

Rapid, General Access to Chiral β -Fluoroamines and β,β - Difluoroamines via Organocatalysis

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General Experimental

All ^1H , ^{19}F and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz), Bruker AV-400 (400 MHz) or Bruker AV-NMR (600 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 (CDCl_3). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), integration, coupling constant (Hz). IR spectra were recorded as thin films and are reported in wavenumbers (cm^{-1}). Low resolution mass spectra were obtained on an Agilent 1200 LCMS with electrospray ionization. High resolution mass spectra were recorded on a Waters Qtof-API-US plus Acquity system. The value Δ is the error in the measurement (in ppm) given by the equation $\Delta = [(ME - MT) / MT] \times 10^6$, where ME is the experimental mass and MT is the theoretical mass. The HRMS results were obtained with ES as the ion source and leucine enkephalin as the reference. Analytical thin layer chromatography was performed on 250 μM silica gel 60 F_{254} plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60 (230-400 mesh) from Sorbent Technologies. Analytical HPLC was performed on an Agilent 1200 analytical LCMS with UV detection at 214 nm and 254 nm along with ELSD detection. Chiral HPLC was performed on an Agilent 1200 Series HPLC utilizing a Chiracel OD, OJ or Chiralpak AD columns (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. Solvents for extraction, washing and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. and were used without purification. All polymer-supported reagents were purchased from Biotage, Inc. Flame-dried (under vacuum) glassware was used for all reactions. All reagents and solvents were commercial grade and purified prior to use when necessary. Mass spectra were obtained on a

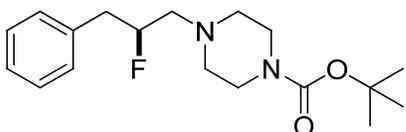
Micromass Q-Tof API-US mass spectrometer was used to acquire high-resolution mass spectrometry (HRMS) data.

General Procedure for β -Fluoroamines Synthesis.

A solution of **3** (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.2 equiv) and *N*-fluorobenzenesulfonimide **2** (1.2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature then cooled to -20 °C and treated with aldehyde substrate **5** (1 equiv). The reaction mixture was stirred at -20 °C for 24 h, and then cooled to -78 °C, diluted with 10 mL Et₂O and filtered through a pad of Davisil® Silica Gel, eluting with Et₂O. Me₂S (5.0 mL) was added, washed with Sat. NaHCO₃ (3x) and brine (1x) and then dried over MgSO₄. Filtration and concentration afforded the crude oil which was dissolved in DCE, followed by the addition of amine (1.0 equiv), and NaBH(OAc)₃ (1.5 equiv). The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. NaHCO₃ and extracted thrice with EtOAc and dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds. The enantioselectivity was determined either by chiral HPLC analysis.

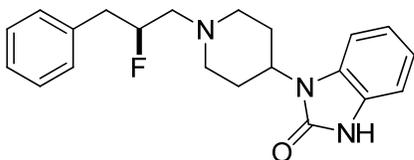
One-Pot Procedure for β -Fluoroamines Synthesis.

A solution of **3** (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt (0.2 equiv) and *N*-fluorobenzenesulfonimide **2** (1.2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature then cooled to -20 °C and treated with aldehyde substrate **5** (1 equiv). The reaction mixture was stirred at -20 °C for 24 h, followed by the addition of amine (1.0 equiv), and NaBH(OAc)₃ (2.2 equiv). The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. NaHCO₃ and extracted thrice with EtOAc and dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds. The enantioselectivity was determined by chiral HPLC analysis.



(S)-tert-butyl 4-(2-fluoro-3-phenylpropyl)piperazine-1-carboxylate (7a).

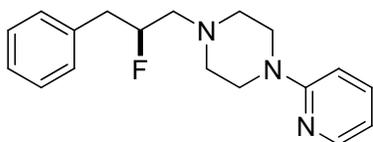
The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a off white solid (128.8 mg, 80%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel[®] OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, *t_R* (major) = 8.9 min, *t_R* (minor) = 10.9 min). *R_f* = 0.75 (10% MeOH/CH₂Cl₂); IR (neat) 2927, 1692, 1420, 1365, 1275, 1260 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 7.30 (d, *J* = 7.28 Hz, 2H), 7.25 (m, 3H), 4.94-4.82 (dm, *J* = 48.0 Hz, 1H), 3.43 (t, *J* = 4.9 Hz, 4H), 2.98 (m, 2H), 2.56 (m, 2H), 2.45 (t, *J* = 4.7 Hz, 4H), 1.45 (s, 9H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.65, 136.7 (d, *J* = 5.0 Hz), 129.3, 128.4, 126.6, 92.6 (d, *J* = 173.0 Hz), 79.5, 61.2 (d, *J* = 21.1 Hz), 53.4, 39.6 (d, *J* = 22.1 Hz) 28.3; ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -176.4; HRMS (TOF, ES⁺) C₁₈H₂₇FN₂O₂ [M+H]⁺ calc'd 323.2135, found 323.2125



(S)-1-(1-(2-fluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (7b).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a white solid (123.5 mg, 70%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel[®] OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, *t_R* (major) = 14.6 min, *t_R* (minor) = 17.0 min). *R_f* = 0.63 (50% EtOAc/hexanes); IR (neat) 3004, 2924, 1694, 1484, 1376 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃)

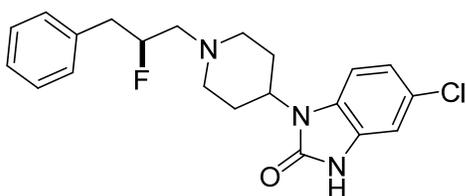
δ (ppm): 10.56 (s, 1H) 7.35 (m, 2H), 7.27 (m, 4H), 7.15(m, 1H), 7.05(m, 2H), 4.93 (dm, J = 47.6 Hz, 1H), 4.41-4.34 (m, 1H), 3.14 (br m, 2H), 3.00 (m, 2H), 2.68 (m, 2H), 2.52 (m, 2H), 2.34-2.27 (m, 2H), 1.81 (br d, J = 11.2 Hz, 2H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 155.3, 136.8 (d, J = 4.0 Hz), 129.3, 128.9, 128.4, 128.1, 126.6, 121.0 (d, J = 23.1 Hz), 109.7, (d, J = 11.0 Hz), 92.7 (d, J = 173.0 Hz), 61.2 (d, J = 21.1 Hz), 53.7 (d, J = 8.0 Hz), 50.5, 39.8 (d, J = 21.1 Hz) 29.1 (d, J = 2.0 Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -176.5; HRMS (TOF, ES+) $\text{C}_{21}\text{H}_{24}\text{FN}_3\text{O}$ $[\text{M}+\text{H}]^+$ calc'd 354.1982, found 354.1990.



(S)-1-(2-fluoro-3-phenylpropyl)-4-(pyridin-2-yl)piperazine (7c).

The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a off white solid (113.6 mg, 76%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel[®] OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 9.4 min, t_R (minor) = 12.3 min).

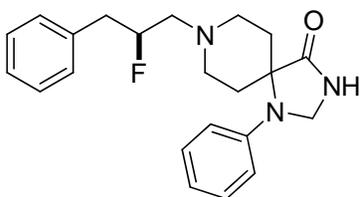
R_f = 0.74 (50% EtOAc/hexanes); IR (neat) 2924, 1625, 1455, 1372 cm^{-1} ; ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 8.2 (dd, J = 4.5 Hz, 1.0 Hz, 1H), 7.48 (dt, J = 7.5 Hz, 1.8 Hz, 1H), 7.26-7.33, (m, 5H), 6.63 (m, 2H), 4.89-5.00 (dm, J = 49.2 Hz, 1H), 3.57 (m, 4H), 3.02 (m, 2H), 2.64 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 159.4, 147.8, 137.3, 136.7 (d, J = 4.0 Hz), 129.3, 128.4, 126.6, 113.2, 107.0, 92.7 (d, J = 173.0 Hz), 61.3 (d, J = 21.1 Hz), 53.4, 45.1, 39.7 (d, J = 21.1 Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -176.4; HRMS (TOF, ES+) $\text{C}_{18}\text{H}_{22}\text{N}_3\text{F}$ $[\text{M}+\text{H}]^+$ calc'd 300.1876, found 300.1876.



(S)-5-chloro-1-(1-(2-fluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (7d).

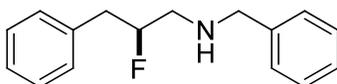
The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/ CH_2Cl_2) to afford the product as a off white solid (133.5 mg,

69%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel[®] OD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 10.6 min, t_R (minor) = 14.0 min). R_f = 0.59 (10% MeOH/CH₂Cl₂); IR (neat) 3011, 2925, 1698, 1487, 1375 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 10.58 (s, 1H) 7.33 (m, 2H), 7.25 (m, 3H), 7.17 (d, J = 6.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 6.4, 2.0 Hz, 1H), 4.93 (dm, J = 49.2 Hz, 1H), 4.29-4.37 (m, 1H), 3.11 (br m, 2H), 3.00 (m, 2H), 2.69 (m, 2H), 2.45 (m, 2H), 2.31 (m, 2H), 1.80 (br d, J = 10.8 Hz, 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 155.3, 136.7 (d, J = 4.0 Hz), 129.3, 129.0, 128.4, 127.5, 126.8, 126.6, 120.9, 110.2 (d, J = 22.1 Hz), 92.6 (d, J = 173.0 Hz), 61.1 (d, J = 21.1 Hz), 53.6 (d, J = 5.0 Hz), 50.6, 39.8 (d, J = 21.1 Hz), 29.1; ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -176.4; HRMS (TOF, ES+) C₂₁H₂₃FN₃OCl [M+H]⁺ calc'd 388.1592, found 388.1584.



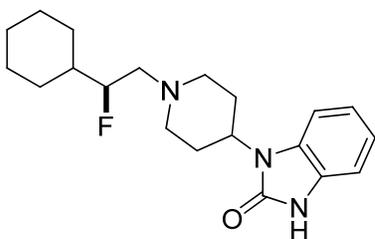
(S)-8-(2-fluoro-3-phenylpropyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (7e).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a white solid (119.2 mg, 65%), which was determined to be >96% ee by chiral HPLC analysis. (Chiralcel[®] OD, Isocratic 2% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 12.1 min, t_R (minor) = 13.4 min). R_f = 0.65 (10% MeOH/CH₂Cl₂); IR (neat) 3005, 2924, 1705, 1557, 1463, 1376 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 7.25-7.32 (m, 7H), 7.15 (s, 1H), 6.91 (d, J = 16.0 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 4.88 (dm, J = 48.0 Hz, 1H), 4.72 (s, 2H), 2.81-3.02 (m, 6H), 2.54-2.74 (m, 4H), 1.7 (d, J = 14.0 Hz 2H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 178.0, 143.0, 137.0 (d, J = 5.0 Hz), 129.2 (d, J = 16.0 Hz), 128.3, 126.5, 119.0, 115.5, 92.8 (d, J = 173.0 Hz), 61.2 (d, J = 21.1 Hz), 59.1 (d, J = 19.1 Hz), 50.2 (d, J = 12.0 Hz) 39.8 (d, J = 21.1 Hz), 29.3 (d, J = 51.3 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -183.9; HRMS (TOF, ES+) C₂₂H₂₆N₃OF [M+H]⁺ calc'd 368.2138, found 368.2126.



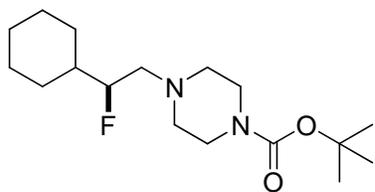
(S)-N-benzyl-2-fluoro-3-phenylpropan-1-amine (7f).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a yellow oil (99.6 mg, 82%), which was determined to be >95% ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, *t_R* (major) = 4.5 min, *t_R* (minor) = 4.9 min). *R_f* = 0.47 (50% EtOAc/hexanes); IR (neat) 3095, 2929, 1609, 1037 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 7.28 (m, 10H) 4.85 (dm, *J* = 52.0 Hz, 1H), 3.81 (m, 2H), 2.75-3.07 (m, 4H), 1.7 (s, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 139.8, 136.7 (d, *J* = 6.0 Hz), 129.2, 128.4, 128.3, 128.3, 128.0, 126.9, 126.5, 93.9 (d, *J* = 172.0 Hz), 53.7, 52.2 (d, *J* = 21.1 Hz), 39.3 (d, *J* = 21.1 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -181.9; HRMS (TOF, ES+) C₁₆H₁₈FN [M+H]⁺ calc'd 244.1502, found 244.1501.



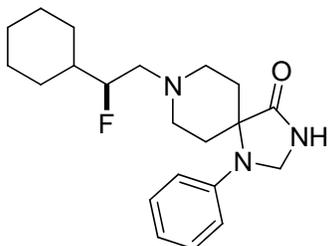
(S)-1-(1-(2-cyclohexyl-2-fluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (15a).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a white solid (15.0 mg, 87%), which was determined to be >99% ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 5% *i*-PrOH/Hexanes, *t_R* (major) = 7.8 min, *t_R* (minor) = 9.4 min). *R_f* = 0.61 (10% MeOH/CH₂Cl₂); IR (neat) 3006, 2924, 1691, 1462, 1377, 1275, 1260 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 9.93 (s, 1H) 7.29 (m, 1H), 7.11 (m, 1H), 7.04 (m, 2H), 4.43-4.51 (dm, *J* = 52.5 Hz, 1H), 4.38 (br m, 1H), 3.13 (m, 2H), 2.70 (m, 1H), 2.54 (m, 2H), 2.28 (m, 2H), 1.77-1.83 (m, 5H), 1.68 (m, 2H) 1.58 (m, 1H), 1.07-1.31 (m, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 155.0, 129.0, 127.9, 121.0 (d, *J* = 13.3 Hz), 109.7, (d, *J* = 18.0 Hz), 95.9 (d, *J* = 171.7 Hz), 60.2 (d, *J* = 21.4 Hz), 53.9, 53.6, 50.5, 41.0 (d, *J* = 19.4 Hz) 29.6, 29.1, 28.7 (d, *J* = 4.2 Hz), 27.1 (d, *J* = 6.1 Hz), 26.2, 25.9, 25.7; ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -183.9; HRMS (TOF, ES+) C₂₀H₂₈FN₃O [M+H]⁺ calc'd 346.2295, found 346.2279.



(S)-tert-butyl 4-(2-cyclohexyl-2-fluoroethyl)piperazine-1-carboxylate (15b).

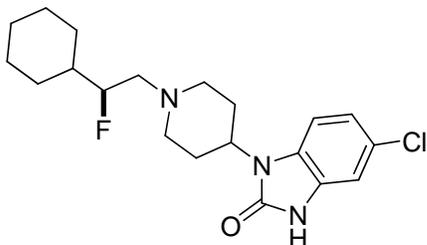
The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a off white solid (14.4 mg, 92%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, *t_R* (major) = 6.7 min, *t_R* (minor) = 8.1 min). *R_f* = 0.73 (10% MeOH/CH₂Cl₂); IR (neat) 2926, 1701, 1681, 1458, 1365, 1275, 1172 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 4.37-4.48 (dm, *J* = 49.2 Hz, 1H), 3.44 (brs, 4H), 2.59-2.66 (m, 1H), 2.46 (brs, 4H), 1.74-1.82 (brs, 3H), 1.66-1.68 (m, 2H), 1.59-1.60(m, 1H), 1.4 (s, 9H), 1.14-1.28 (m, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.6, 95.8 (d, *J* = 172.0 Hz), 79.5, 60.3 (d, *J* = 21.1 Hz), 53.4, 40.9 (d, *J* = 19.1 Hz) 28.6 (d *J* = 4.0 Hz) 28.3, 27.1 (d, *J* = 6.0 Hz), 26.1, 25.8, 25.7; ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -183.7; HRMS (TOF, ES+) C₁₇H₃₁FN₂O₂ [M+H]⁺ calc'd 315.2448, found 315.2437.



(S)-8-(2-cyclohexyl-2-fluoroethyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (15c).

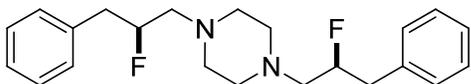
The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a off white solid (16.1 mg, 90%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 3% *i*-PrOH/Hexanes, *t_R* (major) = 10.0 min, *t_R* (minor) = 13.6 min). *R_f* = 0.60 (10% MeOH/CH₂Cl₂); IR (neat) 3013, 2940, 1704, 1598, 1463, 1367, 1302 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 7.52 (s, 1H), 7.29 (m, 2H), 6.93 (d, *J* = 7.8 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 4.47 (dm, *J* = 49.8 Hz, 1H), 4.76 (s, 2H), 2.92 (m, 4H), 2.71 (m, 4H), 1.78 (m, 6H), 1.60 (m, 1H), 1.25 (m, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 178.2, 143.1, 129.1, 119.0, 115.6, 96.0 (d, *J* = 172.0 Hz), 60.2 (d, *J* = 22.1 Hz), 59.2 (d, *J* = 14.0 Hz), 50.2 (d, *J* = 55.3 Hz) 41.1 (d, *J* = 19.1 Hz), 29.1, 28.7 (d, *J* = 5.0 Hz), 27.2 (d, *J* = 5.0 Hz), 26.1 (d, *J* = 5.0 Hz), 25.8;

^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -183.9 ; HRMS (TOF, ES+) $\text{C}_{21}\text{H}_{30}\text{N}_3\text{OF}$ $[\text{M}+\text{Na}]^+$ calc'd 382.2271, found 382.2267.



(S)-5-chloro-1-(1-(2-cyclohexyl-2-fluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (15d).

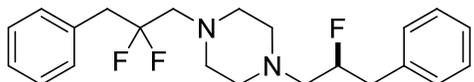
The product was prepared according to the general procedure and purified by SiO_2 chromatography (10% MeOH/ CH_2Cl_2) to afford the product as a white solid (15.9 mg, 84%), which was determined to be $>97\%$ ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 3% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 10.0 min, t_R (minor) = 13.6 min). R_f = 0.61 (10% MeOH/ CH_2Cl_2); IR (neat) 3004, 2924, 1697, 1487, cm^{-1} ; ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 10.4 (s, 1H) 7.19 (d, J = 8.4 Hz, 1H), 7.12 (s, 1H), 7.01 (br d, J = 8.4 Hz, 1H), 4.45-4.53 (dm, J = 49.8 Hz, 1H), 4.36 (br m, 1H), 3.17 (br m, 2H), 2.71 (m, 1H), 2.48 (br m, 2H), 2.33 (br m, 2H), 1.77-1.83 (m, 5H), 1.68 (m, 2H) 1.57 (br m, 1H), 1.07-1.27 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 155.2, 128.9, 127.4, 126.8, 121.0, 110.2 (d, J = 36.2 Hz), 95.6 (d, J = 172.0 Hz), 60.0 (d, J = 21.1 Hz), 53.6, 53.5, 50.4, 41.0 (d, J = 20.1 Hz) 29.6, 28.9, 28.6 (d, J = 4.0 Hz), 27.1 (d, J = 6.0 Hz), 26.1, 25.9, 25.7; ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -183.9 ; HRMS (TOF, ES+) $\text{C}_{20}\text{H}_{27}\text{FN}_3\text{OCl}$ $[\text{M}+\text{H}]^+$ calc'd 380.1905, found 380.1891.



1,4-bis((S)-2-fluoro-3-phenylpropyl)piperazine (15g).

The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as yellow oil (10.3 mg, 58%). Compound **5k** was also isolated as yellow oil. R_f = 0.69 (50% EtOAc/hexanes); IR (neat) 2921, 1453, 1274, 1158 cm^{-1} ; ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 7.34 (m, 4H), 7.29 (m, 2H), 7.19 (d, J = 7.2 Hz, 4H), 5.19 (dm, J = 49.5 Hz, 2H), 3.47 (br s, 4H), 3.35 (br m, 4H), 3.15 (m, 2H), 3.01 (m, 6H); ^{13}C NMR (150.9 MHz, CDCl_3) δ (ppm): 134.2 (d, J = 4.6 Hz), 129.2,

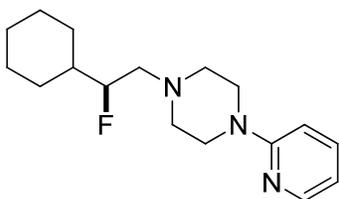
128.8, 127.4, 90.0 (d, $J = 174.7$ Hz), 59.6 (d, $J = 20.6$ Hz), 50.2, 39.2 (d, $J = 21.2$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -175.7 ; HRMS (TOF, ES+) $\text{C}_{22}\text{H}_{28}\text{F}_2\text{N}_2$ $[\text{M}+\text{H}]^+$ calc'd 359.2299, found 359.2293.



(S)-1-(2,2-difluoro-3-phenylpropyl)-4-(2-fluoro-3-phenylpropyl)piperazine.

Isolated alongside compound **15g** as a yellow solid.

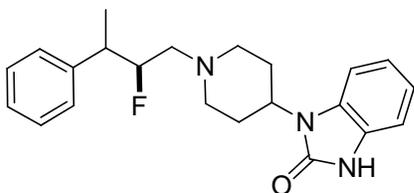
$R_f = 0.74$ (50% EtOAc/hexanes); IR (neat) 2921, 1454, 1275, 1261, 1158, 1096 cm^{-1} ; ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 7.25-7.34 (m, 10H), 4.95 (dm, $J = 48.0$ Hz, 1H), 3.27 (t, $J = 16.2$ Hz, 2H), 3.00 (m, 2H), 2.53-2.66 (m, 12H); ^{13}C NMR (150.9 MHz, CDCl_3) δ (ppm): 136.8 (d, $J = 4.9$ Hz), 133.6 (t, $J = 4.6$ Hz), 130.4, 129.3, 128.4, 128.3, 127.1, 126.6, 124.4 (t, $J = 243.7$ Hz), 92.7 (d, $J = 173.0$ Hz), 61.2 (d, $J = 20.9$ Hz), 60.0 (t, $J = 28.3$ Hz), 53.8 (d, $J = 5.8$ Hz), 40.8 (t, $J = 24.8$ Hz), 39.7 (d, $J = 21.5$ Hz), 29.6; ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -176.4 , -94.4 ; HRMS (TOF, ES+) $\text{C}_{22}\text{H}_{27}\text{F}_3\text{N}_2$ $[\text{M}+\text{H}]^+$ calc'd 377.2205, found 377.2204.



(S)-1-(2-cyclohexyl-2-fluoroethyl)-4-(pyridin-2-yl)piperazine (15e).

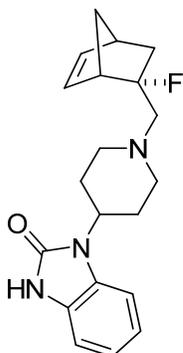
The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a white solid (12.8 mg, 88%), which was determined to be $>99\%$ ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 5% *i*-PrOH/Hexanes/0.1% DEA, t_R (major) = 3.9 min, t_R (minor) = 7.5 min). $R_f = 0.81$ (50% EtOAc/hexanes); IR (neat) 2924, 1608, 1593, 1459, 1272 cm^{-1} ; ^1H NMR (400.1 MHz, CDCl_3) δ (ppm): 8.18 (dd, $J = 4.8$ Hz, 1.2 Hz, 1H), 7.46 (dt, $J = 8.2$ Hz, 2.0 Hz, 1H), 6.62 (m, 2H), 4.41-4.54 (dm, $J = 49.6$ Hz, 1H), 3.56 (m, 4H), 2.63 (m, 5H), 1.78 (m, 3H), 1.69 (m, 2H), 1.57 (m, 1H), 1.19 (m, 6H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 159.4, 147.8, 137.3, 113.1, 106.9, 95.9 (d, $J = 172.0$ Hz), 60.4 (d, $J = 22.1$ Hz), 53.5, 45.0, 41.0 (d, $J = 19.1$ Hz), 28.6 (d,

$J = 4.0$ Hz), 27.2 (d, $J = 6.0$ Hz), 26.1, 25.8 (d, $J = 18.0$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -183.7; HRMS (TOF, ES+) $\text{C}_{17}\text{H}_{26}\text{N}_3\text{F}$ $[\text{M}+\text{H}]^+$ calc'd 292.2189, found 292.2193.



1-(1-((2S)-2-fluoro-3-phenylbutyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (15f).

The product was prepared according to the general procedure and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a off white solid (13.8 mg, 75%), which was determined to be >98% ee by chiral HPLC analysis. (Chiralcel[®] OJ, Isocratic 40% EtOH/60% Hexanes, (t_R (major) = 4.3 min, t_R (minor) = 4.9 min; (t_R (major) = 5.5 min, t_R (minor) = 6.7 min). $R_f = 0.61$ (50% EtOAc/hexanes); IR (neat) 3005, 2920, 1694, 1487, 1376 cm^{-1} ; (^1H NMR spectra of the mixture of two diastereomers); ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 10.7 (s, 1H), 7.27-7.36 (m, 6H), 7.15 (m, 1H), 7.06 (m, 2H), 4.76-4.91 (m, 1H), 4.37 (m, 1H), 3.07 (m, 3H), 2.54 (m, 4H), 2.24 (m, 2H), 1.81 (dt, $J = 12.9, 1.8$ Hz, 2H), 1.43 (m, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 155.3, 143.0 (d, $J = 6.0$ Hz), 141.6 (d, $J = 2.0$ Hz), 128.9, 128.5, 128.3, 128.2, 127.6, 126.6 (d, $J = 6.0$ Hz), 120.9 (d, $J = 26.1$ Hz), 109.7, (d, $J = 12.0$ Hz), 96.0 (d, $J = 176.0$ Hz), 95.3 (d, $J = 175.0$ Hz), 60.3, 60.1 (d, $J = 1.0$ Hz), 53.7 (d, $J = 5.0$ Hz), 53.5, 50.5 (d, $J = 2.0$ Hz), 43.0 (d, $J = 21.1$ Hz), 42.9 (d, $J = 20.1$ Hz), 29.6, 29.2, 29.1, 17.6 (d, $J = 6.0$ Hz), 16.8 (d, $J = 6.0$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -182.3, -184.3; HRMS (TOF, ES+) $\text{C}_{22}\text{H}_{26}\text{FN}_3\text{O}$ $[\text{M}+\text{Na}]^+$ calc'd 390.1958, found 390.1943.

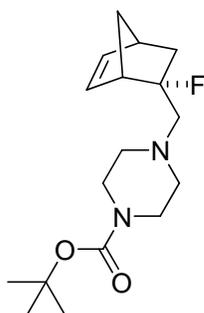


1-(1-(((1S,2S,4S)-2-fluorobicyclo[2.2.1]hept-5-en-2-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (15h).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a off white solid (11.2 mg, 66%), which was determined to be ~12% ee by chiral HPLC analysis.

(Chiralcel[®] AD, Isocratic 2% *i*-PrOH/Hexanes, *t_R* (major) = 14.5 min, *t_R* (minor) = 15.6 min).

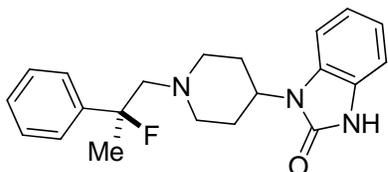
R_f = 0.71 (50% EtOAc/hexanes); IR (neat) 3009, 2926, 1674, 1484, 1386, 1164 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 9.70 (s, 1H), 7.28 (m, 1H), 7.13 (m, 1H), 7.07 (m, 2H), 6.24 (m, 1H), 6.06 (m, 1H), 4.35 (m, 1H), 3.23 (d, *J* = 11.4 Hz, 1H), 3.09 (s, 1H), 3.06 (d, *J* = 11.4 Hz, 1H) 2.92 (s, 1H), 2.59 (m, 1H), 2.49 (m, 3H), 2.35 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 2.30 (ddd, *J* = 1.8, 1.8, 1.2 Hz, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.79 (m, 2H), 1.68 (d, *J* = 8.4, 1H), 1.47 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.9, 140.1 (d, *J* = 4.0 Hz), 133.3 (d, *J* = 9.1 Hz), 129.1, 127.9, 120.9 (d, *J* = 8.0 Hz), 109.6 (d, *J* = 13.1 Hz), 108 (d, *J* = 186.1 Hz), 63.7 (d, *J* = 22.1 Hz), 54.7, 54.1 (d, *J* = 3.0 Hz), 50.7, 50.4 (d, *J* = 23.1 Hz), 47.6, 40.9, 39.3 (d, *J* = 21.1 Hz), 29.3 (d, *J* = 21.1 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -139.4 (major), -143.4 (minor); HRMS (TOF, ES+) C₂₀H₂₄N₃OF [M+H]⁺ calc'd 342.1982, found 342.1970.



***tert*-butyl 4-(((1*S*,2*S*,4*S*)-2-fluorobicyclo[2.2.1]hept-5-en-2-yl)methyl)piperazine-1-carboxylate.**

The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a yellow solid (10.8 mg, 70%), which was determined to be ~15% ee by chiral HPLC analysis. (Chiralcel[®] AD, Isocratic 5% *i*-PrOH/Hexanes, *t_R* (major) = 10.6 min, *t_R* (minor) = 11.9 min). *R_f* = 0.78 (50% EtOAc/hexanes); IR (neat) 2988, 1685, 1459, 1275, 1260 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 6.21 (m, 1H), 6.01 (m, 1H), 3.42 (m, 4H), 3.02 (m, 1H), 2.88 (brs, 1H), 2.57 (m, 3H), 2.42 (m, 3H), 1.88 (m, 1H), 1.80 (m, 1H) 1.64 (m, 1H), 1.45 (s, 9H), 1.39 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.76, 140.1 (d, *J* = 4.0 Hz), 133.2 (d, *J* = 9.0 Hz), 108.1, 106.2, 79.3, 79.5,

64.0 (d, $J = 22.1$ Hz), 54.0 (d, $J = 3.0$ Hz), 50.3 (d, $J = 23.1$ Hz) 47.5, 40.8, 39.2 (d, $J = 21.1$ Hz), 28.3; ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): 139.0 (major), -143.0 (minor); HRMS (TOF, ES+) $\text{C}_{17}\text{H}_{27}\text{FN}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ calc'd 311.2135, found 311.2125.



(S)-1-(1-(2-fluoro-2-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (15i).

The product was prepared according to the general procedure (except that (S)-5-(pyrrolidin-2-yl)-1H-tetrazole **10** was used as the catalyst) and purified by SiO_2 chromatography (50% EtOAc/hexanes) to afford the product as a yellow solid (13.1 mg, 74%), which was determined to be 40% ee by chiral HPLC analysis. (Chiralcel[®] AD, 100% MeOH/0.1 DEA, t_R (major) = 6.4 min, t_R (minor) = 7.4 min). $R_f = 0.60$ (50% EtOAc/hexanes); IR (neat) 3005, 2926, 1694, 1484, 1376 cm^{-1} ; ^1H NMR (600.1 MHz, CDCl_3) δ (ppm): 10.4 (s, 1H), 7.26-7.45 (m, 6H), 7.06 (m, 3H), 4.07 (br s, 1H), 3.77 (m, 2H), 3.52 (m, 2H), 2.98 (m, 4H) 1.95 (br d, $J = 12.0$ Hz, 2H), 1.89 (d, $J = 22.8$ Hz, 3H); ^{13}C NMR (100.6 MHz, CDCl_3) δ (ppm): 154.7, 140.2 (d, $J = 21.1$ Hz), 129.2, 128.9, 128.7, 127.8, 127.6, 126.7, 123.8 (d, $J = 9.0$ Hz), 121.7 (d, $J = 9.0$ Hz), 109.8, 95.8 (d, $J = 178.1$ Hz), 53.9, 52.8 (d, $J = 5.0$ Hz), 50.3, 46.8, 25.6 (d, $J = 23.1$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -145.4; HRMS (TOF, ES+) $\text{C}_{21}\text{H}_{24}\text{N}_3\text{OF}$ $[\text{M}+\text{Na}]^+$ calc'd 376.1801, found 376.1792.

General Procedure for β,β -Difluoroamines Synthesis.

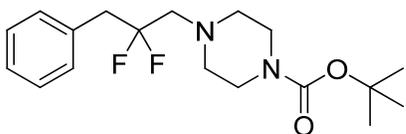
A solution of D,L-Proline (0.4 equiv) and *N*-fluorobenzenesulfonimide **2** (2 equiv) in 10 % *i*-PrOH/THF (0.30 M) was stirred at room temperature and treated with aldehyde substrate **16** (1 equiv). The reaction mixture was stirred at this temperature for 24 h, and then cooled to -78 °C, diluted with 10 mL Et_2O and filtered through a pad of Davisil[®] Silica Gel, eluting with Et_2O . Me_2S (5.0 mL) was added, washed with Sat. NaHCO_3 (3X) and brine (1X) and then dried over MgSO_4 . Filtration and concentration afforded the crude oil which was dissolved in DCE, followed by the addition of amine (1.0 equiv), and $\text{NaBH}(\text{OAc})_3$. The reaction was stirred at 23 °C overnight. The reaction was quenched with Sat. NaHCO_3 and extracted thrice with EtOAc

and dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash column chromatography with silica gel afforded the title compounds.



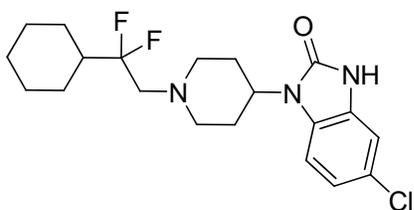
1-(1-(2,2-difluoro-3-phenylpropyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (18a).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a white solid (11.8 mg, 64%). R_f = 0.57 (10% MeOH/CH₂Cl₂); IR (neat) 3003, 2925, 1691, 1481, 1377 cm⁻¹; ¹H NMR (400.1 MHz, CDCl₃) δ (ppm): 8.33 (s, 1H) 7.46 (d, *J* = 6.8 Hz, 1H), 7.37 (m, 2H), 7.28 (m, 3H), 7.13 (m, 3H), 4.63 (br s, 1H), 3.71 (d, *J* = 11.6 Hz, 2H), 3.36 (m, 3H), 3.03 (m, 4H), 2.74 (m, 1H), 1.98 (d, *J* = 11.2 Hz, 2H); ¹³C NMR (150.9 MHz, CDCl₃) δ (ppm): 154.6, 130.6, 130.3, 130.1, 128.9, 128.2, 126.6, 122.0, 120.7 (t, *J* = 245.9 Hz), 110.2, 57.6 (t, *J* = 27.3 Hz), 53.61, 47.1, 42.6 (t, *J* = 24.1 Hz) 25.7, 24.0 (t, *J* = 25.6 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -94.4; HRMS (TOF, ES⁺) C₂₁H₂₃F₂N₃O [M+H]⁺ calc'd 372.1887, found 372.1888.



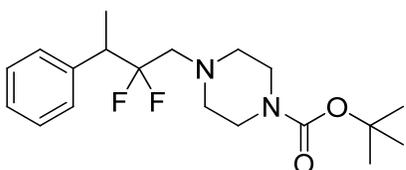
tert-butyl 4-(2,2-difluoro-3-phenylpropyl)piperazine-1-carboxylate (18b).

The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a white solid (11.4 mg, 67%), R_f = 0.78 (50% EtOAc/hexanes); IR (neat) 2927, 1690, 1475, 1373 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 7.27-7.34 (m, 5H), 3.45 (m, 4H), 3.28 (t, *J* = 16.2 Hz, 2H), 2.56 (t, *J* = 13.2 Hz, 2H), 2.49 (m, 4H), 1.47 (s, 9H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.6, 133.5 (t, *J* = 5.0 Hz), 130.3, 128.2, 127.1, 124.3 (t, *J* = 243.4 Hz), 79.6, 60.1 (t, *J* = 28.1 Hz), 53.6, 40.9 (t, *J* = 24.1 Hz), 28.3; ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -94.4; HRMS (TOF, ES⁺) C₁₈H₂₆F₂N₂O₂ [M+H]⁺ calc'd 341.2041, found 341.2040.



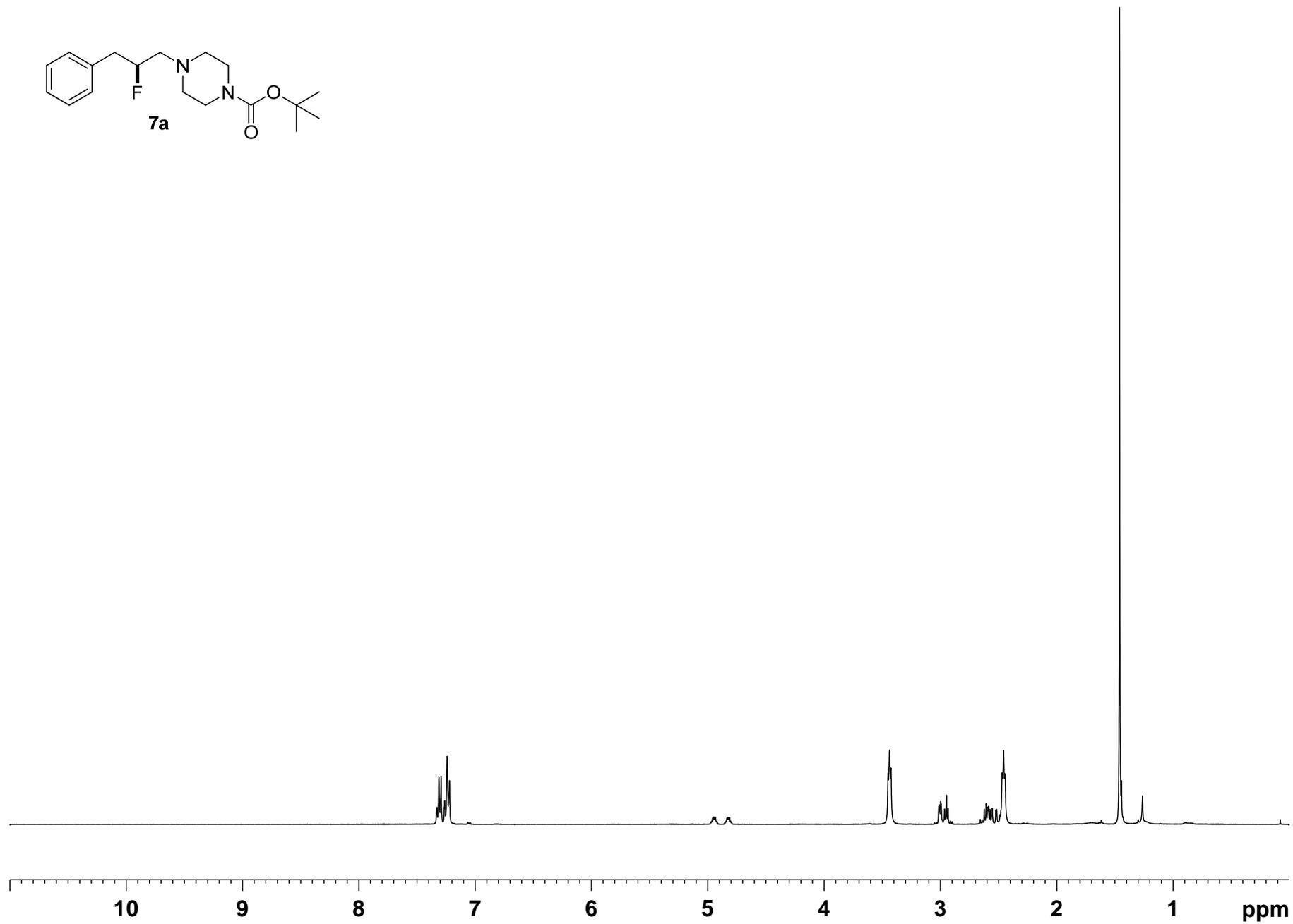
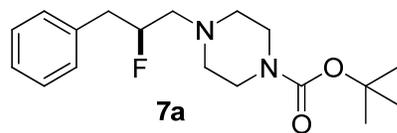
5-chloro-1-(1-(2-cyclohexyl-2,2-difluoroethyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (18c).

