

# A General, Enantioselective Synthesis of Protected Morpholines and Piperazines

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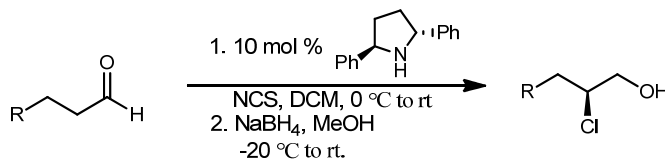
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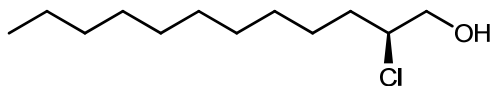
## General Experimental

All reagents were purchased from Sigma-Aldrich Corp., TCI America, Rieke Metals, Inc. and were used without purification. Analytical thin-layer chromatography (TLC) was performed on 250  $\mu\text{m}$  silica plates from Sorbent Technologies. Visualization was accomplished via UV light, and/or the use of ninhydrin, iodine, and potassium permanganate solutions followed by application of heat. Chromatography was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies or Silica RediSep Rf flash columns on a CombiFlash Rf automated flash chromatography system. All  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AV-400 (400 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to  $\delta$  7.26 and  $\delta$  77.16 ( $\text{CDCl}_3$ ). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, dd = doublet of doublets, dq = doublet of quartets, td = triplet of doublets, pd = pentet of doublets, m = multiplet), coupling constant (Hz), integration. Low resolution mass spectra (LCMS) were recorded on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra (HRMS) were recorded on a Waters Qtof-API-US plus Acuity system with ES as the ion source. Analytical high performance liquid chromatography (HPLC) was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral separations were performed on a Thar Investigator II supercritical fluid chromatograph (SFC) utilizing Chiralcel<sup>®</sup> OD, OD-Cl, OJ, and Chiralpak<sup>®</sup> IA columns. Optical rotations were acquired on a Jasco P-2000 polarimeter at 23  $^{\circ}\text{C}$  and 589 nm. The specific rotations were calculated according to the equation  $[\alpha]_D^{23} = 100\alpha/l \times c$  where  $l$  is the path length in decimeters and  $c$  is the concentration in g/100 mL.

## Procedure for Chiral Chloro-alcohol Synthesis

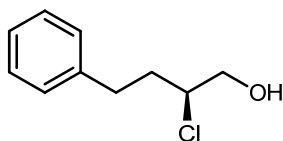


To a solution of aldehyde (1 mmol) and (2R, 5R)-2,5-diphenylpyrrolidine (0.1 eq., 0.1 mmol) in DCM (2.0 mL) was added *N*-chlorosuccinimide (173 mg, 1.3 mmol, 1.3 eq.) at 0 °C. The reaction was kept at 0 °C for 1 hour at which point it was allowed to warm to ambient temperature. It was then stirred until the aldehyde was completely consumed as determined by <sup>1</sup>H NMR spectroscopy of the reaction mixture. The reaction was then cooled to 0 °C and diluted with methanol (10 mL). NaBH<sub>4</sub> (189 mg, 5 mmol, 5 eq) was added in several portions and the mixture was stirred for 30 minutes and quenched via the addition of water. The reaction was extracted 3X with EtOAc, dried with MgSO<sub>4</sub>, and concentrated.



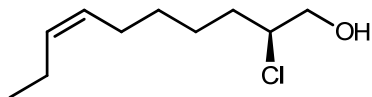
(*S*)-2-chlorododecan-1-ol (**9a**)

The product was prepared according to the chiral chloro-alcohol synthesis procedure and purified by silica chromatography (6:1 Hexanes/EtOAc) to afford the product as a clear oil (159.5 mg, 72.2%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 3.99 (s, br, 1H); 3.78-3.75 (m, 1H); 3.67-3.62 (m, 1H); 2.37-2.27 (m, 1H); 1.80-1.64 (m, 2H); 1.55-1.46 (m, 1H); 1.42-1.36 (m, 1H); 1.25 (s, br, 14H); 0.87 (t, *J* = 6.5 Hz, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 66.92, 65.22, 34.18, 31.81, 29.49, 29.46, 29.34, 29.23, 29.03, 26.24, 22.59, 14.01. Specific rotation [ $\alpha$ ]<sub>D</sub><sup>23</sup> -41.0° (*c* = 100, MeOH).



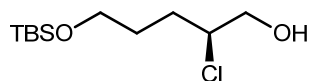
(*S*)-2-chloro-4-phenylbutan-1-ol (**9b**)

The product was prepared according to the chiral chloro-alcohol synthesis procedure and purified by silica chromatography (6:1 Hexanes/EtOAc) to afford the product as a clear oil (154 mg, 83%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.33-7.20 (m, 5H); 4.02-3.96 (m, 1H); 3.82-3.67 (m, 2H); 2.94-2.87 (m, 1H); 2.80-2.73 (m, 1H); 2.09-1.99 (m, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 140.61, 128.49, 128.47, 126.17, 66.92, 64.02, 35.75, 32.30. Specific rotation [ $\alpha$ ]<sub>D</sub><sup>23</sup> -43.1° (*c* = 100, MeOH).



(*S,Z*)-2-chlorodec-7-en-1-ol (**9c**)

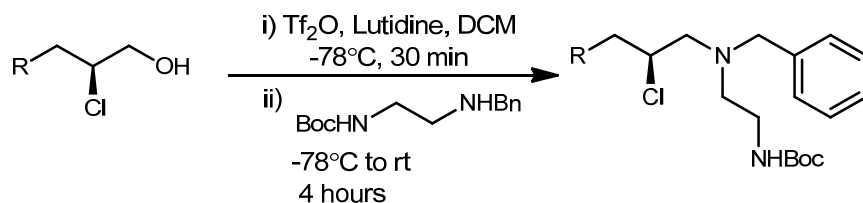
The product was prepared according to the chiral chloro-alcohol synthesis procedure and purified by silica chromatography (6:1 Hexanes/EtOAc) to afford the product as a clear oil (157 mg, 82%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 5.36-5.23 (m, 2H); 3.97-3.91 (m, 1H); 3.74-3.68 (m, 1H); 3.65-3.59 (m, 1H); 2.87 (s, br, 1H); 2.03-1.95 (m, 4H); 1.79-1.60 (m, 2H); 1.56-1.47 (m, 1H); 1.43-1.28 (m, 3H); 0.91 (td, *J*<sub>1</sub> = 1.97 Hz, *J*<sub>2</sub> = 7.50, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 131.86, 128.52, 68.81, 64.80, 34.07, 29.10, 26.73, 25.83, 20.41, 14.23. Specific rotation [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -31.3° (*c* = 100, MeOH).



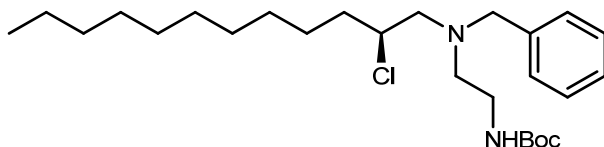
(*S*)-5-((*tert*-butyldimethylsilyloxy)-2-chloropentan-1-ol (**9d**)

The product was prepared according to the chiral chloro-alcohol synthesis procedure and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (199 mg, 79%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 4.10-4.04 (m, 1H); 3.83-3.77 (m, 1H); 3.71-3.63 (m, 3H); 2.11-2.06 (m, 1H); 1.94-1.85 (m, 1H); 1.81-1.71 (m, 2H); 1.68-1.53 (m, 1H); 0.89 (s, 9H); 0.047 (s, 6H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 66.85, 64.86, 62.30, 30.70, 29.25, 25.83, 18.21, -5.43. HRMS (TOF, ES+) C<sub>11</sub>H<sub>25</sub>ClO<sub>2</sub>Si [M+H]<sup>+</sup> calc. mass 253.1391, found 253.1393. Specific rotation [ $\alpha$ ]<sub>D</sub><sup>23</sup> = -13.8 (*c* = 100, MeOH).

## General Procedure for Chiral Chloro-Diamine Synthesis

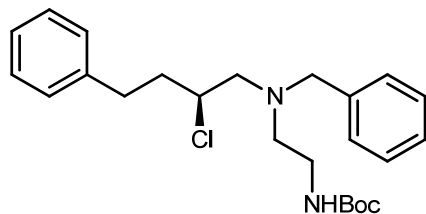


Lutidine (10 eq.) was added to a solution of chloro alcohol (1 eq.) in DCM (0.1 M) in a flame dried flask and the reaction was cooled to  $-78^\circ\text{C}$ . Triflic Anhydride (1.3 eq.) was added dropwise to the reaction and it was allowed to stir for 30 minutes. To this reaction, still at  $-78^\circ\text{C}$ , was added the diamine (2 eq.) dropwise, dissolved in 1 mL of DCM. This reaction was allowed to warm to room temperature over the next 4 hours and was quenched with water and brine. It was extracted 3X with EtOAc, dried with  $\text{MgSO}_4$ , and concentrated before purification.



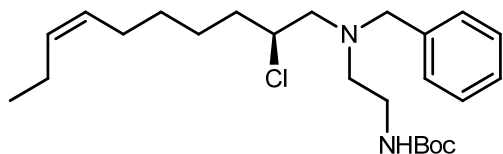
(*S*)-*tert*-butyl (2-(benzyl(2-chlorododecyl)amino)ethyl)carbamate (**6a**)

The product was prepared according to the chloro diamine procedure on a 0.23 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (78 mg, 0.17 mmol, 75%).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.34-7.30 (m, 4H); 7.29-7.24 (m, 1H); 5.04 (s, br, 1H); 3.94-3.86 (m, 1H); 3.71-3.61 (m, 2H); 3.27-3.10 (m, 2H); 2.81-2.69 (m, 2H); 2.67-2.55 (m, 2H); 1.85-1.74 (m, 1H); 1.61-1.55 (m, 1H); 1.44 (s, 9H); 1.28 (s, 16H); 0.90 (t,  $J = 7.01$ , 3H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 156.07, 138.59, 128.87, 128.28, 127.18, 78.84, 61.32, 59.42, 54.01, 38.13, 35.94, 31.82, 29.51, 29.48, 29.39, 29.24, 29.06 (one set of coincident signals), 28.33, 26.11, 22.60, 14.04. HRMS (TOF, ES+)  $\text{C}_{26}\text{H}_{46}\text{N}_2\text{O}_2\text{Cl}$   $[\text{M}+\text{H}]^+$  calc. mass 453.3248, found 453.3245. Specific rotation  $[\alpha]_D^{23} = -7.0^\circ$  ( $c = 100$ , MeOH).



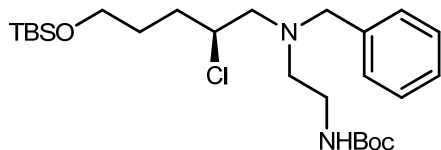
(*S*)-*tert*-butyl (2-(benzyl(2-chloro-4-phenylbutyl)amino)ethyl)carbamate (**6b**)

The product was prepared according to the chloro diamine procedure on a 0.27 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (97 mg, 0.23 mmol, 87%).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.37-7.19 (m, 10H); 5.00 (s, br, 1H); 3.91-3.83 (m, 1H); 3.60 (s, 2H); 3.25-3.08 (m, 2H); 2.92-2.83 (m, 1H); 2.81-2.68 (m, 3H); 2.64-2.51 (m, 2H); 2.23-2.12 (m, 1H); 1.93-1.82 (m, 1H); 1.47 (s, 9H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 155.94, 140.97, 138.62, 128.88, 128.47, 128.33, 127.21, 126.06, 78.84, 61.28, 60.18, 54.00, 39.20, 37.53, 32.29, 28.42. HRMS (TOF, ES+)  $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_2\text{Cl}$   $[\text{M}+\text{H}]^+$  calc. mass 417.2309, found 417.2308. Specific rotation  $[\alpha]_D^{23} = -5.5^\circ$  ( $c = 100$ , MeOH).



(*S,Z*)-*tert*-butyl (2-(benzyl(2-chlorodec-7-en-1-yl)amino)ethyl)carbamate (**6c**)

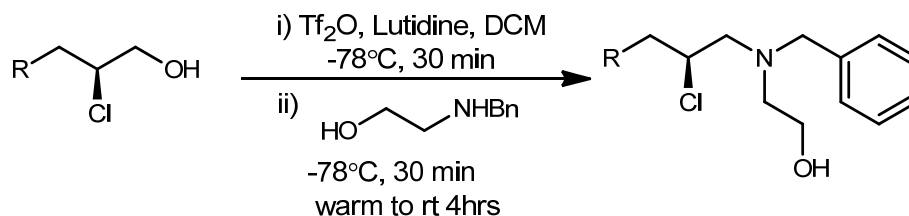
The product was prepared according to the chloro diamine procedure on a 0.41 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (138 mg, 0.33 mmol, 80%).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.35-7.28 (m, 4H); 7.28-7.23 (m, 1H); 5.41-5.26 (m, 2H); 4.97 (s, br, 1H); 3.92-3.84 (m, 1H); 3.69-3.60 (m, 2H); 3.26-3.09 (m, 2H); 2.79-2.66 (m, 2H); 2.66-2.52 (m, 2H); 2.08-1.98 (m, 4H); 1.84-1.74 (m, 1H); 1.63-1.46 (m, 2H); 1.43 (s, 9H); 1.41-1.22 (m, 3H); 0.96 (t,  $J = 7.5$ , 3H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 155.93, 138.69, 131.80, 128.85, 128.68, 128.28, 127.16, 78.79, 61.32 (one set of coincident signals), 59.43, 54.05, 38.19, 35.81, 29.18, 28.36, 26.83, 25.75, 20.46, 14.32. HRMS (TOF, ES+)  $\text{C}_{24}\text{H}_{40}\text{N}_2\text{O}_2\text{Cl}$   $[\text{M}+\text{H}]^+$  calc. mass 423.2778, found 423.2779. Specific rotation  $[\alpha]_D^{23} = -7.0^\circ$  ( $c = 100$ , MeOH).



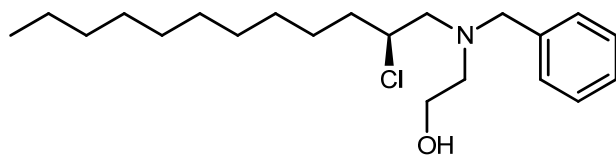
(*S*)-*tert*-butyl (2-(benzyl(5-((*tert*-butyl)dimethylsilyl)oxy)-2-chloropentyl)amino)ethyl)carbamate (**6d**)

The product was prepared according to the chloro diamine procedure on a 0.37 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (113 mg, 0.23 mmol, 63%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.35-7.22 (m, 5H); 5.00 (s, br, 1H); 3.99-3.90 (m, 1H); 7.73-3.55 (m, 4H); 3.26-3.09 (m, 2H); 2.83-2.68 (m, 2H); 2.67-2.53 (m, 2H); 1.96- 1.88 (m, 1H); 1.79-1.68 (m, 1H); 1.66-1.54 (m, 2H); 1.43 (s, 9H); 0.90 (s, 9H); 0.05 (s, 6H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 155.97, 138.66, 128.84, 128.30, 127.15, 78.87, 62.43, 61.40, 61.31, 59.41, 53.95, 38.21, 32.51, 29.41, 28.35, 25.87, 18.24, -5.37. HRMS (TOF, ES+) C<sub>25</sub>H<sub>46</sub>N<sub>2</sub>O<sub>3</sub>ClSi [M+H]<sup>+</sup> calc. mass 485.2966, found 485.2970. Specific rotation  $[\alpha]_{D}^{23} = -2.7^{\circ}$  (*c* = 100, MeOH).

## General Procedure for Chiral Chloro-Aminoalcohol Synthesis

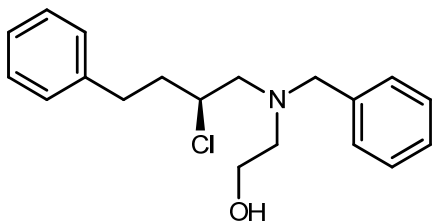


Lutidine (10 eq.) was added to a solution of chloro alcohol (1 eq.) in DCM (0.1 M) in a flame dried flask under an argon atmosphere and the reaction was cooled to  $-78^\circ\text{C}$ . Triflic Anhydride (1.3 eq.) was added dropwise to the reaction and it was allowed to stir for 30 minutes. To this reaction, still at  $-78^\circ\text{C}$ , was added the aminoalcohol (2 eq.) dropwise, dissolved in 1 mL of DCM. This reaction was allowed to warm to room temperature over the next 4 hours and was quenched with water and brine. It was extracted 3X with EtOAc, dried with  $\text{MgSO}_4$ , and concentrated before purification.



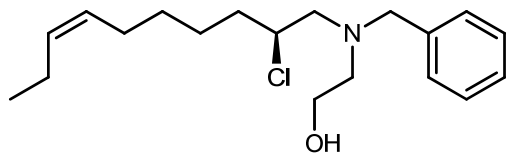
(S)-2-(benzyl(2-chlorododecyl)amino)ethanol (**5a**)

The product was prepared according to the chloro amino alcohol procedure on a 0.36 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (94 mg, 0.27 mmol, 74%).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.39-7.32 (m, 4H); 7.31-7.26 (m, 1H); 4.0-3.9 (m, 1H); 3.79-3.65 (m, 2H); 3.65-3.53 (m, 2H), 2.90-2.62 (m, 5H); 1.81-1.70 (m, 1H); 1.66-1.45 (m, 2H); 1.29 (s, br, 15H); 0.92 (t,  $J = 6.81$ ).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 138.29, 128.97, 128.38, 127.34, 61.44, 61.21, 59.43, 58.75, 56.27, 35.98, 31.84, 29.53, 29.49, 29.39, 29.26, 29.06, 26.14, 22.63, 14.07. HRMS (TOF, ES+)  $\text{C}_{21}\text{H}_{37}\text{NOCl}$   $[\text{M}+\text{H}]^+$  calc. mass 354.2564, found 354.2563. Specific rotation  $[\alpha]_D^{23} = -8.8^\circ$  ( $c = 100$ , MeOH).



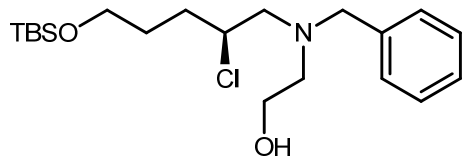
(S)-2-(benzyl(2-chloro-4-phenylbutyl)amino)ethanol (**5b**)

The product was prepared according to the chloro amino alcohol procedure on a 0.38 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (91 mg, 0.29 mmol, 76%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.40-7.20 (m, 10H); 3.99-3.90 (m, 1H); 3.76-3.53 (m, 4H); 2.96-2.63 (m, 7H); 2.18-2.07 (m, 1H); 1.99-1.88 (m, 1H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 140.85, 138.20, 128.97, 128.49, 128.46, 128.42, 127.38, 126.11, 61.14, 60.30, 59.34, 58.82, 56.28, 37.60, 32.30. HRMS (TOF, ES+) C<sub>19</sub>H<sub>25</sub>ClNO [M+H]<sup>+</sup> calc. mass 318.1625, found 318.1624. Specific rotation  $[\alpha]_D^{23} = -15.1^\circ$  (c = 100, MeOH).



(S,Z)-2-(benzyl(2-chlorodec-7-en-1-yl)amino)ethanol (**5c**)

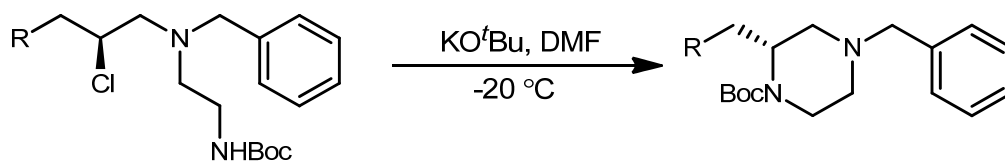
The product was prepared according to the chloro amino alcohol procedure on a 0.29 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (71 mg, 0.22 mmol, 76%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.39-7.30 (m, 4H); 7.30-7.24 (m, 1H); 5.43-5.26 (m, 2H); 3.98-3.88 (m, 1H); 3.78-3.63 (m, 2H); 3.63-3.50 (m, 2H); 2.87-2.61 (m, 5H); 2.09-1.97 (m, 4H); 1.80-1.69 (m, 1H); 1.64-1.45 (m, 2H); 1.43-1.22 (m, 4H); 0.96 (s, J = 7.53, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 138.24, 131.87, 128.96, 128.63, 128.39, 128.35, 61.33, 61.15, 59.39, 58.73, 56.24, 35.87, 29.14, 26.14, 25.76, 20.45, 14.30. HRMS (TOF, ES+) C<sub>19</sub>H<sub>31</sub>ClNO [M+H]<sup>+</sup> calc. mass 324.2094, found 324.2094. Specific rotation  $[\alpha]_D^{23} = -9.5^\circ$  (c = 100, MeOH).



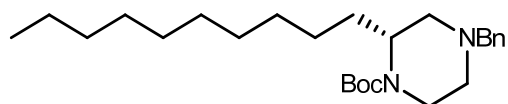
**(S)-2-(benzyl(5-((*tert*-butyldimethylsilyl)oxy)-2-chloropentyl)amino)ethanol (5d)**

The product was prepared according to the chloro amino alcohol procedure on a 0.37 mmol scale and purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (106 mg, 0.27 mmol, 74%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.36-7.23 (m, 5H); 4.03-3.93 (m, 1H); 3.78-3.49 (m, 6H); 2.83-2.69 (m, 4H); 2.68-2.59 (m, 1H); 1.95-1.83 (m, 1H); 1.79-1.67 (m, 1H); 1.66-1.51 (m, 2H); 0.89 (s, 9H); 0.04 (s, 6H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 138.24, 128.95, 128.38, 127.33, 62.30, 61.24, 61.20, 59.40, 58.77, 56.20, 32.45, 29.33, 25.88, 18.24, -5.38. HRMS (TOF, ES+) C<sub>20</sub>H<sub>37</sub>NO<sub>2</sub>ClSi [M+H]<sup>+</sup> calc. mass 386.2282, found 386.2282. Specific rotation  $[\alpha]_D^{23} = -5.7^\circ$  (*c* = 100, MeOH).

## General Procedure for Cyclization to Piperazines

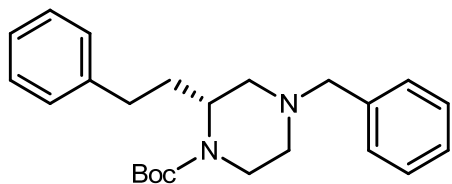


Potassium *tert*-butoxide (5 eq) was added to a solution of chloro-diamine (1 eq) in DMF (0.02 M) at -20 °C. This reaction was followed via TLC and was typically done within 2 hours. Upon consumption of starting material, diethyl ether followed by water was added to the reaction. It was extracted 3X with diethyl ether, dried with MgSO<sub>4</sub>, and concentrated before purification.



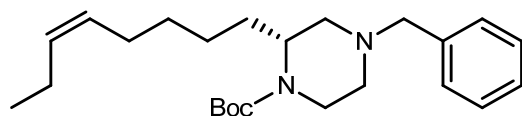
(*R*)-*tert*-butyl 4-benzyl-2-decylpiperazine-1-carboxylate (**8a**)

The product was prepared according to the cyclization to piperazines on a 0.12 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (33mg, 0.08 mmol, 66%), which was determined to have an ee of 89% by chiral SFC analysis (Lux Cellulose-4,  $t_R$  (major) = 4.49 min,  $t_R$  (minor) = 3.78 min, traces shown below). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.32-7.21 (m, 5H); 3.99 (s, br, 1H); 3.90-3.82 (m, 1H); 3.53 (d,  $J$  = 13.2, 1H); 3.37 (d,  $J$  = 13.3, 1H); 3.05 (t,  $J$  = 12.5, 1H); 2.75-2.65 (m, 2H); 2.06-2.00 (m, 2H); 1.78-1.73 (m, 1H); 1.66-1.61 (m, 1H); 1.45 (s, 9H); 1.30-1.15 (m, 16H); 0.88 (t,  $J$  = 7.5, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 154.81, 138.39, 128.68, 128.12, 126.93, 79.18, 62.80, 55.39, 53.29, 51.37, 39.24, 31.84, 29.74, 29.59, 29.56, 29.53, 29.50, 29.27, 28.38, 26.20, 22.52, 14.04. HRMS (TOF, ES+) C<sub>26</sub>H<sub>45</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> calc. mass 417.3481, found 417.3480. Specific rotation  $[\alpha]_D^{23} = -34.68^\circ$  ( $c = 100$ , MeOH).



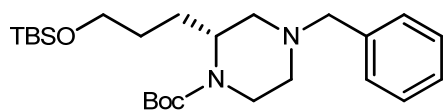
**(R)-tert-butyl 4-benzyl-2-phenethylpiperazine-1-carboxylate (8b)**

The product was prepared according to the cyclization to piperazines on a 0.165 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (42mg, 0.11 mmol, 67%), which was determined to have an ee of 95% by chiral SFC analysis (Chiralpak IA,  $t_R$  (major) = 4.77 min,  $t_R$  (minor) = 4.29 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.40-7.26 (m, 7H); 7.25-7.17 (m, 3H); 4.14 (s, br, 1H); 3.96 (s, br, 1H); 3.60 (d,  $J = 13.4$ , 1H); 3.40 (d,  $J = 13.4$ , 1H); 3.15 (t,  $J = 12.8$ , 1H); 2.86-2.73 (m, 2H); 2.62-2.45 (m, 2H); 2.20-1.99 (m, 4H); 1.50 (s, 9H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 154.81, 142.11, 138.37, 128.78, 128.39 (set of two coincident signals), 128.21, 127.05, 125.70, 79.41, 62.84, 55.10, 53.39, 51.35, 39.45, 32.65, 31.68, 28.40. HRMS (TOF, ES+)  $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  calc. mass 381.2542, found 381.2545. Specific rotation  $[\alpha]_D^{23} = -41.0^\circ$  ( $c = 100$ , MeOH).



**(R,Z)-tert-butyl 4-benzyl-2-(oct-5-en-1-yl)piperazine-1-carboxylate (8c)**

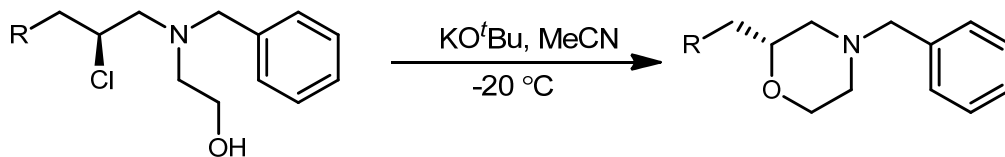
The product was prepared according to the cyclization to piperazines on a 0.15 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (53mg, 0.137 mmol, 91%), which was determined to have an ee of 95% by chiral SFC analysis (Chiralpak IC,  $t_R$  (major) = 4.62 min,  $t_R$  (minor) = 4.10 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.37-7.23 (m, 5H); 5.42-5.27 (m, 2H); 4.03 (s, br, 1H); 3.89 (d,  $J = 11.03$ , 1H); 3.56 (d,  $J = 13.42$ , 1H); 3.40 (d,  $J = 13.42$ , 1H); 3.08 (t,  $J = 10.90$ , 1H); 2.77 (d,  $J = 10.9$ , 1H); 2.68 (d,  $J = 11.32$ , 1H); 2.11-1.98 (m, 6H); 1.86-1.74 (m, 1H); 1.72-1.60 (m, 1H); 1.47 (s, 9H); 1.43-1.31 (m, 2H); 1.26-1.16 (m, 2H); 0.97 (t,  $J = 7.53$ , 3H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 154.79, 138.38, 131.57, 129.00, 128.69, 128.13, 126.94, 79.23, 62.79, 60.31, 55.41, 53.28, 51.31, 39.07, 29.61, 28.38 (one set of coincident signals), 27.01, 25.82, 20.44, 14.31. HRMS (TOF, ES+)  $\text{C}_{24}\text{H}_{39}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  calc. mass 387.3012, found 387.3009. Specific rotation  $[\alpha]_D^{23} = -45.4^\circ$  ( $c = 100$ , MeOH).



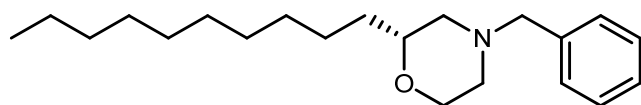
(*R*)-*tert*-butyl 4-benzyl-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)piperazine-1-carboxylate (**8d**)

The product was prepared according to the cyclization to piperazines on a 0.19 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (68.5mg, 0.15 mmol, 78%), which was determined to have an ee of 75% by chiral SFC analysis (Lux Cellulose-2 (OZ),  $t_R$  (major) = 6.54 min,  $t_R$  (minor) = 5.73 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.34-7.20 (m, 5H); 4.02 (s, br, 1H); 3.93-3.81 (m, 1H); 3.61 (t,  $J$  = 6.14, 2H); 3.52 (d,  $J$  = 13.09, 1H); 3.38 (d,  $J$  = 13.59, 1H); 3.05 (t,  $J$  = 11.58, 1H); 2.73 (d,  $J$  = 10.32, 1H); 2.66 (d,  $J$  = 11.27, 1H); 2.11-1.96 (m, 2H); 1.94-1.82 (m, 1H); 1.71-1.59 (m, 1H); 1.50-1.35 (m, 11H); 0.89 (s, 9H); 0.04 (s, 6H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 154.78, 138.41, 129.31, 128.65, 126.94, 79.28, 62.99, 62.76, 55.68, 53.22, 51.24, 38.91, 29.53, 28.37, 26.20, 25.89, 18.25, -5.32. HRMS (TOF, ES+)  $\text{C}_{25}\text{H}_{45}\text{N}_2\text{O}_3\text{Si}$   $[\text{M}+\text{H}]^+$  calc. mass 449.3199, found 449.3198. Specific rotation  $[\alpha]_D^{23} = -29.9^\circ$  ( $c = 100$ , MeOH).

### General Procedure for Chiral Morpholine Synthesis

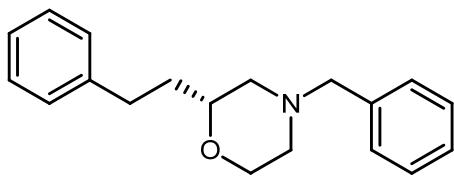


Potassium *tert*-butoxide (5 eq) was added to a solution of chloro-diamine (1 eq) in MeCN (0.02 M) at -20 °C. This reaction was followed via TLC, and upon consumption of starting material, diethyl ether followed by water was added to the reaction. It was extracted 3X with diethyl ether, dried with MgSO<sub>4</sub>, and concentrated before purification.



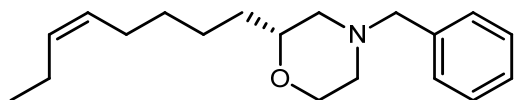
(*R*)-4-benzyl-2-decylmorpholine (**7a**)

The product was prepared according to the cyclization to morpholines procedure on a 0.19 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (39 mg, 0.12 mmol, 65%), which was determined to have an ee of 92% by chiral SFC analysis (Chiralpak IA,  $t_R$  (major) = 2.76 min,  $t_R$  (minor) = 2.12 min, traces shown below). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 7.32-7.24 (m, 5H); 3.84 (dq,  $J_1$  = 11.5 Hz,  $J_2$  = 1.8, 1H); 3.65 (td,  $J_1$  = 11.5,  $J_2$  = 2.5, 1H); 3.52-3.45 (m, 3H); 2.74-2.71, (m, 1H); 2.65 (dq,  $J_1$  = 11.4,  $J_2$  = 1.8, 1H); 2.14 (td,  $J_1$  = 11.4,  $J_2$  = 3.3, 1H); 1.87-1.82 (m, 1H); 1.5-1.25 (m, 18H); 0.87 (t,  $J$  = 7.1, 3H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>)  $\delta$  (ppm): 137.76, 129.11, 128.17, 127.03, 75.76, 66.73, 63.29, 58.80, 53.12, 33.67, 31.83, 29.60, 29.52, 29.51, 29.45, 29.24, 25.33, 22.60, 14.04. HRMS (TOF, ES+) C<sub>21</sub>H<sub>36</sub>NO [M+H]<sup>+</sup> calc. mass 318.2797, found 318.2795. Specific rotation  $[\alpha]_D^{23}$  = +13.04° ( $c$  = 100, MeOH).



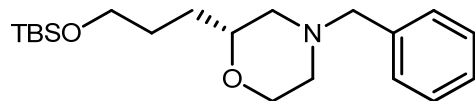
(*R*)-4-benzyl-2-phenethylmorpholine (**7b**)

The product was prepared according to the cyclization to morpholines procedure on a 0.15 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (31 mg, 0.11 mmol, 74%), which was determined to have an ee of 95% by chiral SFC analysis (Chiralpak IB,  $t_R$  (major) = 3.36 min,  $t_R$  (minor) = 2.57 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.39-7.25 (m, 7H); 7.24-7.18 (m, 3H); 3.92 (d,  $J$  = 11.12, 1H); 3.70 (td,  $J_1$  = 2.38,  $J_2$  = 11.12, 1H); 3.58-3.50 (m, 3H); 2.86-2.63 (m, 4H); 2.21 (td,  $J_1$  = 3.18,  $J_2$  = 11.12, 1H); 1.92 (t,  $J$  = 10.73, 1H); 1.89-1.78 (m, 1H); 1.74-1.63 (m, 1H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 141.97, 137.72, 129.12, 128.40, 128.27, 128.20, 127.07, 125.70, 74.82, 66.70, 63.27, 58.62, 53.16, 35.30, 31.54. HRMS (TOF, ES+)  $\text{C}_{19}\text{H}_{24}\text{NO}$   $[\text{M}+\text{H}]^+$  calc. mass 282.1858, found 282.1857. Specific rotation  $[\alpha]_D^{23}$  = +25.2° ( $c$  = 100, MeOH).



(*R,Z*)-4-benzyl-2-(oct-5-en-1-yl)morpholine (**7c**)

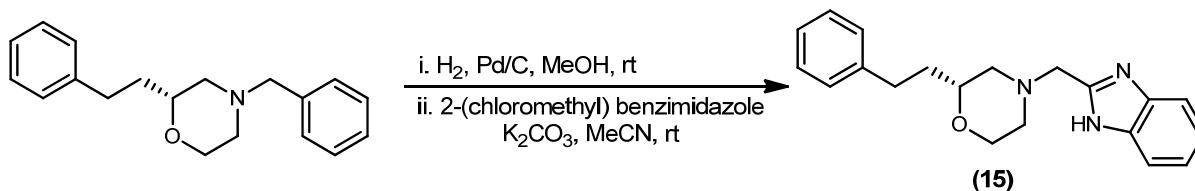
The product was prepared according to the cyclization to morpholines procedure on a 0.13 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (26 mg, 0.09 mmol, 68%), which was determined to have an ee of 98% by chiral SFC analysis (Chiralpak IA,  $t_R$  (major) = 2.68 min,  $t_R$  (minor) = 1.79 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.38-7.25 (m, 5H); 5.43-5.28 (m, 2H); 3.89-3.83 (m, 1H); 3.67 (td,  $J_1$  = 11.34,  $J_2$  = 2.39, 1H); 3.56-3.46 (m, 3H); 2.75 (d,  $J$  = 11.72, 1H); 2.67 (d,  $J$  = 11.73, 1H); 2.16 (td,  $J_1$  = 11.62,  $J_2$  = 3.66, 1H); 2.09-1.98 (m, 4H); 1.87 (t,  $J$  = 10.39, 1H); 1.56-1.21 (m, 7H); 0.97 (t,  $J$  = 7.95, 1H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 137.76, 131.62, 129.10, 128.95, 128.17, 127.03, 75.69, 66.74, 63.28, 58.77, 53.12, 33.56, 29.73, 26.90, 24.99, 20.42, 14.29. HRMS (TOF, ES+)  $\text{C}_{19}\text{H}_{30}\text{NO}$   $[\text{M}+\text{H}]^+$  calc. mass 288.2327, found 288.2328. Specific rotation  $[\alpha]_D^{23}$  = +10.8° ( $c$  = 100, MeOH).



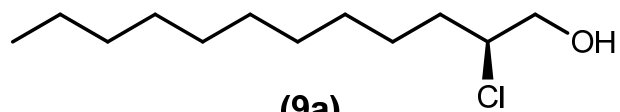
**(R)-4-benzyl-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)morpholine (7d)**

The product was prepared according to the cyclization to morpholines procedure on a 0.13 mmol scale and was purified by silica chromatography (9:1 Hexanes/EtOAc) to afford the product as a clear oil (26 mg, 0.09 mmol, 68%), which was determined to have an ee of 80% by chiral SFC analysis (Chiralpak IA,  $t_R$  (major) = 3.08 min,  $t_R$  (minor) = 2.66 min, traces shown below).  $^1\text{H}$  NMR (400.1 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 7.35-7.23 (m, 5H); 3.84 (dd,  $J_1 = 1.69$ ,  $J_2 = 11.33$ , 1H); 3.69-3.55 (m, 3H); 3.54-3.44 (m, 3H); 2.74 (d,  $J = 10.79$ , 1H); 2.65 (d,  $J = 11.26$ , 1H); 2.15 (td,  $J_1 = 3.13$ ,  $J_2 = 11.21$ , 1H); 1.86 (t,  $J = 10.69$ , 1H); 1.70-1.58 (m, 1H); 1.58-1.40 (m, 3H); 0.89 (s, 9H); 0.039 (s, 6H).  $^{13}\text{C}$  NMR (100.6 MHz,  $\text{CDCl}_3$ )  $\delta$  (ppm): 137.76, 129.08, 128.18, 127.03, 75.56, 66.71, 63.27, 63.01, 58.75, 53.10, 29.97, 28.64, 25.91, 18.27, -5.36. HRMS (TOF, ES+)  $\text{C}_{20}\text{H}_{36}\text{NO}_2\text{Si}$   $[\text{M}+\text{H}]^+$  calc. mass 350.2515, found 350.2514. Specific rotation  $[\alpha]_D^{23} = +11.1^\circ$  ( $c = 100$ , MeOH).

