

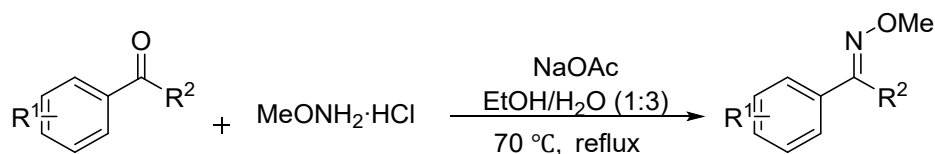
## **Ru-catalyzed C–H activation/cyclization of oximes with sulfoxonium ylides to access isoquinolines**

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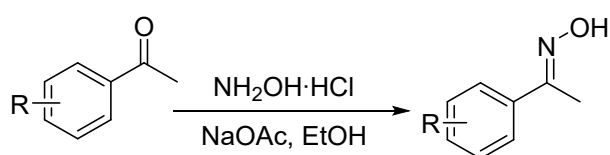
## 1. General comments

All other reagents were purchased from Innochem, TCI, Alfa Aesar, Accela and Adamas used without further purification. The solvents were used without further purification.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (101 MHz) spectra were recorded on Bruker spectrometer with  $\text{CDCl}_3$  as solvent. Chemical shifts are reported in units (ppm) by assigning the TMS resonance in the  $^1\text{H}$  NMR spectra as 0.00 ppm ( $\text{CDCl}_3$ , 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling constant ( $J$  values) in Hz and integration. Flash column chromatography was performed using 300-400 mesh silica with the indicated solvent system according to standard techniques. Analytical thin layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates. The yields of the products reported are the isolated yields and the average of two runs.

## 2. Procedures for the synthesis of acetophenone O-methyl oxime, aromatic oximes and sulfoxonium ylide

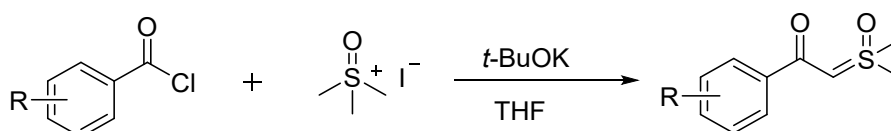


All the oxime derivatives were synthesized according to literature.<sup>1</sup> To a 50 mL round bottom flask equipped with a stir bar was combined ketone (1.7 mmol, 1 equiv.),  $\text{MeONH}_2\cdot\text{HCl}$  (380 mg, 4.6 mmol, 2.7 equiv.),  $\text{NaOAc}$  (610 mg, 7.5 mmol, 4.4 equiv.),  $\text{H}_2\text{O}$  (15 mL), and  $\text{EtOH}$  (5 mL). The flask was equipped with a reflux condenser and heated at  $70\text{ }^\circ\text{C}$  for 2 h. After cooling to room temperature, the mixture was extracted with  $\text{EtOAc}$  (3 x 15 mL). The organic layers were combined, dried with  $\text{MgSO}_4$ , and concentrated to yield the crude product. The crude product was purified by column chromatography on silica gel to get the substrates.



All the aromatic oximes were synthesized according to literature.<sup>2</sup> Combined ketone (1 equiv., 5 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (1.5 equiv., 7.5 mmol),  $\text{NaOAc}$  (2.5 equiv., 12.5 mmol),

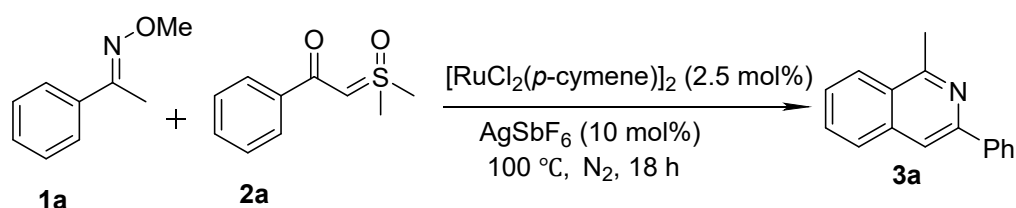
ethyl alcohol (20 mL) were placed in a 100 mL round-bottom flask with a reflux condenser and stirred under reflux. After the completion of the reaction, the mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers was dried by Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum to give corresponding product.



All the sulfoxonium ylides derivatives were synthesized according to literature.<sup>3</sup> To a flame-dried 50 mL round bottom flask, adding potassium tert-butoxide (3.0 g, 27.2 mmol) and dry THF (30 mL) at room temperature. After stirring for 10 mins, trimethylsulfoxonium iodide (5.0 g, 20.6 mmol) was added and the resulting mixture was stirred at reflux for 2 h. Subsequently, the reaction was cooled to 0 °C and acyl chlorides (7 mmol) was added dropwise to the reaction mixture. The reaction was allowed to room temperature and stirred for 3 h. Upon completion, the solvent was evaporated under vacuum and the resulting slurry was exacted with water and ethyl acetate. The combined organic layers were washed with saturated brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After the solvent was evaporated, the crude product was purified by silica gel chromatography using EtOAc/MeOH (95 : 5) to afford the corresponding sulfoxonium ylide.

### 3.Optimization details for the reaction conditions

**Table S1. Optimization of solvents <sup>a</sup>**

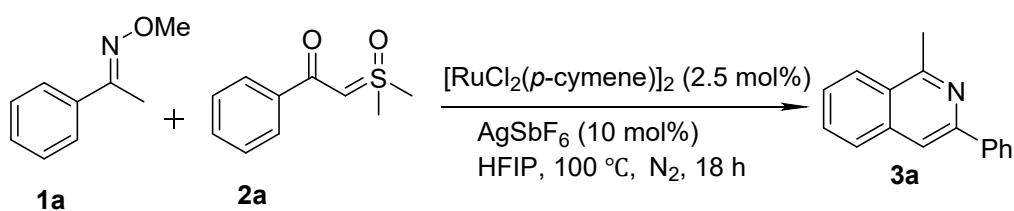


Entry	Solvent (1.5 mL)	Yield (%)
1	DCE	0
2	MeCN	0
3	TFE	5
4	HFIP	9

5	PhCl	0
6	MeOH	0
7	EtOH	0
8	THF	0
9	PhCF <sub>3</sub>	0
10	dioxane	
11	H <sub>2</sub> O	5
12	DCM	0
13	DMF	0
14	PhMe	0

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol%), AgSbF<sub>6</sub> (10 mol%), 100 °C, N<sub>2</sub>, 18 h, isolated yield.

**Table S2. Optimization of additives <sup>a</sup>**

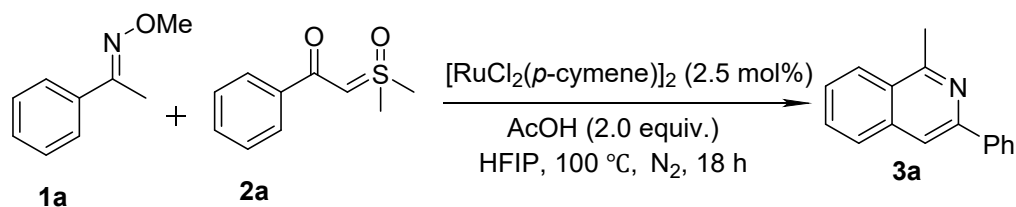


Entry	Additives(equiv.)	Yield (%)
1	Zn(OAc) <sub>2</sub> (0.5)	17
2	KOAc (0.5)	12
3	LiOAc (0.5)	15
4	CsOAc (0.5)	15
5	NaOAc (0.5)	14
6	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	16
7	Li <sub>2</sub> CO <sub>3</sub> (0.5)	10
8	K <sub>2</sub> CO <sub>3</sub> (0.5)	21
9	PhCOONa (0.5)	15
10	KOPiv (0.5)	10
11	PivOH (0.5)	18

12	AcOH (0.5)	32
13	1-AdCOOH (0.5)	20
14	PhCOOH (0.5)	25
15	MesCOOH (0.5)	22
16	AcOH (1.0)	36
17	AcOH (2.0)	42

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol%), AgSbF<sub>6</sub> (10 mol%), HFIP (1.5 mL), 100 °C, N<sub>2</sub>, 18 h, isolated yield.

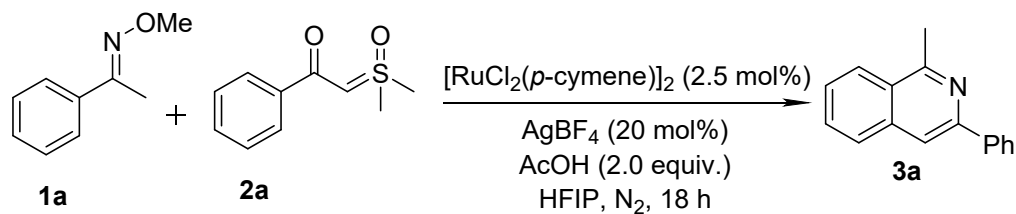
**Table S3. Optimization of Ag salt <sup>a</sup>**



Entry	Ag (mol%)	Yield (%)
1	AgBF <sub>4</sub> (10)	47
2	AgNTf <sub>2</sub> (10)	38
3	AgSbF <sub>6</sub> (10)	42
4	AgOAc (10)	35
5	AgBF <sub>4</sub> (20)	53

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol%), AcOH (2.0 equiv.), HFIP (1.5 mL), 100 °C, N<sub>2</sub>, 18 h, isolated yield.

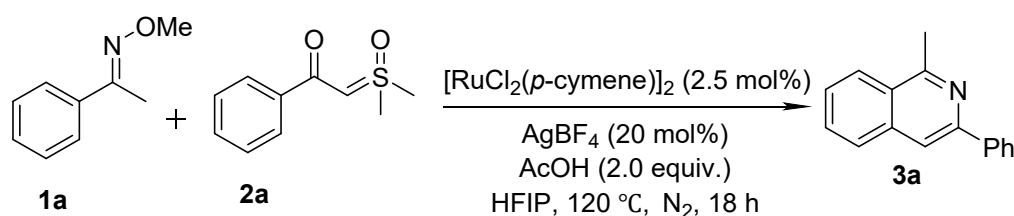
**Table S4. Optimization of reaction temperature. <sup>a</sup>**



Entry	Temp. (°C)	Yield (%)
1	100	53
2	110	56
3	120	60
4	130	58

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol%), AgBF<sub>4</sub> (20 mol%), AcOH (2.0 equiv.), HFIP (1.5 mL), N<sub>2</sub>, 18 h, isolated yield.

**Table S5. Optimization of of substrate ratio.** <sup>a</sup>



Entry	<b>1a</b>	<b>2a</b>	Yield (%)
1	0.2 mmol	0.3 mmol	60
2	0.2 mmol	0.4 mmol	62
3	0.2 mmol	0.35 mmol	66
4	0.2 mmol	0.25 mmol	53

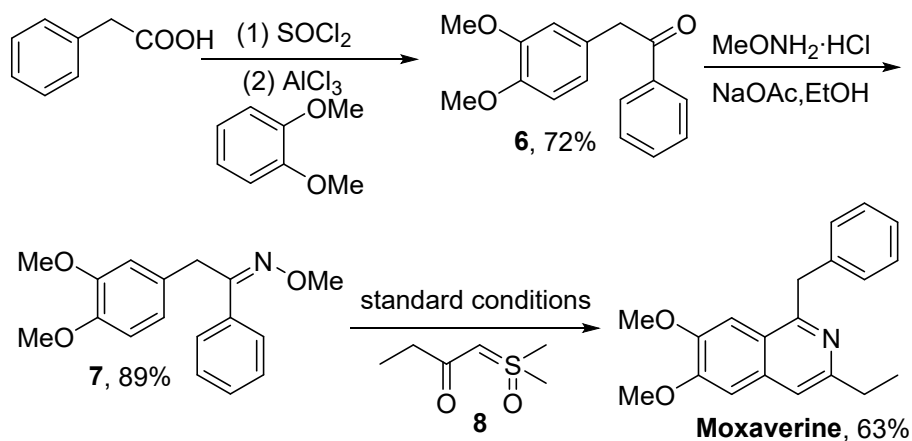
<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (2.5 mol%), AgBF<sub>4</sub> (20 mol%), AcOH (2.0 equiv.), HFIP (1.5 mL), N<sub>2</sub>, 120 °C, 18 h, isolated yield.

#### 4. General experimental procedures for the synthesis of isoquinolines

In a glove box, a 35 mL Schlenk tube equipped with a stir bar was charged with sulfoxonium ylide **2a** (0.35 mmol), [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (2.5 mol %), AgBF<sub>4</sub> (20 mol%). The tube was fitted with a rubber septum, and removed out from the glove box. Then acetophenone O-methyl oxime **1a** (0.2 mmol) and AcOH (2.0 equiv.) were added through the rubber septum using syringe under the atmosphere of N<sub>2</sub>. HFIP (1.5 mL) was added to the Schlenk tube through the rubber septum using a syringe. The septum was replaced by a Teflon screwcap under N<sub>2</sub> flow. The mixture was stirred at 120 °C for 18 h. After cooling, the mixture was diluted with ethyl acetate (10 mL), filtered through a pad of

silica gel, followed by washing the pad of the silica gel with the ethyl acetate (10 mL). The organic phase was concentrated under reduced pressure. The residue was then purified by chromatography on silica gel to provide the corresponding product **3a**.

## 5.The synthesis of Moxaverine<sup>2</sup>



(1) To a 100 mL flask containing phenylacetic acid (2.0 g, 14.7 mmol), 40 ml DCM, thionyl chloride (8.7 g, 73.5 mmol) was added and the reaction mixture was heated to reflux for 3 h and then DCM and excess thionyl chloride were removed by distillation. The resulting oil was transferred to another two necked round bottom flask containing dry DCM (60 mL) and 1,2-dimethoxy benzene (1.7 g, 12.3 mmol). AlCl<sub>3</sub> (2.1 g, 15.9 mmol) was added in small portions and the mixture was stirred at room temperature for 3 h, after which the reaction was quenched by pouring into ice water (25 mL). The mixture was extracted with DCM and the combined organic layers were evaporated under vacuum. Recrystallization from ethyl alcohol gave the desired product **6** as yellow solid (2.35 g, 72% yield)

(2) A mixture of **6** (1.28 g, 5 mmol), MeONH<sub>2</sub>·HCl (1.2 g, 13.5 mmol), NaOAc (1.8 g, 20.1 mmol), ethyl alcohol (20 mL) were placed in a 100 mL round-bottom flask with a reflux condenser and stirred under reflux. After the completion of the reaction, the mixture was cooled to room temperature and extracted with ethyl acetate. The combined organic layers was dried by Na<sub>2</sub>SO<sub>4</sub> and evaporated under vacuum to give the oxime **7** as white solid (1.27 g, 89% yield).

