

Supporting Information

Copper/silver co-mediated three-component bicyclization for accessing indeno[1,2-*c*]azepine-3,6-diones

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Context

General Information.....	S2
X-Ray Structures of Products 3f	S2
Control Experiments	S2
Radical-Trapping Experiment.....	S3
Intermediate Detection.....	S4
General Procedure for the Synthesis of Products 3a	S5
Scale-up transformation of 3a	S5
Lithium Aluminum Hydride Reduction of Compound 3a	S5
Characterization Data of Compounds 3a-3aa and 5a	S6-S16
Copies of ¹ H, ¹³ C and ¹⁹ F NMR Spectra for Compounds 3a-3aa and 5a	S16-S100

General Information

^1H NMR (^{13}C NMR) spectra were measured on a Bruker DPX 400 MHz spectrometer in CDCl_3 ($\text{DMSO}-d_6$) with chemical shift (δ) given in ppm relative to TMS as internal standard [(s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz)]. HRMS (APCI and ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. The melting points were measured with digital melting point detector.

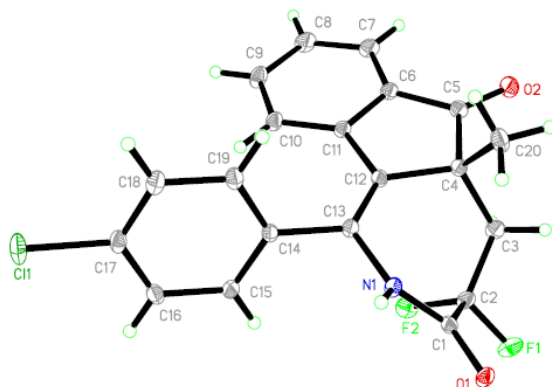
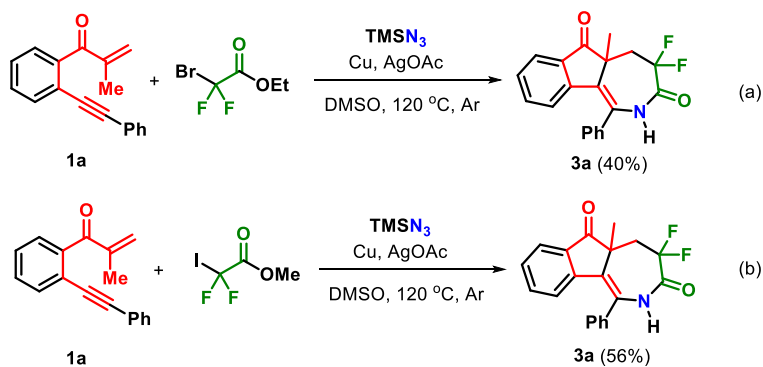


Figure S1. X-Ray Structure of **3f** (CCDC 2088124)

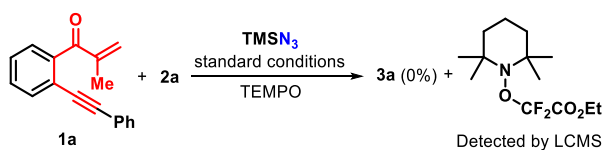


Scheme S1. Control experiments

To gain the influence of halogenated esters into this reaction, two controlled experiments were conducted. When $\text{BrCF}_2\text{CO}_2\text{Et}$ as the halogenation reagent was added into the reaction system under the standard conditions, the reaction can proceed normally, and product **3a** is obtained with a yield of 40%. Meantime, when $\text{ICF}_2\text{CO}_2\text{Me}$ was used in the reaction, product **3a** is obtained with a yield of 56%.

Radical-Trapping Experiment:

TEMPO as the radical trapping reagent — General procedure



To a 25-mL Schlenk tube under Ar conditions, 1,6-enyne **1a** (0.2 mmol, 49 mg), Cu powder (0.5 mmol, 33mg), AgOAc (0.4 mmol, 67 mg), TMSN₃ (0.4 mmol, 46 mg), ethyl difluoroiodoacetate **2** (0.3 mmol, 75 mg) and TEMPO (0.6 mmol, 94 mg) in DMSO (2.0 mL) was stirred at 120 °C for 12 hours. After completion of the reaction, the solution was detected by LC-MS analysis (Figure S2).

Operator:MSQ Timebase:LCMS Sequence:SJ201606132

Page 1-1
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Overlay of Samples and Spectra from Integration View

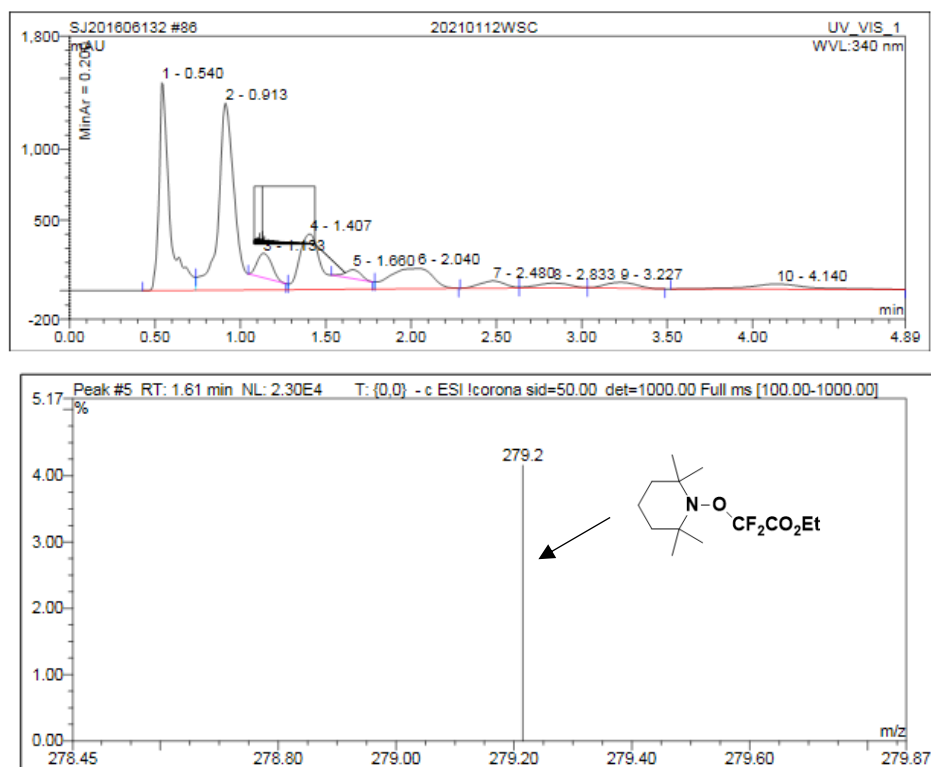


Figure S2. Copy of LC-MS Spectrum of TEMPO-S adduct

Intermediate Detection

To a 25-mL Schlenk tube under Ar conditions, 1,6-enyne **1a** (0.2 mmol, 49 mg), Cu powder (0.5 mmol, 33mg), AgOAc (0.4 mmol, 67 mg), TMSN₃ (0.4 mmol, 46 mg) and ethyl difluoroiodoacetate **2** (0.3 mmol, 75 mg) in DMSO (2.0 mL) was stirred at 120 °C for 2 hours until complete consumption of **1a** as monitored by TLC analysis. Then the reaction system was directly measured by HR-MS analysis. The key intermediates **E**, **F** (or **H**) and **I** (or **J**) were detected by HR-MS (Figures S3-S5).

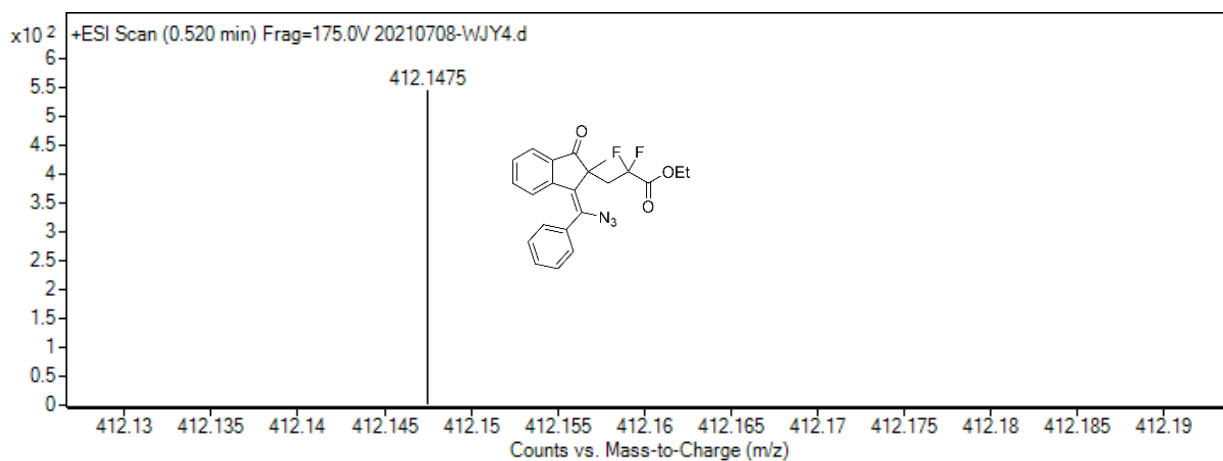


Figure S3. Copy of HR-MS Spectrum of Intermediate E

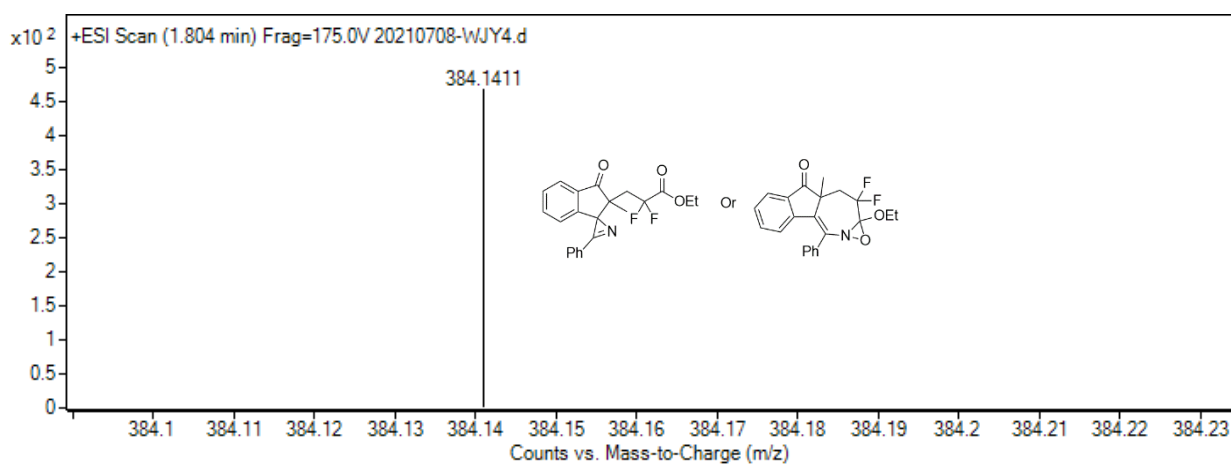


Figure S4. Copy of HR-MS Spectrum of Intermediate F or H

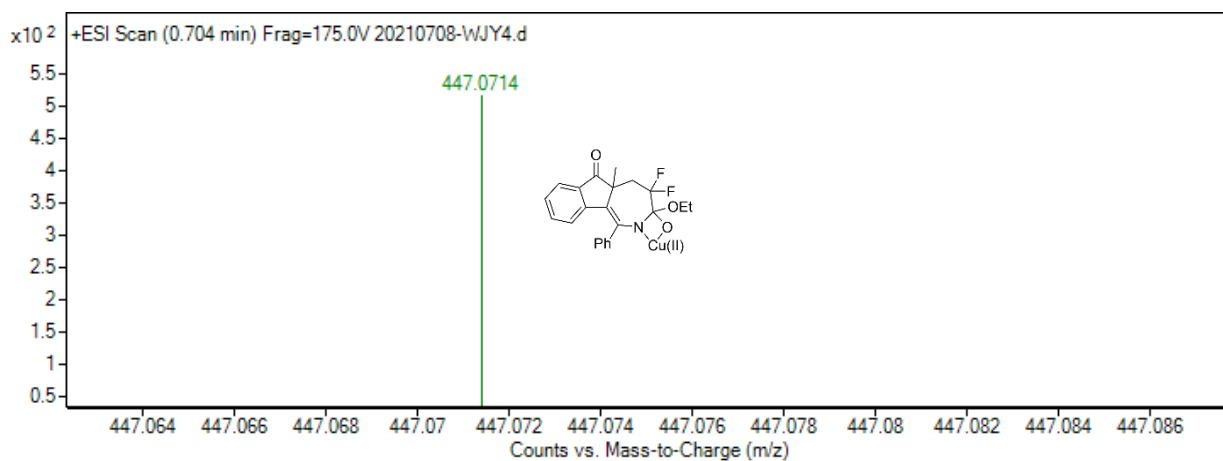
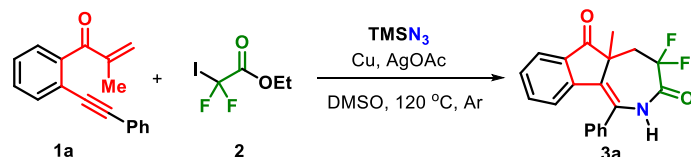


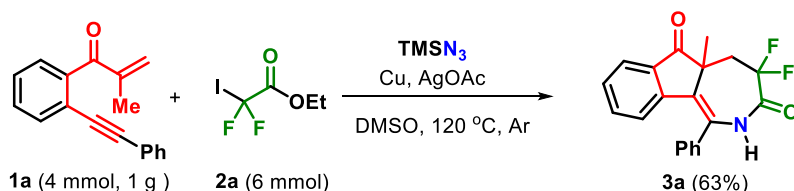
Figure S5. Copy of HR-MS Spectrum of Intermediate I or J

General Procedure for the Synthesis of Products 3a



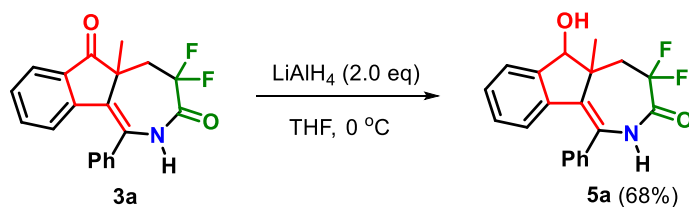
To a 10 mL-Schlenk tube, 1,6-enyne **1a** (0.2 mmol, 49 mg), Cu powder (0.5 mmol, 33 mg), AgOAc (0.4 mmol, 67 mg), TMSN₃ (0.4 mmol, 46 mg), ethyl difluoroiodoacetate **2** (0.3 mmol, 75 mg) and DMSO (2.0 mL) were sequentially added under the protection with argon. The resulting mixture was stirring at 120 °C in metal bath for 12 h. After the reaction was complete (by TLC), the reaction mixture was cooled to room temperature and washed with H₂O (20 ml) and extracted with ethyl acetate (3 ×15 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 10:1 v/v) to afford the desired product **3a** as white solid in 71% yield.

Scale-up transformation of 3a



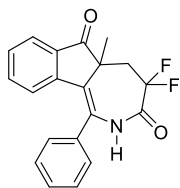
To a 50 mL-Schlenk flask, 1,6-enyne **1a** (4 mmol, 1.00 g), Cu powder (10 mmol, 0.66 g), AgOAc (8 mmol, 1.34 g), TMSN₃ (8 mmol, 0.92 g), ethyl difluoroiodoacetate **2** (6 mmol, 1.5 g) and DMSO (20 mL) were sequentially added under the protection with argon. The resulting mixture was stirring at 120 °C in metal bath for 12h. After the reaction was complete (by TLC), the reaction mixture was cooled to room temperature and washed with H₂O (50 ml) and extracted with ethyl acetate (3 ×45 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 10:1 v/v) to afford the desired product **3a** as white solid in 63% yield.

Lithium aluminum hydride reduction of compound 3a



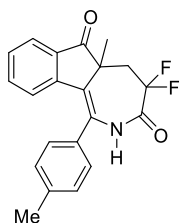
To a solution of **3a** (0.2 mmol, 0.0678g) in THF (2.0 mL) was added LiAlH₄ (1.0 M in THF, 2.5 equiv.) at 0 °C. The reaction mixture stirred for 30 minutes. After completion of the reaction, the residue was quenched with saturated NH₄Cl solution, extracted with ethyl acetate and dried on MgSO₄. The solvent was evaporated under reduced pressure and the products were purified through preparative thin layer chromatography to get desired products **5a**.

4,4-difluoro-5a-methyl-1-phenyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3a)



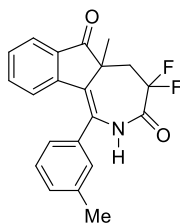
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 48 mg, 71%; mp 215-217 °C
¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.81 - 7.79 (m, 1H), 7.66 - 7.54 (m, 3H), 7.44 (d, *J* = 6.8 Hz, 2H), 7.36 - 7.29 (m, 2H), 6.86 (s, 1H), 6.65 (d, *J* = 7.2 Hz, 1H), 2.85 - 2.67 (m, 2H), 1.66 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 204.6, 164.4 (t, ²*J*_{CF} = 30.0 Hz), 146.5, 135.4, 135.0, 133.9, 132.1, 130.6, 130.3, 129.4, 129.2, 129.0, 128.8, 124.9, 124.3, 114.9, (t, ¹*J*_{CF} = 248.0 Hz), 46.8, 46.7, (t, ³*J*_{CF} = 25.0 Hz), 46.6, 21.8. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.0 (d, *J* = 251.9 Hz, 1F), -98.9 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3244, 1715, 1694, 1473, 1336, 1249, 1172, 1022, 860, 768. HR-MS (ESI) *m/z* calcd for C₂₀H₁₄F₂NO₂ [M-H]⁻ 338.0993, found 338.0985.

4,4-difluoro-5a-methyl-1-(*p*-tolyl)-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3b)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 25 mg, 35%; mp 230-231 °C
¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.79 - 7.77 (m, 1H), 7.41 (s, 2H), 7.34 - 7.30 (m, 3H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.09 - 6.98 (m, 1H), 6.73 - 6.71 (m, 1H), 2.78 - 2.60 (m, 2H), 2.47 (s, 3H), 1.63 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 204.8, 164.7 (t, ²*J*_{CF} = 30.0 Hz), 146.8, 141.0, 135.4, 133.9, 132.4 (t, ⁴*J*_{CF} = 3.0 Hz), 132.1, 131.0, 129.9, 129.4, 128.9, 128.5, 124.9, 124.5, 115.0 (t, ¹*J*_{CF} = 248.0 Hz), 46.8 (t, ³*J*_{CF} = 23.0 Hz), 46.8, 46.5, 21.8, 21.7. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.0 (d, *J* = 251.9 Hz, 1F), -99.0 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3217, 3121, 1714, 1702, 1467, 1326, 1244, 1164, 1023, 826, 773. HR-MS (ESI) *m/z* calcd for C₂₁H₁₆F₂NO₂ [M-H]⁻ 352.1149, found 352.1139.

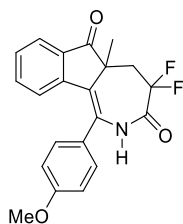
4,4-difluoro-5a-methyl-1-(*m*-tolyl)-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3c)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 30 mg, 42%; mp 168-169 °C
¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm) 10.33 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.60 - 7.37 (m, 4H), 7.27 - 7.23 (m, 2H), 6.53 - 6.47 (m, 1H), 2.75 - 2.66 (m, 2H), 2.38 (d, *J* = 43.2 Hz, 3H), 1.54 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 203.6, 164.8 (t, ²*J*_{CF} = 30.0 Hz), 145.8, 135.8, 135.6, 135.4, 133.9, 130.8, 130.5 (t, ⁵*J*_{CF} = 3.0 Hz), 130.2, 129.5, 129.0, 127.0, 125.6, 124.3, 115.8 (t, ¹*J*_{CF} = 248.0 Hz), 100.0, 46.9 (d, ⁴*J*_{CF} = 10.0 Hz), 46.5 (t, ³*J*_{CF} = 24.0 Hz), 21.5, 21.5. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ, ppm) -95.4 (d, *J* = 251.9 Hz, 1F), -98.1 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3247,

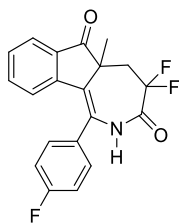
3136, 1713, 1697, 1473, 1334, 1255, 1170, 1034, 963, 797. HR-MS (ESI) m/z calcd for $C_{21}H_{16}F_2NO_2$ $[M-H]^-$ 352.1149, found 352.1149.

4,4-difluoro-1-(4-methoxyphenyl)-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3d)



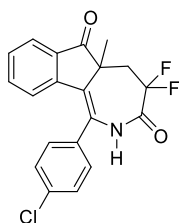
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 25 mg, 34%; mp 211-212 °C 1H NMR (400 MHz, $CDCl_3$) (δ , ppm) 7.80 - 7.76 (m, 1H), 7.41 (s, 2H), 7.34 - 7.30 (m, 3H), 7.23 (d, $J = 6.4$ Hz, 1H), 7.04 (s, 1H), 6.74 - 6.71 (m, 1H), 2.79 - 2.63 (m, 2H), 2.47 (s, 3H), 1.64 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ , ppm) 204.82, 164.67 (t, $^2J_{CF} = 30.0$ Hz), 161.43, 146.96, 135.42, 133.92, 132.14 (t, $^5J_{CF} = 3.0$ Hz), 131.18, 130.45, 128.87, 128.26, 127.07, 124.95, 124.38, 115.05 (t, $^1J_{CF} = 249.0$ Hz), 100.00, 55.61, 46.89 (t, $^3J_{CF} = 23.0$ Hz), 46.65 (d, $^4J_{CF} = 9.0$ Hz), 29.82, 21.80. -97.1 (d, $J = 251.9$ Hz, 1F), -99.2 (d, $J = 251.9$ Hz, 1F). HR-MS (ESI) m/z calcd for $C_{21}H_{16}F_2NO_3$ $[M-H]^-$ 368.1098, found 368.1098.

4,4-difluoro-1-(4-fluorophenyl)-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3e)



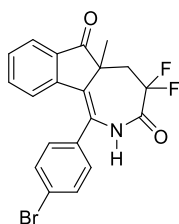
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 43 mg, 60%; mp 216-217 °C 1H NMR (400 MHz, $CDCl_3$) (δ , ppm) 7.82 - 7.80 (m, 1H), 7.55 (s, 1H), 7.42 (d, $J = 5.6$ Hz, 1H), 7.38 - 7.34 (m, 2H), 7.33 - 7.30 (m, 1H), 7.17 - 7.13 (m, 1H), 7.04 (d, $J = 3.2$ Hz, 1H), 6.68 - 6.65 (m, 1H), 2.80 - 2.62 (m, 2H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ , ppm) 204.4, 164.6 (t, $^3J_{CF} = 30.0$ Hz), 164.0 (d, $^1J_{CF} = 251.0$ Hz), 160.2, 146.3, 135.5, 134.0, 131.6 (t, $^8J_{CF} = 8.0$ Hz), 131.3, 131.1 (t, $^9J_{CF} = 3.0$ Hz), 129.2, 125.1, 124.2, 117.6 (d, $^6J_{CF} = 22.0$ Hz), 116.5 (d, $^5J_{CF} = 22.0$ Hz), 115.0 (t, $^2J_{CF} = 248.0$ Hz), 100.0, 46.8 (t, $^4J_{CF} = 24.0$ Hz), 46.6 (d, $^7J_{CF} = 9.0$ Hz), 21.8. ^{19}F NMR (376 MHz, $CDCl_3$) (δ , ppm) -97.1 (d, $J = 251.9$ Hz, 1F), -99.1 (d, $J = 251.9$ Hz, 1F), -108.8. IR (KBr, ν , cm^{-1}) 3232, 3137, 1715, 1697, 1603, 1511, 1337, 1226, 1159, 1018, 845, 768 HR-MS (ESI) m/z calcd for $C_{20}H_{13}F_3NO_2$ $[M-H]^-$ 356.0898, found 356.0903.

1-(4-chlorophenyl)-4,4-difluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3f)



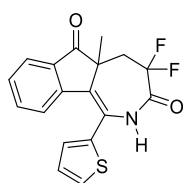
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 52 mg, 70%; mp 231-233 °C
¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.82 - 7.80 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.40 - 7.36 (m, 3H), 6.94 (s, 1H), 6.72 - 6.70 (m, 1H), 2.80 - 2.62 (m, 2H), 1.65 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 204.3, 164.5 (t, ²*J*_{CF} = 30.0 Hz), 146.1, 136.8, 135.5, 134.1, 133.4, 130.9 (d, ⁶*J*_{CF} = 3.0 Hz), 130.8 (t, ⁴*J*_{CF} = 21.0 Hz), 129.6, 129.5, 129.3, 125.1, 124.2, 114.9 (t, ¹*J*_{CF} = 248.0 Hz), 46.8 (t, ³*J*_{CF} = 24.0 Hz), 46.6 (d, ⁵*J*_{CF} = 9.0 Hz), 21.8. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.1 (d, *J* = 251.9 Hz, 1F), -99.1 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3235, 3137, 1716, 1692, 1597, 1473, 1340, 1299, 1172, 1019, 840, 768 HR-MS (ESI) m/z calcd for C₂₀H₁₃ClF₂NO₂ [M-H]⁻ 372.0603, found 372.0616.

1-(4-bromophenyl)-4,4-difluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3g)



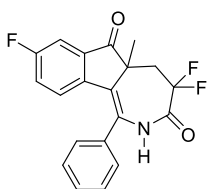
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 53 mg, 64%; mp 208-209 °C
¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.82 - 7.75 (m, 2H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.39 - 7.37 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.97 (s, 1H), 6.73 - 6.71 (m, 1H), 2.80 - 2.62 (m, 2H), 1.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 204.2, 164.5 (t, ²*J*_{CF} = 30.0 Hz), 146.0, 135.5, 133.8 (t, ⁴*J*_{CF} = 18.0 Hz), 132.5, 131.1, 130.9 (d, ⁶*J*_{CF} = 3.0 Hz), 130.7, 129.5, 129.3, 125.1, 124.2, 114.9 (t, ¹*J*_{CF} = 248.0 Hz), 46.8 (t, ³*J*_{CF} = 24.0 Hz), 46.6 (d, ⁵*J*_{CF} = 9.0 Hz), 21.7. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.1 (d, *J* = 251.9 Hz, 1F), -99.1 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3233, 3131, 1716, 1693, 1472, 1341, 1299, 1172, 1015, 840, 768 HR-MS (ESI) m/z calcd for C₂₀H₁₃BrF₂NO₂ [M-H]⁻ 416.0098, found 416.0100.

4,4-difluoro-5a-methyl-1-(thiophen-2-yl)-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3h)



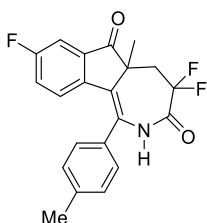
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 56 mg, 65%; mp 219-220 °C
¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm) 10.51 (s, 1H), 7.90 - 7.88 (m, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.55 - 7.50 (m, 1H), 7.46 - 7.43 (m, 1H), 7.33 - 7.32 (m, 1H), 7.25 - 7.23 (m, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 2.76 - 2.66 (m, 2H), 1.53 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 204.2, 164.1 (t, ²*J*_{CF} = 30.0 Hz), 146.6, 136.6, 136.1, 133.8, 130.1 (t, ⁴*J*_{CF} = 21.0 Hz), 129.7, 128.5, 126.9 (d, ⁶*J*_{CF} = 3.0 Hz), 124.9, 124.1, 115.7 (t, ¹*J*_{CF} = 248.0 Hz), 60.2, 46.6 (d, ⁵*J*_{CF} = 9.0 Hz), 46.5 (t, ³*J*_{CF} = 24.0 Hz), 45.4, 21.3. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ, ppm) -95.7 (d, *J* = 251.9 Hz, 1F), -98.8 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3213, 3113, 1717, 1640, 1468, 1328, 1296, 1241, 1164, 1112, 965, 773 HR-MS (ESI) m/z calcd for C₁₈H₁₂F₂NO₂S [M-H]⁻ 344.0557, found 344.0552.

4,4,8-trifluoro-5a-methyl-1-phenyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3i)



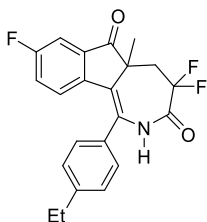
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 40 mg, 56%; mp 235-236 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.63 - 7.53 (m, 3H), 7.46 - 7.39 (m, 3H), 7.06 - 7.01 (m, 1H), 6.86 (s, 1H), 6.63 - 6.58 (m, 1H), 2.81 - 2.67 (m, 2H), 1.66 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 203.8, 164.4 (t, ³J_{CF} = 28.0 Hz), 162.4 (d, ¹J_{CF} = 248.0 Hz), 143.6, 135.7, 133.9 (t, ⁸J_{CF} = 3.0 Hz), 130.6, 130.4, 130.1, 129.6, 129.0, 127.1, 126.0 (d, ⁷J_{CF} = 8.0 Hz), 124.0, 123.8, 115.8 (t, ¹J_{CF} = 248.0 Hz), 110.4 (d, ⁵J_{CF} = 22.0 Hz), 47.0 (d, ⁶J_{CF} = 9.0 Hz), 46.4 (t, ⁴J_{CF} = 25.0 Hz), 21.6. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ, ppm) -97.1 (d, *J* = 251.9 Hz, 1F), -99.1 (d, *J* = 251.9 Hz, 1F), -110.4. IR (KBr, ν, cm⁻¹) 3240, 3131, 1716, 1697, 1486, 1341, 1272, 1148, 1029, 882, 721 HR-MS (ESI) *m/z* calcd for C₂₀H₁₃F₃NO₂ [M-H]⁻ 356.0898, found 356.0887.

4,4,8-trifluoro-5a-methyl-1-(p-tolyl)-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3j)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 46 mg, 62%; mp 249-250 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.41 - 7.39 (m, 3H), 7.29 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.07 - 7.01 (m, 1H), 6.89 (s, 1H), 6.70 - 6.67 (m, 1H), 2.78 - 2.65 (m, 2H), 2.47 (s, 3H), 1.64 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 204.0, 164.5 (t, ³J_{CF} = 28.0 Hz), 162.5 (d, ¹J_{CF} = 248.0 Hz), 143.8, 143.8, 140.3, 135.7, 134.0 (t, ⁸J_{CF} = 3.0 Hz), 132.8, 131.0, 130.0, 129.0, 126.8, 126.1 (d, ⁷J_{CF} = 8.0 Hz), 124.1, 123.9, 115.8 (t, ¹J_{CF} = 248.0 Hz), 110.4 (d, ⁵J_{CF} = 22.0 Hz), 47.1 (d, ⁶J_{CF} = 9.0 Hz), 46.5 (t, ⁴J_{CF} = 24.0 Hz), 21.6. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.2 (d, *J* = 251.9 Hz, 1F), -99.2 (d, *J* = 251.9 Hz, 1F), -110.7. IR (KBr, ν, cm⁻¹) 3248, 3135, 1716, 1698, 1482, 1343, 1271, 1148, 1027, 885, 758 HR-MS (ESI) *m/z* calcd for C₂₁H₁₅F₃NO₂ [M-H]⁻ 370.1055, found 370.1055.

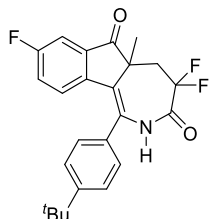
1-(4-ethylphenyl)-4,4,8-trifluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3k)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 39 mg, 51%; mp 215-216 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.44 - 7.40 (m, 3H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.25 (s, 1H), 7.07 - 7.02 (m, 1H), 6.85 (s, 1H), 6.70 - 6.67 (m, 1H), 2.80 - 2.76 (m, 2H), 2.74 - 2.65 (m, 2H), 1.64 (s, 3H), 1.32 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 203.9, 164.4 (t, ³J_{CF} = 28.0 Hz), 161.4 (d, ¹J_{CF} = 248.0 Hz), 146.5, 143.7, 135.6 (d, ⁸J_{CF} = 8.0 Hz), 134.0 (t, ⁹J_{CF} = 3.0 Hz), 133.0, 130.1, 129.8, 128.8, 126.8, 126.0 (d, ⁶J_{CF} = 9.0 Hz), 124.0, 123.8, 115.8 (t, ¹J_{CF} = 248.0 Hz), 110.3 (d, ⁵J_{CF} = 22.0 Hz), 47.0 (d, ⁶J_{CF} = 9.0 Hz), 46.4 (t, ⁴J_{CF} = 24.0 Hz), 28.6, 21.5, 15.9. ¹⁹F NMR (376 MHz,

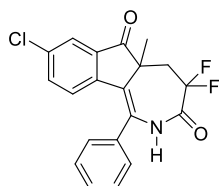
DMSO-*d*₆) (δ , ppm) -95.5 (d, J = 251.9 Hz, 1F), -98.4 (d, J = 251.9 Hz, 1F), -111.9. IR (KBr, ν , cm⁻¹) 3256, 3136, 1717, 1694, 1483, 1341, 1270, 1147, 1026, 838, 748 HR-MS (ESI) m/z calcd for C₂₂H₁₇F₃NO₂ [M-H]⁻ 384.1211, found 384.1208.

1-(4-(*tert*-butyl)phenyl)-4,4,8-trifluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3l)



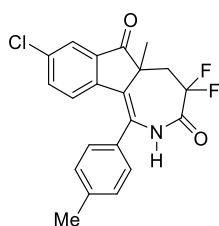
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 43 mg, 52%; mp 180-181 °C ¹H NMR (400 MHz, DMSO-*d*₆) (δ , ppm) 10.29 (d, J = 3.6 Hz, 1H), 7.67 (s, 1H), 7.51 - 7.48 (m, 2H), 7.39 - 7.32 (m, 3H), 6.54 - 6.51 (m, 1H), 2.76 - 2.66 (m, 2H), 1.54 (s, 3H), 1.36 (s, 9H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ , ppm) 203.9, 164.4 (t, ³ J_{CF} = 28.0 Hz), 162.5 (d, ¹ J_{CF} = 248.0 Hz), 153.4, 143.8, 135.7 (d, ⁷ J_{CF} = 8.0 Hz), 134.0 (t, ⁹ J_{CF} = 3.0 Hz), 132.9, 129.9, 128.8, 127.3, 126.9, 126.0 (d, ⁷ J_{CF} = 8.0 Hz), 123.9, 115.8 (t, ¹ J_{CF} = 248.0 Hz), 110.5 (d, ⁵ J_{CF} = 22.0 Hz), 65.5, 47.1 (d, ⁶ J_{CF} = 9.0 Hz), 46.5 (t, ⁴ J_{CF} = 24.0 Hz), 35.2, 31.6, 21.5, 15.7. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ , ppm) -97.2 (d, J = 251.9 Hz, 1F), -99.2 (d, J = 251.9 Hz, 1F), -110.7. IR (KBr, ν , cm⁻¹) 3252, 3072, 1717, 1608, 1584, 1380, 1270, 1148, 1104, 1027, 852, 785 HR-MS (ESI) m/z calcd for C₂₄H₂₁F₃NO₂ [M-H]⁻ 412.1524, found 412.1526.

8-chloro-4,4-difluoro-5a-methyl-1-phenyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3m)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 45 mg, 60%; mp 232-234 °C ¹H NMR (400 MHz, DMSO-*d*₆) (δ , ppm) 10.42 (s, 1H), 7.73 - 7.72 (m, 1H), 7.64 - 7.58 (m, 1H), 7.55 - 7.45 (m, 4H), 6.52 - 6.42 (m, 1H), 2.82 - 2.67 (m, 2H), 1.55 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ , ppm) 203.9, 164.4 (t, ⁴ J_{CF} = 28.0 Hz), 161.4 (d, ¹ J_{CF} = 248.0 Hz), 146.4, 143.7, 135.6 (d, ⁷ J_{CF} = 8.0 Hz), 134.0, 133.0, 129.9 (d, ³ J_{CF} = 30.0 Hz), 129.0, 126.8, 126.0, 124.0, 115.8 (t, ¹ J_{CF} = 248.0 Hz), 110.5, 47.0 (d, ⁶ J_{CF} = 10.0 Hz), 46.4 (t, ⁵ J_{CF} = 24.0 Hz), 28.6, 21.5, 15.9. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ , ppm) -95.4 (d, J = 251.9 Hz, 1F), -98.2 (d, J = 251.9 Hz, 1F), -110.4. IR (KBr, ν , cm⁻¹) 3222, 3125, 1719, 1698, 1468, 1340, 1246, 1171, 1030, 847, 787 HR-MS (ESI) m/z calcd for C₂₀H₁₃ClF₂NO₂ [M-H]⁻ 372.0603, found 372.0613.

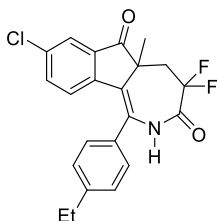
8-chloro-4,4-difluoro-5a-methyl-1-(*p*-tolyl)-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3n)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 42 mg, 54%; mp 221-222 °C

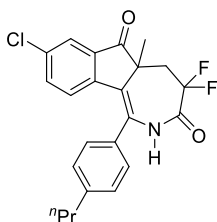
¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm) 10.36 (s, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.53 - 7.50 (m, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 2.77 - 2.66 (m, 2H), 2.42 (s, 3H), 1.53 (s, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 203.6, 164.5 (t, ²*J*_{CF} = 30.0 Hz), 146.0, 140.4, 135.8, 135.2, 135.0 (d, ⁵*J*_{CF} = 3.0 Hz), 133.7, 132.6, 131.0 (t, ⁵*J*_{CF} = 3.0 Hz), 130.1, 128.9, 126.5, 125.6, 124.2, 115.8 (t, ¹*J*_{CF} = 247.0 Hz), 46.9 (d, ⁴*J*_{CF} = 10.0 Hz), 46.5 (t, ³*J*_{CF} = 24.0 Hz), 43.8, 21.6, 21.4. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ, ppm) -95.5 (d, *J* = 251.9 Hz, 1F), -98.4 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3239, 3131, 1719, 1692, 1469, 1377, 1245, 1168, 1028, 830, 780 HR-MS (ESI) *m/z* calcd for C₂₁H₁₅ClF₂NO₂ [M-H]⁻ 386.0759, found 386.0759.

8-chloro-1-(4-ethylphenyl)-4,4-difluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3o)



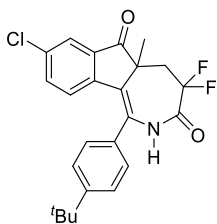
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 47 mg, 59%; mp 177-178 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.73 (d, *J* = 2.4 Hz, 1H), 7.44 (s, 2H), 7.31 - 7.27 (m, 2H), 7.25 (d, *J* = 2.4 Hz, 1H), 6.98 (d, *J* = 3.6 Hz, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 2.79 - 2.76 (m, 2H), 2.74 - 2.64 (m, 2H), 1.63 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 203.6, 164.5 (t, ²*J*_{CF} = 30.0 Hz), 147.5, 145.1, 135.5, 135.1, 132.9 (d, ⁵*J*_{CF} = 3.0 Hz), 132.0, 129.9, 129.4, 128.9, 128.7, 127.5, 125.5, 124.4, 114.9 (t, ¹*J*_{CF} = 248.0 Hz), 100.0, 46.0 (d, ⁴*J*_{CF} = 9.0 Hz), 46.7 (t, ³*J*_{CF} = 24.0 Hz), 28.9, 21.9, 15.4. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -97.1 (d, *J* = 251.9 Hz, 1F), -99.2 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3265, 3137, 1719, 1694, 1469, 1340, 1244, 1124, 1027, 839, 794 HR-MS (ESI) *m/z* calcd for C₂₂H₁₇ClF₂NO₂ [M-H]⁻ 400.0916, found 400.0930.

8-chloro-4,4-difluoro-5a-methyl-1-(4-propylphenyl)-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3p)



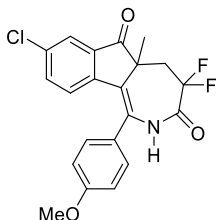
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 52 mg, 63%; mp 140-142 °C ¹H NMR (400 MHz, DMSO-*d*₆) (δ, ppm) 10.37 (s, 1H), 7.71 (d, *J* = 2.0 Hz, 1H), 7.49 - 7.46 (m, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 2.77 - 2.65 (m, 4H), 1.68 - 1.63 (m, 2H), 1.53 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, DMSO-*d*₆) (δ, ppm) 203.5, 164.5 (t, ²*J*_{CF} = 30.0 Hz), 146.0, 145.0, 135.7, 135.2, 135.1, 133.7, 132.9, 130.4, 129.9, 129.4, 128.9, 126.6, 125.5, 124.2, 115.8 (t, ¹*J*_{CF} = 247.0 Hz), 46.9 (d, ⁴*J*_{CF} = 9.0 Hz), 46.5 (t, ³*J*_{CF} = 24.0 Hz), 37.6, 24.5, 21.4, 14.1. ¹⁹F NMR (376 MHz, DMSO-*d*₆) (δ, ppm) -95.4 (d, *J* = 251.9 Hz, 1F), -98.4 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3244, 3157, 1718, 1699, 1466, 1325, 1250, 1166, 1032, 837, 728 HR-MS (ESI) *m/z* calcd for C₂₃H₁₉ClF₂NO₂ [M-H]⁻ 414.1072, found 414.1065.

1-(4-*tert*-butylphenyl)-8-chloro-4,4-difluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3q)



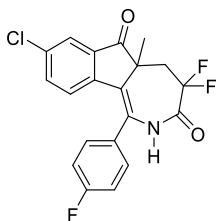
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 55 mg, 64%; mp 194-195 °C ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm) 10.34 (s, 1H), 7.72 - 7.67 (m, 2H), 7.51 - 7.48 (m, 2H), 7.38 (d, $J = 8.8$ Hz, 2H), 6.49 (d, $J = 8.8$ Hz, 1H), 2.76 - 2.66 (m, 2H), 1.53 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 203.5, 164.4 (t, $^2J_{\text{CF}} = 30.0$ Hz), 154.5, 145.1, 135.5, 135.1 (d, $^5J_{\text{CF}} = 3.0$ Hz), 132.7 (d, $^5J_{\text{CF}} = 3.0$ Hz), 131.7, 129.1, 128.6, 127.4, 127.4, 126.1, 125.5, 124.4, 114.8 (t, $^1J_{\text{CF}} = 248.0$ Hz), 47.0 (d, $^4J_{\text{CF}} = 8.0$ Hz), 46.7 (t, $^3J_{\text{CF}} = 24.0$ Hz), 35.1, 31.3, 21.8. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) (δ , ppm) -95.5 (d, $J = 251.9$ Hz, 1F), -98.4 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3244, 3153, 1721, 1703, 1465, 1328, 1251, 1192, 1034, 828, 777 HR-MS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{21}\text{ClF}_2\text{NO}_2$ [M-H] $^-$ 428.1229, found 428.1229.

8-chloro-4,4-difluoro-1-(4-methoxyphenyl)-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3r)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 56 mg, 65%; mp 216-218 °C ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm) 10.33 (d, $J = 4.0$ Hz, 1H), 7.70 (d, $J = 1.6$ Hz, 1H), 7.53 - 7.50 (m, 1H), 7.38 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 7.2$ Hz, 1H), 7.01 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 8.8$ Hz, 1H), 3.84 (s, 3H), 2.74 - 2.64 (m, 2H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm) 203.6, 164.6 (t, $^2J_{\text{CF}} = 30.0$ Hz), 161.1, 146.2, 135.7, 135.2, 134.9 (d, $^5J_{\text{CF}} = 3.0$ Hz), 133.5, 131.8, 130.5, 129.0, 127.4, 126.2, 125.6, 124.1, 115.8 (t, $^1J_{\text{CF}} = 248.0$ Hz), 55.8, 46.9 (d, $^4J_{\text{CF}} = 9.0$ Hz), 46.5 (t, $^3J_{\text{CF}} = 24.0$ Hz), 21.4. ^{19}F NMR (376 MHz, $\text{DMSO-}d_6$) (δ , ppm) -95.5 (d, $J = 251.9$ Hz, 1F), -98.6 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3230, 3133, 1720, 1695, 1514, 1469, 1346, 1248, 1166, 1028, 843, 780 HR-MS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{15}\text{ClF}_2\text{NO}_3$ [M-H] $^-$ 402.0709, found 402.0709.

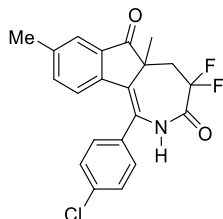
8-chloro-4,4-difluoro-1-(4-fluorophenyl)-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3s)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 51 mg, 65%; mp 227-229 °C ^1H NMR (400 MHz, $\text{DMSO-}d_6$) (δ , ppm) 10.42 (d, $J = 4.4$ Hz, 1H), 8.33 (s, 1H), 7.73 (d, $J = 2.4$ Hz, 1H), 7.55 - 7.47 (m, 4H), 7.32 (t, $J = 8.4$ Hz, 1H), 6.51 (d, $J = 8.4$ Hz, 1H), 2.78 - 2.67 (m, 2H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm) 203.4, 164.5 (t, $^2J_{\text{CF}} = 28.0$ Hz), 162.3, 145.7, 135.9, 135.4, 133.8 (d, $^9J_{\text{CF}} = 3.0$ Hz), 132.6 (d, $^6J_{\text{CF}} = 9.0$ Hz), 131.8 (d, $^9J_{\text{CF}} = 3.0$ Hz), 131.5 (d, $^6J_{\text{CF}} = 9.0$ Hz), 127.1, 125.6, 124.3, 117.5 (d, $^4J_{\text{CF}} = 22.0$ Hz), 116.6 (d, $^4J_{\text{CF}} = 22.0$ Hz),

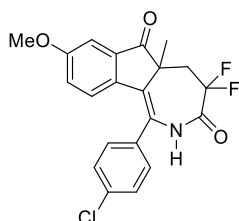
115.8 (t, $^1J_{CF} = 247.0$ Hz), 79.7, 46.9 (d, $^6J_{CF} = 9.0$ Hz), 46.4 (t, $^3J_{CF} = 24.0$ Hz), 21.4. ^{19}F NMR (376 MHz, DMSO- d_6) (δ , ppm) -95.5 (d, $J = 251.9$ Hz, 1F), -98.4 (d, $J = 251.9$ Hz, 1F), -110.4. IR (KBr, ν , cm^{-1}) 3219, 3125, 1720, 1701, 1511, 1468, 1341, 1248, 1170, 1030, 849, 789 HR-MS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{12}\text{ClF}_3\text{NO}_2$ $[\text{M}-\text{H}]^-$ 390.0509, found 390.0507.

1-(4-chlorophenyl)-4,4-difluoro-5a,8-dimethyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3t)



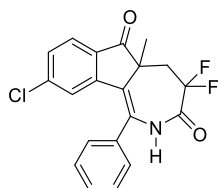
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 45 mg, 43%; mp 227-229 °C ^1H NMR (400 MHz, CDCl_3) (δ , ppm) 7.70 (d, $J = 8.0$ Hz, 1H), 7.60 (s, 1H), 7.53 - 7.36 (m, 3H), 7.19 (d, $J = 8.0$ Hz, 1H), 6.95 (d, $J = 3.6$ Hz, 1H), 6.49 (s, 1H), 2.79 - 2.59 (m, 2H), 2.20 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 203.6, 164.5 (t, $^2J_{CF} = 30.0$ Hz), 146.7, 146.4, 136.7, 133.5, 131.9, 131.0, 130.7, 130.6 (d, $^5J_{CF} = 3.0$ Hz), 129.6, 129.3, 127.4, 124.9, 124.4, 114.9 (t, $^1J_{CF} = 248.0$ Hz), 46.9 (t, $^3J_{CF} = 24.0$ Hz), 46.8 (d, $^4J_{CF} = 9.0$ Hz), 22.4, 21.7. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -97.1 (d, $J = 251.9$ Hz, 1F), -99.1 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3253, 3083 1716, 1599, 1456, 1332, 1171, 1014, 970, 820, 799 HR-MS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{15}\text{ClF}_2\text{NO}_2$ $[\text{M}-\text{H}]^-$ 386.0759, found 386.0758.