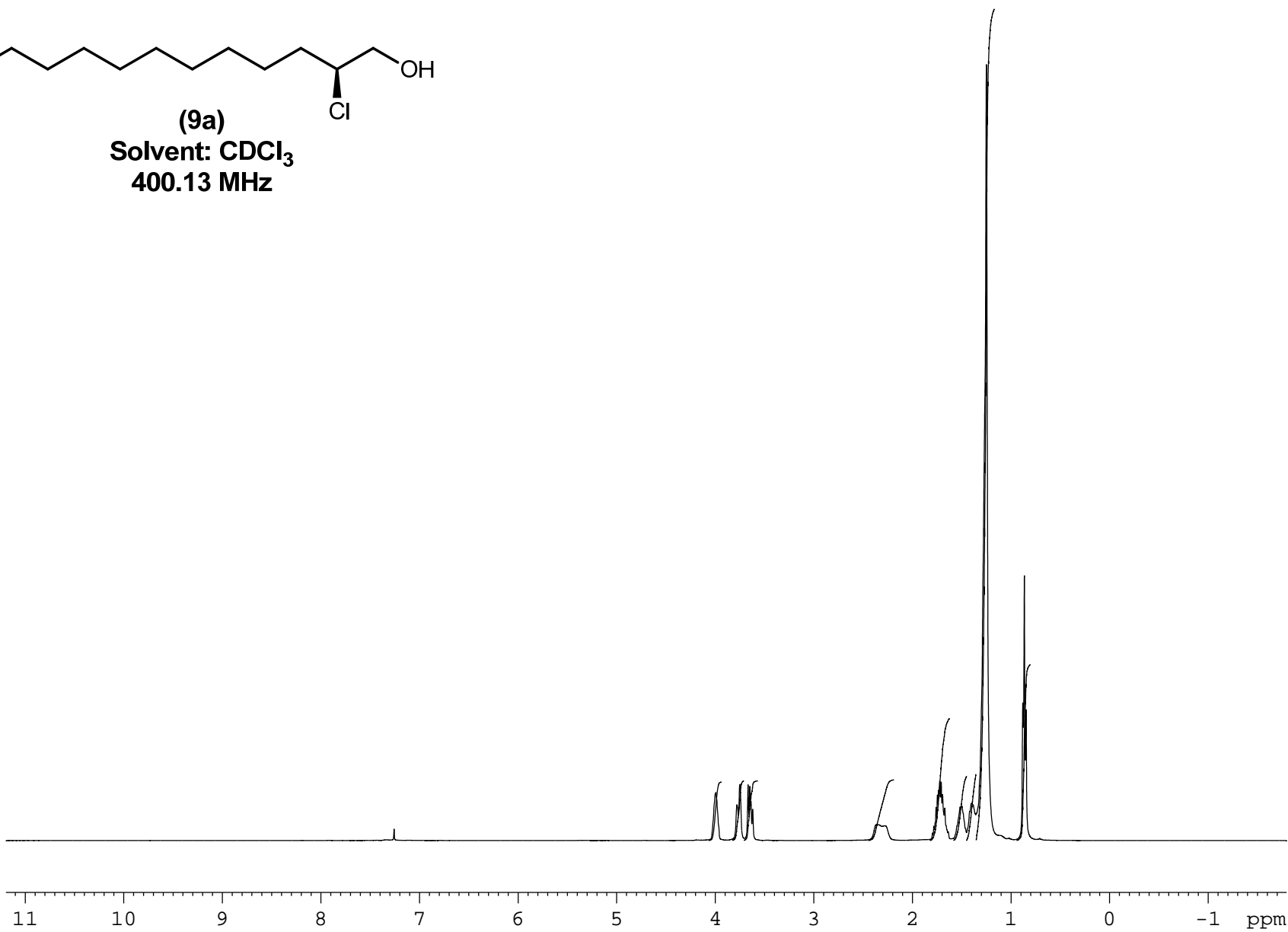
## Procedure for Debenzylation and Formation of Dopamine Antagonist



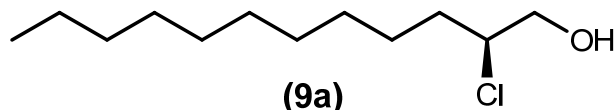
To a solution of benzyl protected morpholine (435 mg, 1.54 mmol) in methanol (31 mL, 0.05 M) under an argon atmosphere was added 0.2 eq of 10% Pd/C. The flask was then purged with H<sub>2</sub> and was left to react under a hydrogen atmosphere and followed via TLC and LC-MS until consumption of the starting material was determined. Upon consumption of the starting material, the reaction was filtered through celite, concentrated, and resuspended in MeCN (7.7 mL, 0.2 M). To this solution was added potassium carbonate (1,064 mg, 7.7 mmol) and 2-(chloromethyl) benzimidazole (256.6 mg, 1.54 mmol) and the reaction was left to stir overnight. The reaction was then quenched with water and was extracted 3X with ethyl acetate. The organic layer was dried with magnesium sulfate, filtered, and was concentrated. It was purified using flash column chromatography (5% methanol in dichloromethane) to afford the product as a waxy solid (376 mg, 1.17 mmol, 76%). <sup>1</sup>H NMR (400.1 MHz, CDCl<sub>3</sub>) δ (ppm): 7.62 (s, br, 2H); 7.31-7.23 (m, 4H); 7.21-7.12 (m, 3H); 3.90-3.77 (m, 3H); 3.57 (td, *J*<sub>1</sub> = 11.63, *J*<sub>2</sub> = 2.10, 1H); 3.42-3.44 (m, 1H); 2.78-2.56 (m, 4H); 2.34 (td, *J*<sub>1</sub> = 11.65, *J*<sub>2</sub> = 3.43, 1H); 2.04 (t, *J* = 10.28, 1H); 1.84-1.73 (m, 1H); 1.63-1.53 (m, 1H). <sup>13</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm): 151.82, 141.73, 138.69, 128.43, 128.35, 125.82, 122.45, 114.94, 74.68, 66.50, 58.69, 56.60, 53.35, 35.04, 31.36. HRMS (TOF, ES+) C<sub>20</sub>H<sub>24</sub>N<sub>3</sub>O [M+H]<sup>+</sup> calc. mass 322.1919, found 322.1917. Specific rotation [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +38.3° (*c* = 100, MeOH).



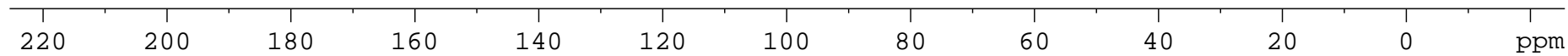
(9a)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz

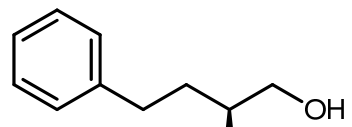


0.979  
1.002  
1.000  
1.016  
2.042  
1.082  
1.122  
13.943  
2.953

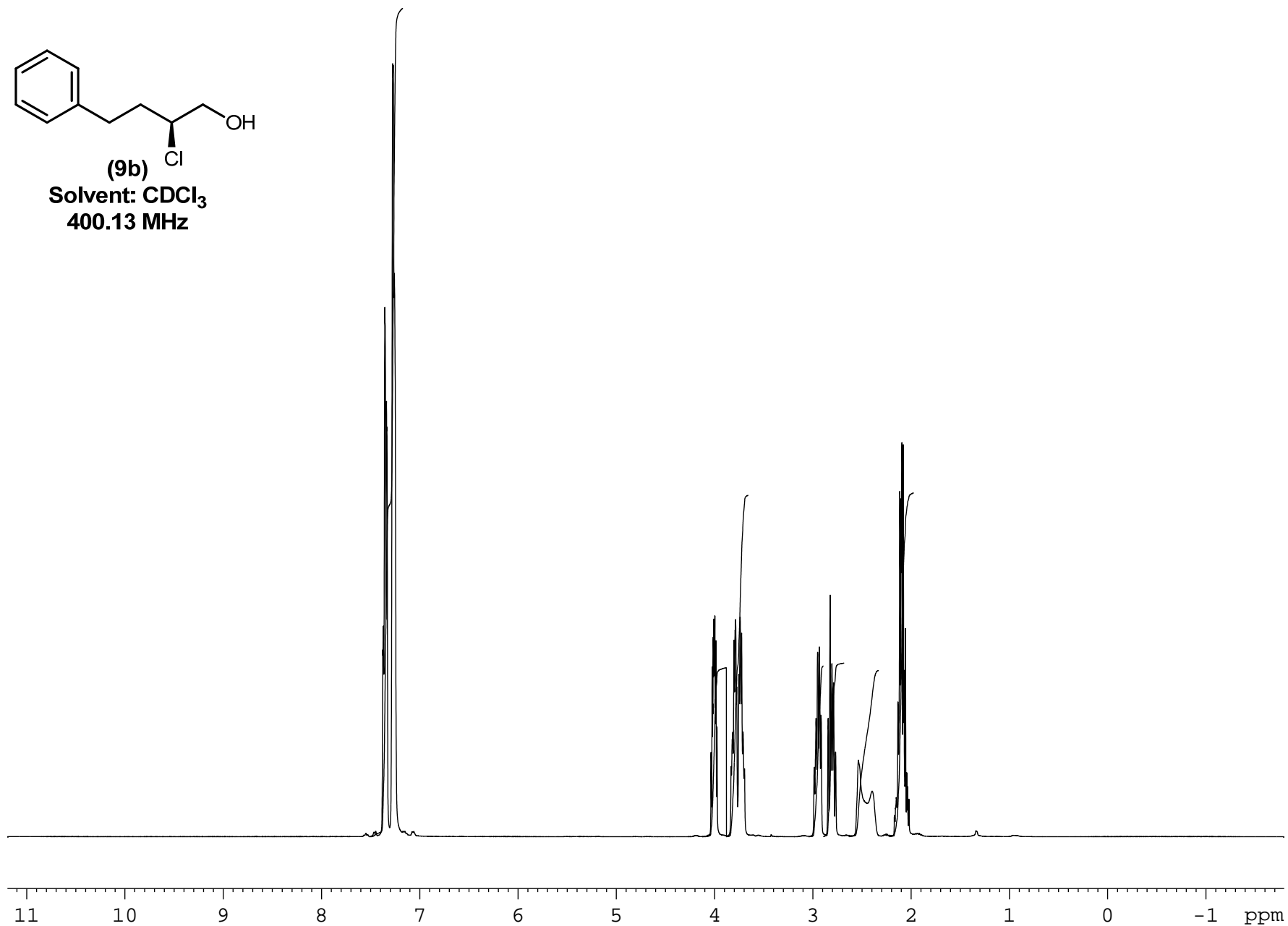


(9a)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





(9b)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz

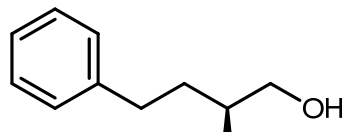


4.898

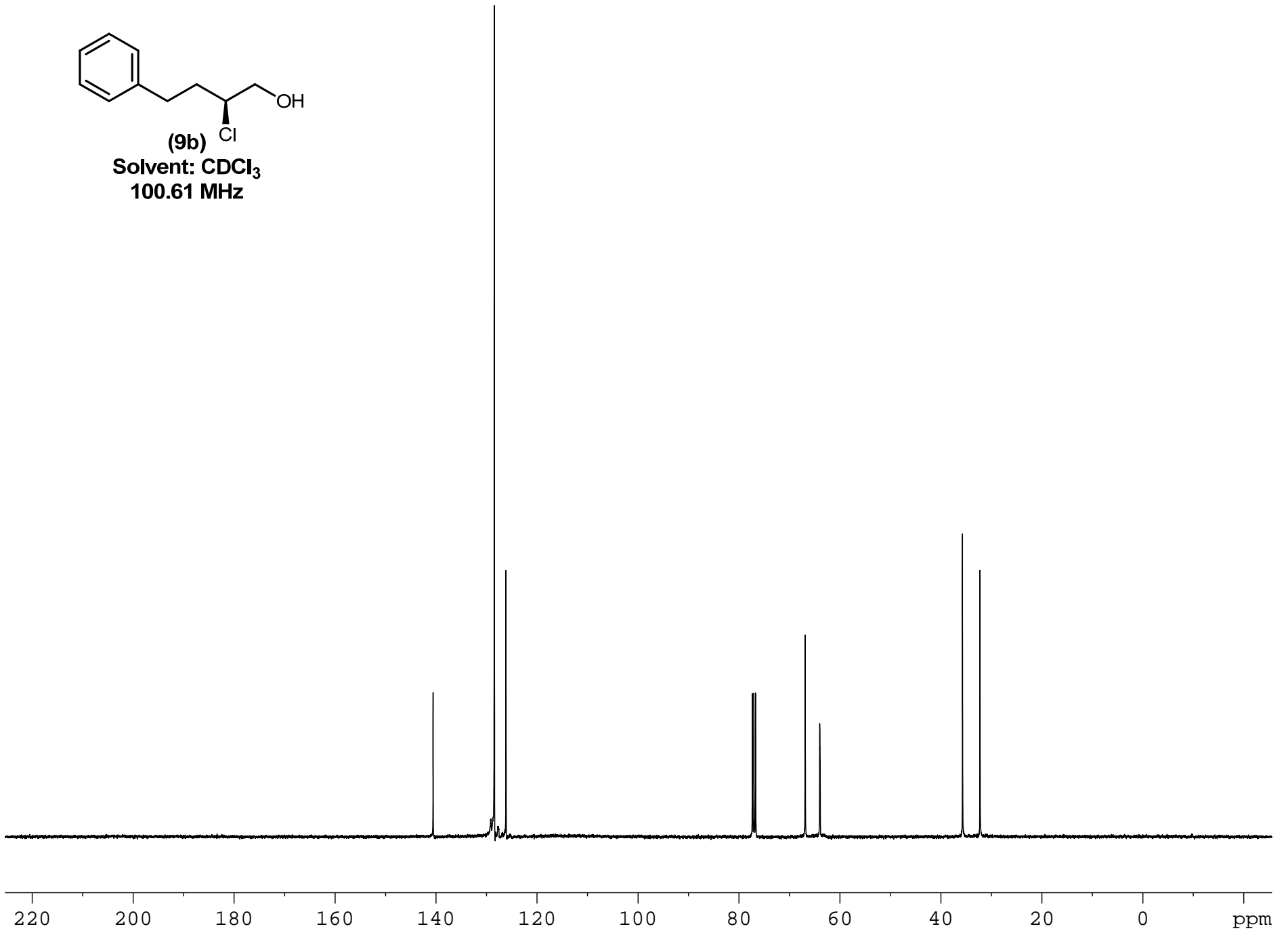
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2.019

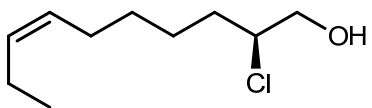
1.009  
1.027

0.983  
2.033

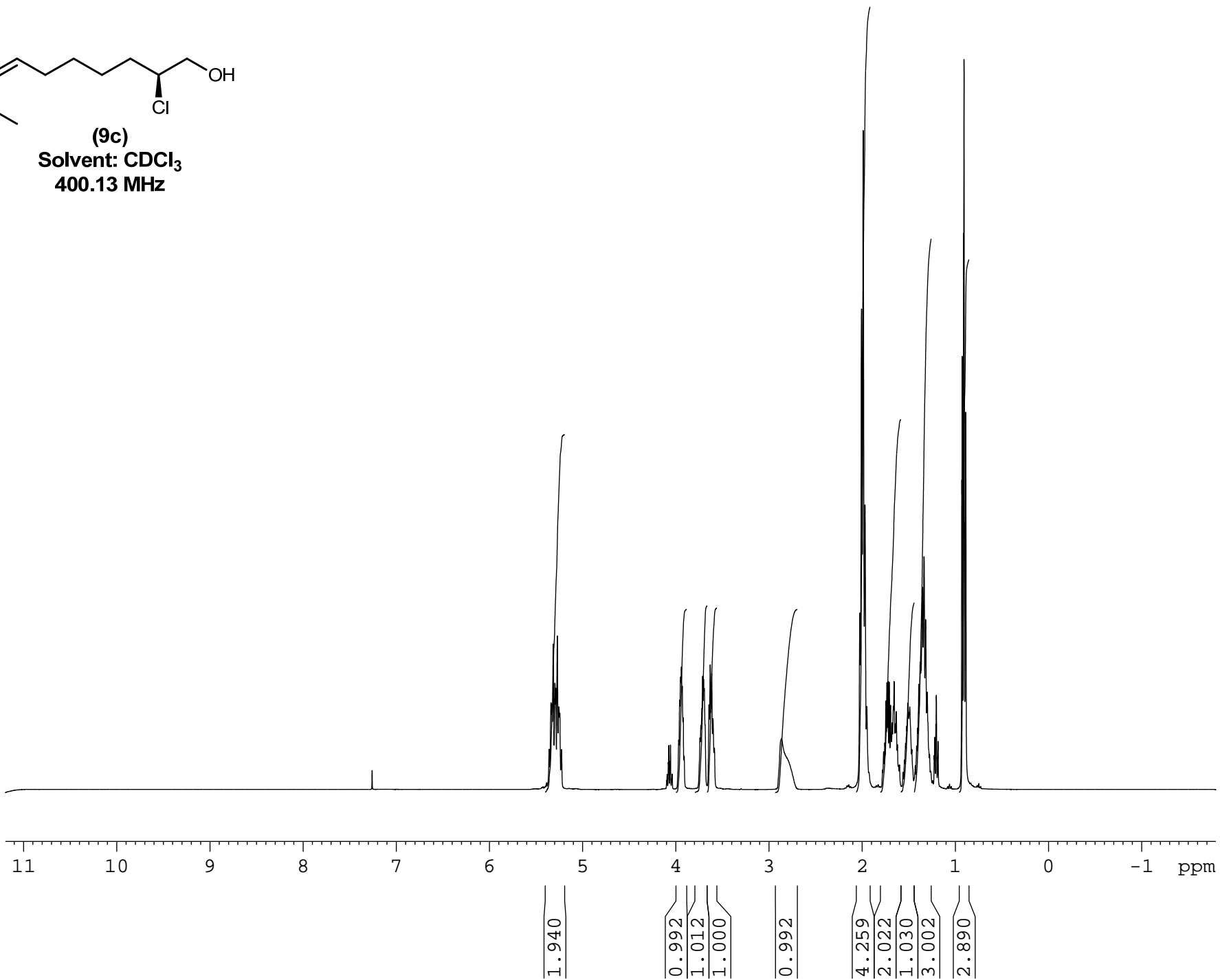


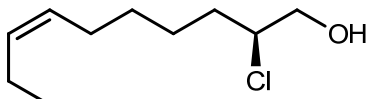
(9b)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz



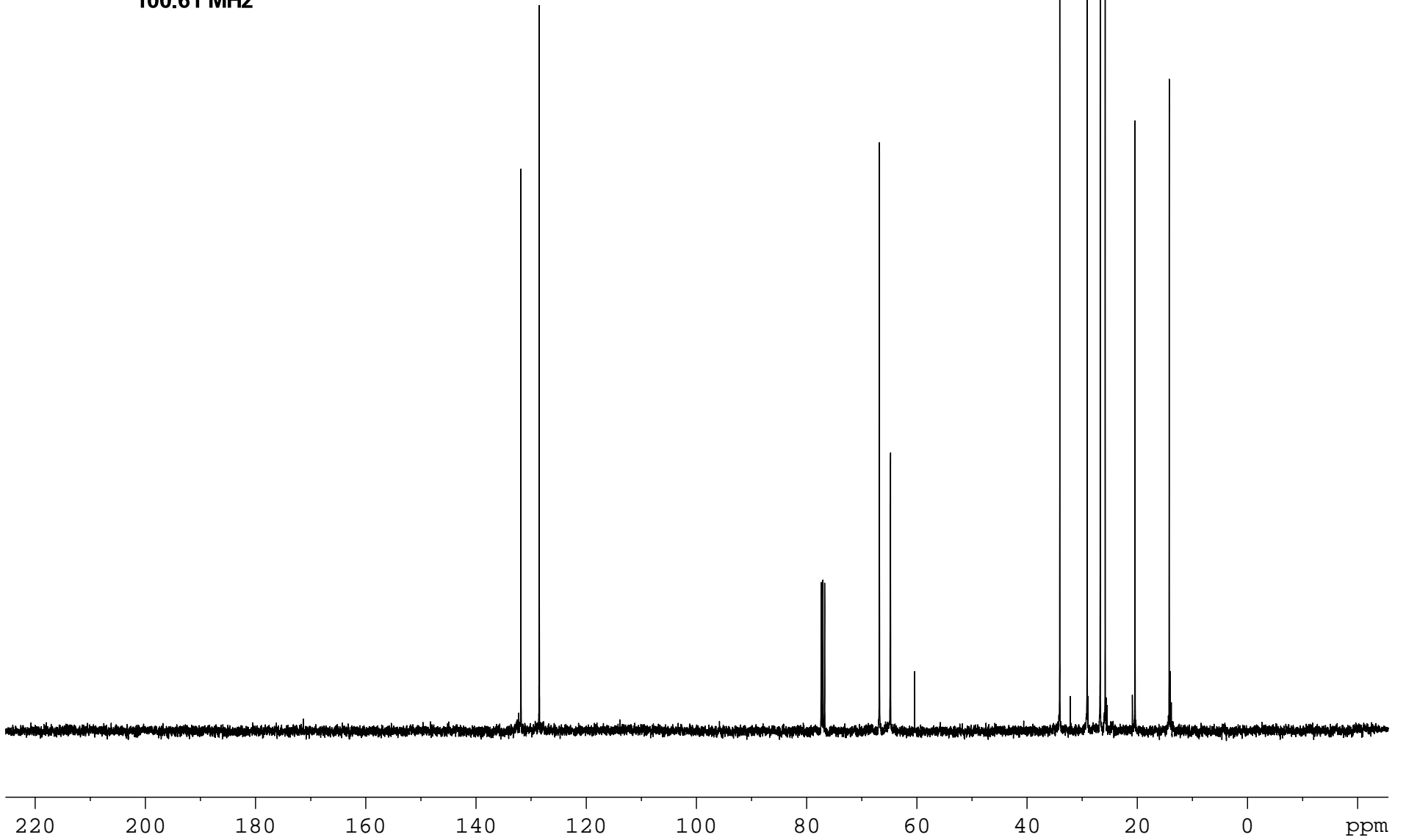


(9c)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz



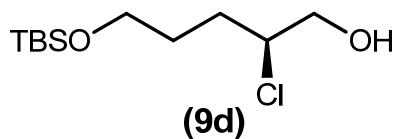


(9c)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz









## Elemental Composition Report

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

13 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 10-500 H: 10-1000 O: 1-200 Si: 1-1 Cl: 1-1

MCO-III-43

S/N: UH193

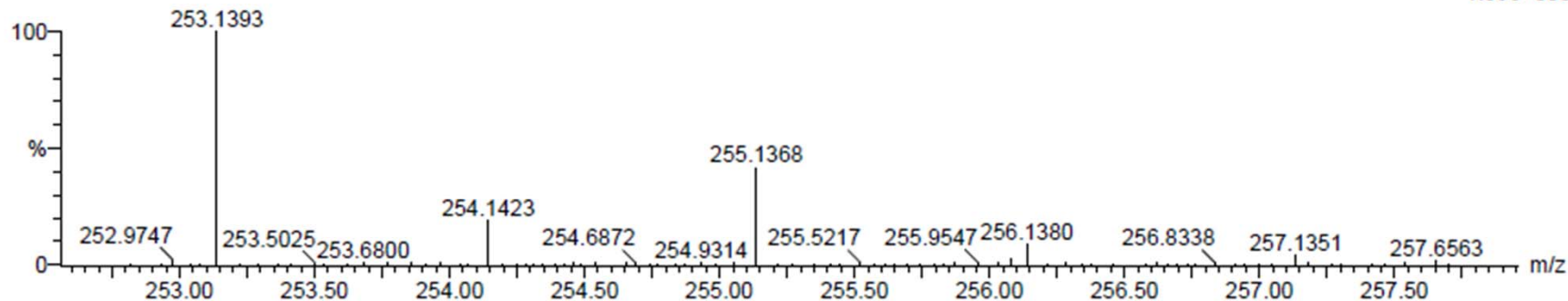
27-Oct-2011

13:27:08

MCO-III-43\_102711\_001 80 (1.491) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

TOF MS ES+

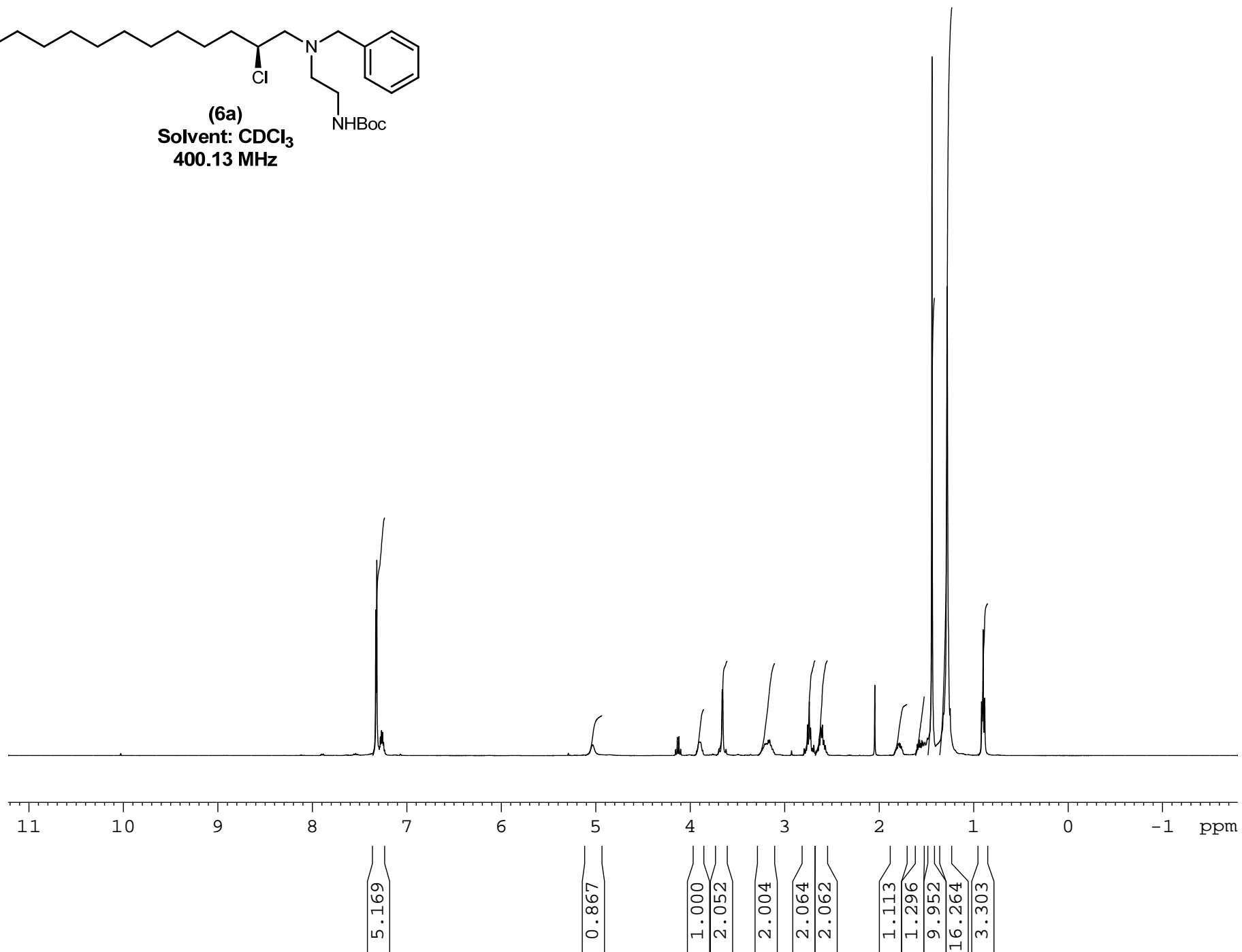
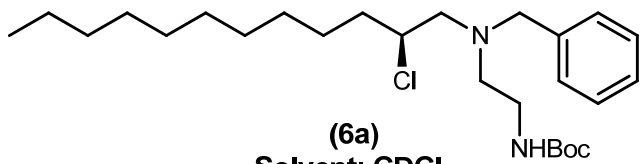
1.39e+003

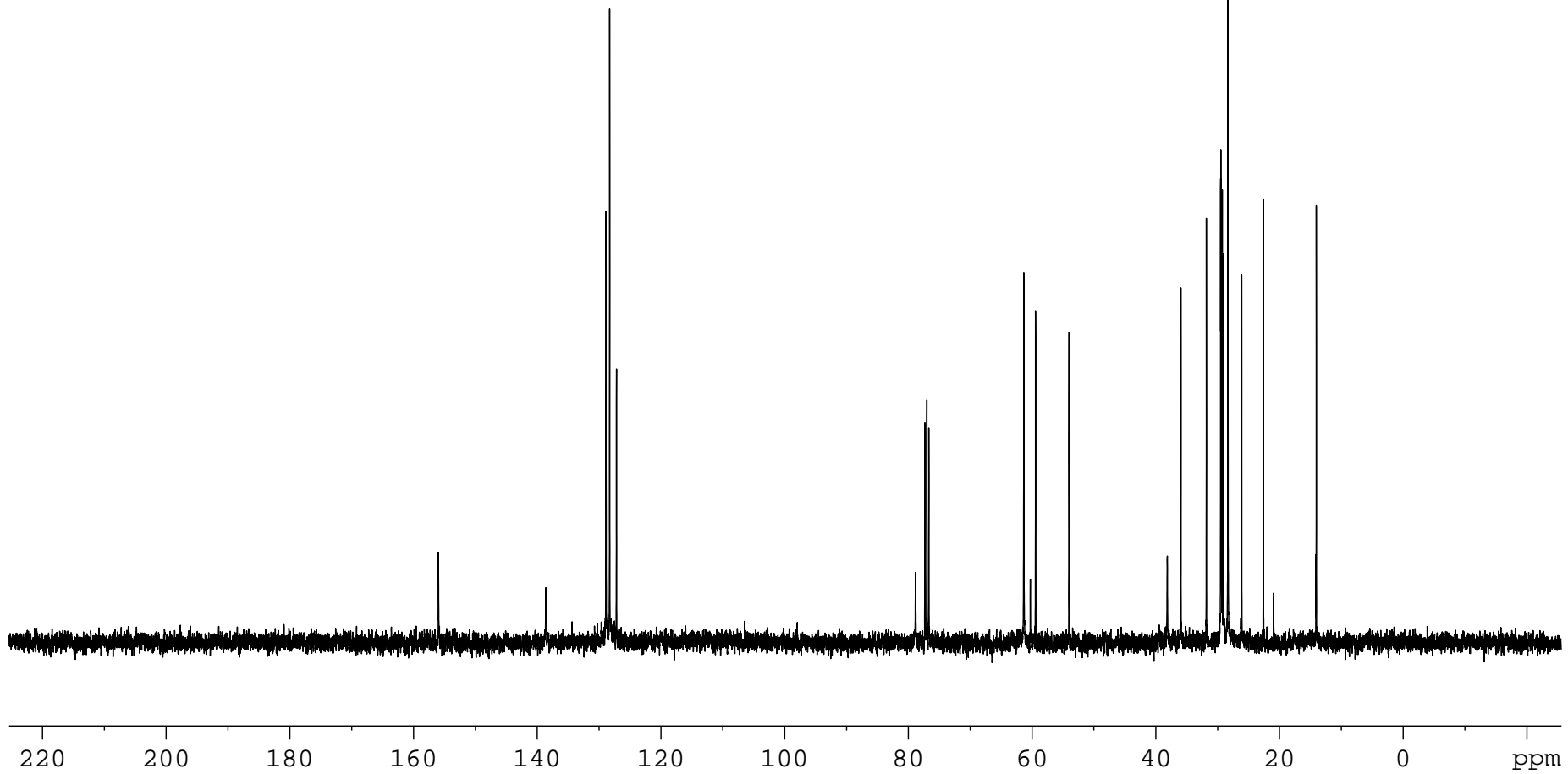
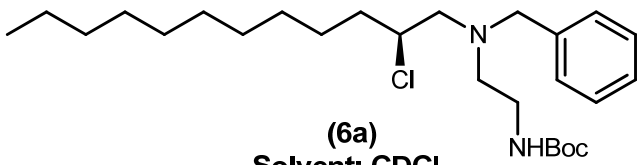


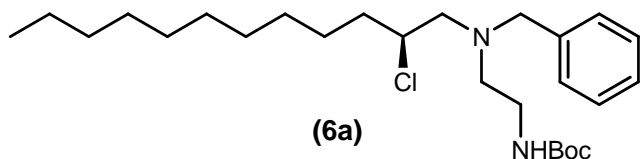
Minimum: -0.5

Maximum: 5.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
253.1393	253.1391	0.2	0.8	-0.5	0.3	C11 H26 O2 Si Cl







## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

394 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 25-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-30

S/N: UH193

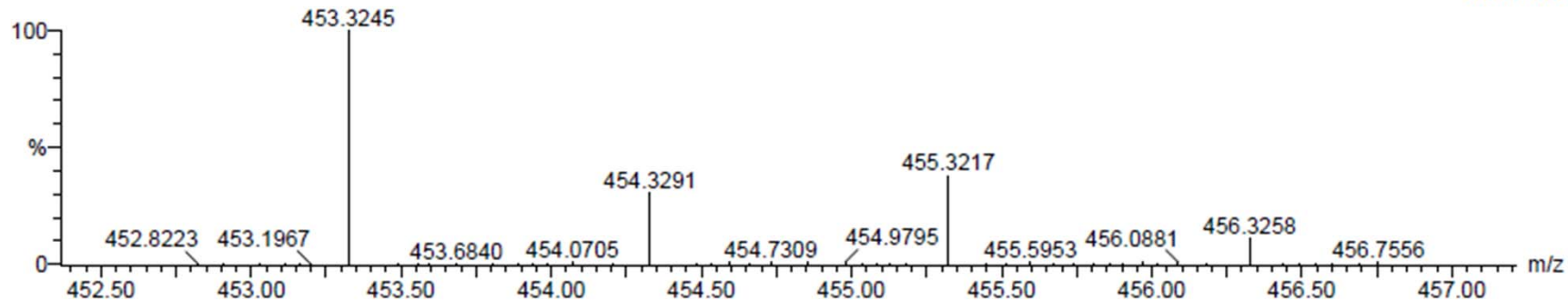
MCO-III-30\_102011\_001 50 (0.935) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (50:60)

20-Oct-2011

15:06:46

TOF MS ES+

6.52e+003



Minimum:

Maximum:

-0.5

5.0

5.0

25.0

Mass

Calc. Mass

mDa

PPM

DBE

i-FIT

Formula

453.3245

453.3248

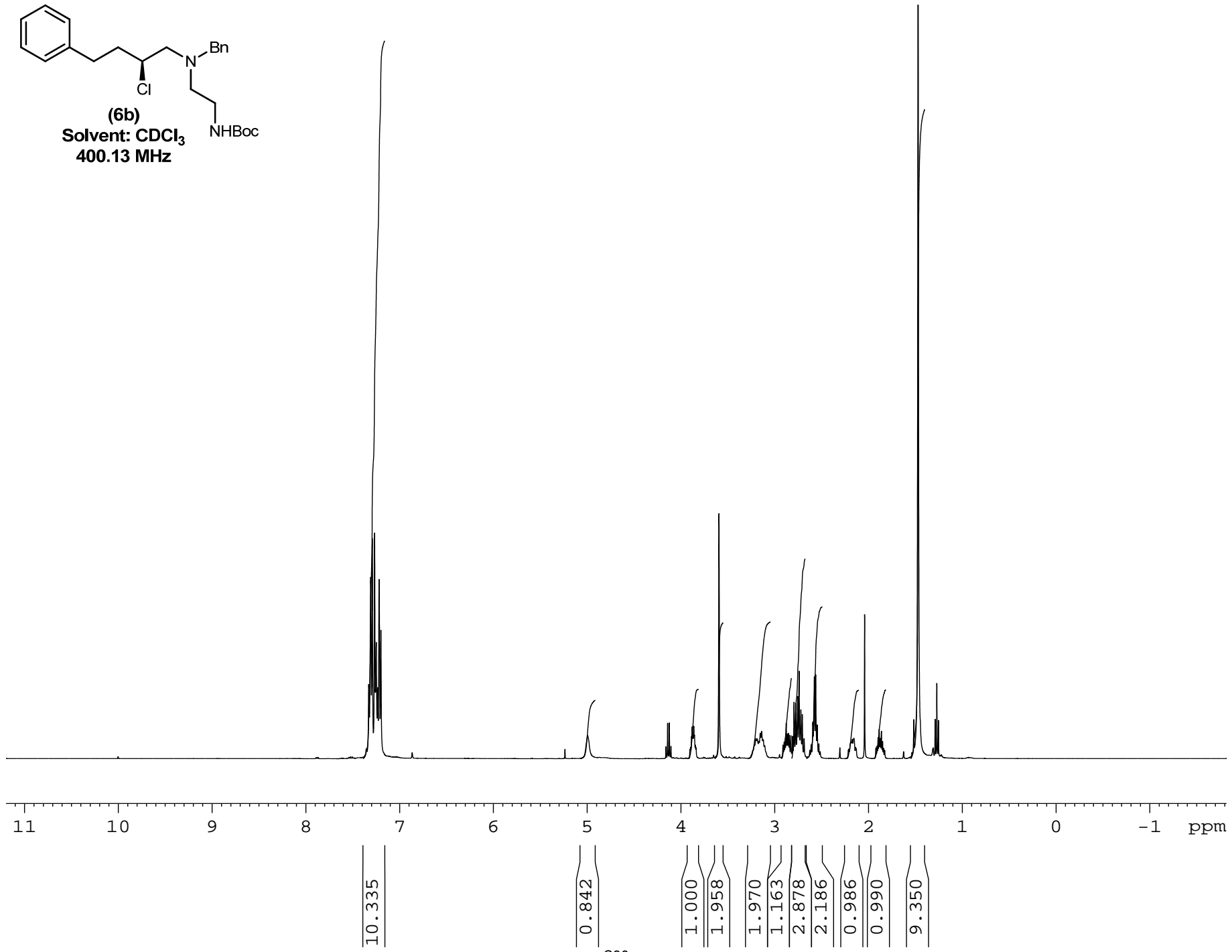
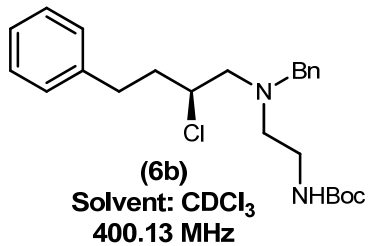
-0.3

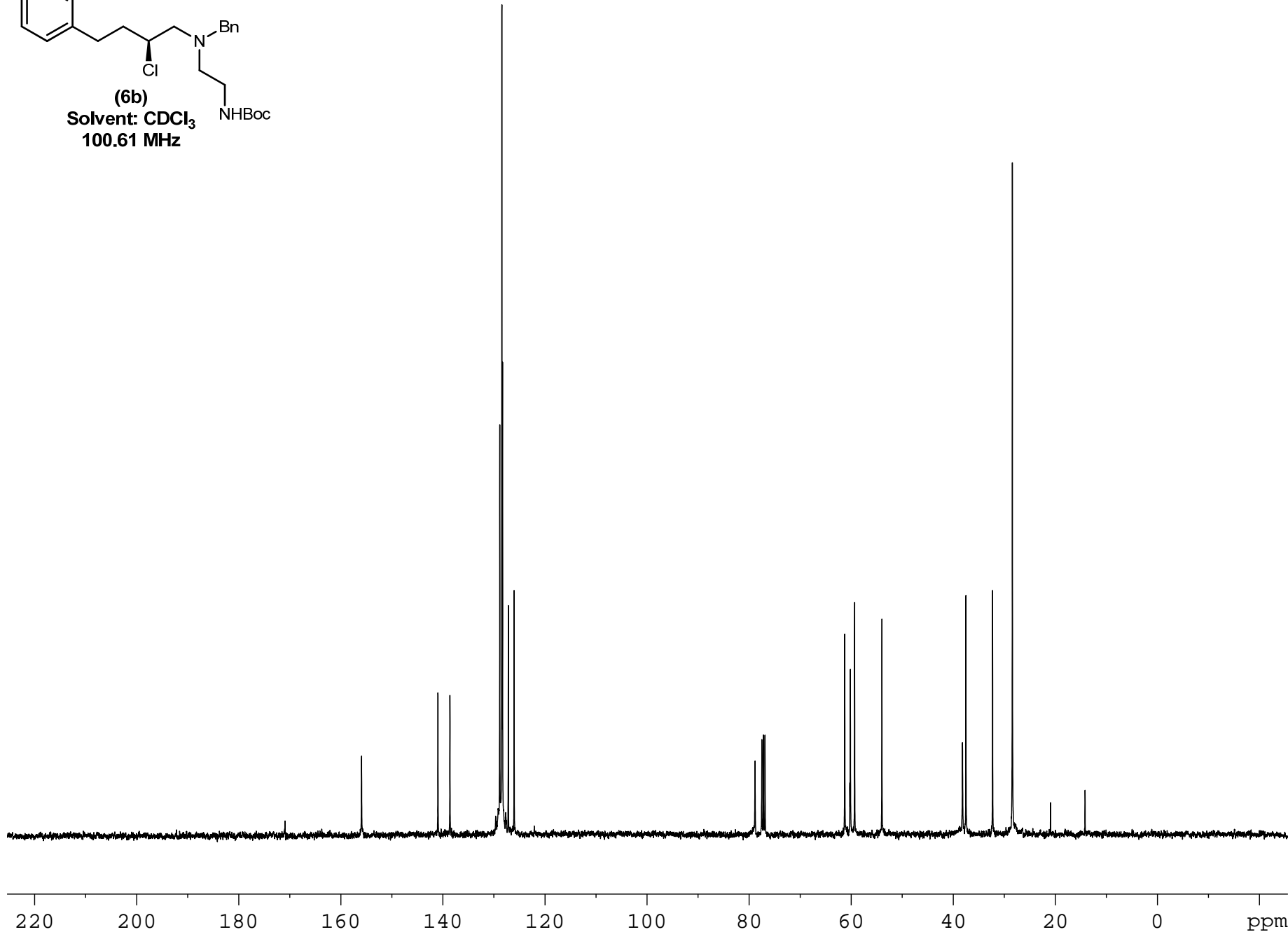
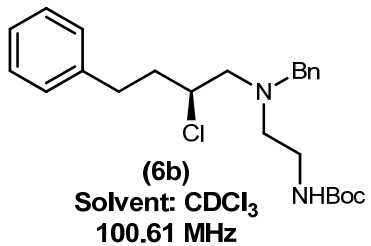
-0.7

