Manganese-Catalyzed [4+2] Annulation of N-H Amidines with Vinylene Carbonate via C-H Activation

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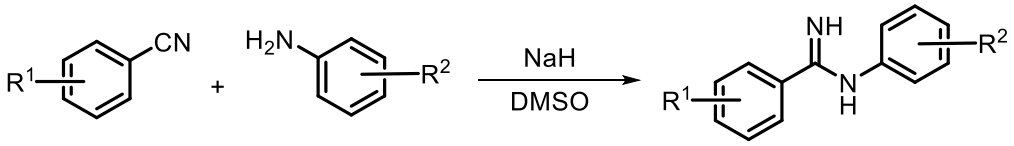
EXPERIMENTAL SECTION

1. General information

Air- and moisture-sensitive syntheses were performed under argon atmosphere. $MnBr(CO)_5$ was purchased from Alfa. Other chemicals were purchased from Adamas, Energy Chemical, Aldrich, TCI, Bide Pharmatech Ltd. Unless otherwise noted, all commercial reagents were used without further purification. And the NMR spectroscopy was in full accordance with the data in the literature. The products were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS spectroscopy. ^{1}H and ^{13}C NMR spectra were recorded on Zhongke Niujin WNMR-I 400 (400 MHz). Chemical shift δ (ppm) was given relative to solvent: references for $CDCl_3$ were 7.26 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR), and for *d*-DMSO were 2.50 ppm (^{1}H NMR) and 39.60 ppm (^{13}C NMR), ^{13}C NMR spectra were acquired on a broad band decoupled mode. Multiplets were assigned as s (singlet), d (doublet), dd (doublet doublet), and m (multiplet) etc. EI (Electron Impact) mass spectra were recorded on a GCMS-QP2010 SE spectrometer (70 eV). ESI (electrospray ionization) high resolution mass spectra were recorded on an Agilent Technologies 6530 TOF LC/MS. All measurements were carried out at room temperature unless otherwise stated.

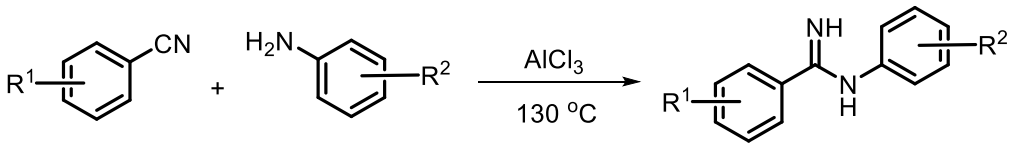
2. Typical procedure for preparation of amidines

Method A:



NaH (11.0 mmol, 1.1 equiv) was introduced in a flask (25 mL in volume) sealed with a rubber septum, evacuated and backfilled with argon (balloon). DMSO (5 mL) was added and the reaction was cooled down to 0°C (ice-water bath), then aniline (12.0 mmol, 1.2 equiv) and the carbonitrile (10.0 mmol) were added. The mixture was kept at 0 °C for 60 min and stirred for 24 h at room temperature. The mixture was quenched with ice-water while maintaining vigorous stirring and extracted with EtOAc (3×20 mL). The combined organic layers layer were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue which was recrystallized (solvent: DCM/Heptane) to provide the corresponding product.

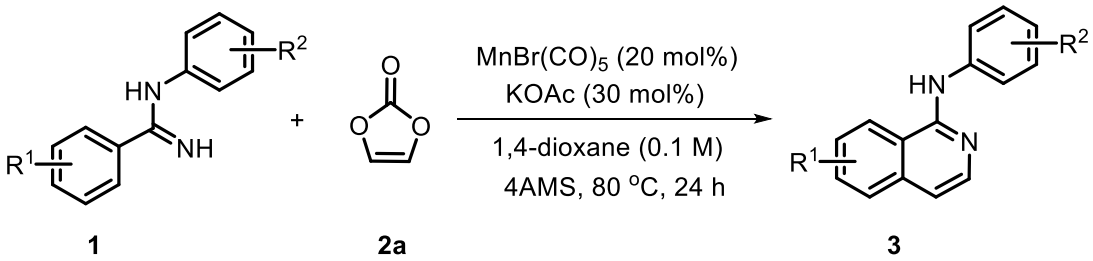
Method B:



A mixture of $AlCl_3$ (11.0 mmol, 1.1 equiv), aniline (11.0 mmol, 1.1 equiv) and carbonitrile (10.0 mmol) was stirred at 130 ^{o}C under an inert atmosphere in a sealed tube for about an hour. The hot mixture was poured into a solution of concentrated NaOH solution (40 mL) in mixed water and ice (100 mL) and stirred for about 15 minutes. Then the mixture was extracted with EtOAc (25 mL × 3). The combined organic layers were washed with brine (30 mL × 3), dried over anhydrous Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography on silica gel.

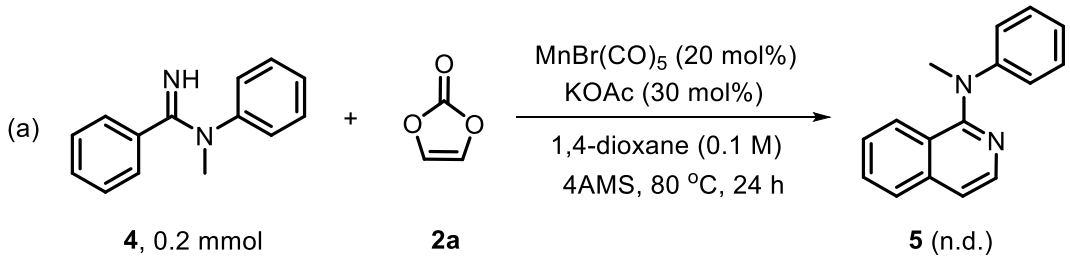
Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1932-1934.

3. General procedure

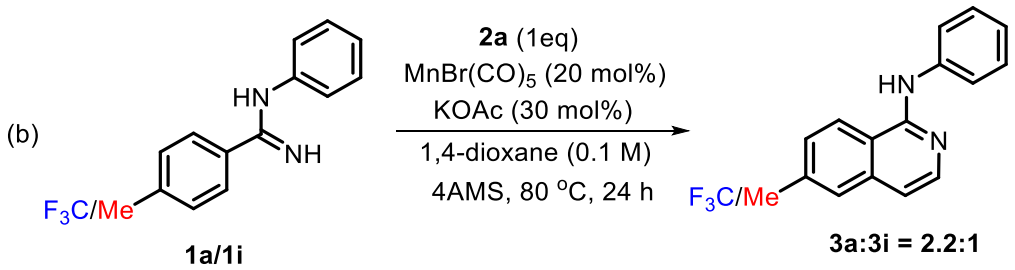


N-PhenylbenzaMidine **1** (0.20 mmol, 1.0 equiv), vinylene carbonate **2a** (2.0 mmol, 10.0 equiv), $MnBr(CO)_5$ (4.3 mg, 7.5 mol%), 4AMS (50 mg), KOAc (5.9 mg, 30 mol%), in 1,4-dioxane (2.0 mL) was stirred at 80 °C in heating mantle for 24 h under N_2. After cooling to ambient temperature, the mixture was transferred into a round bottom flask diluted with EtOAc (20 mL) and washed with brine (5.0 mL). The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (300−400 mesh) using a mixture of PE and EtOAc to afford the desired product **3** (eluent: EA/PE= 1/10)

4. Control experiment

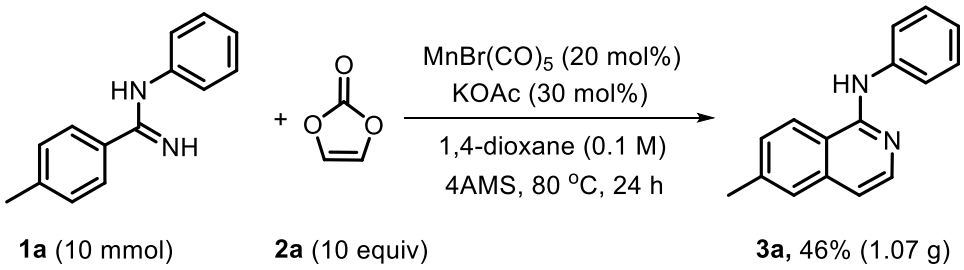


N-methyl-N-phenylbenzimidamide **4** (0.20 mmol, 1.0 equiv), vinylene carbonate **2a** (2.0 mmol, 10.0 equiv), $MnBr(CO)_5$ (4.3 mg, 7.5 mol%), 4AMS (50 mg), KOAc (5.9 mg, 30 mol%), in 1,4-dioxane (2.0 mL) was stirred at 80 °C for 24 h under N_2. After cooling to ambient temperature, the reaction was determined by TLC and GCMS, and we did not found any desired products (**5**).



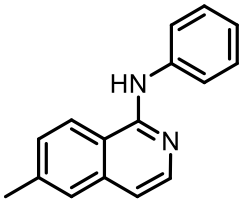
To gain more insight of the reaction nature, a series of competition reactions were conducted. Firstly, equal amounts of N-phenyl-4- methylbenzamidine (**1a**) and N-Phenyl-4-(trifluoromethyl)benzamidine (**1i**) were treated with phenylacetylene (**2a**, 1.0 equiv) in the presence of $Mn(CO)_5Br$. After reaction, a ratio of 2.2/1 was obtained for the product of **3a**/**3i**.

5. Gram-Scale Reaction



4-methyl-N-phenylbenzimidamide **1a** (10.0 mmol, 1.0 equiv), vinylene carbonate **2a** (10.0 mmol, 10.0 equiv), $MnBr(CO)_5$ (215.0 mg, 7.5 mol%), 4AMS (2500 mg), KOAc (295.0 mg, 30 mol%), in 1,4-dioxane (100.0 mL) was stirred at 80 °C in heating mantle for 24 h under N_2. After cooling to ambient temperature, the mixture was transferred into a round bottom flask diluted with EtOAc and washed with brine. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography on silica gel (300−400 mesh) using a mixture of PE and EtOAc to afford the desired product **3a** (1.07 g, 46% yield).

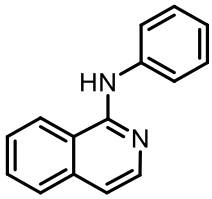
6. Analytical data for products



6-methyl-*N*-phenylisoquinolin-1-amine 3a[1]

Yield 67% (31.8 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

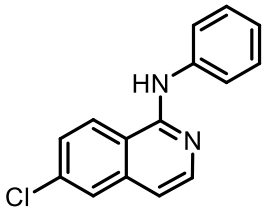
^{1}H NMR (400 MHz, Chloroform-d) δ 8.07 (d, J = 5.8 Hz, 1H), 7.81 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.0 Hz, 2H), 7.52 (s, 1H), 7.41 – 7.31 (m, 3H), 7.08 – 7.04 (m, 2H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-d) δ 152.2, 141.0, 140.7, 140.1, 137.8, 129.0, 128.5, 126.6, 122.6, 121.4, 120.2, 117.1, 113.2, 21.7.



***N*-phenylisoquinolin-1-amine 3b[1]**

Yield 58% (25.5 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 5.8 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.76 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.57-7.53 (m, 1H), 7.41 – 7.34 (m, 2H), 7.14 (d, *J* = 5.8 Hz, 1H), 7.10 – 7.05 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.3, 141.0, 140.5, 137.5, 129.9, 129.0, 127.5, 126.5, 122.7, 121.5, 120.3, 118.9, 113.5.

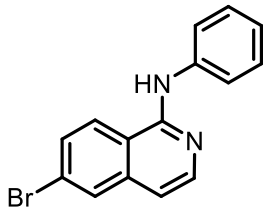


6-chloro-*N*-phenylisoquinolin-1-amine 3c[1]

Yield 52% (26.4 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 5.8 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 2.1 Hz, 1H), 7.65 – 7.60 (m, 2H), 7.46 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.39 – 7.34

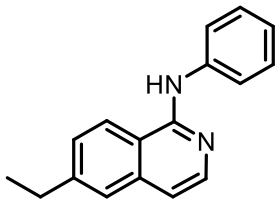
(m, 2H), 7.10 – 7.03 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 152.4, 142.3, 140.2, 138.6, 136.2, 129.1, 127.2, 126.3, 123.5, 123.1, 120.5, 117.1, 112.6.



6-bromo-*N*-phenylisoquinolin-1-amine 3d[1]

Yield 60% (35.8 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

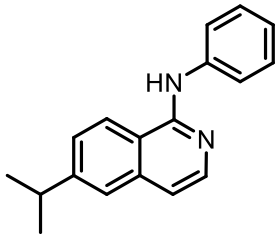
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.61 (dd, *J* = 13.1, 7.5 Hz, 3H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 5.9 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 152.4, 142.3, 140.2, 138.8, 129.7, 129.6, 129.0, 124.6, 123.4, 123.1, 120.5, 117.3, 112.4.



6-ethyl-*N*-phenylisoquinolin-1-amine 3e

Yield 71% (35.2 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

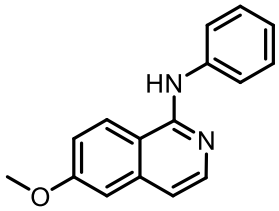
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 5.8 Hz, 1H), 7.85 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.54 (d, *J* = 1.7 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.11 – 7.04 (m, 2H), 2.83 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 152.2, 146.3, 140.9, 140.7, 137.9, 129.0, 127.5, 125.3, 122.6, 121.5, 120.2, 117.3, 113.4, 29.0, 15.2. **HRMS (ESI)** calcd for C17H17N2 m/z $[M+H]_{+}$: 249.1386; found: 249.1384.



6-isopropyl-*N*-phenylisoquinolin-1-amine 3f

Yield 72% (37.7 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

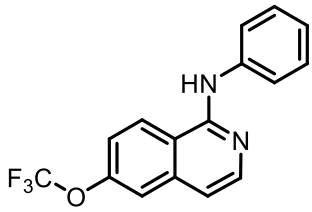
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 5.8 Hz, 1H), 7.86 (d, *J* = 8.7 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.56 (d, *J* = 1.8 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.15 – 6.99 (m, 2H), 3.09 (p, *J* = 6.9 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.2, 150.8, 141.0, 140.6, 137.9, 129.0, 126.2, 123.9, 122.5, 121.5, 120.2, 117.4, 113.5, 34.2, 23.7. **HRMS (ESI)** calcd for C18H19N2 m/z $[M+H]_{+}$: 263.1543; found: 263.1549.



6-methoxy-*N*-phenylisoquinolin-1-amine 3g[1]

Yield 76% (38.1 mg). White solid. Eluent: petroleum ether/ethyl acetate (10:1)

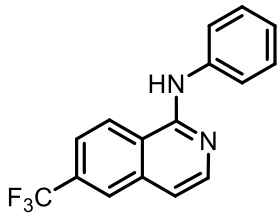
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 5.8 Hz, 1H), 7.83 (d, *J* = 9.1 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.14 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.07 – 6.99 (m, 3H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.6, 152.3, 141.7, 140.7, 139.6, 129.0, 123.6, 122.5, 120.2, 118.4, 114.0, 113.3, 105.8, 55.4.



N-phenyl-6-(trifluoromethoxy)isoquinolin-1-amine 3h

Yield 41% (24.9 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

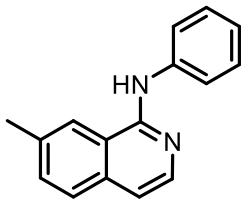
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 5.8 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 2H), 7.55 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 3H), 7.13 – 7.08 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.3, 150.0, 142.5, 140.1, 138.7, 124.5, 129.1, 124.3, 123.2, 121.8, 120.6, 119.9, 117.1, 113.2. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -57.57. **HRMS (ESI)** calcd for C16H12F3N2O m/z $[M+H]_{+}$: 305.0896; found: 305.0886.



***N*-phenyl-6-(trifluoromethyl)isoquinolin-1-amine 3i**

Yield 35% (20.1 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

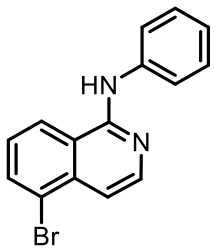
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (d, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 2H), 7.70 – 7.64 (m, 3H), 7.41 – 7.34 (m, 2H), 7.18 (d, *J* = 5.8 Hz, 1H), 7.12 – 7.07 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.3, 142.6, 140.0, 136.9, 131.7 ($J_{C\text{-}F}$ = 33.3 Hz), 129.1, 125.0 ($J_{C\text{-}F}$ = 262.6 Hz), 123.3, 122.9, 122.4, 122.1, 120.7, 119.9, 113.5. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -62.94. **HRMS (ESI)** calcd for $C_{16}H_{12}F_3N_2$ m/z $[M+H]_+$: 289.0947; found: 289.0947.



7-methyl-*N*-phenylisoquinolin-1-amine 3j[1]

Yield 55% (25.8 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

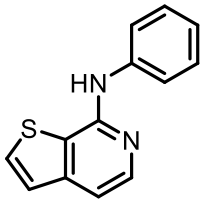
^{1}H NMR (400 MHz, Chloroform-d) δ 8.05 (d, J = 5.8 Hz, 1H), 7.71 (s, 1H), 7.66 (d, J = 7.4 Hz,3H), 7.49 (dd, J = 8.4, 1.5 Hz, 1H), 7.36 (d, J = 7.7 Hz, 2H), 7.10 (d, J = 5.8 Hz,1H), 7.06 (t, J = 7.4 Hz, 1H), 2.57 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 151.8, 140.6, 140.1, 136.4, 135.6, 131.9, 129.0, 127.4, 122.5, 120.6, 120.2, 119.0, 113.4, 22.0.



5-bromo-*N*-phenylisoquinolin-1-amine 3k

Yield 51% (30.4 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

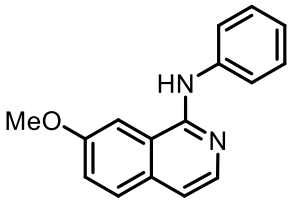
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 – 8.06 (m, 2H), 7.73 – 7.70 (m, 1H), 7.65 – 7.61 (m, 3H), 7.41 – 7.33 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 2H), 7.03 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 151.4, 141.5, 140.1, 136.0, 133.3, 129.1, 129.0, 124.3, 123.1, 120.5, 119.9, 113.0. **HRMS (ESI)** calcd for C15H12BrN2 m/z $[M+H]_{+}$: 299.0178; found: 299.0169.



***N*-phenylthieno[2,3-c]pyridin-7-amine 3l**

Yield 33% (14.9 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

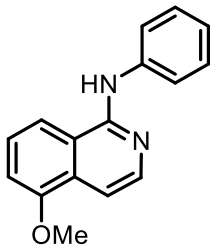
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.14 (d, *J* = 5.6 Hz, 1H), 7.62 – 7.55 (m, 3H), 7.40 – 7.31 (m, 3H), 7.27 – 7.25 (m, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.50 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 150.5, 146.7, 141.8, 140.0, 129.4, 129.0, 124.3, 123.1, 122.1, 121.0, 111.0. **HRMS (ESI)** calcd for C13H11N2S m/z $[M+H]_{+}$: 227.0637; found: 227.0629.



7-methoxy-*N*-phenylisoquinolin-1-amine 3m

Yield 58% (28.4 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

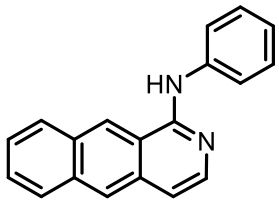
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 (d, *J* = 5.9 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 5.9 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.08 – 7.04 (m, 1H), 6.99 (dd, *J* = 7.0, 1.4 Hz, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.2, 151.9, 140.6, 140.6, 129.9, 129.0, 126.5, 122.6, 120.2, 119.5, 113.2, 107.7, 107.6, 55.7. **HRMS (ESI)** calcd for C16H15N2O m/z $[M+H]_{+}$: 251.1179; found: 251.1189.



5-methoxy-*N*-phenylisoquinolin-1-amine 3n

Yield 14% (7.0 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

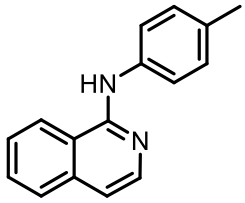
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 5.7 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.38 – 7.30 (m, 3H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 5.9 Hz, 1H), 7.07 – 7.03 (m, 1H), 6.88 (s, 1H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 158.2, 151.5, 140.9, 138.9, 132.7, 129.1, 129.0, 122.5, 121.7, 120.2, 120.0, 113.7, 101.3, 55.6. **HRMS (ESI)** calcd for C16H15N2O m/z [M+H]+: 251.1179; found: 251.1187.



***N*-phenylbenzo[*g*]isoquinolin-1-amine 3o**

Yield 62% (33.5 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

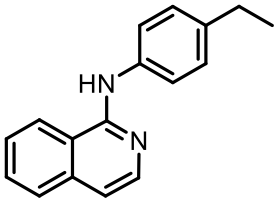
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 9.28 (s, 1H), 8.39 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.91 (d, *J* = 6.0 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.42 – 7.33 (m, 2H), 7.27 (d, *J* = 6.1 Hz, 1H), 7.03 (t, *J* = 7.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 153.5, 141.6, 139.4, 134.0, 133.9, 131.7, 129.4, 128.8, 128.0, 128.0, 126.3, 124.9, 123.7, 122.4, 121.2, 118.9, 112.4. **HRMS (ESI)** calcd for C19H15N2 m/z [M+H]+: 271.1230; found: 271.1224.



***N*-(*p*-tolyl)isoquinolin-1-amine 3p[1]**

Yield 60% (28.1 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

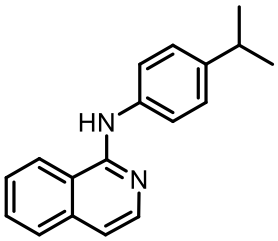
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 5.8 Hz, 1H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.7, 141.1, 137.8, 137.5, 132.5, 129.8, 129.5, 127.4, 126.4, 121.5, 120.9, 118.8, 113.1, 20.9.



***N*-(4-ethylphenyl)isoquinolin-1-amine 3q**

Yield 63% (31.2 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

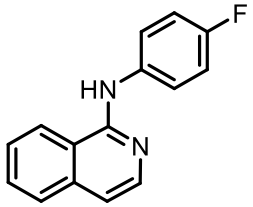
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.75 – 7.73 (m, 1H), 7.65 – 7.61 (m, 1H), 7.60 – 7.50 (m, 3H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 5.8 Hz, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.6, 141.1, 138.9, 138.0, 137.5, 129.8, 128.4, 127.4, 126.4, 121.5, 120.9, 118.8, 113.1, 28.4, 15.8. **HRMS (ESI)** calcd for C17H17N2 m/z $[M+H]_{+}$: 249.1386; found: 249.1383.



***N*-(4-isopropylphenyl)isoquinolin-1-amine 3r**

Yield 63% (33.1 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

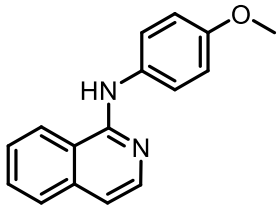
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.66 - 7.62 (m, 1H), 7.61 - 7.50 (m, 3H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 1H), 2.92 (p, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.6, 143.5, 141.1, 138.0, 137.5, 129.8, 127.4, 126.9, 126.4, 121.5, 120.8, 118.8, 113.1, 33.6, 24.1. **HRMS (ESI)** calcd for C18H19N2 m/z $[M+H]_{+}$: 263.1543; found: 263.1551.



***N*-(4-fluorophenyl)isoquinolin-1-amine 3s**

Yield 42% (20.1 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

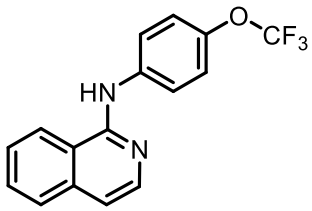
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.06 (d, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.68 – 7.51 (m, 4H), 7.13 (d, *J* = 5.7 Hz, 1H), 7.06 (t, *J* = 8.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.0, 157.6, 152.4, 140.8, 137.5, 136.4 (d, *J*= 2.9 Hz), 130.1, 127.0 (d, *J*= 98.3 Hz), 122.5 (d, *J*= 7.9 Hz), 121.4, 118.6, 115.6 (d, *J*= 22.5 Hz), 113.4. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -120.23. **HRMS (ESI)** calcd for C15H12FN2 m/z $[M+H]_{+}$: 239.0979; found: 239.0974.



***N*-(4-methoxyphenyl)isoquinolin-1-amine 3t**

Yield 68% (34.1 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

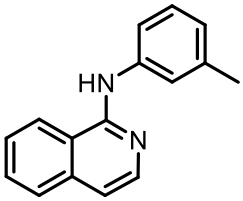
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.08 (d, *J* = 5.6 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.9, 153.0, 141.0, 137.5, 133.5, 129.9, 127.4, 126.3, 123.1, 121.6, 118.6, 114.4, 112.8, 55.6. **HRMS (ESI)** calcd for C16H15N2O m/z $[M+H]_{+}$: 251.1179; found: 251.1173.



***N*-(4-(trifluoromethoxy)phenyl)isoquinolin-1-amine 3u**

Yield 50% (30.4 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

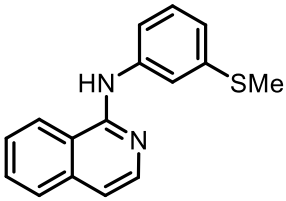
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 (d, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.74 - 7.63 (m, 3H), 7.57 (td, *J* = 7.5, 6.8, 1.3 Hz, 1H), 7.20 (dd, *J* = 18.2, 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 151.9, 144.1, 140.7, 139.2, 137.5, 130.1, 127.6, 126.7, 121.8, 121.2, 121.1, 118.8, 114.0, 29.7. ^{19}F NMR (377 MHz, Chloroform-*d*) δ -58.09. **HRMS (ESI)** calcd for C16H12F3N2O m/z $[M+H]_{+}$: 305.0896; found: 305.0890.



***N*-(*m*-tolyl)isoquinolin-1-amine 3v[1]**

Yield 57% (26.7 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

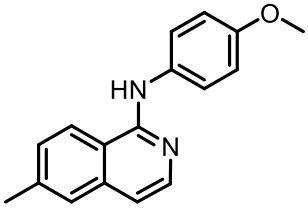
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 5.8 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.66 – 7.62 (m, 1H), 7.57 – 7.45 (m, 3H), 7.30 – 7.23 (m, 1H), 7.13 (d, *J* = 5.8 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.4, 141.1, 140.4, 138.8, 137.5, 129.9, 128.9, 127.5, 126.4, 123.7, 121.5, 121.0, 118.9, 117.6, 113.3, 21.6.



