

## Supporting Information

### Copper-Catalyzed Cyclization of 2-Cyanobenzaldehydes and 2-Isocyanoacetates: an Efficient Strategy for the Synthesis of Substituted 1-Aminoisoquinolines

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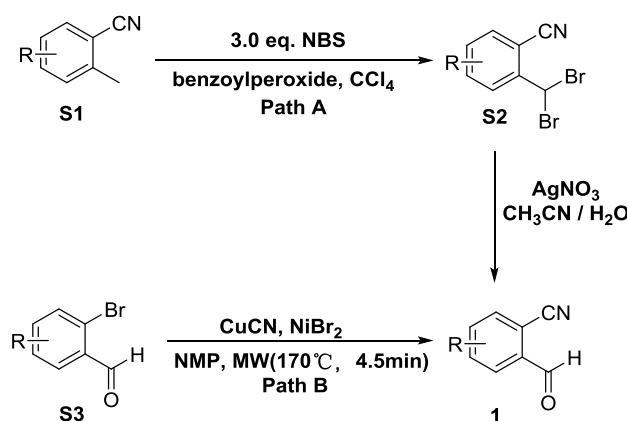
## 1. General Information

All reactions under standard conditions were carried out under dry atmosphere and monitored by thin-layer chromatography (TLC) on gel F254 plates. All products were purified through silica gel chromatography (200~300 mesh). Column chromatography was carried out with light petroleum ether (b.p. 60~90 °C), ethyl acetate and dichloromethane as eluent.  $^1\text{H}$  and  $^{13}\text{C}$  spectra were recorded in  $\text{CDCl}_3$  or DMSO on 400 MHz or 600 MHz instruments. Chemical shifts ( $\delta$ ) are reported in ppm, and coupling constants (J) are in hertz (Hz). High-resolution mass spectral analysis (HRMS) data were measured on the Apex II by means of the ESI technique. Melting point was measured with SGW-X4B instrument. Unless specified, general procedure C was carried out in a reaction seal tube. All the chemicals were used as obtained from vendors. The substrates 2-formylbenzonitrile (**1a**), 2-acetylbenzonitrile (**1t**), ethyl isocyanoacetate (**2a**), methyl isocyanoacetate (**2b**) and *tert*-Butyl isocyanoacetate (**2c**) are commercially available.

## 2. General experimental procedure

### 2.1 General procedure for the synthesis of 2-formylbenzonitriles 1b-1n

Substrates **1** were prepared according to the procedure reported in literature.



#### General Procedure A: using the preparation of 4-chloro-2-formylbenzonitrile (**1b**) from 4-chloro-2-methylbenzonitrile as an example<sup>1</sup>

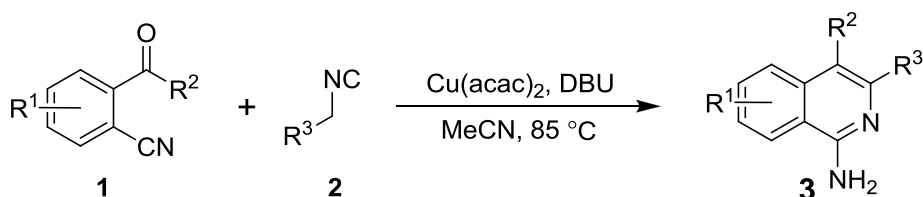
To a solution of 4-chloro-2-methylbenzonitrile (1.00 g, 6.60 mmol) in  $\text{CCl}_4$  (10 mL) was added NBS (3.52 g, 3.0 equiv) and BPO (159 mg, 0.1 equiv) successively. The reaction mixture was subsequently stirred for 24 h at  $85^\circ\text{C}$  and monitored by TLC. The reaction was cooled and the precipitate of succinimide and unreacted NBS was removed by filtration and washed with EtOAc. The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether : EtOAc=100:1 to 20:1) to give 4-chloro-2-(dibromomethyl)benzonitrile as a white solid (1.76 g, 86%).

To a solution of 4-chloro-2-(dibromomethyl)benzonitrile (1.76 g, 5.70 mmol) in acetonitrile (15 mL) was added a solution of  $\text{AgNO}_3$  (2.90 g, 3.0 equiv) in water (3 mL), and the mixture was heated for 20 min under reflux. After the solution was allowed to cool,  $\text{AgBr}$  was filtered off and washed with  $\text{CH}_2\text{Cl}_2$  (3×30 mL), the combined filtrate was washed with water (20 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether : EtOAc=20:1 to 4:1) to afford 4-chloro-2-formylbenzonitrile (**1b**) as a white solid (0.78 g, 83%).

## General Procedure B: using the preparation of 2-formyl-5-methylbenzonitrile (**1g**) from 2-bromo-4-methylbenzaldehyde as an example<sup>2</sup>

2-bromo-4-methylbenzaldehyde (1.00 g, 5.0 mmol), CuCN (2.25 g, 5.0 equiv) and NiBr<sub>2</sub> (384mg, 0.35 equiv) were dissolved in 10 mL NMP. The reaction mixture was irradiated in a microwave oven for 4.5 min (T = 170 °C, pmax = 17 bar, 200 W). Next, the reaction mixture was poured into H<sub>2</sub>O (10 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 60 mL). The combined organic phases were dried over MgSO<sub>4</sub>, evaporated in vacuo, and the residue was purified by flash chromatography on silica gel (petroleum ether:EtOAc=10:1 to 4:1) to give 2-formyl-5-methylbenzonitrile (**1g**) as a white solid (0.53 g, 73%).

## 2.2 General experimental procedure C for products 3a-3t.

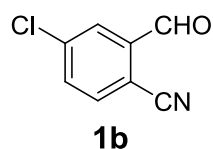


## Using the preparation of ethyl 1-aminoisoquinoline-3-carboxylate from 2-formylbenzonitrile and 2-isocyanoacetate as an example

To a reaction seal tube were added 2-formylbenzonitrile **1a** (100 mg, 0.76 mmol) in CH<sub>3</sub>CN (2.0 mL), Cu(acac)<sub>2</sub> (40 mg, 0.2 equiv), 2-isocyanoacetate **2a** (100 μL, 1.2 equiv), and DBU (137 μL, 1.2equiv). The mixture was stirred at 85 °C for 12 hours. After completion of reaction as indicated by TLC, the mixture was concentrated *in vacuo*, and the residue was purified by flash column chromatograph (petroleum ether : EtOAc=4:1 to 1:1) to give the desired product **3a**.

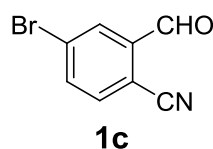
## 3. Characterization of substrates and products.

### 3.1 Characterization of substrates 1b-1n.



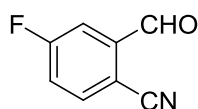
#### 4-chloro-2-formylbenzonitrile (**1b**):

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.31 (s, 1H), 8.01 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.73-7.70 (m, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.16, 140.46, 137.96, 135.04, 134.35, 129.54, 115.16, 112.08.



#### 4-bromo-2-formylbenzonitrile (**1c**):

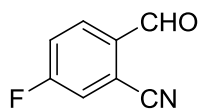
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.28 (s, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 7.90-7.87 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.10, 137.80, 137.30, 135.00, 132.56, 128.69, 115.27, 112.52.



**1d**

**4-fluoro-2-formylbenzonitrile (1d):**

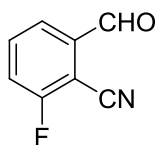
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.31 (d,  $J = 2.4$  Hz, 1H), 7.88-7.85 (m, 1H), 7.73-7.70 (m, 1H), 7.47-7.43 (m, 1H);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  187.06, 164.90 (d,  $J = 258.3$  Hz), 139.45 (d,  $J = 7.5$  Hz), 136.37 (d,  $J = 8.8$  Hz), 121.67 (d,  $J = 22.8$  Hz), 116.33 (d,  $J = 23.6$  Hz), 115.03, 109.82 (d,  $J = 3.4$  Hz).



**1e**

**5-fluoro-2-formylbenzonitrile (1e):**

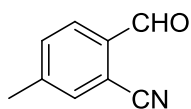
$^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  10.26 (s, 1H), 8.09-8.07 (m, 1H), 7.53-7.51 (m, 1H), 7.50-7.47 (m, 1H);  $^{13}\text{C NMR}$  (150 MHz,  $\text{CDCl}_3$ )  $\delta$  186.81, 165.19 (d,  $J = 259.0$  Hz), 133.52, 132.30 (d,  $J = 9.4$  Hz), 121.16 (d,  $J = 25.8$  Hz), 120.94 (d,  $J = 21.0$  Hz), 115.96 (d,  $J = 10.4$  Hz), 114.60.



**1f**

**2-fluoro-6-formylbenzonitrile (1f):**

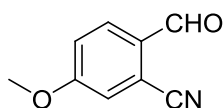
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.23 (s, 1H), 7.86-7.80 (m, 2H), 7.55-7.50 (m, 1H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  187.36 (d,  $J = 3.0$  Hz), 164.02 (d,  $J = 260.5$  Hz), 137.95, 135.09 (d,  $J = 8.4$  Hz), 126.99 (d,  $J = 3.2$  Hz), 121.73 (d,  $J = 20.2$  Hz), 110.92, 101.61 (d,  $J = 16.0$  Hz); **HRMS** (ESI) calcd for  $\text{C}_8\text{H}_4\text{FNO}$   $[\text{M}+\text{Na}]^+$ : 172.0169, found 172.0168.



**1g**

**2-formyl-5-methylbenzonitrile (1g):**

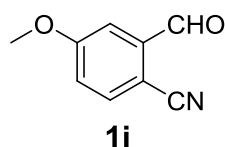
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.19 (s, 1H), 7.87 (d,  $J = 8.0$  Hz, 1H), 7.58 (s, 1H), 7.55 (d,  $J = 8.0$  Hz, 1H), 2.45 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.10, 145.69, 134.36, 134.31, 133.84, 129.70, 115.98, 113.27, 21.33.



**1h**

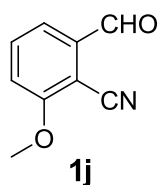
**2-formyl-5-methoxybenzonitrile (1h):**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.06 (s, 1H), 7.88 (d,  $J = 8.8$  Hz, 1H), 7.19 (s, 1H), 7.17 (d,  $J = 2.4$  Hz, 1H), 3.88 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  187.16, 163.54, 131.90, 129.60, 119.13, 118.44, 115.67, 114.83, 56.00.



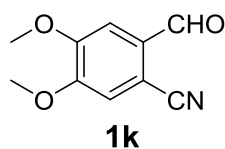
**2-formyl-4-methoxybenzonitrile (1i):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.28 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.22-7.19 (m, 1H), 3.92 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 188.40, 163.06, 138.66, 135.40, 120.71, 116.19, 113.20, 105.71, 55.98.



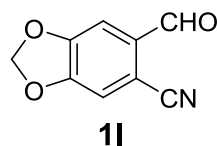
**2-formyl-6-methoxybenzonitrile (1j):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.28 (s, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.60-7.58 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 4.03 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 188.68, 162.16, 137.86, 134.28, 121.15, 116.58, 113.21, 102.41, 56.59; HRMS (ESI) calcd for C<sub>9</sub>H<sub>7</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 162.0550, found 162.0552.



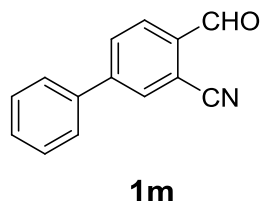
**2-formyl-4,5-dimethoxybenzonitrile (1k):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.22 (s, 1H), 7.46 (s, 1H), 7.17 (s, 1H), 3.98 (d, *J* = 2.4 Hz, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 187.42, 153.62, 152.81, 131.69, 115.95, 114.39, 109.39, 108.12, 56.61, 56.40.



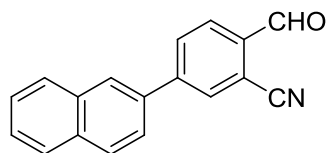
**6-formylbenzo[d][1,3]dioxole-5-carbonitrile (1l):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.23 (s, 1H), 7.43 (s, 1H), 7.15 (s, 1H), 6.19 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 186.90, 152.54, 152.11, 134.22, 115.66, 112.22, 110.15, 107.57, 103.47.



**2-formyl-5-phenylbenzonitrile(1m):**

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 10.33 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.62-7.59 (m, 2H), 7.53-7.45 (m, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 188.05, 146.98, 137.08, 134.88, 132.26, 131.30, 130.17, 129.35, 129.18, 127.04, 115.94, 113.92.

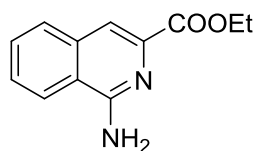


**1n**

**2-formyl-5-(naphthalen-2-yl)benzonitrile(1n):**

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.40 (s, 1H), 8.16-8.08 (m, 4H), 8.00-7.89 (m, 3H), 7.74-7.71 (m, 1H), 7.59-7.57 (m, 2H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  188.18, 147.31, 135.14, 134.63, 133.47, 133.40, 132.63, 131.71, 130.11, 129.35, 128.51, 127.77, 127.32, 127.06, 127.02, 124.38, 116.06, 114.59; **HRMS** (ESI) calcd for  $\text{C}_{18}\text{H}_{11}\text{NO}$   $[\text{M}+\text{Na}]^+$ : 280.0733, found 280.0733.

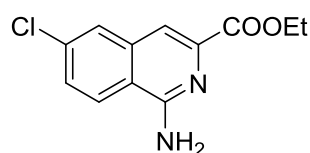
**3.2 Characterization of products 3a-3t.**



**3a**

**ethyl 1-aminoisoquinoline-3-carboxylate (3a):**

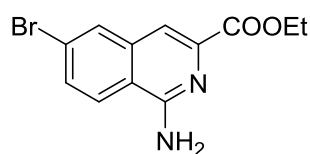
**3a** (132 mg) was obtained through the general procedure C in 80% yield as a light yellow solid. mp 204-206 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (s, 1H), 7.87 (d,  $J = 8.4$  Hz, 1H), 7.81 (d,  $J = 8.0$  Hz, 1H), 7.68-7.64 (m, 1H), 7.60-7.56 (m, 1H), 5.88 (s, 2H), 4.46 (q,  $J = 7.2$  Hz, 2H), 1.43 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.09, 156.49, 140.05, 136.77, 130.60, 128.55, 128.27, 122.75, 119.41, 115.78, 61.40, 14.39; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 217.0972, found 217.0967.



**3b**

**ethyl 1-amino-6-chloroisoquinoline-3-carboxylate (3b):**

**3b** (116 mg) was obtained through the general procedure C in 77 % yield as a light yellow solid. mp 164-167 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.81 (d,  $J = 8.8$  Hz, 1H), 7.74-7.72 (m, 2H), 7.47-7.44 (m, 1H), 6.38 (s, 2H), 4.42 (q,  $J = 7.2$  Hz, 2H), 1.42 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100MHz,  $\text{CDCl}_3$ )  $\delta$  165.69, 156.74, 141.08, 137.81, 136.75, 128.72, 127.15, 124.60, 117.44, 114.19, 61.47, 14.32; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{11}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 251.0582, found 251.0578.

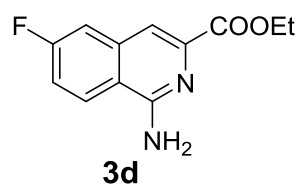


**3c**

**ethyl 1-amino-6-bromoisoquinoline-3-carboxylate (3c):**

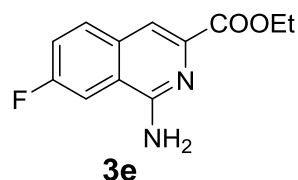
**3c** (86 mg) was obtained through the general procedure C in 61% yield as a light yellow solid. mp

190-195 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J = 2.0$  Hz, 1H), 7.83 (s, 1H), 7.72 (d,  $J = 8.8$  Hz, 1H), 7.68-7.66 (m, 1H), 5.76 (s, 2H), 4.46 (q,  $J = 7.2$  Hz, 2H), 1.44 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  165.71, 156.41, 141.35, 138.30, 131.55, 130.69, 125.38, 124.45, 117.74, 114.61, 61.64, 14.38; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{11}\text{BrN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 295.0077, found 295.0074.



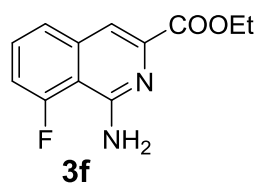
**ethyl 1-amino-6-fluoroisoquinoline-3-carboxylate (3d):**

**3d** (111 mg) was obtained through the general procedure C in 71% yield as a light yellow solid. mp 199-201 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.38-8.34 (m, 1H), 7.72-7.68 (m, 2H), 7.50-7.45 (m, 1H), 7.28 (s, 2H), 4.30 (q,  $J = 7.2$  Hz, 2H), 1.30 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.74, 162.92 (d,  $J = 247.2$  Hz), 157.43, 141.76, 138.69 (d,  $J = 10.6$  Hz), 127.61 (d,  $J = 9.6$  Hz), 117.14 (d,  $J = 24.4$  Hz), 115.97, 112.69 (d,  $J = 3.6$  Hz), 111.75 (d,  $J = 20.7$  Hz), 60.77, 14.41; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{11}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 235.0877, found 235.0872.



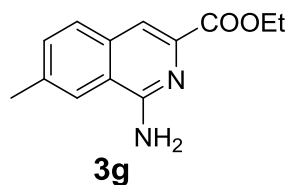
**ethyl 1-amino-7-fluoroisoquinoline-3-carboxylate(3e):**

**3e** (95 mg) was obtained through the general procedure C in 60% yield as a light yellow solid. mp 192-195 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.12 (d,  $J = 10.8$  Hz, 1H), 8.02-7.99 (m, 1H), 7.78 (s, 1H), 7.63-7.58 (m, 1H), 7.17 (s, 2H), 4.30 (q,  $J = 7.2$  Hz, 2H), 1.31 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.73, 161.20 (d,  $J = 244.7$  Hz), 156.97 (d,  $J = 4.3$  Hz), 140.05 (d,  $J = 2.5$  Hz), 133.57, 131.18 (d,  $J = 8.6$  Hz), 120.22 (d,  $J = 24.3$  Hz), 119.77 (d,  $J = 8.1$  Hz), 112.86, 108.58 (d,  $J = 22.1$  Hz), 60.61, 14.38; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{11}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 235.0877, found 235.0872.



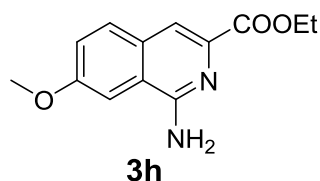
**ethyl 1-amino-8-fluoroisoquinoline-3-carboxylate (3f):**

**3f** (118 mg) was obtained through the general procedure C in 75% yield as a light yellow solid. mp 183-186 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  7.76-7.74 (m, 2H), 7.70-7.65 (m, 1H), 7.41-7.36 (m, 1H), 7.03 (s, 2H), 4.31 (q,  $J = 7.2$  Hz, 2H), 1.32 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.39, 159.11 (d,  $J = 249.9$  Hz), 154.96 (d,  $J = 4.2$  Hz), 141.42, 139.53, 131.55 (d,  $J = 9.9$  Hz), 124.50 (d,  $J = 3.5$  Hz), 113.40 (d,  $J = 23.3$  Hz), 112.32, 108.41 (d,  $J = 11.7$  Hz), 60.84, 14.40; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{11}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 235.0877, found 235.0870.



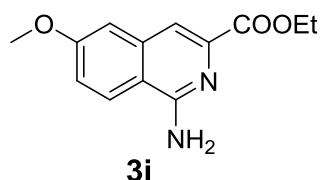
**ethyl 1-amino-7-methylisoquinoline-3-carboxylate (3g):**

**3g** (120 mg) was obtained through the general procedure C in 76% yield as a light yellow solid. mp 198-201 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  8.09 (s, 1H), 7.79 (d,  $J$  = 8.4 Hz, 1H), 7.72 (s, 1H), 7.52 (d,  $J$  = 8.0 Hz, 1H), 7.04 (s, 2H), 4.30 (q,  $J$  = 7.2 Hz, 2H), 2.47 (s, 3H), 1.31 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  165.89, 156.90, 139.59, 137.75, 134.37, 132.31, 127.98, 123.28, 119.07, 113.30, 60.46, 21.61, 14.41; **HRMS** (ESI) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 231.1128, found 231.1121.



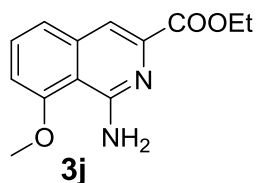
**ethyl 1-amino-7-methoxyisoquinoline-3-carboxylate (3h):**

**3h** (101 mg) was obtained through the general procedure C in 66% yield as a light yellow solid. mp 203-205 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  7.83 (d,  $J$  = 8.8 Hz, 1H), 7.74 (s, 1H), 7.68 (d,  $J$  = 2.0 Hz, 1H), 7.34-7.31 (m, 1H), 7.07 (s, 2H), 4.29 (q,  $J$  = 7.2 Hz, 2H), 3.89 (s, 3H), 1.30 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  166.02, 159.27, 156.56, 138.27, 131.11, 129.90, 121.97, 120.30, 113.56, 103.96, 60.46, 55.86, 14.48; **HRMS** (ESI) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 247.1077, found 247.1072.



**ethyl 1-amino-6-methoxyisoquinoline-3-carboxylate (3i):**

**3i** (117 mg) was obtained through the general procedure C in 77% yield as a light yellow solid. mp 195-199 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  8.18 (d,  $J$  = 8.8 Hz, 1H), 7.69 (s, 1H), 7.34 (d,  $J$  = 2.4 Hz, 1H), 7.22-7.19 (m, 1H), 7.05 (s, 2H), 4.29 (q,  $J$  = 7.2 Hz, 2H), 3.87 (s, 3H), 1.31 (t,  $J$  = 7.2 Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz, DMSO- $d_6$ )  $\delta$  165.98, 160.62, 157.28, 141.12, 138.71, 126.00, 119.06, 113.72, 113.03, 107.19, 60.60, 55.56, 14.44; **HRMS** (ESI) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 247.1077, found 247.1075.

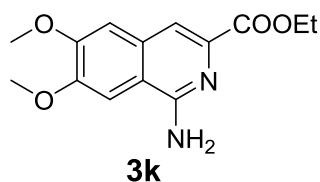


**ethyl 1-amino-8-methoxyisoquinoline-3-carboxylate (3j):**

**3j** (106 mg) was obtained through the general procedure C in 69% yield as a light yellow solid. mp 136-141 °C;  $^1\text{H NMR}$  (400 MHz, DMSO- $d_6$ )  $\delta$  7.61 (s, 1H), 7.56 (t,  $J$  = 8.0 Hz, 1H), 7.41 (d,  $J$  = 8.0 Hz,

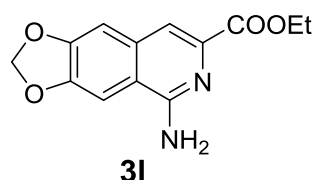


1H), 7.34 (s, 2H), 7.06 (d,  $J = 8.0$  Hz, 1H), 4.30 (q,  $J = 7.2$  Hz, 2H), 3.97 (s, 3H), 1.31 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  165.67, 157.23, 156.93, 140.90, 139.44, 131.27, 120.29, 112.48, 109.90, 108.23, 60.66, 56.21, 14.42; HRMS (ESI) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 247.1077, found 247.1073.



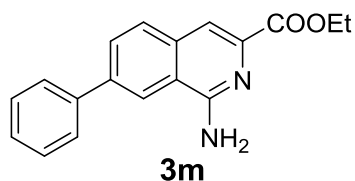
**ethyl 1-amino-6,7-dimethoxyisoquinoline-3-carboxylate (3k):**

**3k** (110 mg) was obtained through the general procedure C in 76% yield as a light yellow solid. mp 236-238 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (s, 1H), 7.11 (s, 1H), 7.09 (s, 1H), 5.51 (s, 2H), 4.43 (q,  $J = 7.2$  Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 1.41 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  166.05, 156.15, 152.22, 150.40, 138.85, 132.44, 113.88, 113.12, 107.32, 103.93, 60.39, 56.12, 55.79, 14.48; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 277.1183, found 277.1177.



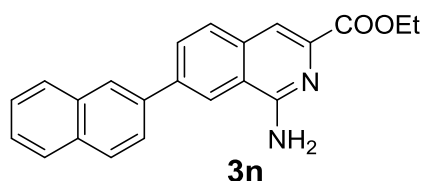
**ethyl 5-amino-[1,3]dioxolo[4,5-g]isoquinoline-7-carboxylate (3l):**

**3l** (110 mg) was obtained through the general procedure C in 74% yield as a light yellow solid. mp 208-211 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  7.69 (s, 1H), 7.65 (s, 1H), 7.35 (s, 1H), 6.82 (s, 2H), 6.18 (s, 2H), 4.28 (q,  $J = 7.2$  Hz, 2H), 1.30 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  165.94, 156.46, 150.37, 148.84, 139.29, 134.23, 115.01, 113.51, 104.47, 102.10, 100.99, 60.47, 14.47; HRMS (ESI) calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_4$   $[\text{M}+\text{H}]^+$ : 261.0870, found 261.0860.



**ethyl 1-amino-7-phenylisoquinoline-3-carboxylate (3m):**

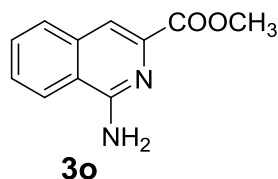
**3m** (125 mg) was obtained through the general procedure C in 89% yield as a light yellow solid. mp 184-187 °C;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  8.65 (s, 1H), 8.01-7.95 (m, 2H), 7.86 (d,  $J = 7.2$  Hz, 2H), 7.79 (s, 1H), 7.51-7.37 (m, 5H), 4.32 (q,  $J = 7.2$  Hz, 2H), 1.32 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz, DMSO- $d_6$ )  $\delta$  165.90, 157.76, 140.55, 139.60, 139.40, 135.66, 129.26, 129.11, 128.91, 128.01, 127.19, 121.73, 119.39, 113.02, 60.67, 14.46; HRMS (ESI) calcd for  $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 293.1285, found 293.1279.



**ethyl 1-amino-7-(naphthalen-2-yl)isoquinoline-3-carboxylate (3n):**

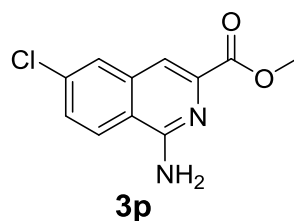
**3n** (89 mg) was obtained through the general procedure C in 67% yield as a light yellow amorphous solid

$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.77 (s, 1H), 8.45 (s, 1H), 8.24-8.21 (m, 1H), 8.11-8.08 (m, 2H), 8.05-8.01 (m, 2H), 7.98-7.96 (m, 1H), 7.80 (s, 1H), 7.60-7.53 (m, 2H), 7.36 (s, 2H), 4.33 (q,  $J = 7.2$  Hz, 2H), 1.34 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  165.80, 157.65, 140.51, 139.29, 136.63, 135.68, 133.40, 132.54, 129.43, 128.94, 128.63, 128.35, 127.64, 126.65, 126.48, 125.88, 125.28, 121.93, 119.34, 112.93, 60.61, 14.43; **HRMS** (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 343.1441, found 343.1434.



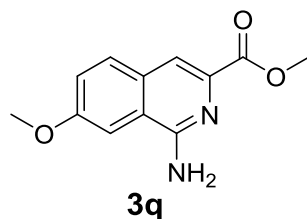
**methyl 1-aminoisoquinoline-3-carboxylate (3o):**

**3o** (107 mg) was obtained through the general procedure C in 69% yield as a light yellow solid. mp 209-210 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.27 (d,  $J = 8.0$  Hz, 1H), 7.90 (d,  $J = 8.0$  Hz, 1H), 7.76 (s, 1H), 7.69 (t,  $J = 8.0$  Hz, 1H), 7.63-7.59 (m, 1H), 7.20 (s, 2H), 3.84 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  166.37, 157.47, 140.19, 136.47, 130.65, 128.22, 128.05, 124.12, 118.98, 113.32, 51.97; **HRMS** (ESI) calcd for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 203.0815, found 203.0810.



