Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

A highly efficient metal-free and selective 1,4-addition of difluoroenoxysilanes to chromones

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General information

Reactions were monitored by thin layer chromatography (TLC) using UV light to visualize the progress of reaction. Purification of reaction products was carried out by flash chromatography on 300−400 mesh silica gel. Chemical yields referred to pure isolated substances. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) units using $(CH_3)_4Si$ as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets. Coupling constants (*J*) are reported in Hertz.

Anhydrous toluene and THF were prepared by distillation over sodium-benzophenone ketyl prior to use. Anhydrous CH_2Cl_2, and CH_3CN were prepared by first distillation over P_2O_5 and then from CaH_2. Difluoroenoxysilanes **2** were prepared by using the literature methods.[1] The chromones **1** were purchased from commercial companies.

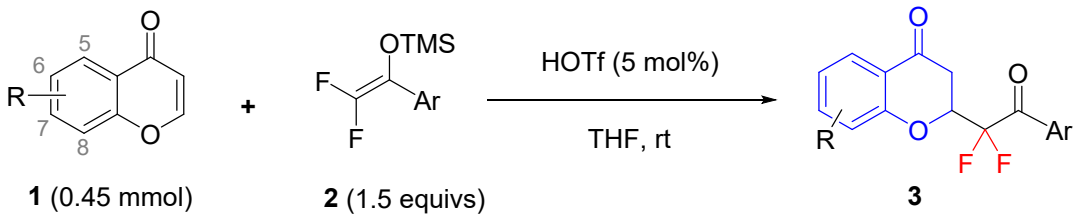
List of abbreviation:

Entry	Chemical name	Abbreviation
1	Tetrahydrofuran	THF
2	Dichloromethane	DCM/CH_2Cl_2
3	Petroleum ether	PE
4	Ethyl acetate	EtOAc
5	Acetonitrile	CH_3CN

[1] (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323; (b) Prakash, G. K. S.; Hu, J.; Olah, G. A. *J. Fluorine Chem.* **2001**, *112*, 357; (c) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1034.

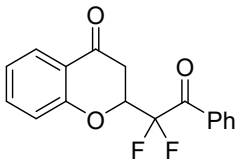
Part I. General procedure for the 1,4-addition

1) **The 1,4-addition of difluoroenoxysilanes to chromones.**



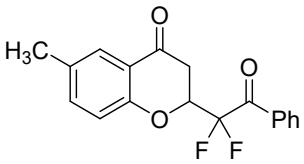
1 (0.45 mmol) **2** (1.5 equivs) **3**

To a 10 mL vial were added chromones **1** (0.45 mmol, 1.0 equiv) and freshly distilled THF (4.5 mL), followed by the addition of HOTf (3.4 mg, 0.0225 mmol, 5.0 mol%). The mixture was stirred at room temperature for 5 min and then difluoroenoxysilanes **2** (0.675 mmol, 1.5 equivs) was added. The reactions were continually stirred at room temperature till the full consumption of **2** by TLC analysis (9-27 h), and then the reaction mixture was concentrated in vacuo to give the crude residue, which was directly subjected to the column chromatography by using PE/EtOAc(20:1, v/v) as the elution to afford the products **3**.



3a

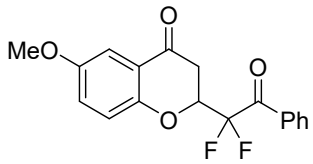
Product **3a** was obtained in 74% yield (100.8 mg) as white solid, m.p. = 99-101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.0 Hz, 2H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.24-5.15 (m, 1H), 3.14 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.98 (dd, *J* = 16.8, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 188.5 (dd, *J* = 29.8, 26.4 Hz), 159.8, 136.4, 134.7, 132.4, 130.1 (dd, *J* = 3.9, 2.8 Hz), 128.8, 127.0, 122.4, 120.8, 117.8, 115.3 (dd, *J* = 261.5, 252.0 Hz), 75.7 (dd, *J* = 31.6, 24.4 Hz), 35.7 (t, *J* = 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.04 (d, *J* = 285.8 Hz, 1F), -115.65 (d, *J* = 285.8 Hz, 1F). IR (ATR): 3054, 2933, 1693, 1606, 1599, 1464, 1078, 927, 765, 713, 686, 654 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{12}F_2NaO_3$ $[M+Na]^+$: 325.0647, Found: 325.0642.



3b

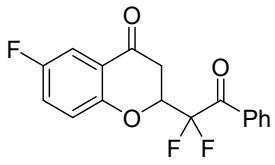
Product **3b** was obtained in 68% yield (96.1 mg) as white solid, m.p. = 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.68-7.65 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 5.19-5.10 (m, 1H), 3.10 (dd, *J* = 16.8, 13.2 Hz, 1H), 2.94 (dd, *J* = 16.8, 2.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 188.6 (dd, *J* = 30.1, 26.8 Hz),

157.8, 137.4, 134.6, 132.5, 132.0, 130.1 (t, *J* = 2.9 Hz), 128.7, 126.6, 120.4, 117.6 , 115.4 (dd, *J* = 262.2, 252.7 Hz), 75.8 (dd, *J* = 31.5, 24.3 Hz), 35.7, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.01 (d, *J* = 284.3 Hz, 1F), -115.70 (d, *J* = 284.6 Hz, 1F). IR (ATR): 3081, 2923, 1695, 1618, 1597, 1489, 1209, 1076, 842, 827, 717, 667 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_3$ $[M+Na]^+$: 339.0803, Found: 339.0798.



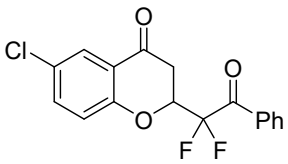
3c

Product **3c** was obtained in 60% yield (88.9 mg) as white solid, m.p. = 164-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.31 (s, 1H) 7.07 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.84 (d, *J* = 9.2 Hz, 1H), 5.18-5.09 (m, 1H), 3.80 (s, 3H), 3.11 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.95 (dd, *J* = 16.8, 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 188.6 (dd, J = 29.8, 26.6 Hz), 154.6 (d, *J* = 39.1 Hz), 134.6, 132.5(t, *J* = 1.5 Hz), 130.1 (dd, *J* = 3.8, 2.8 Hz), 128.8, 125.4, 120.8 , 119.1, 115.4 (dd, *J* = 262.7, 253.0 Hz), 107.4, 75.9 (dd, *J* = 31.3, 24.2 Hz), 55.8, 35.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.97 (d, *J* = 284.6 Hz, 1F), -115.59 (d, *J* = 285.0 Hz, 1F). IR (ATR): 3075, 2917, 1693, 1597, 1487, 1282, 1031, 844, 827, 715, 686, cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_4$ $[M+Na]^+$: 355.0752, Found: 355.0748.



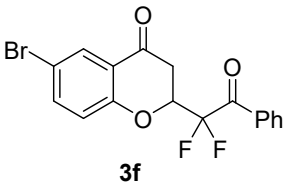
3d

Product **3d** was obtained in 64% yield (91.9 mg) as white solid, m.p. = 129-131 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.56-7.52 (m, 3H), 7.22-7.18 (m, 1H), 6.92 (dd, J = 8.8, 4.0 Hz, 1H), 5.23-5.14 (m, 1H), 3.11 (dd, *J* = 17.2, 12.8 Hz, 1H), 2.99 (dd, *J* = 13.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6 (d, *J* = 1.5 Hz), 188.3 (dd, *J* = 30.0, 26.7 Hz), 159.0, 156.3 (d, *J* = 242.1 Hz), 156.0 (d, *J* = 1.9 Hz) 134.8, 132.3 (t, *J* = 2.1 Hz), 130.1 (dd, *J* = 3.9, 2.7 Hz), 128.8, 123.8 (d, *J* = 24.5 Hz), 121.4 (d, *J* = 6.5 Hz), 119.6 (d, *J* = 7.4 Hz), 115.2 (dd, *J* = 264.1, 253.7 Hz), 112.1 (d, *J* = 23.5 Hz), 75.9 (dd, *J* = 31.3, 24.2 Hz), 35.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.89 (d, *J* = 288.0 Hz, 1F), -115.37 (d, *J* = 288.0 Hz, 1F), -119.71 (s, 1F). IR (ATR): 3057, 2980, 1697, 1483, 1274, 1194, 1078, 832, 717, 704 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}F_3NaO_3$ $[M+Na]^+$: 343.0552, Found: 343.0544.



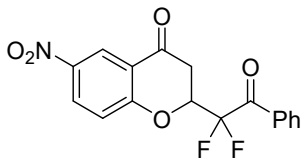
3e

Product **3e** was obtained in 66% yield (101.2 mg) as white solid, m.p. = 165-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 1.2 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 6.89 (t, *J* = 8.8 Hz, 1H), 5.25-5.15 (m, 1H), 3.11 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.99 (dd, *J* = 16.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 188.1 (dd, *J* = 29.9, 26.7 Hz), 158.2, 136.2, 134.8, 132.2 (t, *J* = 2.1 Hz), 130.1 (dd, *J* = 3.8, 2.7 Hz), 128.8, 128.1, 126.4, 121.6 , 119.6, 115.2 (dd, *J* = 263.2, 253.8 Hz), 75.8 (dd, *J* = 31.3, 24.2 Hz), 35.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.85 (d, *J* = 288.8 Hz, 1F), -115.26 (d, *J* = 288.8 Hz, 1F). IR (ATR): 3060, 2986, 1697, 1597, 1483, 1078, 883, 821, 717, 704 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}ClF_2NaO_3$ $[M+Na]^+$: 359.0257, Found: 359.0243.



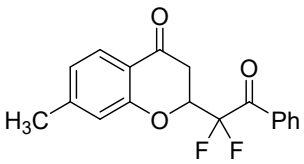
3f

Product **3f** was obtained in 72% yield (124.3 mg) as white solid, m.p. = 143-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.0 Hz, 2H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.57-7.52 (m, 3H), 6.84 (d, *J* = 9.2 Hz, 1H), 5.25-5.15 (m, 1H), 3.11 (dd, *J* = 16.8, 12.4 Hz, 1H), 2.99 (dd, *J* = 16.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2 (dd, *J* = 29.8, 27.1 Hz), 188.1, 158.6, 139.0, 134.8, 132.2 (t, *J* = 2.3 Hz), 130.1 (dd, *J* = 3.7, 2.7 Hz), 129.5, 128.8, 122.0 , 119.9, 115.2, 115.1 (dd, *J* = 263.4, 253.4 Hz) , 75.7 (dd, *J* = 31.3, 24.2 Hz), 35.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.85 (d, *J* = 288.8 Hz, 1F), -115.26 (d, *J* = 288.8 Hz, 1F). IR (ATR): 3022, 2987, 1697, 1599, 1467, 1273, 1188, 1080, 823, 715 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}BrF_2NaO_3$ $[M+Na]^+$: 402.9752, Found: 402.9737.



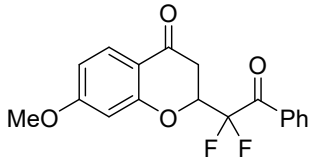
3g

Product **3g** was obtained in 78% yield (121.2 mg) as white solid. m.p. = 197-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 2.0 Hz, 1H), 8.35 (dd, *J* = 9.2, 2.4 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 2H), 7.71 (t, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 9.2 Hz, 1H), 5.41-5.32 (m, 1H), 3.23-3.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5 (dd, *J* = 29.9, 27.1 Hz), 187.2, 163.5, 142.9, 135.1, 131.8 (t, *J* = 2 Hz) 130.6, 130.1 (dd, *J* = 3.6, 2.9 Hz), 128.9, 123.4, 120.4, 119.3, 115.0 (dd, *J* = 265.2, 256.4 Hz), 76.0 (dd, *J* = 31.4, 24.2 Hz), 35.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.62 (d, *J* = 294.8 Hz, 1F), -114.53 (d, *J* = 294.8 Hz, 1F). IR (ATR): 3065, 2919, 1705, 1616, 1587, 1473, 1276, 1078, 906, 715 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}F_2NNaO_5$ $[M+Na]^+$: 370.0497, Found: 370.0484.



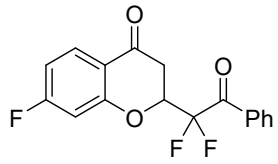
3h

Product **3h** was obtained in 80% yield (114.5 mg) as yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.72 (s, 1H), 5.21-5.11 (m, 1H), 3.09 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.93 (dd, *J* = 16.8, 2.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 188.6 (dd, *J* = 29.9, 26.5 Hz), 159.8, 148.1, 134.6, 132.5 (t, *J* = 2.4 Hz), 130.1 (dd, *J* = 3.8, 2.7 Hz), 128.7, 126.9, 123.7, 118.6, 117.8, 115.3 (dd, *J* = 262.5, 252.8 Hz), 75.7 (dd, *J* = 31.6, 24.5 Hz), 35.6, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.00 (d, *J* = 284.6 Hz, 1F), -115.82 (d, *J* = 285.0 Hz, 1F). IR (ATR): 3042, 2950, 1697, 1618, 1448, 1294, 1078, 815, 715 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_3$ $[M+Na]^+$: 339.0803, Found: 339.0796.



3i

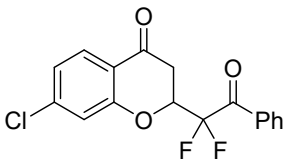
Product **3i** was obtained in 83% yield (123.8 mg) as white solid, m.p. = 126-127 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.8 Hz, 1H), 6.36 (s, 1H), 5.23-5.14 (m, 1H), 3.80 (s, 3H), 3.07 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.89 (dd, *J* = 16.8, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3 (dd, *J* = 30.0, 26.6 Hz), 188.0, 166.3, 161.7, 134.7, 132.4 (t, *J* = 2.1 Hz) 130.1 (dd, *J* = 3.8, 2.7 Hz), 128.8 (d, *J* = 4.7 Hz), 115.3 (dd, *J* = 262.7, 253.3 Hz), 114.6, 110.9, 100.9, 76.0 (dd, *J* = 31.4, 24.1 Hz), 55.7, 35.3; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.13 (d, *J* = 286.9 Hz, 1F), -115.62 (d, *J* = 286.5 Hz, 1F). IR (ATR): 3057, 2920, 1689, 1577, 1498, 1162, 1031, 729, 702, 686 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_4$ $[M+Na]^+$: 355.0752, Found: 355.0749.



3j

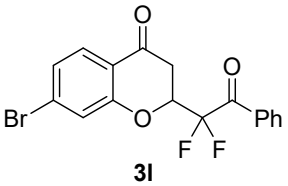
Product **3j** was obtained in 68% yield (97.7 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.93 (t, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 2H), 6.79 (t, *J* = 8.0 Hz, 1H), 6.63 (dd, *J* = 9.6, 1.6 Hz, 1H), 5.29-5.18 (m, 1H), 3.11 (dd, *J* = 17.2, 12.8 Hz, 1H), 2.97 (dd, *J* = 17.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1 (dd, *J* = 29.8, 26.7 Hz), 187.9, 167.5 (d, *J* = 255.9 Hz), 161.3 (d, *J* = 13.6 Hz), 134.8, 132.2 (t, *J* = 2.4 Hz), 130.1 (dd, *J* = 3.8, 2.8 Hz), 129.7 (d, *J* = 11.3 Hz), 128.8, 117.7, 115.1 (dd, *J* = 267.1, 257.9 Hz), 110.8 (d, *J* = 22.5 Hz), 104.9 (d, *J* = 25.0 Hz), 76.1 (dd, *J* = 31.4, 24.2 Hz), 35.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -99.23 (s, 1F) , -108.96 (d, *J* = 288.8 Hz, 1F), -115.38 (d, *J* = 288.8 Hz, 1F). IR (ATR): 3024, 2980, 1697, 1614, 1593, 1258, 1143, 854, 815, 714 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}F_3NaO_3$ $[M+Na]^+$:

343.0552, Found: 343.0545.



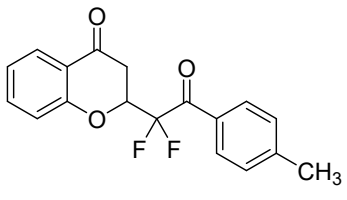
3k

Product **3k** was obtained in 63% yield (96.2 mg) as white solid, m.p. = 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (s, 1H), 5.27-5.17 (m, 1H), 3.12 (dd, *J* = 17.2, 12.4 Hz, 1H), 2.98 (dd, *J* = 16.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 188.1 (dd, *J* = 30.1, 26.8 Hz), 160.0, 142.3, 132.2 (t, *J* = 2.3 Hz), 130.1 (dd, *J* = 3.9, 2.8 Hz), 128.8, 128.2, 123.3, 119.4, 118.1, 115.1 (dd, *J* = 263.3, 253.9 Hz), 75.9 (dd, *J* = 31.6, 24.3 Hz), 35.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.86 (d, *J* = 288.4 Hz, 1F), -115.41 (d, *J* = 288.8 Hz, 1F). IR (ATR): 3036, 2976, 1697, 1600, 1427, 1205, 1082, 929, 813, 715 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}ClF_2NaO_3$ $[M+Na]^+$: 359.0257, Found: 359.0250.



3l

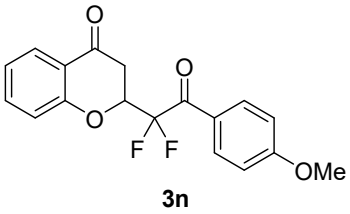
Product **3l** was obtained in 79% yield (135.2 mg) as white solid, m.p. = 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 2H) 7.19 (d, *J* = 8.4 Hz, 1H), 7.12 (s, 1H), 5.24-5.17 (m, 1H), 3.09 (dd, *J* = 17.2, 12.8 Hz, 1H), 2.96 (dd, *J* = 17.2, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 188.1 (dd, *J* = 31.6, 28.3 Hz), 159.8, 134.8, 132.1 (t, *J* = 2.5 Hz), 130.7, 130.0(dd, *J* = 3.8, 2.8 Hz), 128.8, 128.1, 126.0, 121.0, 119.6, 115.1 (dd, *J* = 263.3, 253.9 Hz), 75.9 (dd, *J* = 31.7, 24.4 Hz), 35.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.83 (d, *J* = 288.4 Hz, 1F), -115.35 (d, *J* = 288.4 Hz, 1F). IR (ATR): 3074, 2987, 1697, 1595, 1423, 1327, 1072, 902, 813, 715 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{11}BrF_2NaO_3$ $[M+H]^+$: 380.9932, Found: 380.9929.



3m

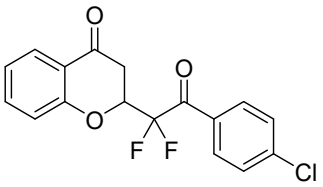
Product **3m** was obtained in 93% yield (132.6 mg) as white solid, m.p. = 94-96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 5.23-5.13 (m, 1H), 3.11 (dd, *J* = 17.2, 12.8 Hz, 1H), 2.96 (dd, *J* = 16.8, 3.2 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 187.9 (dd, *J* = 29.4, 26.4 Hz), 159.8, 146.0, 136.3, 130.3 (dd, *J* = 3.7, 2.8 Hz), 129.9 (t, *J* = 2.2 Hz), 129.5, 127.0, 122.3, 120.8, 117.8, 115.4 (dd, *J* = 262.6, 253.3 Hz), 75.7 (dd, *J* = 31.3, 24.4 Hz), 35.7, 21.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ

-109.17 (d, *J* = 284.6 Hz, 1F), -115.31 (d, *J* = 284.6 Hz, 1F). IR (ATR): 3047, 2990, 1693, 1603, 1579, 1473, 1303, 1207, 1076, 927, 887, 765, 667 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_3$ $[M+Na]^+$: 339.0803, Found: 339.0801.



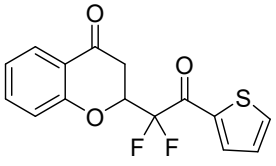
3n

Product **3n** was obtained in 90% yield (134.1 mg) as white solid, m.p. = 116-117 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 1H), 5.21-5.14 (m, 1H), 3.91 (s, 3H), 3.10 (dd, *J* = 15.9, 13.8 Hz, 1H), 2.96 (d, J = 16.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 186.5 (dd, *J* = 28.8, 26.5 Hz), 164.8, 159.9, 136.3, 132.8 (dd, *J* = 3.8, 3.0 Hz) 127.0, 125.2, 122.3, 120.8, 117.9, 115.6 (dd, *J* = 262.3, 253.5 Hz), 114.1, 75.8 (dd, *J* = 30.9, 24.4 Hz), 55.6, 35.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -109.09 (d, *J* = 284.3 Hz, 1F), -114.61 (d, *J* = 284.3 Hz, 1F). IR (ATR): 3055, 2959, 1693, 1598, 1319, 1267, 1180, 1028, 837, 765 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{14}F_2NaO_4$ $[M+Na]^+$: 355.0752, Found: 355.0759.



3o

Product **3o** was obtained in 89% yield (135.1 mg) as white solid, m.p. = 129-131 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.52-7.45 (m, 3H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.4Hz, 1H), 5.21-5.12 (m, 1H), 3.11 (dd, *J* = 16.8, 12.8 Hz, 1H), 2.96 (dd, *J* = 16.8, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 187.5 (dd, *J* = 30.4, 26.8 Hz), 159.6, 141.5, 136.4, 131.6 (dd, *J* = 4.2, 2.7 Hz), 130.7 (t, *J* = 2.0 Hz), 129.2, 127.0, 122.5, 120.9, 117.8, 115.2 (dd, *J* = 262.4, 253.0 Hz), 75.6 (dd, *J* = 31.7, 24.6 Hz), 35.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -108.88 (d, *J* = 285.8 Hz, 1F), -115.72 (d, *J* = 285.8 Hz, 1F). IR (ATR): 3058, 2962, 1697, 1603, 1587, 1473, 1463, 1209, 1078, 927, 846, 763 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{11}ClF_2NaO_3$ $[M+Na]^+$: 359.0257, Found: 359.0244.

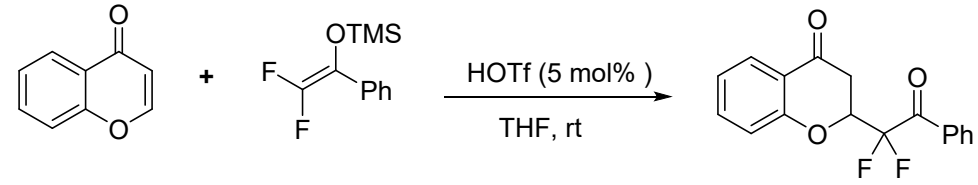


3p

Product **3p** was obtained in 79% yield (109.2 mg) as white solid, m.p. = 160-161 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.09-8.08 (m, 1H), 7.90-7.86 (m, 2H), 7.48-7.44 (m, 1H), 7.24 (dd, *J* = 5.2, 4.0 Hz, 1H), 7.08-7.04 (m, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.19-5.10 (m, 1H), 3.11 (dd, *J* = 17.2, 12.8 Hz, 1H), 2.98-2.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 181.2 (dd, *J* = 30.5, 27.3 Hz), 138.5(dd, *J* =

3.1, 1.5 Hz), 137.2, 136.4 (t, J = 4.1 Hz),136.3, 128.9, 127.0, 122.4, 120.8, 117.8, 115.1 (dd, J = 261.7, 253.0 Hz), 75.7 (dd, J = 31.8, 25.0 Hz), 35.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -110.07 (d, J = 276.0 Hz, 1F), -117.30 (d, J = 276.4 Hz, 1F). IR (ATR): 2955, 2922, 1691, 1606, 1464, 1401, 1095, 763, 729 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{15}H_{10}O_3F_2NaS$ $[M+Na]^+$: 331.0211, Found: 331.0219.

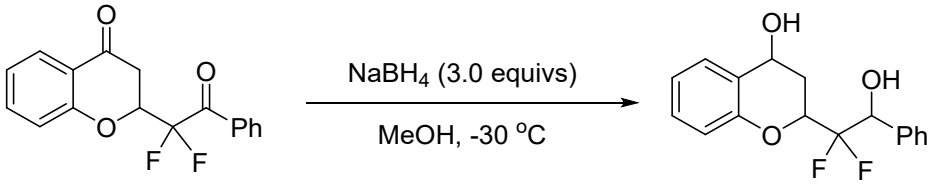
2) Gram-scale synthesis of 3a.



1a (5.0 mmol) **2a** (1.5 equivs) **3a**, 1.292 g, 85% yield

To a 50 mL round-bottom flask were added chromone **1a** (5.0 mmol, 1.0 equiv) and anhydrous THF (20.0 mL), followed by the addition of HOTf (37.5 mg, 0.25 mmol, 5.0 mol%). The mixture was stirred at room temperature for 5 min and then **2a** (7.5 mmol, 1.5 equivs) was added. The reaction was continually stirred at room temperature for 11 h, and then the reaction mixture was concentrated in vacuo to give the crude residue, which was directly subjected to the column chromatography by using PE/EtOAc (20:1, v/v) as the elution to afford the product **3a** as white solid (1.292 g, 85% yield).

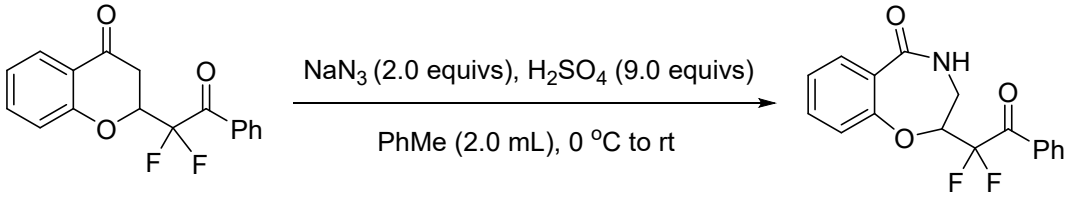
Part II. Product elaborations



3a (0.2 mmol) **4**, 88% yield, dr = 1.5:1

Compound **3a** (60.4 mg, 0.2 mmol) was dissolved in 2.0 mL anhydrous MeOH. The resulting solution was cooled to -30 °C, then $NaBH_4$ (22.7 mg, 0.60 mmol) was added in portions over a few minutes. The resulting mixture was stirred until the complete consumption of **3a** as indicated by TLC analysis (about 20 minutes). Then the reaction was quenched by saturated NH_4Cl (aq.), and extracted with CH_2Cl_2 (2.0 mL × 3). The combined organic layer was washed with saturated brine (10.0 mL × 2), respectively. The solution was dried over anhydrous Na_2SO_4, filtered, and concentrated under

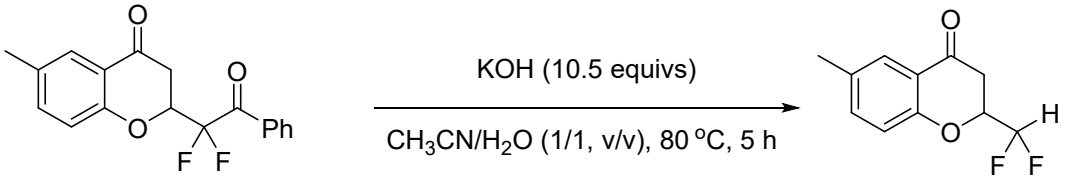
reduced pressure. the residue was purified by column chromatography (CH_2Cl_2/EtOAc = 10:1, v/v) to afford diol **4** in 88% yield (62.5 mg)with 1.5:1 dr as yellow soild. For the major isomer: m.p. = 196-197 °C; ^{1}H NMR (400 MHz, Acetone-d_6): δ 7.53 (d, J =7.2 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.35-7.29 (m, 3H), 7.12 (t, J = 7.2 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 6.81 (t, J = 8.4 Hz, 1H), 5.27 (t, J = 13.2 Hz, 1H), 4.87 (dd, J = 10.8, 6.0Hz, 1H), 4.27 (dd, J = 22.0, 10.4Hz, 1H), 3.36 (s, 1H), 2.42 (dd, J = 12.8, 6.0 Hz, 1H), 2.05-1.98 (m, 2H); ^{13}C NMR (100 MHz, Acetone-d_6): δ 153.9, 138.7, 129.2, 129.0, 128.9, 128.8, 128.3, 127.9, 121.8, 121.2 (dd, J = 250.2, 246.2 Hz), 116.8, 74.4 (dd, J = 30.2, 27.1 Hz), 73.0 (t, J = 24.7 Hz), 64.4, 31.2 (t, J = 2.5 Hz); ^{19}F NMR (376 MHz, Acetone-d_6): δ -124.12 (d, J = 251.9 Hz, 1F), -124.88 (d, J = 251.9 Hz, 1F); IR (ATR): 3329, 2914, 2850, 1716, 1583, 1485, 1458, 1186, 1080, 1006, 754, 740 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{16}F_2NaO_3$ $[M+Na]^+$: 329.0960, Found: 329.0947. for the minor isomer: m.p. = 190-192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.48 (m, 3H), 7.43-7.36 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.26 (dd, J = 20.8, 2.4 Hz, 1H), 4.95 (dd, J = 10.8, 6.4 Hz, 1H), 4.66 (dd, J = 19.6, 12.0 Hz, 1H), 2.88 (s, 1H), 2.46 (dd, J = 13.2 Hz, 6.4, 1H), 2.05-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 136.0, 129.2, 128.8, 128.3, 127.9, 126.8, 125.9, 121.7, 119.1 (dd, J = 250.5, 246.3 Hz), 116.5, 72.5 (dd, J = 37.8, 25.7 Hz), 72.1 (dd, J = 32.6, 23.7 Hz), 64.7, 29.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ -121.69 (d, J = 262.1 Hz, 1F), -124.15 (d, J = 262.1 Hz, 1F); IR (ATR): 3383, 3035, 2929, 1583, 1485, 1458, 1236, 1186, 1034, 761, 729, 711 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{16}F_2NaO_3$ $[M+Na]^+$: 329.0960, Found: 329.0952.



3a (0.2 mmol) **5**, 54% yield

Compound **3a** (60.4 mg, 0.2 mmol) was dissolved in 2.0 mL anhydrous PhMe and the resulting solution was cooled to 0 °C. Sodium azide (26.0 mg, 0.4 mmol, 2.0 equivs) was added in a single portion, followed by concentrated H_2SO_4 (97 μL, 1.8 mmol, 9.0 equivs) dropwise. The resulting yellow biphasic mixture was stirred vigorously at 0 °C. After 1h, the reaction was allowed to warm to room temperature and was stirred overnight. The following morning, the reaction was quenched

by 3 M NaOH (2 mL), and extracted with EtOAc (2.0 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. the residue was purified by column chromatography (PE/EtOAc = 2:1, v/v) to afford product **5** in 54% yield (31.5 mg) as white solid, m.p. = 318-320 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.46 (t, *J* = 5.6 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.13-5.03 (m, 1H), 3.51-3.48 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 160.4 (t, *J* = 26.8 Hz), 152.2, 137.0, 133.1, 130.2, 129.3, 128.9, 127.1, 125.3, 124.7, 122.4, 121.1, 81.8 (dd, *J* = 28.0, 22.6 Hz), 37.5; ^{19}F NMR (376 MHz, DMSO-d_6): δ -111.48 (d, *J* = 258.7 Hz, 1F), -118.53 (d, *J* = 258.7 Hz, 1F). IR (ATR): 3323, 3070, 2922, 1687, 1676, 1604, 1460, 1448, 1101, 796, 754, 690 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{13}F_2NNaO_3$ $[M+Na]^+$: 340.0756, Found: 340.0745.