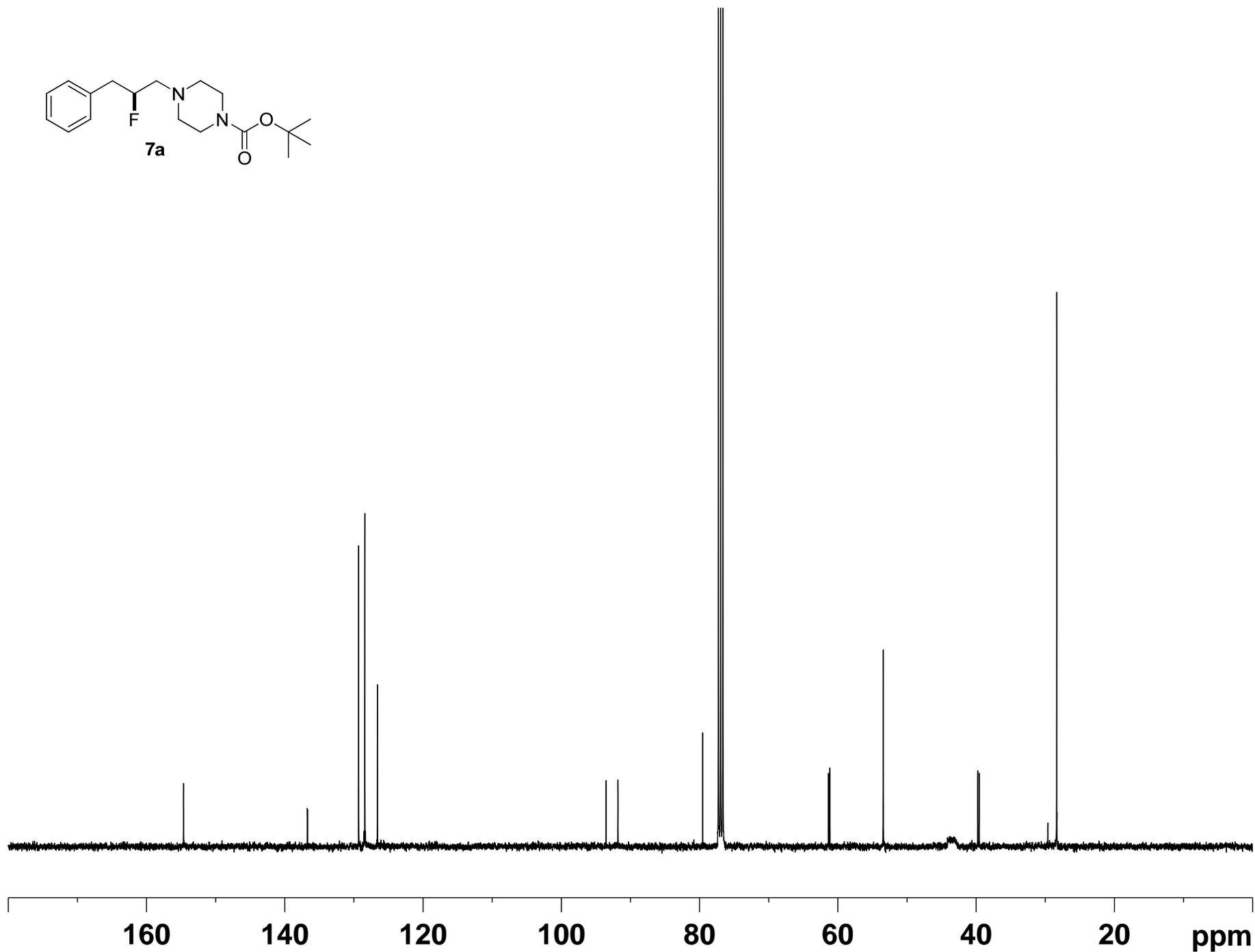
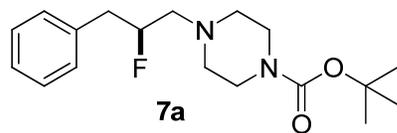
The product was prepared according to the general procedure and purified by SiO₂ chromatography (10% MeOH/CH₂Cl₂) to afford the product as a white solid (15.2 mg, 77%). R_f = 0.62 (10% MeOH/CH₂Cl₂); IR (neat) 3003, 2924, 1691, 1481, 1377 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 9.83 (s, 1H) 7.13 (m, 2H), 7.04 (dd, *J* = 1.8, 8.4 Hz, 1H), 4.31 (br m, 1H), 3.11 (m, 2H), 2.76 (t, *J* = 15.0 Hz, 2H), 2.42 (m, 4H), 1.97 (m, 1H), 1.82 (m, 5H), 1.72 (d, *J* = 13.2 Hz, 1H), 1.22 (m, 6H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.9, 128.8, 127.7 (t, *J* = 231.4 Hz), 126.8, 125.5, 121.0, 110.0 (d, *J* = 22.1 Hz), 68.1, 59.3 (t, *J* = 28.1 Hz), 54.3, 50.8, 42.2 (t, *J* = 22.1 Hz) 29.6, 29.3, 25.7 (t, *J* = 25.1 Hz), 25.4 (t, *J* = 4.0 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -104.26; HRMS (TOF, ES⁺) C₂₀H₂₆FN₃OCl [M+H]⁺ calc'd 398.1811, found 398.1796.

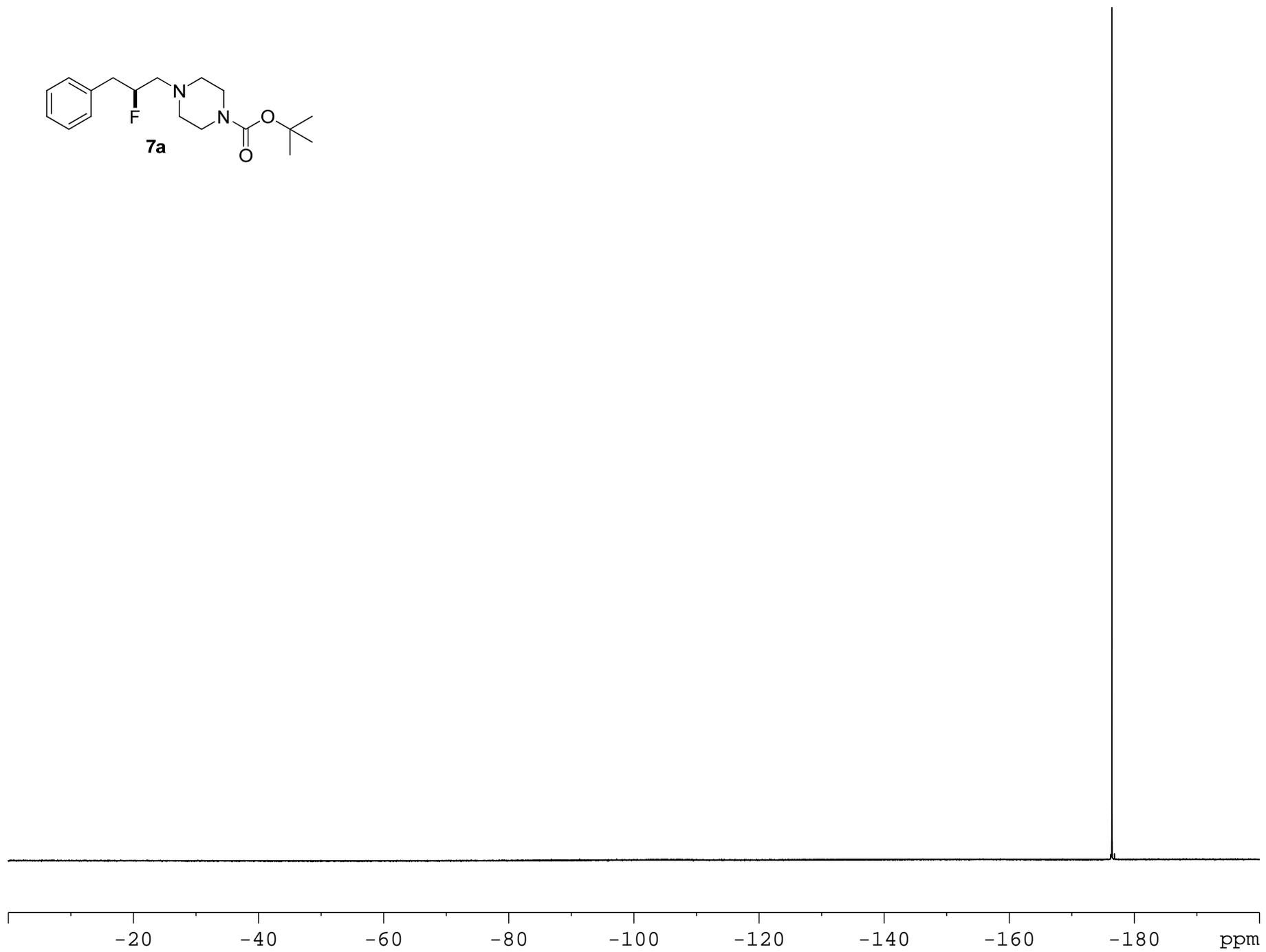
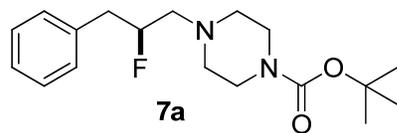


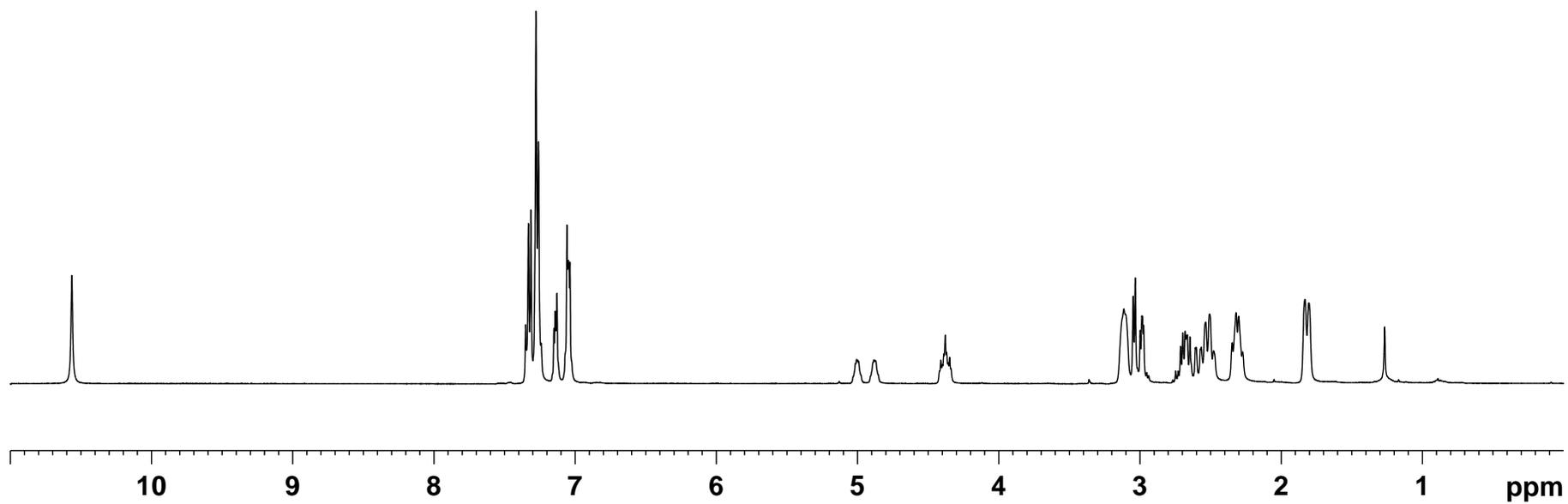
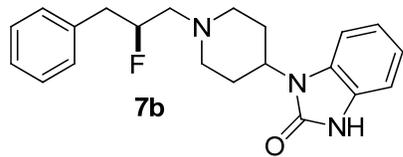
tert-butyl 4-(2,2-difluoro-3-phenylbutyl)piperazine-1-carboxylate (18d).

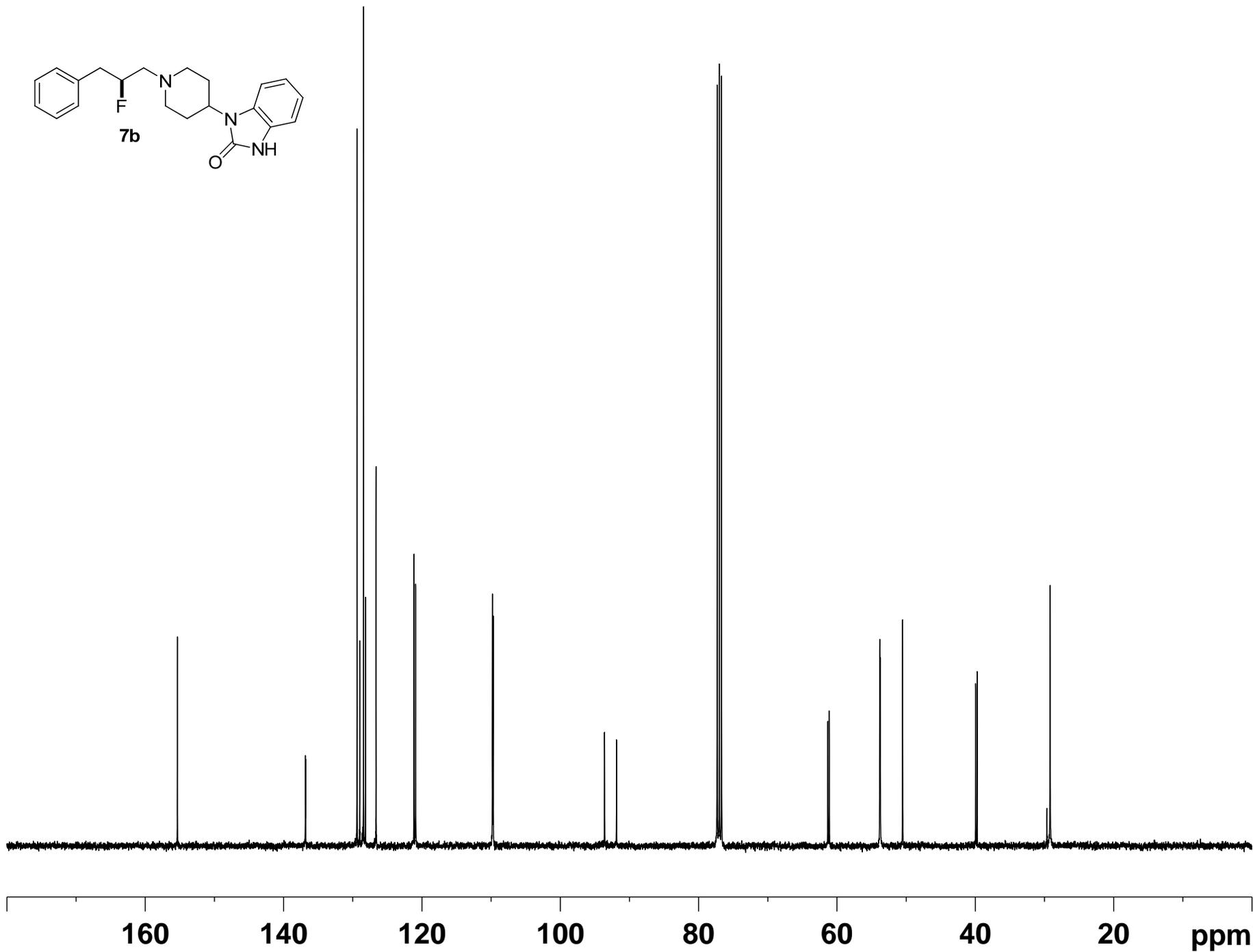
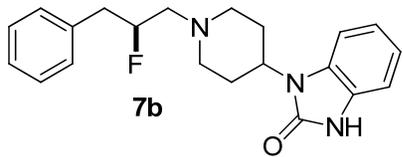
The product was prepared according to the general procedure and purified by SiO₂ chromatography (50% EtOAc/hexanes) to afford the product as a white solid (12.0 mg, 68%), R_f = 0.78 (50% EtOAc/hexanes); IR (neat) 2927, 1691, 1477, 1373 cm⁻¹; ¹H NMR (600.1 MHz, CDCl₃) δ (ppm): 7.25-7.33 (m, 5H), 3.49 (m, 1H), 3.41 (br s, 4H), 2.53 (m, 3H), 2.42 (m, 1H), 2.27 (m, 2H), 1.46 (s, 9H), 1.43 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm): 154.6, 140.0 (d, *J* = 7.0 Hz), 128.7, 128.2, 127.1, 125.2 (t, *J* = 246.4 Hz), 79.5, 59.9 (dd, *J* = 6.0, 57.3 Hz), 53.6, 43.9 (dd, *J* = 3.0, 46.2 Hz), 28.3, 14.3 (t, *J* = 4.5 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -98.7, -99.6, -106.1, -106.9; HRMS (TOF, ES⁺) C₁₉H₂₈F₂N₂O₂ [M+H]⁺ calc'd 355.2186, found 355.2194.

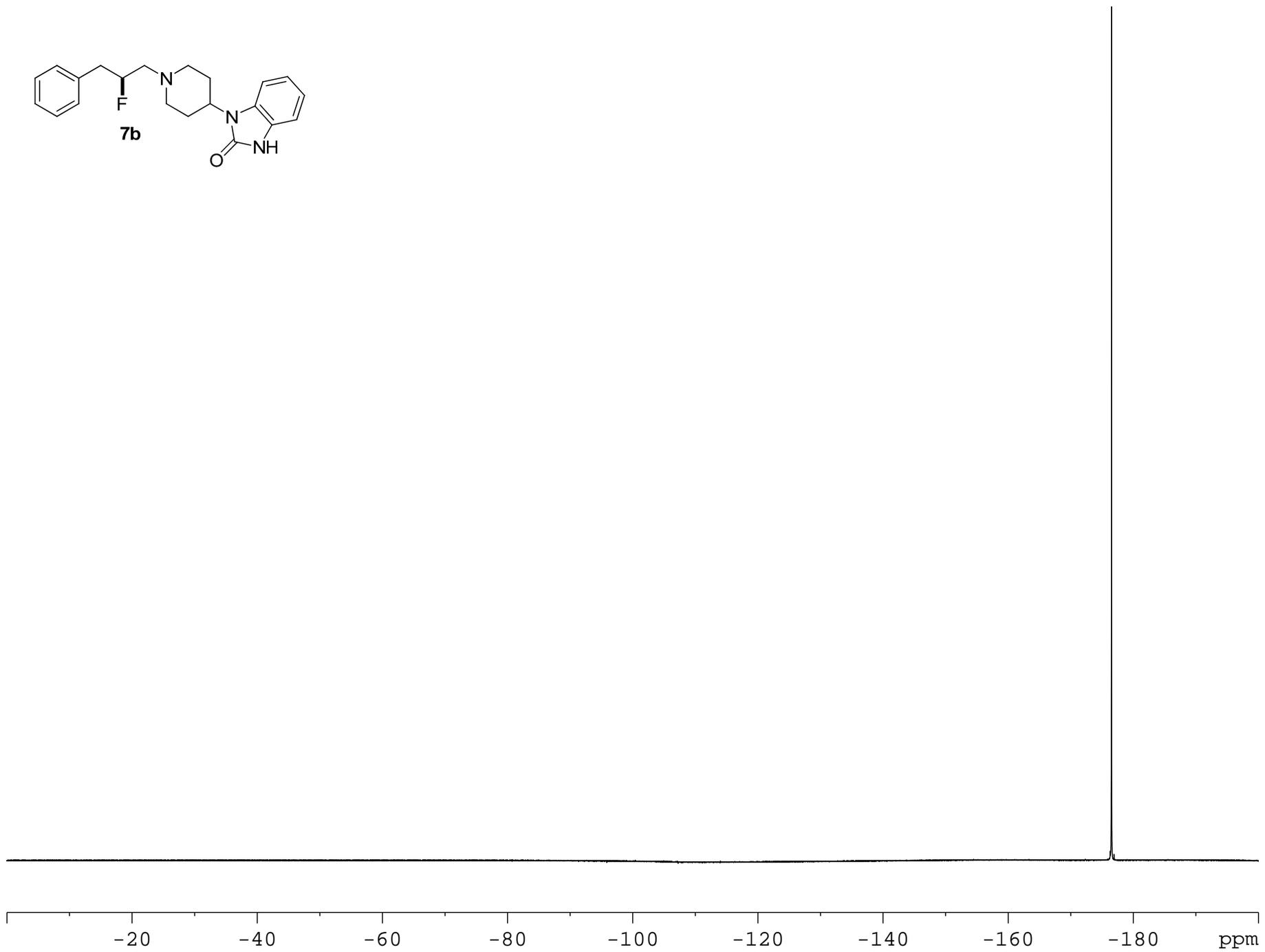
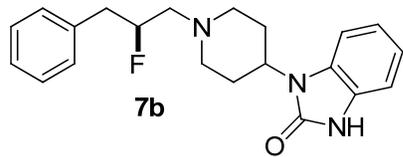


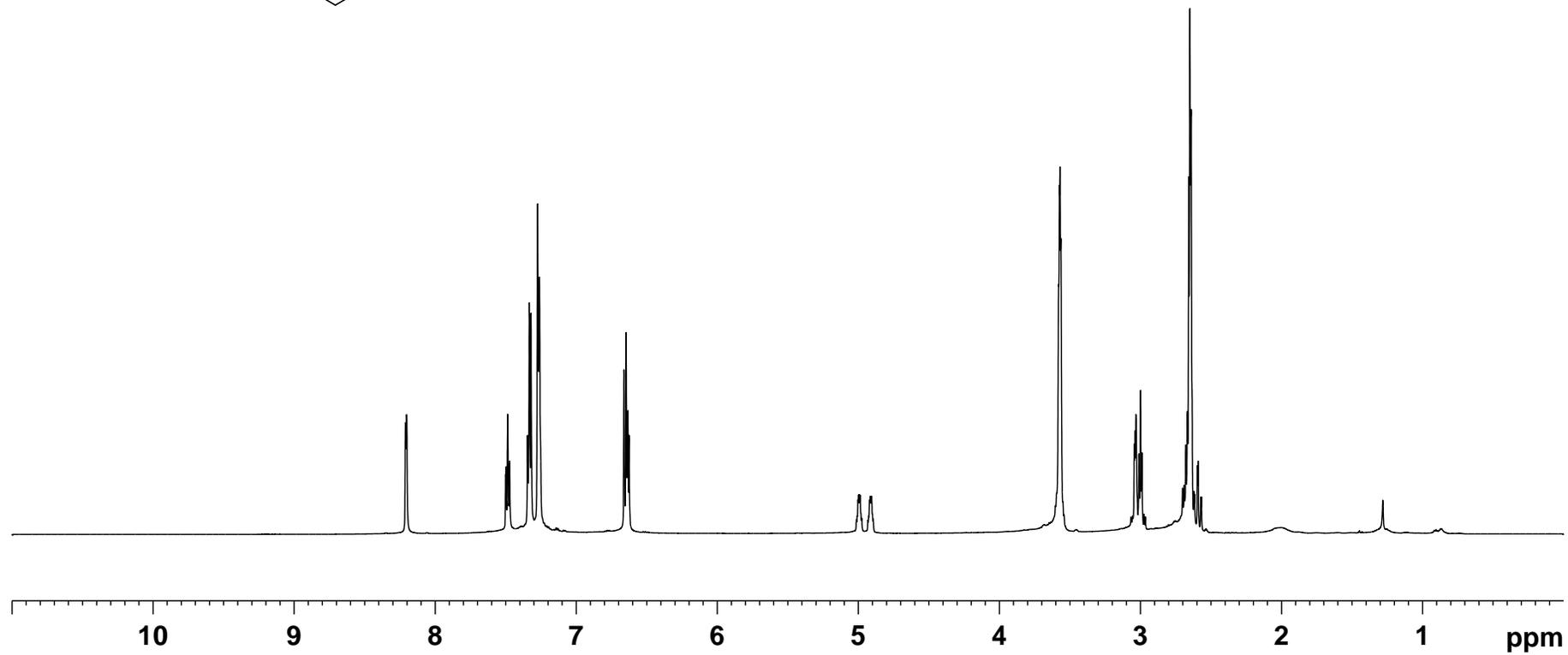
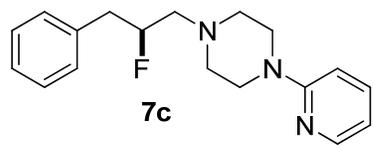


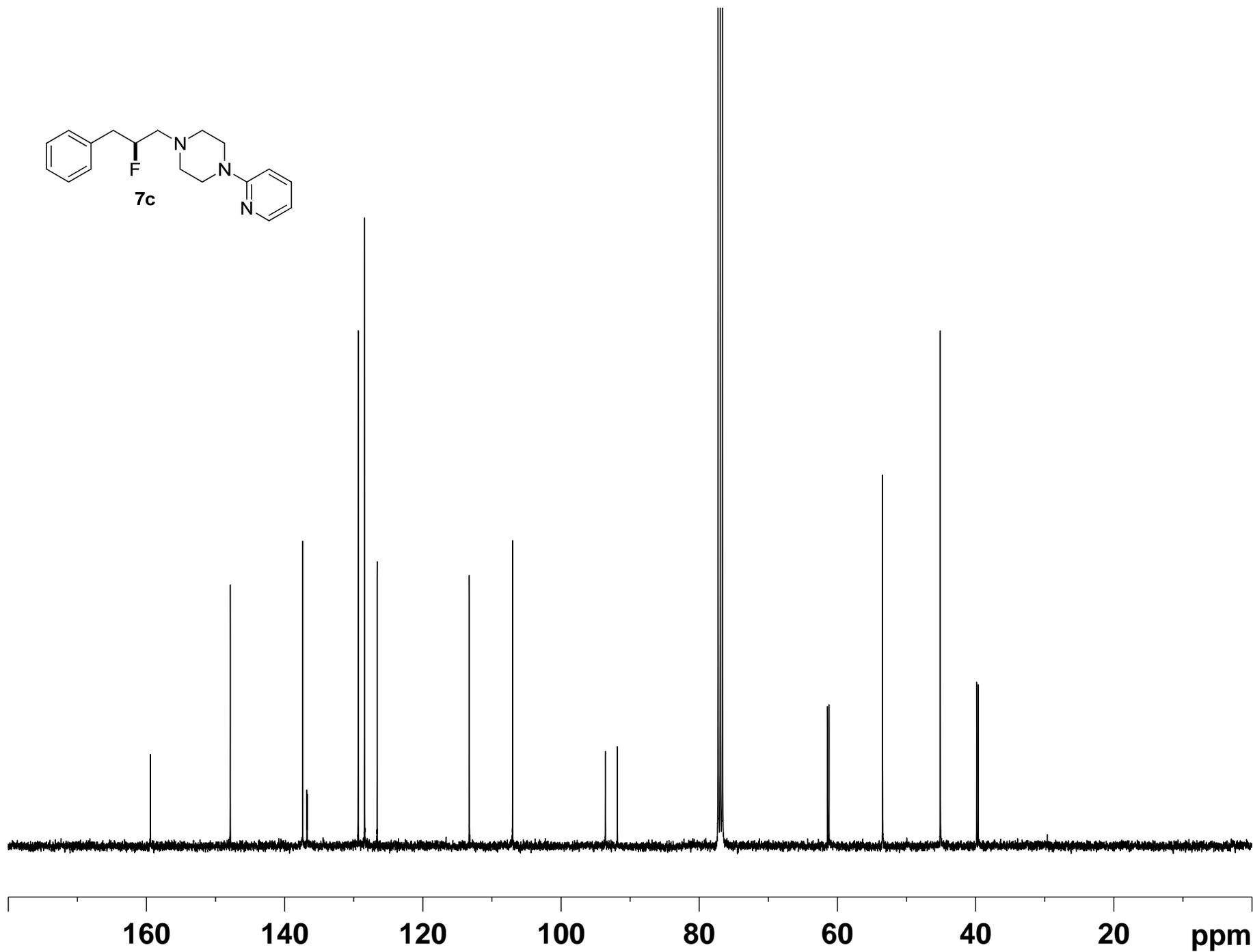
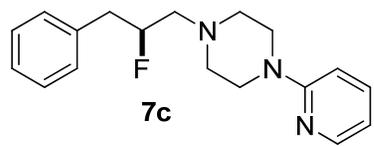


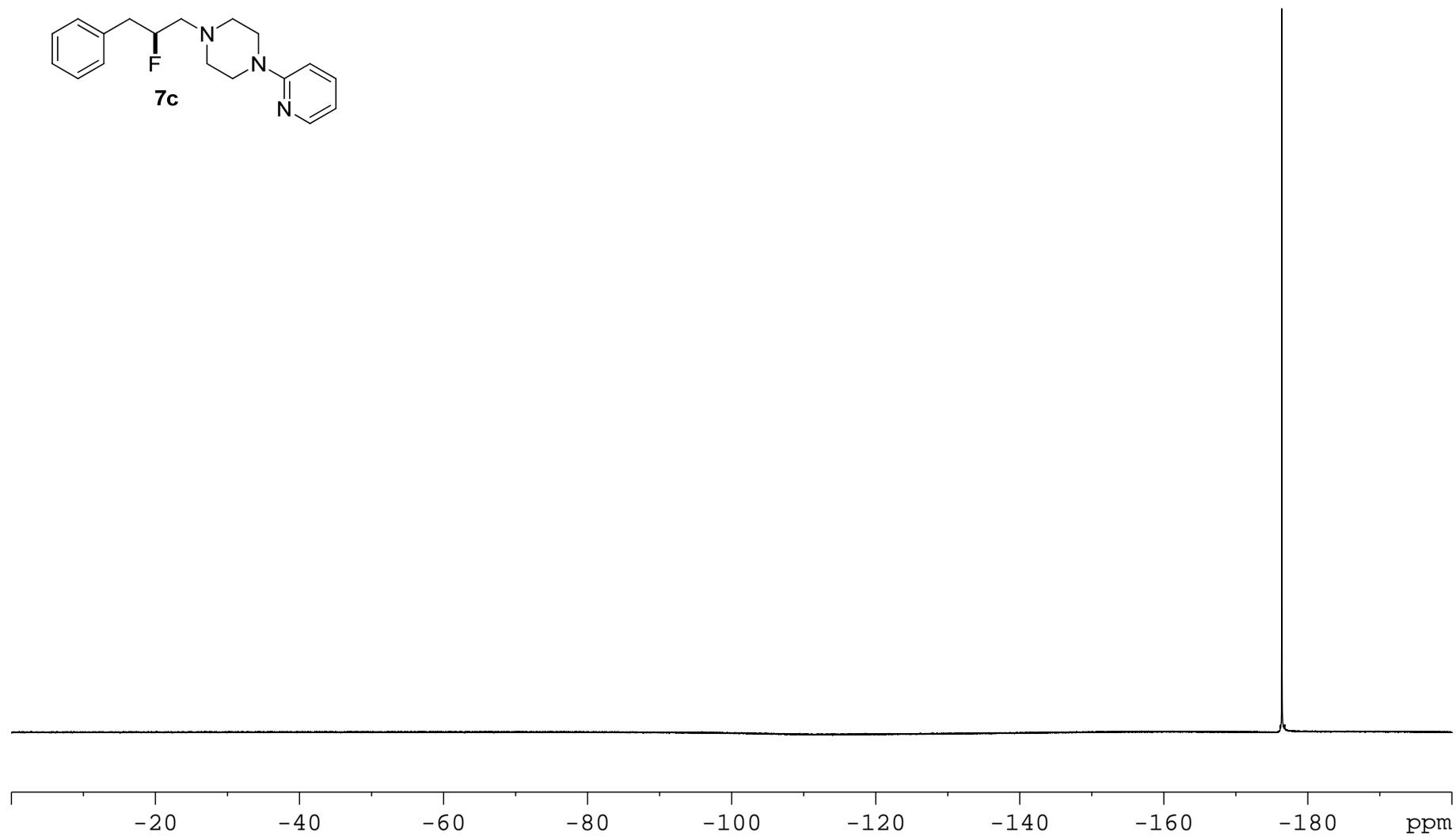
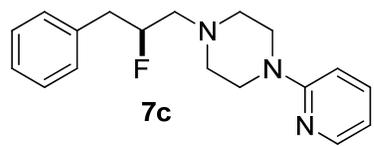


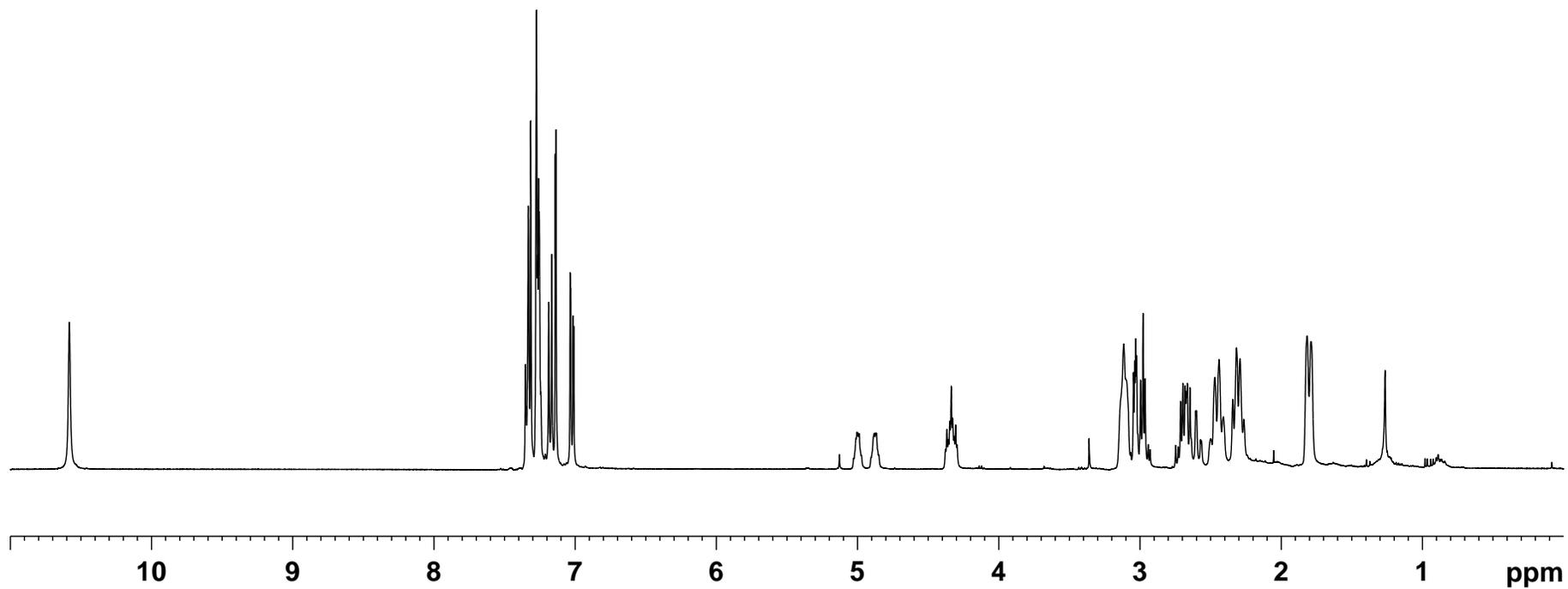
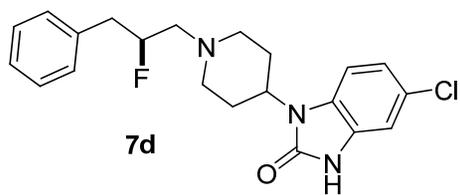


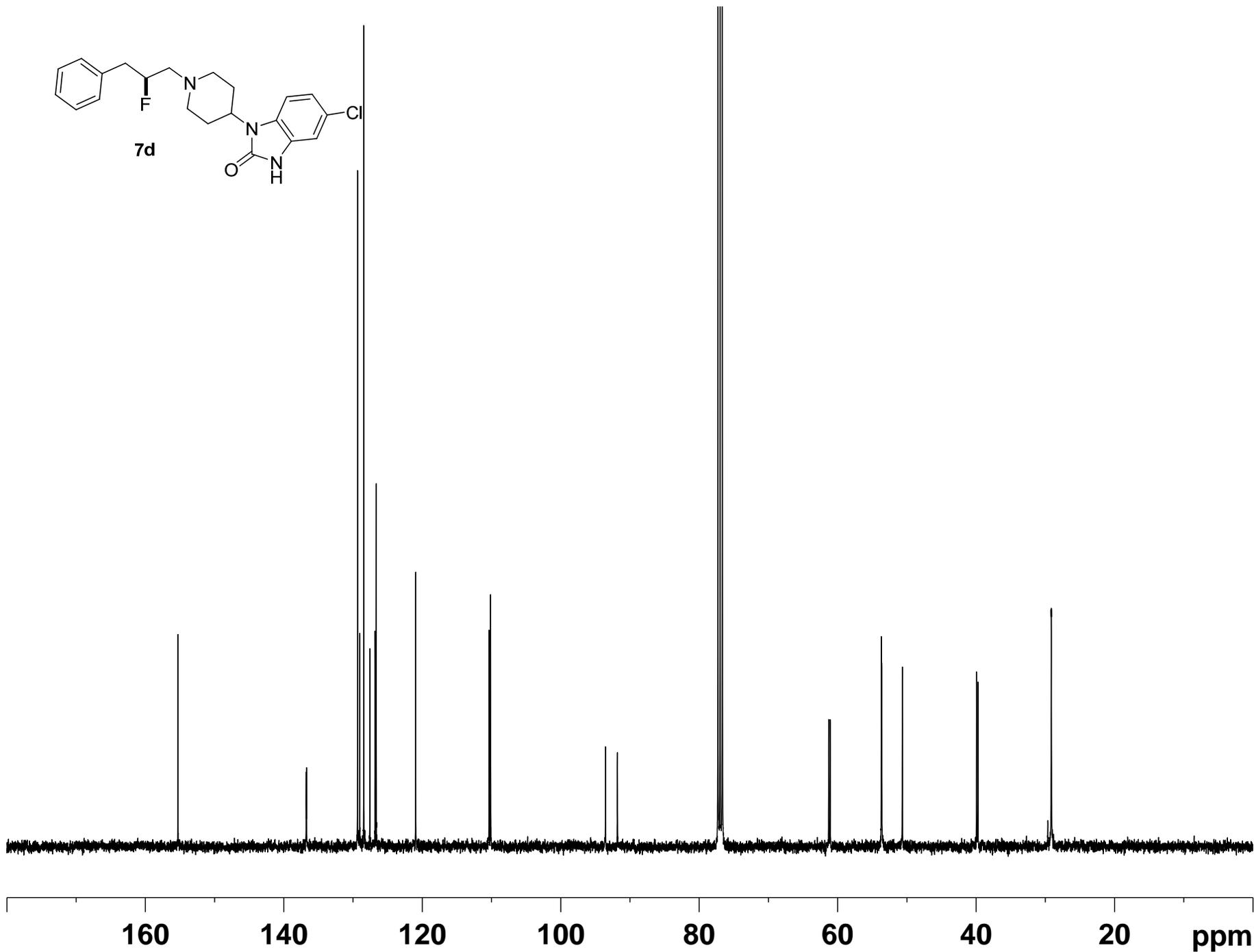
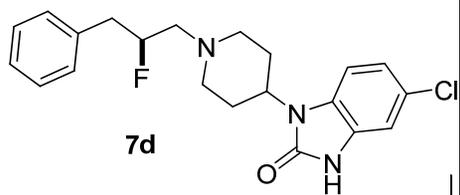


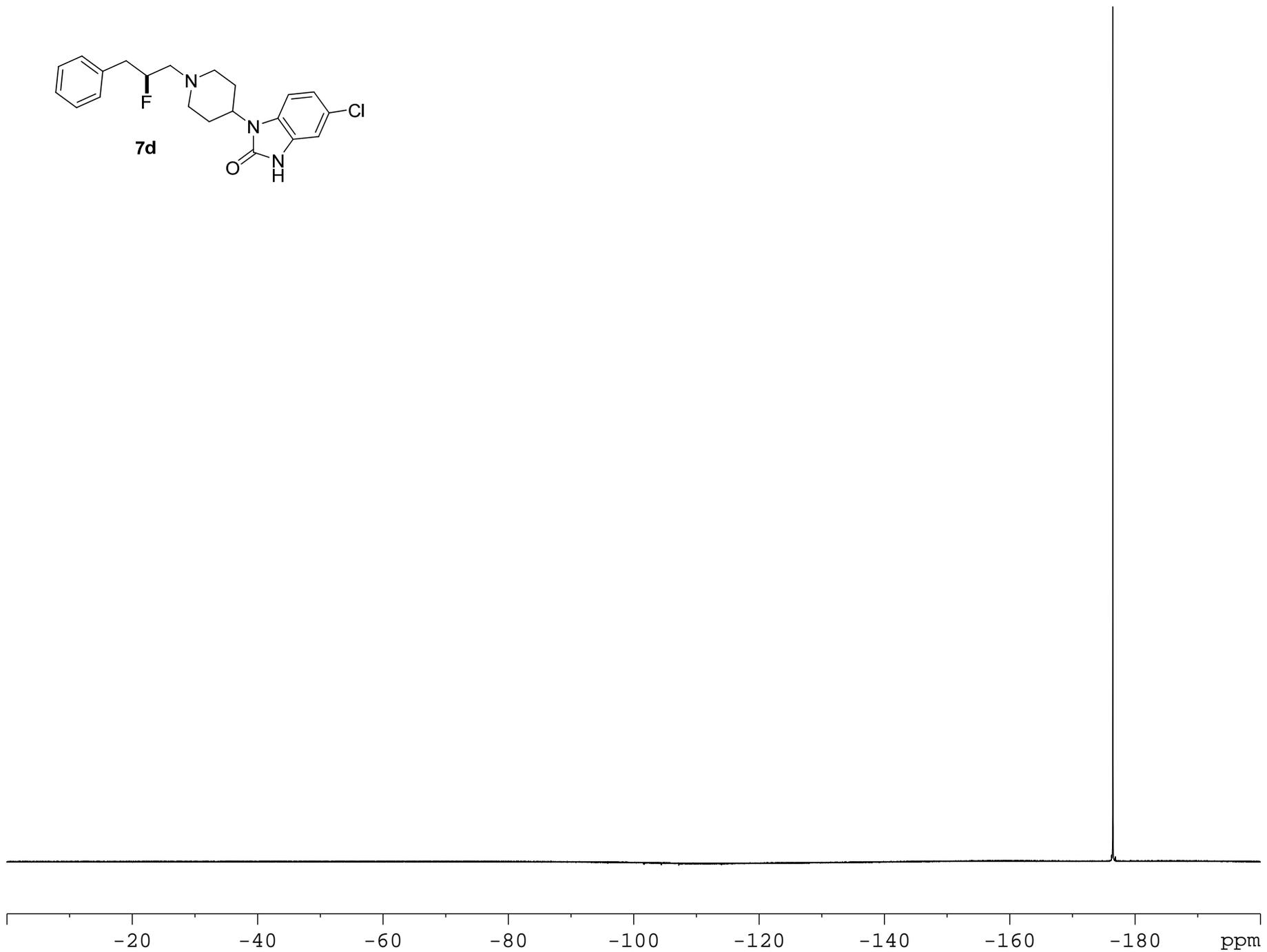
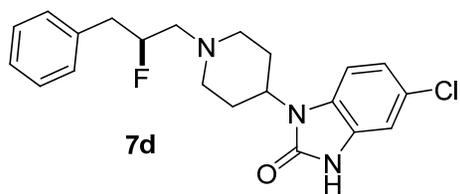