1-(4-chlorophenyl)-4,4-difluoro-8-methoxy-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3u)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 48 mg, 60%; mp 237-238 °C ^1H NMR (400 MHz, DMSO- d_6) (δ , ppm) 10.26 (d, $J = 4.0$ Hz, 1H), 7.69 - 7.47 (m, 5H), 7.18 (d, $J = 2.4$ Hz, 1H), 7.14 - 7.11 (m, 1H), 6.50 (d, $J = 8.8$ Hz, 1H), 3.80 (s, 3H), 2.75 - 2.65 (m, 2H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 204.2, 164.5 (t, $^2J_{CF} = 30.0$ Hz), 160.8, 139.5, 136.5, 135.7, 133.5, 131.0, 130.6, 129.5, 129.4, 128.4 (d, $^5J_{CF} = 30.0$ Hz), 125.3, 125.2, 114.9 (t, $^1J_{CF} = 248.0$ Hz), 105.6, 55.8, 47.2 (d, $^4J_{CF} = 9.0$ Hz), 46.6 (t, $^3J_{CF} = 24.0$ Hz), 21.8. ^{19}F NMR (376 MHz, DMSO- d_6) (δ , ppm) -95.6 (d, $J = 251.9$ Hz, 1F), -98.6 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3237, 3130, 1719, 1693, 1489, 1338, 1288, 1157, 1030, 939 850, 764 HR-MS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{15}\text{ClF}_2\text{NO}_3$ $[\text{M}-\text{H}]^-$ 402.0709, found 402.0709.

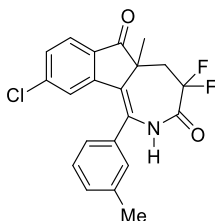
9-chloro-4,4-difluoro-5a-methyl-1-phenyl-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3v)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 51 mg, 68%; mp 230-232 °C

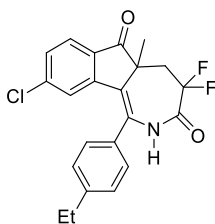
^1H NMR (400 MHz, CDCl_3) (δ , ppm) 7.72 (d, $J = 8.0$ Hz, 1H), 7.66 - 7.59 (m, 2H), 7.55 - 7.47 (m, 2H), 7.41 (d, $J = 7.6$ Hz, 1H), 7.31 - 7.29 (m, 1H), 6.92 (d, $J = 2.4$ Hz, 1H), 6.53 (d, $J = 1.6$ Hz, 1H), 2.81 - 2.68 (m, 2H), 1.65 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 203.3, 164.3 (t, $^2J_{\text{CF}} = 30.0$ Hz), 147.9, 142.1, 134.3, 133.5 (d, $^5J_{\text{CF}} = 3.0$ Hz), 132.1, 131.1, 130.5, 129.5, 129.3, 129.2, 128.9, 127.5, 125.9, 124.4, 114.8 (t, $^1J_{\text{CF}} = 248.0$ Hz), 46.8 (d, $^4J_{\text{CF}} = 9.0$ Hz), 46.7 (t, $^3J_{\text{CF}} = 24.0$ Hz), 21.9. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -97.0 (d, $J = 251.9$ Hz, 1F), -98.9 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3247, 1702, 1600, 1490, 1397, 1290, 1167, 1106, 1016, 835, 797 HR-MS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{13}\text{ClF}_2\text{NO}_2$ $[\text{M-H}]^-$ 372.0603, found 372.0603.

9-chloro-4,4-difluoro-5a-methyl-1-(*m*-tolyl)-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3w)



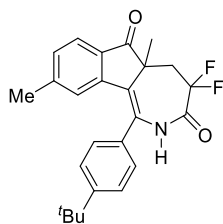
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 33 mg, 43%; mp 214-216 °C ^1H NMR (400 MHz, CDCl_3) (δ , ppm) 7.70 (d, $J = 8.4$ Hz, 1H), 7.44 - 7.39 (m, 2H), 7.29 - 7.25 (m, 3H), 7.12 (d, $J = 3.6$ Hz, 1H), 6.63 (d, $J = 1.2$ Hz, 1H), 2.75 - 2.62 (m, 2H), 2.48 (s, 3H), 1.61 (s, 3H). ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$) (δ , ppm) 203.5, 164.5 (t, $^2J_{\text{CF}} = 29.0$ Hz), 146.0, 140.4, 135.7, 135.2, 135.0 (d, $^6J_{\text{CF}} = 3.0$ Hz), 133.7, 132.6, 131.0, 130.0 (d, $^4J_{\text{CF}} = 9.0$ Hz), 128.9, 127.5, 126.5, 125.6, 124.2, 115.8 (t, $^1J_{\text{CF}} = 248.0$ Hz), 46.9 (d, $^4J_{\text{CF}} = 9.0$ Hz), 46.5 (t, $^3J_{\text{CF}} = 25.0$ Hz), 21.5, 21.4. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -97.1 (d, $J = 251.9$ Hz, 1F), -99.0 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3255, 3150, 1704, 1651, 1591, 1395, 1269, 1165, 1031, 973, 824, 790 HR-MS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{15}\text{ClF}_2\text{NO}_2$ $[\text{M-H}]^-$ 386.0759, found 386.0732.

9-chloro-1-(4-ethylphenyl)-4,4-difluoro-5a-methyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3x)



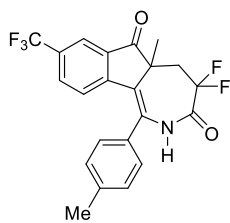
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 45 mg, 56%; mp 159-160 °C ^1H NMR (400 MHz, CDCl_3) (δ , ppm) 7.70 (d, $J = 8.0$ Hz, 1H), 7.44 (s, 2H), 7.30 - 7.29 (m, 3H), 6.99 (s, 1H), 6.56 (d, $J = 1.6$ Hz, 1H), 2.80 - 2.77 (m, 2H), 2.75 - 2.70 (m, 1H), 2.67 - 2.64 (m, 1H), 1.63 (s, 3H), 1.32 (t, $J = 7.6$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 203.4, 164.4 (t, $^2J_{\text{CF}} = 30.0$ Hz), 148.1, 147.8, 142.1, 133.7 (d, $^5J_{\text{CF}} = 3.0$ Hz), 132.0, 131.6, 130.0, 129.3, 129.3, 129.0, 128.8, 127.2, 125.8, 124.4, 114.8 (t, $^1J_{\text{CF}} = 248.0$ Hz), 46.8(7) (d, $^4J_{\text{CF}} = 9.0$ Hz), 46.8(6) (t, $^3J_{\text{CF}} = 24.0$ Hz), 28.9, 21.8, 15.6. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -96.9 (d, $J = 251.9$ Hz, 1F), -98.9 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3247, 1702, 1600, 1490, 1397, 1290, 1167, 1106, 1016, 835, 797 HR-MS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{17}\text{ClF}_2\text{NO}_2$ $[\text{M-H}]^-$ 400.0916, found 400.0910.

1-(4-*tert*-butylphenyl)-4,4-difluoro-5a,9-dimethyl-2,4,5,5a-tetrahydroindeno[1,2-*c*]azepine-3,6-dione (3y)



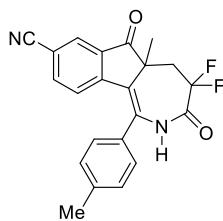
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 35 mg, 43%; mp 242-244 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 7.68 - 7.63 (m, 2H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.32 (s, 1H), 2.78 - 2.64 (m, 2H), 2.12 (s, 3H), 1.63 (s, 3H), 1.40 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 204.3, 164.7 (t, ²*J*_{CF} = 30.0 Hz), 154.3, 147.2, 146.5, 132.2, 132.0, 131.8, 130.3, 129.4, 128.8, 128.7, 127.1, 126.0, 124.8, 124.7, 115.1 (t, ¹*J*_{CF} = 248.0 Hz), 46.9 (t, ³*J*_{CF} = 22.0 Hz), 46.8, 35.1, 31.4, 22.4, 21.9. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -96.9 (d, *J* = 251.9 Hz, 1F), -99.0 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3231, 3138, 1716, 1697, 1599, 1397, 1331, 1257, 1168, 1105, 1033, 831, 796 HR-MS (ESI) *m/z* calcd for C₂₅H₂₄F₂NO₂ [M-H]⁻ 408.1775, found 408.1770.

4,4-difluoro-5a-methyl-1-(p-tolyl)-8-(trifluoromethyl)-2,4,5,5a-tetrahydroindeno[1,2-c]azepine-3,6-dione (3z)



Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) White solid, 52 mg, 62%; mp 199-201 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 8.03 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 1H), 7.43 (s, 2H), 7.30 - 7.28 (m, 1H), 7.24 (s, 1H), 7.07 (s, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 2.83 - 2.62 (m, 2H), 2.48 (s, 3H), 1.65 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ, ppm) 203.70, 164.43 (t, ⁴*J*_{CF} = 30.0 Hz), 149.62, 141.57, 134.91 (d, ⁸*J*_{CF} = 3.0 Hz), 133.85, 131.68 (dd, ⁸*J*_{CF} = 3.0 Hz), 131.43 (t, ⁵*J*_{CF} = 25.0 Hz), 130.90 (t, ³*J*_{CF} = 33.0 Hz), 130.04, 129.24, 128.68, 127.52 (t, ¹*J*_{CF} = 272.0 Hz), 127.02, 124.92, 124.80, 122.06 (dd, ⁷*J*_{CF} = 4.0 Hz), 114.75 (t, ²*J*_{CF} = 248.0 Hz), 47.01, 46.67 (t, ⁶*J*_{CF} = 24.0 Hz), 21.79, 21.60. ¹⁹F NMR (376 MHz, CDCl₃) (δ, ppm) -62.88, -97.0 (d, *J* = 251.9 Hz, 1F), -99.1 (d, *J* = 251.9 Hz, 1F). IR (KBr, ν, cm⁻¹) 3227, 3132, 1725, 1697, 1618, 1513, 1405, 1337, 1243, 1170, 1127, 1028, 918, 829, 760. HR-MS (ESI) *m/z* calcd for C₂₂H₁₇F₅NO₂ [M+H]⁺ 422.1179, found 422.1164.

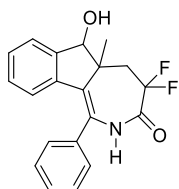
4,4-difluoro-5a-methyl-3,6-dioxo-1-(p-tolyl)-2,3,4,5,5a,6-hexahydroindeno[1,2-c]azepine-8-carbonitrile (3aa)



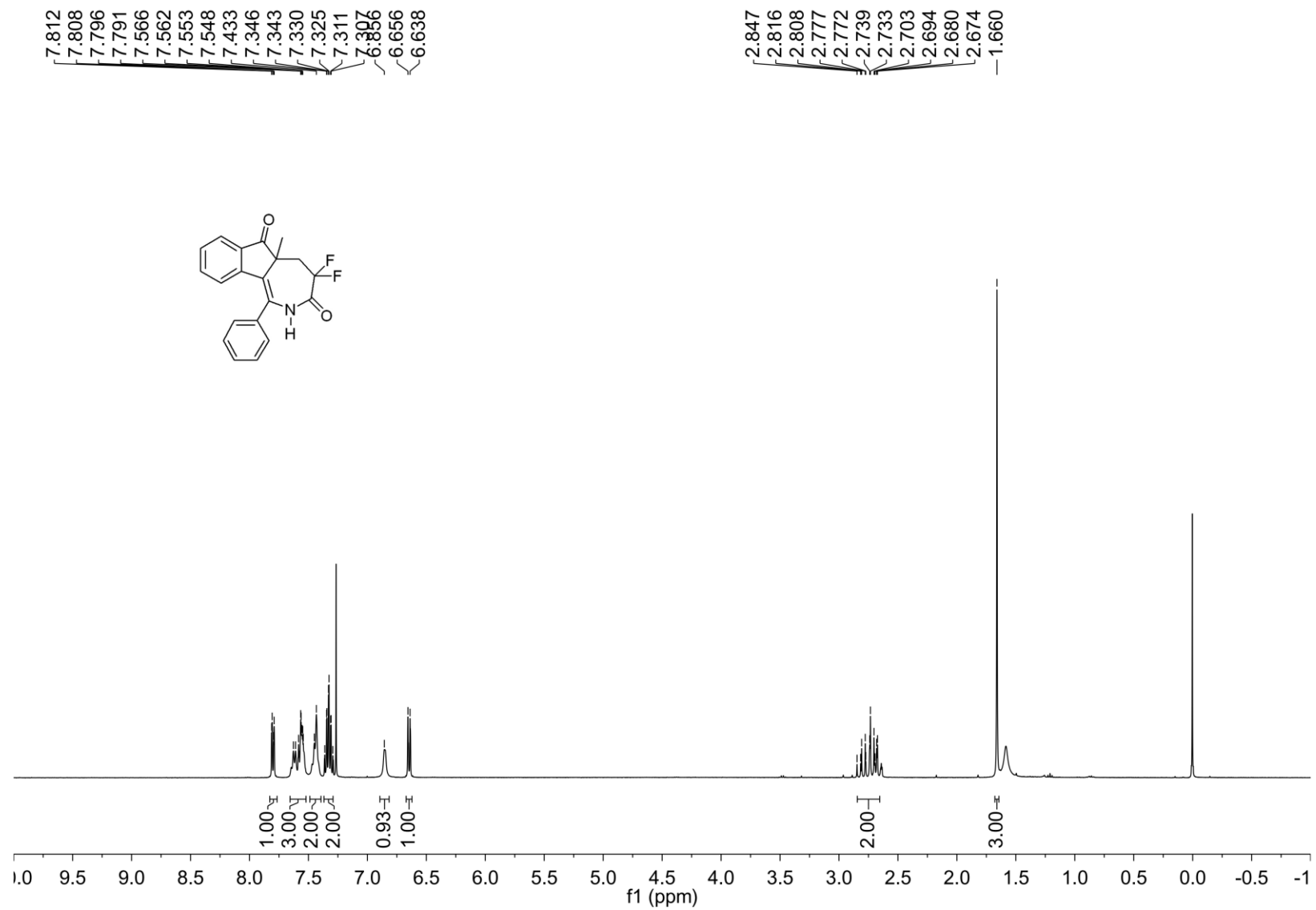
Isolation by column chromatography (petroleum ether/ ethyl acetate = 10/1 v/v) Yellow solid, 45 mg, 60%; mp 263-265 °C ¹H NMR (400 MHz, CDCl₃) (δ, ppm) 8.04 (s, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.48 - 7.40 (m, 2H), 7.26 (s, 2H), 7.01 (d, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 2.82 - 2.61 (m, 2H), 2.49 (s, 3H), 1.65 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) (δ,

ppm) 203.0, 164.3 (t, $^2J_{CF} = 30.0$ Hz), 150.1, 141.9, 137.5, 136.2 (t, $^5J_{CF} = 3.0$ Hz), 133.9, 131.3, 131.1, 130.1, 129.2, 129.1, 128.7, 126.6, 125.1, 117.7, 114.7 (t, $^1J_{CF} = 248.0$ Hz), 112.0, 46.9 (t, $^4J_{CF} = 8.0$ Hz), 46.7 (t, $^3J_{CF} = 24.0$ Hz), 21.8, 21.6. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -97.0 (d, $J = 255.7$ Hz, 1F), -99.0 (d, $J = 255.7$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3237, 3137, 2232, 1724, 1698, 1604, 1401, 1345, 1249, 1177, 1031, 915, 828. HR-MS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{16}\text{F}_2\text{N}_2\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 401.1078, found 401.1070.

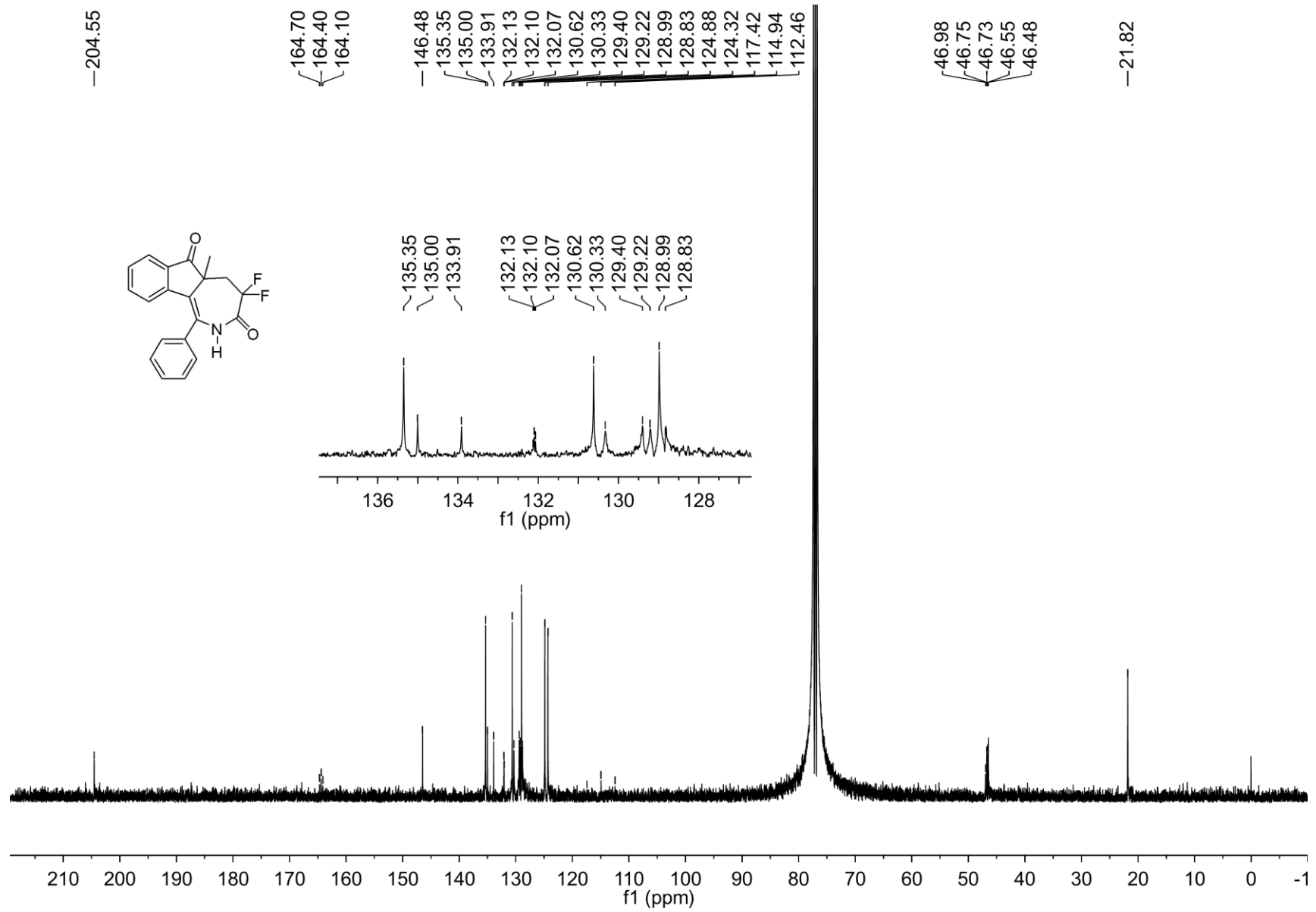
4,4-difluoro-6-hydroxy-5a-methyl-1-phenyl-4,5,5a,6-tetrahydroindeno[1,2-c]azepin-3(2H)-one (5a)



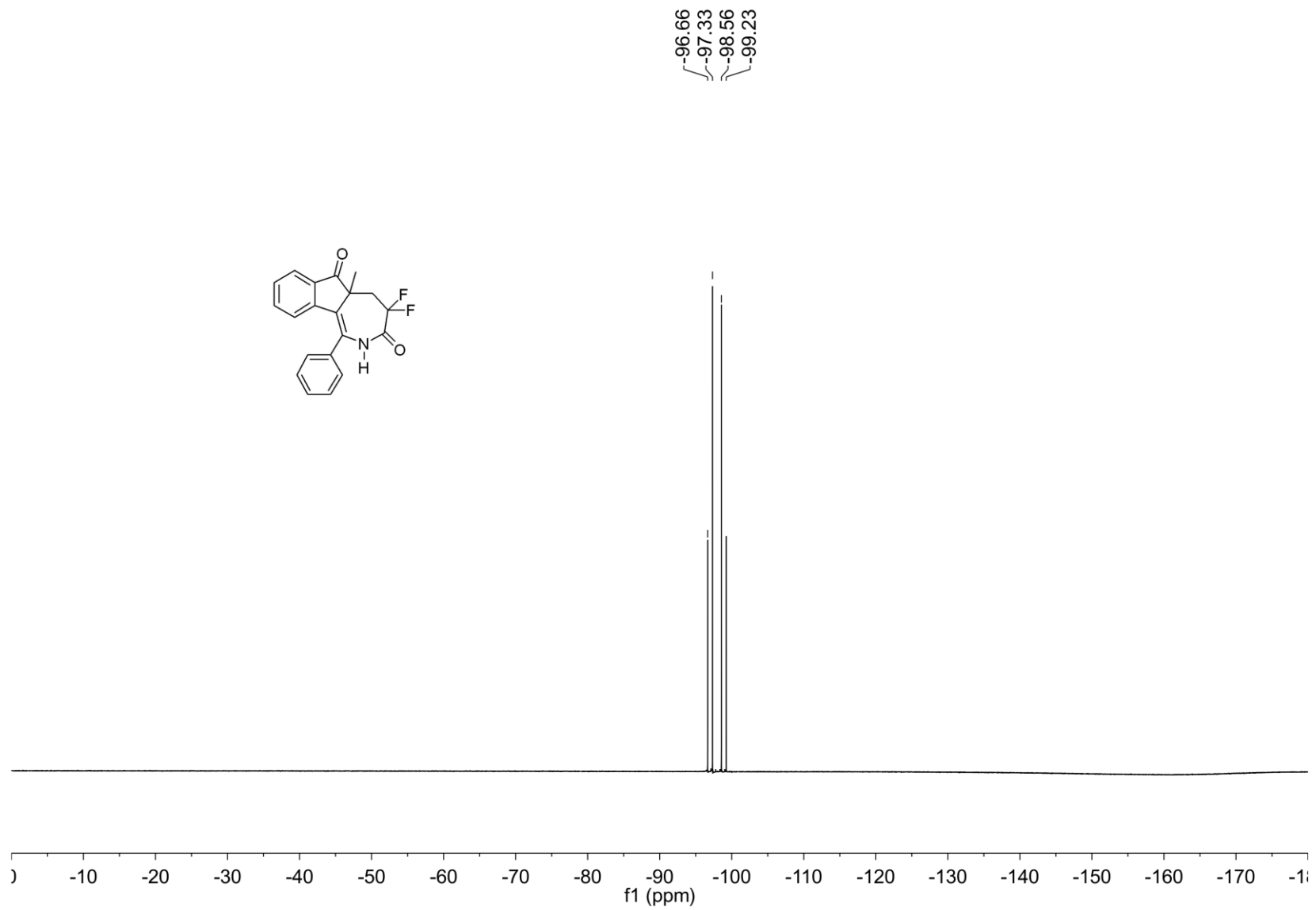
Isolation by column chromatography (petroleum ether/ ethyl acetate = 5/1 v/v) White solid, 47 mg, 68%; mp 120-122 °C ^1H NMR (400 MHz, CDCl_3) (δ , ppm) 7.52 - 7.44 (m, 4H), 7.37 (d, $J = 7.6$ Hz, 1H), 7.23 - 7.19 (m, 1H), 6.98 - 6.94 (m, 1H), 6.69 (s, 1H), 6.44 (d, $J = 8.0$ Hz, 1H), 5.07 (s, 1H), 3.10 - 3.04 (m, 1H), 2.53 - 2.46 (m, 1H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3) (δ , ppm) 165.36 (t, $^2J_{CF} = 30.0$ Hz), 144.39, 136.73, 135.68, 134.16, 130.42, 130.39, 130.04, 128.77, 128.76, 124.49, 123.66, 115.69 (t, $^1J_{CF} = 248.0$ Hz), 83.10, 48.18 (t, $^4J_{CF} = 9.0$ Hz), 47.89 (t, $^3J_{CF} = 24.0$ Hz), 29.74, 25.43. ^{19}F NMR (376 MHz, CDCl_3) (δ , ppm) -95.5 (d, $J = 251.9$ Hz, 1F), -98.0 (d, $J = 251.9$ Hz, 1F). IR (KBr, ν , cm^{-1}) 3227, 2925, 1693, 1598, 1461, 1324, 1168, 1115, 1056, 913, 770. HR-MS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{17}\text{F}_2\text{NNaO}_2$ $[\text{M}+\text{Na}]^+$ 364.1125, found 364.1122.



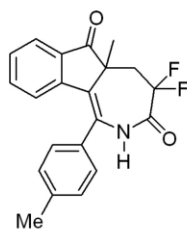
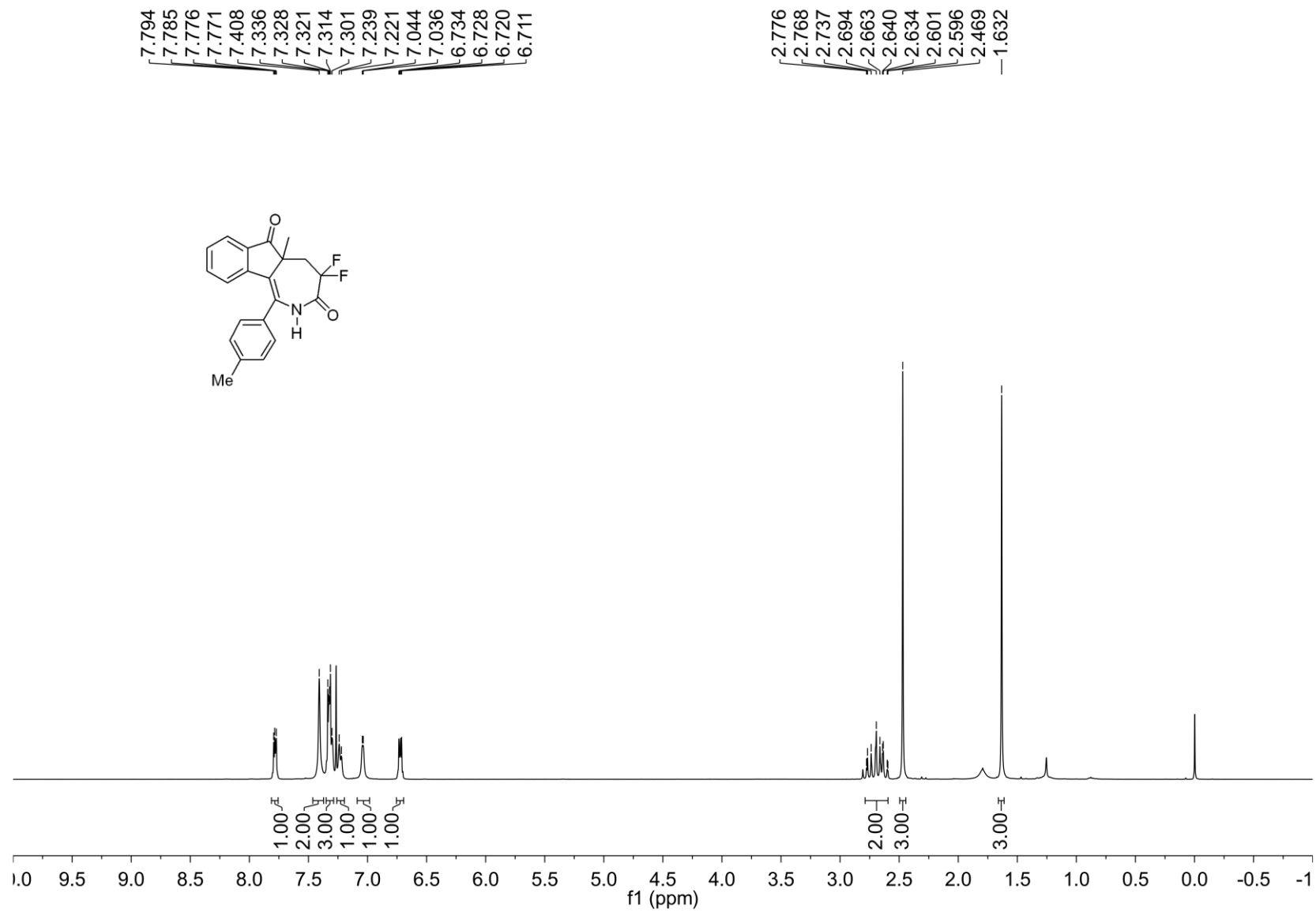
¹H NMR Spectrum of Compound 3a



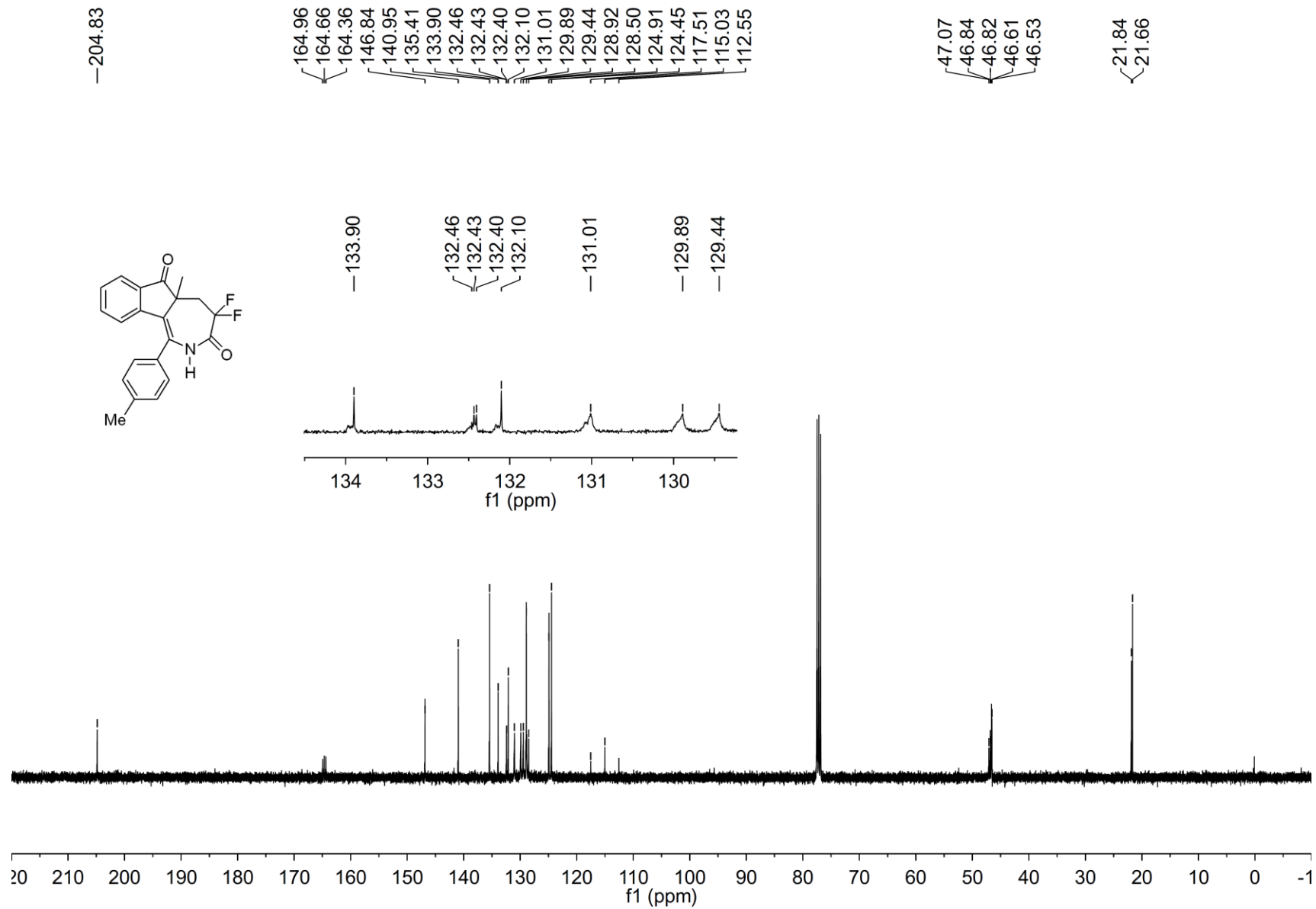
¹³C NMR Spectrum of Compound 3a

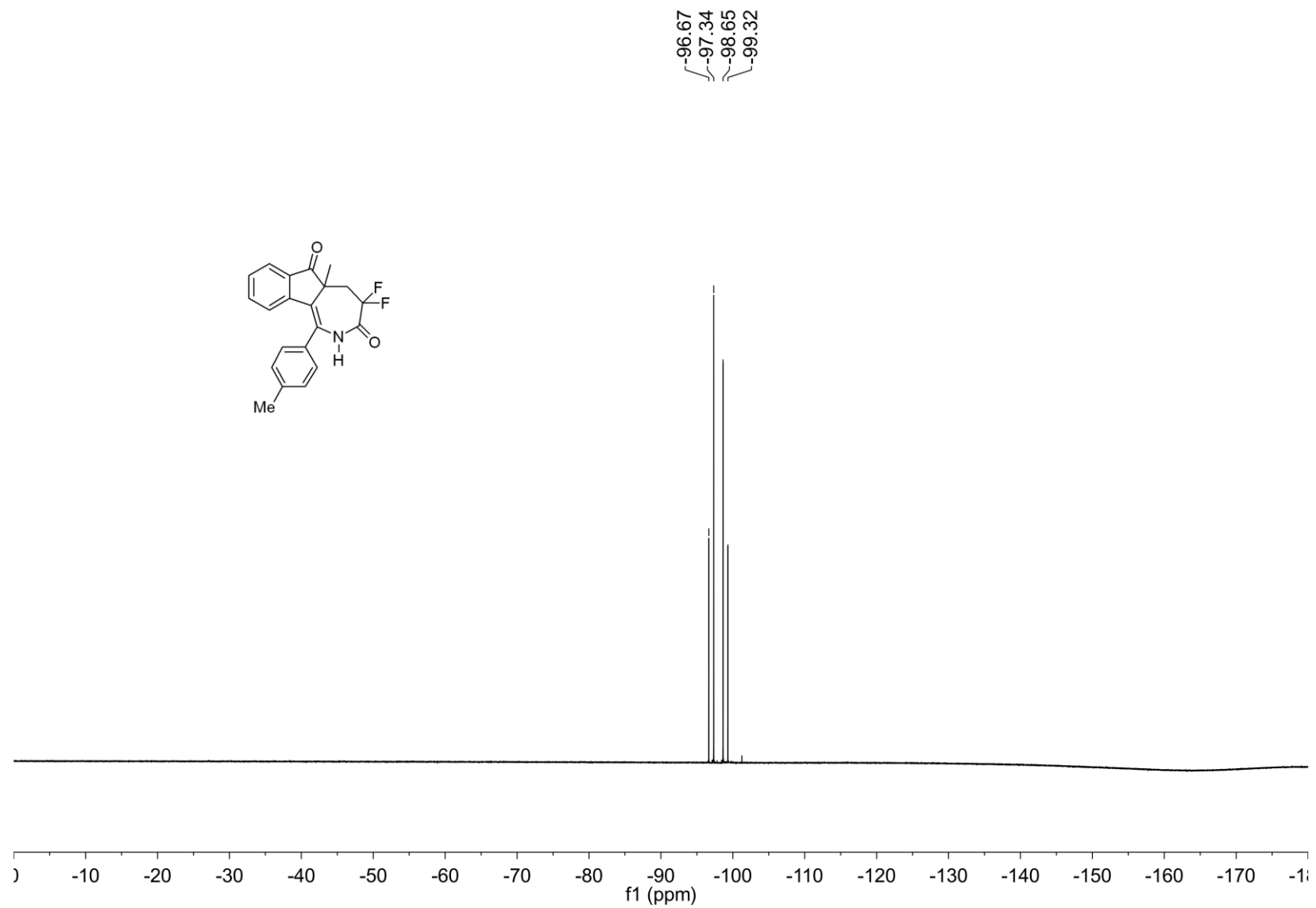


^{19}F NMR Spectrum of Compound 3a

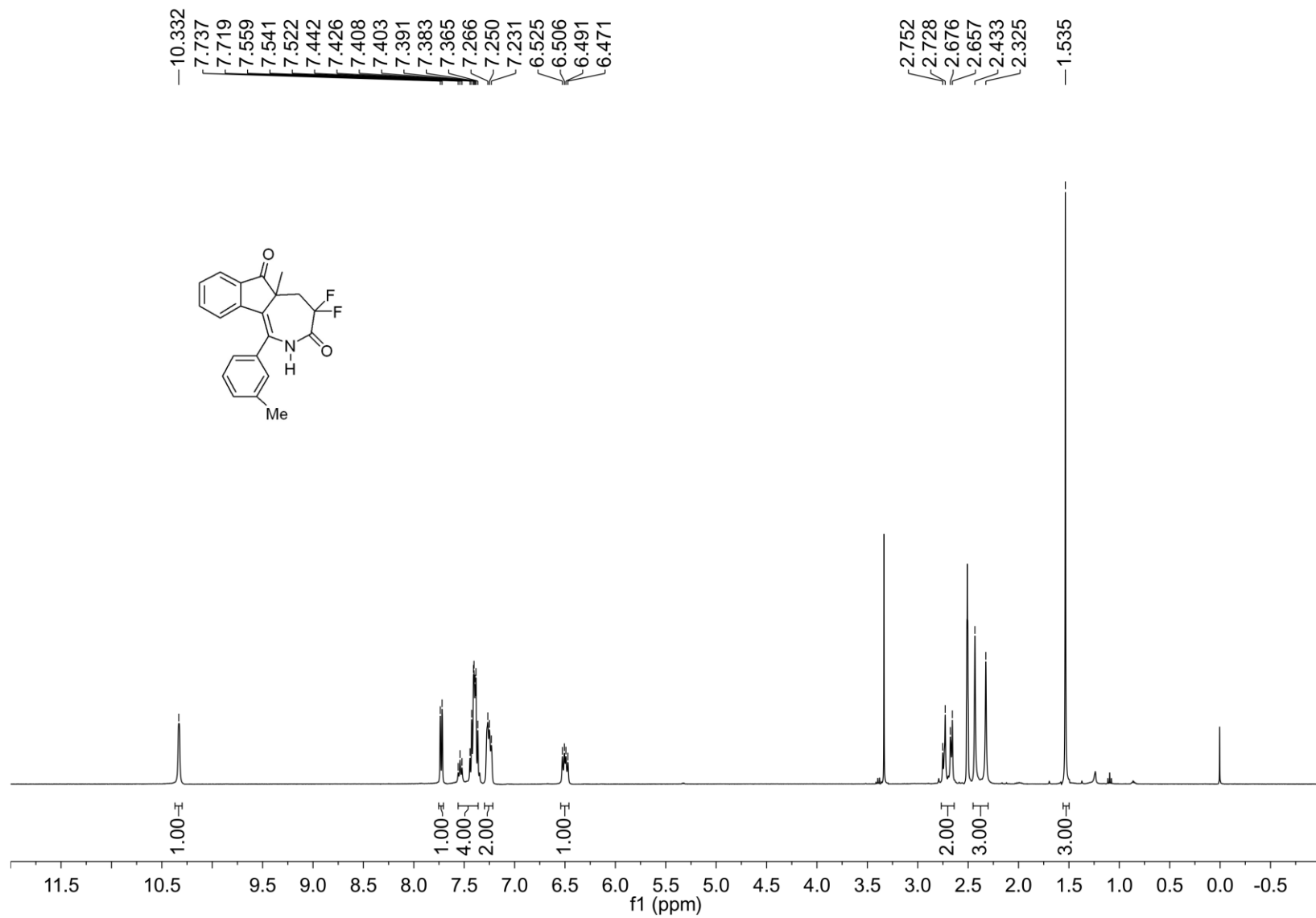


¹H NMR Spectrum of Compound 3b

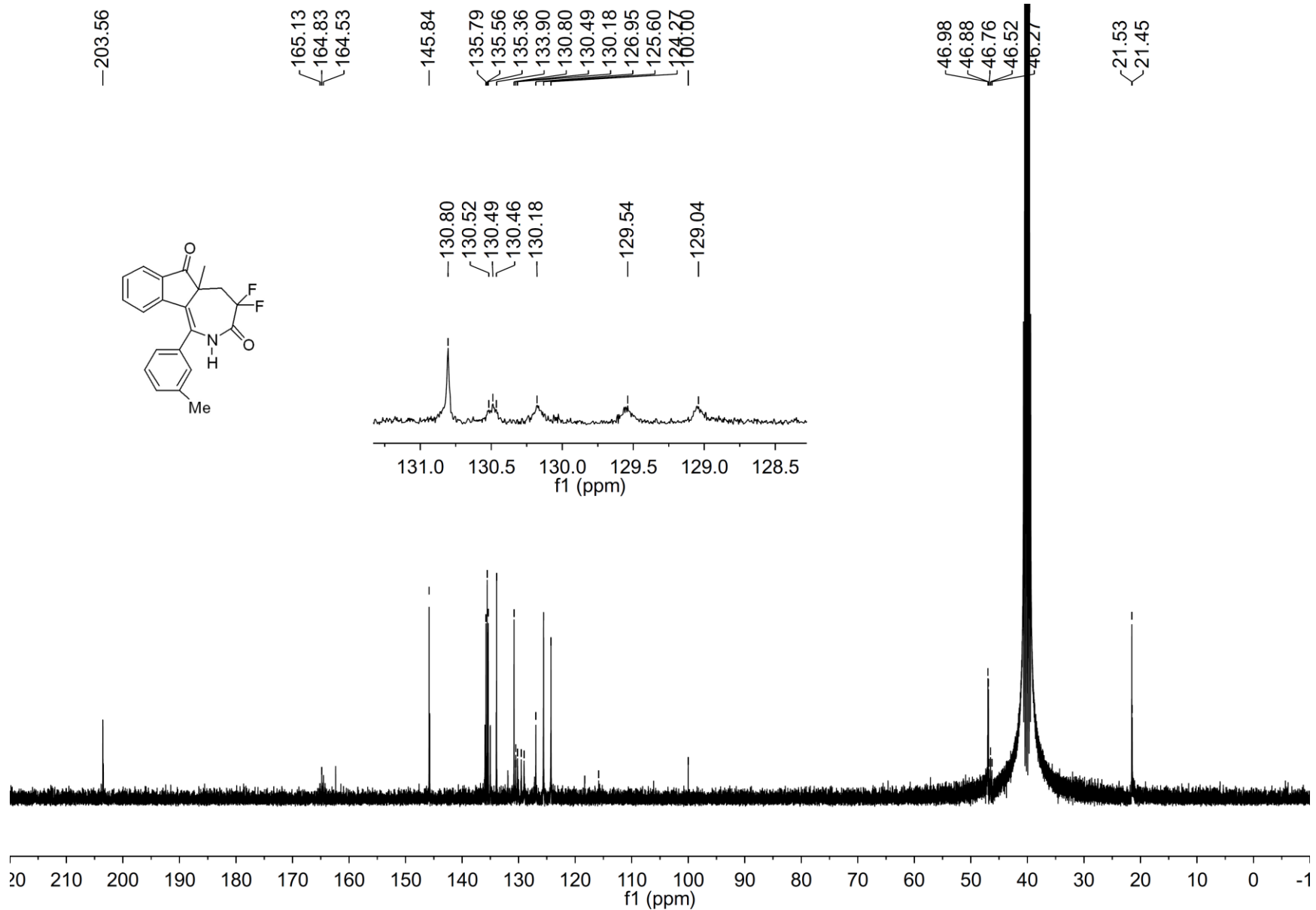




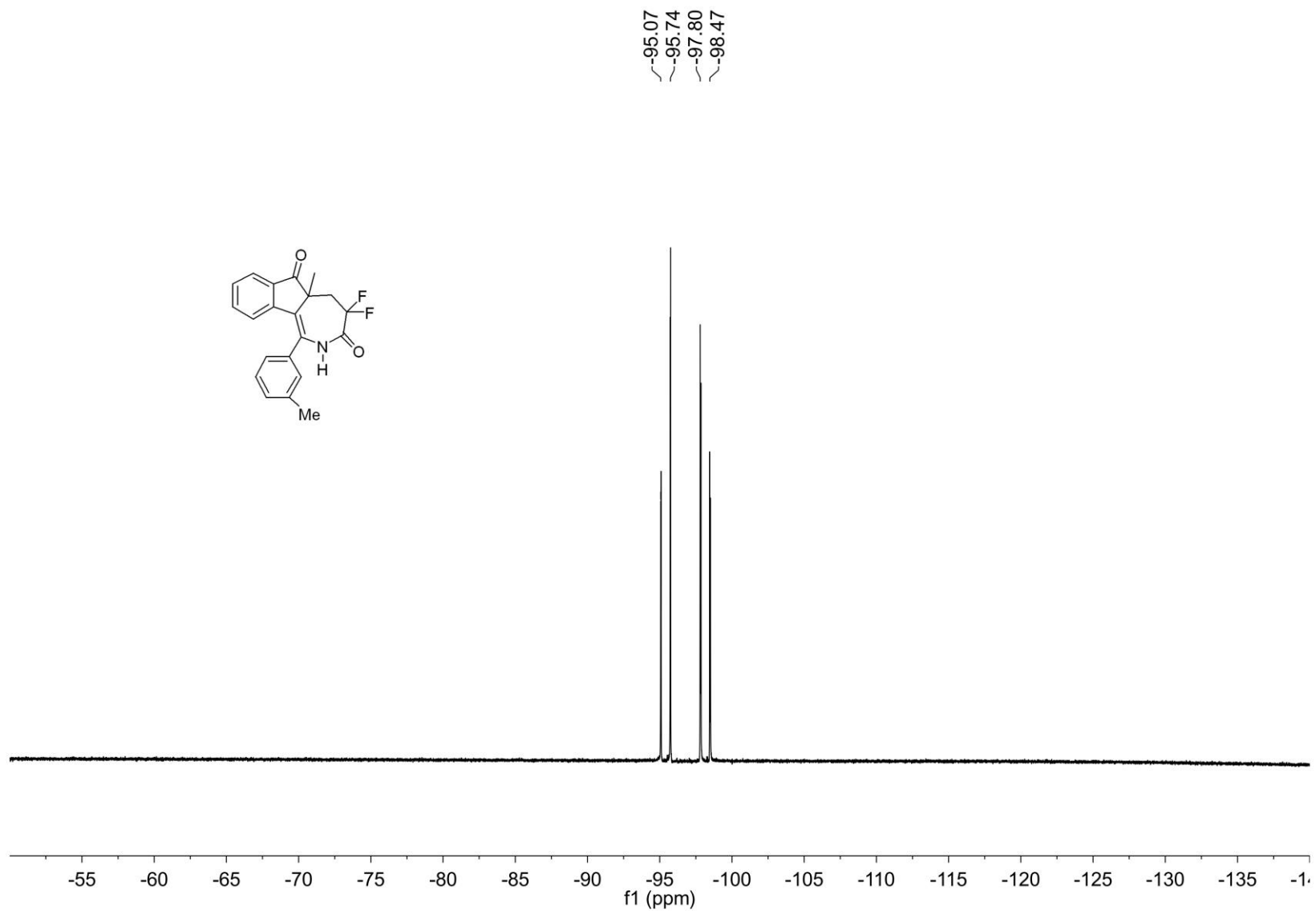
^{19}F NMR Spectrum of Compound 3b



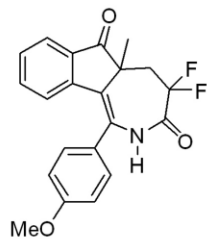
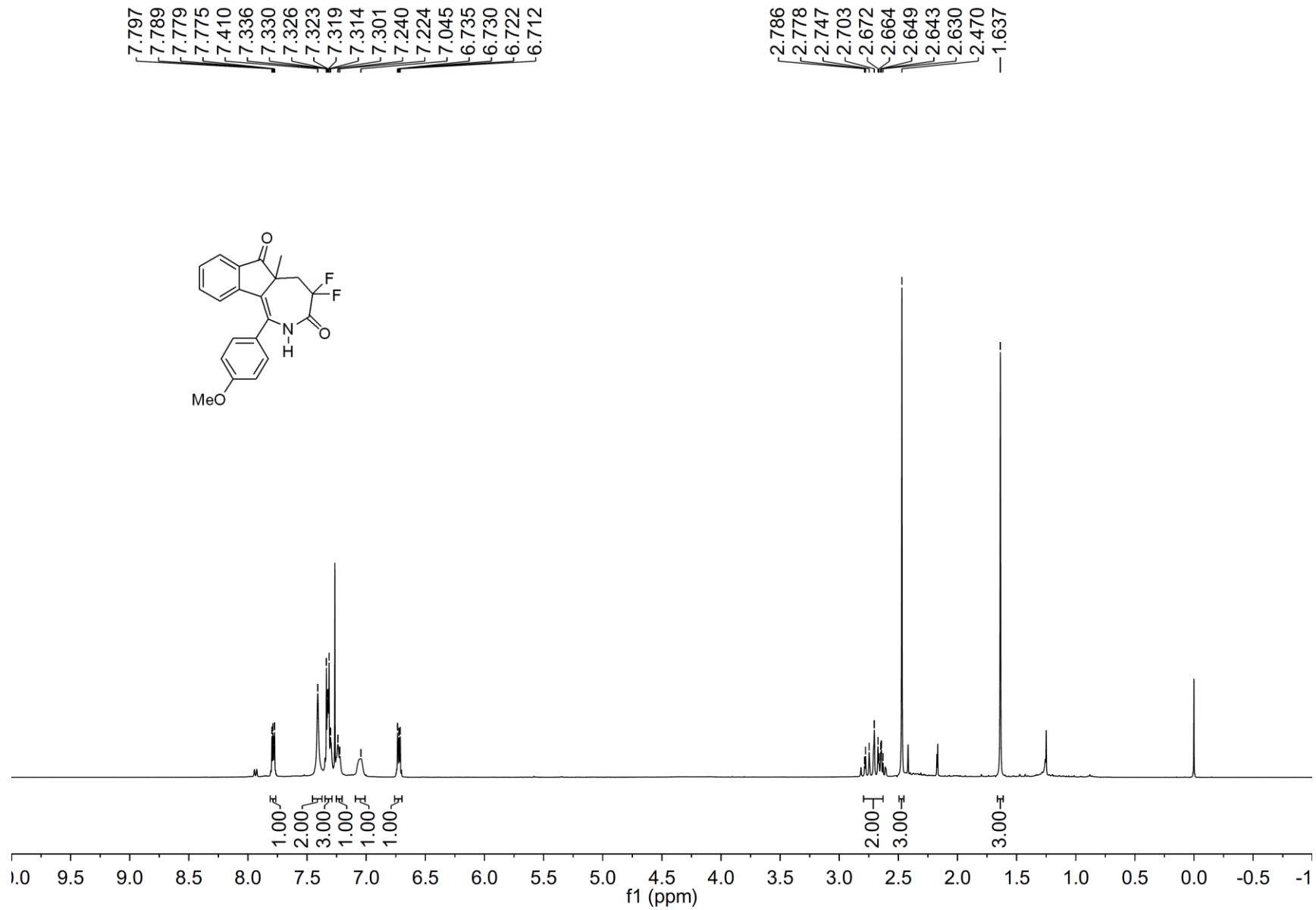
¹H NMR Spectrum of Compound 3c



