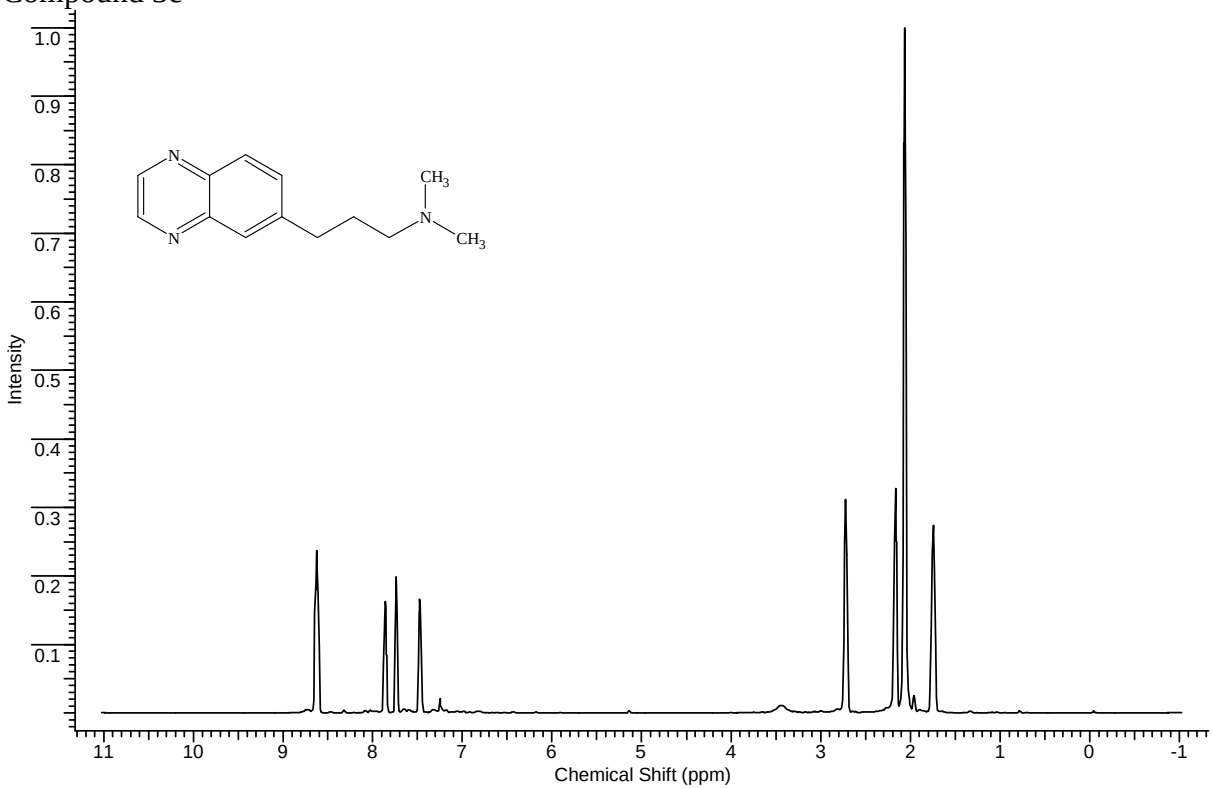
Compound 3b



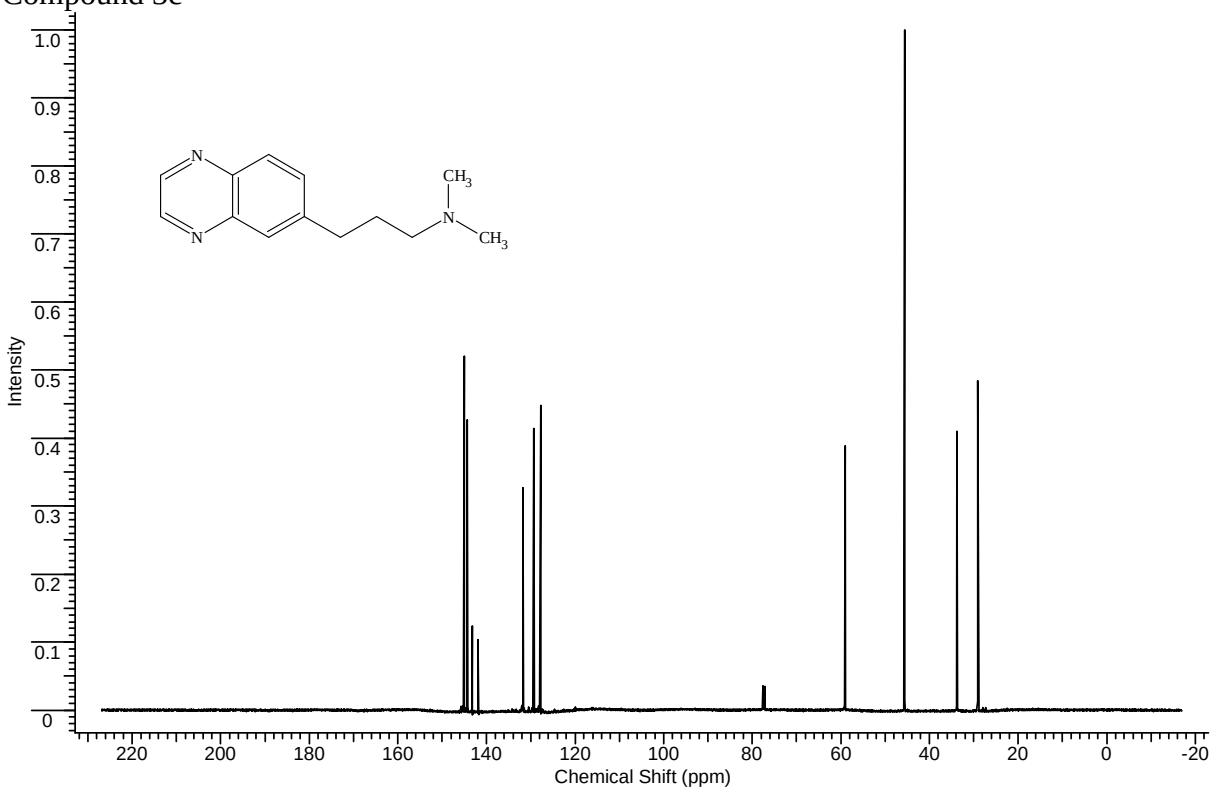

Compound 3b



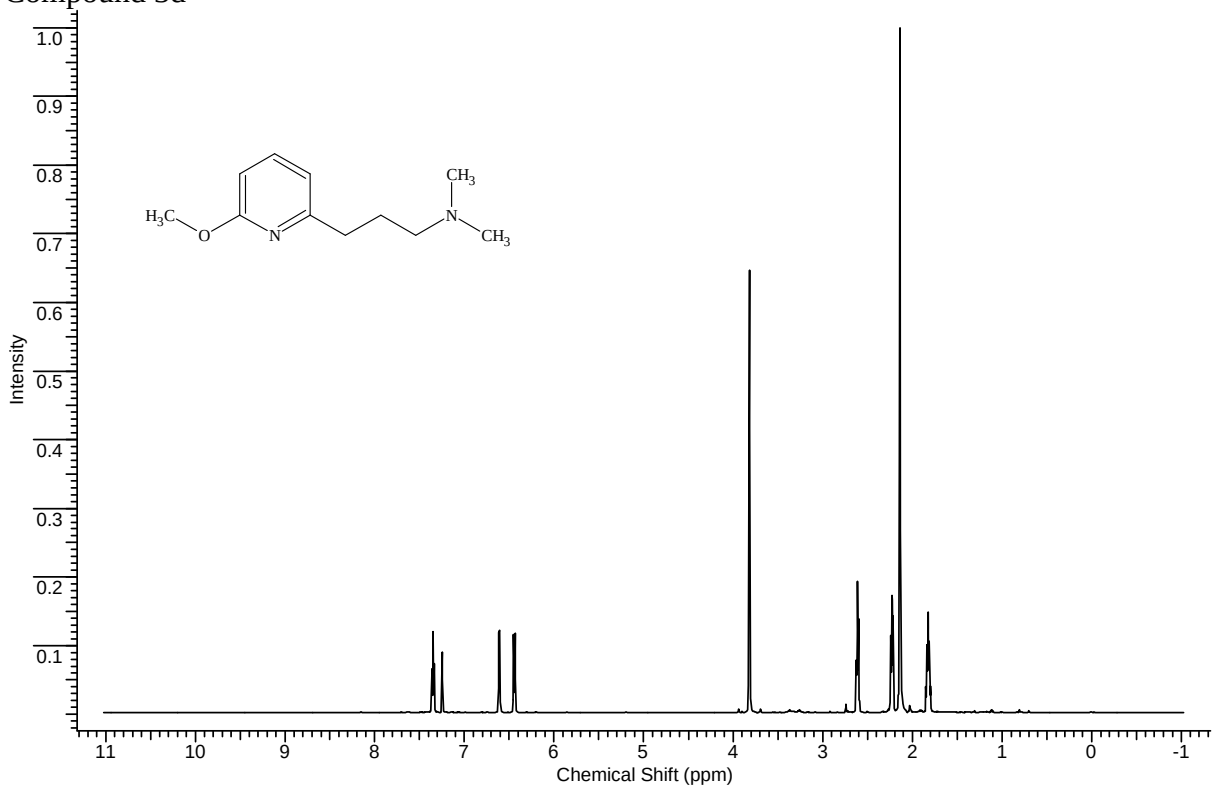
Compound 3c



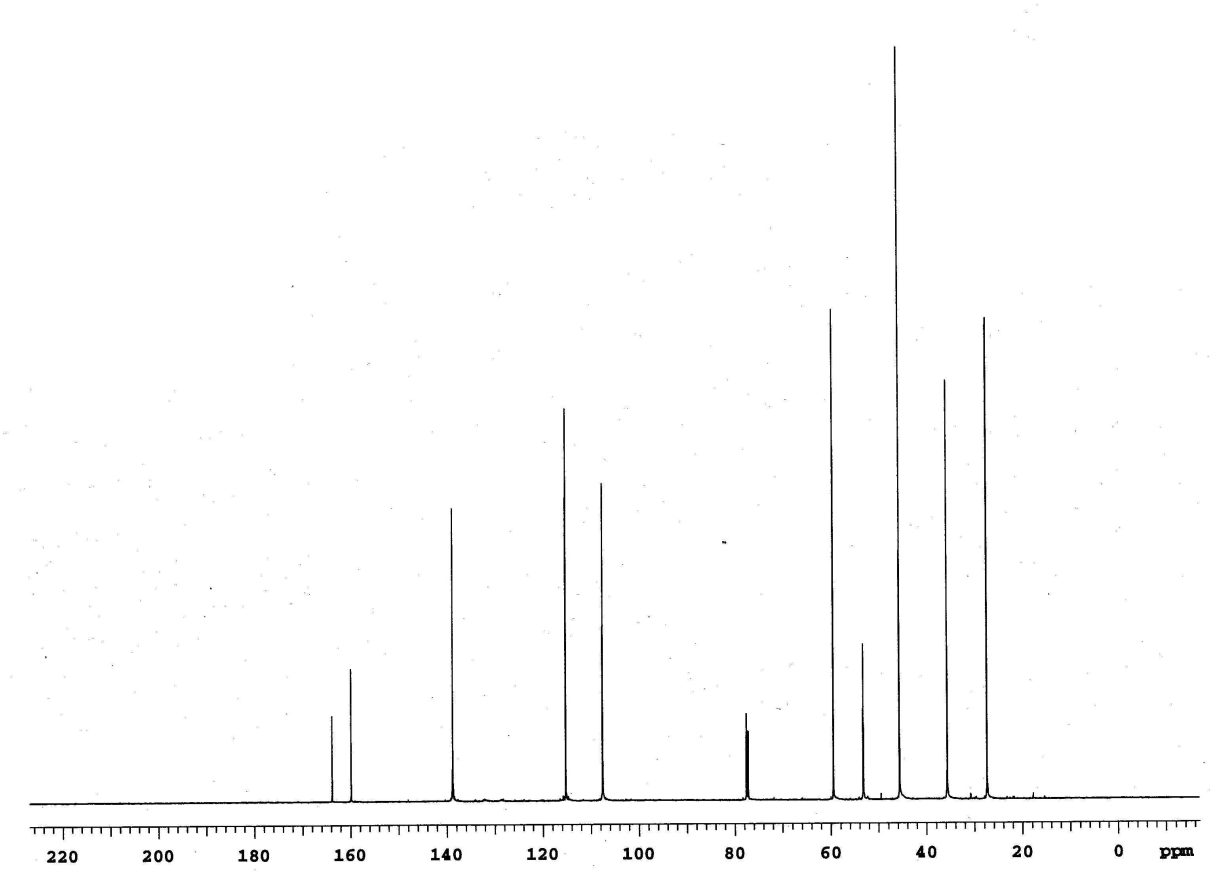

Compound 3c



