Electronic Supplementary Information

Tandem Strecker/C(sp^3)-H Amination Reactions for the Construction of Cyanide-Functionalized Imidazo[1,5-*a*]pyridines with NH_4SCN as a Cyanating Agent

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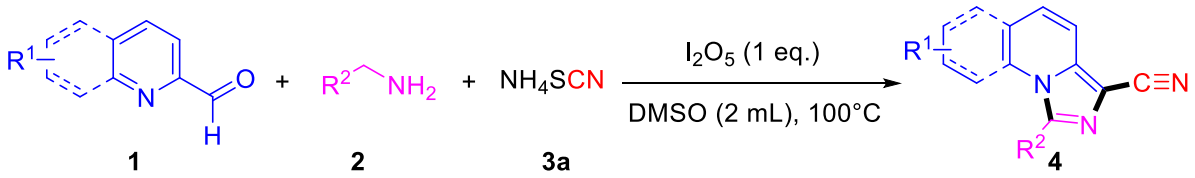
1. General Information

All reagents were purchased from commercial sources and used without further purification. Thin layer chromatography (TLC) employed glass 0.20-0.25 mm silica gel plates. Flash chromatography columns were packed with 200-300 mesh silica gel in petroleum (boiling point is between 60-90 ℃). Flash chromatography was conducted eluting with with PE/EA, and they are listed as volume/volume ratios. ^{1}H NMR spectra were determined on 400 MHz spectrometer as solutions in $CDCl_3$ or DMSO-d_6. Chemical shifts are expressed in parts per million (δ) and the signals were reported as s (singlet), d (doublet), t (triplet), m(multiplet), and coupling constants (J) were given in Hz. ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ or DMSO-d_6 solution. Chemical shifts as internal standard are referenced to $CDCl_3$ (δ = 7.26 for ^{1}H and δ = 77.0 for ^{13}C NMR) or DMSO-d_6 (δ = 2.50 for ^{1}H and δ = 39.5 for ^{13}C NMR) as internal standard. High resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) and the time-of-flight (TOF) mass analyzer, accurate masses are reported for the molecular ion + hydrogen ($[M+H]^+$). Melting point was recorded on a Hanon MP430 Auto Melting Point System and were uncorrected.

2. Experimental Procedure

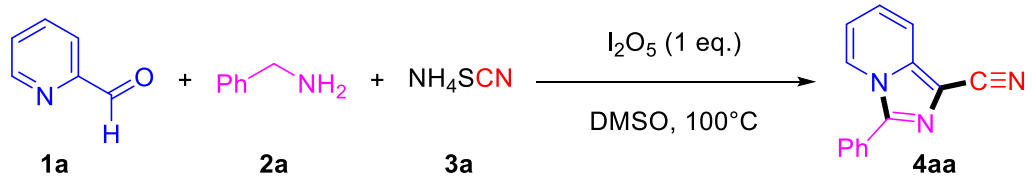
2.1 General procedure for the synthesis of **4**:



1 **2** **3a** **4**

An oven-dried reaction vessel was charged with NH_4SCN **3a** (0.6 mmol, 46 mg), aldehyde **1** (0.3 mmol) and amine **2** (0.6 mmol) in DMSO (2 mL). After the mixture was stirred for 5 min at room temperature, I_2O_5 (0.3 mmol, 100 mg) was added, and the mixture was further stirred at 100 °C for 5 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and quenched with saturated $Na_2S_2O_3$ solution. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate as an eluent to afford the pure products **4**.

2.2 A procedure for the synthesis of **4aa** at 9 mmol scale



1a **2a** **3a** **4aa**

An oven-dried round-bottom flask (150 mL), equipped with reflux condenser, was charged with NH_4SCN **3a** (18 mmol, 1.37 g), pyridine-2-carboxaldehyde **1a** (9 mmol, 856 uL) and benzylamine **2a** (18 mmol, 1965 uL) in DMSO (60 mL). After the mixture was stirred for 5 min at room temperature, I_2O_5 (9 mmol, 3.00 g) was added, and the mixture was further stirred at 100 °C for 5 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and quenched with saturated $Na_2S_2O_3$ solution. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate (P:E = 3:1) as an eluent to afford the pure product **4aa** (1.82 g, 92%).

2.3 One-pot two-step synthesis of cyano-substituted imidazo[1,5-*a*]quinolones **4**

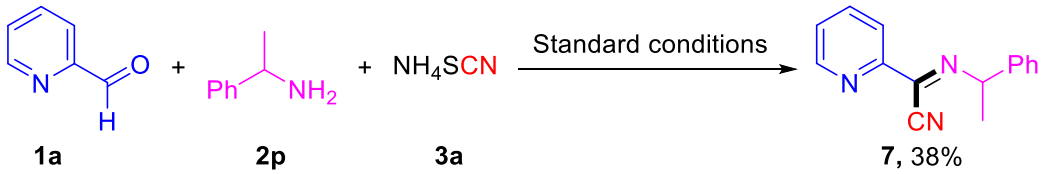
5 **4**

An oven-dried reaction vessel was charged with 2-methylquinoline **5** (0.3 mmol) and I_2O_5 (0.3 mmol, 100 mg) in DMSO (2 mL), and the mixture was stirred at room temperature for 24 hours. After the **5** was completely consumed, amine **2** (0.6 mmol) and NH_4SCN **3a** (0.6 mmol, 46 mg) were added, and the mixture was further stirred at 100 °C for 5 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and quenched

with saturated $Na_2S_2O_3$ solution. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate as an eluent to afford the pure products **4**.

2.4 Preliminary mechanistic studies

1) L(-)-alpha-methybenzylamine was used as substrate.

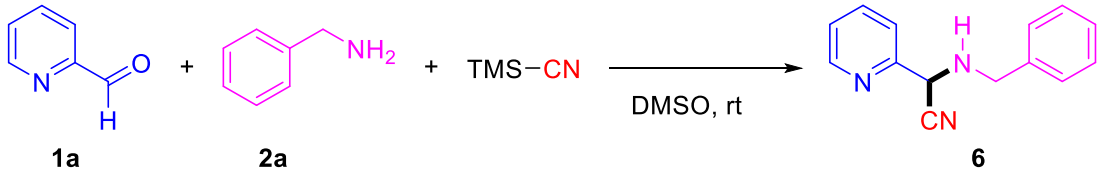


1a **2p** **3a** **7**, 38%

NH_4SCN **3a** (0.6 mmol, 45.7 mg), pyridine-2-carboxaldehyde **1a** (0.3 mmol, 29 uL) and L(-)-alpha-methybenzylamine **2p** (0.6 mmol, 77 uL) in DMSO (2mL) were taken in a sealed tube. Then I_2O_5 (0.3 mmol, 100.1 mg) was added to it and stirred at room temperature for 5 min. Then the mixture was stirred at 100 °C for 5 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and quenched with saturated $Na_2S_2O_3$ solution. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate (P:E = 4:1) as an eluent to afford (Z)-N-(1-phenylethyl)picolinimidoyl cyanide **7** (27 mg, 38%) as an orange oil.

(Z)-N-(1-phenylethyl)picolinimidoyl cyanide **7**: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.75 – 8.72 (m, 1H), 8.16 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.78 (td, *J* = 7.8, 1.7 Hz, 1H), 7.51 – 7.48 (m, 2H), 7.42 – 7.35 (m, 3H), 7.31 – 7.27 (m, 1H), 5.28 (q, *J* = 6.5 Hz, 1H), 1.67 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, Chloroform-d) δ 151.8, 149.6, 142.9, 141.5, 136.9, 128.8, 127.8, 126.8, 126.1, 121.5, 109.9, 67.7, 24.4; HRMS (ESI): calcd for $C_{15}H_{14}N_3$ $[M+H]^+$ 236.1182, found 236.1180.

2) A procedure for the synthesis of intermediate **6**

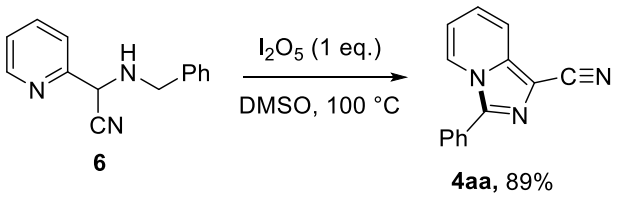


1a **2a** **6**

An oven-dried reaction vessel was charged with **1a** (0.3 mmol, 29 μL) and **2a** (0.6 mmol, 66 μL) in DMSO (2 mL), and the mixture was stirred at room temperature for 1 hours. After the **1a** was completely consumed, TMS-CN (0.6 mmol, 80 μL) was added, and the mixture was further stirred at room temperature for 6 h. After completion of the reaction (TLC), the reaction mixture was quenched with water. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate (P:E = 1:1) as an eluent to afford the compound **6** (44 mg, 65%) as a red oil.

2-(benzylamino)-2-phenylacetonitrile **6:** ^{1}H NMR (400 MHz, Chloroform-d) δ 8.55 (d, J = 5.0 Hz, 1H), 7.66 (td, J = 7.7, 1.6 Hz, 1H), 7.39 – 7.20 (m, 7H), 4.73 (s, 1H), 4.05 – 3.88 (m, 2H), 2.54 (s, 1H). ^{13}C NMR (100 MHz, Chloroform-d) δ 153.7, 149.9, 137.9, 137.4, 128.7, 128.5, 127.7, 123.9, 122.1, 118.3, 54.9, 51.5.

3) The synthesis of **4aa** from **6**



6 **4aa**, 89%

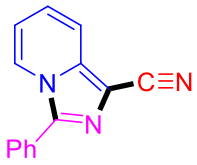
An oven-dried reaction vessel was charged with **6** (0.3mmol, 66.9 mg) and I_2O_5 (0.3mmol, 100.1 mg) in DMSO (2 mL), and the mixture was stirred at 100 °C for 4 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and quenched with saturated $Na_2S_2O_3$ solution. Then the reaction mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to get the crude residue. Finally, it was purified by column chromatography on silica gel (200-300 mesh) using petroleum ether/ethylacetate (P:E = 3:1) as an eluent to afford the product **4aa** (58.5 mg, 89%).

4) The starch-iodine test

After the reaction, the starch-iodine test of the reaction mixture was carried out. As shown in Fig. S1, an obvious colour change, which suggests the formation of iodine during the reaction.

Fig S1. The result of starch iodine test. (**A**) Upper liquid: the reaction solution diluted with ethyl acetate; bottom liquid: distilled water. (**B**) Upper liquid: the reaction solution diluted with ethyl acetate; bottom liquid: aqueous solution of starch. (**C**) Upper liquid: ethyl acetate; bottom liquid: aqueous solution of starch.

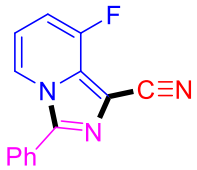
3. Characterization Data of Products



3-Phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4aa**):

Following the general procedure 2.1, compound **4aa** was obtained as a white crystalline solid in 95% yield (62.4 mg) by flash chromatography (P:E = 3:1); mp = 132-133 °C.

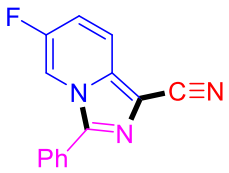
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.35 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.78 – 7.70 (m, 3H), 7.59 – 7.50 (m, 3H), 7.18 – 7.14 (m, 1H), 6.85 – 6.81 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.1, 137.7, 130.0, 129.3, 128.5, 128.4, 124.5, 122.9, 117.4, 115.3, 114.8, 103.6. HRMS (ESI): calcd for $C_{14}H_{10}N_3$ $[M+H]^+$ 220.0869, found 220.0869.



8-Fluoro-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ba**):

Following the general 2.1, compound **4ba** was obtained as a white crystalline solid in 81% yield (57.6 mg) by flash chromatography (P:E = 3:1); mp = 181-182 °C.

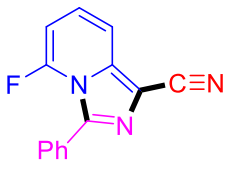
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.77 – 7.73 (m, 2H), 7.60 – 7.54 (m, 3H), 6.84 – 6.77 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 152.9 ($^{1}J_{CF}$ = 256 Hz), 141.5, 130.4, 129.4, 128.6, 128.0, 119.4 ($^{4}J_{CF}$ = 5 Hz), 114.7, 114.5 ($^{3}J_{CF}$ = 7 Hz), 106.8 ($^{2}J_{CF}$ = 16 Hz). HRMS (ESI): calcd for $C_{14}H_9FN_3$ $[M+H]^+$ 238.0775, found 238.0768.



6-Fluoro-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ca**):

Following the general 2.1, compound 4ca was obtained as a white crystalline solid in 92% yield (65.4 mg) by flash chromatography (P:E = 4:1); mp = 112-113 °C.

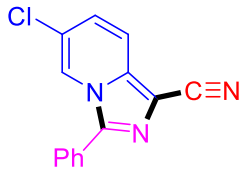
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dd, *J* = 4.5, 1.9 Hz, 1H), 7.75 – 7.71 (m, 3H), 7.60 – 7.53 (m, 3H), 7.13 – 7.08 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 154.6 ($^{1}J_{CF}$ = 244 Hz), 140.9, 135.3, 130.3, 129.4, 128.2, 128.0, 118.5 ($^{3}J_{CF}$ = 9 Hz), 117.8, 117.5, 114.8, 109.7, 109.2, 104.9; HRMS (ESI): calcd for $C_{14}H_9FN_3$ $[M+H]^+$ 238.0775, found 238.0775.



5-Fluoro-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4da**):

Following the general 2.1, compound **4da** was obtained as a white crystalline solid in 62% yield (44.1 mg) by flash chromatography (P:E = 3:1); mp = 167-169 °C.

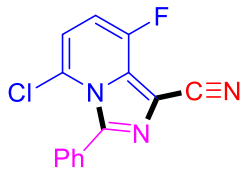
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 (ddd, *J* = 7.9, 3.8, 2.0 Hz, 2H), 7.57 – 7.46 (m, 4H), 7.19 – 7.14 (m, 1H), 6.47 (td, *J* = 7.0, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 149.3 ($^1J_{CF}$ = 272 Hz), 140.0 (J_{CF} = 2 Hz), 138.7 (J_{CF} = 3 Hz), 129.89, 129.87, 129.84, 129.78, 129.75, 128.1, 125.7 (J_{CF} = 5 Hz), 114.8, 113.1 (J_{CF} = 6 Hz), 104.7, 95.2, 95.0. HRMS (ESI): calcd for $C_{14}H_9FN_3$ $[M+H]^+$ 238.0775, found 238.0775.



6-Chloro-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ea**):

Following the general 2.1, compound **4ea** was obtained as a pale yellow crystalline solid in 98% yield (74.4 mg) by flash chromatography (P:E = 8:1); mp = 140-142 °C.

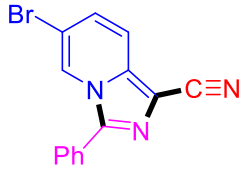
^{1}H NMR (400 MHz, Chloroform-d) δ 8.36 (t, *J* = 1.3 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.68 (dd, *J* = 9.5, 1.0 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.11 (dd, *J* = 9.6, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-d) δ 140.2, 135.7, 130.4, 129.5, 128.4, 127.8, 126.1, 123.7, 120.6, 117.9, 114.7, 104.8; HRMS (ESI): calcd for $C_{14}H_9ClN_3$ $[M+H]^+$ 254.0480, found 254.0480.



5-Chloro-8-fluoro-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4fa**):

Following the general 2.1, compound **4fa** was obtained as a white crystalline solid in 87% yield (70.7 mg) by flash chromatography (P:E = 4:1); mp = 178-179 °C.

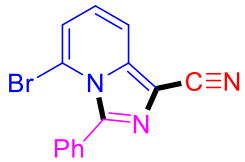
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.43 (m, 5H), 6.78 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 151.6 ($^1J_{CF}$ = 256 Hz), 142.7, 131.4, 131.1, 130.2, 129.9, 127.6, 122.5 (J_{CF} = 5 Hz), 115.4 (J_{CF} = 7 Hz), 114.0, 107.2 (J_{CF} = 18 Hz), 103.3 (J_{CF} = 4 Hz). HRMS (ESI): calcd for $C_{14}H_8ClFN_3$ $[M+H]^+$ 272.0385, found 272.0385.



6-Bromo-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ga**):

Following the general 2.1, compound **4ga** was obtained as a pale yellow crystalline solid in 85% yield (75.7 mg) by flash chromatography (P:E = 8:1); mp = 177-179 °C.

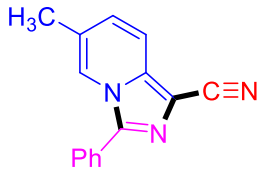
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.47 (t, *J* = 1.2 Hz, 1H), 7.75 – 7.72 (m, 2H), 7.65 – 7.53 (m, 4H), 7.22 – 7.19 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.1, 135.7, 130.4, 129.5, 128.5, 128.0, 127.8, 122.8, 117.9, 114.7, 110.5, 104.9. HRMS (ESI): calcd for $C_{14}H_9BrN_3$ $[M+H]^+$ 297.9974, found 297.9963.



5-Bromo-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ha**):

Following the general 2.1, compound **4ha** was obtained as a white crystalline solid in 78% yield (69.5 mg) by flash chromatography (P:E = 6:1); mp = 153-155 °C.

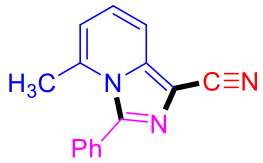
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (dd, *J* = 8.9, 1.2 Hz, 1H), 7.53 – 7.43 (m, 5H), 7.08 – 6.98 (m, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 141.9, 139.7, 131.5, 130.6, 130.0, 127.5, 124.6, 121.2, 116.5, 114.7, 113.9, 104.1. HRMS (ESI): calcd for $C_{14}H_9BrN_3$ $[M+H]^+$ 297.9974, found 297.9960.



6-Methyl-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ia**):

Following the general 2.1, compound **4ia** was obtained as a white crystalline solid in 83% yield (58.0 mg) by flash chromatography (P:E = 3:1); mp = 144-145 °C.

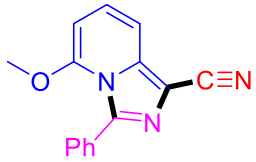
^{1}H NMR (400 MHz, Chloroform-d) δ 8.11 (q, *J* = 1.3 Hz, 1H), 7.74 – 7.71 (m, 2H), 7.62 – 7.50 (m, 4H), 7.01 (dd, *J* = 9.3, 1.3 Hz, 1H), 2.31 (d, *J* = 1.2 Hz, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 139.5, 136.8, 129.9, 129.2, 128.6, 128.5, 128.1, 124.9, 120.1, 116.6, 115.6, 103.2, 18.5. HRMS (ESI): calcd for $C_{15}H_{12}N_3$ $[M+H]^+$ 234.1026, found 234.1026.



5-Methyl-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ja**):

Following the general 2.1, compound **4ja** was obtained as a white crystalline solid in 56% yield (39.2 mg) by flash chromatography (P:E = 4:1); mp = 141-143 °C.

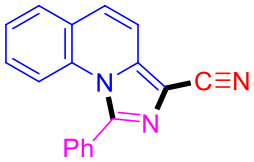
^{1}H NMR (400 MHz, Chloroform-d) δ 7.62 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.45 (m, 5H), 7.07 (dd, *J* = 9.1, 6.6 Hz, 1H), 6.54 (d, *J* = 6.7 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-d) δ 140.7, 139.0, 135.3, 132.0, 131.0, 129.9, 127.8, 124.9, 115.7, 115.5, 115.2, 102.7, 21.7. HRMS (ESI): calcd for $C_{15}H_{12}N_3$ $[M+H]^+$ 234.1026, found 234.1019.



5-Methoxy-3-phenylimidazo[1,5-*a*]pyridine-1-carbonitrile (**4ka**):

Following the general 2.1, compound **4ka** was obtained as a gray crystalline solid in 60% yield (44.8 mg) by flash chromatography (P:E = 2:1); mp = 189-192 °C.

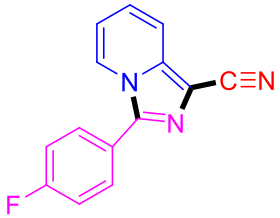
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.53 (m, 2H), 7.44 – 7.32 (m, 4H), 7.14 (dd, *J* = 8.9, 7.3 Hz, 1H), 6.01 (dd, *J* = 7.3, 0.8 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 150.4, 139.9, 139.7, 131.9, 130.4, 128.9, 127.2, 126.5, 115.6, 108.9, 103.0, 89.9, 56.3. HRMS (ESI): calcd for $C_{15}H_{12}N_3O$ $[M+H]^+$ 250.0975, found 250.0968.



1-Phenylimidazo[1,5-*a*]quinoline-3-carbonitrile (**4la**):

Following the general 2.1, compound **4la** was obtained as a pale yellow crystalline solid in 98% yield (79.1 mg) by flash chromatography (P:E = 8:1); mp = 189-190 °C.

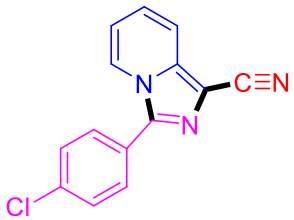
^{1}H NMR (400 MHz, Chloroform-d) δ 7.76 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.64 – 7.52 (m, 7H), 7.47 – 7.42 (m, 2H), 7.33 – 7.28 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-d) δ 143.6, 137.1, 132.1, 132.0, 130.4, 129.7, 129.4, 129.2, 129.0, 127.0, 126.5, 125.2, 117.5, 115.0, 114.8, 105.8. HRMS (ESI): calcd for $C_{18}H_{12}N_3$ $[M+H]^+$ 270.1026, found 270.1026.



3-(4-Fluorophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ab**):

Following the general 2.1, compound **4ab** was obtained as a white crystalline solid in 96% yield (68.3 mg) by flash chromatography (P:E = 3:1); mp = 191-193 °C.

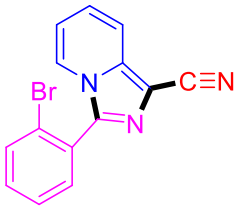
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.28 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.77 – 7.72 (m, 3H), 7.29 – 7.26 (m, 2H), 7.19 – 7.15 (m, 1H), 6.87 – 6.83 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 163.5 ($^{1}J_{CF}$ = 253 Hz), 139.1, 137.7, 130.6 ($^{3}J_{CF}$ = 8 Hz), 124.7, 124.5 ($^{4}J_{CF}$ = 3 Hz), 122.7, 117.5, 116.6 ($^{2}J_{CF}$ = 22 Hz), 115.3, 115.1, 103.5. HRMS (ESI): calcd for $C_{14}H_9FN_3$ $[M+H]^+$ 238.0775, found 238.0766.



3-(4-Chlorophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ac**):

Following the general 2.1, compound **4ac** was obtained as a white crystalline solid in 98% yield (74.4 mg) by flash chromatography (P:E = 2.5:1); mp = 204-205 °C.

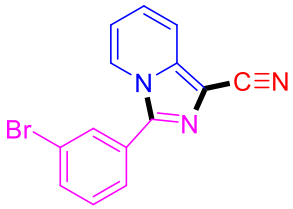
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.77 – 7.71 (m, 3H), 7.57 – 7.53 (m, 2H), 7.20 – 7.16 (m, 1H), 6.88 – 6.85 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.9, 137.8, 136.2, 129.7, 129.6, 126.8, 124.7, 122.7, 117.6, 115.2, 115.2, 103.8. HRMS (ESI): calcd for $C_{14}H_9ClN_3$ $[M+H]^+$ 254.0480, found 254.0471.



3-(2-Bromophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ad**):

Following the general 2.1, compound **4ad** was obtained as a pale yellow crystalline solid in 90% yield (80.2 mg) by flash chromatography (P:E = 3:1); mp = 171-173 °C.

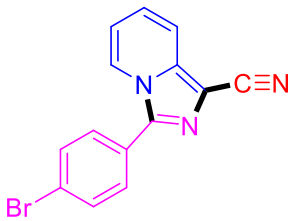
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.78 – 7.72 (m, 3H), 7.57 – 7.45 (m, 3H), 7.23 – 7.19 (m, 1H), 6.85 (td, *J* = 6.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.7, 137.1, 133.5, 133.4, 132.1, 129.6, 128.1, 124.9, 124.0, 123.7, 117.1, 115.3, 114.5, 103.0. HRMS (ESI): calcd for $C_{14}H_9BrN_3$ $[M+H]^+$ 297.9974, found 297.9964.



3-(3-Bromophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ae**):

Following the general 2.1, compound **4ae** was obtained as a white crystalline solid in 97% yield (86.4 mg) by flash chromatography (P:E = 3:1); mp = 198-200 °C.

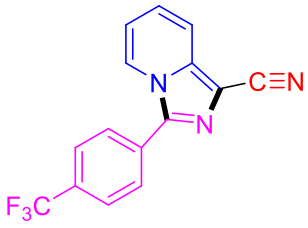
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.94 (t, *J* = 1.8 Hz, 1H), 7.77 – 7.65 (m, 3H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.22 – 7.18 (m, 1H), 6.91 – 6.87 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.4, 137.8, 133.1, 131.4, 130.8, 130.3, 126.9, 124.8, 123.4, 122.8, 117.6, 115.3, 115.1, 103.90. HRMS (ESI): calcd for $C_{14}H_9BrN_3$ $[M+H]^+$ 297.9974, found 297.9970.



3-(4-Bromophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4af**):

Following the general 2.1, compound **4af** was obtained as a white crystalline solid in 97% yield (86.4 mg) by flash chromatography (P:E = 3:1); mp = 204-205 °C.

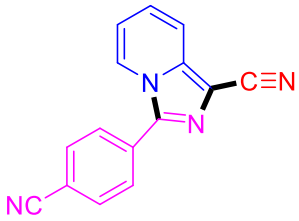
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.75 – 7.63 (m, 5H), 7.20 – 7.16 (m, 1H), 6.87 (td, *J* = 6.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.9, 137.8, 132.6, 129.9, 127.3, 124.7, 124.4, 122.7, 117.6, 115.2, 115.1, 103.0. HRMS (ESI): calcd for $C_{14}H_9BrN_3$ $[M+H]^+$ 297.9974, found 297.9973.



3-(4-(Trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ag**):

Following the general 2.1, compound **4ag** was obtained as a white crystalline solid in 89% yield (76.6 mg) by flash chromatography (P:E = 2:1); mp = 157-158 °C.

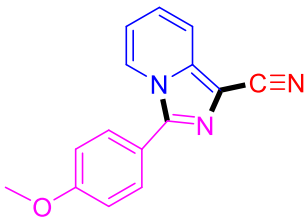
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.94 – 7.92 (m, 2H), 7.84 – 7.77 (m, 3H), 7.24 – 7.20 (m, 1H), 6.93 – 6.89 (m, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 138.4, 137.9, 131.9, 131.88, 131.6, 128.7, 126.3 (q, J_{CF3} = 4 Hz), 125.0 (d, *J* = 3.0 Hz), 122.7, 122.3, 117.7, 115.5 (d, *J* = 3.0 Hz), 115.0 (d, *J* = 4.0 Hz). HRMS (ESI): calcd for $C_{15}H_9F_3N_3$ $[M+H]^+$ 288.0743, found 288.0745.



3-(4-Cyanophenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ah**):

Following the general 2.1, compound **4ah** was obtained as a pale yellow crystalline solid in 97% yield (71.0 mg) by flash chromatography (P:E = 1:1.5); mp = 236-238 °C.

