Borrowing Hydrogen Methodology for Amine Synthesis under Solvent Free Microwave Conditions

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General Methods:

Reactions which required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of nitrogen. All reactions were carried out in oven-dried, nitrogen-purged glassware.. TLC using polythene backed plates precoated with Macherey-Nagel Sil G/UV_{254nm} neutral silica were used to monitor reactions where appropriate. Visualisation of these plates was by 254 nm UV light and/or $KMnO_4$ dip followed by gentle warming. Flash column chromatography was carried out using Davisil LC 60 Å silica gel (35-70 micron). IR spectra were recorded with only selected absorbances quoted as ν in cm^{-1}. NMR spectra were run in $CDCl_3$ on a 300 MHz instrument and recorded at the following frequencies: proton (^1H – 300 MHz), carbon (^{13}C – 75.4 MHz). The following abbreviations are used: s, singlet; d, doublet; t, triplet; app. t, apparent triplet; q, quartet; app. q, apparent quartet; dd, doublet of doublets; m, multiplet and br, broad. Structural assignments of both protons and carbons were achieved with comparisons from analogous literature compounds; references are given in most cases.

An electrospray time-of-flight (ESI-TOF) mass spectrometer was used; this was coupled to an LC system. The LC system was used as an autosampler only. 10 μL of sample was injected into a 30:70 flow of water:acetonitrile at 0.6 mL/min to the mass spectrometer. For each acquisition 10 μL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern perfectly matched the corresponding theoretical values as calculated from the expected elemental formula. Unless preparative details are provided, all reagents were commercially available.

A Discover microwave reactor (CEM, North Carolina, USA) was used to heat the reactions set no higher than 50 Watts. Reaction mixture temperatures were measured by external surface sensor.

Experimental Procedures:

Representative Procedure for the Alkylation of Secondary Amines: To a microwave vial DPEphos (80.8 mg, 0.15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (45.9 mg, 0.075 mmol), amine (3 mmol) and alcohol (4.8 mmol, 1.6 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 115 °C (external surface sensor) for 90 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding tertiary amine in good yield.

Representative Procedure for the Alkylation of 1,2-Diols: To a microwave vial DPEphos (26.9 mg, 0.05 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), diol (1 mmol) and alcohol (2 mmol, 2 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 115 °C (external surface sensor) for 90 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding aminoalcohol in good yield.

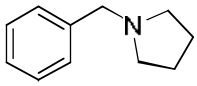
Representative Procedure for the Alkylation of Primary Amines: To a microwave vial DPEphos (80.8 mg, 0.15 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (45.9 mg, 0.075 mmol), amine (3 mmol) and alcohol (4.8 mmol, 1.6 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 125 °C (external surface sensor) for 90 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding secondary amine in good yield.

Representative Procedure for the Dialkylation of Primary Amines: To a microwave vial DPEphos (26.9 mg, 0.05 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), amine (1 mmol) and diol (1.6 mmol, 1.6 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 135 °C (external surface sensor) for 90 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding secondary amine in good yield.

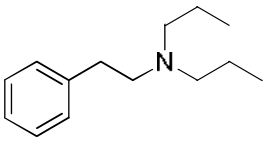
Representative Procedure for the Alkylation of Sulfonamides: To a microwave vial DPEphos (26.9 mg, 0.05 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), sulfonamide (1 mmol) and alcohol (3 mmol, 3 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 165 °C (external surface sensor) for 180 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding secondary amine in good yield.

Representative Procedure for the Alkylation of Primary Amides: To a microwave vial DPEphos (26.9 mg, 0.05 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (15.3 mg, 0.025 mmol), amide (1 mmol) and alcohol (3 mmol, 3 eq.) were added before the vial was sealed with a rubber septum. The vial was then purged with N_2 for 5 min before heating to 175 °C (external surface sensor) for 120 min using a microwave. After heating, the vial was allowed to cool to room temperature before the crude product was purified by silica column chromatography to afford the corresponding secondary amine in good yield.

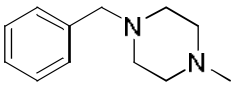
Experimental Data:



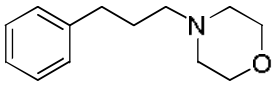
1-Benzylpyrrolidine[1] (Entry 1, Table 2): According to the representative procedure the title compound was purified by silica column chromatography (95:5 CH_2Cl_2/MeOH, R_f = 0.20) afforded the title compound as a brown oil (348 mg, 72%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.14-7.29 (5H, m), 3.55 (2H, s), 2.42-2.47 (4H, m), 1.69-1.74 (4H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 139.3, 128.9, 128.2, 126.8, 60.7, 54.1, 23.4; HRMS(ESI-TOF) : calcd. For $C_{11}H_{15}NH^+$: 162.1283. Found : 162.1272 (MH^+).



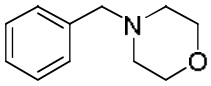
***N*-Phenethyl-*N*-propylpropan-1-amine[2] (Entry 2, Table 2):** According to the representative procedure the title compound was purified by silica column chromatography (95:5 CH_2Cl_2/MeOH, R_f = 0.19) afforded the title compound as a yellow oil (581 mg, 94%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.26-7.31 (2H, m), 7.16-7.21 (3H, m), 2.69-2.79 (4H, m), 2.46-2.51 (4H, m), 1.44-1.57 (4H, m), 0.89 (6H, t, *J* = 7.5 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 141.1, 128.9, 128.4, 126.0, 56.3, 33.6, 20.5, 12.1; HRMS(ESI-TOF) : calcd. for $C_{14}H_{23}NH^+$: 206.1909. Found : 206.1923 (MH^+).



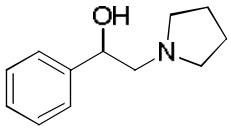
1-Benzyl-4-methylpiperazine[3] (Entry 3, Table 2): According to the representative procedure the title compound was purified by silica column chromatography (9:1 CH_2Cl_2/MeOH, R_f = 0.19) afforded the title compound as a yellow oil (451 mg, 79%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.21-7.32 (5H, m), 3.51 (2H, s), 2.47 (8H, br s), 2.29 (3H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 138.3, 129.3, 128.3, 127.1, 63.2, 55.3, 53.2, 46.2; HRMS(ESI-TOF) : calcd. for $C_{12}H_{18}N_2H^+$: 191.1548. Found : 191.1543 (MH^+).



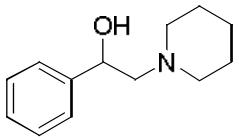
4-(3-Phenylpropyl)morpholine[3] (Entry 4, Table 2): According to the representative procedure the title compound was purified by silica column chromatography (3:1 Et_2O/Petroleum Ether (b.p. 40-60 °C), R_f = 0.20) afforded the title compound as a brown oil (511 mg, 83%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.26-7.31 (2H, m), 7.16-7.20 (3H, m), 3.73 (4H, app t, *J* = 4.7 Hz), 2.65 (2H, t, *J* = 7.7 Hz), 2.45 (4H, m, H), 2.38 (2H, t, *J* = 7.7 Hz), 1.78-1.89 (2H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.2, 128.5, 128.4, 125.9, 67.1, 58.5, 53.4, 33.7, 28.4; HRMS(ESI-TOF) : calcd. for $C_{13}H_{19}NOH^+$: 206.1545. Found : 206.1548 (MH^+).



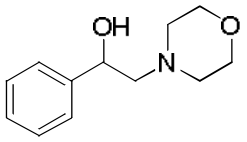
***N*-Benzylmorpholine[3] (Entry 5, Table 2):** According to the representative procedure the title compound was purified by silica column chromatography (3:1 Petroleum Ether (b.p. 40-60 °C)/EtOAc, R_f = 0.19) afforded the title compound as a yellow oil (431 mg, 81%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.20-7.27 (5H, m), 3.66 (4H, t, *J* = 4.7 Hz), 3.45 (2H, s), 2.39 (4H, t, *J* = 4.5 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 137.7, 129.3, 128.3, 127.2, 67.0, 63.5, 53.6; HRMS(ESI-TOF) : calcd. for $C_{11}H_{16}NOH^+$: 178.1232. Found : 178.1229 (MH^+).



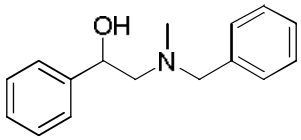
1-Phenyl-2-(pyrrolidin-1-yl)ethanol[4] (Entry 1, Table 3): According to the representative procedure the title compound was purified by silica column chromatography (2:1 Et_2O/CH_2Cl_2, R_f = 0.16) afforded the title compound as a colourless solid (144 mg, 75%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.24-7.41 (5H, m), 4.74 (1H, dd, *J* = 10.8 3.3 Hz), 3.89 (1H, br s), 2.78-2.85 (3H, m), 2.50-2.63 (3H, m), 1.81-1.85 (4H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.5, 128.4, 127.5, 126.0, 70.8, 64.2, 54.0, 23.8; HRMS(ESI-TOF) : calcd. for $C_{12}H_{17}NOH^+$: 192.1388. Found : 192.1399 (MH^+).



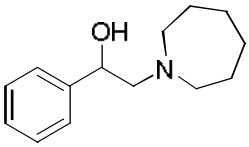
1-Phenyl-2(piperidin-1-yl)ethanol[4] (Entry 2, Table 3): According to the representative procedure the title compound was purified by silica column chromatography (2:1 Et_2O/CH_2Cl_2, R_f = 0.23) afforded the title compound as a colourless solid (162 mg, 79%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.23-7.40 (5H, m), 4.73 (1H, dd, *J* = 10.5 3.9 Hz), 4.19 (1H, br s), 2.69-2.71 (2H, m), 2.36-2.53 (4H, m), 1.59-1.66 (4H, m), 1.46-1.51 (2H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.6, 128.4, 127.5, 126.0, 68.8, 67.1, 54.6, 26.3, 24.4; HRMS(ESI-TOF) : calcd. for $C_{13}H_{19}NOH^+$: 206.1545. Found : 206.1544 (MH^+).



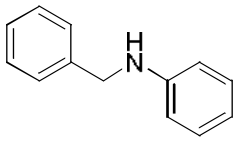
2-Morpholino-1-phenylethanol[4] (Entry 3, Table 3): According to the representative procedure the title compound was purified by silica column chromatography (30:1 EtOAc/EtOH, R_f = 0.26) afforded the title compound as a colourless solid (187 mg, 90%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.28-7.39 (5H, m), 4.80 (1H, dd, *J* = 10.2 4.2 Hz), 3.76-3.80 (4H, m), 2.75-2.82 (2H, m), 2.47-2.57 (4H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.0, 128.5, 127.7, 126.0, 68.7, 67.2, 66.8, 53.6; HRMS(ESI-TOF) : calcd. for $C_{12}H_{17}NO_2H^+$: 208.1338. Found : 208.1338 (MH^+).



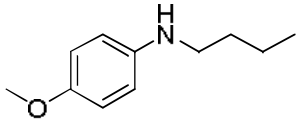
2-(Benzyl(methyl)amino-1-phenylethanol[5] (Entry 4, Table 3): According to the representative procedure the title compound was purified by silica column chromatography (3:2 Hexane/EtOAc R_f = 0.25) afforded the title compound as a brown oil (147 mg, 61%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.26-7.38 (10H, m), 4.77 (1H, dd, *J* = 10.2 3.9 Hz), 3.77 (1H, d, *J* = 13.2 Hz), 3.57 (1H, d, *J* = 13.2 Hz), 2.63 (1H, dd, *J* = 12.3 10.3 Hz), 2.55 (1H, dd, *J* = 12.6 10.3 Hz), 2.35 (3H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.3, 138.2, 129.2, 128.5, 128.4, 127.6, 127.5, 126.0, 69.5, 65.6, 62.5, 41.9; HRMS(ESI-TOF) : calcd. for $C_{16}H_{19}NOH^+$: 242.1545. Found : 242.1557 (MH^+).



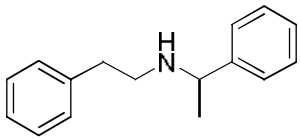
2-(Azepan-1-yl)-1-phenylethanol[6] (Entry 5, Table 3): According to the representative procedure the title compound was purified by silica column chromatography (3:2 CH_2Cl_2/Et_2O R_f = 0.24) afforded the title compound as a yellow oil (145 mg, 63%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.23-7.42 (5H, m), 4.70 (1H, dd, *J* = 10.8 3.3 Hz), 3.59 (1H, br s), 2.88-2.96 (2H, m), 2.73-2.84 (3H, m), 2.51 (1H, dd, *J* = 12.6 10.8 Hz), 1.63-1.77 (8H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 142.5, 128.4, 127.5, 126.0, 69.4, 66.3, 55.7, 28.3, 27.1; HRMS(ESI-TOF) : calcd. for $C_{14}H_{21}NOH^+$: 220.1701. Found : 220.1686 (MH^+).



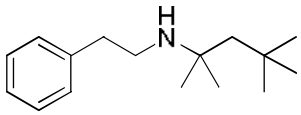
***N*-Benzylaniline[3] (Entry 1, Table 4):** According to the representative procedure the title compound was purified by silica column chromatography (20:1 Petroleum Ether (b.p. 40-60 °C)/Et_2O R_f = 0.30) afforded the title compound as a brown oil (500 mg, 91%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.27-7.40 (5H, m), 7.15-7.21 (2H, m), 6.76 (1H, t, *J* = 7.5 Hz), 6.69 (2H, d, *J* = 7.5 Hz), 4.88 (1H, br s), 4.34 (2H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 148.2, 139.5, 129.4, 128.8, 127.7, 127.4, 117.8, 113.1, 48.5; HRMS(ESI-TOF) : calcd. for $C_{13}H_{13}NH^+$: 184.1126. Found : 184.1104 (MH^+).



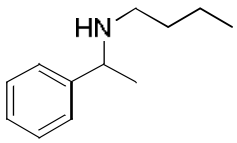
***N*-Butyl-4-methoxyaniline[7] (Entry 2, Table 4):** According to the representative procedure the title compound was purified by silica column chromatography (9:1 Petroleum Ether (b.p. 40-60 °C)/Et_2O R_f = 0.17) afforded the title compound as a yellow oil (393 mg, 73%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 6.76-6.81 (2H, m), 6.57-6.63 (2H, m), 3.75 (3H, s), 3.07 (2H, t, *J* = 7.2 Hz), 1.55-1.65 (2H, m), 1.36-1.49 (2H, m), 0.95 (3H, t, *J* = 7.2 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 152.1, 143.0, 115.0, 114.2, 56.0, 44.9, 31.9, 20.5, 14.1; HRMS(ESI-TOF) : calcd. for $C_{11}H_{17}NOH^+$: 180.1388. Found : 180.1369 (MH^+).



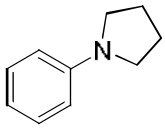
***N*-Phenethyl-1-phenethanamine[3] (Entry 3, Table 4):** According to the representative procedure the title compound was purified by silica column chromatography (4:1 CH_2Cl_2/Et_2O R_f = 0.24) afforded the title compound as a brown oil (635 mg, 94%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.15-7.34 (10H, m), 3.79 (1H, q, *J* = 6.6 Hz), 2.68-2.83 (4H, m), 1.35 (3H, d, *J* = 6.6 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 145.7, 140.2, 128.8, 128.5, 128.5, 127.0, 126.7, 126.2, 58.3, 49.0, 36.5, 24.4; HRMS(ESI-TOF) : calcd. for $C_{16}H_{19}NH^+$: 226.1596. Found : 226.1569 (MH^+).



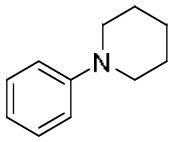
2,4,4-Trimethyl-*N*-phenethylpentan-2-amine[8] (Entry 4, Table 4): According to the representative procedure the title compound was purified by silica column chromatography (92:8 CH_2Cl_2/MeOH R_f = 0.31) afforded the title compound as a brown oil (574 mg, 82%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.20-7.32 (5H, m), 2.84 (4H, br s), 1.44 (2H, s), 1.16 (6H, s), 0.95 (9H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 140.5, 128.9, 128.5, 126.2, 54.4, 53.1, 43.8, 37.3, 31.8, 31.7, 29.0; HRMS(ESI-TOF) : calcd. for $C_{16}H_{27}NH^+$: 234.2222. Found : 234.2229 (MH^+).



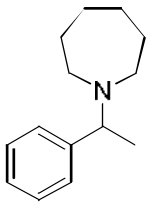
2,4,4-Trimethyl-*N*-phenethylpentan-2-amine[9] (Entry 5, Table 4): According to the representative procedure the title compound was purified by silica column chromatography (1:1 Petroleum Ether (b.p. 40-60 °C)/Et_2O R_f = 0.25) afforded the title compound as a yellow oil (425 mg, 80%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.21-7.36 (5H, m), 3.77 (1H, q, *J* = 6.6 Hz), 2.38-2.55 (2H, m), 1.78 (1H, br s), 1.41-1.52 (2H, m), 1.38 (3H, d, *J* = 6.6 Hz), 1.23-1.34 (2H, m), 0.87 (3H, t, *J* = 7.2 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 146.0, 128.5, 126.9, 126.7, 58.5, 47.7, 32.5, 24.5, 20.6, 14.1; HRMS(ESI-TOF) : calcd. for $C_{12}H_{19}NH^+$: 178.1596. Found : 178.1592 (MH^+).



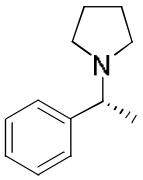
1-Phenylpyrrolidine[3] (Entry 1, Table 5): According to the representative procedure the title compound was purified by silica column chromatography (20:1 Hexane/EtOAc R_f = 0.52) afforded the title compound as a yellow oil (130 mg, 88%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.23 (2H, dd, *J* = 8.7 7.2 Hz), 6.67 (1H, t, *J* = 7.2 Hz), 6.59 (2H, d, *J* = 8.1 Hz), 3.27 – 3.32 (4H, m), 1.97 – 2.05 (4H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 148.1, 129.3, 115.5, 111.8, 47.7, 25.6; HRMS(ESI-TOF) : calcd. For $C_{10}H_{13}NH^+$: 148.1126. Found : 148.1106 (MH^+).



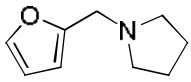
1-Phenylpiperidine[3] (Entry 2, Table 5): According to the representative procedure the title compound was purified by silica column chromatography (20:1 Hexane/EtOAc R_f = 0.45) afforded the title compound as a yellow oil (131 mg, 81%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.23-7.28 (2H, m), 6.96-6.98 (2H, br s), 6.82-6.86 (1H, m), 3.16 (4H, t, *J* = 5.4 Hz), 1.73 (4H, br s), 1.58 – 1.62 (2H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 152.4, 129.1, 119.3, 116.7, 50.8, 26.0, 24.5; HRMS(ESI-TOF) : calcd. For $C_{11}H_{15}NH^+$: 162.1283 Found : 162.1260 (MH^+).



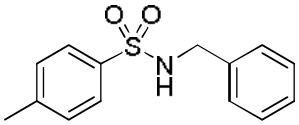
1-(Phenylethyl)azepane[3] (Entry 3, Table 5): According to the representative procedure the title compound was purified by silica column chromatography (10:1 Hexane/EtOAc R_f = 0.19) afforded the title compound as a colourless oil (156 mg, 77%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.19 – 7.39 (5H, m), 3.77 (1H, q, *J* = 6.6 Hz), 2.63 (4H, br s), 1.58 (8H, br s), 1.36 (3H, d); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 145.1, 128.1, 127.7, 126.6, 63.4, 52.2, 29.1, 27.2, 18.4; HRMS(ESI-TOF) : calcd. for $C_{14}H_{21}NH^+$: 204.1752. Found : 204.1743 (MH^+).



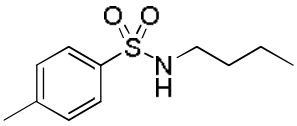
(*R*)-1-(1-Phenylethyl)pyrrolidine[10] (Entry 4, Table 5): According to the representative procedure the title compound was purified by silica column chromatography (2:1 Hexane/EtOAc R_f = 0.23) afforded the title compound as a colourless oil (144 mg, 82%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.12-7.29 (5H, m), 3.12 (1H, q, *J* = 6.6 Hz), 2.46-2.51 (2H, m), 2.27 – 2.33 (2H, m), 1.67 – 1.72 (4H, m), 1.34 (3H, d, *J* = 6.6 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 145.9, 128.4, 127.3, 126.9, 66.1, 53.1, 23.5, 23.3; HRMS(ESI-TOF) : calcd. for $C_{12}H_{17}NH^+$: 176.1439. Found : 176.1422 (MH^+); $[\alpha]_D^{26}$: +62.1° (*c* 2.1, $CHCl_3$).



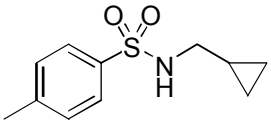
1-(Furan-2-ylmethyl)pyrrolidine[3] (Entry 5, Table 5): According to the representative procedure the title compound was purified by kugerrohl distillation to afford the title compound as a colourless oil (82 mg, 54%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.35 (1H, dd, *J* = 1.8 0.6 Hz), 6.30 (1H, dd, *J* = 3.2 1.8 Hz), 6.18 (1H, dd, *J* = 3.2 0.6 Hz), 3.63 (2H, s), 2.52-2.56 (4H, m), 1.77-1.81 (4H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 153.1, 141.9, 110.1, 107.6, 54.0, 52.2, 23.6; HRMS(ESI-TOF) : calcd. For $C_9H_{13}NOH^+$: 152.1075. Found : 152.1071 (MH^+).



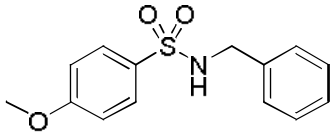
***N*-Benzyl-4-methylbenzenesulfonamide[3] (Entry 1, Table 6):** According to the representative procedure the title compound was purified by silica column chromatography (CH_2Cl_2 R_f = 0.27) afforded the title compound as a colourless solid (238 mg, 91%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.77 (2H, d, *J* = 8.4 Hz), 7.26-7.33 (5H, m), 7.18-7.23 (2H, m), 4.59 (1H, br t, *J* = 5.7 Hz), 4.13 (2H, d, *J* = 6.0 Hz), 2.44 (3H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 143.6, 137.0, 136.4, 129.9, 128.8, 128.0, 128.0, 127.3, 47.4, 21.7; HRMS(ESI-TOF) : calcd. for $C_{14}H_{15}NO_2SH^+$: 262.0912. Found : 262.0903 (MH^+), 284.0723 (MNa^+).



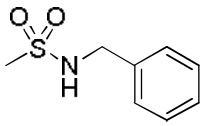
***N*-Butyl-4-methylbenzenesulfonamide[11] (Entry 2, Table 6):** According to the representative procedure the title compound was purified by silica column chromatography (CH_2Cl_2 R_f = 0.25) afforded the title compound as a colourless solid (219 mg, 96%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.74 (2H, d, *J* = 8.1 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 4.30 (1H, br s), 2.93 (2H, t, *J* = 6.9 Hz), 2.43 (3H, s), 1.39-1.49 (2H, m), 1.23-1.35 (2H, m), 0.85 (3H, t, *J* = 7.2 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 143.4, 137.0, 129.8, 127.2, 43.0, 31.6, 21.6, 19.8, 13.6; HRMS(ESI-TOF) : calcd. for $C_{11}H_{17}NO_2SH^+$: 228.1058. Found : 228.1051 (MH^+), 250.0871 (MNa^+).



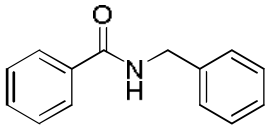
***N*-(Cyclopropylmethyl)-4-methylbenzenesulfonamide[3] (Entry 3, Table 6):** According to the representative procedure the title compound was purified by silica column chromatography (CH_2Cl_2 R_f = 0.22) afforded the title compound as a colourless solid (167 mg, 74%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.75 (2H, d, *J* = 8.1 Hz), 7.30 (2H, d, *J* = 8.1 Hz), 4.45 (1H, br t, *J* = 5.4 Hz), 2.81 (2H, dd, *J* = 7.2 6.0 Hz), 2.43 (3H, s), 0.81-0.94 (1H, m), 0.43-0.49 (2H, m), 0.06-0.11 (2H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 143.4, 137.2, 129.8, 127.2, 48.4, 21.6, 10.8, 3.6; HRMS(ESI-TOF) : calcd. for $C_{11}H_{15}NO_2SH^+$: 226.0902. Found : 226.0902 (MH^+), 248.0724 (MNa^+).



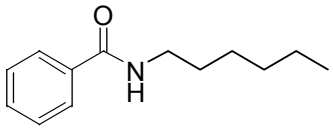
***N*-Benzyl-4-methoxybenzenesulfonamide[3] (Entry 4, Table 6):** According to the representative procedure the title compound was purified by silica column chromatography (99:1 CH_2Cl_2/MeOH R_f = 0.43) afforded the title compound as a colourless solid (252 mg, 91%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.82 (2H, d, *J* = 8.9 Hz), 7.27-7.29 (3H, m), 7.18-7.21 (2H, m), 6.98 (2H, d, *J* = 8.9 Hz), 4.53 (1H, br t, *J* = 6.0 Hz), 4.13 (2H, d, *J* = 6.3 Hz), 3.88 (3H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 163.1, 136.5, 131.6, 129.4, 128.8, 128.0, 114.4, 55.8, 47.4; HRMS(ESI-TOF) : calcd. for $C_{14}H_{15}NO_3SNa^+$: 300.0670. Found : 300.0636 (MNa^+).