(3) In a glove box, a 35 mL Schlenk tube equipped with a stir bar was charged with **8** (0.2 mmol), **8** (0.35 mmol), [Ru(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> (2.5 mol %), AgBF<sub>4</sub> (20 mol%). The tube was

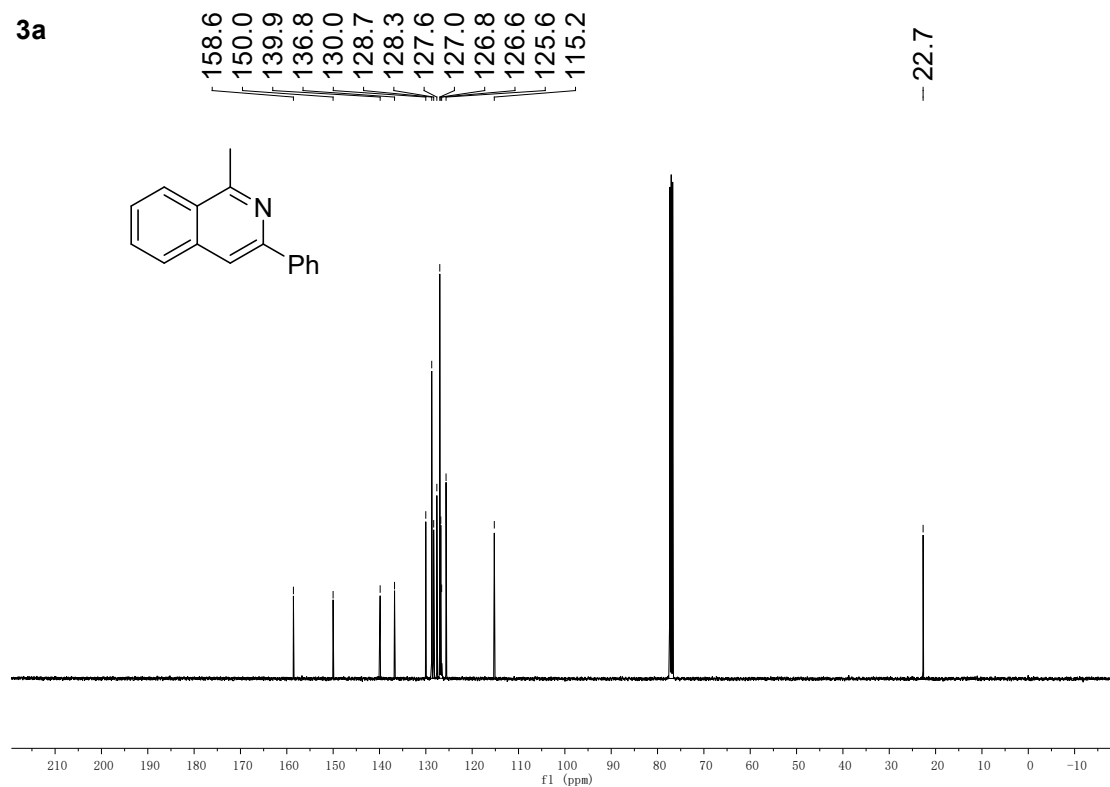
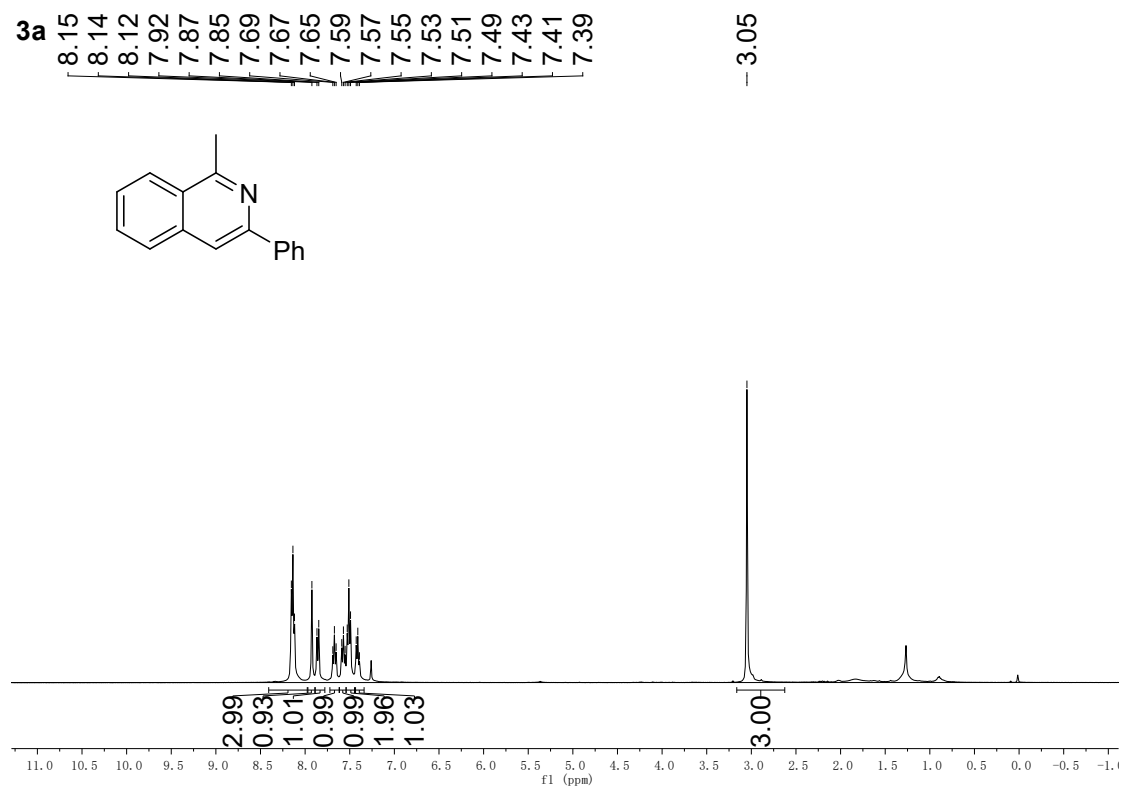
fitted with a rubber septum, and removed out from the glove box. Then AcOH (2.0 equiv.) was added through the rubber septum using syringe under the atmosphere of N<sub>2</sub>. HFIP (1.5 mL) was added to the Schlenk tube through the rubber septum using a syringe. The septum was replaced by a Teflon screwcap under N<sub>2</sub> flow. The mixture was stirred at 120 °C for 18 h. After cooling, the mixture was diluted with ethyl acetate (10 mL), filtered through a pad of silica gel, followed by washing the pad of the silica gel with the ethyl acetate (10 mL). The organic phase was concentrated under reduced pressure. The residue was then purified by chromatography on silica gel to provide the corresponding product Moxaverine.



## 6. References

1. Y. -Q. Li, Q. -L. Yang, P. Fang, T. -S. Mei and D. Zhang, Palladium-Catalyzed C(sp<sup>2</sup>)-H Acetoxylation via Electrochemical Oxidation, *Org. Lett.*, 2017, **19**, 2905–2908.
2. R. Chen, J. Qi, Z. Mao and S. Cui, Rh(III)-catalyzed C–H activation/cyclization of oximes with alkenes for regioselective synthesis of isoquinolines, *Org. Biomol. Chem.*, 2016, **14**, 6201-6204.
3. C. Hong, S. Yu, Z. Liu and Y. Zhang, Rhodium(III)-catalyzed annulation of enamides with sulfoxonium ylides toward isoquinolines, *RSC Adv.*, 2021, **11**, 11490–11494.

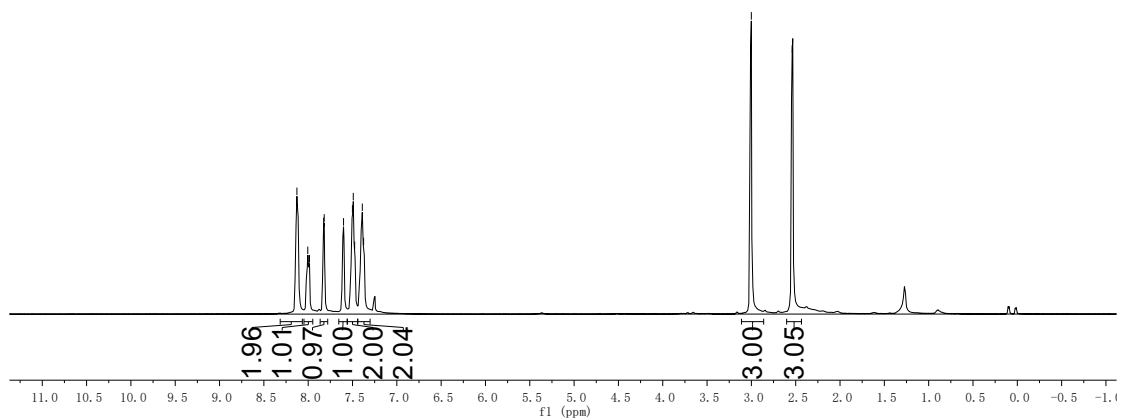
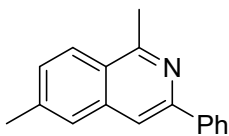
## 7. <sup>1</sup>H and <sup>13</sup>C NMR spectra



3b

8.13  
8.00  
7.99  
7.99  
7.83  
7.82  
7.60  
7.50  
7.49  
7.48  
7.39  
7.37

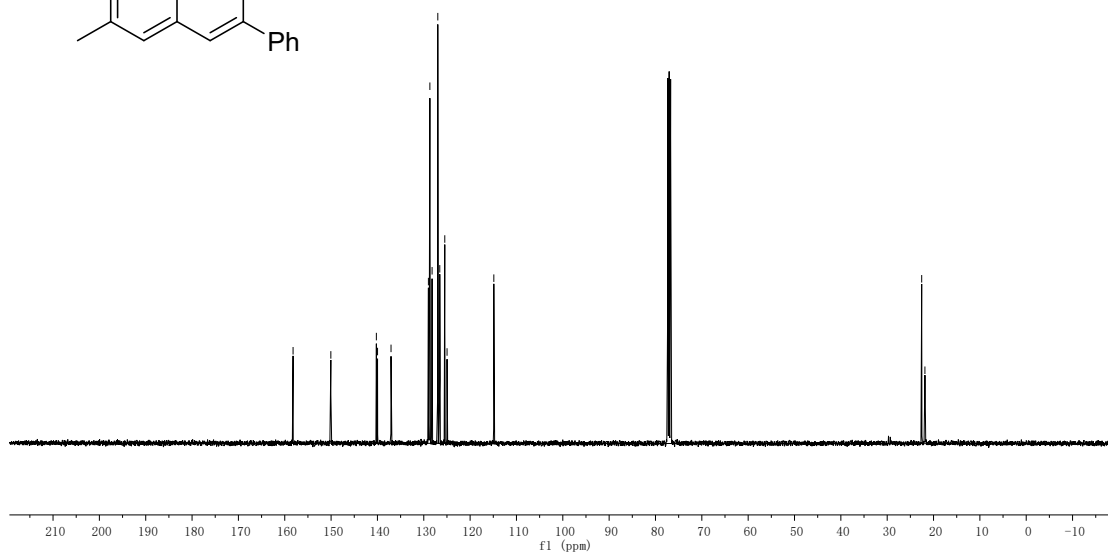
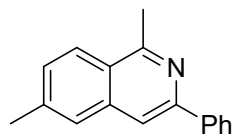
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2.54

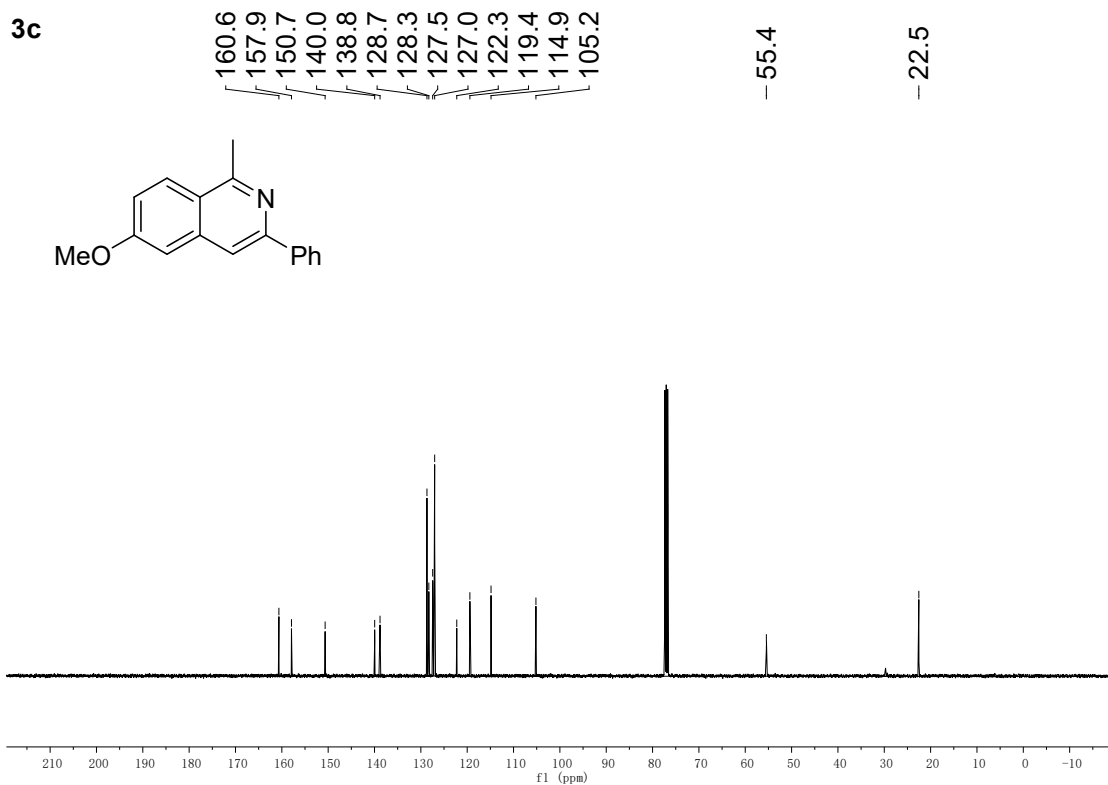
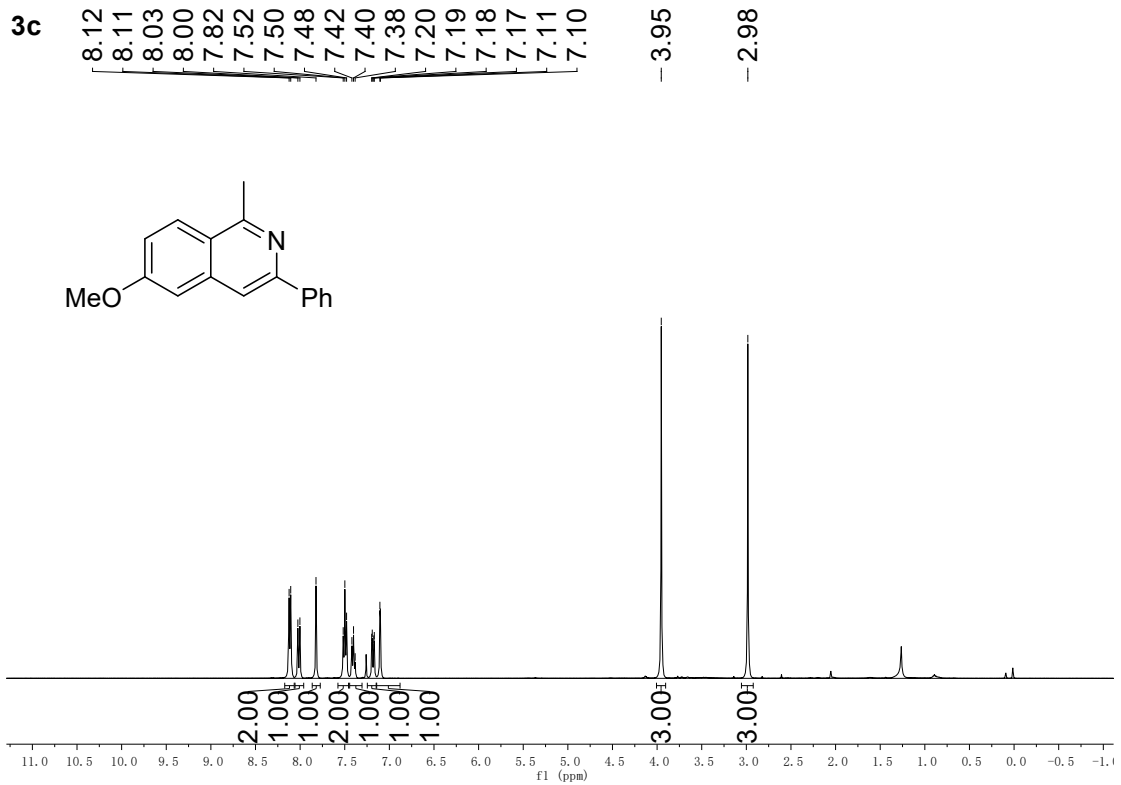