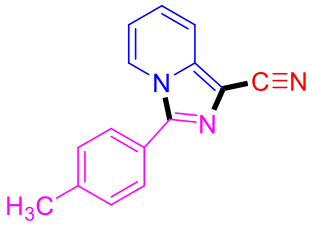
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.38 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.96 – 7.94 (m, 2H), 7.87 – 7.85 (m, 2H), 7.81 – 7.78 (m, 1H), 7.27 – 7.23 (m, 1H), 6.94 (td, *J* = 6.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 138.5, 138.4, 133.5, 132.9 , 129.5, 127.2, 125.0, 118.9, 117.0, 116.4, 115.9, 112.3, 102.7. HRMS (ESI): calcd for $C_{15}H_9N_4$ $[M+H]^+$ 245.0822, found 245.0819.



3-(4-Methoxyphenyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ai**):

Following the general 2.1, compound **4ai** was obtained as a pale yellow crystalline solid in 92% yield (68.7 mg) by flash chromatography (P:E = 2.5:1); mp = 129-131 °C.

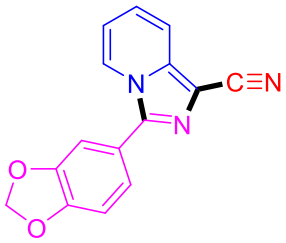
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.72 – 7.66 (m, 3H), 7.15 – 7.05 (m, 3H), 6.82 – 6.79 (m, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 160.9, 140.1, 137.5, 123.0, 124.4, 123.0, 120.6, 117.4, 115.6, 114.8, 114.7, 103.1, 55.5. HRMS (ESI): calcd for $C_{15}H_{12}N_3O$ $[M+H]^+$ 250.0975, found 250.0968.



3-(P-tolyl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4aj**):

Following the general 2.1, compound **4aj** was obtained as a white crystalline solid in 68% yield (47.6 mg) by flash chromatography (P:E = 1:1); mp = 150-151 °C.

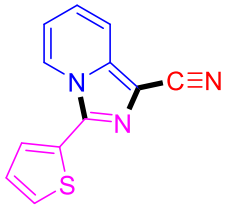
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 7.3, 1.1 Hz, 1H), 7.73 – 7.63 (m, 3H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.14 (dd, *J* = 9.1, 6.5 Hz, 1H), 6.83 – 6.79 (m, 1H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 140.3, 140.3, 137.6, 130.0, 128.3, 125.4, 124.4, 123.0, 117.4, 115.5, 114.7, 103.3, 21.5. HRMS (ESI): calcd for $C_{15}H_{12}N_3$ $[M+H]^+$ 234.1026, found 234.1023.



3-(Benzo[d][1,3]dioxol-5-yl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4ak**):

Following the general 2.1, compound **4ak** was obtained as a pale yellow crystalline solid in 40% yield (31.6 mg) by flash chromatography (P:E = 1:1); mp = 189-190 °C.

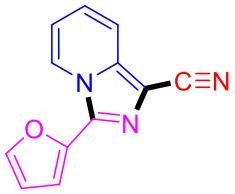
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.69 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.23 – 7.11 (m, 3H), 6.96 (d, *J* = 8.0 Hz, 1H), 6.82 (td, *J* = 7.0, 1.2 Hz, 1H), 6.07 (s, 2H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 149.1, 148.5, 139.8, 137.6, 124.5, 123.0, 122.6, 121.9, 117.4, 115.5, 114.8, 109.0, 108.9, 103.1, 101.8. HRMS (ESI): calcd for $C_{15}H_{10}N_3O_2$ $[M+H]^+$ 264.0768, found 264.0767.



3-(Thiophen-2-yl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4al**):

Following the general 2.1, compound **4al** was obtained as a white crystalline solid in 55% yield (37.1 mg) by flash chromatography (P:E = 1:1); mp = 108-109 °C.

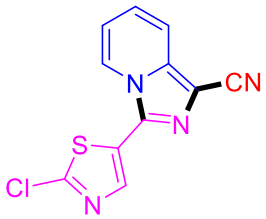
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.46 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.72 (dt, *J* = 9.2, 1.3 Hz, 1H), 7.59 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.53 (dd, *J* =5.1, 1.1 Hz, 1H), 7.23 – 7.16 (m, 2H), 6.92 (td, *J* = 6.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 137.7, 134.7, 129.9, 127.9, 127.9, 126.94, 124.6, 123.2, 117.4, 115.4, 115.1, 103.7. HRMS (ESI): calcd for $C_{12}H_8N_3S$ $[M+H]^+$ 226.0433, found 226.0429.



3-(Furan-2-yl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4am**):

Following the general 2.1, compound **4am** was obtained as a pale yellow crystalline solid in 92% yield (57.7 mg) by flash chromatography (P:E = 2:1); mp = 146-147 °C.

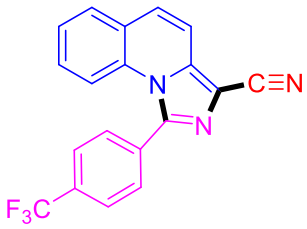
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.69 (dt, *J* = 9.1, 1.2 Hz, 1H), 7.61 (d, *J* = 1.7 Hz, 1H), 7.19 – 7.15 (m, 1H), 7.11 (d, *J* = 3.5 Hz, 1H), 6.91 (td, *J* = 7.0, 1.2 Hz, 1H), 6.62 (dd, *J* = 3.5, 1.8 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 144.6, 143.1, 137.2, 131,9, 124.8, 124.6, 117.1, 115.3, 115.1, 112.1, 110.8, 103.7. HRMS (ESI): calcd for $C_{12}H_8N_3O$ $[M+H]^+$ 210.0662, found 210.0662.



3-(2-Chlorothiazol-5-yl)imidazo[1,5-*a*]pyridine-1-carbonitrile (**4an**):

Following the general 2.1, compound **4an** was obtained as a orange crystalline solid in 98% yield (76.4 mg) by flash chromatography (P:E = 1:2); mp = 207-209 °C.

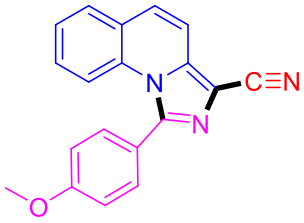
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dt, *J* = 7.2, 1.1 Hz, 1H), 7.99 (s, 1H), 7.80 (dt, *J* = 9.2, 1.2 Hz, 1H), 7.28 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.04 (td, *J* = 6.9, 1.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.9, 139.99, 138.3, 131.2, 129.3, 127.3, 125.6, 117.0, 116.8, 115.4, 102.7. HRMS (ESI): calcd for $C_{11}H_6ClN_4S$ $[M+H]^+$ 260.9996, found 260.9995.



1-(4-(Trifluoromethyl)phenyl)imidazo[1,5-*a*]quinoline-3-carbonitrile (**4ap**):

Following the general 2.3, compound **4ap** was obtained as a pale yellow crystalline solid in 83% yield (83.9 mg) by flash chromatography (P:E = 2.5:1); mp = 200-203 °C.

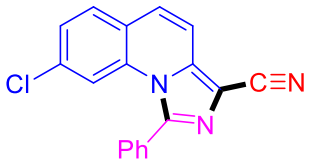
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 – 7.79 (m, 5H), 7.60 (d, *J* = 9.3 Hz, 1H), 7.53 – 7.48 (m, 3H), 7.38 (td, *J* = 7.8, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 141.9, 137.4, 135.6, 132.4, 132.1, 131.7, 130.2, 129.7, 129.2, 127.4, 126.8, 126.1 (q, J_{CF3} = 4 Hz), 125.3, 125.1, 122.4, 117.3, 114.74, 114.72, 106.4. HRMS (ESI): calcd for $C_{19}H_{11}F_3N_3$ $[M+H]^+$ 338.0900, found 338.0900.



1-(4-Methoxyphenyl)imidazo[1,5-*a*]quinoline-3-carbonitrile (**4aq**):

Following the general 2.3, compound **4aq** was obtained as a white crystalline solid in 90% yield (80.8 mg) by flash chromatography (P:E = 1:1); mp = 212-213 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.62 – 7.53 (m, 4H), 7.47 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 7.09 – 7.06 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, Chloroform-*d*) δ 161.1, 143.7, 137.1, 132.2, 131.1, 129.3, 128.9, 126.8, 126.4, 125.2, 124.1, 117.4, 115.2, 114.8, 114.5, 105.6, 55.5. HRMS (ESI): calcd for $C_{19}H_{14}N_3O$ $[M+H]^+$ 300.1131, found 300.1129.



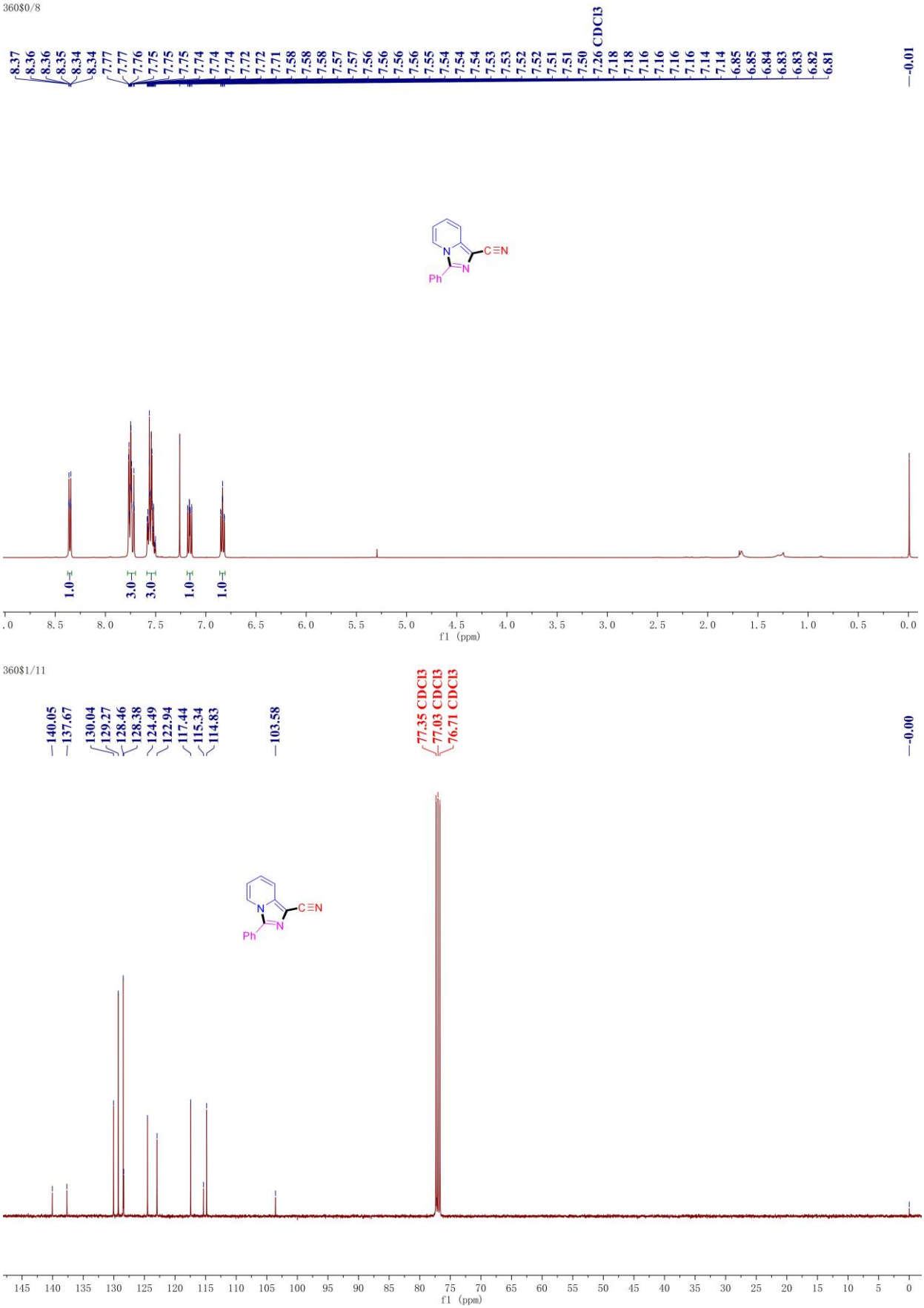
8-Chloro-1-phenylimidazo[1,5-*a*]quinoline-3-carbonitrile (**4ma**):

Following the general 2.3, compound **4ma** was obtained as a pale yellow crystalline solid in 55% yield (50.0 mg) by flash chromatography (P:E= 3:2); mp = 197-199 °C.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 – 7.57 (m, 7H), 7.48 (d, *J* = 1.9 Hz, 1H), 7.43 – 7.38 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.9, 137.2, 133.5, 132.5, 131.8, 131.6, 131.2, 130.2, 129.7, 127.4, 127.1, 124.1, 117.1, 115.6, 115.2, 104.5; HRMS (ESI): calcd for $C_{18}H_{11}ClN_3$ $[M+H]^+$ 304.0636, found 304.0634.

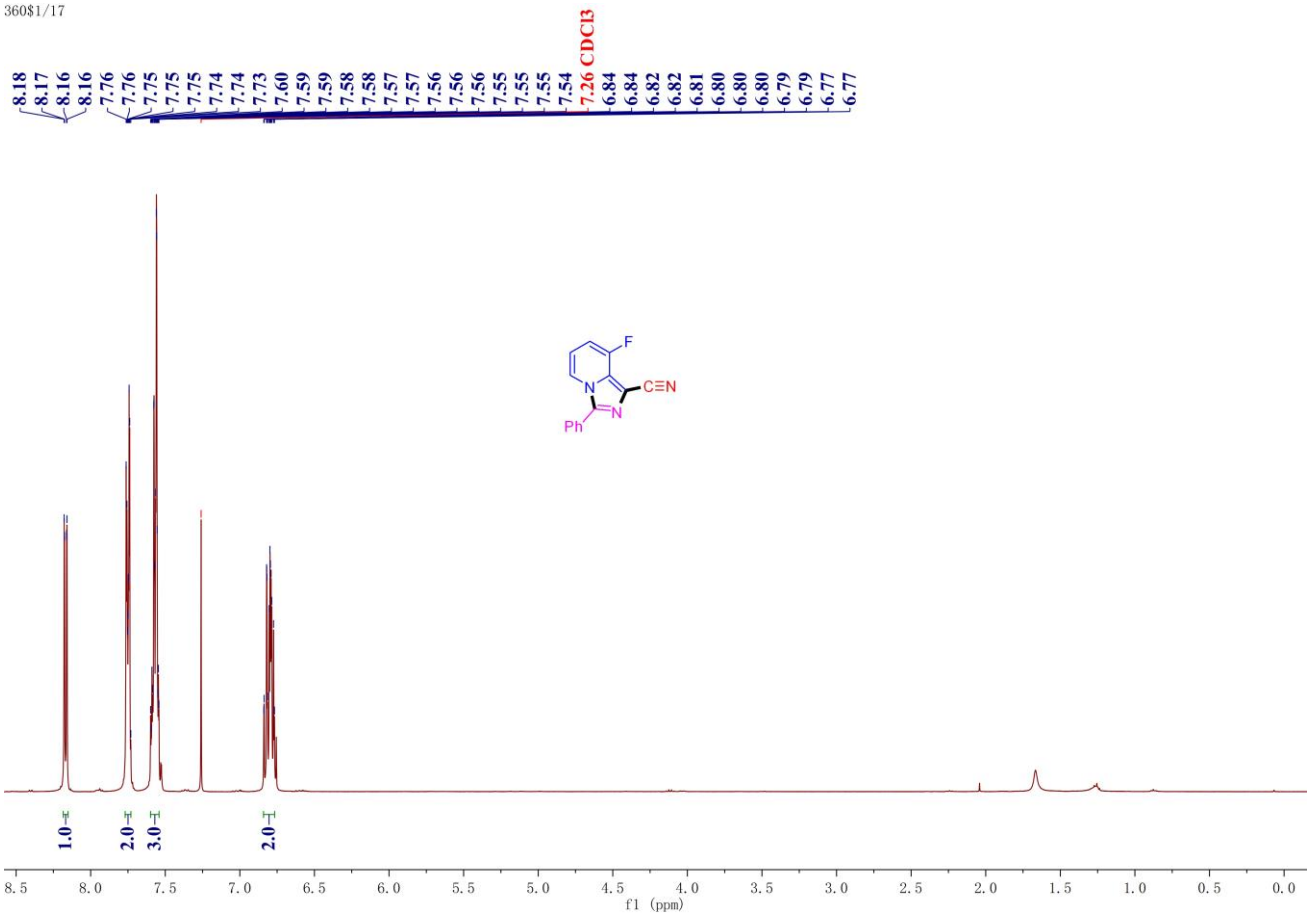
4. ^{1}H NMR and ^{13}C NMR Spectra of synthesized products