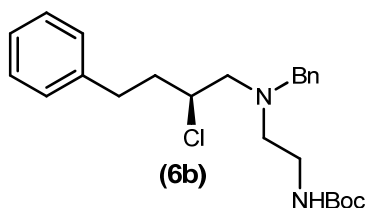
4.5

0.1

C26 H46 N2 O2 Cl







## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

360 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 20-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-75

S/N: UH193

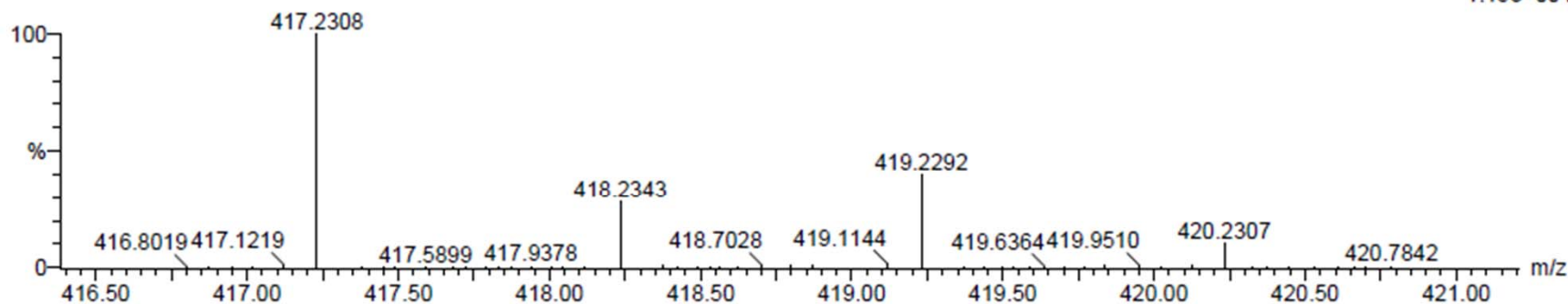
21-Nov-2011

15:16:08

MCO-III-75\_112111\_001 97 (1.832) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

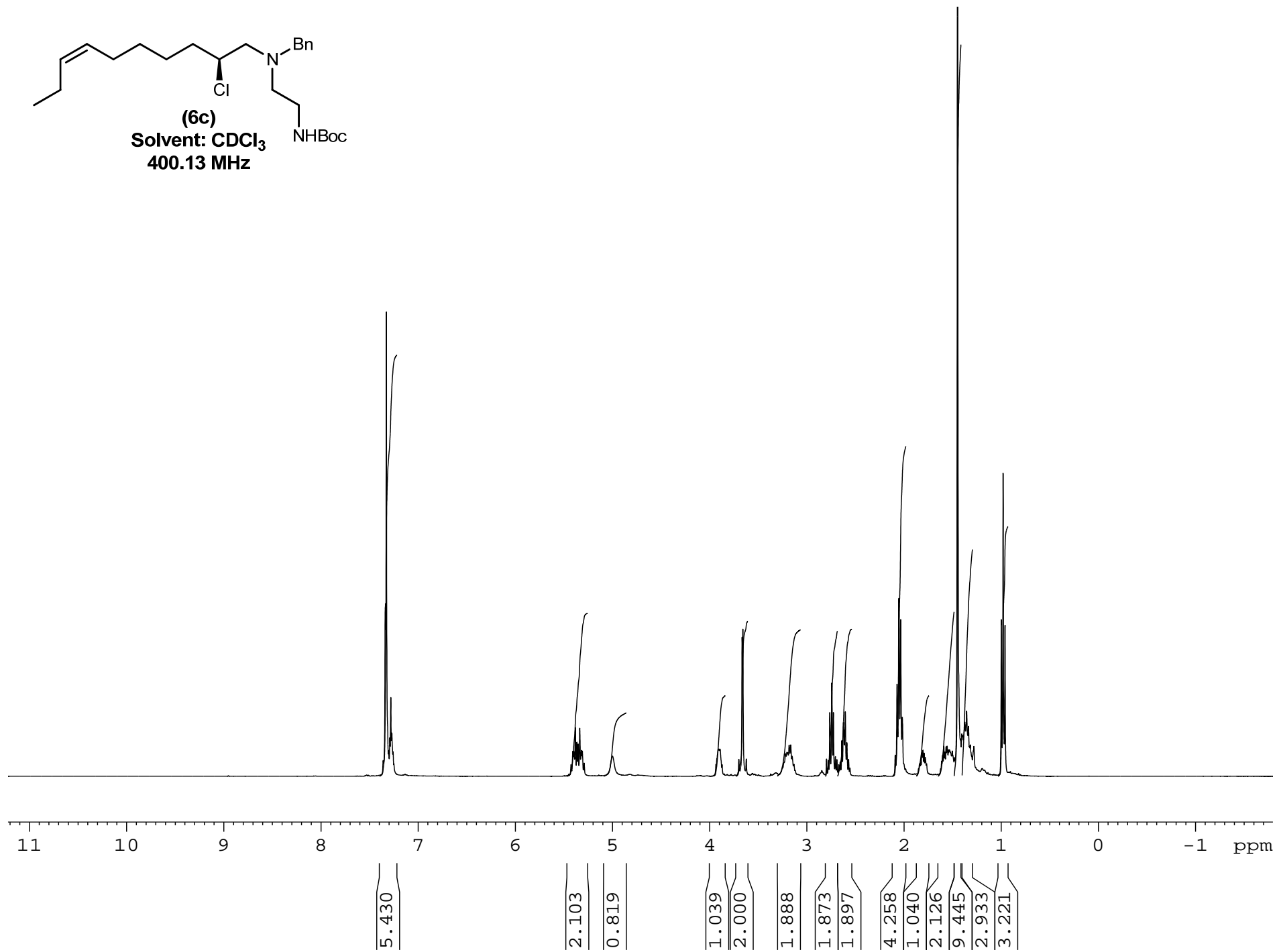
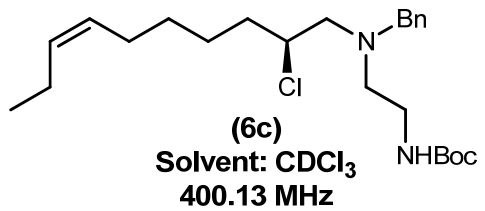
TOF MS ES+

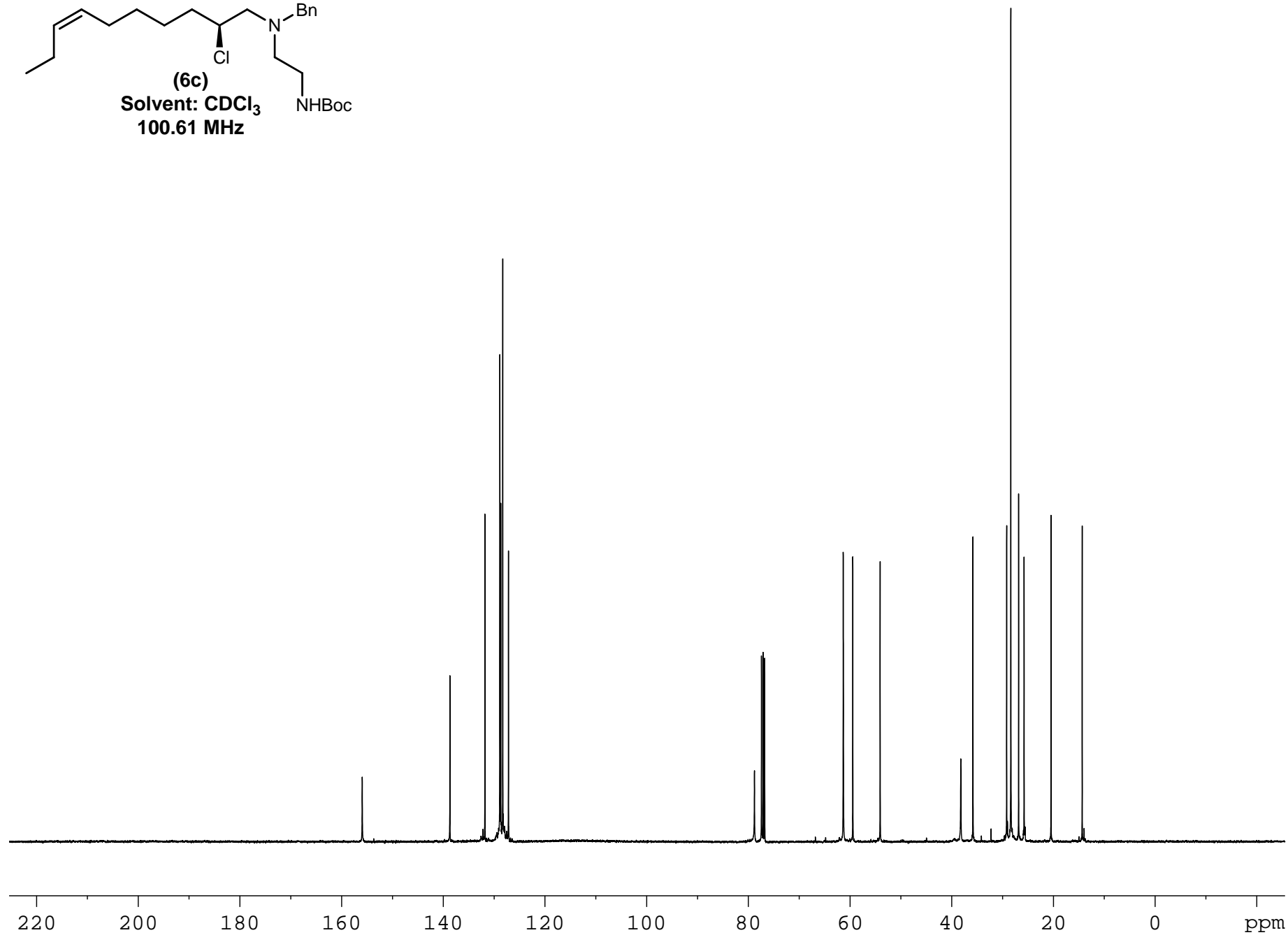
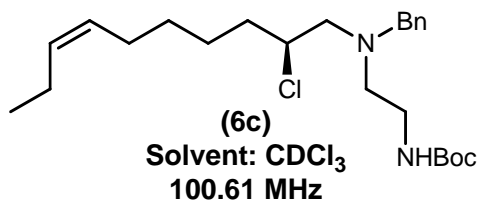
1.15e+004

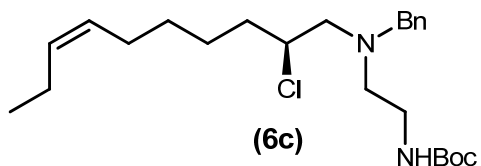


Minimum: -0.5  
Maximum: 5.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
417.2308	417.2309	-0.1	-0.2	8.5	0.1	C24 H34 N2 O2 Cl







## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

372 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 20-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-41

S/N: UH193

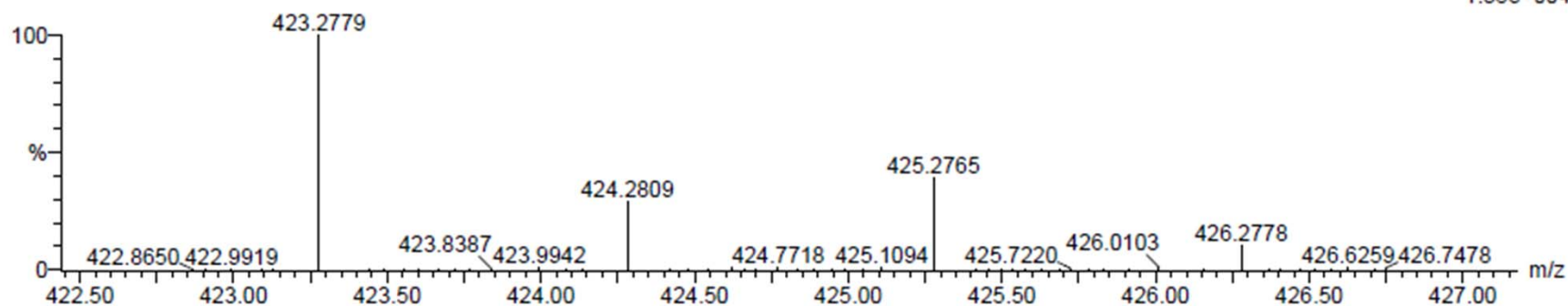
MCO-III-41\_102711\_001 88 (1.640) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

27-Oct-2011

12:46:37

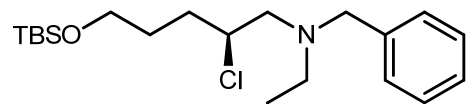
TOF MS ES+

1.38e+004



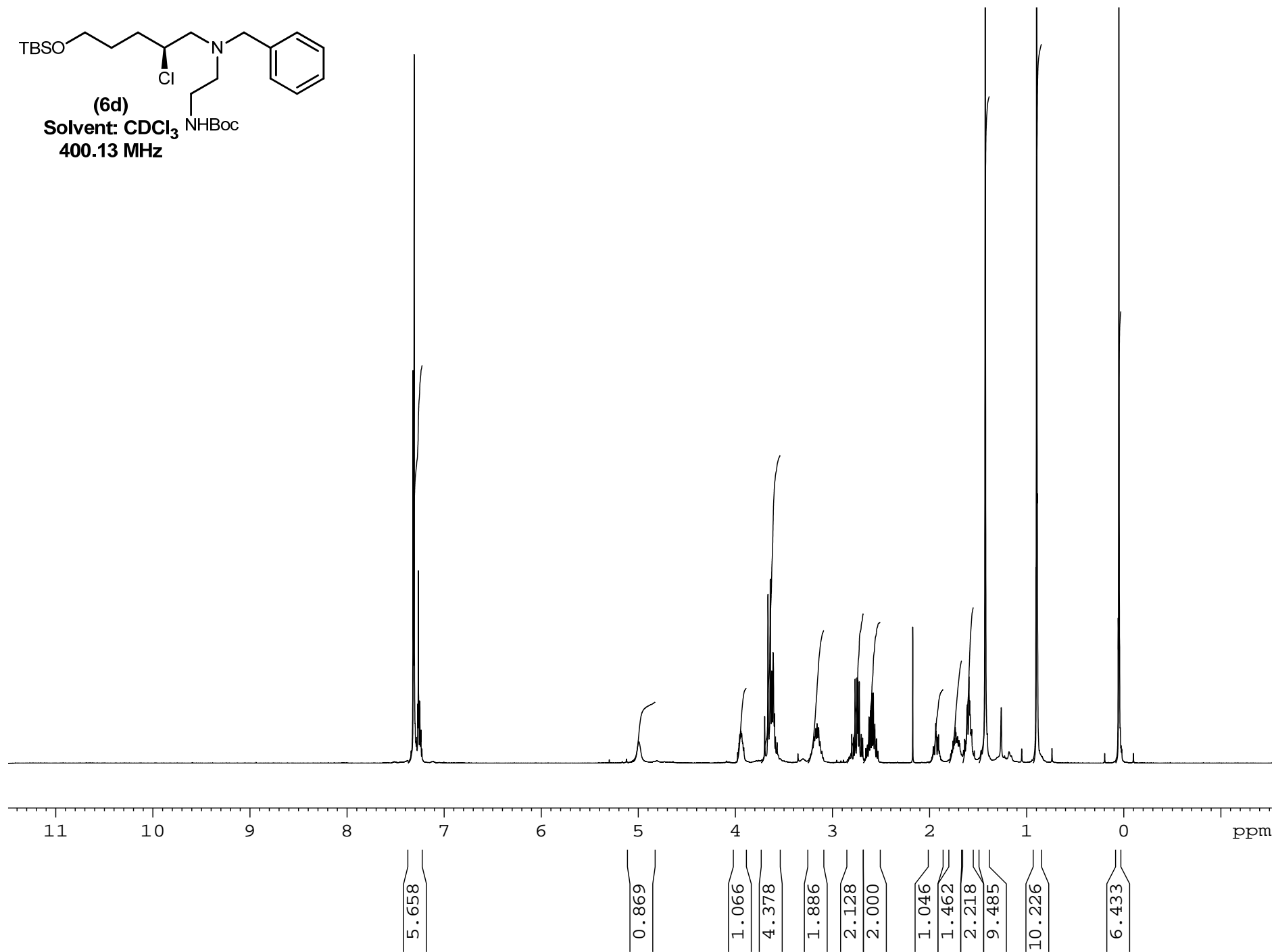
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

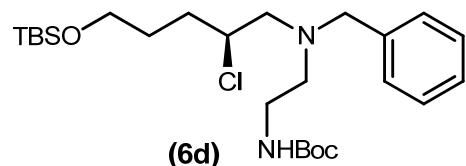
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
423.2779	423.2778	0.1	0.2	5.5	0.8	C24 H40 N2 O2 Cl



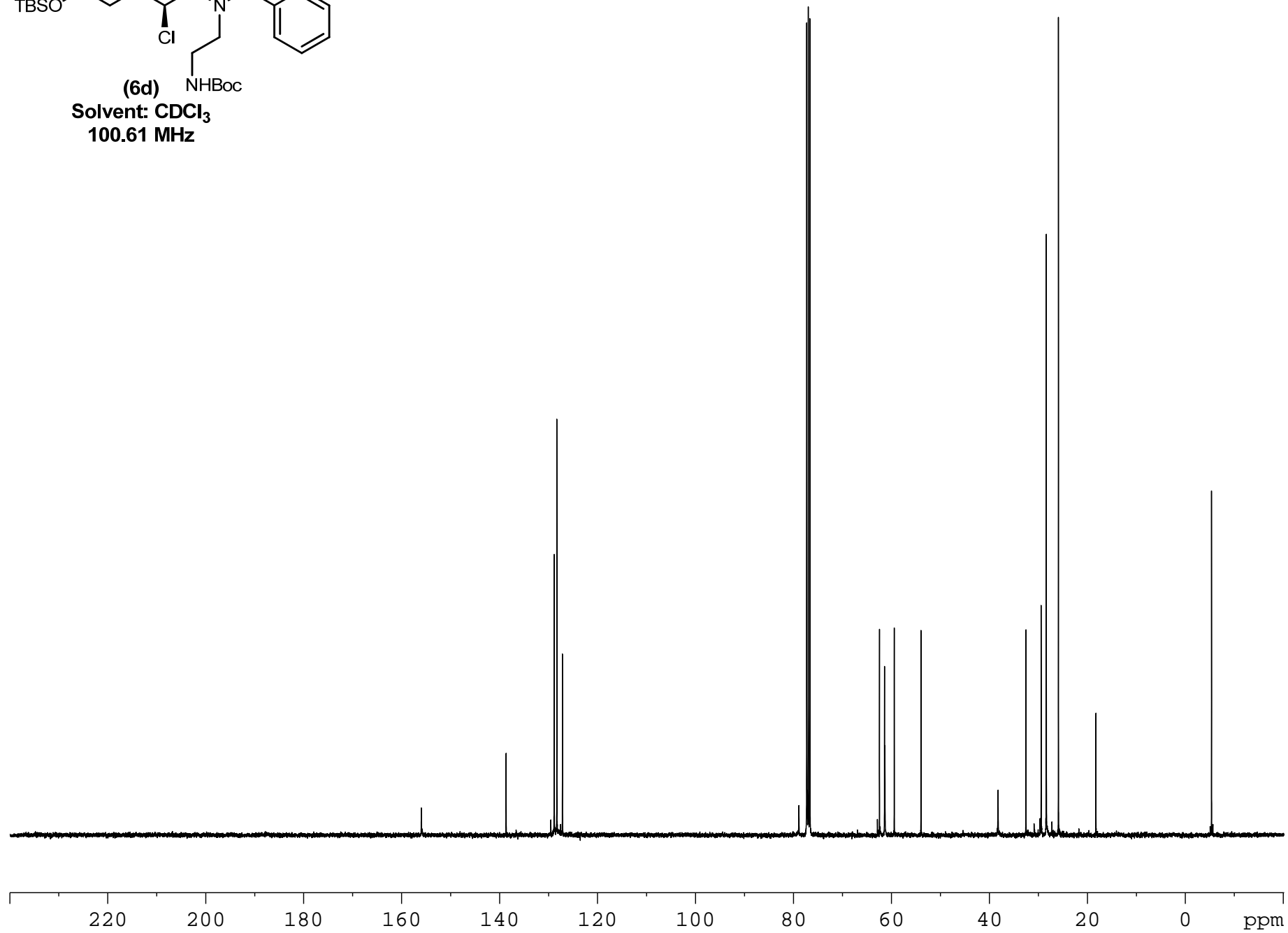
(6d)

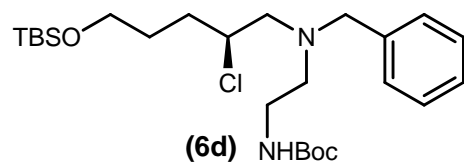
Solvent: CDCl<sub>3</sub>  
400.13 MHz





Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

406 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 25-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1 Si: 1-1

MCO-III-50

S/N: UH193

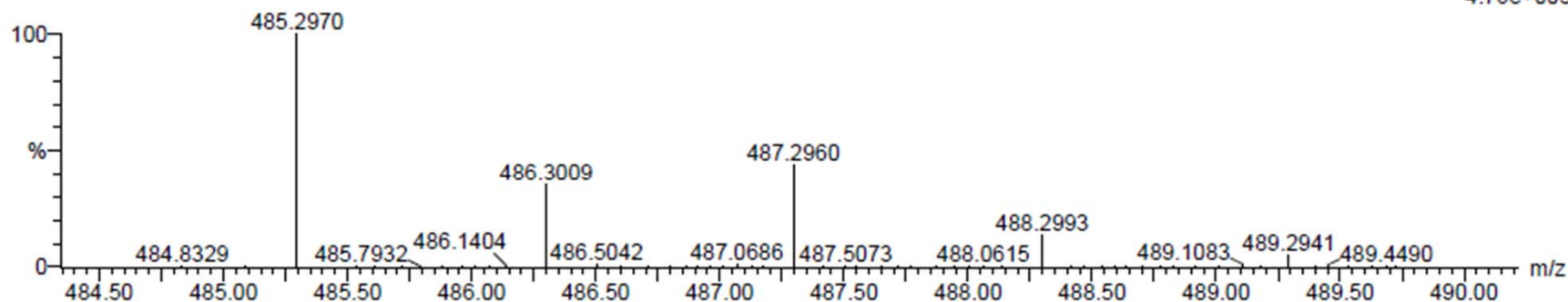
17-Nov-2011

14:50:49

MCO-III-50\_111711\_001 59 (1.117) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (50:60)

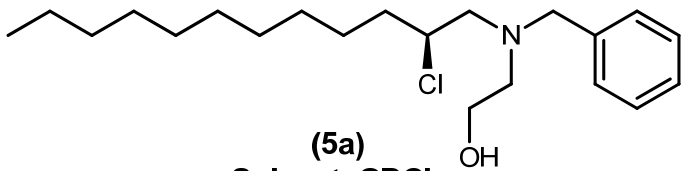
TOF MS ES+

4.76e+003

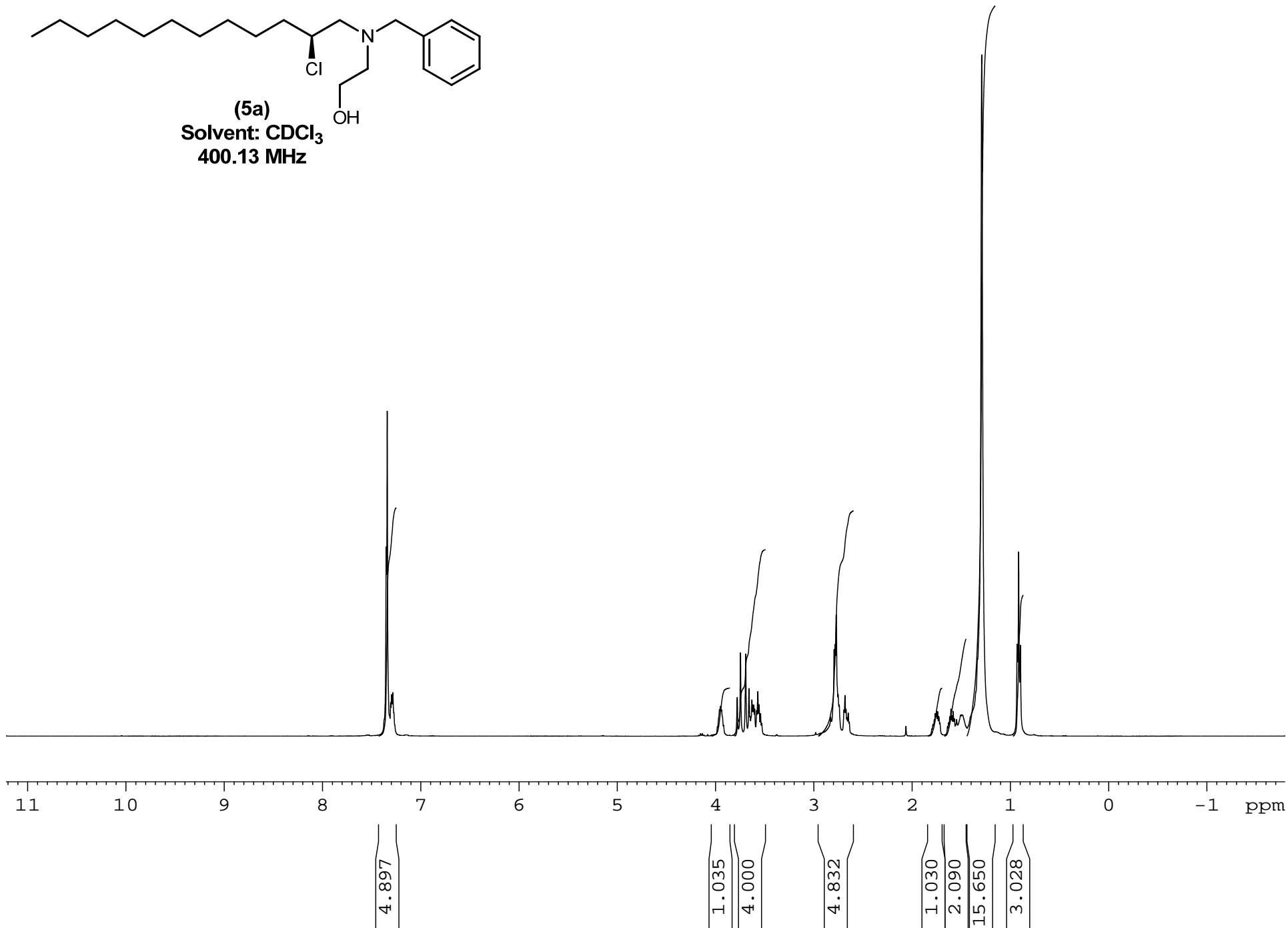


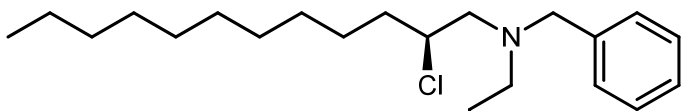
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
485.2970	485.2966	0.4	0.8	4.5	0.2	C25 H46 N2 O3 Cl Si

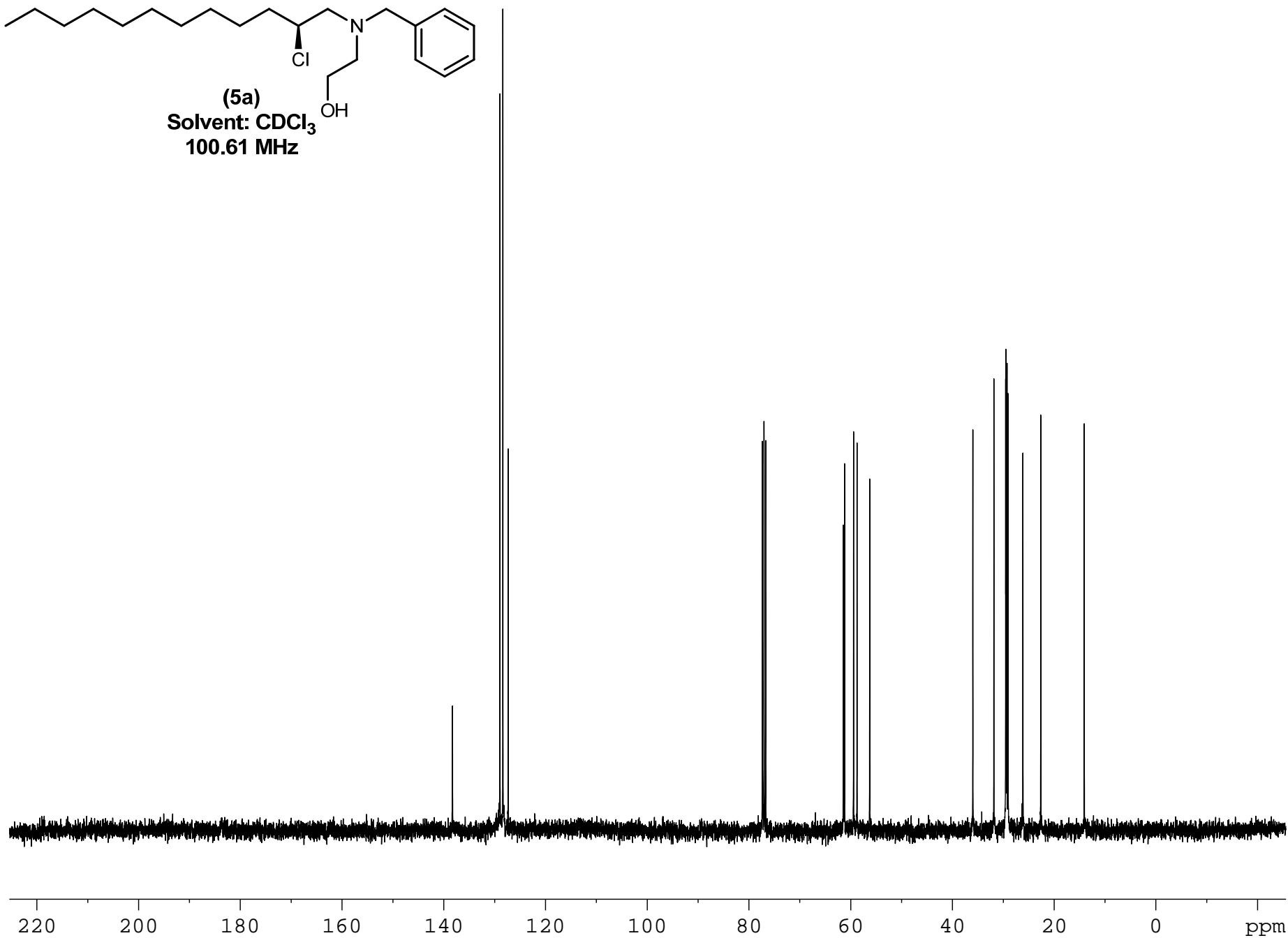


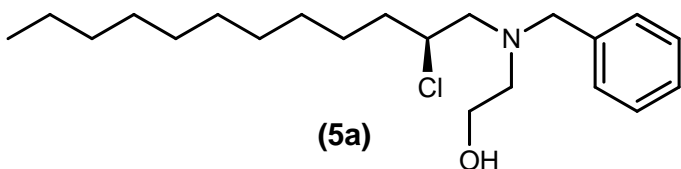
(5a)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz





(5a)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

209 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

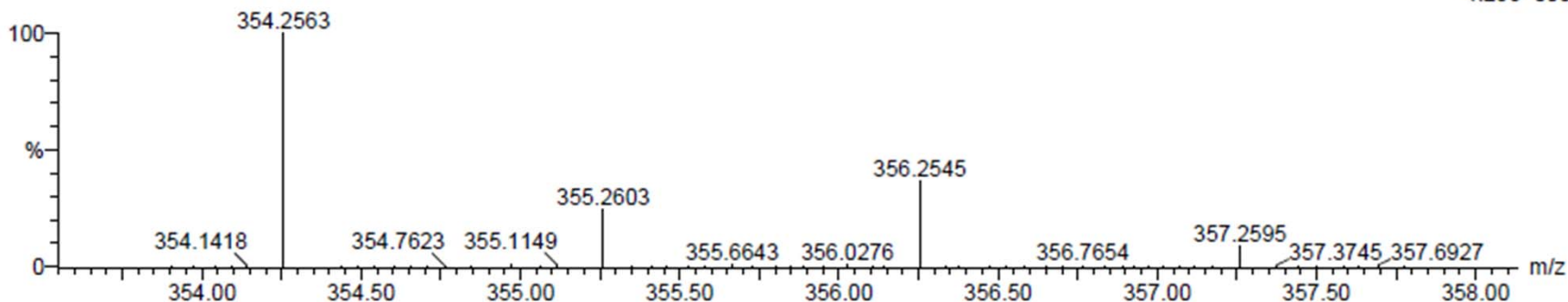
C: 20-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-72

S/N: UH193

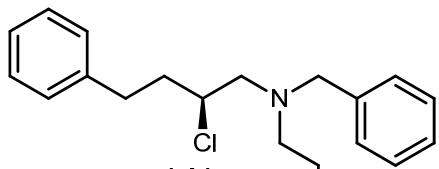
MCO-III-72\_112111\_002 59 (1.117) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (50:60)

21-Nov-2011  
14:09:01  
TOF MS ES+  
4.23e+003

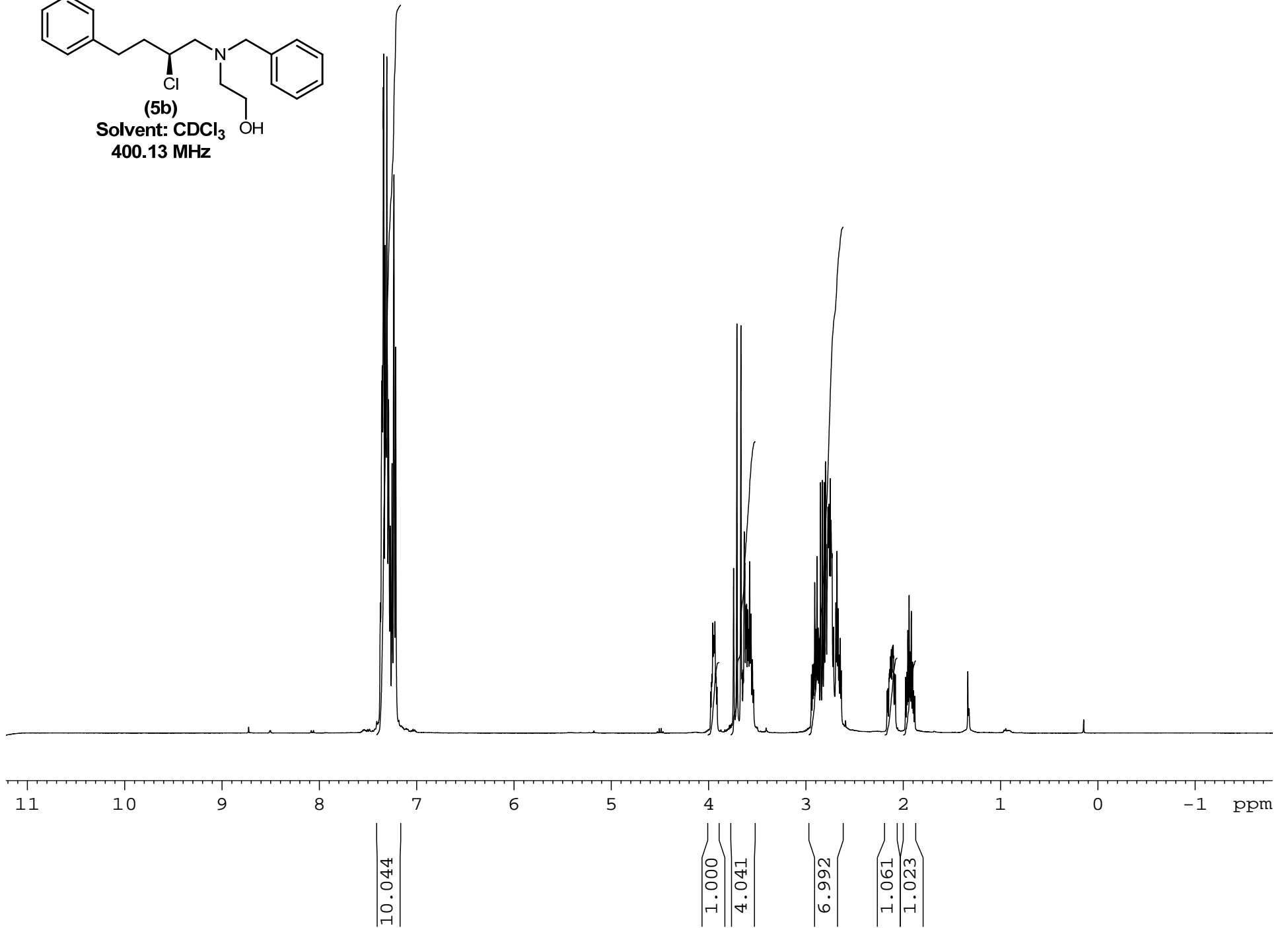


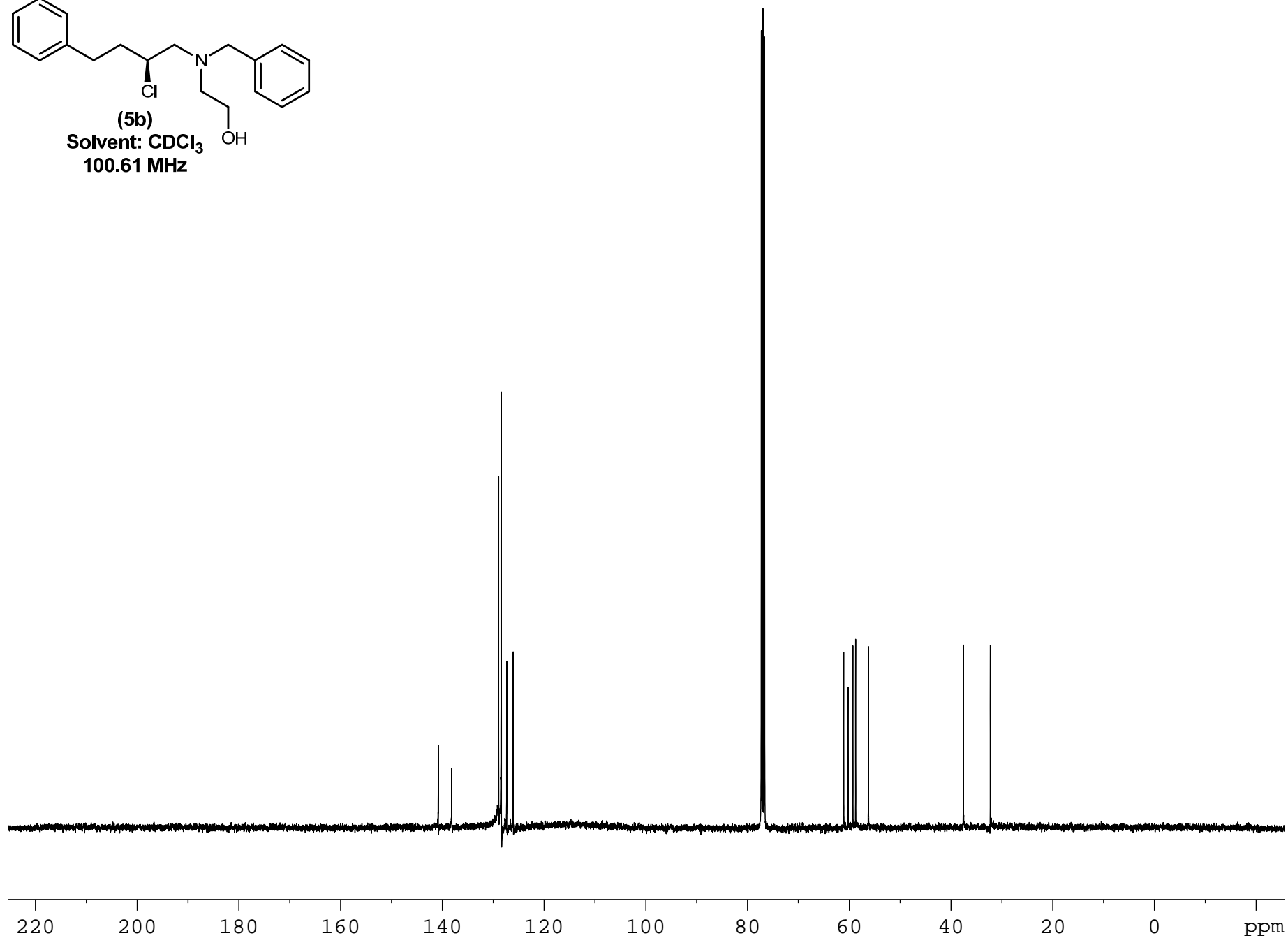
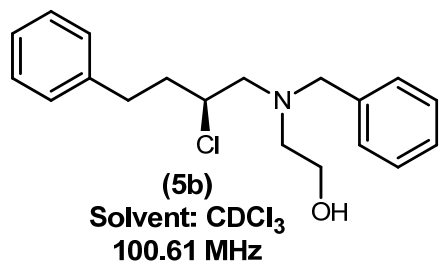
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