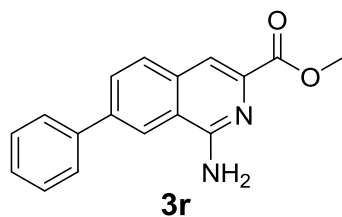
**methyl 1-amino-6-chloroisoquinoline-3-carboxylate (3p):**

**3p** (83 mg) was obtained through the general procedure C in 58% yield as a light yellow solid. mp 203-207 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.29 (d,  $J = 8.8$  Hz, 1H), 8.02 (d,  $J = 2.4$  Hz, 1H), 7.71 (s, 1H), 7.64-7.61 (m, 1H), 7.28 (s, 2H), 3.84 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  166.06, 157.39, 141.49, 137.89, 135.46, 128.09, 126.81, 126.46, 117.19, 112.17, 52.00; **HRMS** (ESI) calcd for  $\text{C}_{11}\text{H}_9\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 237.0425, found 237.0427.



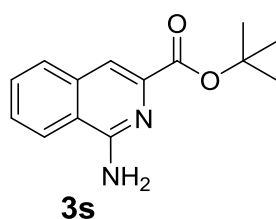
**methyl 1-amino-7-methoxyisoquinoline-3-carboxylate (3q):**

**3q** (89 mg) was obtained through the general procedure C in 62% yield as a light yellow solid. mp 211-214 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  7.83 (d,  $J = 8.8$  Hz, 1H), 7.74 (s, 1H), 7.68 (d,  $J = 2.4$  Hz, 1H), 7.34-7.32 (m, 1H), 7.04 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  166.45, 159.28, 156.52, 137.97, 131.06, 129.88, 121.91, 120.30, 113.60, 103.98, 55.83, 51.76; **HRMS** (ESI) calcd for  $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$ : 233.0921, found 233.0925.



**methyl 1-amino-7-phenylisoquinoline-3-carboxylate(3r):**

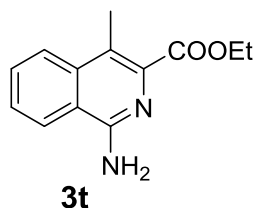
**3r** (95 mg) was obtained through the general procedure C in 71% yield as a light yellow solid. mp 206-208 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (s, 2H), 7.94-7.88 (m, 2H), 7.68-7.66 (m, 2H), 7.51-7.47 (m, 2H), 7.43-7.39 (m, 1H), 5.68 (s, 2H), 4.00 (s, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.53, 156.60, 141.37, 140.02, 139.54, 135.69, 130.16, 128.97, 127.96, 127.31, 120.83, 119.74, 115.74, 53.37, 52.53; **HRMS** (ESI) calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 279.1128, found 279.1131.



**tert-butyl 1-aminoisoquinoline-3-carboxylate (3s):**

**3s** (100 mg) was obtained through the general procedure C in 54% yield as a light yellow amorphous solid.

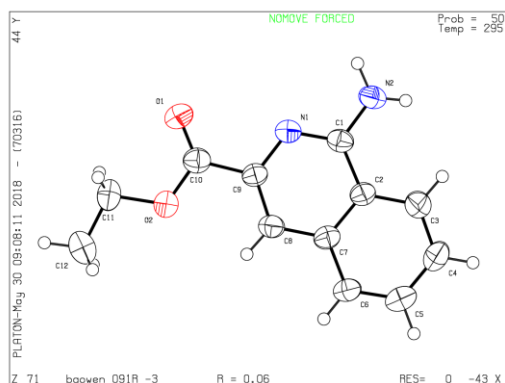
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86-7.82 (m, 3H), 7.70-7.66 (m, 1H), 7.63-7.59 (m, 1H), 5.36 (s, 2H), 1.65 (s, 9H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  164.98, 157.23, 141.76, 136.45, 130.47, 127.98, 127.67, 124.04, 118.68, 112.71, 80.33, 27.96; **HRMS** (ESI) calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 245.1285, found 245.1281.



**ethyl 1-amino-4-methylisoquinoline-3-carboxylate (3t):**

**3t** (32 mg) was obtained through the general procedure C in 20% yield as a light yellow solid. mp 145-146 °C;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (d,  $J = 8.4$  Hz, 1H), 7.85 (d,  $J = 8.0$  Hz, 1H), 7.76-7.72 (m, 1H), 7.62-7.58 (m, 1H), 5.12 (s, 2H), 4.47 (q,  $J = 7.2$  Hz, 2H), 2.67 (s, 3H), 1.45 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C NMR}$  (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  167.87, 155.57, 141.30, 136.47, 130.49, 126.59, 124.36, 124.19, 118.00, 114.11, 60.57, 14.27, 13.24; **HRMS** (ESI) calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$ : 231.1128, found 231.1120.

#### 4. X-Ray ellipsoid plots of 3a (CDCC 1846237)

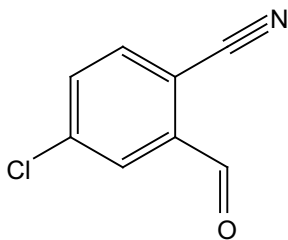


#### 5. References

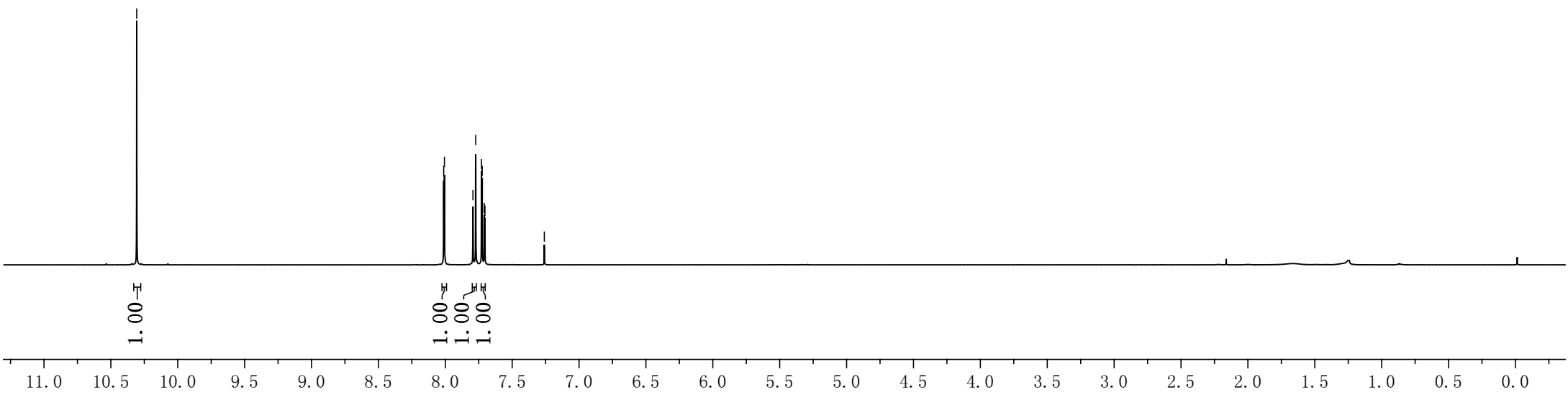
- (1) Sun, C.; Xu, B. *J. Org. Chem.*, **2008**, *73*, 7361.
- (2) Bert, K.; Noel, T.; Kimpe, W.; Goeman, J. L.; Van der Eycken, J. *Org. Biomol. Chem.*, **2012**, *10*, 8539.

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1b

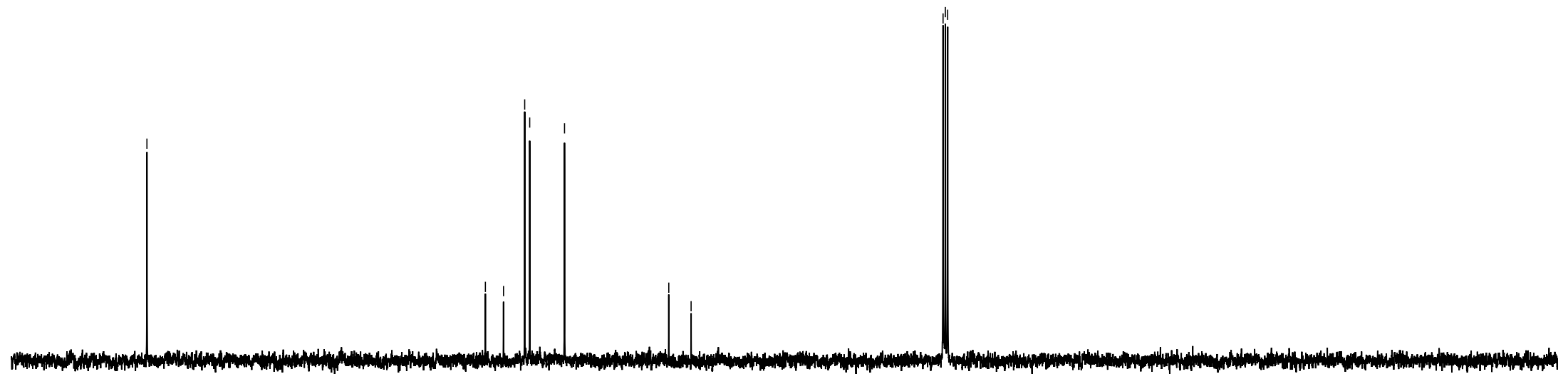
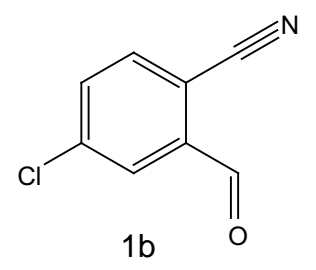


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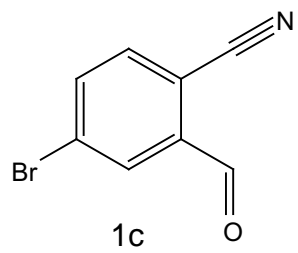
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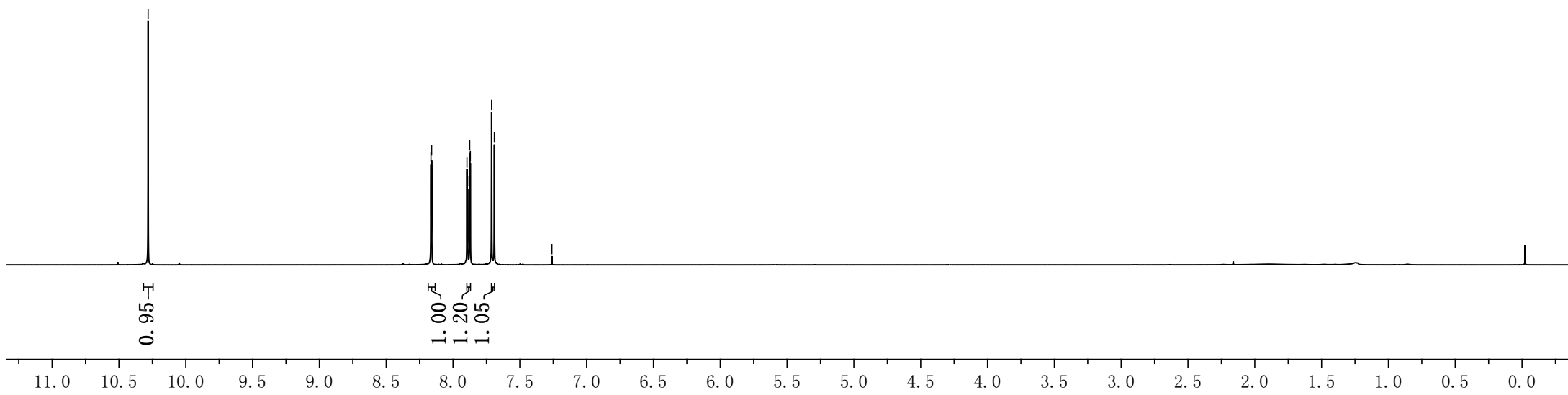
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S14



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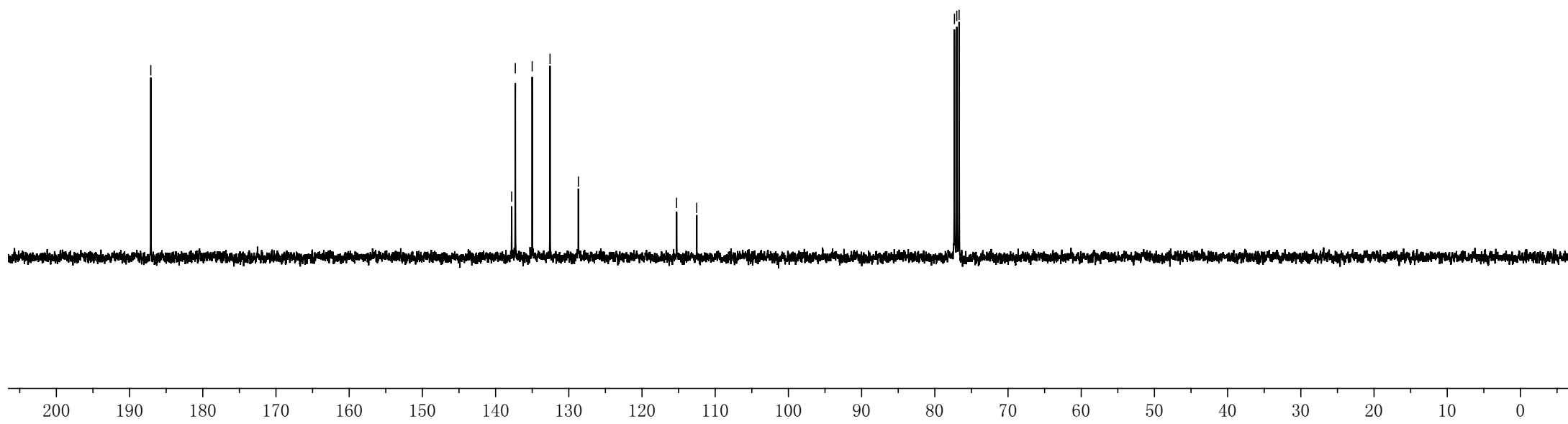
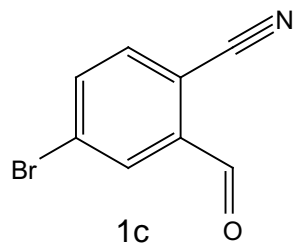


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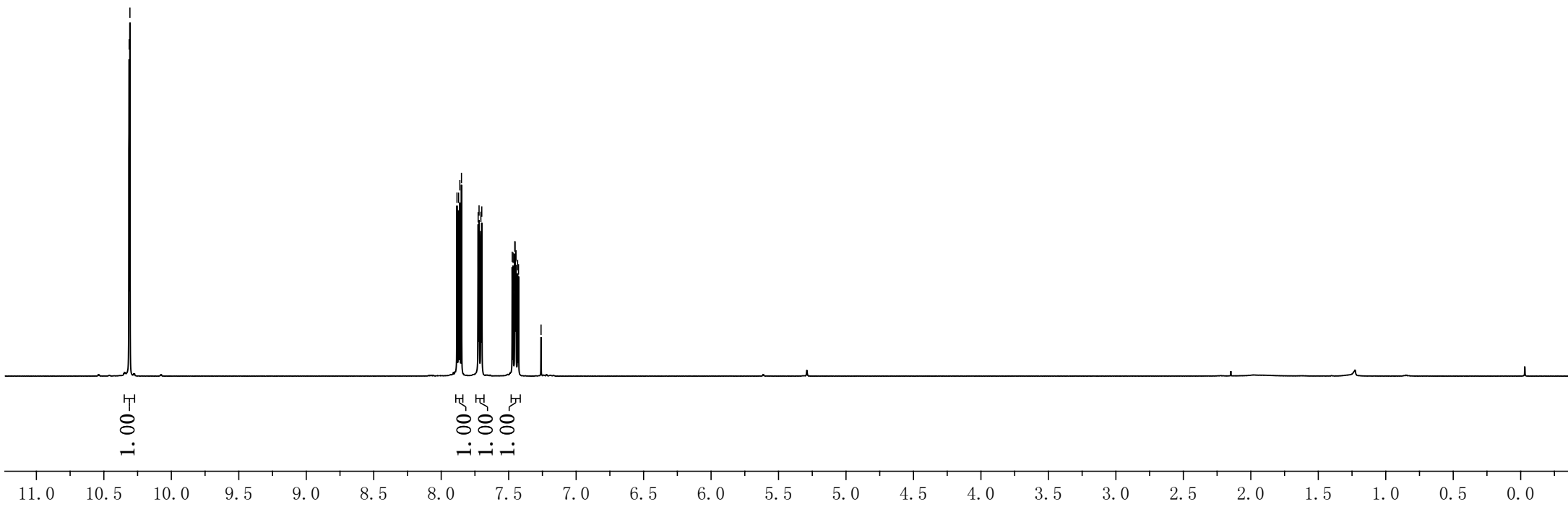
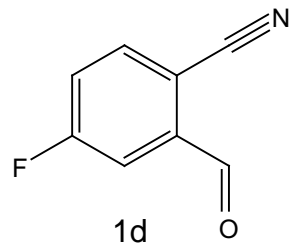
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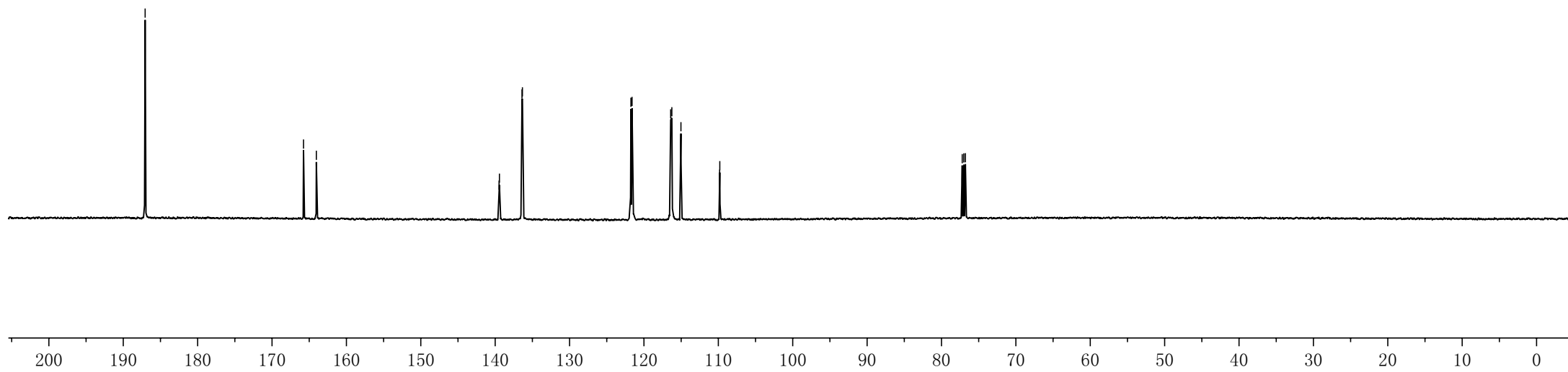
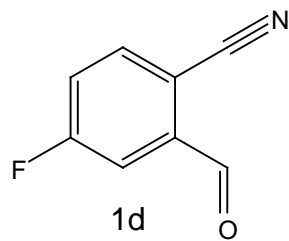
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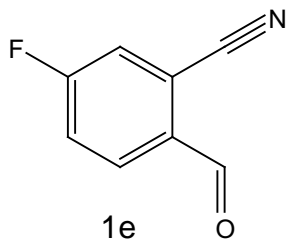
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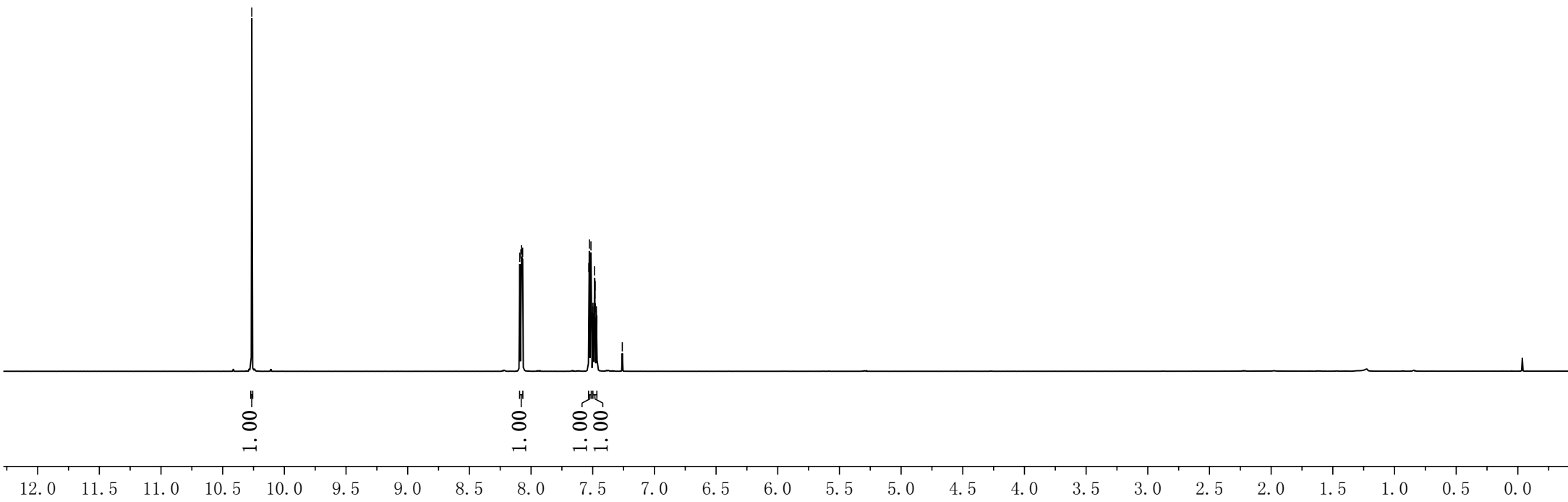
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7.466  
7.260

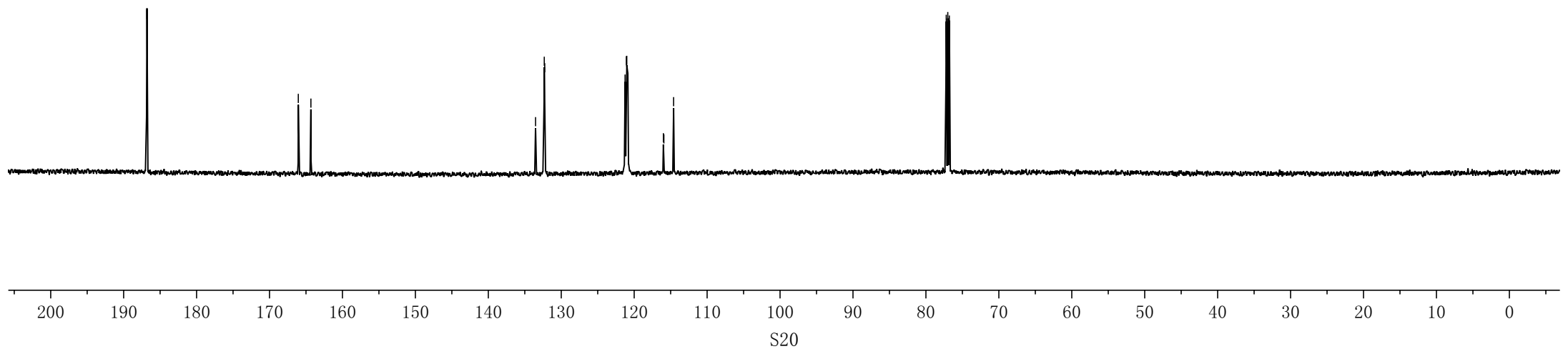
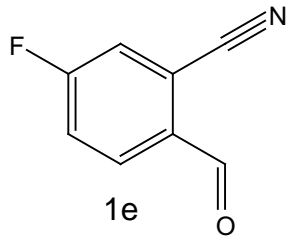


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~164.326

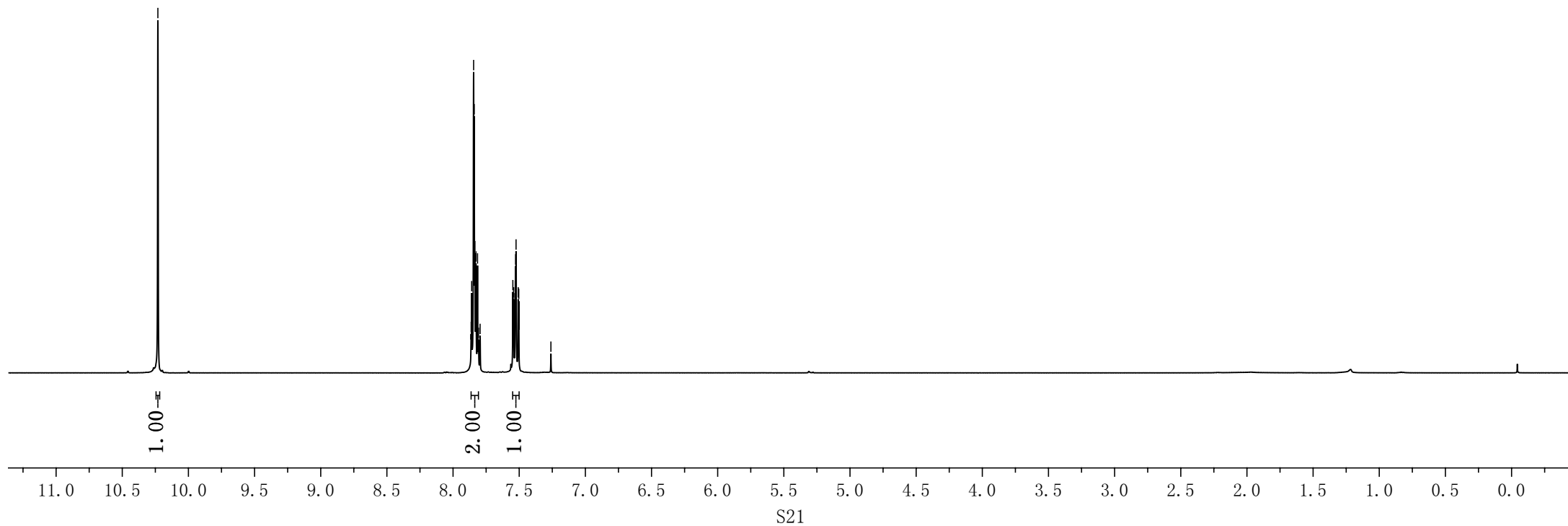
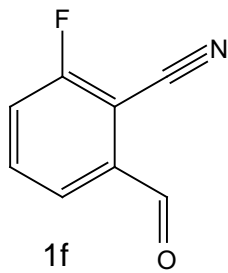
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121.077  
121.014  
120.874  
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115.928  
114.596

77.215  
77.003  
76.791



-10.231

7.863  
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7.840  
7.835  
7.827  
7.815  
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7.796  
7.548  
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7.503  
7.260