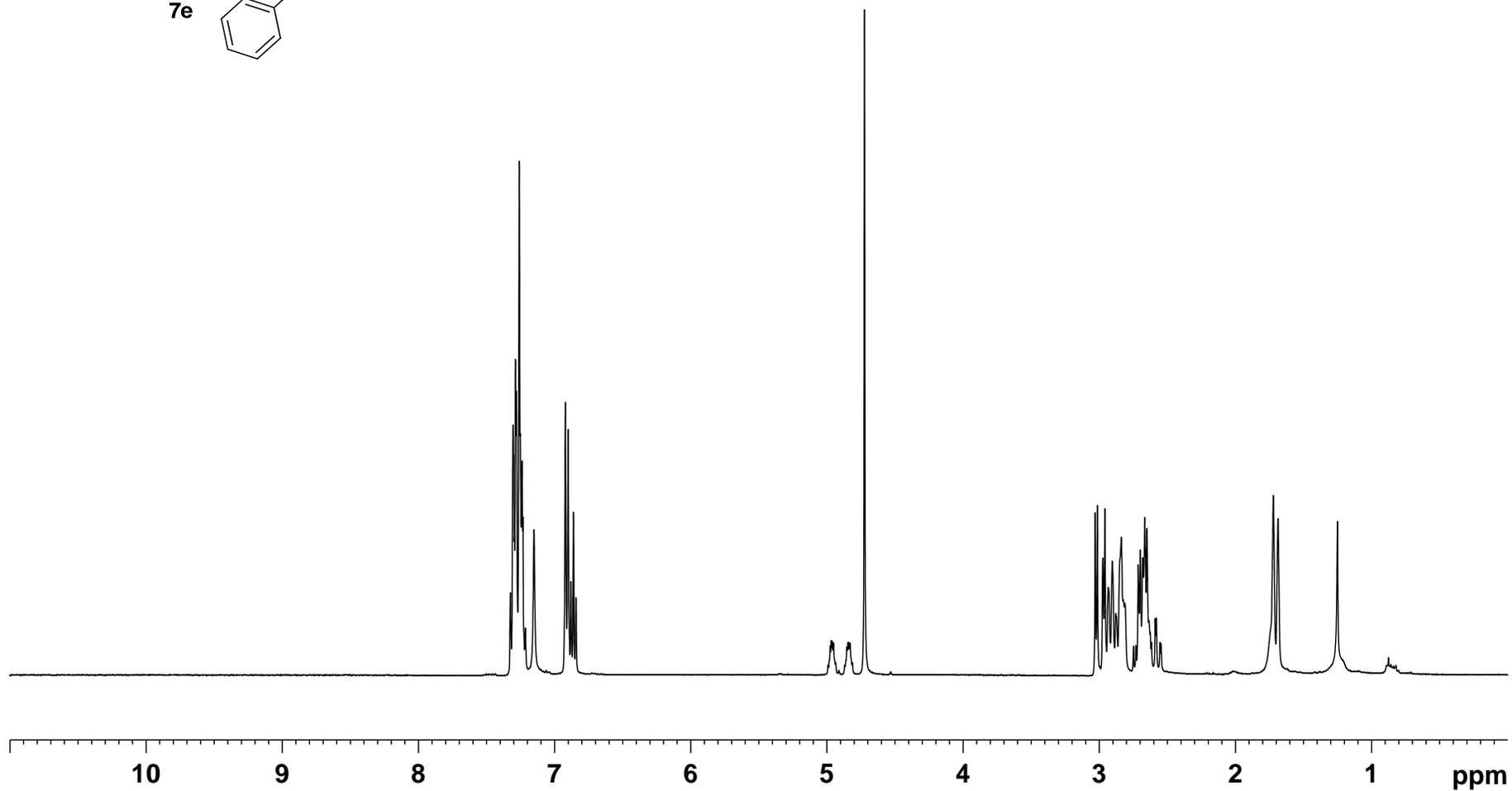
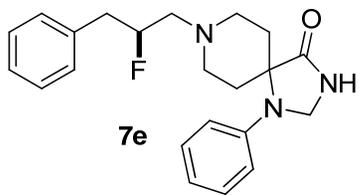


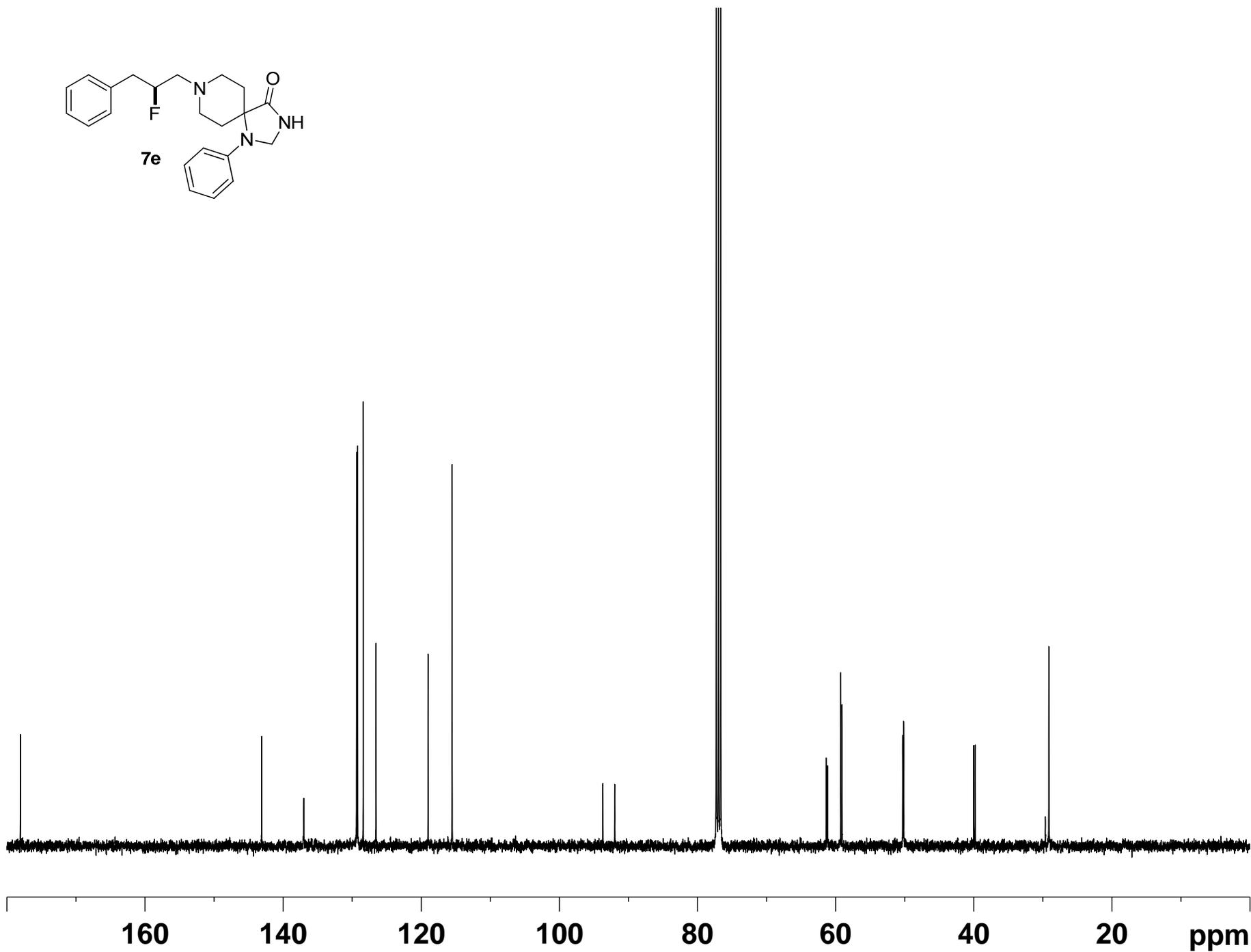
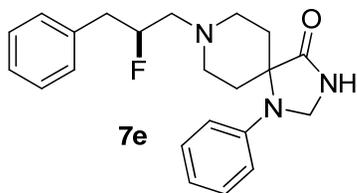


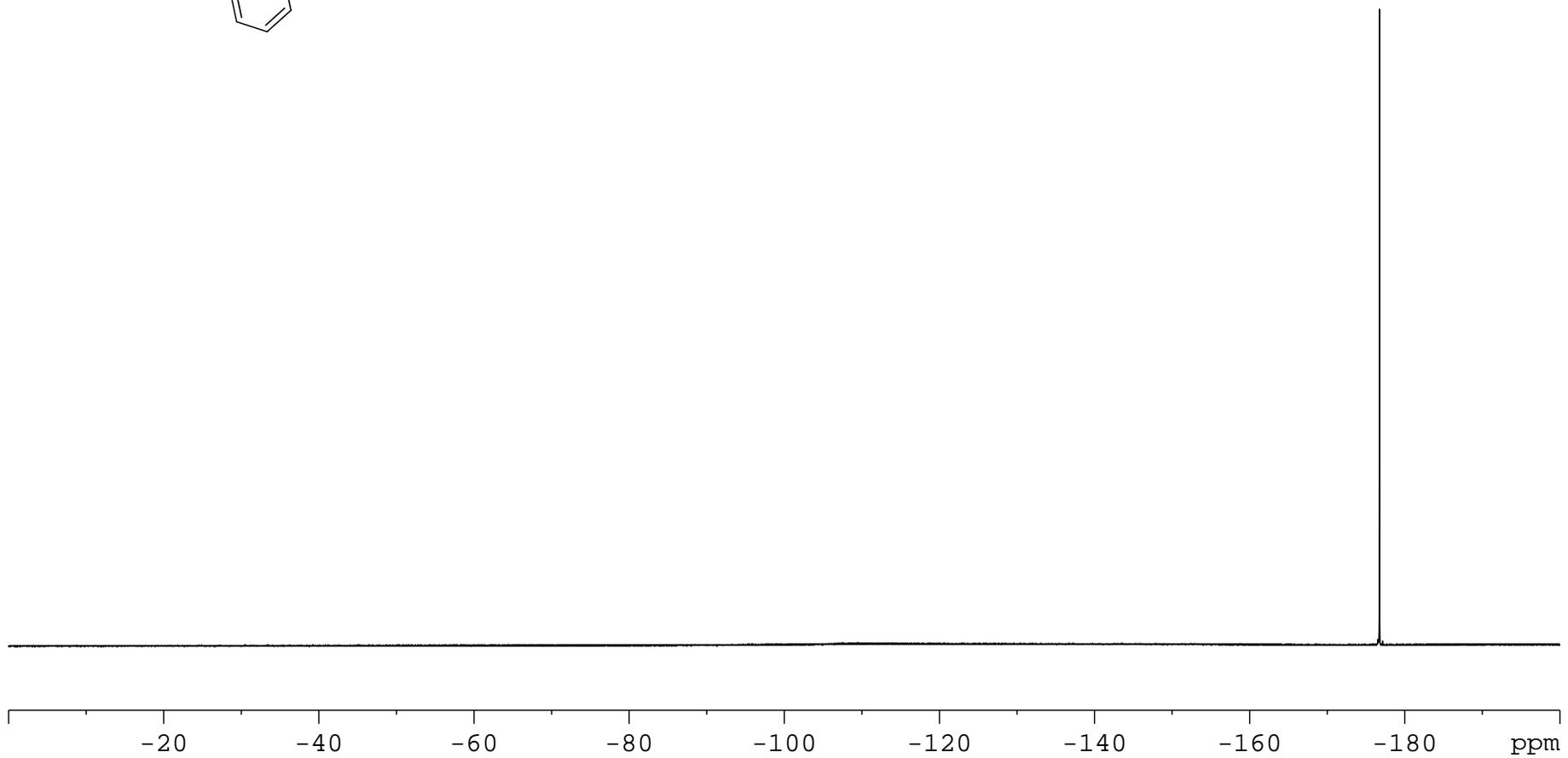
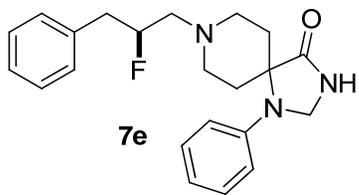


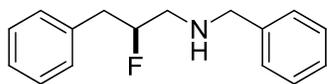




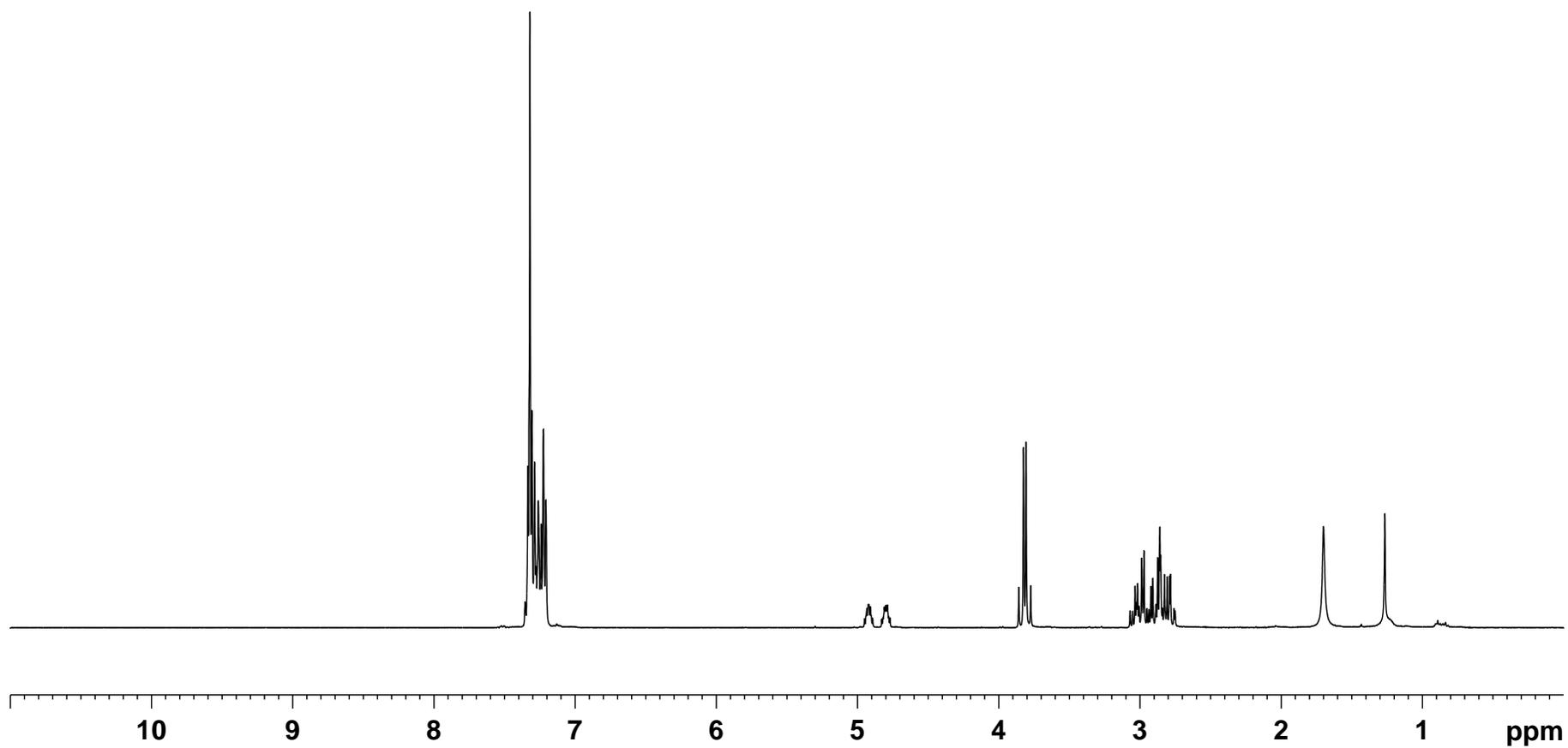


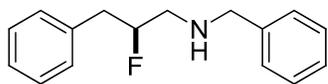




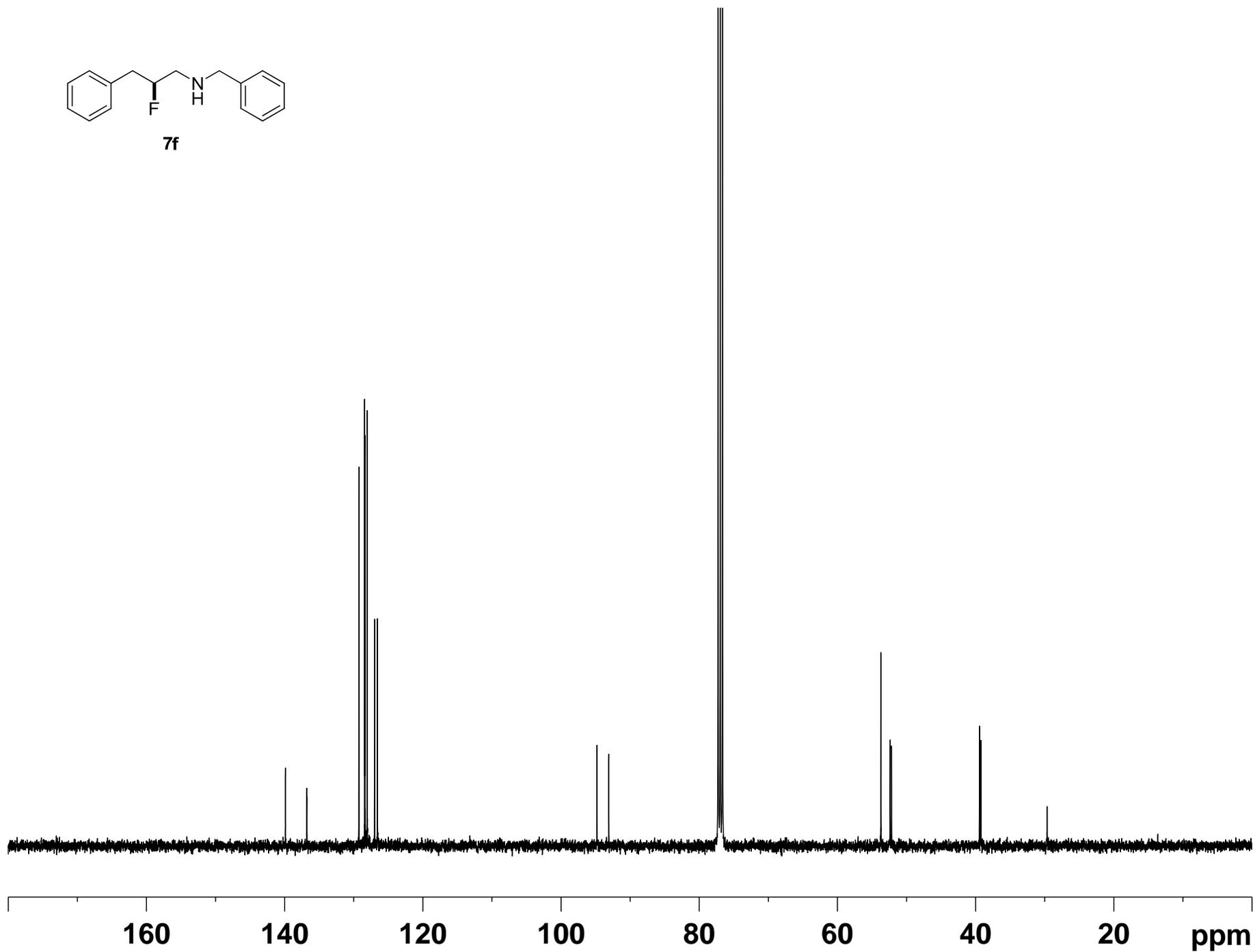


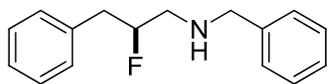
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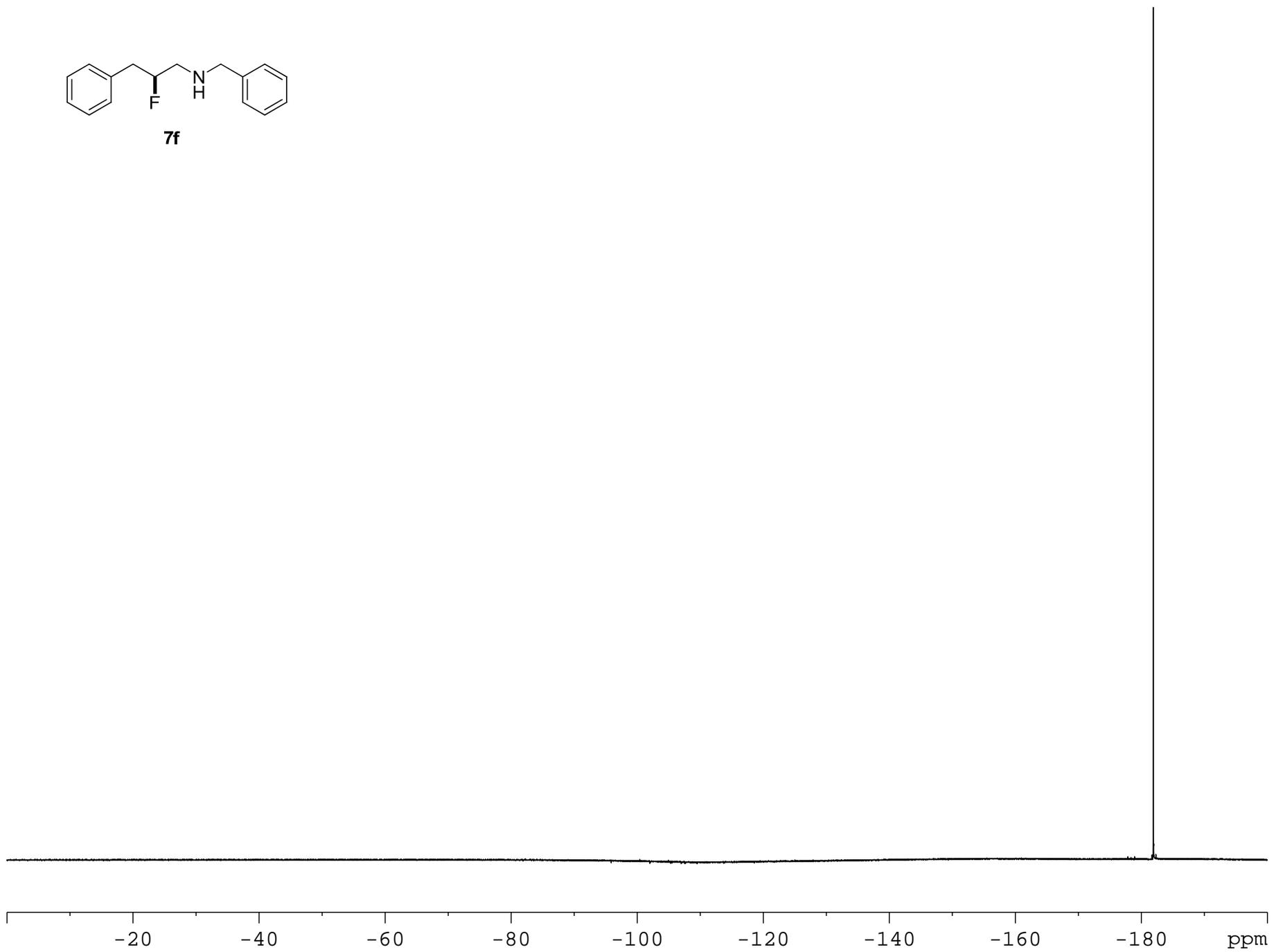


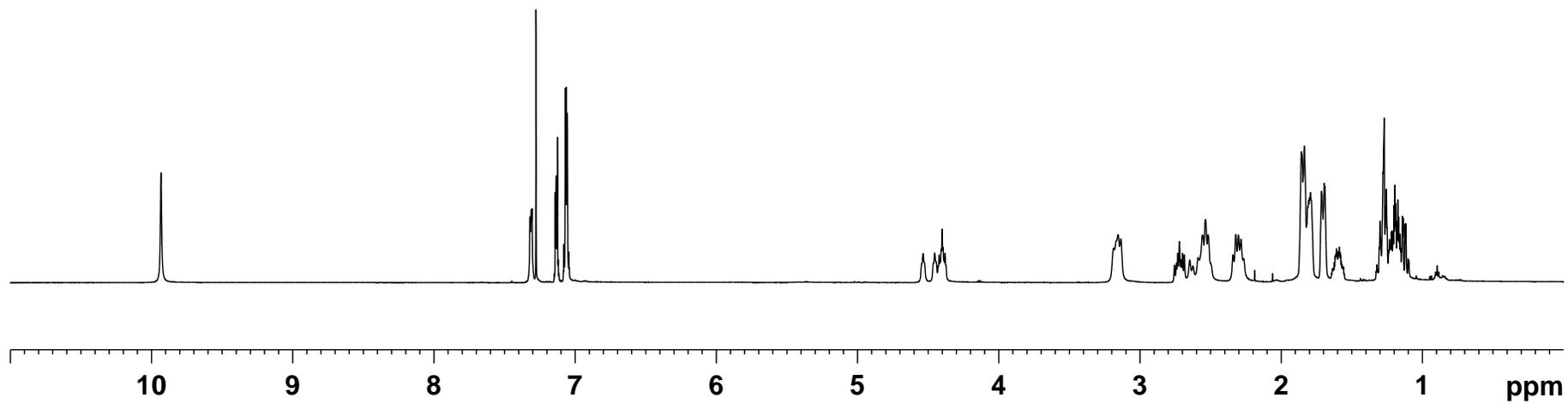
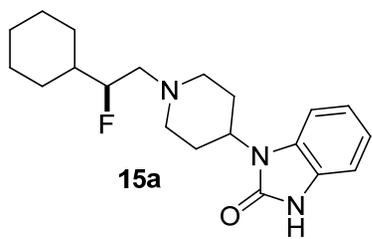
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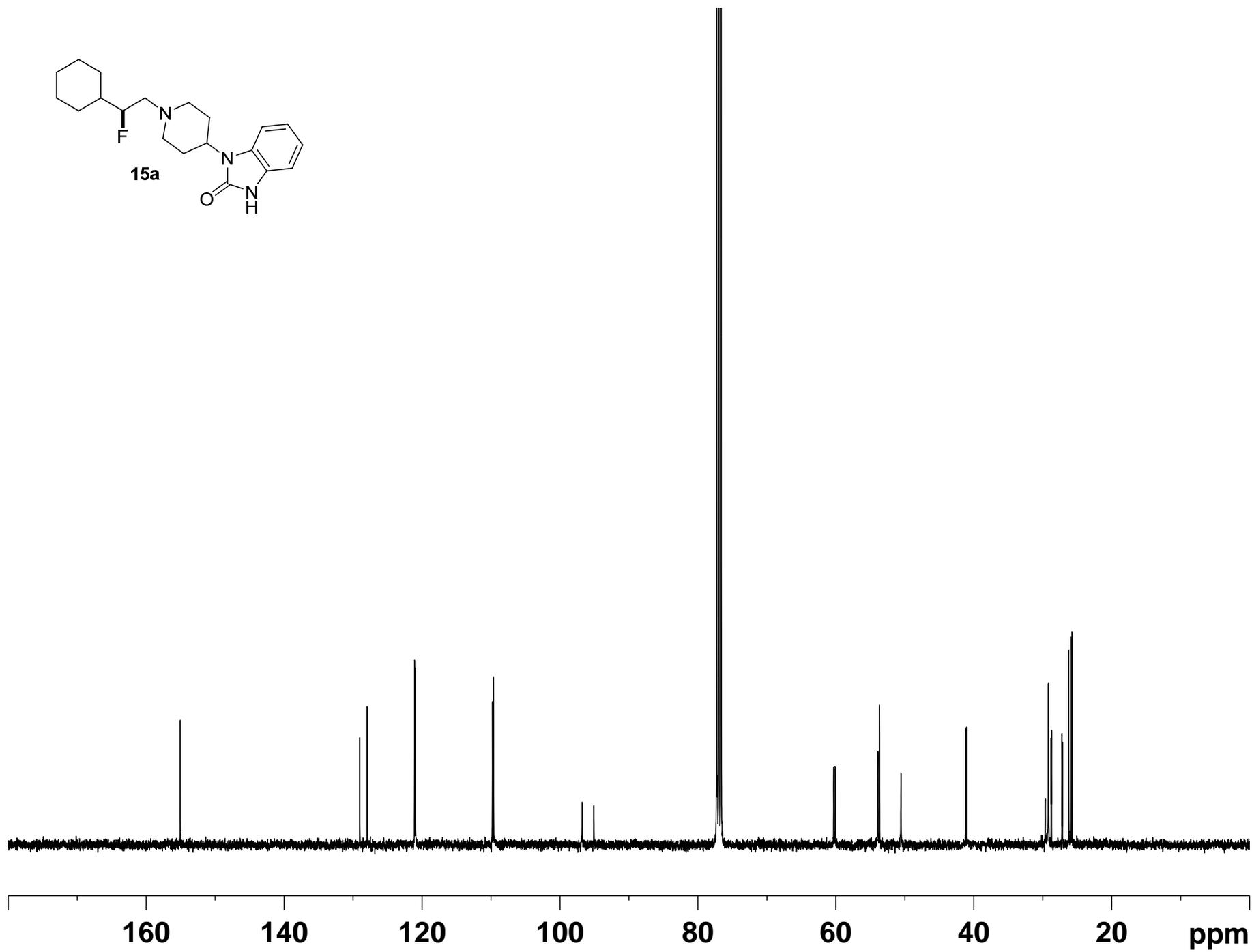
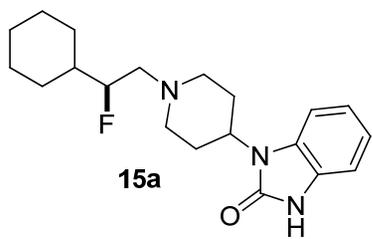


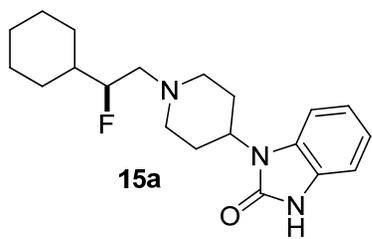


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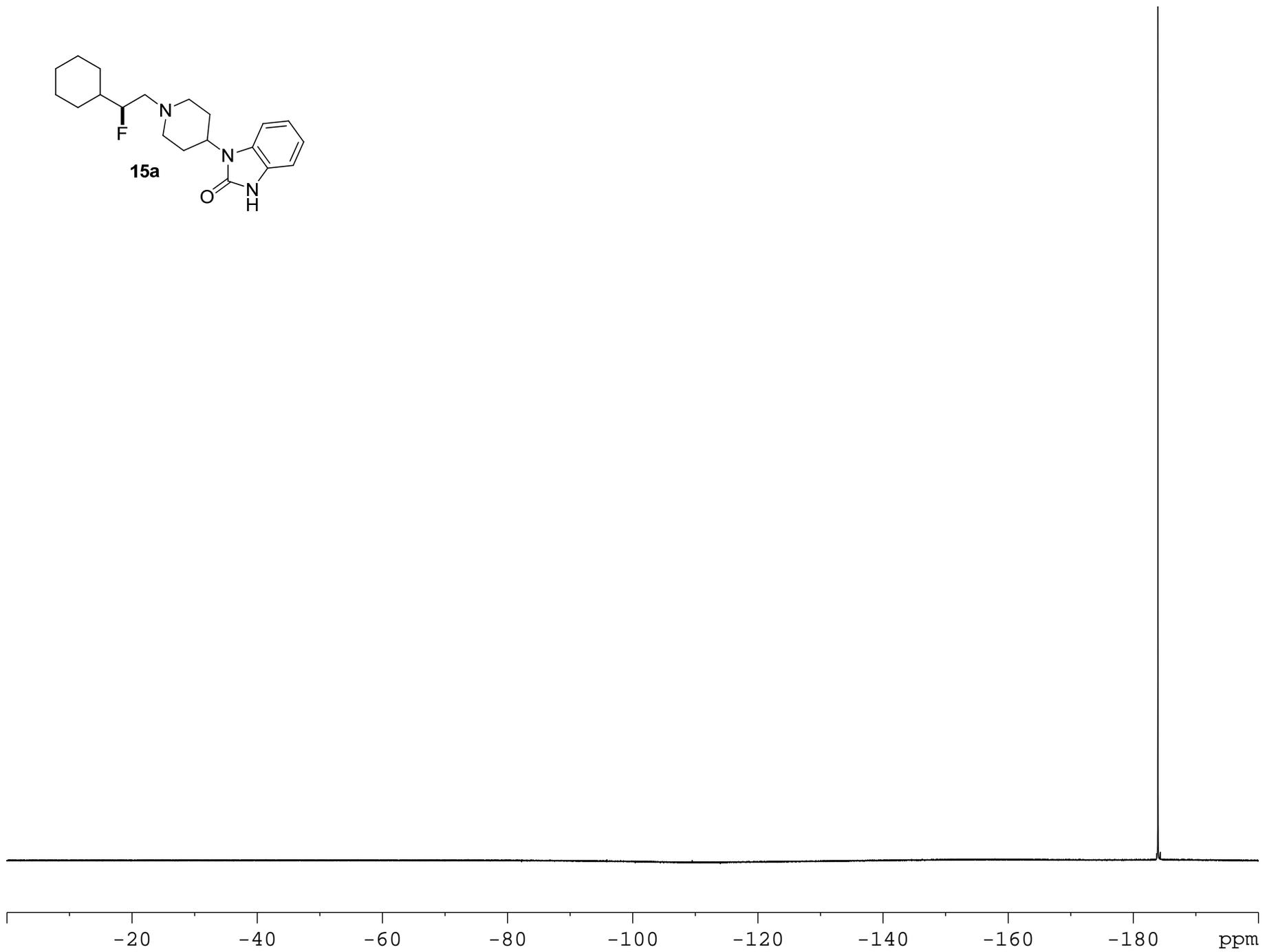


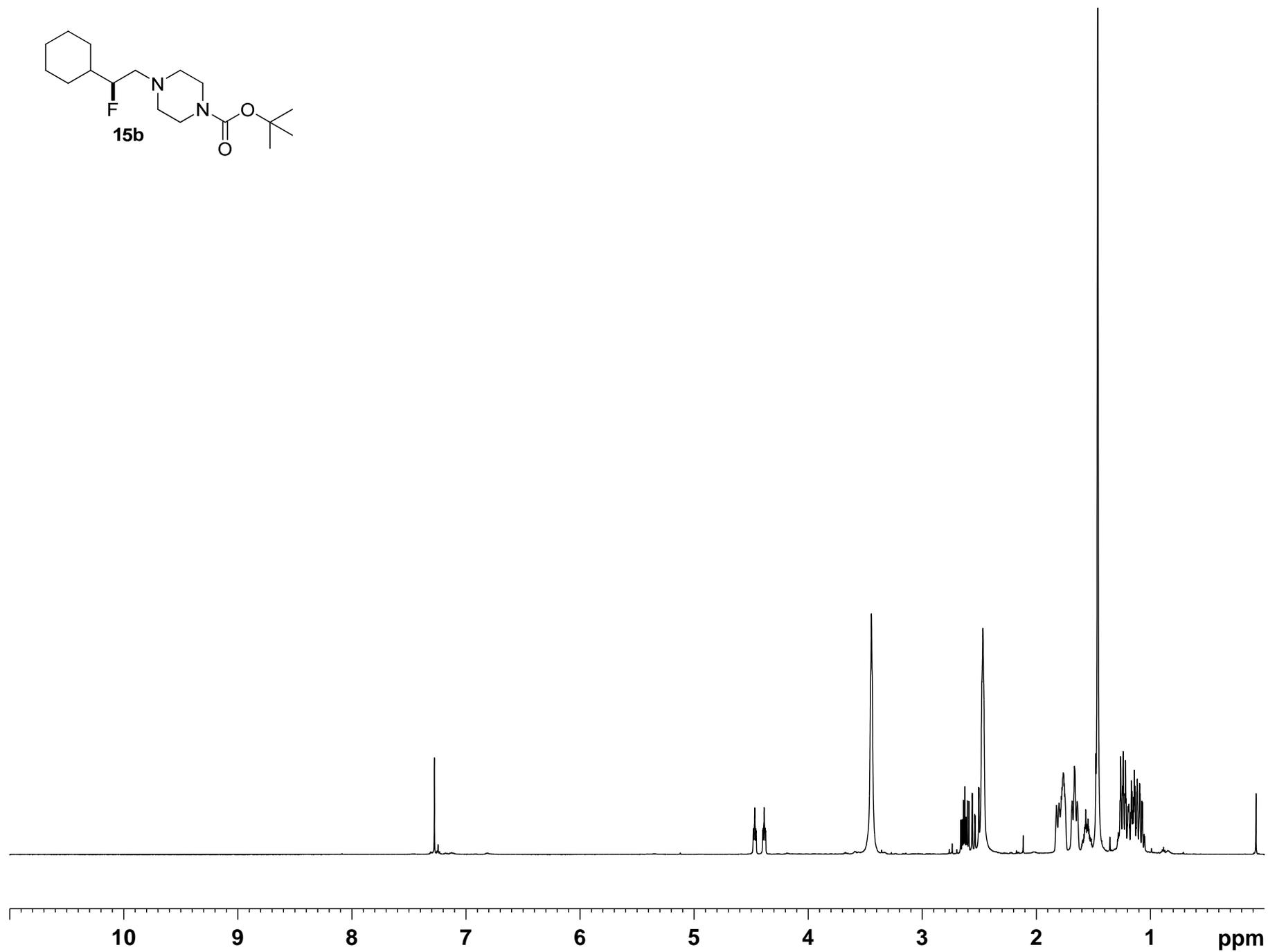
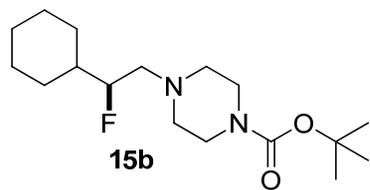


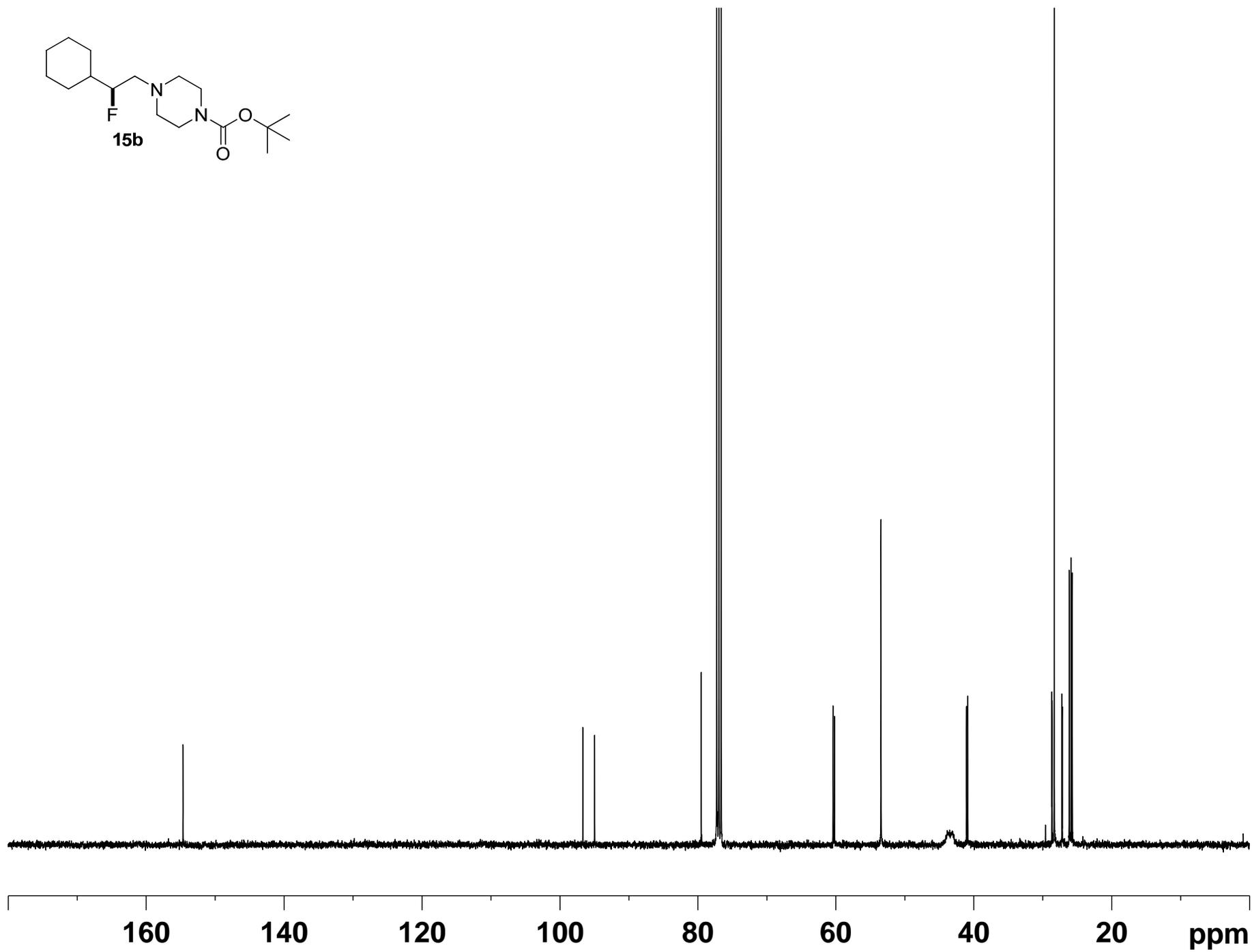
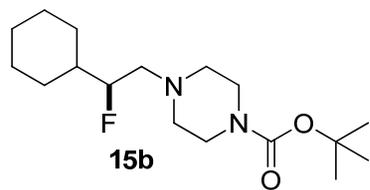