3b (0.2 mmol) **6**, 38% yield

Into a pressure tube containing a mixture of product **3b** (0.2 mmol, 1.0 equiv) and aqueous KOH (10.5 equivs), then add CH_3CN and H_2O (1.0 mL, 1/1, v/v) into the tube. The resulting mixture was stirred at 80 °C. After full consumption of **3b** by TLC analysis (about 5 h), EtOAc (10 mL) and saturated aqueous NH_4Cl (5.0 mL) were added subsequently. The mixture was transferred to a separating funnel. The organic layer was separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography (PE/EtOAc = 10/1, v/v) to afford product **6** in 38% yield (16.1 mg) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* =1.6 Hz, 1H), 7.33 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 6.02 (ddd, *J* = 55.6, 54.3, 3.4 Hz, 1H), 4.66-4.58 (m, 1H), 2.91 (dd, *J* = 16.9, 12.7 Hz, 1H), 2.79 (dd, *J* = 16.9, 3.6 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 189.7, 158.0, 137.5, 131.9, 126.6, 120.5, 117.6, 113.5 (dd, J = 245.0, 243.5 Hz), 75.7 (dd, *J* = 28.3, 26.3 Hz), 35.6 (t, *J* = 2.7 Hz) 20.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -128.40 (d, *J* = 294.4 Hz, 1F), -131.88 (d, *J* = 294.4 Hz, 1F)； IR (ATR): 2918, 2914, 1747, 1442，

1307, 1095, 954, 860, 820 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{11}H_{10}F_2O_2$ $[M+H]^+$: 213.0722, Found: 213.0724

Part III. Biological activities evaluation

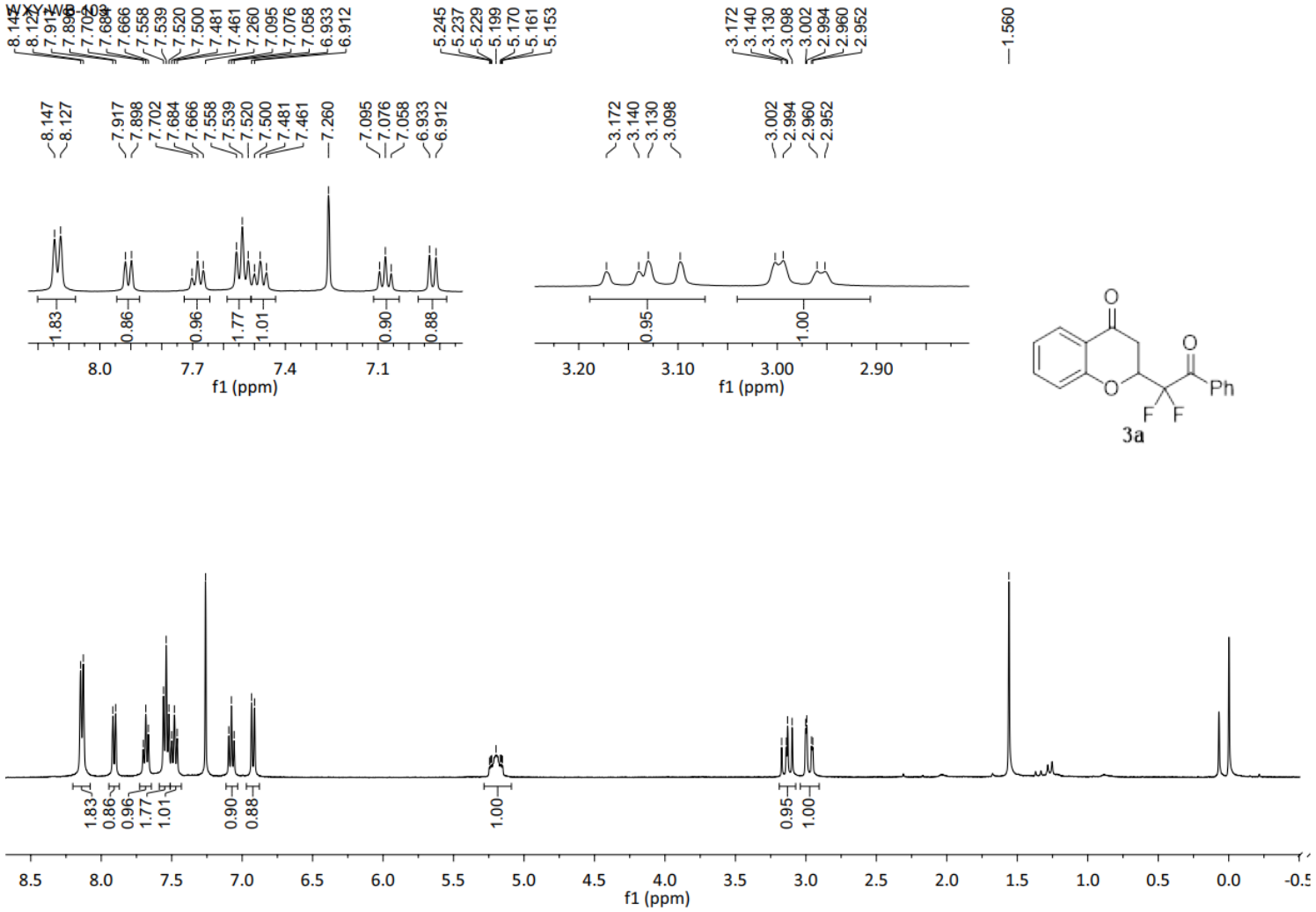
Cells culture

Human cancer cell lines HCT116 was purchased from the American Tissue Culture Collection (ATCC). Cells were cultured aseptically at 37 °C with 5% CO_2 using McCoy's 5A, MEM and ECM (Gibco) with 10% (v/v) FBS and 1% (v/v) penicillin-streptomycin (Sigma).

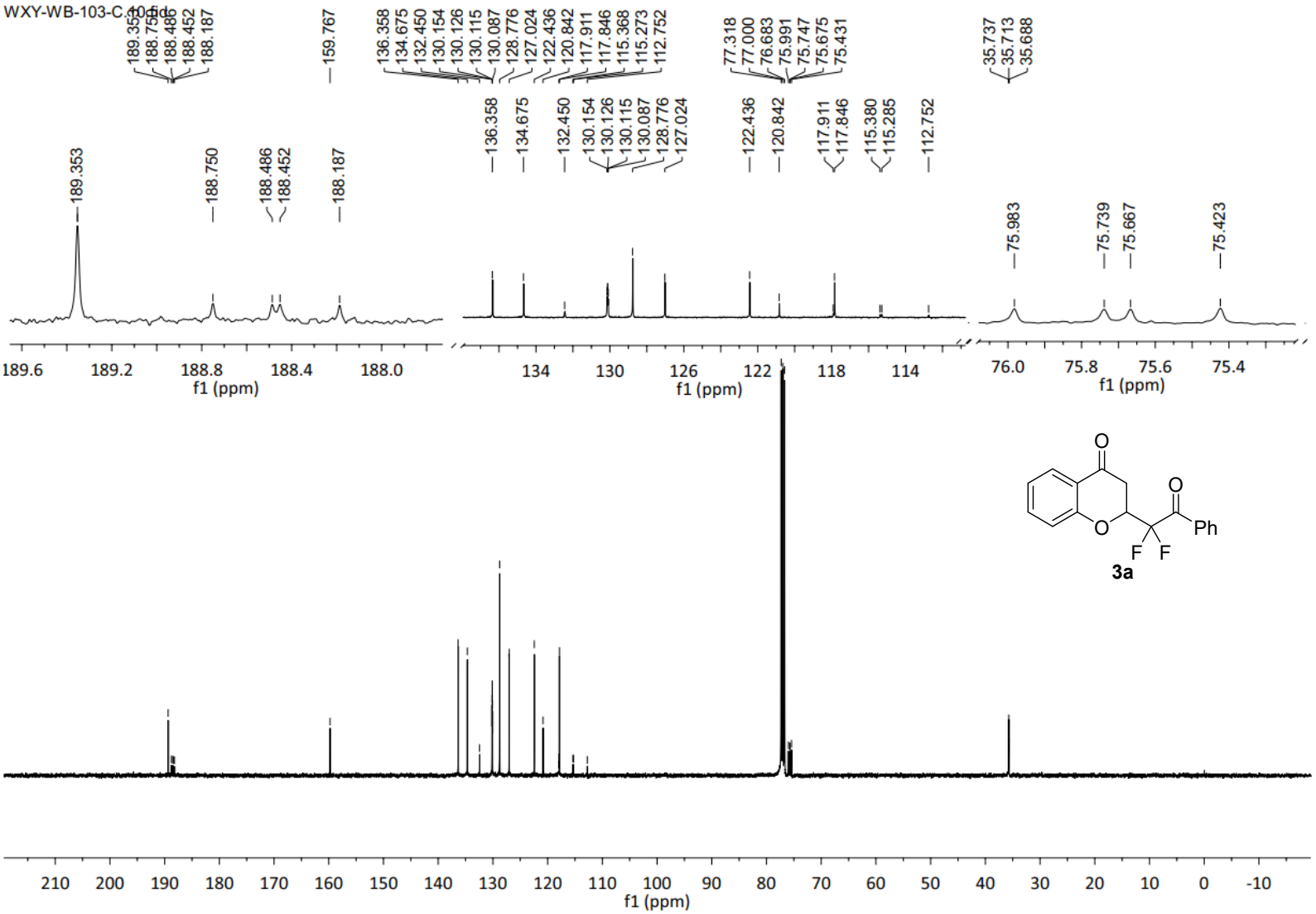
CCK-8 assay

The in vitro inhibitory effects on cell proliferation were measured using CCK-8 assay. The cells were seeded in 96-well plates at a concentration of 3,000 cells/well. After 24 h incubation, compounds were added into each well at 20 μM. Seventy-two hours later, the old medium was replaced with fresh medium containing 10% CCK-8, and the cells were incubated for additional 4 h. The optical density was measured at 450 nm and 620 nm (reference wavelength) using a microplate reader (Berthold). If the inhibition rate of compounds on cells is higher than 70%, the IC_{50} value was determined by testing the inhibitory effects of the compound with 8 gradient-dilution concentrations. The IC_{50} values were calculated using GraphPad software.

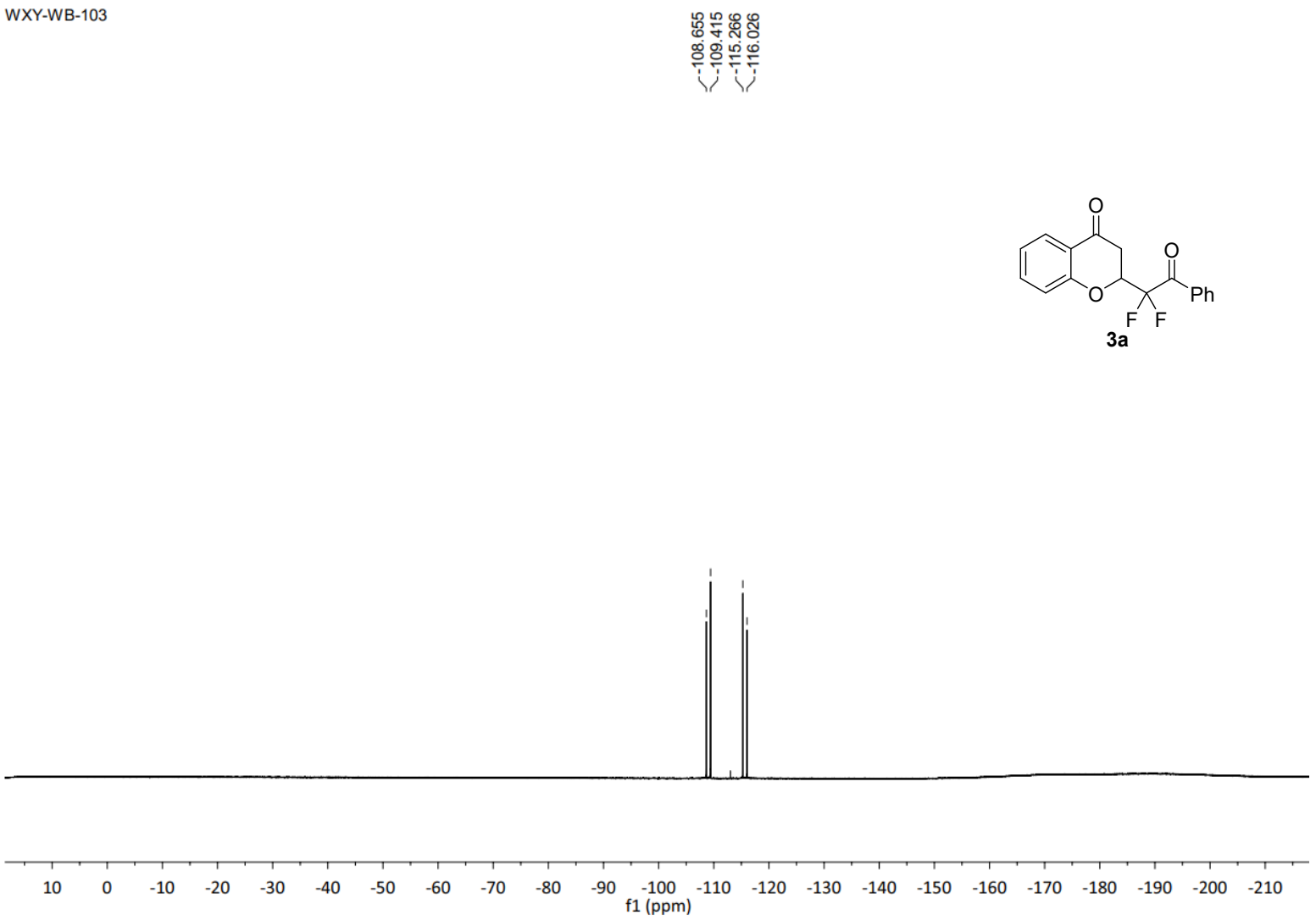
Part IV. ^{1}H, ^{13}C, and ^{19}F NMR spectra



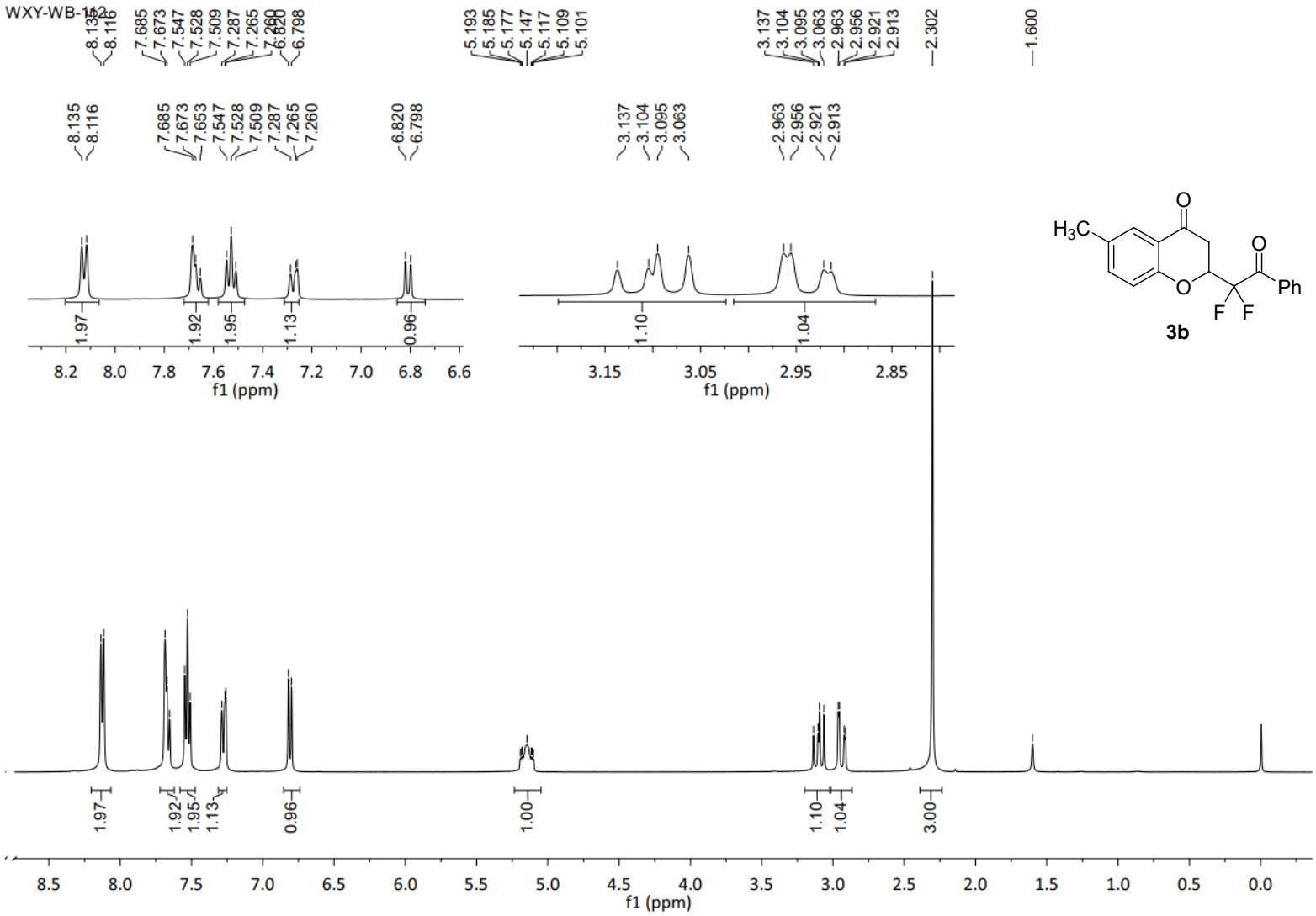
^{1}H NMR of Compound **3a** (400 MHz, $CDCl_3$)



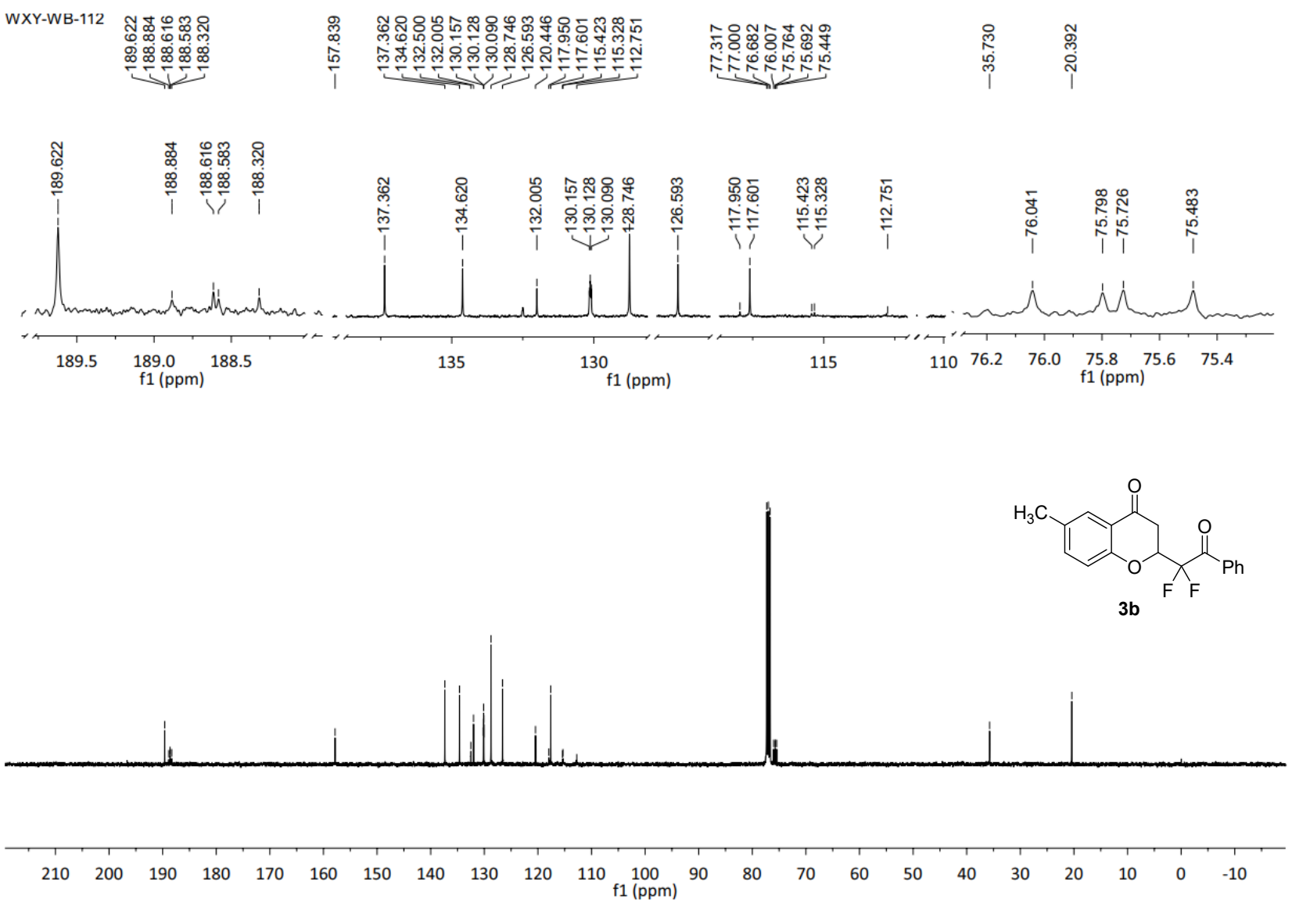
^{13}C NMR of Compound **3a** (100 MHz, $CDCl_3$)



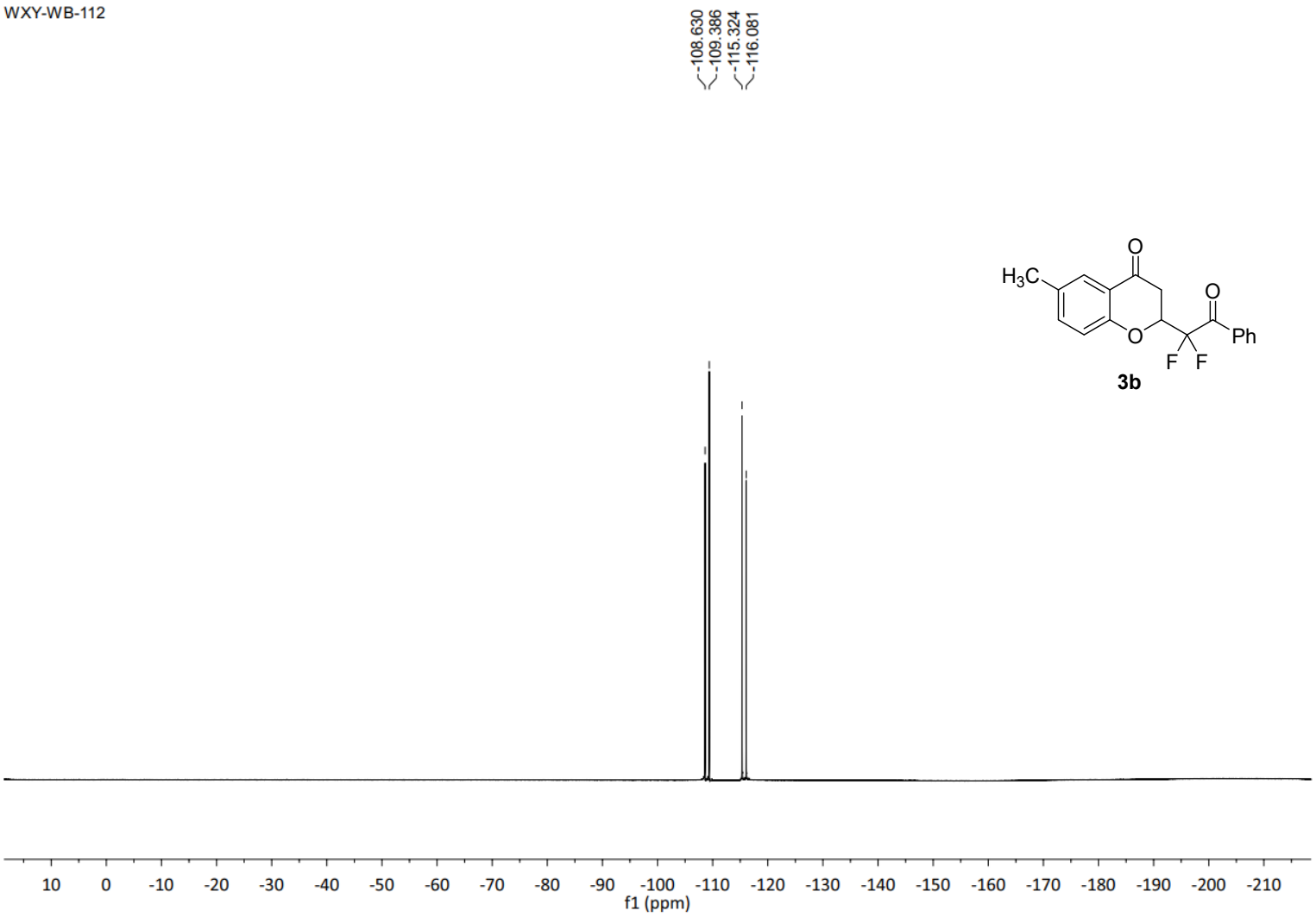
^{19}F NMR of Compound **3a** (376 MHz, $CDCl_3$)



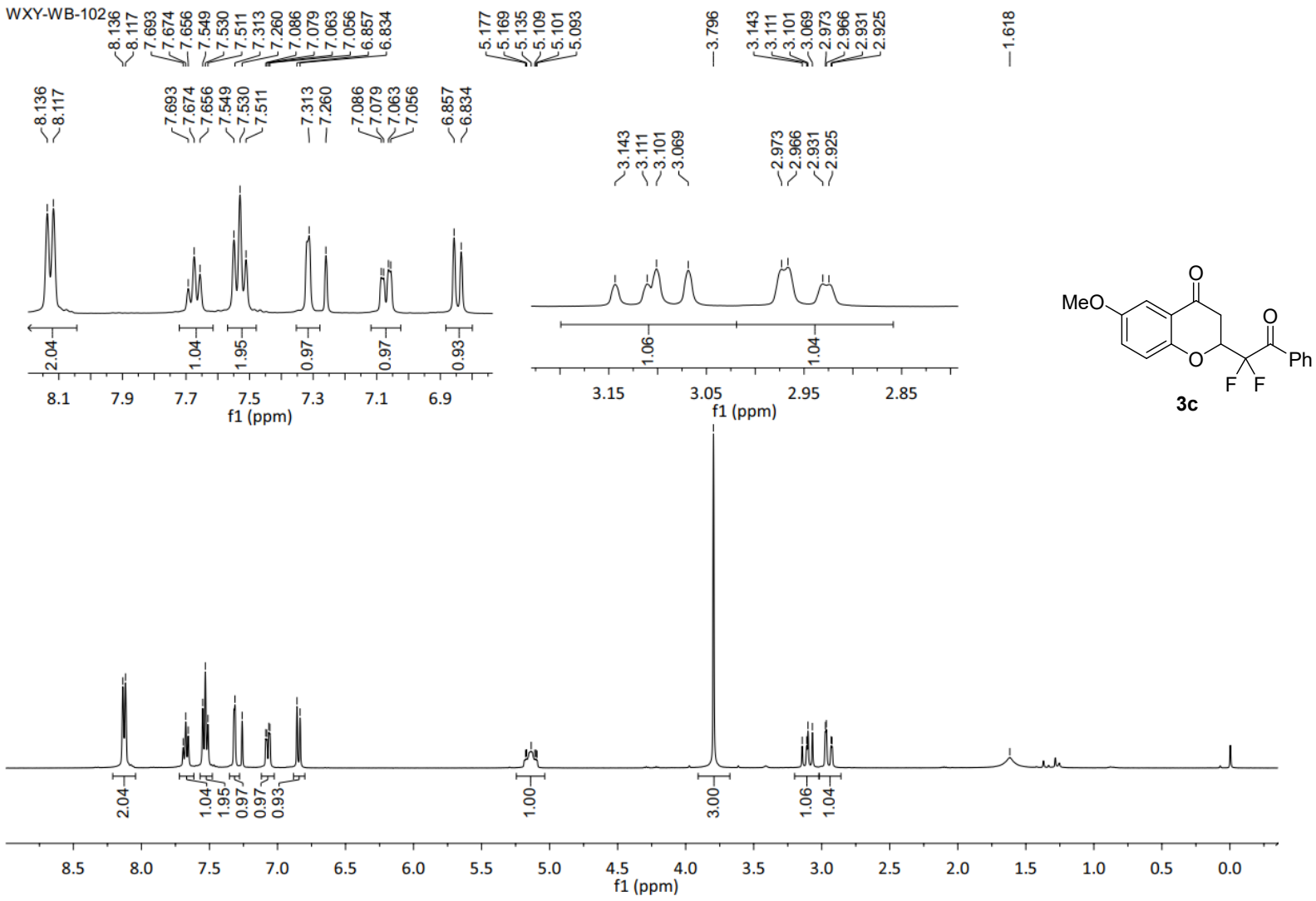
^{1}H NMR of Compound **3b** (400 MHz, $CDCl_3$)



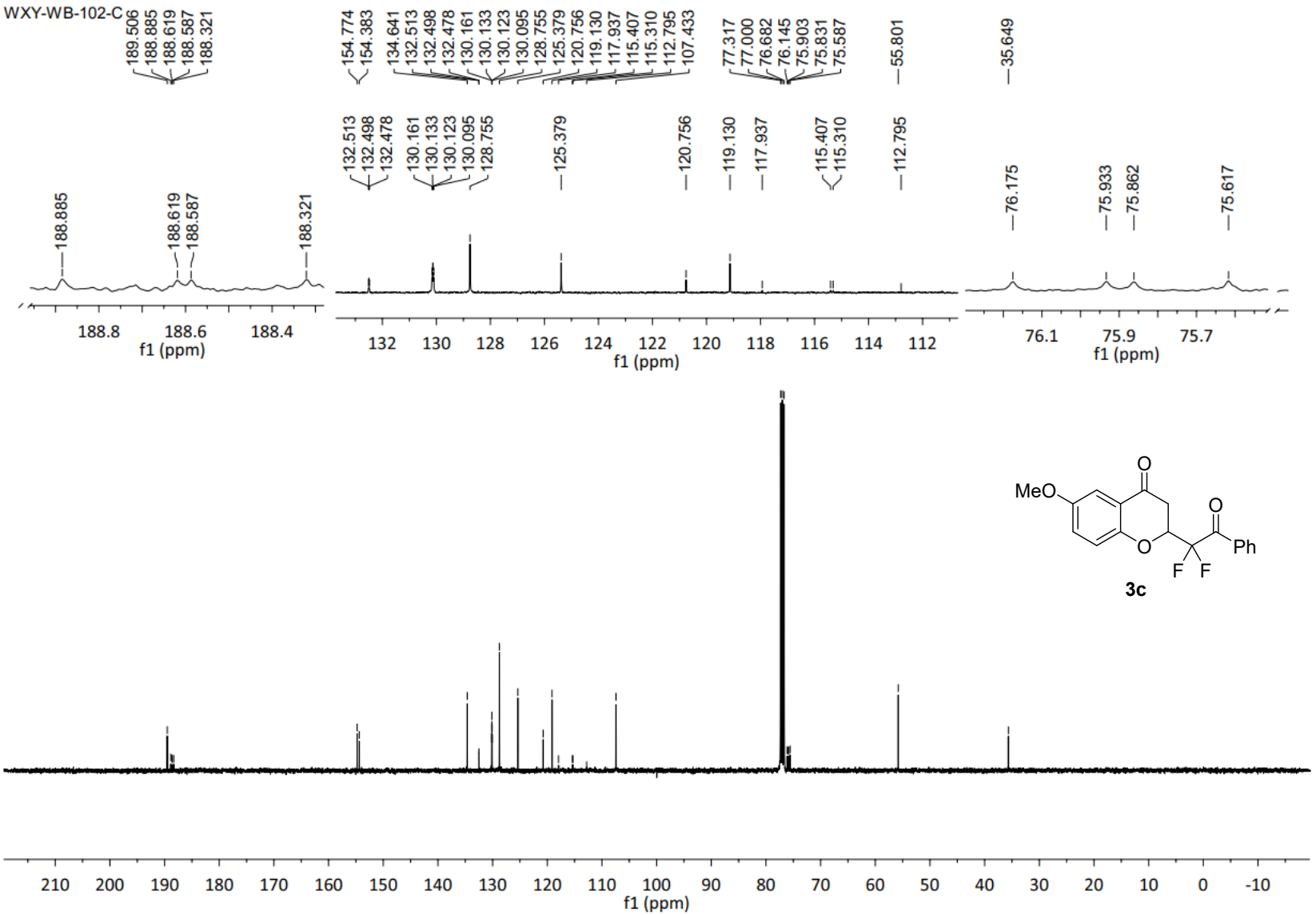
^{13}C NMR of Compound **3b** (100 MHz, $CDCl_3$)