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187.347

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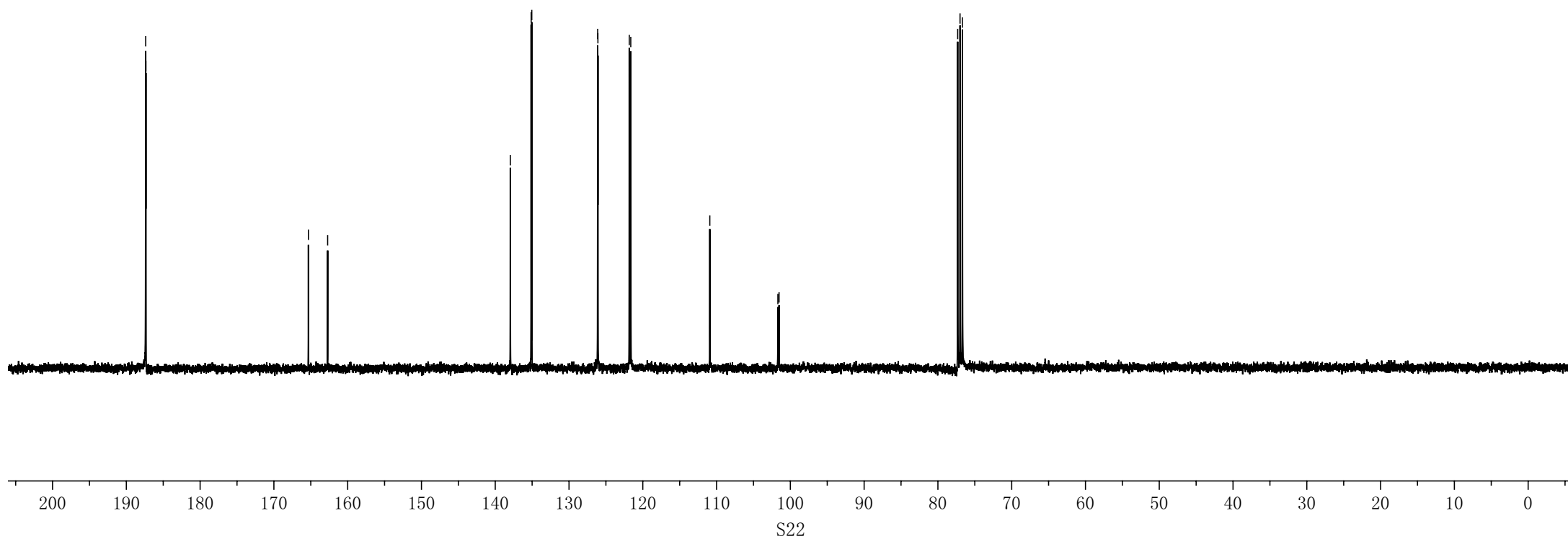
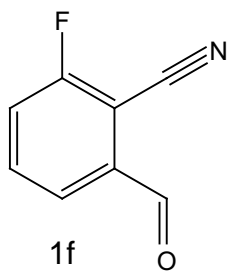
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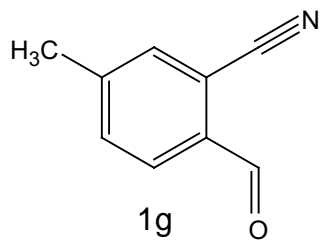
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76.682



—10.189

7.879  
7.859  
7.576  
7.557  
7.537  
7.260

—2.452



1.00

1.00

1.00

1.00

3.00

11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

S23

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—145.693

134.361

134.306

133.842

129.699

—115.984

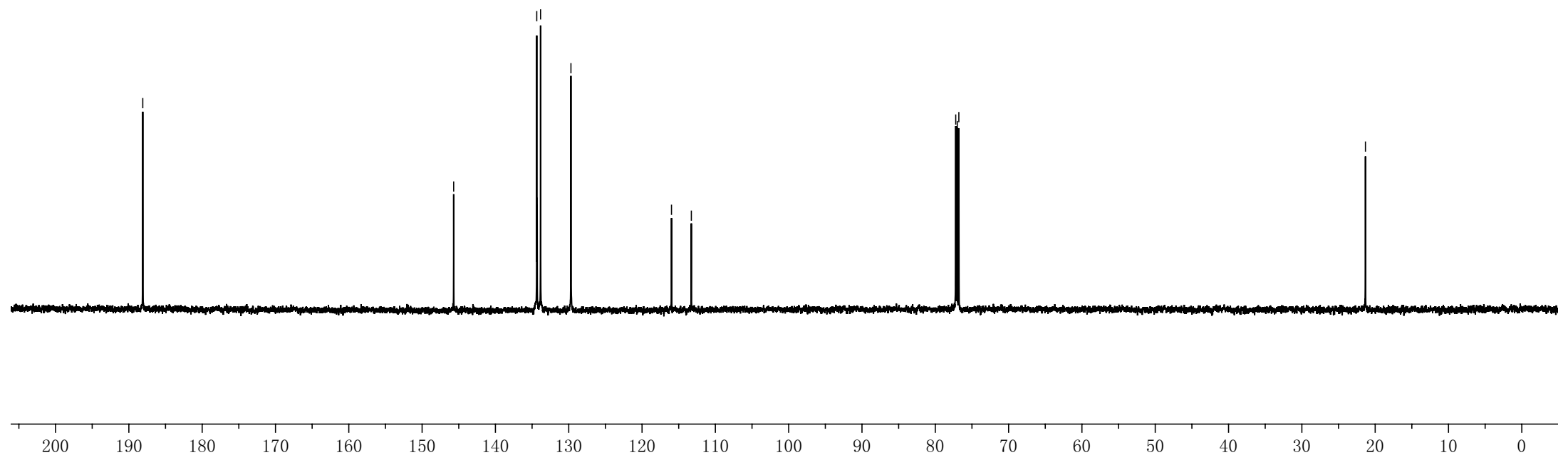
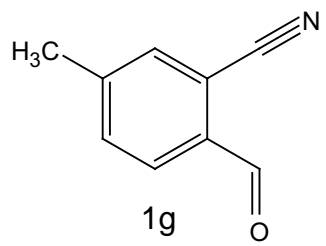
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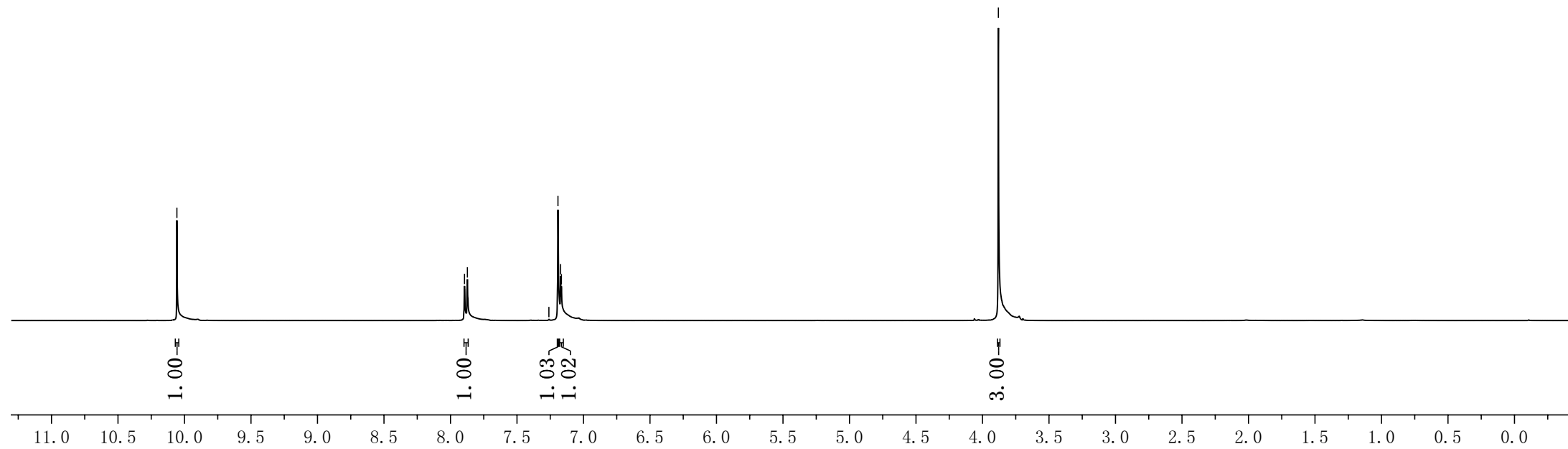
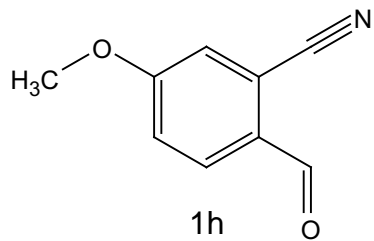


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7.166

—3.880



—187.159

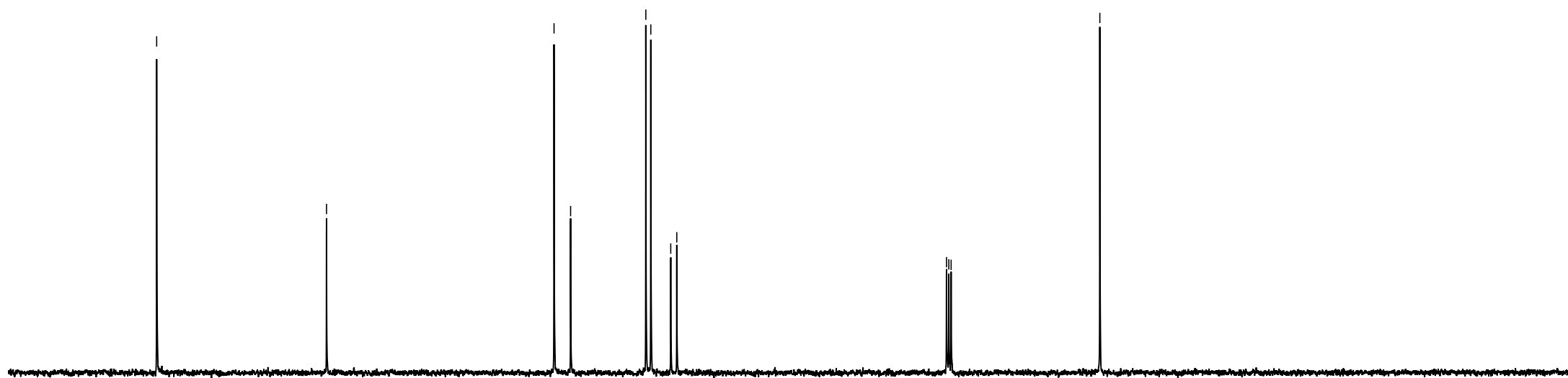
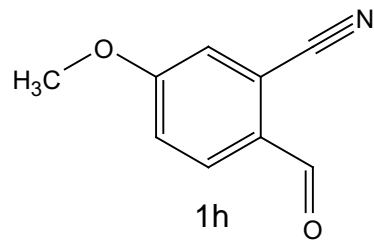
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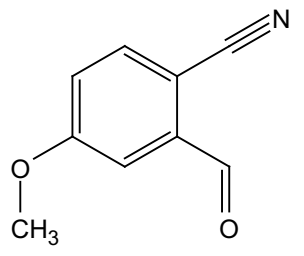
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~76.680

—55.998



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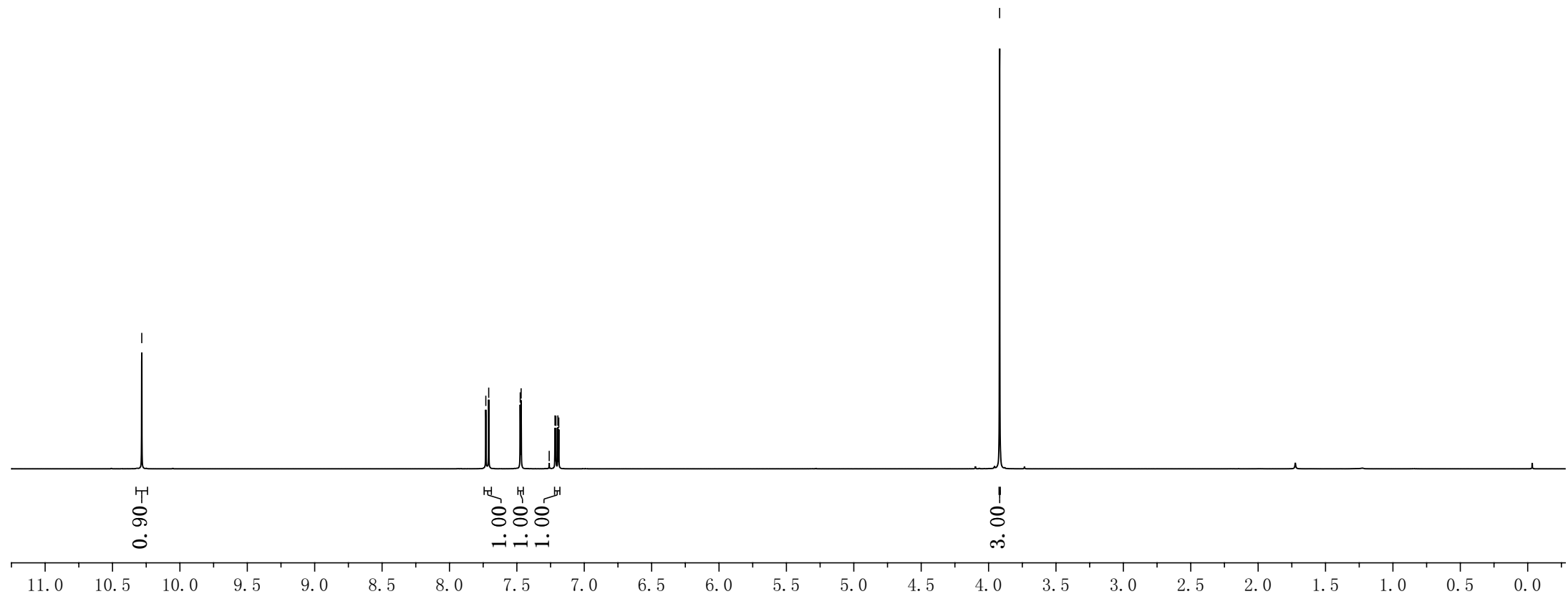
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7.260  
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—3.918



—188.396

—163.058

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~116.188

~113.196

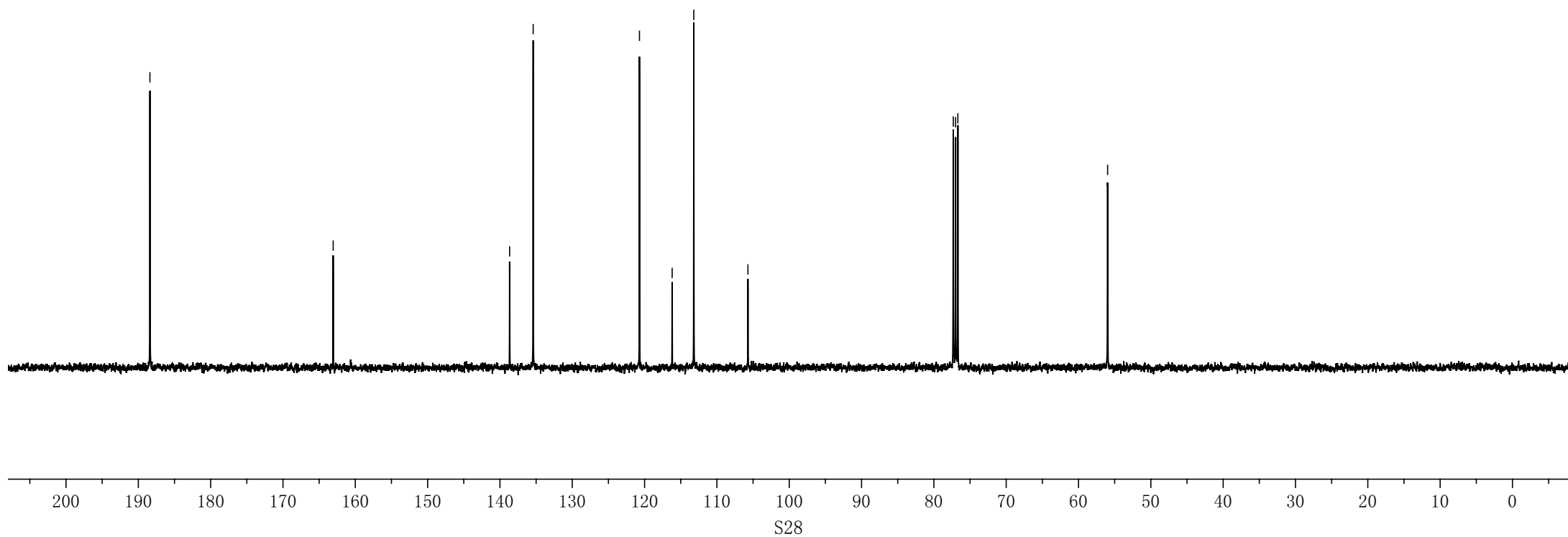
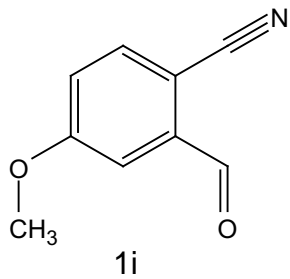
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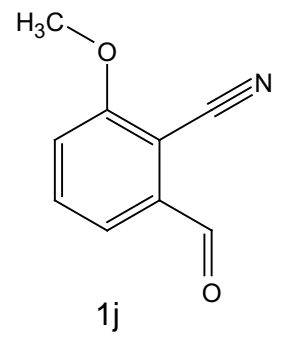


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7.584  
7.325  
7.304

—4.033

—0.000



11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

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~116.576

~113.215

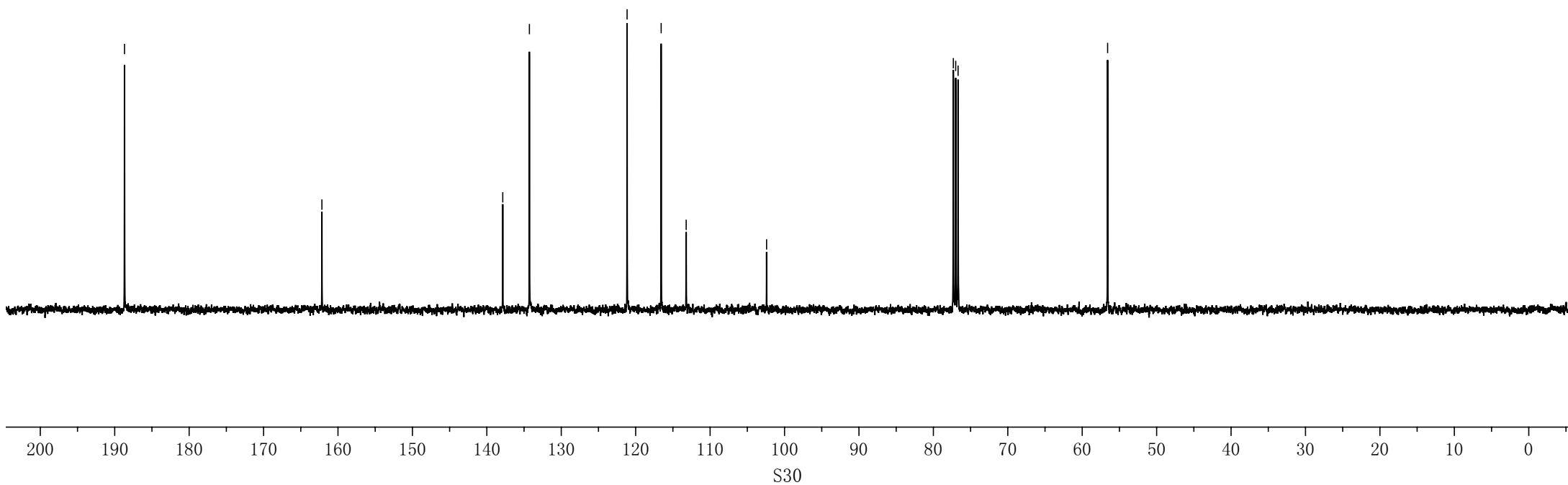
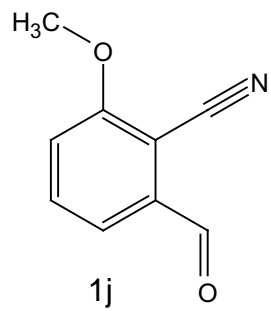
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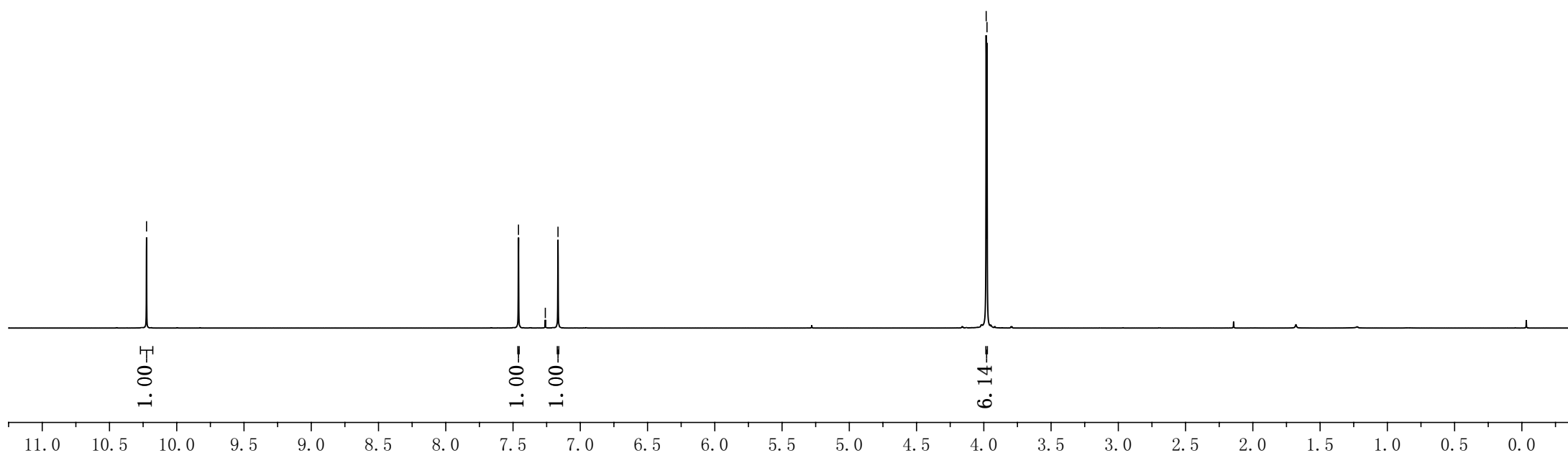
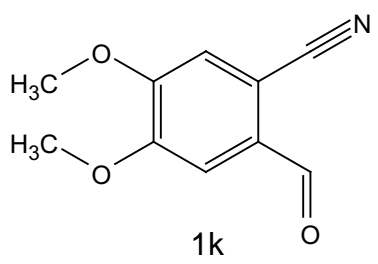
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S31

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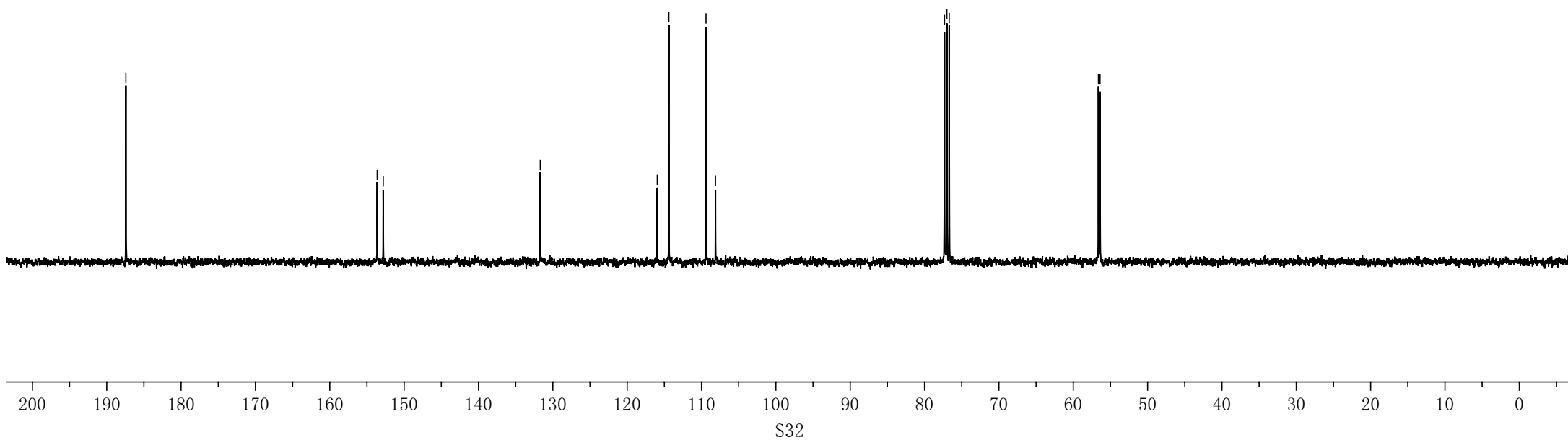
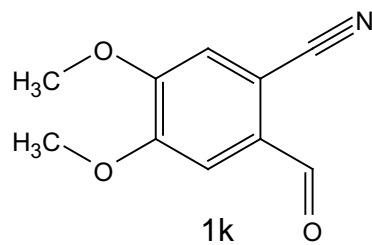
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76.682

56.613  
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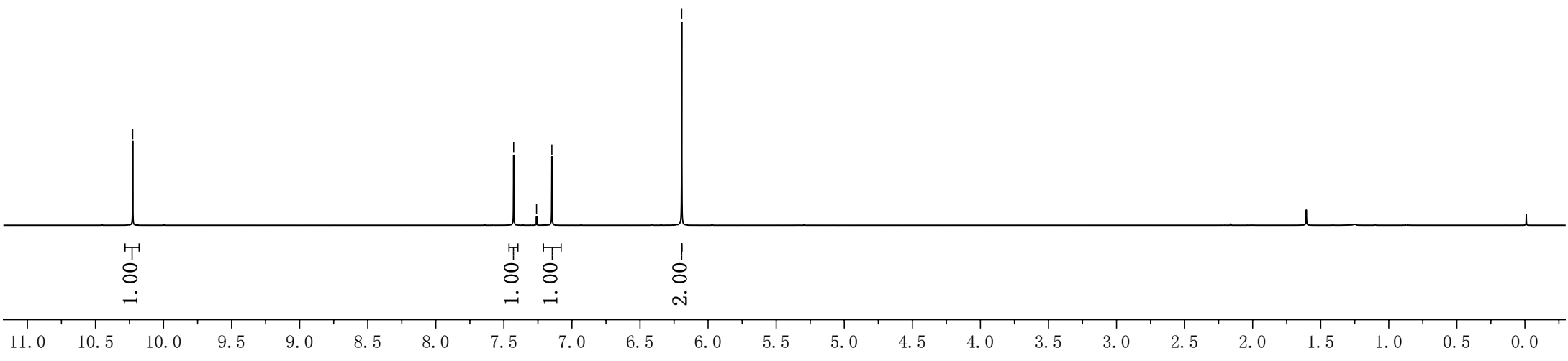
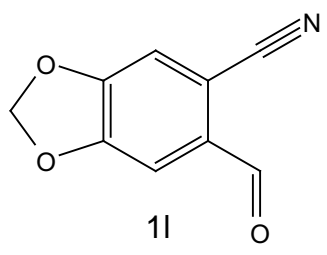




