Electronic Supplementary Material (ESI) for ChemComm.

Supplementary Information

Rh-catalyzed sequential oxidative C−H activation/annulation with geminal-substituted vinyl acetates to access isoquinolines

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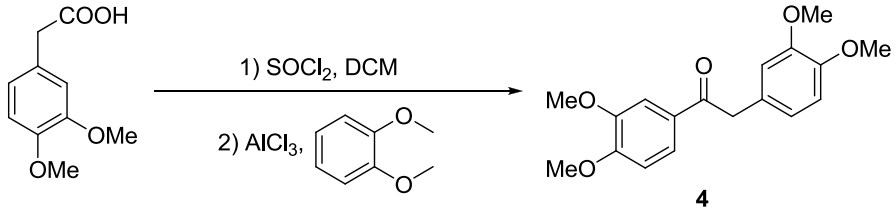
1. General Considerations

Unless otherwise noted, all chemicals were purchased from commercial suppliers (Adamas, Aladdin, etc) and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a 300 or 400 MHz NMR spectrometer (75 or 100 MHz for ^{13}C). NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) or DMSO-d_6 (δ 2.50 or 39.52 ppm) as the internal standard. The coupling constants *J* are given in Hz. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

2. Experimental Procedures

Under air, a 20 mL Schlenk tube equipped with a stir bar was charged with **1** (0.4 mmol), vinyl acetate **2** (1.2 mmol, 3 eq.), $[Cp^*RhCl_2]_2$ (9.9 mg, 4 mol%), Ag salt (AgOAc or $AgBF_4$, 16 mol%), MeOH (2 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 100 ℃ for 12 h in oil bath. After the completion of the reaction, the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc as the eluent to give the desired product.

3. Total Synthesis of Papaverine



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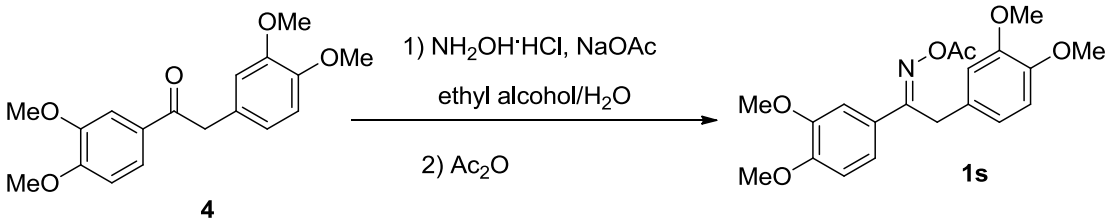
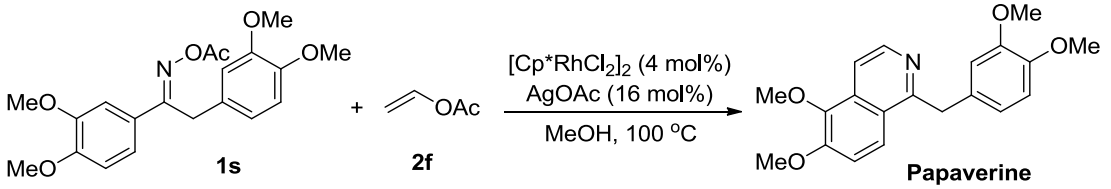
To a dry two necked round bottom flask containing 3,4-dimethylprotocatechuic acid (CAS: 93-40-3, 4.12 g, 2184.10 mmol) in dry DCM (7 mL) was added thionyl chloride ($SOCl_2$, 4.64 g, 39 mmol) drop-wise. The reaction mixture was heated to reflux for 1 h and then DCM and excess thionyl chloride were removed by distillation. The resulting oil was transferred to another two necked round bottom flask containing dry DCM (40 mL) and 1,2-dimethoxybenzene (4.0 g, 29.4 mmol). $AlCl_3$ (3.92 g, 29.4 mmol) was added in small portions and the mixture was refluxed for 3 h after which

the reaction was quenched by pouring into ice water (25 mL) containing 6 M HCl (7.5 mL). The mixture was extracted with DCM and the combined organic layers were evaporated under vacuum. Recrystallization from ethyl alcohol gave the desired product **4** as a yellow solid (4.98 g, 80%).



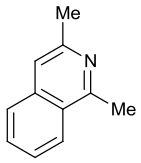
A mixture of **4** (12.5 mmol, 3.95 g), NH_2OH HCl (25.0 mmol, 1.75 g), NaOAc (37.5 mmol, 3.0 g), ethyl alcohol (5.0 mL) and water (15.0 mL) were placed in a 50 mL round-bottom flask with a reflux condenser and stirred under reflux. After the completion of the reaction (monitored by TLC), the mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers was dried by Na_2SO_4 and evaporated under vacuum to give the oxime. Next, a mixture of oxime and acetic anhydride (15 mmol, 2.5 mL) was gently heated with stirring at 85 ℃ under nitrogen for 4 hours. Then cooled and ethyl acetate was added. The contents were washed with aqueous sodium bicarbonate solution followed by brine and evaporated to leave the product **1s** which was purified by column chromatography over silica gel in 78% (3.63 g) yield.



Under air, a 20 mL of Schlenk tube equipped with a stir bar was charged with **1s** (149 mg, 0.4 mmol), vinyl acetate **2f** (1.2 mmol), $[Cp^*RhCl_2]_2$ (9.9 mg, 4 mol%), AgOAc (16 mol%), MeOH (2 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 100 ℃ for 12 h in oil bath. After the completion of the reaction, the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc (5: 1) as the eluent to give the product papaverine in 52% (70.5 mg) yield.

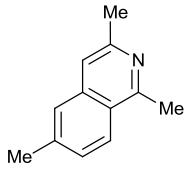
4. Characterization Data for the Products

1,3-Dimethylisoquinoline (3aa)[1]:



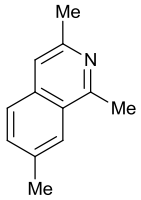
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **4ab** (47.8 mg, 76% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.30 (s, 1H), 2.92 (s, 1H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.9, 150.1, 136.6, 129.8, 126.5, 125.9, 125.5, 125.4, 117.1, 24.2, 22.2.

1,3,6-Trimethylisoquinoline (3ba)[2]:



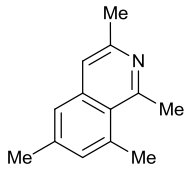
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ba** (45.8 mg, 67% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, J = 8.6 Hz, 1H), 7.42 (s, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.20 (s, 1H), 2.89 (s, 3H), 2.62 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5, 150.1, 139.9, 136.9, 128.1, 125.4, 125.3, 123.9, 116.6, 24.1, 22.1, 21.7.

1,3,7-Trimethylisoquinoline (3ca)[2]:



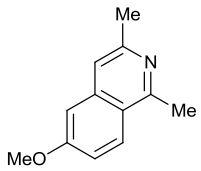
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ca** (41.7 mg, 61% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.26 (s, 1H), 2.89 (s, 3H), 2.62 (s, 3H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5, 150.1, 139.9, 136.9, 128.1, 125.4, 125.3, 123.9, 116.6, 24.1, 22.1, 21.7.

1,3,6,8-Tetramethylisoquinoline (3da):



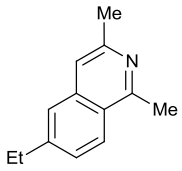
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3da** (24.5 mg, 33% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (s, 1H), 7.20 (s, 1H), 7.10 (s, 1H), 3.08 (s, 3H), 2.86 (s, 3H), 2.58 (s, 3H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.7, 149.3, 139.2, 139.2, 135.8, 131.8, 124.9, 124.5, 117.8, 29.1, 25.6, 23.8, 21.3; HRMS (ESI) m/z calcd for $C_{13}H_{15}N$ $(M + H)^+$ 186.1277, found 186.1279.

6-Methoxy-1,3-dimethylisoquinoline (3ea)[2]:



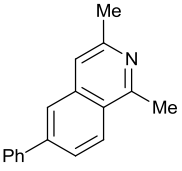
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ea** (47.1 mg, 63% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 9.2 Hz, 1H), 7.21 (s, 1H), 7.09 (dd, J = 9.1 Hz, 1H), 6.92 (s, 1H), 3.89 (s, 3H), 2.86 (s, 3H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 157.3, 150.8, 138.7, 127.3, 121.2, 118.6, 116.6, 104.1, 55.3, 24.2, 22.1.

6-Ethyl-1,3-dimethylisoquinoline (3fa):



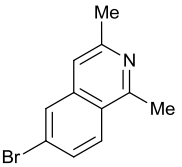
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3fa** (60.7 mg, 82% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (d, J = 8.6 Hz, 1H), 7.44 (s, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.23 (s, 1H), 2.88 (s, 3H), 2.77 (q, J = 7.6 Hz, 2H), 2.62 (s, 3H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5, 150.1, 146.1, 137.0, 128.7, 127.1, 125.4, 124.1, 116.8, 29.0, 24.1, 22.1, 15.1; HRMS (ESI) m/z calcd for $C_{13}H_{15}N$ $(M + H)^+$ 186.1277, found 186.1279.

1,3-Dimethyl-6-phenylisoquinoline (3ga):



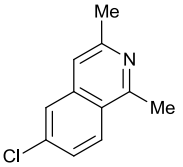
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ga** (59.6 mg, 64% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, J = 8.6 Hz, 1H), 7.85 (s, 1H), 7.74-7.68 (m, 3H), 7.50-7.39 (m, 3H), 7.34 (s, 1H), 2.94 (s, 3H), 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 150.6, 142.3, 140.2, 136.9, 128.8, 127.9, 127.4, 126.0, 125.6, 124.5, 124.2, 117.3, 24.2, 22.2; HRMS (ESI) m/z calcd for $C_{17}H_{15}N$ $(M + H)^+$ 234.1277, found 234.1280.

6-Bromo-1,3-dimethylisoquinoline (3ha):



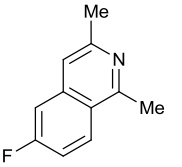
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ha** (65.1 mg, 69% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.9 Hz, 1H), 7.81 (s, 1H), 7.53 (d, J = 8.9 Hz, 1H), 7.18 (s, 1H), 2.88 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 151.6, 137.8, 129.4, 128.6, 127.2, 124.5, 123.9, 116.1, 24.3, 22.2; HRMS (ESI) m/z calcd for $C_{11}H_{10}BrN$ $(M + H)^+$ 234.9997, found 234.9999.

6-Chloro-1,3-dimethylisoquinoline (3ia)[2]:



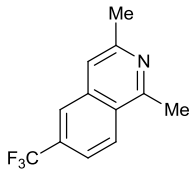
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ia** (48.9 mg, 64% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, J = 8.9 Hz, 1H), 7.64 (s, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.21 (s, 1H), 2.89 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 151.6, 137.5, 135.9, 127.3, 126.9, 125.2, 123.7, 116.3, 24.2, 22.3.

6-Fluoro-1,3-dimethylisoquinoline (3ja):



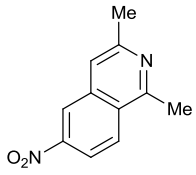
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ja** (41.3 mg, 59% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03-8.00 (m, 1H), 7.24-7.18 (m, 3H), 2.87 (s, 3H), 2.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9 (d, $J_{C\text{-}F}$ = 249.8 Hz), 157.8 (d, $J_{C\text{-}F}$ = 0.8 Hz), 151.4 (d, $J_{C\text{-}F}$ = 0.8 Hz), 138.2 (d, $J_{C\text{-}F}$ = 10.5 Hz), 128.5 (d, $J_{C\text{-}F}$ = 9.8 Hz), 122.7 (d, $J_{C\text{-}F}$ = 0.8 Hz), 116.8 (d, $J_{C\text{-}F}$ = 5.2 Hz), 116.1 (d, $J_{C\text{-}F}$ = 24.8 Hz), 109.6 (d, $J_{C\text{-}F}$ = 20.2 Hz), 24.1, 22.3; HRMS (ESI) m/z calcd for $C_{11}H_{10}FN$ $(M + H)^+$ 176.0870, found 176.0872.

1,3-Dimethyl-6-(trifluoromethyl)isoquinoline (3ka):



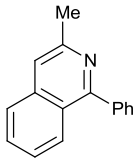
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ka** (63.0 mg, 70% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J = 8.7 Hz, 1H), 7.93 (s, 1H), 7.61 (d, J = 8.7 Hz, 1H), 7.34 (s, 1H), 2.92 (s, 3H), 2.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 151.9, 135.7, 131.4 (q, $J_{C\text{-}F}$ = 33.0 Hz), 126.7, 126.2, 124.2 (q, $J_{C\text{-}F}$ = 4.0 Hz), 123.8 (d, $J_{C\text{-}F}$ = 270.0 Hz), 121.5 (q, $J_{C\text{-}F}$ = 3.0 Hz) 117.5, 24.2, 22.3; HRMS (ESI) m/z calcd for $C_{12}H_{10}F_3N$ $(M + H)^+$ 226.0838, found 226.0842.

1,3-Dimethyl-6-nitroisoquinoline (3la)[3]:



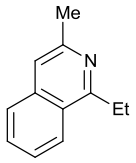
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **4mb** (42.8 mg, 53% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.61 (s, 1H), 8.24-8.19 (m, 2H), 7.50 (s, 1H), 2.99 (s, 3H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 152.9, 148.1, 136.0, 127.7, 127.1, 122.9, 119.3, 118.3, 24.3, 22.5.

3-Methyl-1-phenylisoquinoline (3ma)[5].



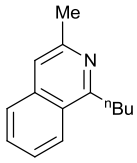
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ma** (64.8 mg, 74% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, J = 8.5 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.55-7.41 (m, 5H), 2.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 150.7, 139.6, 137.4, 129.8, 129.8, 128.3, 128.2, 127.4, 126.2, 126.0, 124.8, 117.9, 24.4.

1-Ethyl-3-methylisoquinoline (3na)[6].



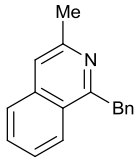
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3na** (39.7 mg, 58% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.32 (s, 1H), 3.30 (q, J = 7.6 Hz, 2H), 2.66 (s, 3H), 1.42 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.9, 150.4, 137.1, 129.6, 126.8, 125.9, 125.2, 124.6, 117.09, 28.8, 24.3, 14.4.

1-(n-Butyl)-3-methylisoquinoline (3oa)[7].



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3oa** (48.6 mg, 61% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.31 (s, 1H), 3.25 (t, J = 8.1 Hz, 2H), 2.65 (s, 3H), 1.80 (m, J = 7.7 Hz, 2H), 1.50 (m, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 150.3, 137.0, 129.6, 126.7, 125.8, 125.3, 124.8, 117.0, 35.6, 32.5, 24.3, 23.1, 14.0.

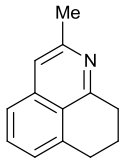
1-Benzyl-3-methylisoquinoline (3pa)[8]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3pa** (60.6 mg, 65% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.14 (m, 5H), 4.66 (s, 2H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.4, 150.5, 139.6, 137.3, 129.7, 128.5, 128.4, 126.7, 126.2, 126.1, 125.8, 125.3, 117.8, 42.1, 24.3.

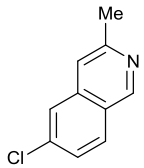
2-Methyl-8,9-dihydro-7H-benzo[de]quinoline (3qa):



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3qa** (43.9 mg, 60% yield) as yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52-7.47 (m, 2H), 7.29 (s, 1H), 7.23-7.22 (m, 1H), 3.22 (t, J = 6.2 Hz, 2H), 3.08 (t, J = 6.0 Hz, 2H), 2.64 (s, 3H), 2.17 (m, J = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.6, 150.2, 138.6, 136.8, 129.9, 123.9, 123.7, 123.3, 116.8, 34.3, 30.4, 24.2, 23.2; HRMS (ESI) m/z calcd for $C_{13}H_{13}N$ $(M + H)^+$ 184.1121, found 184.1123.

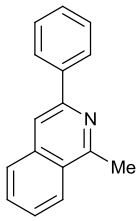
6-Chloro-3-methylisoquinoline (3ra)[9]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ra** (7.1 mg, 10% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (s, 1H), 7.86 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 1.4 Hz, 1H), 7.47-7.45 (m, 1H), 7.40 (s, 1H), 2.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 151.6, 137.2, 136.6, 129.2, 127.4, 125.0, 124.8, 117.6, 24.2.

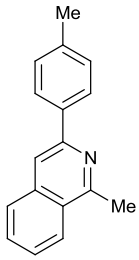
1-Methyl-3-phenylisoquinoline (3ab)[10]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ab** (51.6 mg, 60% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.16-8.12 (m, 3H), 7.92 (s, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.67 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.41 (t, J = 7.3 Hz, 1H), 3.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5, 150.0, 139.8, 136.7, 130.0, 128.7, 128.3, 127.6, 127.0, 126.7, 126.6, 125.6, 115.2, 22.6.

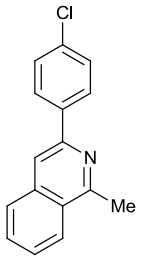
1-Methyl-3-(*p*-tolyl)isoquinoline (3ac)[11]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ac** (63.4 mg, 68% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.1 Hz, 2H), 7.89 (s, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 150.0, 138.1, 137.0, 136.8, 129.9, 129.4, 127.5, 126.8, 126.5, 126.4, 125.6, 114.7, 22.6, 21.2.

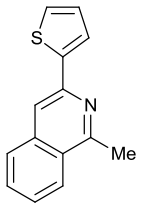
3-(4-Chlorophenyl)-1-methylisoquinoline (3ad)[12]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ad** (88.0 mg, 87% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13-8.07 (m, 3H), 7.88-7.83 (m, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.47-7.44 (m, 2H), 3.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 148.6, 138.2, 136.6, 134.3, 130.1, 128.8, 128.2, 127.6, 127.0, 126.6, 125.6, 115.1, 22.6.

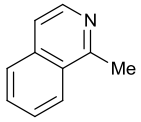
1-Methyl-3-(thiophen-2-yl)isoquinoline (3ae)



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 100) give **3ae** (52.2 mg, 58% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, J = 8.4 Hz, 1H), 7.82-7.77 (m, 2H), 7.70-7.61 (m, 2H), 7.54-7.50 (m, 1H), 7.39-7.38 (m, 1H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.7, 145.4, 145.3, 136.5, 130.2, 128.0, 127.3, 126.6, 126.5, 126.5, 125.7, 123.7, 113.0, 22.4; HRMS (ESI) m/z calcd for $C_{14}H_{11}NS$ $(M + H)^+$ 225.0685, found 226.0688.

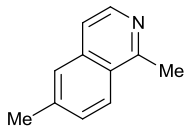
1-Methylisoquinoline (3af)[13]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3af** (44.1 mg, 77% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, J = 5.8 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.46 (d, J = 5.7 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 141.7, 135.7, 129.8, 127.4, 127.0, 126.9, 125.5, 119.1, 22.3.

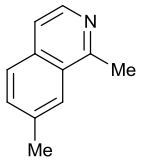
1,6-Dimethylisoquinoline (3bf)[14]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3bf** (51.5 mg, 82% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 5.8 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.52 (s, 1H), 7.39-7.38 (m, 2H), 2.90 (s, 3H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 141.8, 140.1, 136.1, 129.1, 126.0, 125.8, 125.4, 118.7, 22.2, 21.7.

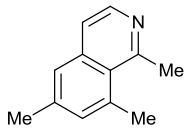
1,7-Dimethylisoquinoline (3cf)[14]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3cf** (34.5 mg, 55% yield) as yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (d, J = 5.8 Hz, 1H), 7.84 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.48-7.42 (m, 2H), 2.91 (s, 3H), 2.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.7, 140.9, 136.8, 134.0, 132.0, 127.5, 126.9, 124.4, 119.0, 22.3, 22.0.

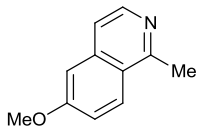
1,6,8-Trimethylisoquinoline (3df):



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3df** (27.4 mg, 40% yield) as yellow oil.

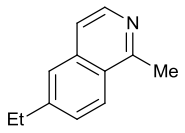
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, J = 5.5 Hz, 1H), 7.38-7.36 (m, 2H), 7.19 (s, 1H), 3.10 (s, 3H), 2.89 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 141.0, 139.2, 138.4, 135.9, 132.8, 126.8, 125.1, 119.8, 29.2, 25.6, 21.3; HRMS (ESI) m/z calcd for $C_{12}H_{13}N$ $(M + H)^+$ 172.1121, found 172.1123.

6-Methoxy-1-methylisoquinoline (3ef)[15]:



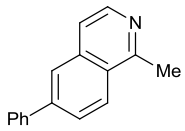
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ef** (60.2 mg, 87% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28-8.26 (m, 1H), 7.94 (t, J = 8.4 Hz, 1H), 7.35-7.34 (m, 1H), 7.15-7.13 (m, 1H), 6.99 (d, J = 6.0 Hz, 1H), 3.88 (d, J = 6.3 Hz, 3H), 2.86 (d, J = 4.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.3, 157.7, 142.3, 137.8, 127.3, 123.0, 119.5, 118.6, 104.6, 55.3, 22.1.

6-Ethyl-1-methylisoquinoline (3ff):



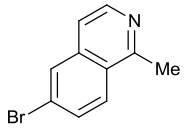
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3ff** (61.6 mg, 90% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, J = 5.8 Hz, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.52 (s, 1H), 7.41-7.39 (m, 2H), 2.90 (s, 3H), 2.79 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 146.2, 141.6, 136.1, 128.0, 125.9, 125.4, 124.6, 118.9, 28.9, 22.2, 15.0; HRMS (ESI) m/z calcd for $C_{12}H_{13}N$ $(M + H)^+$ 172.1121, found 172.1121.

1-Methyl-6-phenylisoquinoline (3gf):



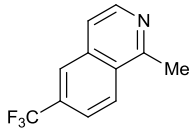
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3gf** (59.6 mg, 68% yield) as yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (m, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.71-7.69 (m, 2H), 7.52-7.42 (m, 4H), 2.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.4, 142.4, 142.2, 140.0, 136.0, 128.9, 128.0, 127.4, 126.6, 126.4, 126.1, 124.7, 119.4, 22.3; HRMS (ESI) m/z calcd for $C_{16}H_{13}N$ $(M + H)^+$ 220.1121, found 220.1123.

6-Bromo-1-methylisoquinoline (3hf):



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3hf** (34.3 mg, 39% yield) as yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.40 (d, J = 5.6 Hz, 1H), 7.97-7.95 (m, 2H), 7.65 (d, J = 9.0 Hz, 1H), 7.40 (d, J = 5.6 Hz, 1H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.8, 142.9, 137.0, 130.5, 129.3, 127.4, 125.8, 124.6, 118.2, 22.3; HRMS (ESI) m/z calcd for $C_{10}H_8BrN$ $(M + H)^+$ 220.9840, found 220.9842.

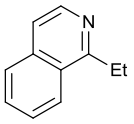
1-Methyl-6-(trifluoromethyl)isoquinoline (3kf):



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3kf** 38.0 mg, 45% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.50 (d, J = 5.6 Hz, 1H), 8.23 (d, J =

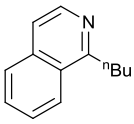
8.8 Hz, 1H), 8.10 (s, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 5.6 Hz, 1H), 2.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.9, 143.1, 135.0, 131.5 (q, J_{C-F} = 32.0 Hz), 128.3, 126.9, 124.9 (q, J_{C-F} = 4.0 Hz), 122.7 (q, J_{C-F} = 3.0 Hz) 122.4, 119.7, 22.5; HRMS (ESI) m/z calcd for $C_{11}H_8F_3N$ $(M + H)^+$ 212.0682, found 212.0683.

1-Ethylisoquinoline (3nf)[16]:



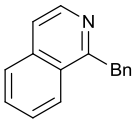
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3nf** (40.8 mg, 65% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.43 (d, *J* = 5.8 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.66-7.55 (m, 2H), 7.48 (d, *J* = 5.8 Hz, 1H), 3.33 (q, *J* = 7.6 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.1, 141.8, 136.2, 129.7, 127.3, 126.9, 126.6, 125.2, 119.1, 28.4, 13.6.

1-(n-Butyl)isoquinoline (3of)[17]:



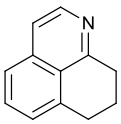
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3of** (50.3 mg, 68% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.41 (d, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 5.6 Hz, 1H), 3.28 (t, *J* = 7.9 Hz, 2H), 1.83 (m, *J* = 7.7 Hz, 2H), 1.49 (m, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3, 141.8, 136.1, 129.6, 127.3, 126.8, 126.8, 125.3, 119.0, 35.2, 31.9, 22.9, 14.0.

1-Benzylisoquinoline (3pf)[18]:



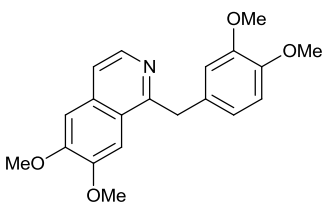
Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3pf** (49.1 mg, 56% yield) as yellow oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.52 (d, *J* = 5.8 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.65-7.50 (m, 3H), 7.30-7.16 (m, 5H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.1, 142.0, 139.4, 136.5, 129.8, 128.6, 128.4, 127.3, 127.2, 127.2, 126.2, 125.8, 119.8, 42.0.

8,9-Dihydro-7H-benzo[de]quinolone (3qf):



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3qf** (35.2 mg, 52% yield) as blue oil.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.36 (d, *J* = 5.8 Hz, 1H), 7.62-7.53 (m, 2H), 7.46 (d, *J* = 5.8 Hz, 1H), 7.33-7.31 (m, 1H), 3.25 (t, *J* = 6.3 Hz, 2H), 3.12 (t, *J* = 6.1Hz, 2H), 2.19 (m, *J* = 6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 141.8, 138.6, 136.1, 129.9, 125.2, 125.0, 124.3, 118.9, 34.3, 30.5, 23.2; HRMS (ESI) m/z calcd for $C_{12}H_{11}N$ $(M + H)^+$ 170.0964, found 170.0965.

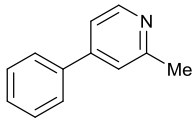
1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (Papaverine):[19]



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 5) give papaverine (70.5 mg, 52% yield) as yellow solid.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34 (d, *J* = 5.6 Hz, 1H),

7.39 (d, J = 5.7 Hz, 1H), 7.31 (s, 1H), 7.01 (s, 1H), 6.80-7.72 (m, 3H), 4.51 (s, 2H), 3.96 (s, 3H), 3.87 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.6, 152.3, 149.6, 148.9, 147.4, 140.8, 133.3, 132.1, 122.8, 120.4, 118.6, 111.7, 111.0, 105.1, 104.1, 55.8, 55.7, 55.7, 55.6, 42.0.

2-Methyl-4-phenylpyridine (3tf)[20]:



Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 50) give **3tf** (44.6 mg, 66% yield) as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, J = 5.2 Hz, 1H), 7.62-7.60 (m, 2H), 7.48-7.36 (m, 4H), 7.30 (d, J = 5.1 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.6, 149.3, 148.8, 138.3, 129.0, 128.9, 126.9, 121.2, 118.8, 24.3.