4aa

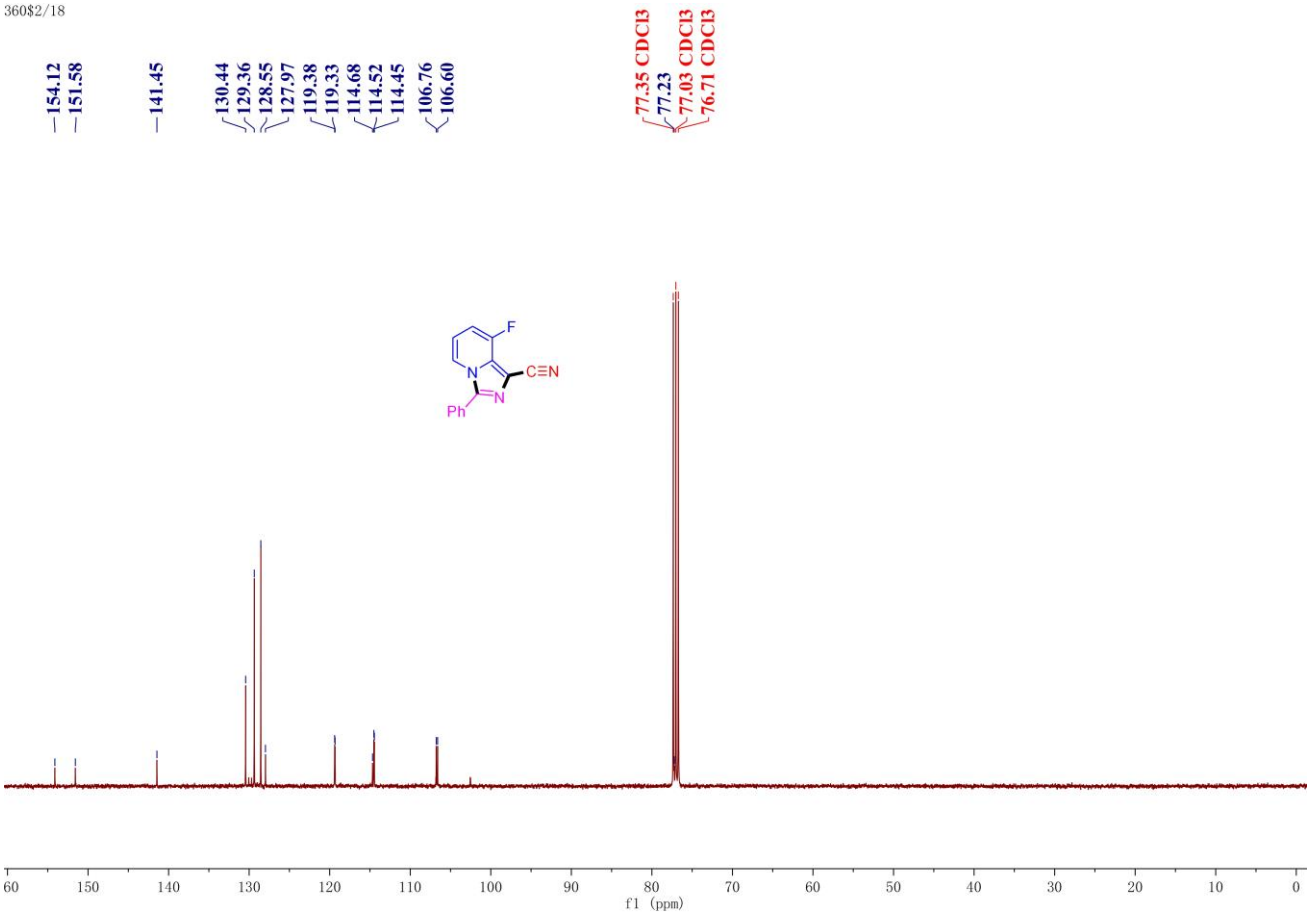


4ba

360$1/17

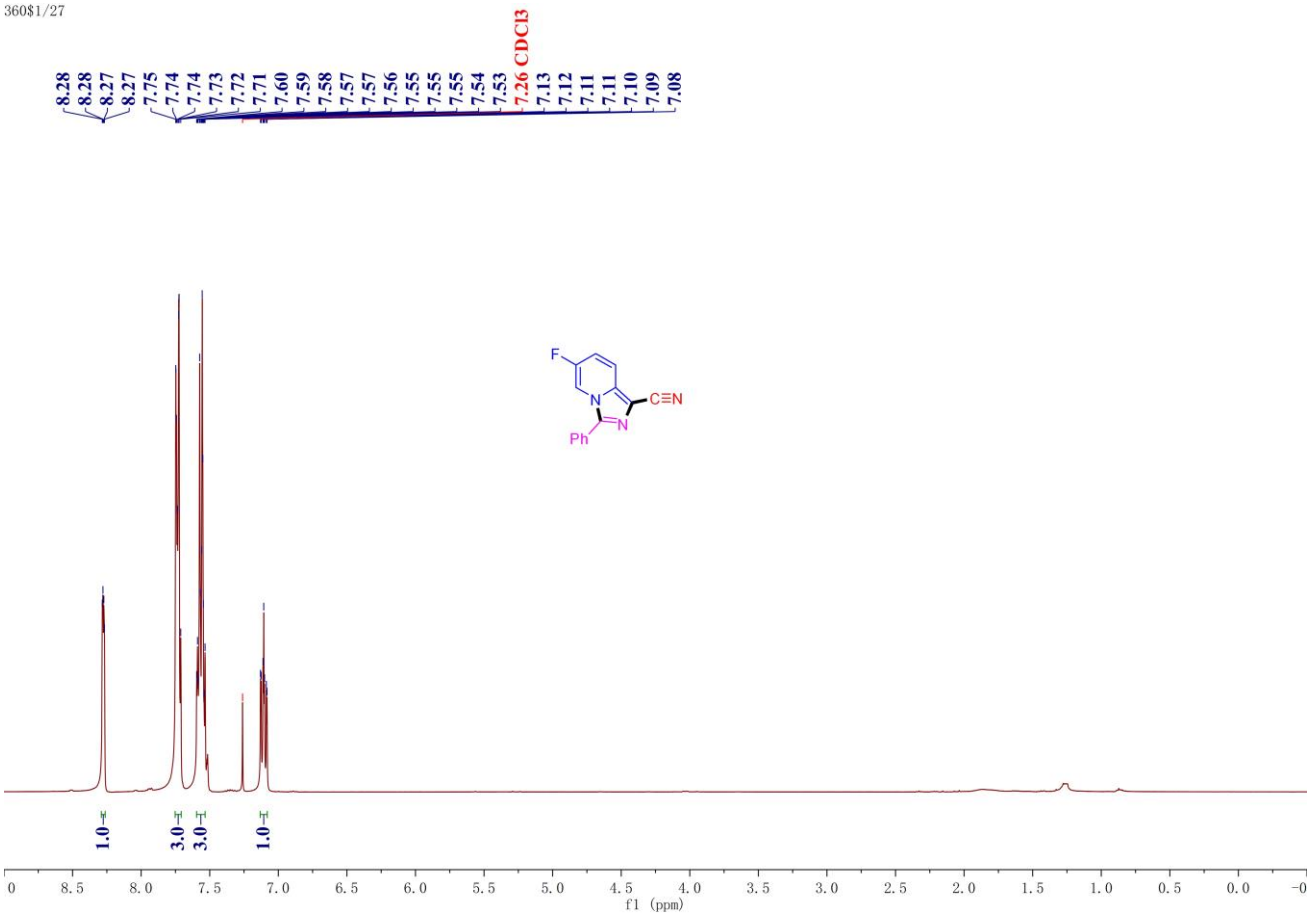


360$2/18

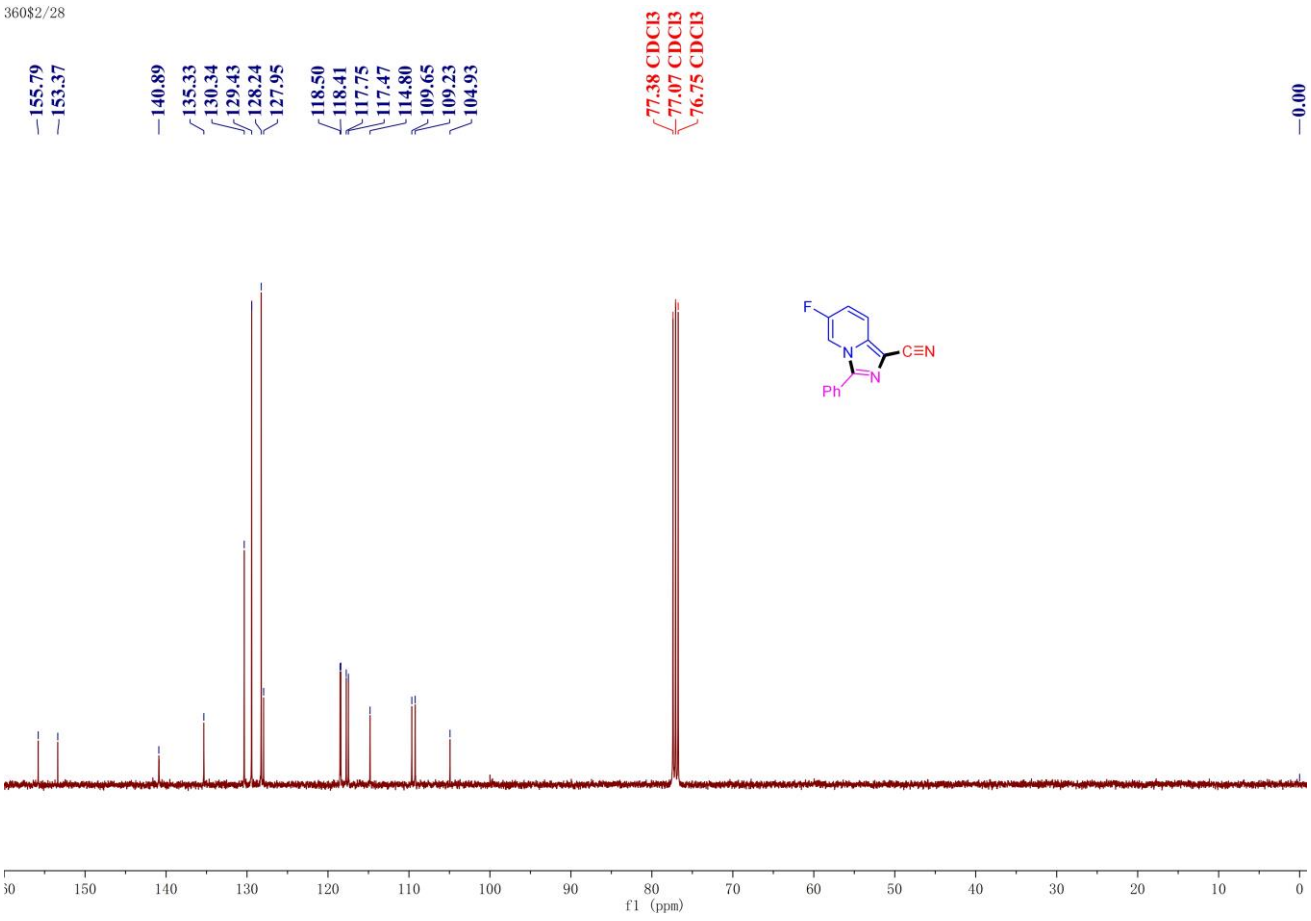


4ca

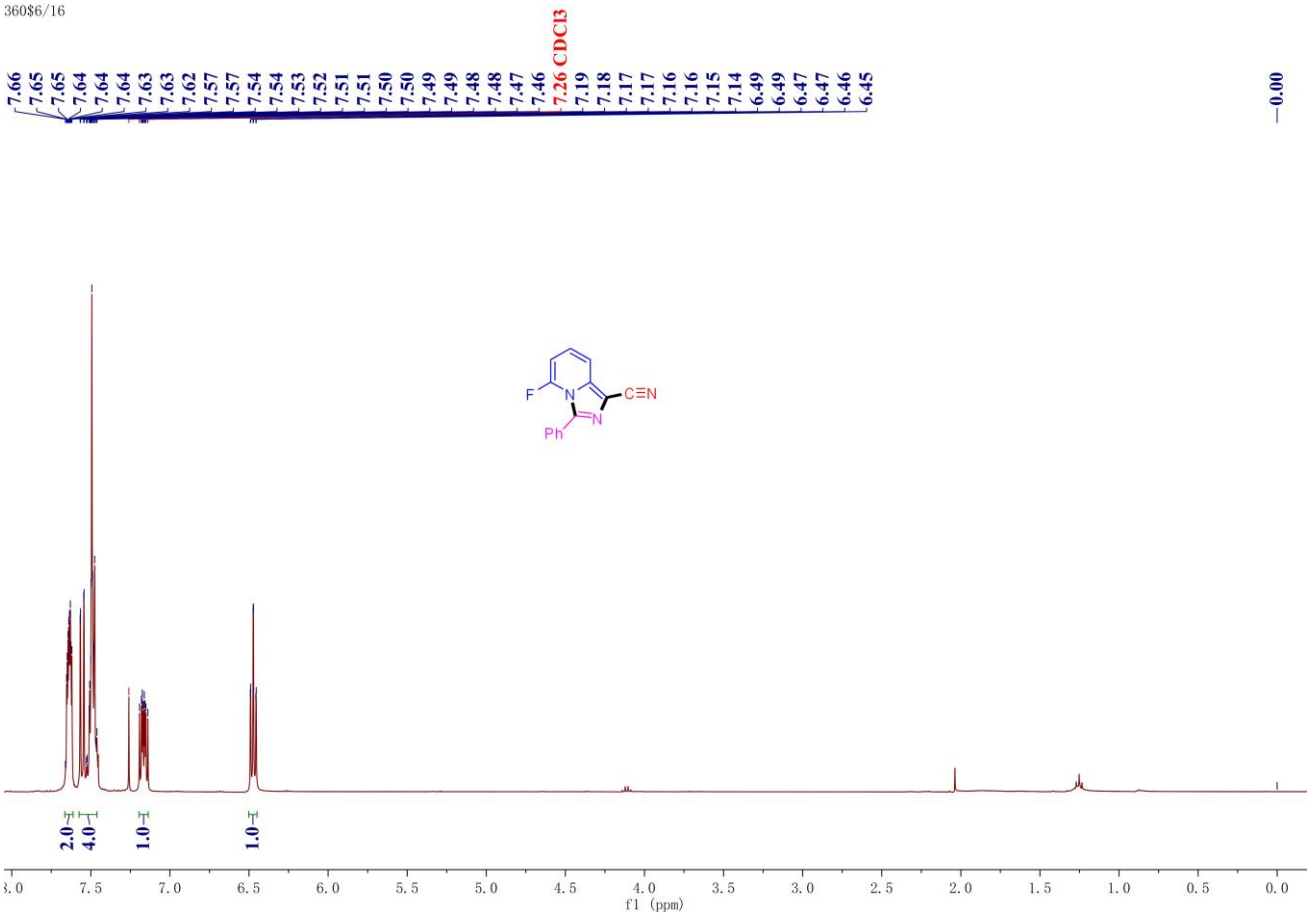
360$1/27



360$2/28



4da


360$6/16
7.66
7.65
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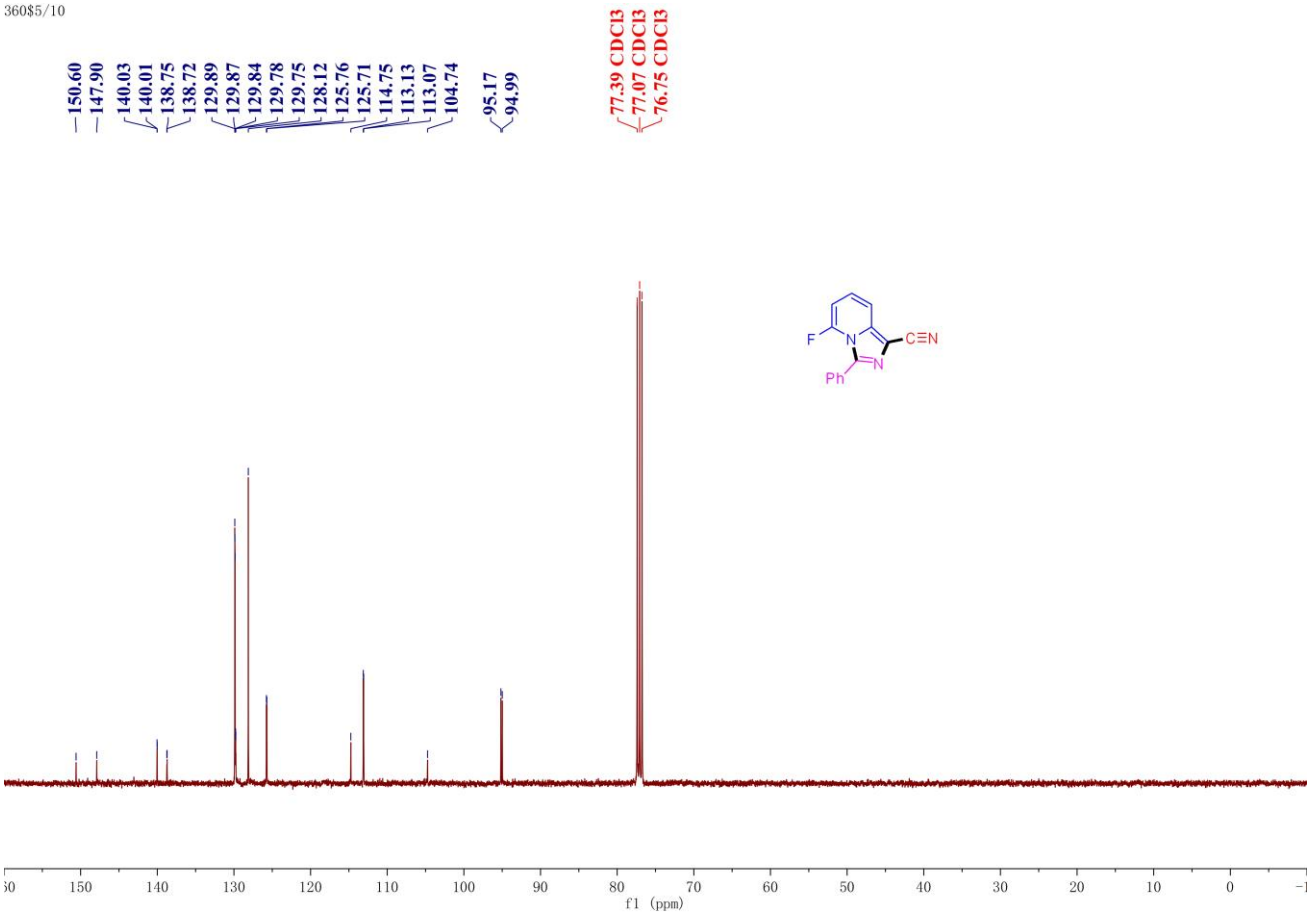
7.48
7.47
7.46
7.26 CDCl3
7.19
7.18
7.17
7.17
7.16
7.16
7.15
7.14
6.49
6.49
6.47
6.47
6.46
6.45
0.00
F
N
C≡N
N
Ph
2.0
4.0
1.0
1.0
f1 (ppm)


360$5/10
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147.90
140.03
140.01
138.75
138.72
129.89
129.87
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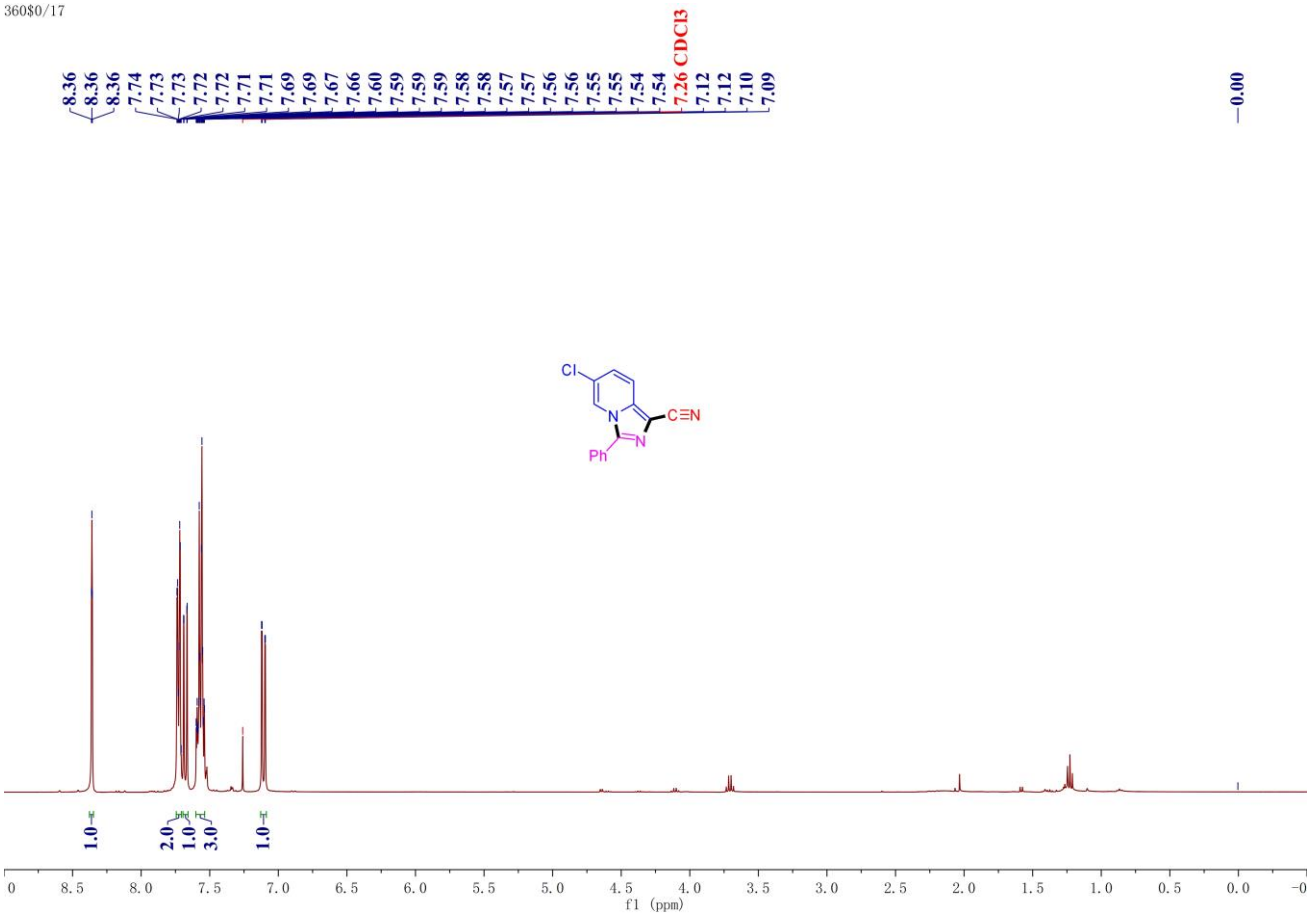
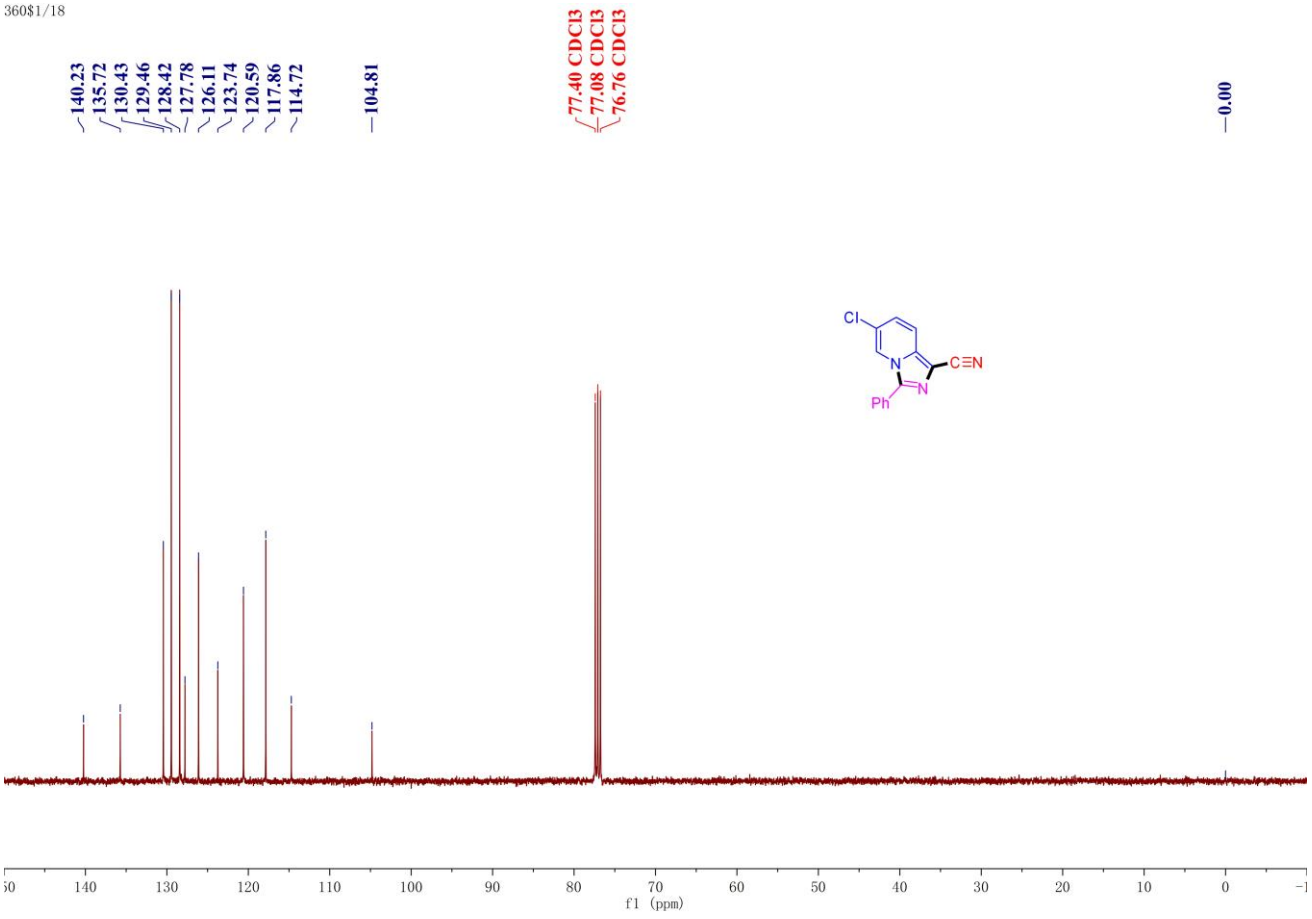
129.78
129.75
128.12
125.76
125.71
114.75
113.13
113.07
104.74
95.17
94.99
77.39 CDCl3
77.07 CDCl3
76.75 CDCl3
F
N
C≡N
N
Ph
f1 (ppm)

4ea

360$0/17



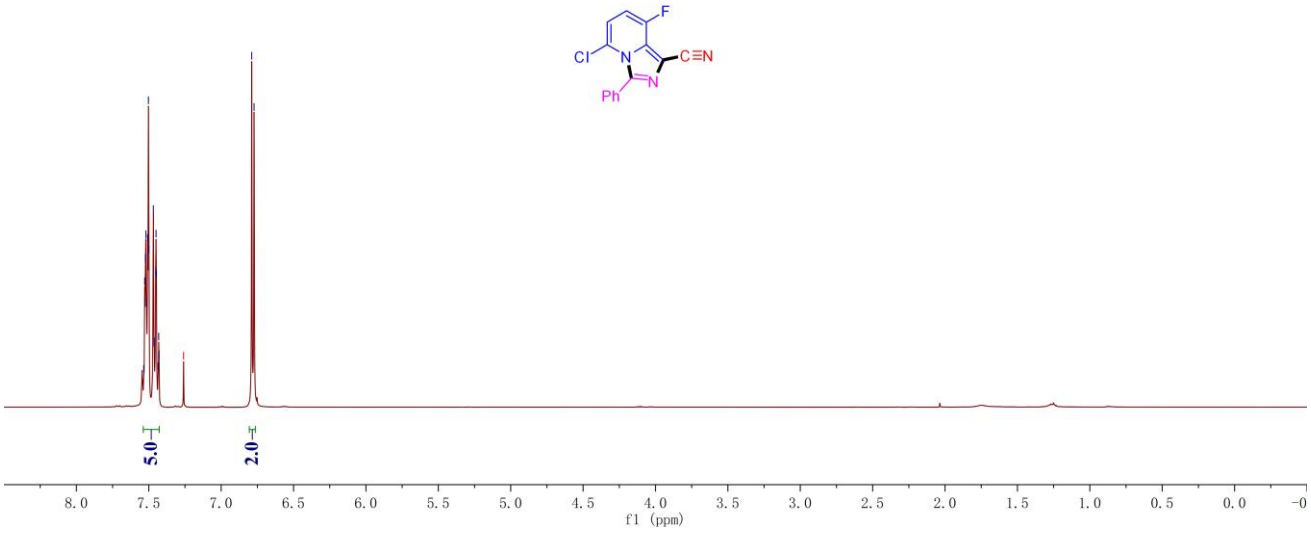
360$1/18



4fa

360$7/23

7.53 7.53 7.52 7.52 7.52 7.51 7.50 7.50 7.47 7.46 7.45 7.45 7.45 7.44 7.43 7.43 7.26 CDCl3 6.79 6.77



360$8/24

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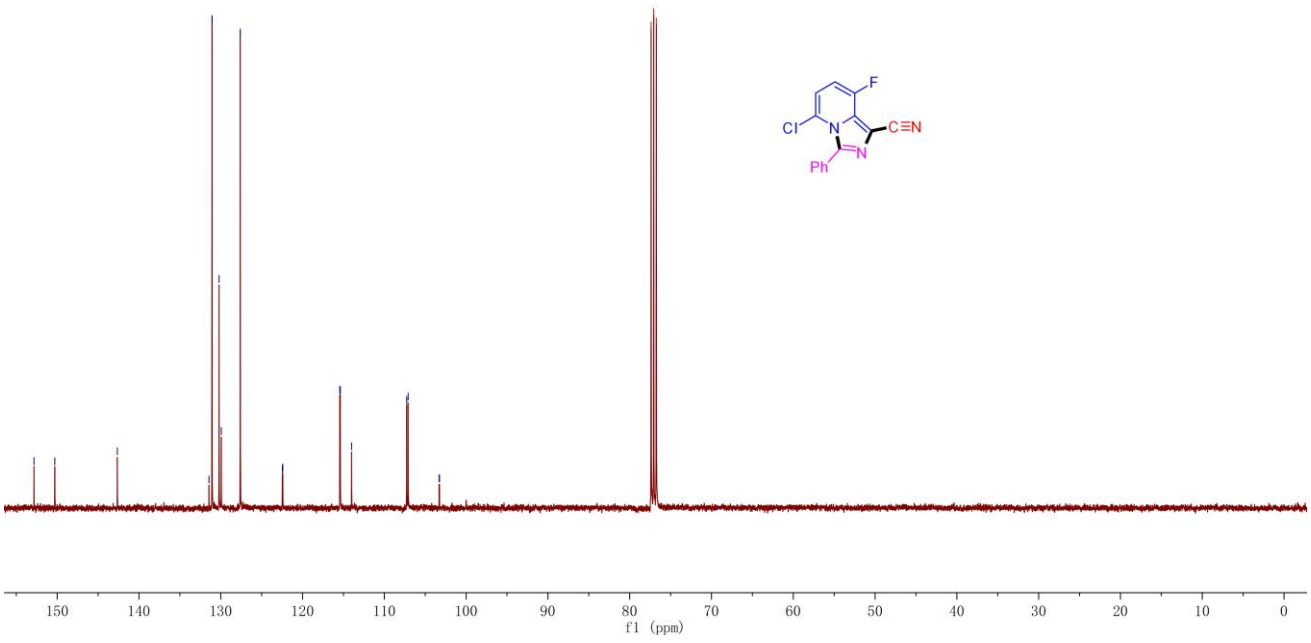

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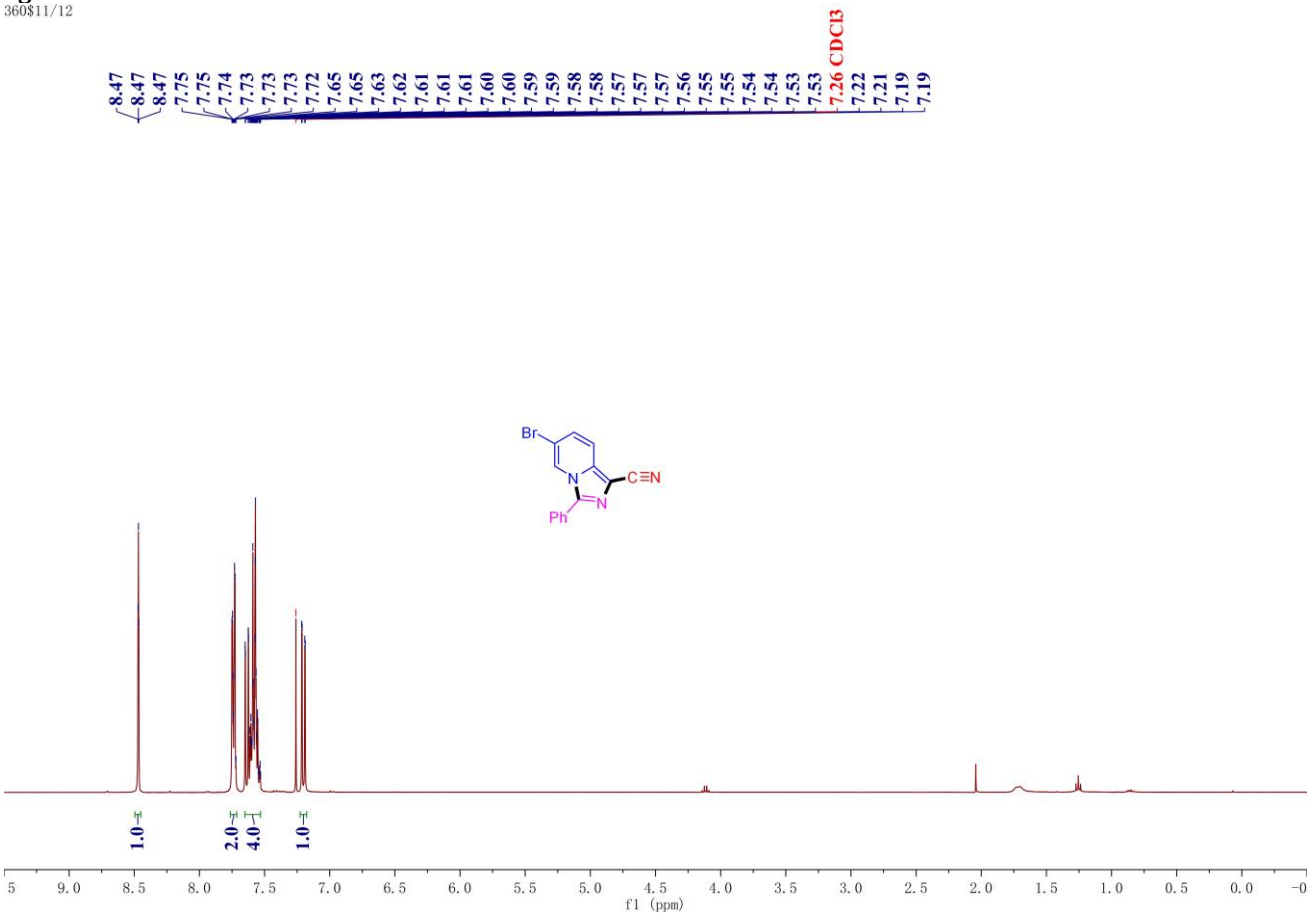
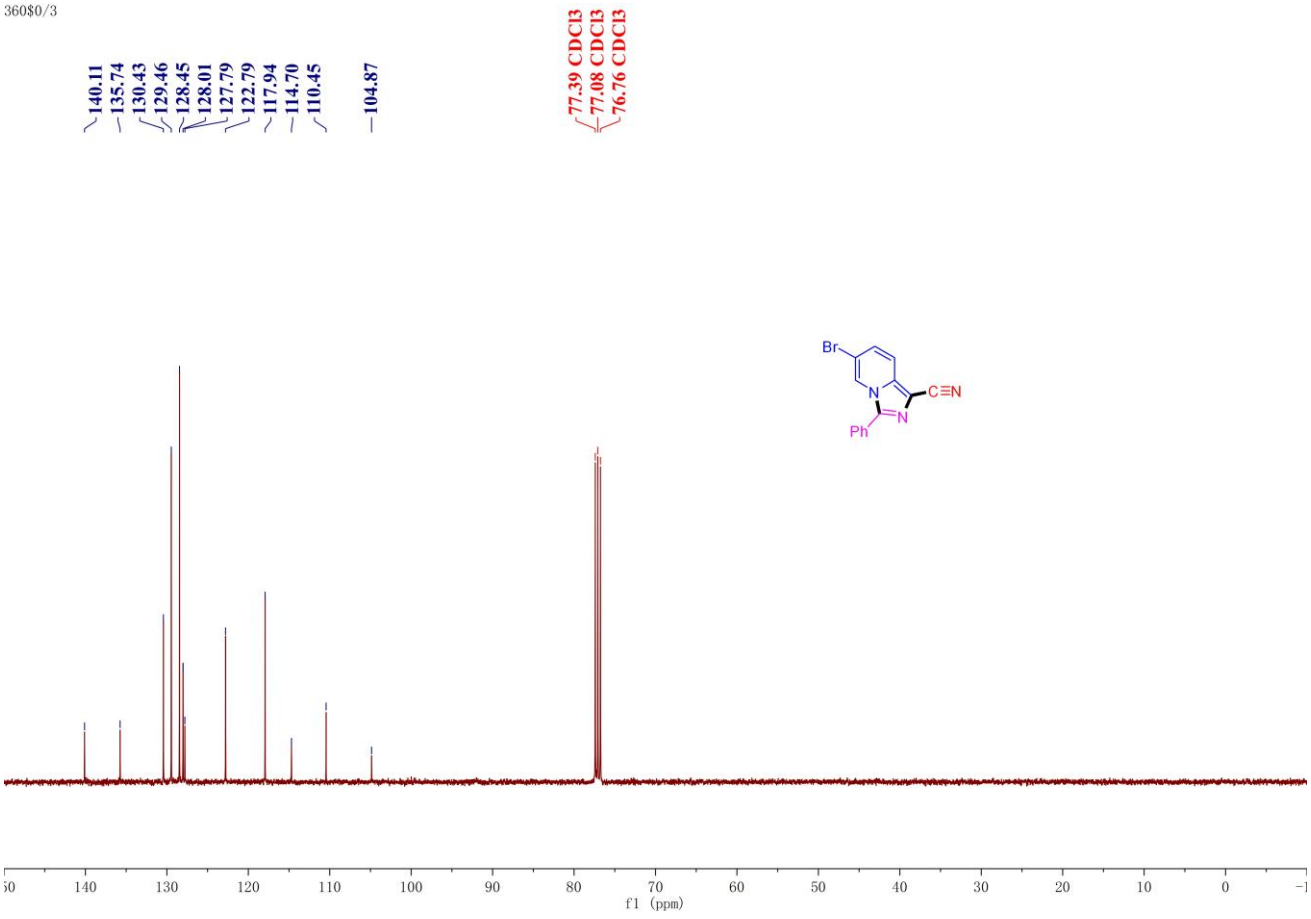
360$11/12