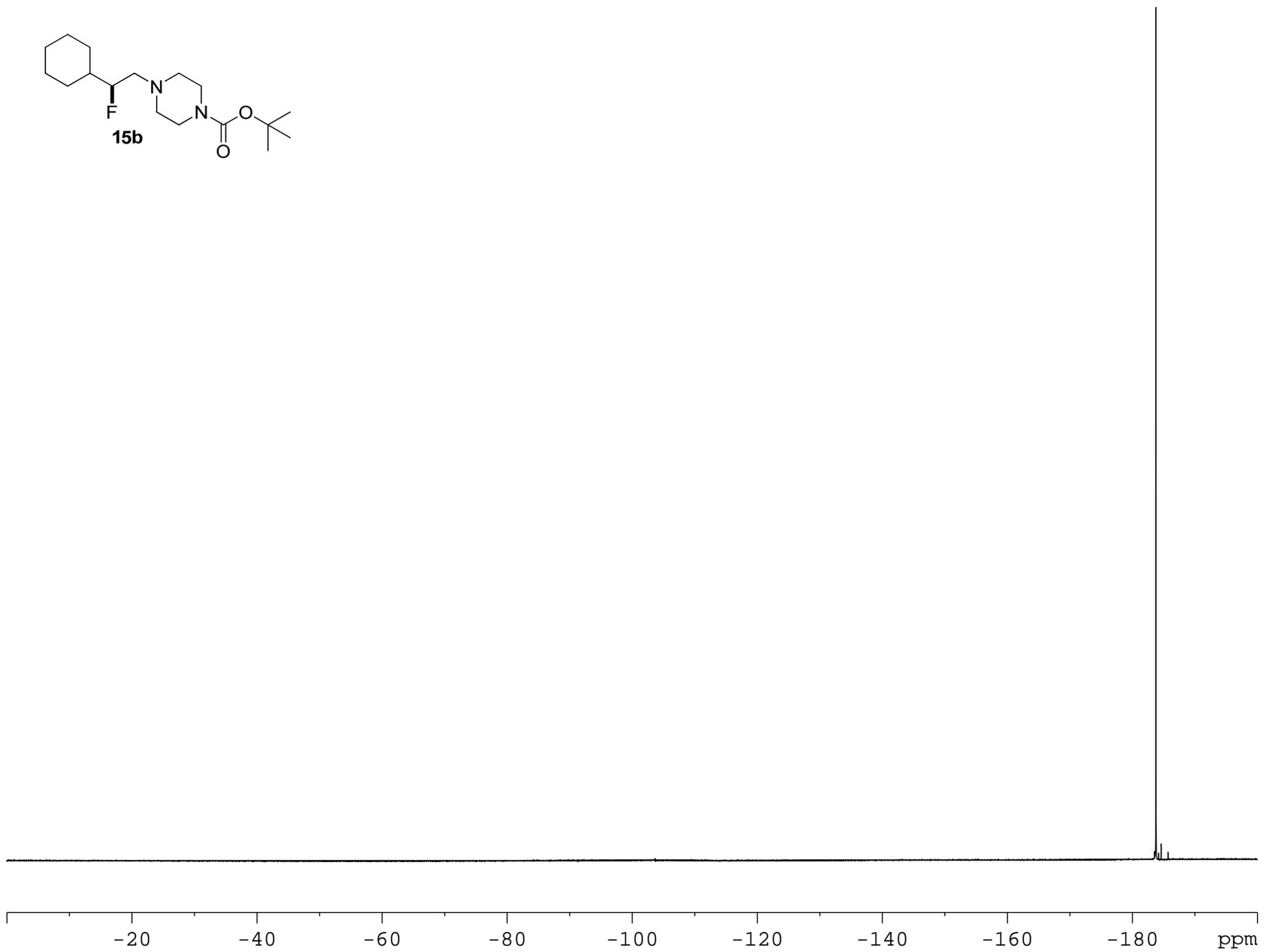
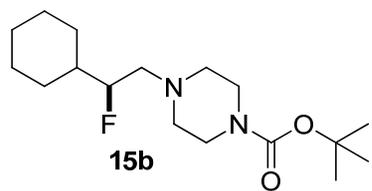


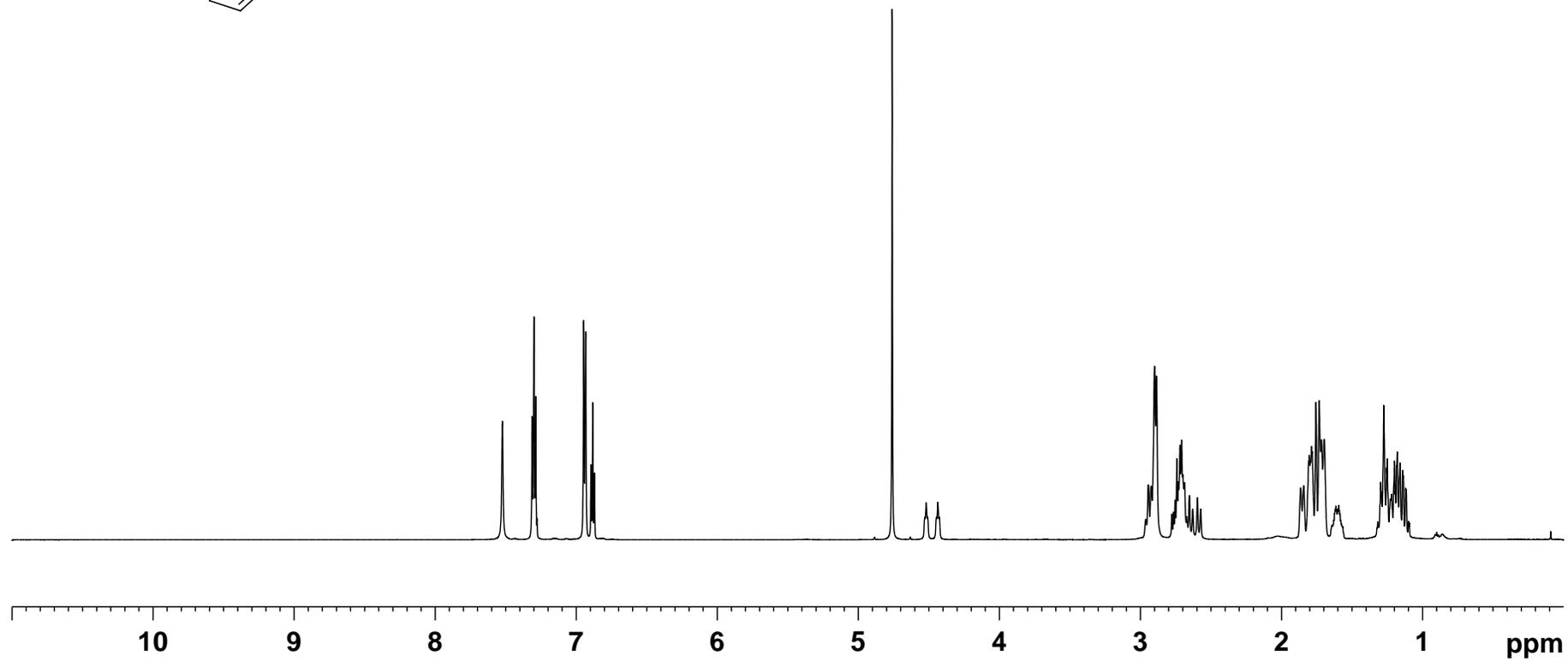
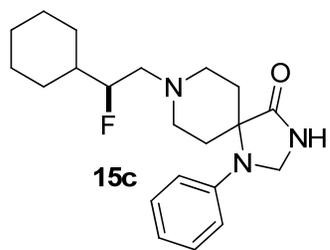
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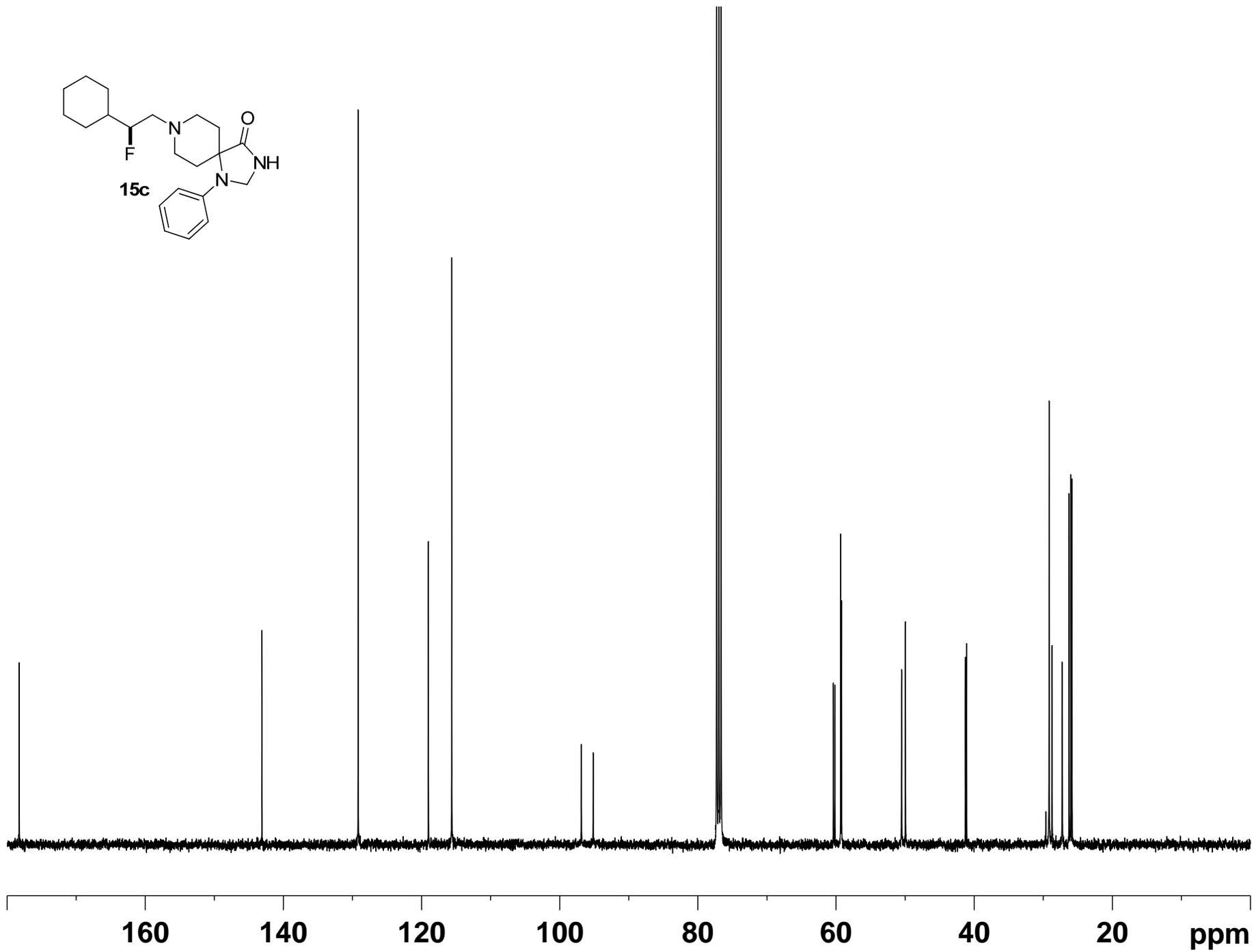
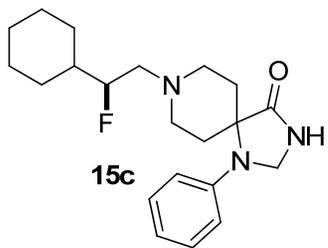


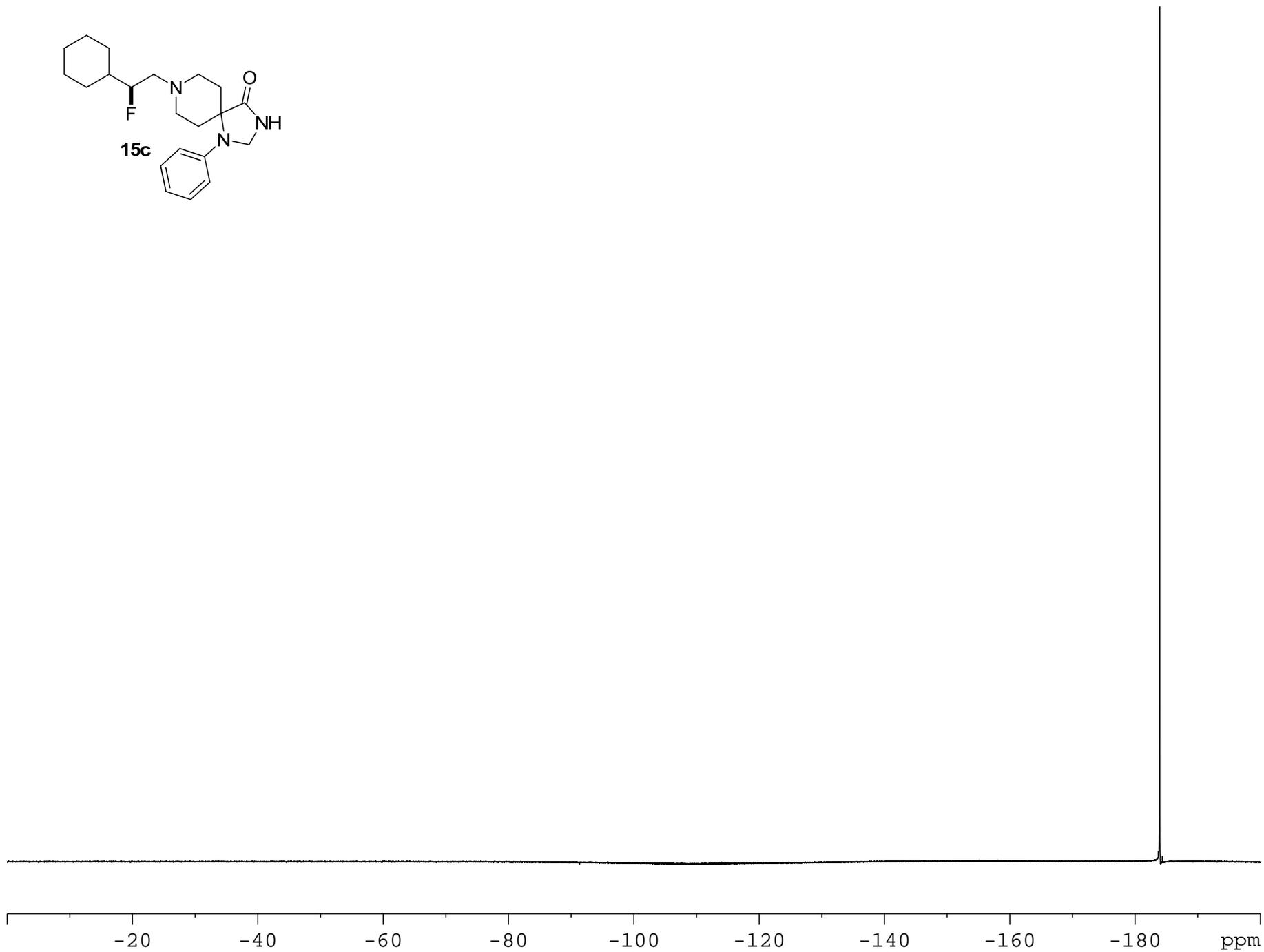
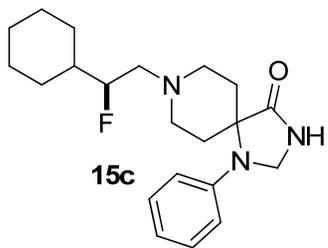


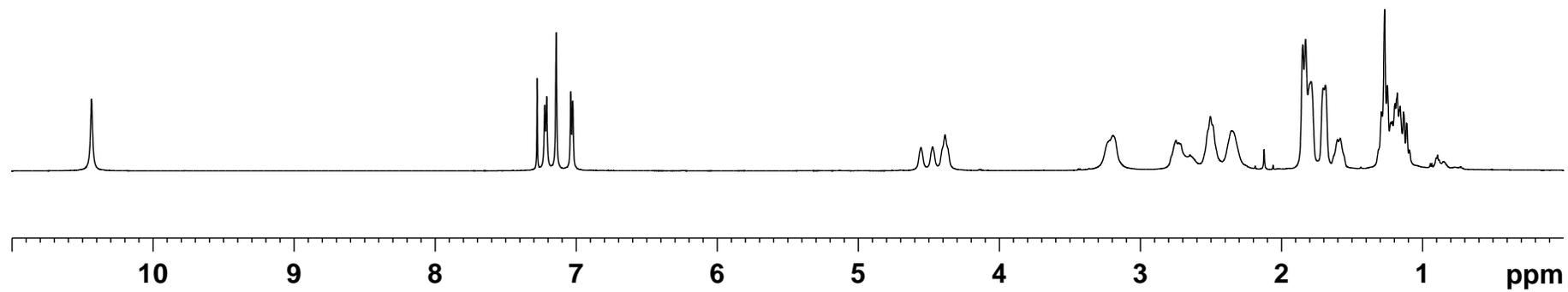
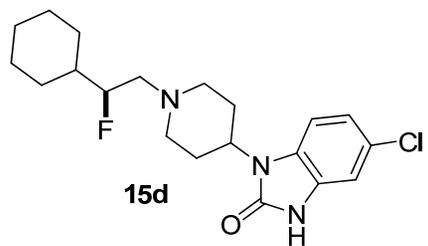


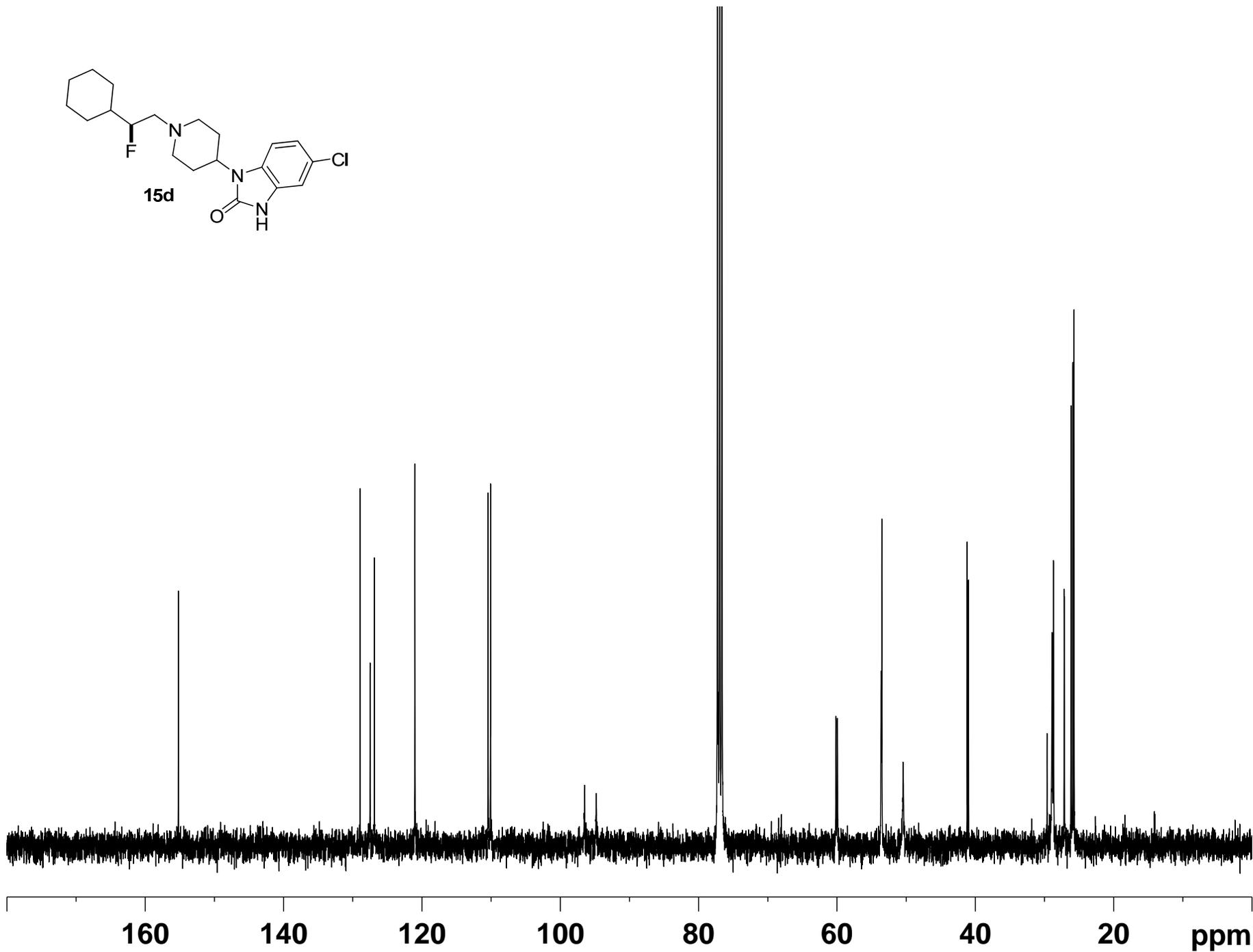
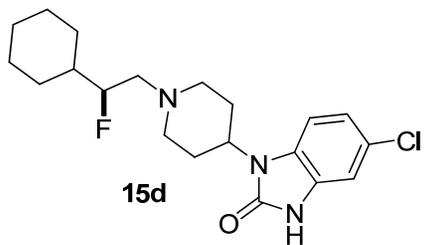


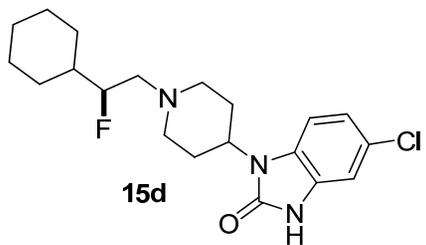




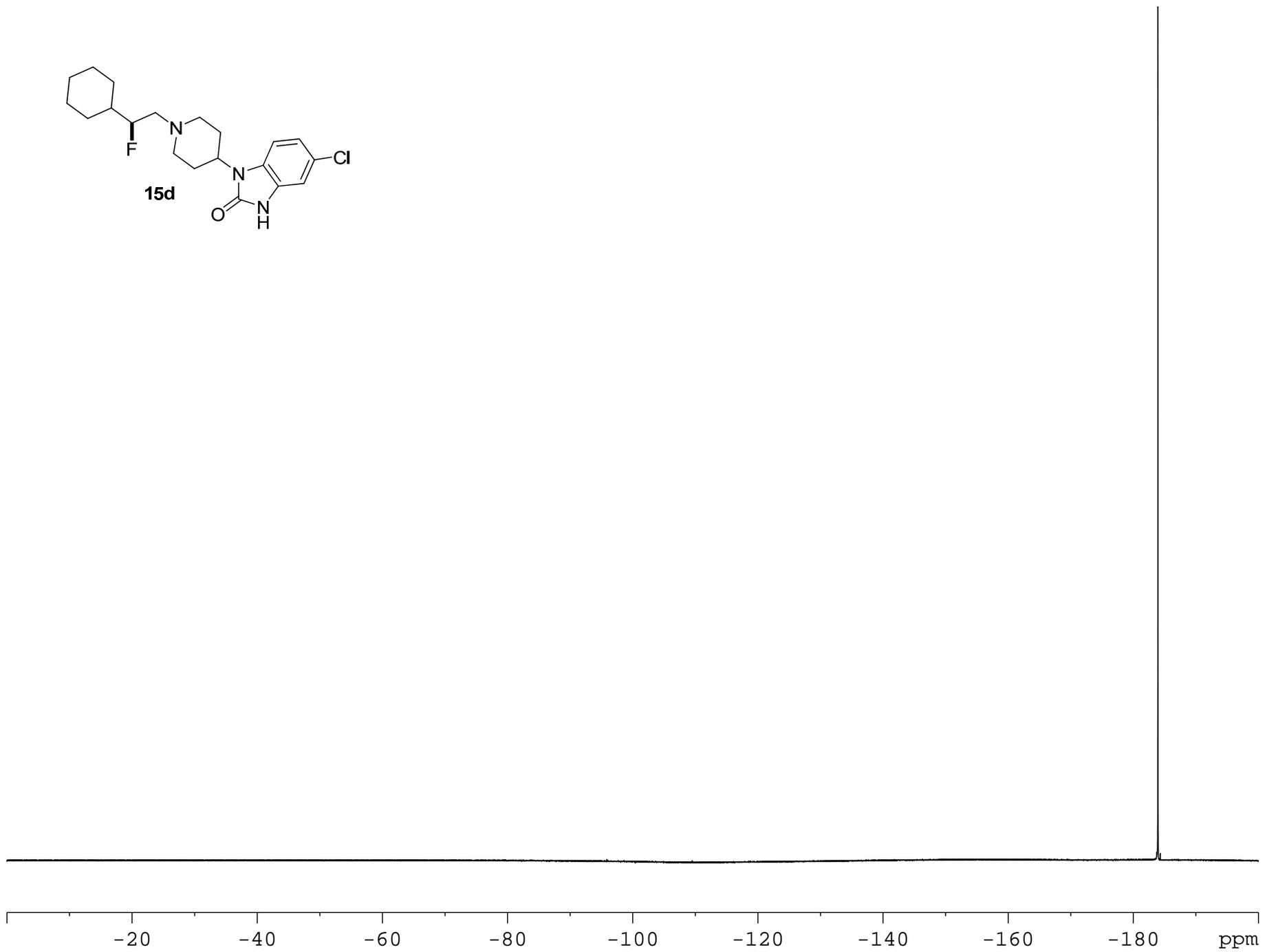


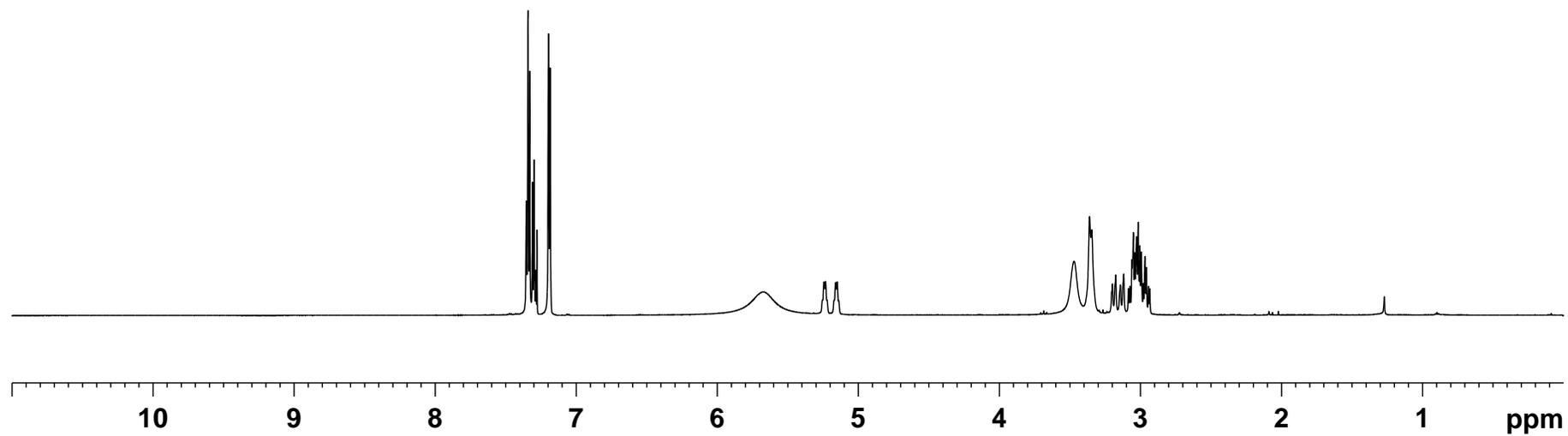
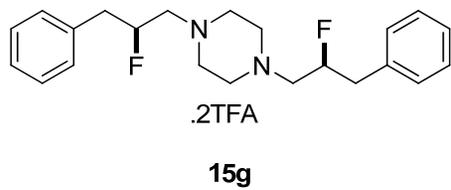


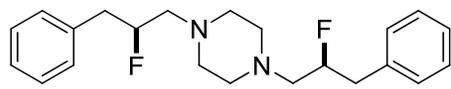




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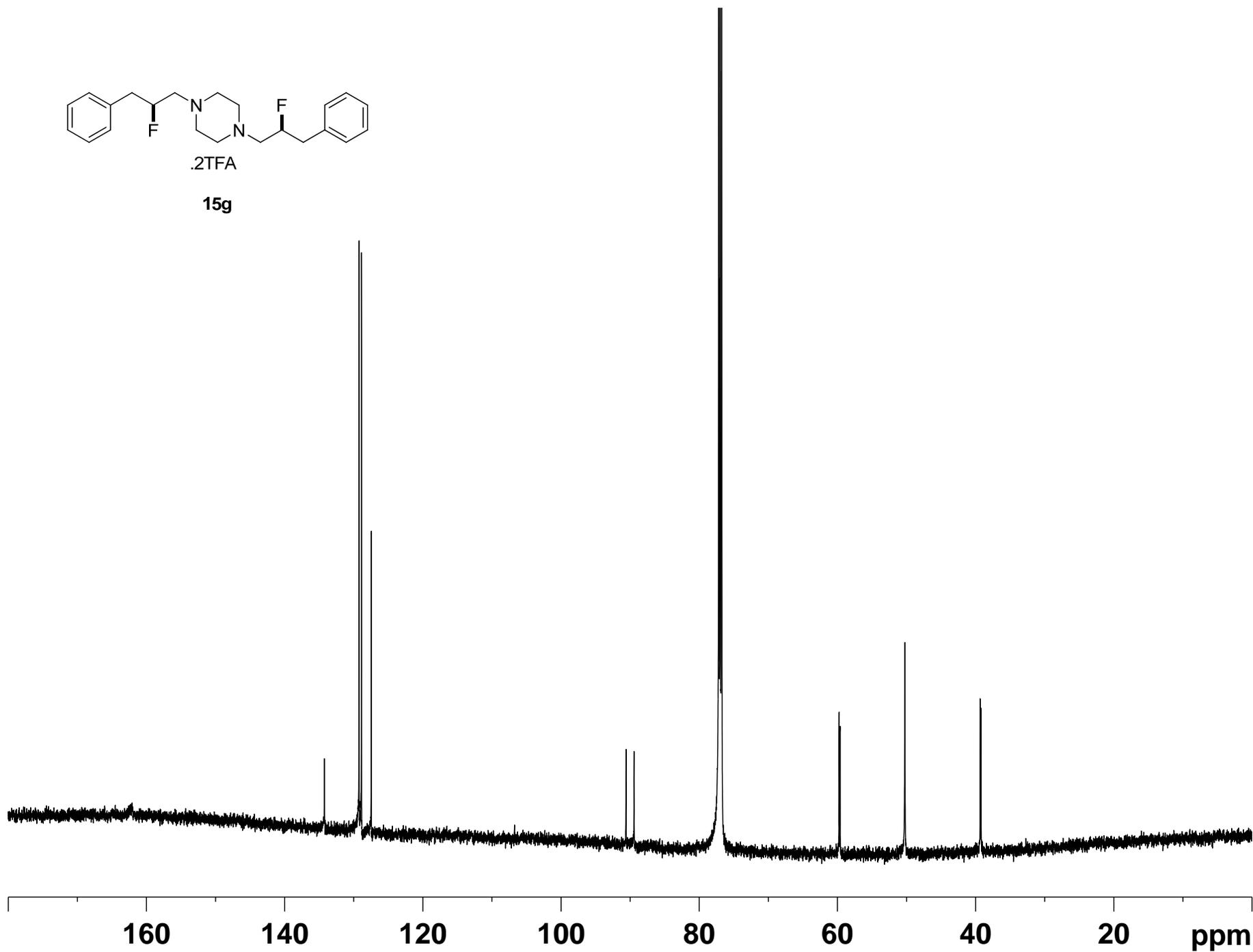


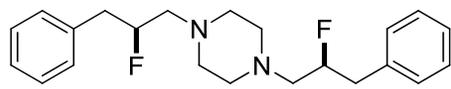




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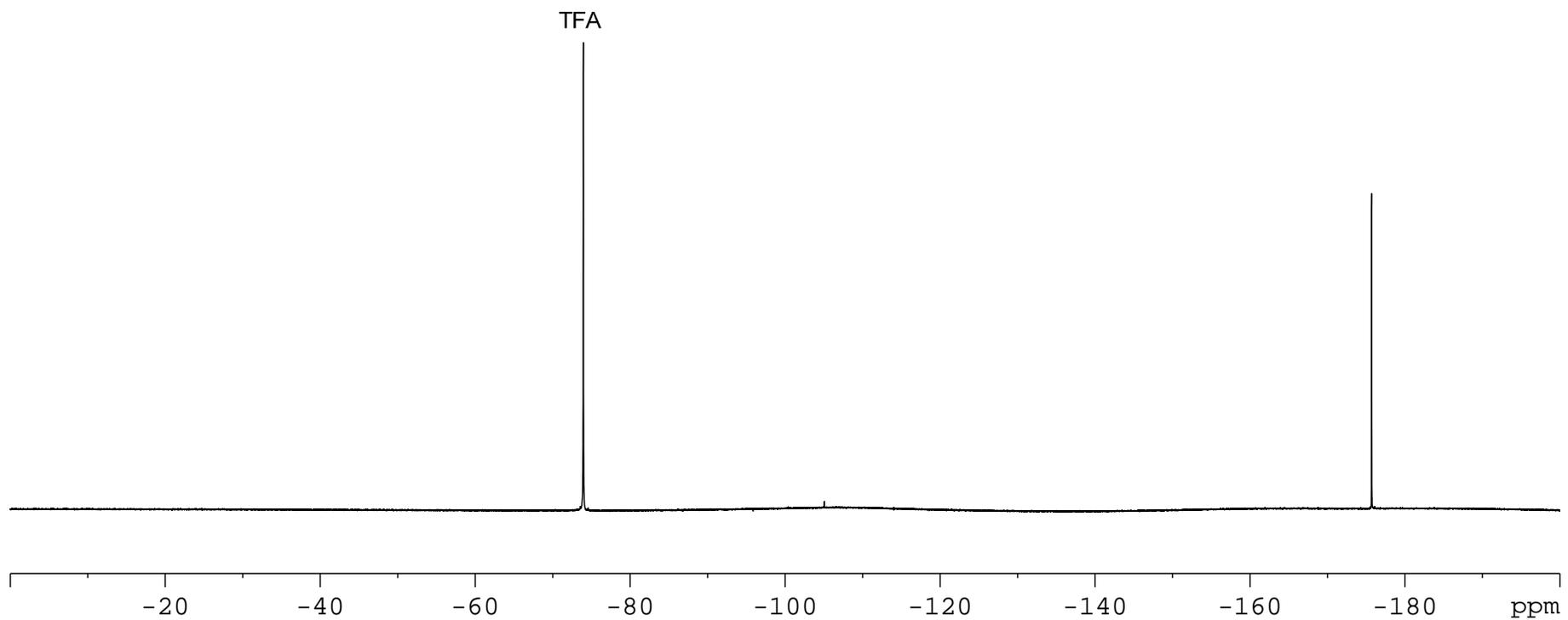
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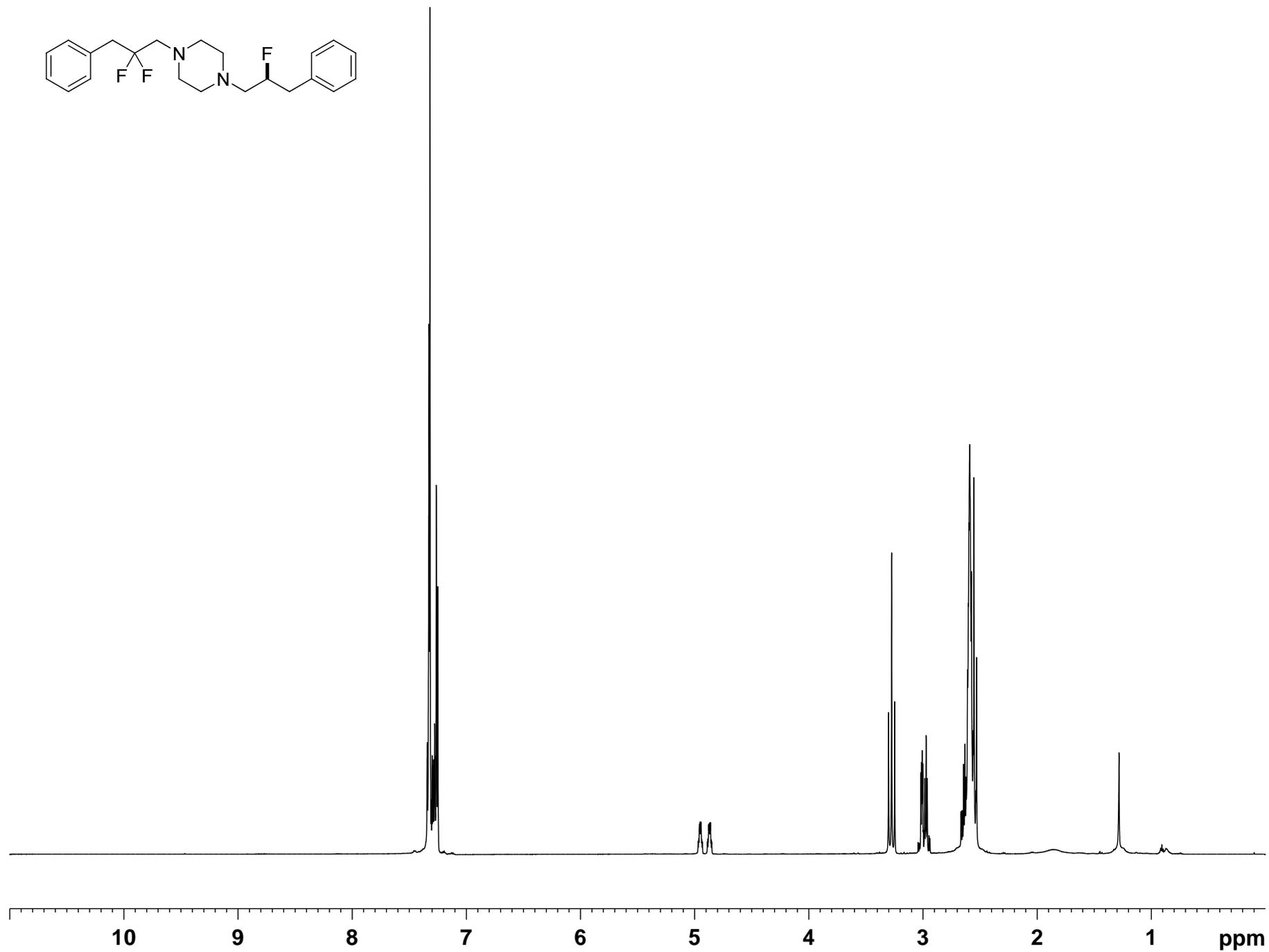
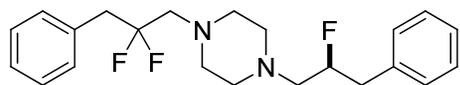


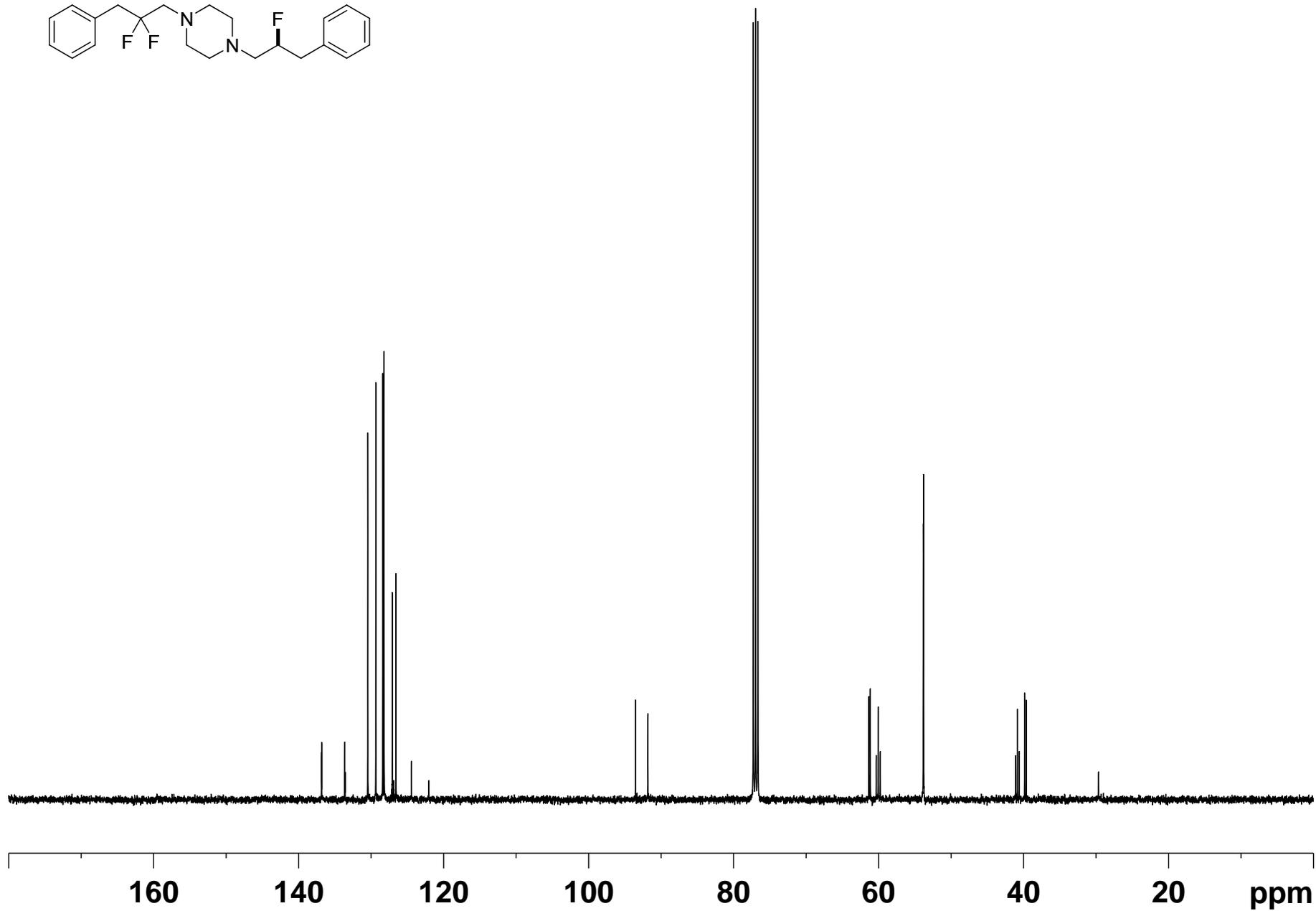
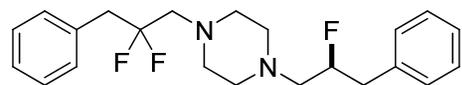