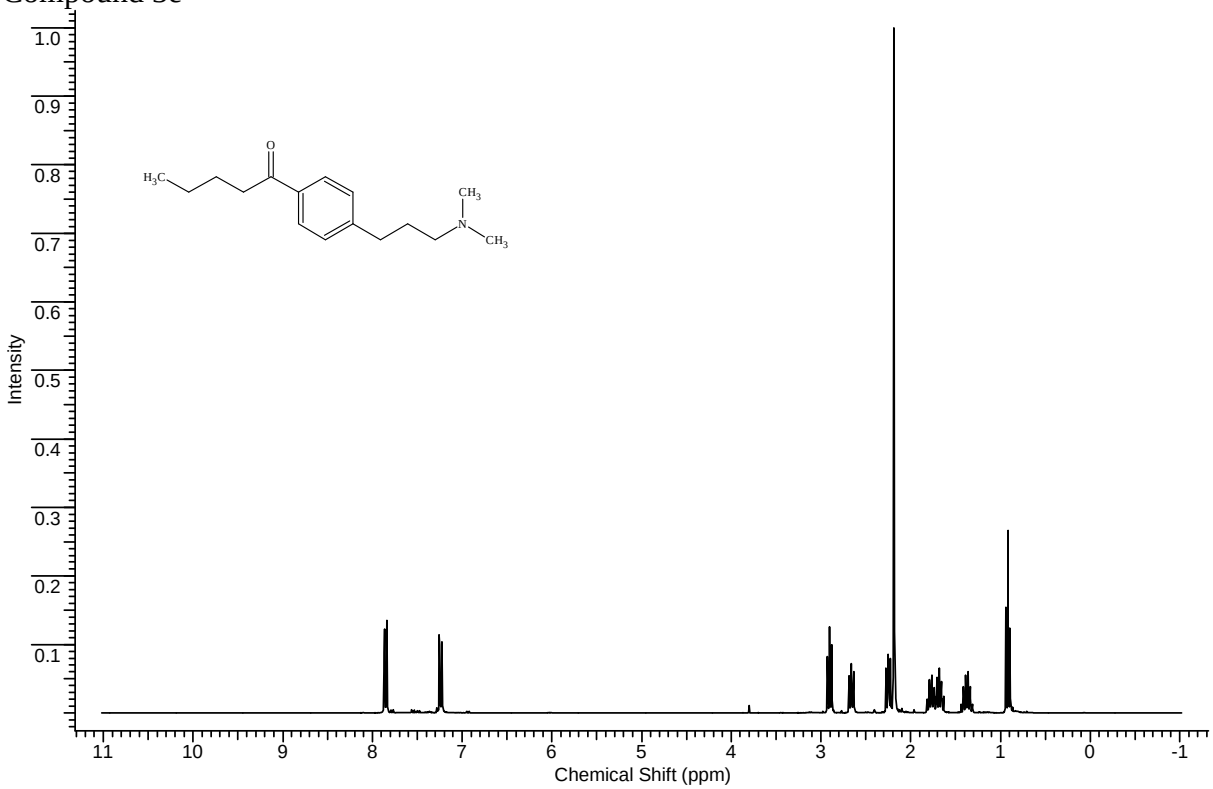
Compound 3d



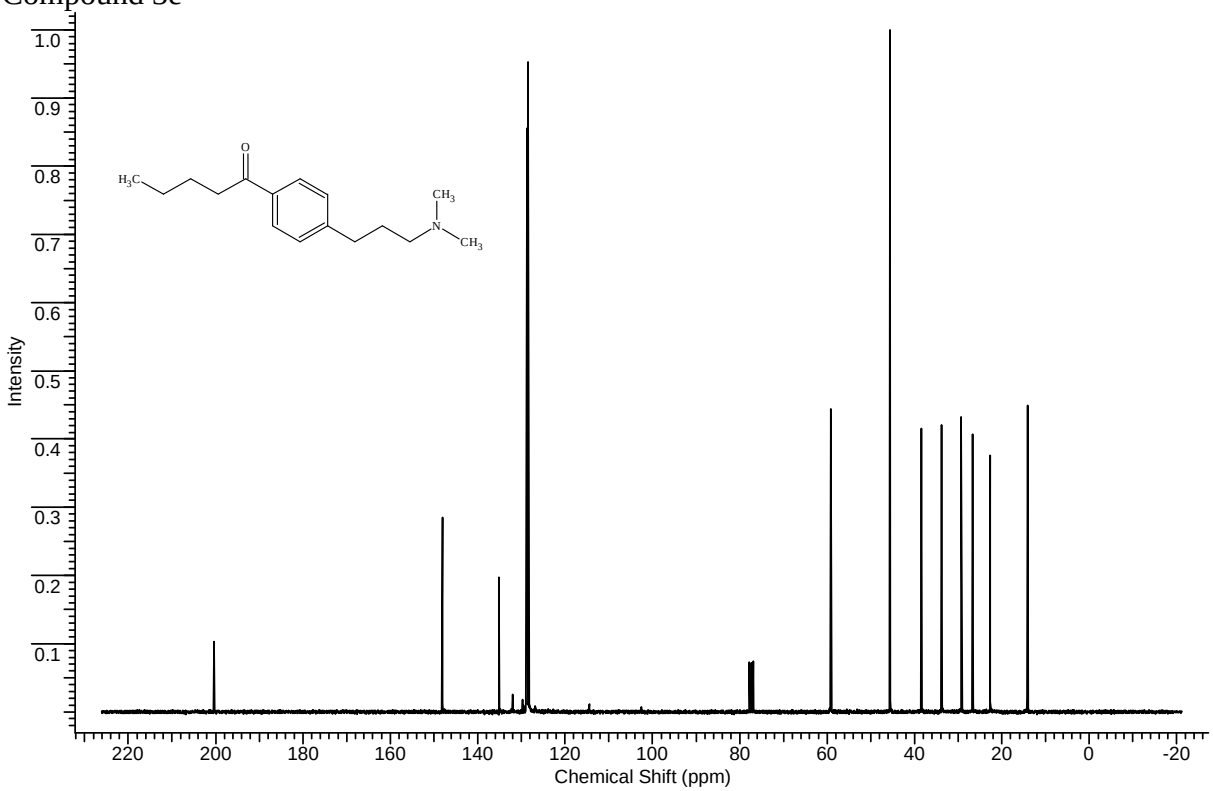

Compound 3d



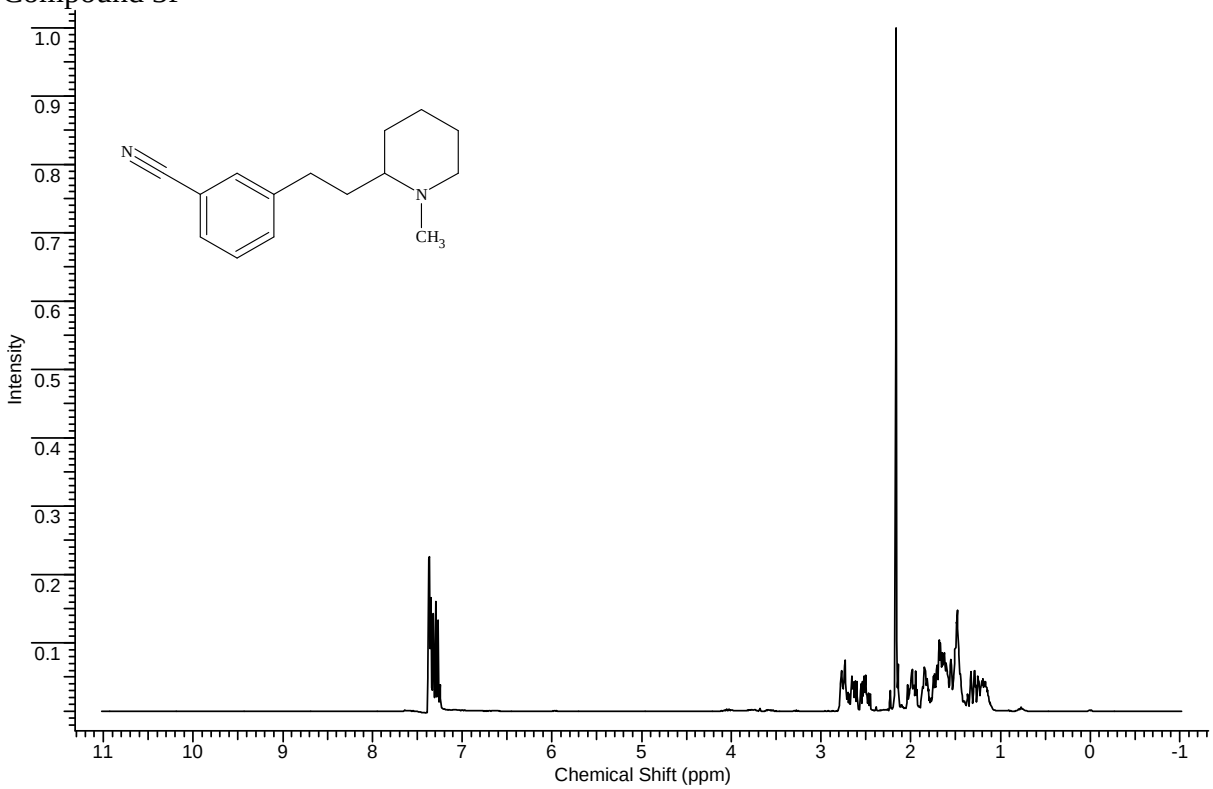
Compound 3e



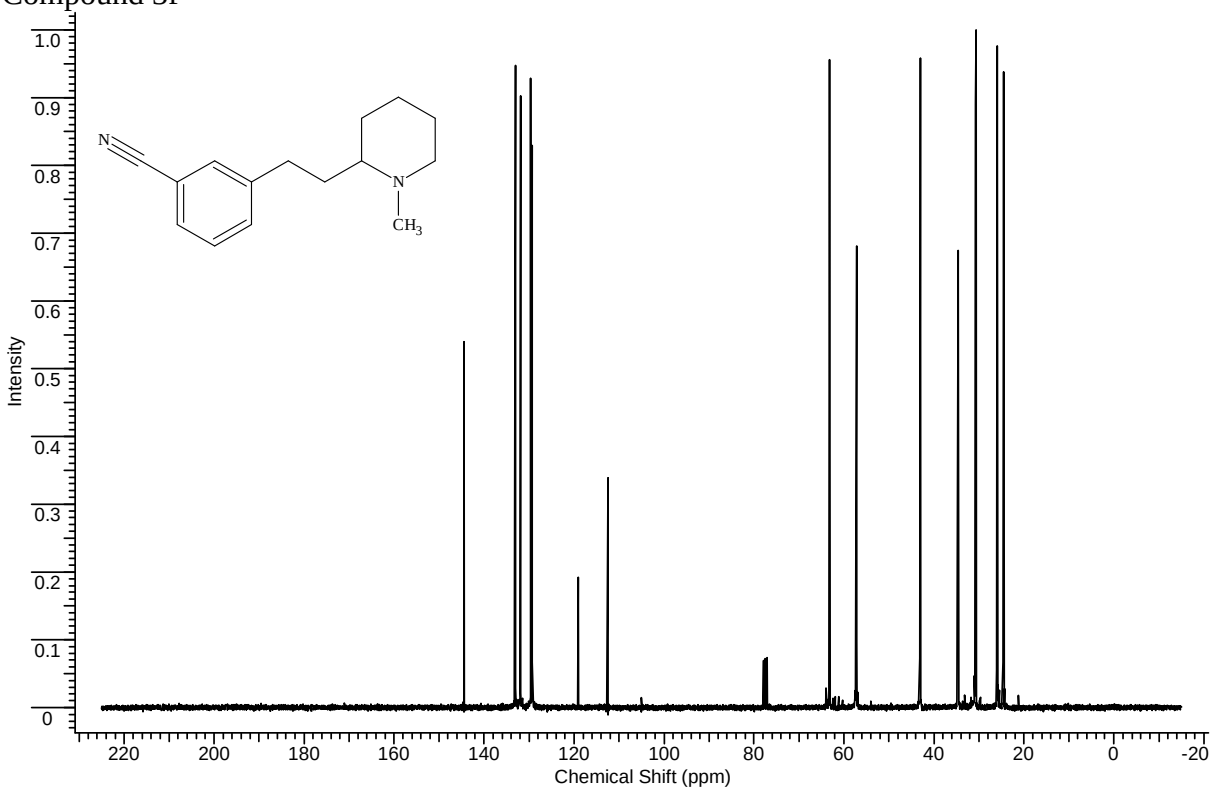

Compound 3e



