Selective Fluorination of 4-Substituted 2-Aminopyridines and Pyridin-2(1*H*)-ones in Aqueous Solution

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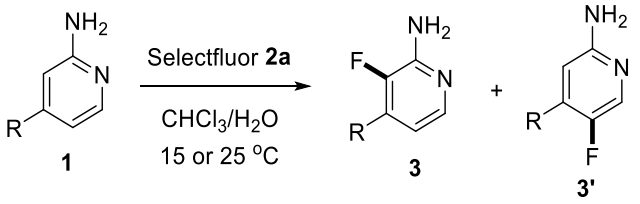
General Experimental Conditions

All manipulations were carried out under the air atmosphere using standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise. All reagents were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were obtained at 400 or 600 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protio-solvent. ^{13}C NMR spectra were obtained at 100 MHz or 151 Hz, and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm; DMSO, 40.0).^{19}F NMR spectra were obtained at 376 or 565 MHz. Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on a KBr plate. High-resolution mass spectra (HRMS) were recorded on a microTOF II mass spectrometer using electrospray ionization (ESI). Data collections for crystal structures were performed at room temperature (293 K) or 150 K using an X-ray single-crystal diffractometer (D8 VENTURE). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). The 4-aryl-2-aminopyridine and 4-aryl-2-pyridones were prepared according to the known procedures.[1]

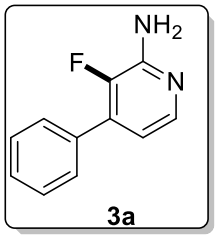
General Procedure for the Synthesis of 3a–3l



4-Aryl-2-aminopyridine **1** (0.20 mmol) and selectfluor **2a** (0.10 mmol) were dissolved in $CHCl_3$ (1 mL) and H_2O (1 mL) in a sealed tube, then the reaction mixture was stirred at 15 or 25 ℃ for 24 h. The mixture was diluted with NaCl solution and DCM (3 × 20 mL), dried with Na_2SO_4. After concentration of the filtrate to dryness, purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1–1/8) gave the desired products **3a-3l**.

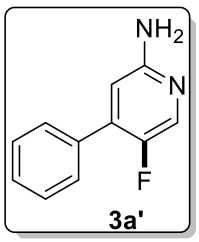
Compound Characterization

3-Fluoro-4-phenylpyridin-2-amine (3a)



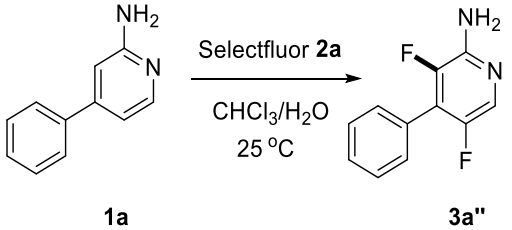
Pale yellow solid; mp 117.1-118.5 °C; 73% yield (13.7 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J* = 5.2 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.37 (m, 3H), 6.73 (t, *J* = 5.2 Hz, 1H), 4.73 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.1 (d, *J* = 13.6 Hz), 143.9 (d, *J* = 252.8 Hz), 142.8 (d, *J* = 7.3 Hz), 134.9 (d, *J* = 8.6 Hz), 133.6, 128.8, 128.7 (d, *J* = 3.2 Hz), 128.6, 114.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.7. IR (KBr): 3459, 3281, 1635, 1259, 1012, 796 cm^{-1}. HRMS (ESI): *m/z* [M +H]$^+$ calcd for $C_{11}H_{10}FN_2$: 189.0828; Found: 189.0809.

3-Fluoro-4-phenylpyridin-2-amine (3a')



Pale yellow solid; mp 125.9-127.3 °C; 9% yield (1.7 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 2.6 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 3H), 7.26 (s, 1H), 6.56 (d, *J* = 5.2 Hz, 1H), 4.38 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ =155.2 (d, *J* = 2.0 Hz), 151.5 (d, *J* = 244.3 Hz), 138.7 (d, *J* = 13.0 Hz), 135.6 (d, *J* = 27.4 Hz), 133.7, 129.0, 128.7, 128.7, 108.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -148.4. IR (KBr): 3476, 3302, 1669, 1629, 1485, 1418 cm^{-1}. HRMS (ESI): *m/z* [M +H]$^+$ calcd for $C_{11}H_{10}FN_2$: 189.0828; Found: 189.0823.

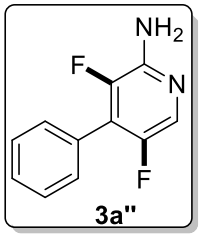
General Procedure for the Synthesis of 3a''



4-Phenylpyridin-2-amine **1a** (0. 10 mmol) and Selectfluor **2a** (0.20 mmol) were dissolved in $CHCl_3$ (1 mL) and H_2O (1 mL) in a sealed tube, then the reaction mixture was stirred at 25 ℃ for 24 h. The mixture was diluted with NaCl solution and DCM (3 × 20 mL), dried with Na_2SO_4. After

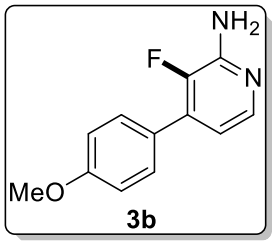
concentration of the filtrate to dryness, purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) gave the desired products **3a''**.

3,5-Difluoro-4-phenylpyridin-2-amine (3a'')



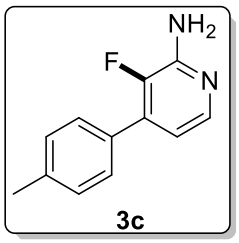
Pale yellow solid; mp 131.3-132.9 °C; 6% yield (1.2 mg).
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 7.53 – 7.44 (m, 2H), 4.56 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 150.0 (d, *J* = 248.2 Hz), 145.4 (d, *J* = 11.7 Hz), 142.7 (d, *J* = 258.9 Hz), 129.950, 129.949 (d, *J* = 3.7 Hz), 129.7 (dd, *J* = 26.2, 6.3 Hz), 129.3, 128.5, 127.4. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -141.4, -144.6. HRMS (ESI): *m/z* [M + H] $^+$calcd for 207.0734; Found: 207.0715.

3-Fluoro-4-(4-methoxyphenyl)pyridin-2-amine (3b)



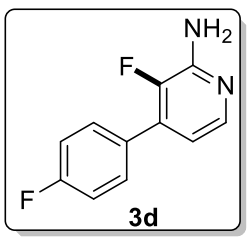
White solid; 126.0-127.4 92.8 °C; 68% yield (14.8 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 5.2 Hz, 1H), 7.61 – 7.50 (m, 2H), 7.02 – 6.95 (m, 2H), 6.72 (t, *J* = 5.3 Hz, 1H), 4.66 (s, 2H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.1 , 149.0 (d, *J* = 13.7 Hz), 143.9 (d, *J* = 251.9 Hz), 142.8 (d, *J* = 7.3 Hz), 134.4 (d, *J* = 8.3 Hz), 130.0 (d, *J* = 3.6 Hz), 125.8, 114.6, 114.1, 55.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -147.0. IR (KBr): 3462, 3289, 1636, 1607, 1520, 1473 cm^{-1}. HRMS (ESI): *m/z* [M + H] $^+$calcd for $C_{12}H_{12}FN_2O$: 219.0934; Found: 219.0911.

3-Fluoro-4-(*p*-tolyl)pyridin-2-amine (3c)



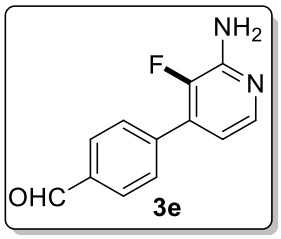
Pale yellow solid; mp 115.3-116.4 °C; 70% yield (14.1 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.87 (d, *J* = 5.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.33 – 7.23 (m, 2H), 6.73 (t, *J* = 5.2 Hz, 1H), 4.68 (s, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.0 (d, *J* = 13.7 Hz), 143.9 (d, *J* = 252.3 Hz), 142.8 (d, *J* = 7.3 Hz), 138.9, 134.8 (d, *J* = 8.4 Hz), 130.6, 129.4, 128.6 (d, *J* = 3.3 Hz), 114.8, 21.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.7. IR (KBr): 3468, 3286, 1634, 1518, 1478, 1193 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{12}H_{12}FN_2$: 203.0985; Found: 203.0969.

3-Fluoro-4-(4-fluorophenyl)pyridin-2-amine (3d)



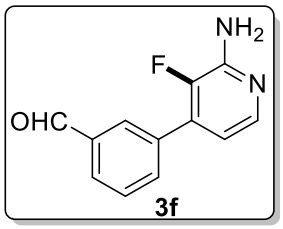
White solid; mp 143.0-144.8 °C; 71% yield (14.6 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (d, *J* = 5.2 Hz, 1H), 7.49 (dd, *J* = 8.3, 5.4 Hz, 2H), 7.08 (t, *J* = 8.5 Hz, 2H), 6.62 (t, *J* = 5.2 Hz, 1H), 4.69 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 163.1 (d, *J* = 249.1 Hz), 149.1 (d, *J* = 13.6 Hz), 143.8 (d, *J* = 252.8 Hz), 142.9 (d, *J* = 7.4 Hz), 133.8 (d, *J* = 8.4 Hz), 130.6 (dd, *J* = 8.3, 3.3 Hz), 129.5 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 21.6 Hz), 114.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -112.4, -146.9. IR (KBr): 3461, 3285, 1644, 1521, 1467, 1185 cm^{-1}. HRMS (ESI): *m/z* [M +H]$^+$ calcd for $C_{11}H_9F_2N_2$: 207.0734; Found: 207.0708.

4-(2-Amino-3-fluoropyridin-4-yl)benzaldehyde (3e)



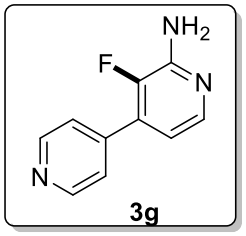
White solid; mp 127.8-130.9 °C; 62% yield (13.4 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 7.96 (dd, *J* = 20.9, 6.6 Hz, 3H), 7.75 (d, *J* = 7.8 Hz, 2H), 6.74 (t, *J* = 5.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ =191.7 , 149.2 (d, *J* = 13.3 Hz), 143.7 (d, *J* = 254.4 Hz), 143.2 (d, *J* = 7.4 Hz), 139.6, 136.3, 133.5 (d, *J* = 8.4 Hz), 129.9, 129.5 (d, *J* = 3.3 Hz), 114.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.0. IR (KBr): 3478, 3140, 1685, 1606, 1485, 1193 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}FN_2O$: 217.0777; Found: 217.0772.

3-(2-Amino-3-fluoropyridin-4-yl)benzaldehyde (3f)



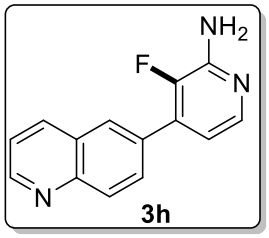
Pale yellow solid; mp 132.3-134.1. °C; 60% yield (13 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.09 (s, 1H), 8.10 (s, 1H), 7.98 – 7.80 (m, 3H), 7.66 (t, *J* = 7.7 Hz, 1H), 6.76 (t, *J* = 5.2 Hz, 1H), 4.79 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ= 191.8, 149.1 (d, *J* = 13.4 Hz), 143.8 (d, *J* = 253.5 Hz), 143.2 (d, *J* = 7.4 Hz), 136.8, 134.6, 134.5 (d, *J* = 3.4 Hz), 133.4 (d, *J* = 8.4 Hz), 130.0, 129.9, 129.4, 114.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.6. IR (KBr): 1700, 1671, 1507, 1473, 738cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{10}FN_2O$: 217.0777; Found: 217.0797.

3-Fluoro-[4,4'-bipyridin]-2-amine (3g)



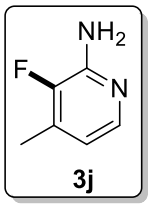
Pale yellow solid; mp 132.4-133.7 °C; 47% yield (8.9 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (d, *J* = 5.6 Hz, 2H), 7.97 (d, *J* = 5.2 Hz, 1H), 7.57 – 7.45 (m, 2H), 6.75 (t, *J* = 5.1 Hz, 1H), 4.81 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.3 , 149.1 (d, *J* = 13.1 Hz), 143.7 (d, *J* = 255.5 Hz), 143.4 (d, *J* = 7.4 Hz), 141.3, 132.1 (d, *J* = 8.1 Hz), 123.2 (d, *J* = 3.3 Hz), 113.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -145.8. IR (KBr): 3641, 3145, 1653, 1507, 1474, 1192 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_9FN_3$: 190.0781; Found: 190.0769.

3-Fluoro-4-(quinolin-6-yl)pyridin-2-amine (3h)



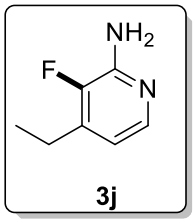
White solid; mp 188.7-189.9 °C; 63% yield (15.1mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.98 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.22 (dd, *J* = 10.4, 8.3 Hz, 2H), 8.06 (s, 1H), 7.99 – 7.86 (m, 2H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.85 (t, *J* = 5.2 Hz, 1H), 4.79 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 151.3, 149.1 (d, *J* = 13.4 Hz), 148.1, 144.0 (d, *J* = 253.5 Hz), 143.1 (d, *J* = 7.4 Hz), 136.5, 134.1 (d, *J* = 8.4 Hz), 131.8, 129.9, 129.8 (d, *J* = 3.0 Hz), 128.2 (d, *J* = 3.5 Hz), 128.1, 121.7, 114.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.4. IR (KBr): 3474, 3170, 1644, 1480, 1450, 1186 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{11}FN_3$: 240.0937; Found: 240.0925.

3-Fluoro-4-methylpyridin-2-amine (3i)



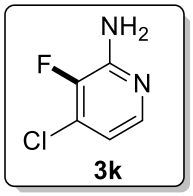
Pale yellow solid; mp 55.1-56.2 °C; 58% yield (7.3 mg).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 5.1 Hz, 1H), 6.48 (t, *J* = 5.1 Hz, 1H), 4.56 (s, 2H), 2.23 (d, *J* = 1.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.0 (d, *J* = 13.2 Hz), 145.9 (d, *J* = 248.5 Hz), 142.2 (d, *J* = 7.2 Hz), 132.3 (d, *J* = 12.2 Hz), 116.7, 13.7 (d, *J* = 4.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -146.0. IR (KBr): 3486, 3105, 1640, 1620, 1474, 1199 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_6H_8FN_2$: 127.0672; Found: 127.0679.

4-Ethyl-3-fluoropyridin-2-amine (3j)



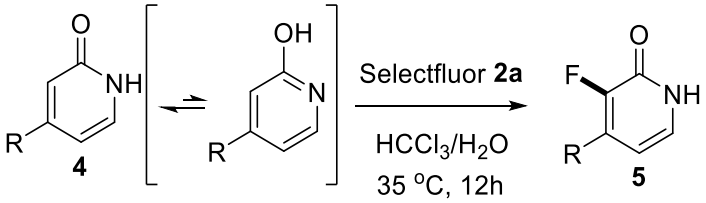
Pale yellow liquid; 52% yield (7.3 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 5.1 Hz, 1H), 6.51 (t, *J* = 5.1 Hz, 1H), 4.66 (s, 2H), 2.62 (qd, *J* = 7.6, 1.1 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 148.1 (d, *J* = 13.3 Hz), 145.4 (d, *J* = 248.5 Hz), 142.5 (d, *J* = 7.1 Hz), 138.1 (d, *J* = 11.5 Hz), 114.9, 21.3 (d, *J* = 3.5 Hz), 13.5. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -147.4. IR (KBr): 3481, 3191, 1671, 1636, 1479, 1192 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_7H_{10}FN_2$: 141.0828; Found: 141.0816.

4-Chloro-3-fluoropyridin-2-amine (3k)



Pale yellow solid; mp 86.5-87.2 °C; 41% yield (6 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 5.4 Hz, 1H), 6.68 (t, *J* = 5.1 Hz, 1H), 4.81 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 149.1 (d, *J* = 11.9 Hz), 143.1 (d, *J* = 253.8 Hz), 143.0 (d, *J* = 8.0 Hz), 128.9 (d, *J* = 12.8 Hz), 115.4 (d, *J* = 3.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -143.8. IR (KBr): 3373, 3148, 1662, 1480, 1463, 1202 cm^{-1}. HRMS (ESI): *m/z* $[M +H]^+$ calcd for $C_5H_5ClFN_2$: 147.0125; Found: 147.0116.

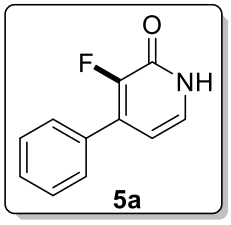
General Procedure for the Synthesis of 5a–5l



4-Substituted-2-pyridones **4** (0.20 mmol) and selectfluor **2a** (0.10 mmol) were dissolved in $CHCl_3$ (1 mL) and H_2O (1 mL) in a sealed tube, then the reaction mixture was stirred at 35 °C for 12h, monitoring by TLC. The mixture was diluted with NaCl solution and DCM (3 × 20 mL), dried with Na_2SO_4. After concentration of the filtrate to dryness, purification of the residue by column chromatography on silica gel (ethyl acetate) afforded the desired product **5a-5g**.

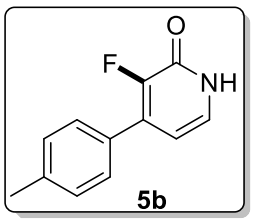
Compound Characterization

3-Fluoro-4-phenylpyridin-2(*1H*)-one (5a)



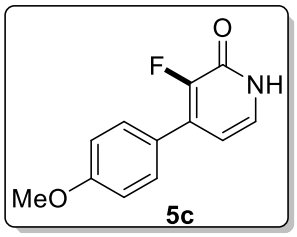
White solid; mp 207.4-207.7 °C; 81% yield (15.3 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.17 (s, 1H), 7.59 (dd, *J* = 6.8, 1.8 Hz, 2H), 7.55 – 7.44 (m, 3H), 7.33 – 7.27 (m, 1H), 6.31 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 156.3 (d, *J* = 26.1 Hz), 148.5 (d, *J* = 246.9 Hz), 134.3 (d, *J* = 8.8 Hz), 133.1, 130.5 (d, *J* = 6.1 Hz), 129.7, 129.2, 128.9 (d, *J* = 3.8 Hz), 105.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ = -141.0. IR (KBr): 2919, 2849, 1654, 1624, 751, 696 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{11}H_9FNO$: 190.0668; Found: 190.0661.

3-Fluoro-4-(*p*-tolyl)pyridin-2(*1H*)-one (5b)



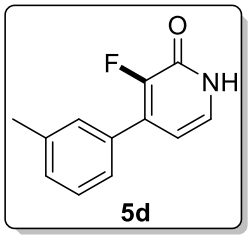
White solid; mp 211.1-213.0. °C; 85% yield (17.3 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.08 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.30 (dd, *J* = 15.7, 7.3 Hz, 3H), 6.30 (t, *J* = 6.4 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 156.4 (d, *J* = 26.0 Hz), 148.4 (d, *J* = 246.6 Hz), 139.4, 134.2 (d, *J* = 8.6 Hz), 130.4 (d, *J* = 6.1 Hz), 130.2, 129.8, 128.8 (d, *J* = 3.9 Hz), 105.4, 21.3. ^{19}F NMR (376 MHz, DMSO-d_6) δ = -141.1. IR (KBr): 3405, 3095, 1652, 1596, 1470, 785 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{12}H_{11}FNO$: 204.0825; Found: 204.0821.

3-Fluoro-4-(4-methoxyphenyl)pyridin-2(*1H*)-one (5c)



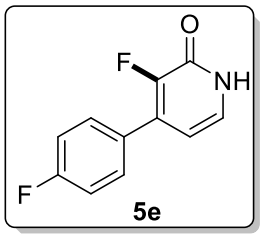
White solid; mp 194.2-195.7 °C; 86% yield (18.8 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.06 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 6.8 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.31 (t, *J* = 6.5 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 160.4, 156.4 (d, *J* = 26.1 Hz), 148.2 (d, *J* = 245.8 Hz), 133.9 (d, *J* = 8.5 Hz), 130.5 (d, *J* = 4.3 Hz), 130.2 (d, *J* = 6.1 Hz), 125.1, 114.7, 105.3, 55.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ = -141.6. IR (KBr): 2956, 2836, 1659, 1622, 1606, 779 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{12}H_{11}FNO_2$: 220.0774; Found: 220.0768.

3-Fluoro-4-(*m*-tolyl)pyridin-2(*1H*)-one (5d)



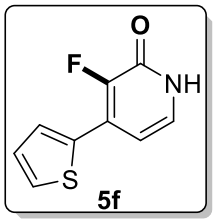
White solid; mp 139.2-140.6 °C; 76% yield (15.4 mg).
^{1}H NMR (600 MHz, DMSO-d_6) δ = 12.15 (s, 1H), 7.45 – 7.34 (m, 3H), 7.29 (d, *J* = 6.9 Hz, 2H), 6.29 (t, *J* = 6.4 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 156.4 (d, *J* = 26.1 Hz), 148.5 (d, *J* = 246.8 Hz), 138.5, 134.5 (d, *J* = 8.9 Hz), 133.1, 130.5 (d, *J* = 6.3 Hz), 130.3, 129.4 (d, *J* = 3.4 Hz), 129.1, 126.1 (d, *J* = 3.7 Hz), 105.6, 21.4. ^{19}F NMR (565 MHz, DMSO-d_6) δ = -140.8. IR (KBr): 2924, 2856, 1655, 1627, 1204, 774 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^{+}$ calcd for $C_{12}H_{11}FNO$: 204.0825; Found: 204.0823.

3-Fluoro-4-(4-fluorophenyl)pyridin-2(*1H*)-one (5e)



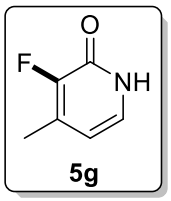
White solid; mp 229.8-230.9 °C; 58% yield (12.0 mg).
^{1}H NMR (600 MHz, DMSO-d_6) δ = 12.19 (s, 1H), 7.66 (dd, *J* = 8.3, 5.5 Hz, 2H), 7.43 – 7.27 (m, 3H), 6.32 (t, *J* = 6.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ = 162.9 (d, *J* = 247.2 Hz), 156.3 (d, *J* = 25.9 Hz), 148.5 (d, *J* = 247.1 Hz), 133.4 (d, *J* = 8.6 Hz), 131.4 (dd, *J* = 8.5, 3.7 Hz), 130.6 (d, *J* = 6.1 Hz), 129.5 (d, *J* = 3.0 Hz), 116.3 (d, *J* = 21.6 Hz), 105.4. ^{19}F NMR (565 MHz, DMSO-d_6) δ = -111.9, -141.0. IR (KBr): 2849, 1663, 1630, 1265, 737, 705 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{11}H_8F_2NO$: 208.0574; Found: 208.0572.

3-Fluoro-4-(thiophen-2-yl)pyridin-2(*1H*)-one (5f)



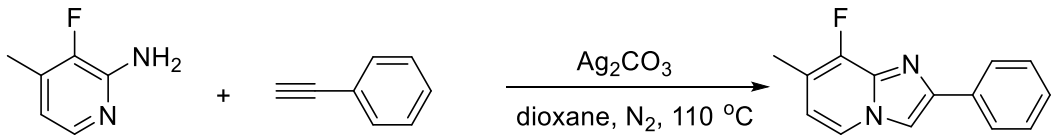
White solid, mp 195.7-196.9 °C; 89% yield (17.4 mg).
^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.04 (s, 1H), 7.88 (d, *J* = 5.0 Hz, 1H), 7.80 (d, *J* = 3.7 Hz, 1H), 7.25 (d, *J* = 6.5 Hz, 2H), 6.61 (t, *J* = 6.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 156.2 (d, *J* = 25.4 Hz), 147.1 (d, *J* = 248.6 Hz), 133.6 (d, *J* = 5.2 Hz), 130.8 (d, *J* = 8.3 Hz), 130.5 (d, *J* = 5.8 Hz), 130.0 (d, *J* = 4.6 Hz), 128.5 , 127.3 (d, *J* = 8.6 Hz), 102.9 (d, *J* = 1.7 Hz).^{19}F NMR (376 MHz, DMSO-d_6) δ = -135.3. IR (KBr): 2931, 2804, 1663, 1622, 1263, 779 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for C_9H_7FNOS: 196.0232; Found: 196.0231.

3-Fluoro-4-methylpyridin-2(*1H*)-one (5g)



White solid; mp 95.8-97.2 °C; 79% yield (10.0 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ = 13.46 (s, 1H), 7.15 (d, *J* = 6.6 Hz, 1H), 6.14 (t, *J* = 6.1 Hz, 1H), 2.24 (d, *J* = 2.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.1 (d, *J* = 25.3 Hz), 149.9 (d, *J* = 243.5 Hz), 134.5 (d, *J* = 13.1 Hz), 128.5 (d, *J* = 6.2 Hz), 109.4 (d, *J* = 2.6 Hz), 14.2 (d, *J* = 3.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ = -140.0. IR (KBr): 2925, 2848, 1659, 1624, 1226, 794 cm^{-1}. HRMS (ESI): *m/z* [M + H]$^+$ calcd for C_6H_7FNO: 128.0512; Found: 128.0501.

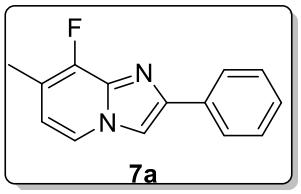
General Procedure for the Synthesis of 7a[2]



3j **6** **7a**

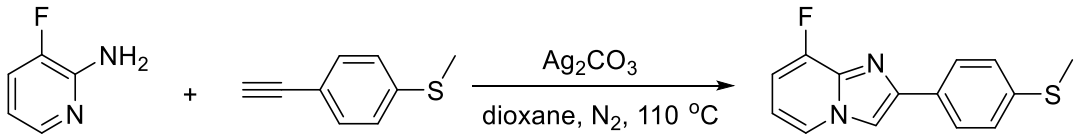
A mixture of 3-fluoro-4-methylpyridin-2-amine **3j** (0.20 mmol), phenylacetylene **6** (0.10 mmol), and Ag_2CO_3 (0.20 mmol) in dioxane (2 mL) was stirred in N_2 at 110 °C. After completion of the reaction, as indicated by TLC, the solid was filtered out and washed with dichloromethane. After removal of the solvent of the filtrate, the pure product was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 2/1) to afford **7**.

8-Fluoro-7-methyl-2-phenylimidazo [1,2-*a*] pyridine (7a)



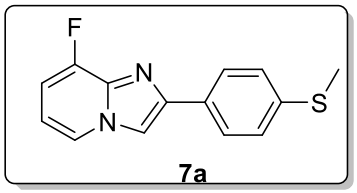
Pale yellow solid; 73% yield (16.5 mg).
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.93 – 7.89 (m, 2H), 7.78 – 7.74 (m, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.29 – 7.25 (m, 1H), 6.51 (t, *J* = 6.4 Hz, 1H), 2.28 (d, *J* = 2.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.8 (d, *J* = 248.8 Hz), 145.9, 138.7 (d, *J* = 28.8 Hz), 133.3, 128.7, 128.1, 126.2, 120.9 (d, *J* = 5.4 Hz), 117.6 (d, *J* = 13.9 Hz), 115.2 (d, *J* = 4.0 Hz), 108.8, 13.5 (d, *J* = 3.4 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -135.7. IR (KBr): 1372, 1264, 1175, 1085, 908, 728 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}FN_2$: 227.0985; Found: 227.0982.

General Procedure for Preparation of the Fluorinated Zolimidine 7b'[2]



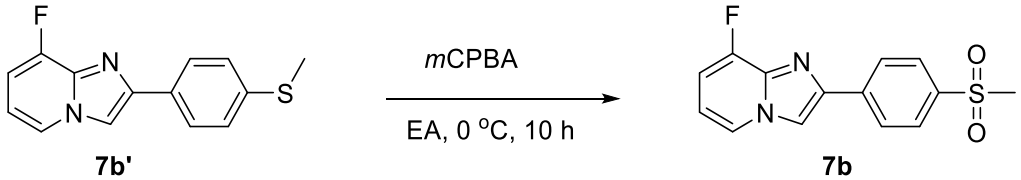
A mixture of 3-Fluoropyridin-2-amine **3'** (0.20 mmol), phenylacetylene **6b** (0.10 mmol), and Ag_2CO_3 (0.20 mmol) in dioxane (2 mL) was stirred in N_2 at 110 °C for 10 h. After completion of the reaction, as indicated by TLC, the solid was filtered out and washed with dichloromethane. After removal of the solvent of the filtrate, the pure product was obtained by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 2/1) to afford **7b'**.

