Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

One-Pot Multistep Synthesis of 1-Fluoroalkylisoquinolines and Fused Fluoroalkylpyridines from *N*-Fluoroalkyl-1,2,3-triazoles

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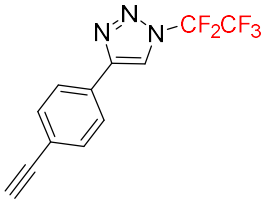
1 General information

All commercially available chemicals were used as received unless stated otherwise, column chromatography was performed using silica gel 60 (0.040–0.063 mm). Automated flash column chromatography was performed on Teledyne ISCO CombiFlash Rf+ Lumen Automated Flash Chromatography System with UV/Vis detection. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured at ambient temperature using 5 mm diameter NMR tubes. ^{13}C NMR spectra were proton decoupled. The chemical shift values (δ) are reported in ppm relative to internal Me_4Si (0 ppm for ^{1}H and ^{13}C NMR) or residual solvents and internal $CFCl_3$ (0 ppm for ^{19}F NMR). Coupling constants (J) are reported in Hertz. Structural elucidation was aided by additional acquisition of ^{13}C APT, 1D ^{1}H NOESY and/or various 2D spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{13}C-^{19}F HMBC, ^{1}H-^{1}H ROESY). High resolution mass spectra (HRMS) were recorded on a Waters Micromass AutoSpec Ultima or Agilent 7890A GC coupled with Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) ionization, on an LTQ Orbitrap XL using electrospray ionization (ESI), and on a Bruker solariX 94 ESI/MALDI-FT-ICR using dual ESI/MALDI ionization. Microwave experiments were done on CEM Focused Microwave™ Synthesis System, Model Discover. The method was set-up to 300 W, temperature 100-185 °C, hold time 20-180 min. LRMS spectra were recorded on Agilent 7890A GC (column HP-5MS, 30 m × 0.25 mm × 0.25 µm, 5% phenyl methylpolysiloxane) coupled with 5975C quadrupole mass selective electron impact (EI) detector (70 eV). IR spectra ($CHCl_3$ film) were measured on Bruker IFS 55 Equinox or Bruker Alpha-P spectrometer.

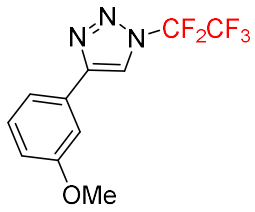
2 Synthesis of starting triazoles **1**

Procedure **A**: Triazoles **1f**, **1i**, **1j**, **1m**, **1o** were prepared according to the literature.[1]

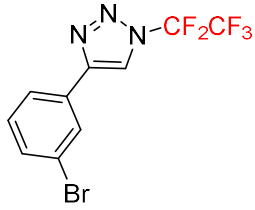
4-(4-Ethynylphenyl)-1-(perfluoroethyl)-1*H*-1,2,3-triazole (1f) Product **1f** was a side product in the synthesis of **1o**. Yield: 30%, white solid, m.p. 108-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.13 (m, 1H), 7.85 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 3.17 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.1, 133.0, 128.9, 126.1, 123.3, 118.3, 117.1 (qt, *J* = 287.6 Hz, *J* = 40.6 Hz), 110.3 (td, *J* = 271.3, 43.2 Hz), 83.1, 78.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.4 (s, 3F), -99.2 (s, 2F); HRMS (ESI$^+$) *m/z* calcd for $C_{12}H_7N_3F_5$: 288.05546, found 288.05554.



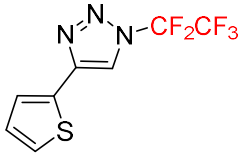
4-(3-Methoxyphenyl)-1-(perfluoroethyl)-1*H*-1,2,3-triazole (1i) Yield: 87%, off-white solid, m.p. 35-37 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.11 (m, 1H), 7.49 – 7.45 (m, 1H), 7.44 – 7.32 (m, 2H), 7.00 – 6.92 (m, 1H), 3.88 – 3.87 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 148.7, 130.3, 129.8, 118.6, 118.1, 117.1 (qt, *J* = 287.2, 41.3 Hz), 115.5, 111.5, 110.3 (tq, *J* = 271.6, 42.9 Hz), 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.4 (s, 3F), -99.2 (s, 2F); HRMS (ESI$^+$) *m/z* calcd for $C_{11}H_9F_5N_3O$: 294.06603, found 294.06577.



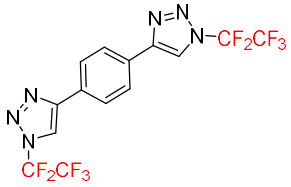
4-(3-Bromophenyl)-1-(perfluoroethyl)-1*H*-1,2,3-triazole (1j) Yield: 99%, white solid, m.p. 59-60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 1H), 8.06 – 8.01 (m, 1H), 7.86 – 7.77 (m, 1H), 7.57 – 7.49 (m, 1H), 7.39 – 7.31 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.5, 132.5, 130.8, 130.6, 129.3, 124.9, 123.3, 118.4, 117.1 (qt, *J* = 287.6, 41.1 Hz), 110.3 (qt, *J* = 271.8, 43.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.4 (s, 3F), -99.2 (s, 2F); HRMS (ESI$^+$) *m/z* calcd for $C_{10}H_6BrF_5N_3$: 341.96598, found 341.96612.



4-(Thiophen-2-yl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (1m) Yield: 86%, brown solid, m.p. 61-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.01 (m, 1H), 7.52 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.41 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.13 (dd, *J* = 5.1, 3.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 130.4, 128.1, 126.8, 126.1, 117.1, 117.1 (qt, *J* = 287.6, 41.3 Hz), 110.3 (tq, *J* = 271.1 Hz, 42.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.4 (s, 3F), -99.2 (s, 2F); HRMS (ESI$^+$) *m/z* calcd for $C_8H_5N_3F_5S$: 270.01189, found 270.01209.



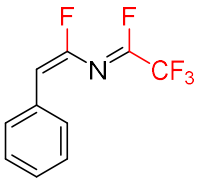
1,4-Bis(1-(perfluoroethyl)-1*H*-1,2,3-triazol-4-yl)benzene (1o) Compound **1o** is poorly soluble in $CHCl_3$ acetone, toluene, or DMSO, therefore only partial ^{13}C NMR could be interpreted. Yield: 35%, off-white solid, m.p. 238-241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 2H), 8.01 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.1, 129.6, 127.0, 118.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.3 (s, 6F), -99.2 (s, 4F); HRMS (ESI$^+$) *m/z* calcd for $C_{14}H_7N_6F_{10}$: 449.05670, found 449.05663.



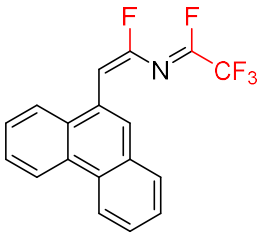
3 Preparation of azadienes **4** and **6** (General procedure)

A 10 ml MW tube was charged with triazole **1** (0.5 mmol) and under inert atmosphere $CDCl_3$ was added (3 ml). The reaction mixture was heated under MW irradiation to 165 °C for 1 h. CsF (2 equiv.; 152 mg; 1 mmol) or AcONa (2 equiv.; 82 mg; 1 mmol) was then added to the reaction mixture and that was then stirred at RT for 1-2 hours. After completion of the reaction the crude reaction mixture was filtered on a PTFE filter and was used for characterization, or was concentrated on vacuo and purified by column chromatography (silica gel, pentane).

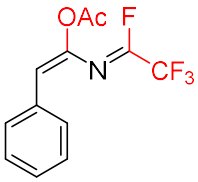
Ethyl 2,2-difluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate ((*Z*,*E*)-4a) ^{19}F NMR yield: 89%; ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.70 – 7.61 (m, 2H), 7.43 – 7.28 (m, 3H), 6.24 (dd, *J* = 10.1, 2.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0 (dd, *J* = 286.1, 11.4 Hz), 134.7 (dqd, *J* = 368.9, 45.3, 5.9 Hz), 131.6 (dd, *J* = 7.7, 2.1 Hz), 129.9 (dd, *J* = 4.0, 1.6 Hz), 129.1 (dd, *J* = 2.2, 0.6 Hz), 128.8, 115.6 (qdd, J = 275.5, 63.3, 3.5 Hz), 114.2 (dd, *J* = 35.4, 8.6 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -44.0 (dqd, *J* = 20.0, 5.5, 2.5 Hz, 1F), -72.8 (d, *J* = 5.5 Hz, 3F), -89.3 (dd, *J* = 20.0, 10.1 Hz, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_6F_5N$: 235.0415, found 235.0412.



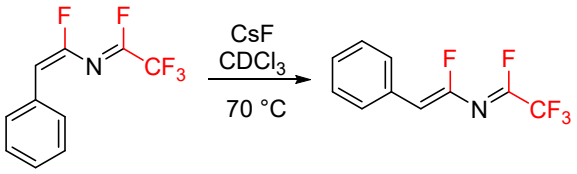
(*Z*)-2,2,2-trifluoro-*N*-((*E*)-1-fluoro-2-(phenanthren-9-yl)vinyl)acetimidoyl fluoride ((*Z*,*E*)-4m) Yield: 29%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 8.71 (m, 1H), 8.71 – 8.64 (m, 1H), 8.05 – 8.01 (m, 1H), 8.00 (s, 1H), 7.92 – 7.86 (m, 1H), 7.75 – 7.59 (m, 4H), 6.97 (dd, *J* = 9.2, 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8 (dd, *J* = 286.7, 10.8 Hz), 135.7 (dqd, *J* = 369.7, 45.4, 5.9 Hz), 131.3, 130.6, 130.5, 130.4 (dd, *J* = 2.3, 0.6 Hz), 129.3, 127.6, 127.1, 127.1, 126.9, 124.3, 123.4, 122.6, 115.5 (qdd, *J* = 275.5, 63.4, 3.3 Hz), 111.1 (dd, *J* = 35.2, 7.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -42.3 (dm, *J* = 20.6 Hz, 1F), -72.8 (d, *J* = 5.1 Hz, 3F), -88.1 (dd, *J* = 20.6, 9.2 Hz, 1F); HRMS (APCI$^+$) *m/z* calcd for $C_{18}H_{11}NF_5$: 336.08082, found 336.08062. For crystal structure, see section 13.



Ethyl 2,2-difluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate (6a) ^{19}F NMR yield: 93%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 2H), 7.45 – 7.31 (m, 4H), 6.27 (d, *J* = 2.2 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 136.5 (d, *J* = 11.5 Hz), 132.8 (dq, *J* = 367.6, 45.3 Hz), 132.3 (d, *J* = 1.8 Hz), 130.5 (d, *J* = 1.4 Hz), 129.5, 128.7, 125.4 (d, *J* = 7.8 Hz), 115.6 (qd, *J* = 275.4, 66.6 Hz), 20.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -50.2 (qd, *J* = 5.7, 2.2 Hz, 1F), -72.7 (d, *J* = 5.7 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{12}H_9F_4NO_2$: 275.0564, found 275.0554.



4 Isomerisation of **4a** with CsF



A high-pressure NMR tube was charged with CsF (2 equiv.; 25 mg; 0.167 mmol) and then solution of (*Z*,*E*)-**4a** in $CDCl_3$ (0.167M ; 0.5 ml) was added. $PhCF_3$ was used as an internal standard. The sample was then heated in the NMR machine to 70 °C. ^{19}F NMR data were collected and further fitted (Figure S1).

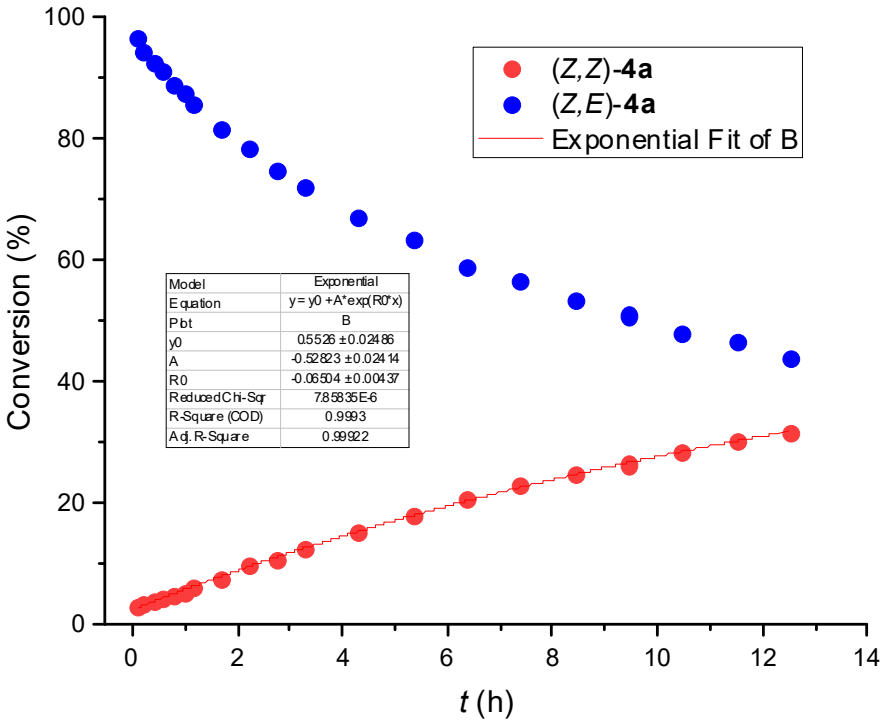
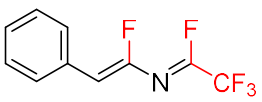


Figure S1. Conversion of (*Z*,*E*)-**4a** to (*Z*,*Z*)-**4a** at 70 °C followed by ^{19}F NMR.

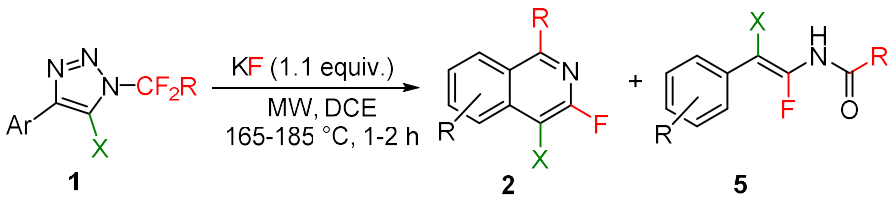


Ethyl 2,2-difluoro-2-(4-phenyl-1*H*-1,2,3-triazol-1-yl)acetate ((*Z*,*Z*)-4a) ^{19}F NMR yield: 32% after 12.5 h; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.27 (m, 5H), 6.22 (dd, *J* = 28.4, 2.3 Hz, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -46.9 (dqd, *J* = 20.5, 5.5, 2.3 Hz, 1F), -72.8 (d, *J* = 5.5 Hz, 3F), -91.2 (dd, *J* = 28.4, 20.5 Hz, 1F).

5 Synthesis of isoquinolines **2** (General procedure)

A 10 ml MW vial was charged with triazole **1** and KF (1.1 equiv), the reaction mixture was then heated in DCE (1.5 or 3 ml) or neat under MW irradiation to 165-185 °C under the conditions given in Table S1. After reaction completion the solution was filtered on a pad of cotton and the solvent was evaporated under reduced pressure. The product was obtained by purification using flash chromatography (silica gel, cyclohexane to DCM).

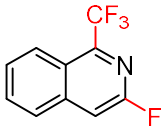
Table S1. Reaction conditions in the synthesis of isoquinolines **2**.



1 **2** **5**

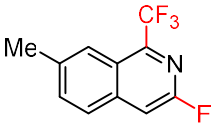
Entry	**1** (mmol)	Temp. (°C)	Time (h)	Product	Yield of **2**[a] (%)
1	0.5	165	1	**2a**	87
2	0.5	185	1	**2b**	74
3	0.5	185	1	**2c**	73
4	0.5	185	1	**2d**	72
5	0.5	165	1	**2e**	78 (12)
6	0.5	165	1	**2f**	25
7	0.5	185	1.5	**2g**	64
8	0.5	185	2.5	**2h**	50
9	0.5	185	1.5	**2i**	69
10	0.44	175	2	**2j**	75
11	0.5	165	1.5	**2k**	69
12	0.28	165	1	**2l**	74
13	0.37	165	1	**2m**	49
14	0.5	165	1	**2n**	0
15	0.01	185	2	**2o**	19
16	0.5	165	1	**2p**	66
17	0.5	175	2	**2q**	58
18	0.5	165	1	**2r**	41
19	0.7	165	11	**2s**	47
20	0.5	185	3.5	**2t**	77 (18)
21	0.5	165	3	**2u**	68
22	0.5	165	3	**2v**	70 (18)
23	0.5	185	5	**2w**	83
24	1.9	170	3	**2x**	12[b]

[a] Yield of isolated product **2** (in parentheses yield of **5**); [b] Neat (no solvent).

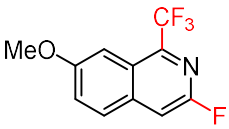


3-Fluoro-1-(trifluoromethyl)isoquinoline (**2a**): Yield: 87%; white solid, m.p. 49-50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.27 (m, 1H), 7.96 – 7.89 (m, 1H), 7.83 – 7.74 (m, 1H), 7.71 – 7.63 (m, 1H), 7.51 – 7.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (d, J = 238.1 Hz), 145.3 (qd, J = 34.8, 13.5 Hz), 141.6 (d, J = 7.4 Hz), 131.8 (d, J = 1.2 Hz), 128.2 (d, J = 2.3 Hz), 127.3 (d, J = 6.3 Hz), 125.0 (q, J = 3.1 Hz), 123.5 (d, J = 2.9 Hz), 121.5 (q, J = 276.2 Hz), 107.3 (d, J = 34.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (”d”, J = 2.1 Hz, 3F), -78.3 (s, 1F).; IR (cm^{-1}, $CHCl_3$) 1367s (CF_3), 3081m, 3023m, 1634m, 1597m, 1569m, 1001m, 945m, 720m (isoquinoline); HRMS (APCI^{+}) *m/z* calcd for $C_{10}H_6F_4N$: 216.04309, found 216.04299. For crystal structure, see section 13.

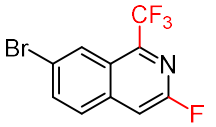
3-Fluoro-7-methyl-1-(trifluoromethyl)isoquinoline (**2b**): Yield: 74%; white solid, m.p. 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.95 (m, 1H), 7.82 (dm, *J* = 8.5 Hz, 1H), 7.61 (dm, *J* = 8.5, 1H), 7.46 – 7.41 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (d, *J* = 236.7 Hz), 144.2 (qd, *J* = 34.6, 13.5 Hz), 140.0 (d, *J* = 7.3 Hz), 138.5 (d, *J* = 2.9 Hz), 134.3, 126.9 (d, *J* = 6.2 Hz), 123.8 (d, *J* = 2.8 Hz), 123.5 (q, *J* = 3.0 Hz), 121.6 (q, *J* = 276.2 Hz), 107.1 (d, *J* = 34.4 Hz), 22.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 ("d", *J* = 1.4 Hz, 3F), -79.5 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{11}H_8F_4N$: 229.0509, found 229.0508.



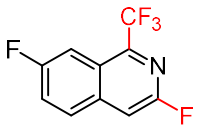
3-Fluoro-7-methoxy-1-(trifluoromethyl)isoquinoline (**2c**): Yield: 73%; white solid, m.p. 65-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 1H), 7.51 – 7.40 (m, 3H), 3.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9 (d, *J* = 2.4 Hz), 157.7 (d, *J* = 235.5 Hz), 142.7 (qd, *J* = 34.5, 13.2 Hz), 137.6 (d, *J* = 7.0 Hz), 128.5 (d, *J* = 6.0 Hz), 126.0, 124.9 (d, *J* = 2.9 Hz), 121.8 (q, *J* = 275.8 Hz), 107.5 (d, *J* = 35.1 Hz), 101.7 (q, *J* = 3.2 Hz), 55.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.1 (s, 3F), -81.1 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{11}H_7F_4NO$: 245.0458, found 245.0457.



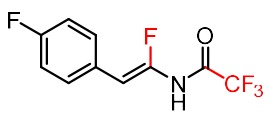
7-Bromo-3-fluoro-1-(trifluoromethyl)isoquinoline (**2d**): Yield: 72%; white solid, m.p. 101-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.37 (m, 1H), 7.86 (dm, *J* = 8.9, 1H), 7.81 (dm, *J* = 8.9, 1H), 7.52 – 7.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (d, *J* = 239.6 Hz), 144.4 (qd, *J* = 35.3, 13.8 Hz), 140.0 (d, *J* = 7.4 Hz), 135.5, 128.7 (d, *J* = 6.3 Hz), 127.1 (q, *J* = 3.3 Hz), 124.2 (d, *J* = 2.9 Hz), 122.6, 121.2 (d, *J* = 277.7 Hz), 107.5 (d, *J* = 34.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 (s, 3F), -76.9 (s, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_4BrF_4N$: 292.9458, found 292.9462.



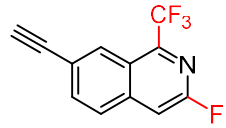
3,7-Difluoro-1-(trifluoromethyl)isoquinoline (**2e**): Yield: 78% white solid, m.p. 70-71 °C; ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.00 – 7.88 (m, 2H), 7.65 – 7.56 (m, 1H), 7.54 – 7.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (dd, *J* = 252.0, 3.0 Hz), 158.1 (dd, *J* = 238.1, 2.6 Hz), 144.6 (qdd, *J* = 35.3, 13.5, 6.9 Hz), 138.7 (d, *J* = 7.3 Hz), 129.8 (dd, *J* = 9.0, 6.4 Hz), 124.1 (dd, *J* = 9.5, 3.0 Hz), 123.3 (d, *J* = 26.3 Hz), 121.3 (q, *J* = 276.2 Hz), 108.7 (dq, *J* = 23.8, 3.2 Hz), 107.6 (d, *J* = 35.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.9 ("d", *J* = 1.8 Hz, 3F), -78.9 – -79.0 (m, 1F), -108.6 – -108.7 (m, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_4F_5N$: 233.0264, found 233.0259.



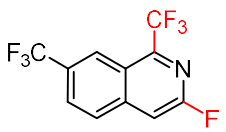
(*Z*)-2,2,2-Trifluoro-*N*-(1-fluoro-2-(4-fluorophenyl)vinyl)acetamide (**5e**): Was isolated as a side product when the reaction was done without the addition of KF. Yield: 12%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.45 – 7.39 (m, 2H), 7.07 – 7.00 (m, 2H), 6.34 (d, *J* = 36.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (dd, *J* = 248.2, 3.4 Hz), 154.0 (qd, *J* = 39.3, 3.0 Hz), 143.1 (dd, *J* = 262.0, 2.2 Hz), 130.4 (dd, *J* = 7.7, 7.7 Hz), 127.7 (dd, *J* = 4.0, 4.0 Hz), 115.8 (d, *J* = 21.6 Hz), 115.3 (qd, *J* = 288.0. 4.0 Hz), 99.2 (d, *J* = 8.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -76.2 (s, 3F), -99.9 (dt, *J* = 36.5, 2.3 Hz, 1F), -113.7 – -113.9 (m, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_6F_5NO$: 251.0370, found 251.0375.



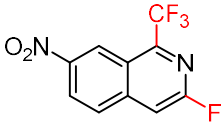
7-Ethynyl-3-fluoro-1-(trifluoromethyl)isoquinoline (**2f**): Yield: 25%; white solid, m.p. 75-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.34 (m, 1H), 7.97 – 7.84 (m, 1H), 7.83 – 7.75 (m, 1H), 7.52 – 7.44 (m, 1H), 3.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2 (d, *J* = 240.1 Hz), 145.2 (qd, *J* = 35.0, 13.5 Hz), 141.0 (d, *J* = 7.6 Hz), 134.4, 129.0 (q, *J* = 3.1 Hz), 127.4 (d, *J* = 6.3 Hz), 123.1 (d, *J* = 3.1 Hz), 122.4 (m), 121.2 (q, *J* = 276.6 Hz), 107.4 (d, *J* = 34.6 Hz), 82.4, 80.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 ("d", *J* = 1.3 Hz, 3F), -76.5 (s, 1F); HRMS (APCI^{+}) *m/z* calcd for $C_{12}H_6NF_4$: 240.04309, found 240.04320.



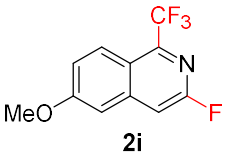
3-Fluoro-1,7-bis(trifluoromethyl)isoquinoline (**2g**): Yield: 64%; white solid, m.p. 76-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.56 (m, 1H), 8.15 – 8.02 (m, 1H), 7.99 – 7.91 (m, 1H), 7.65 – 7.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (d, *J* = 242.1 Hz), 146.9 (qd, *J* = 35.4, 13.7 Hz), 142.8 (d, *J* = 7.8 Hz), 130.3 (qd, *J* = 33.4, 2.7 Hz), 128.7 (d, *J* = 6.3 Hz), 127.6 (q, *J* = 3.3 Hz), 123.4 (q, *J* = 272.5 Hz), 123.0 (m), 122.4 (d, *J* = 4.0 Hz), 121.1 (q, *J* = 276.5 Hz), 107.5 (d, *J* = 34.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (s, 3F), -63.7 (s, 3F), -74.5 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{11}H_4F_7N$: 283.0226, found 283.0226.



3-Fluoro-7-nitro-1-(trifluoromethyl)isoquinoline (**2h**): Yield: 50%; white solid, m.p. 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 – 9.23 (m, 1H), 8.63 – 8.50 (m, 1H), 8.16 – 8.07 (m, 1H), 7.65 – 7.62 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8 (d, *J* = 244.8 Hz), 148.3 (qd, *J* = 35.9, 13.9 Hz), 146.7, 143.7 (d, *J* = 8.2 Hz), 129.3 (d, *J* = 6.4 Hz), 125.3, 122.1 (d, *J* = 3.1 Hz), 122.0 (q, *J* = 3.5 Hz), 120.9 (d, *J* = 276.6 Hz), 107.7 (d, *J* = 34.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (s, 3F), -72.3 (s, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_4F_4N_2O_2$: 260.0203, found 260.0203. For crystal structure, see section 13.

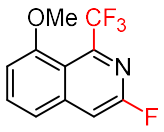


3-Fluoro-6-methoxy-1-(trifluoromethyl)isoquinoline (**2i**): Yield: 69%, **2i**:**2i´** 95:5; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.14 (m, 1H), 7.35 – 7.31 (m, 1H), 7.29 – 7.25 (m, 1H), 7.12 – 7.09 (m, 1H), 3.98 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 159.4 (d, *J* = 237.2 Hz), 144.7 (qd, *J* = 34.4, 14.5 Hz), 144.2 (d, *J* = 8.1 Hz), 126.6 (q, *J* = 3.1 Hz), 122.1 (d, *J* = 2.4 Hz), 121.6 (q, *J* = 276.0 Hz), 119.3 (d, *J* = 2.6 Hz), 106.0 (d, *J* = 35.3 Hz), 104.2 (d, *J* = 6.2 Hz), 55.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (”d”, *J* = 1.3 Hz, 3F), -78.2 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{11}H_7F_4NO$: 245.0458, found 245.0458.

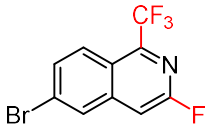


2i

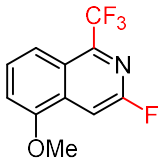
3-Fluoro-6-methoxy-1-(trifluoromethyl)isoquinoline (**2i´**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 1H), 7.48 – 7.41 (m, 1H), 7.42 – 7.38 (m, 1H), 7.00 – 6.94 (m, 1H), 4.04 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 (s, 3F), -78.4 (s, 1F).



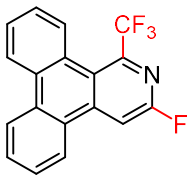
6-Bromo-3-fluoro-1-(trifluoromethyl)isoquinoline (**2j**): Yield: 75%, white solid, m.p. 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.10 (m, 1H), 8.12 – 8.06 (m, 1H), 7.77 – 7.63 (m, 1H), 7.43 – 7.34 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (d, *J* = 240.0 Hz), 145.8 (qd, *J* = 35.2, 13.8 Hz), 142.5 (d, *J* = 7.7 Hz), 131.9 (d, *J* = 2.9 Hz), 129.3 (d, *J* = 6.4 Hz), 127.5, 126.4 (q, *J* = 3.2 Hz), 121.9 (d, *J* = 3.1 Hz), 121.2 (q, *J* = 276.2 Hz), 106.3 (d, *J* = 35.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (”d”, *J* = 1.3 Hz, 3F), -76.2 (s, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_4BrF_4N$: 292.9458, found 292.9455.



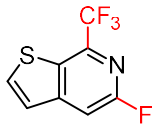
3-Fluoro-5-methoxy-1-(trifluoromethyl)isoquinoline (**2k**): Yield: 69%, white solid, m.p. 132-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 1H), 7.85 – 7.77 (m, 1H), 7.58 – 7.48 (m, 1H), 7.07 – 6.96 (m, 1H), 4.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6 (d, *J* = 237.0 Hz), 154.6 (d, *J* = 5.8 Hz), 144.5 (qd, *J* = 34.8, 13.2 Hz), 134.8 (d, *J* = 7.4 Hz), 128.3 (d, *J* = 2.4 Hz), 124.3 (d, *J* = 3.0 Hz), 121.6 (q, *J* = 276.0 Hz), 116.4 (q, *J* = 3.2 Hz), 108.1, 102.9 (d, *J* = 36.4 Hz), 56.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 (”d”, *J* = 1.5 Hz, 3F), -77.8 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{11}H_7F_4NO$: 245.0458, found 245.0457.



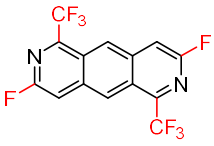
3-Fluoro-1-(trifluoromethyl)dibenzo[f,h]isoquinoline (**2l**): Yield: 74%, white solid, m.p. 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.45 (m, 1H), 8.45 – 8.42 (m, 1H), 8.40 – 8.34 (m, 1H), 8.31 – 8.24 (m, 1H), 7.96 – 7.90 (m, 1H), 7.77 – 7.66 (m, 2H), 7.64 – 7.54 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1 (d, *J* = 239.8 Hz), 144.0 (d, *J* = 7.2 Hz), 142.2 (qd, *J* = 35.1, 13.1 Hz), 131.8, 131.0, 130.6, 129.3 (q, *J* = 6.9 Hz), 129.3, 128.2, 127.1, 126.5 (d, *J* = 4.0 Hz), 125.8, 124.1, 124.0 (d, *J* = 3.9 Hz), 123.5, 123.4, 122.1 (q, *J* = 275.5 Hz), 103.6 (d, *J* = 37.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.5 (s, 3F), -73.3 (s, 1F); HRMS (EI) *m/z* calcd for $C_{18}H_9F_4N$: 315.0666, found 315.0666.



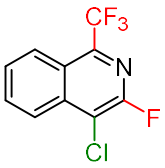
5-Fluoro-7-(trifluoromethyl)thieno[2,3-c]pyridine (**2m**): Yield: 49%, white solid, m.p. 73-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.63 (m, 2H), 7.62 – 7.61 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.84 (d, *J* = 237.8 Hz), 154.31 (d, *J* = 8.7 Hz), 139.67 (qd, *J* = 36.9, 14.8 Hz), 130.88 (d, *J* = 2.9 Hz), 130.24 (q, *J* = 3.2 Hz), 121.22 (q, *J* = 274.7 Hz), 120.74 (q, *J* = 2.9 Hz), 105.47 (d, *J* = 40.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.6 (s, 3F), -77.2 (s, 1F); HRMS (EI) *m/z* calcd for $C_8H_3F_4NS$: 220.9917, found 220.9912.



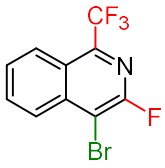
3,8-difluoro-1,6-bis(trifluoromethyl)pyrido[3,4-g]isoquinoline (**2o**): Yield: 19%, brown solid, m.p. 182-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 2H), 7.48 – 7.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.9 (d, *J* = 246.7 Hz), 146.3 – 145.0 (m), 143.9 (d, *J* = 8.0 Hz), 130.4 (d, *J* = 3.7 Hz), 120.8 (q, *J* = 277.9, 277.0 Hz), 117.9, 107.1 (d, *J* = 36.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (s, 6F), -70.6 (m, 2F); HRMS (APCI$^+$) *m/z* calcd for $C_{14}H_5F_8N_2$: 353.03195, found 353.03211.



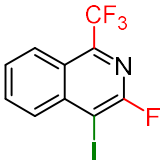
4-Chloro-3-fluoro-1-(trifluoromethyl)isoquinoline (**2p**): Yield: 66%, white solid, m.p. 95-96 °C; ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.37 – 8.30 (m, 2H), 7.96 – 7.88 (m, 1H), 7.81 – 7.69 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (d, *J* = 236.6 Hz), 142.7 (qd, *J* = 35.4, 1 2.5 Hz), 138.5 (d, *J* = 1.7 Hz), 132.7, 128.7 (d, *J* = 2.6 Hz), 125.3 (qd, *J* = 3.3, 1.0 Hz), 124.4 (d, *J* = 3.0 Hz), 124.2 (d, *J* = 6.8 Hz), 121.3 (q, *J* = 275.8 Hz), 115.1 (d, *J* = 31.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.9 (”d”, *J* = 1.9 Hz, 3F), -79.0 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{10}H_4ClF_3N$: 248.9963, found 248.9964.



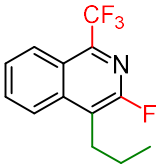
4-Bromo-3-fluoro-1-(trifluoromethyl)isoquinoline (**2q**): Yield: 58%, white solid, m.p. 108-110 °C; ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.38 – 8.27 (m, 2H), 7.95 – 7.87 (m, 1H), 7.78 – 7.71 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (d, *J* = 234.6 Hz), 143.8 (qd, *J* = 35.4, 12.7 Hz), 140.0 (d, *J* = 2.2 Hz), 133.0, 128.8 (d, *J* = 2.7 Hz), 126.7 (d, *J* = 6.7 Hz), 125.34 (qd, *J* = 3.4, 1.0 Hz), 124.4 (d, *J* = 2.9 Hz), 121.3 (q, *J* = 276.3 Hz), 105.7 (d, *J* = 34.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.0 (”d”, *J* = 2.0 Hz, 3F), -71.9 (s, 1F); HRMS (APCI$^+$) *m/z* calcd for $C_{10}H_5BrF_4N$: 293.95360, found 293.95391.



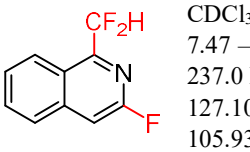
3-Fluoro-4-iodo-1-(trifluoromethyl)isoquinoline (**2r**): Yield: 41%, white solid, m.p. 84-86 °C; ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.34 – 8.26 (m, 1H), 8.25 – 8.20 (m, 1H), 7.93 – 7.83 (m, 1H), 7.77 – 7.70 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4 (d, *J* = 232.4 Hz), 145.4 (qd, *J* = 35.0, 13.0 Hz), 142.6 (d, *J* = 3.0 Hz), 133.3, 131.4 (d, *J* = 6.7 Hz), 128.8 (d, *J* = 2.8 Hz), 125.3 (q, *J* = 3.0 Hz), 123.8 (d, *J* = 2.9 Hz), 121.1 (q, *J* = 276.4 Hz), 82.1 (d, *J* = 40.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ -60.2 (s, 1F), -63.0 (”d”, *J* = 2.1 Hz, 3F); HRMS (APCI$^+$) *m/z* calcd for $C_{10}H_5F_4IN$: 341.93967, found 341.93973.



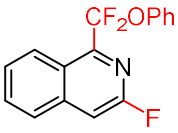
3-Fluoro-4-propyl-1-(trifluoromethyl)isoquinoline (**2s**): Yield: 47%, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.28 (m, 1H), 8.16 – 8.08 (m, 1H), 7.87 – 7.77 (m, 1H), 7.71 – 7.62 (m, 1H), 3.14 – 3.05 (m, 2H), 1.85 – 1.70 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7 (d, *J* = 234.7 Hz), 142.6 (qd, *J* = 34.6, 14.0 Hz), 140.1 (d, *J* = 5.5 Hz), 131.3, 127.4 (d, *J* = 2.4 Hz), 125.5 (q, *J* = 3.1 Hz), 123.9 (d, *J* = 6.9 Hz), 123.7 (d, *J* = 2.6 Hz), 121.7 (q, *J* = 275.8 Hz), 120.1, 26.7, 23.3, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 (”d”, *J* = 2.1 Hz, 3F), -81.8 (s, 1F); HRMS (ESI$^+$) *m/z* calcd for $C_{13}H_{11}F_4N$: 257.0822, found 257.0823.



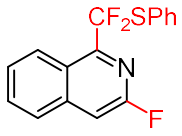
1-(Difluoromethyl)-3-fluoroisoquinoline (**2t**): Yield: 77%, off-white solid, m.p. 31-32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.44 (m, 1H), 7.93 – 7.85 (m, 1H), 7.80 – 7.71 (m, 1H), 7.67 – 7.58 (m, 1H), 7.47 – 7.37 (m, 1H), 6.91 (t, *J* = 54.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.33 (d, *J* = 237.0 Hz), 150.31 (td, *J* = 27.2, 13.3 Hz), 141.36 (d, *J* = 7.5 Hz), 131.68, 127.62 – 127.48 (m), 127.10 (d, *J* = 6.3 Hz), 125.58 (t, *J* = 3.6 Hz), 123.99 – 123.88 (m), 116.61 (t, *J* = 242.2 Hz), 105.93 (d, *J* = 34.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -79.6 (s, 1F), -110.5 (d, *J* = 54.0 Hz, 2F); HRMS (EI) *m/z* calcd for $C_{10}H_6F_3N$: 197.0447, found 197.0449.



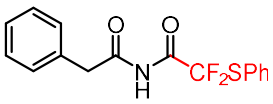
(*Z*)-2,2-Difluoro-*N*-(1-fluoro-2-phenylvinyl)acetamide (**5t**): Was isolated as a side product when the reaction was done without the addition of KF. Yield: 18%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (br d, *J* = 8.3 Hz, 1H), 7.51 – 7.47 (m, 2H), 7.42 – 7.34 (m, 3H), 7.08 (ddt, *J* = 27.0, 10.5, 0.8 Hz, 1H), 6.04 (t, *J* = 54.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3 (t, *J* = 25.7 Hz), 149.6 (d, *J* = 245.1 Hz), 130.0 (d, *J* = 24.8 Hz), 129.3, 128.9 (d, *J* = 2.2 Hz), 123.4 (d, *J* = 6.8 Hz), 108.3 (t, *J* = 252.9 Hz), 101.3 (d, *J* = 11.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -126.8 (dd, *J* = 53.9, 1.9 Hz, 2F), -131.5 (dd, *J* = 27.1, 2.3 Hz, 1F); HRMS (EI) *m/z* calcd for $C_{10}H_8F_3NO$: 215.0552, found 215.0555.

1-(Difluoro(phenoxy)methyl)-3-fluoro-7-methoxyisoquinoline (**2u**): Yield: 68%, white solid, m.p. 54-55 °C; 

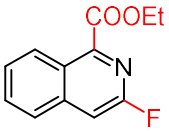
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 – 8.54 (m, 1H), 7.92 – 7.86 (m, 1H), 7.79 – 7.71 (m, 1H), 7.69 – 7.60 (m, 1H), 7.47 – 7.33 (m, 5H), 7.31 – 7.19 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8 (d, *J* = 236.9 Hz), 150.3 (t, *J* = 1.8 Hz), 148.5 (td, *J* = 33.7, 13.4 Hz), 141.6 (d, *J* = 7.3 Hz), 131.5, 129.7, 127.6 (d, *J* = 2.4 Hz), 127.1 (d, *J* = 6.4 Hz), 126.1, 126.1 (t, *J* = 3.0 Hz), 123.8 (d, *J* = 2.9 Hz), 121.8, 119.9 (t, *J* = 265.7 Hz), 106.3 (d, *J* = 34.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.8 (s, 2F), -78.5 (s, 1F).; HRMS (ESI^+) *m/z* calcd for $C_{16}H_{11}F_3NO$: 290.07873, found 290.07871.

1-(Difluoro(phenylthio)methyl)-3-fluoroisoquinoline (**2v**): Yield: 70%, white solid, m.p. 74-76 °C; ^{1}H NMR 

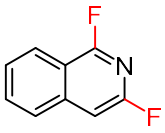
(400 MHz, $CDCl_3$) δ 8.57 – 8.49 (m, 1H), 7.91 – 7.84 (m, 1H), 7.78 – 7.70 (m, 3H), 7.65 – 7.55 (m, 1H), 7.51 – 7.37 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (d, *J* = 237.5 Hz), 150.4 (td, *J* = 27.8, 12.6 Hz), 141.6 (d, *J* = 7.2 Hz), 137.1, 131.5, 130.3, 129.2, 127.6, 127.4, 127.1 (d, *J* = 6.2 Hz), 126.5, 126.2 (t, *J* = 4.7 Hz), 126.1 (t, *J* = 272.8 Hz), 106.3 (d, *J* = 34.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.7 (”d”, *J* = 2.1 Hz, 2F), -78.8 (”d”, *J* = 2.3 Hz, 1F); HRMS (EI) *m/z* calcd for $C_{16}H_{10}F_3NS$: 305.0481, found 305.0484.

2,2-Difluoro-*N*-(2-phenylacetyl)-2-(phenylthio)acetamide (**5v'**): Was isolated as a side product when the reaction was done without the addition of KF. Yield: 18%; yellow liquid; ^{1}H NMR 

(400 MHz, $CDCl_3$) δ 8.37 (bs, 1H), 7.58 – 7.52 (m, 2H), 7.51 – 7.46 (m, 1H), 7.40 – 7.32 (m, 5H), 7.27 – 7.24 (m, 2H), 4.09 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7 (d, *J* = 2.2 Hz), 159.9 (t, *J* = 30.8 Hz), 136.9, 132.4, 131.1, 129.7, 129.7, 128.8, 127.7, 123.8 (t, *J* = 2.6 Hz), 121.4 (t, *J* = 290.2 Hz), 43.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.6 (s, 2F); HRMS (EI) *m/z* calcd for $C_{16}H_{13}F_2NO_2S$: 321.0630, found 321.0628.

Ethyl 3-fluoroisoquinoline-1-carboxylate (**2w**): Yield: 83%, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 – 

8.64 (m, 1H), 7.87 – 7.76 (m, 1H), 7.72 – 7.65 (m, 1H), 7.63 – 7.54 (m, 1H), 7.44 – 7.38 (m, 1H), 4.55 (q, *J* = 7.2 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.9, 159.2 (d, *J* = 236.7 Hz), 147.5 (d, *J* = 13.5 Hz), 141.2 (d, *J* = 7.5 Hz), 131.4 (d, *J* = 1.1 Hz), 127.9 (d, *J* = 2.4 Hz), 126.8 (d, *J* = 3.0 Hz), 126.8 (d, *J* = 3.0 Hz), 125.5 (d, *J* = 2.7 Hz), 106.9 (d, *J* = 34.9 Hz), 62.5, 14.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -77.4 (s, 1F); HRMS (ESI^+) *m/z* calcd for $C_{12}H_{11}O_2NF$: 220.07683, found 220.07692.

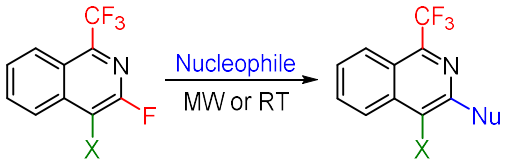
1,3-Difluoroisoquinoline (**2x**): Yield: 12%, white solid, m.p. 62-63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.11 

(m, 1H), 7.88 – 7.81 (m, 1H), 7.81 – 7.72 (m, 1H), 7.63 – 7.54 (m, 1H), 7.15 – 7.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7 (d, *J* = 254.3 Hz), 157.7 (dd, *J* = 240.8, 15.2 Hz), 142.5 (d, *J* = 5.7 Hz), 132.6, 127.0, 126.3 (dd, *J* = 6.6, 3.6 Hz), 123.6, 115.6 (d, *J* = 26.0 Hz), 100.2 (dd, *J* = 33.3, 6.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -70.3 (d, *J* = 11.4 Hz, 1F), -79.7 (d, *J* = 11.4 Hz, 1F); HRMS (EI) *m/z* calcd for $C_9H_5F_2N$: 165.0385, found 165.0387.

6 Synthesis of 3-substituted 1-trifluoromethylisoquinolines **7a-7k** (General procedure)

Isoquinoline **2** (0.1-0.2 mmol) was dissolved in the solvent given in Table S2 (2.5 ml) and the corresponding nucleophile was added. The reaction mixture was stirred at ambient temperature or heated (MW irradiation) under the conditions given in Table S2. After complete conversion of 3-fluoroisoquinoline (monitoring by UPLC-MS) the solvent was evaporated under reduced pressure and the residue was chromatographed (silica gel, cyclohexane-ethyl acetate or hexane-DCM).

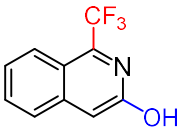
Table S2. S_NAr of 3-fluoroisoquinolines



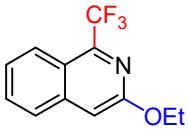
2 **7**

Entry	Nucleophile (equiv.)	X	Solvent	Temp. (°C)	**7**, Yield (%)
1	NaOH (15)	H	H_2O	155	**7a**, 88
2	EtONa (12)	H	EtOH	80	**7b**, 96
3	EtONa (12)	Cl	EtOH	155	**7c**, 99
4	*t*-BuOK (1.2)	H	*t*-BuOH	80	**7d**, 80
5	PhONa (1.5)	H	DMA	80	**7e**, 89
6	MeSNa (5)	H	DMA	20	**7f**, 85
7	MeSNa (2)	Ph	DMF	20	**7g**, 91
8	*p*-Tol-SNa (1)	H	DMA	80	**7h**, 91
9	*p*-Tol-SO_2Li (2.5)	H	DMSO	155	**7i**, 58
10	NH_2NH_2 (20)	H	*i*-PrOH	100	**7j**, 95
11	*p*-Tol-CH_2NH_2 (2)	H	DMSO	155	**7k**, 42

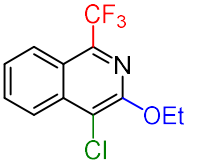
1-(Trifluoromethyl)isoquinolin-3-ol (**7a**): Yield: 88%; white solid, m.p. 162-163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.22 – 8.17 (m, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.53 – 7.44 (m, 1H), 7.30 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 144.3 (q, J = 33.7 Hz), 141.8, 131.3, 126.7, 126.25, 124.8 (q, J = 2.9 Hz), 121.9 (q, J = 276.3 Hz), 121.2, 106.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7 ("d", J = 2.1 Hz, 3F); IR (cm^{-1}, $CHCl_3$) 1250m, 1140s (CF_3); 3549m, 3100m, 1320m (OH); 1635m, 1606m, 1564m, 1508m, 1453m, 949s, 692m (isoquinoline); HRMS (ESI^+) *m/z* calcd for $C_{10}H_7F_3NO$: 214.04743, found 214.04732.



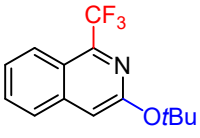
3-Ethoxy-1-(trifluoromethyl)isoquinoline (**7b**): Yield: 96%; white solid, m.p. 50-52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 1H), 7.78 – 7.74 (m, 1H), 7.66 – 7.56 (m, 1H), 7.51 – 7.40 (m, 1H), 7.21 – 7.16 (m, 1H), 4.46 (q, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H);; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 144.5 (q, J = 33.7 Hz), 141.1, 130.7, 126.6, 126.0, 124.7 (q, J = 3.0 Hz), 122.1 (q, J = 276.2 Hz), 121.1, 106.2, 63.1, 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 ("d", J = 2.1 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{12}H_{10}F_3NO$: 241.0709, found 241.0704.



4-Chloro-3-ethoxy-1-(trifluoromethyl)isoquinoline (**7c**): Yield: 99%; white solid, m.p. 95-96 °C^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.14 (m, 2H), 7.79 – 7.70 (m, 1H), 7.57 – 7.47 (m, 1H), 4.63 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 141.5 (q, J = 34.0 Hz), 137.8, 131.5, 126.3, 124.8 (q, J = 3.0 Hz), 123.5, 122.0 (q, J = 275.9 Hz), 121.8, 114.3, 63.9, 14.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 ("d", J = 1.7 Hz, 3F); HRMS ($APCI^+$) *m/z* calcd for $C_{12}H_{10}ONClF_3$: 276.03975, found 276.03995.

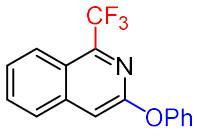


3-(*tert*-Butoxy)-1-(trifluoromethyl)isoquinoline (**7d**): Yield: 80%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.12 (m, 1H), 7.78 – 7.69 (m, 1H), 7.62 – 7.55 (m, 1H), 7.47 – 7.41 (m, 1H), 7.20 – 7.18 (m, 1H), 1.63 (s, 9H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 143.5 (d, J = 33.6 Hz), 141.0, 130.4, 126.6, 126.0, 124.5 (q, J = 2.9 Hz), 122.3 (q, J = 276.0 Hz) 120.9, 80.9, 29.1;

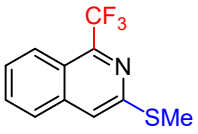


^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 ("d", J = 2.2 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{14}H_{14}F_3NO$: 269.1022, found 269.1021.

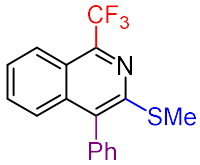
3-Phenoxy-1-(trifluoromethyl)isoquinoline (**7e**): Yield: 89%; white solid, m.p. 62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.22 (m, 1H), 7.78 – 7.73 (m, 1H), 7.72 – 7.63 (m, 1H), 7.61 – 7.52 (m, 1H), 7.49 – 7.40 (m, 2H), 7.30 – 7.21 (m, 1H), 7.22 – 7.19 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 154.7, 145.7 (d, J = 34.2 Hz), 141.0, 131.3, 130.2, 127.1, 127.0, 125.1, 124.9 (q, J = 3.1 Hz), 122.1, 121.8 (d, J = 276.2 Hz), 120.8, 107.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 ("d", J = 2.1 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{16}H_{10}F_3NO$: 289.0707, found 289.0709.



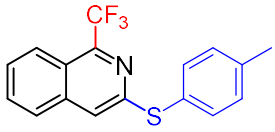
3-(Methylthio)-1-(trifluoromethyl)isoquinoline (**7f**): Yield: 85%; light yellow solid, m.p. 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.24 – 8.16 (m, 1H), 7.79 – 7.72 (m, 1H), 7.71 – 7.66 (m, 2H), 7.61 – 7.53 (m, 1H), 2.69 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 146.1 (q, J = 33.6 Hz), 138.2, 131.3, 127.6, 126.5, 124.8 (q, J = 3.1 Hz), 122.3, 122.1 (q, J = 276.6 Hz), 120.0, 14.2^{19}F NMR (377 MHz, $CDCl_3$) δ -63.4 ("d", J = 2.1 Hz, 3F). HRMS (EI) *m/z* calcd for $C_{11}H_8F_3NS$: 243.0324, found 243.0326.



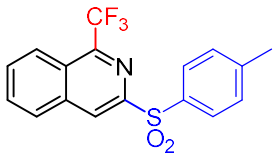
3-(Methylthio)-4-phenyl-1-(trifluoromethyl)isoquinoline (**7g**): Yield: 91%; white solid, m.p. 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.23 (m, 1H), 7.64 – 7.48 (m, 6H), 7.50 – 7.41 (m, 1H), 7.39 – 7.30 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 145.1 (q, J = 33.5 Hz), 137.1, 135.4, 133.0, 130.9, 130.2, 129.1, 128.9, 127.1, 125.2, 124.5 (q, J = 3.0 Hz), 122.4 (q, J = 276.4 Hz), 122.1, 14.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 ("d", J = 2.3 Hz, 3F).; HRMS (ESI^+) *m/z* calcd for $C_{17}H_{13}NF_3S$: 320.07153, found 320.07181.



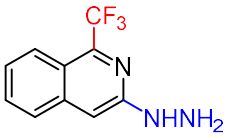
3-(*p*-Tolylthio)-1-(trifluoromethyl)isoquinoline (**7h**): Yield: 91%; white solid, m.p. 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 1H), 7.68 – 7.59 (m, 2H), 7.60 – 7.54 (m, 3H), 7.32 – 7.26 (m, 2H), 7.26 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 146.2 (q, J = 33.6 Hz), 140.0, 138.5, 135.4, 131.2, 130.9, 127.8, 127.2, 126.7, 124.8 (q, J = 3.0 Hz), 122.4, 121.9 (q, J = 276.9 Hz), 120.1, 21.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 ("d", J = 2.1 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{17}H_{12}F_3NS$: 319.0637, found 319.0629.



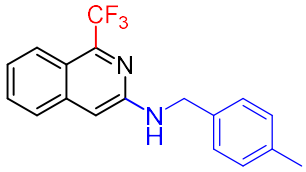
3-Tosyl-1-(trifluoromethyl)isoquinoline (**7i**): Yield: 58%; white solid, m.p. 195-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.36 – 8.30 (m, 1H), 8.15 – 8.10 (m, 1H), 8.08 – 8.02 (m, 2H), 7.97 – 7.84 (m, 2H), 7.38 – 7.30 (m, 2H), 2.42 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 147.6 (q, J = 34.8 Hz), 145.2, 137.2, 135.7, 132.5, 131.7, 129.9, 129.4, 129.4, 125.6, 125.2 (q, J = 3.1 Hz), 124.1, 121.4 (q, J = 277.0 Hz), 21.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8 ("d", J = 2.1 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{17}H_{13}F_3NO_2S$: 352.06136, found 352.06122.



3-Hydrazineyl-1-(trifluoromethyl)isoquinoline (**7j**): Yield: 95%; white solid, m.p. 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 1H), 7.73 – 7.68 (m, 1H), 7.60 – 7.54 (m, 1H), 7.39 – 7.32 (m, 1H), 7.22 (s, 1H), 6.07 (s, 1H), 3.84 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.4, 145.2 (q, J = 33.2 Hz), 140.6, 130.8, 126.3, 124.8 (q, J = 2.9 Hz), 124.8, 122.2 (q, J = 276.5 Hz), 120.1, 101.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5 ("d", J = 2.2 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{10}H_8F_3N_3$: 227.0665, found 227.0668.



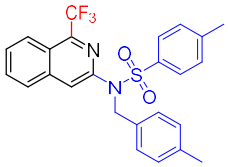
***N*-(4-Methylbenzyl)-1-(trifluoromethyl)isoquinolin-3-amine** (**7k**): Yield: 42%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.02 (m, 1H), 7.61 – 7.54 (m, 1H), 7.54 – 7.46 (m, 1H), 7.34 – 7.24 (m, 3H), 7.19 – 7.15 (m, 2H), 6.66 (s, 1H), 5.19 (t, *J* = 5.7 Hz, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 145.5 (q, *J* = 33.0 Hz), 140.7, 137.3, 135.3, 130.7, 129.6, 127.5, 126.0, 124.8 (q, *J* = 3.0 Hz), 124.1, 122.2 (q, *J* = 276.6 Hz), 119.3, 100.2, 47.0, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5 ("d", *J* = 2.2 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{18}H_{15}F_3N_2$: 316.1182, found 316.1182.



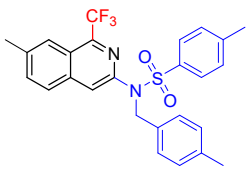
7 Synthesis of *N*-(isoquinolin-3-yl)benzenesulfonamides **8a-8i** (General procedure)

Sodium hydride (60-70% suspension in mineral oil; 10.4 mg, 0.26 mmol, 1.3 eq) was suspended in DMA (1 ml) and the starting benzenesulfonamide (0.27 mmol, 1.35 eq) was added. The suspension was heated to 50 °C for 10 min to dissolve the amide salt. Fluoroisoquinoline **2** (0.2 mmol) was added and the reaction mixture was heated (MW irradiation) under the conditions given in the text. The reaction was monitored with UPLC-MS. After reaching the maximal conversion, the solvent was evaporated under reduced pressure and the residue was chromatographed (silica gel, cyclohexane-ethyl acetate or hexane-DCM).

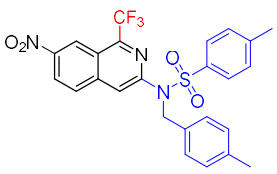
4-Methyl-*N*-(4-methylbenzyl)-*N*-(1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (**8a**): Yield: 51%; conditions of MW irradiation: 155 °C, 1.5 h; white solid, m.p. 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 1H), 8.03 (s, 1H), 7.91 – 7.84 (m, 1H), 7.73 – 7.67 (m, 1H), 7.67 – 7.59 (m, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.20 (m, 4H), 7.00 (d, *J* = 8.1 Hz, 2H), 5.01 (s, 2H), 2.42 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 144.9 (q, *J* = 34.1 Hz), 144.8, 144.0, 139.0, 137.3, 135.6, 133.2, 131.1, 129.7, 129.1, 128.9, 128.8, 128.1, 127.7, 124.4 (q, *J* = 3.0 Hz), 123.3, 123.1, 121.8 (q, *J* = 276.6 Hz), 51.5, 21.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 ("d", *J* = 2.1 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{25}H_{21}F_3N_2O_2S$: 470.1270, found 470.1266.

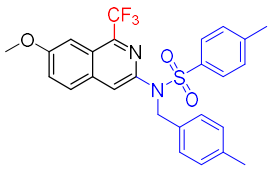


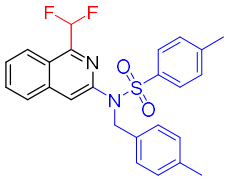
4-Methyl-*N*-(7-methyl-1-(trifluoromethyl)isoquinolin-3-yl)-*N*-(4-methylbenzyl)benzenesulfonamide (**8b**): Yield: 41%; conditions of MW irradiation: 145 °C, 1 h; white solid, m.p. 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.93 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 4H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.97 (s, 2H), 2.55 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (q, *J* = 10.3 Hz), 143.9, 139.3, 137.4, 135.6, 133.5, 132.8, 129.6, 129.1, 128.9, 127.9, 127.8, 123.7, 123.3, 123.1 (q, *J* = 2.9 Hz), 121.9 (q, *J* = 276.6 Hz), 51.6, 22.4, 21.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.7 ("d", *J* = 2.0 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{26}H_{24}F_3N_2O_2S$: 485.15051, found 485.15018.

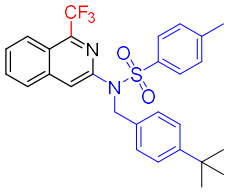


4-Methyl-*N*-(4-methylbenzyl)-*N*-(7-nitro-1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (**8c**): Yield: 65%; conditions of MW irradiation: 100 °C, 1 h; white solid, m.p. 118-120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 – 9.07 (m, 1H), 8.49 – 8.42 (m, 1H), 8.17 (s, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.30 – 7.22 (m, 4H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.09 (s, 2H), 2.42 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 148.1, 147.0 (q, *J* = 34.9 Hz), 146.7, 144.6, 141.2, 137.6, 135.5, 132.8, 129.9, 129.3, 128.8, 128.3, 127.6, 124.5, 121.5 (q, *J* = 3.5 Hz), 121.3, 121.2 (q, *J* = 276.7 Hz), 120.2, 51.3, 21.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 ("d", *J* = 1.5 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{25}H_{21}F_3N_3O_4S$: 516.11994, found 516.11954.

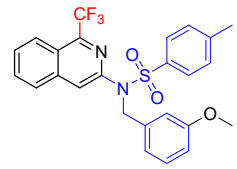


4-Methyl-*N*-(4-methylbenzyl)-*N*-(7-methoxy-1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (8d): 
Yield: 38%; conditions of MW irradiation: 150 °C, 1 h; white solid, m.p. 57-58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.80 – 7.70 (m, 1H), 7.53 – 7.46 (m, 2H), 7.40 – 7.32 (m, 2H), 7.27 – 7.15 (m, 4H), 7.02 – 6.95 (m, 2H), 4.93 (s, 2H), 3.94 (s, 3H), 2.42 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 143.9, 143.2, 142.8 (q, *J* = 33.7 Hz), 137.3, 135.5, 134.8, 133.2, 129.6, 129.1, 128.9, 127.8, 127.7, 125.0, 124.8, 123.8, 122.0 (q, *J* = 276.6 Hz), 101.7 (q, *J* = 3.4 Hz), 55.7, 51.7, 21.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.3 ("d", *J* = 1.6 Hz, 3F); HRMS (EI) *m/z* calcd for $C_{26}H_{23}F_3N_2O_3S$: 500.1376, found 500.1369.

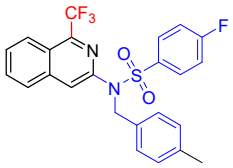
4-Methyl-*N*-(4-methylbenzyl)-*N*-(1-(difluoromethyl)isoquinolin-3-yl)benzenesulfonamide (8e): Yield: 55%; 
conditions of MW irradiation: 150 °C, 2 h; white solid, m.p. 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.33 (m, 1H), 7.95 (s, 1H), 7.89 – 7.82 (m, 1H), 7.73 – 7.66 (m, 1H), 7.62 – 7.58 (m, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.19 (m, 4H), 7.02 – 6.97 (m, 2H), 6.68 (t, *J* = 54.4 Hz, 1H), 5.00 (s, 2H), 2.42 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) 149.9 (t, *J* = 26.8 Hz), 145.0 (t, *J* = 1.7 Hz), 143.9, 138.8, 137.3, 135.8, 133.3, 131.0, 129.6, 129.2, 128.6, 128.4, 128.0, 127.8, 125.0 (t, *J* = 3.6 Hz), 123.9, 122.7, 117.2 (t, *J* = 242.6 Hz), 51.5, 21.7, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.8 (d, *J* = 54.4 Hz, 2F); HRMS (ESI^+) *m/z* calcd for $C_{25}H_{23}F_2N_2O_2S$: 453.14428, found 453.14405.

***N*-(4-(*tert*-Butyl)benzyl)-4-methyl-*N*-(1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (8f)**: Yield: 
56%; conditions of MW irradiation: 155 °C, 1 h; white solid, m.p. 142-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.16 (m, 1H), 8.07 (s, 1H), 7.90 – 7.84 (m, 1H), 7.75 – 7.65 (m, 1H), 7.68 – 7.58 (m, 1H), 7.57 – 7.50 (m, 2H), 7.34 – 7.29 (m, 2H), 7.29 – 7.22 (m, 4H), 5.06 (s, 2H), 2.42 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.5, 144.9, 144.9 (q, *J* = 34.1 Hz), 144.0, 139.0, 135.7, 133.3, 131.1, 129.6, 128.7, 128.5, 128.1, 127.7, 125.4, 124.5 (q, *J* = 3.1 Hz), 123.3, 122.9, 121.8 (q, *J* = 276.6 Hz), 51.4, 34.5, 31.4, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 ("d", *J* = 2.1 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{28}H_{28}F_3N_2O_2S$: 513.18181, found 513.18170.

***N*-(4-(*tert*-Butyl)benzyl)-*N*-(7-methoxy-1-(trifluoromethyl)isoquinolin-3-yl)-4-methylbenzenesulfonamide (8g)**: Yield: 46%; conditions of MW irradiation: 155 °C, 1 h; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 – 7.31 (m, 2H), 7.27 – 7.24 (m, 2H), 7.23 – 7.19 (m, 4H), 4.96 (s, 2H), 3.94 (s, 3H), 2.41 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 150.3, 143.7, 143.2, 142.8 (q, *J* = 33.7 Hz), 135.5, 134.7, 133.2, 129.7, 129.5, 128.4, 128.1, 127.7, 125.2, 124.7, 123.5, 121.9 (q, *J* = 276.3 Hz), 101.6 (q, *J* = 3.3 Hz), 55.5, 51.4, 34.4, 31.3, 21.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.3 ("d", *J* = 1.7 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{29}H_{30}F_3N_2O_3S$: 543.19237, found 543.19223.

***N*-(3-Methoxybenzyl)-4-methyl-*N*-(1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (8h)**: Yield: 
38%; conditions of MW irradiation: 155 °C, 1 h; white solid, m.p. 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 1H), 8.05 (s, 1H), 7.94 – 7.85 (m, 1H), 7.76 – 7.67 (m, 1H), 7.68 – 7.56 (m, 1H), 7.57 – 7.47 (m, 2H), 7.29 – 7.20 (m, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.88 (m, 2H), 6.74 – 6.65 (m, 1H), 5.02 (s, 2H), 3.70 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 144.9 (q, *J* = 34.0 Hz), 144.8, 144.1, 139.0, 137.9, 135.5, 131.2, 129.7, 129.4, 128.9, 128.2, 127.7, 124.5 (q, *J* = 3.1 Hz), 123.3, 123.0, 121.8 (d, *J* = 276.6 Hz), 121.2, 114.0, 113.7, 55.2, 51.8, 21.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 ("d", *J* = 2.0 Hz, 3F); HRMS (ESI^+) *m/z* calcd for $C_{25}H_{22}F_3N_2O_3S$: 487.12977, found 487.12970.

4-Fluoro-*N*-(4-methylbenzyl)-*N*-(1-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (8i): Yield: 44%;

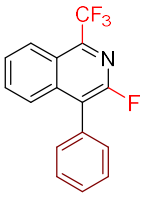


conditions of MW irradiation: 150 °C, 1 h; white solid, m.p. 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 7.97 (s, 1H), 7.90 – 7.85 (m, 1H), 7.77 – 7.68 (m, 1H), 7.69 – 7.63 (m, 2H), 7.25 – 7.18 (m, 2H), 7.16 – 7.09 (m, 2H), 7.03 – 6.97 (m, 2H), 4.97 (s, 2H), 2.22 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (d, *J* = 255.3 Hz), 145.1 (q, *J* = 34.1 Hz), 144.6, 139.0, 137.5, 134.6 (d, *J* = 3.4 Hz), 132.8, 131.3, 130.5 (d, *J* = 9.5 Hz), 129.2, 129.1, 128.9, 128.2, 124.5 (q, *J* = 3.1 Hz), 123.6, 123.5, 121.7 (q, *J* = 276.7 Hz), 116.3 (d, *J* = 22.6 Hz), 52.0, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 (s, 3F), -105.2 – -105.3 (m, 1 F); HRMS (EI) *m/z* calcd for $C_{24}H_{19}F4N_2O_2S$: 475.10979, found 475.10965.

8 Suzuki coupling of **2q** (General procedure)

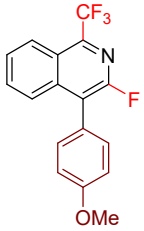
A 10 ml MW tube was charged with isoquinoline **2q** (50 mg; 0.2 mmol), boronic acid (0.3 mmol), $Pd(OAc)_2$ (0.7 mg; 0.004 mmol), PPh_3 (5mg; 0.02 mmol) and Na_2CO_3 (64 mg; 0.6 mmol). Under inert atmosphere degassed THF/water (1:1) solution was added (1 ml) and the reaction mixture was heated under MW irradiation to 120 °C for 40 min. The mixture was then diluted with DCM (15 ml) and extracted with brine (20 ml). The aqueous phase was extracted with DCM (10 ml), the combined organic layers were then washed with brine (2 × 20 ml) and water (20 ml), and dried over $MgSO_4$. The crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane to DCM).

3-Fluoro-4-phenyl-1-(trifluoromethyl)isoquinoline (9a): Yield: 98%; white solid, m.p. 61-62 °C; ^{1}H NMR (400



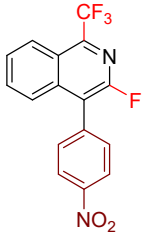
MHz, $CDCl_3$) δ 8.40 – 8.34 (m, 1H), 7.89 – 7.82 (m, 1H), 7.74 – 7.64 (m, 2H), 7.61 – 7.50 (m, 3H), 7.50 – 7.42 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (d, *J* = 236.2 Hz), 144.1 (qd, *J* = 34.8, 13.6 Hz), 140.4 (d, *J* = 4.0 Hz), 131.6, 131.0 (d, *J* = 3.2 Hz), 130.6 (d, *J* = 1.4 Hz), 129.1, 128.9, 127.8 (d, *J* = 2.5 Hz), 125.9 (d, *J* = 7.0 Hz), 124.9 (q, *J* = 3.1 Hz), 123.8 (d, *J* = 2.7 Hz), 121.6 (q, *J* = 276.2 Hz), 120.8 (d, *J* = 28.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (”d”, *J* = 2.1 Hz, 3F), -79.8 (s, 1F).; HRMS (ESI^{+}) *m/z* calcd for $C_{16}H_{10}F_4N$: 292.07439, found 292.07429.

3-Fluoro-4-(4-methoxyphenyl)-1-(trifluoromethyl)isoquinoline (9b): Yield: 87%: white solid, m.p. 111-112



°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.30 (m, 1H), 7.94 – 7.86 (m, 1H), 7.75 – 7.61 (m, 2H), 7.44 – 7.31 (m, 2H), 7.14 – 7.04 (m, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.2, 155.5 (d, *J* = 235.5 Hz), 143.6 (qd, *J* = 34.7, 13.5 Hz), 140.5 (d, *J* = 4.0 Hz), 131.9 (d, *J* = 1.4 Hz), 131.5, 127.7 (d, *J* = 2.5 Hz), 126.0 (d, *J* = 6.9 Hz), 124.9 (q, *J* = 3.1 Hz), 123.8 (d, *J* = 2.7 Hz), 122.9 (d, *J* = 3.3 Hz), 121.6 (q, *J* = 275.8 Hz), 120.7 (d, *J* = 28.5 Hz), 114.4, 55.5; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (”d”, *J* = 1.4 Hz, 3F), -80.1 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{17}H_{11}F_4NO$: 321.0771, found 321.0766.

3-Fluoro-4-(4-nitrophenyl)-1-(trifluoromethyl)isoquinoline (9c): Yield: 91%; white solid, m.p. 131-132 °C; ^{1}H

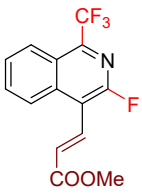


NMR (400 MHz, $CDCl_3$) δ 8.46 – 8.39 (m, 3H), 7.84 – 7.72 (m, 3H), 7.71 – 7.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (d, *J* = 237.2 Hz), 148.3, 145.5 (qd, *J* = 34.9, 13.7 Hz), 139.7 (d, *J* = 3.4 Hz), 137.9 (d, *J* = 3.4 Hz), 132.5, 131.8, 128.3 (d, *J* = 2.5 Hz), 125.4 (q, *J* = 3.2 Hz), 125.1 (d, *J* = 6.9 Hz), 124.1, 123.7 (d, *J* = 2.8 Hz), 121.4 (q, *J* = 276.3 Hz), 118.4 (d, *J* = 28.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 (”d”, *J* = 1.6 Hz, 3F), -79.1 (s, 1F); HRMS (EI) *m/z* calcd for $C_{16}H_8F_2N_2O_2$: 335.0516, found 335.0515.

9 Heck coupling of **2q** with Jeffery´s conditions[2] (General procedure)

A 10 ml MW tube was charged with isoquinoline **2q** (20 mg; 0.07 mmol), methyl acrylate (18 mg; 0.2 mmol), $Pd(OAc)_2$ (0.7 mg; 0.003 mmol), $NBu_4^+Cl^-$ (11 mg; 0.07 mmol) and K_2CO_3 (28 mg; 0.14 mmol). Under inert atmosphere degassed DMF was added (0.5 ml) and the mixture was heated under MW irradiation to 120 °C for 2 h. The mixture was then diluted with DCM (15 ml) and extracted with brine (20 ml). Water phase was extracted with DCM (10 ml), the combined organic layers were then washed with brine (2 × 20 ml) and water (20 ml), and dried over $MgSO_4$. The crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane to DCM).

(*E*)-3-(3-Fluoro-1-(trifluoromethyl)isoquinolin-4-yl)acrylate (10a): Yield: 59%; white solid, m.p. 116-119 °C;

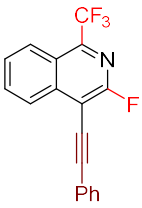


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.31 (m, 1H), 8.31 – 8.25 (m, 1H), 8.18 (d, *J* = 16.2 Hz, 1H), 7.94 – 7.80 (m, 1H), 7.77 – 7.64 (m, 1H), 6.84 (dd, *J* = 16.2, 1.2 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 156.5 (d, *J* = 243.2 Hz), 145.1 (qd, *J* = 34.9, 14.4 Hz), 139.3 (d, *J* = 3.7 Hz), 132.5 (m, 2C), 128.2 (d, *J* = 2.4 Hz), 128.0 (d, *J* = 11.7 Hz), 125.6 (q, *J* = 3.0 Hz), 123.8 (d, *J* = 6.8 Hz), 123.6 (d, *J* = 2.9 Hz), 121.3 (q, *J* = 276.2 Hz), 113.5 (d, *J* = 24.4 Hz), 52.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (”d”, *J* = 1.3 Hz, 3F), -73.5 (s, 1F); HRMS (ESI^+) *m/z* calcd for $C_{14}H_{10}F_4NO_2$: 300.06422, found 300.06406.

10 Sonogashira coupling of **2q** (General procedure)

A 10 ml MW tube was charged with isoquinoline **2q** (50 mg; 0.17 mmol), phenylacetylene (36 mg; 0.34 mmol), $Pd(OAc)_2$ (0.7 mg; 0.003 mmol), PPh_3 (4 mg; 0.014 mmol), CuI (2 mg; 0.009 mmol) and K_2CO_3 (47 mg; 0.34 mmol). Under inert atmosphere degassed THF was added (1 ml) and the mixture was heated under MW irradiation to 120 °C for 1 h. The mixture was then filtered, crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane to DCM).

3-Fluoro-4-(phenylethynyl)-1-(trifluoromethyl)isoquinoline (10b): Yield: 75%; off-white solid, m.p. 96-98 °C;

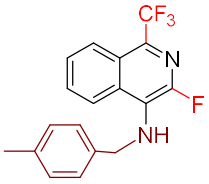


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.43 (m, 1H), 8.37 – 8.31 (m, 1H), 7.94 – 7.85 (m, 1H), 7.77 – 7.66 (m, 3H), 7.50 – 7.39 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5 (d, *J* = 241.7 Hz), 143.2 (qd, *J* = 35.1, 13.0 Hz), 140.9 (d, *J* = 2.7 Hz), 132.3, 132.1, 129.8, 128.7, 128.5 (d, *J* = 2.4 Hz), 126.0 (d, *J* = 6.8 Hz), 125.3 (q, *J* = 3.1 Hz), 123.0 (d, *J* = 2.9 Hz), 122.1, 121.4 (q, *J* = 276.2 Hz), 104.6 (d, *J* = 29.1 Hz), 103.1 (d, *J* = 3.3 Hz), 79.1 (d, *J* = 5.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (”d”, *J* = 1.7 Hz, 3F), -72.4 (s, 1F).; HRMS (EI) *m/z* calcd for $C_{18}H_9F_4N$: 315.0669, found 315.0666.

11 Buchwald-Hartwig coupling of **2r** (General procedure)

A 10 ml MW tube was charged with isoquinoline **2r** (50 mg; 0.17 mmol), 4-methylbenzylamine (41 mg; 0.34 mmol), $Pd(OAc)_2$ (2 mg; 0.009 mmol), XantPhos (5 mg; 0.0009 mmol) and *t*BuONa (33 mg; 0.34 mmol). Under inert atmosphere degassed toluene was added (1 ml) and the mixture was heated under MW irradiation to 110 °C for 30 min. The mixture was then filtered, crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane to DCM).

3-Fluoro-*N*-(4-methylbenzyl)-1-(trifluoromethyl)isoquinolin-4-amine (10c): Yield: 90%; yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 – 8.19 (m, 1H), 7.97 – 7.90 (m, 1H), 7.71 – 7.53 (m, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 4.75 – 4.67 (m, 2H), 4.55 – 4.34 (m, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4 (d, *J* = 227.3 Hz), 137.8, 136.0 (d, *J* = 1.7 Hz), 131.5 (qd, *J* = 34.8, 12.4 Hz), 131.0 (d, *J* = 6.1 Hz), 129.7, 129.5, 127.9, 127.6 (d, *J* = 1.9 Hz), 127.6 (d, *J* = 23.1 Hz), 125.3 (q, *J* = 3.0 Hz), 124.7 (d, *J* = 2.0 Hz), 122.1 (q, *J* = 275.5 Hz), 121.3 (d, *J* = 6.2 Hz), 51.3 (d, *J* = 7.7 Hz), 21.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.0 (s, 3F), -91.5 (s, 1F).; HRMS (ESI^+) *m/z* calcd for $C_{18}H_{15}F_4N_2$: 335.11659, found 335.11679.

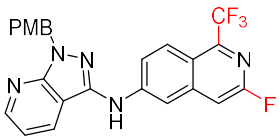


12 Synthesis of Valiglurax analogue **12**

Preparation of 11

A 10 ml MW tube was charged with isoquinoline **2j** (20 mg; 0.07 mmol), 1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-amine (20 mg; 0.08 mmol), $Pd(OAc)_2$ (1 mg; 0.003 mmol), XantPhos (2 mg; 0.0003 mmol) and *t*BuONa (10 mg; 0.1 mmol). Under inert atmosphere degassed toluene was added (0.5 ml) and the mixture was heated under MW irradiation to 110 °C for 30 min. The mixture was then filtered, the crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane/EtOAc/Et_3N, 99.5:0:0.5 to 0:95:5).

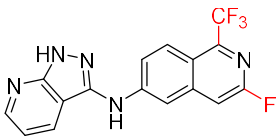
3-Fluoro-*N*-(1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-1-(trifluoromethyl)isoquinolin-6-amine (11): Yield: 94%; yellow solid, m.p. 193-194 °C ^{1}H NMR (401 MHz, acetone-d_6) δ 9.28 (s, 1H), 8.62 (dm, *J* = 2.1 Hz, 1H), 8.58 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.31 (ddm, *J* = 8.1, 1.5 Hz, 1H), 8.15 (dq, *J* = 9.4, 2.2 Hz, 1H), 7.73 (dd, *J* = 9.4, 2.2 Hz, 1H), 7.51 (s, 1H), 7.48 – 7.37 (m, 2H), 7.15 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.93 – 6.83 (m, 2H), 5.62 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 160.3 (d, *J* = 233.7 Hz), 160.2, 150.8, 150.7, 145.5 (d, *J* = 11.9 Hz), 145.2 (d, *J* = 8.4 Hz), 144.2 (qd, *J* = 34.1, 15.1 Hz), 142.5 (d, *J* = 6.9 Hz), 130.7, 130.4, 129.9, 125.8 (q, *J* = 3.1 Hz), 123.11 – 122.52 (m, 2C), 122.7 (q, *J* = 275.5 Hz), 119.1 (d, *J* = 2.3 Hz), 116.5, 114.7, 108.7 – 108.4 (m, 2C), 106.4 (d, *J* = 35.6 Hz), 55.5, 50.4; ^{19}F NMR (377 MHz, acetone-d_6) δ -62.3 ("d", *J* = 2.1 Hz, 3F), -79.0 – -79.7 (m, 1F).; HRMS (ESI^+) *m/z* calcd for $C_{24}H_{18}F_4N_5O$: 468.14420, found 468.14372.



Preparation of 12

A 10 ml MW tube was charged with isoquinoline **10** (29 mg; 0.06 mmol), then solution of TFA (0.3 ml) and toluene (0.3 ml) were added and the reaction mixture was heated under MW irradiation to 120 °C for 30 min. The mixture was then concentrated and saturated solution of $NaHCO_3$ (2ml) was added. EtOAc was then added (20 ml) and the aqueous phase was extracted with EtOAc (2 × 20 ml) and dried over $MgSO_4$. The crude product was then concentrated and purified with gradient column chromatography (silica gel, cyclohexane/EtOAc/Et_3N, 90:9.5:0.5 to 0:95:5).