5. References

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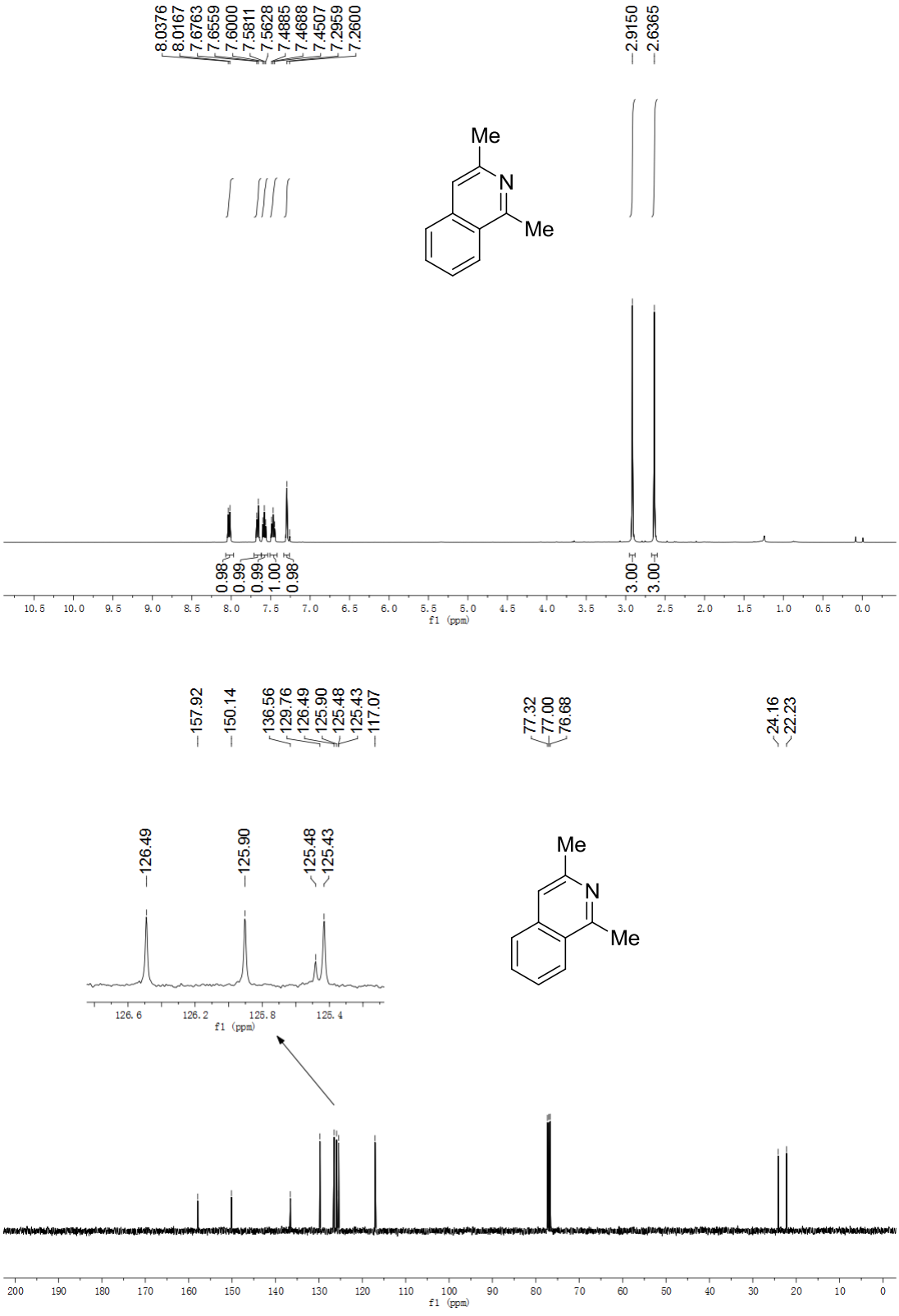
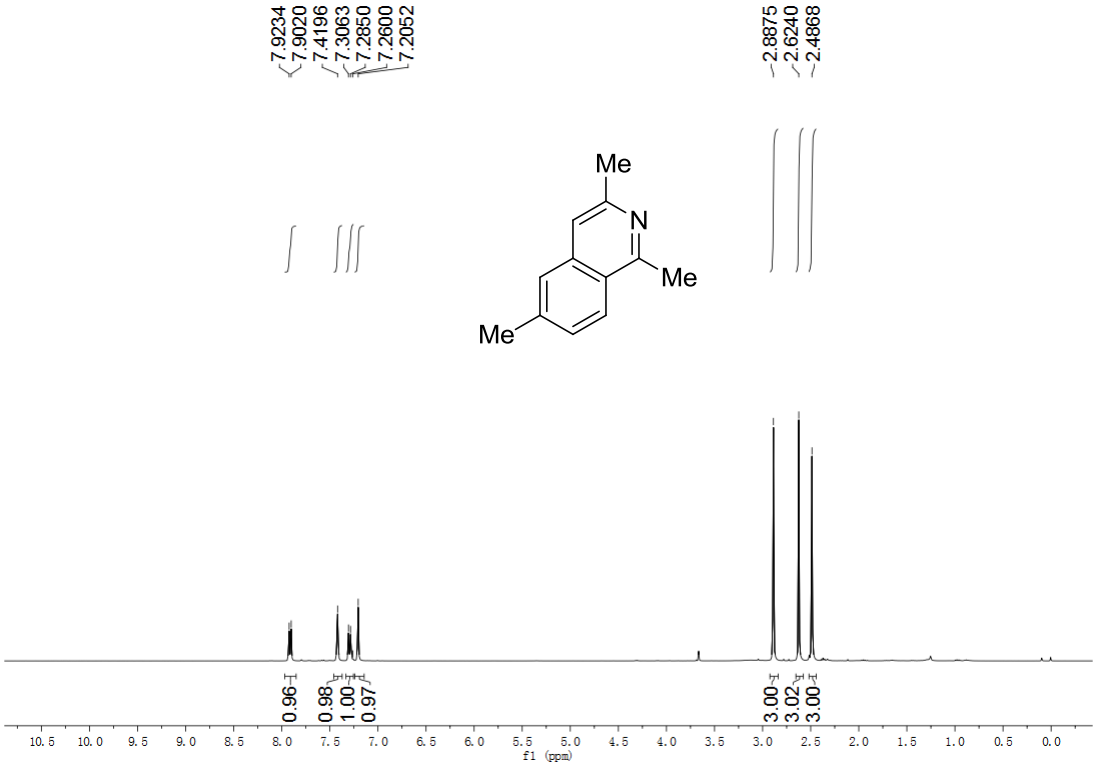
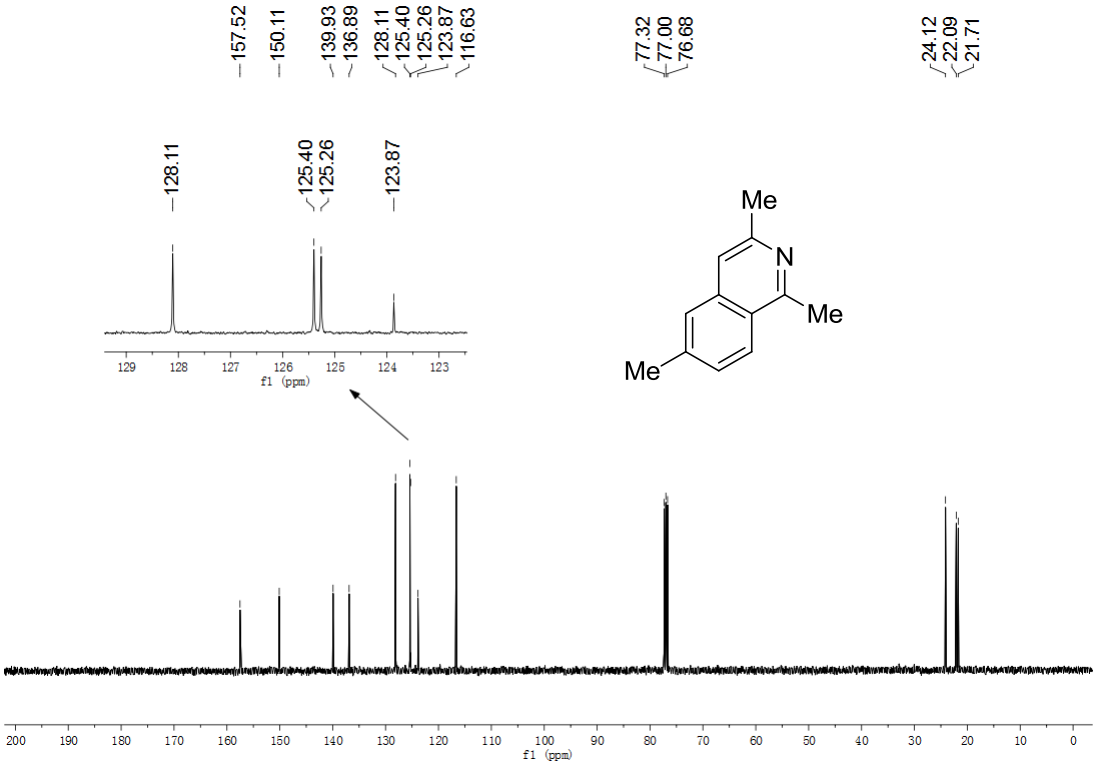
6. Copies of the ^{1}H NMR and ^{13}C NMR Spectra

1,3-Dimethylisoquinoline (3aa)

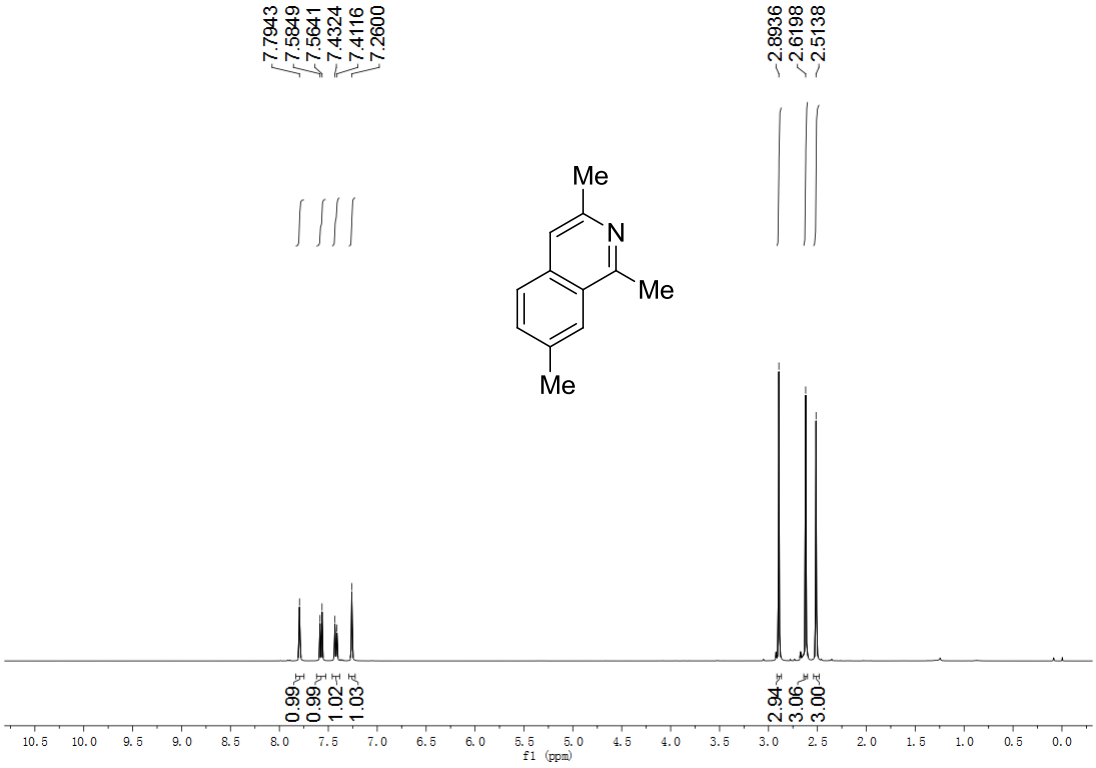


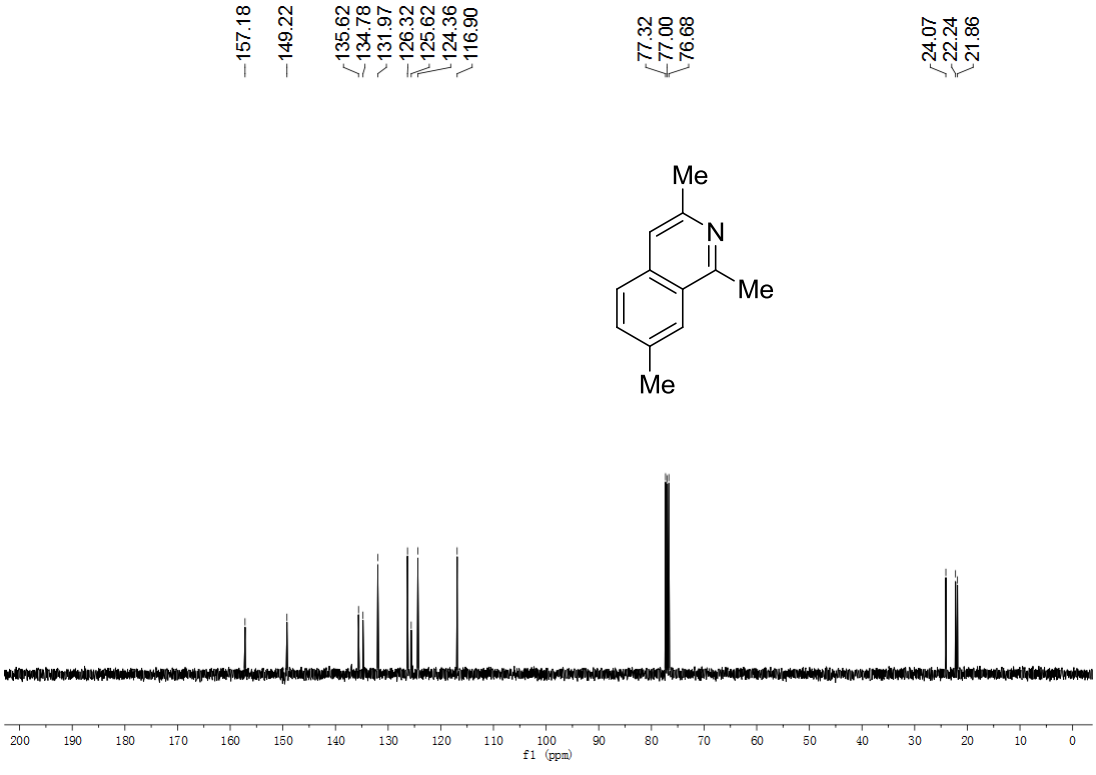
1,3,6-Trimethylisoquinoline (3ba)



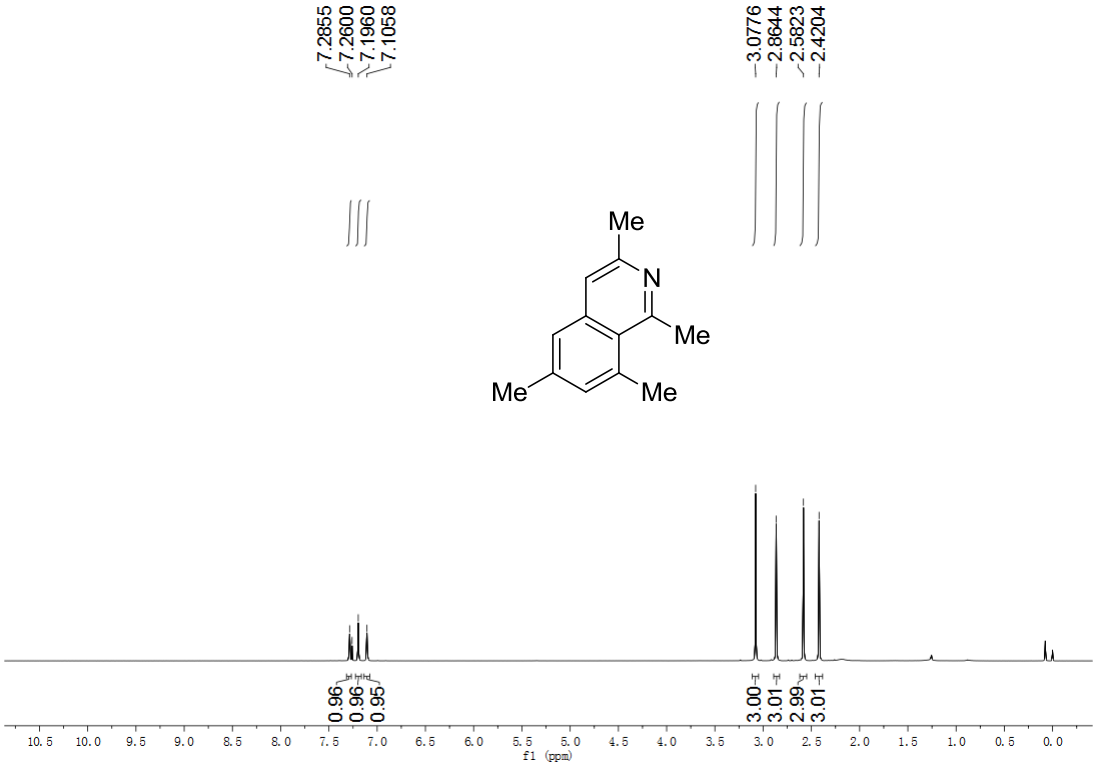


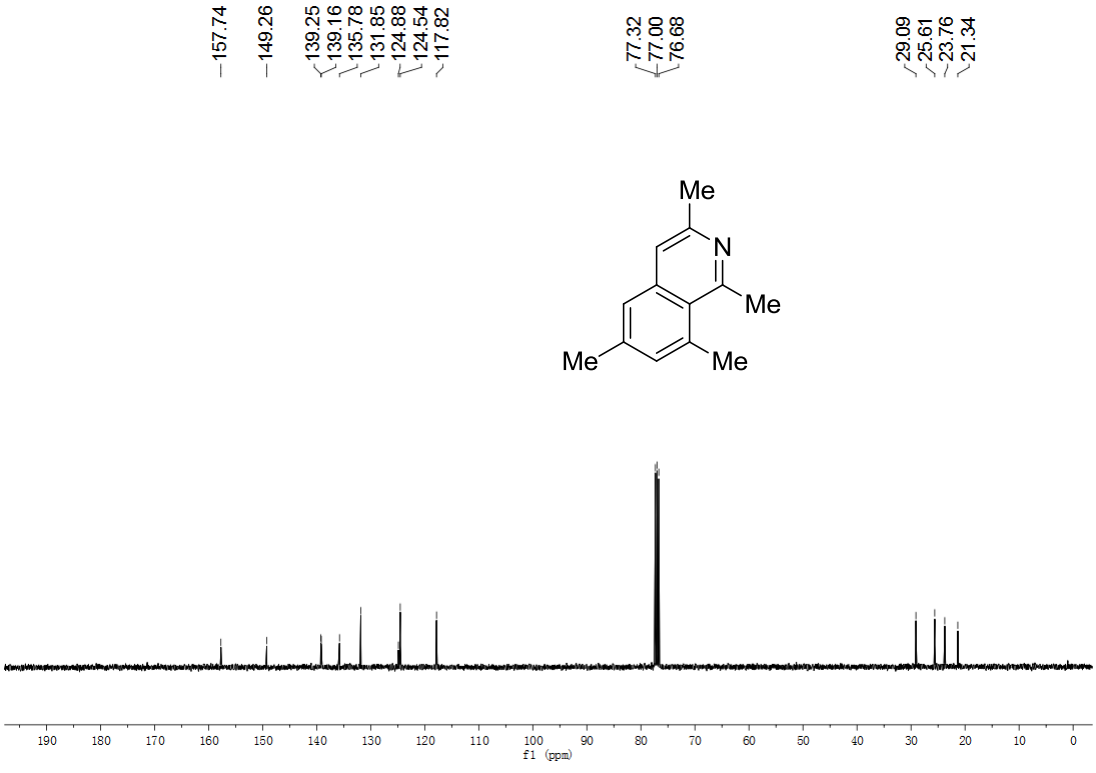
1,3,7-Trimethylisoquinoline (3ca)



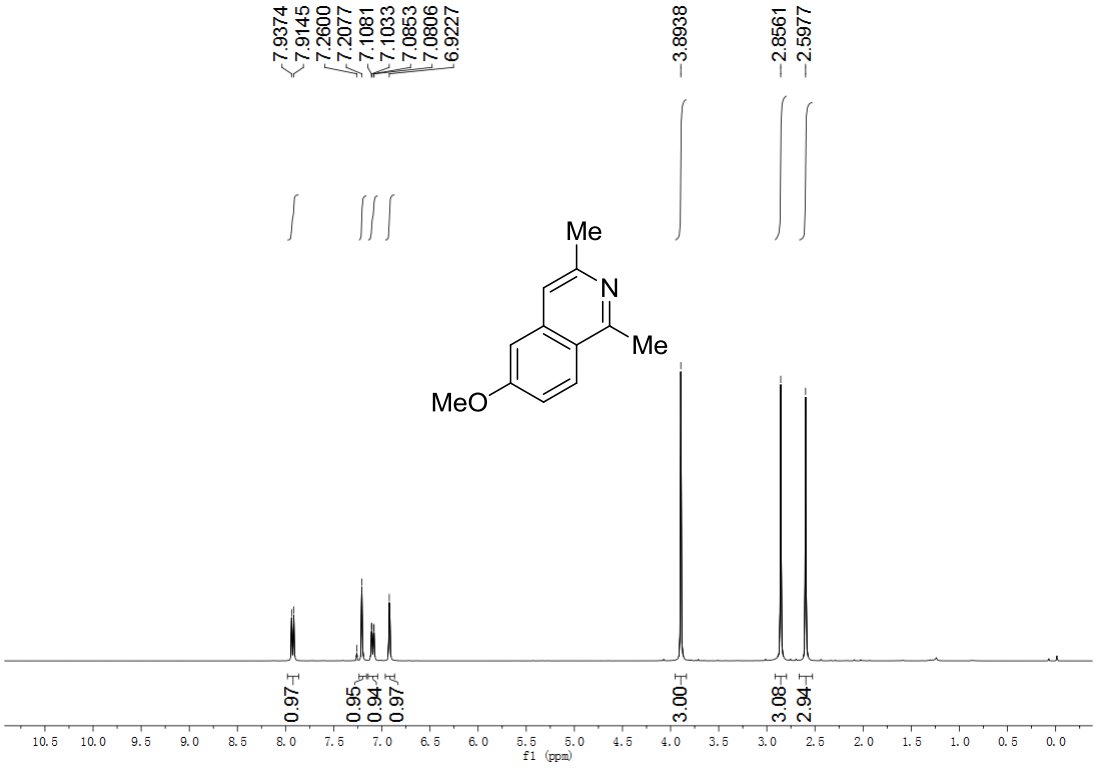


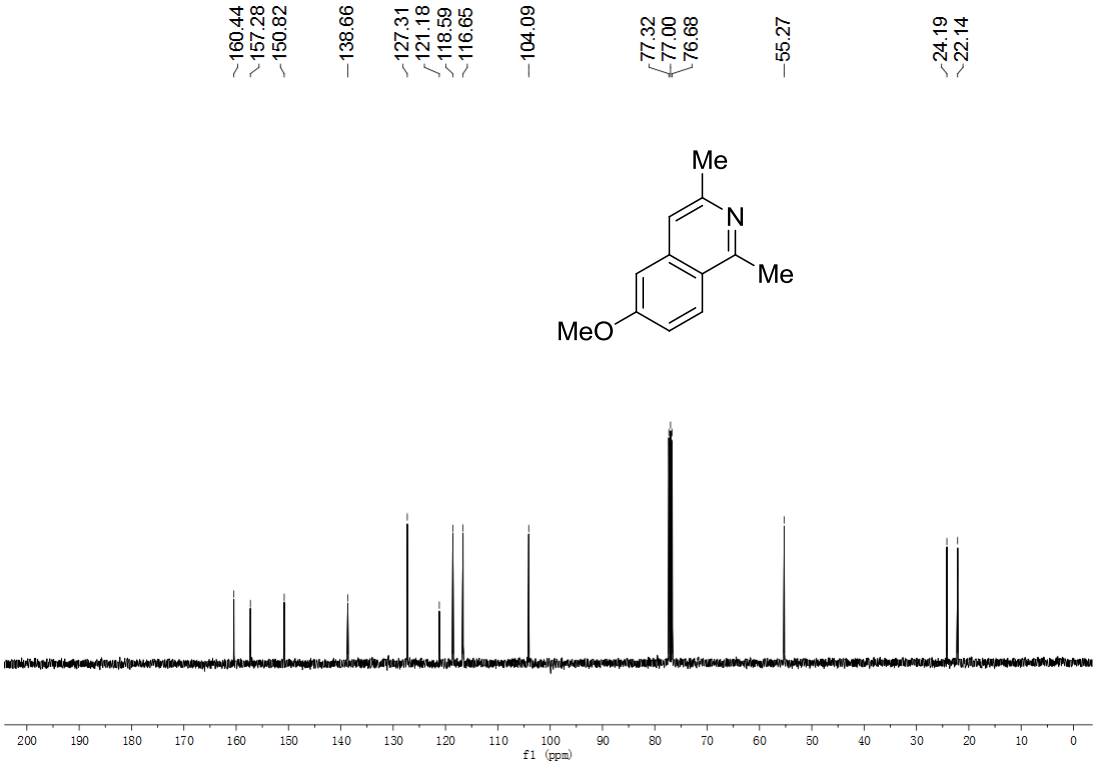
1,3,6,8-Tetramethylisoquinoline (3da)





6-Methoxy-1,3-dimethylisoquinoline (3ea)





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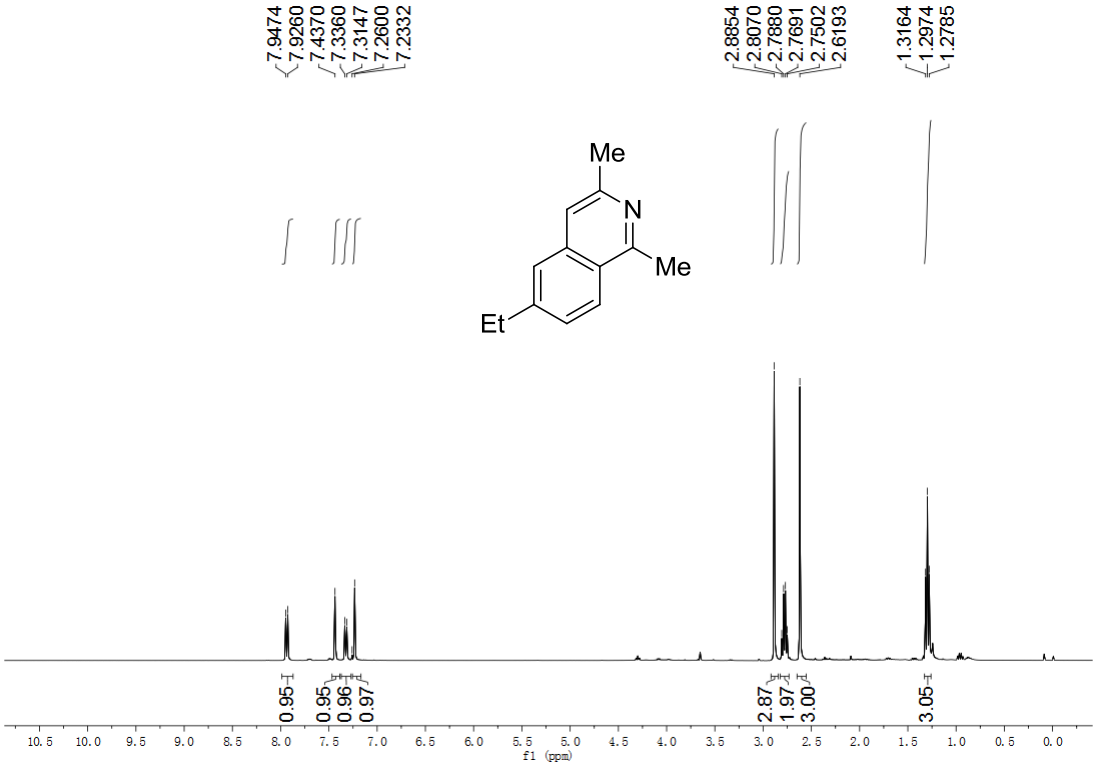