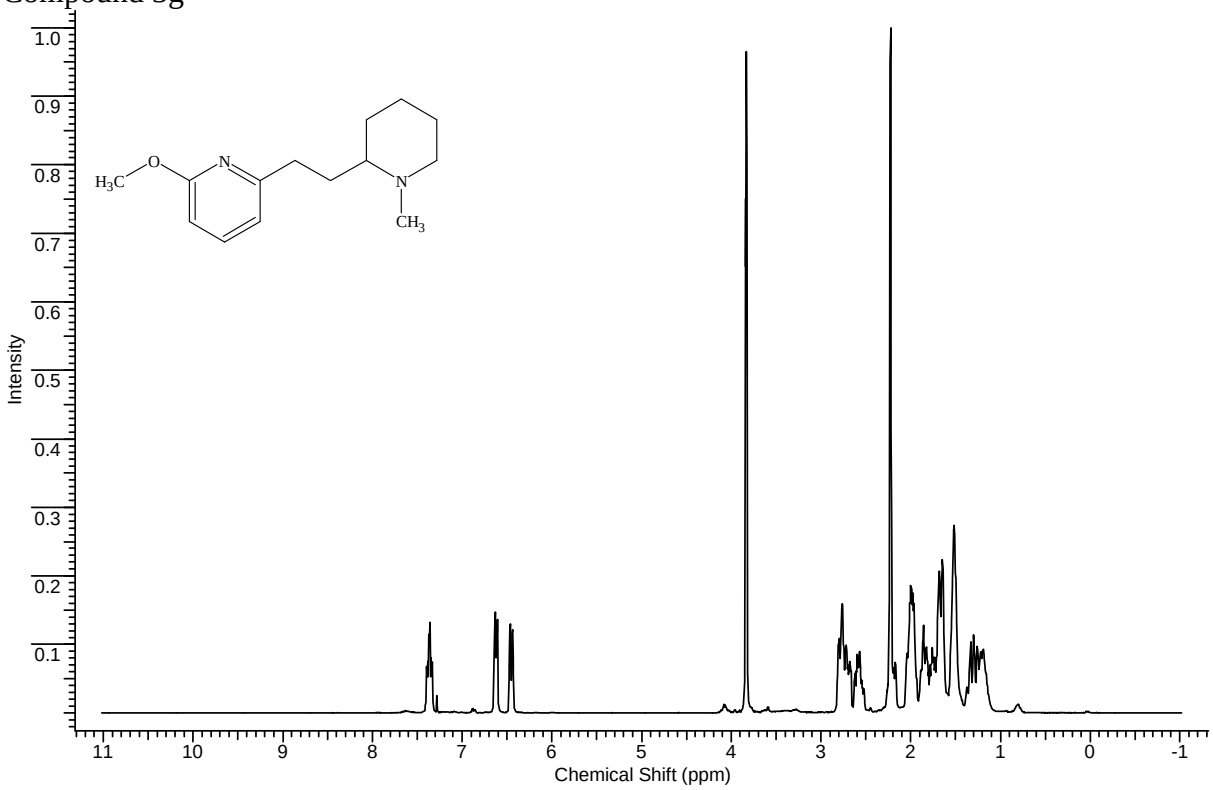
Compound 3f



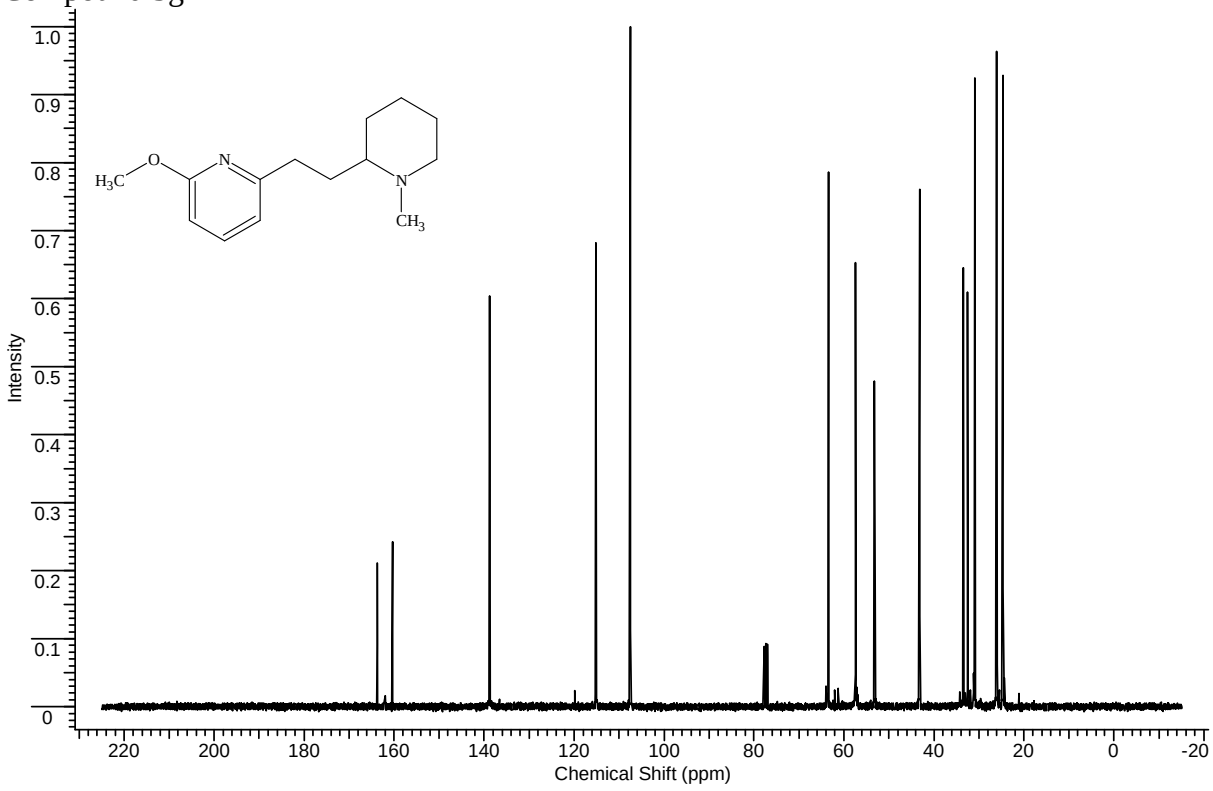

Compound 3f



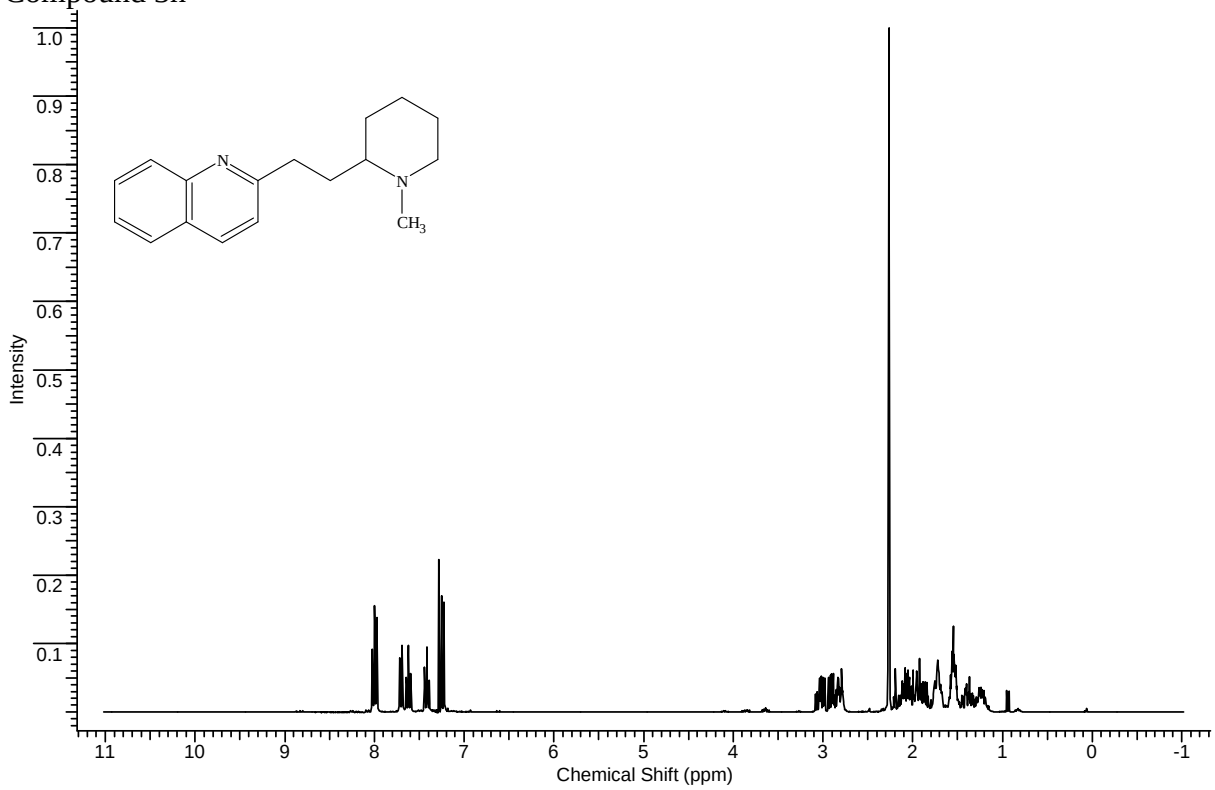
Compound 3g




Compound 3g



Compound 3h

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