—10.226

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~7.148

—6.194



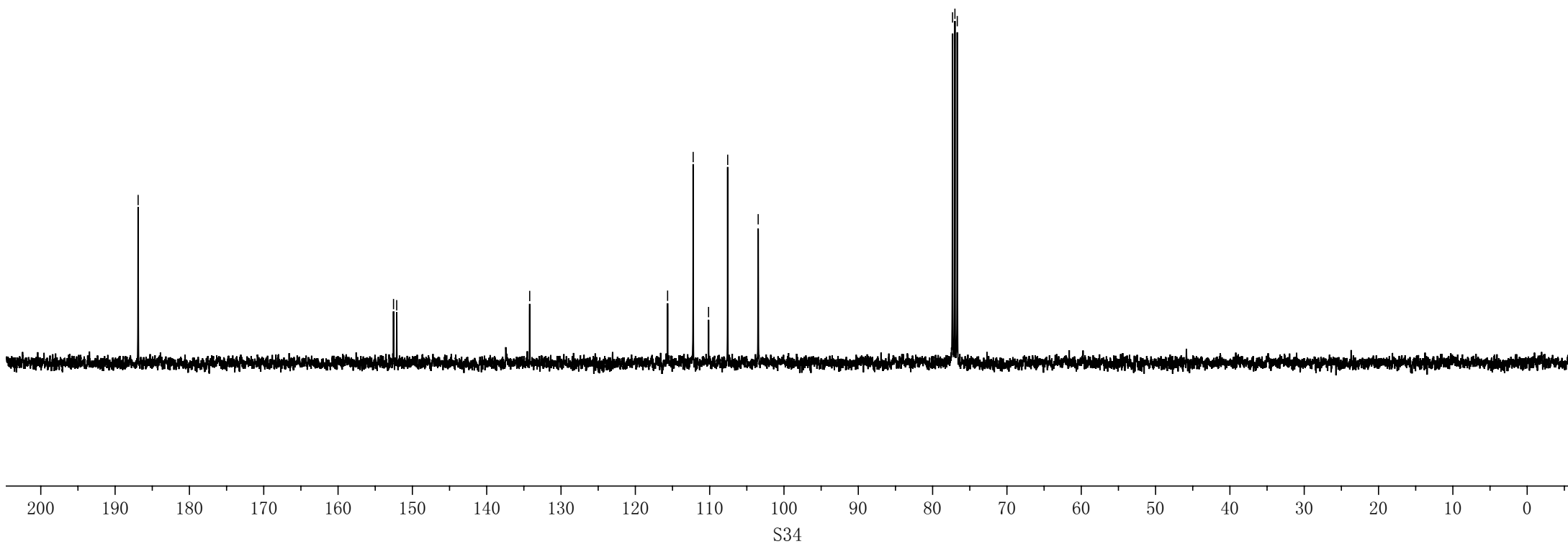
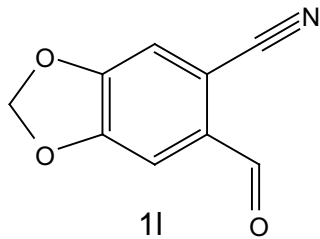
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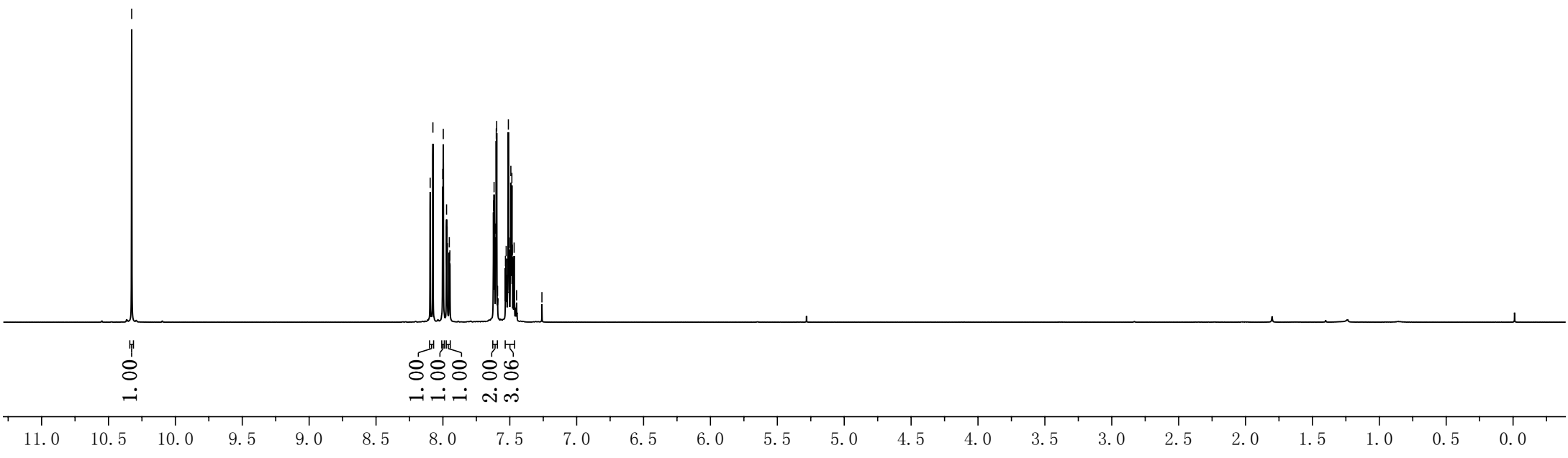
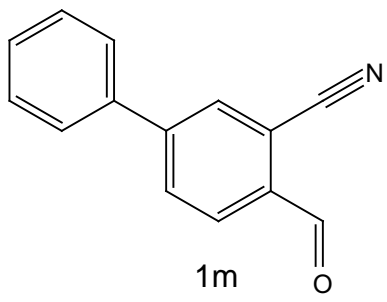
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77.318  
77.000  
76.682



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8.002  
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7.973  
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7.598  
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7.468  
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7.260



—188.051

—146.979

└─137.084

└─134.880

└─132.265

└─131.302

└─130.170

└─129.353

└─129.177

└─127.043

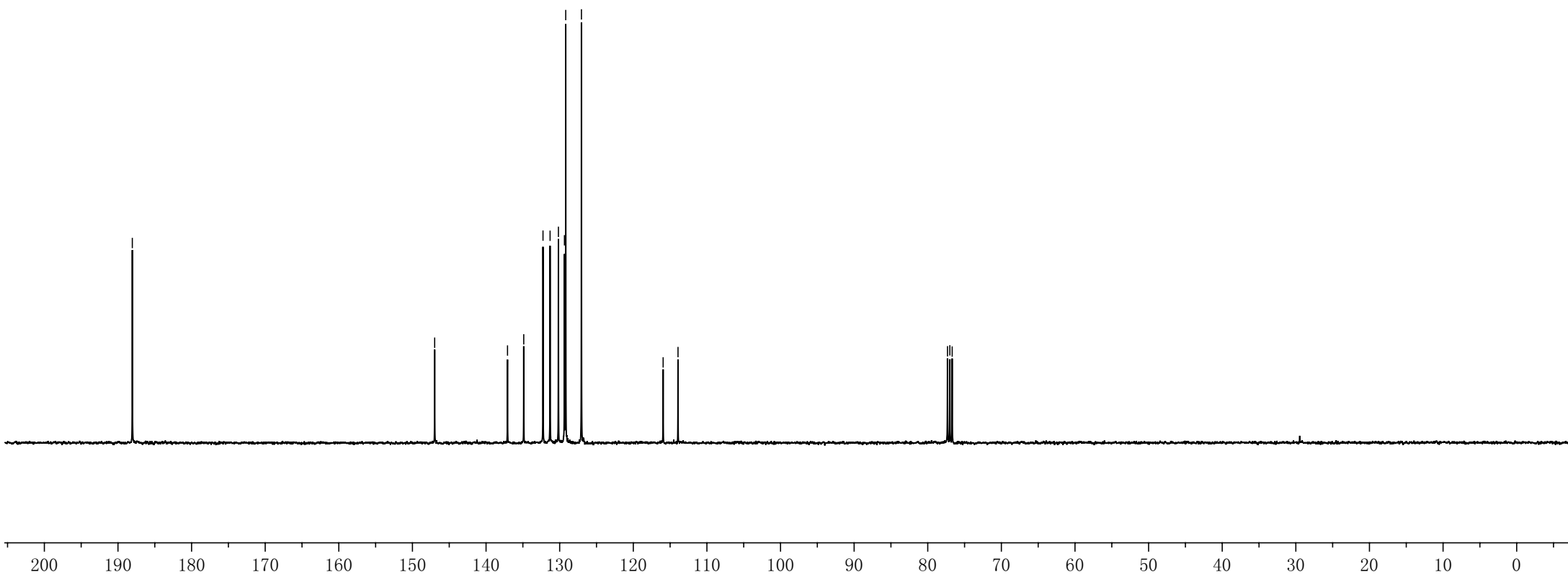
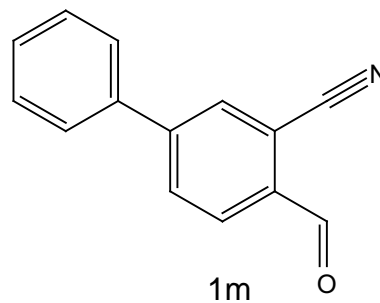
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└─113.924

└─77.320

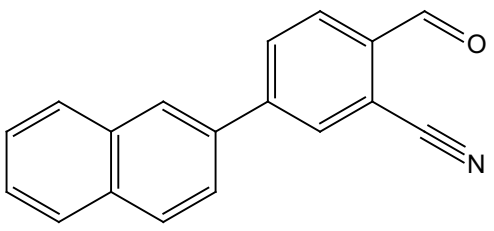
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└─76.682

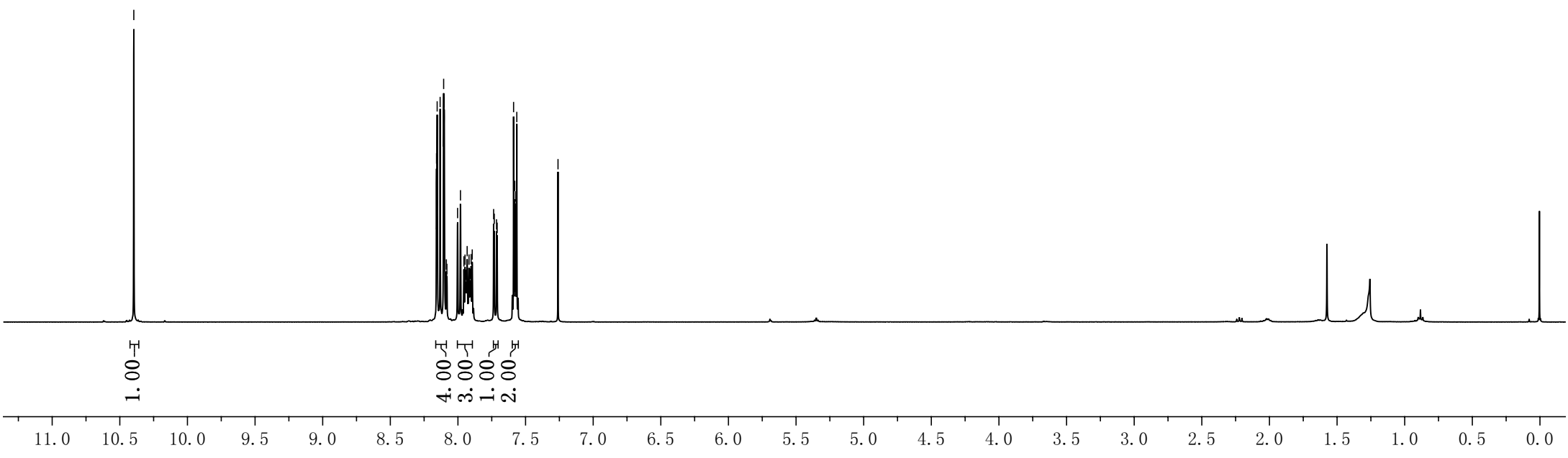


10.396

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7.580  
7.573  
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1n



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127.058

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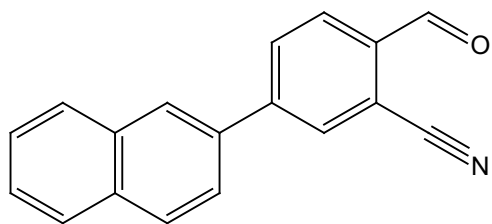
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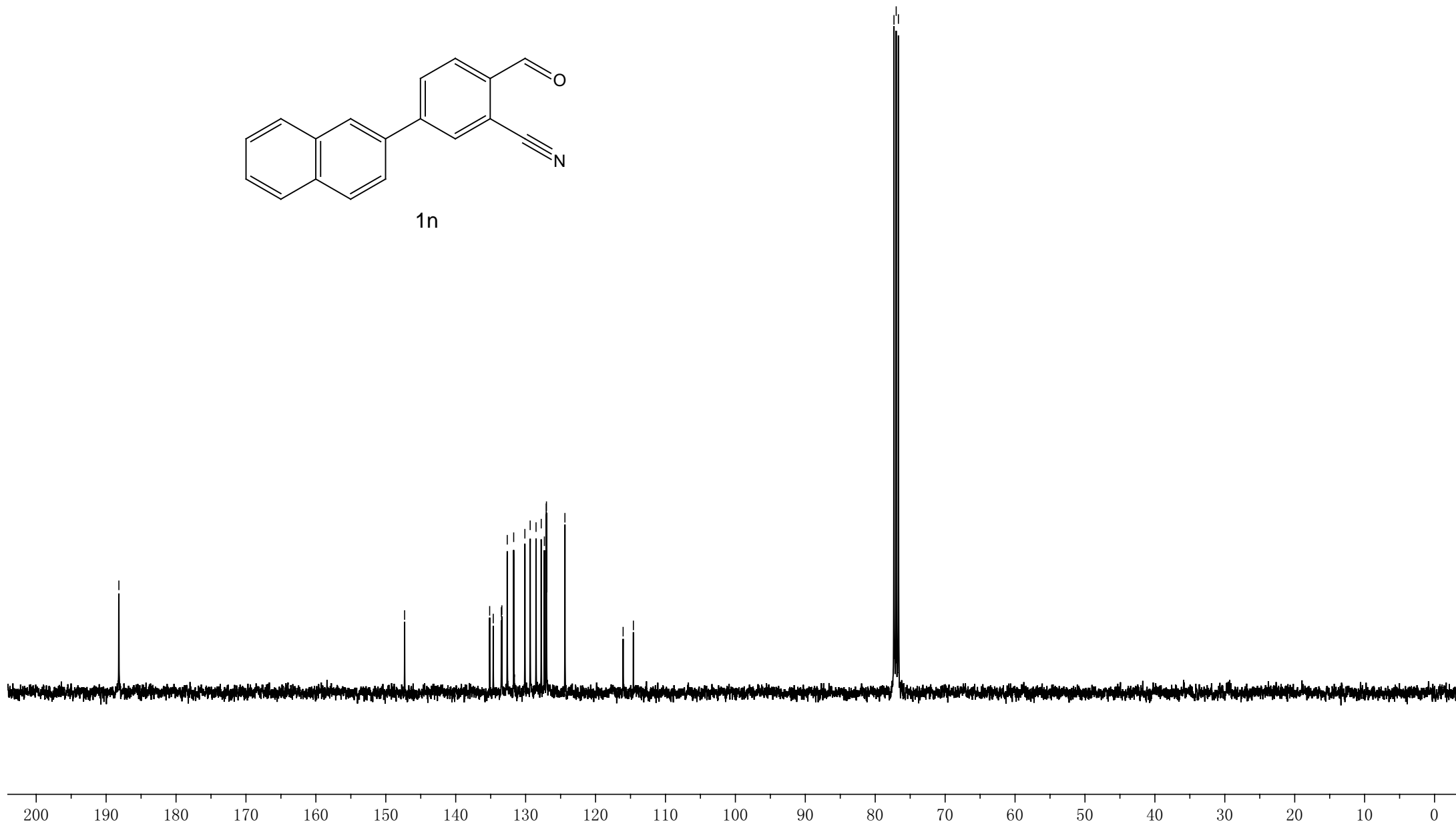
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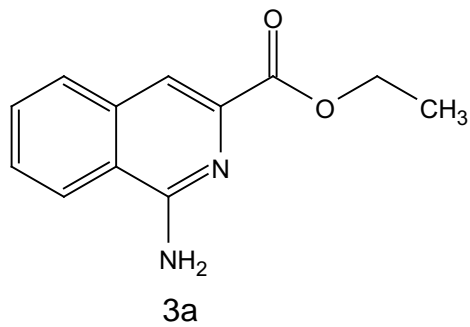
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76.682



1n



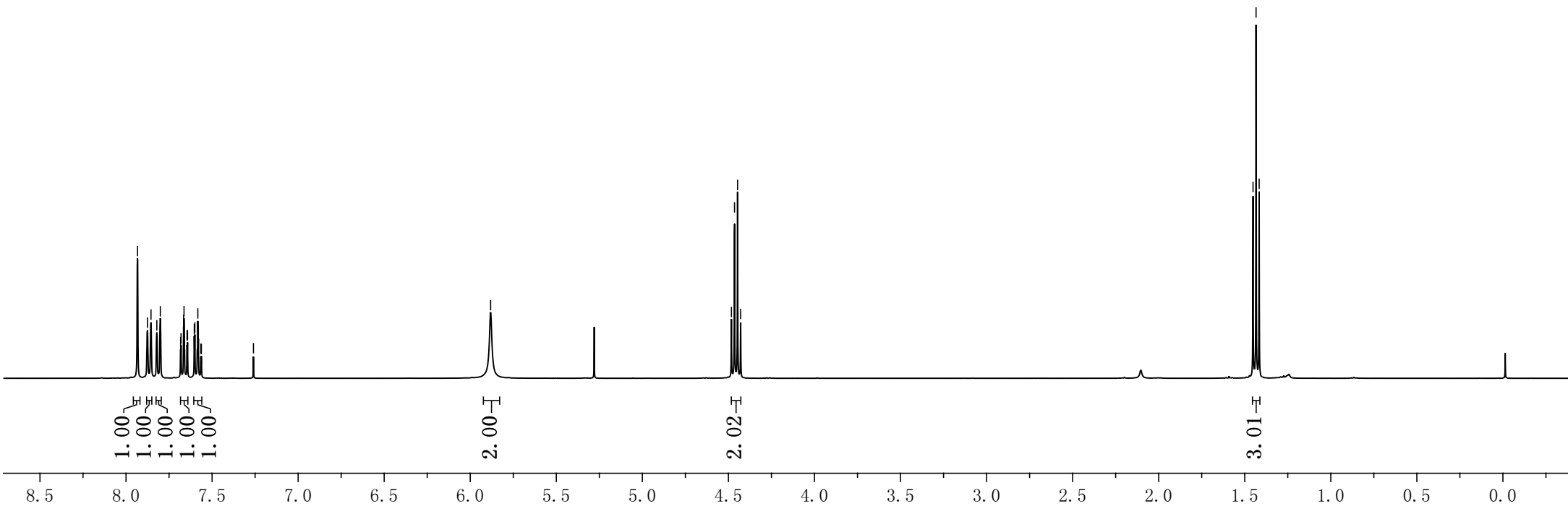


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7.663  
7.603  
7.600  
7.583

5.882

4.482  
4.465  
4.447  
4.429

1.452  
1.434  
1.416



—166.088

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—140.048

—136.769

~130.595

~128.554

~128.272

~122.754

~119.406

~115.782

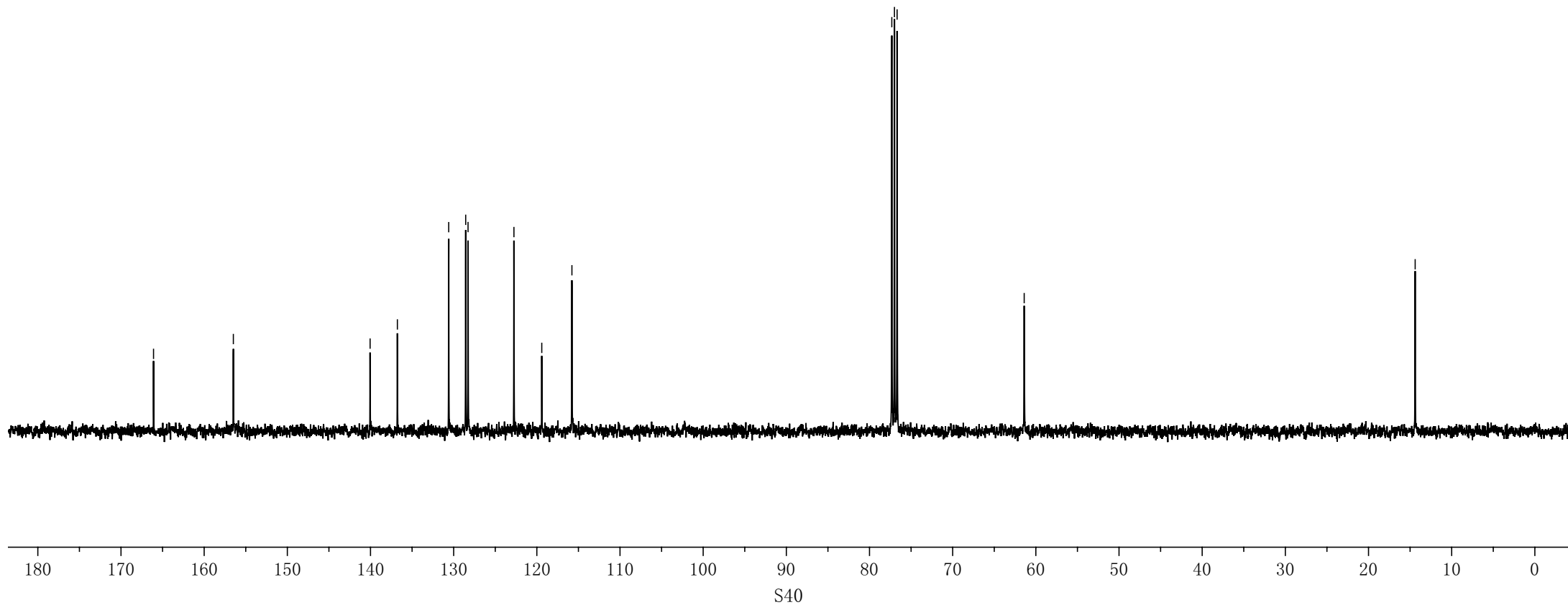
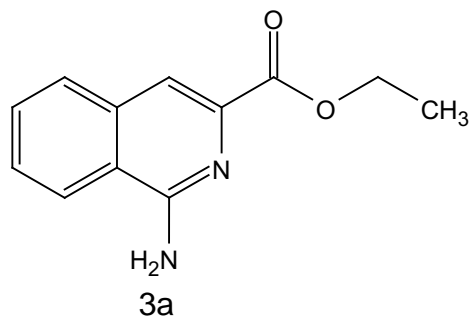
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—14.390



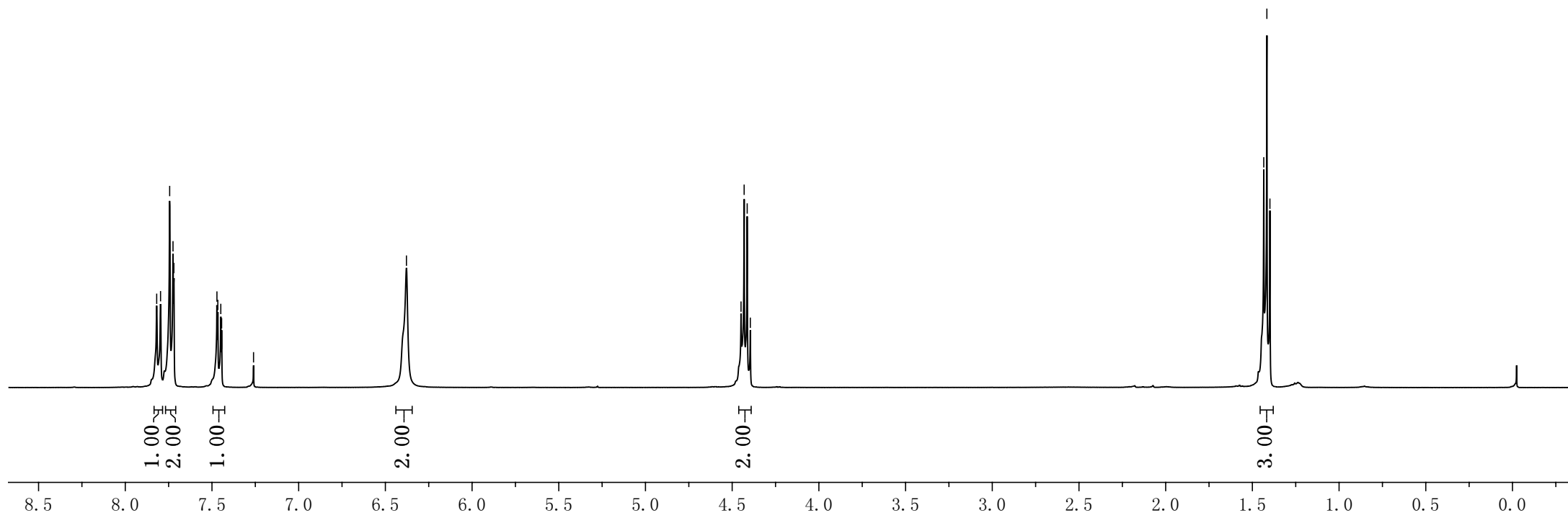
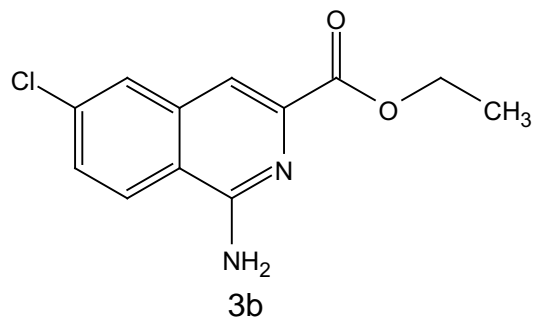


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7.444  
7.260

6.379

4.449  
4.431  
4.413  
4.395

1.434  
1.416  
1.399



1.00H  
2.00H

1.00H

2.00H

2.00H

3.00H

—165.689

—156.739

~141.081

~137.810

~136.746

~128.723

~127.145

~124.604

—117.442

—114.193

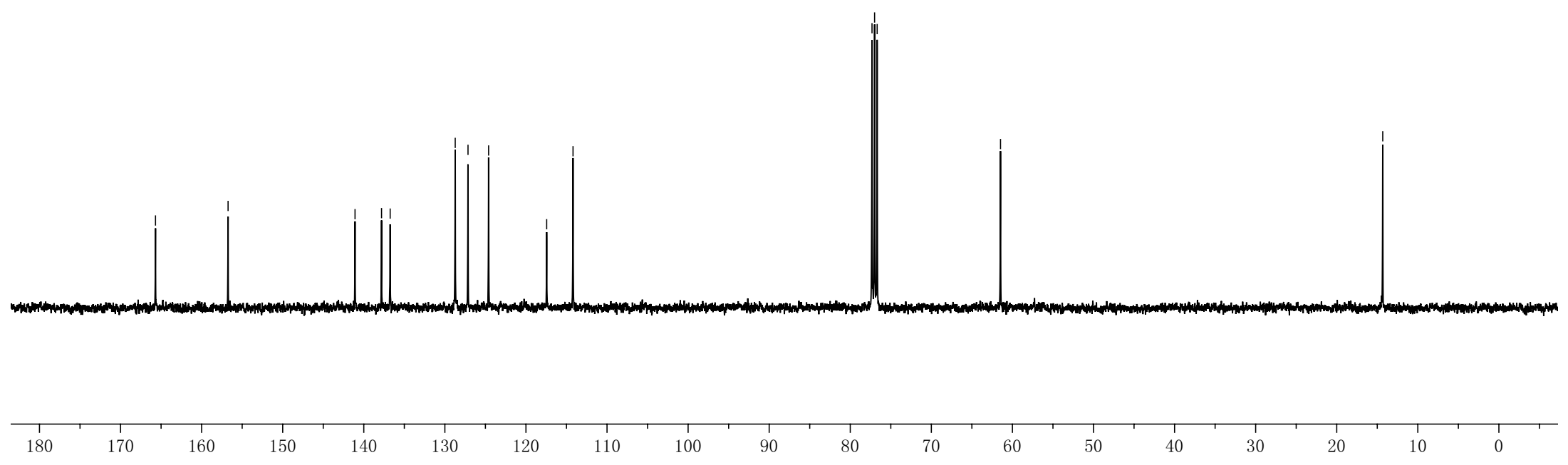
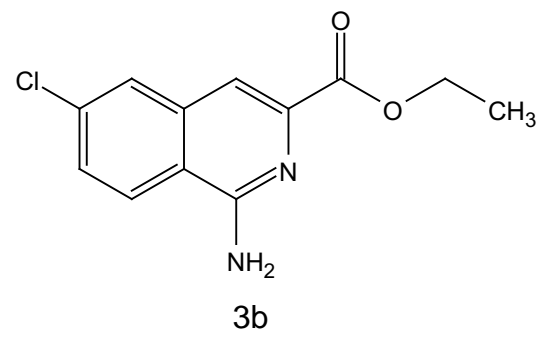
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77.000