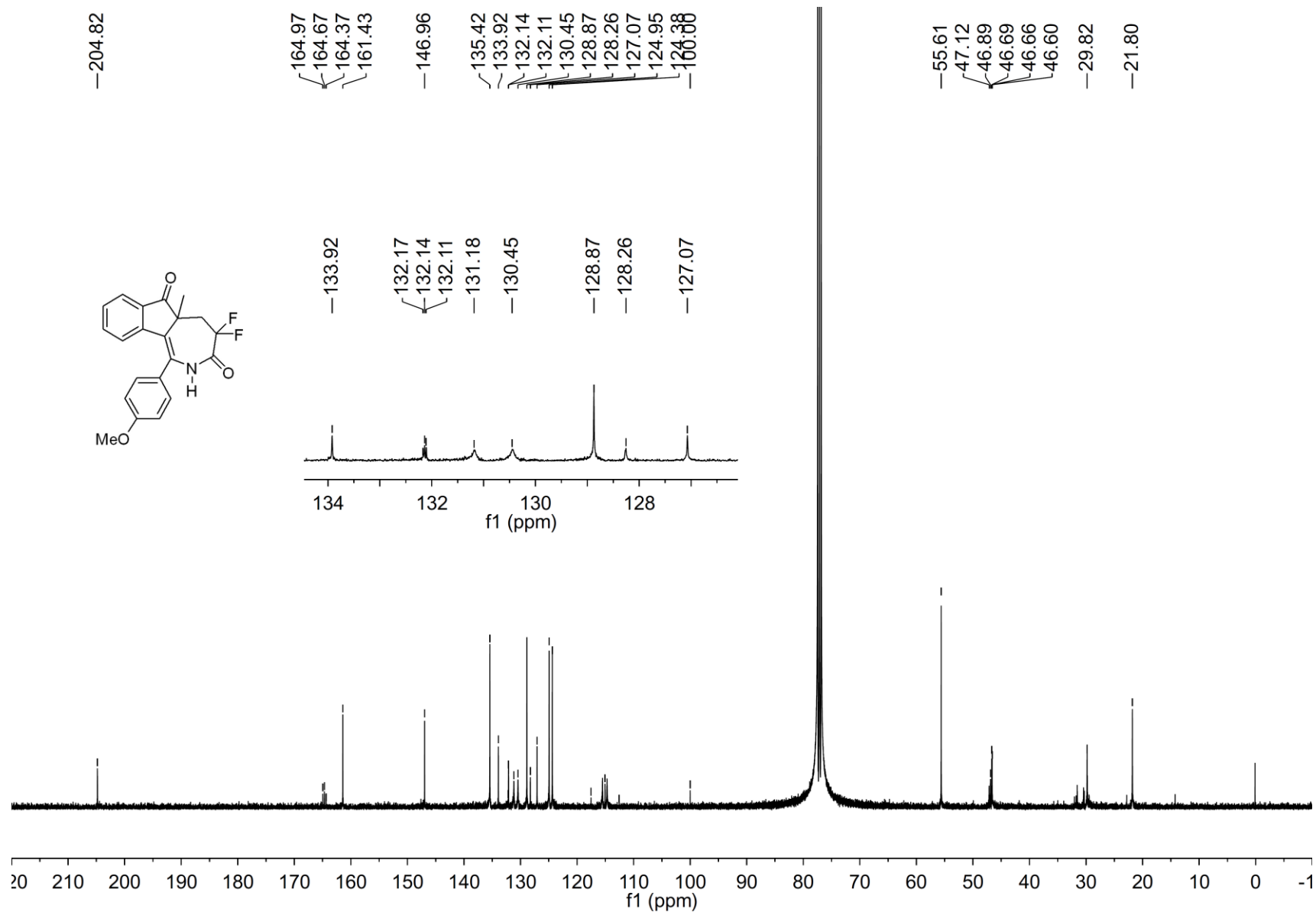
¹³C NMR Spectrum of Compound 3c



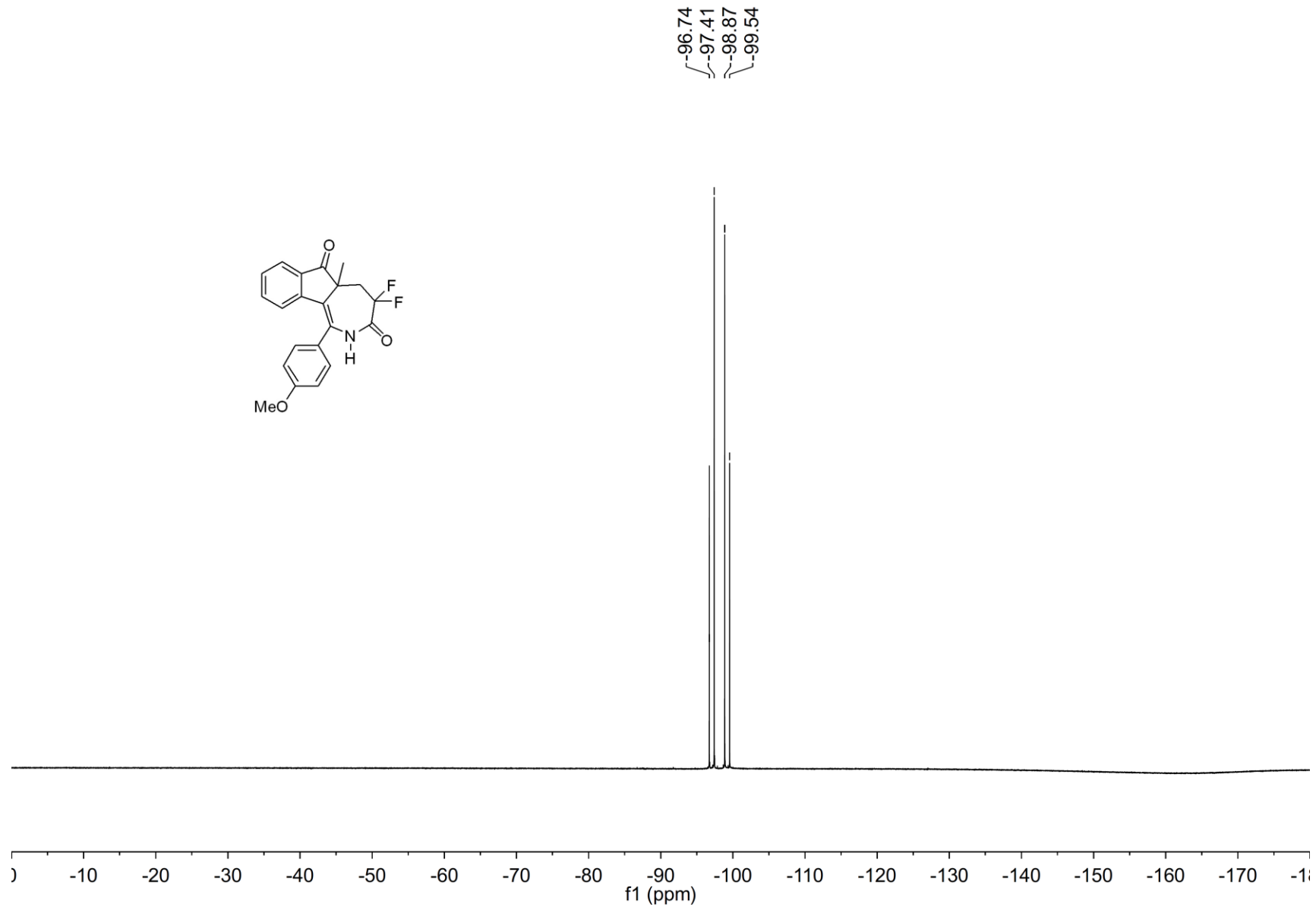
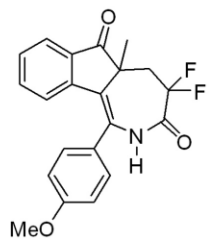
^{19}F NMR Spectrum of Compound 3c



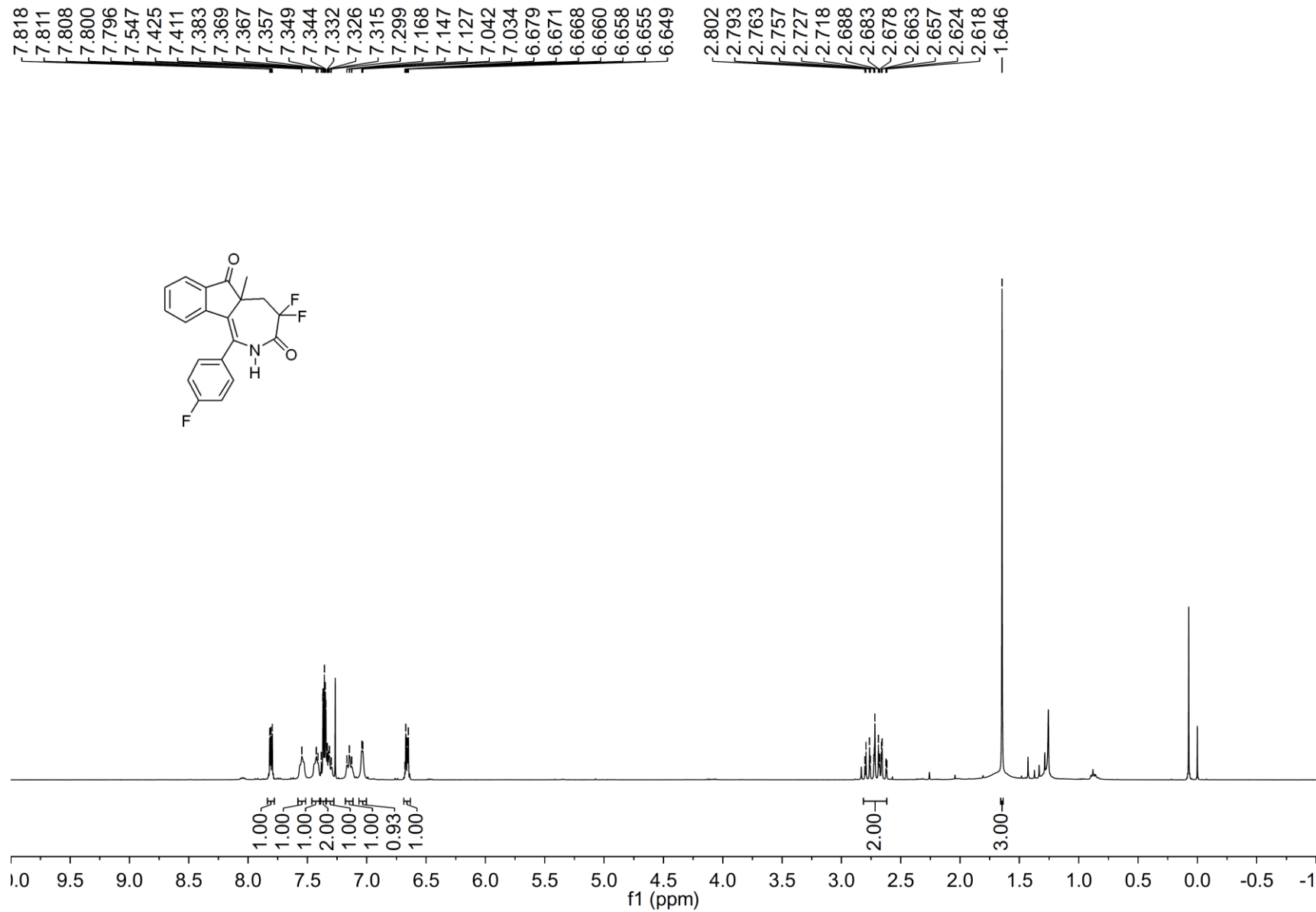
¹H NMR Spectrum of Compound 3d



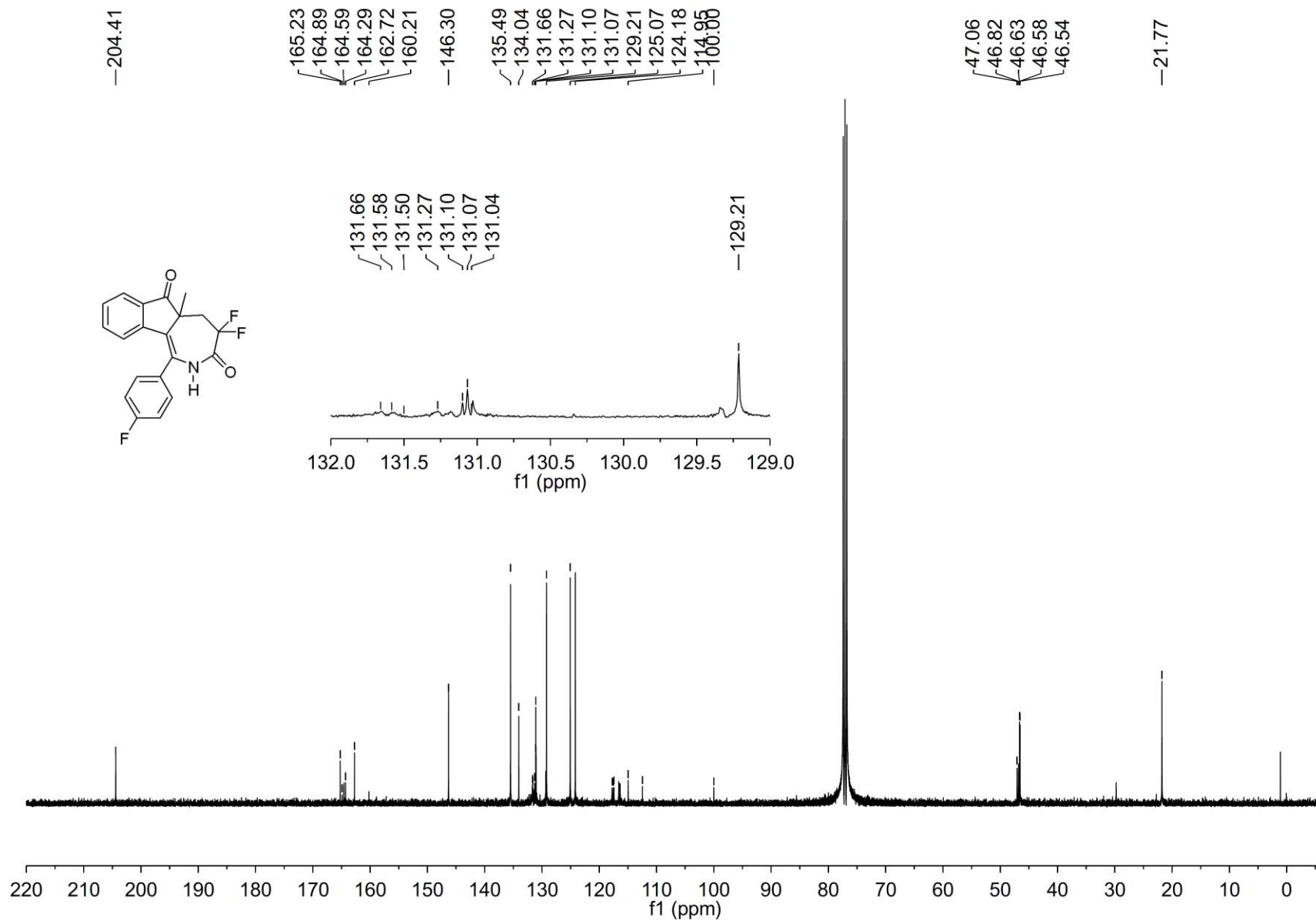
¹³C NMR Spectrum of Compound 3d

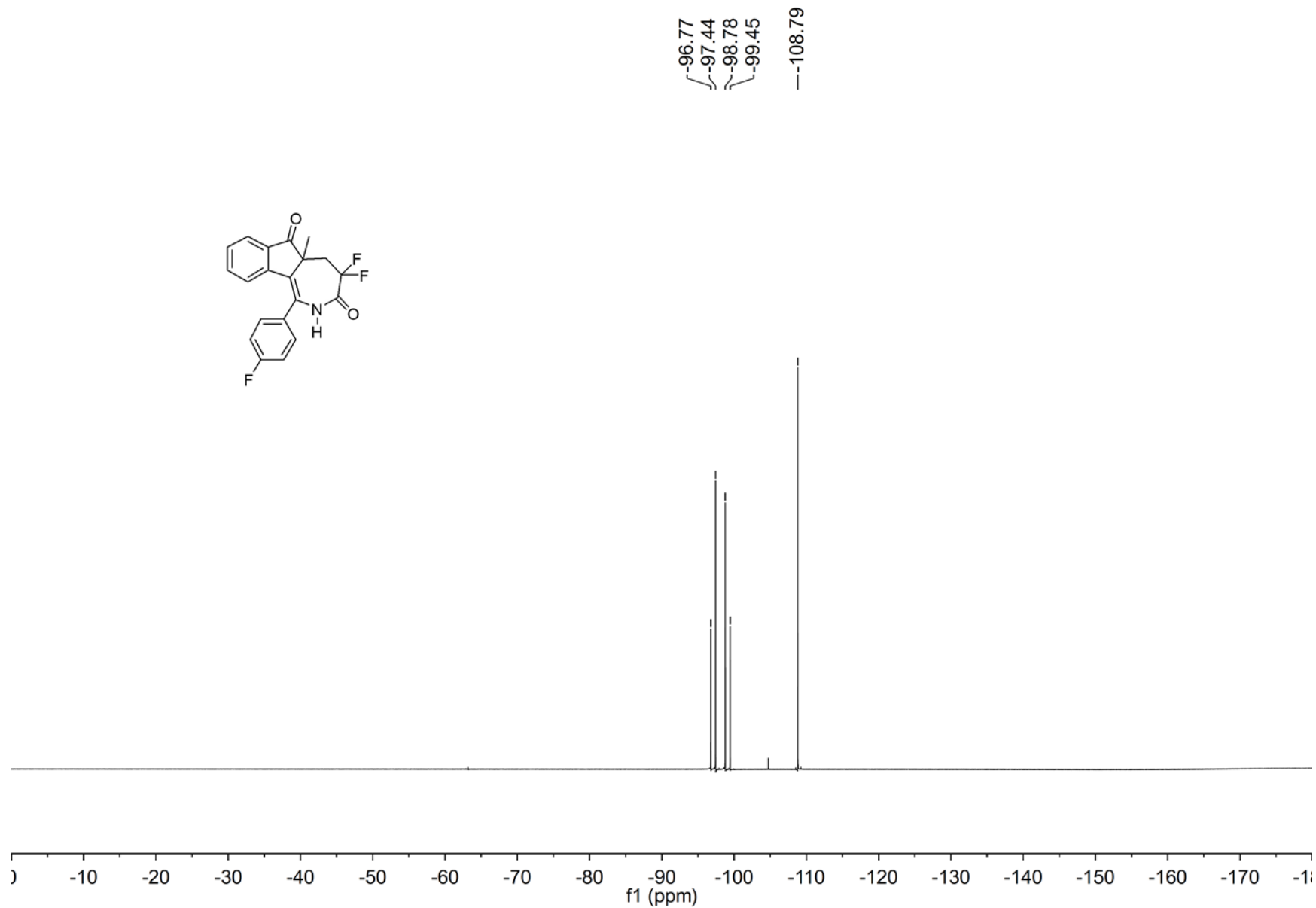
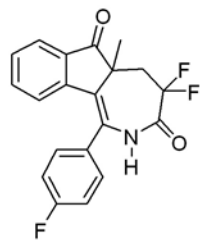


^{19}F NMR Spectrum of Compound 3d



¹H NMR Spectrum of Compound 3e

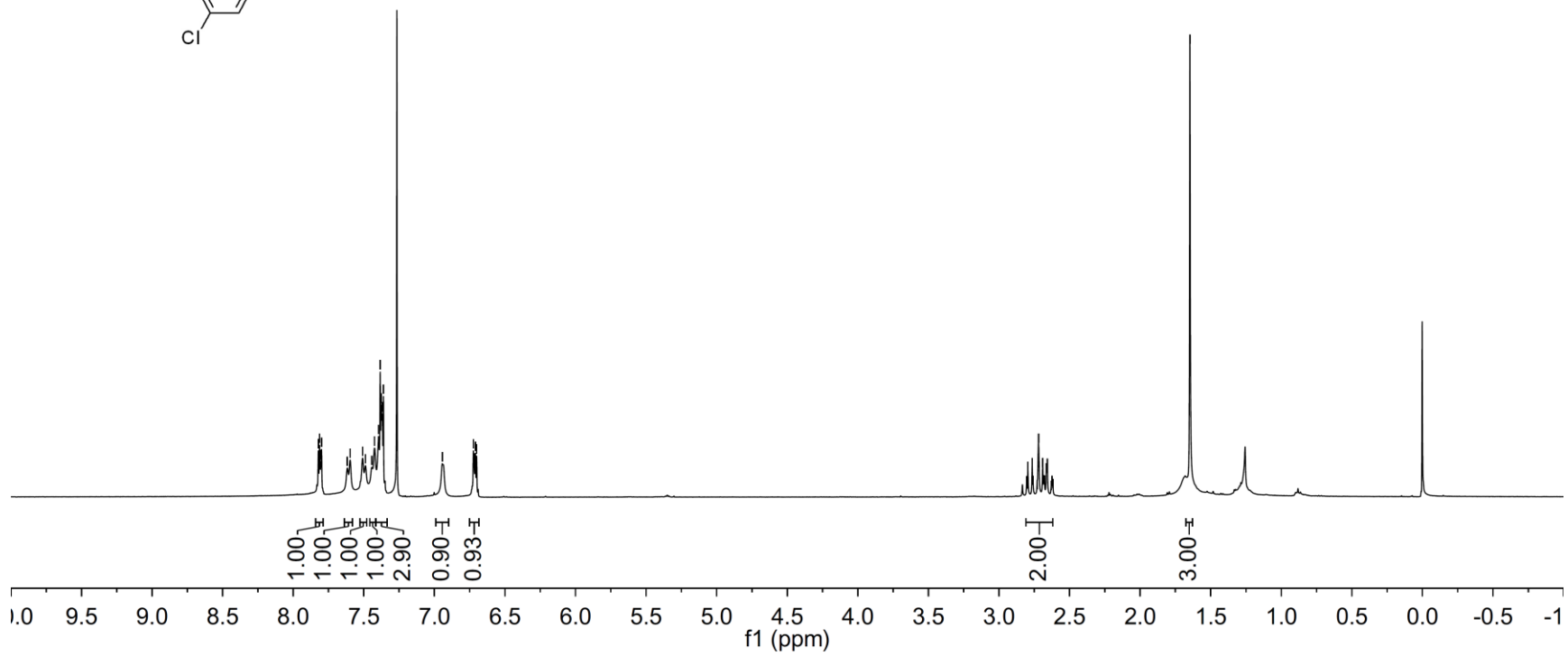
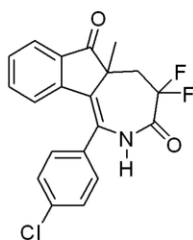




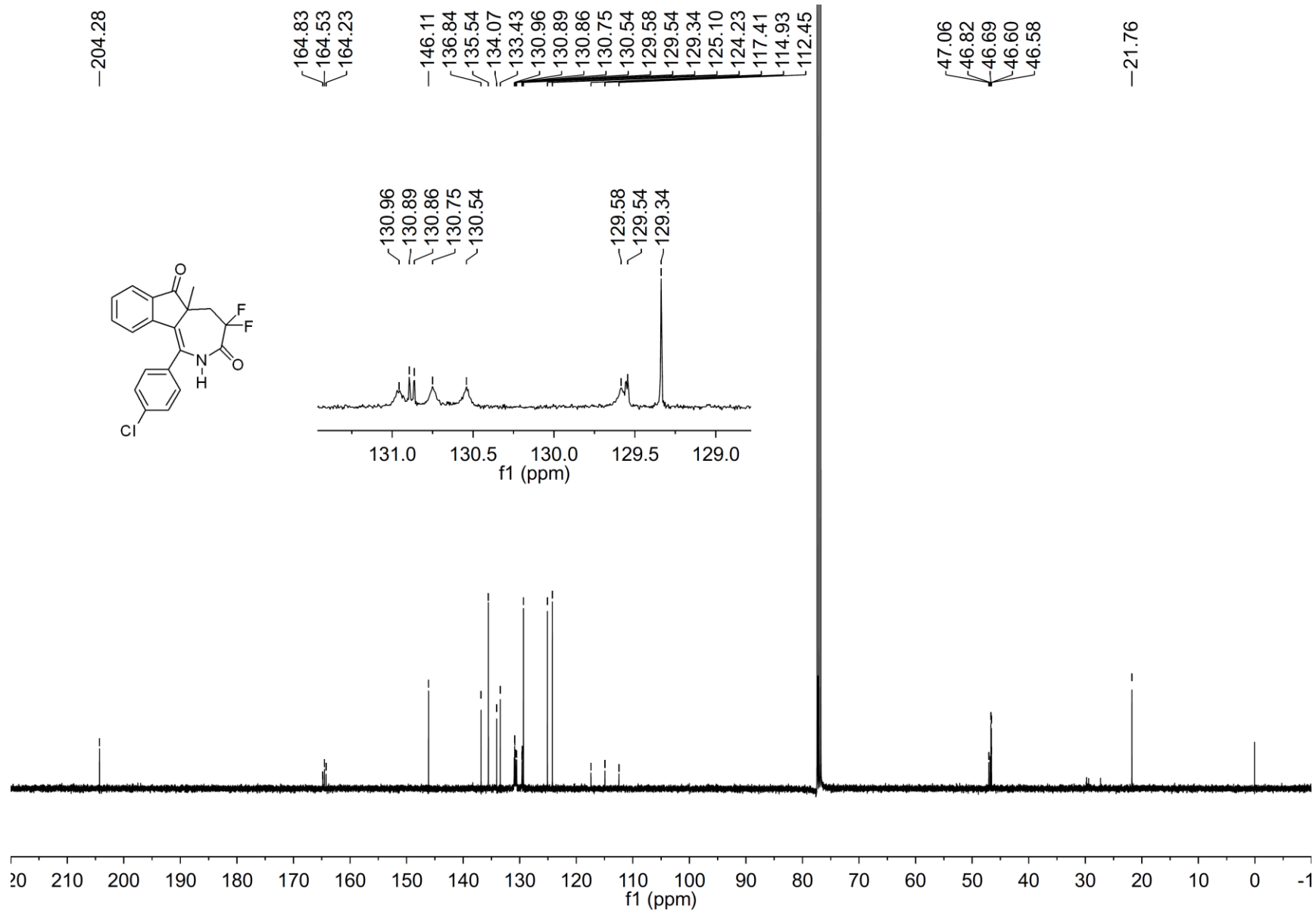
^{19}F NMR Spectrum of Compound 3e

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6.701

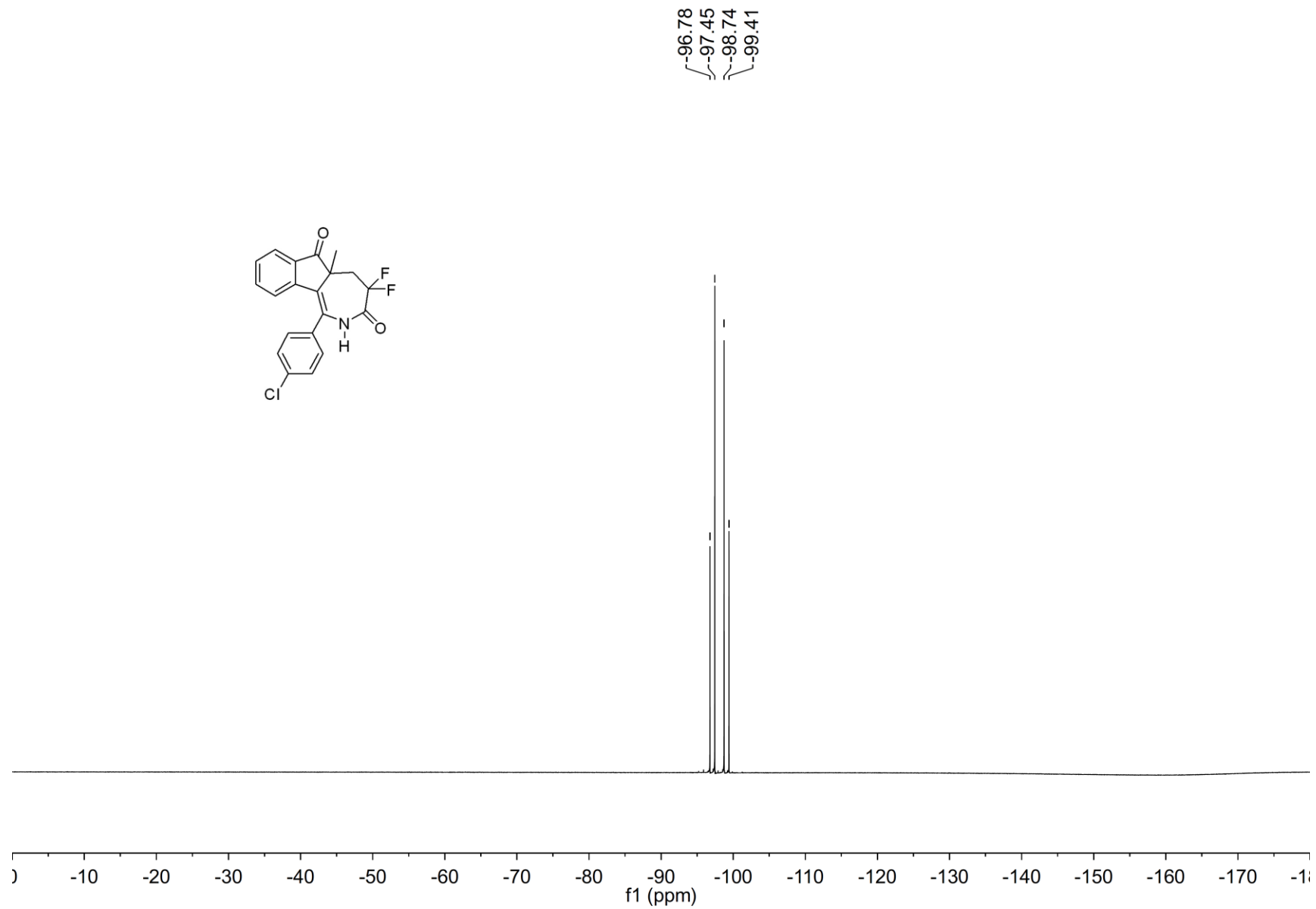
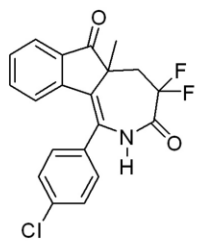
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2.618
1.647



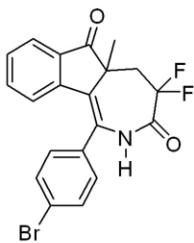
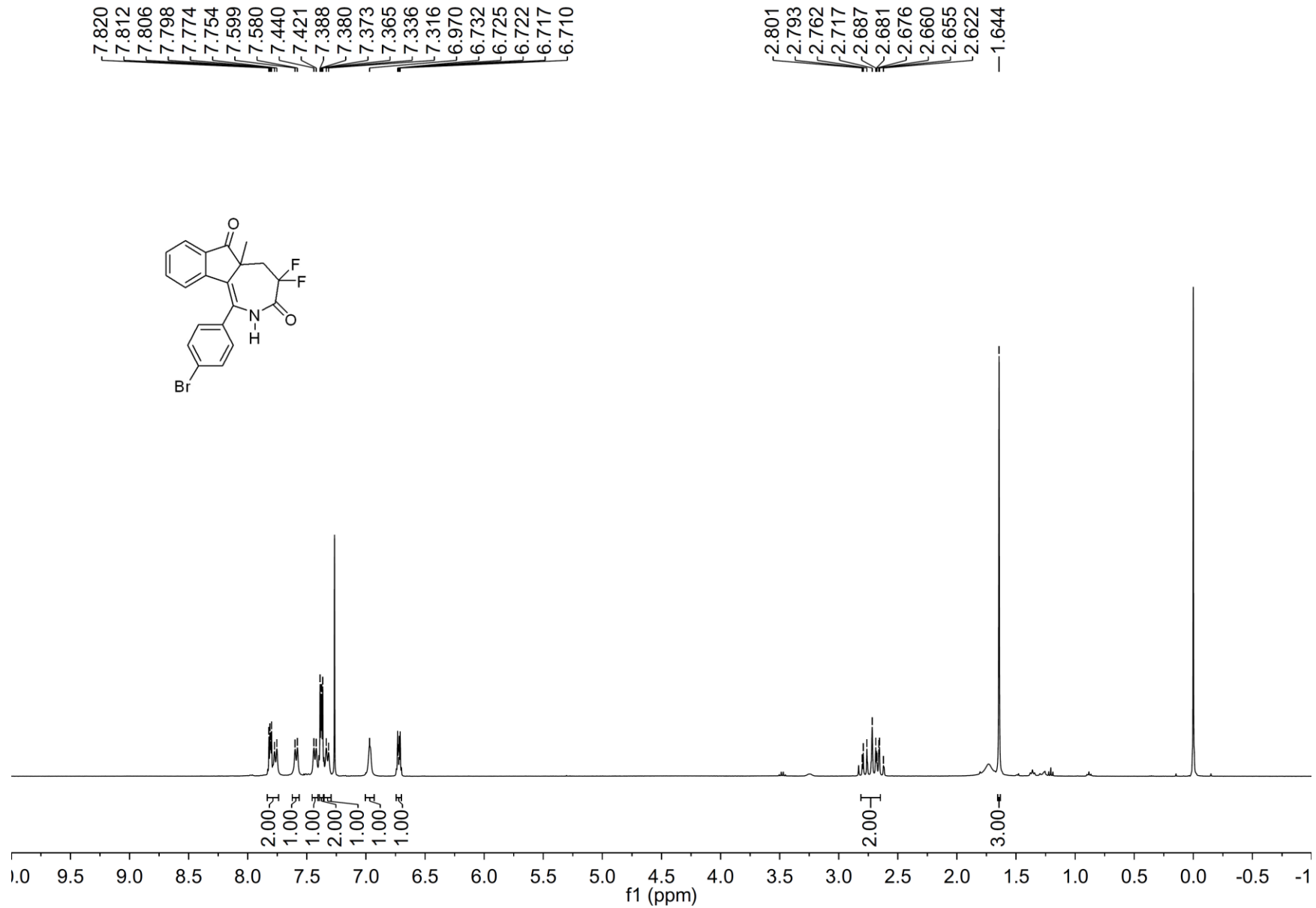
¹H NMR Spectrum of Compound 3f



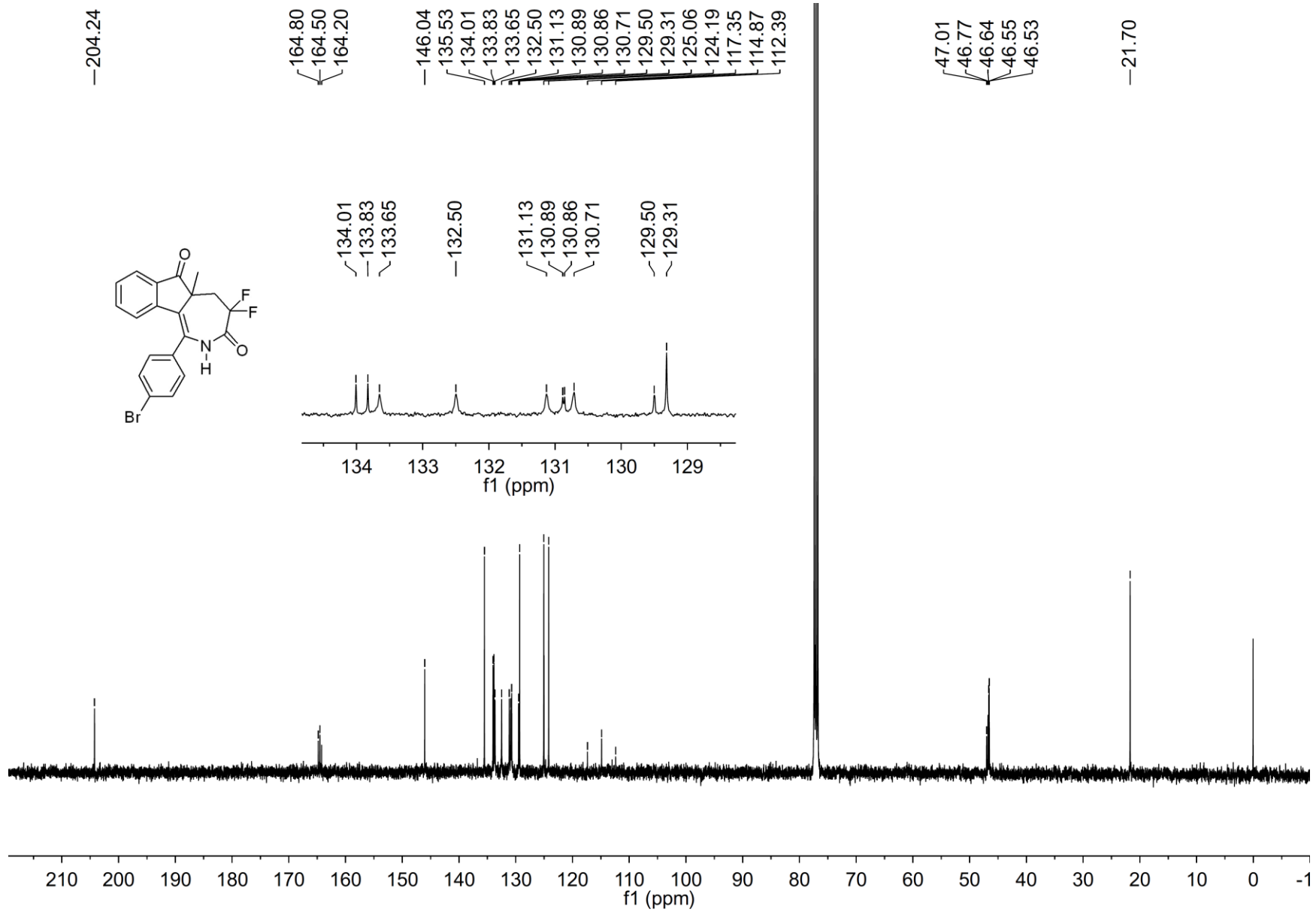
¹³C NMR Spectrum of Compound 3f

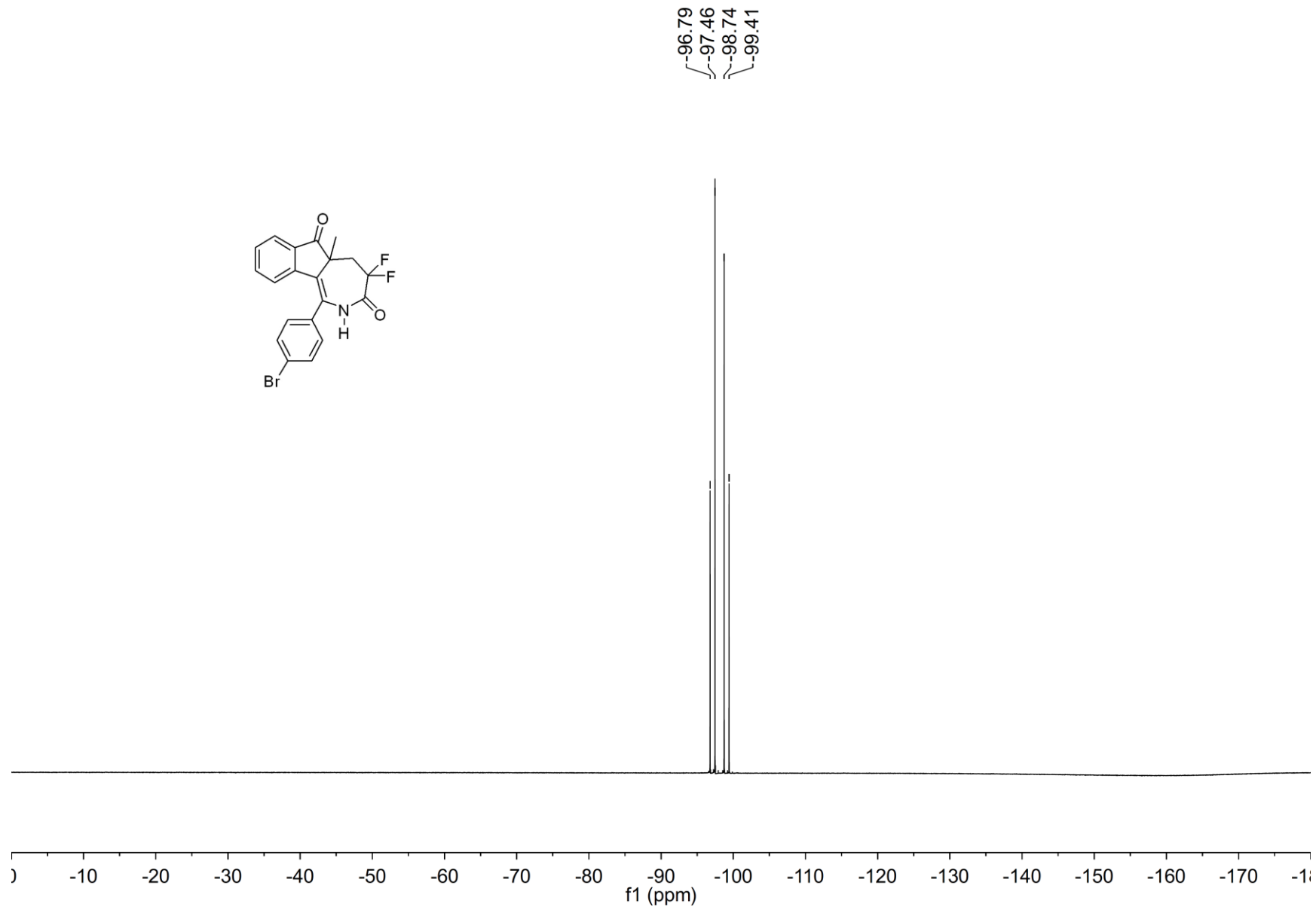
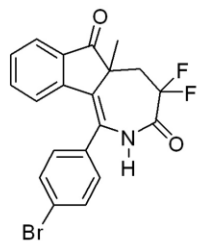