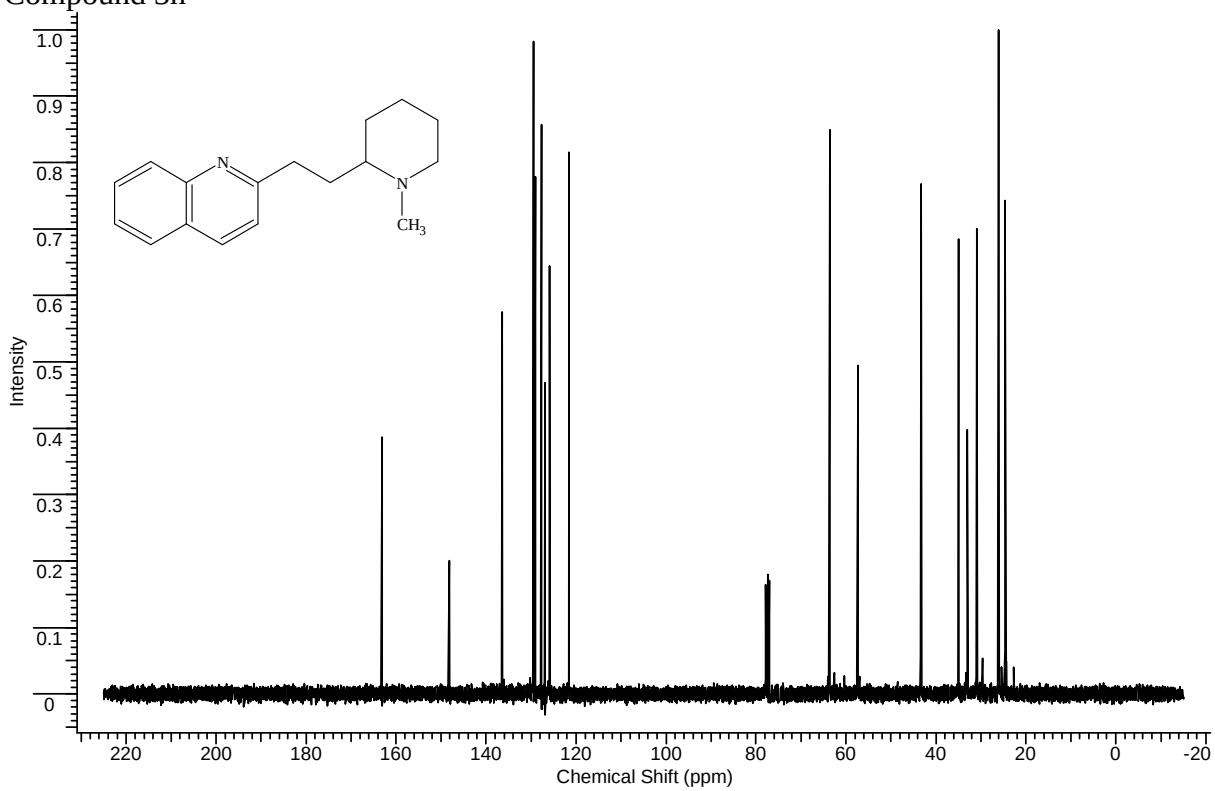

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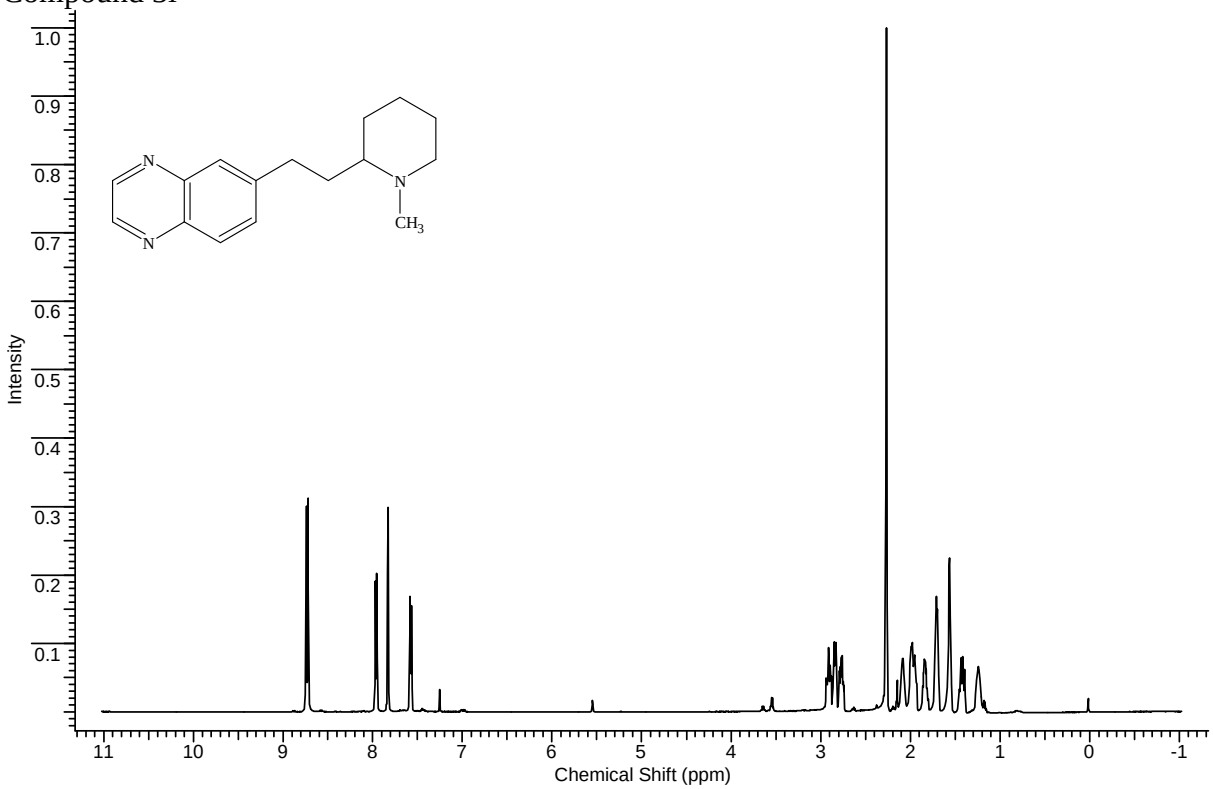


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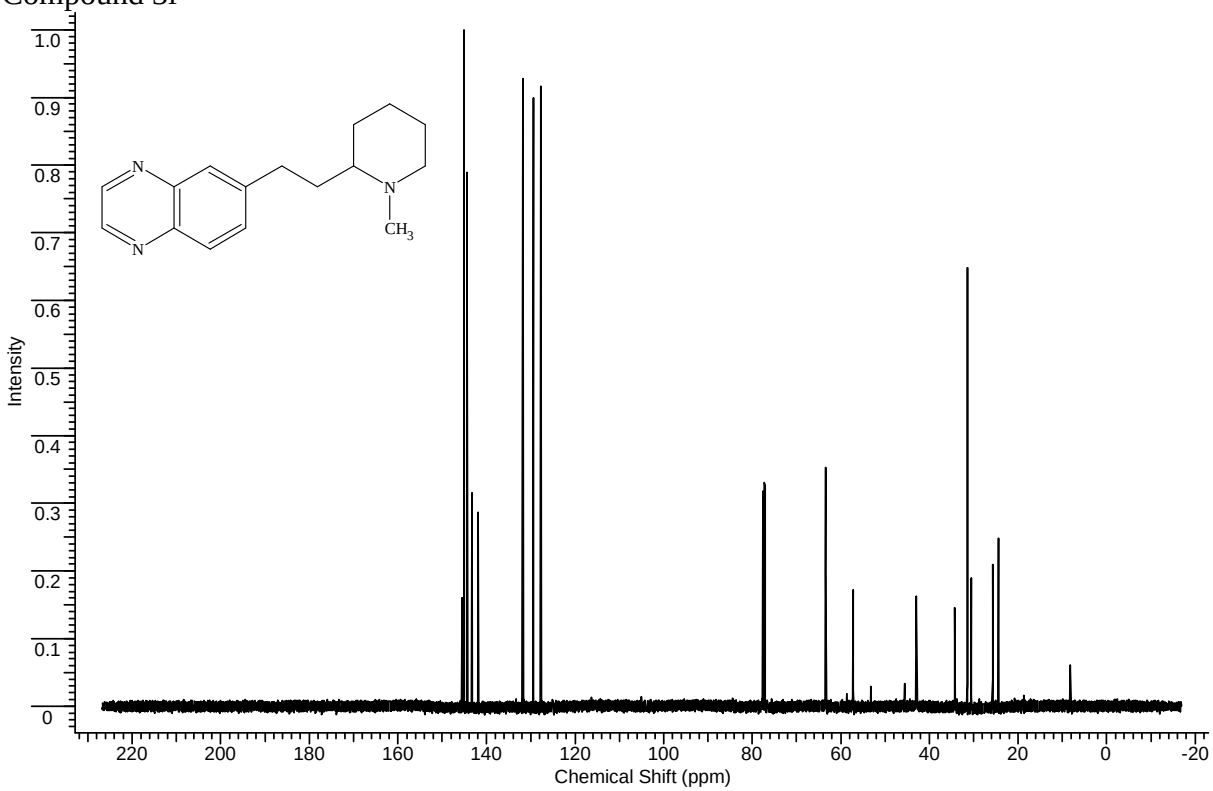