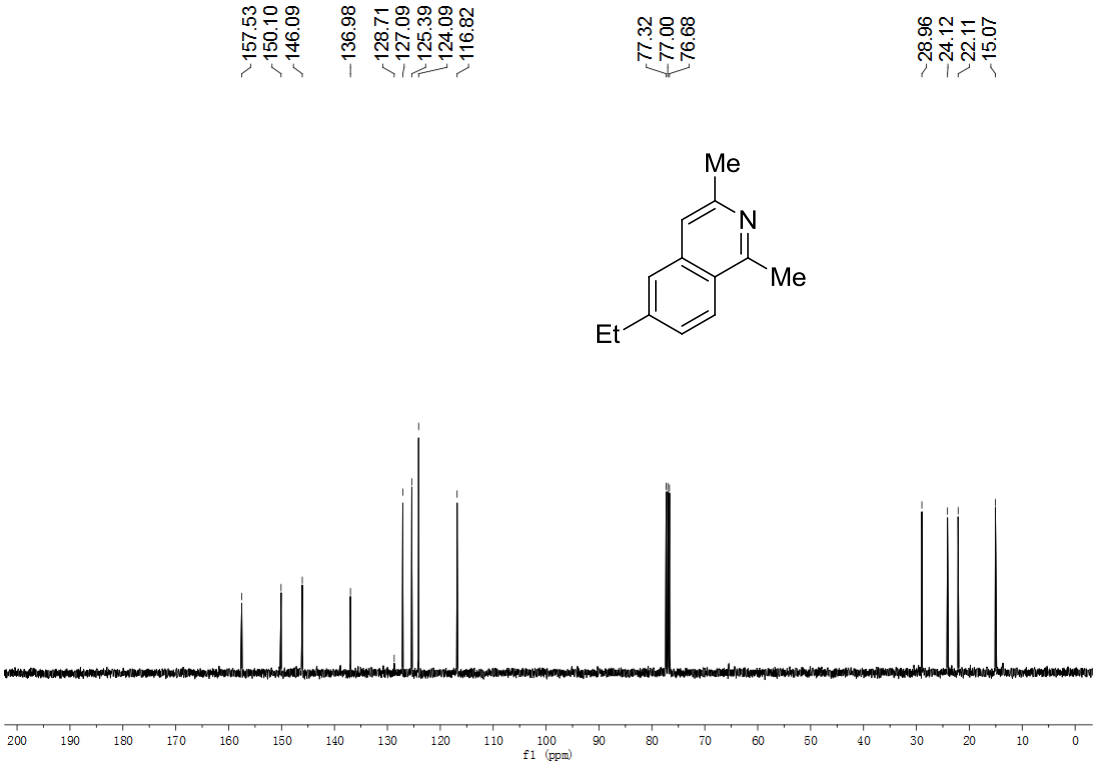

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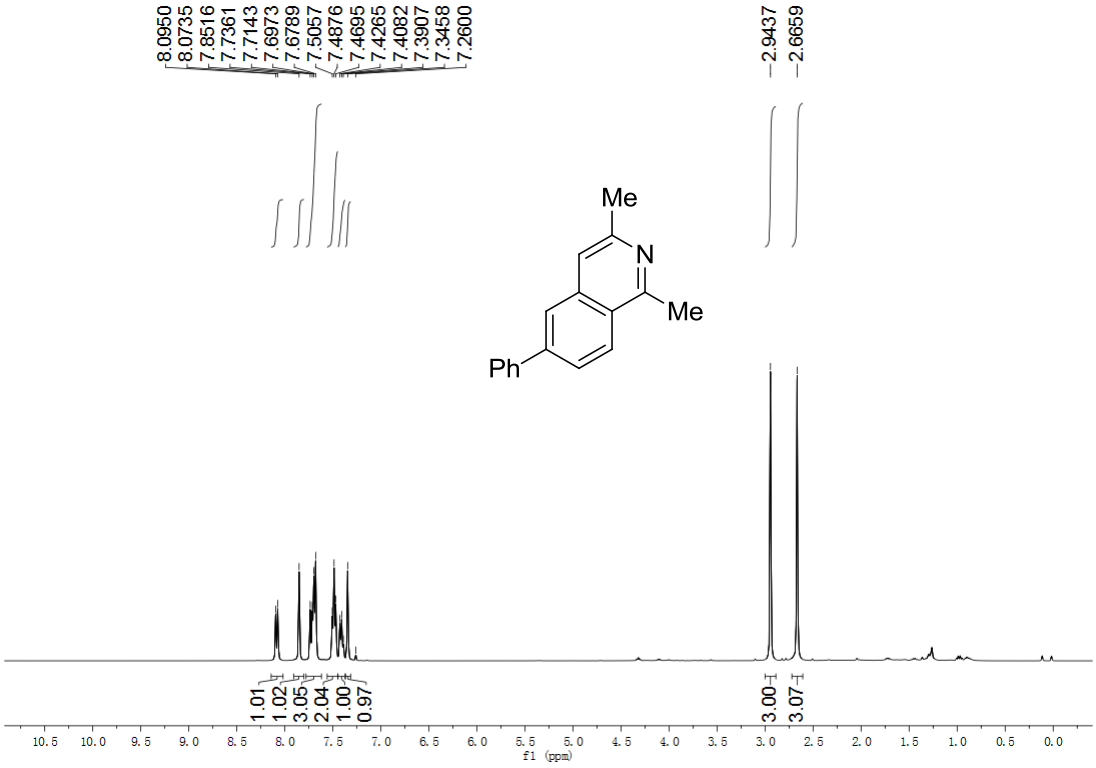

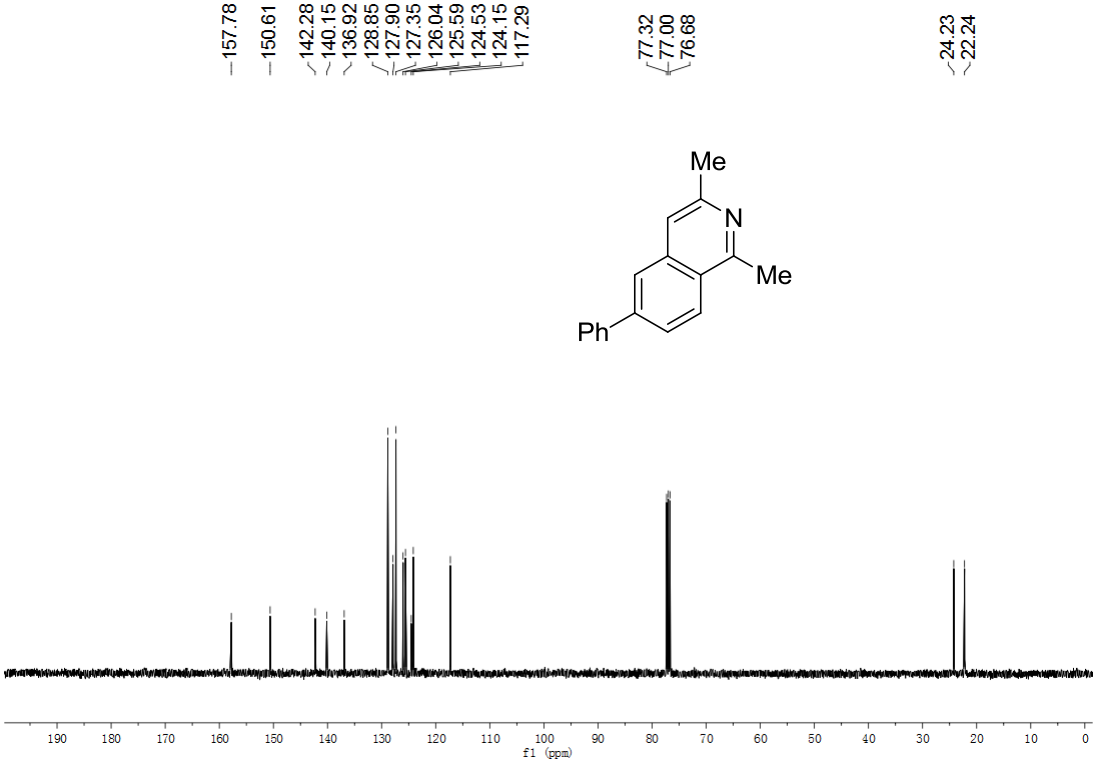

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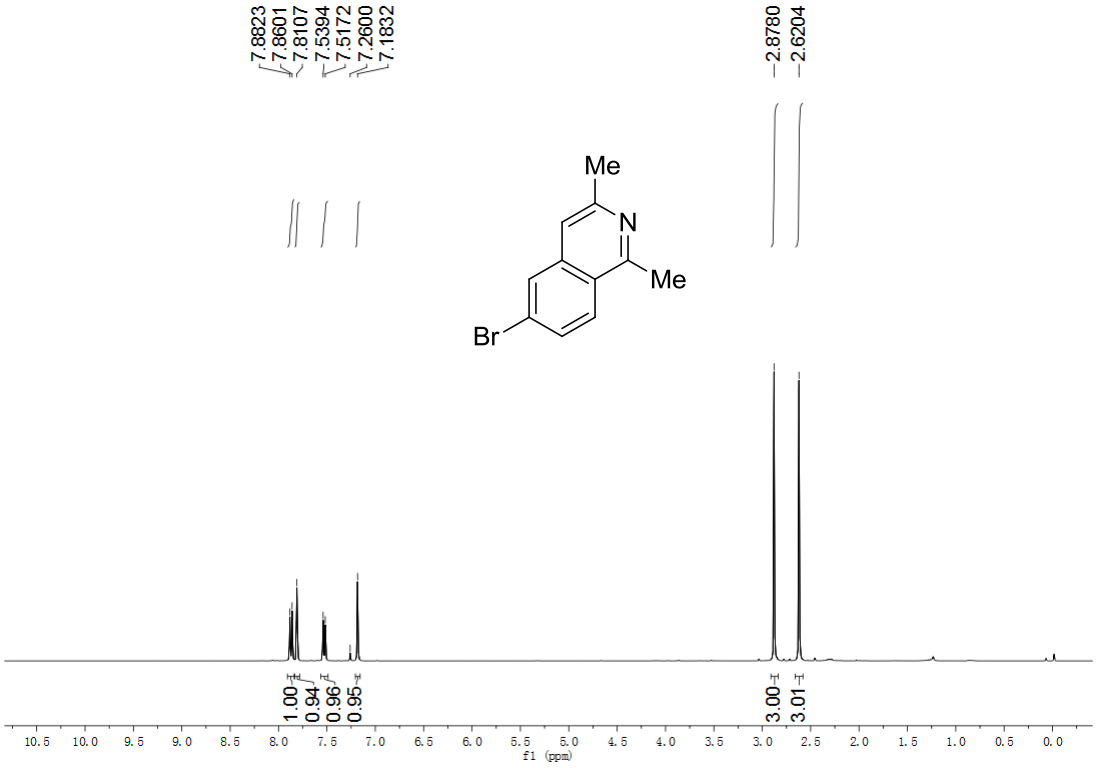

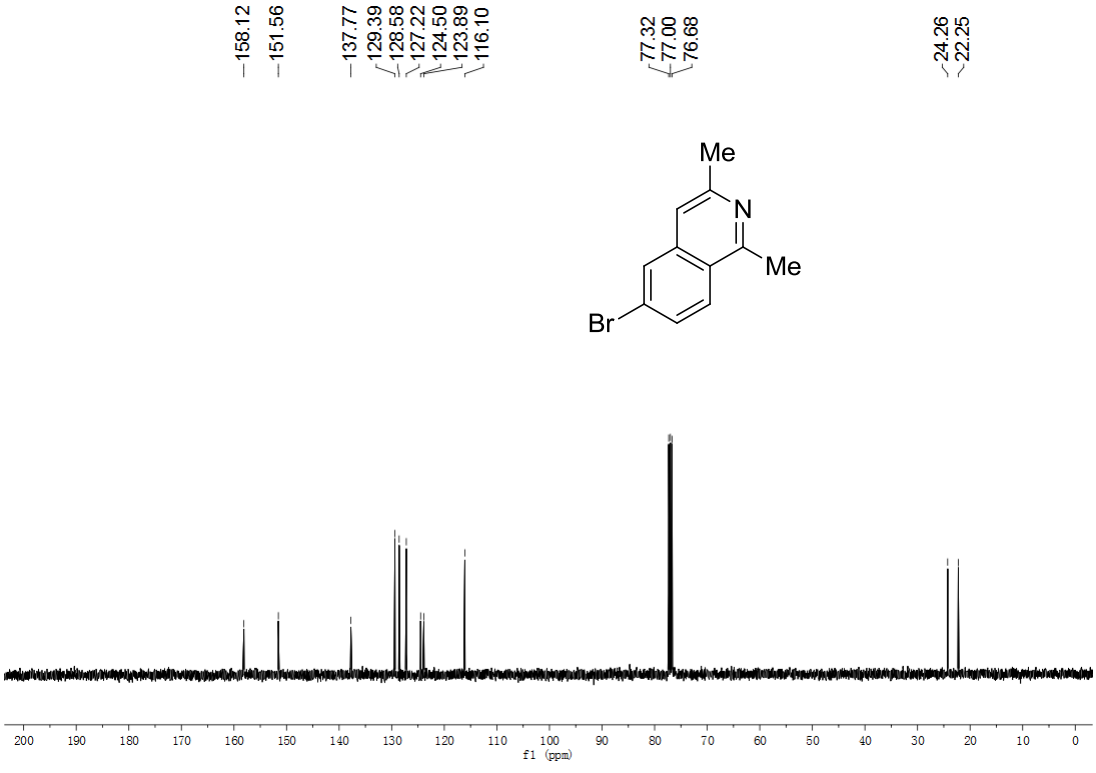

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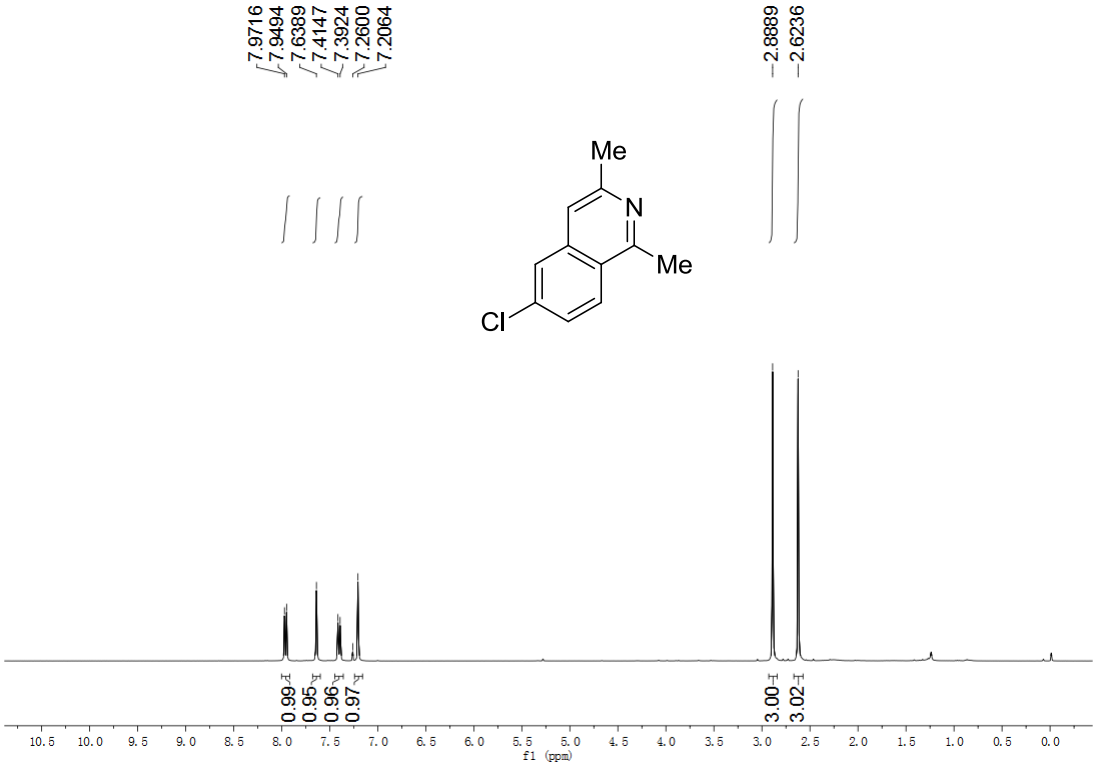

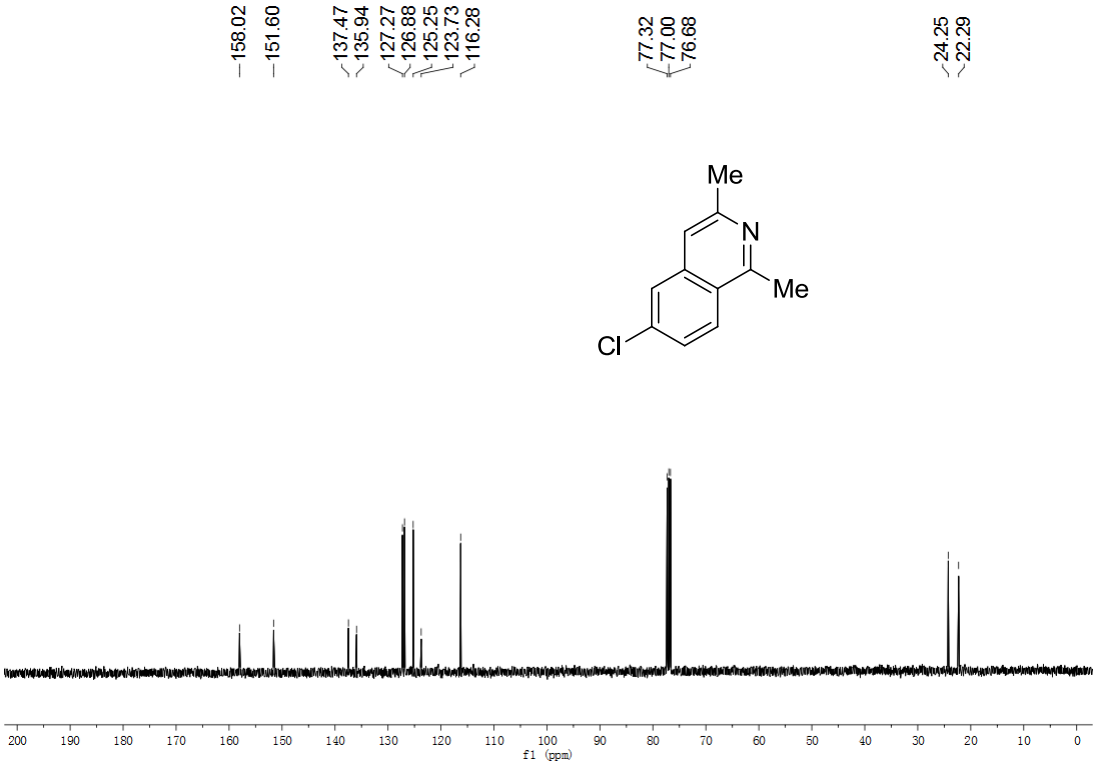

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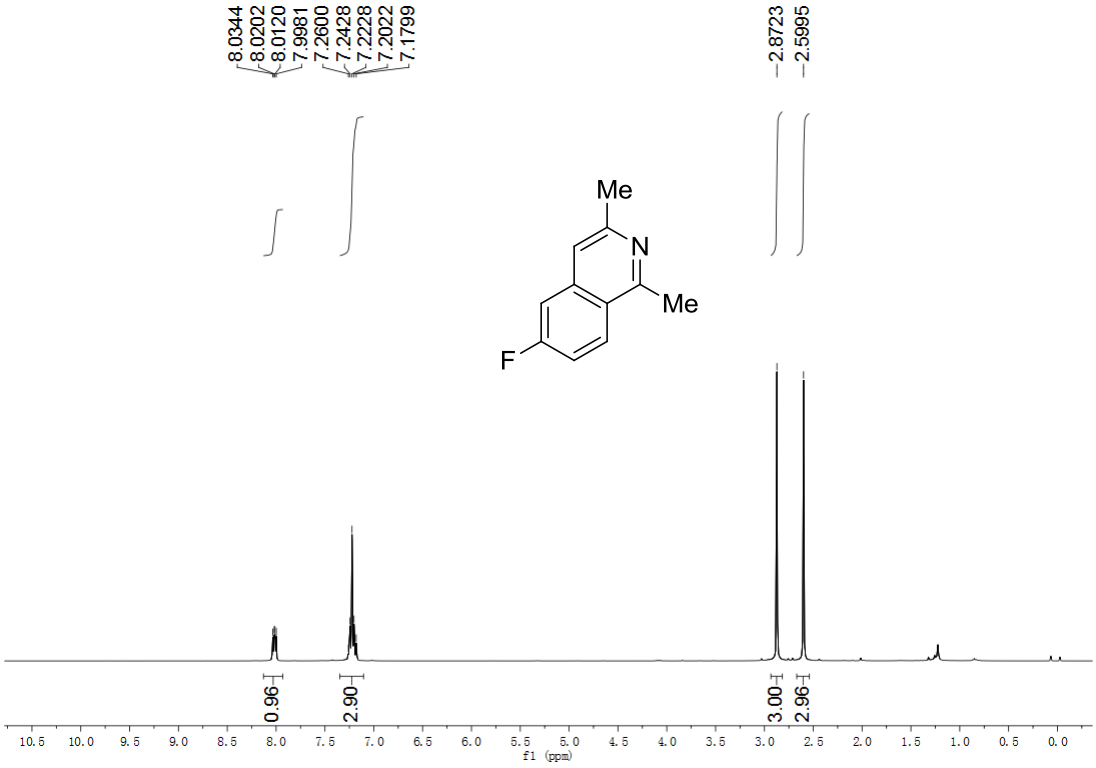

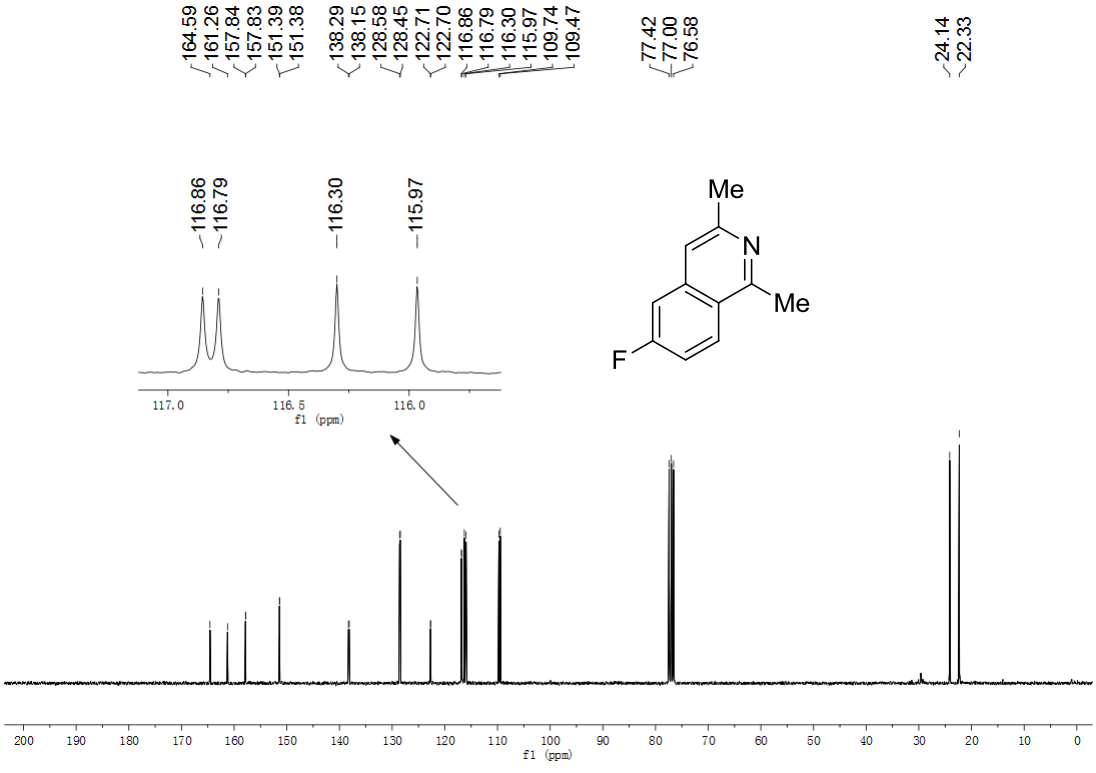

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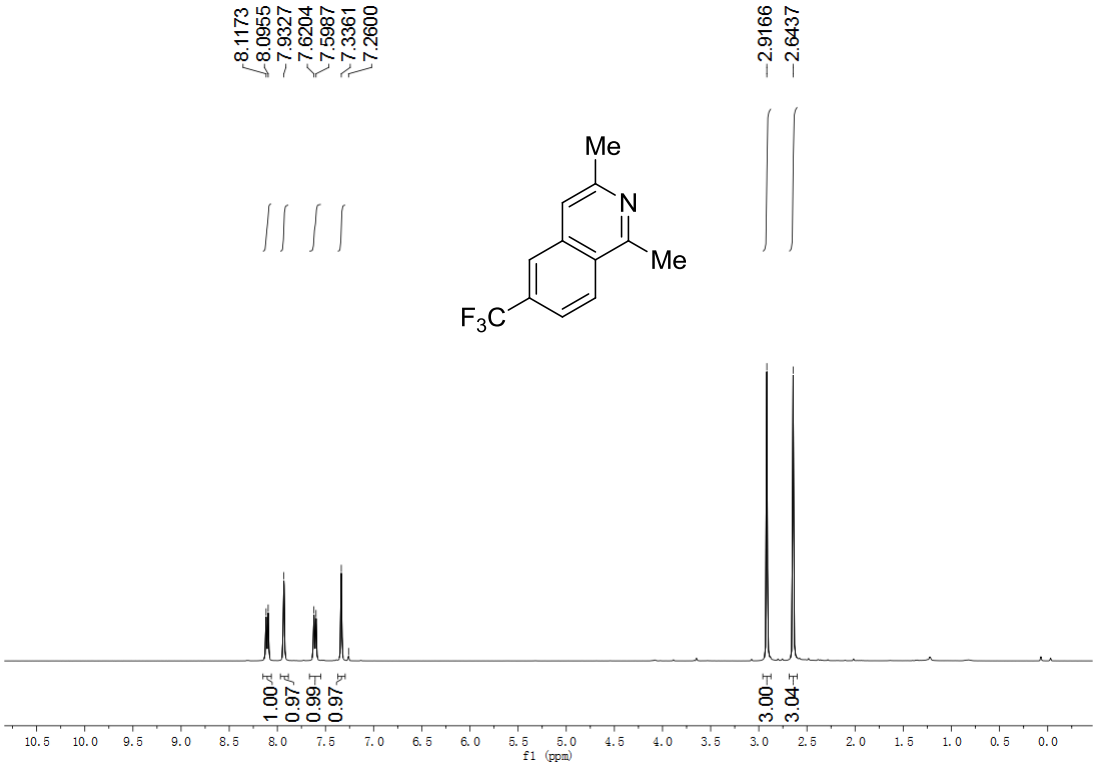