^{19}F NMR Spectrum of Compound 3f

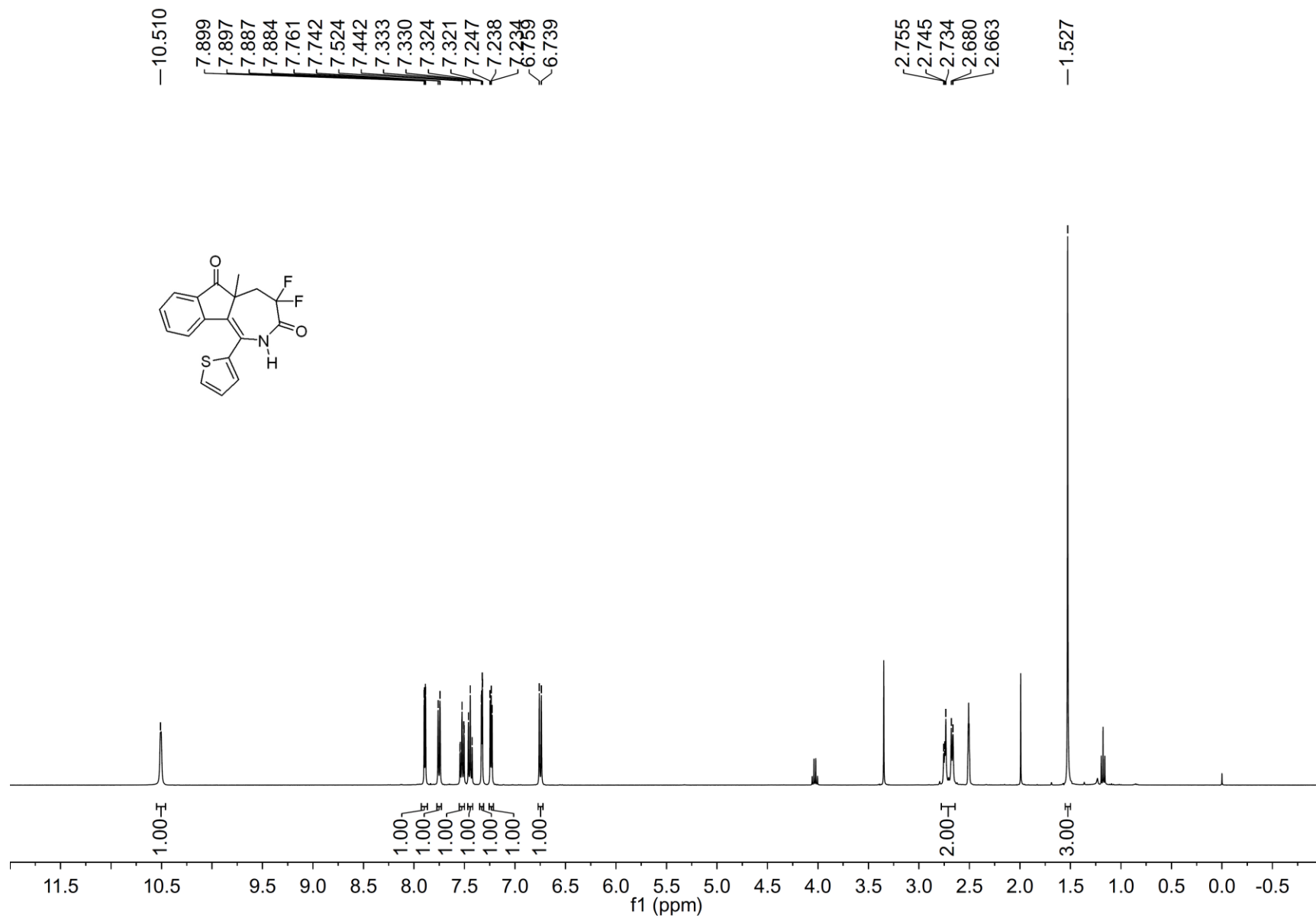


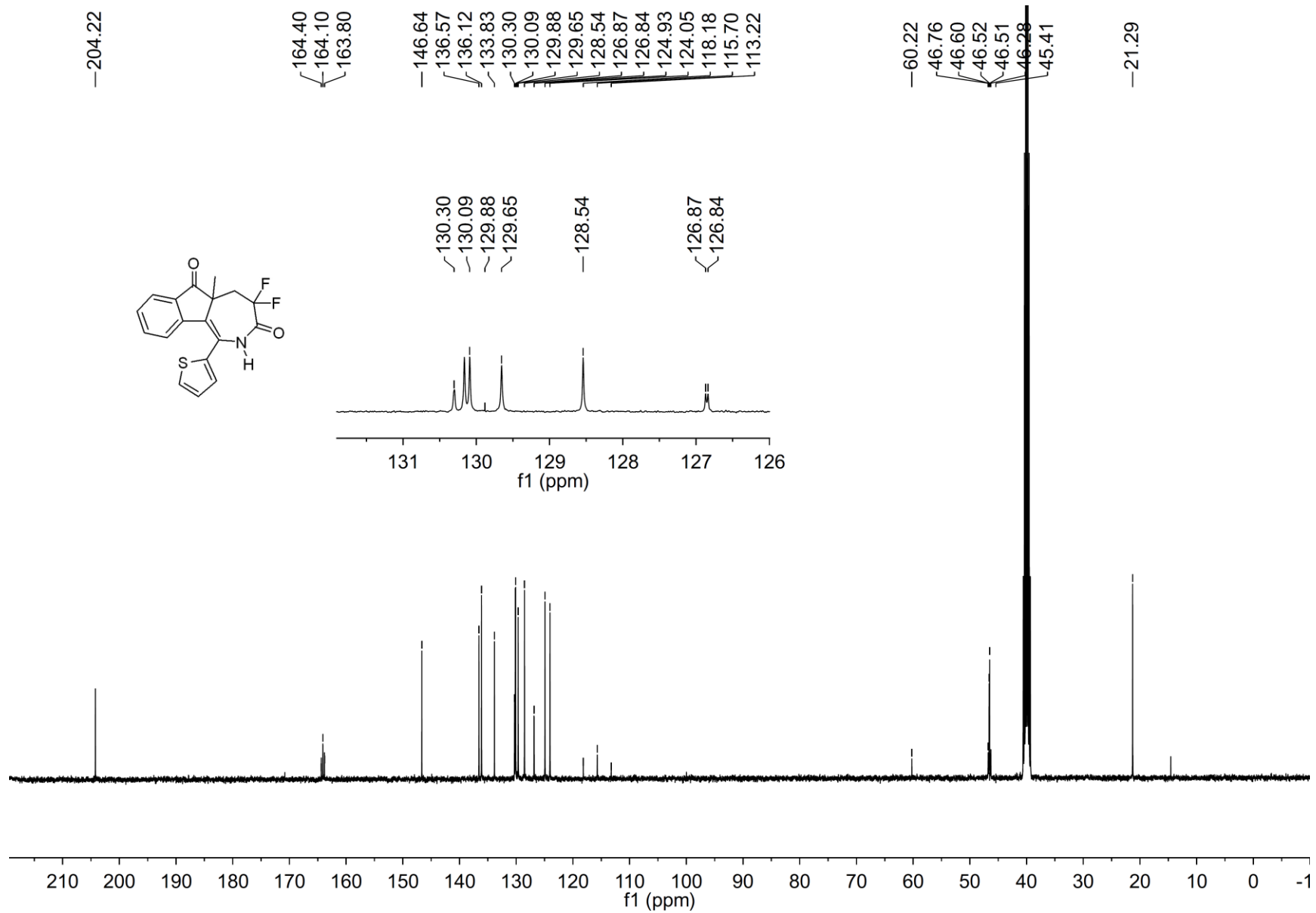
¹H NMR Spectrum of Compound 3g

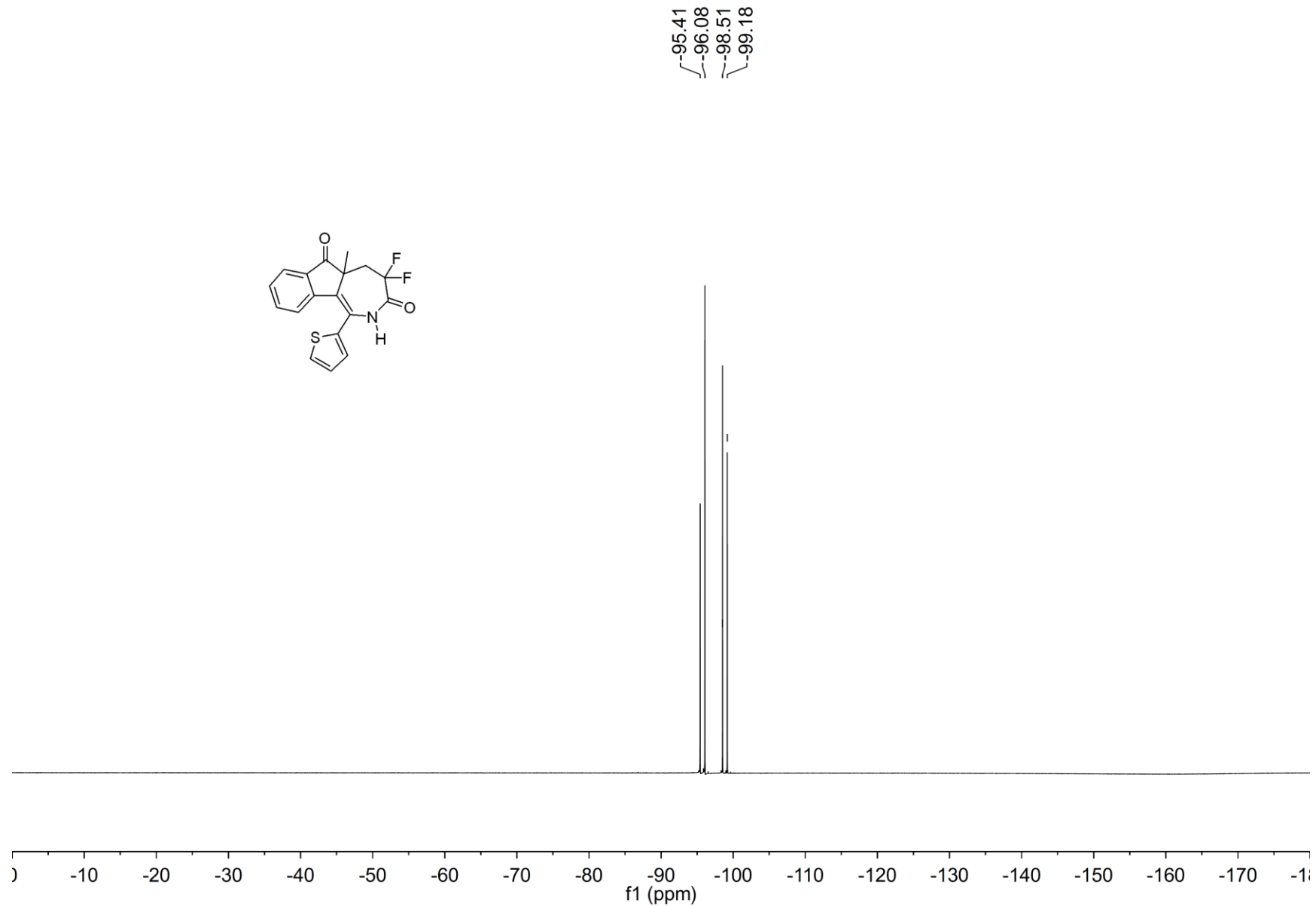
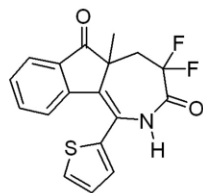




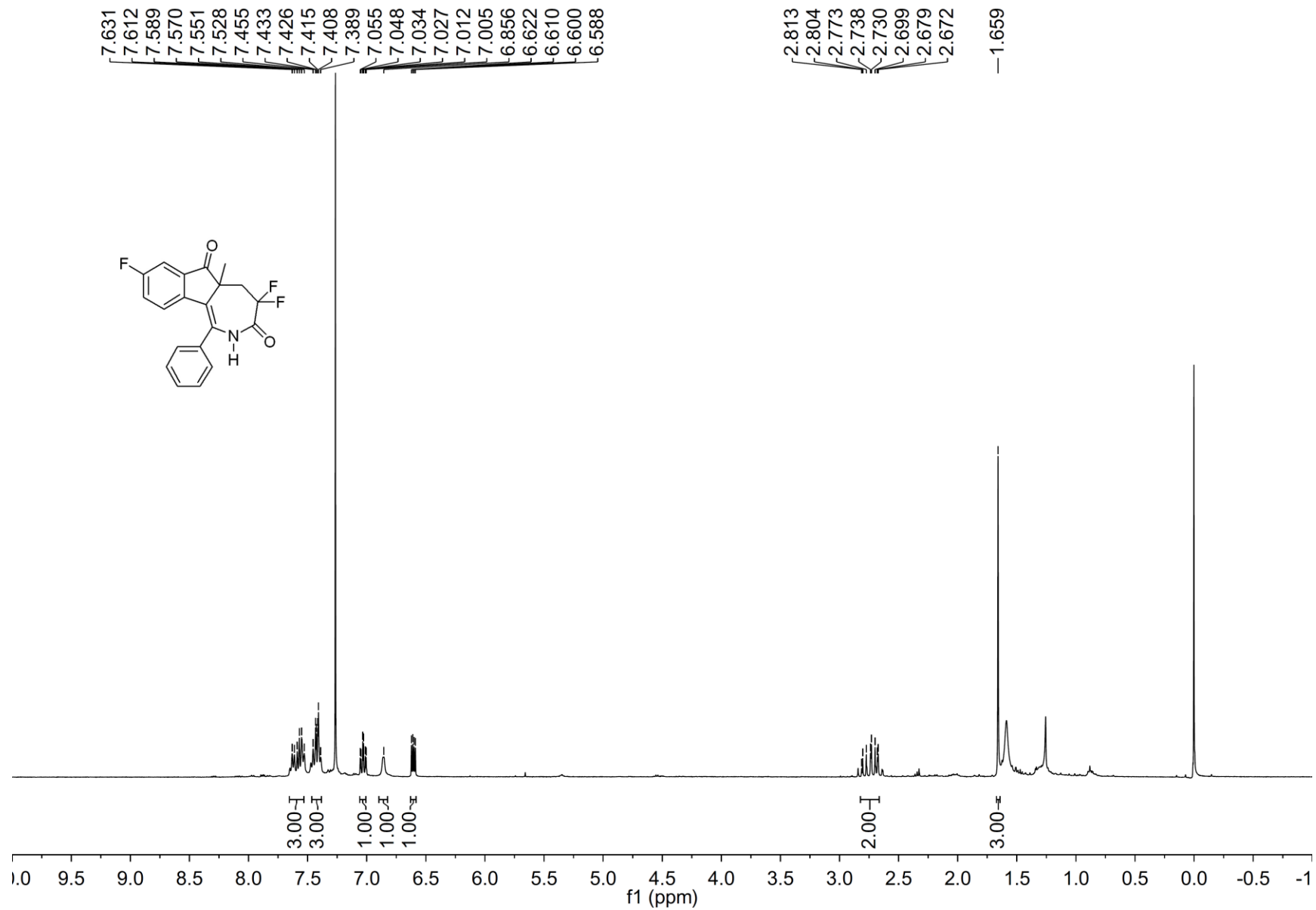
^{19}F NMR Spectrum of Compound 3g



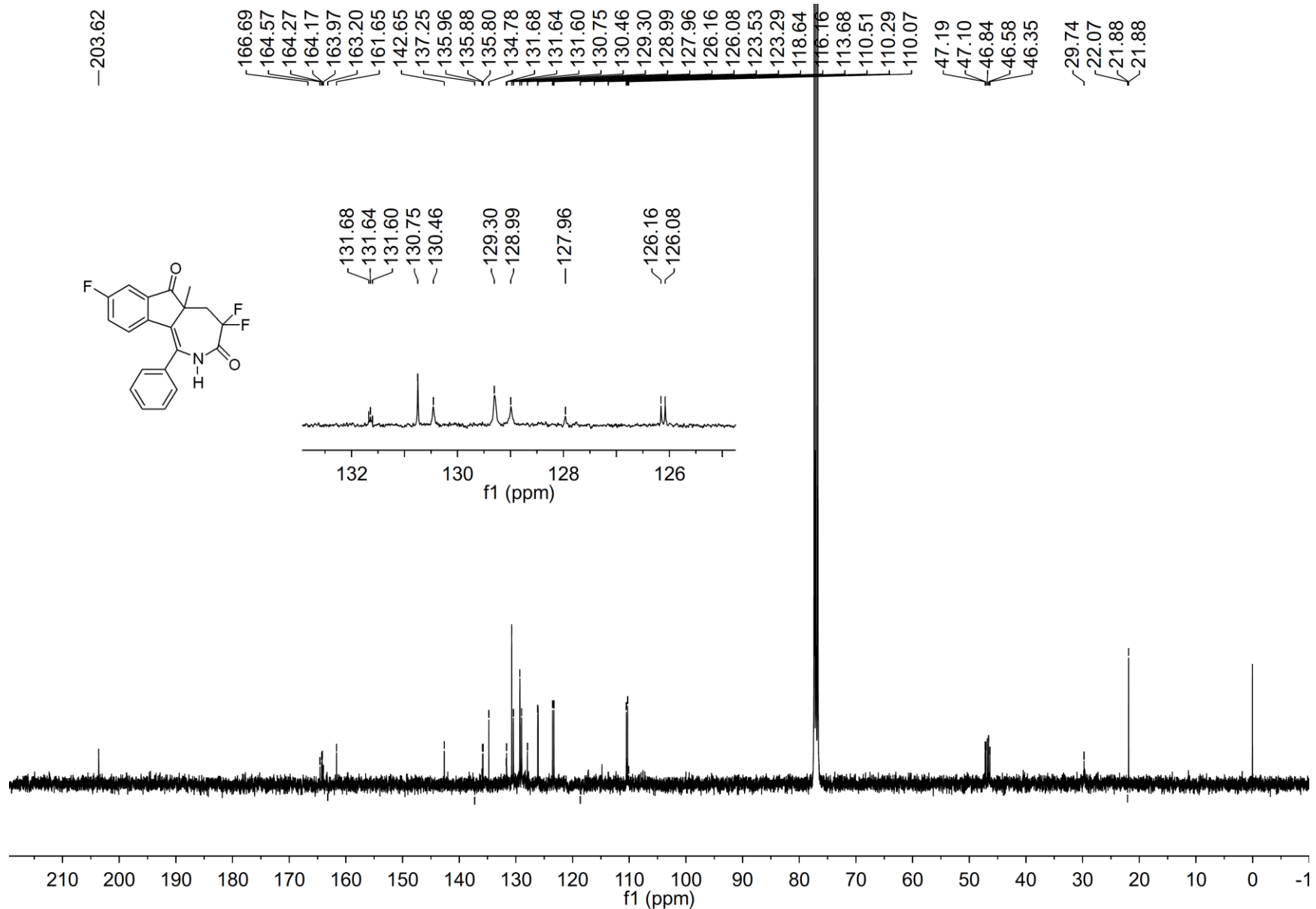




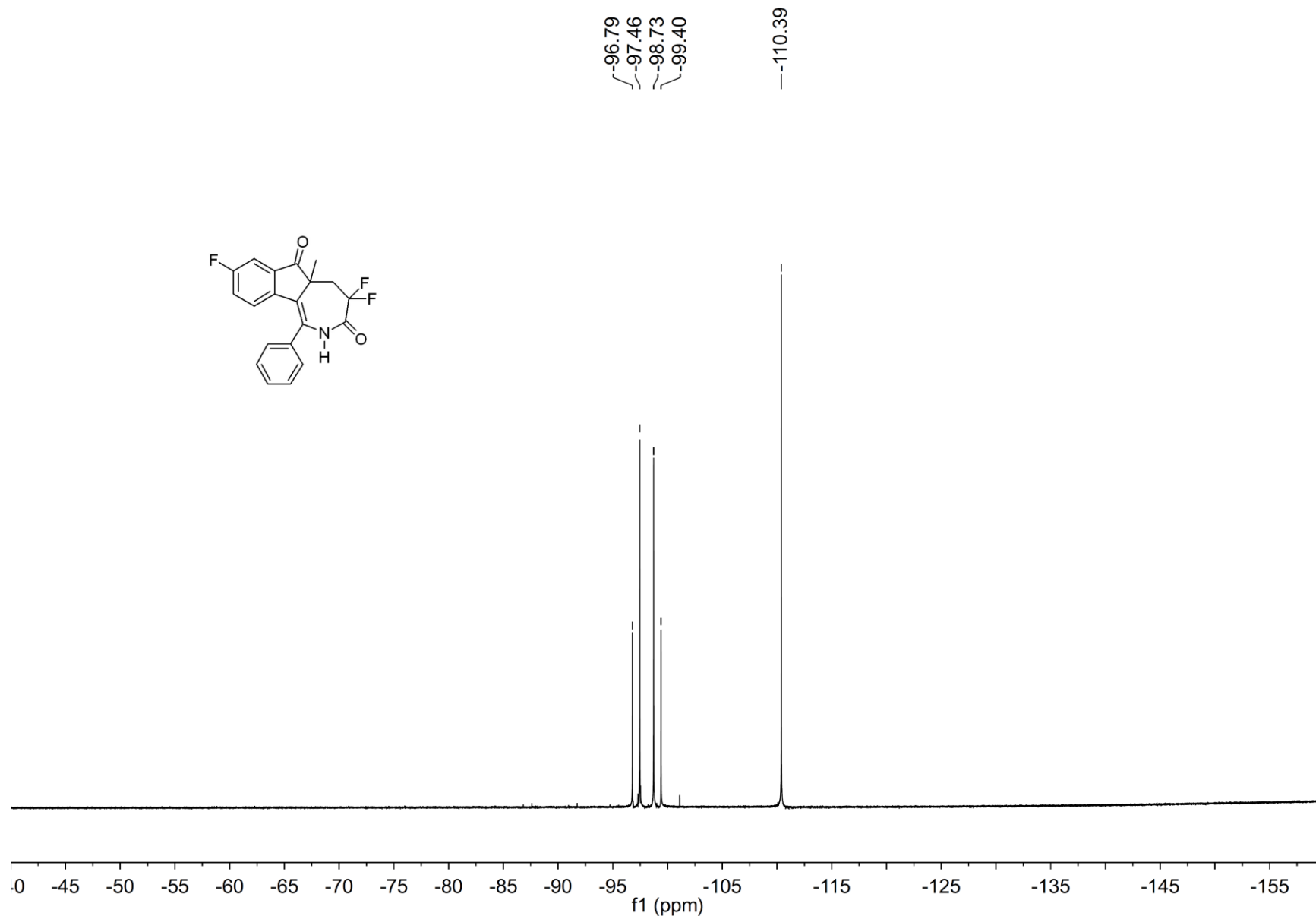
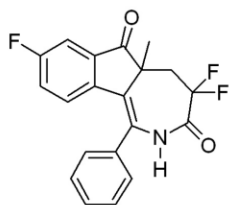
^{19}F NMR Spectrum of Compound 3h



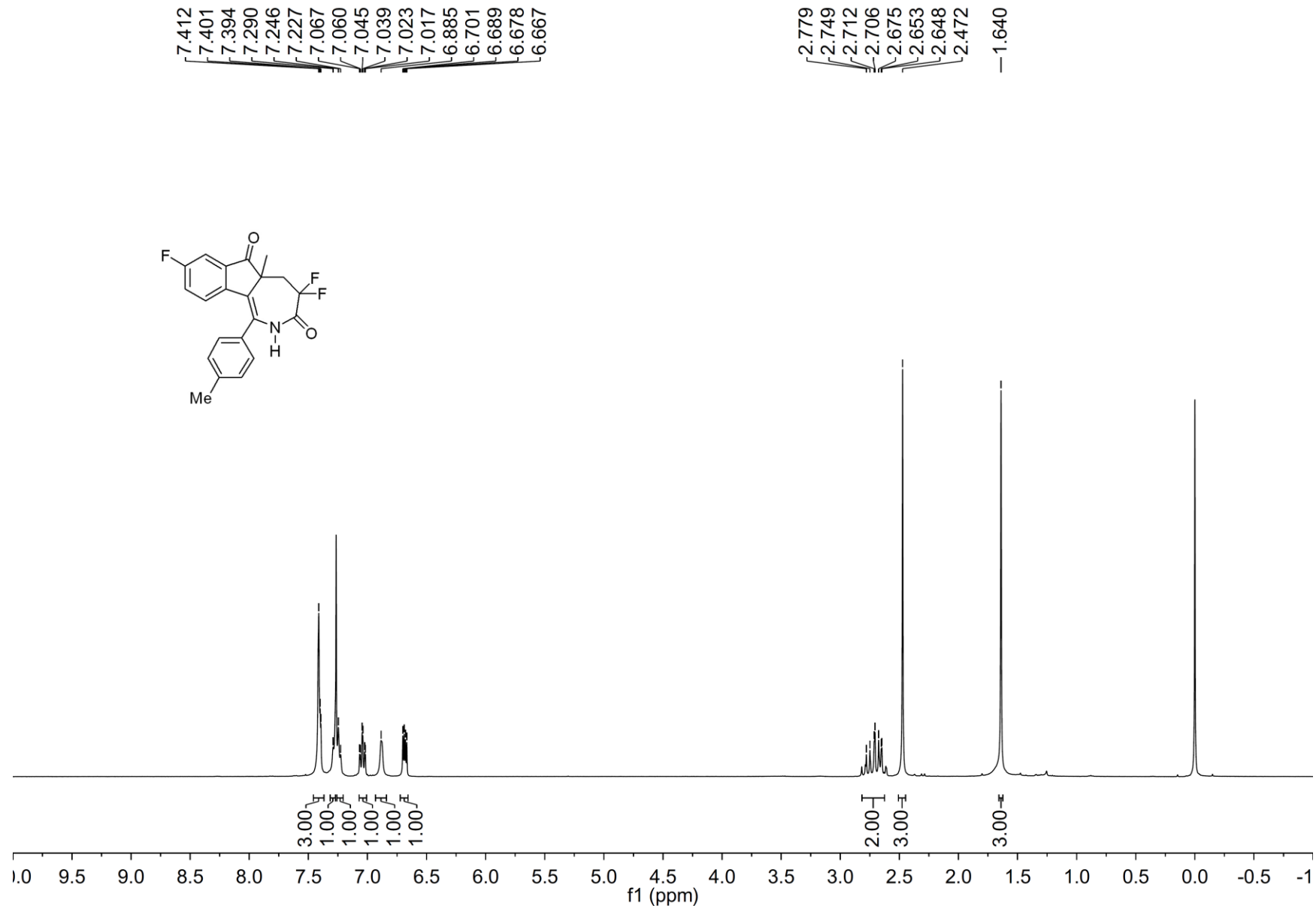
¹H NMR Spectrum of Compound 3i

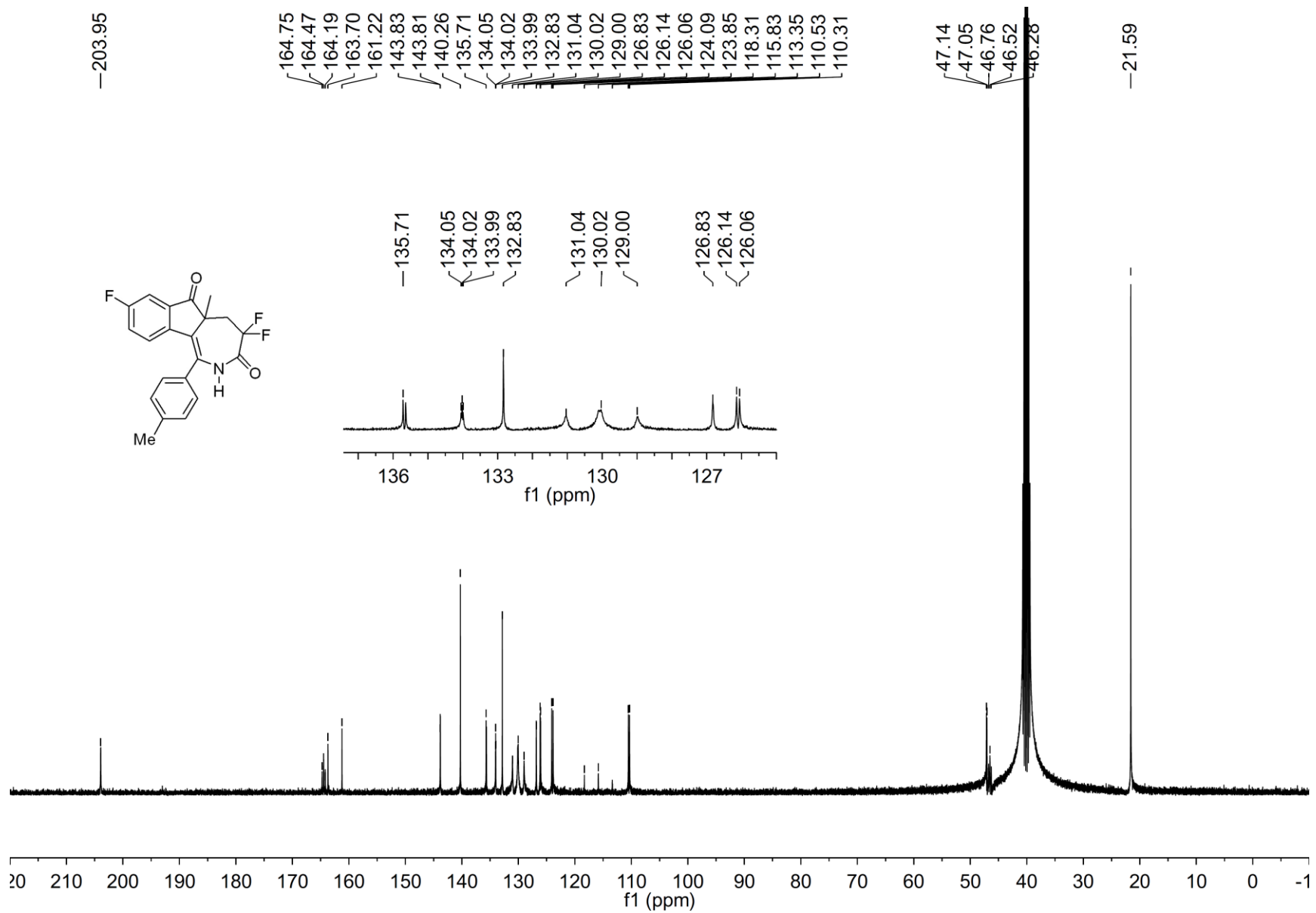


¹³C NMR Spectrum of Compound 3i

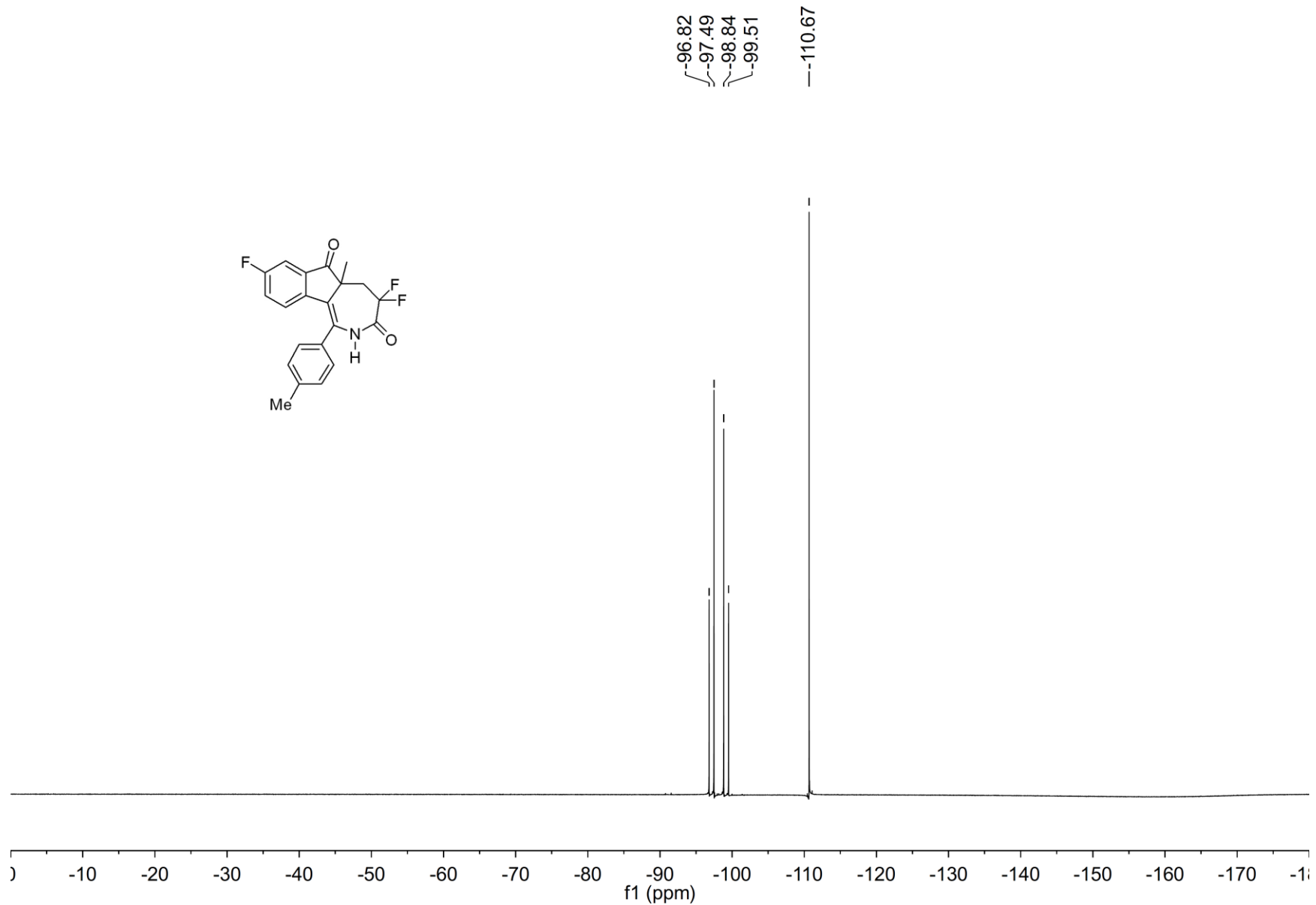
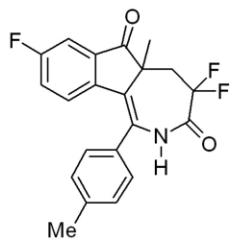


¹⁹F NMR Spectrum of Compound 3i

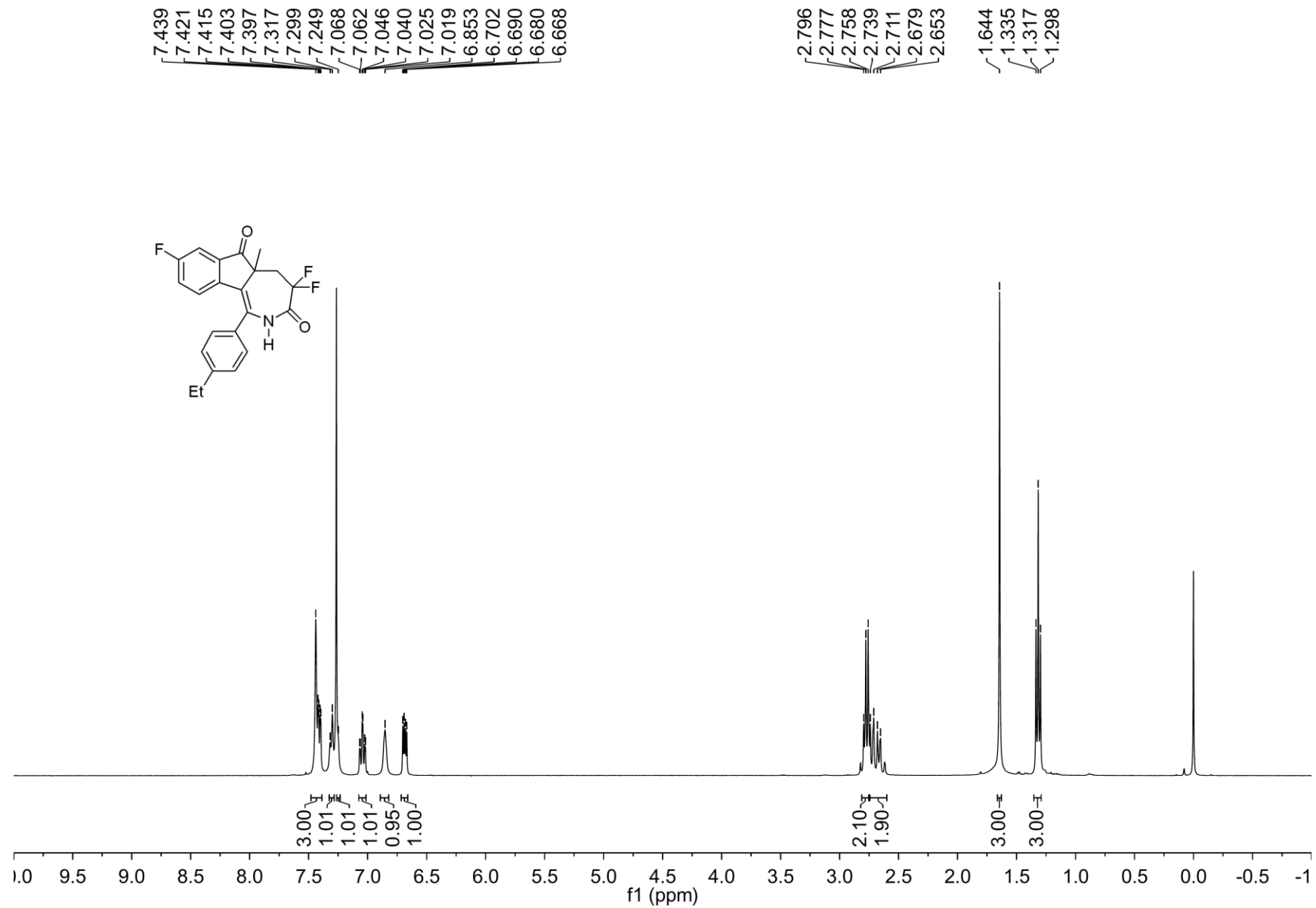


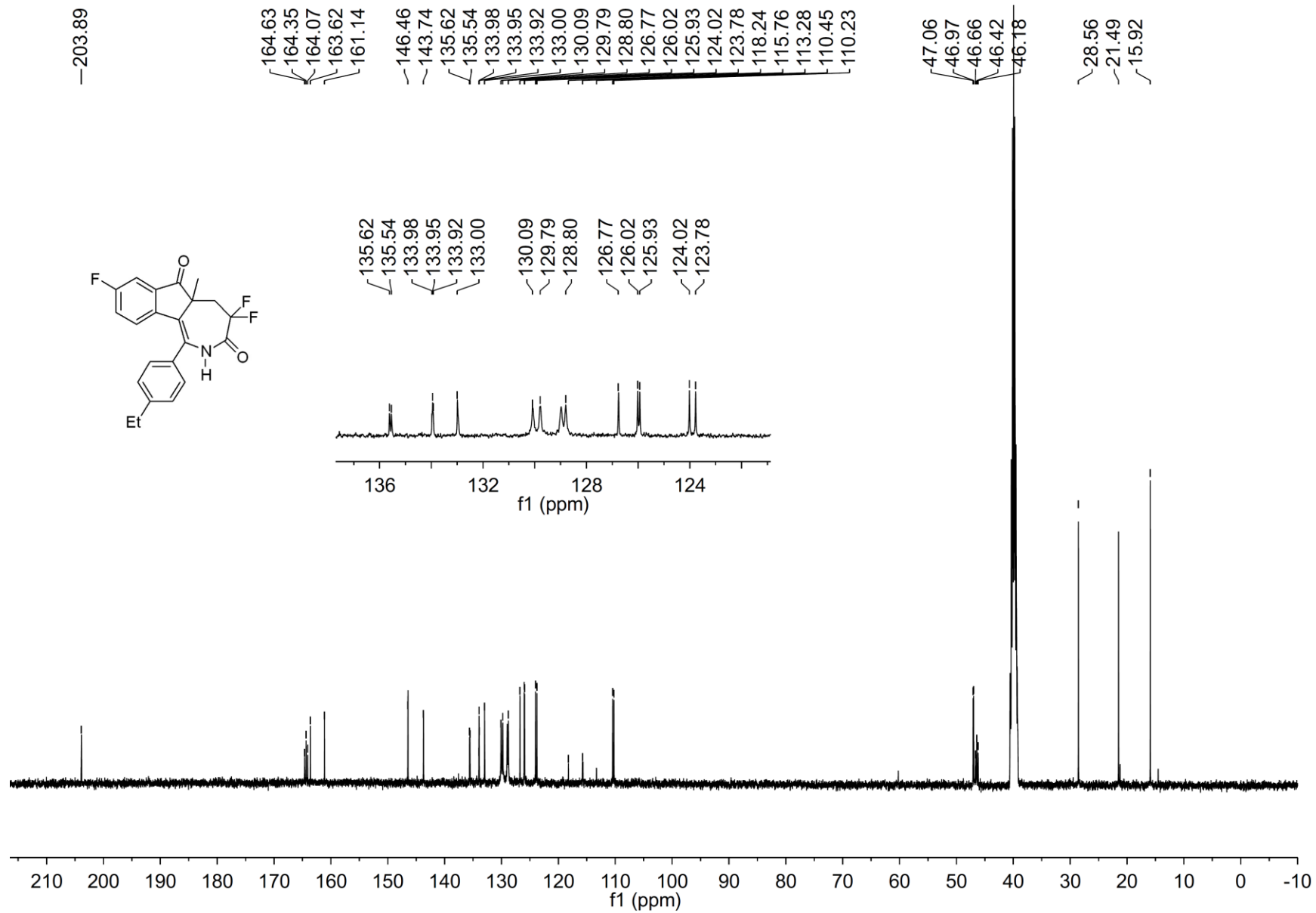


¹³C NMR Spectrum of Compound 3j

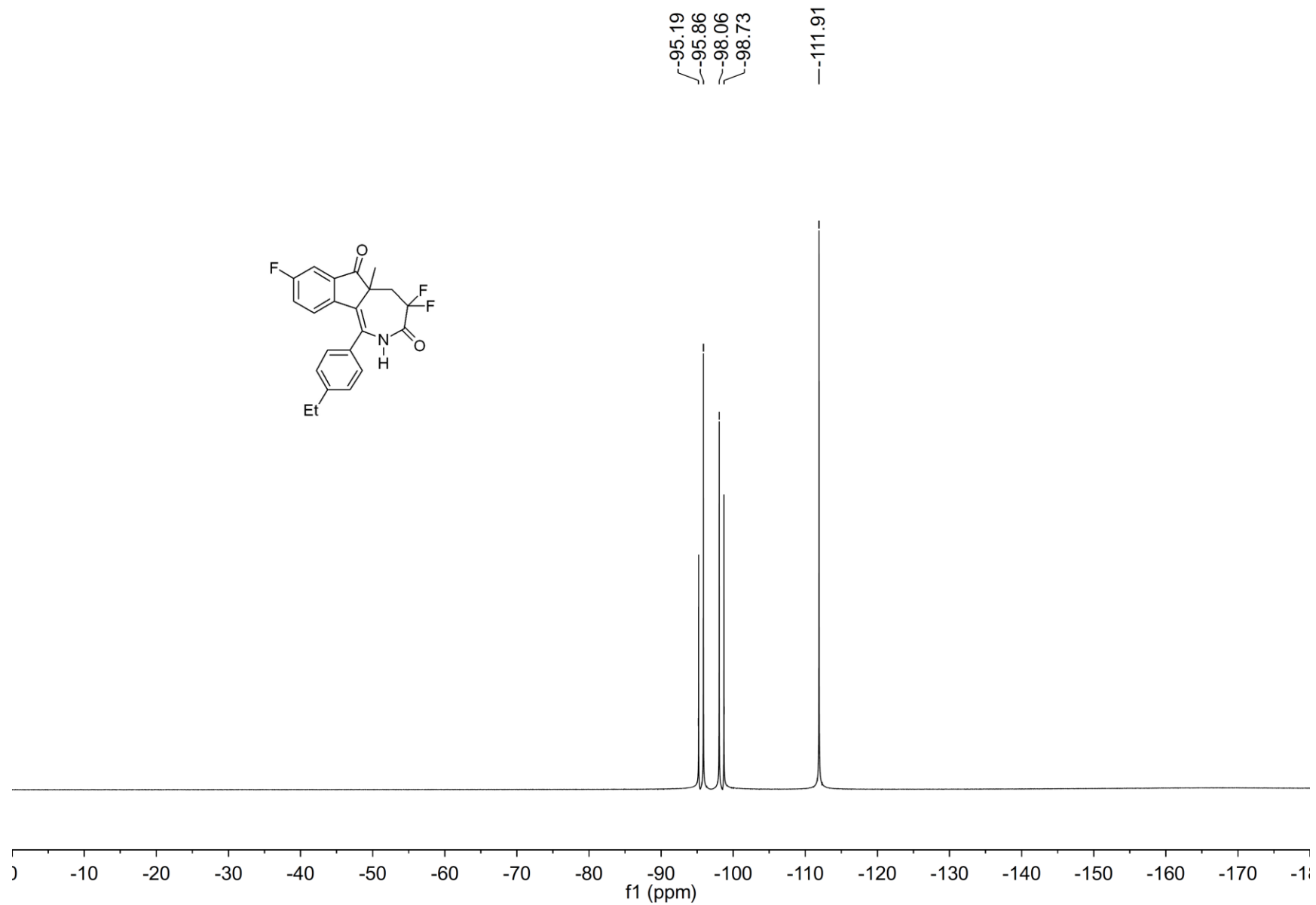


^{19}F NMR Spectrum of Compound 3j

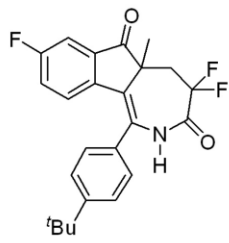
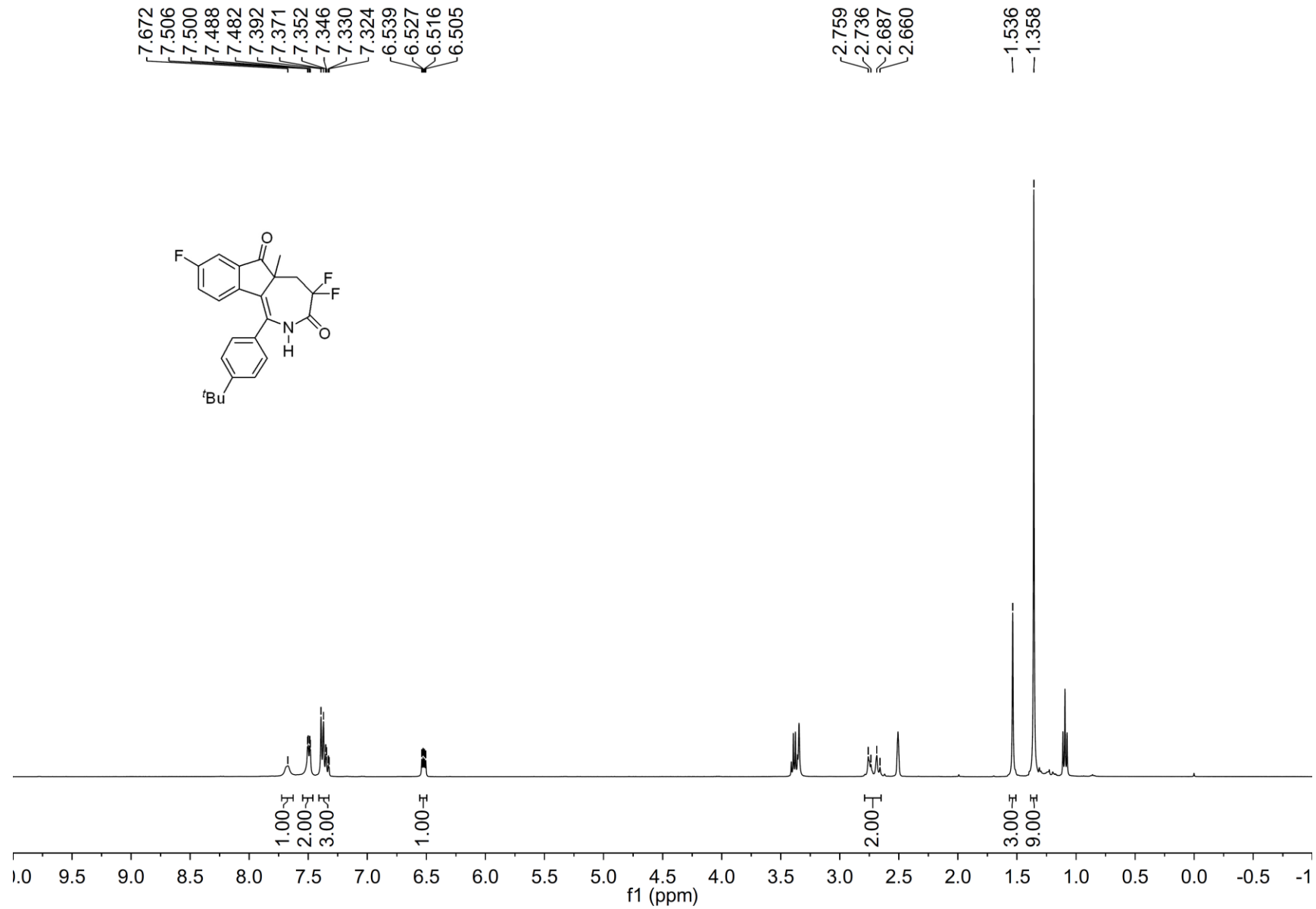