8-Fluoro-2-(4-(methylthio)phenyl)imidazo[1,2-a]pyridine (7b')



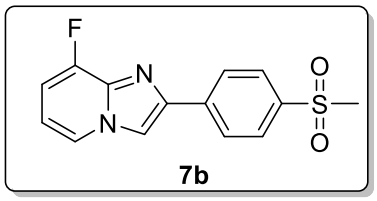
Pale yellow solid; 61% yield (15.7 mg).
^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.86 – 7.80 (m, 3H), 7.79 (d, *J* = 3.0 Hz, 1H), 7.25 – 7.21 (m, 2H), 6.82 – 6.76 (m, 1H), 6.61 (td, *J* = 7.1, 4.4 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 148.8 (d, *J* = 248.8 Hz), 145.9, 138.7 (d, *J* = 28.8 Hz), 133.3, 128.7, 128.1, 126.2, 120.9 (d, *J* = 5.4 Hz), 117.6 (d, *J* = 13.9 Hz), 115.2 (d, *J* = 4.0 Hz), 108.8, 13.5 (d, *J* = 3.4 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ = -129.7. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{11}FN_2SNa$: 281.0525; Found: 281.0488.

General Procedure for Preparation of the fFluorinated Zolimidine 7b[2]



To a solution of 8-Fluoro-2-(4-(methylthio)phenyl)imidazo[1,2-a]pyridine **7b'** (0.10 mol) in EtOAc (1 mL) was added *m*CPBA (0.20 mmol) at 0 °C. After stirring for 10 h, the mixture was quenched with water, and extracted with ethyl acetate, and the extract was washed with brine, and dried over sodium sulfate. The pure product was obtained by flash column chromatography on silica gel to afford **7b**.

8-Fluoro-2-(4-(methylsulfonyl)phenyl)imidazo[1,2-a]pyridine (7b)



White solid; 66% yield (19.1 mg).

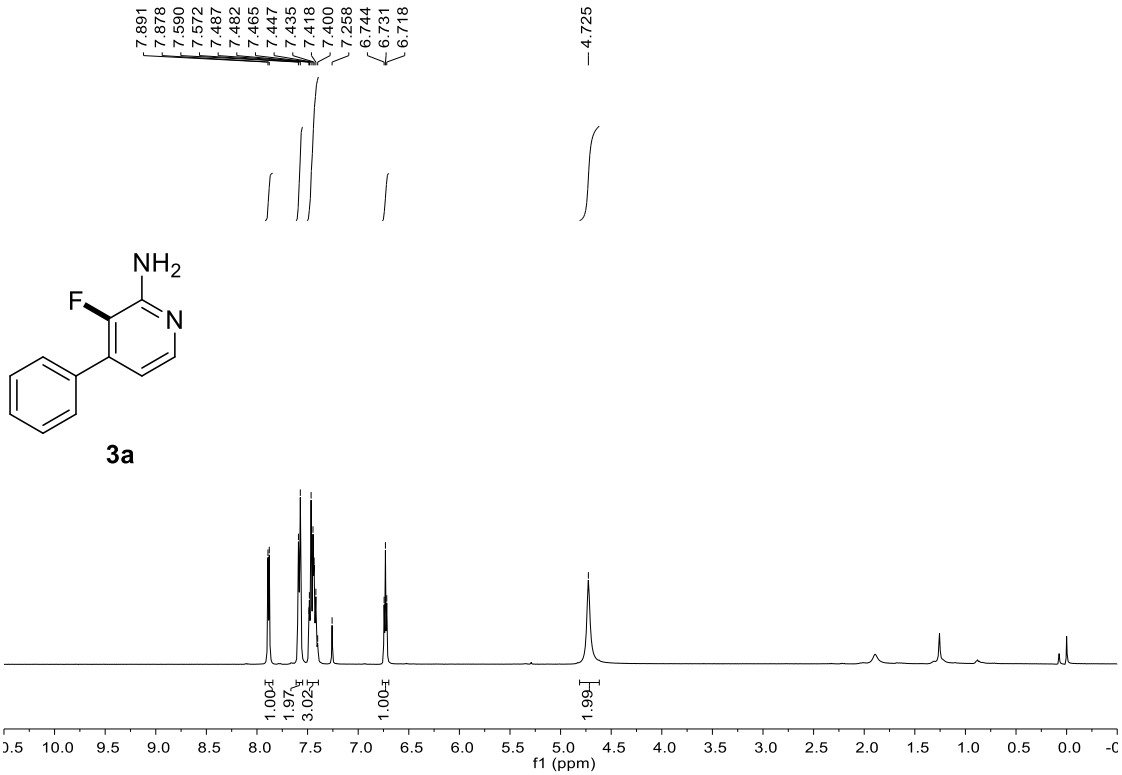
^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.21 – 8.16 (m, 2H), 8.06 (d, *J* = 2.9 Hz, 1H), 8.02 – 7.98 (m, 3H), 6.95 (ddd, *J* = 10.3, 7.6, 0.9 Hz, 1H), 6.78 (ddd, *J* = 7.6, 6.7, 4.4 Hz, 1H), 3.10 (s, 3H).^{13}C NMR (151 MHz, $CDCl_3$) δ = 151.7 (d, *J* = 254.3 Hz), 144.0, 139.6, 138.8, 138.6, 127.9, 126.8, 122.1 (d, *J* = 5.0 Hz), 112.2 (d, *J* = 6.7 Hz), 110.9, 107.9 (d, *J* = 16.6 Hz), 44.6. ^{19}F NMR (565 MHz, $CDCl_3$) δ = -129. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{12}FN_2O_2S$: 291.0604; Found: 291.0605.

References:

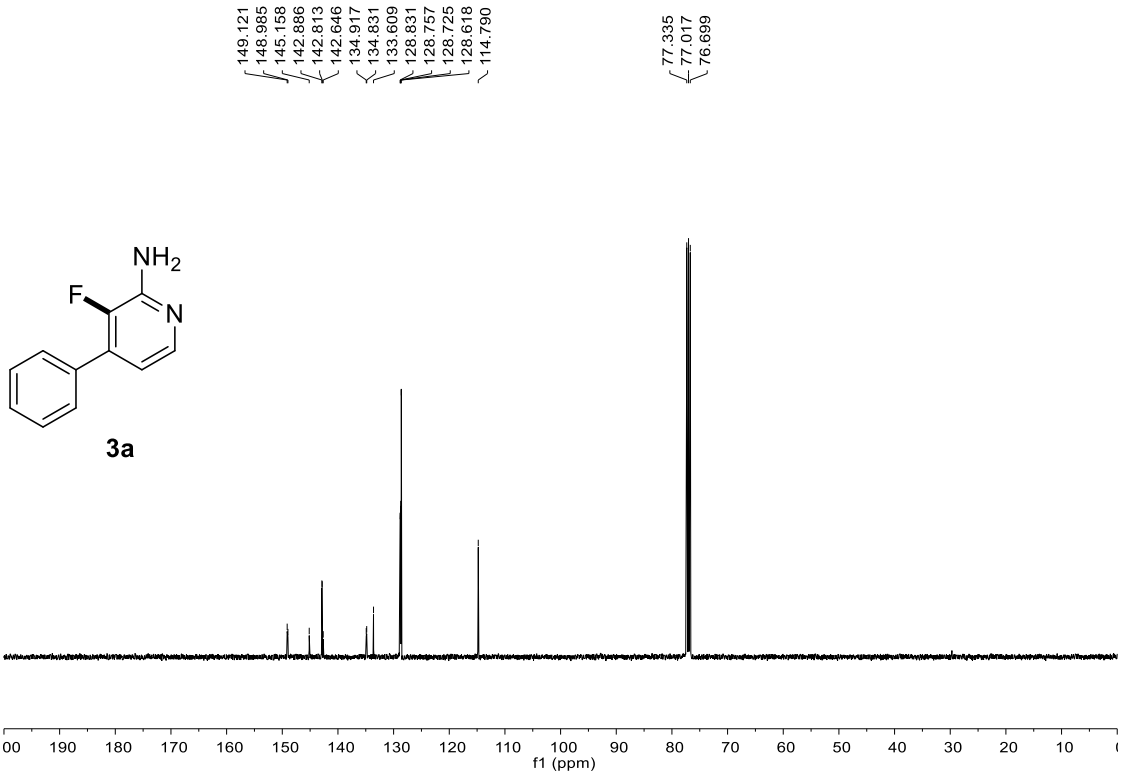
(1) Cook J.; Zusi F. C.; *J. Med. Chem*. **2016**, *59*, 11171.

(2) He C.; Hao J.; Xu H.; Mo Y.; Liu H.; Han J.; Lei A., *Chem. Commun.* **2012**, *48*, 11073.

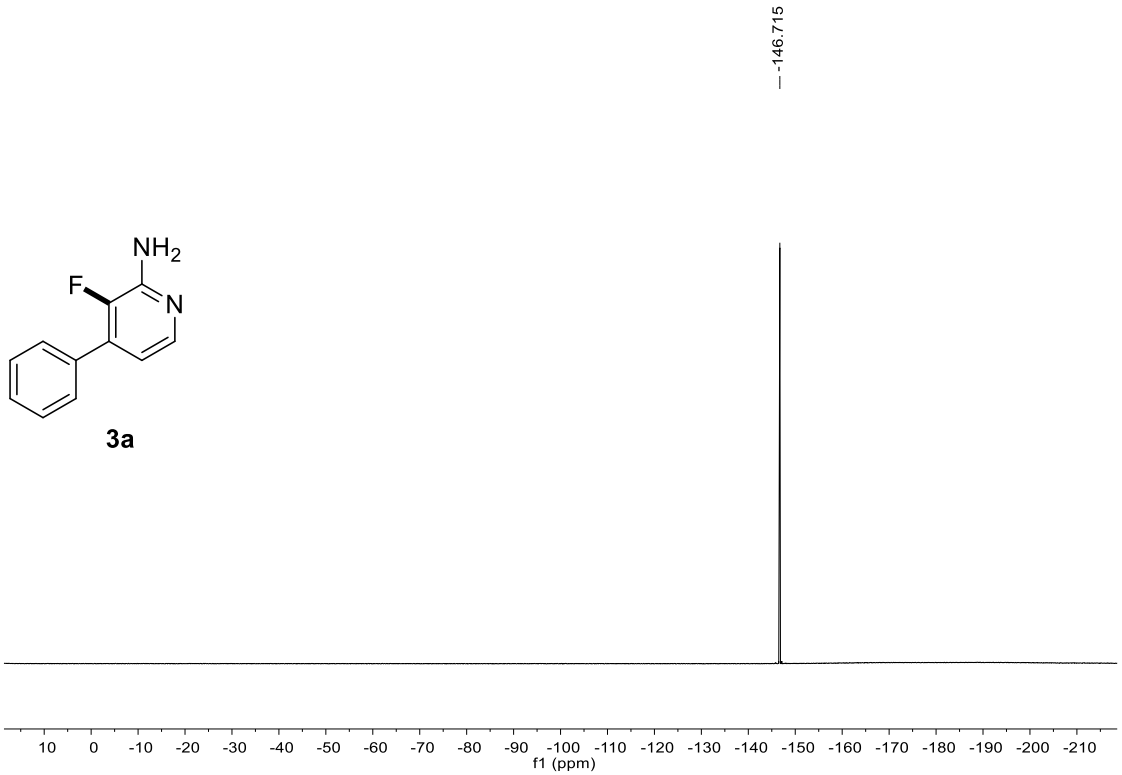
^{1}H NMR spectrum of the compound **3a (**400MHz, $CDCl_3$)



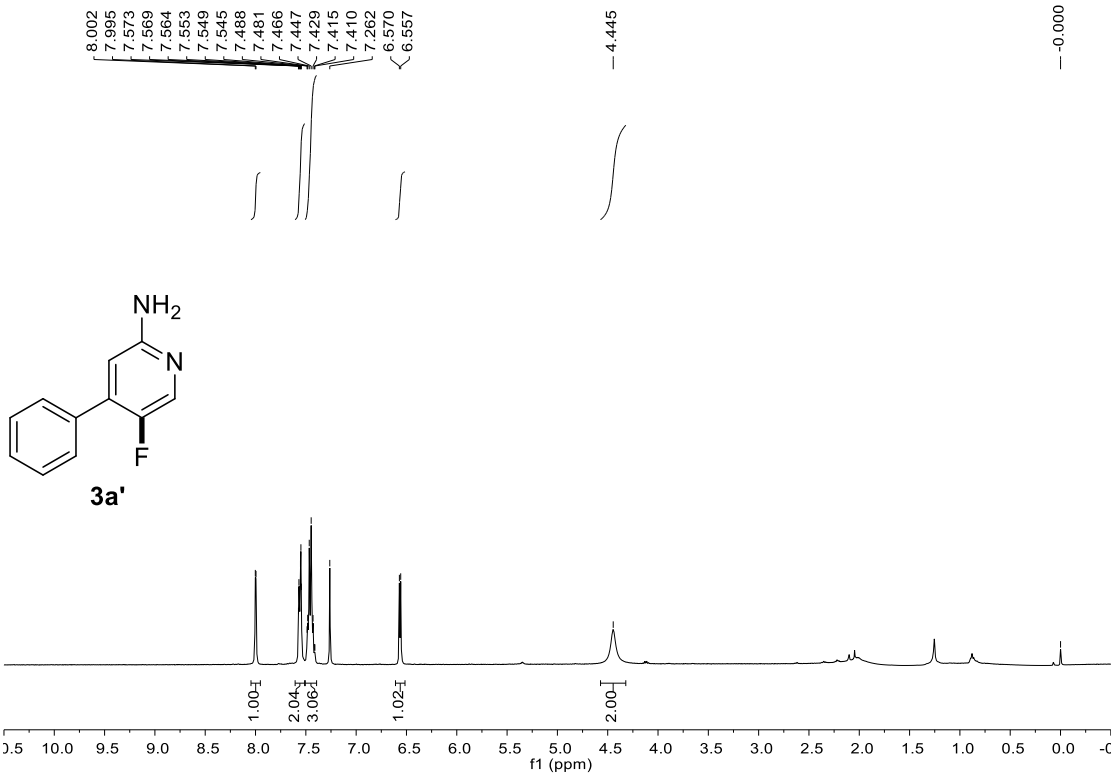
^{13}C NMR spectrum of the compound **3a** (101 MHz, $CDCl_3$)



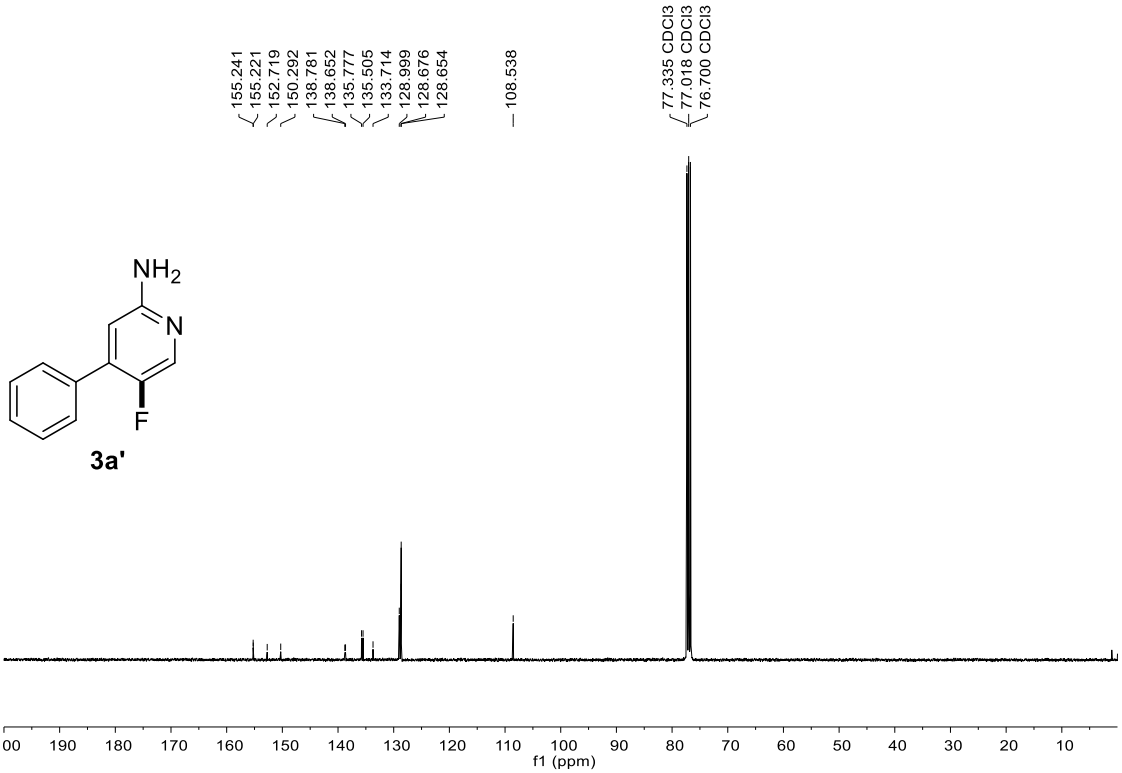
^{19}F NMR spectrum of the compound **3a** (376MHz, $CDCl_3$)



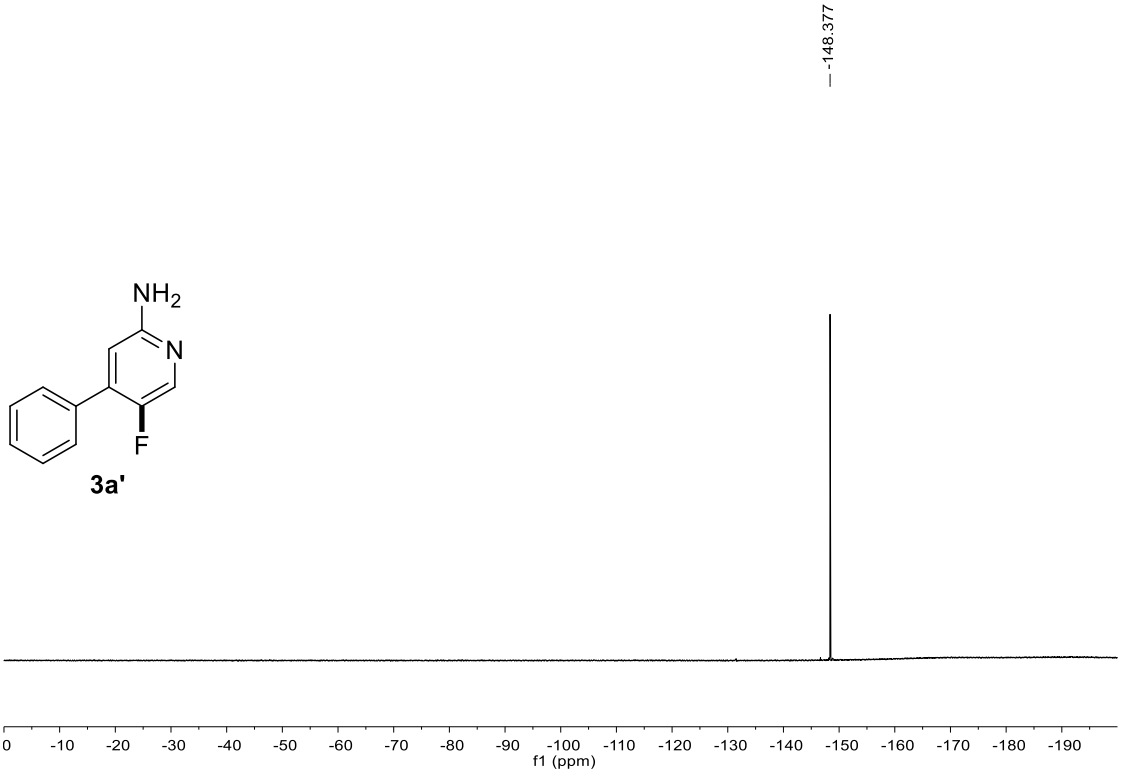
^{1}H NMR spectrum of the compound **3a' (**400 MHz, $CDCl_3$)



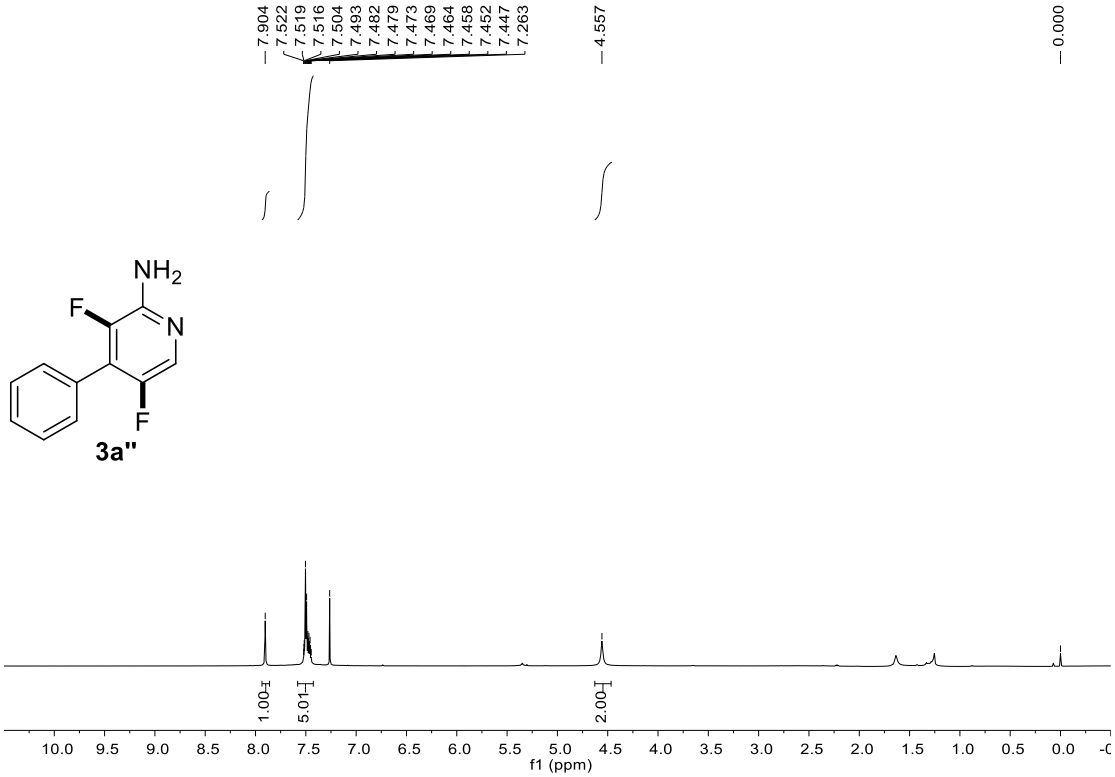
^{13}C NMR spectrum of the compound **3a'** (101 MHz, $CDCl_3$)



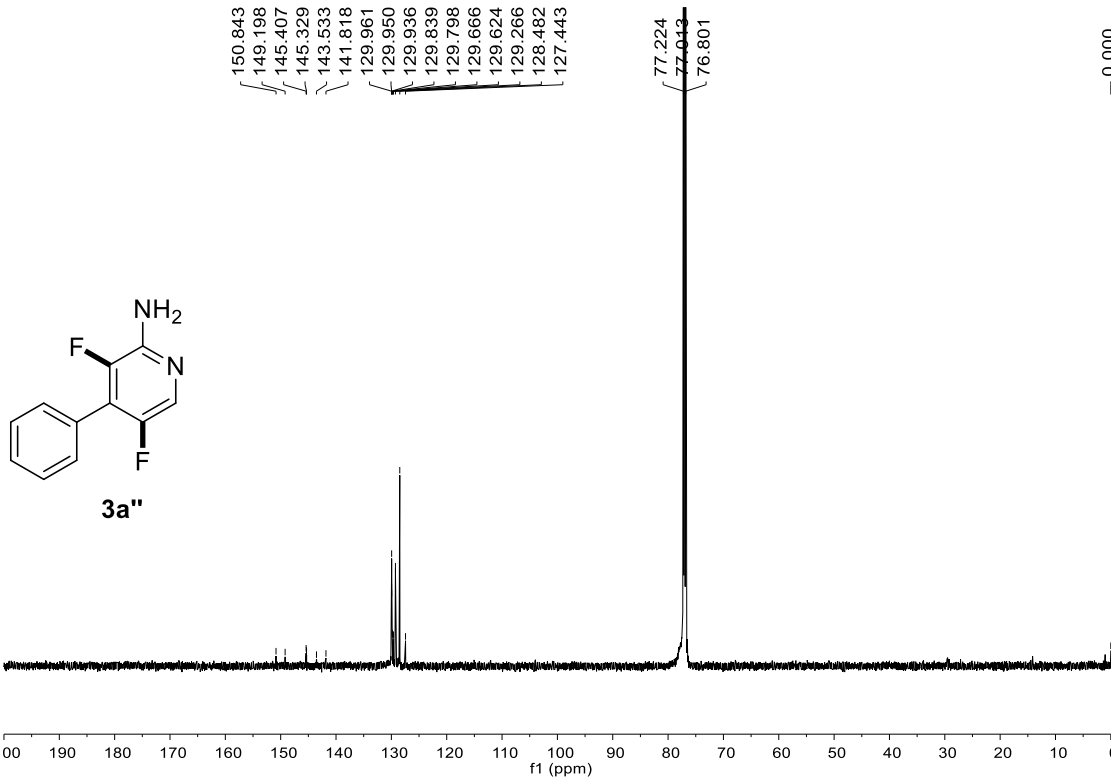
^{19}F NMR spectrum of the compound **3a'** (376 MHz, $CDCl_3$)



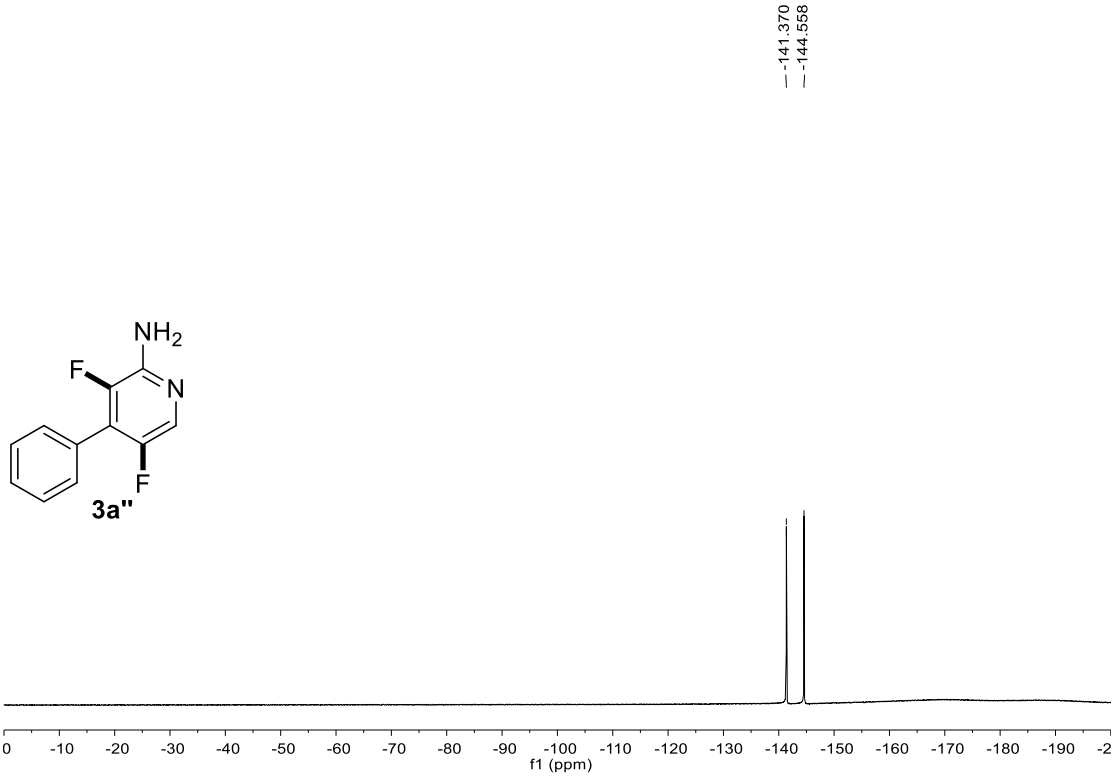
^{1}H NMR spectrum of the compound **3a'' (**600MHz, $CDCl_3$)