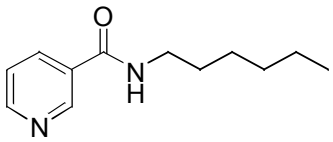
***N*-Benzylmethanesulfonamide[3] (Entry 5, Table 6):** According to the representative procedure the title compound was purified by silica column chromatography (98:2 CH_2Cl_2/MeOH R_f = 0.37) afforded the title compound as a colourless solid (160 mg, 86%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.32-7.41 (5H, m), 4.59 (1H, br s), 4.33 (2H, d, *J* = 6.0 Hz), 2.88 (3H, s); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 136.8, 129.0, 128.2, 128.0, 47.3, 41.2; HRMS(ESI-TOF) : calcd. for $C_8H_{11}NO_2SNa^+$: 208.0408. Found : 208.0404 (MNa^+).



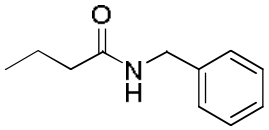
***N*-Benzylbenzamide[12] (Entry 1, Table 7):** According to the representative procedure the title compound was purified by silica column chromatography (1:1 Et_2O/Petroleum Ether (b.p. 40-60 °C) R_f = 0.22) afforded the title compound as a colourless solid (139 mg, 66%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.78-7.81 (2H, m), 7.29-7.53 (8H, m), 6.39 (1H, br s), 4.66 (2H, d, *J* = 5.4 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 167.5, 138.3, 134.5, 131.7, 128.9, 128.7, 128.0, 127.7, 127.1, 44.3; HRMS(ESI-TOF) : calcd. for $C_{14}H_{13}NOH^+$: 212.1075. Found : 212.1070 (MH^+), 234.0885 (MNa^+).



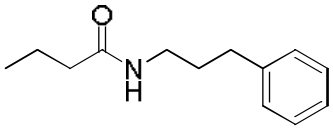
***N*-Hexylbenzamide[13] (Entry 2, Table 7):** According to the representative procedure the title compound was purified by silica column chromatography (1:1 Et_2O/Petroleum Ether (b.p. 40-60 °C) R_f = 0.30) afforded the title compound as a colourless solid (148 mg, 72%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.74-7.77 (2H, m), 7.40-7.52 (3H, m), 6.10 (1H, br s), 3.42-3.49 (2H, m), 1.57-1.67 (2H, m), 1.28-1.44 (6H, m), 0.90 (3H, t, *J* = 6.9 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 167.6, 135.0, 131.4, 128.6, 127.0, 40.2, 31.6, 29.8, 26.8, 22.7, 14.1; HRMS(ESI-TOF) : calcd. for $C_{13}H_{19}NOH^+$: 206.1545. Found : 206.1535 (MH^+), 228.1349 (MNa^+).



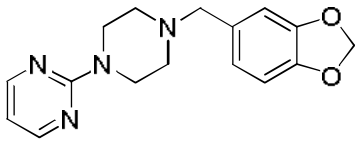
***N*-Hexylnicotinamide[14] (Entry 3, Table 7):** According to the representative procedure the title compound was purified by silica column chromatography (50:1 Et_2O/MeOH R_f = 0.18) afforded the title compound as a colourless solid (111 mg, 54%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 9.04 (1H, d, *J* = 1.8 Hz), 8.71 (1H, dd, *J* = 5.1 1.5 Hz), 8.18 (1H, app. dt, *J* = 7.8 2.0 Hz), 7.42 (1H, ddd, 7.8 4.8 0.6 Hz), 6.41 (1H, br s), 3.47 (1H, dt, 7.2 6.0 Hz), 1.59-1.68 (2H, m), 1.29-1.44 (6H, m), 0.87-0.92 (3H, m); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °) δ 165.7, 152.0, 147.9, 135.3, 130.7, 123.6, 40.4, 31.6, 29.6, 26.7, 22.6, 14.1; HRMS(ESI-TOF) : calcd. for $C_{12}H_{18}N_2OH^+$: 207.1497. Found : 207.1511 (MH^+), 229.1323 (MNa^+).



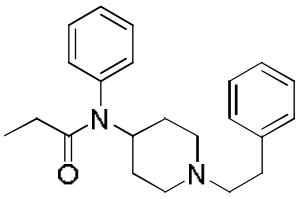
***N*-Benzylbutyramide[15] (Entry 4, Table 7):** According to the representative procedure the title compound was purified by silica column chromatography (2:1 Et_2O/Petroleum Ether (b.p. 40-60 °C) R_f = 0.24) afforded the title compound as a colourless solid (131 mg, 74%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.26-7.36 (5H, m), 5.70 (1H, br s), 4.45 (2H, d, *J* = 5.7 Hz), 2.20 (2H, t, *J* = 7.5 Hz), 1.64-1.76 (2H, m), 0.96 (3H, t, *J* = 7.5 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 172.9, 138.6, 128.8, 127.9, 127.6, 43.7, 38.8, 19.3, 13.9; HRMS(ESI-TOF) : calcd. for $C_{11}H_{15}NOH^+$: 178.1232. Found : 178.1218 (MH^+), 200.1037 (MNa^+).



***N*-(3-Phenylpropyl)butyramide (Entry 5, Table 7):** According to the representative procedure the title compound was purified by silica column chromatography (3:1 Et_2O/Petroleum Ether (b.p. 40-60 °C) R_f = 0.24) afforded the title compound as a yellow oil (162 mg, 79%). IR : ν_{max}/cm^{-1} (neat) 3291, 2962, 2934, 1638, 1546, 1454, 744, 697; ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.26-7.31 (2H, m), 7.17-7.21 (3H, m), 5.42 (1H, br s), 3.30 (2H, q, *J* = 6.6 Hz), 2.66 (2H, t, *J* = 7.2 Hz), 2.11 (2H, t, *J* = 7.5 Hz), 1.80-1.89 (2H, m), 1.57-1.70 (2H, m), 0.94 (3H, t, *J* = 7.5 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz. 25 °C) δ 173.1, 141.6, 128.6, 128.5, 126.1, 39.3, 38.9, 33.5, 31.4, 19.3, 13.9; HRMS(ESI-TOF) : calcd. for $C_{13}H_{19}NOH^+$: 206.1545. Found : 206.1534 (MH^+), 228.1349 (MNa^+); CHN : *Anal. Calc*. for $C_{13}H_{19}NO$: C, 76.06%, H, 9.33%, N, 6.82%; Found : C, 75.90%, H, 9.14%, N, 6.74%.



Piribedil (Scheme 2): According to the representative procedure the title compound was purified by silica column chromatography (20:1 Et_2O/Petroleum Ether (b.p. 40-60 °C) R_f = 0.22) afforded the title compound as a colourless solid (266 mg, 89%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 8.29 (2H, d, *J* = 4.8 Hz), 6.89 (1H, s), 6.76 (1H, s), 6.76 (1H, s), 6.46 (1H, t, *J* = 4.8 Hz), 5.95 (2H, s), 3.82 (4H, t, *J* = 5.1 Hz), 3.46 (2H, s), 2.48 (4H, t, *J* = 5.1 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 161.8, 157.8, 147.8, 146.8, 132.0, 122.4, 109.8, 109.6, 108.0, 101.0, 63.0, 53.0, 43.8; HRMS(ESI-TOF) : calcd. for $C_{16}H_{19}N_4O_2H^+$: 299.1508. Found : 299.1522 (MH^+).



Fentanyl[16] (Scheme 2): According to the representative procedure the title compound was purified by silica column chromatography (4:1 Et_2O/Hexane R_f = 0.25) afforded the title compound as a colourless solid (259 mg, 77%). ^{1}H NMR : ($CDCl_3$, 300 MHz, 25 °C) δ 7.35-7.43 (3H, m), 7.23-7.29 (2H, m), 7.14-7.20 (3H, m), 7.07-7.10 (2H, m), 4.69 (1H, tt, *J* = 12.2 3.9 Hz), 3.02 (2H, d, *J* = 11.1 Hz), 2.72-2.77 (2H, m), 2.53-2.58 (2H, m), 2.18 (2H, t, *J* = 11.1 Hz), 1.93 (2H, q, *J* = 7.5 Hz), 1.81 (2H, d, *J* = 13.2 Hz), 1.48 (2H, t, *J* = 12.3 Hz), 1.01 (3H, t, *J* = 7.5 Hz); ^{13}C NMR : ($CDCl_3$, 75.4 MHz, 25 °C) δ 173.7, 140.3, 139.0, 130.6, 129.4, 128.7, 128.5, 128.4, 126.1, 60.6, 53.2, 52.3, 33.9, 30.7, 28.6, 9.7; HRMS(ESI-TOF) : calcd. for $C_{22}H_{28}N_2OH^+$: 337.2280. Found : 337.2287 (MH^+), 359.2096 (MNa^+).

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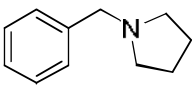
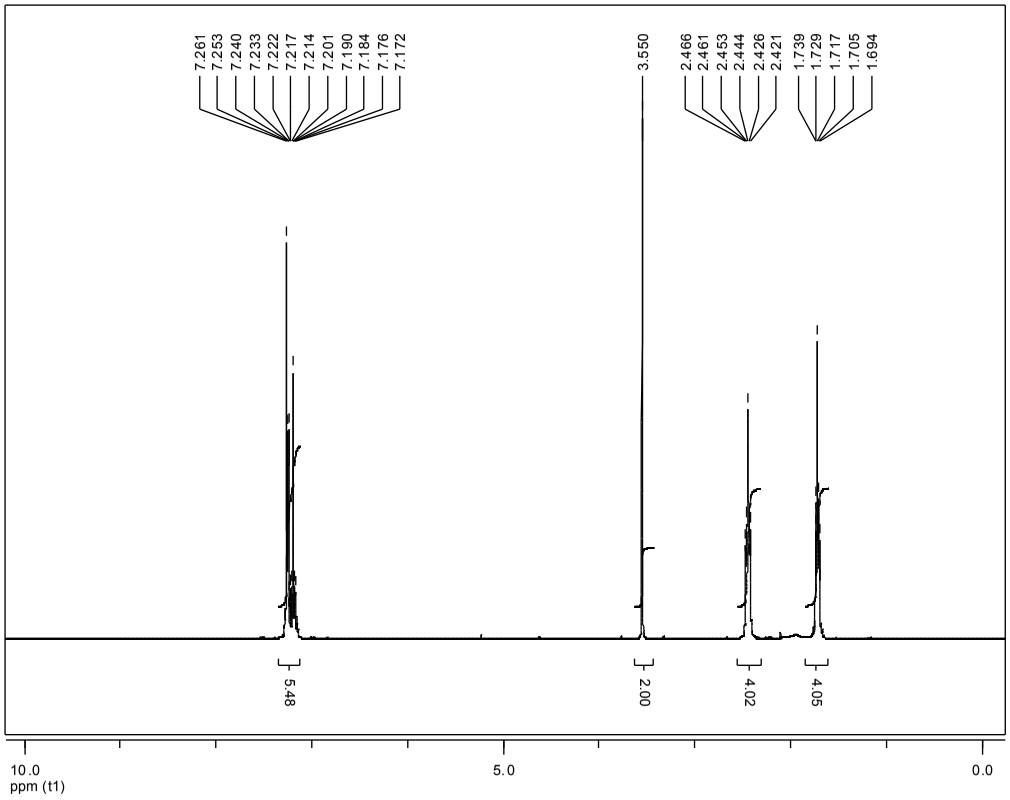
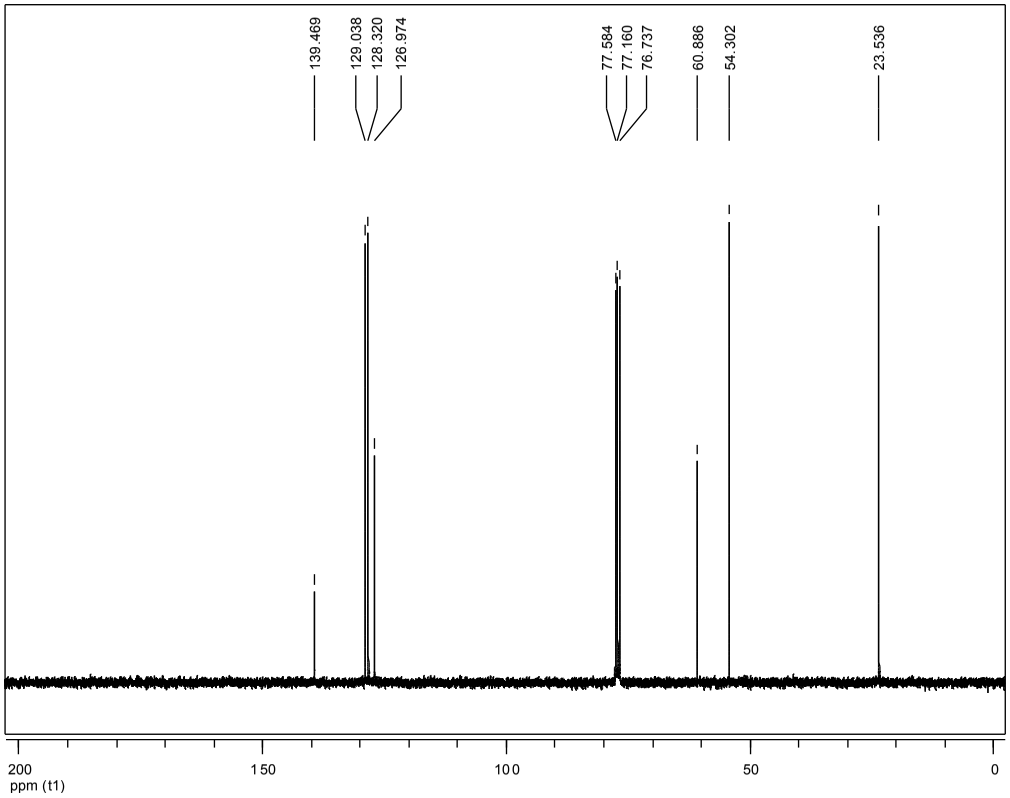
Entry 1, Table 2







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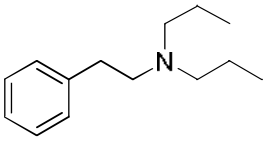

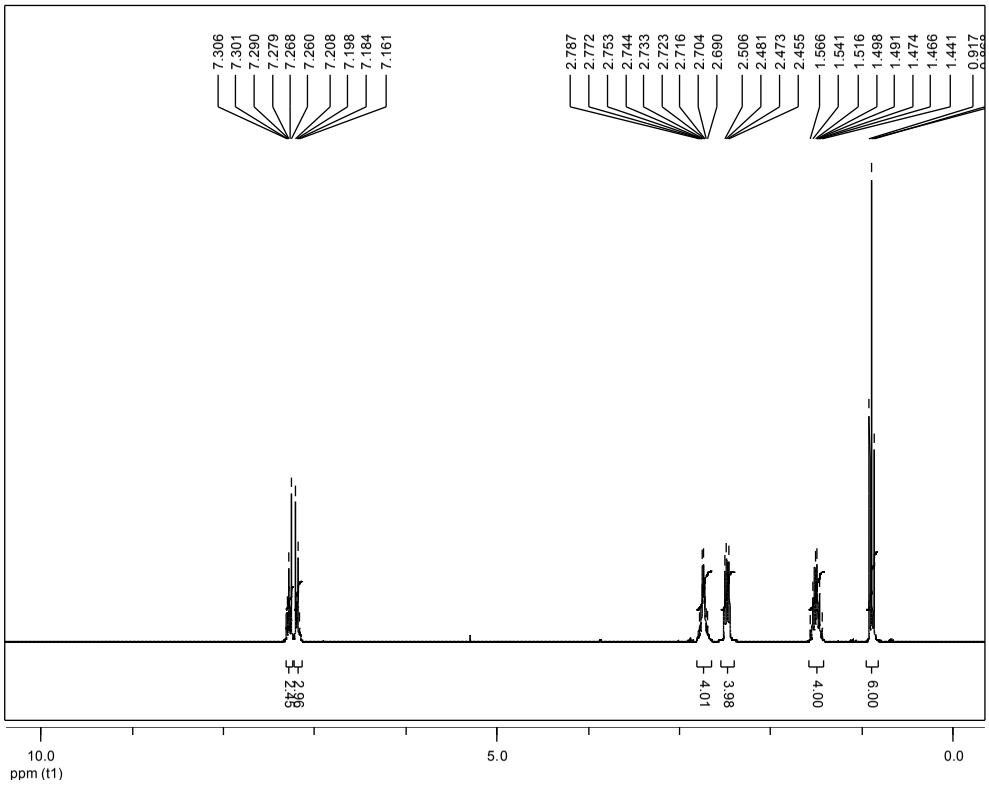

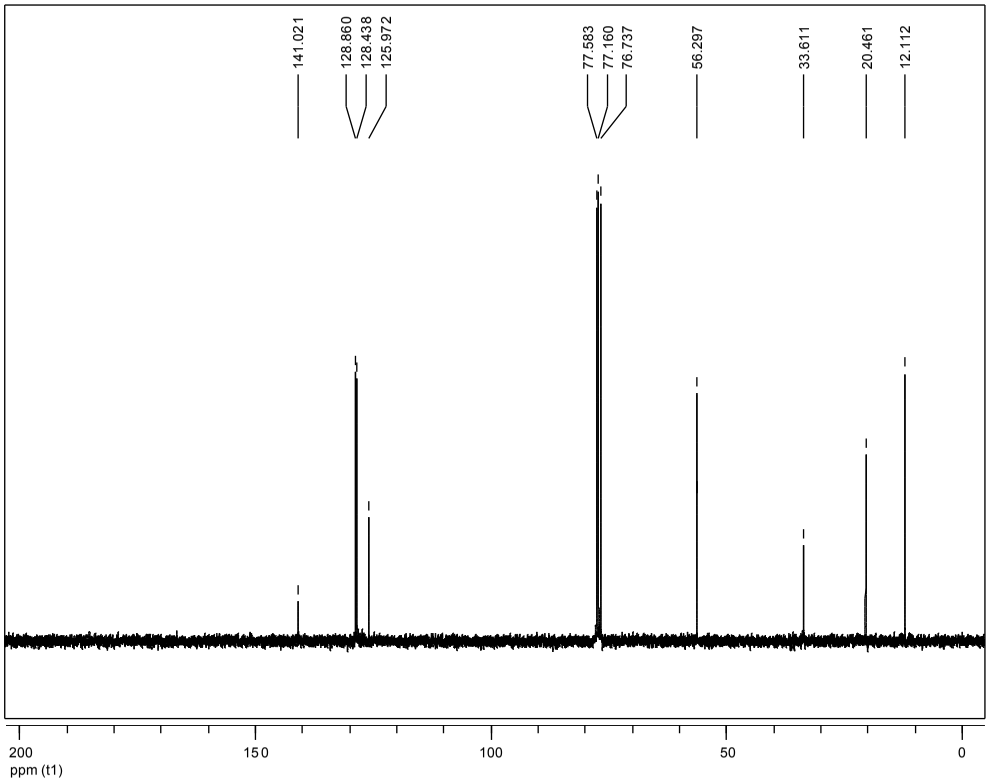

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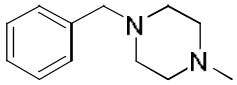

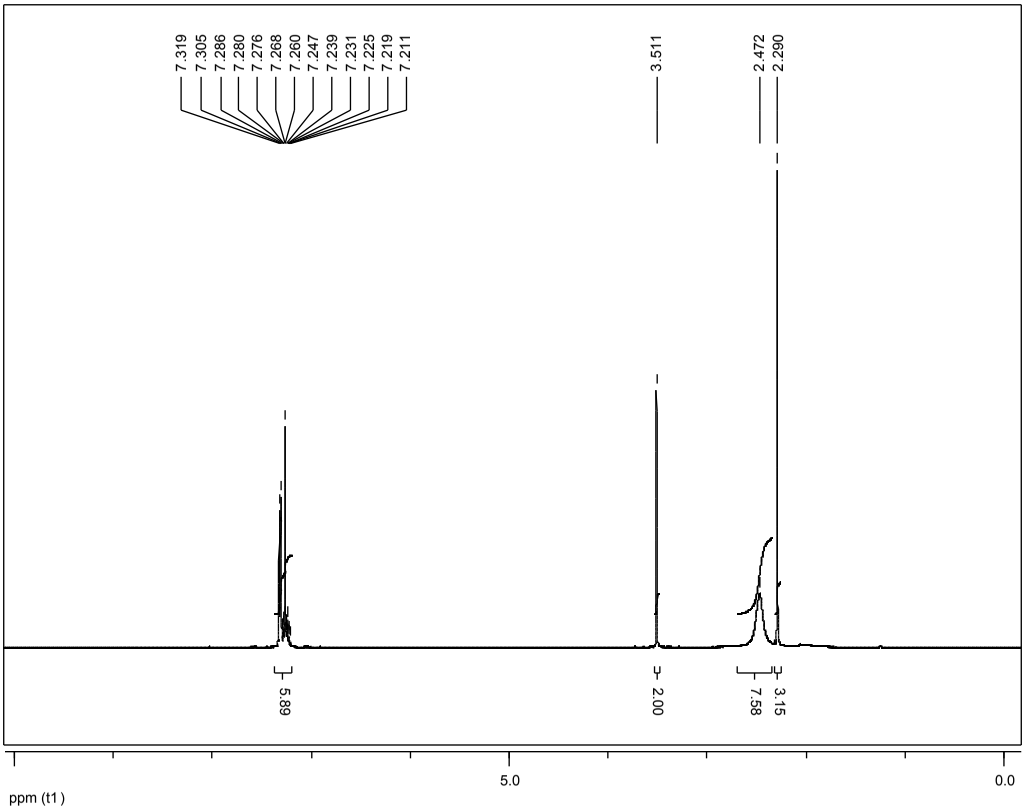

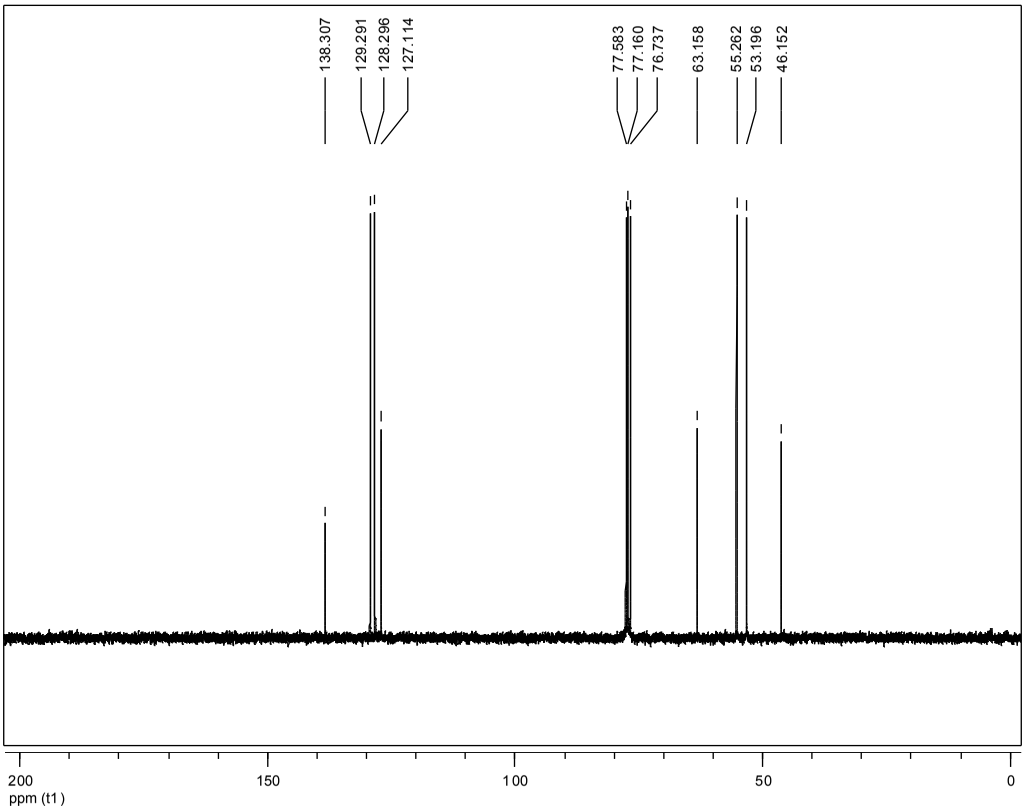

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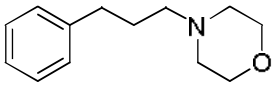