76.682

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—14.324

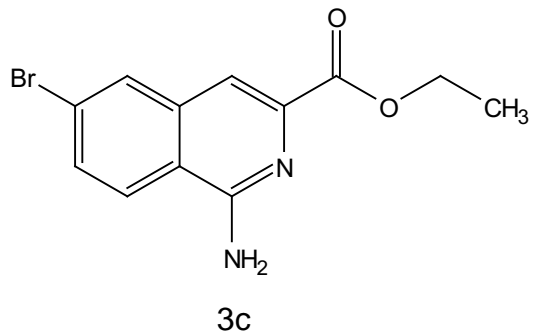


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7.662  
7.657  
7.260

5.764

4.489  
4.471  
4.453  
4.436

1.458  
1.440  
1.422



1.00  
1.00  
1.00  
1.00

2.00

2.00

3.00

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

S43

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—141.349

—138.296

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—130.694

—125.375

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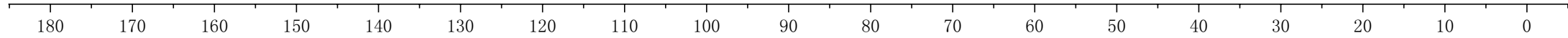
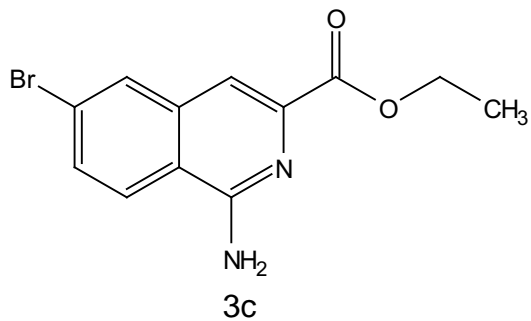
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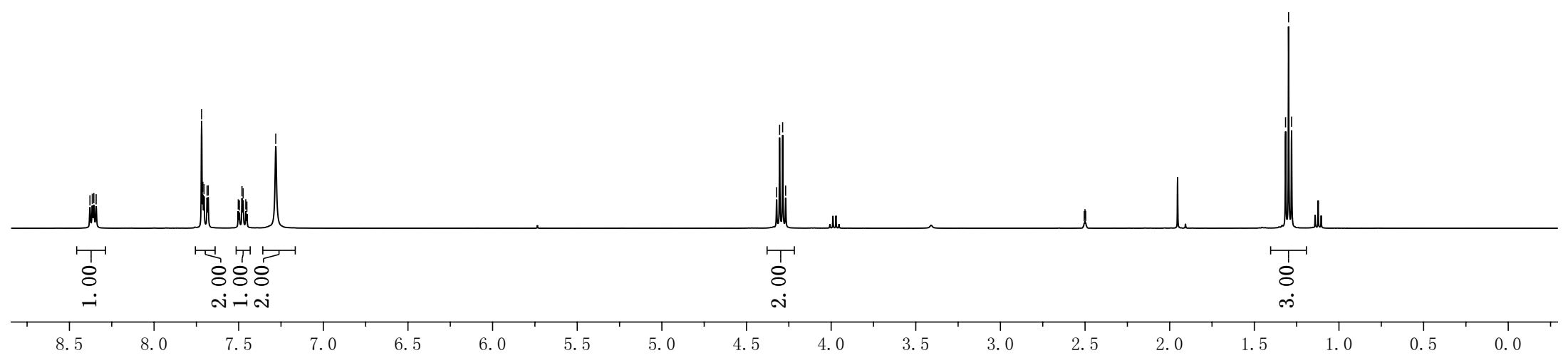
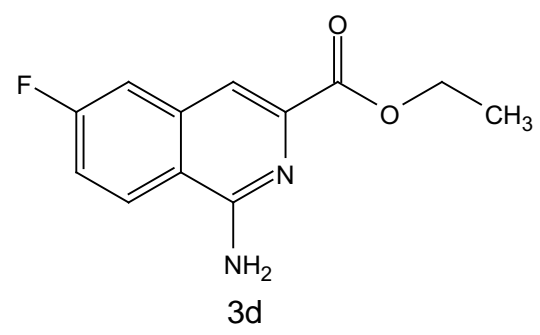


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7.503  
7.496  
7.481  
7.474  
7.458  
7.452  
7.281

4.322  
4.304  
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1.280



165.737  
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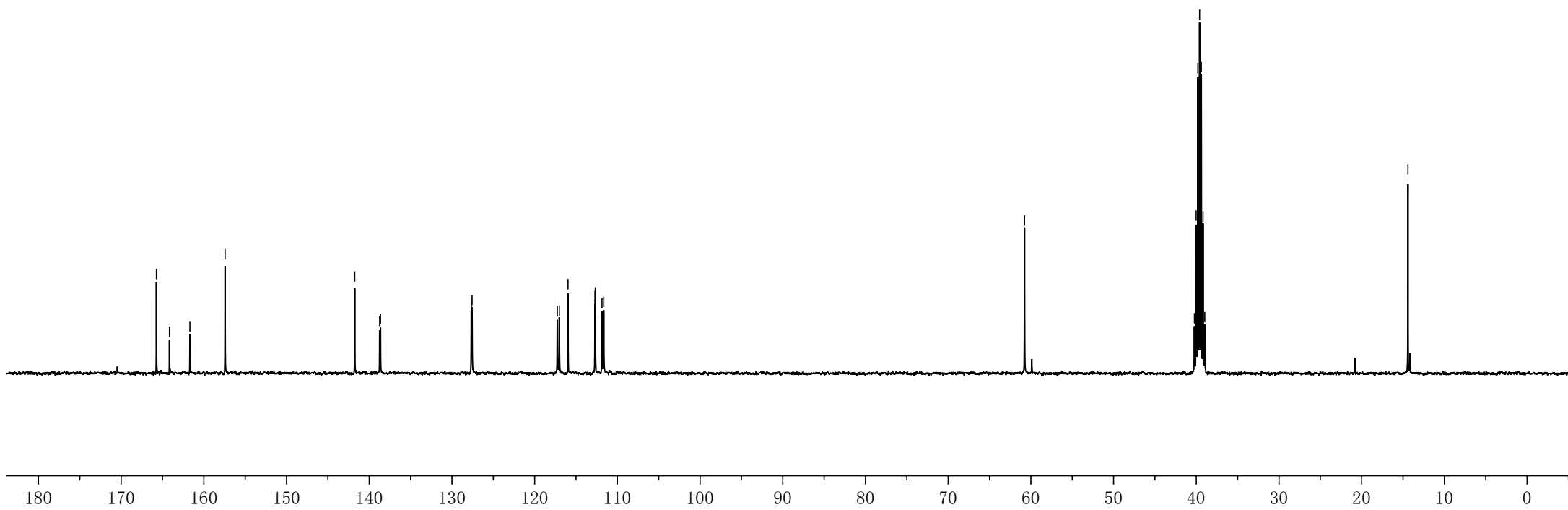
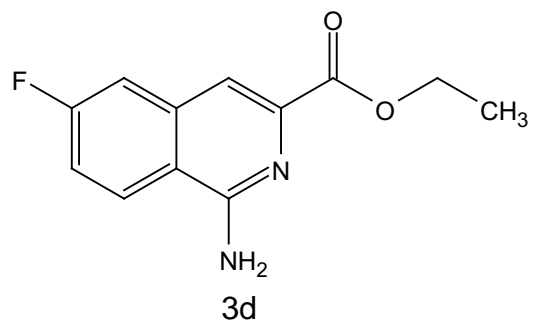
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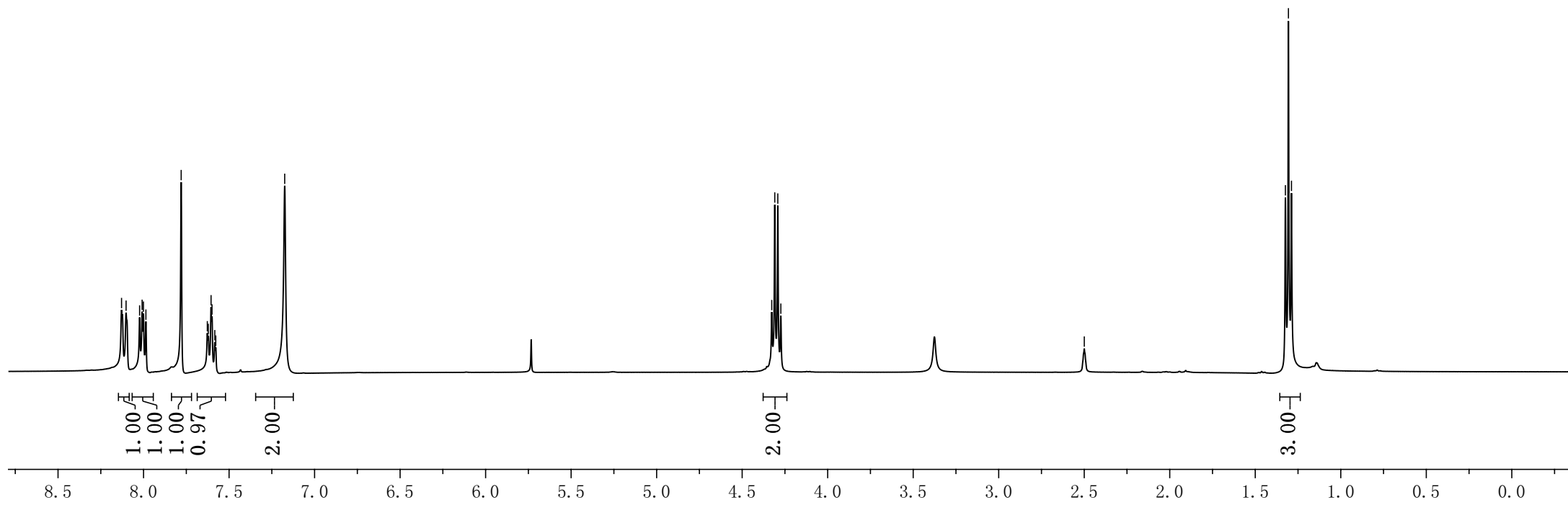
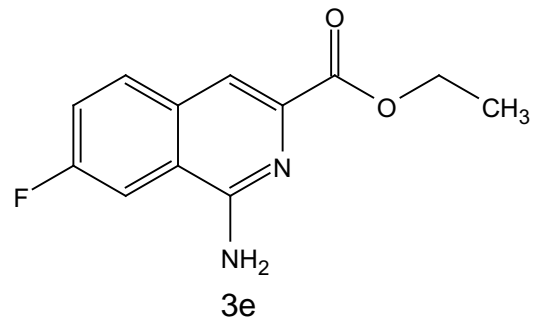


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7.621  
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4.274

2.500

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1.306  
1.288



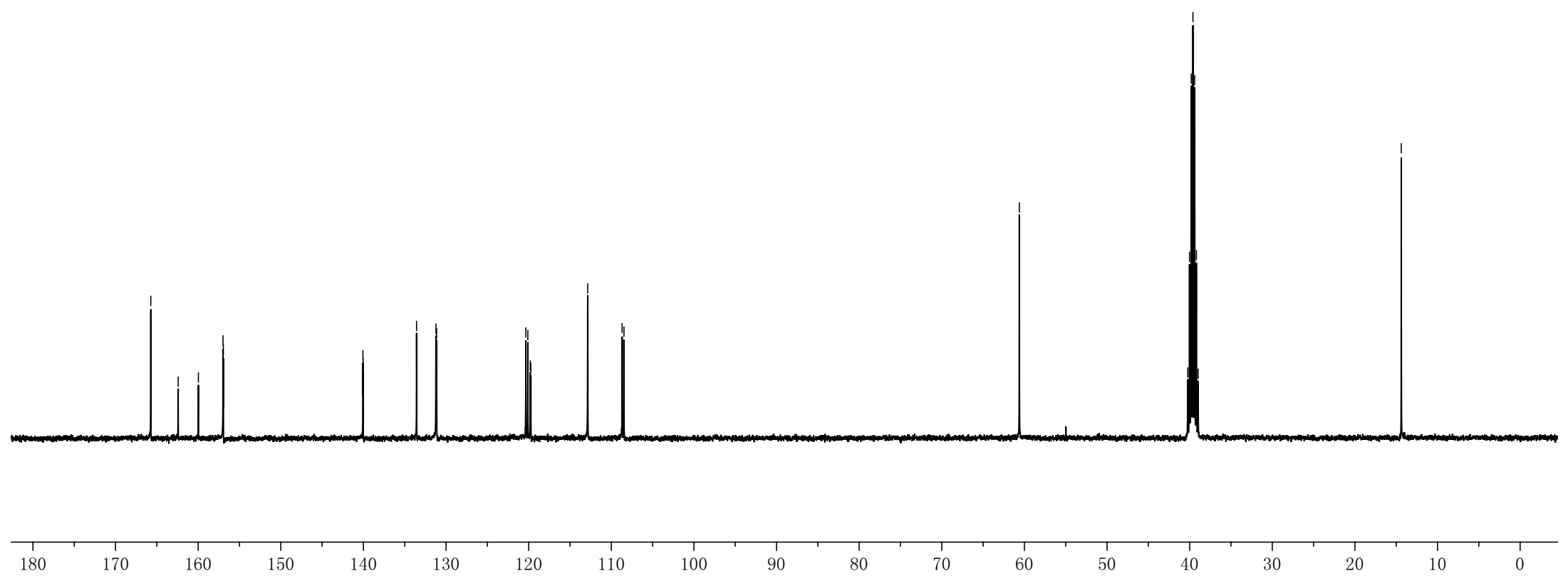
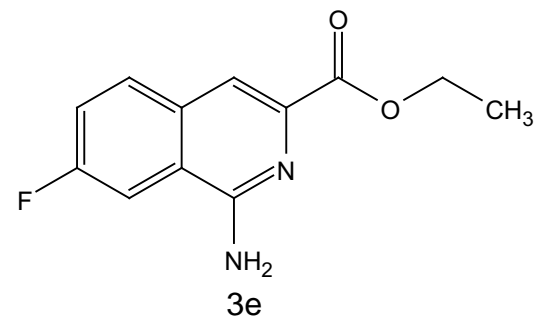
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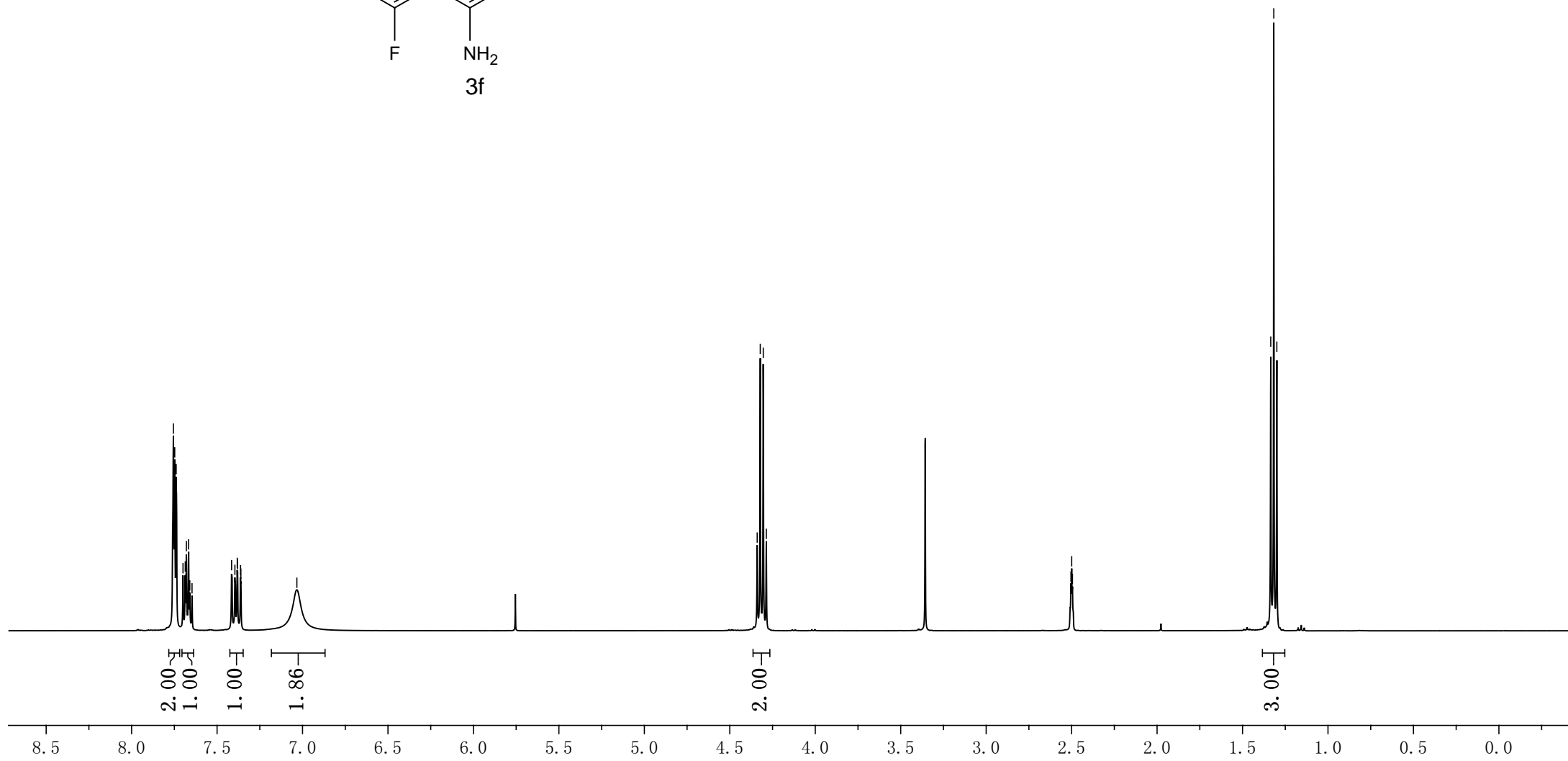
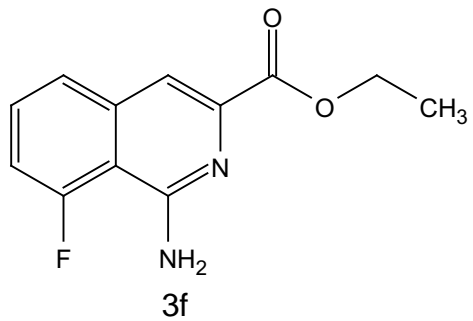


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1.00  
1.86

2.00

3.00

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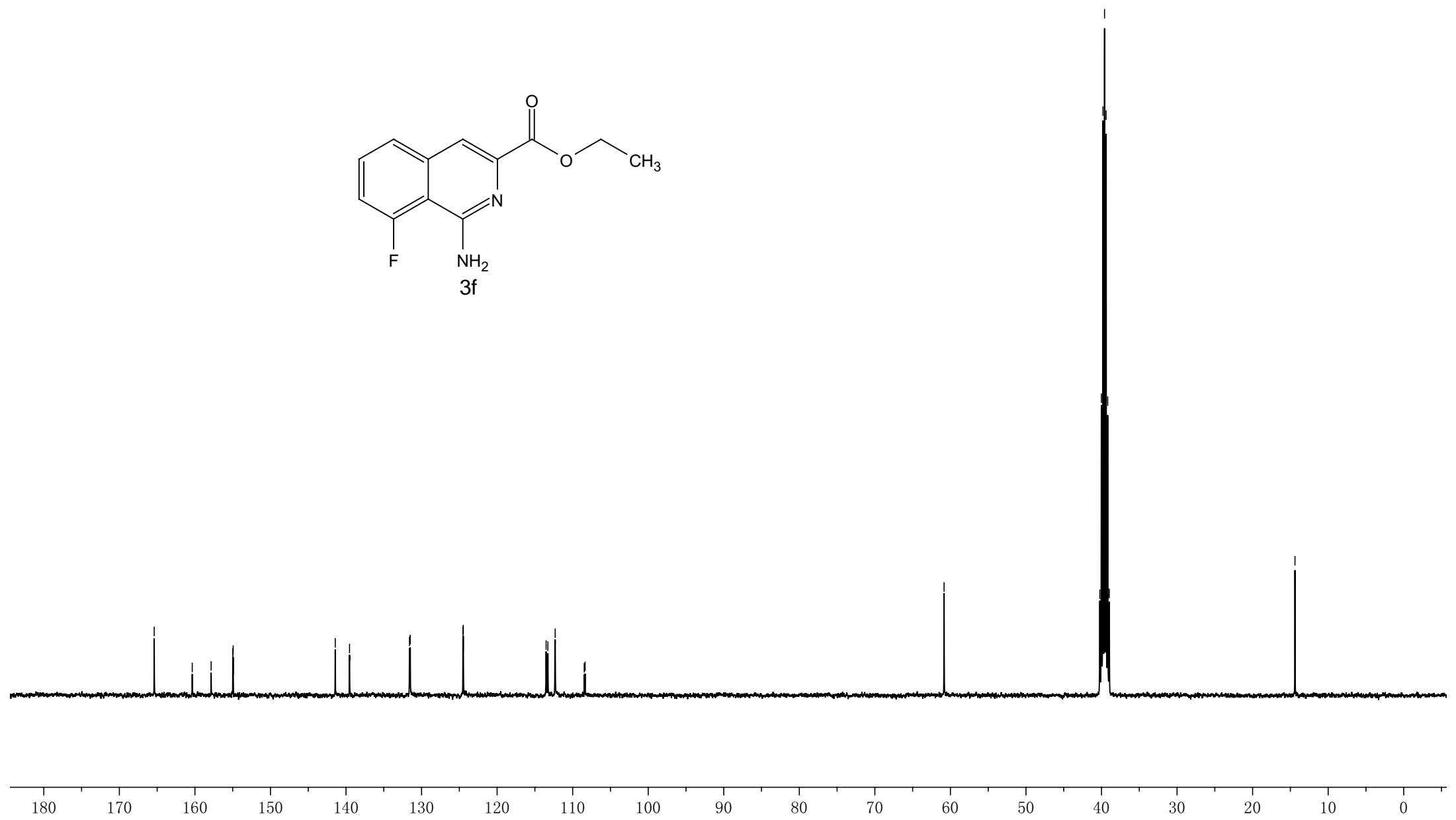
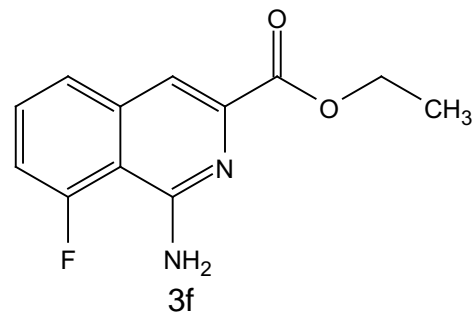
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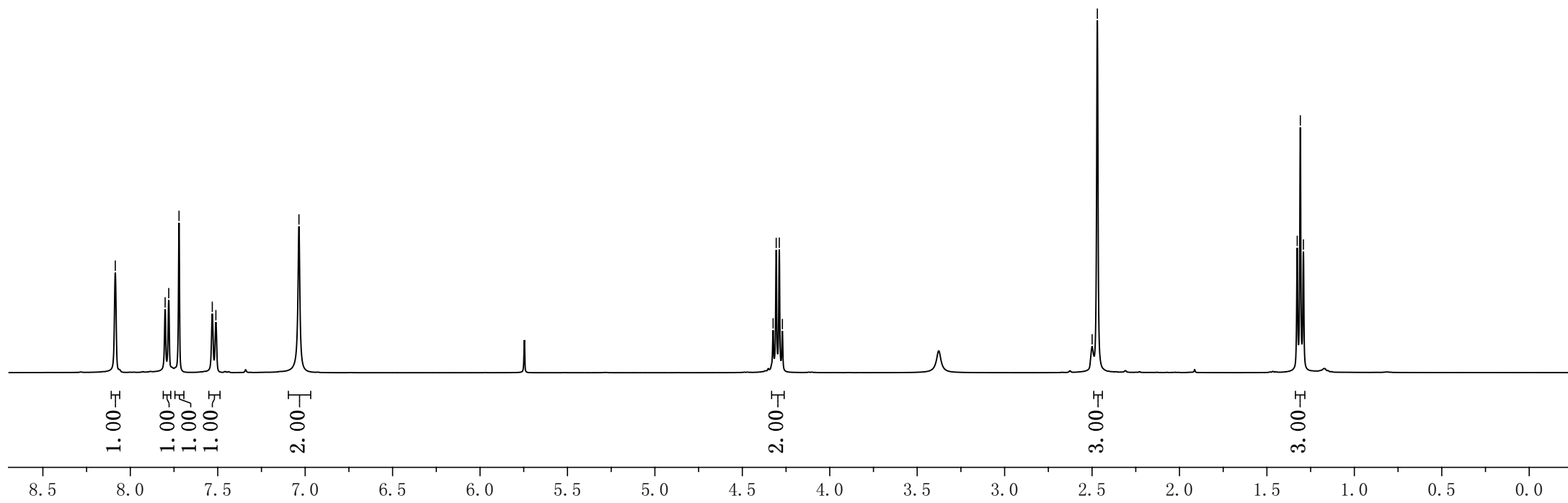
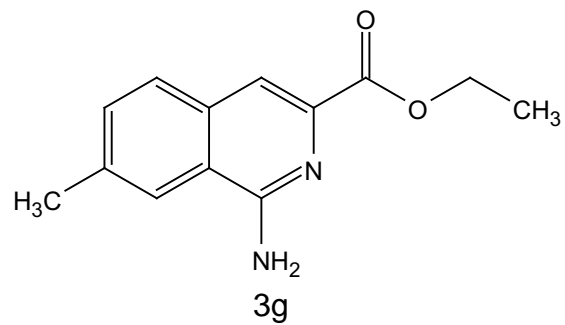