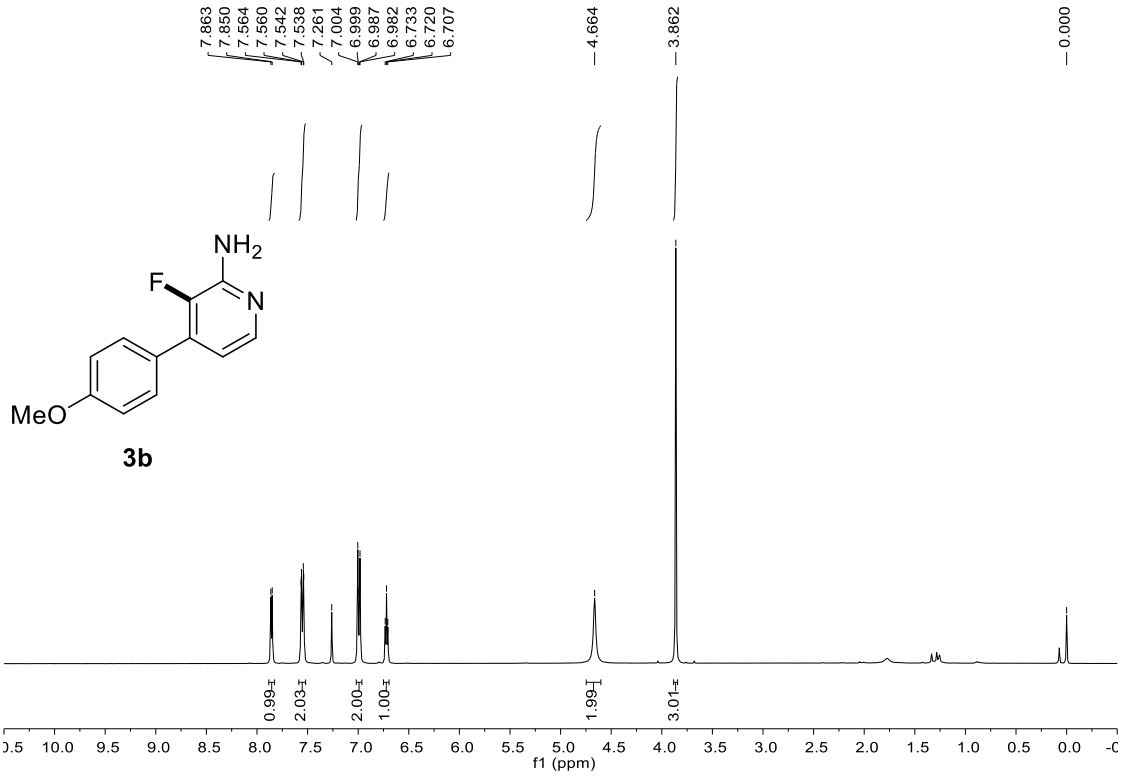
^{13}C NMR spectrum of the compound **3a''** (151 MHz, $CDCl_3$)



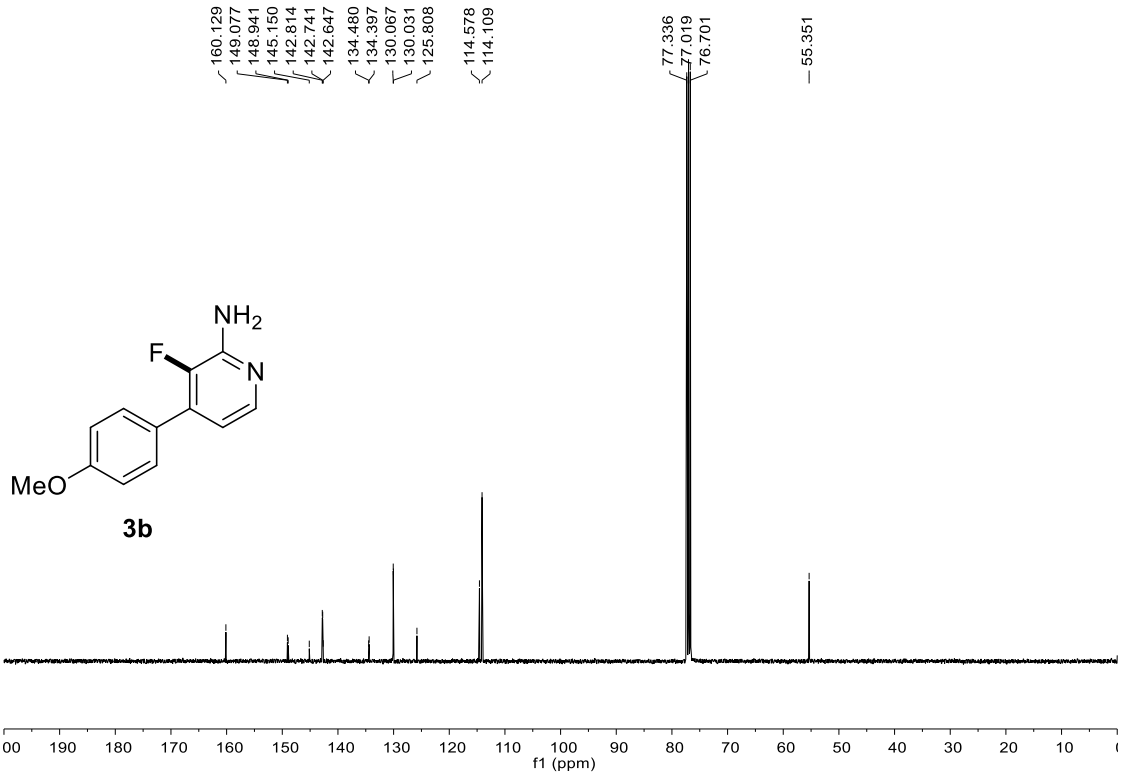
^{19}F NMR spectrum of the compound **3a''** (565 MHz, $CDCl_3$)



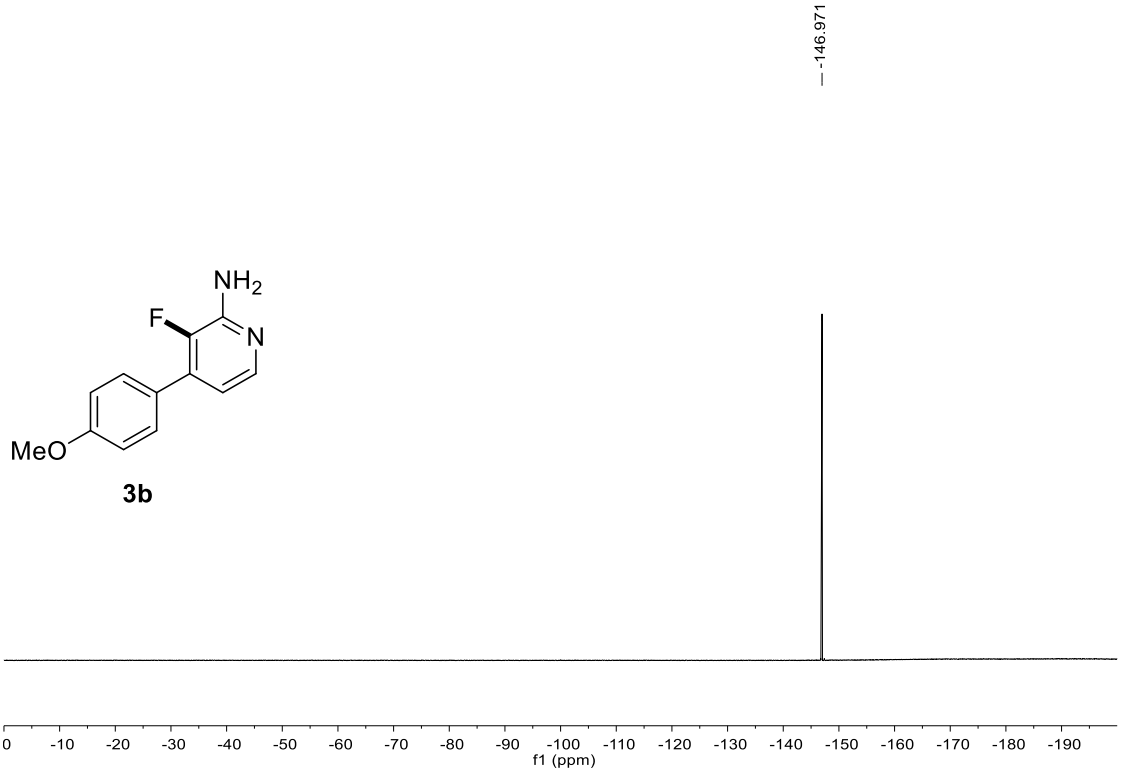
^{1}H NMR spectrum of the compound **3b (**400MHz, $CDCl_3$)



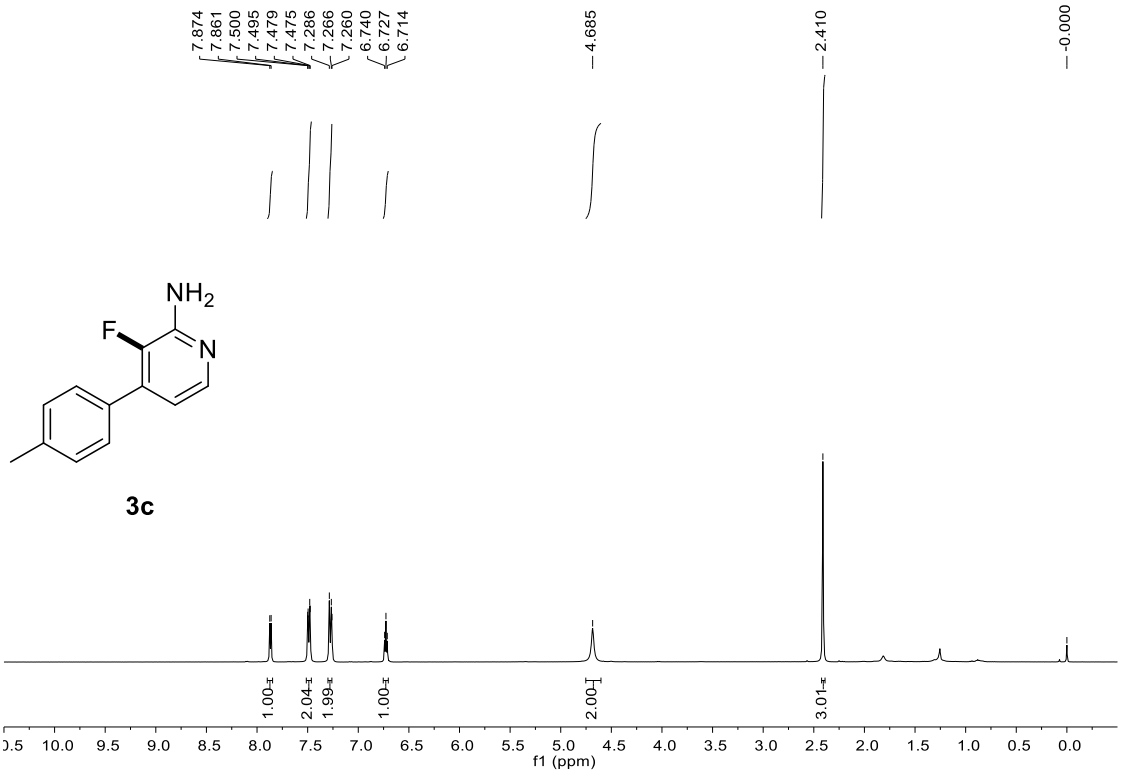
^{13}C NMR spectrum of the compound **3b** (101 MHz, $CDCl_3$)



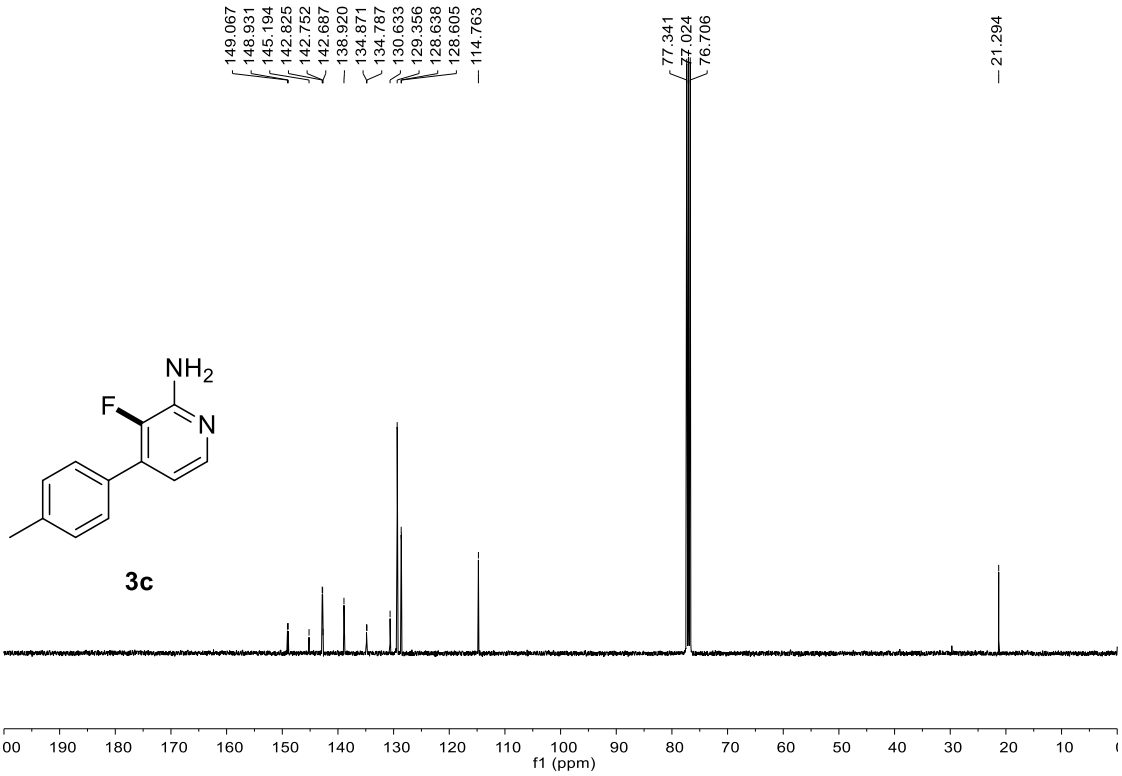
^{19}F NMR spectrum of the compound **3b** (376MHz, $CDCl_3$)



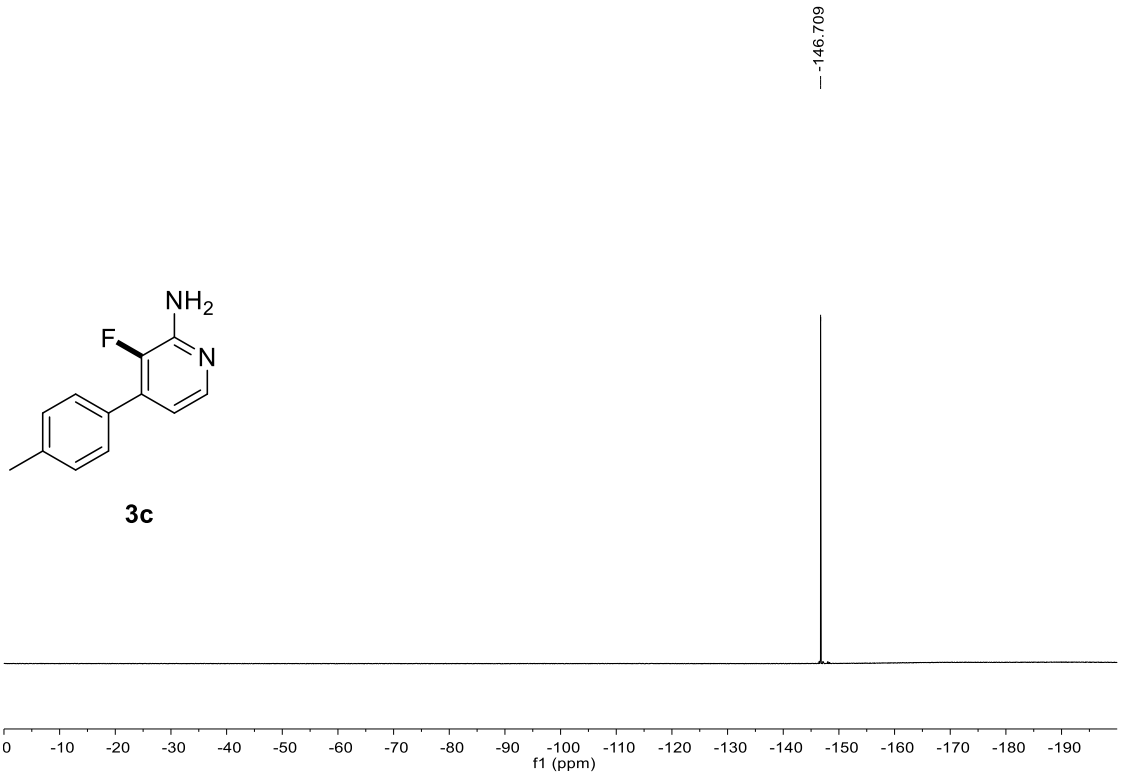
^{1}H NMR spectrum of the compound **3c (**400MHz, $CDCl_3$)



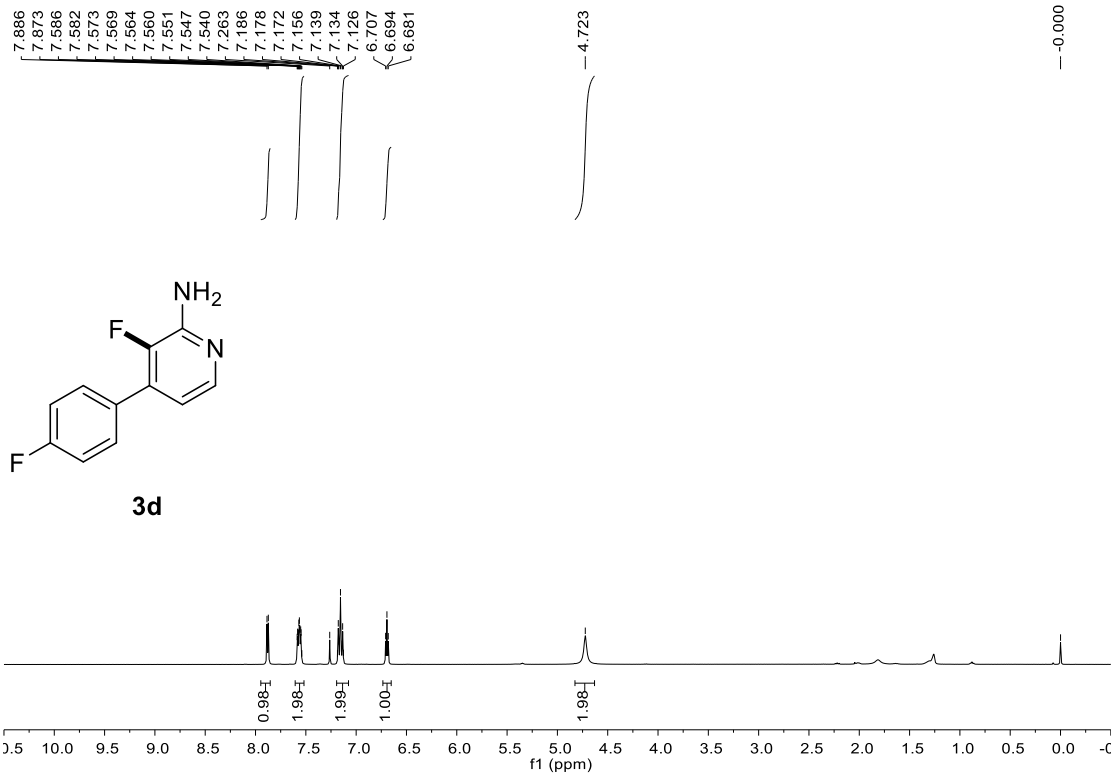
^{13}C NMR spectrum of the compound **3c** (101 MHz, $CDCl_3$)



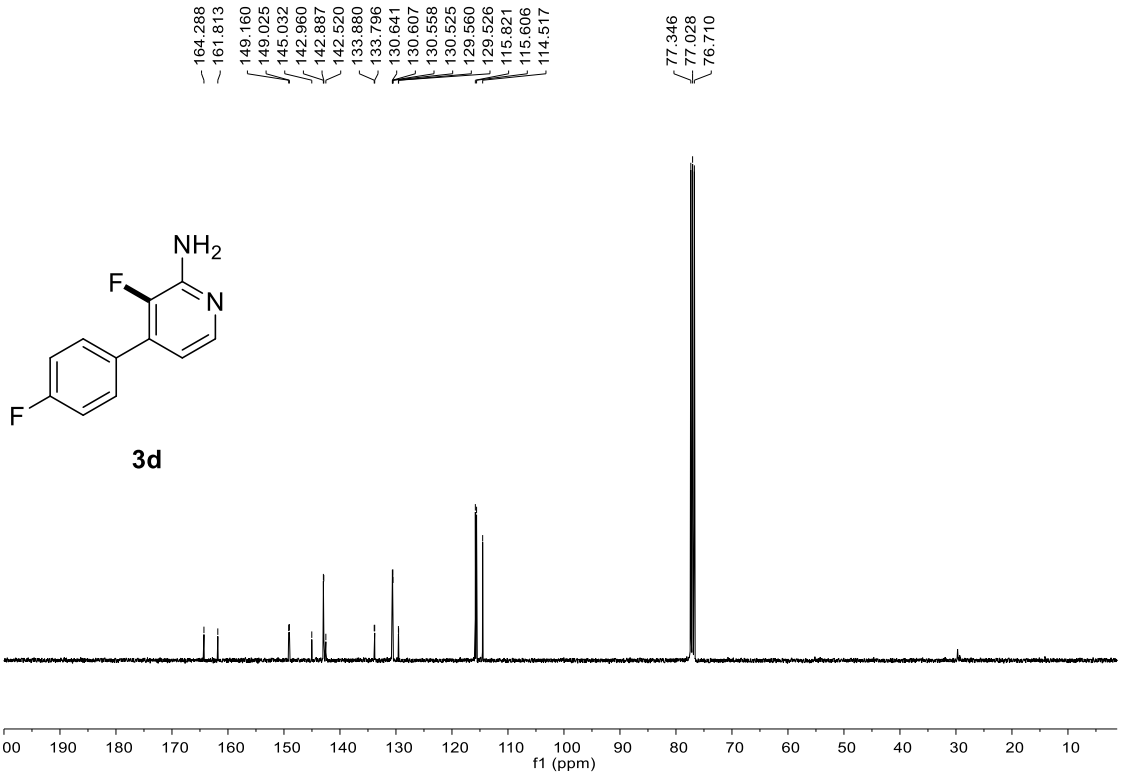
^{19}F NMR spectrum of the compound **3c** (376 MHz, $CDCl_3$)



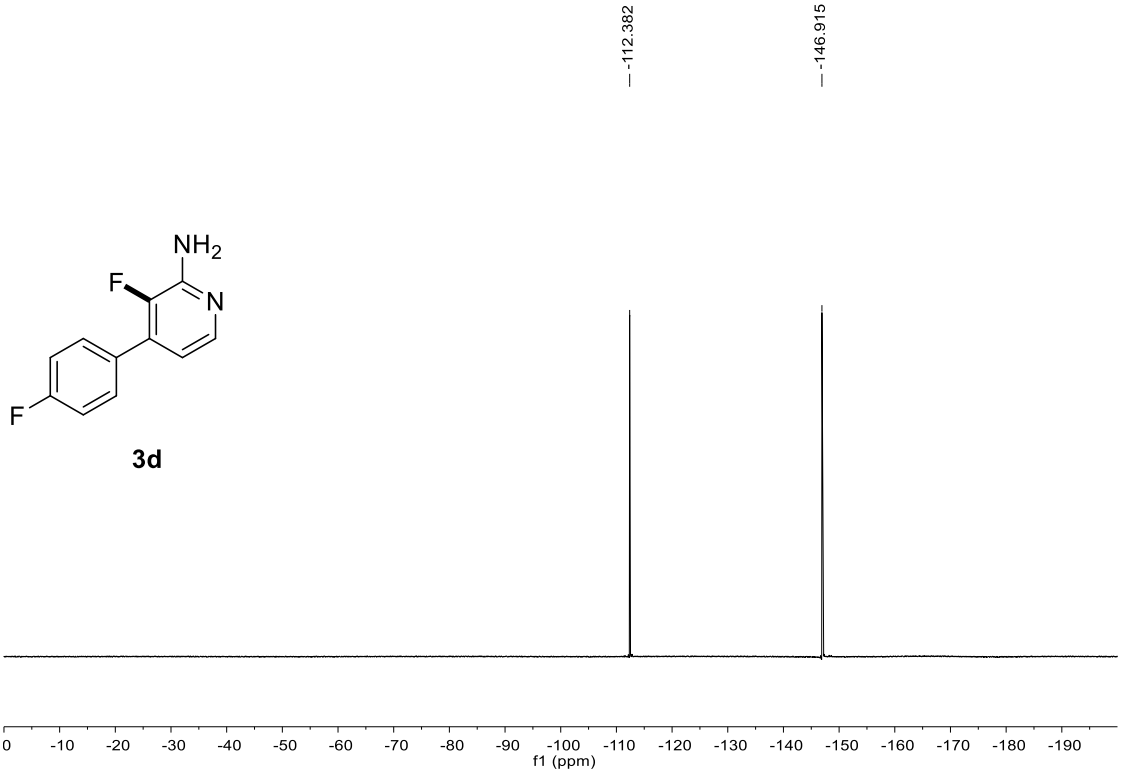
^{1}H NMR spectrum of the compound **3d (**400 MHz, $CDCl_3$)



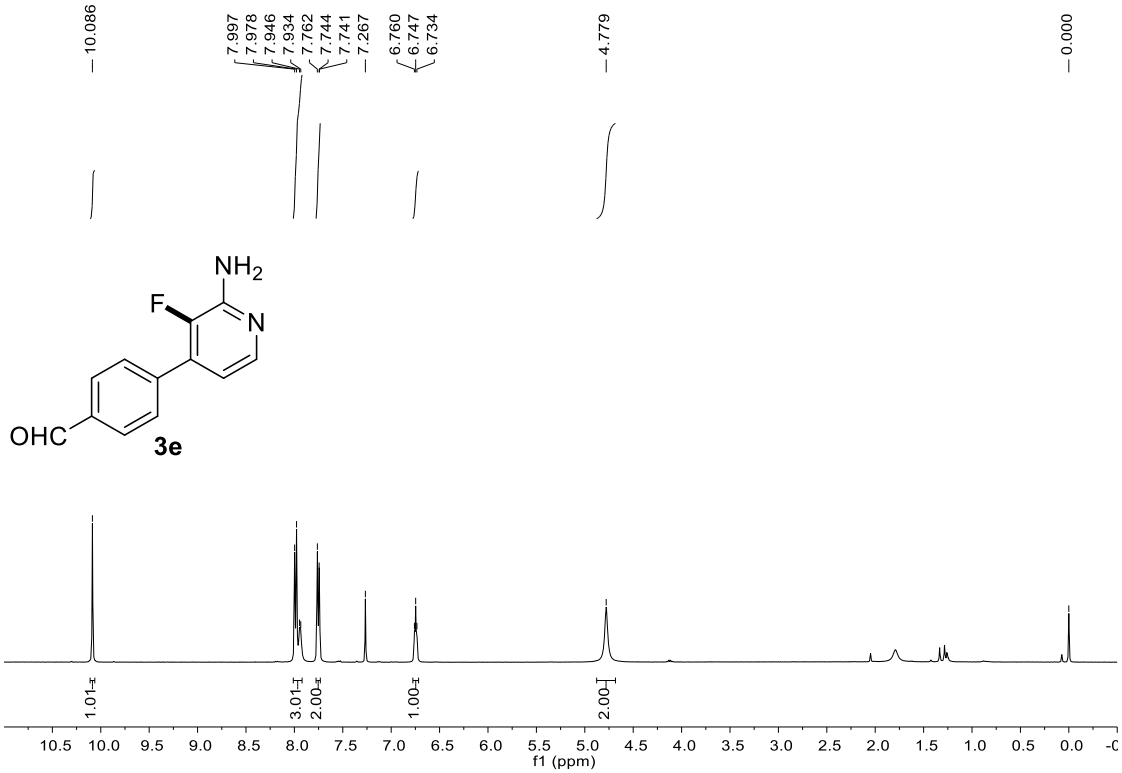
^{13}C NMR spectrum of the compound **3d** (101 MHz, $CDCl_3$)



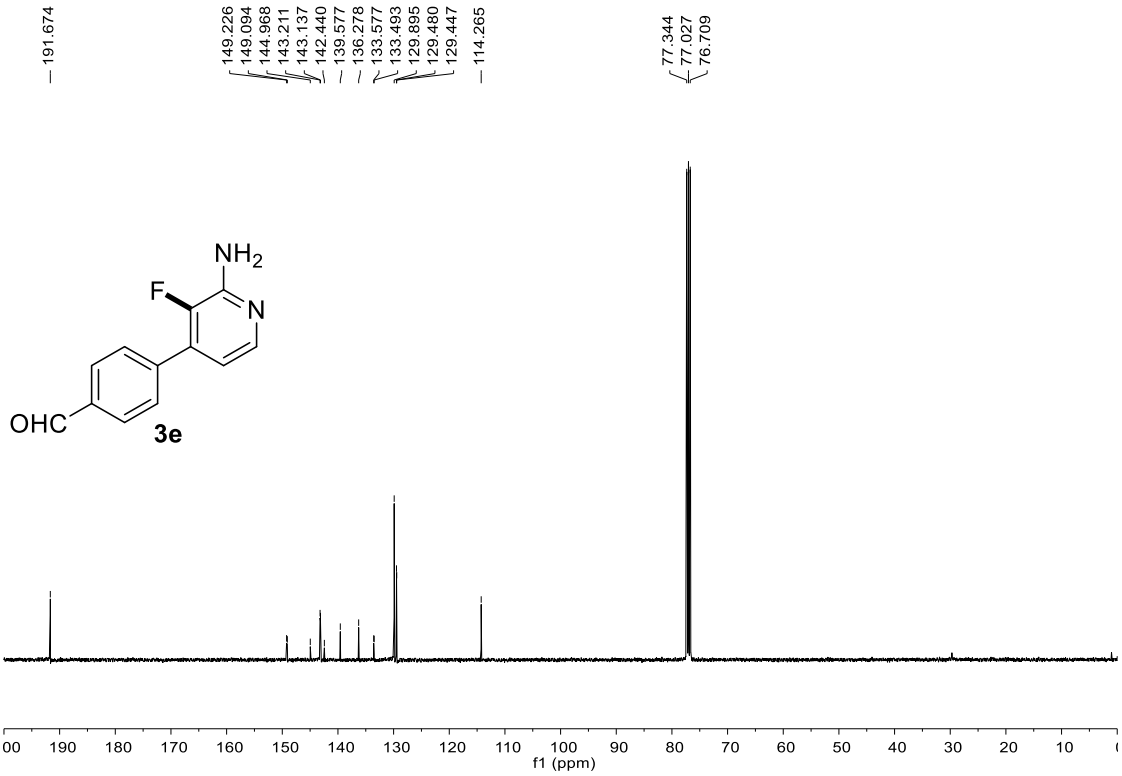
^{19}F NMR spectrum of the compound **3d** (376 MHz, $CDCl_3$)