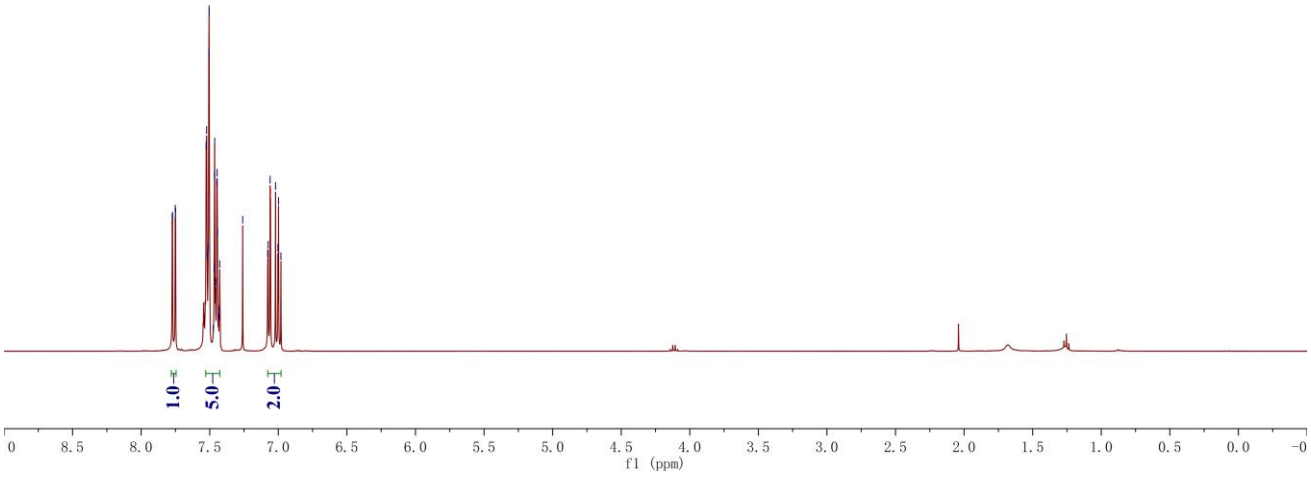


360$0/3

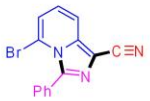


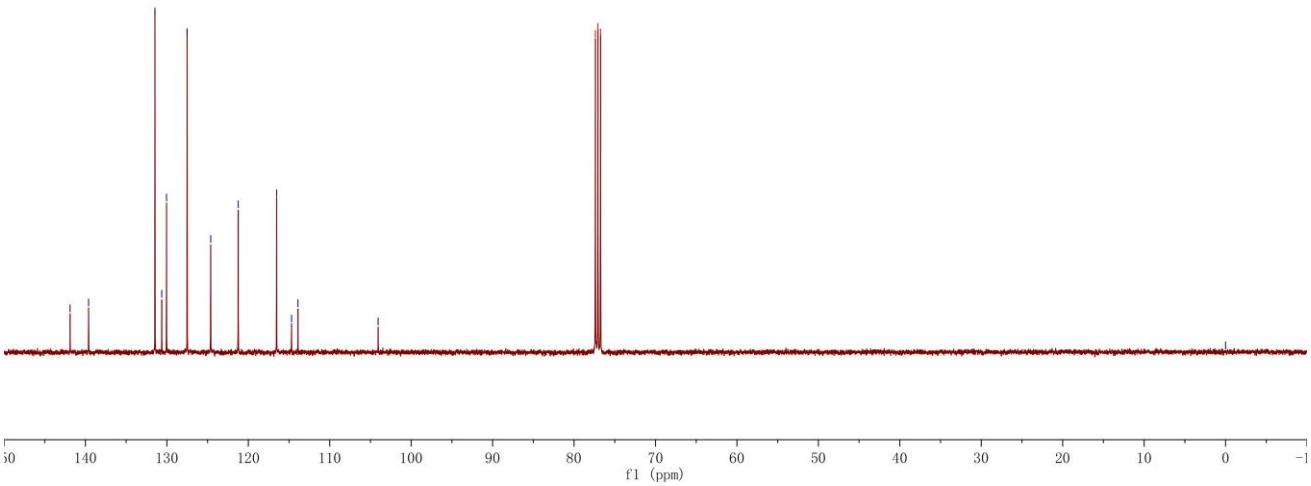
4ha

360$13/10



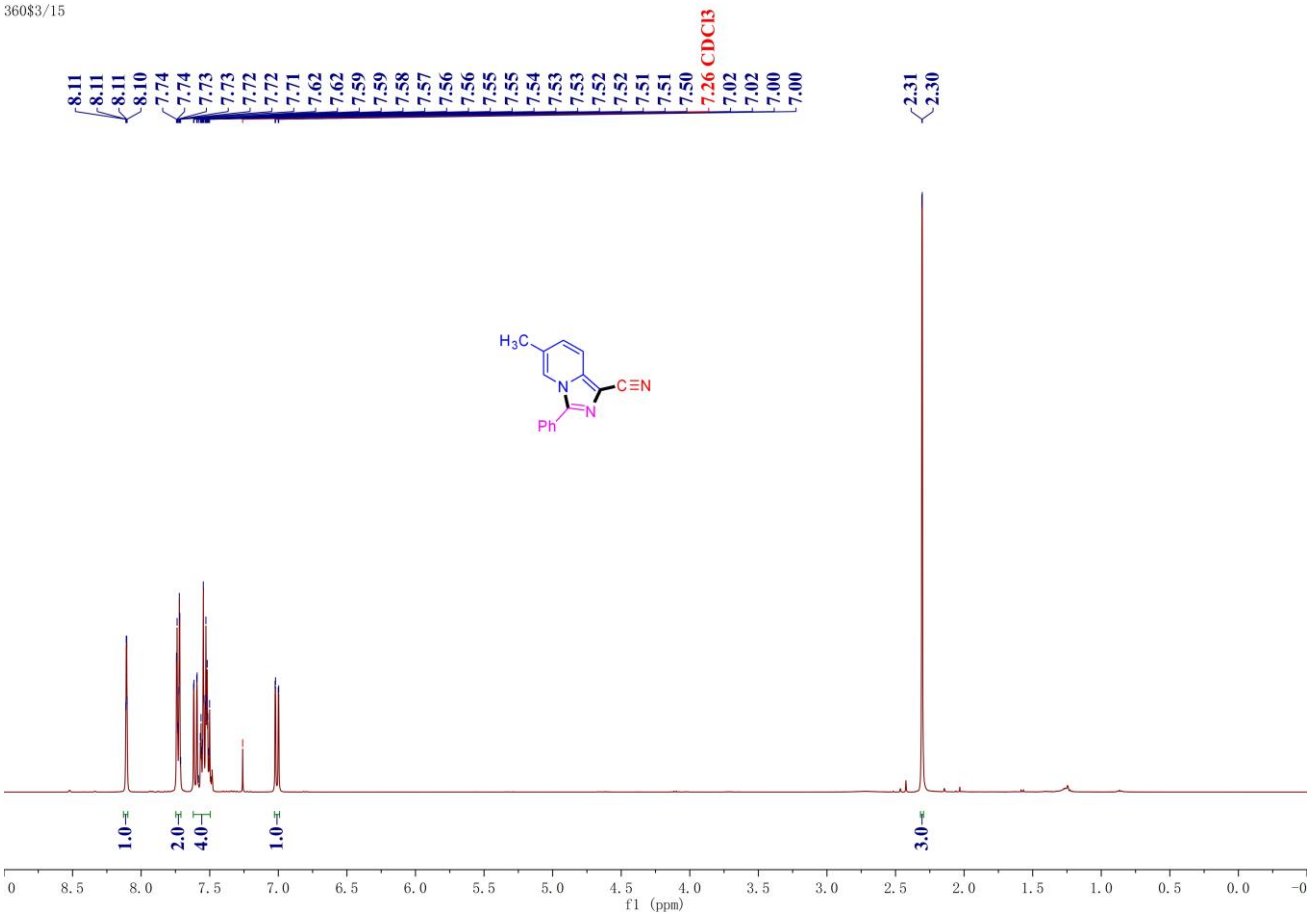
360$2/2



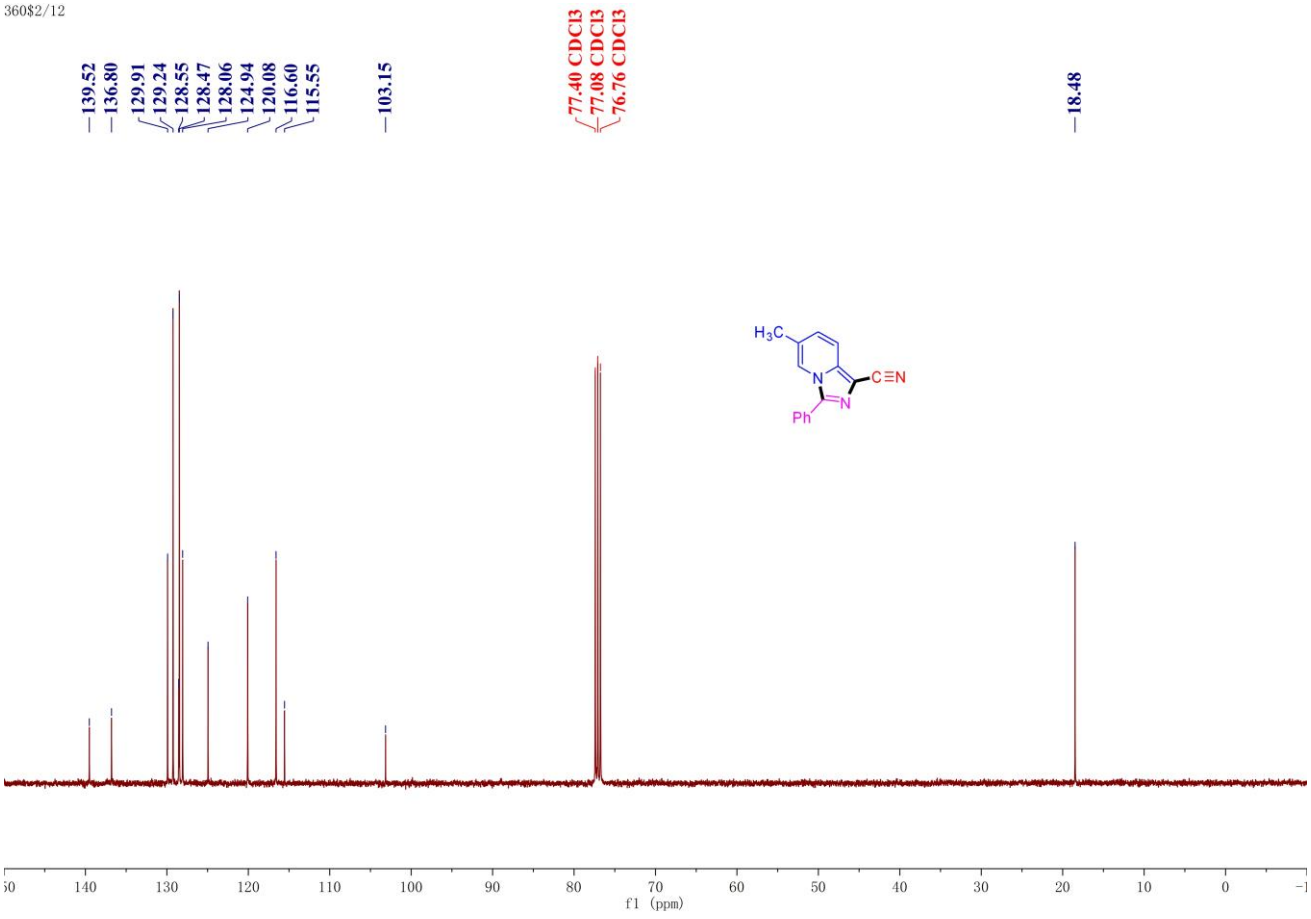


4ia

360$3/15

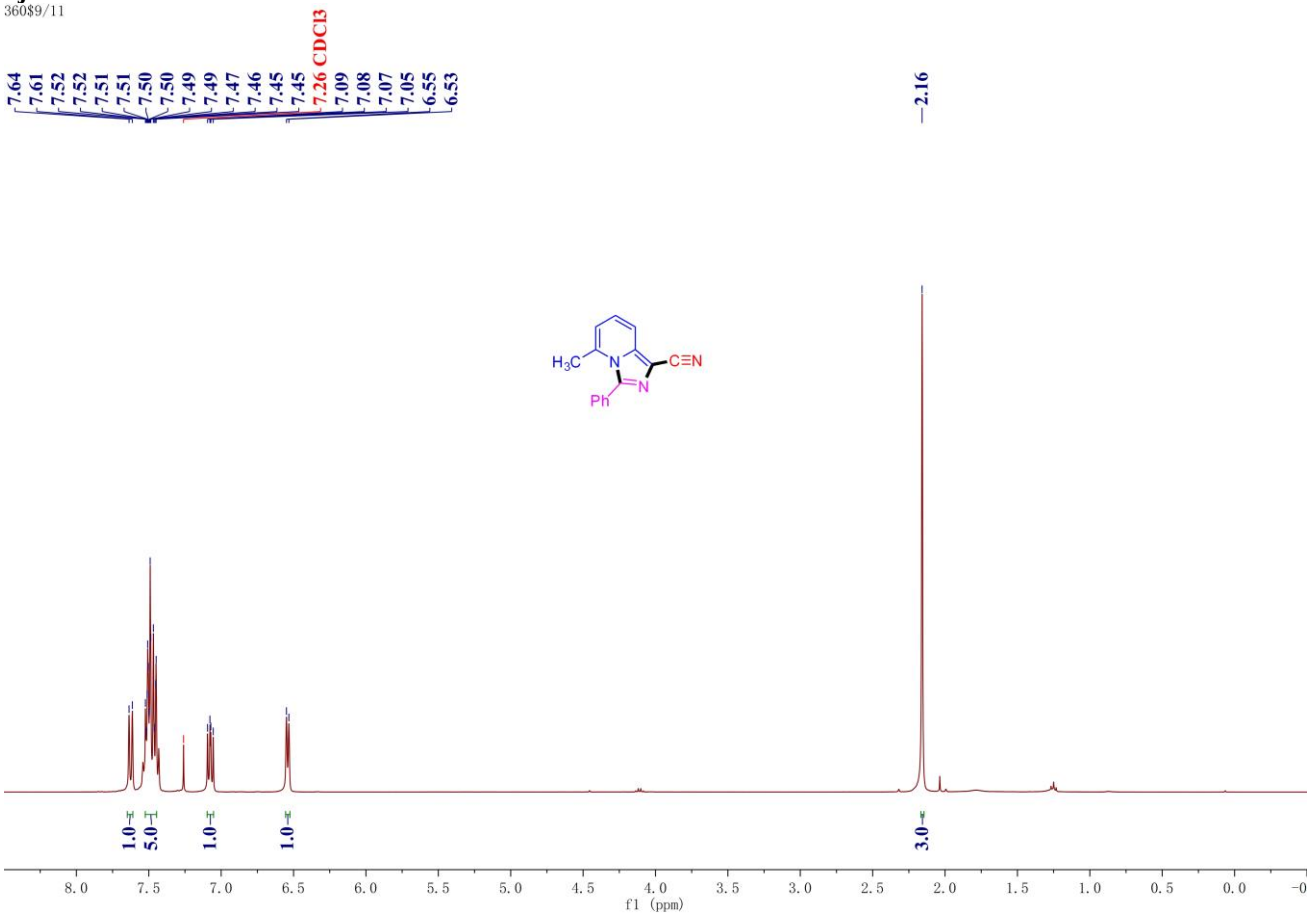


360$2/12

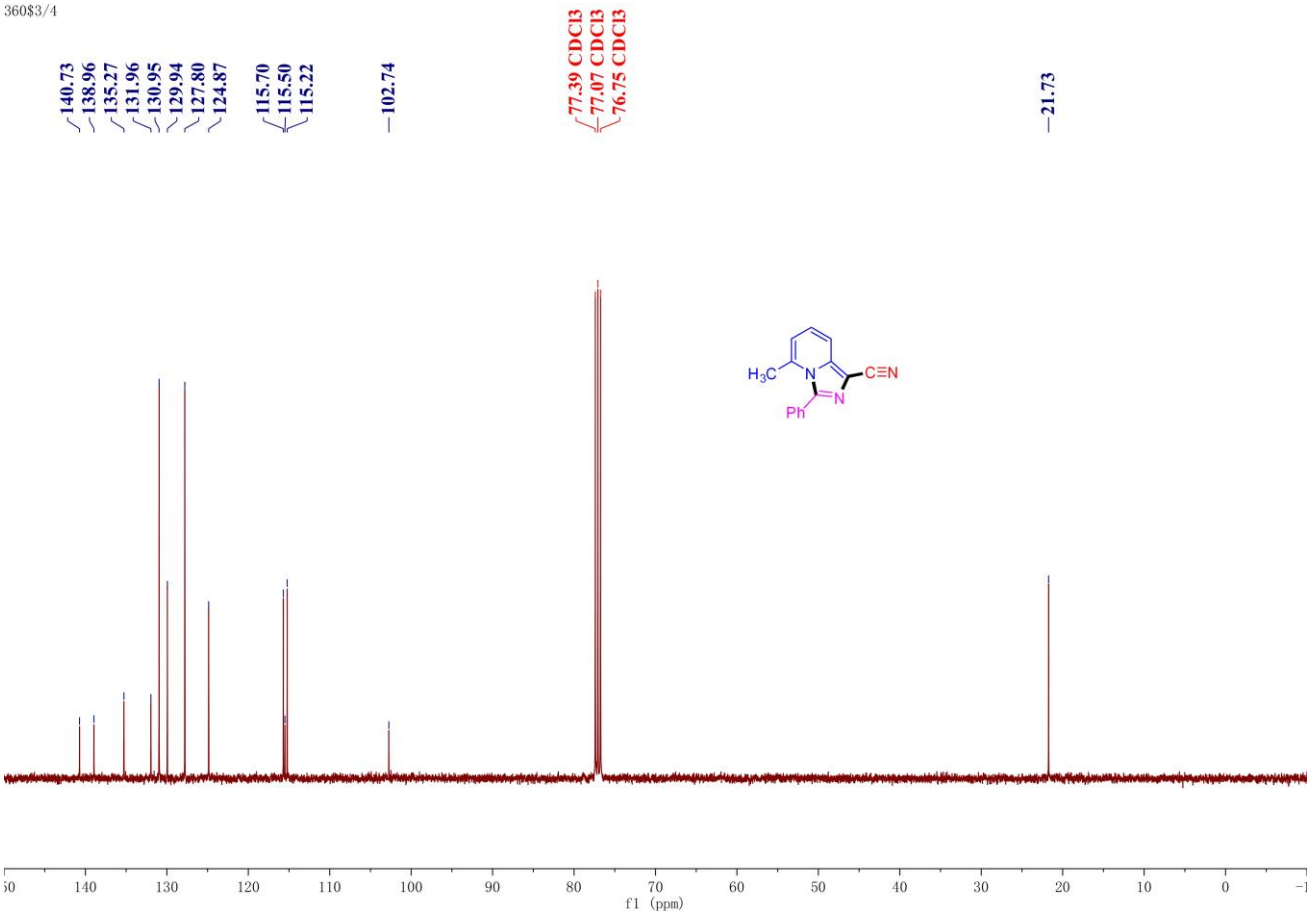


4ja

360$9/11

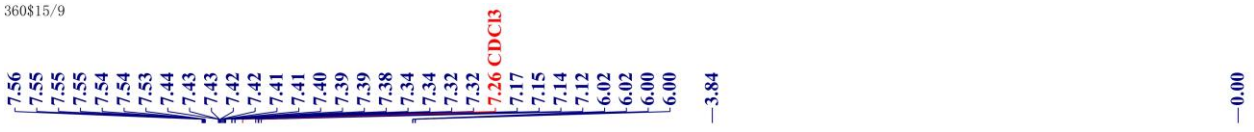


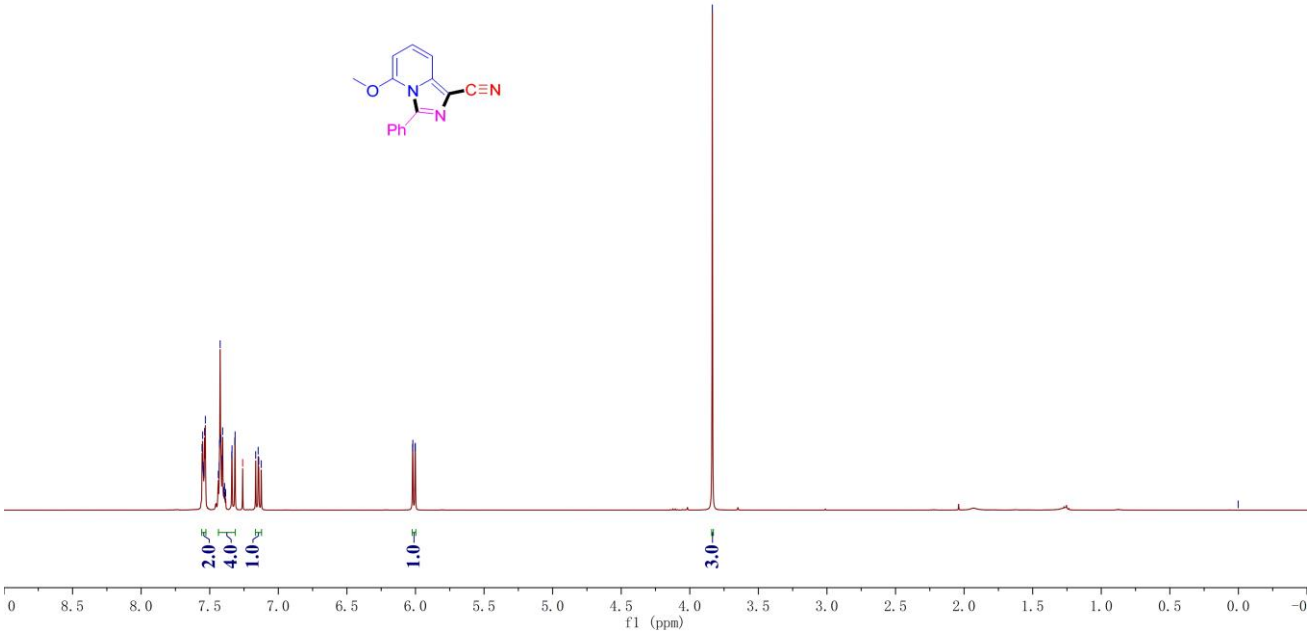
360$3/4



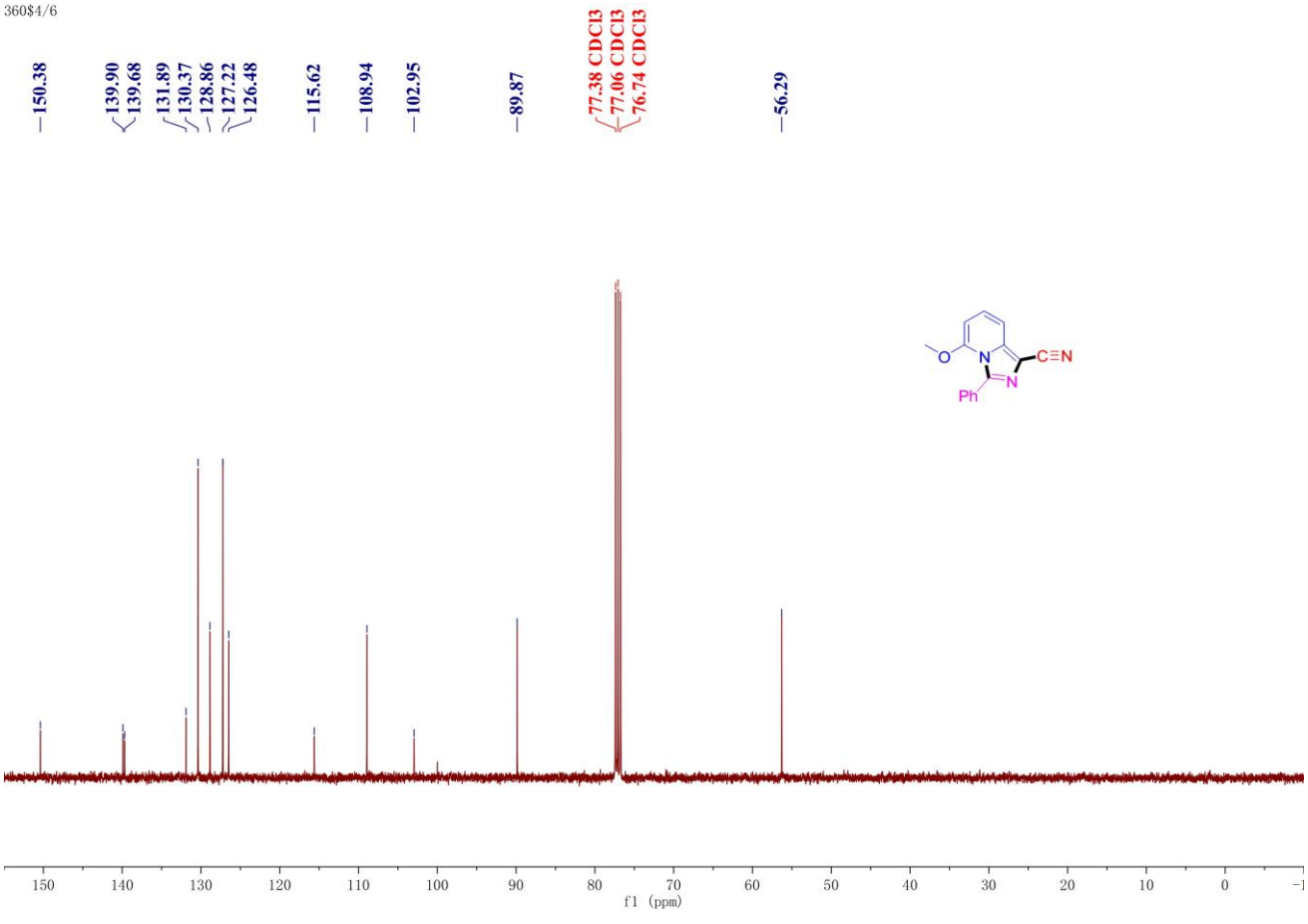
4ka

360$15/9



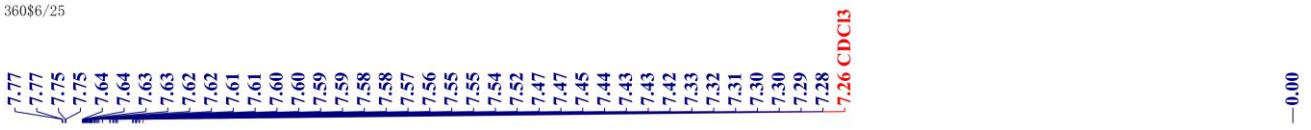


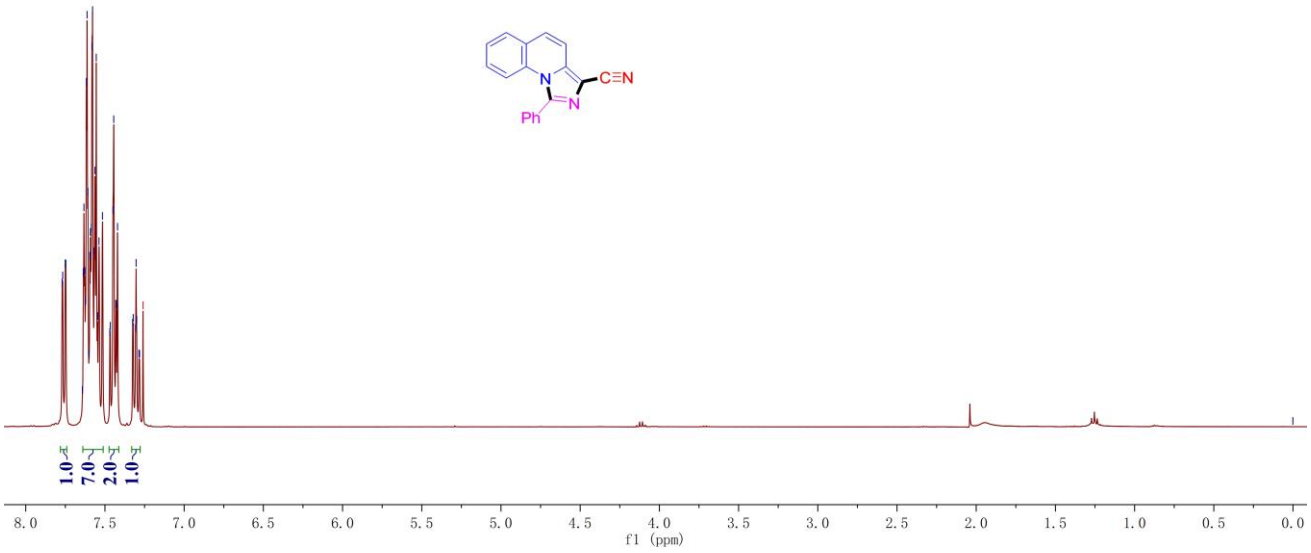
360$4/6



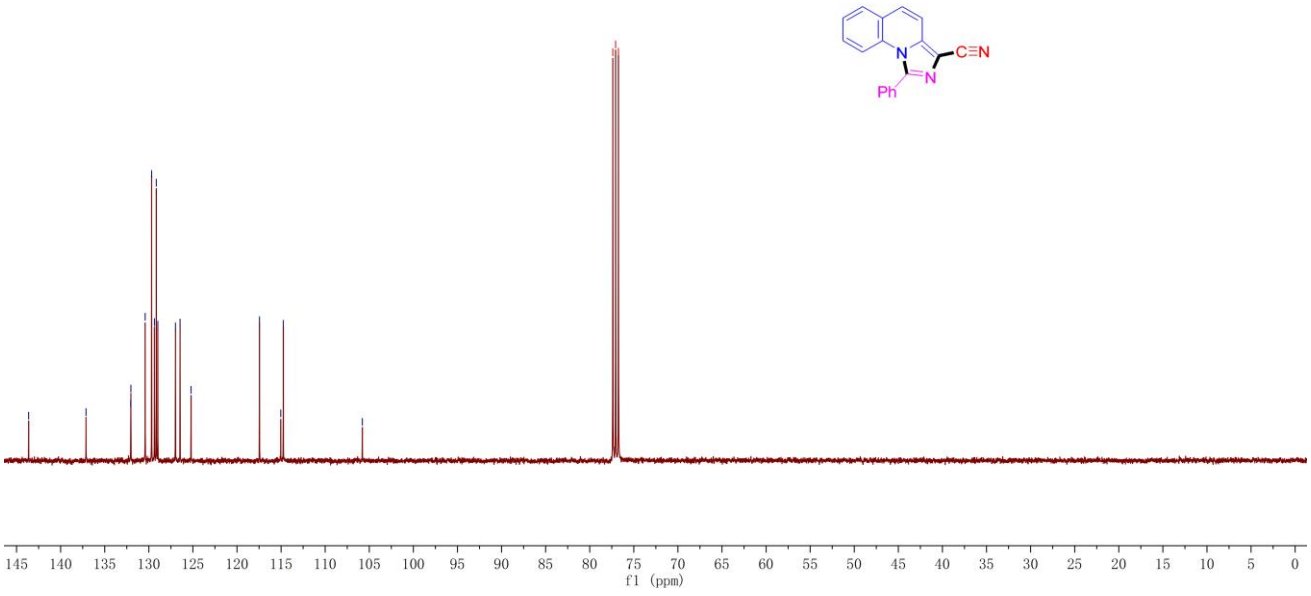
4la

360$6/25





360$1/26



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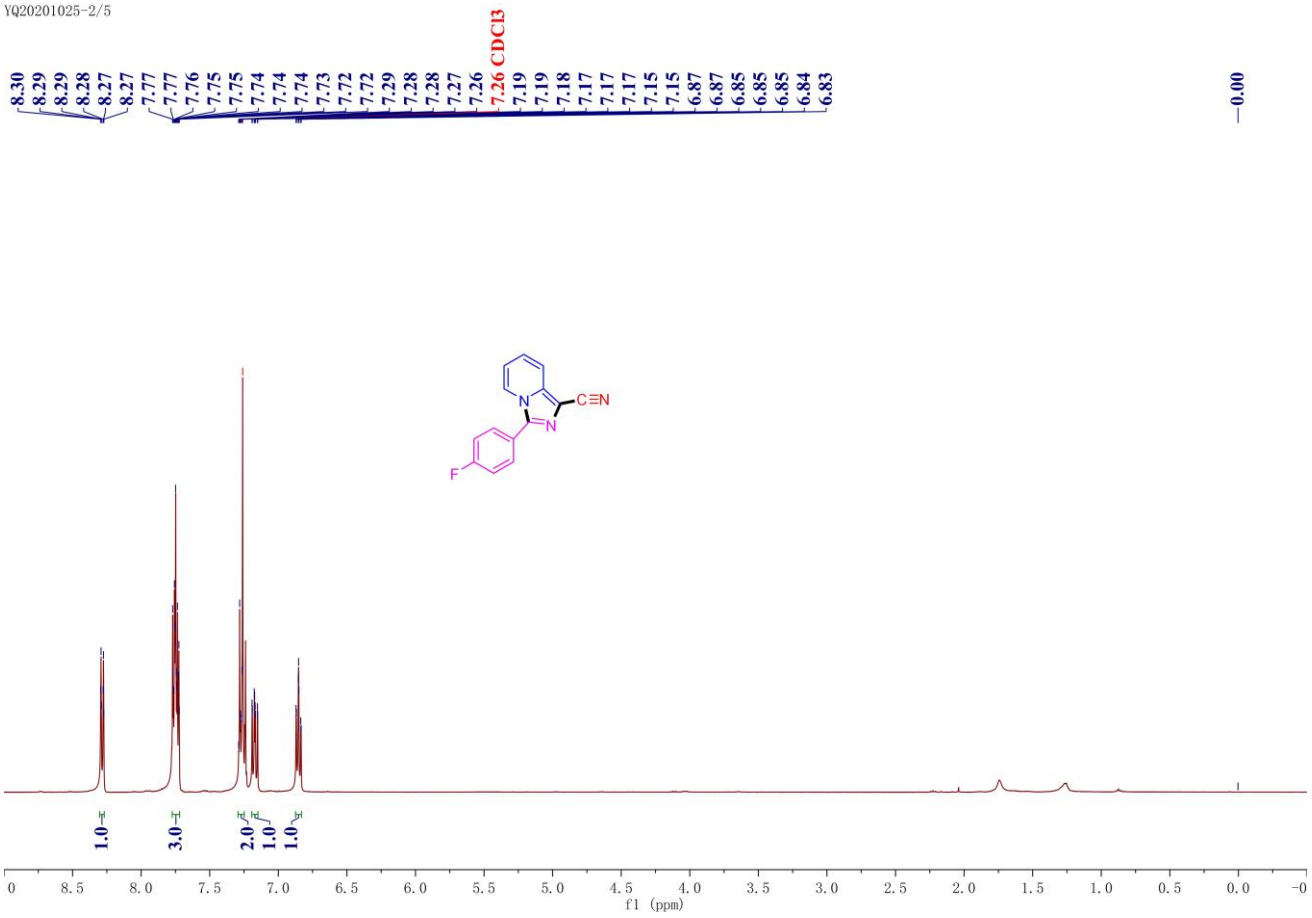