***N*-(3-(methylthio)phenyl)isoquinolin-1-amine 3w**

Yield 55% (29.3 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

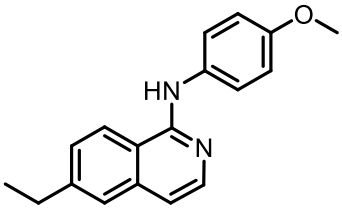
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 5.7 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.66 - 7.59 (m, 2H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.25 - 7.21 (m, 1H), 7.12 (d, *J* = 5.8 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.1, 141.1, 140.9, 139.2, 137.5, 130.0, 129.3, 127.5, 126.6, 121.4, 120.9, 118.9, 118.2, 117.0, 113.7, 15.9. **HRMS (ESI)** calcd for C16H15N2S m/z $[M+H]_{+}$: 267.0950; found: 267.0940.



***N*-(4-methoxyphenyl)-6-methylisoquinolin-1-amine 3x**

Yield 53% (28.0 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

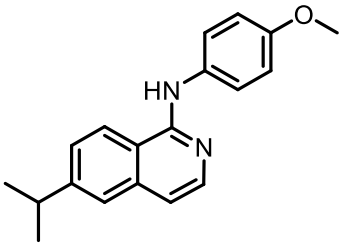
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 5.8 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 9.1 Hz, 3H), 7.34 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.00 (d, *J* = 5.8 Hz, 1H), 6.94 – 6.90 (m, 2H), 3.82 (s, 3H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.8, 152.9, 141.1, 140.1, 137.8, 133.6, 128.3, 126.6, 123.0, 121.4, 116.8, 114.4, 112.5, 55.6, 21.7. **HRMS (ESI)** calcd for C17H17N2O m/z $[M+H]_+$: 265.1335; found: 265.1342.



6-ethyl-*N*-(4-methoxyphenyl)isoquinolin-1-amine 3y

Yield 54% (30.0 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

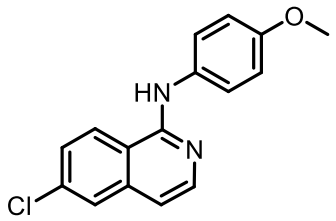
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 5.8 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.56 – 7.48 (m, 3H), 7.38 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.02 (d, *J* = 5.9 Hz, 1H), 6.95 – 6.90 (m, 2H), 3.82 (s, 3H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.33 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.8, 152.9, 146.2, 141.1, 137.8, 133.6, 127.3, 125.3, 123.0, 121.5, 117.0, 114.4, 112.7, 55.6, 29.0, 15.2. **HRMS (ESI)** calcd for C18H19N2O m/z $[M+H]_+$: 279.1492; found: 279.1497.



6-isopropyl-*N*-(4-methoxyphenyl)isoquinolin-1-amine 3z

Yield 51% (29.8 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

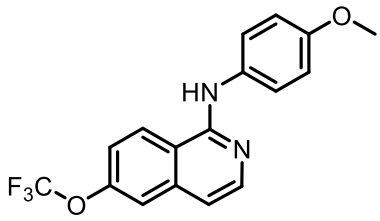
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 5.8 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.49 (m, 3H), 7.41 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.03 (d, *J* = 5.7 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 3.07 (p, *J* = 6.9 Hz, 1H), 1.35 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.8, 152.9, 150.8, 141.0, 137.9, 133.6, 126.0, 123.9, 123.1, 121.6, 117.1, 114.4, 112.8, 55.6, 34.2, 23.7. **HRMS (ESI)** calcd for C19H21N2O m/z $[M+H]_+$: 293.1648; found: 293.1657.



6-chloro-*N*-(4-methoxyphenyl)isoquinolin-1-amine 3aa

Yield 52% (29.5 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 5.8 Hz, 1H), 7.84 (d, *J* = 8.9 Hz, 1H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.52 – 7.43 (m, 3H), 6.98 (d, *J* = 5.8 Hz, 1H), 6.96 – 6.90 (m, 2H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.1, 153.1, 142.5, 138.5, 136.0, 133.1, 127.0, 126.2, 123.4, 123.3, 114.4, 111.9, 55.6. **HRMS (ESI)** calcd for C16H14ClN2O m/z $[M+H]_+$: 285.0789; found: 285.0783.

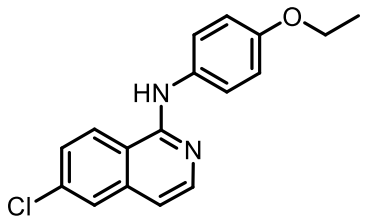


***N*-(4-methoxyphenyl)-6-(trifluoromethoxy)isoquinolin-1-amine 3ab**

Yield 41% (27.4 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 5.8 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.34 (dd, *J* = 9.6, 2.1 Hz, 1H), 7.05 (d, *J* = 5.8 Hz, 1H), 6.95 – 6.90 (m, 2H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.2, 153.0, 149.9, 142.7, 138.7, 133.0, 124.2, 123.4, 121.8, 119.6, 117.0, 116.7, 114.4, 112.5, 55.6. ^{19}F

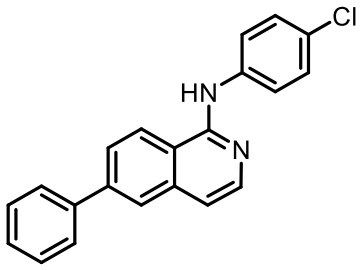
NMR (377 MHz, Chloroform-*d*) δ -57.58. **HRMS (ESI)** calcd for C17H14F3N2O2 m/z $[M+H]_+$: 335.1002; found: 335.0998.



6-chloro-*N*-(4-ethoxyphenyl)isoquinolin-1-amine 3ac

Yield 57% (34.0 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 5.8 Hz, 1H), 7.82 (d, *J* = 8.9 Hz, 1H), 7.70 (d, *J* = 2.1 Hz, 1H), 7.51 - 7.40 (m, 3H), 6.97 (d, *J* = 5.8 Hz, 1H), 6.93 - 6.88 (m, 2H), 4.03 (q, *J* = 7.0 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.4, 153.1, 142.5, 138.5, 136.0, 133.0, 126.9, 126.2, 123.4, 123.3, 116.7, 115.1, 111.8, 63.8, 14.9. **HRMS (ESI)** calcd for C17H16ClN2O m/z $[M+H]_+$: 299.0946; found: 299.0945.



***N*,6-diphenylisoquinolin-1-amine 3ad**

Yield 60% (35.5 mg). Yellow solid. Eluent: petroleum ether/ethyl acetate (10:1)

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 5.8 Hz, 1H), 8.00 – 7.92 (m, 2H), 7.79 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.75 – 7.69 (m, 2H), 7.68 – 7.62 (m, 2H), 7.53 – 7.50 (m, 2H), 7.47 – 7.40 (m, 1H), 7.36 – 7.30 (m, 2H), 7.20 (d, *J* = 5.8 Hz, 1H), 7.11 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 152.0, 142.7, 141.3, 140.0, 139.1, 137.9, 129.0, 128.9, 128.2, 127.4, 127.5, 126.2, 125.3, 122.0, 121.5, 117.8, 114.0. **HRMS (ESI)** calcd for C21H16ClN2 m/z $[M+H]_+$: 331.0997; found: 331.0992.

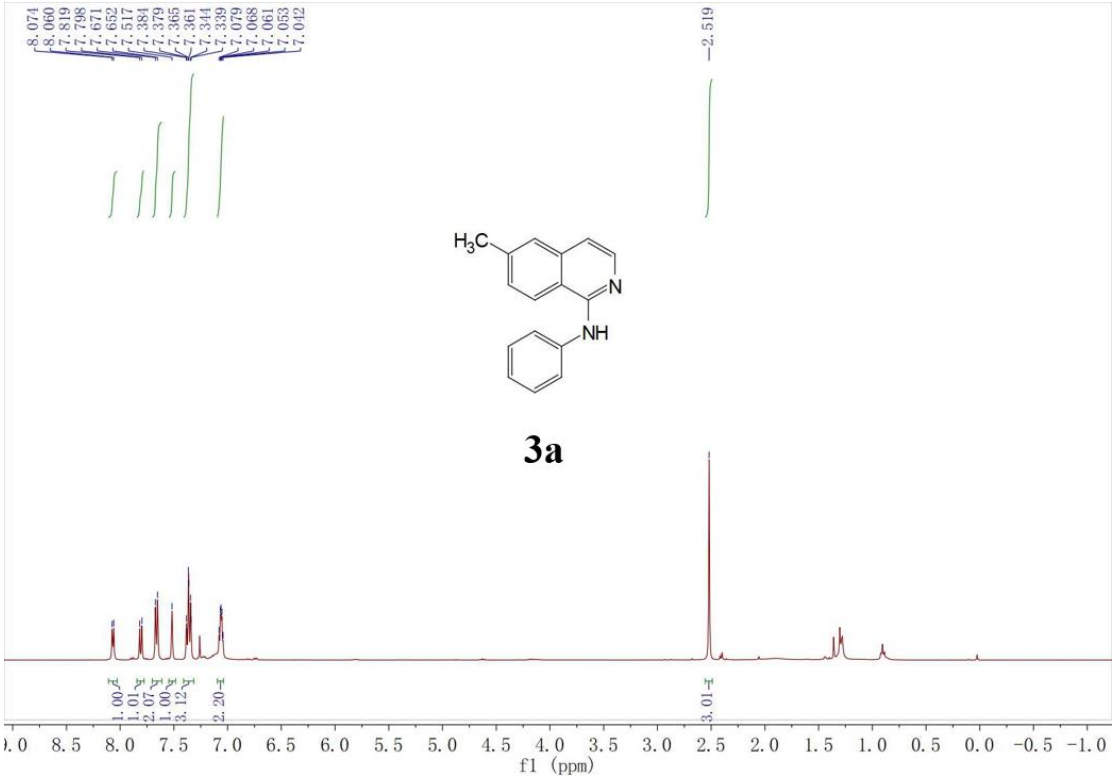
7. Reference

(1): Huang, X.; Xu, Y.; Li, J.; Lai, R.; Luo, Y.; Wang, Q.; Yang, Z.; Wu, Y. *Chinese*

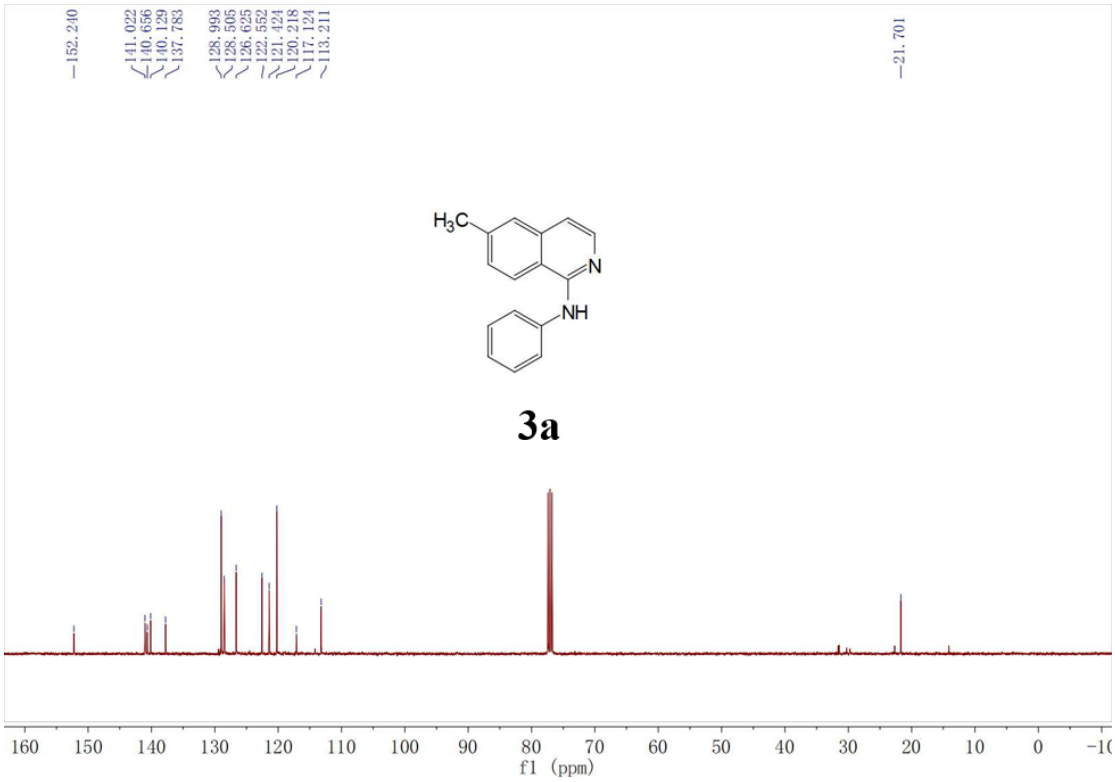
*Chemical Lett*ers, https://doi.org/10.1016/j.cclet.2021.04.058

8. Copies of NMR Spectra

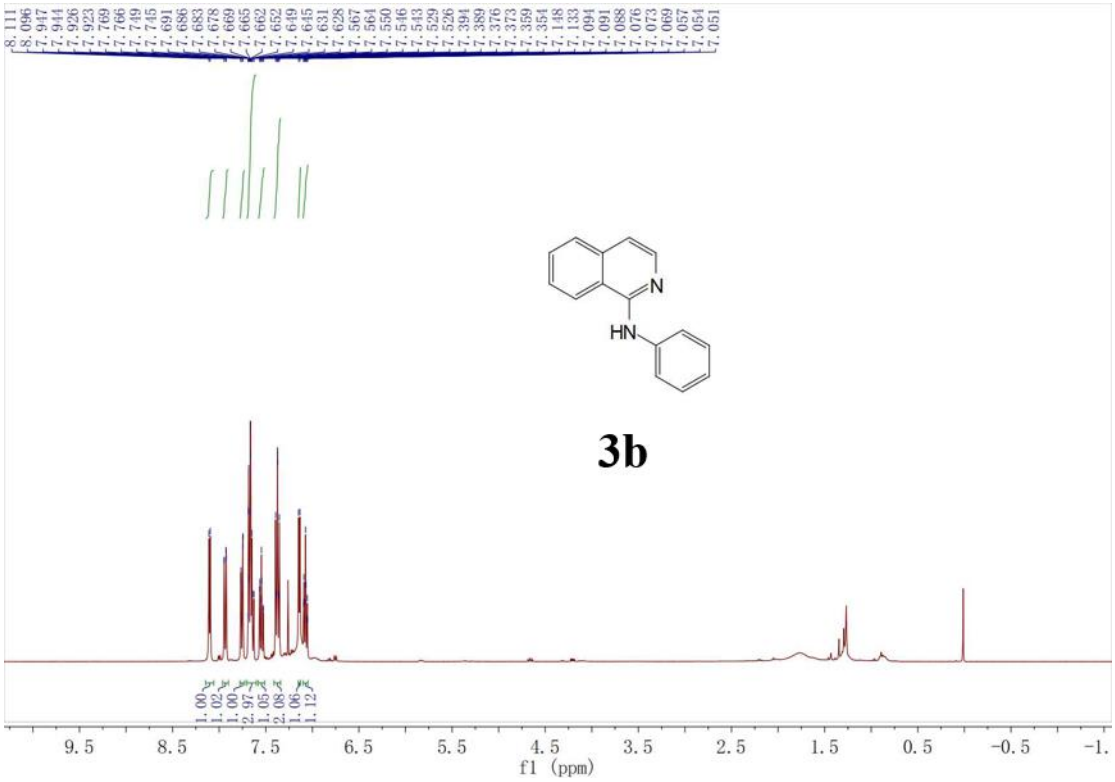
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3a



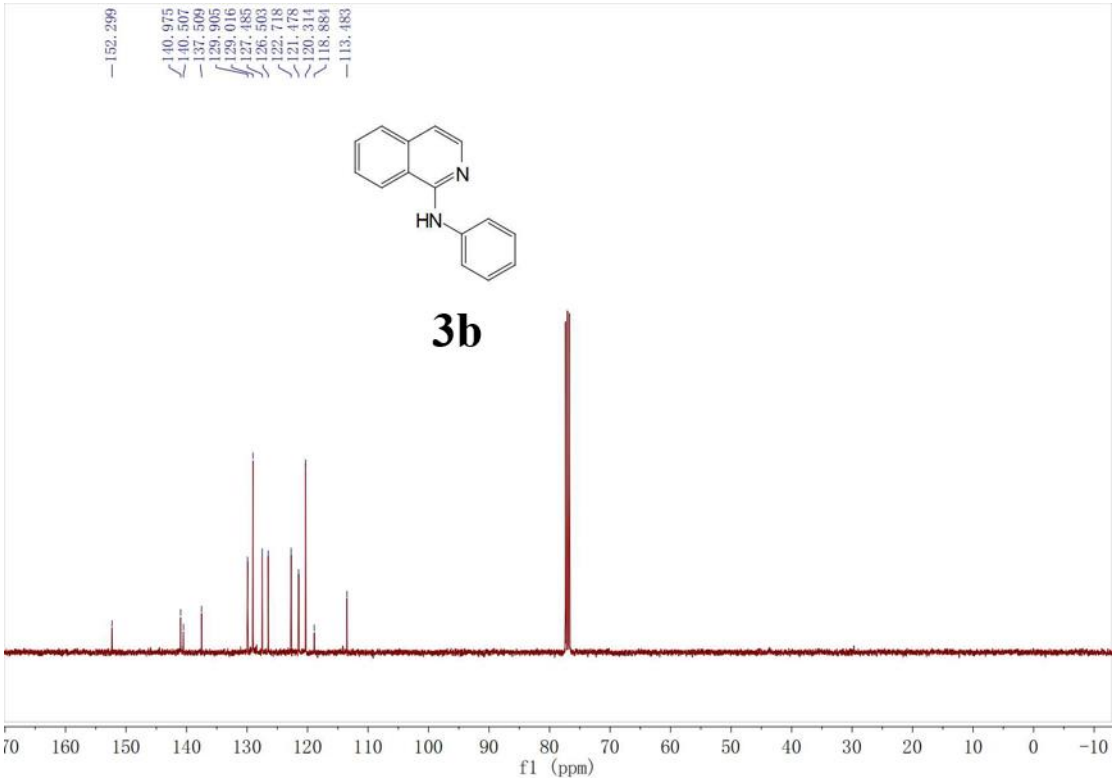
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3a



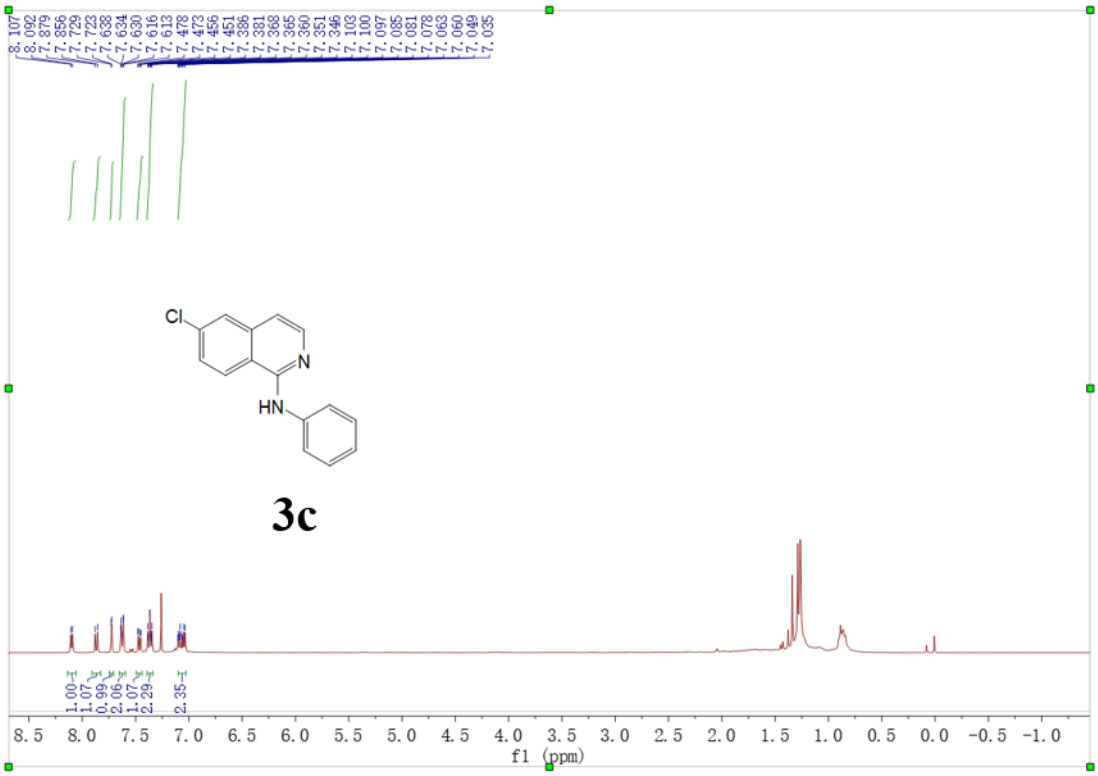
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3b



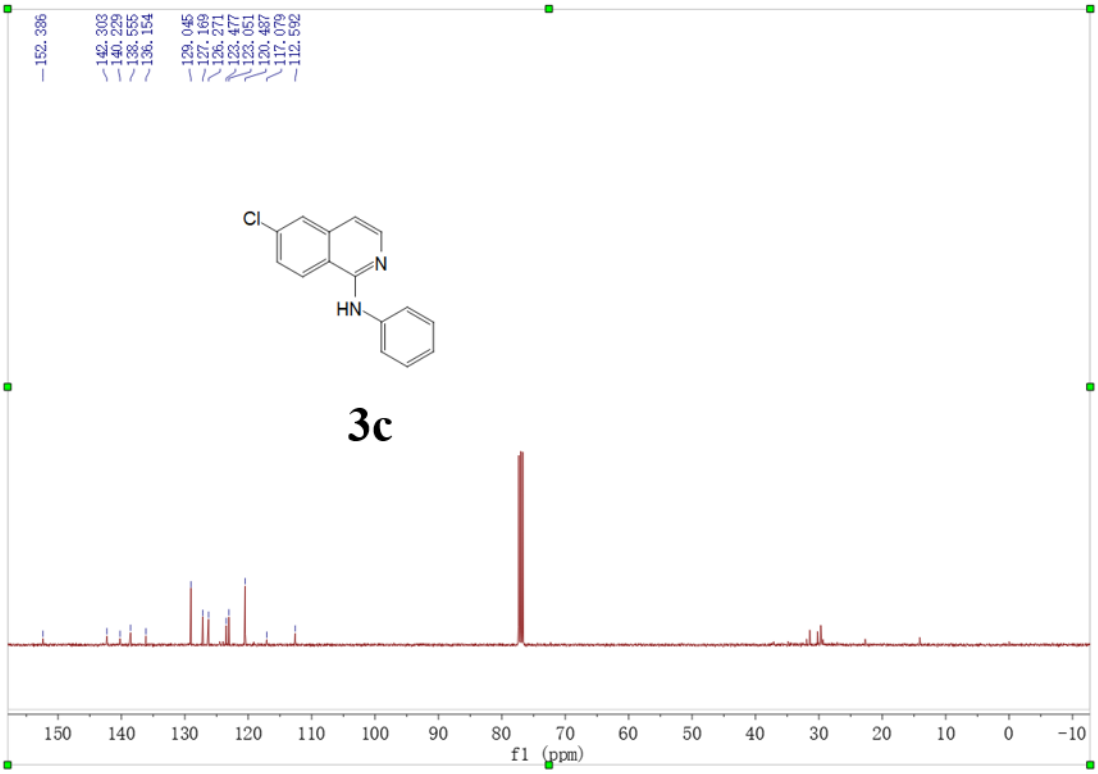
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3b



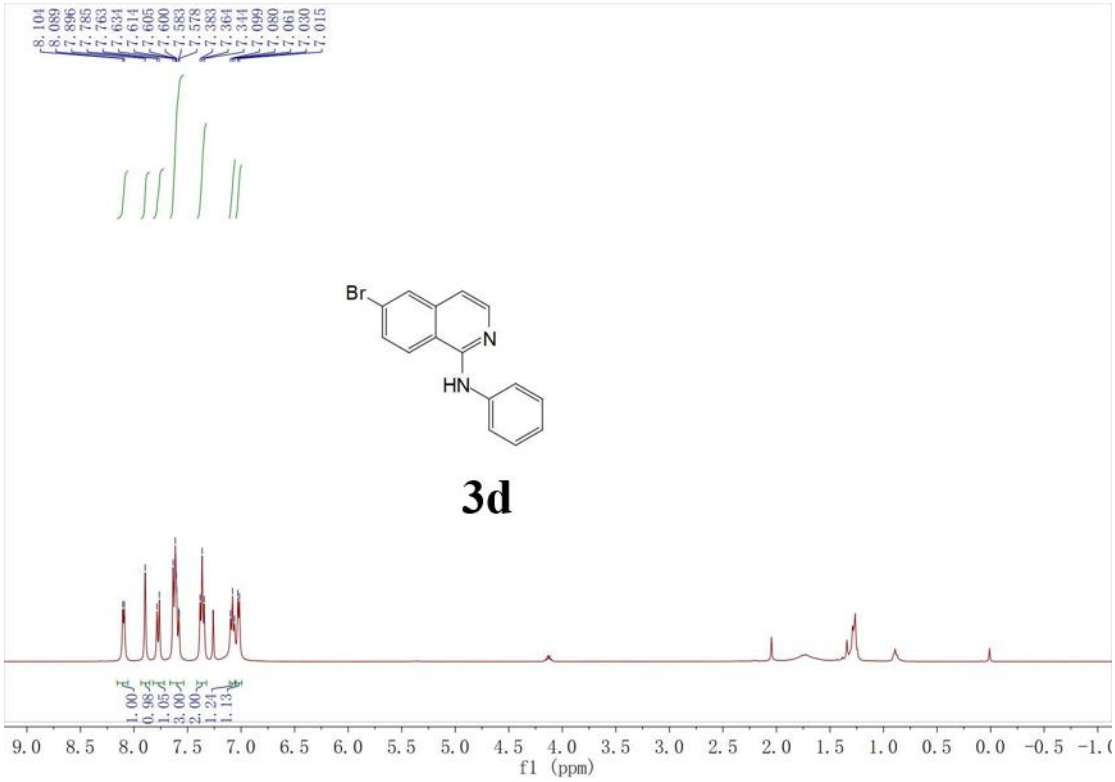
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3c