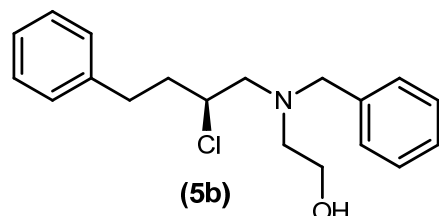
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
354.2563	354.2564	-0.1	-0.3	3.5	0.0	C21 H37 N O Cl



(5b)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz







## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

159 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

C: 18-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-94

S/N: UH193

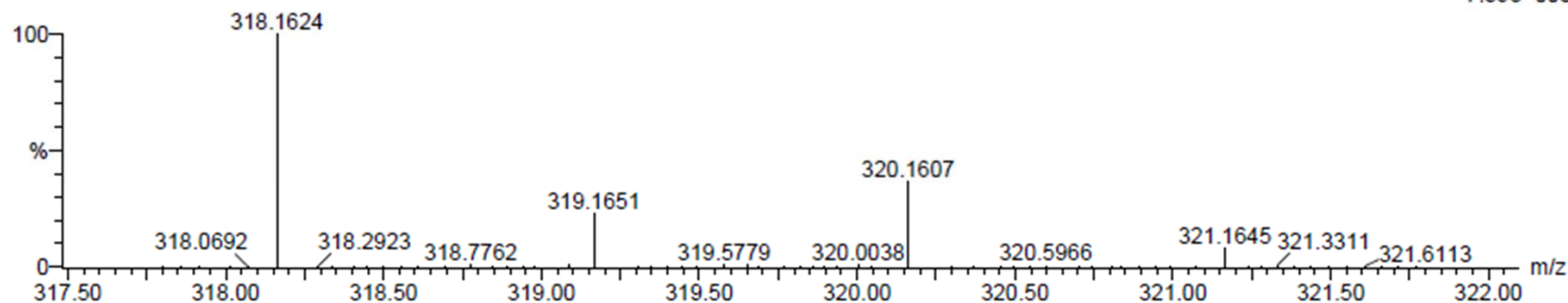
01-Mar-2012

13:03:03

MCO-III-94\_030112\_001 80 (1.512) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

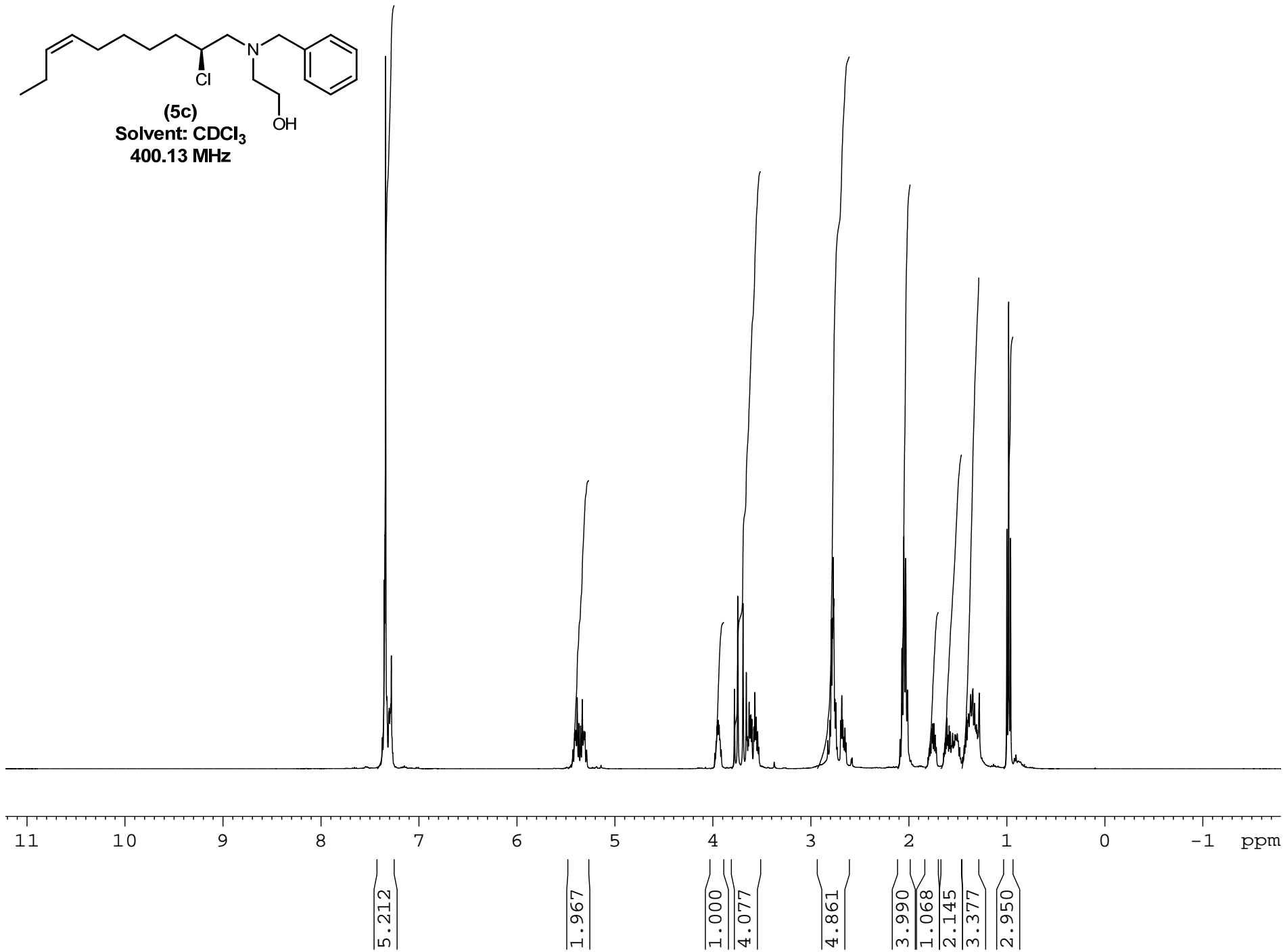
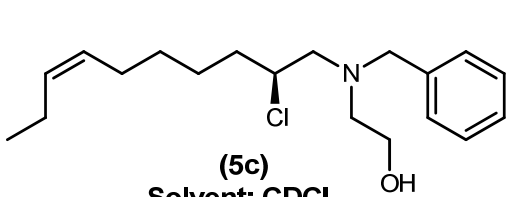
TOF MS ES+

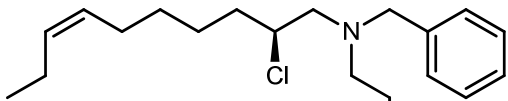
7.39e+003



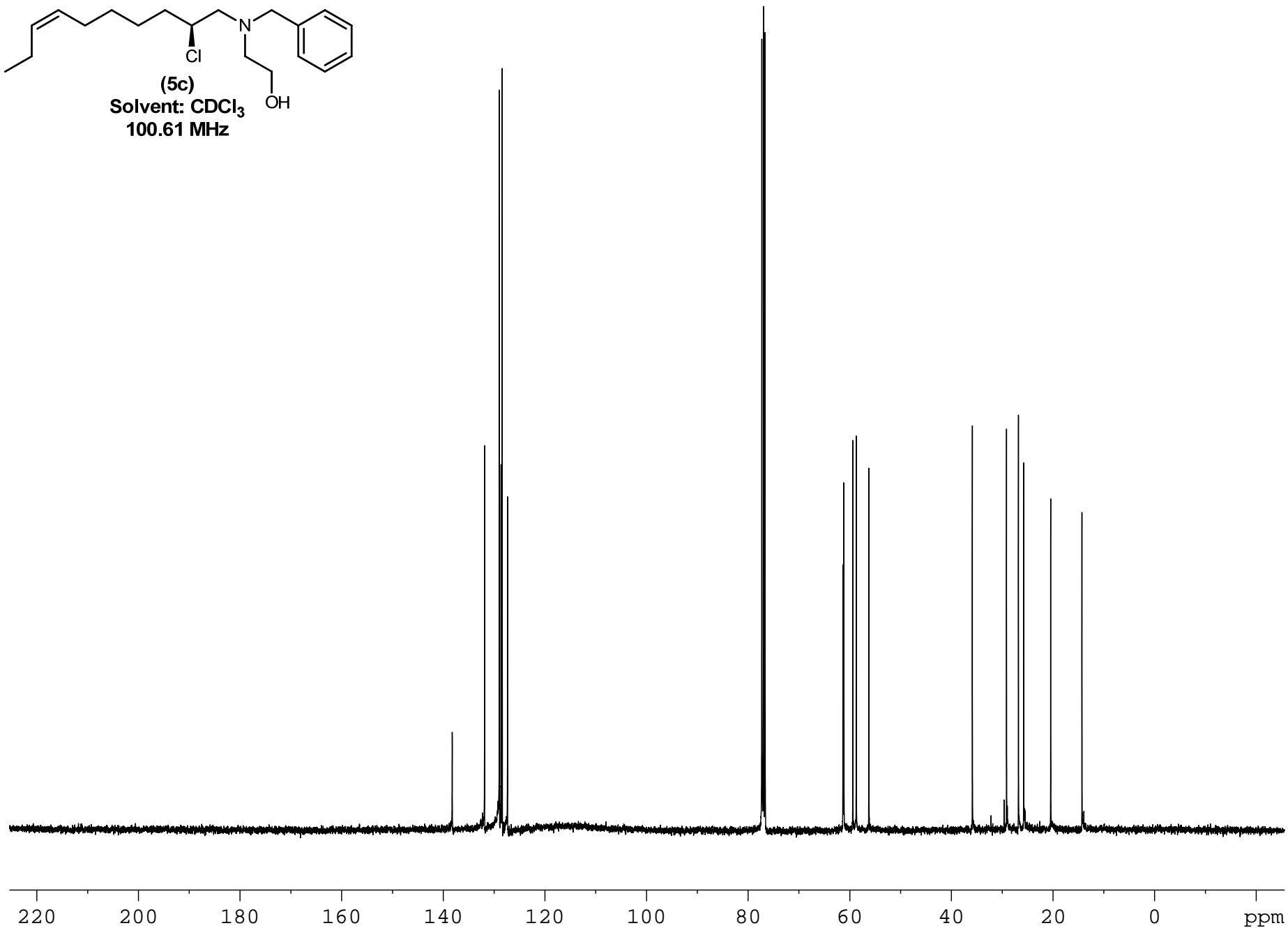
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

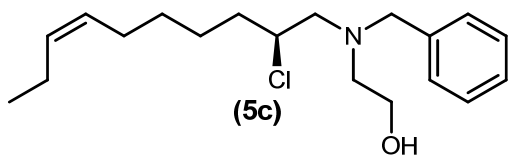
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
318.1624	318.1625	-0.1	-0.3	7.5	0.6	C19 H25 N O Cl





(5c)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

168 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

C: 18-500 H: 10-1000 N: 1-200 O: 1-200 Cl: 1-1

MCO-III-174

S/N: UH193

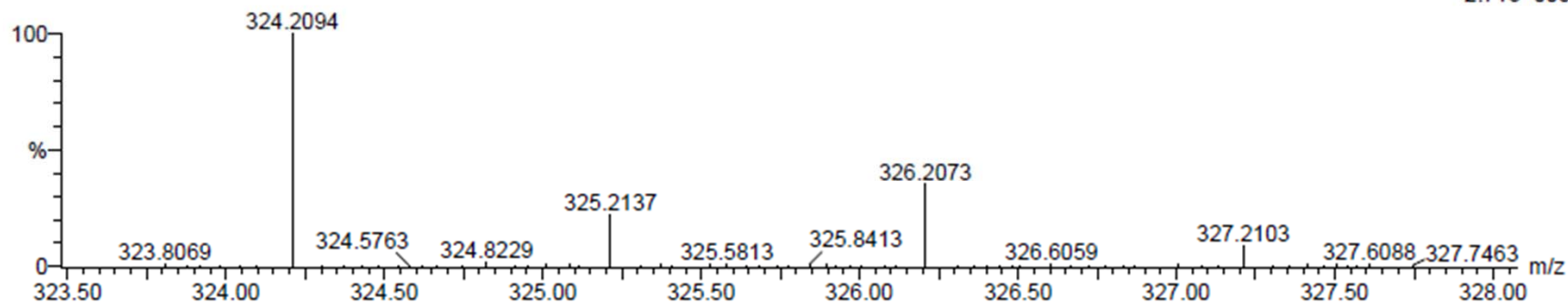
01-Mar-2012

14:04:54

TOF MS ES+

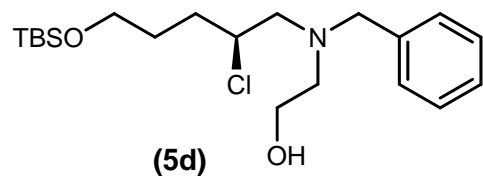
2.71e+003

MCO-III-174\_030112\_001 84 (1.587) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

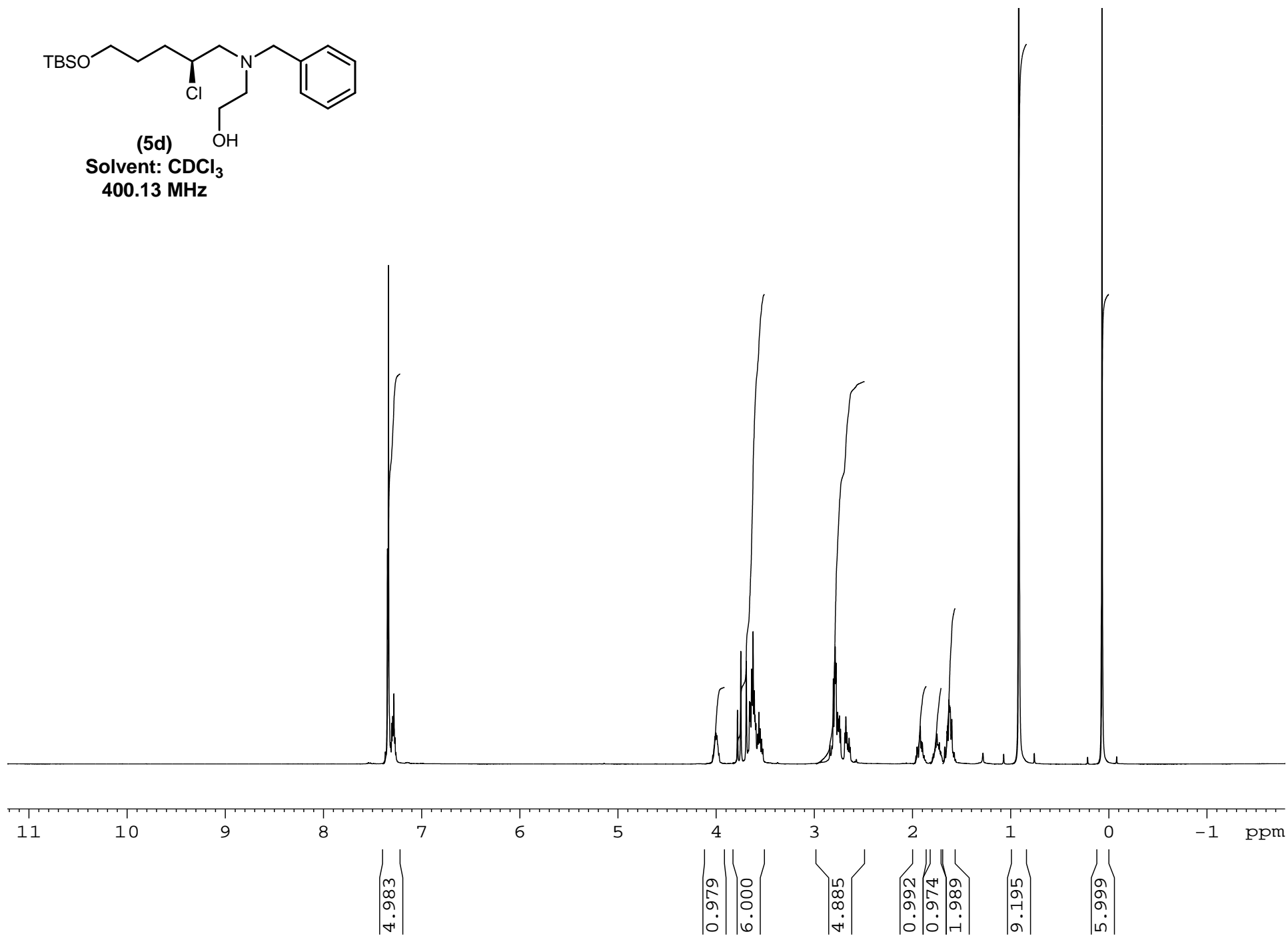


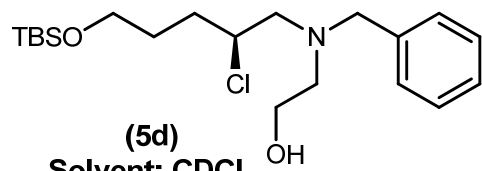
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
324.2094	324.2094	0.0	0.0	4.5	0.0	C19 H31 N O Cl

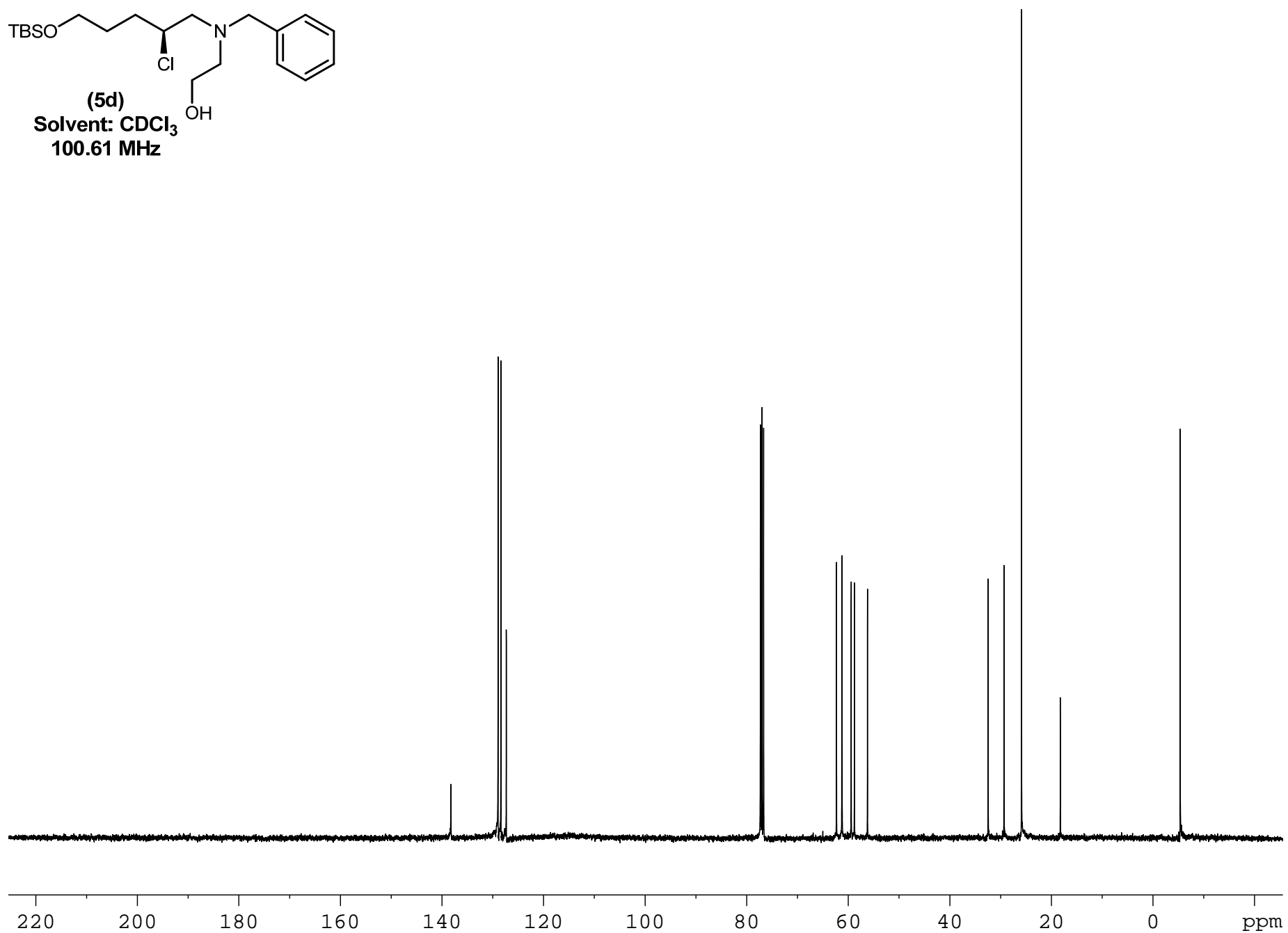


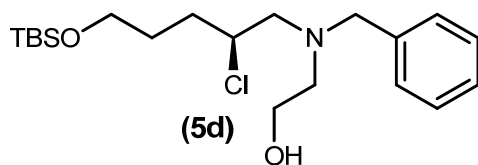
Solvent: CDCl<sub>3</sub>  
400.13 MHz





Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

215 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

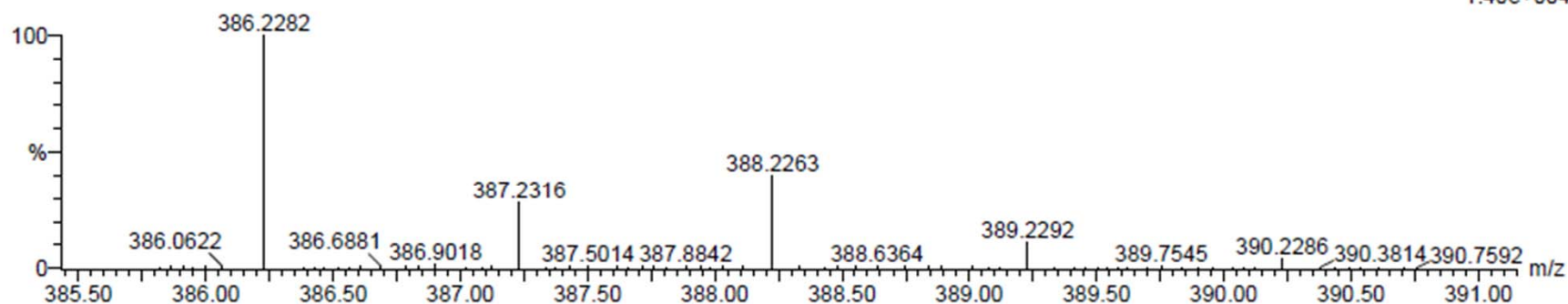
C: 20-500 H: 10-1000 N: 1-200 O: 1-200 Si: 1-1 Cl: 1-1

MCO-III-158A

S/N: UH193

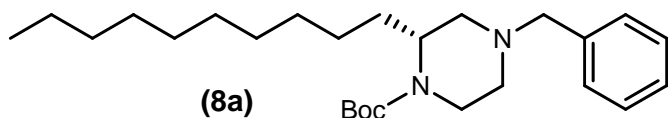
MCO-III-158A\_030112\_001 83 (1.568) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

01-Mar-2012  
16:10:43  
TOF MS ES+  
1.40e+004

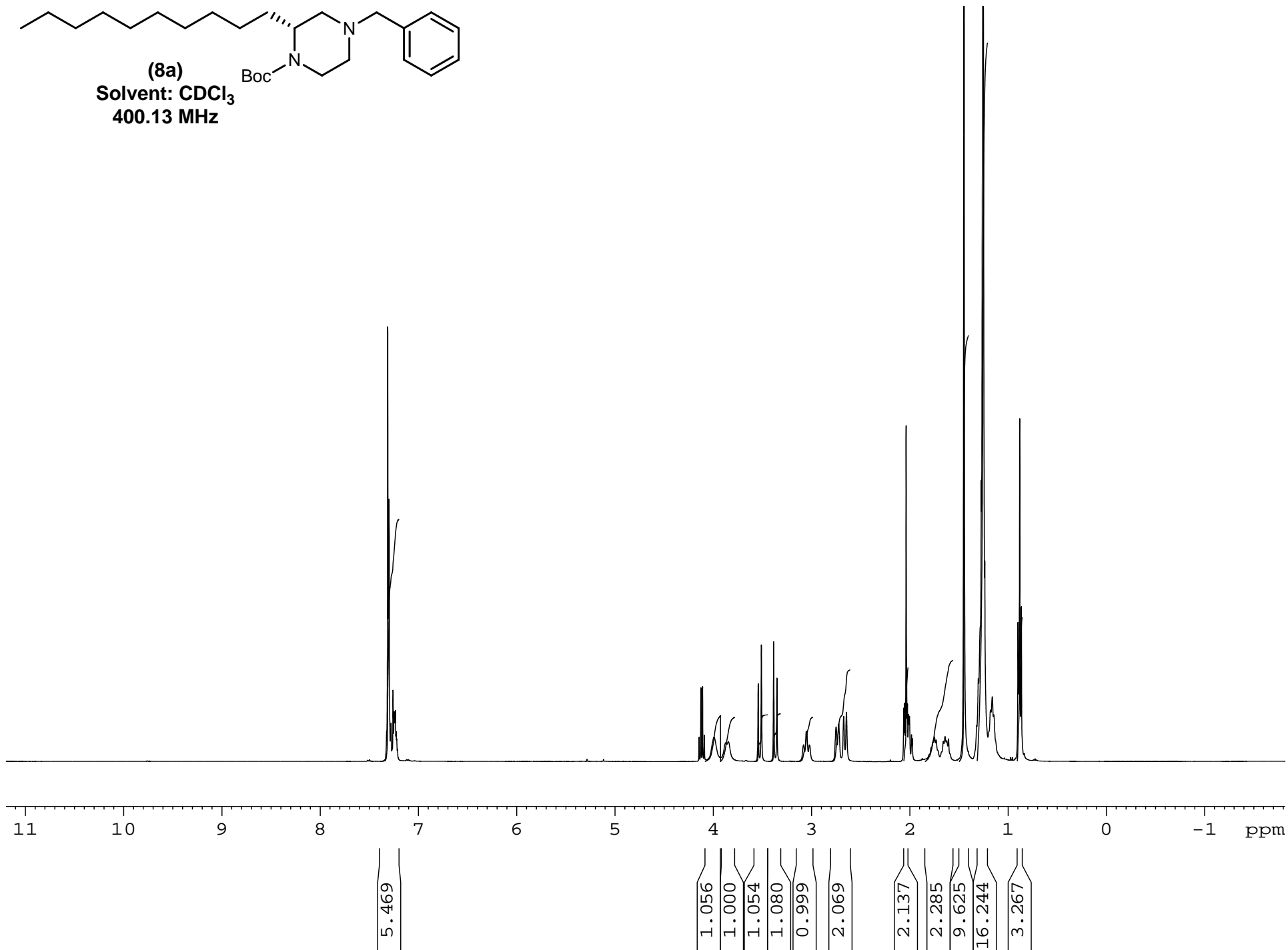


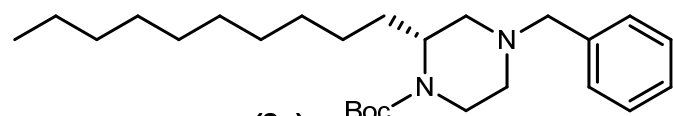
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
386.2282	386.2282	0.0	0.0	3.5	0.0	C20 H37 N O2 Si Cl

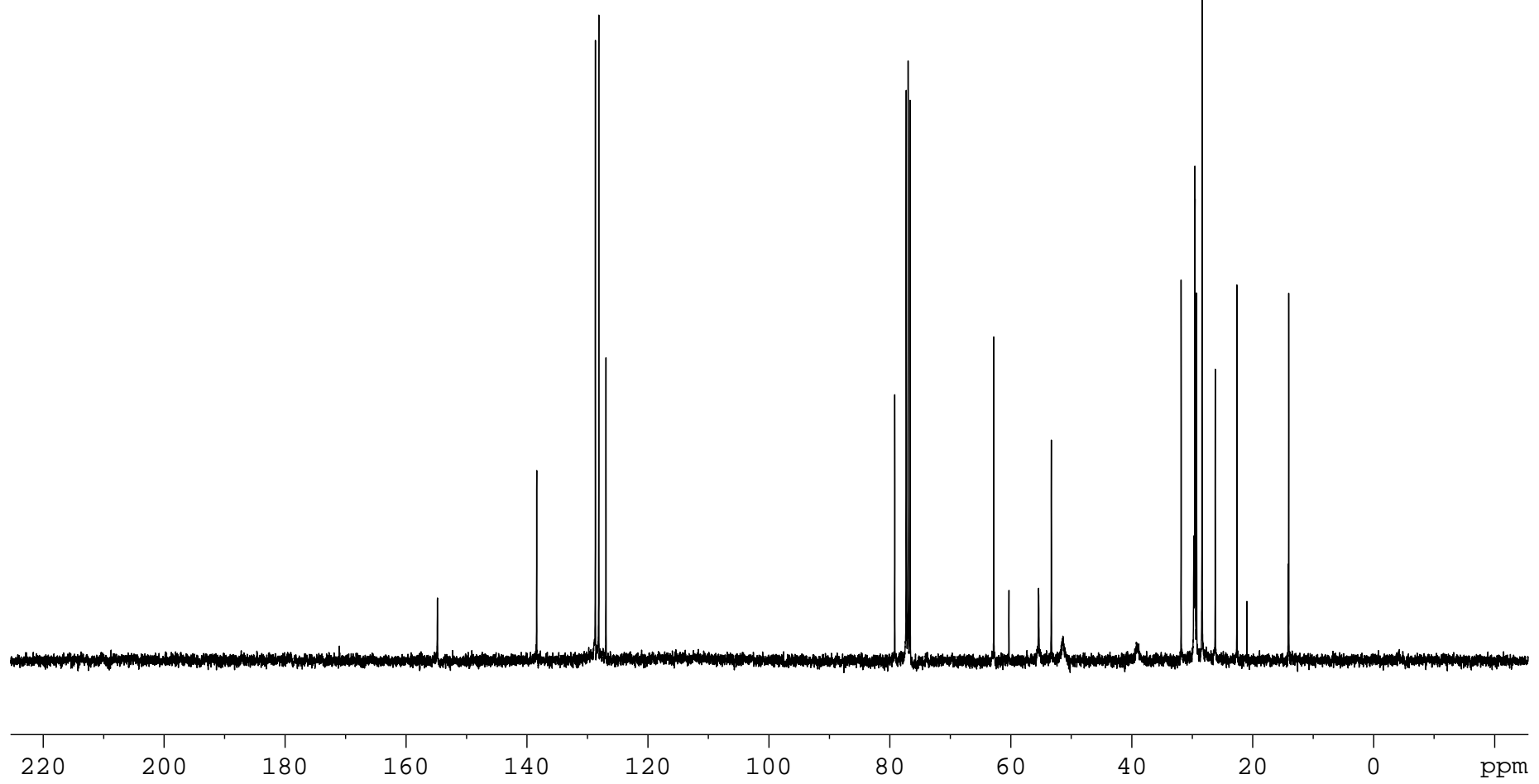


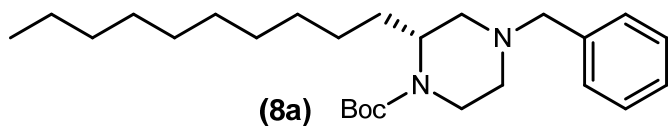
(8a)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz





(8a)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

507 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

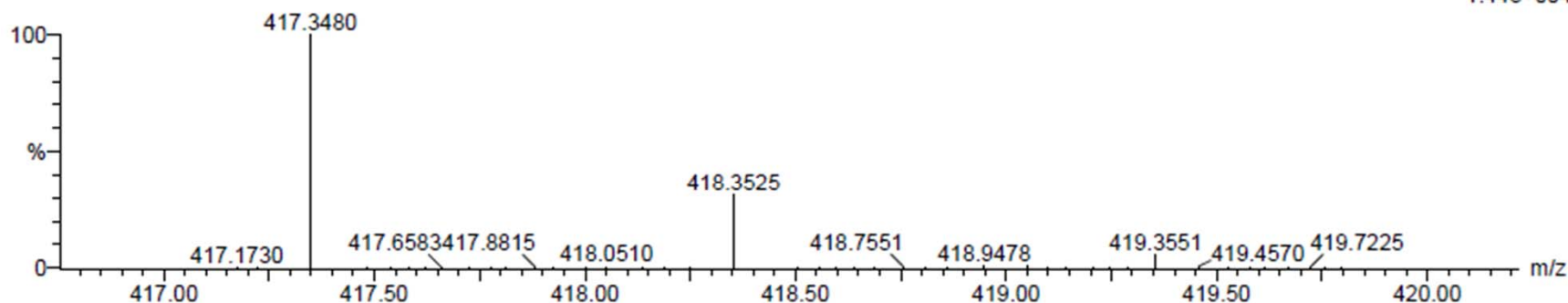
C: 18-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-109

S/N: UH193

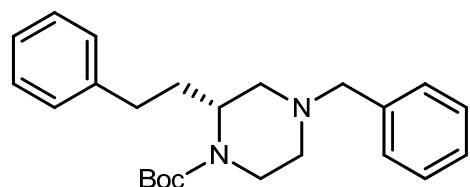
MCO-III-109\_030112\_001 94 (1.775) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

01-Mar-2012  
13:36:44  
TOF MS ES+  
1.44e+004



Minimum: -0.5  
Maximum: 10.0 5.0 25.0

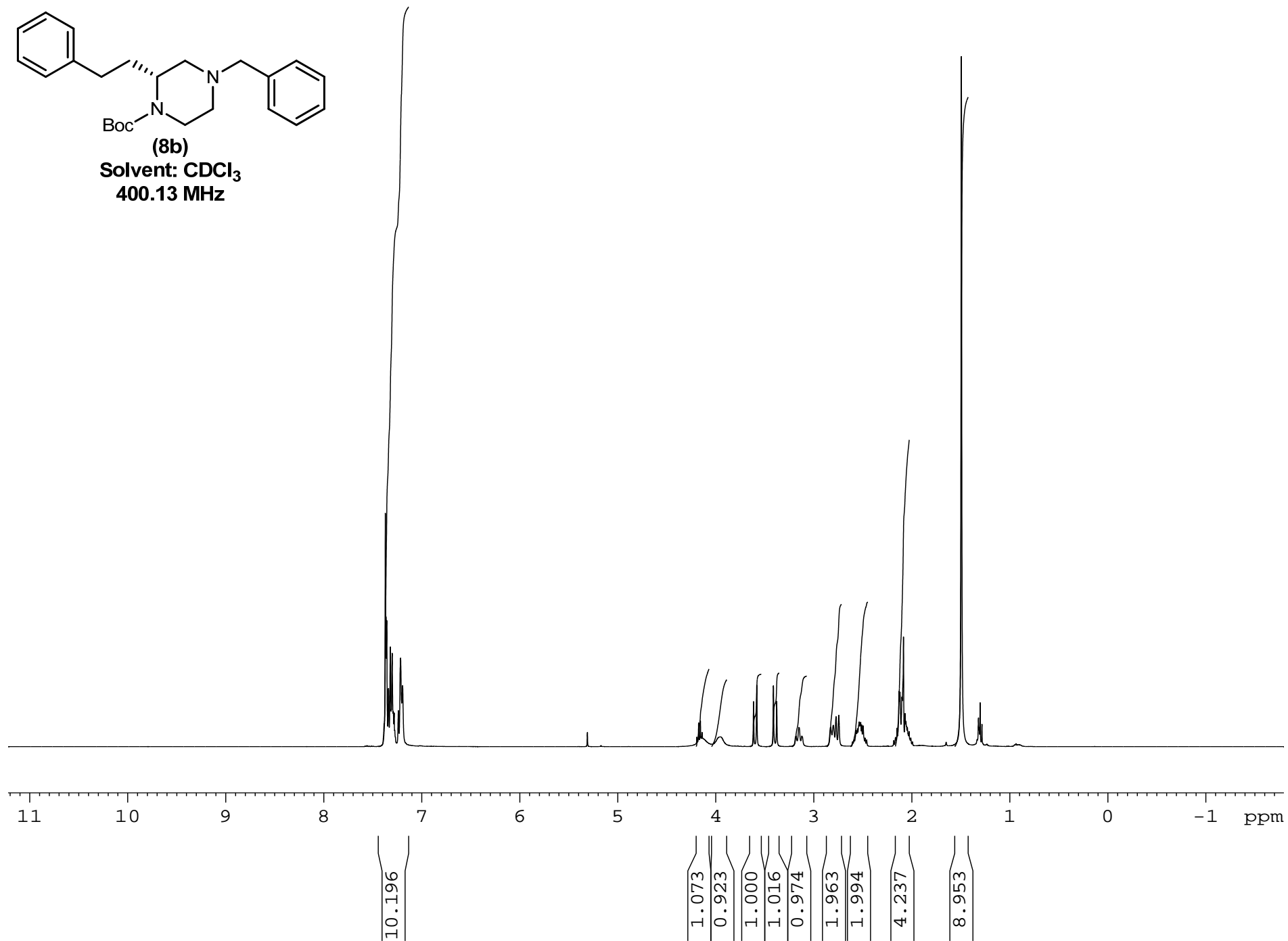
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
417.3480	417.3481	-0.1	-0.2	5.5	1.5	C26 H45 N2 O2

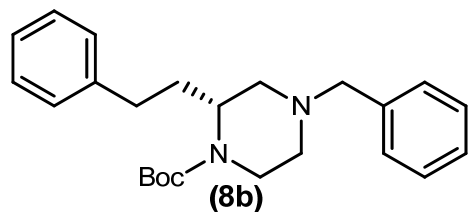


(8b)