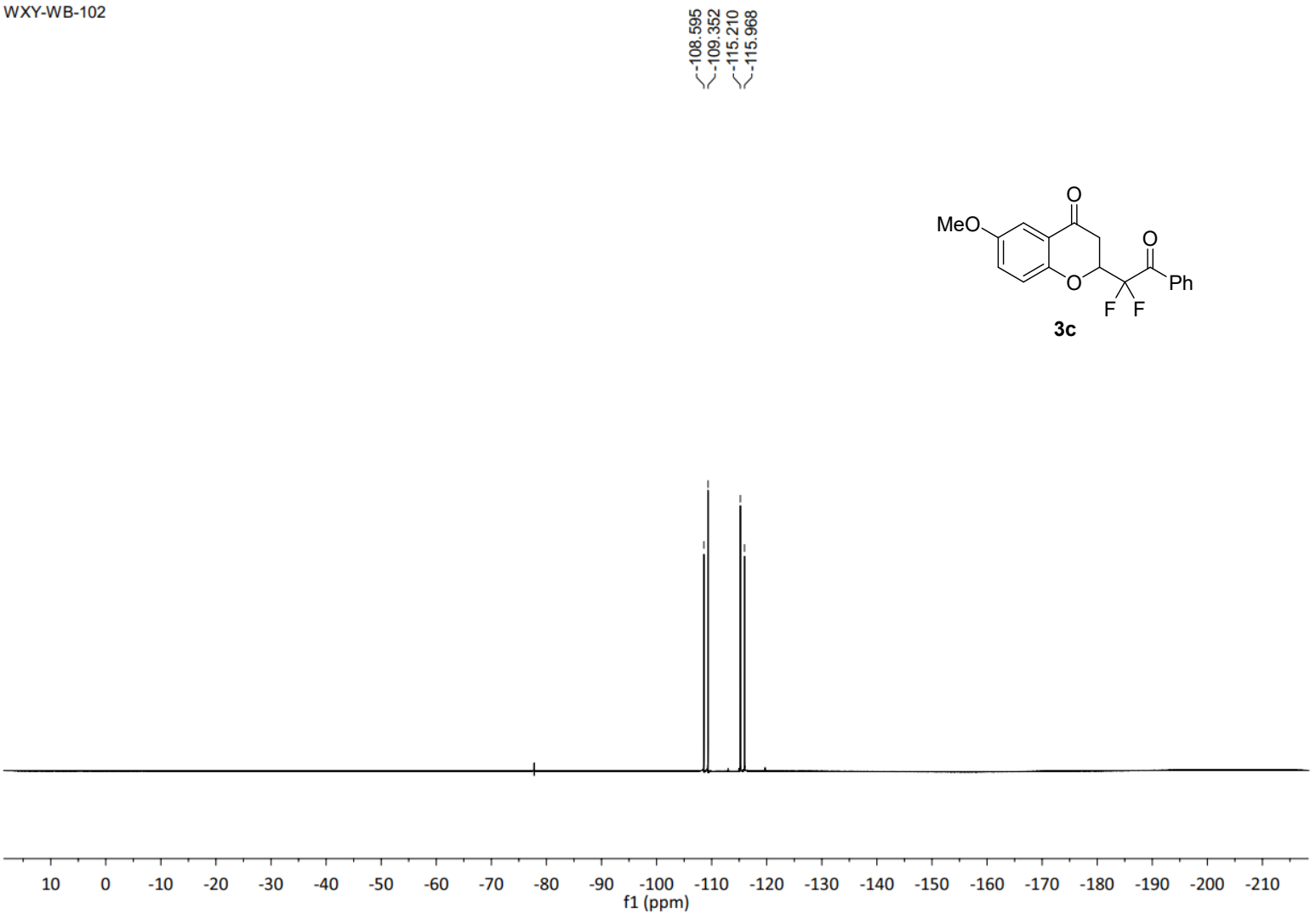
^{19}F NMR of Compound **3b** (376 MHz, $CDCl_3$)



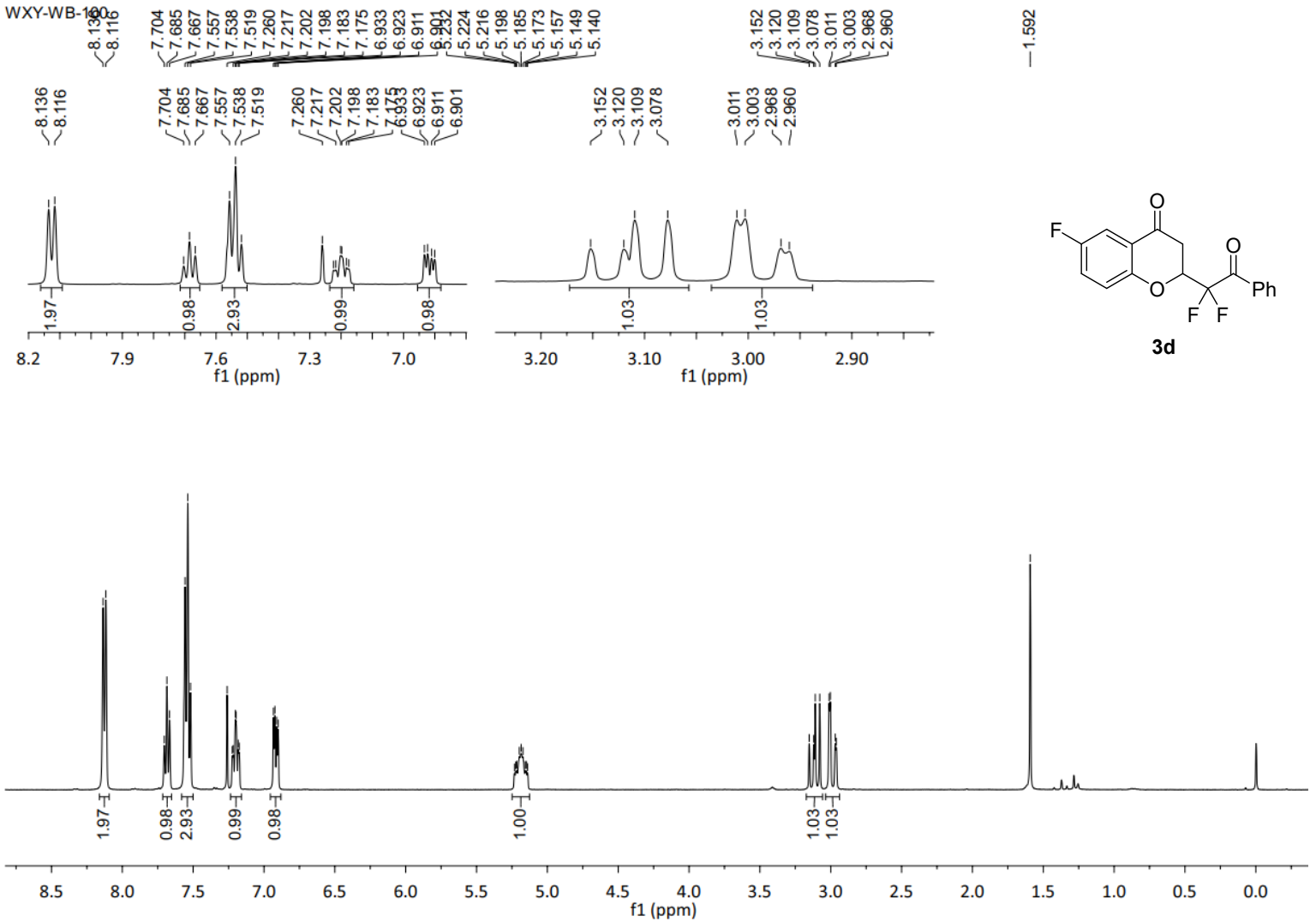
^{1}H NMR of Compound **3c** (400 MHz, $CDCl_3$)



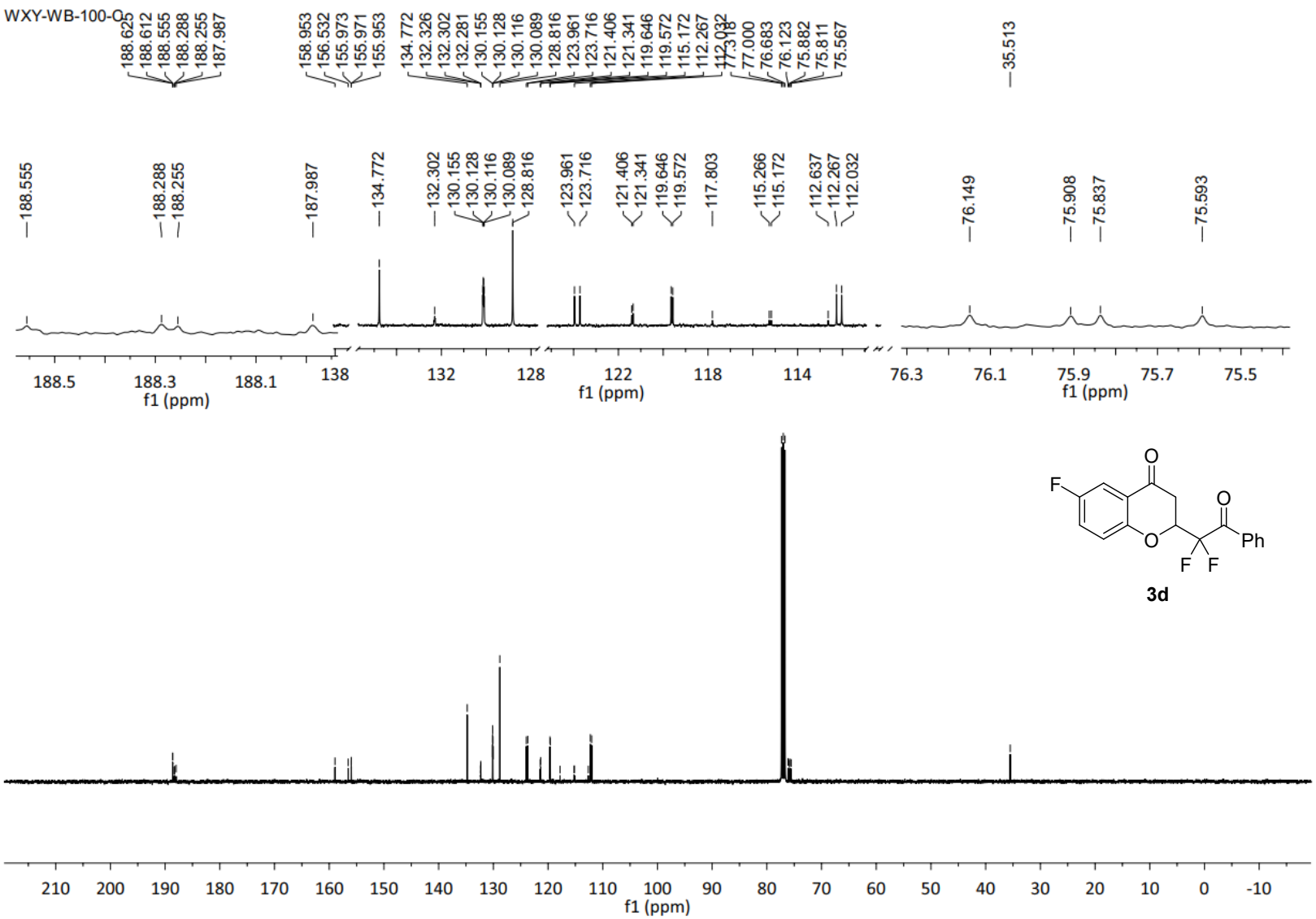
^{13}C NMR of Compound **3c** (100 MHz, $CDCl_3$)



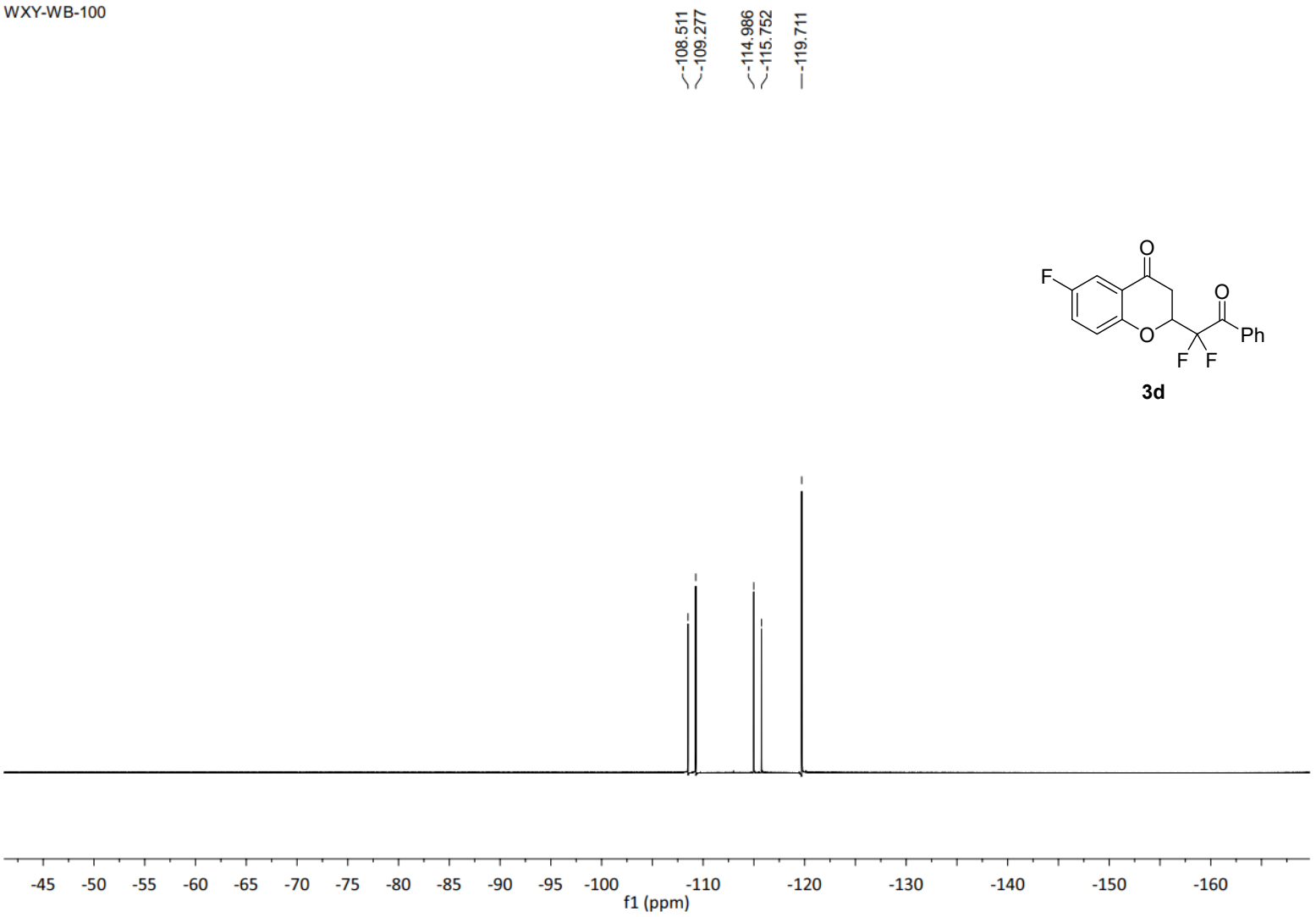
^{19}F NMR of Compound **3c** (376 MHz, $CDCl_3$)



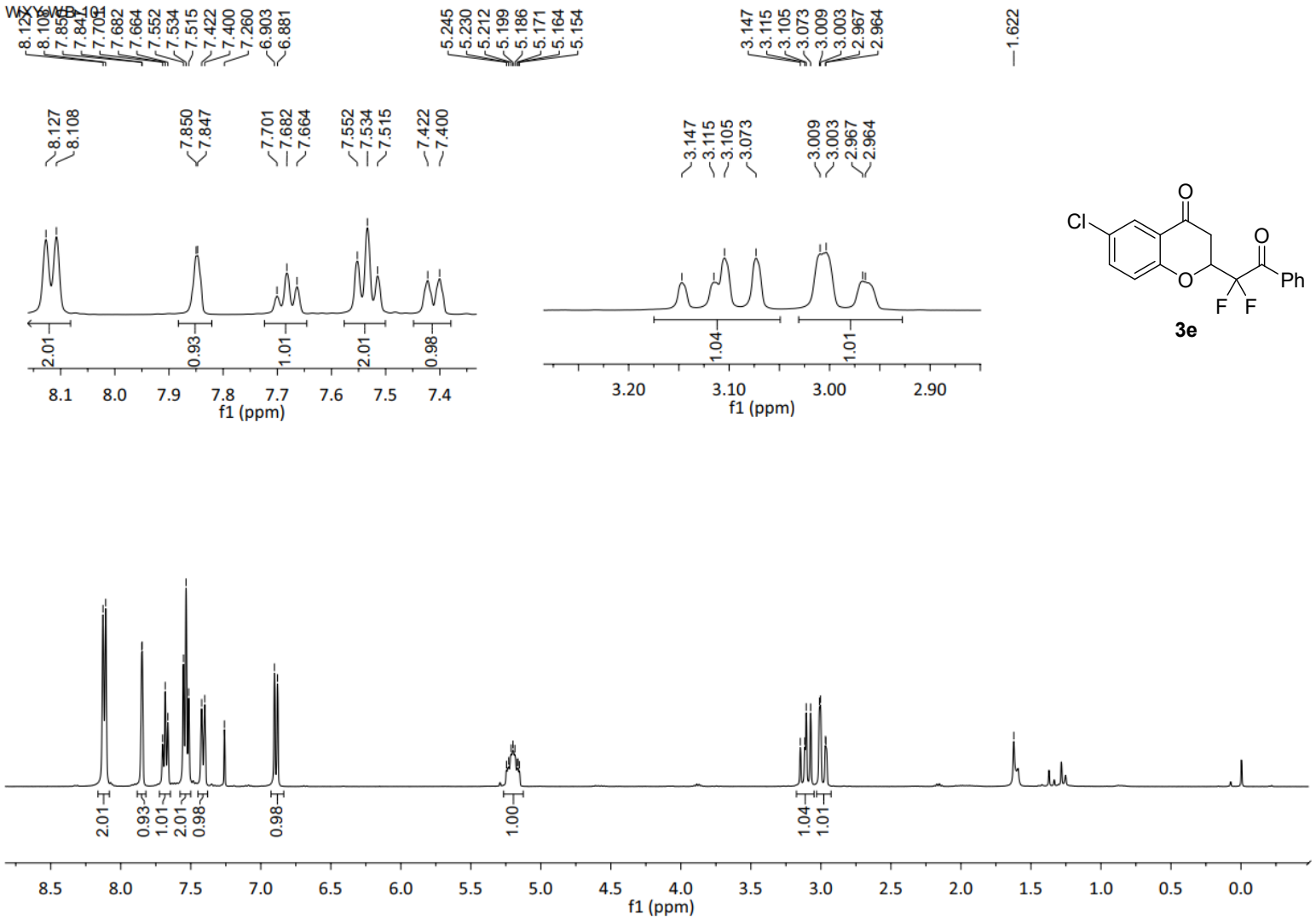
^{1}H NMR of Compound **3d** (400 MHz, $CDCl_3$)



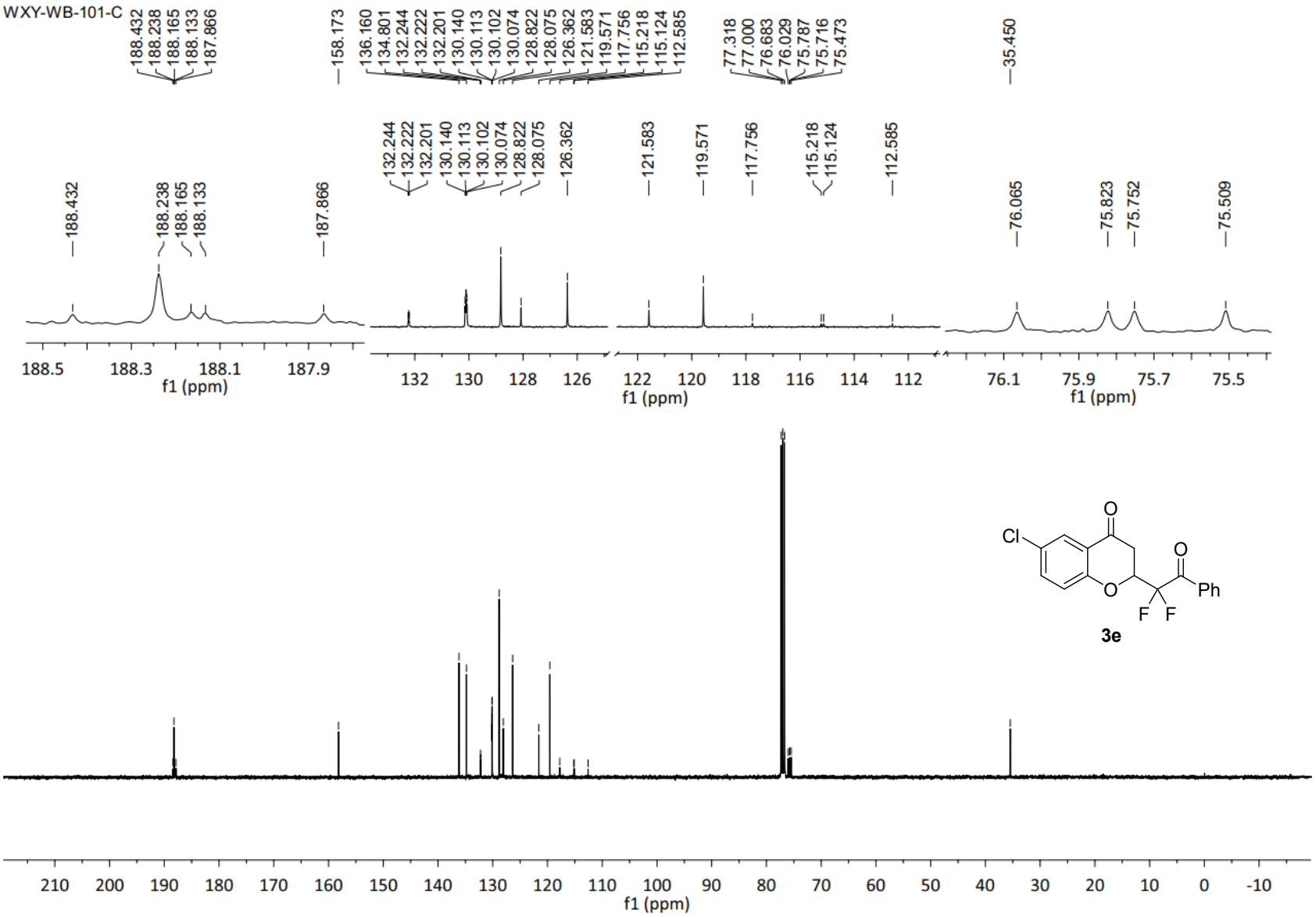
^{13}C NMR of Compound **3d** (100 MHz, $CDCl_3$)



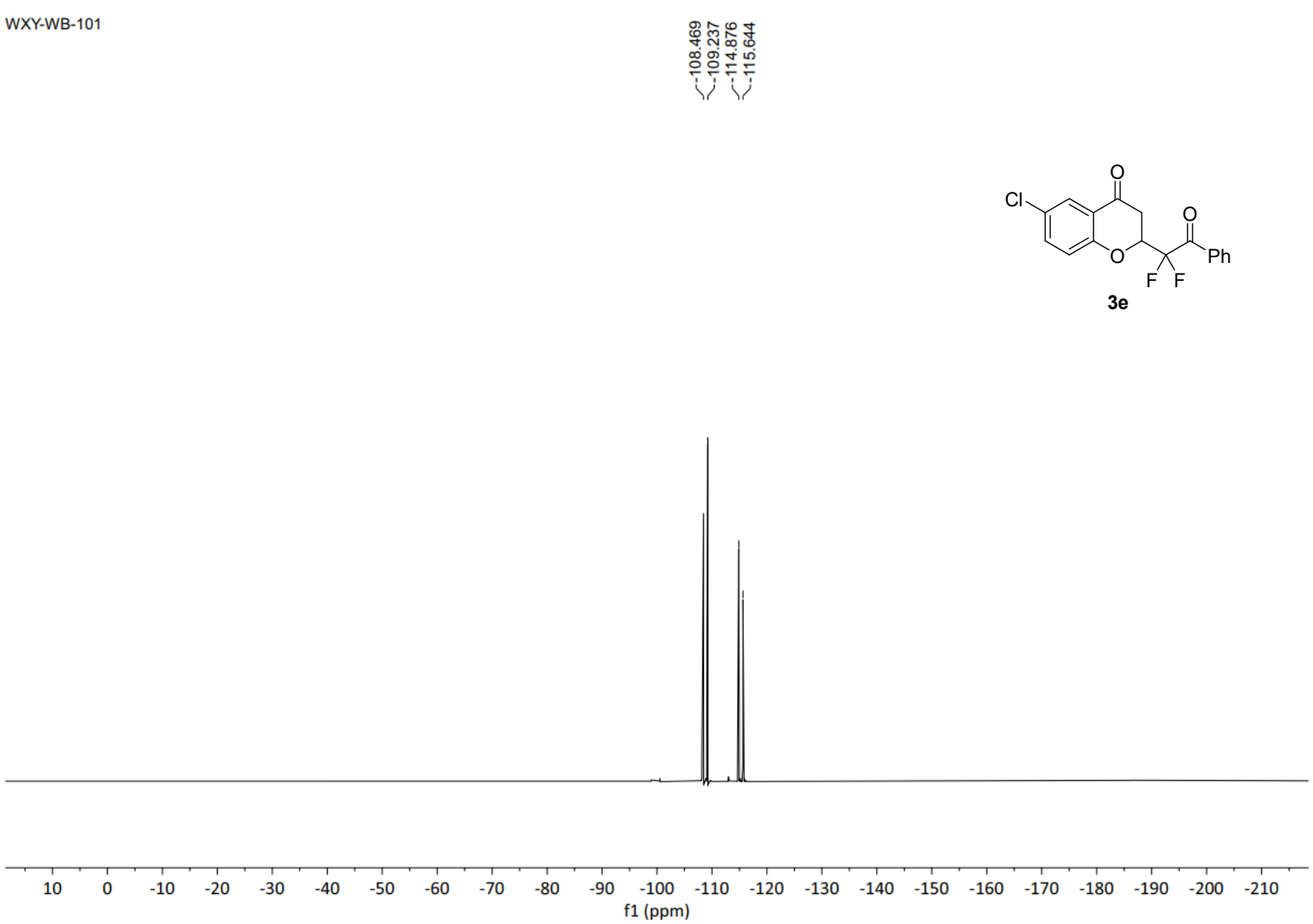
^{19}F NMR of Compound **3d** (376 MHz, $CDCl_3$)



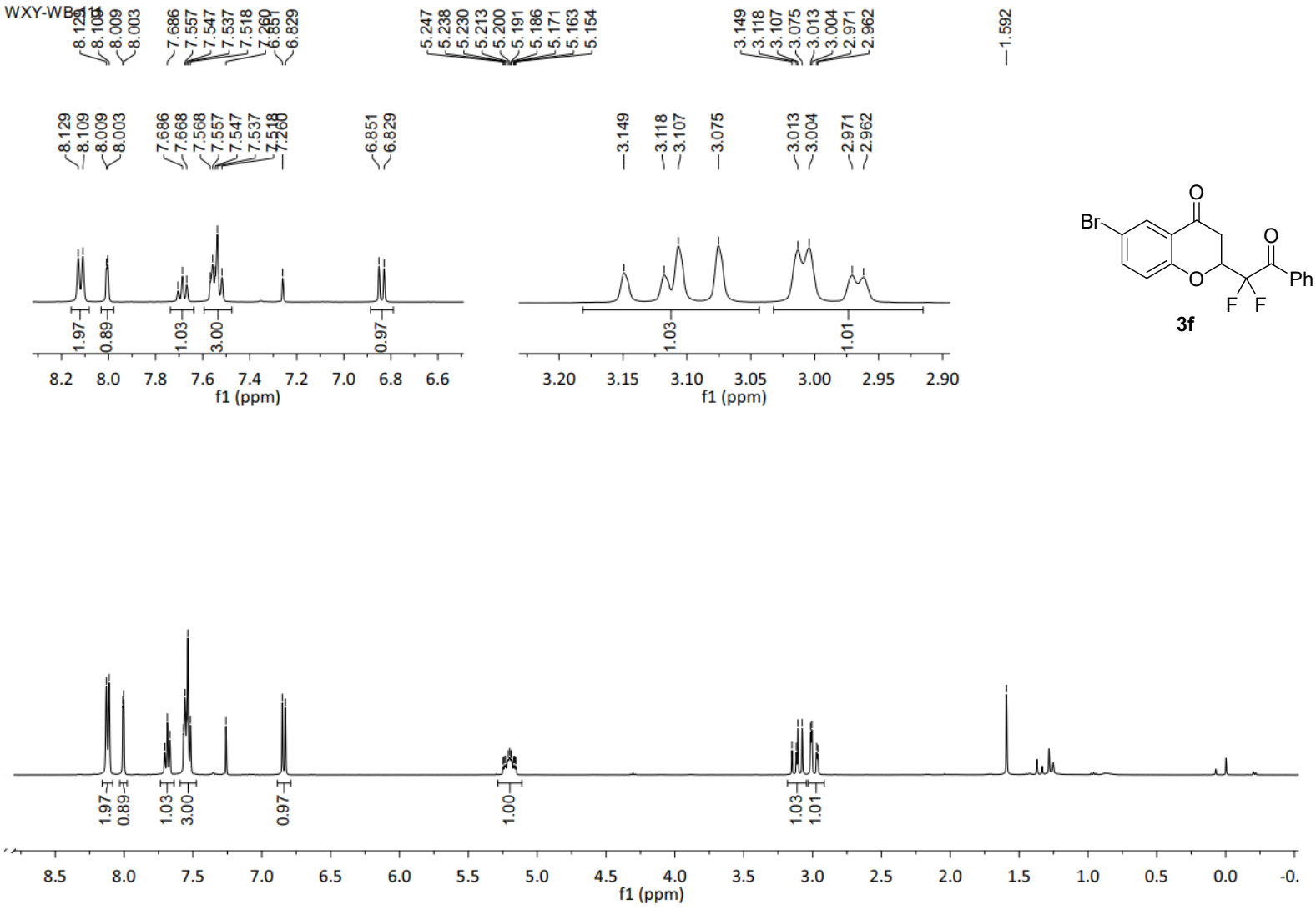
^{1}H NMR of Compound **3e** (400 MHz, $CDCl_3$)



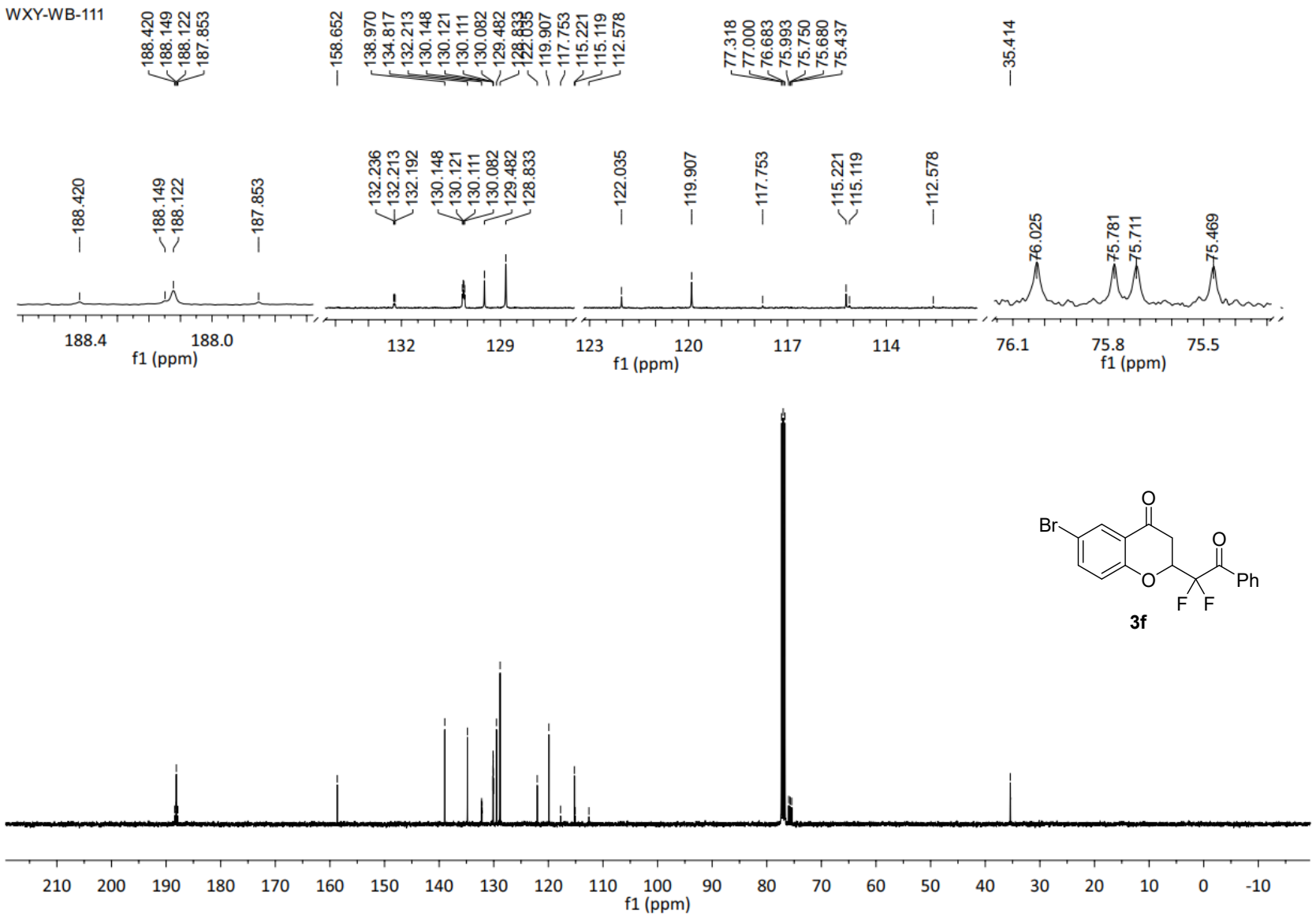
^{13}C NMR of Compound **3e** (100 MHz, $CDCl_3$)