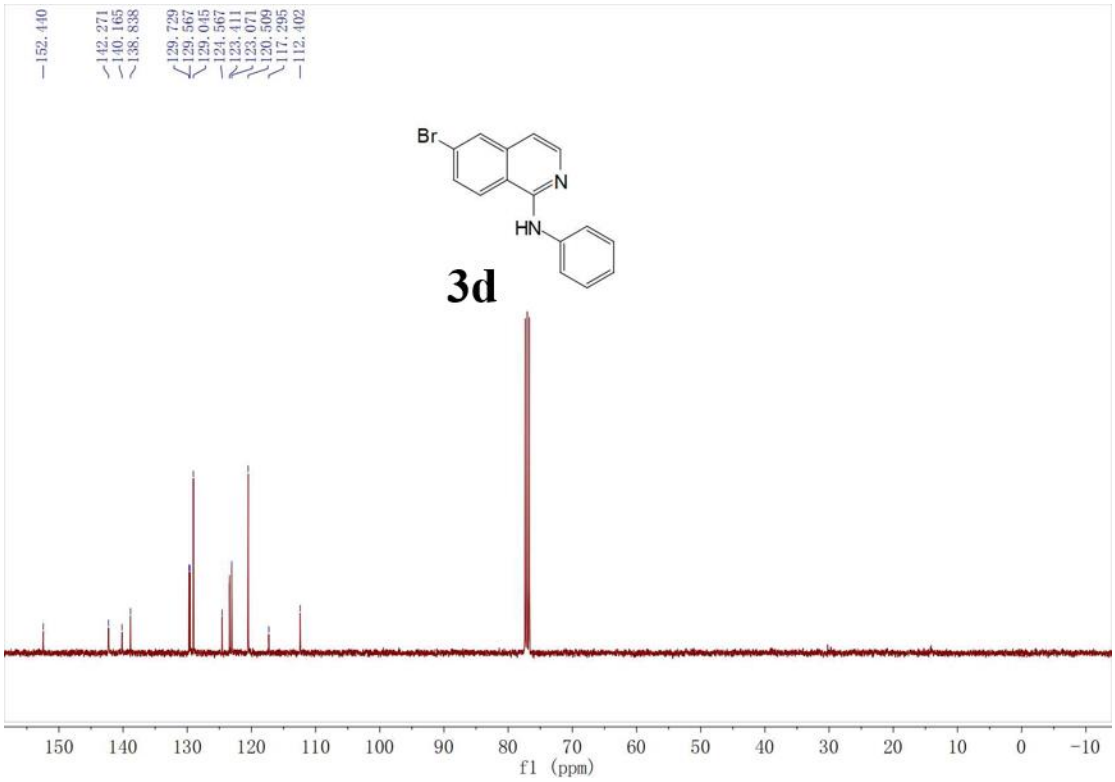
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3c



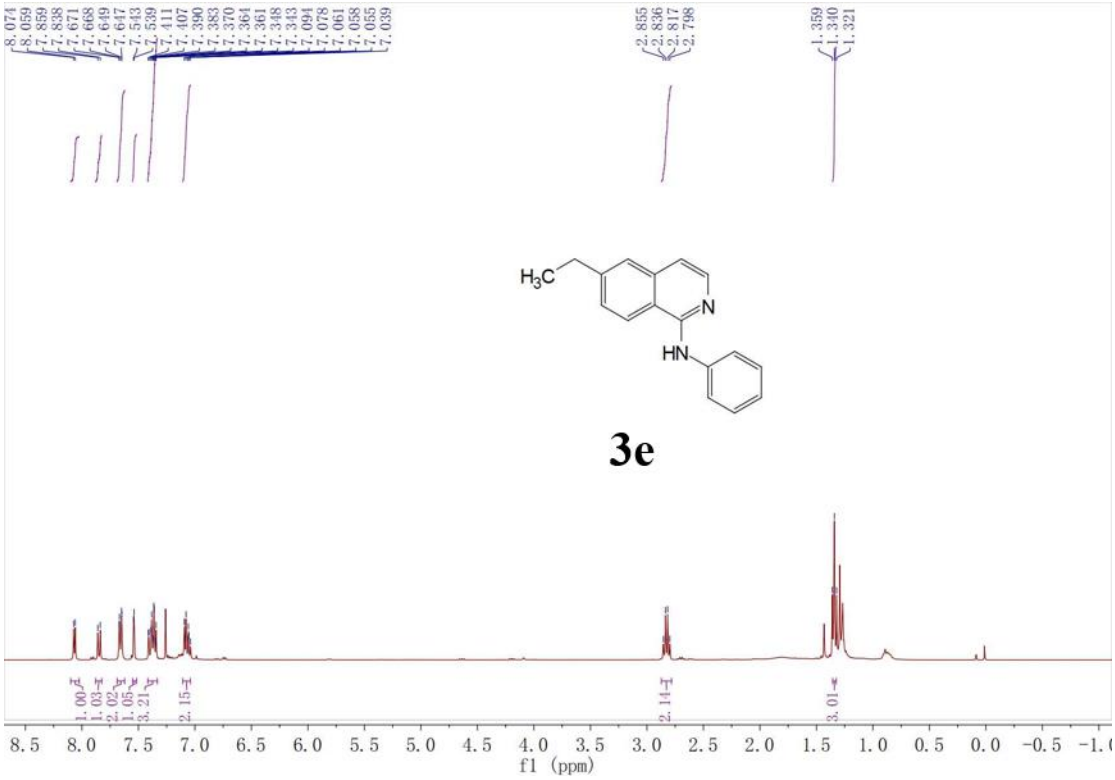
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3d



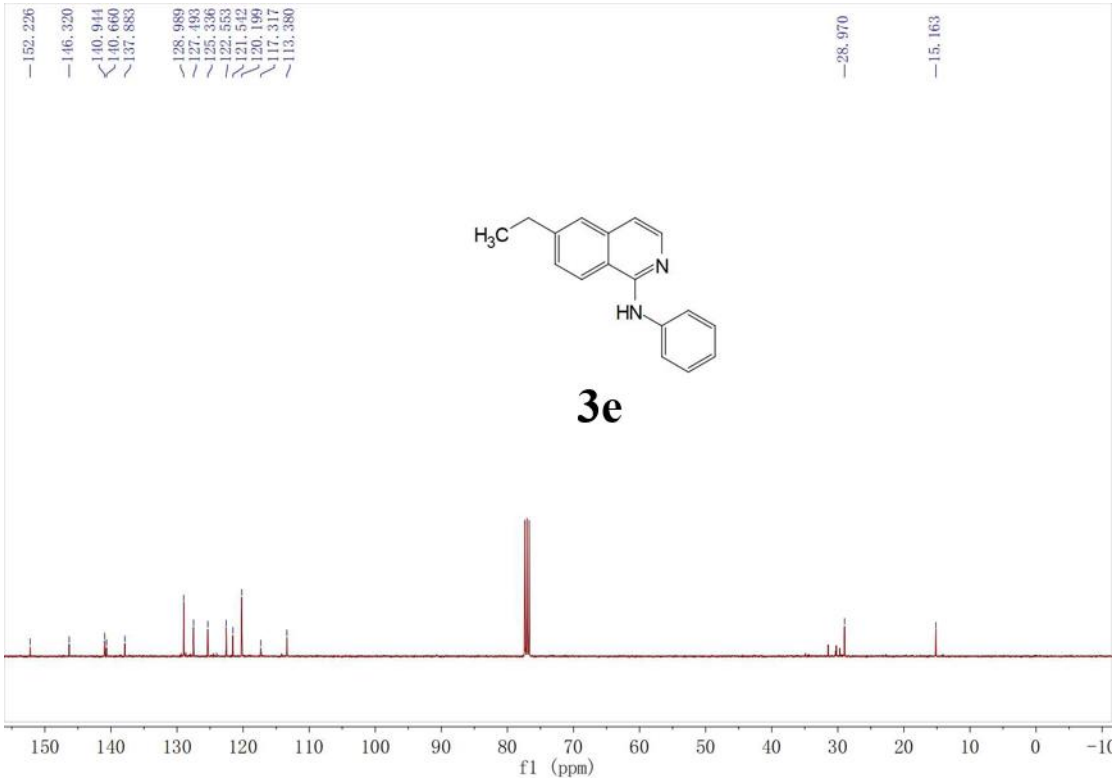
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3d



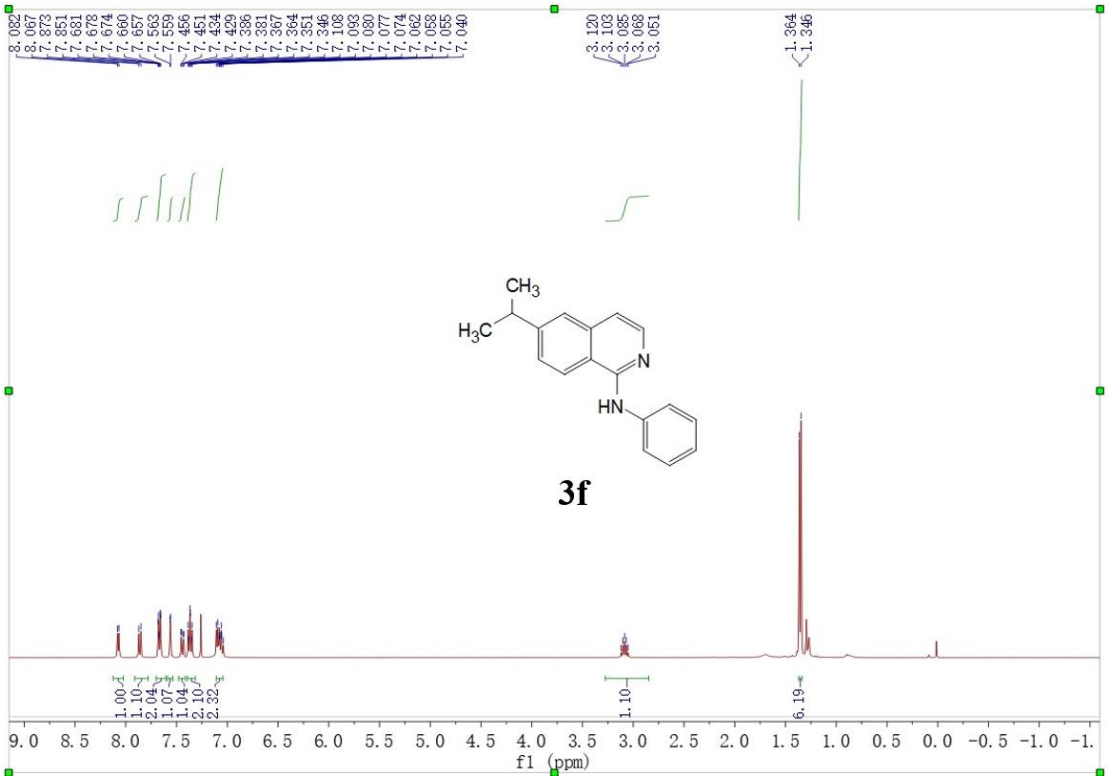
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3e



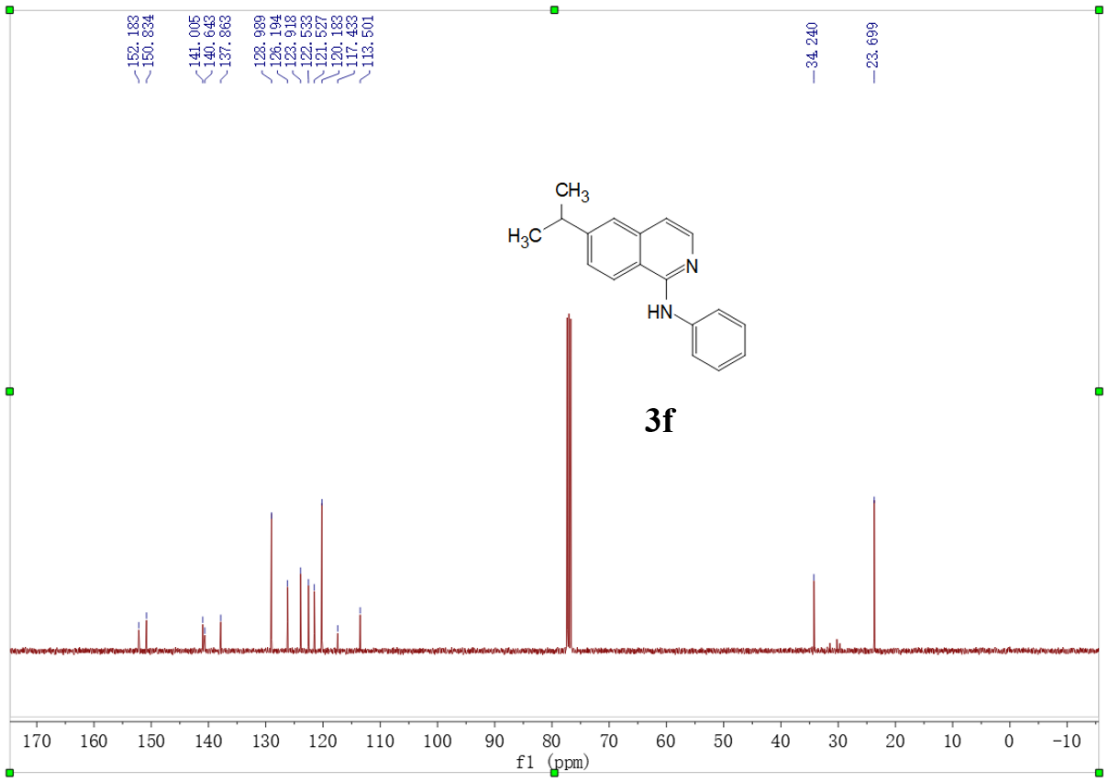
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3e



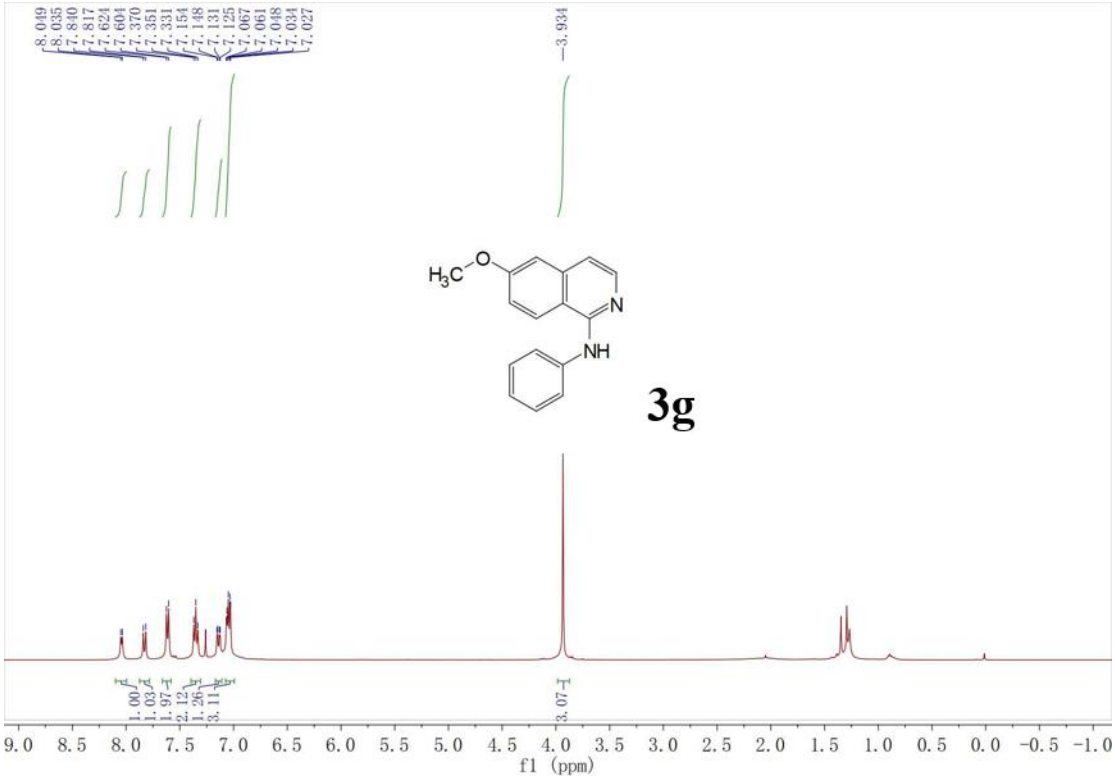
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3f



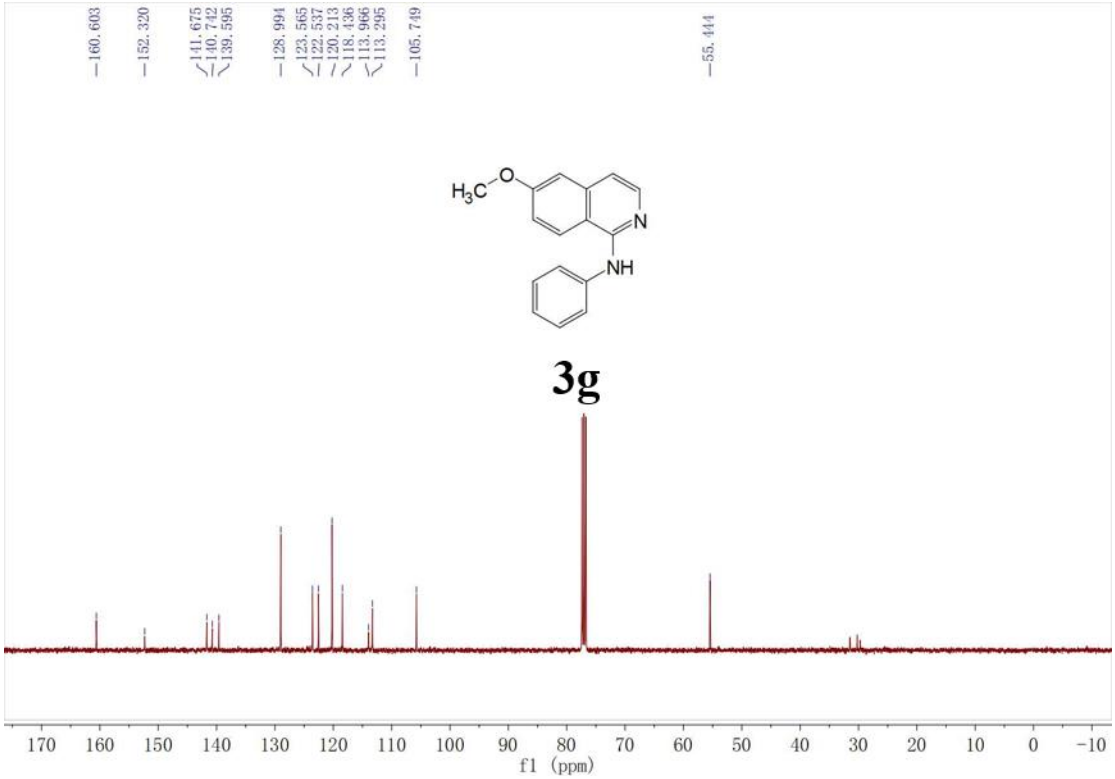
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3f



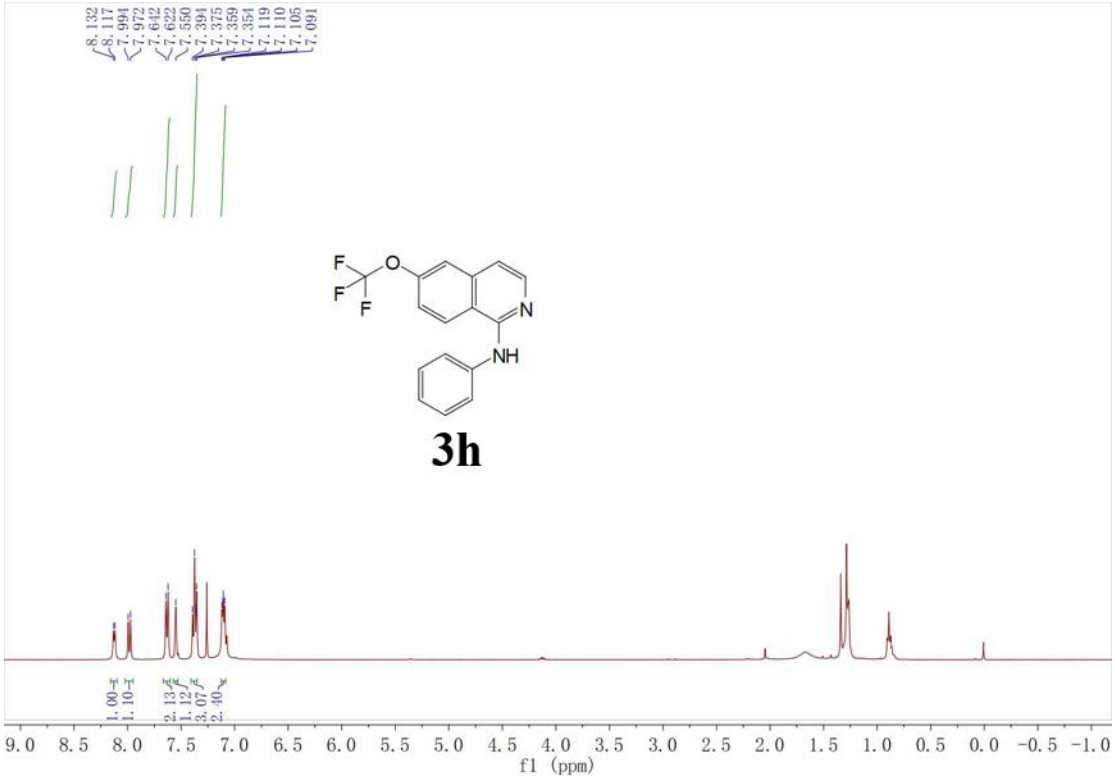
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3g



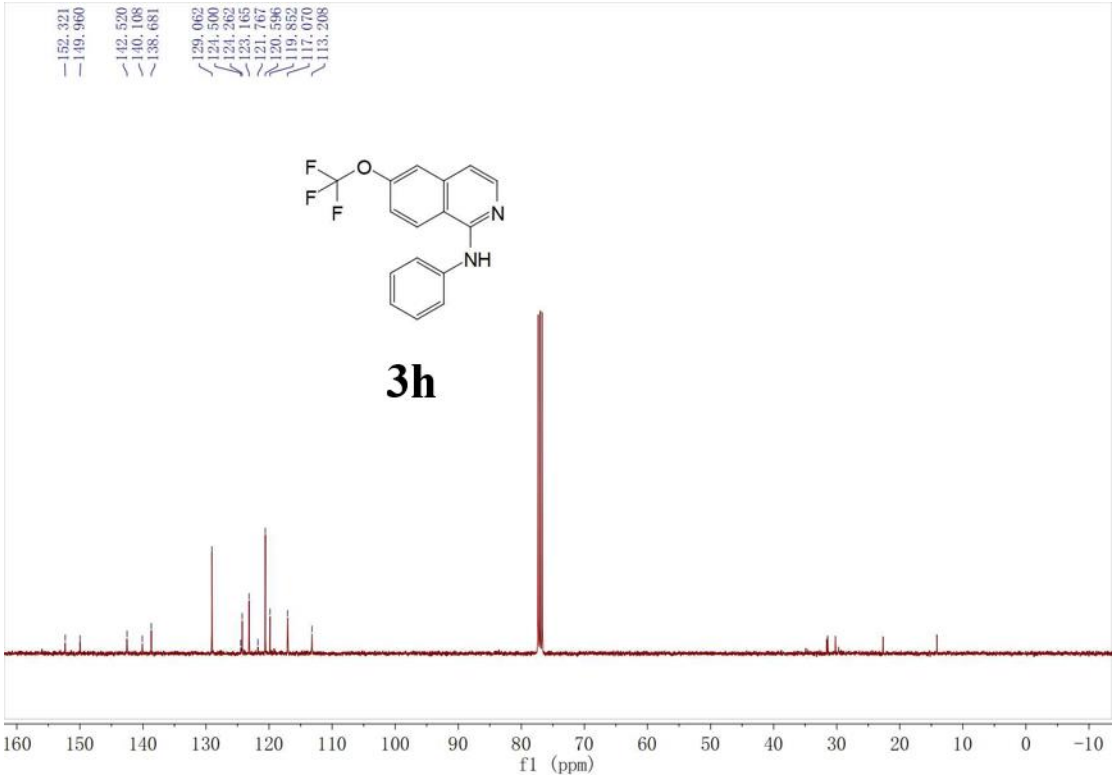
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3g



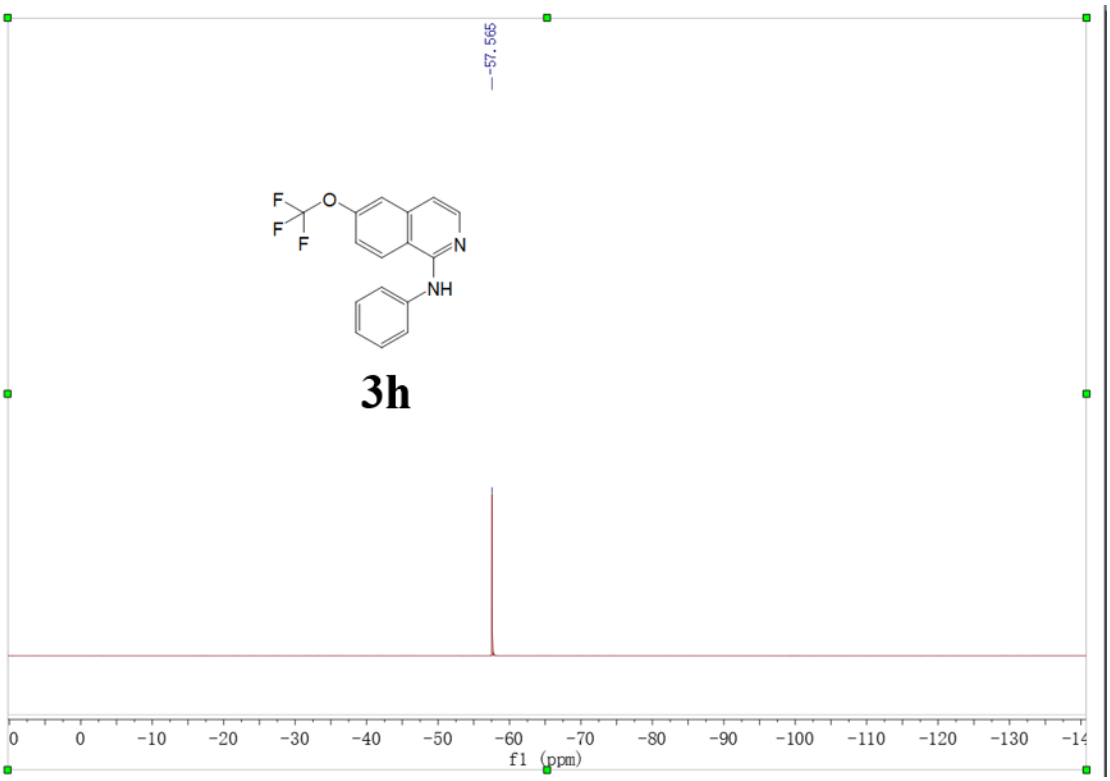
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3h