3-Fluoro-*N*-(1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)-1-(trifluoromethyl)isoquinolin-6-amine (12): Yield: 88%; yellow solid, m.p. 282-283 °C; ^{1}H NMR (401 MHz, methanol-d_4) δ 8.51 (d, *J* = 2.3 Hz, 1H), 8.50 (s, 1H), 8.39 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.16 (dd, *J* = 9.5, 2.2 Hz, 1H), 7.70 (dd, *J* = 9.4, 2.3 Hz, 1H), 7.46 (s, 1H), 7.19 (dd, *J* = 8.1, 4.6 Hz, 1H); ^{1}H NMR (401 MHz, acetone-d_6) δ 12.19 (s, 1H), 9.27 (s, 1H), 8.63 (d, *J* = 2.3 Hz, 1H), 8.55 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.35 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.18 (dq, *J* = 9.4, 2.2 Hz, 1H), 7.77 (dd, *J* = 9.4, 2.3 Hz, 1H), 7.58 (s, 1H), 7.17 (dd, *J* = 8.1, 4.5 Hz, 1H); ^{13}C NMR (126 MHz, acetone-d_6) δ 160.3 (d, *J* = 233.7 Hz), 153.0, 150.8, 145.8, 145.3 (d, *J* = 8.5 Hz), 144.2 (qd, *J* = 34.0, 15.3 Hz), 143.8, 129.6, 125.9 (q, *J* = 3.0 Hz), 123.0 – 122.7 (m), 122.8 (q, *J* = 275.7 Hz), 119.1 (d, *J* = 2.3 Hz), 116.6, 108.5 (d, *J* = 6.0 Hz), 107.9, 106.5 (d, *J* = 35.7 Hz); ^{19}F NMR (377 MHz, acetone-d_6) δ -62.3 ("d", *J* = 2.2 Hz, 3F), -79.3 (s, 1F).; HRMS (ESI^+) *m/z* calcd for $C_{16}H_{10}F_4N_5$: 348.08668, found 348.08663.

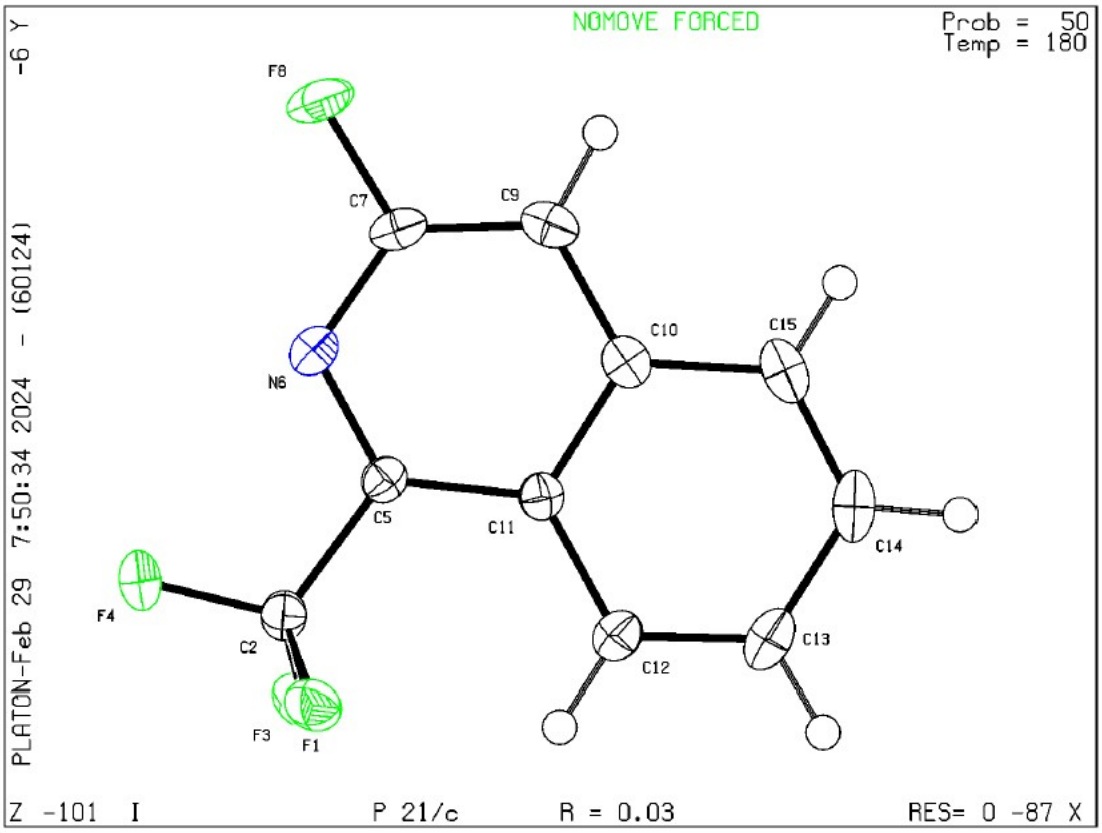


13 Crystallographic data

Single-crystal diffraction data of all structures were collected using MicroMax-007 HF Microfocus Cu rotating anode (λ = 1.54178 Å) X-ray generator equipped with a Hybrid Pixel Array Detector (Rigaku) (**2a**) or using Bruker D8 VENTURE system equipped with a Photon 100 CMOS detector, a multilayer monochromator, and a Cu-Kα Incoatec microfocus sealed tube (λ = 1.54178 Å) (**2h** and **(*Z*,*E*)-4m**) at 180 K. The frames were integrated with CrysAlisPro[3] (**2a**) or Bruker SAINT[4] software package (**2h** and **(*Z*,*E*)-4m**). The structures were solved by charge-flipping methods using Superflip[5] (**2a**) or by direct methods with SIR92[6] (**2h** and **(*Z*,*E*)-4m**) and were refined by full-matrix least-squares on F with CRYSTALS.[7] The positional and anisotropic thermal parameters of all non-hydrogen atoms were refined. All hydrogen atoms were located in a difference Fourier map and then they were repositioned geometrically. They were initially refined with soft restraints on the bond lengths and angles to regularise their geometry, then their positions were refined with riding constraints.

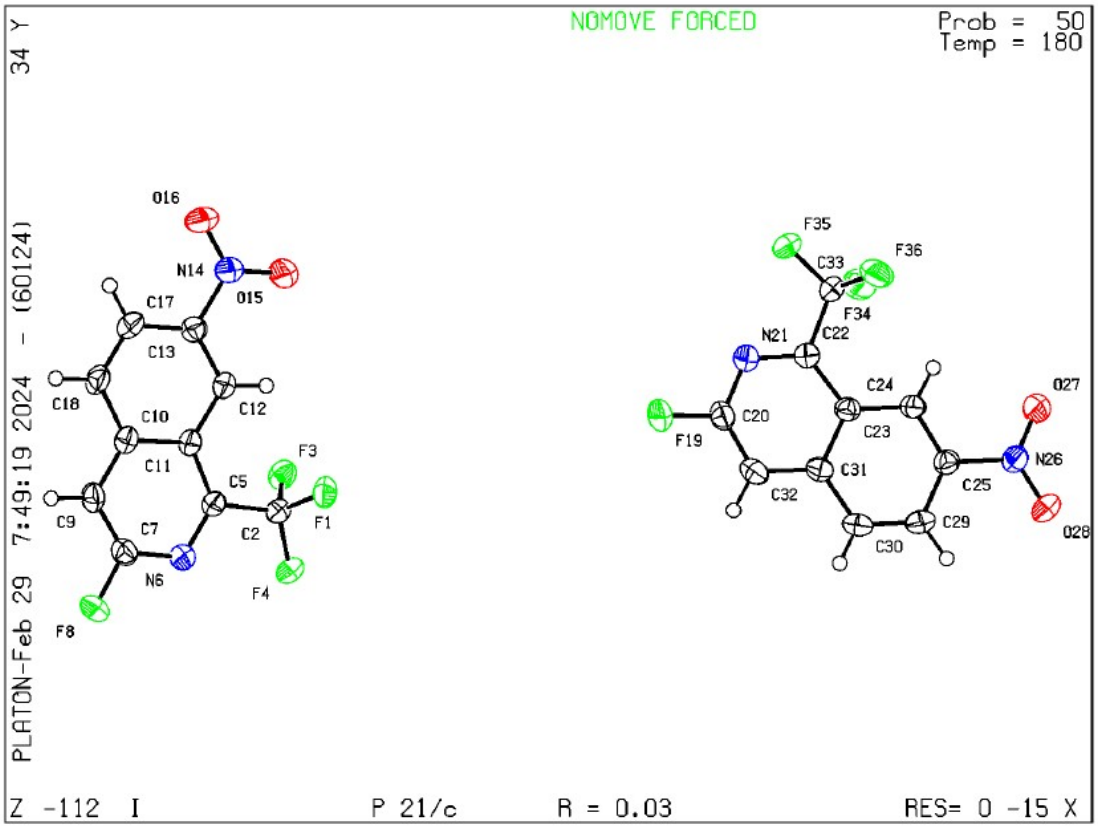
Crystal data for 2a (light yellow, 0.036 x 0.078 x 0.212 mm):

$C_{10}H_5F_4N_1$, monoclinic, space group $P2_1/c$, a = 8.18502(15) Å, b = 13.51475(17) Å, c = 8.59865(14) Å, β = 117.183(2)°, V = 846.117(14) Å^3, Z = 4, M = 215.15, 8064 reflections measured, 1847 independent reflections. Final R = 0.030, wR = 0.039, GoF = 1.008 for 1814 reflections with $I > 2\sigma(I)$ and 137 parameters. CCDC 2336080.



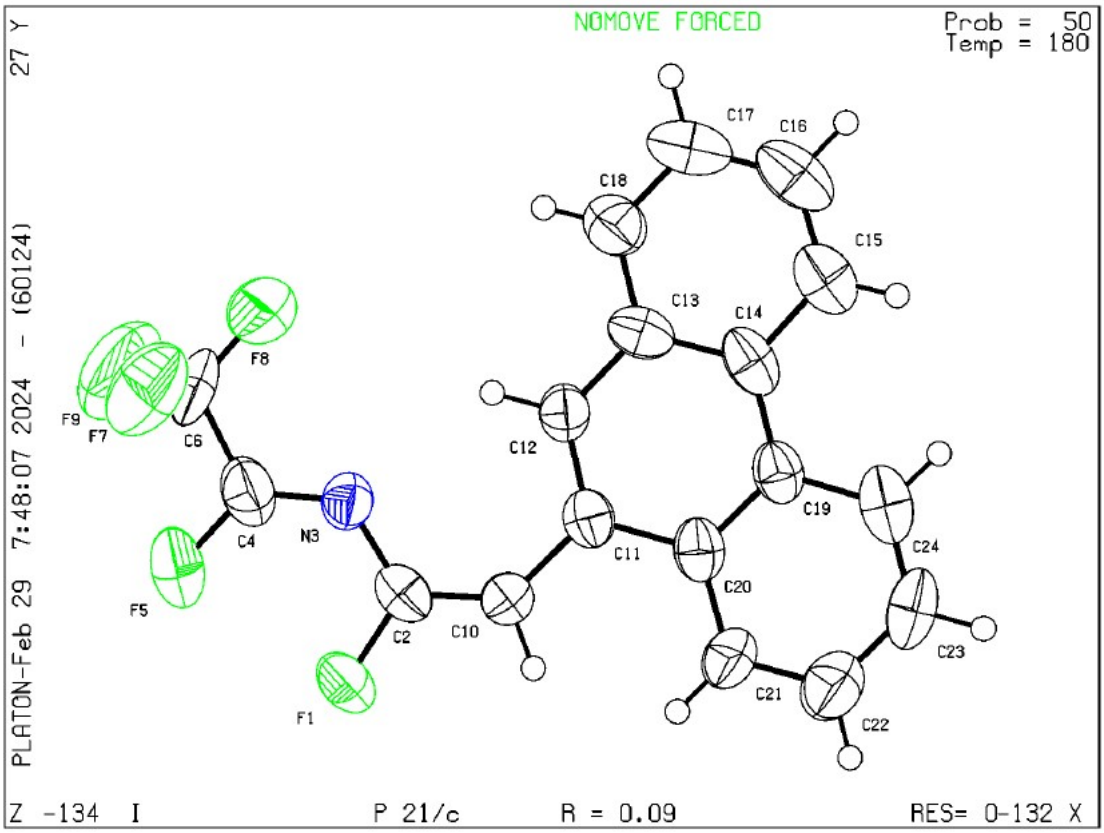
Crystal data for 2h (light yellow, 0. 0.070 x 0.084 x 0.336 mm):

$C_{10}H_4F_4N_2O_2$, monoclinic, space group $P2_1/c$, $a = 13.5573(4)$ Å, $b = 16.3320(5)$ Å, $c = 8.8755(3)$ Å, $\beta = 99.9980(14)°$, $V = 1935.35(11)$ Å^3, $Z = 8$, $M = 520.29$, 38767 reflections measured, 3554 independent reflections. Final $R = 0.033$, $wR = 0.044$, $GoF = 1.027$ for 2993 reflections with $I > 2\sigma(I)$ and 326 parameters. CCDC 2336081.



Crystal data for (*Z*,*E*)-4m (light yellow, 0.052 x 0.065 x 0.410 mm):

$C_{18}H_{10}F_5N_1$, monoclinic, space group $P2_1/c$, a = 20993 Å, b = 5.2160(3) Å, c = 24.2707(16) Å, β = 90.344(4)°, V = 1470.42(16) Å^3, Z = 4, M = 335.27, 20993 reflections measured, 2706 independent reflections. Final R = 0.094, wR = 0.081, GoF = 0.937 for 2993 reflections with $I > 2\sigma(I)$ and 217 parameters. CCDC 2336082.



14 References

(1) Blastik, Z. E.; Voltrová, S.; Matoušek, V.; Jurásek, B.; Manley, D. W.; Klepetářová, B.; Beier, P. *Angew. Chem., Int. Ed.* **2017**, *56*, 346.

(2) Jeffery, T. *Tetrahedron.* **1996**, *52*, 10113.

(3) CrysAlisPro, Oxford Diffraction, 2021.

(4) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA, 2015.

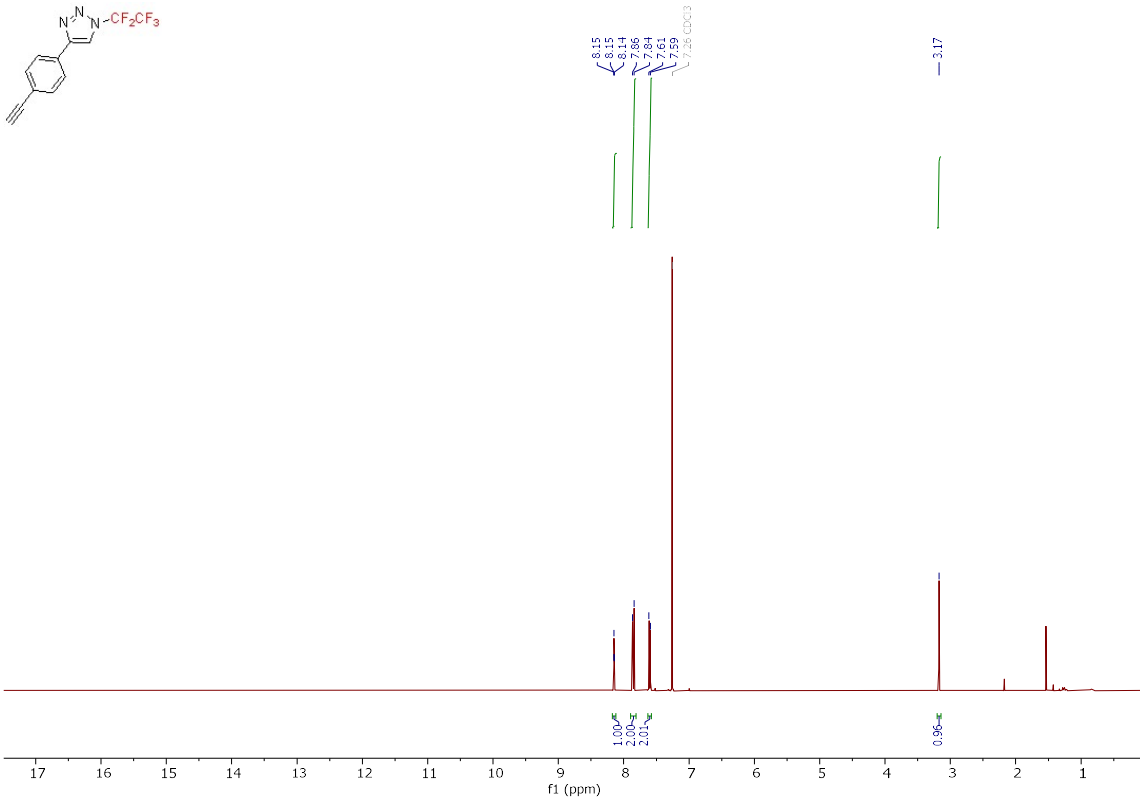
(5) Palatinus L., Chapuis G. J. Appl. Cryst. 2007, 40, 786-790.

(6) Altomare, A.; Cascarano, G.; Giacovazzo G.; Guagliardi A.; Burla M. C.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994,** *27*, 435.

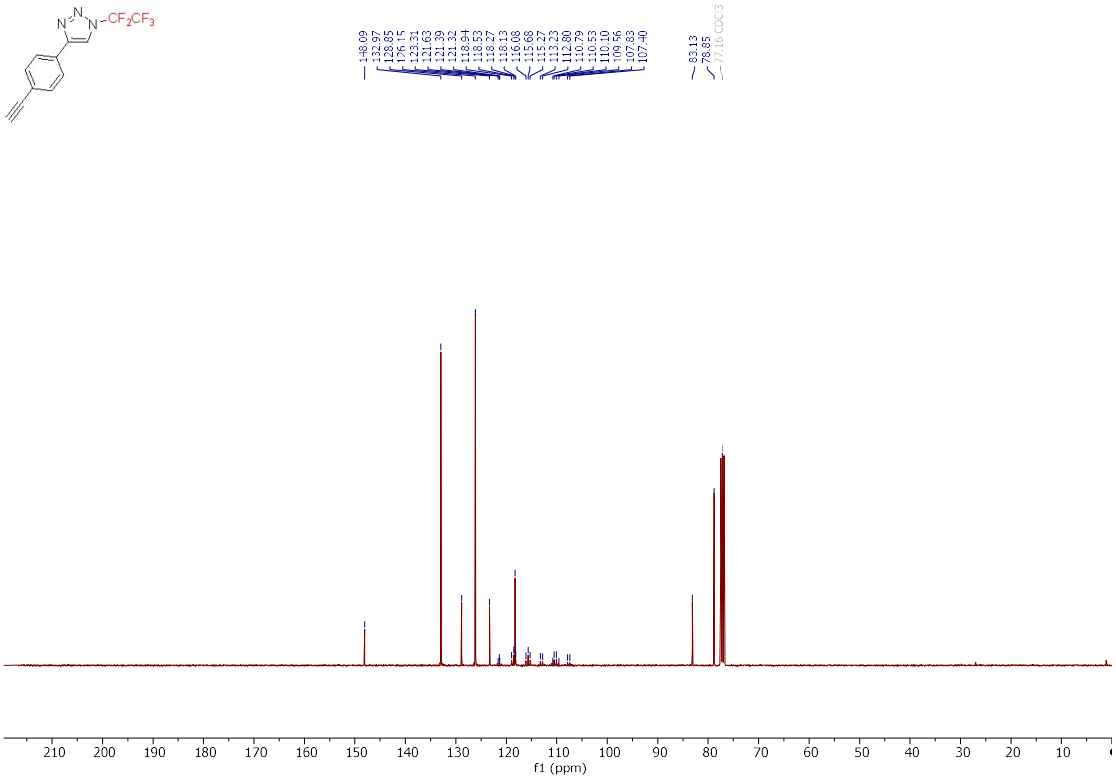
(7) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K., Watkin, D. J. *J. Appl. Cryst.* **2003**, *36*, 1487.

15 Copies of NMR spectra

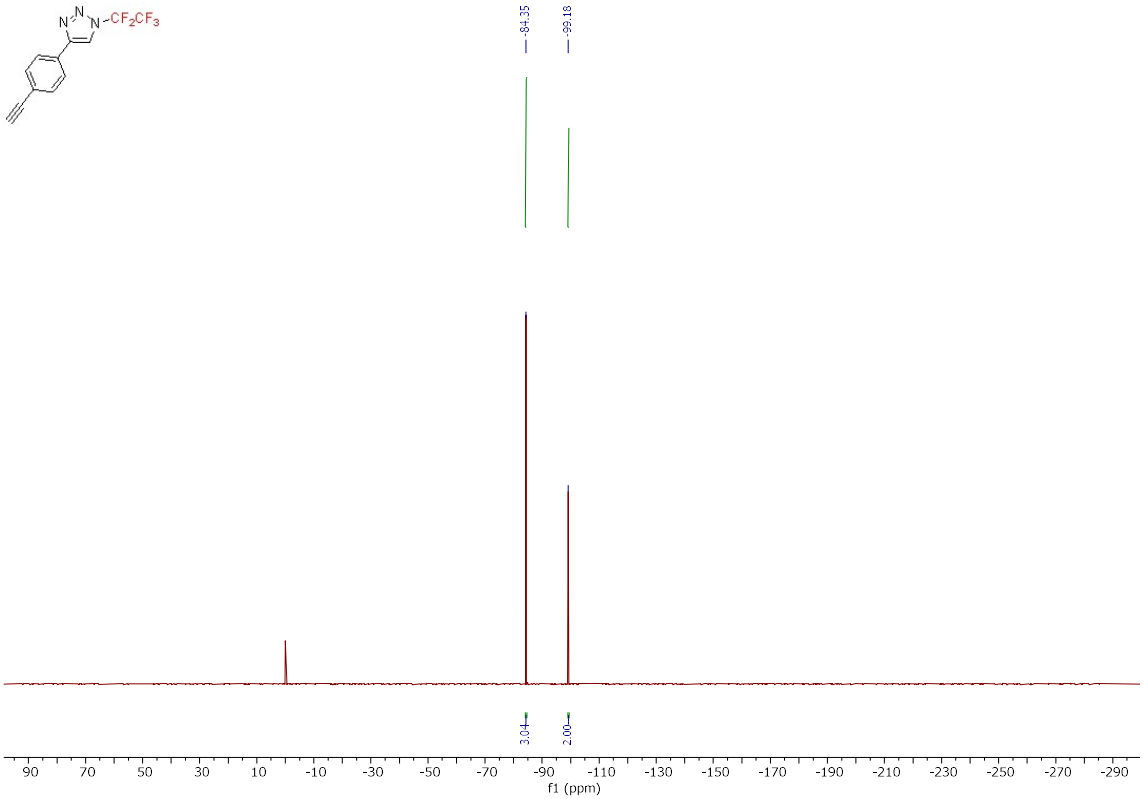
^{1}H NMR spectrum of **1f** ($CDCl_3$, 400 MHz)



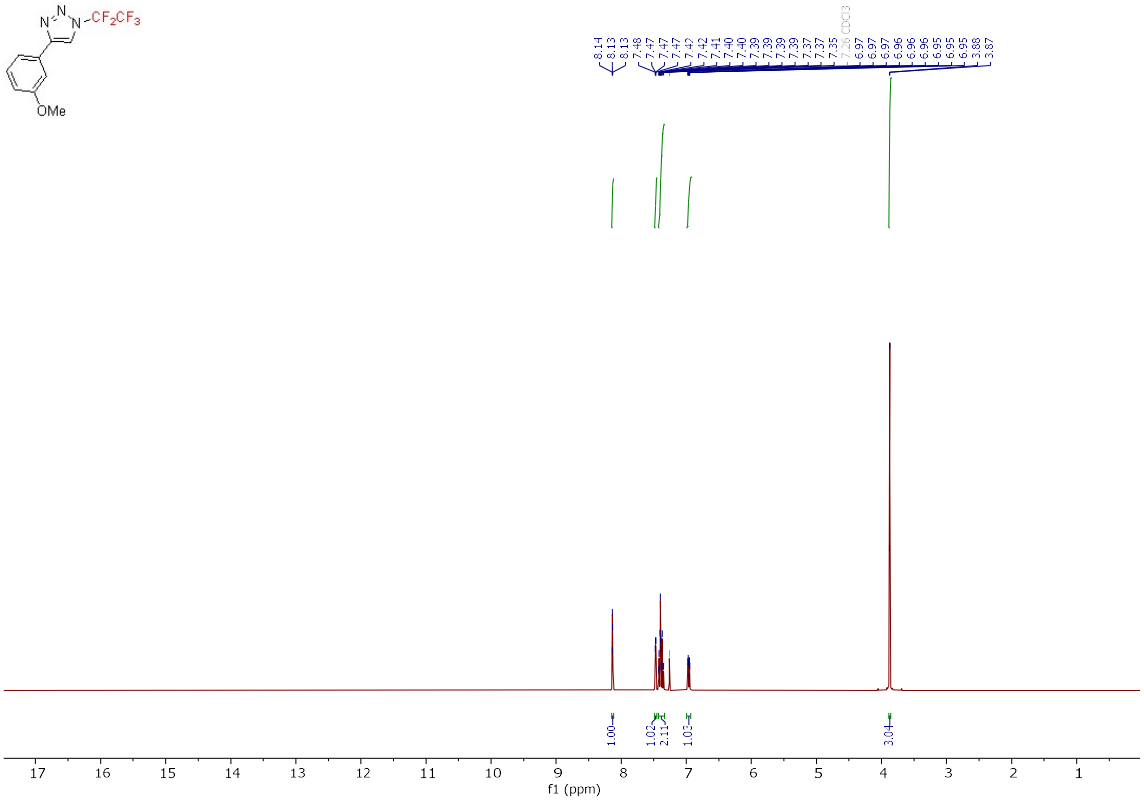
^{13}C NMR spectrum of **1f** ($CDCl_3$, 101 MHz)



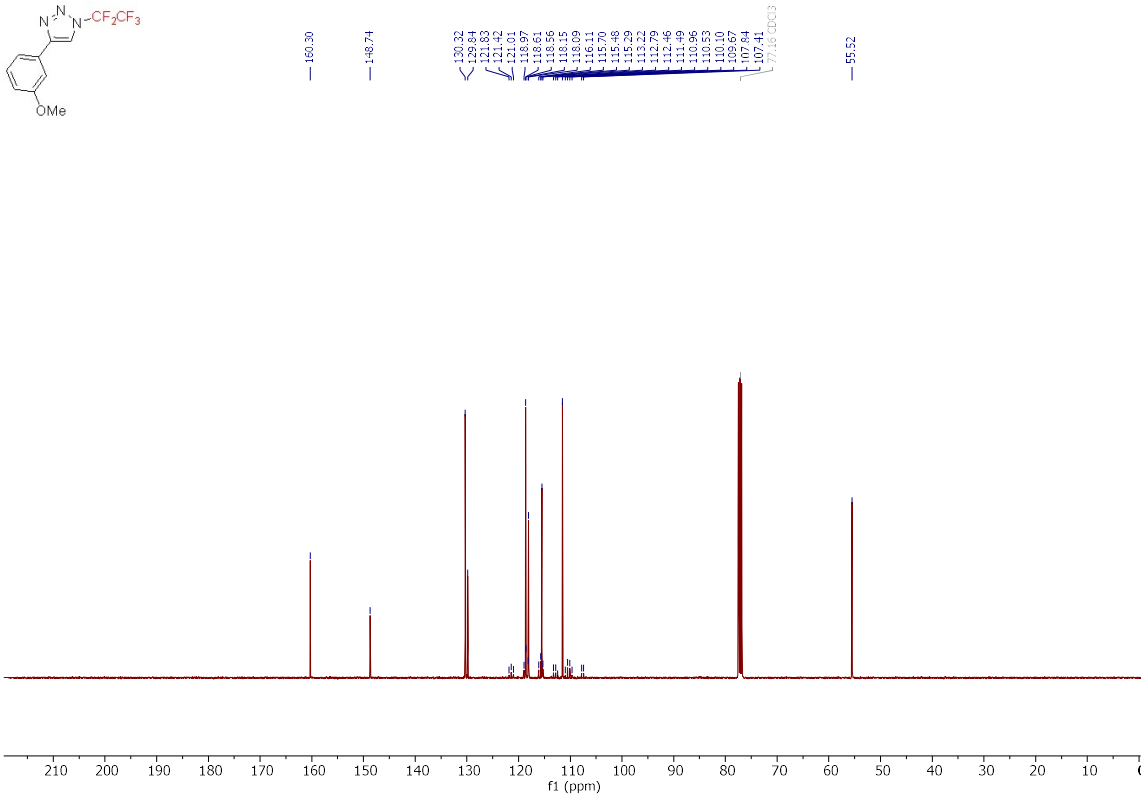
^{19}F NMR spectrum of **1f** ($CDCl_3$, 376 MHz)



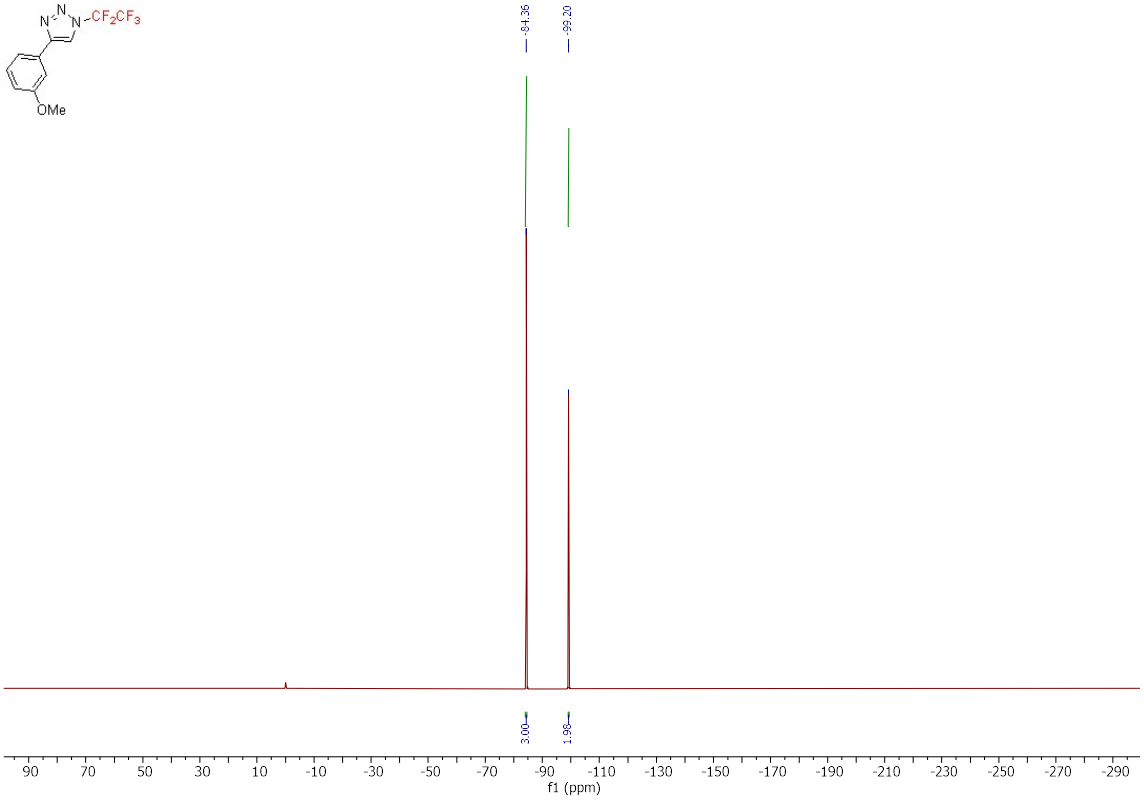
^{1}H NMR spectrum of **1i** ($CDCl_3$, 400 MHz)



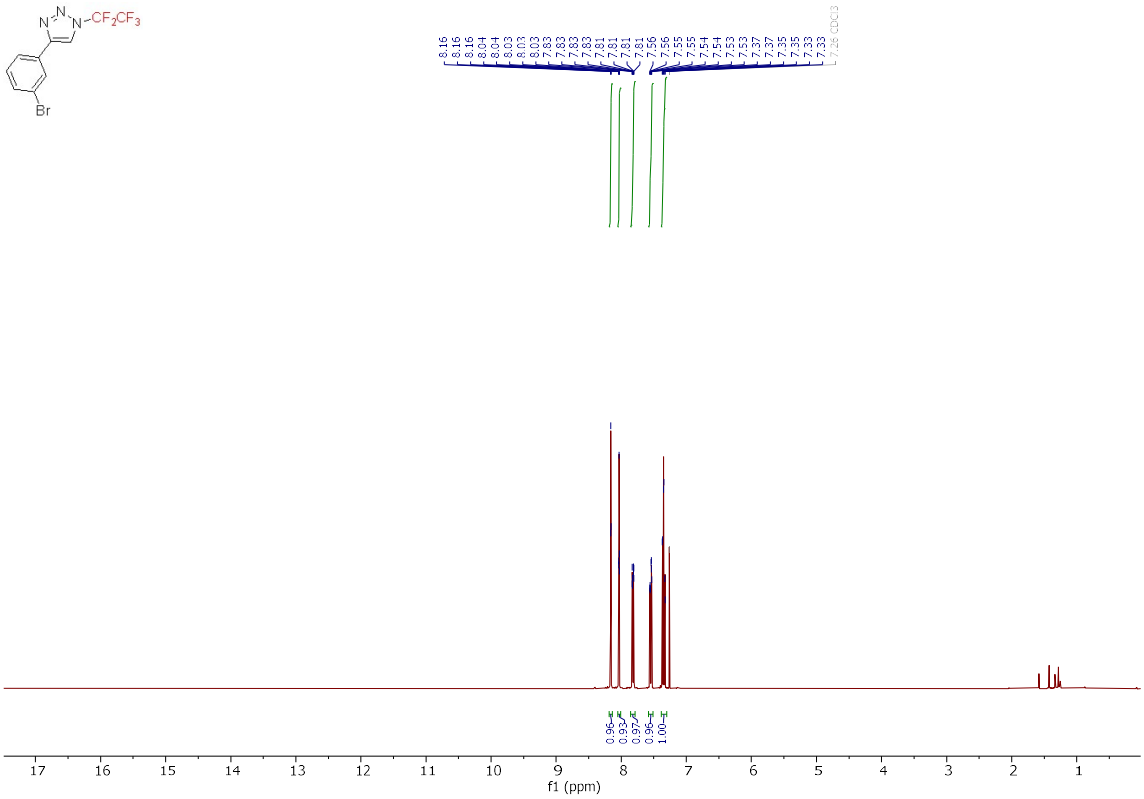
^{13}C NMR spectrum of **1i** ($CDCl_3$, 101 MHz)



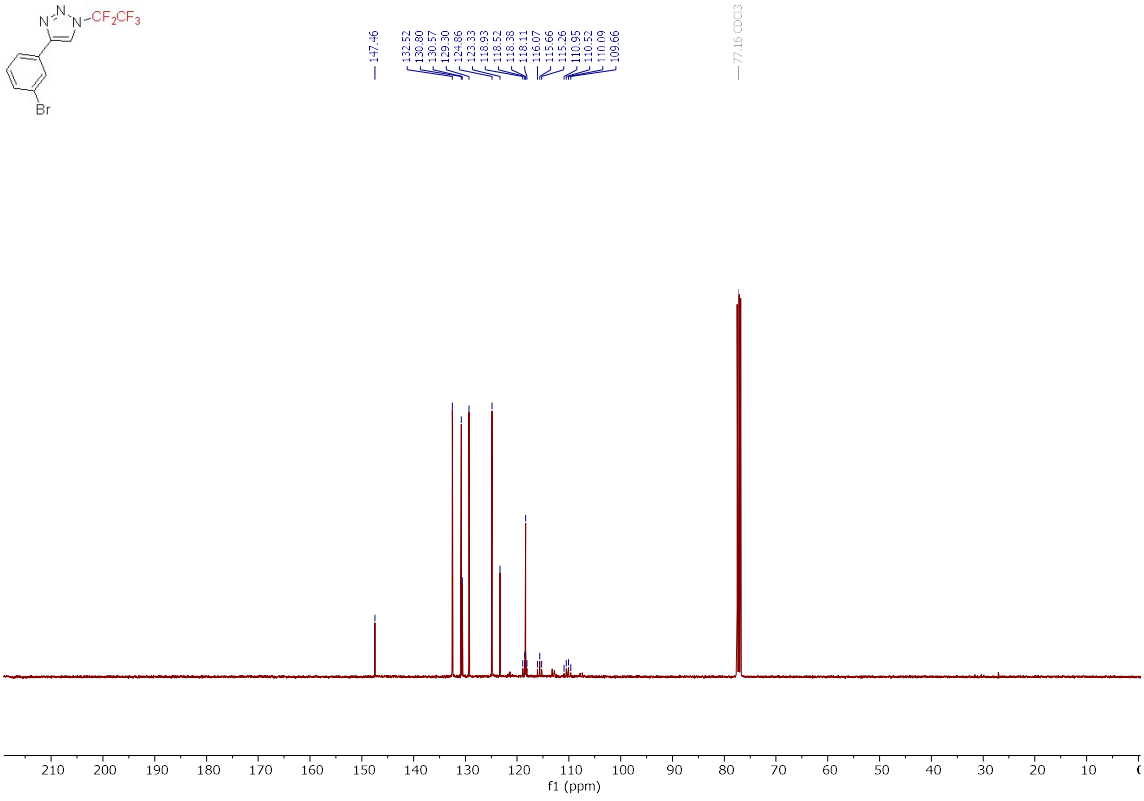
^{19}F NMR spectrum of **1i** ($CDCl_3$, 376 MHz)



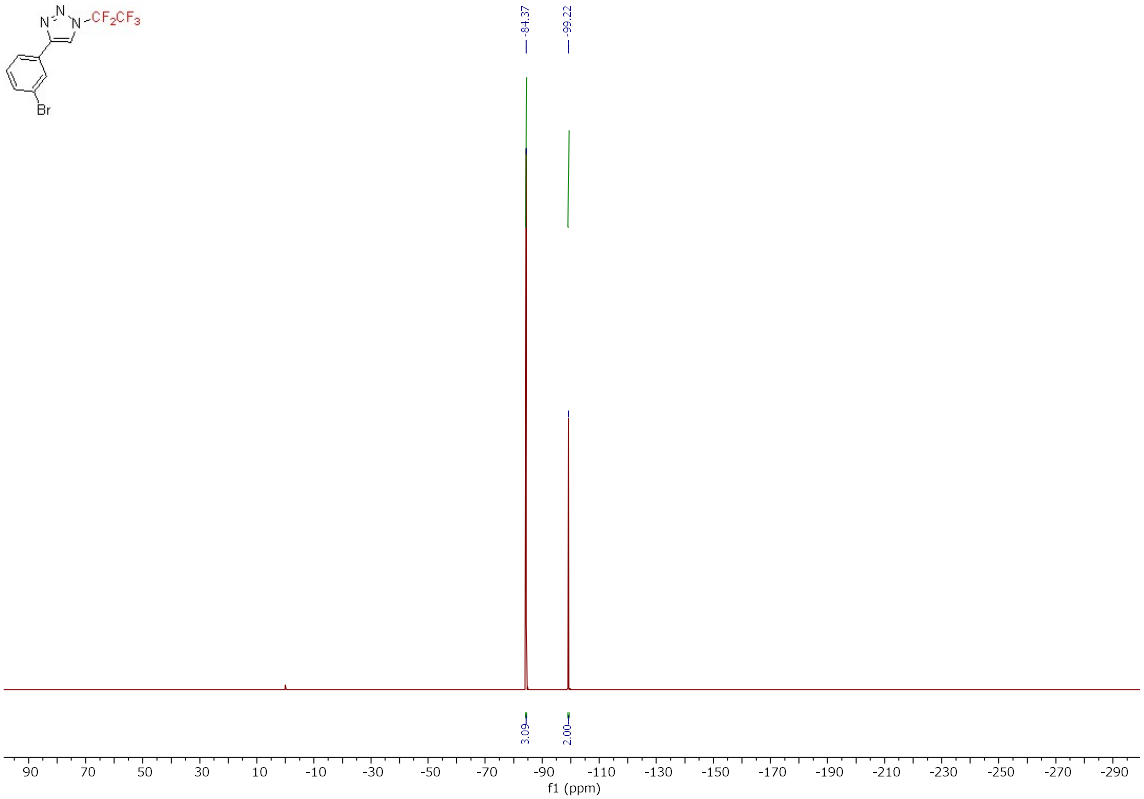
^{1}H NMR spectrum of **1j** ($CDCl_3$, 400 MHz)



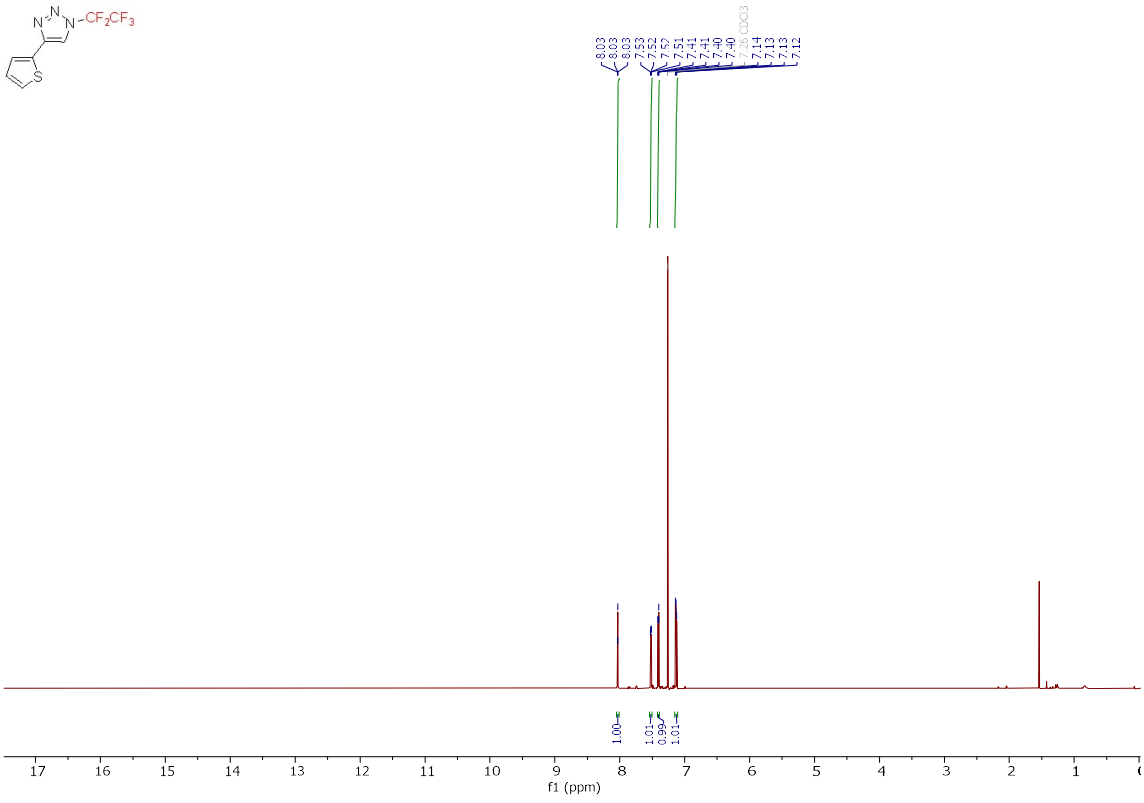
^{13}C NMR spectrum of **1j** ($CDCl_3$, 101 MHz)



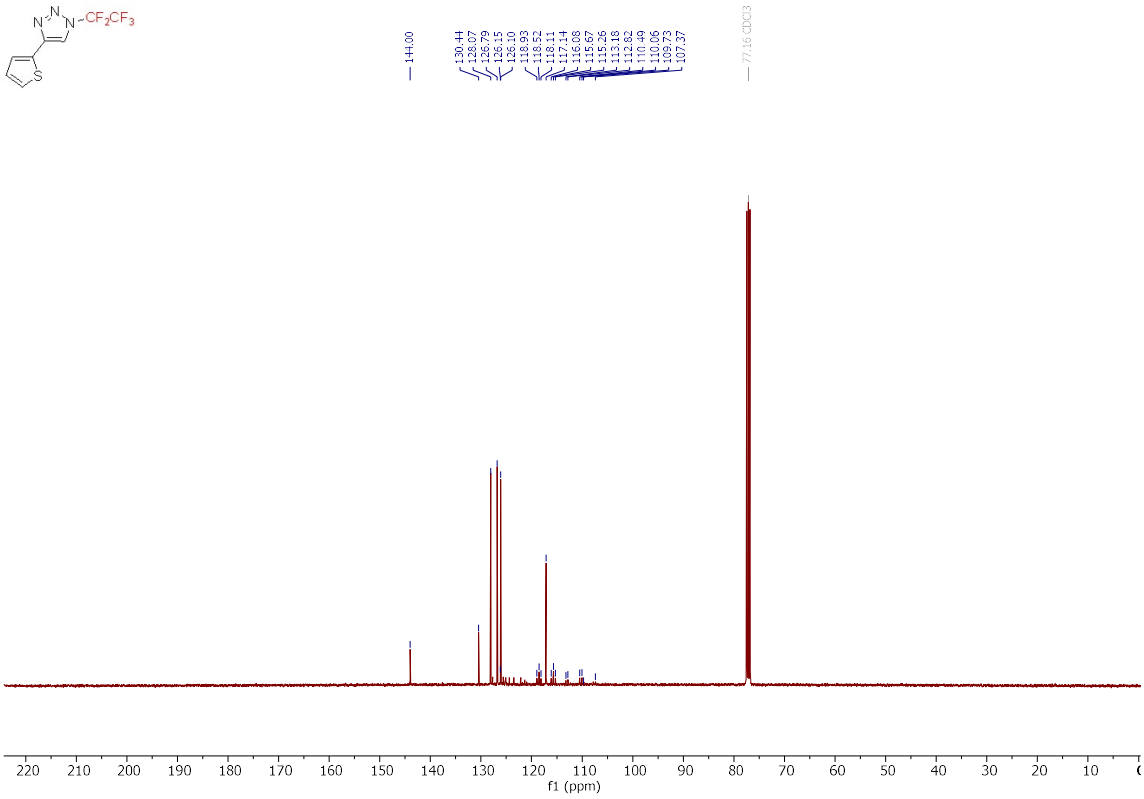
^{19}F NMR spectrum of **1j** ($CDCl_3$, 376 MHz)



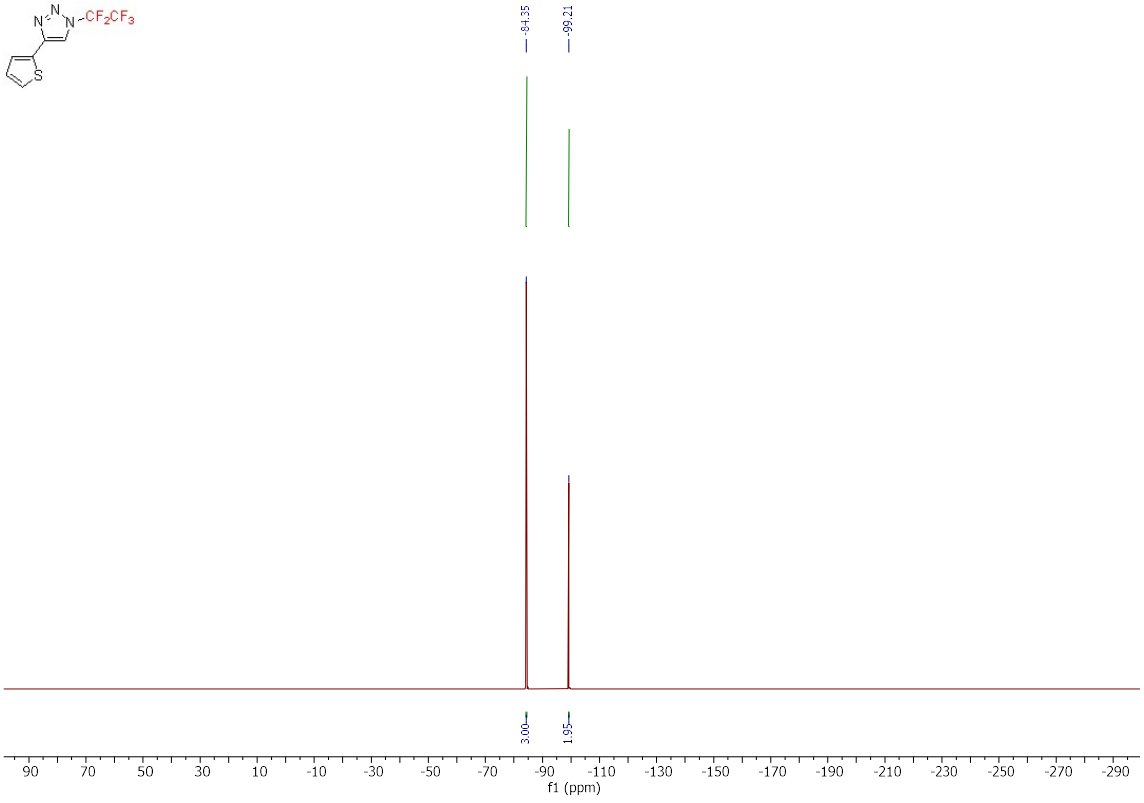
^{1}H NMR spectrum of **1m** ($CDCl_3$, 400 MHz)



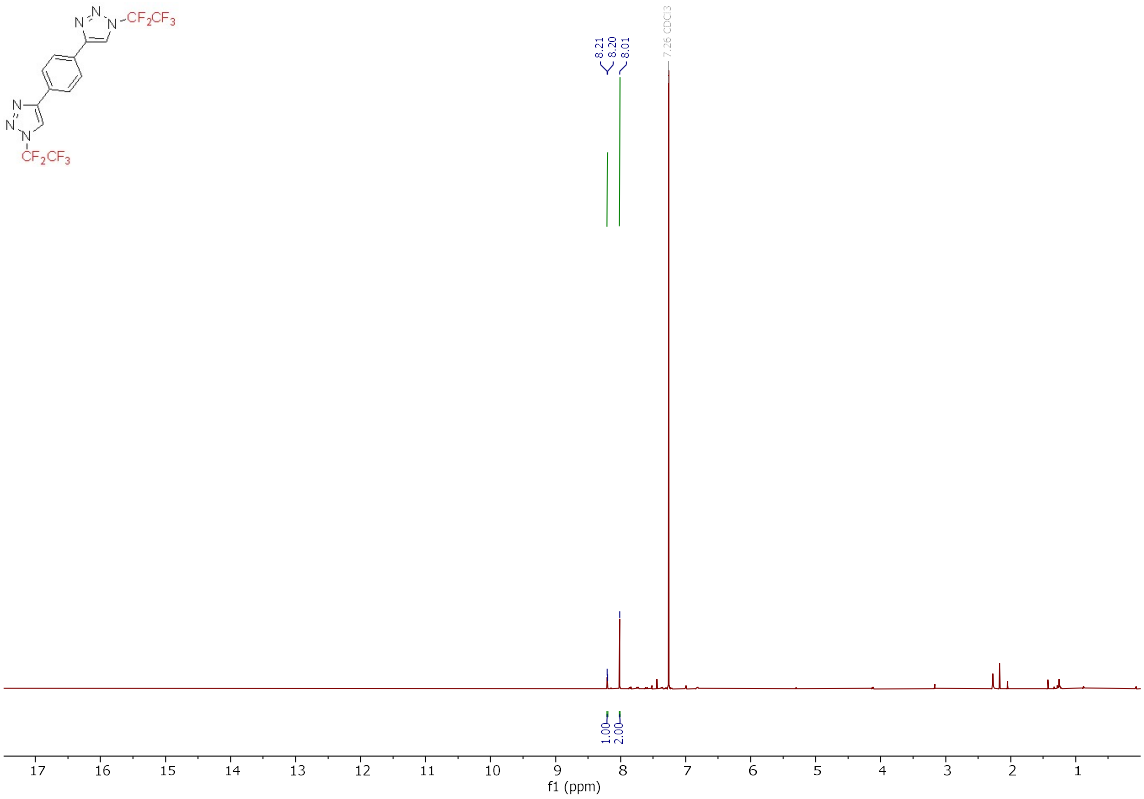
^{13}C NMR spectrum of **1m** ($CDCl_3$, 101 MHz)



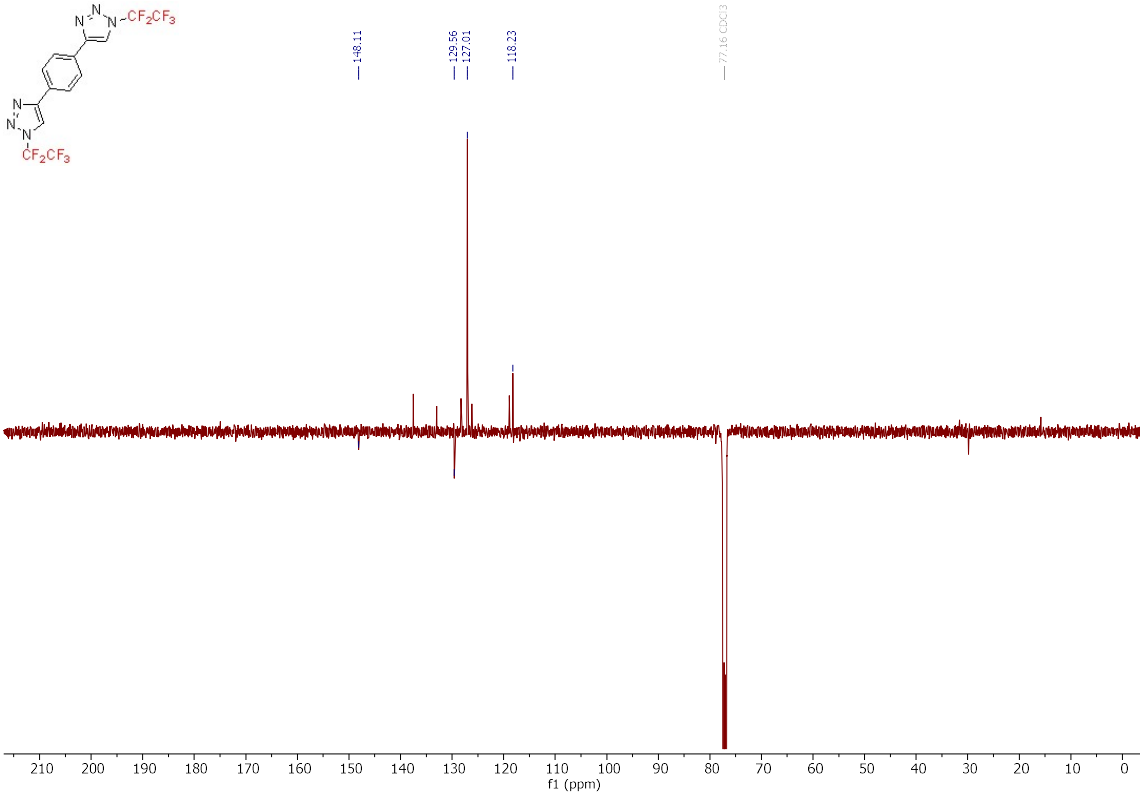
^{19}F NMR spectrum of **1m** ($CDCl_3$, 376 MHz)



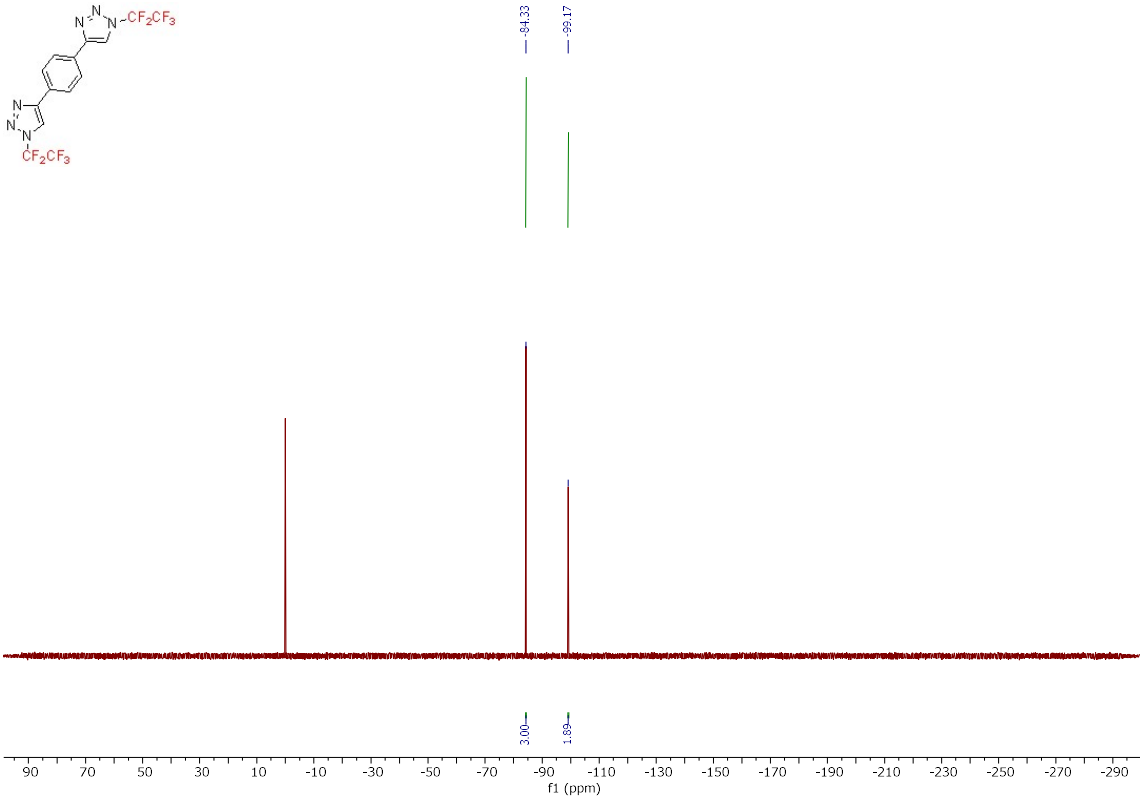
^{1}H NMR spectrum of **1o** ($CDCl_3$, 400 MHz)



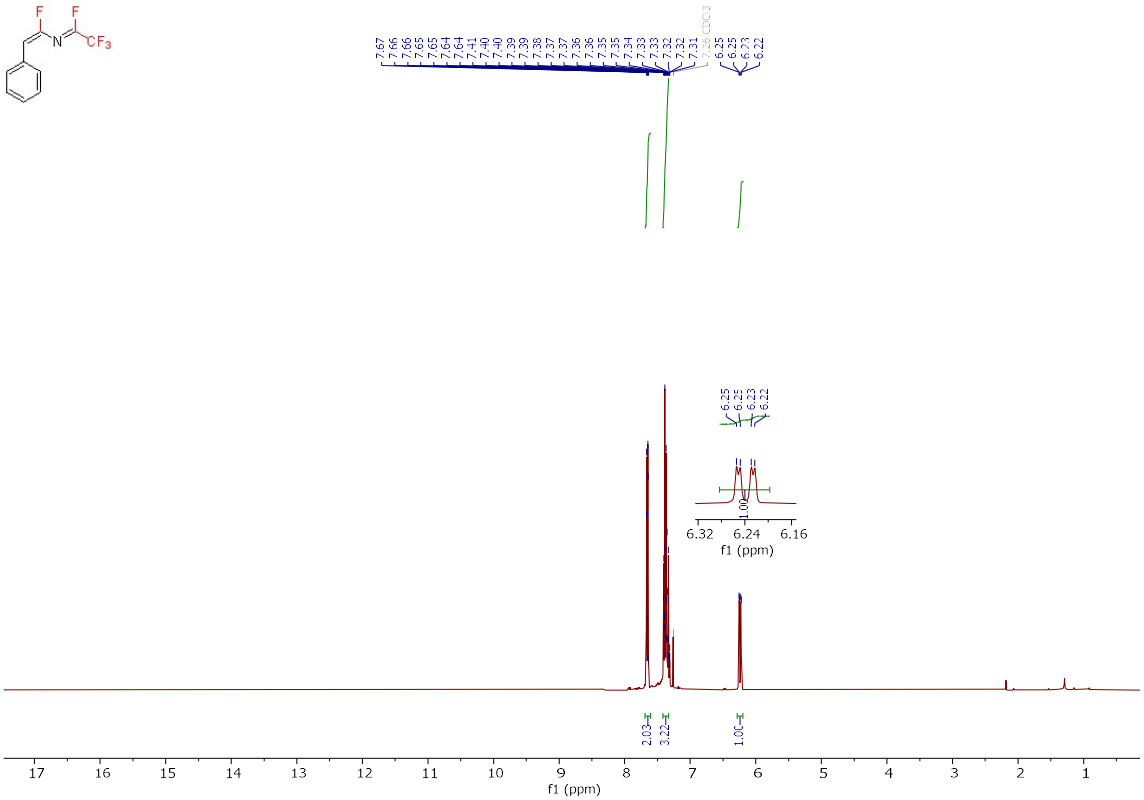
^{13}C NMR spectrum of **1o** ($CDCl_3$, 101 MHz)



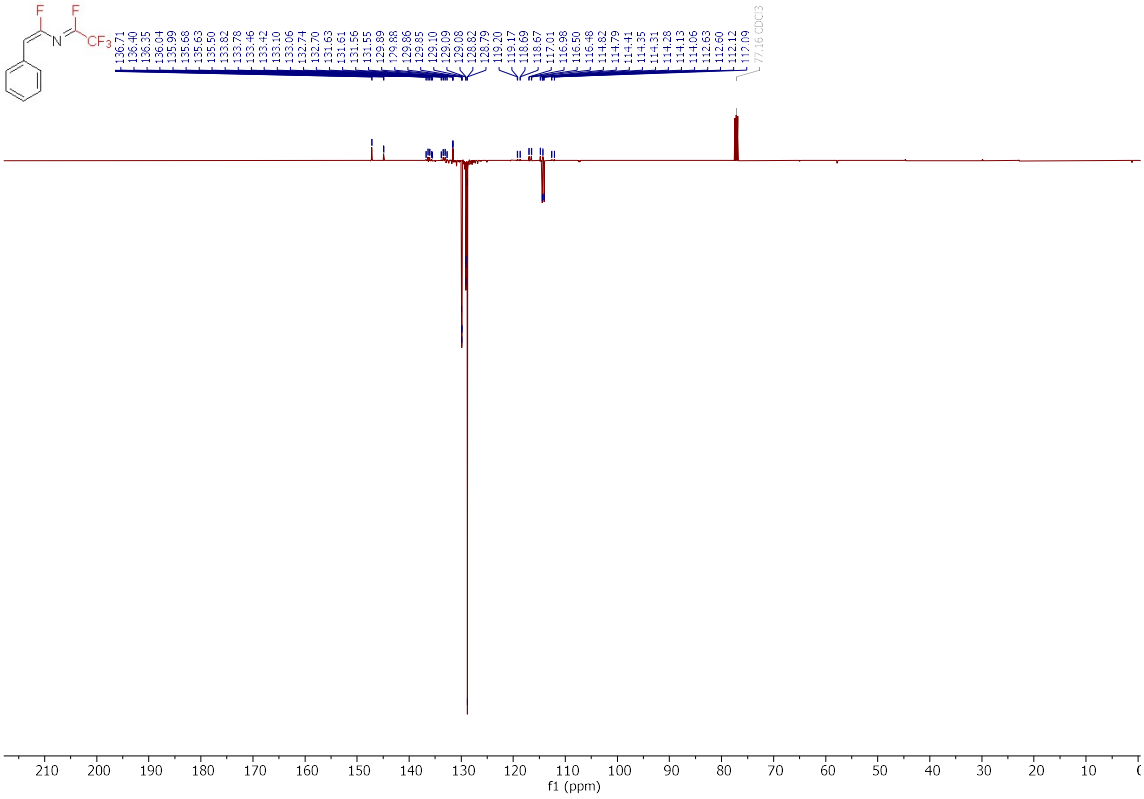
^{19}F NMR spectrum of **1o** ($CDCl_3$, 376 MHz)



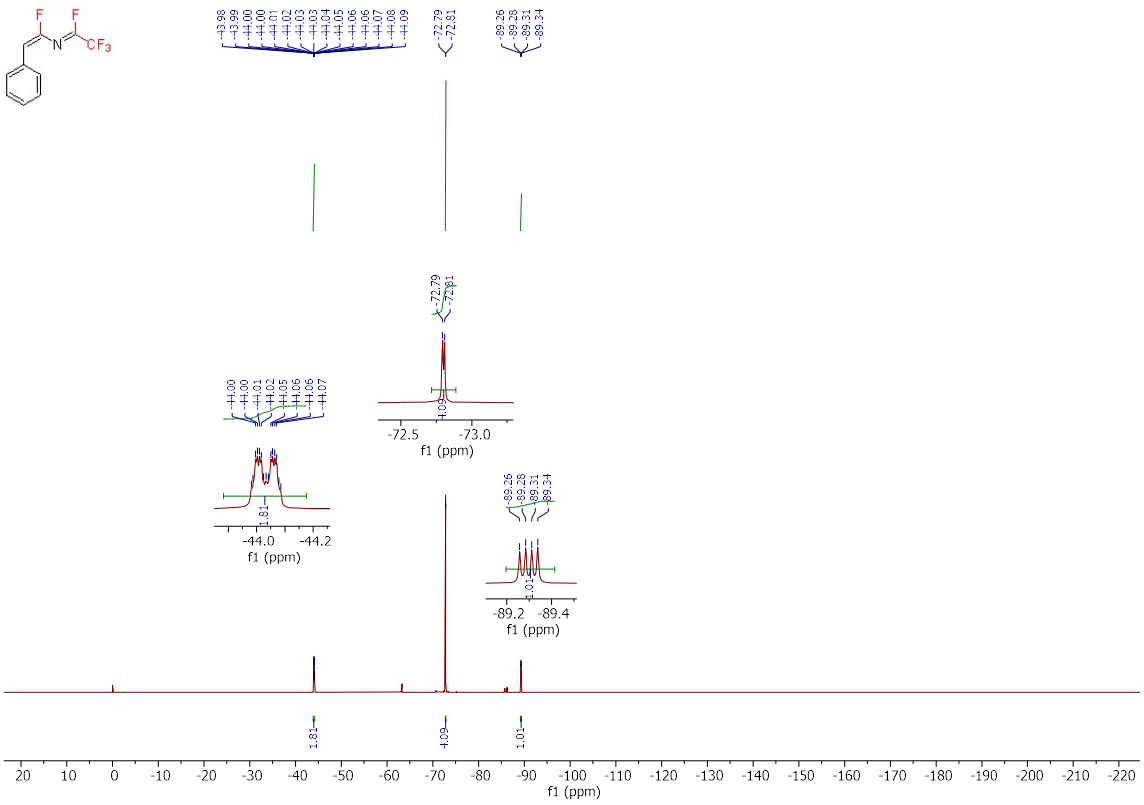
^{1}H NMR spectrum of (*Z*,*E*)-**4a** ($CDCl_3$, 400 MHz)



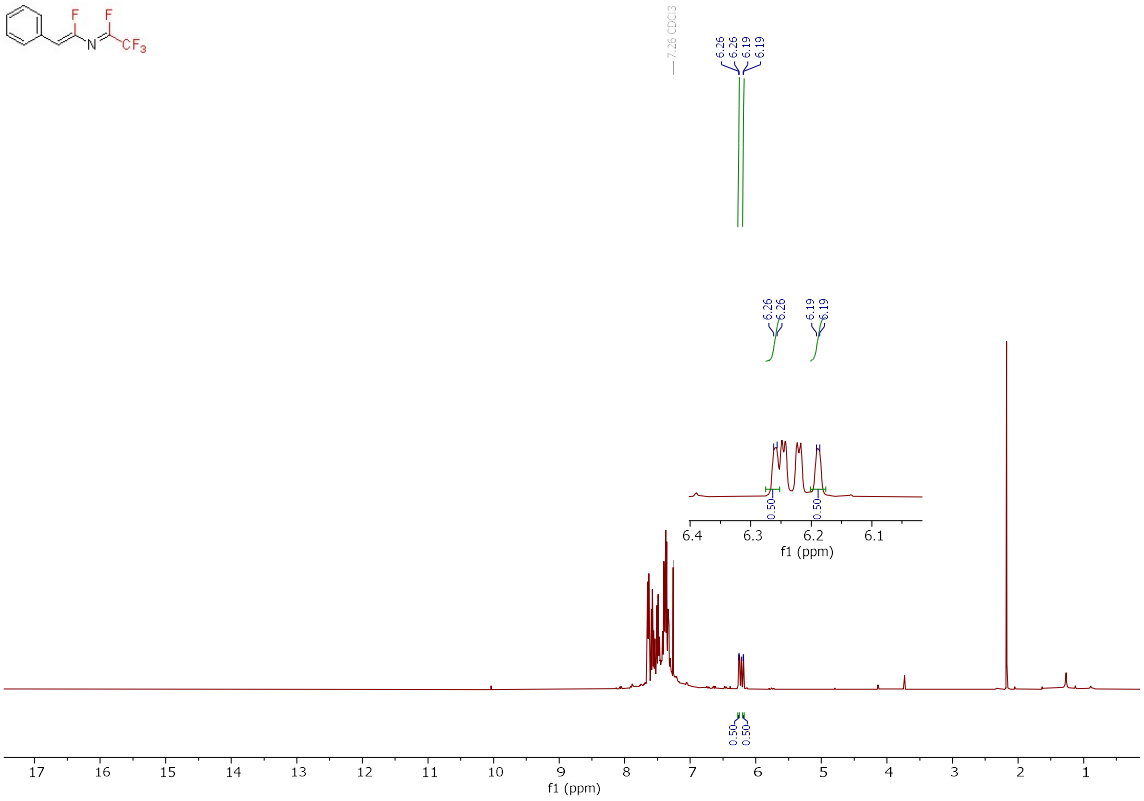
^{13}C NMR spectrum of (*Z*,*E*)-**4a** ($CDCl_3$, 101 MHz)



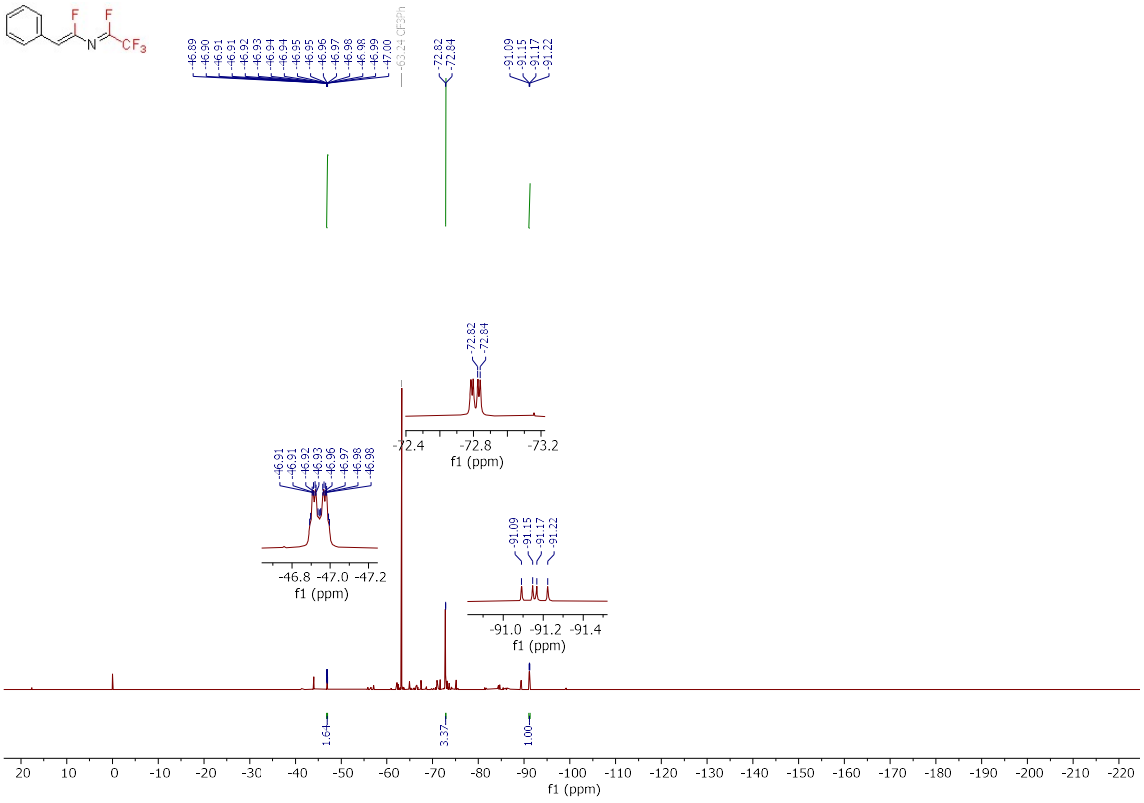
^{19}F NMR spectrum of (*Z*,*E*)-**4a** ($CDCl_3$, 376 MHz)



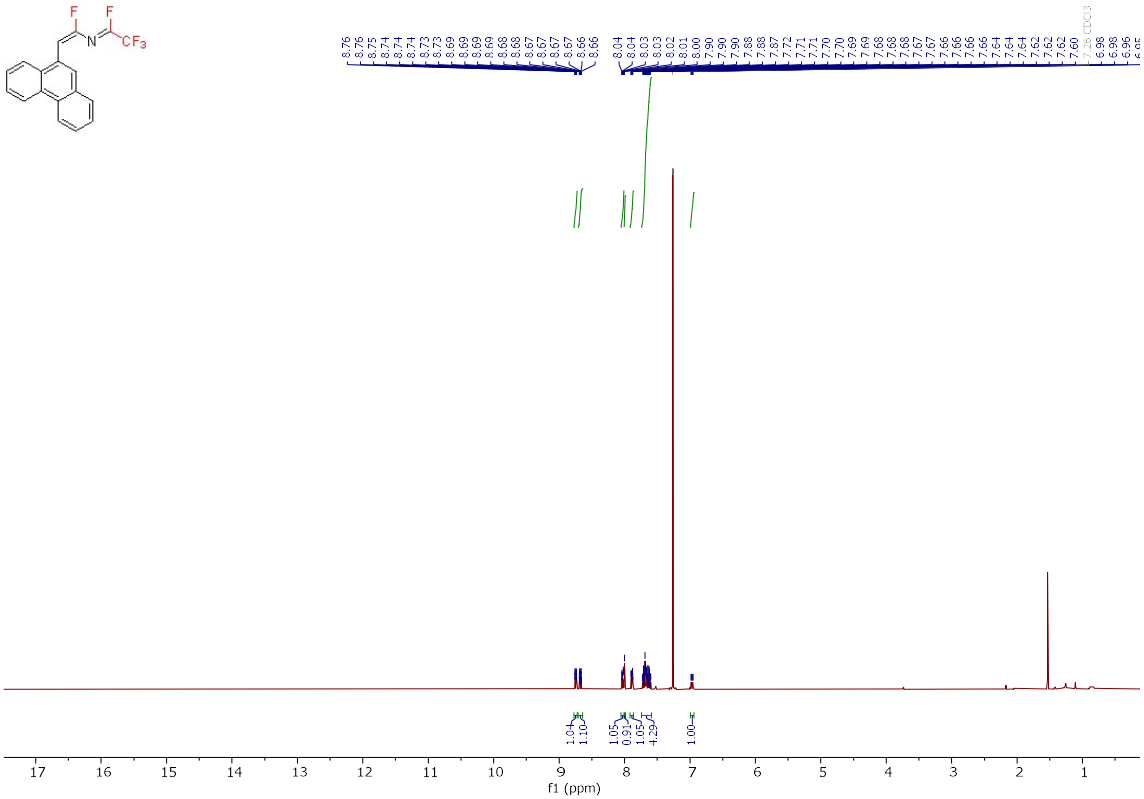
^{1}H NMR spectrum of (*Z*,*Z*)-**4a** ($CDCl_3$, 400 MHz)



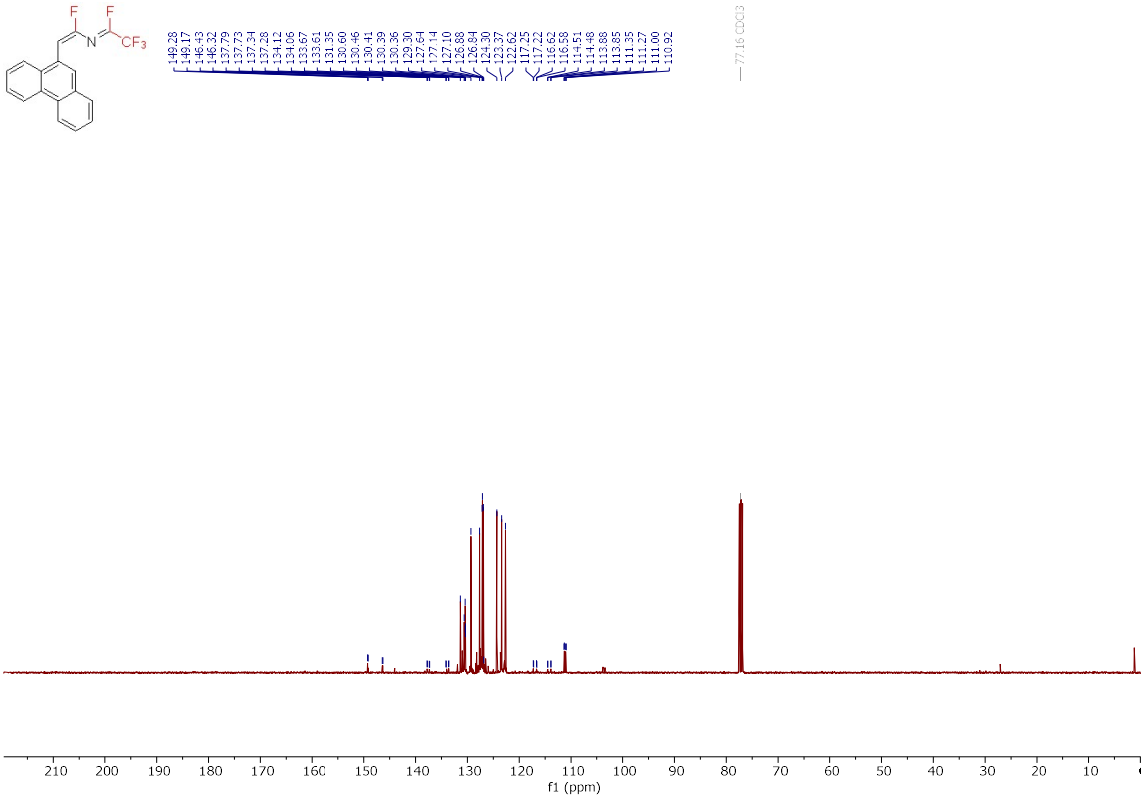
^{19}F NMR spectrum of (*Z*,*Z*)-**4a** ($CDCl_3$, 376 MHz)



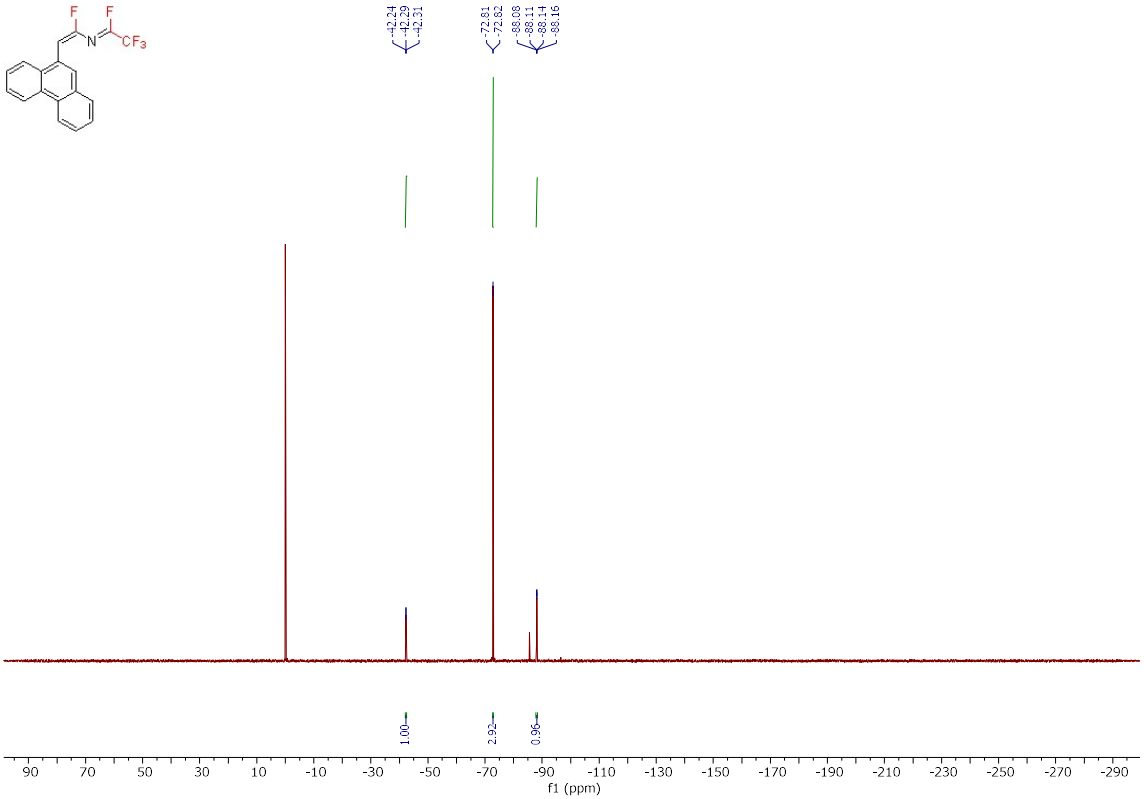
^{1}H NMR spectrum of (*Z*,*E*)-**4m** ($CDCl_3$, 400 MHz)