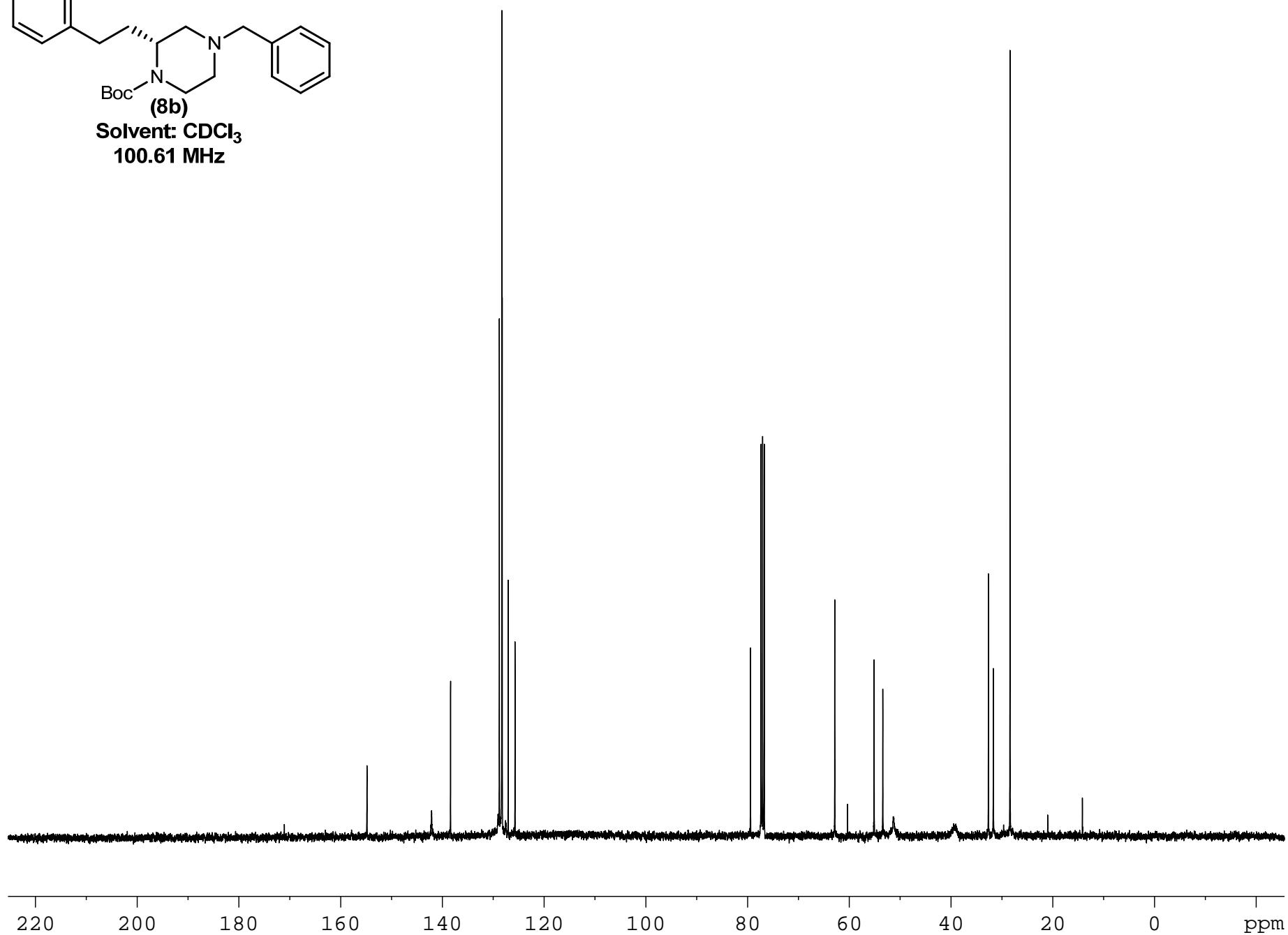
Solvent: CDCl<sub>3</sub>

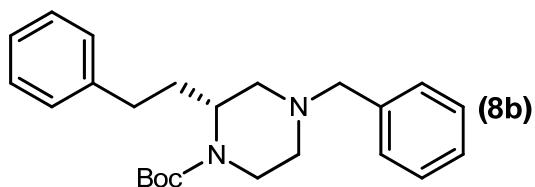
400.13 MHz





Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

352 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 20-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-40

S/N: UH193

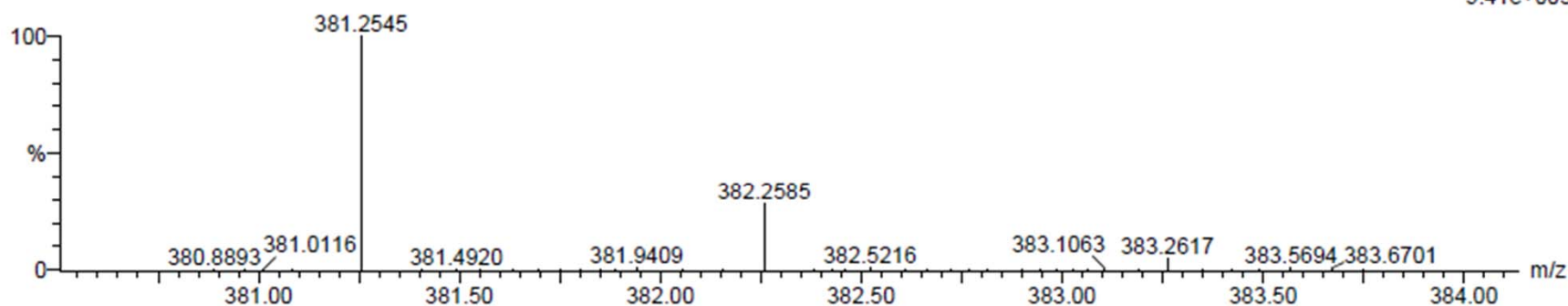
20-Oct-2011

15:34:02

MCO-III-40\_102011\_002 90 (1.677) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (80:90)

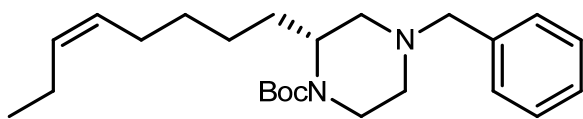
TOF MS ES+

9.41e+003



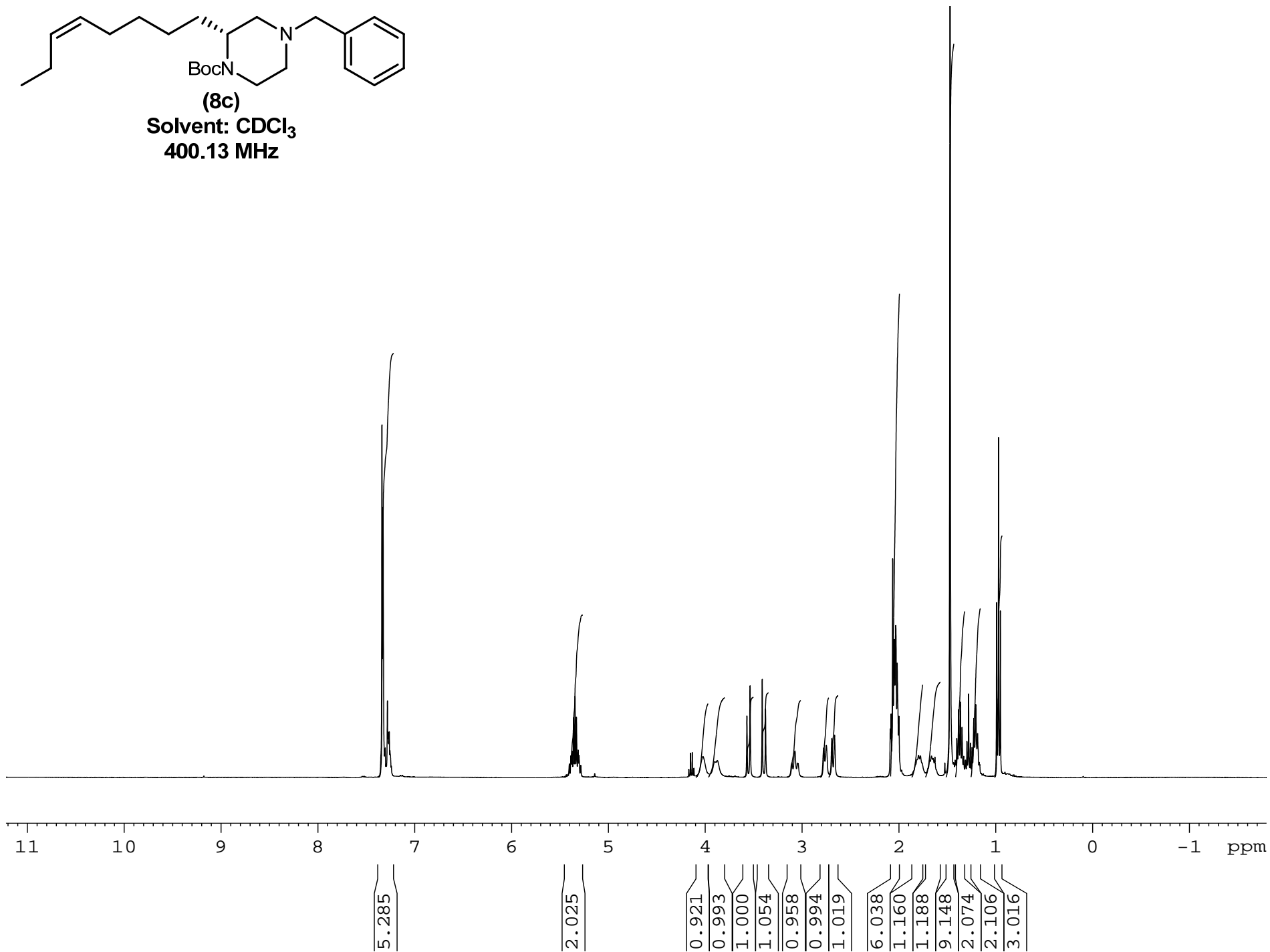
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

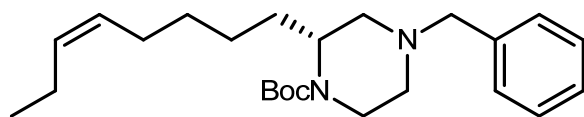
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
381.2545	381.2542	0.3	0.8	9.5	0.3	C24 H33 N2 O2



(8c)

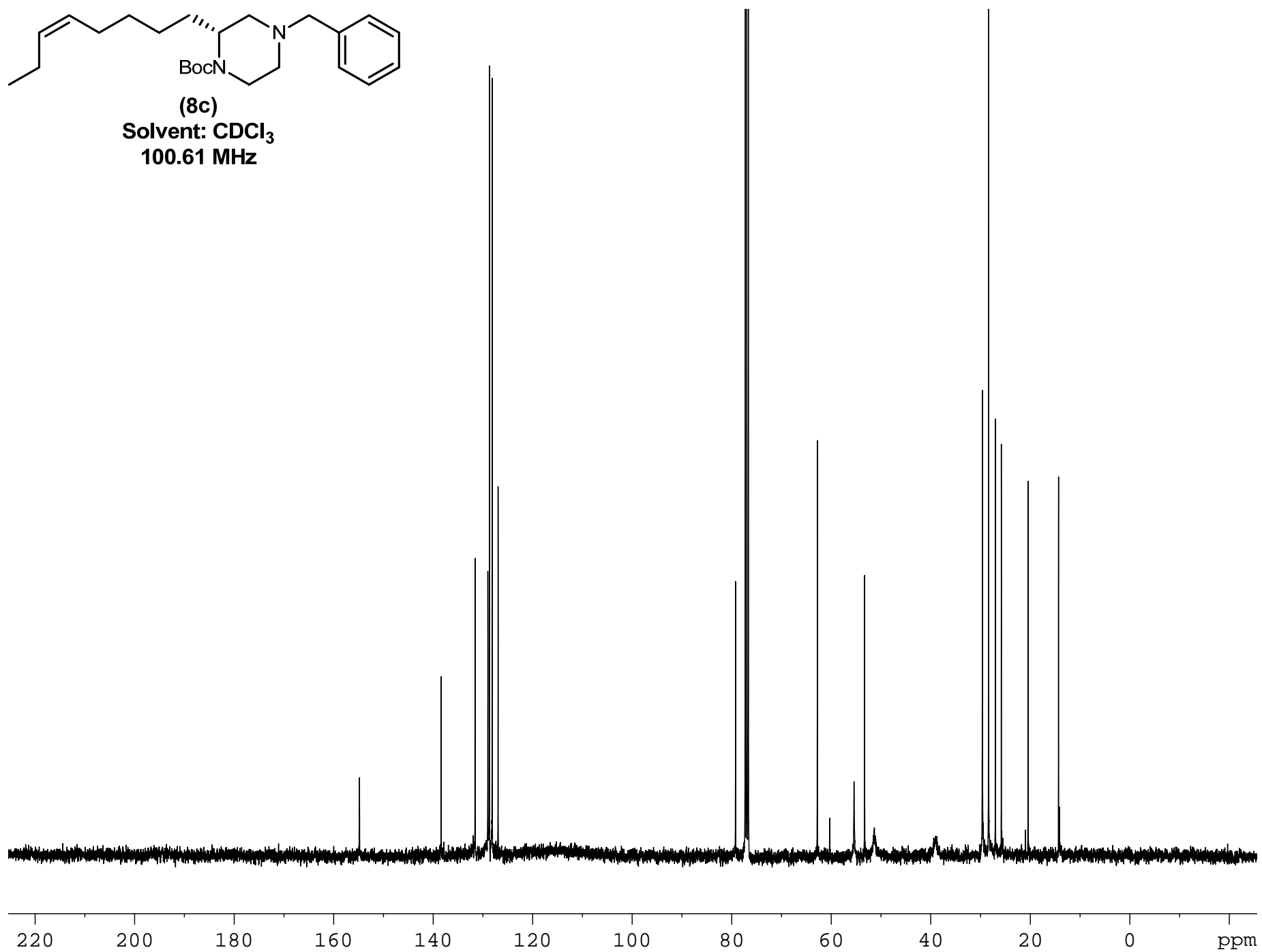
Solvent: CDCl<sub>3</sub>  
400.13 MHz

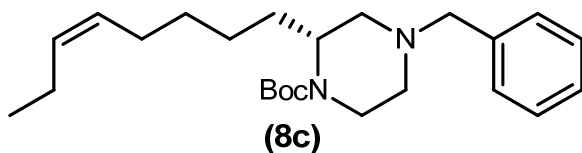




(8c)

Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

366 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

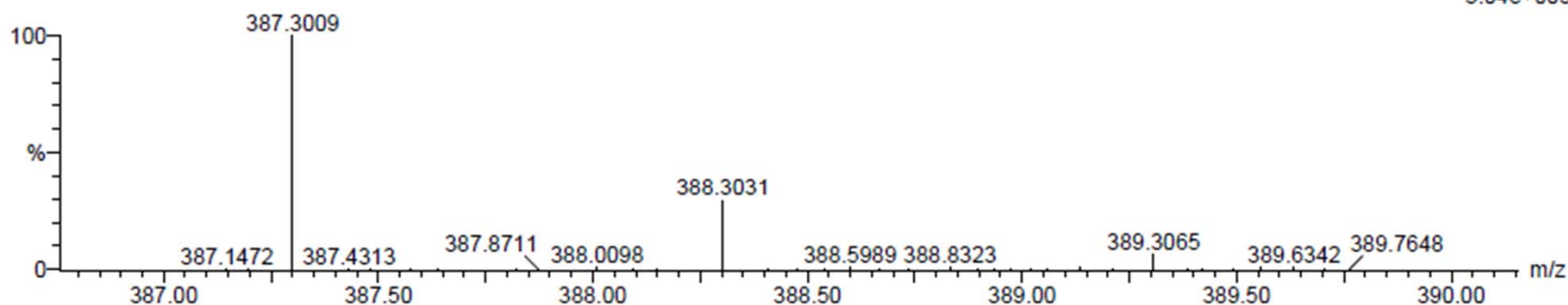
C: 20-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-55

S/N: UH193

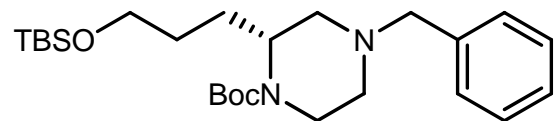
MCO-III-55\_111711\_001 94 (1.775) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

17-Nov-2011  
15:19:26  
TOF MS ES+  
3.04e+003



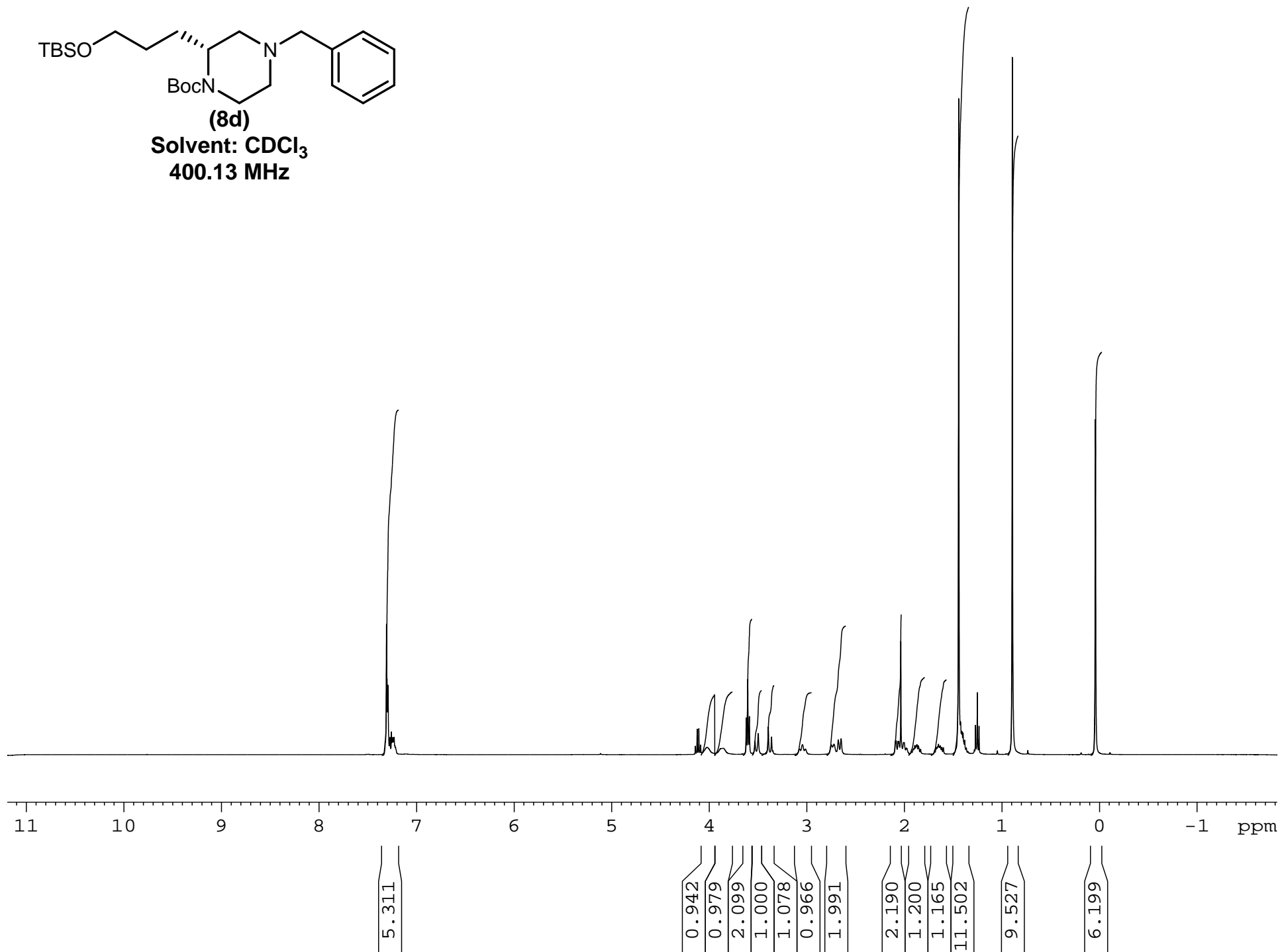
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

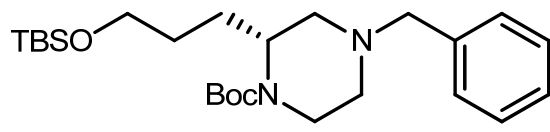
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
387.3009	387.3012	-0.3	-0.8	6.5	0.6	C24 H39 N2 O2



(8d)

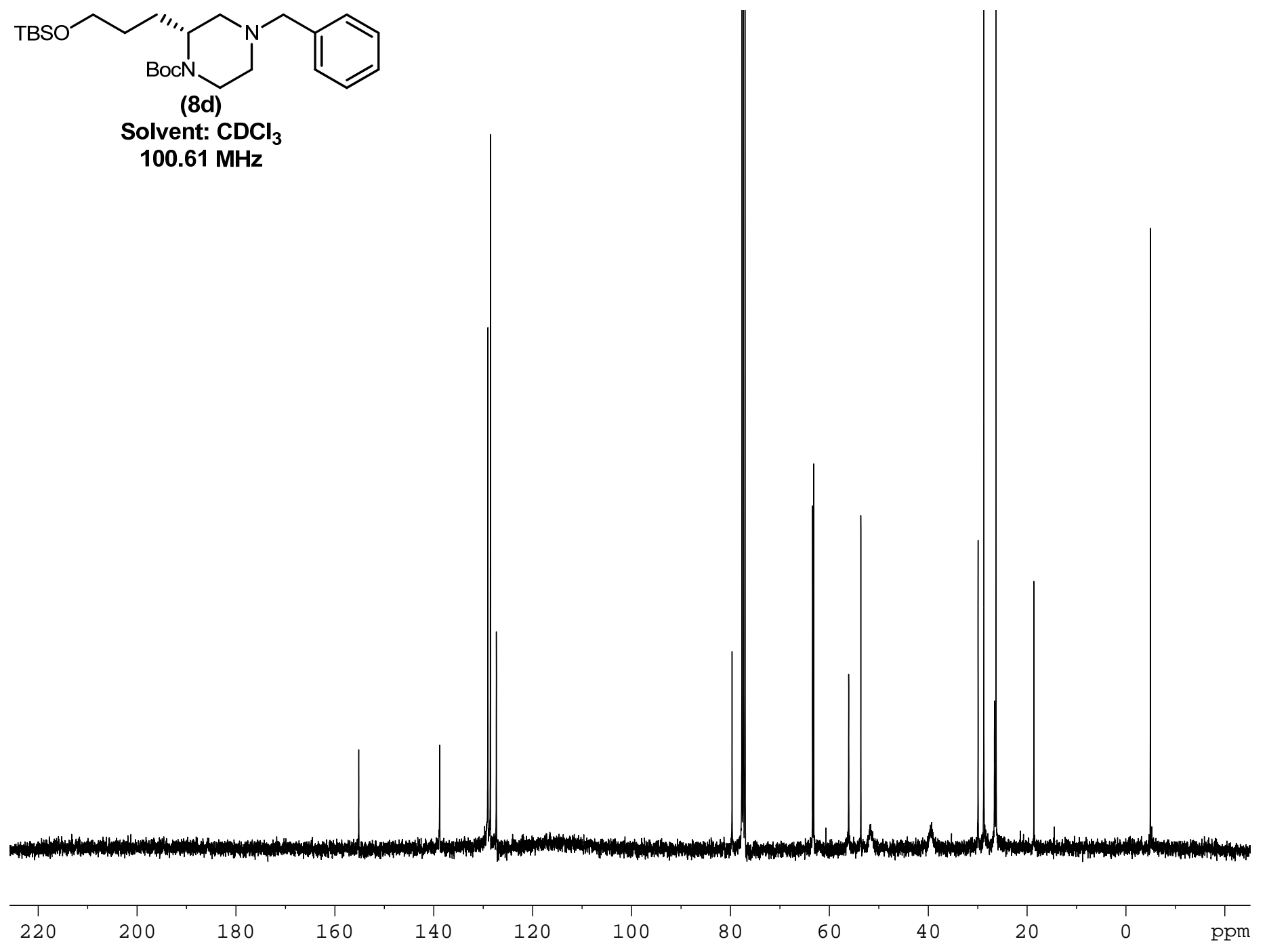
Solvent: CDCl<sub>3</sub>  
400.13 MHz

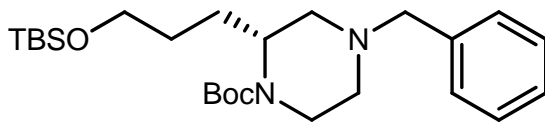




(8d)

Solvent: CDCl<sub>3</sub>  
100.61 MHz





(8d)

## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

400 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

C: 25-500 H: 10-1000 N: 1-200 O: 1-200 Si: 1-1

MCO-III-53

S/N: UH193

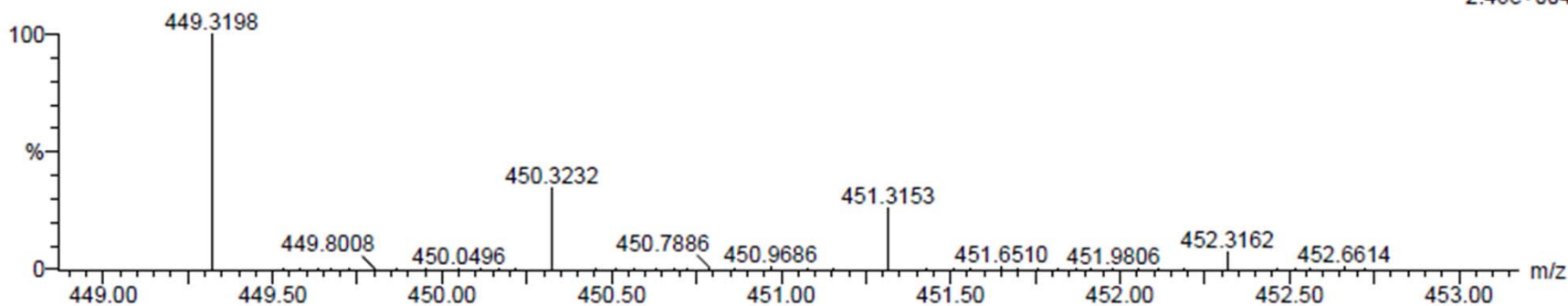
17-Nov-2011

15:07:33

MCO-III-53\_111711\_002 99 (1.869) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

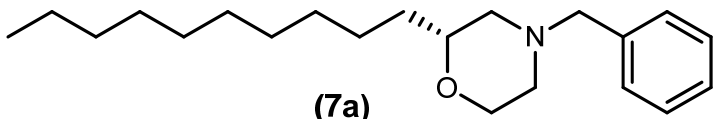
TOF MS ES+

2.46e+004

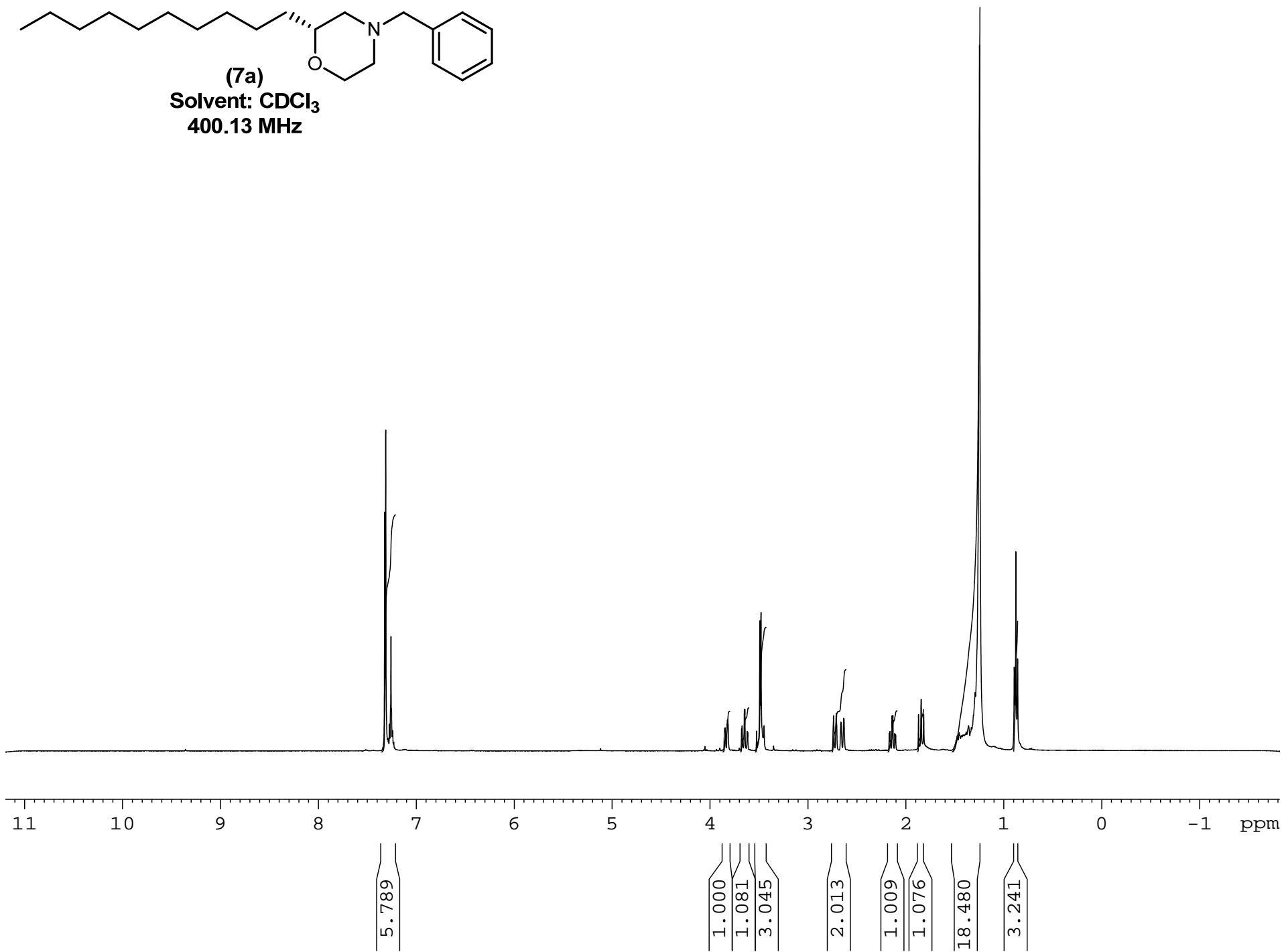


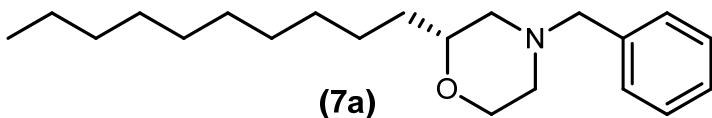
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
449.3198	449.3199	-0.1	-0.2	5.5	0.0	C25 H45 N2 O3 Si

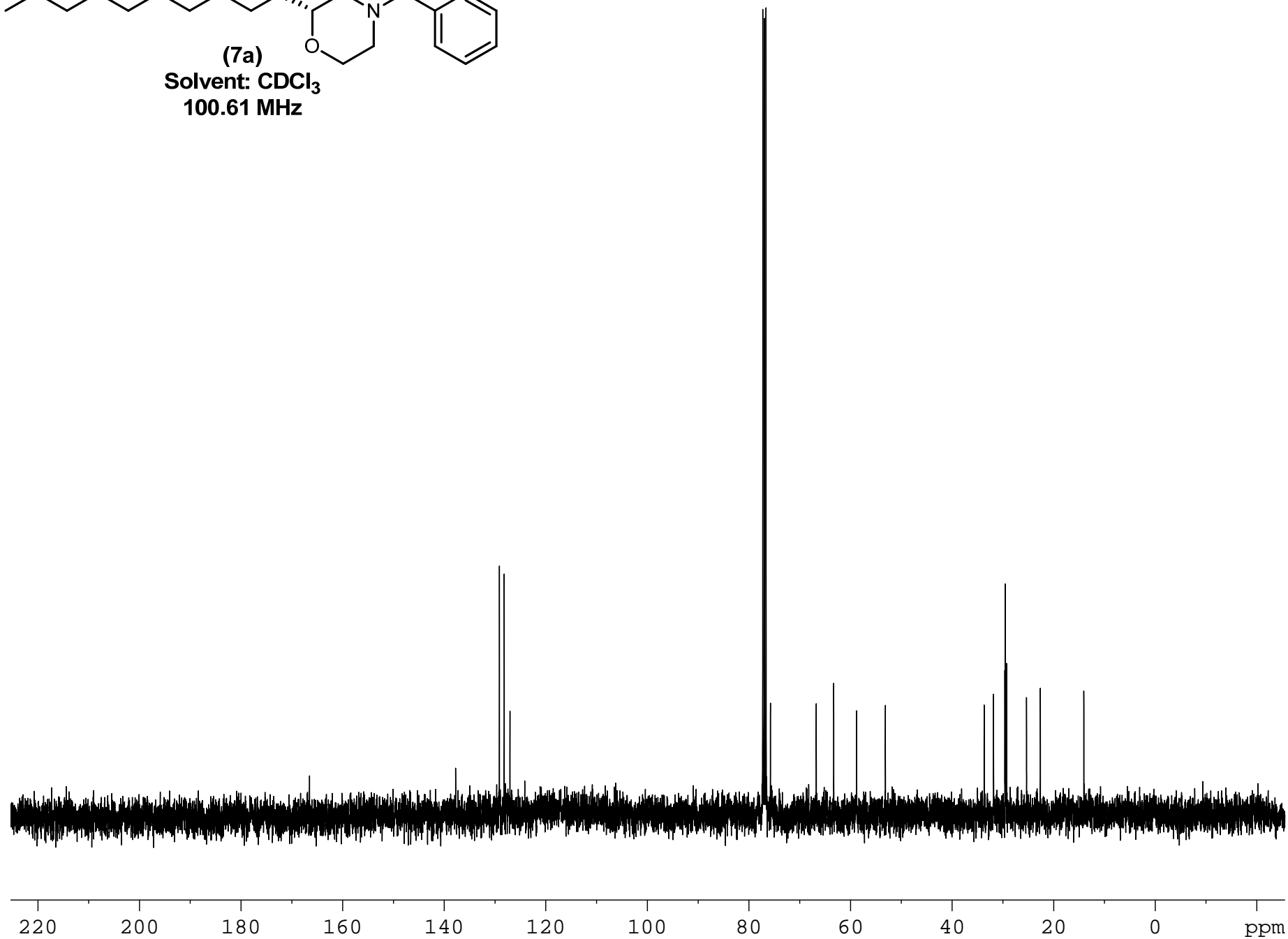


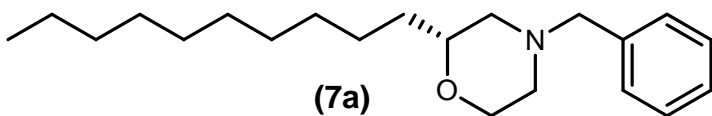
(7a)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz





(7a)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

294 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

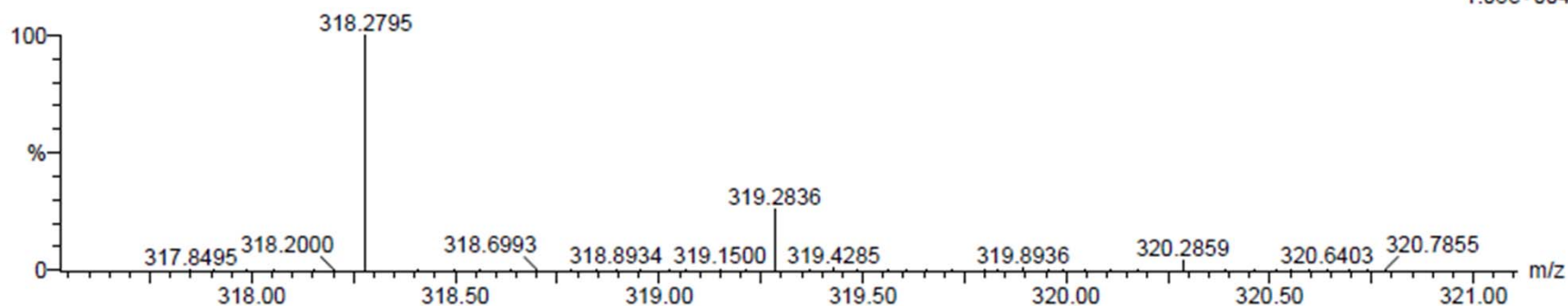
C: 10-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-46

S/N: UH193

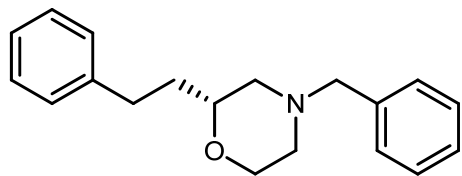
MCO-III-46\_102711\_001 60 (1.120) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (60:70)

27-Oct-2011  
14:31:35  
TOF MS ES+  
1.08e+004



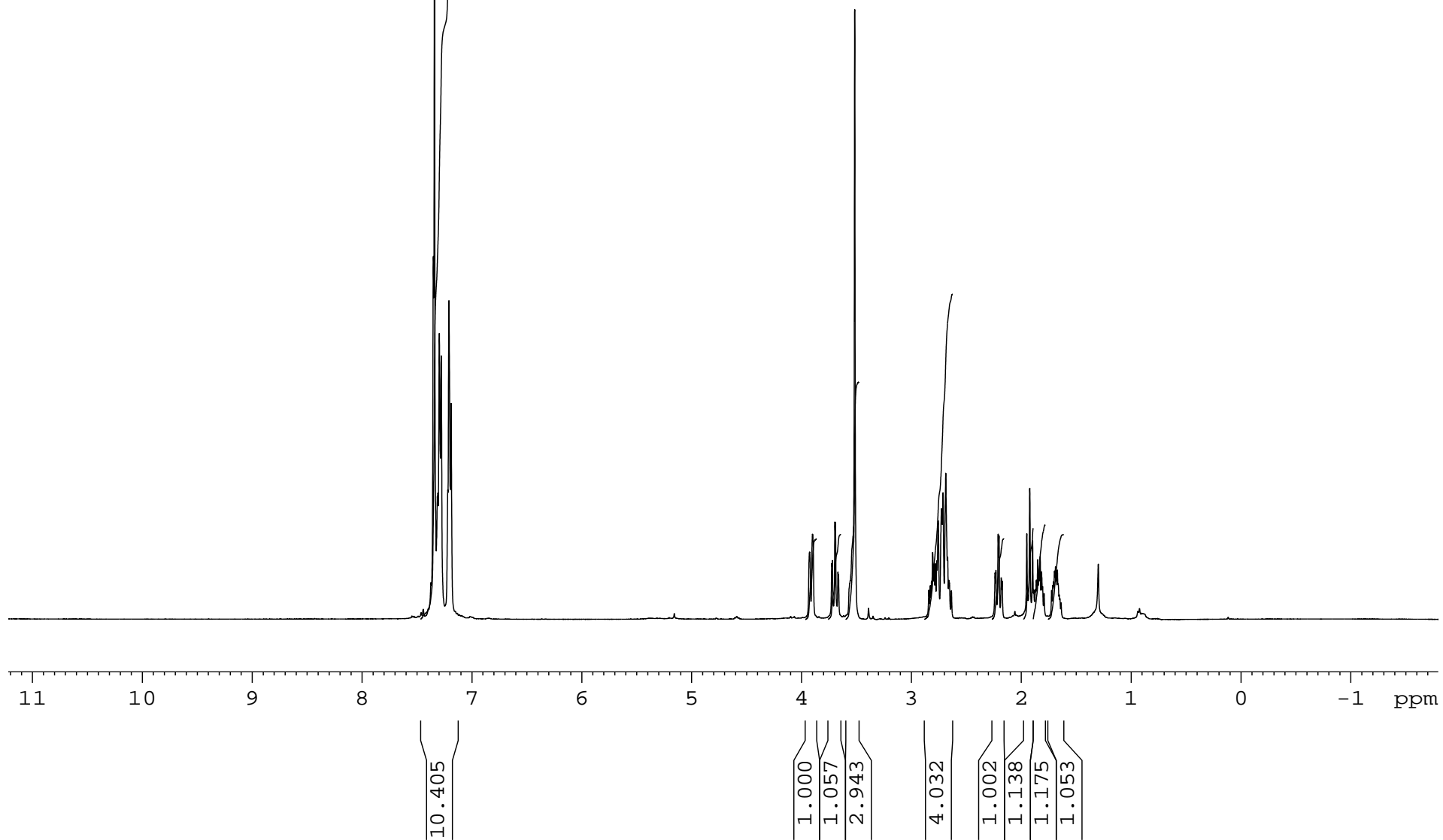
Minimum: -0.5  
Maximum: 5.0 5.0 25.0

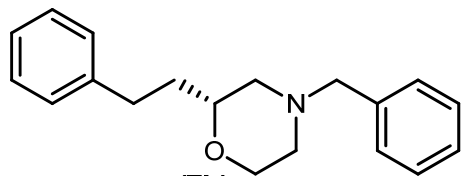
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
318.2795	318.2797	-0.2	-0.6	4.5	1.9	C21 H36 N O