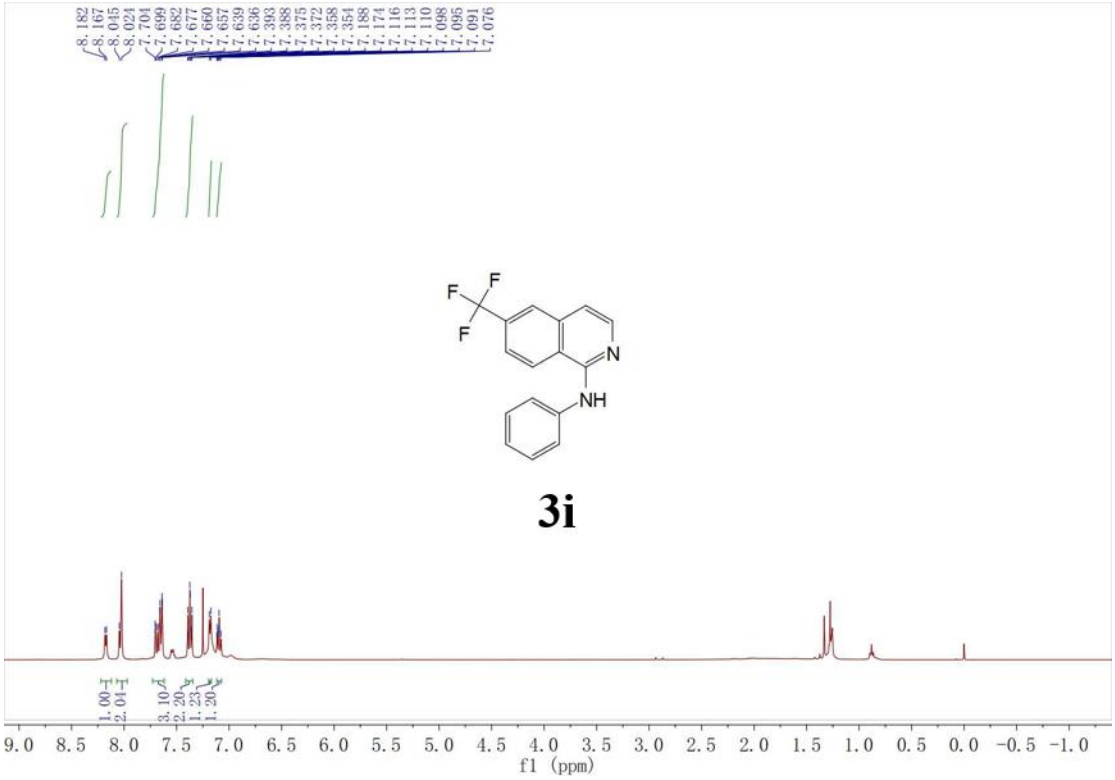
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3h



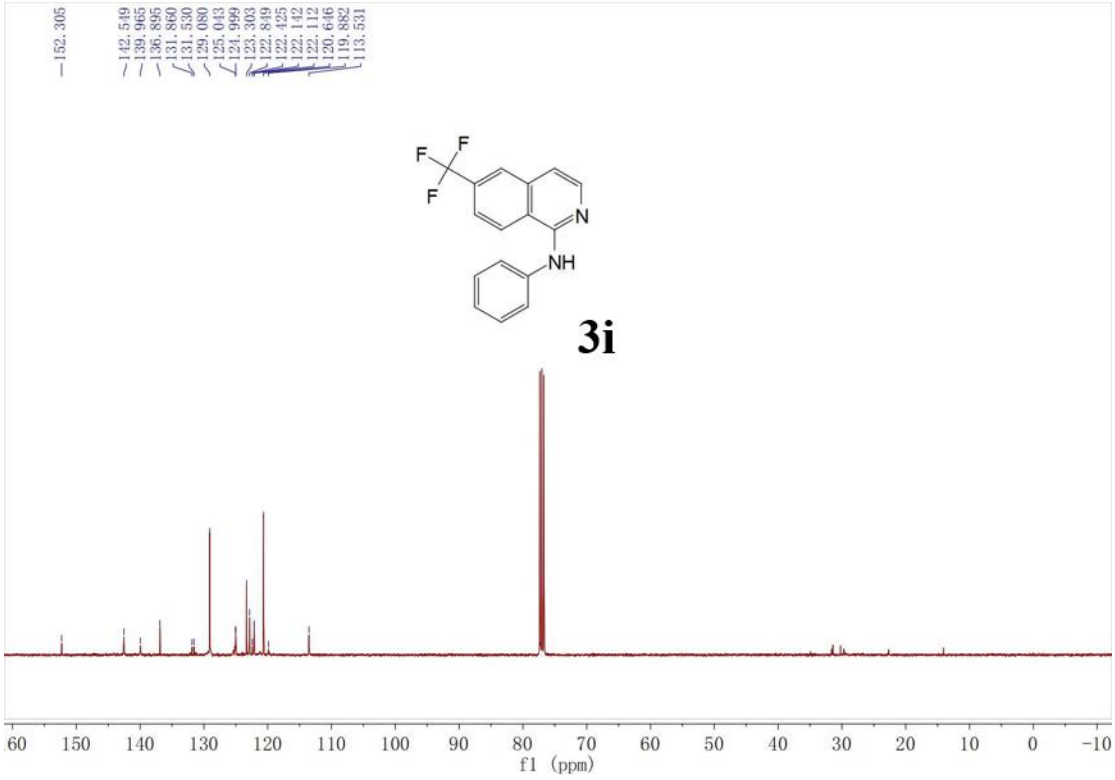
^{19}F NMR (377 MHz,CDCl3) spectrum of compound 3h



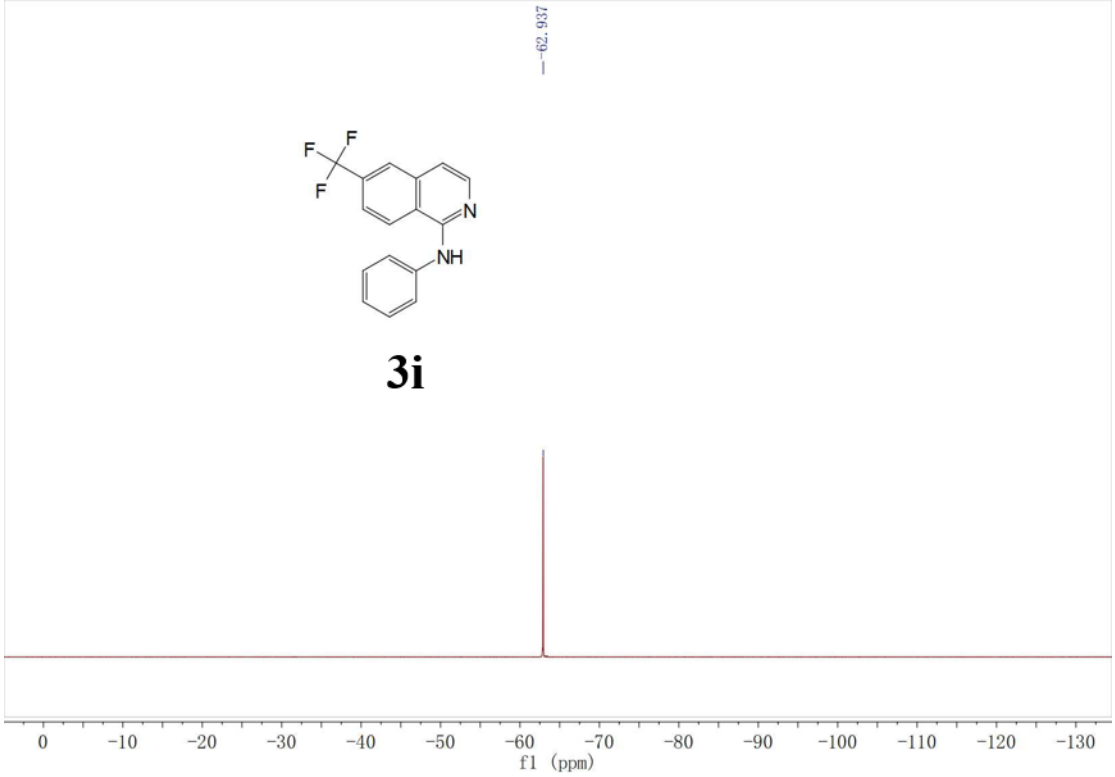
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3i



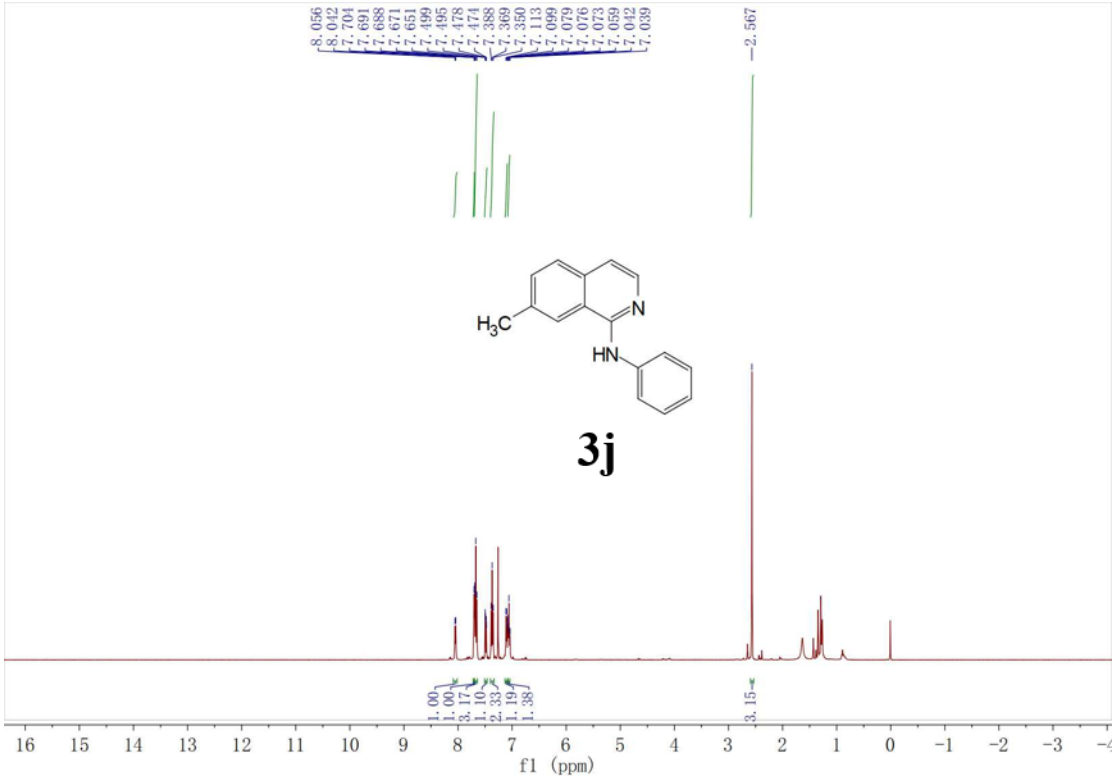
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3i



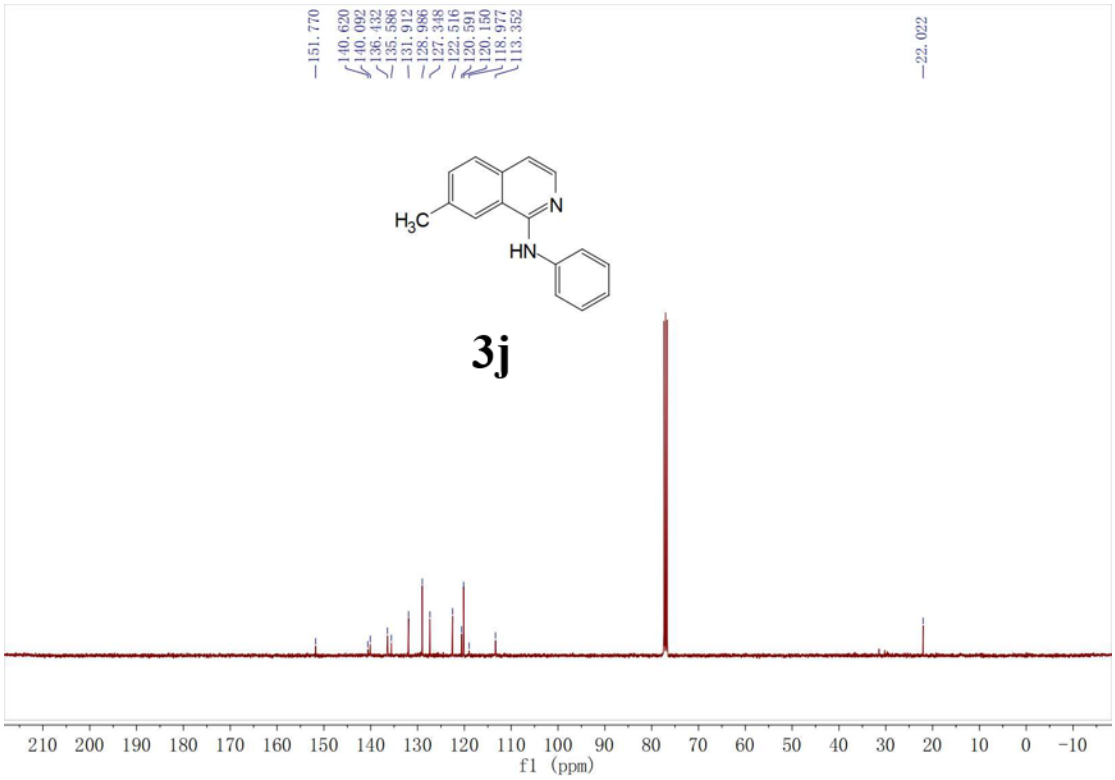
^{19}F NMR (377 MHz,CDCl3) spectrum of compound 3i



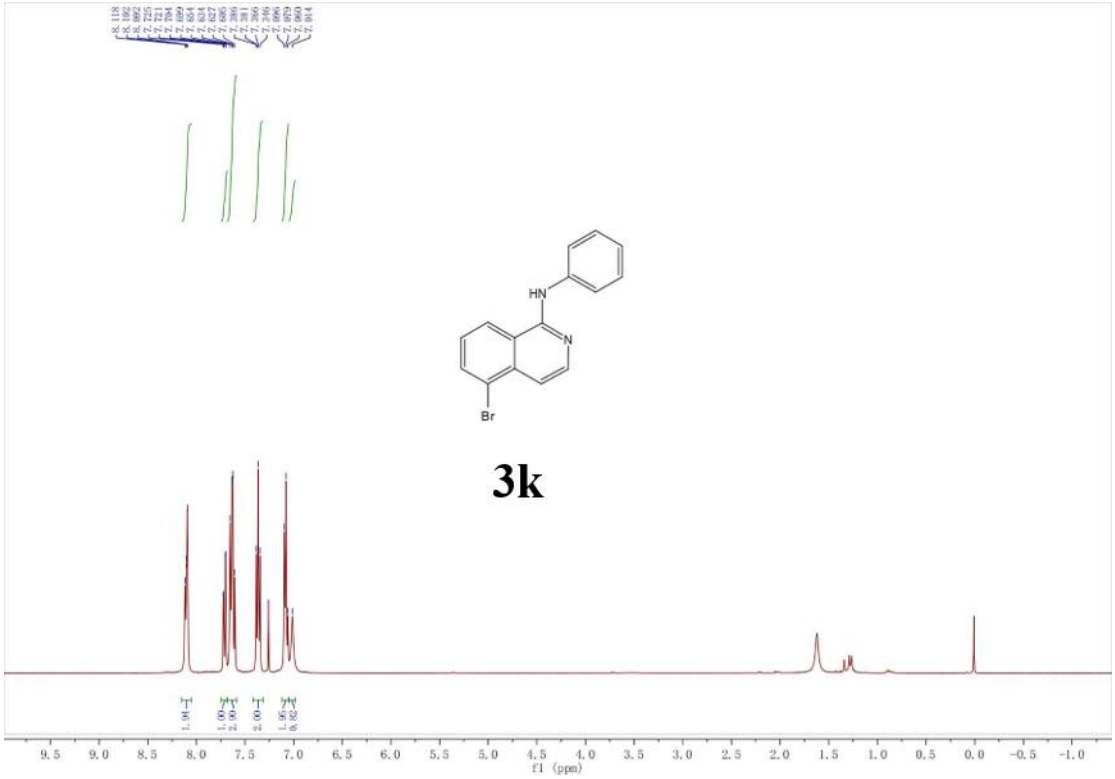
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3j



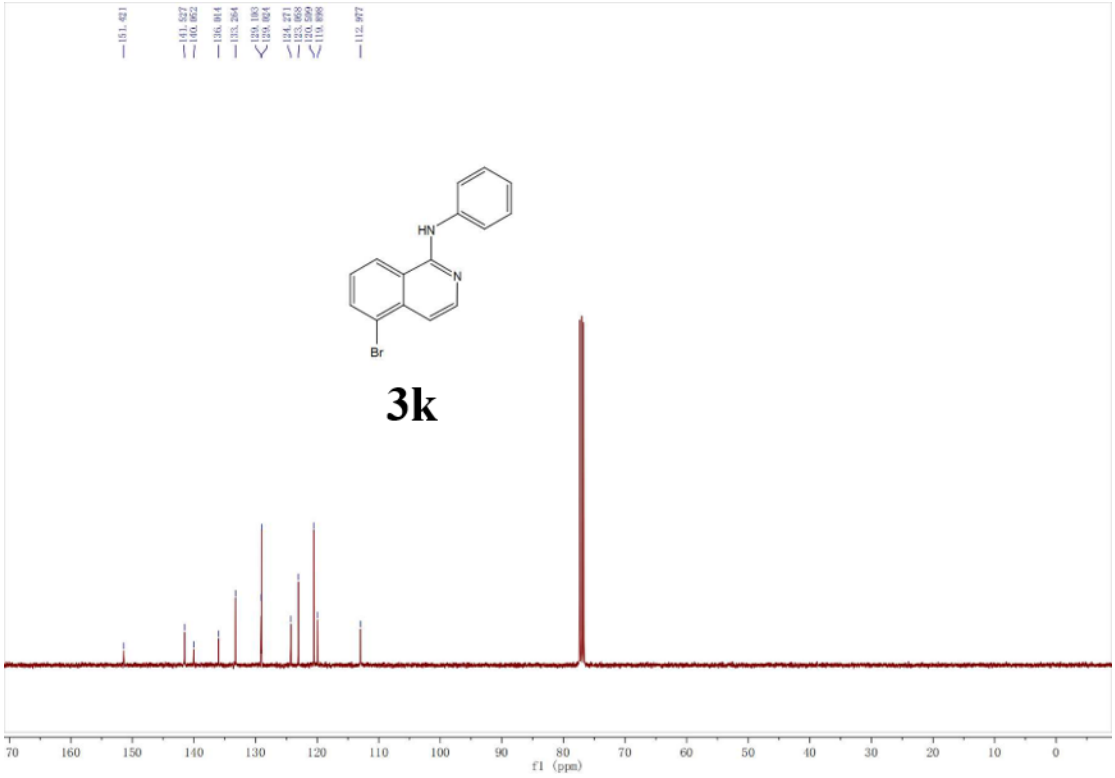
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3j



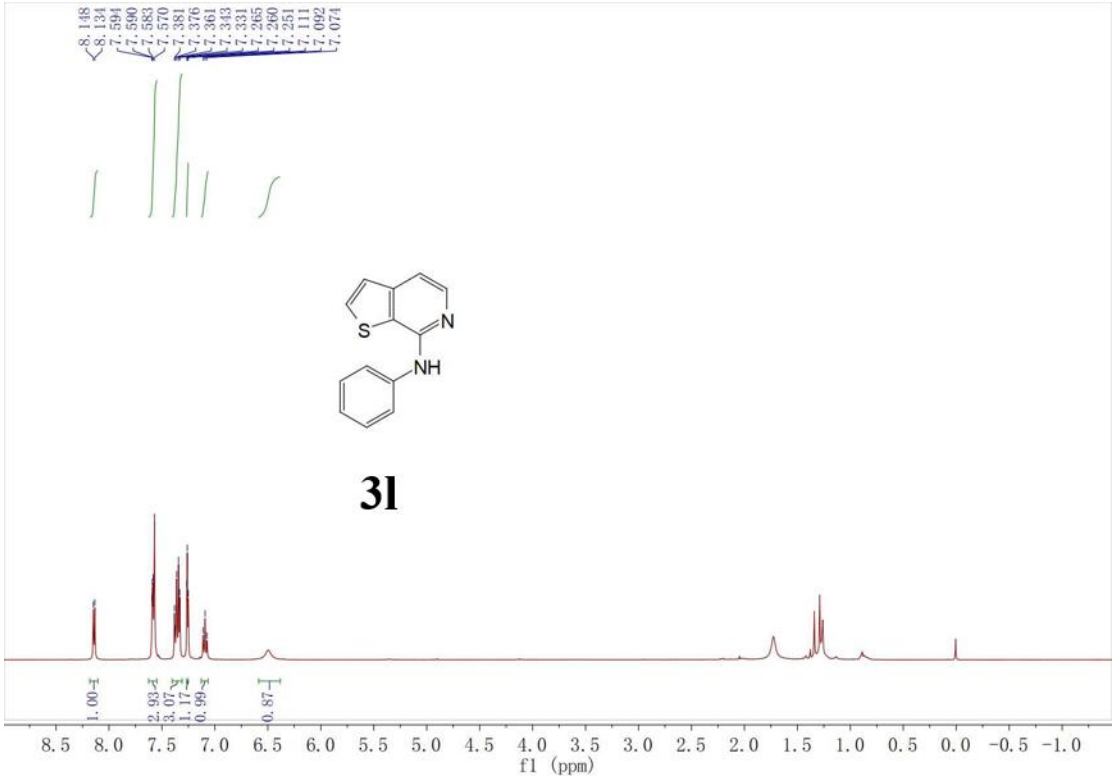
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3k



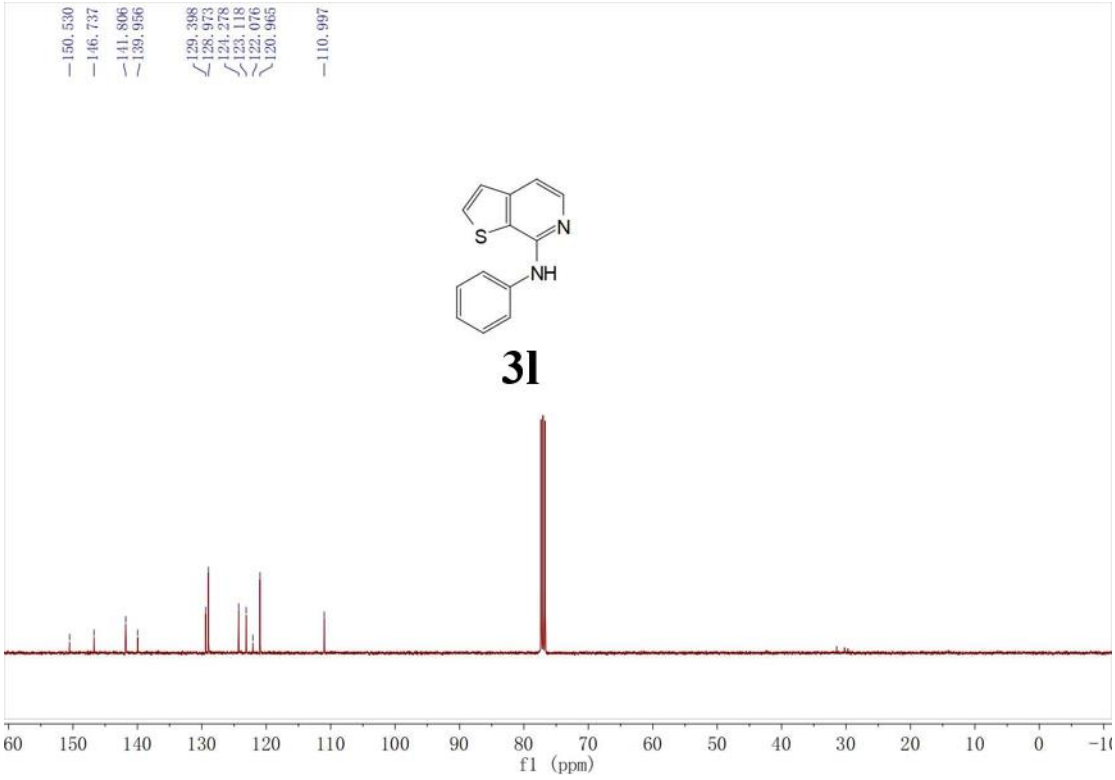
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3k