YQ20201025-2/5



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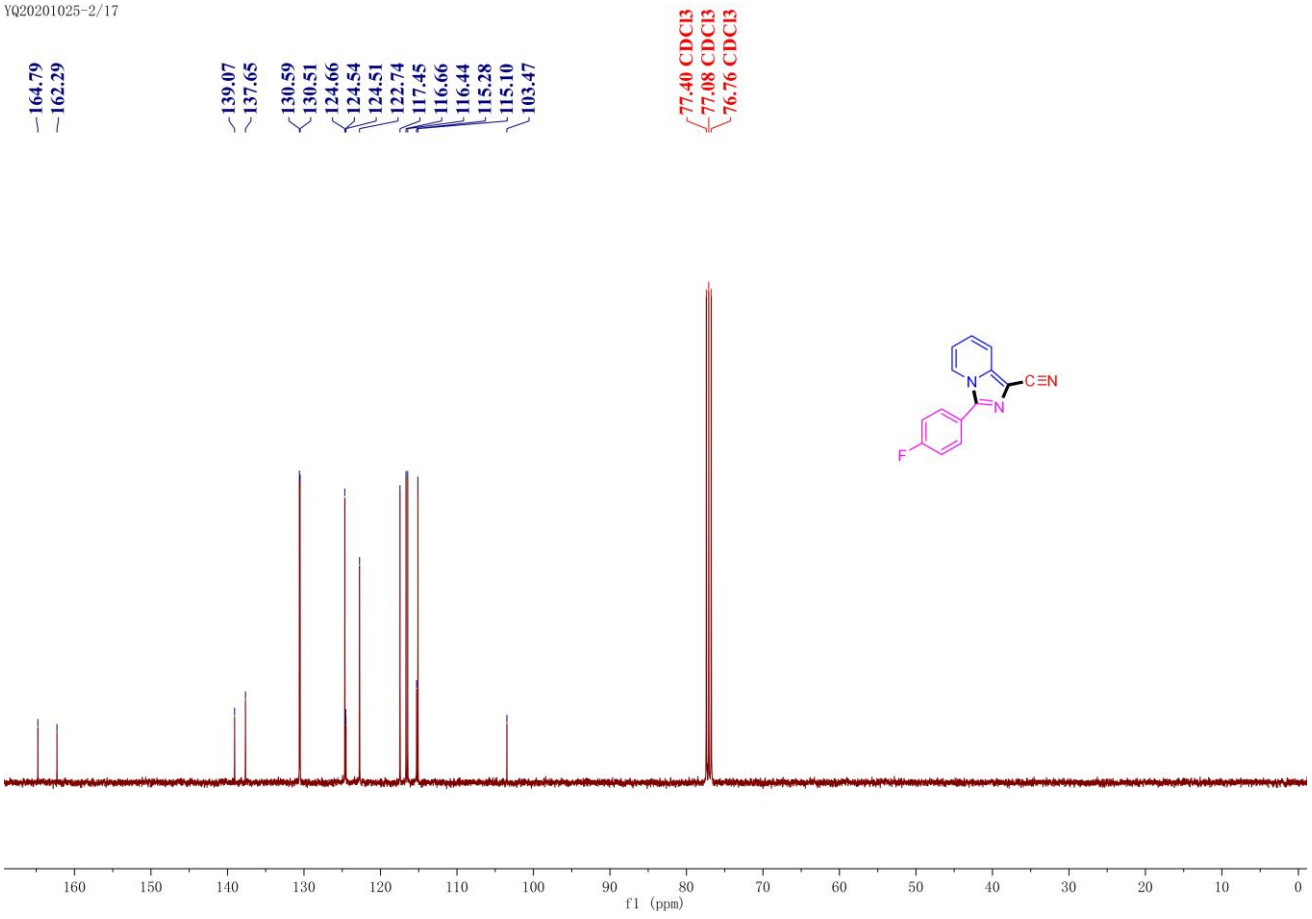

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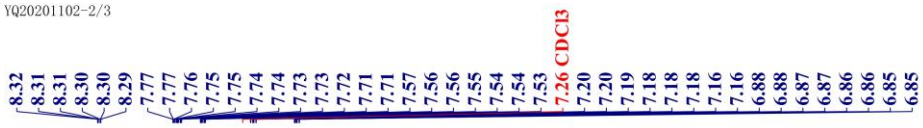
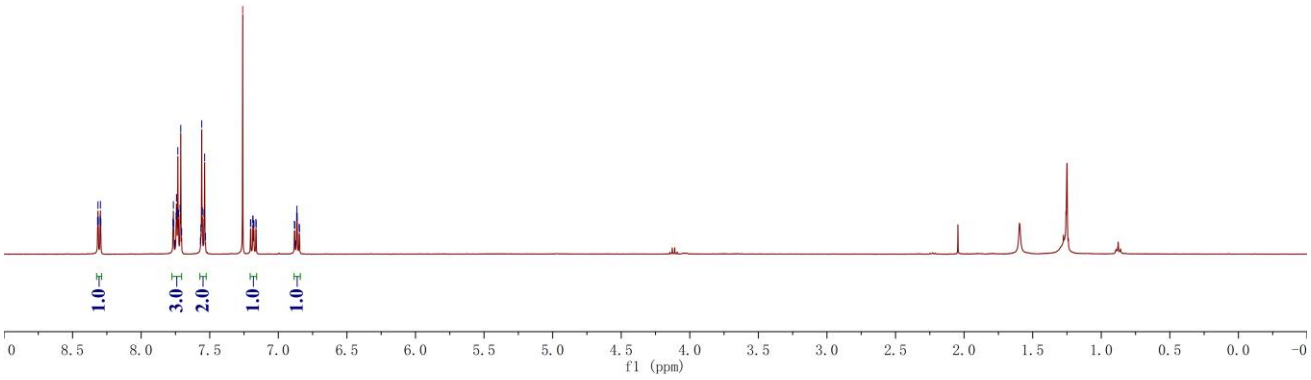
YQ20201102-2/3





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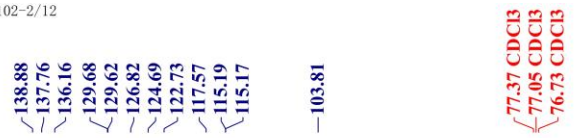

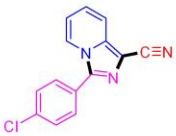

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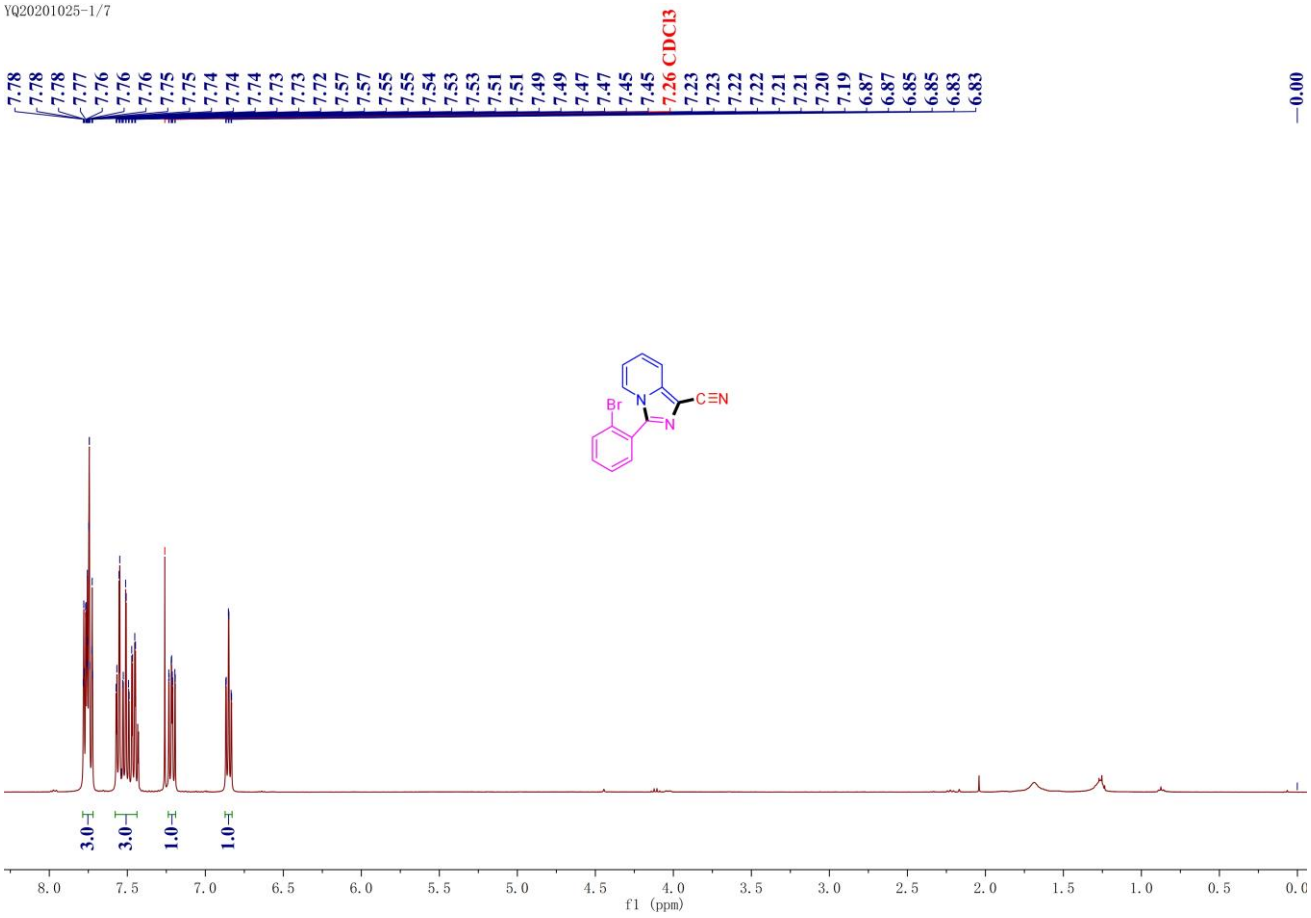
YQ20201025-1/7



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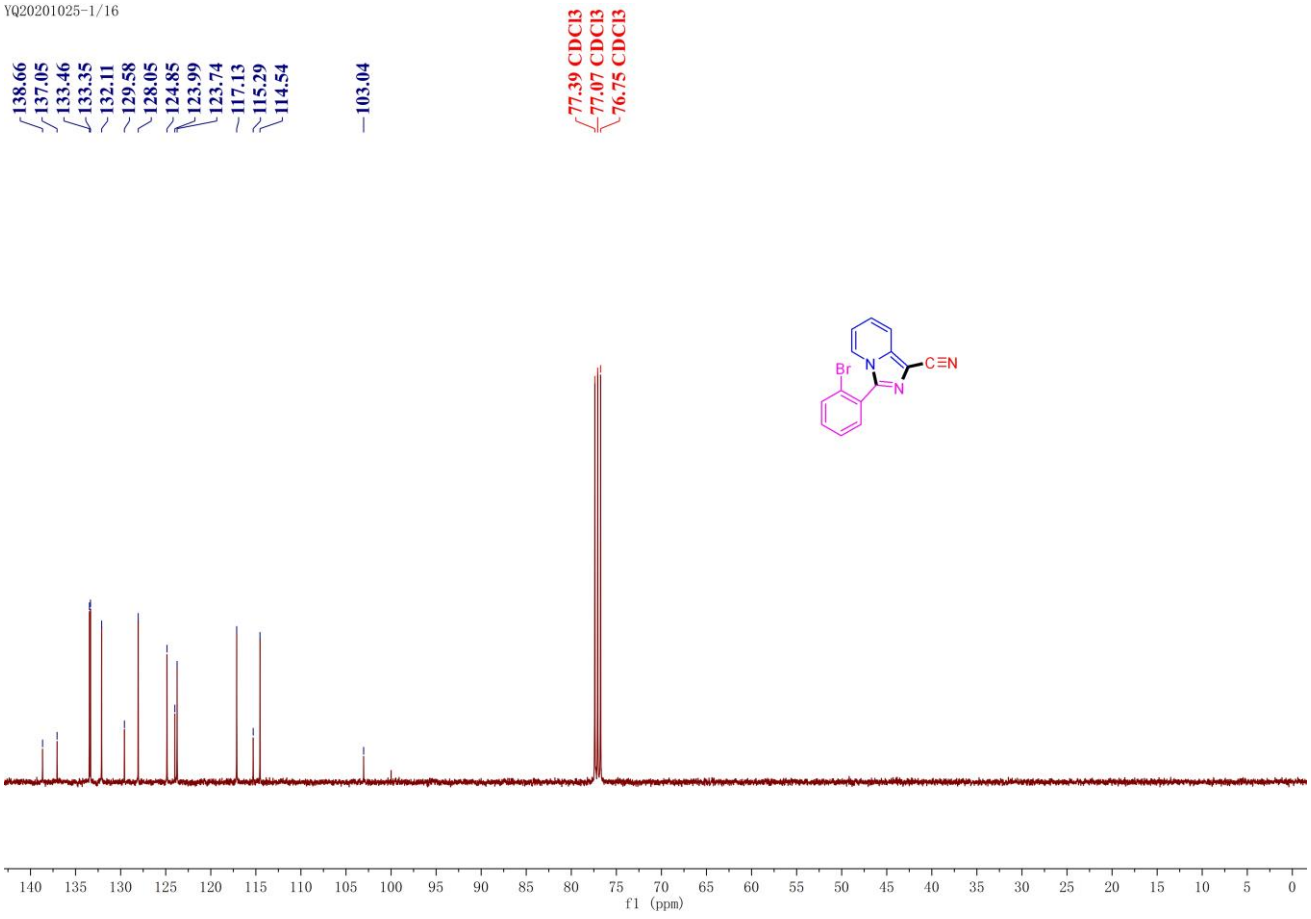

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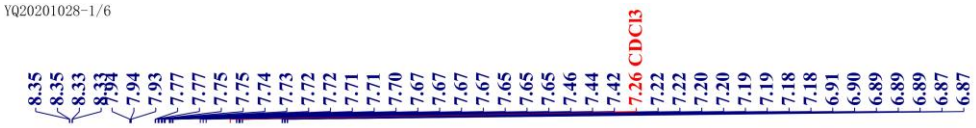
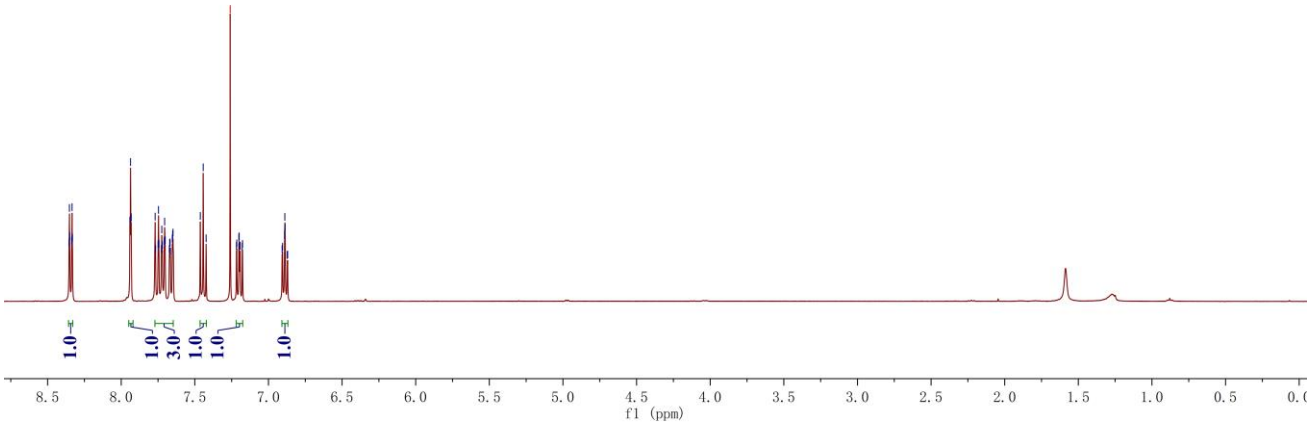
YQ20201028-1/6