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2.500  
2.470

1.327  
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—165.889

—156.904

—139.591

—137.747

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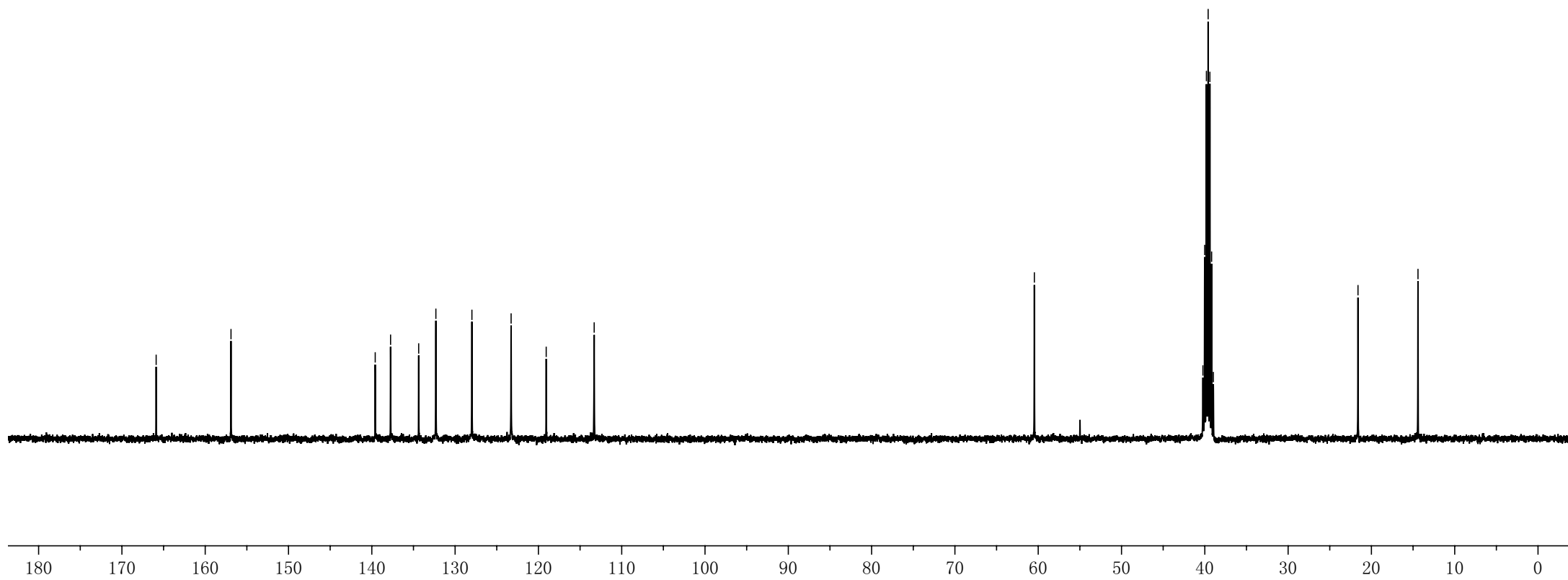
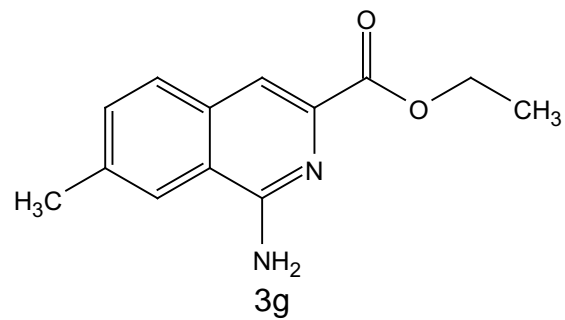
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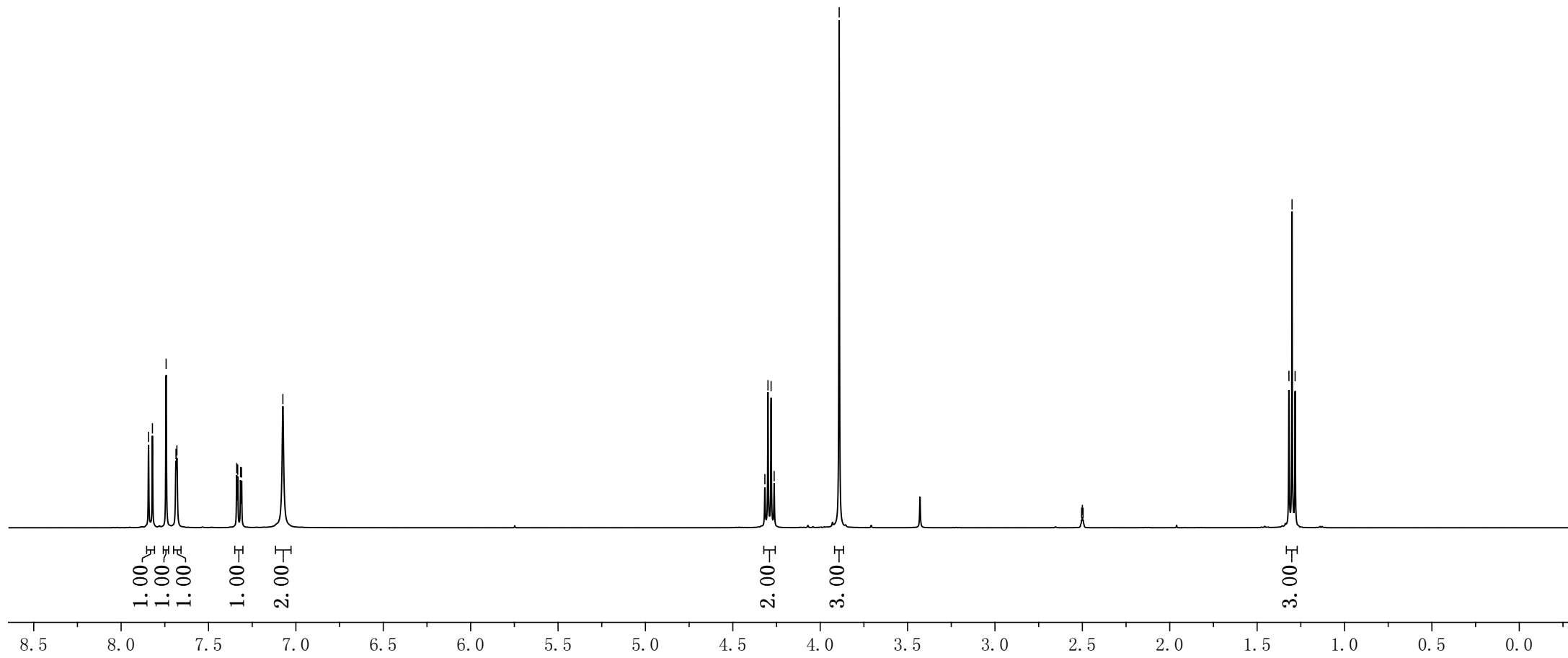
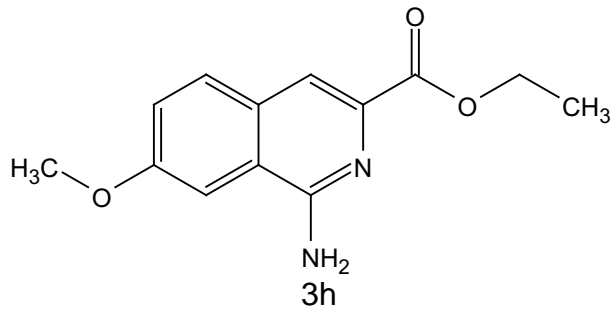


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4.317  
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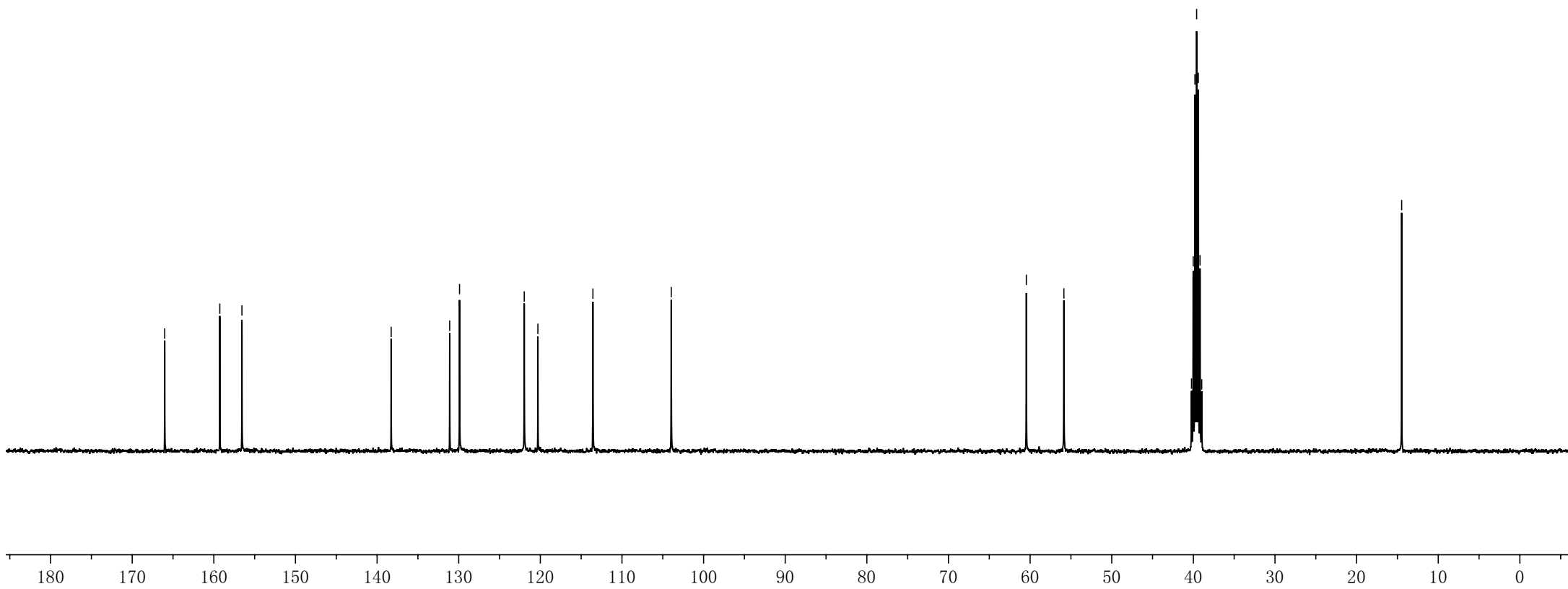
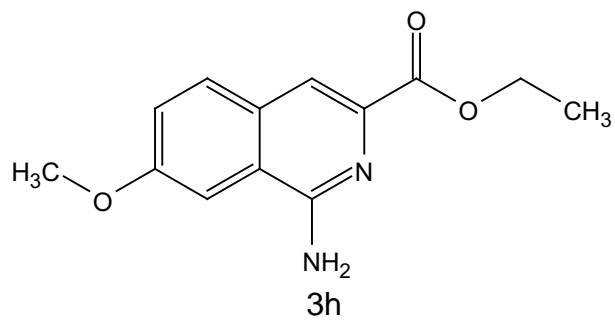
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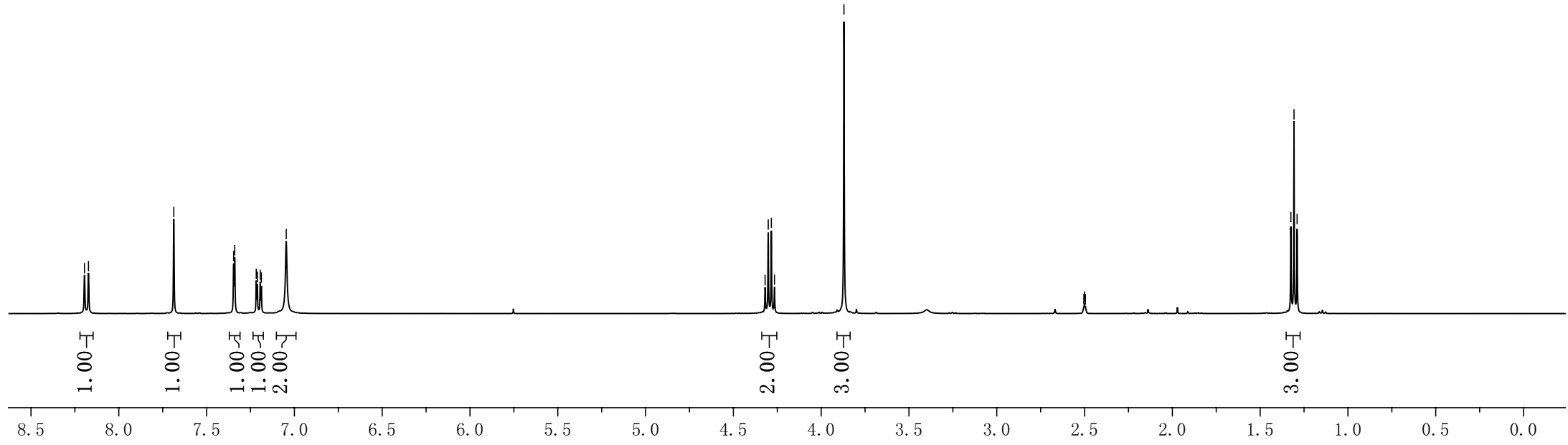
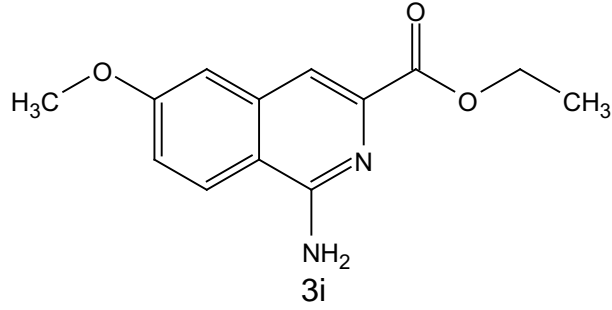


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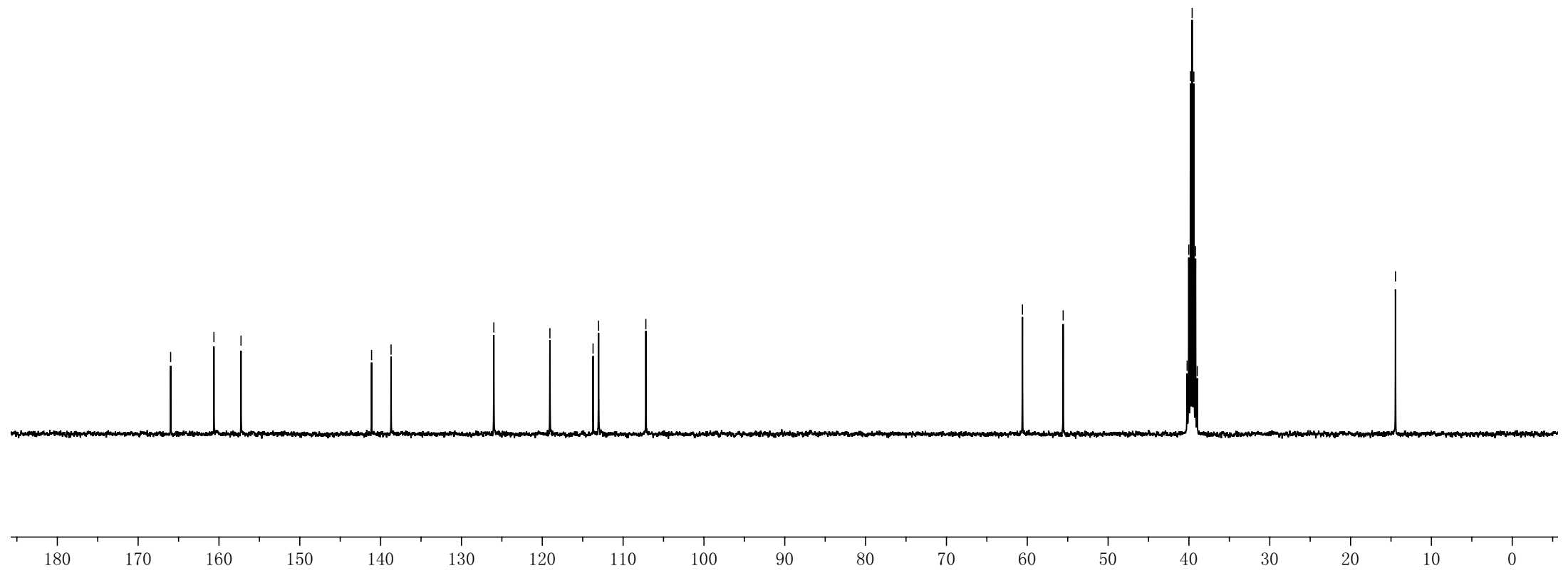
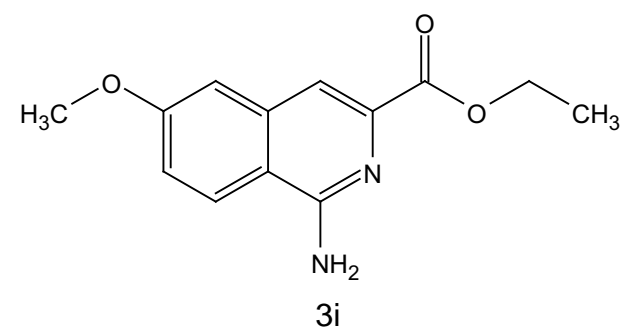
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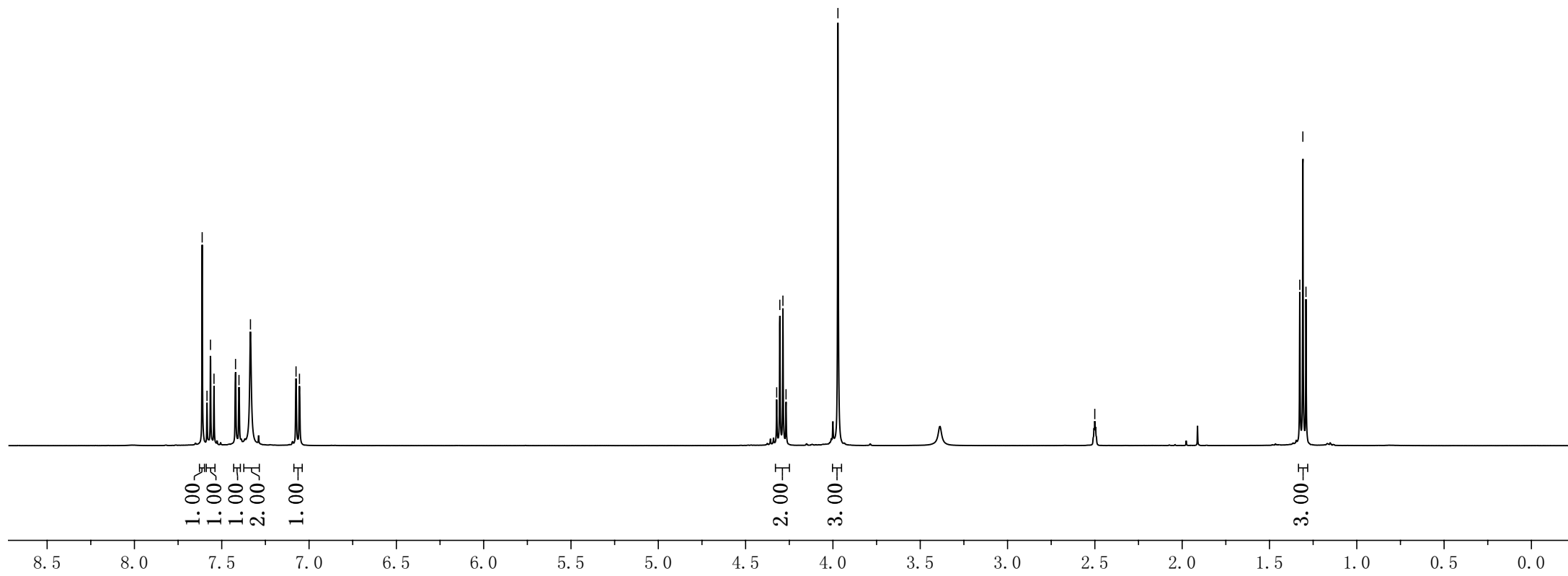
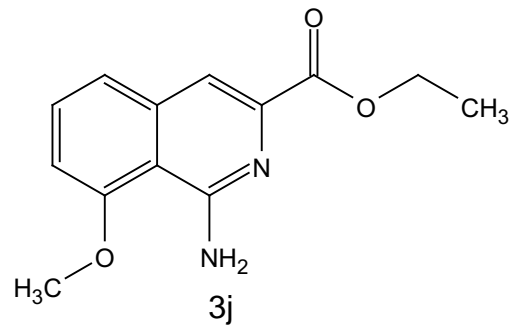