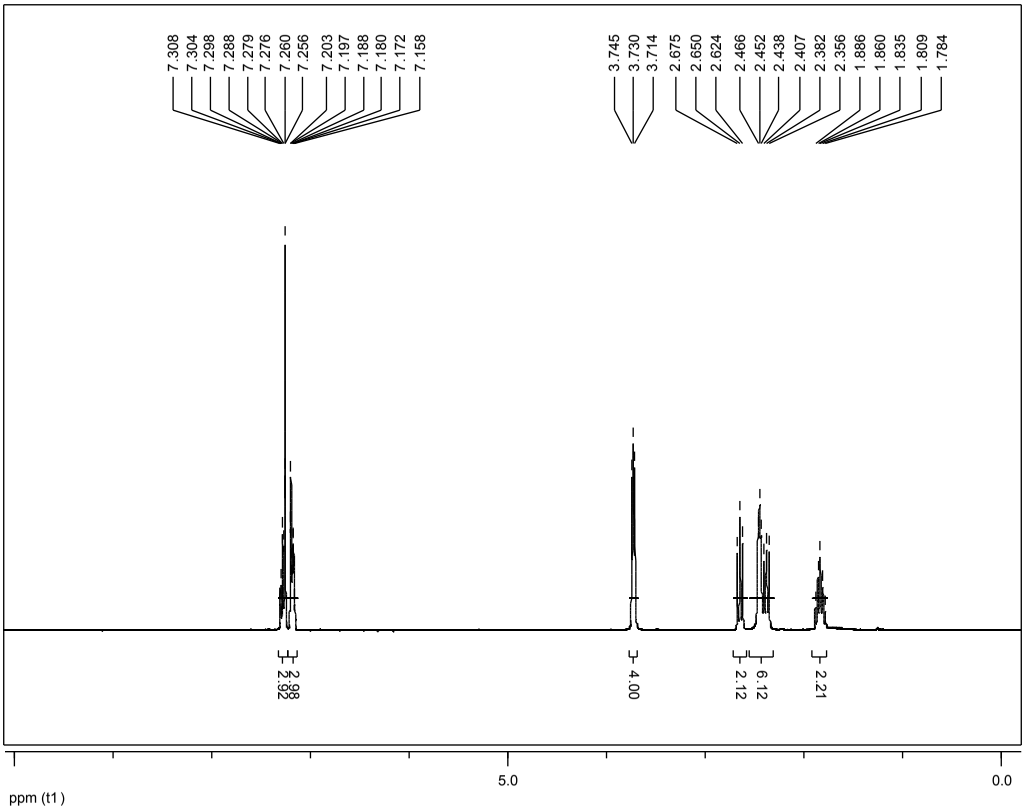

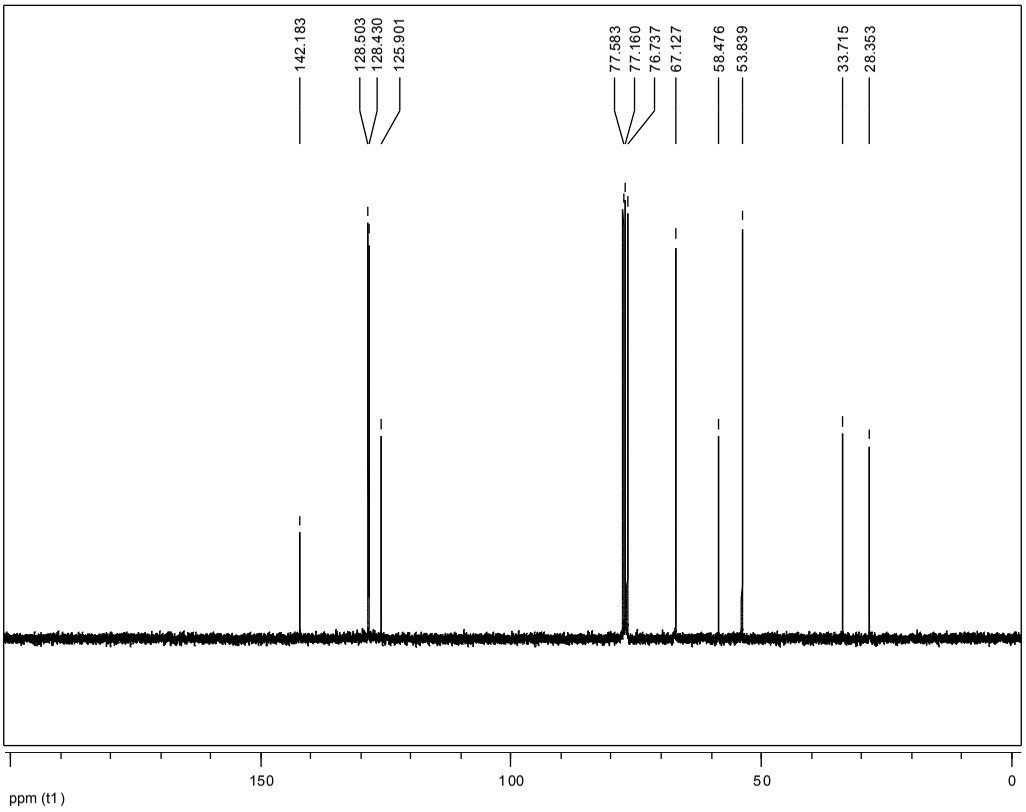

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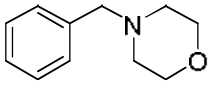

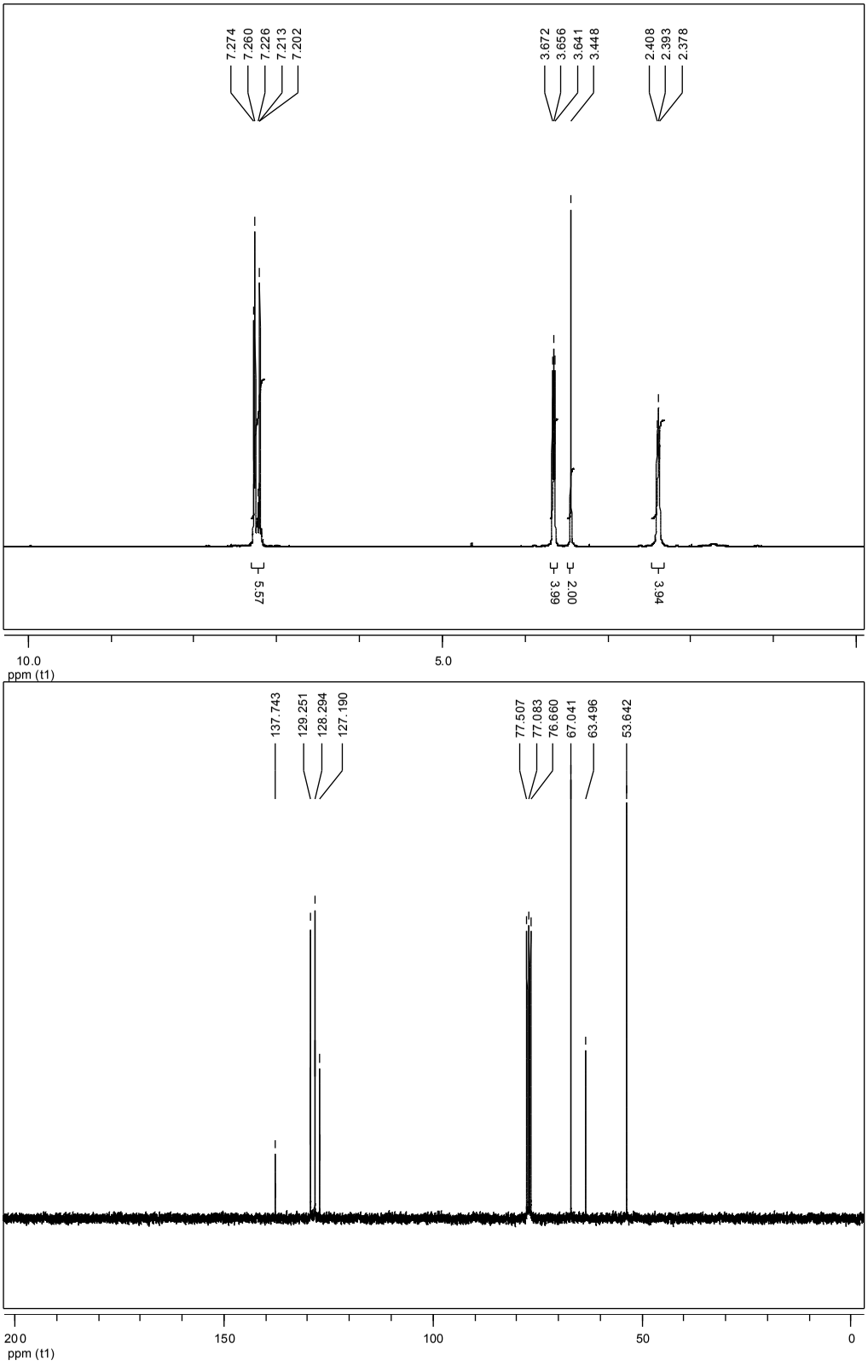

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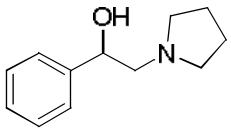

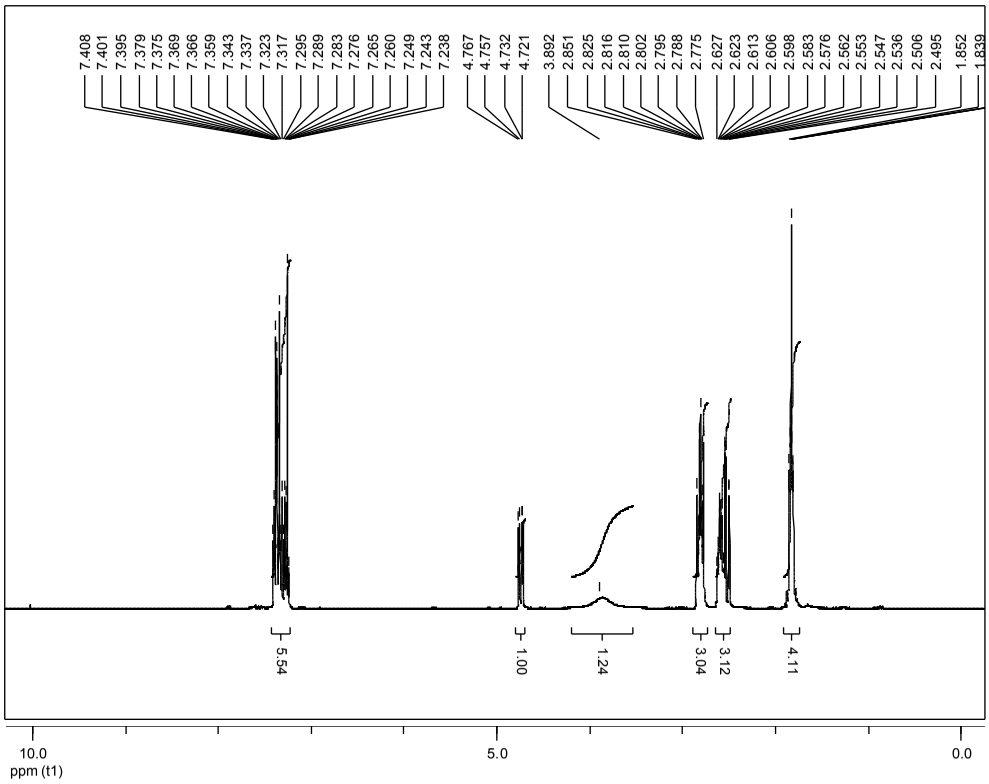

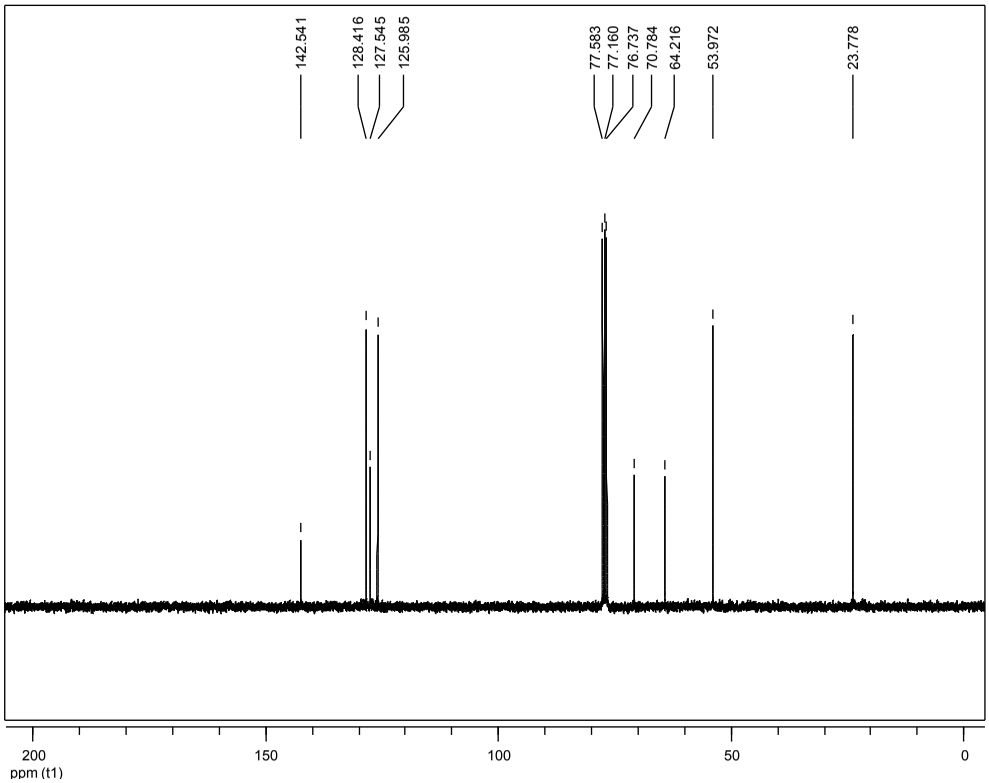

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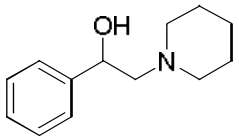

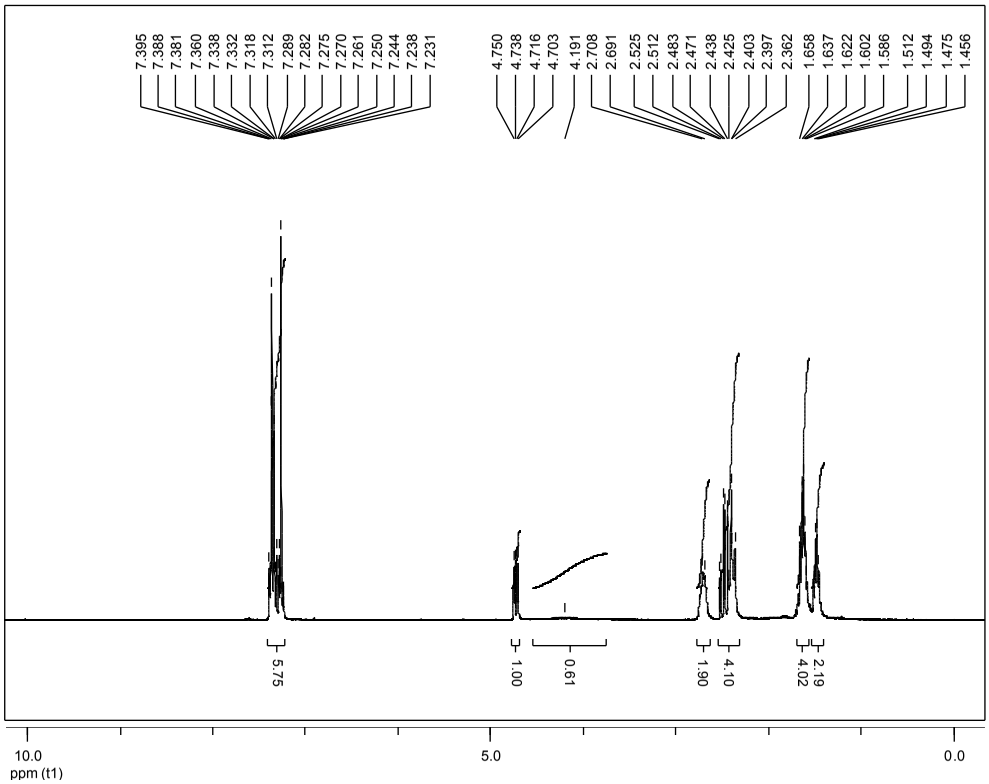

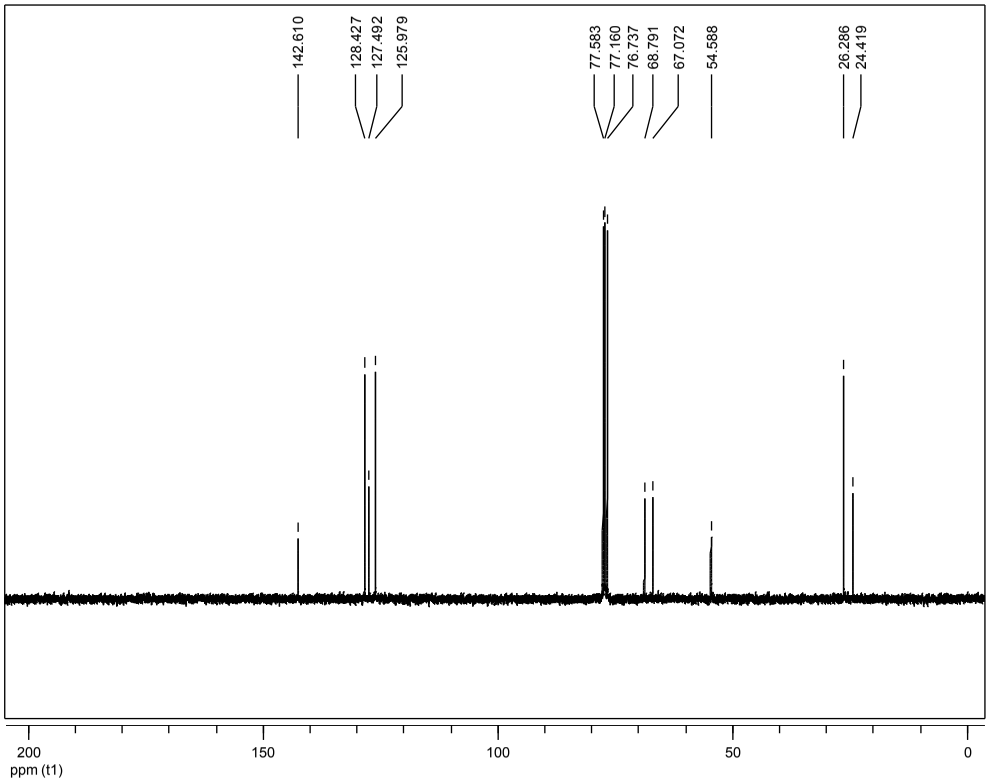

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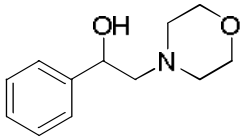

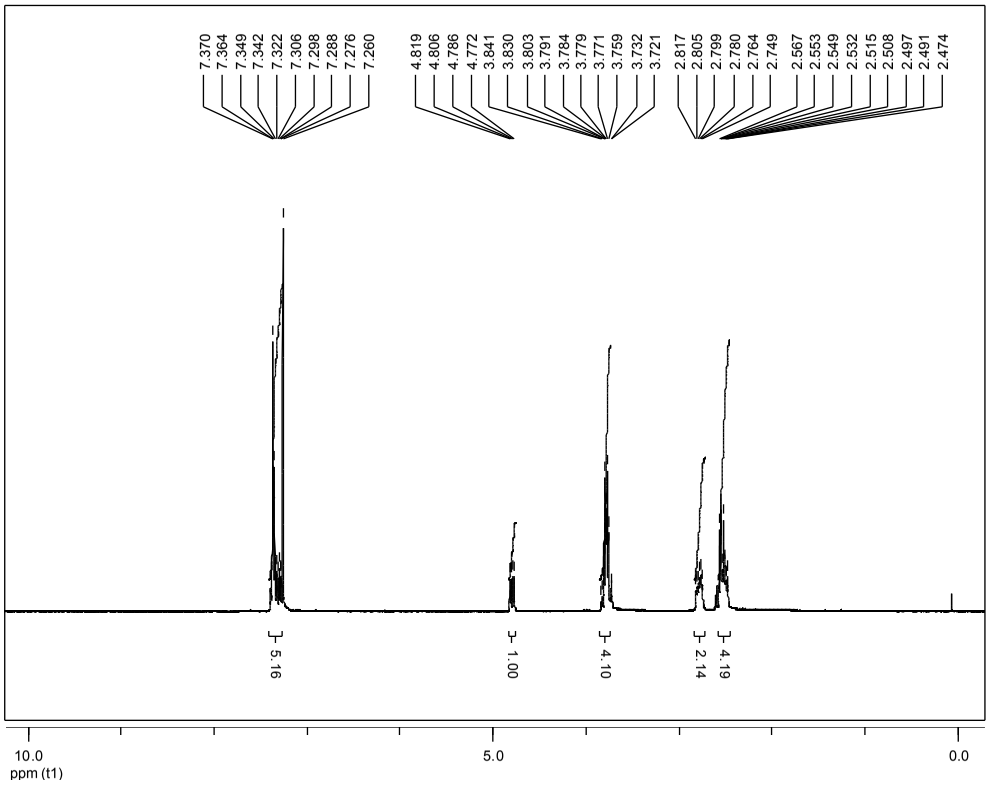

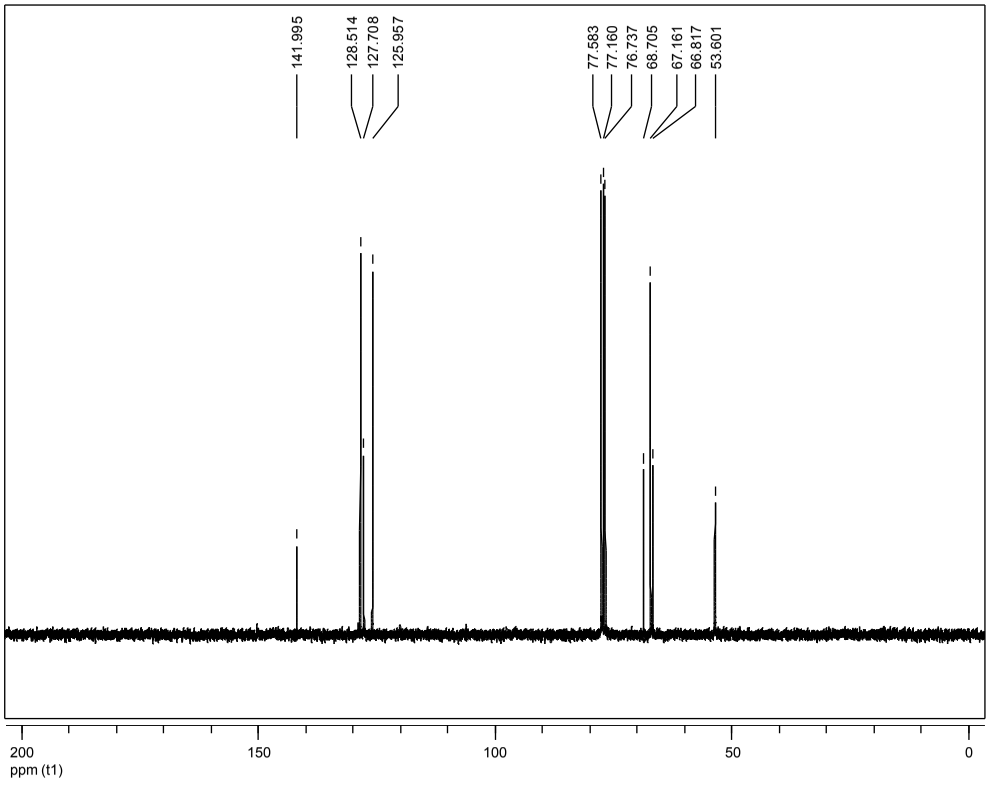

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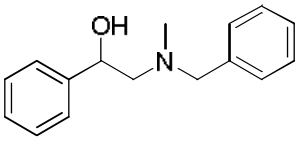