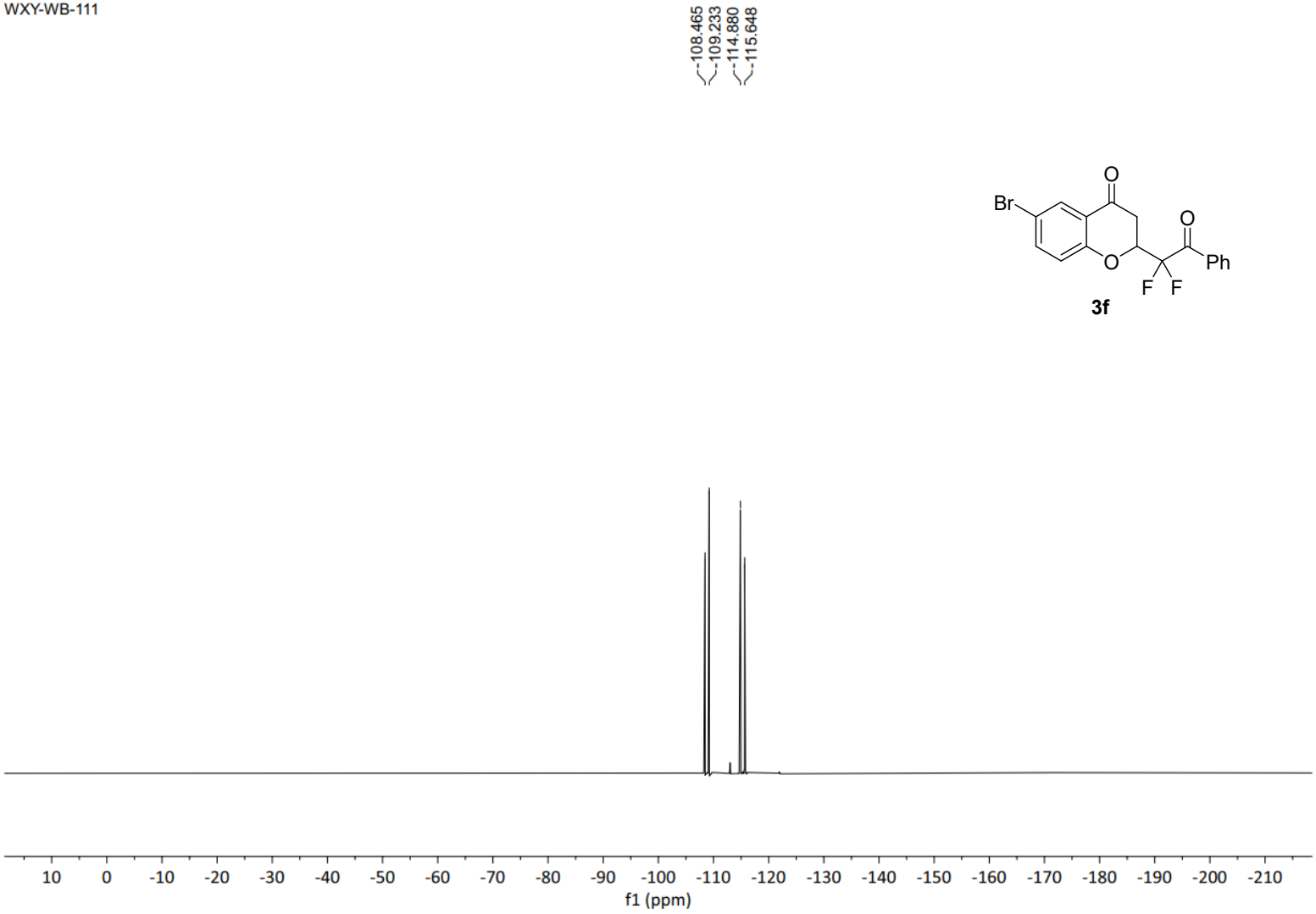
^{19}F NMR of Compound **3e** (376 MHz, $CDCl_3$)



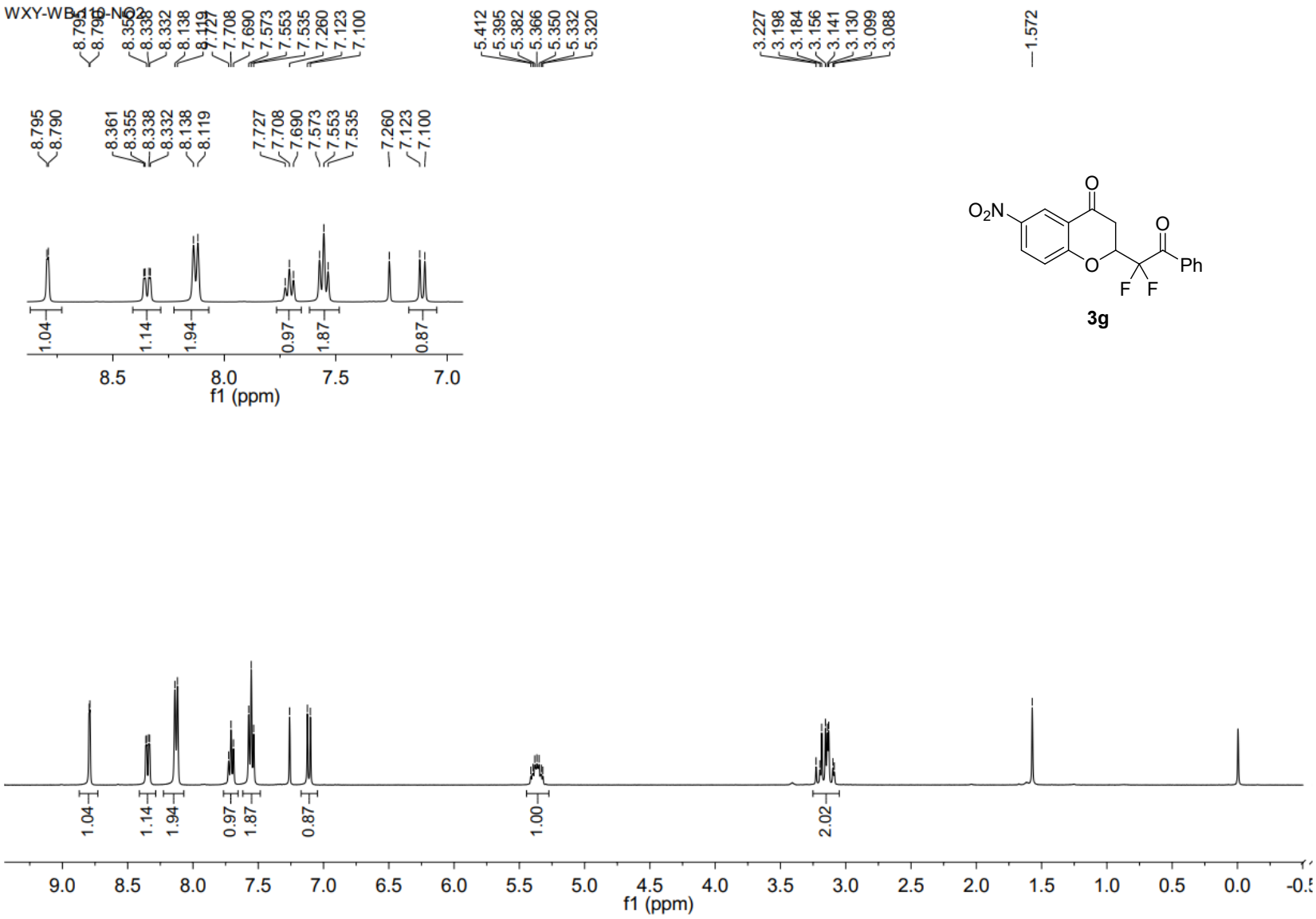
^{1}H NMR of Compound **3f** (400 MHz, $CDCl_3$)



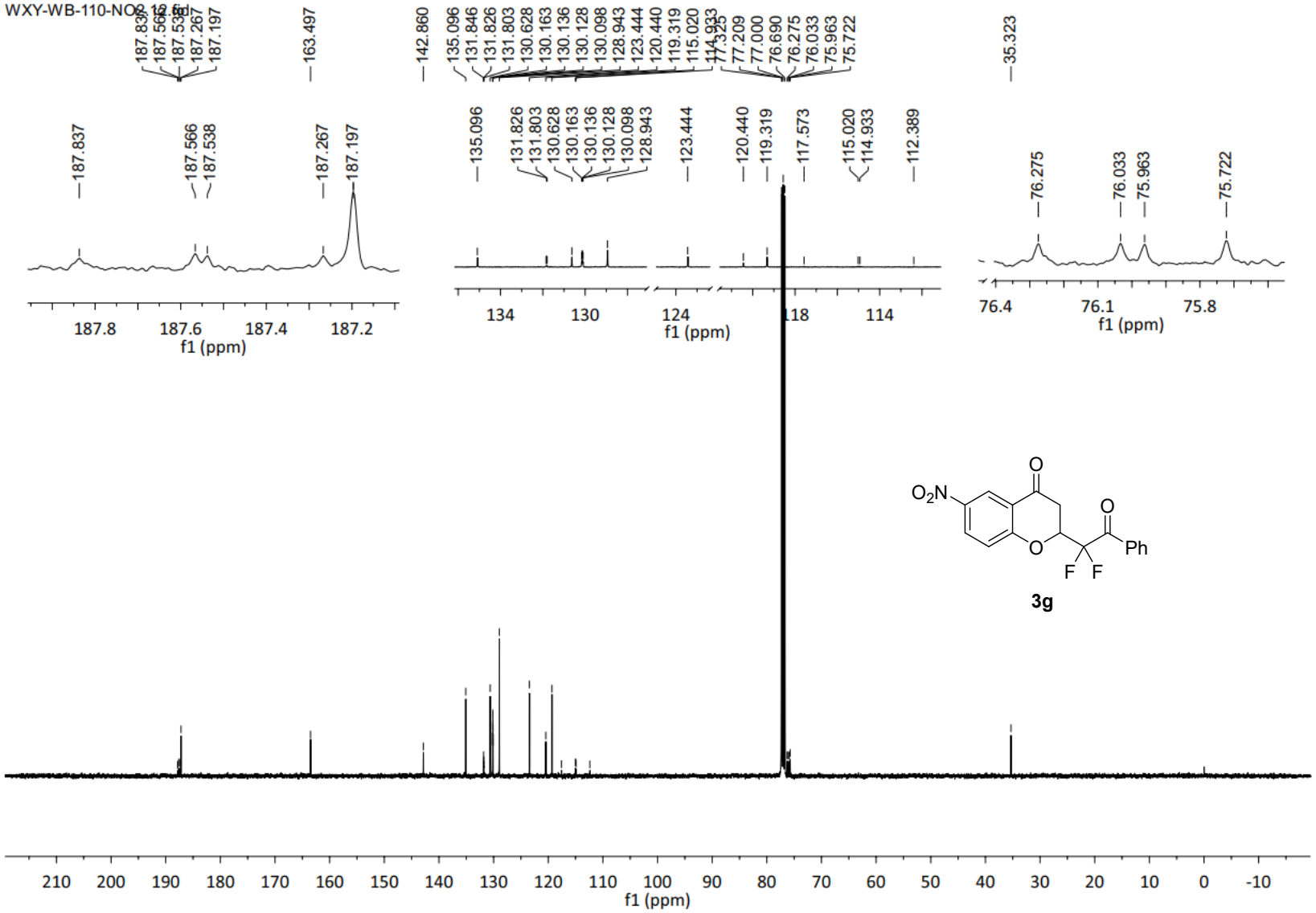
^{13}C NMR of Compound **3f** (100 MHz, $CDCl_3$)



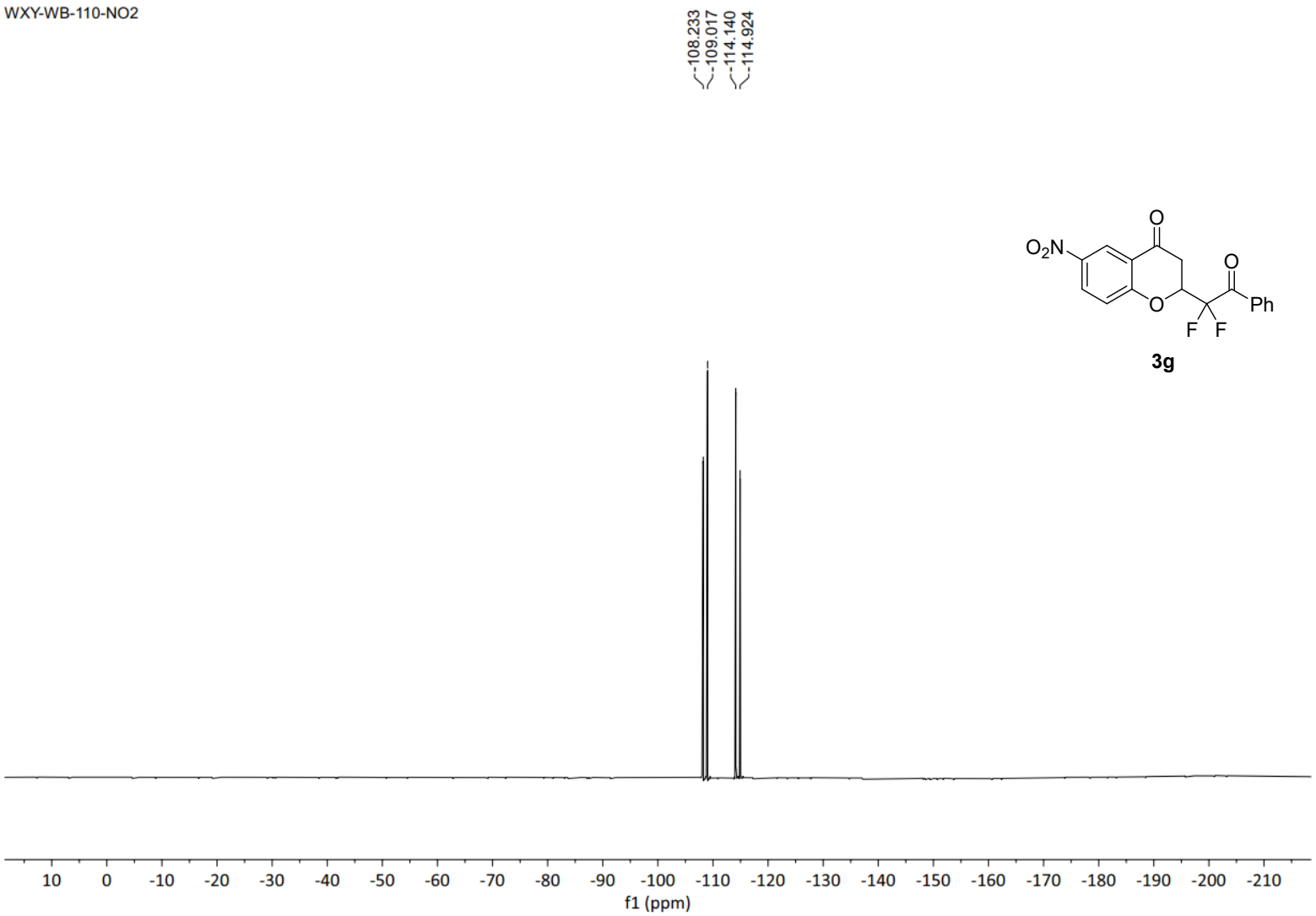
^{19}F NMR of Compound **3f** (376 MHz, $CDCl_3$)



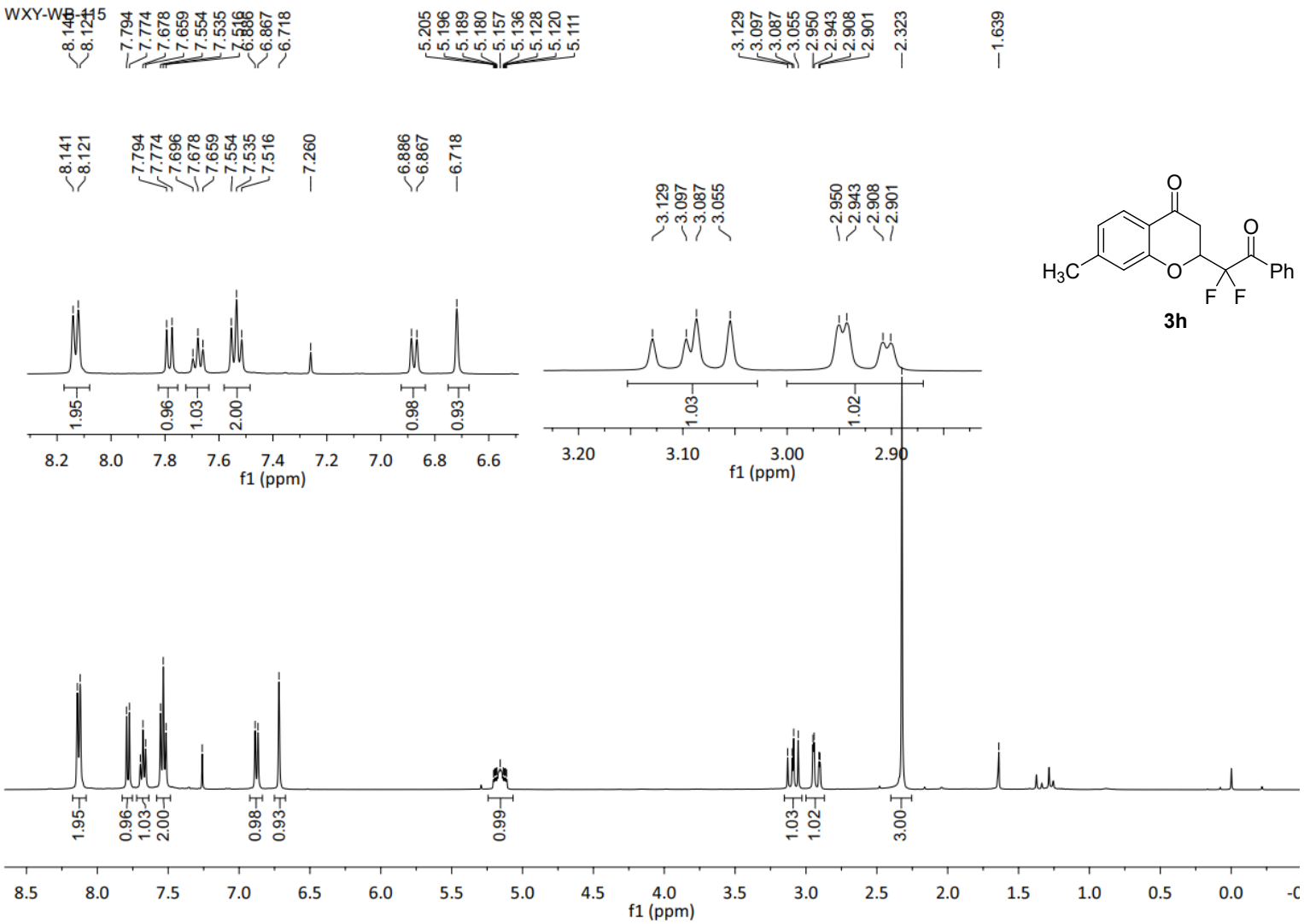
^{1}H NMR of Compound **3g** (400 MHz, $CDCl_3$)



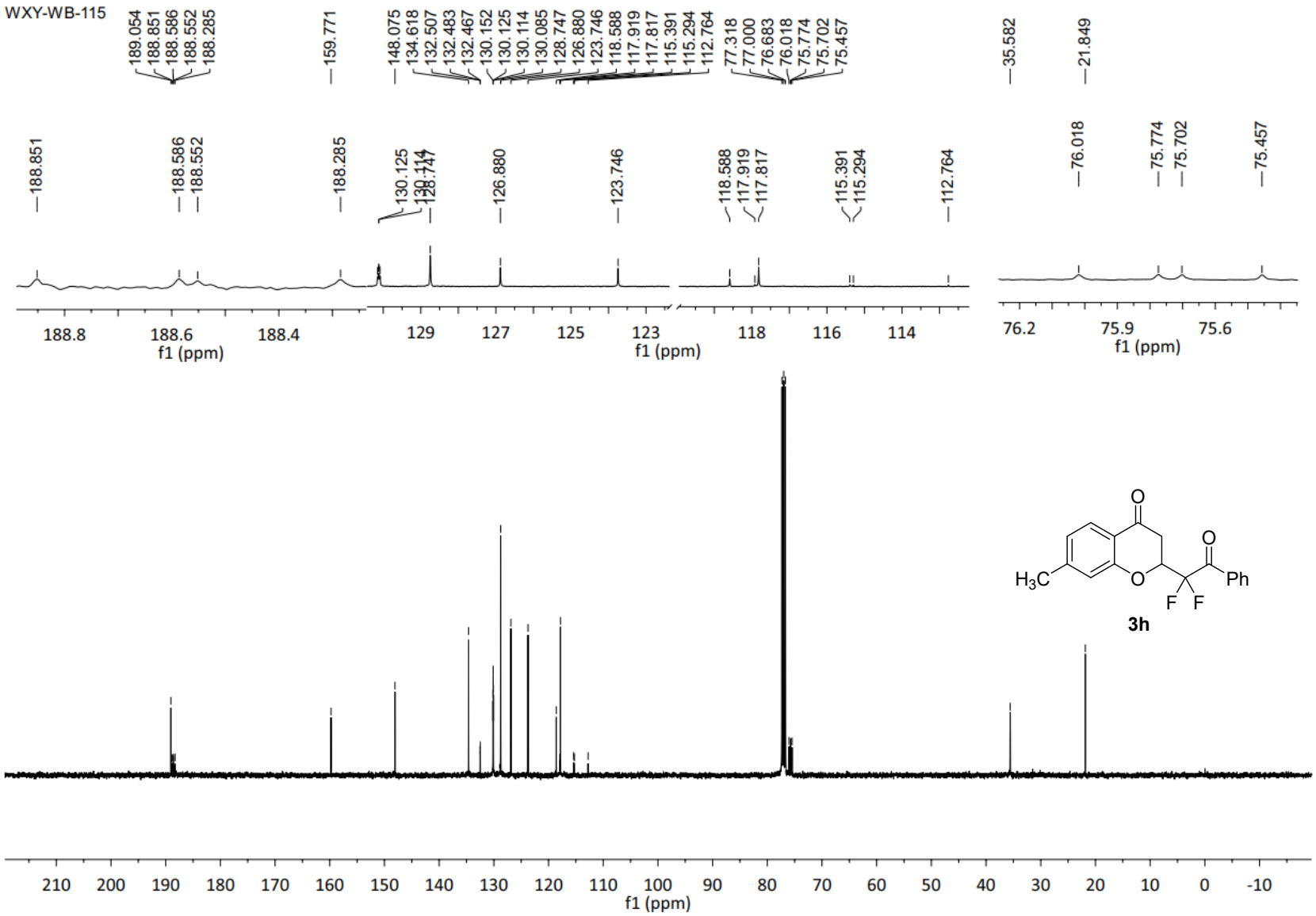
^{13}C NMR of Compound **3g** (100 MHz, $CDCl_3$)



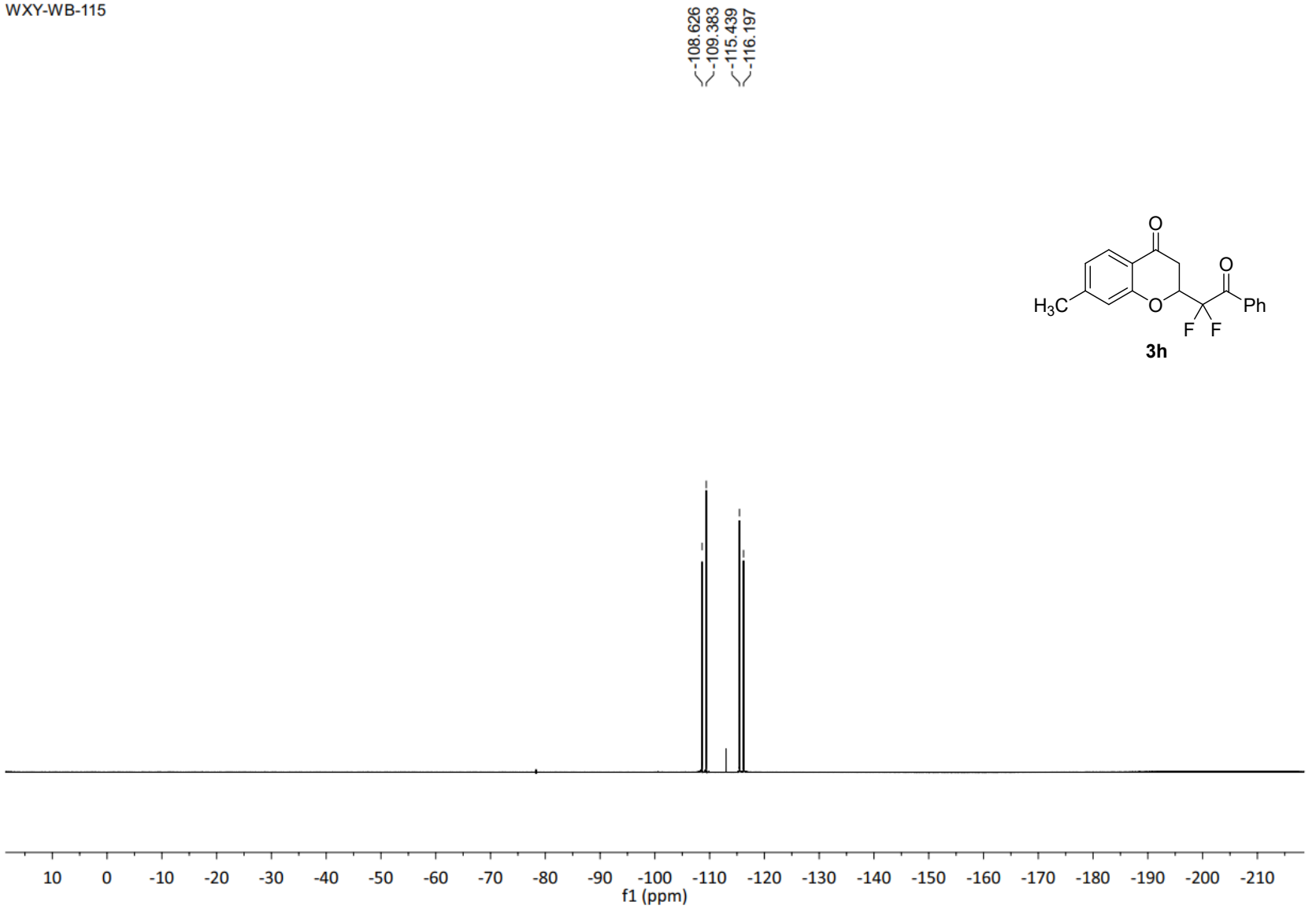
^{19}F NMR of Compound **3g** (376 MHz, $CDCl_3$)



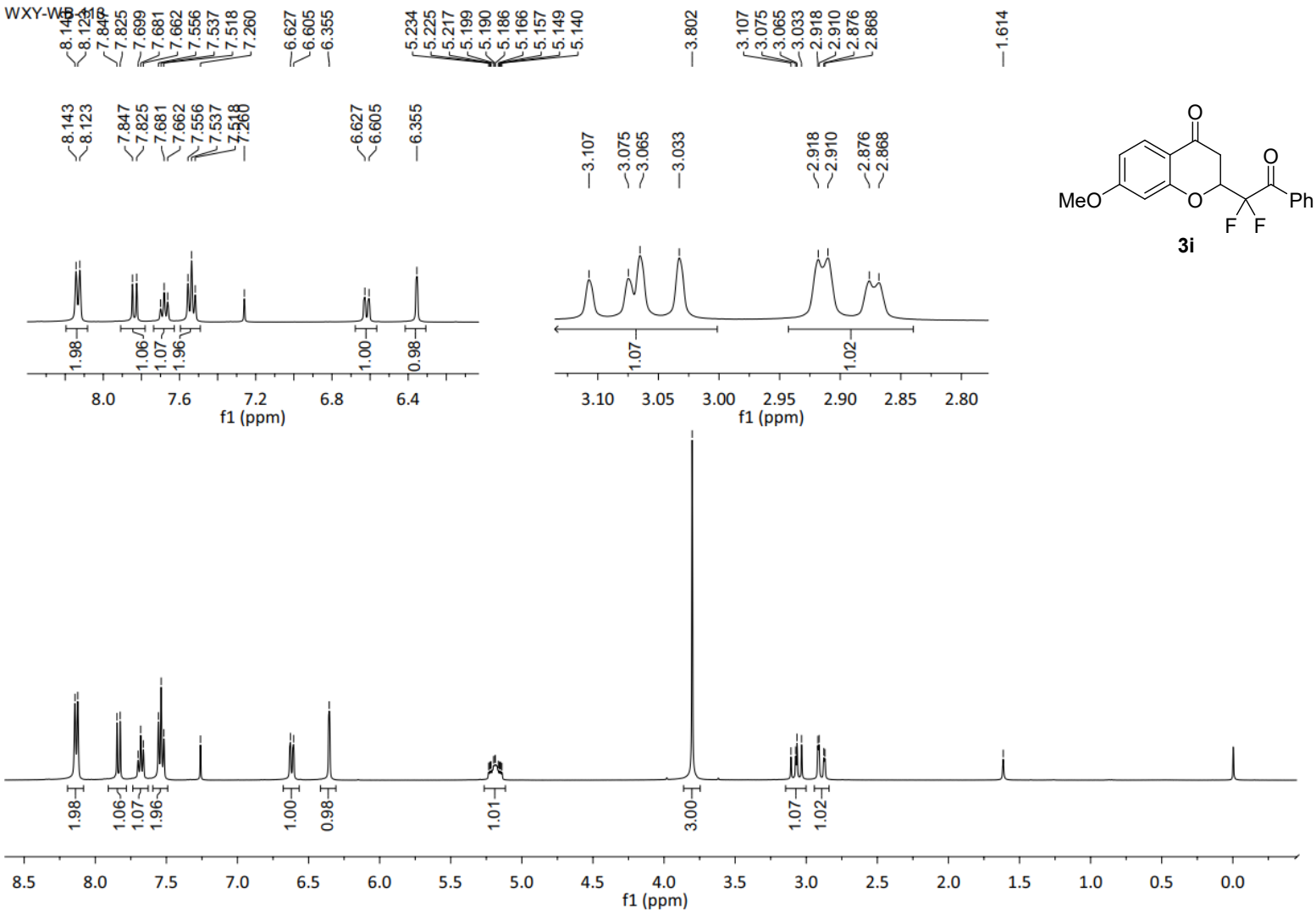
^{1}H NMR of Compound **3h** (400 MHz, $CDCl_3$)



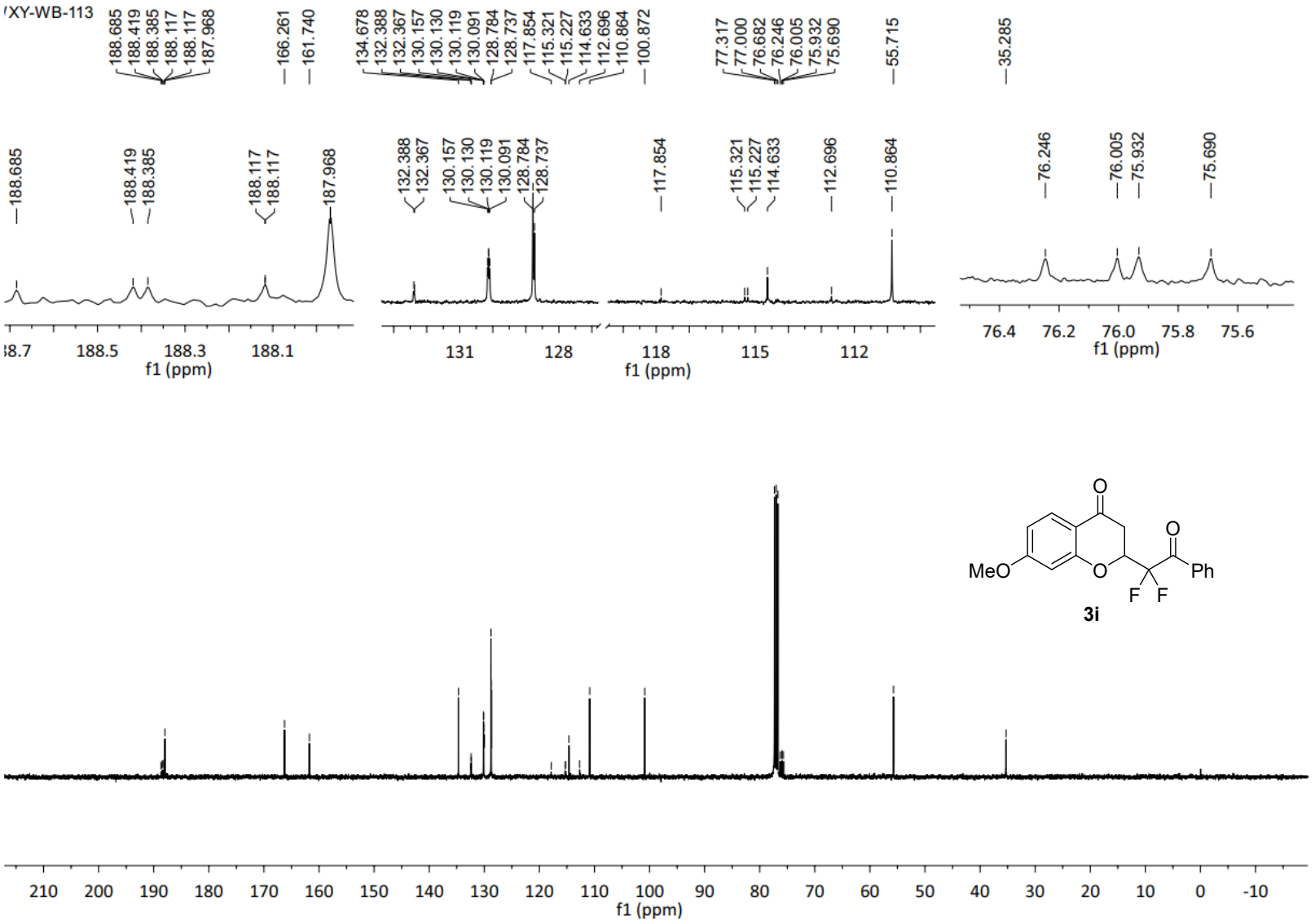
^{13}C NMR of Compound **3h** (100 MHz, $CDCl_3$)