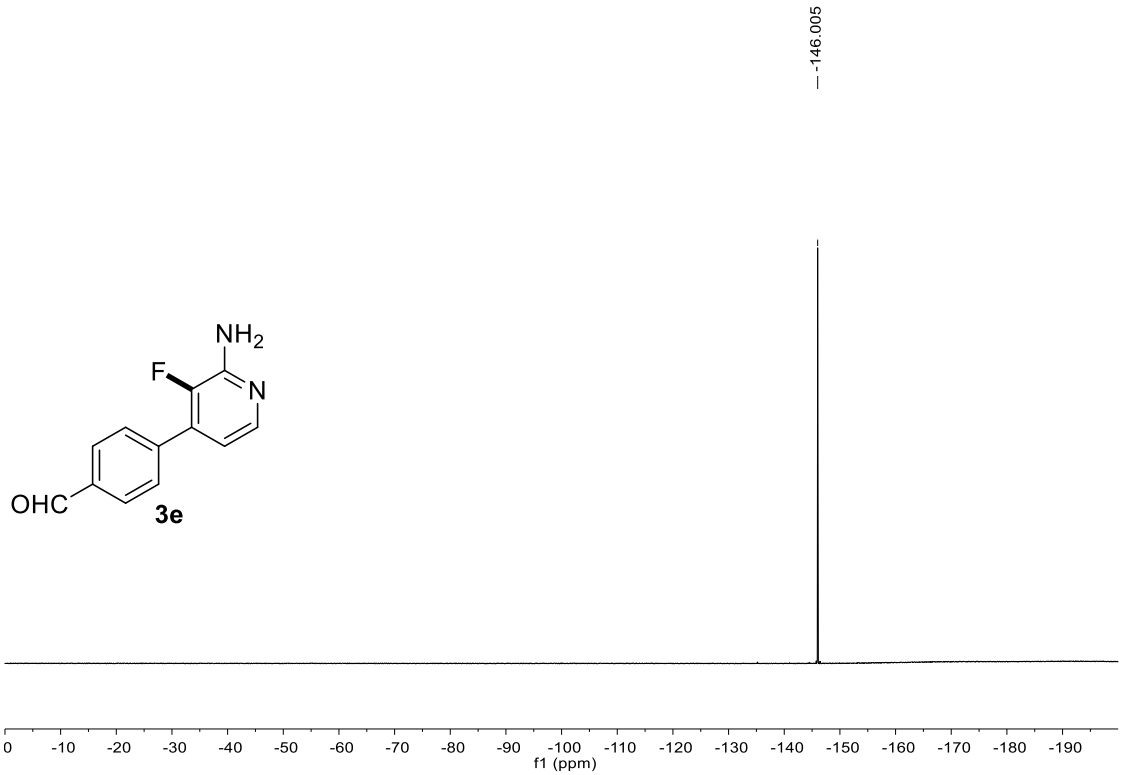
^{1}H NMR spectrum of the compound **3e (**400 MHz, $CDCl_3$)



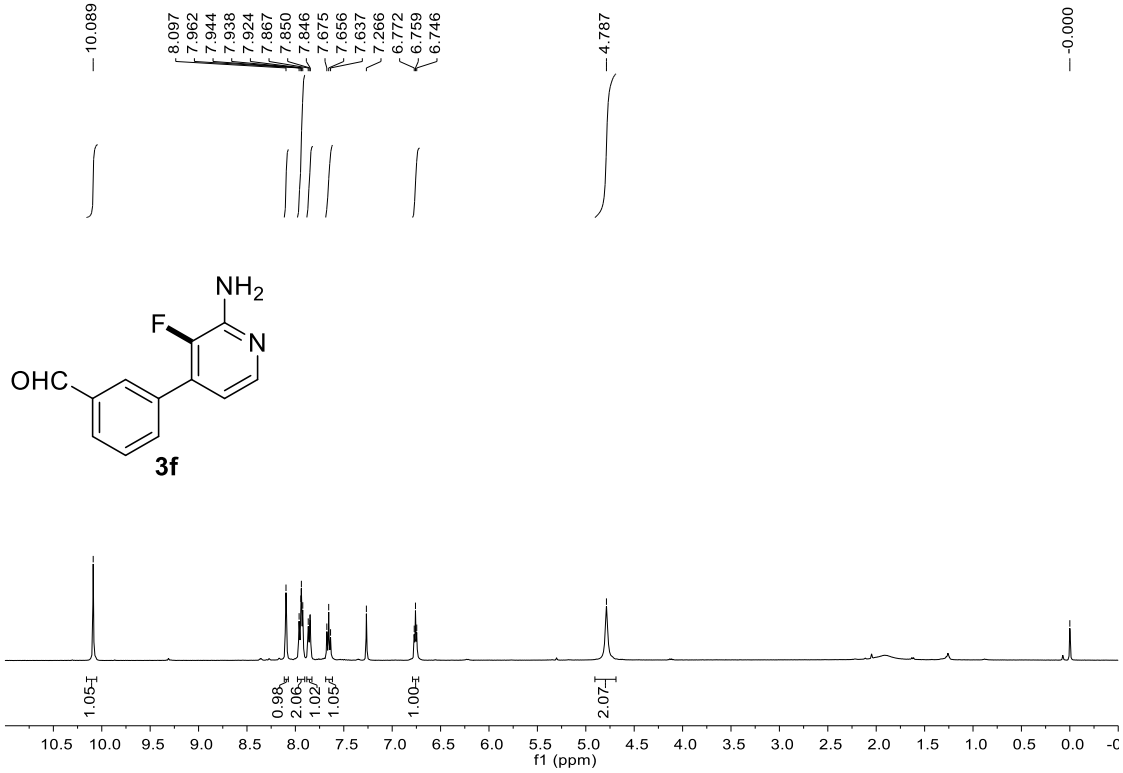
^{13}C NMR spectrum of the compound **3e** (101 MHz, $CDCl_3$)



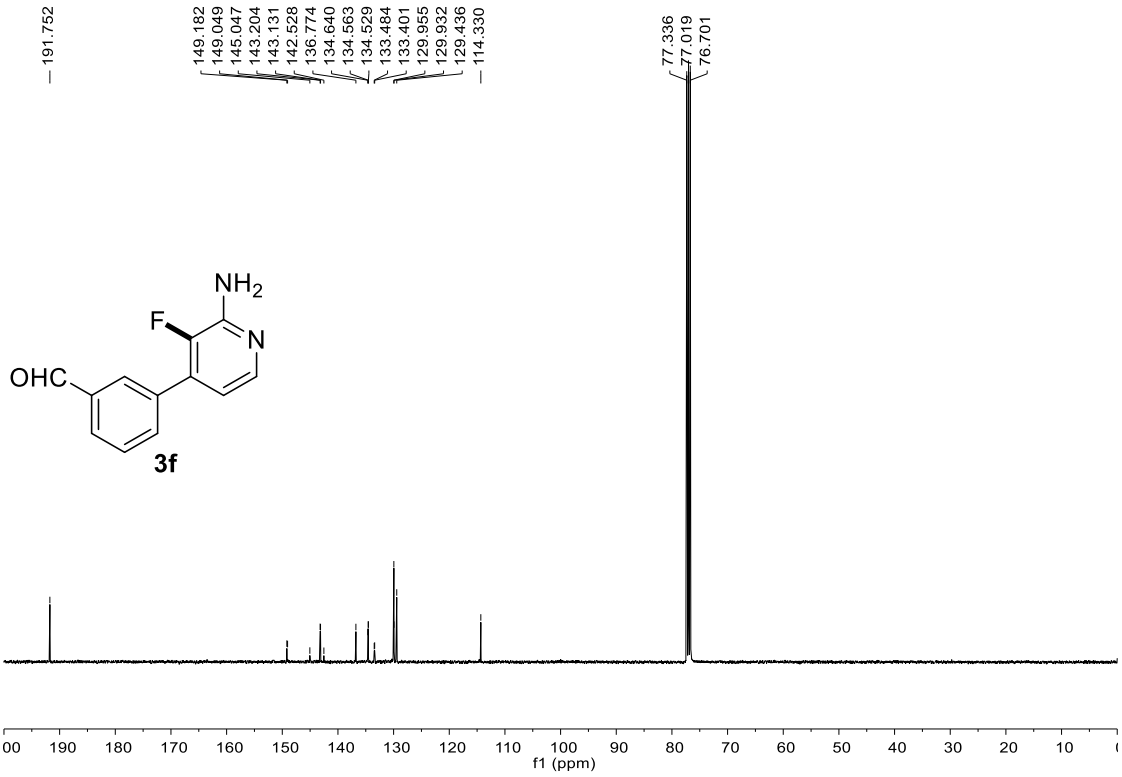
^{19}F NMR spectrum of the compound **3e** (376 MHz, $CDCl_3$)



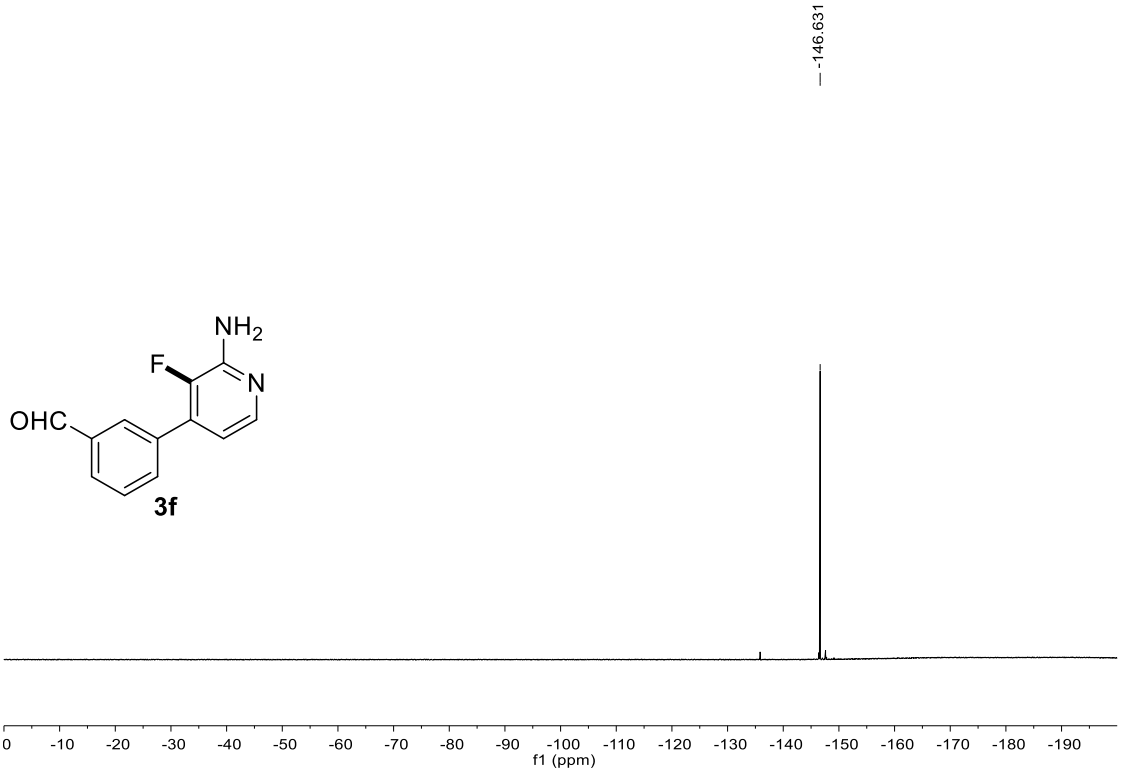
^{1}H NMR spectrum of the compound **3f (** 400MHz, $CDCl_3$)



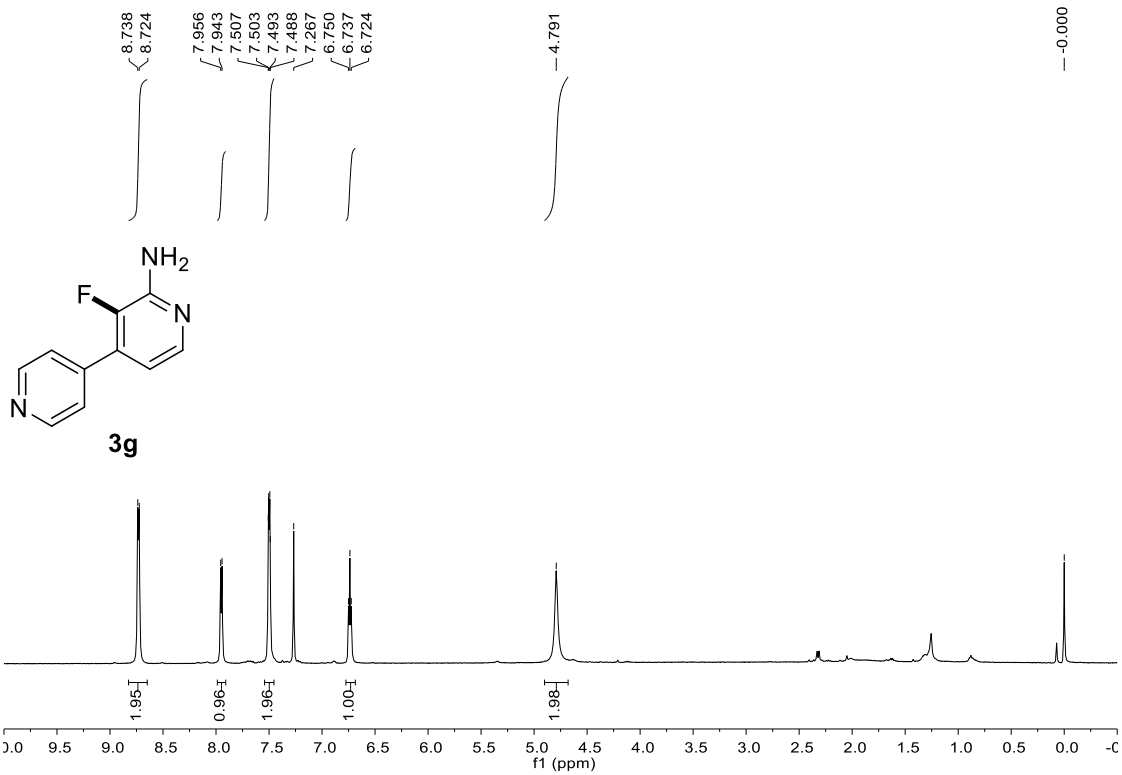
^{13}C NMR spectrum of the compound **3f** (101 MHz, $CDCl_3$)



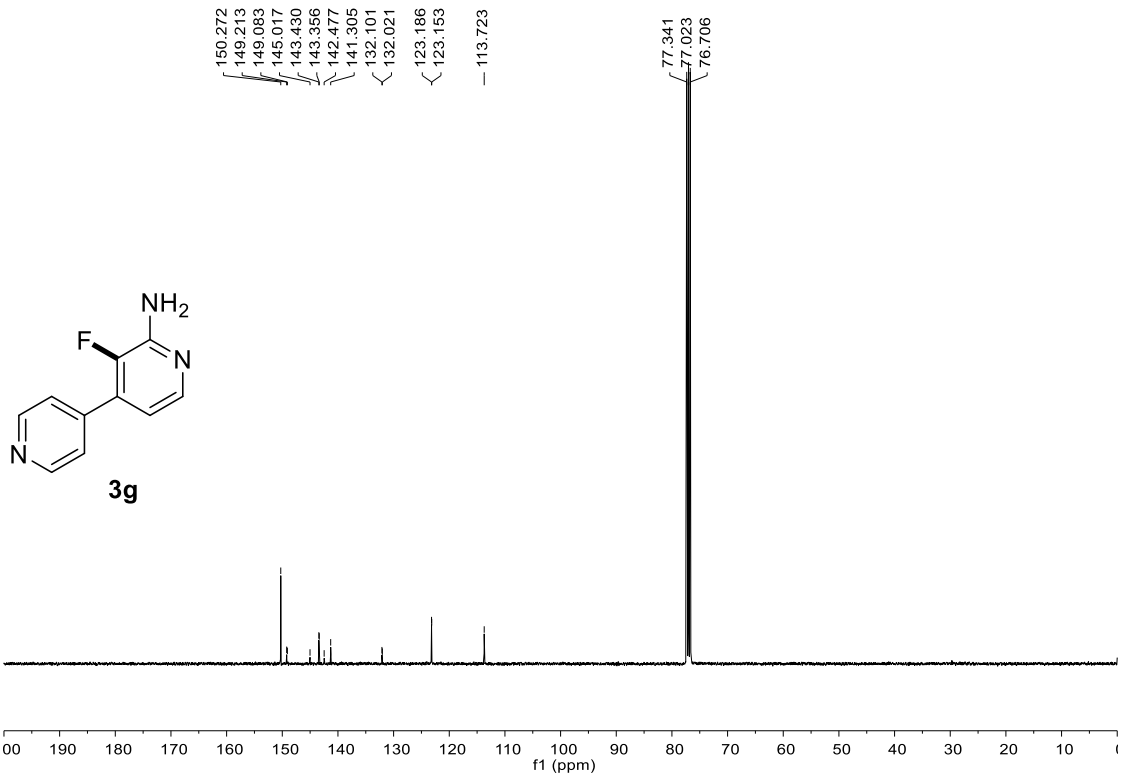
^{19}F NMR spectrum of the compound **3f** (376 MHz, $CDCl_3$)



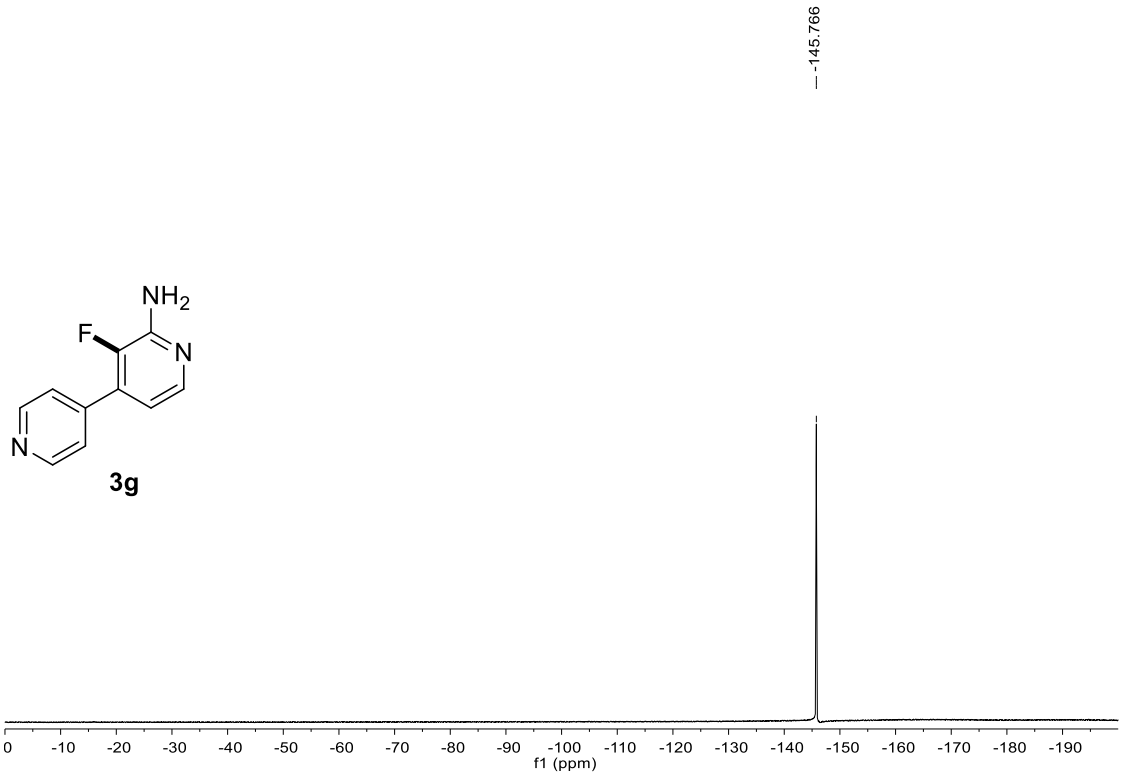
^{1}H NMR spectrum of the compound **3g (**400 MHz, $CDCl_3$)



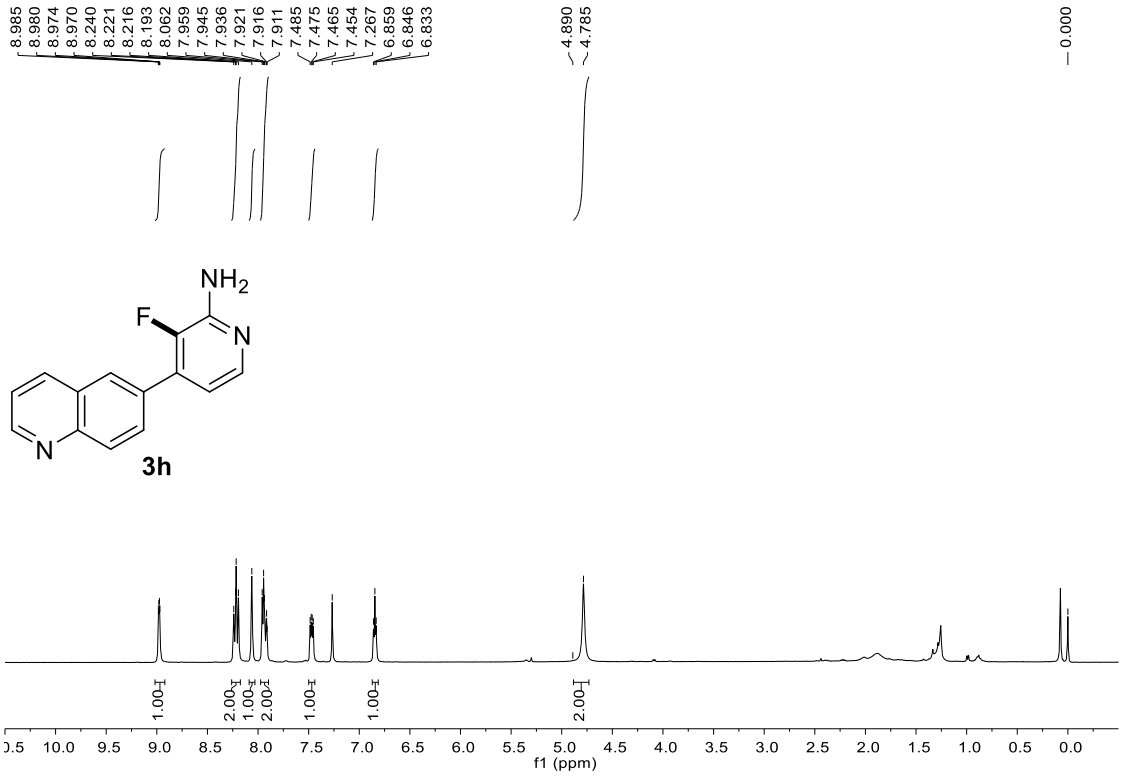
^{13}C NMR spectrum of the compound **3g** (101 MHz, $CDCl_3$)



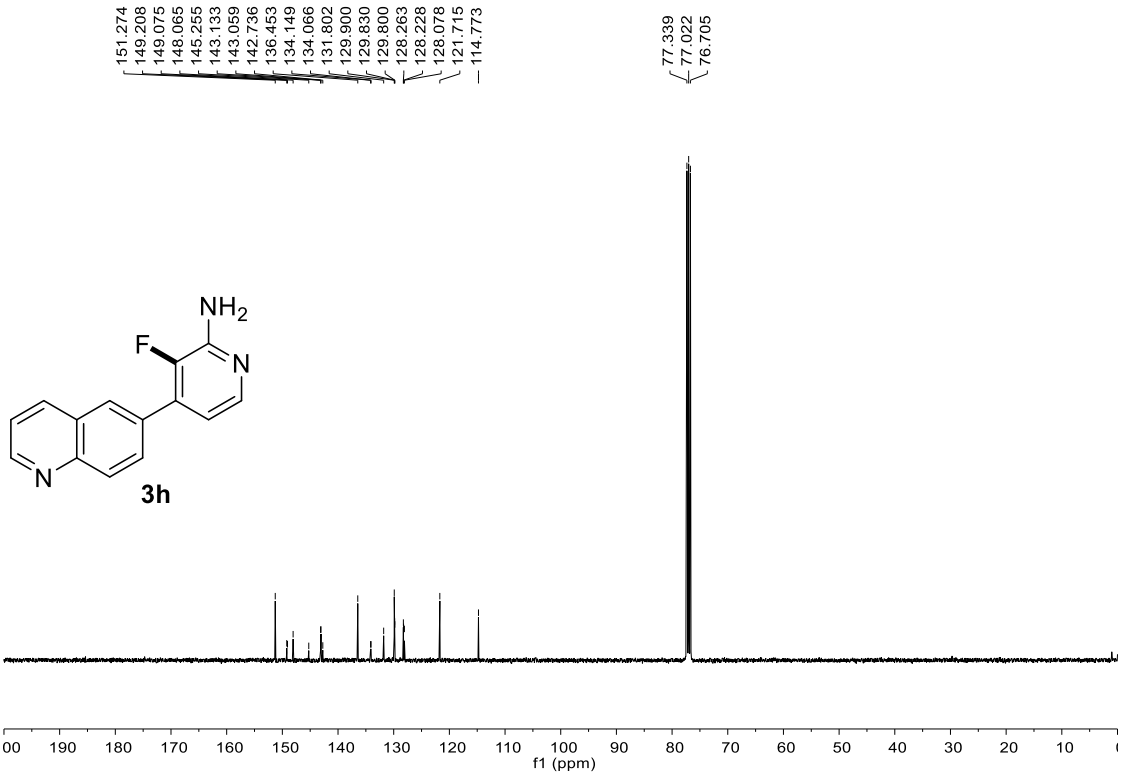
^{19}F NMR spectrum of the compound **3g** (376 MHz, $CDCl_3$)



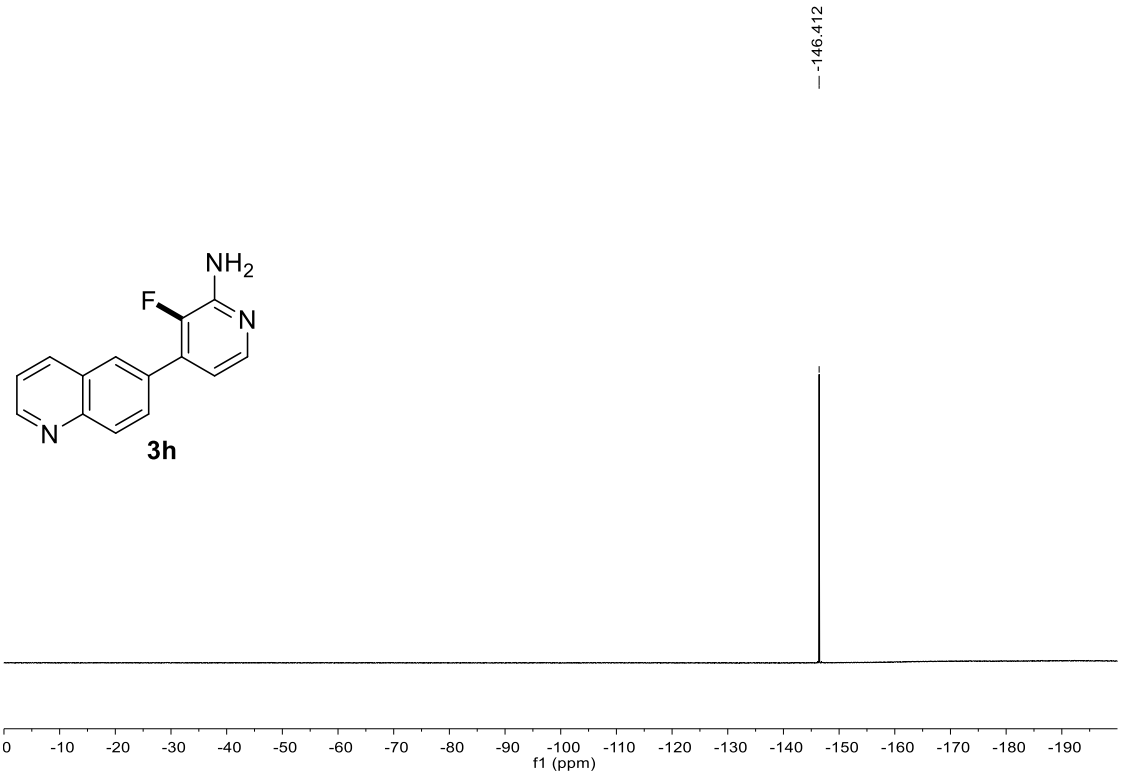
^{1}H NMR spectrum of the compound **3h (**400 MHz, $CDCl_3$)