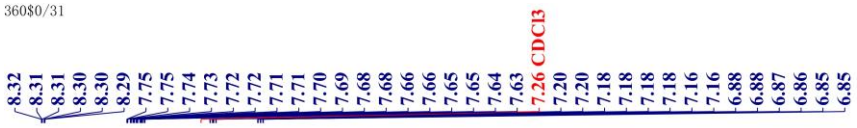


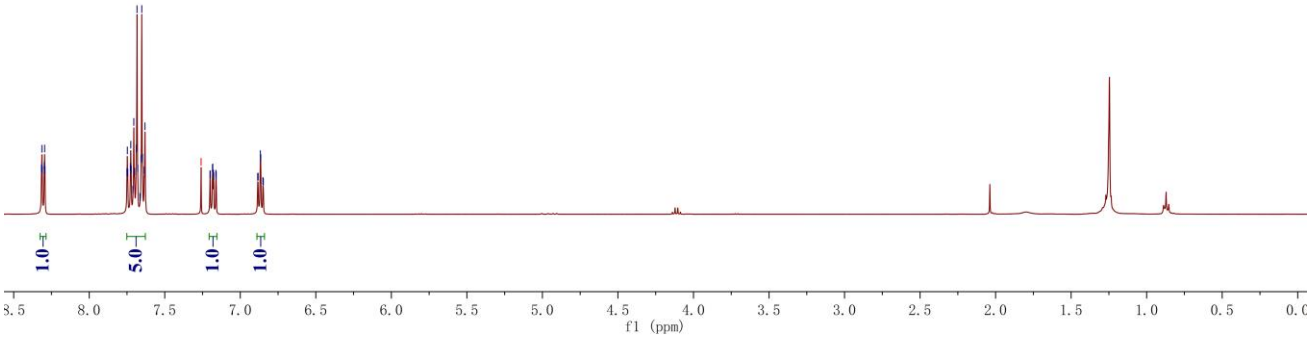


YQ20201028-1/15

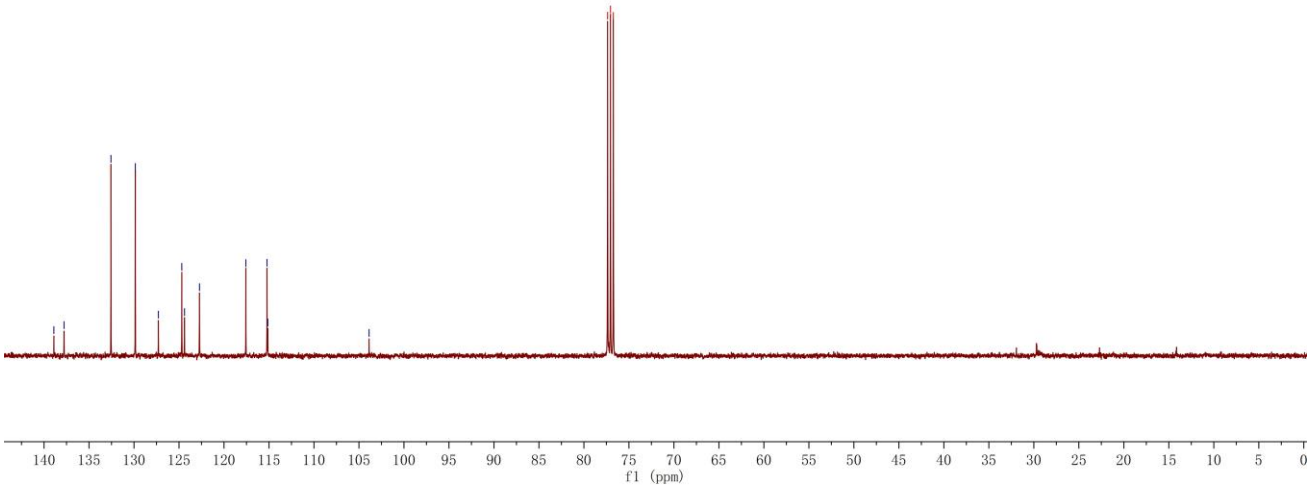
4af

360$0/31





360$1/32



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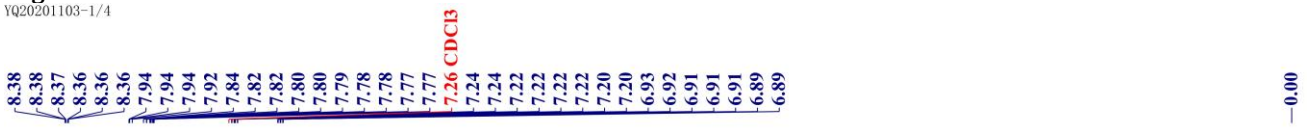
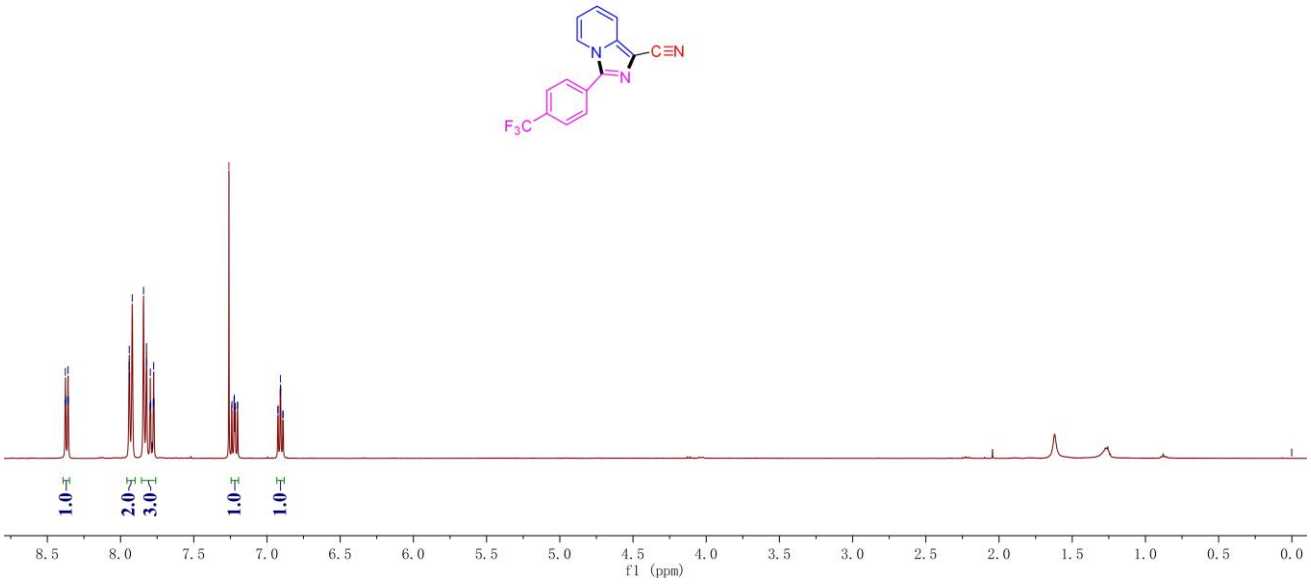
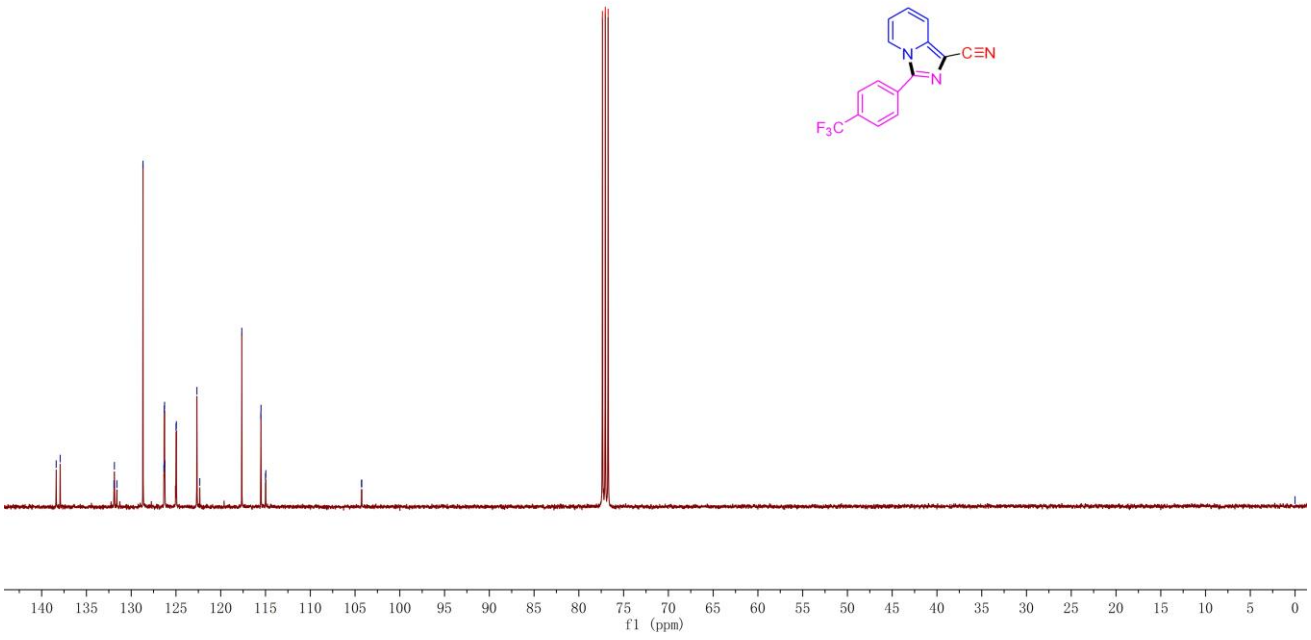
YQ20201103-1/4





YQ20201103-1/13



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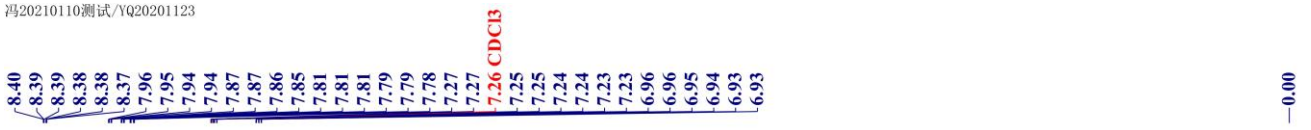
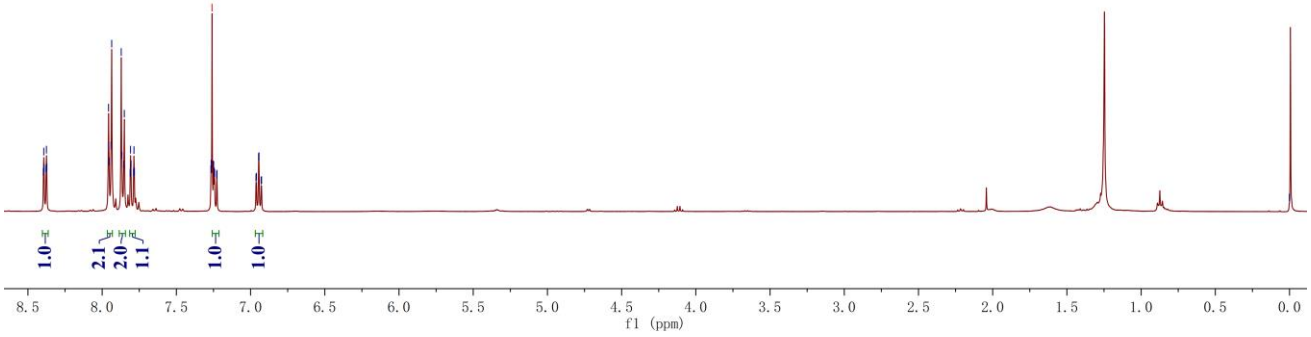
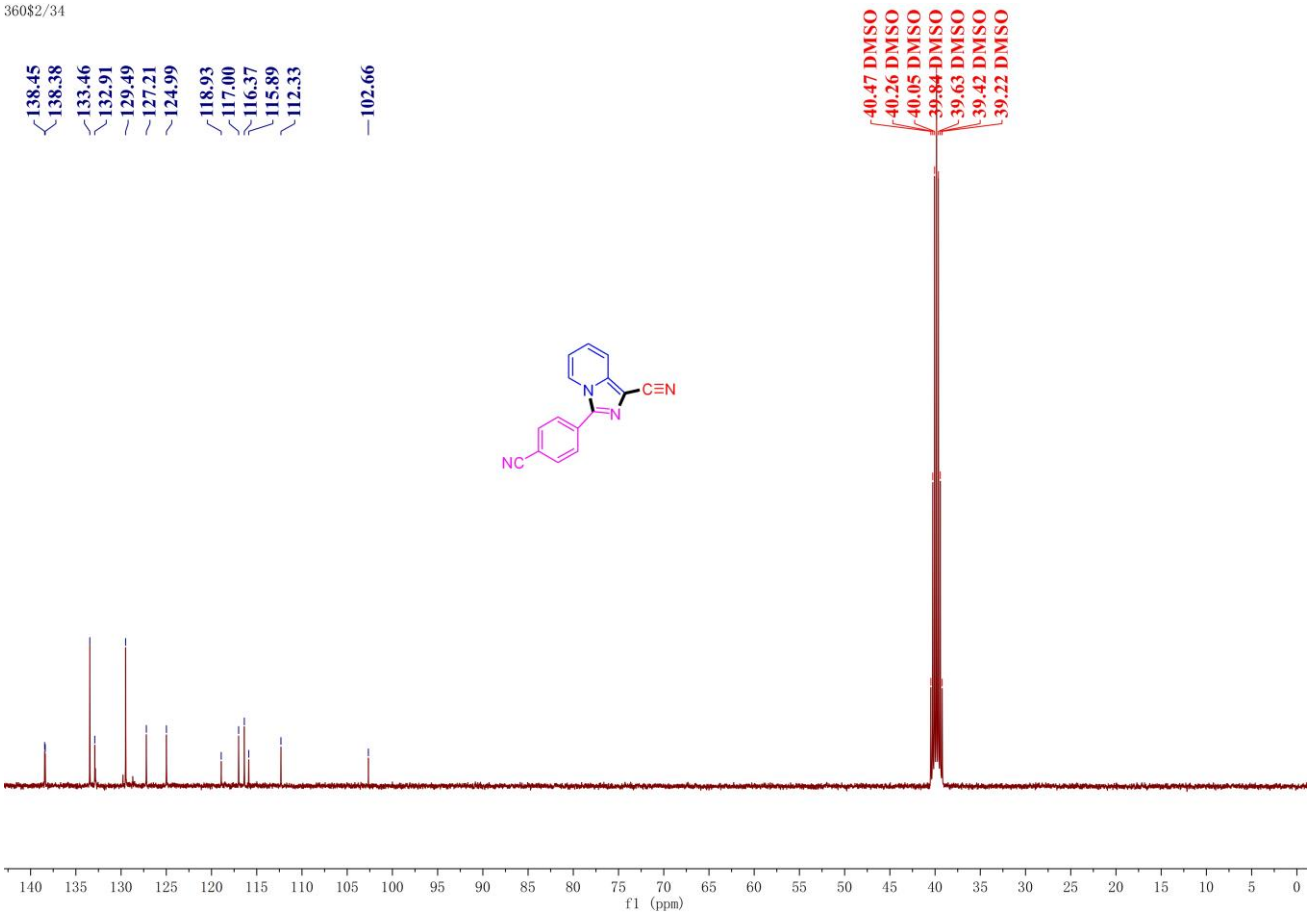
冯20210110测试/YQ20201123



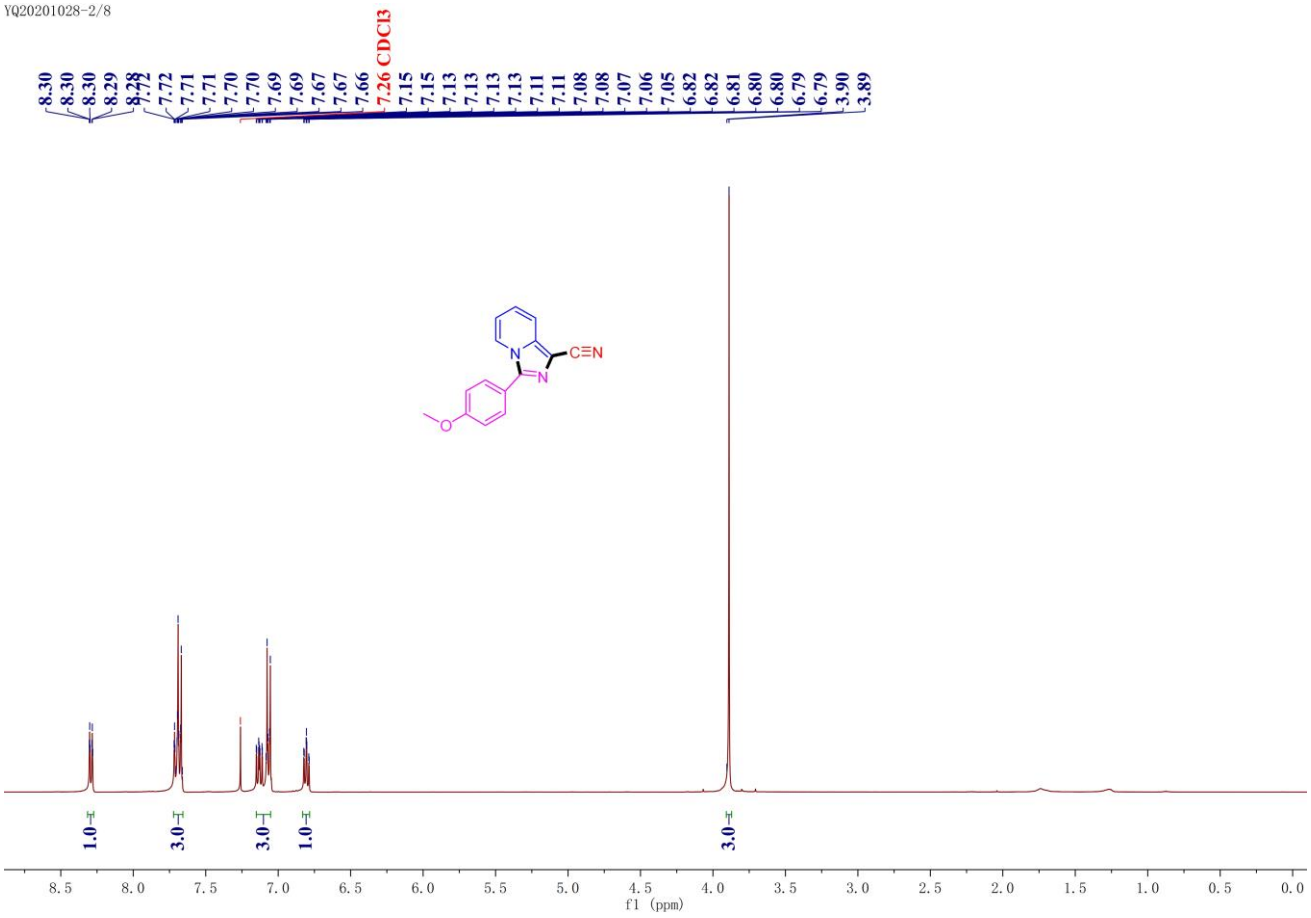


360$2/34

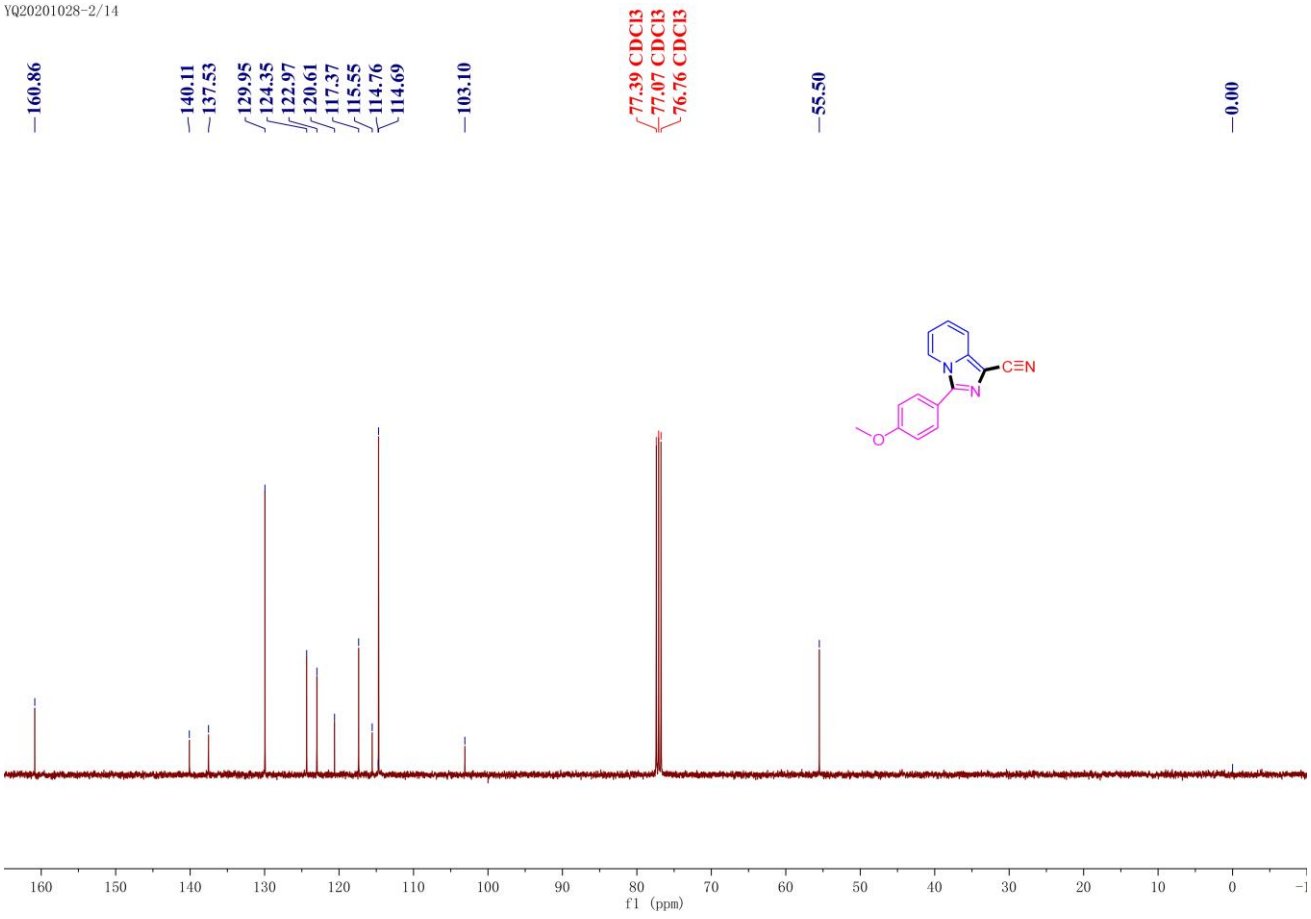


4ai

YQ20201028-2/8



YQ20201028-2/14



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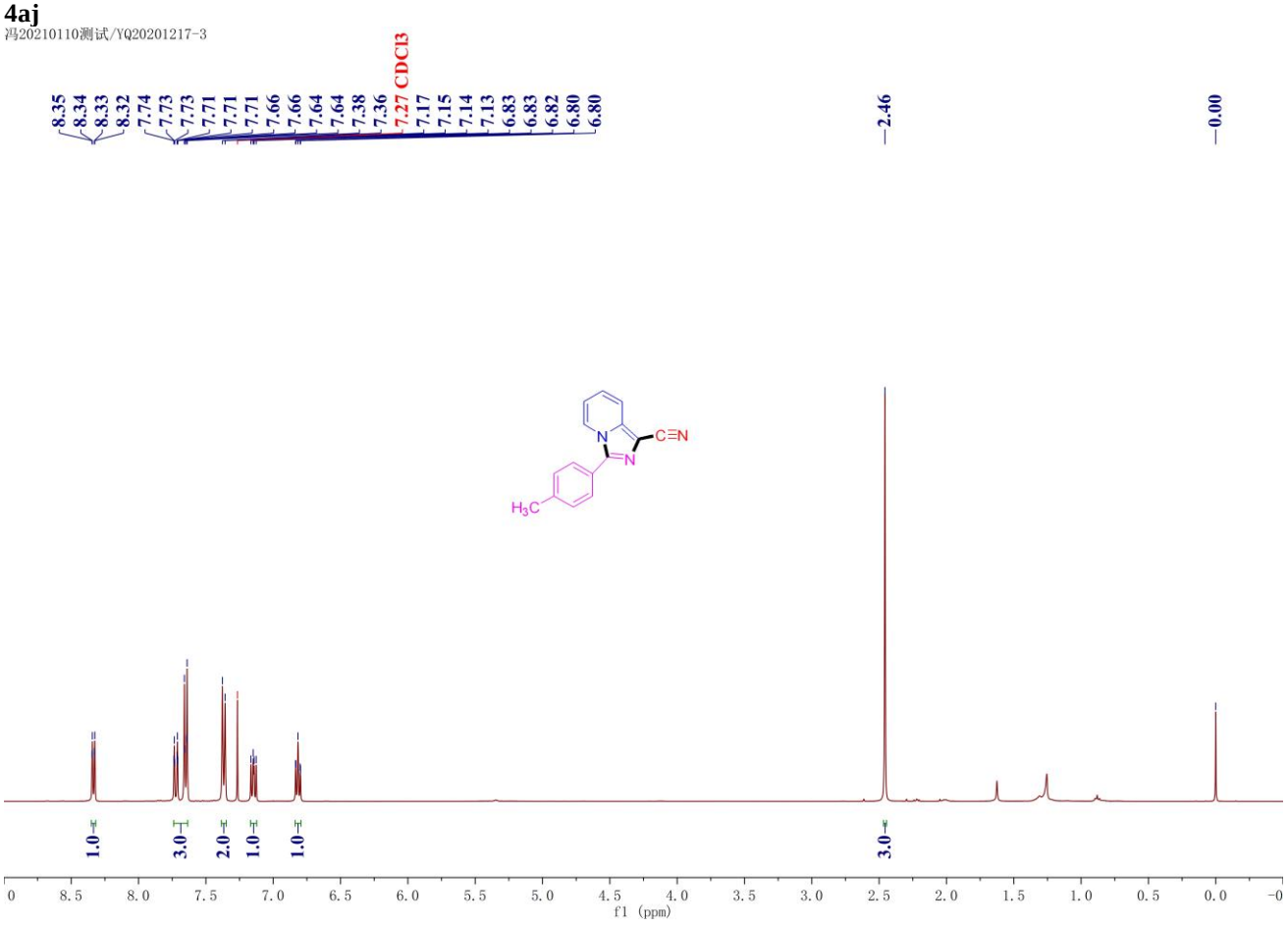
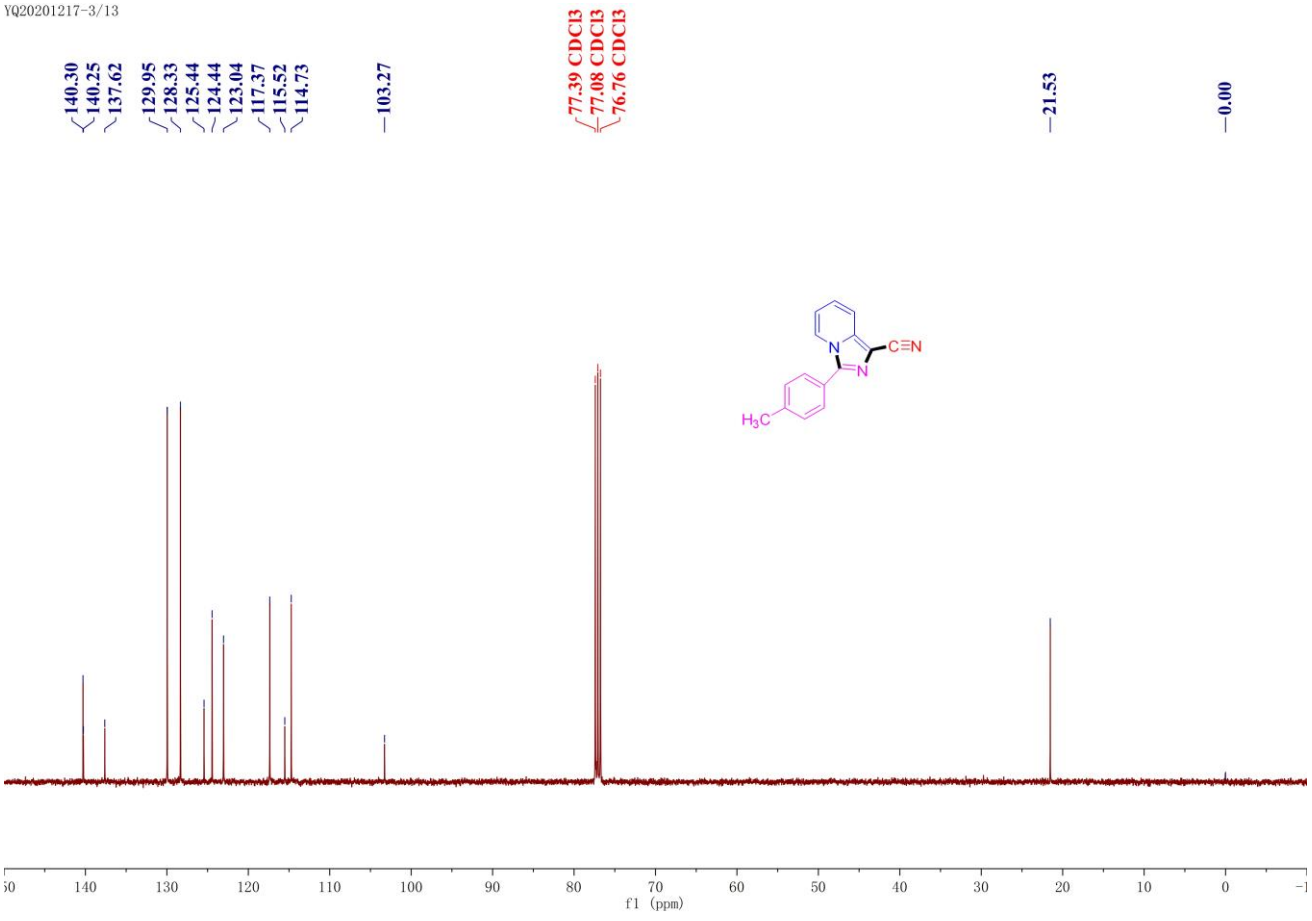
冯20210110测试/YQ20201217-3