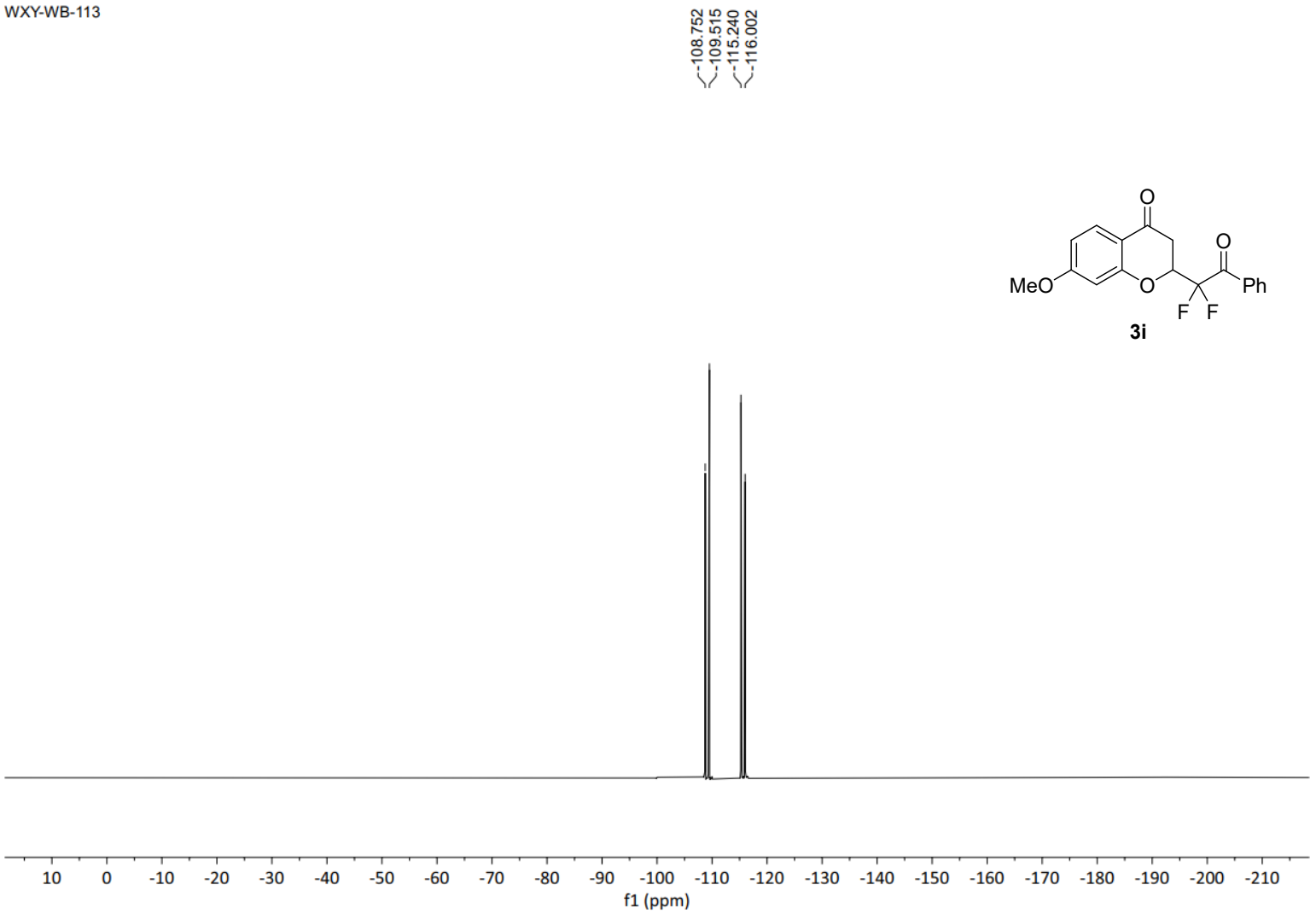
^{19}F NMR of Compound **3h** (376 MHz, $CDCl_3$)



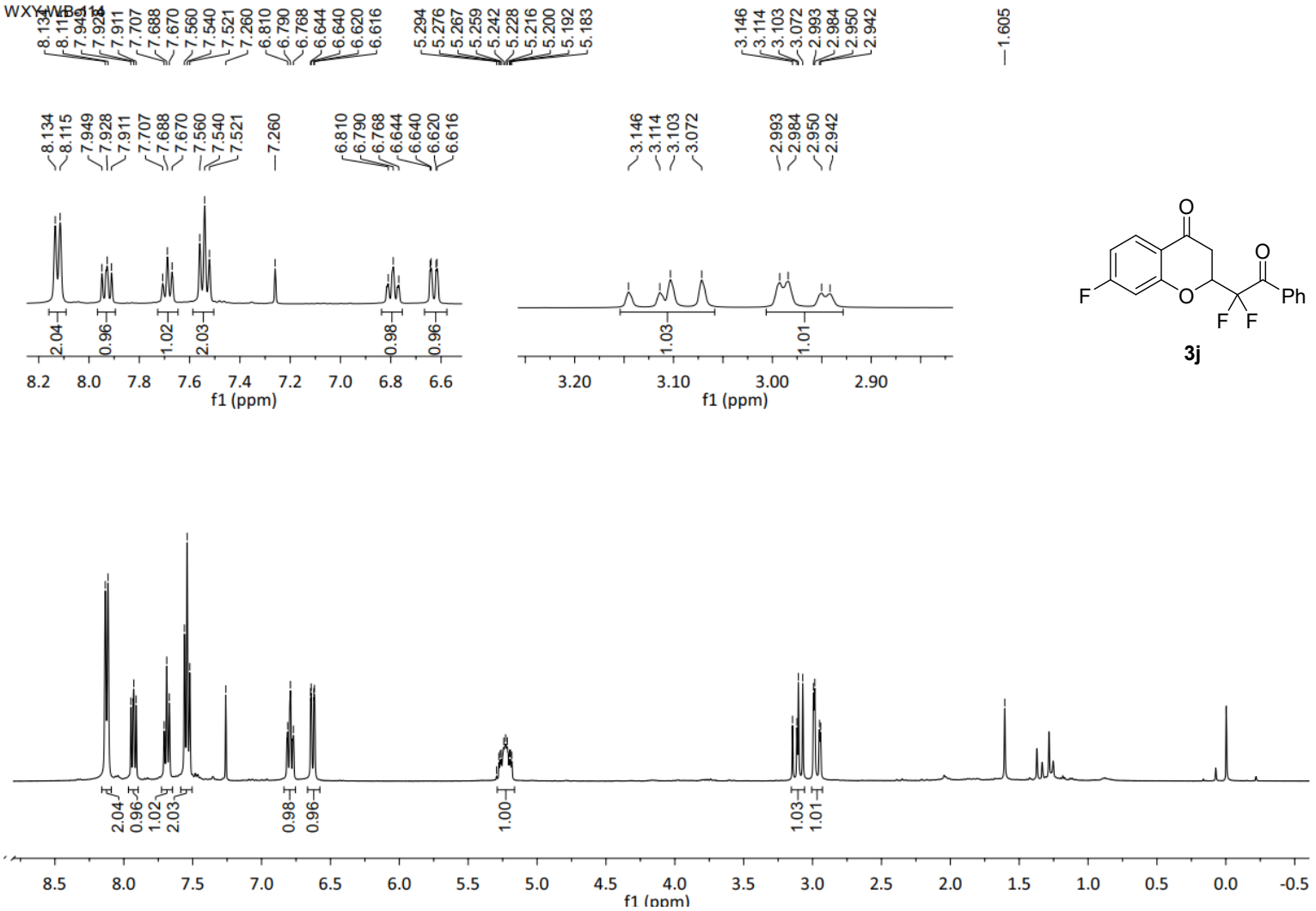
^{1}H NMR of Compound **3i** (400 MHz, $CDCl_3$)



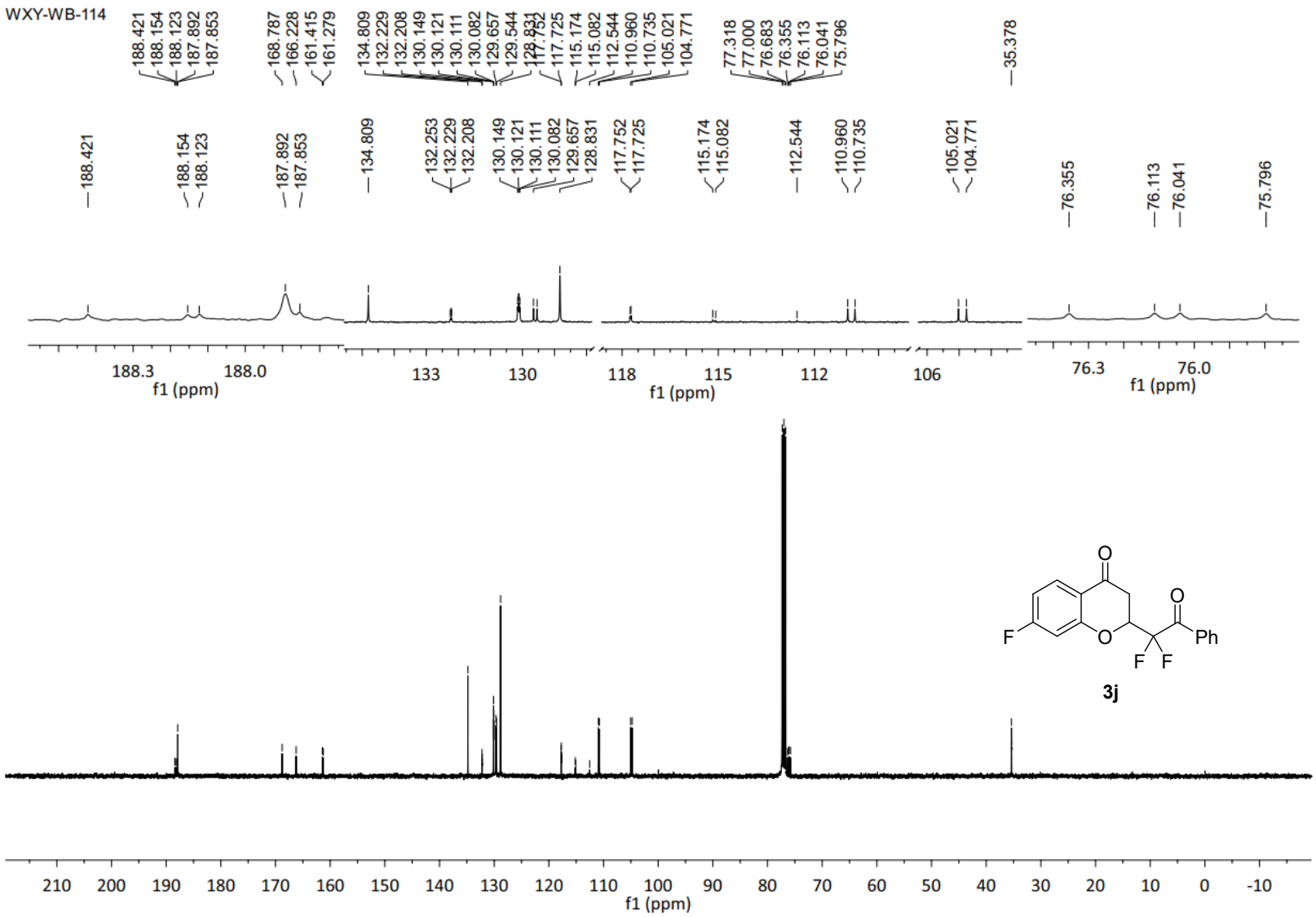
^{13}C NMR of Compound **3i** (100 MHz, $CDCl_3$)



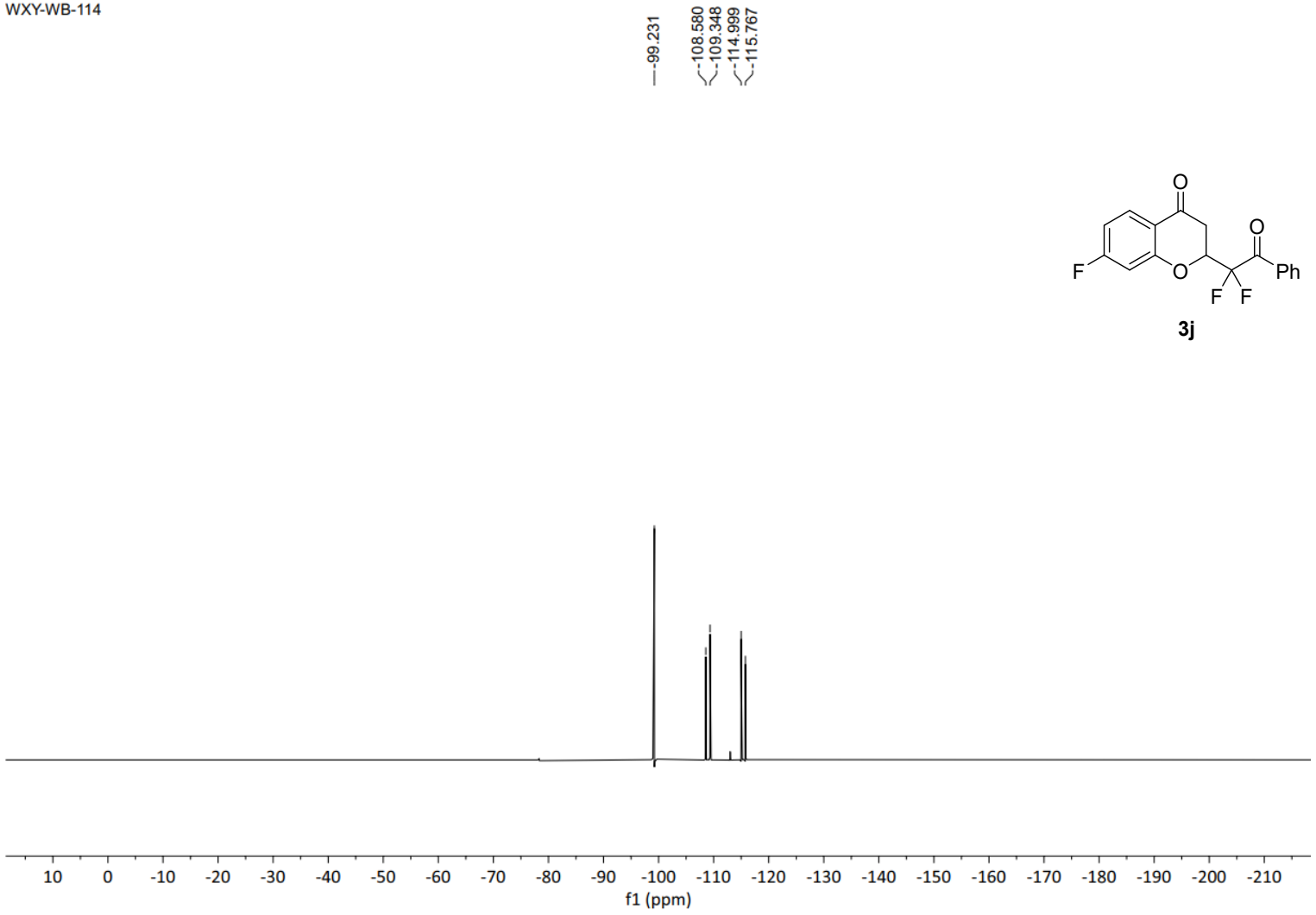
^{19}F NMR of Compound **3i** (376 MHz, $CDCl_3$)



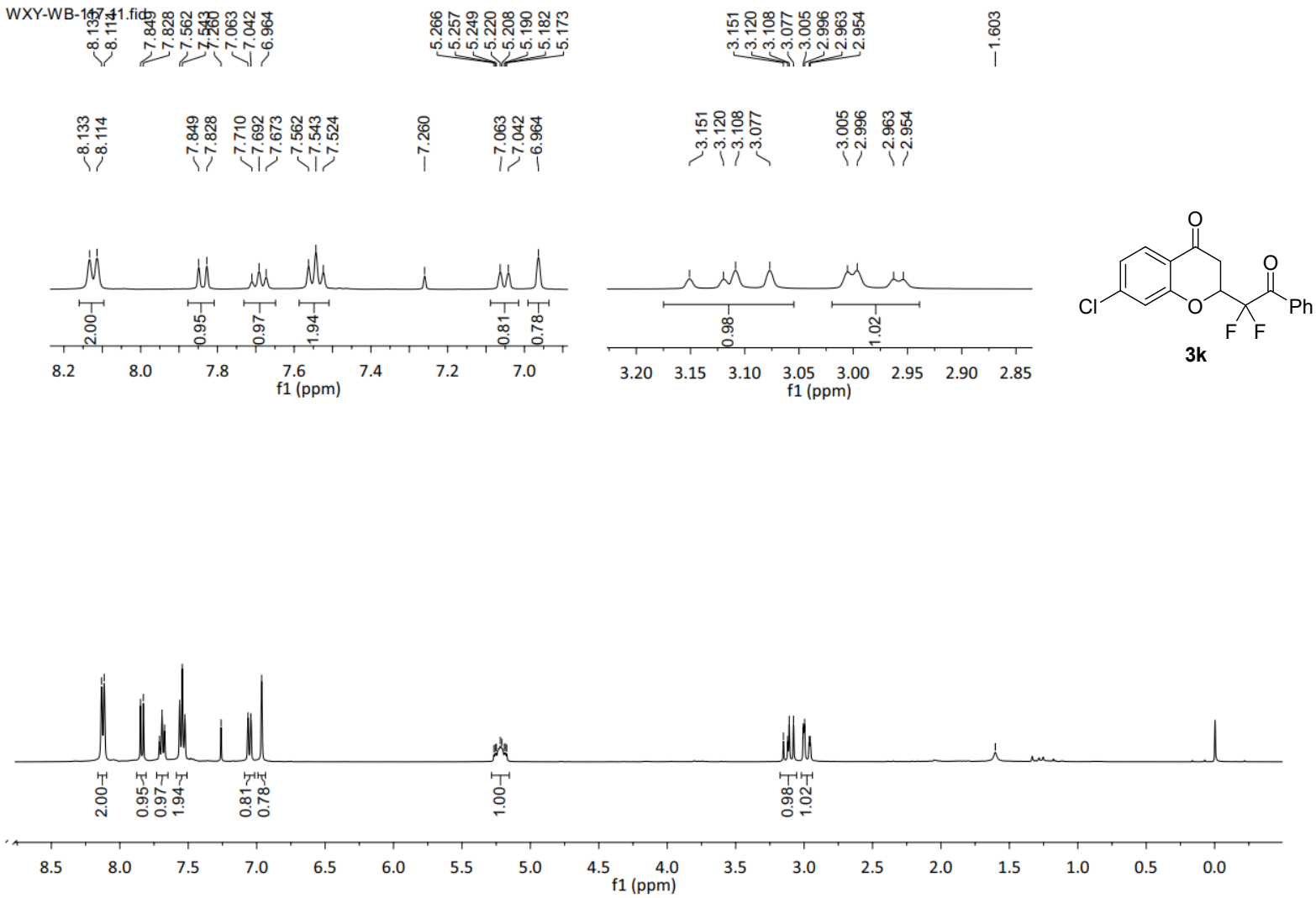
^{1}H NMR of Compound **3j** (400 MHz, $CDCl_3$)



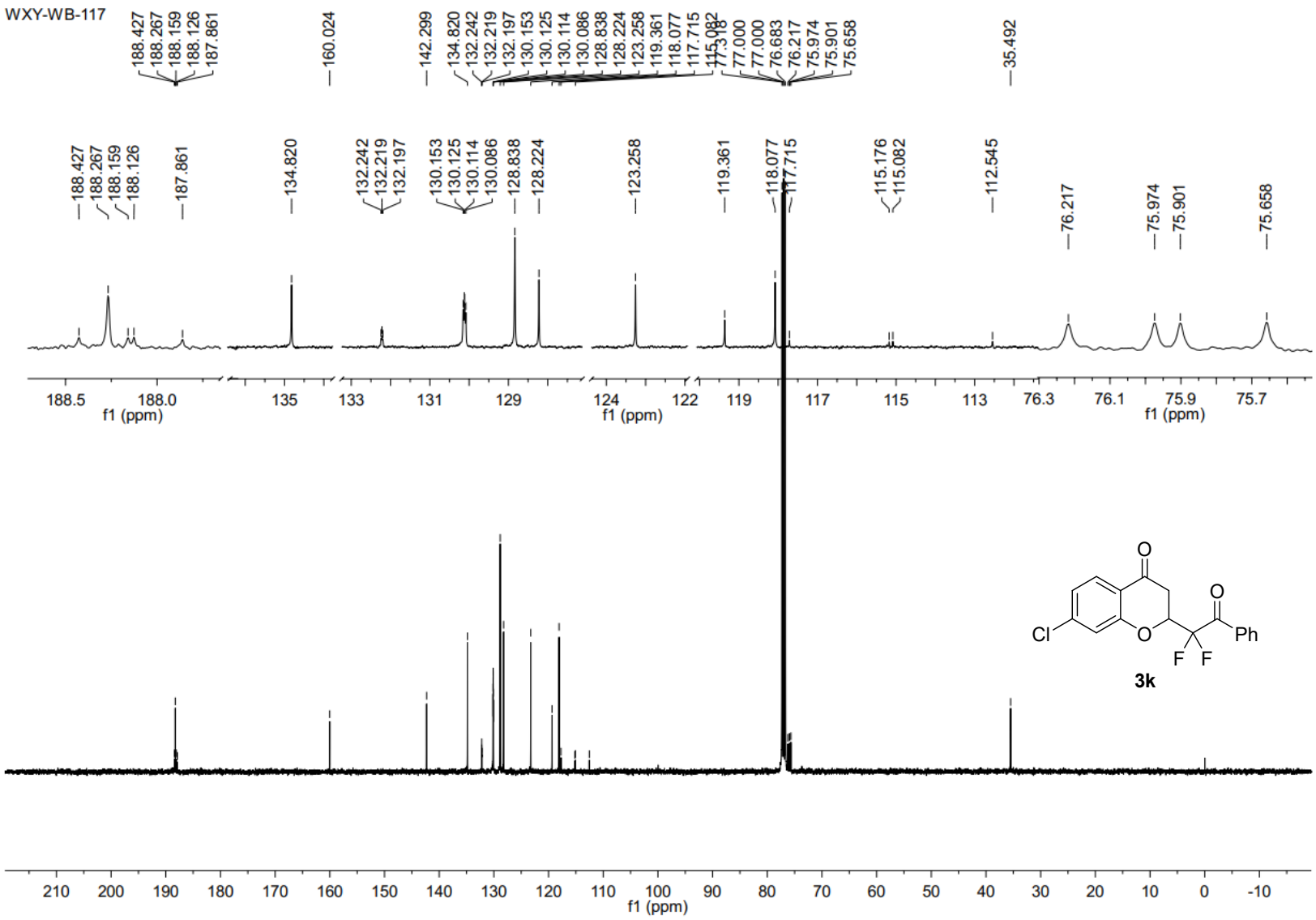
^{13}C NMR of Compound **3j** (100 MHz, $CDCl_3$)



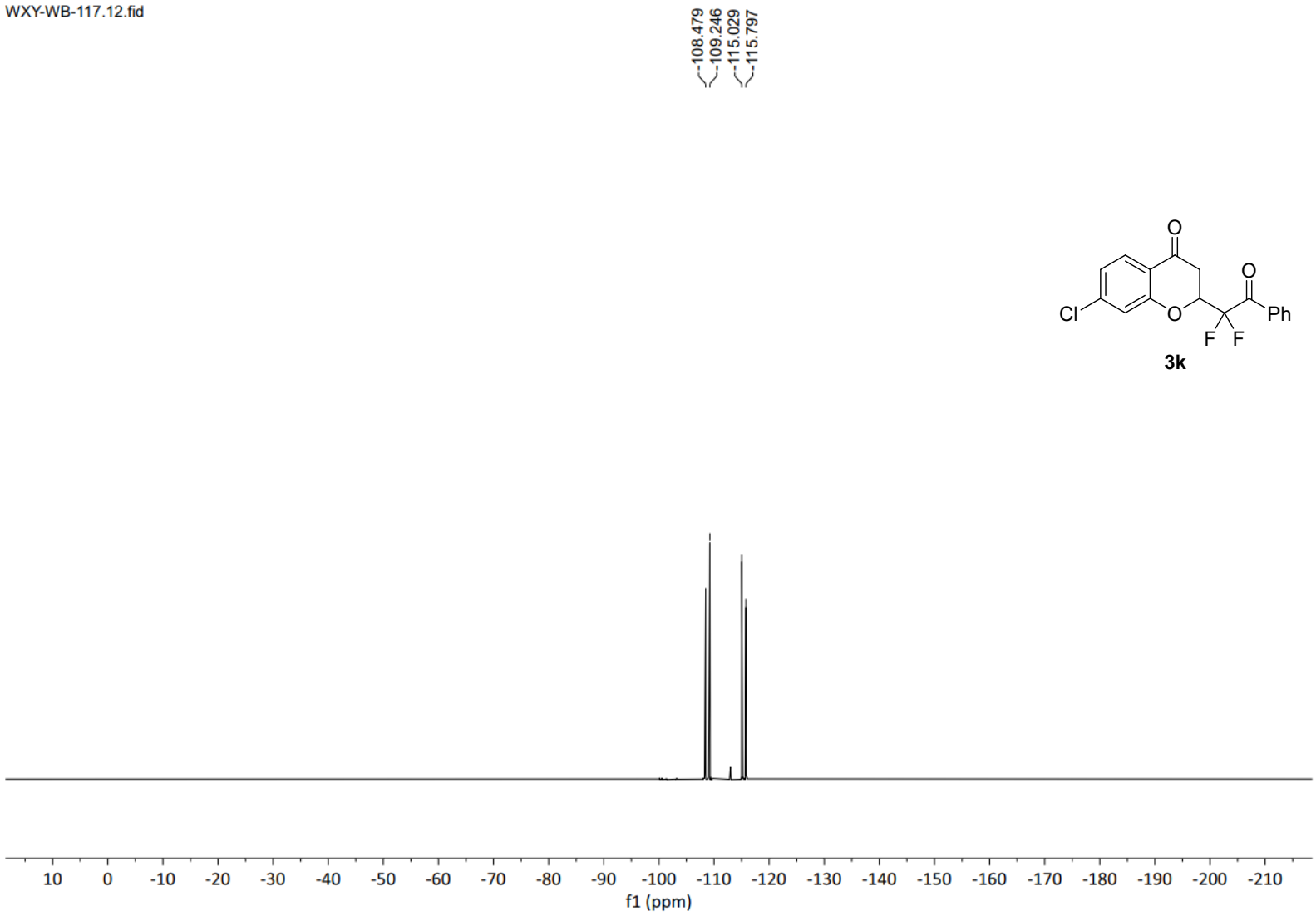
^{19}F NMR of Compound **3j** (376 MHz, $CDCl_3$)



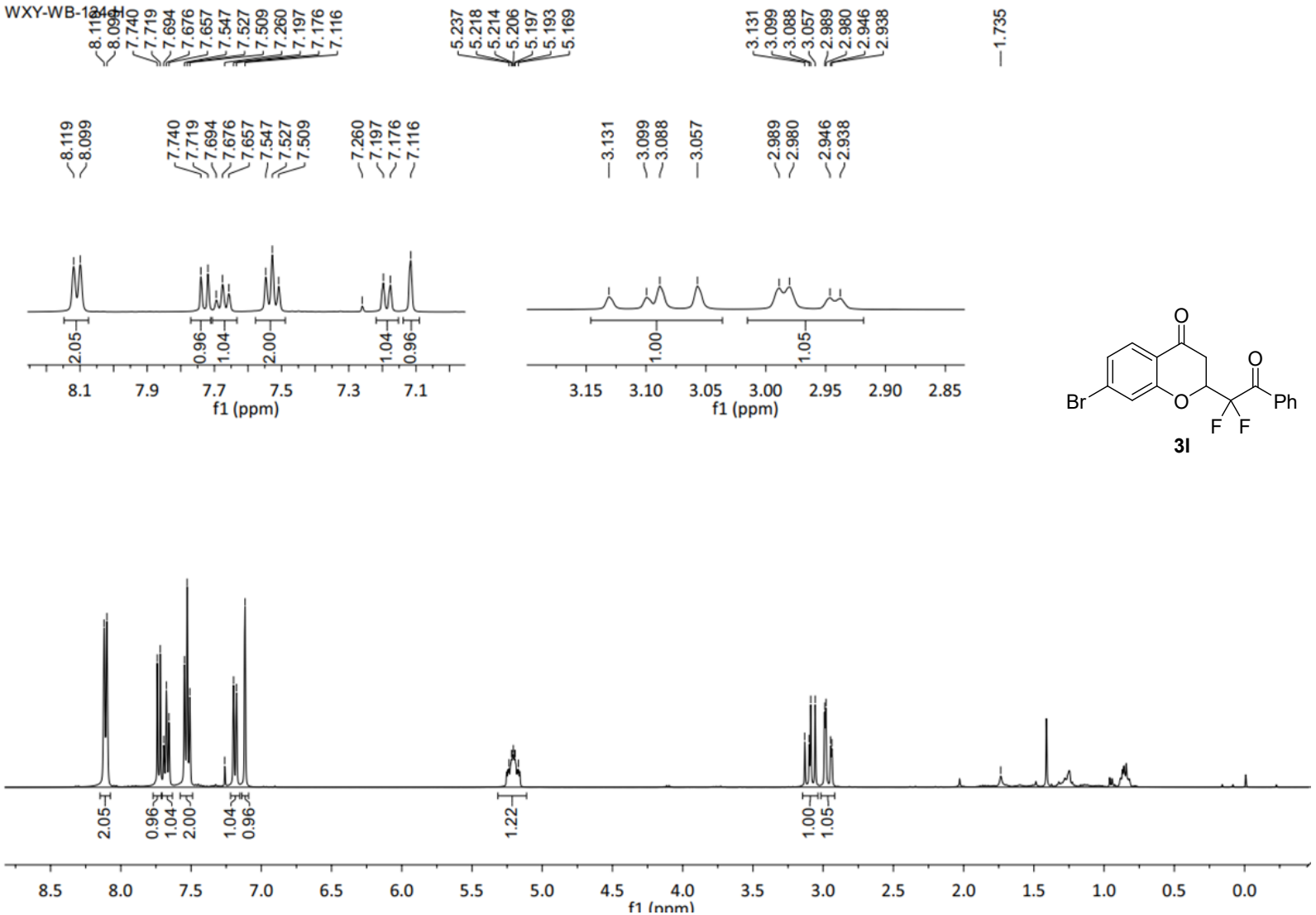
^{1}H NMR of Compound **3k** (400 MHz, $CDCl_3$)