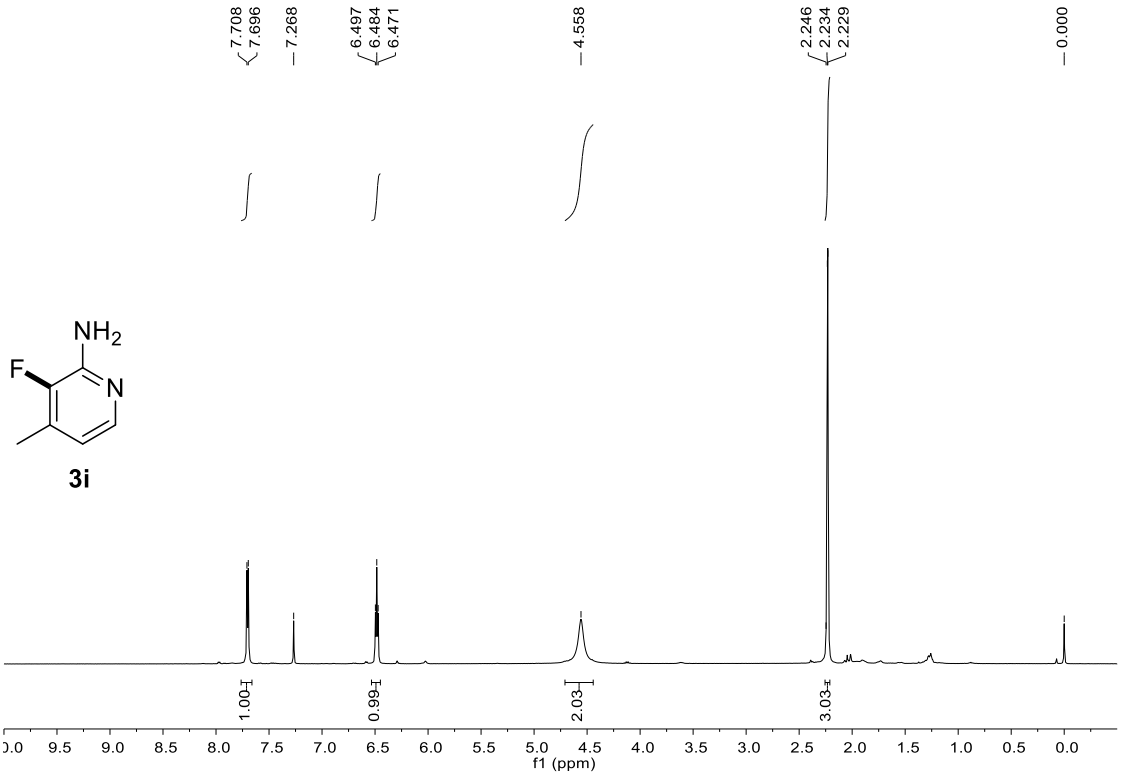
^{13}C NMR spectrum of the compound **3h** (101 MHz, $CDCl_3$)



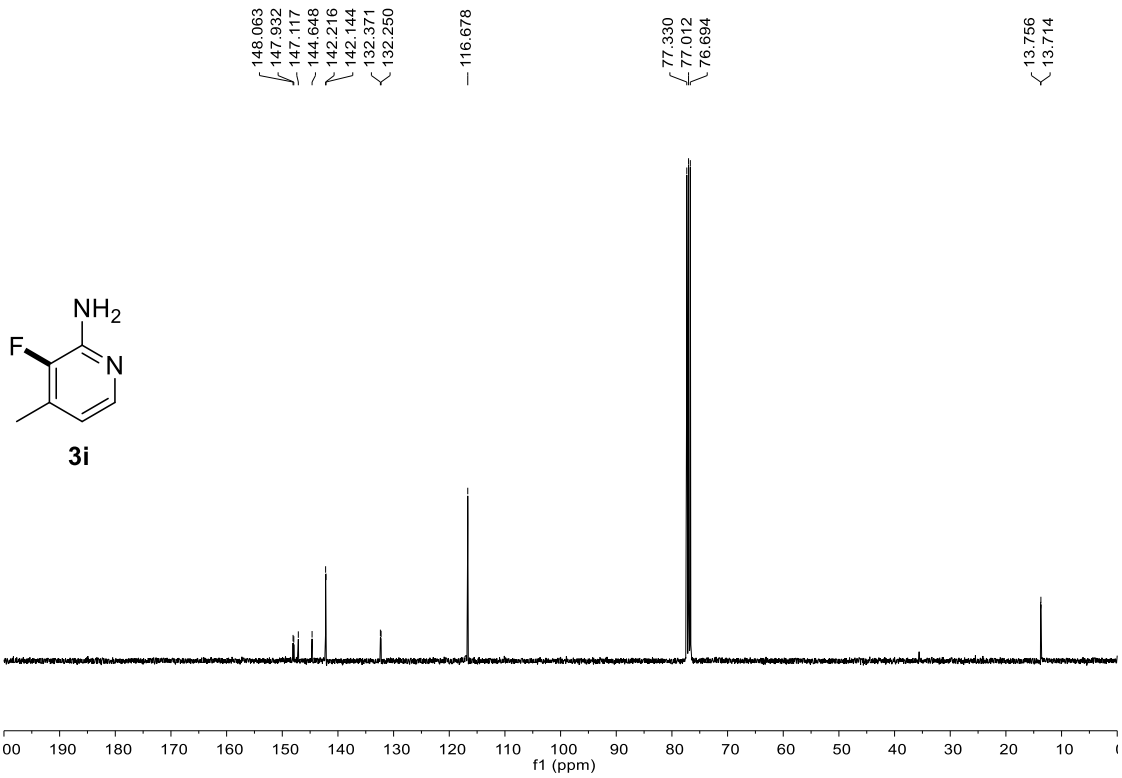
^{19}F NMR spectrum of the compound **3h** (376 MHz, $CDCl_3$)



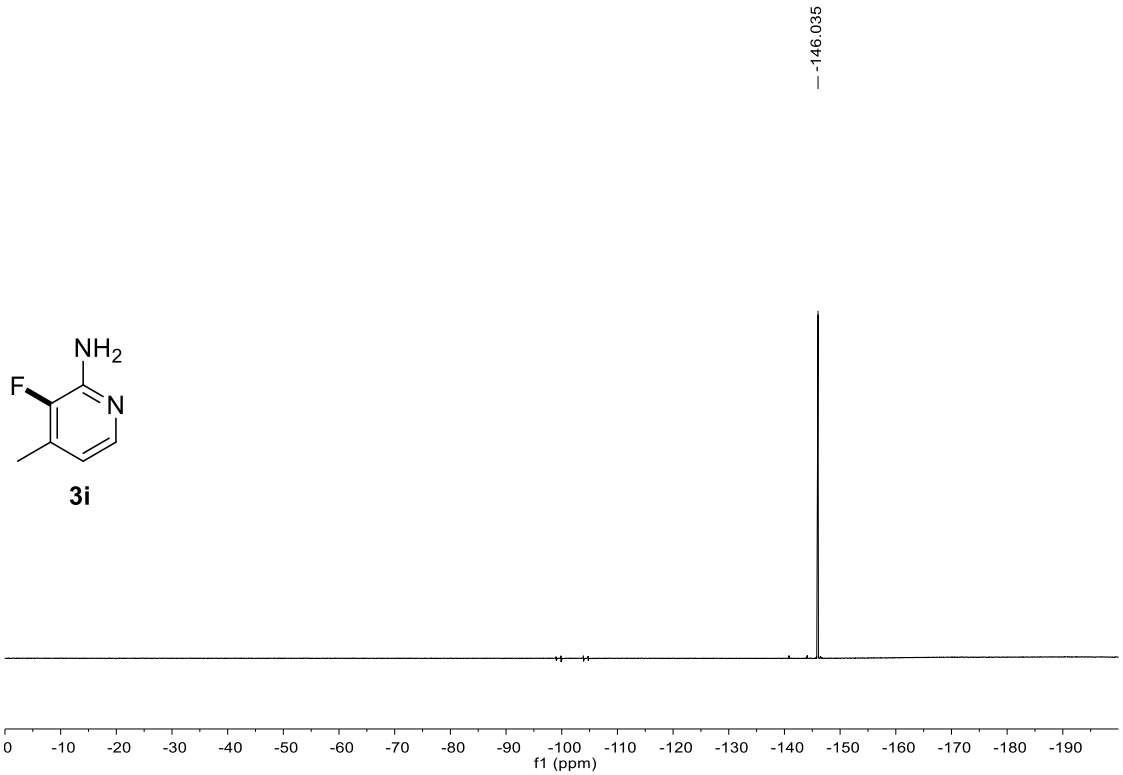
^{1}H NMR spectrum of the compound **3i** (400 MHz, $CDCl_3$)



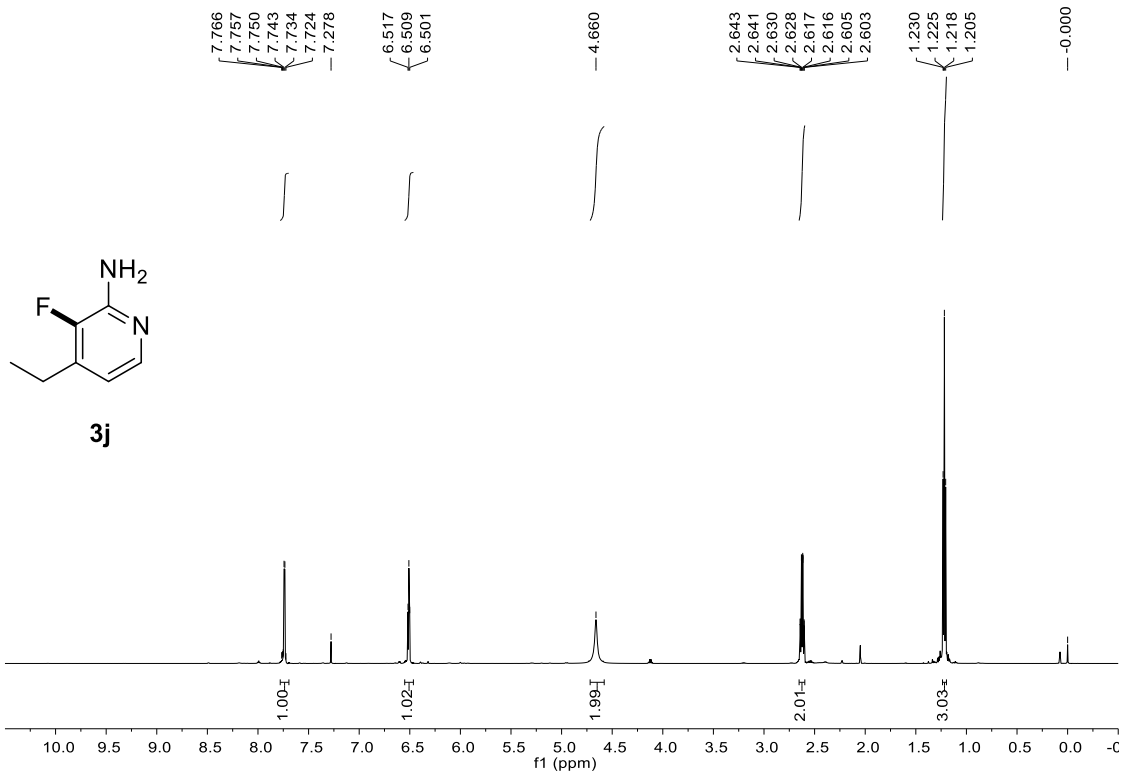
^{13}C NMR spectrum of the compound **3i** (101 MHz, $CDCl_3$)



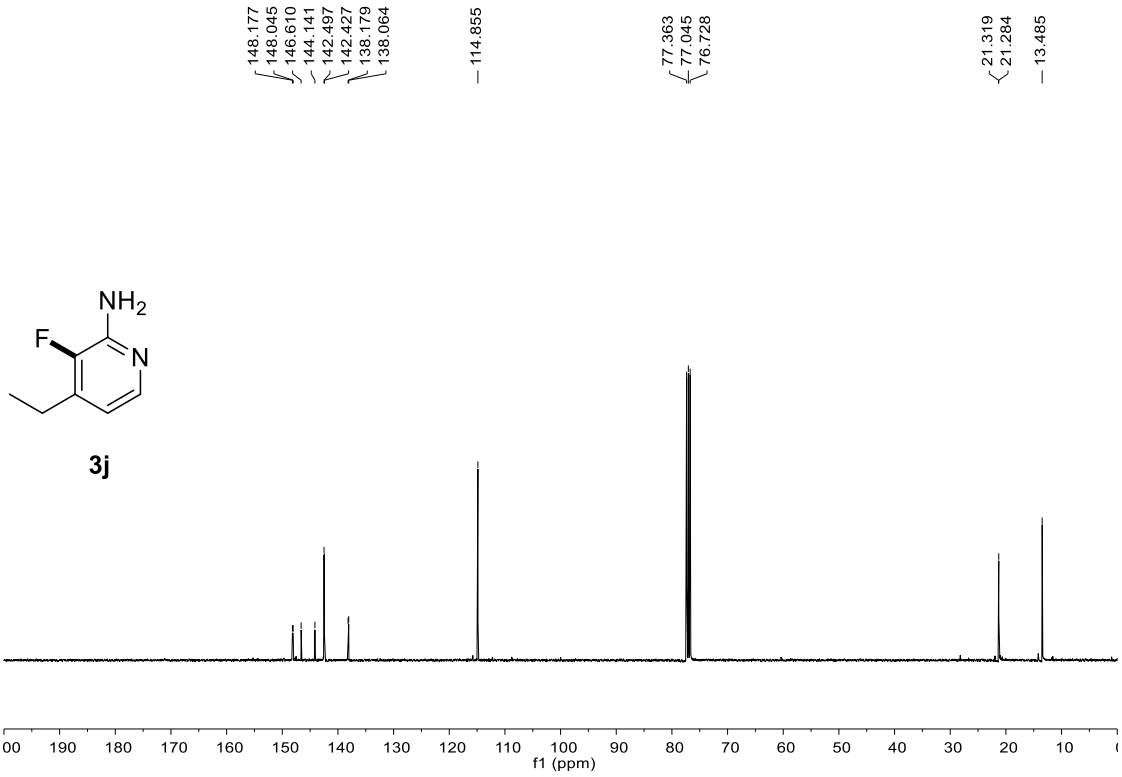
^{19}F NMR spectrum of the compound **3i** (376 MHz, $CDCl_3$)



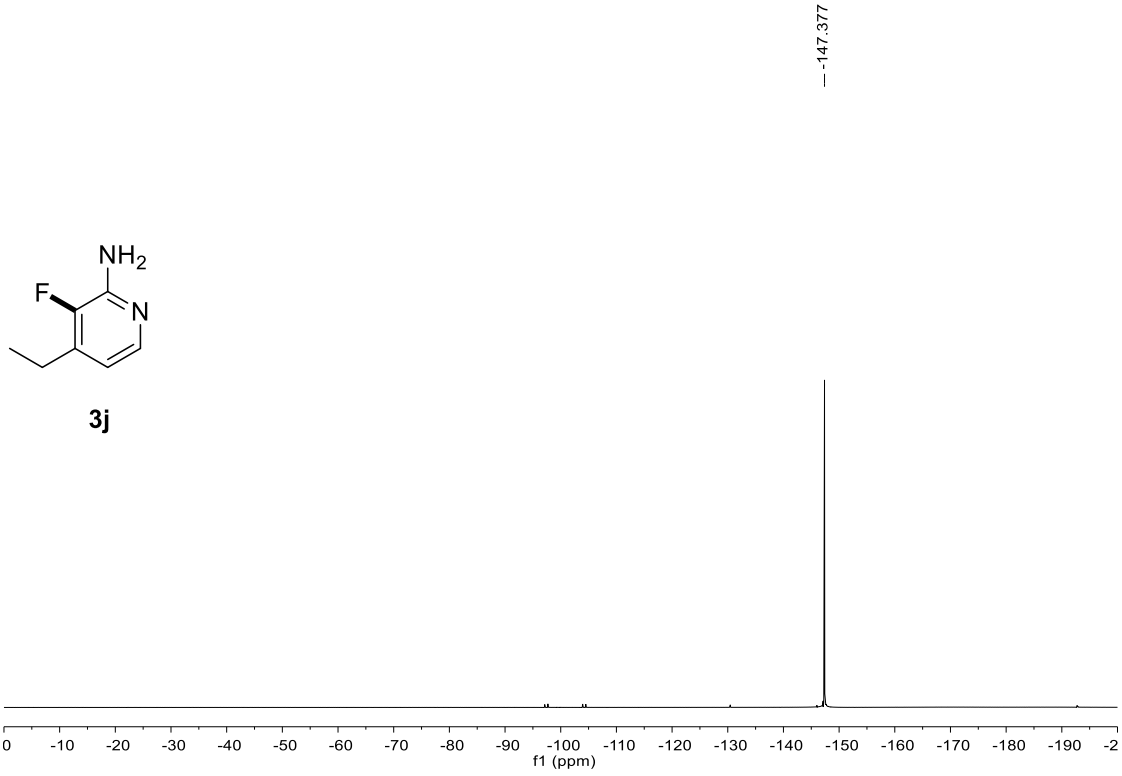
^{1}H NMR spectrum of the compound **3j (**600 MHz, $CDCl_3$)



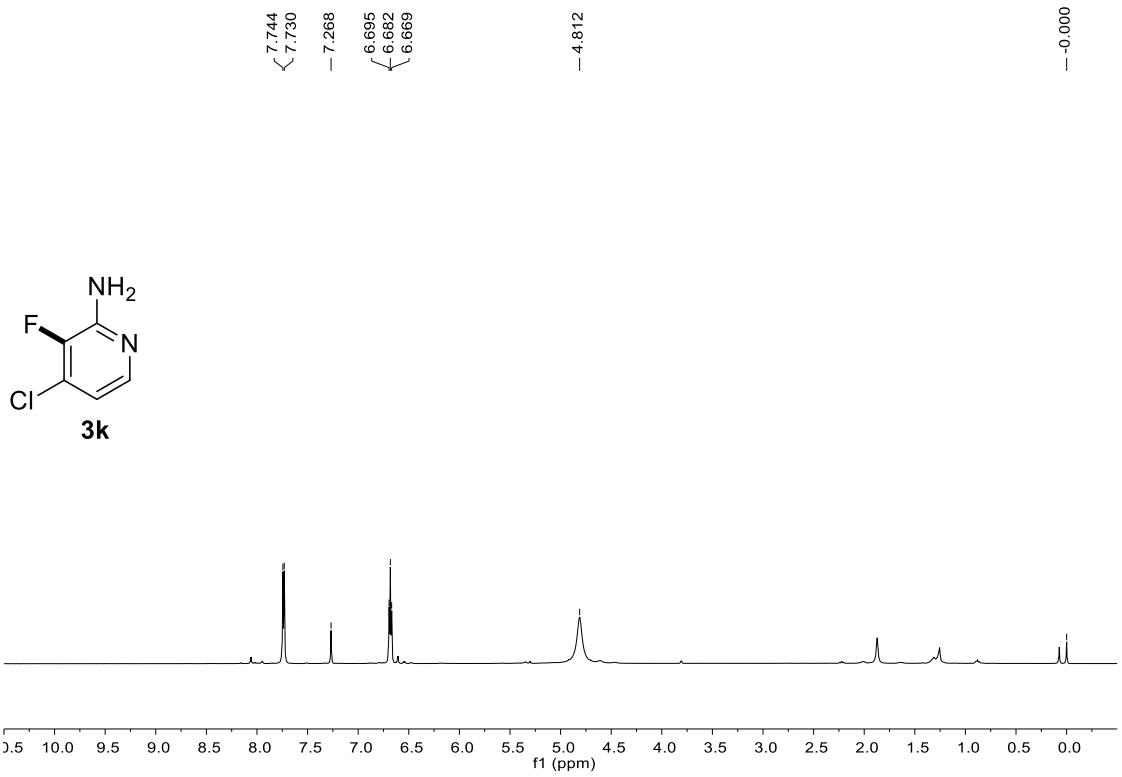
^{13}C NMR spectrum of the compound **3j** (101 MHz, $CDCl_3$)



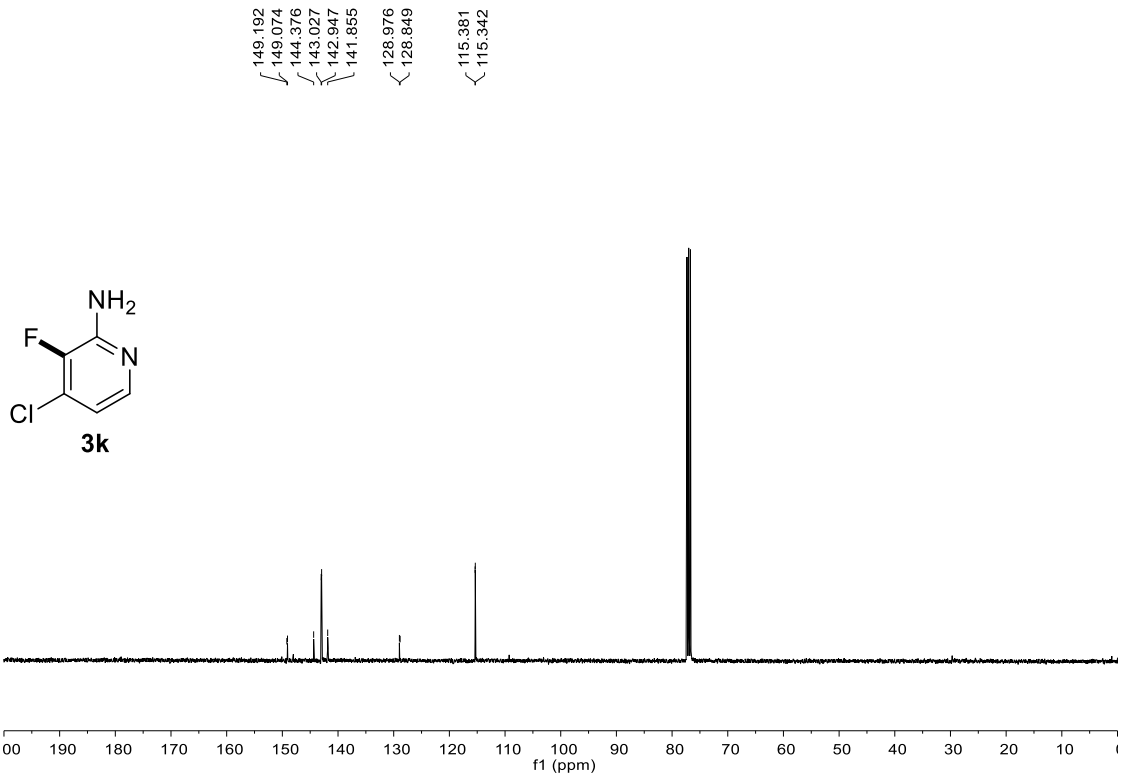
^{19}F NMR spectrum of the compound **3j (**565 MHz, $CDCl_3$)



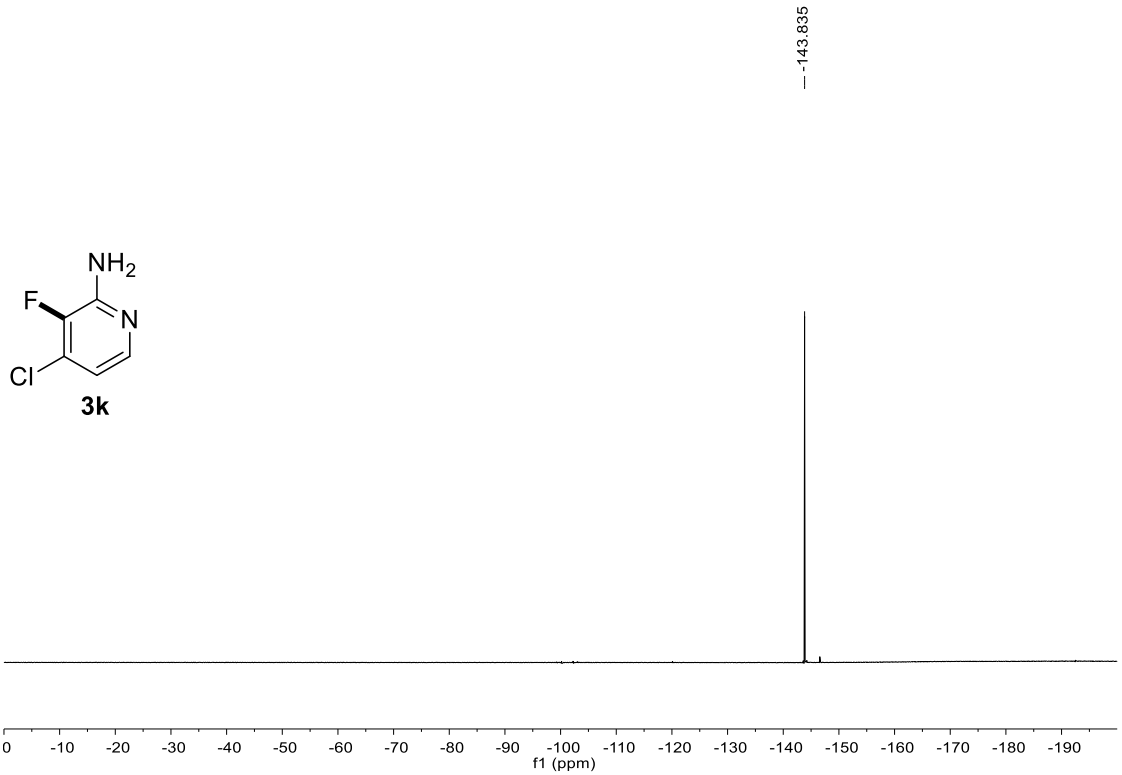
^{1}H NMR spectrum of the compound **3k (**400 MHz, $CDCl_3$)



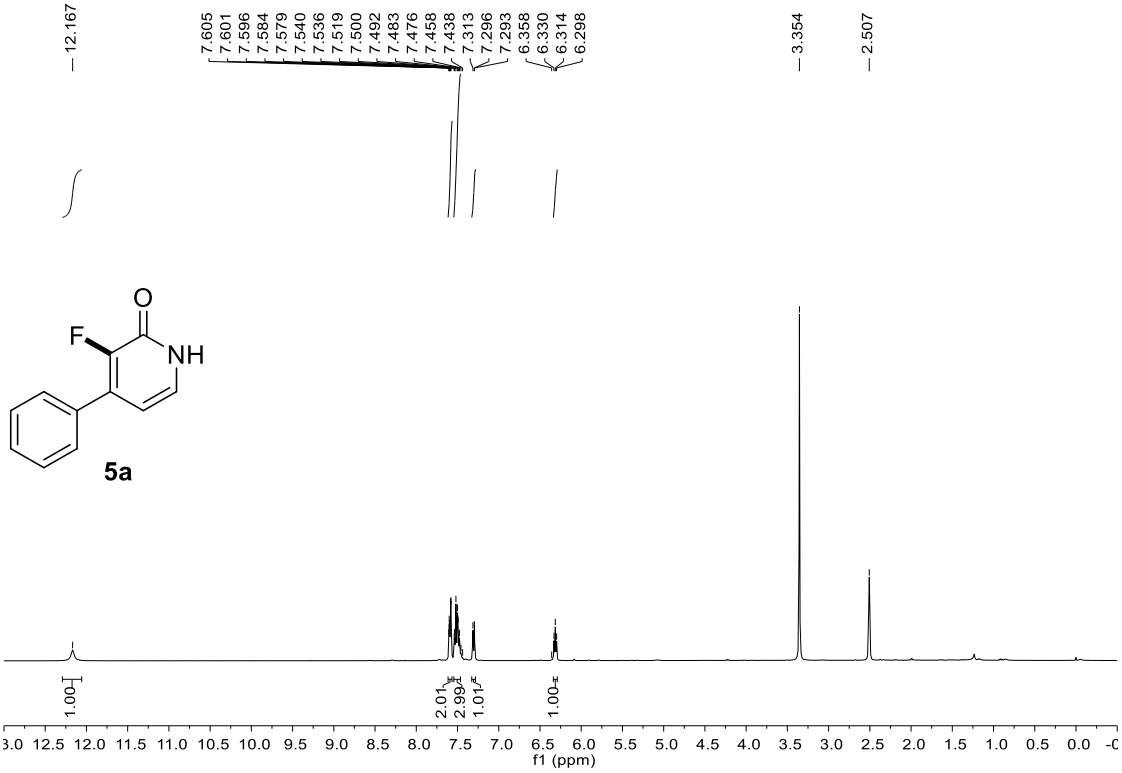
^{13}C NMR spectrum of the compound **3k (**101 MHz, $CDCl_3$)