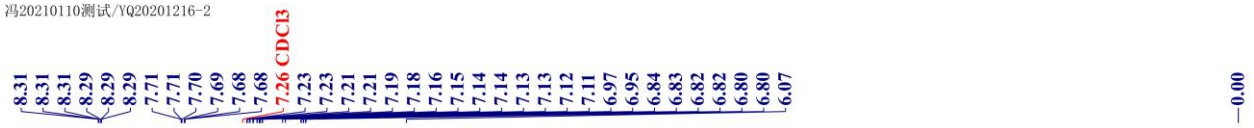


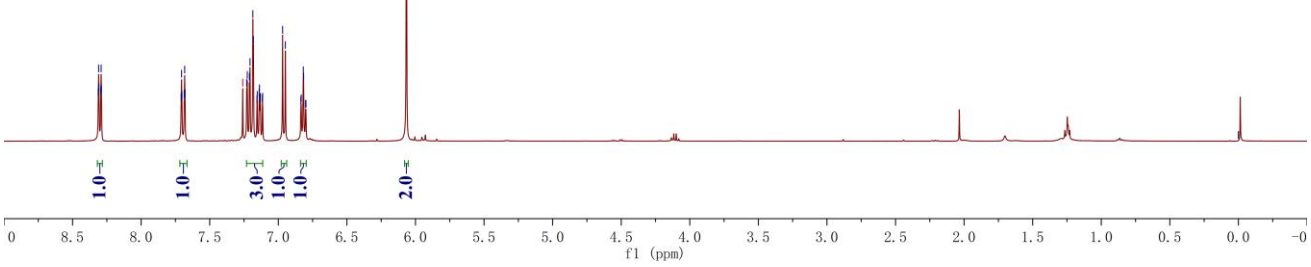
YQ20201217-3/13



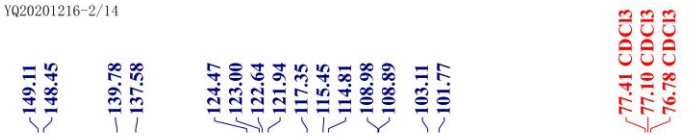
4ak

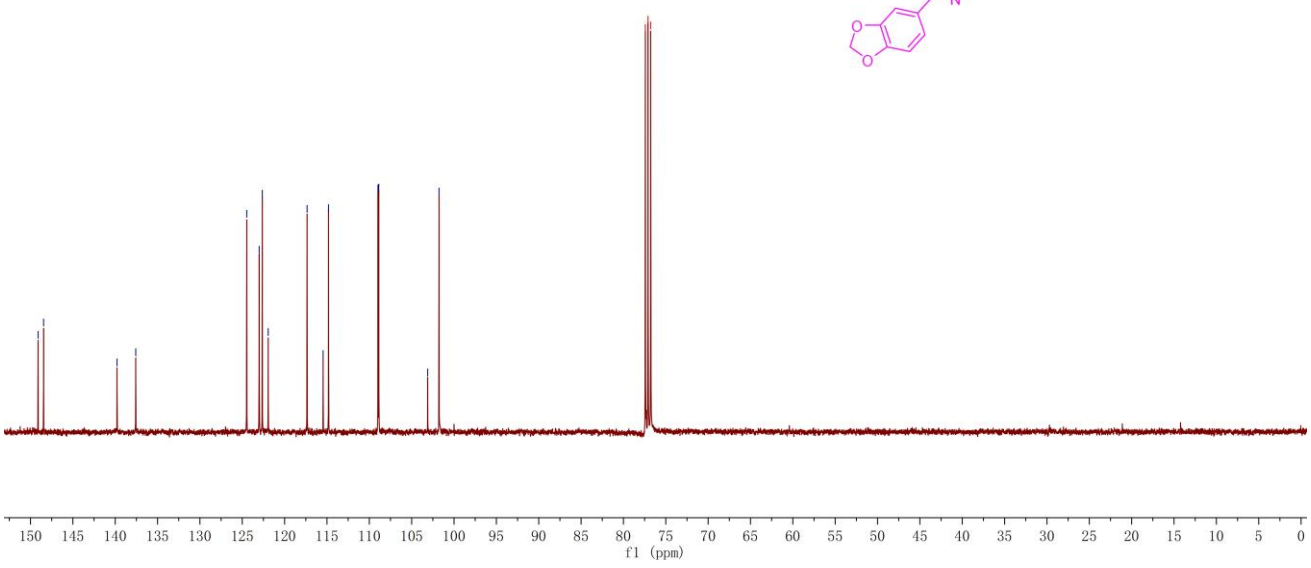
冯20210110测试/YQ20201216-2





YQ20201216-2/14





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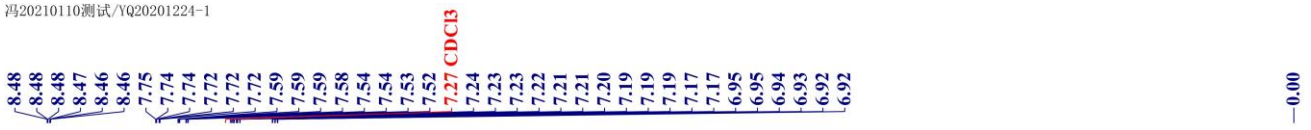
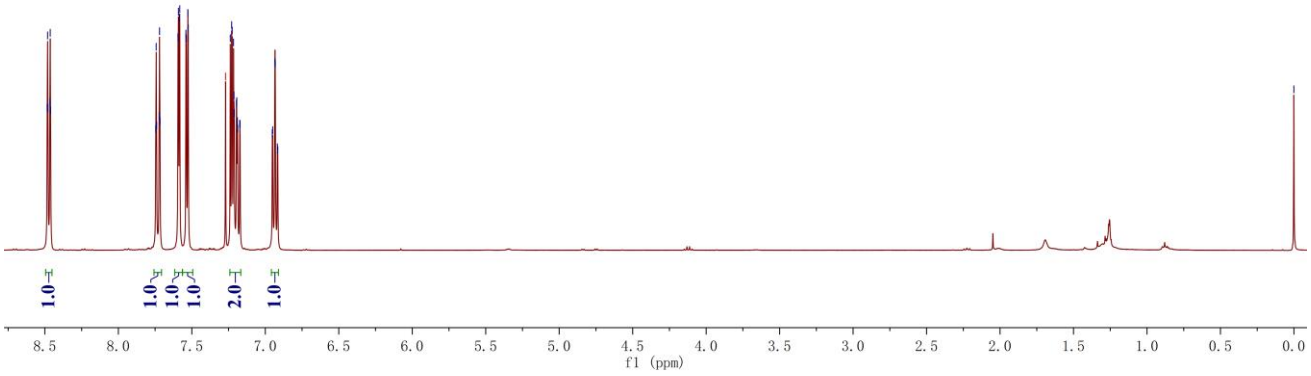
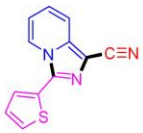