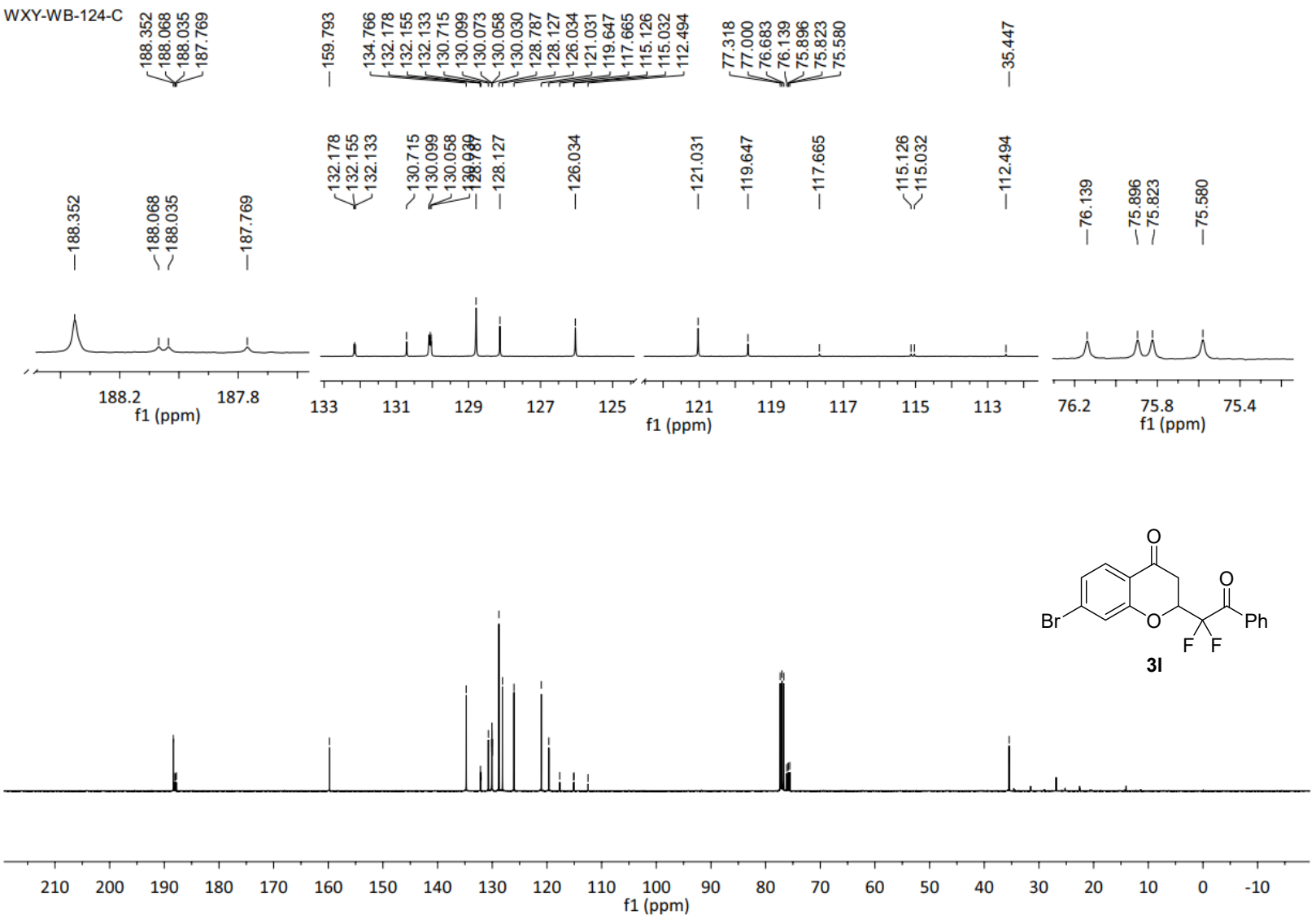
^{13}C NMR of Compound **3k** (100 MHz, $CDCl_3$)



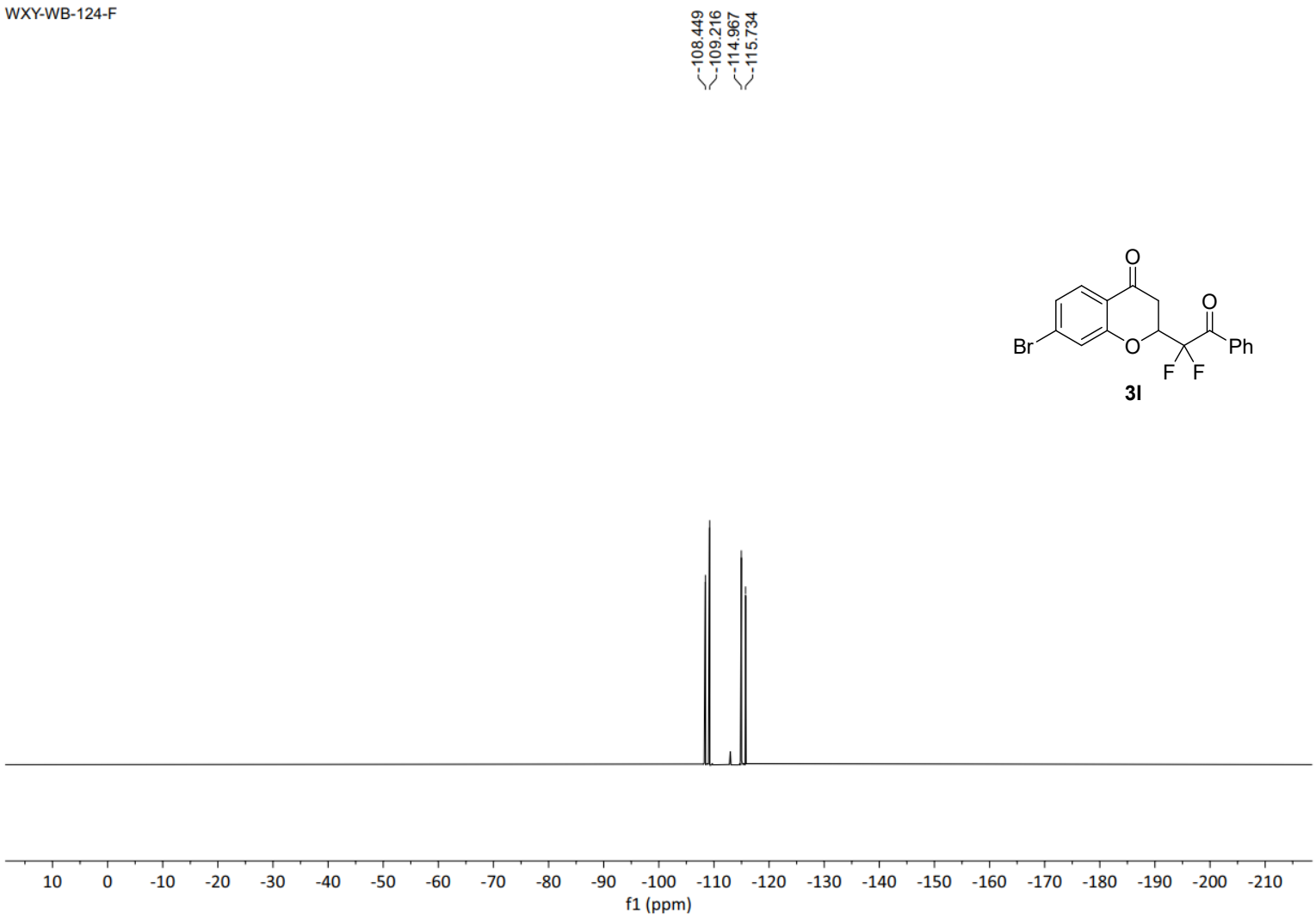
^{19}F NMR of Compound **3k** (376 MHz, $CDCl_3$)



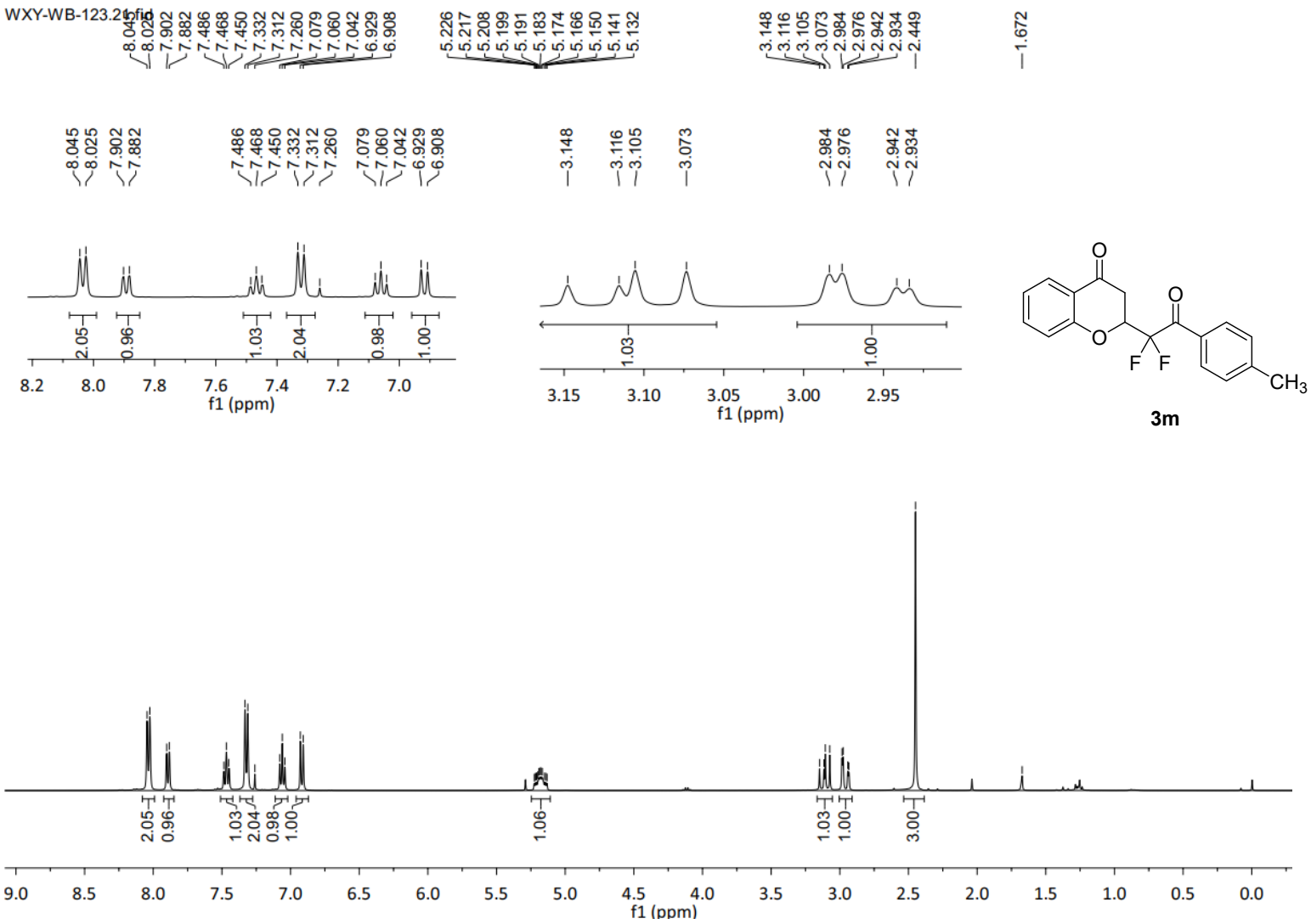
^{1}H NMR of Compound **3l** (400 MHz, $CDCl_3$)



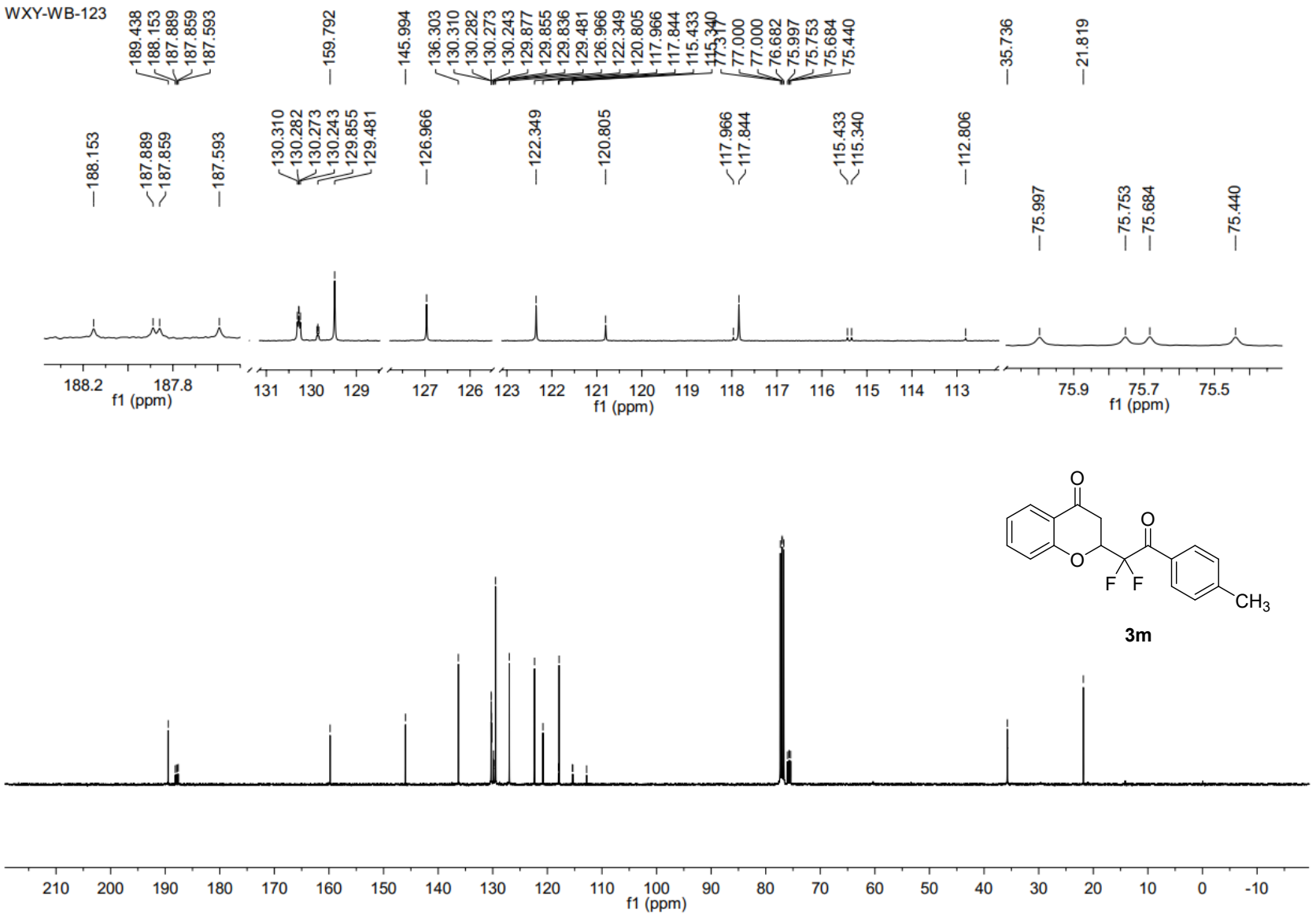
^{13}C NMR of Compound **3l** (100 MHz, $CDCl_3$)



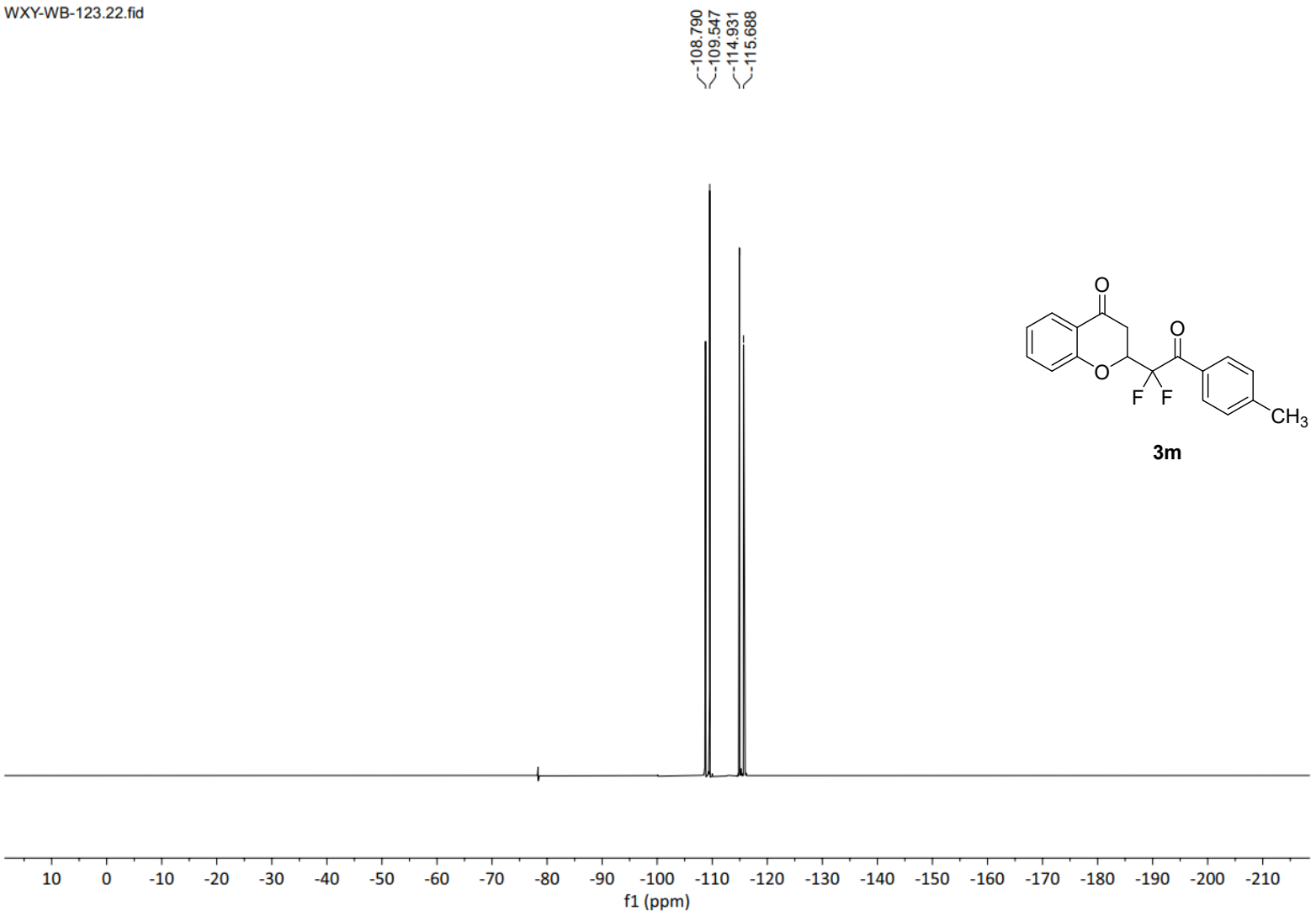
^{19}F NMR of Compound **3l** (376 MHz, $CDCl_3$)



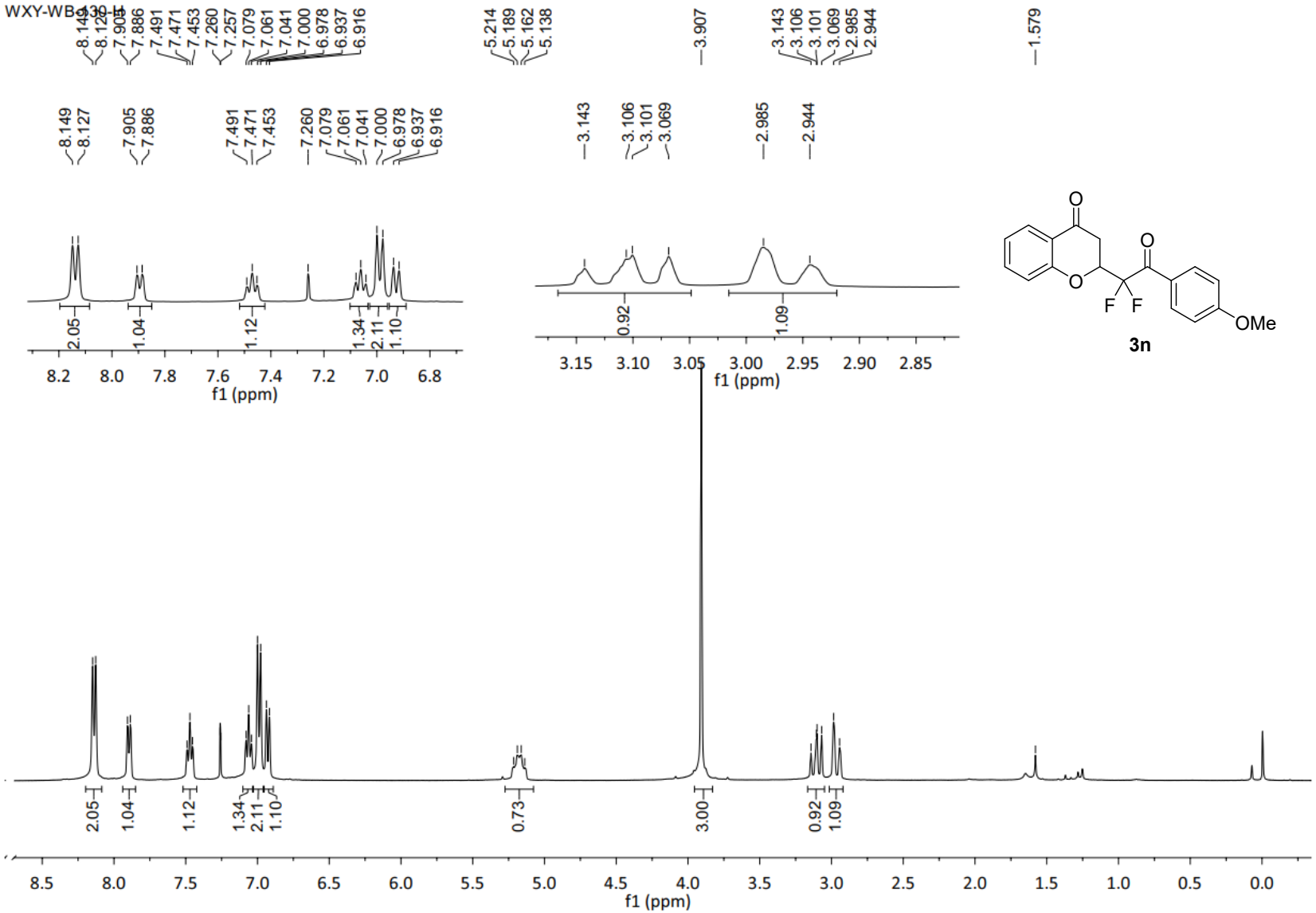
^{1}H NMR of Compound **3m** (400 MHz, $CDCl_3$)



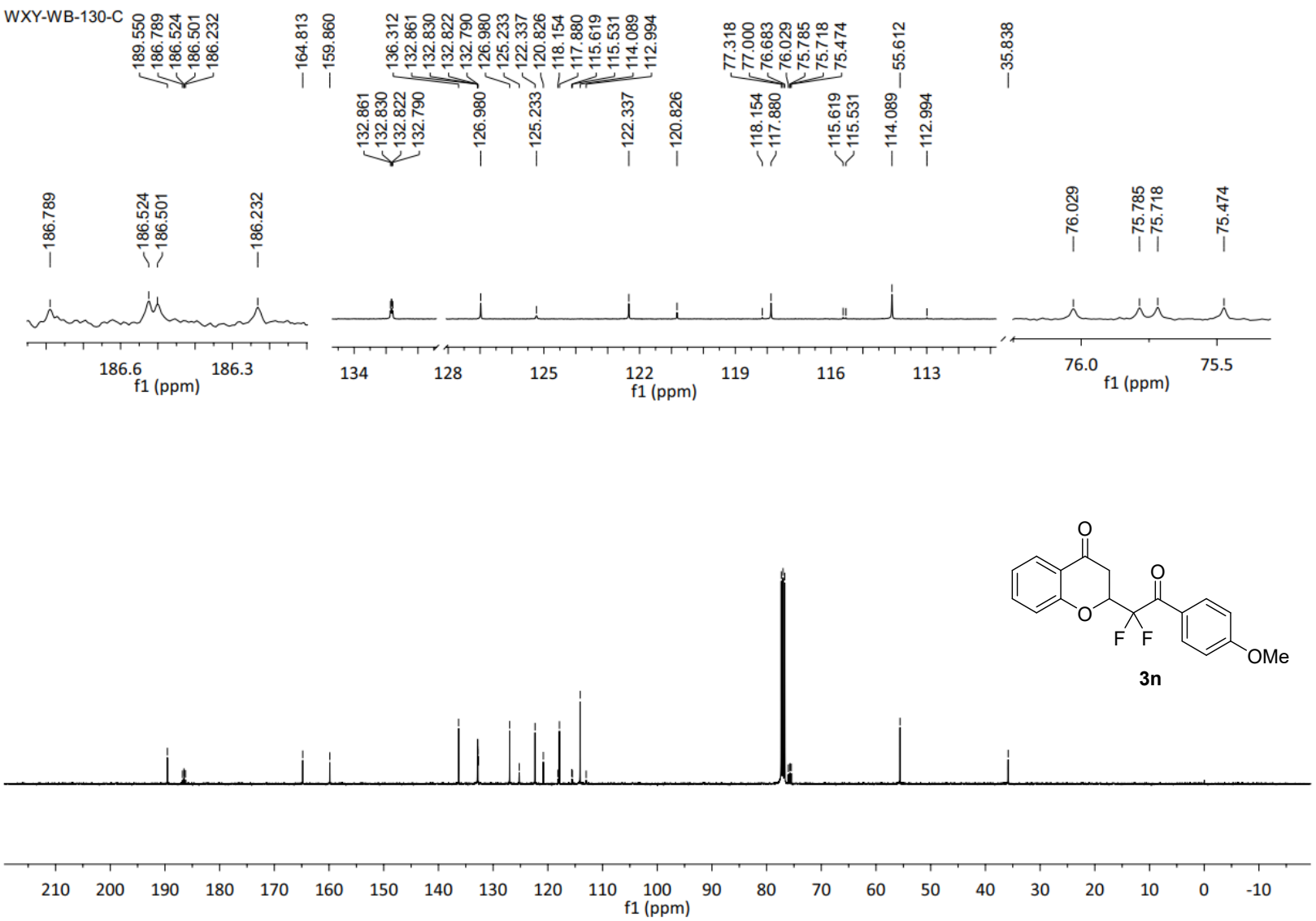
^{13}C NMR of Compound **3m** (100 MHz, $CDCl_3$)



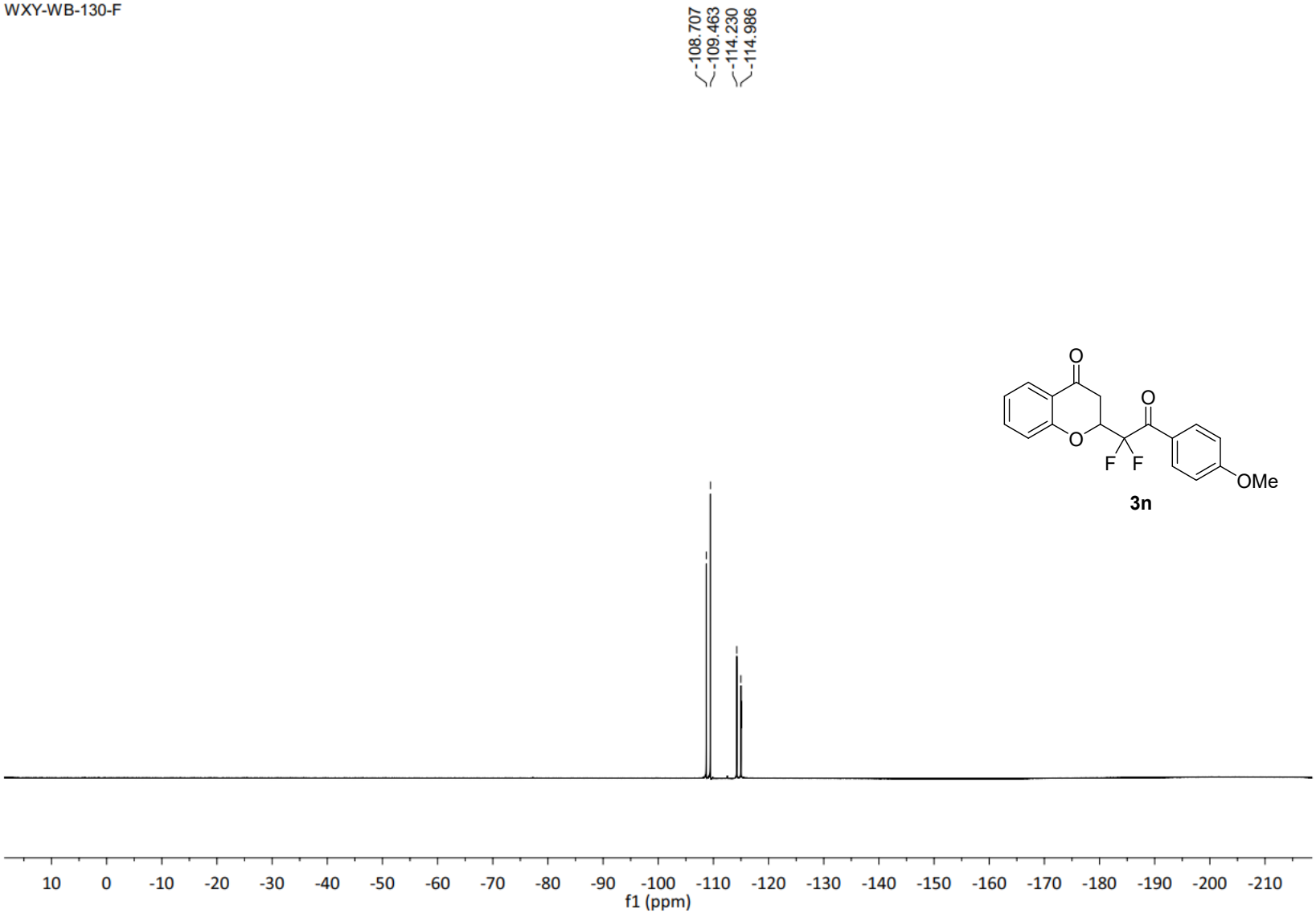
^{19}F NMR of Compound **3m** (376 MHz, $CDCl_3$)



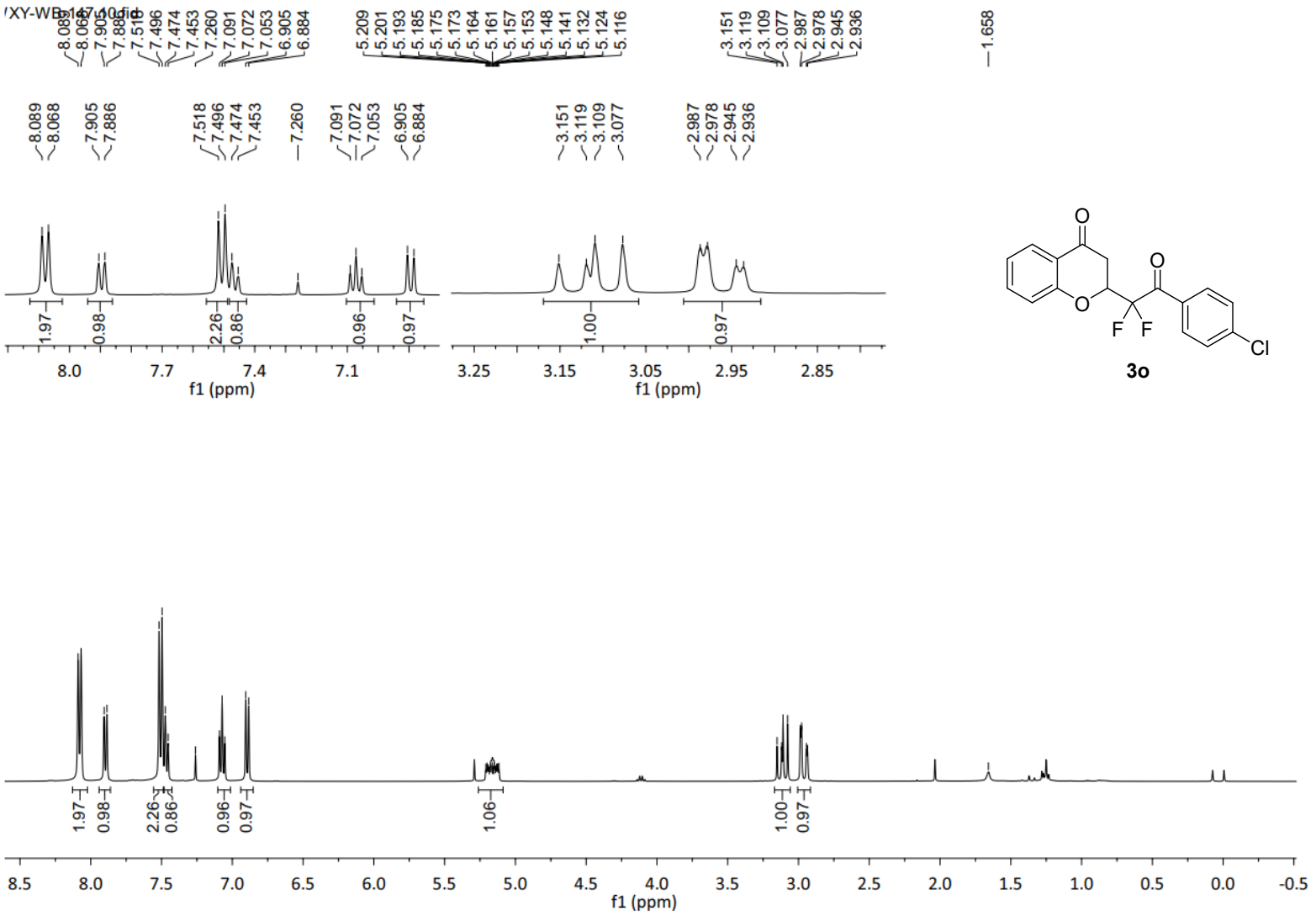
^{1}H NMR of Compound **3n** (400 MHz, $CDCl_3$)