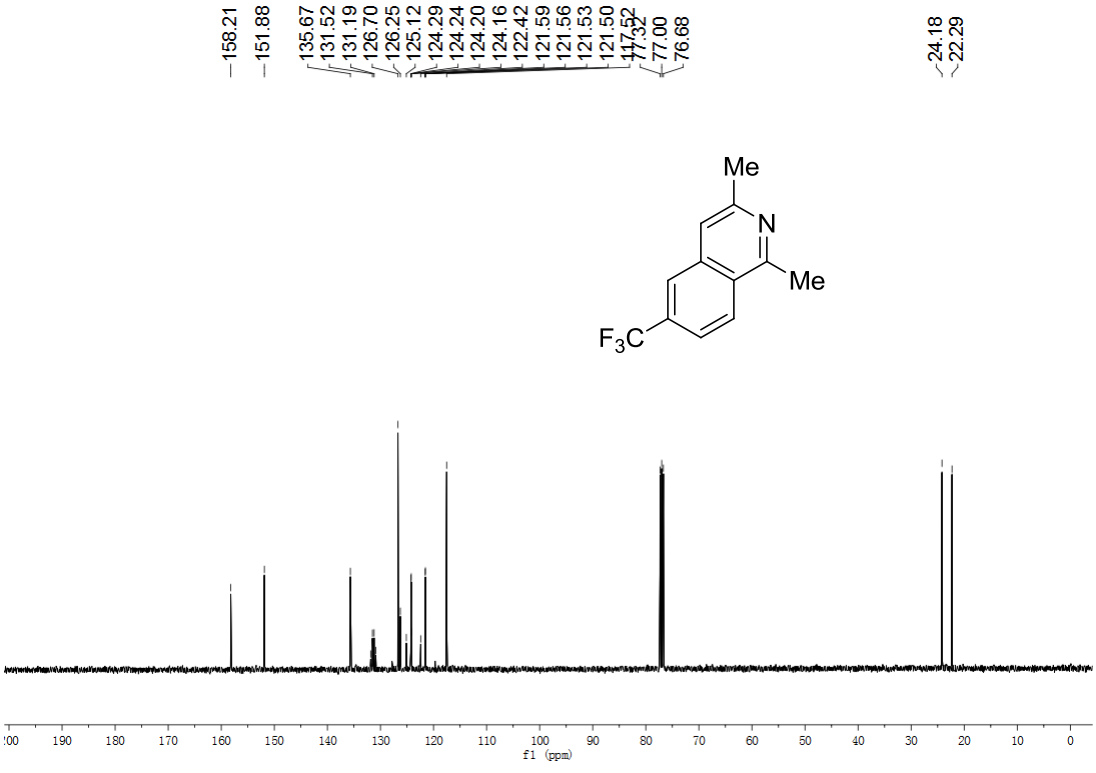

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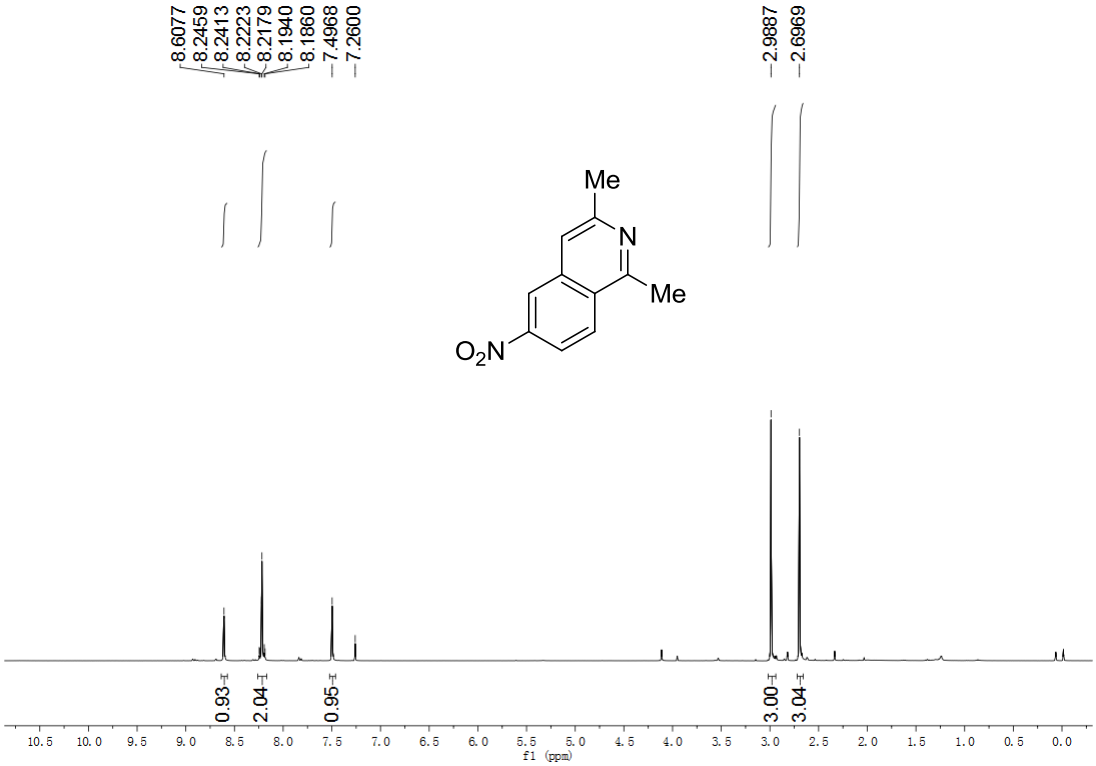

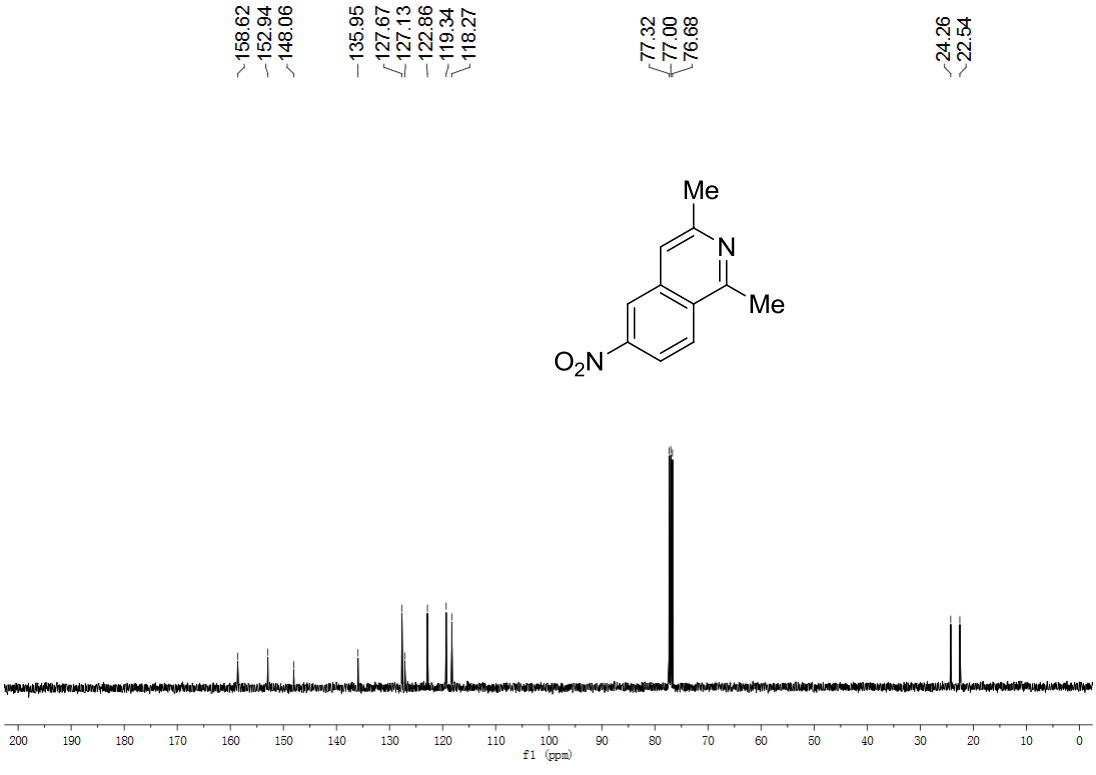

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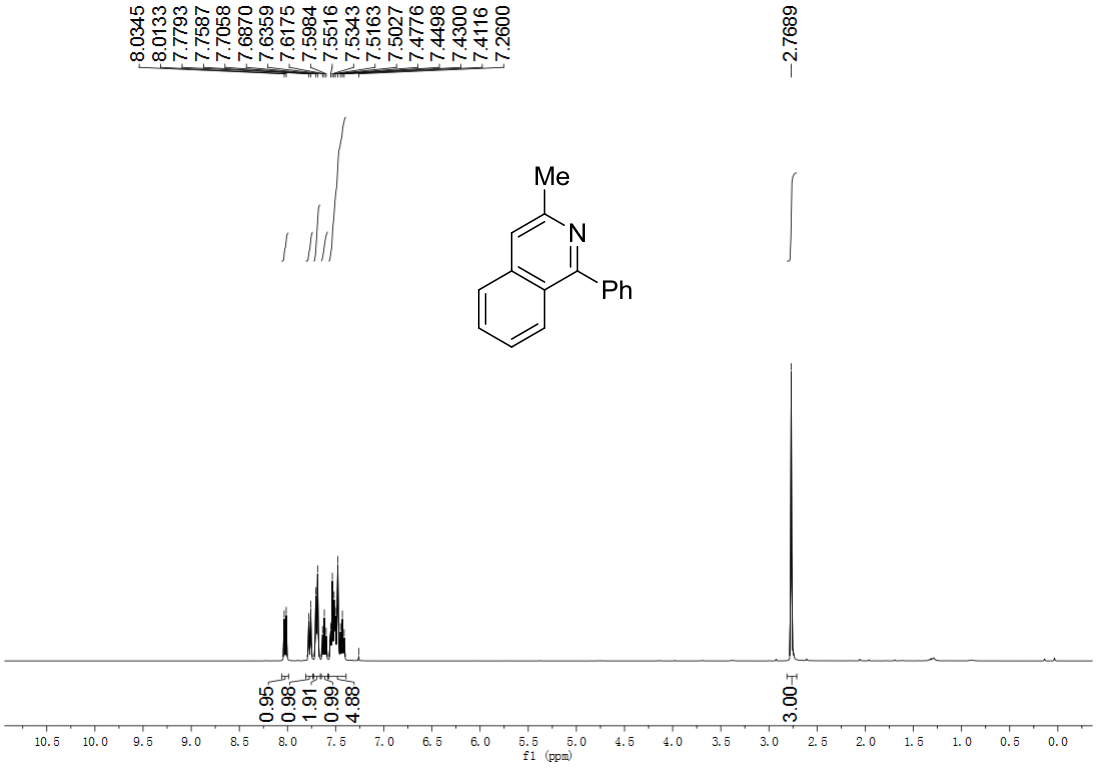

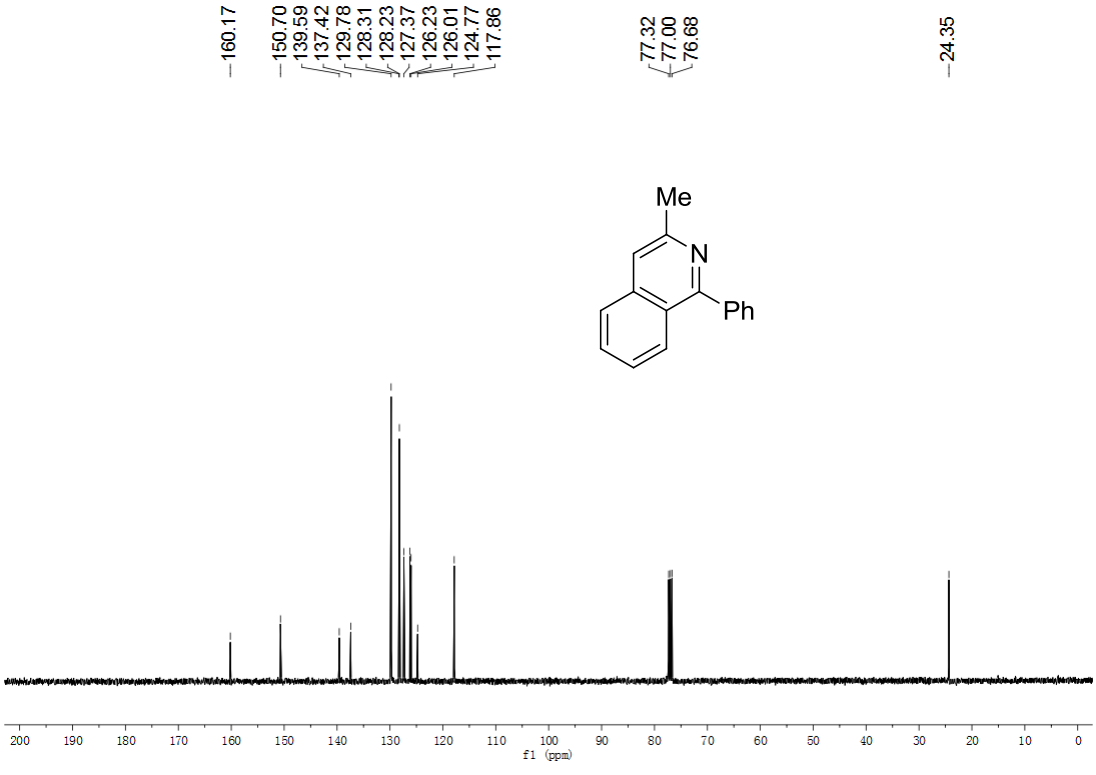

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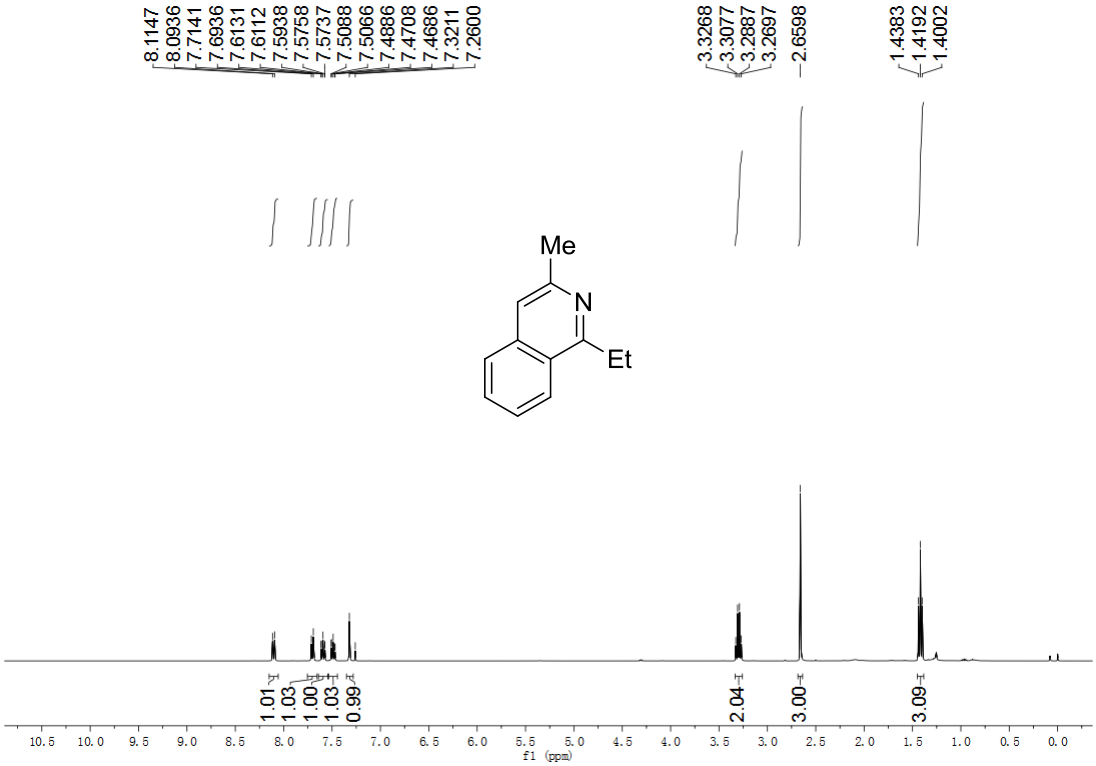

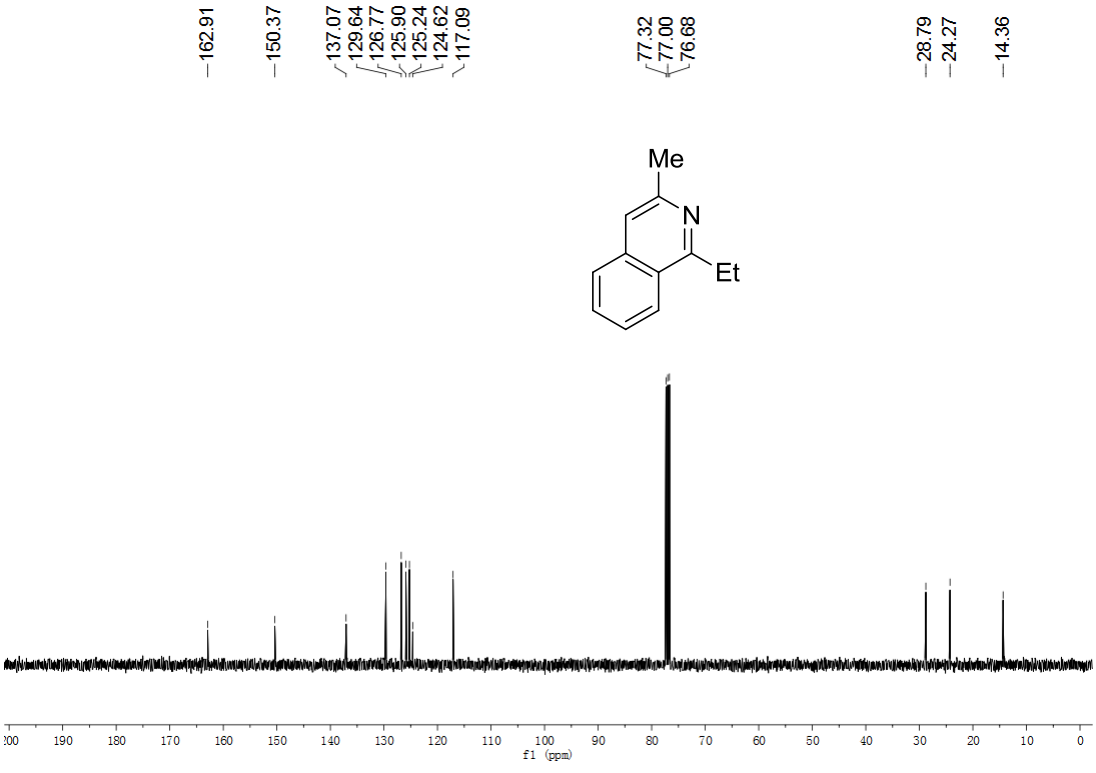

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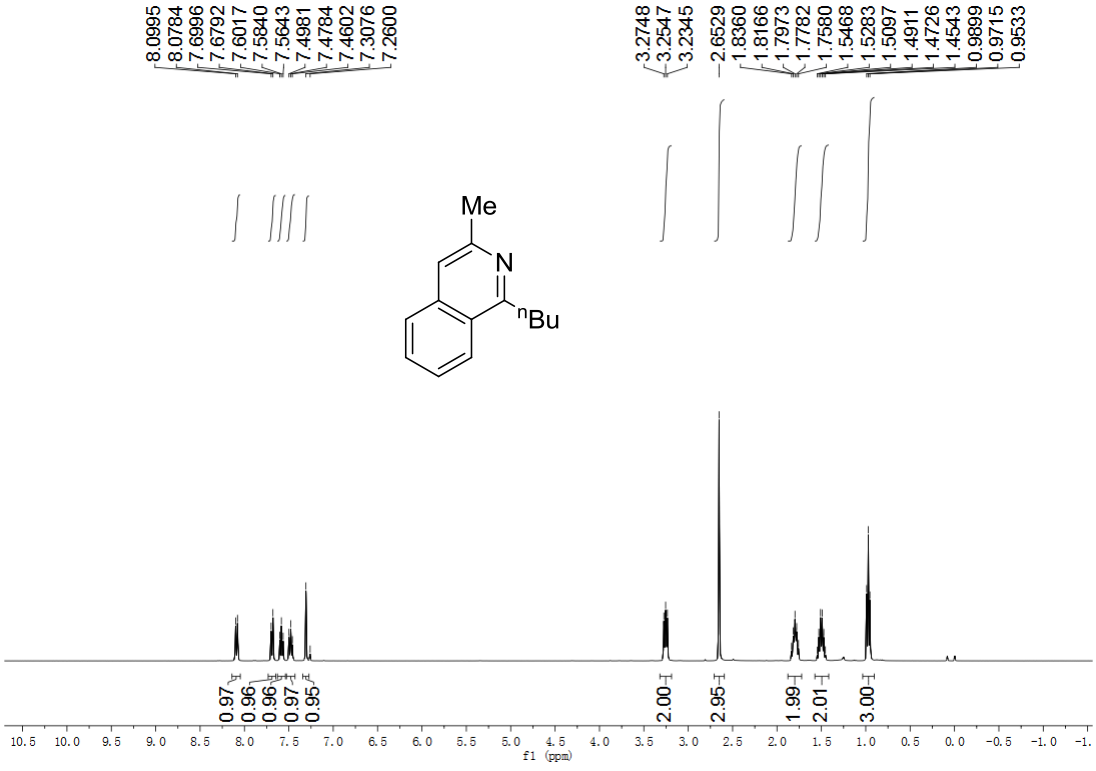

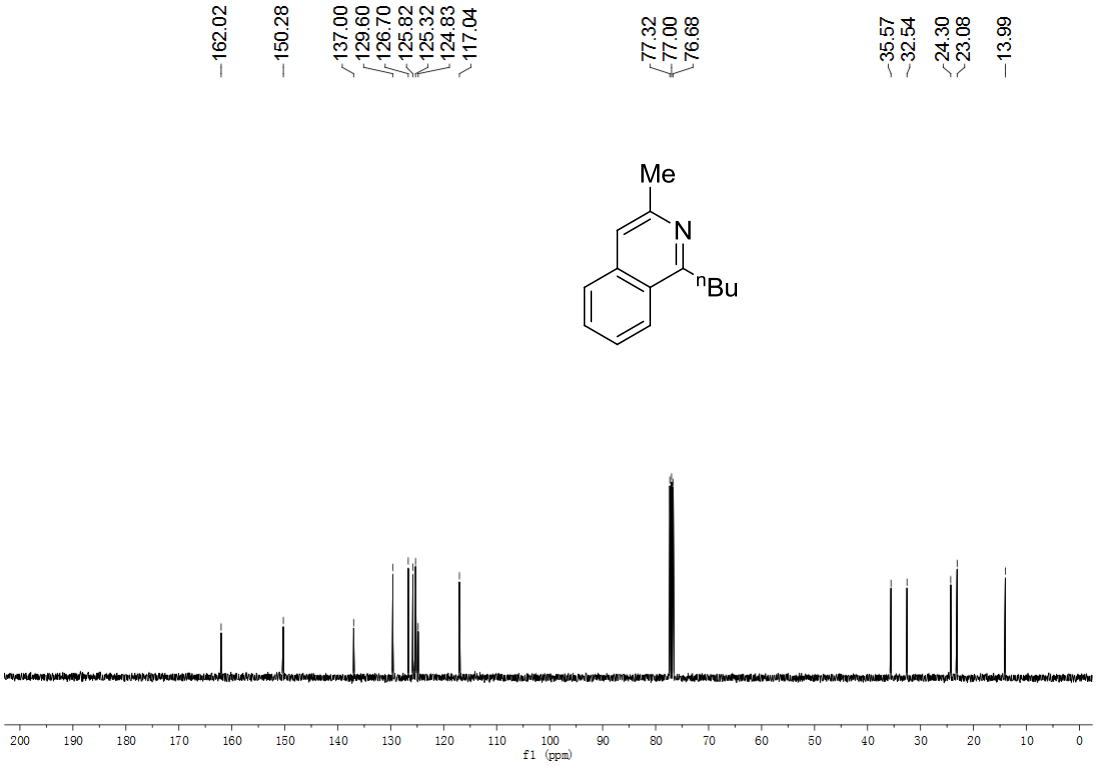

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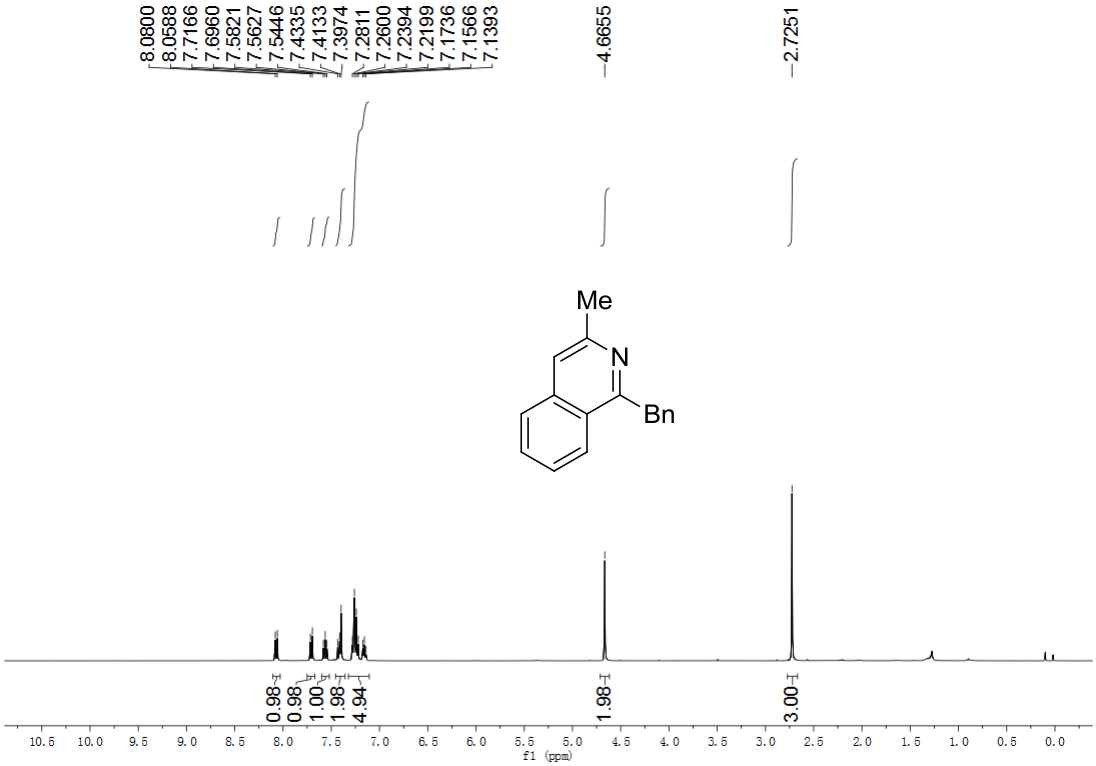