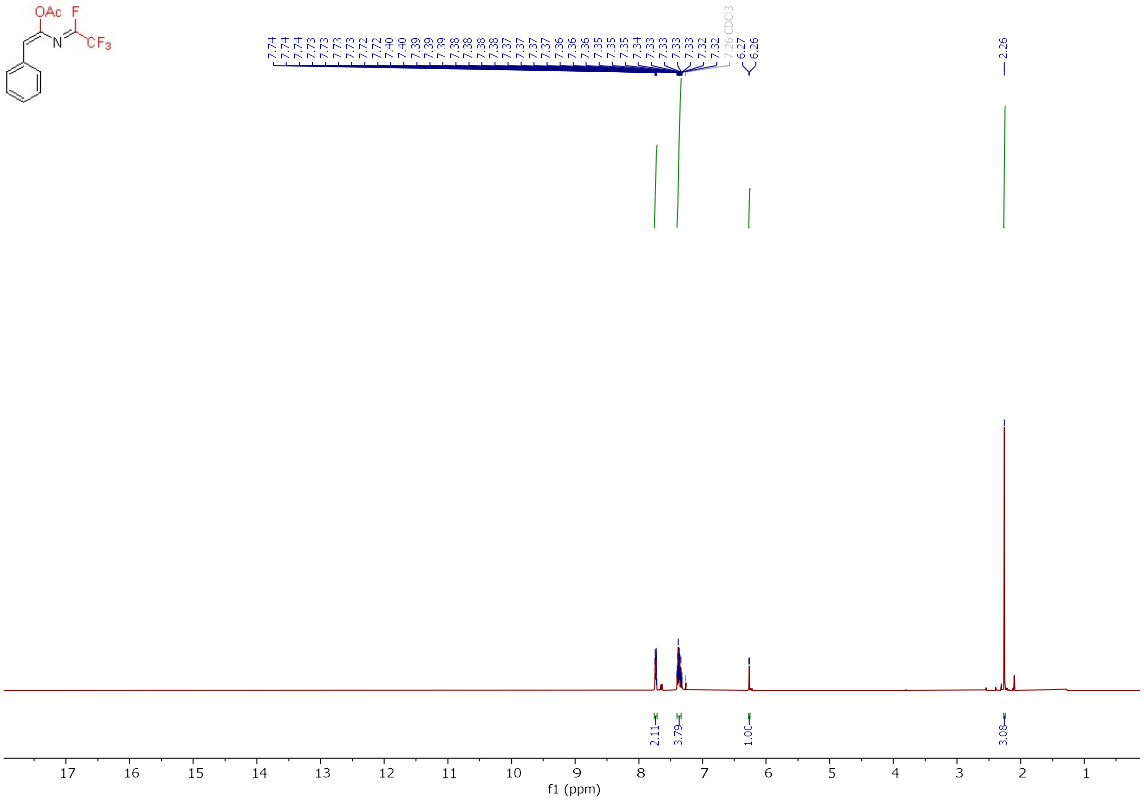
^{13}C NMR spectrum of (*Z*,*E*)-**4m** ($CDCl_3$, 101 MHz)



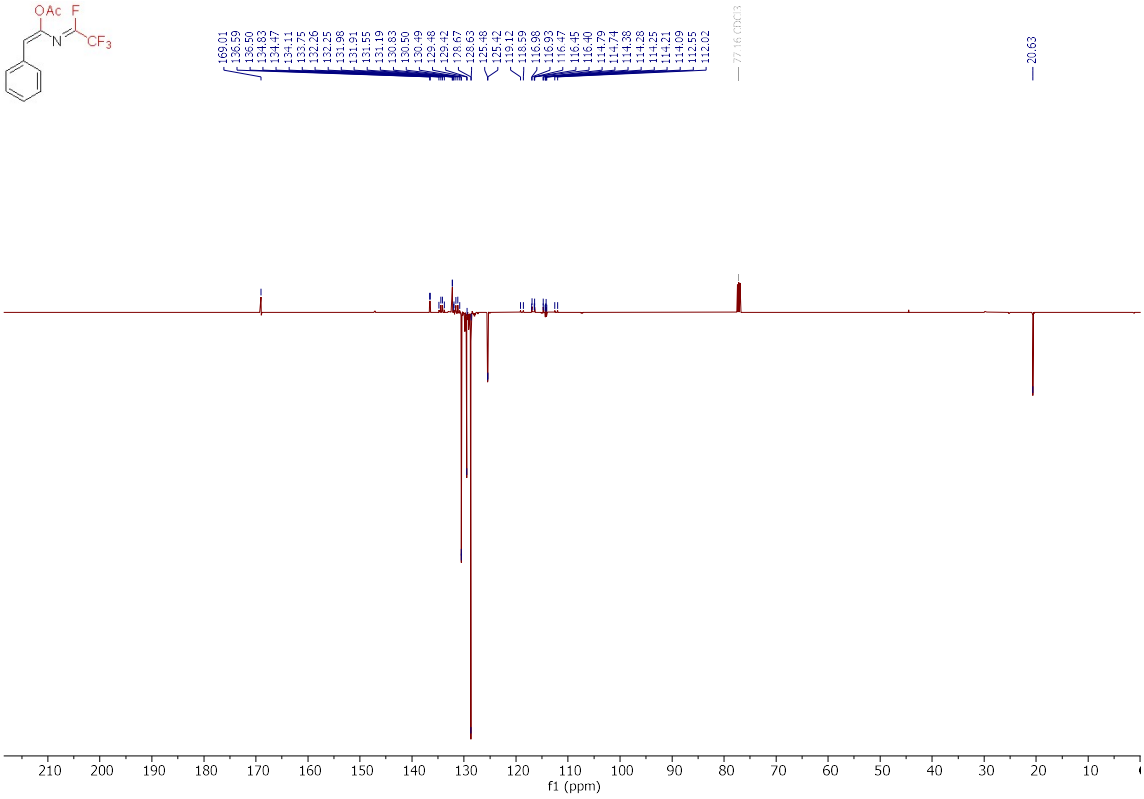
^{19}F NMR spectrum of (*Z*,*E*)-**4m** ($CDCl_3$, 376 MHz)



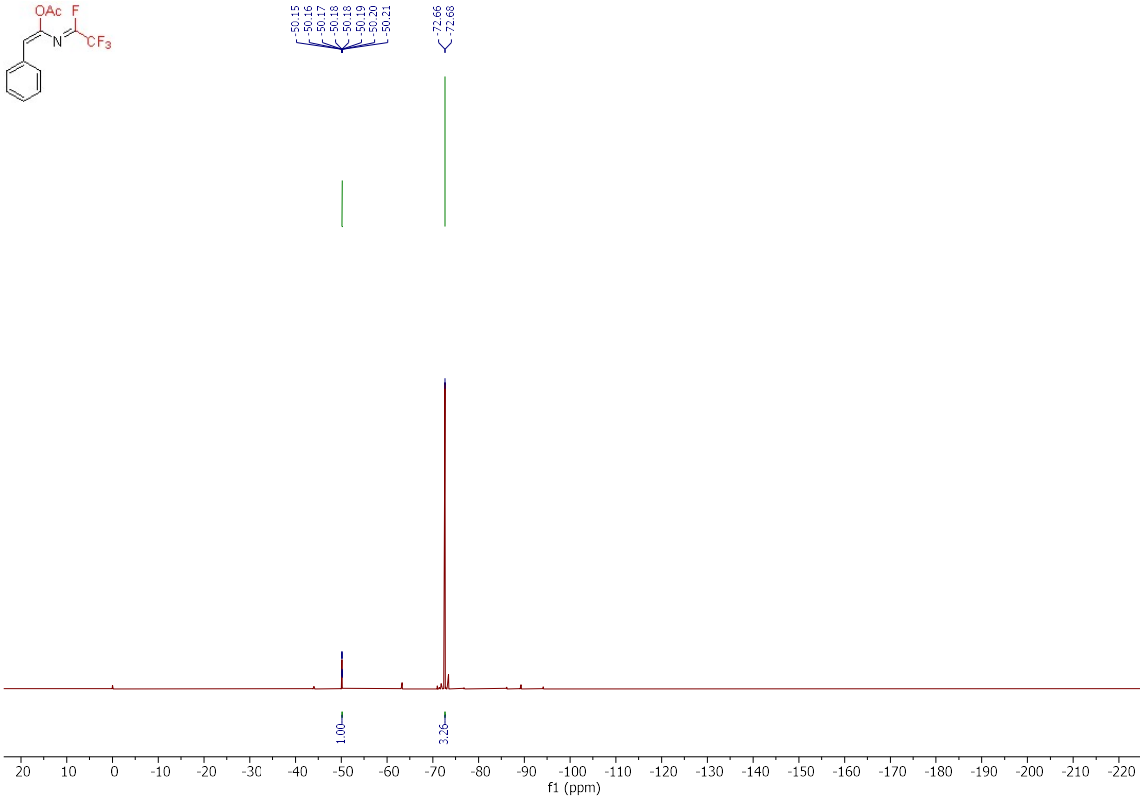
^{1}H NMR spectrum of **6a** ($CDCl_3$, 400 MHz)



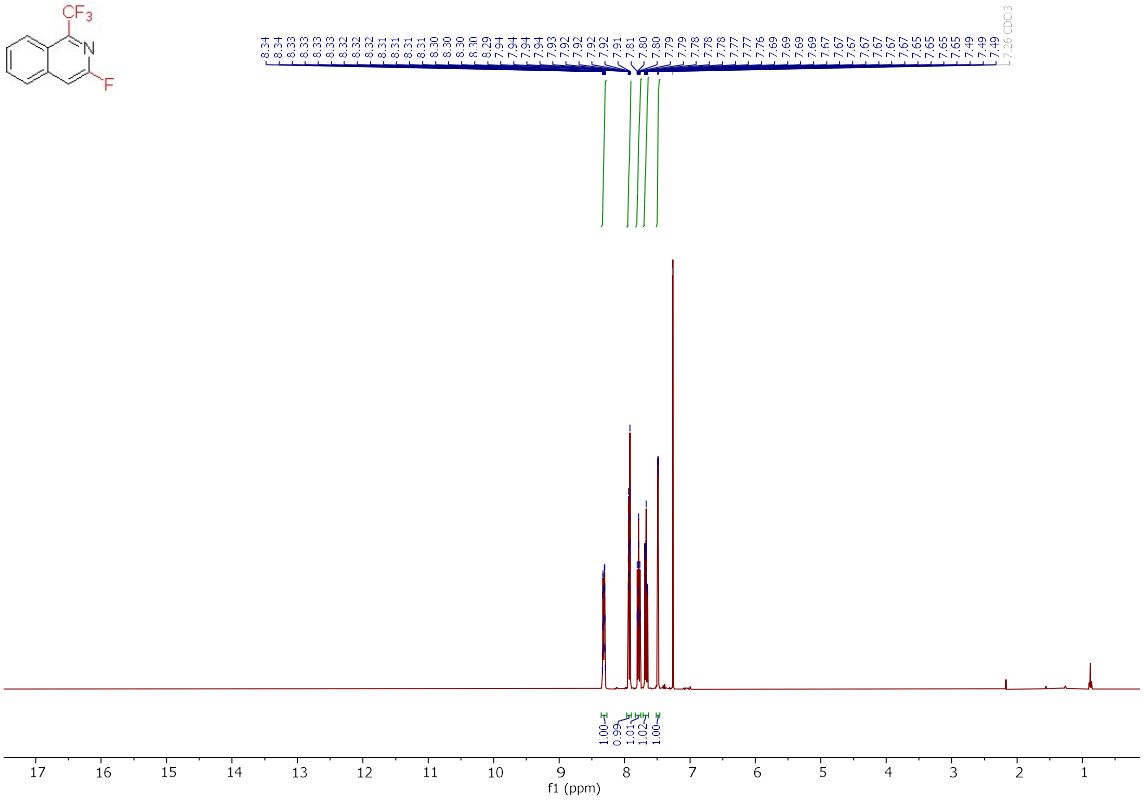
^{13}C NMR spectrum of **6a** ($CDCl_3$, 101 MHz)



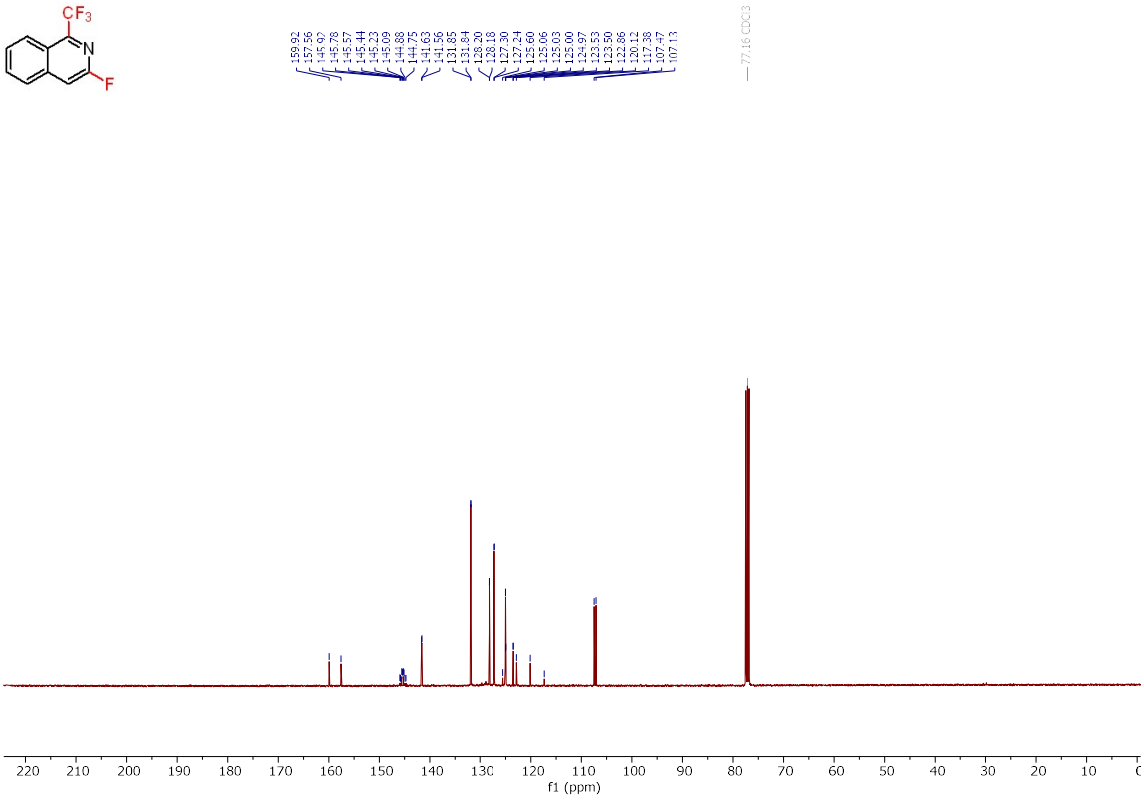
^{19}F NMR spectrum of **6a** ($CDCl_3$, 376 MHz)



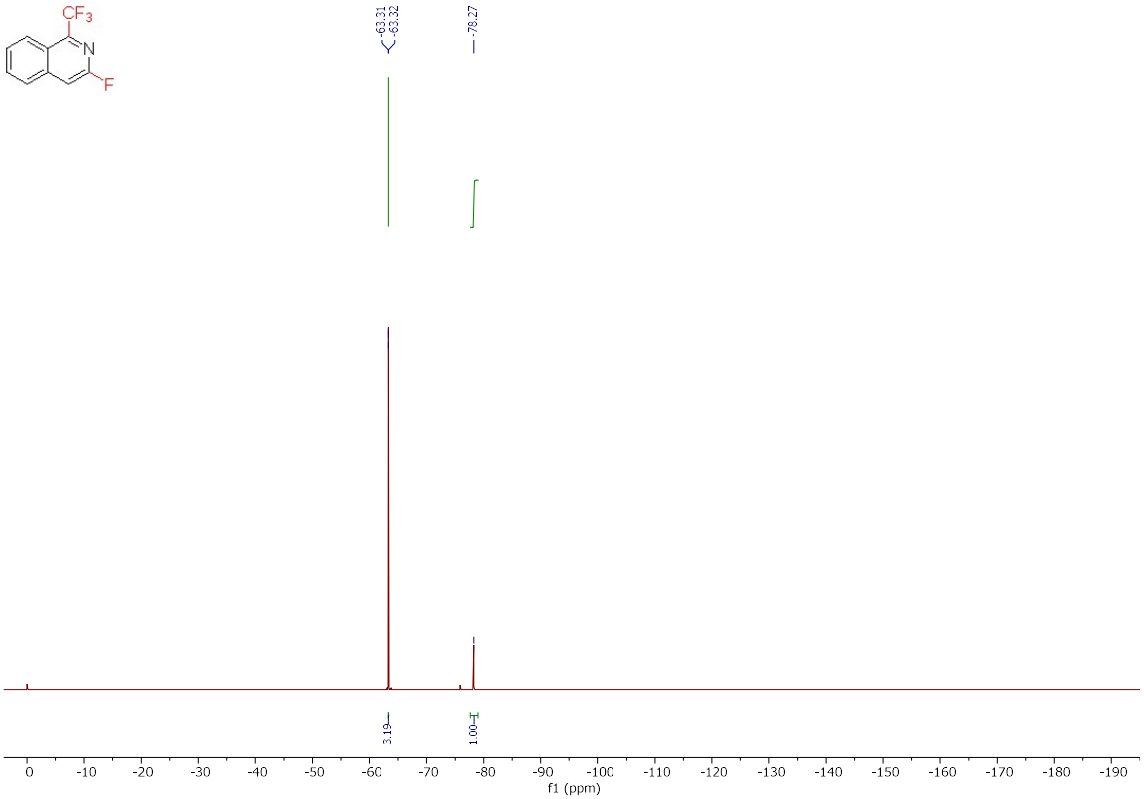
^{1}H NMR spectrum of **2a** ($CDCl_3$, 400 MHz)



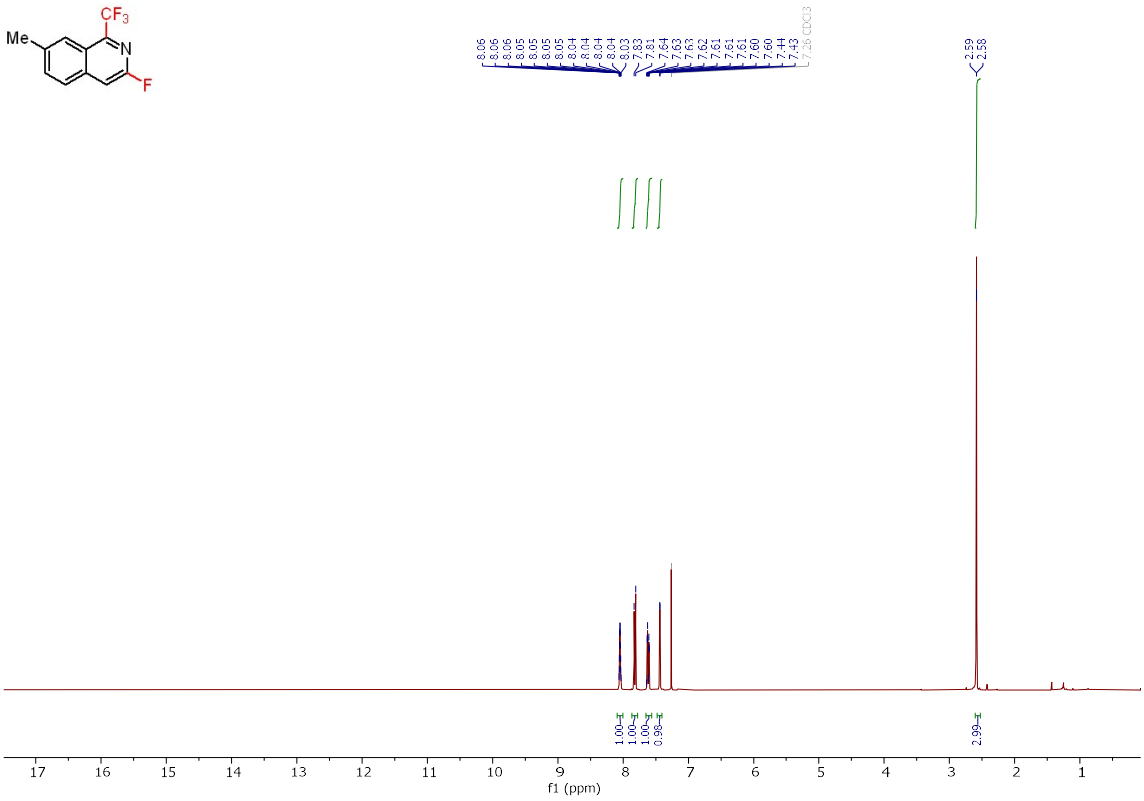
^{13}C NMR spectrum of **2a** ($CDCl_3$, 101 MHz)



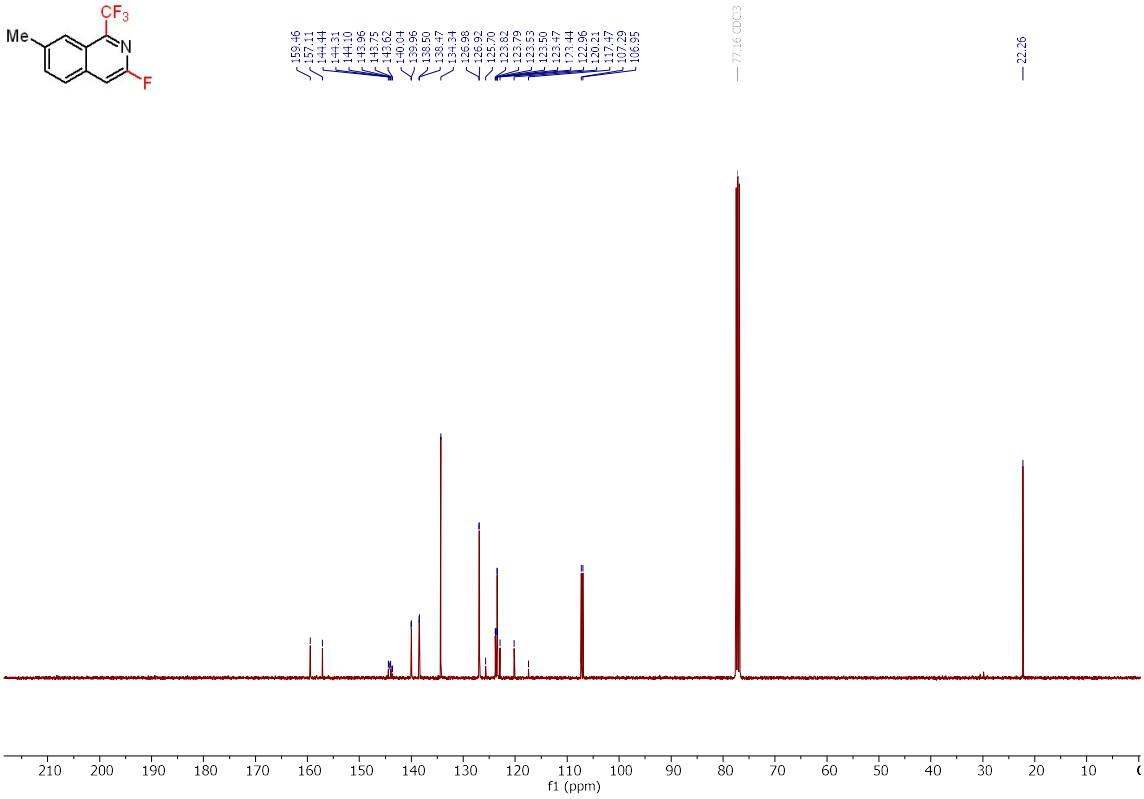
^{19}F NMR spectrum of **2a** ($CDCl_3$, 376 MHz)



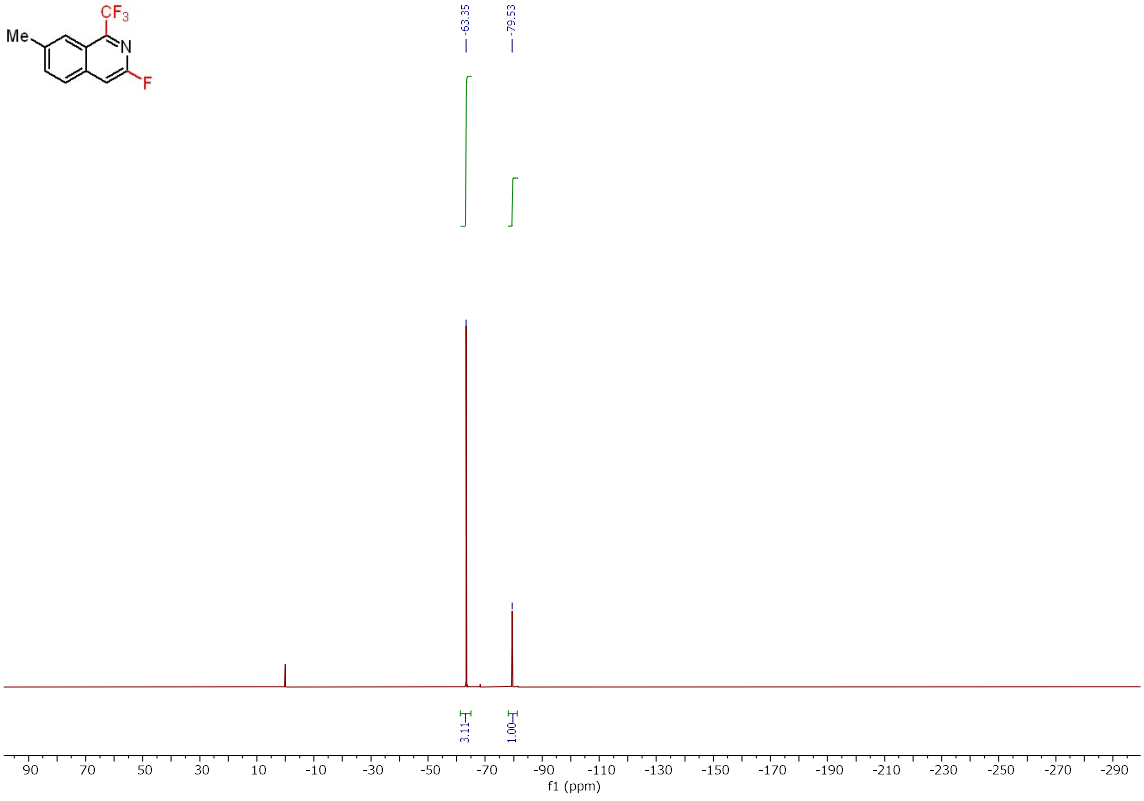
^{1}H NMR spectrum of **2b** ($CDCl_3$, 400 MHz)



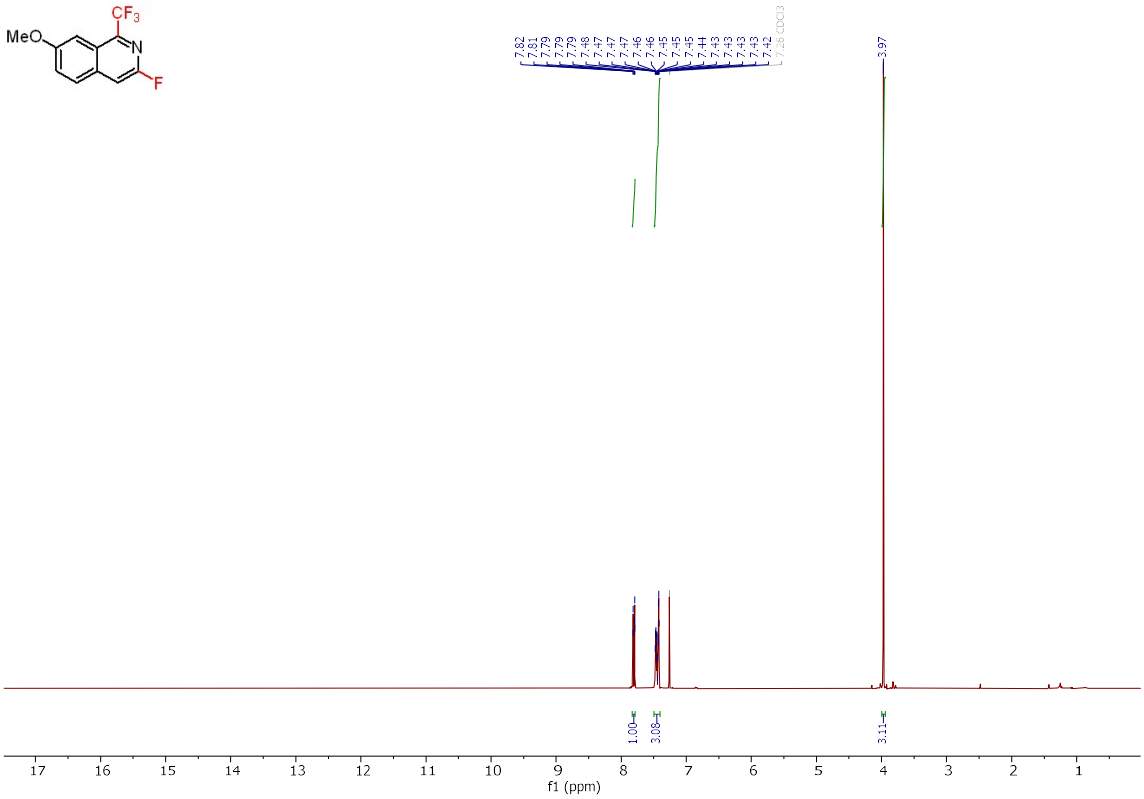
^{13}C NMR spectrum of **2b** ($CDCl_3$, 101 MHz)



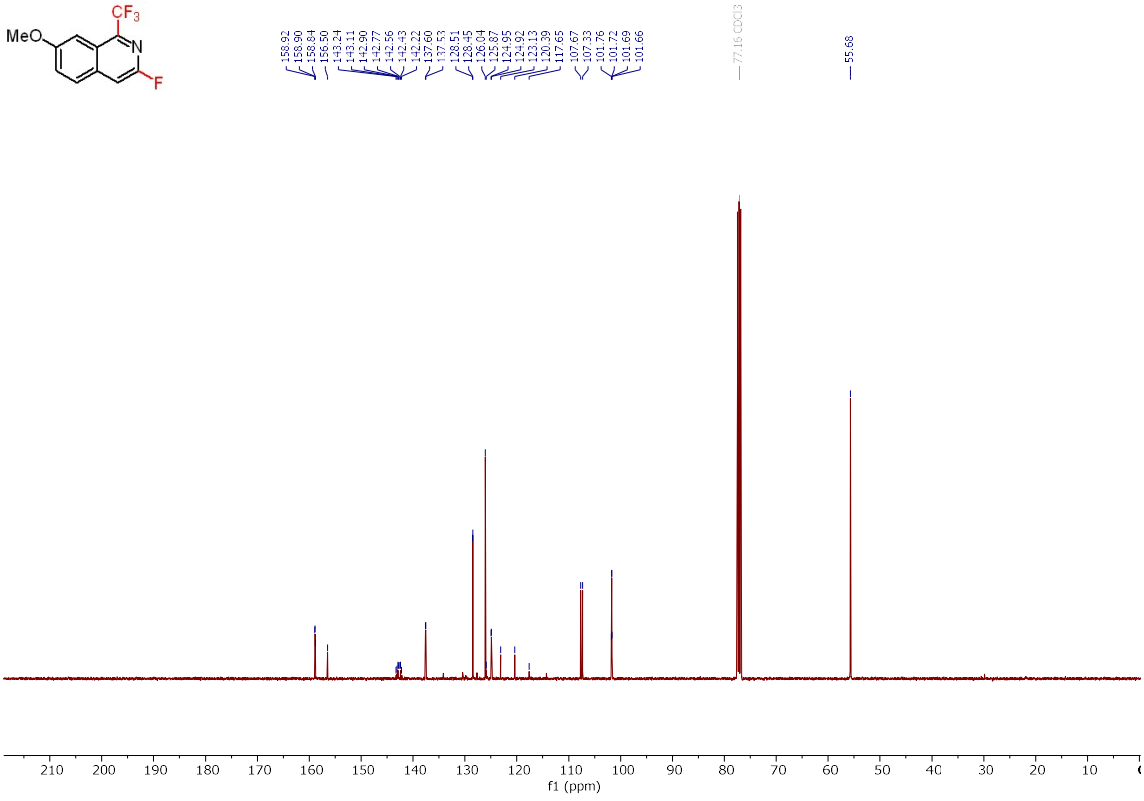
^{19}F NMR spectrum of **2b** ($CDCl_3$, 376 MHz)



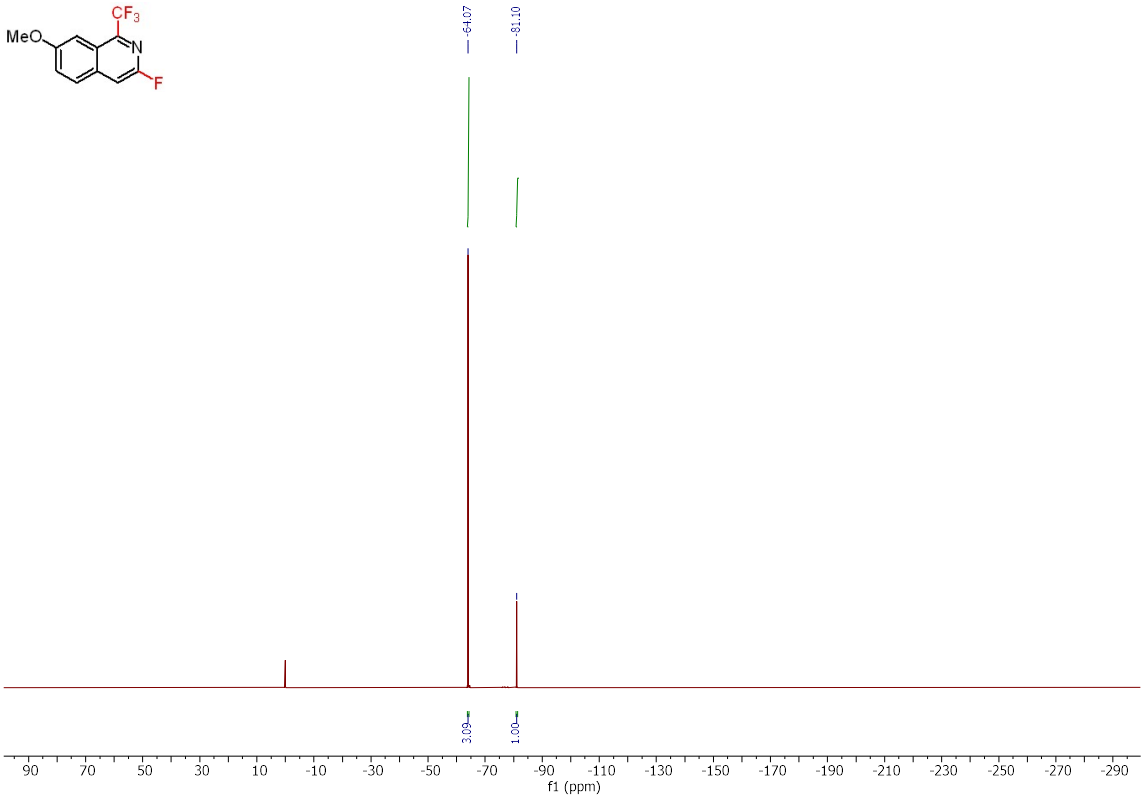
^{1}H NMR spectrum of **2c** ($CDCl_3$, 400 MHz)



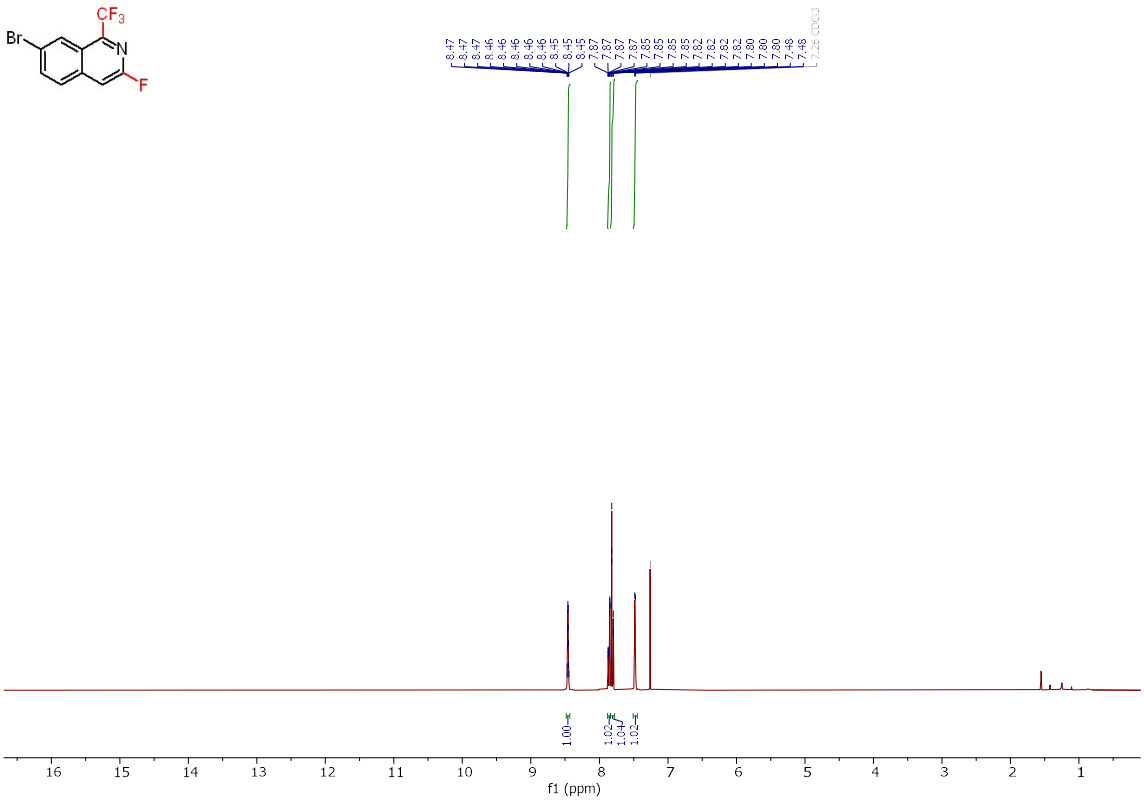
^{13}C NMR spectrum of **2c** ($CDCl_3$, 101 MHz)



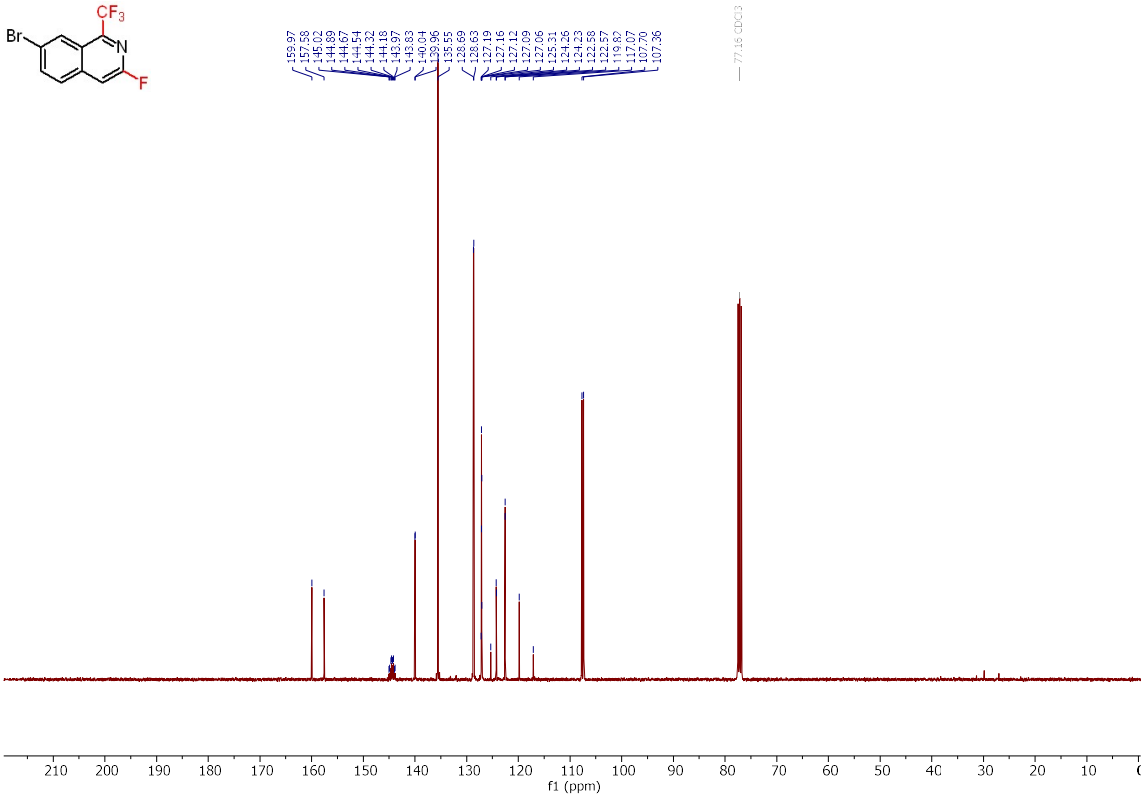
^{19}F NMR spectrum of **2c** ($CDCl_3$, 376 MHz)



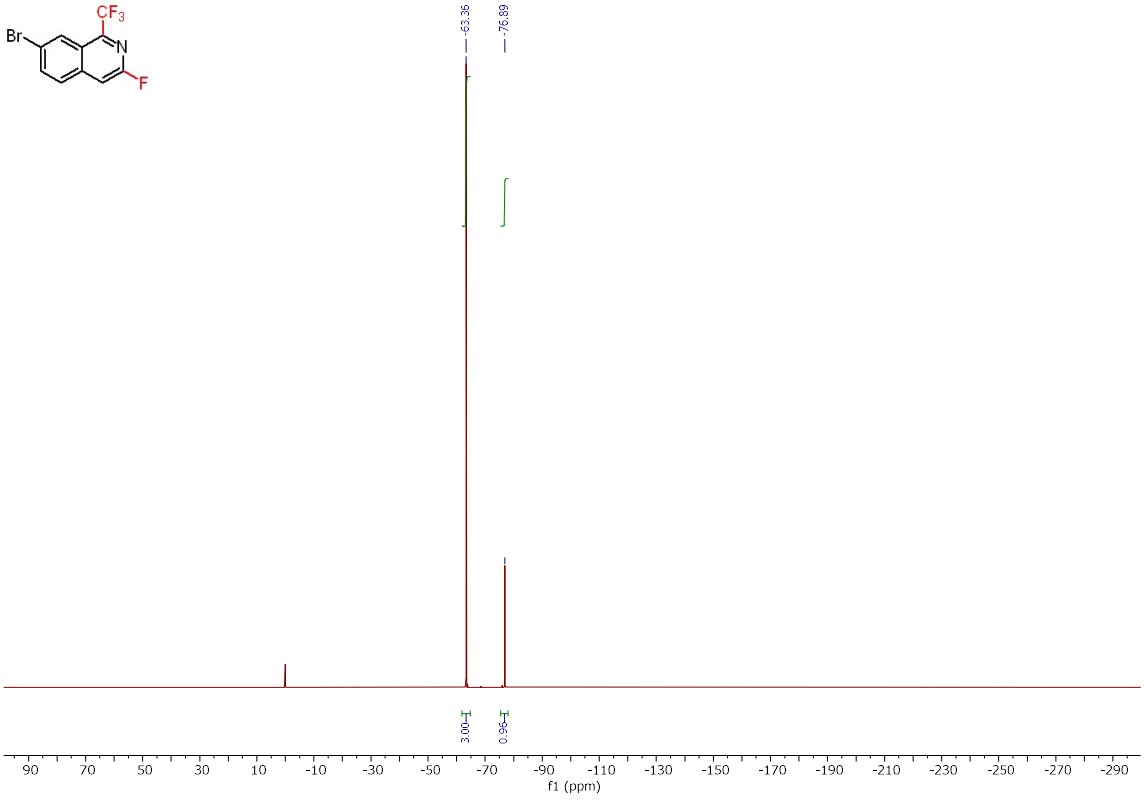
^{1}H NMR spectrum of **2d** ($CDCl_3$, 400 MHz)



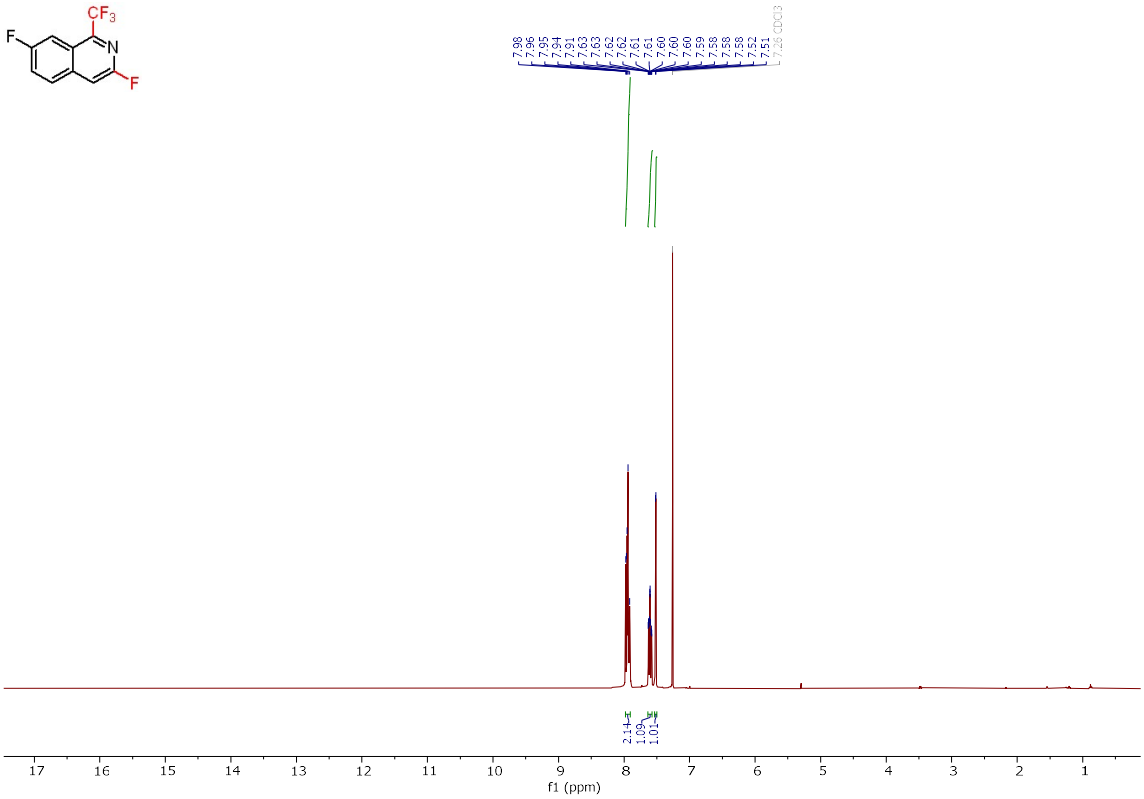
^{13}C NMR spectrum of **2d** ($CDCl_3$, 101 MHz)



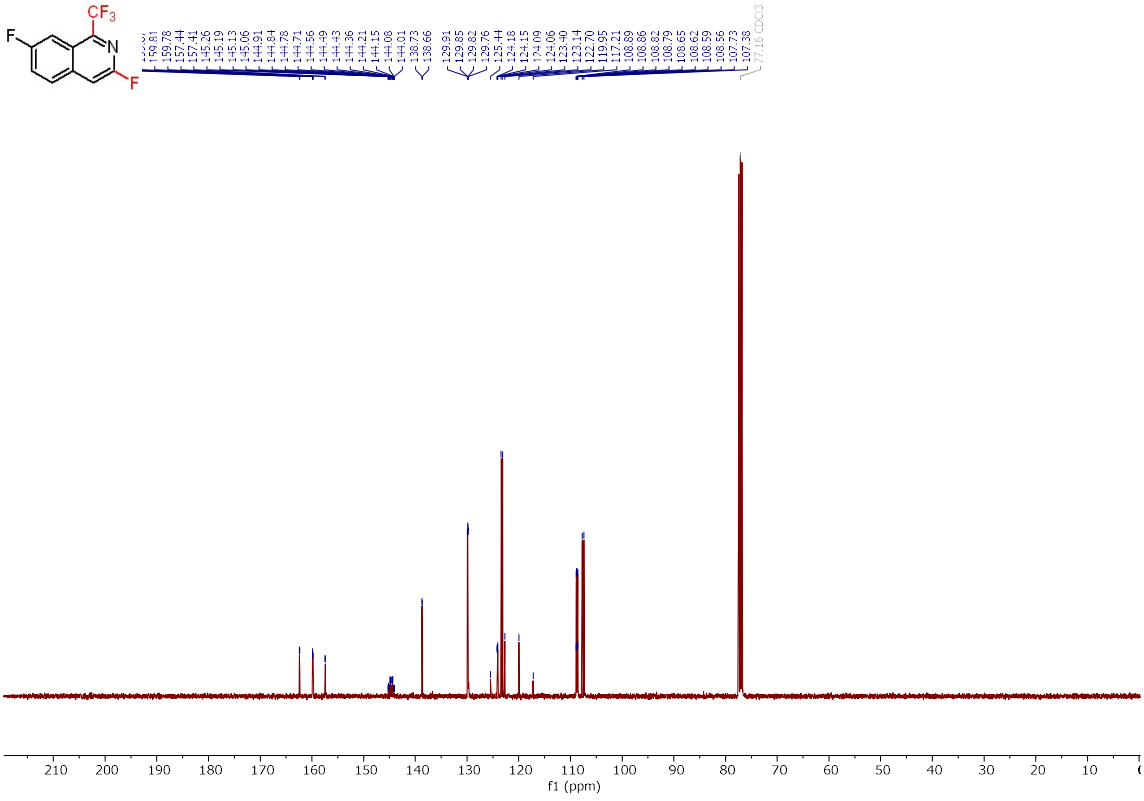
^{19}F NMR spectrum of **2d** ($CDCl_3$, 376 MHz)



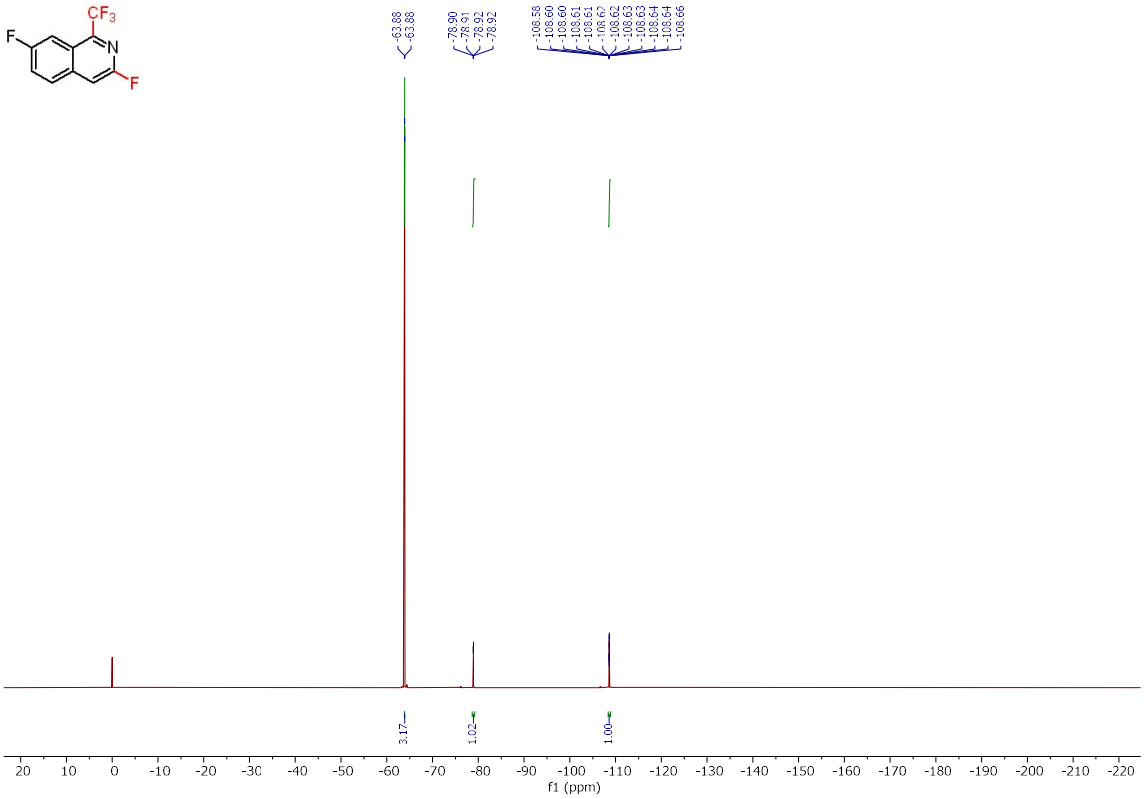
^{1}H NMR spectrum of **2e** ($CDCl_3$, 400 MHz)



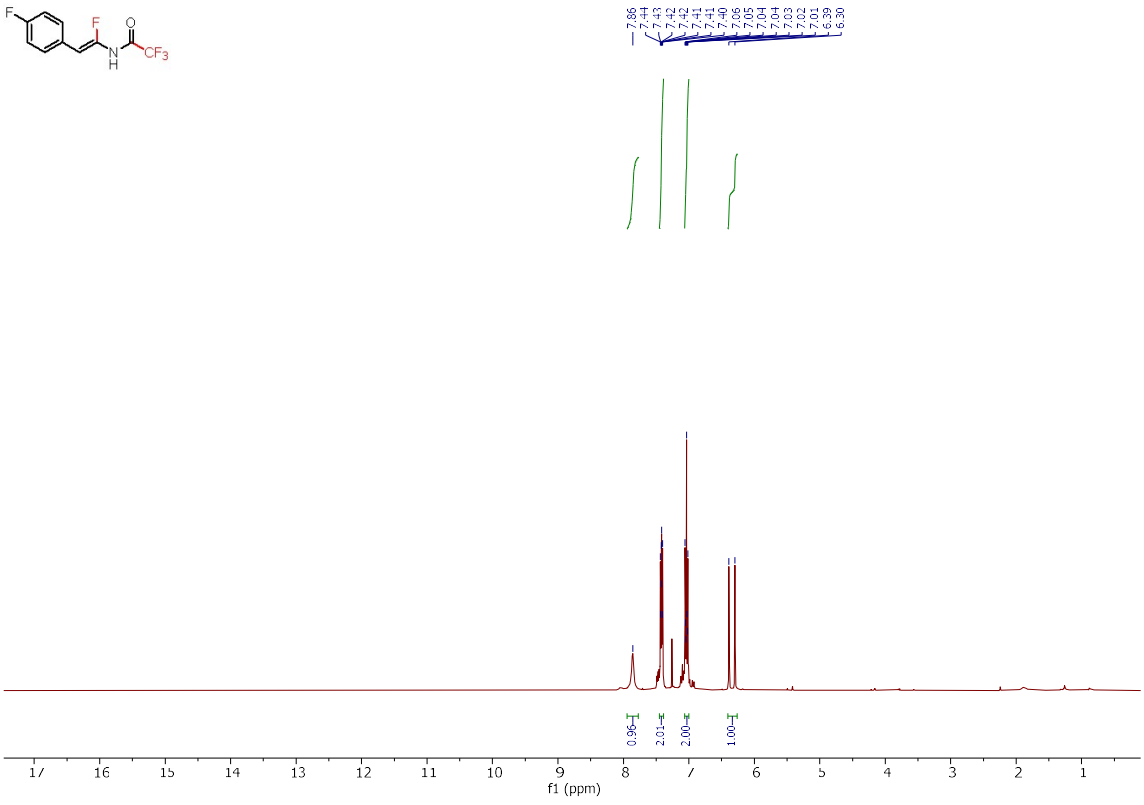
^{13}C NMR spectrum of **2e** ($CDCl_3$, 101 MHz)



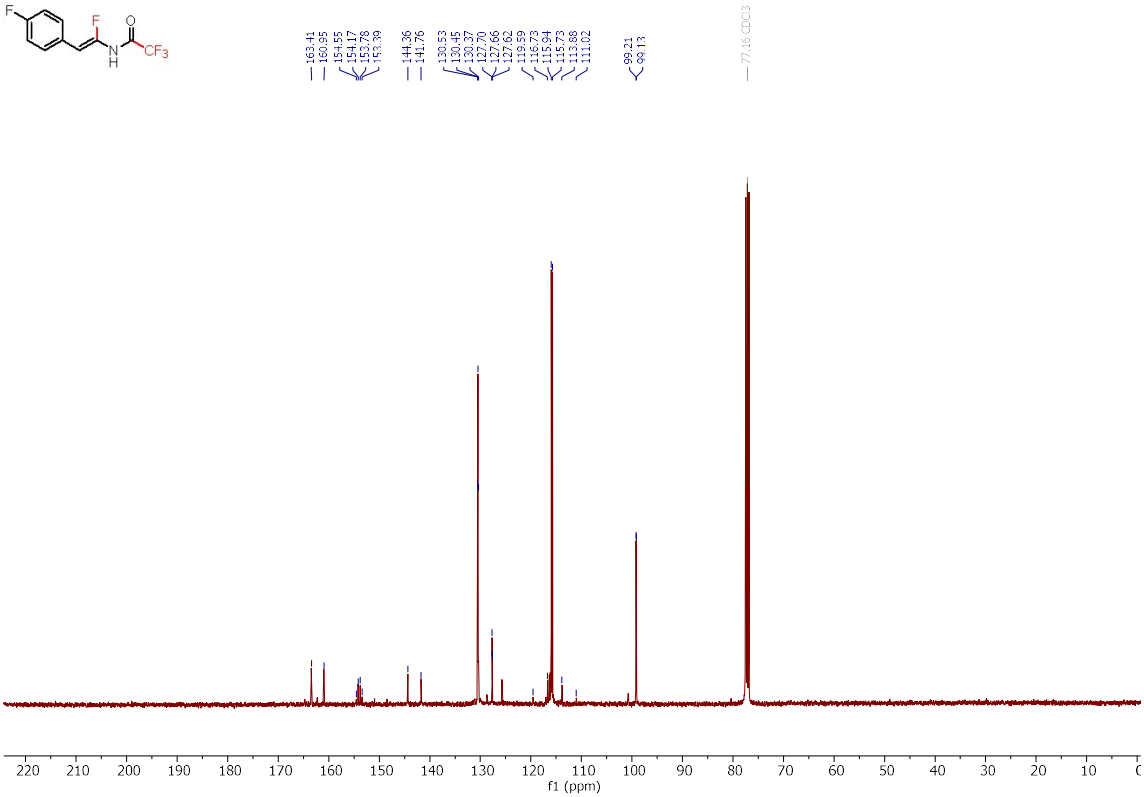
^{19}F NMR spectrum of **2e** ($CDCl_3$, 376 MHz)



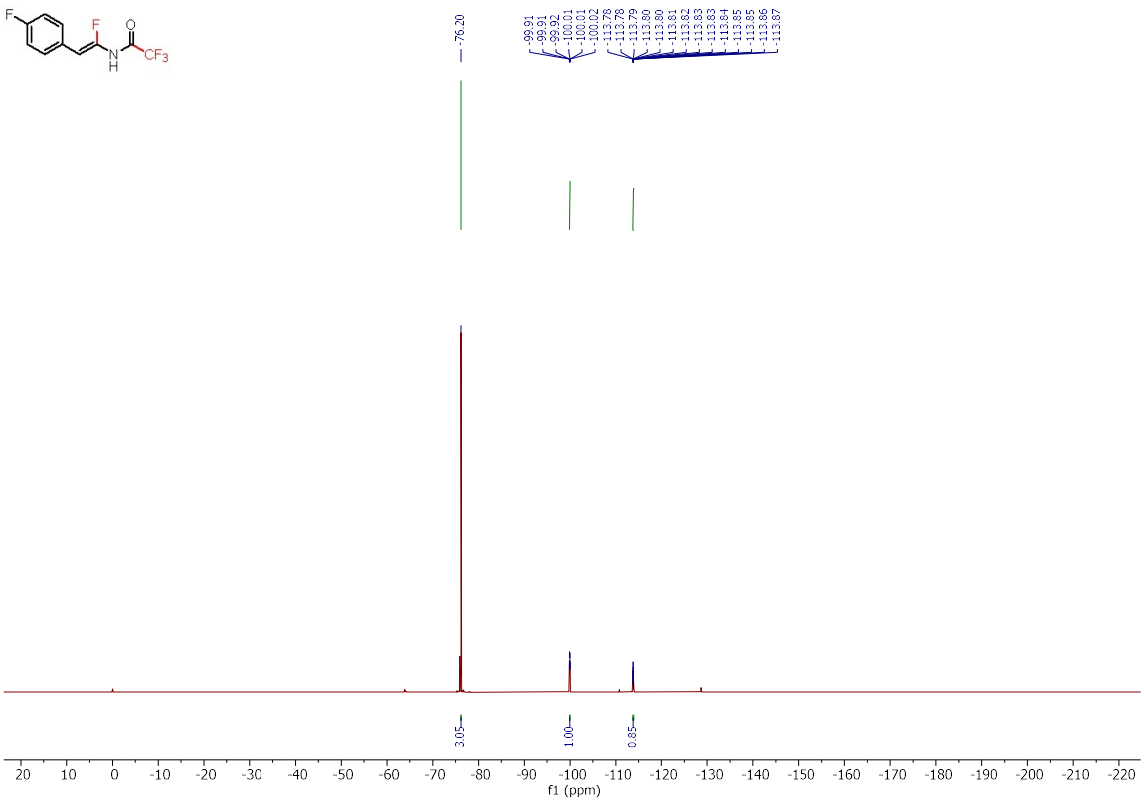
^{1}H NMR spectrum of **5e** ($CDCl_3$, 400 MHz)



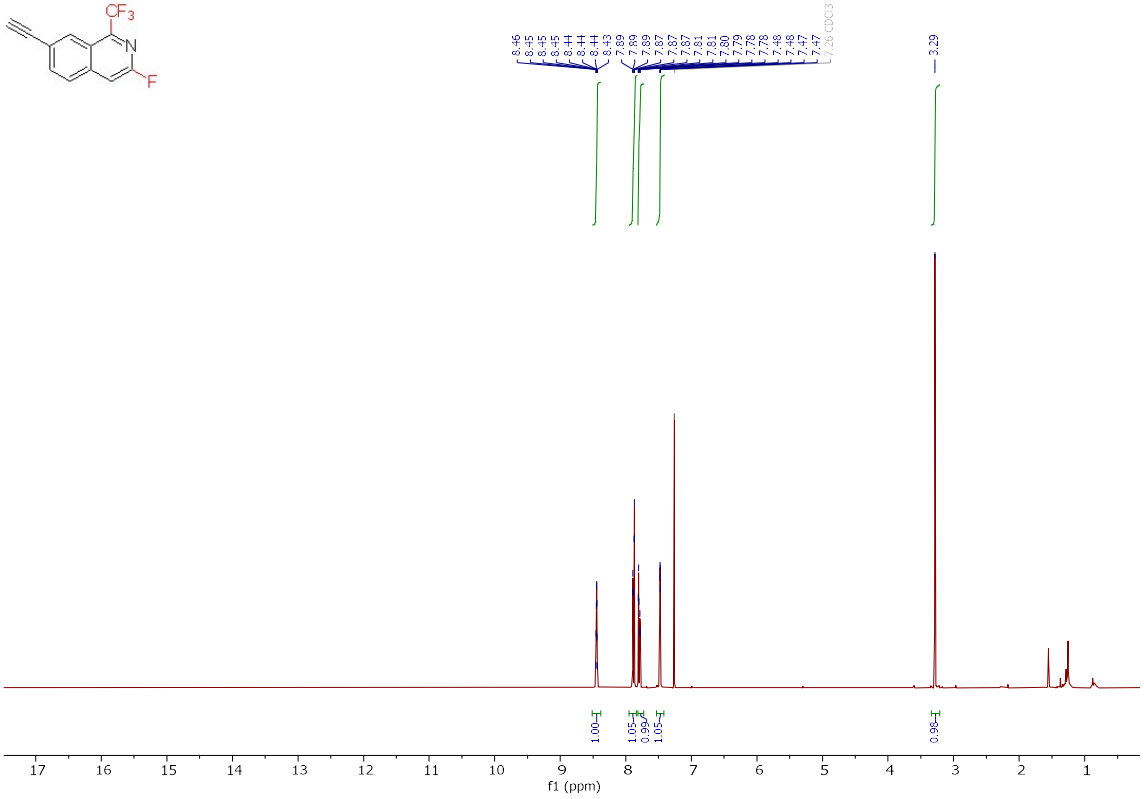
^{13}C NMR spectrum of **5e** ($CDCl_3$, 101 MHz)



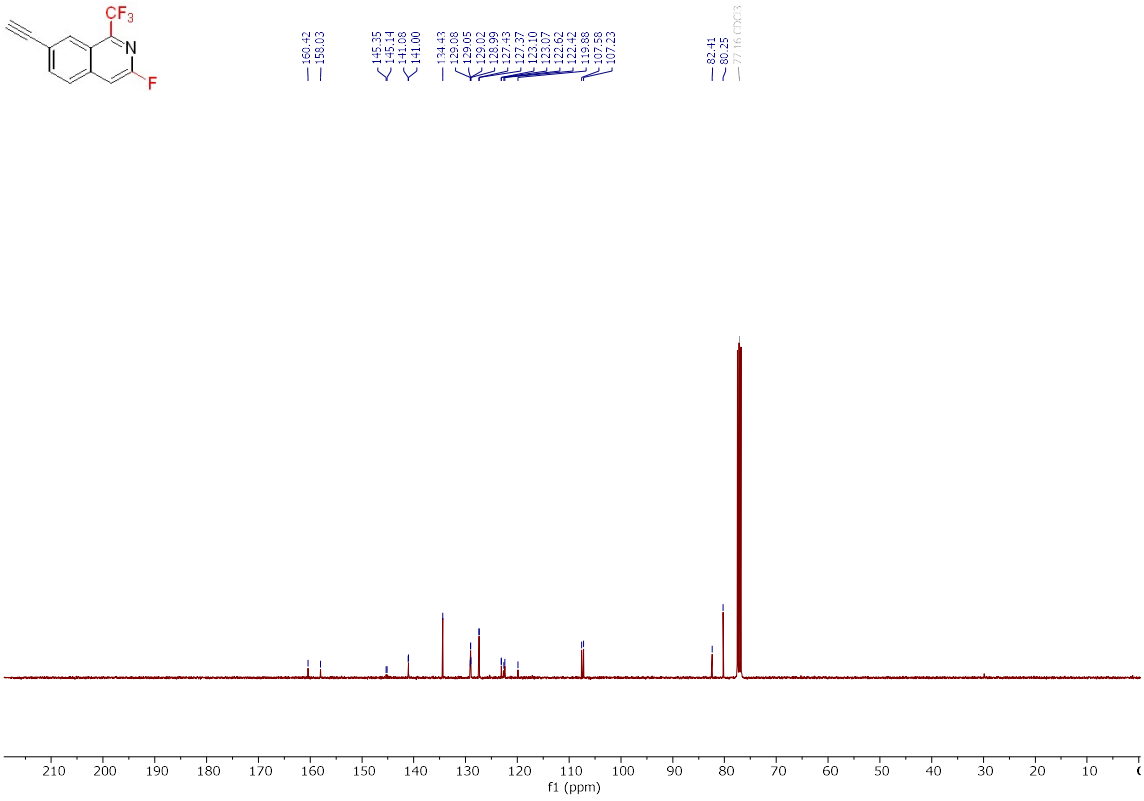
^{19}F NMR spectrum of **5e** ($CDCl_3$, 376 MHz)



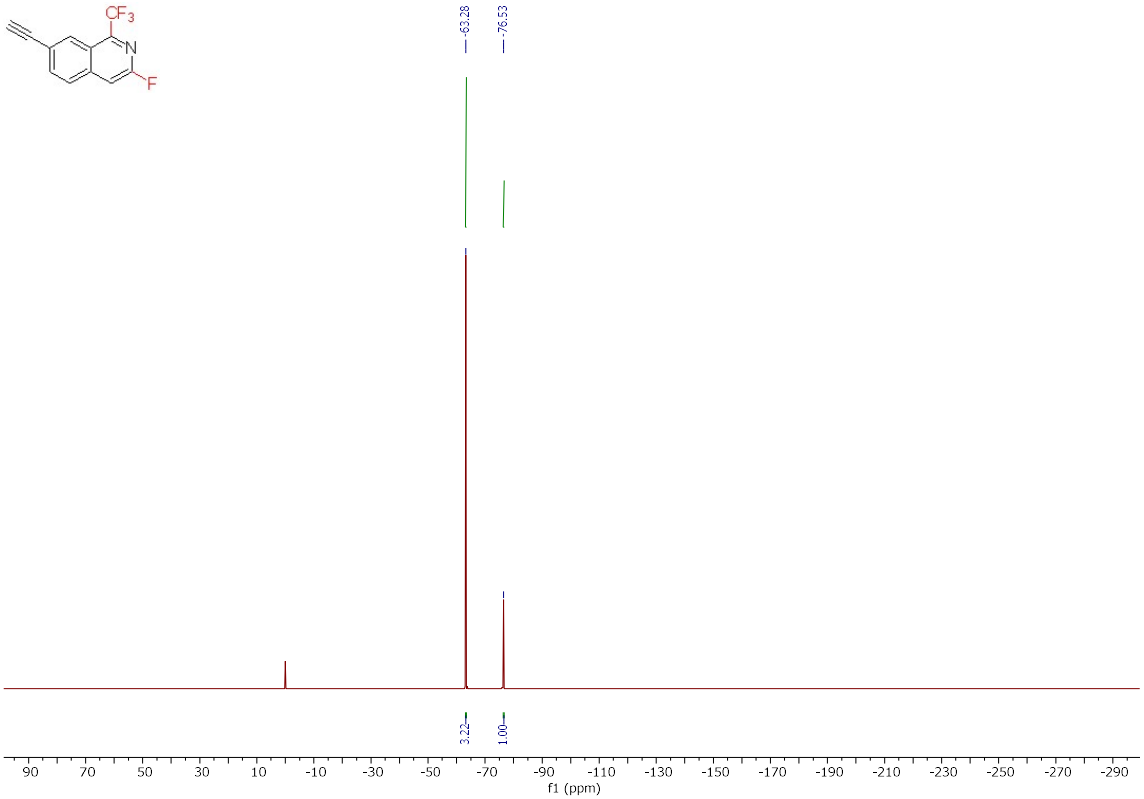
^{1}H NMR spectrum of **2f** ($CDCl_3$, 400 MHz)



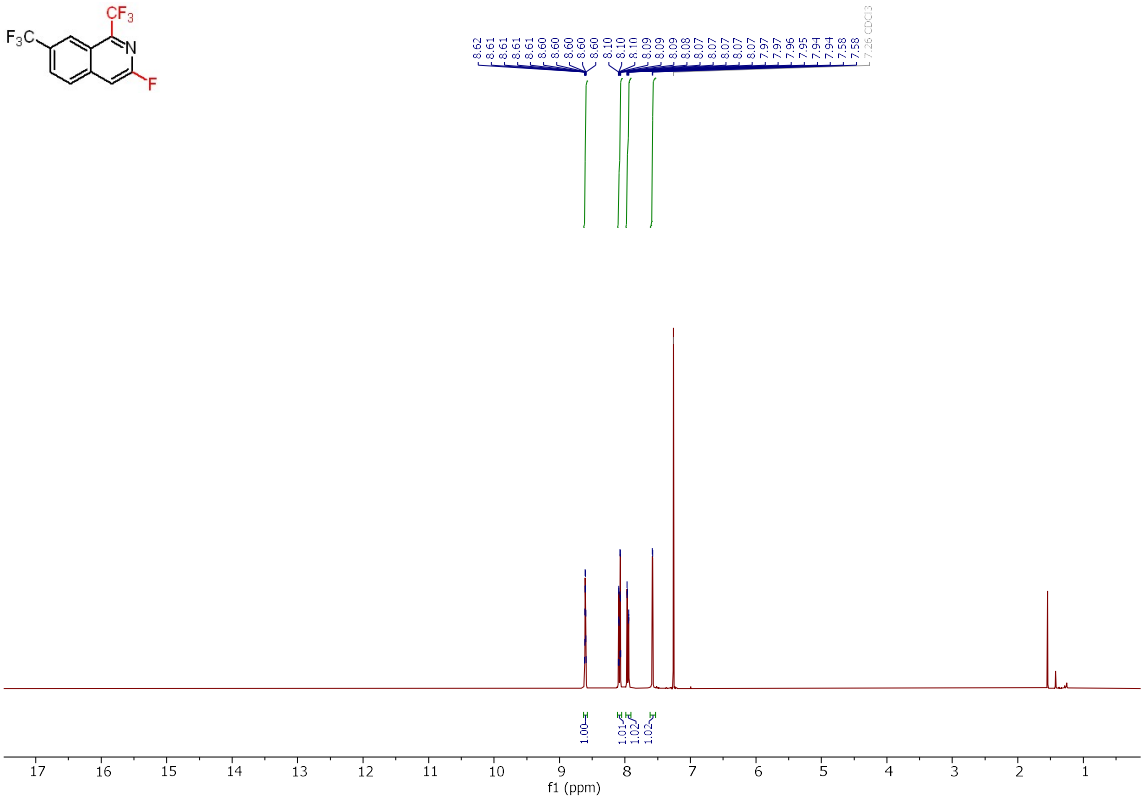
^{13}C NMR spectrum of **2f** ($CDCl_3$, 101 MHz)



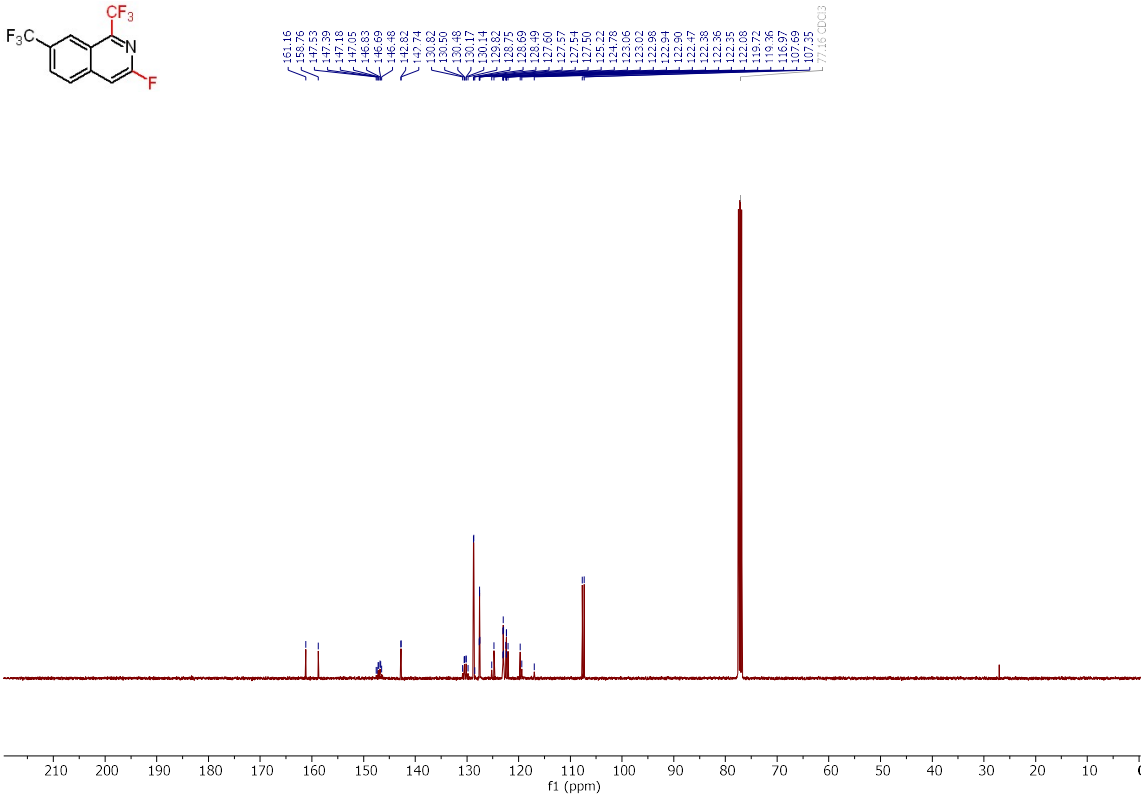
^{19}F NMR spectrum of **2f** ($CDCl_3$, 376 MHz)



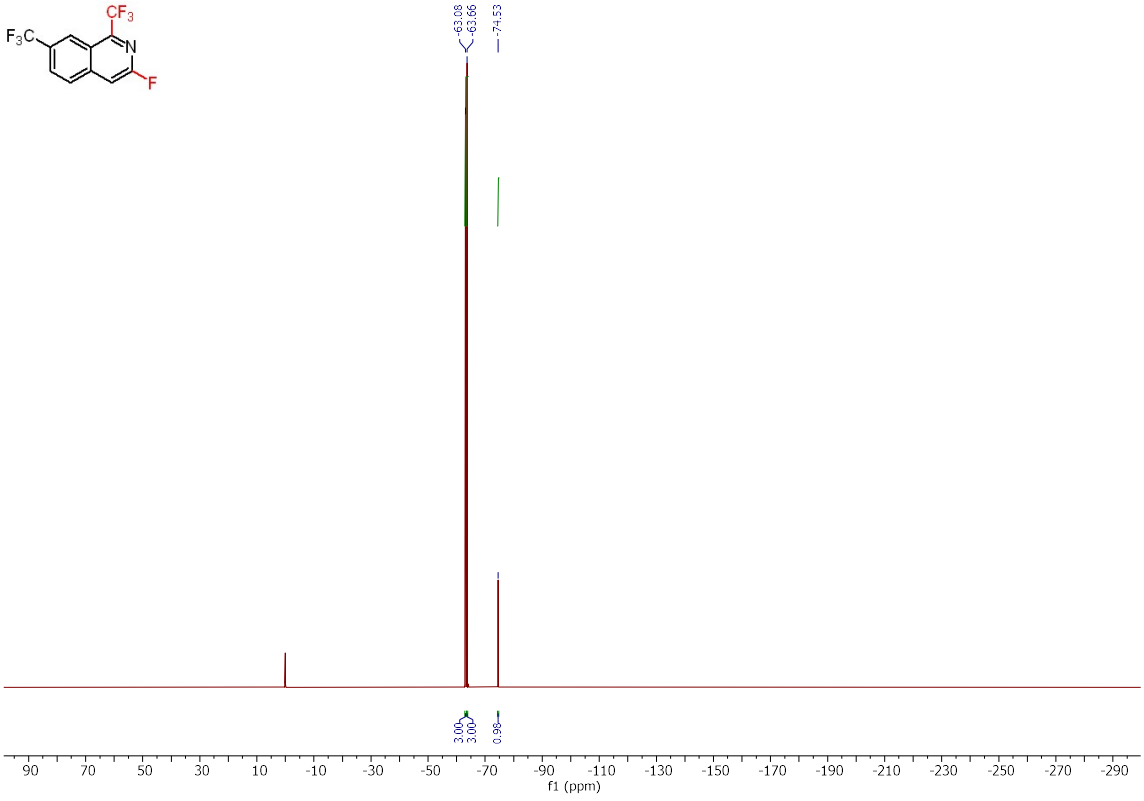
^{1}H NMR spectrum of **2g** ($CDCl_3$, 400 MHz)