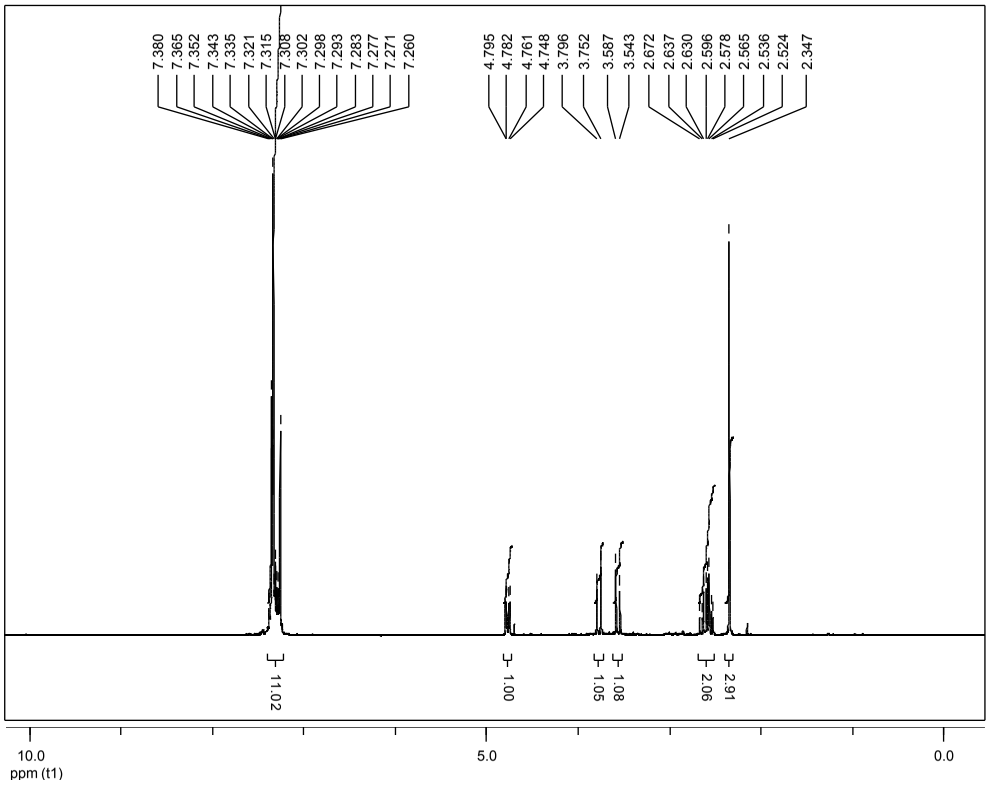

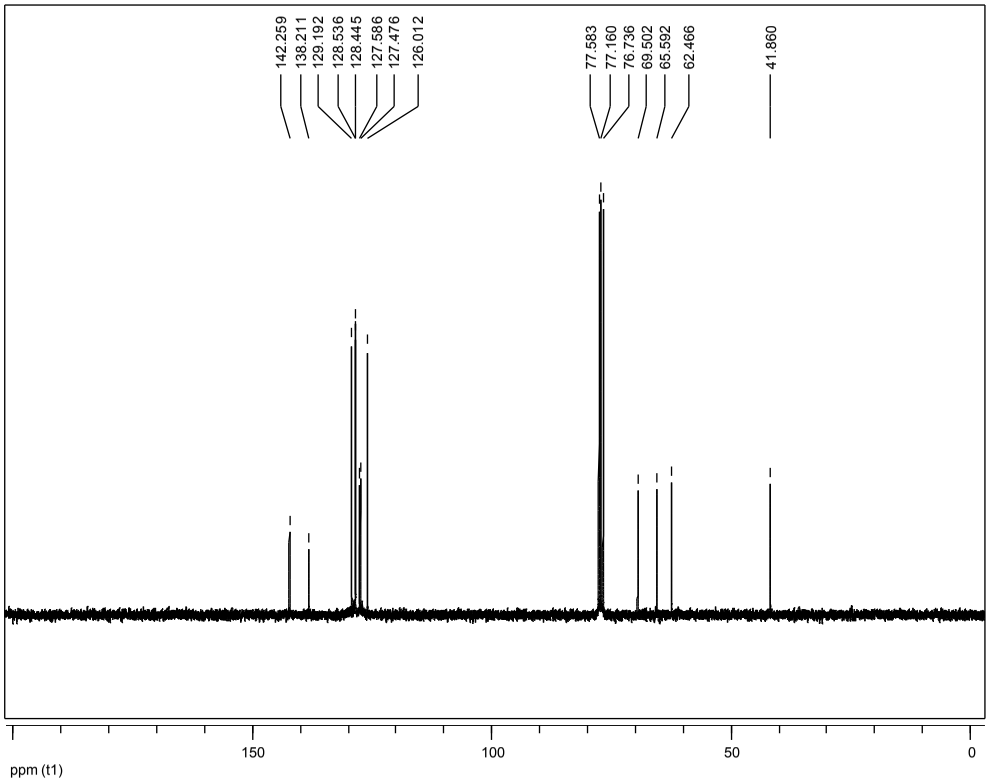

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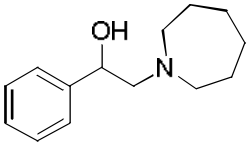

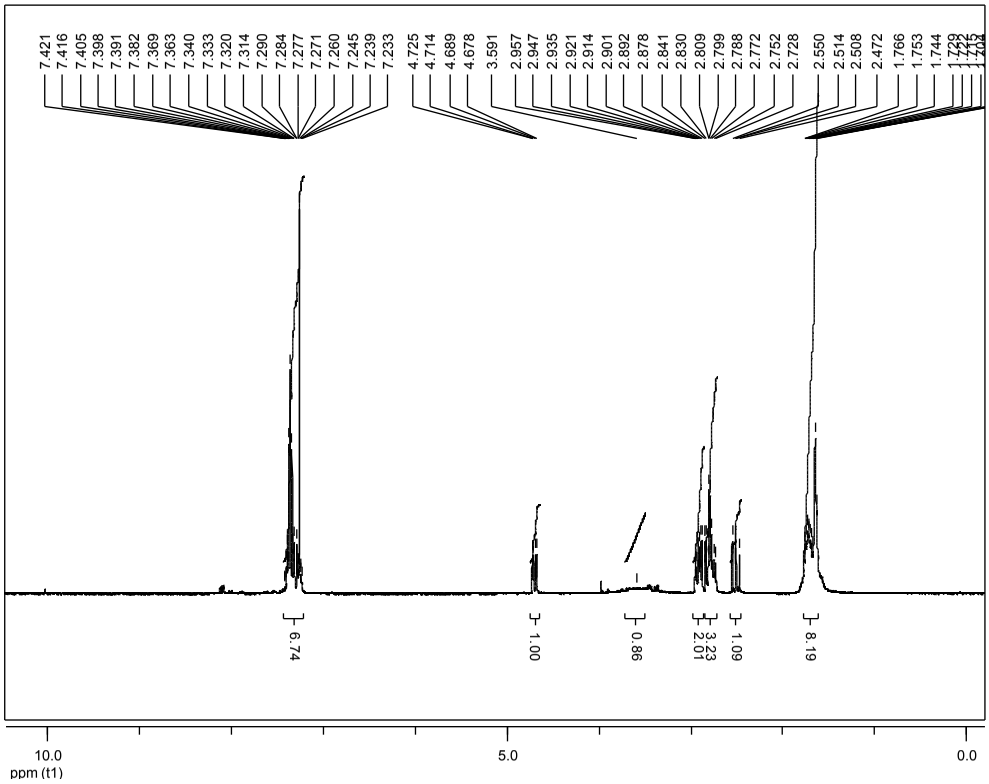

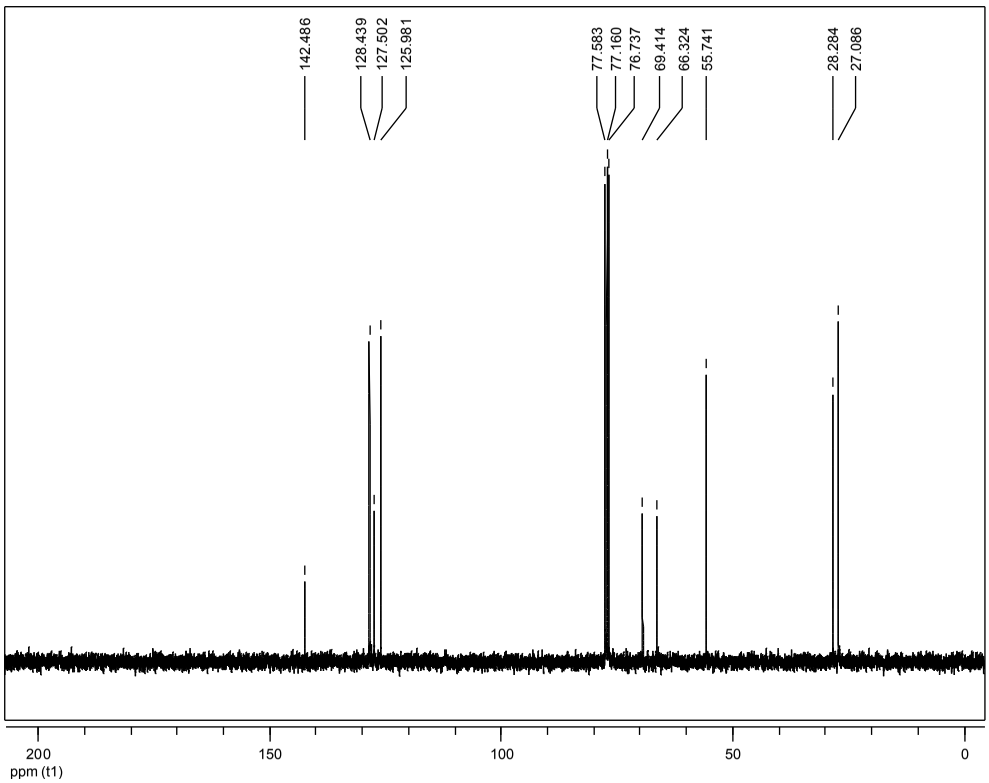

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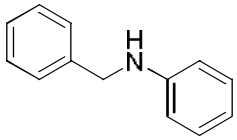

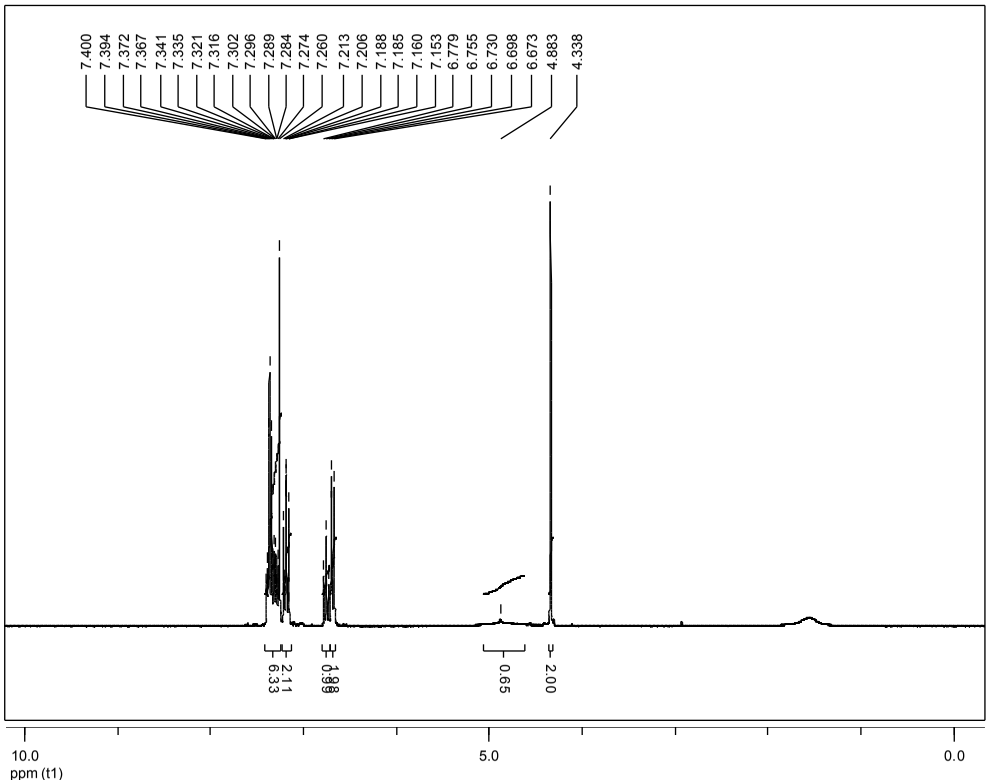

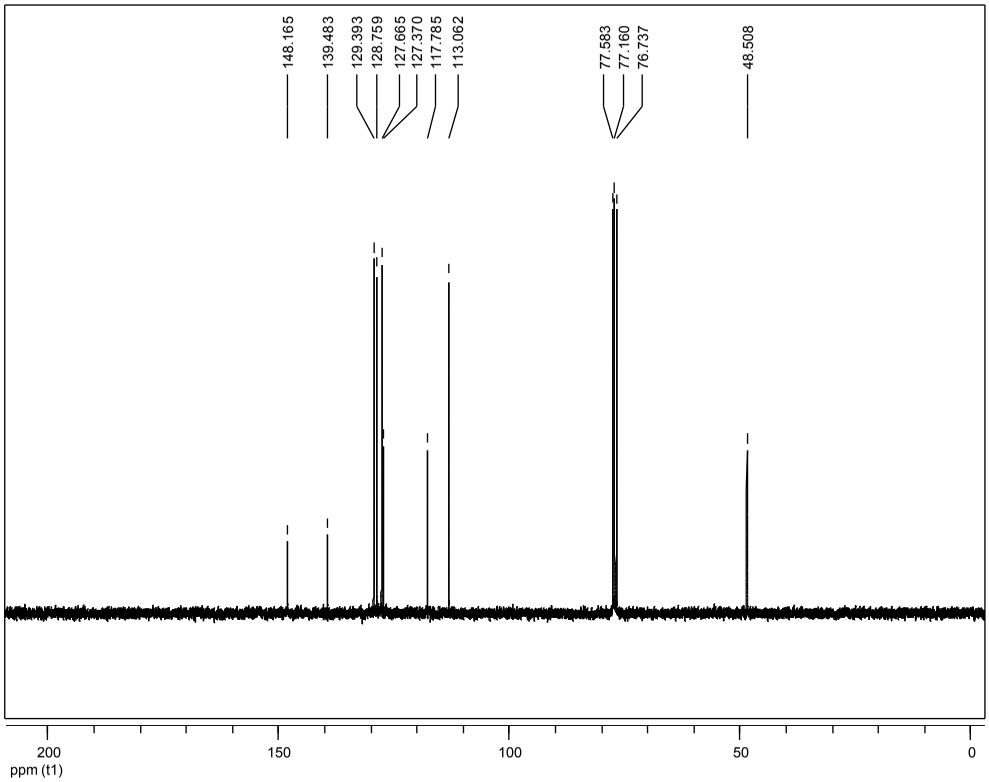

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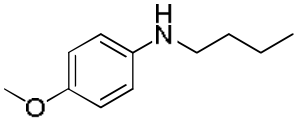

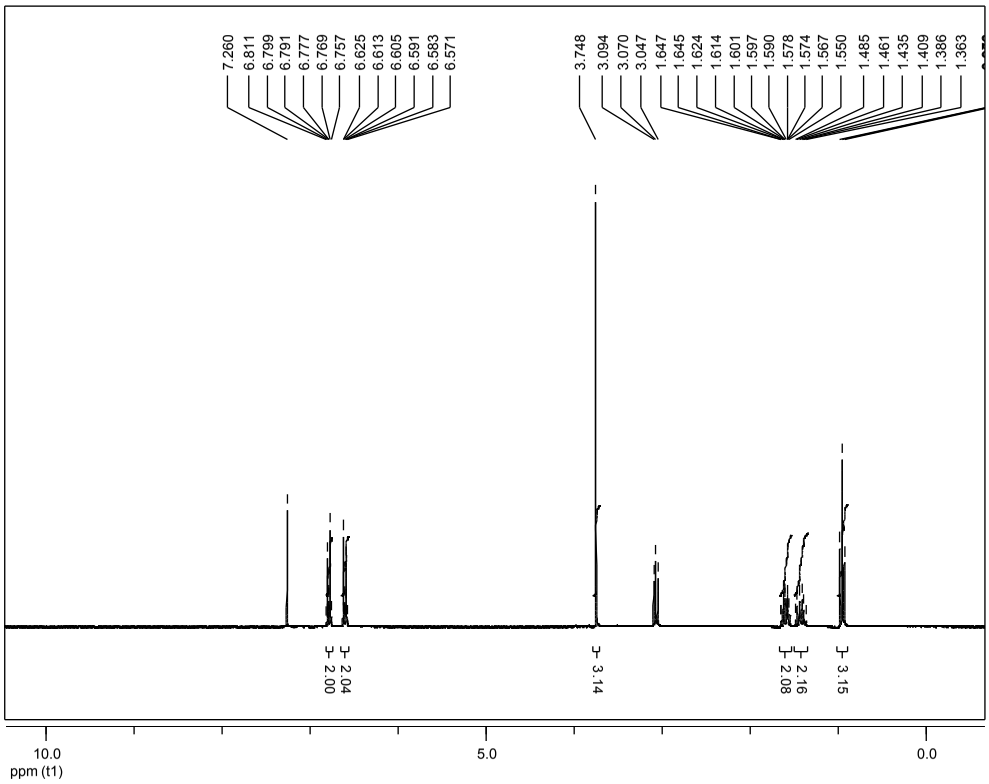

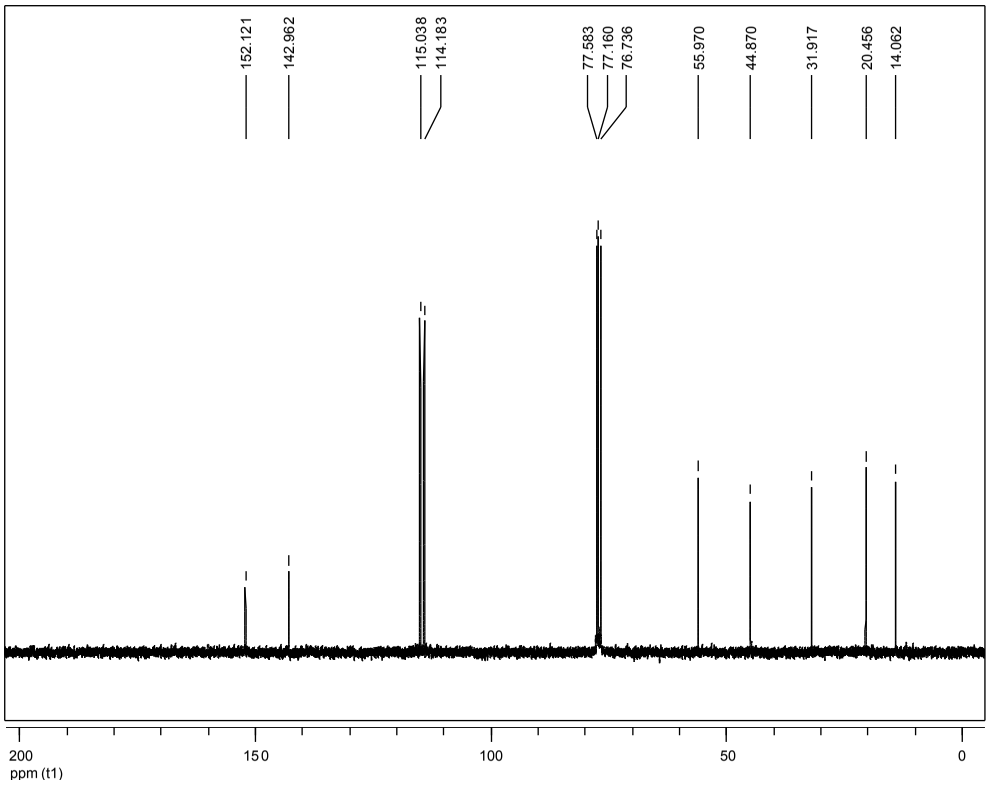

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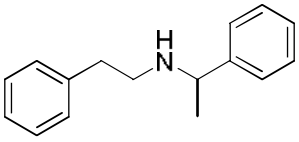

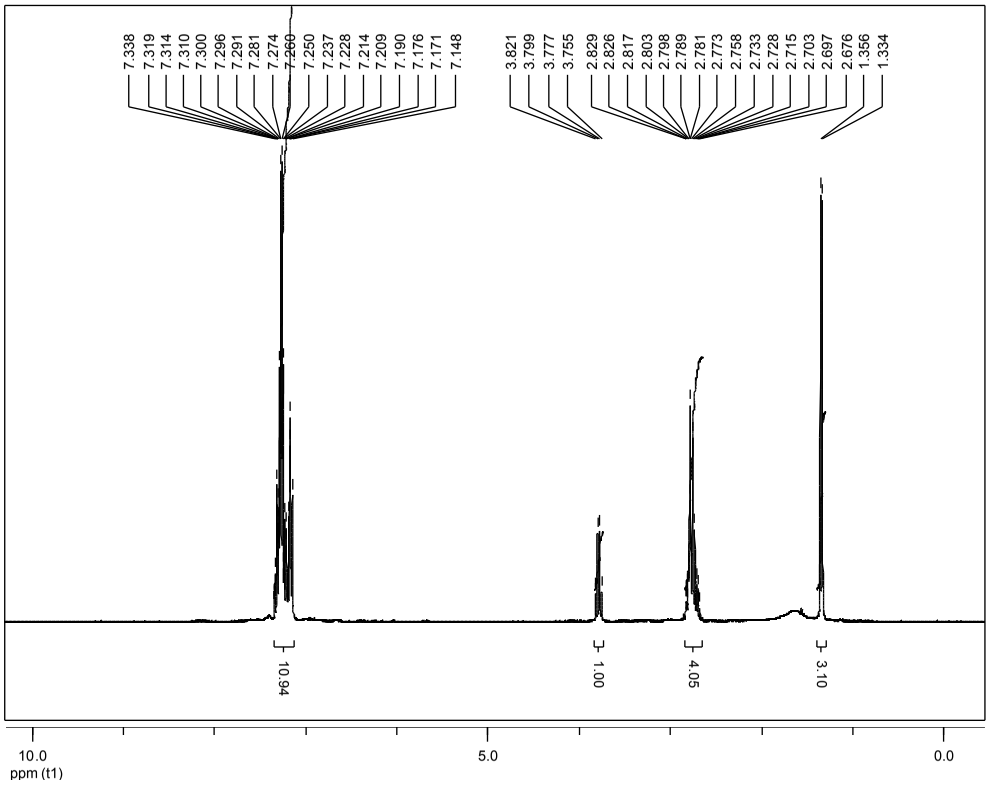

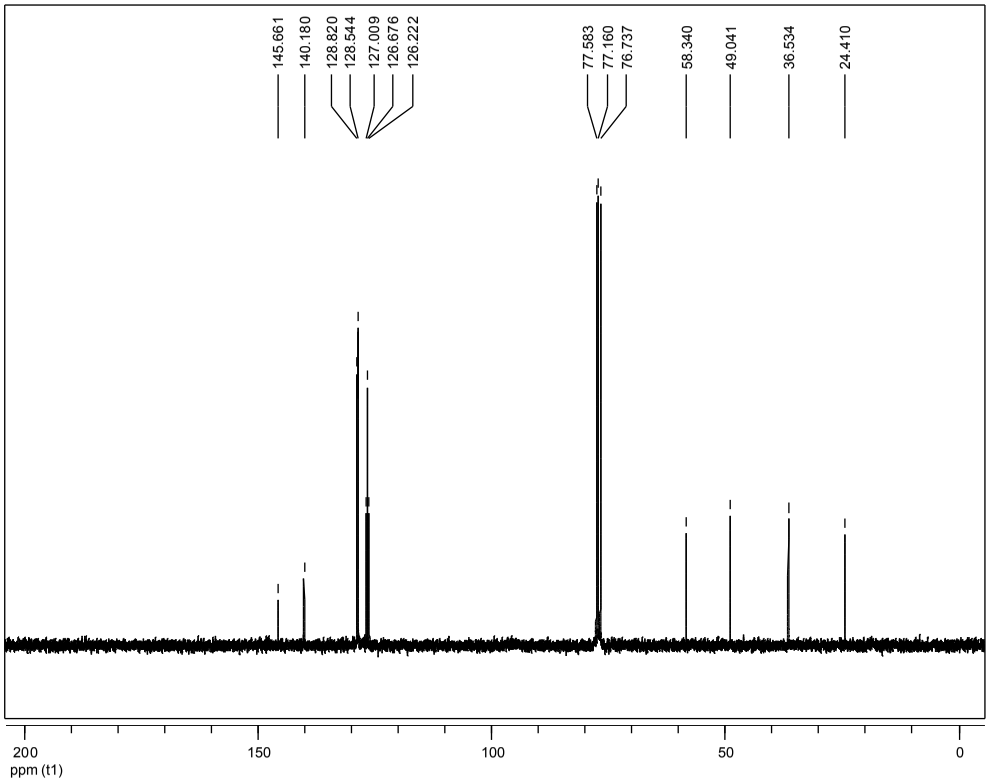

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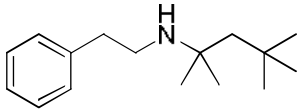