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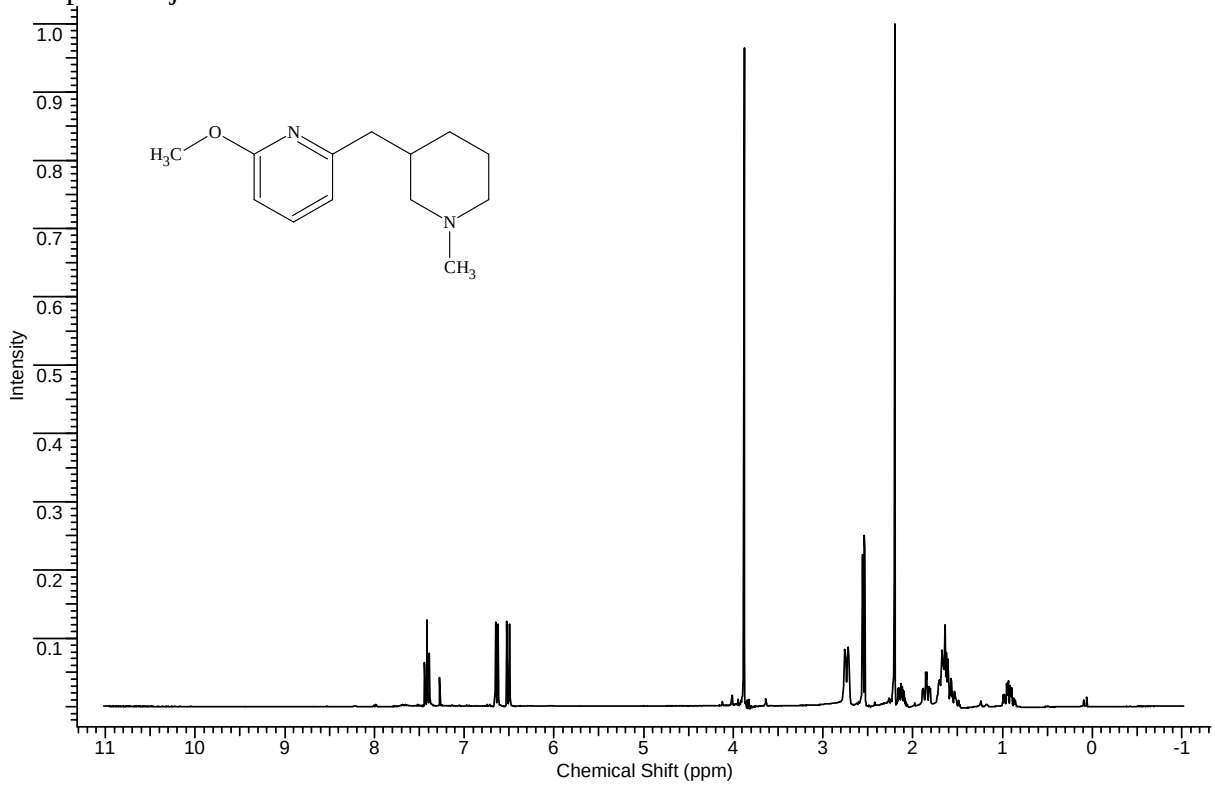


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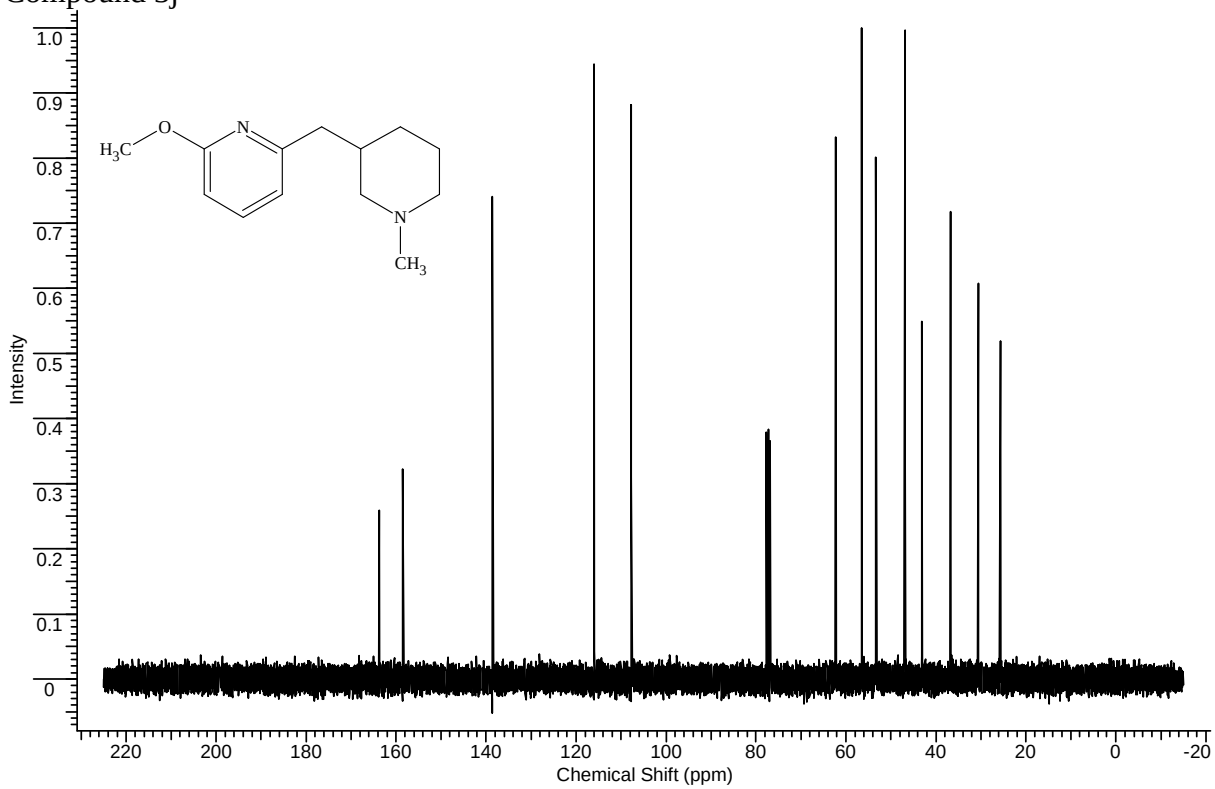

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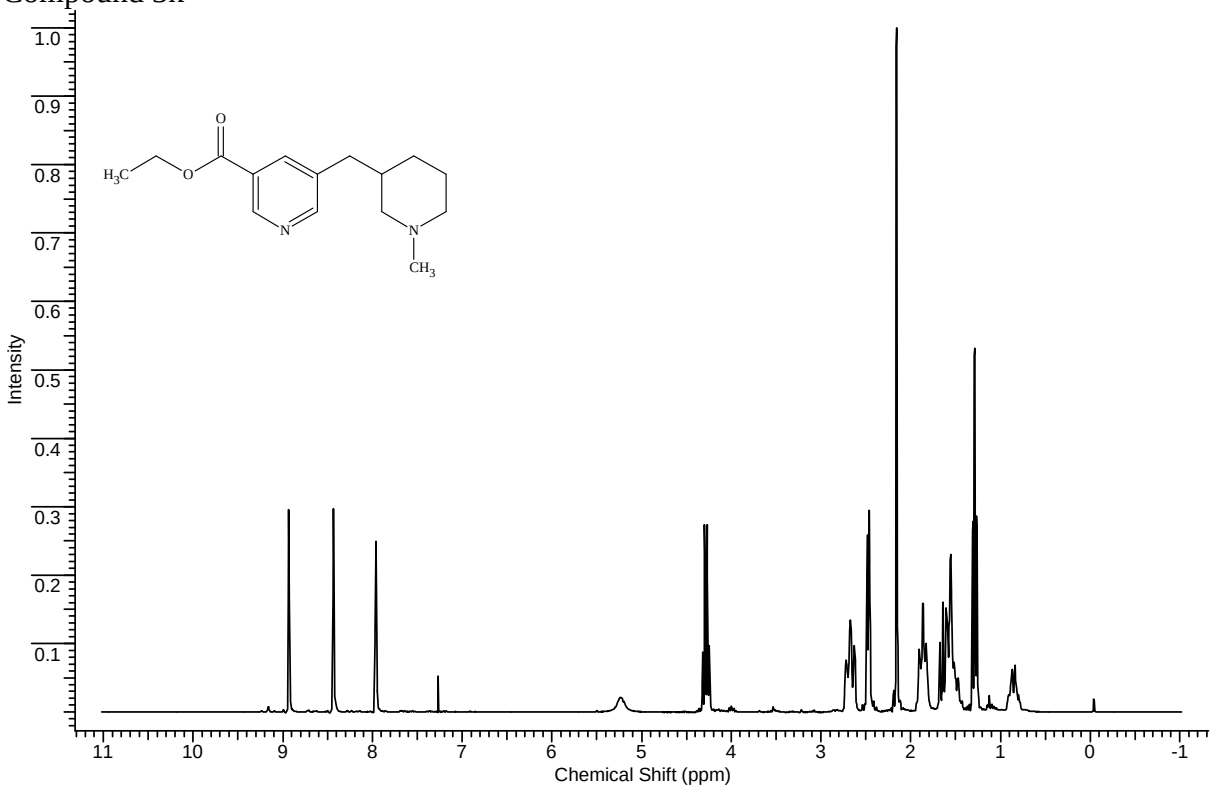


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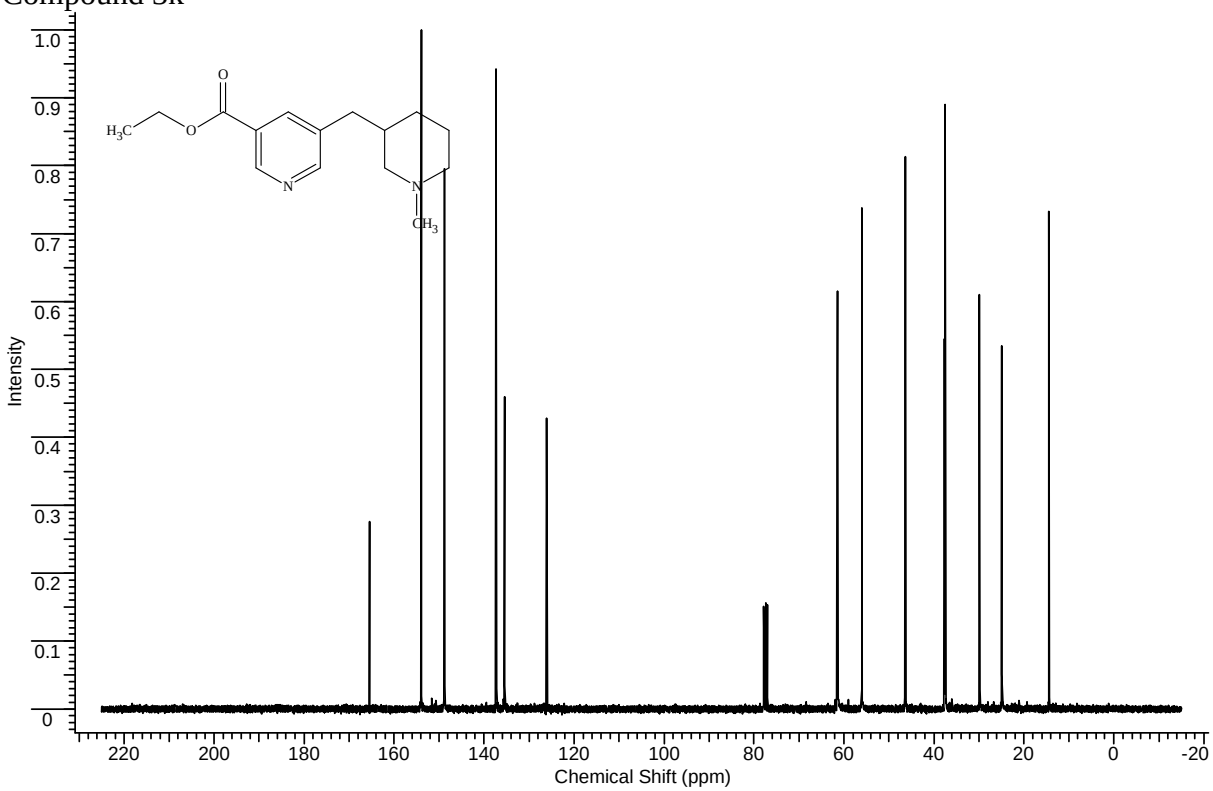