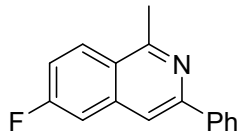
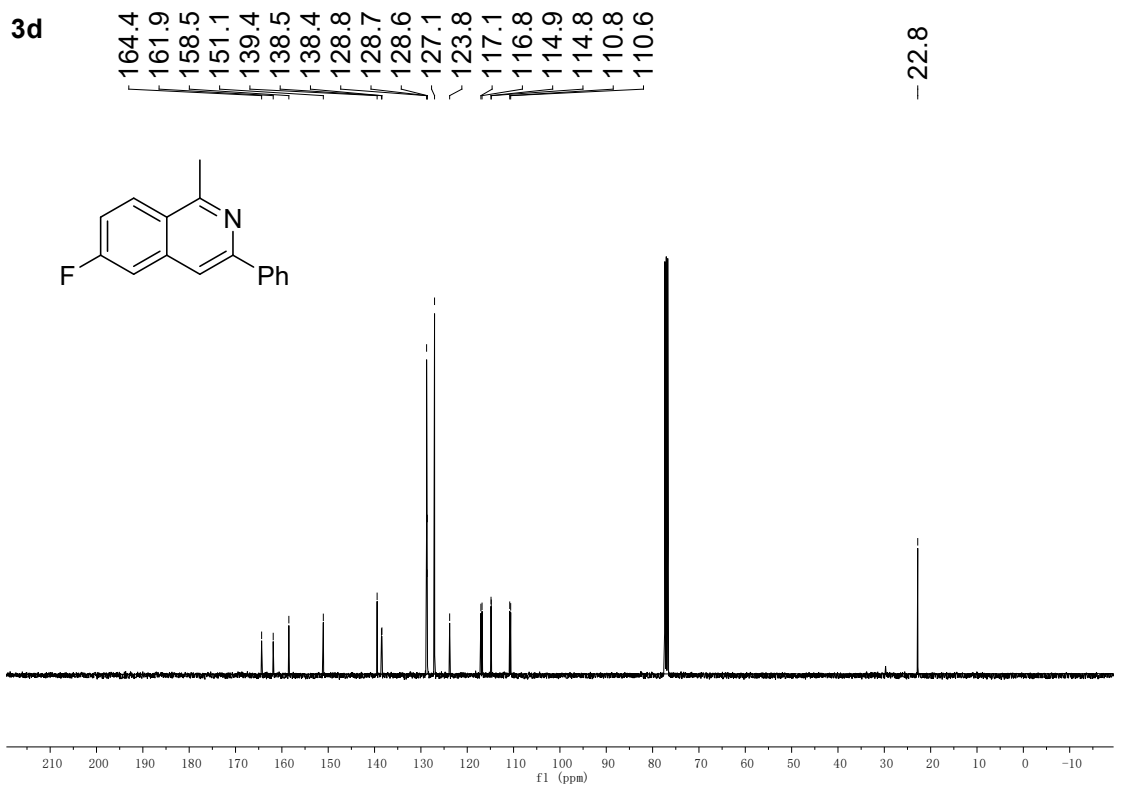
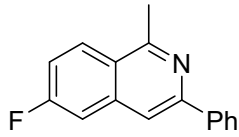
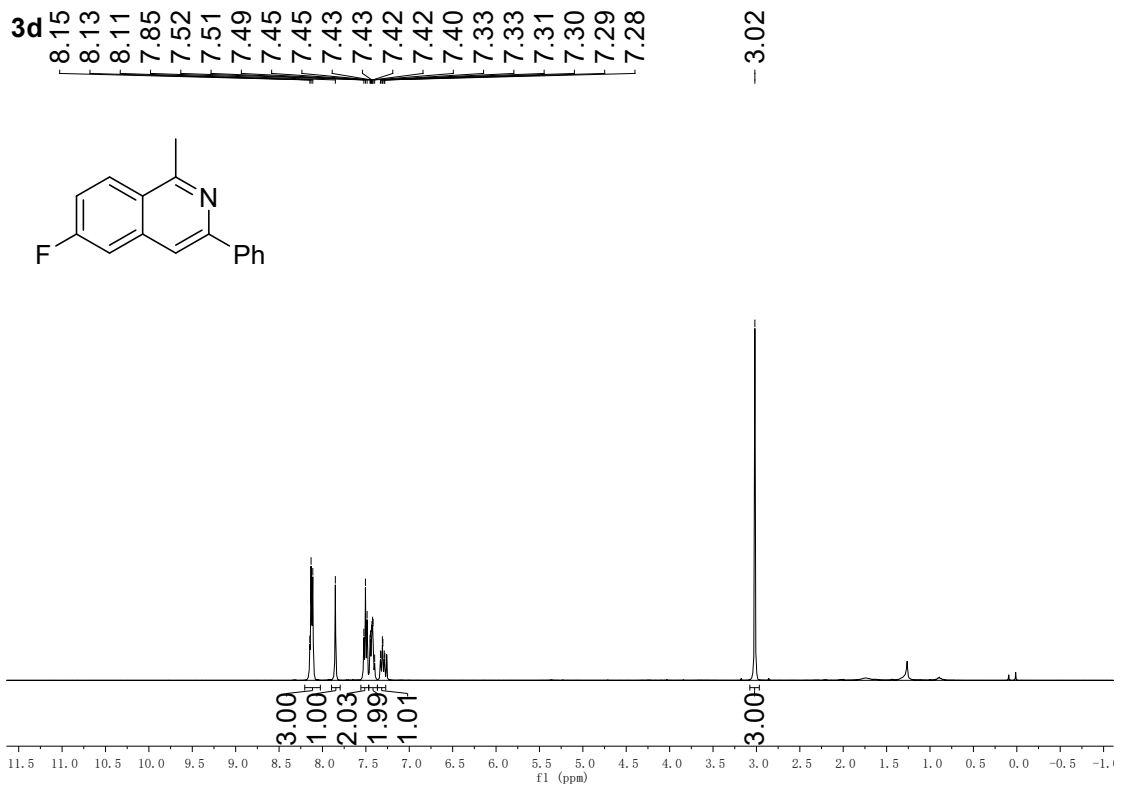
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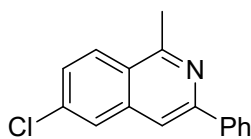
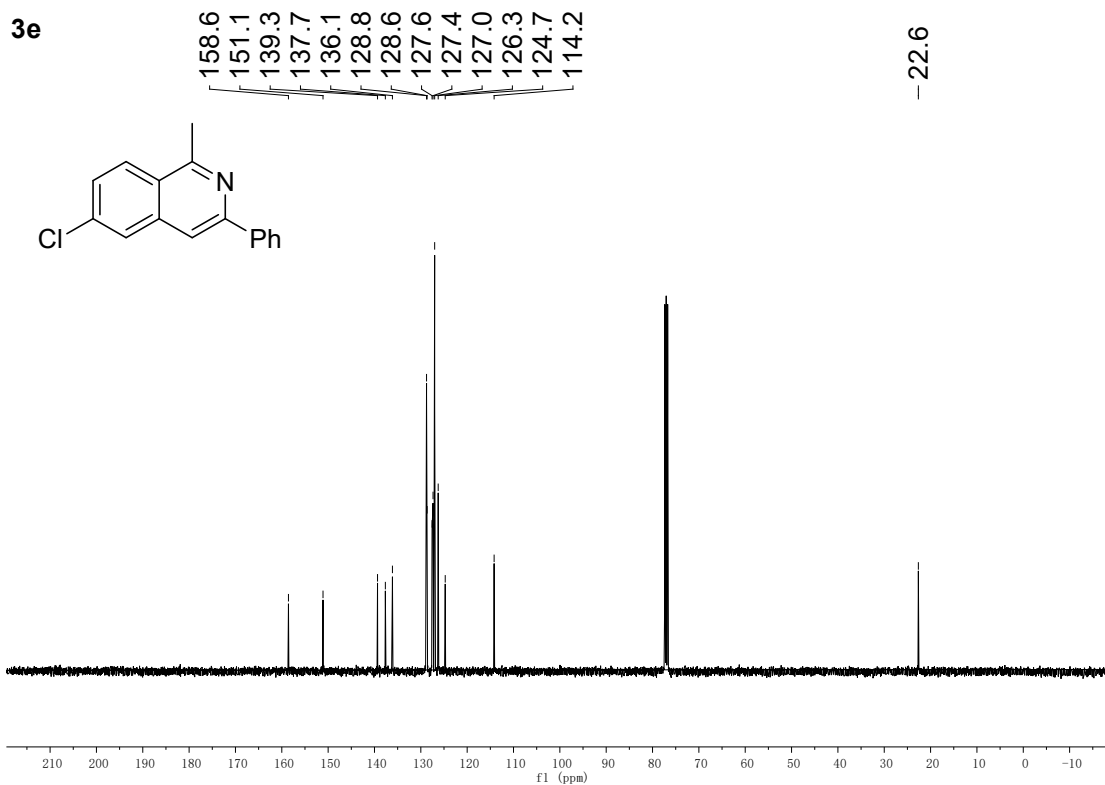
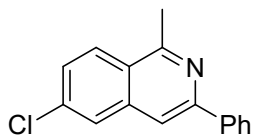
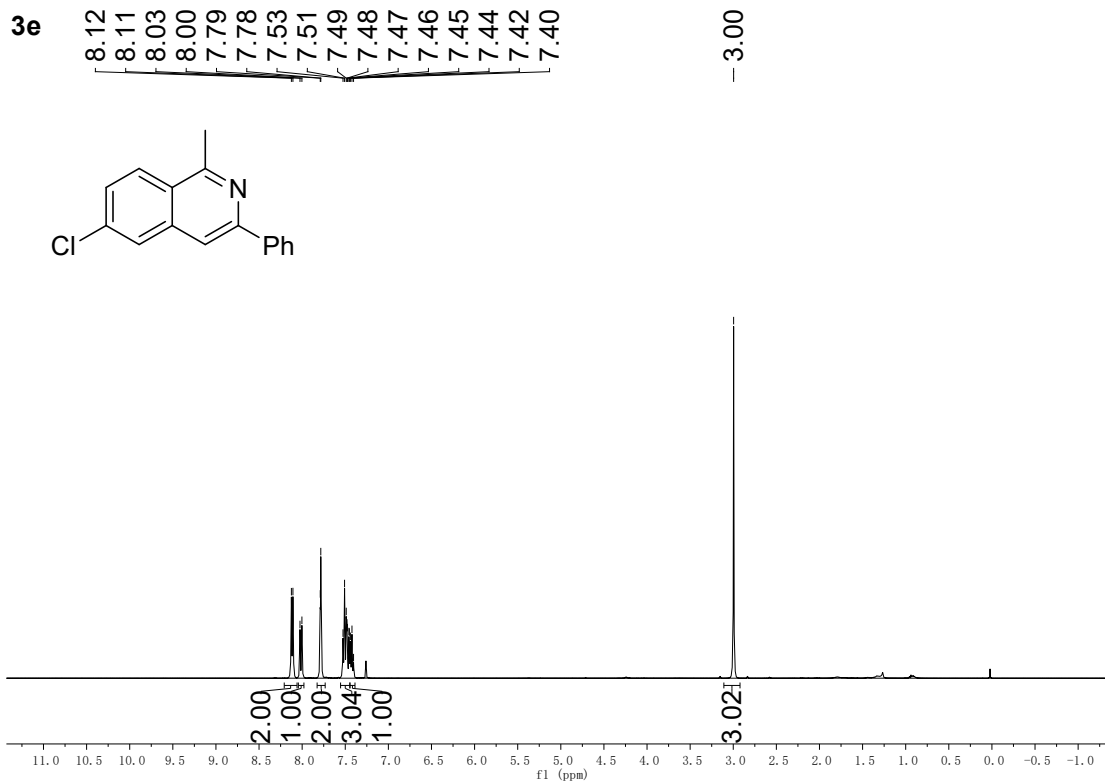
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140.2  
140.0  
137.1  
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125.0  
114.9