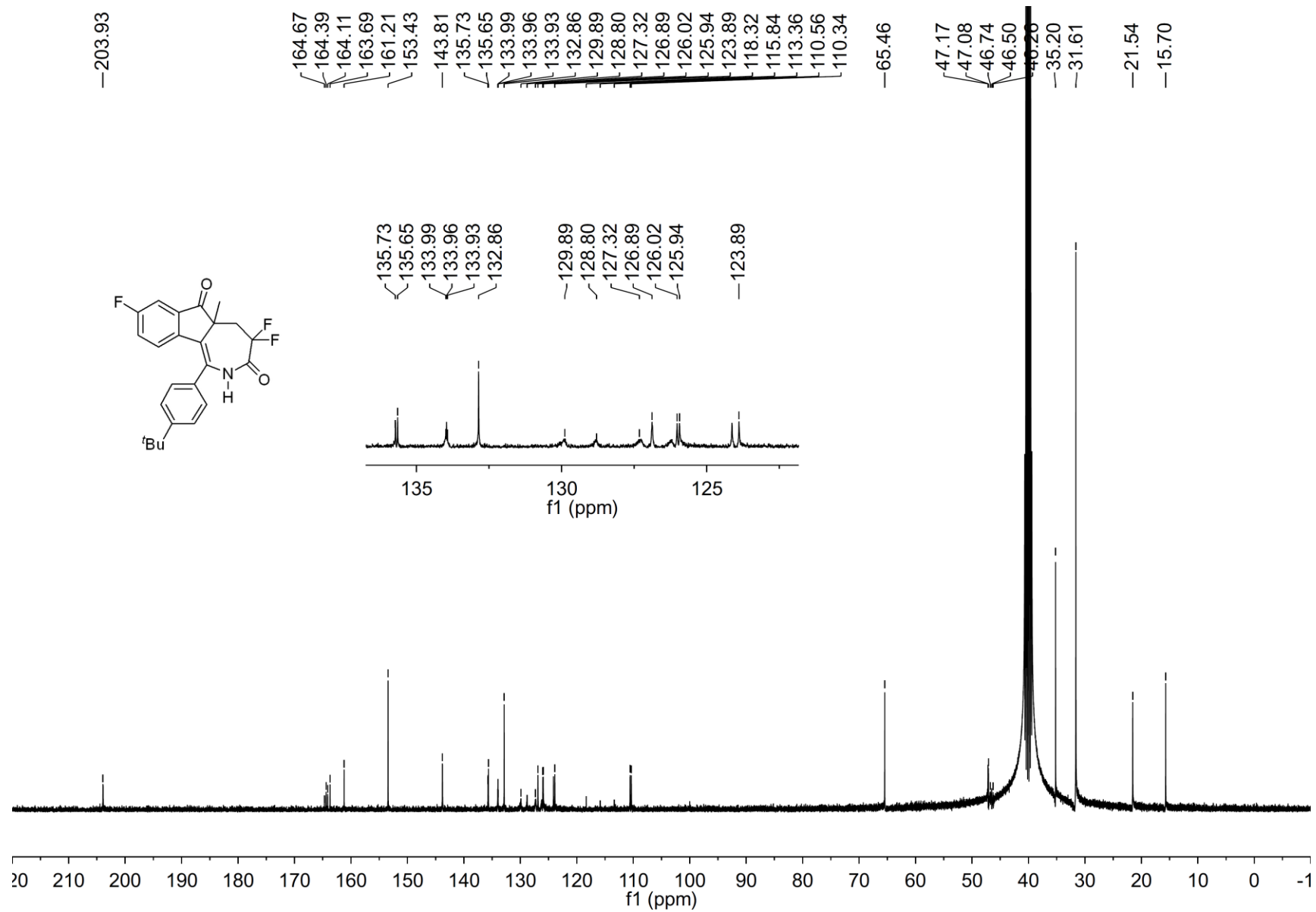
¹³C NMR Spectrum of Compound 3k

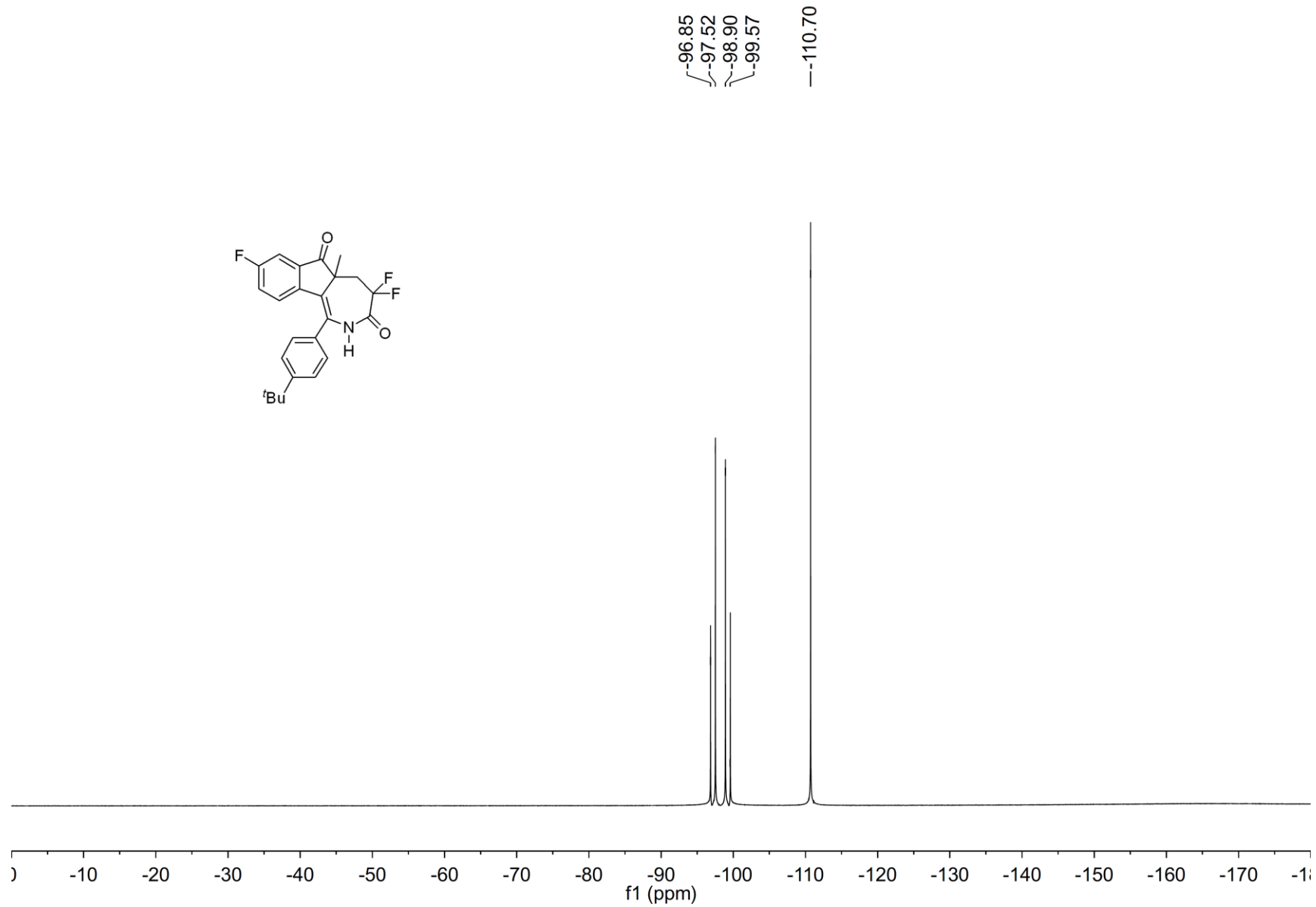
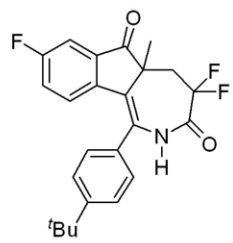


^{19}F NMR Spectrum of Compound 3k

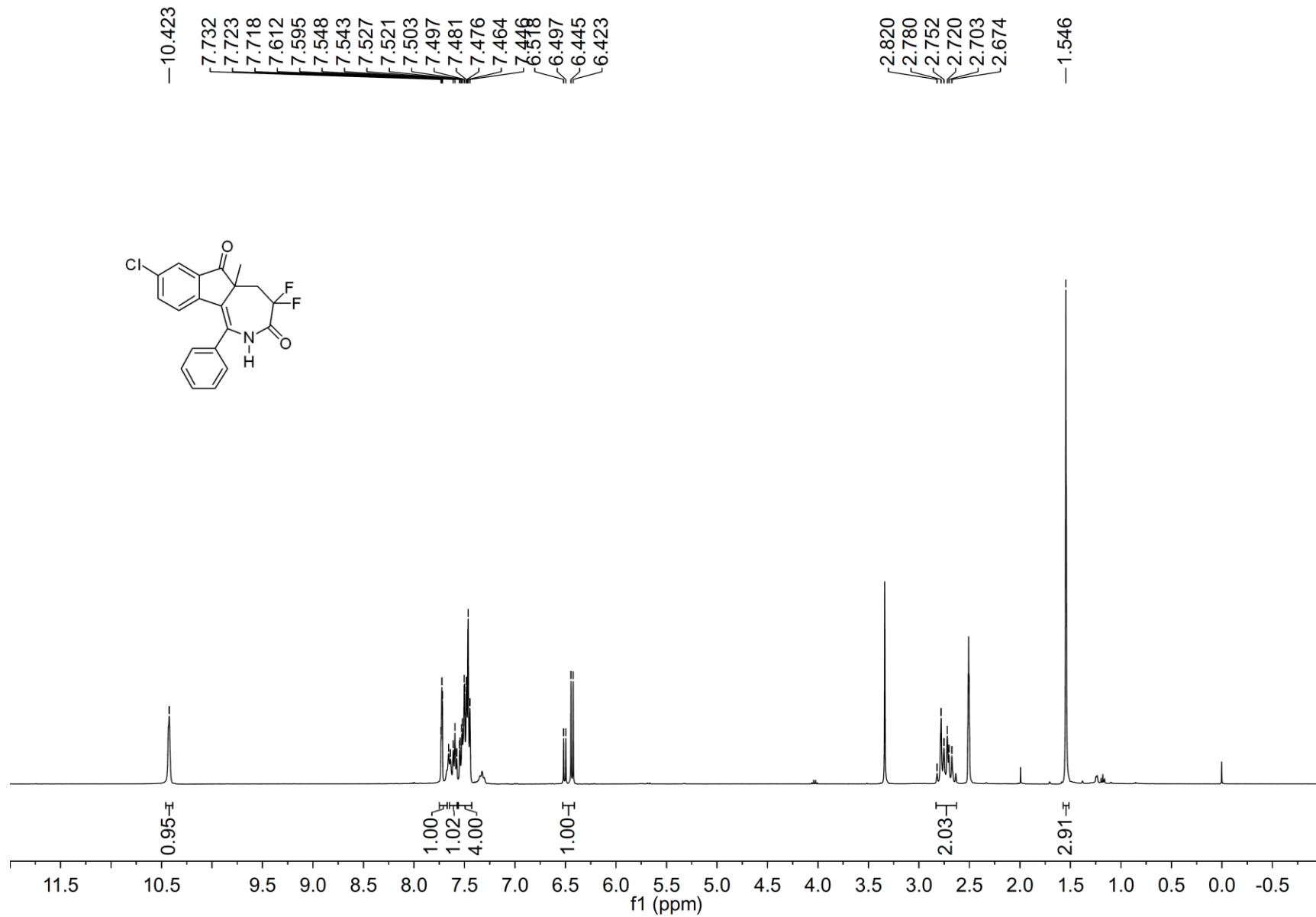


¹H NMR Spectrum of Compound 3I

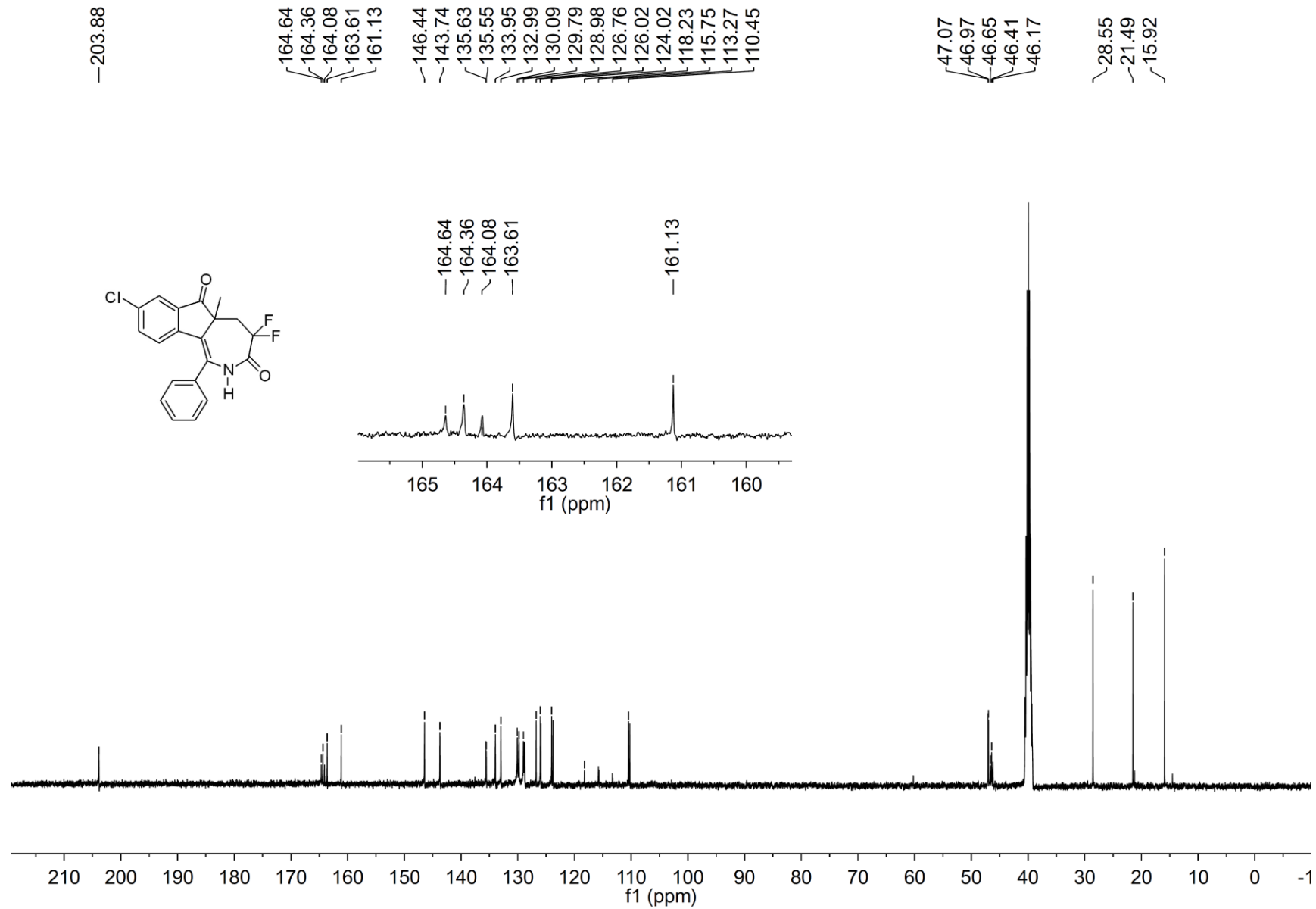


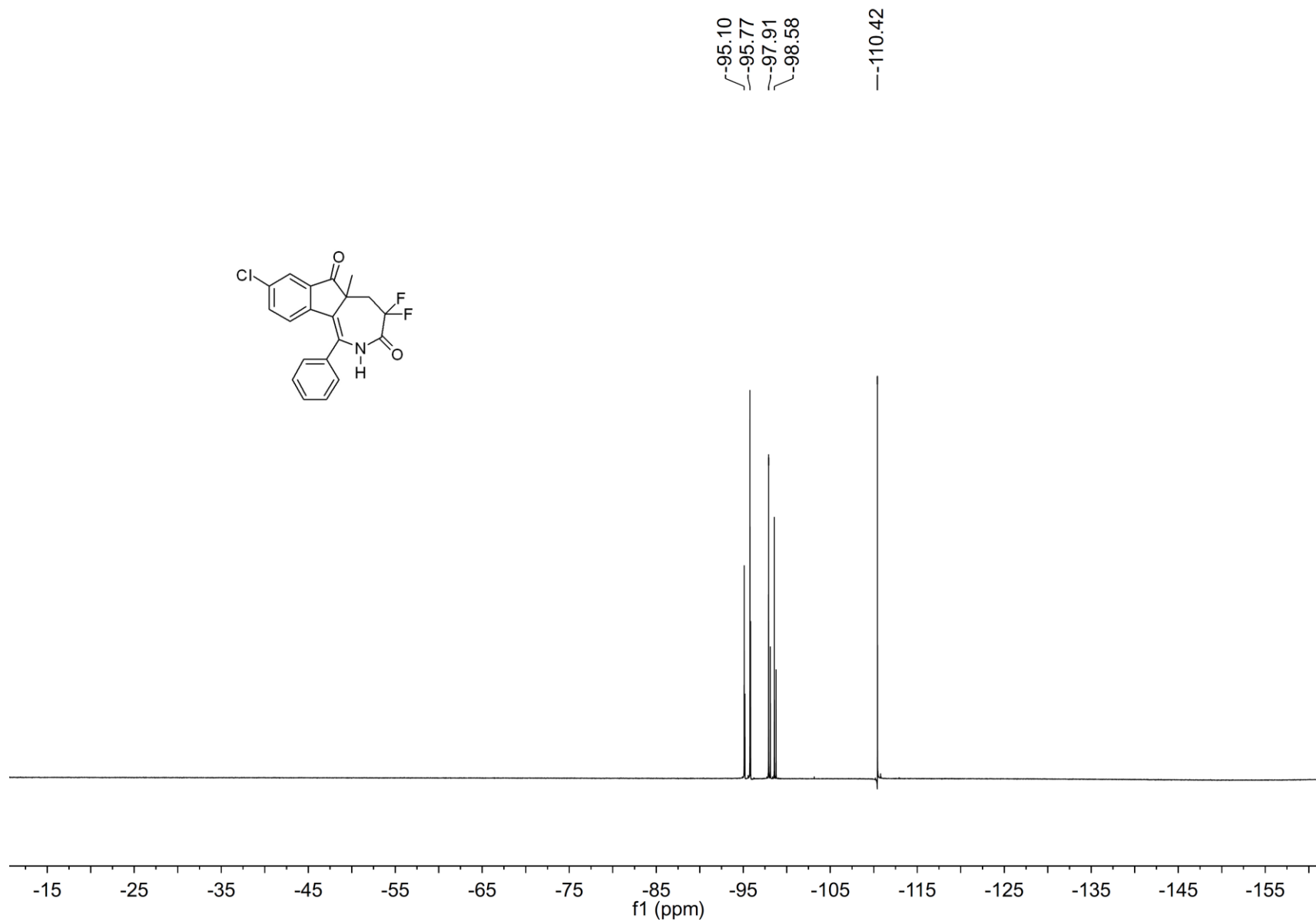
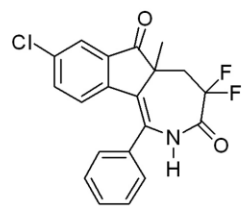


^{19}F NMR Spectrum of Compound 31

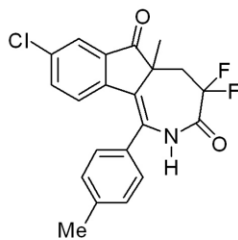
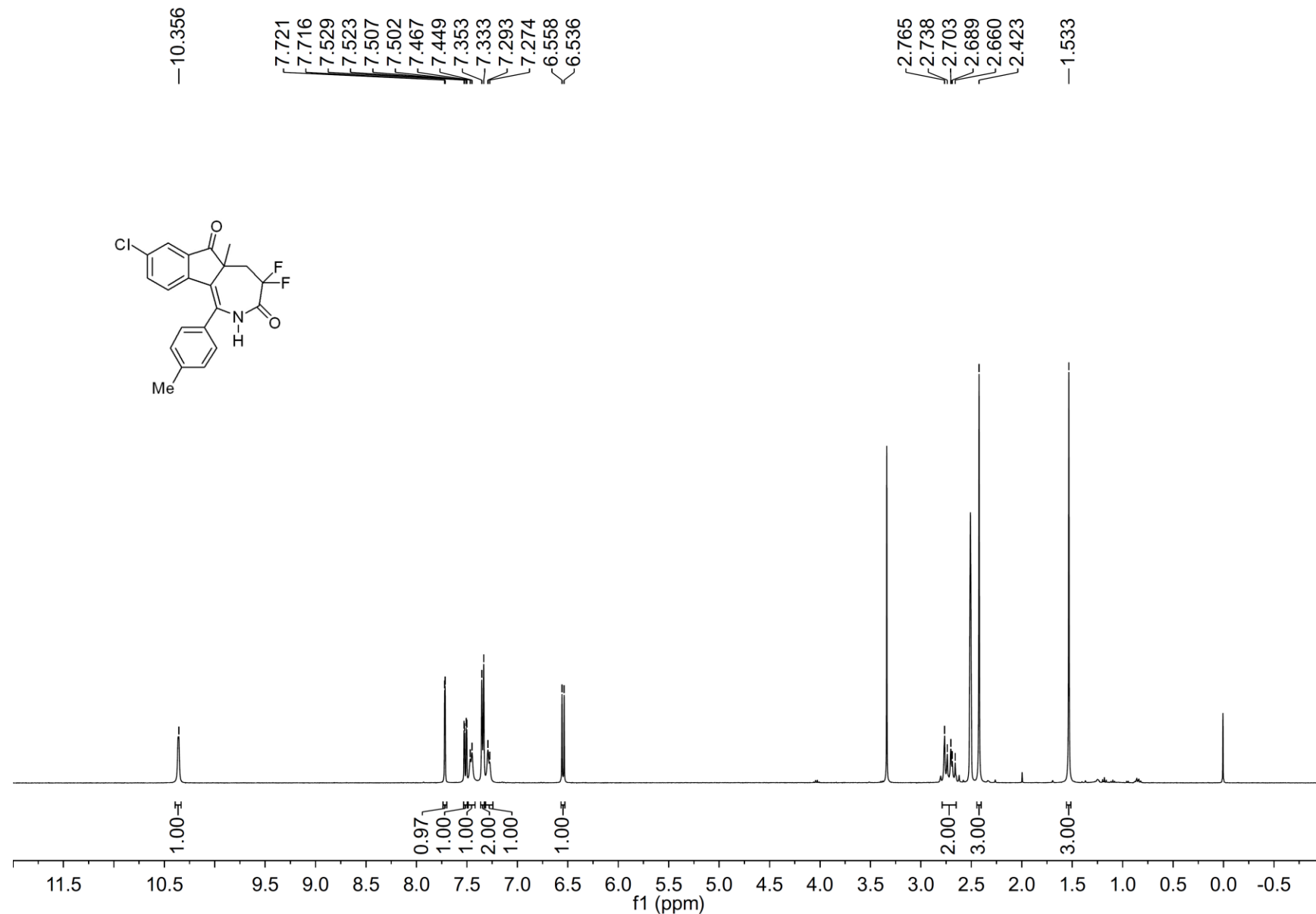


¹H NMR Spectrum of Compound 3m

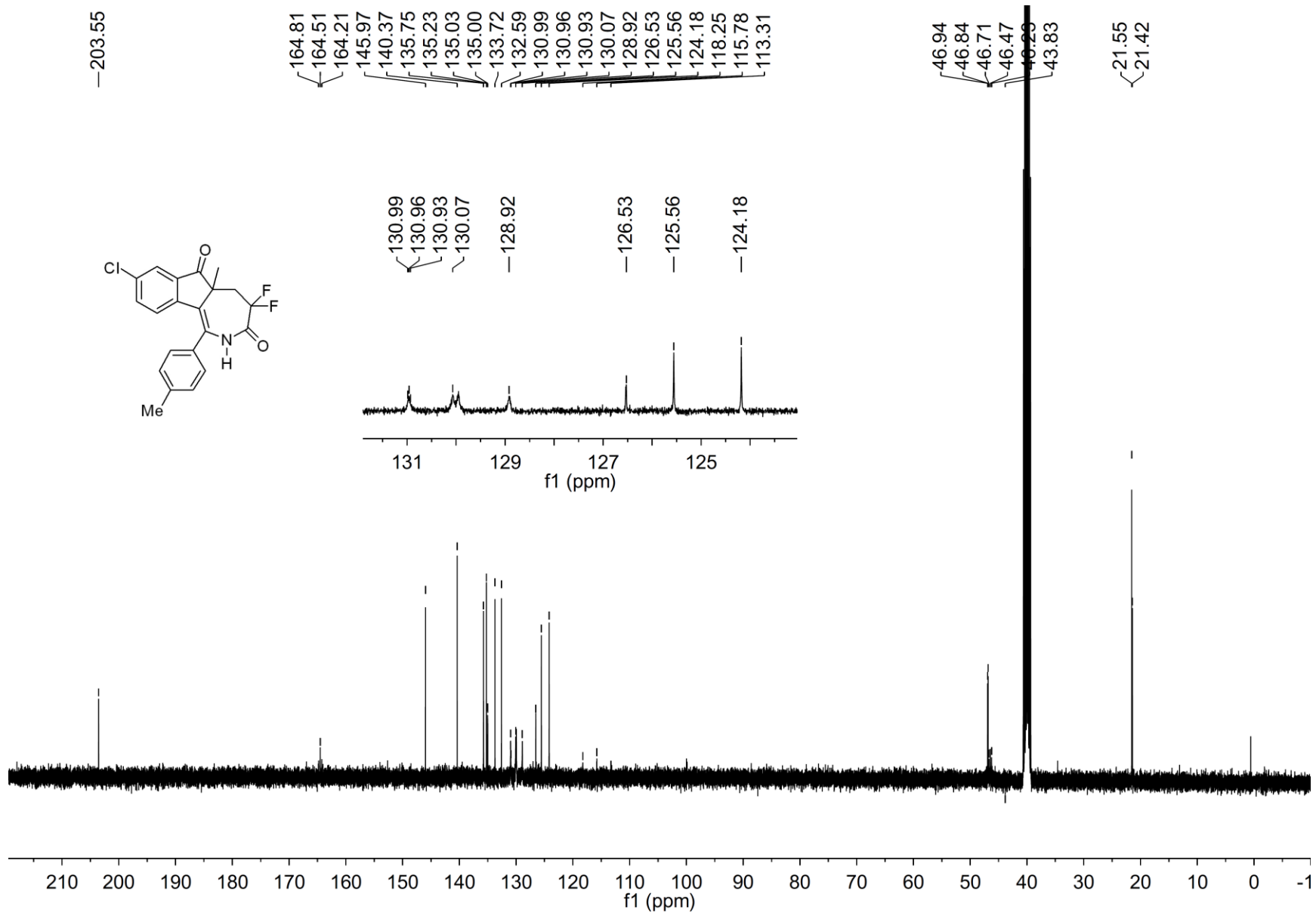




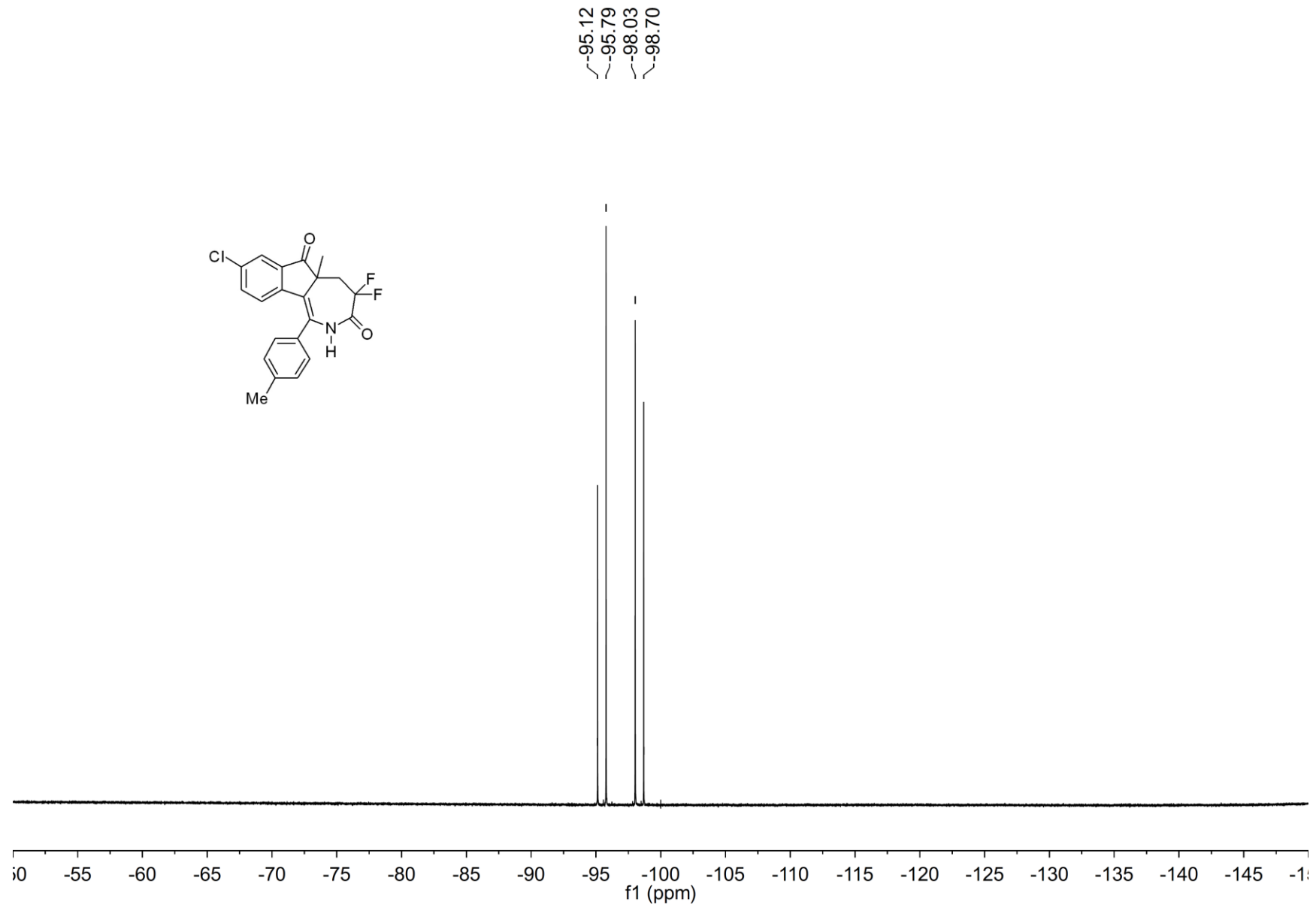
^{19}F NMR Spectrum of Compound 3m



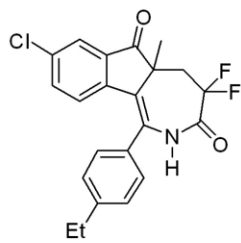
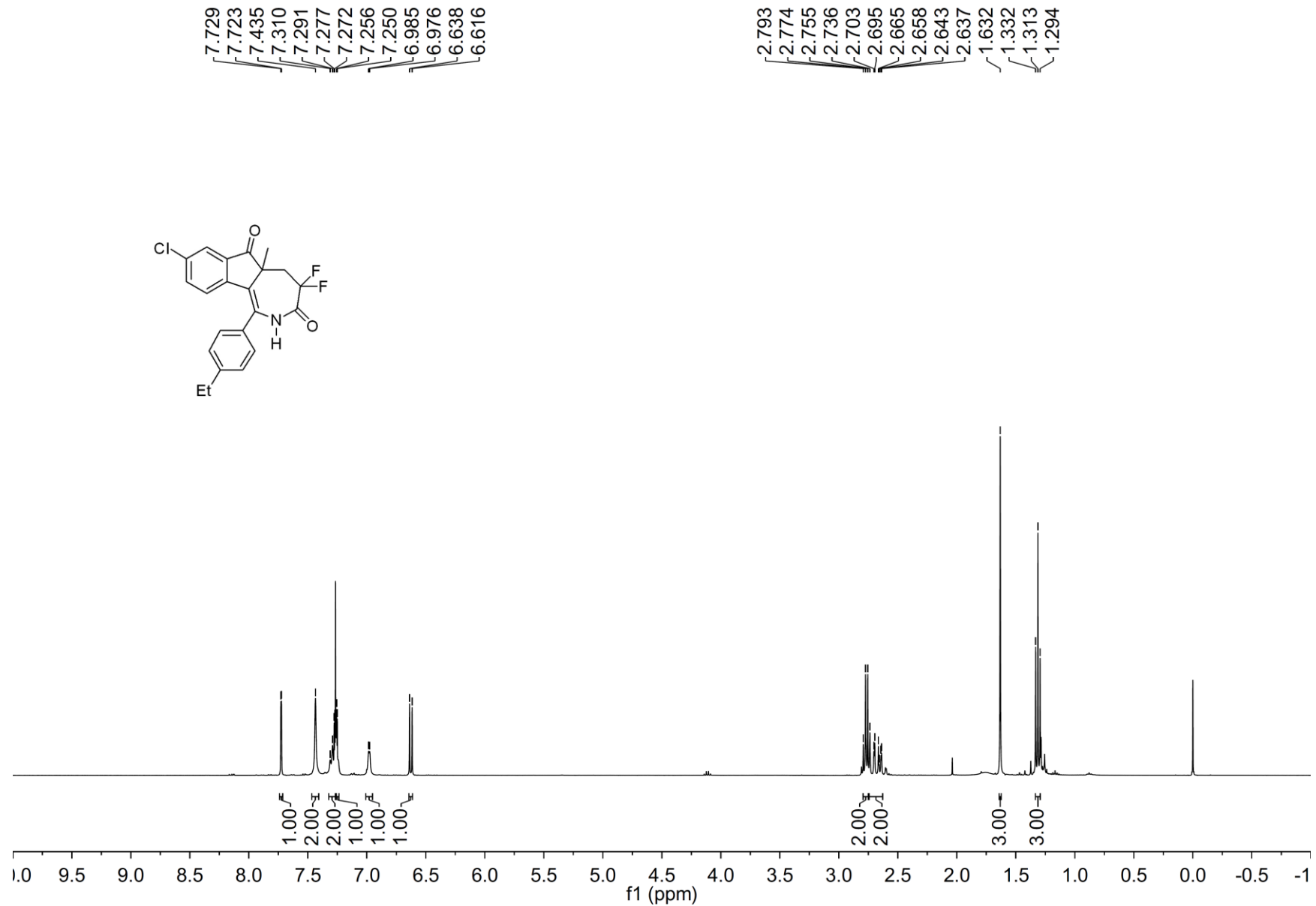
¹H NMR Spectrum of Compound 3n



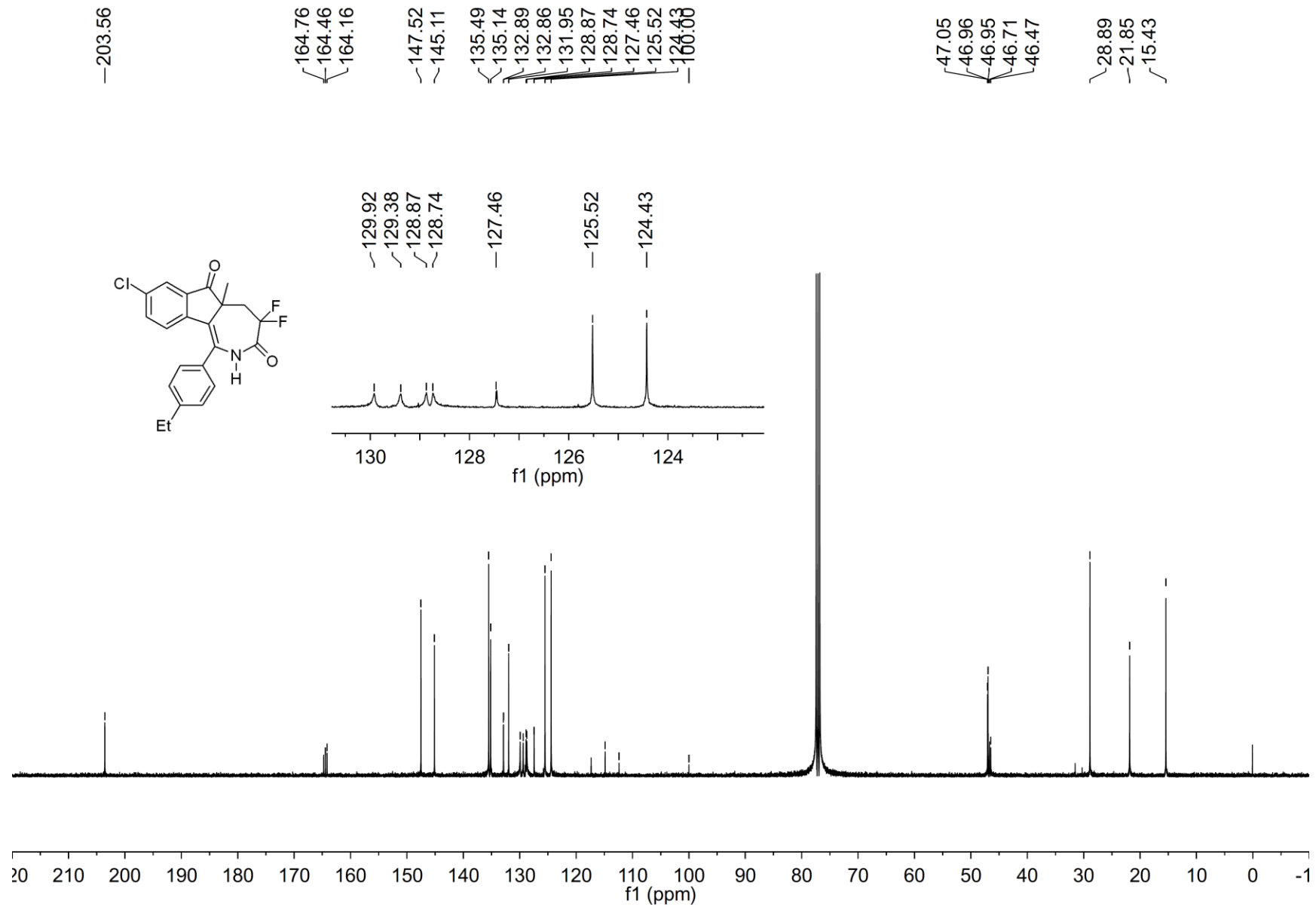
¹³C NMR Spectrum of Compound 3n

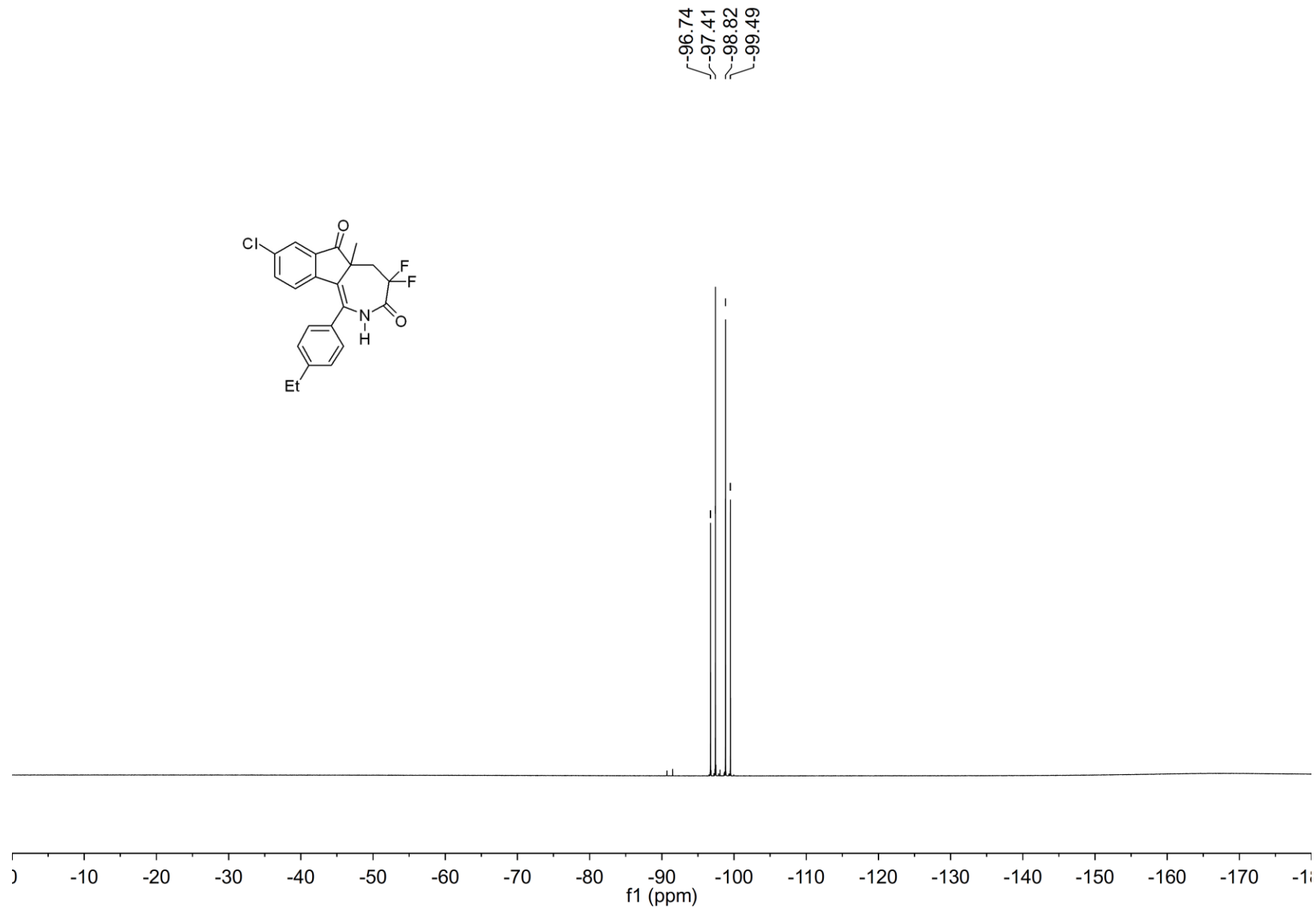
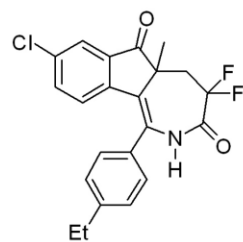


^{19}F NMR Spectrum of Compound 3n

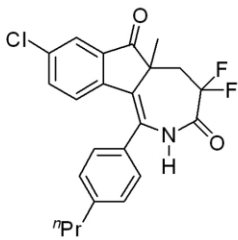
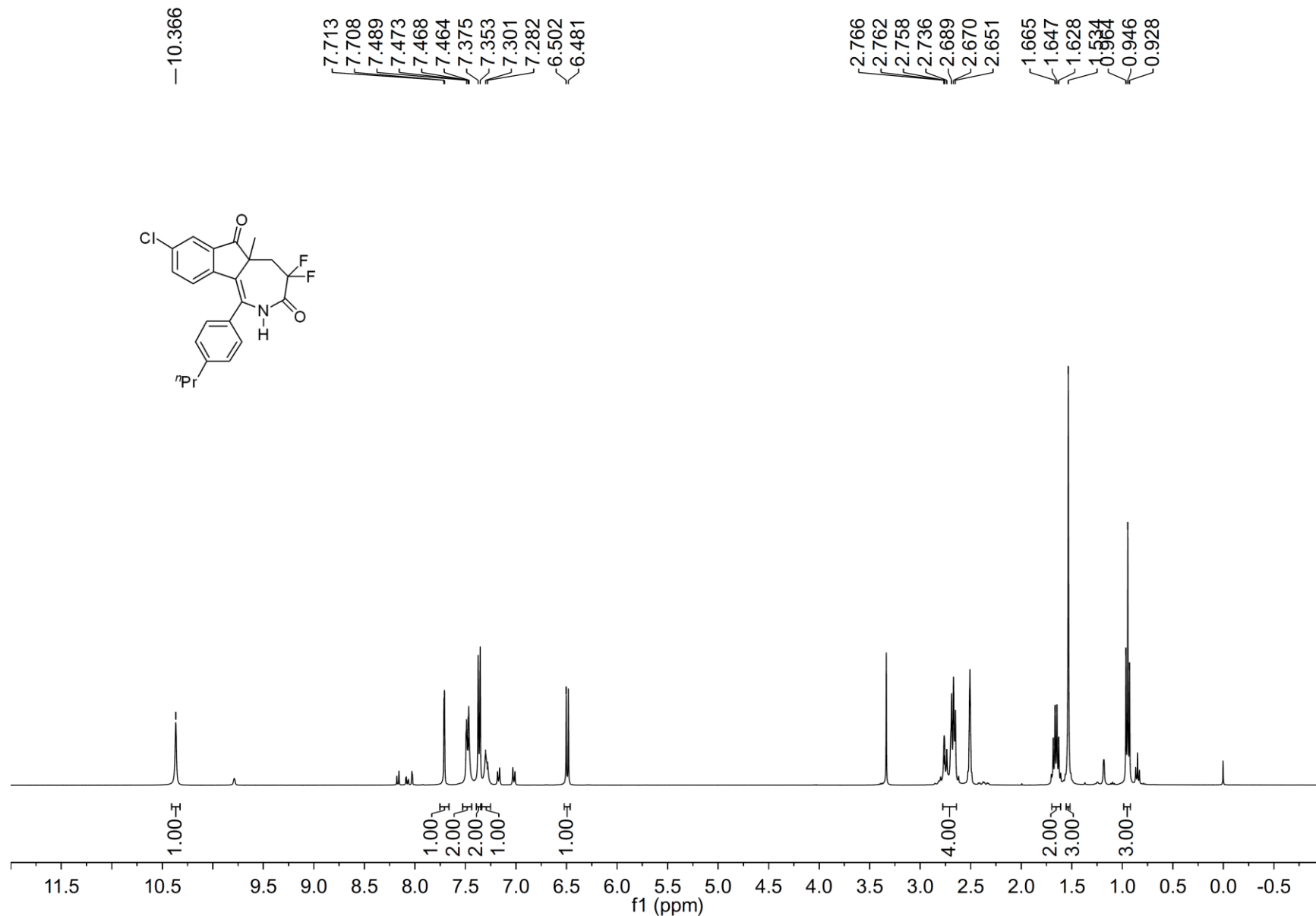