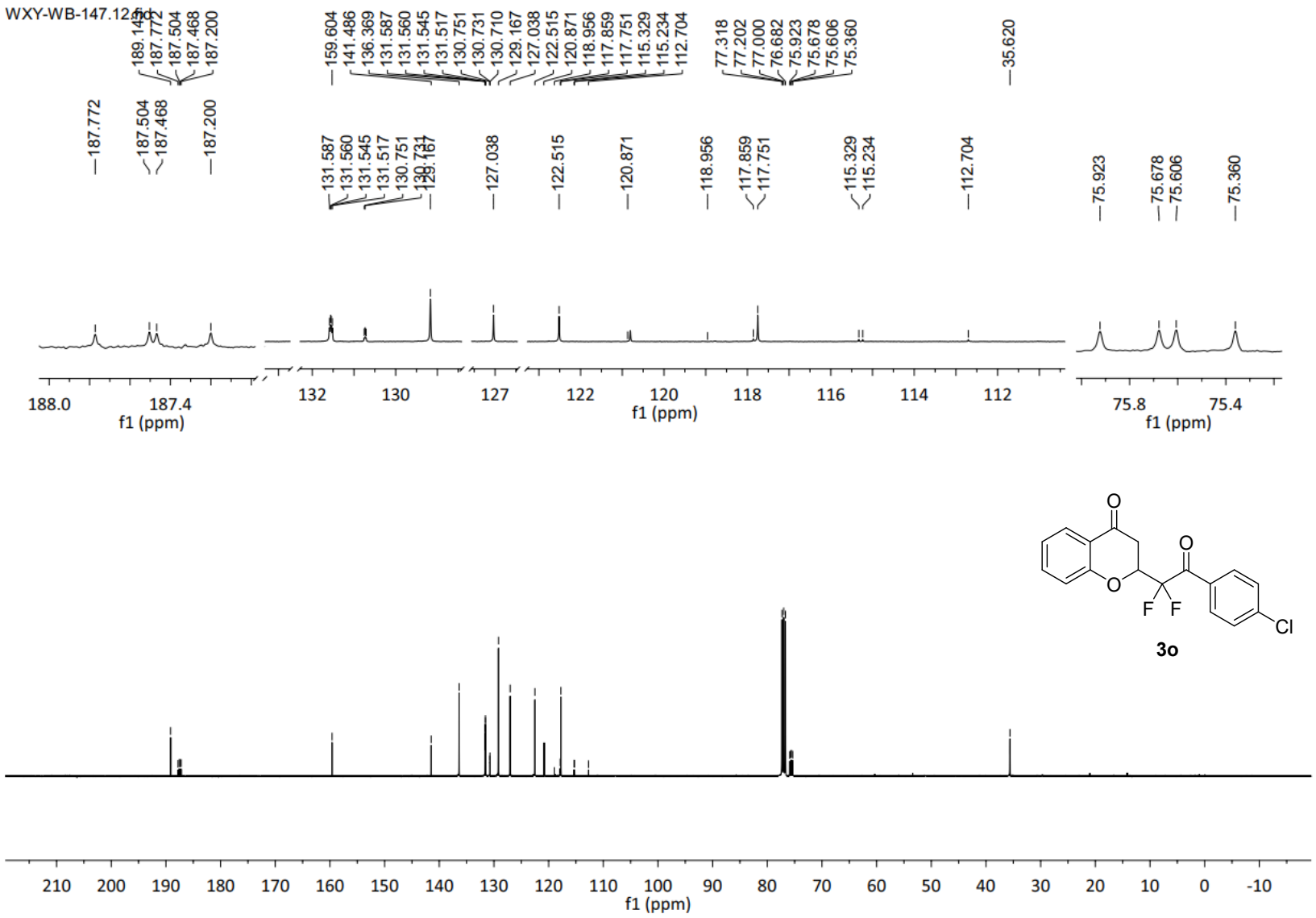
^{13}C NMR of Compound **3n** (100 MHz, $CDCl_3$)



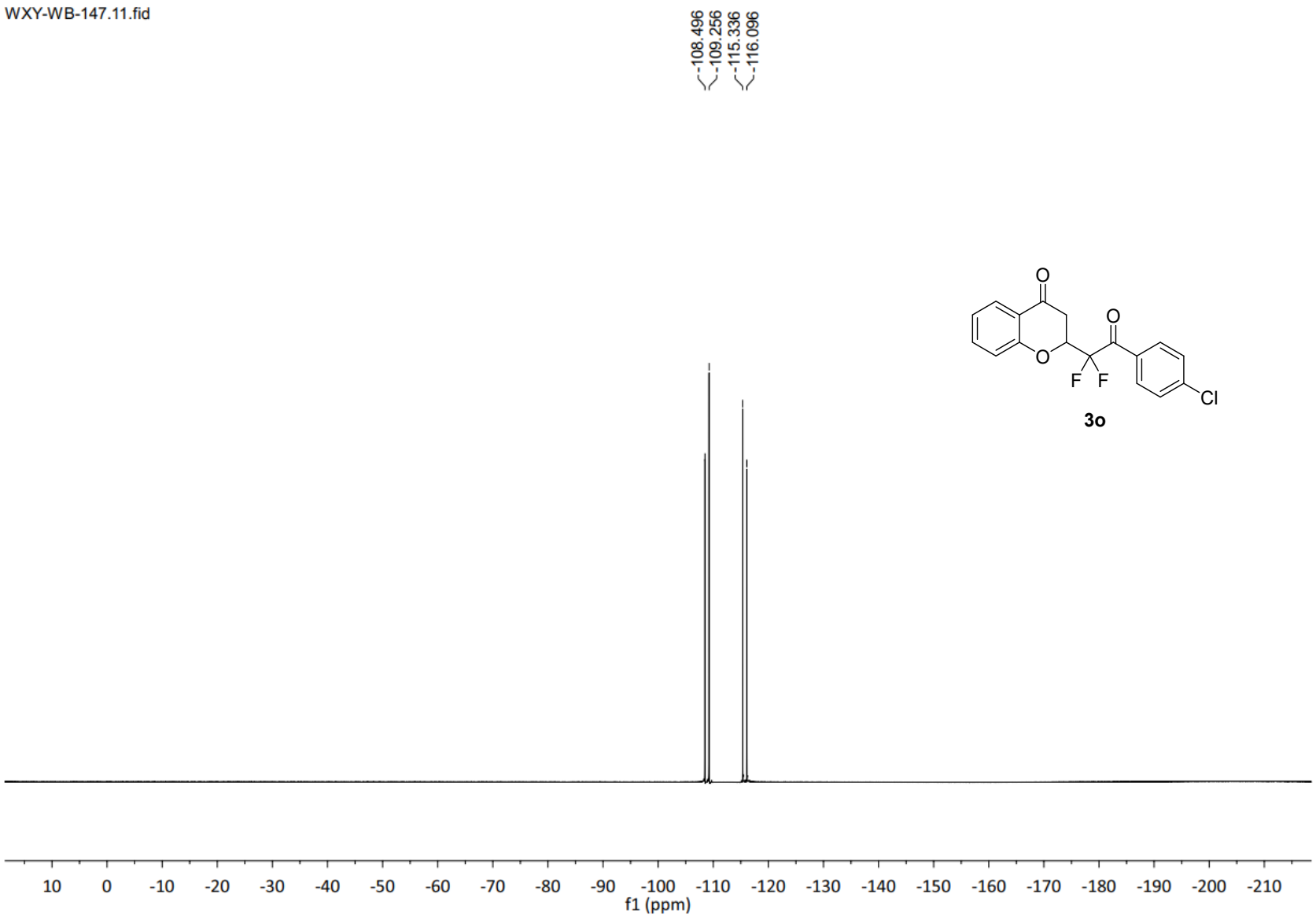
^{19}F NMR of Compound **3n** (376 MHz, $CDCl_3$)



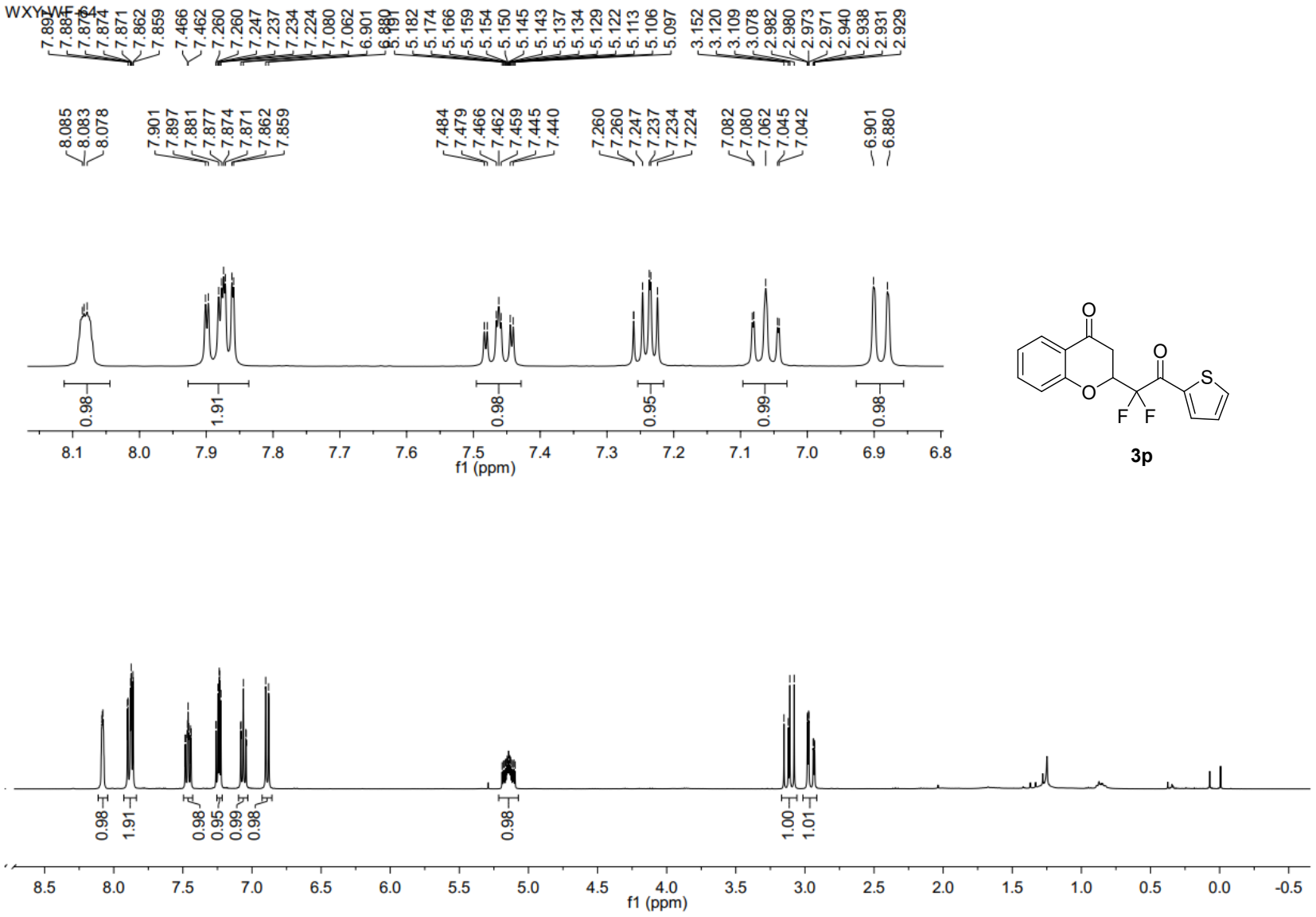
^{1}H NMR of Compound **3o** (400 MHz, $CDCl_3$)



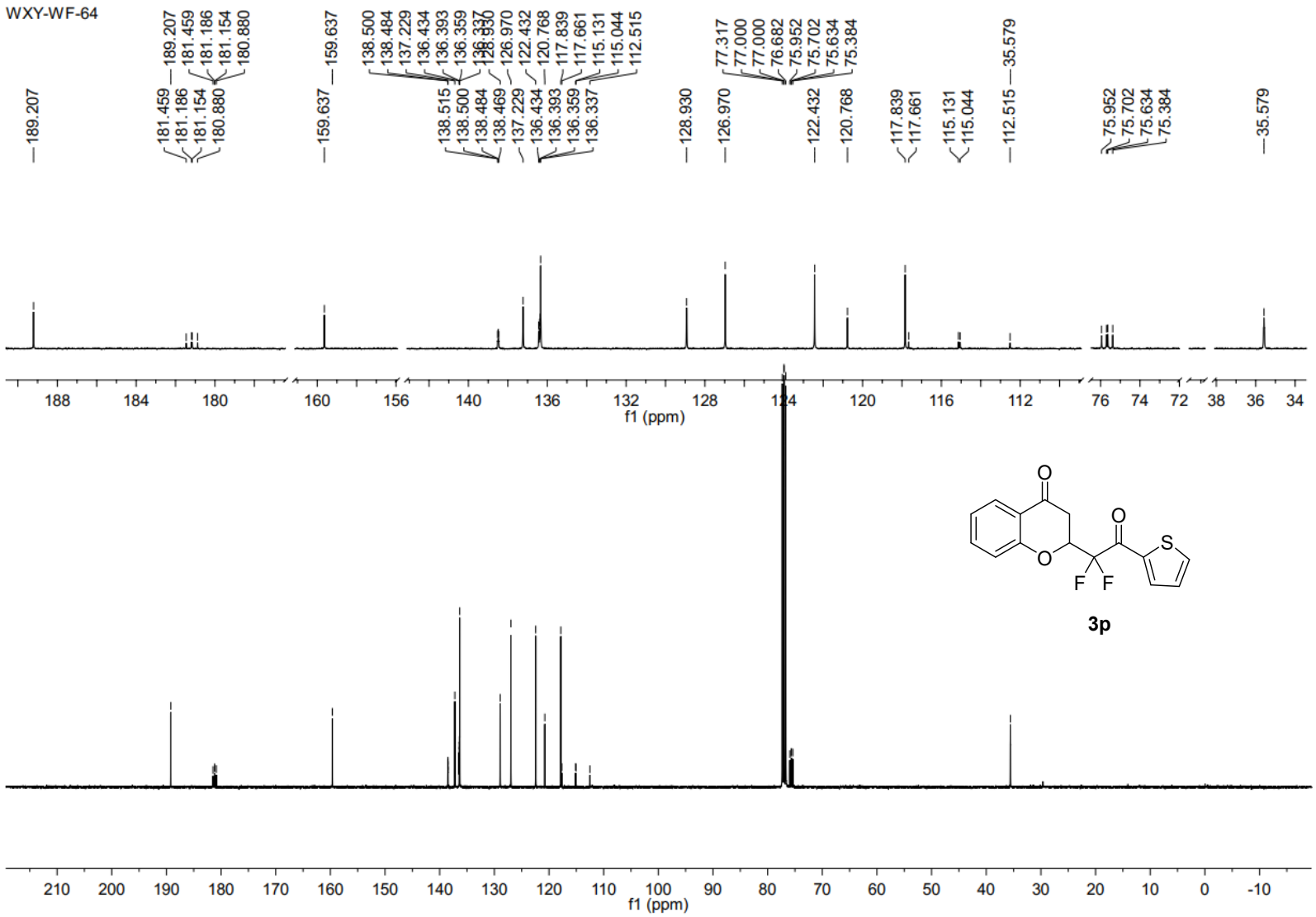
^{13}C NMR of Compound **3o** (100 MHz, $CDCl_3$)



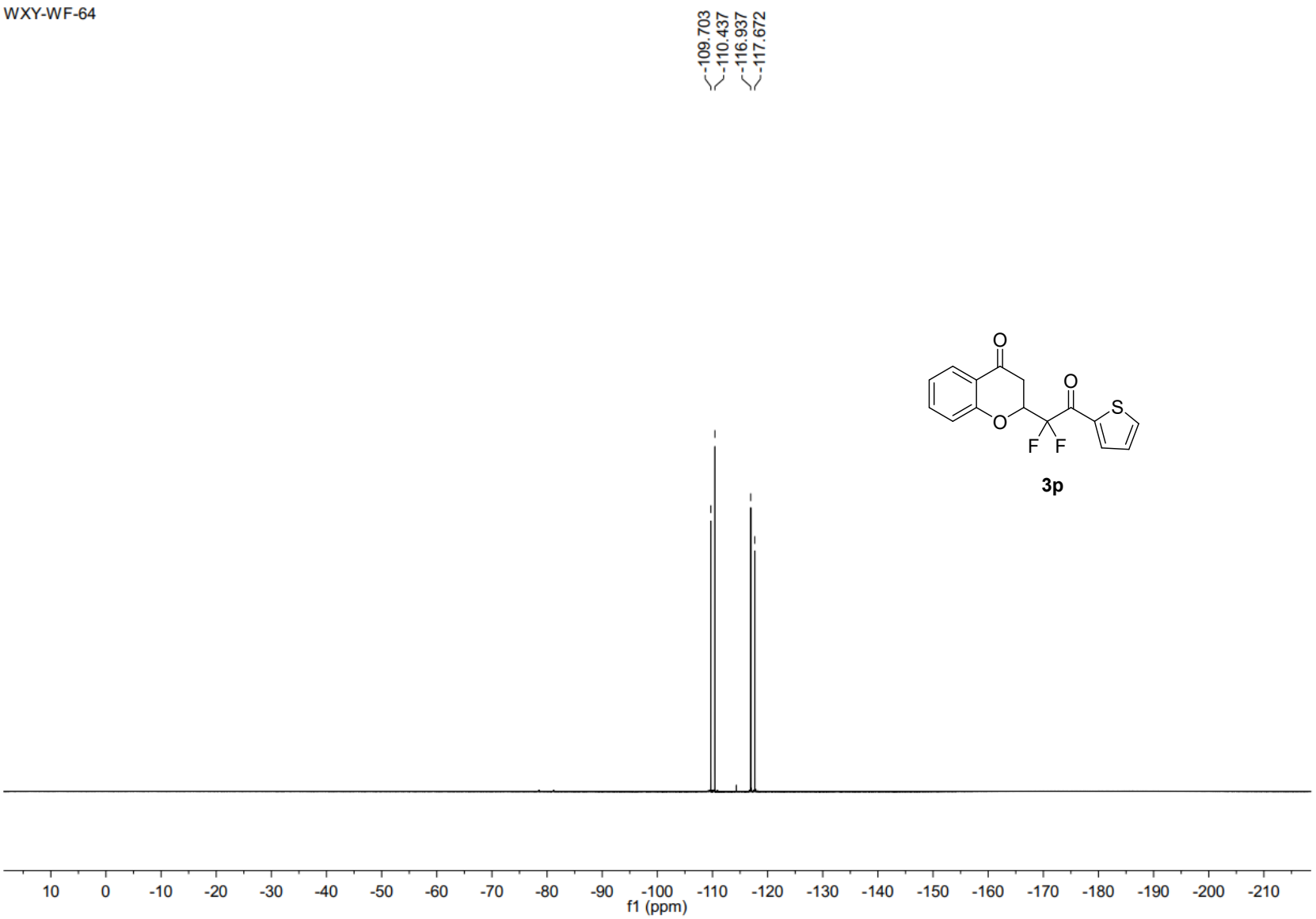
^{19}F NMR of Compound **3o** (376 MHz, $CDCl_3$)



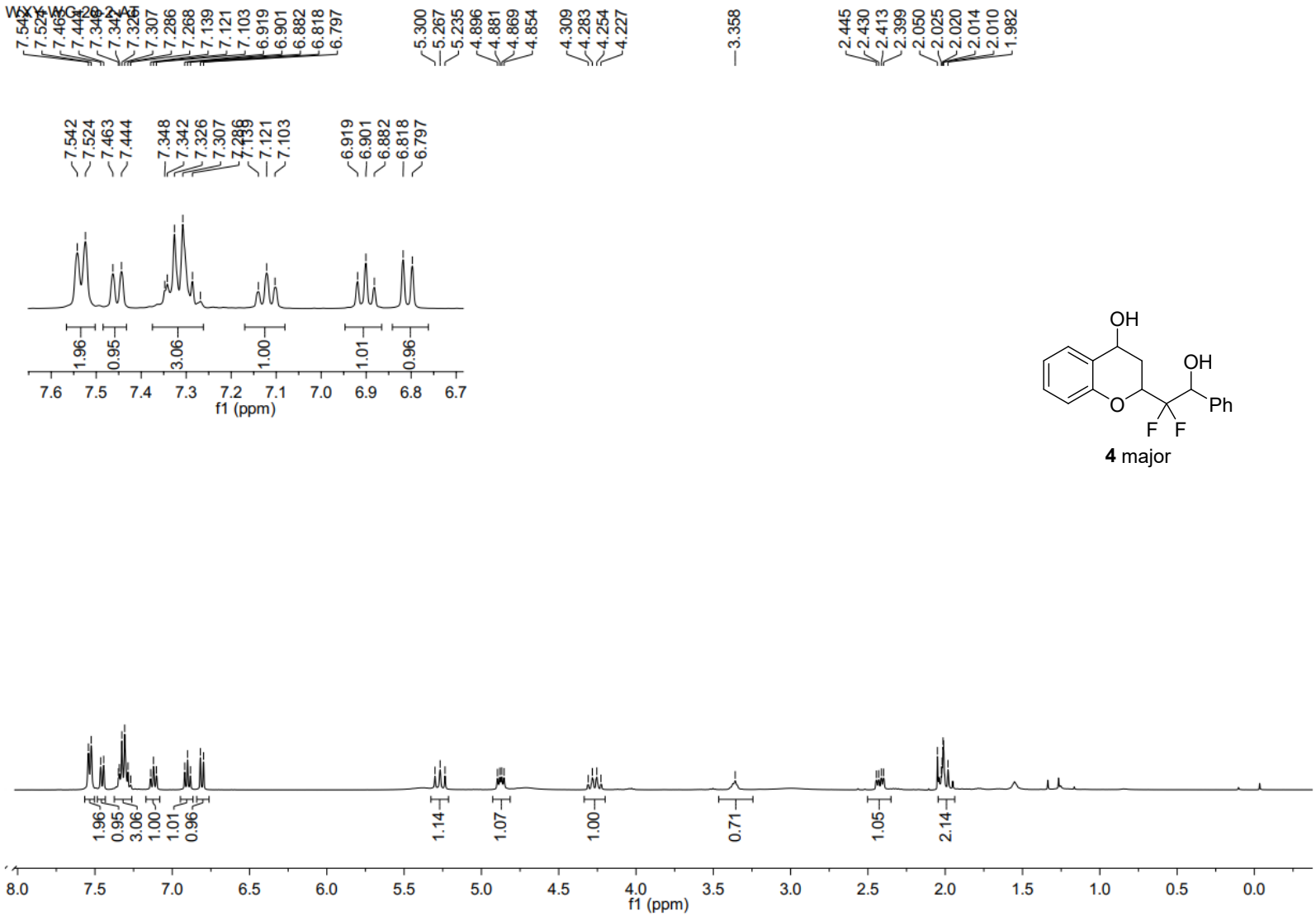
^{1}H NMR of Compound **3p** (400 MHz, $CDCl_3$)



^{13}C NMR of Compound **3p** (100 MHz, $CDCl_3$)

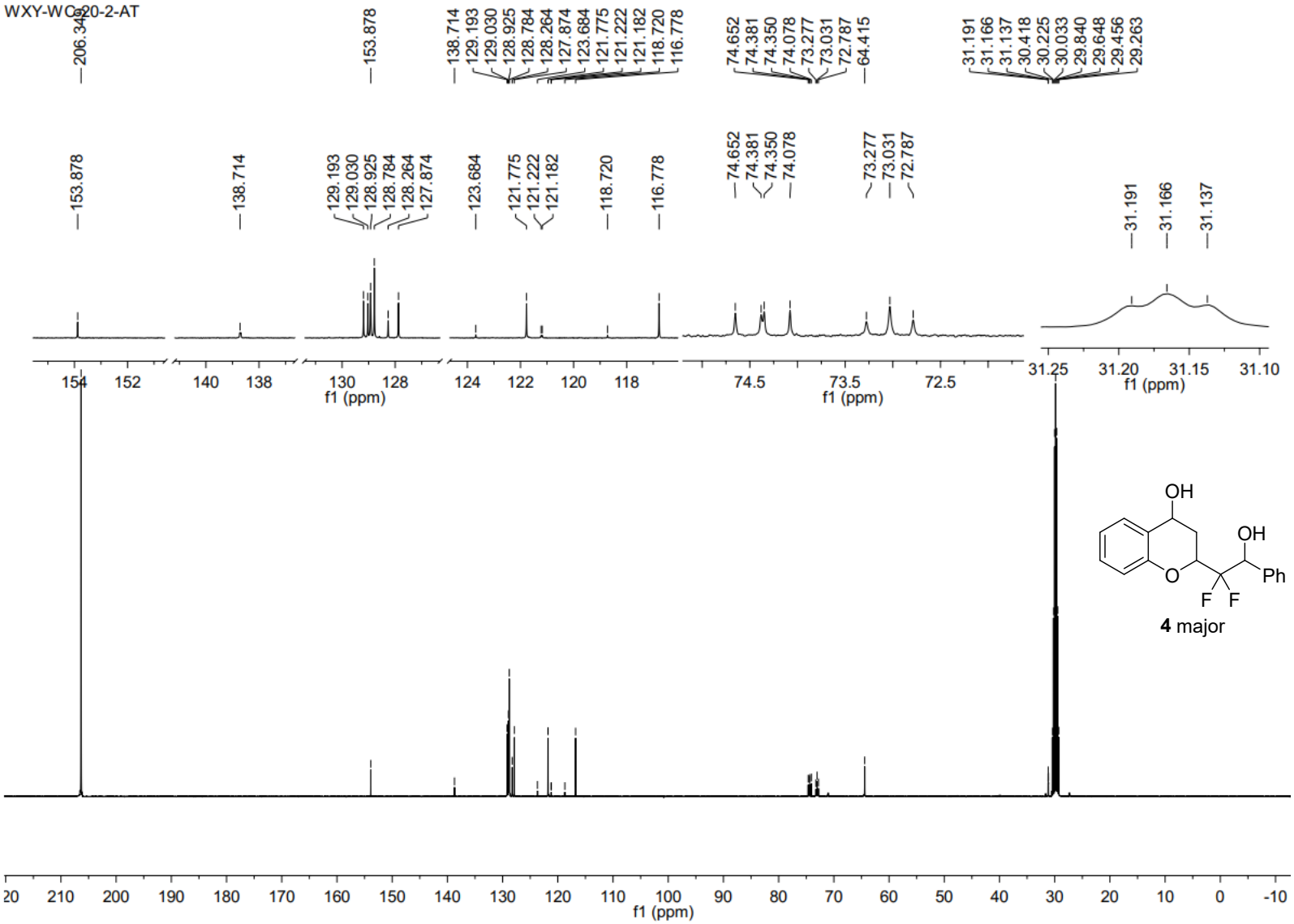


^{19}F NMR of Compound **3p** (376 MHz, $CDCl_3$)

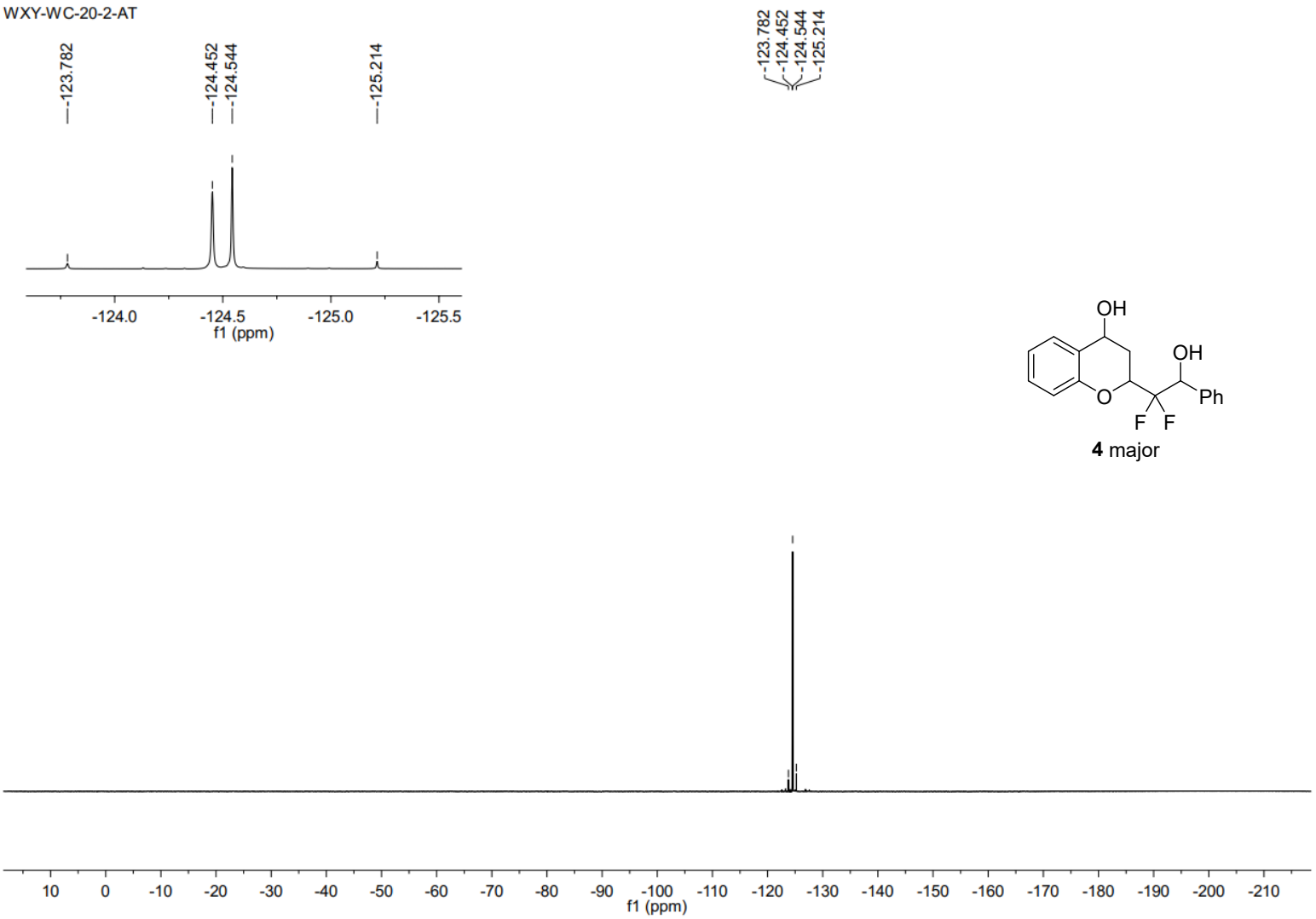


4 major

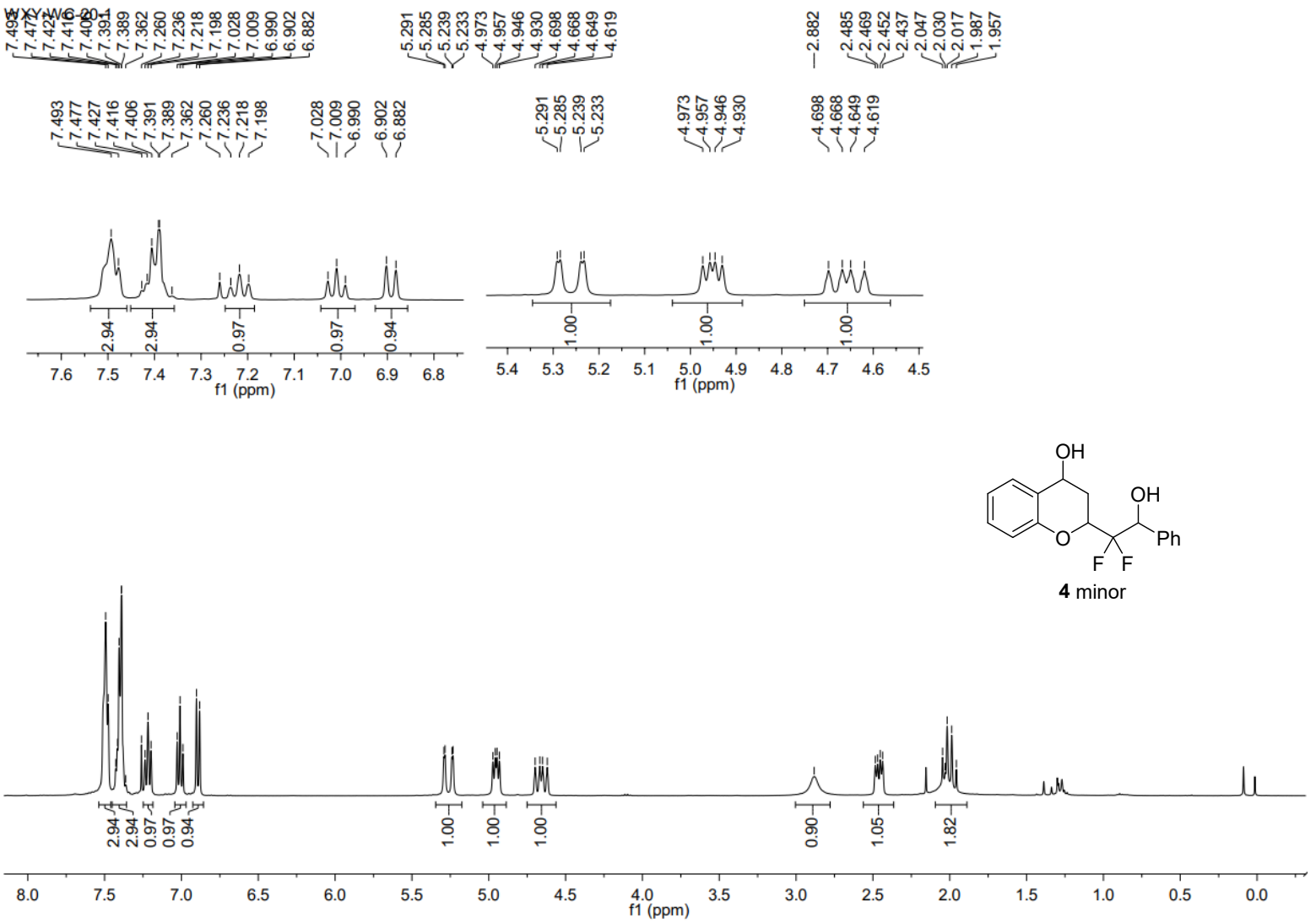
^{1}H NMR of Compound **4** major (400 MHz, Acetone-d_6)