22.6  
21.9

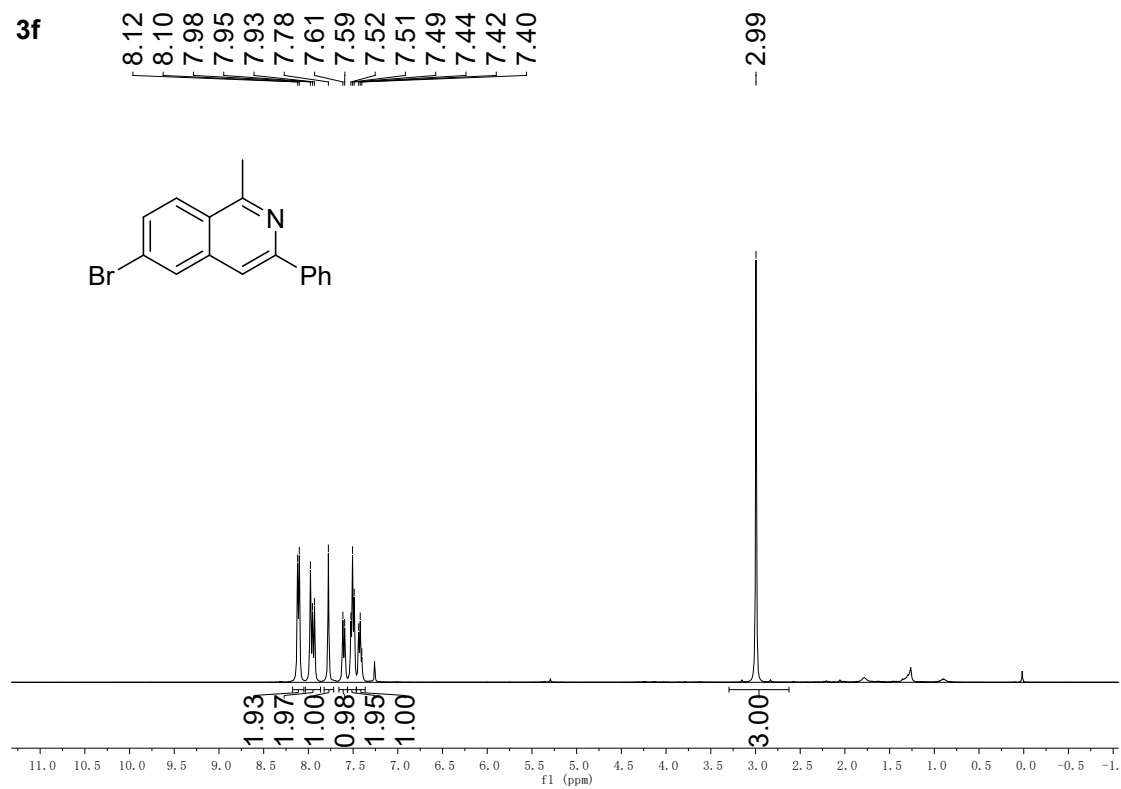




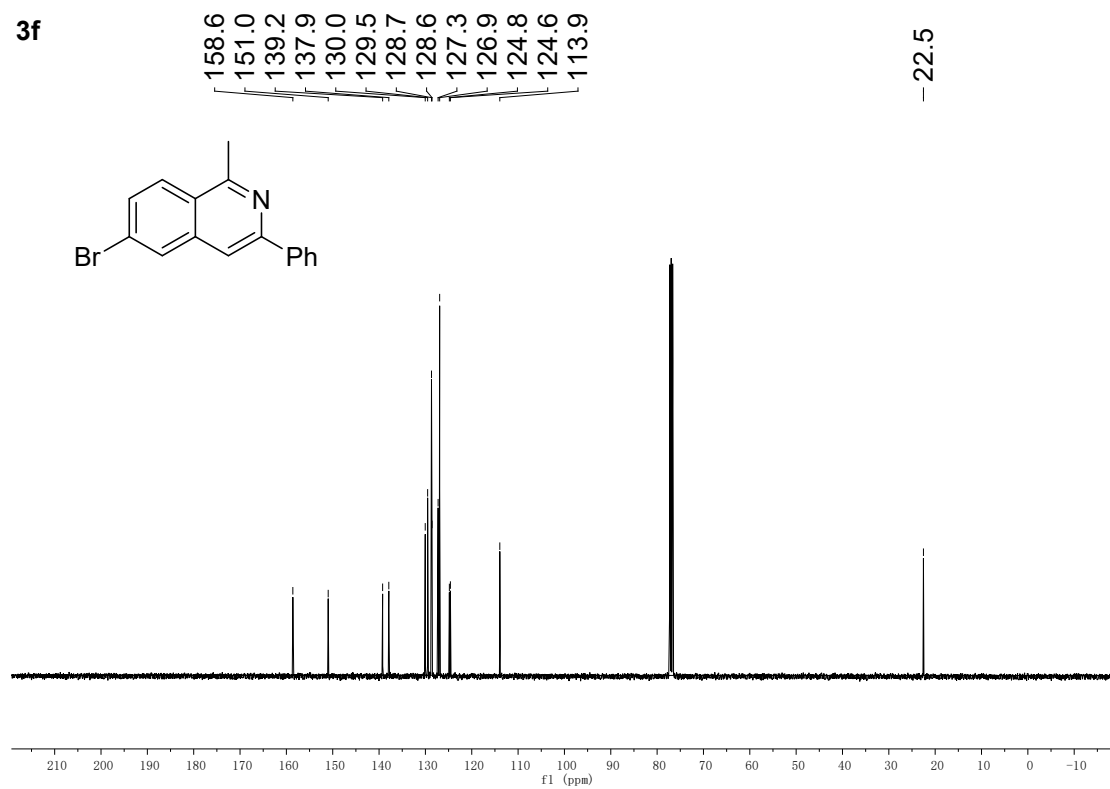


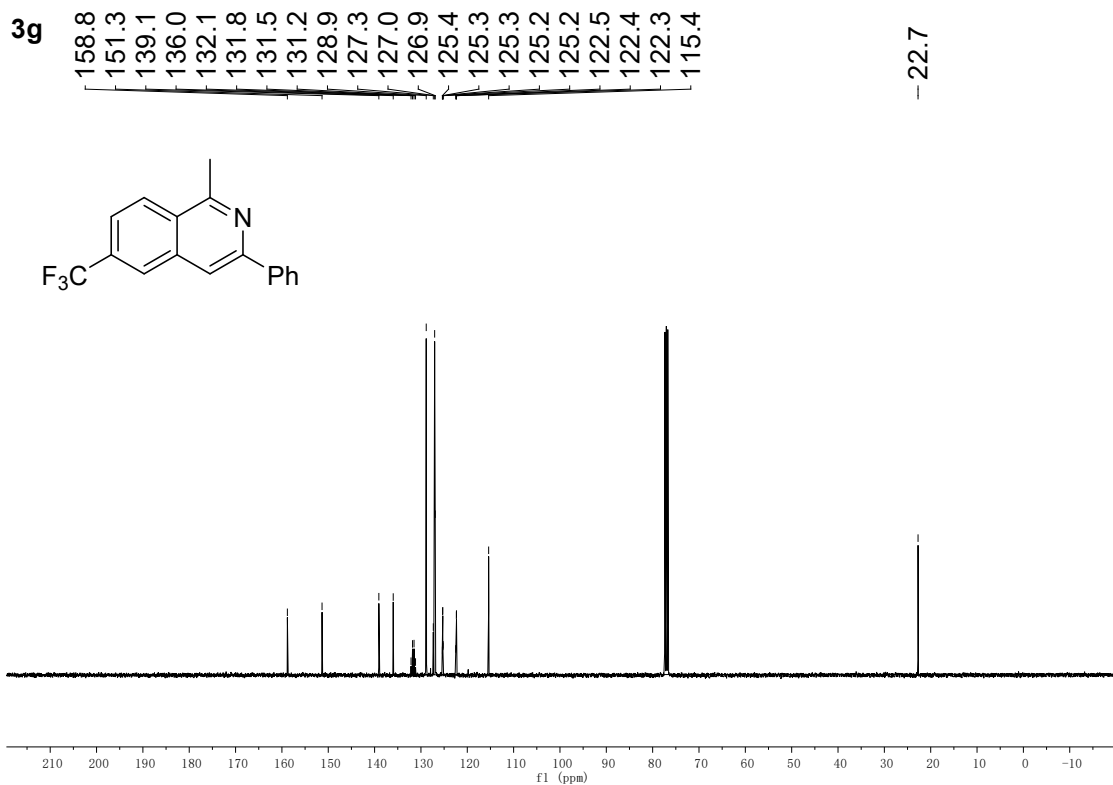
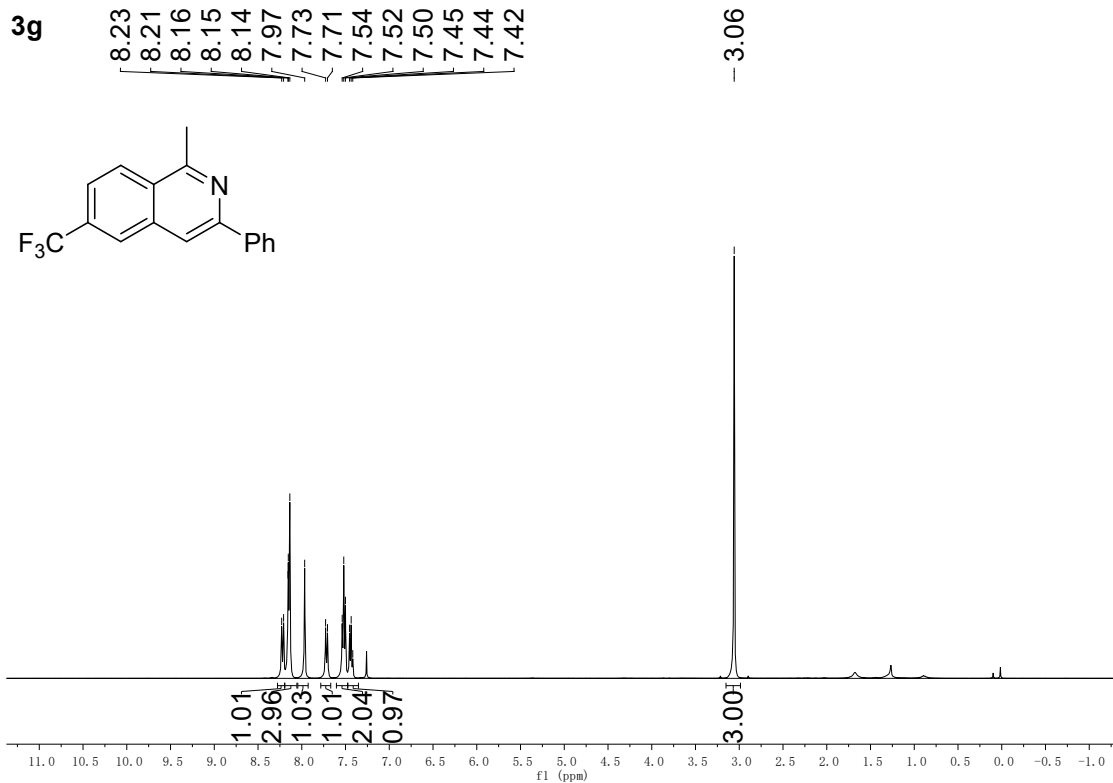


3f



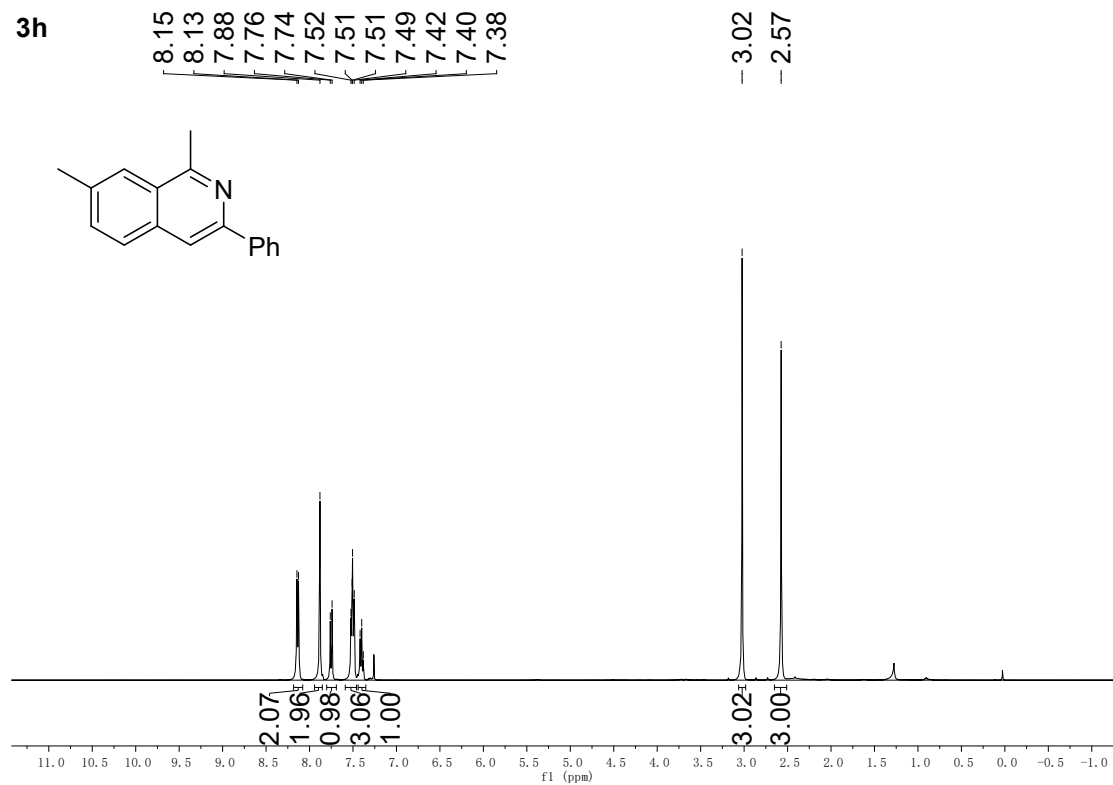
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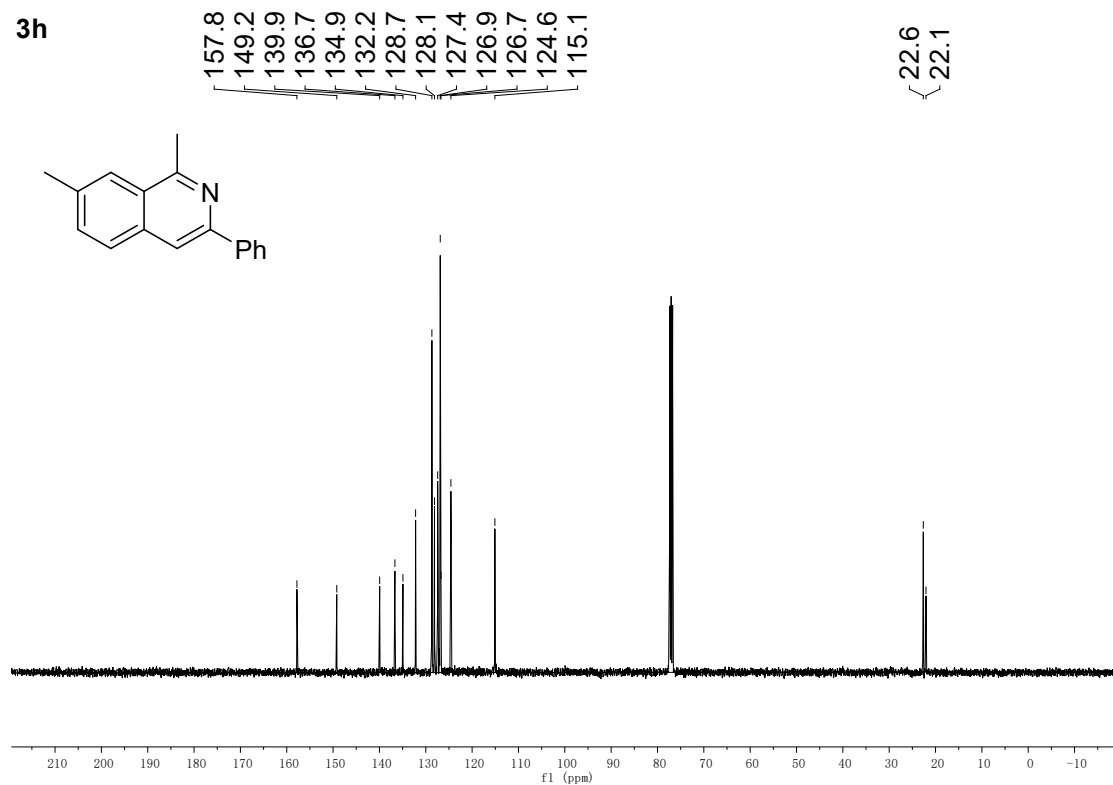




3h



3h

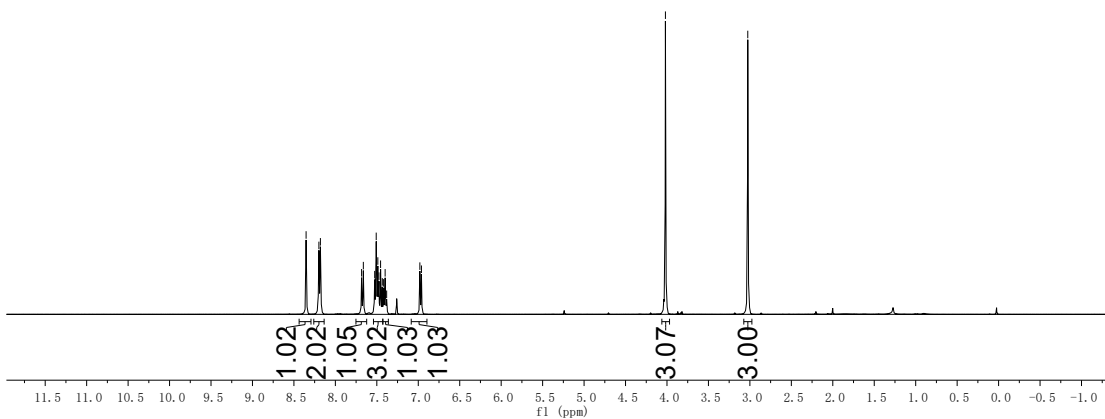
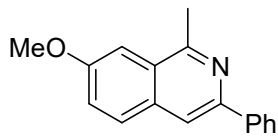


3i

8.35  
8.20  
8.18  
7.68  
7.66  
7.53  
7.51  
7.49  
7.47  
7.45  
7.43  
7.42  
7.40  
7.38  
6.98  
6.96

- 4.02

- 3.03

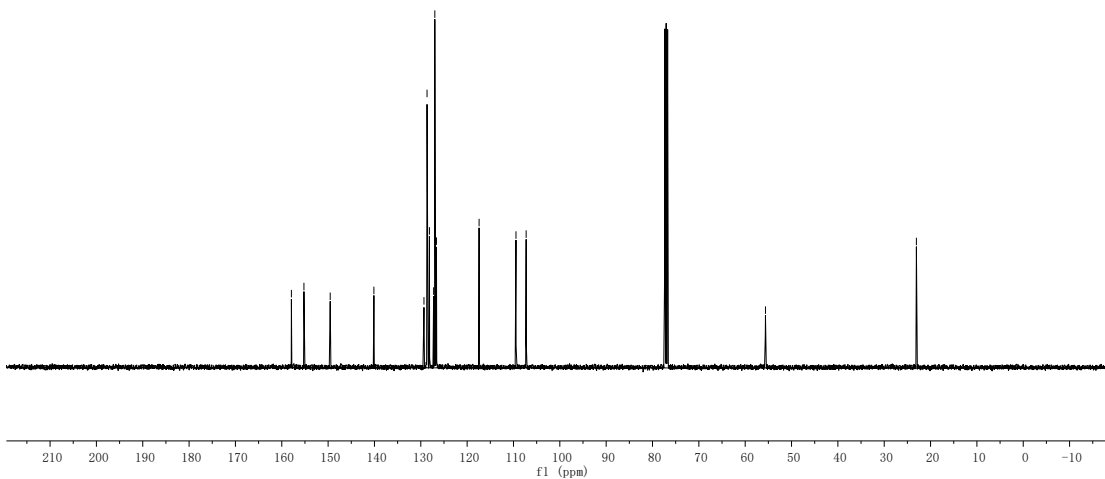
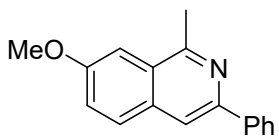