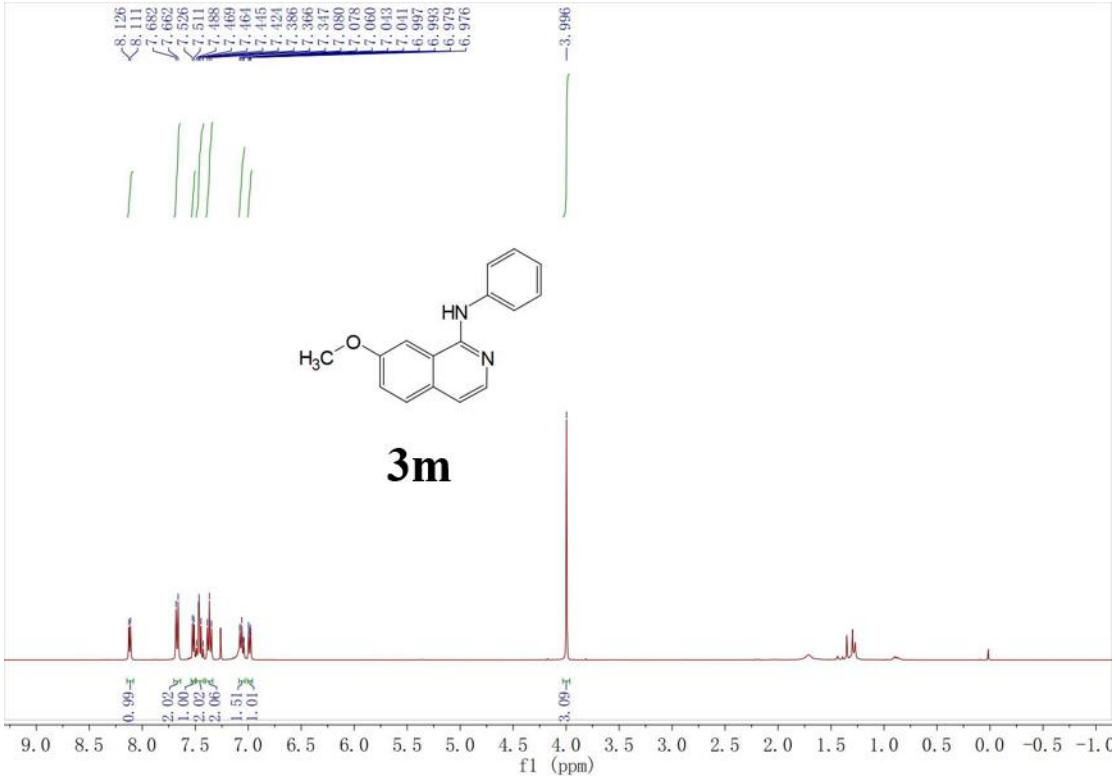
H NMR (400 MHz, CDCl3) spectrum of compound 3l



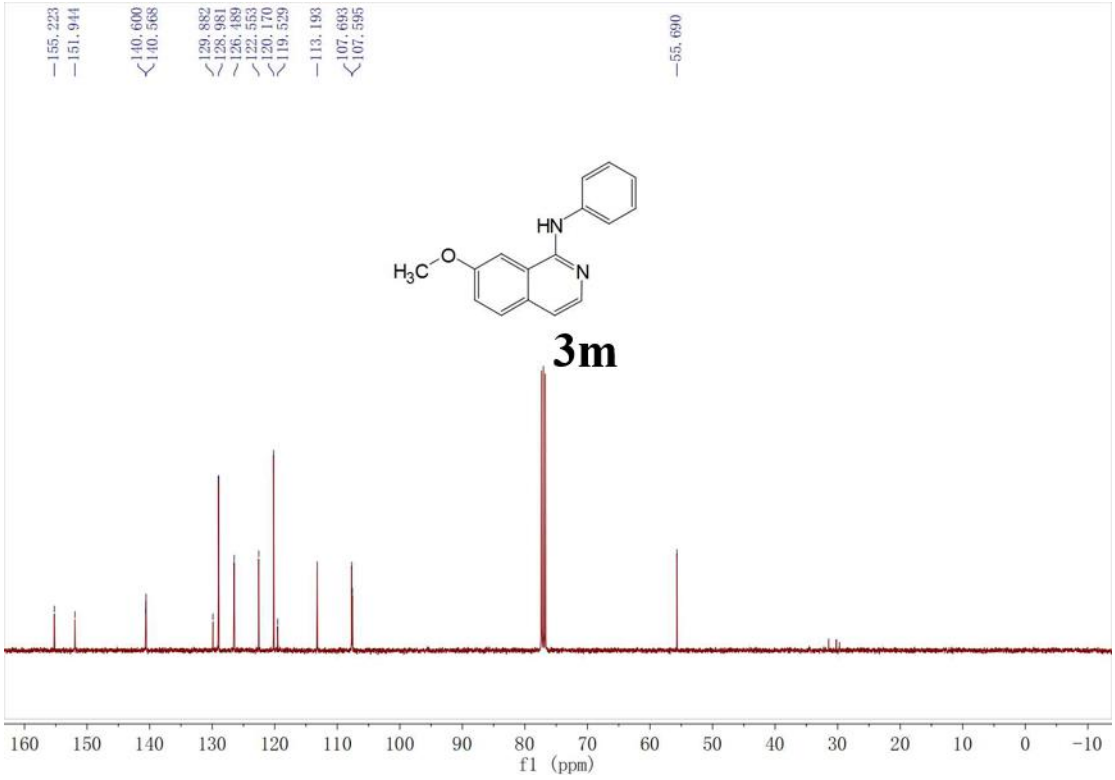
$^{13}C\{^{1}H\}$ NMR (101 MHz, CDCl3) spectrum of compound 3l



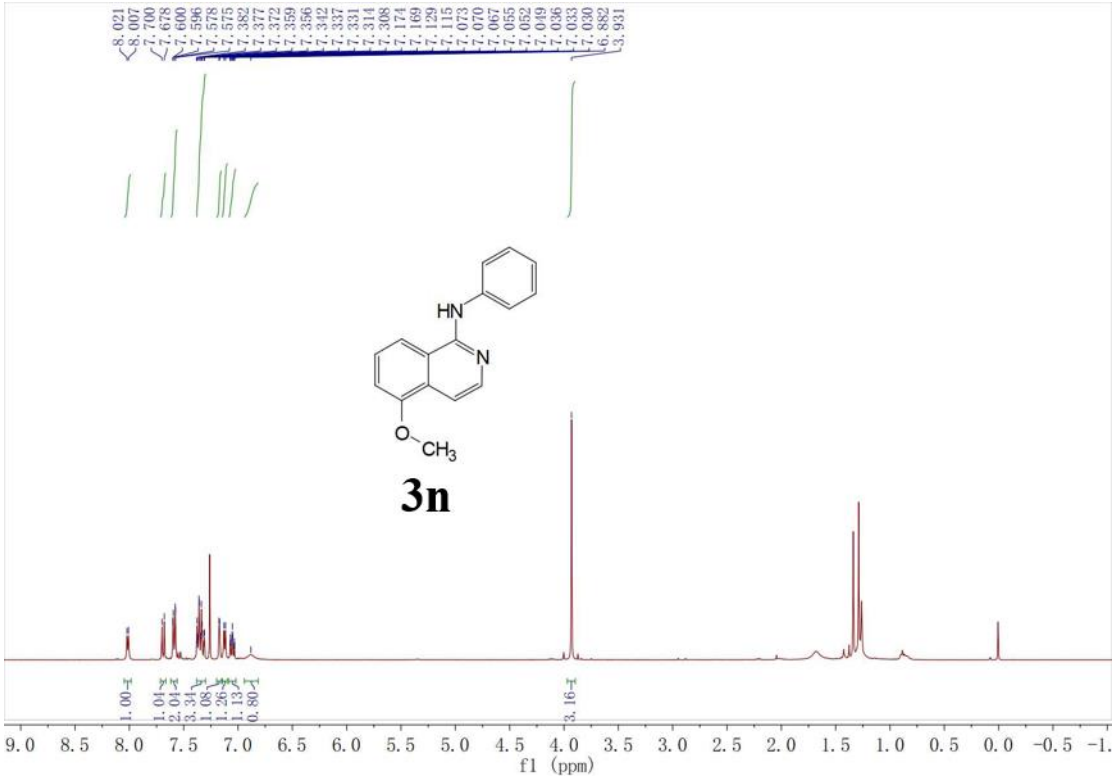
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3m



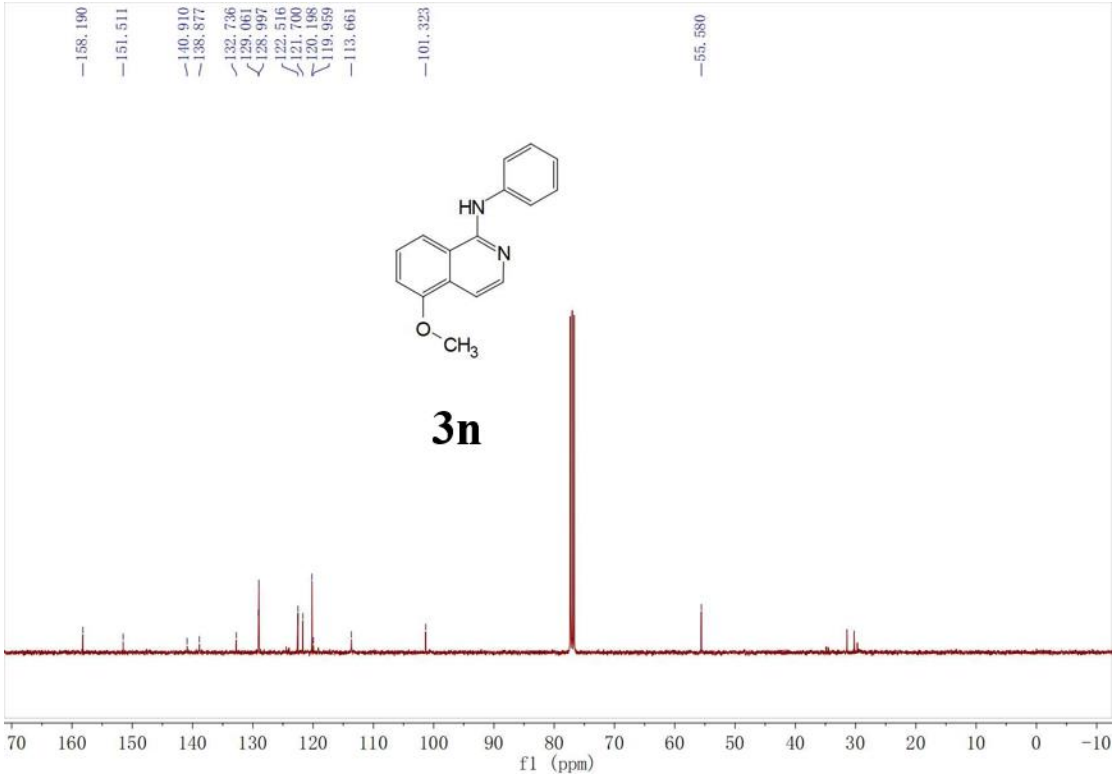
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3m



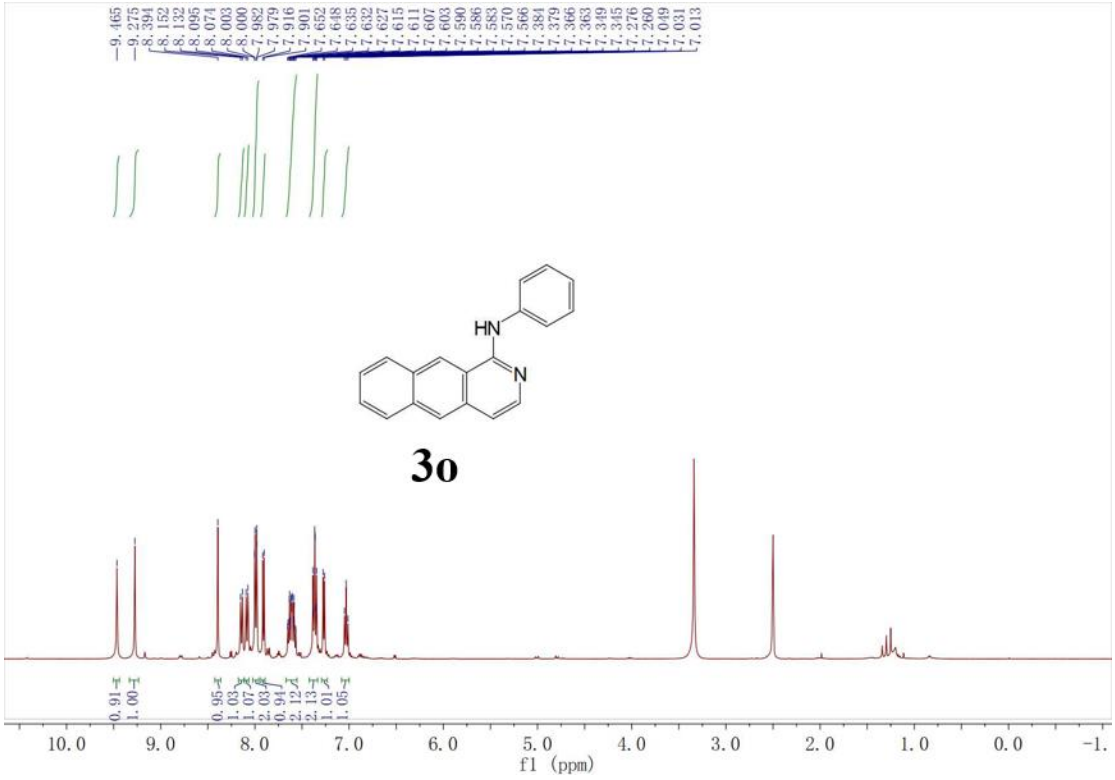
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3n



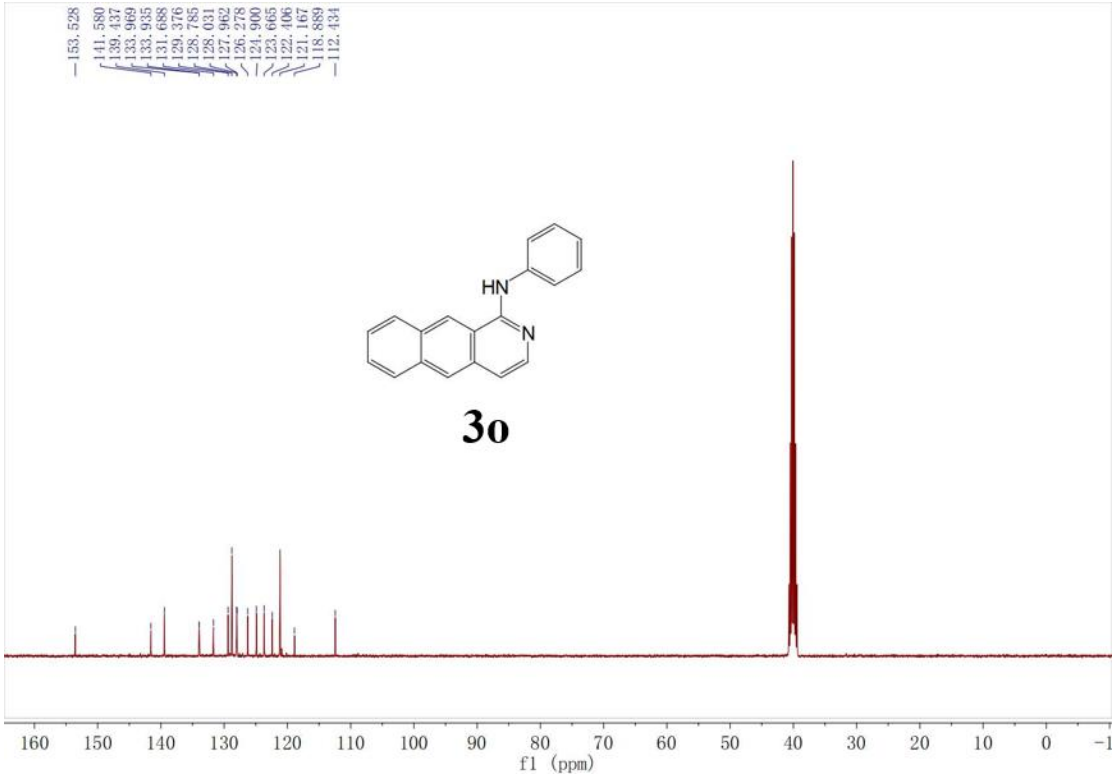
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3n



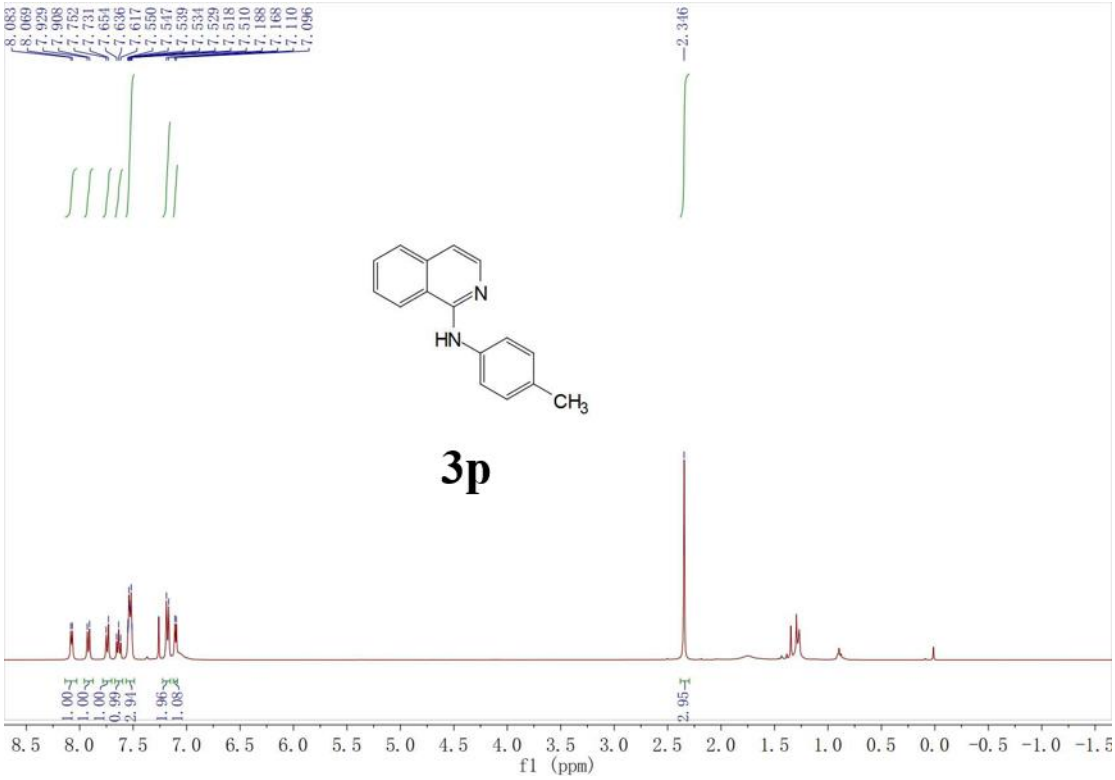
^{1}H NMR (400 MHz, DMSO-*d*$_6$) spectrum of compound 3o



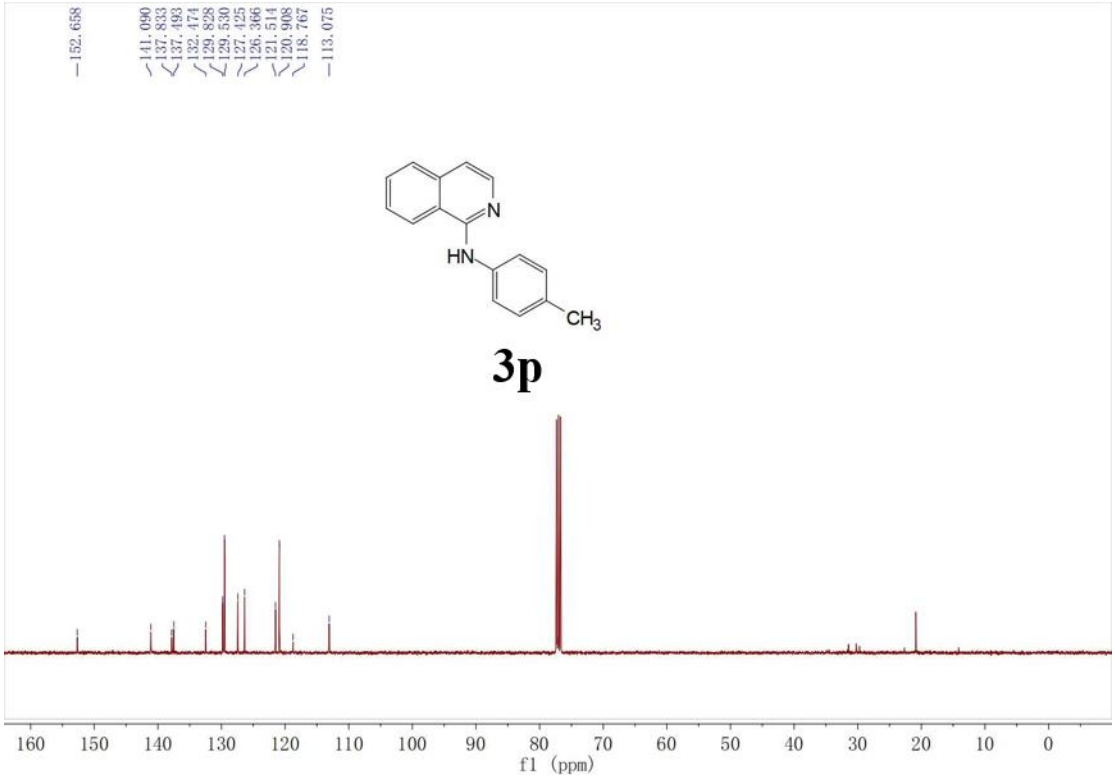
^{13}C{^{1}H} NMR (101 MHz, DMSO-*d*$_6$) spectrum of compound 3o



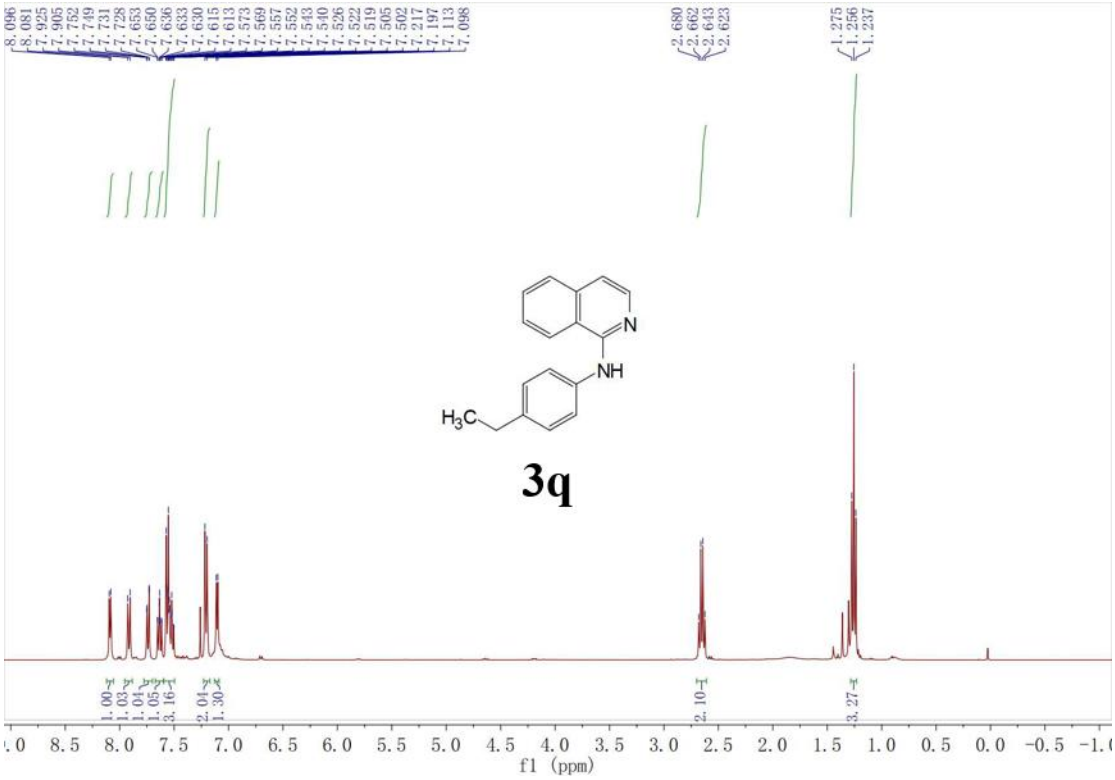
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3p



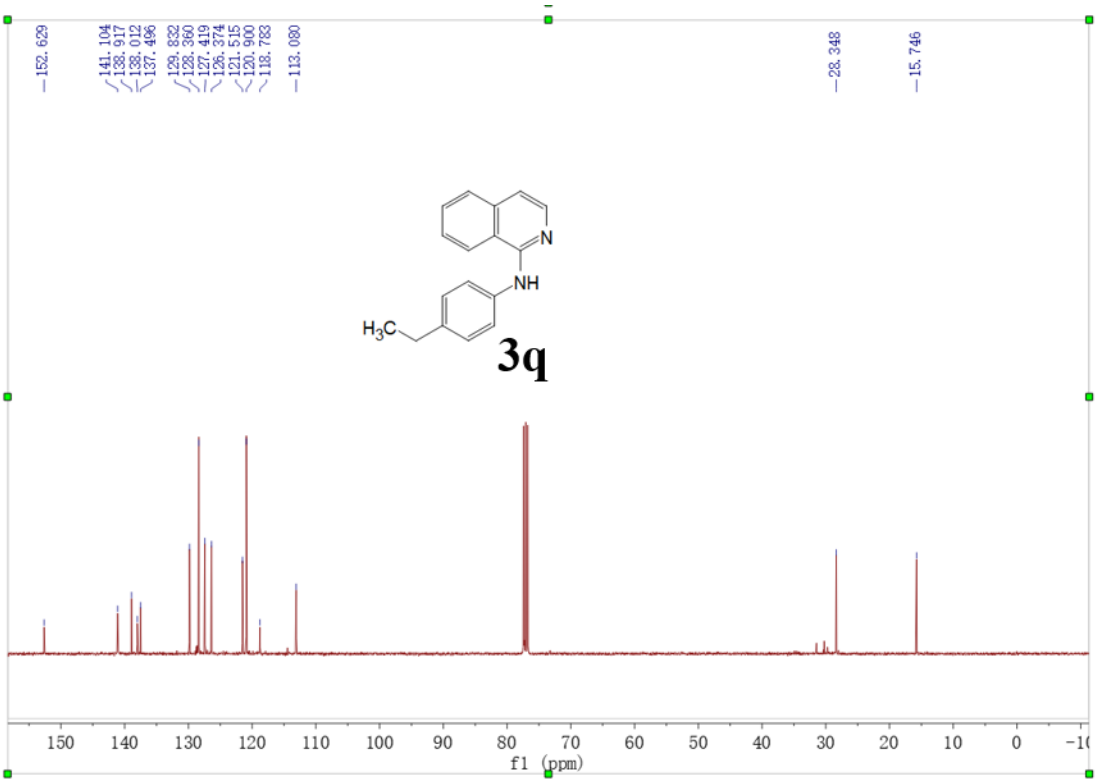
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3p