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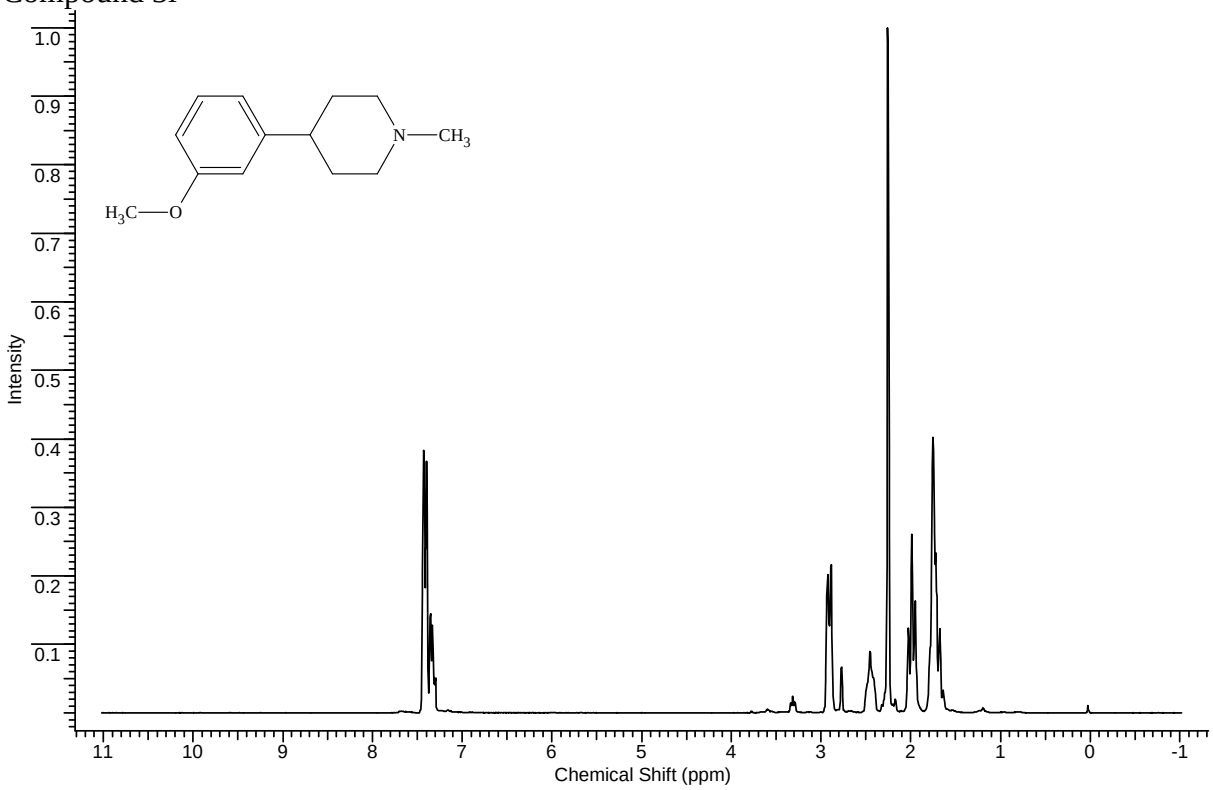


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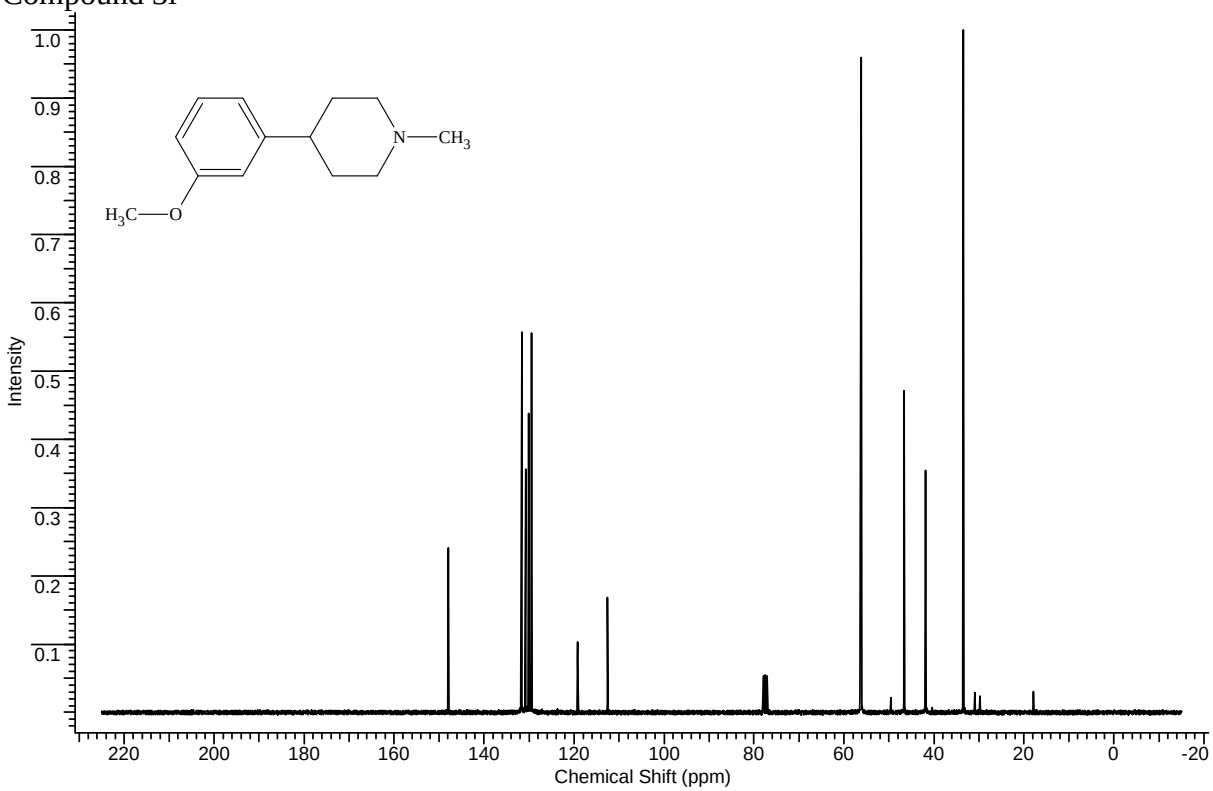
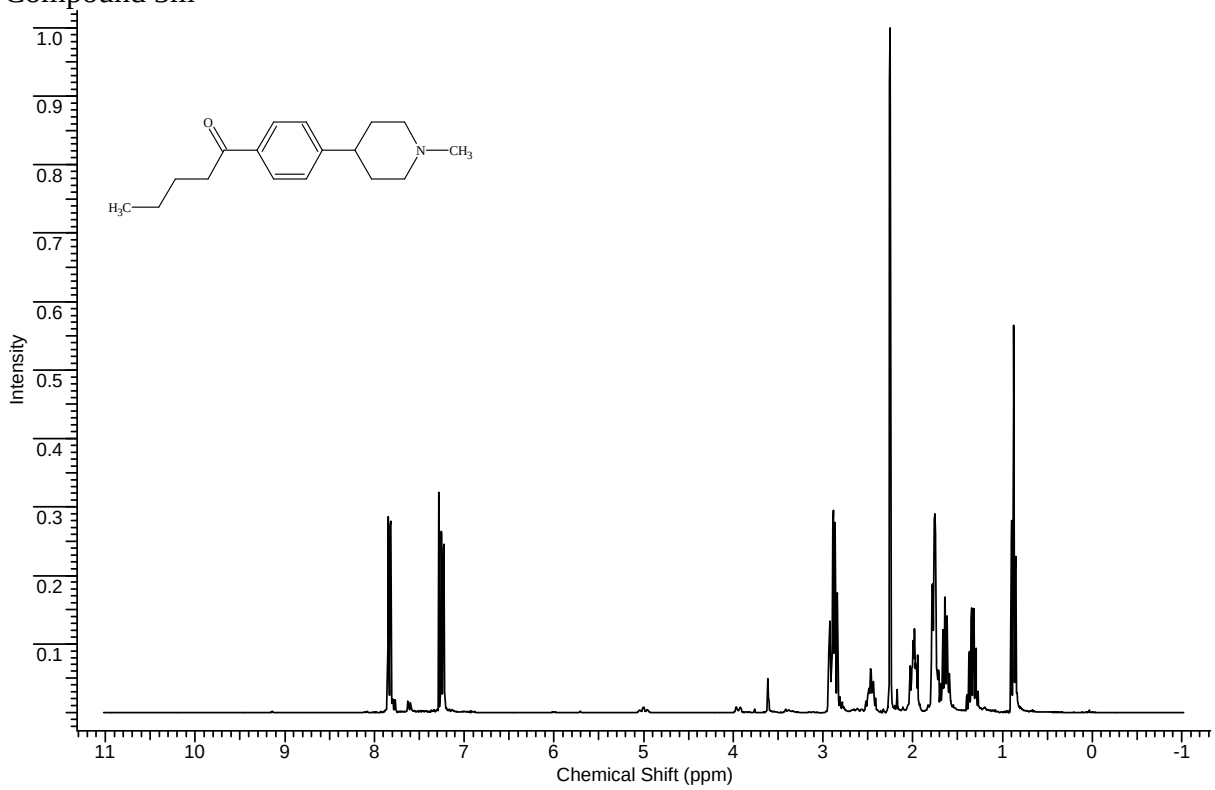
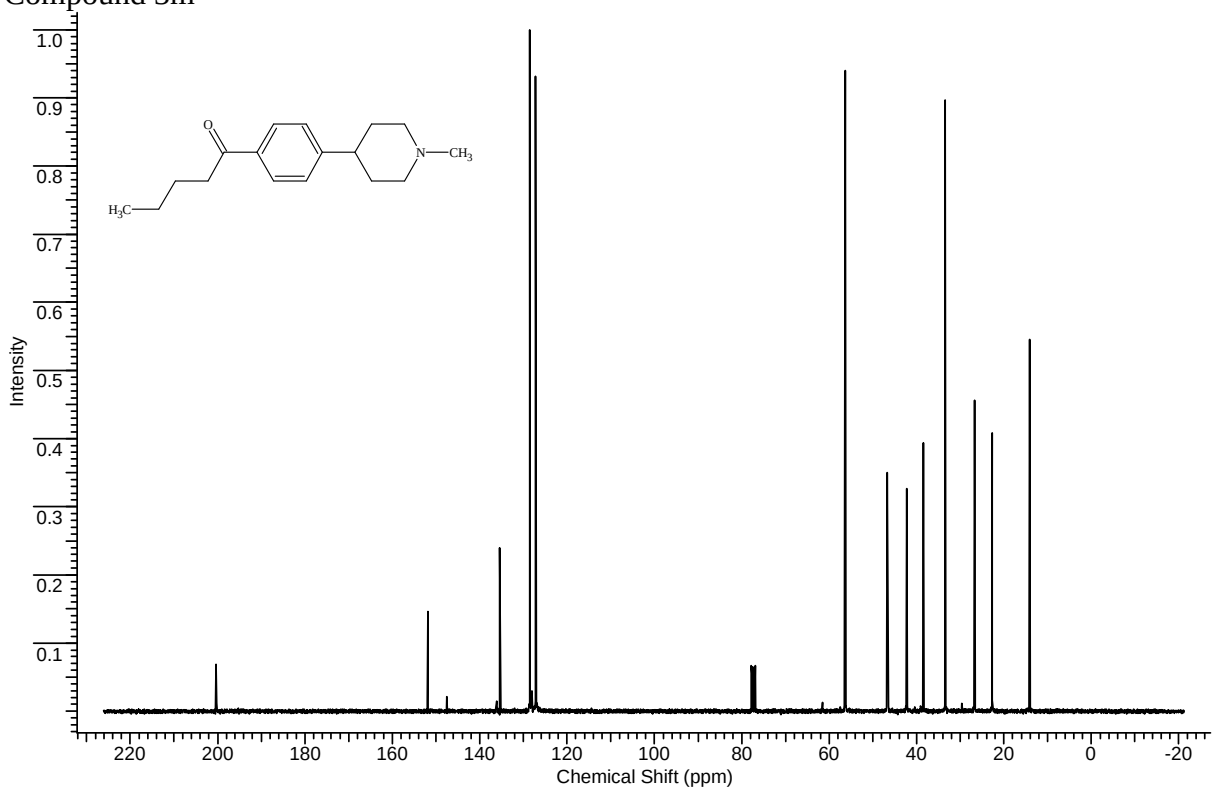