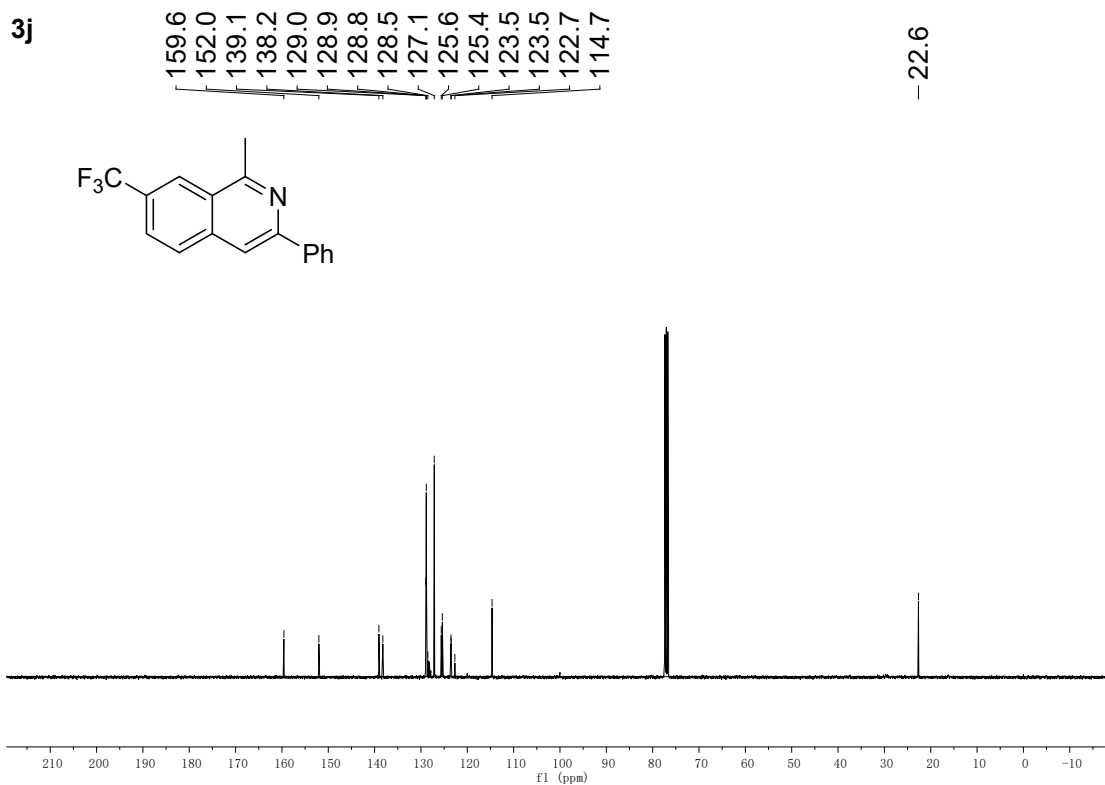
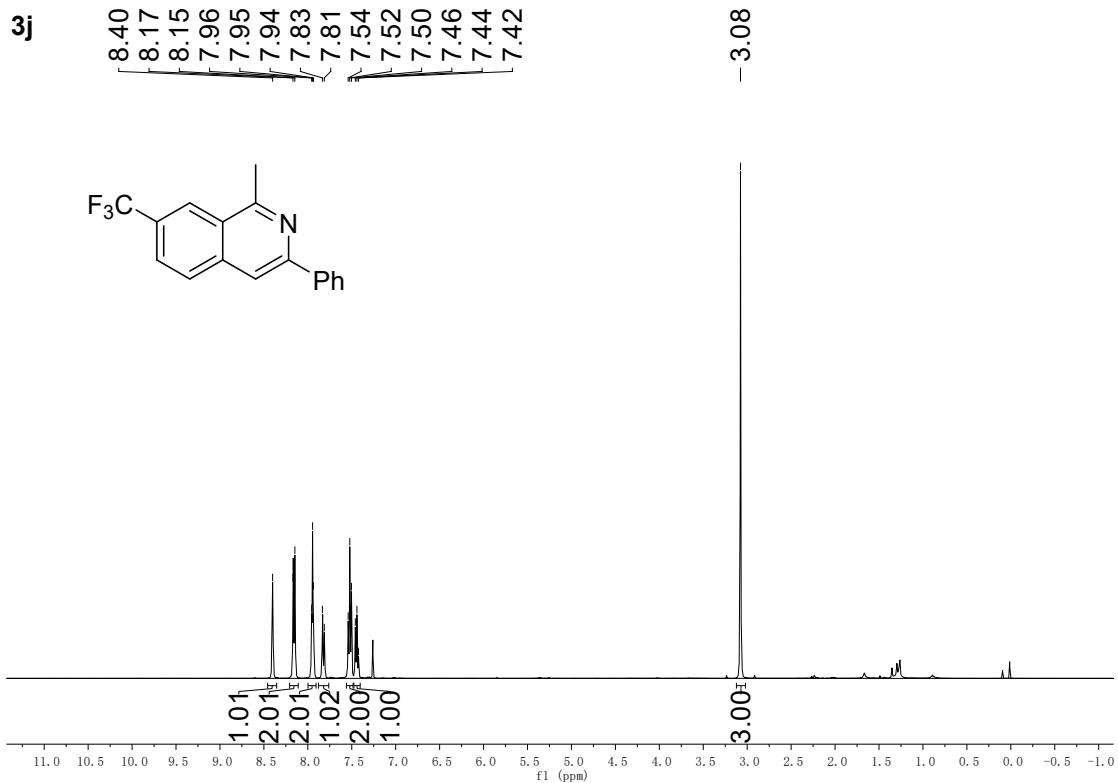
3i

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155.2  
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140.1  
129.3  
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127.2  
127.0  
126.6  
117.4  
109.5  
107.3

- 55.6

- 23.1



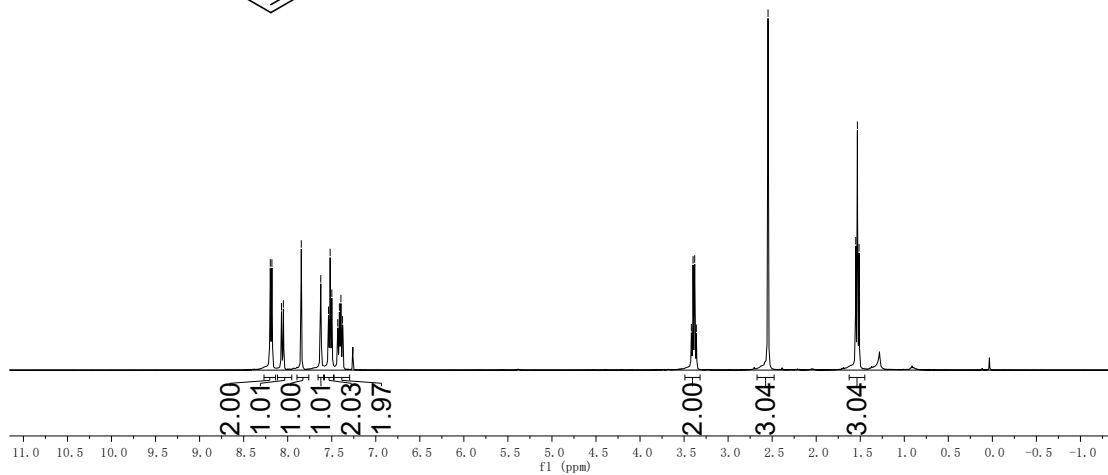
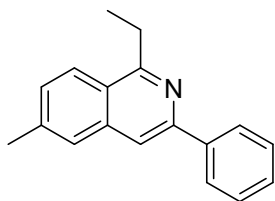


3m

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8.07  
8.05  
7.85  
7.62  
7.54  
7.52  
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7.41  
7.40  
7.38

3.42  
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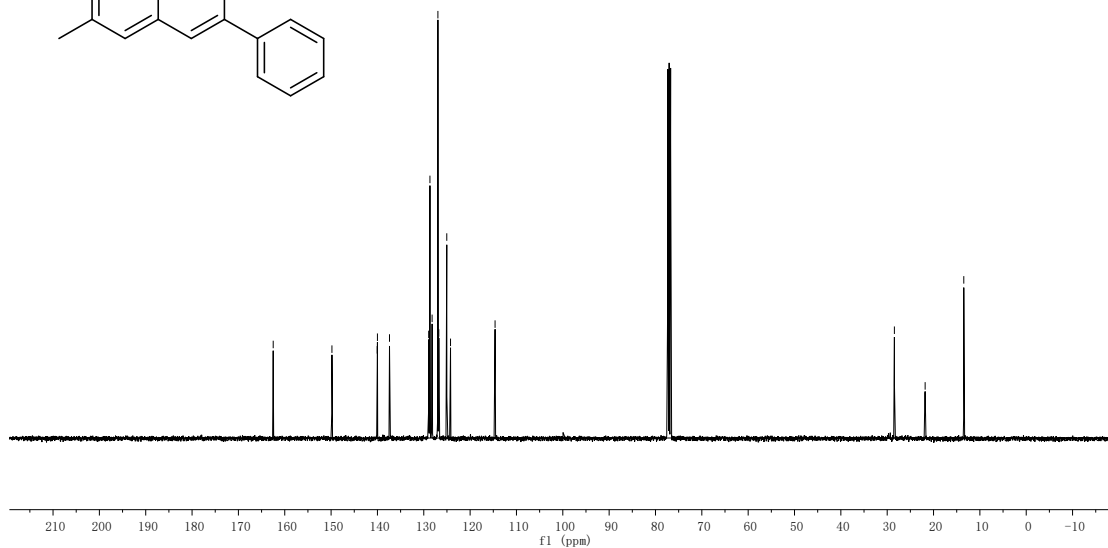
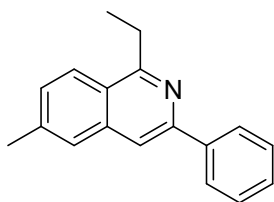
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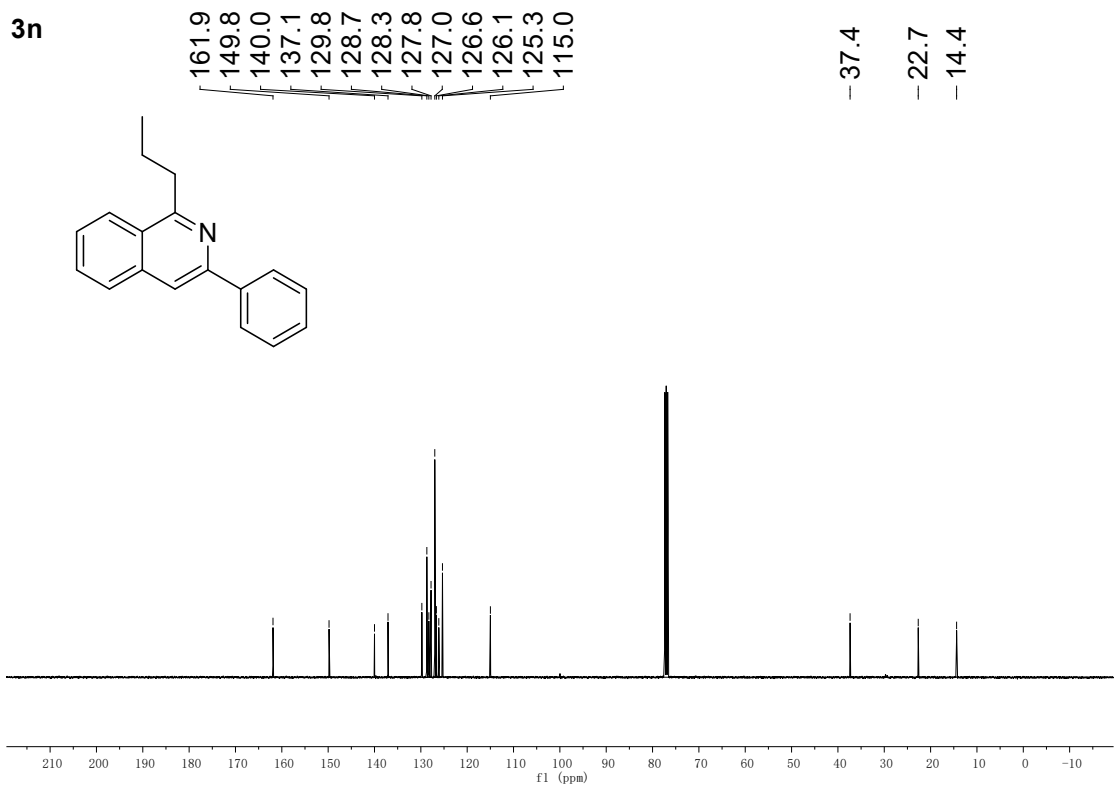
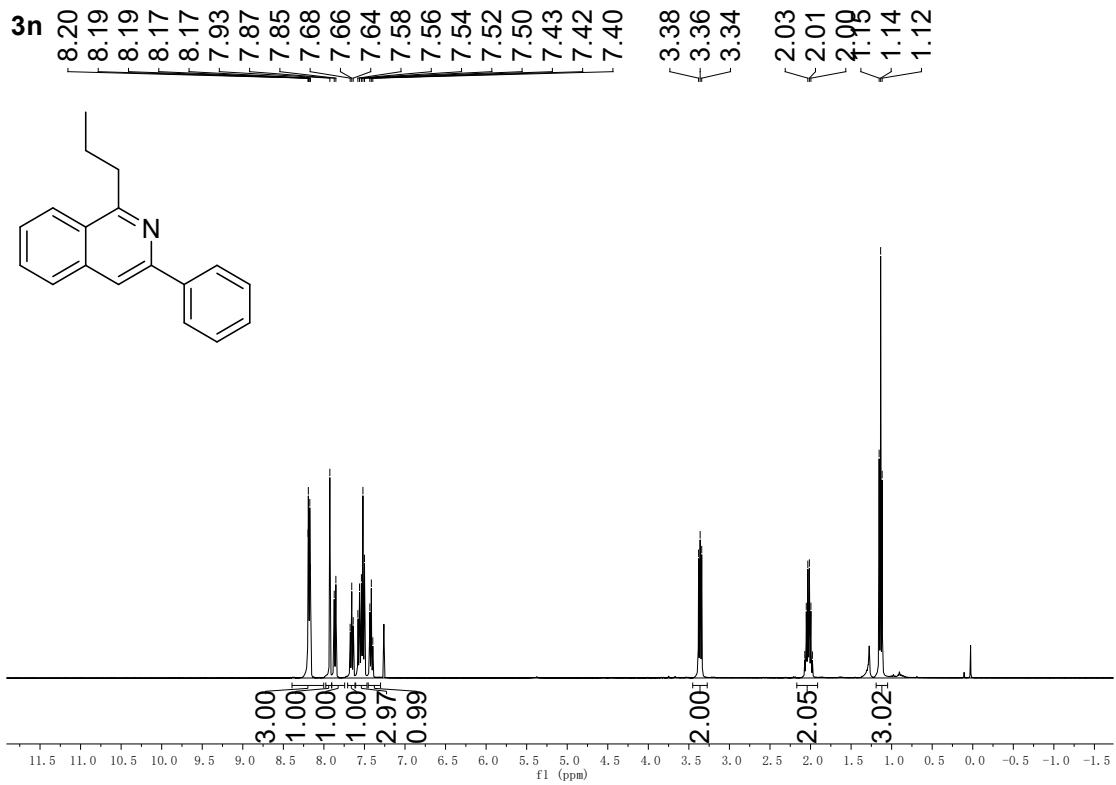