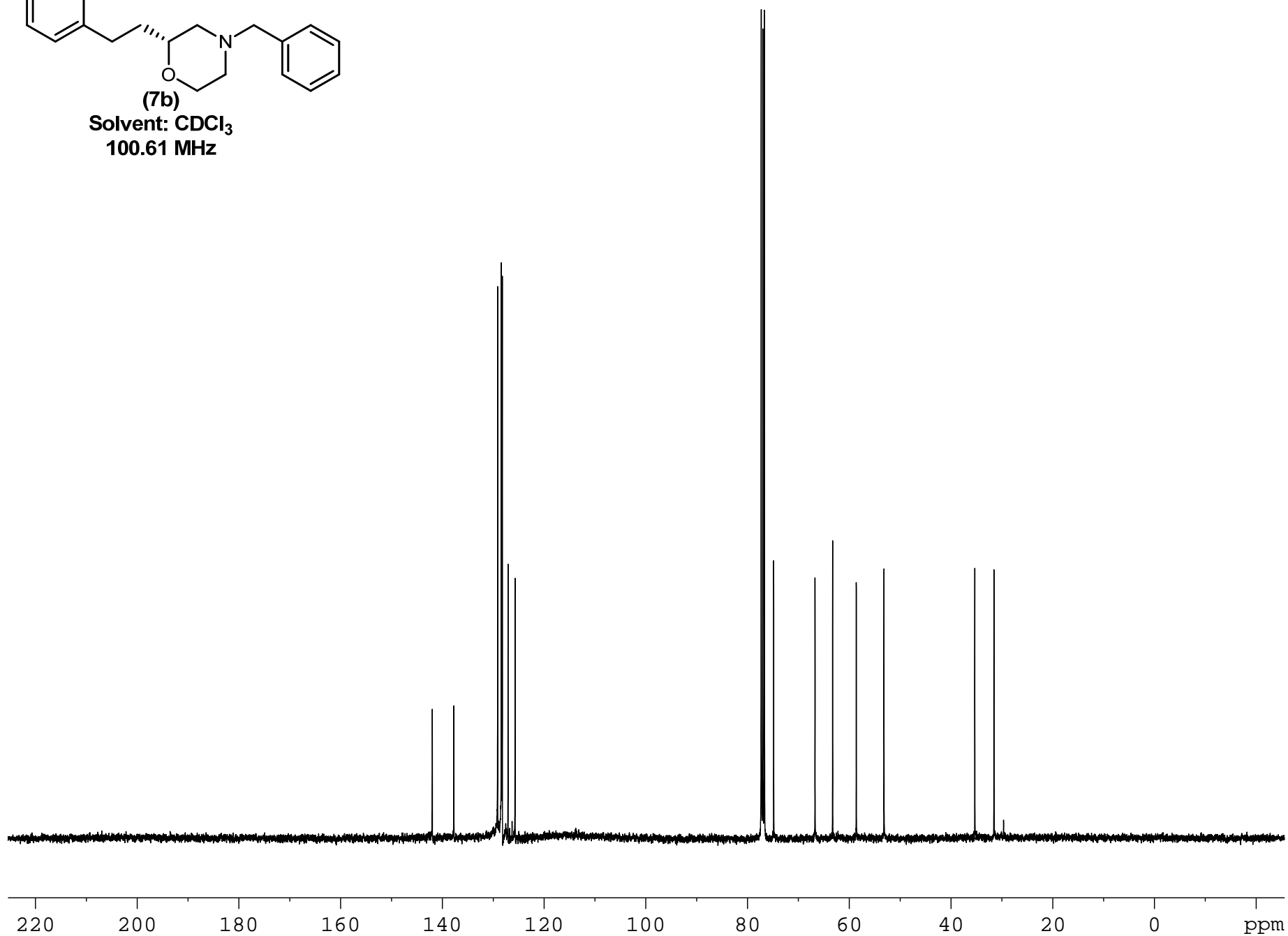
(7b)

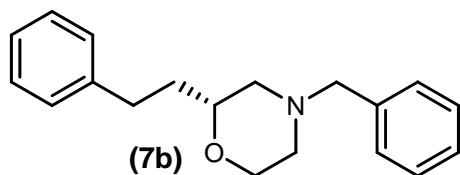
Solvent: CDCl<sub>3</sub>  
400.13 MHz





Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

159 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

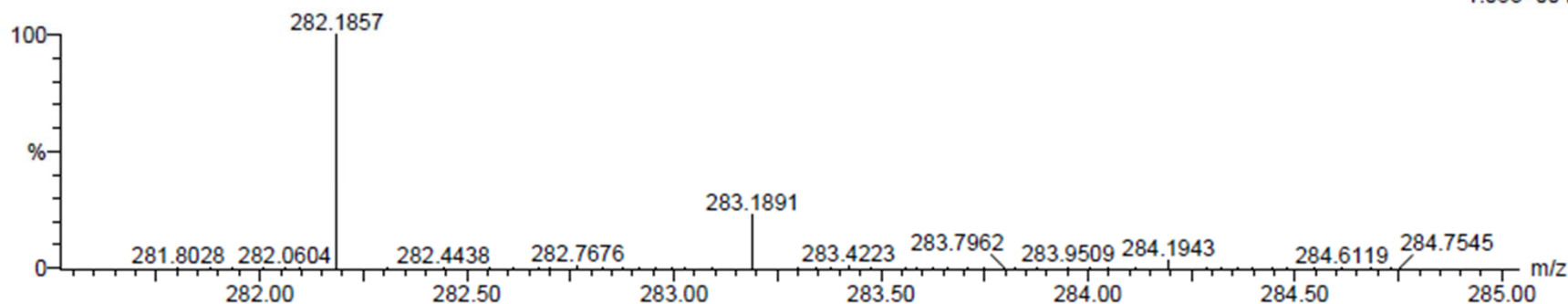
C: 18-500 H: 10-1000 N: 1-200 O: 1-200

**MCO-III-97**

S/N: UH193

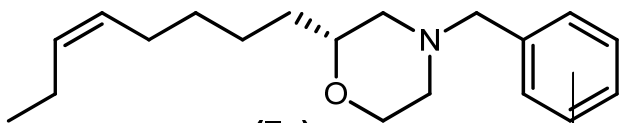
MCO-III-97\_030112\_001 90 (1.700) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

01-Mar-2012  
13:24:57  
TOF MS ES+  
1.08e+004

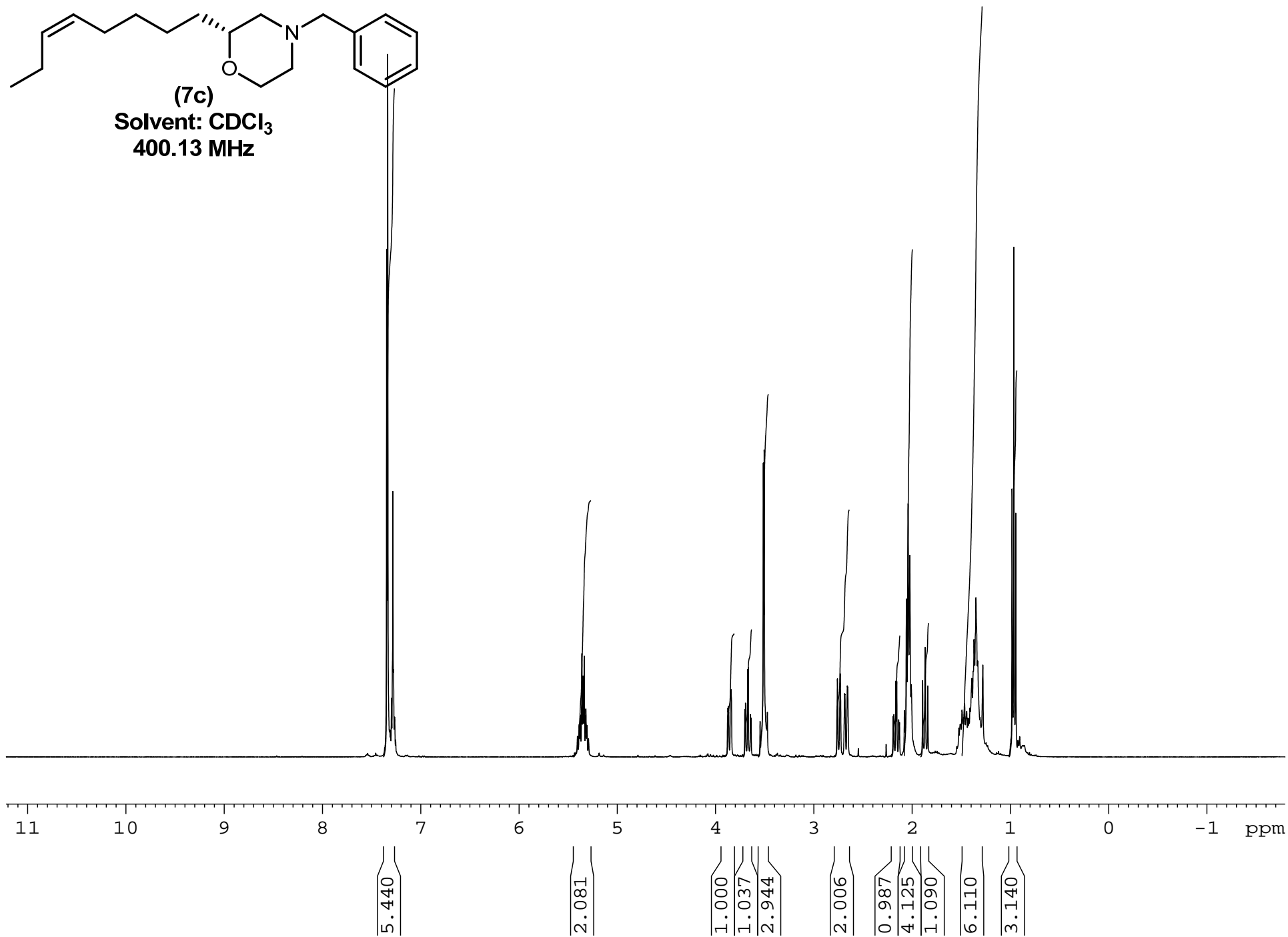


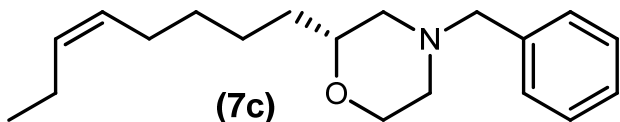
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
<b>282.1857</b>	<b>282.1858</b>	<b>-0.1</b>	<b>-0.4</b>	<b>8.5</b>	<b>1.0</b>	<b>C19 H24 N O</b>



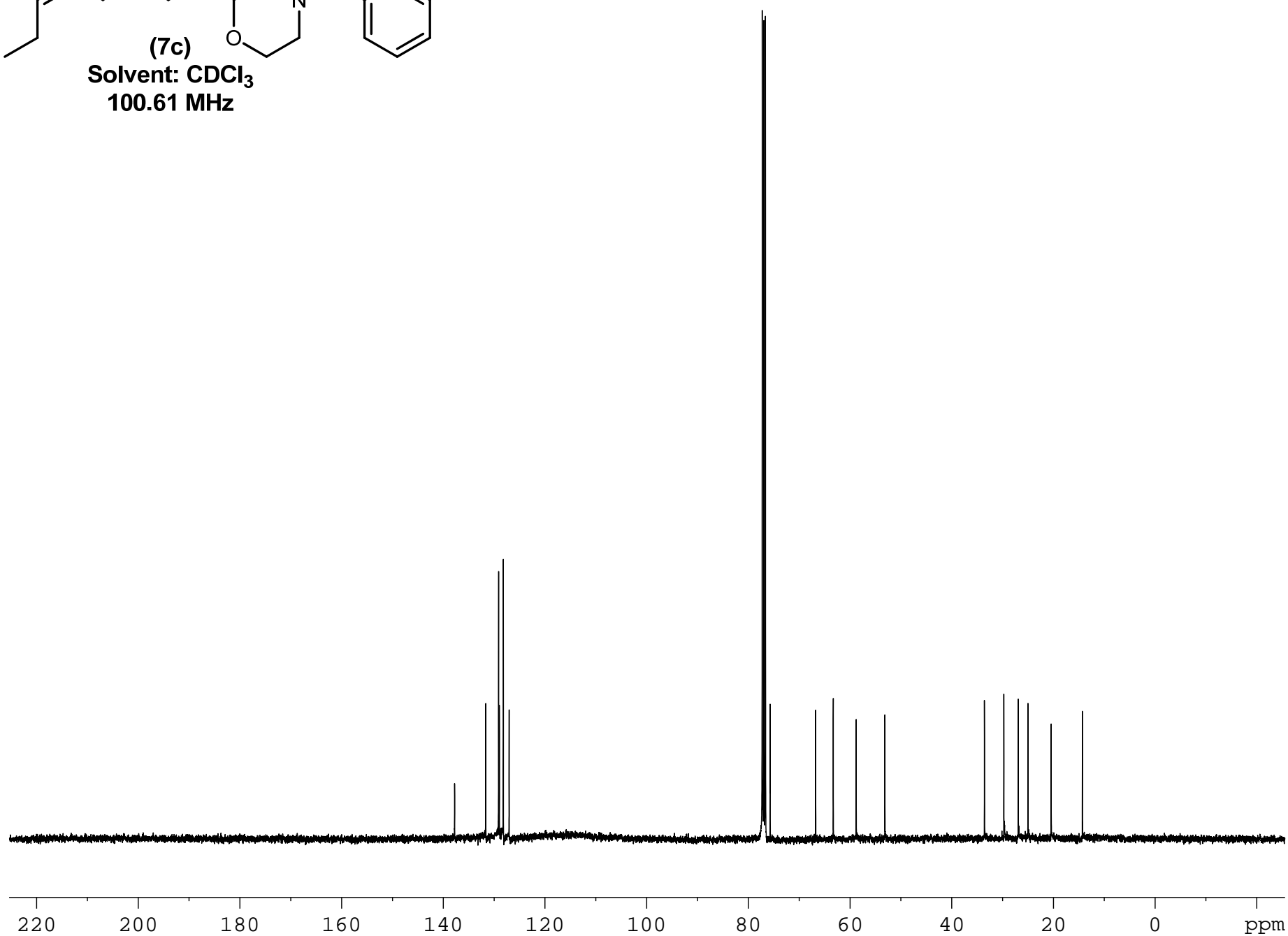
(7c)  
Solvent: CDCl<sub>3</sub>  
400.13 MHz

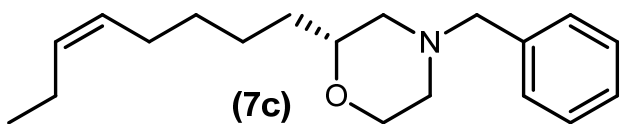




(7c)

Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

168 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

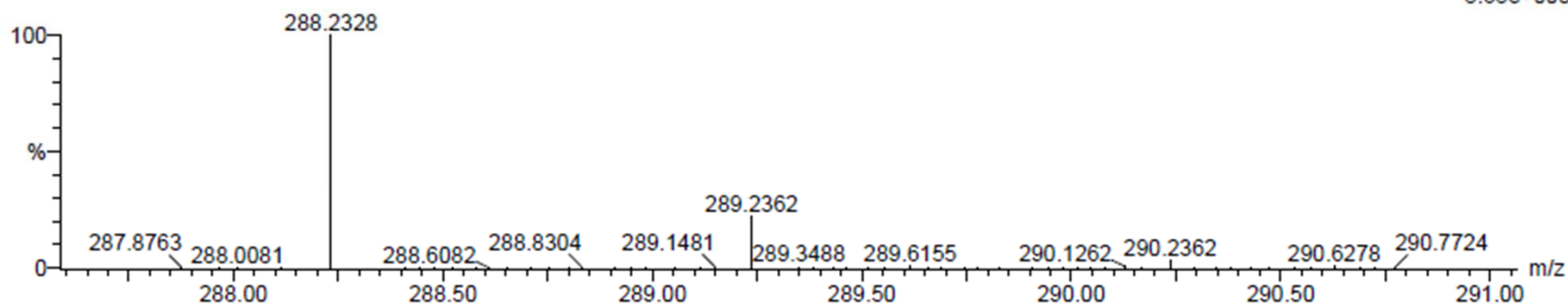
C: 18-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-175

S/N: UH193

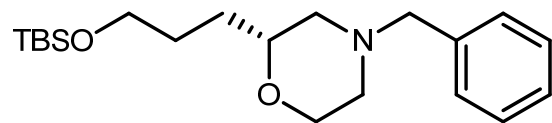
MCO-III-175\_030112\_001 55 (1.041) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (50:60)

01-Mar-2012  
14:31:08  
TOF MS ES+  
8.68e+003



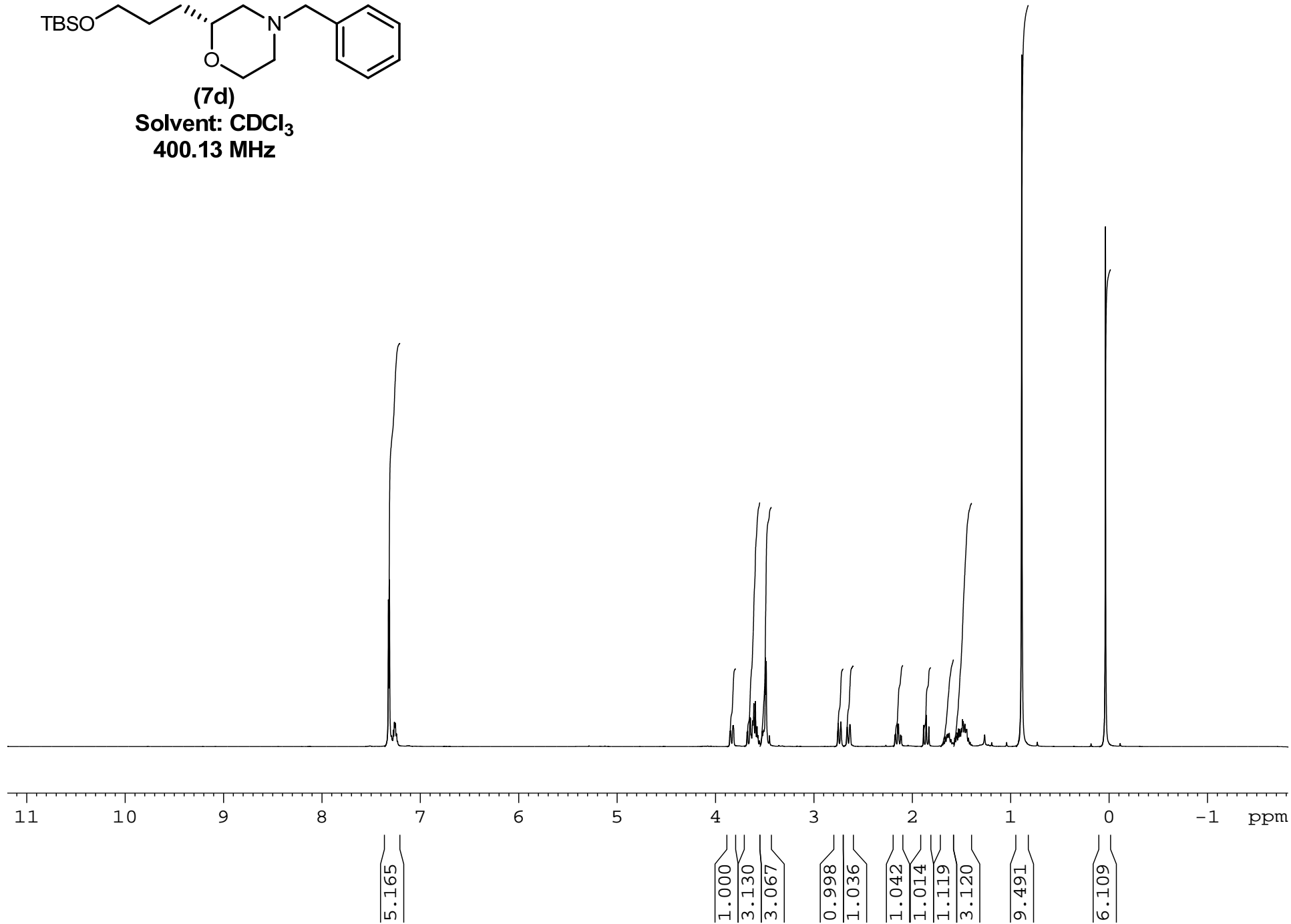
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

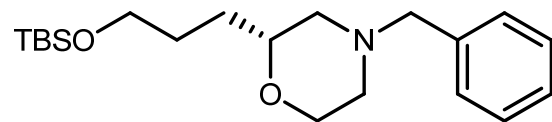
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
288.2328	288.2327	0.1	0.3	5.5	0.1	C19 H30 N O



(7d)

Solvent: CDCl<sub>3</sub>  
400.13 MHz

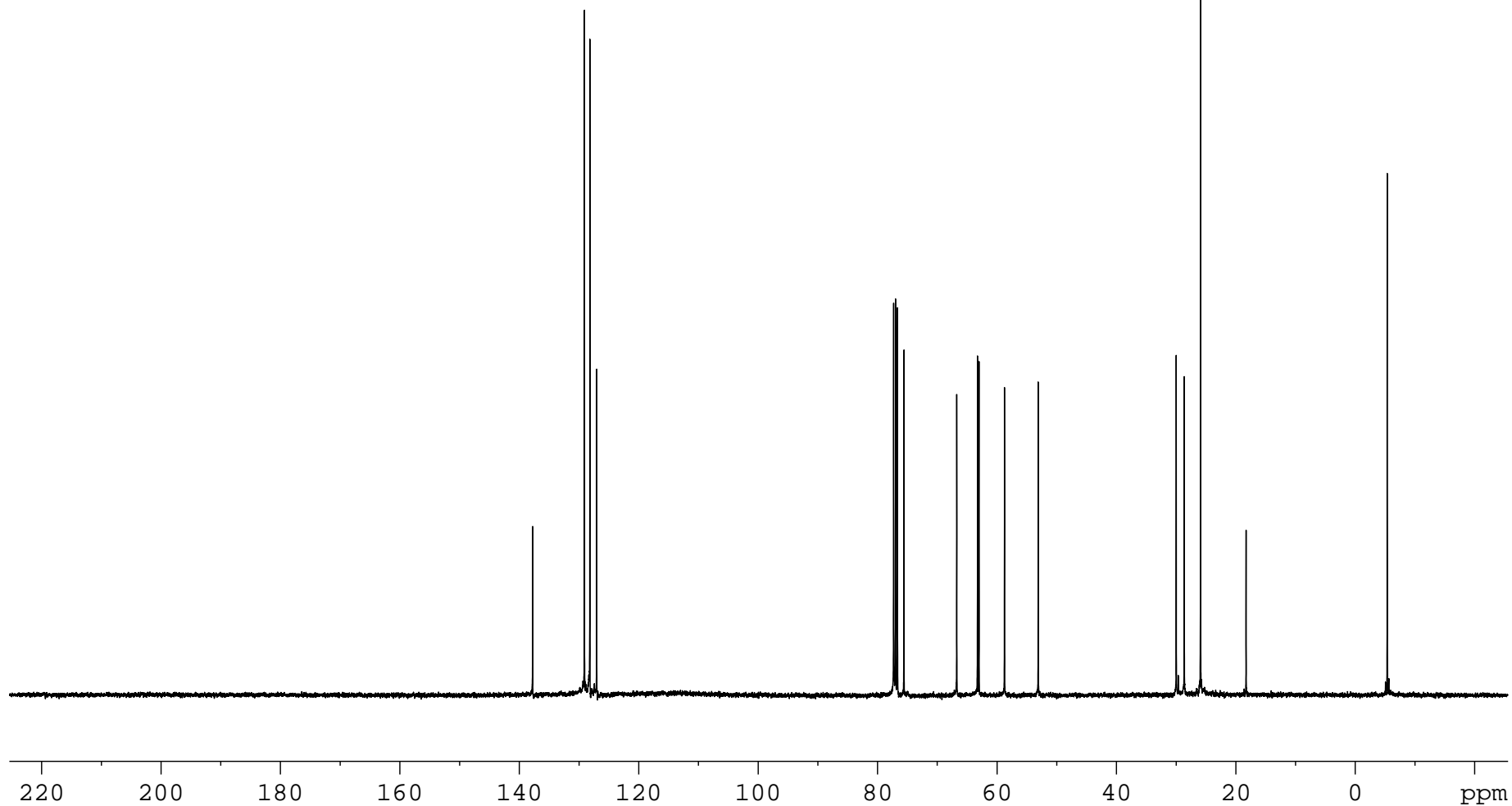


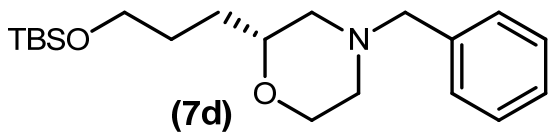


(7d)

Solvent: CDCl<sub>3</sub>

100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

227 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

C: 18-500 H: 10-1000 N: 1-200 O: 1-200 Si: 1-1

MCO-III-160

S/N: UH193

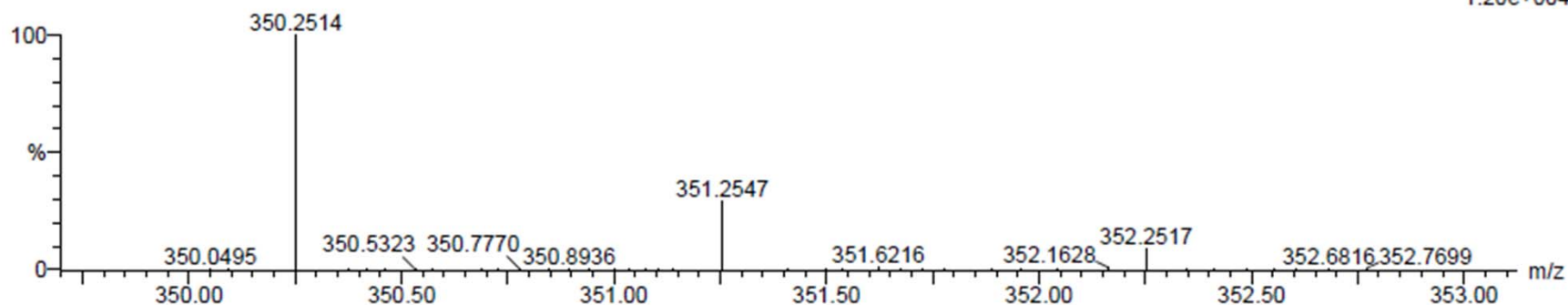
01-Mar-2012

13:53:12

MCO-III-160\_030112\_001 99 (1.869) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (90:100)

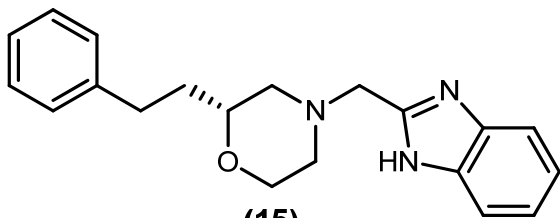
TOF MS ES+

1.20e+004



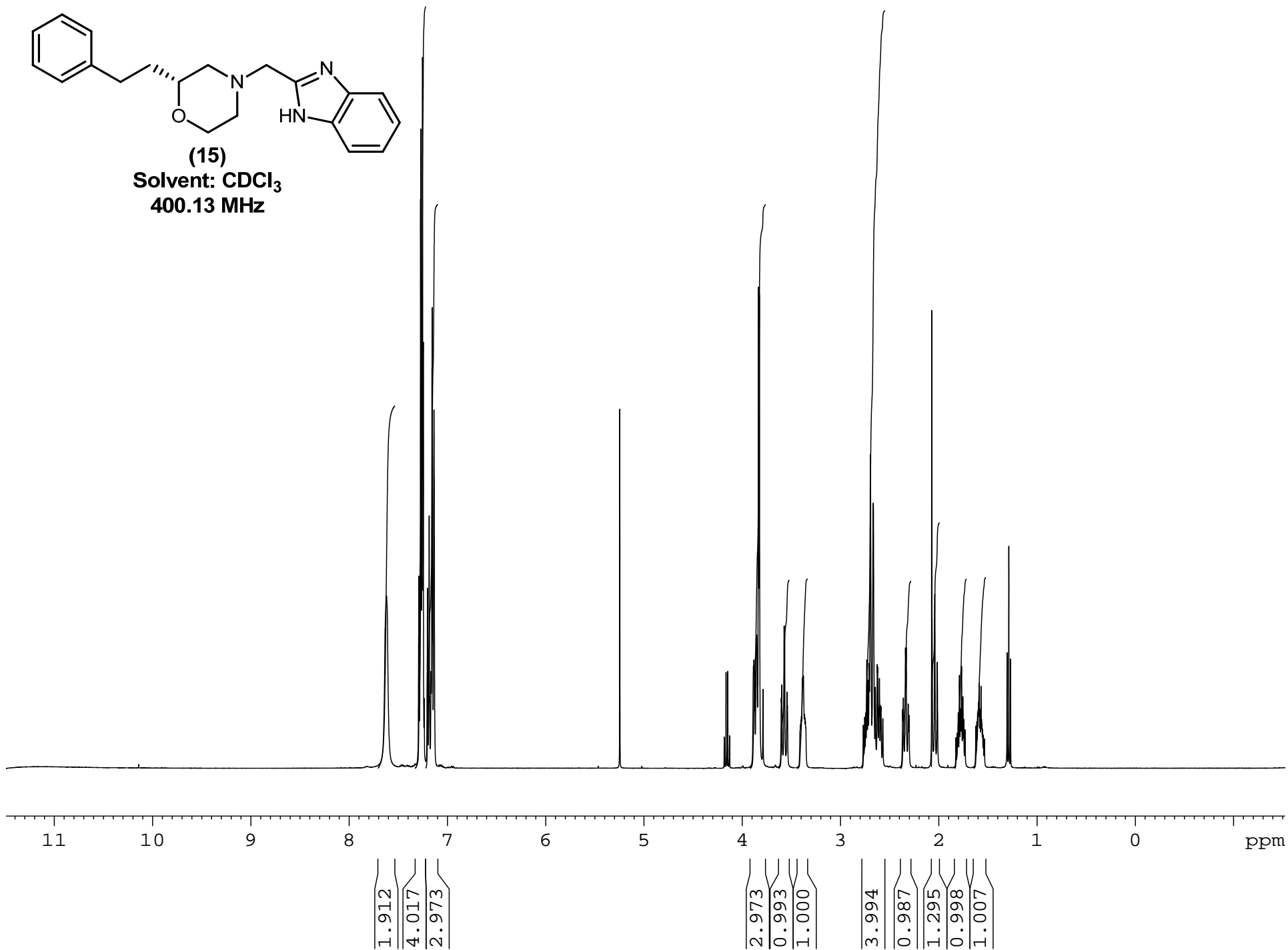
Minimum: -0.5  
Maximum: 10.0 5.0 25.0

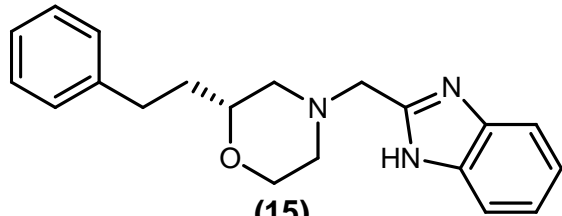
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
350.2514	350.2515	-0.1	-0.3	4.5	0.3	C20 H36 N O2 Si



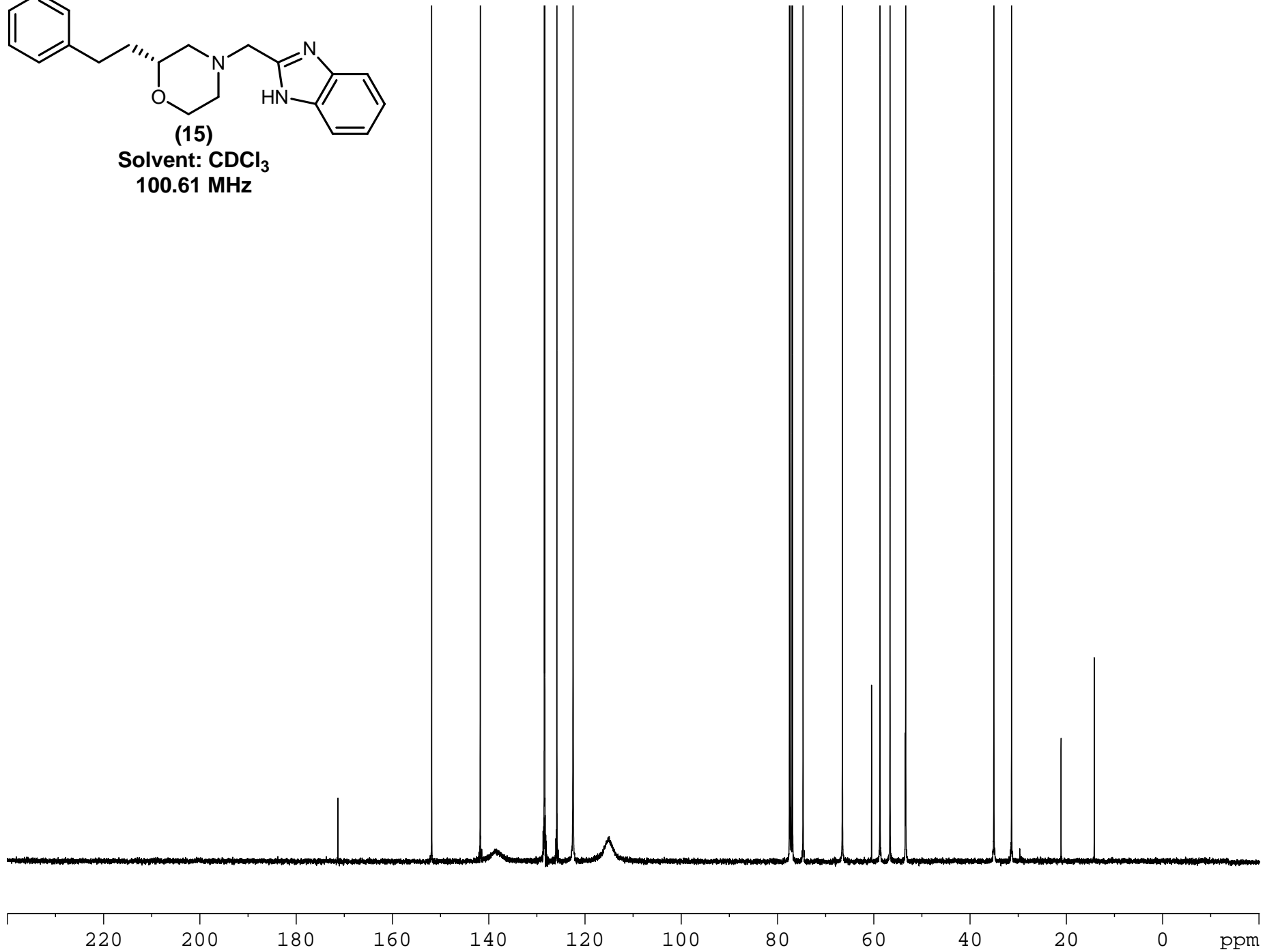
(15)

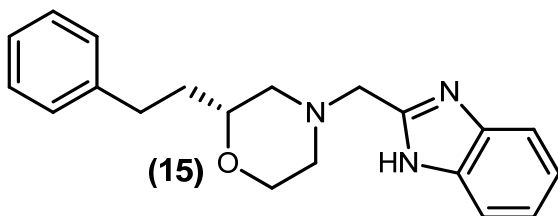
Solvent: CDCl<sub>3</sub>  
400.13 MHz





(15)  
Solvent: CDCl<sub>3</sub>  
100.61 MHz





## Elemental Composition Report

Page 1

### Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -0.5, max = 25.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 2

Monoisotopic Mass, Even Electron Ions

215 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)

Elements Used:

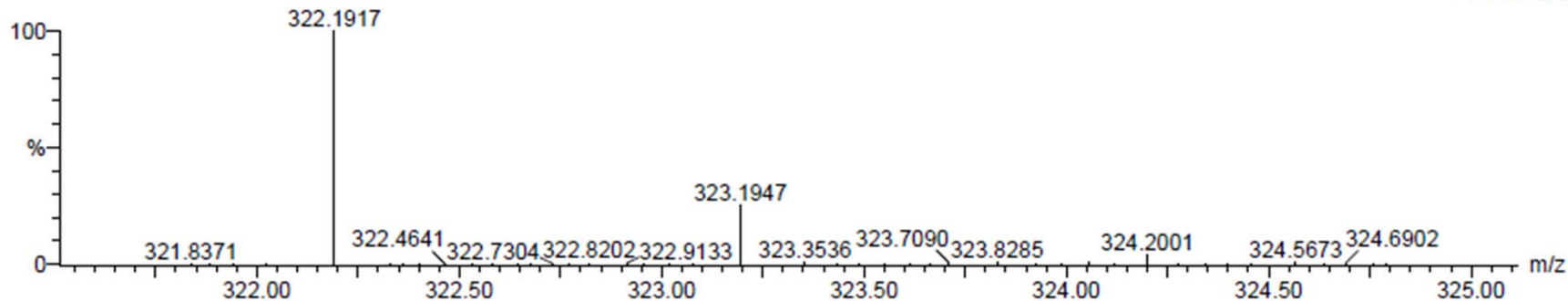
C: 20-500 H: 10-1000 N: 1-200 O: 1-200

MCO-III-157

S/N: UH193

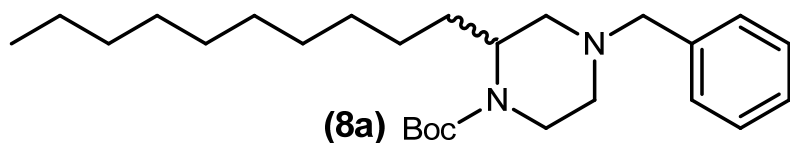
MCO-III-157\_030512\_001 70 (1.324) AM (Cen,4, 80.00, Ar,8000.0,556.28,0.70); Sm (SG, 2x1.00); Cm (60:70)

05-Mar-2012  
11:03:16  
TOF MS ES+  
8.64e+003

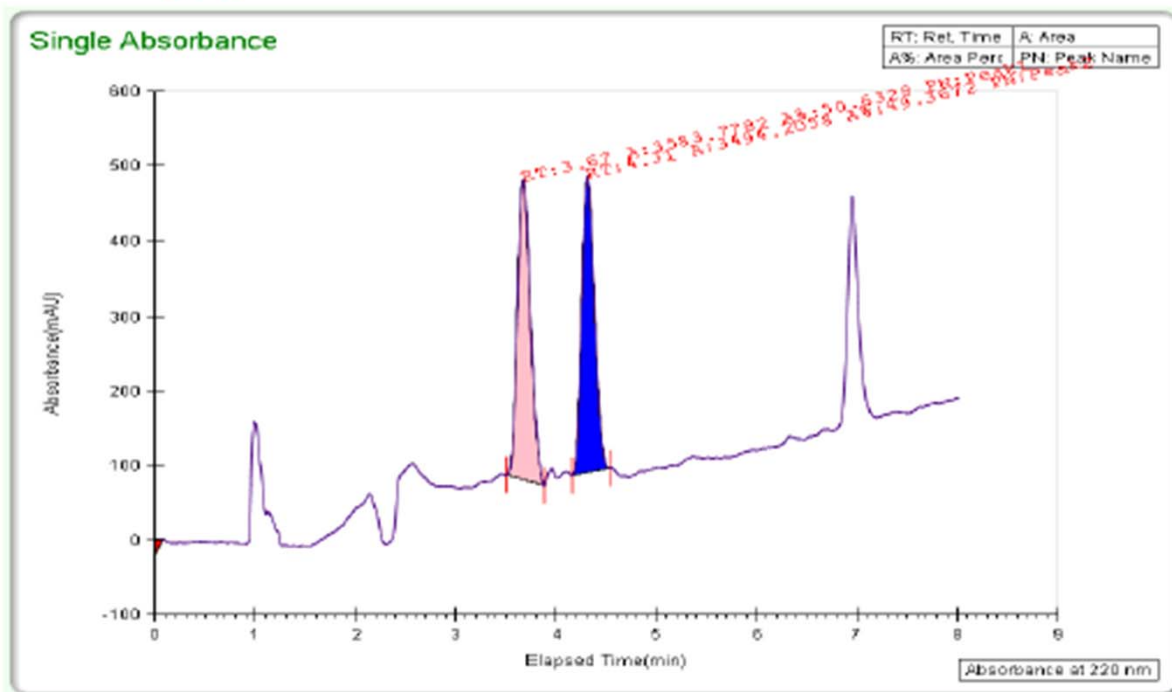


Minimum: -0.5  
Maximum: 10.0 5.0 25.0

Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Formula
322.1917	322.1919	-0.2	-0.6	10.5	2.1	C20 H24 N3 O