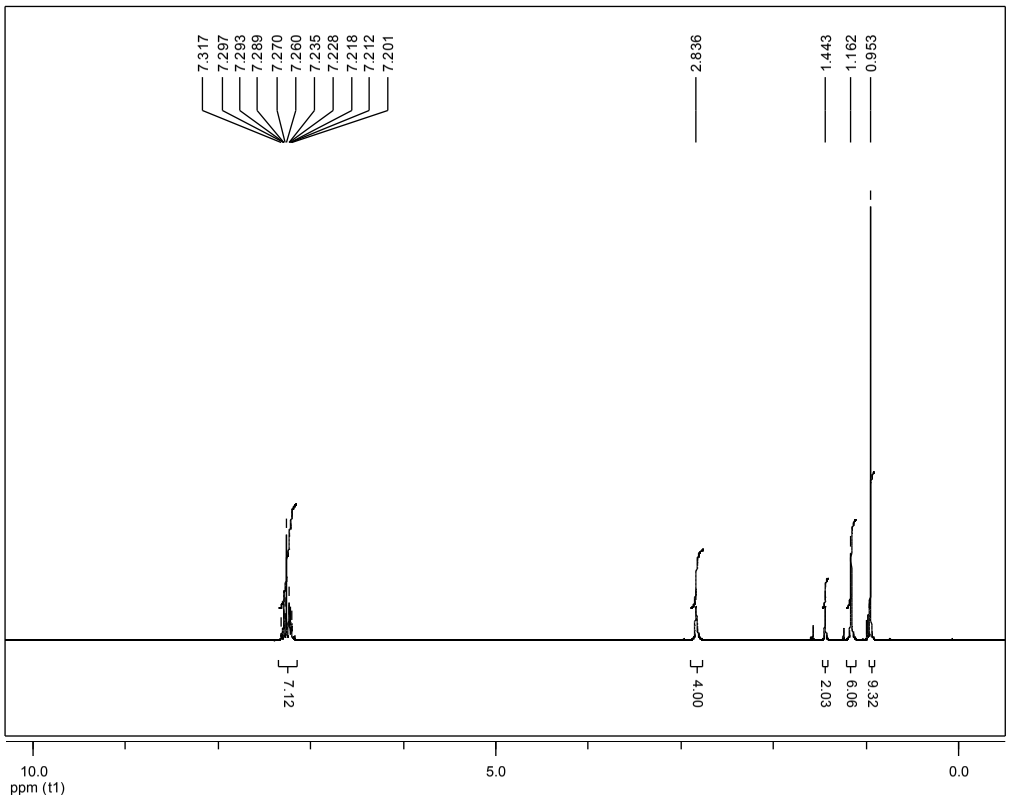

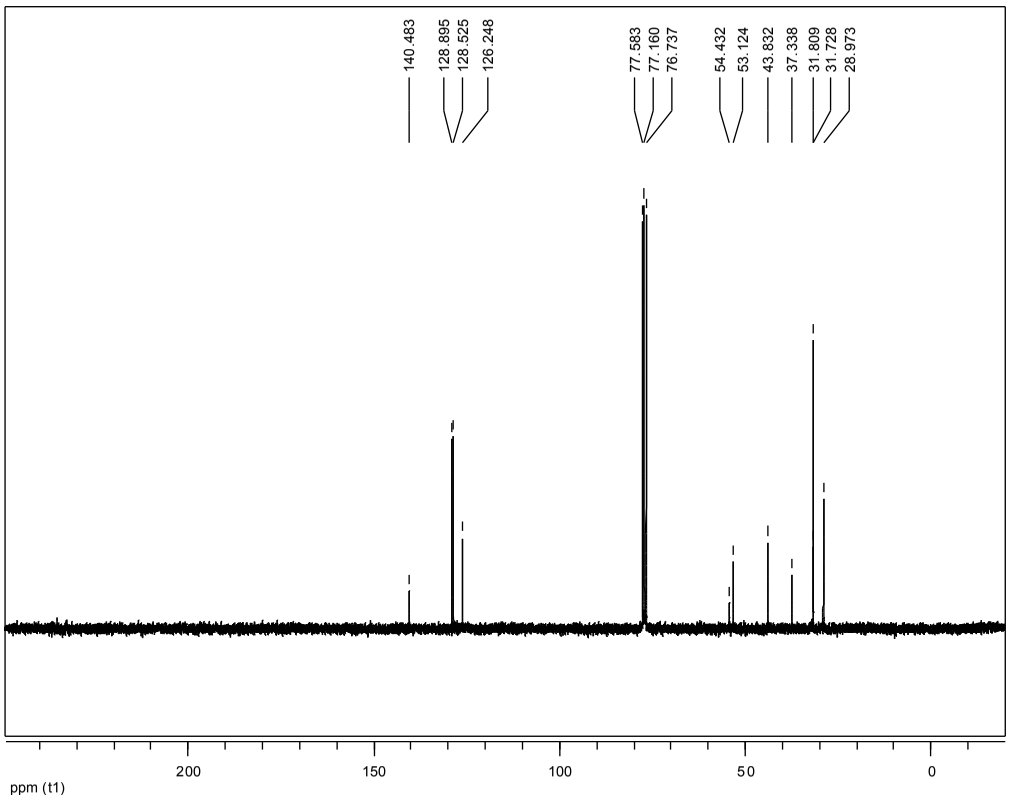

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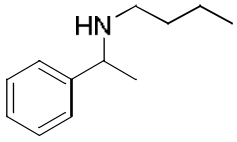

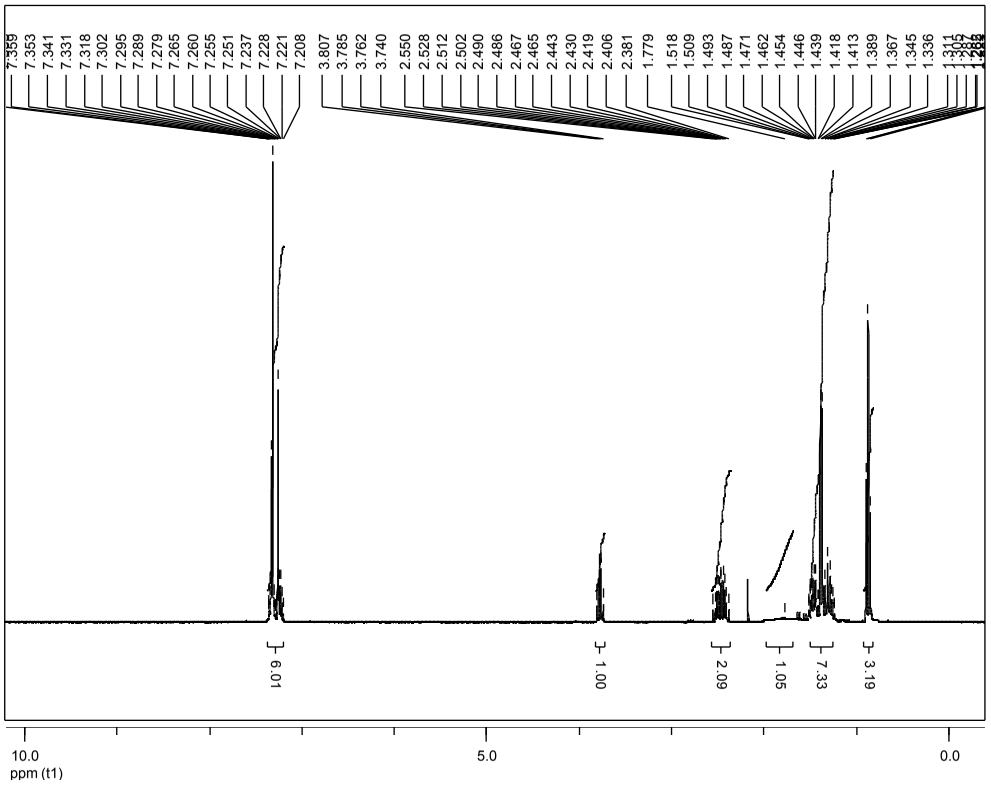

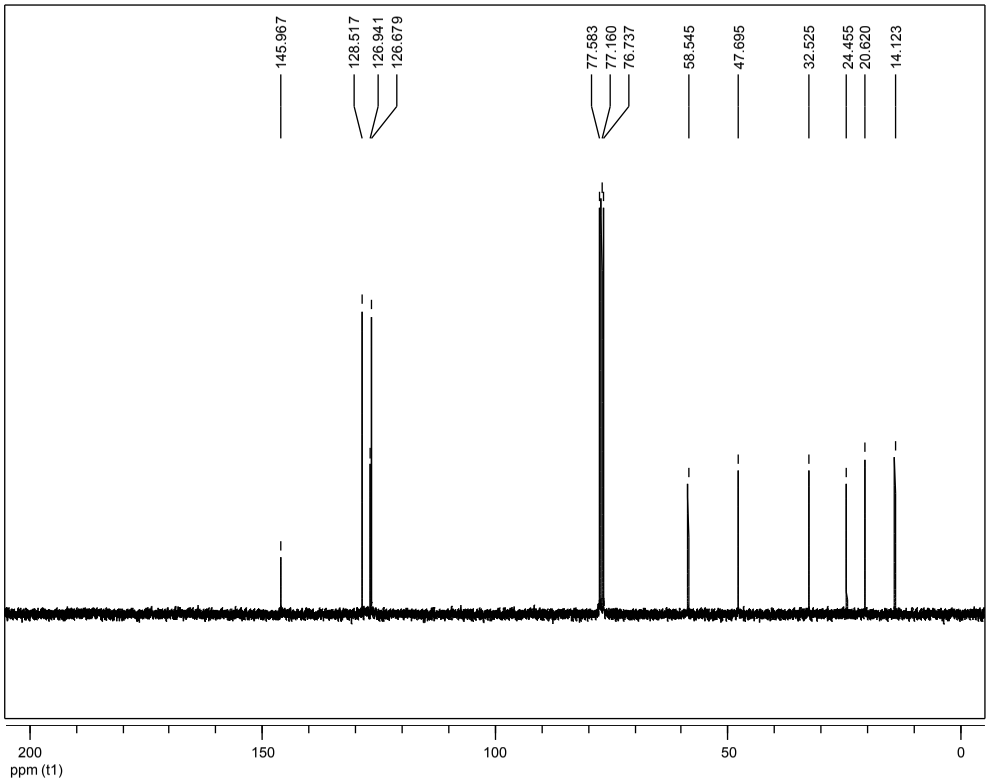

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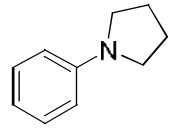

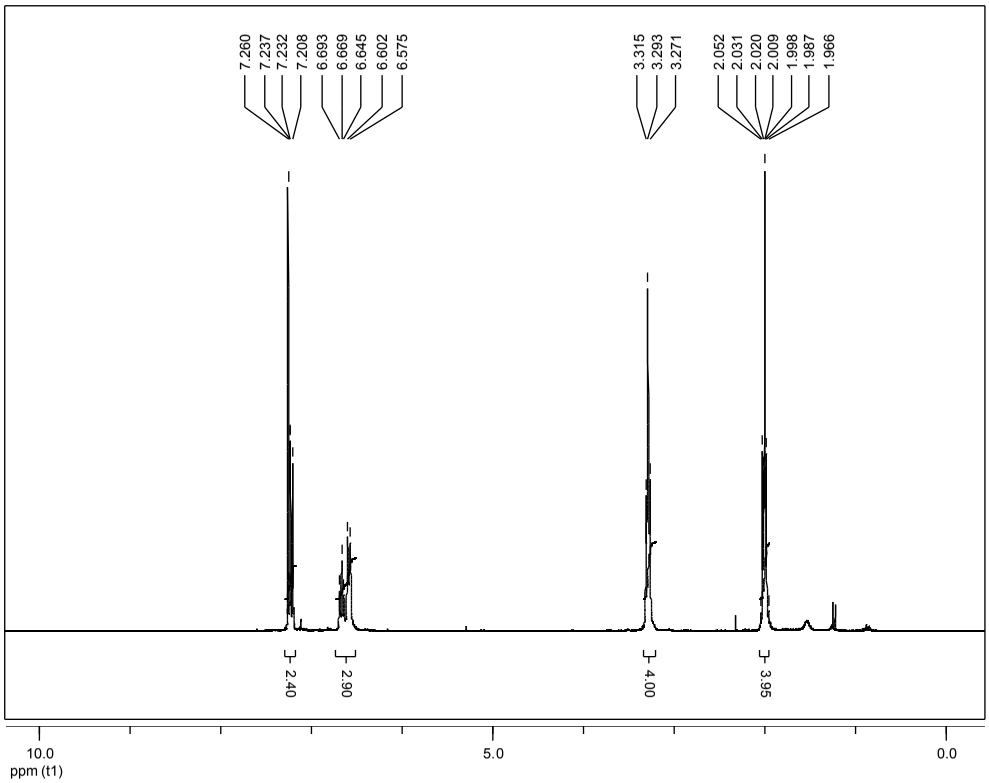

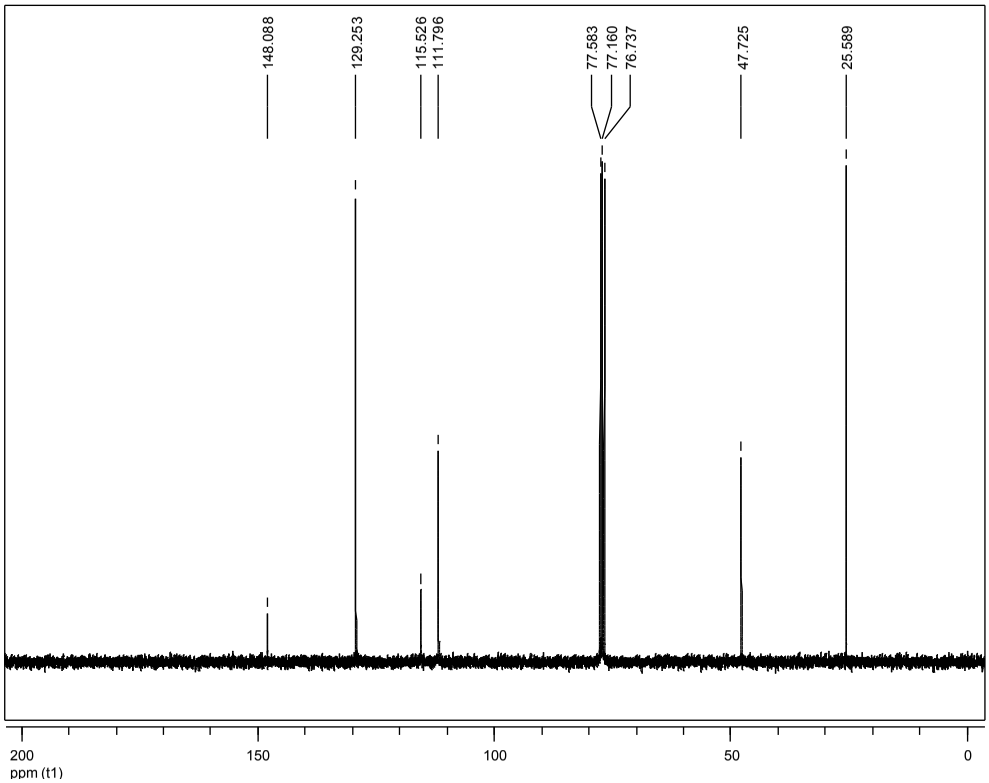

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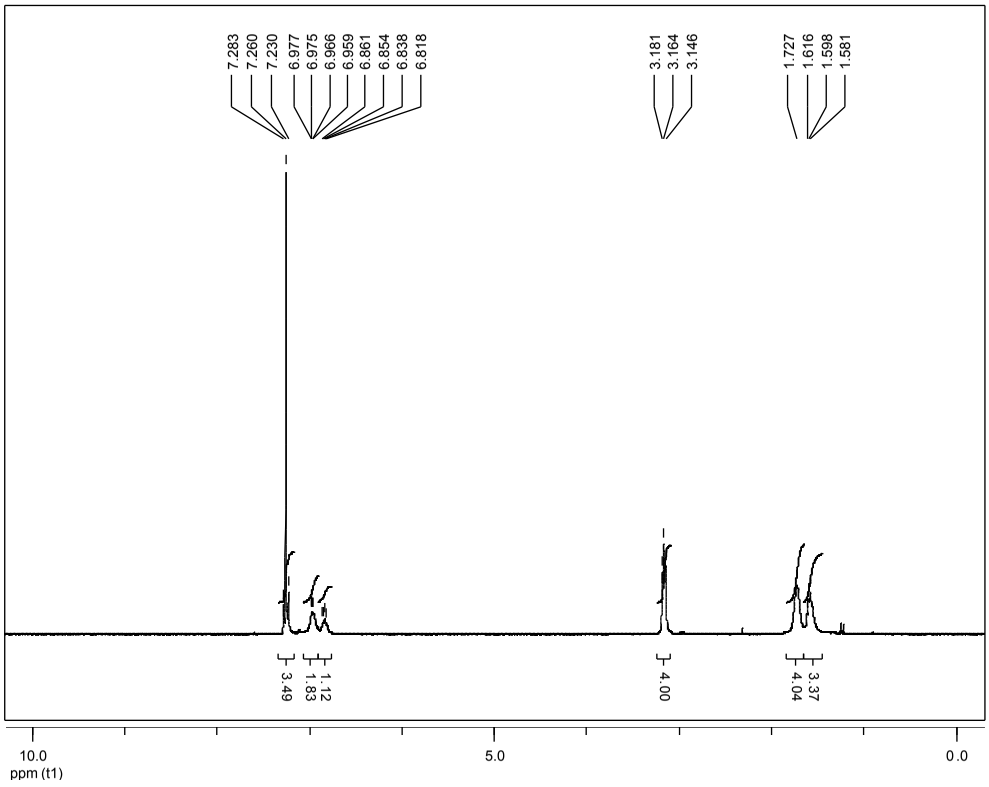

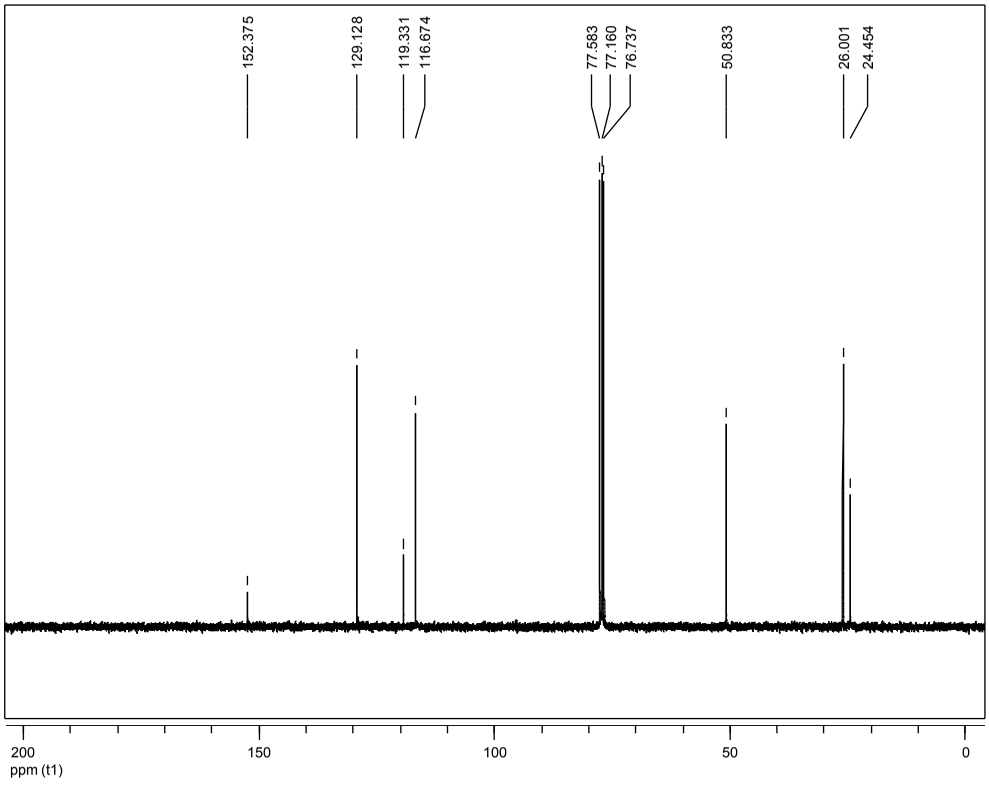

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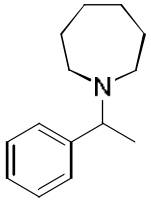

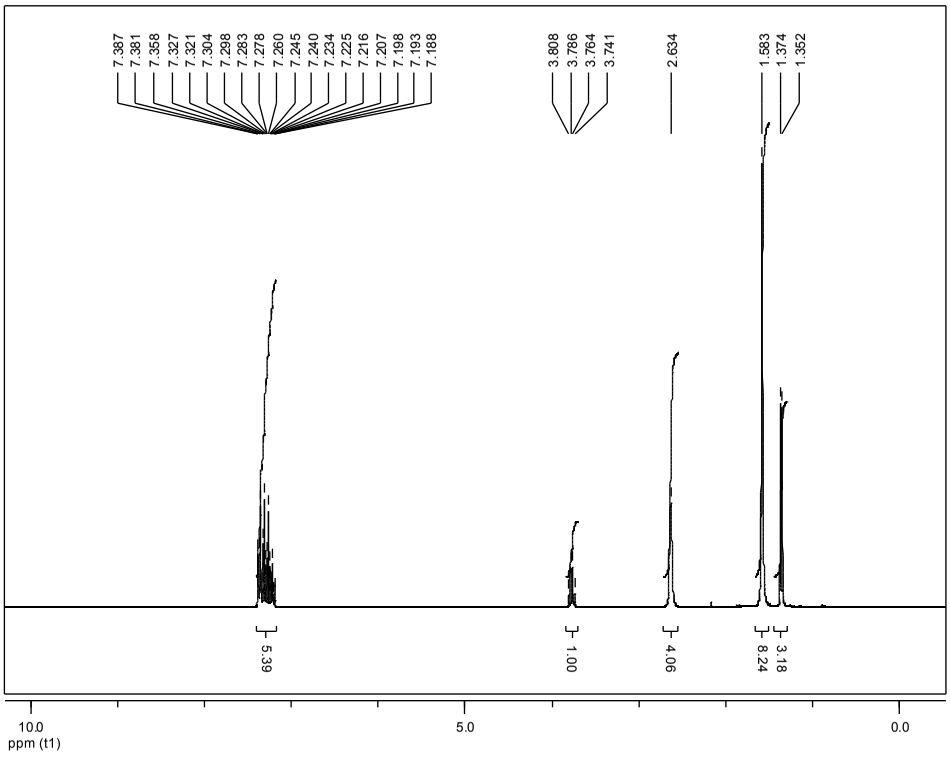

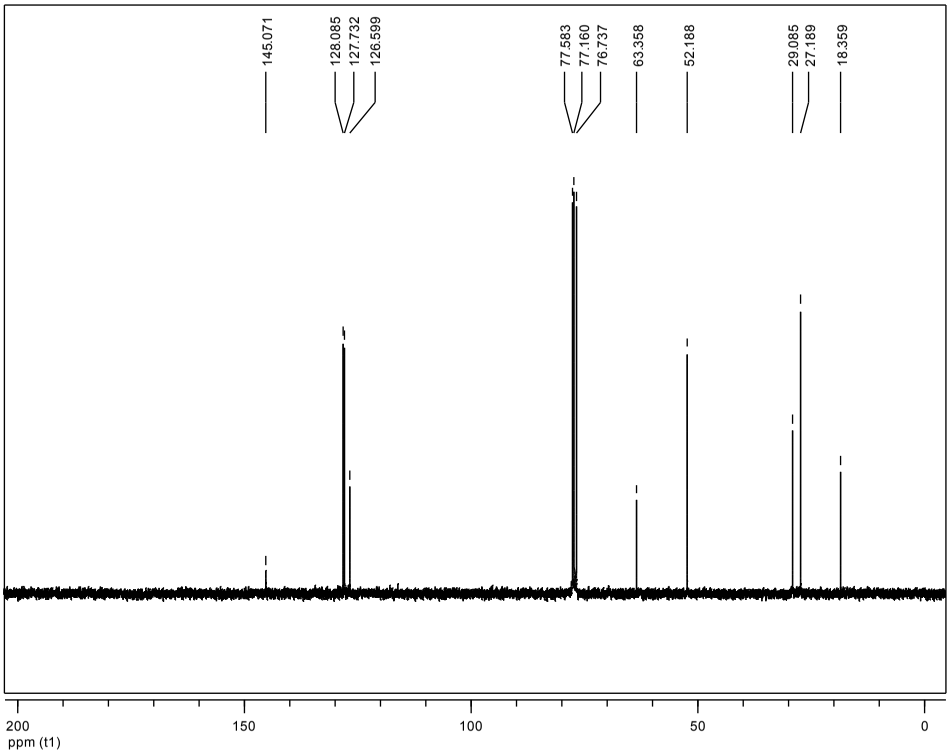

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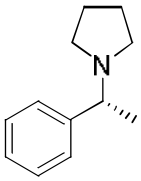