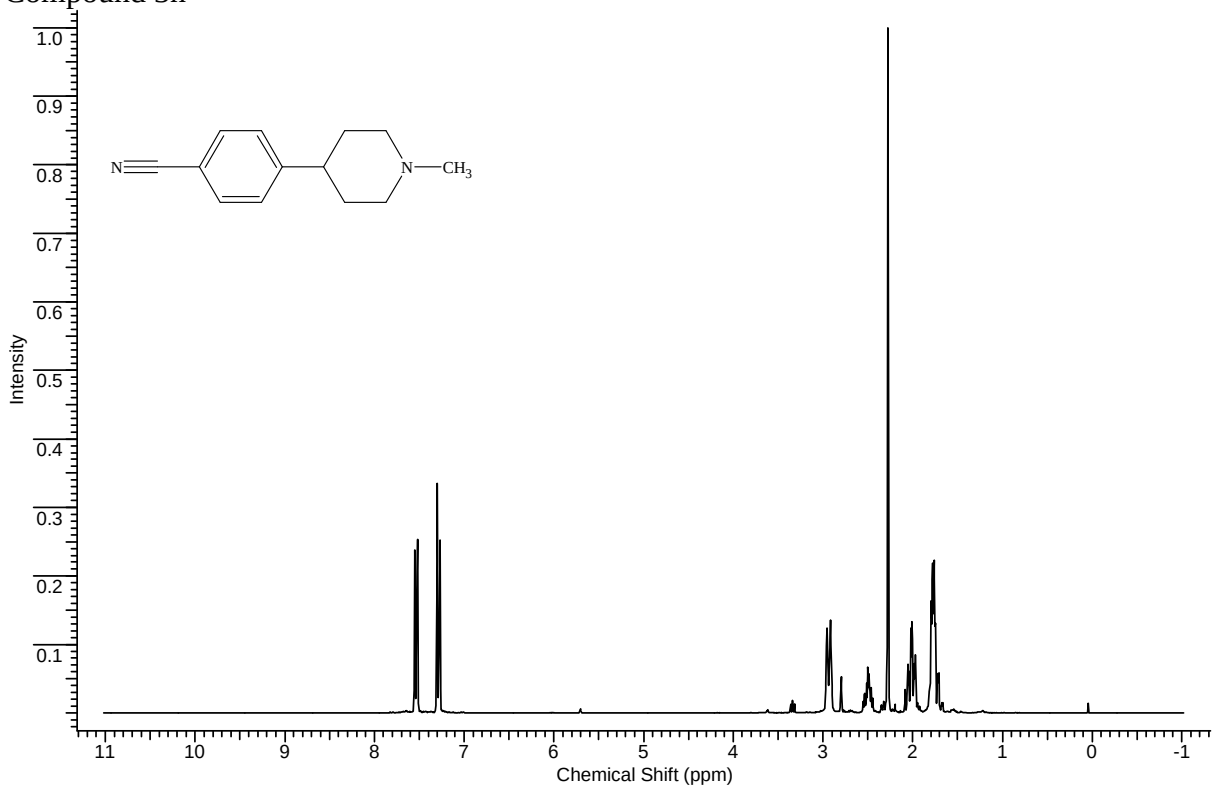
Compound 3m



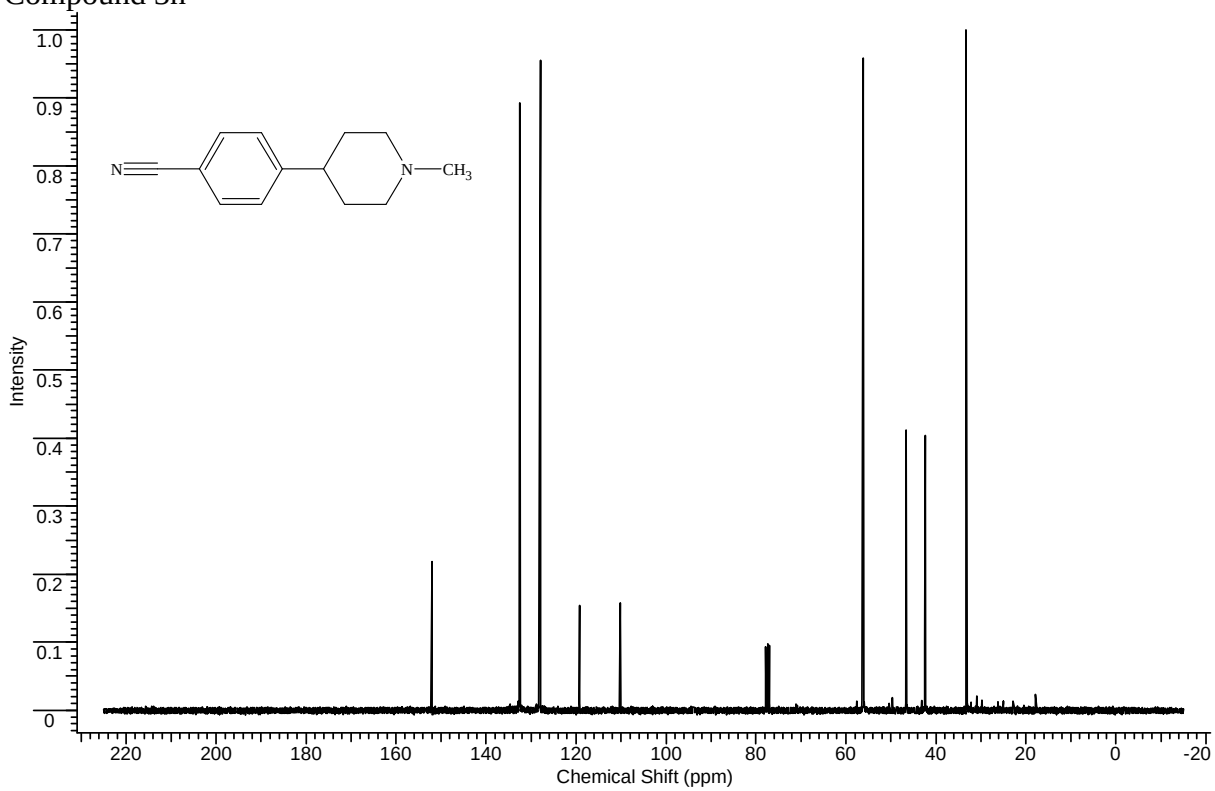

Compound 3m



Compound 3n




Compound 3n



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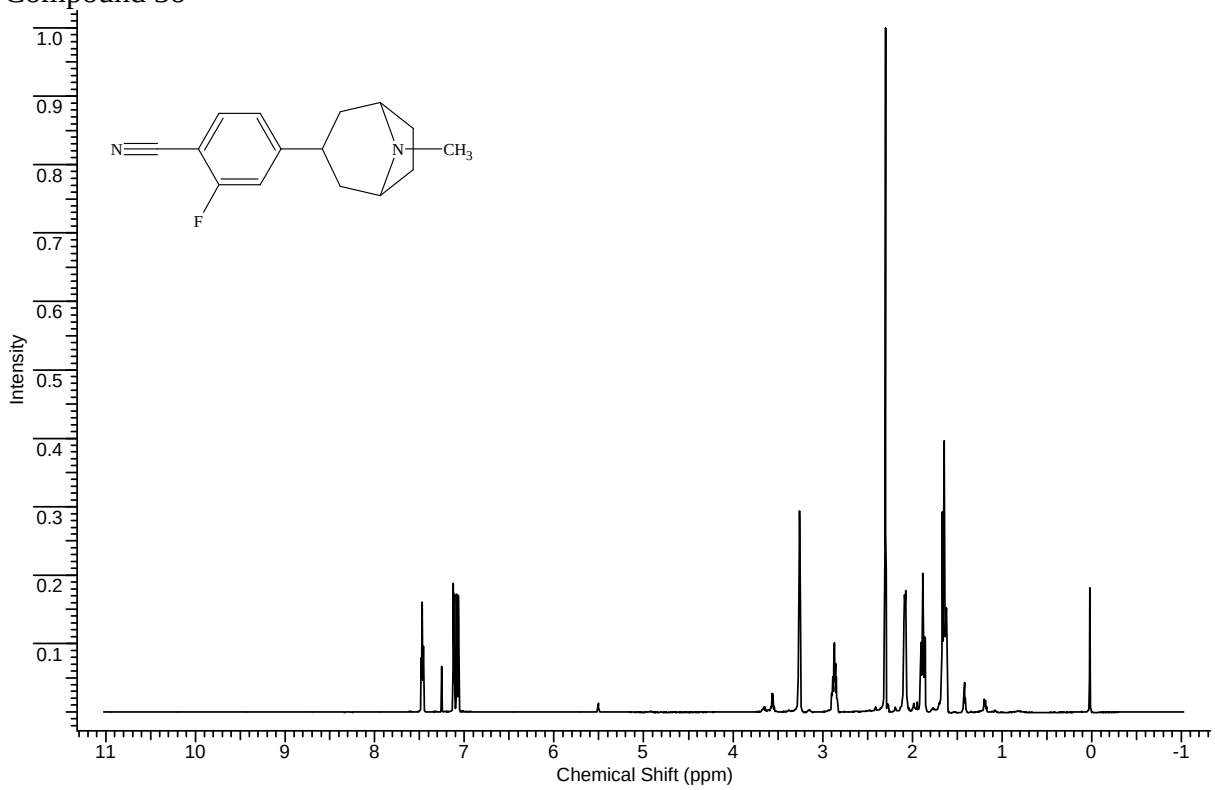