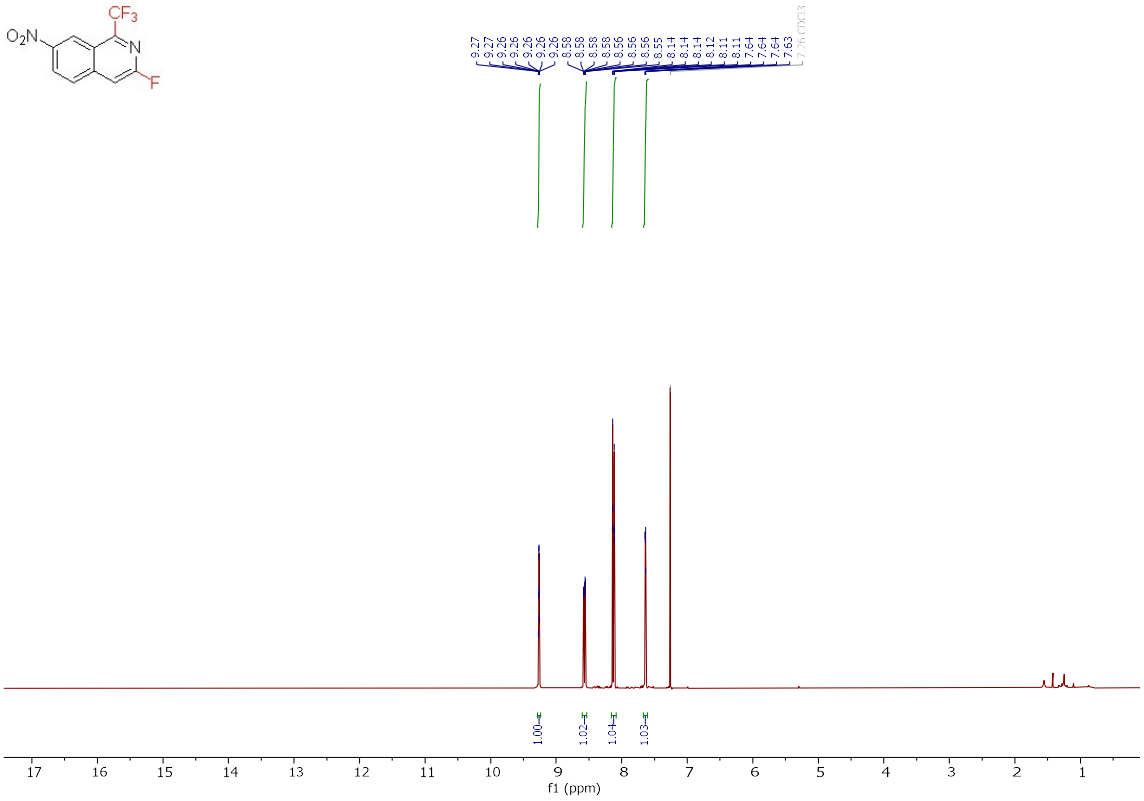
^{13}C NMR spectrum of **2g** ($CDCl_3$, 101 MHz)



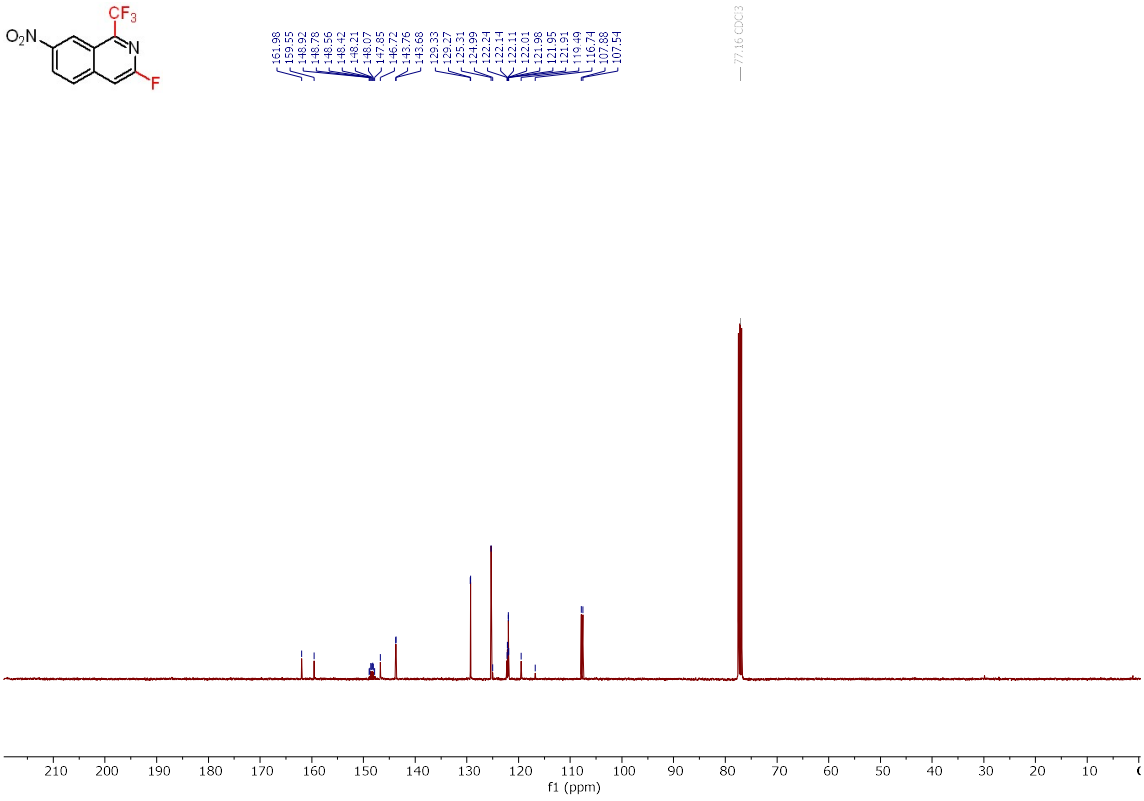
^{19}F NMR spectrum of **2g** ($CDCl_3$, 376 MHz)



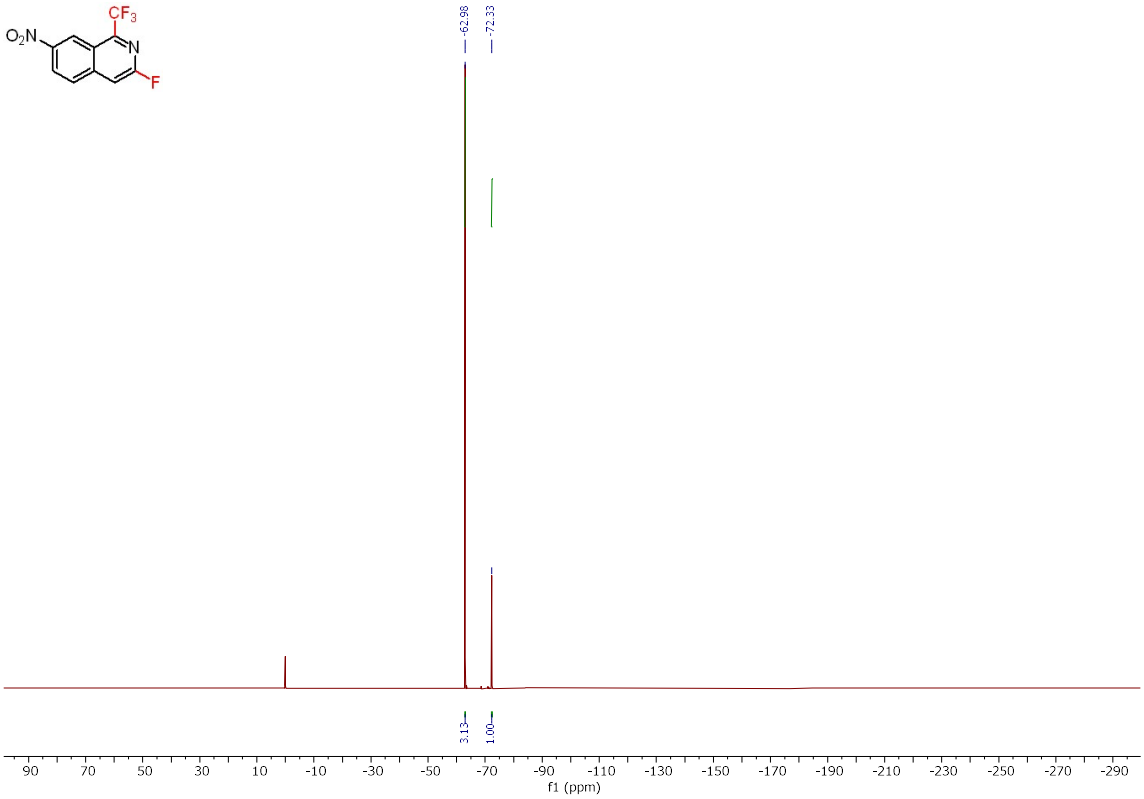
^{1}H NMR spectrum of **2h** ($CDCl_3$, 400 MHz)



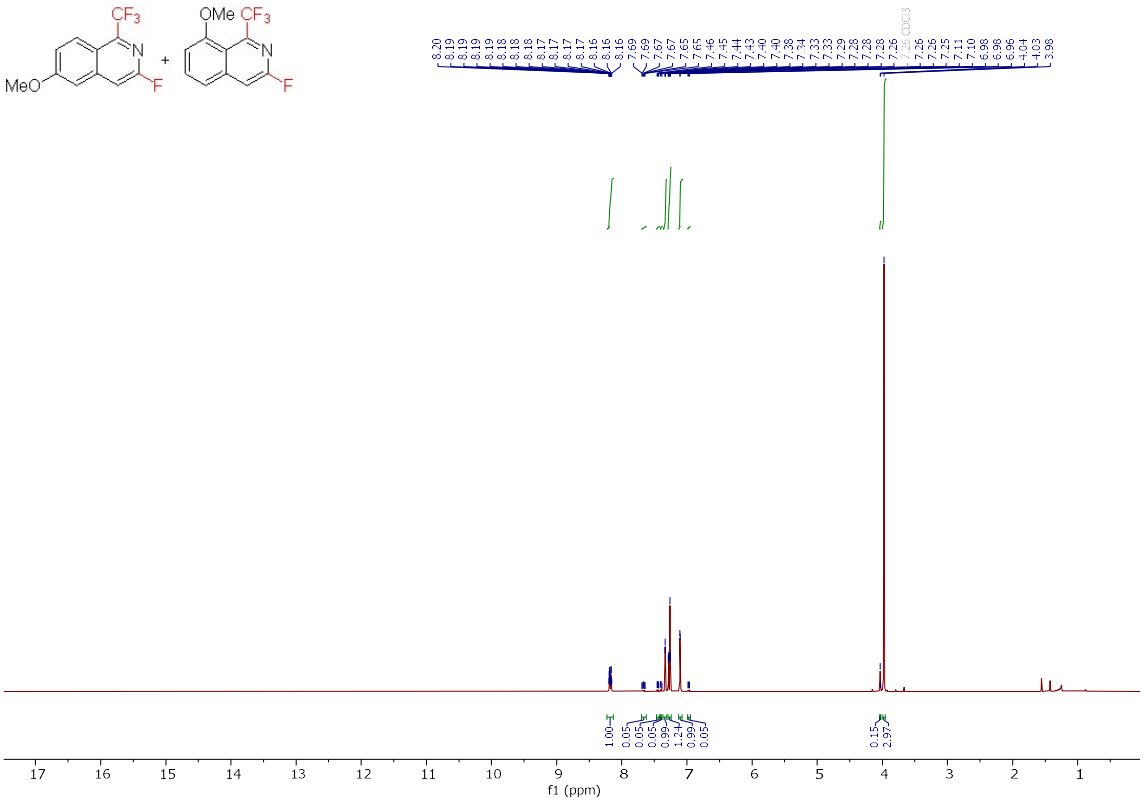
^{13}C NMR spectrum of **2h** ($CDCl_3$, 101 MHz)



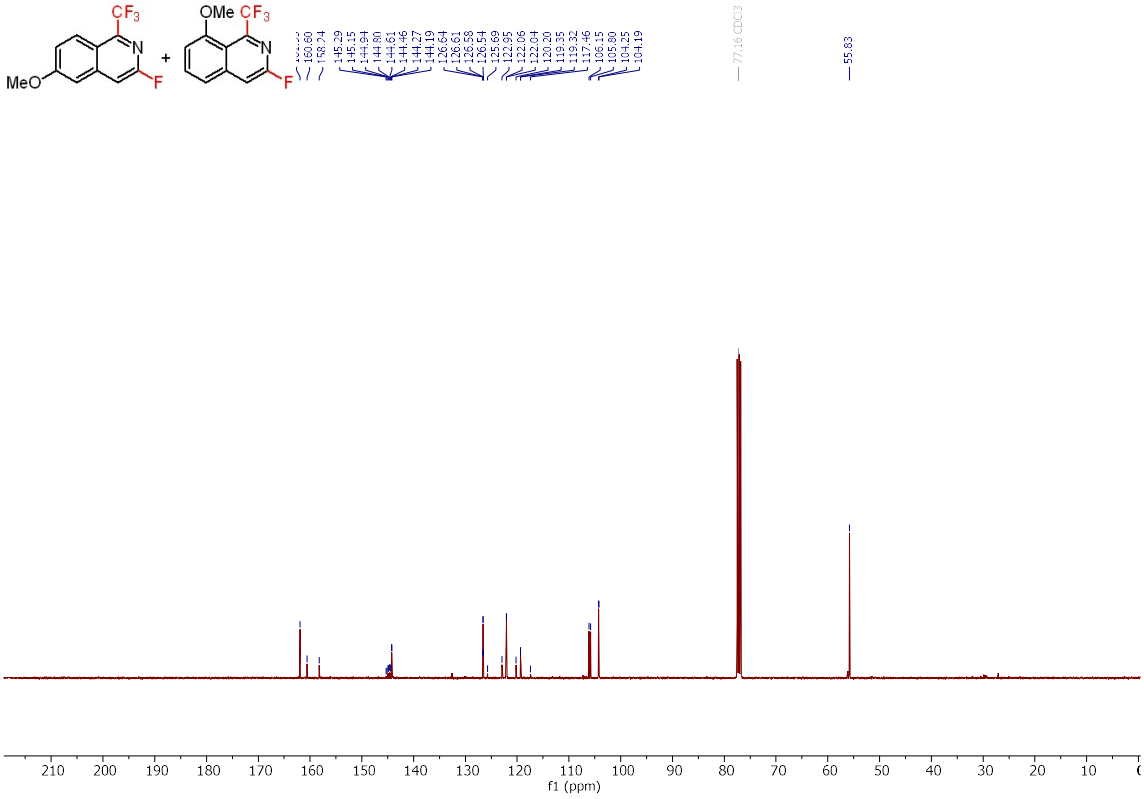
^{19}F NMR spectrum of **2h** ($CDCl_3$, 376 MHz)



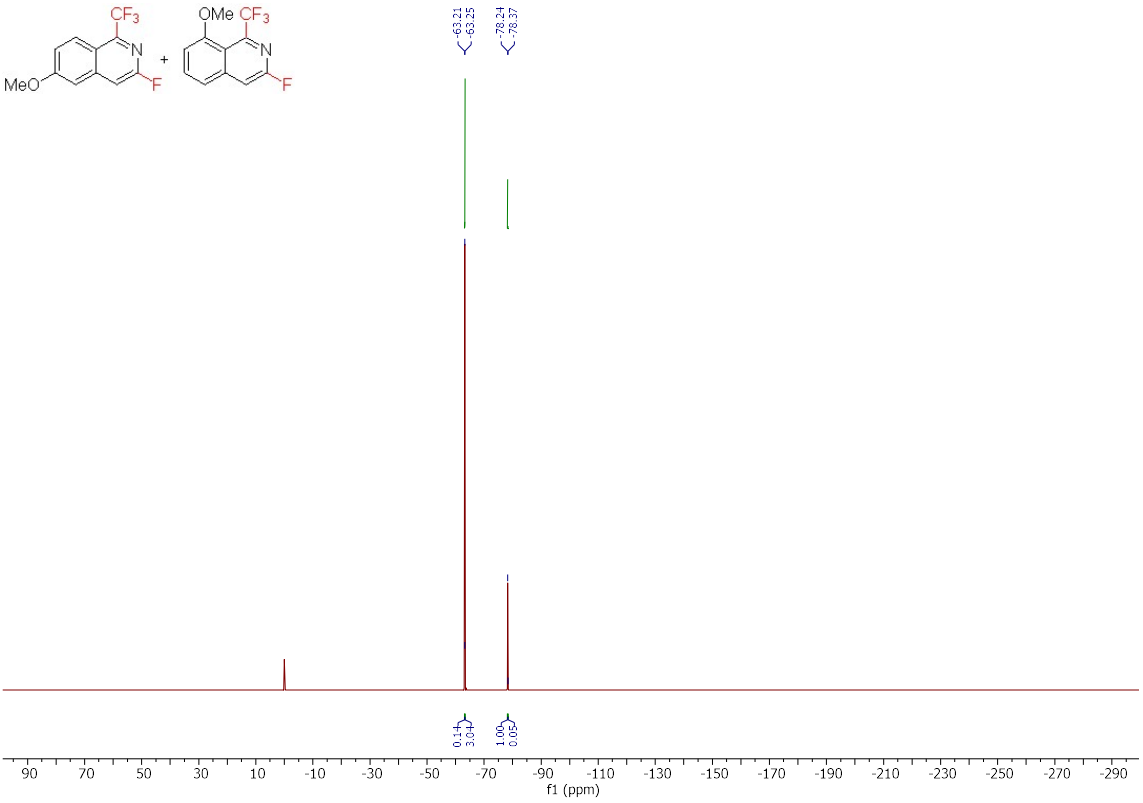
^{1}H NMR spectrum of **2i** + **2i'** ($CDCl_3$, 400 MHz)



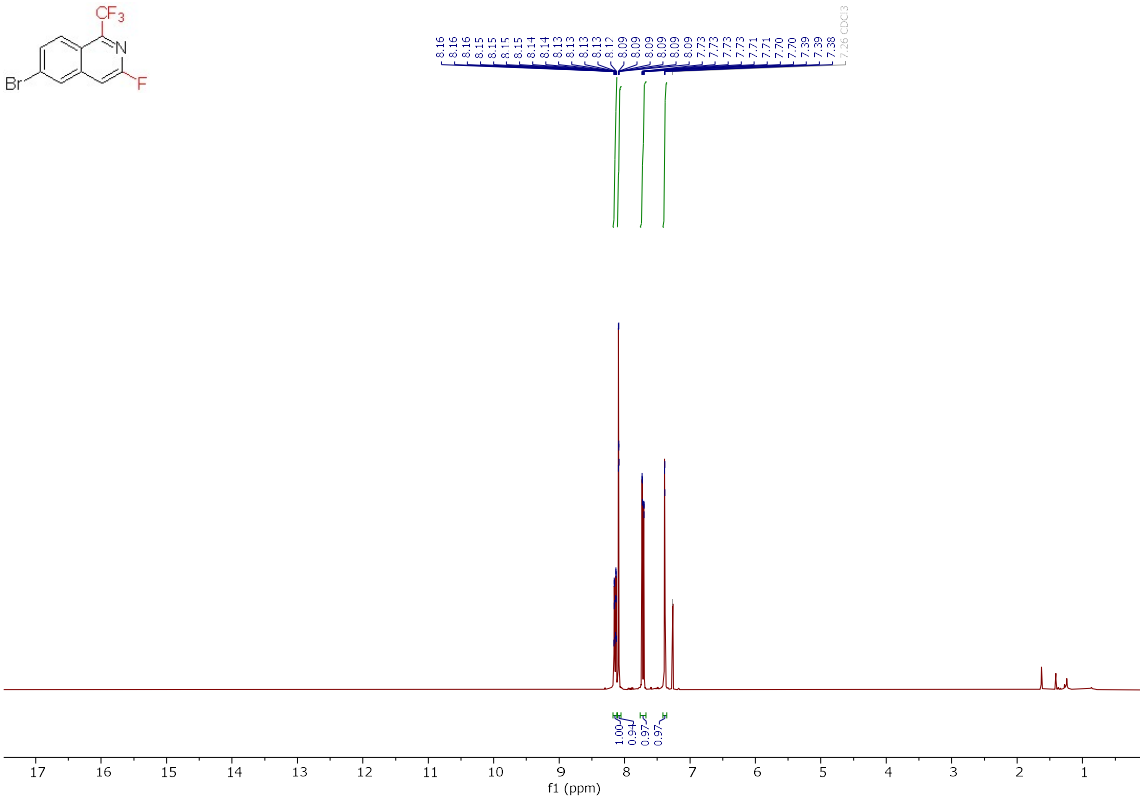
^{13}C NMR spectrum of **2i** + **2i'** ($CDCl_3$, 101 MHz)



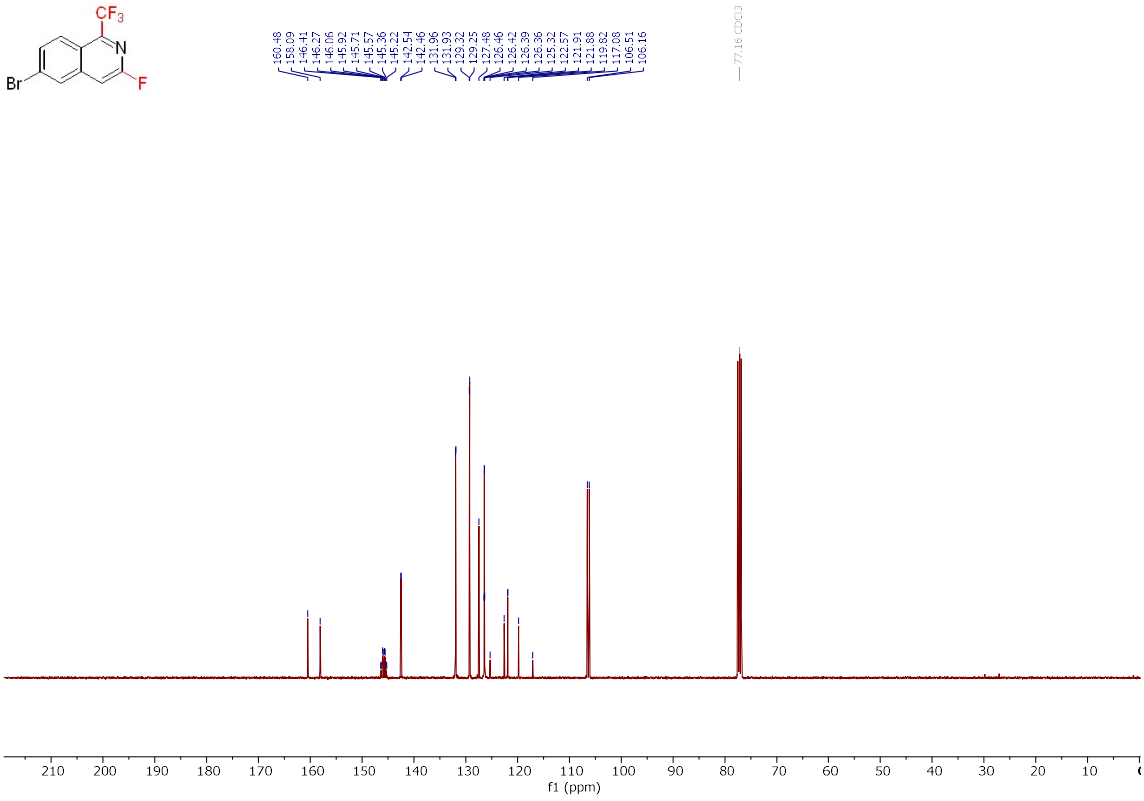
^{19}F NMR spectrum of **2i** + **2i'** ($CDCl_3$, 376 MHz)



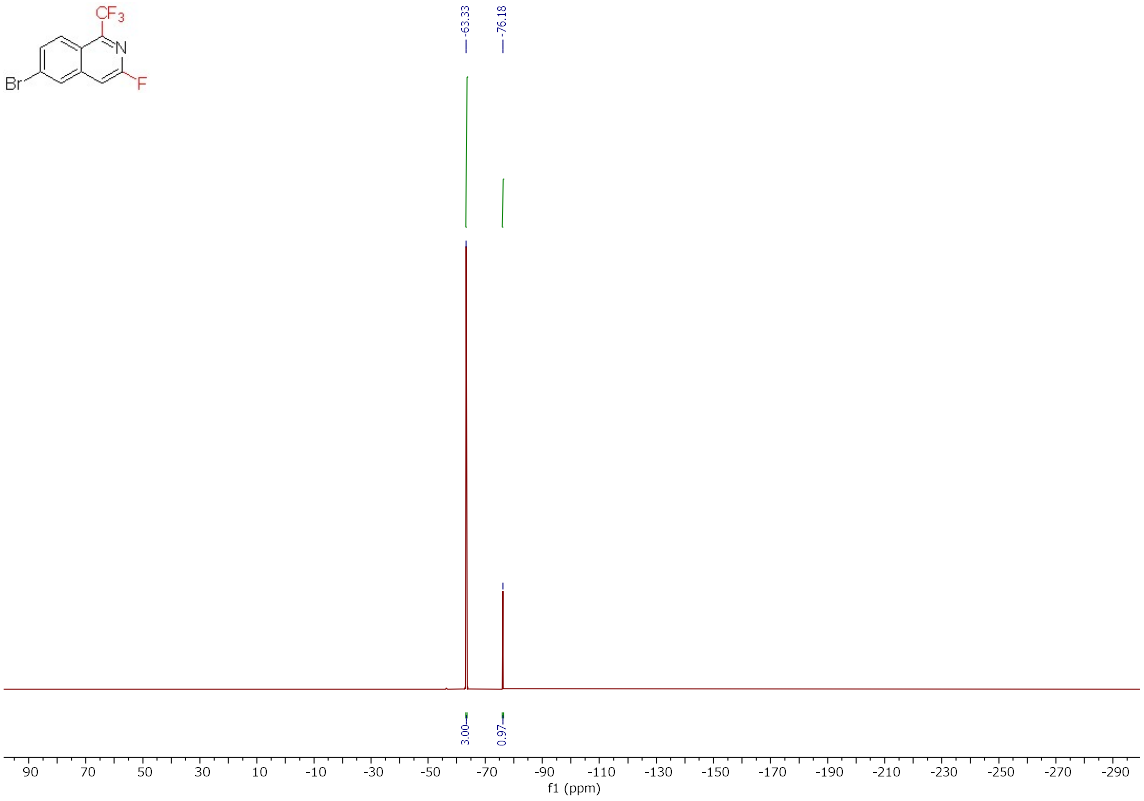
^{1}H NMR spectrum of **2j** ($CDCl_3$, 400 MHz)



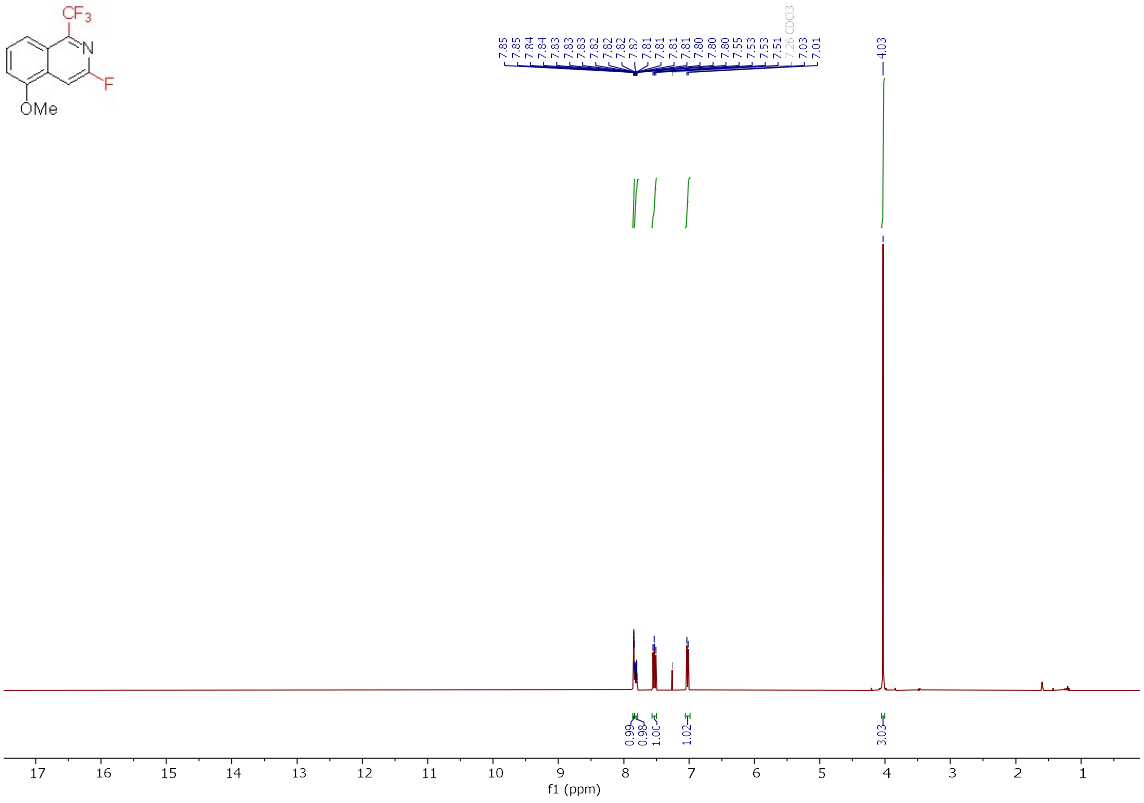
^{13}C NMR spectrum of **2j** ($CDCl_3$, 101 MHz)



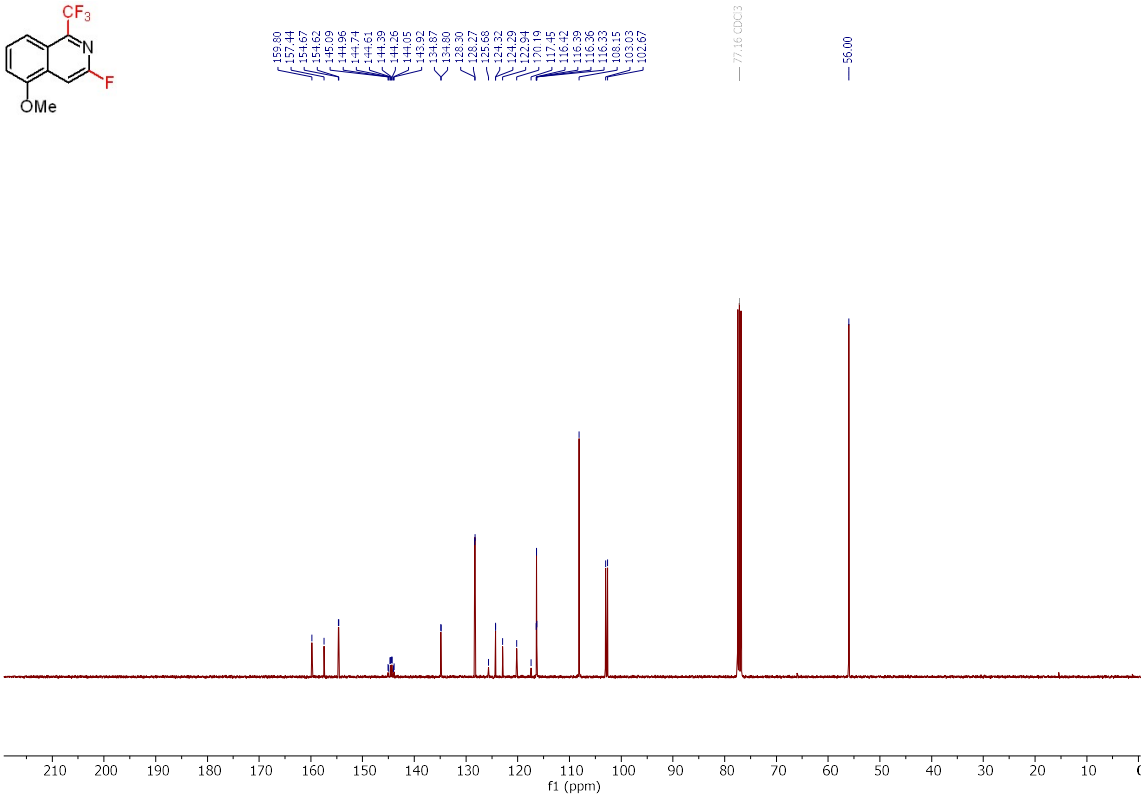
^{19}F NMR spectrum of **2j** ($CDCl_3$, 376 MHz)



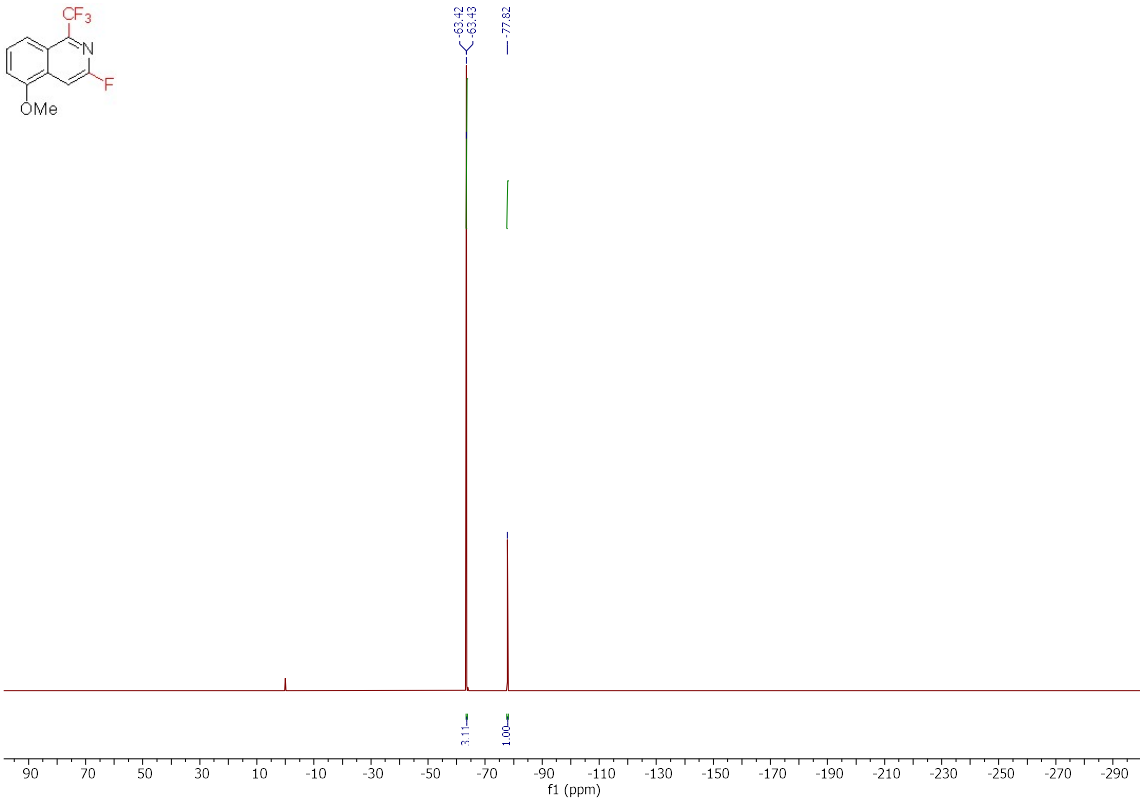
^{1}H NMR spectrum of **2k** ($CDCl_3$, 400 MHz)



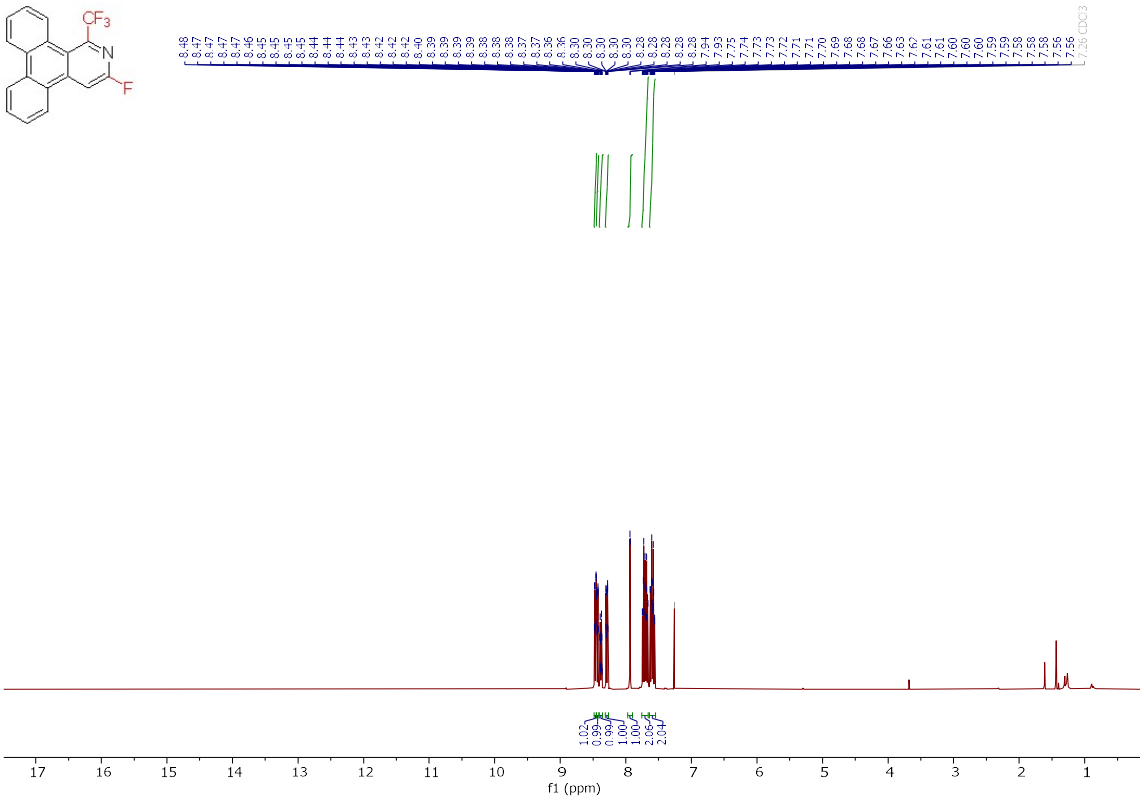
^{13}C NMR spectrum of **2k** ($CDCl_3$, 101 MHz)



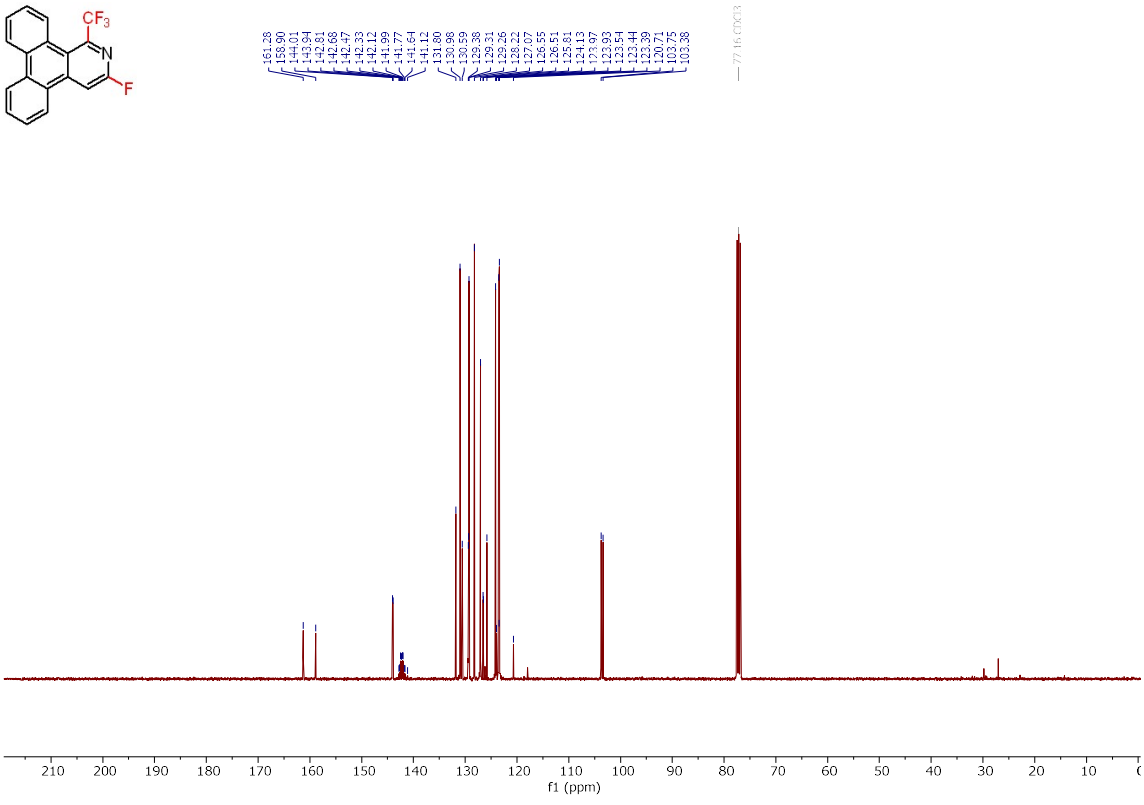
^{19}F NMR spectrum of **2k** ($CDCl_3$, 376 MHz)



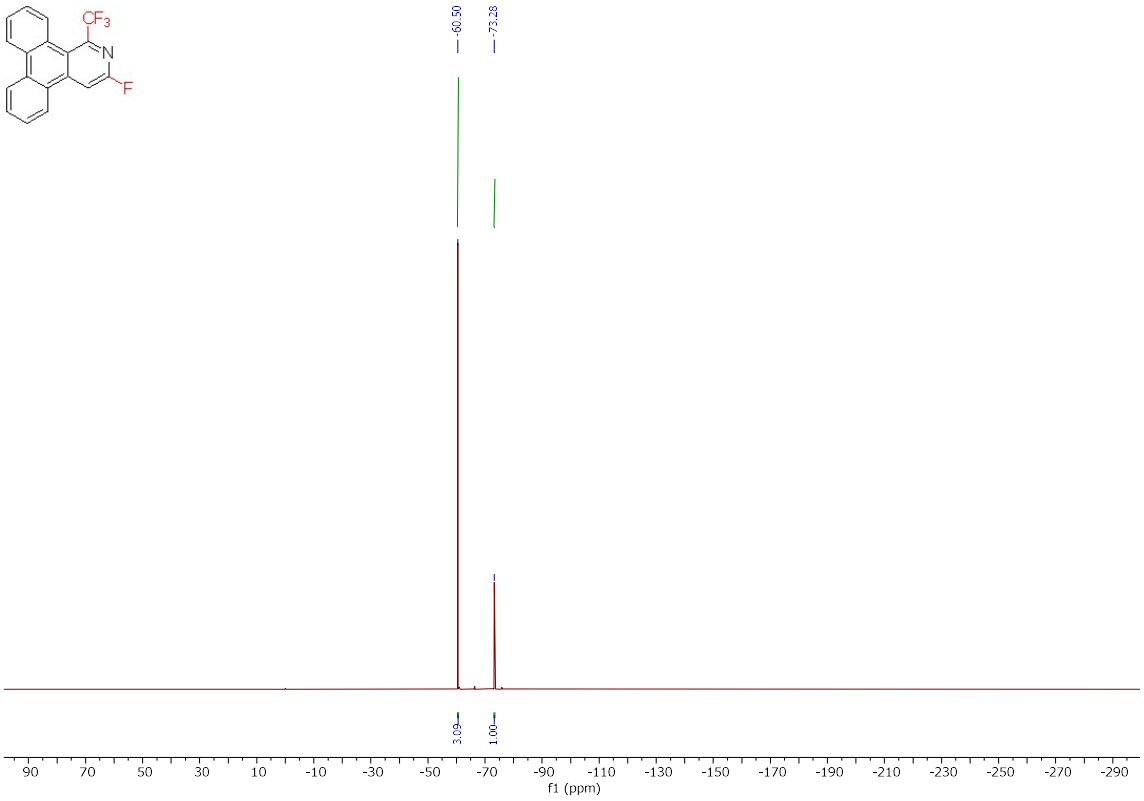
^{1}H NMR spectrum of **2l** ($CDCl_3$, 400 MHz)



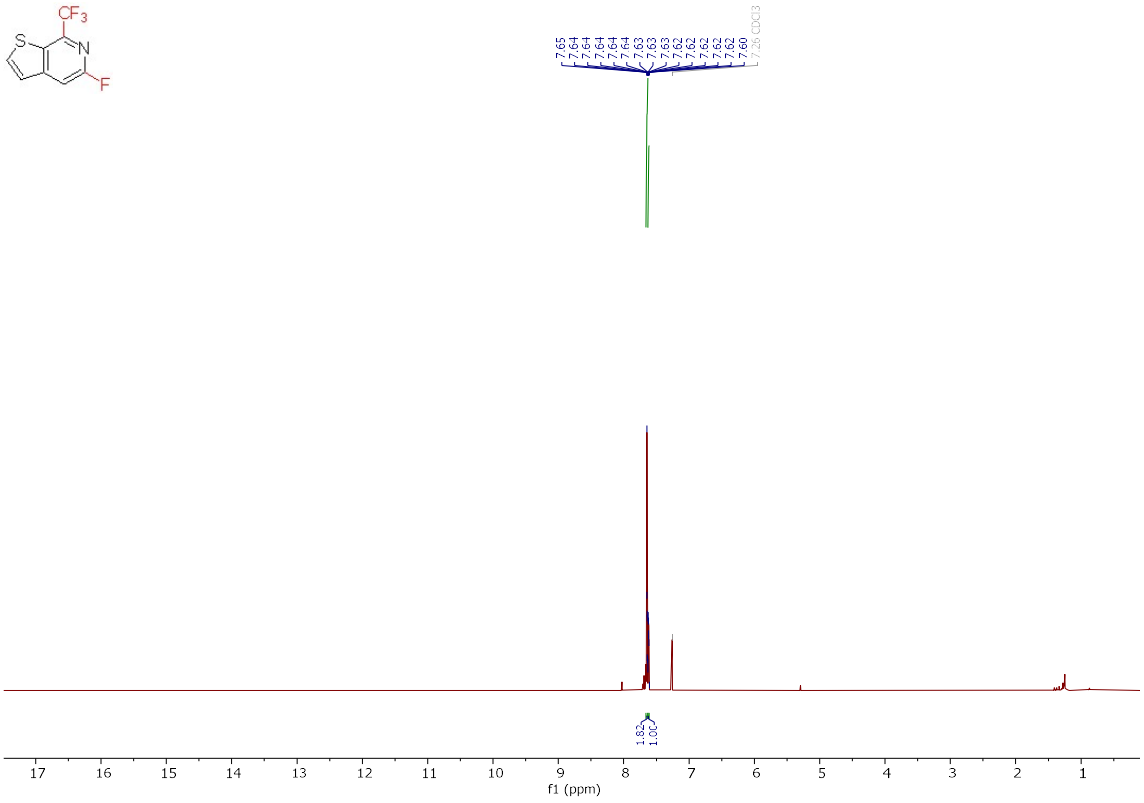
^{13}C NMR spectrum of **2l** ($CDCl_3$, 101 MHz)



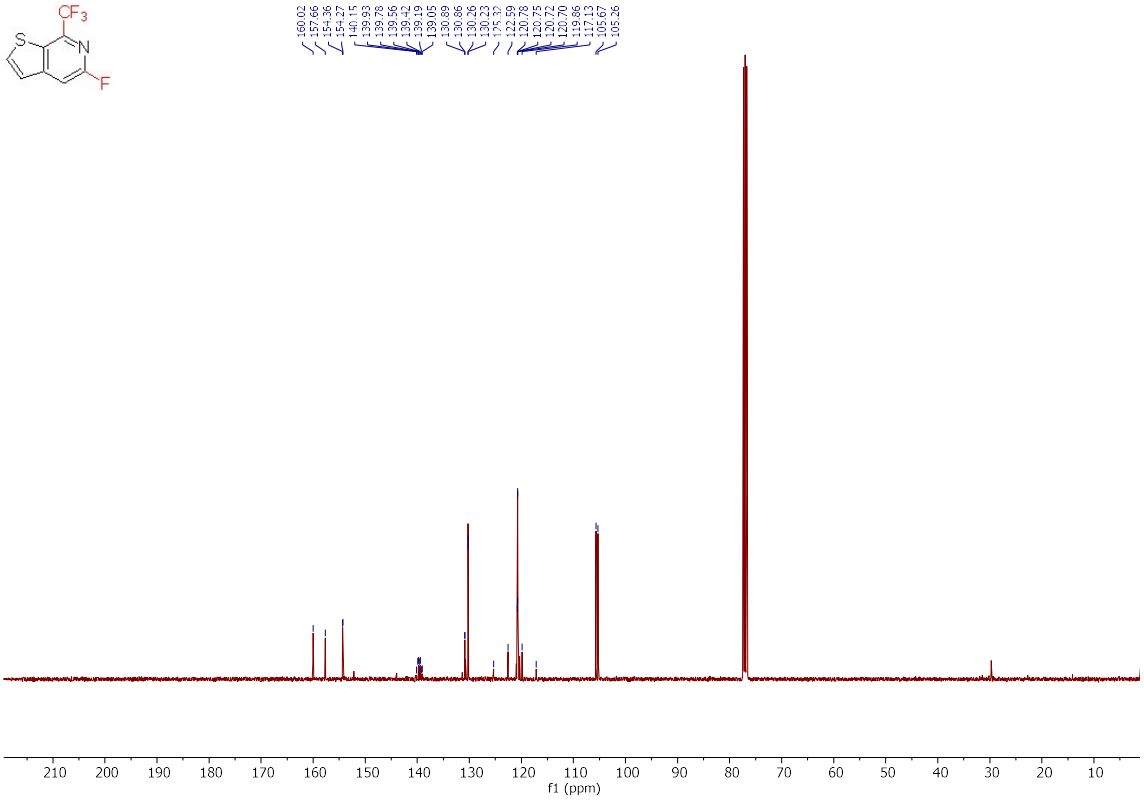
^{19}F NMR spectrum of **2l** ($CDCl_3$, 376 MHz)



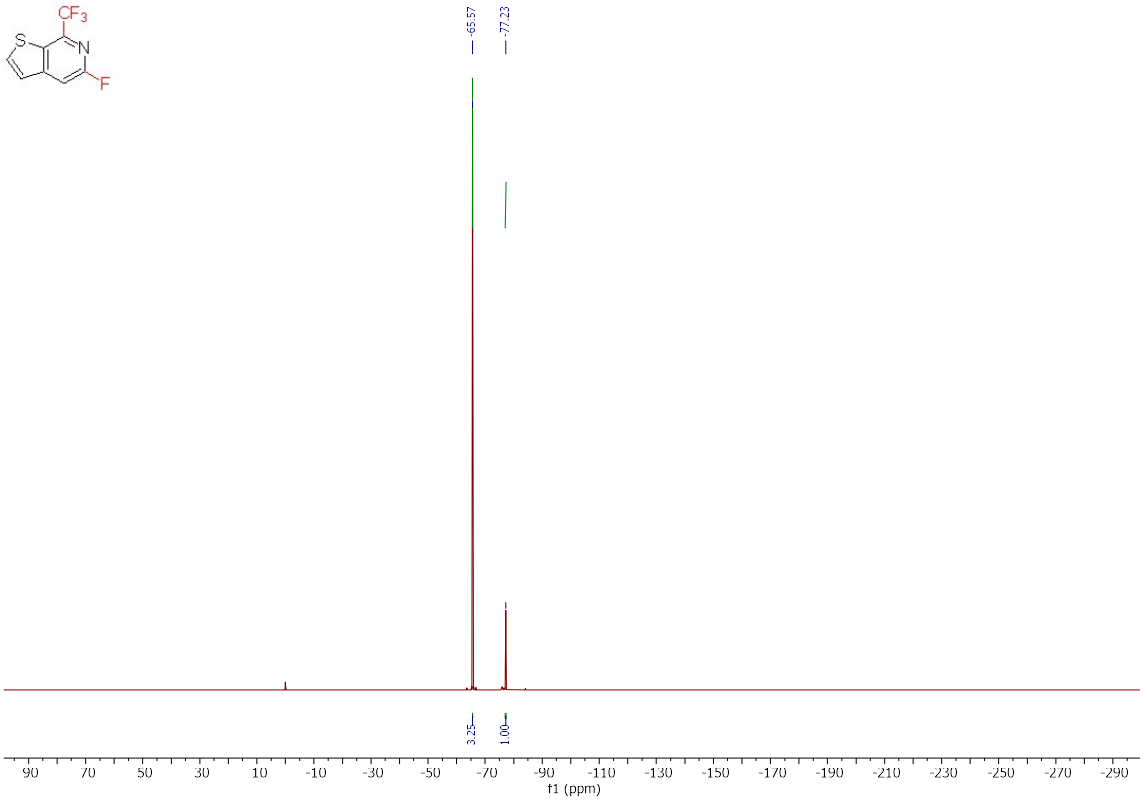
^{1}H NMR spectrum of **2m** ($CDCl_3$, 400 MHz)



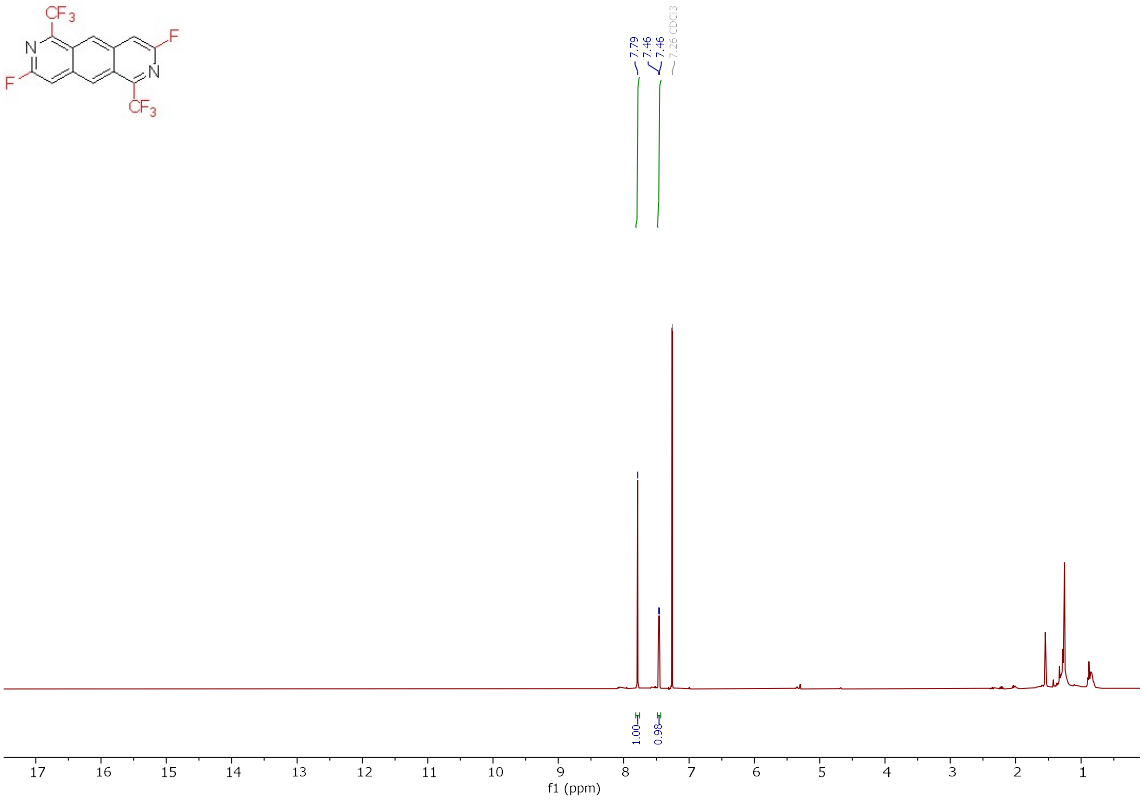
^{13}C NMR spectrum of **2m** ($CDCl_3$, 101 MHz)



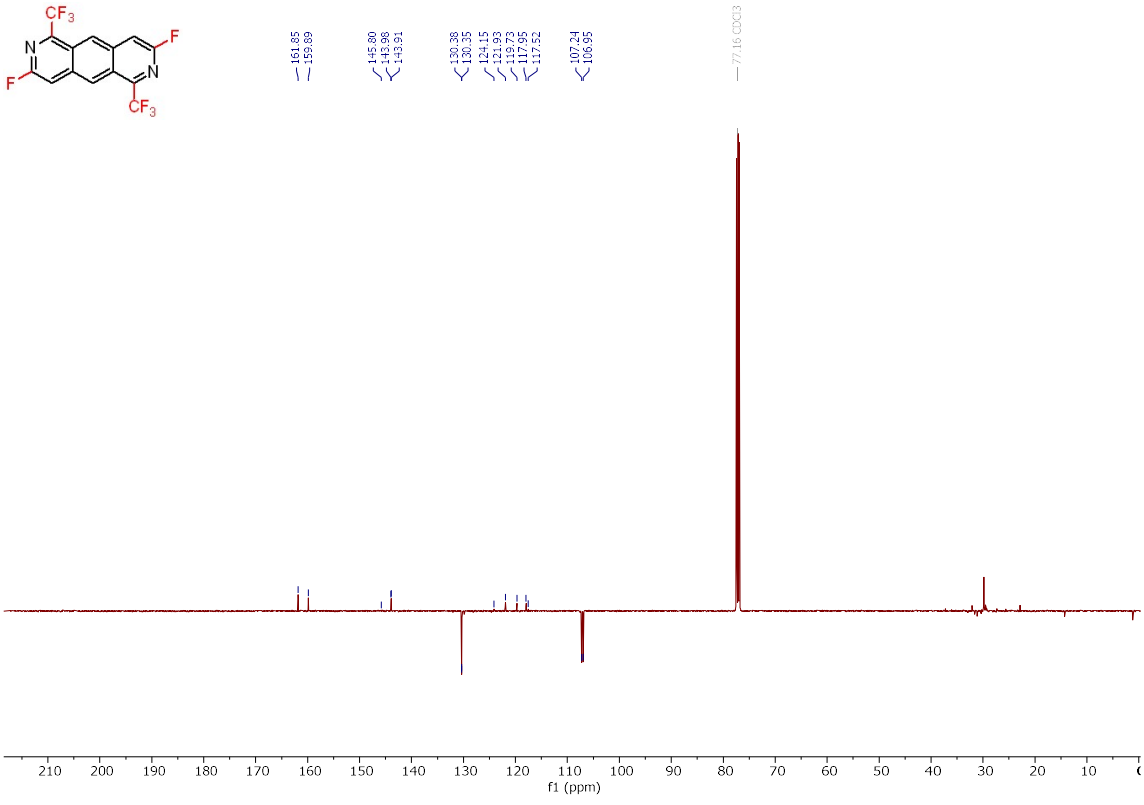
^{19}F NMR spectrum of **2m** ($CDCl_3$, 376 MHz)



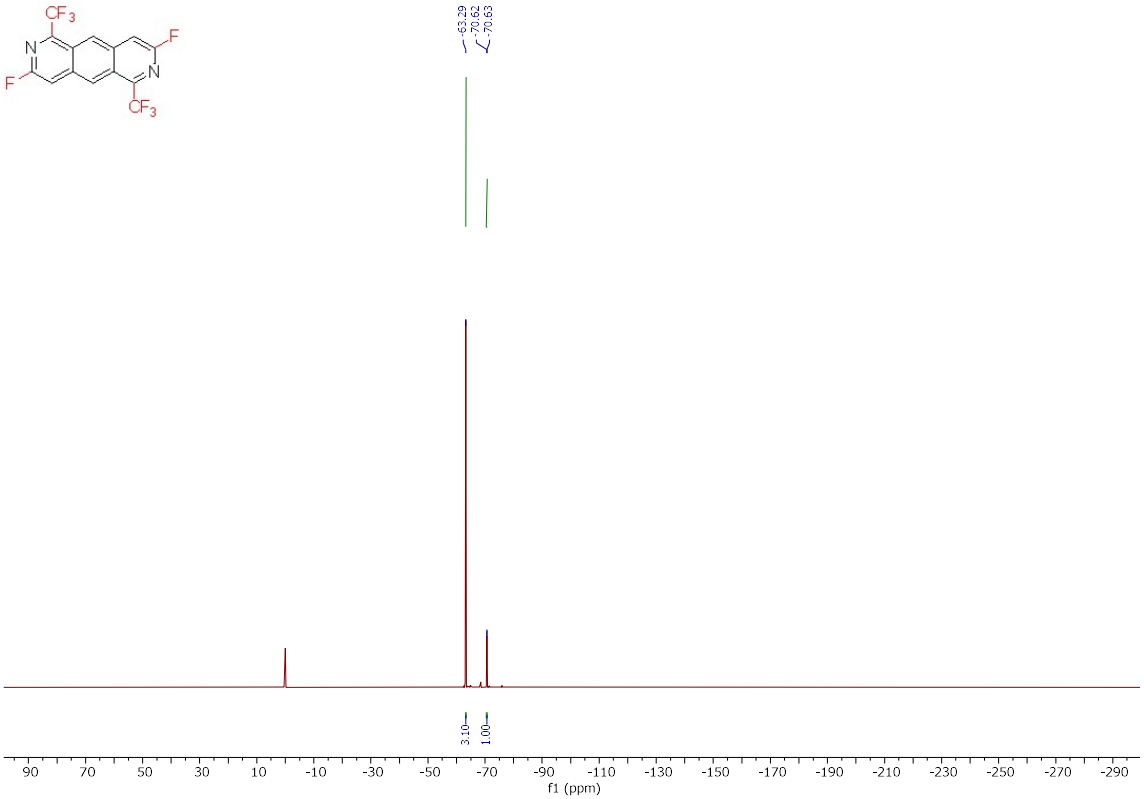
^{1}H NMR spectrum of **2o** ($CDCl_3$, 400 MHz)



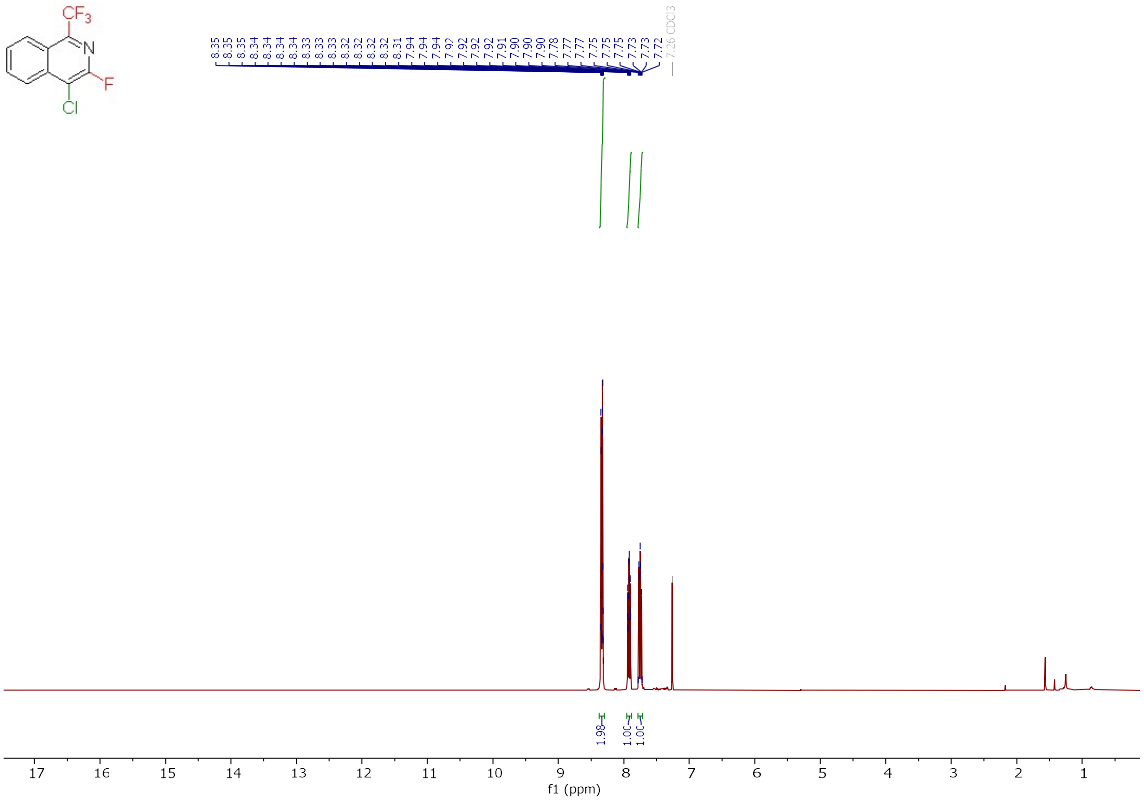
^{13}C NMR spectrum of **2o** ($CDCl_3$, 101 MHz)



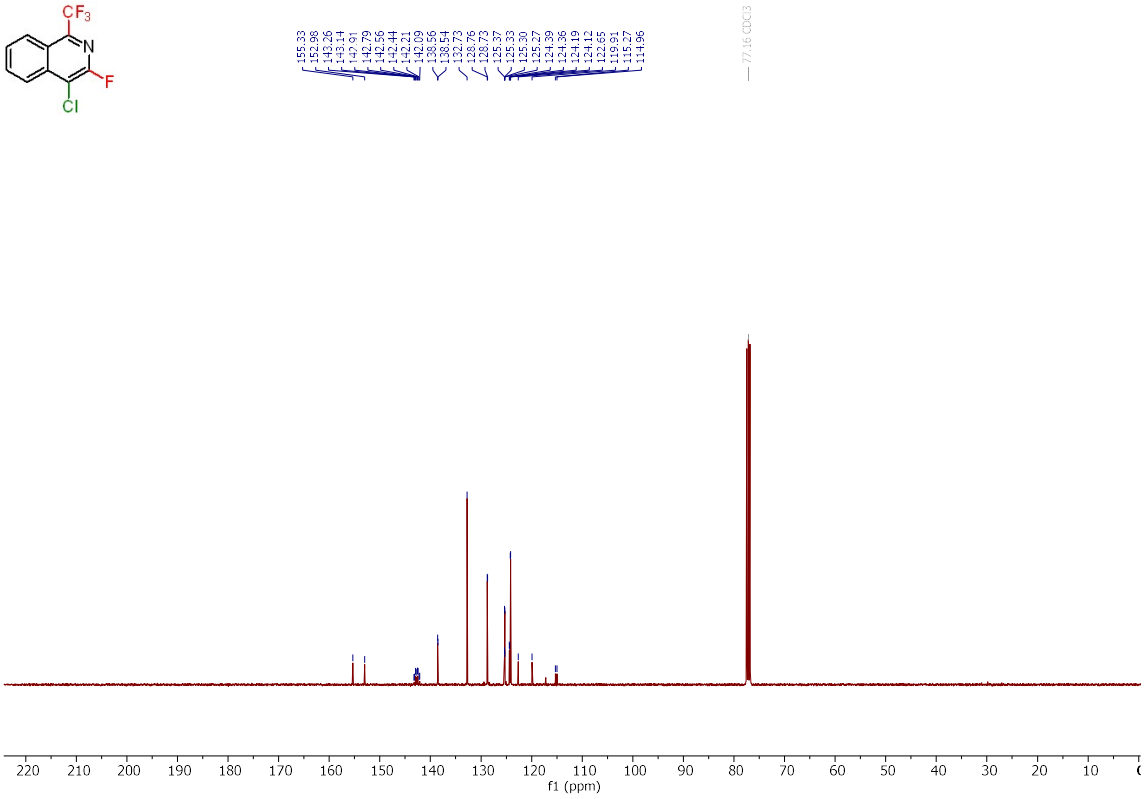
^{19}F NMR spectrum of **2o** ($CDCl_3$, 376 MHz)



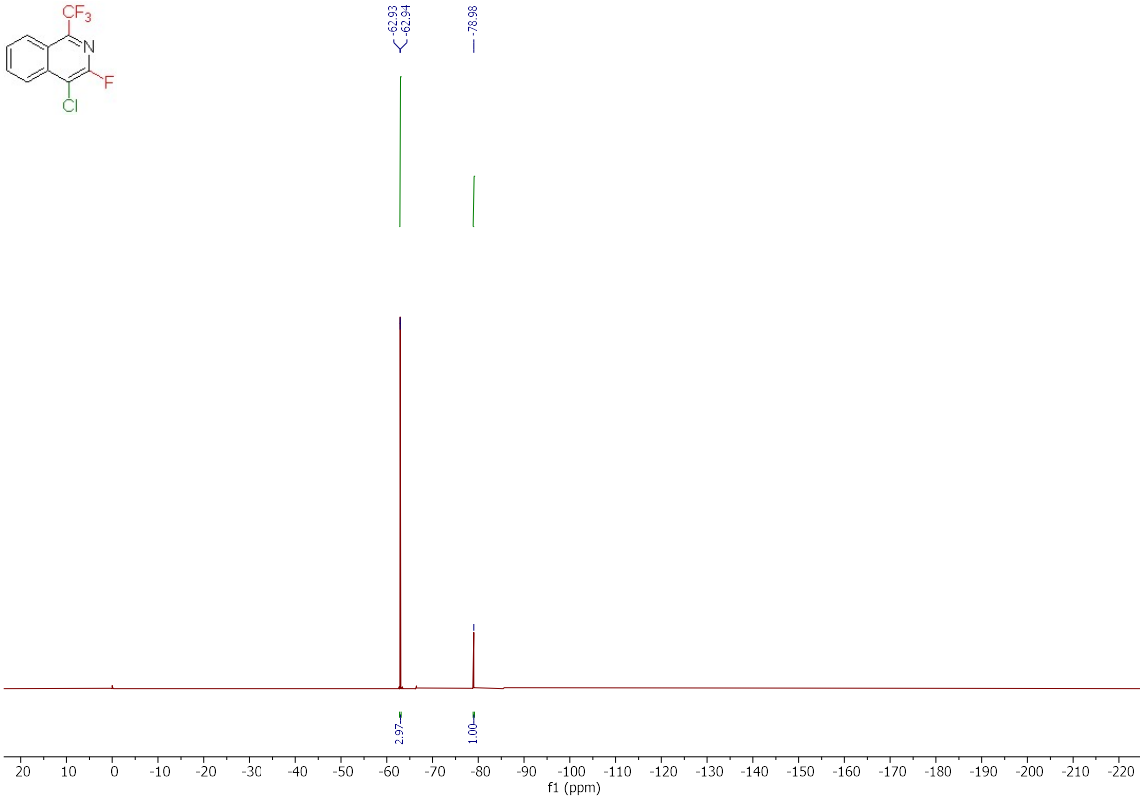
^{1}H NMR spectrum of **2p** ($CDCl_3$, 400 MHz)



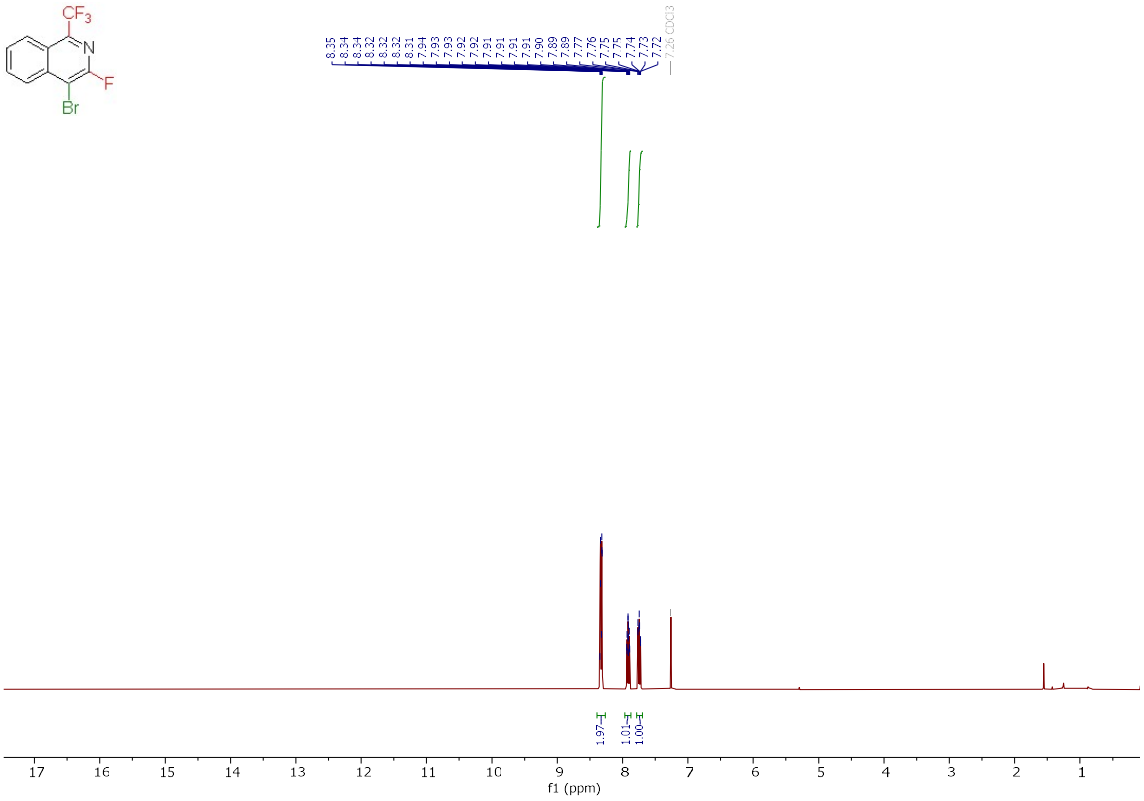
^{13}C NMR spectrum of **2p** ($CDCl_3$, 101 MHz)



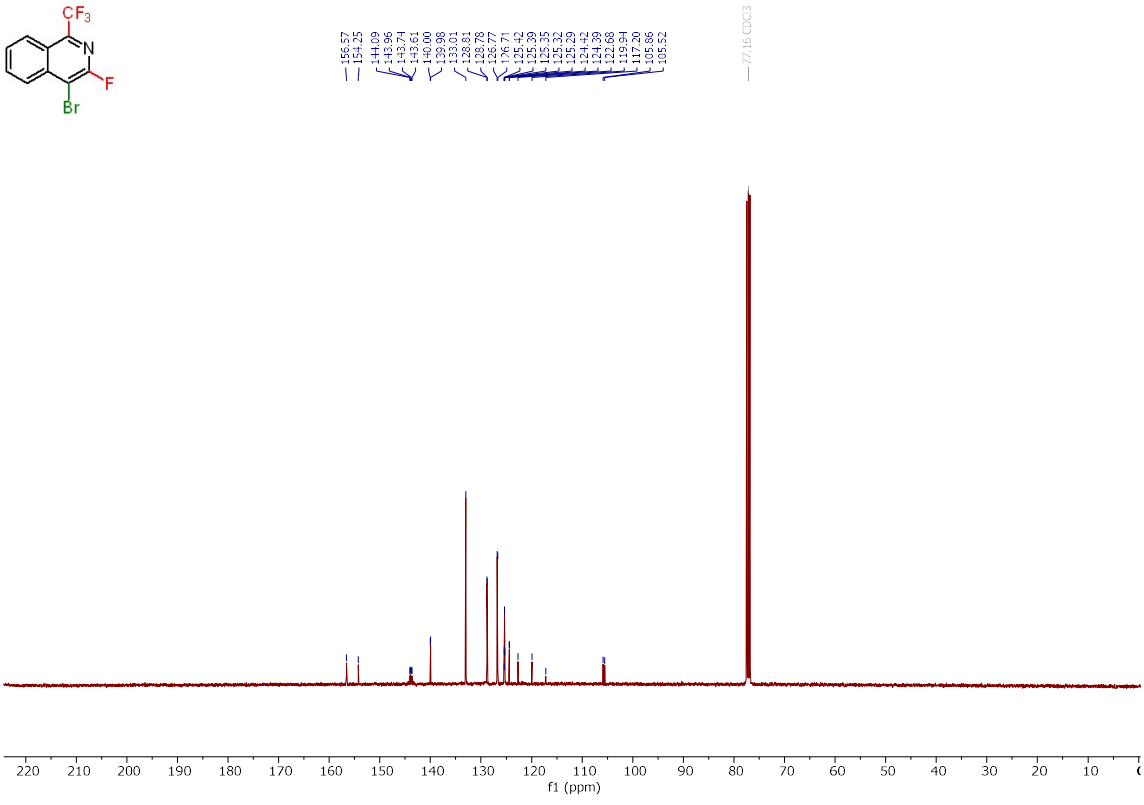
^{19}F NMR spectrum of **2p** ($CDCl_3$, 376 MHz)



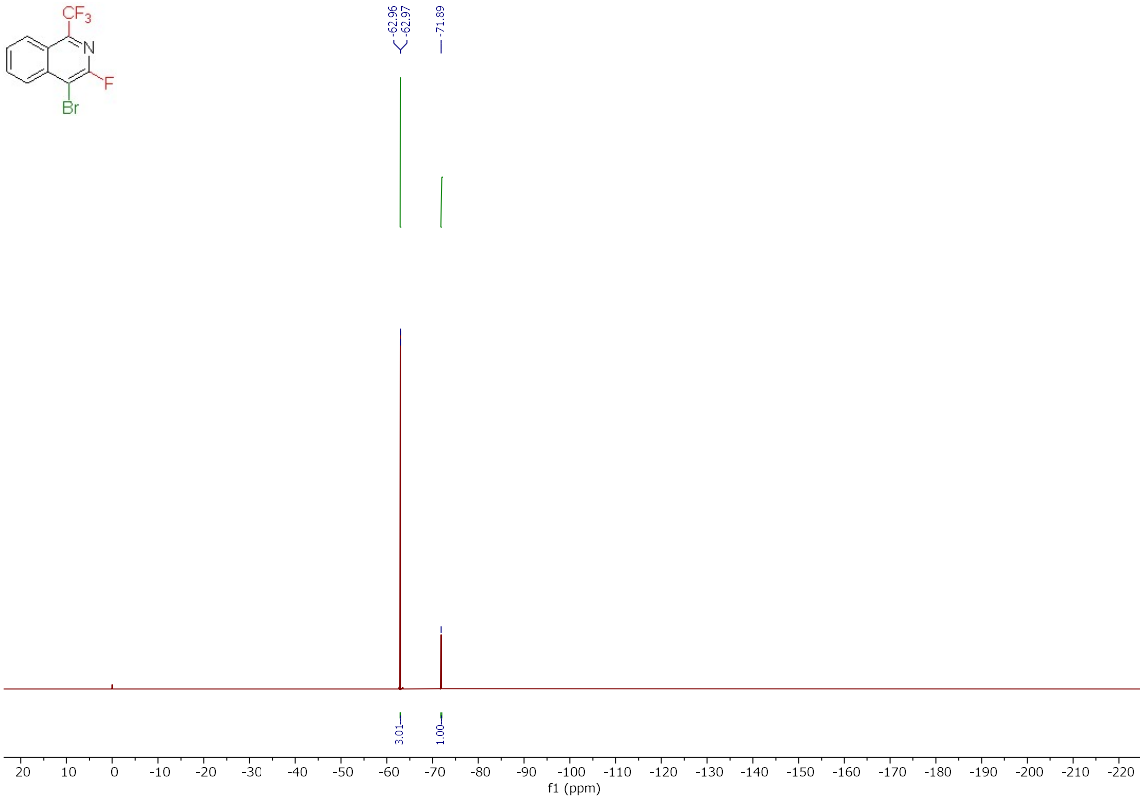
^{1}H NMR spectrum of **2q** ($CDCl_3$, 400 MHz)



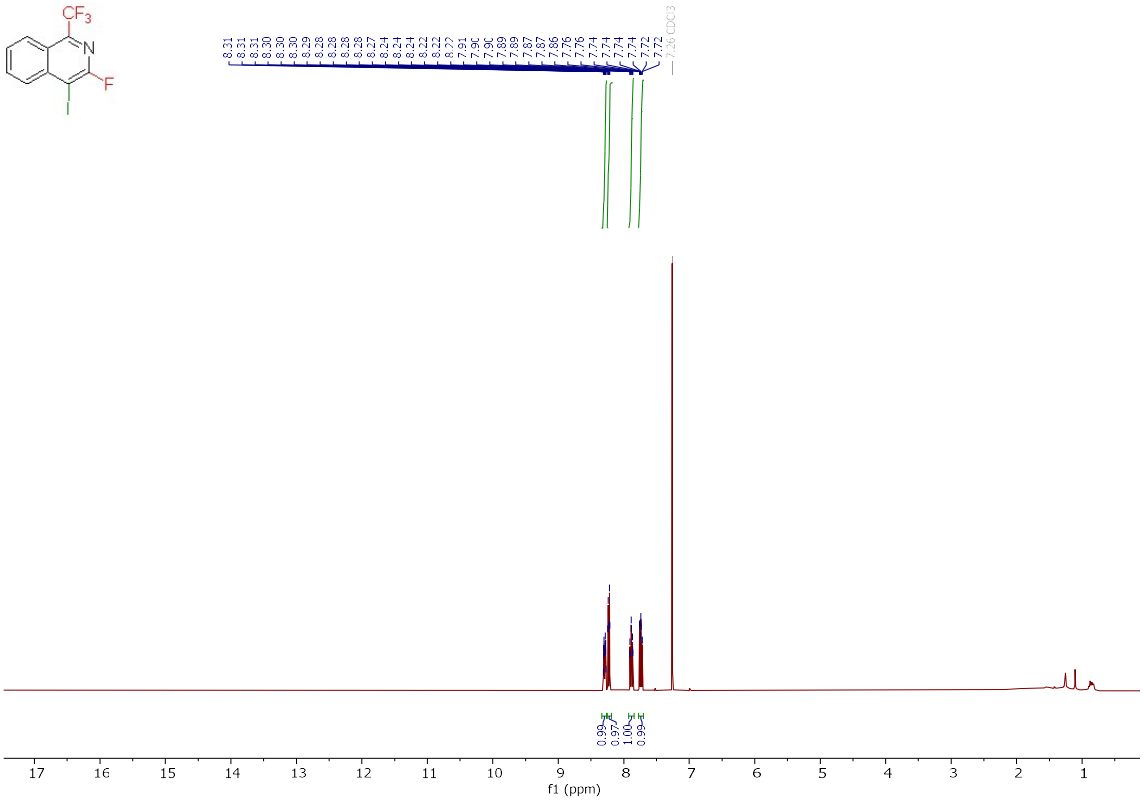
^{13}C NMR spectrum of **2q** ($CDCl_3$, 101 MHz)