**TharSFC**



**General Info**

Log Author  
 Log Date 7/28/2011 10:01:41 AM  
 Report By current\_User  
 Report Date 7/28/2011  
 Method Name 5\_50\_gradient.net

**Notes**

**Injection Info**

Inj Vol 10  
 Solvent MeOH 0.1% DEA  
 Column Lux Cellulose-4  
 Sample MCO-II-141 racemic  
 Well location P1: 1A

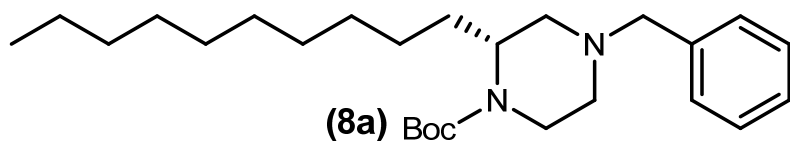
Temp 40.2  
 Flow 3.5  
 % Modifier 5  
 Pressure 101

**Peak Info**

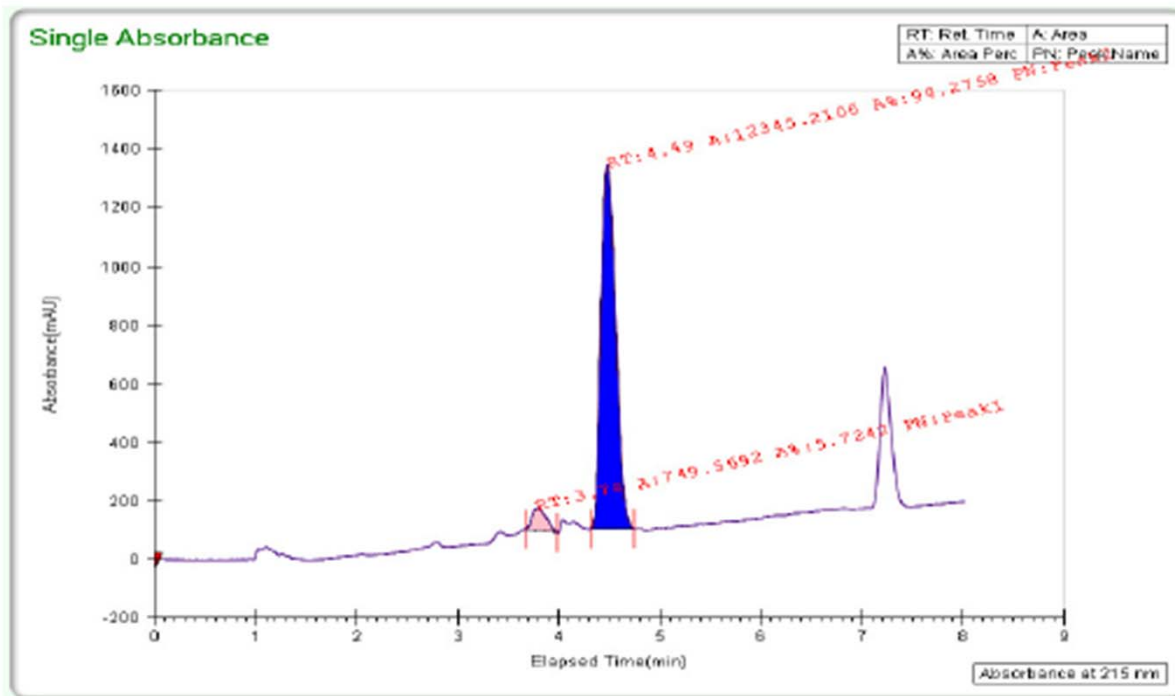
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	50.6328	3583.7782	3.67	400.0073	0.0061
2	49.3672	3494.2058	4.31	395.3763	0.0072
Total:	100	7077.984			

TharSFC

C:\SFC\Data\General\MCO-II-141 racemic\_7-28-2011\_10\_01\_41 AM.tta



TharSFC



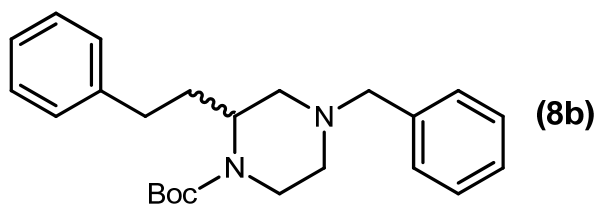
General Info	Report Date	11/2/2011
Log Author	Method Name	5_50_gradient.net
Log Date	11/2/2011 2:53:38 PM	Notes
Report By	current User	

Injection Info	Temp	39.2	
Inj Vol	Flow	3.5	
Solvent	MeOH (0.1% DEA)	% Modifier	5
Column	Lux Cellulose-4	Pressure	99
Sample	MCO-III-67		
Well location	Pl: 1B		

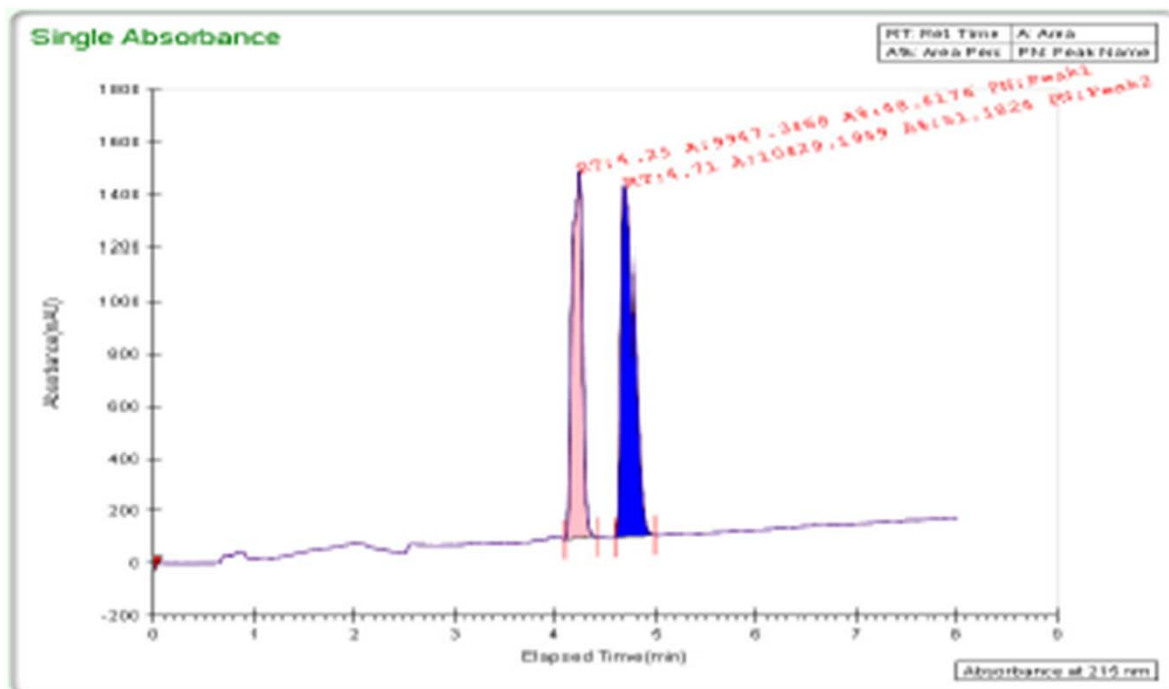
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	5.7242	749.5692	3.78	76.6515	0.0042
2	94.2758	12345.2106	4.49	1239.2579	0.005
Total:	100	13094.7798			

TharSFC

C:\SFC\Data\General\MCO-III-67\_11-2-2011\_2\_53\_38 PM.tta



TharSFC



General Info

Log Author  
 Log Date 11/16/2011 8:48:54 AM  
 Report By current\_User  
 Report Date 11/16/2011  
 Method Name 5\_50\_gradient.met  
 Notes

Injection Info

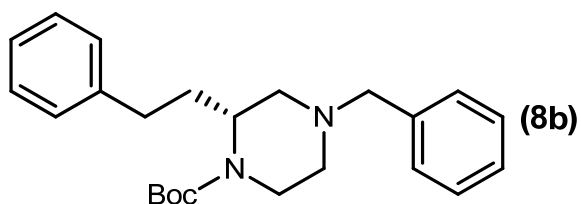
Inj Vol	5	Temp	40.2
Solvent	MeOH (0.1% DEA)	Flow	3.5
Column	CHIRALPAK IA	# Modifier	5
Sample	NCO-III-44	Pressure	100
Well location	PI: 4A		

Peak Info

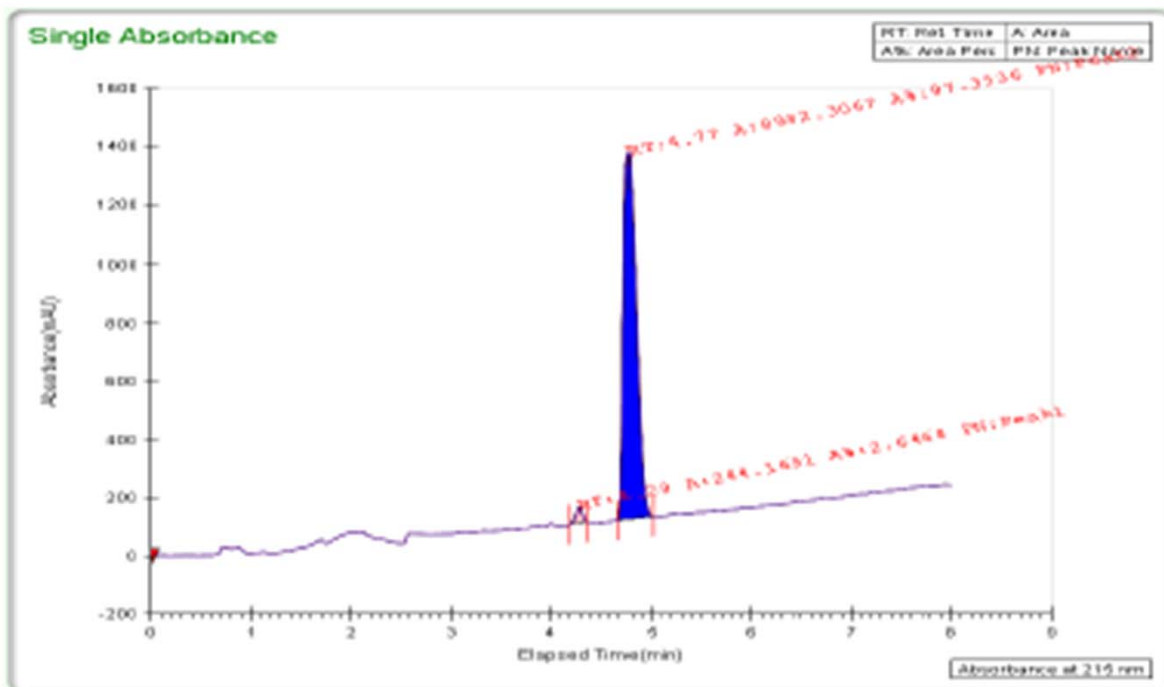
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	48.8176	9947.3468	4.25	1392.1597	0.008
2	51.1824	10429.1959	4.71	1333.5602	0.0089
Total:	100	20376.5427			

TharSFC

C:\SFC\Data\General\NCO-III-44\_11-16-2011\_8\_48\_54 AM.tta



TharSFC



General Info

Log Author  
 Log Date 11/16/2011 8:59:14 AM  
 Report By current\_User  
 Report Date 11/16/2011  
 Method Name 5\_50\_gradient.met  
 Notes

Injection Info

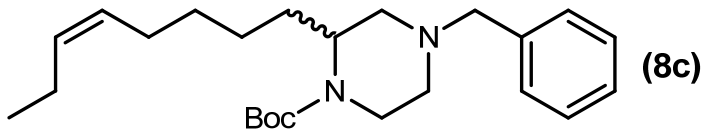
Inj Vol	5	Temp	39.8
Solvent	MeOH (0.1% DRA)	Flow	3.5
Column	CHIRALPAK IA	% Modifier	5
Sample	MCO-III-82	Pressure	100
Well location	P1: 4B		

Peak Info

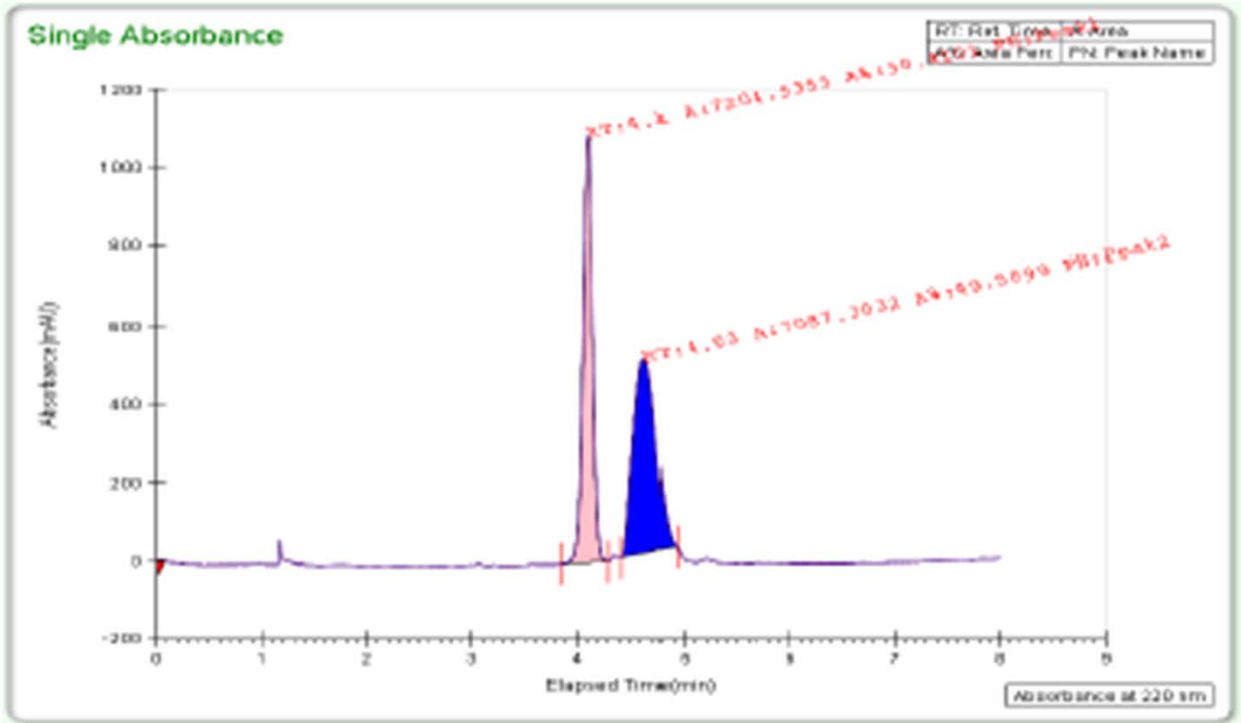
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	2.6464	244.1691	4.29	56.7093	0.008
2	97.3536	8982.3067	4.77	1251.4887	0.0089
Total:	100	9226.4758			

TharSFC

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TharSFC



General Info

Log Author  
 Log Date 12/14/2011 2:44:59 PM  
 Report By current\_User  
 Report Date 12/14/2011  
 Method Name 5\_50\_gradient.met  
 Notes

Injection Info

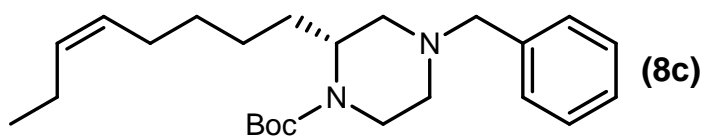
Inj Vol	10	Temp	39.9
Solvent	MeOH (0.1% DRA)	Flow	3.5
Column	CHIRALPAK IC	% Modifier	5
Sample	MCO-II-139	Pressure	100
Well location	P1: 2A		

Peak Info

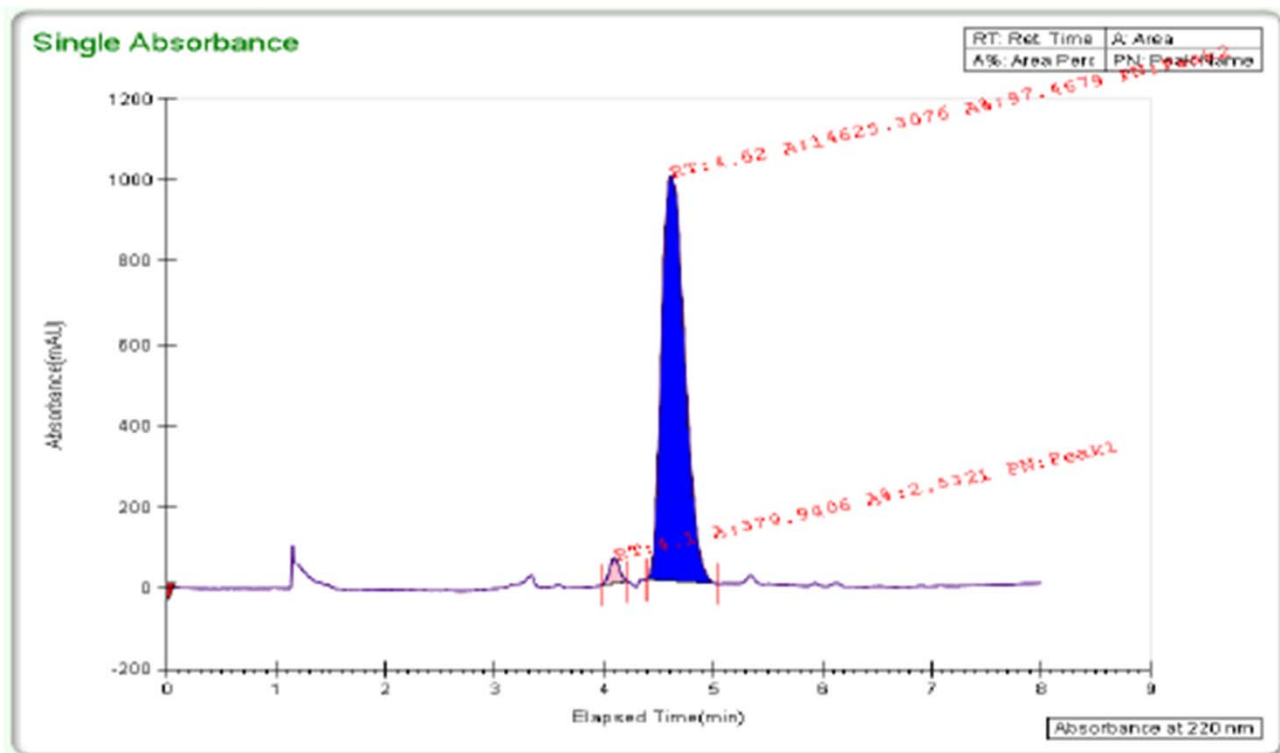
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	50.4101	7204.5355	4.1	1085.3186	0.0046
2	49.5899	7087.3032	4.63	495.944	0.0052
Total:	100	14291.8387			

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TharSFC



General Info

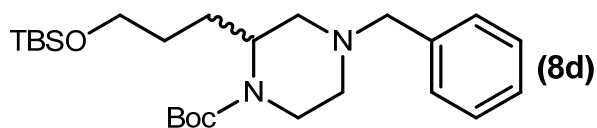
Log Author  
 Log Date 12/14/2011 2:55:19 PM  
 Report By current\_User  
 Report Date 12/14/2011  
 Method Name 5\_50\_gradient.met  
 Notes

Injection Info

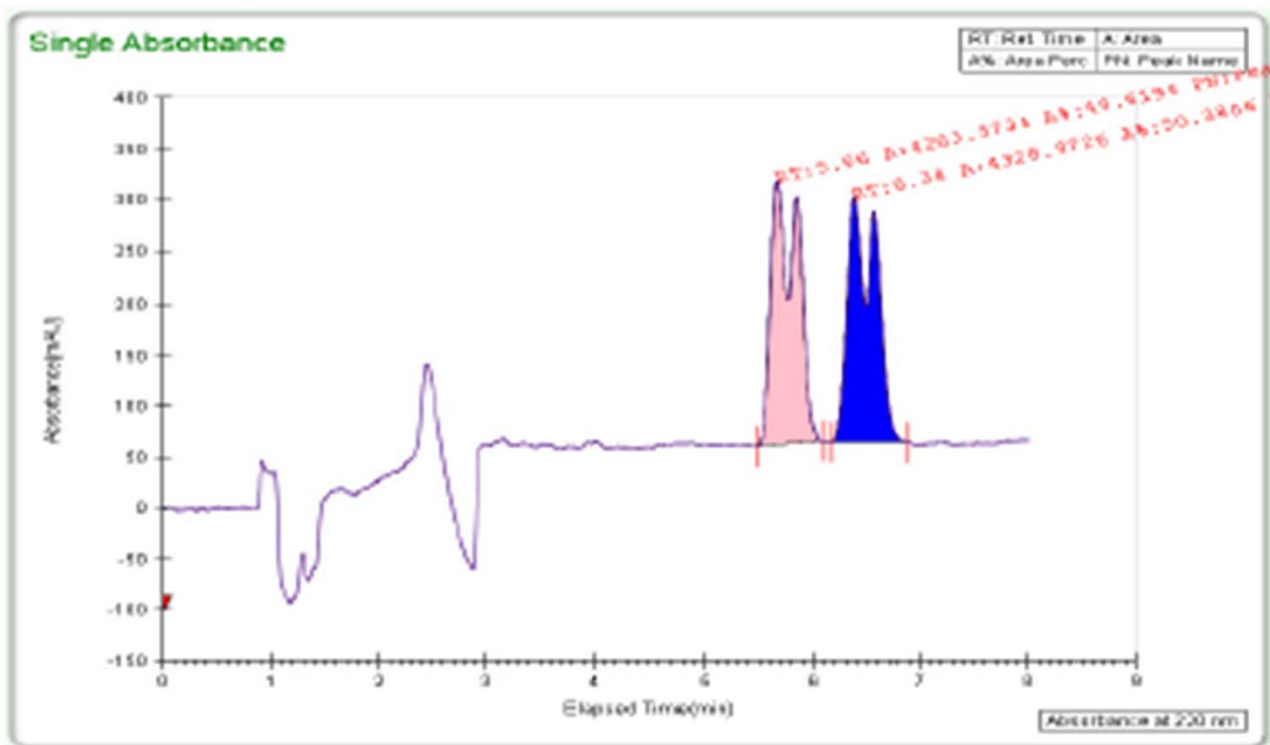
Inj Vol	10	Temp	40.1
Solvent	MeOH (0.1% DEA)	Flow	3.5
Column	CHIRALPAK IC	% Modifier	5
Sample	MCO-III-107	Pressure	100
Well location	P1: 2B		

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	2.5321	379.9406	4.1	65.0481	0.0046
2	97.4679	14625.3076	4.62	994.909	0.0052
Total:	100	15005.2482			



TharSFC



General Info

Log Author  
 Log Date 2/9/2012 11:09:02 AM  
 Report By current\_User  
 Report Date 2/9/2012  
 Method Name 15\_60\_gradient.met  
 Notes

Injection Info

Inj Vol	15	Temp	39.9
Solvent	IPA 0.1% DEA	Flow	3.5
Column	Lux Cellulose-2 (02)	% Modifier	15
Sample	MCO-III-128	Pressure	100
Well location	P1: 4A		

Peak Info

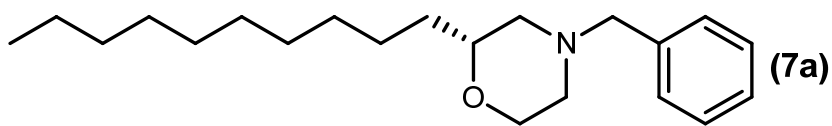
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	49.6194	4263.5734	5.66	256.0257	0.0085
2	50.3806	4328.9726	6.38	237.3683	0.0095
Total:	100	8592.546			

TharSFC

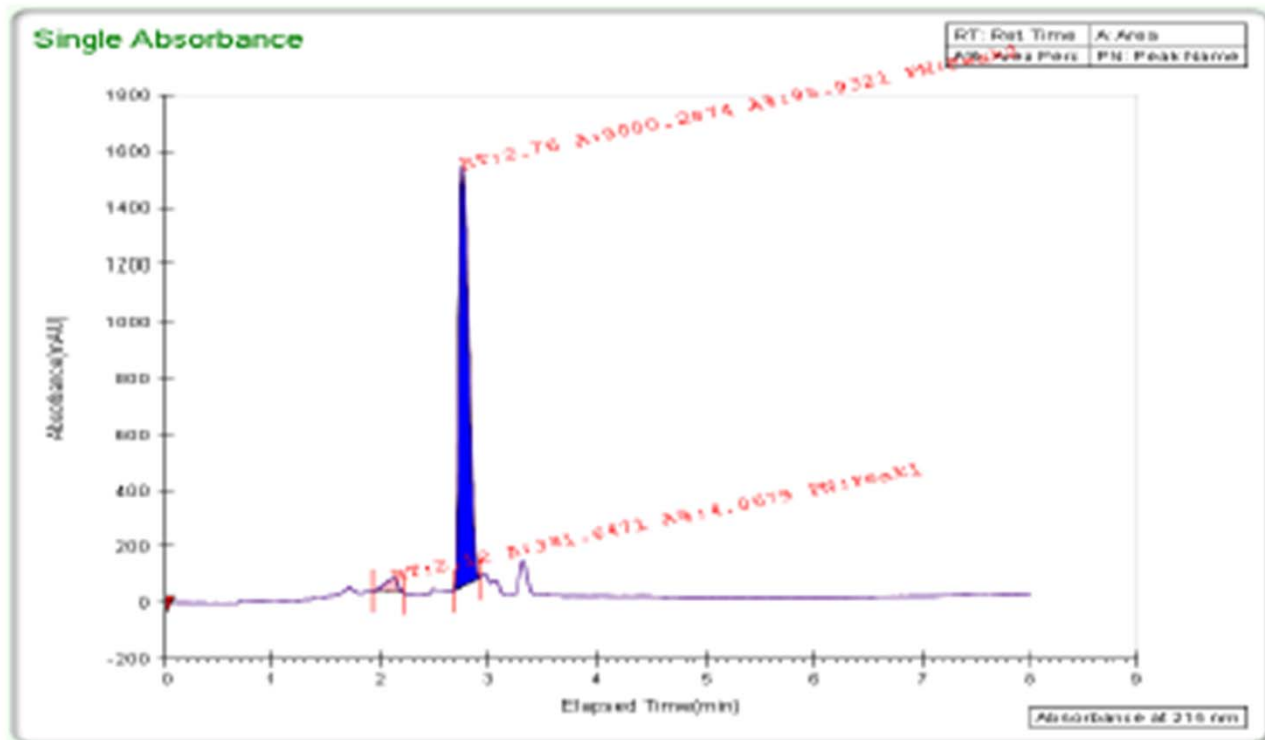
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TharSFC



General Info

Log Author  
 Log Date 11/22/2011 4:33:15 PM  
 Report By current\_User  
 Report Date 11/22/2011  
 Method Name 5\_50\_gradient.met

Notes

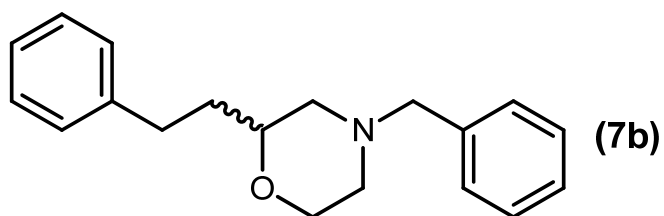
Injection Info	Temp	39.9
Inj Vol	Flow	3.5
Solvent MeOH (0.1% DEA)	# Modifier	5
Column CHIRALPAK IA	Pressure	100
Sample MCO-III-79		
Well location P1: 4B		

Peak Info

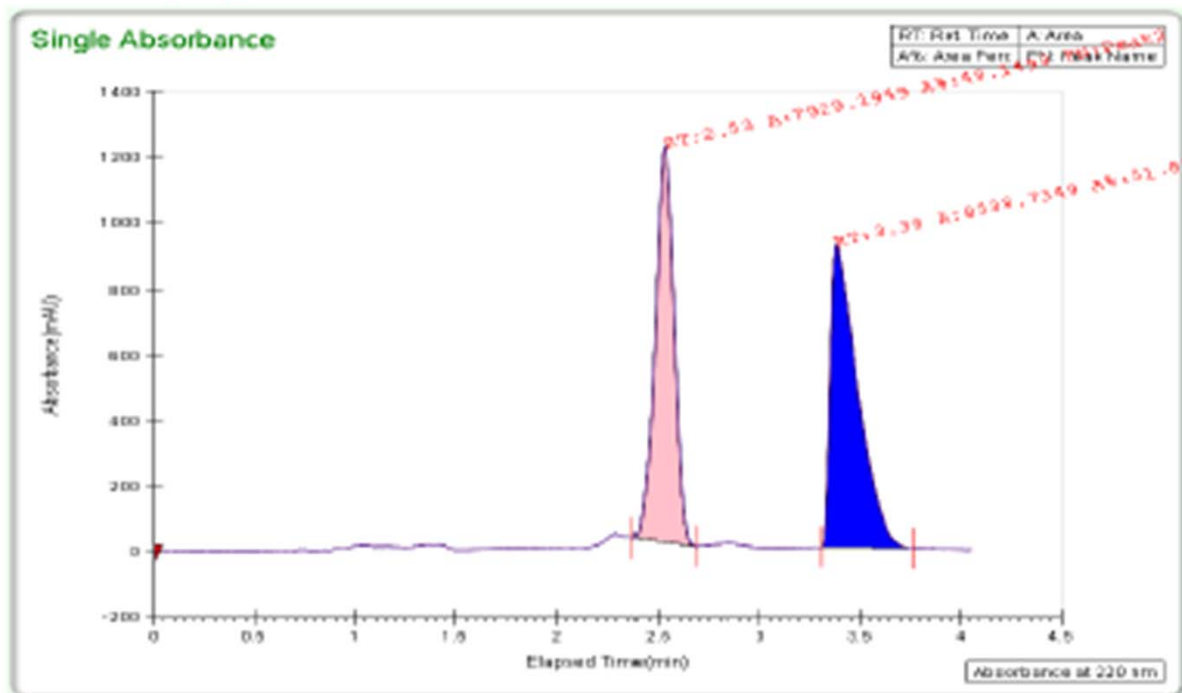
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	4.0679	381.6471	2.12	49.4921	0.0021
2	95.9321	9000.2874	2.76	1486.41	0.0028
Total:	100	9381.9345			

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TharSFC



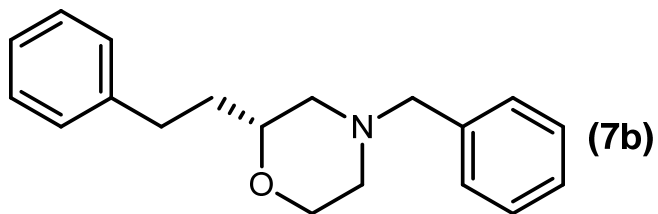
General Info		Report Date	12/14/2011
Log Author		Method Name	ISOCRATIC.met
Log Date	12/14/2011 9:58:49 AM	Notes	
Report By	current_User		

Injection Info		Temp	41.4
Inj Vol	10	Flow	5
Solvent	MeOH (0.1% DEA)	% Modifier	10
Column	CHIRALPAK IB	Pressure	100
Sample	MCO-III-97		
Well location	Pl: 4B		

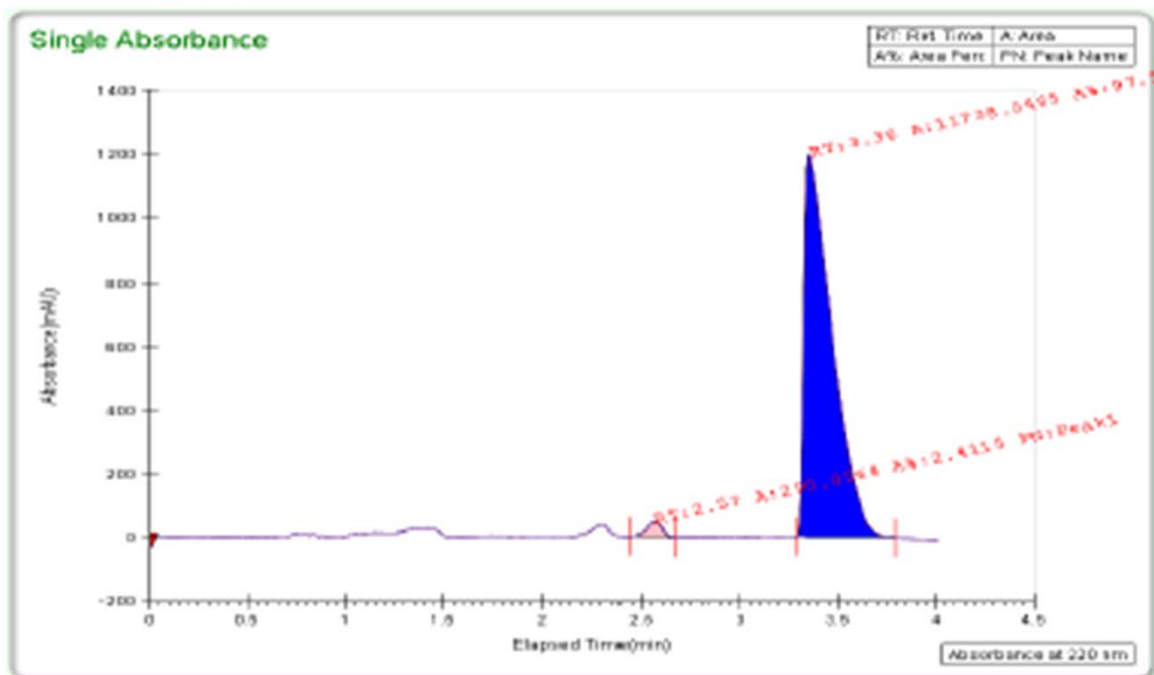
Peak Info					
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	48.1493	7929.1949	2.53	1203.0953	0.0042
2	51.8507	8538.7349	3.39	918.2954	0.0056
Total:	100	16467.9298			

TharSFC

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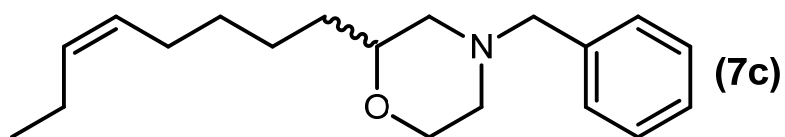
TharSFC



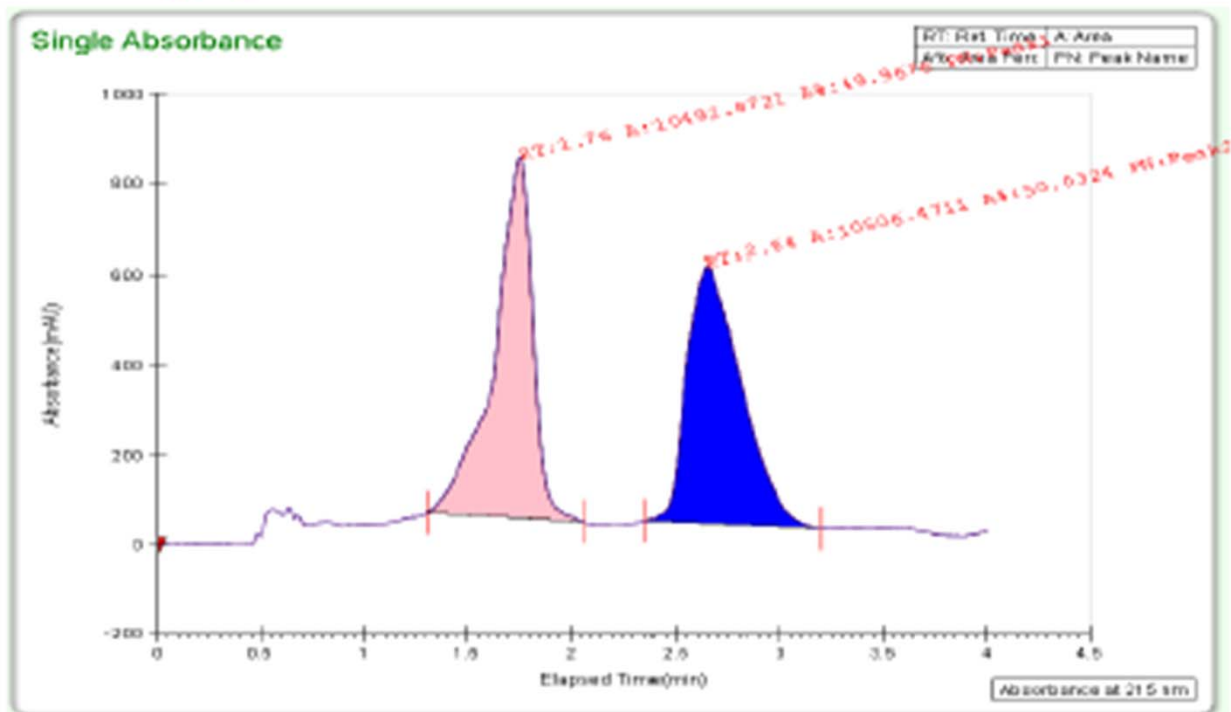
General Info		Report Date	12/14/2011		
Log Author		Method Name	ISOCRATIC.net		
Log Date	12/14/2011 10:04:37 AM	Notes			
Report By	current_User				
Injection Info		Temp	42.3		
Inj Vol	10	Flow	5		
Solvent	MeOH (0.1% DEA)	% Modifier	10		
Column	CHIRALPAK ID	Pressure	100		
Sample	MCO-III-91				
Well location	P1: 5A				
Peak Info					
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	2.4115	290.0564	2.57	50.6099	0.0042
2	97.5885	11738.0485	3.36	1195.4413	0.0055
Total:	100	12028.1049			

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TharSFC



General Info

Log Author  
 Log Date 12/14/2011 12:26:24 PM  
 Report By current\_User

Report Date 12/14/2011  
 Method Name ISOCRATIC.net  
 Notes

Injection Info

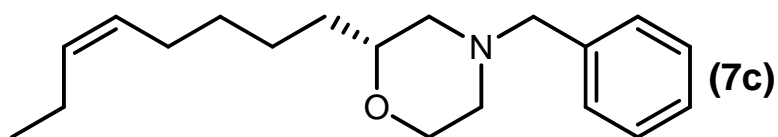
Inj Vol 10  
 Solvent MeOH (0.1% DRA)  
 Column CHIRALPAK IA (4.6 x 150 mm)  
 Sample MCO-II-70  
 Well location P1: 1A  
 Temp 39.8  
 Flow 5  
 # Modifier 5  
 Pressure 100