¹H NMR Spectrum of Compound 30

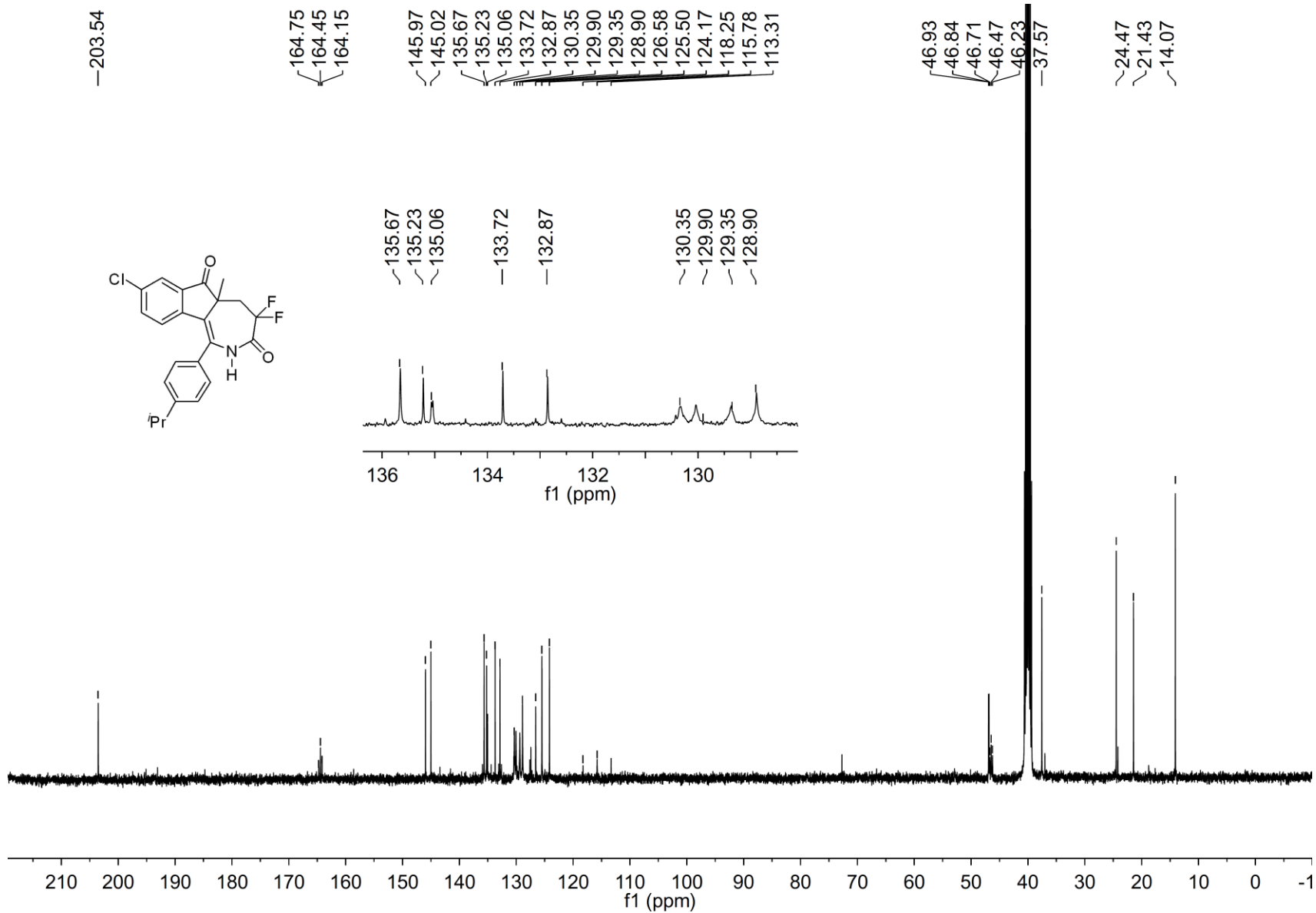




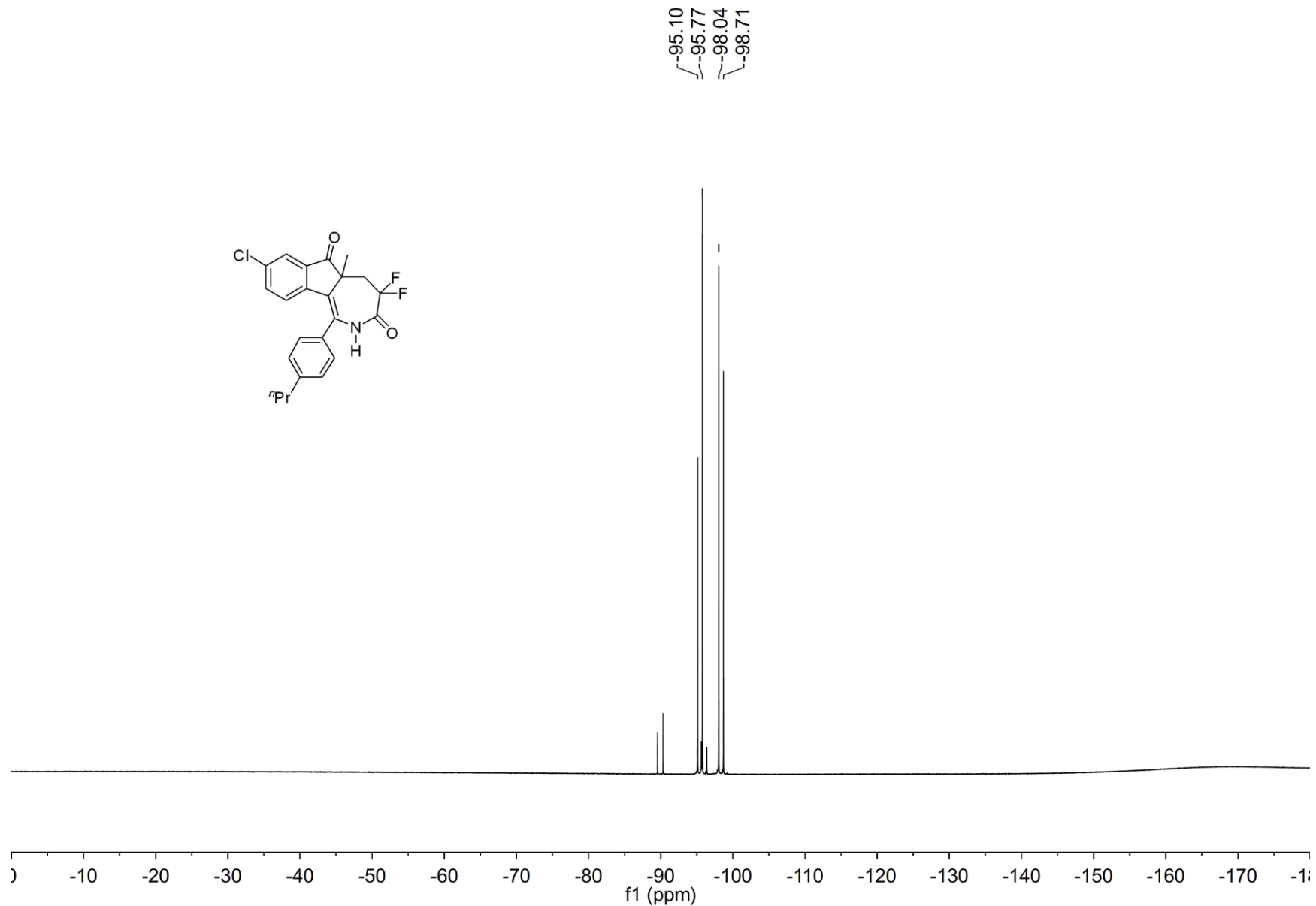
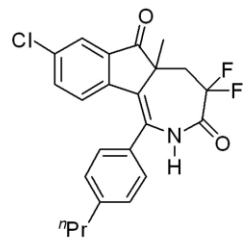
^{19}F NMR Spectrum of Compound 30



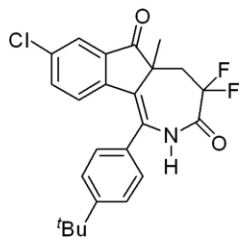
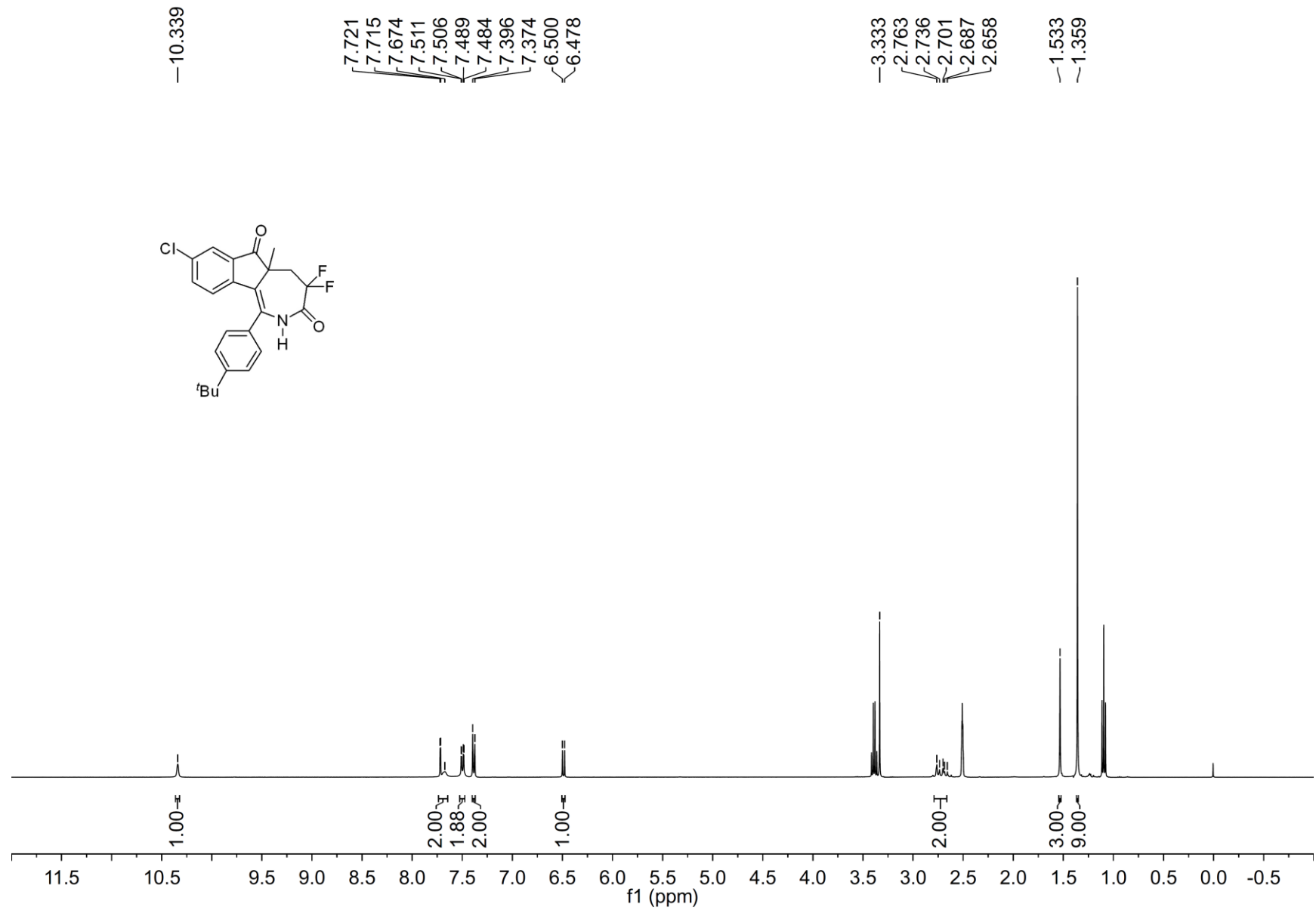
¹H NMR Spectrum of Compound 3p



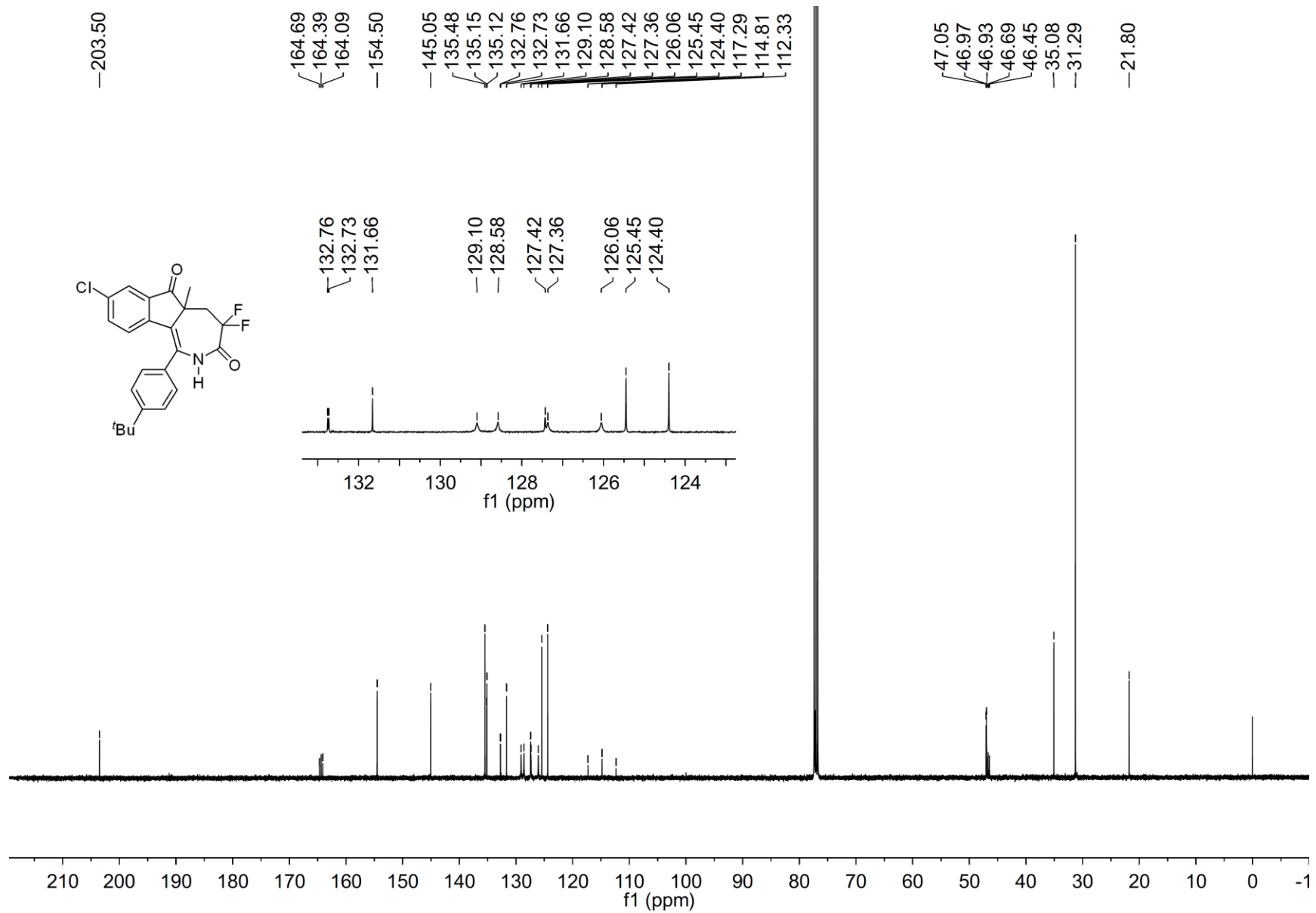
¹³C NMR Spectrum of Compound 3p



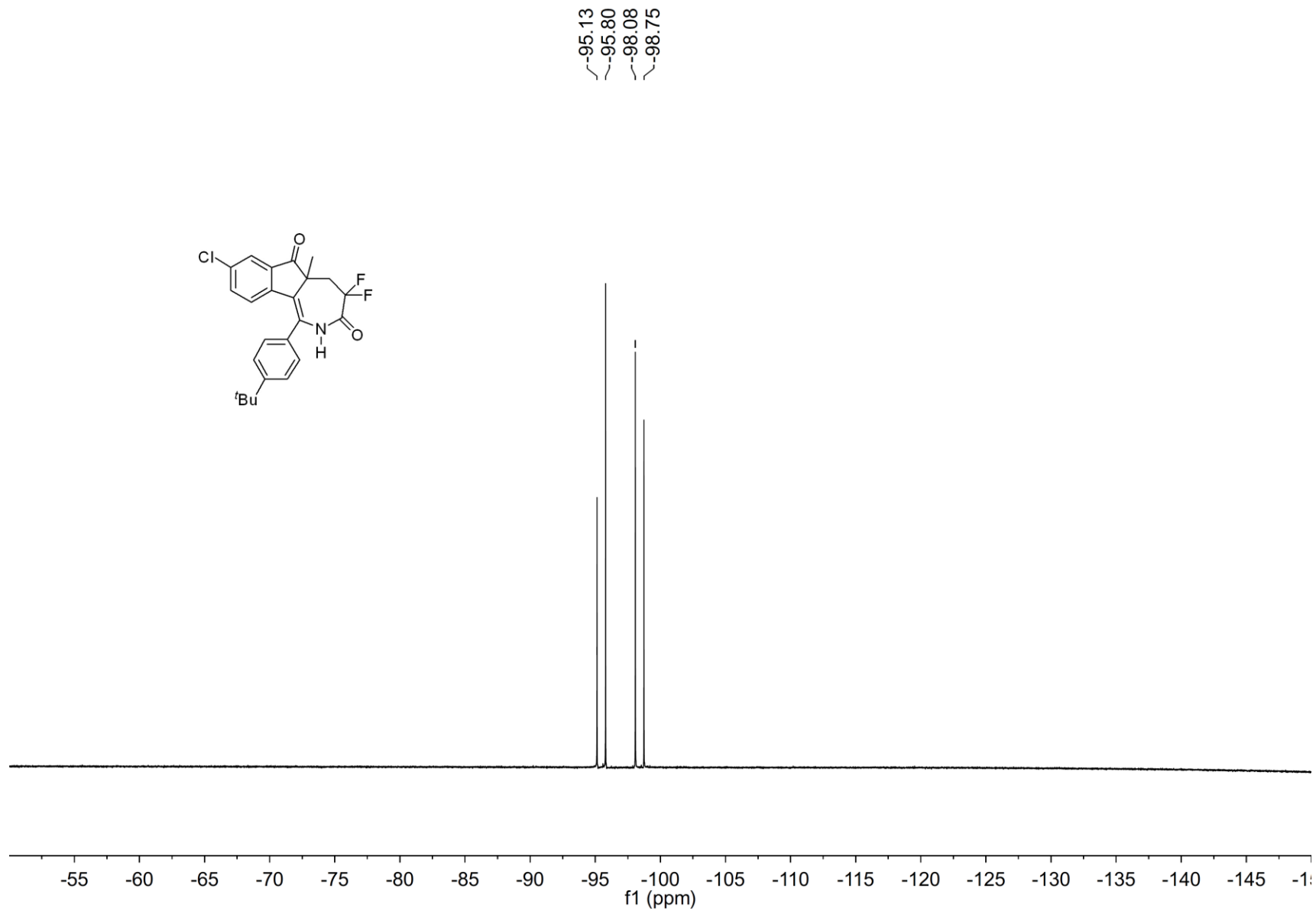
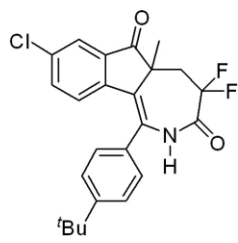
^{19}F NMR Spectrum of Compound 3p



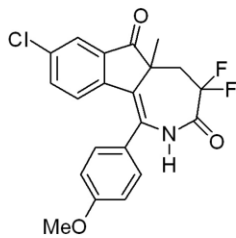
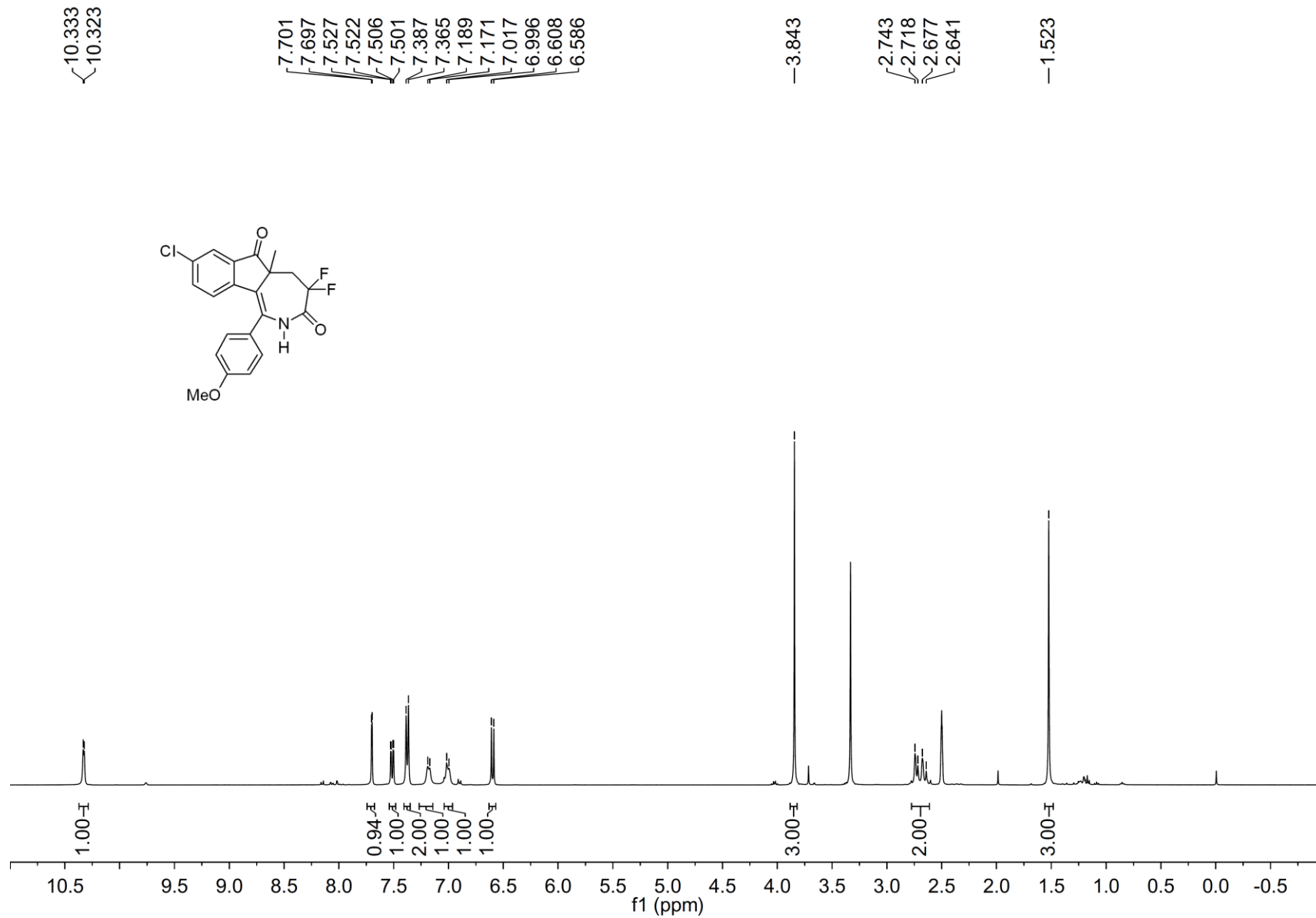
¹H NMR Spectrum of Compound 3q



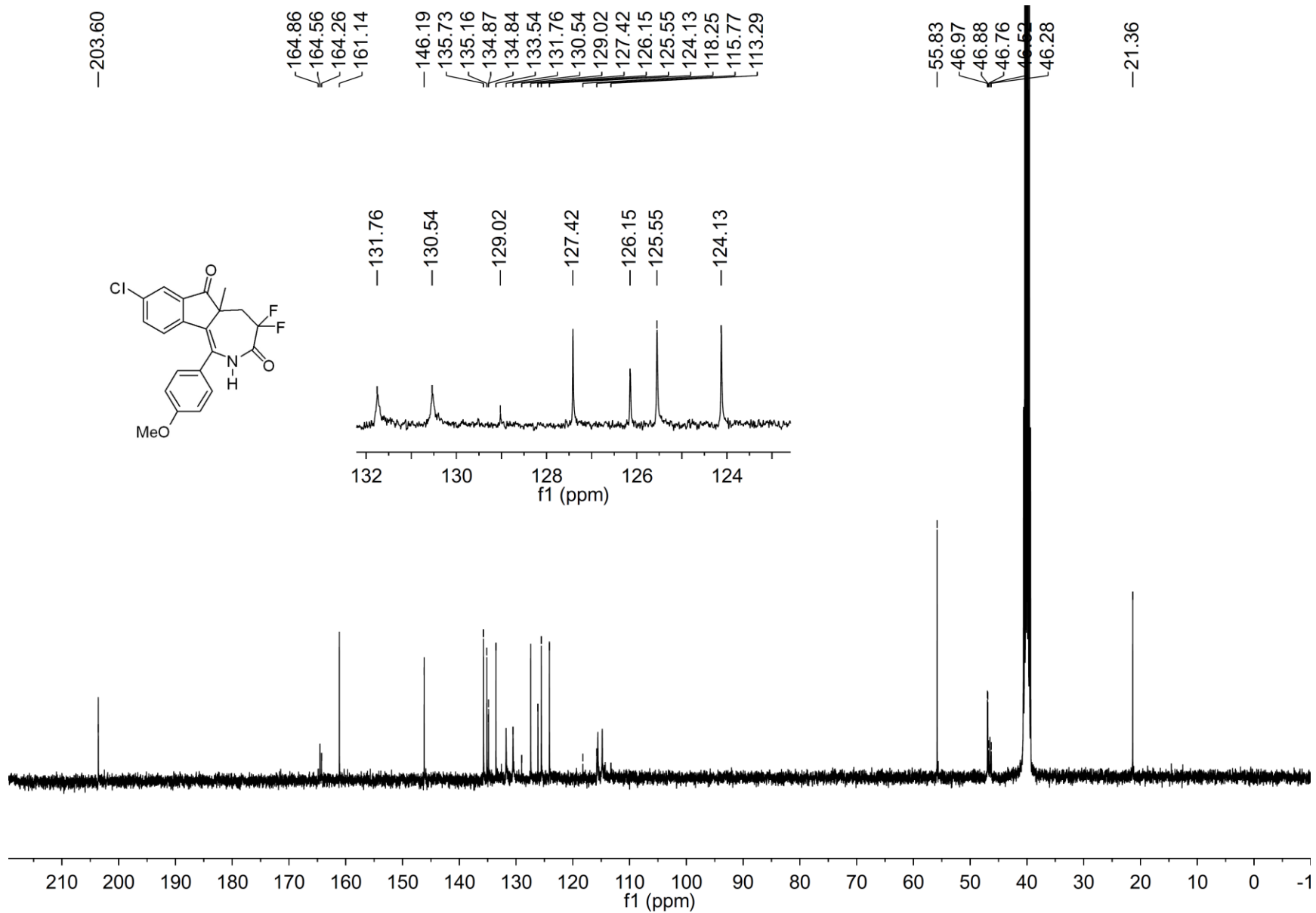
¹³C NMR Spectrum of Compound 3q

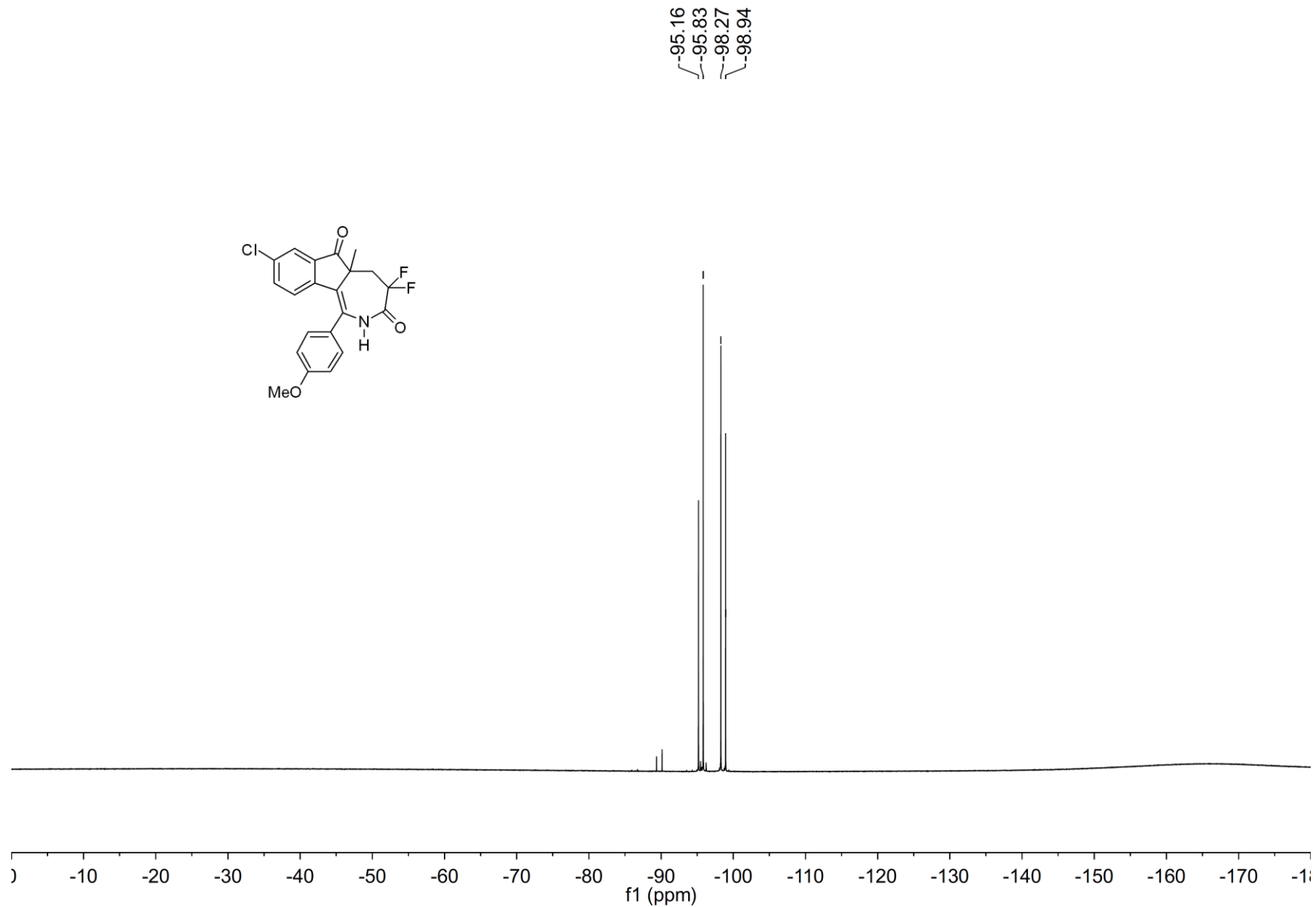
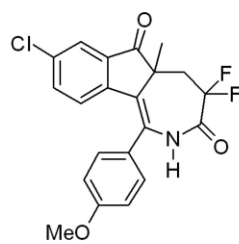


^{19}F NMR Spectrum of Compound 3q

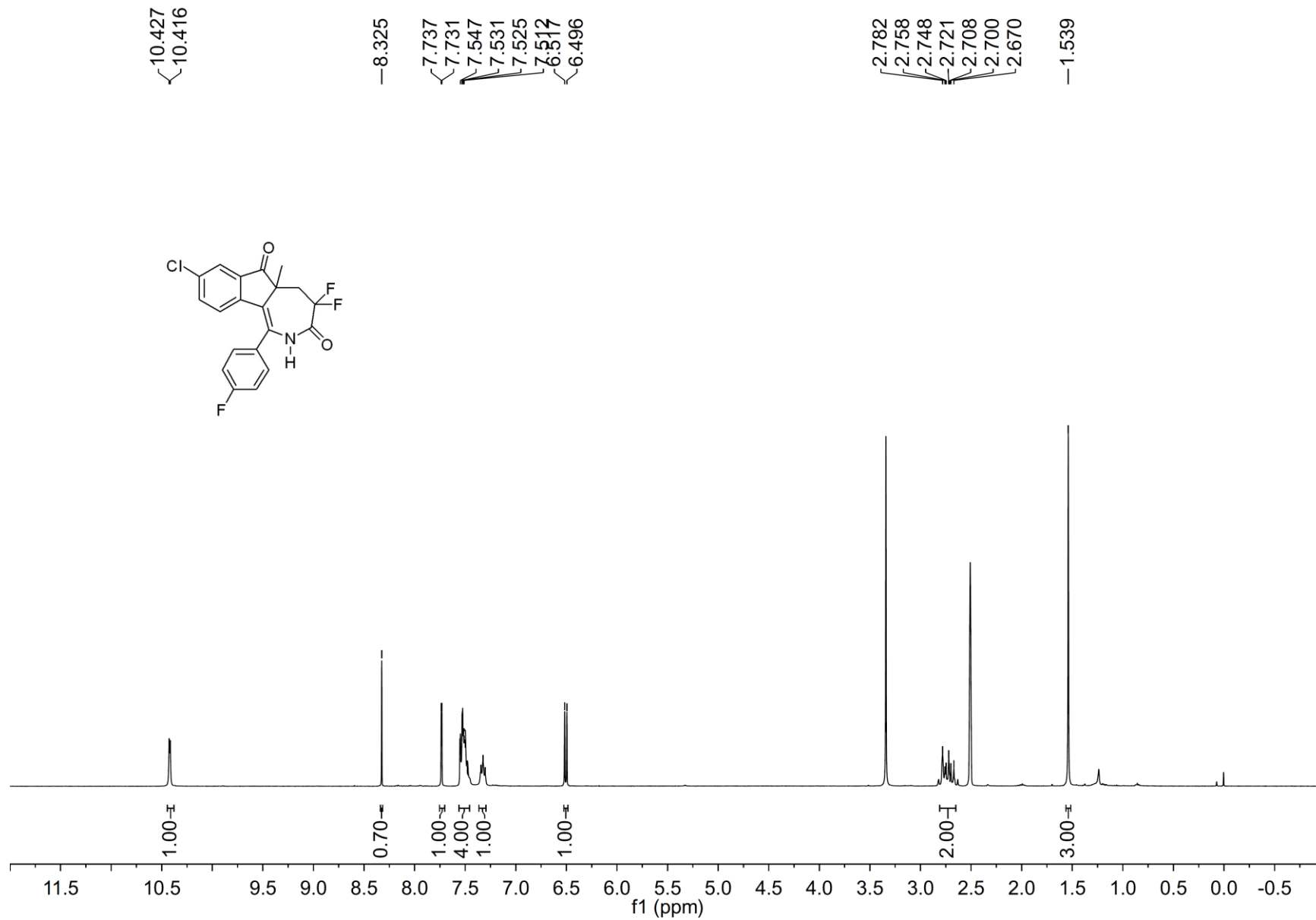


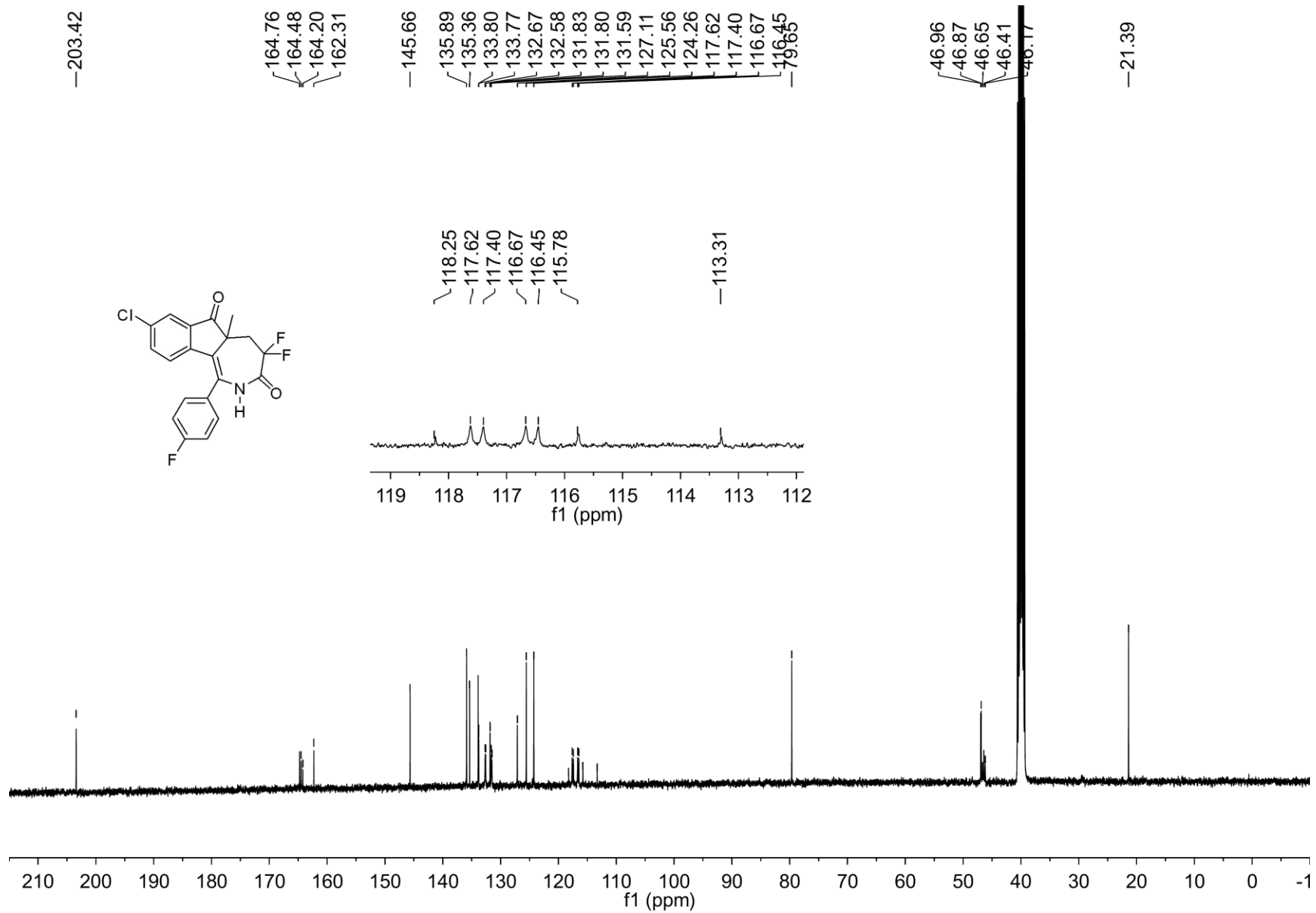
¹H NMR Spectrum of Compound 3r



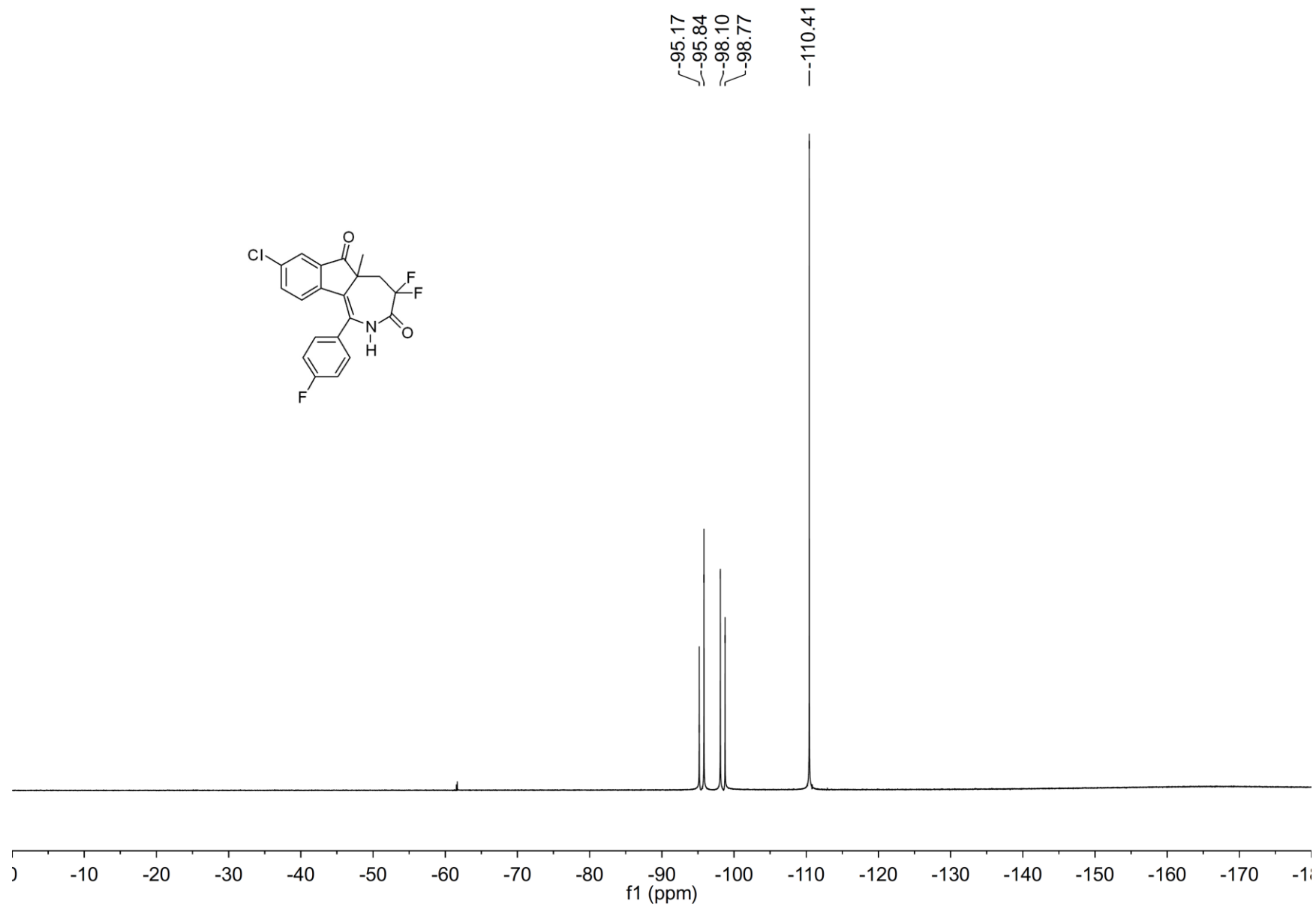
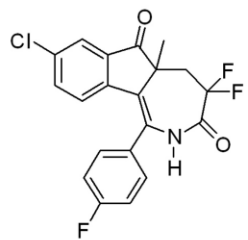


^{19}F NMR Spectrum of Compound 3r

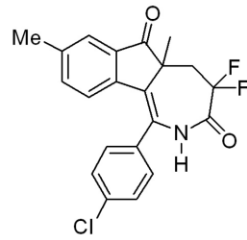
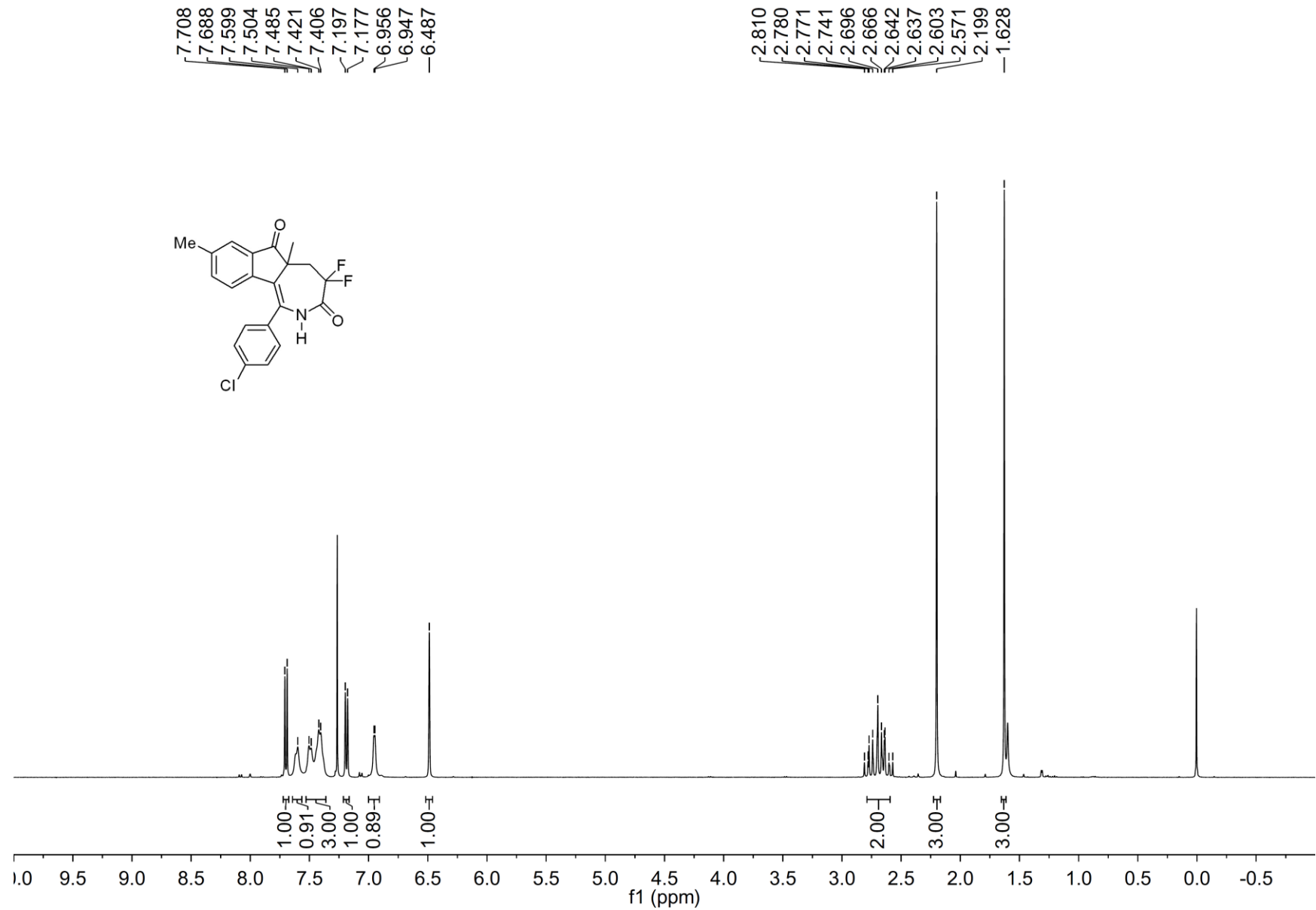