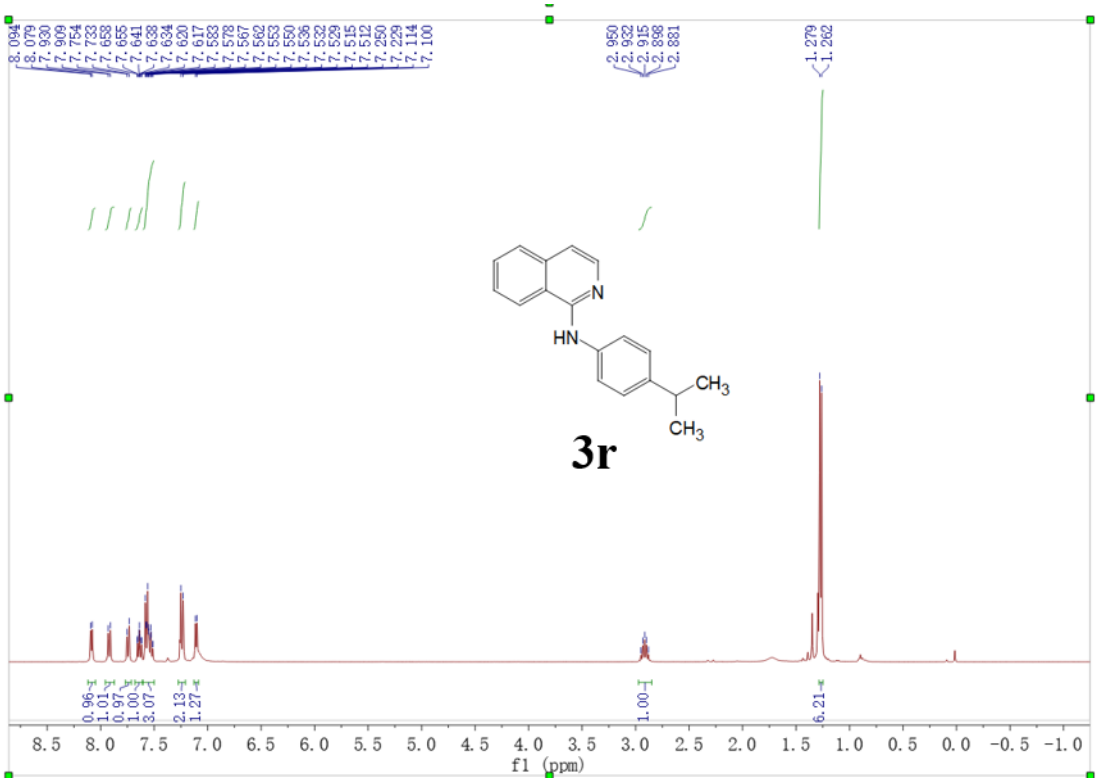
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3q



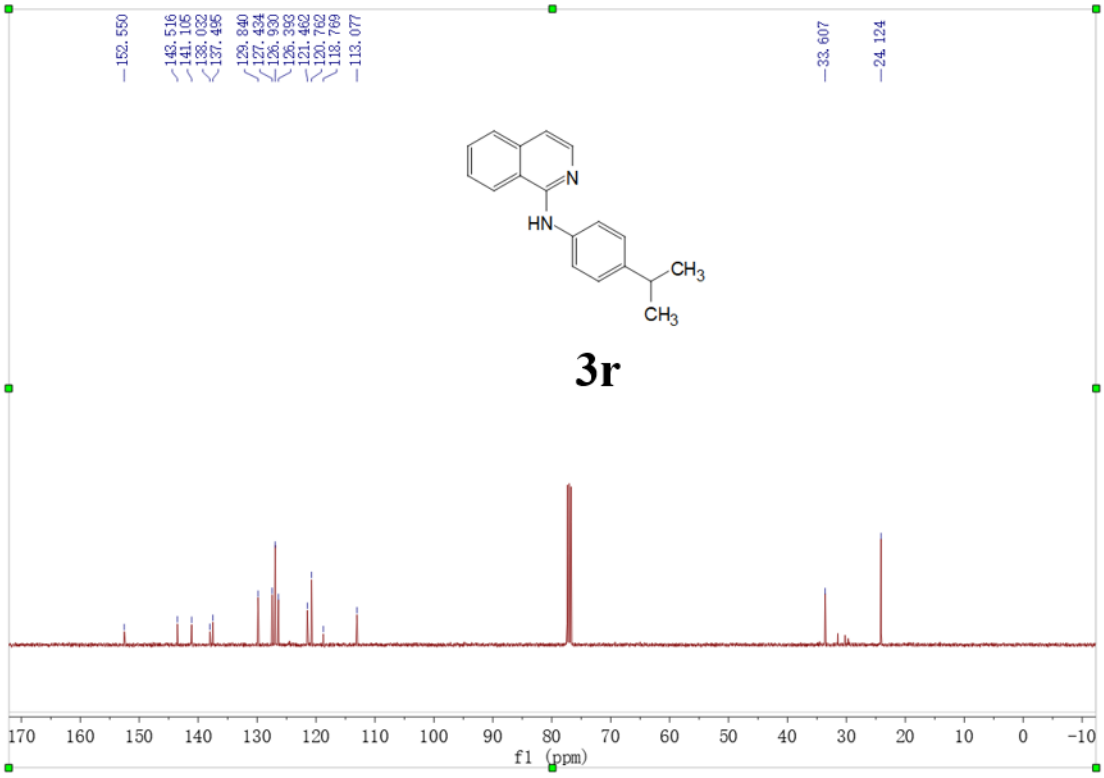
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3q



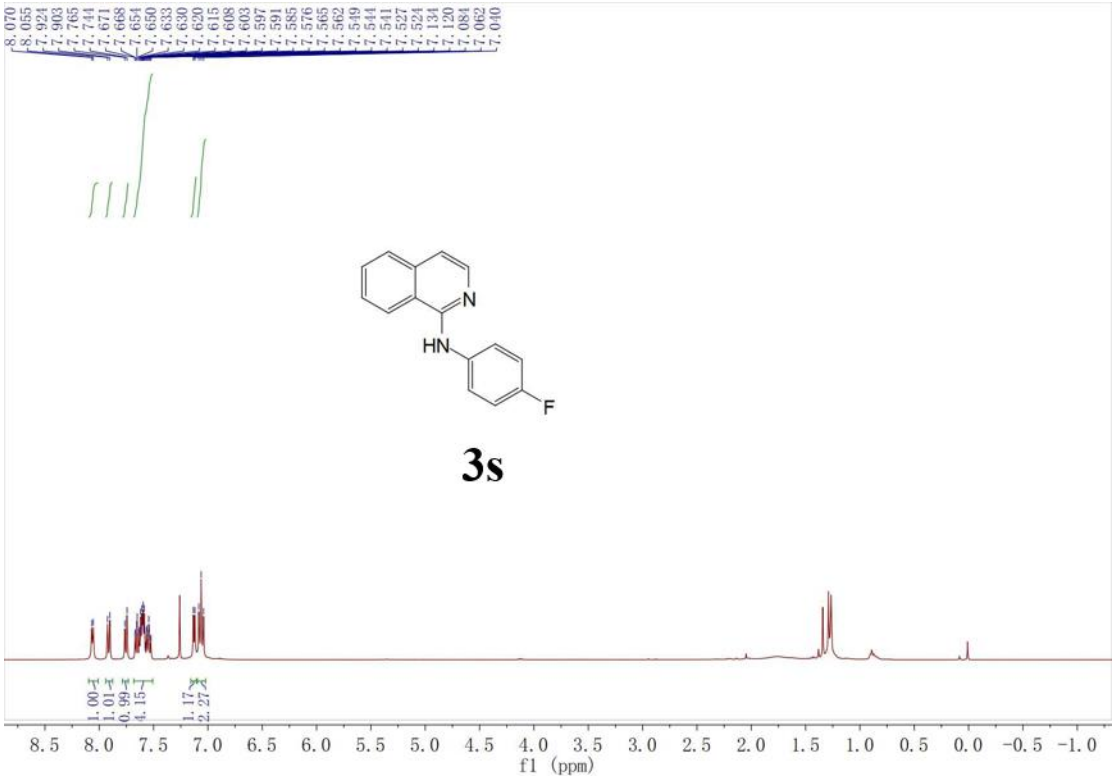
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3r



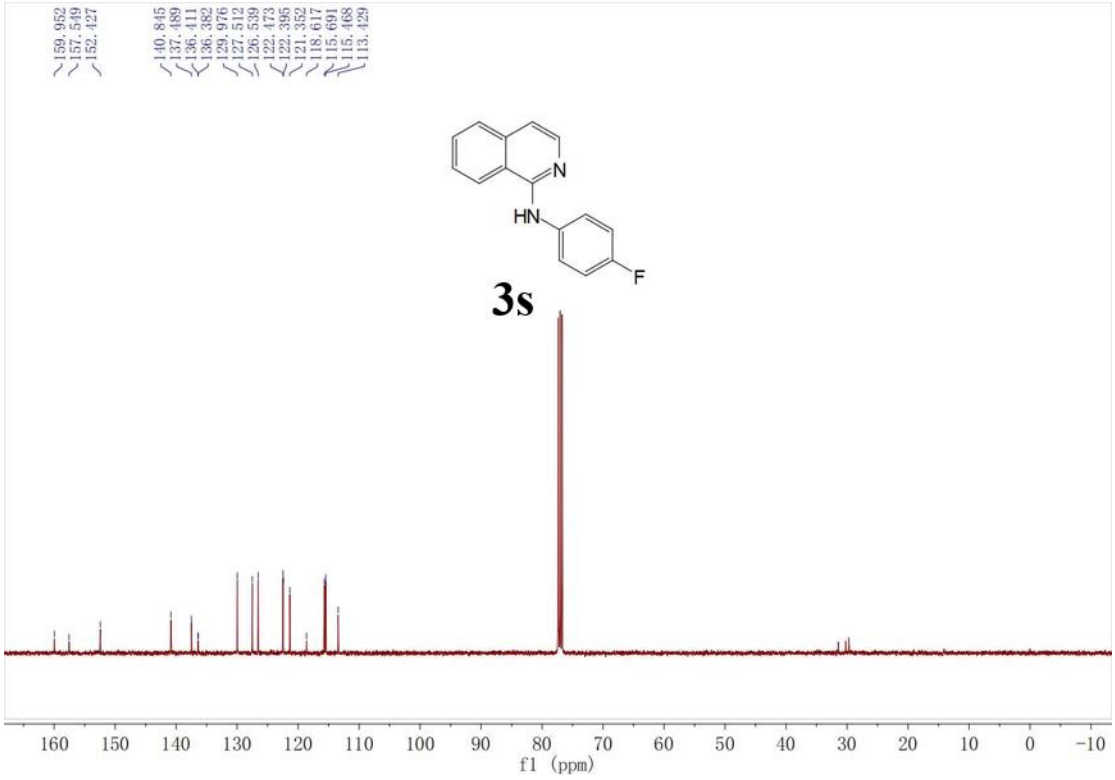
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3r



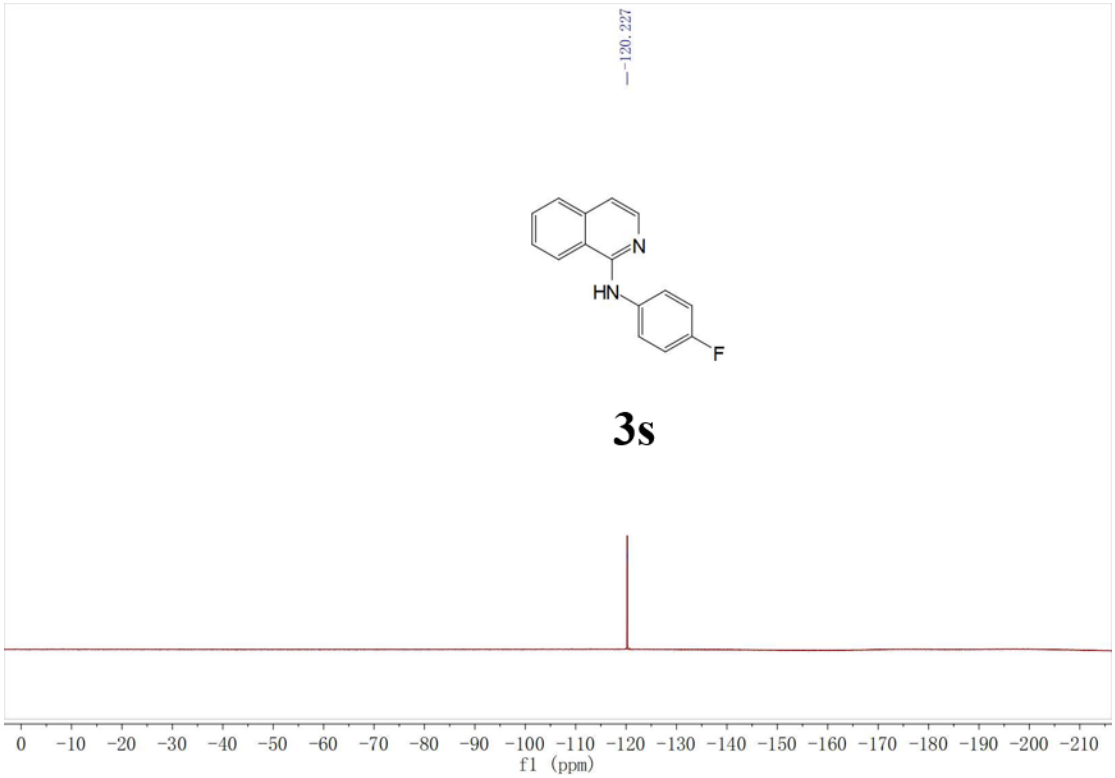
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3s



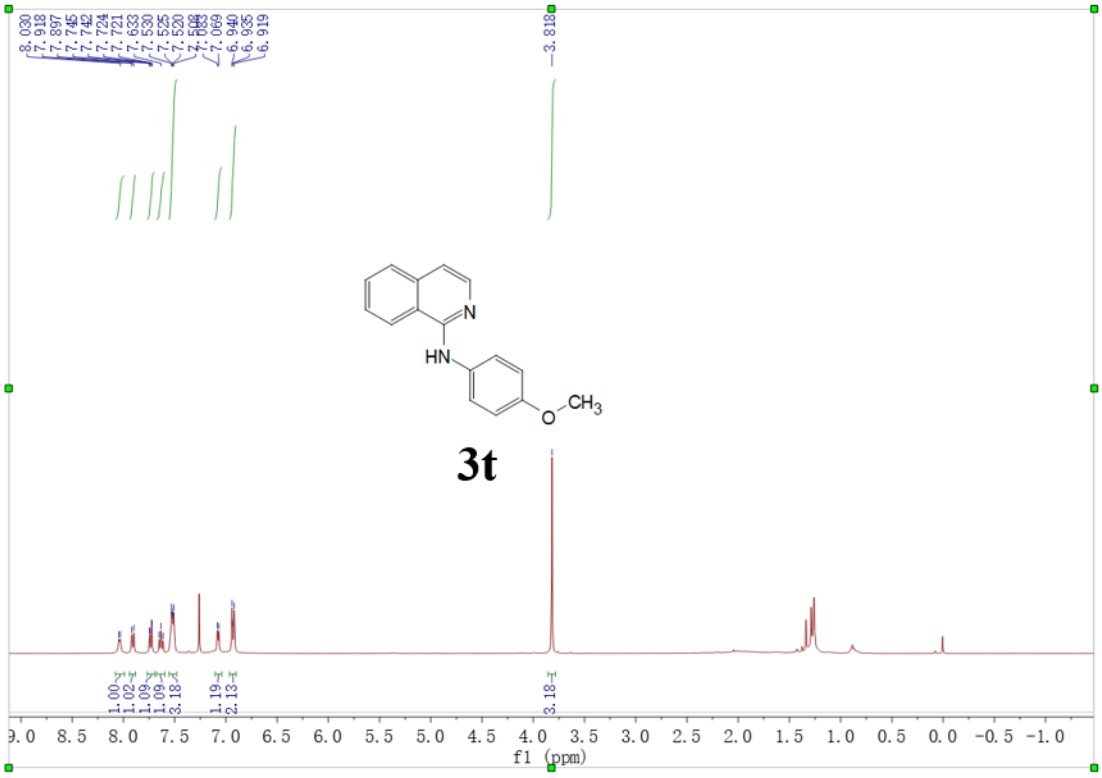
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3s



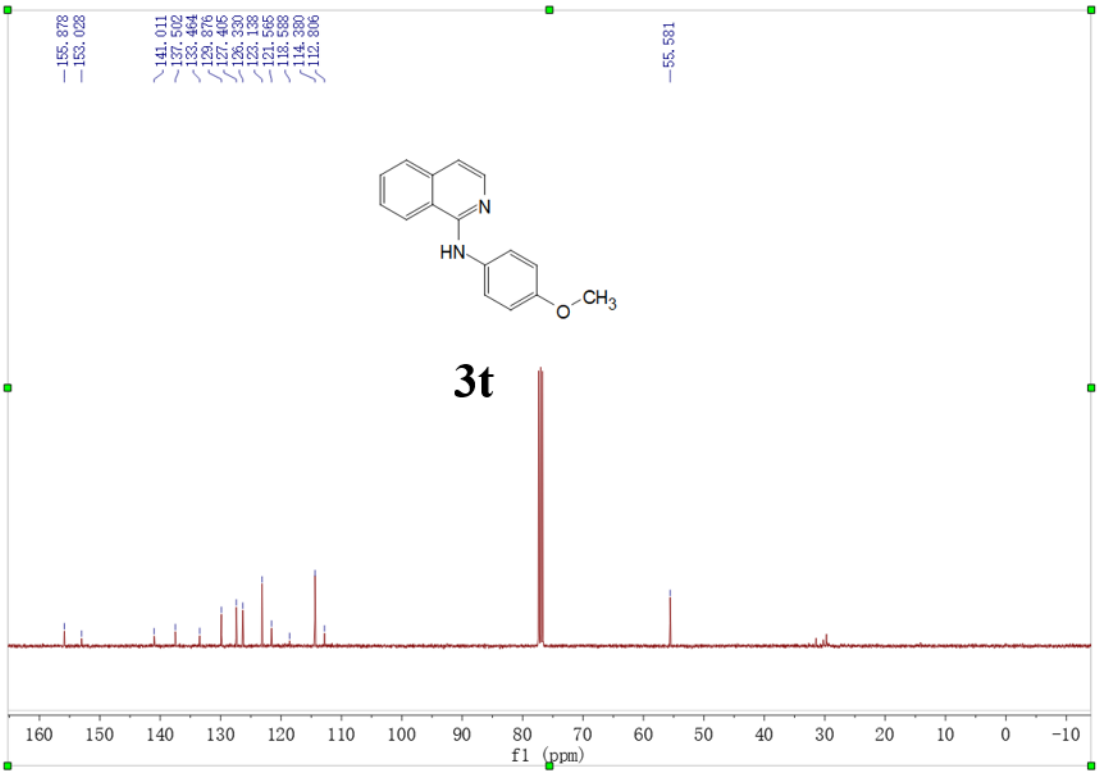
^{19}F NMR (377 MHz,CDCl3) spectrum of compound 3s



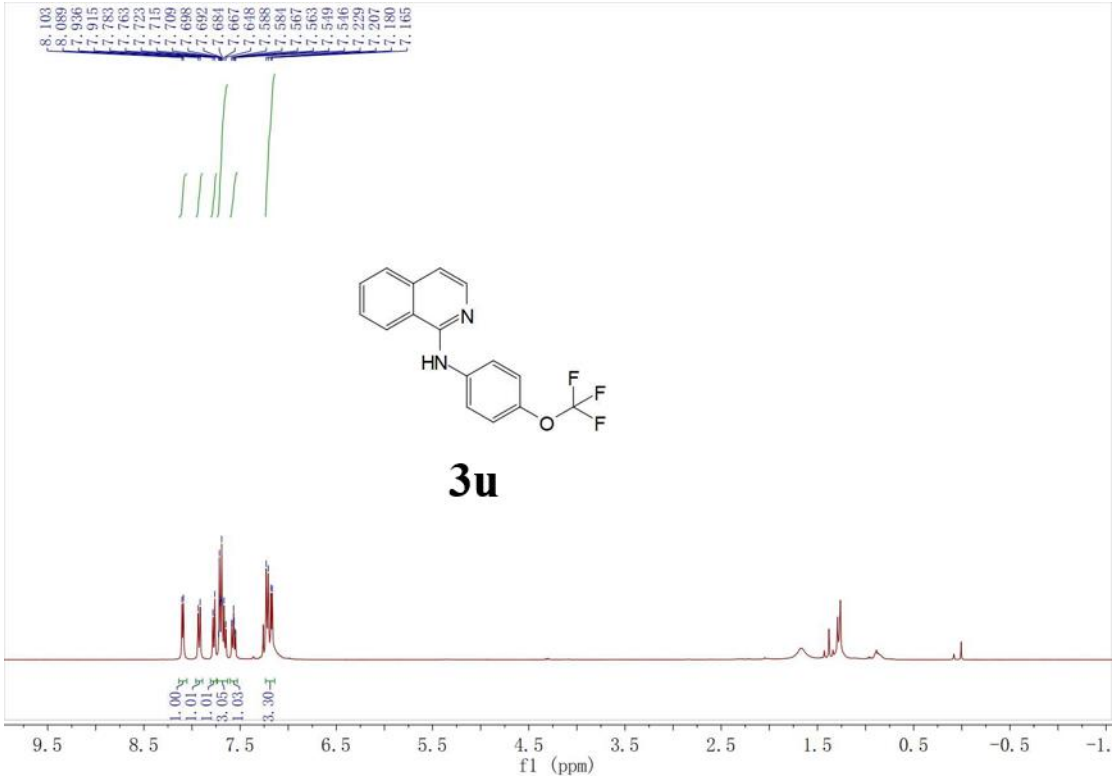
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3t



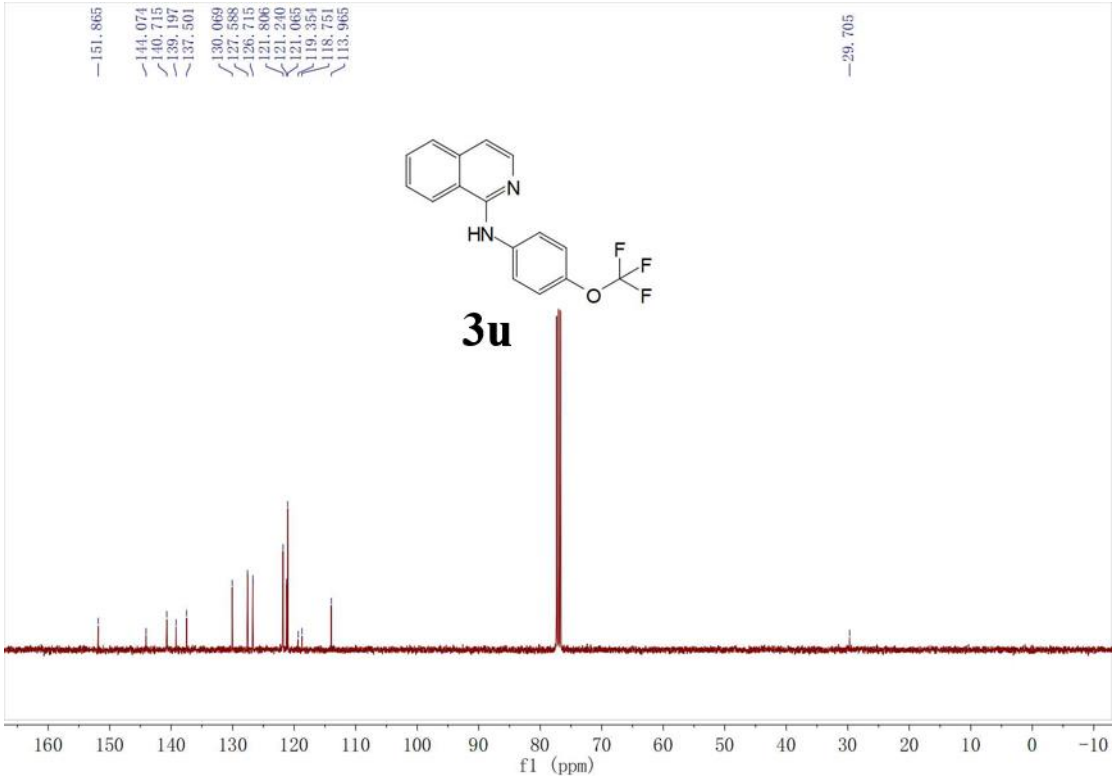
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3t



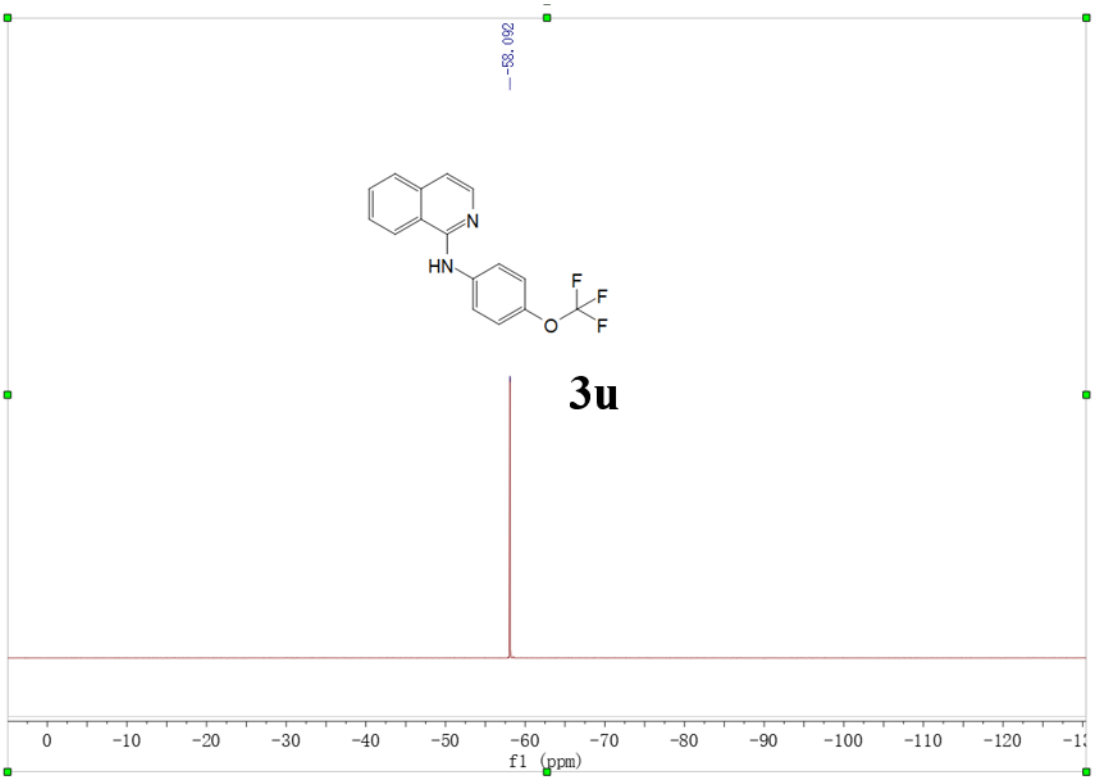
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3u