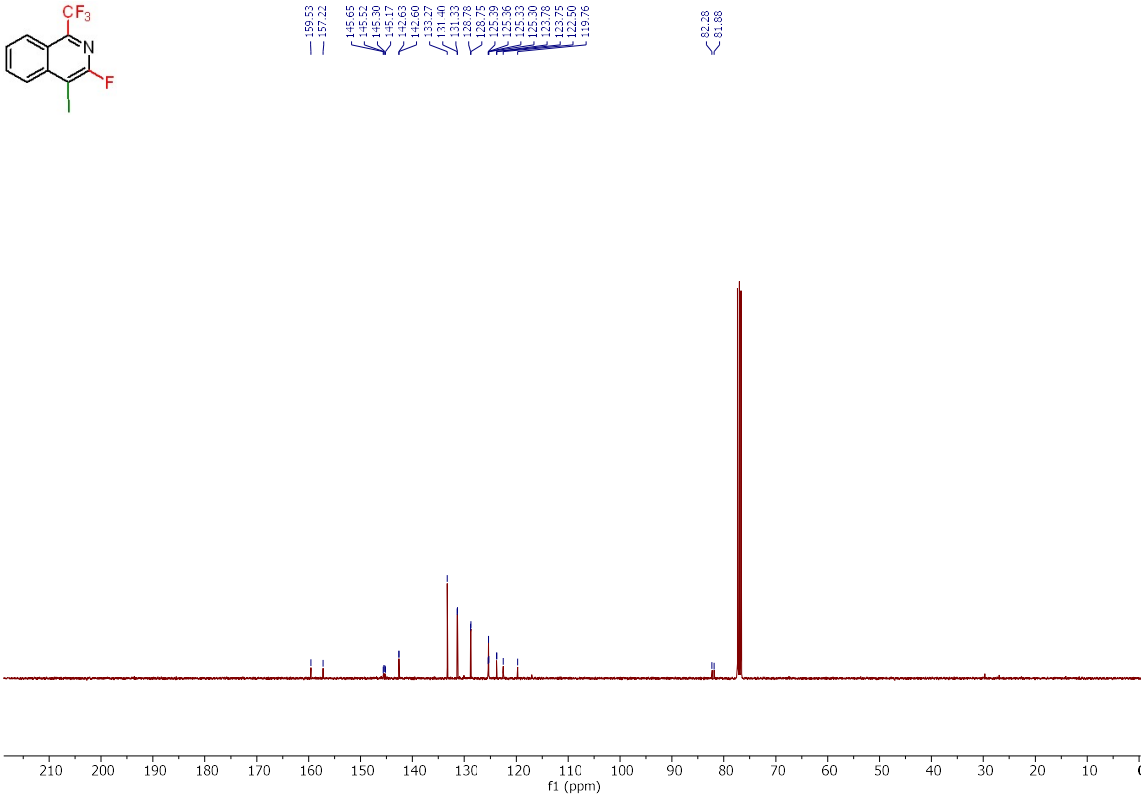
^{19}F NMR spectrum of **2q** ($CDCl_3$, 376 MHz)



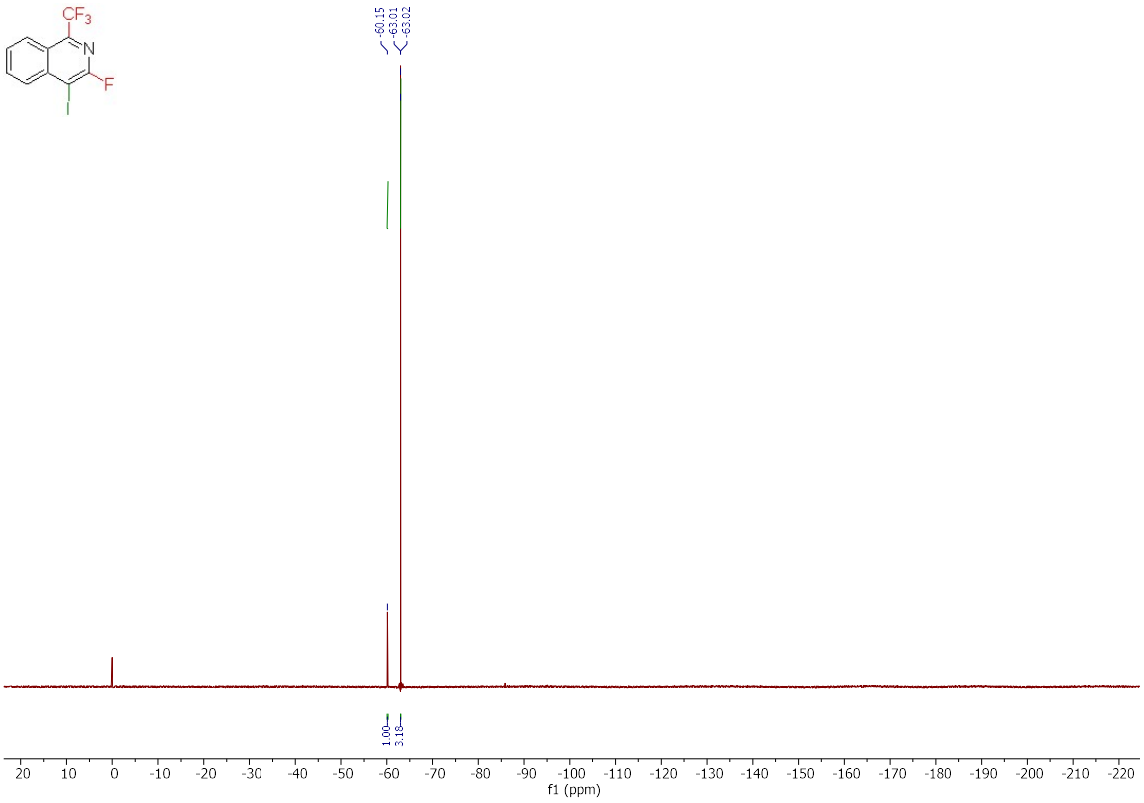
^{1}H NMR spectrum of **2r** ($CDCl_3$, 400 MHz)



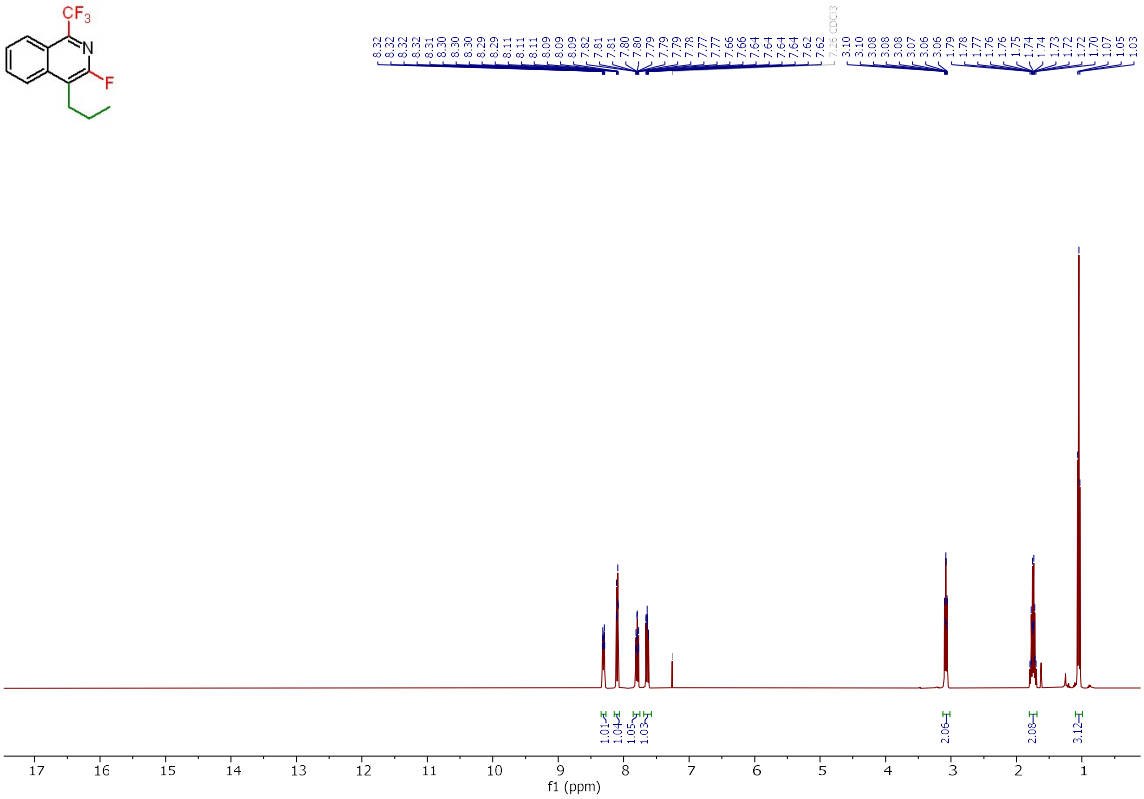
^{13}C NMR spectrum of **2r** ($CDCl_3$, 101 MHz)



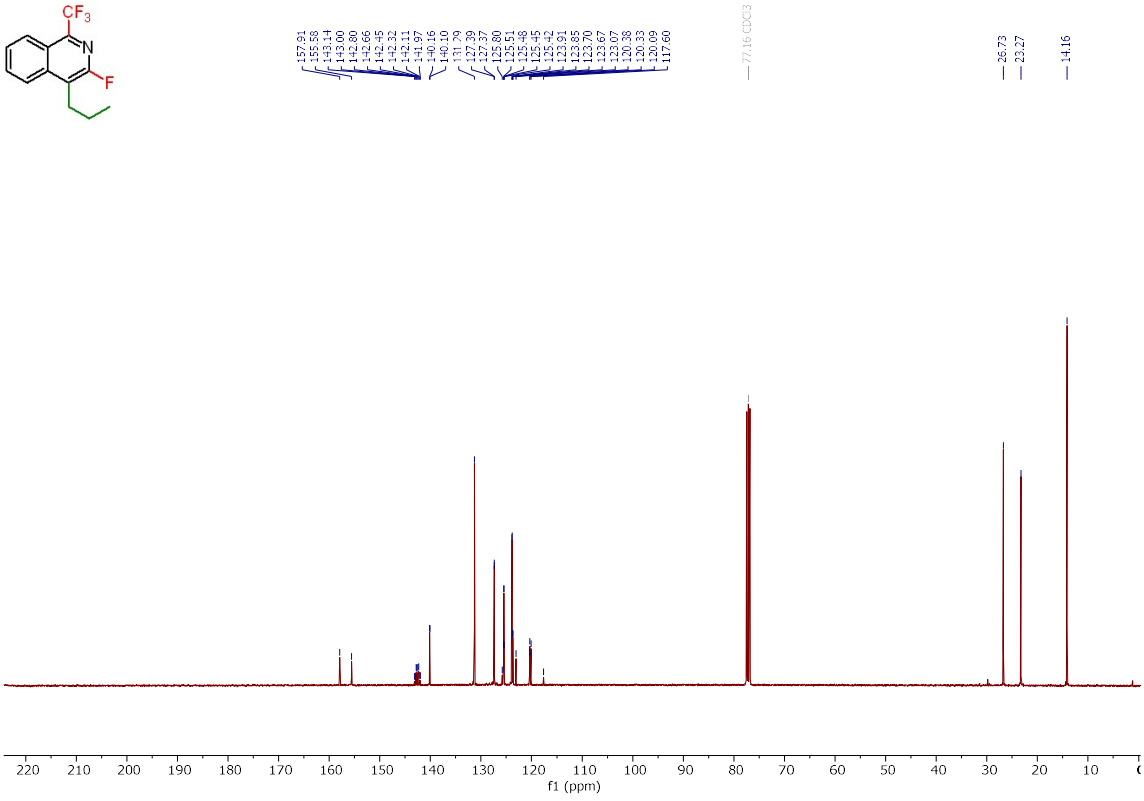
^{19}F NMR spectrum of **2r** ($CDCl_3$, 376 MHz)



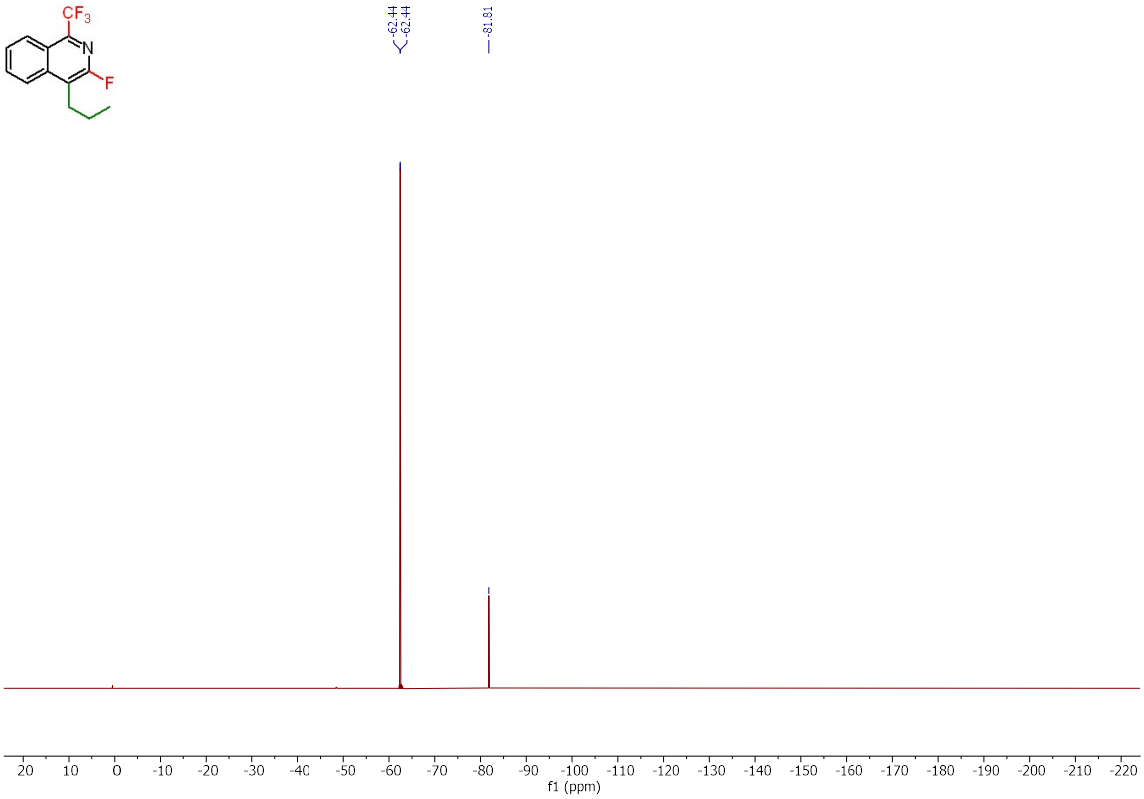
^{1}H NMR spectrum of **2s** ($CDCl_3$, 400 MHz)



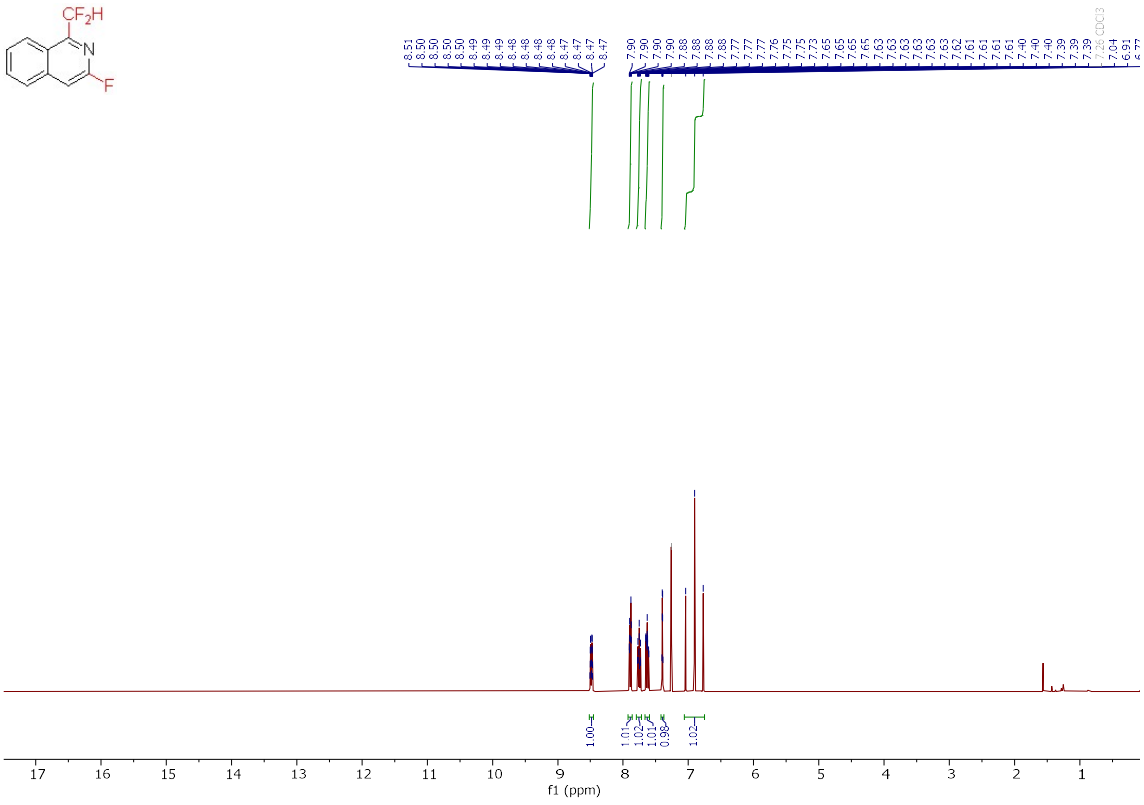
^{13}C NMR spectrum of **2s** ($CDCl_3$, 101 MHz)



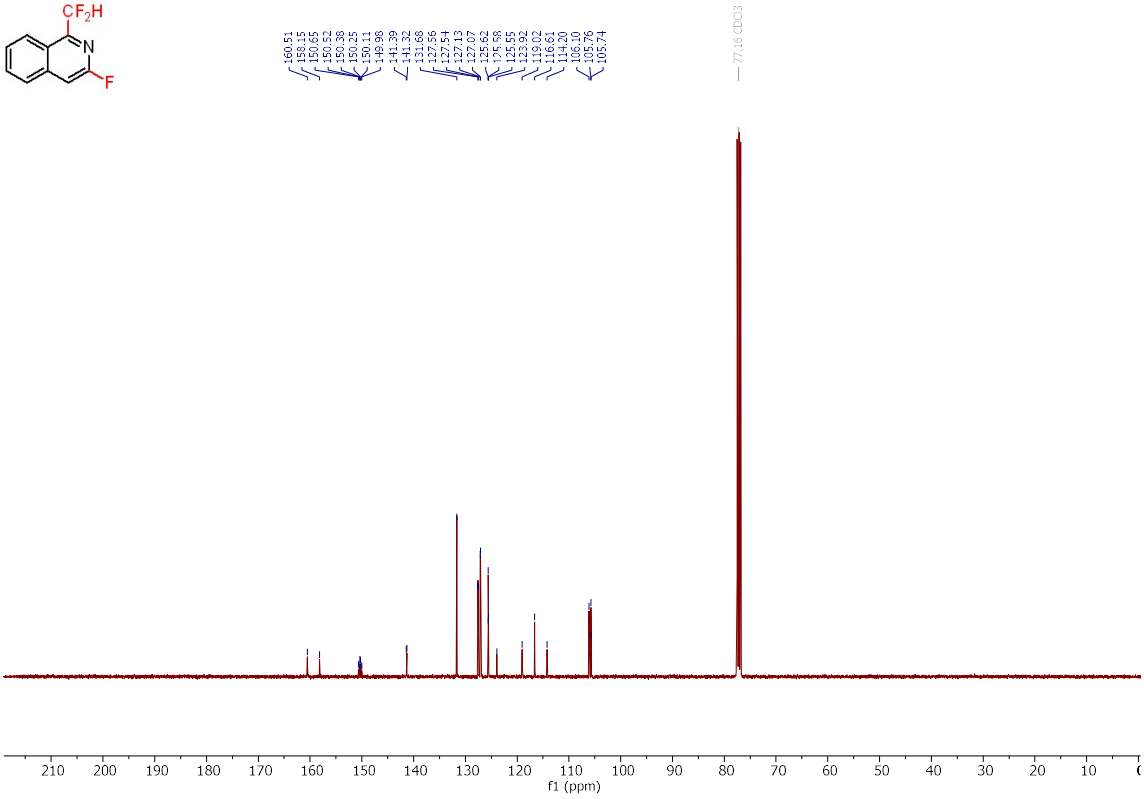
^{19}F NMR spectrum of **2s** ($CDCl_3$, 376 MHz)



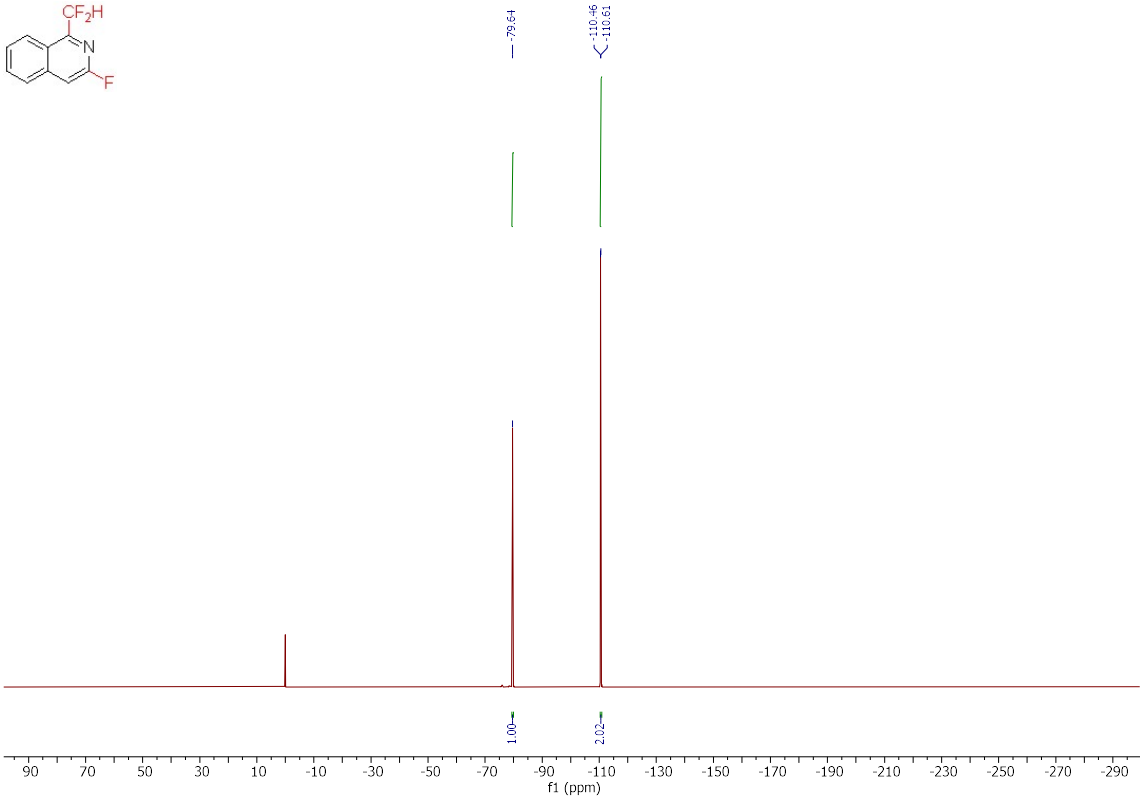
^{1}H NMR spectrum of **2t** ($CDCl_3$, 400 MHz)



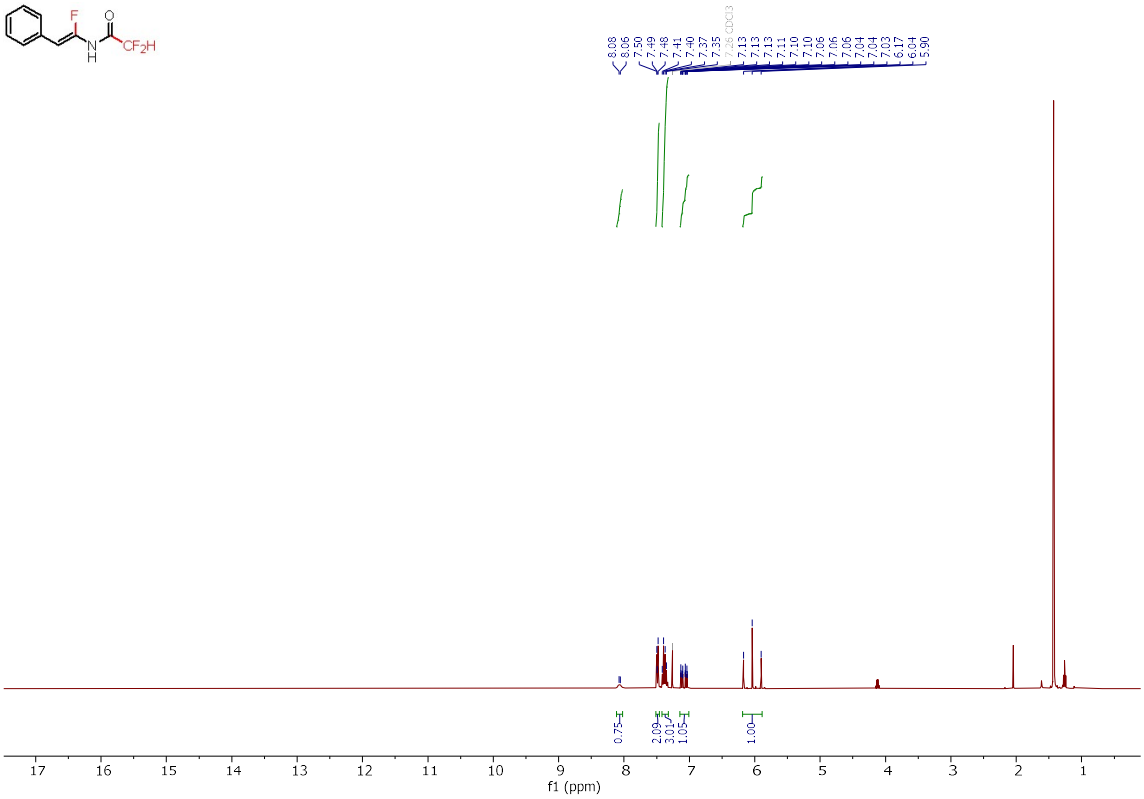
^{13}C NMR spectrum of **2t** ($CDCl_3$, 101 MHz)



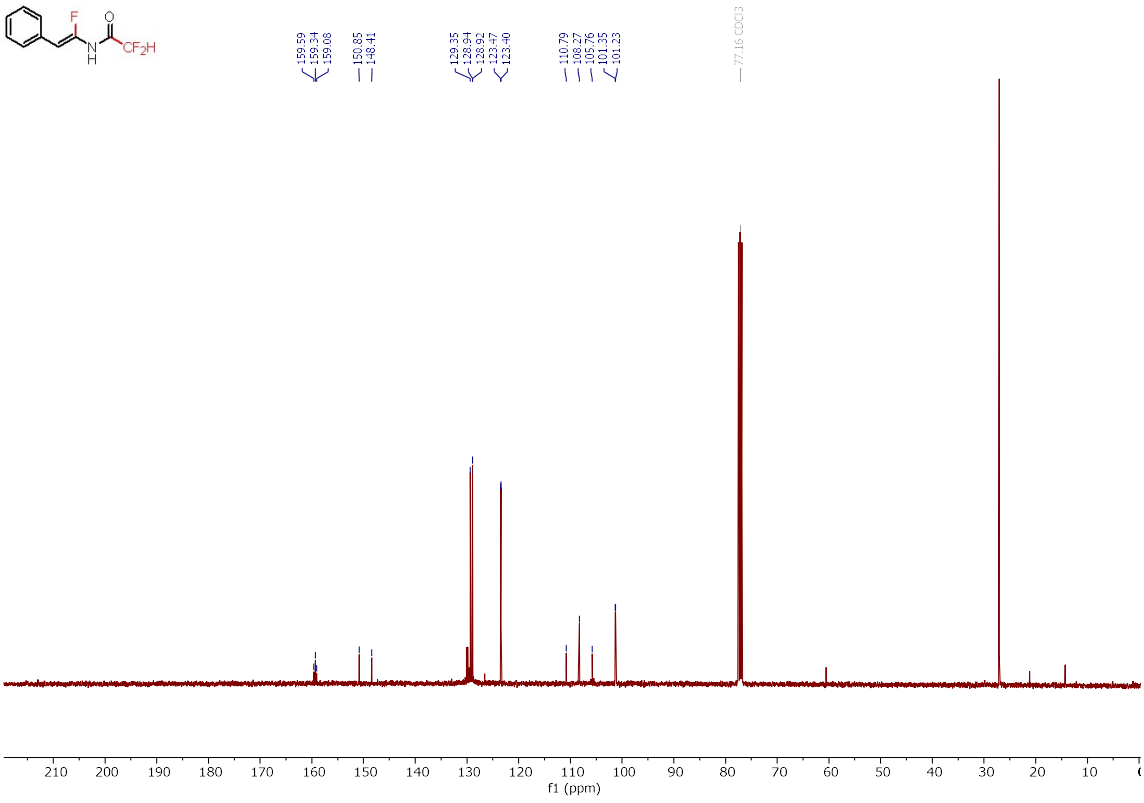
^{19}F NMR spectrum of **2t** ($CDCl_3$, 376 MHz)



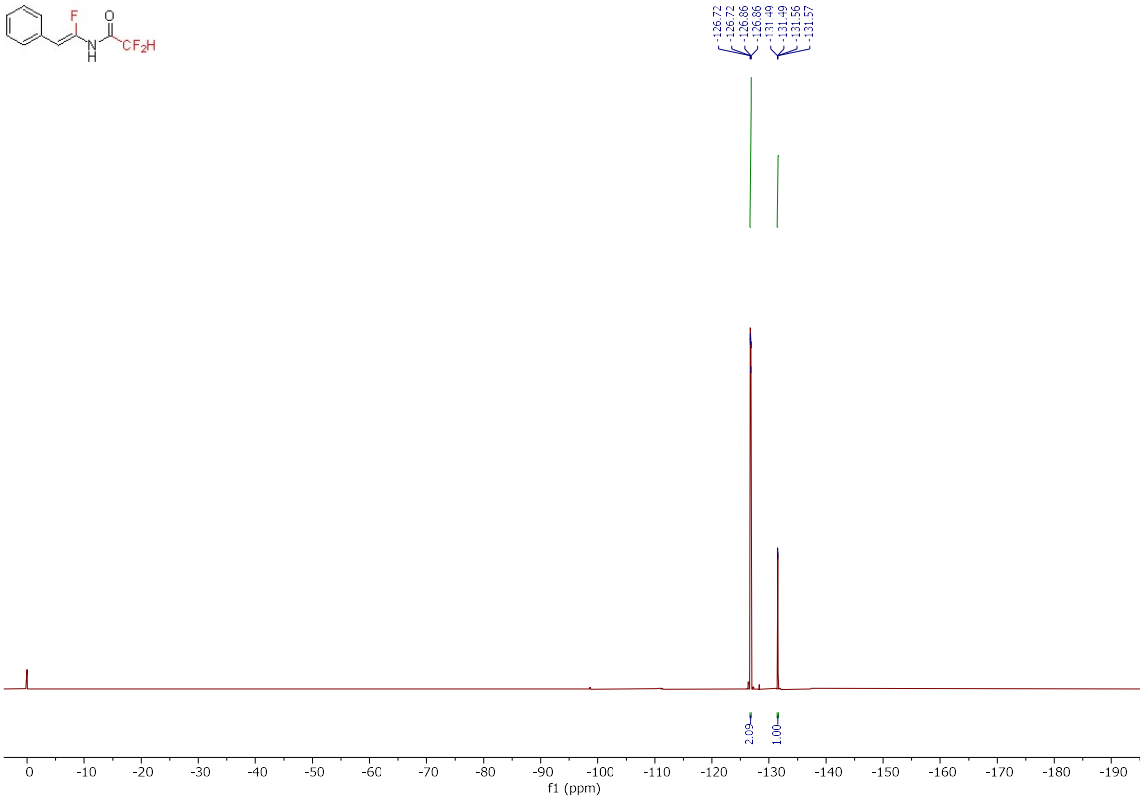
^{1}H NMR spectrum of **5t** ($CDCl_3$, 400 MHz)



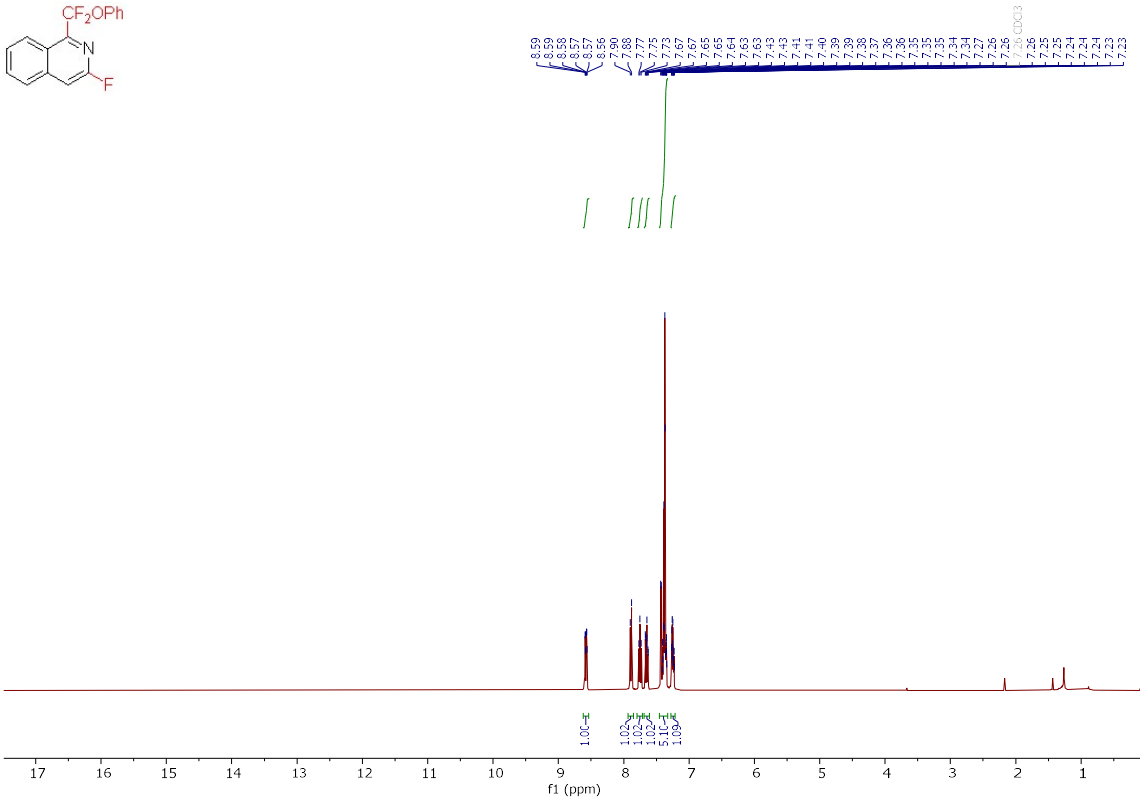
^{13}C NMR spectrum of **5t** ($CDCl_3$, 101 MHz)



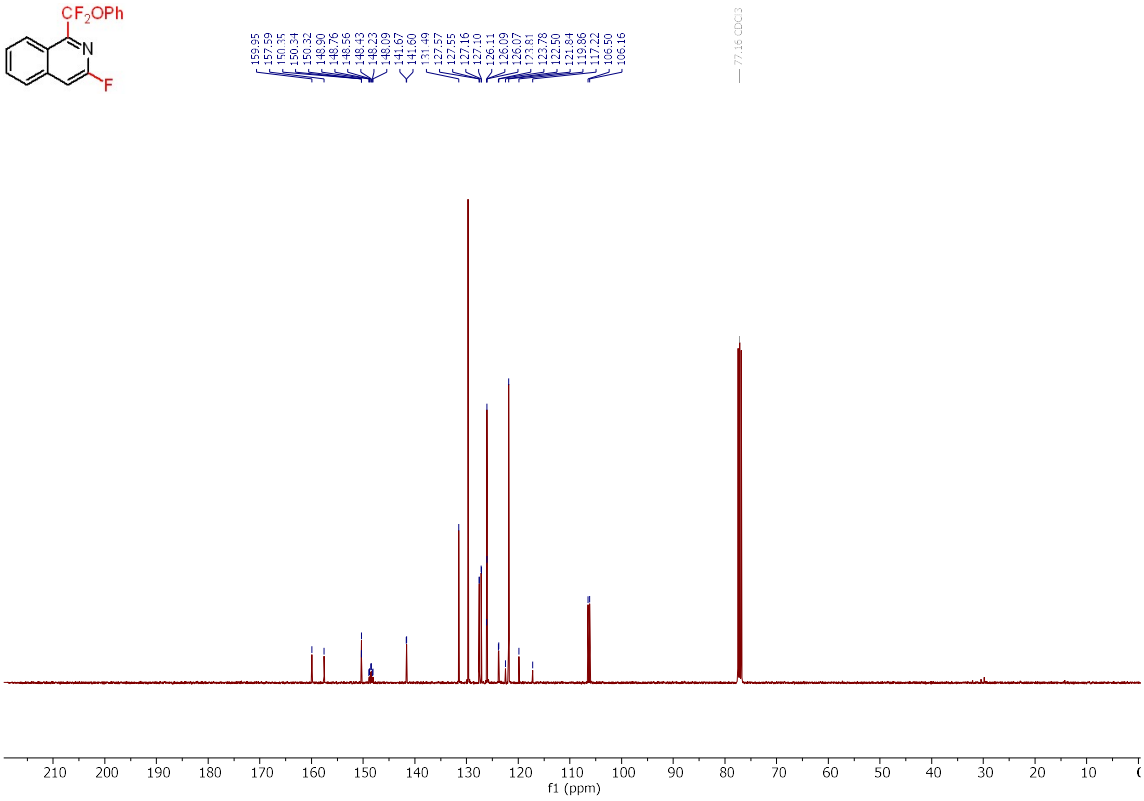
^{19}F NMR spectrum of **5t** ($CDCl_3$, 376 MHz)



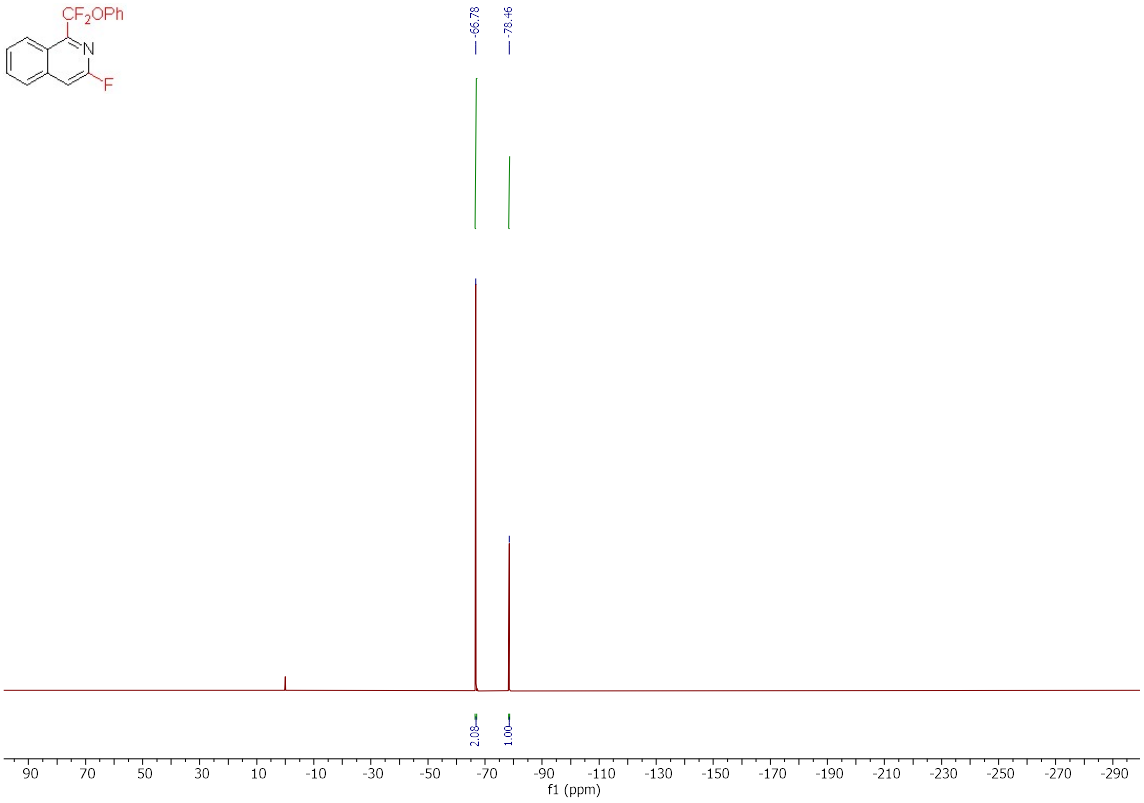
^{1}H NMR spectrum of **2u** ($CDCl_3$, 400 MHz)



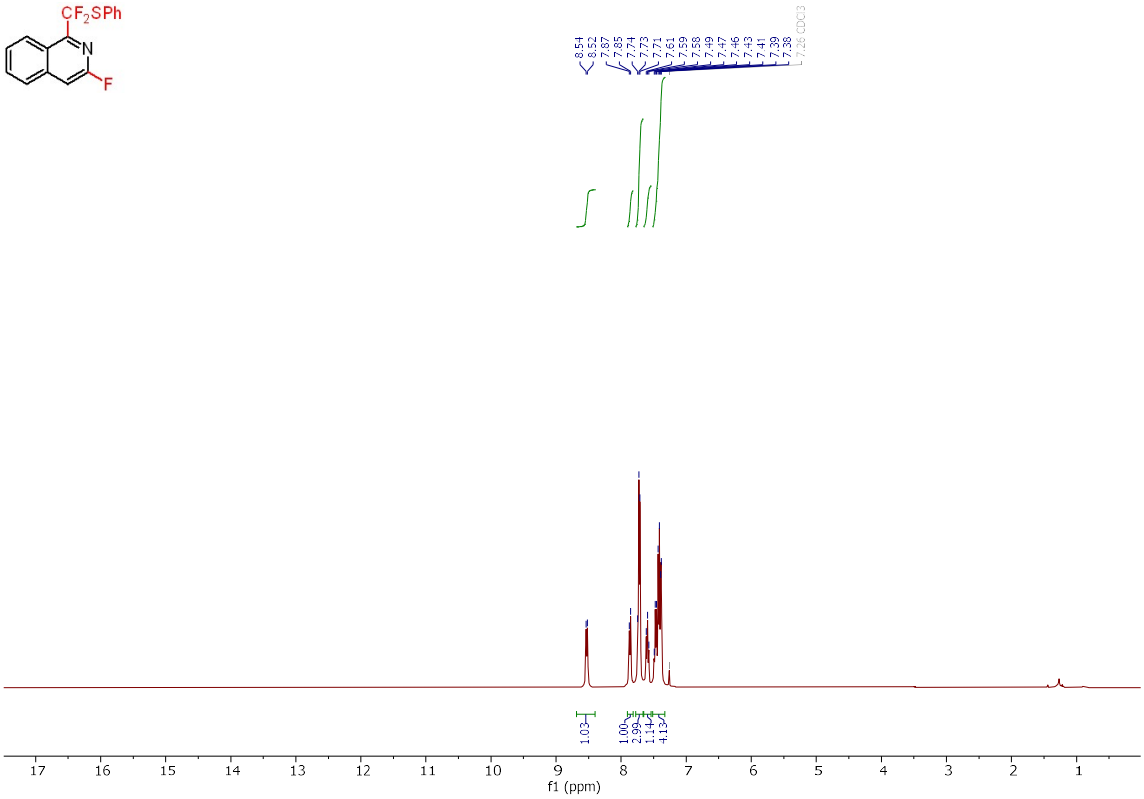
^{13}C NMR spectrum of **2u** ($CDCl_3$, 101 MHz)



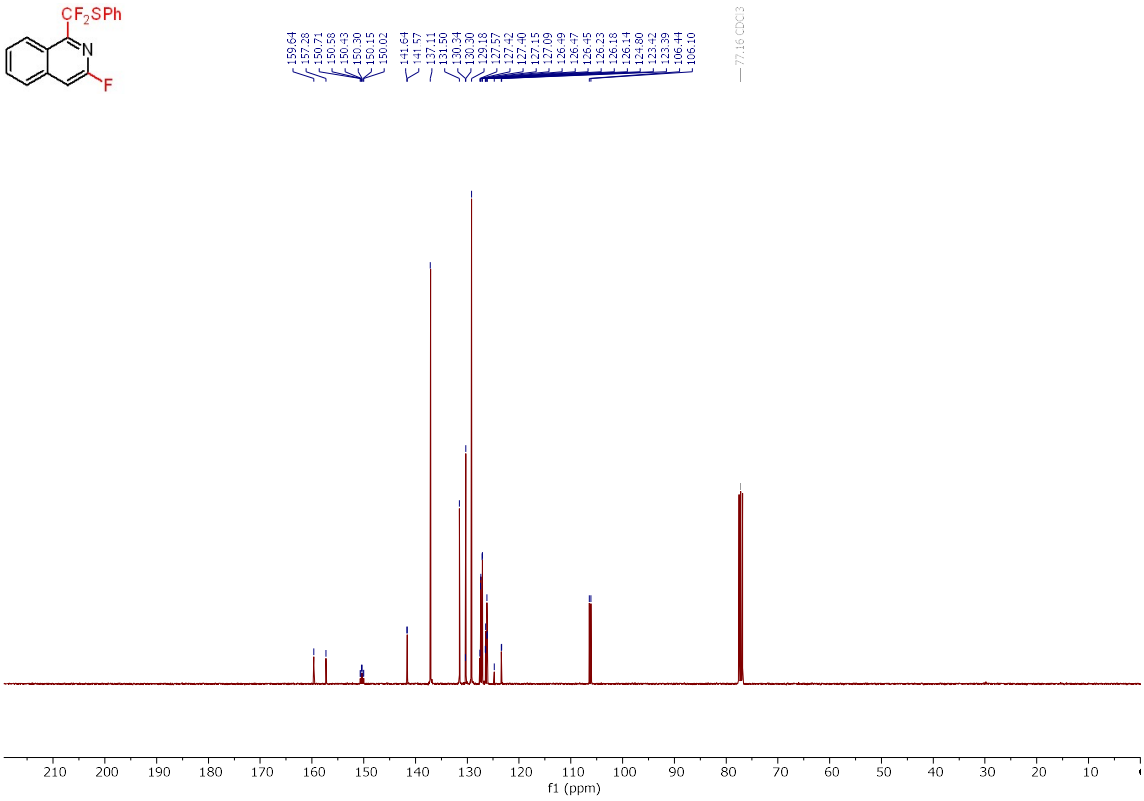
^{19}F NMR spectrum of **2u** ($CDCl_3$, 376 MHz)



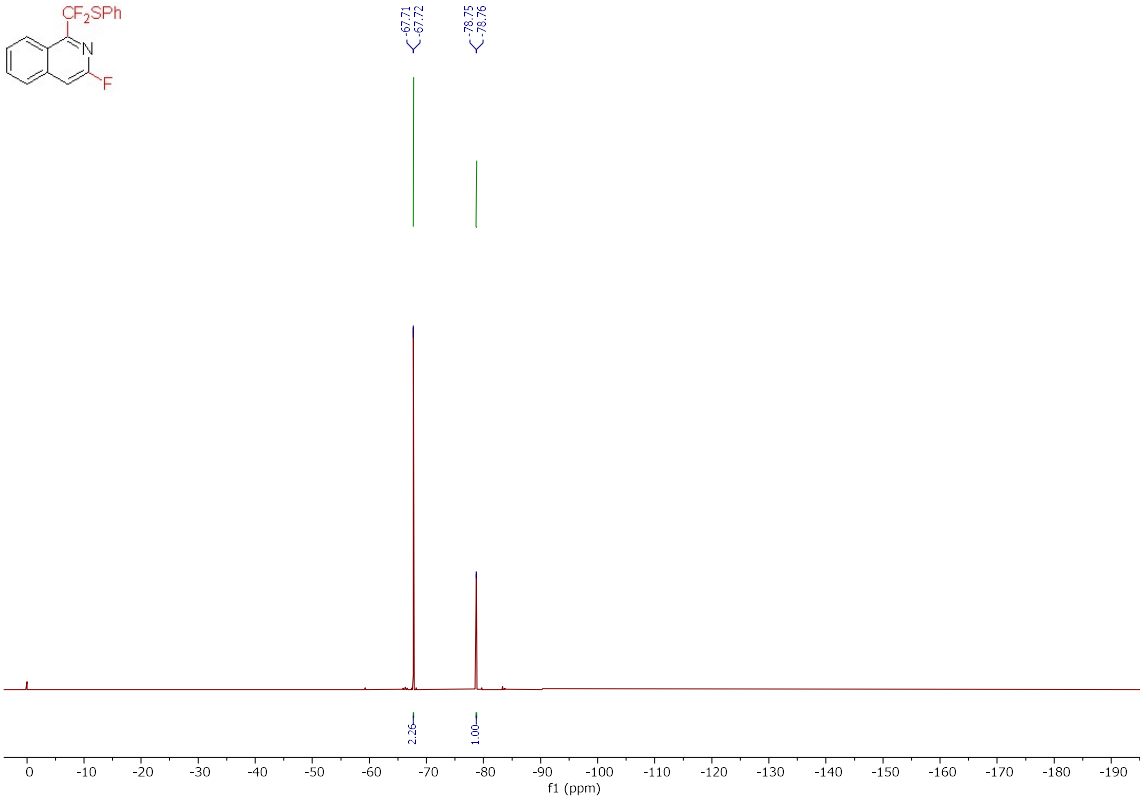
^{1}H NMR spectrum of **2v** ($CDCl_3$, 400 MHz)



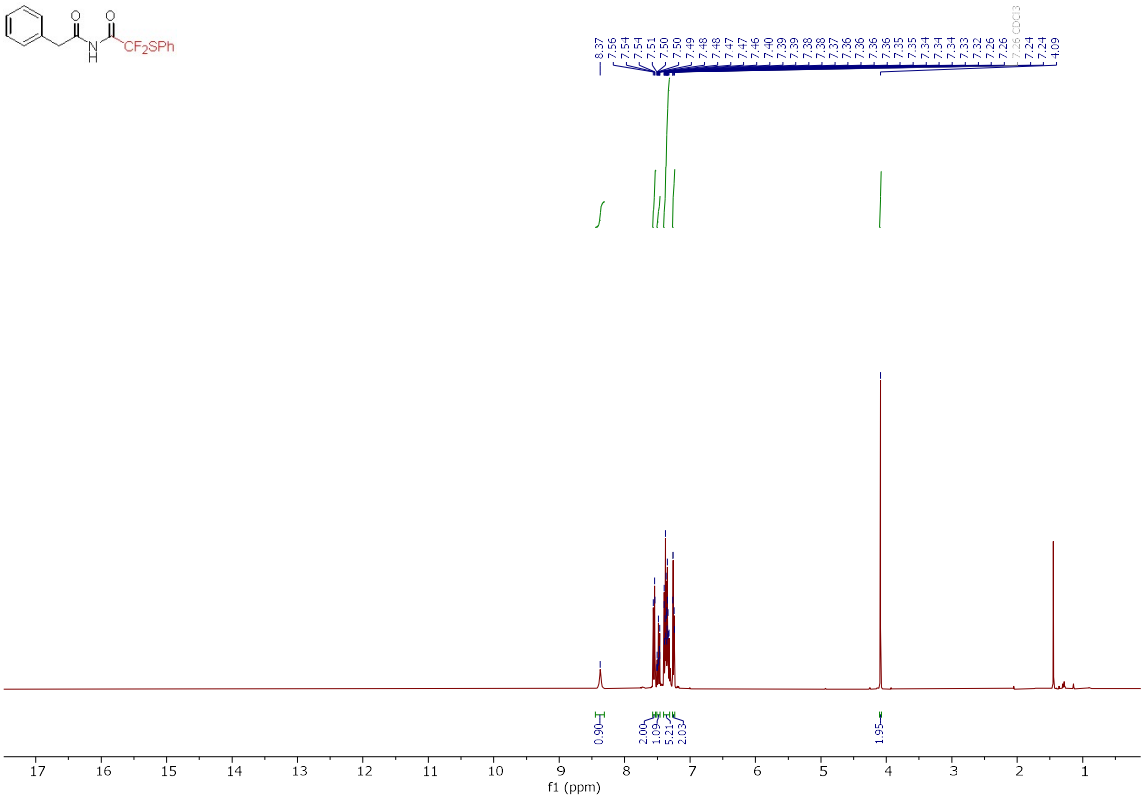
^{13}C NMR spectrum of **2v** ($CDCl_3$, 101 MHz)



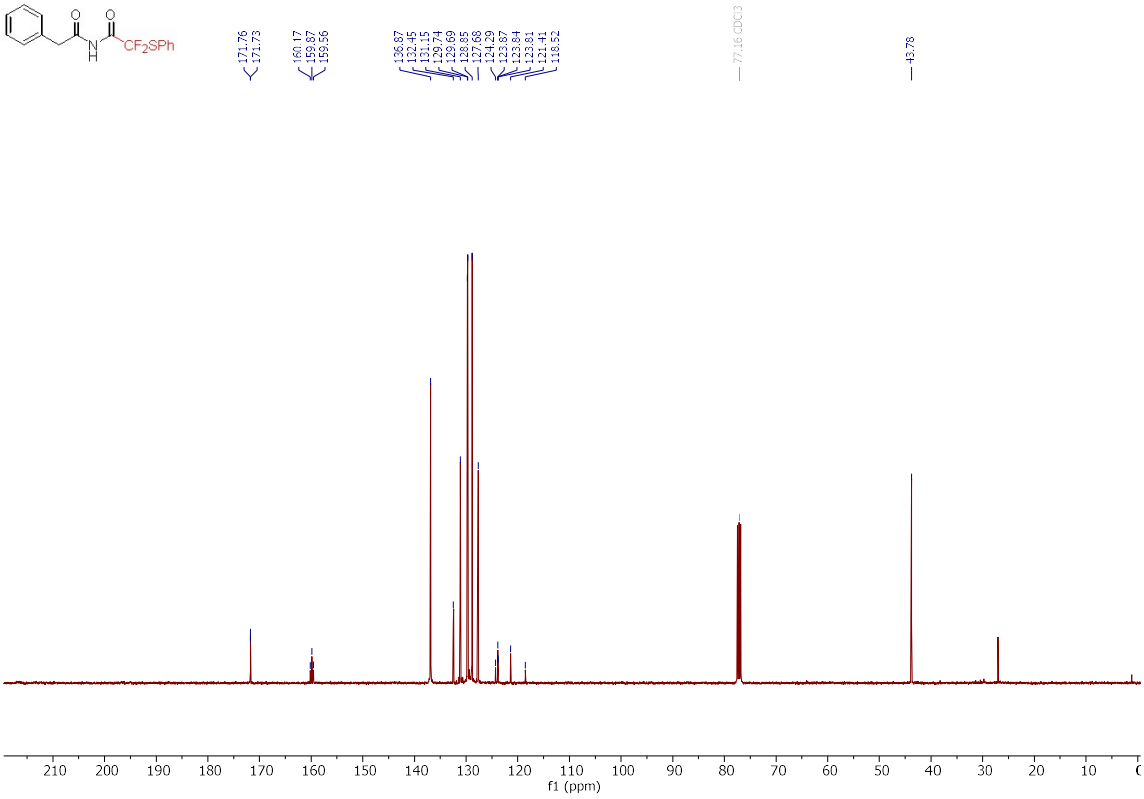
^{19}F NMR spectrum of **2v** ($CDCl_3$, 376 MHz)



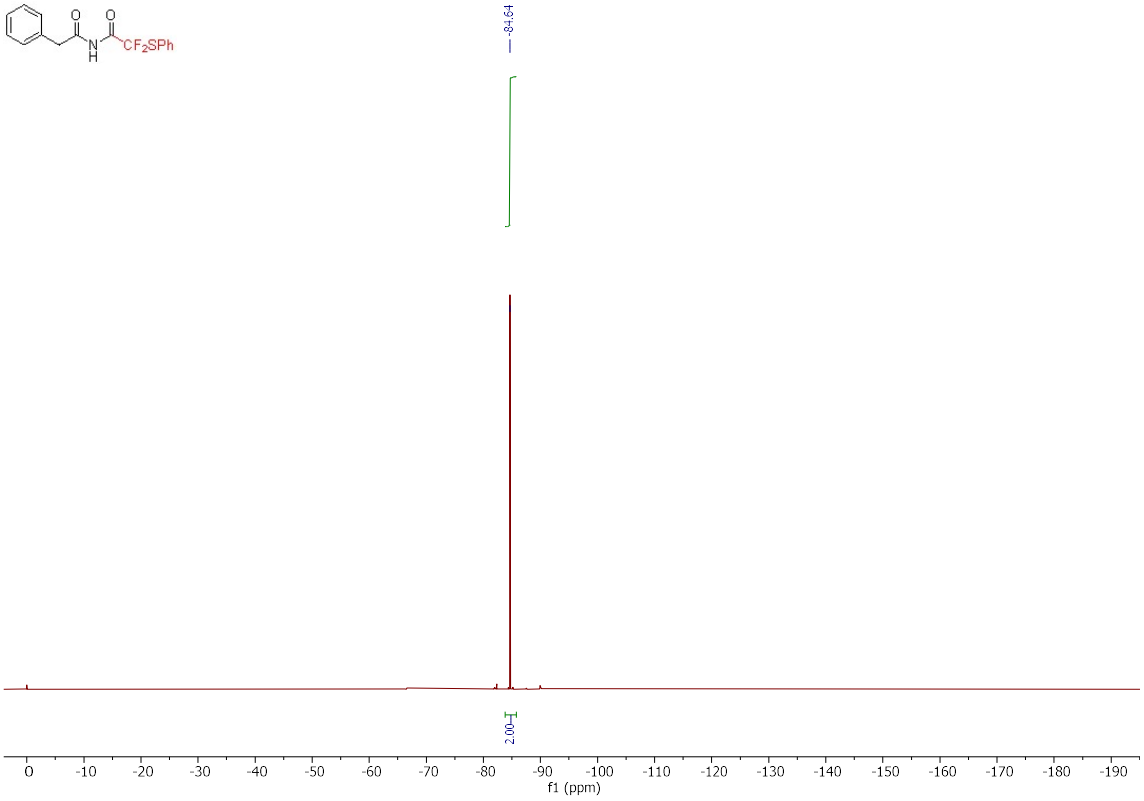
^{1}H NMR spectrum of **5v'** ($CDCl_3$, 400 MHz)



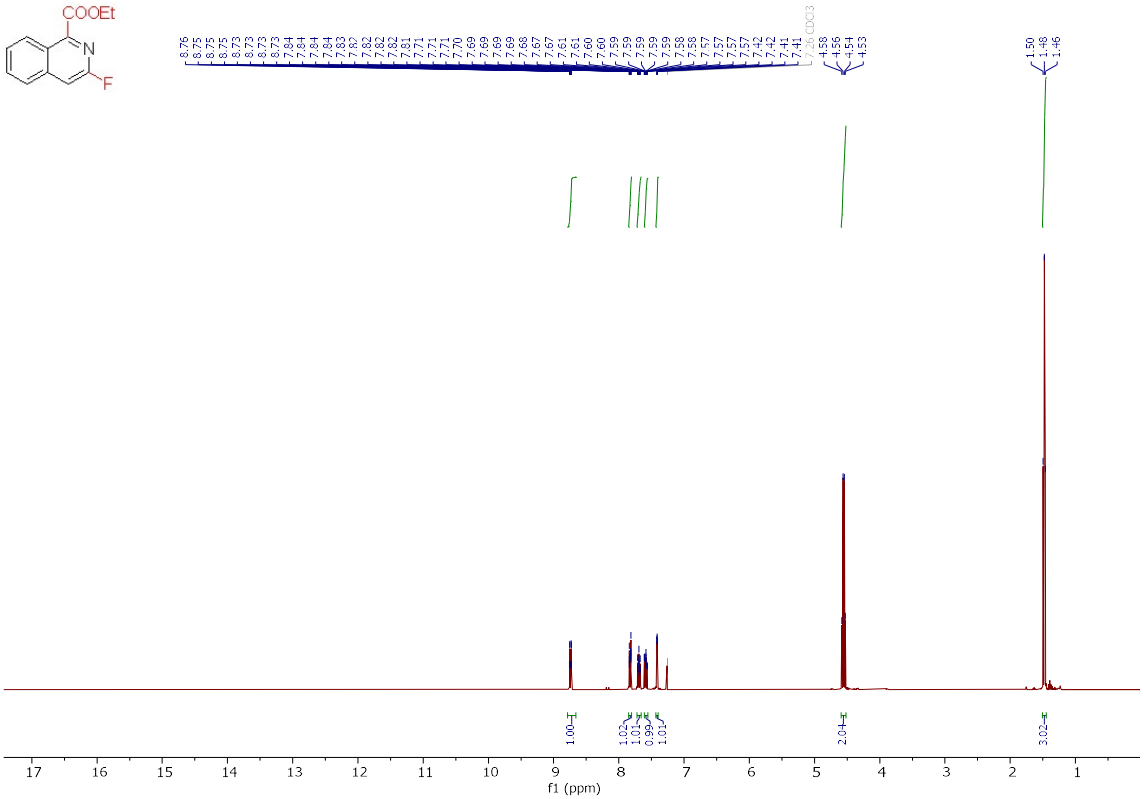
^{13}C NMR spectrum of **5v'** ($CDCl_3$, 101 MHz)



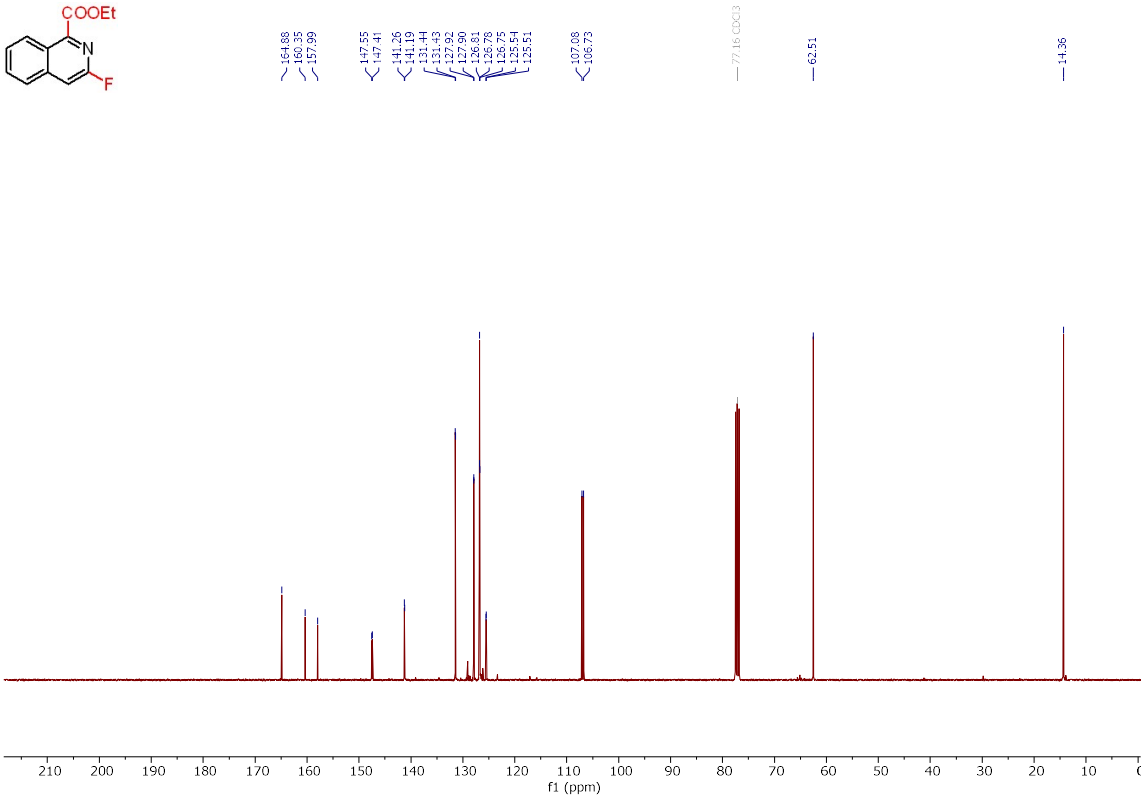
^{19}F NMR spectrum of **5v'** ($CDCl_3$, 376 MHz)



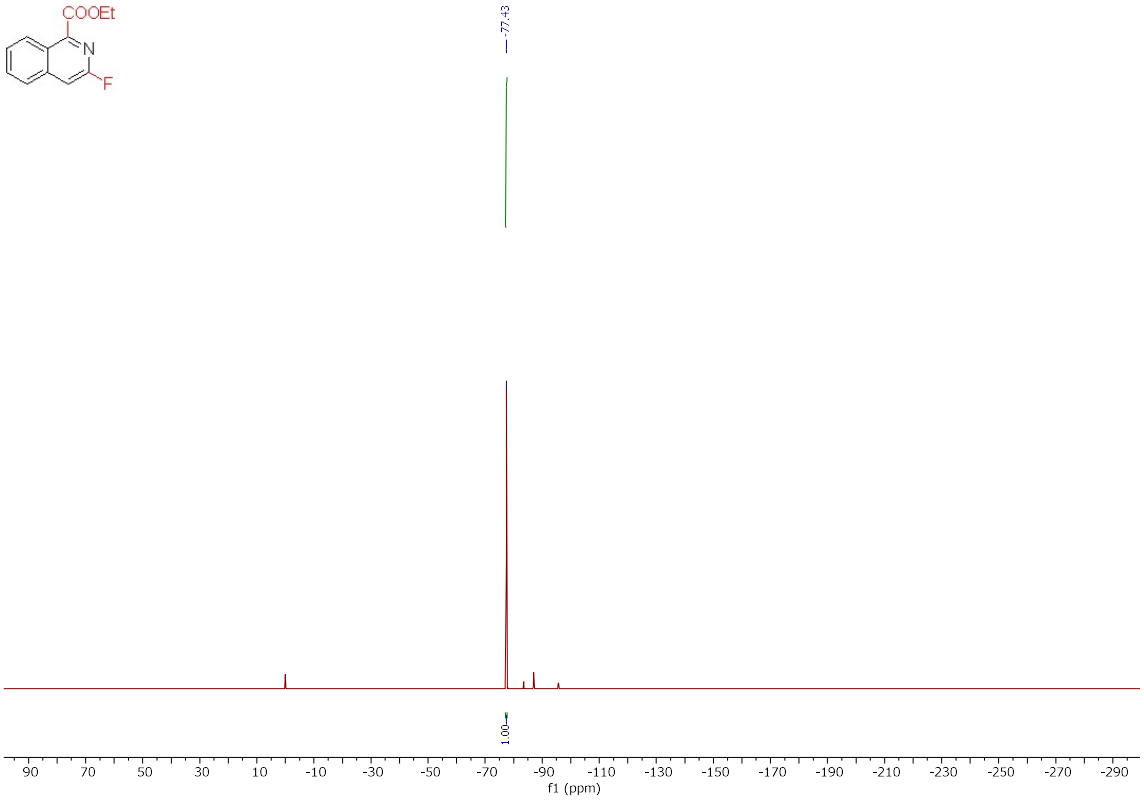
^{1}H NMR spectrum of **2w** ($CDCl_3$, 400 MHz)



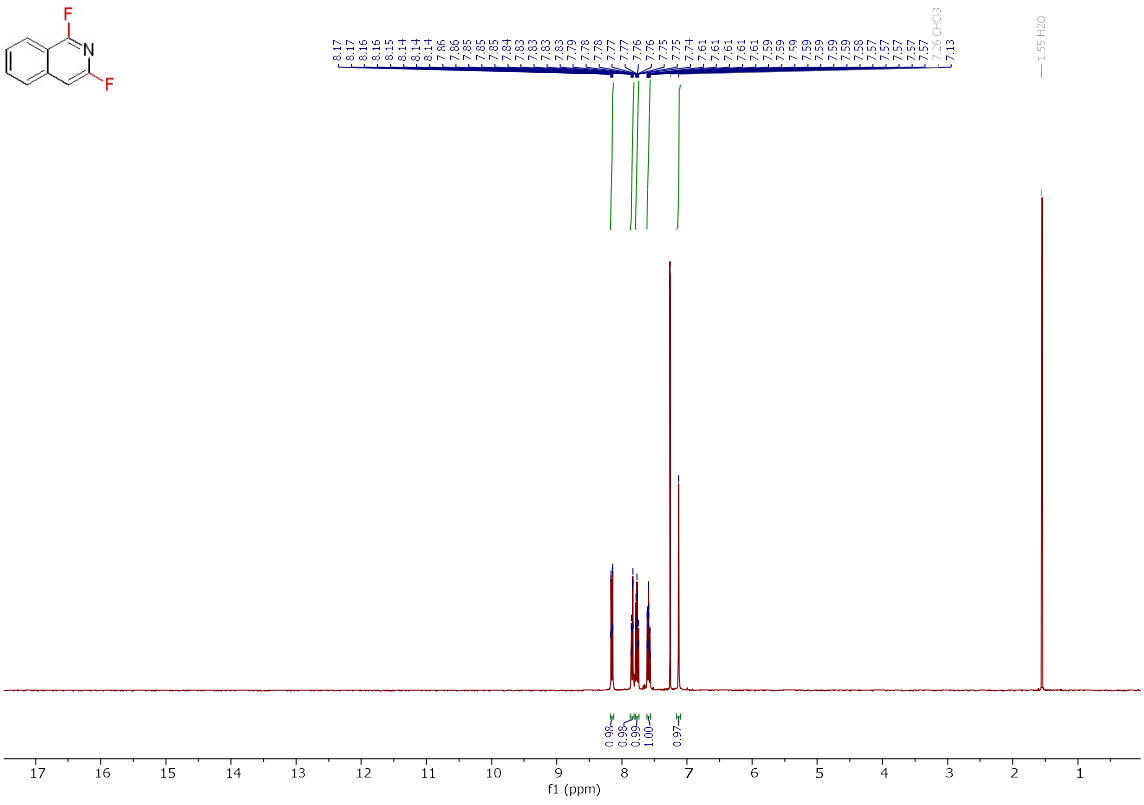
^{13}C NMR spectrum of **2w** ($CDCl_3$, 101 MHz)



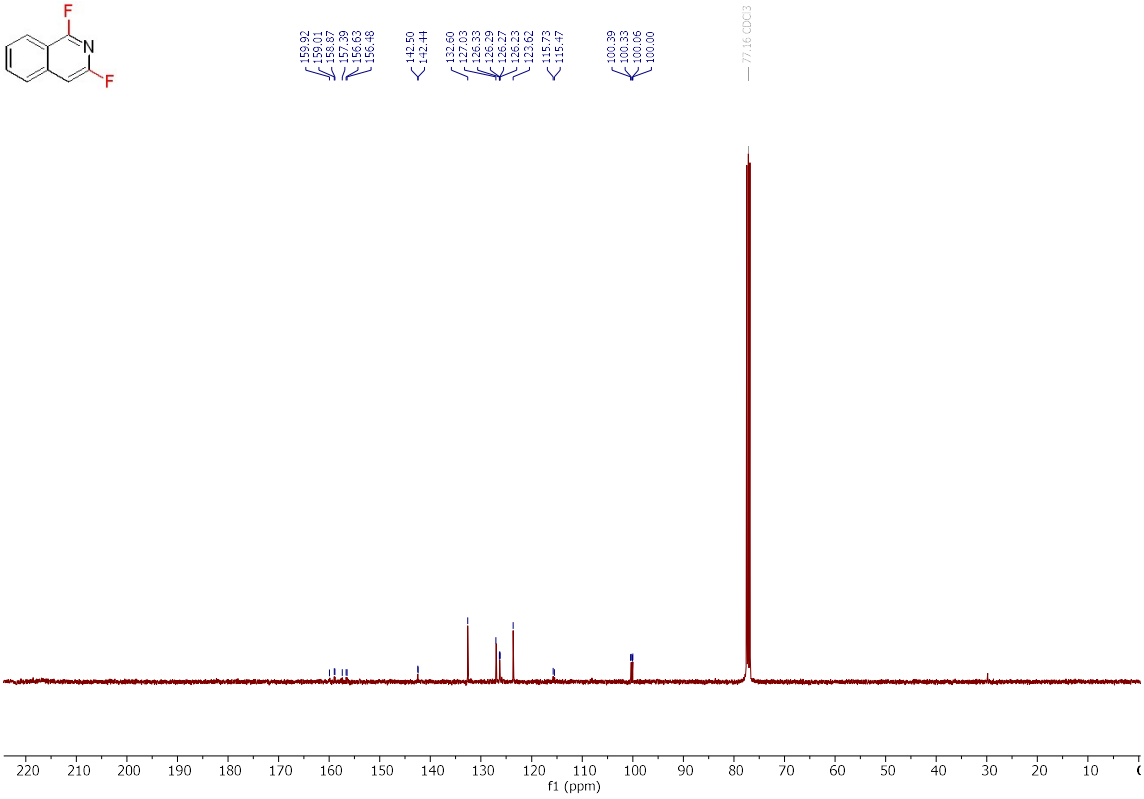
^{19}F NMR spectrum of **2w** ($CDCl_3$, 376 MHz)



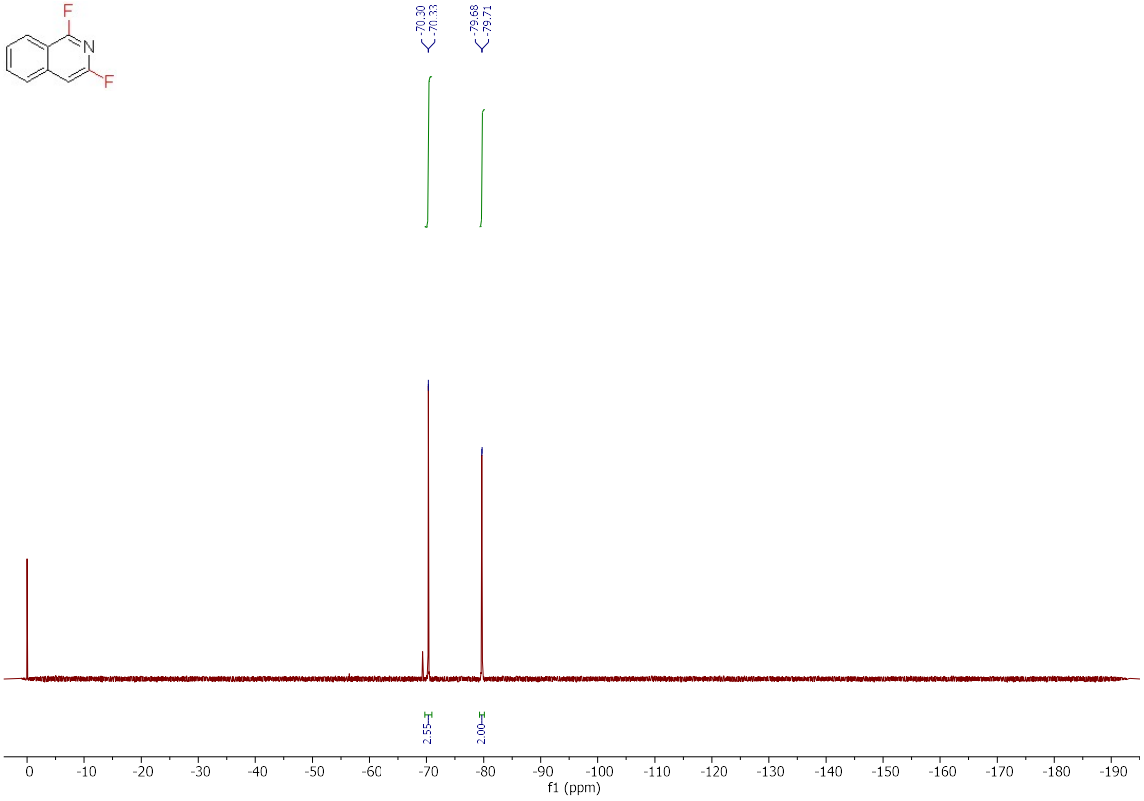
^{1}H NMR spectrum of **2x** ($CDCl_3$, 400 MHz)



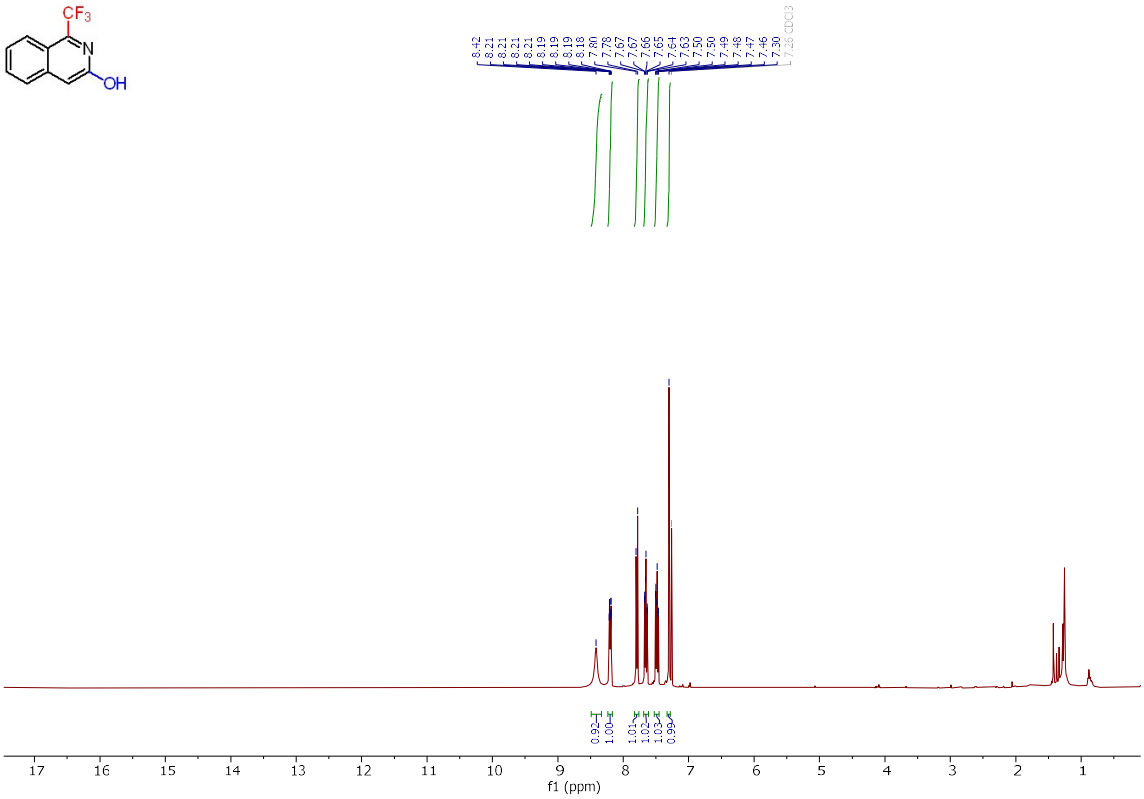
^{13}C NMR spectrum of **2x** ($CDCl_3$, 101 MHz)