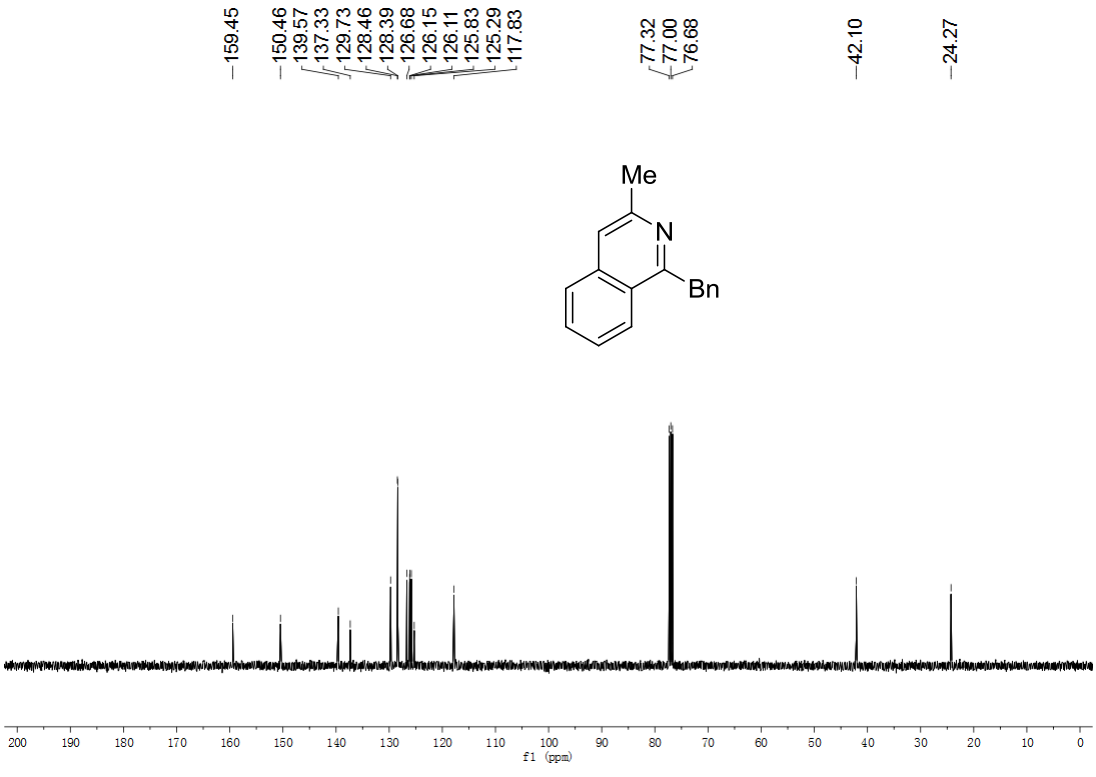

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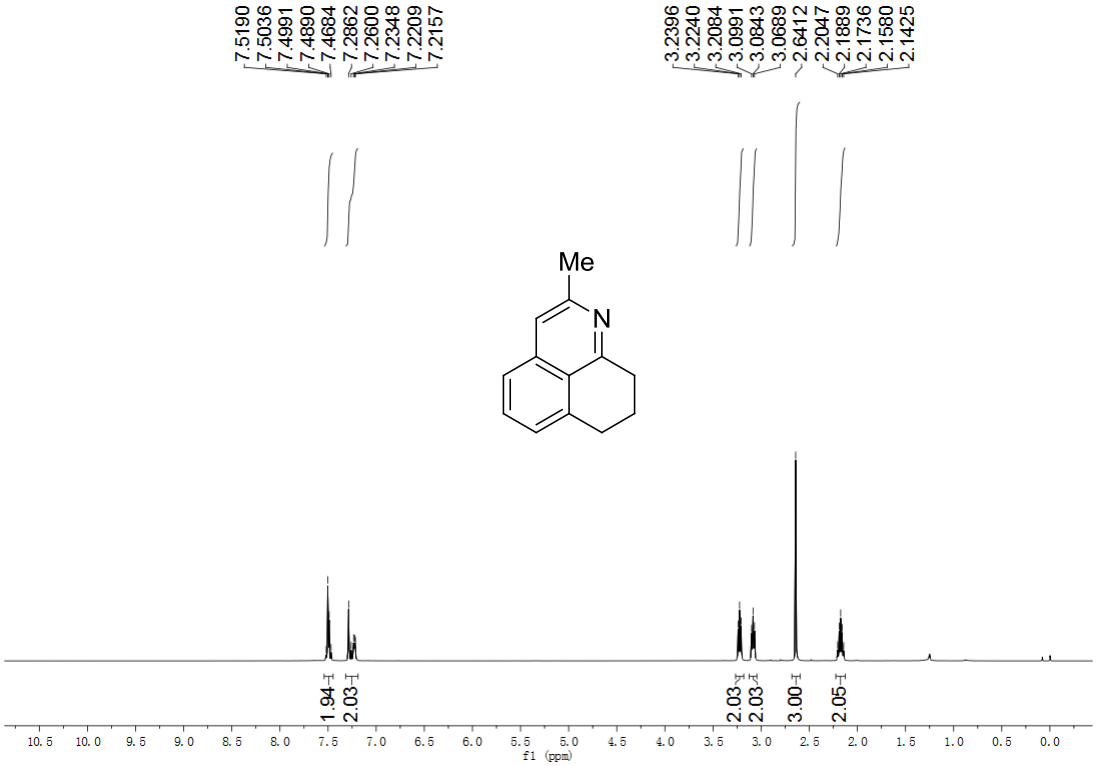

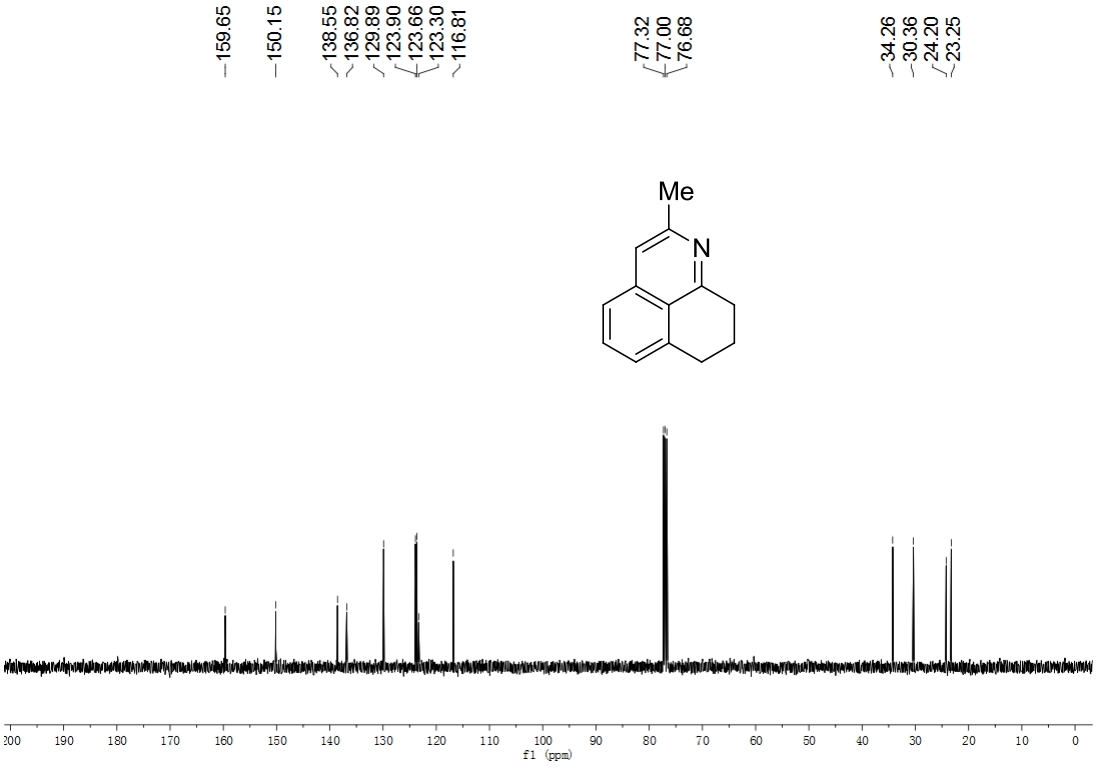

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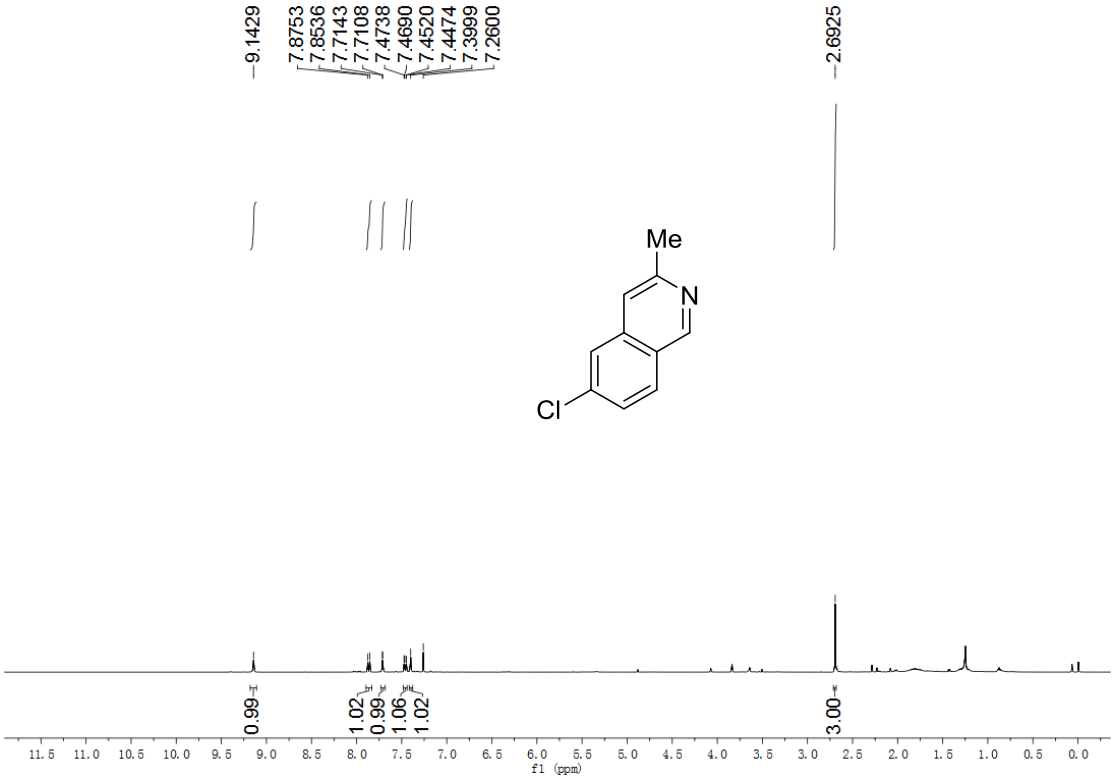

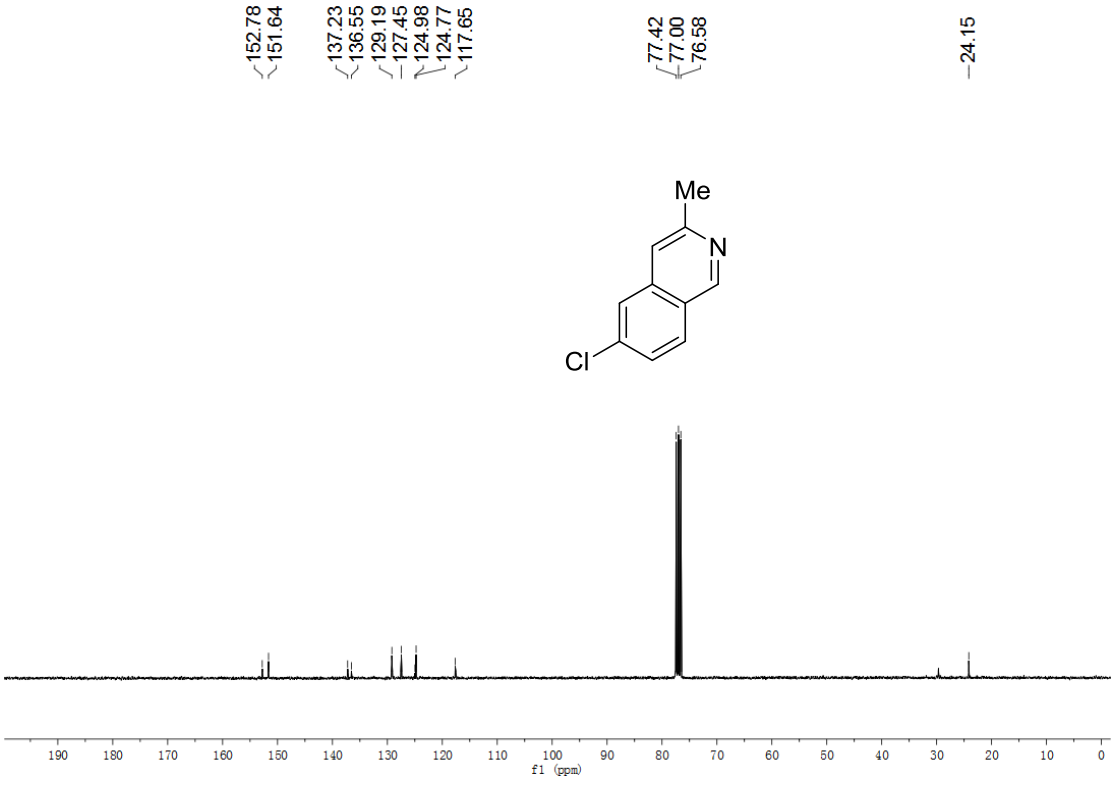

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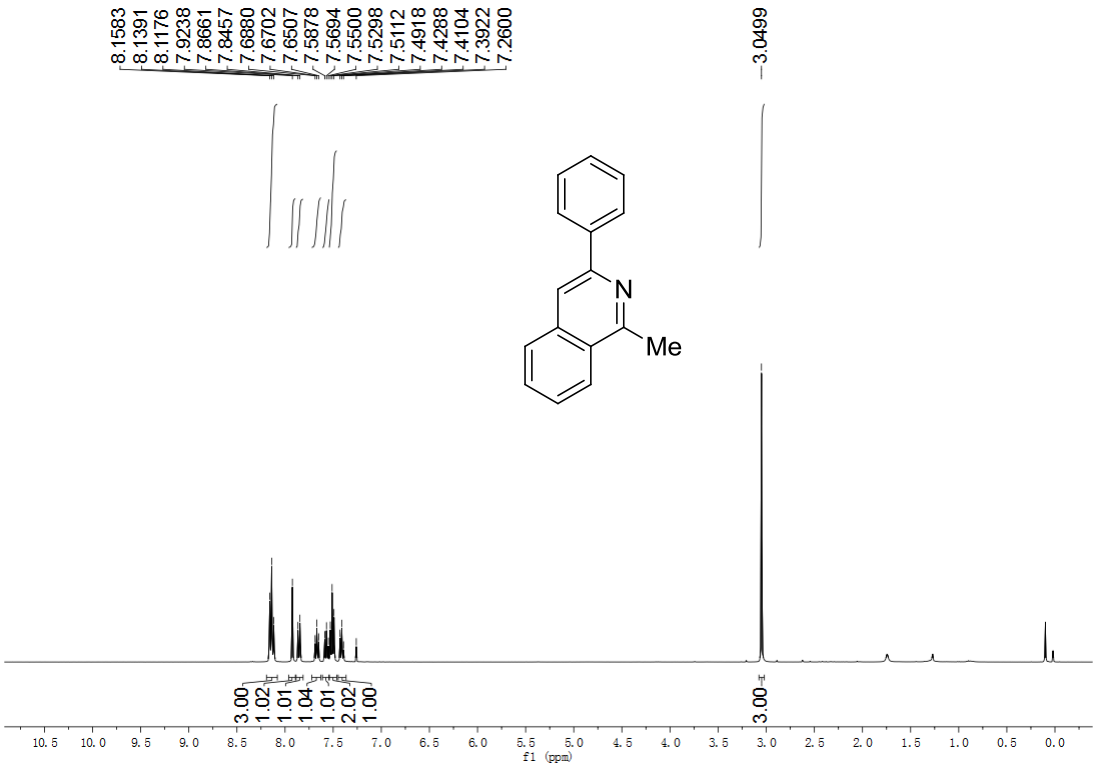

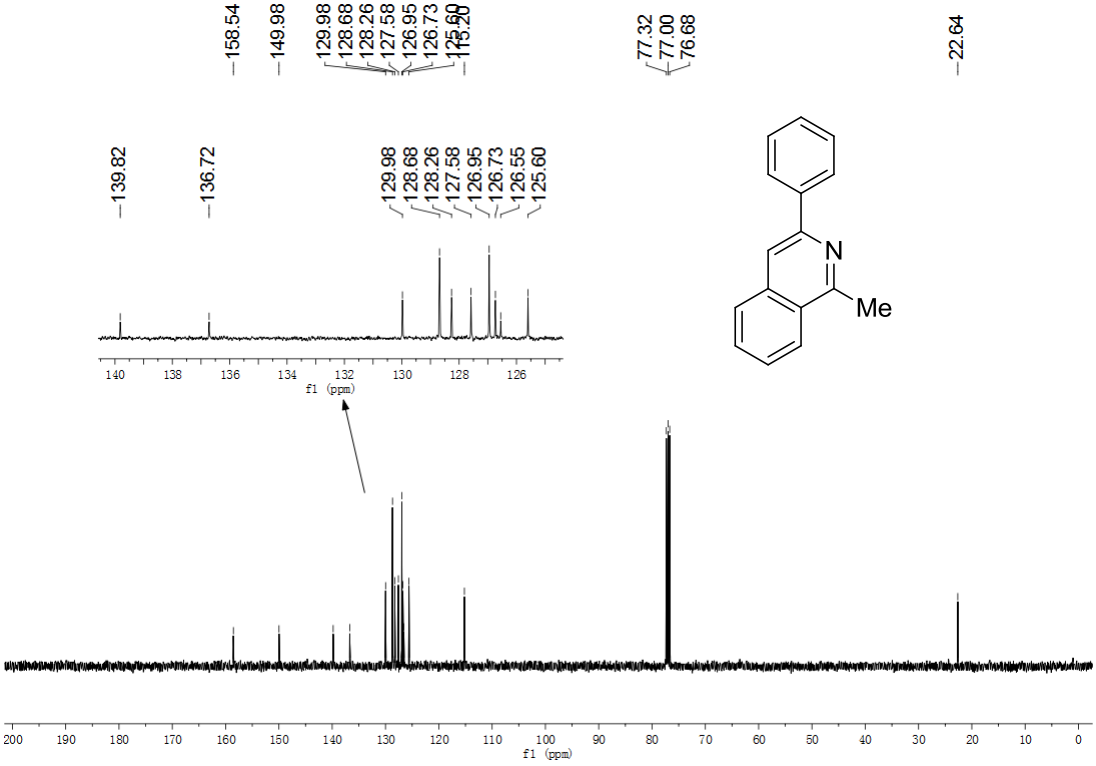

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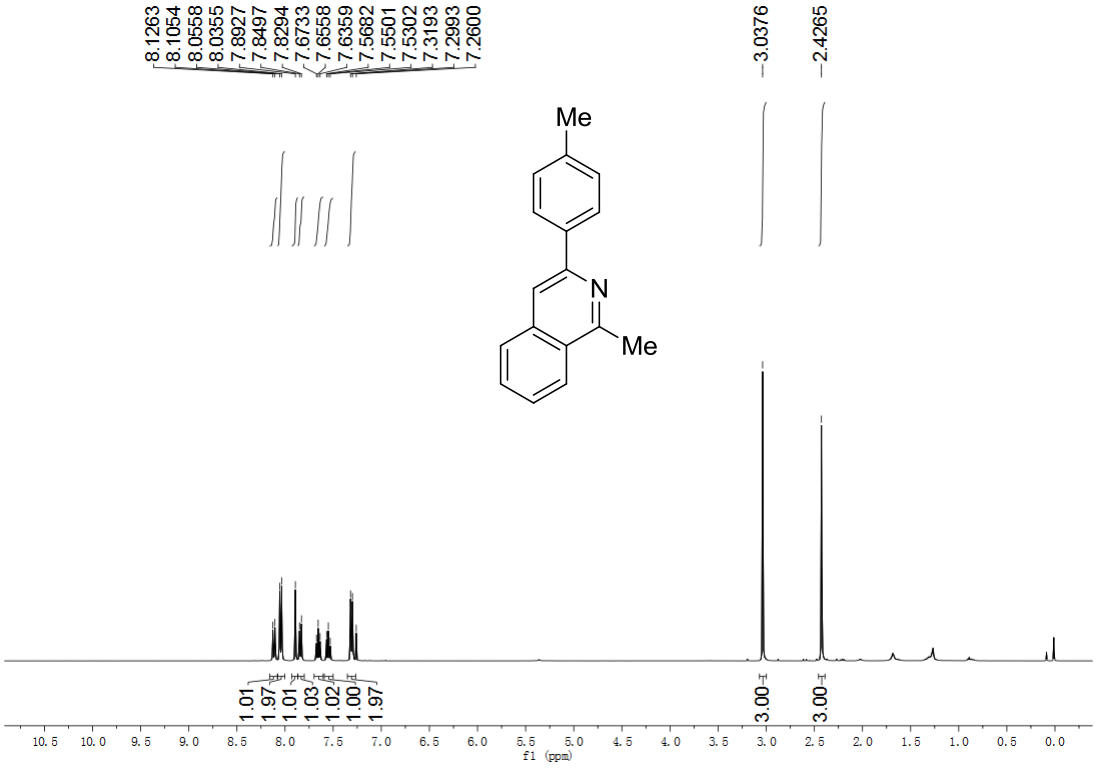

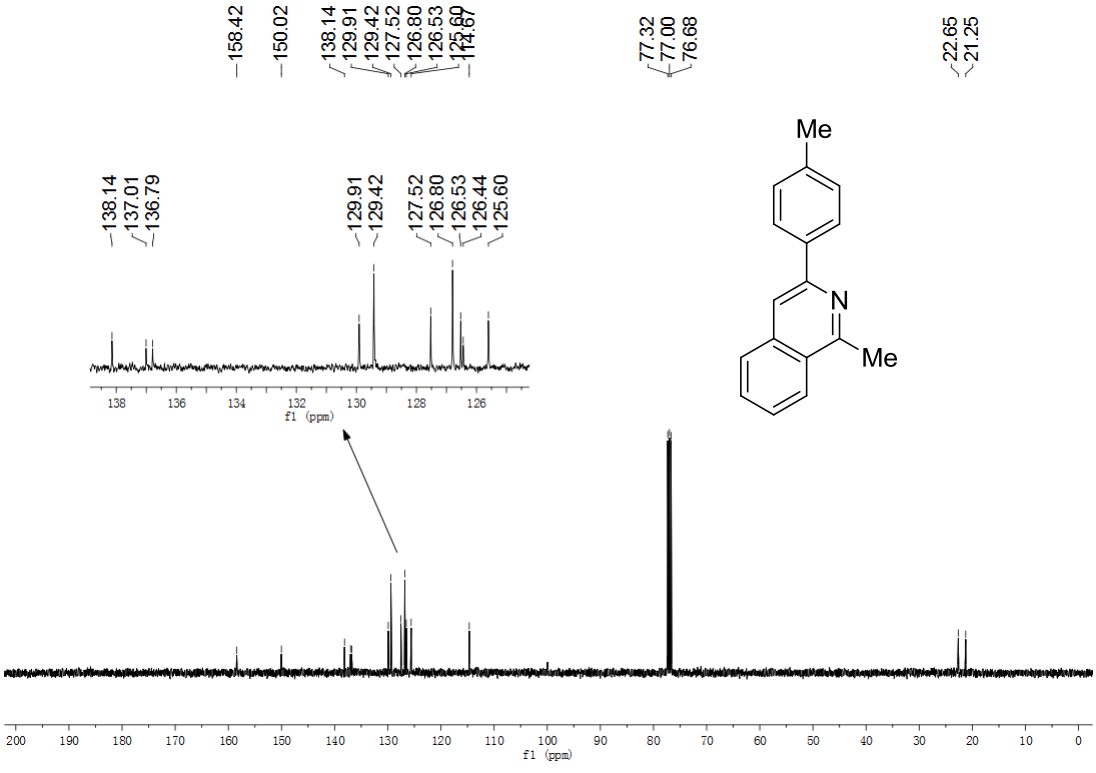

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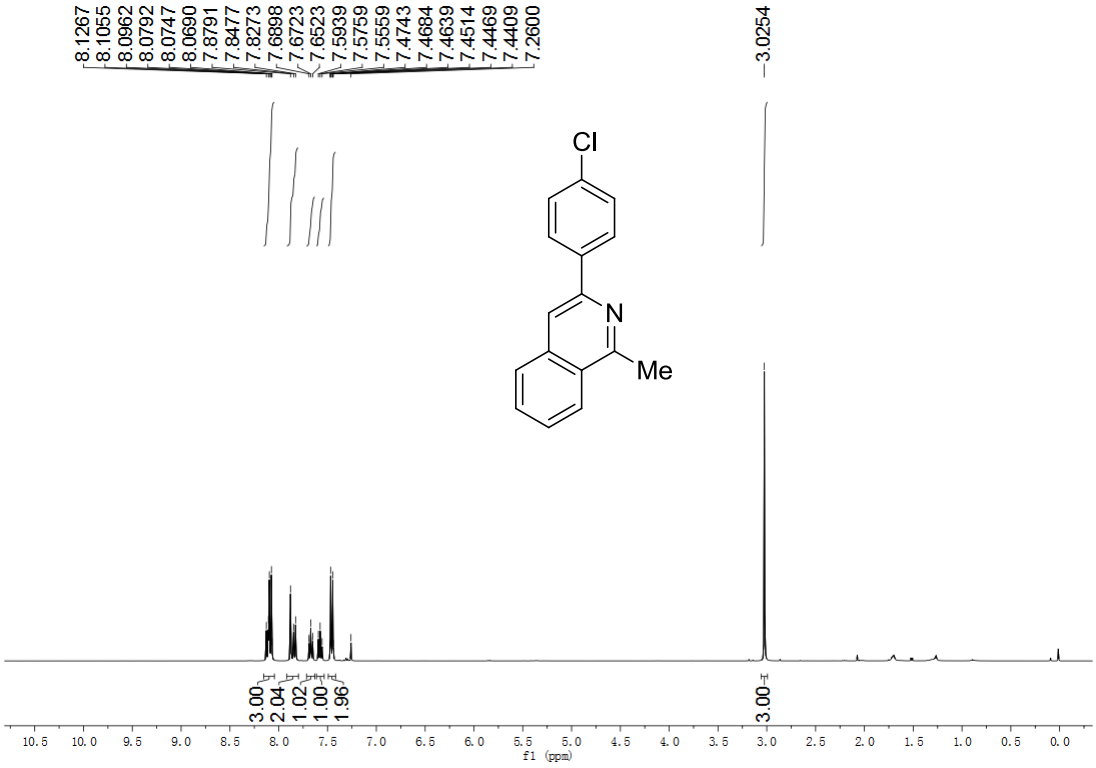