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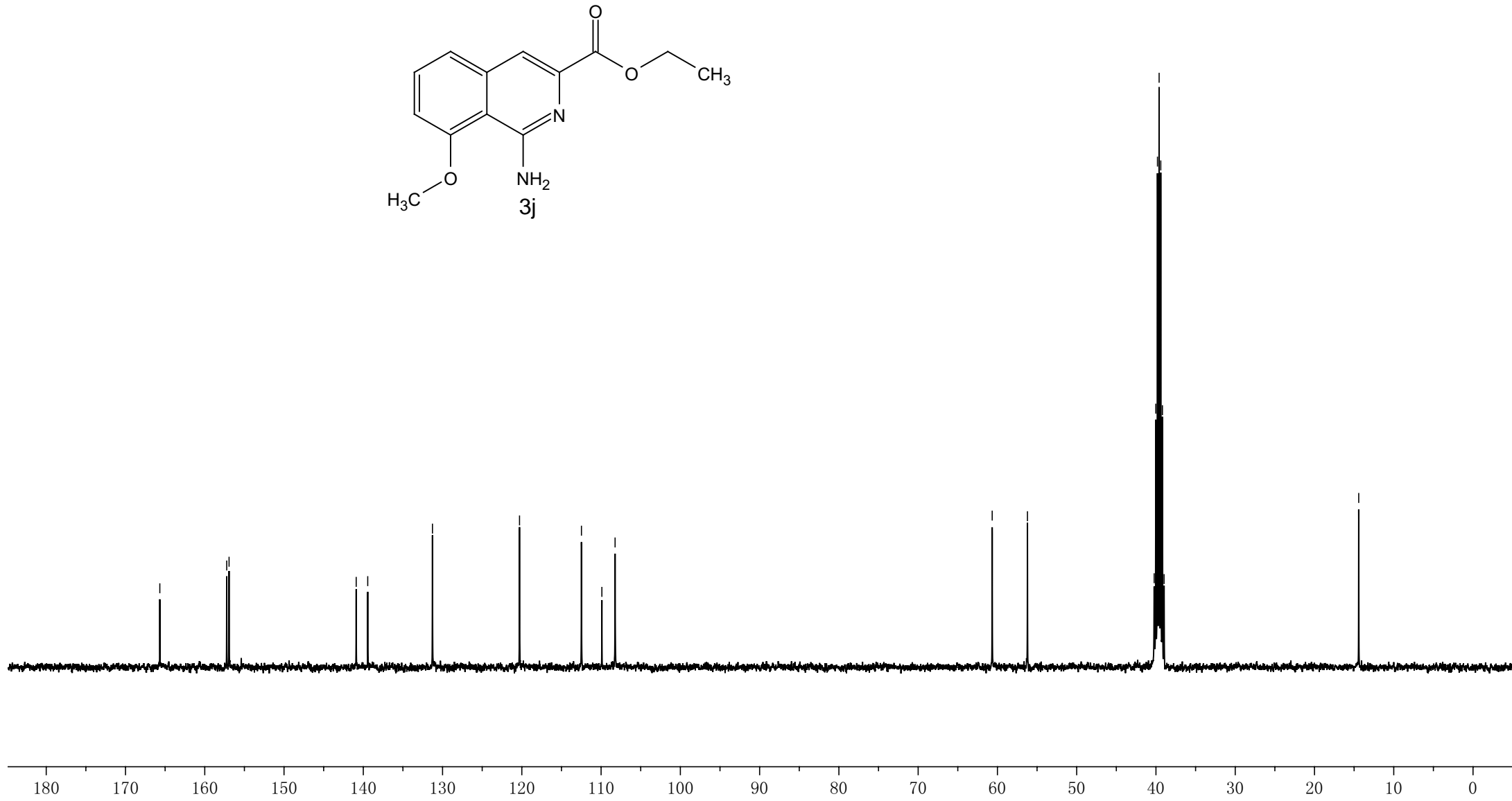
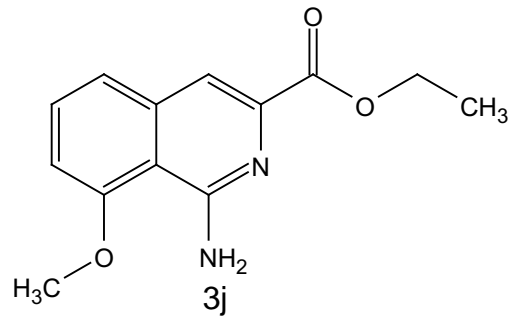
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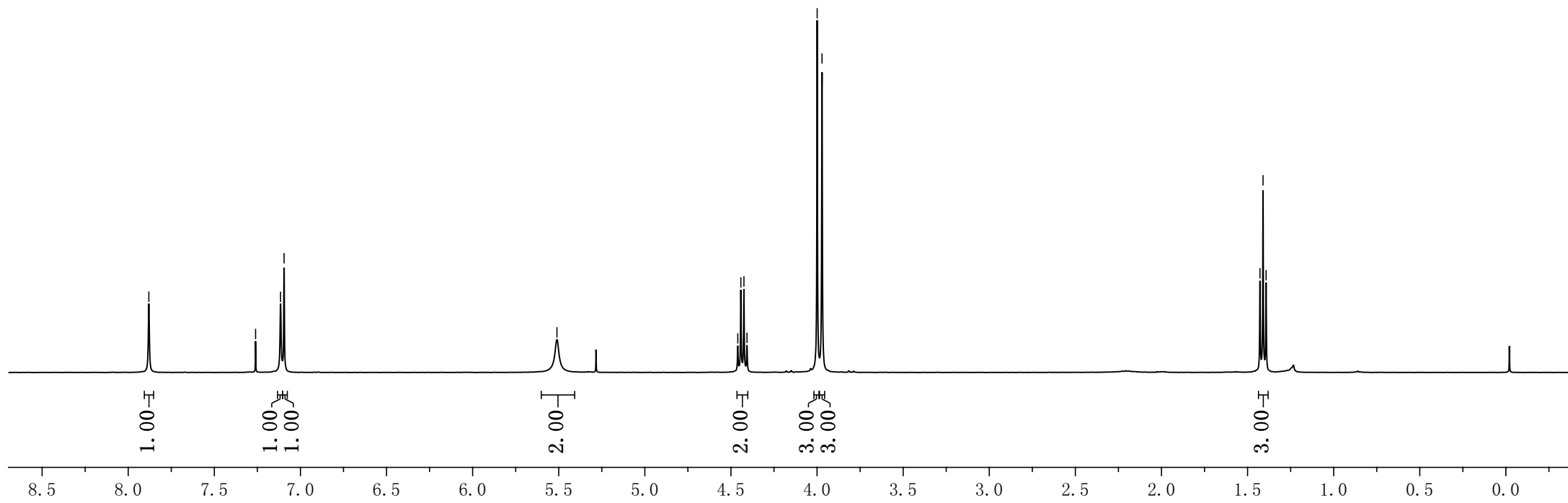
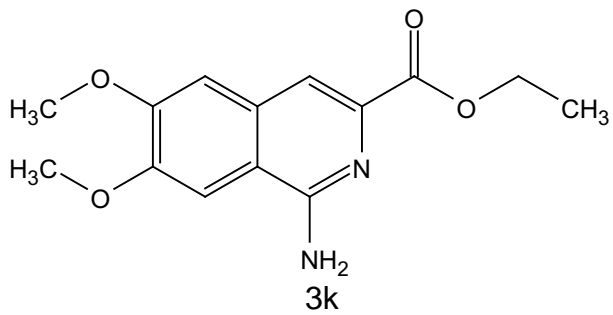
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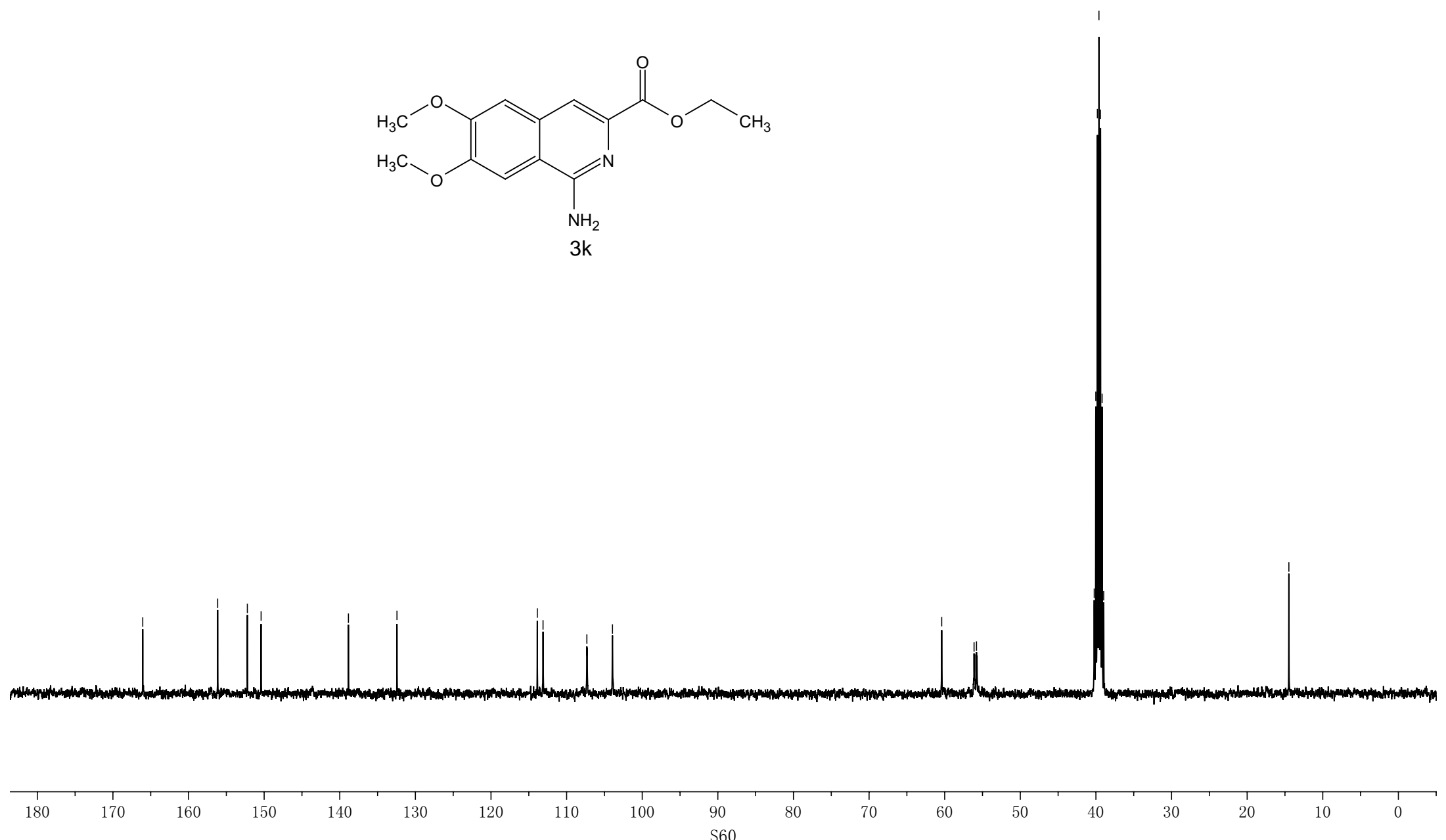
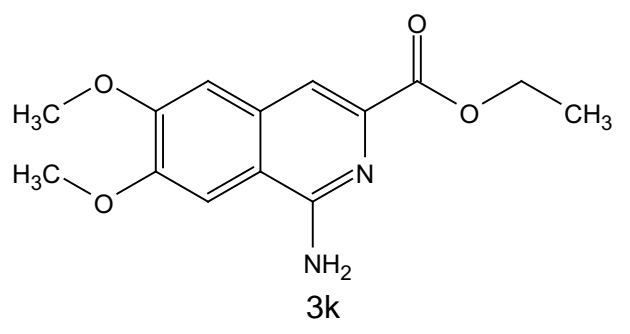
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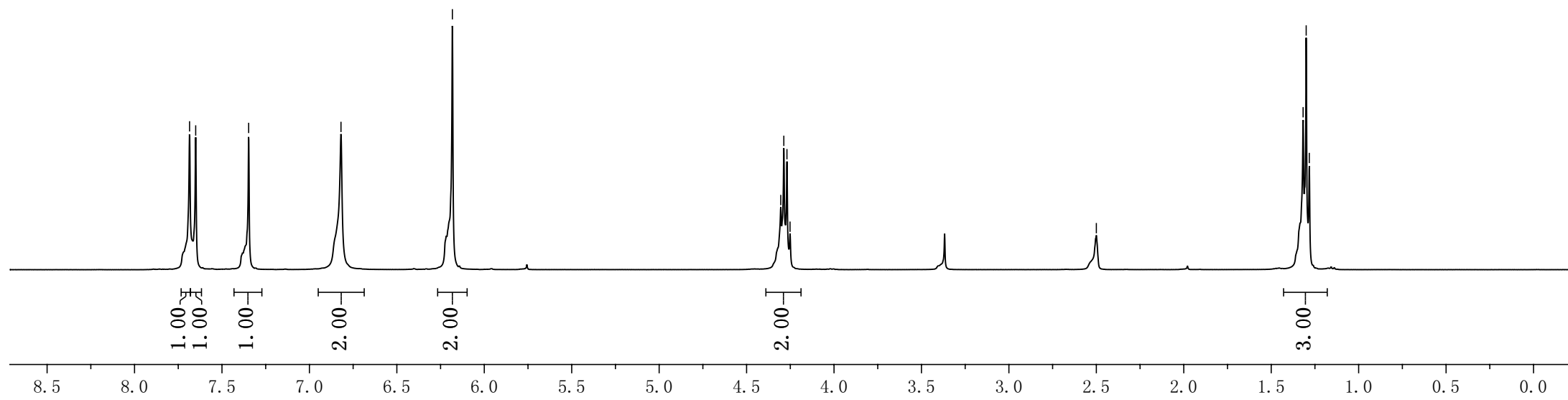
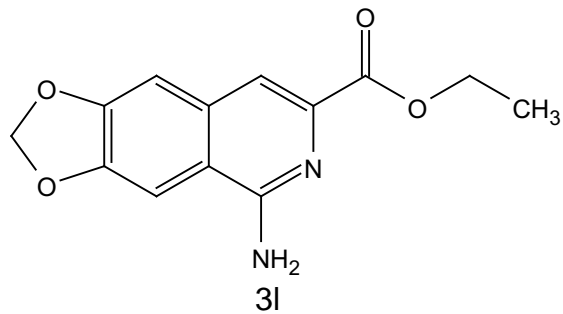
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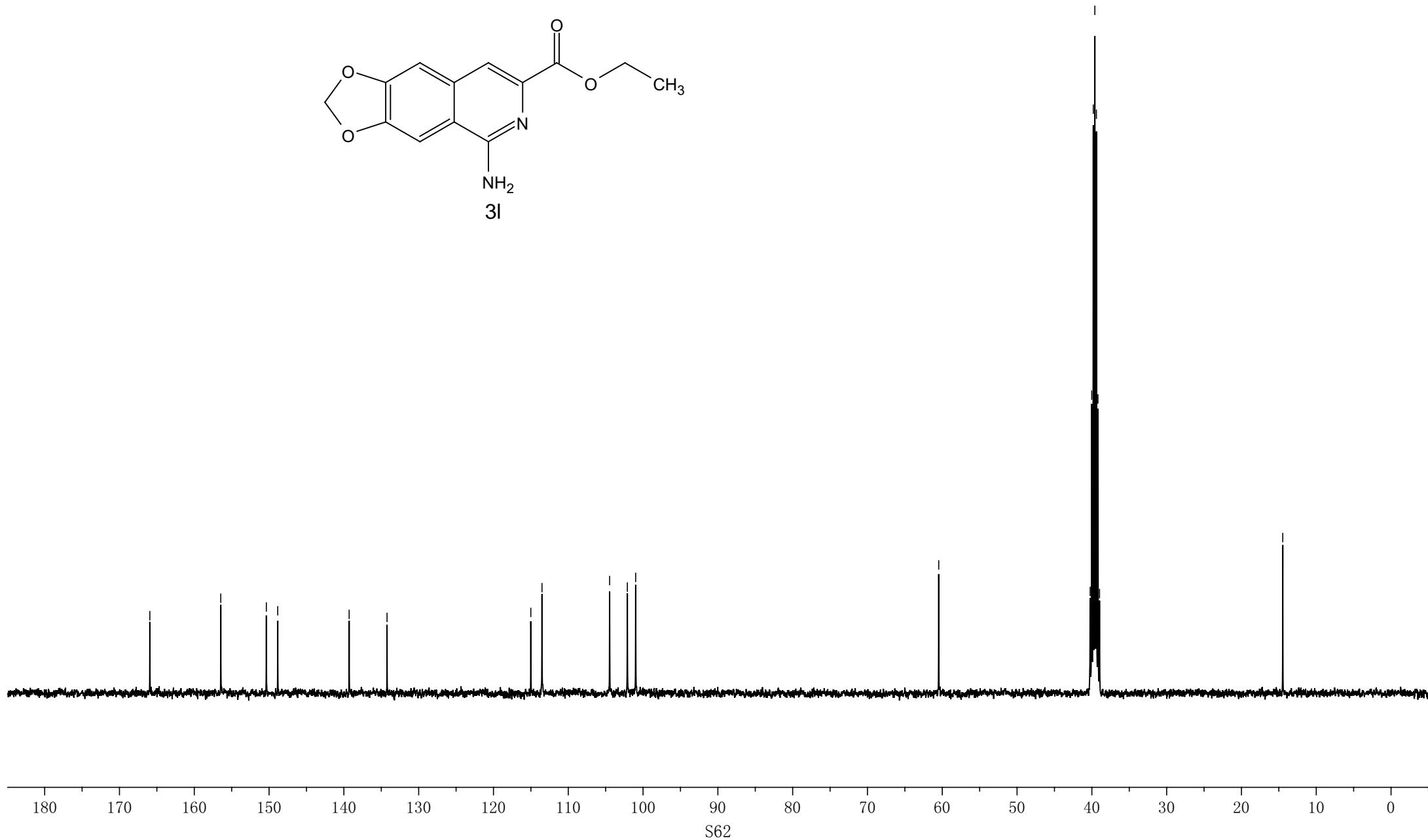
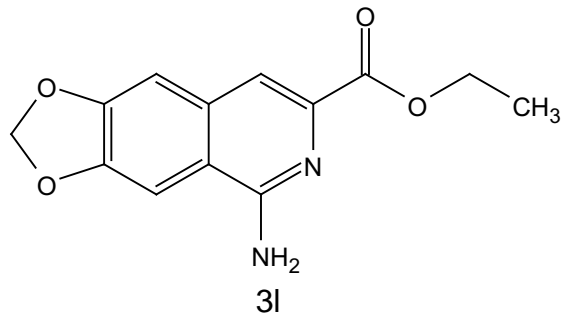
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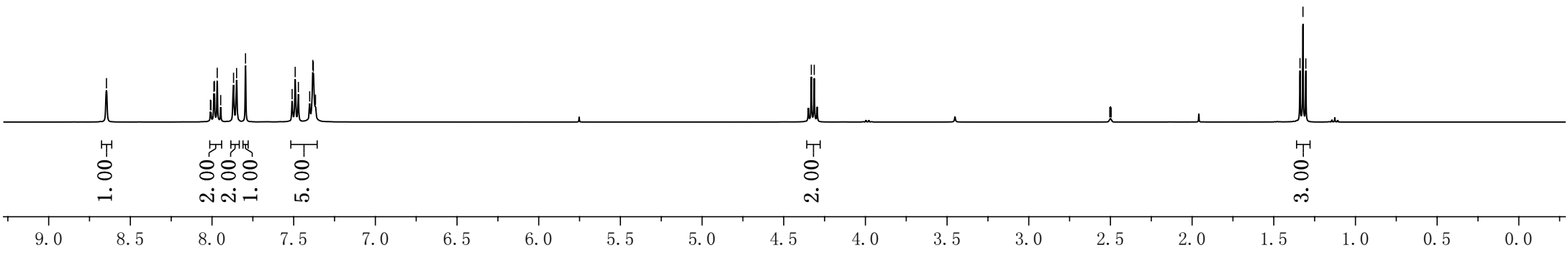
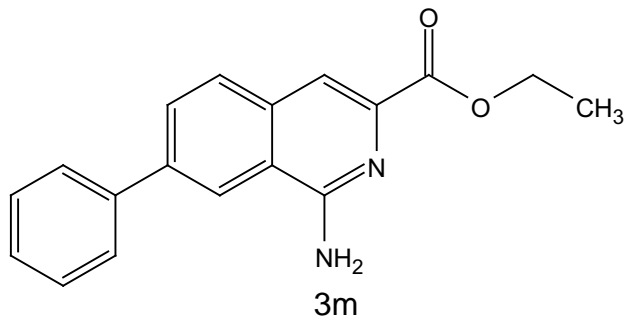


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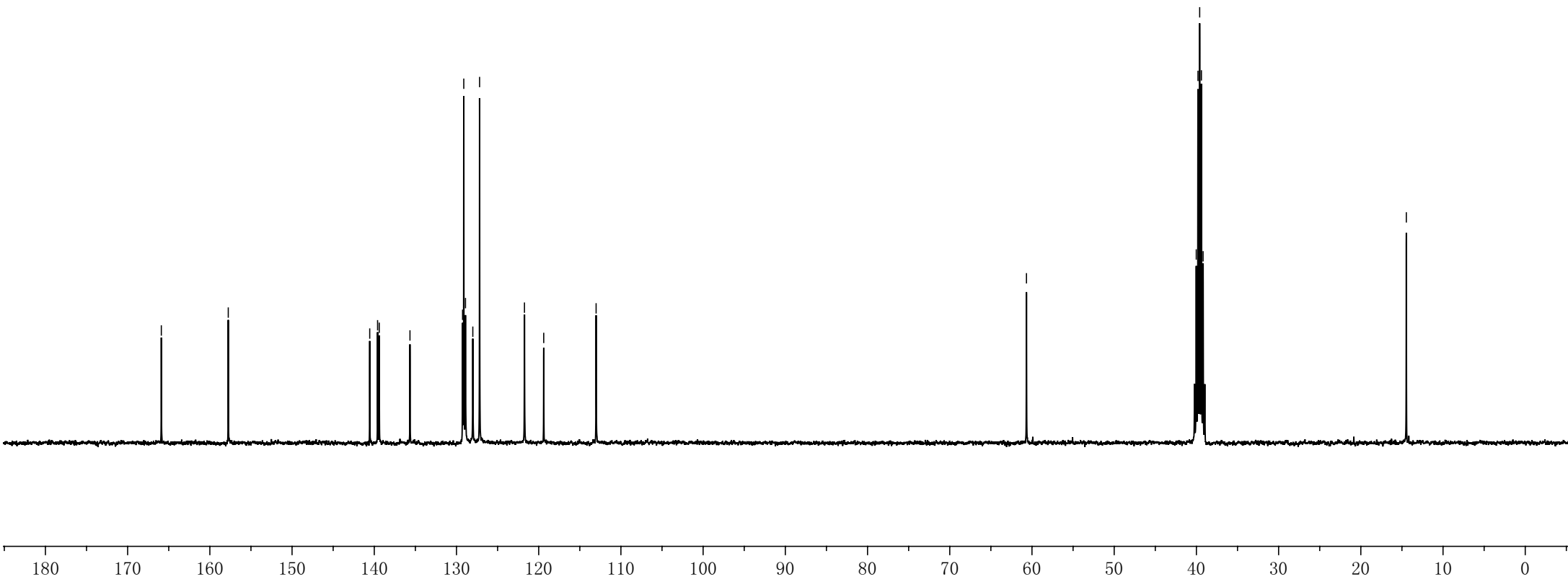
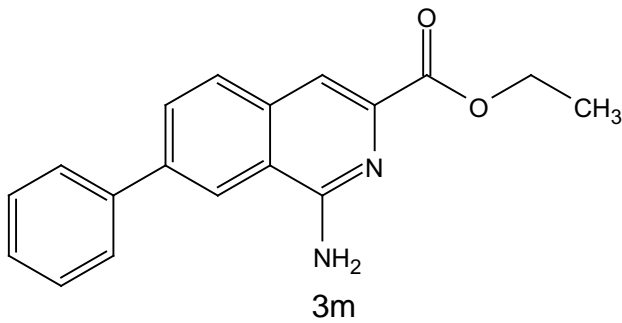
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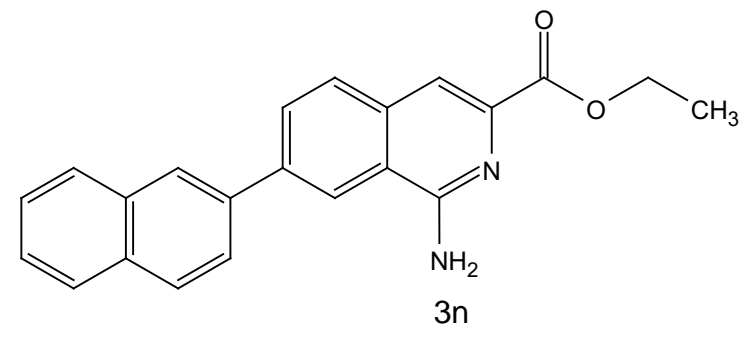




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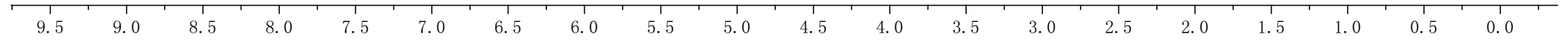
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3.00



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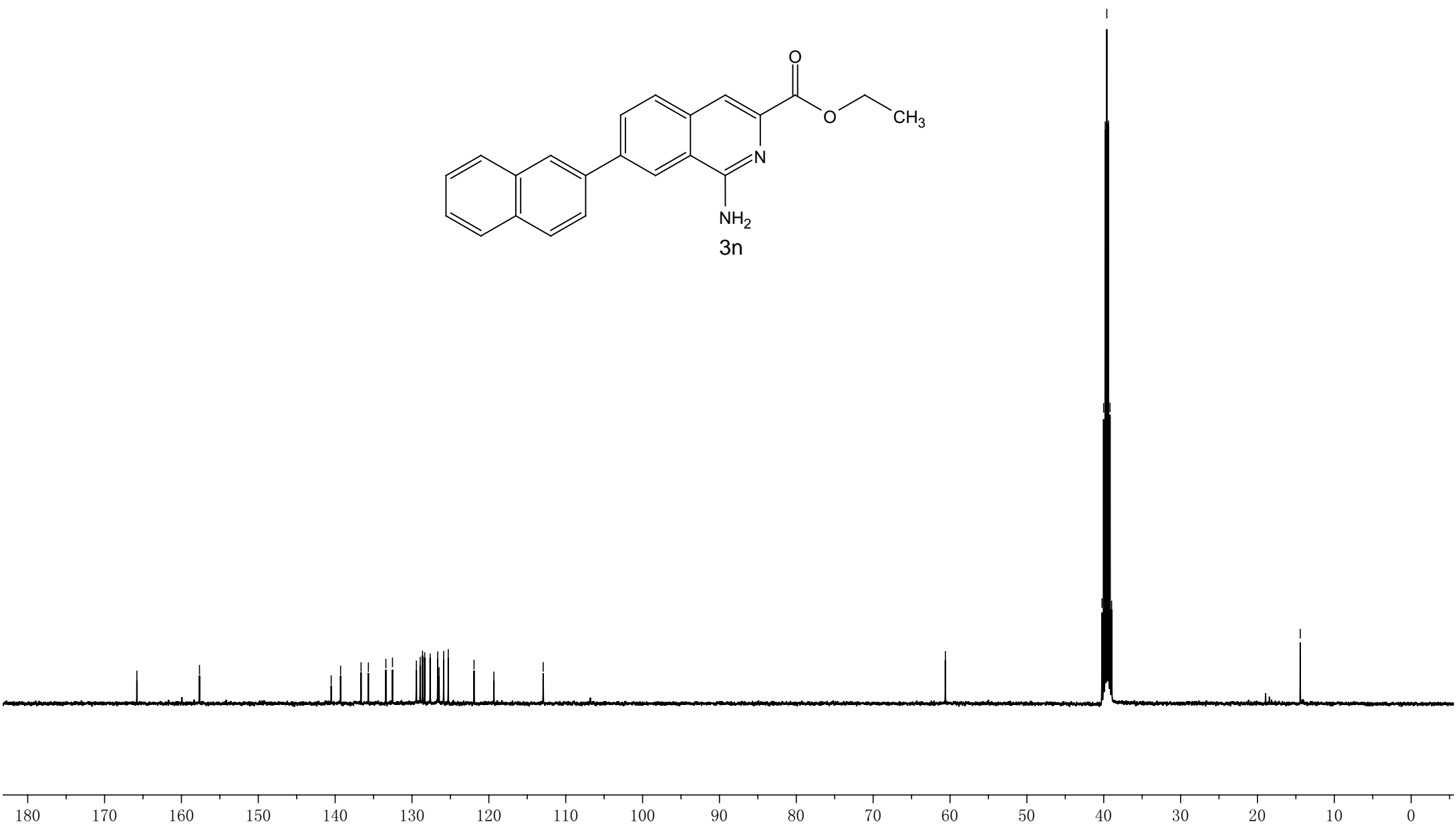
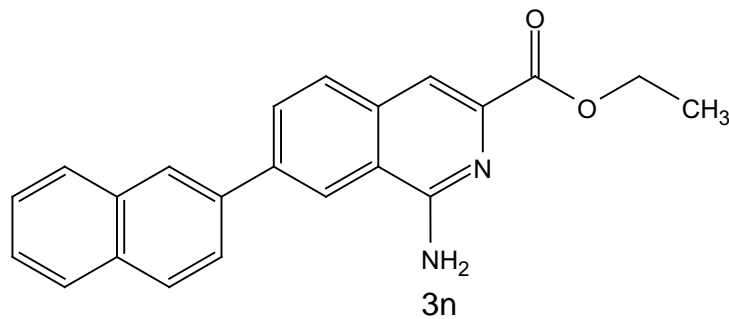
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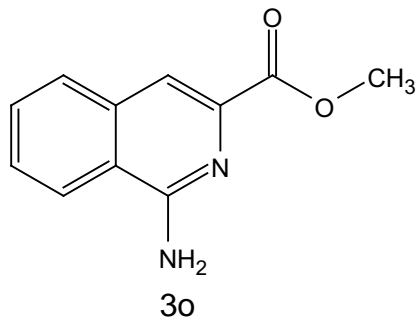
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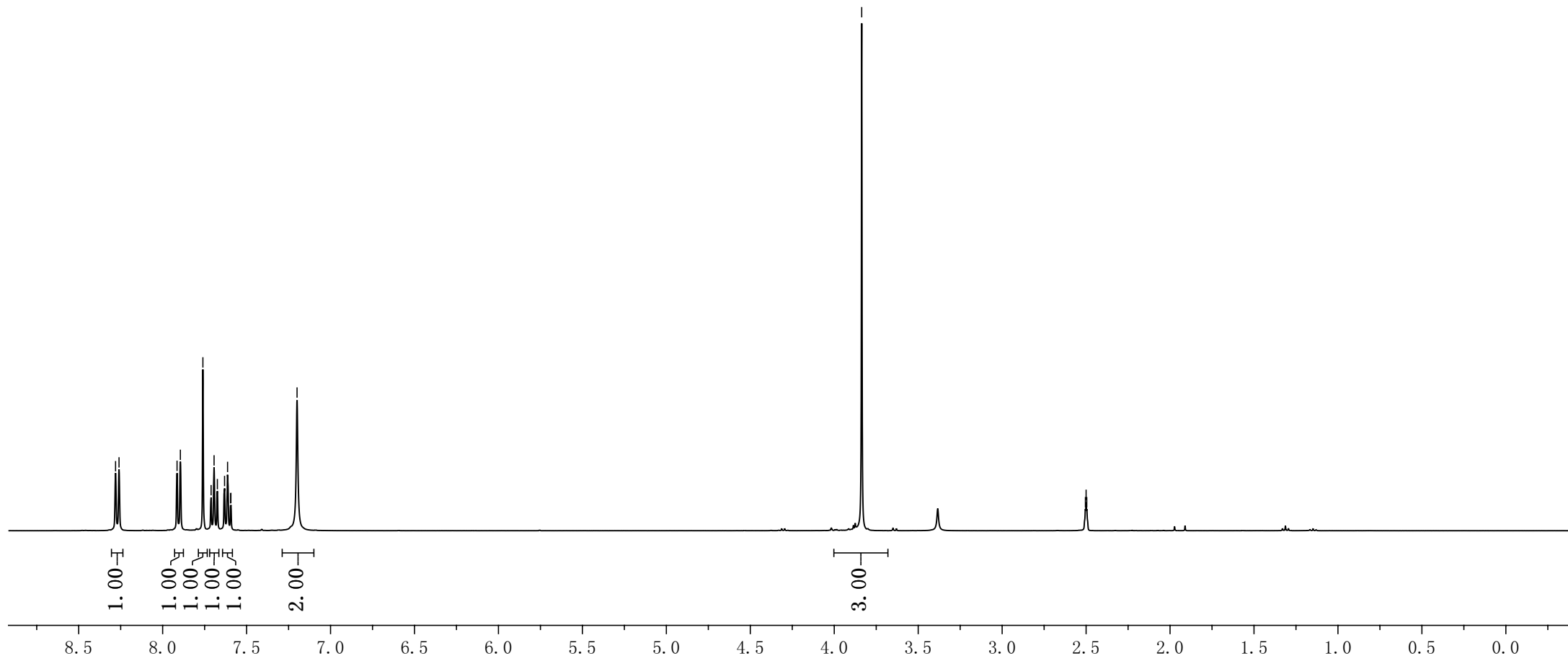