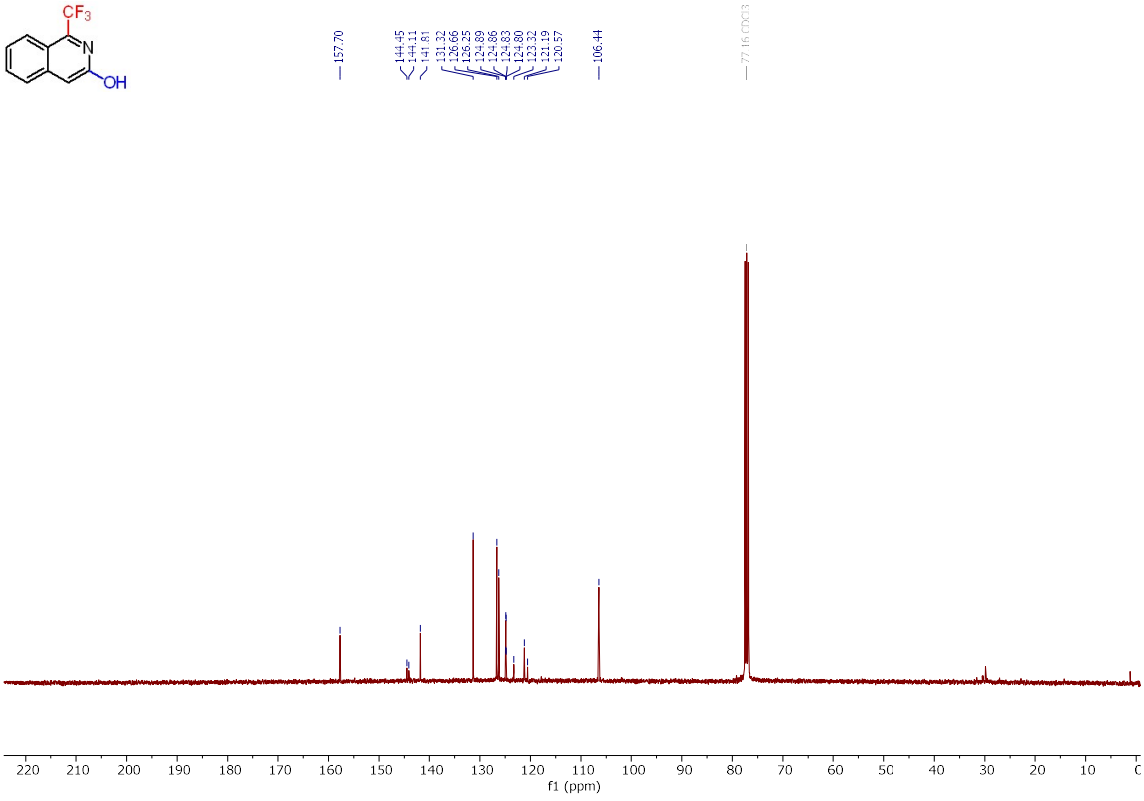
^{19}F NMR spectrum of **2x** ($CDCl_3$, 376 MHz)



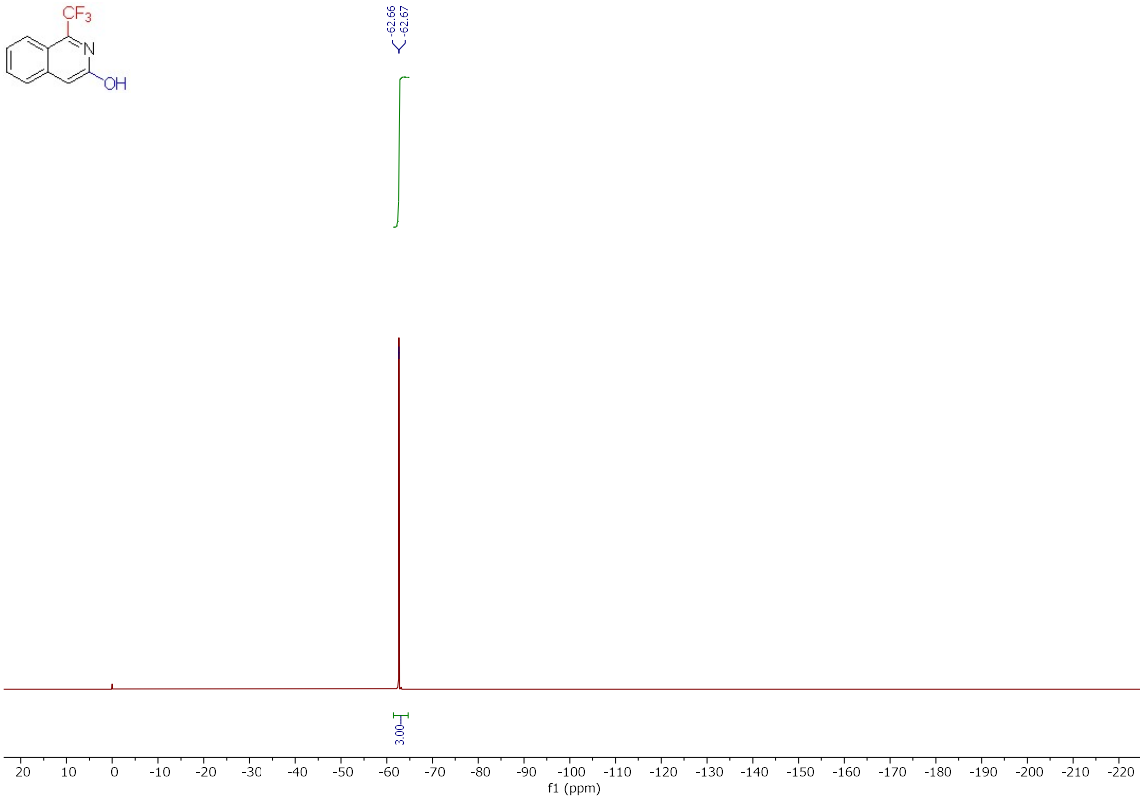
^{1}H NMR spectrum of **7a** ($CDCl_3$, 400 MHz)



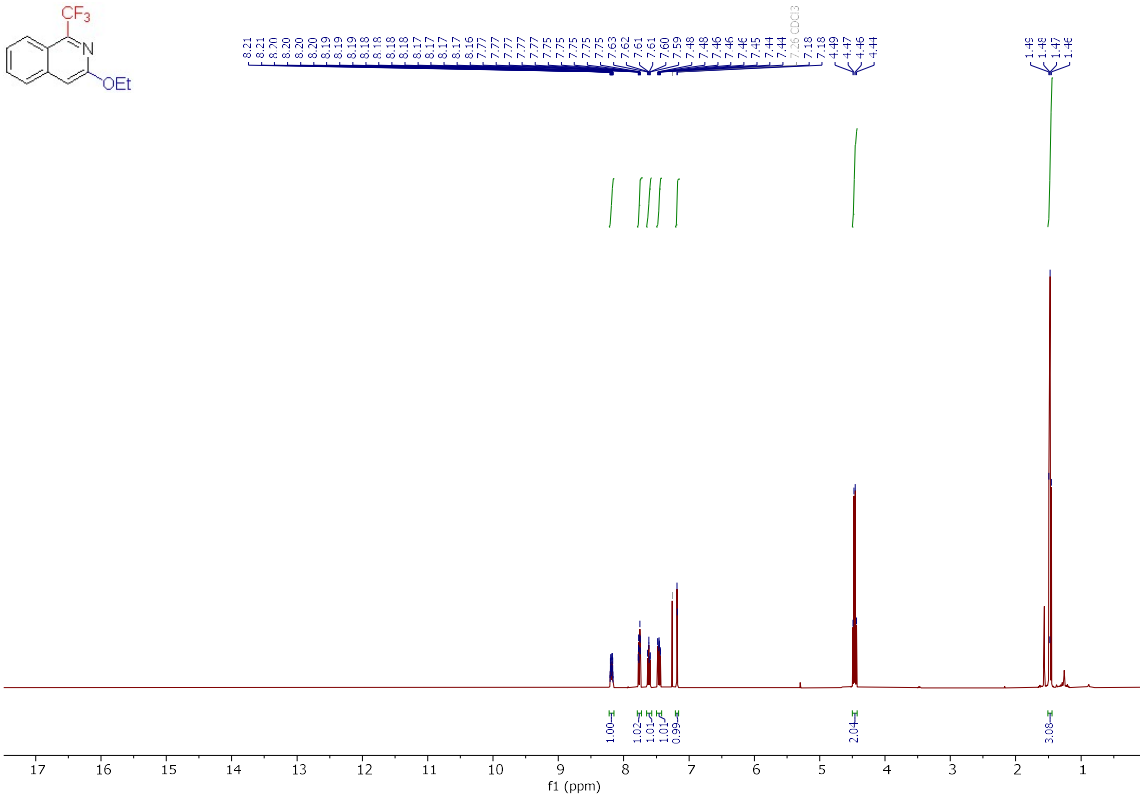
^{13}C NMR spectrum of **7a** ($CDCl_3$, 101 MHz)



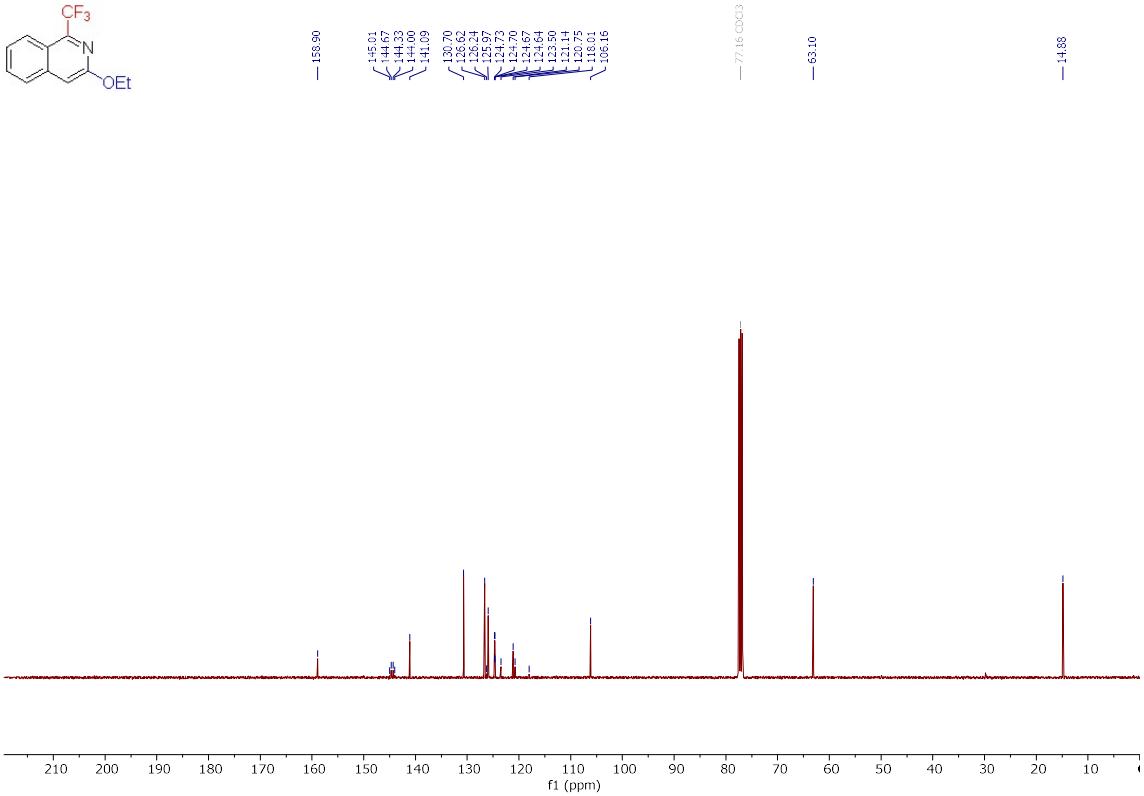
^{19}F NMR spectrum of **7a** ($CDCl_3$, 376 MHz)



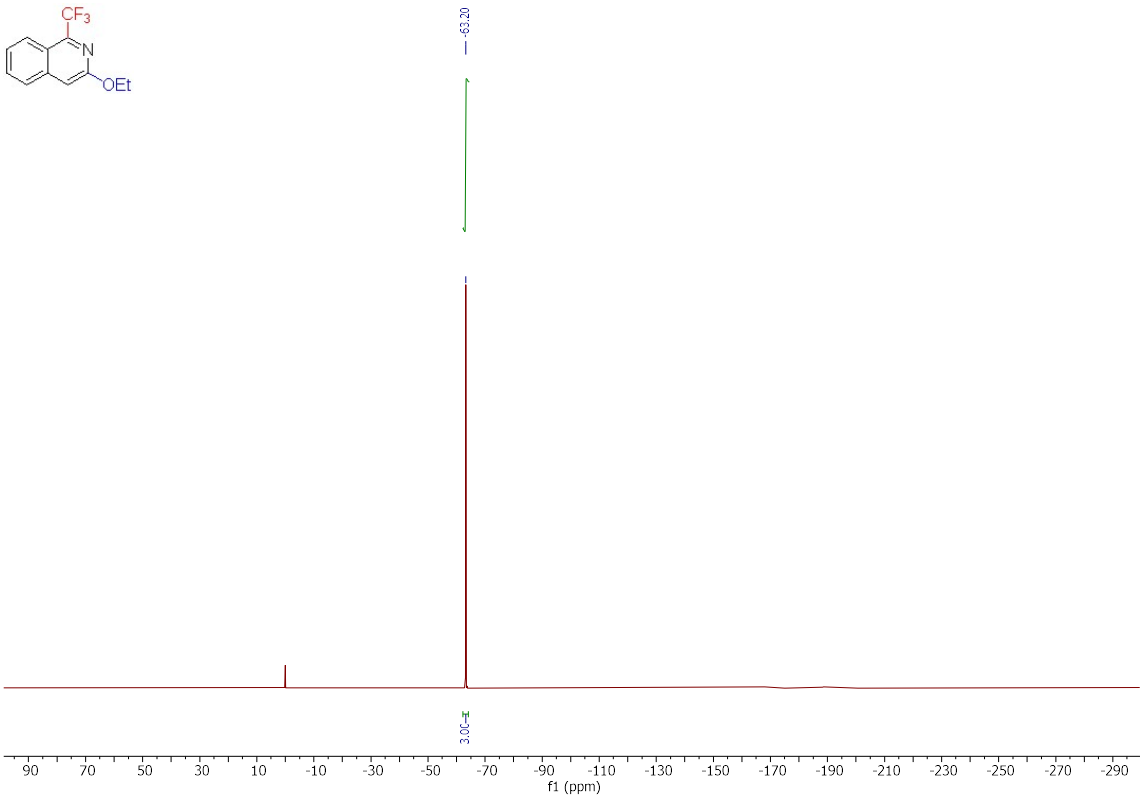
^{1}H NMR spectrum of **7b** ($CDCl_3$, 400 MHz)



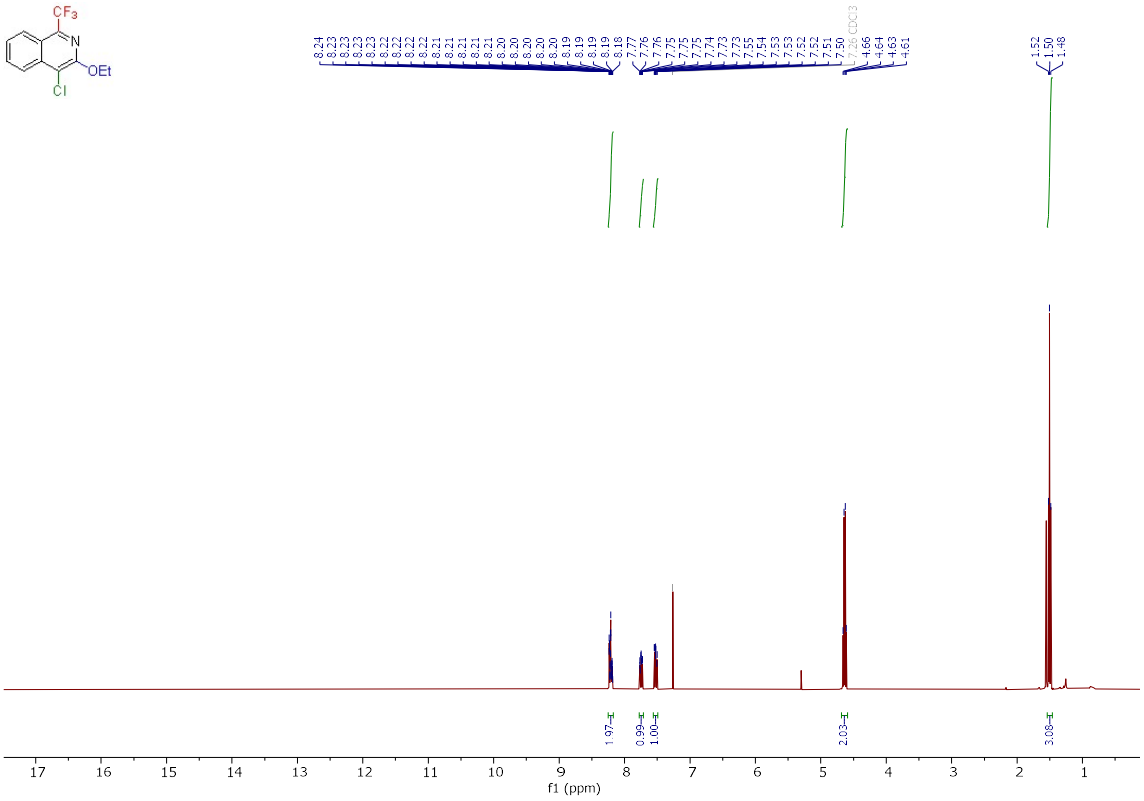
^{13}C NMR spectrum of **7b** ($CDCl_3$, 101 MHz)



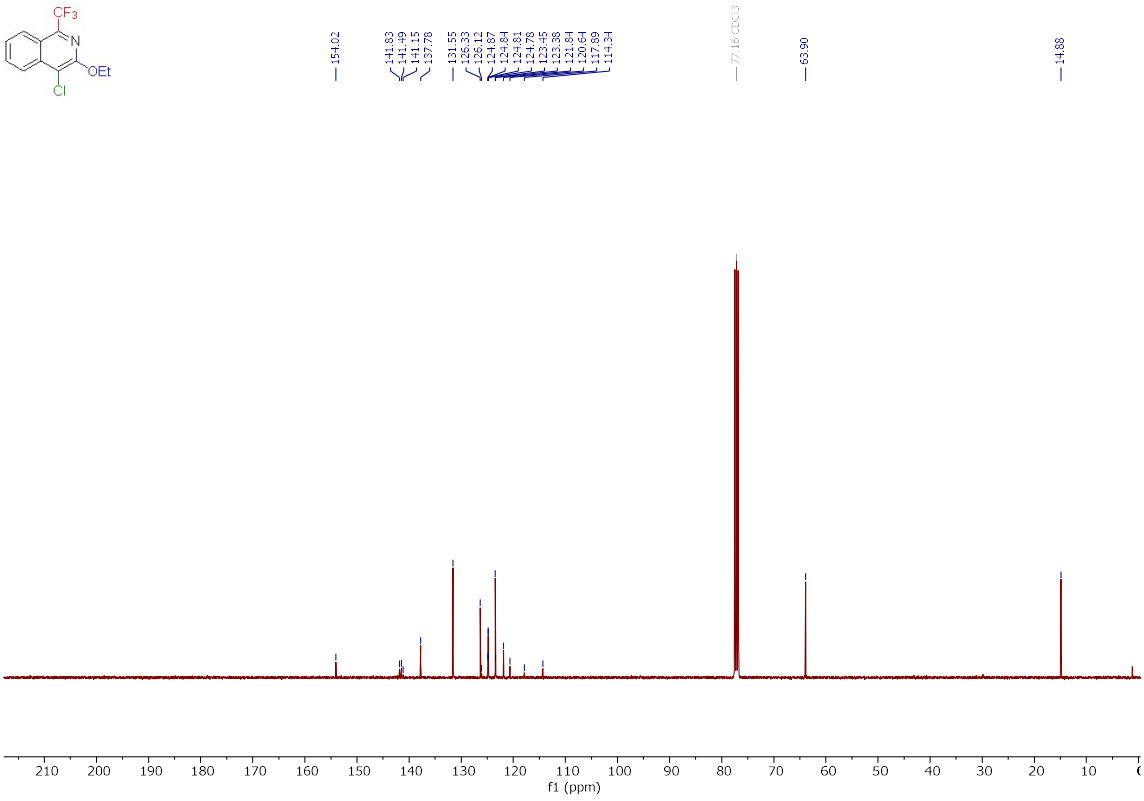
^{19}F NMR spectrum of **7b** ($CDCl_3$, 376 MHz)



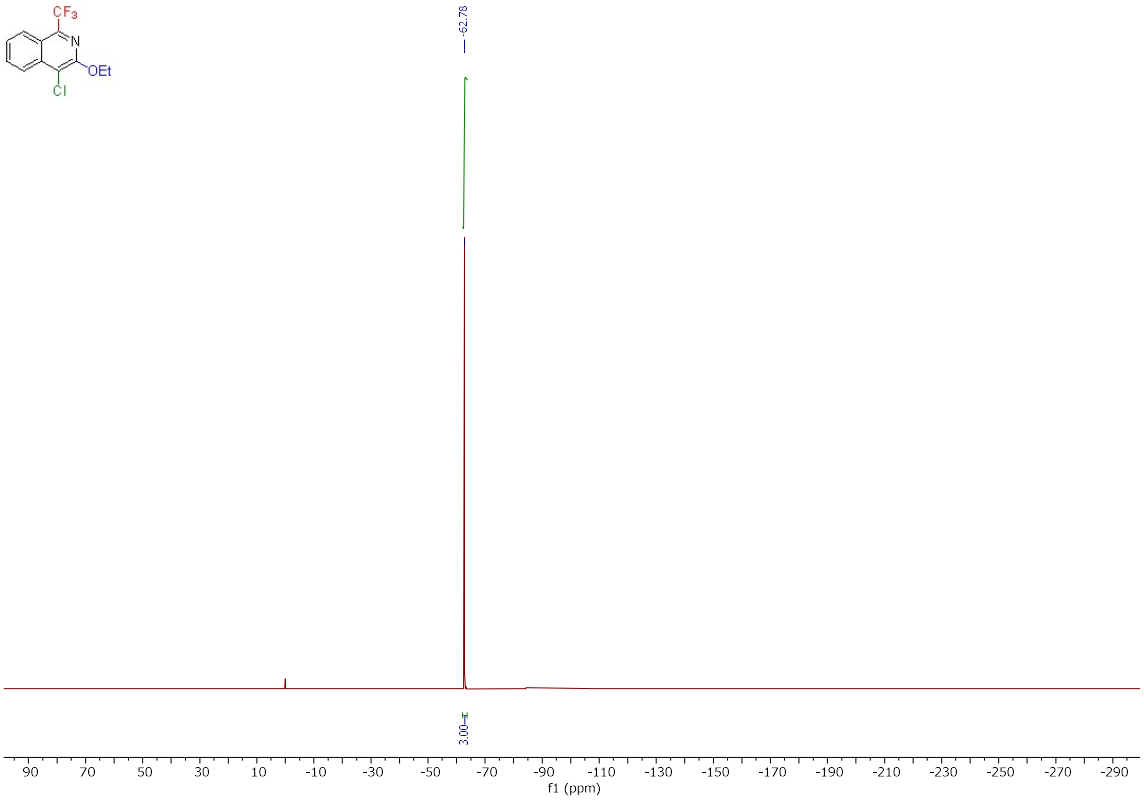
^{1}H NMR spectrum of **7c** ($CDCl_3$, 400 MHz)



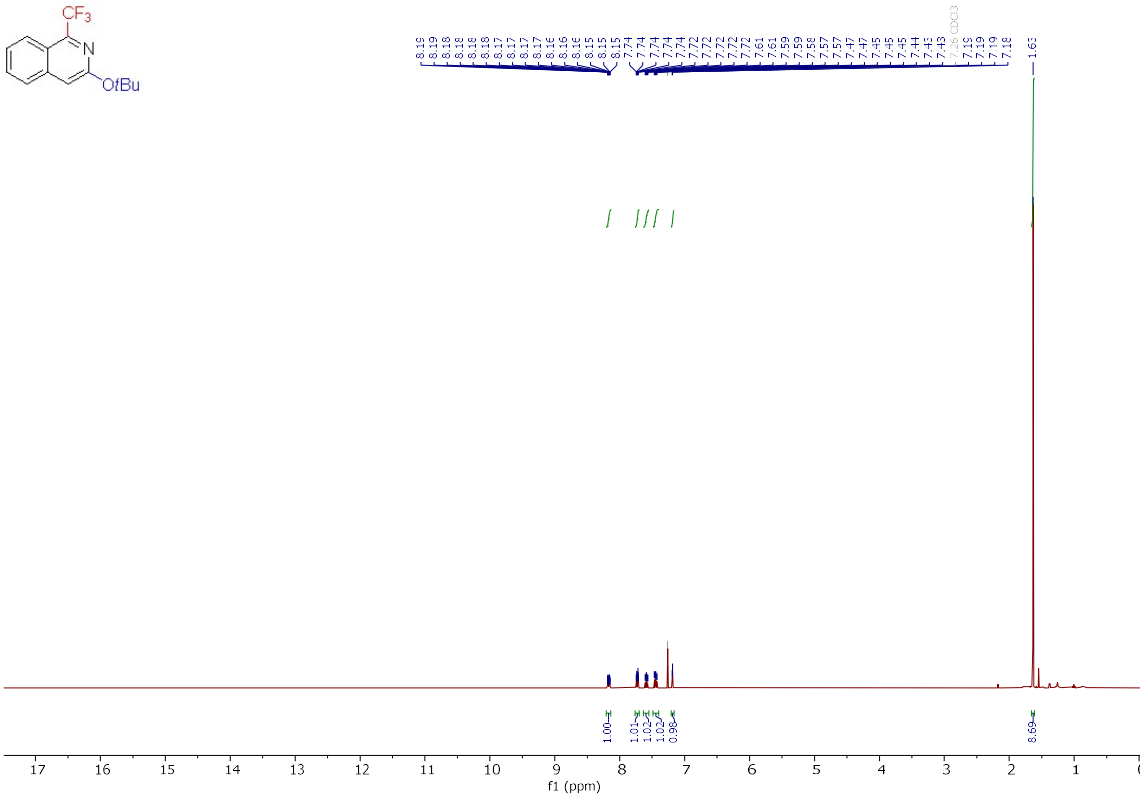
^{13}C NMR spectrum of **7c** ($CDCl_3$, 101 MHz)



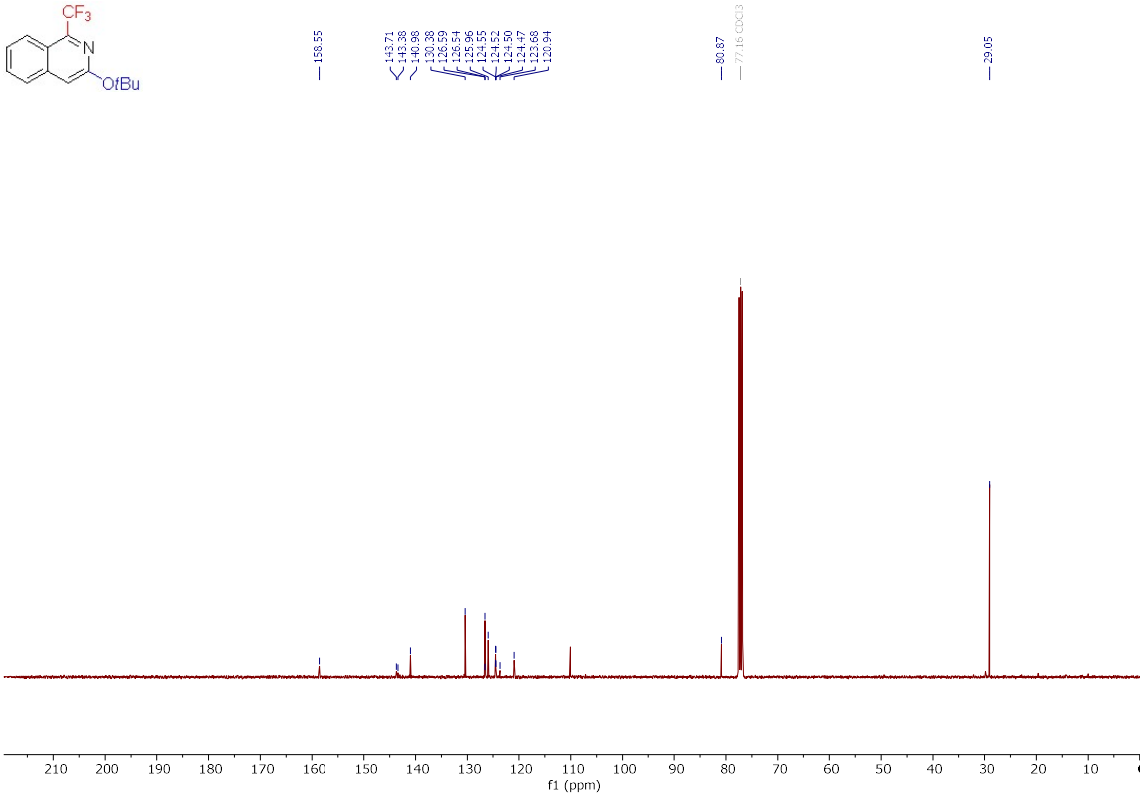
^{19}F NMR spectrum of **7c** ($CDCl_3$, 376 MHz)



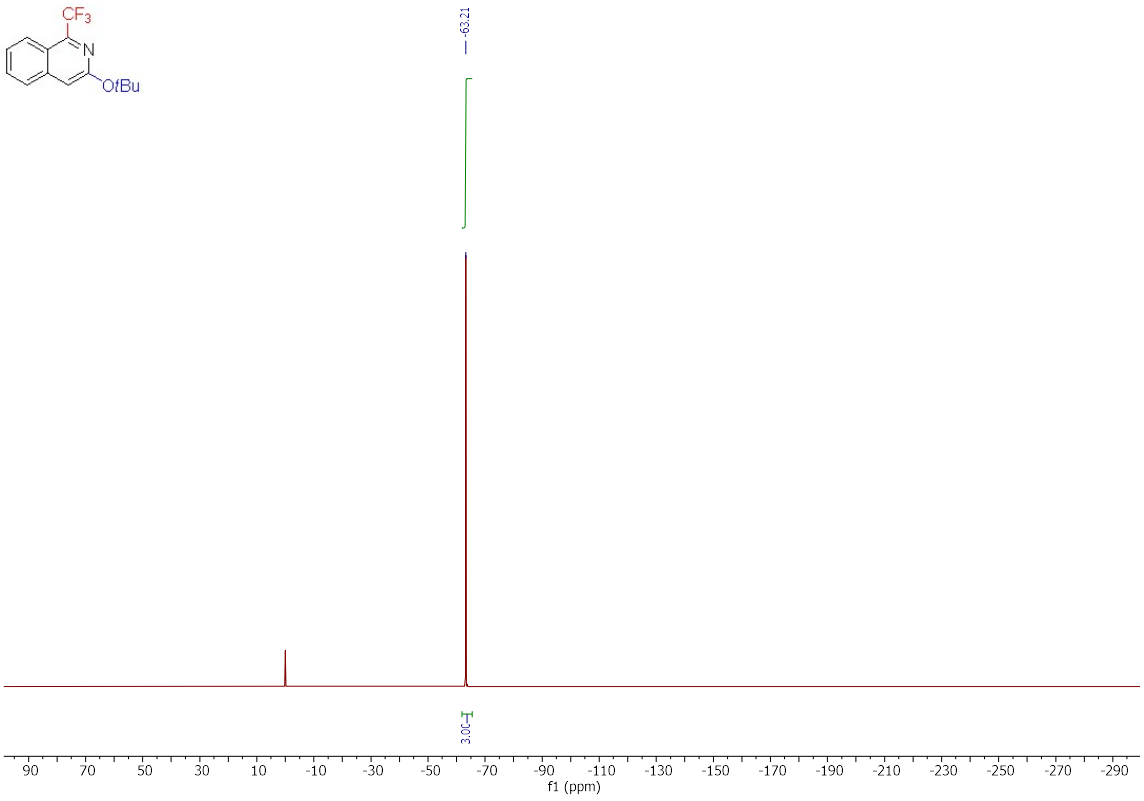
^{1}H NMR spectrum of **7d** ($CDCl_3$, 400 MHz)



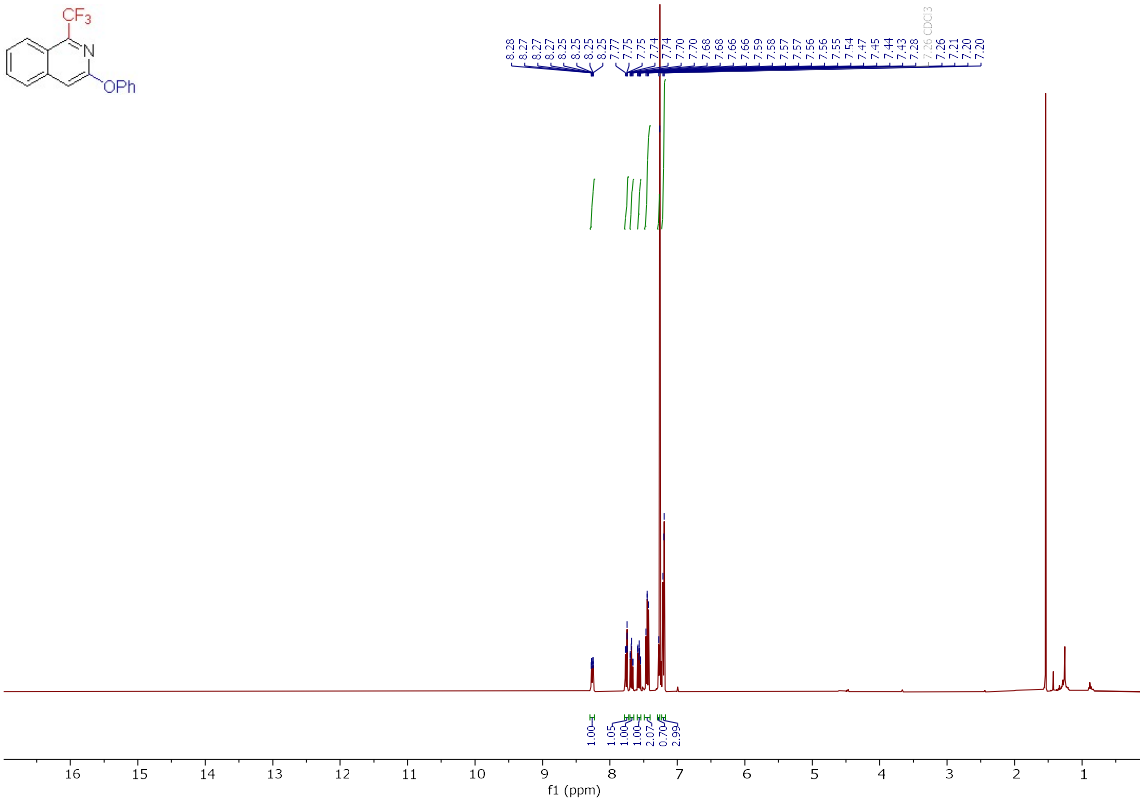
^{13}C NMR spectrum of **7d** ($CDCl_3$, 101 MHz)



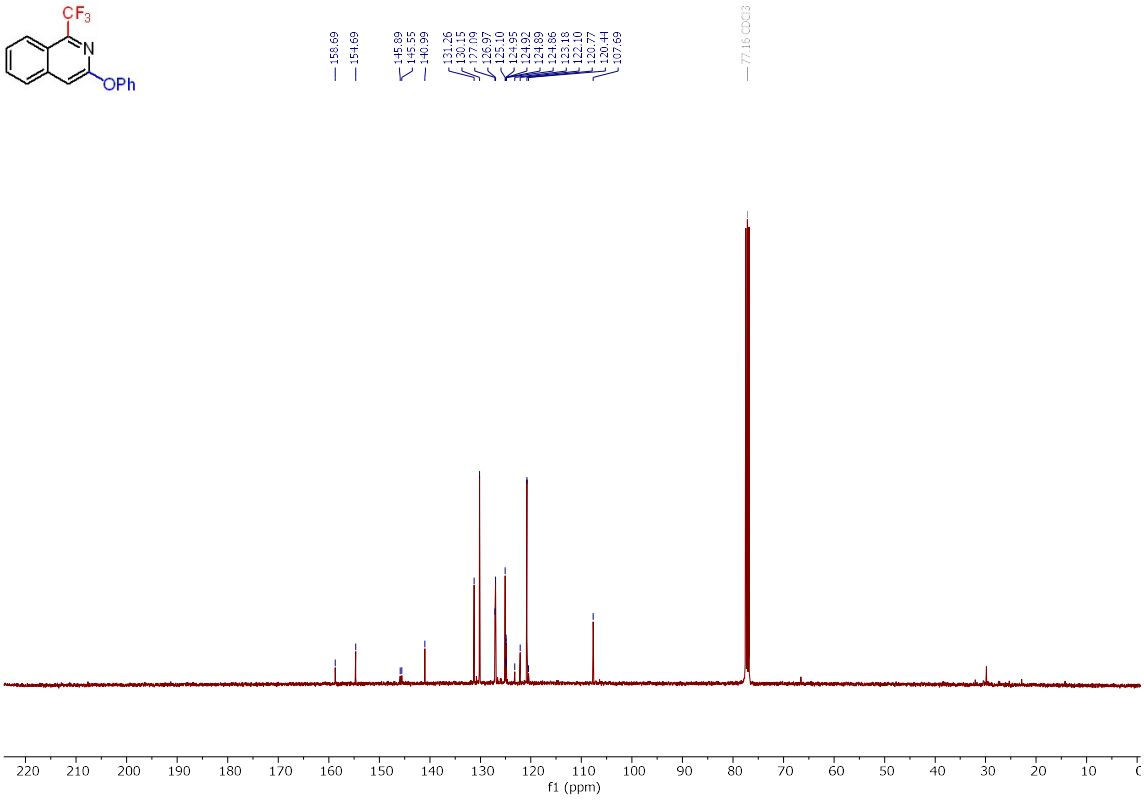
^{19}F NMR spectrum of **7d** ($CDCl_3$, 376 MHz)



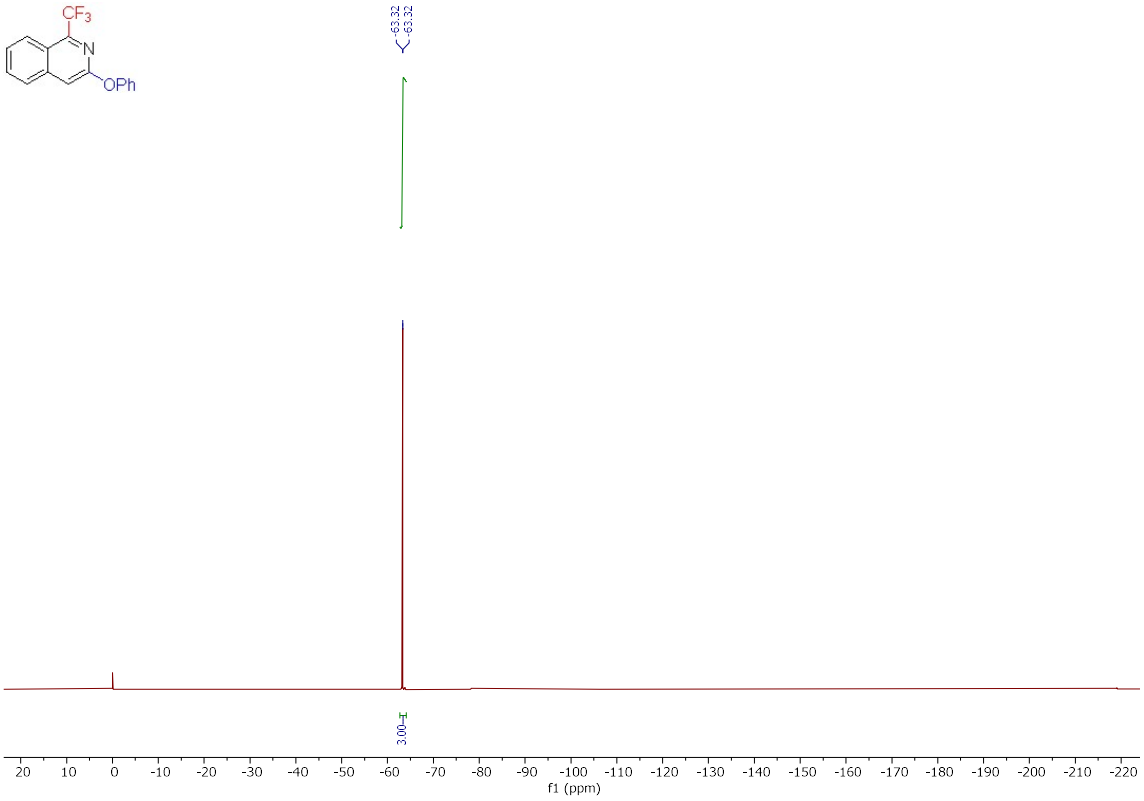
^{1}H NMR spectrum of **7e** ($CDCl_3$, 400 MHz)



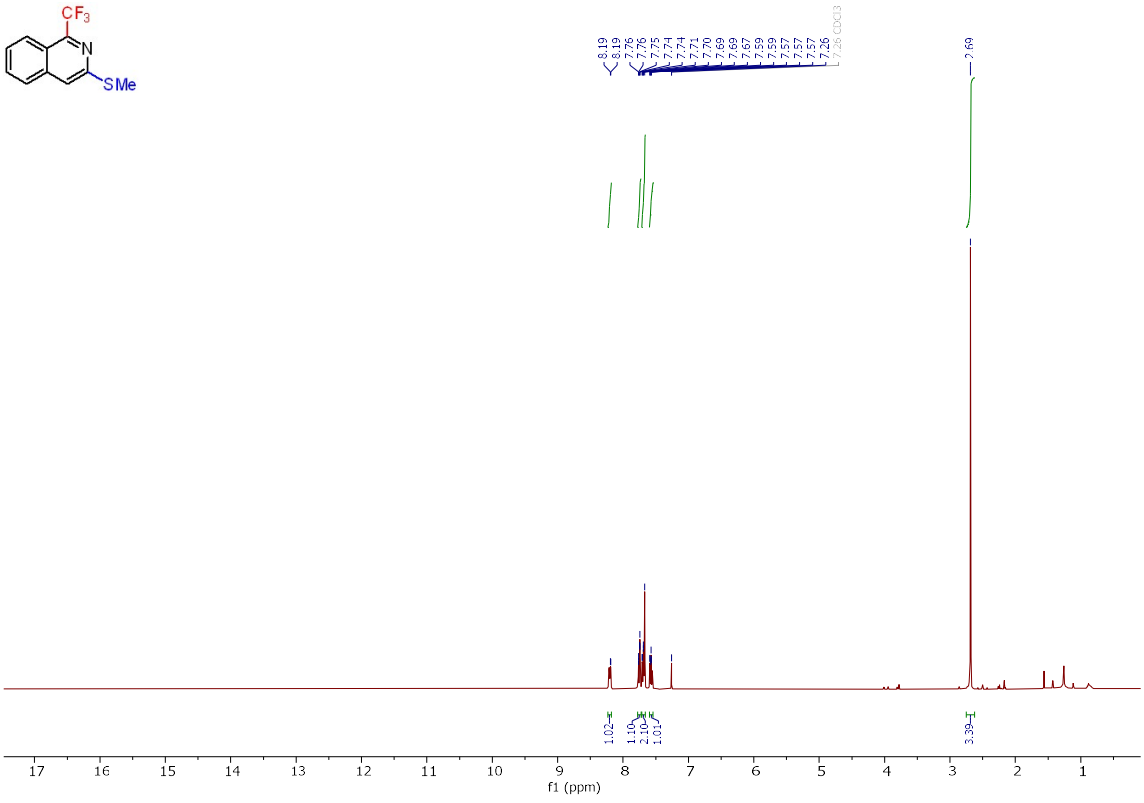
^{13}C NMR spectrum of **7e** ($CDCl_3$, 101 MHz)



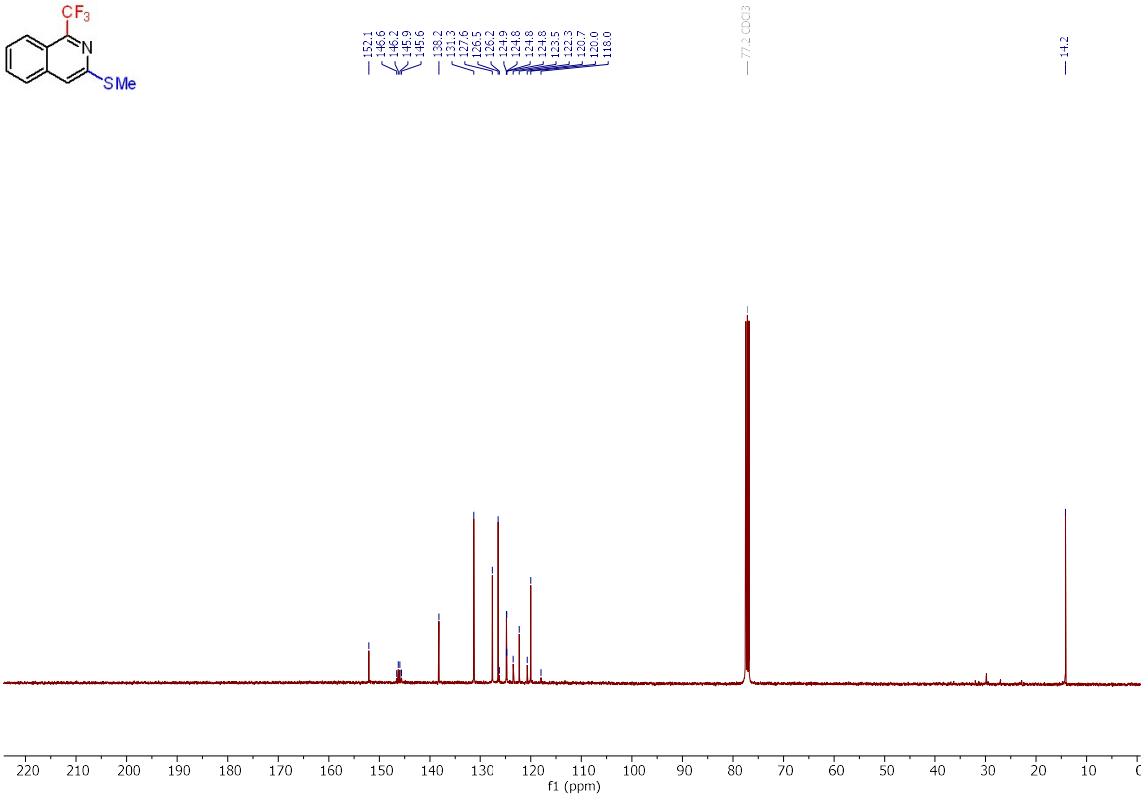
^{19}F NMR spectrum of **7e** ($CDCl_3$, 376 MHz)



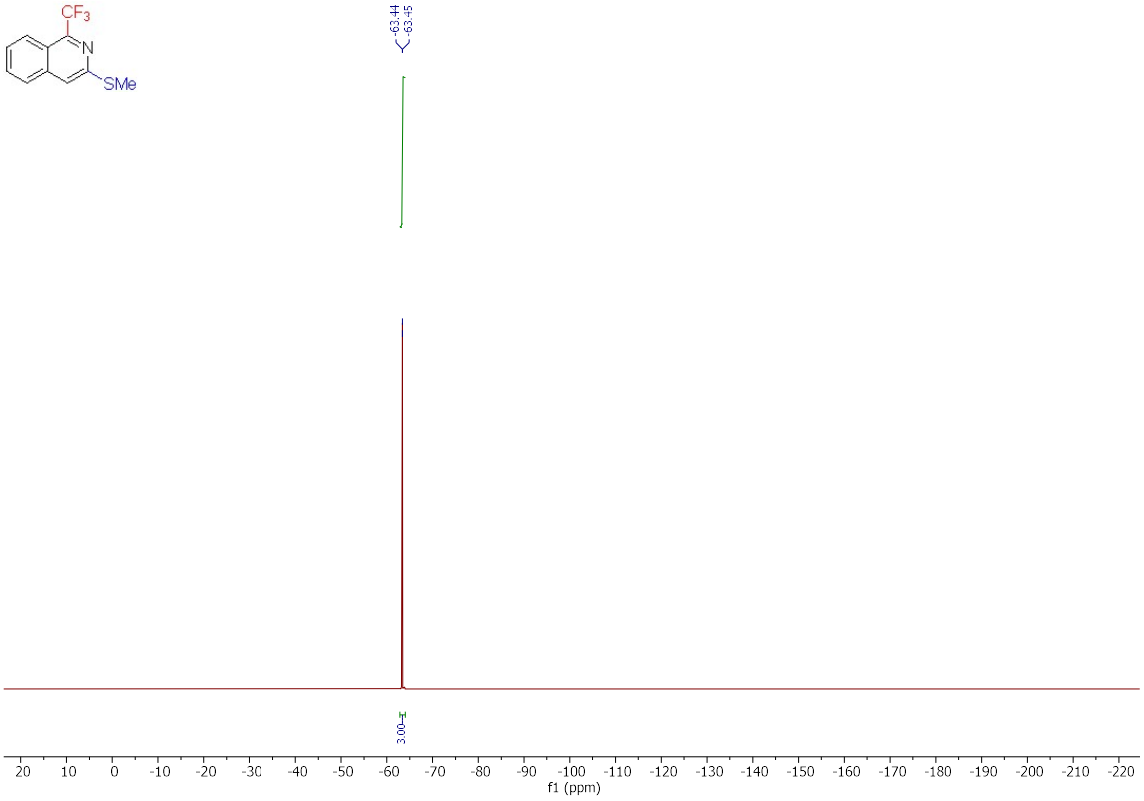
^{1}H NMR spectrum of **7f** ($CDCl_3$, 400 MHz)



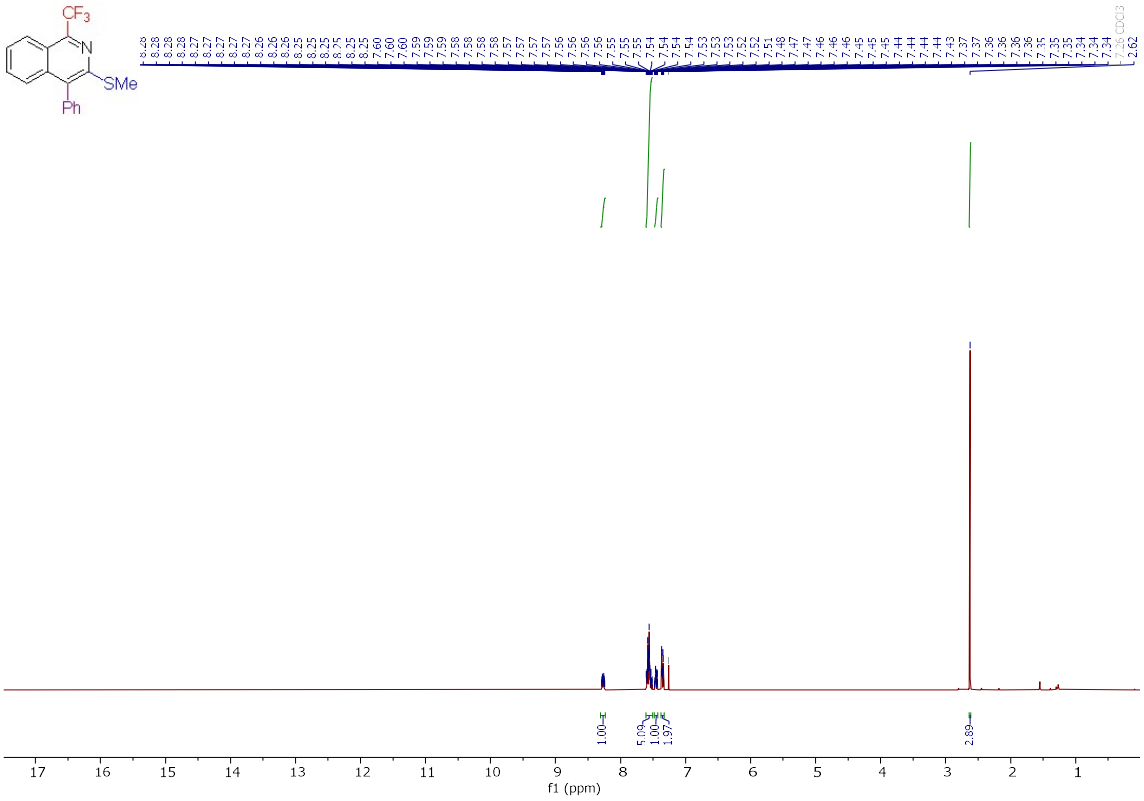
^{13}C NMR spectrum of **7f** ($CDCl_3$, 101 MHz)



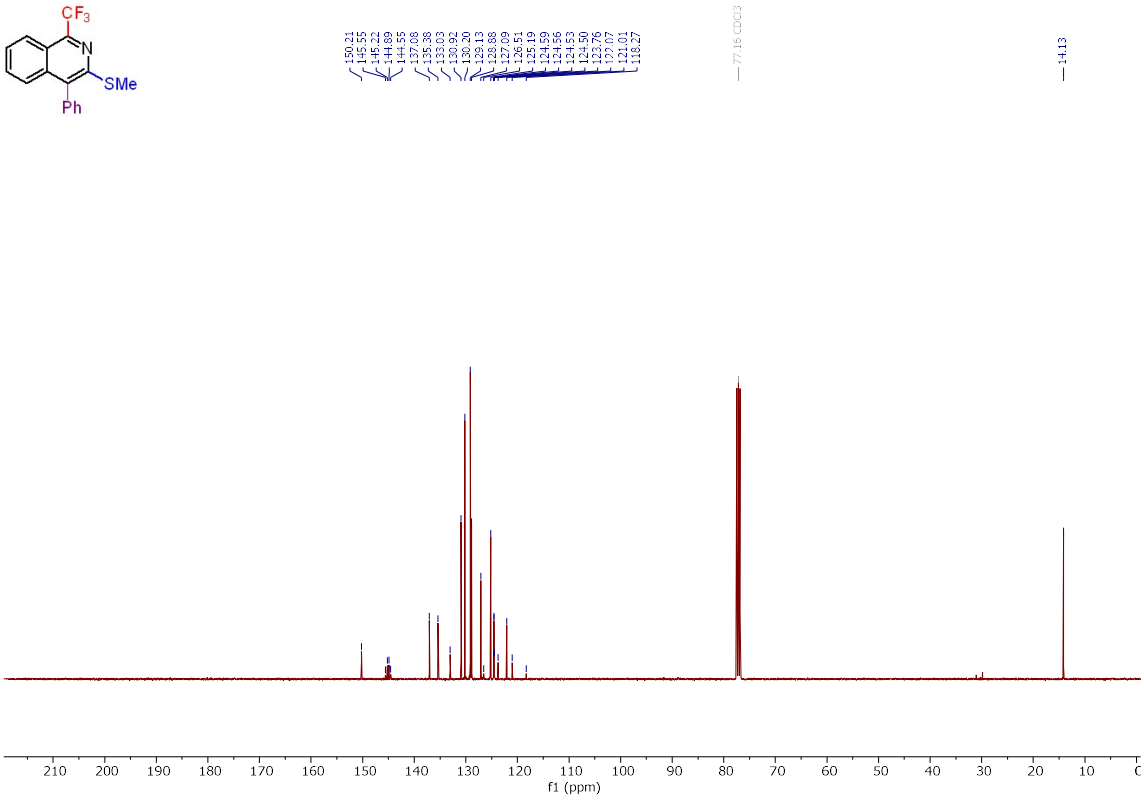
^{19}F NMR spectrum of **7f** ($CDCl_3$, 376 MHz)



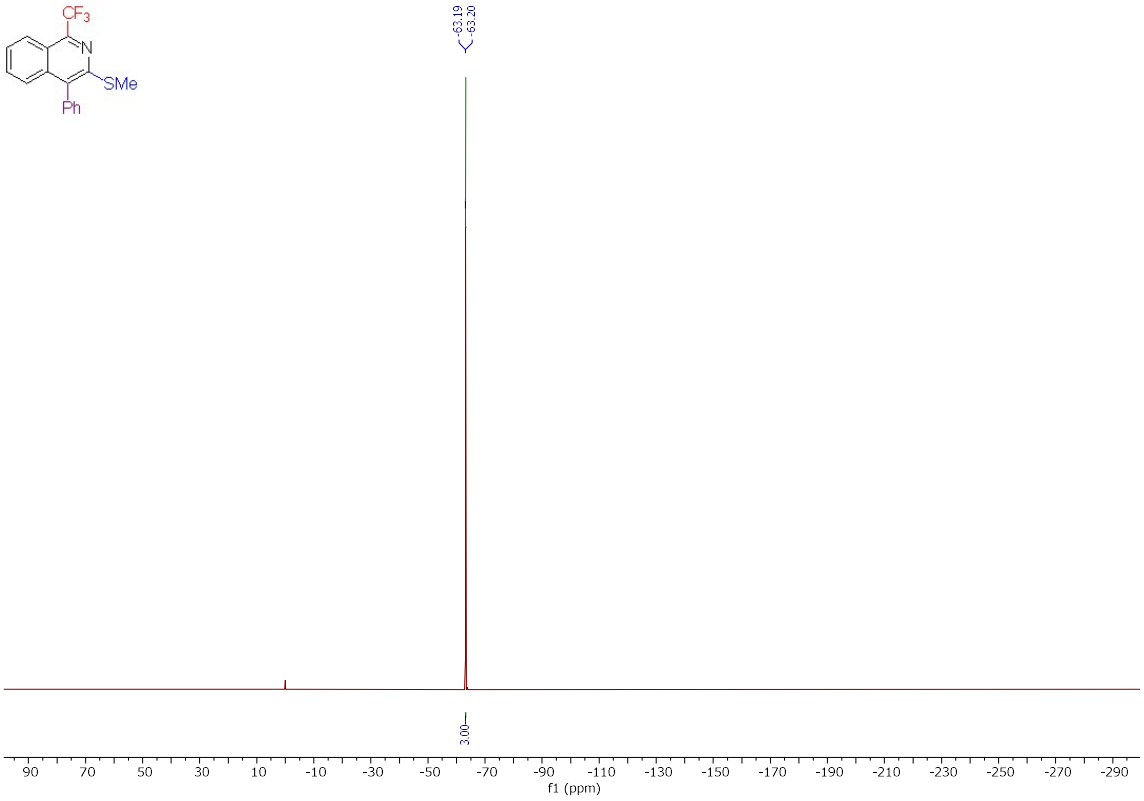
^{1}H NMR spectrum of **7g** ($CDCl_3$, 400 MHz)



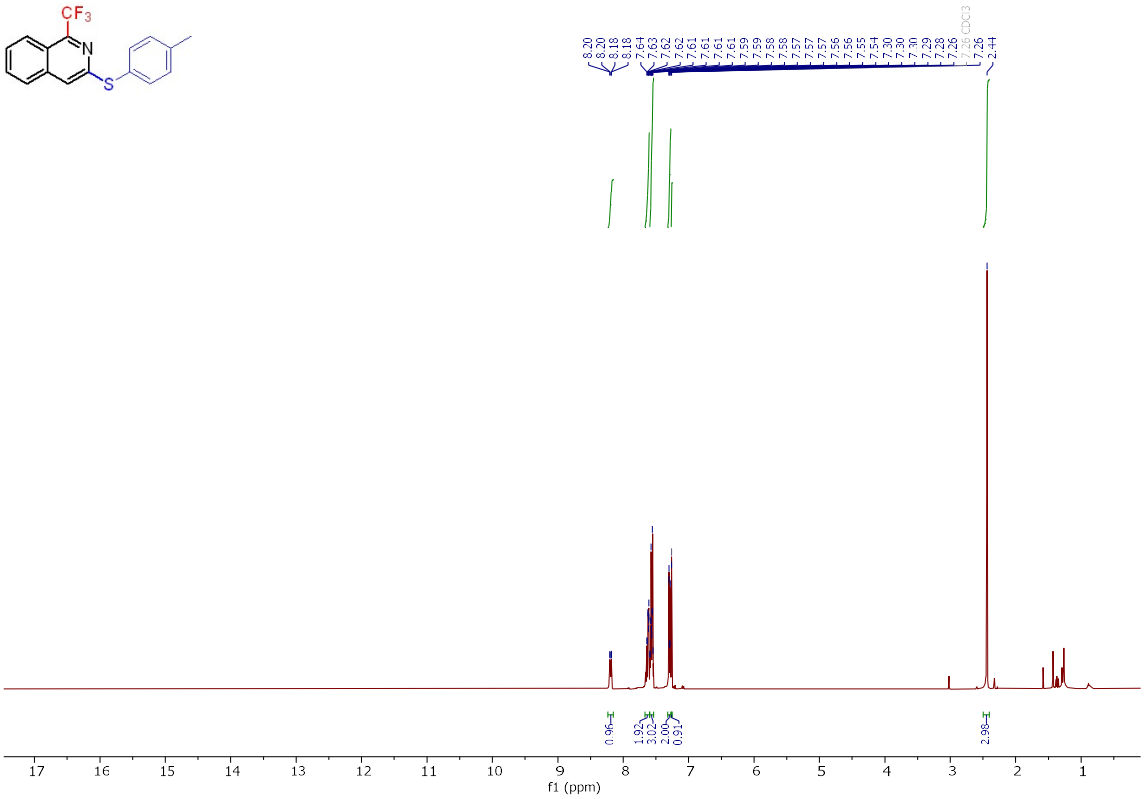
^{13}C NMR spectrum of **7g** ($CDCl_3$, 101 MHz)



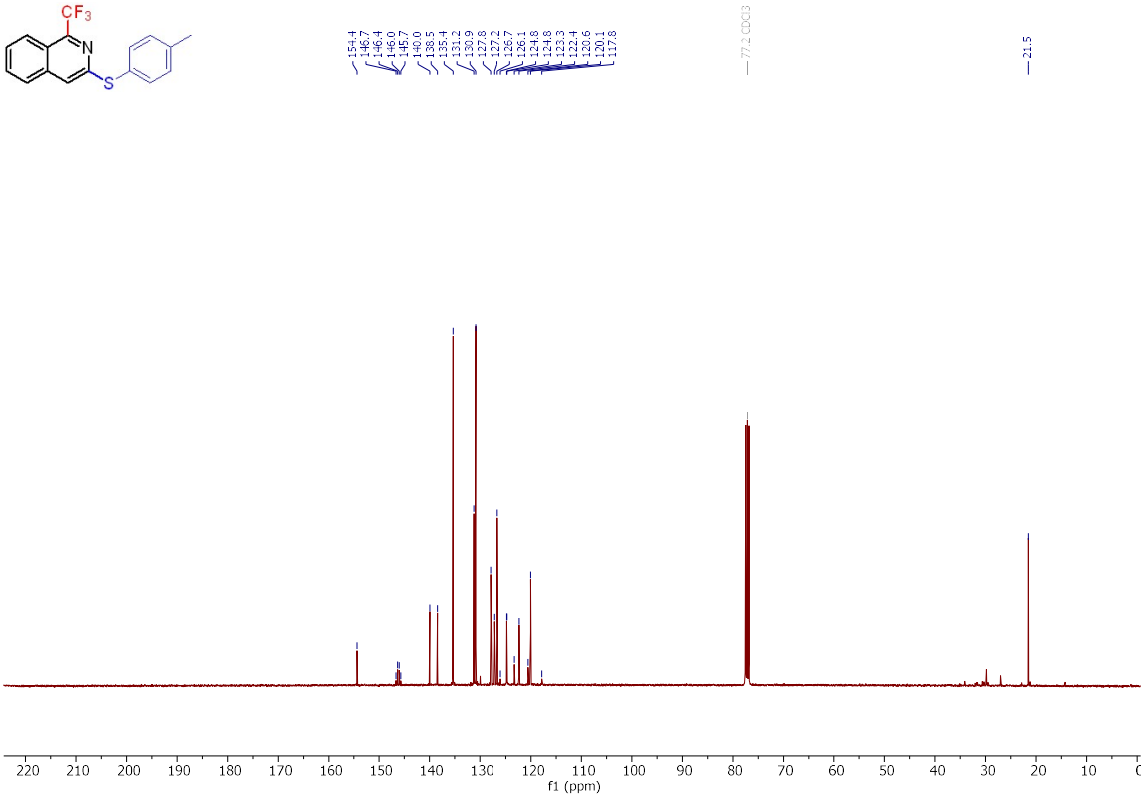
^{19}F NMR spectrum of **7g** ($CDCl_3$, 376 MHz)



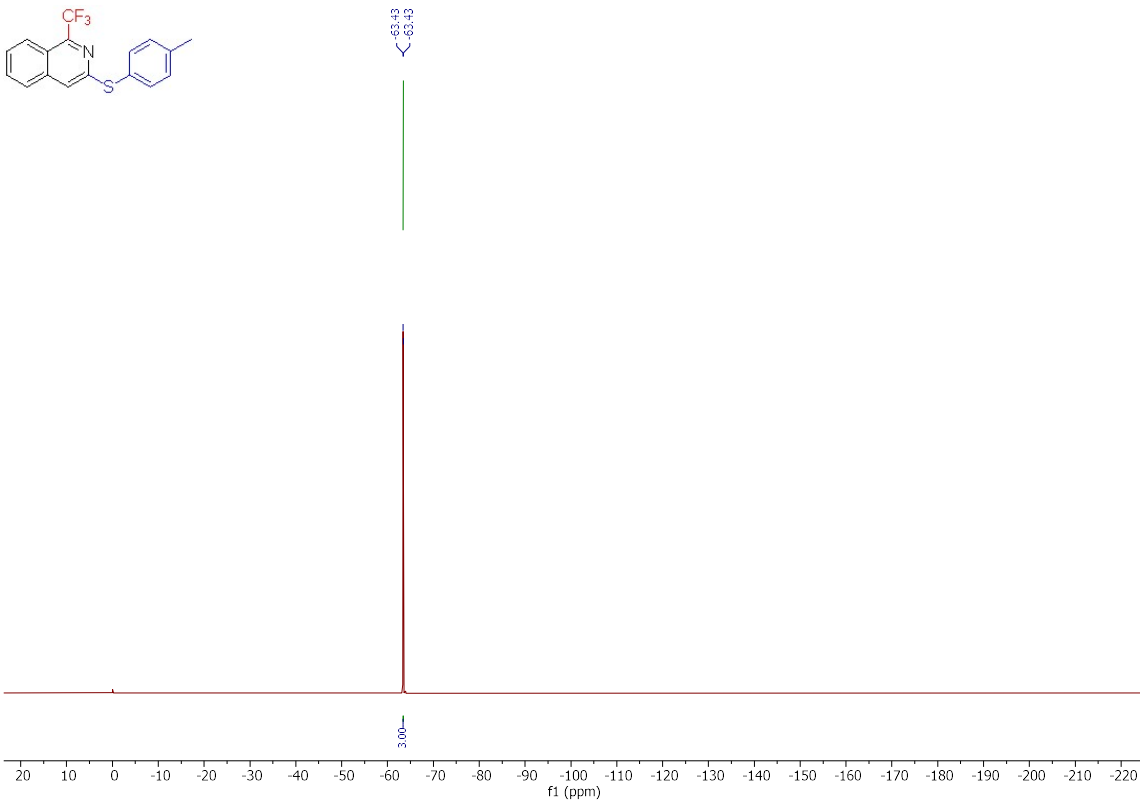
^{1}H NMR spectrum of **7h** ($CDCl_3$, 400 MHz)



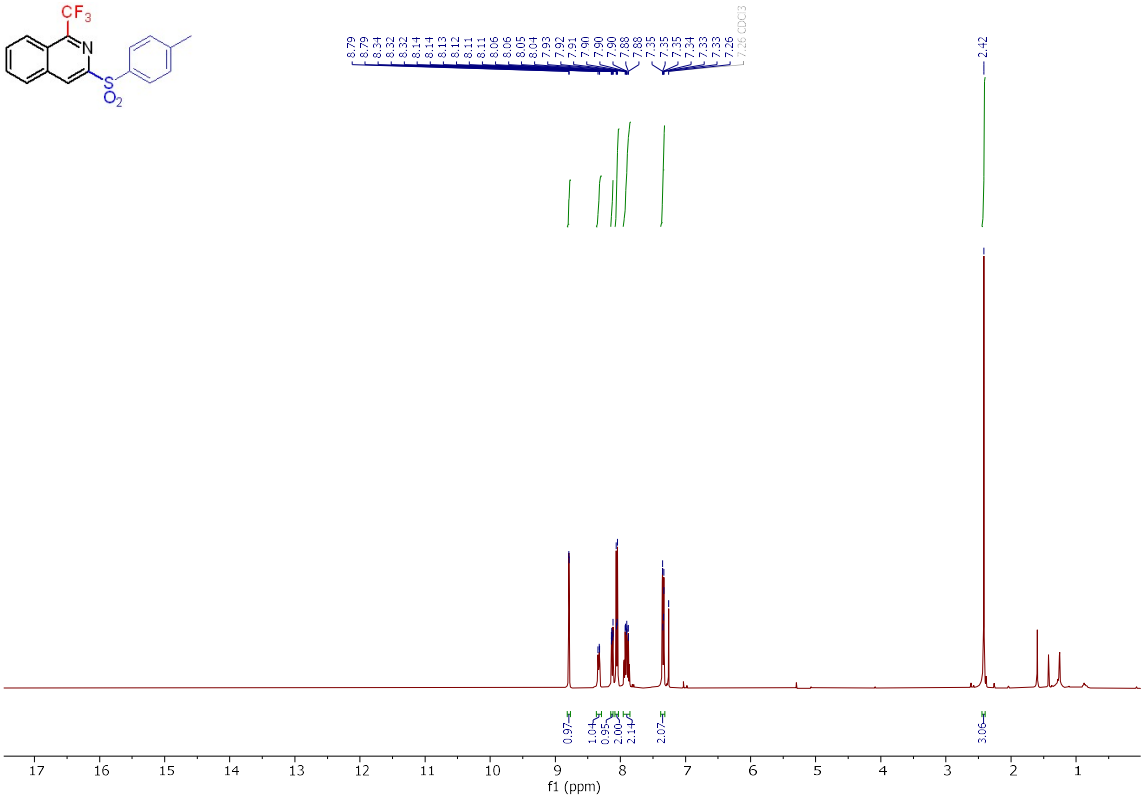
^{13}C NMR spectrum of **7h** ($CDCl_3$, 101 MHz)



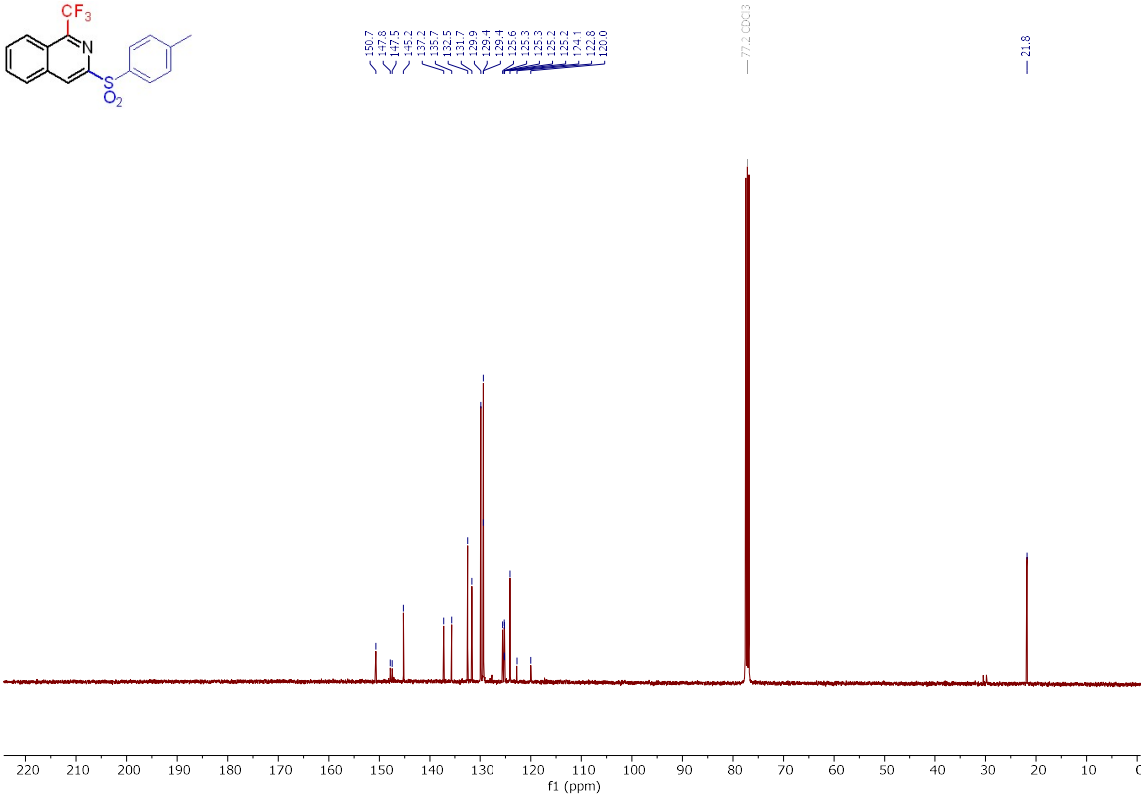
^{19}F NMR spectrum of **7h** ($CDCl_3$, 376 MHz)



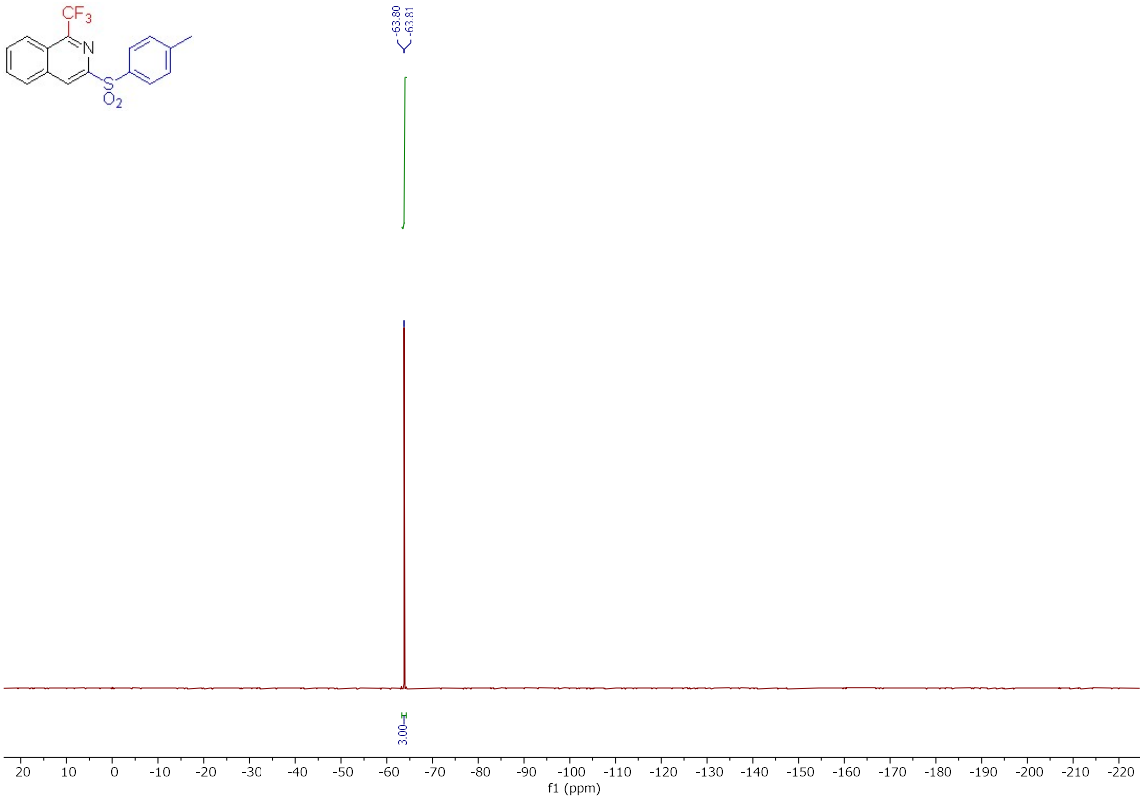
^{1}H NMR spectrum of **7i** ($CDCl_3$, 400 MHz)



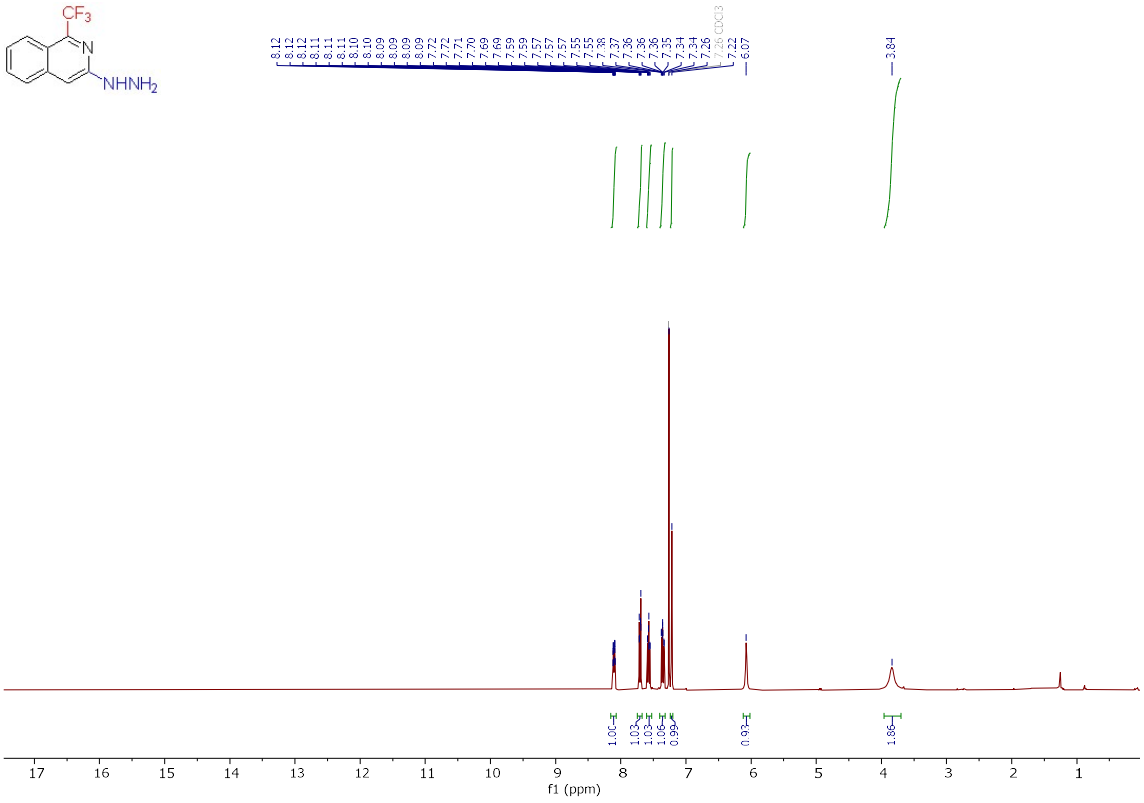
^{13}C NMR spectrum of **7i** ($CDCl_3$, 101 MHz)