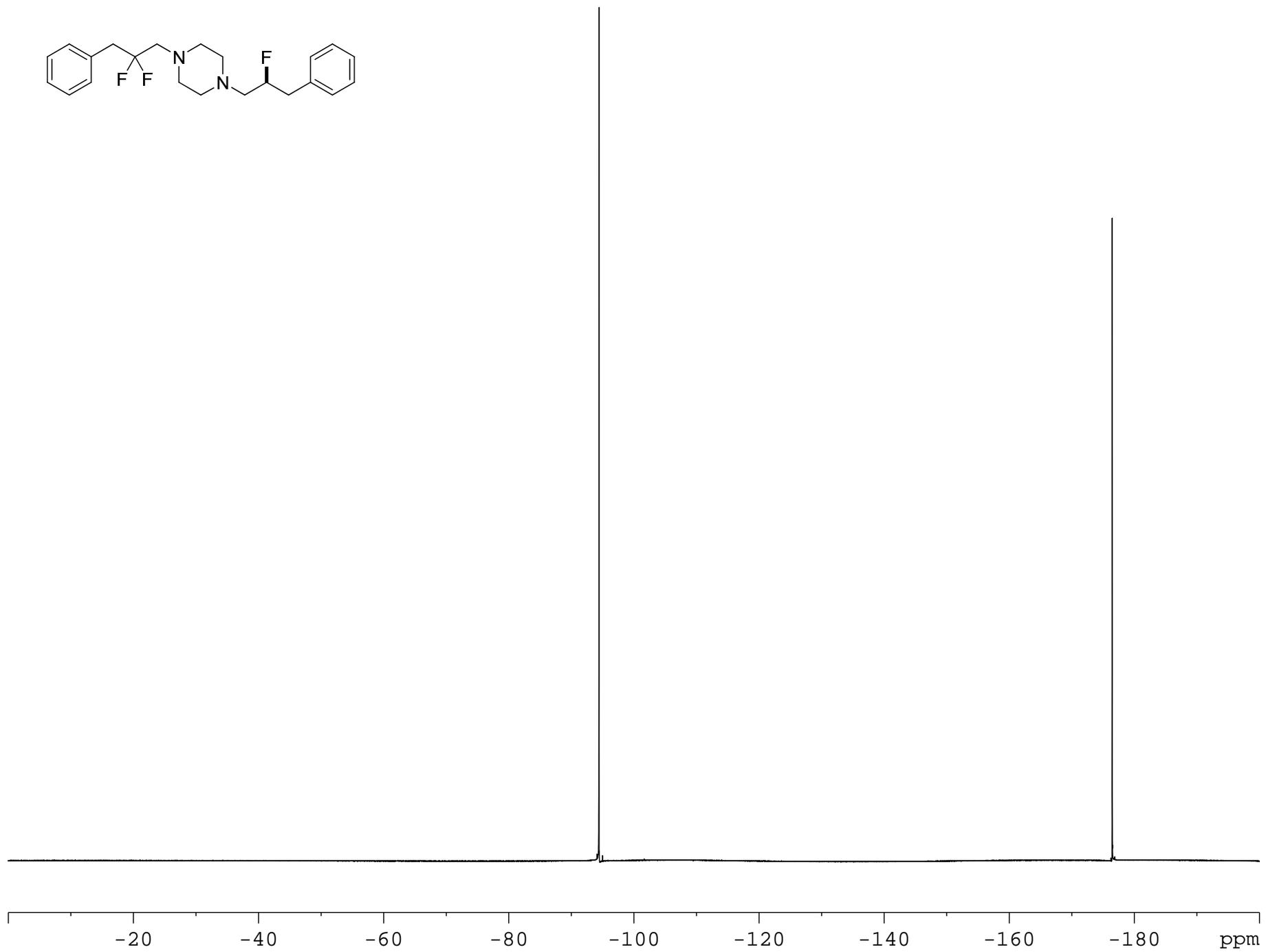
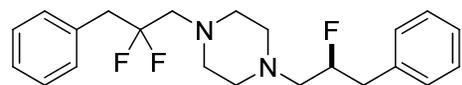
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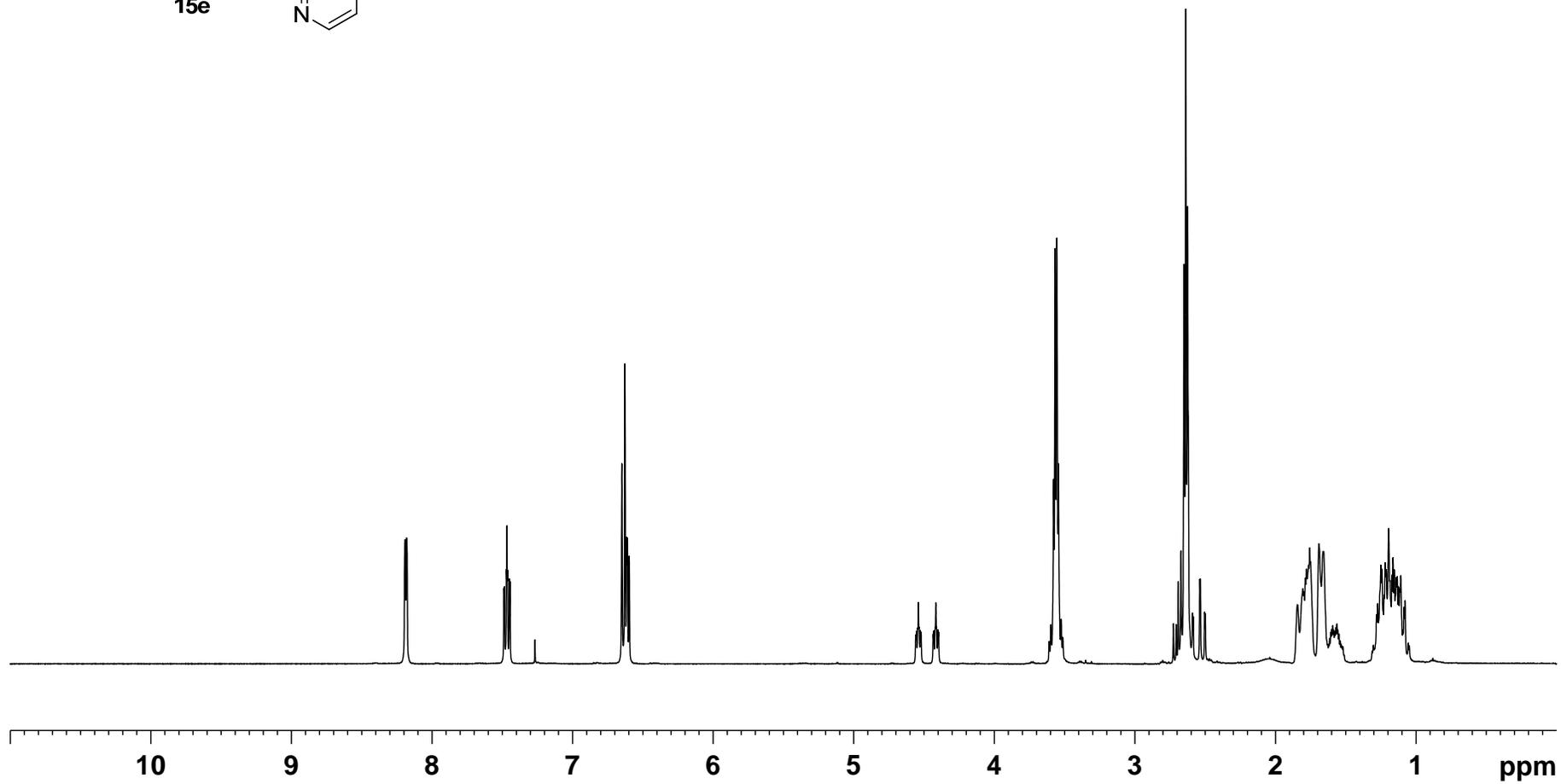
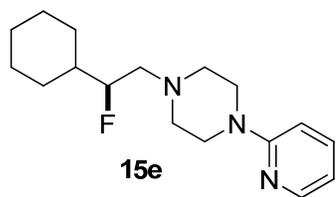
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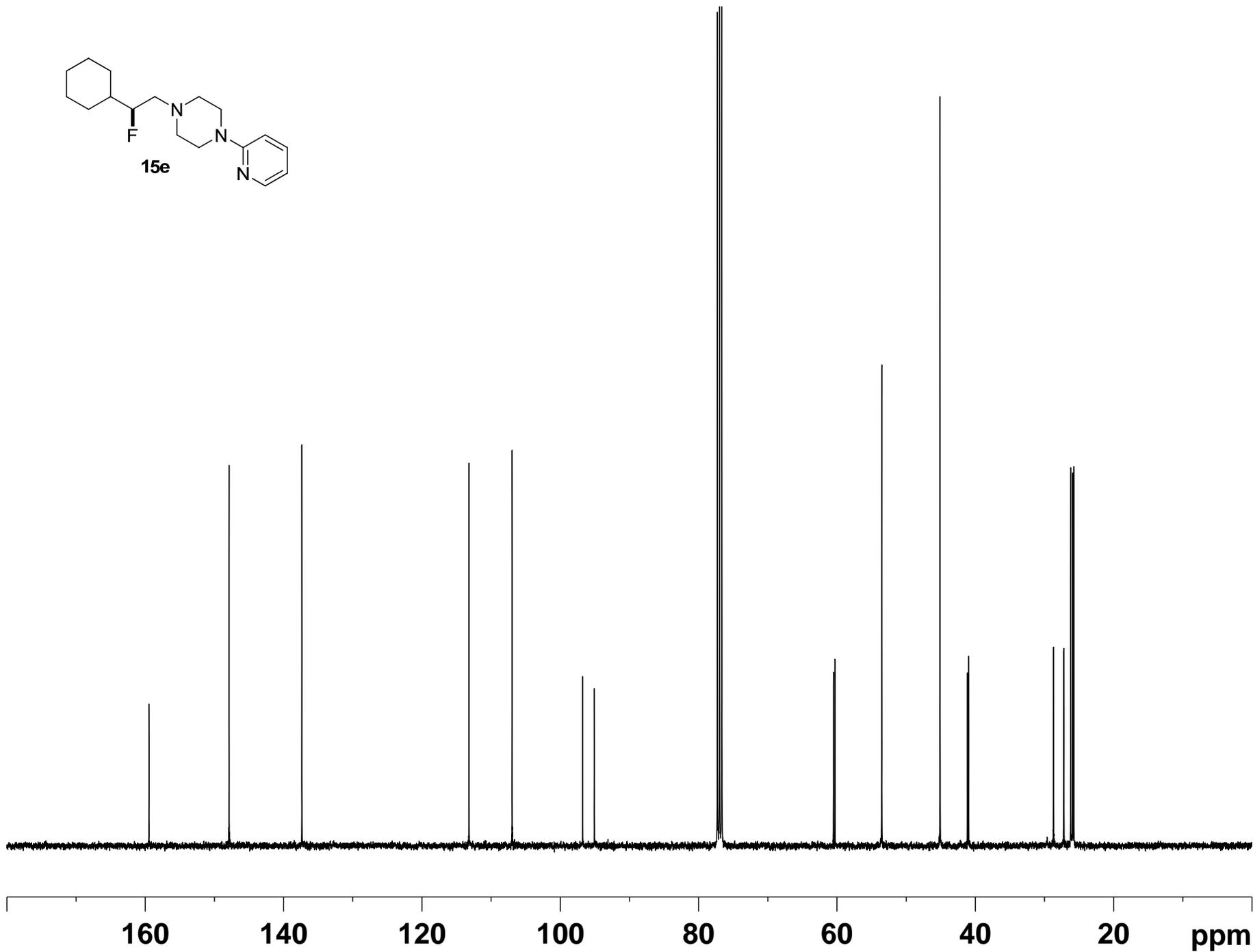
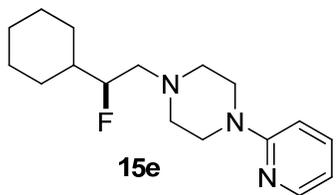


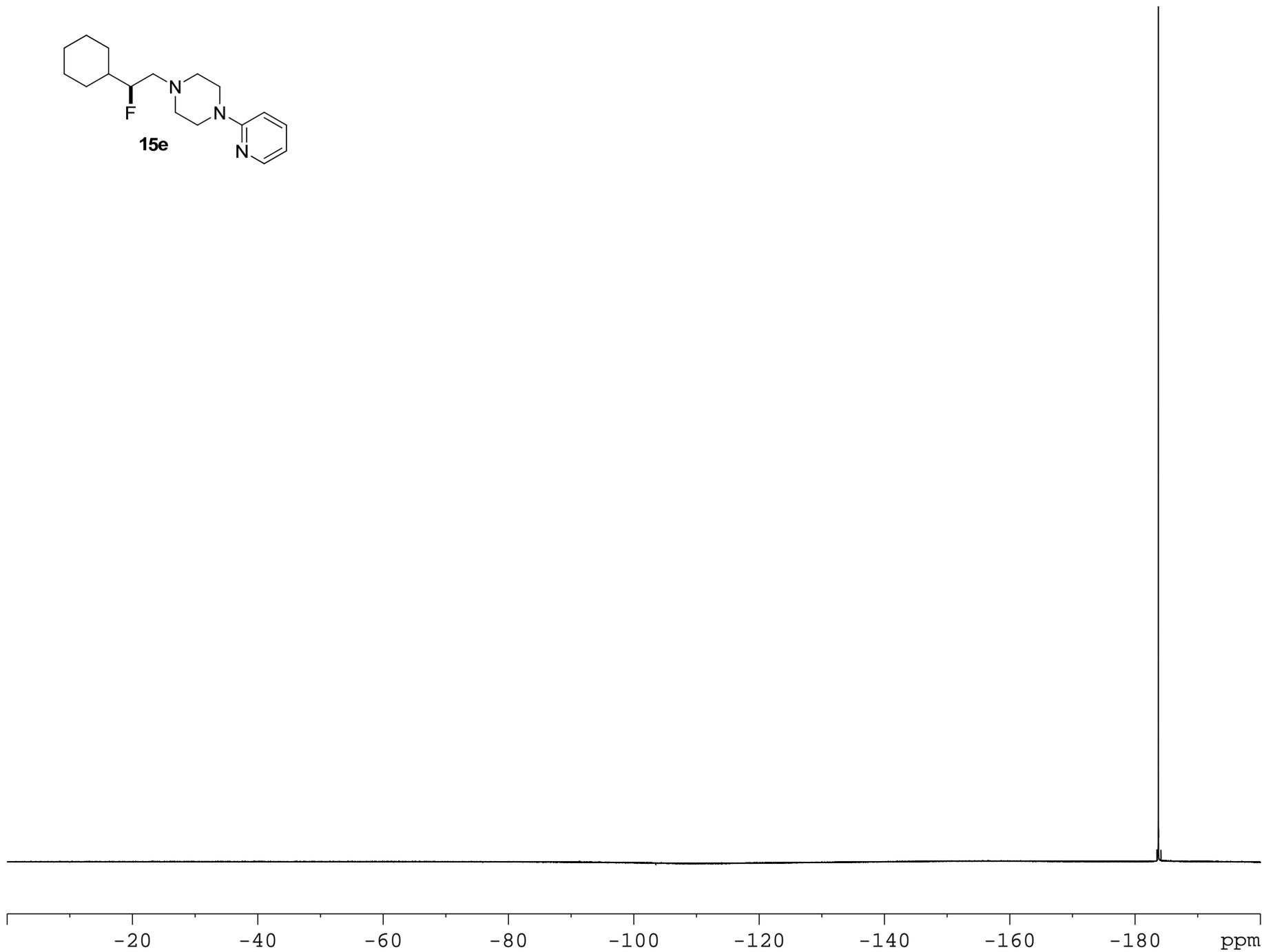
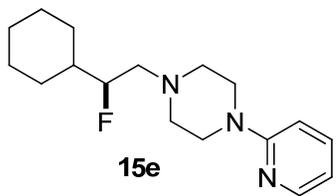


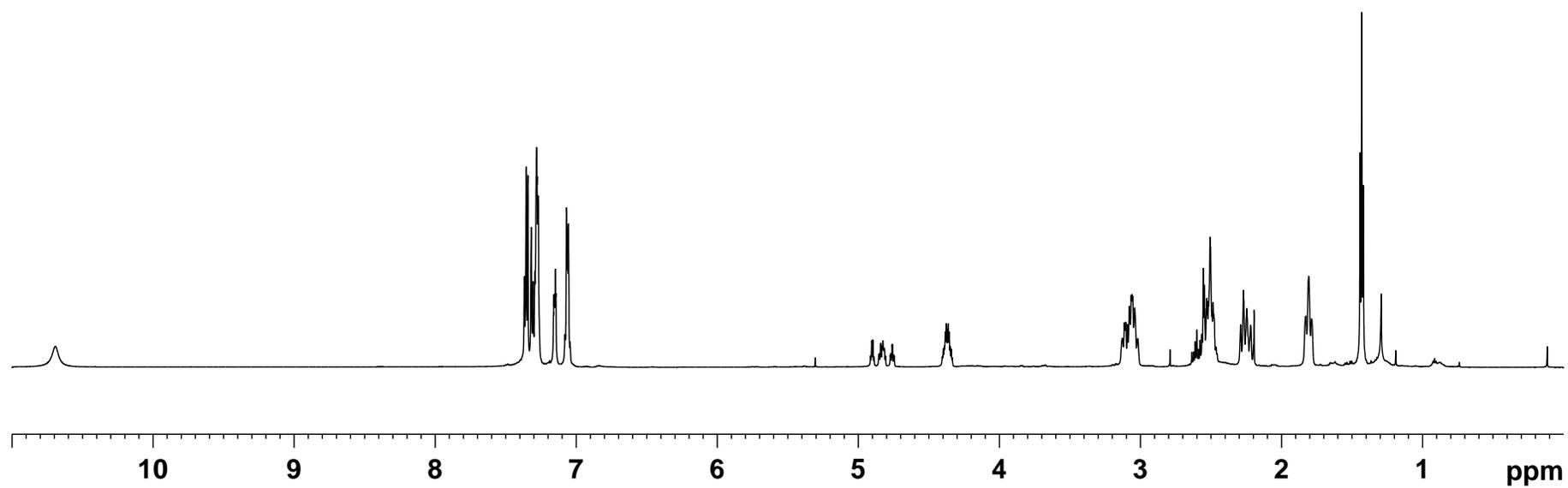
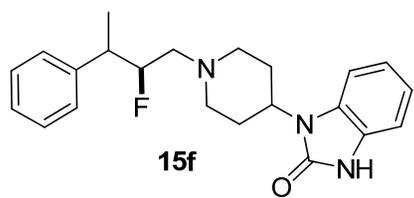


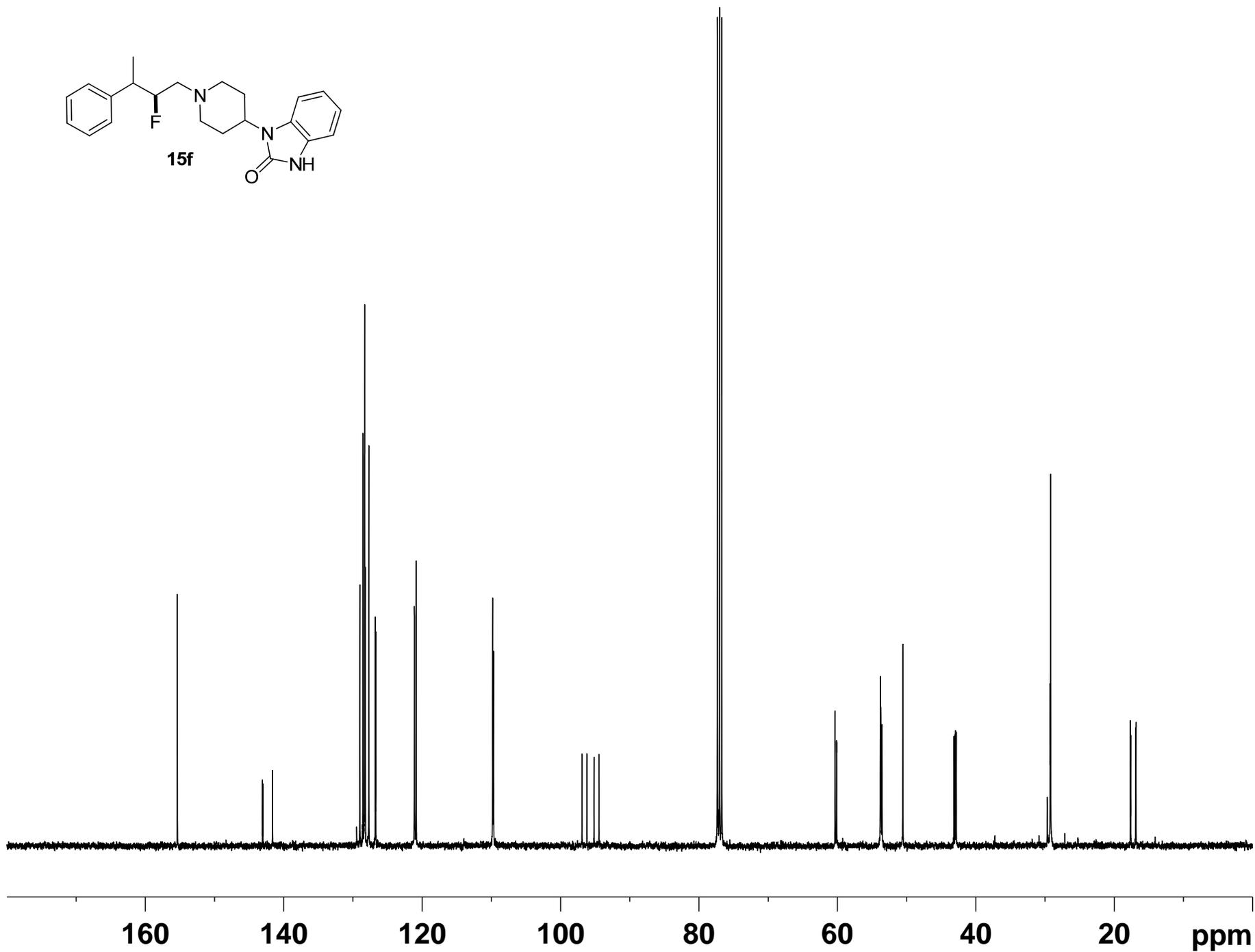
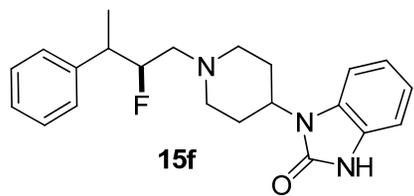


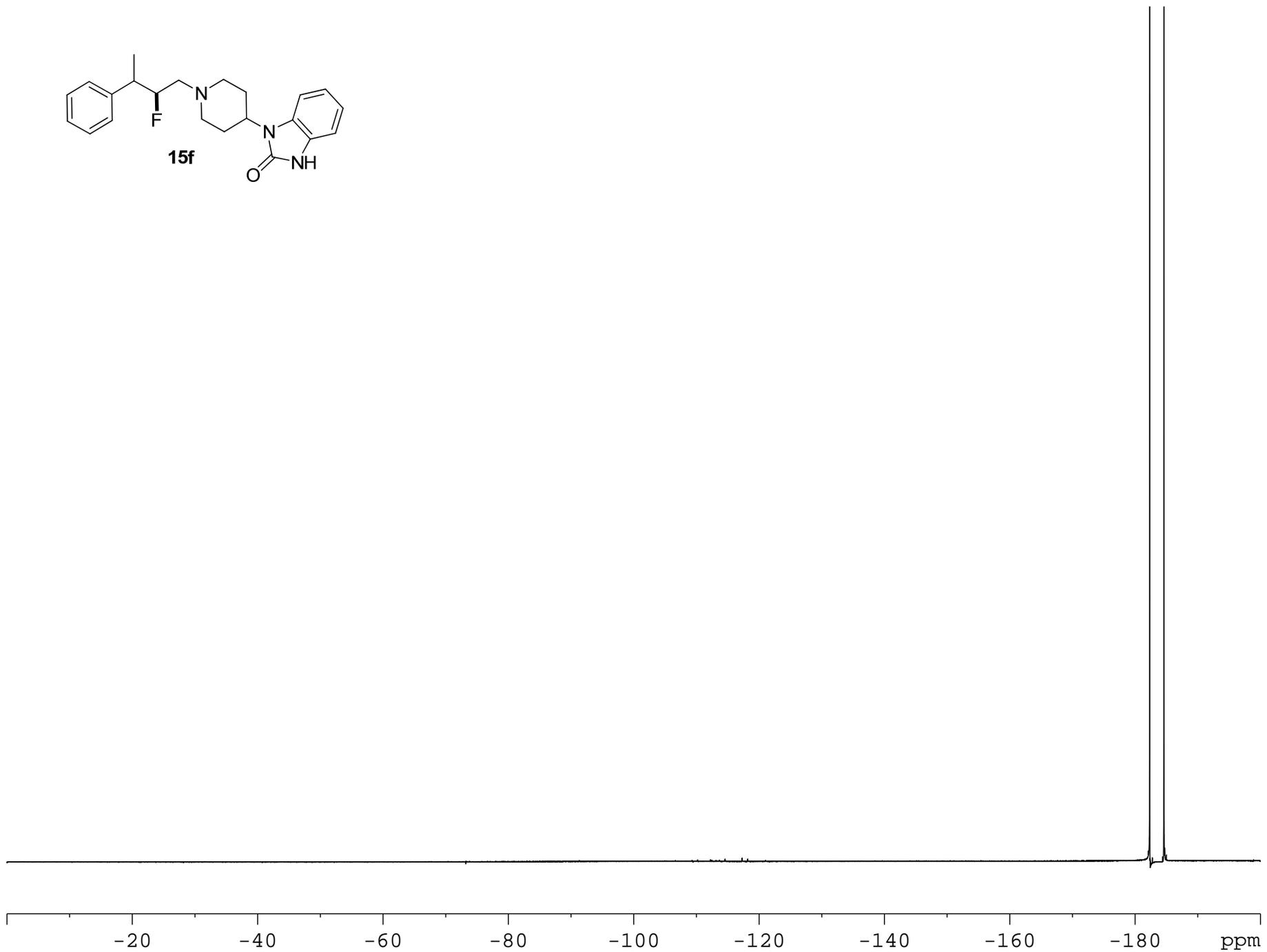
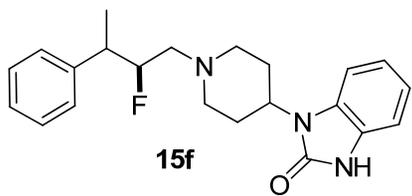


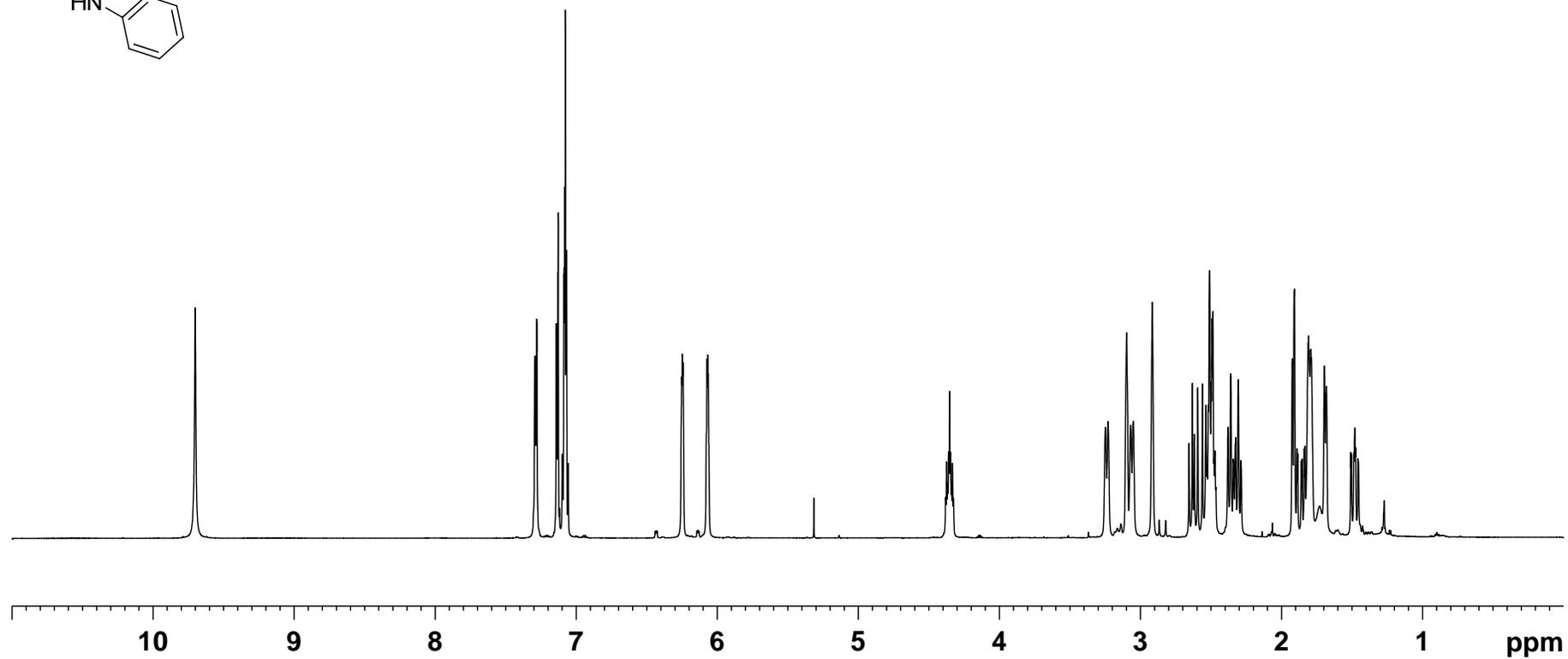
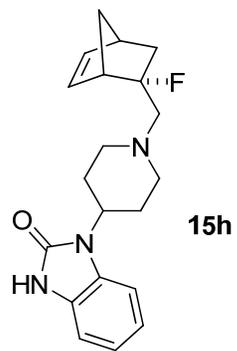


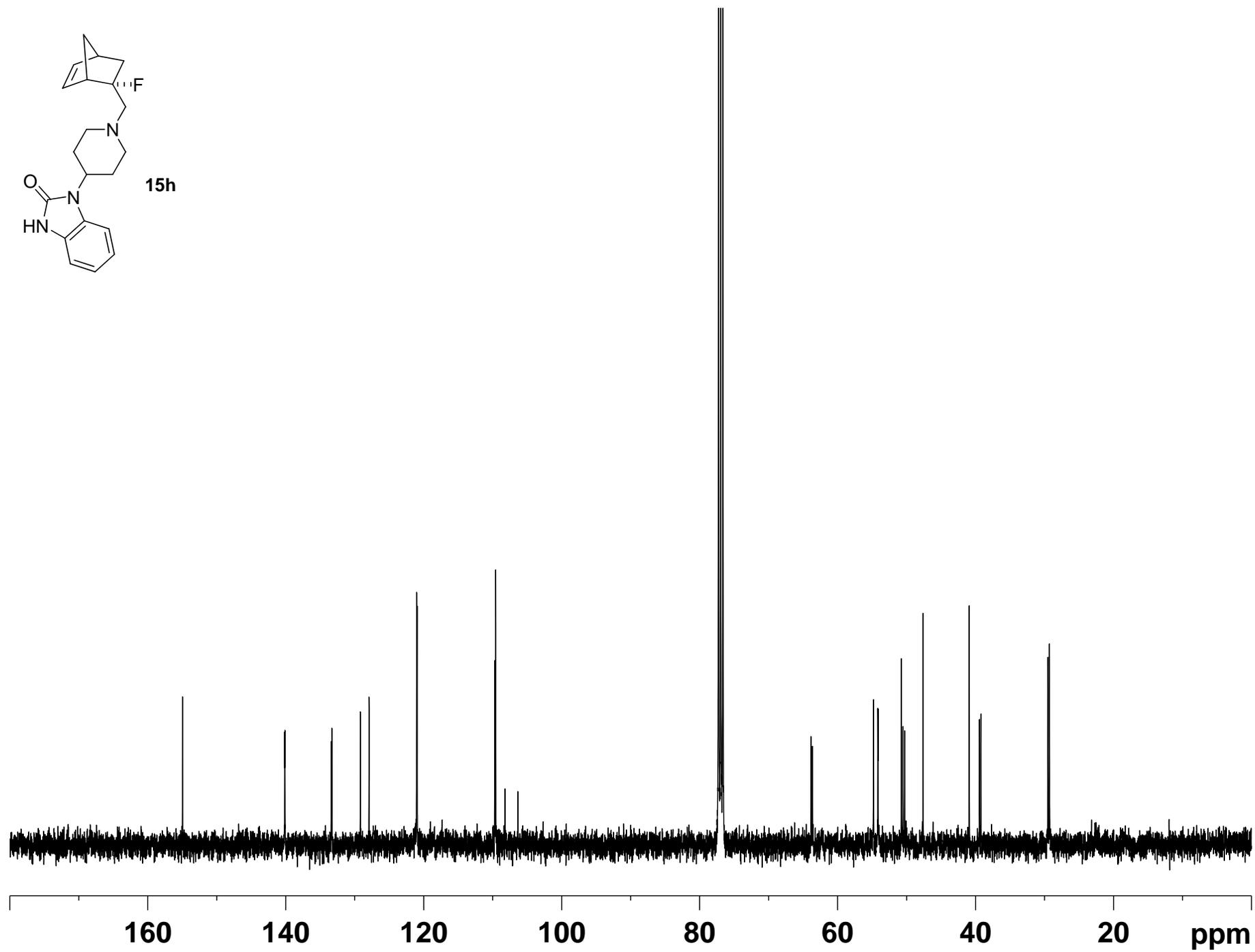
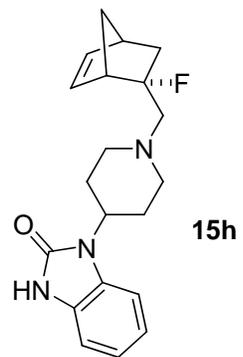


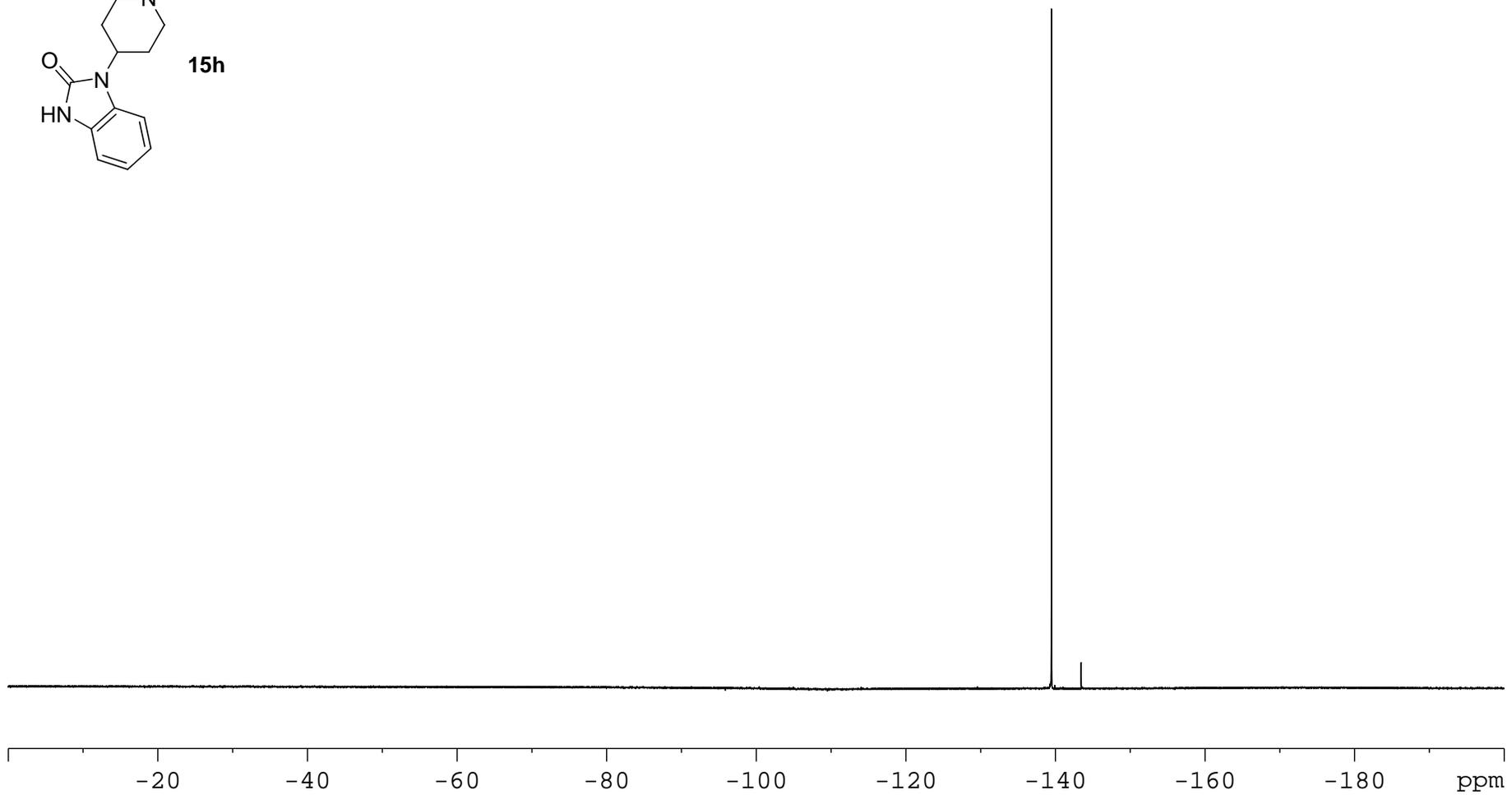
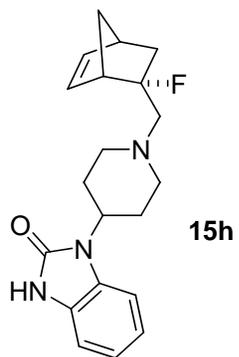


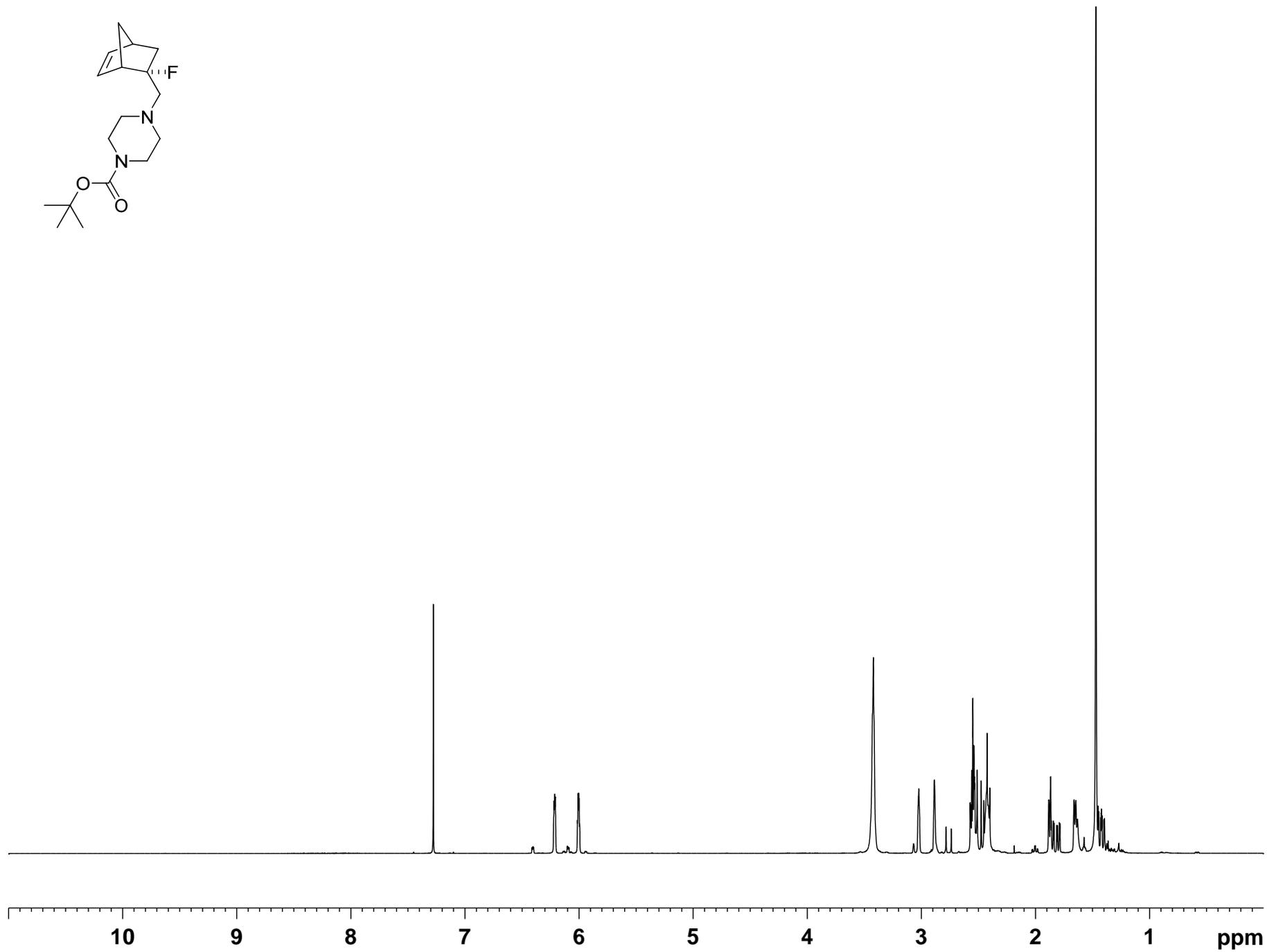
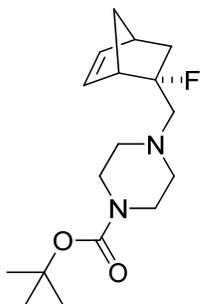