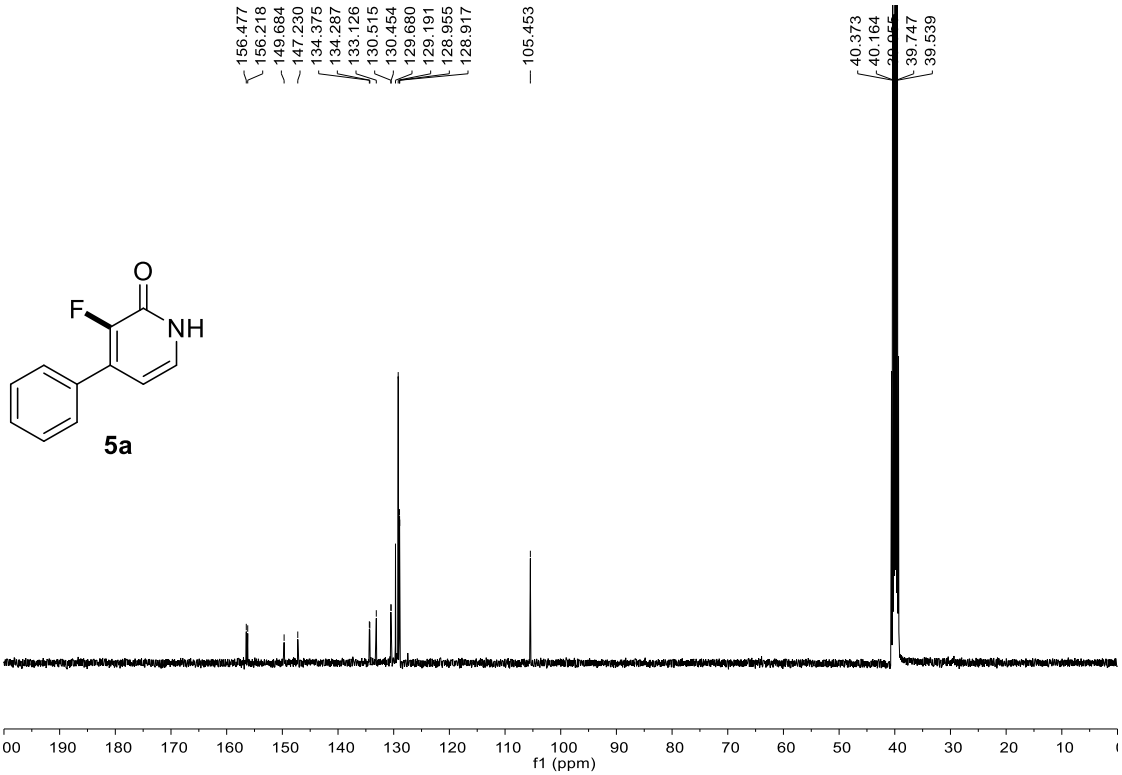
^{19}FNMR spectrum of the compound **3k (**376 MHz, $CDCl_3$)



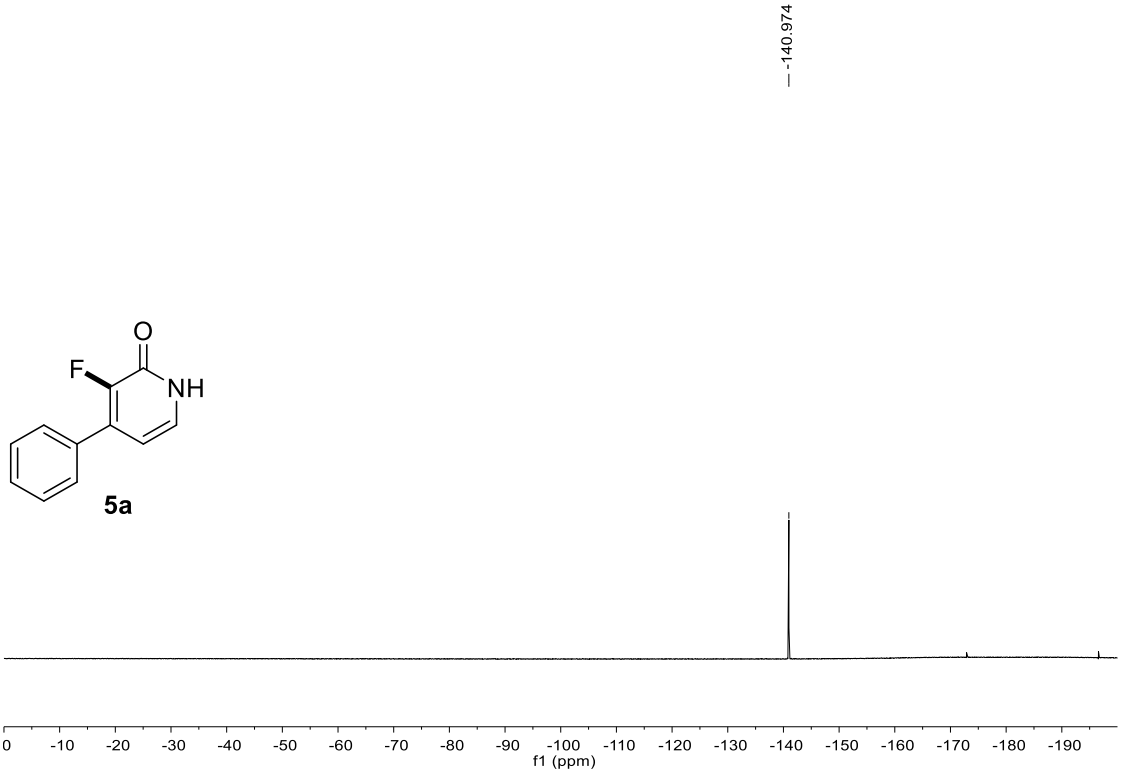
^{1}H NMR spectrum of the compound **5a (**400 MHz, DMSO-d_6)



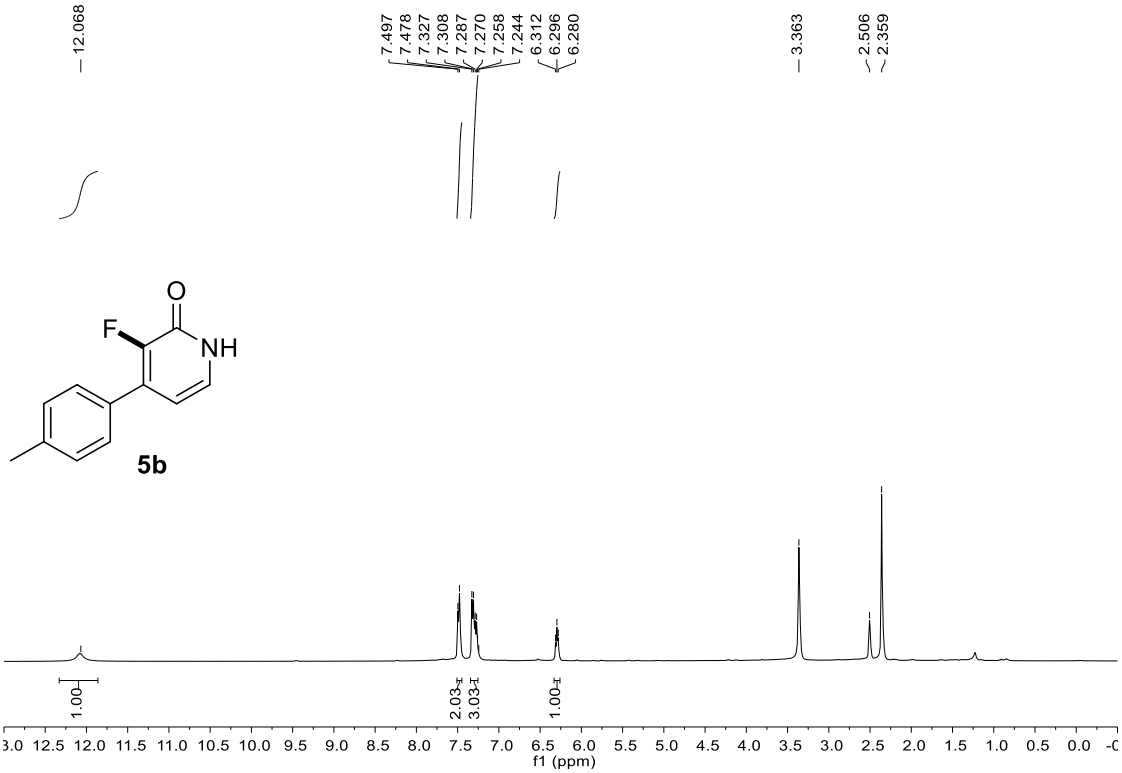
^{13}C NMR spectrum of the compound **5a (**101 MHz, DMSO-d_6)



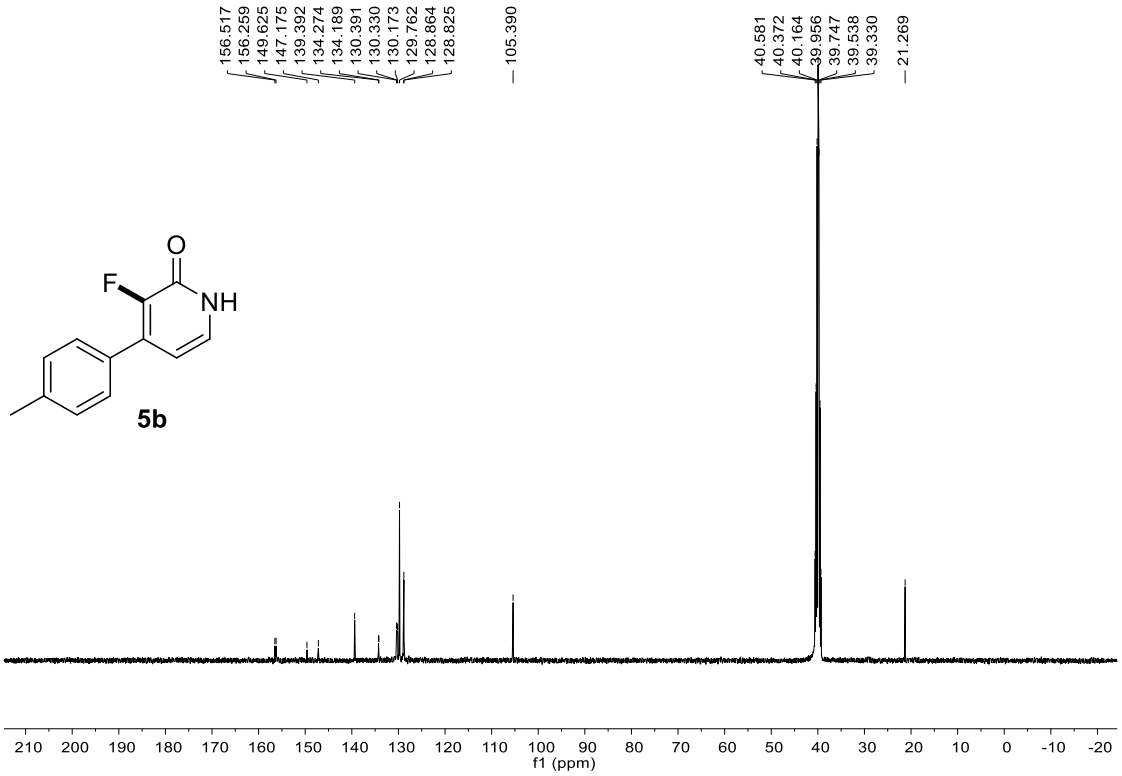
^{19}F NMR spectrum of the compound **5a (**101 MHz, DMSO-d_6)



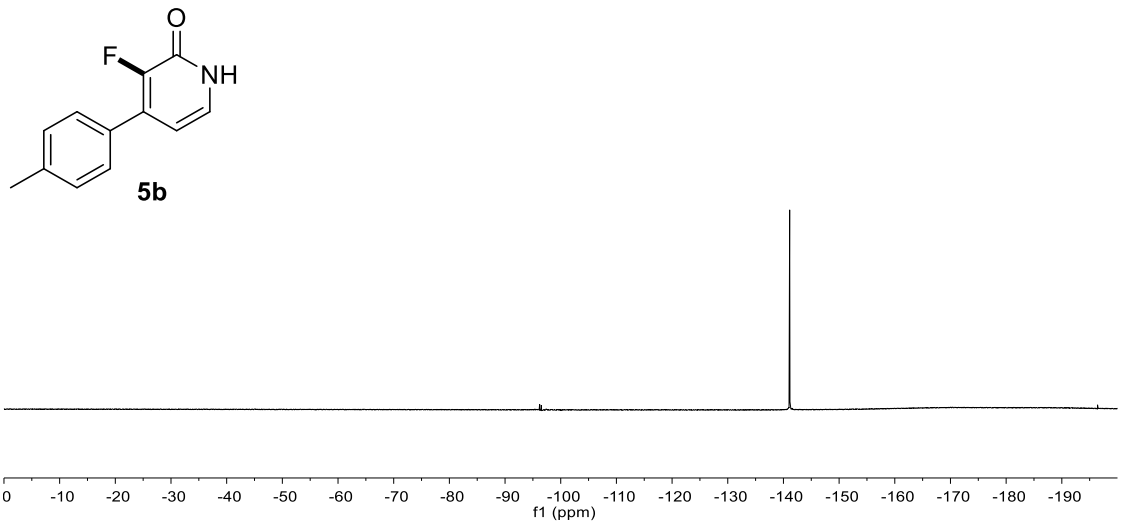
^{1}H NMR spectrum of the compound **5b (**400 MHz, DMSO-d_6)



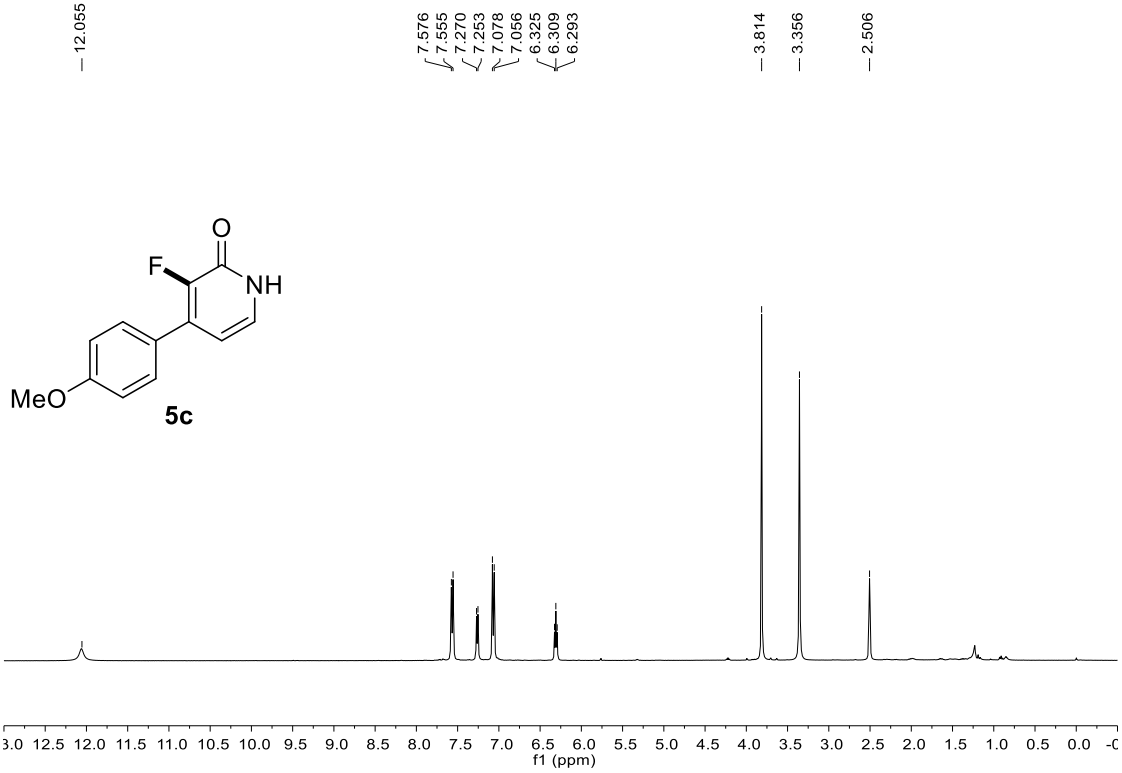
^{13}C NMR spectrum of the compound **5b (**101 MHz, DMSO-d_6)



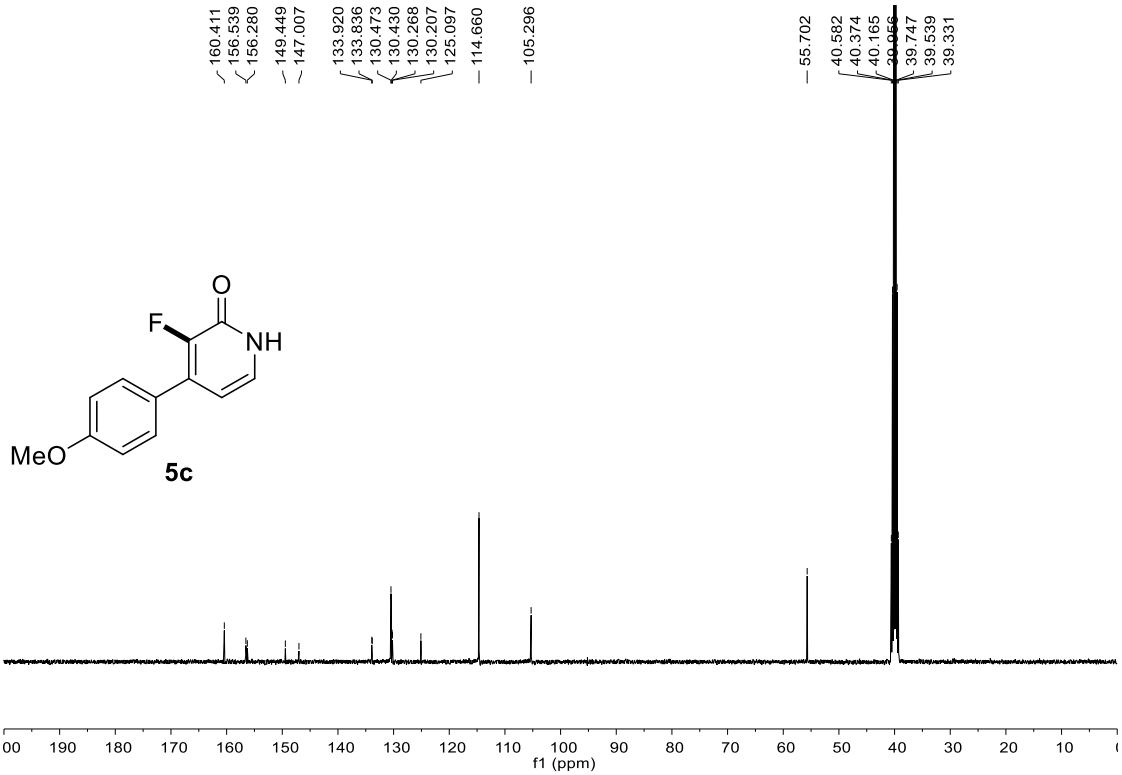
^{19}F NMR spectrum of the compound **5b (**376 MHz, DMSO-d_6)



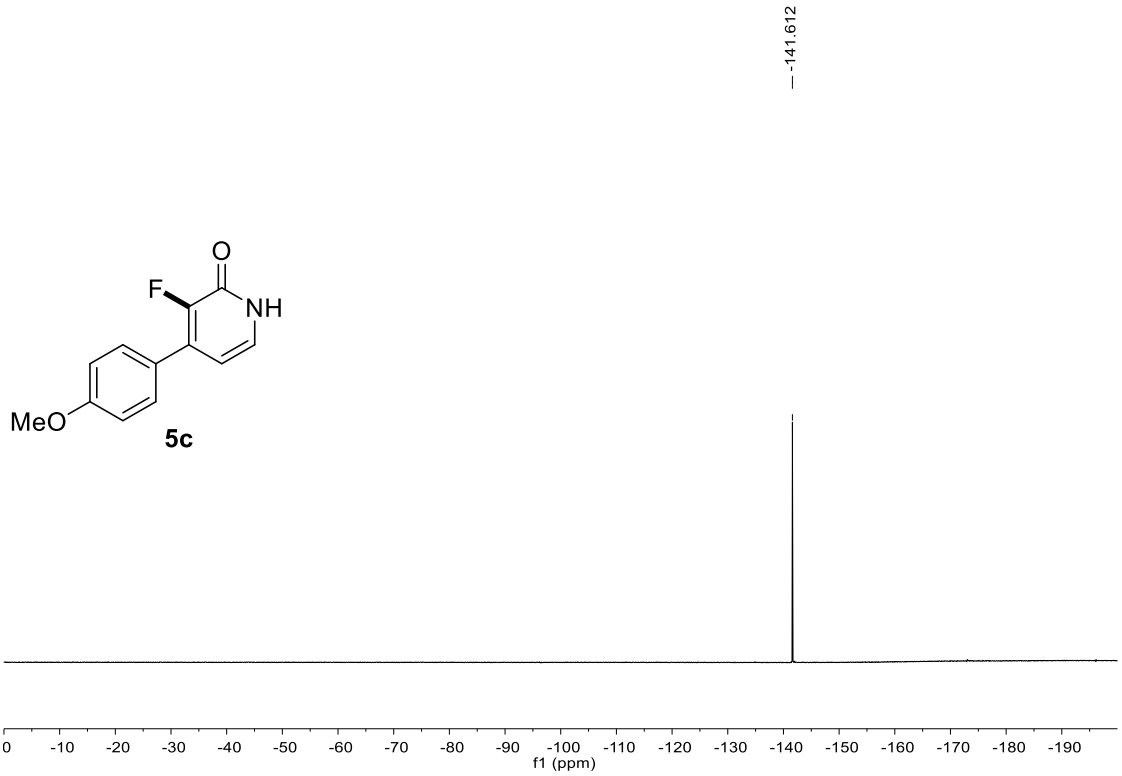
^{1}H NMR spectrum of the compound **5c (**400 MHz, DMSO-d_6)



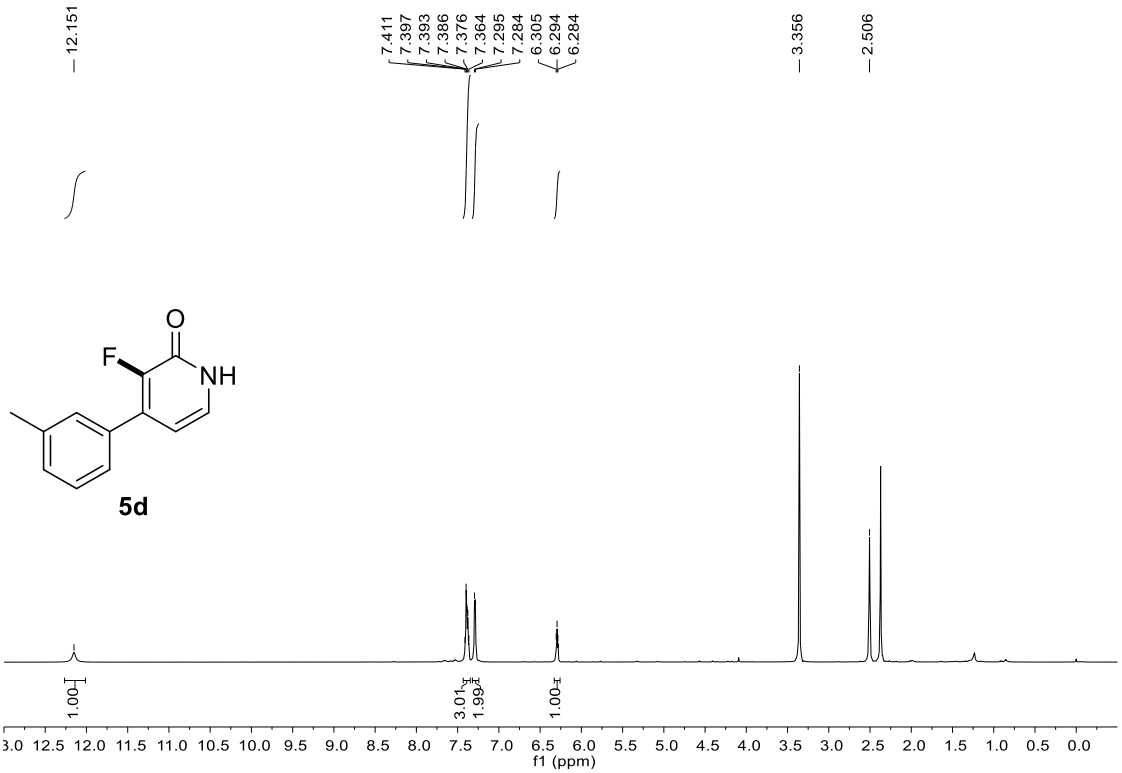
^{13}C NMR spectrum of the compound **5c (**101 MHz, DMSO-d_6)



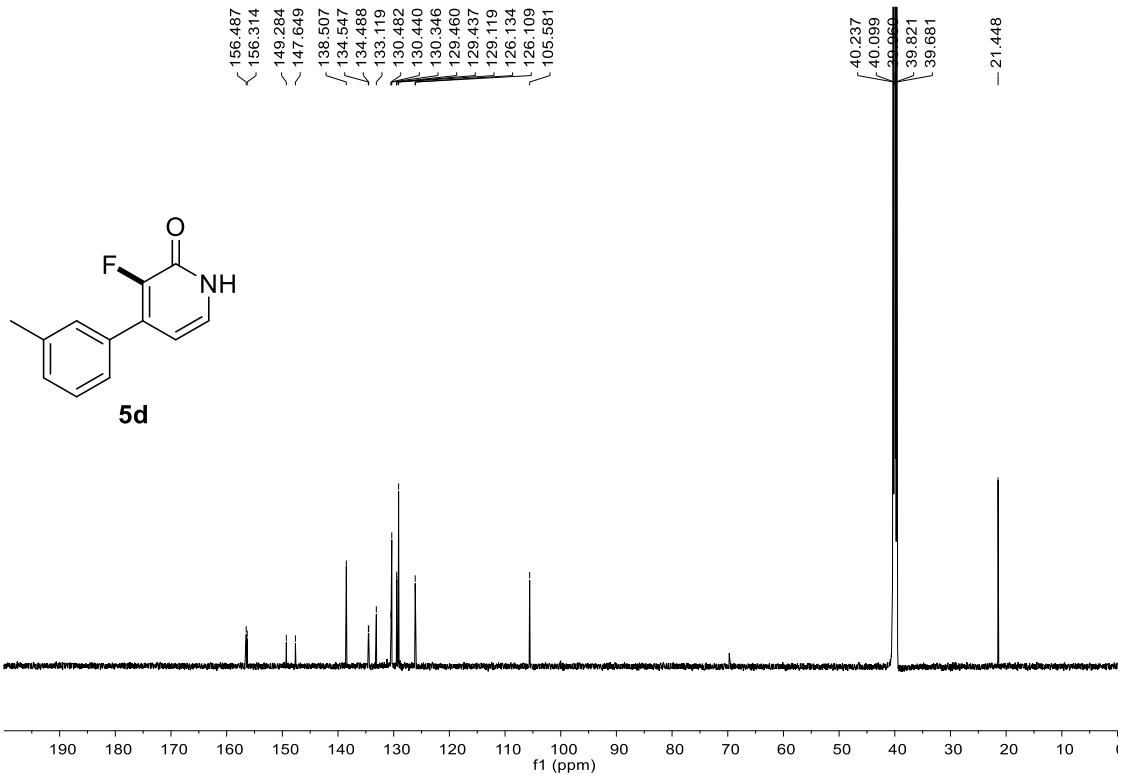
^{19}F NMR spectrum of the compound **5c (**376 MHz, DMSO-d_6)