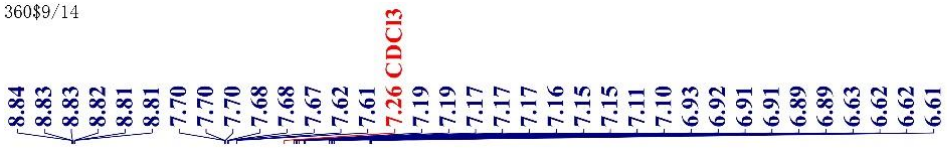


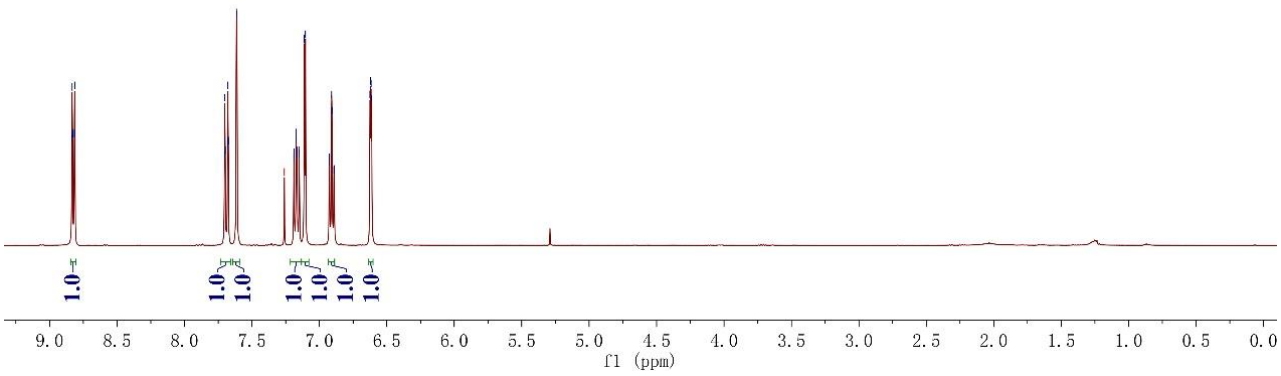
YQ20201224-1/21



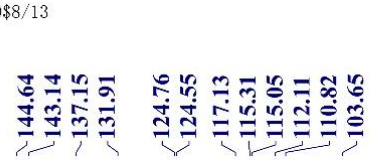
4am

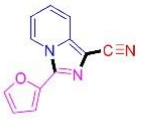
360$9/14

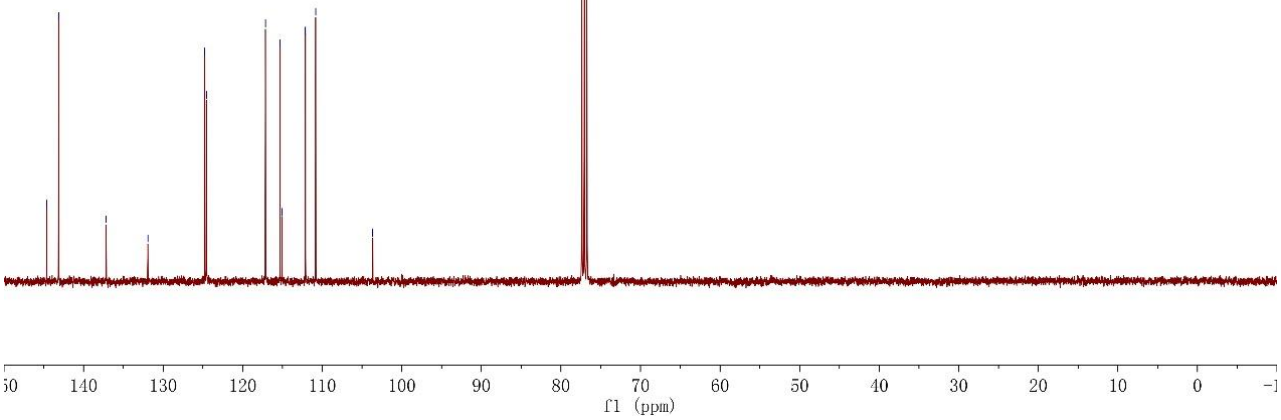




360$8/13

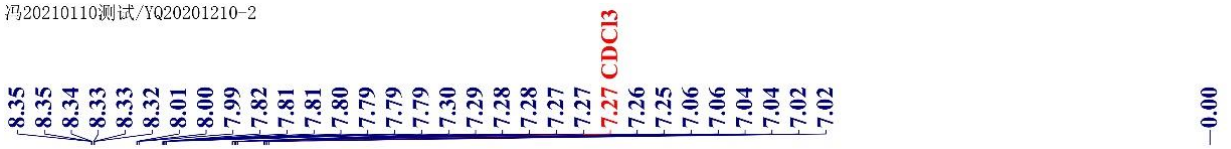


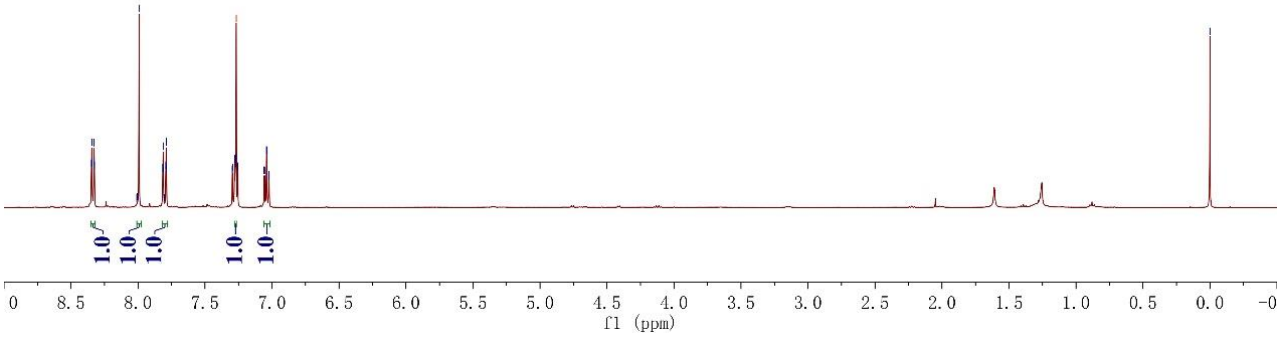




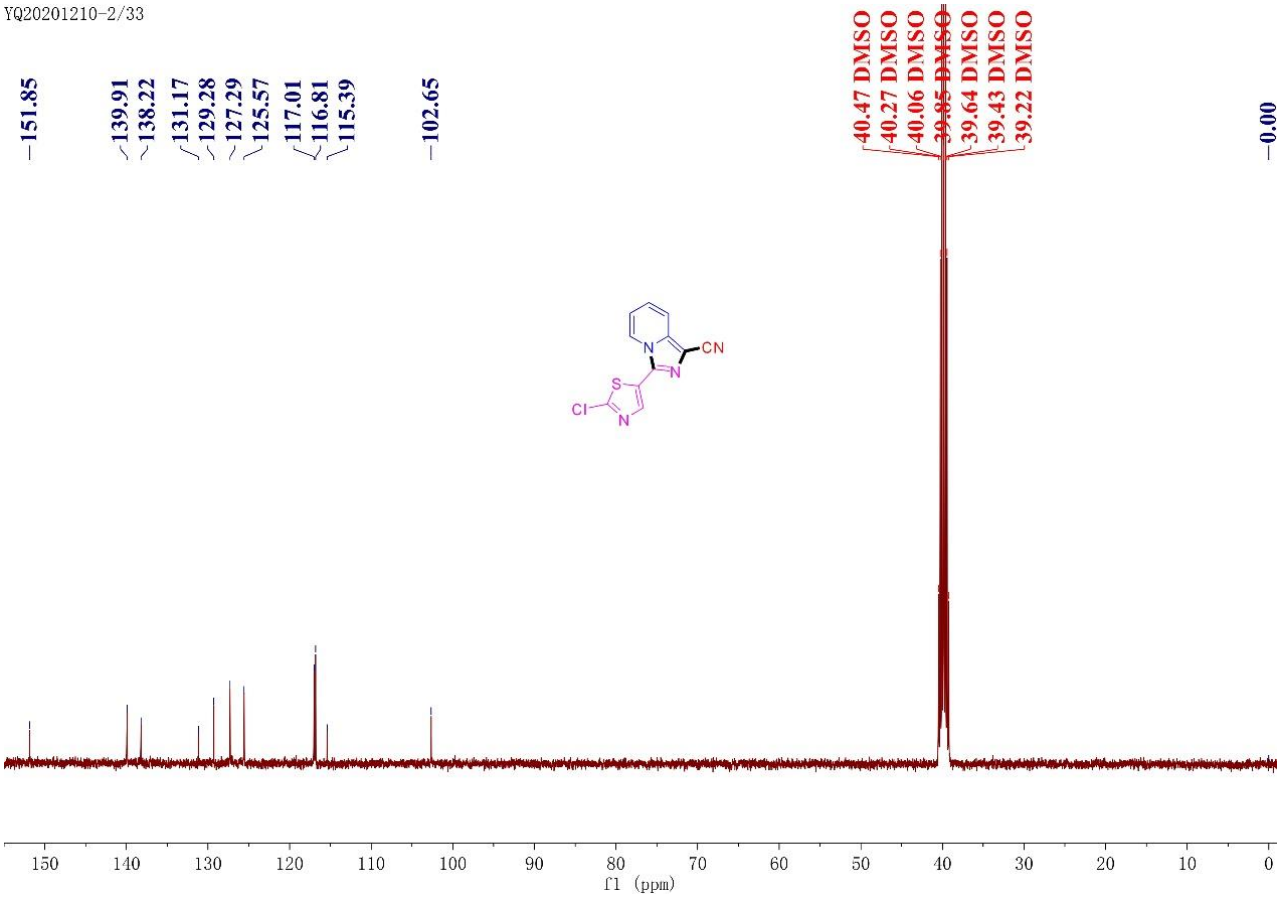
4an

冯20210110测试/YQ20201210-2



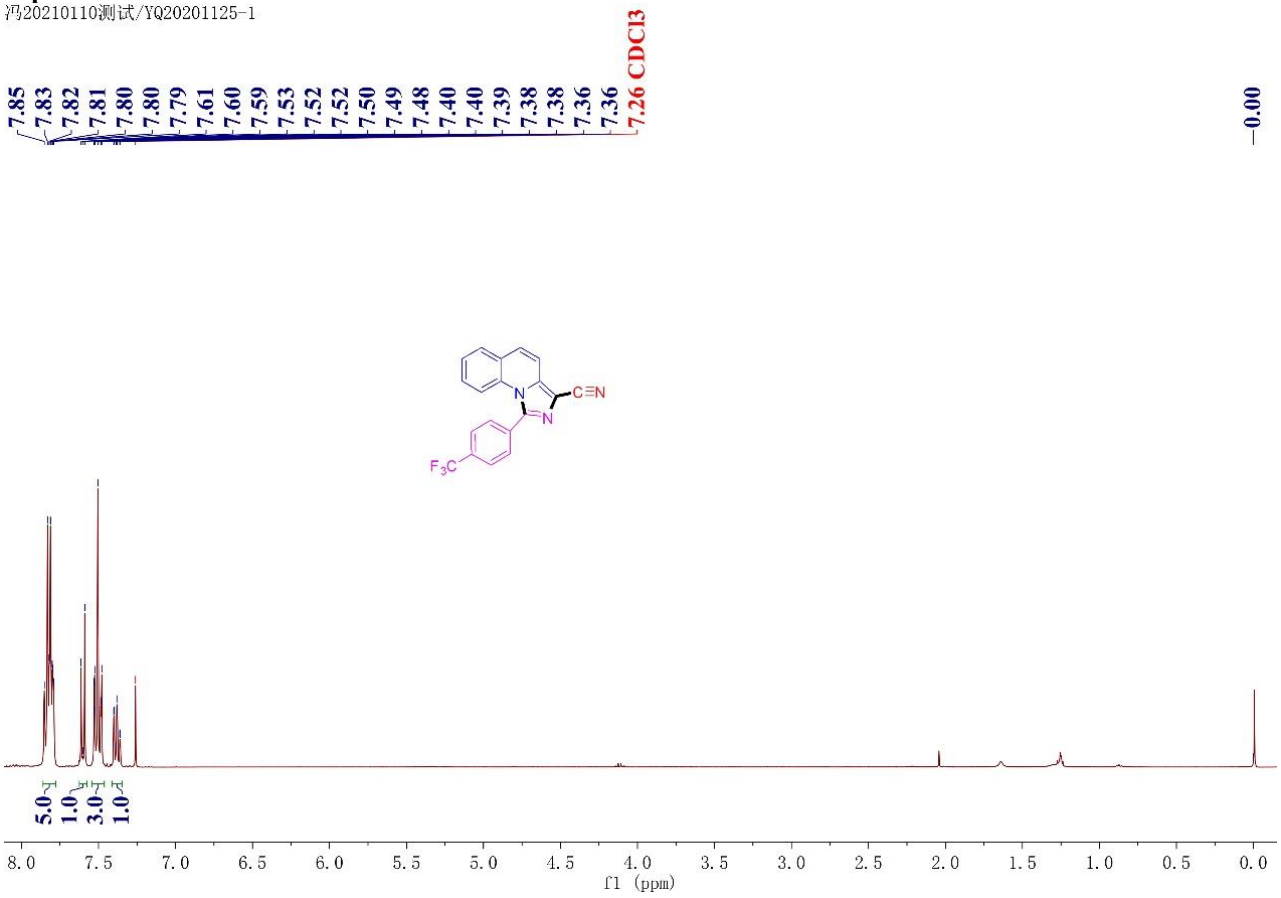


YQ20201210-2/33

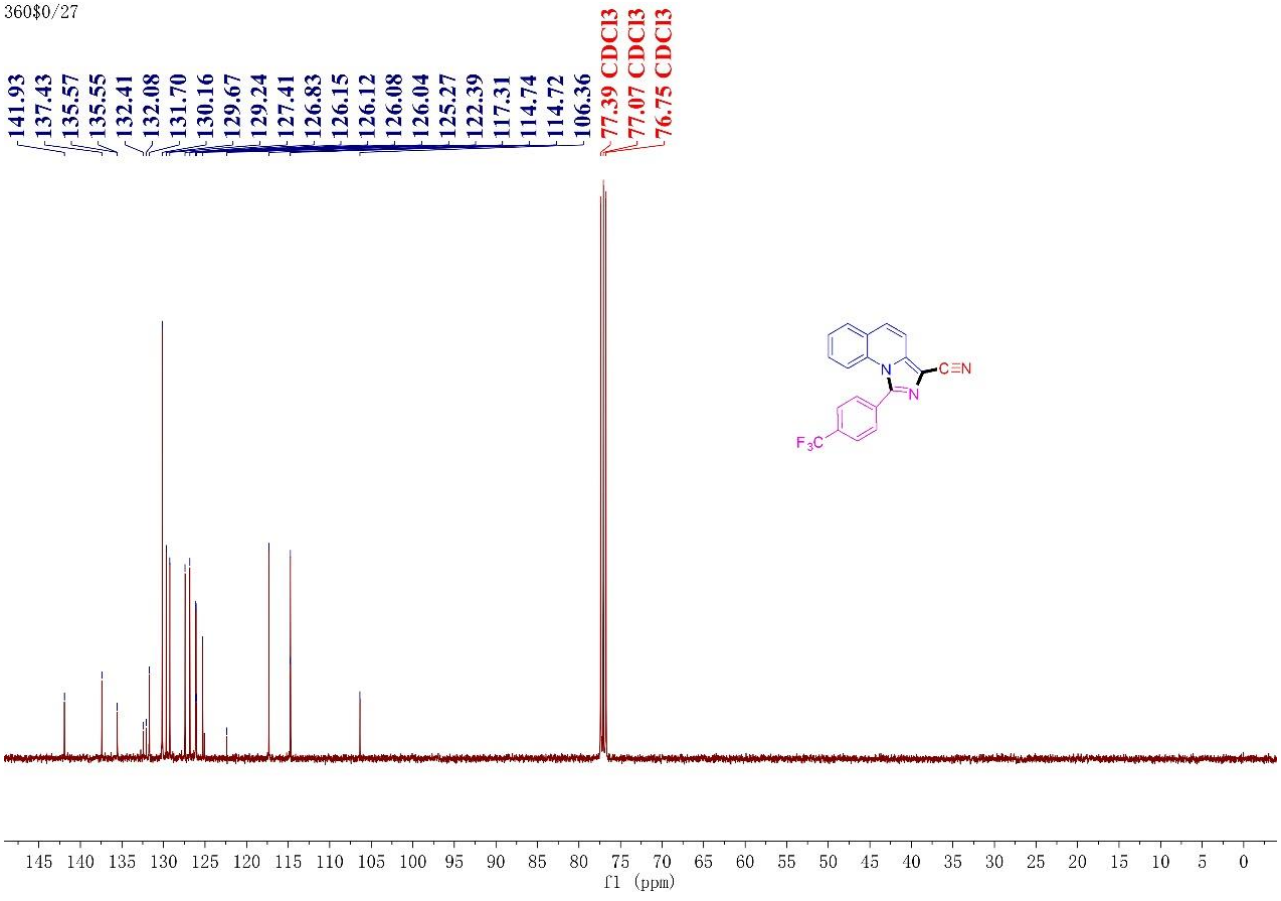


4ap

冯20210110测试/YQ20201125-1

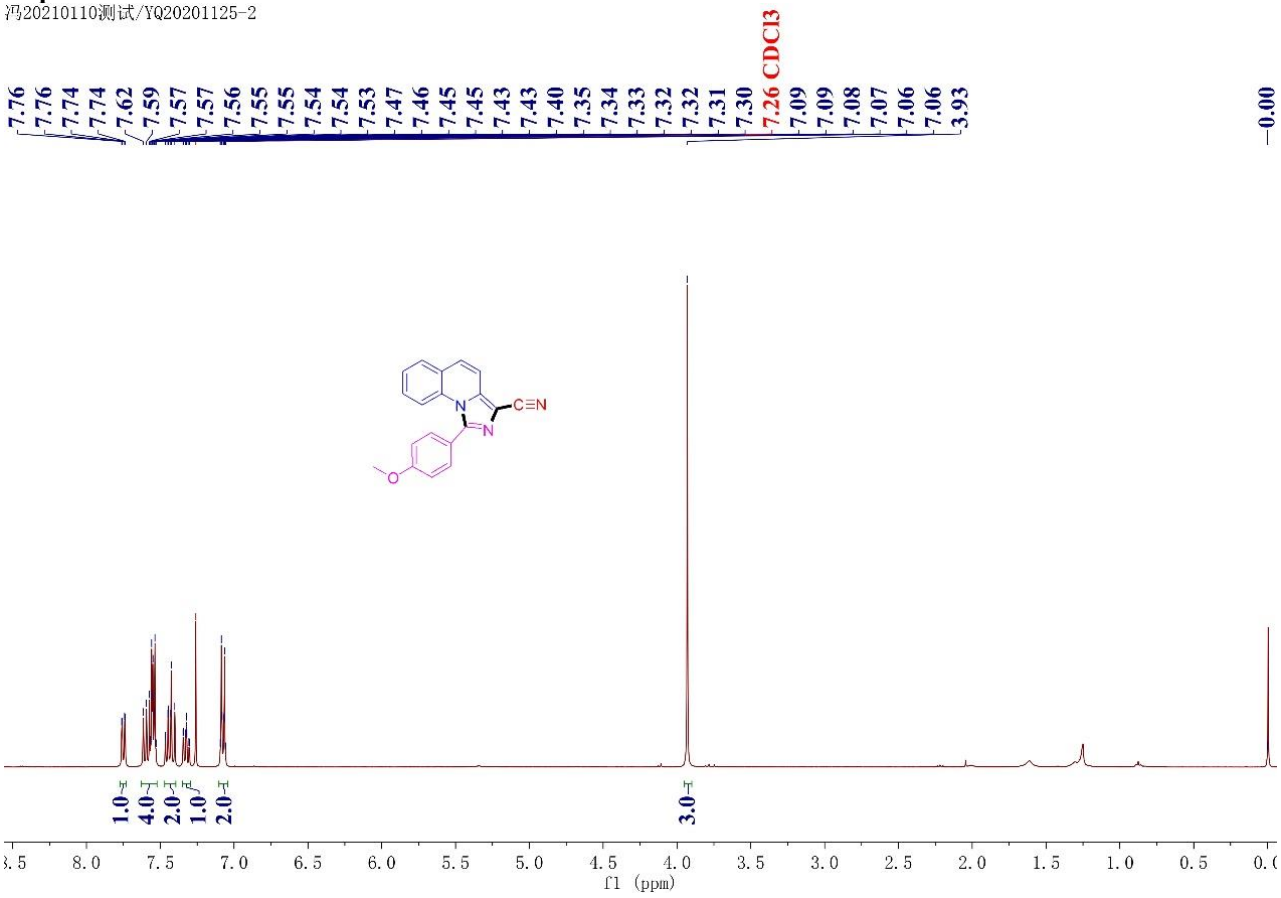


360$0/27

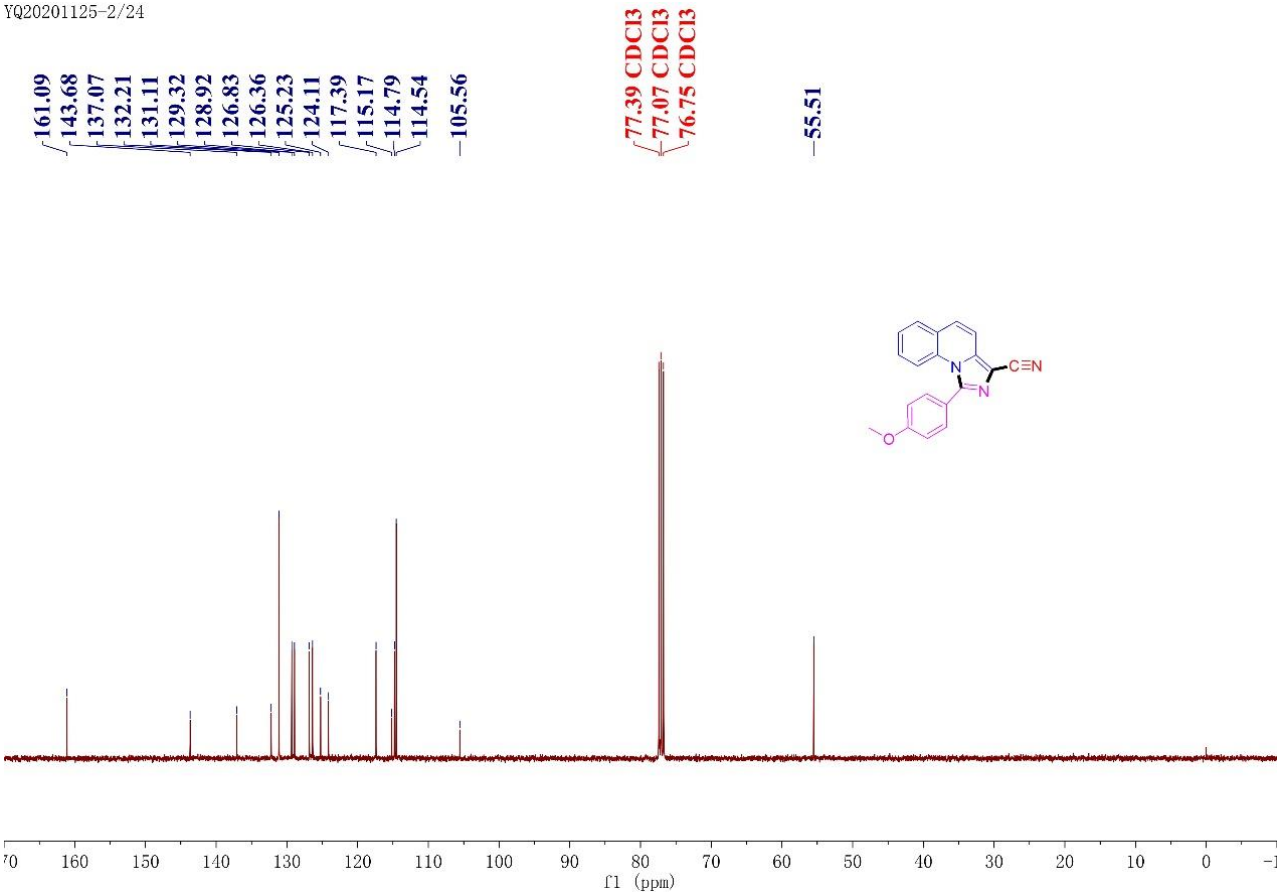


4aq

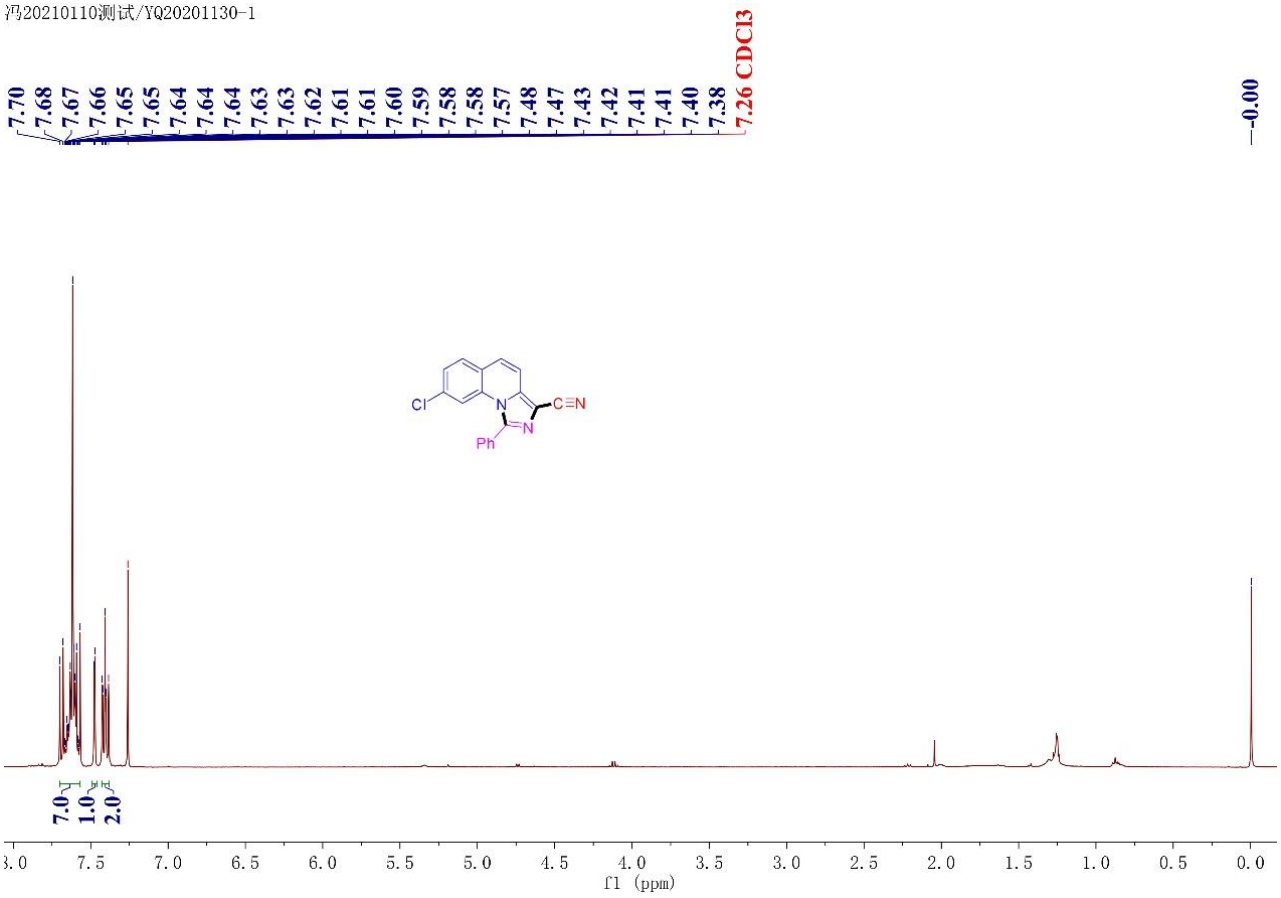
冯20210110测试/YQ20201125-2

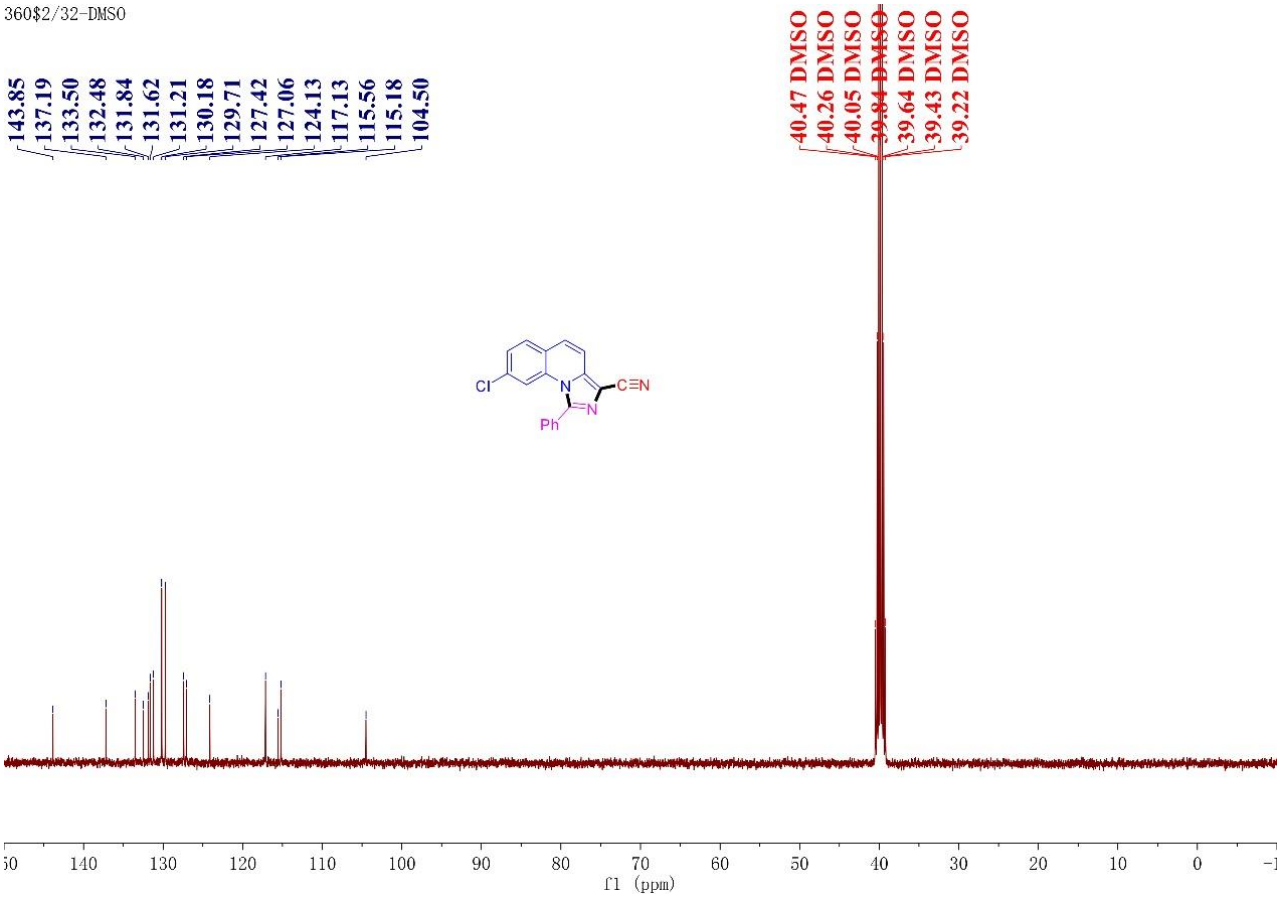


YQ20201125-2/24

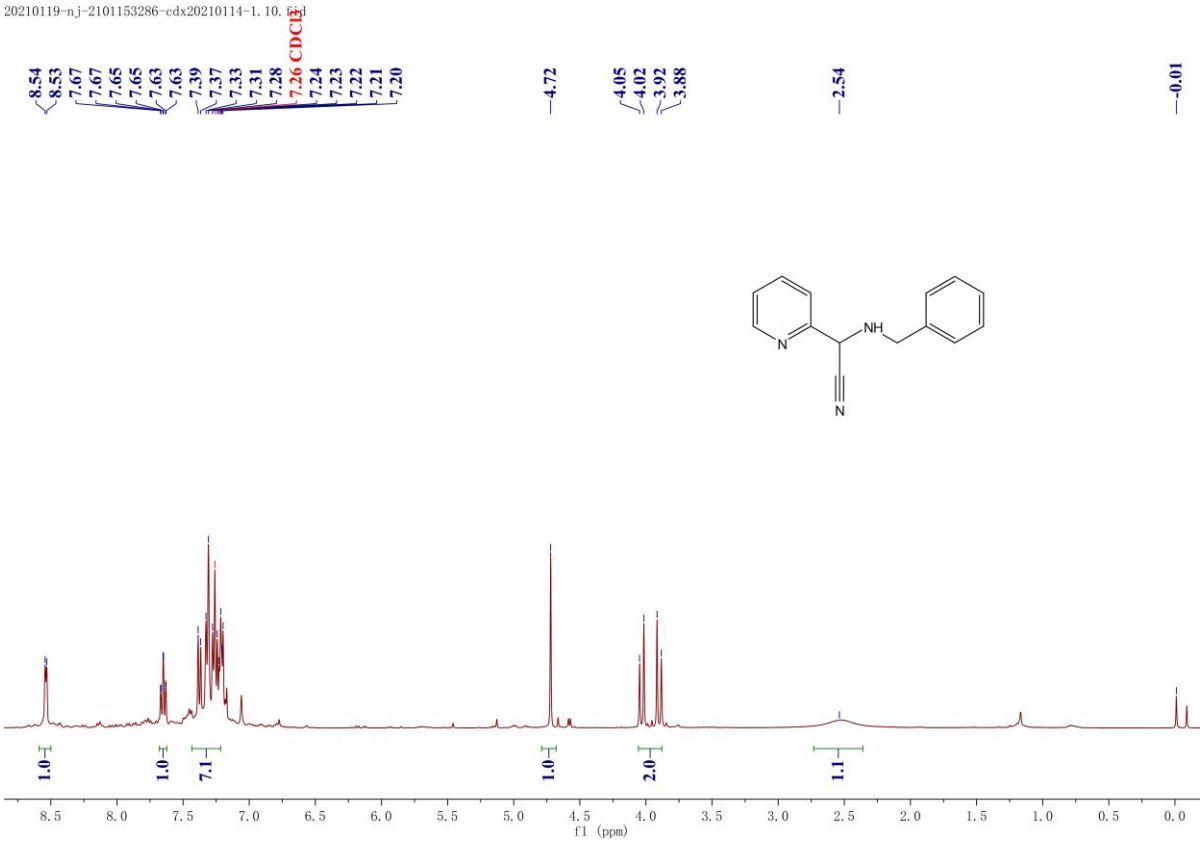


4ma


7.70
7.68
7.67
7.66
7.65
7.65
7.64
7.64
7.64
7.63
7.63
7.62
7.61
7.61
7.60
7.59
7.58
7.58
7.57
7.48
7.47
7.43
7.42
7.41
7.41
7.40
7.38
7.26 CDCl3
0.00
Cl
N
N
C≡N
Ph
7.0
1.0
2.0
f1 (ppm)


360$2/32-DMSO
143.85
137.19
133.50
132.48
131.84
131.62
131.21
130.18
129.71
127.42
127.06
124.13
117.13
115.56
115.18
104.50
40.47 DMSO
40.26 DMSO
40.05 DMSO
39.84 DMSO
39.64 DMSO
39.43 DMSO
39.22 DMSO
Cl
N
N
C≡N
Ph
f1 (ppm)

Compound 6


20210119-nj-2101153286-cdx20210114-1.10.fid
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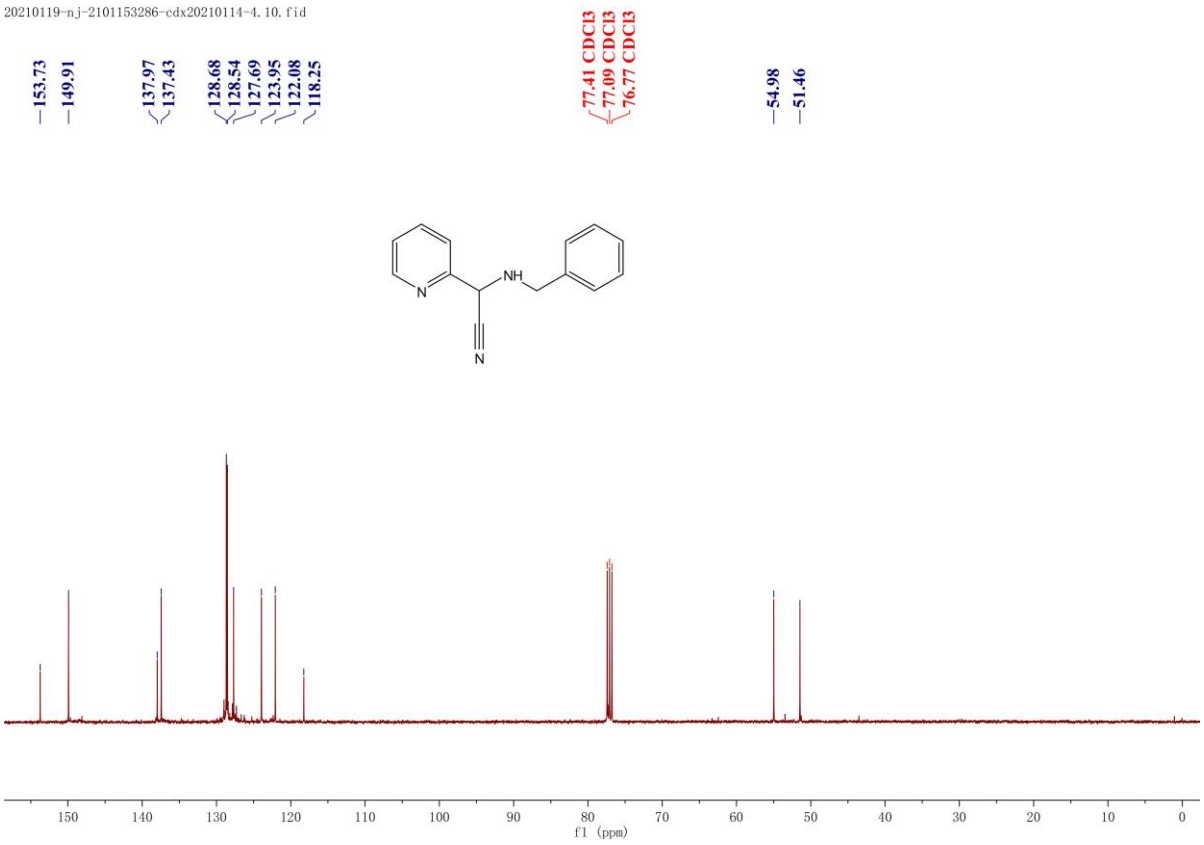
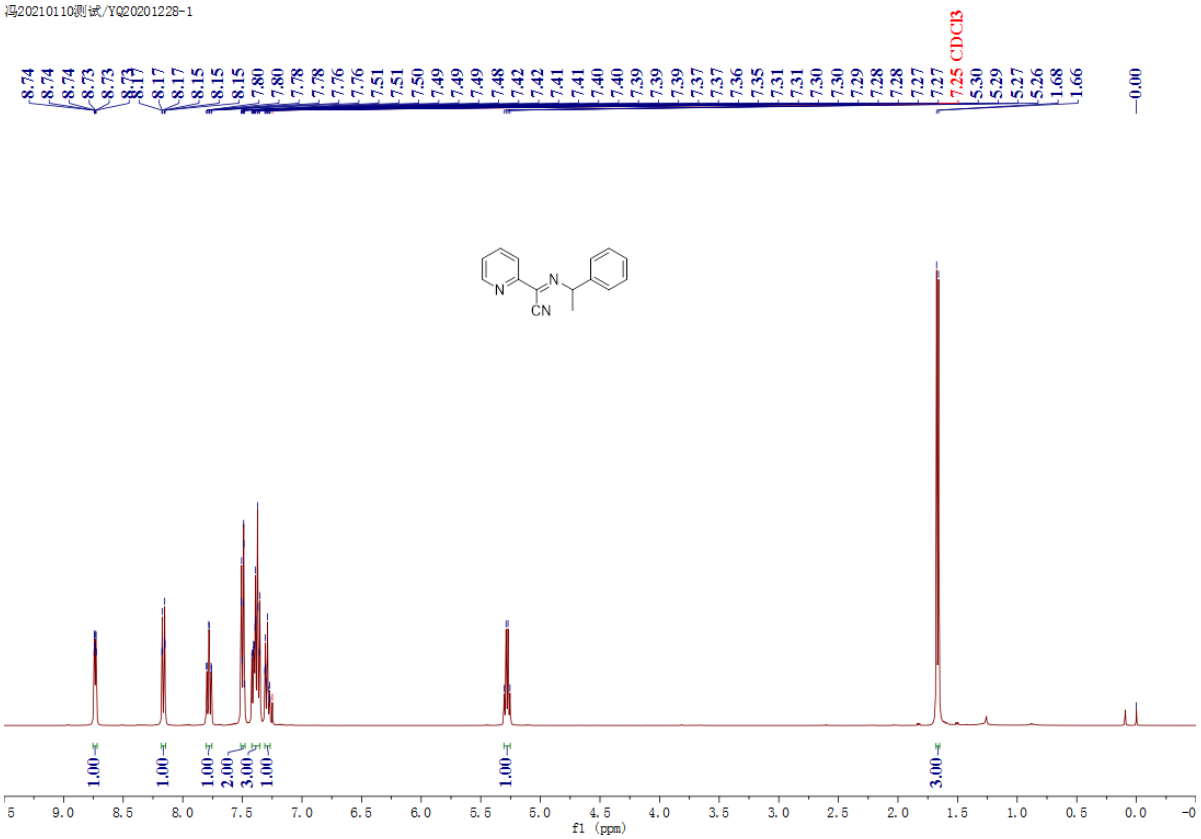
8.53
7.67
7.67
7.65
7.65
7.63
7.63
7.39
7.37
7.33
7.31
7.28
7.26 CDCl3
7.24
7.23
7.22
7.21
7.20
4.72
4.05
4.02
3.92
3.88
2.54
0.01
NH
N
N
1.0
1.0
7.1
1.0
2.0
1.1
f1 (ppm)


20210119-nj-2101153286-cdx20210114-4.10.fid
153.73
149.91
137.97
137.43
128.68
128.54
127.69
123.95
122.08
118.25
77.41 CDCl3
77.09 CDCl3
76.77 CDCl3
54.98
51.46
NH
N
N
f1 (ppm)

Compound 7


冯20210110测试/YQ20201228-1
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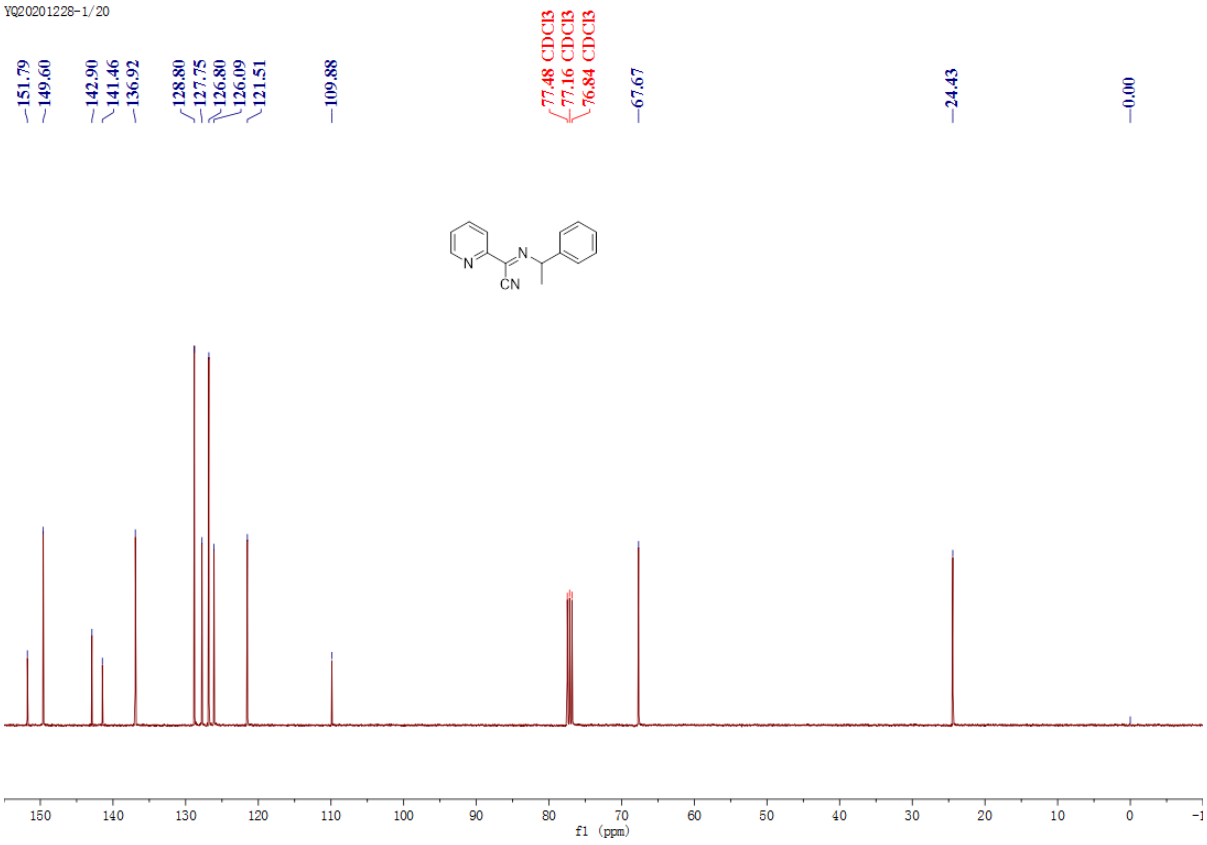
8.74
8.74
8.73
8.73
8.73
8.17
8.17
8.17
8.15
8.15
8.15
7.80
7.80
7.78
7.78
7.76
7.76
7.51
7.51
7.50
7.49
7.49
7.49
7.48
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.39
7.37
7.37
7.36
7.35
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.27
7.25 CDCl3
5.30
5.29
5.27
5.26
1.68
1.66
0.00
N
N
CN
1.00
1.00
1.00
2.00
3.00
1.00
1.00
3.00
f1 (ppm)


YQ20201228-1/20
151.79
149.60
142.90
141.46
136.92
128.80
127.75
126.80
126.09
121.51
109.88
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
67.67
24.43
0.00
N
N
CN
f1 (ppm)