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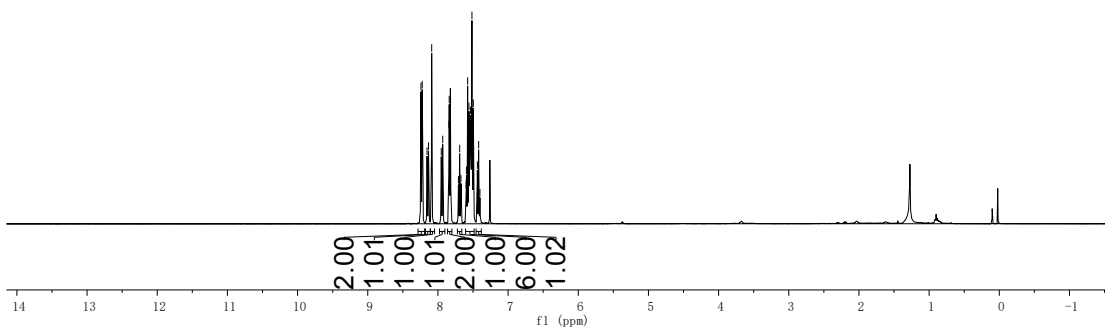
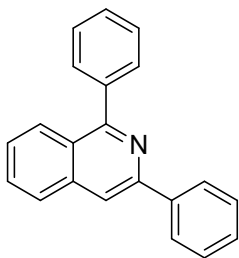
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114.6

~28.4  
~21.8  
~13.5

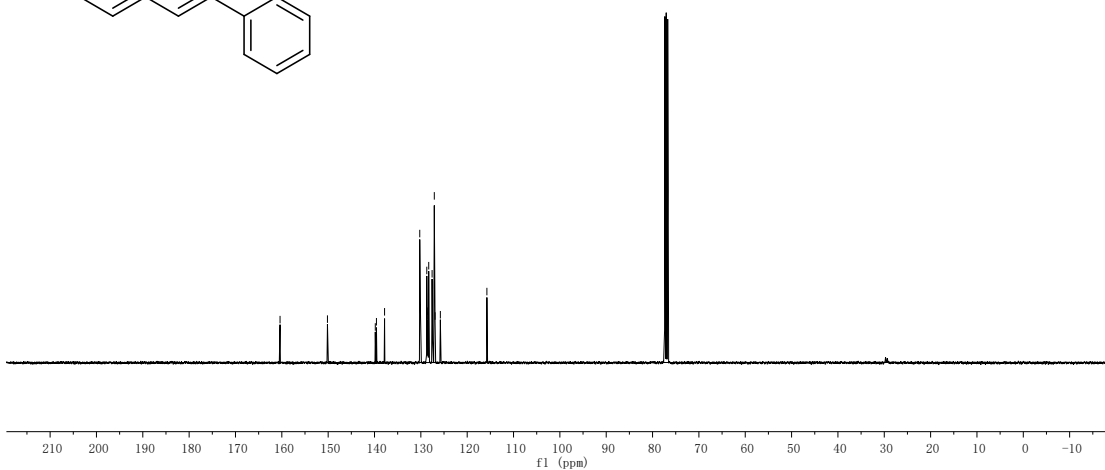
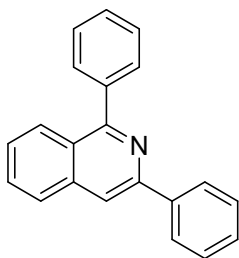


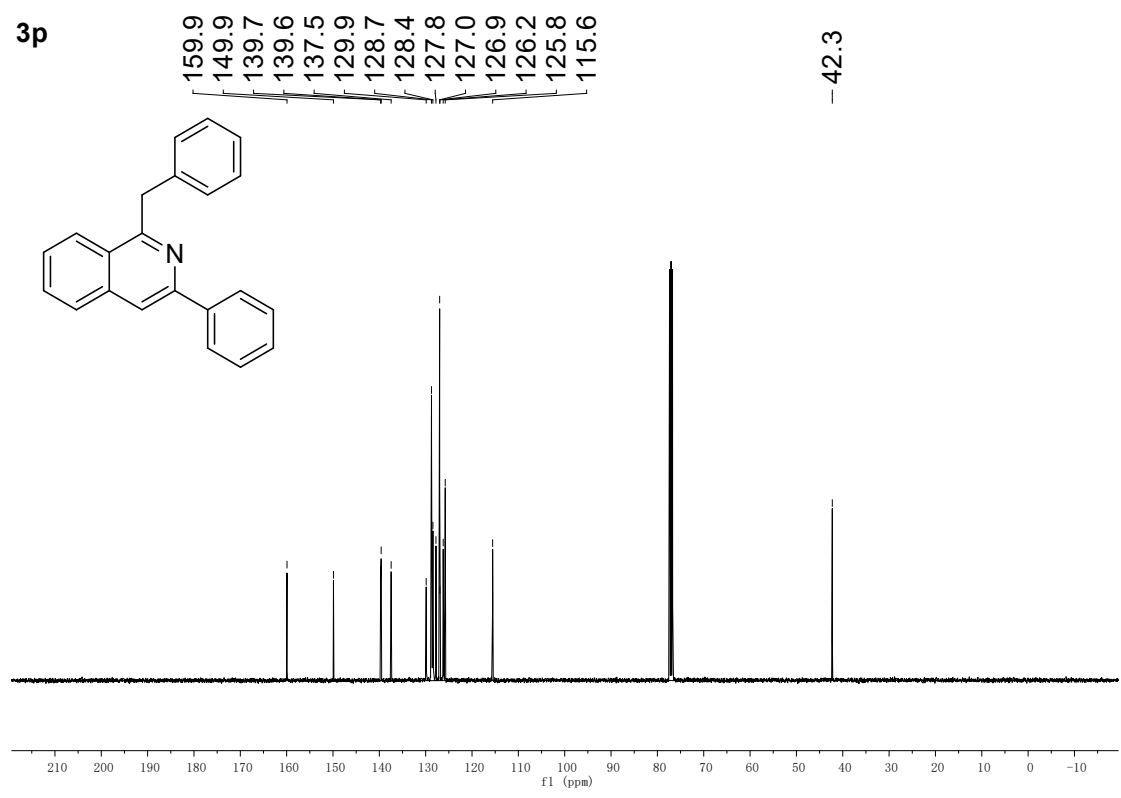
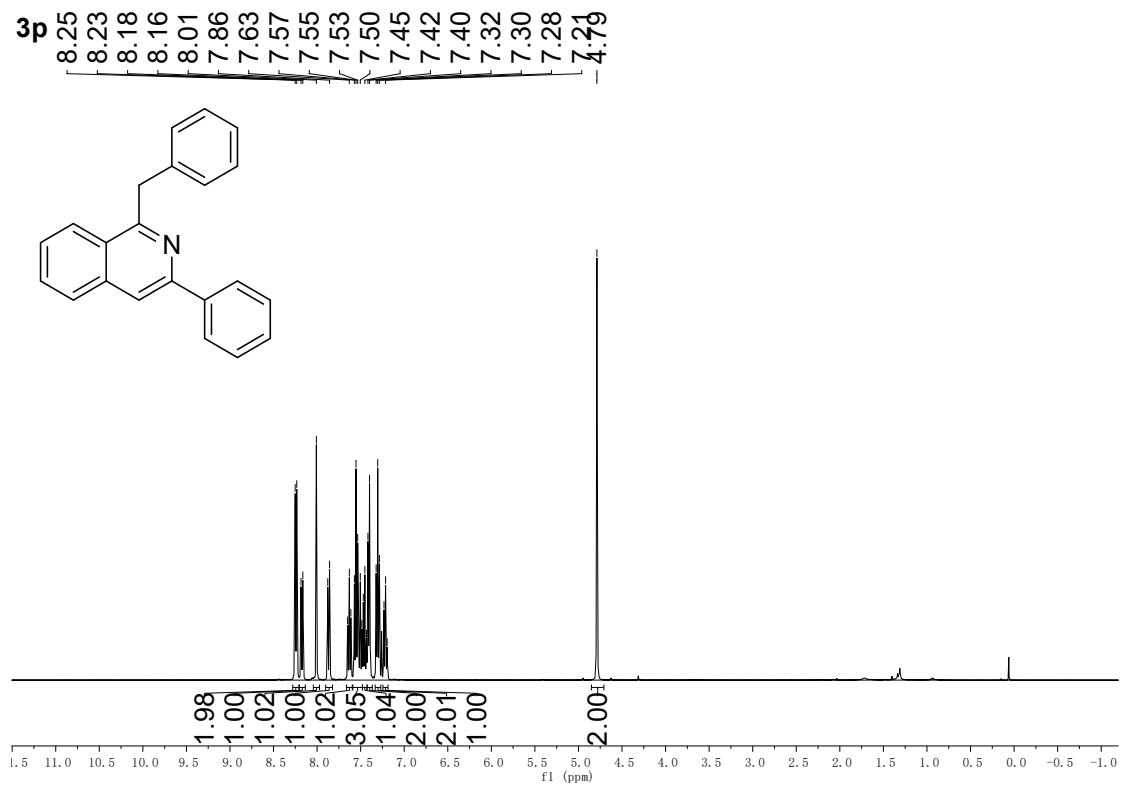


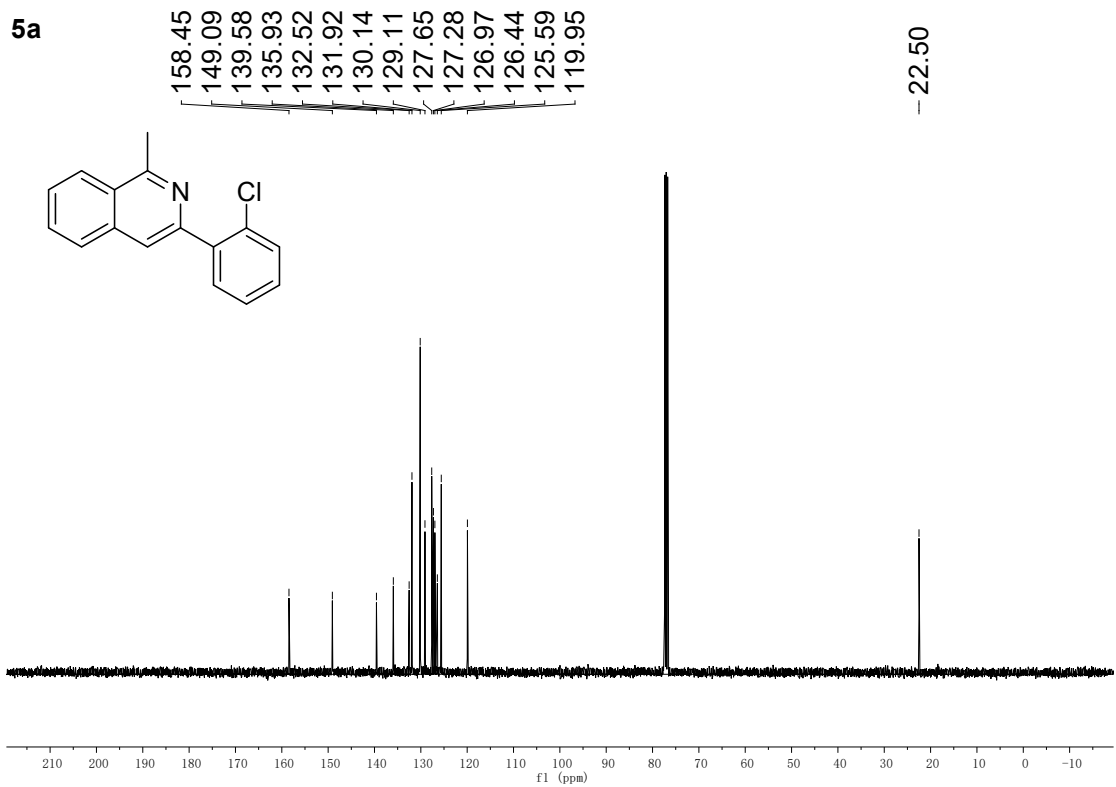
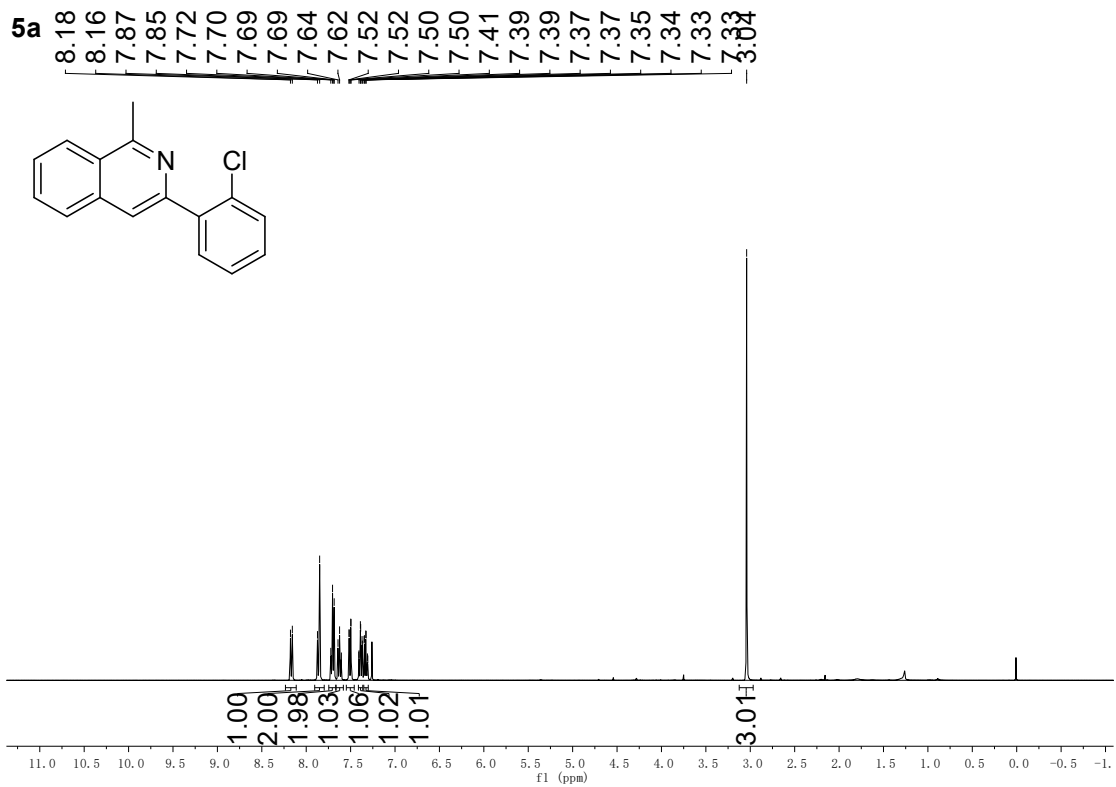
3o 8.24 8.22 8.15 8.13 8.09 7.95 7.93 7.84 7.84 7.82 7.71 7.69 7.67 7.60 7.59 7.58 7.56 7.55 7.55 7.54 7.53 7.52 7.50 7.44 7.42 7.40