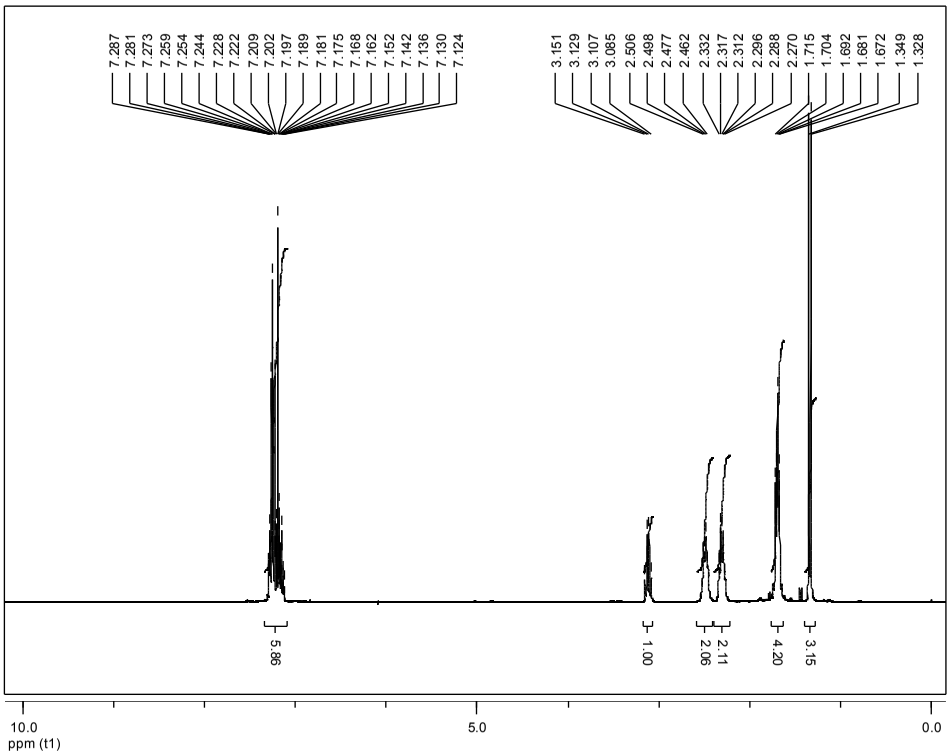

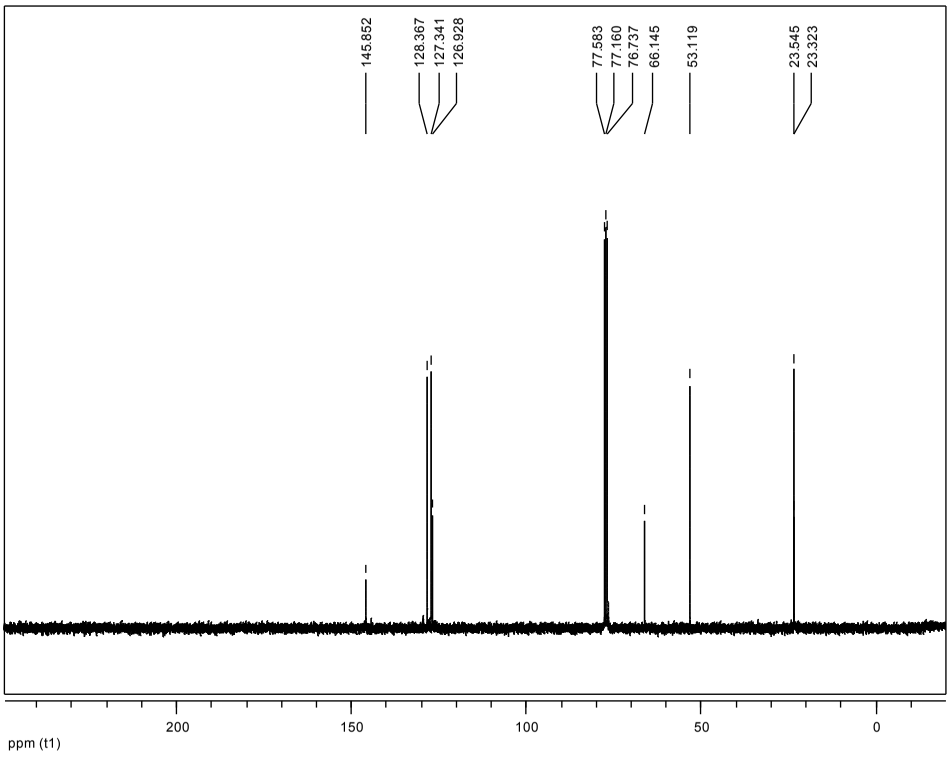

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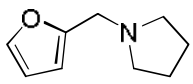
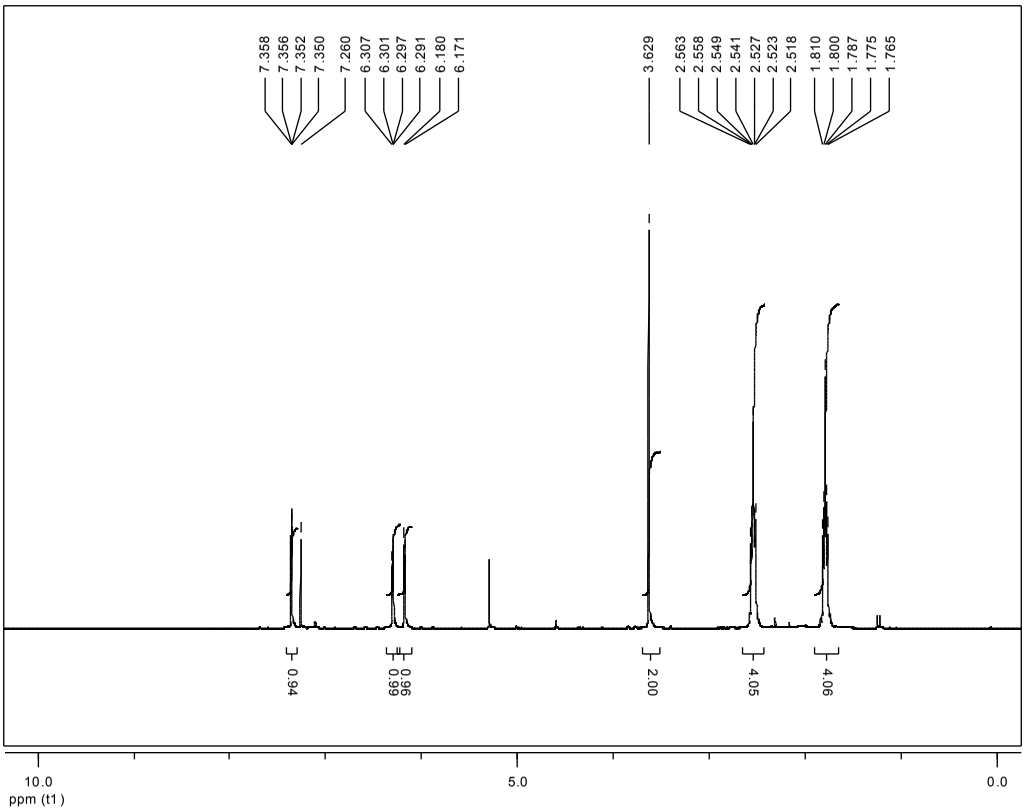
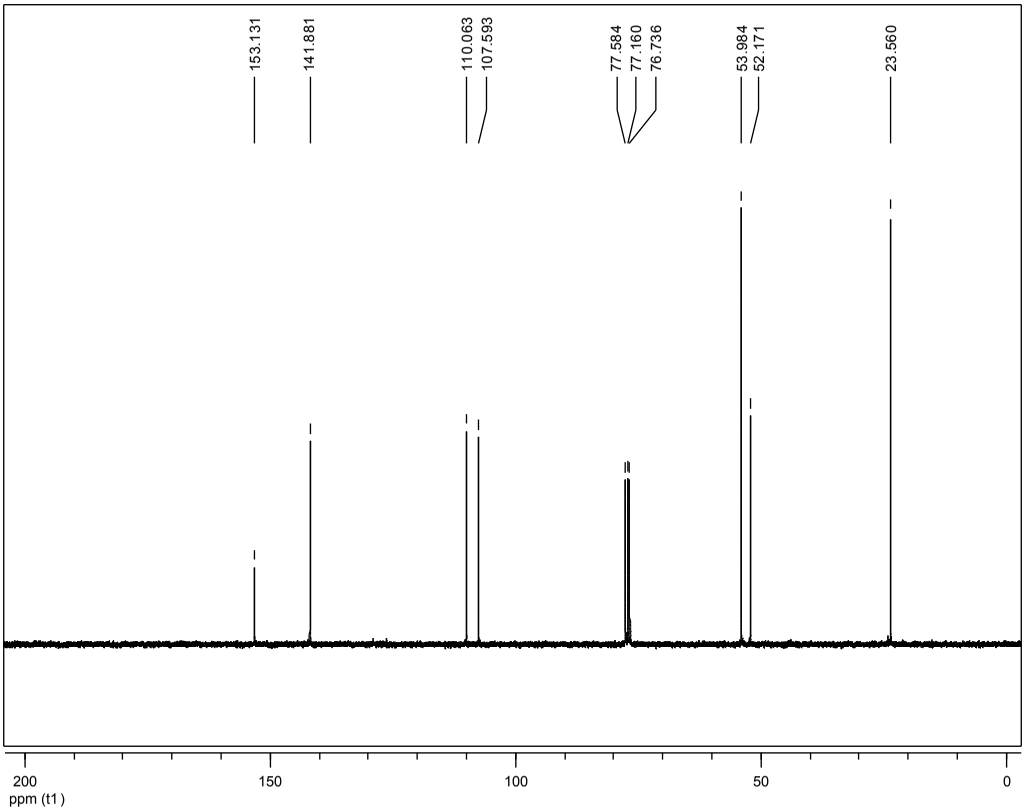
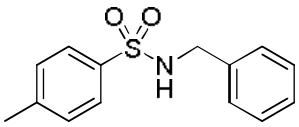
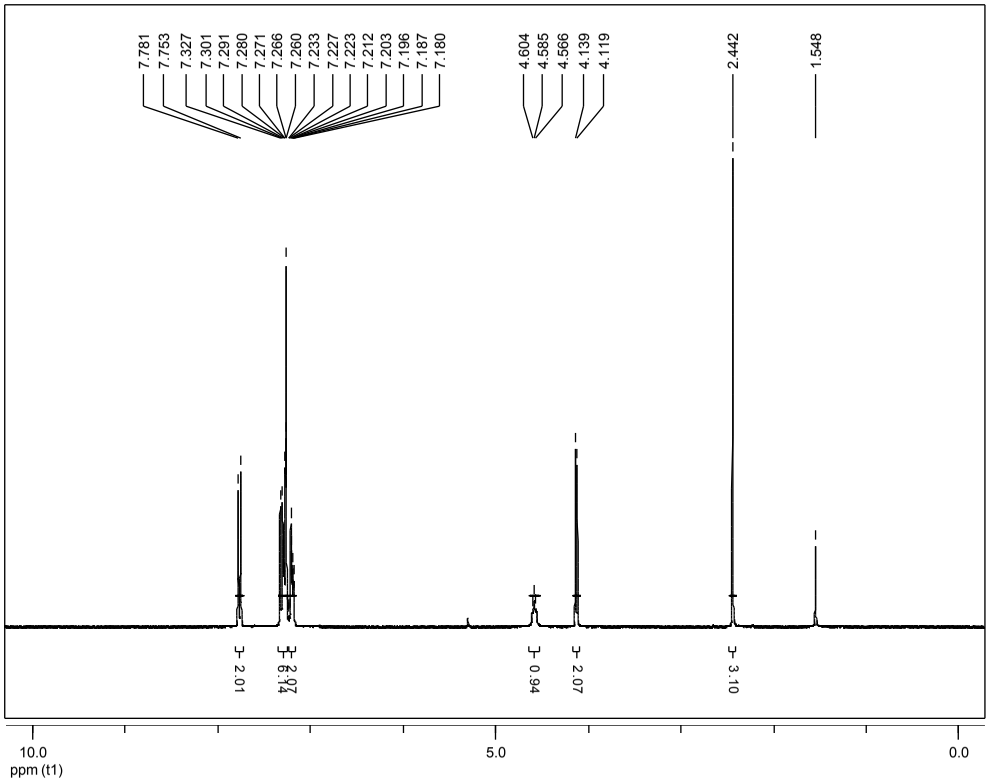