Peak Info

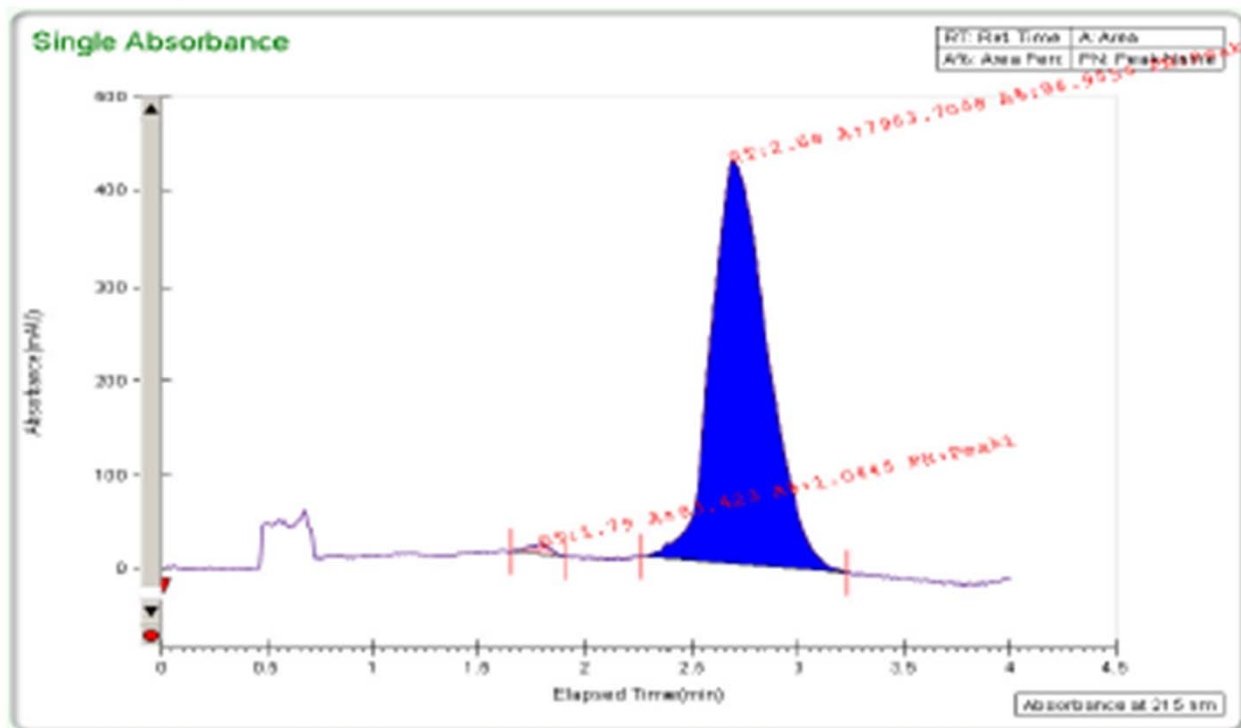
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	49.9676	10492.8721	1.76	801.4662	0.0024
2	50.0324	10506.4711	2.64	575.1337	0.0035
Total:	100	20999.3432			

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TharSFC



<b>General Info</b>	<b>Report Date</b> 12/14/2011
Log Author	<b>Method Name</b> ISOCRATIC.met
<b>Log Date</b> 12/14/2011 12:21:19 PM	<b>Notes</b>
<b>Report By</b> current_User	

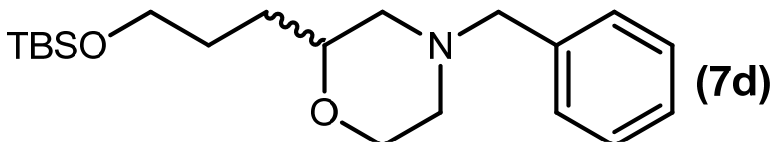
**Injection Info**

Inj Vol 15  
 Solvent MeOH (0.1% DEA)  
 Column CHIRALPAK IA (4.6 x 150 mm)  
 Sample MCO-III-104  
 Well location P1: 1B  
 Temp 40  
 Flow 5  
 # Modifier 5  
 Pressure 101

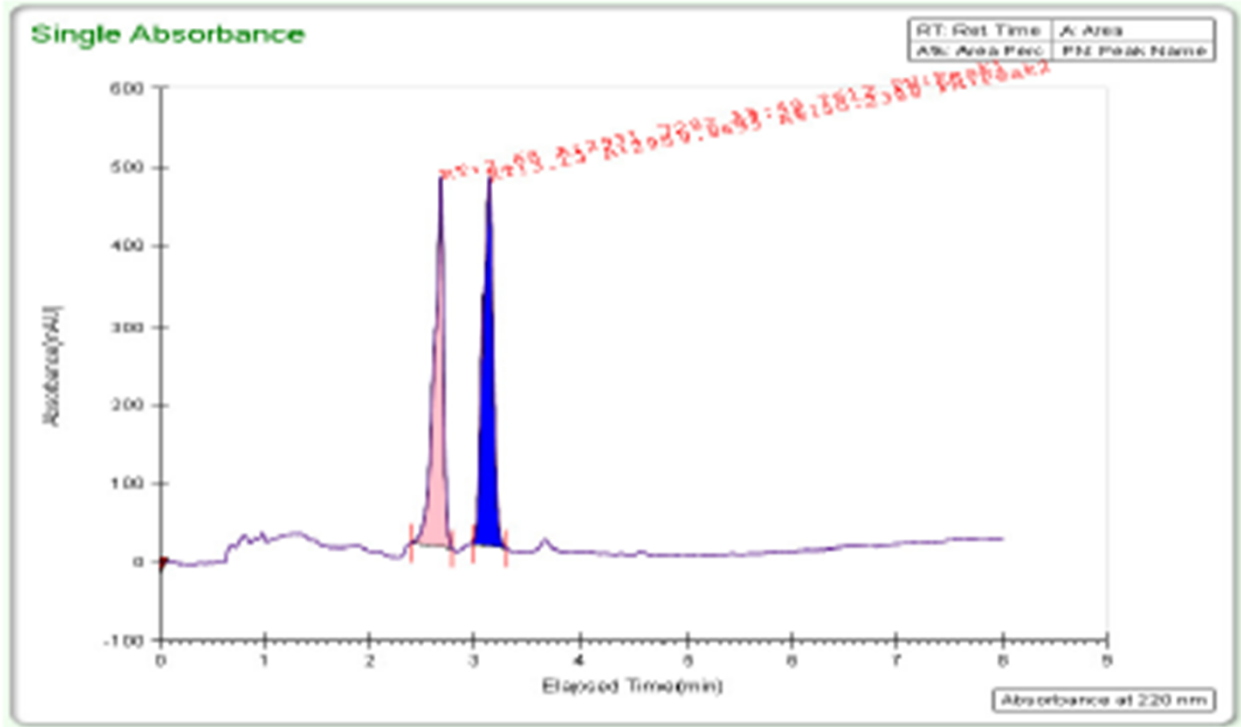
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	1.0445	83.423	1.79	10.9276	0.0024
2	98.9555	7903.7008	2.68	425.9888	0.0036
Total:	100	7987.1238			

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TharSFC



<b>General Info</b>	<b>Report Date</b> 2/10/2012
Log Author	<b>Method Name</b> 5_50_gradient.met
Log Date 2/9/2012 11:46:30 AM	<b>Notes</b>
Report By current_User	

**Injection Info**

Inj Vol 10  
 Solvent MeOH (0.1% DEA)  
 Column CHIRALPAK IA (4.6 x 150 mm)  
 Sample MCO-III-111  
 Well location P1: 1A  
 Temp 40.1  
 Flow 3.5  
 # Modifier 5  
 Pressure 100

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	49.7612	2931.7282	2.68	467.3516	0.0038
2	50.2388	2959.8695	3.13	465.0256	0.0044
Total:	100	5891.5977			

TharSFC

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## Data Report for Pharmacology Services

### Vanderbilt University

1205 Light Hall, Vanderbilt Medical Center, Nashville, TN 37232-0697, United States

### Thomas Ekman

615-936-6427

tom.ekman@vanderbilt.edu

**Study Number:** AB12129

**Client Study Number:**

**Quote Number:** 29888-2

**PO Number:**

5012265388

**Study Date:** Apr 10, 2012 - Apr 19, 2012

### Compound Information

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**Compounds:** MCO-III-157-Rac, MCO-III-157-A, MCO-III-157-B

### Ricerca Biosciences, LLC

Pharmacology Laboratories

158 Li-Teh Road, Peitou

Taipei, Taiwan 112

Taiwan R.O.C.

Tel: 425-487-8217 • Fax: 425-487-8211 • e-mail: [pharmacology@ricerca.com](mailto:pharmacology@ricerca.com) • <http://www.ricerca.com>

## Compound Information

Ricerca #	Ricerca Code	Alt. Code 1	Alt. Code 2	Alt. Code 3	Molecular Weight
1160665	VU-206	MCO-III-157-Rac			321.42
1160666	VU-207	MCO-III-157-A			321.42
1160667	VU-208	MCO-III-157-B			321.42

## Services Performed

Individual Tests (Total # of Assays: 5)

## Study Objectives

To evaluate, in Radioligand Binding assays, the activity of test compound(s).

## Study Signatures




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Hua-Chou Hsing  
Study Director for Binding Assays




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Gonzalo Castillo, Ph.D.  
Technical Director

"This study was conducted according to the procedures described in this report. All data presented are authentic, accurate and correct to the best of our knowledge."

## Table of Contents

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## Summary

### STUDY OBJECTIVE

To evaluate, in Radioligand Binding assays, the activity of the test compound(s) MCO-III-157-Rac (VU-206, PT# 1160665), MCO-III-157-A (VU-207, PT# 1160666), MCO-III-157-B (VU-208, PT# 1160667).

### METHODS

Methods employed in this study have been adapted from the scientific literature to maximize reliability and reproducibility. Reference standards were run as an integral part of each assay to ensure the validity of the results obtained. Assays were performed under conditions described in the accompanying "Methods" section of this report.

Where presented,  $IC_{50}$  values were determined by a non-linear, least squares regression analysis using MathIQ™ (ID Business Solutions Ltd., UK). Where inhibition constants ( $K_i$ ) are presented, the  $K_i$  values were calculated using the equation of Cheng and Prusoff (Cheng, Y., Prusoff, W.H., *Biochem. Pharmacol.* 22:3099-3108, 1973) using the observed  $IC_{50}$  of the tested compound, the concentration of radioligand employed in the assay, and the historical values for the  $K_D$  of the ligand (obtained experimentally at **Ricerca Biosciences, LLC**). Where presented, the Hill coefficient ( $n_H$ ), defining the slope of the competitive binding curve, was calculated using MathIQ™. Hill coefficients significantly different than 1.0, may suggest that the binding displacement does not follow the laws of mass action with a single binding site. Where  $IC_{50}$ ,  $K_i$ , and/or  $n_H$  data are presented without Standard Error of the Mean (SEM), data are insufficient to be quantitative, and the values presented ( $K_i$ ,  $IC_{50}$ ,  $n_H$ ) should be interpreted with caution.

### RESULTS

A summary of results meeting the significance criteria is presented in the following sections. Complete results are presented under the section labeled "Experimental Results". Individual responses, if requested, are presented under the section labeled "Individual Responses".

### SUMMARY/CONCLUSION

Significant results are displayed in the following table(s) in rank order of potency for estimated  $IC_{50}$  and/or  $K_i$  values.

## Summary of Significant Results

Biochemical assay results are presented as the percent inhibition of specific binding or activity throughout the report. All other results are expressed in terms of that assay's quantitation method.

- For primary assays, only the lowest concentration with a significant response judged by the assays' criteria, is shown in this summary.
- Where applicable, either the secondary assay results with the lowest dose/concentration meeting the significance criteria or, if inactive, the highest dose/concentration that did not meet the significance criteria is shown.
- Unless otherwise requested, primary screening in duplicate with quantitative data (e.g.,  $IC_{50} \pm SEM$ ,  $K_i \pm SEM$  and  $n_H$ ) are shown where applicable for individual requested assays. In screening packages, primary screening in duplicate with semi-quantitative data (e.g., estimated  $IC_{50}$ ,  $K_i$  and  $n_H$ ) are shown where applicable (concentration range of 4 log units); available secondary functional assays are carried out (30 mM) and MEC or MIC determined only if active in primary assays >50% at 1 log unit below initial test concentration.

Significant responses ( $\geq 50\%$  inhibition or stimulation for Biochemical assays) were noted in the primary assays listed below:

Cat #	Assay Name	Species	Conc.	% Inh.	$IC_{50}^*$	$K_i$	$n_H$
<b>Compound: MCO-III-157-A, PT #: 1160666</b>							
219800	Dopamine D <sub>3</sub>	hum	100 $\mu$ M	74	46.2 $\mu$ M	15.7 $\mu$ M	1.23
219900	Dopamine D <sub>4.2</sub>	hum	0.3 $\mu$ M	66	0.18 $\mu$ M	0.071 $\mu$ M	0.94
<b>Compound: MCO-III-157-B, PT #: 1160667</b>							
219800	Dopamine D <sub>3</sub>	hum	100 $\mu$ M	55	76.4 $\mu$ M	25.9 $\mu$ M	1.04
<b>Compound: MCO-III-157-Rac, PT #: 1160665</b>							
219800	Dopamine D <sub>3</sub>	hum	30 $\mu$ M	51	31.8 $\mu$ M	10.8 $\mu$ M	1.01
219900	Dopamine D <sub>4.2</sub>	hum	1 $\mu$ M	69	0.36 $\mu$ M	0.14 $\mu$ M	0.94

\* A standard error of the mean is presented where results are based on multiple, independent determinations.  
hum=Human

## Summary of Significant Results

*Above Primary Tests in Rank Order of Potency*

Compound Name	Species	Conc.	% Inh.	IC <sub>50</sub> *	K <sub>i</sub>	n <sub>H</sub>
<b>219800 Dopamine D<sub>3</sub></b>						
MCO-III-157-Rac (1160665)	hum	30 µM	51	31.8 µM	10.8 µM	1.01
MCO-III-157-A (1160666)	hum	100 µM	74	46.2 µM	15.7 µM	1.23
MCO-III-157-B (1160667)	hum	100 µM	55	76.4 µM	25.9 µM	1.04
<b>219900 Dopamine D<sub>4.2</sub></b>						
MCO-III-157-A (1160666)	hum	0.3 µM	66	0.18 µM	0.071 µM	0.94
MCO-III-157-Rac (1160665)	hum	1 µM	69	0.36 µM	0.14 µM	0.94

\* A standard error of the mean is presented where results are based on multiple, independent determinations.  
hum=Human

## Experimental Results

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC <sub>50</sub> *	K <sub>i</sub>	n <sub>H</sub>	R
<b>Compound: MCO-III-157-A, PT #: 1160666</b>										
219500	Dopamine D <sub>1</sub>	314852	hum	2	100 µM	22	>100 µM			
			hum	2	30 µM	4				
			hum	2	10 µM	-9				
			hum	2	3 µM	-1				
			hum	2	1 µM	-8				
219600	Dopamine D <sub>2L</sub>	314851	hum	2	100 µM	32	>100 µM			
			hum	2	30 µM	25				
			hum	2	10 µM	26				
			hum	2	3 µM	12				
			hum	2	1 µM	11				
219800	Dopamine D <sub>3</sub>	314850	hum	2	100 µM	74	46.2 µM	15.7 µM	1.23	
			hum	2	30 µM	35				
			hum	2	10 µM	14				
			hum	2	3 µM	6				
			hum	2	1 µM	2				
219900	Dopamine D <sub>4,2</sub>	314853	hum	2	3 µM	93	0.18 µM	0.070 µM	0.94	
			hum	2	1 µM	79				
			hum	2	0.3 µM	66				
			hum	2	0.1 µM	37				
			hum	2	0.03 µM	13				
220200	Dopamine D <sub>5</sub>	314854	hum	2	100 µM	21	>100 µM			
			hum	2	30 µM	13				
			hum	2	10 µM	-2				
			hum	2	3 µM	1				
			hum	2	1 µM	-1				
<b>Compound: MCO-III-157-B, PT #: 1160667</b>										
219500	Dopamine D <sub>1</sub>	314852	hum	2	100 µM	9	>100 µM			
			hum	2	30 µM	15				
			hum	2	10 µM	2				
			hum	2	3 µM	0				
			hum	2	1 µM	7				
219600	Dopamine D <sub>2L</sub>	314851	hum	2	100 µM	14	>100 µM			
			hum	2	30 µM	2				
			hum	2	10 µM	-16				

Note: Items meeting criteria for significance (≥50% stimulation or inhibition) are highlighted.

\* Batch: Represents compounds tested concurrently in the same assay(s).

hum=Human

## Experimental Results

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC <sub>50</sub> *	K <sub>i</sub>	n <sub>H</sub>	R
			hum	2	3 µM	2				
			hum	2	1 µM	-7				
219800	Dopamine D <sub>3</sub>	314850	hum	2	100 µM	55	76.4 µM	25.9 µM	1.04	
			hum	2	30 µM	33				
			hum	2	10 µM	7				
			hum	2	3 µM	-2				
			hum	2	1 µM	2				
219900	Dopamine D <sub>4,2</sub>	314853	hum	2	100 µM	40	>100 µM			
			hum	2	30 µM	35				
			hum	2	10 µM	18				
			hum	2	3 µM	2				
			hum	2	1 µM	14				
220200	Dopamine D <sub>5</sub>	314854	hum	2	100 µM	6	>100 µM			
			hum	2	30 µM	16				
			hum	2	10 µM	3				
			hum	2	3 µM	0				
			hum	2	1 µM	6				
<b>Compound: MCO-III-157-Rac, PT #: 1160665</b>										
219500	Dopamine D <sub>1</sub>	314852	hum	2	100 µM	4	>100 µM			
			hum	2	30 µM	6				
			hum	2	10 µM	-2				
			hum	2	3 µM	-10				
			hum	2	1 µM	-3				
219600	Dopamine D <sub>2L</sub>	314851	hum	2	100 µM	20	>100 µM			
			hum	2	30 µM	-8				
			hum	2	10 µM	-9				
			hum	2	3 µM	3				
			hum	2	1 µM	-5				
219800	Dopamine D <sub>3</sub>	314850	hum	2	100 µM	75	31.8 µM	10.8 µM	1.01	
			hum	2	30 µM	51				
			hum	2	10 µM	22				
			hum	2	3 µM	7				
			hum	2	1 µM	7				
219900	Dopamine D <sub>4,2</sub>	314853	hum	2	10 µM	98	0.36 µM	0.14 µM	0.94	
			hum	2	3 µM	90				

Note: Items meeting criteria for significance (≥50% stimulation or inhibition) are highlighted.

\* Batch: Represents compounds tested concurrently in the same assay(s).

hum=Human

## Experimental Results

Cat #	Assay Name	Batch*	Spec.	Rep.	Conc.	% Inh.	IC <sub>50</sub> *	K <sub>i</sub>	n <sub>H</sub>	R
			hum	2	1 µM	69				
			hum	2	0.3 µM	48				
			hum	2	0.1 µM	22				
220200	Dopamine D <sub>5</sub>	314854	hum	2	100 µM	3	>100 µM			
			hum	2	30 µM	13				
			hum	2	10 µM	5				
			hum	2	3 µM	1				
			hum	2	1 µM	6				

Ricerca Biosciences, LLC has an exclusive, worldwide limited use license from Synaptic Pharmaceutical Corporation to perform these assays: Adrenergic Alpha 1D, Adrenergic Alpha 2B, and Dopamine D5 for safety and selectivity profiling. Ricerca's license excludes performing those assays in connection with drug discovery or development activities where the principal therapeutic mechanism of action of the test compound involves selective binding to a licensed receptor. Customers may contact Synaptic directly if they believe they need a broader license.

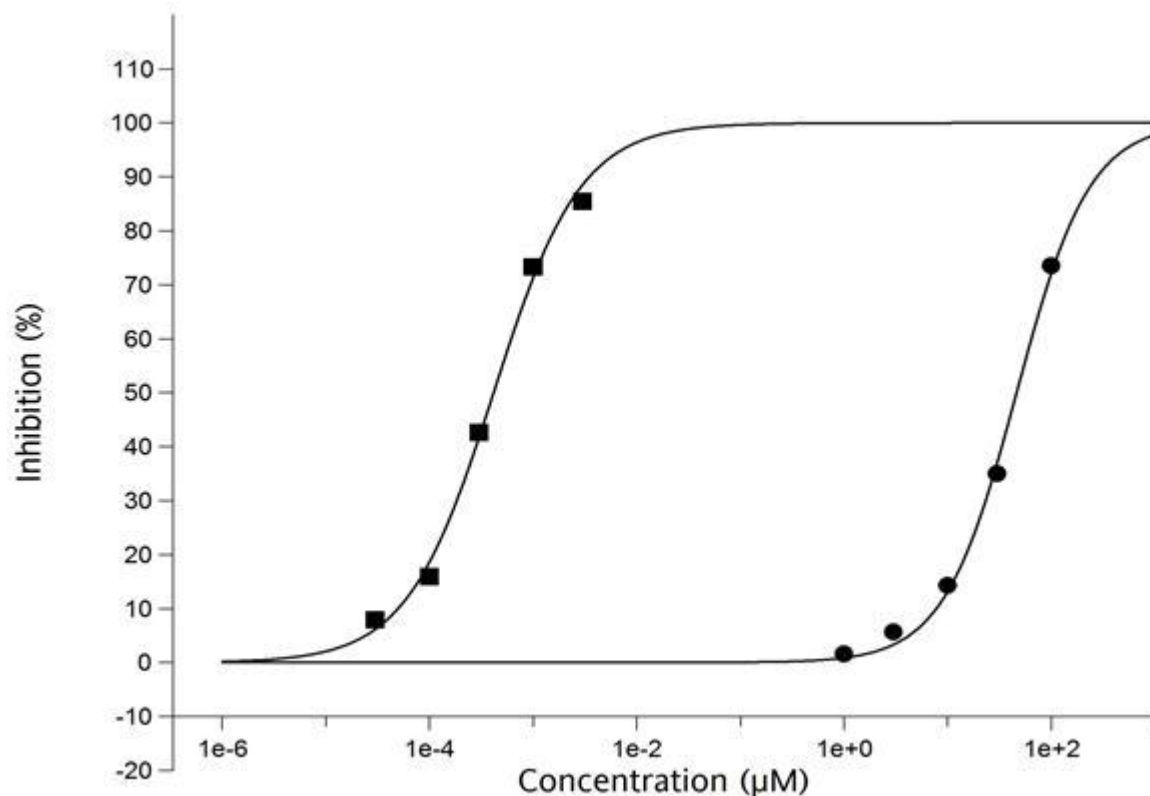
Note: Items meeting criteria for significance (≥50% stimulation or inhibition) are highlighted.

\* Batch: Represents compounds tested concurrently in the same assay(s).

hum=Human

## Response Curves

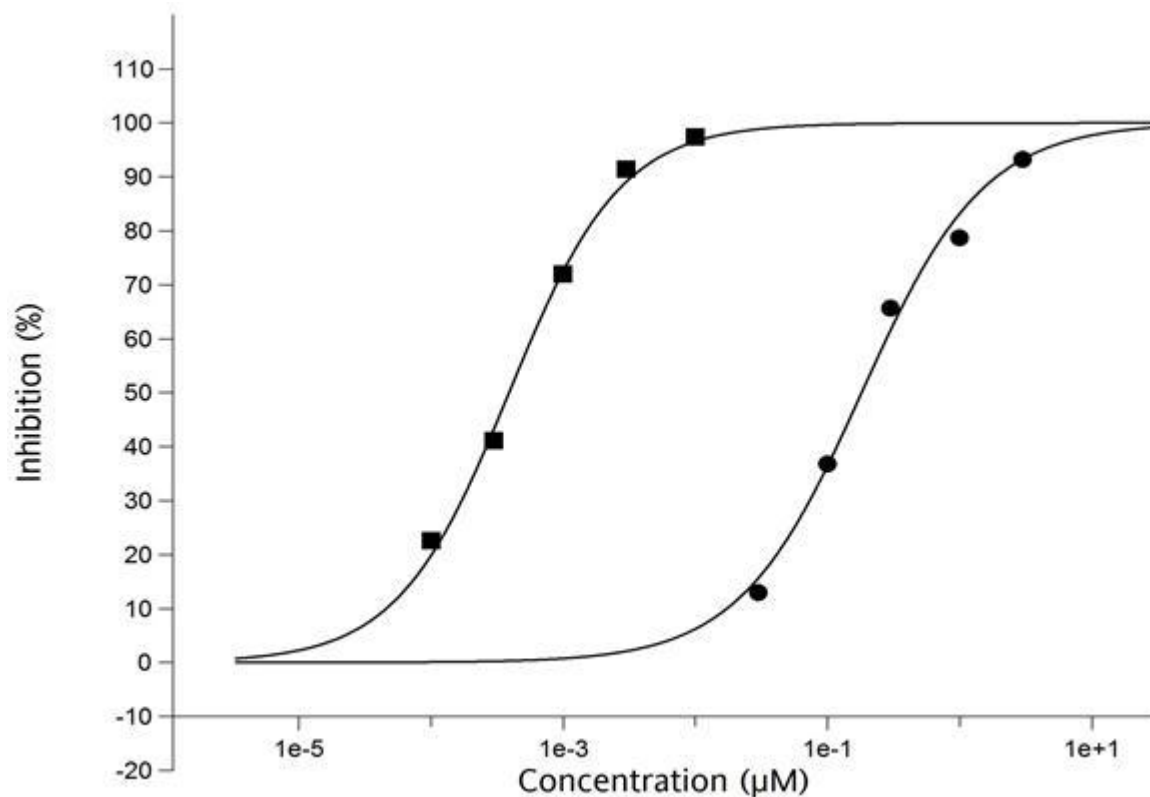
Assay: 219800 - 1 Dopamine D<sub>3</sub>



Compound Name	IC <sub>50</sub>	K <sub>i</sub>	n <sub>H</sub>
● MCO-III-157-A (1160666)	46.2 µM	15.7 µM	1.23
■ Spiperone	0.41 nM	0.14 nM	1.03

## Response Curves

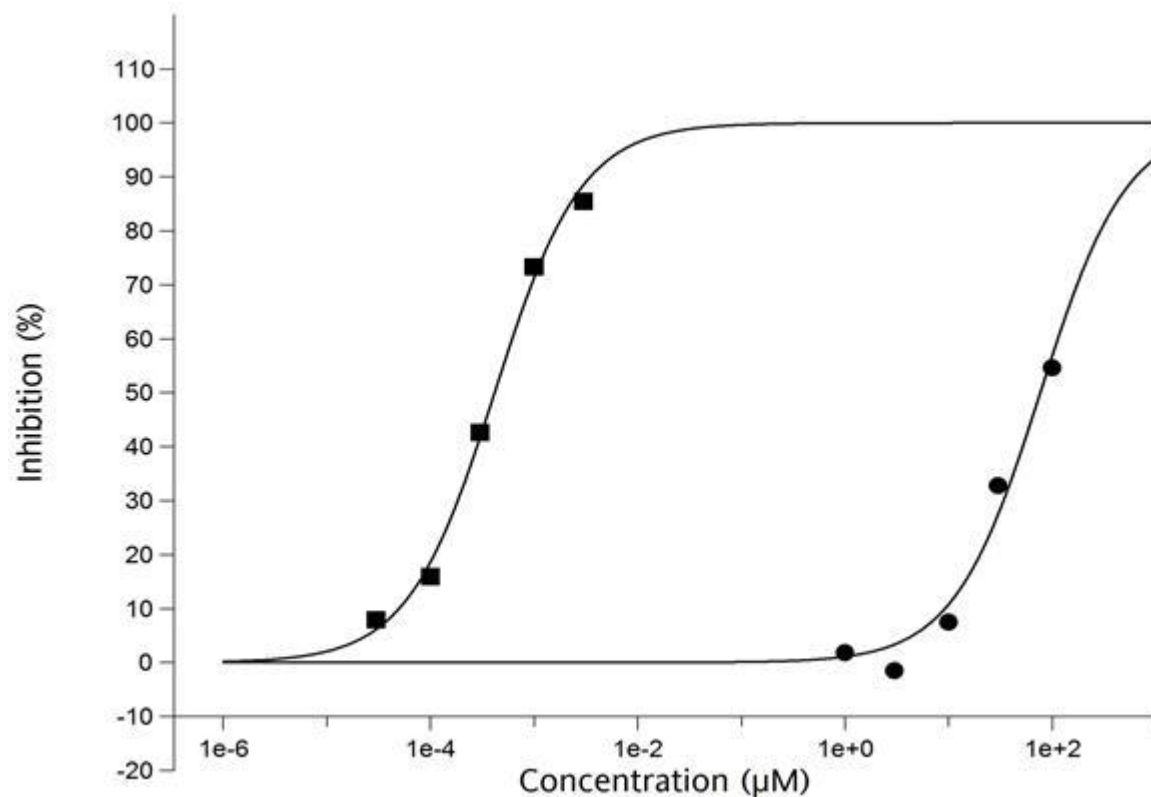
Assay: 219900 - 1 Dopamine D<sub>4.2</sub>



Compound Name	IC <sub>50</sub>	K <sub>i</sub>	n <sub>H</sub>
● MCO-III-157-A (1160666)	0.18 µM	0.071 µM	0.94
■ Spiperone	0.39 nM	0.15 nM	1.03

## Response Curves

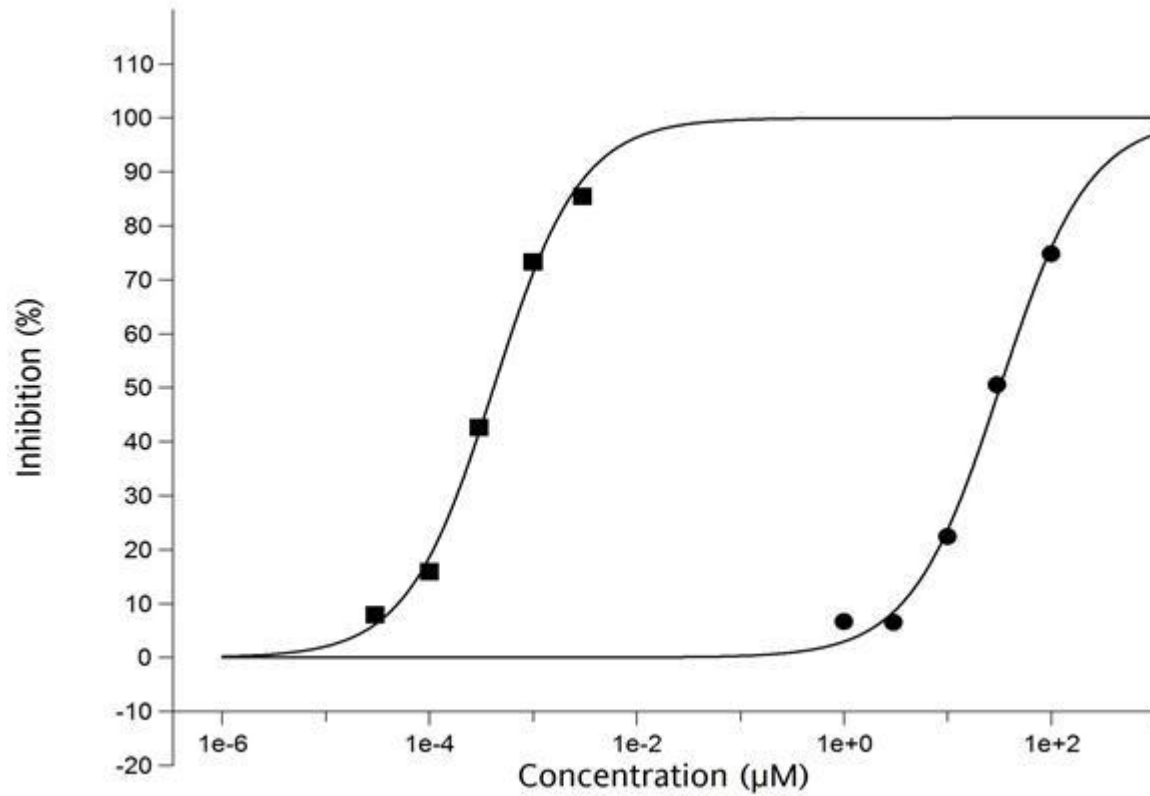
Assay: 219800 - 1 Dopamine D<sub>3</sub>



Compound Name	IC <sub>50</sub>	K <sub>i</sub>	n <sub>H</sub>
● MCO-III-157-B (1160667)	76.4 µM	25.9 µM	1.04
■ Spiperone	0.41 nM	0.14 nM	1.03

## Response Curves

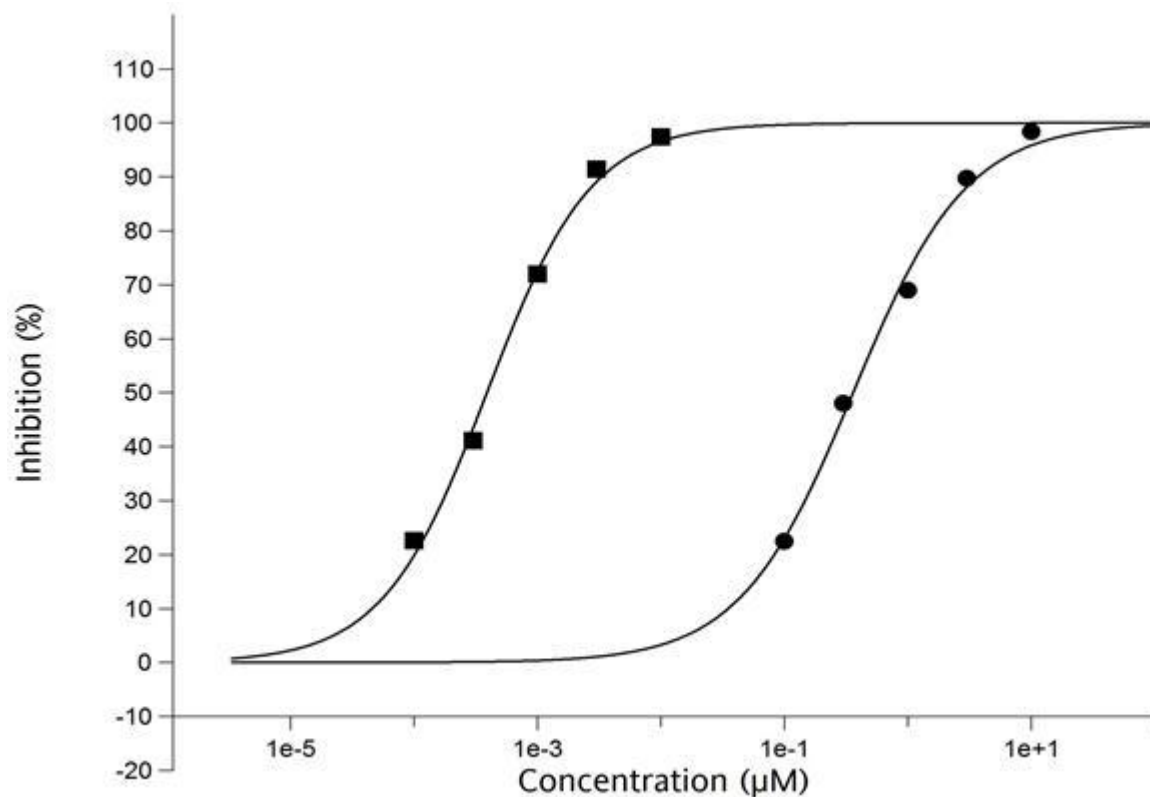
Assay: 219800 - 1 Dopamine D<sub>3</sub>



Compound Name	IC <sub>50</sub>	K <sub>i</sub>	n <sub>H</sub>
● MCO-III-157-Rac (1160665)	31.8 µM	10.8 µM	1.01
■ Spiperone	0.41 nM	0.14 nM	1.03

## Response Curves

Assay: 219900 - 1 Dopamine D<sub>4.2</sub>



Compound Name	IC <sub>50</sub>	K <sub>i</sub>	n <sub>H</sub>
● MCO-III-157-Rac (1160665)	0.36 µM	0.14 µM	0.94
■ Spiperone	0.39 nM	0.15 nM	1.03

## Methods

### ■ 219500 Dopamine D<sub>1</sub>

<b>Source:</b>	Human recombinant CHO cells	<b>Ligand:</b>	1.40 nM [ <sup>3</sup> H] SCH-23390
<b>Vehicle:</b>	1% DMSO	<b>Non-Specific Ligand:</b>	10.0 μM (+)-Butaclamol
<b>Incubation Time/Temp:</b>	2 hours @ 37°C	<b>Specific Binding:</b>	90% *
<b>Incubation Buffer:</b>	50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl	<b>Quantitation Method:</b>	Radioligand Binding
<b>Kd:</b>	1.40 nM *	<b>Significance Criteria:</b>	≥50% of max stimulation or inhibition
		<b>Bmax:</b>	0.63 pmole/mg Protein *

### ■ 219600 Dopamine D<sub>2L</sub>

<b>Source:</b>	Human recombinant CHO cells	<b>Ligand:</b>	0.16 nM [ <sup>3</sup> H] Spiperone
<b>Vehicle:</b>	1% DMSO	<b>Non-Specific Ligand:</b>	10.0 μM Haloperidol
<b>Incubation Time/Temp:</b>	2 hours @ 25°C	<b>Specific Binding:</b>	85% *
<b>Incubation Buffer:</b>	50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl	<b>Quantitation Method:</b>	Radioligand Binding
<b>Kd:</b>	0.080 nM *	<b>Significance Criteria:</b>	≥50% of max stimulation or inhibition
		<b>Bmax:</b>	0.48 pmole/mg Protein *

### ■ 219800 Dopamine D<sub>3</sub>

<b>Source:</b>	Human recombinant CHO cells	<b>Ligand:</b>	0.70 nM [ <sup>3</sup> H] Spiperone
<b>Vehicle:</b>	1% DMSO	<b>Non-Specific Ligand:</b>	25.0 μM S(-)-Sulpiride
<b>Incubation Time/Temp:</b>	2 hours @ 37°C	<b>Specific Binding:</b>	85% *
<b>Incubation Buffer:</b>	50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl	<b>Quantitation Method:</b>	Radioligand Binding
<b>Kd:</b>	0.36 nM *	<b>Significance Criteria:</b>	≥50% of max stimulation or inhibition
		<b>Bmax:</b>	1.10 pmole/mg Protein *

### ■ 219900 Dopamine D<sub>4.2</sub>

<b>Source:</b>	Human recombinant CHO-K1 cells	<b>Ligand:</b>	0.50 nM [ <sup>3</sup> H] Spiperone
<b>Vehicle:</b>	1% DMSO	<b>Non-Specific Ligand:</b>	10.0 μM Haloperidol
<b>Incubation Time/Temp:</b>	2 hours @ 25°C	<b>Specific Binding:</b>	90% *
<b>Incubation Buffer:</b>	50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl	<b>Quantitation Method:</b>	Radioligand Binding
<b>Kd:</b>	0.32 nM *	<b>Significance Criteria:</b>	≥50% of max stimulation or inhibition
		<b>Bmax:</b>	0.55 pmole/mg Protein *

\* Historical Values

## Methods

### ■ 220200 Dopamine D<sub>5</sub>

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<b>Source:</b>	Human recombinant CHO cells	<b>Ligand:</b>	2.0 nM [ <sup>3</sup> H] SCH-23390
<b>Vehicle:</b>	1% DMSO	<b>Non-Specific Ligand:</b>	10.0 μM Flupentixol
<b>Incubation Time/Temp:</b>	2 hours @ 37°C	<b>Specific Binding:</b>	85% *
<b>Incubation Buffer:</b>	50 mM Tris-HCl, pH 7.4, 1.4 mM Ascorbic Acid, 0.001% BSA, 150 mM NaCl	<b>Quantitation Method:</b>	Radioligand Binding
<b>Kd:</b>	0.73 nM *	<b>Significance Criteria:</b>	≥50% of max stimulation or inhibition
		<b>Bmax:</b>	0.47 pmole/mg Protein *

\* Historical Values

## Reference Compounds

Cat #	Assay Name	Reference Compound	Historical			Concurrent	
			IC <sub>50</sub> *	K <sub>i</sub>	n <sub>H</sub>	Batch *	IC <sub>50</sub> *
219500	Dopamine D <sub>1</sub>	R(+)-SCH-23390	1.40 nM	0.70 nM	0.90	314852	0.90 nM
219600	Dopamine D <sub>2L</sub>	Spiperone	0.26 nM	0.082 nM	1.20	314851	0.33 nM
219800	Dopamine D <sub>3</sub>	Spiperone	0.36 nM	0.12 nM	0.90	314850	0.41 nM
219900	Dopamine D <sub>4.2</sub>	Spiperone	0.50 nM	0.20 nM	0.90	314853	0.39 nM
220200	Dopamine D <sub>5</sub>	R(+)-SCH-23390	1.50 nM	0.40 nM	0.90	314854	1.26 nM

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\* Batch: Represents compounds tested concurrently in the same assay(s).