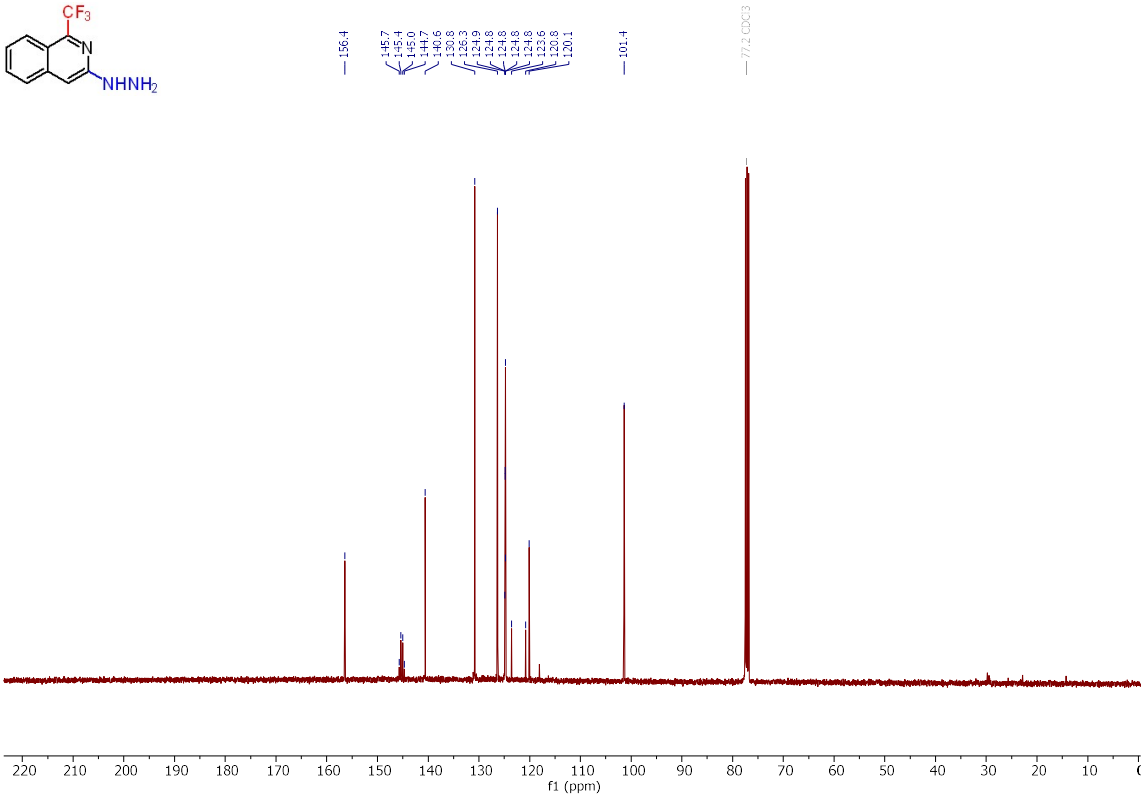
^{19}F NMR spectrum of **7i** ($CDCl_3$, 376 MHz)



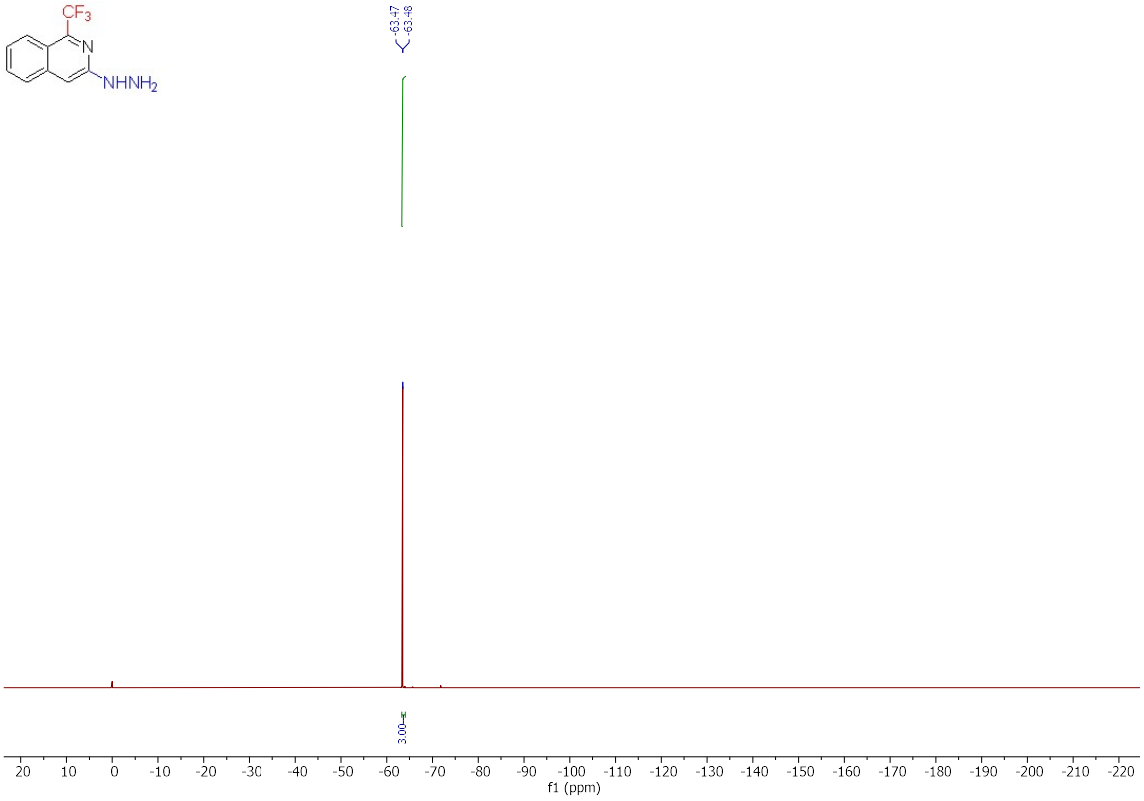
^{1}H NMR spectrum of **7j** ($CDCl_3$, 400 MHz)



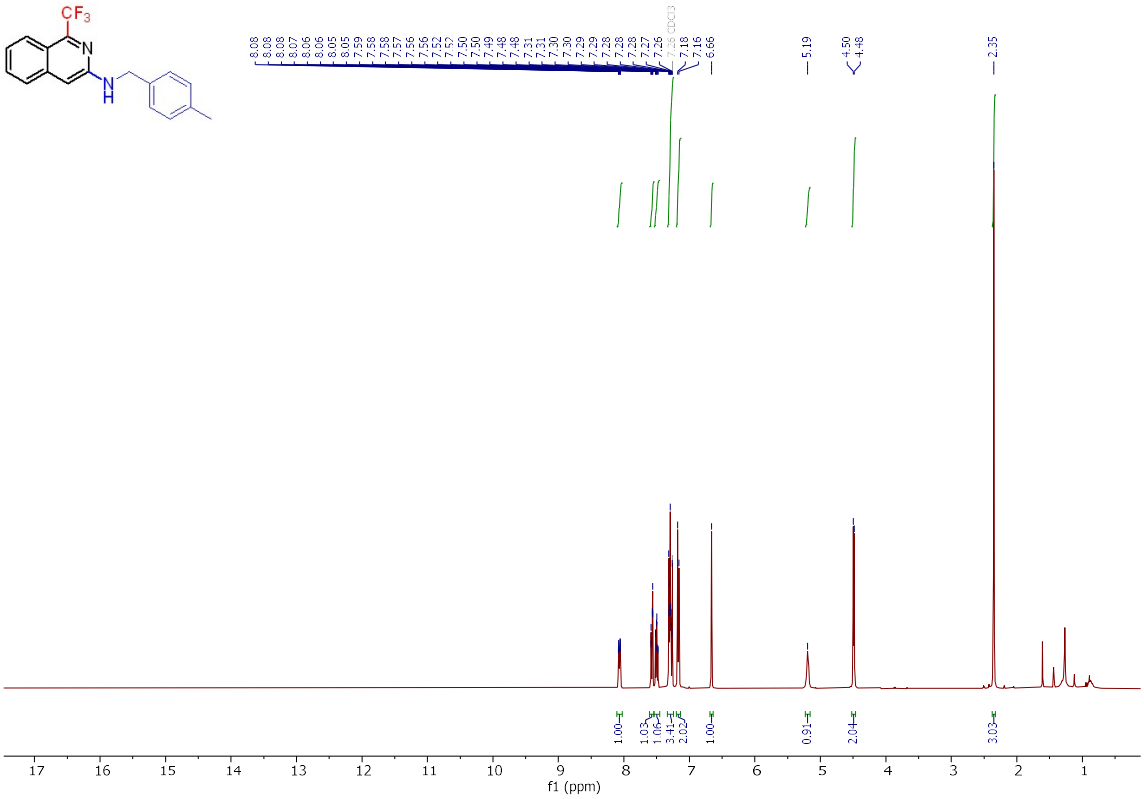
^{13}C NMR spectrum of **7j** ($CDCl_3$, 101 MHz)



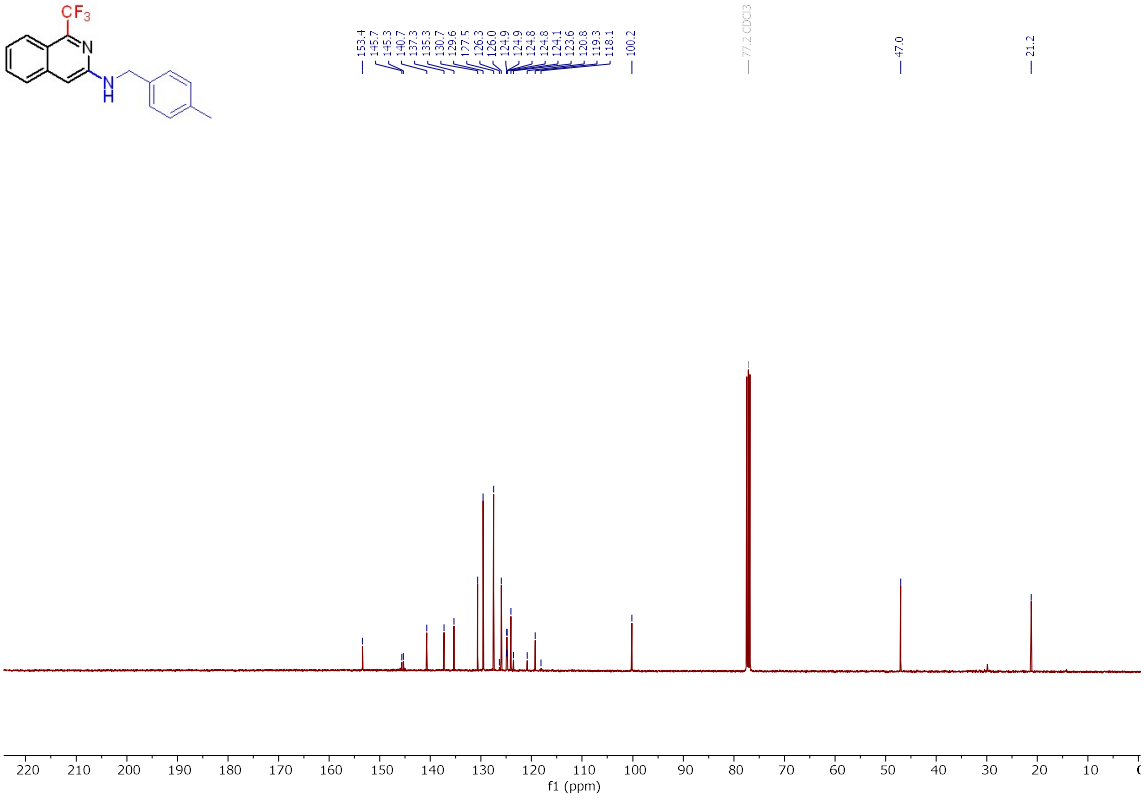
^{19}F NMR spectrum of **7j** ($CDCl_3$, 376 MHz)



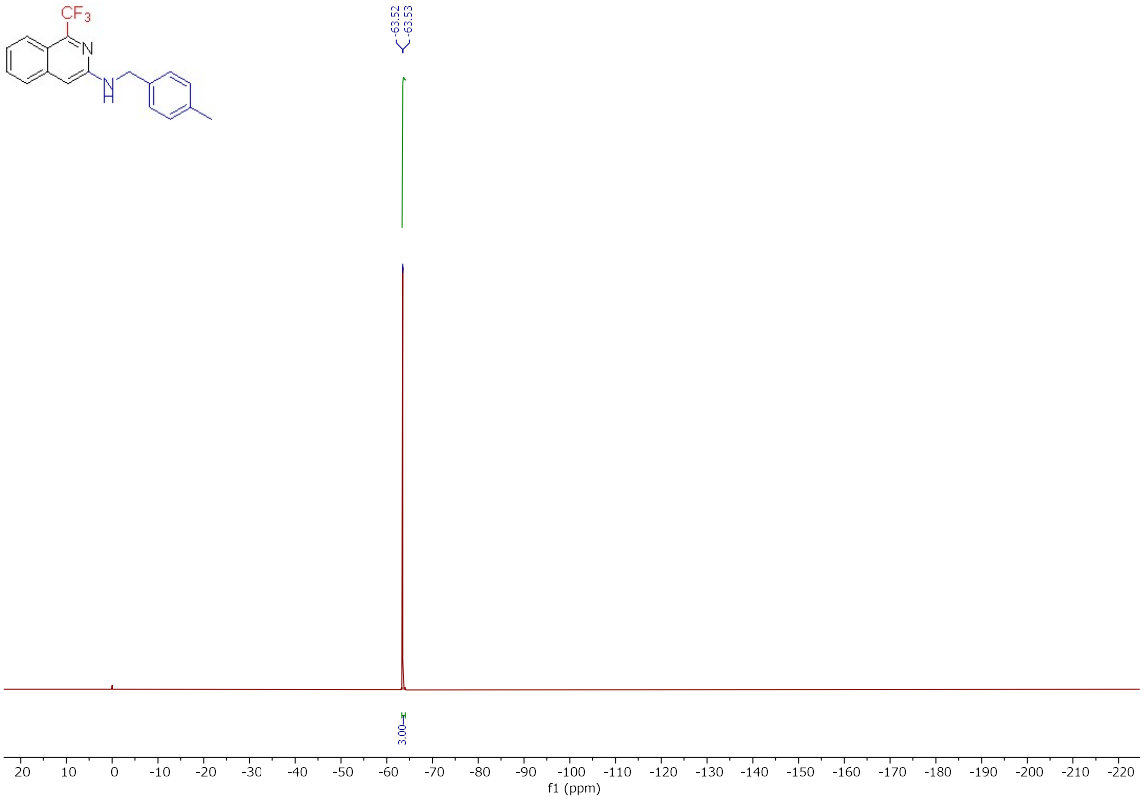
^{1}H NMR spectrum of **7k** ($CDCl_3$, 400 MHz)



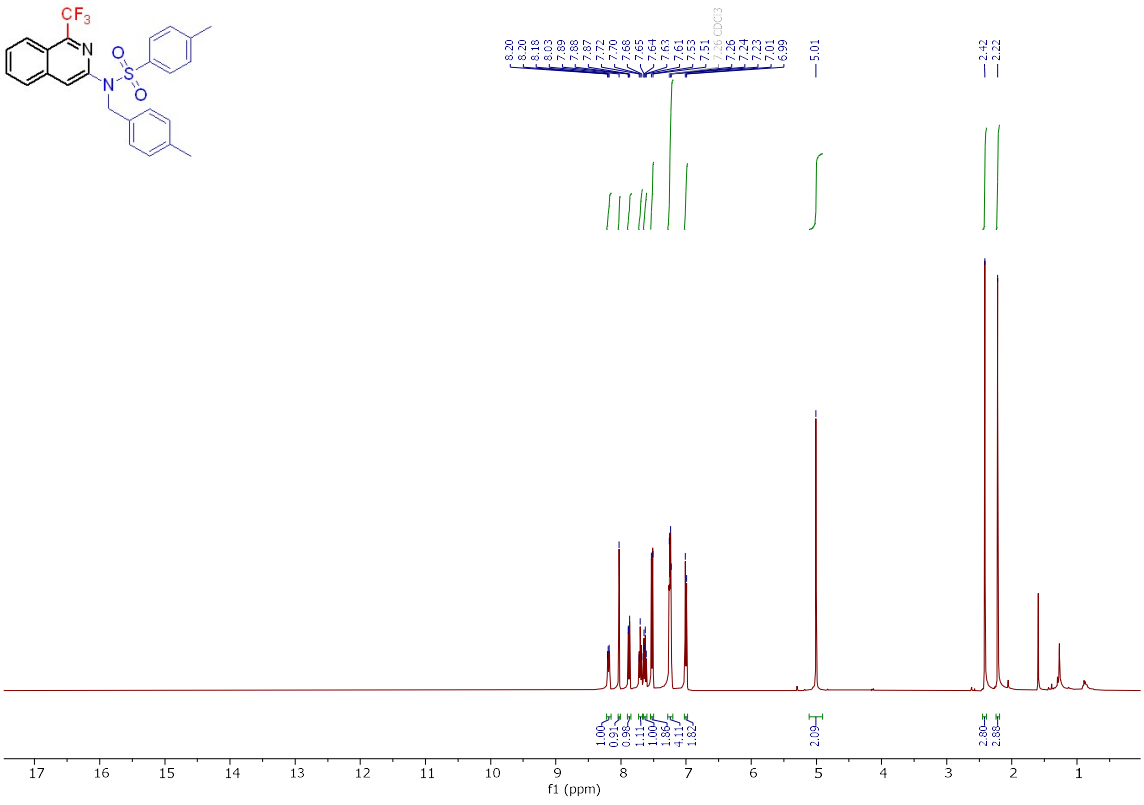
^{13}C NMR spectrum of **7k** ($CDCl_3$, 101 MHz)



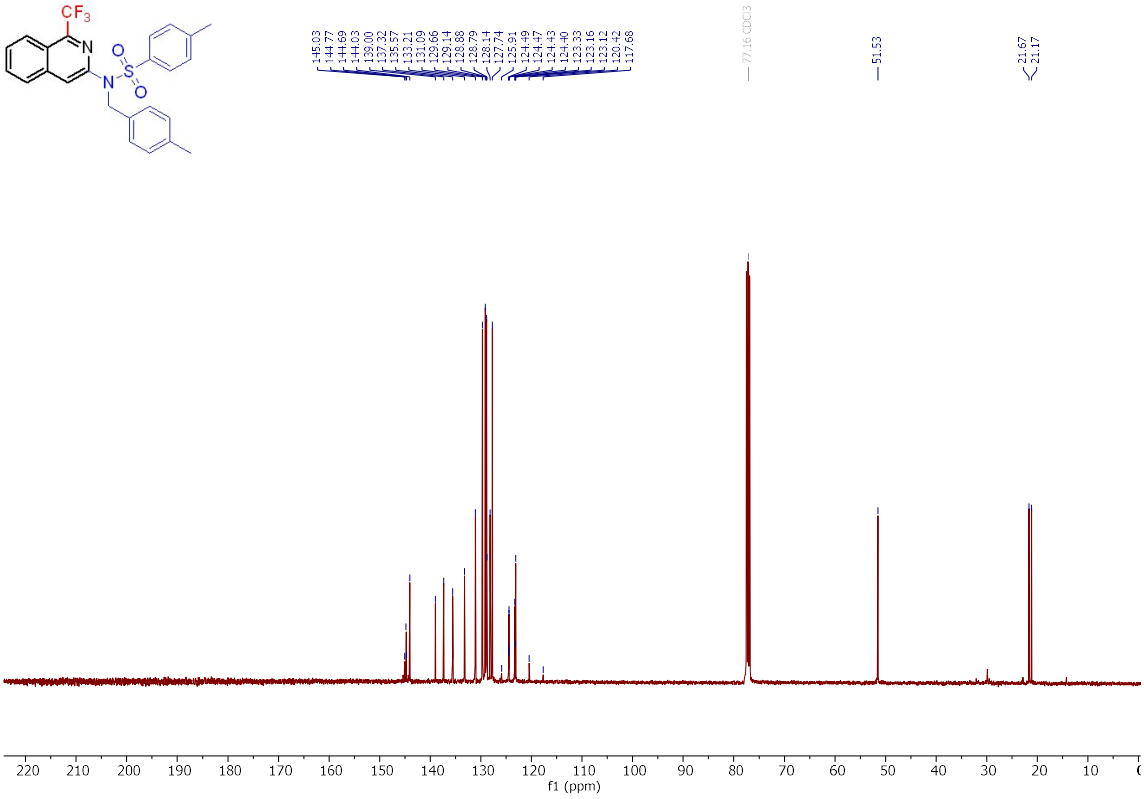
^{19}F NMR spectrum of **7k** ($CDCl_3$, 376 MHz)



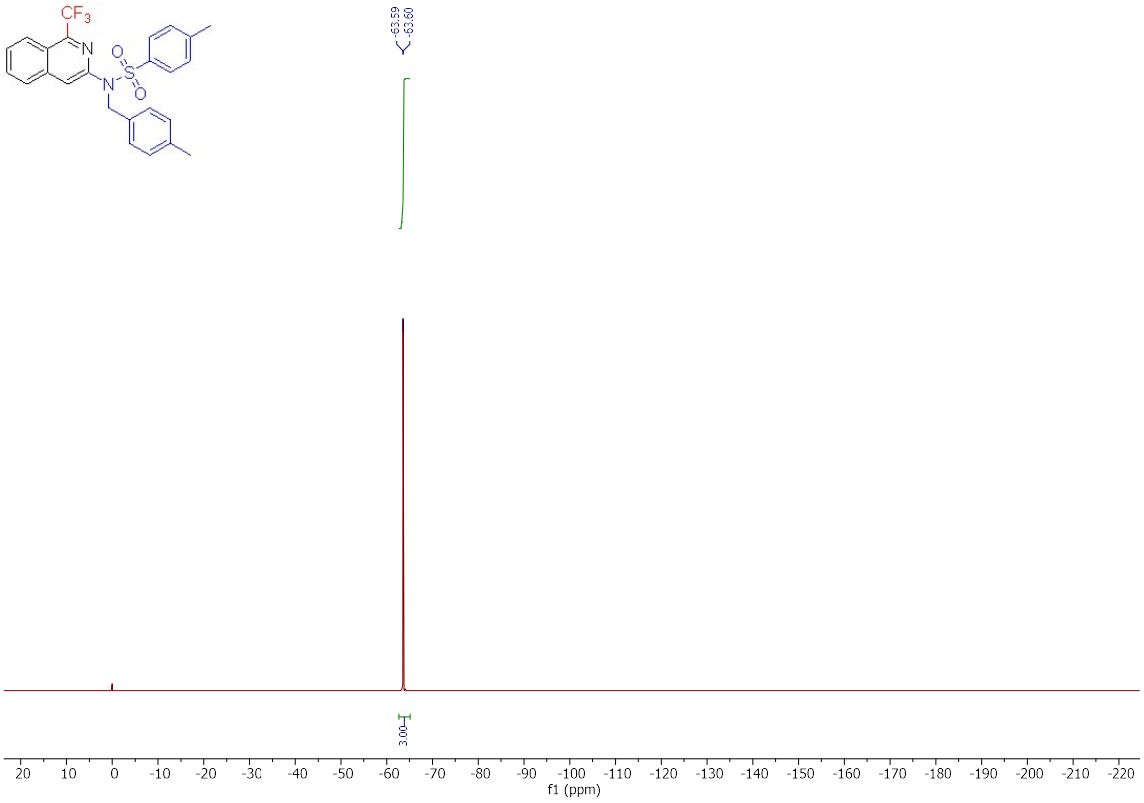
^{1}H NMR spectrum of **8a** ($CDCl_3$, 400 MHz)



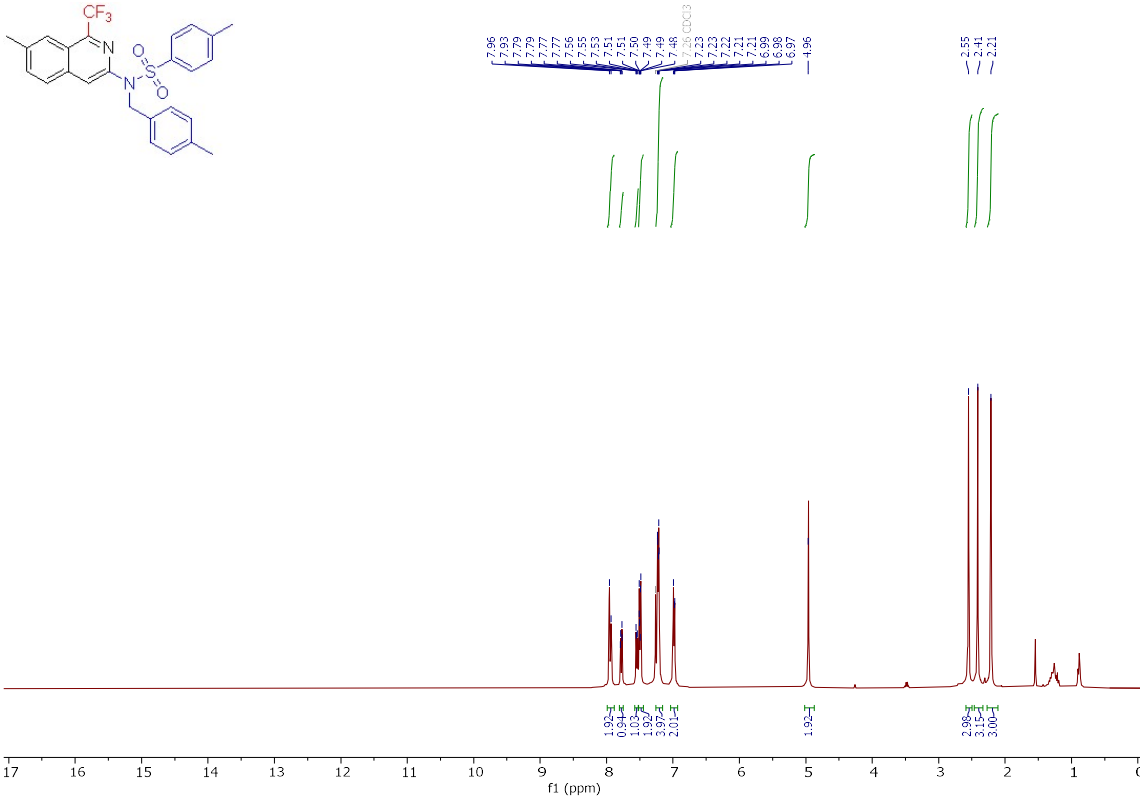
^{13}C NMR spectrum of **8a** ($CDCl_3$, 101 MHz)



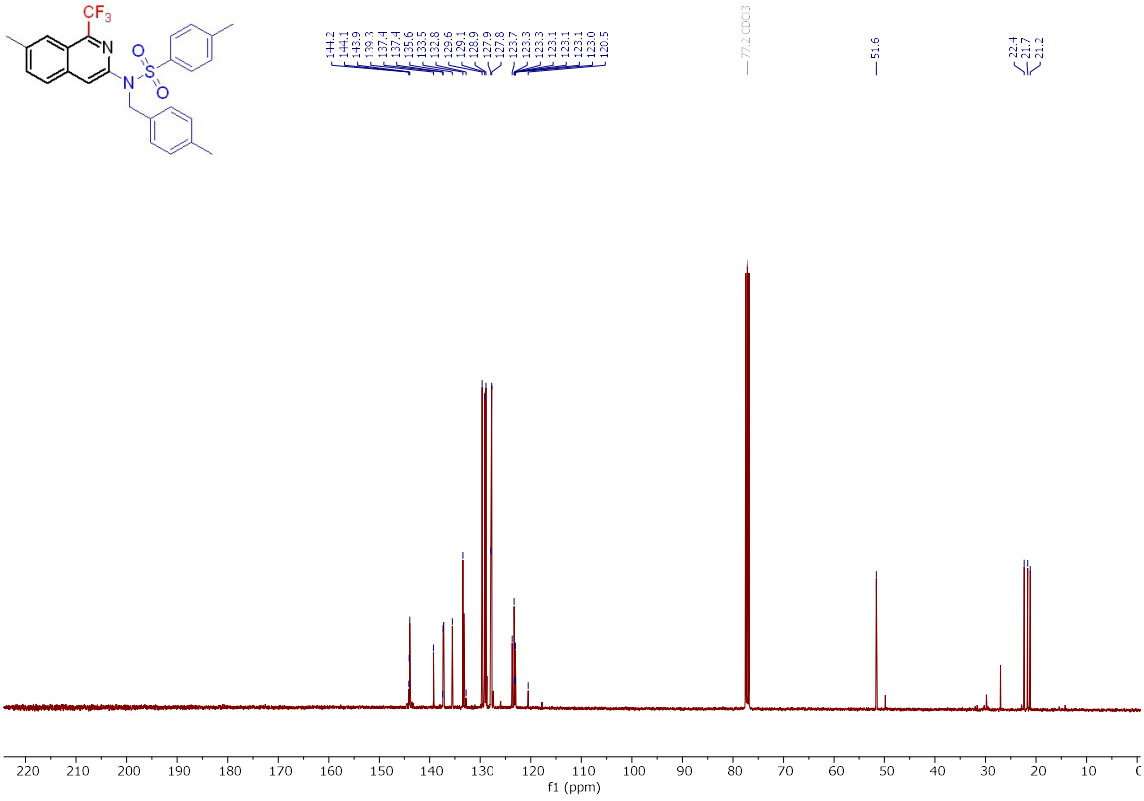
^{19}F NMR spectrum of **8a** ($CDCl_3$, 376 MHz)



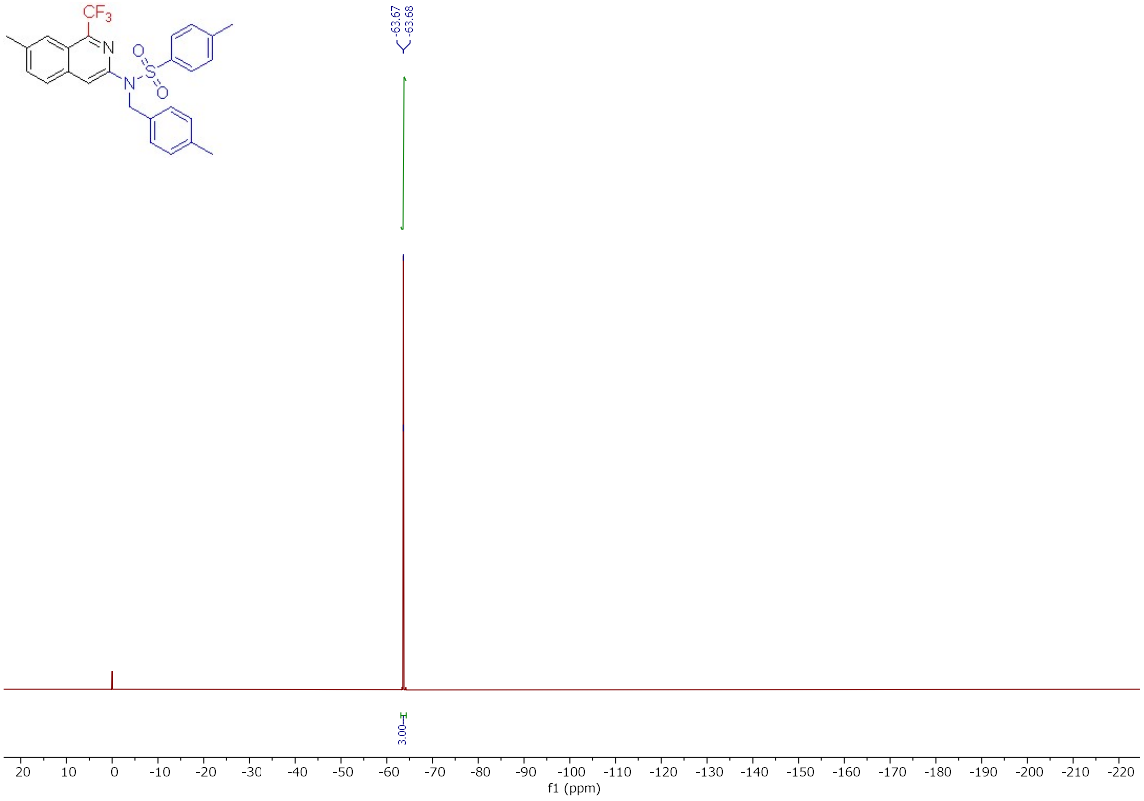
^{1}H NMR spectrum of **8b** ($CDCl_3$, 400 MHz)



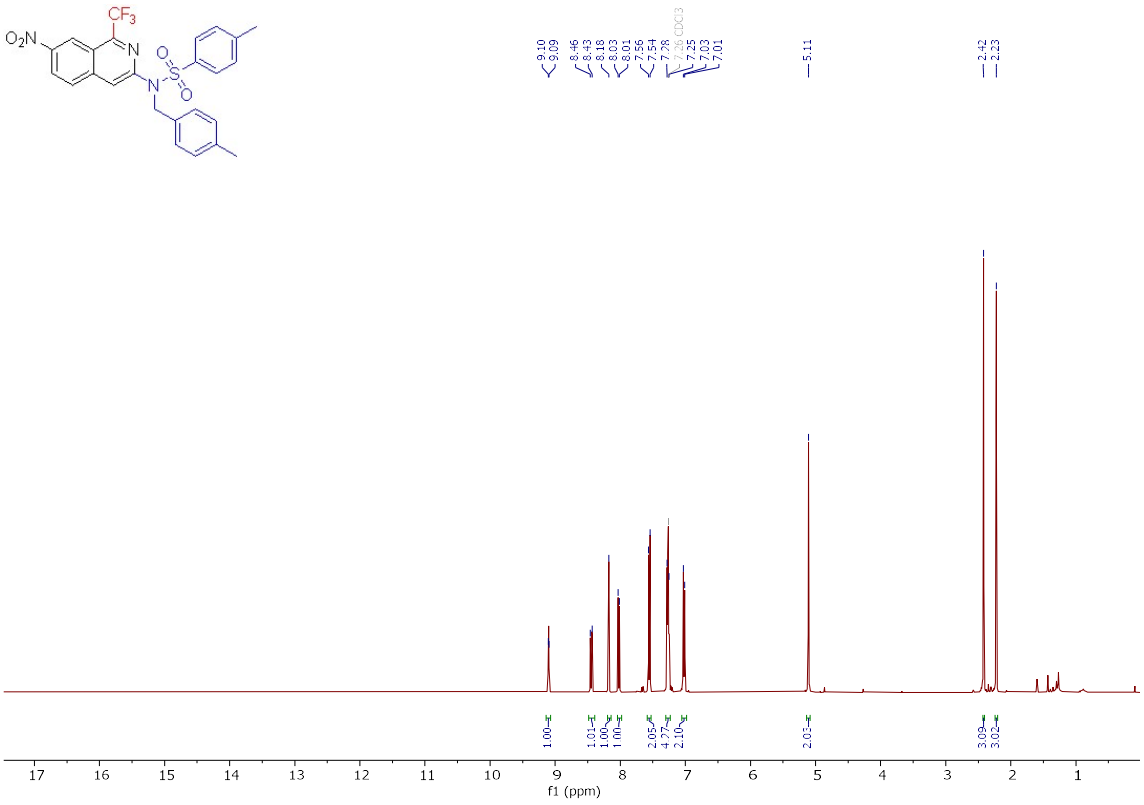
^{13}C NMR spectrum of **8b** ($CDCl_3$, 101 MHz)



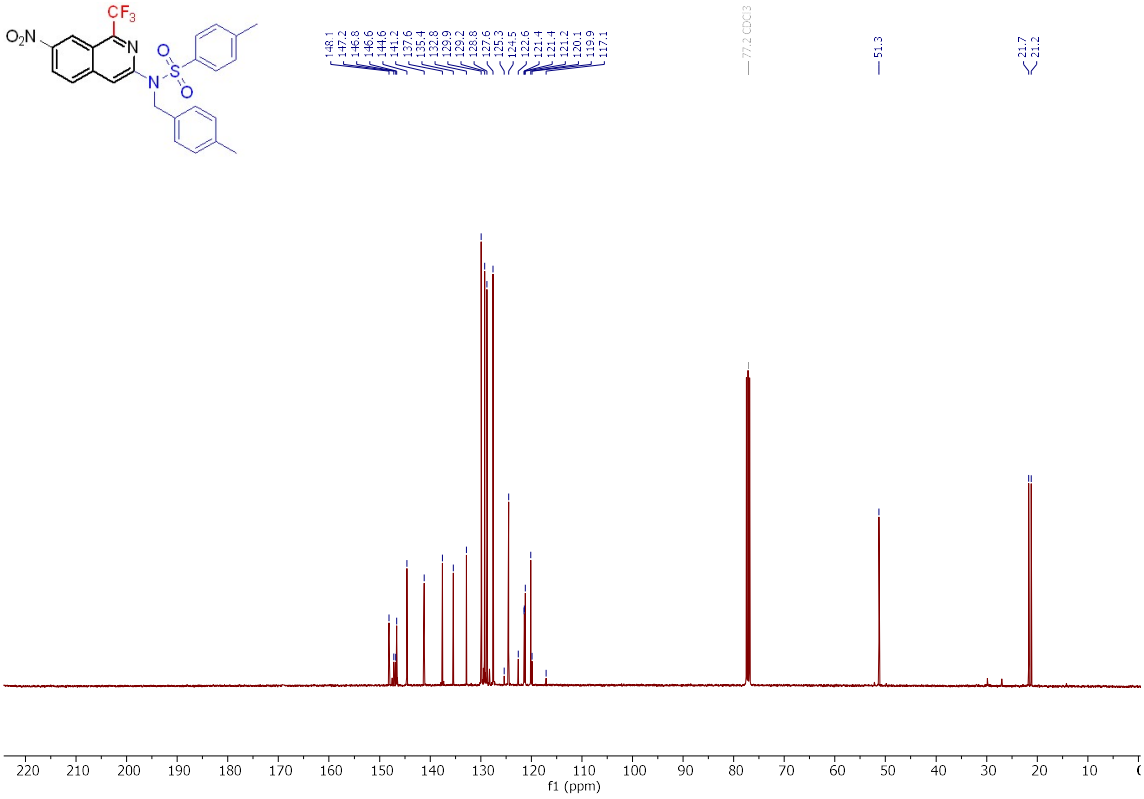
^{19}F NMR spectrum of **8b** ($CDCl_3$, 376 MHz)



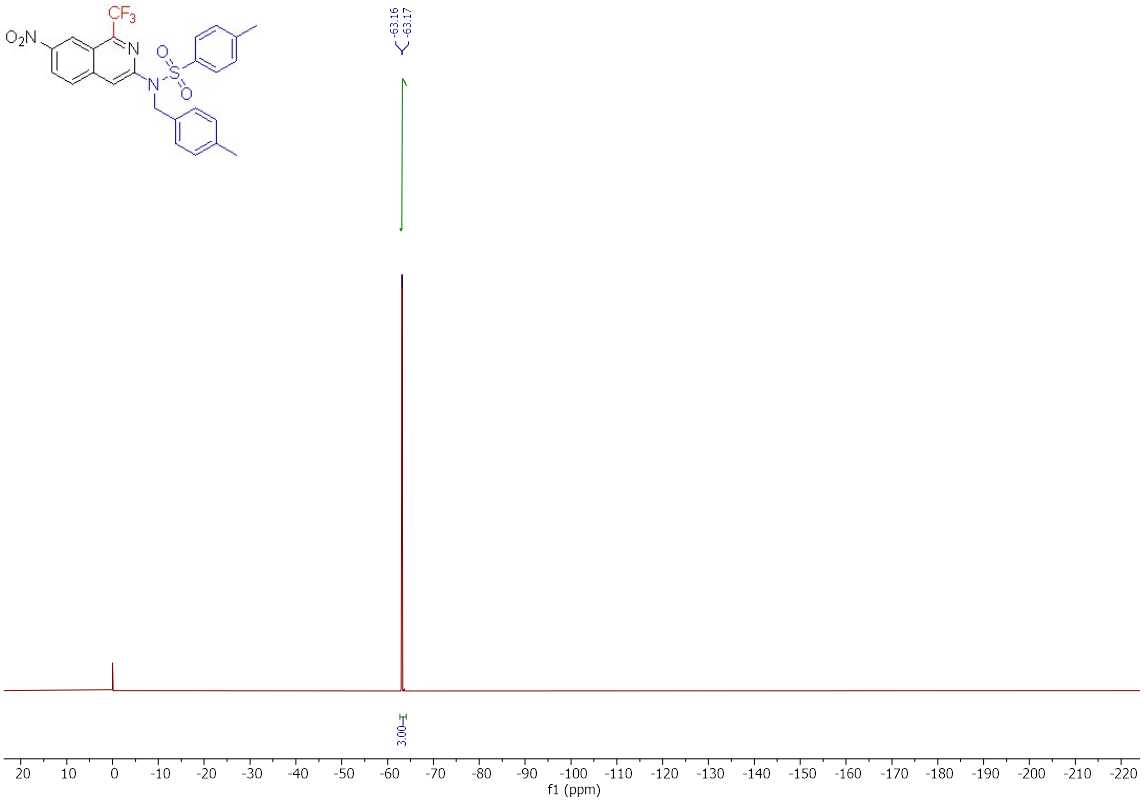
^{1}H NMR spectrum of **8c** ($CDCl_3$, 400 MHz)



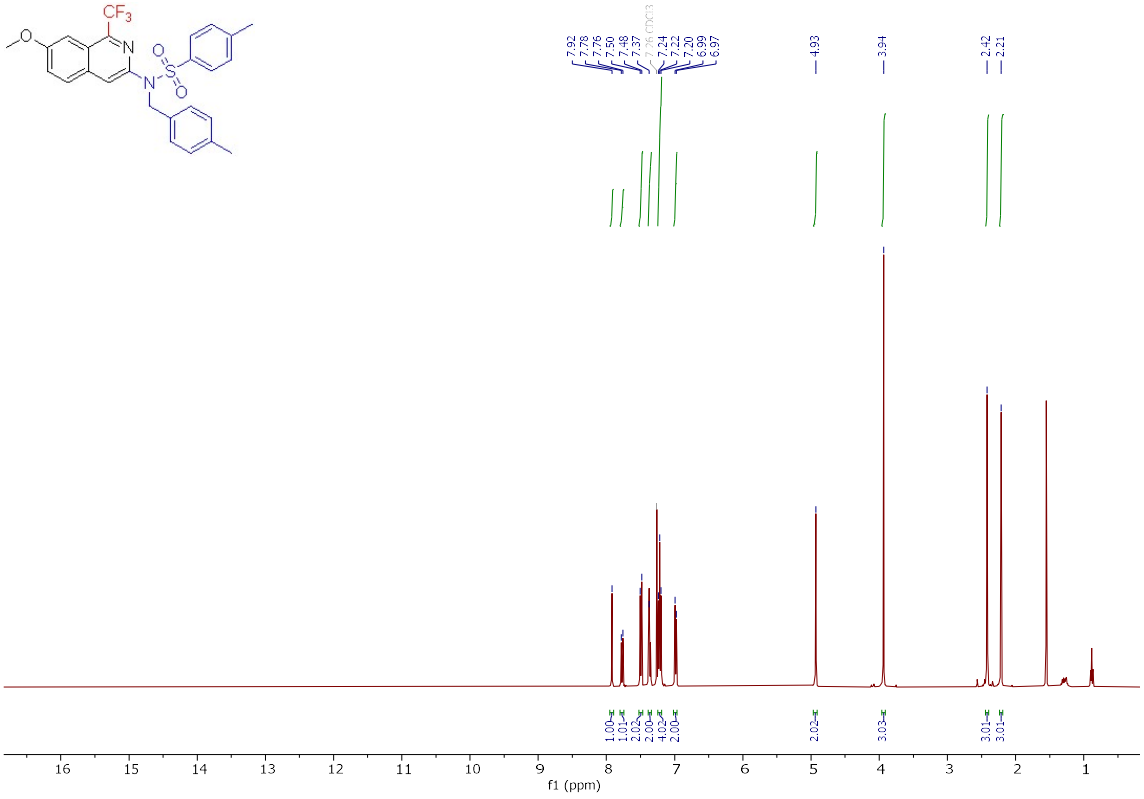
^{13}C NMR spectrum of **8c** ($CDCl_3$, 101 MHz)



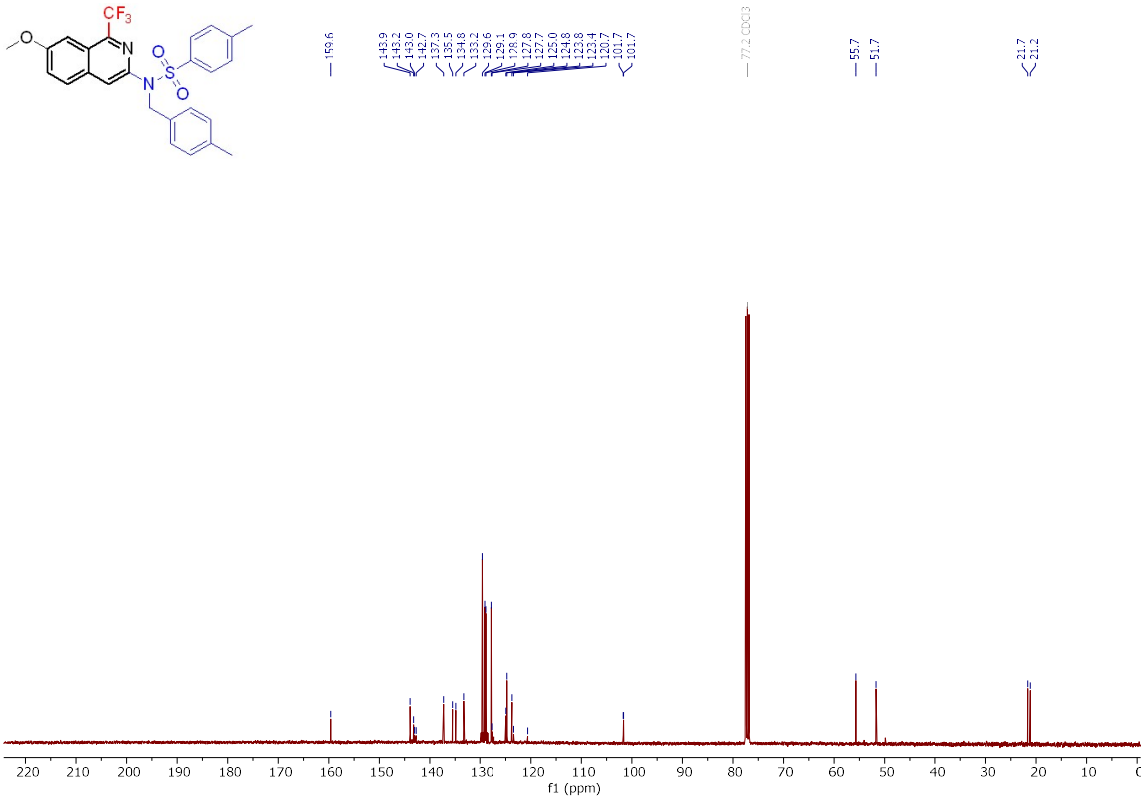
^{19}F NMR spectrum of **8c** ($CDCl_3$, 376 MHz)



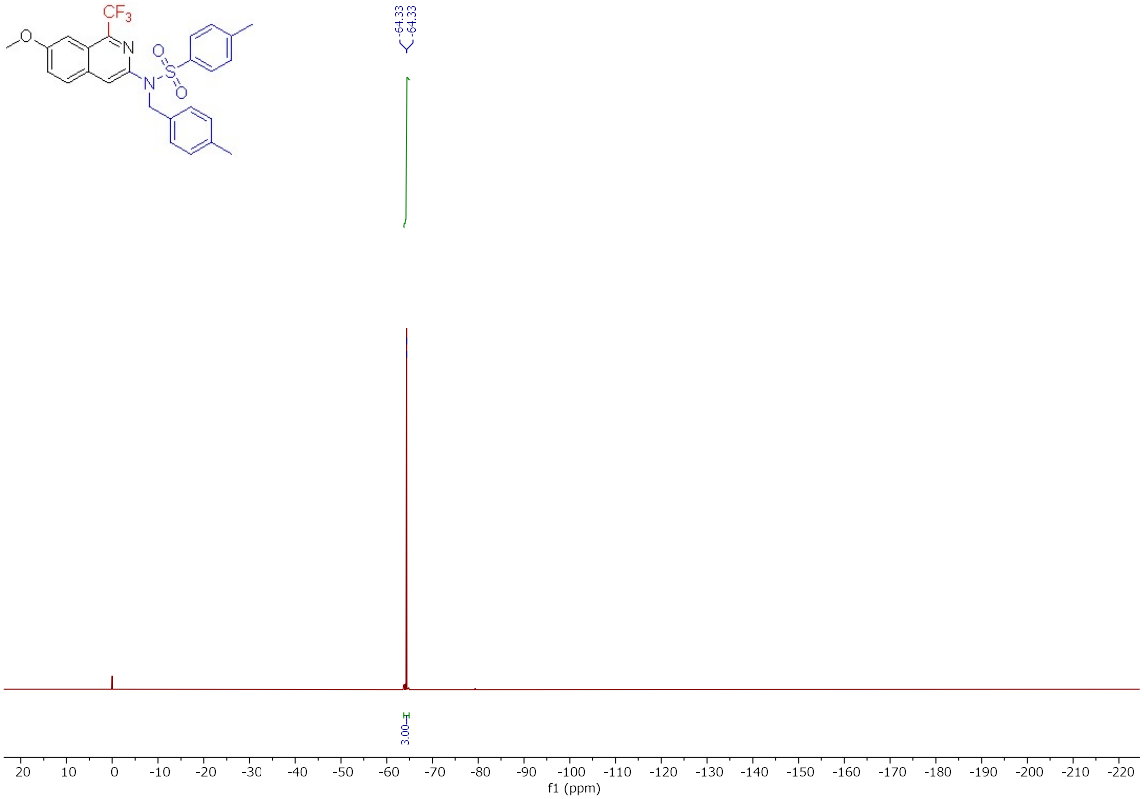
^{1}H NMR spectrum of **8d** ($CDCl_3$, 400 MHz)



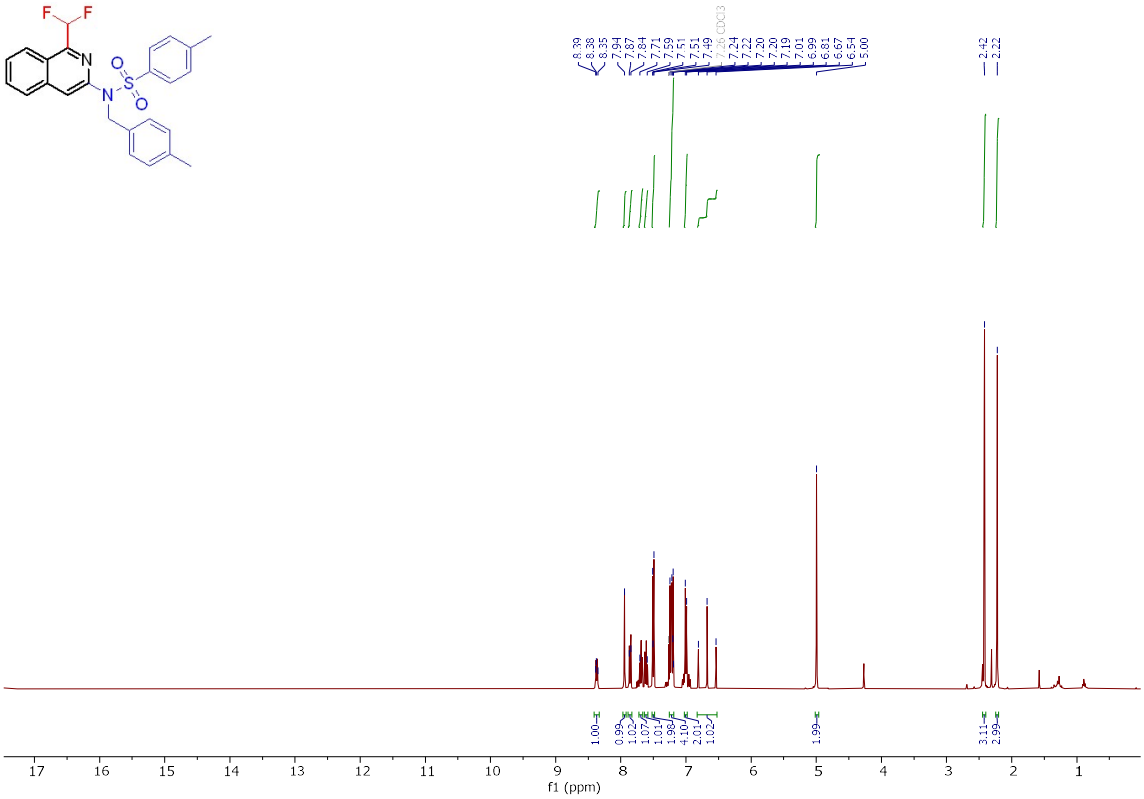
^{13}C NMR spectrum of **8d** ($CDCl_3$, 101 MHz)



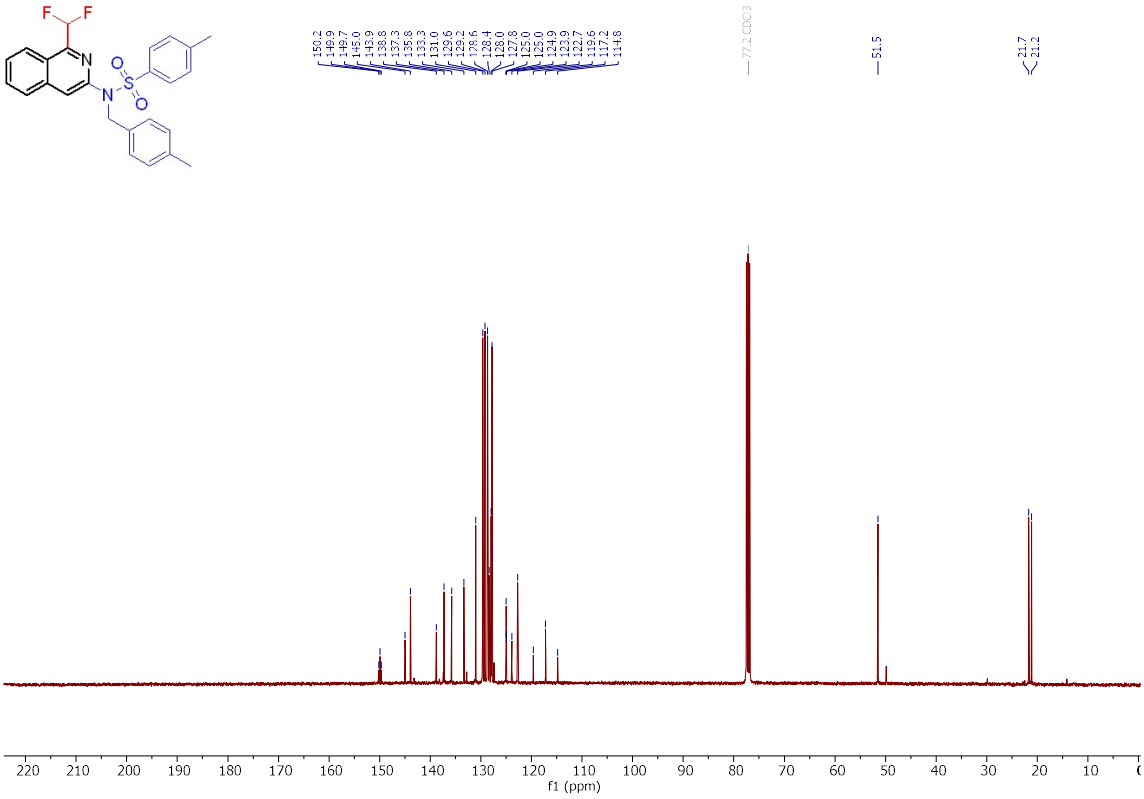
^{19}F NMR spectrum of **8d** ($CDCl_3$, 376 MHz)



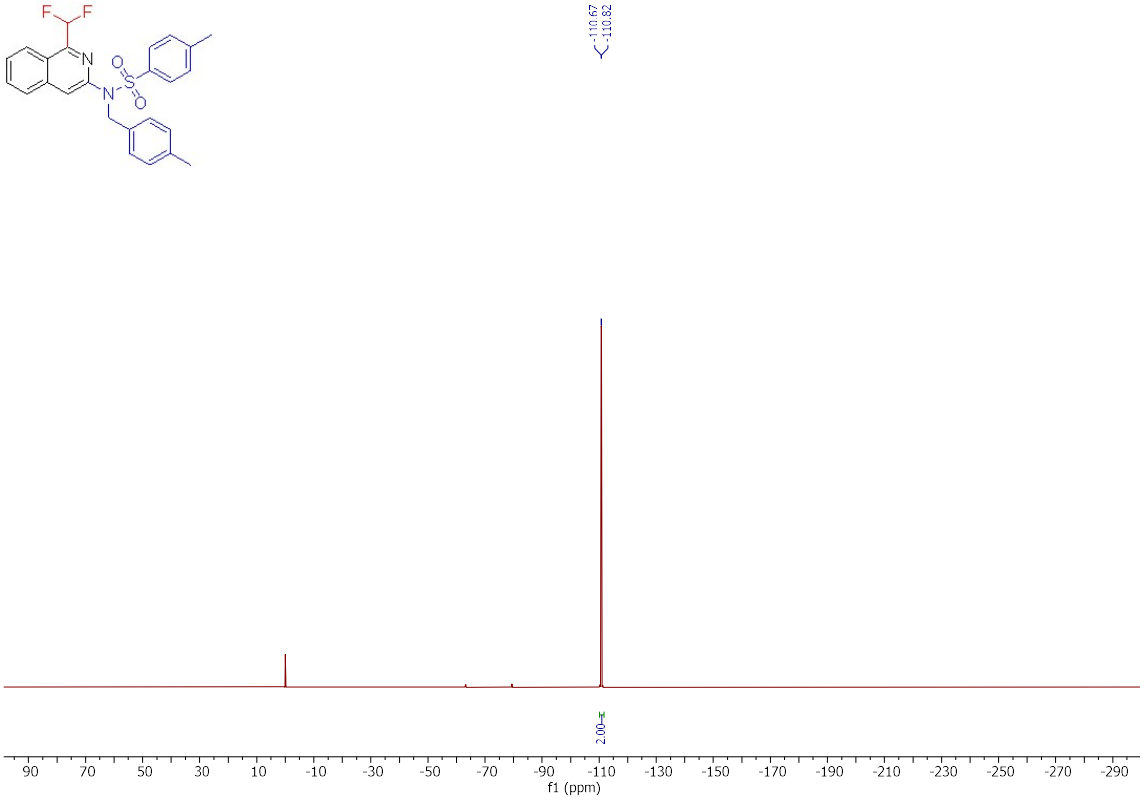
^{1}H NMR spectrum of **8e** ($CDCl_3$, 400 MHz)



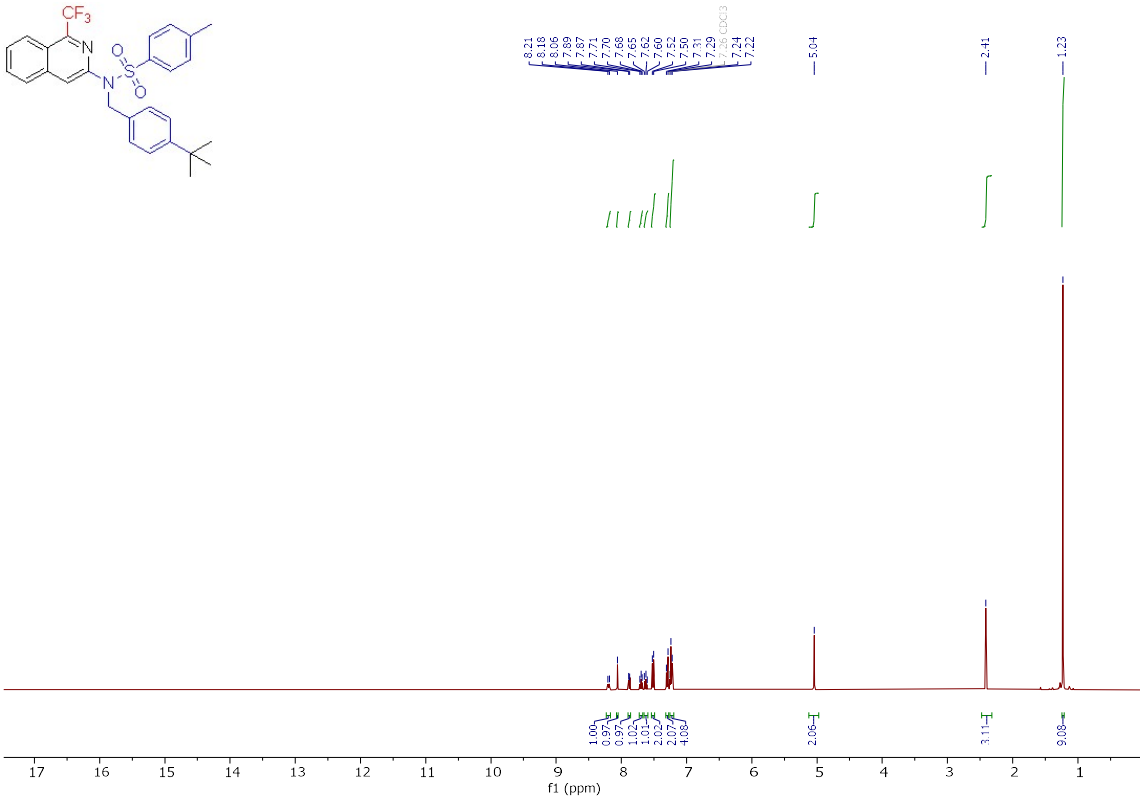
^{13}C NMR spectrum of **8e** ($CDCl_3$, 101 MHz)



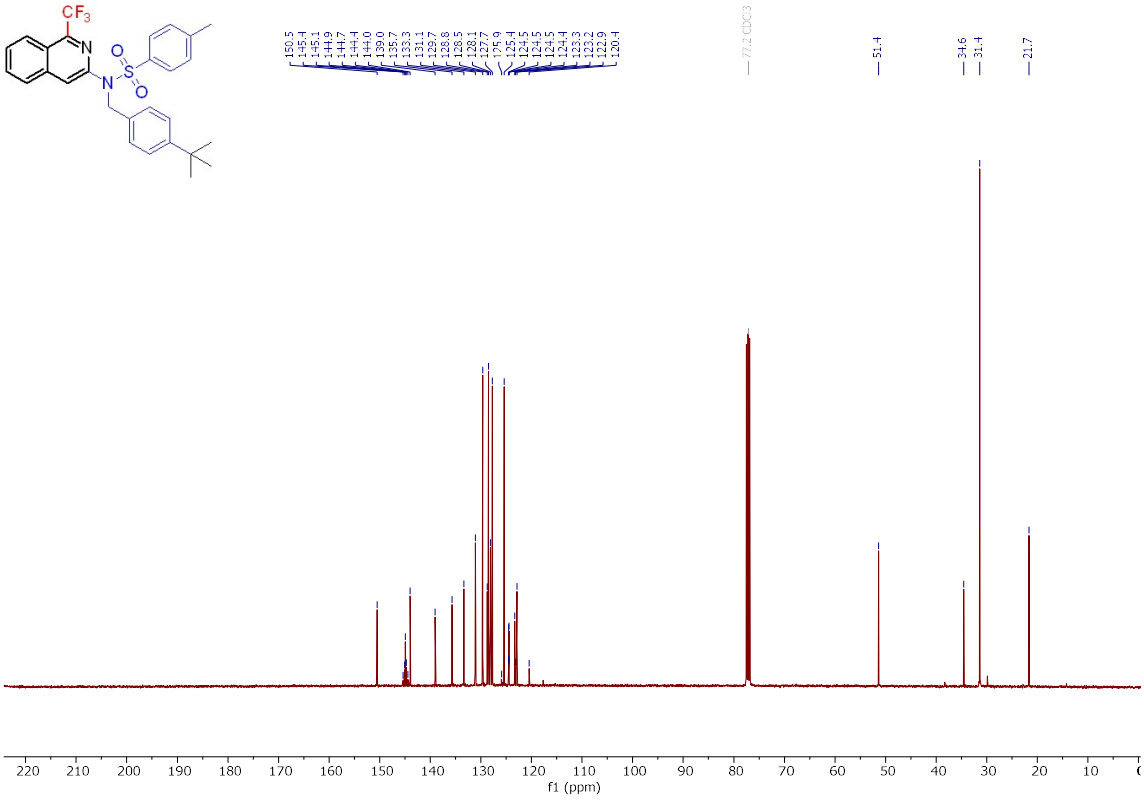
^{19}F NMR spectrum of **8e** ($CDCl_3$, 376 MHz)



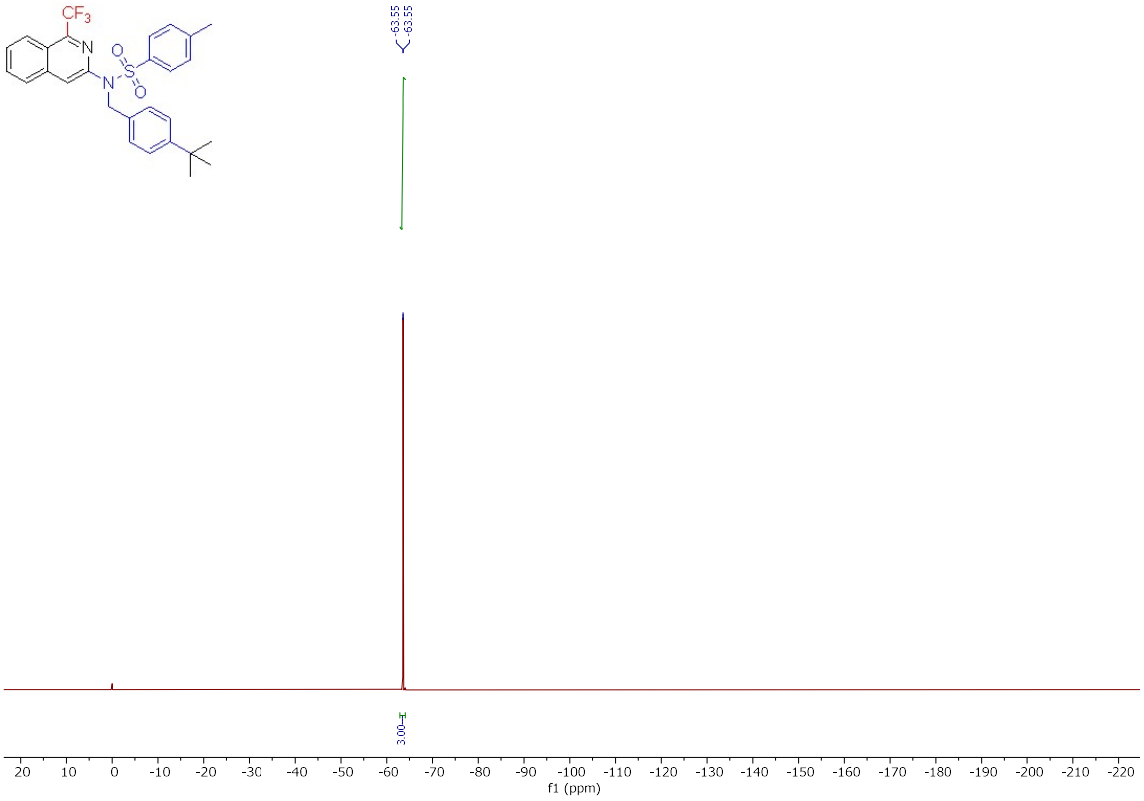
^{1}H NMR spectrum of **8f** ($CDCl_3$, 400 MHz)



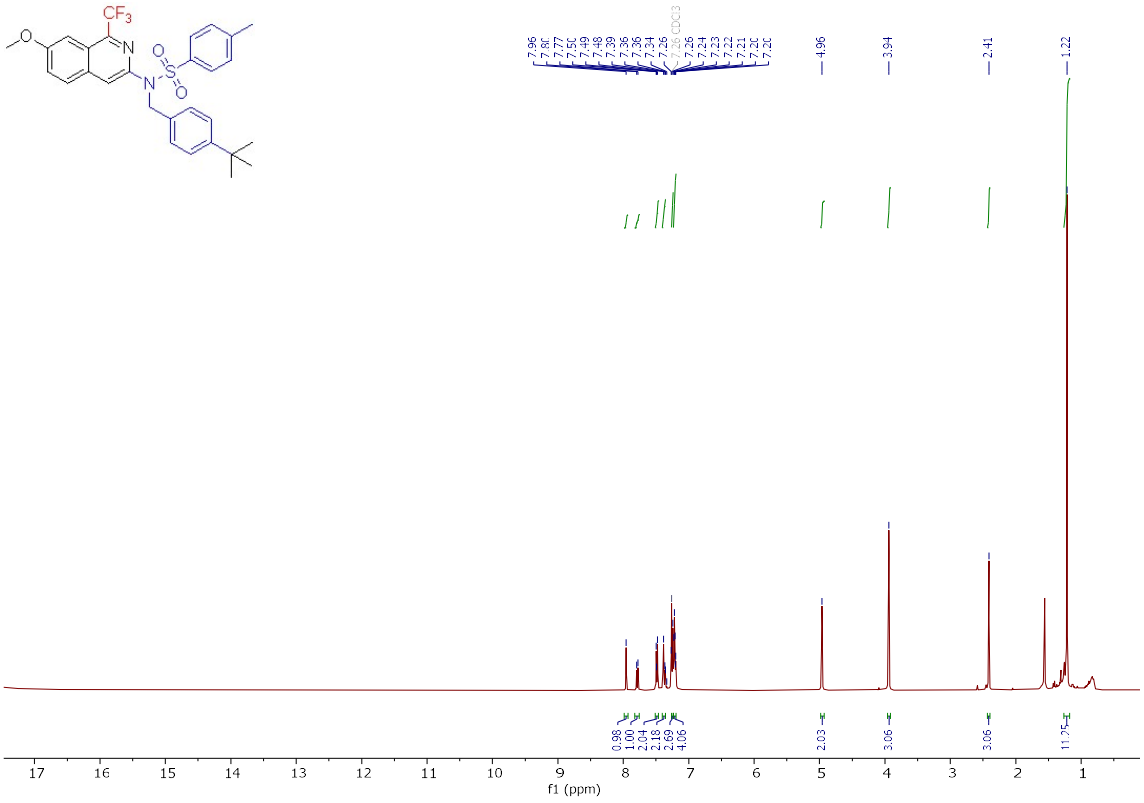
^{13}C NMR spectrum of **8f** ($CDCl_3$, 101 MHz)



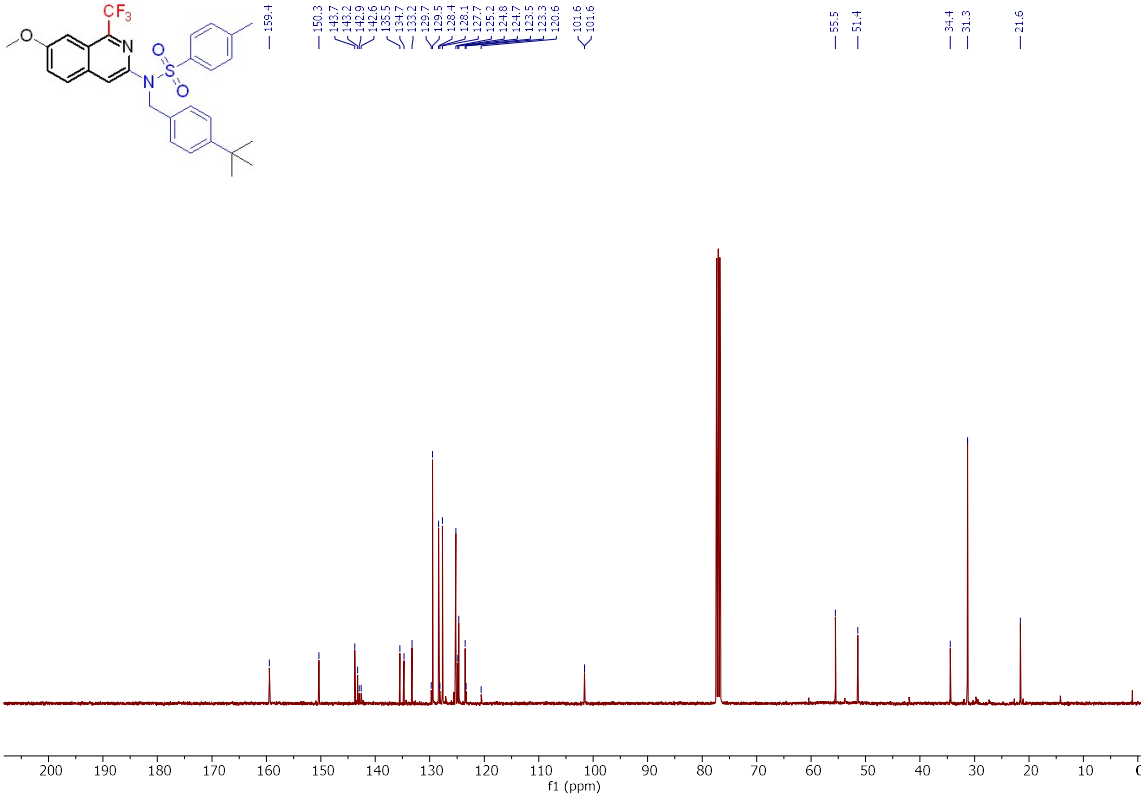
^{19}F NMR spectrum of **8f** ($CDCl_3$, 376 MHz)



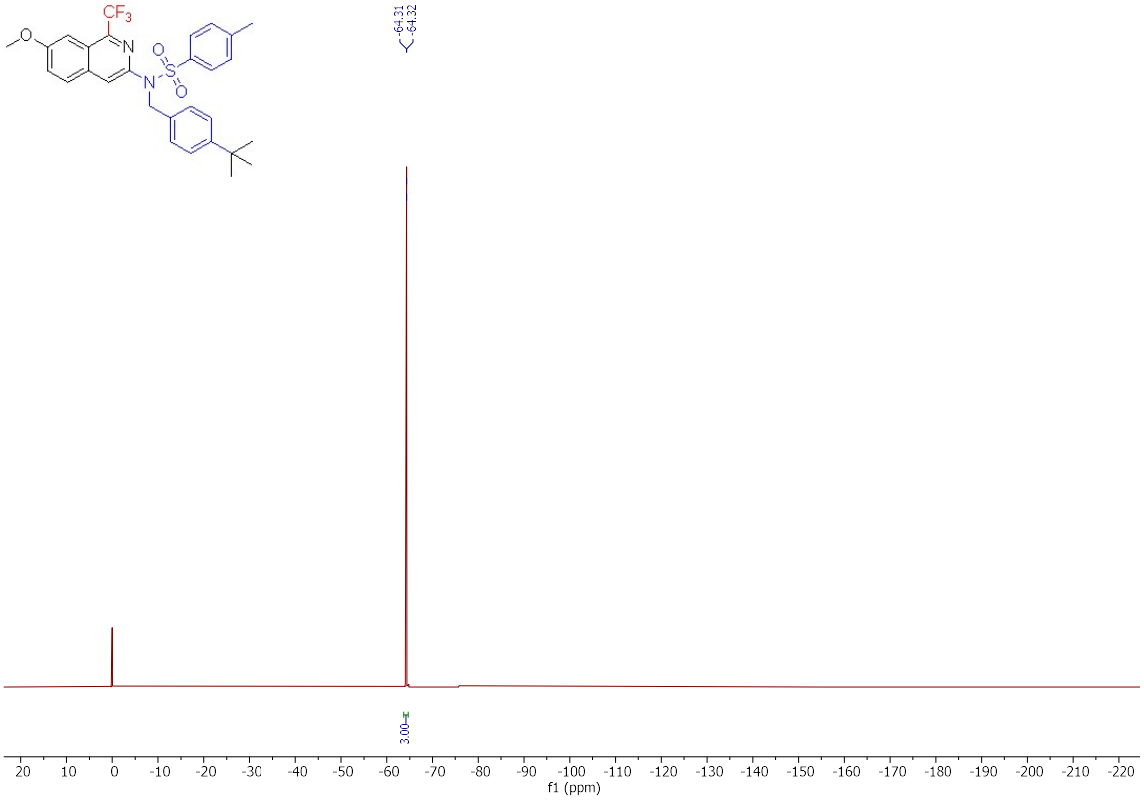
^{1}H NMR spectrum of **8g** ($CDCl_3$, 400 MHz)



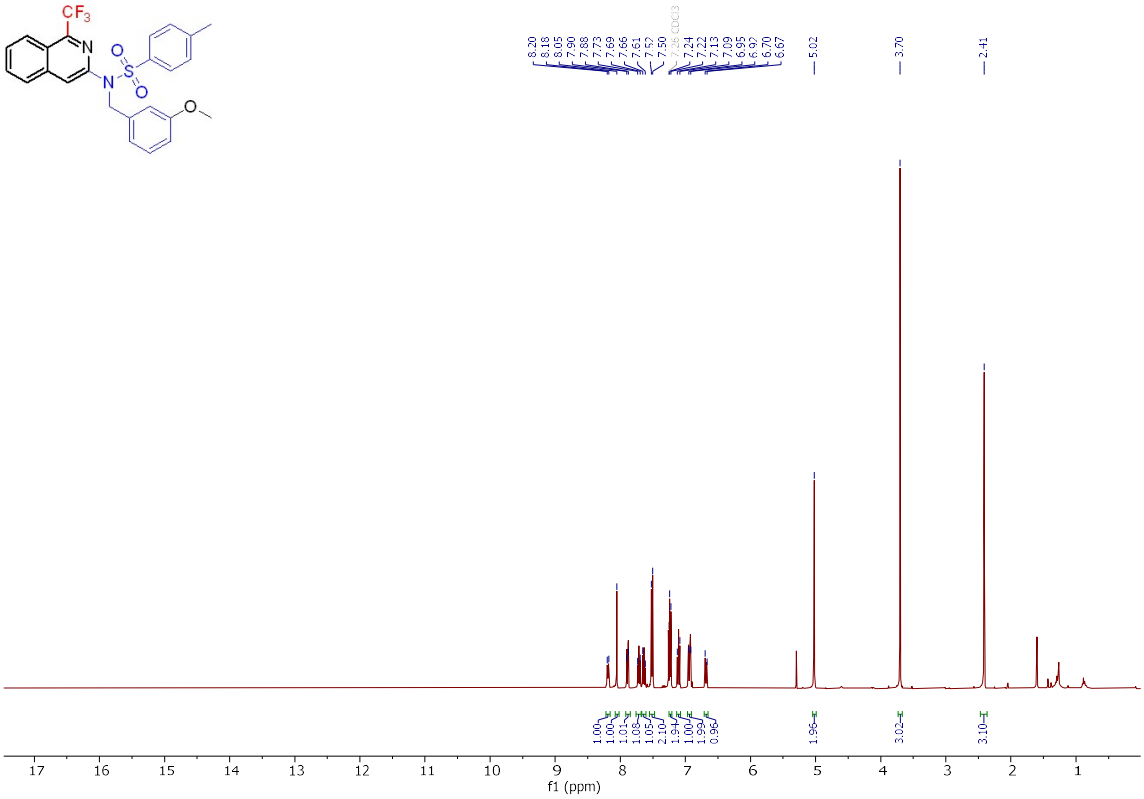
^{13}C NMR spectrum of **8g** ($CDCl_3$, 101 MHz)



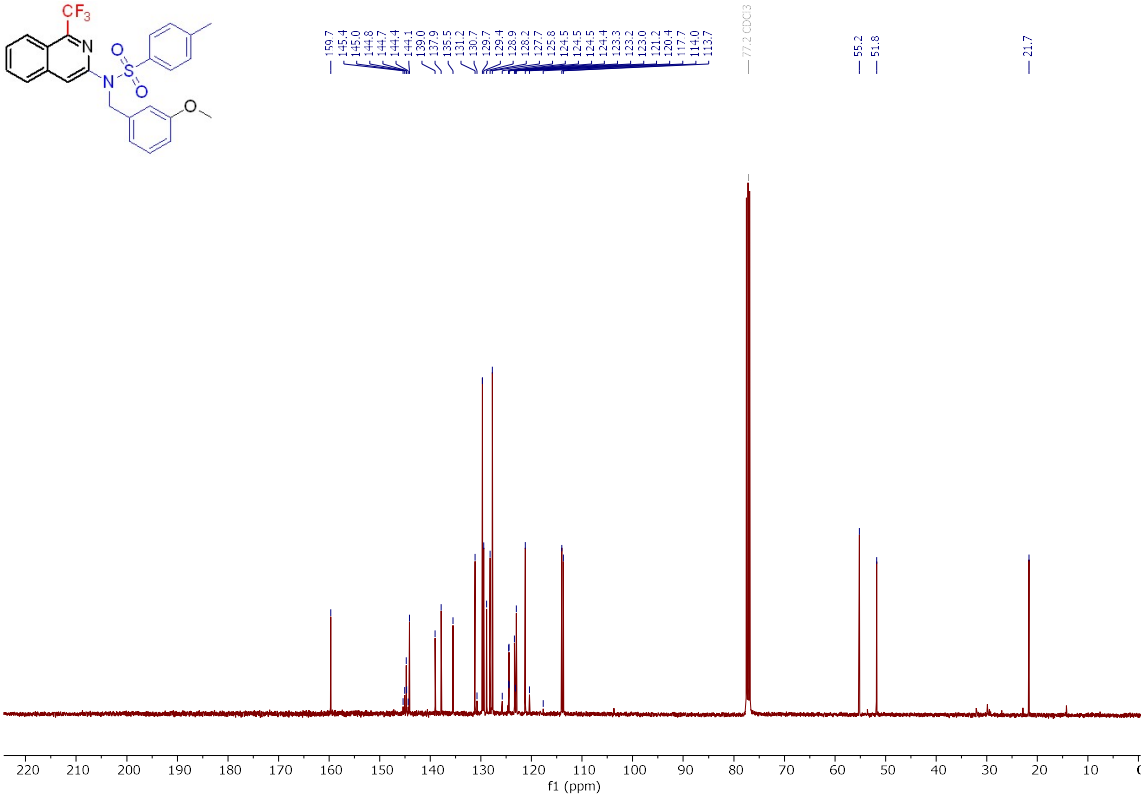
^{19}F NMR spectrum of **8g** ($CDCl_3$, 376 MHz)