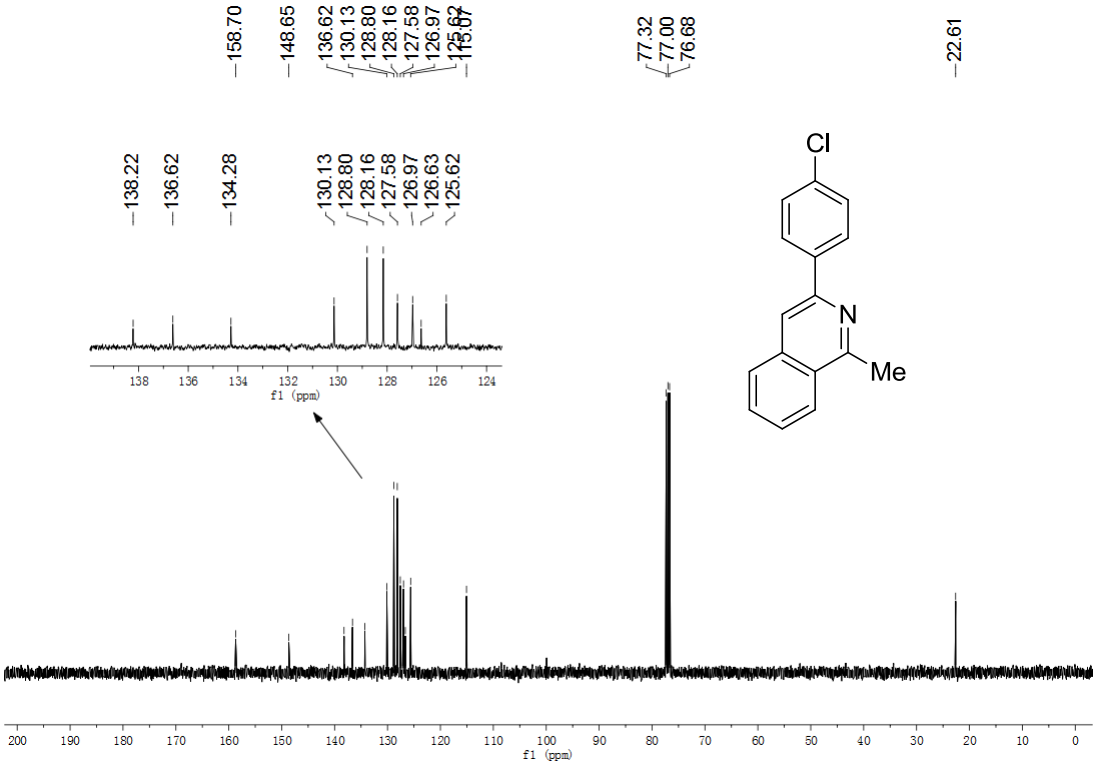

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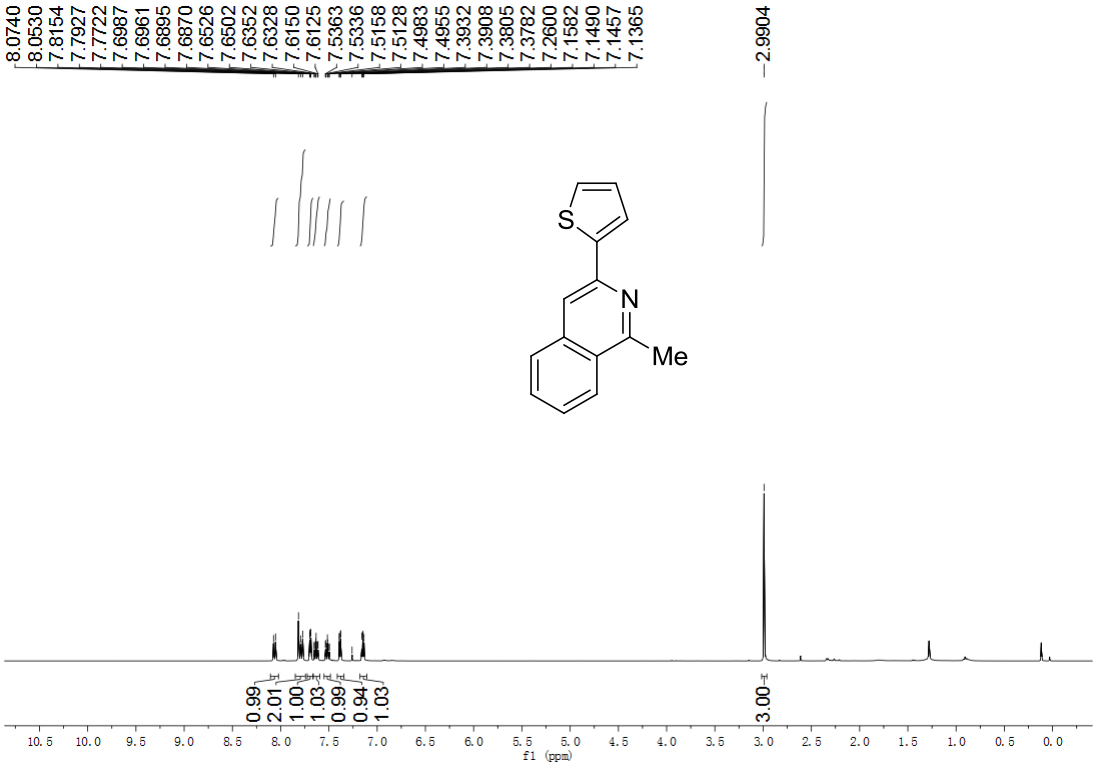

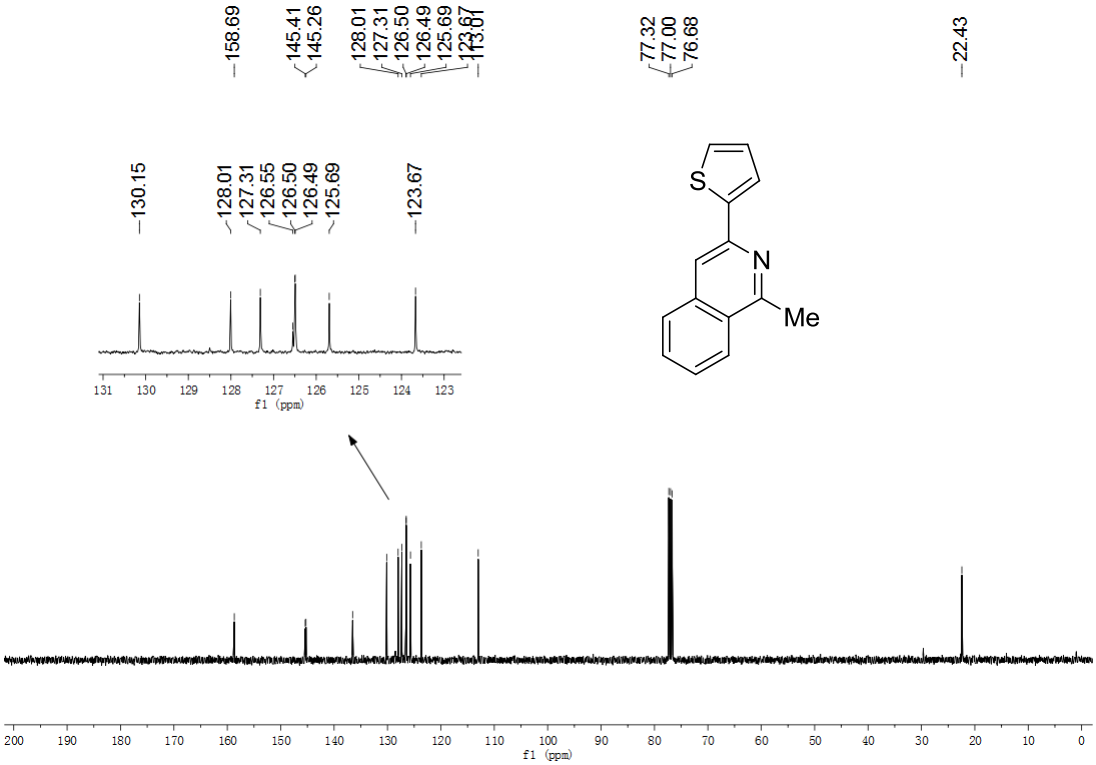

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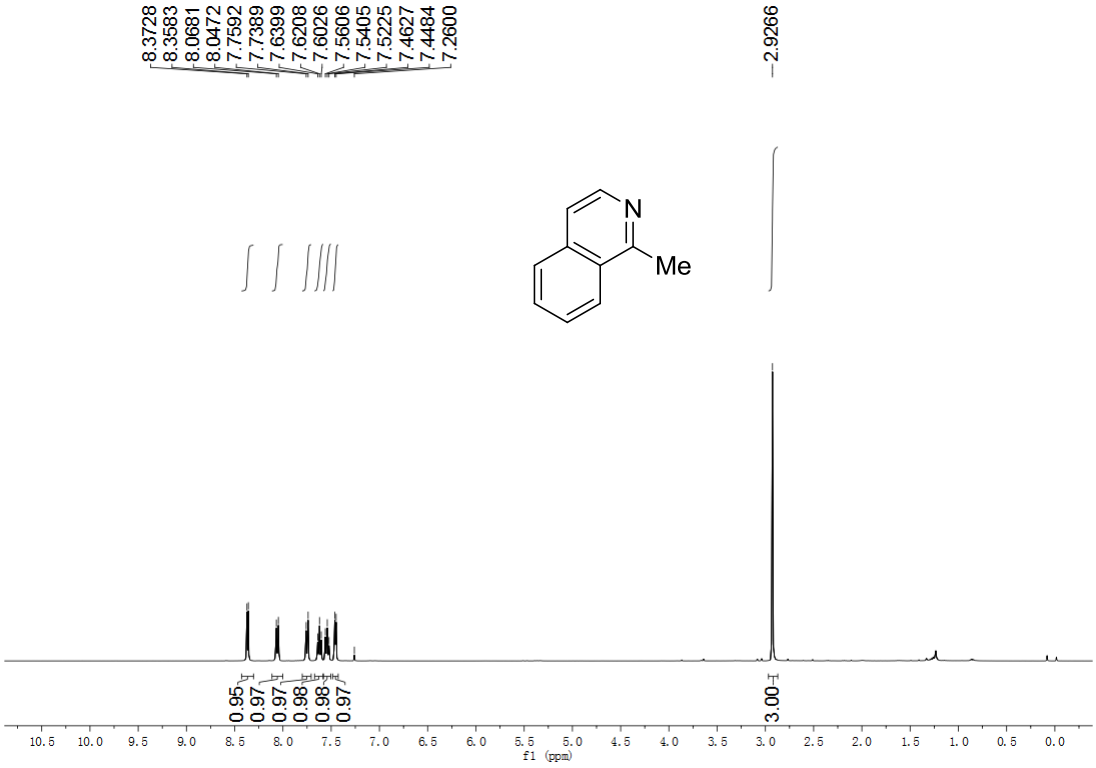

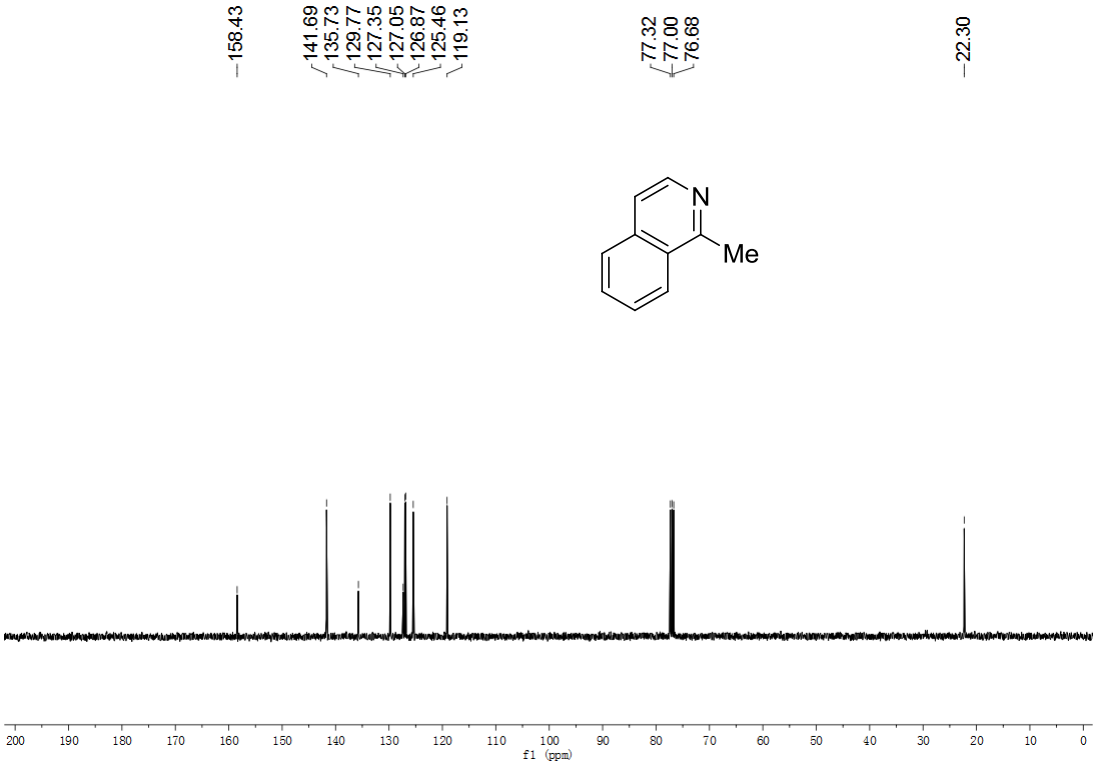

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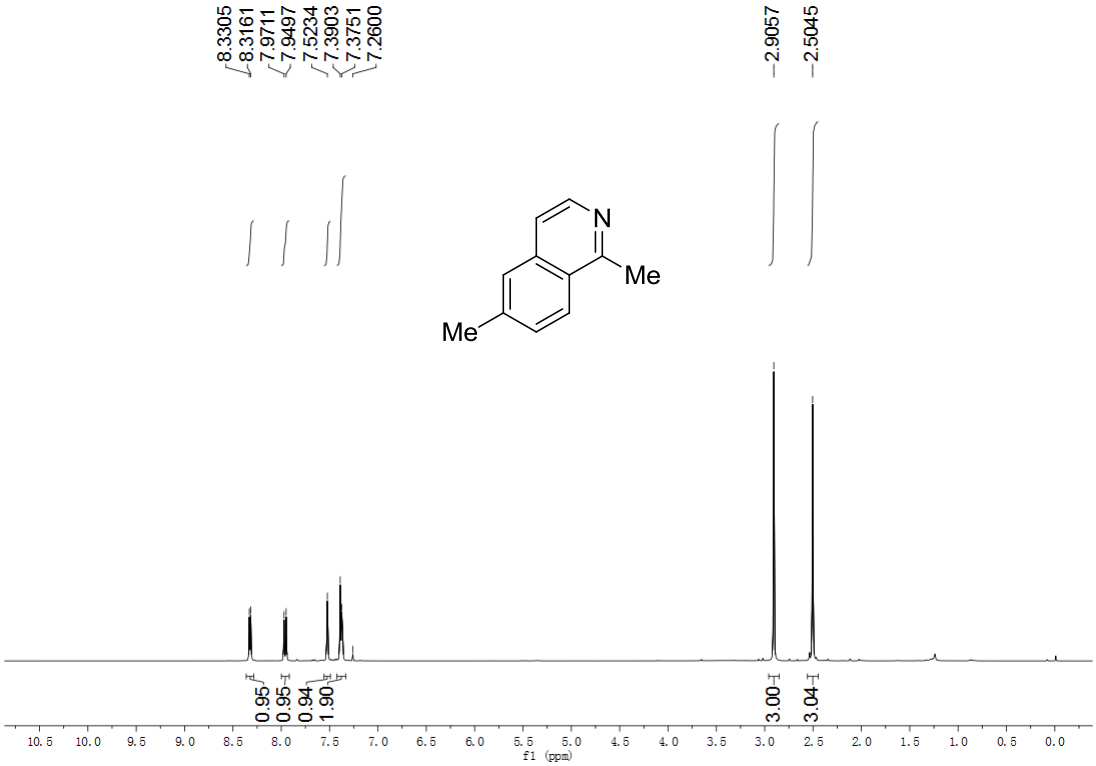

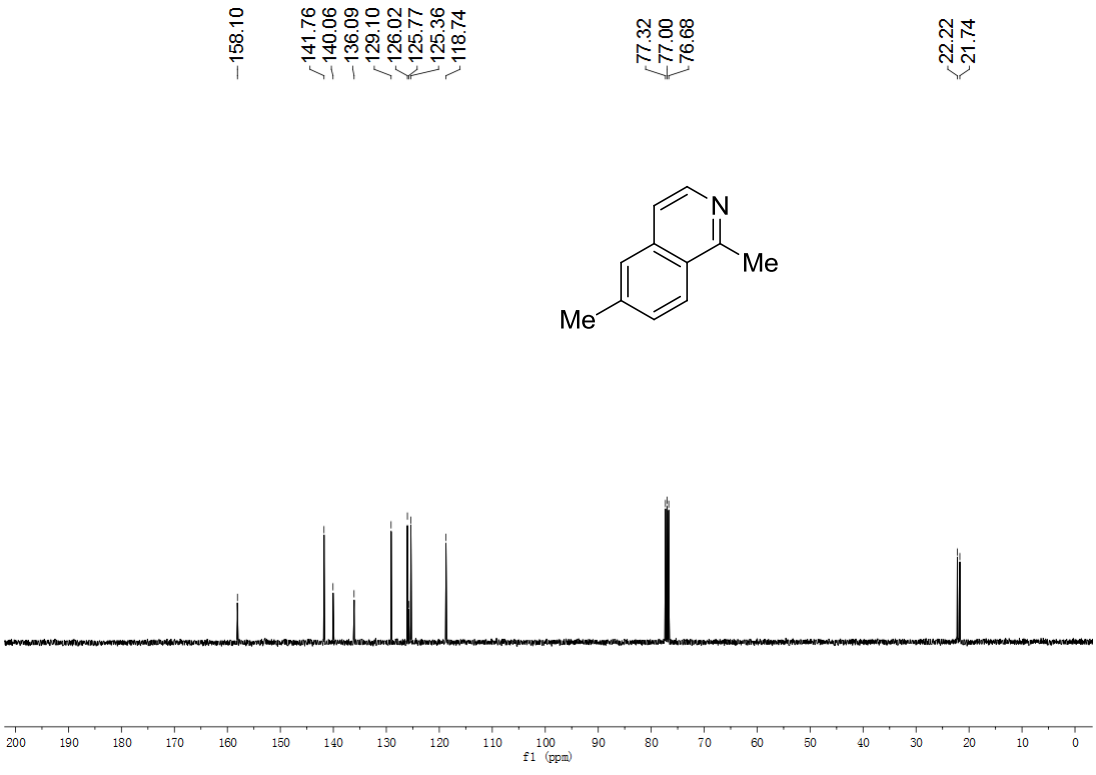

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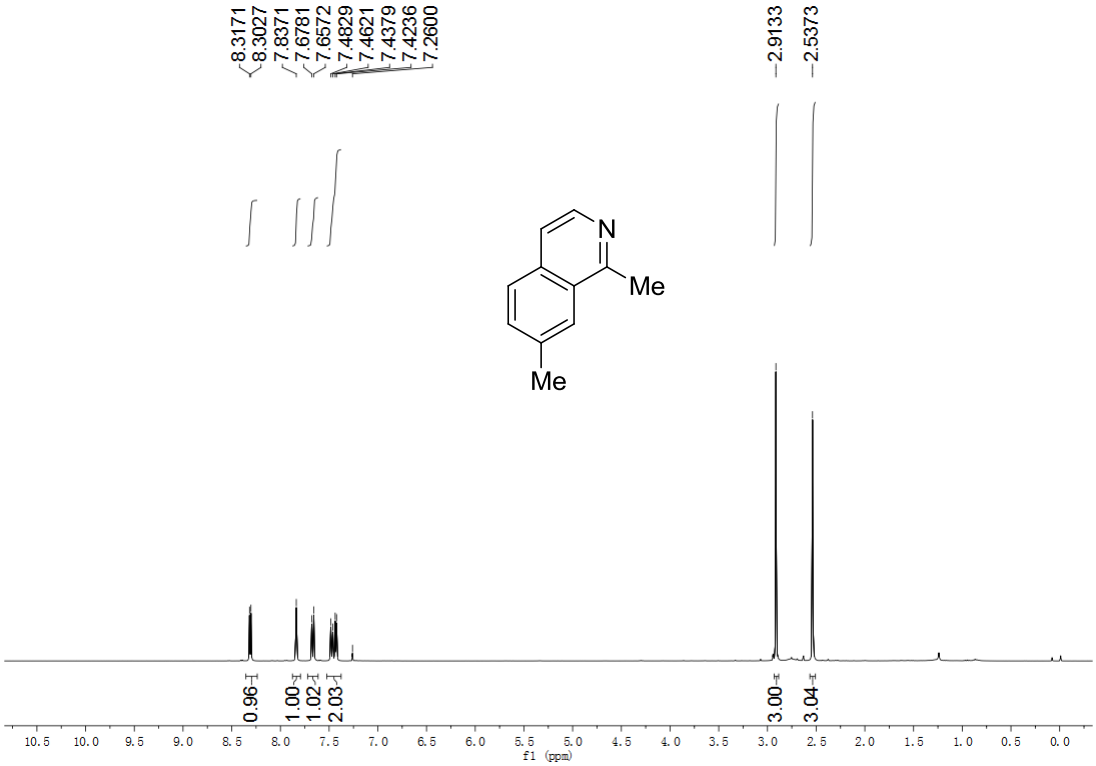

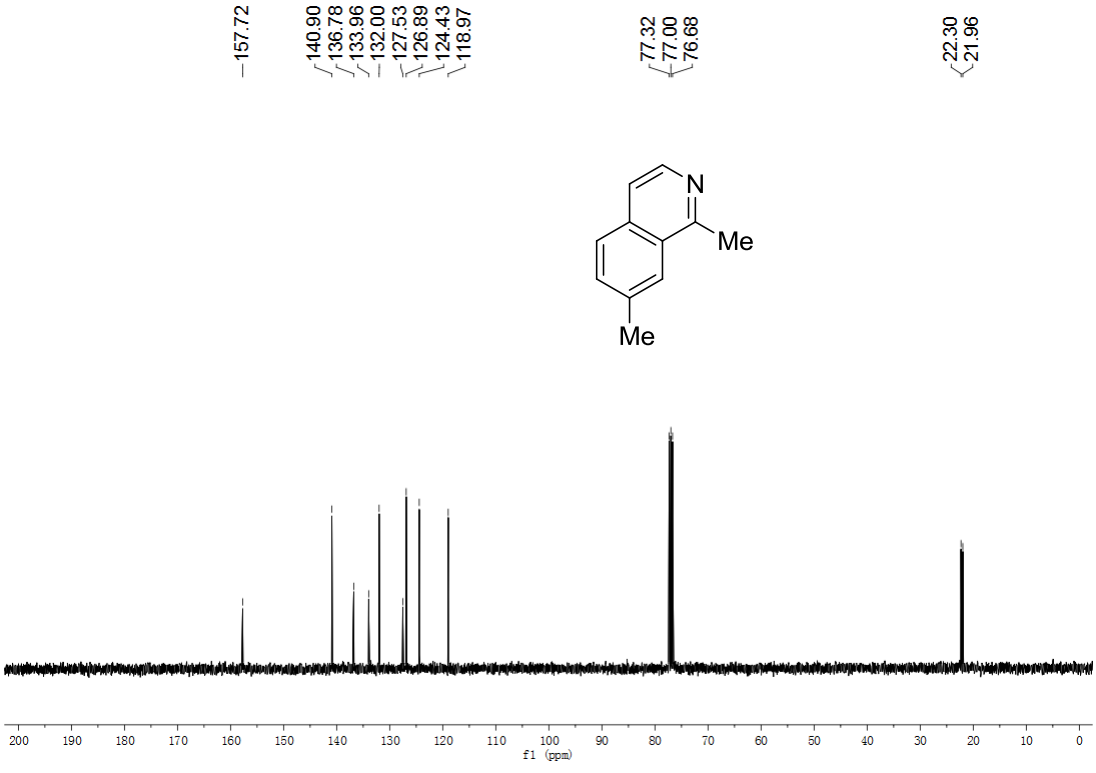

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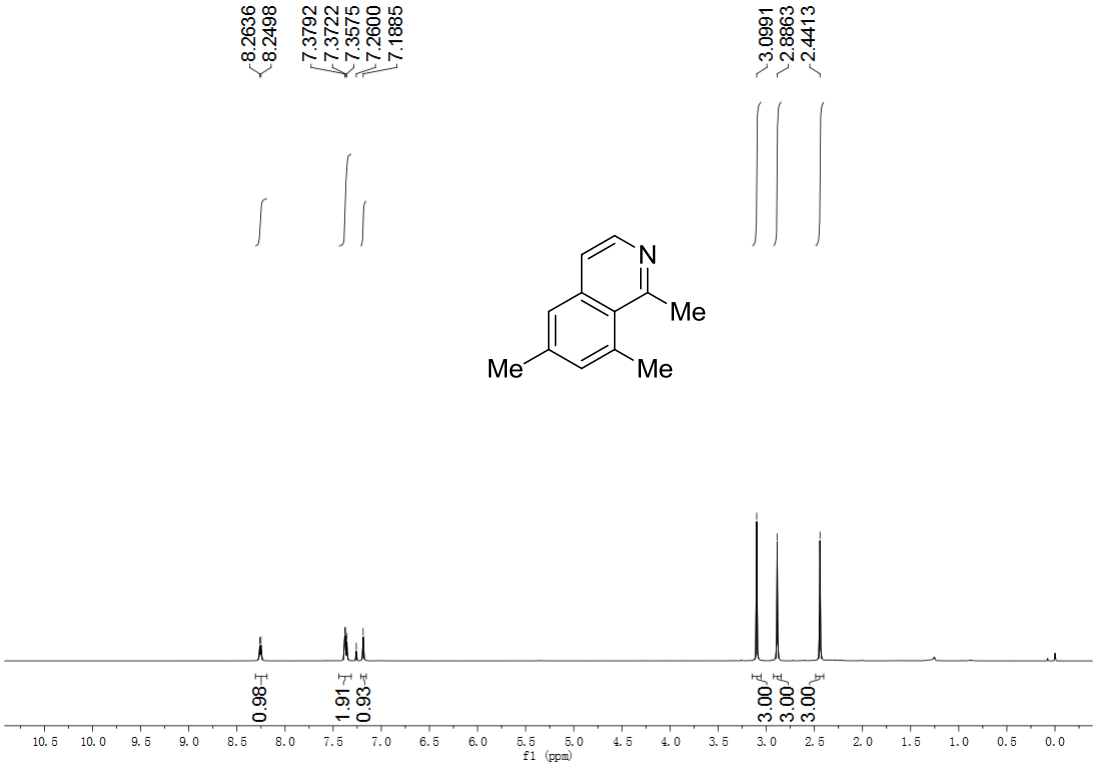