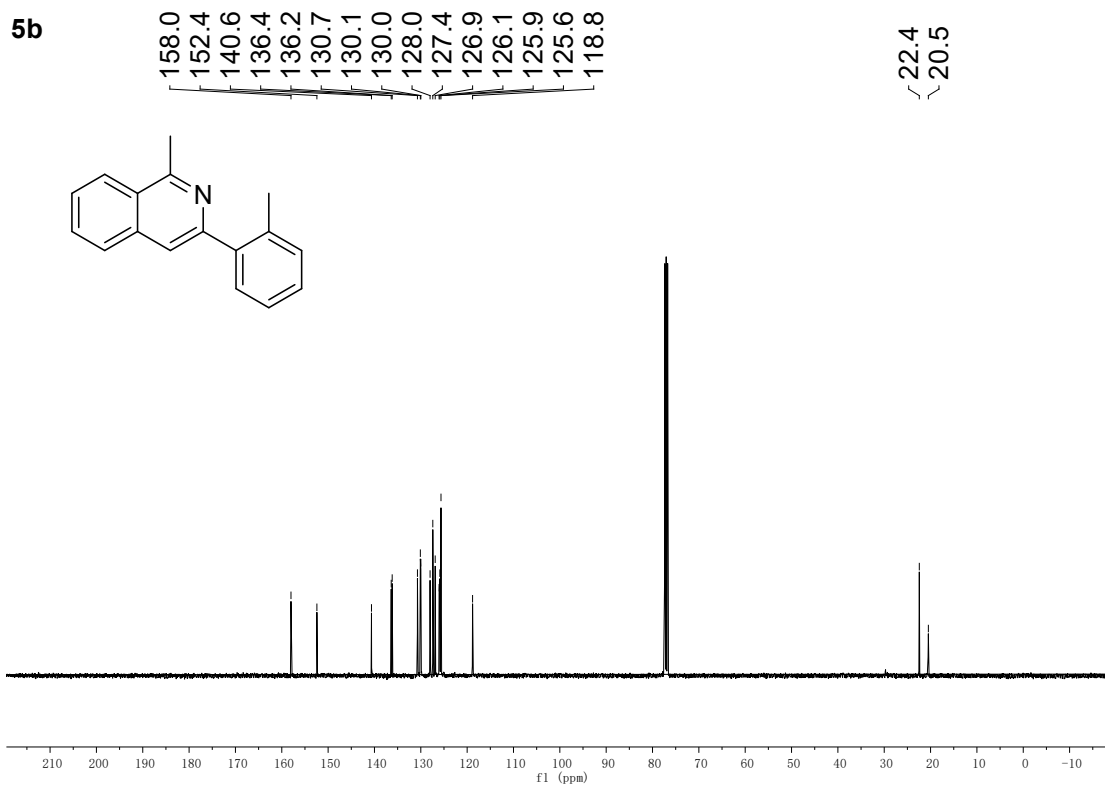
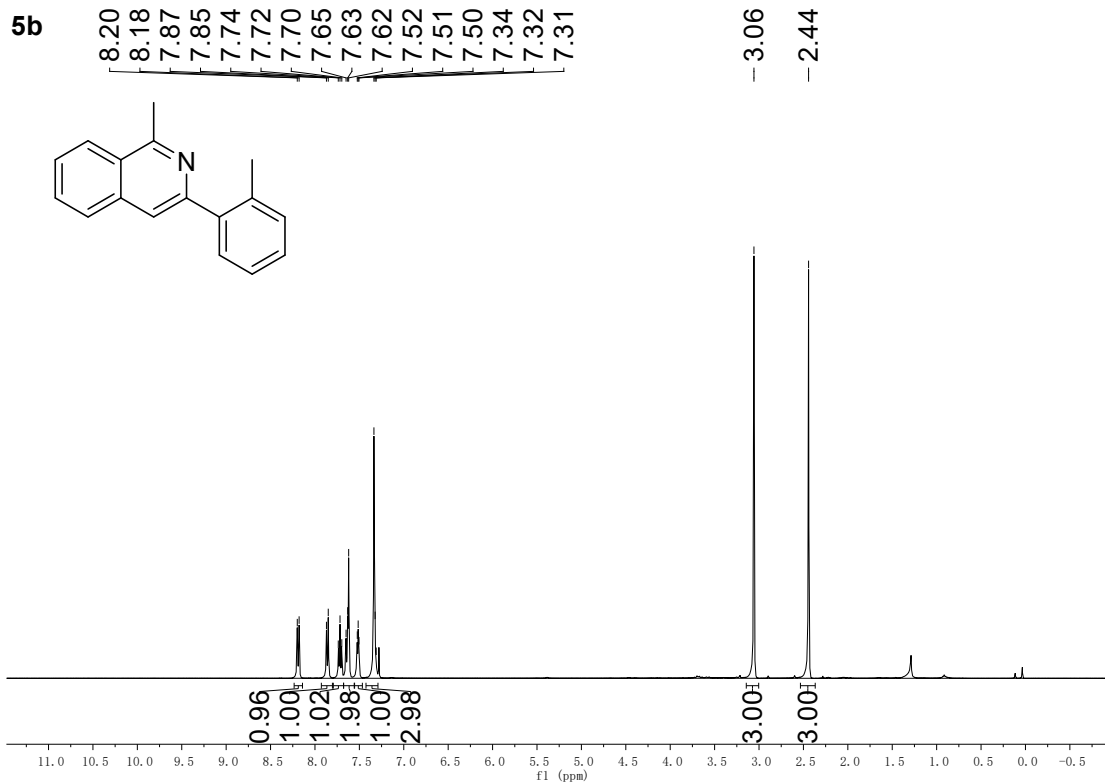
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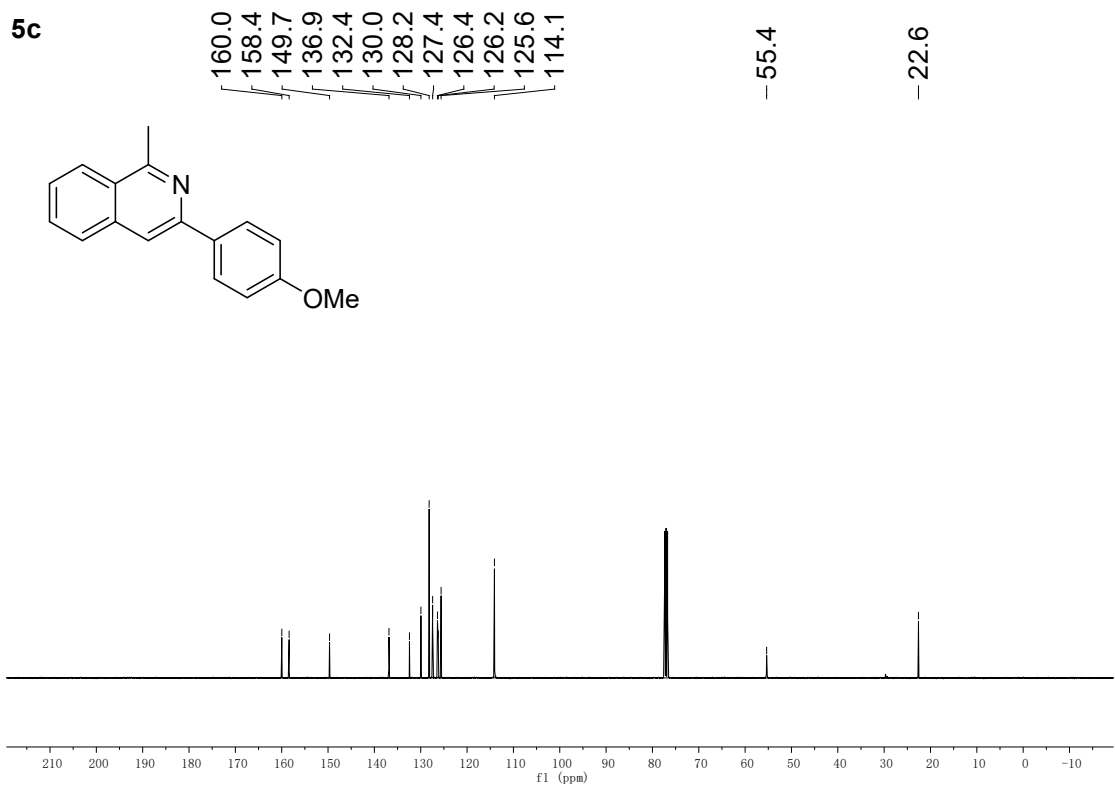
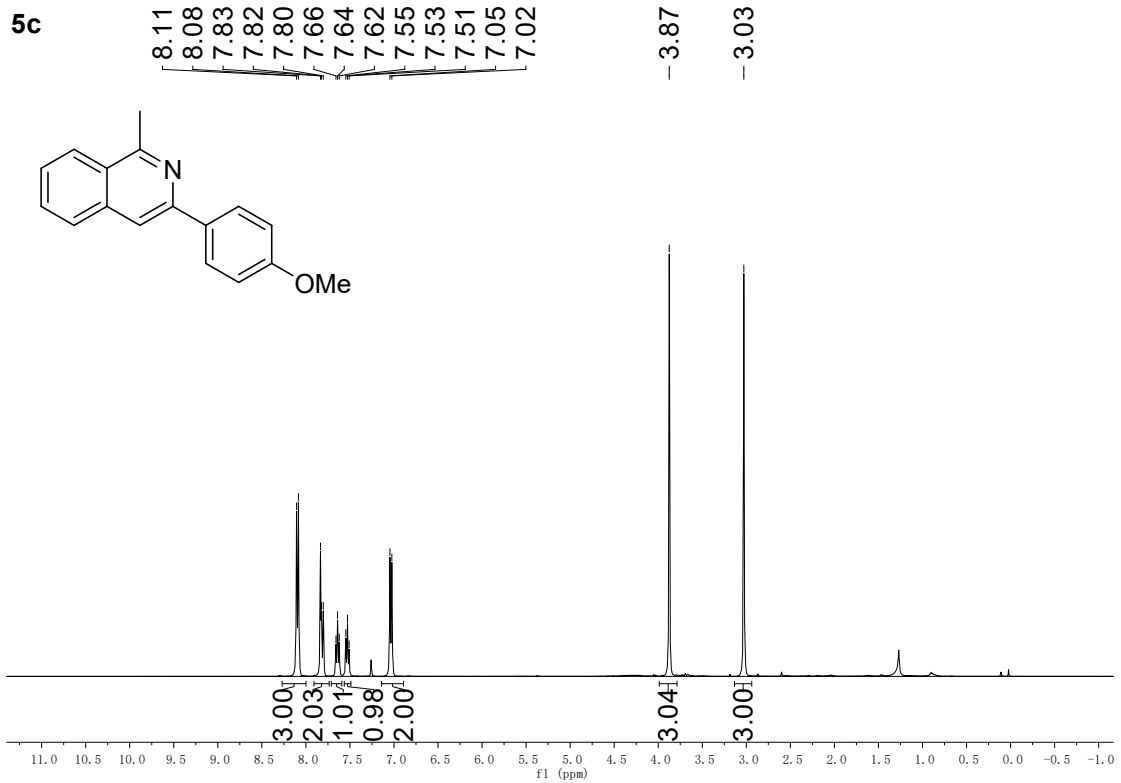