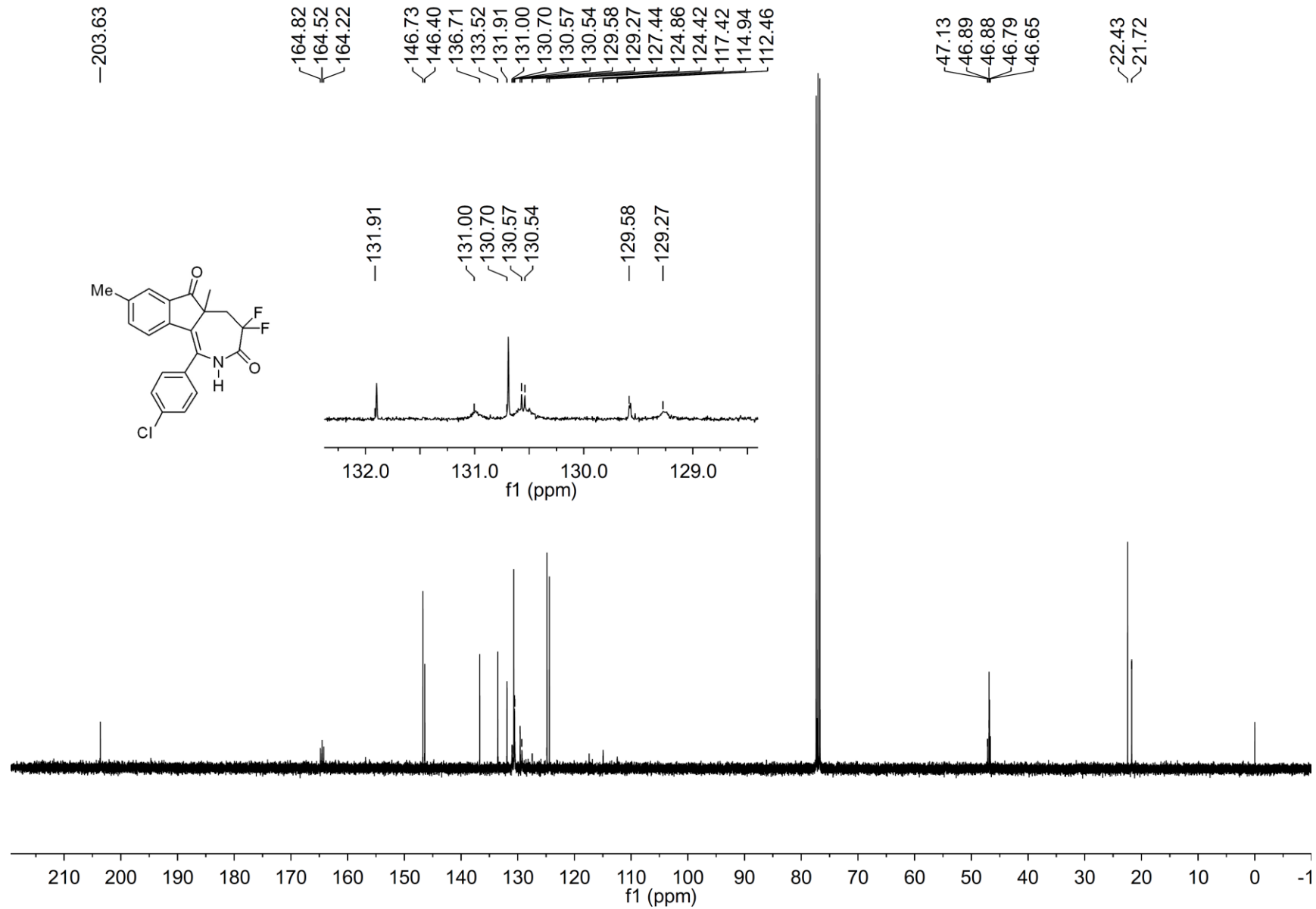
¹³C NMR Spectrum of Compound 3s

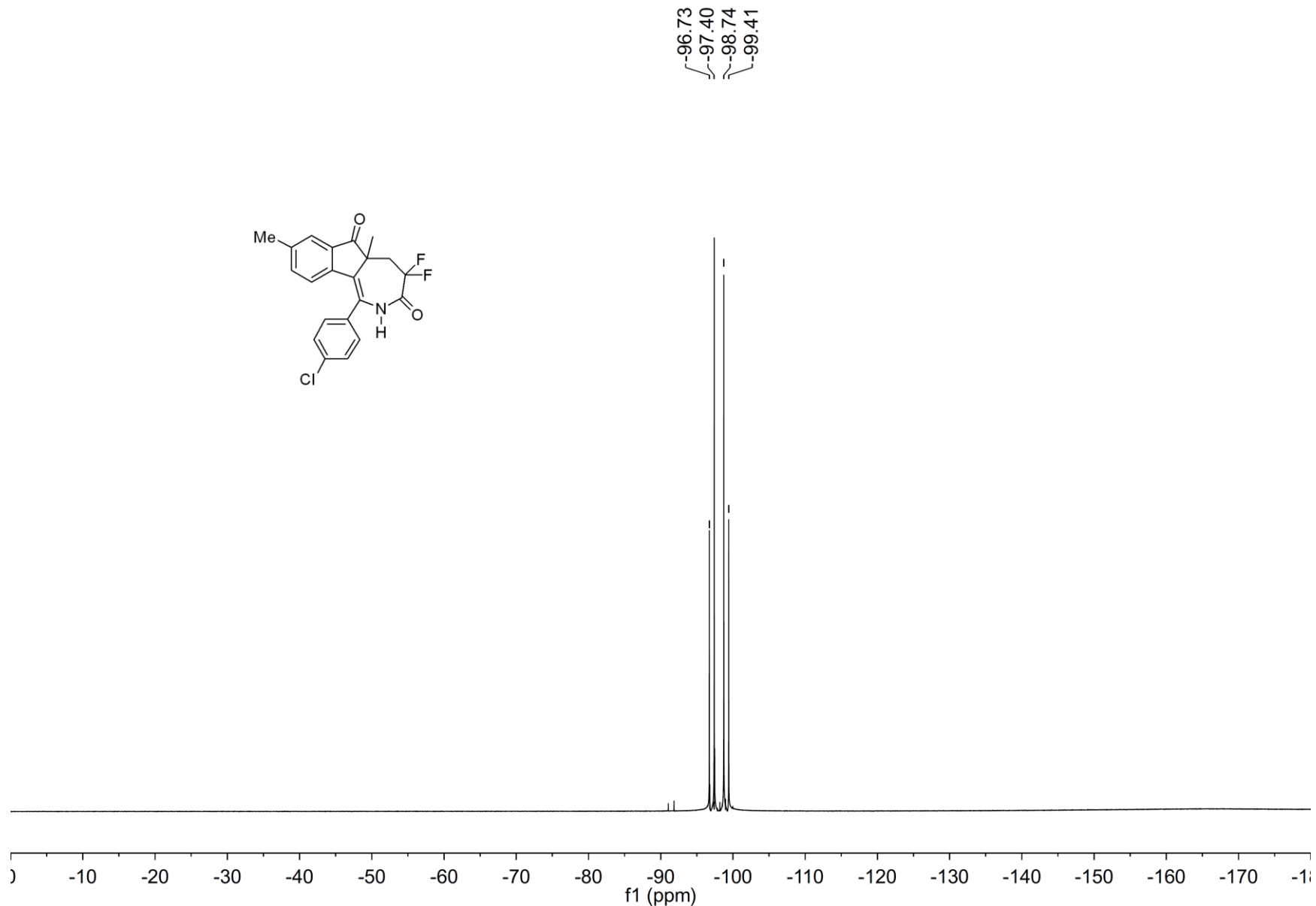
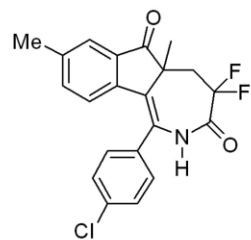


^{19}F NMR Spectrum of Compound 3s

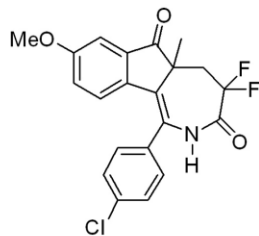
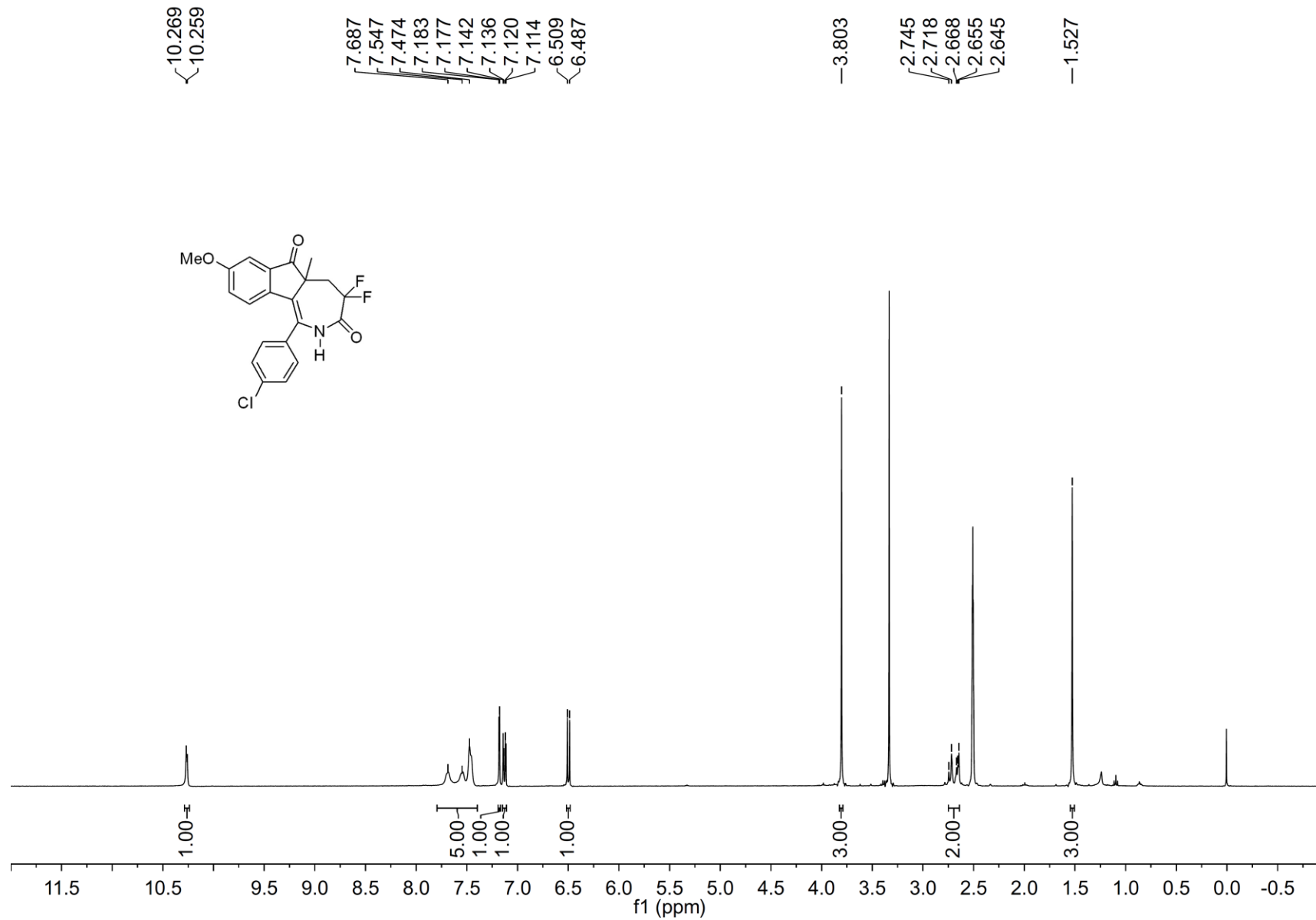


¹H NMR Spectrum of Compound 3t

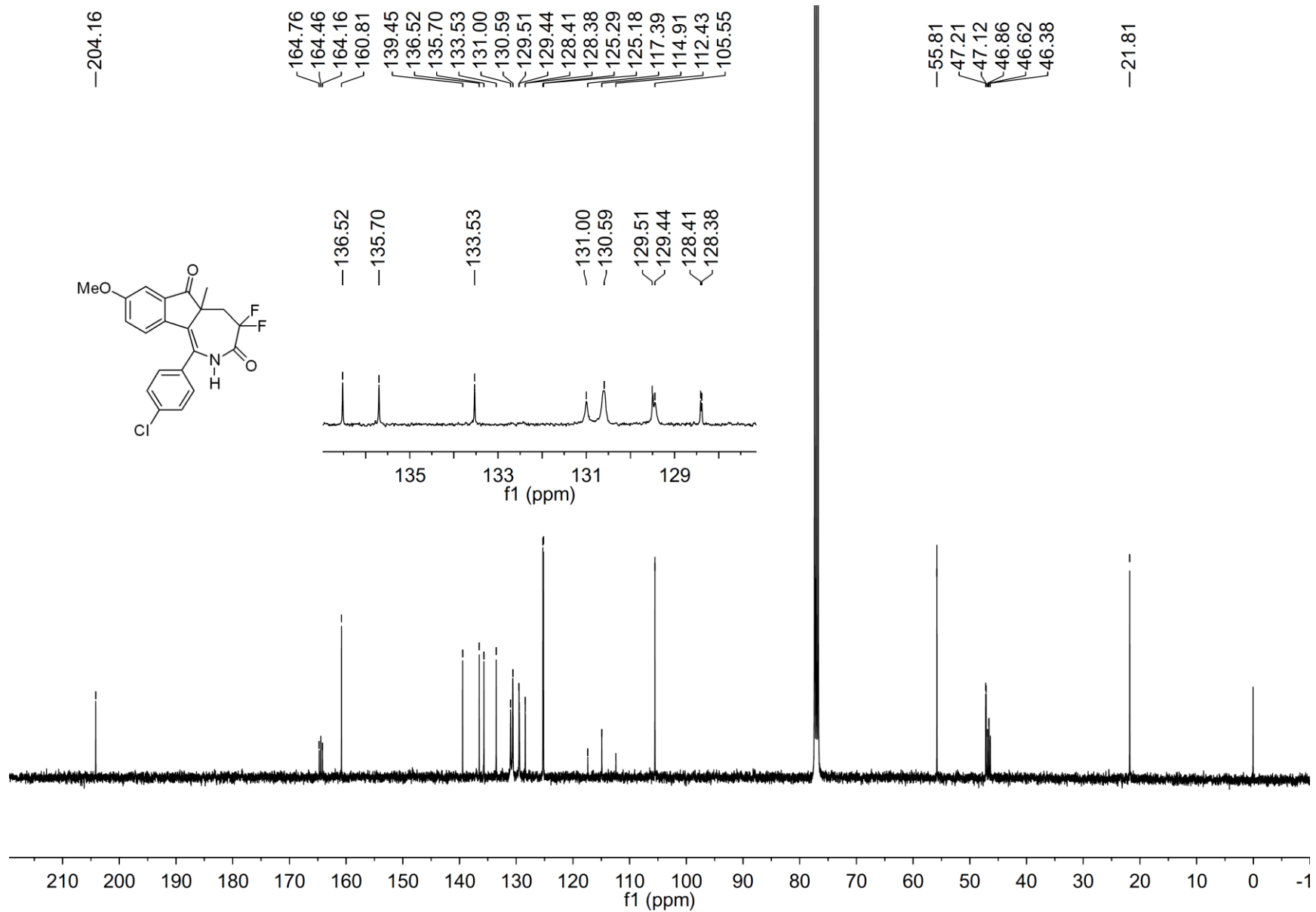


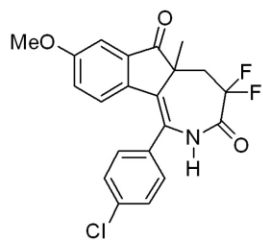


¹⁹F NMR Spectrum of Compound 3t

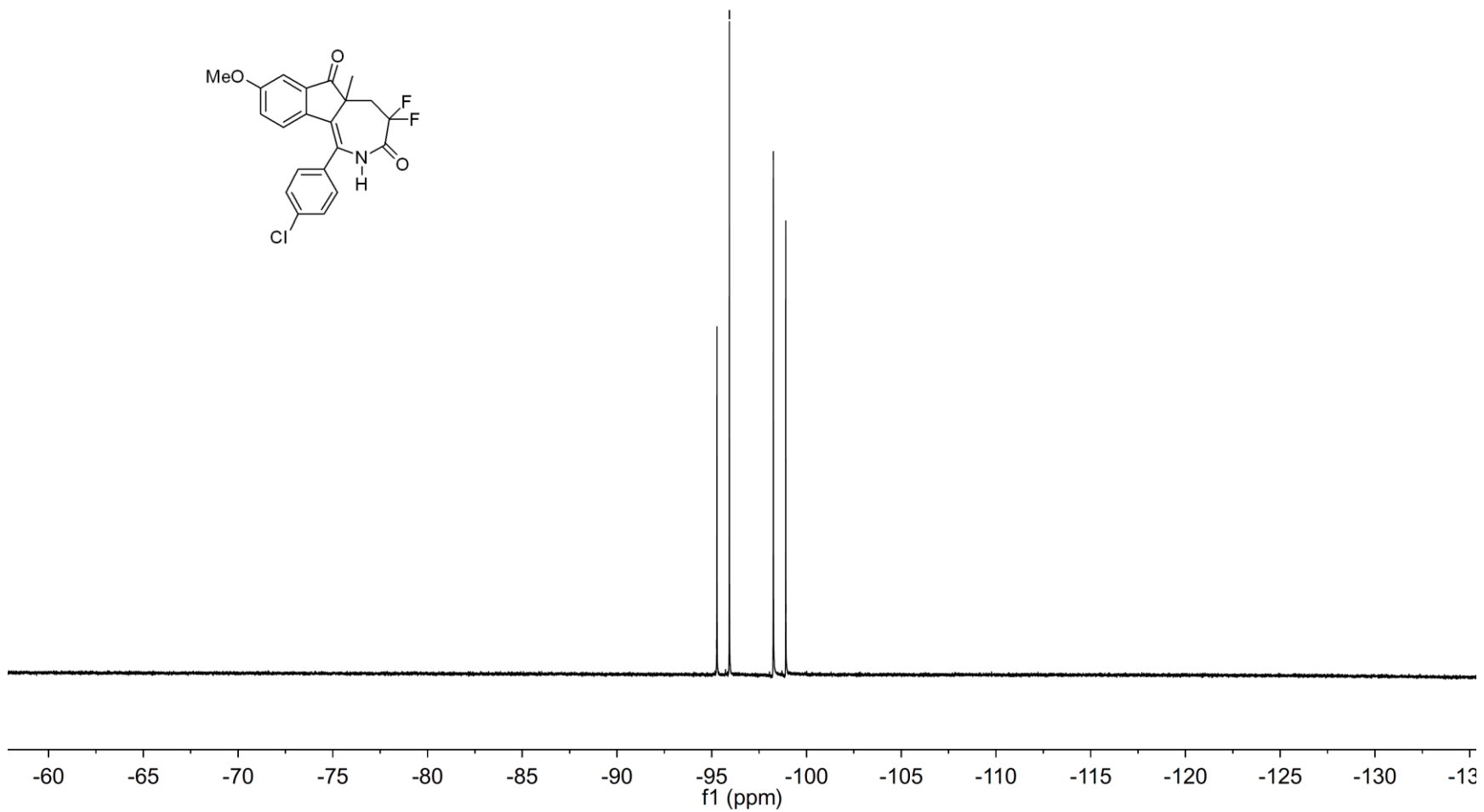


¹H NMR Spectrum of Compound 3u

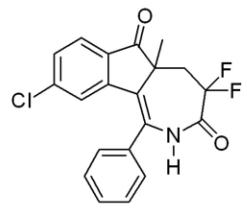
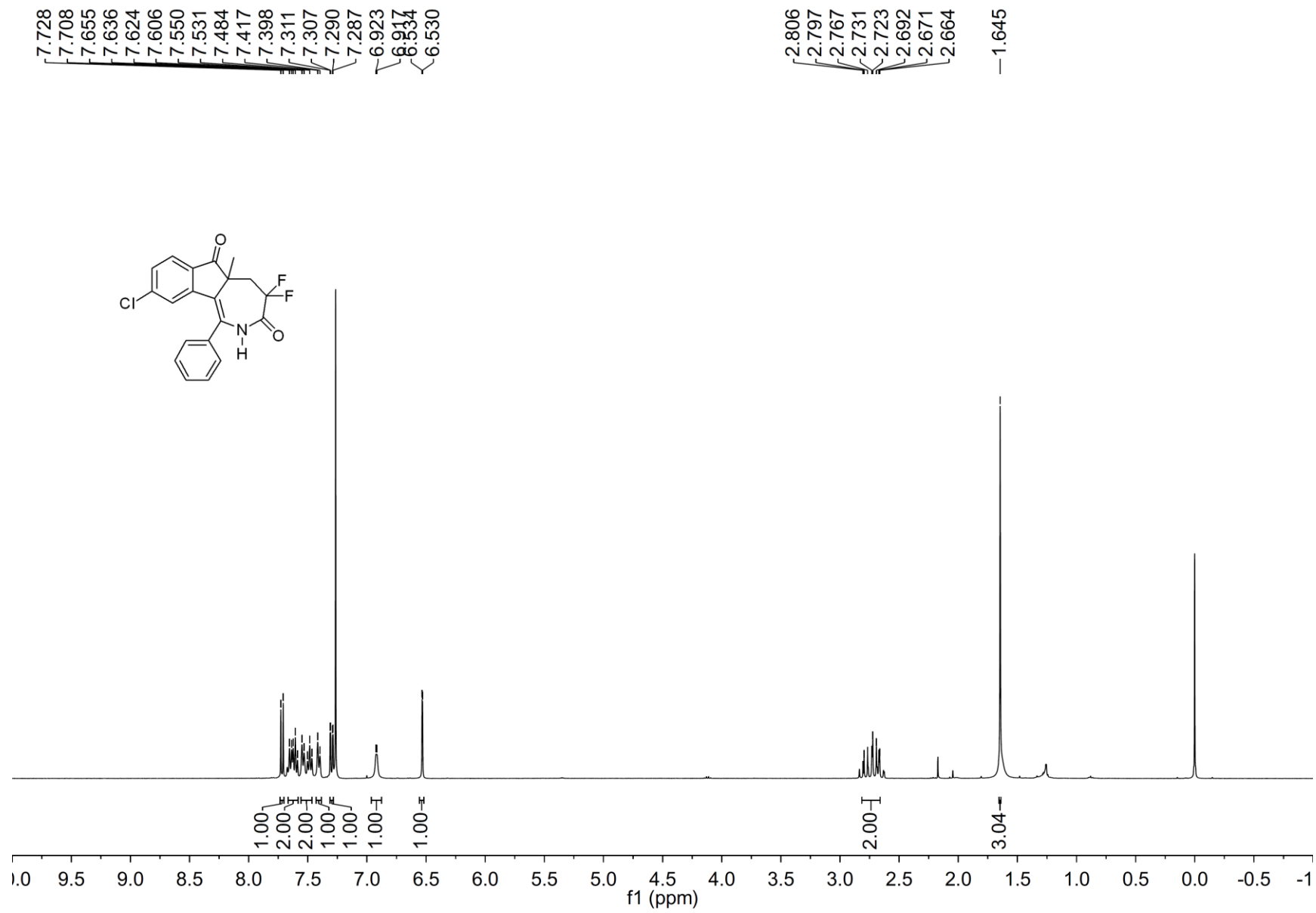




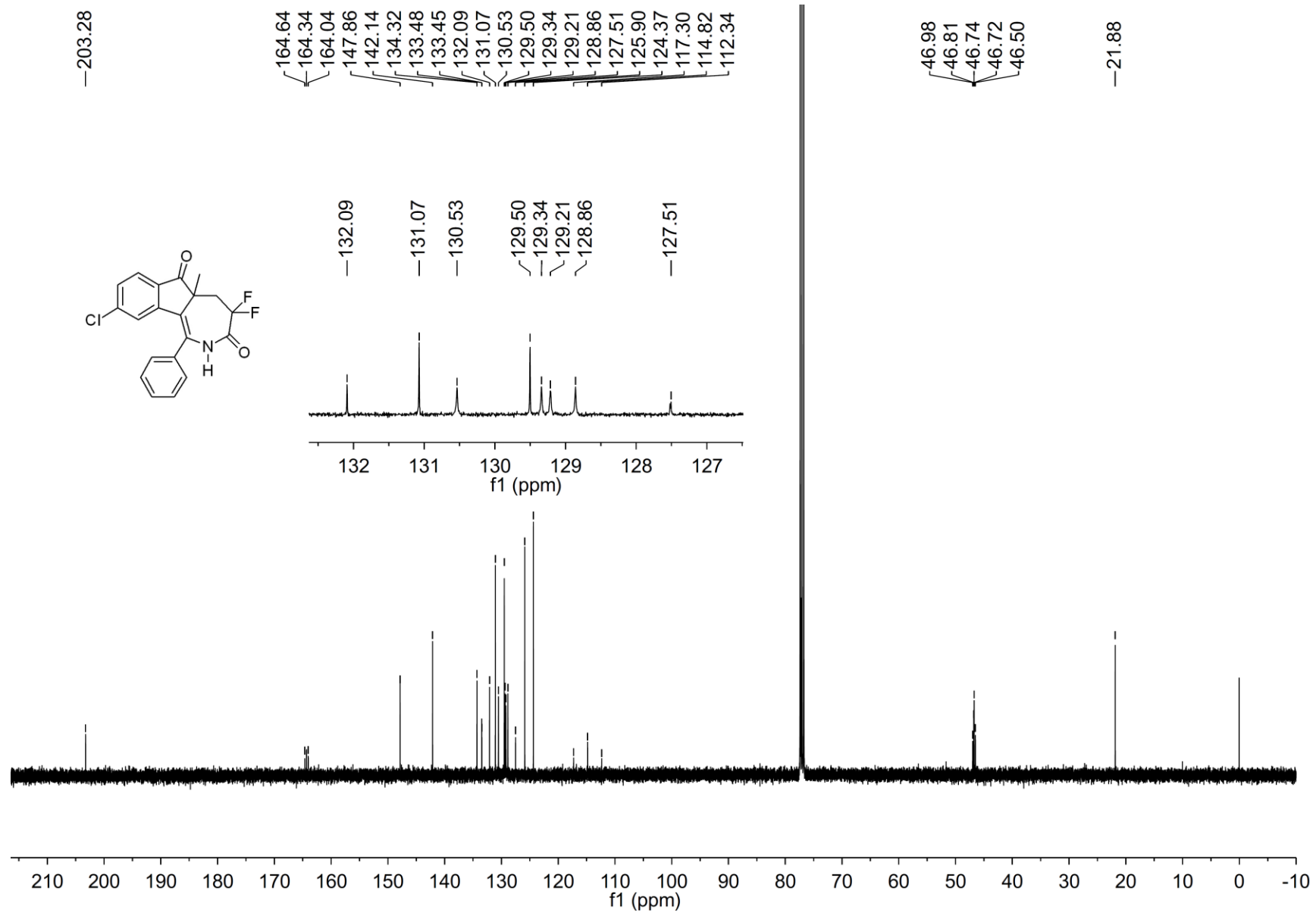
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~ -98.92

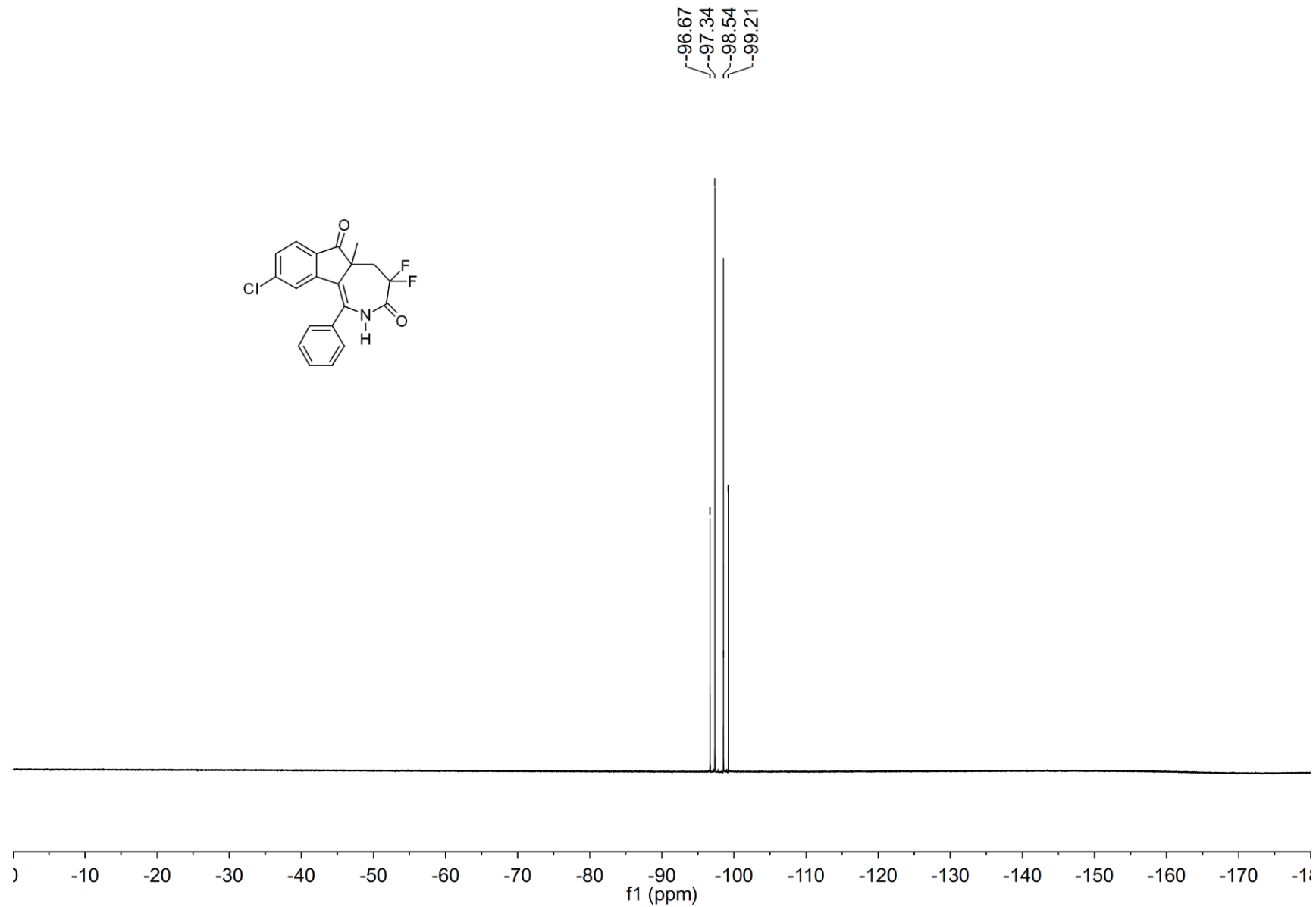
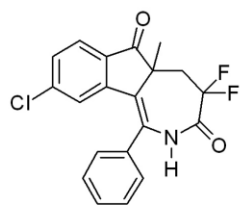


¹⁹F NMR Spectrum of Compound 3u

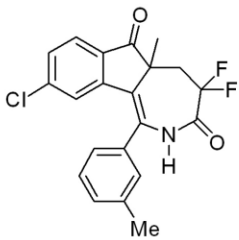
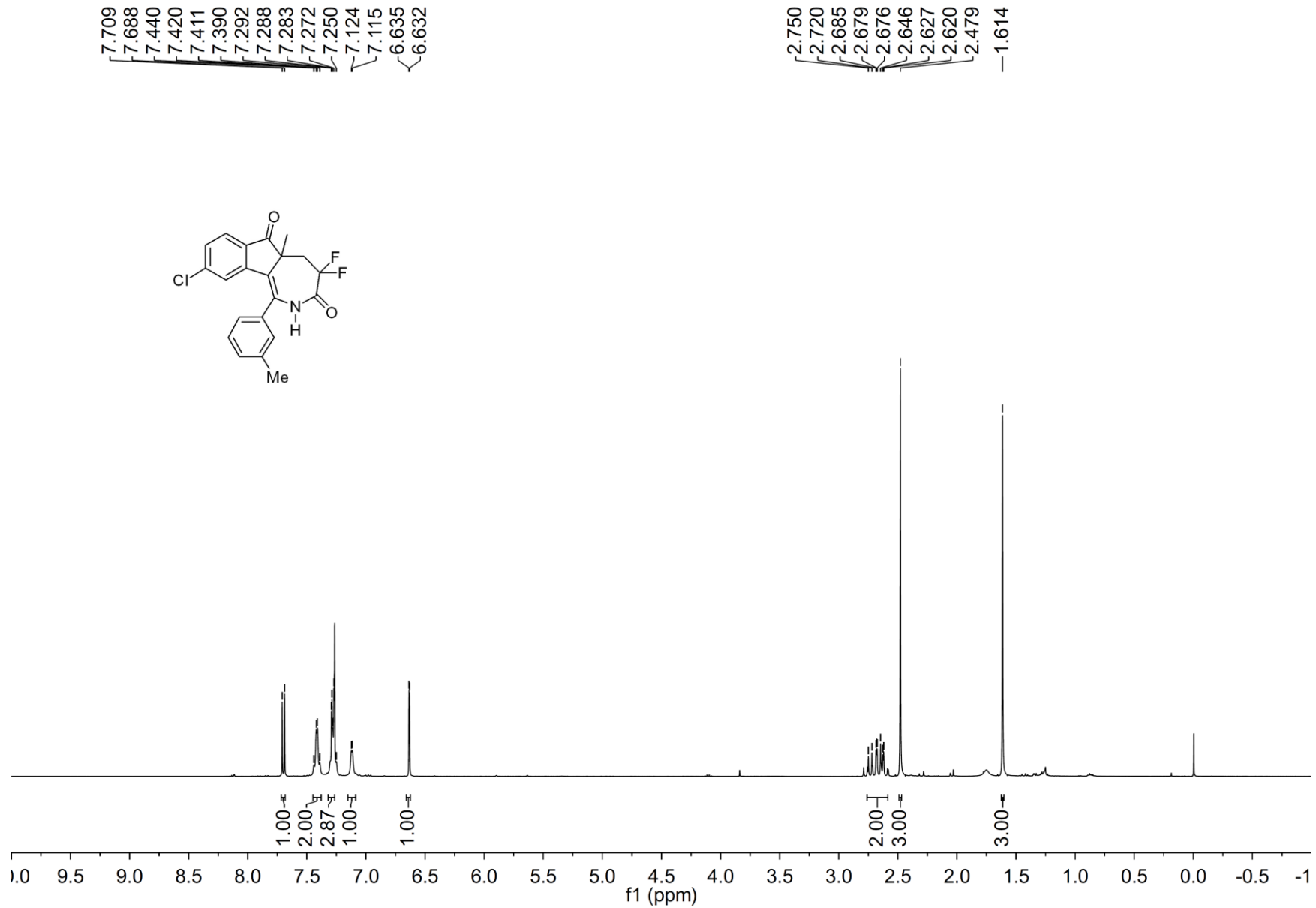


¹H NMR Spectrum of Compound 3v

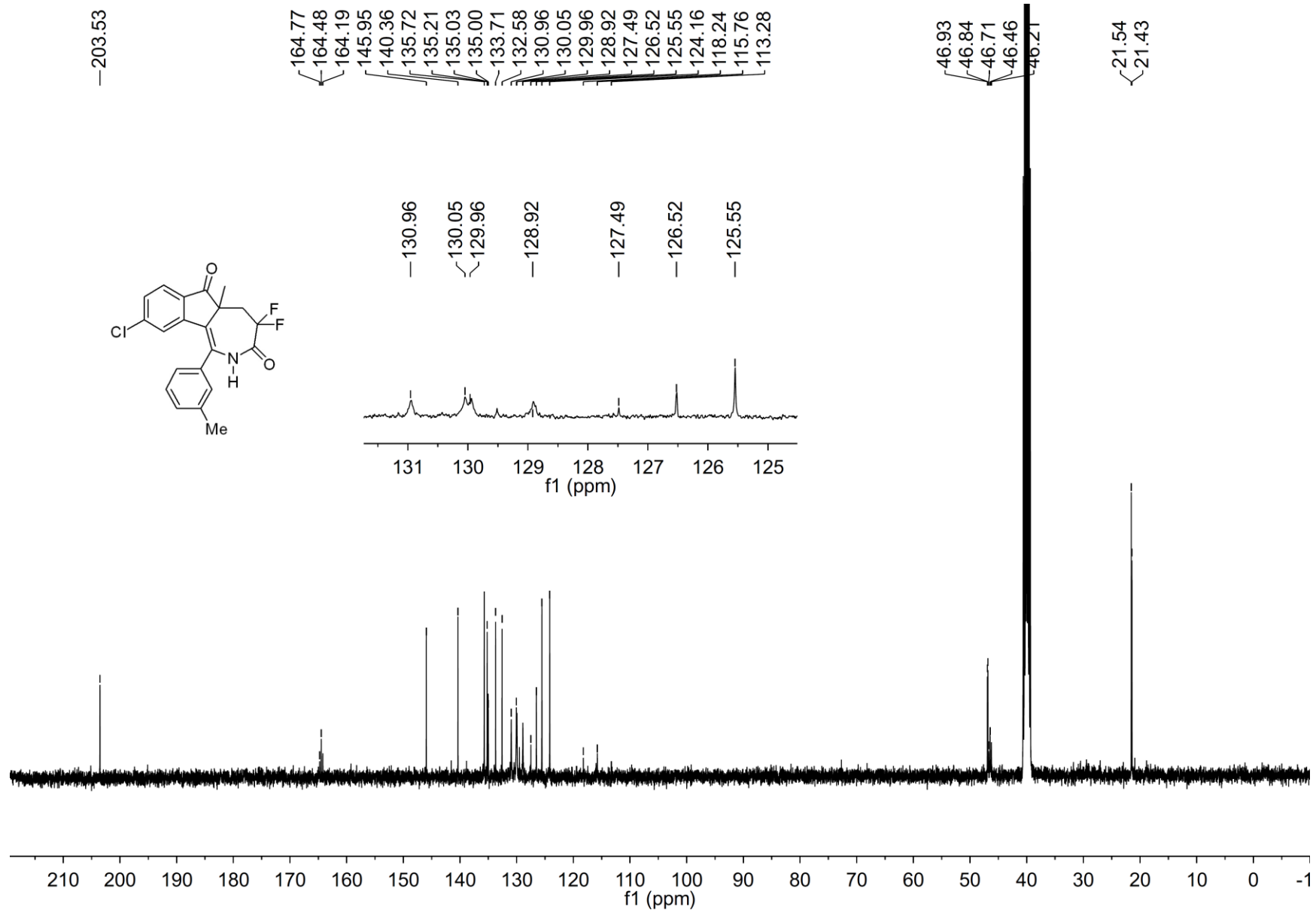


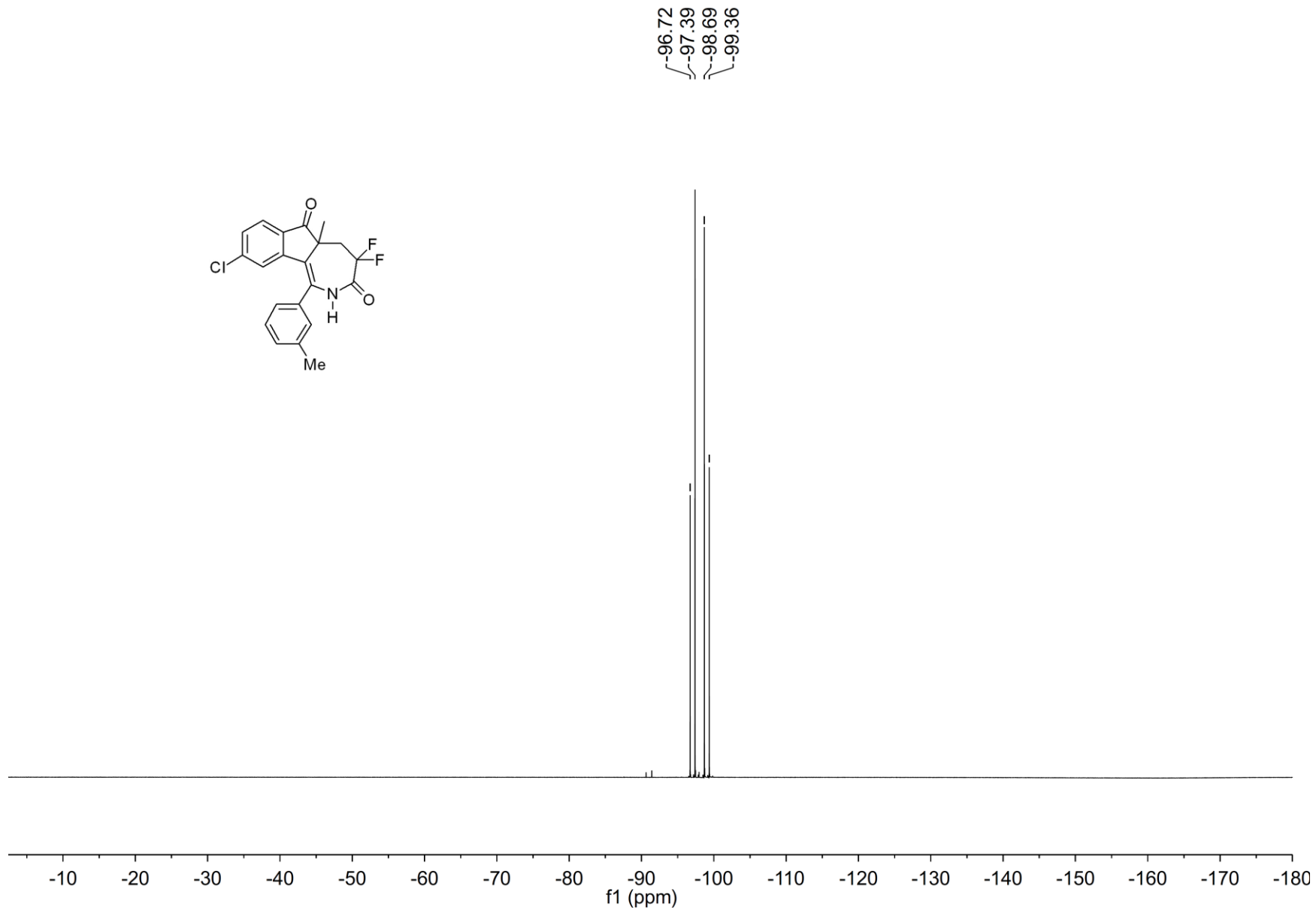
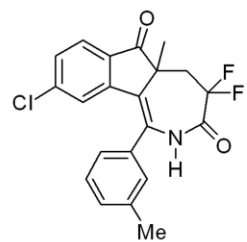


^{19}F NMR Spectrum of Compound 3v

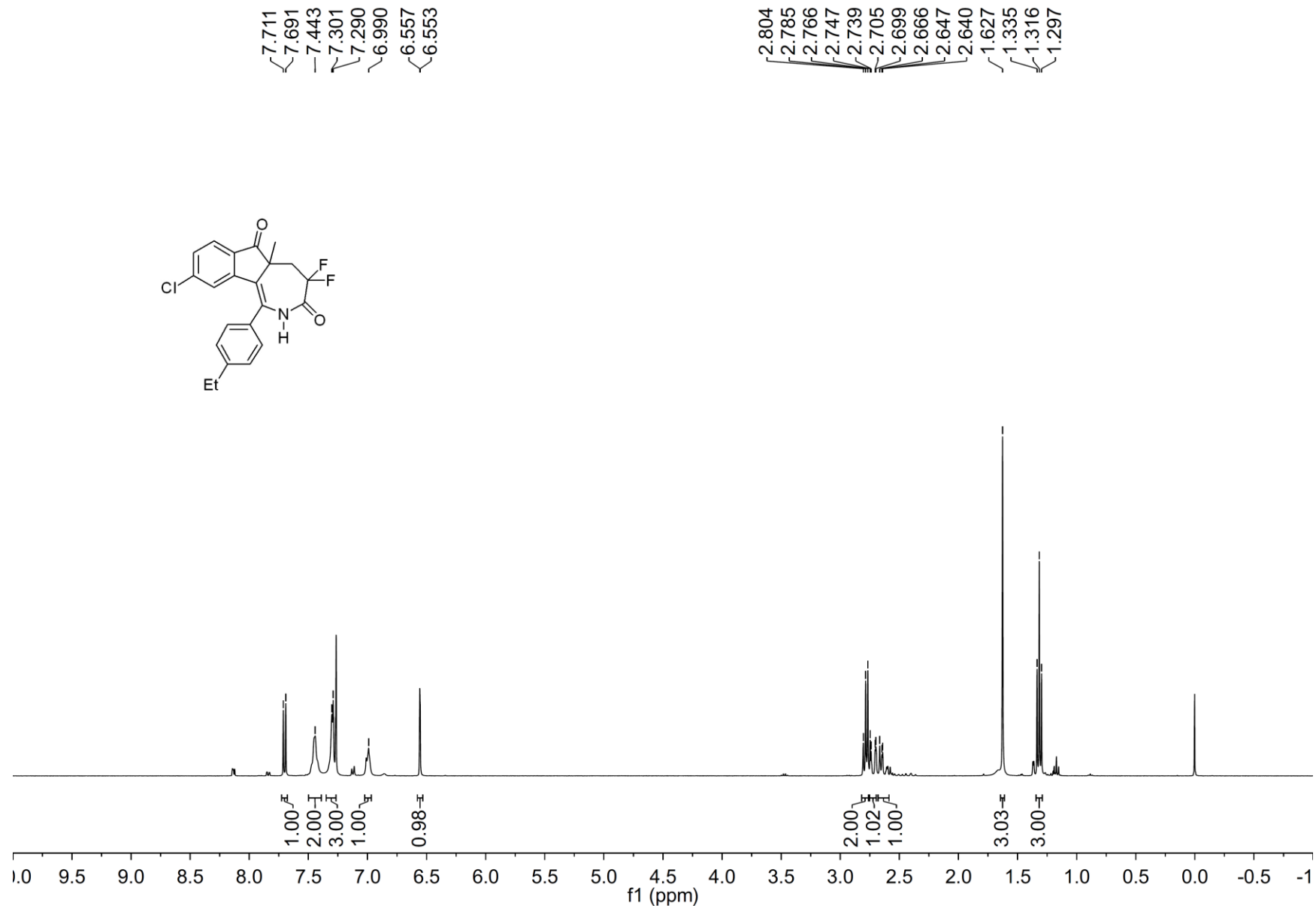


¹H NMR Spectrum of Compound 3w

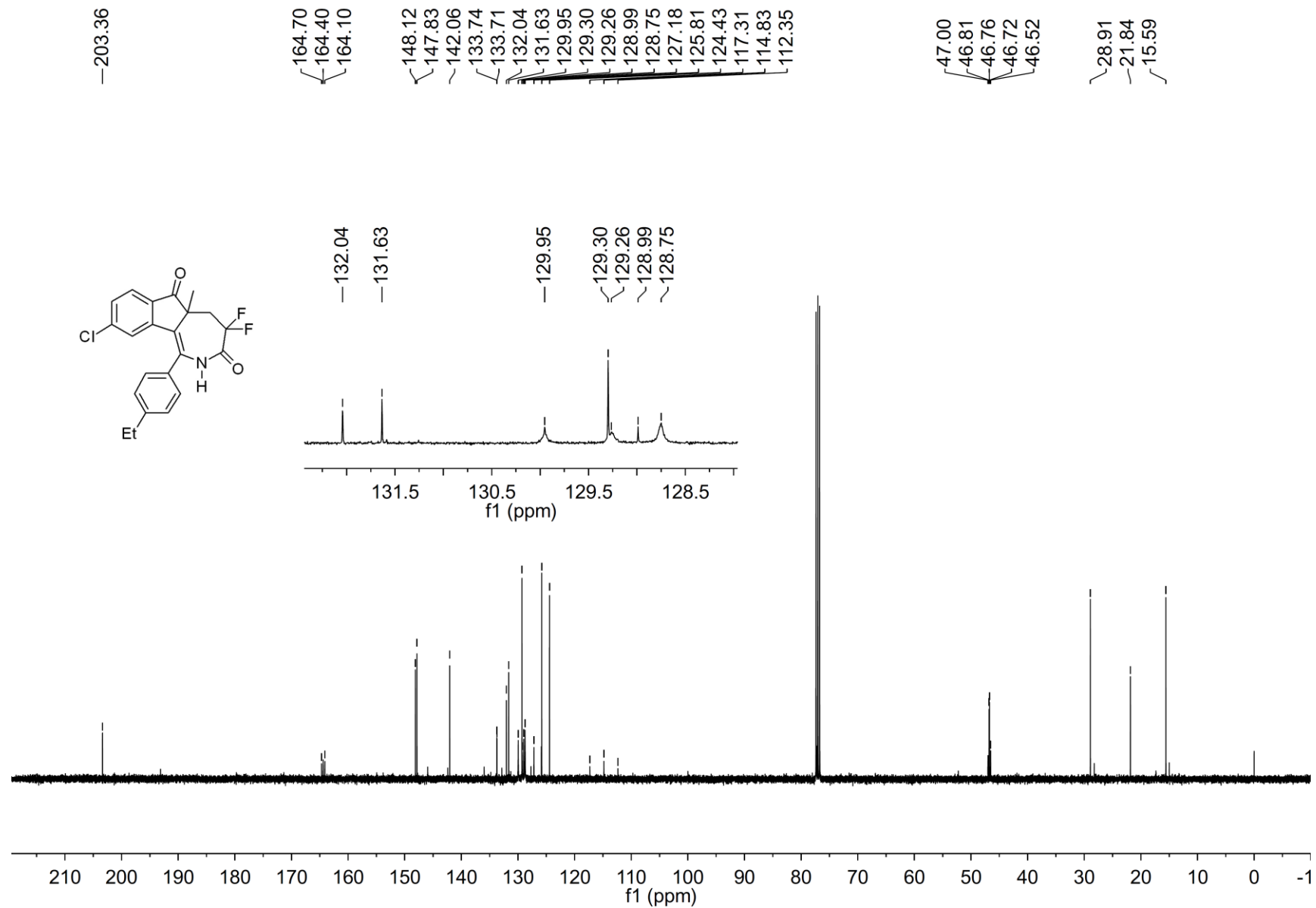




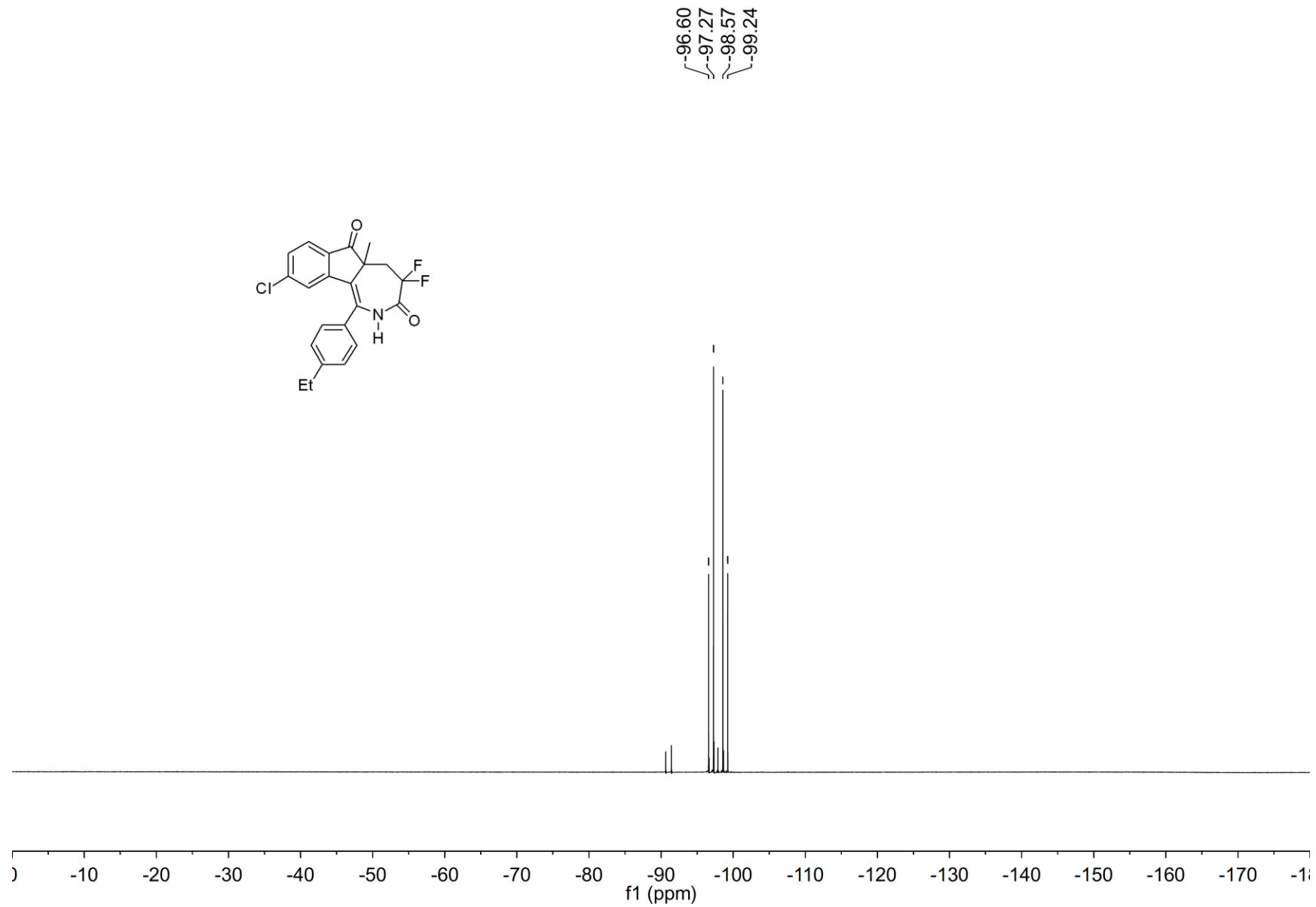
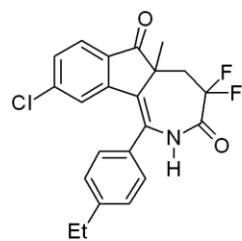
^{19}F NMR Spectrum of Compound 3w