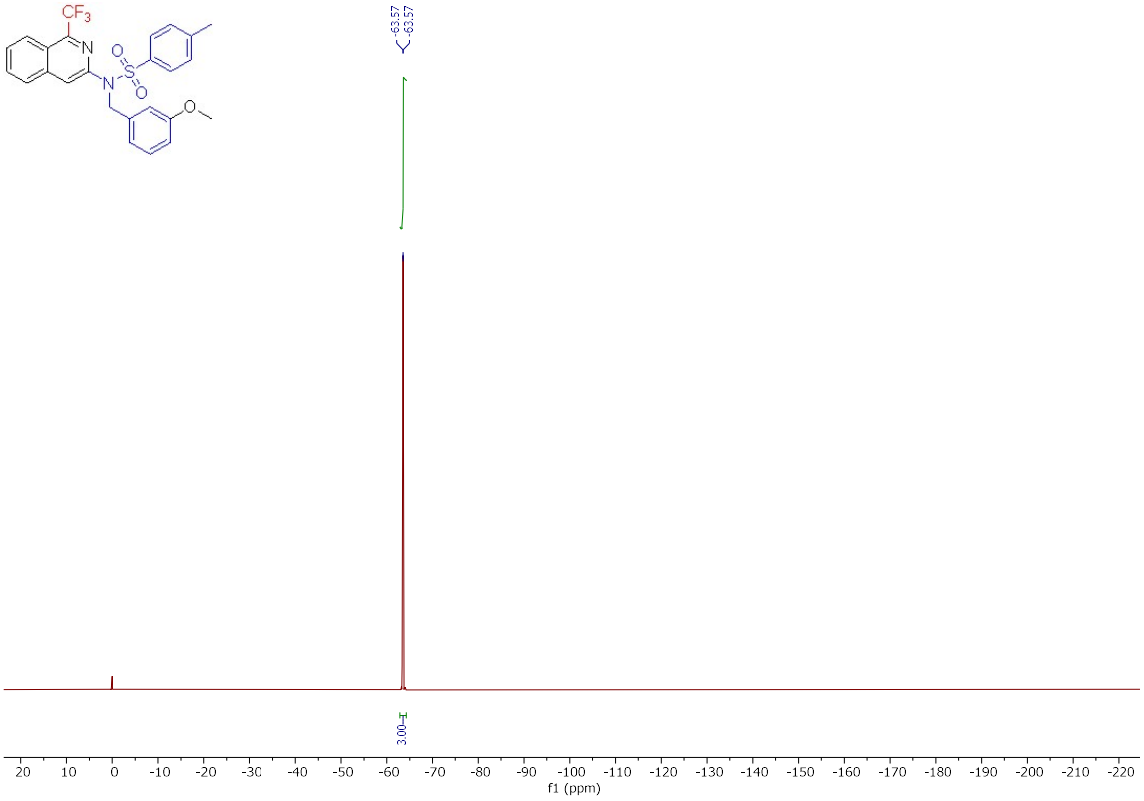
^{1}H NMR spectrum of **8h** ($CDCl_3$, 400 MHz)



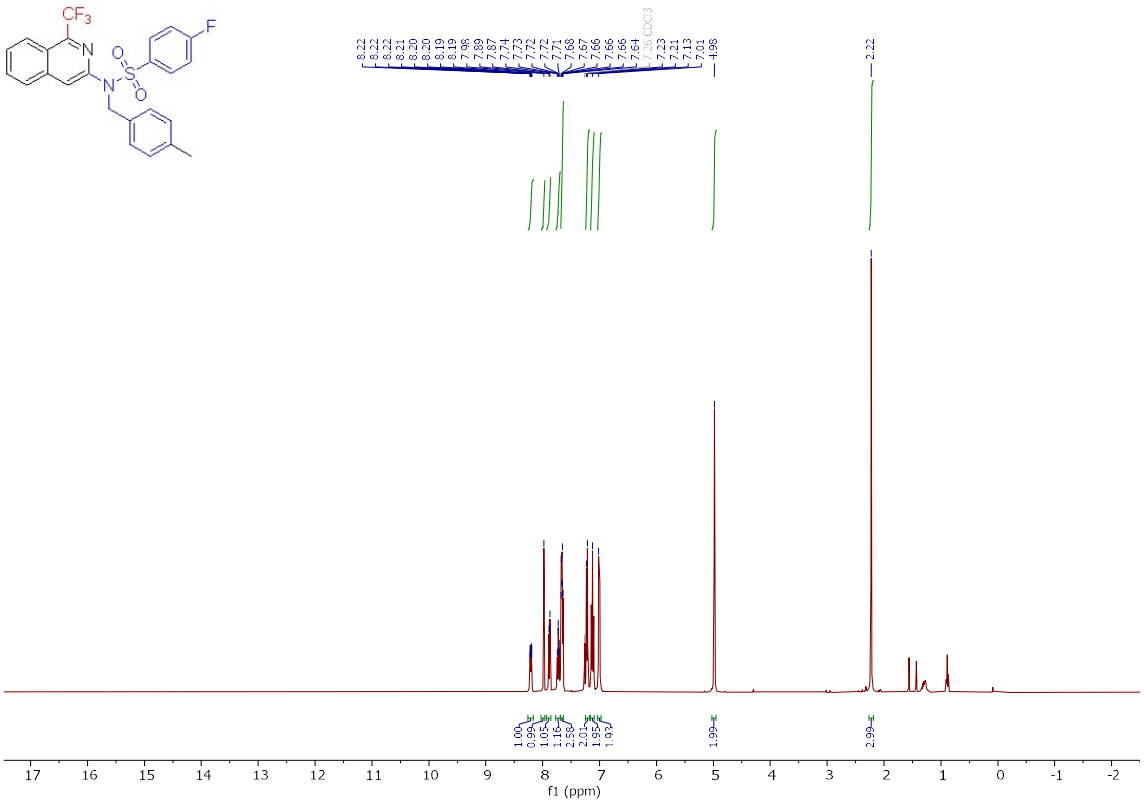
^{13}C NMR spectrum of **8h** ($CDCl_3$, 101 MHz)



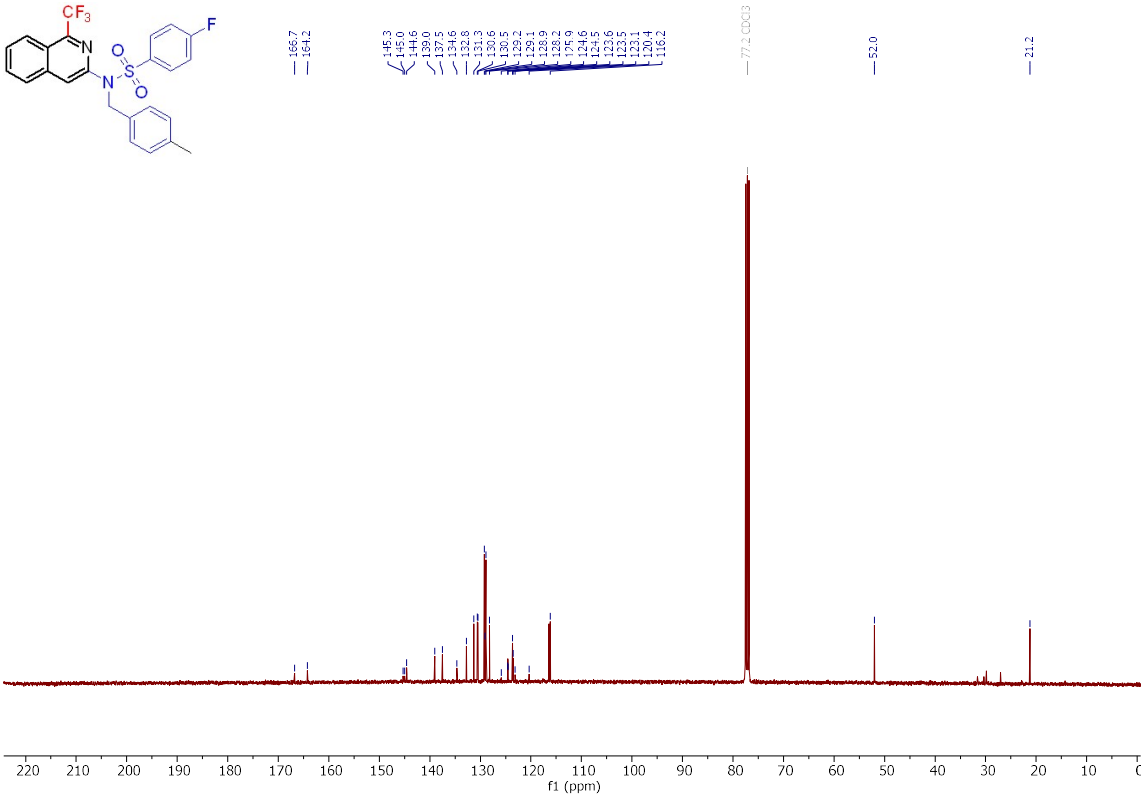
^{19}F NMR spectrum of **8h** ($CDCl_3$, 376 MHz)



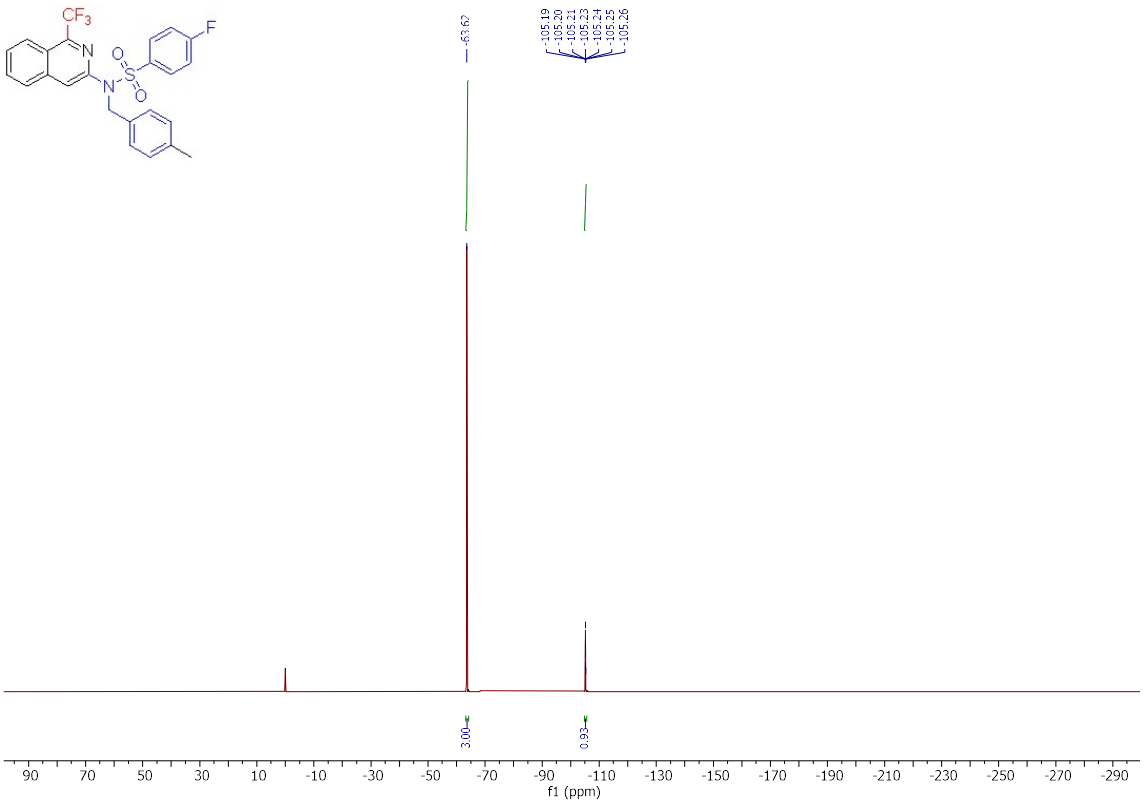
^{1}H NMR spectrum of **8i** ($CDCl_3$, 400 MHz)



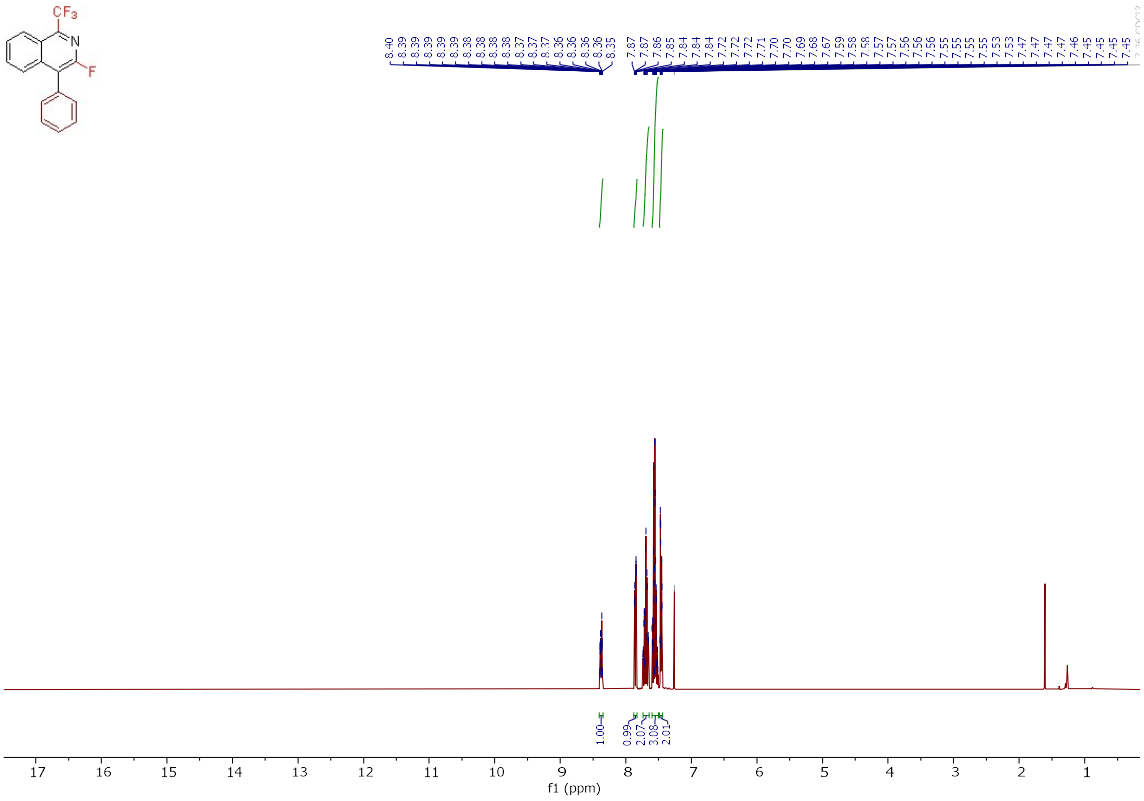
^{13}C NMR spectrum of **8i** ($CDCl_3$, 101 MHz)



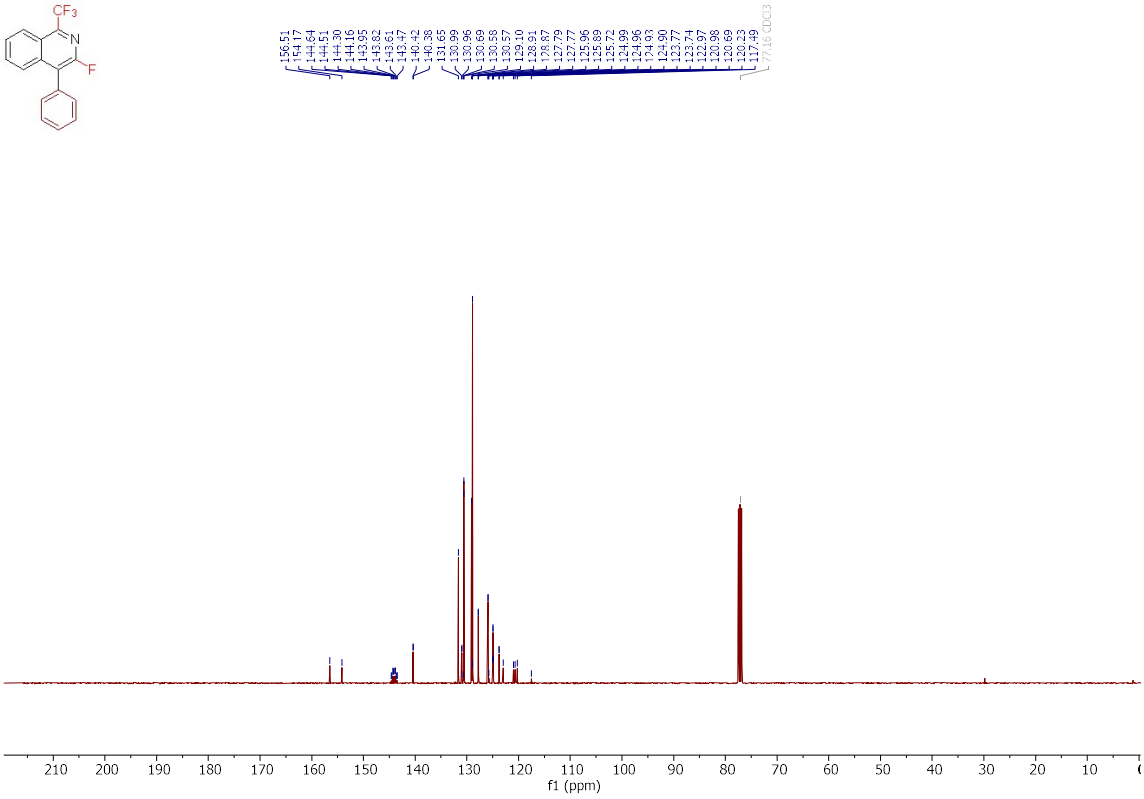
^{19}F NMR spectrum of **8i** ($CDCl_3$, 376 MHz)



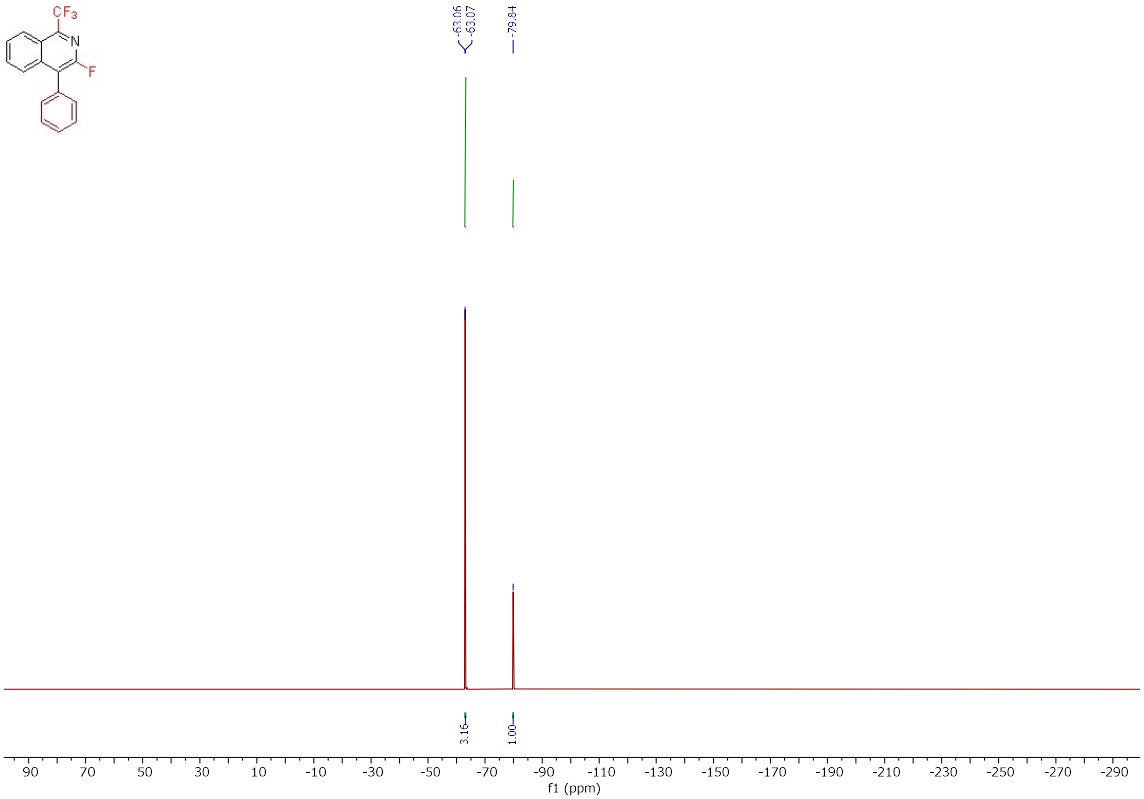
^{1}H NMR spectrum of **9a** ($CDCl_3$, 400 MHz)



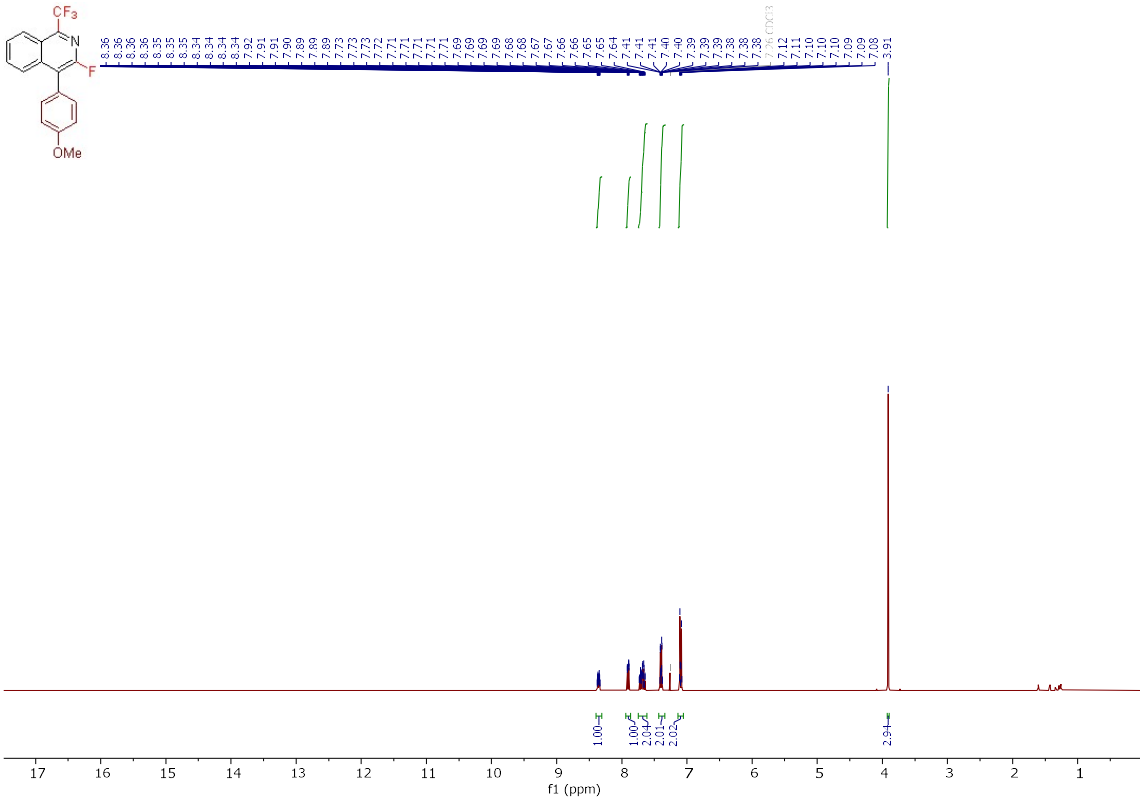
^{13}C NMR spectrum of **9a** ($CDCl_3$, 101 MHz)



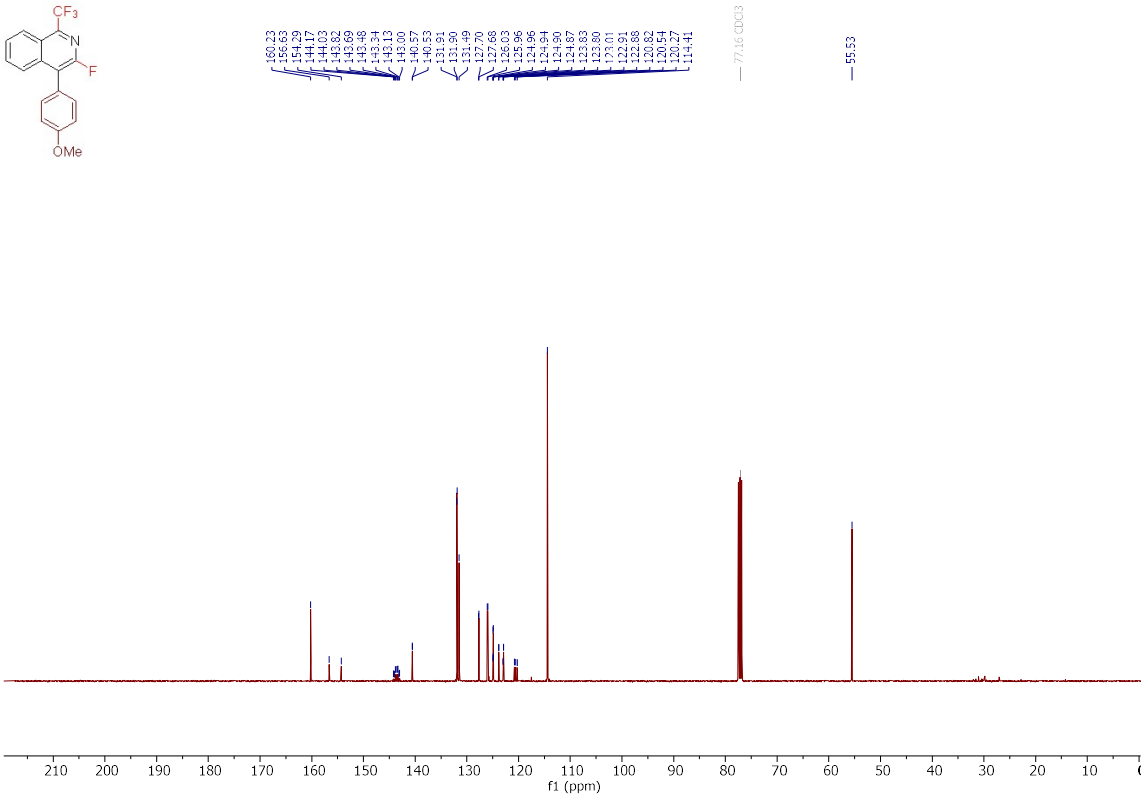
^{19}F NMR spectrum of **9a** ($CDCl_3$, 376 MHz)



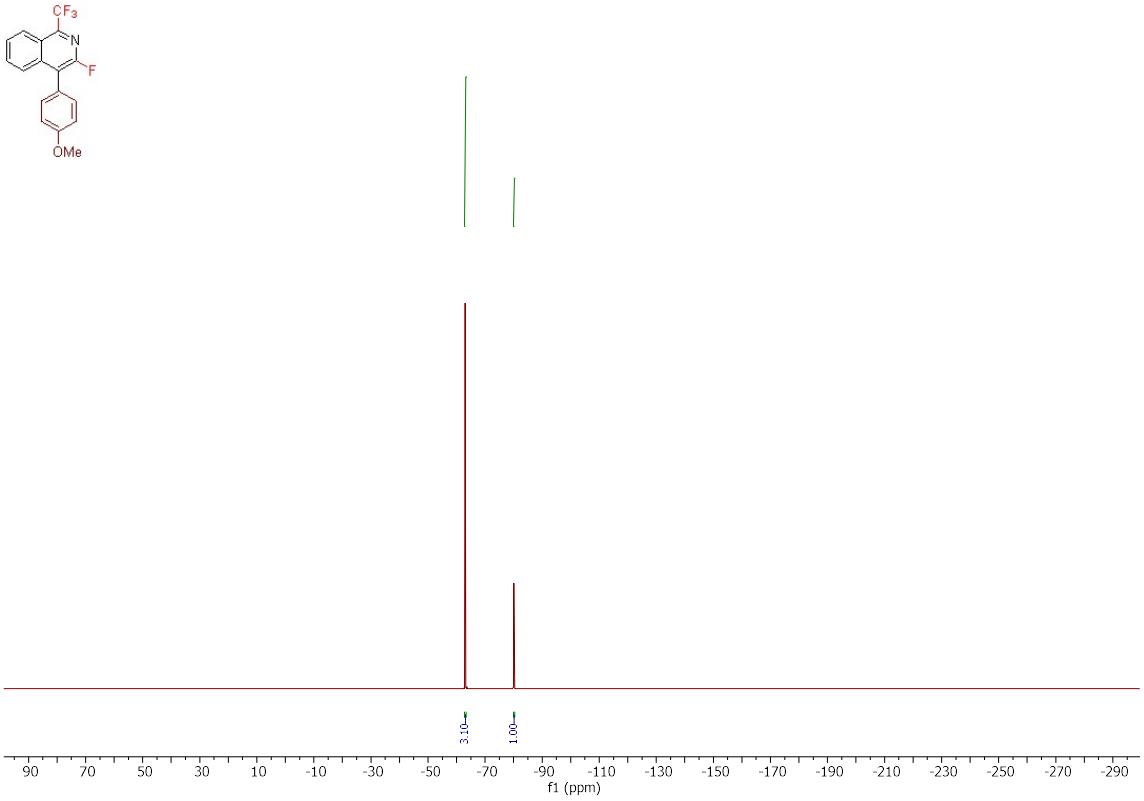
^{1}H NMR spectrum of **9b** ($CDCl_3$, 400 MHz)



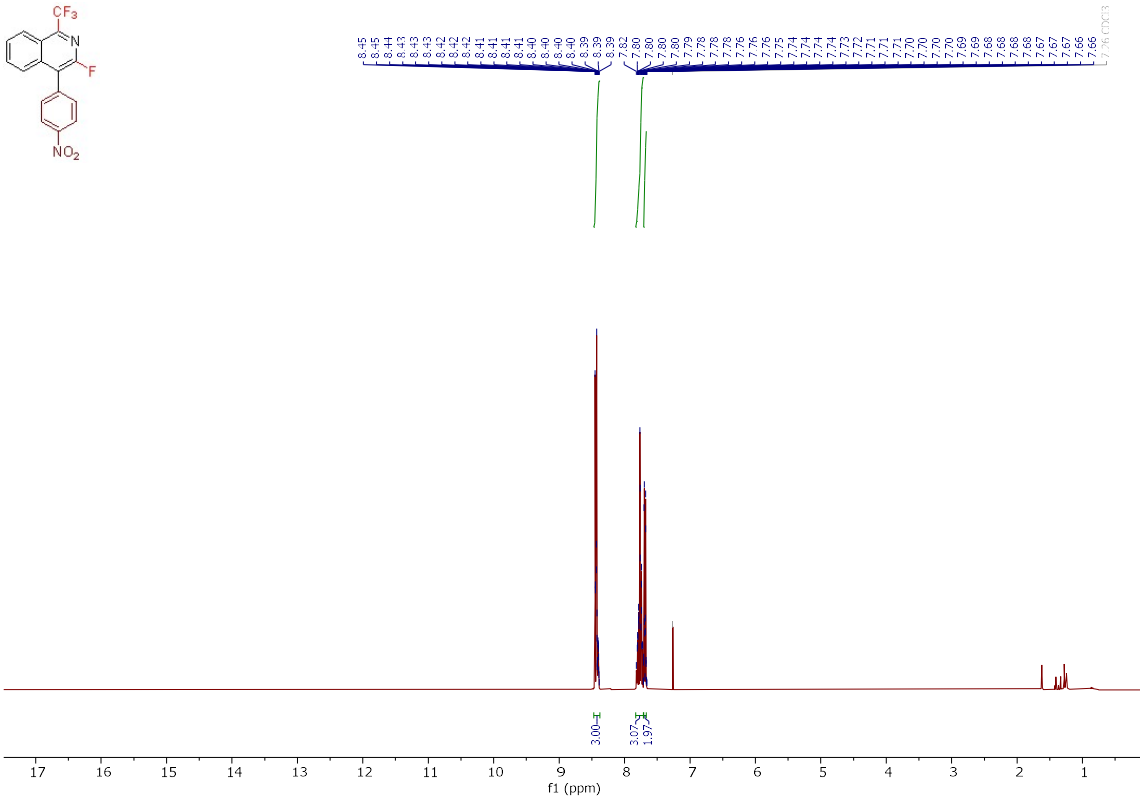
^{13}C NMR spectrum of **9b** ($CDCl_3$, 101 MHz)



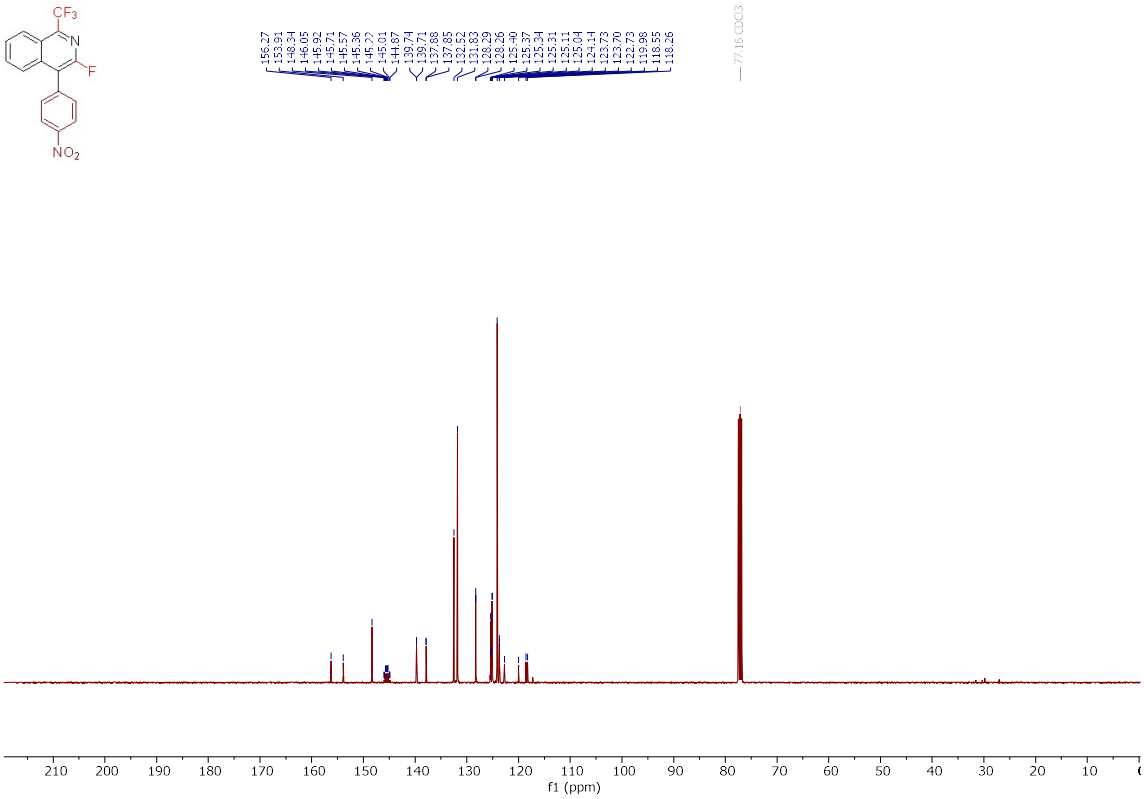
^{19}F NMR spectrum of **9b** ($CDCl_3$, 376 MHz)



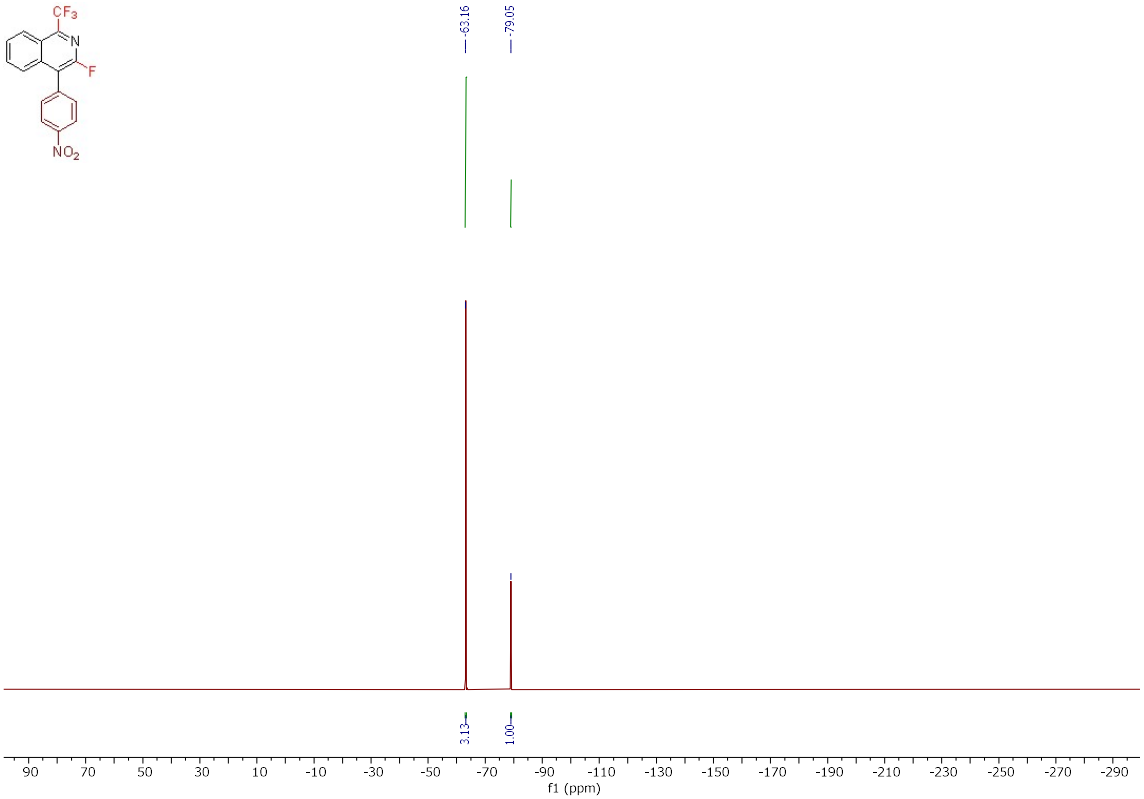
^{1}H NMR spectrum of **9c** ($CDCl_3$, 400 MHz)



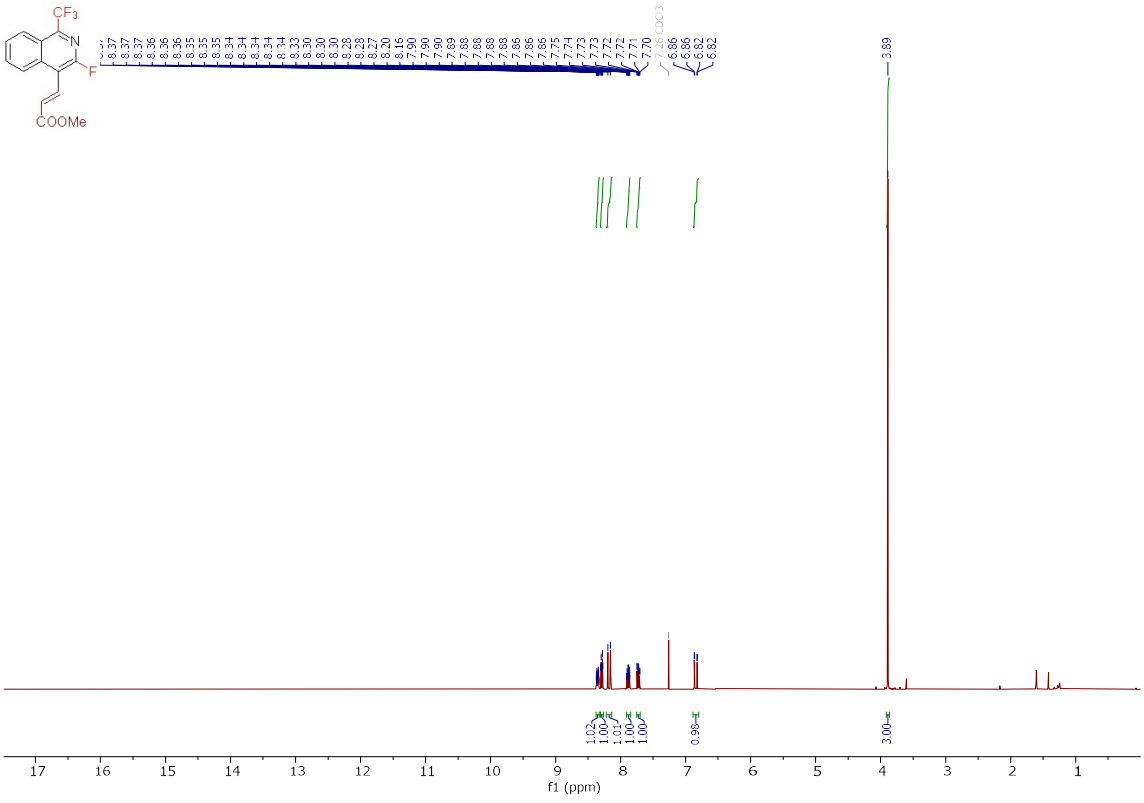
^{13}C NMR spectrum of **9c** ($CDCl_3$, 101 MHz)



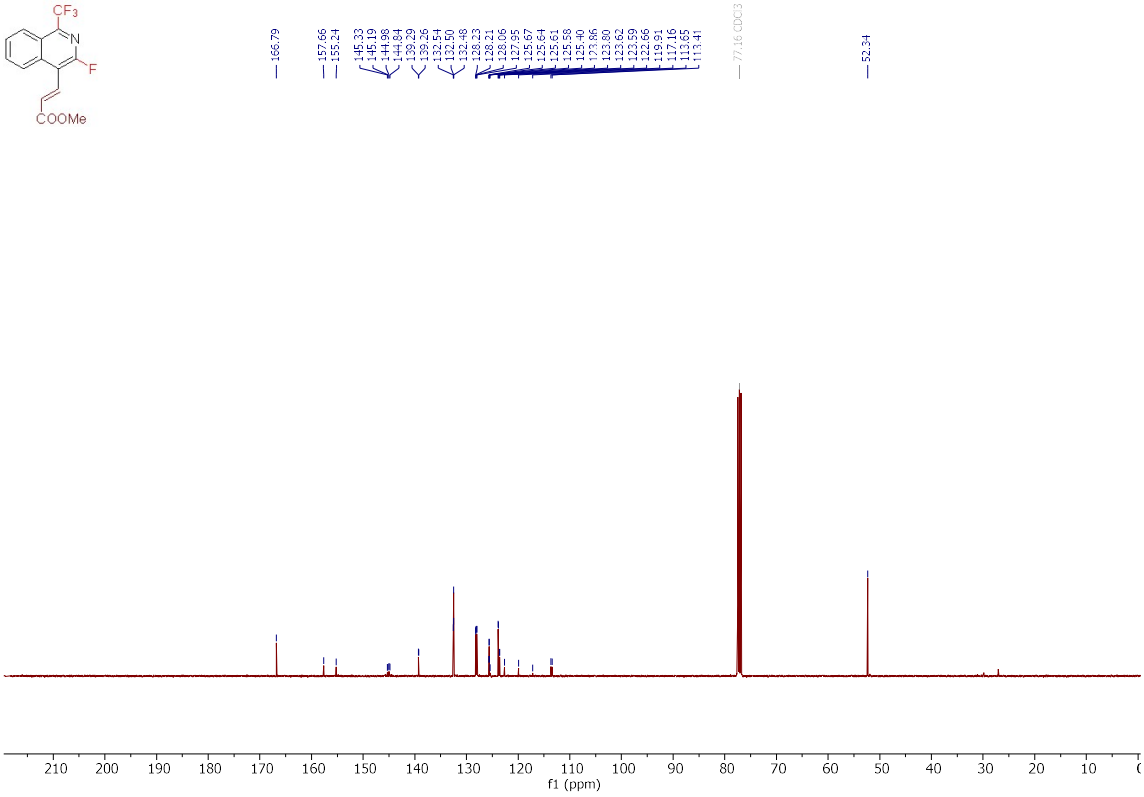
^{19}F NMR spectrum of **9c** ($CDCl_3$, 376 MHz)



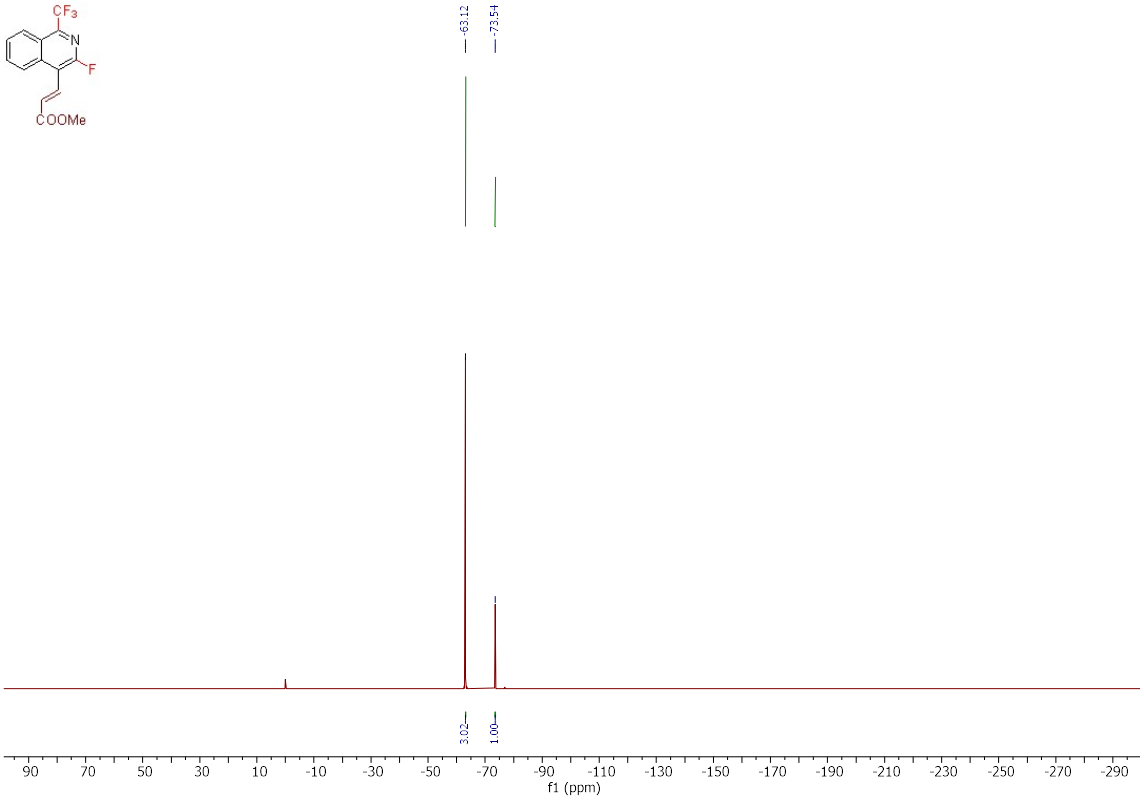
^{1}H NMR spectrum of **10a** ($CDCl_3$, 400 MHz)



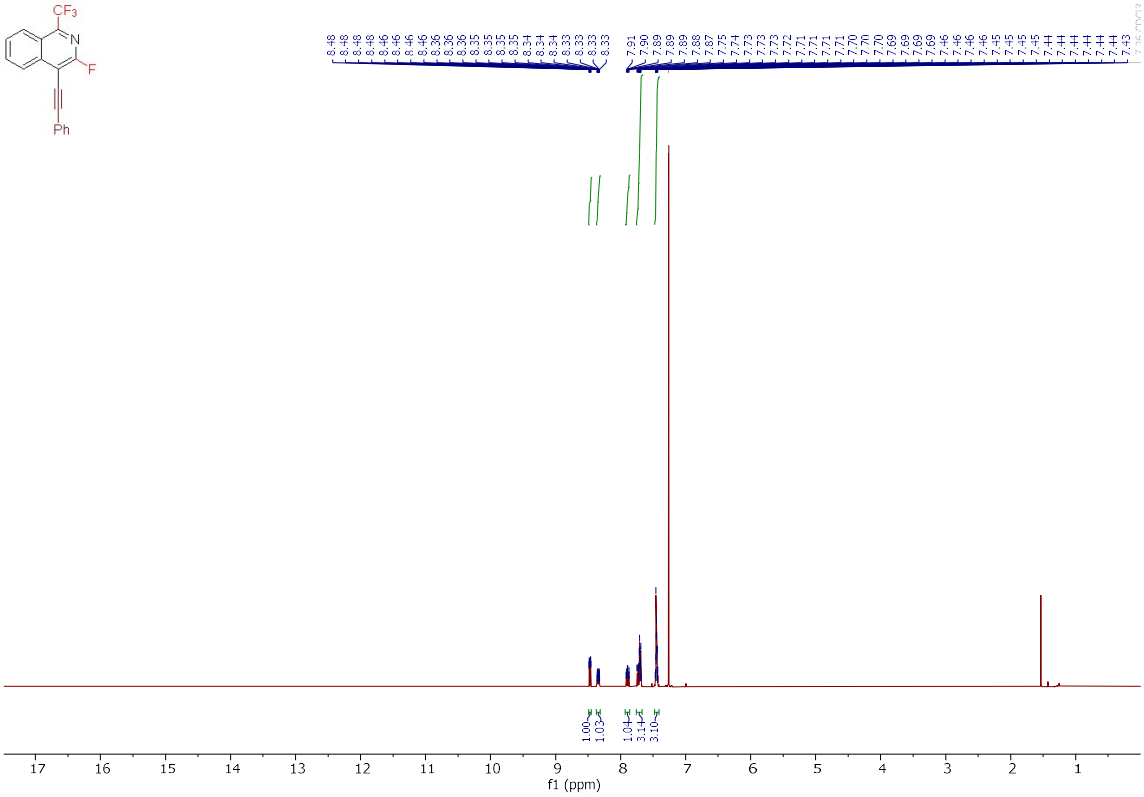
^{13}C NMR spectrum of **10a** ($CDCl_3$, 101 MHz)



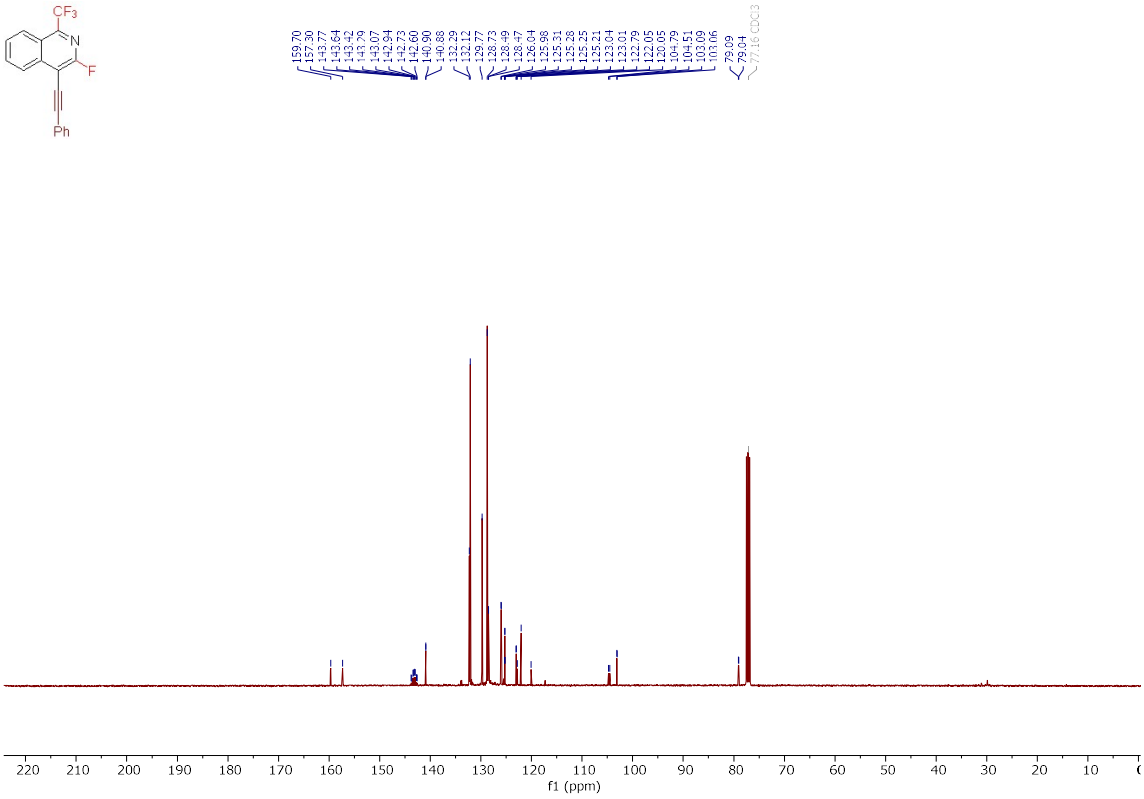
^{19}F NMR spectrum of **10a** ($CDCl_3$, 376 MHz)



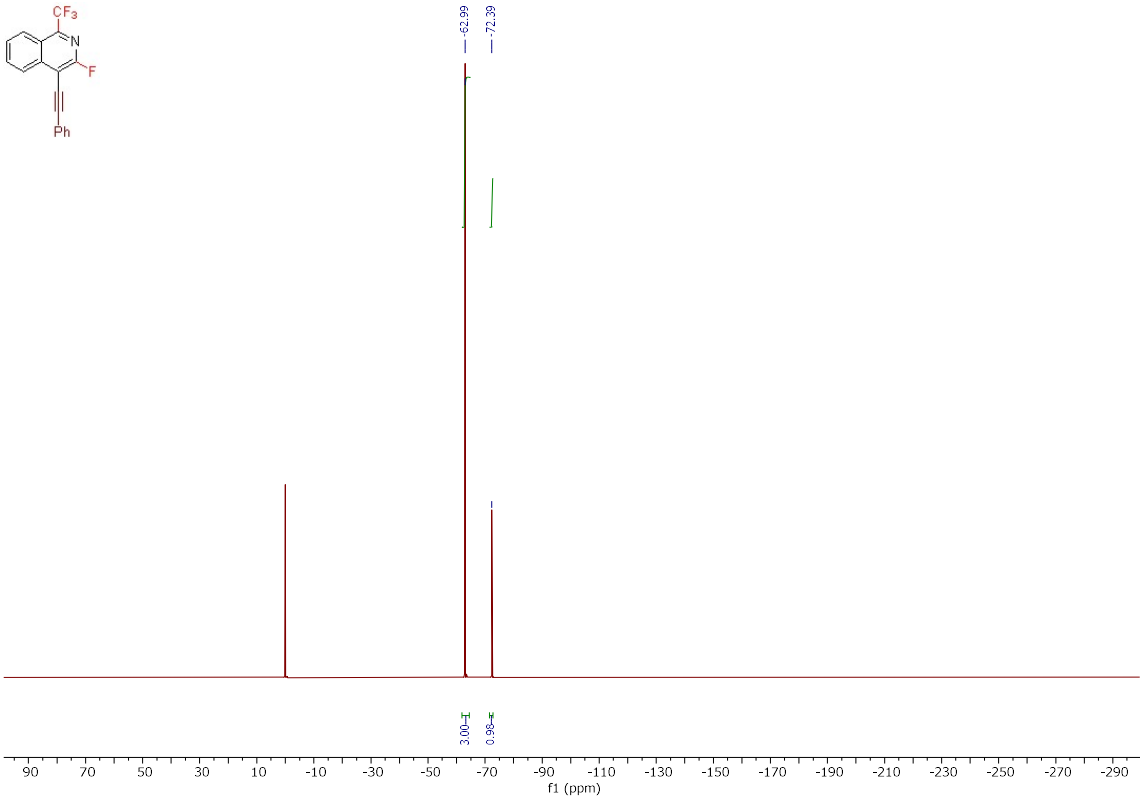
^{1}H NMR spectrum of **10b** ($CDCl_3$, 400 MHz)



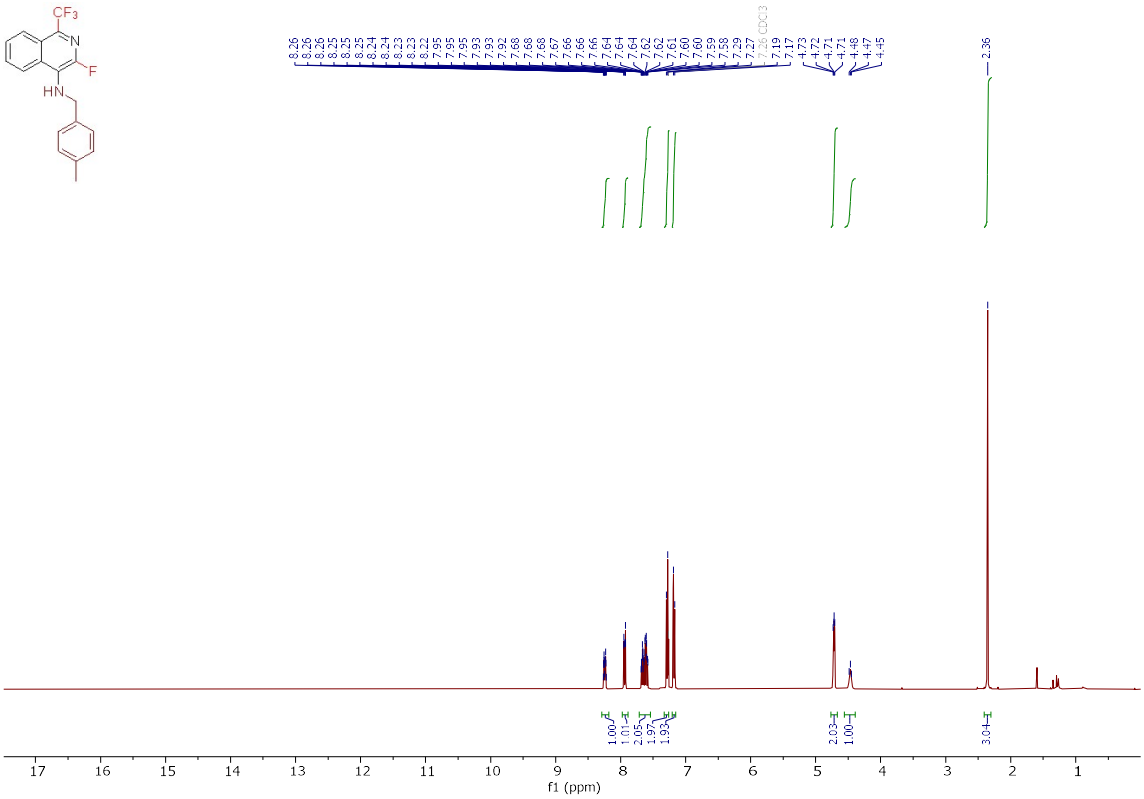
^{13}C NMR spectrum of **10b** ($CDCl_3$, 101 MHz)



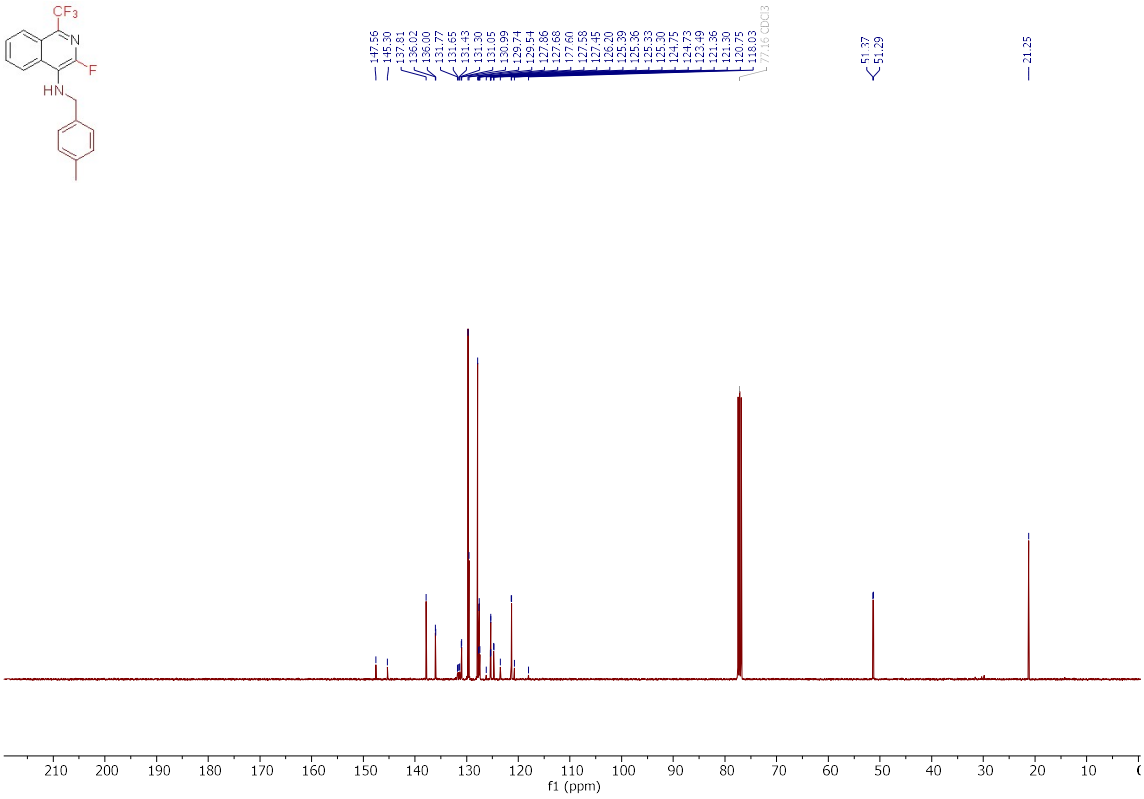
^{19}F NMR spectrum of **10b** ($CDCl_3$, 376 MHz)



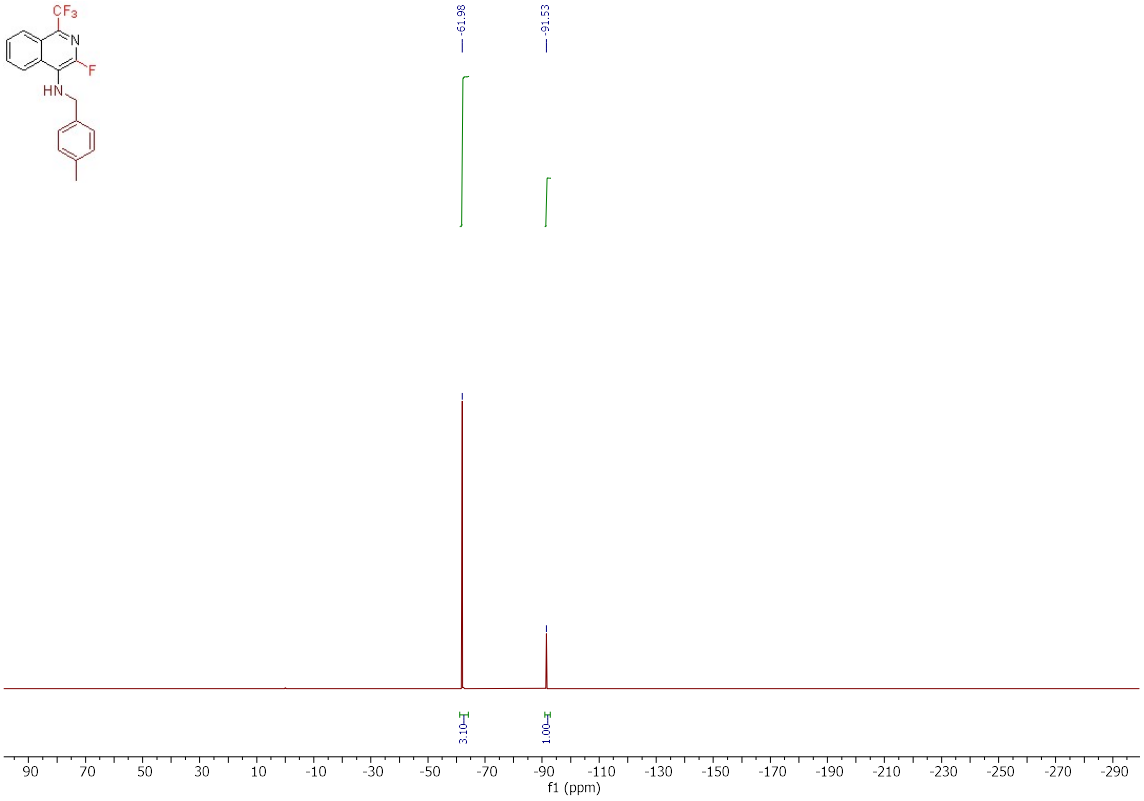
^{1}H NMR spectrum of **10c** ($CDCl_3$, 400 MHz)



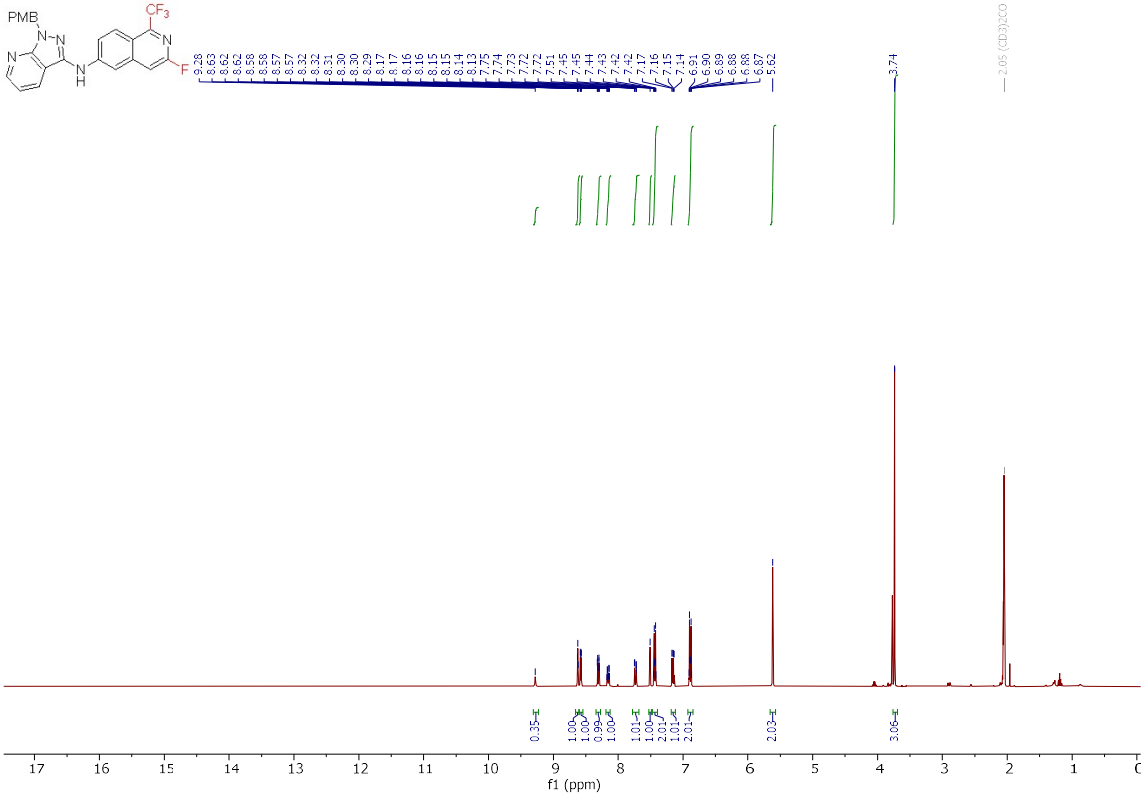
^{13}C NMR spectrum of **10c** ($CDCl_3$, 101 MHz)



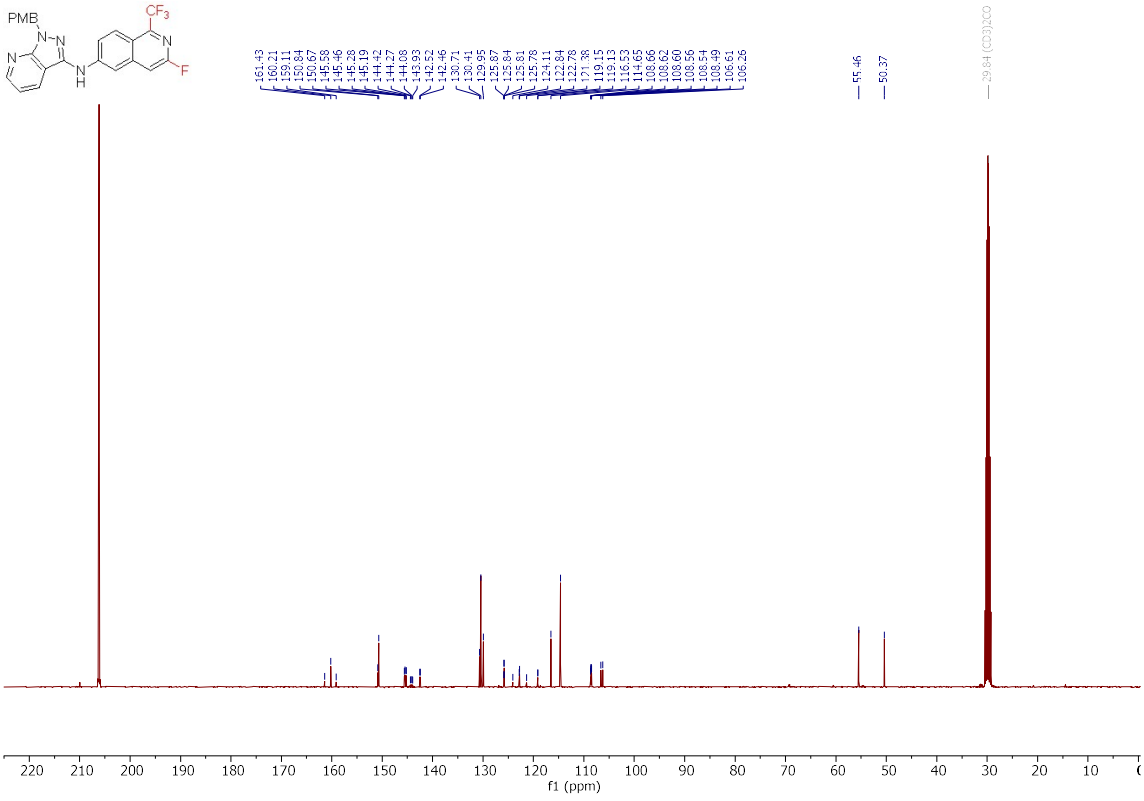
^{19}F NMR spectrum of **10c** ($CDCl_3$, 376 MHz)



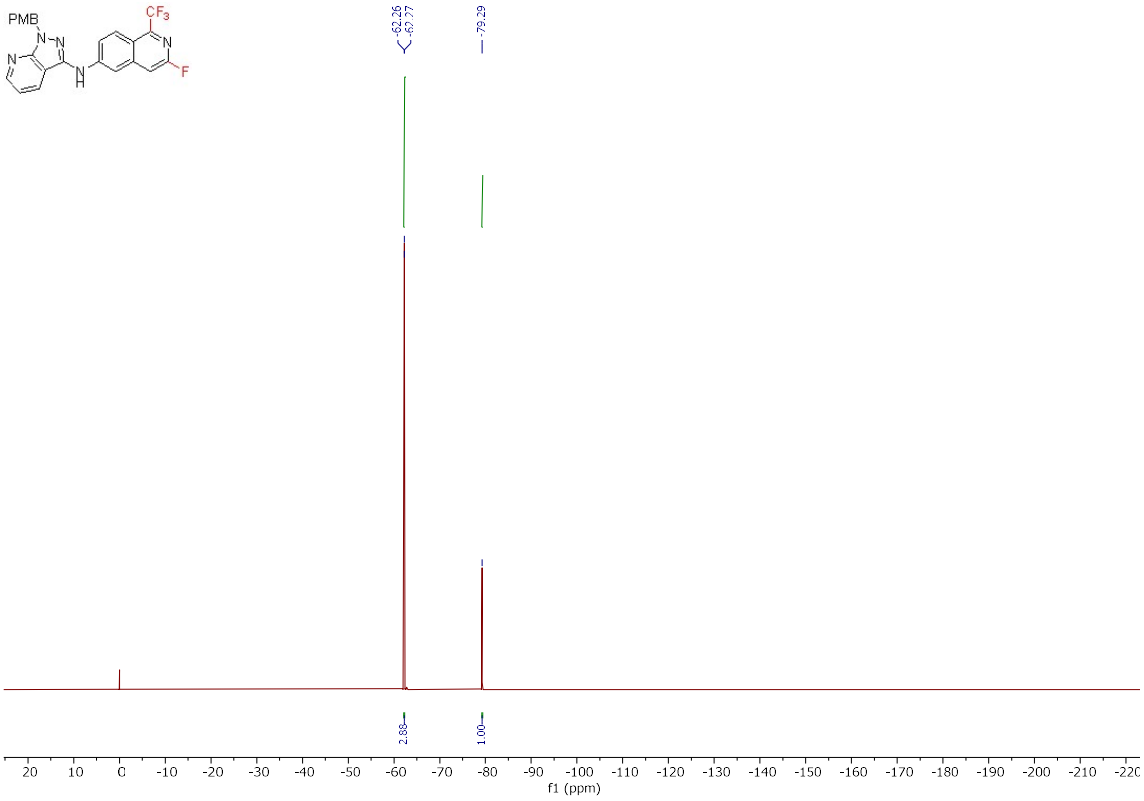
^{1}H NMR spectrum of **11** (Acetone-d_6, 400 MHz)



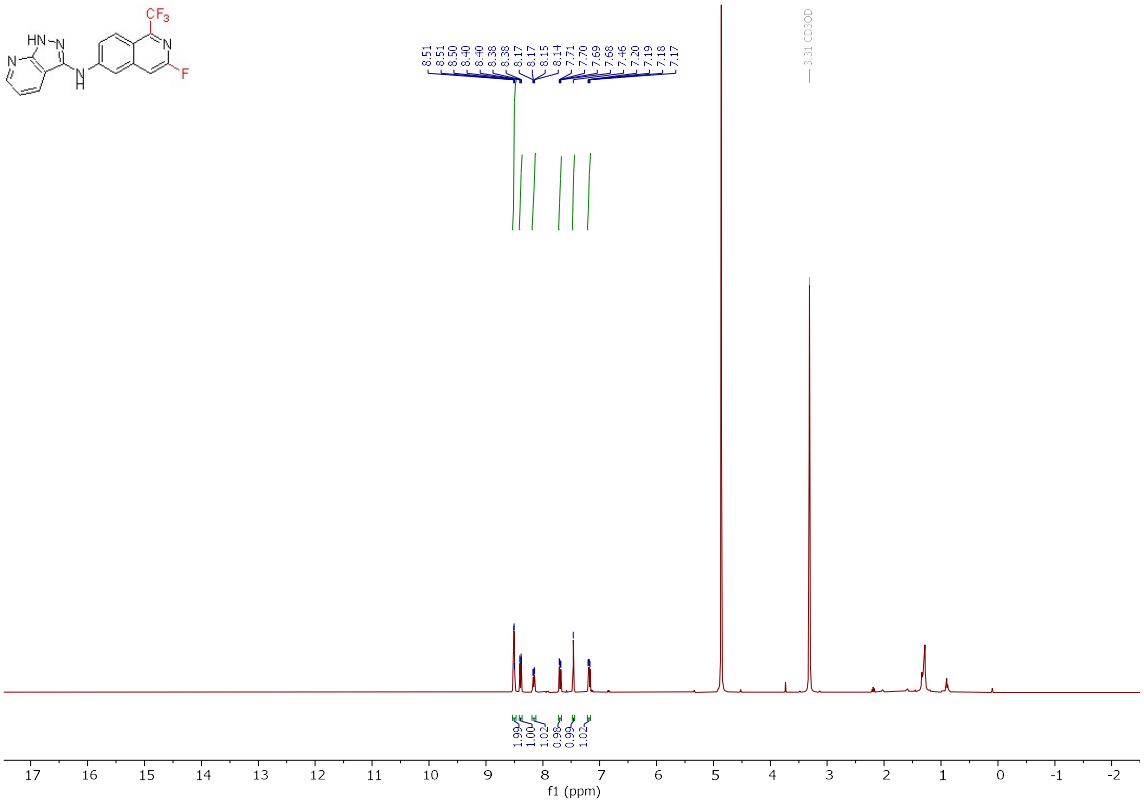
^{13}C NMR spectrum of **11** (Acetone-d_6, 101 MHz)



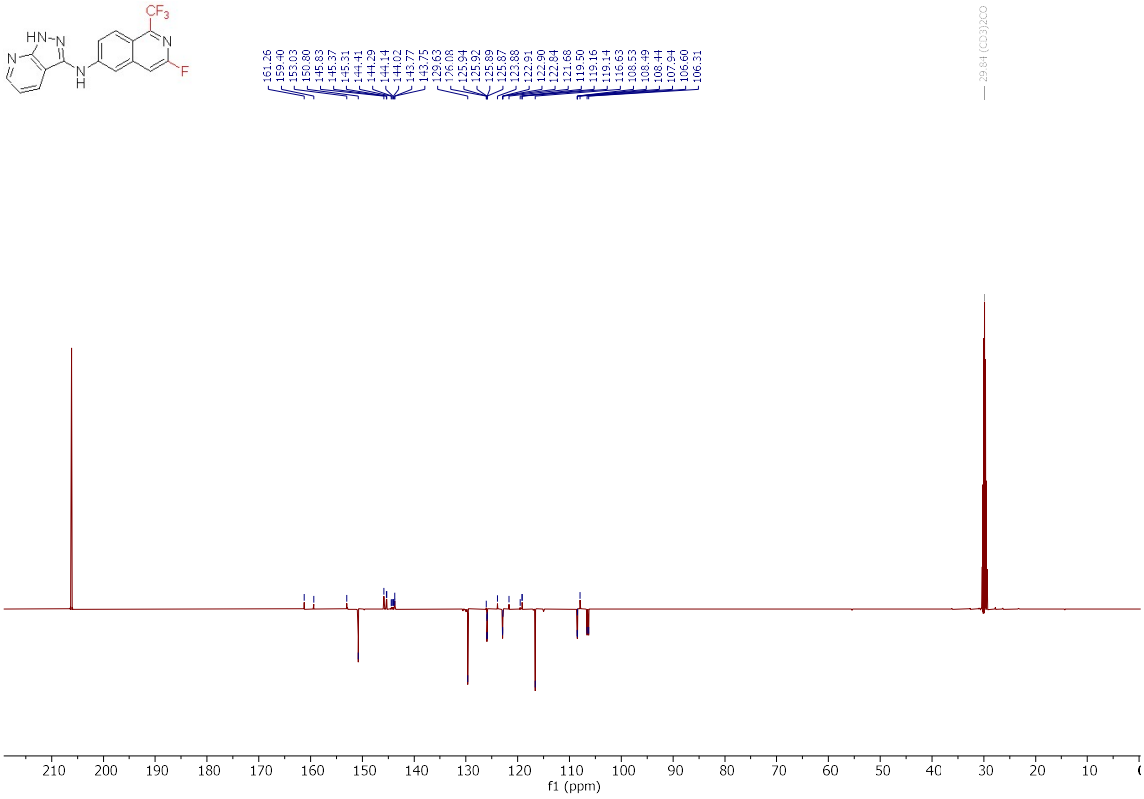
^{19}F NMR spectrum of **11** (Acetone-d_6, 376 MHz)



^{1}H NMR spectrum of **12** (Methanol-d_4, 400 MHz)



^{13}C NMR spectrum of **12** (Acetone-d_6, 101 MHz)



^{19}F NMR spectrum of **12** (Acetone-d_6, 376 MHz)