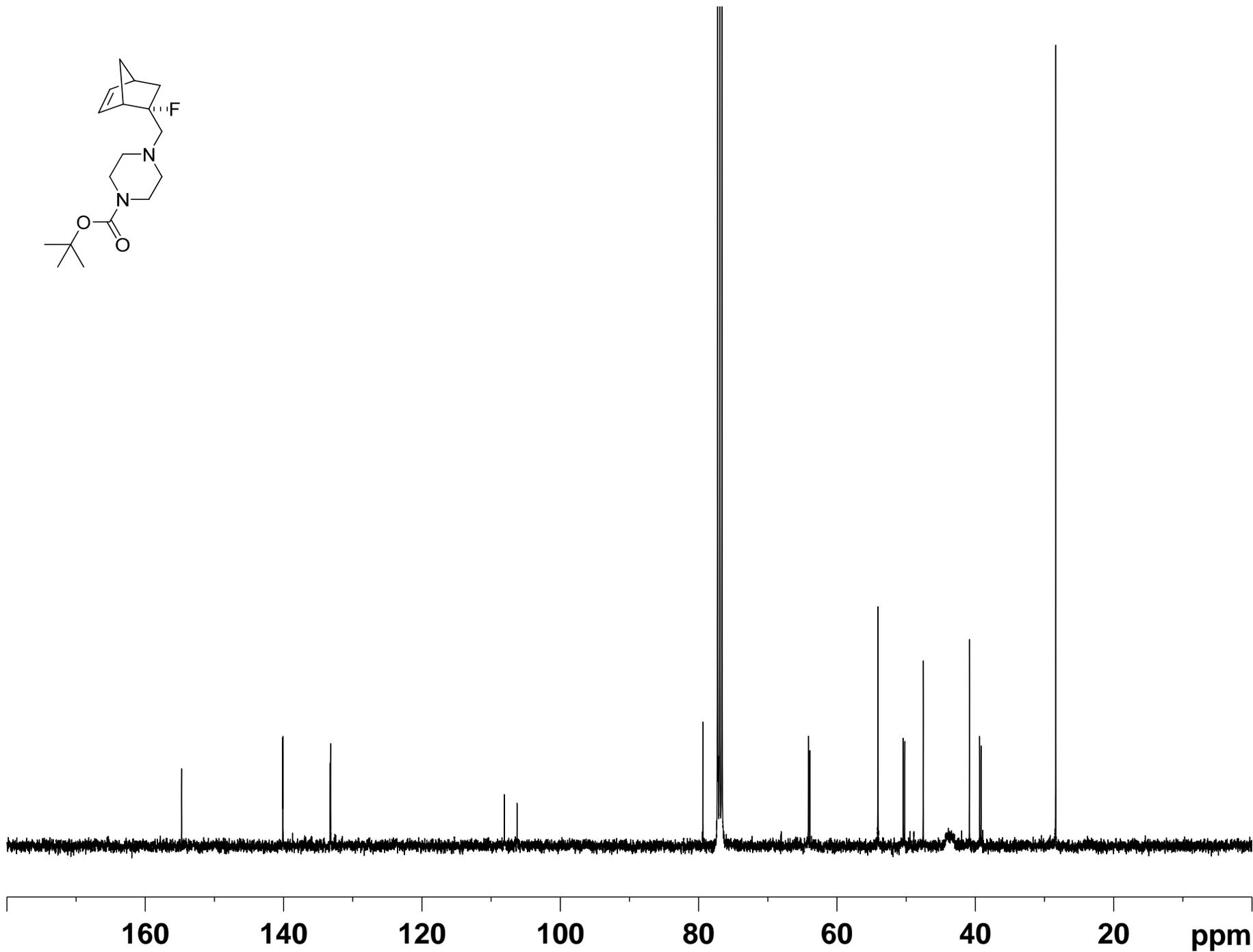
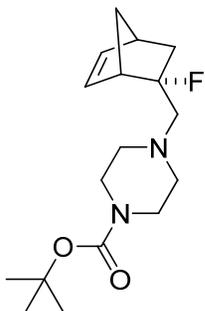


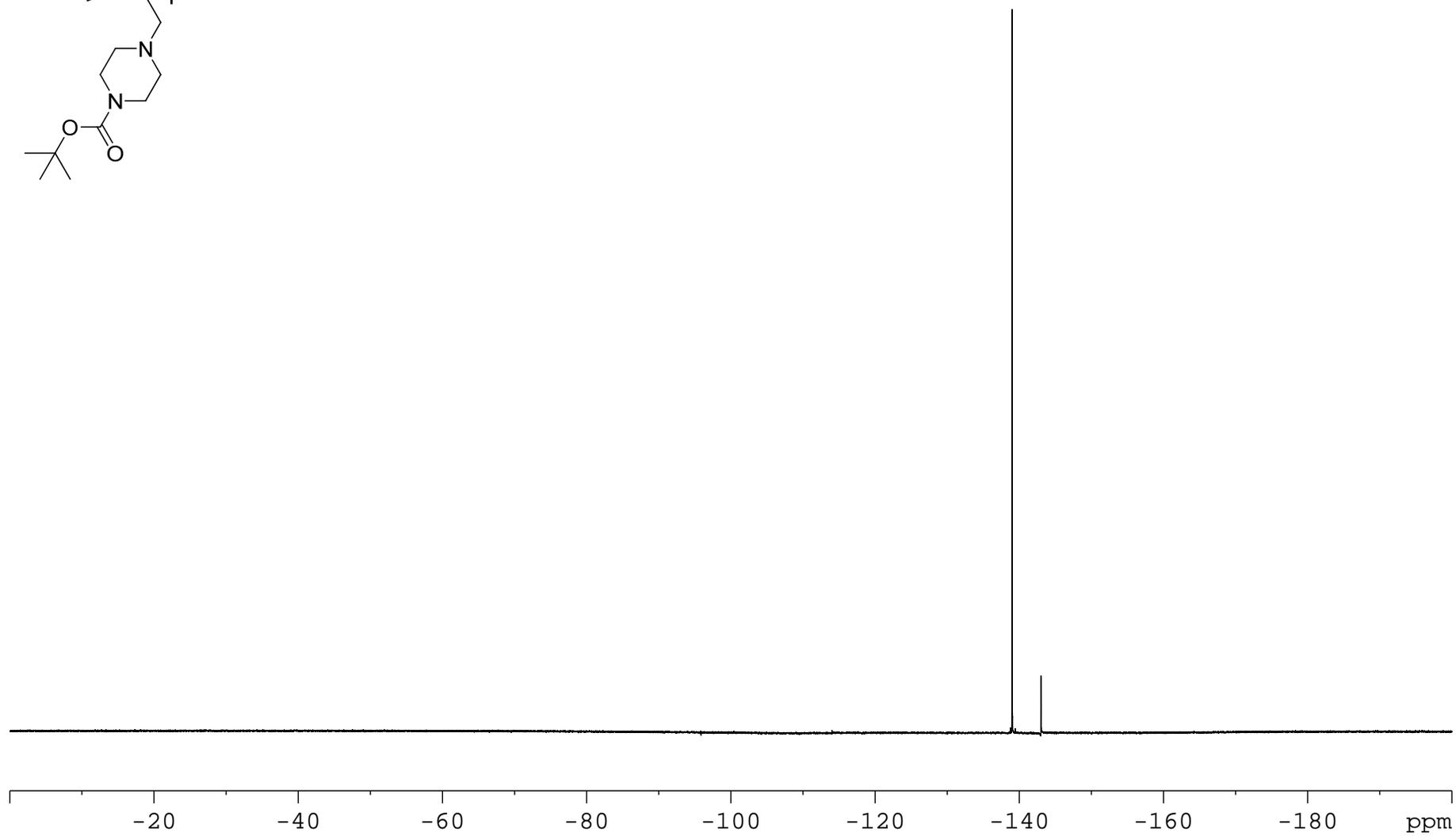
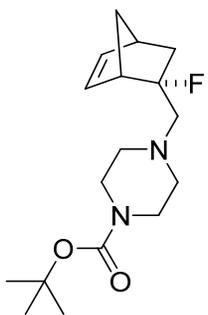


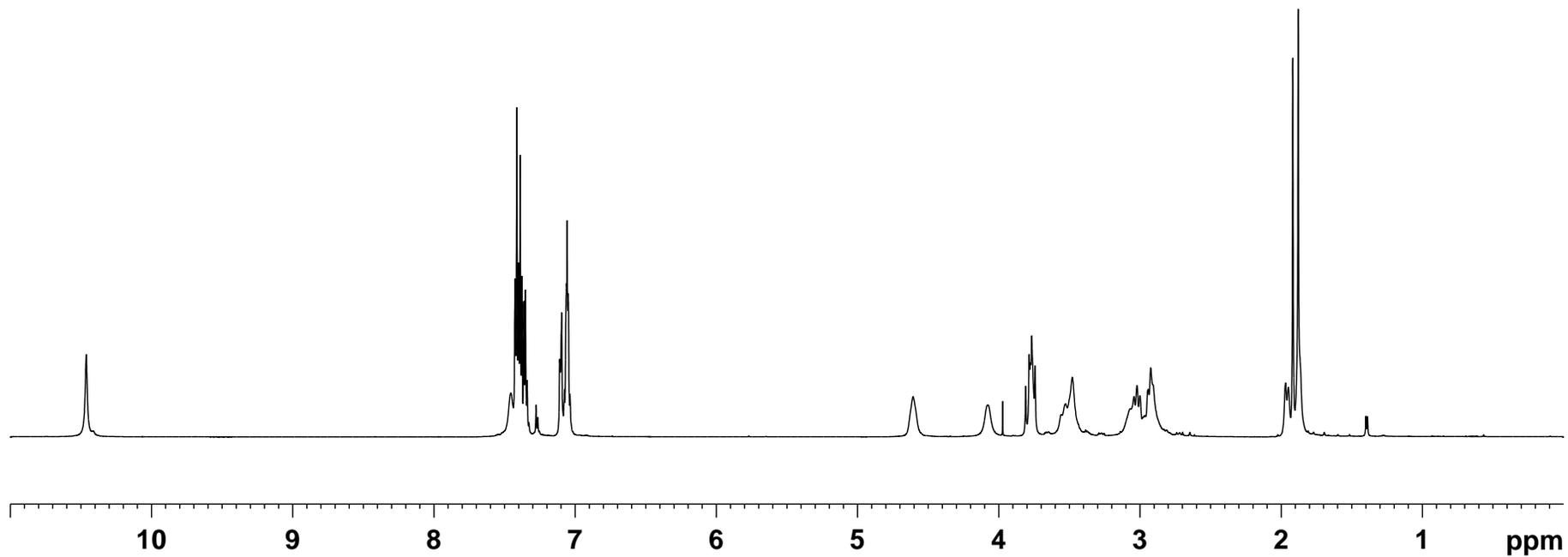
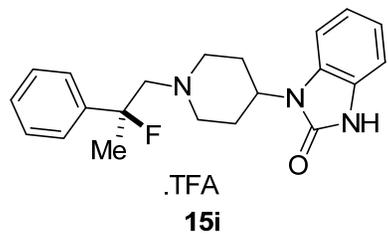


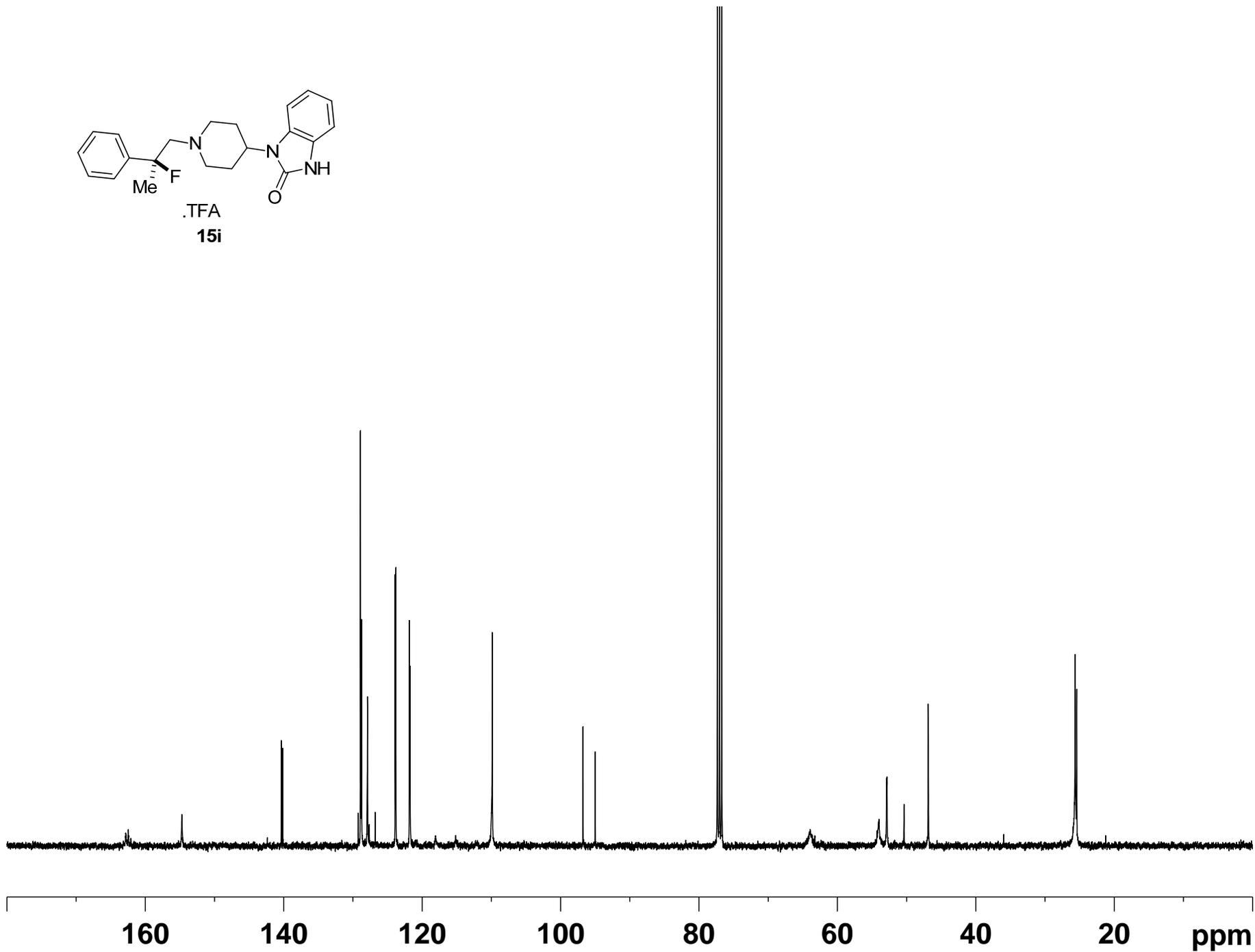
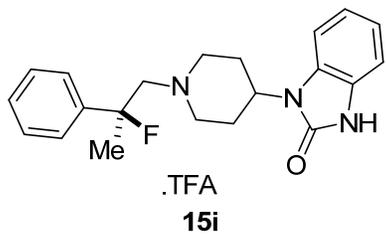


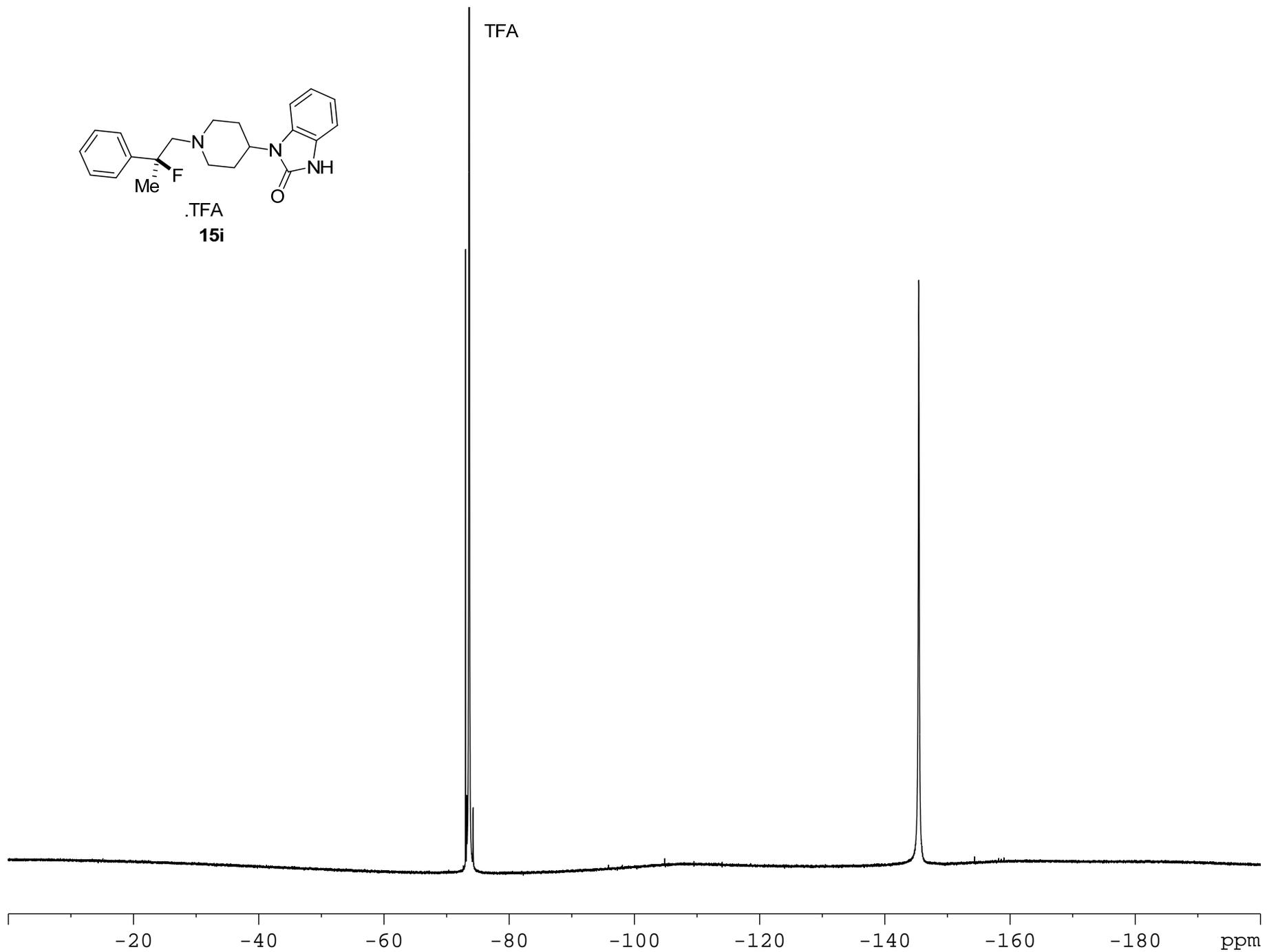
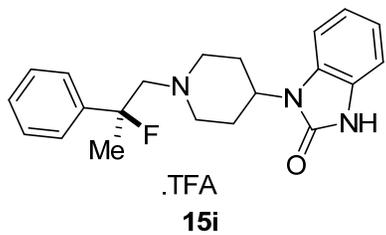


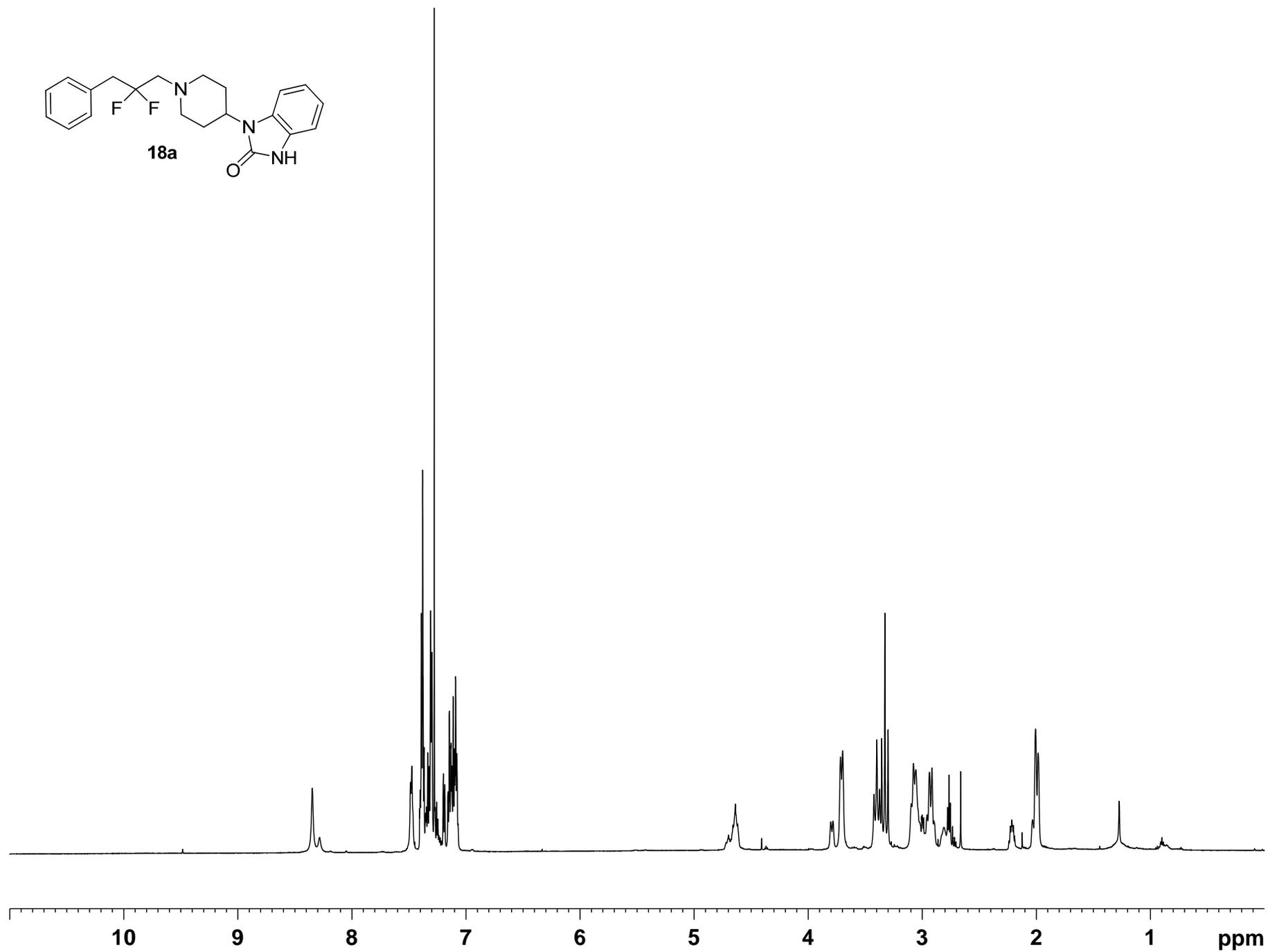
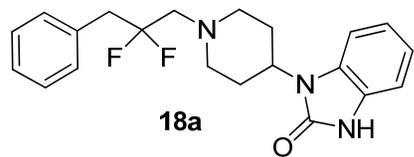


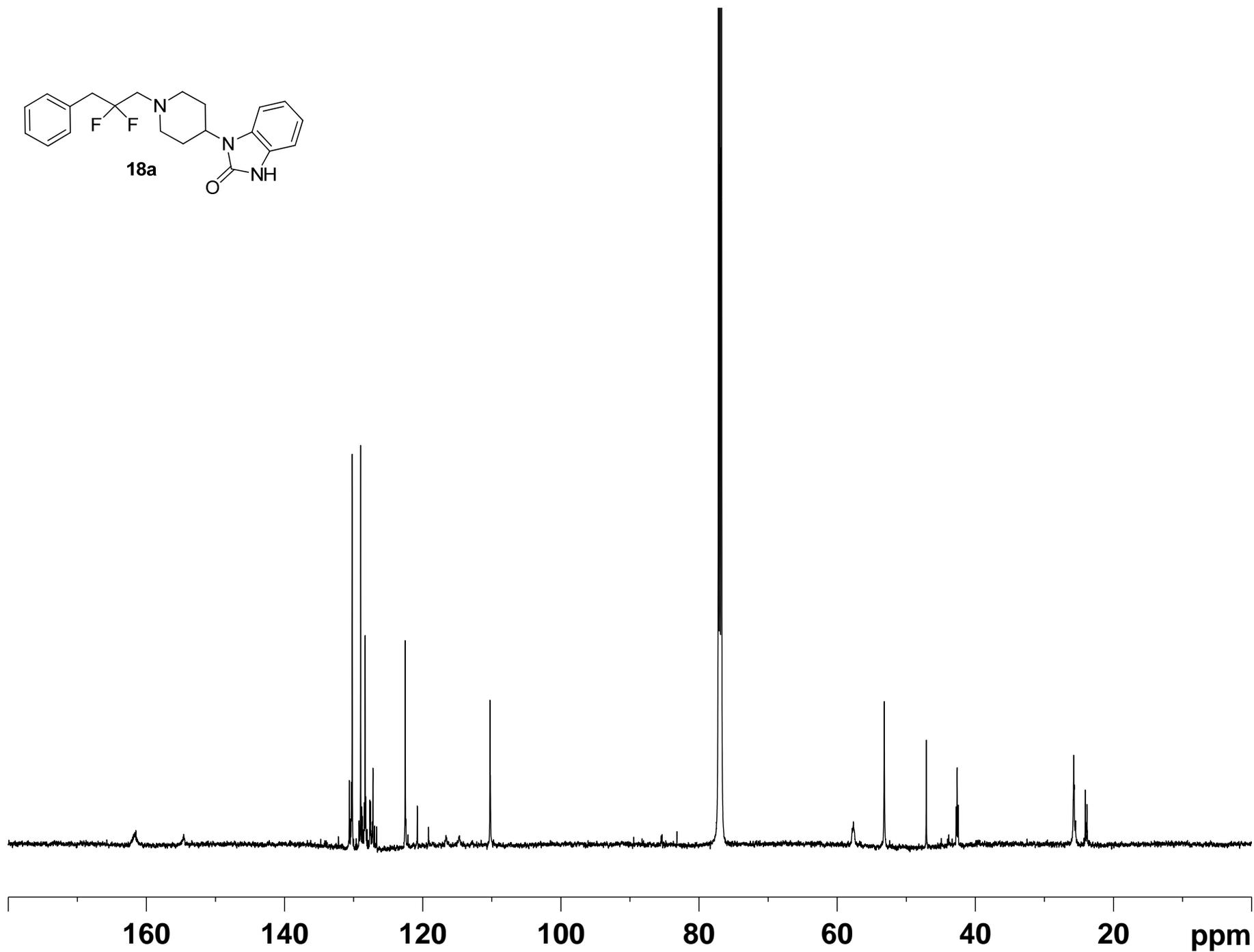
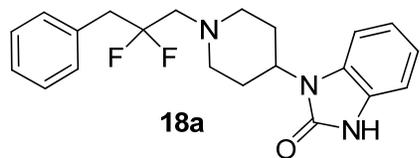


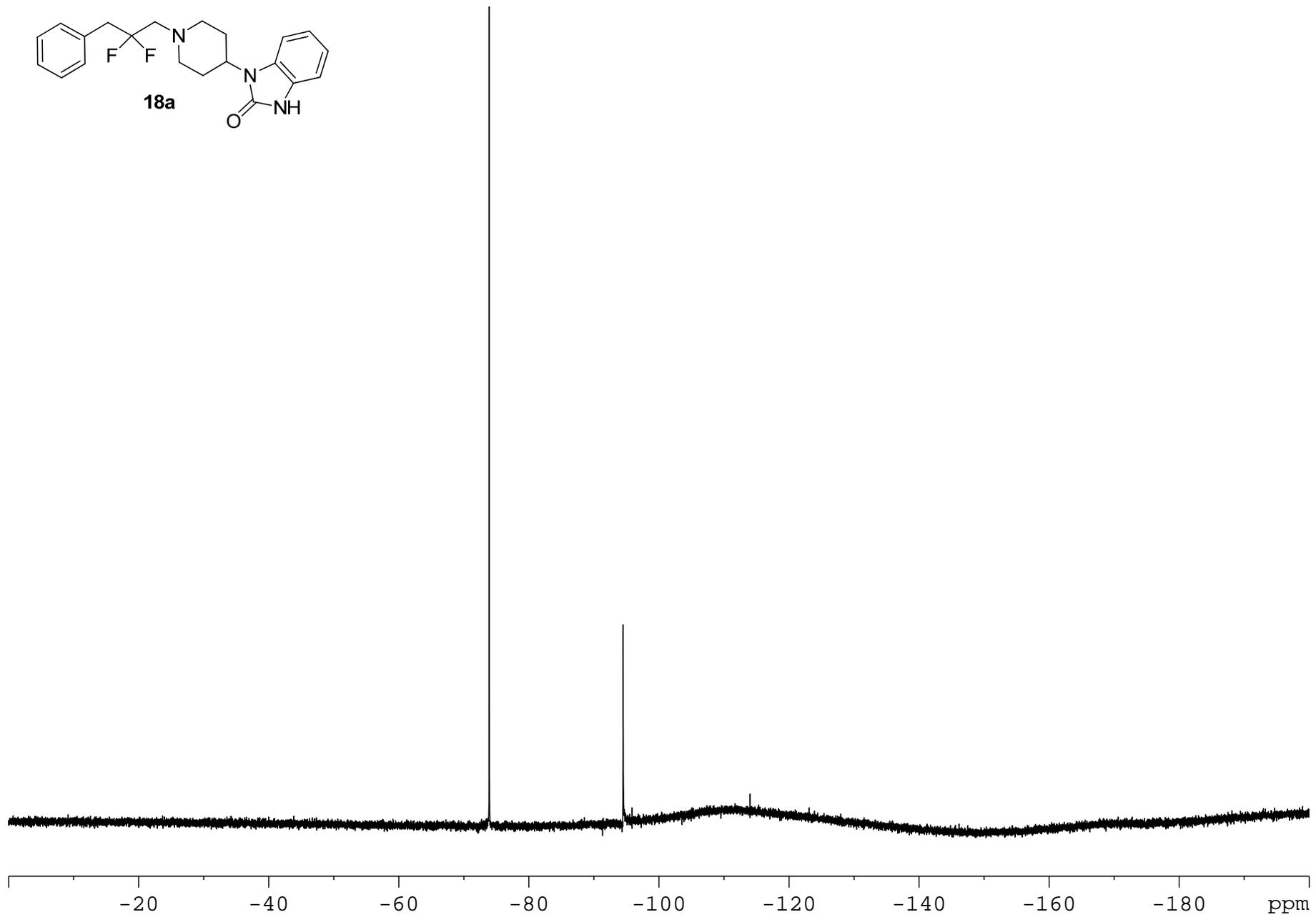
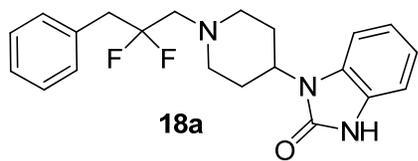


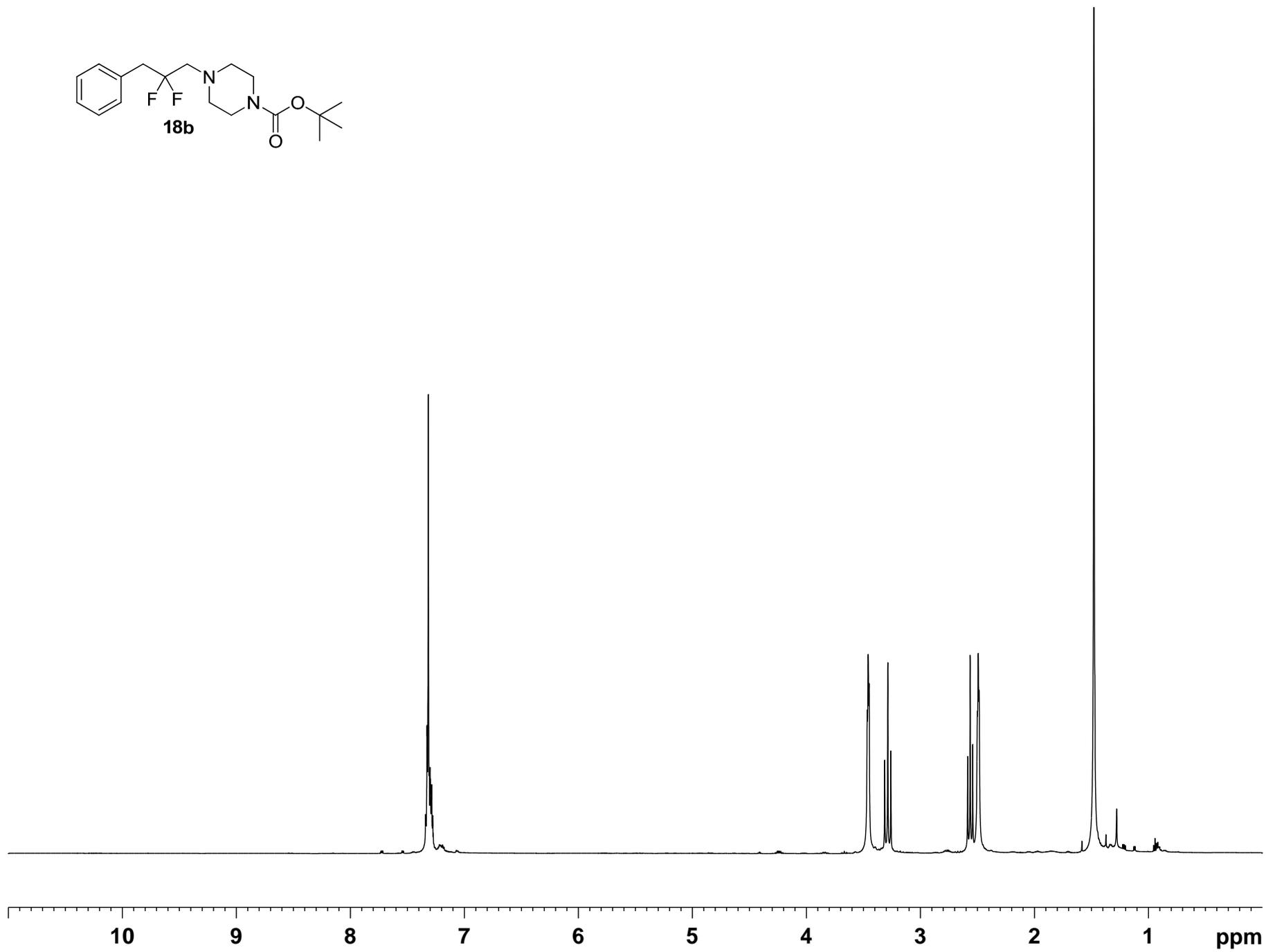
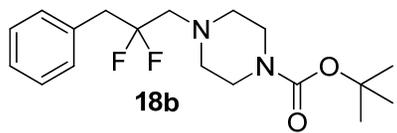


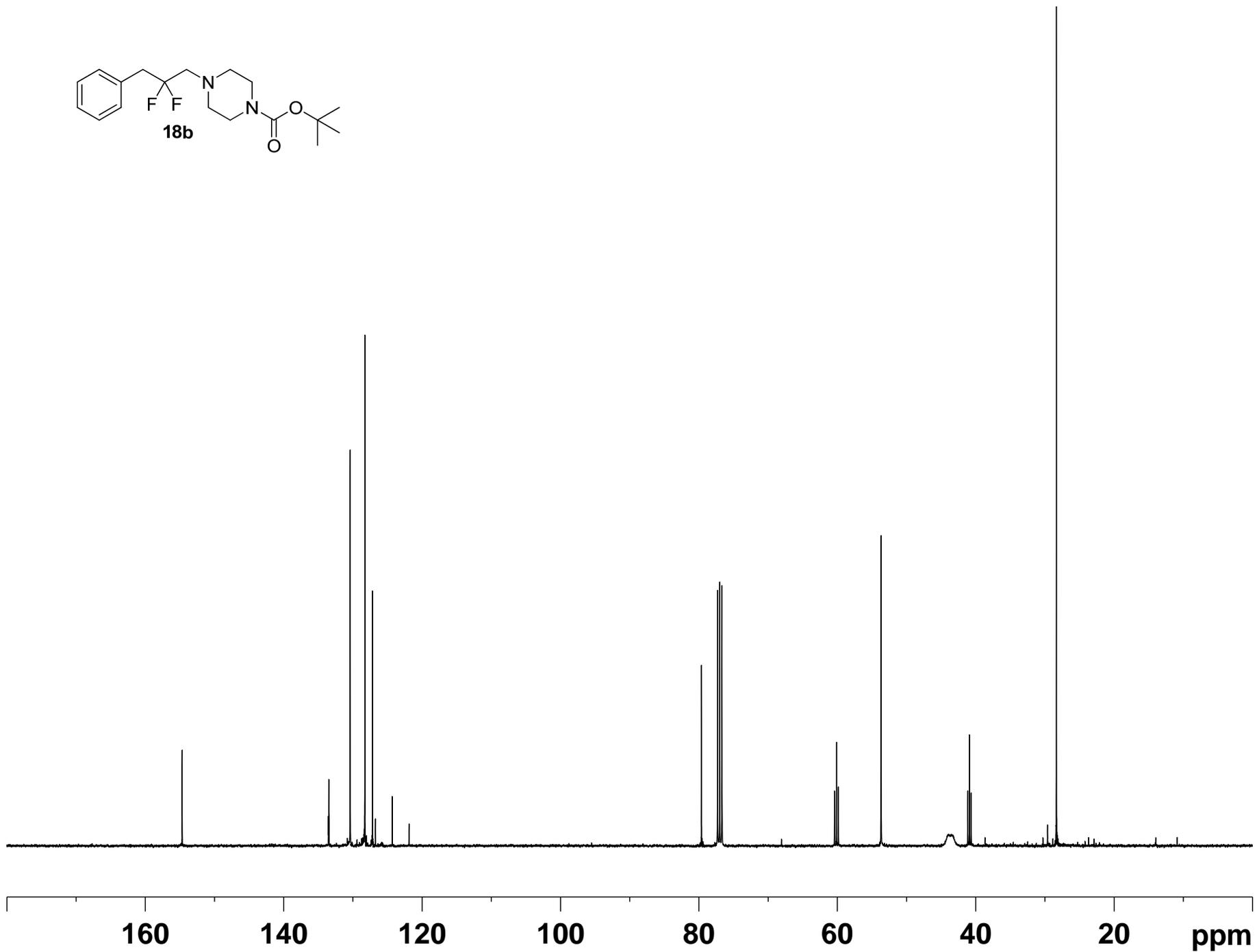
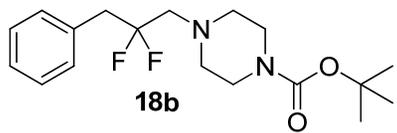


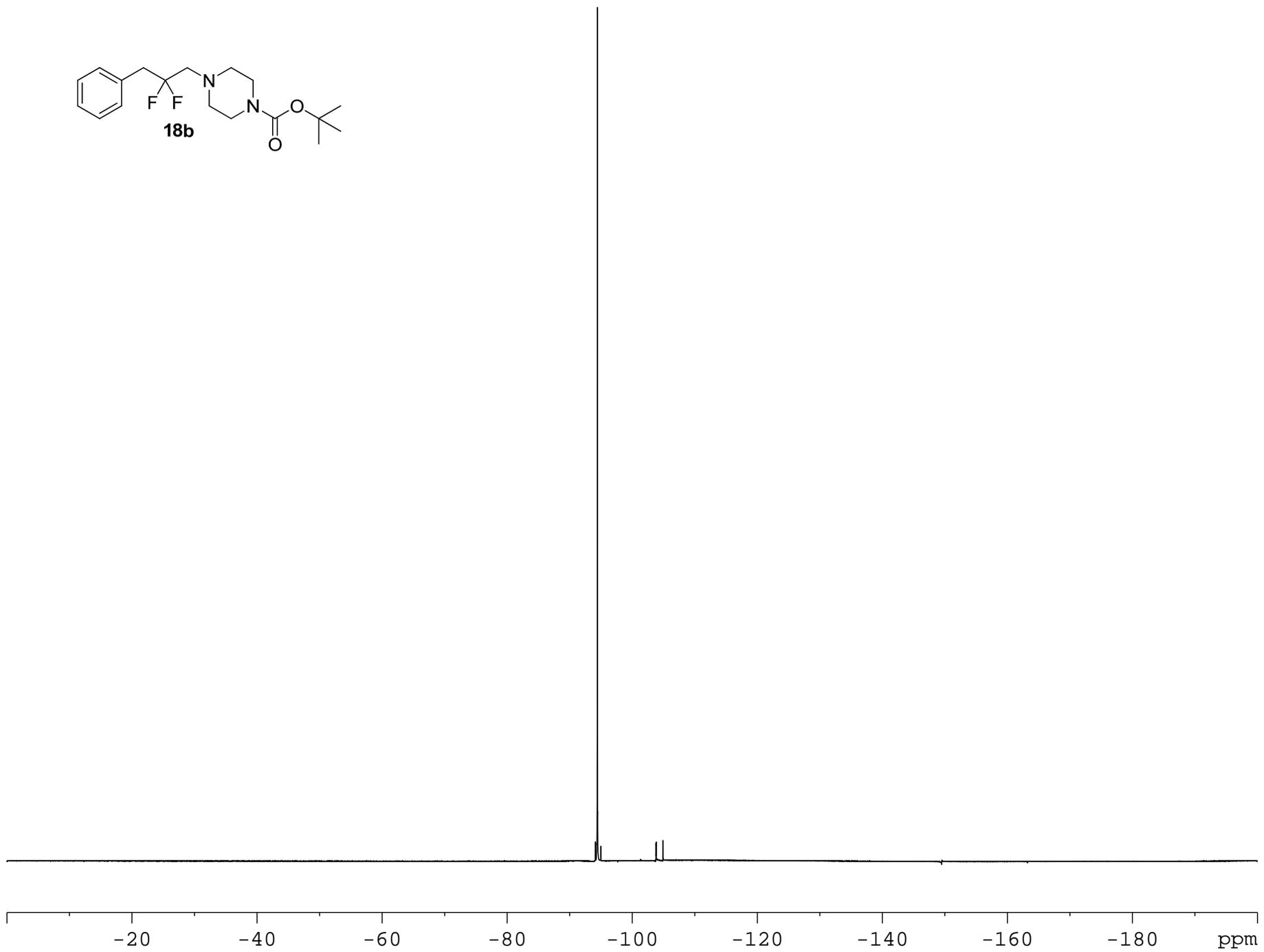
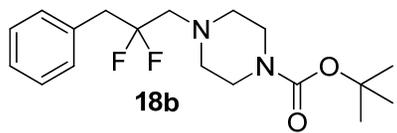