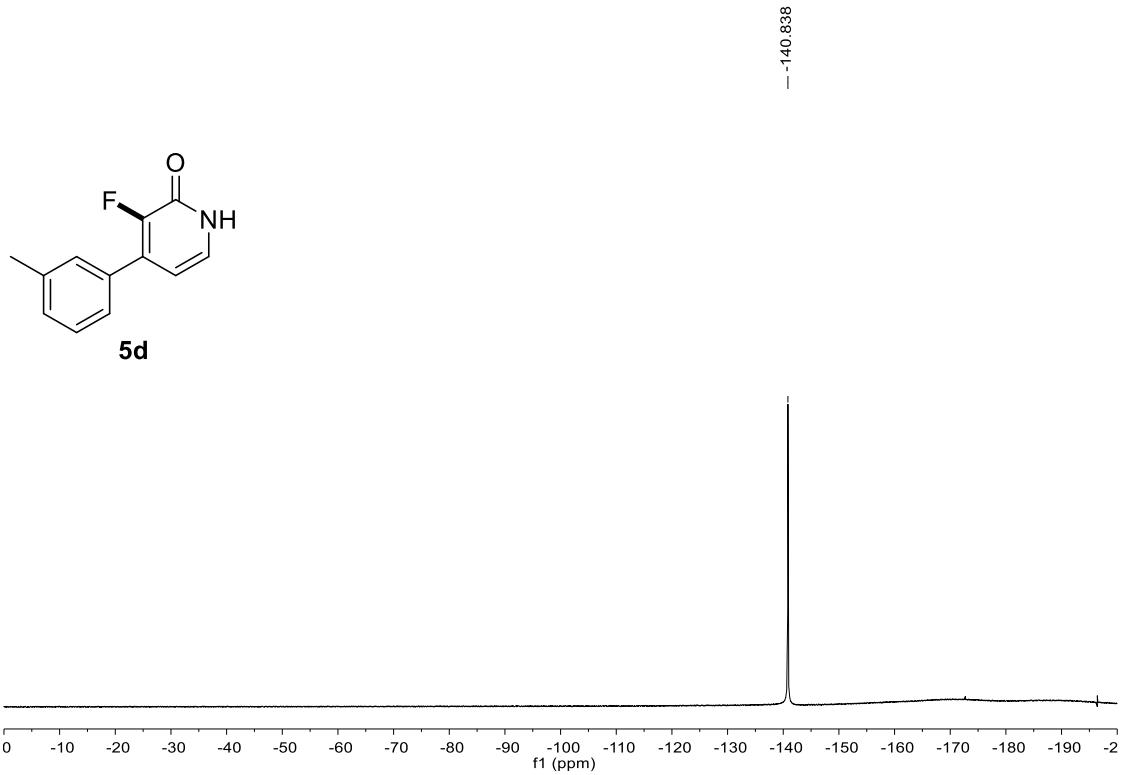
^{1}H NMR spectrum of the compound **5d (**600 MHz, DMSO-d_6)



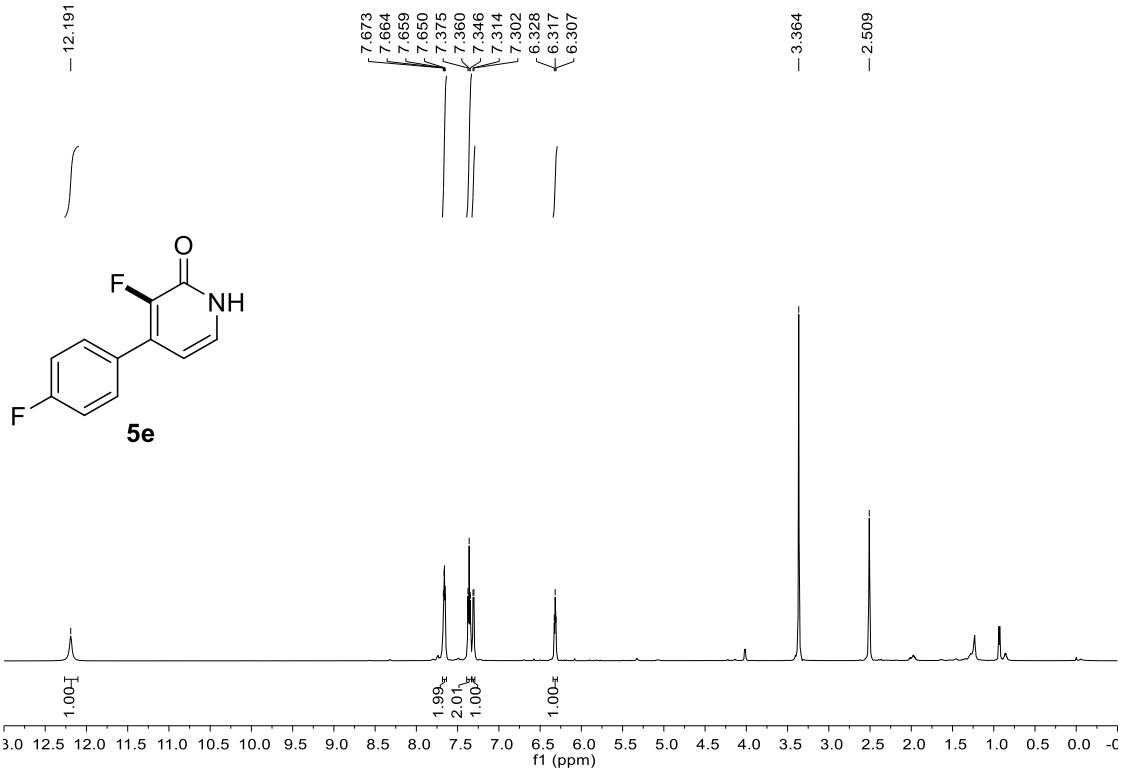
^{19}F MR spectrum of the compound **5d (**565 MHz, DMSO-d_6)



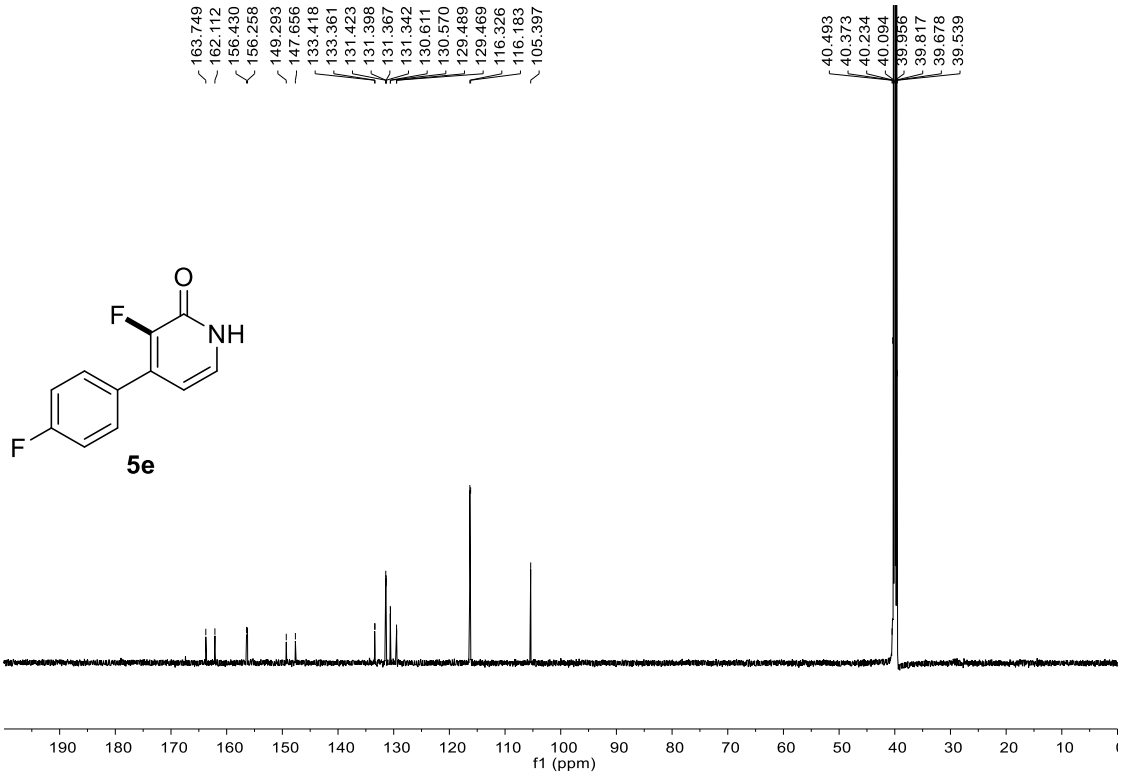
^{19}F MR spectrum of the compound **5d (**565 MHz, DMSO-d_6)



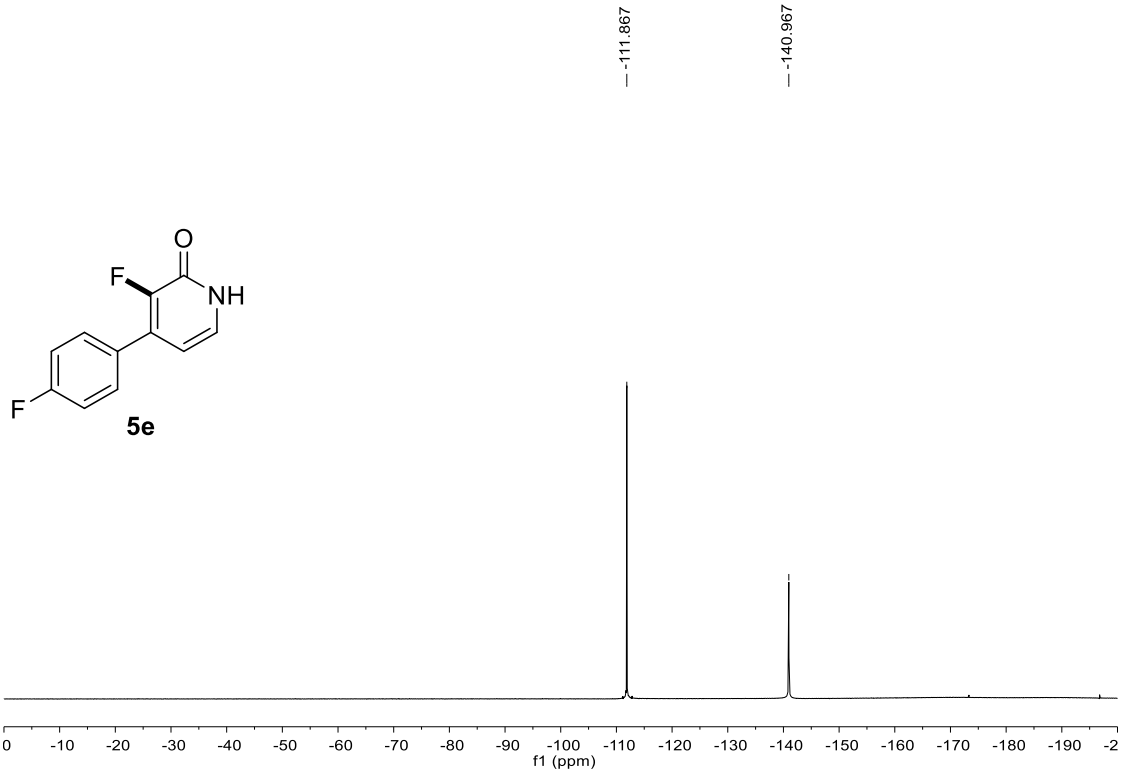
^{1}H NMR spectrum of the compound **5e (**600 MHz, DMSO-d_6)



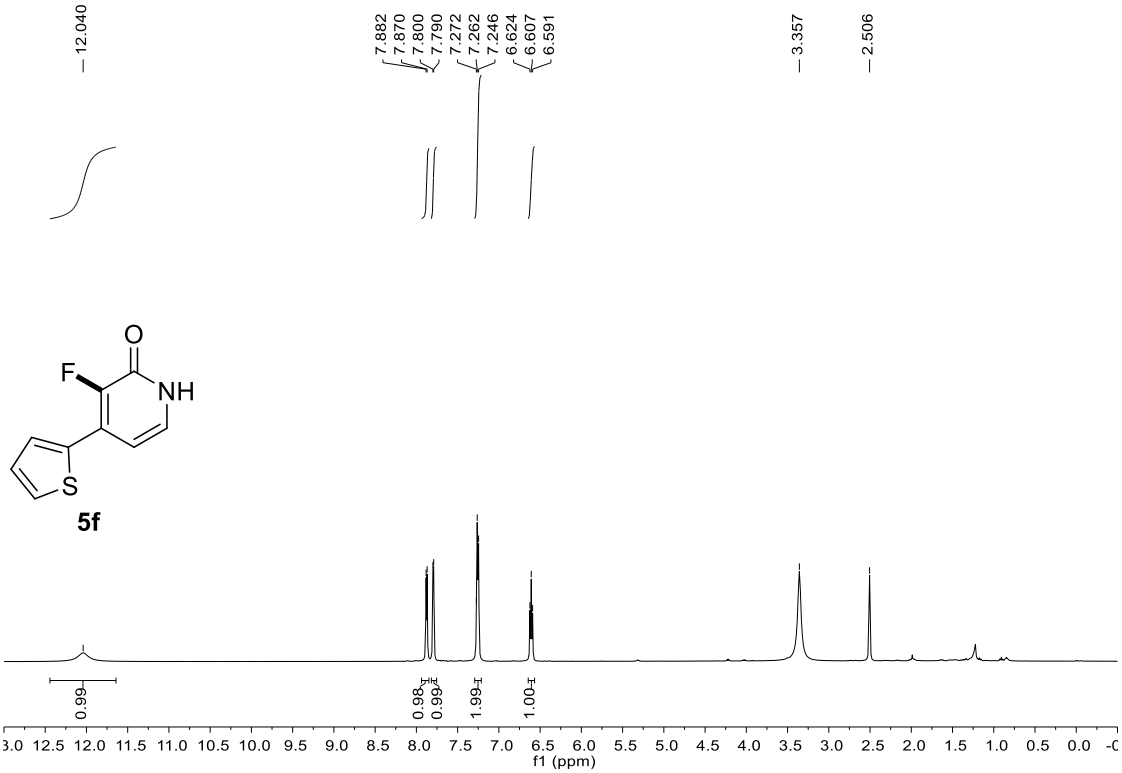
^{13}C NMR spectrum of the compound **5e (**151 MHz, DMSO-d_6)



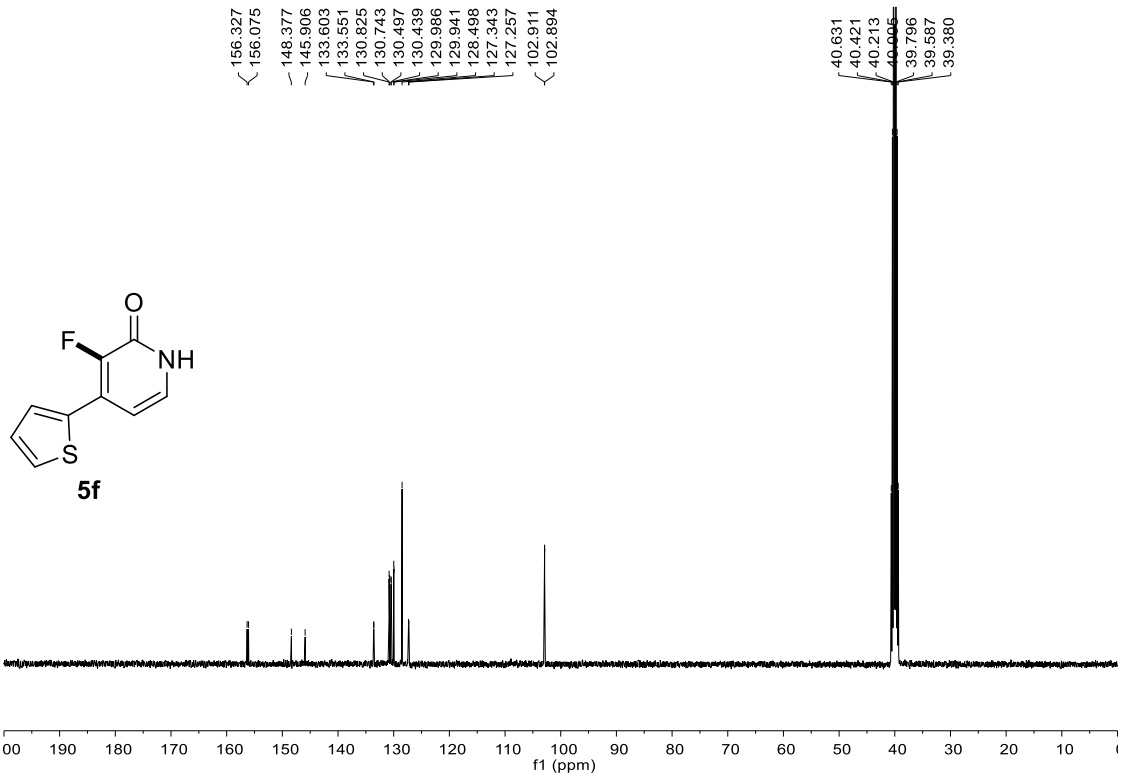
^{19}F MR spectrum of the compound **5e (**565 MHz, DMSO-d_6)



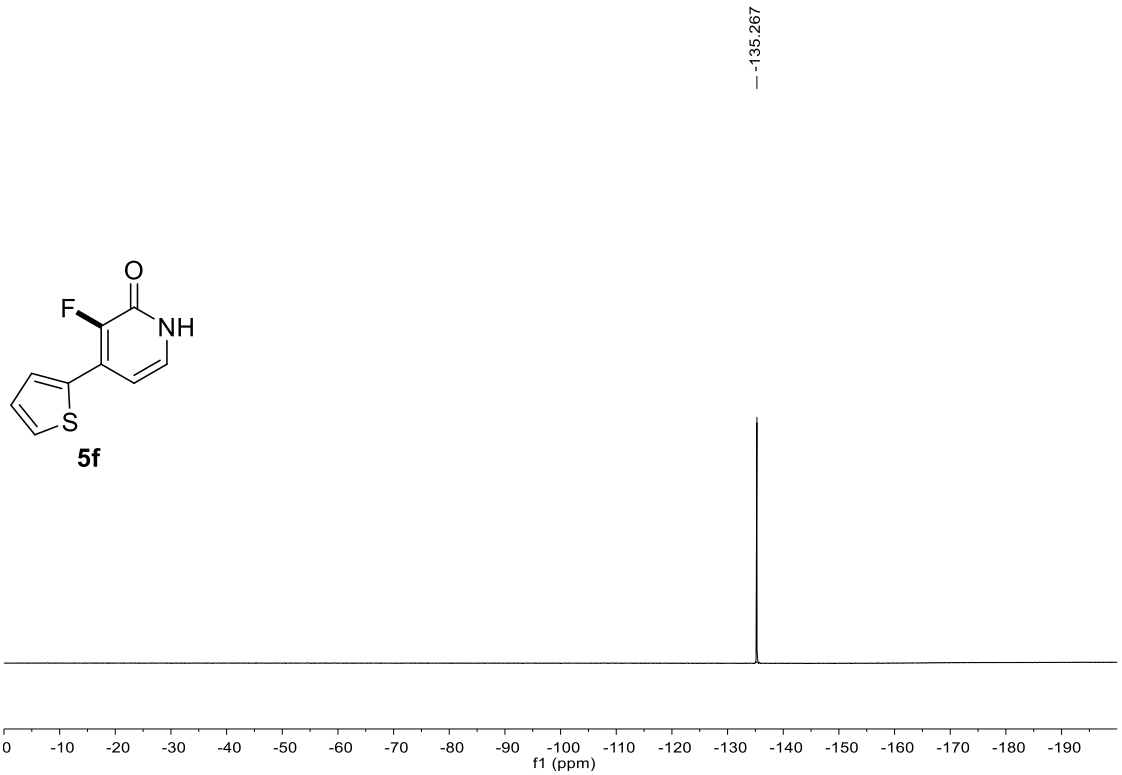
^{1}H NMR spectrum of the compound **5f (**400 MHz, DMSO-d_6)



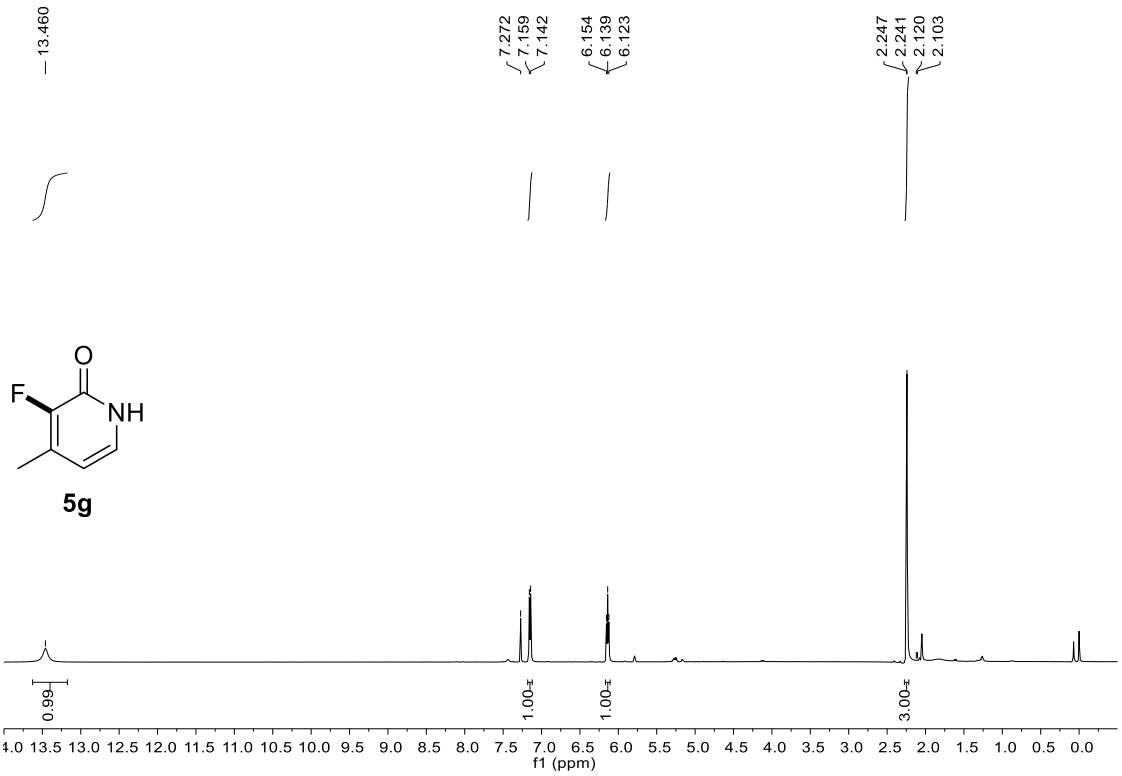
^{13}C NMR spectrum of the compound **5f (**101 MHz, DMSO-d_6)



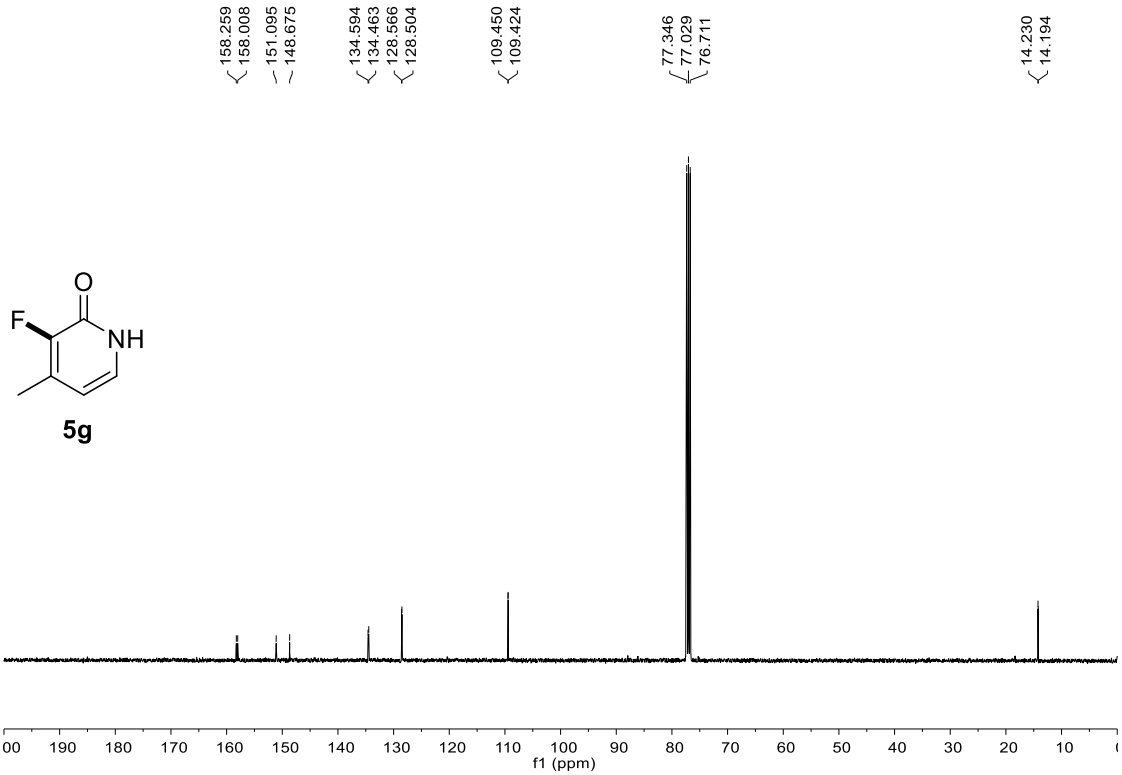
^{19}F NMR spectrum of the compound **5f (**376 MHz, DMSO-d_6)



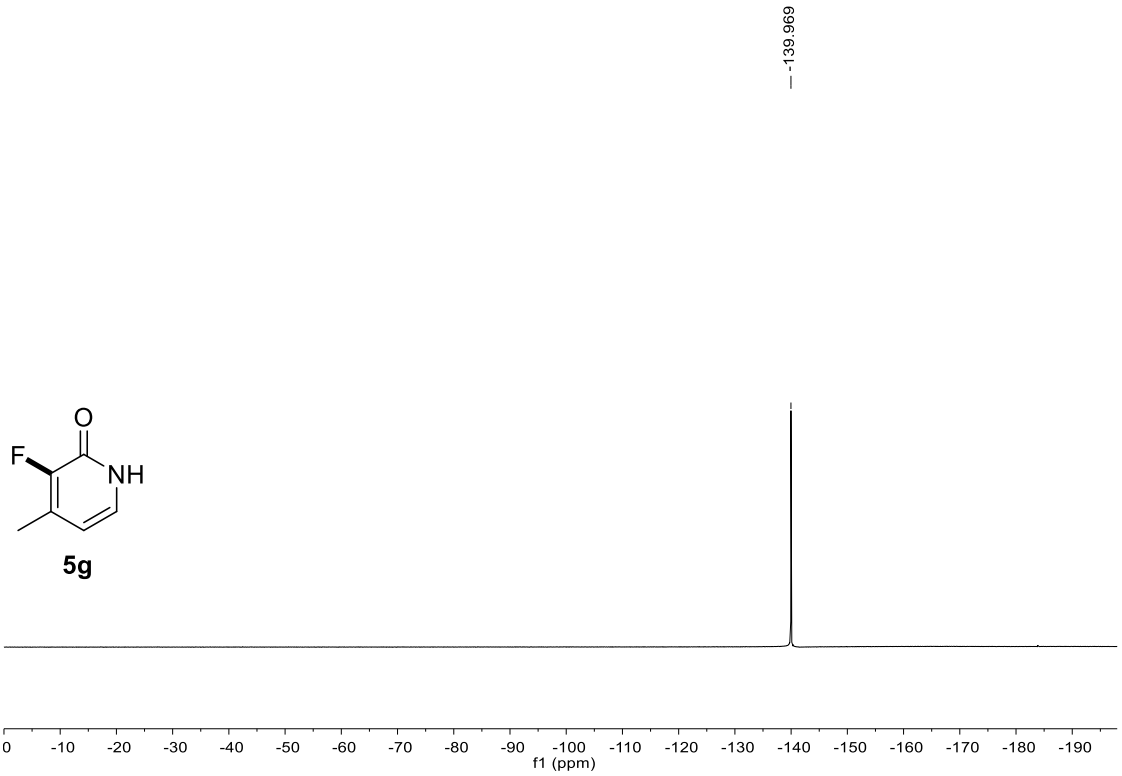
^{1}H NMR spectrum of the compound **5g** (400 MHz, $CDCl_3$)



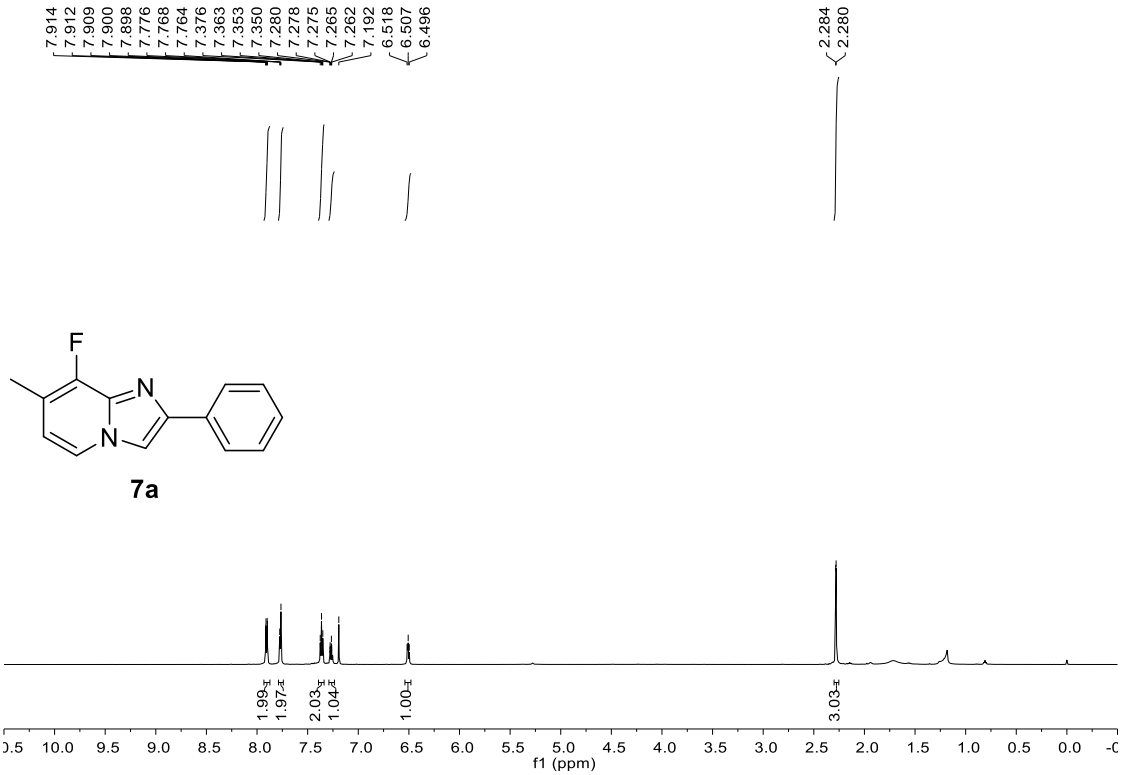
^{13}C NMR spectrum of the compound **5g** (101 MHz, $CDCl_3$)