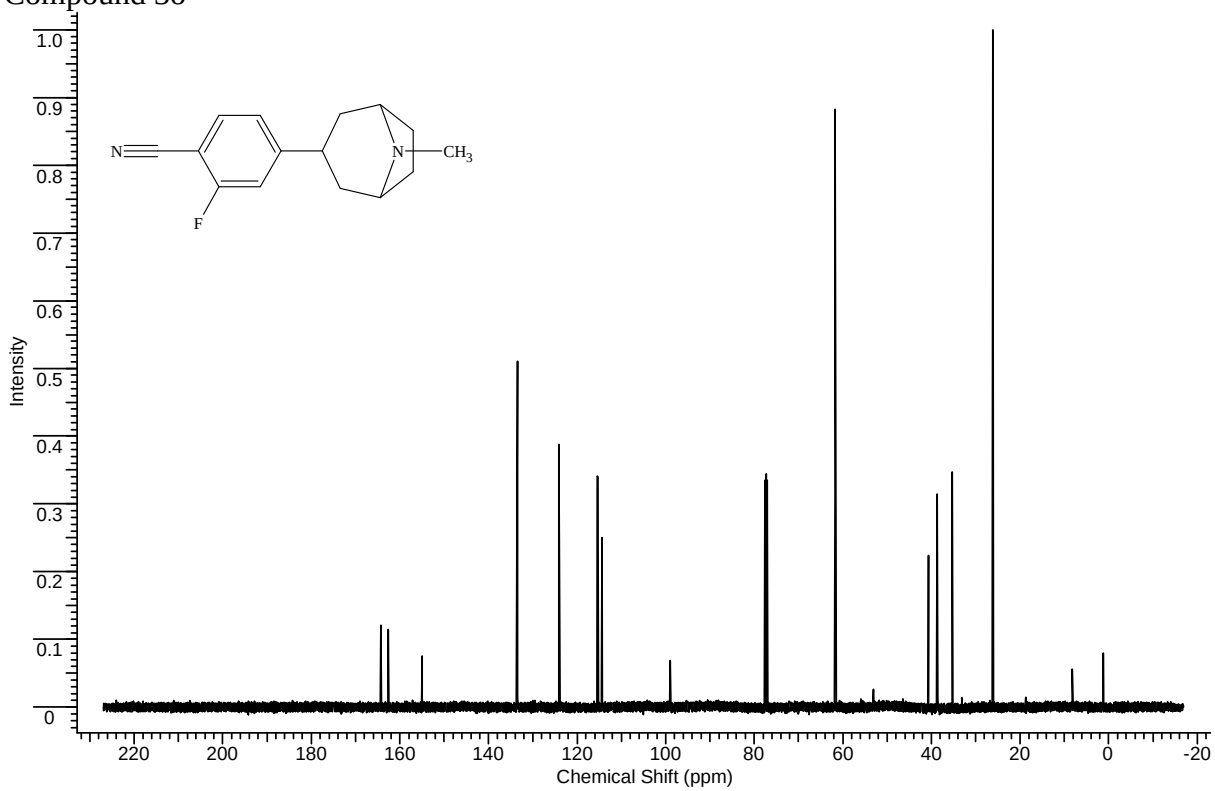
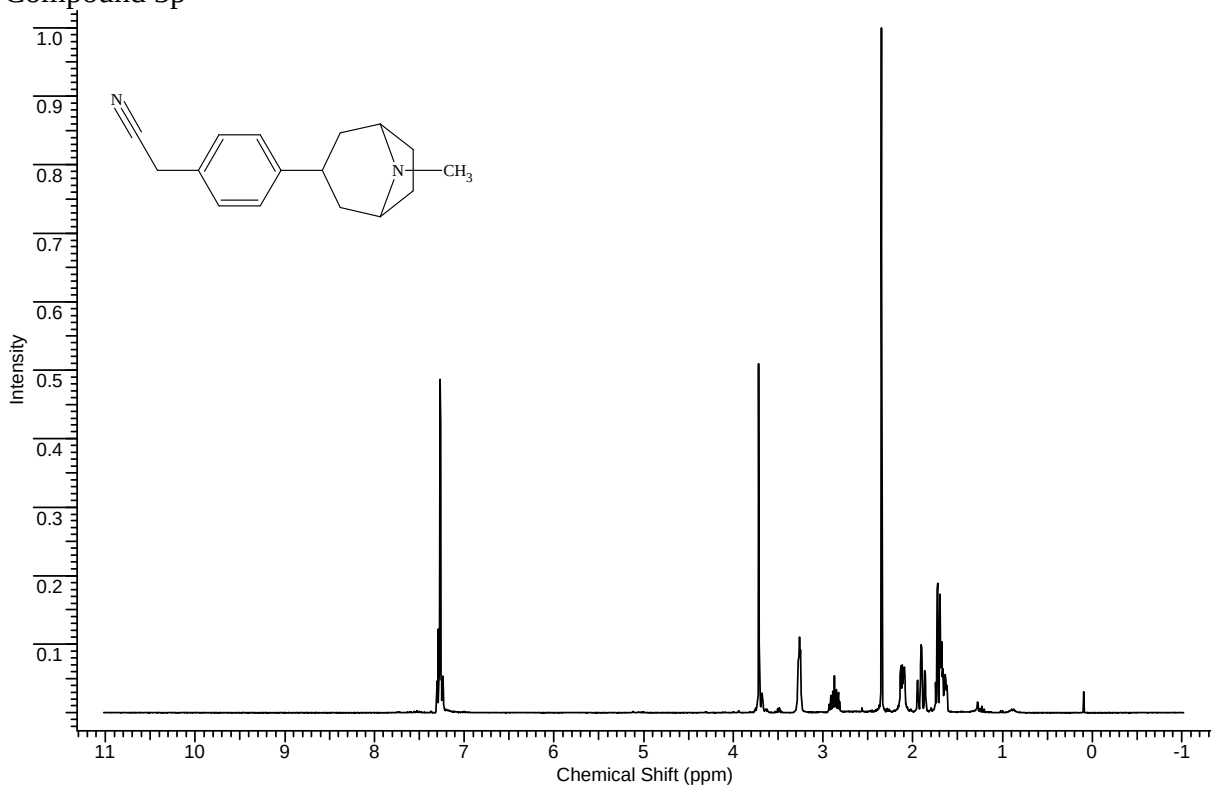



Compound 3o



Compound 3p

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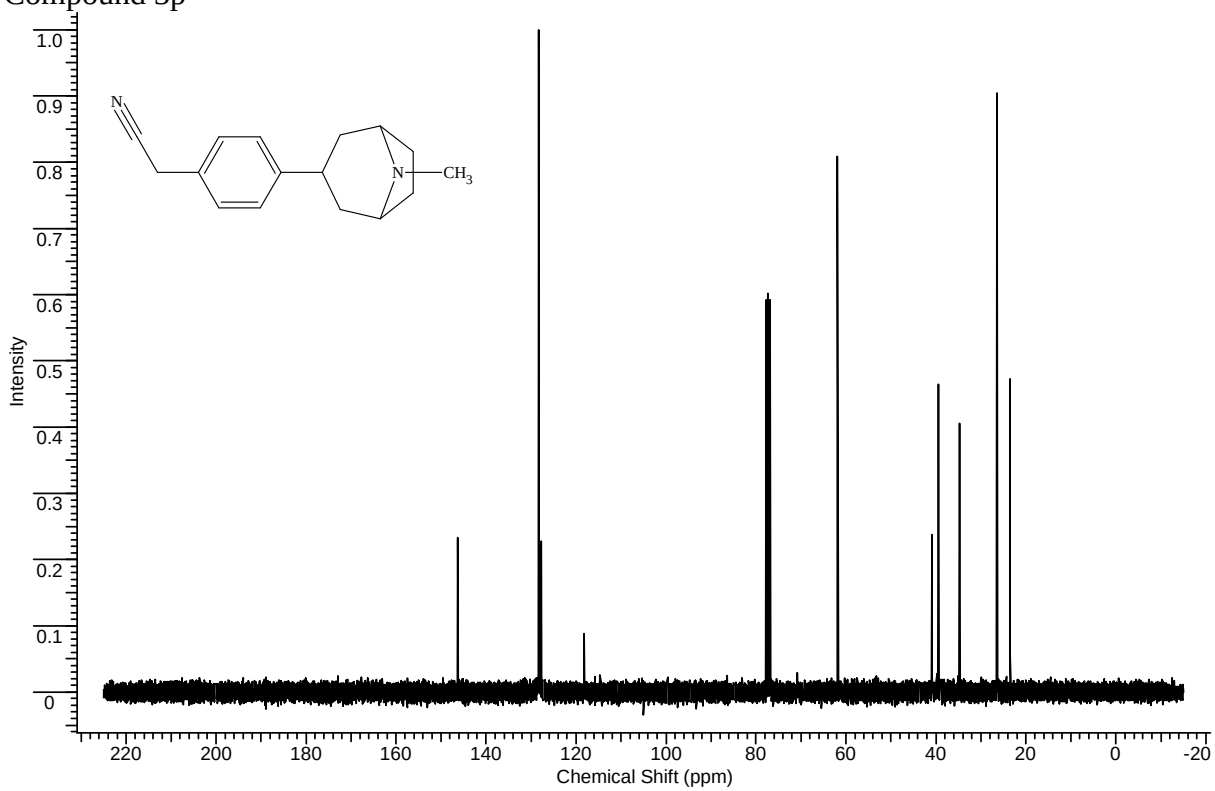
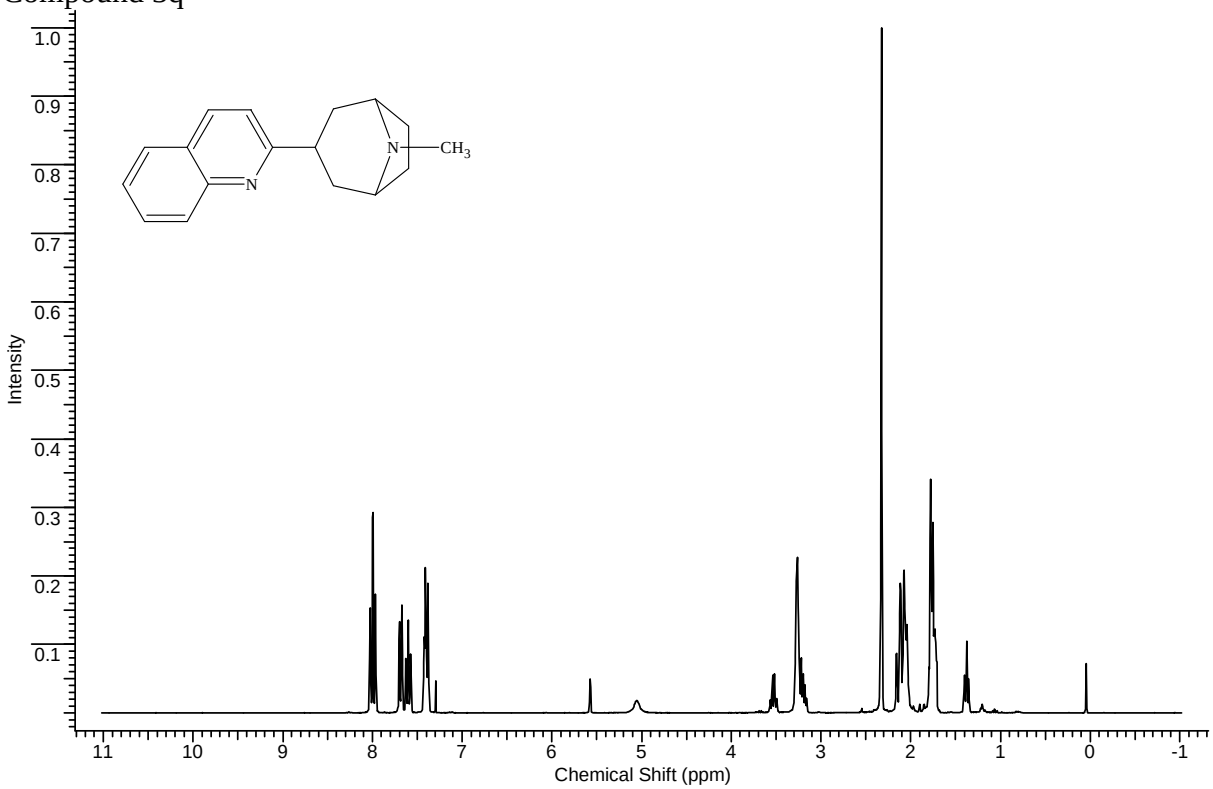


Compound 3q




Compound 3q