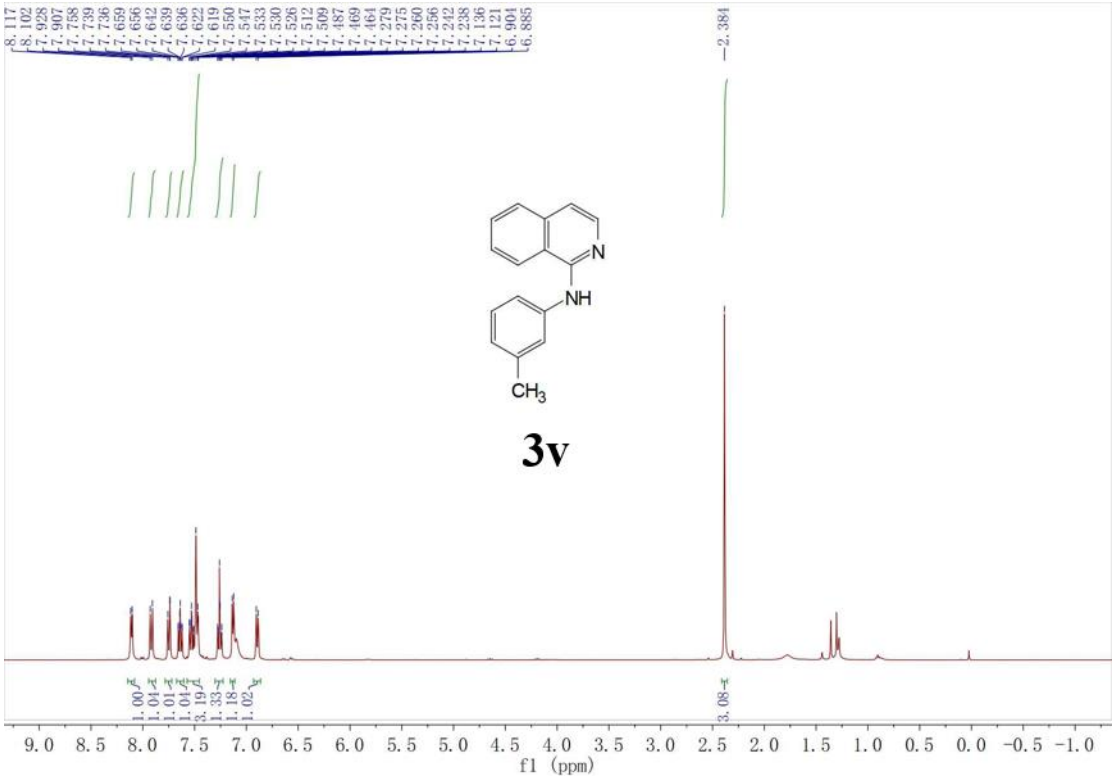
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3u



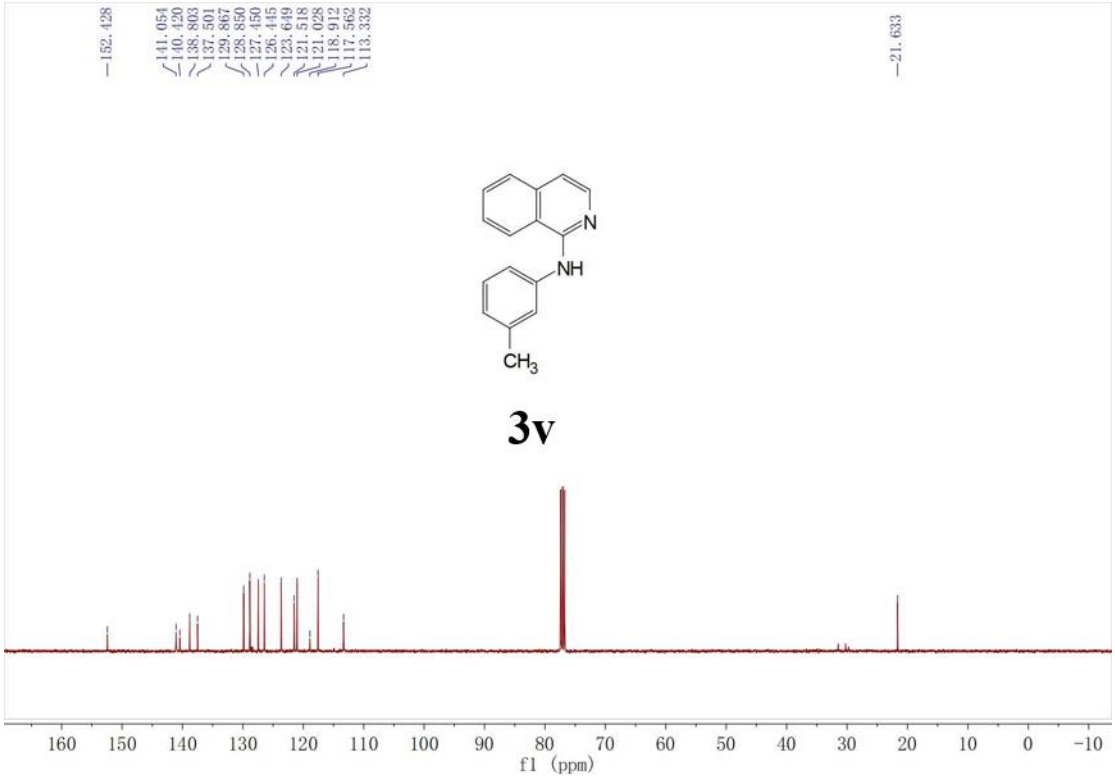
^{19}F NMR (377 MHz,CDCl3) spectrum of compound 3u



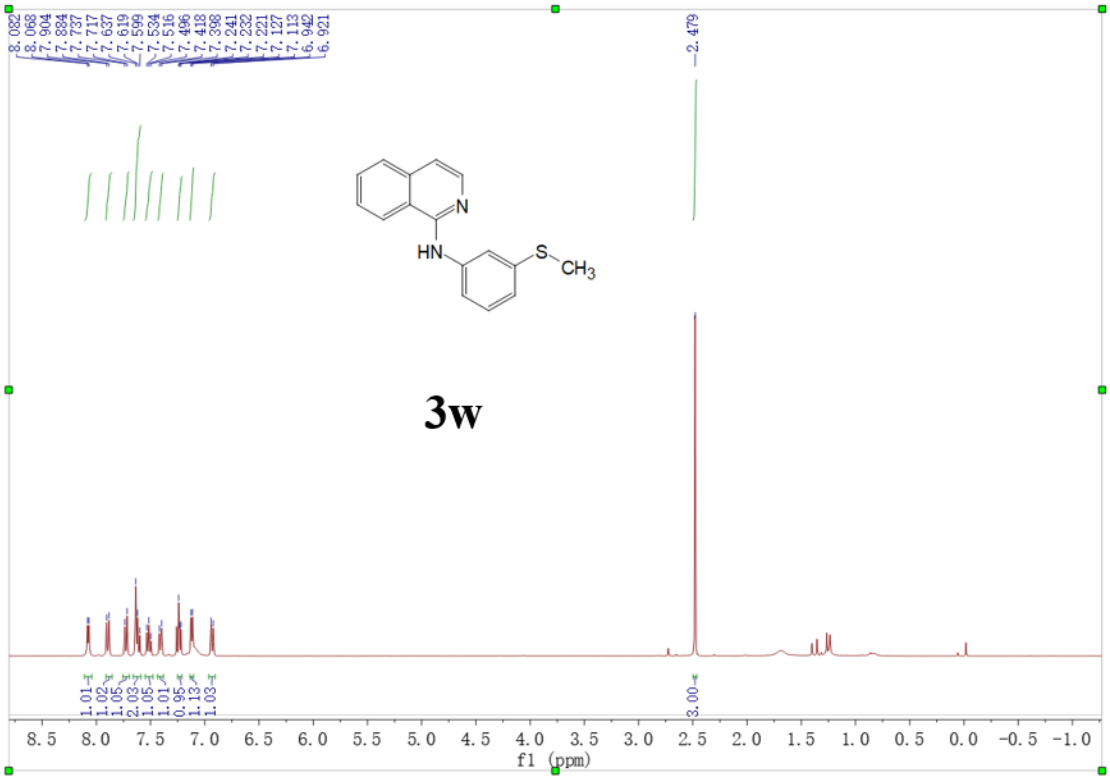
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3v



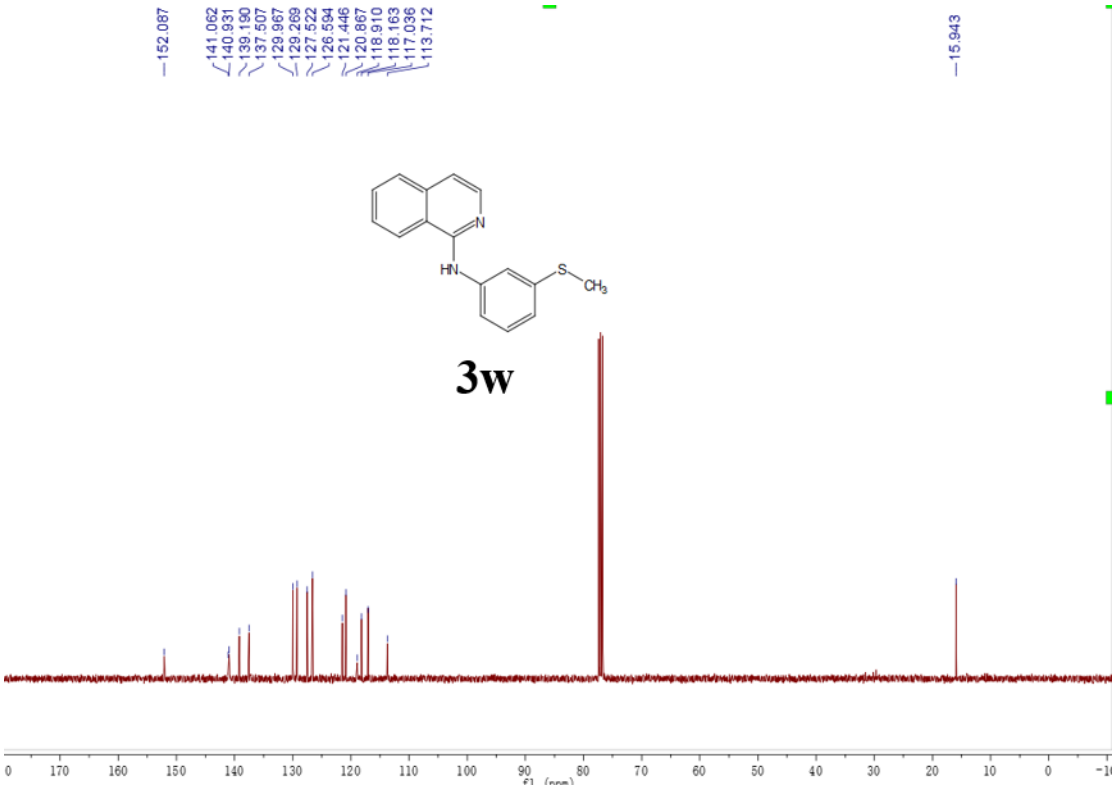
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3v



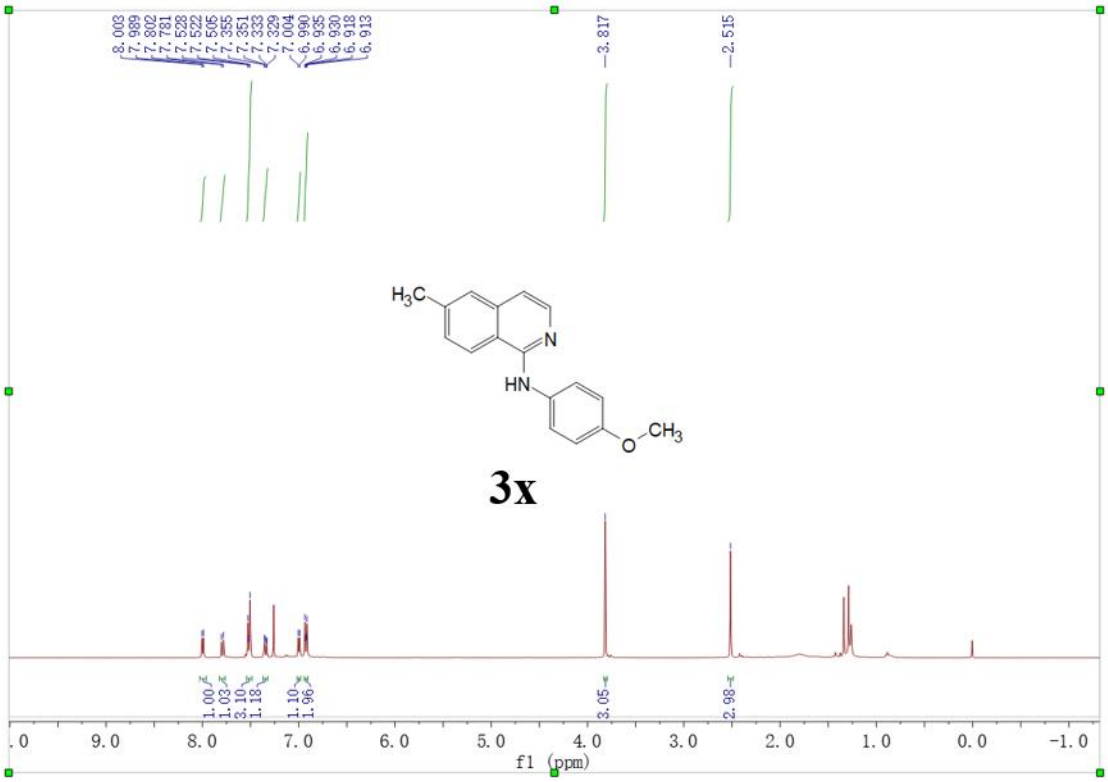
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3w



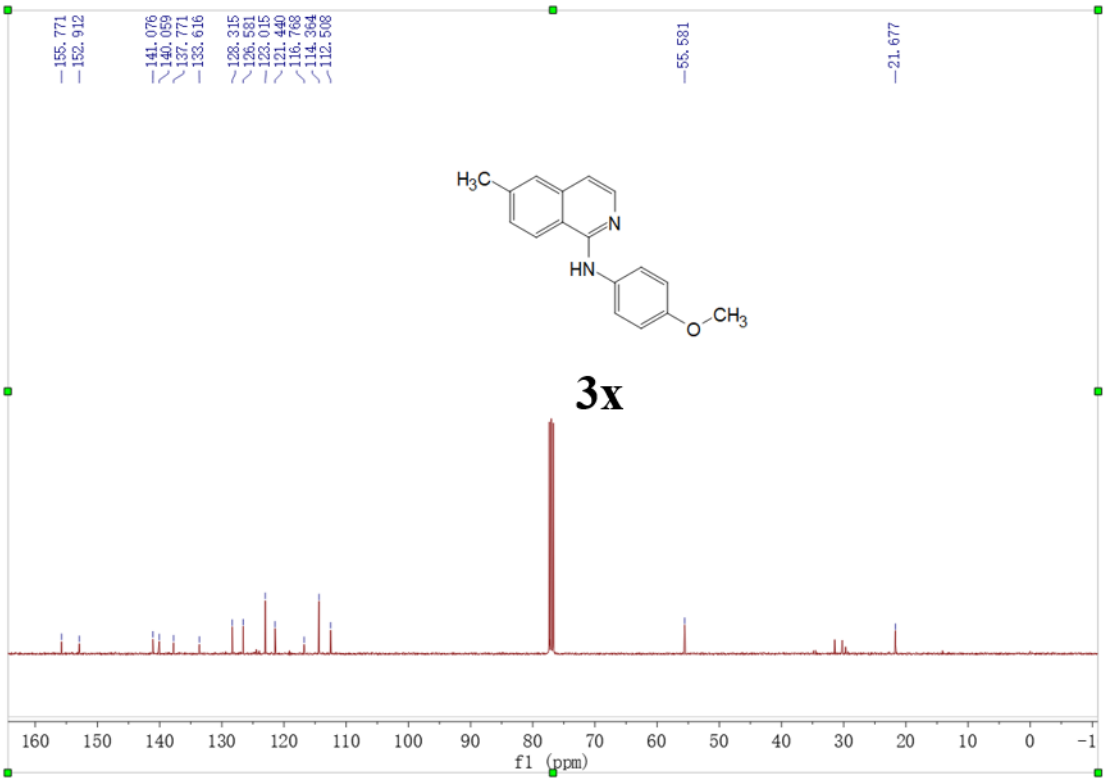
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3w



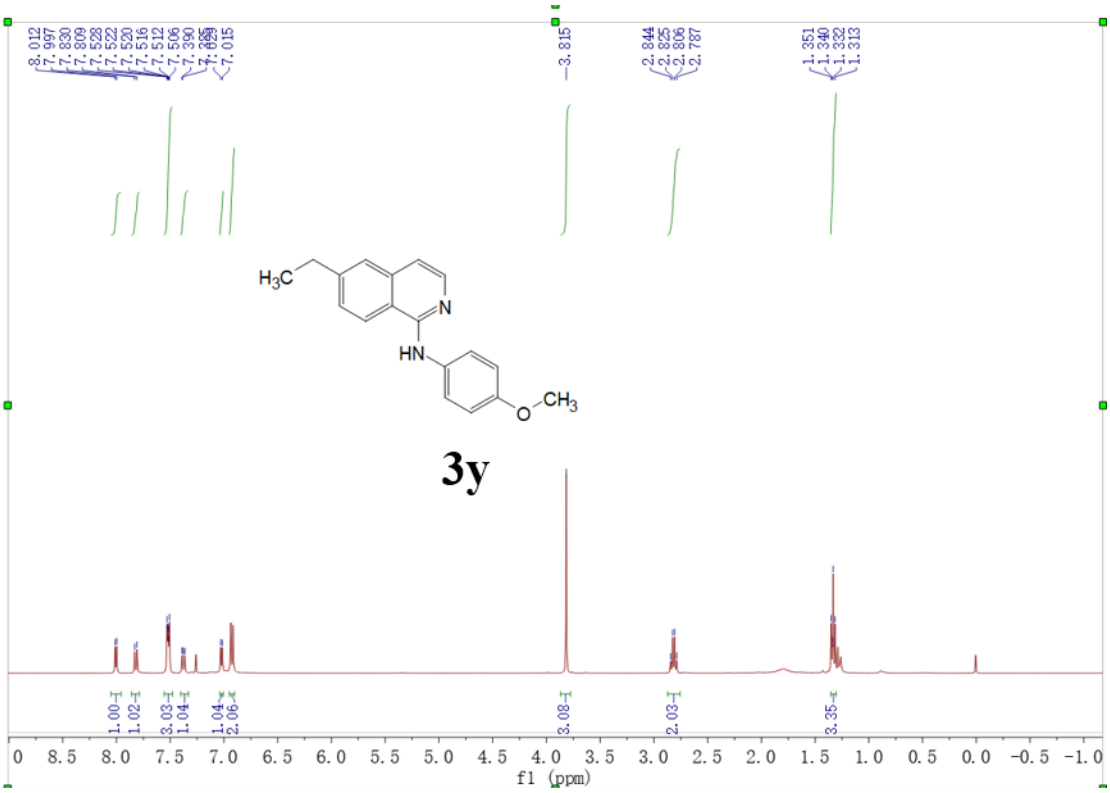
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3x



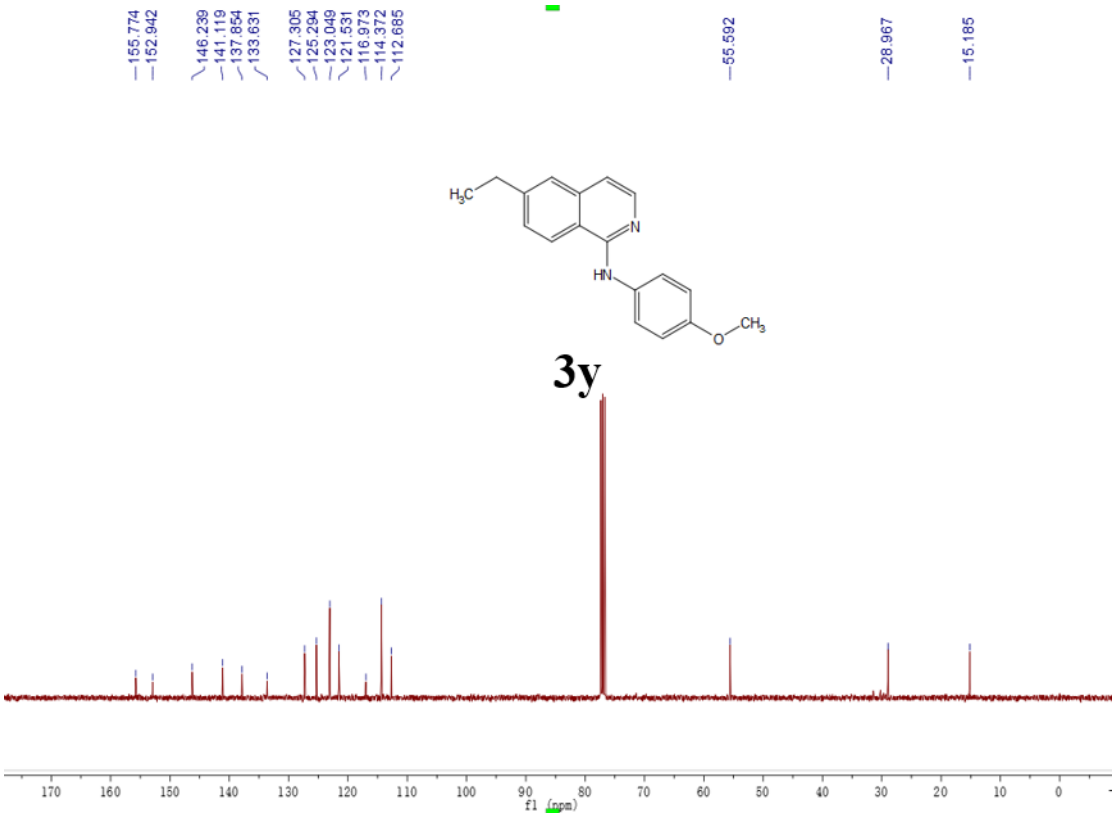
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3x



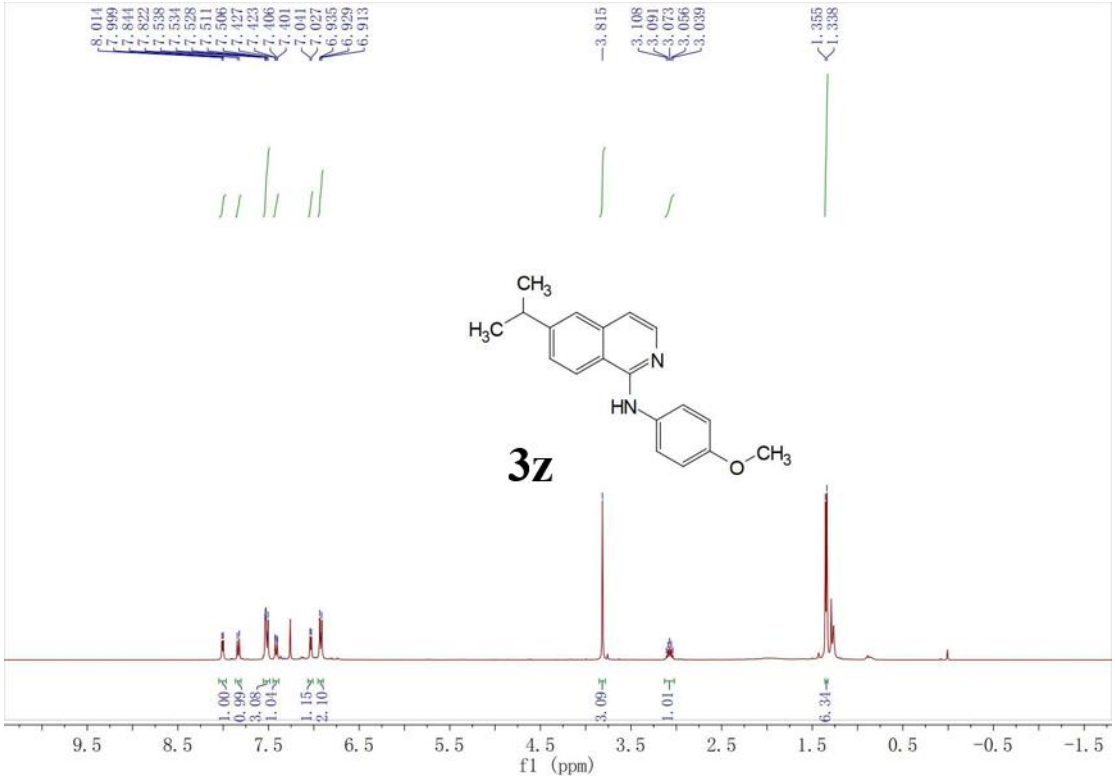
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3y