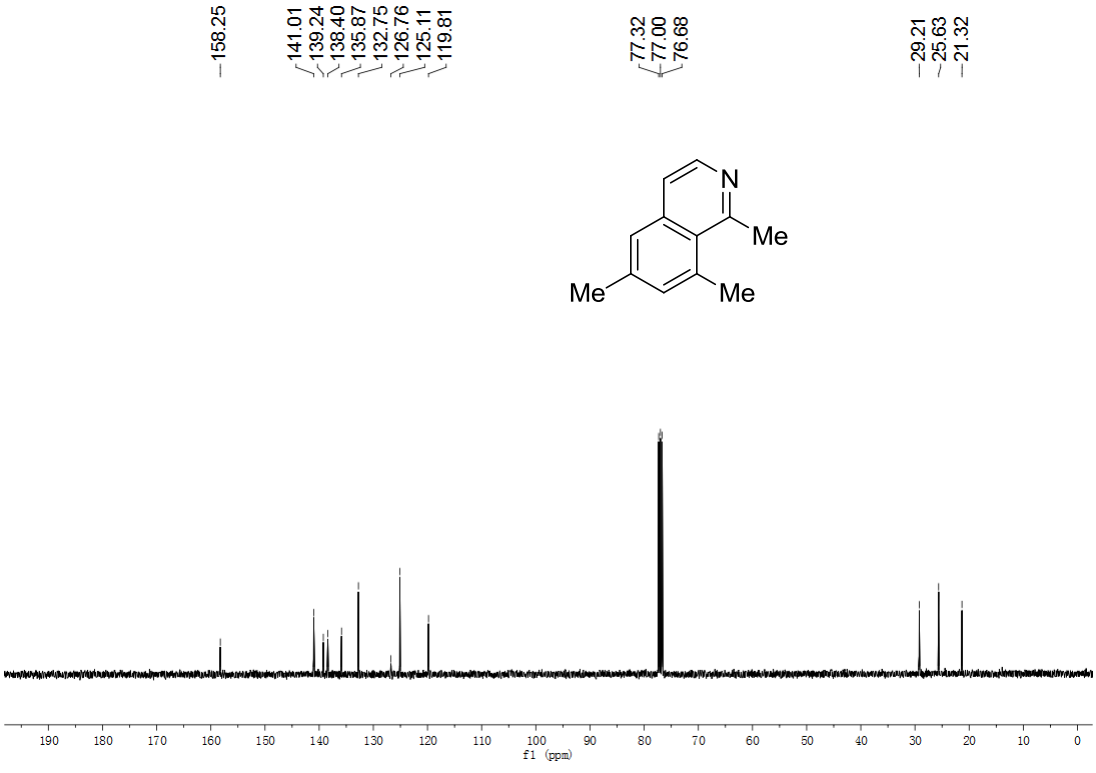

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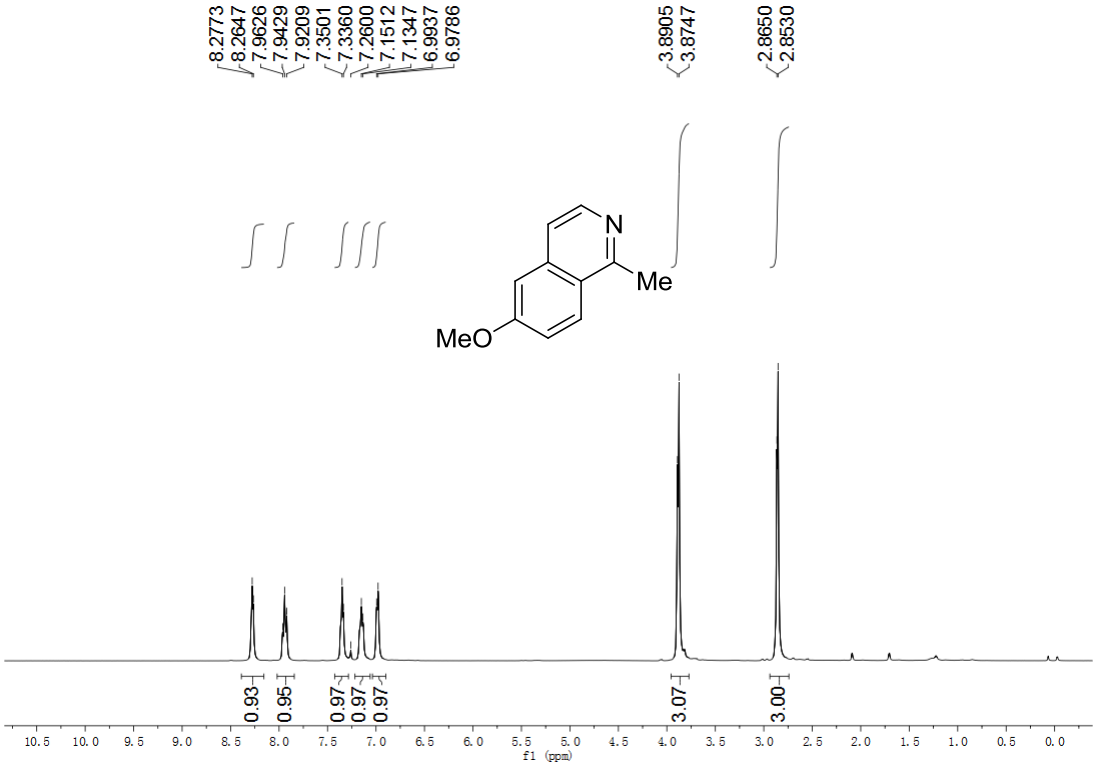

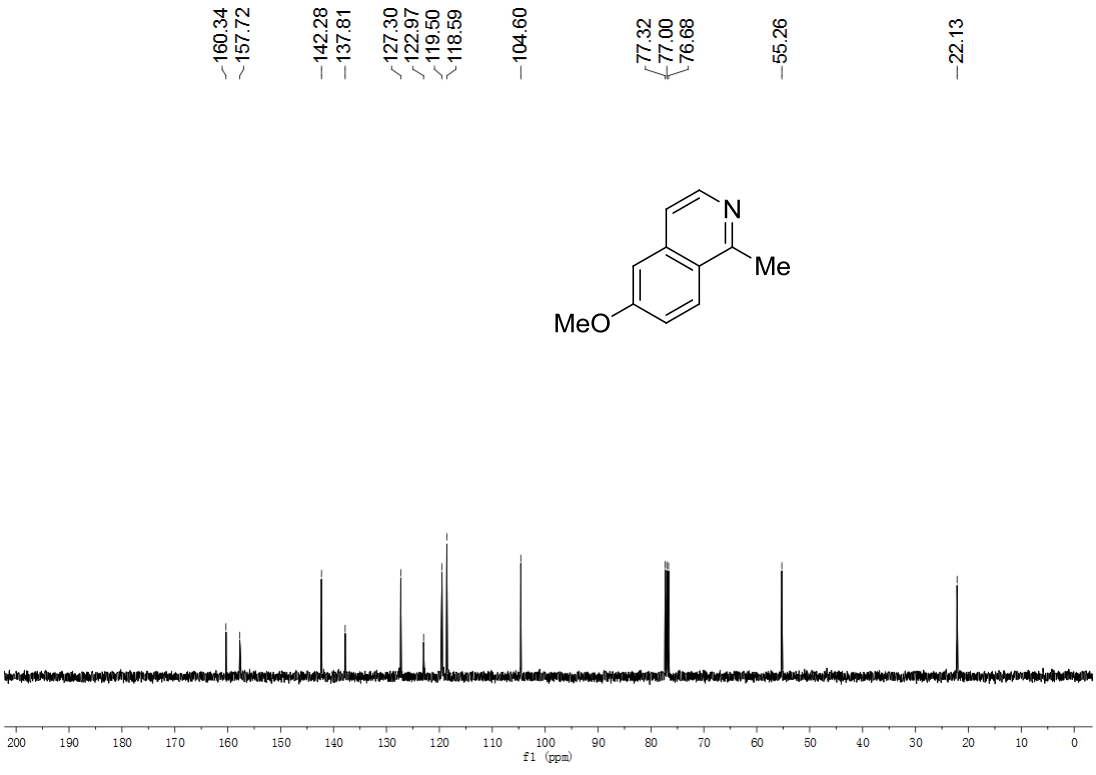

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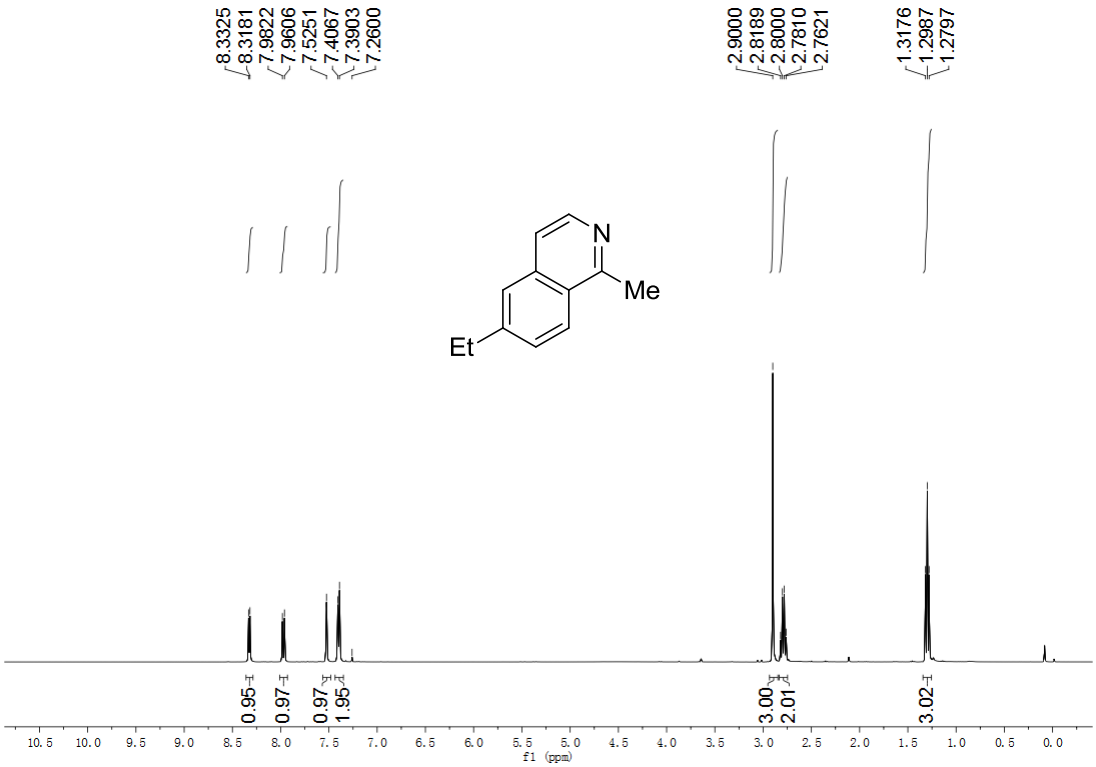
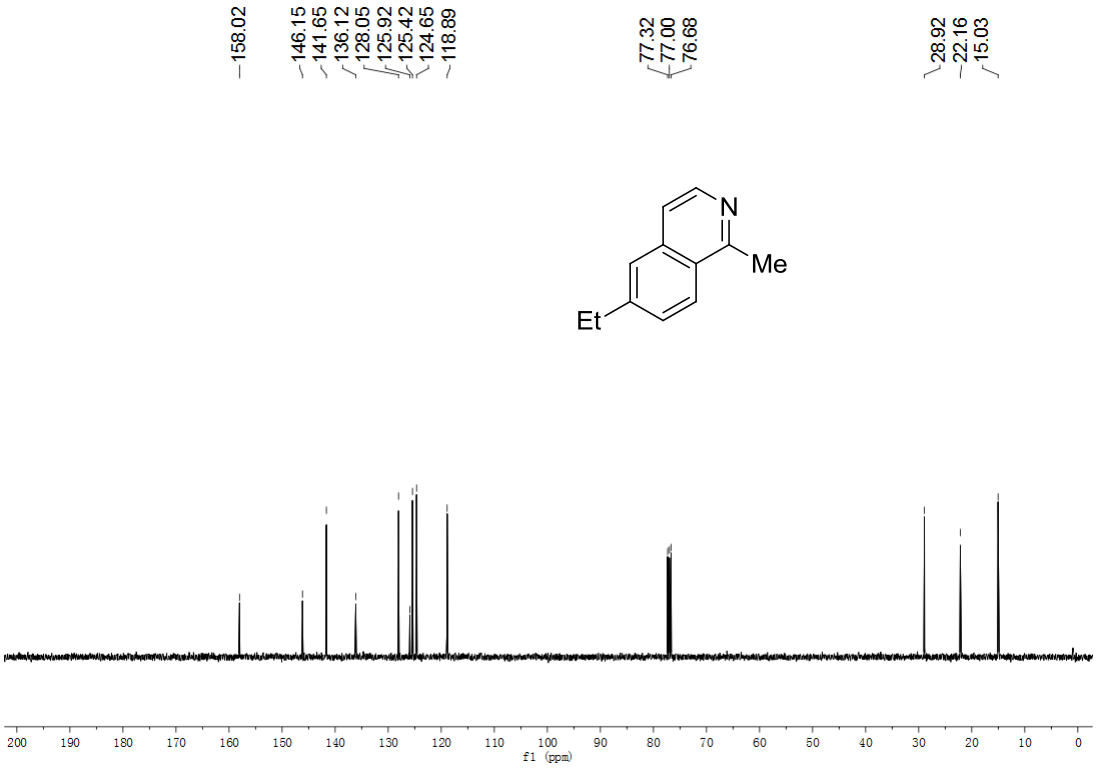
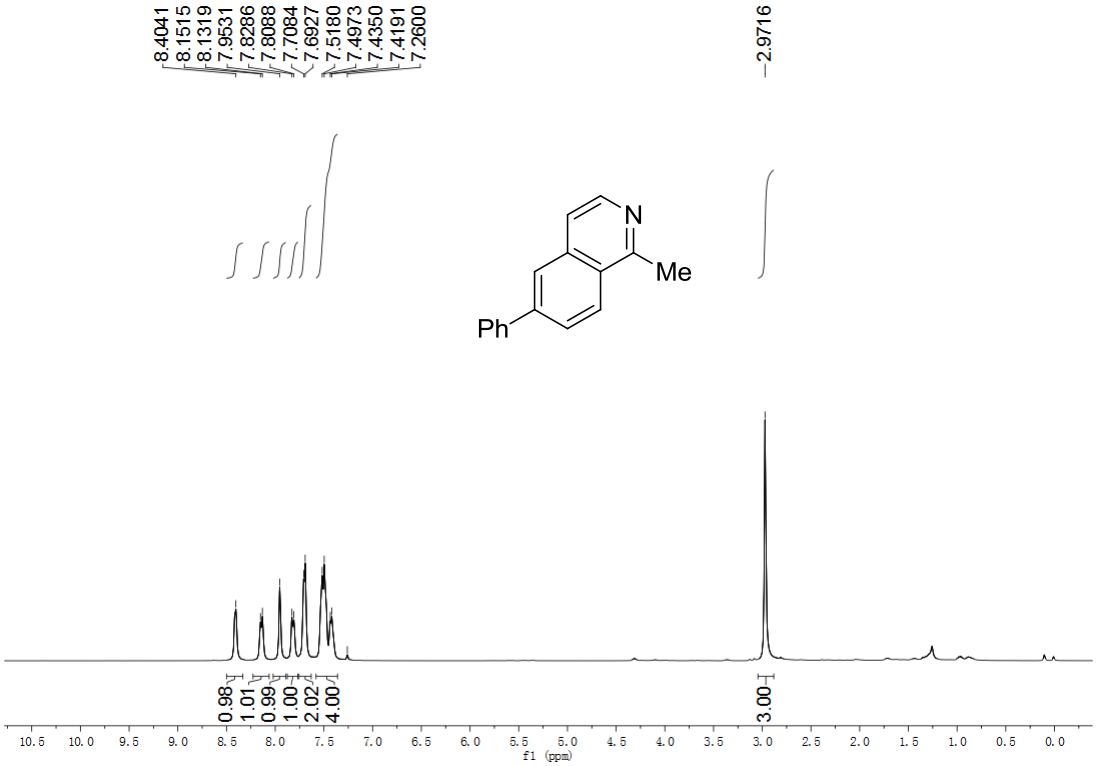
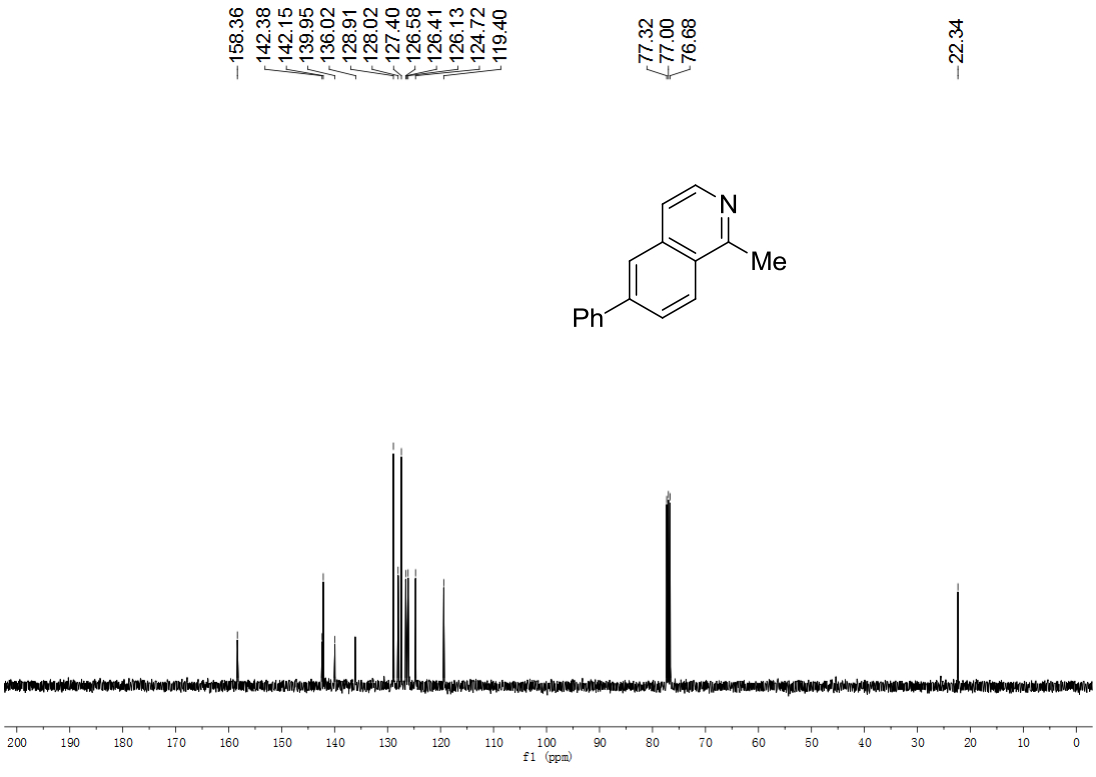


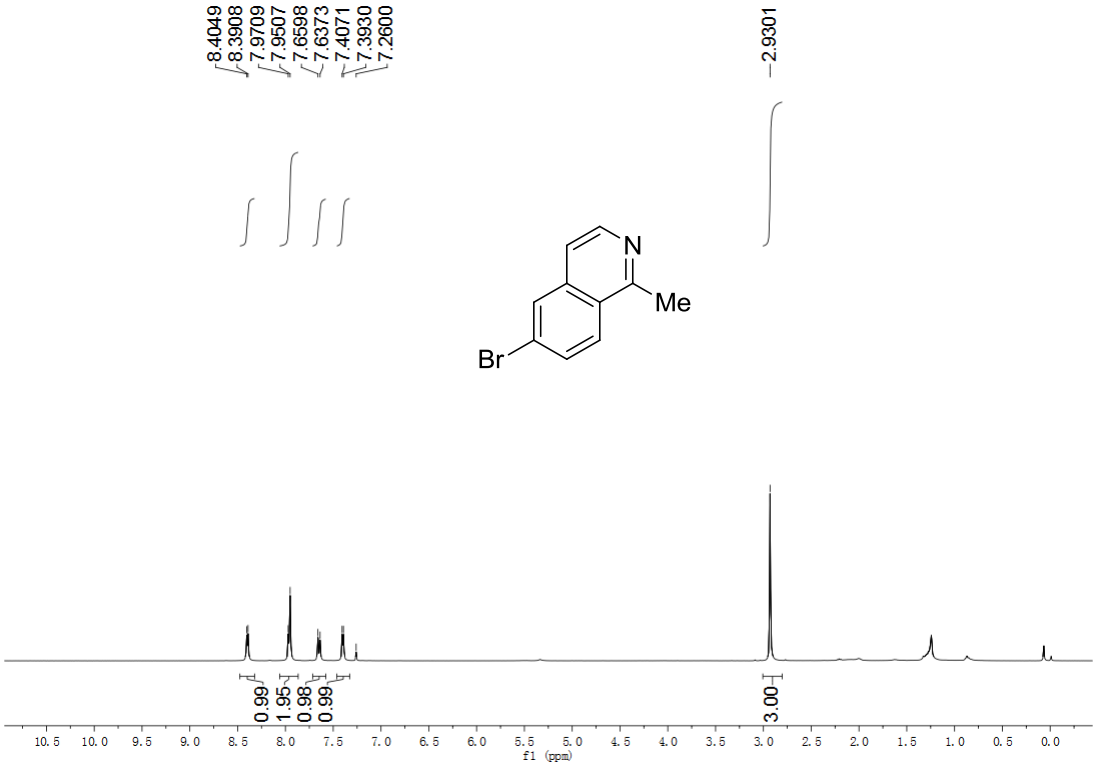


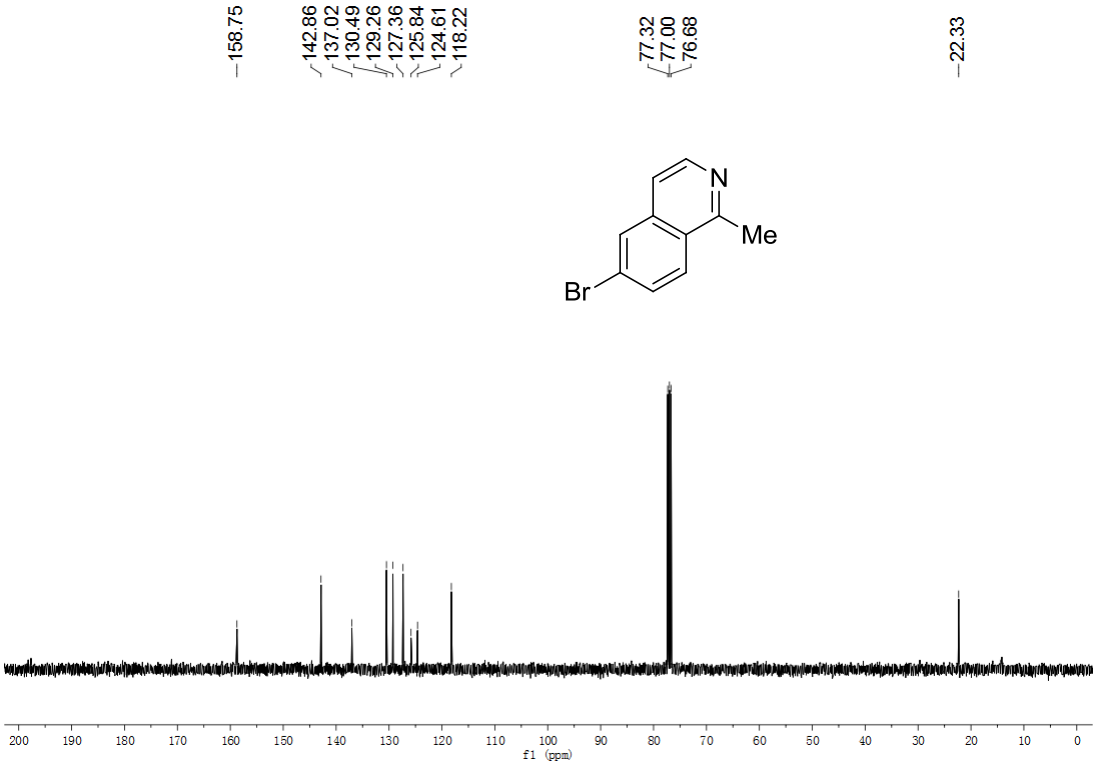
1-Methyl-6-phenylisoquinoline (3gf)