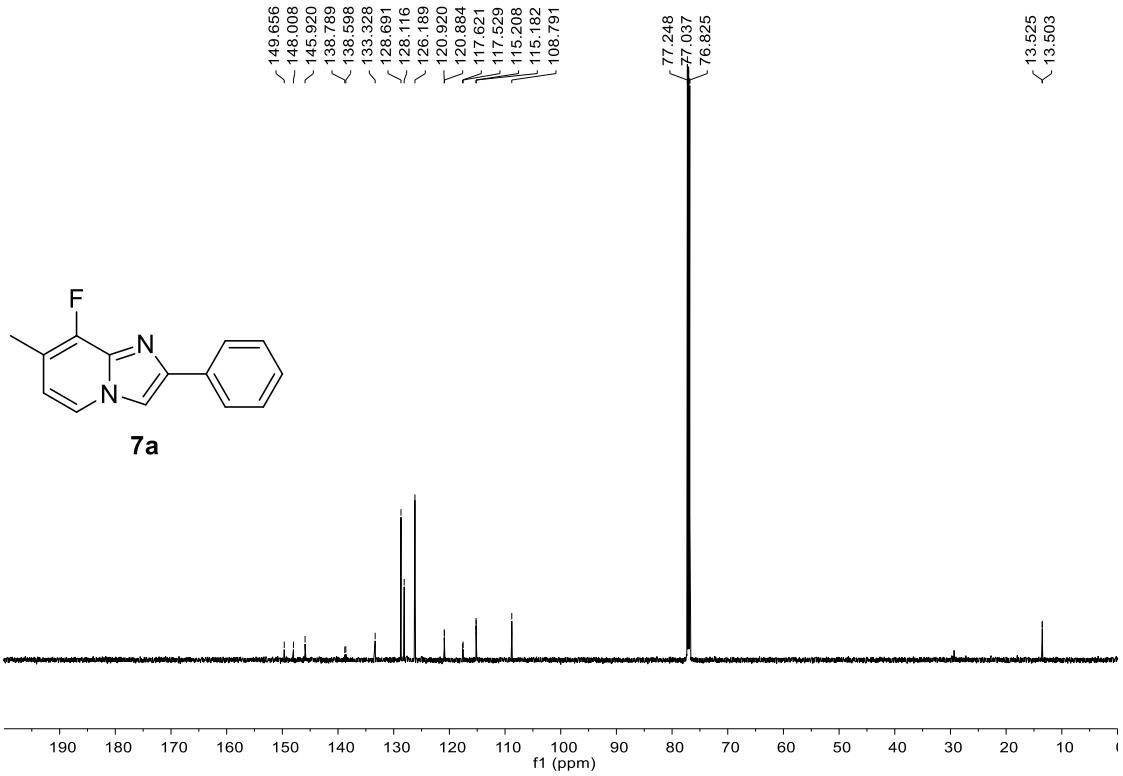
^{19}F NMR spectrum of the compound **5g** (376 MHz, $CDCl_3$)



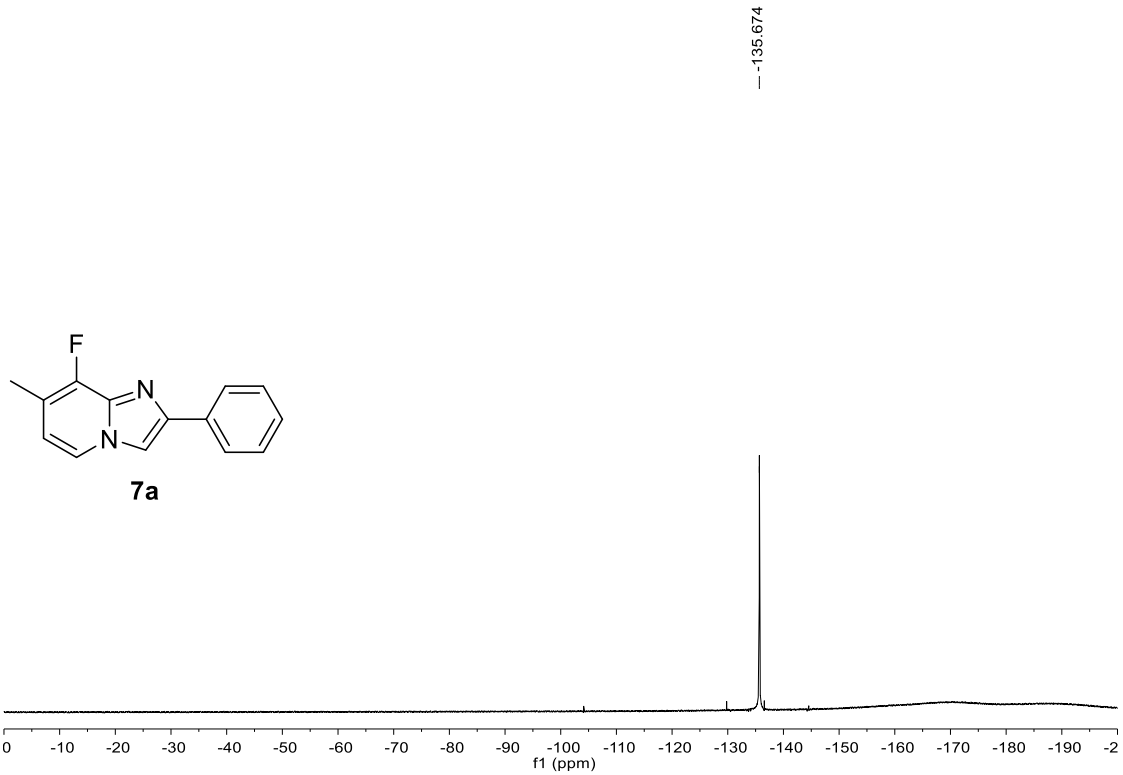
^{1}H NMR spectrum of the compound **7a** (600 MHz, $CDCl_3$)



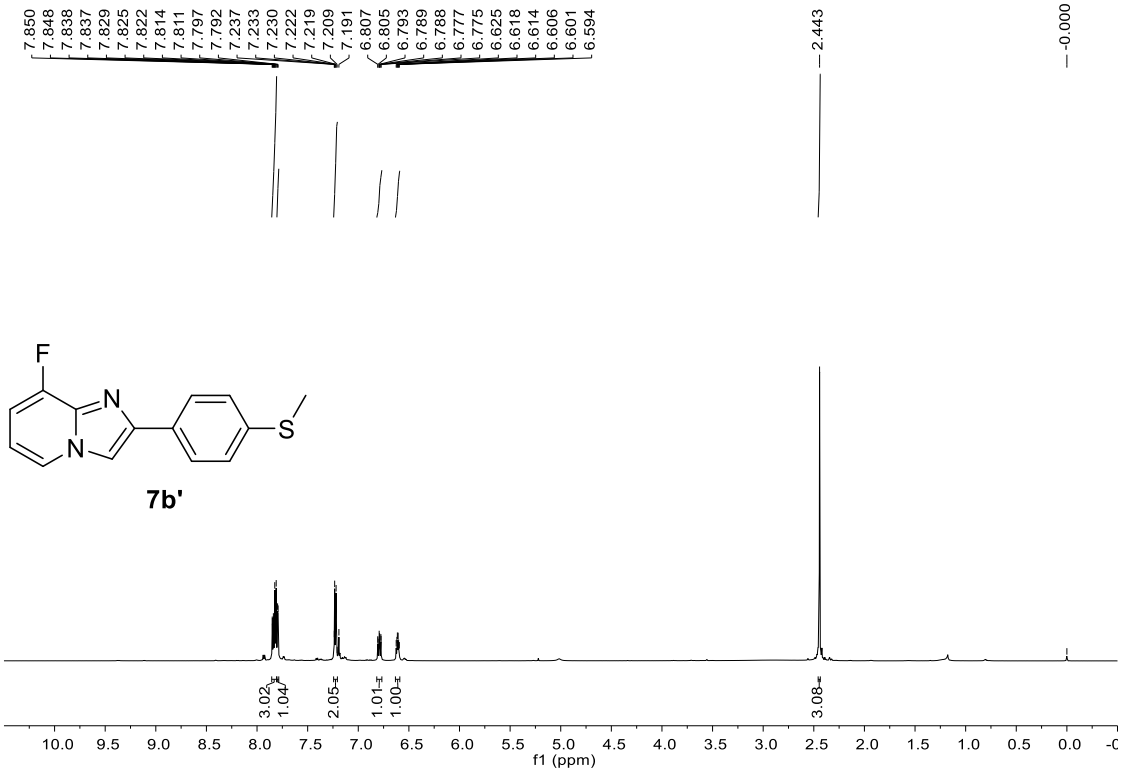
^{13}C NMR spectrum of the compound **7a** (151 MHz, $CDCl_3$)



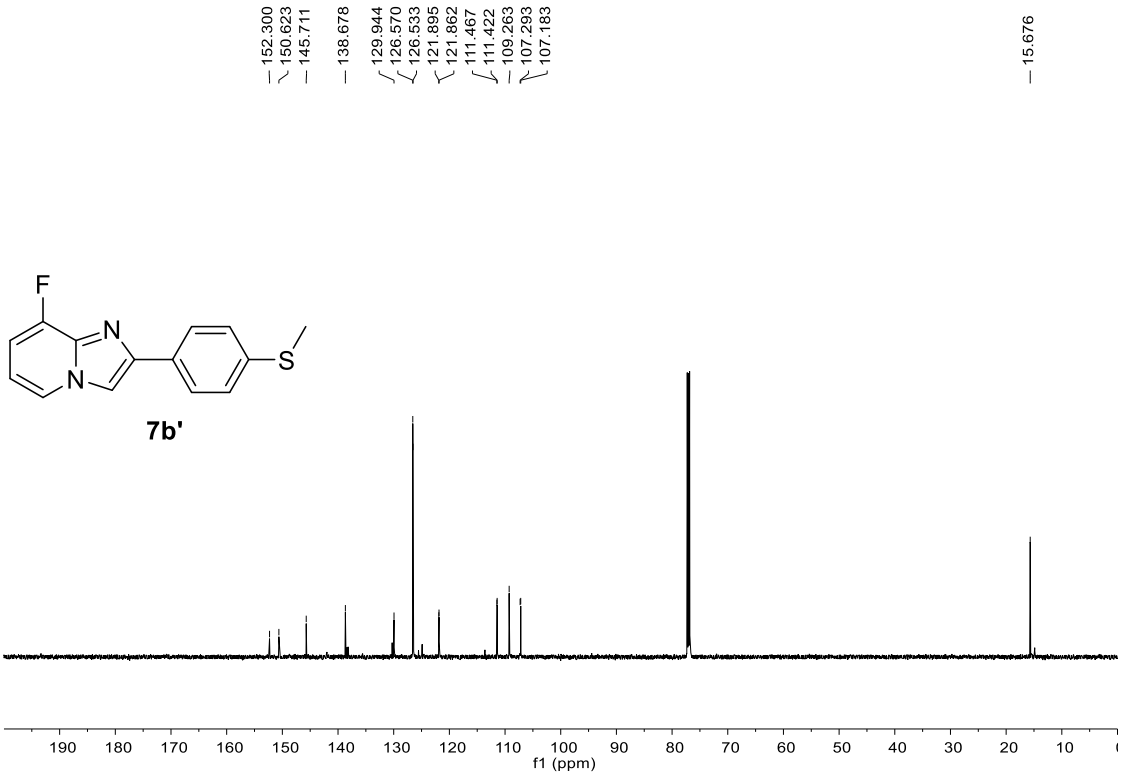
^{19}F NMR spectrum of the compound **7a** (565 MHz, $CDCl_3$)



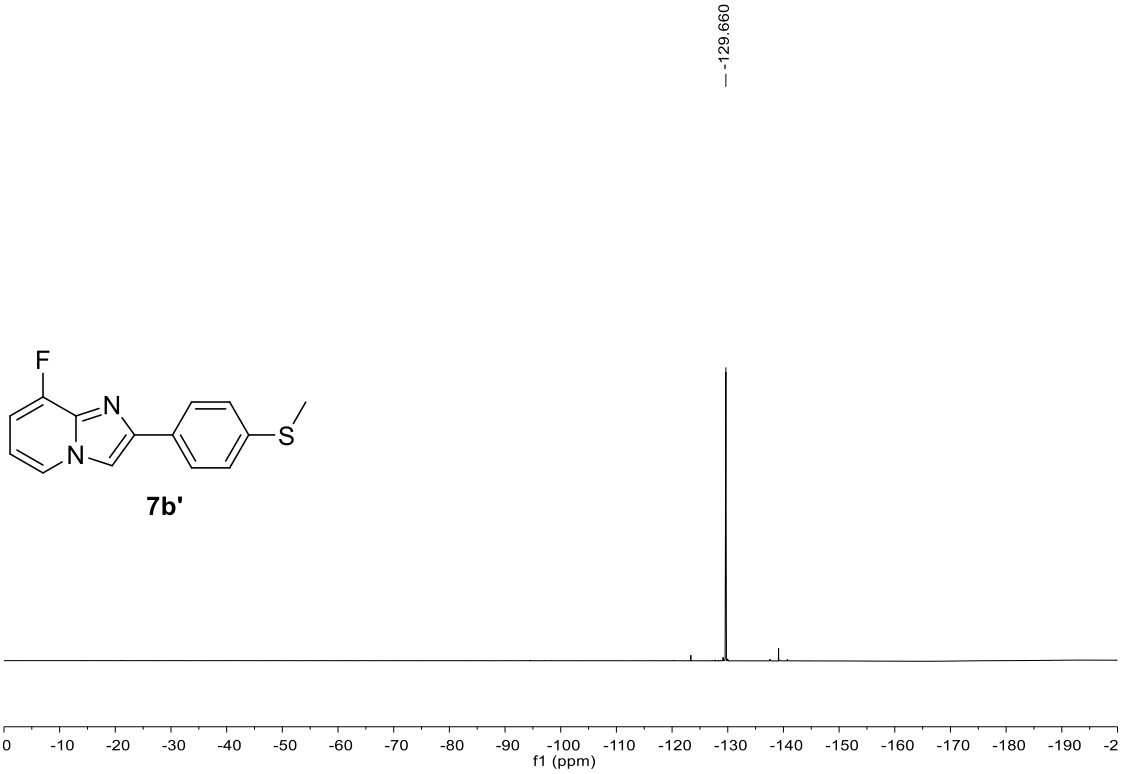
^{1}H NMR spectrum of the compound **7b' (**600 MHz, $CDCl_3$)



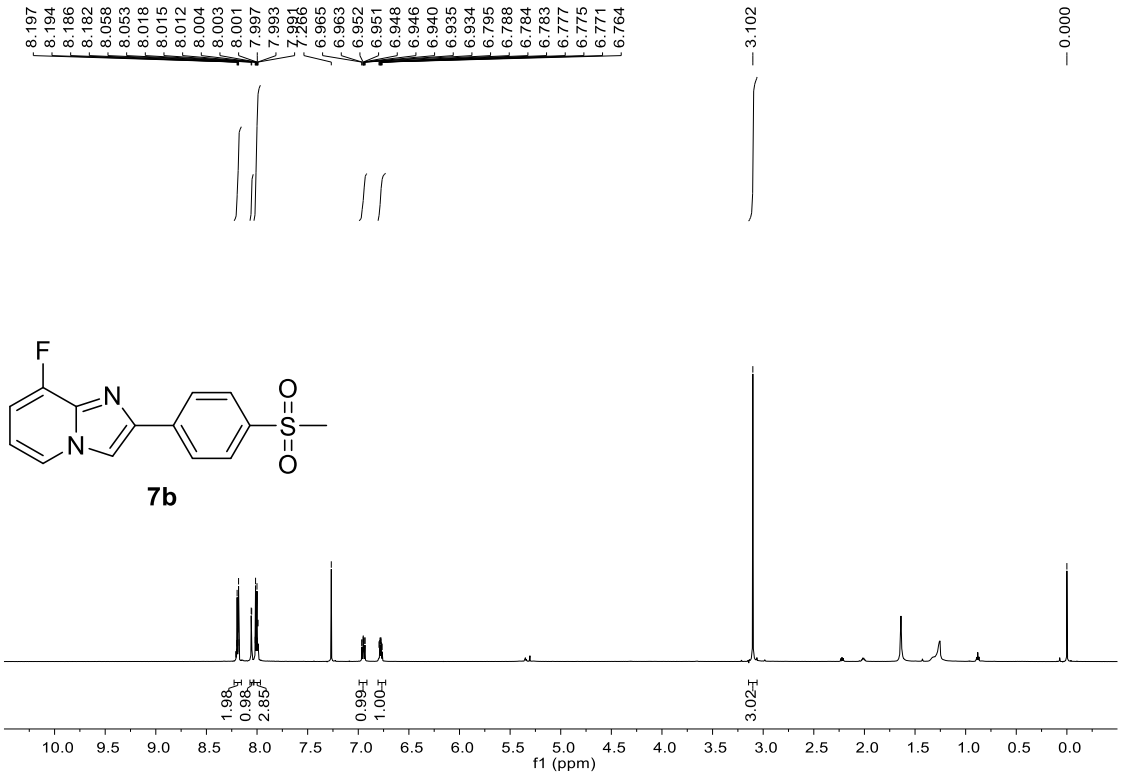
^{13}C NMR spectrum of the compound **7b' (**151 MHz, $CDCl_3$)



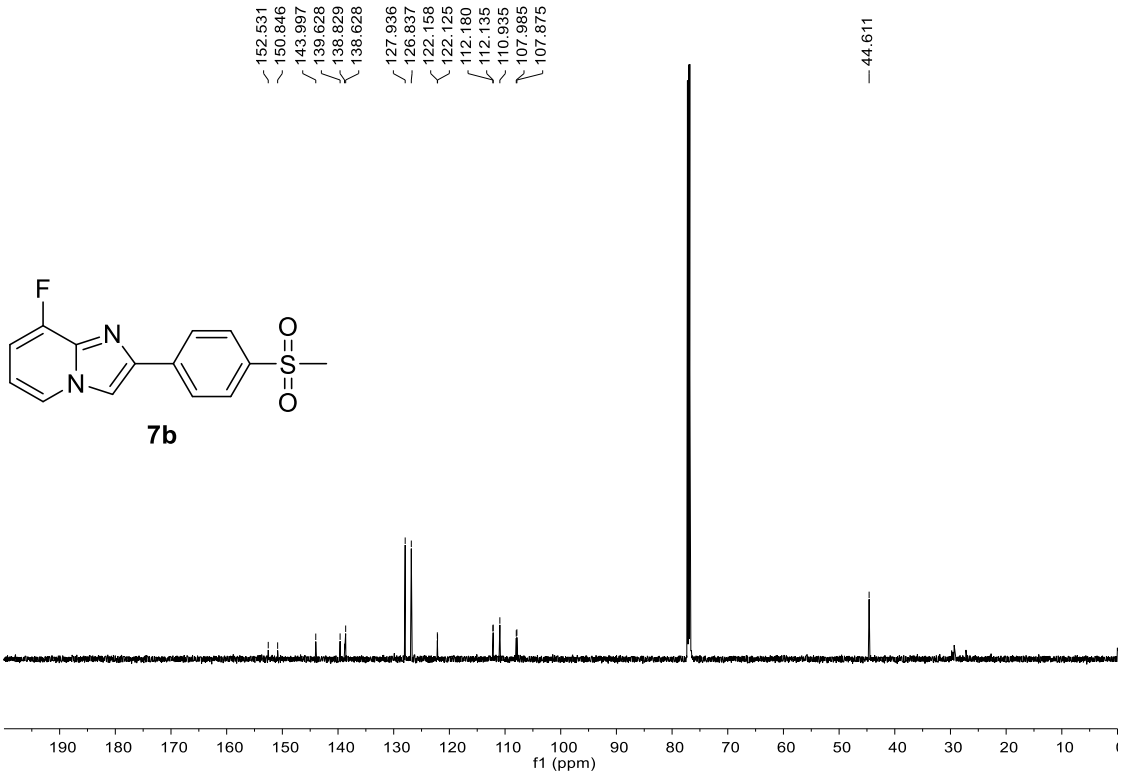
^{19}F NMR spectrum of the compound **7b' (**565 MHz, $CDCl_3$)



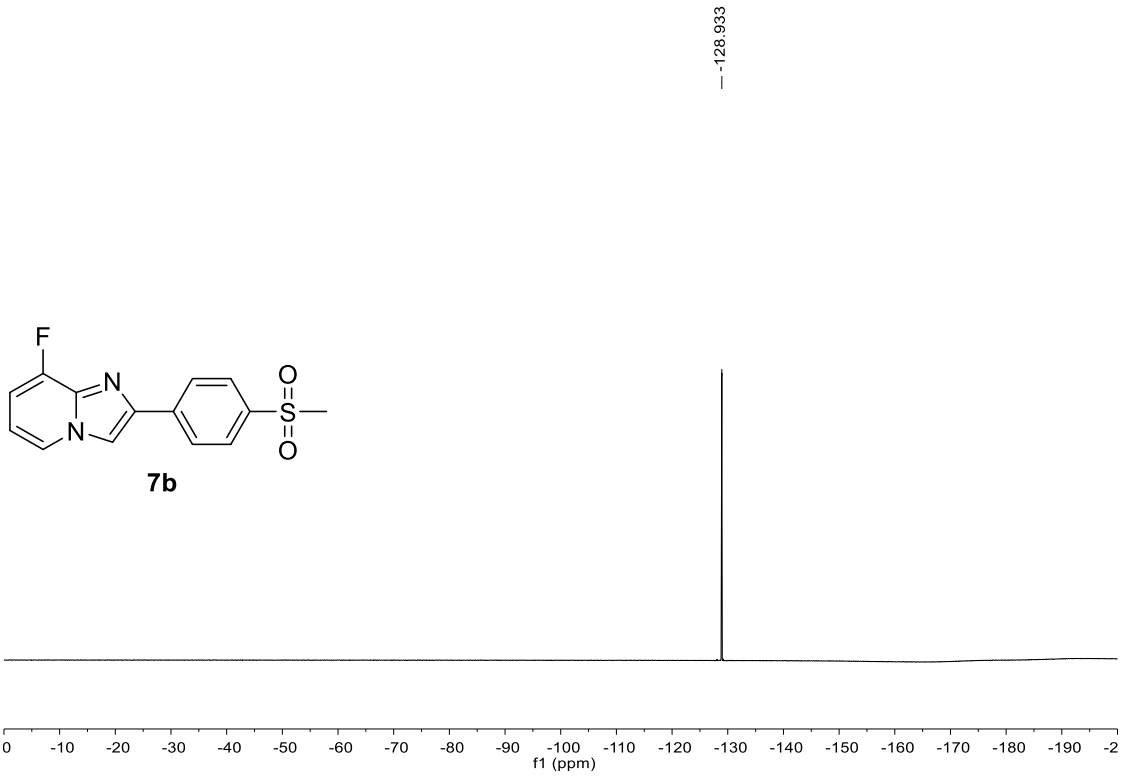
^{1}H NMR spectrum of the compound **7b (**600 MHz, $CDCl_3$)



^{13}C NMR spectrum of the compound **7b (**151 MHz, $CDCl_3$)



^{19}F NMR spectrum of the compound **7b (**565 MHz, $CDCl_3$)



X-ray Crystallography of 3a

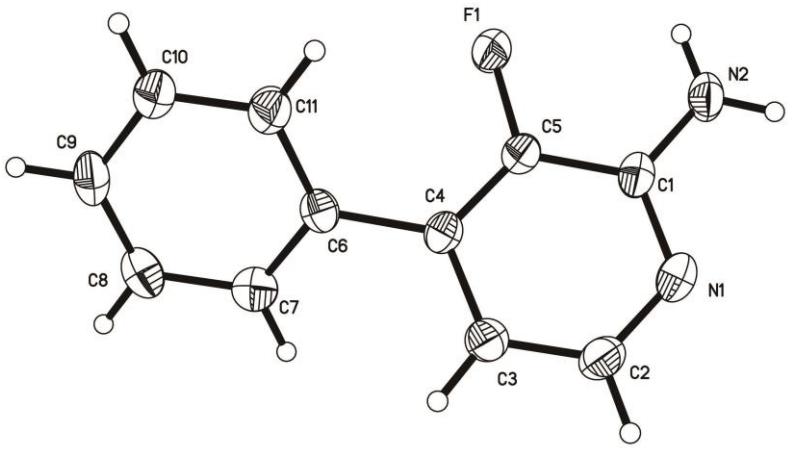


Table 1. Crystal data and structure refinement for compound **3a.**

Identification code	cu_180227a	
Empirical formula	C11 H9 F N2	
Formula weight	188.20	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.9549(2) Å	a= 94.5260(10)°.
	b = 9.9577(2) Å	b= 94.4300(10)°.
	c = 37.1535(9) Å	g = 90.0110(10)°.
Volume	3660.42(14) $Å^3$	
Z	16	
Density (calculated)	1.366 Mg/m^3	
Absorption coefficient	0.804 mm^{-1}	
F(000)	1568	
Crystal size	0.200 x 0.160 x 0.150 mm^3	
Theta range for data collection	3.591 to 68.449°.	
Index ranges	-11<=h<=11, -11<=k<=10, -44<=l<=42	
Reflections collected	38675	
Independent reflections	12773 [R(int) = 0.0550]	
Completeness to theta = 67.679°	99.3 %	

Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12773 / 0 / 1010
Goodness-of-fit on F^2	1.066
Final R indices [I>2sigma(I)]	R1 = 0.0678, wR2 = 0.1668
R indices (all data)	R1 = 0.0950, wR2 = 0.1901
Largest diff. peak and hole	0.416 and -0.292 e.Å^{-3}

X-ray Crystallography of 5b

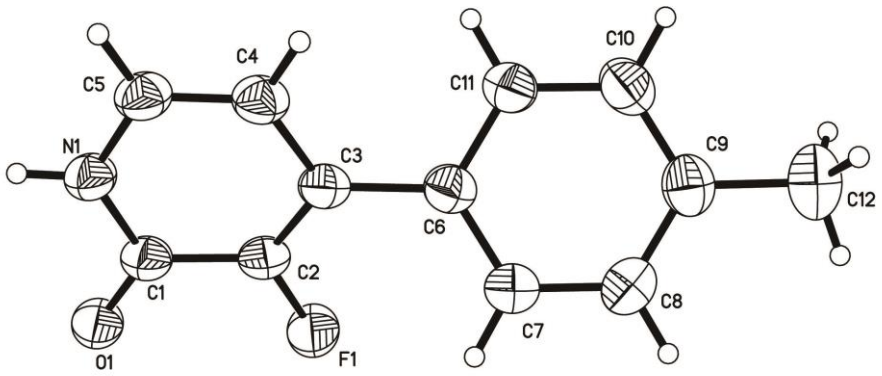


Table 2. Crystal data and structure refinement for **5b**.

Identification code	180327b_a	
Empirical formula	C12 H10 F N O	
Formula weight	203.21	
Temperature	292(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.9079(5) Å	α= 90°.

	b = 6.4765(2) Å	β= 116.995(2)°.
	c = 13.3924(5) Å	γ = 90°.
Volume	997.60(6) Å^3	
Z	4	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.826 mm^{-1}	
F(000)	424	
Crystal size	0.350 x 0.170 x 0.070 mm^3	
Theta range for data collection	6.628 to 68.151°.	
Index ranges	-15<=h<=15, -7<=k<=7, -14<=l<=16	
Reflections collected	10100	
Independent reflections	1804 [R(int) = 0.0424]	
Completeness to theta = 67.679°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1804 / 0 / 138	
Goodness-of-fit on F^2	0.967	
Final R indices [I>2sigma(I)]	R1 = 0.0532, wR2 = 0.1513	
R indices (all data)	R1 = 0.0721, wR2 = 0.1778	
Extinction coefficient	0.013(3)	
Largest diff. peak and hole	0.266 and -0.202 e.Å^{-3}	