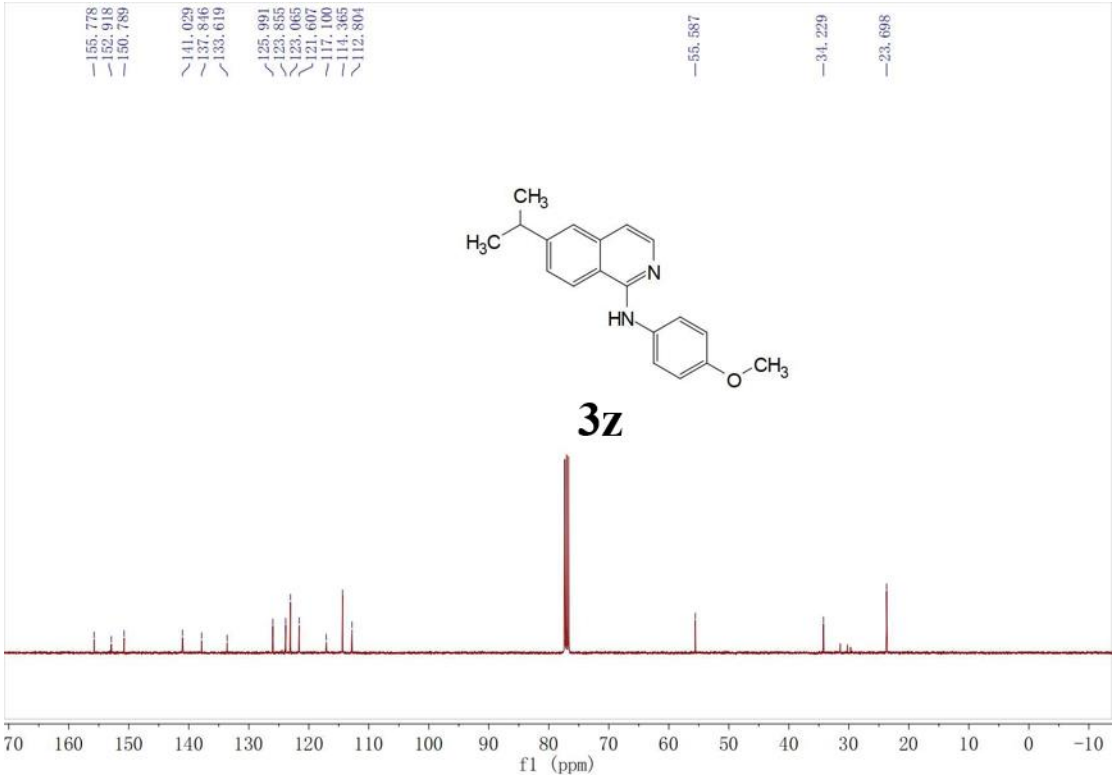
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3y



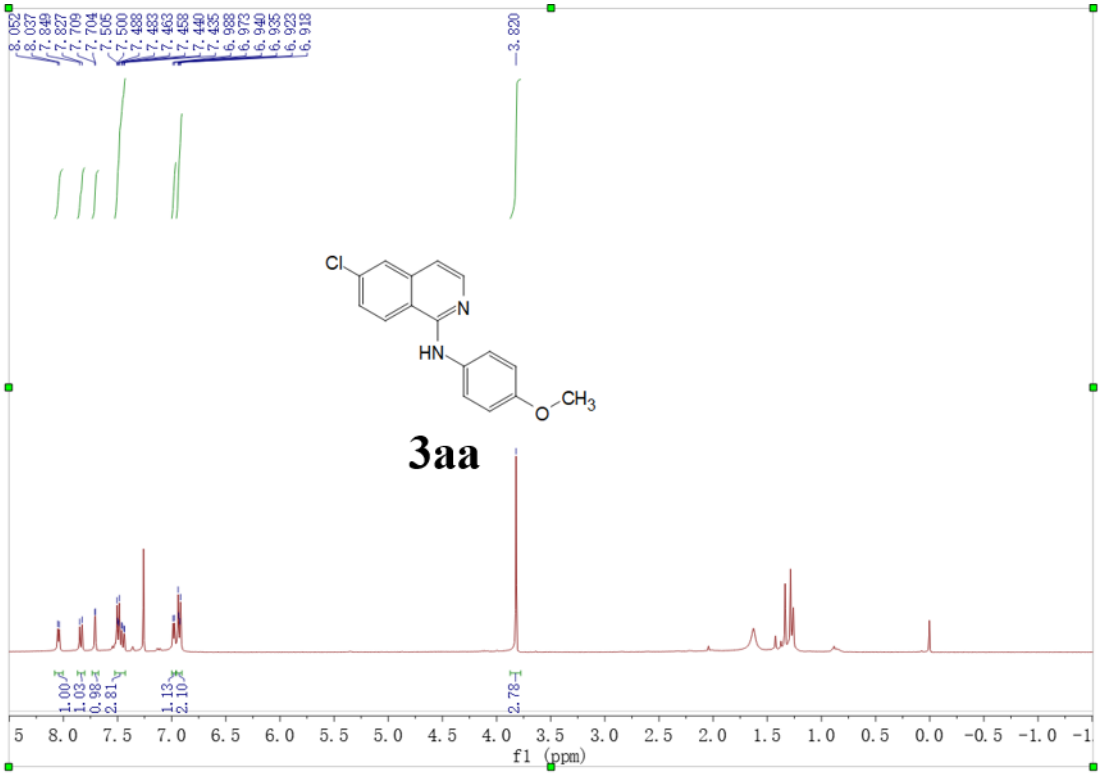
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3z



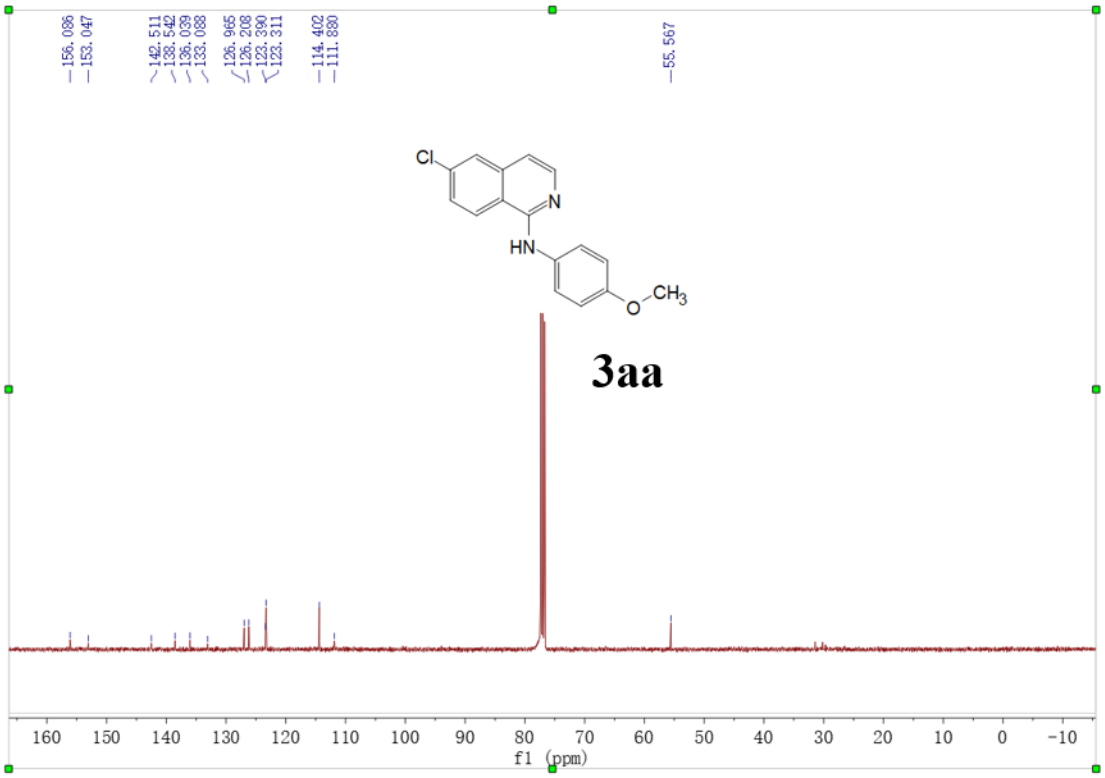
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3z



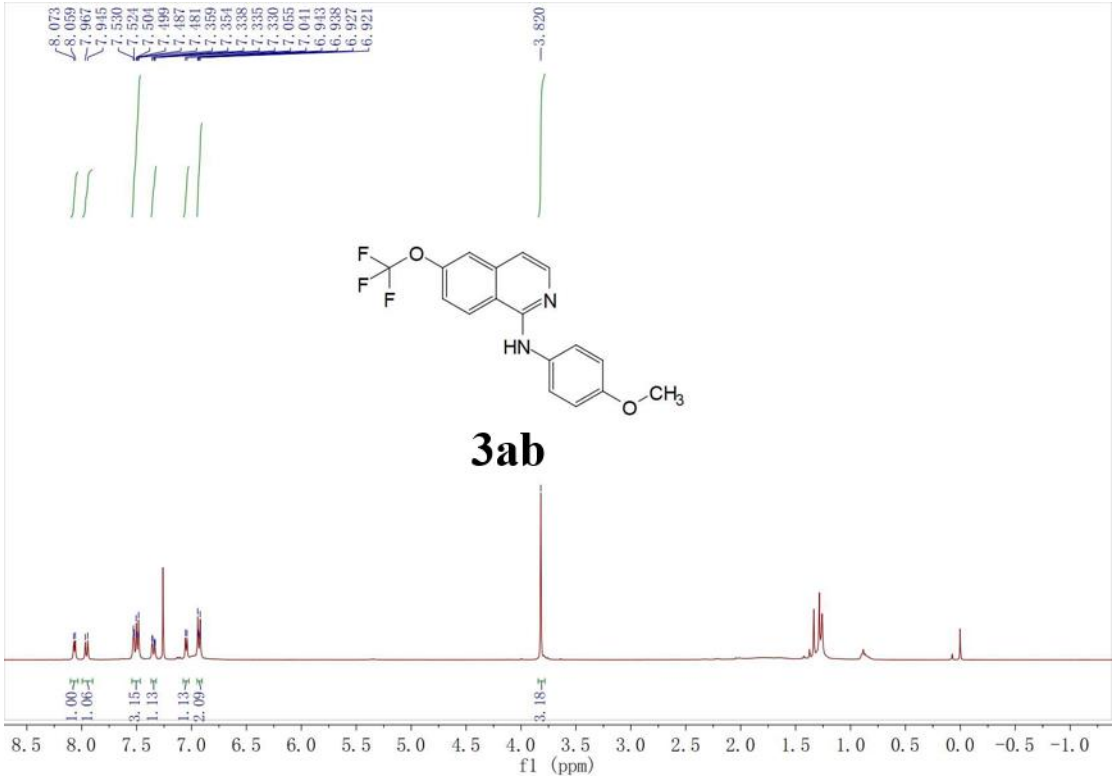
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3aa



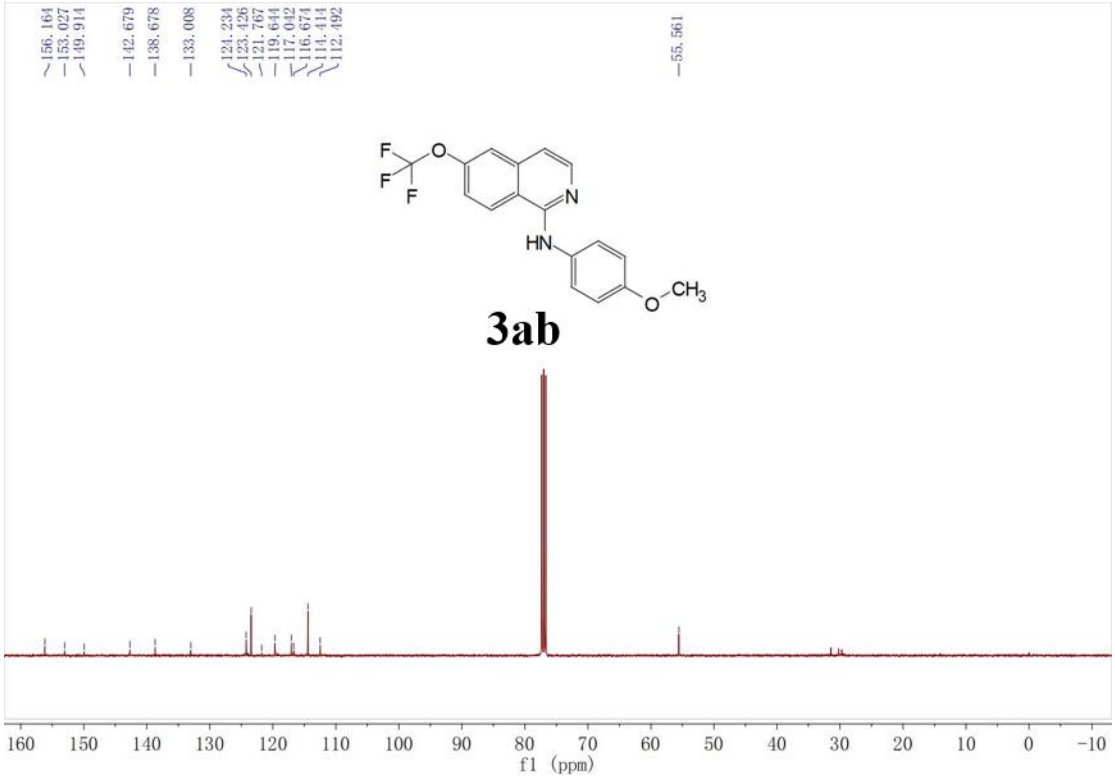
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3aa



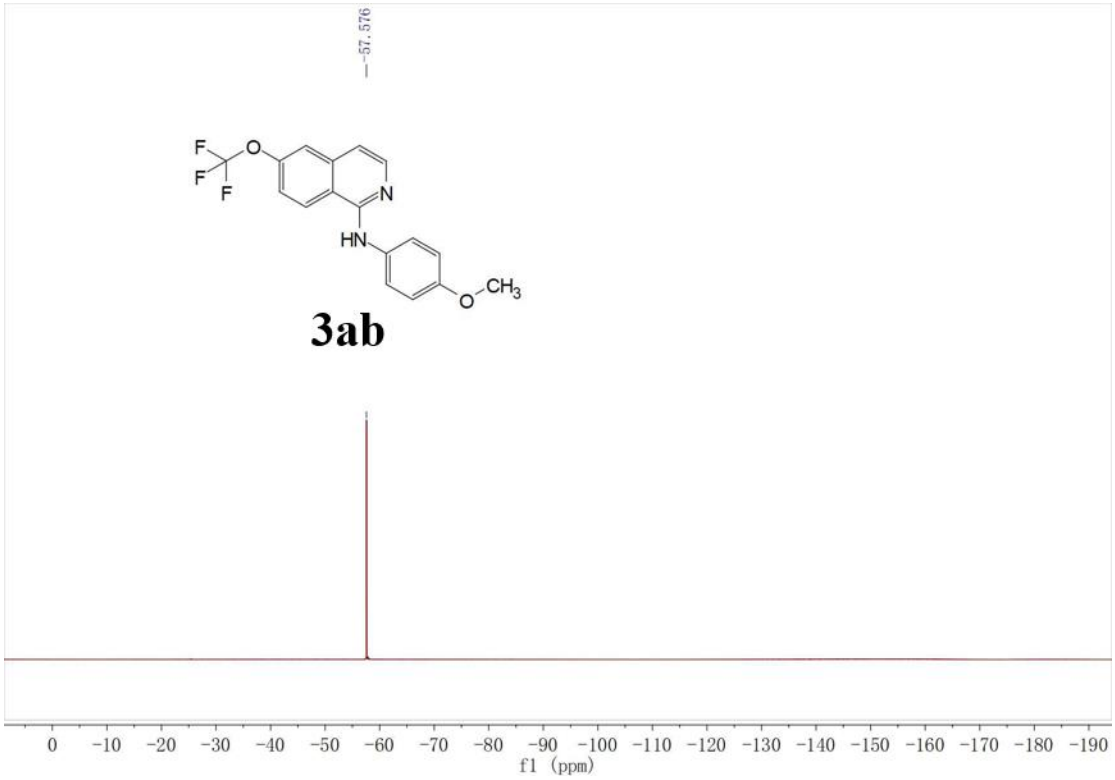
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3ab



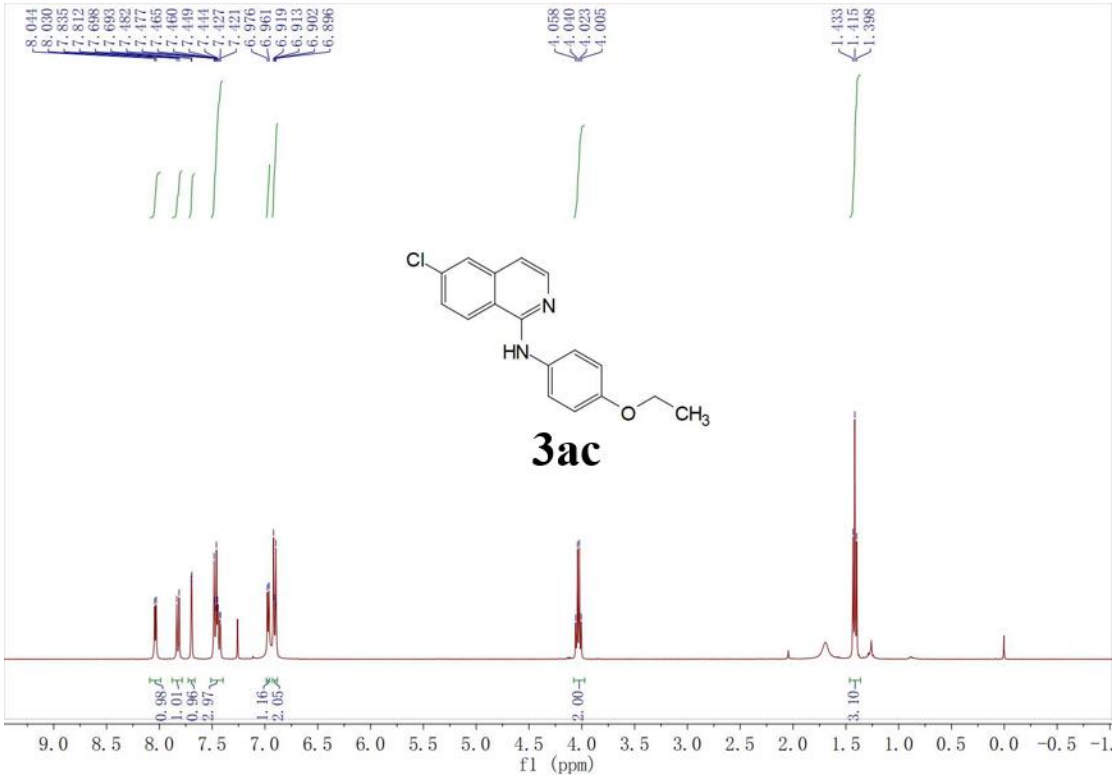
^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3ab



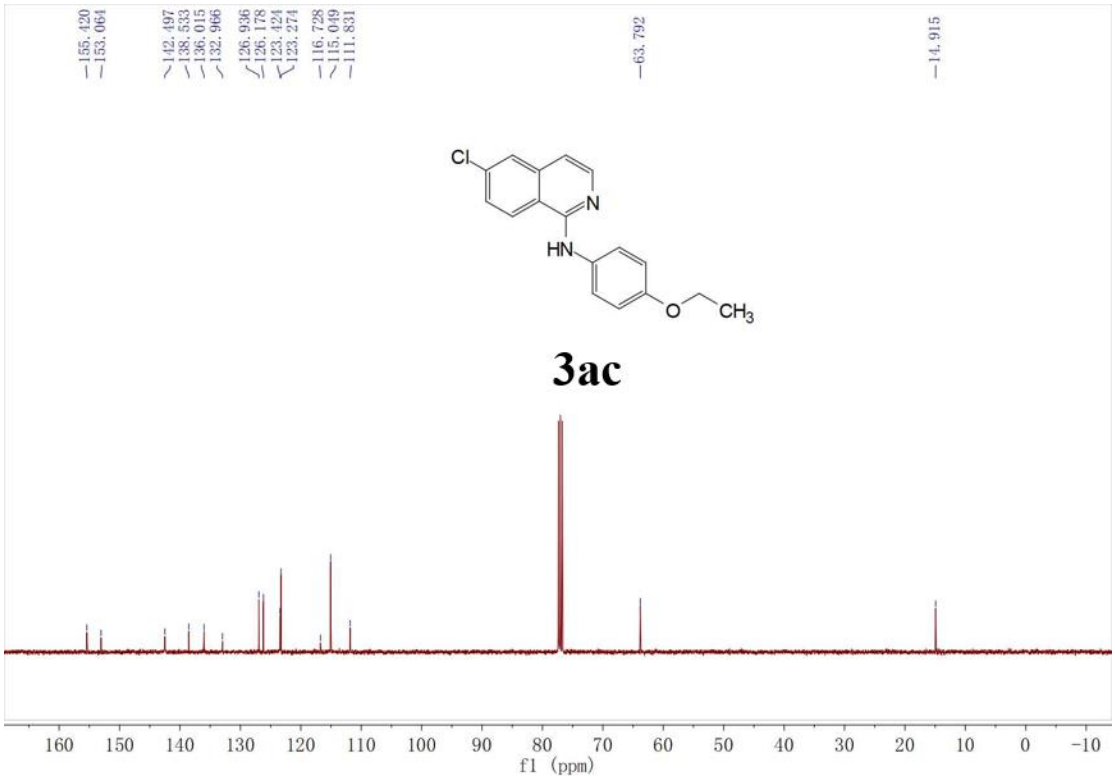
^{19}F NMR (377 MHz,CDCl3) spectrum of compound 3ab



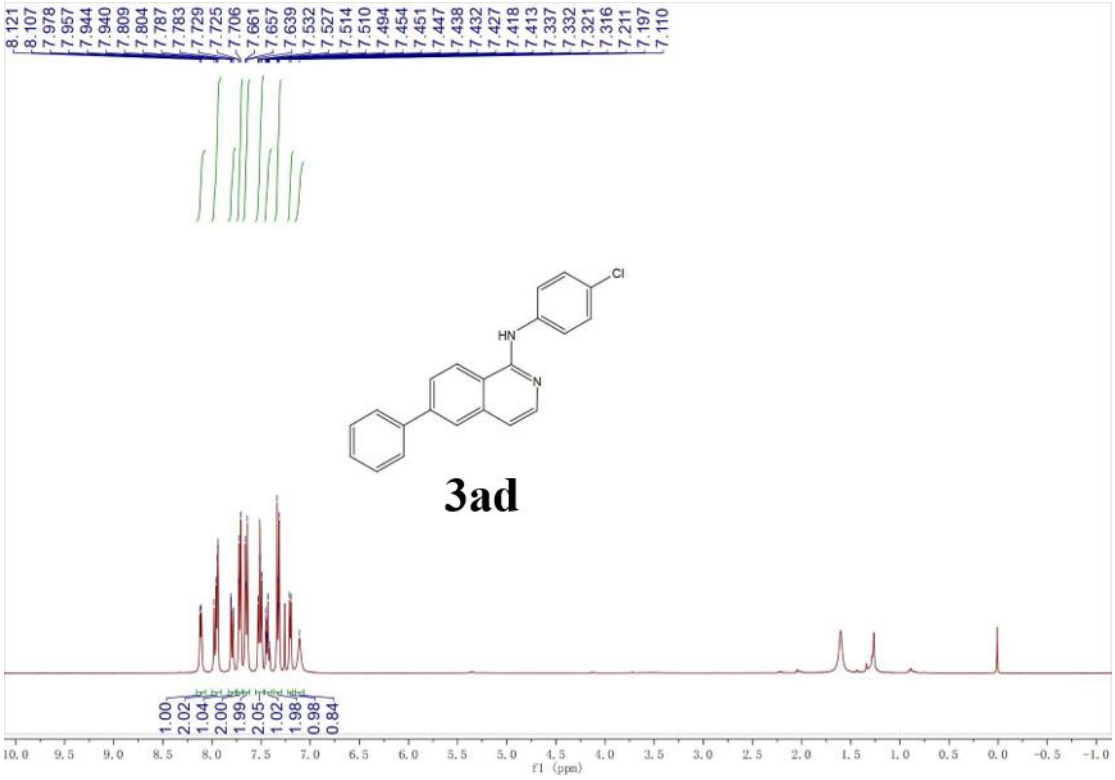
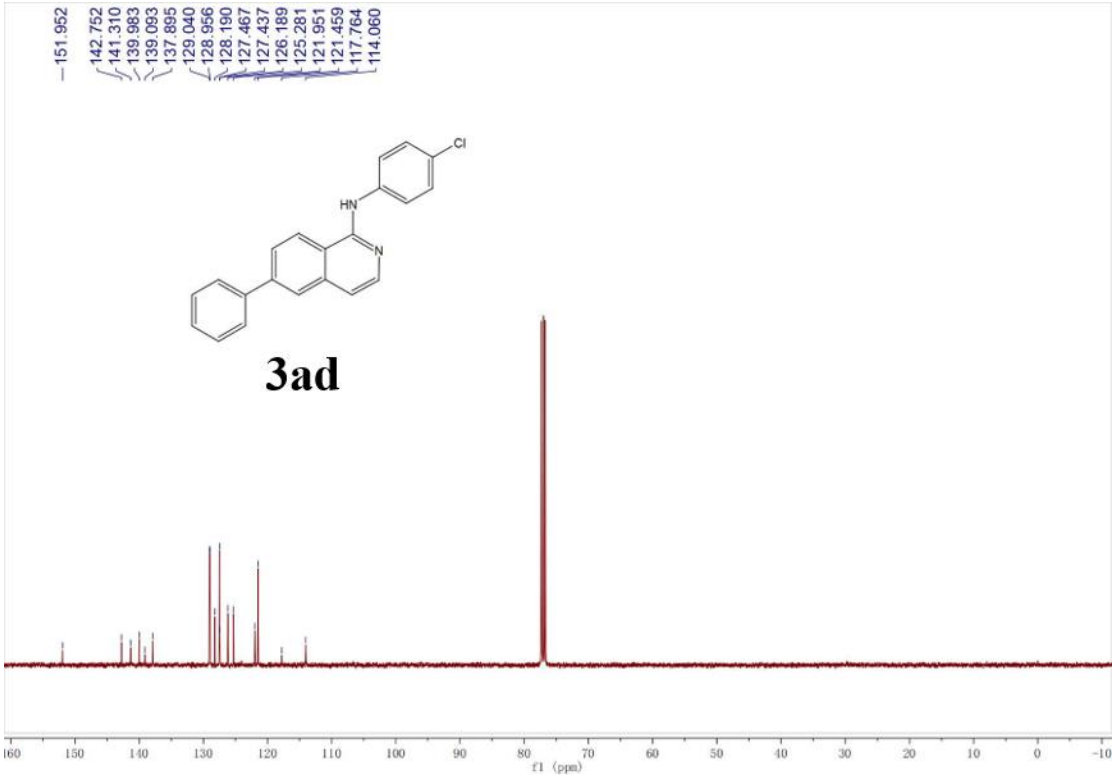
^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3ac



^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3ac



^{1}H NMR (400 MHz, CDCl3) spectrum of compound 3ad



^{13}C{^{1}H} NMR (101 MHz, CDCl3) spectrum of compound 3ad