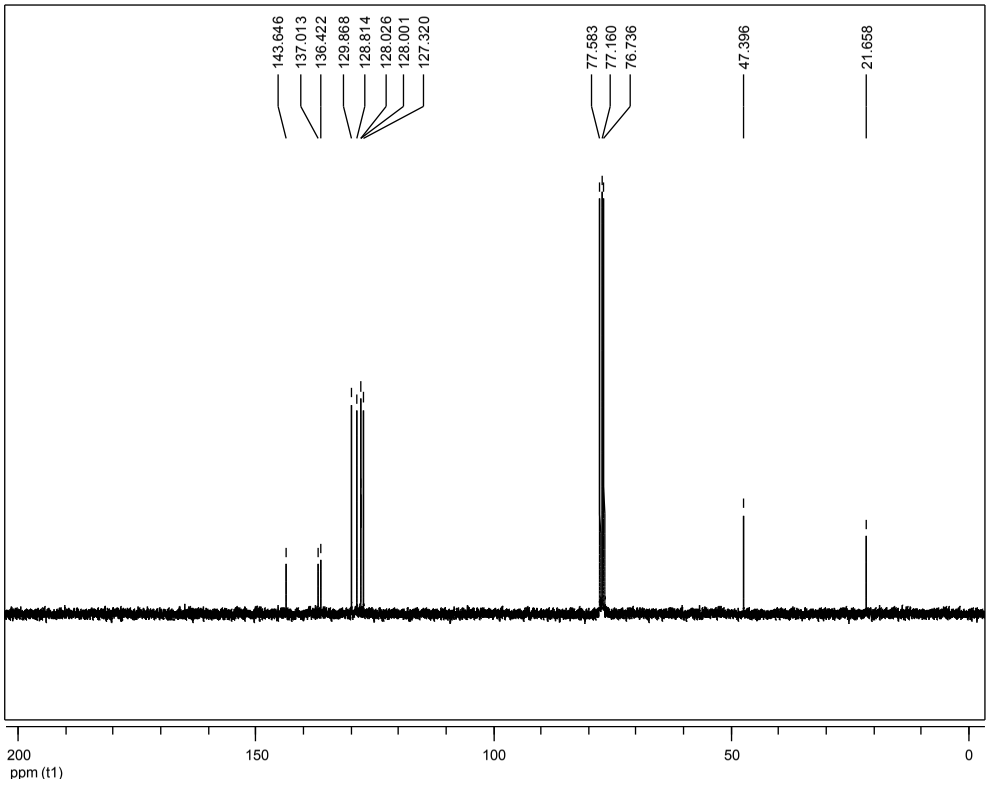




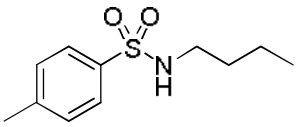
Entry 1, Table 6

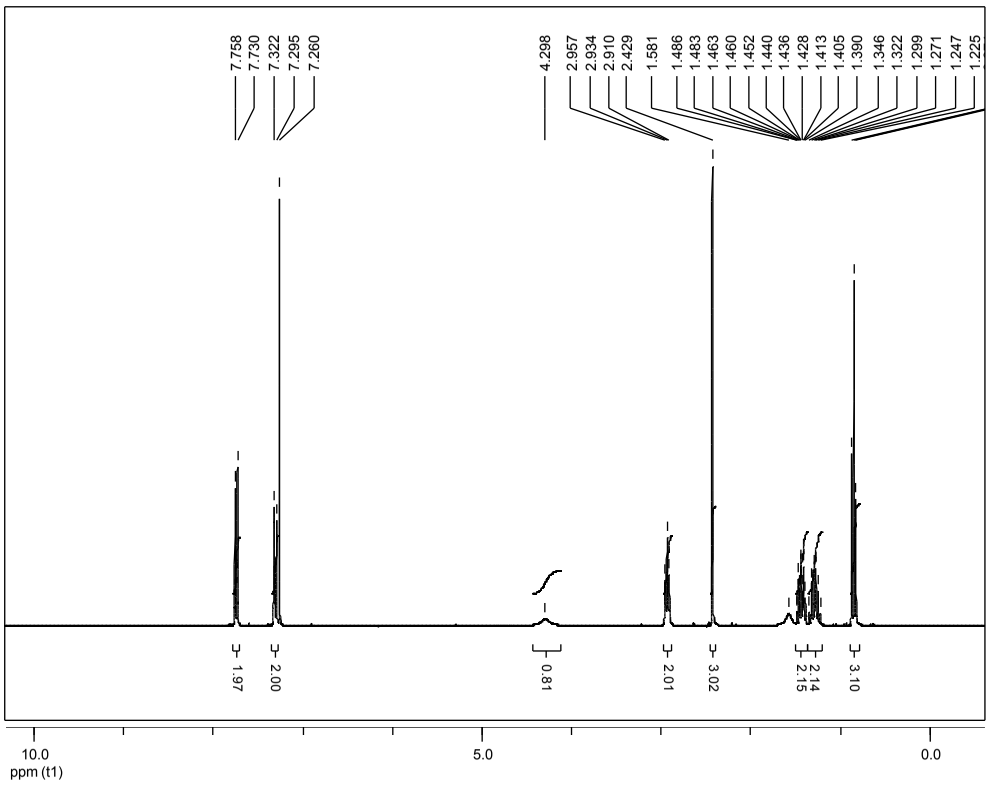


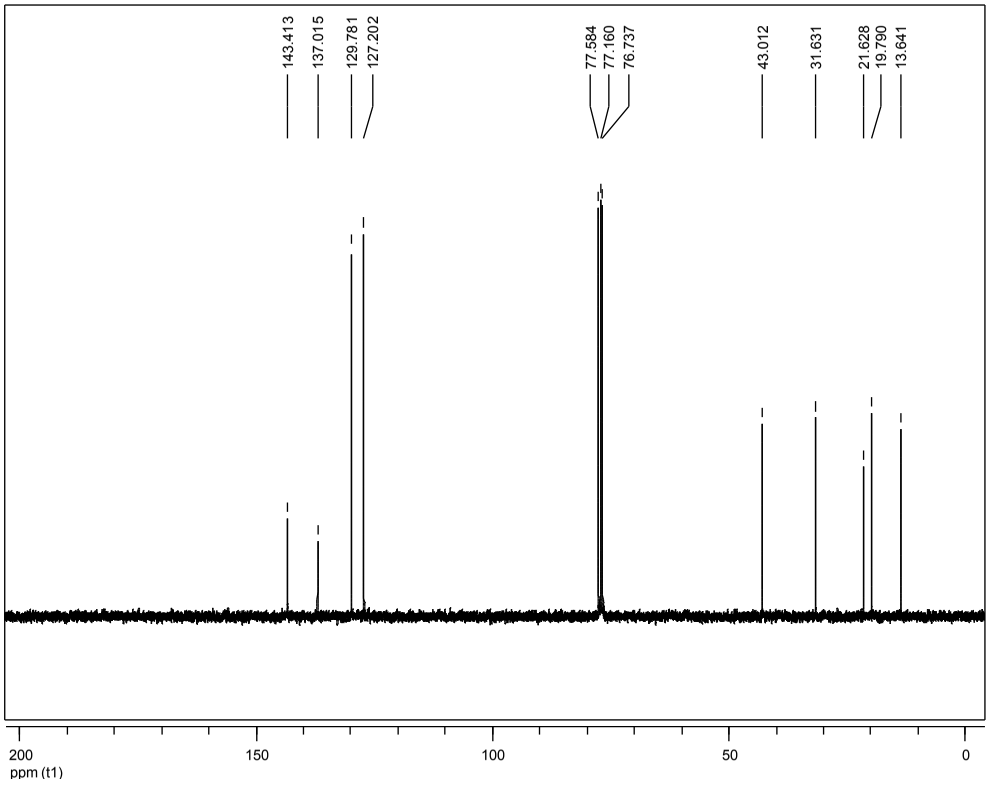




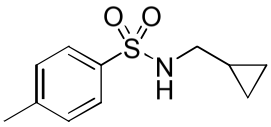
Entry 2, Table 6

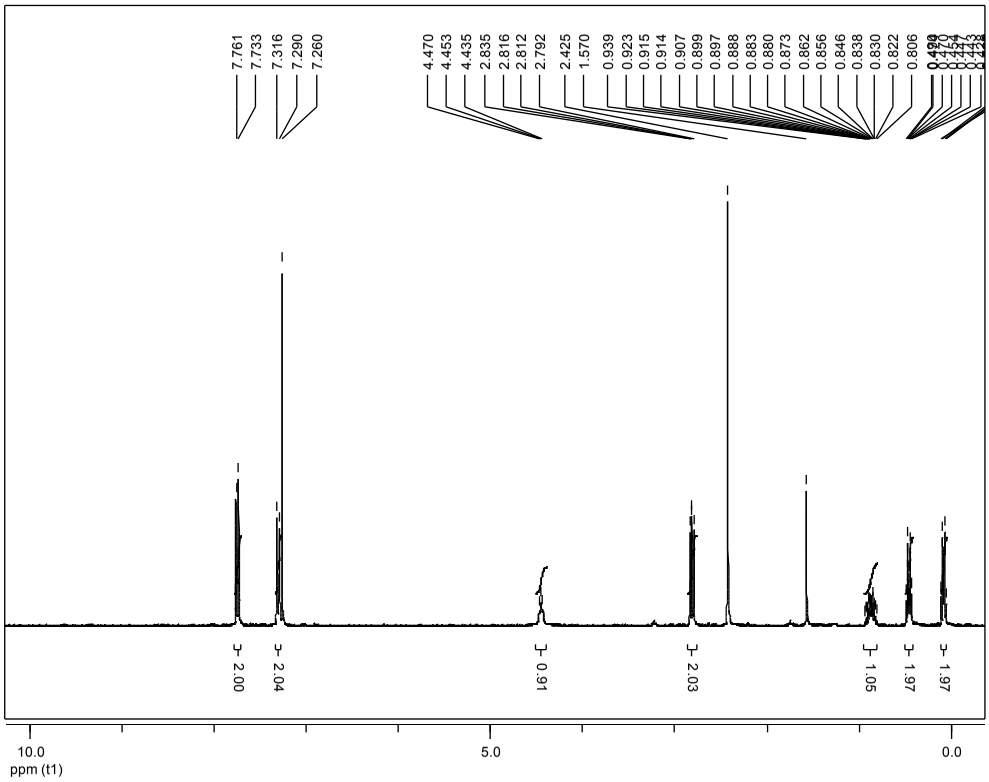


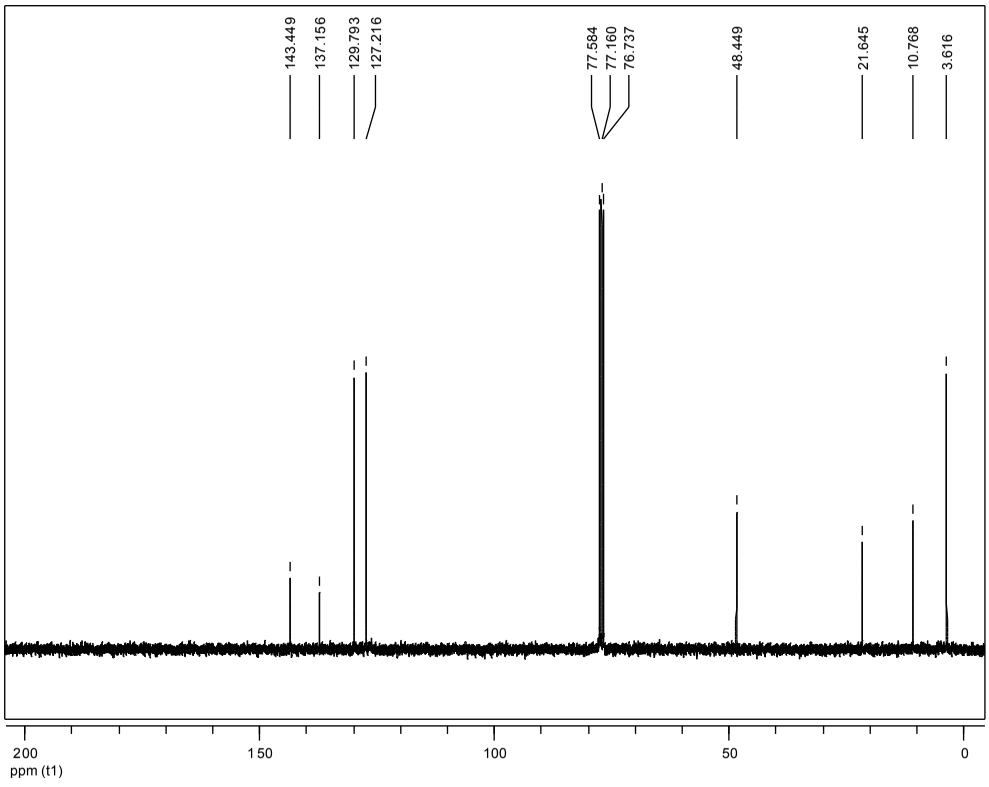




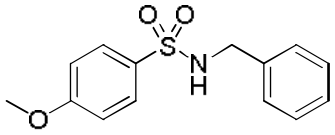
Entry 3, Table 6

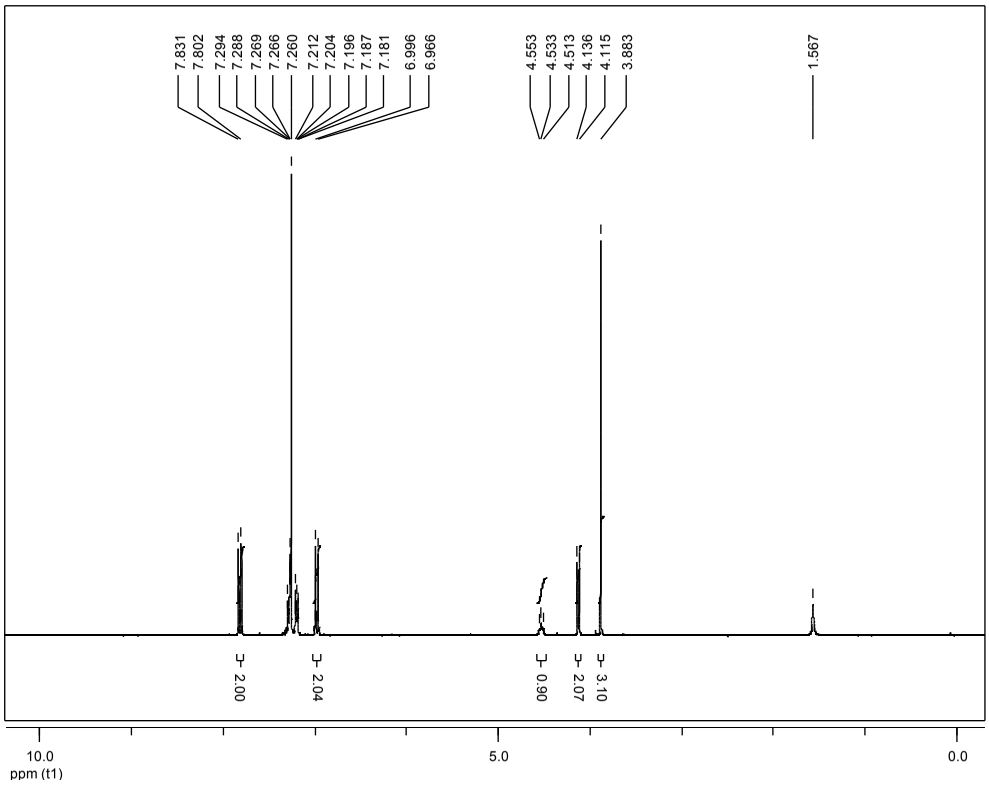


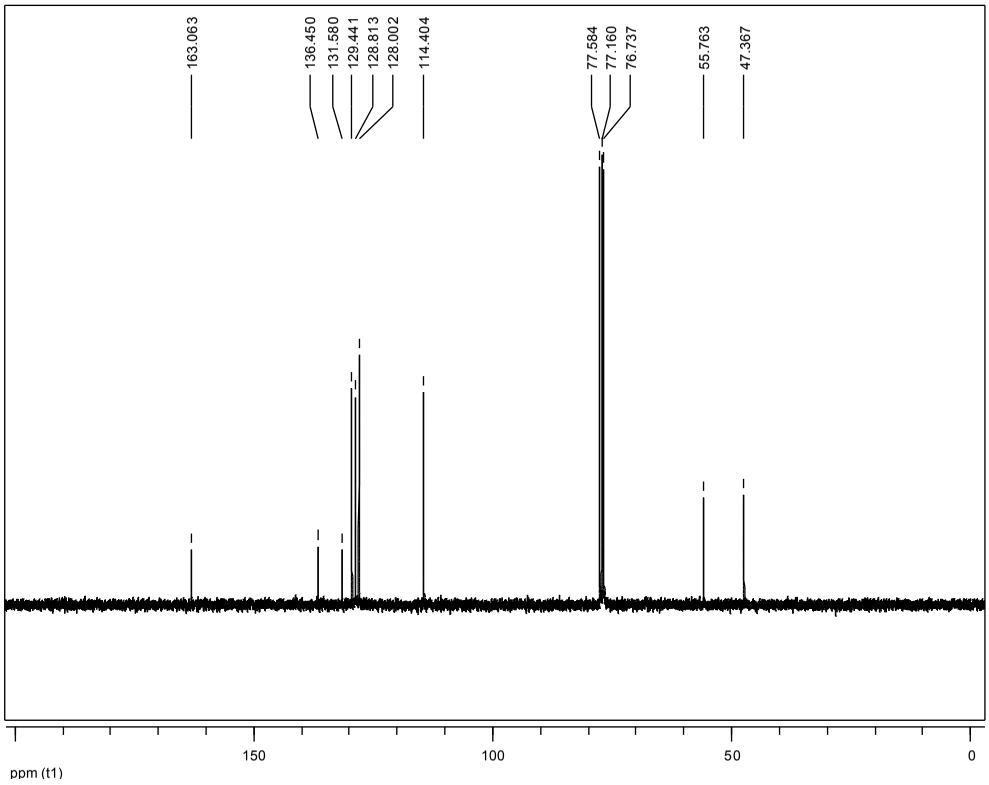




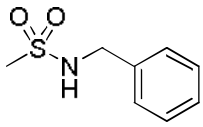
Entry 4, Table 6

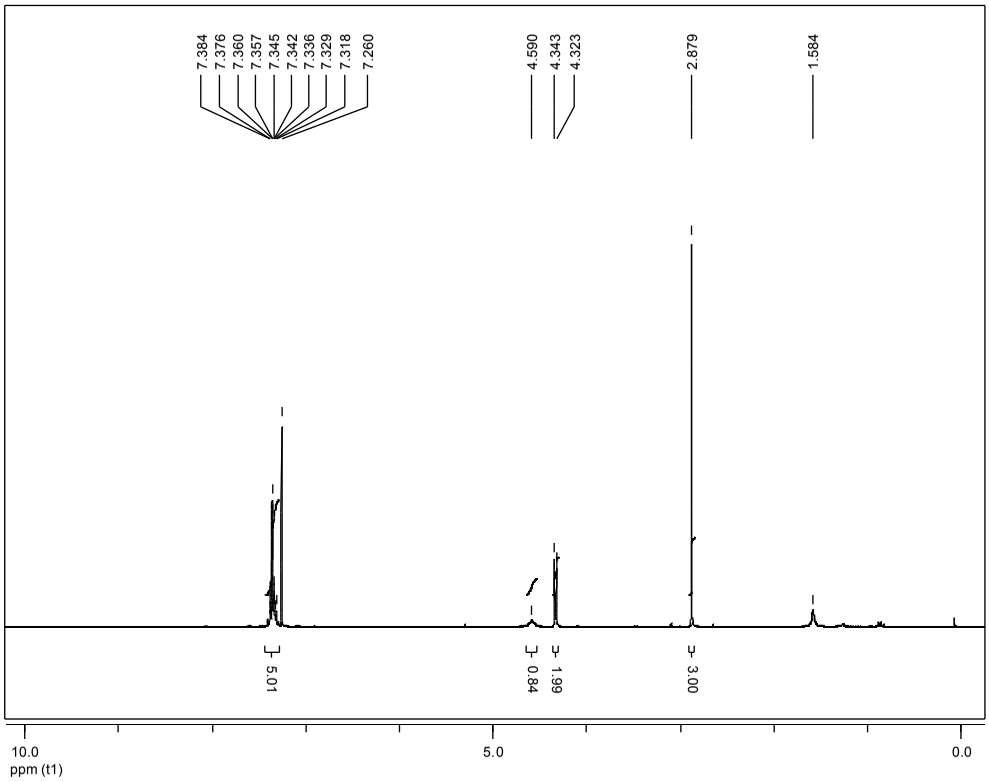


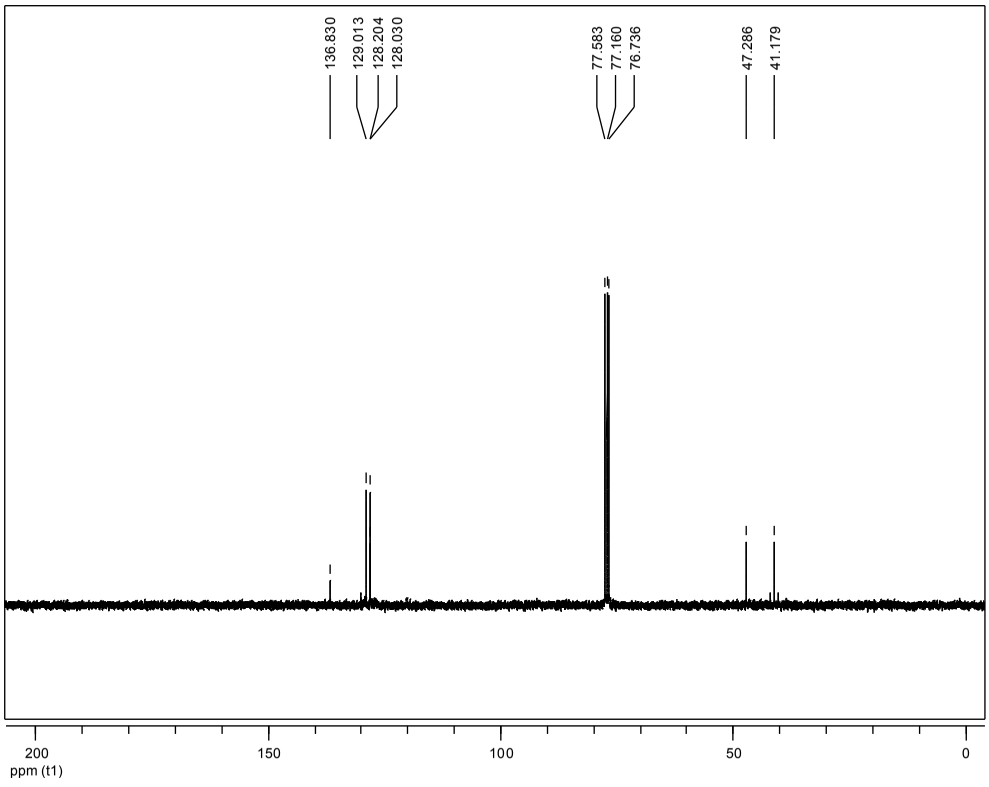




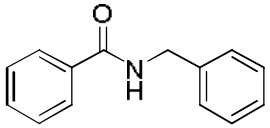
Entry 5, Table 6

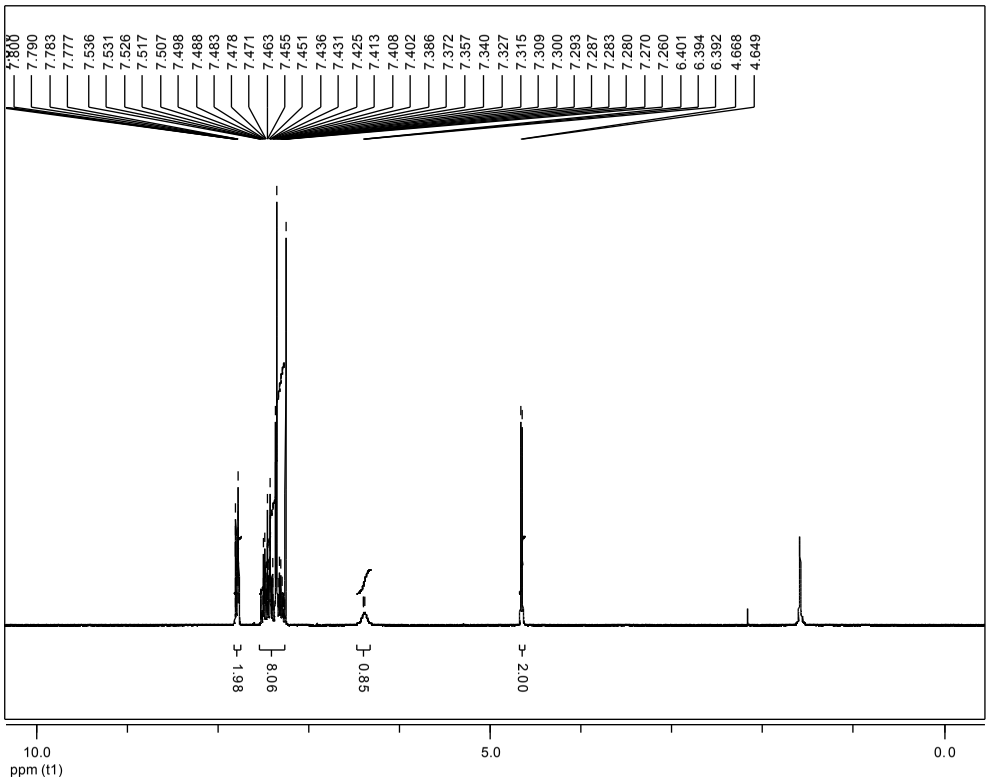


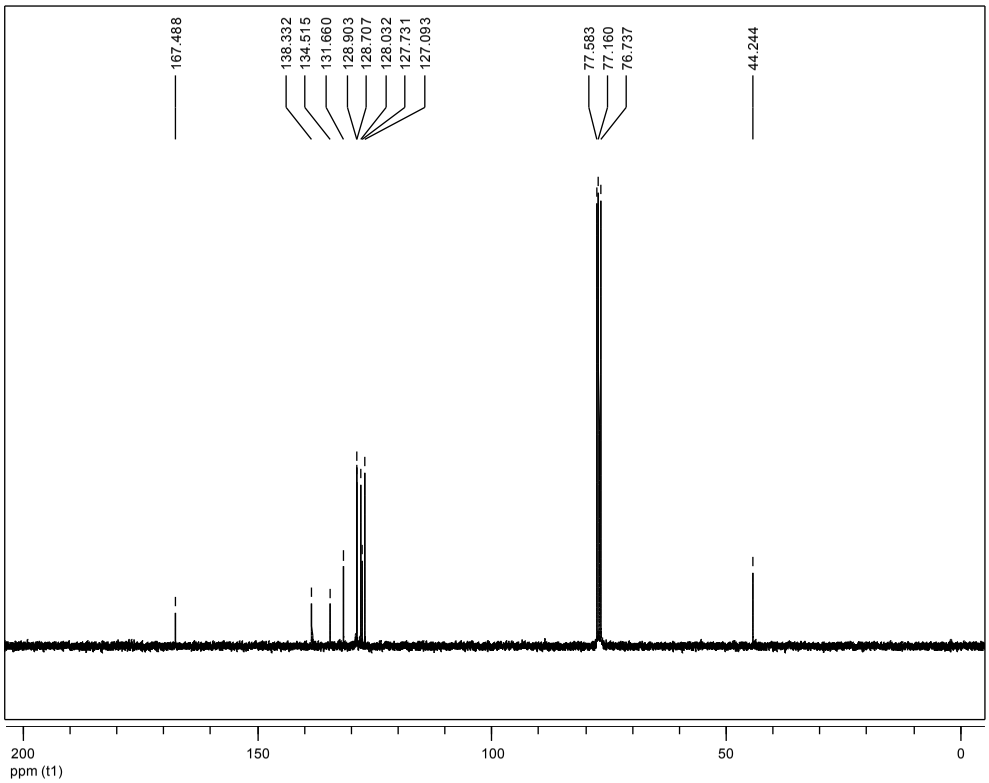




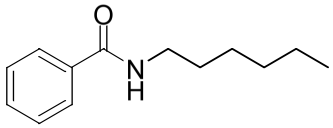
Entry 1, Table 7

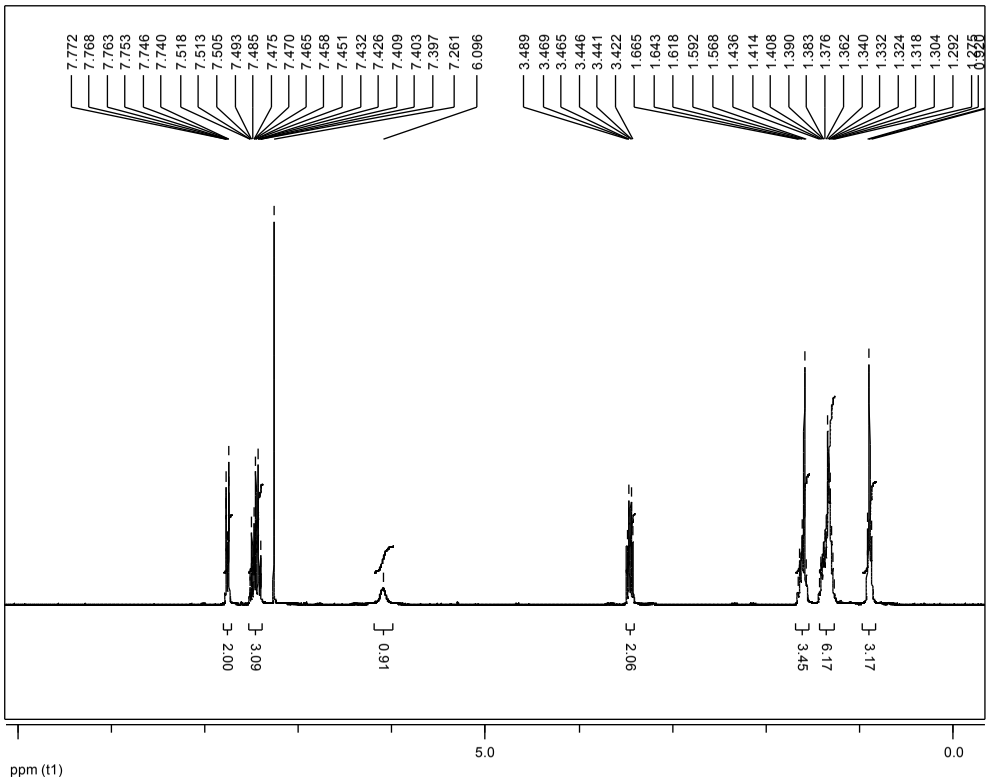


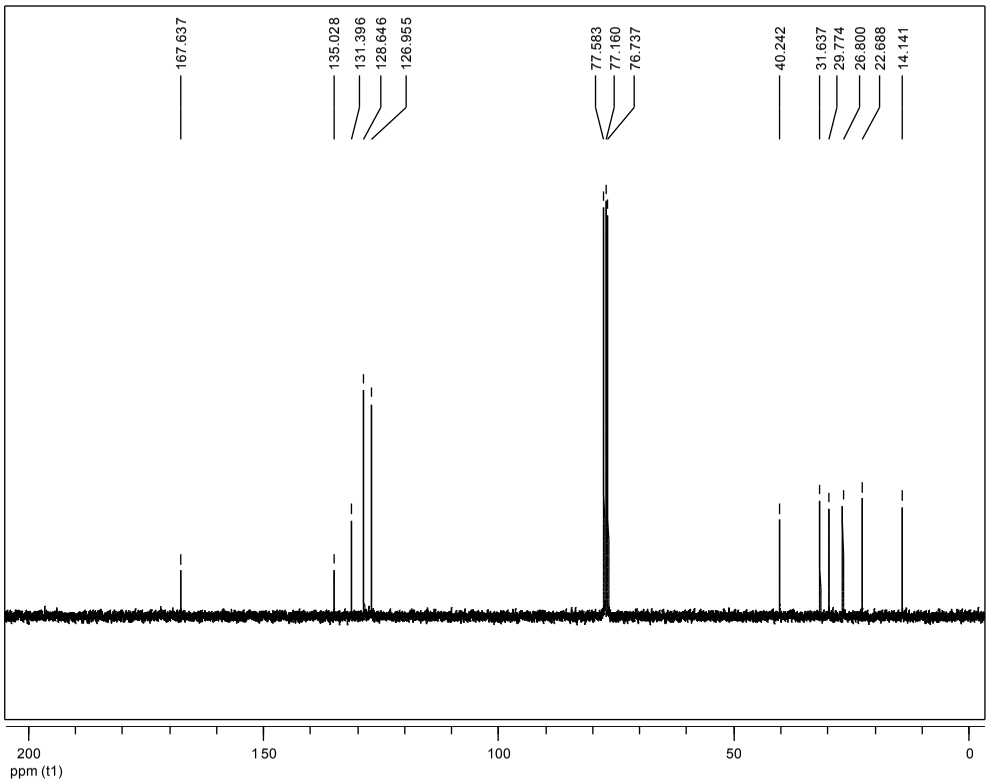




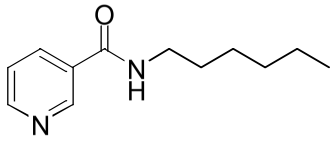
Entry 2, Table 7

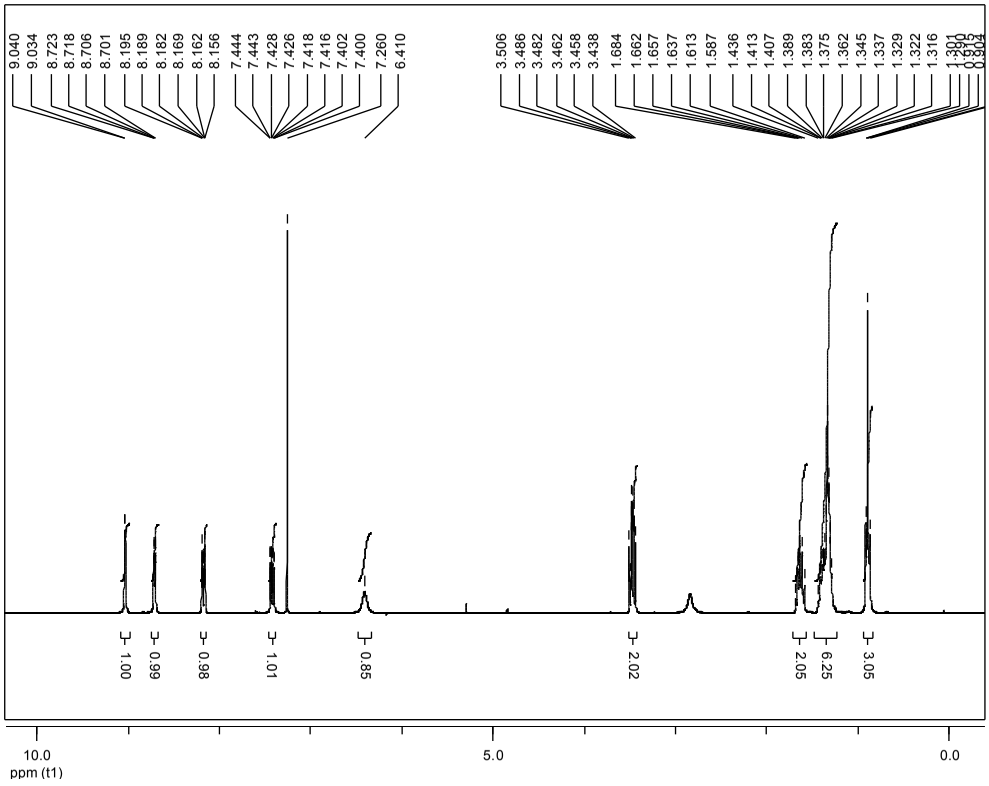


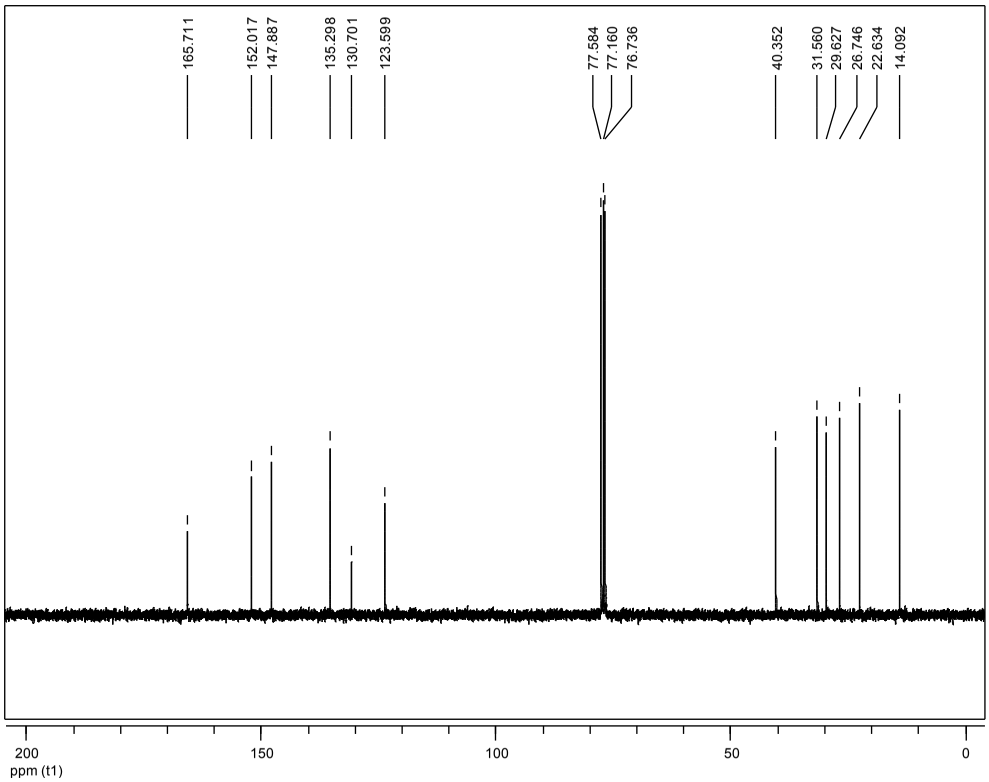




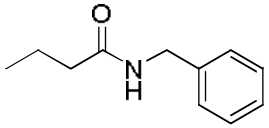
Entry 3, Table 7

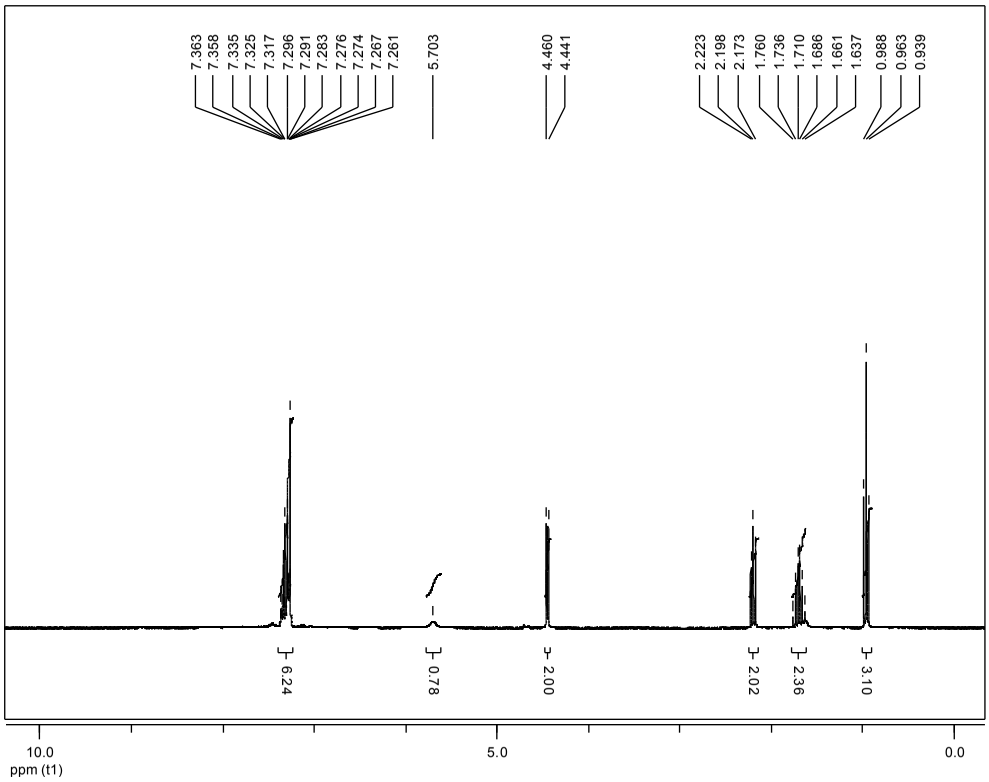


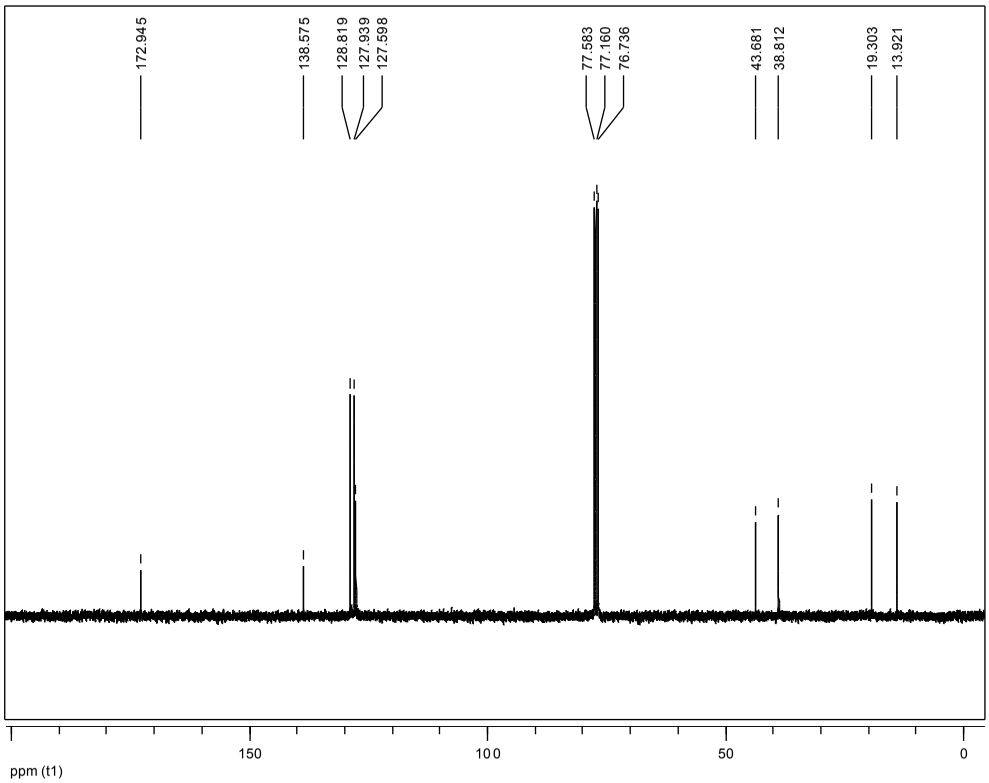




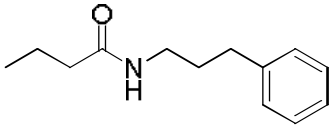
Entry 4, Table 7

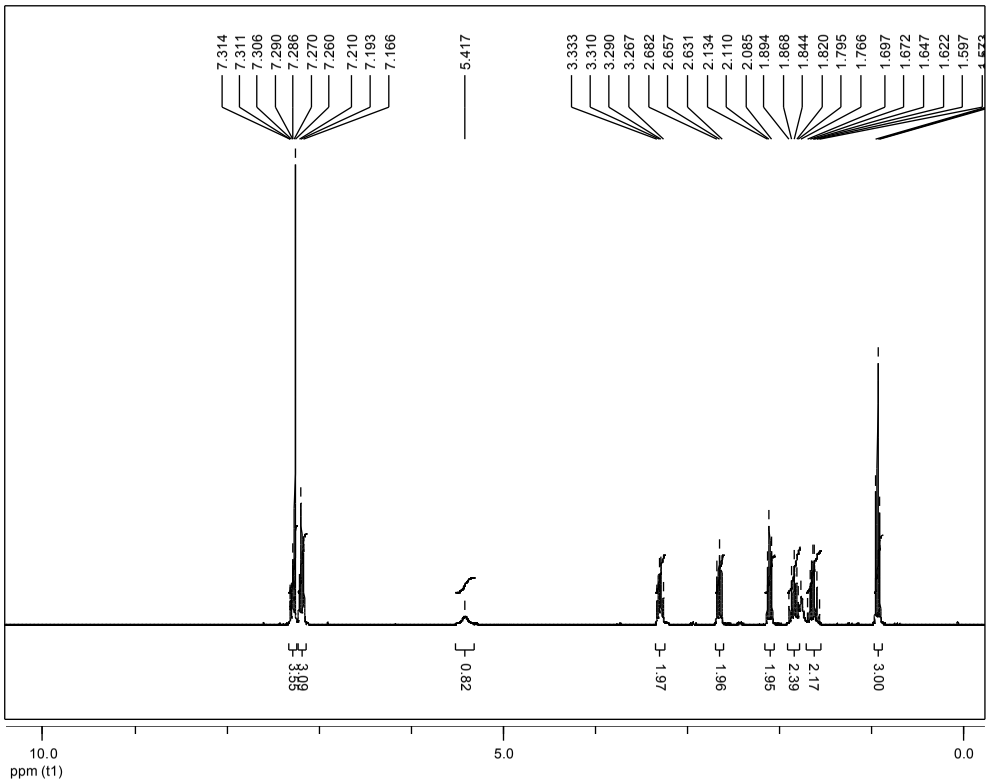


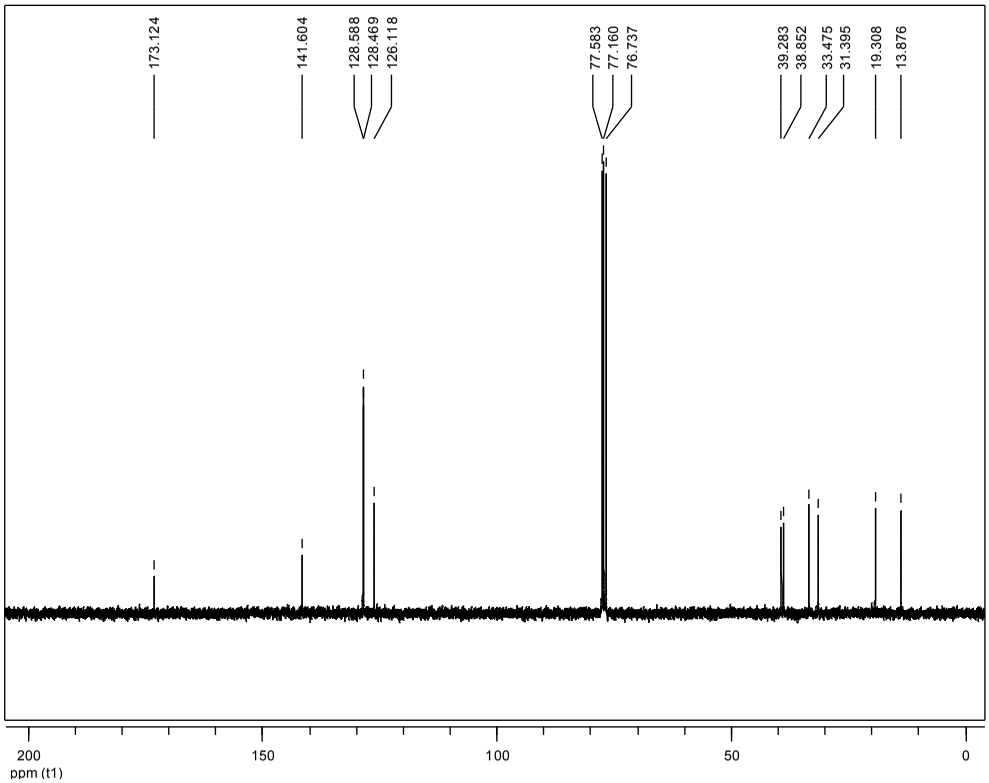




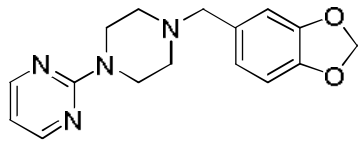
Entry 5, Table 7

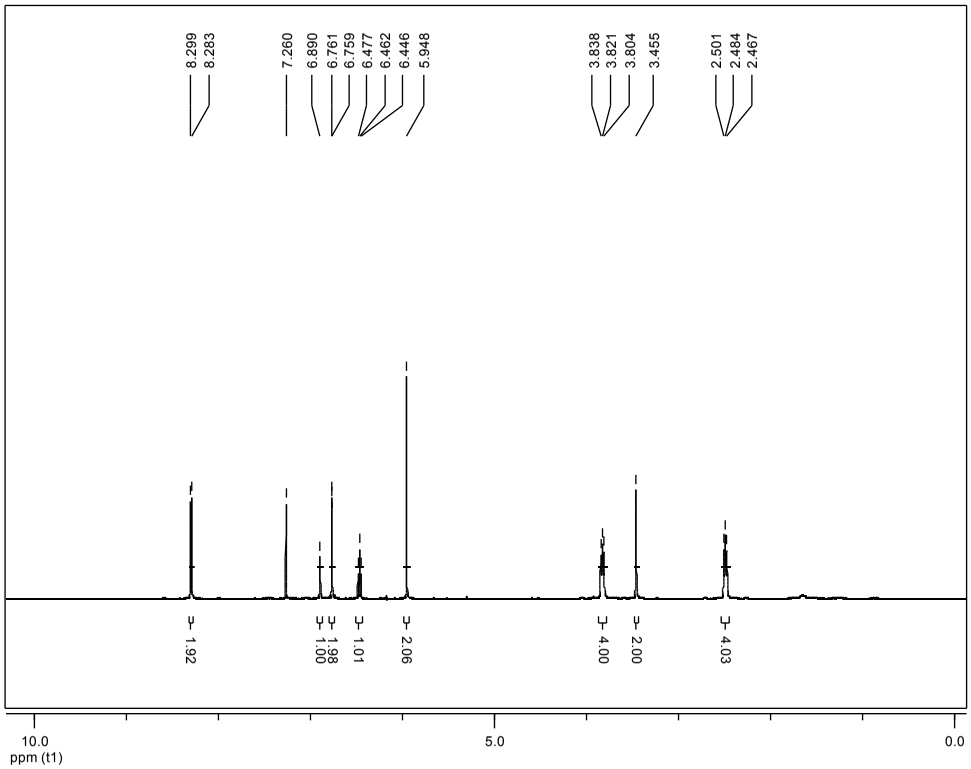