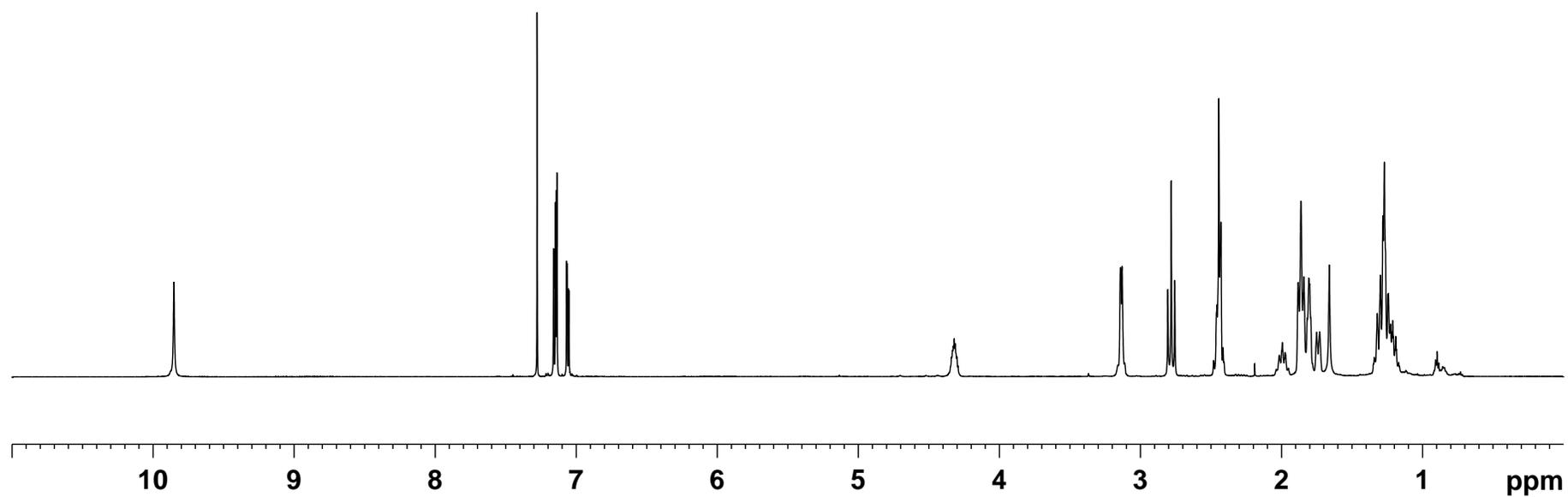
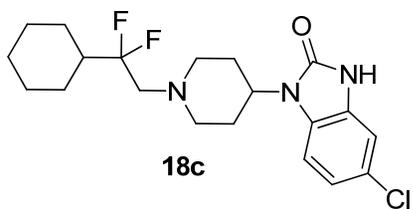


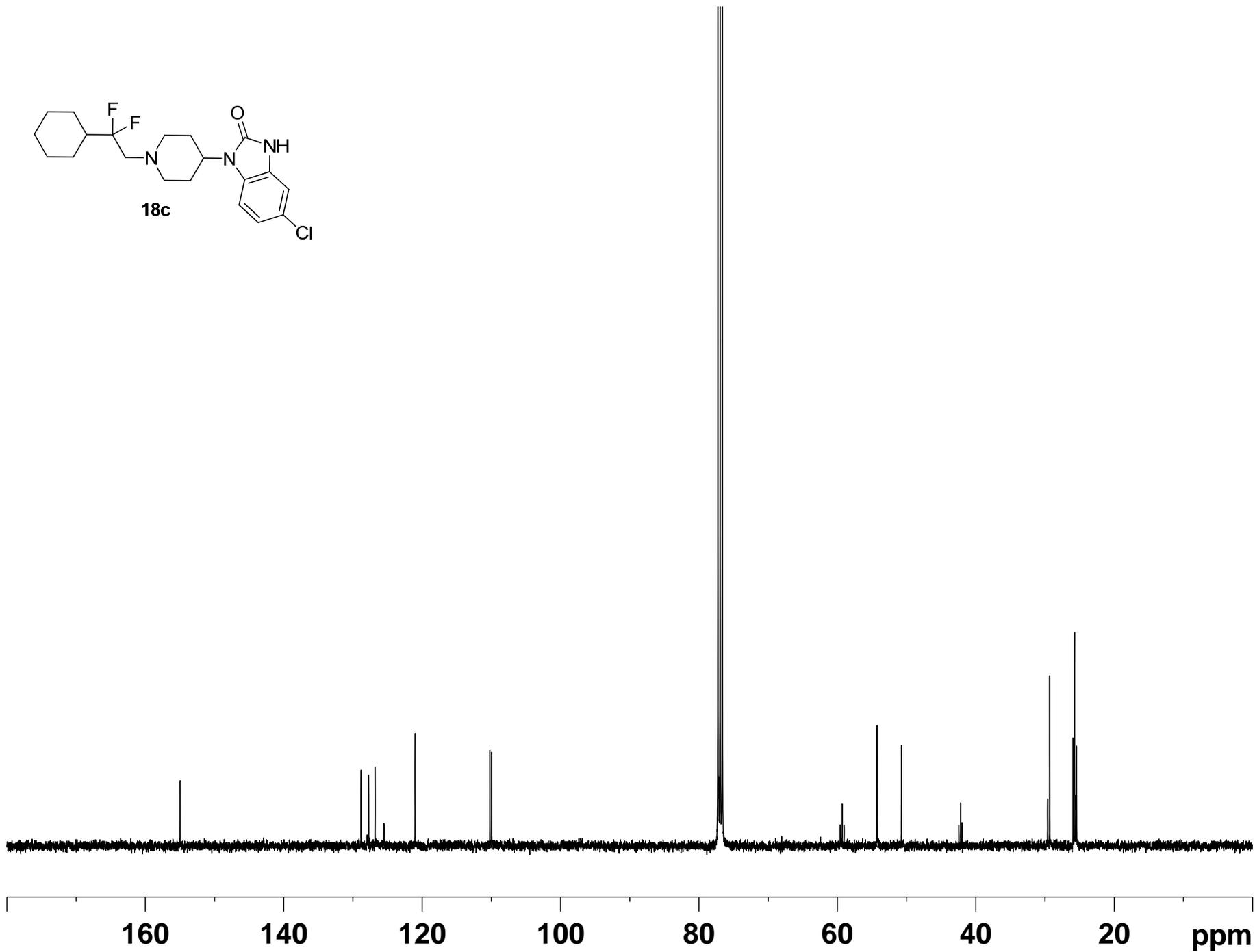
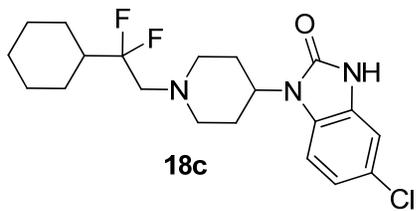


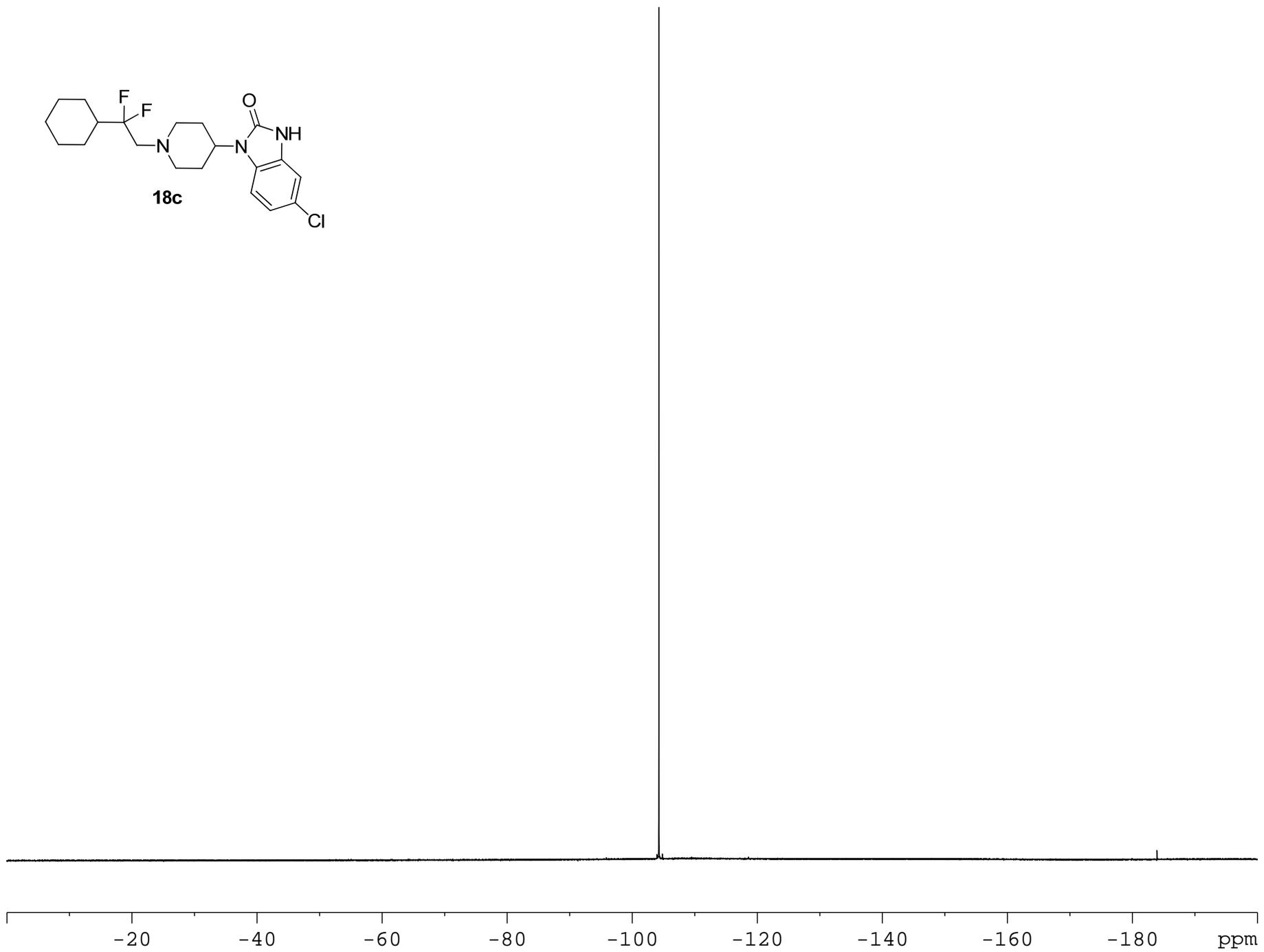
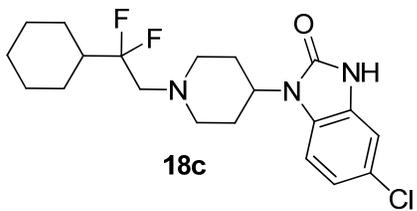


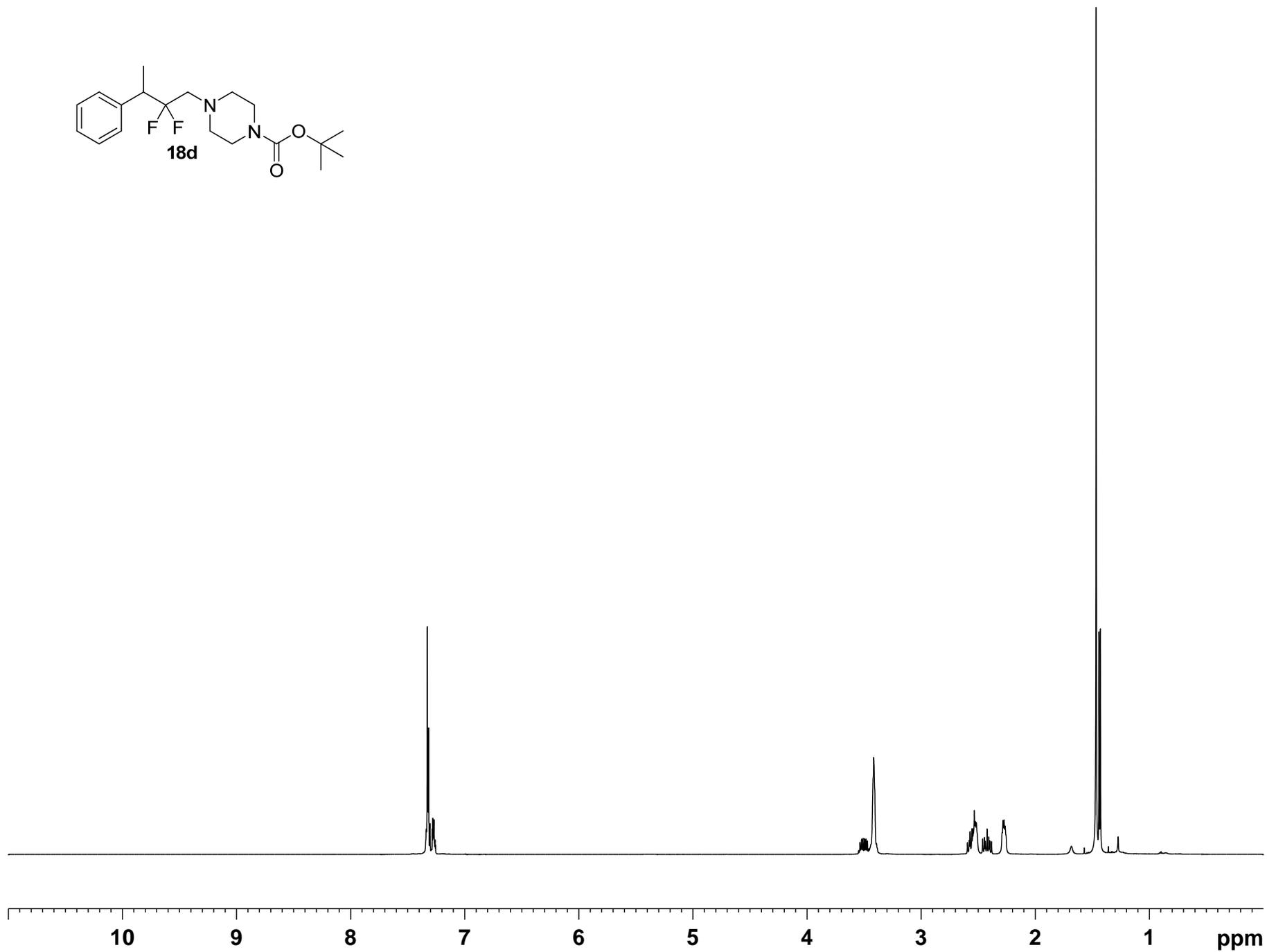
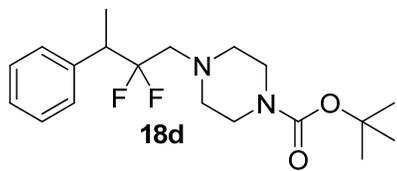


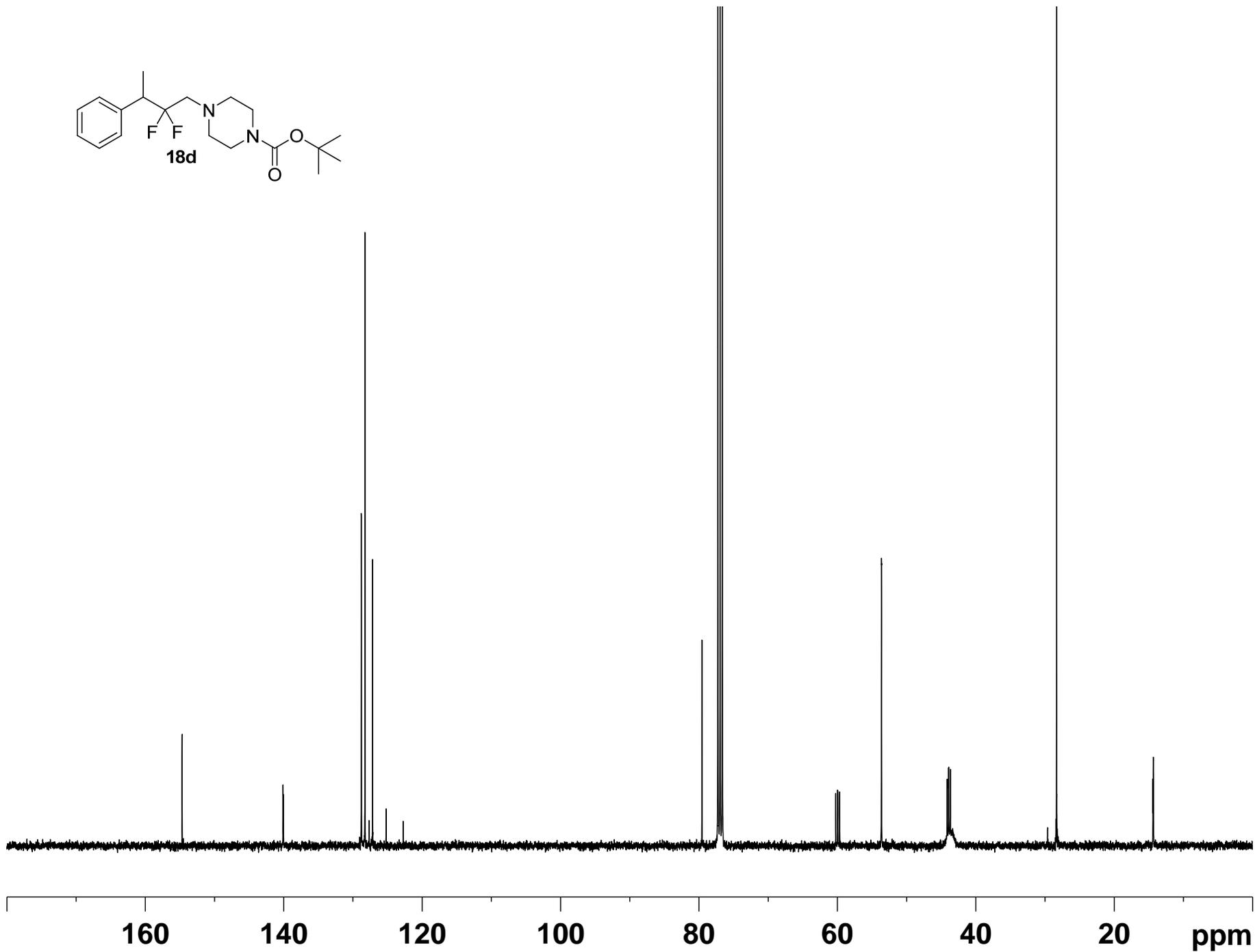
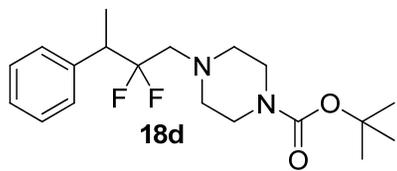


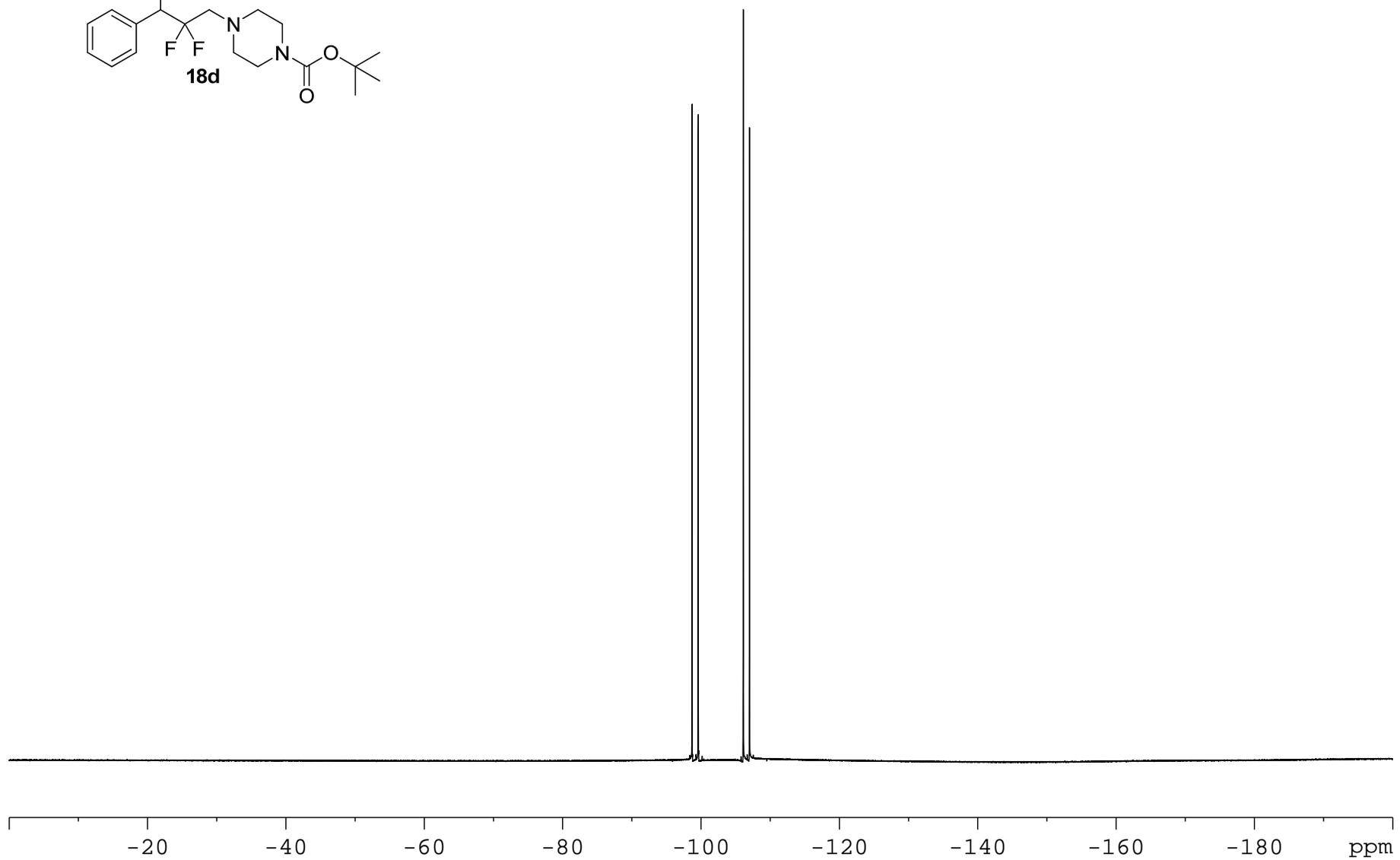
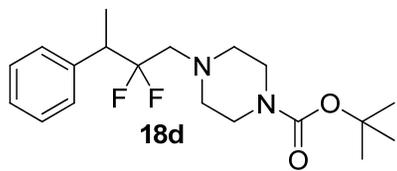


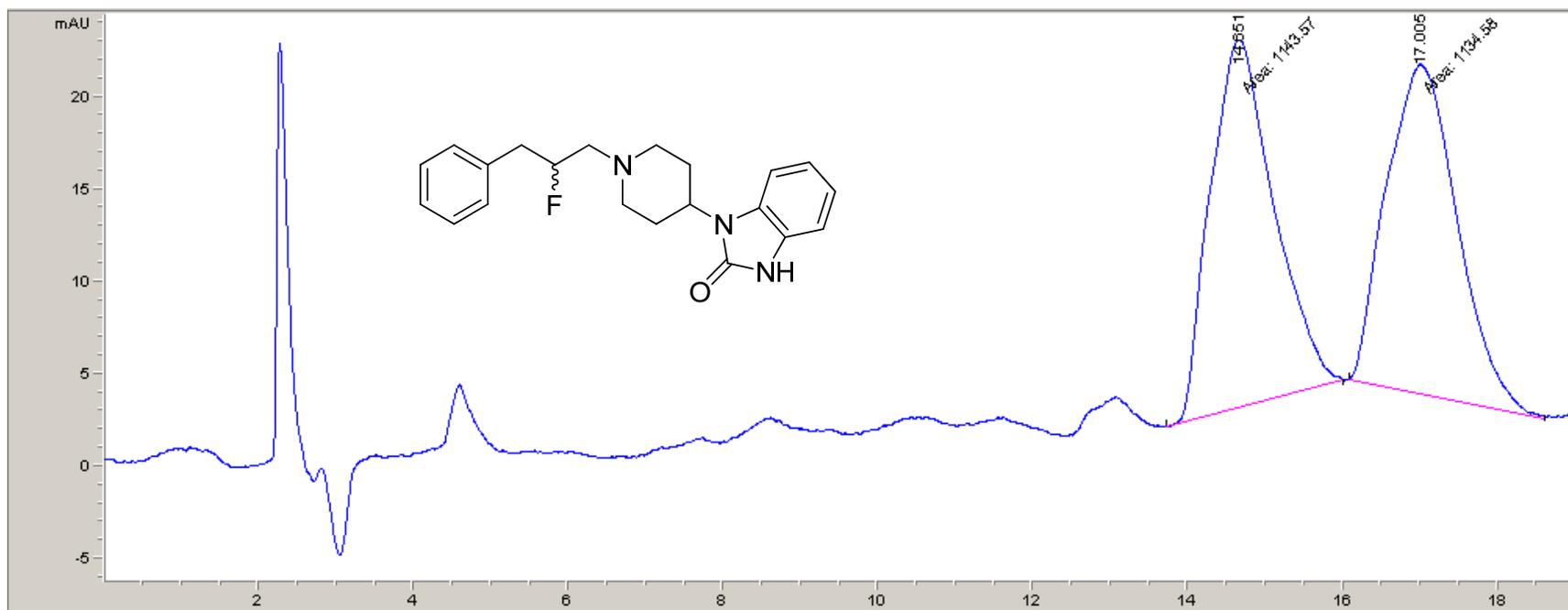




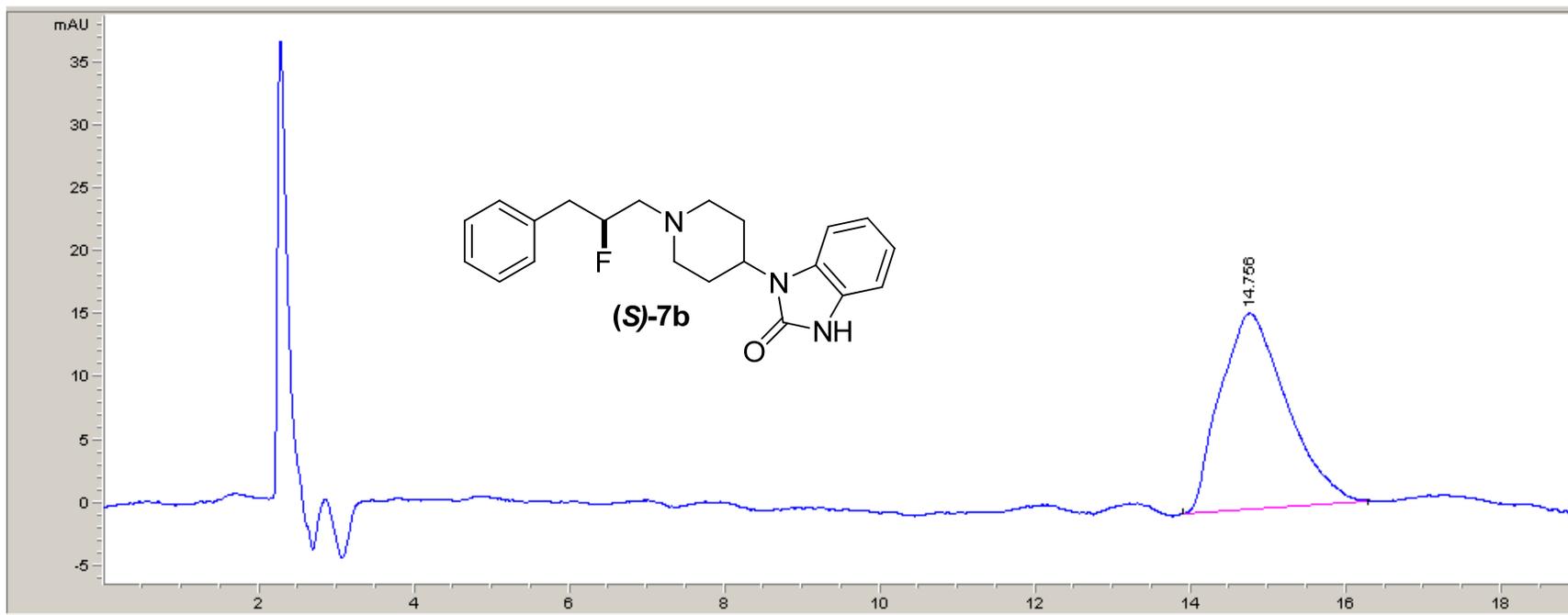




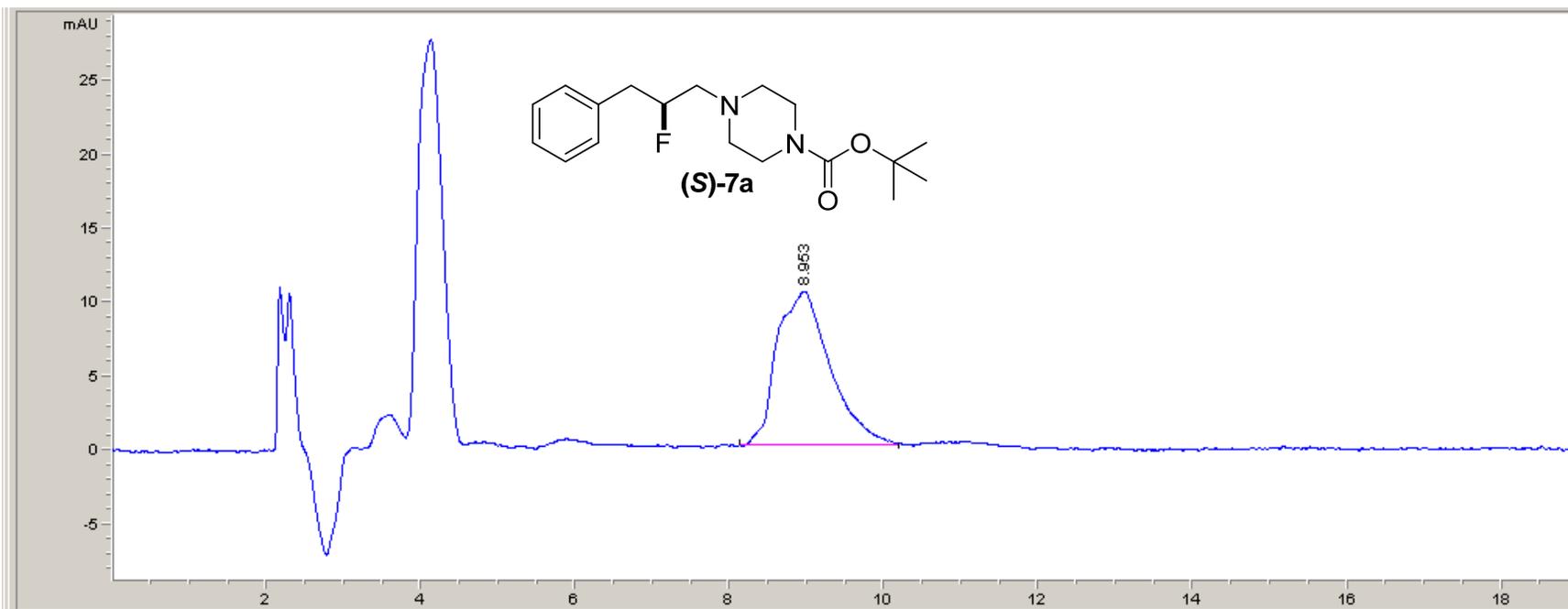




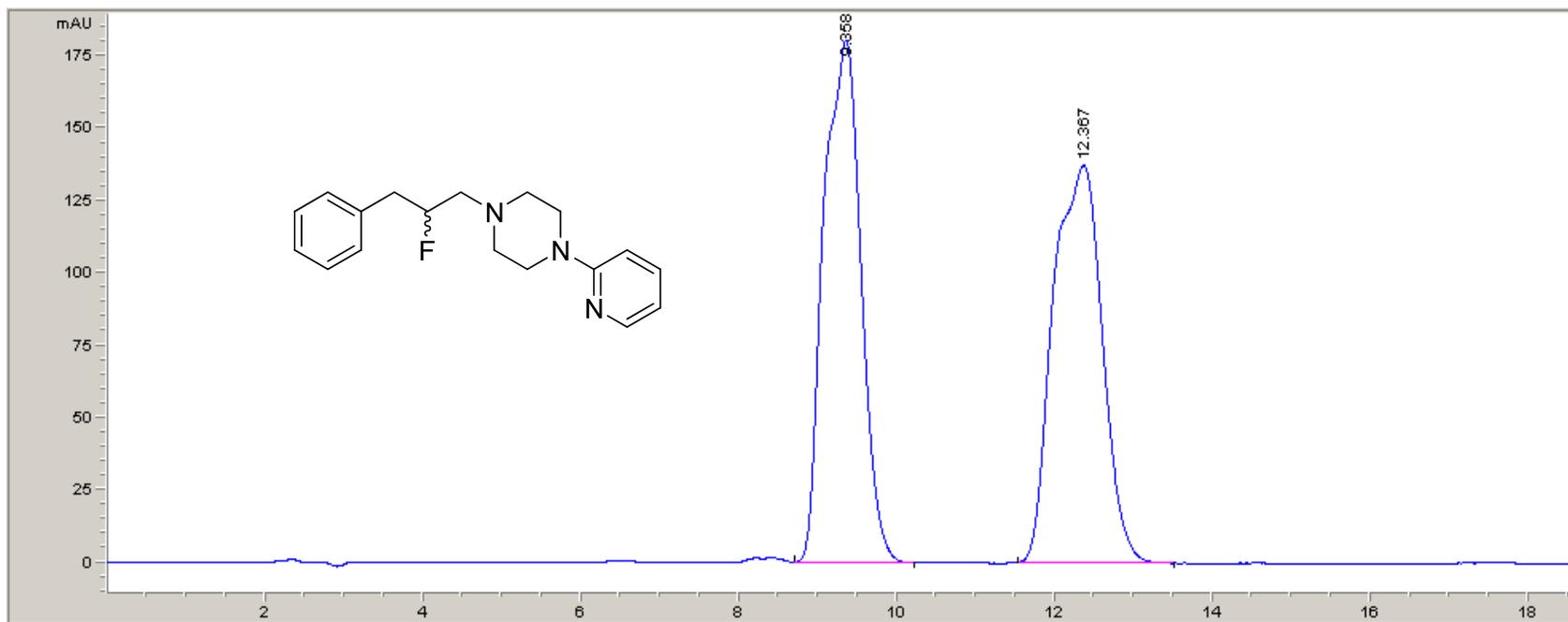
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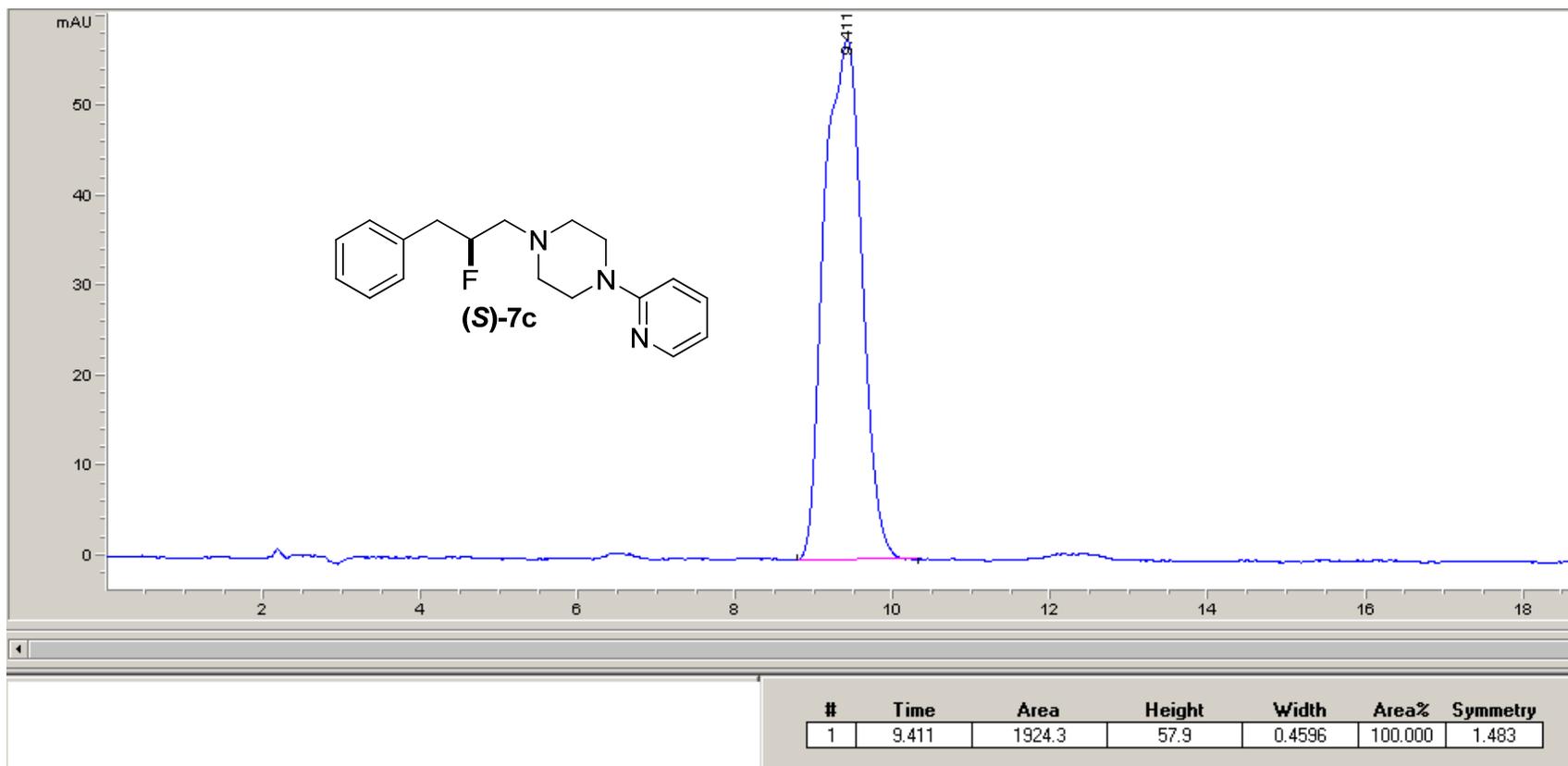
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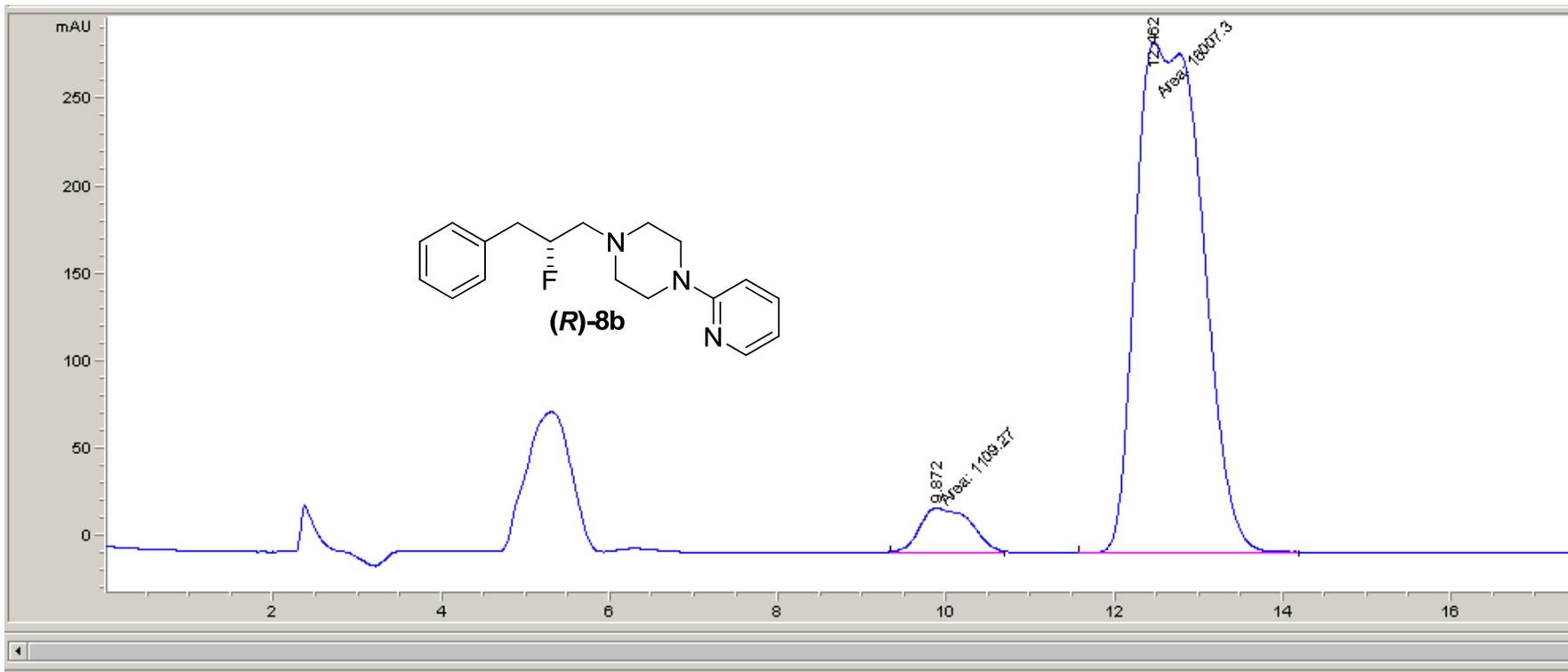