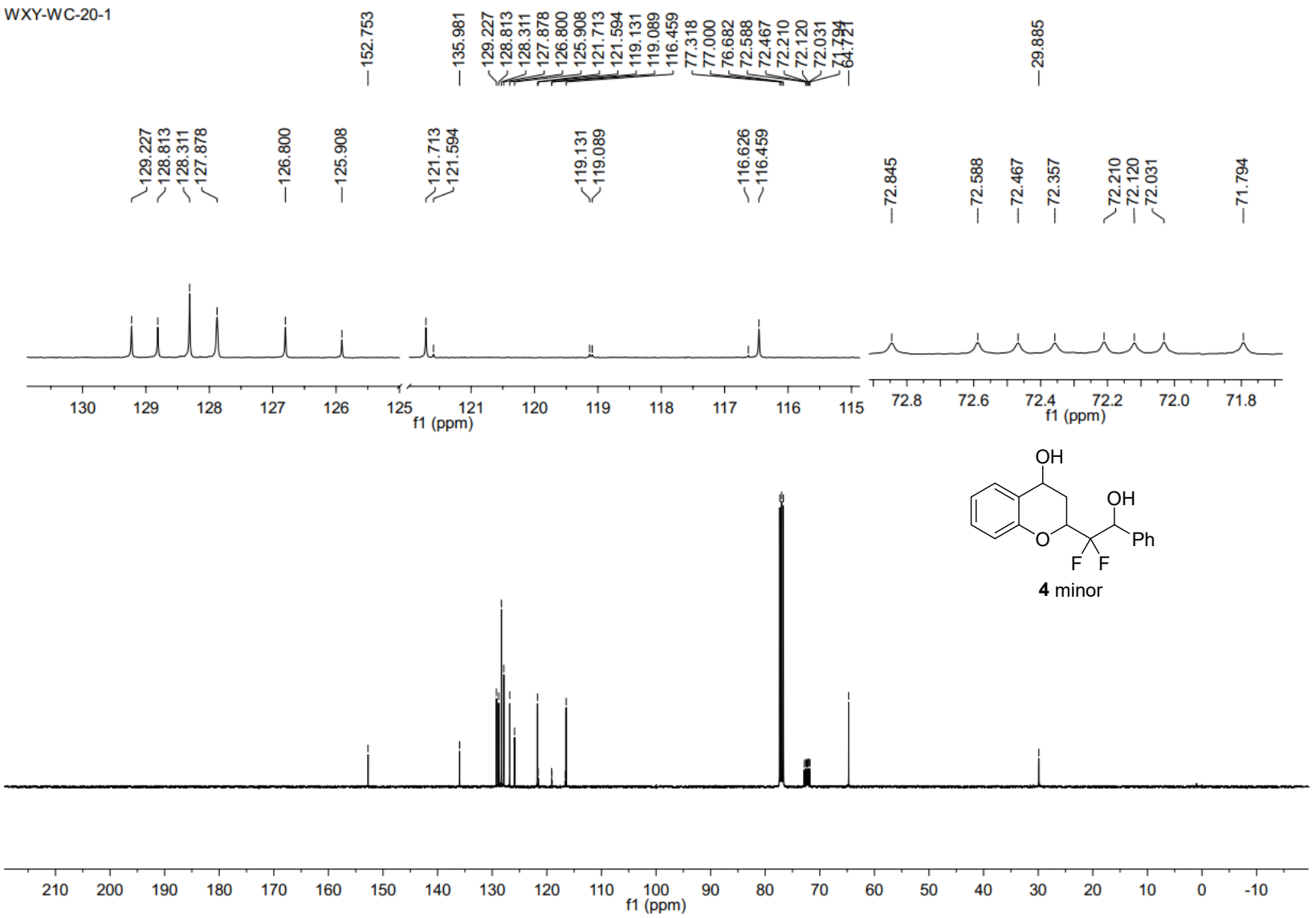
^{13}C NMR of Compound **4** major (100 MHz, Acetone-d_6)



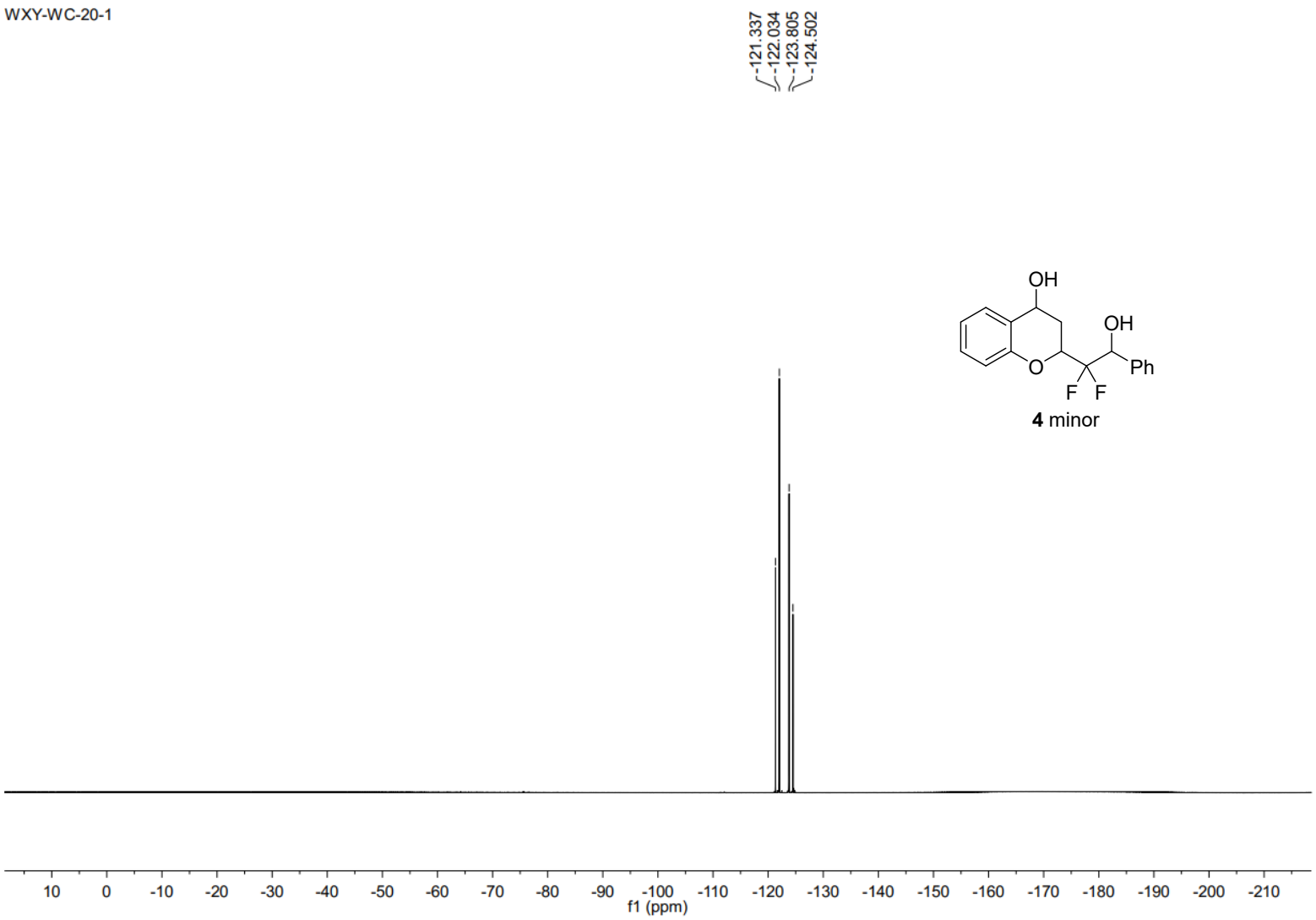
^{19}F NMR of Compound **4** major (376 MHz, Acetone-d_6)



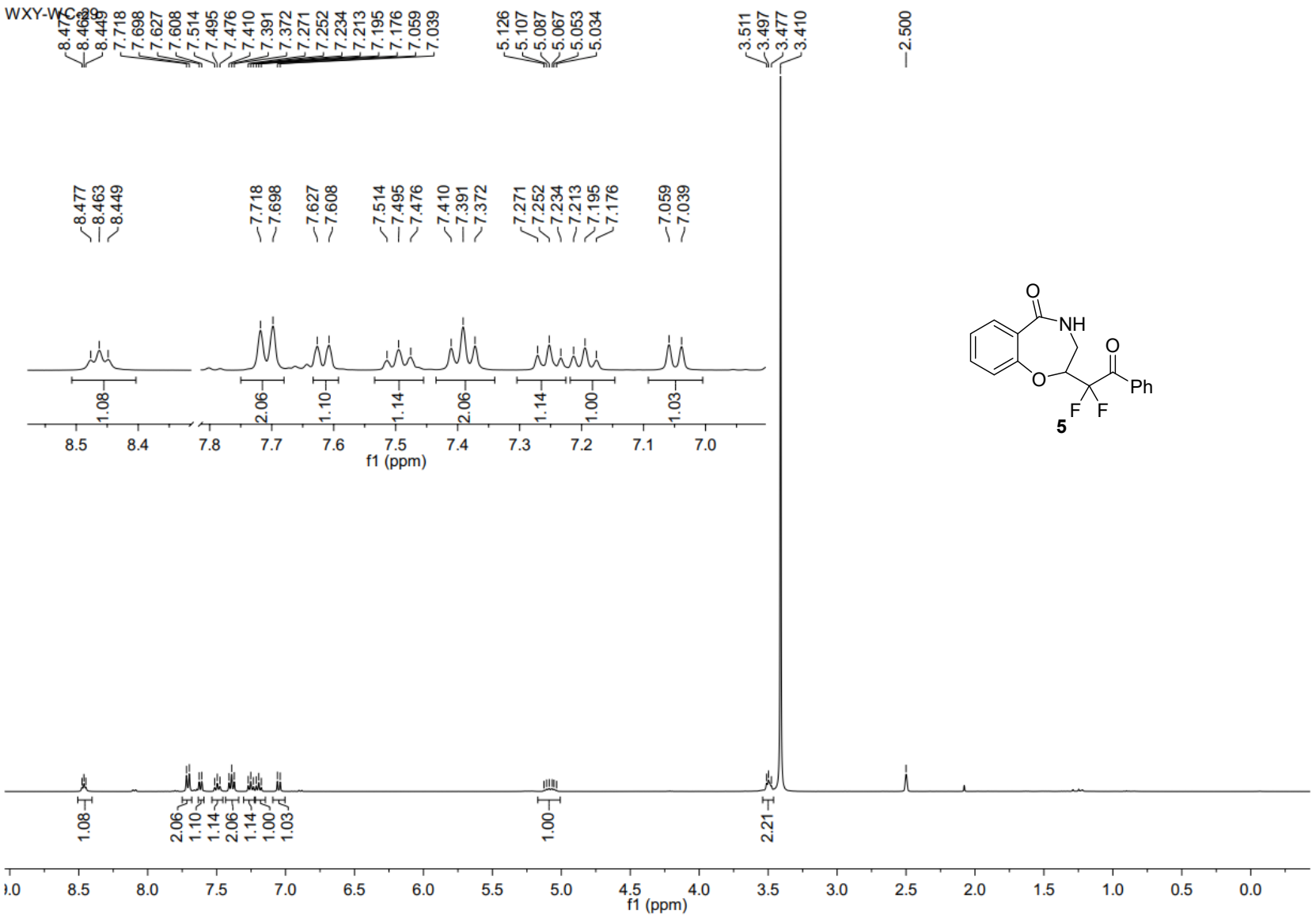
^{1}H NMR of Compound **4** minor (400 MHz, $CDCl_3$)



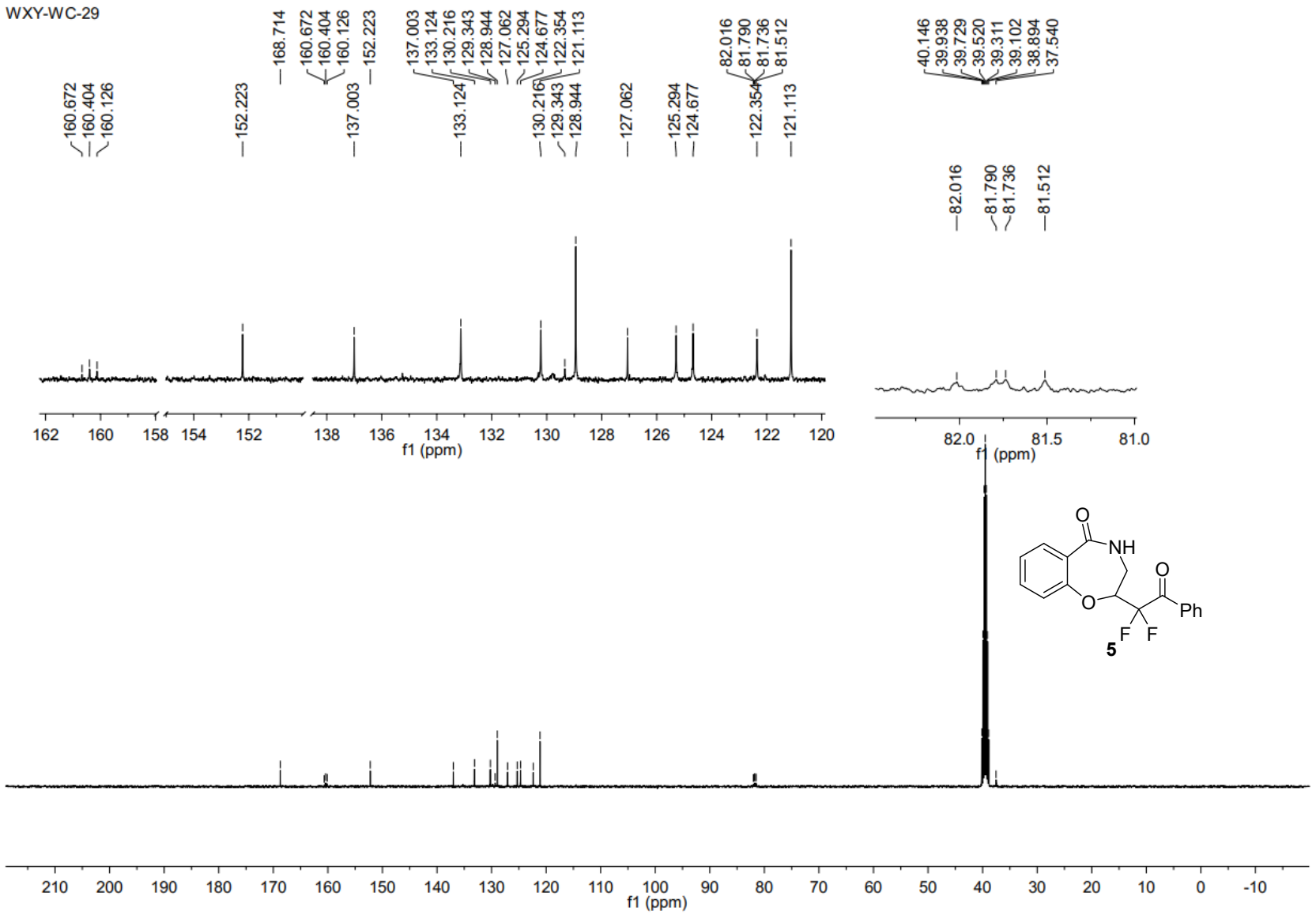
^{13}C NMR of Compound **4** minor (100 MHz, $CDCl_3$)



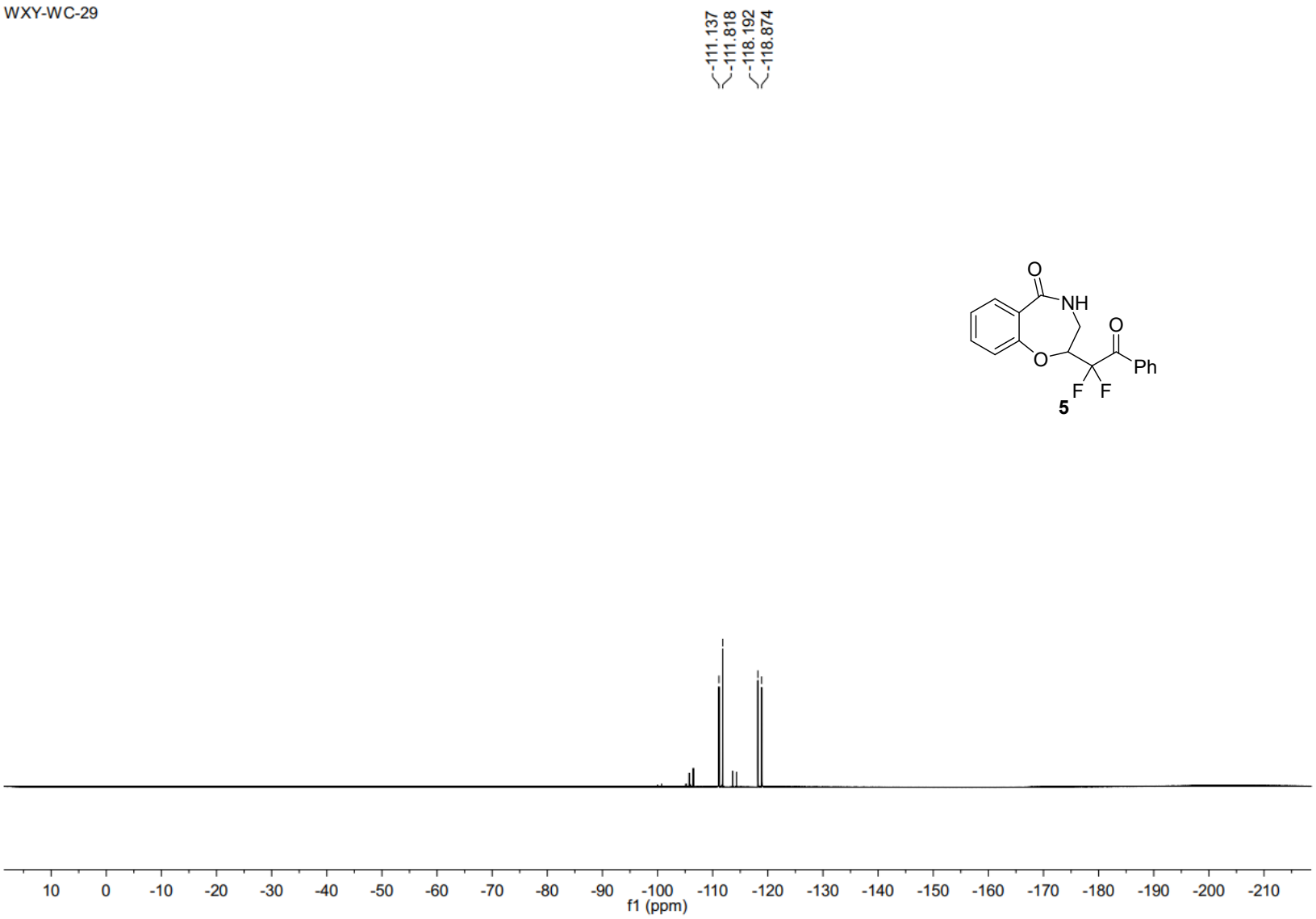
^{19}F NMR of Compound **4** minor (376 MHz, $CDCl_3$)



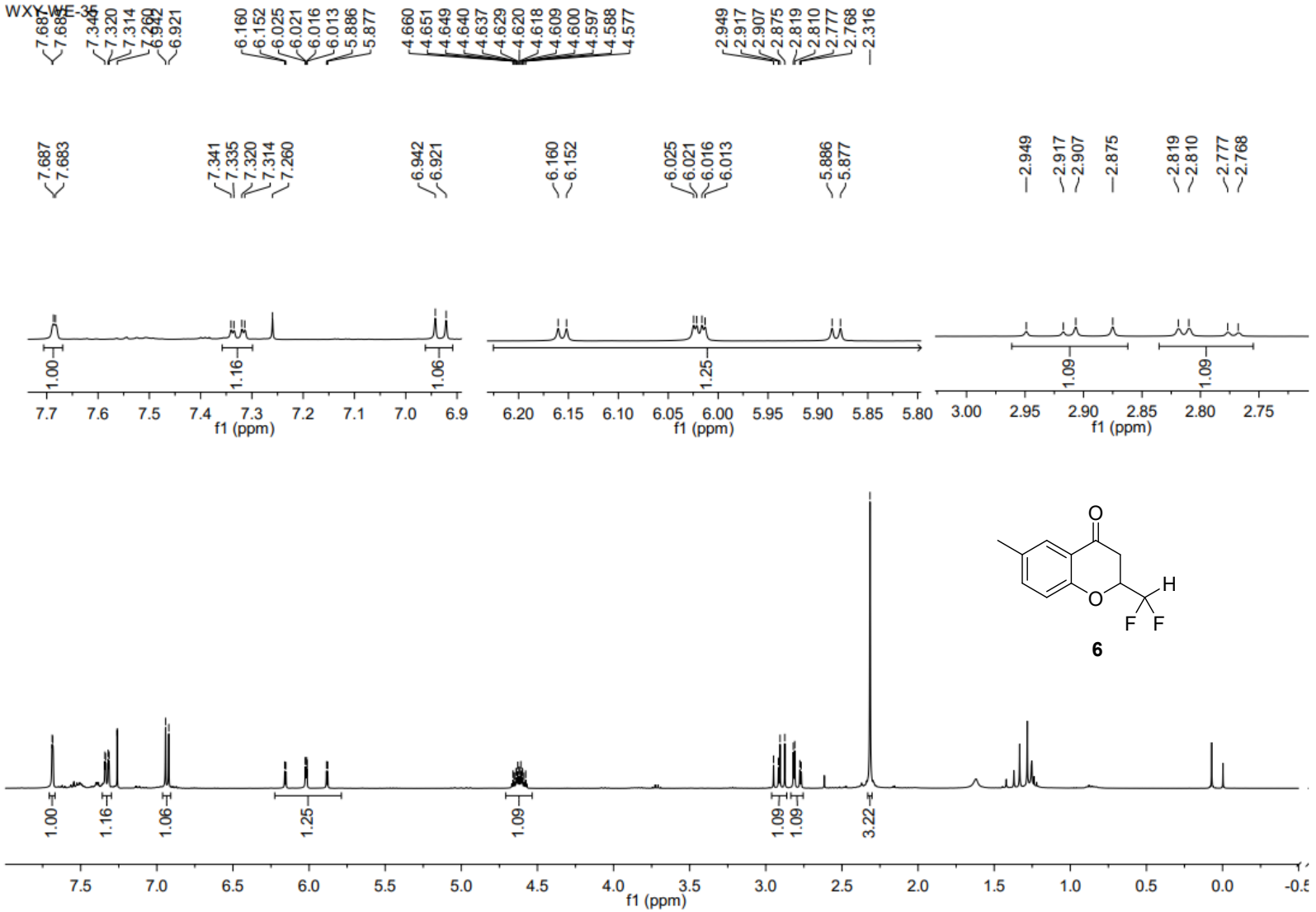
^{1}H NMR of Compound **5** (400 MHz, DMSO-d_6)



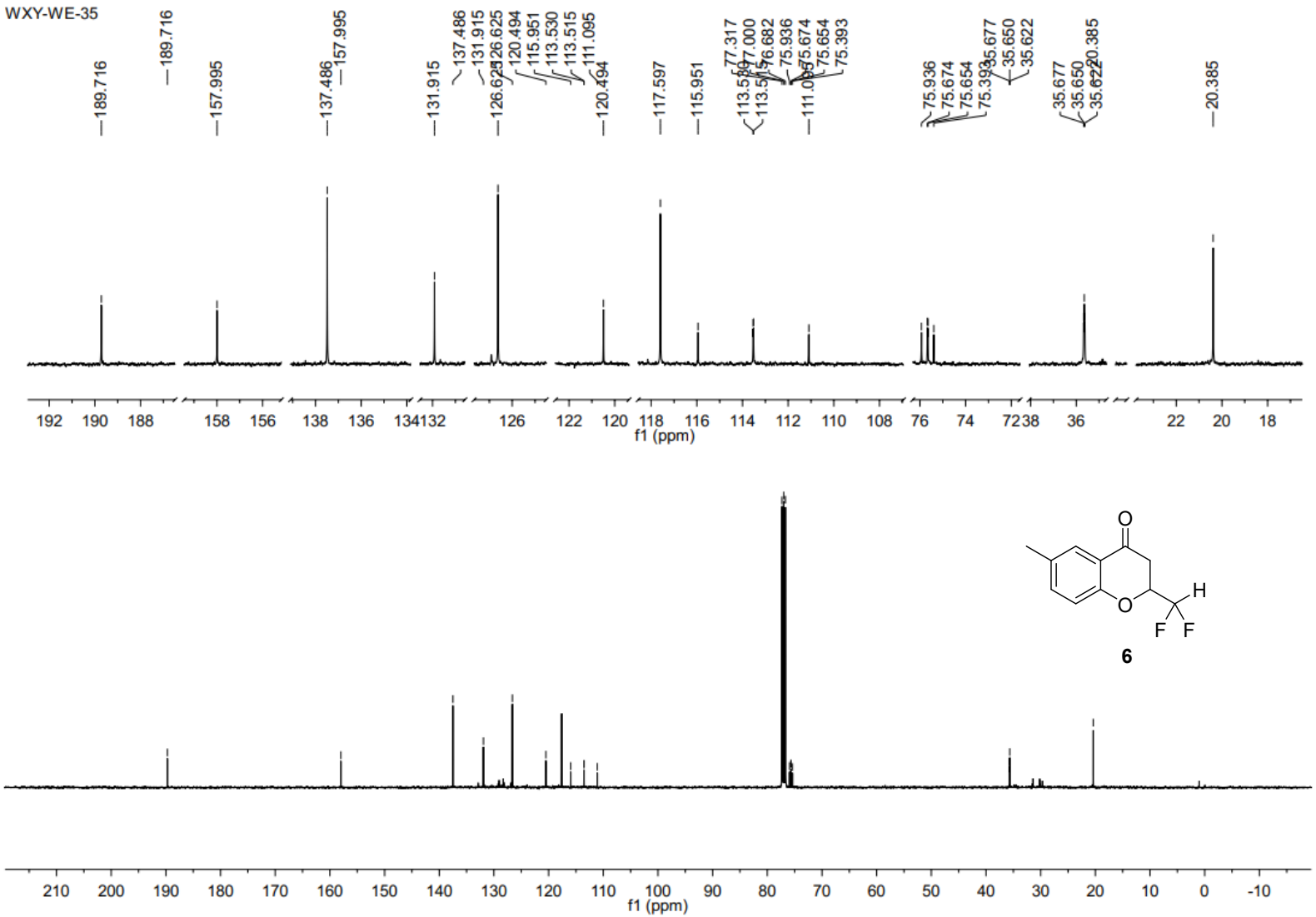
^{13}C NMR of Compound **5** (100 MHz, DMSO-d_6)



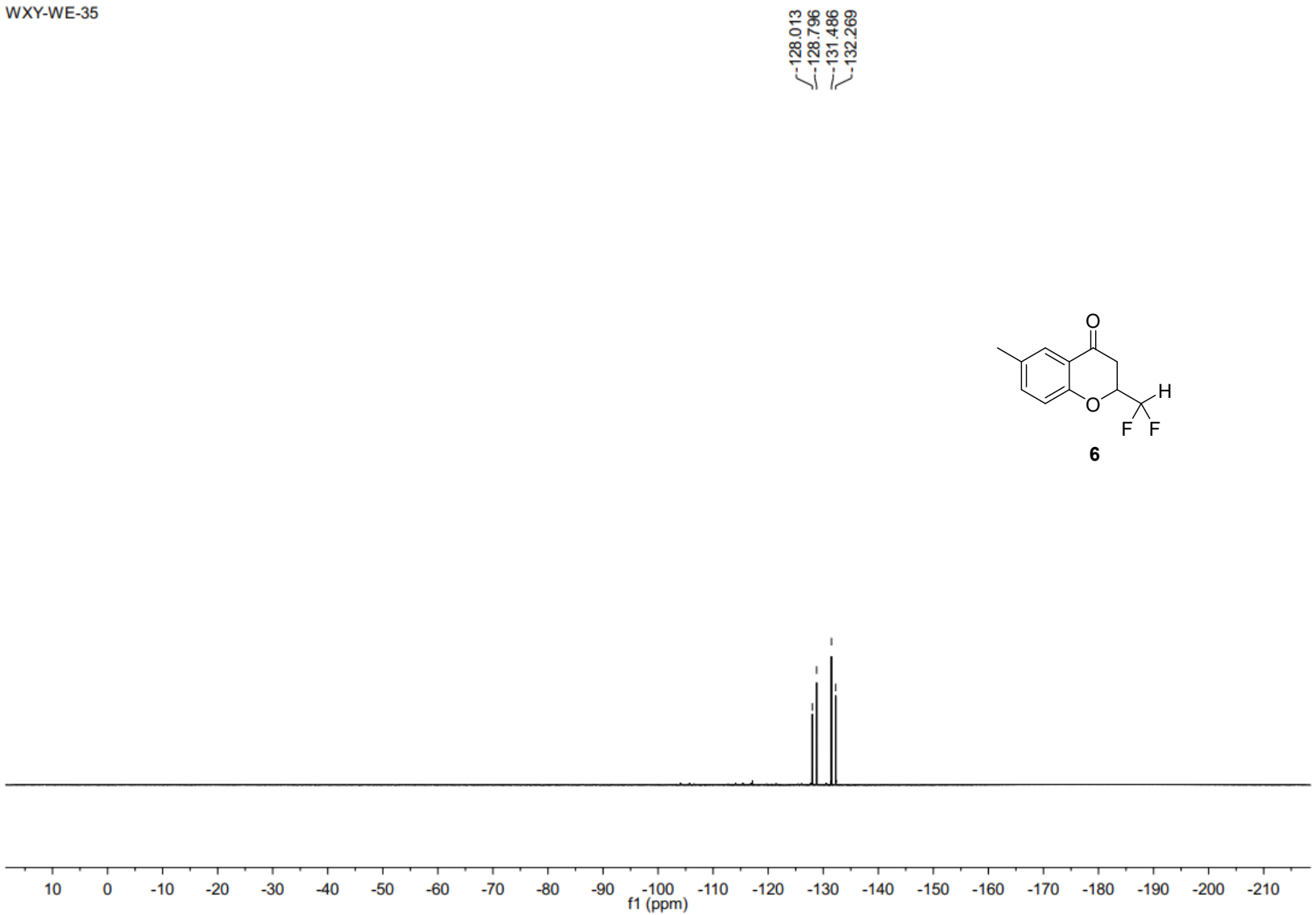
^{19}F NMR of Compound **5** (376 MHz, DMSO-d_6)



^{1}H NMR of Compound **6** (400 MHz, $CDCl_3$)



^{13}C NMR of Compound **6** (100 MHz, $CDCl_3$)



^{19}F NMR of Compound **6** (376 MHz, $CDCl_3$)