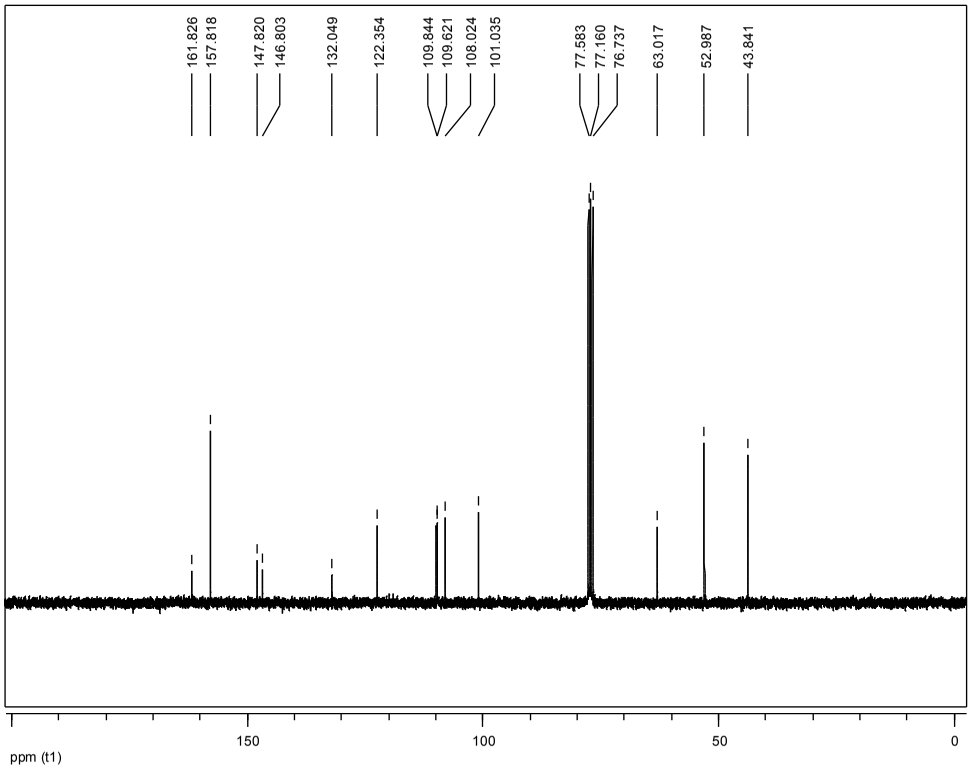




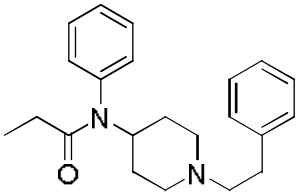
Piribedil

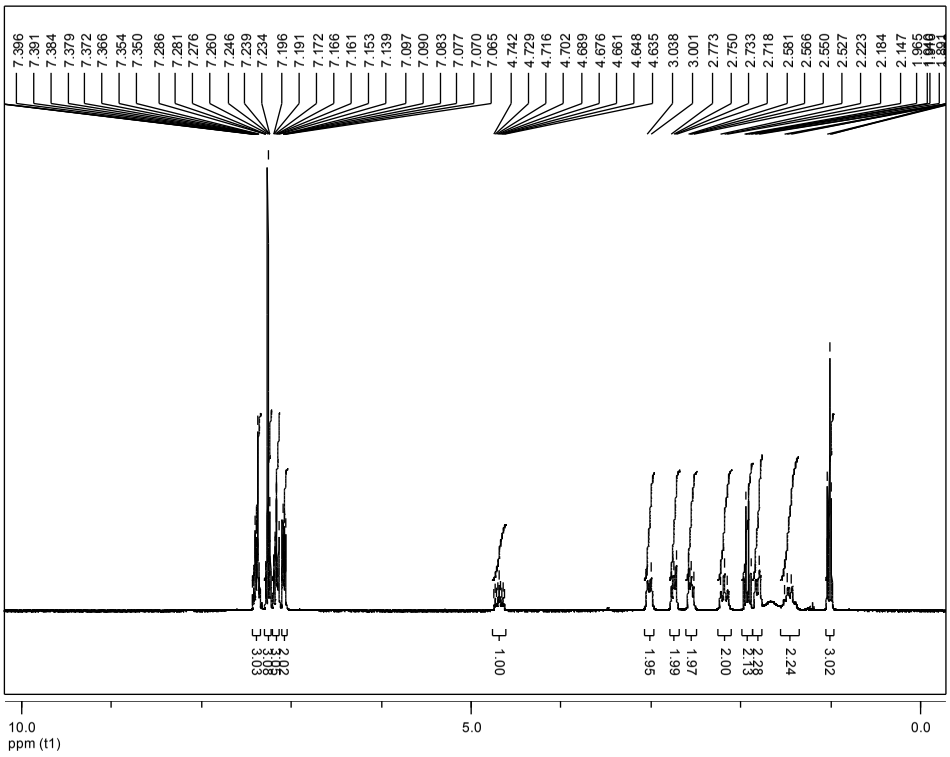


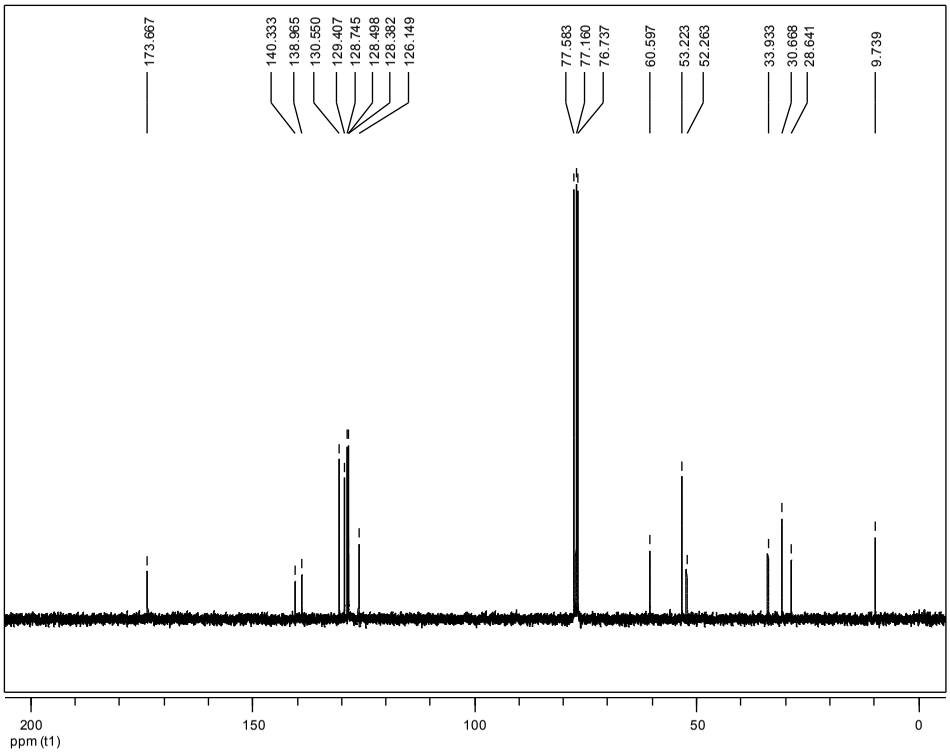

8.299
8.283
7.260
6.890
6.761
6.759
6.477
6.462
6.446
5.948
3.838
3.821
3.804
3.455
2.501
2.484
2.467
1.92
1.98
1.00
1.01
2.06
4.00
2.00
4.03
10.0
ppm (t1)
5.0
0.0

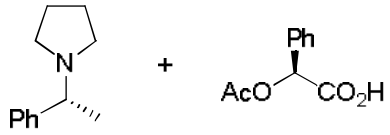

161.826
157.818
147.820
146.803
132.049
122.354
109.844
109.621
108.024
101.035
77.583
77.160
76.737
63.017
52.987
43.841
150
100
50
0
ppm (t1)

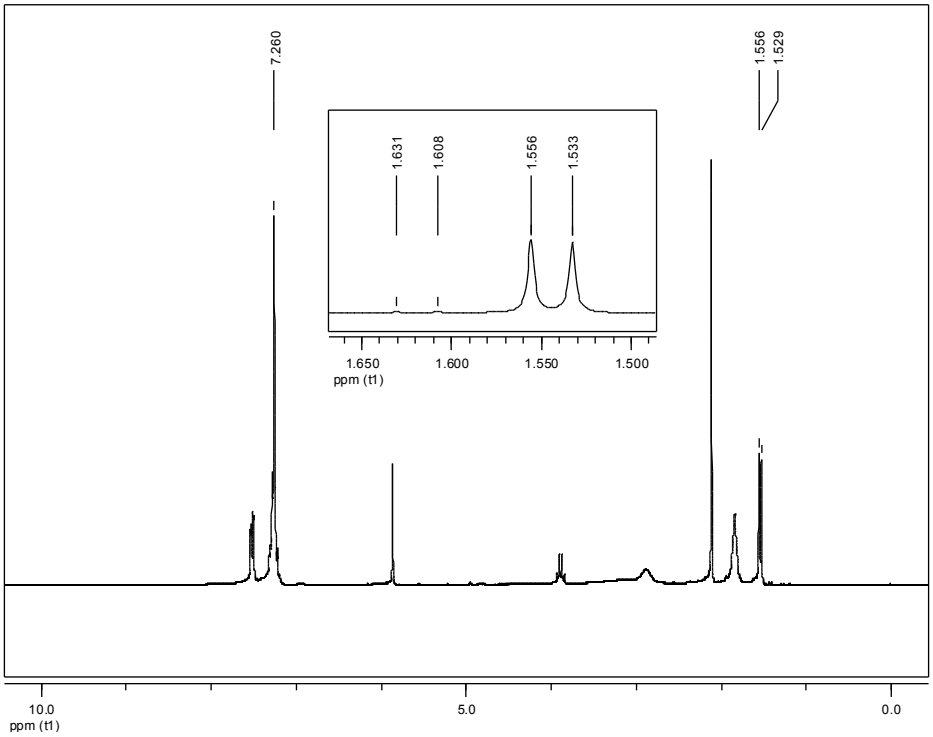
Fentanyl

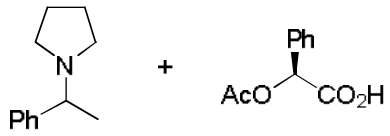


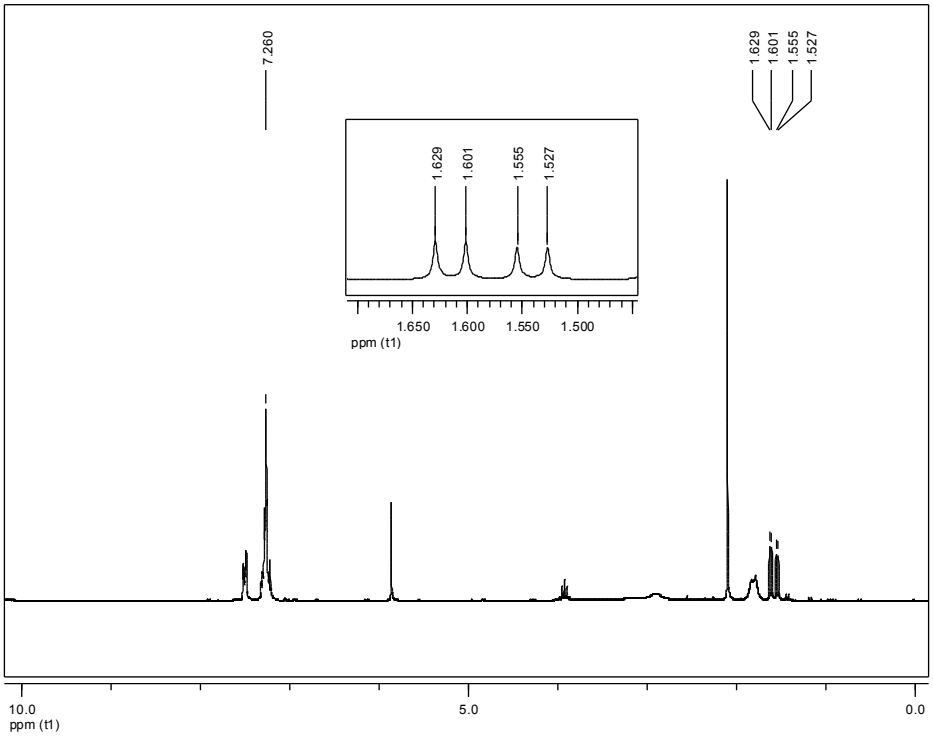

7.396
7.391
7.384
7.379
7.372
7.366
7.354
7.350
7.286
7.281
7.276
7.260
7.246
7.239
7.234
7.196
7.191
7.172
7.166
7.161
7.153
7.139
7.097
7.090
7.083
7.077
7.070
7.065
4.742
4.729
4.716
4.702
4.689
4.676
4.661
4.648
4.635
3.038
3.001
2.773
2.750
2.733
2.718
2.581
2.566
2.550
2.527
2.223
2.184
2.147
1.00
1.95
1.99
1.97
2.00
2.24
3.02
10.0
5.0
0.0
ppm (t1)


173.667
140.333
138.965
130.550
129.407
128.745
128.498
128.382
126.149
77.583
77.160
76.737
60.597
53.223
52.263
33.933
30.668
28.641
9.739
200
150
100
50
0
ppm (t1)


N
Ph
+
Ph
AcO
CO2H


7.260
1.556
1.529
1.631
1.608
1.556
1.533
1.650
1.600
1.550
1.500
ppm (t1)
10.0
5.0
0.0
ppm (t1)


N
Ph
+
Ph
AcO
CO2H


7.260
1.629
1.601
1.555
1.527
1.629
1.601
1.555
1.527
1.650
1.600
1.550
1.500
ppm (t1)
10.0
5.0
0.0
ppm (t1)