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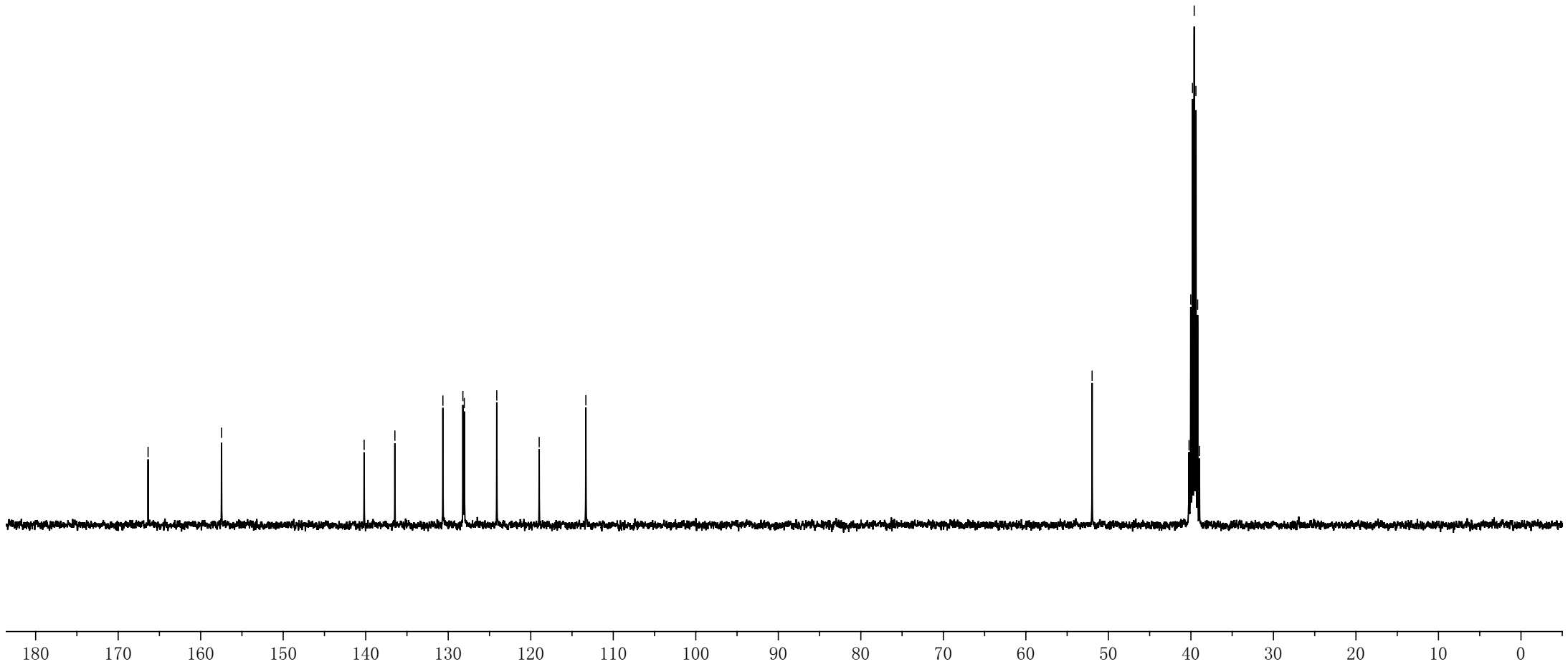
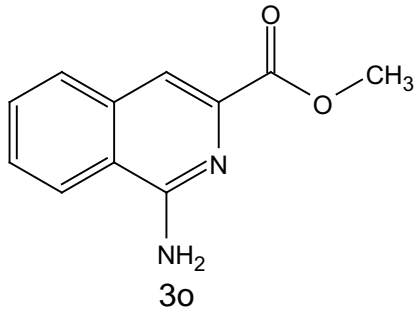
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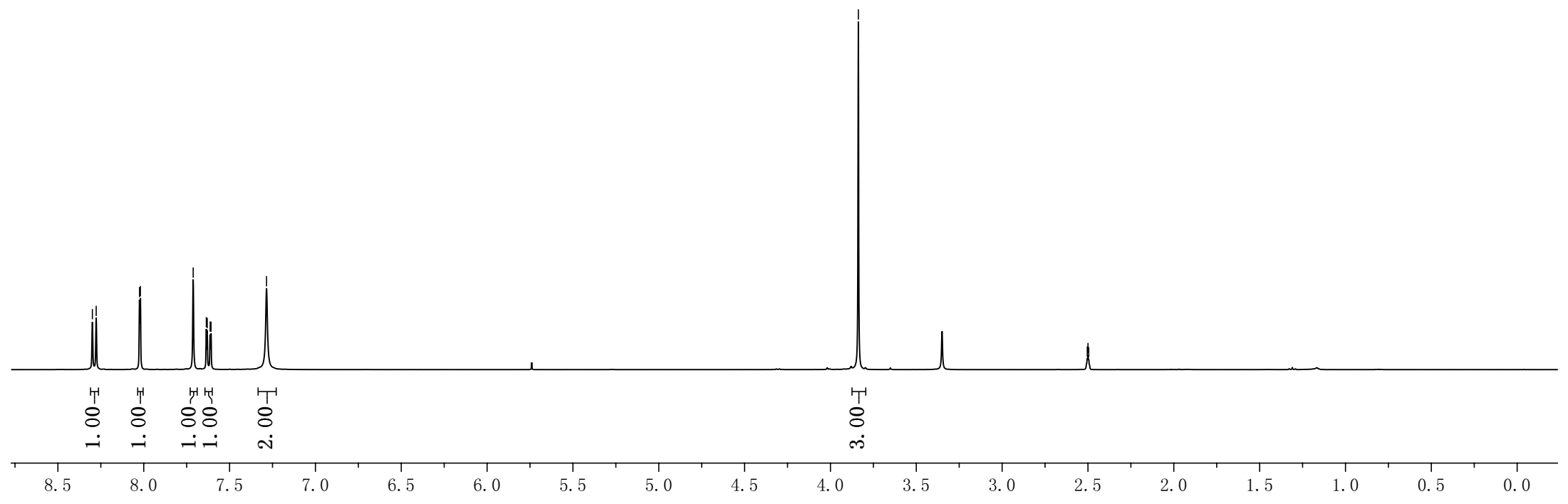
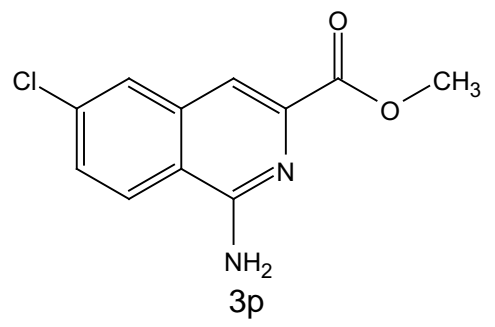
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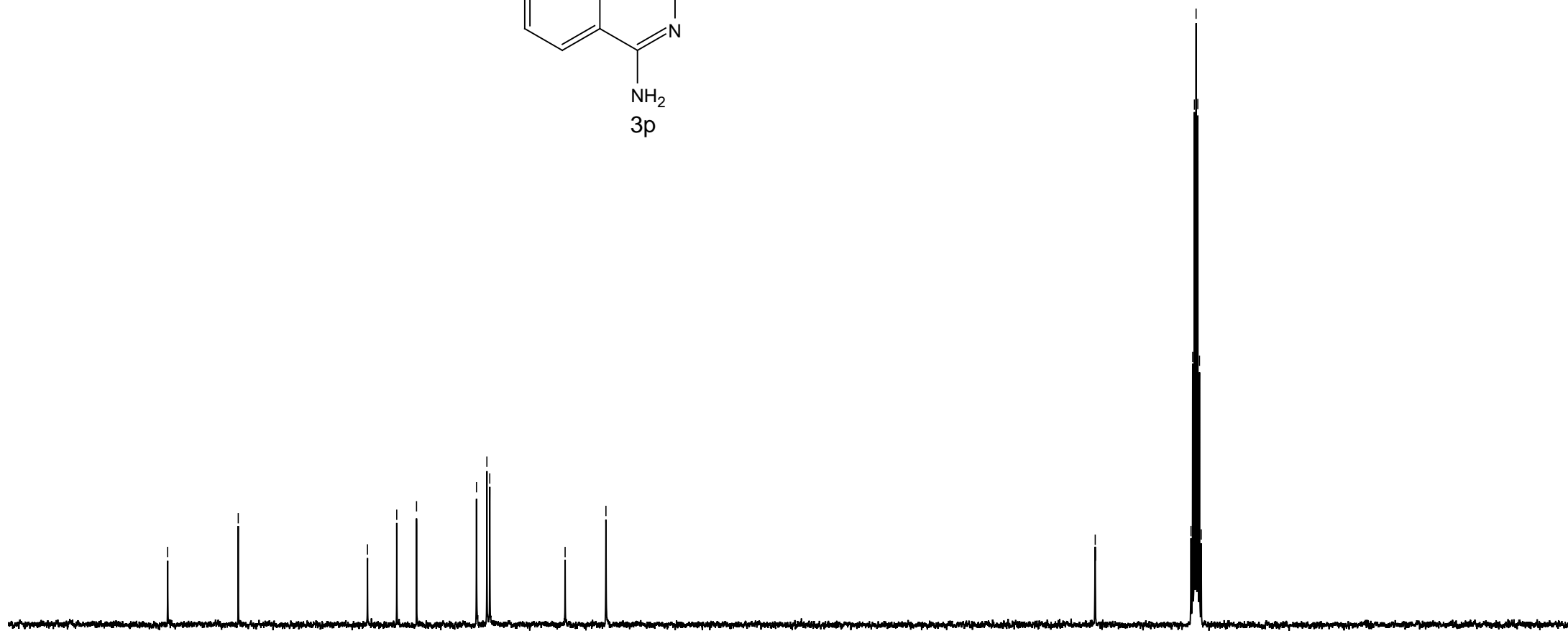
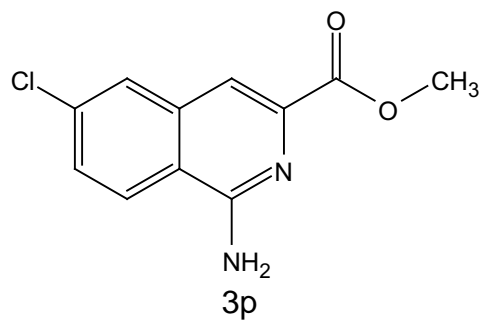
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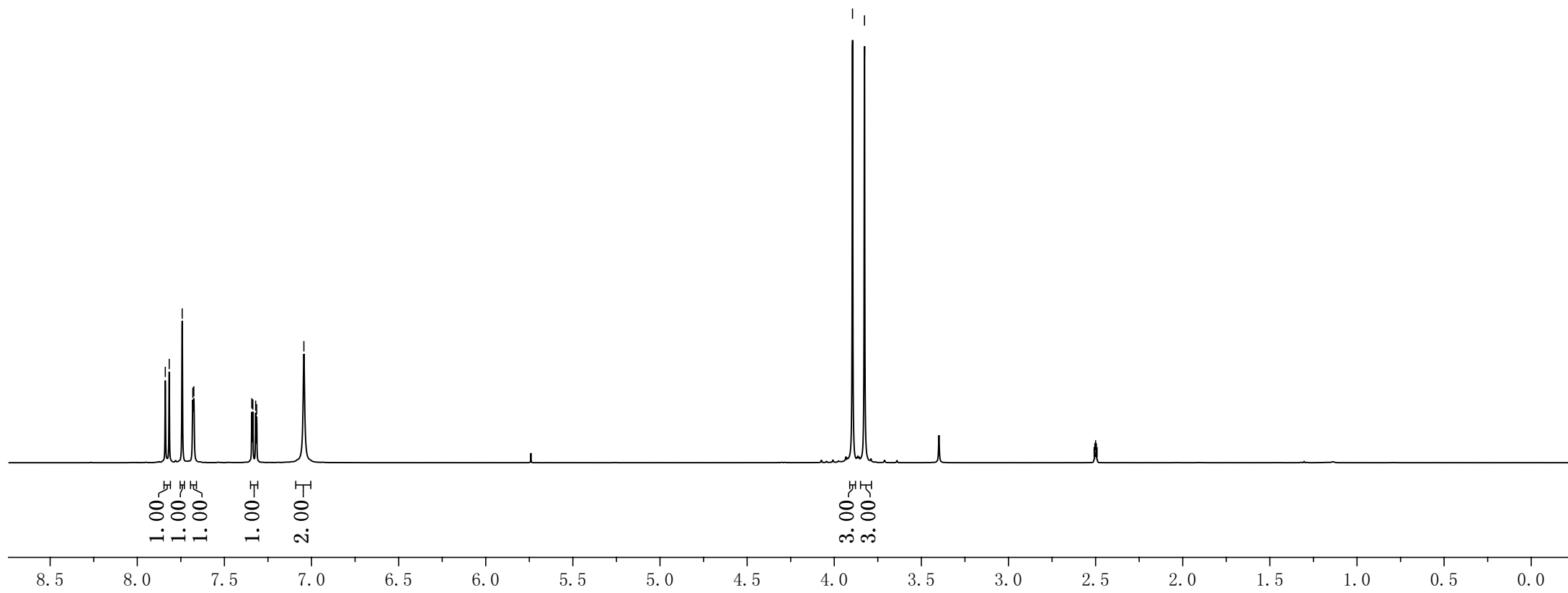
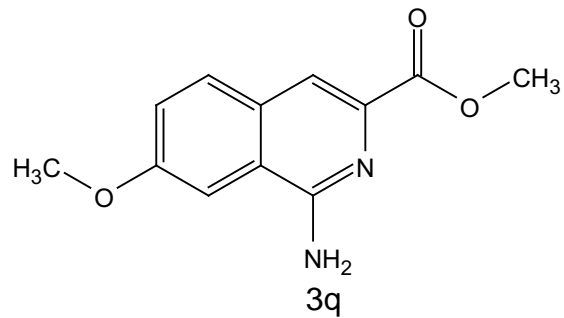
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S70

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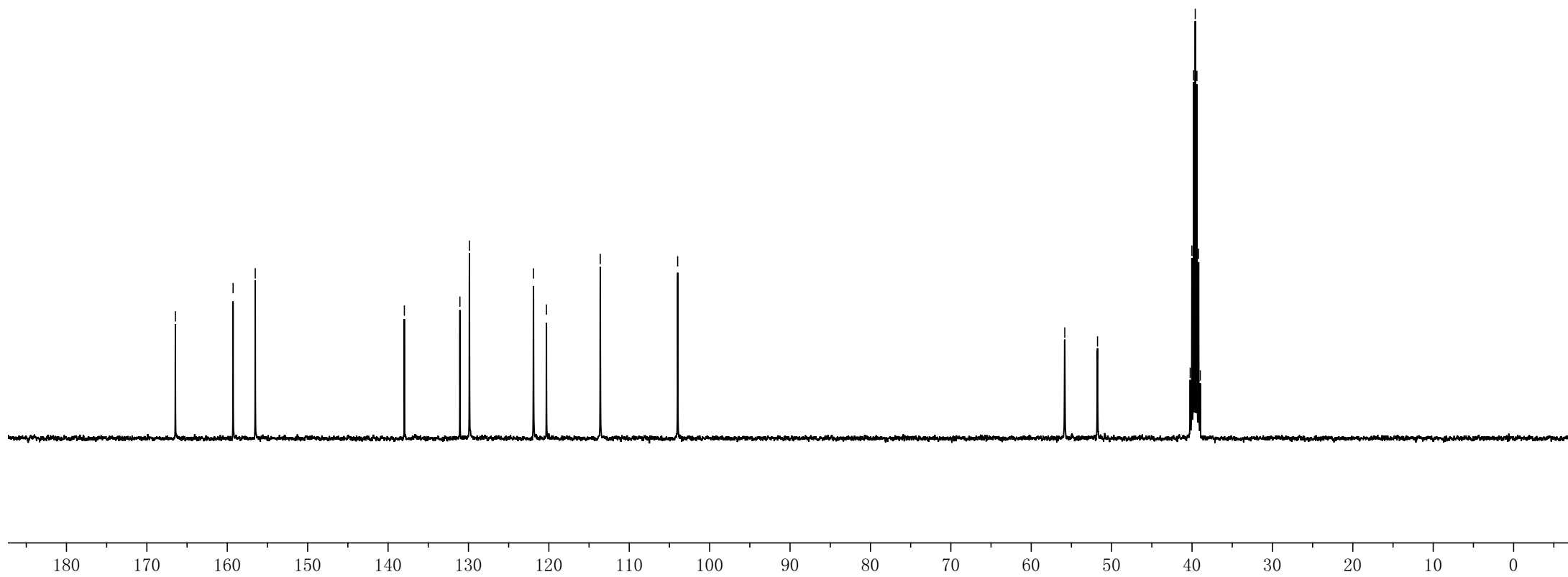
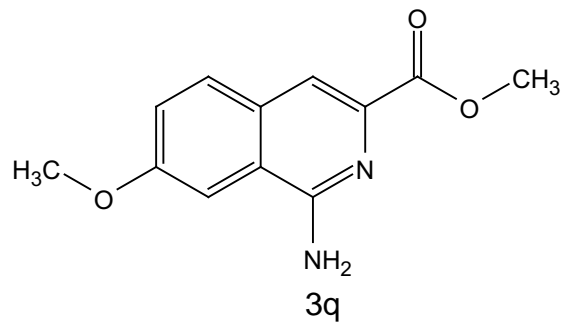
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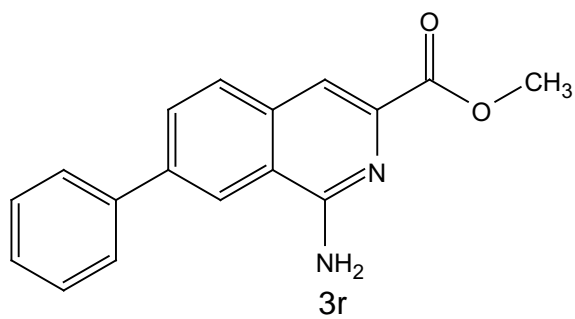
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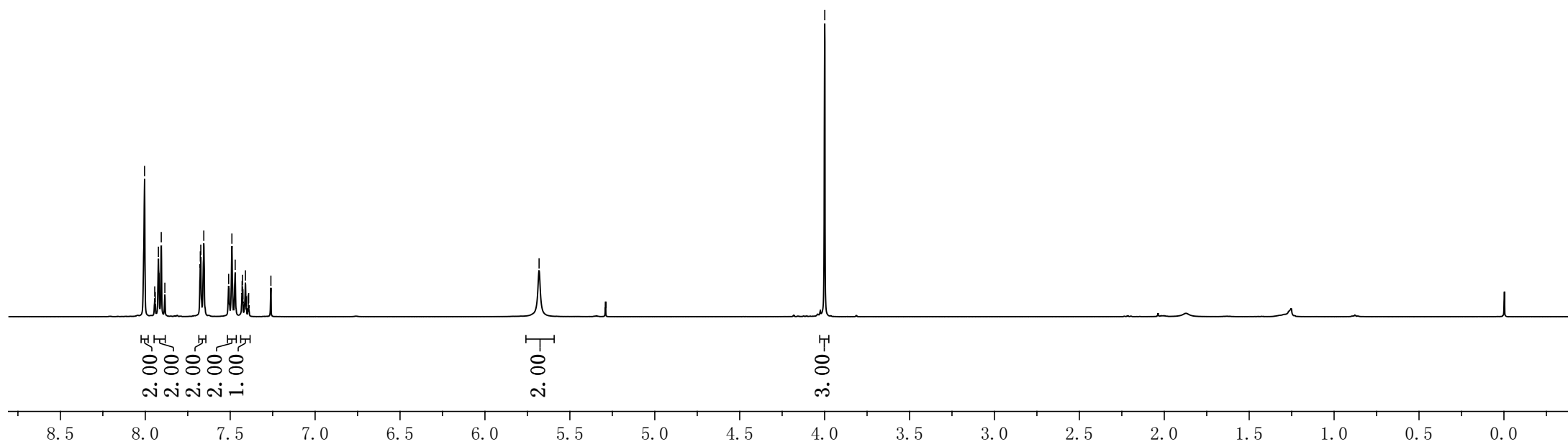




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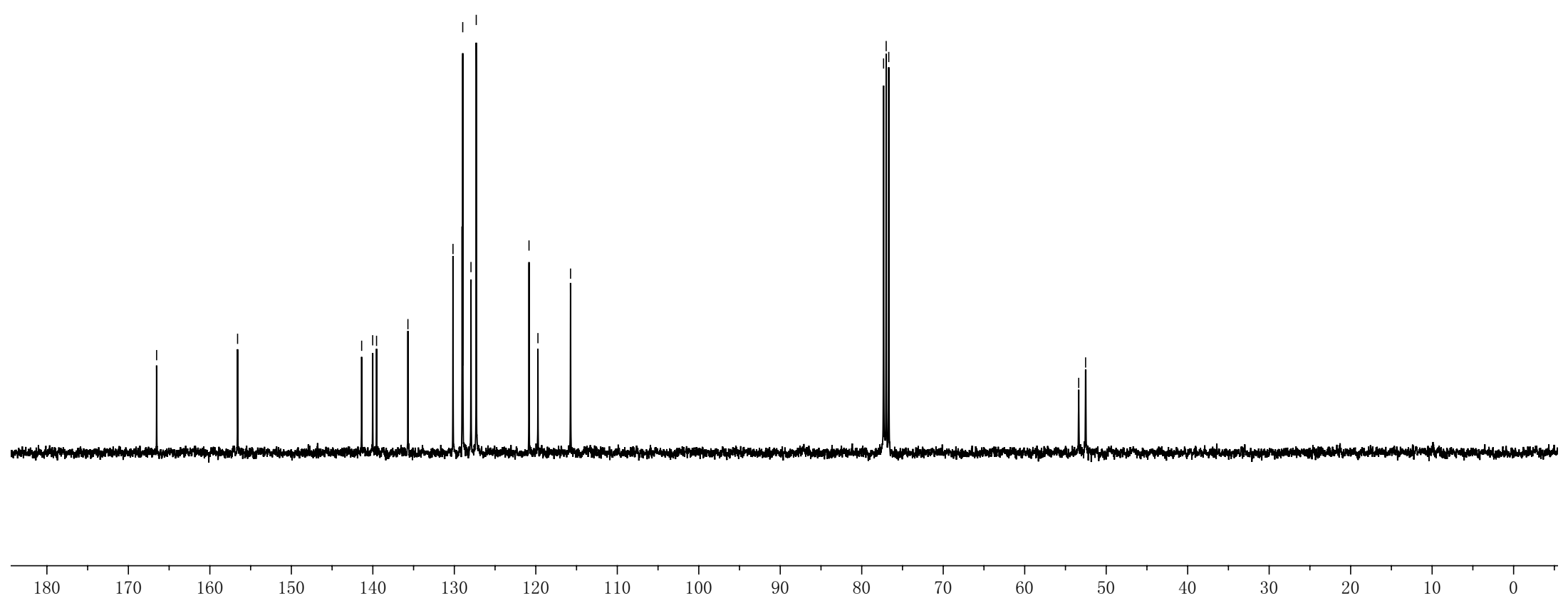
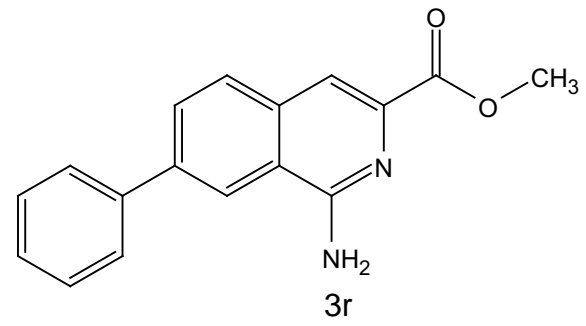
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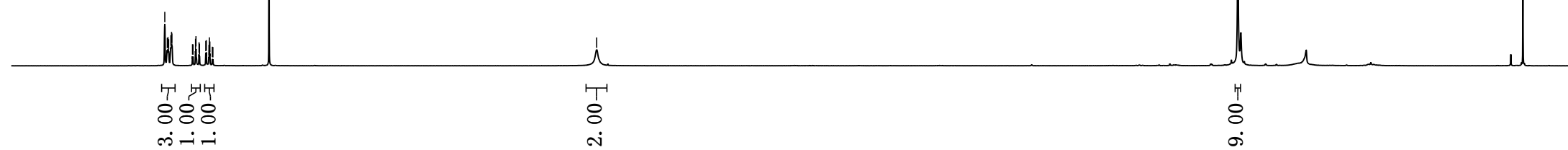
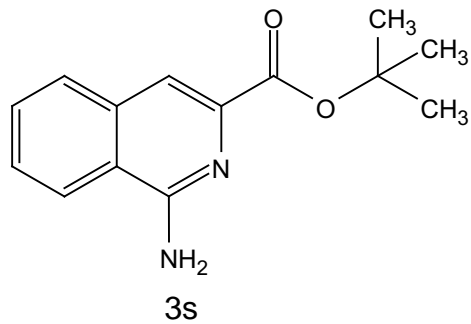
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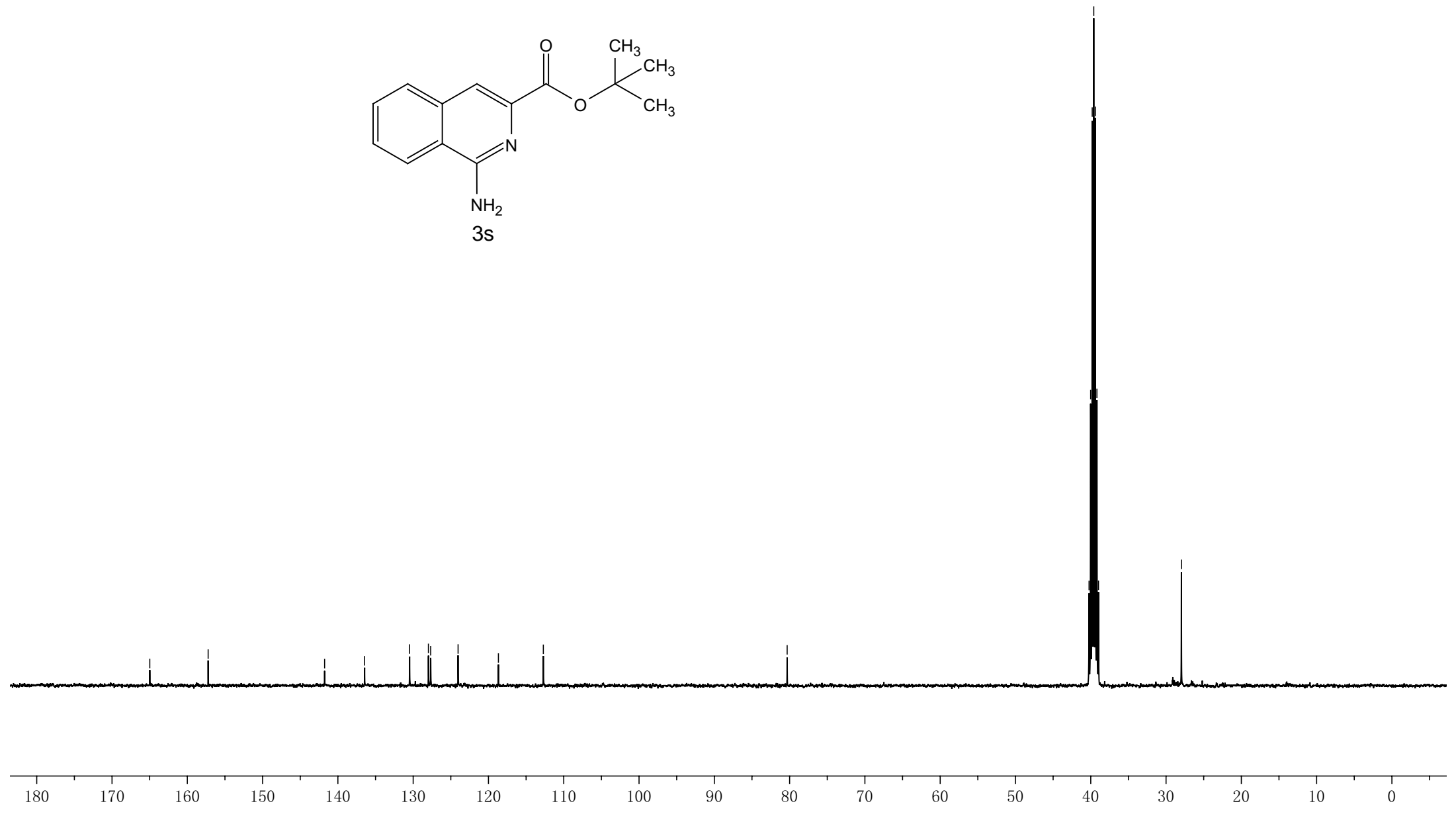
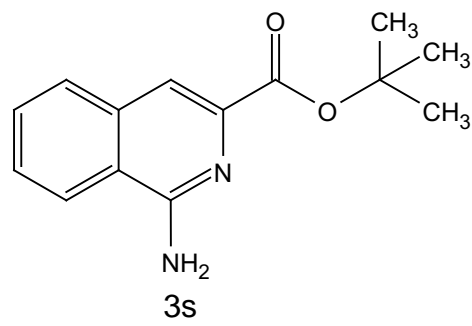
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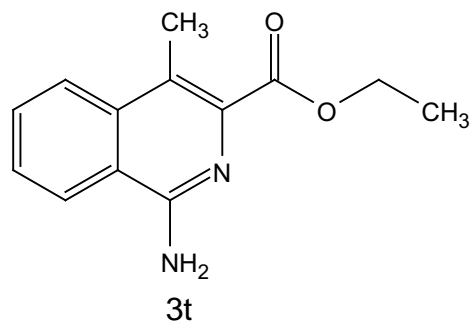
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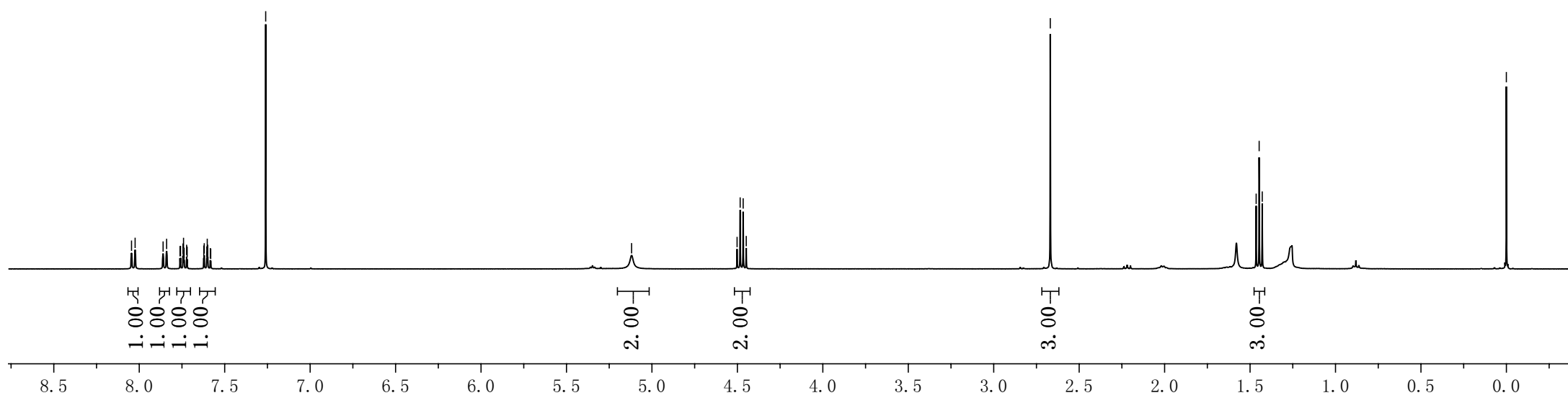
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39.809

39.600

39.392

39.183

38.974

14.267

13.245