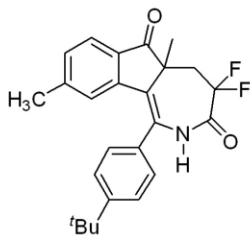
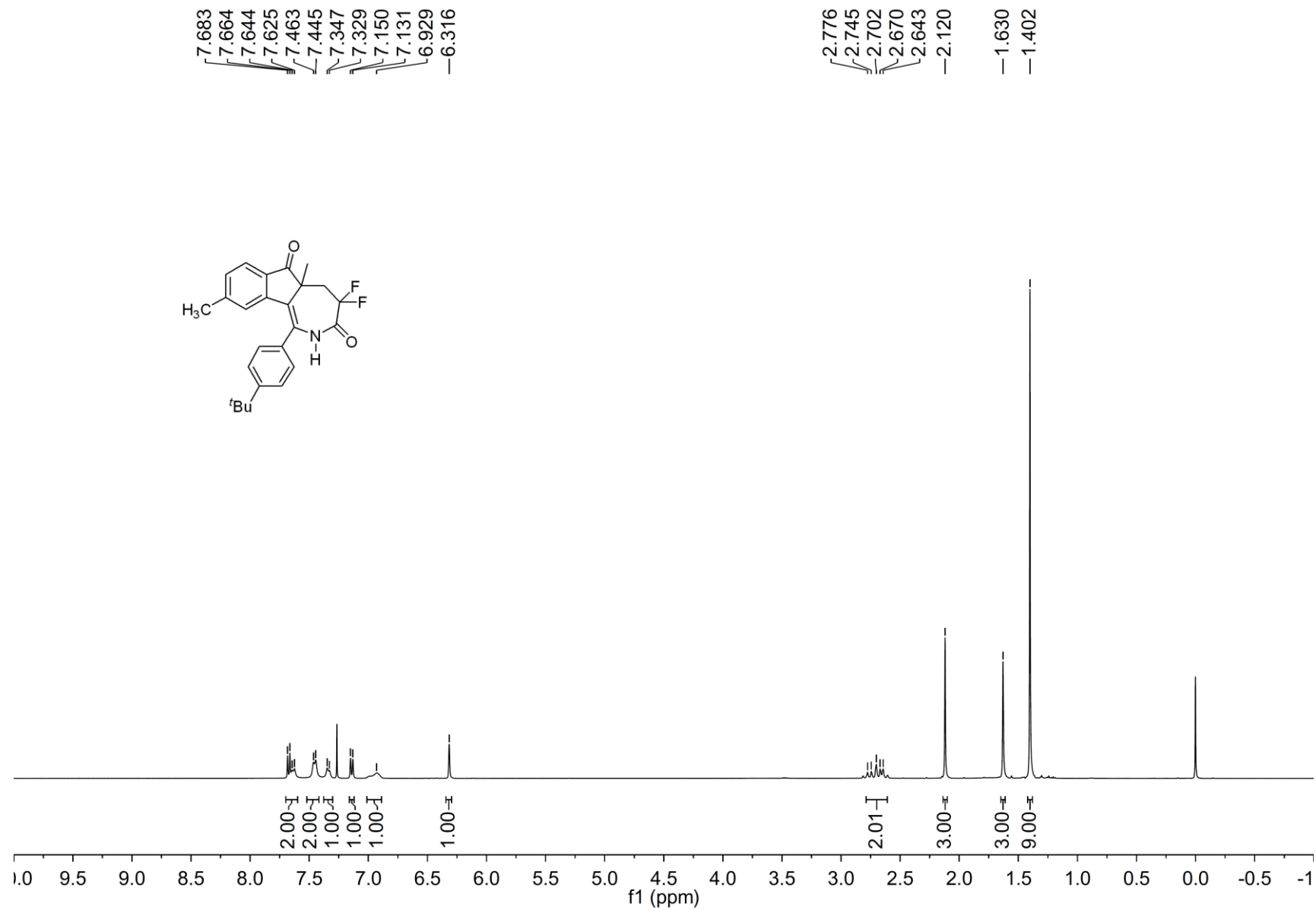
¹H NMR Spectrum of Compound 3x



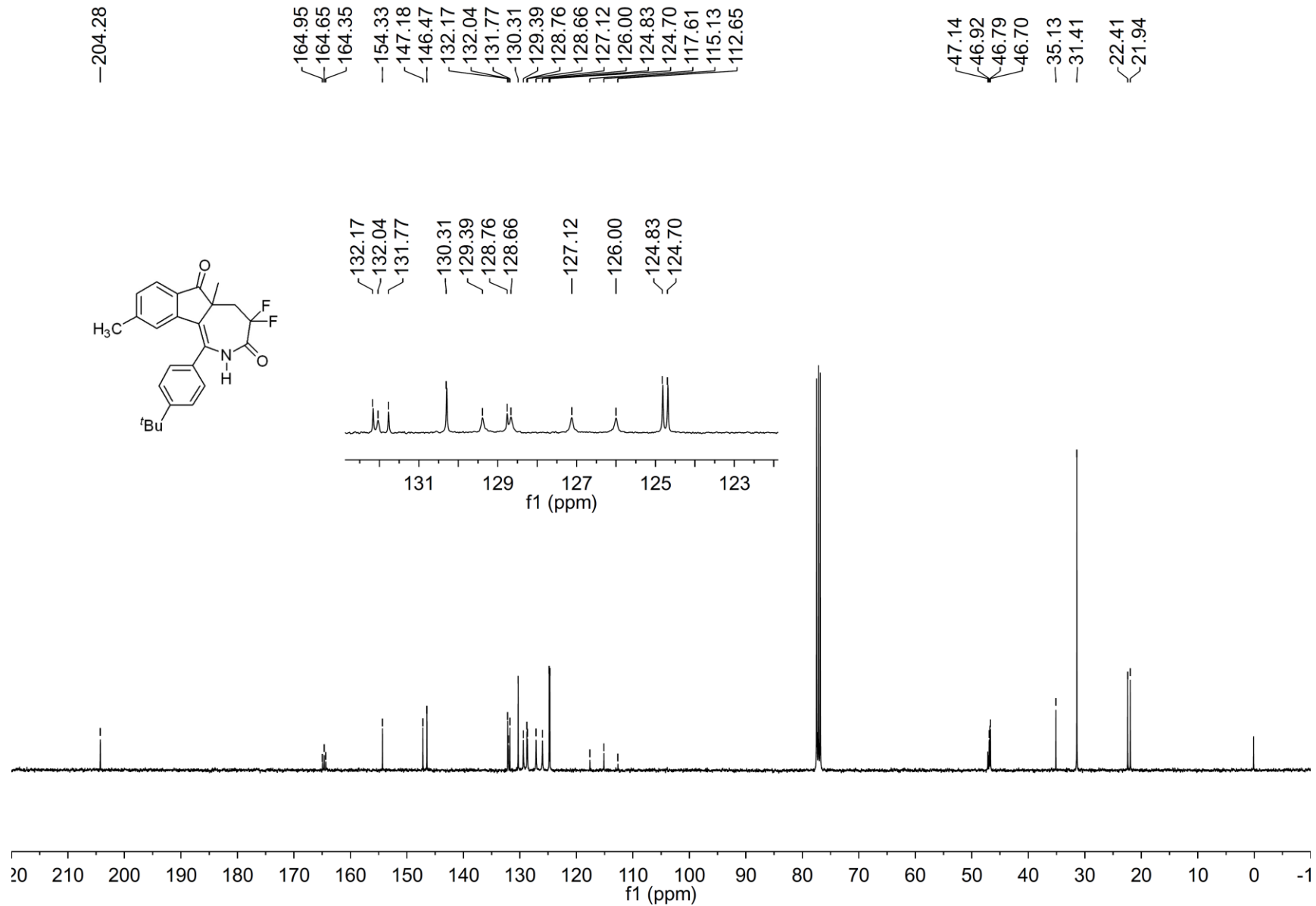
¹³C NMR Spectrum of Compound 3x



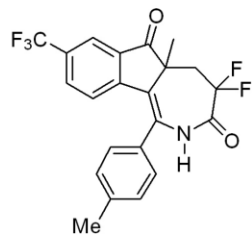
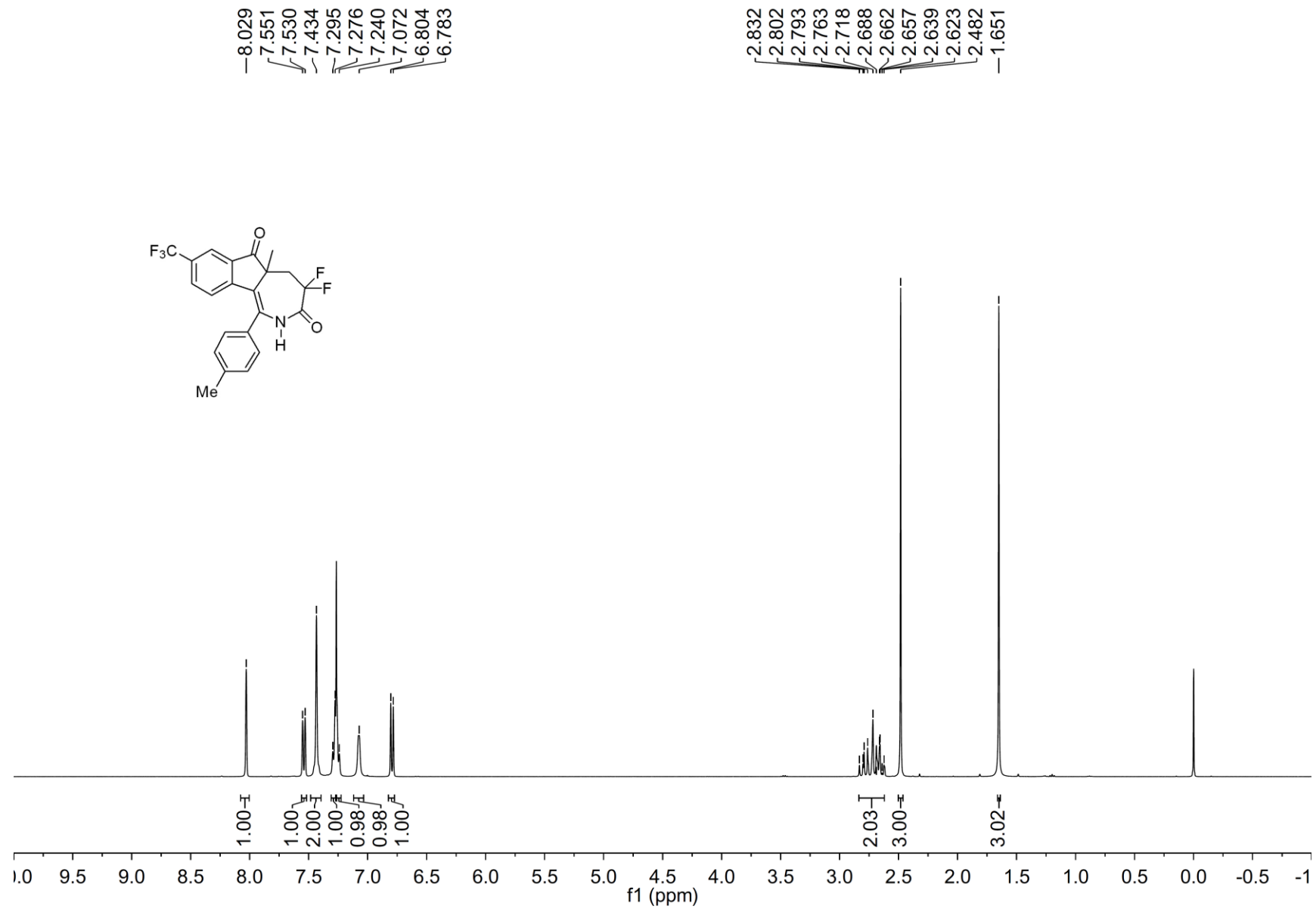
^{19}F NMR Spectrum of Compound 3x



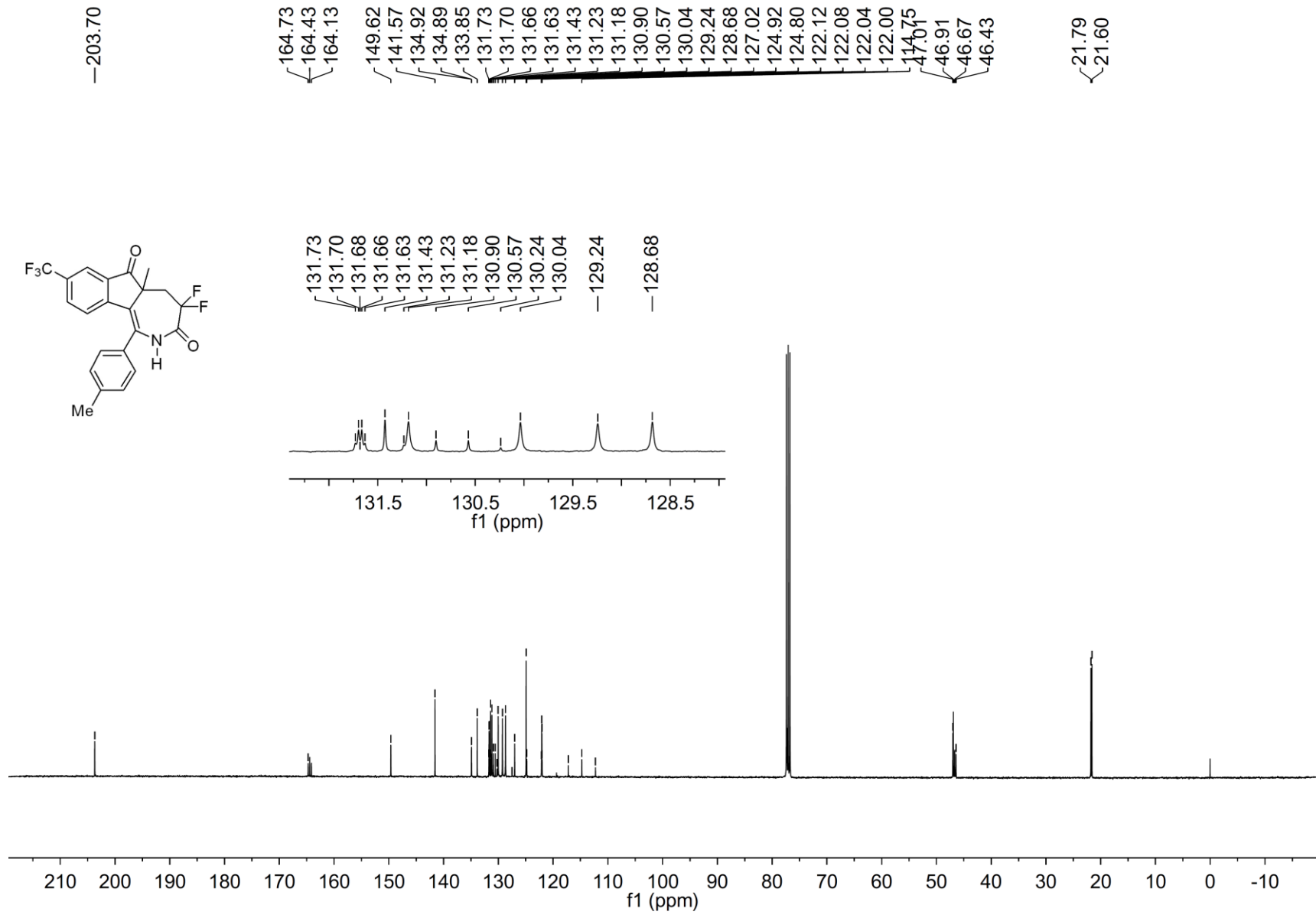
¹H NMR Spectrum of Compound 3y

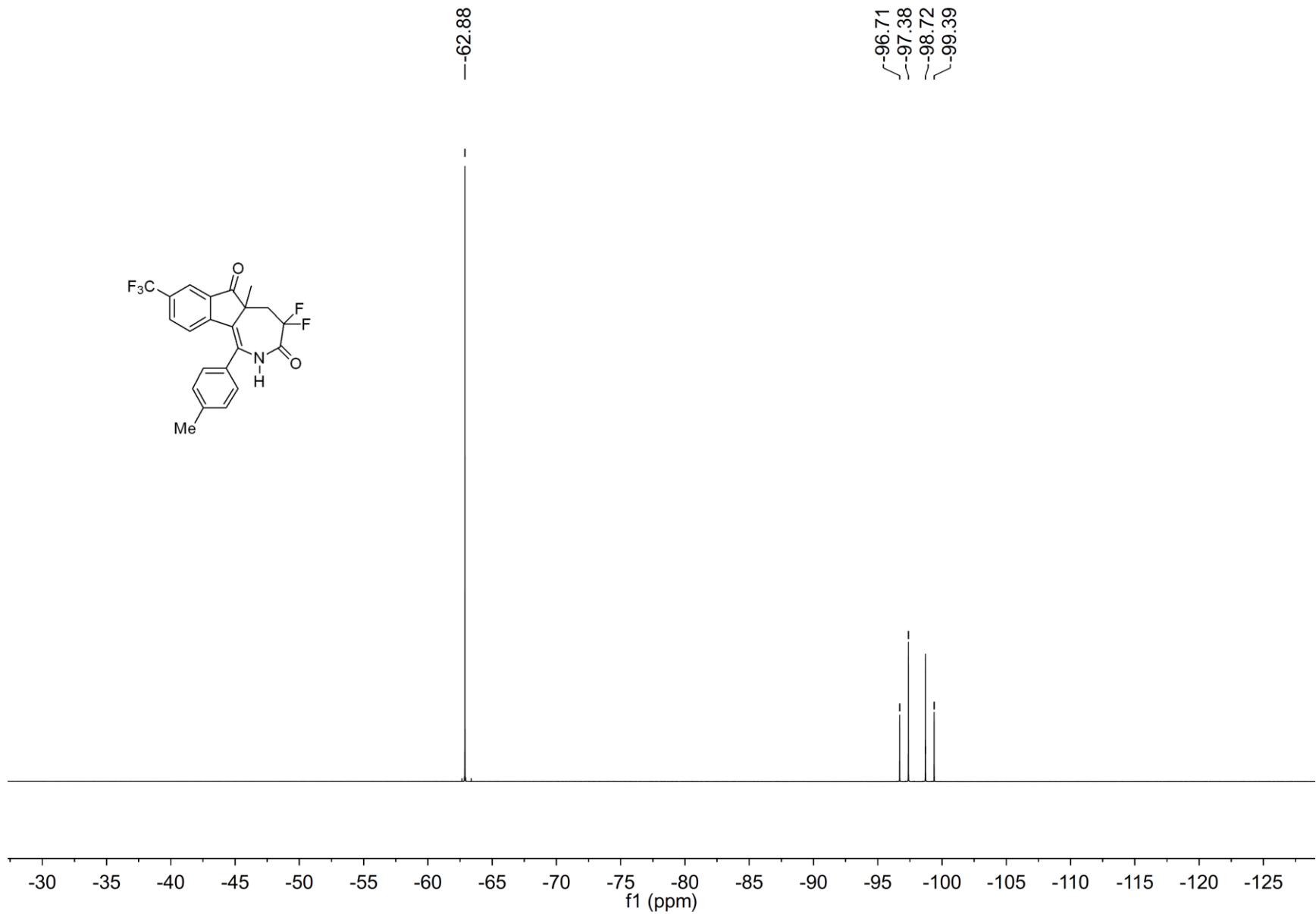


¹³C NMR Spectrum of Compound 3y

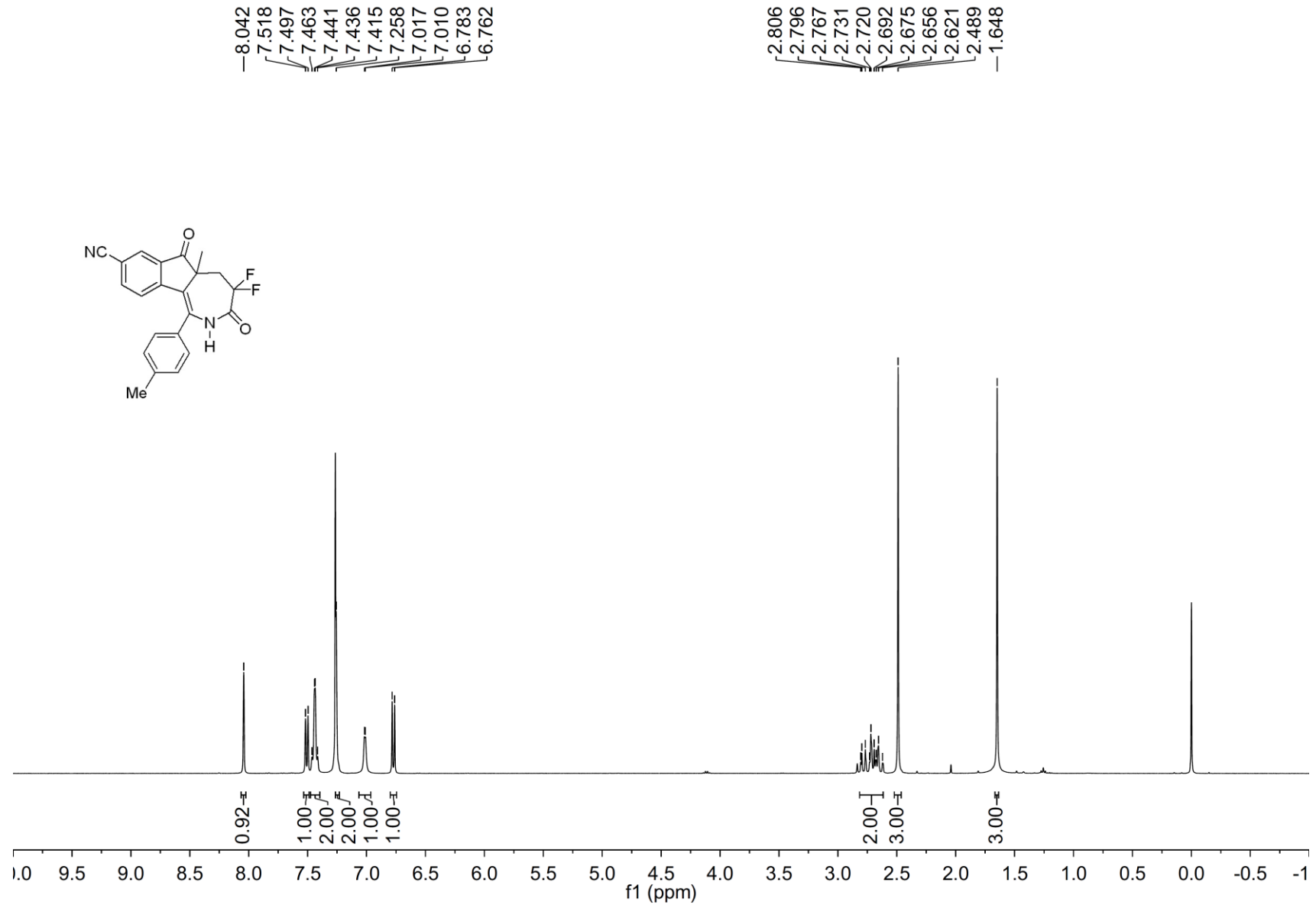


¹H NMR Spectrum of Compound 3z

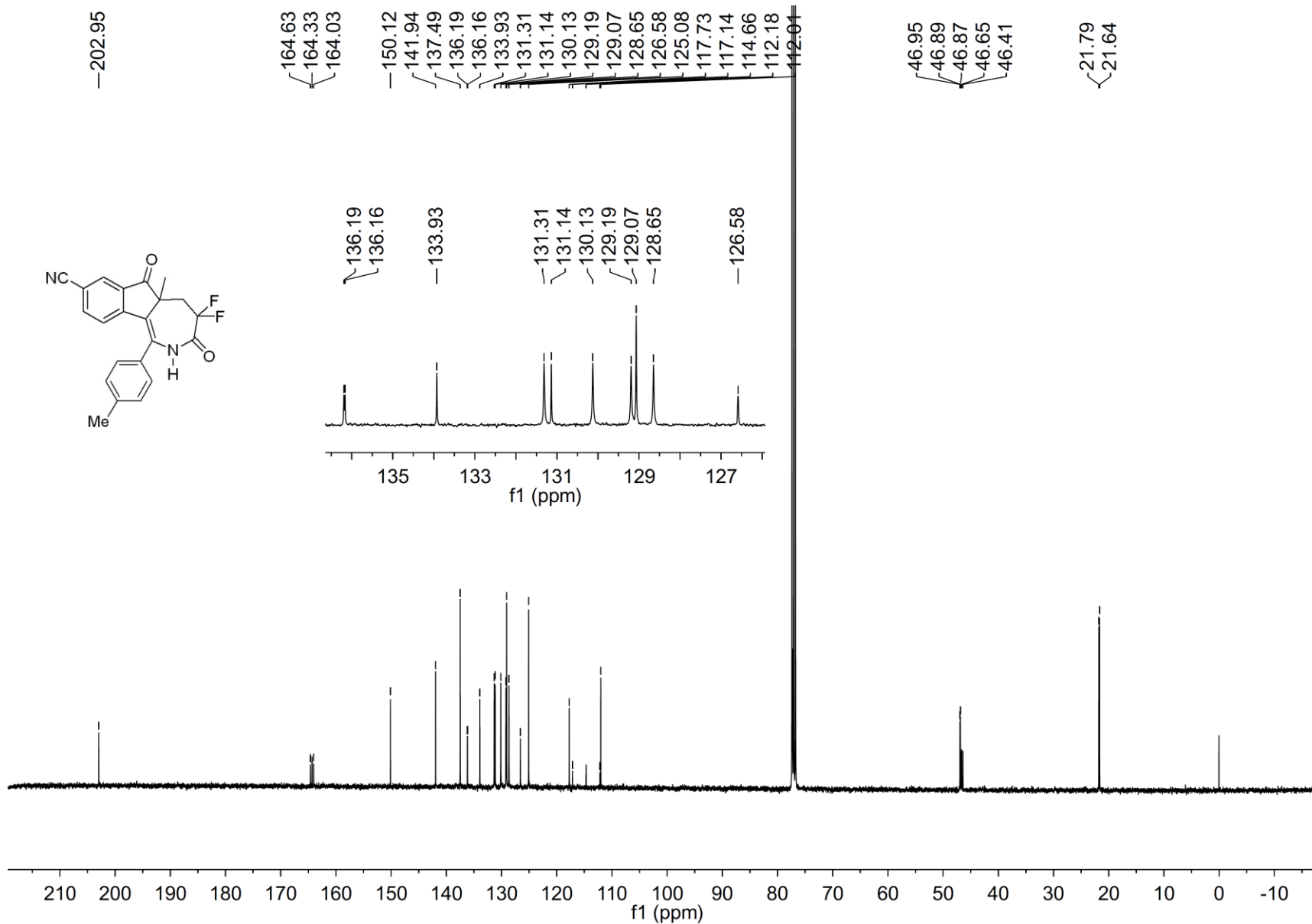


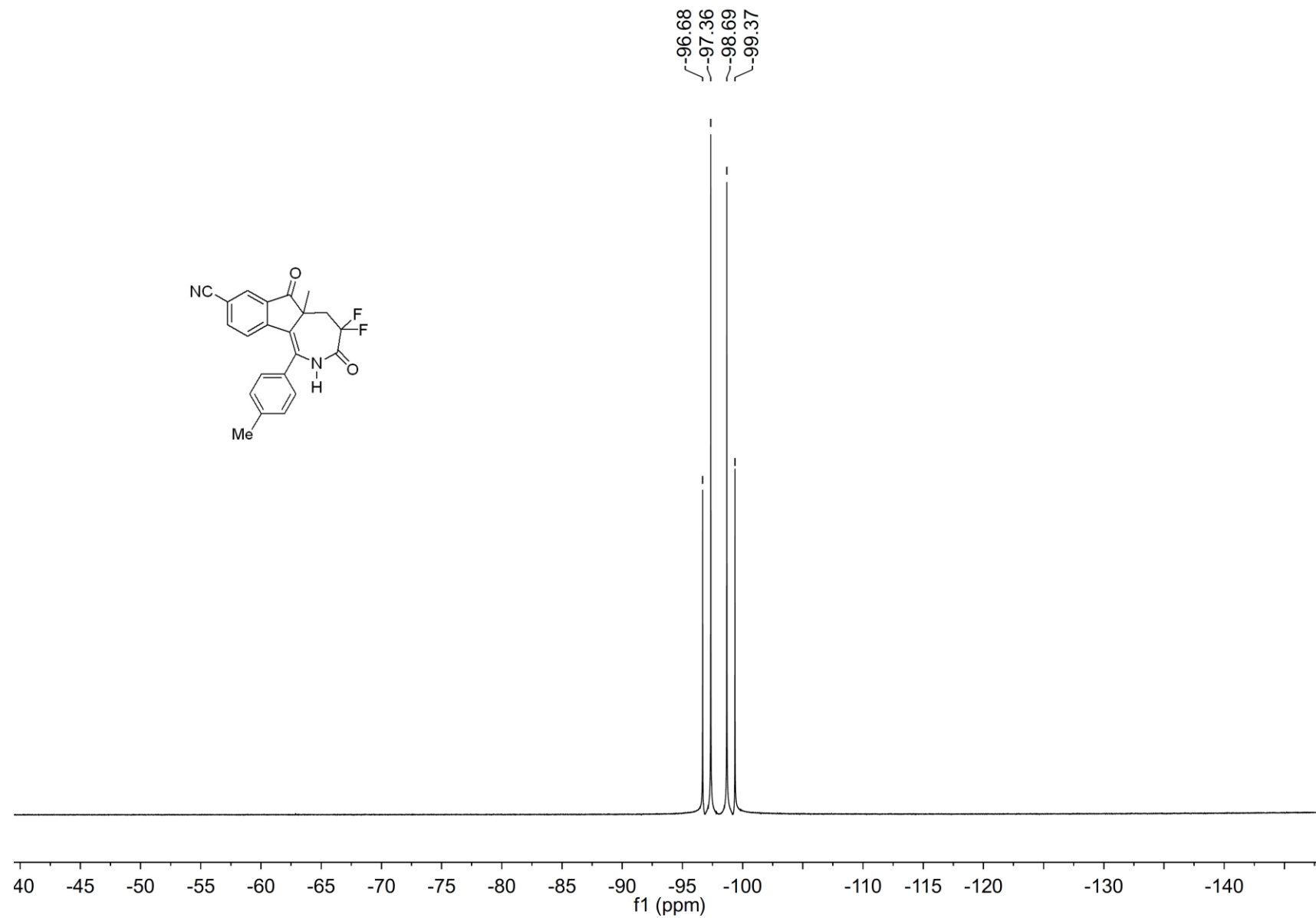


^{19}F NMR Spectrum of Compound 3z

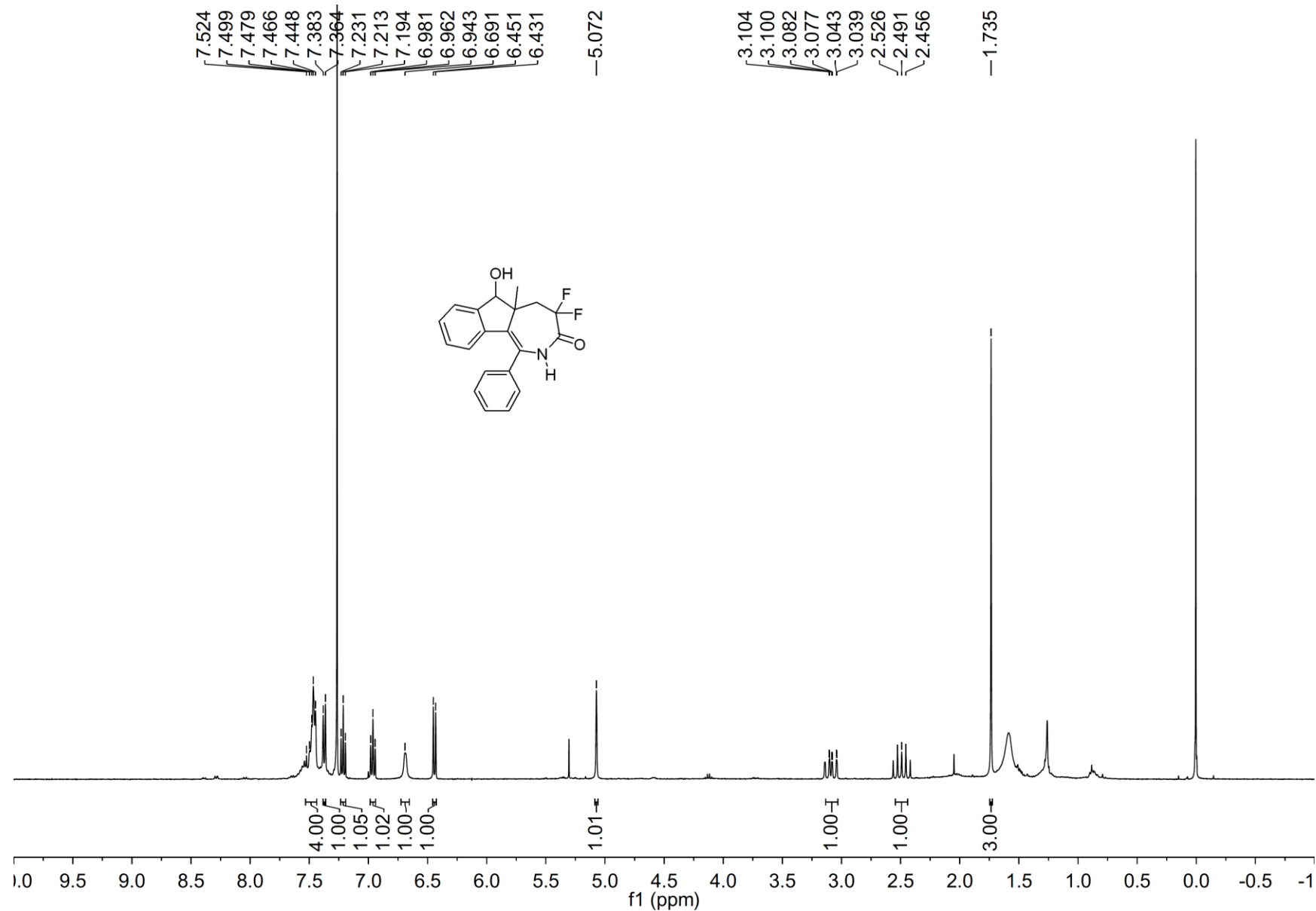


¹H NMR Spectrum of Compound 3aa

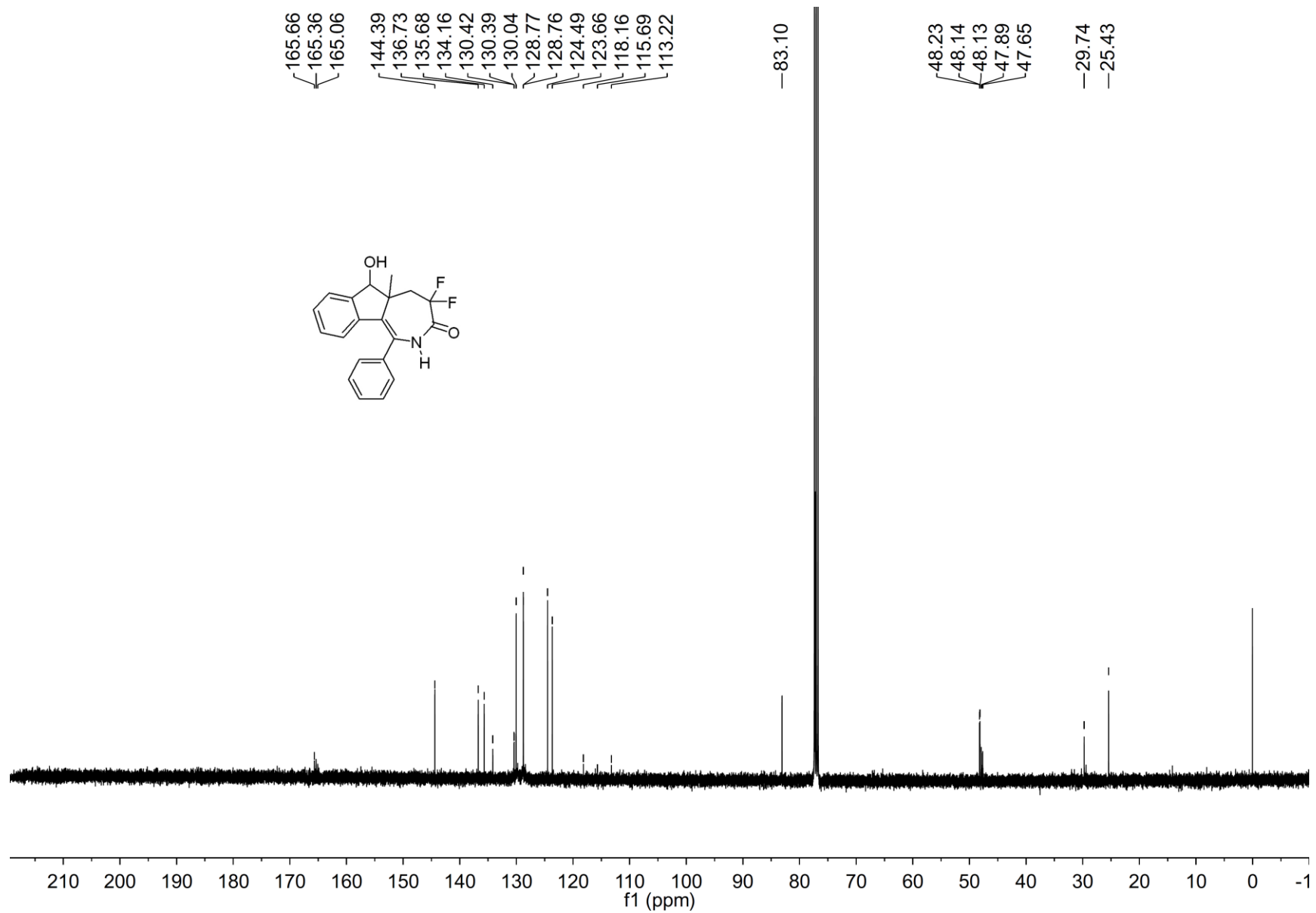




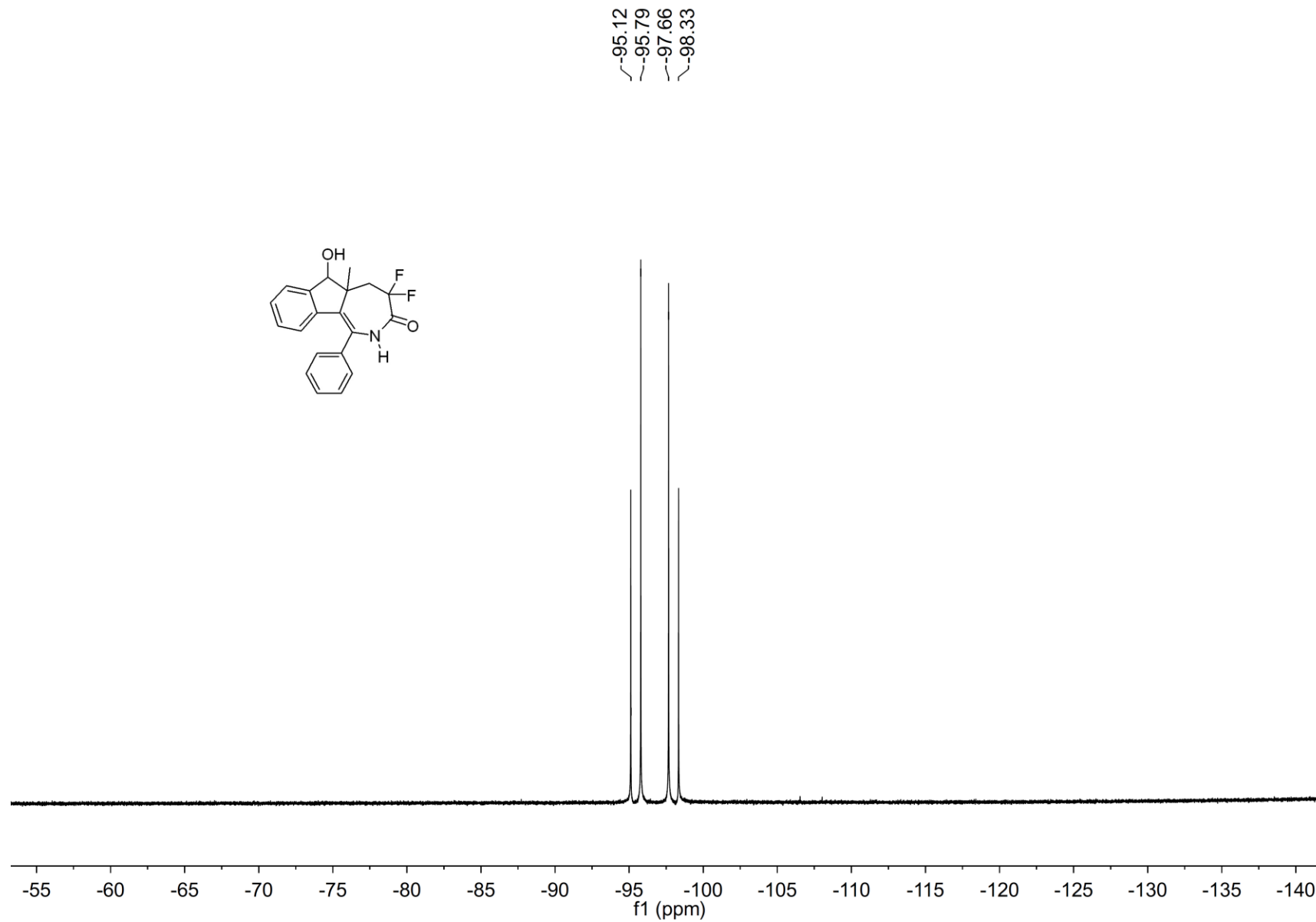
^{19}F NMR Spectrum of Compound 3aa



¹H NMR Spectrum of Compound 5a



¹³C NMR Spectrum of Compound 5a



^{19}F NMR Spectrum of Compound 5a