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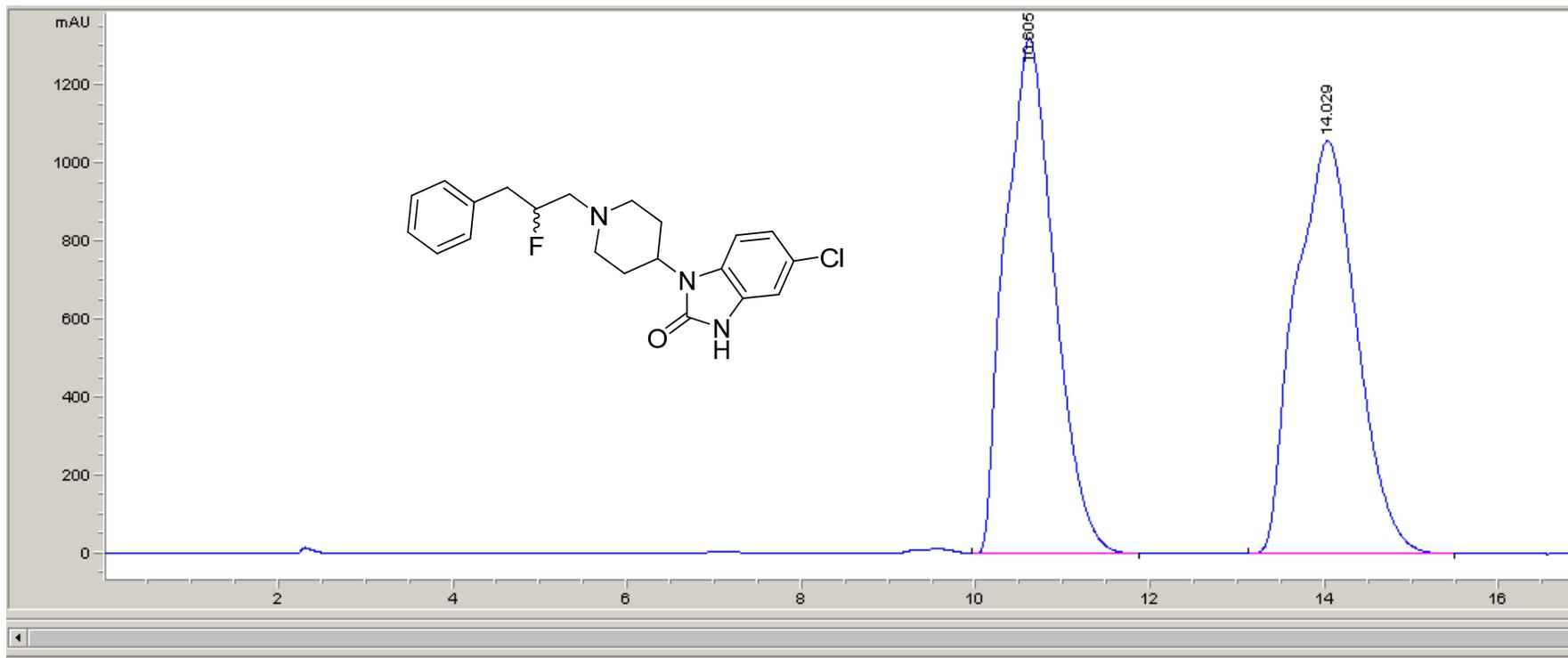


#	Time	Area	Height	Width	Area%	Symmetry
1	9.358	5934.6	180.7	0.4591	50.050	1.386
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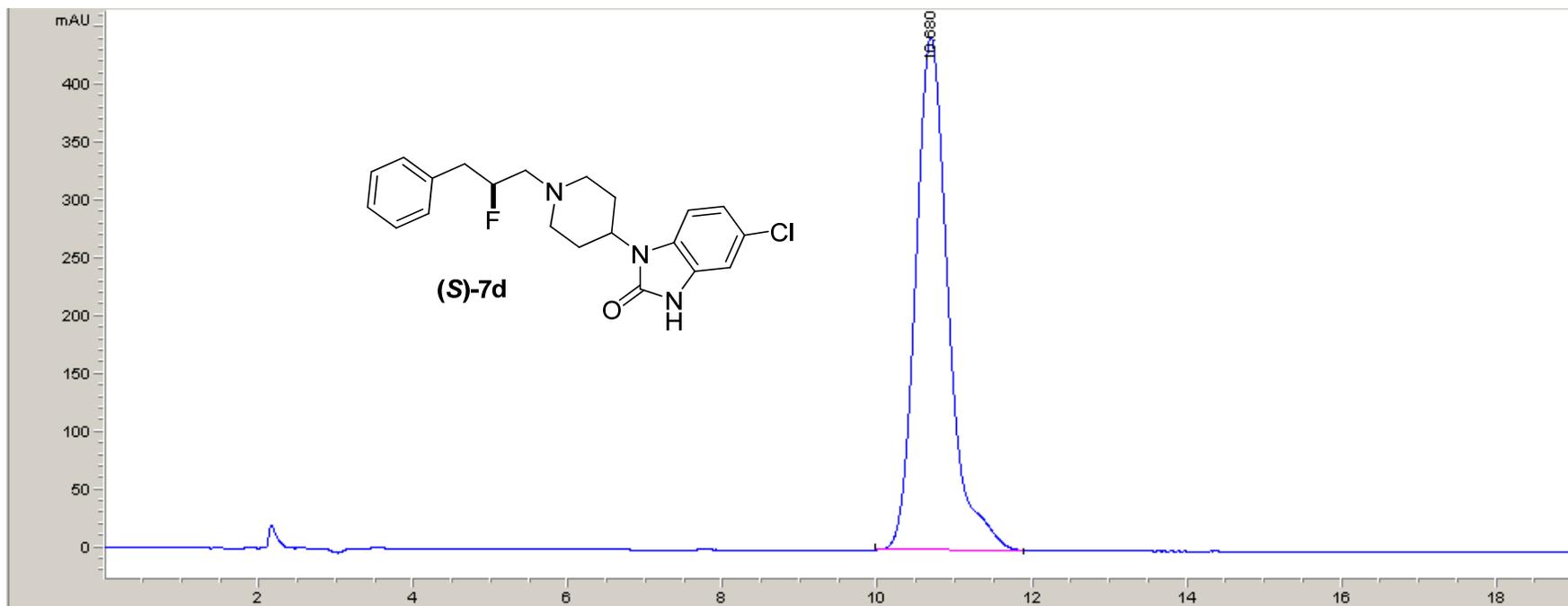




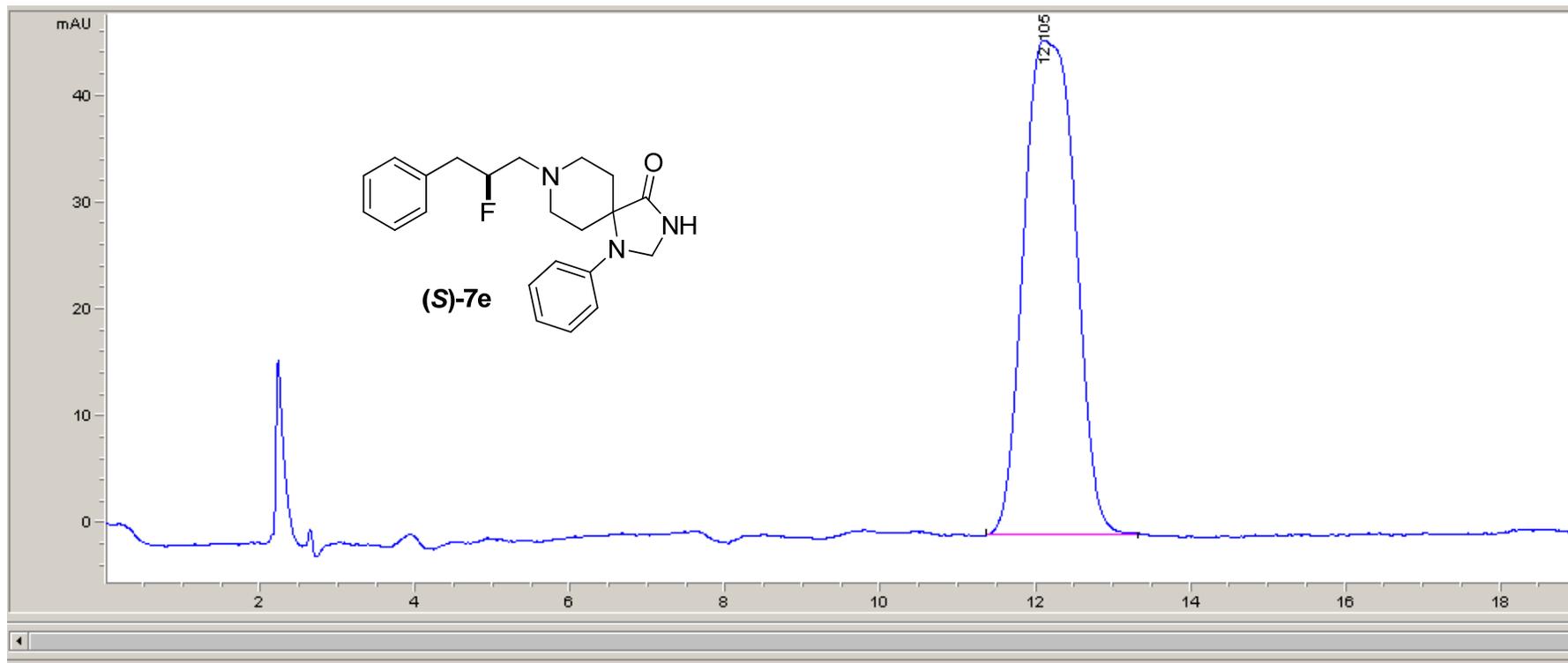
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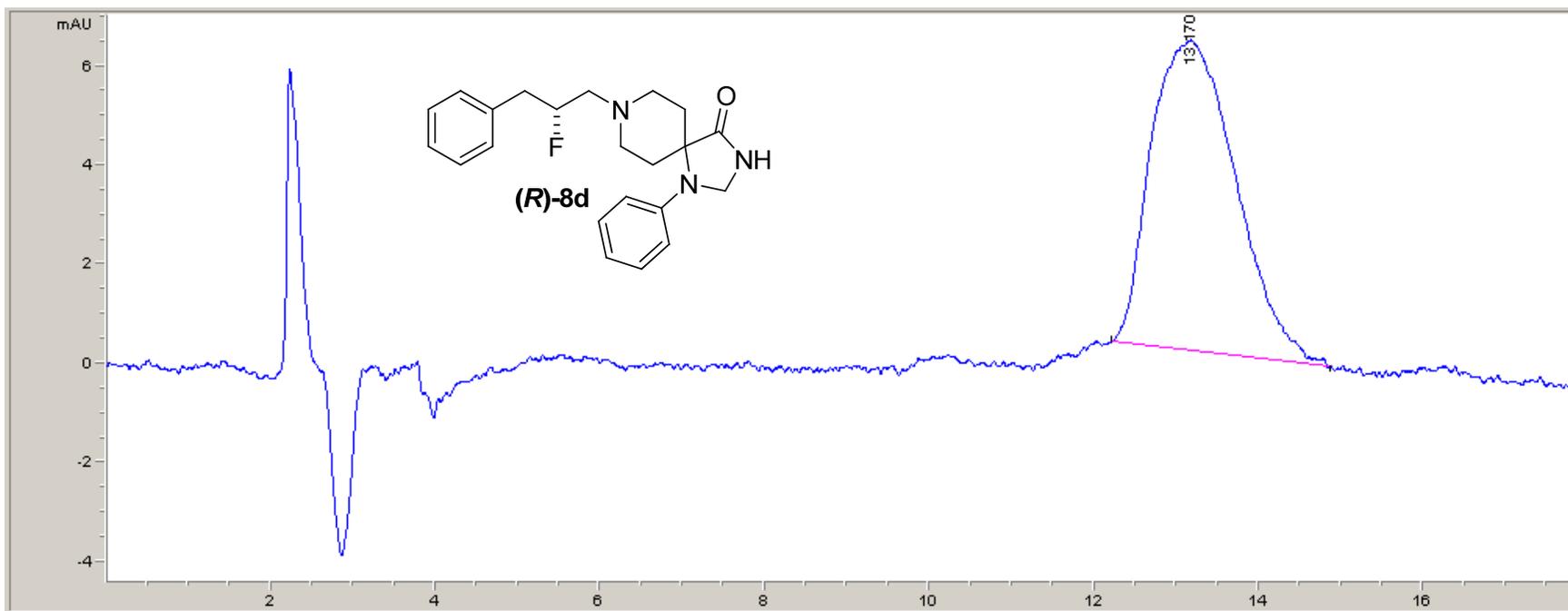
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2	14.029	51948	1058	0.6748	50.118	1.068



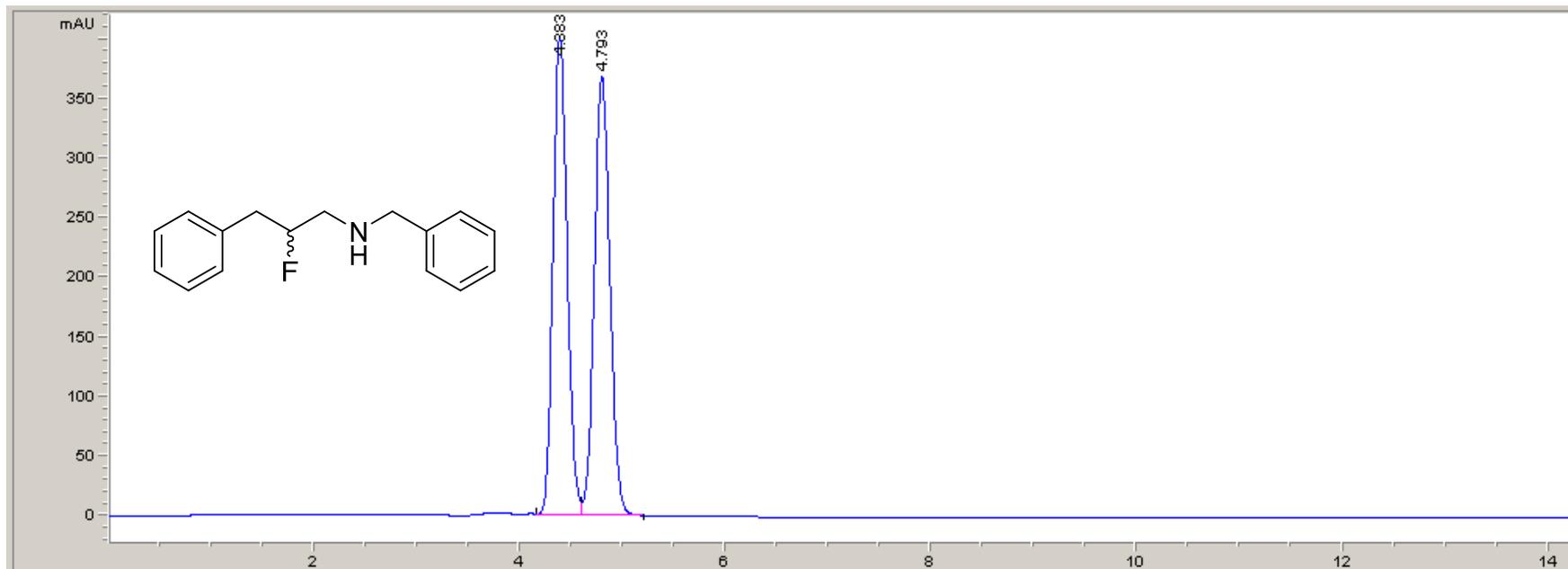
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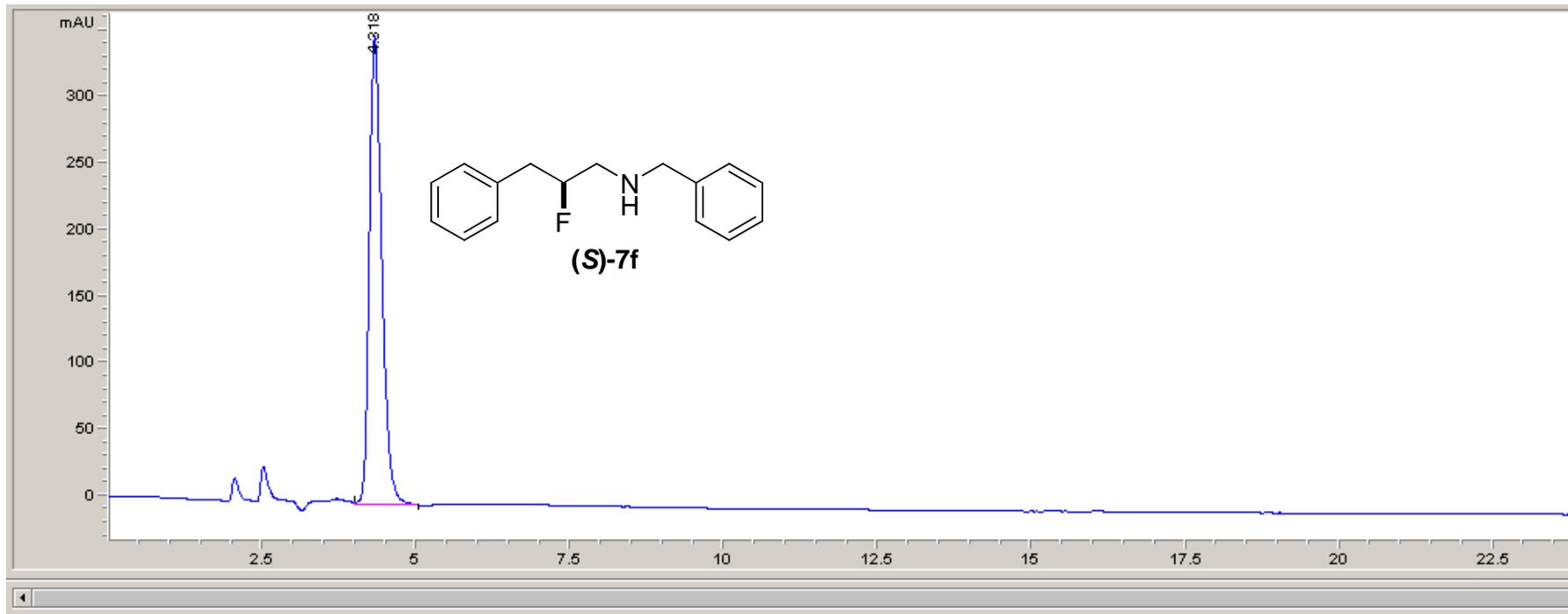
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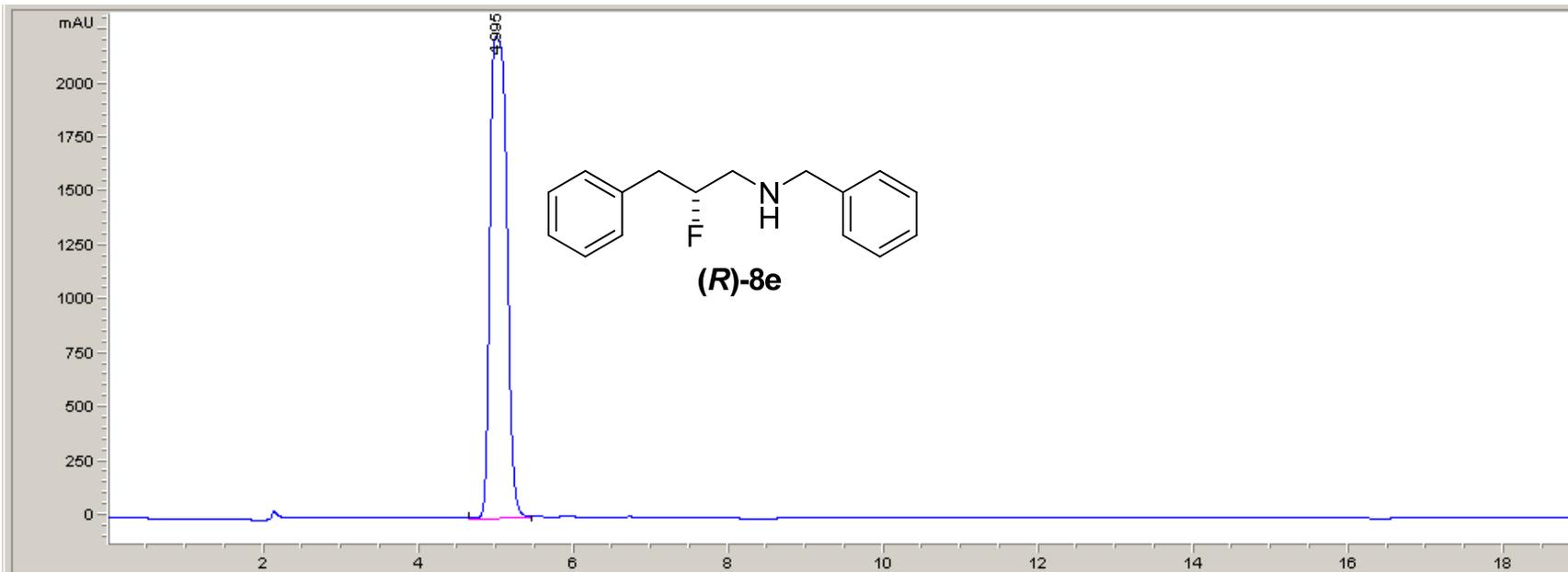
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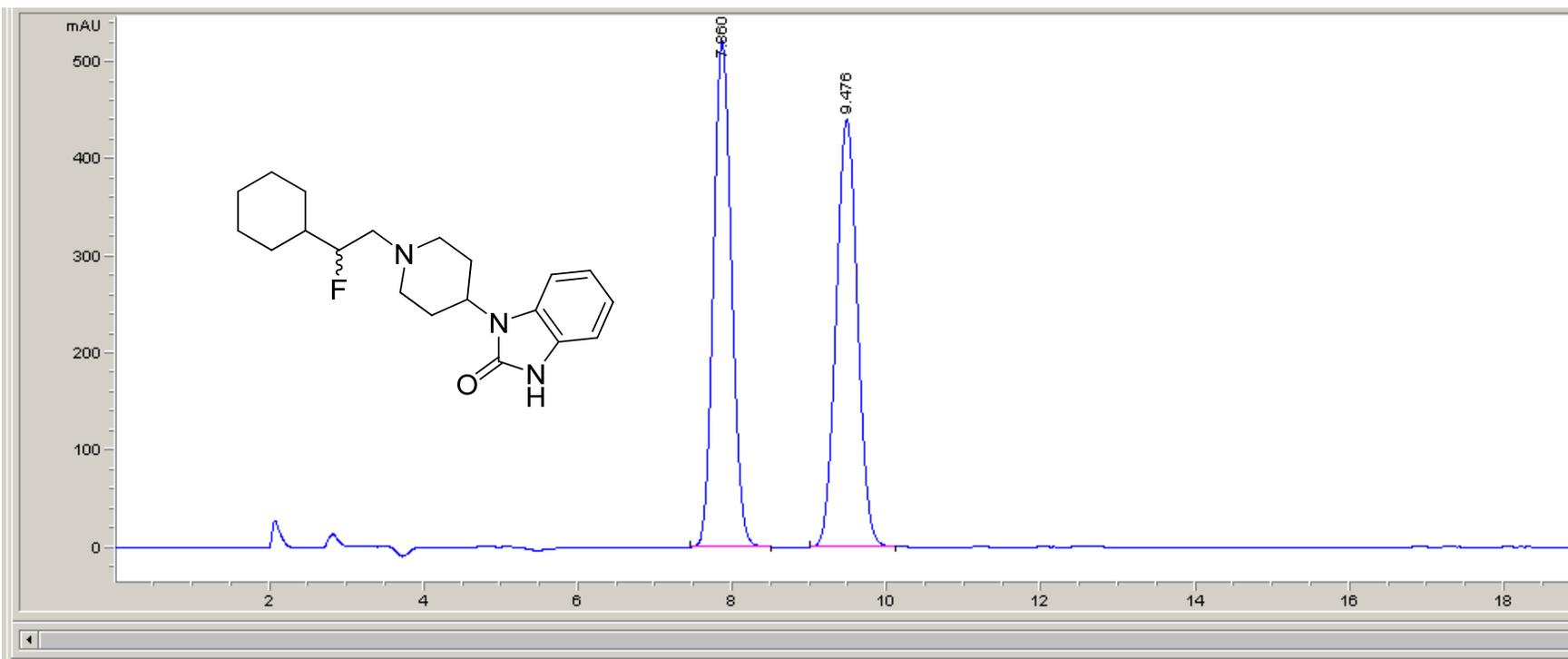
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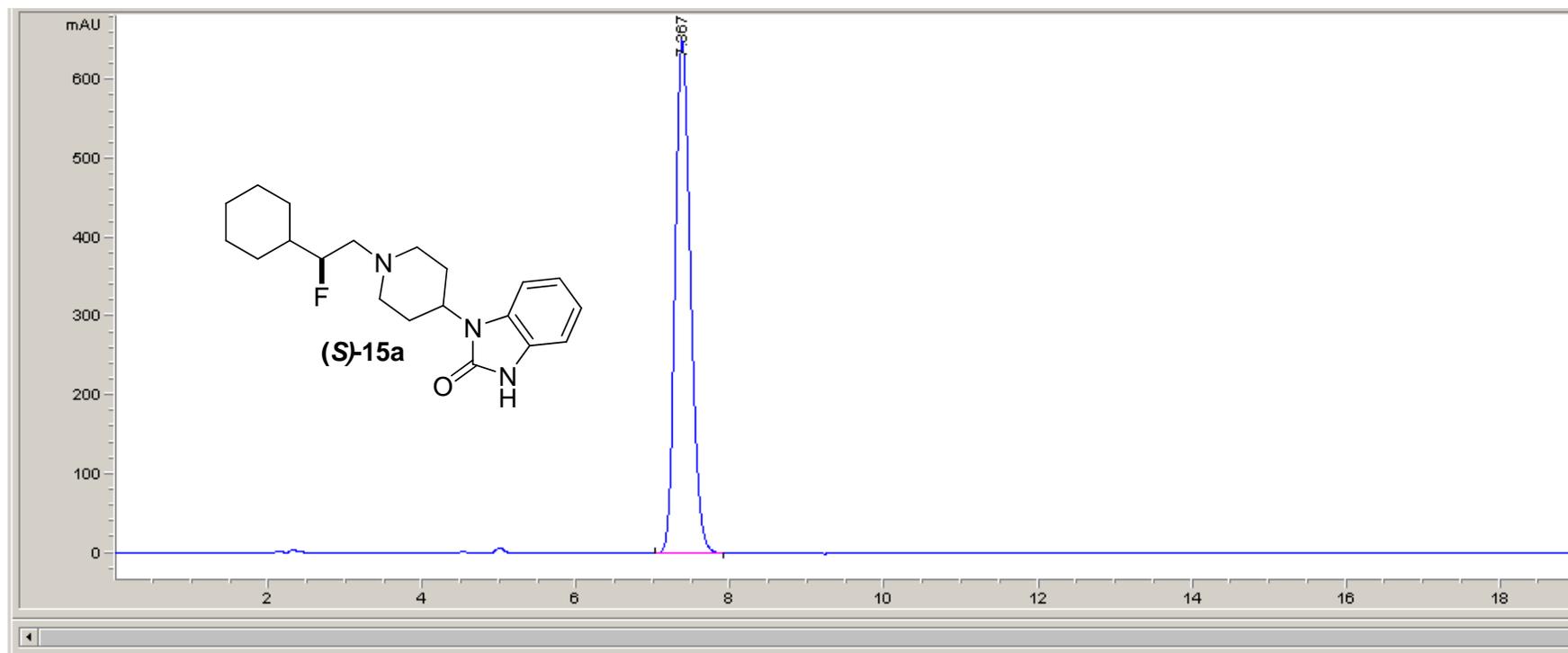
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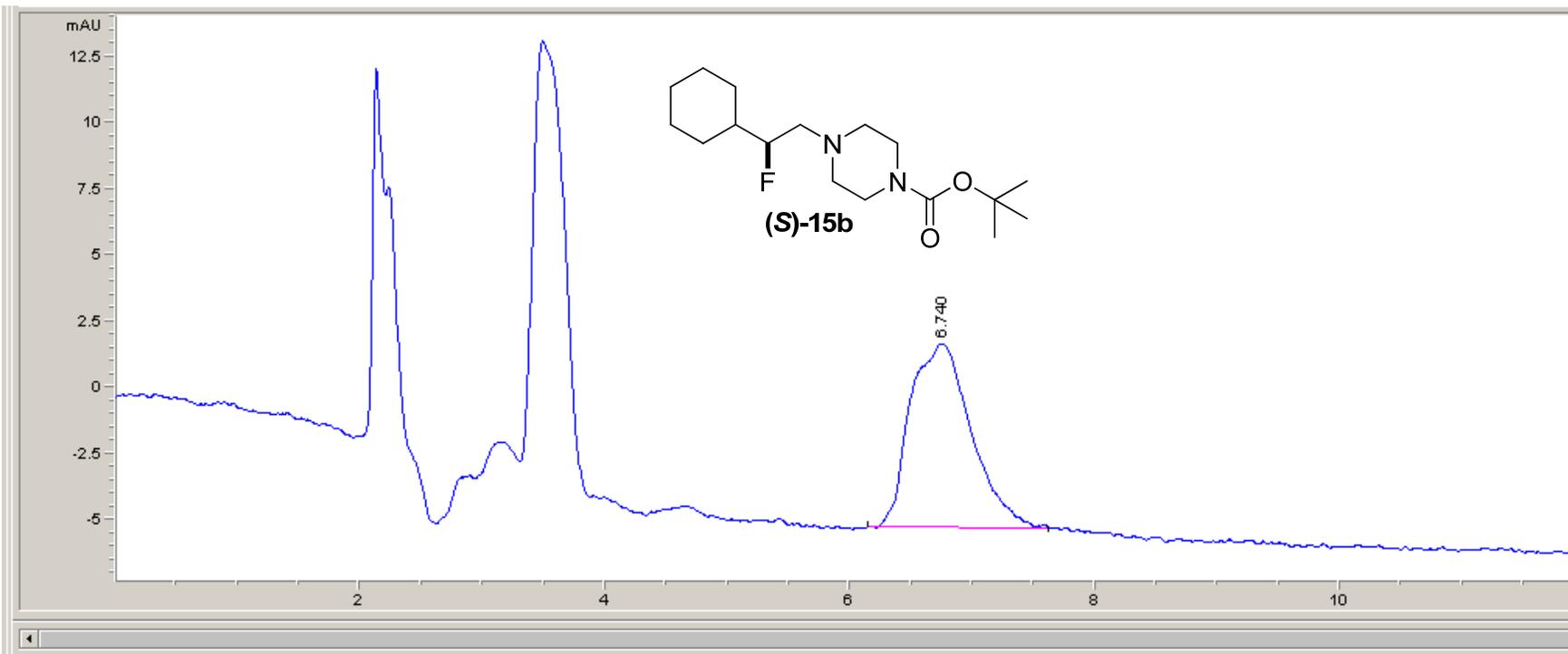
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1	4.995	33676.4	2233.2	0.2419	100.000	0.556



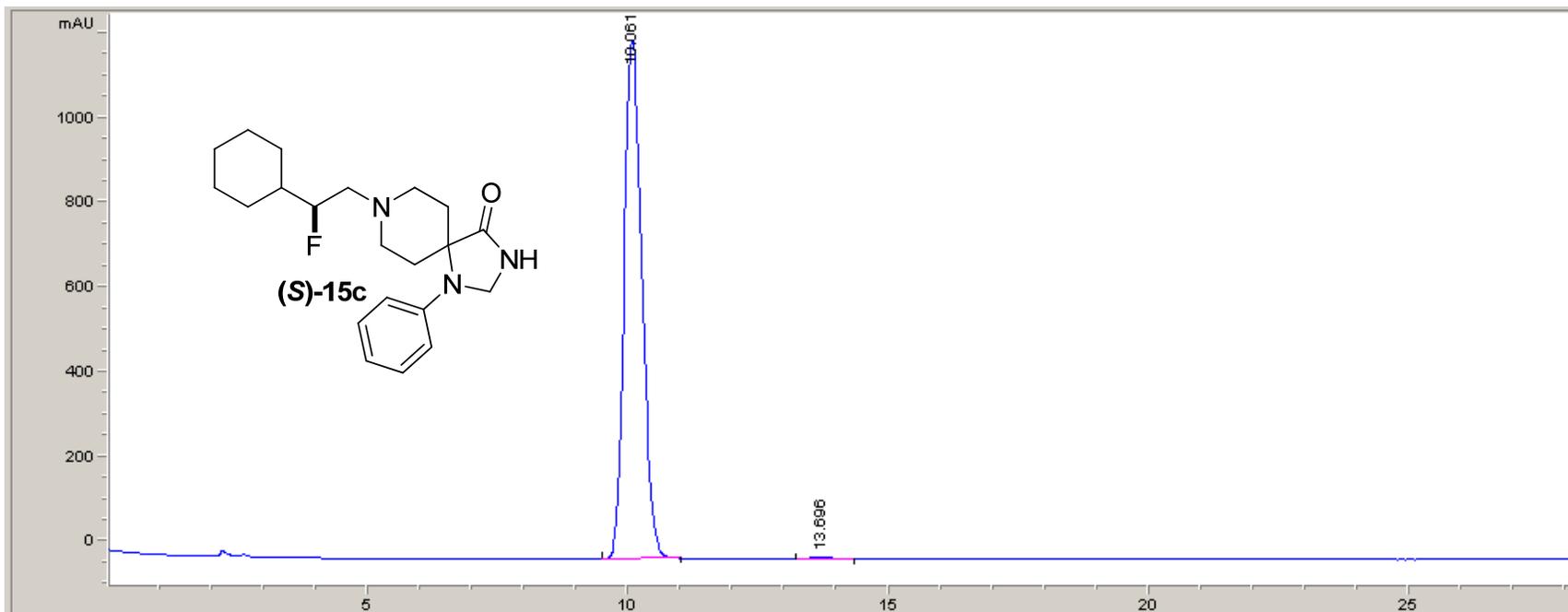
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2	9.476	8448.6	440.8	0.2996	49.985	0.958



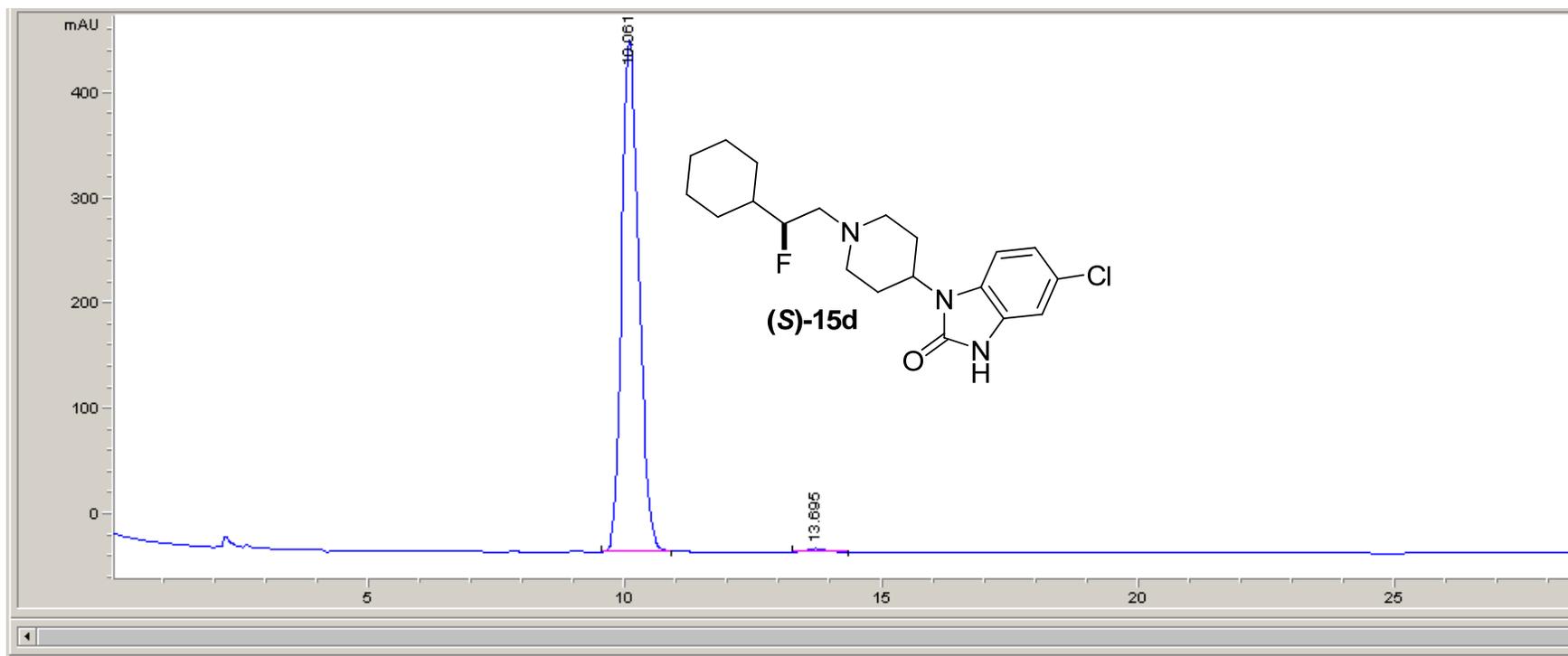
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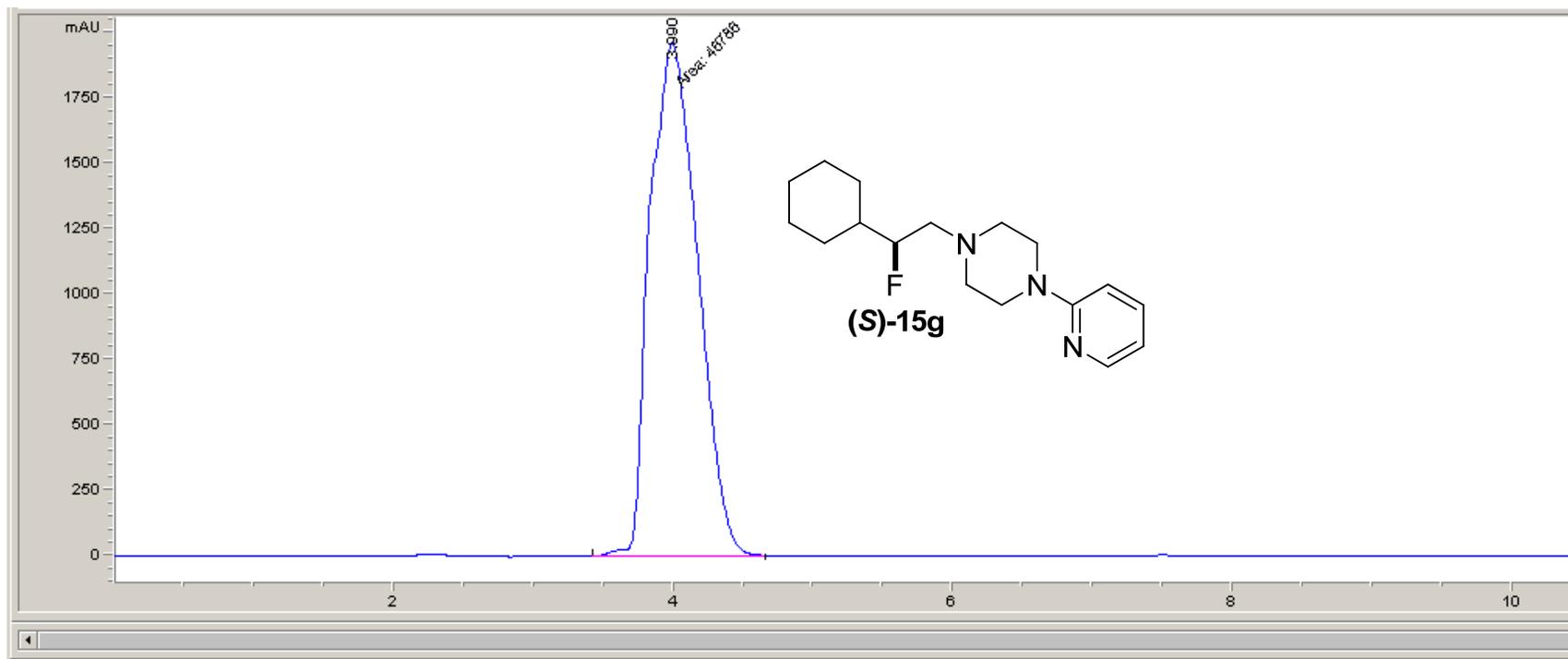
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1	6.74	242	6.9	0.4506	100.000	0.972



#	Time	Area	Height	Width	Area%	Symmetry
1	10.061	29082.8	1225.9	0.3708	99.526	0.771
2	13.696	138.4	5.3	0.4024	0.474	0.913



#	Time	Area	Height	Width	Area%	Symmetry
1	10.061	11362.9	485.4	0.3651	99.262	0.774
2	13.695	84.5	3.3	0.3919	0.738	0.922



#	Time	Area	Height	Width	Area%	Symmetry
1	3.99	46786	1965.2	0.3968	100.000	0.837