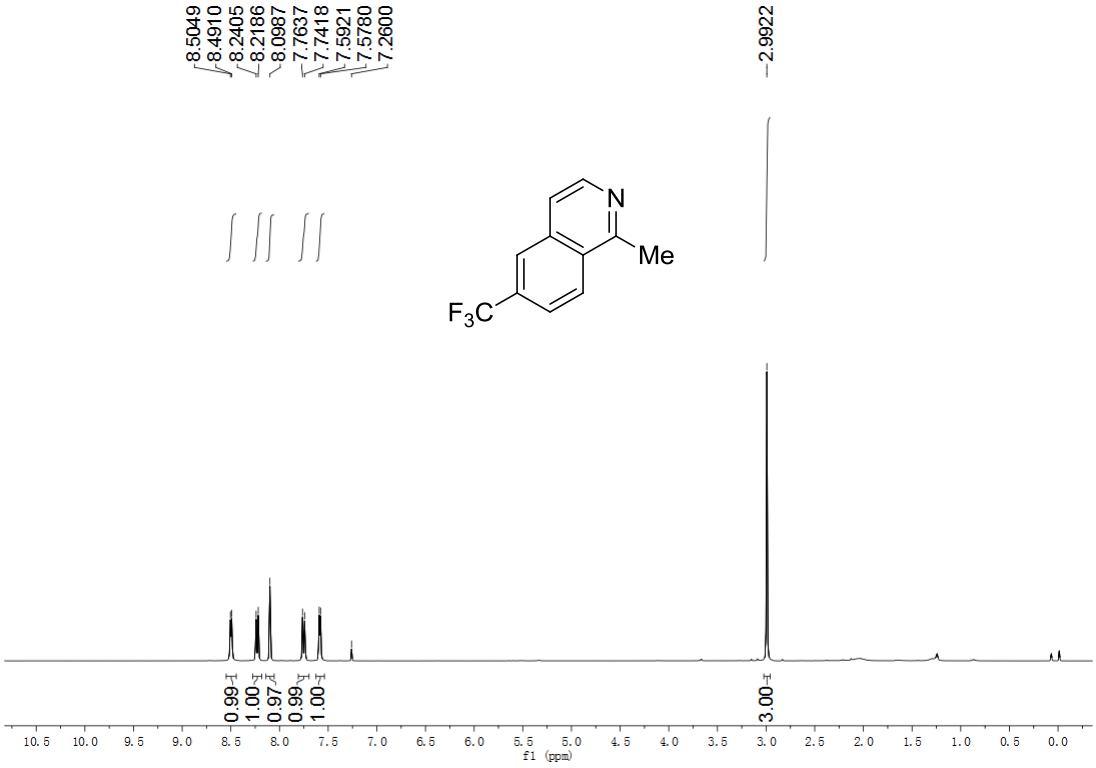


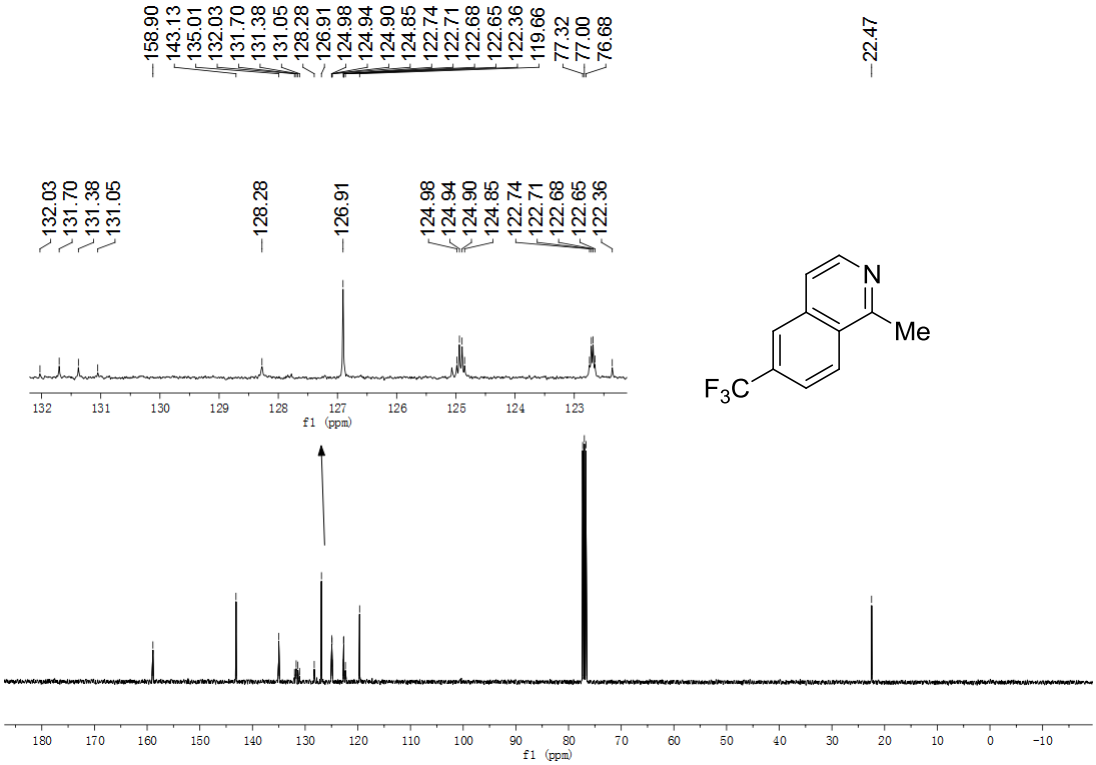
6-Bromo-1-methylisoquinoline (3hf)



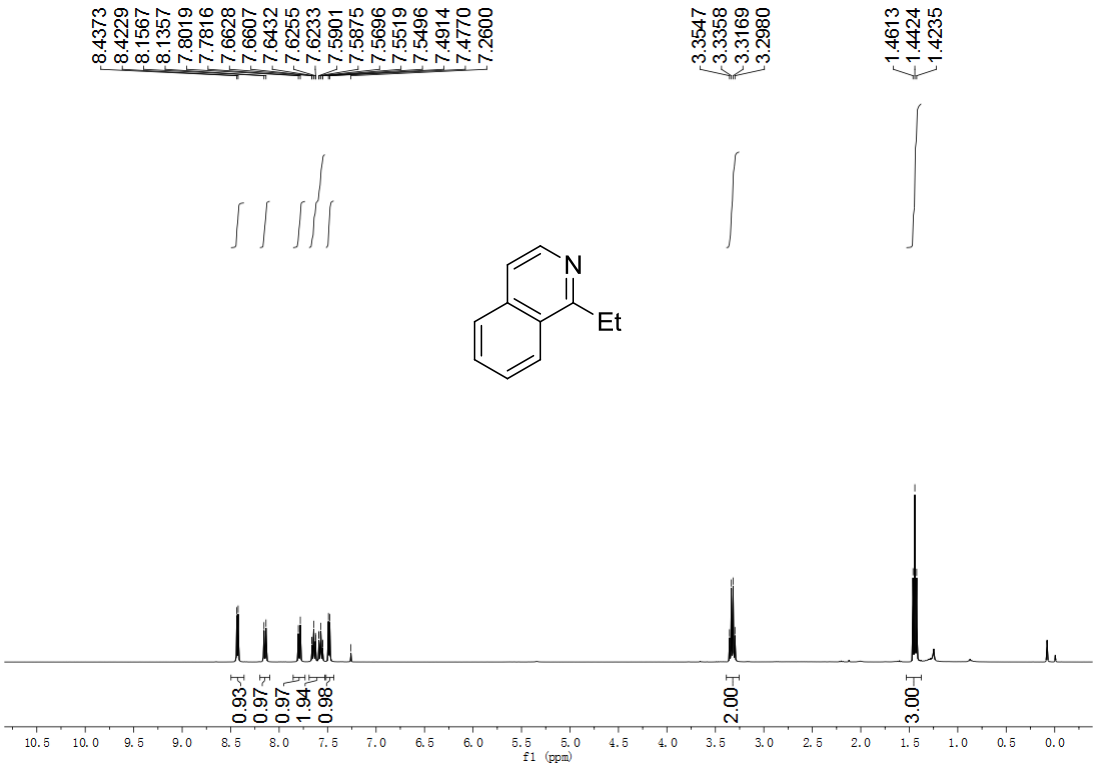


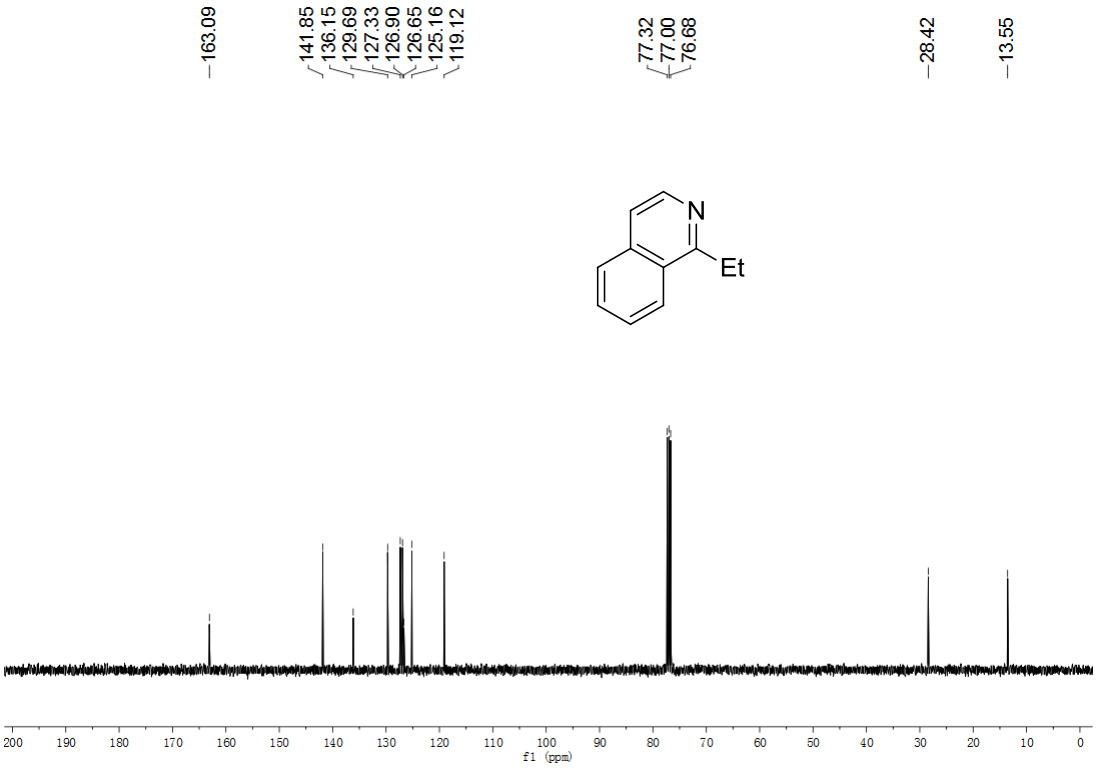
1-Methyl-6-(trifluoromethyl)isoquinoline (3kf)



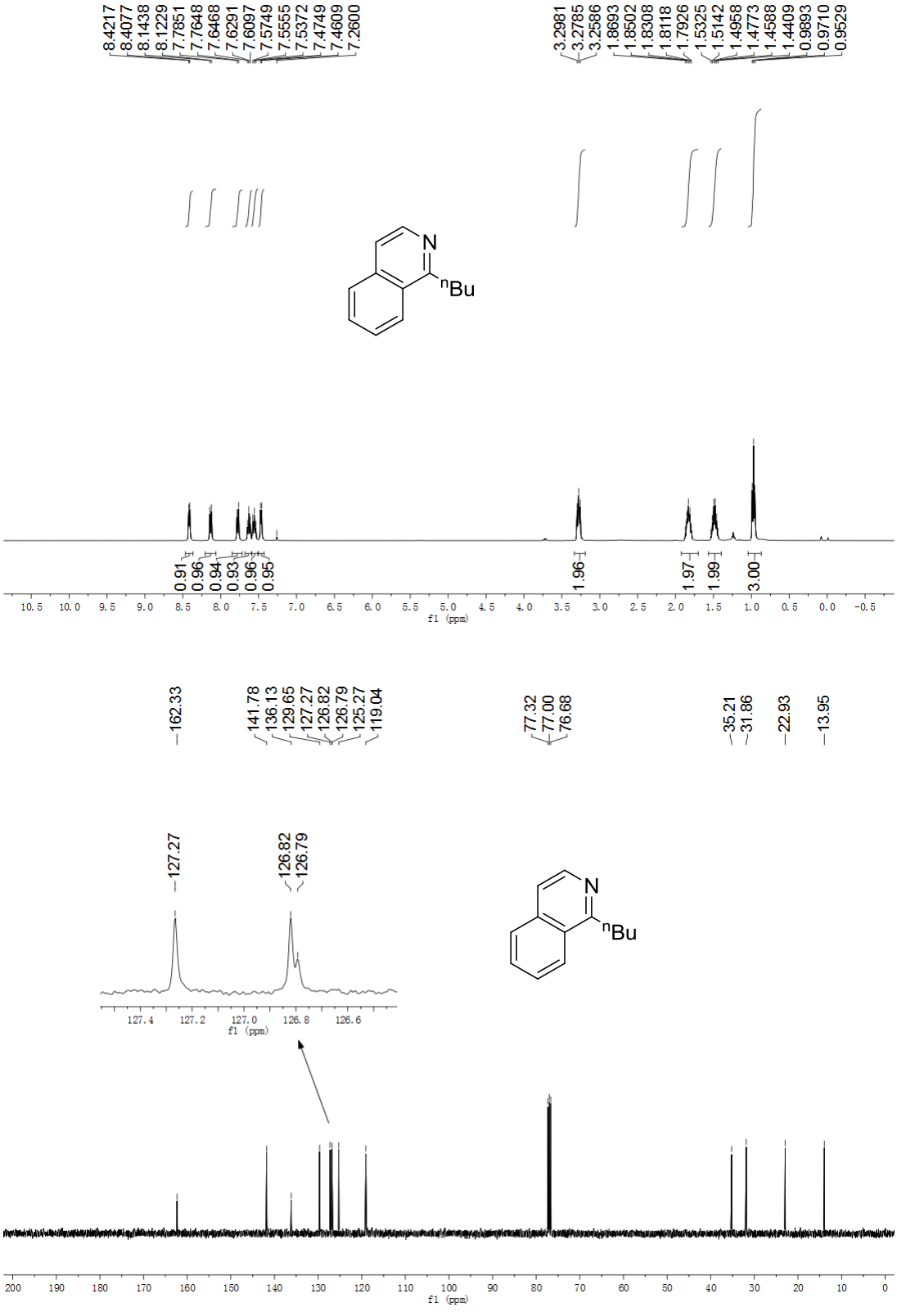


1-Ethylisoquinoline (3nf)

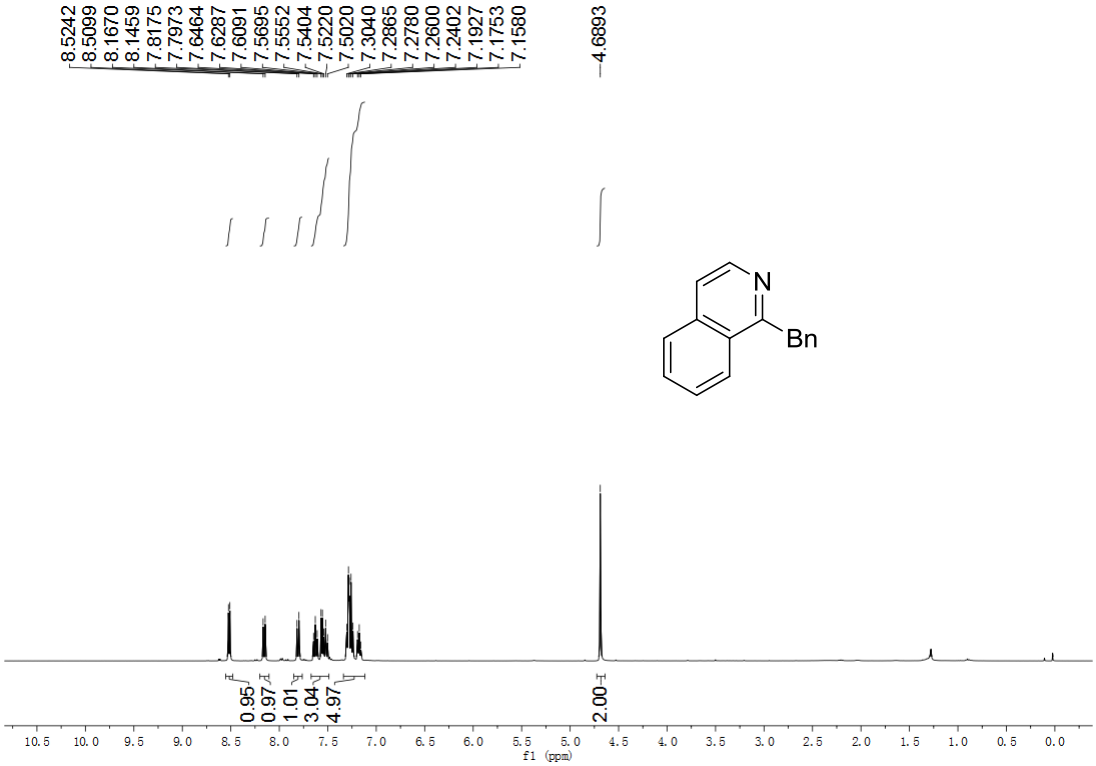


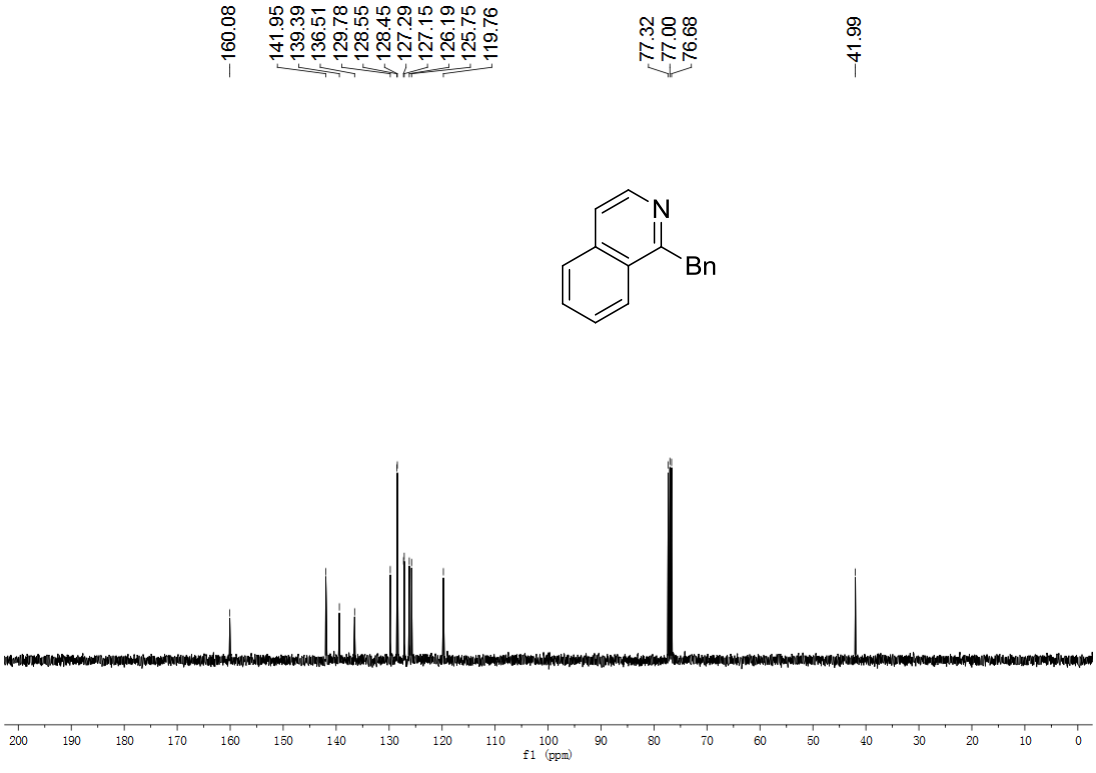


1-(*n*-Butyl)isoquinoline (3of)

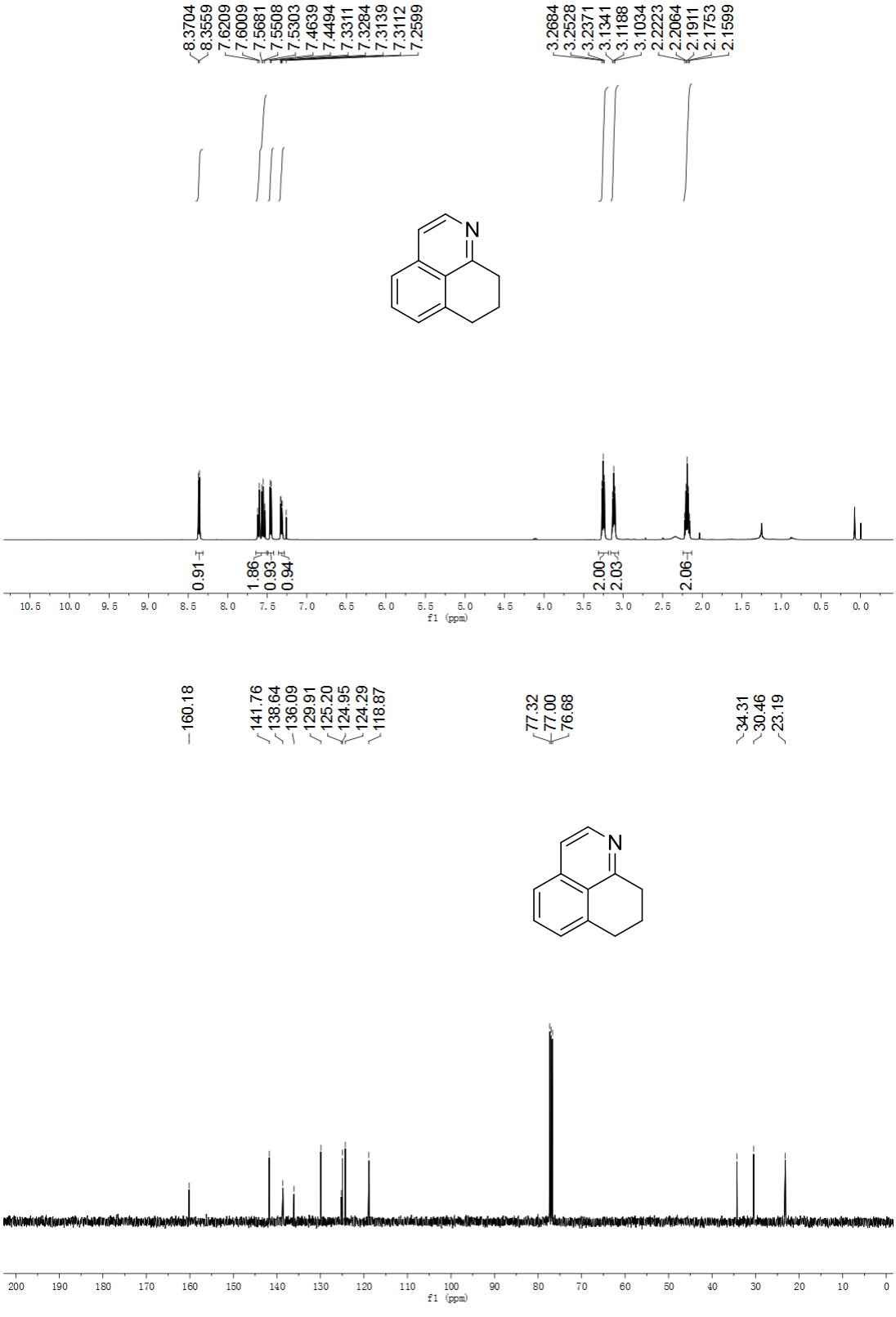


1-Benzylisoquinoline (3pf)

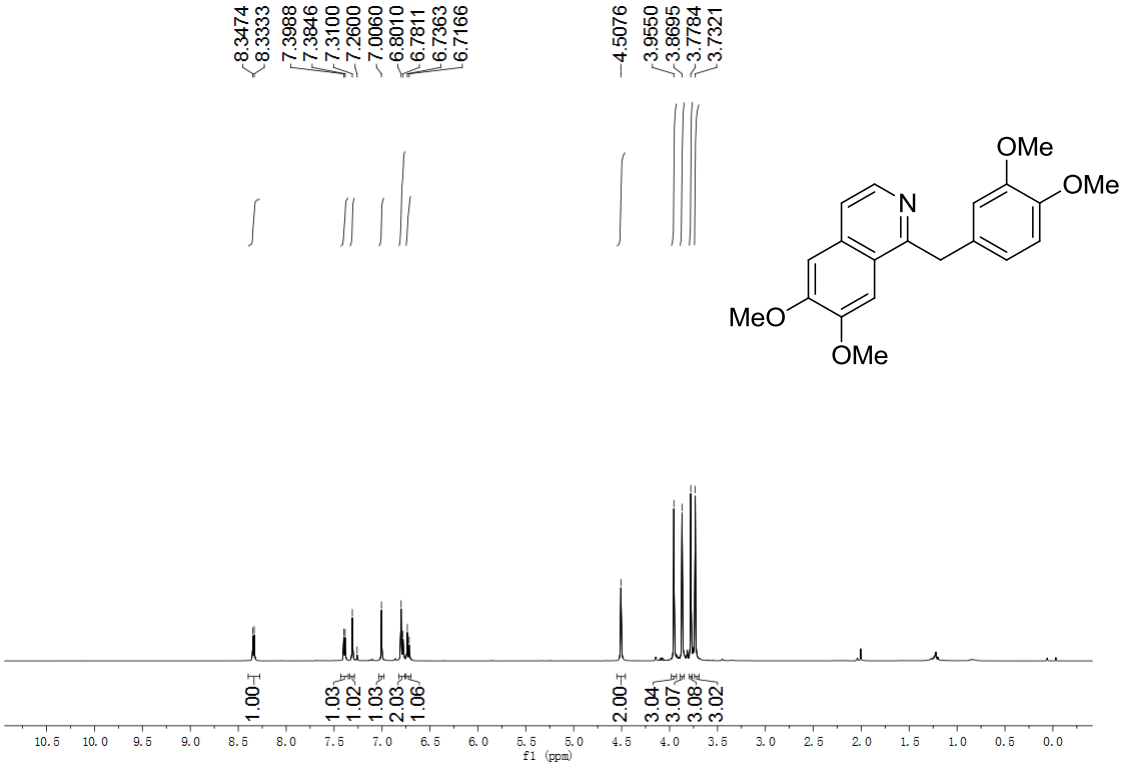


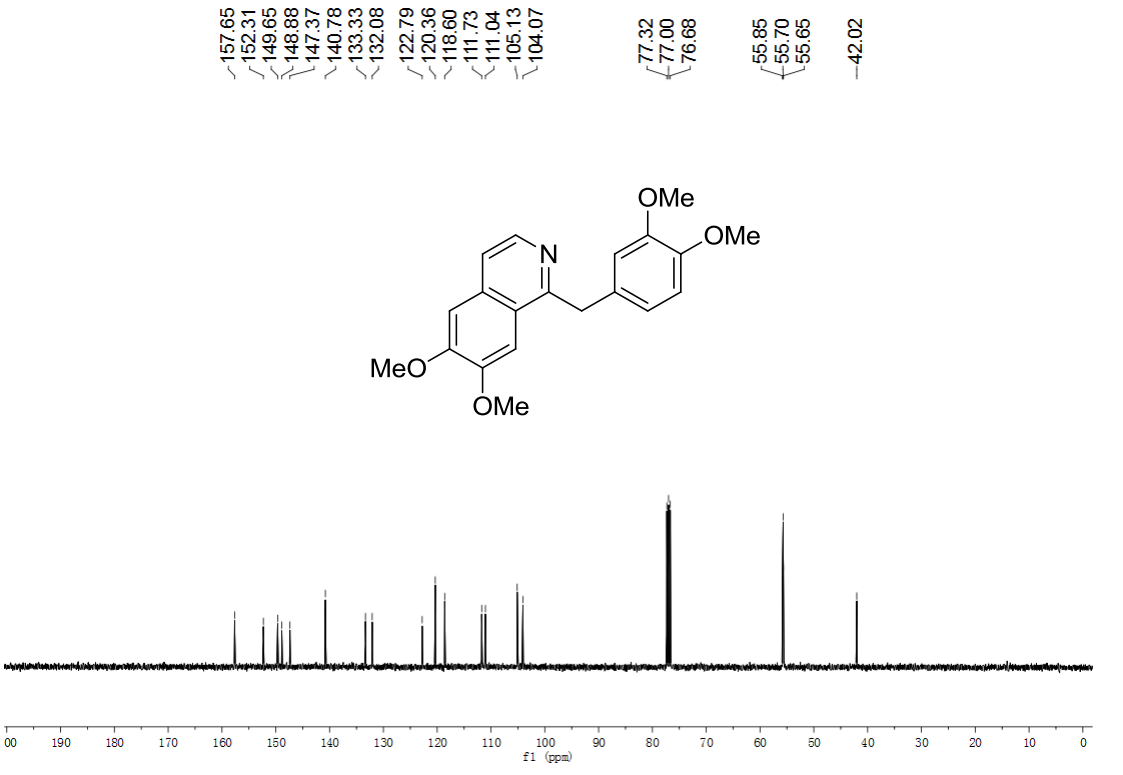


8,9-Dihydro-7*H*-benzo[de]quinolone (3qf)



1-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline (Papaverine)





2-Methyl-4-phenylpyridine (3tf)