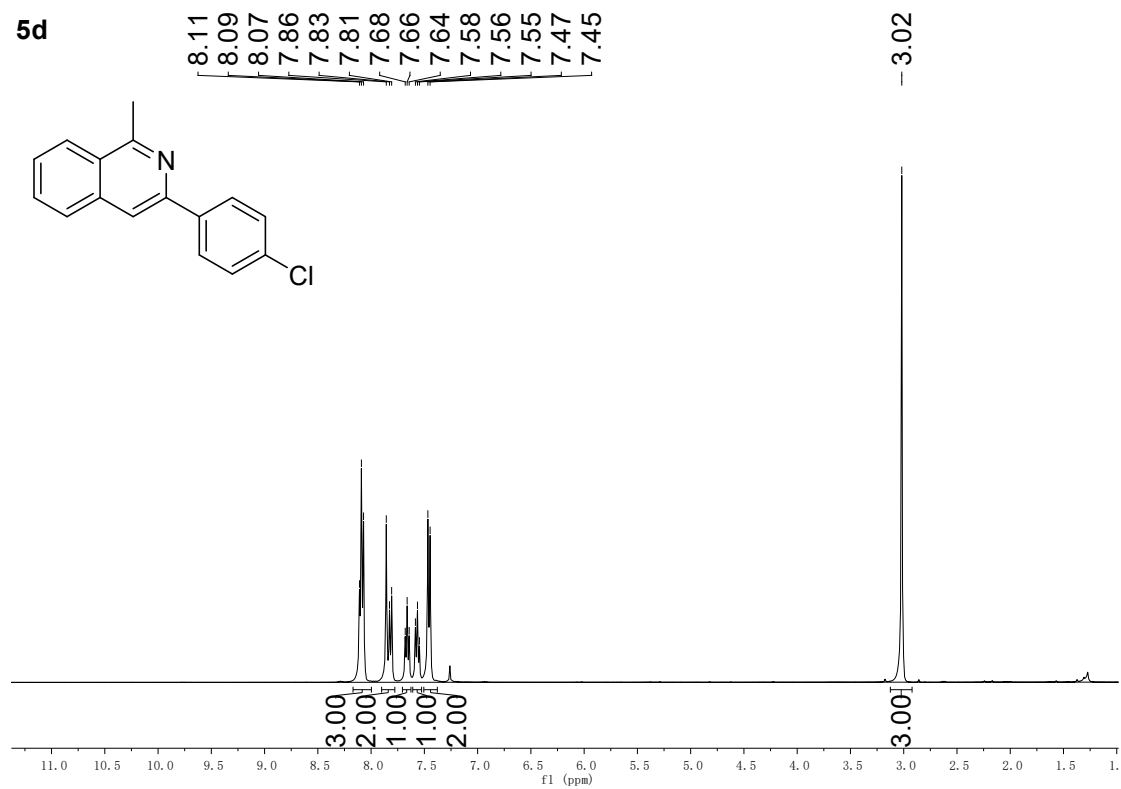




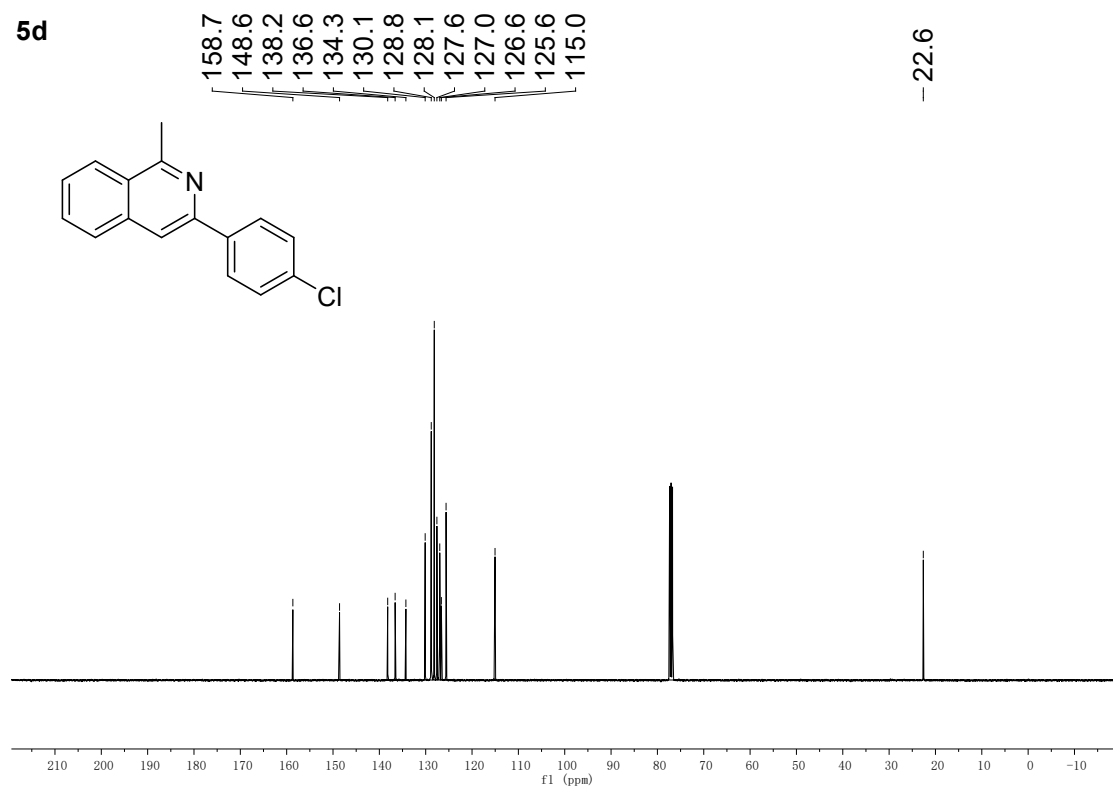


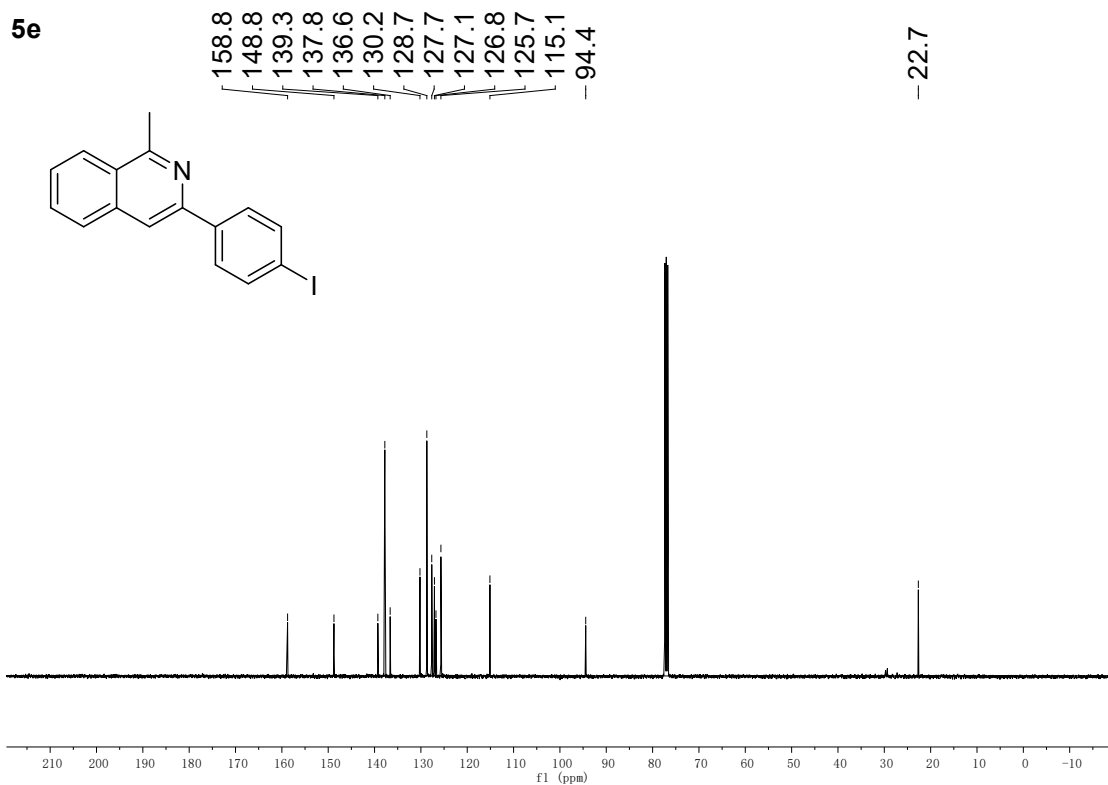
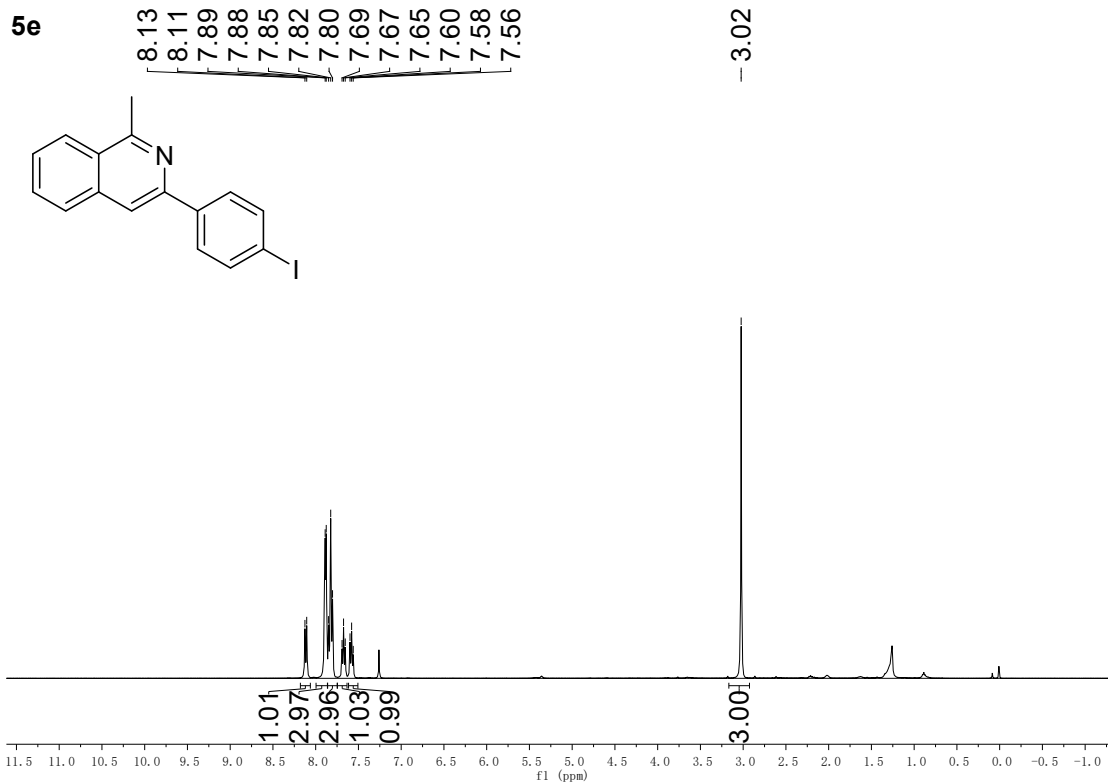


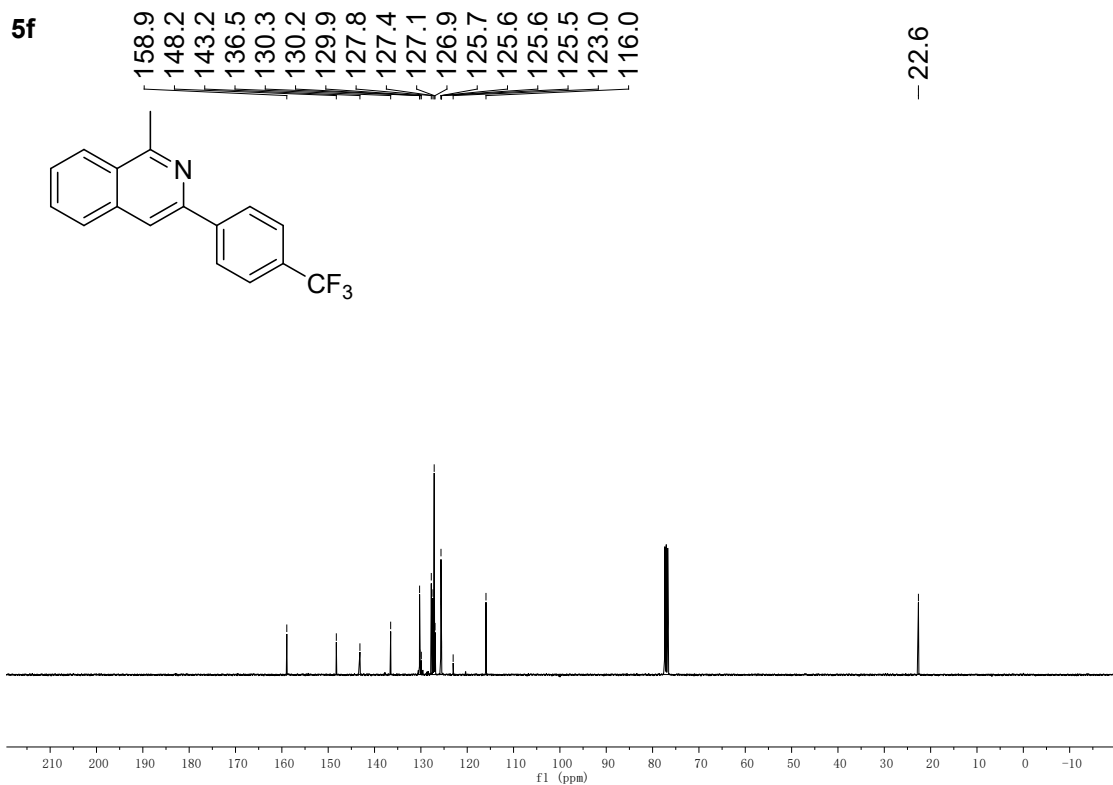
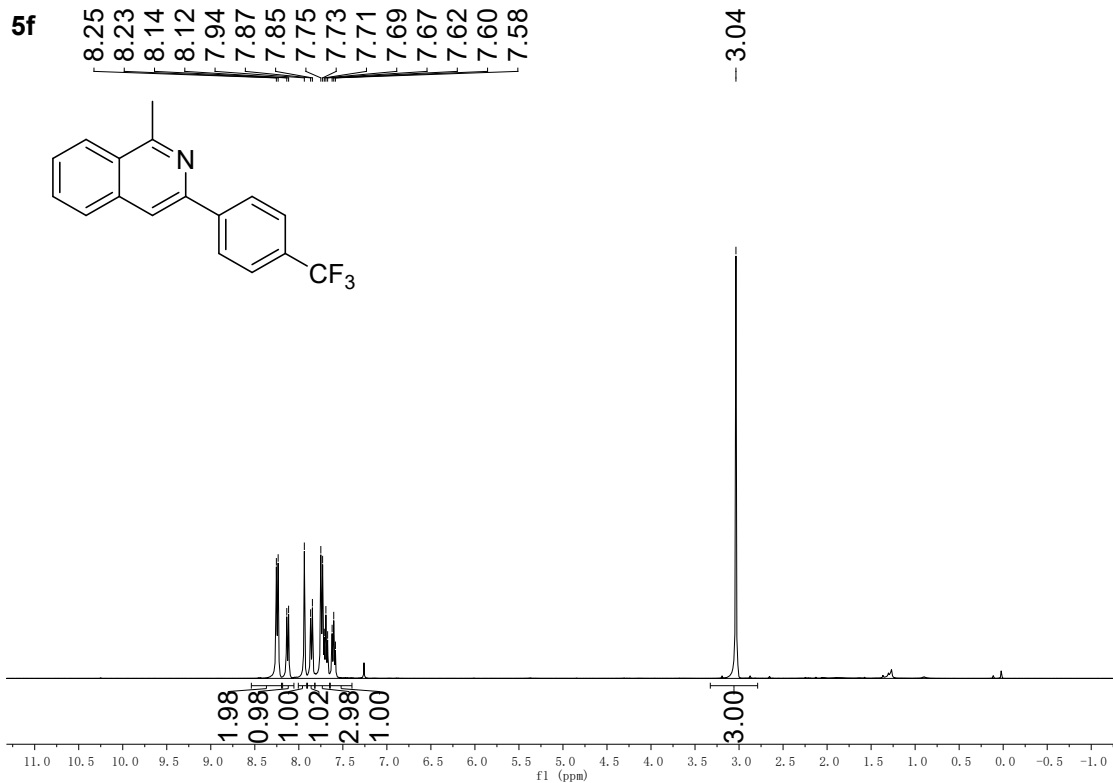
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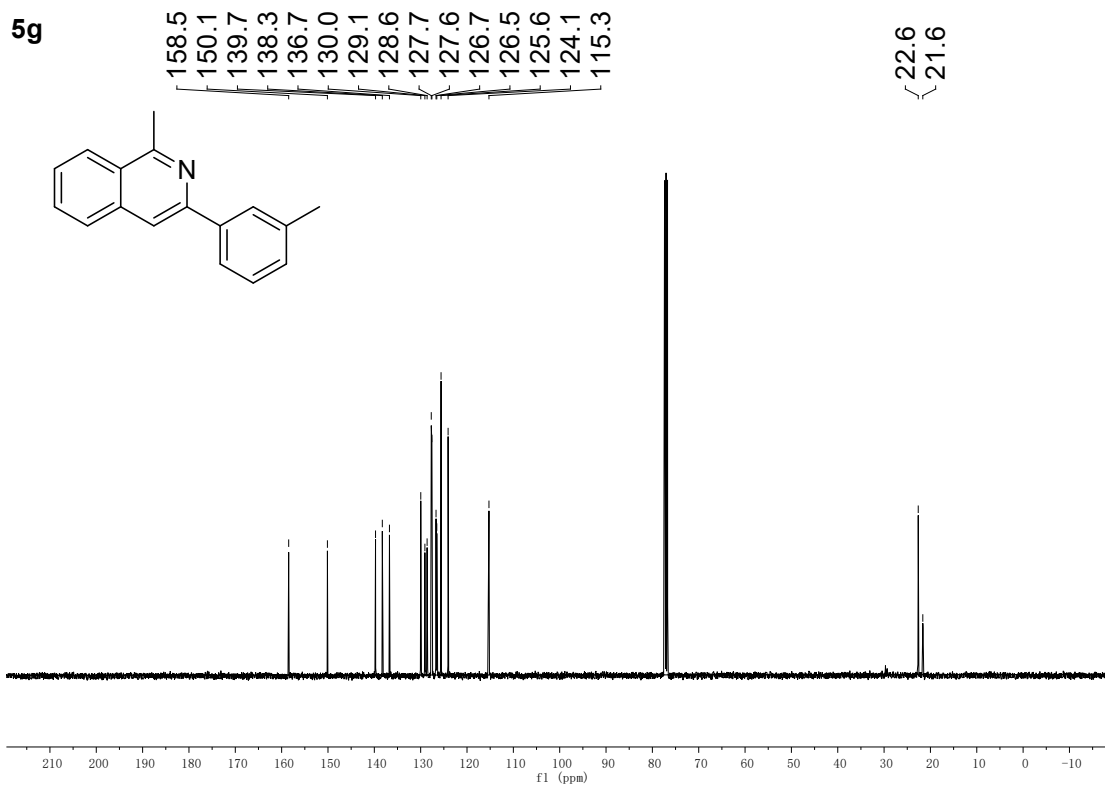
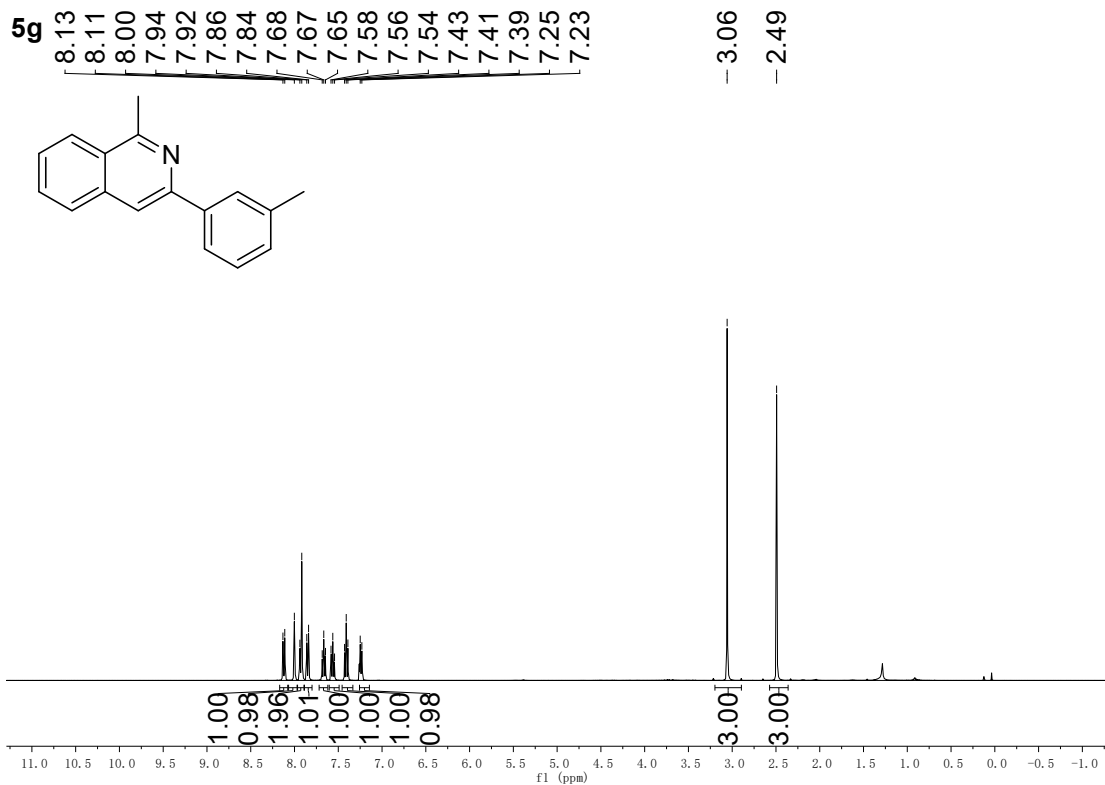


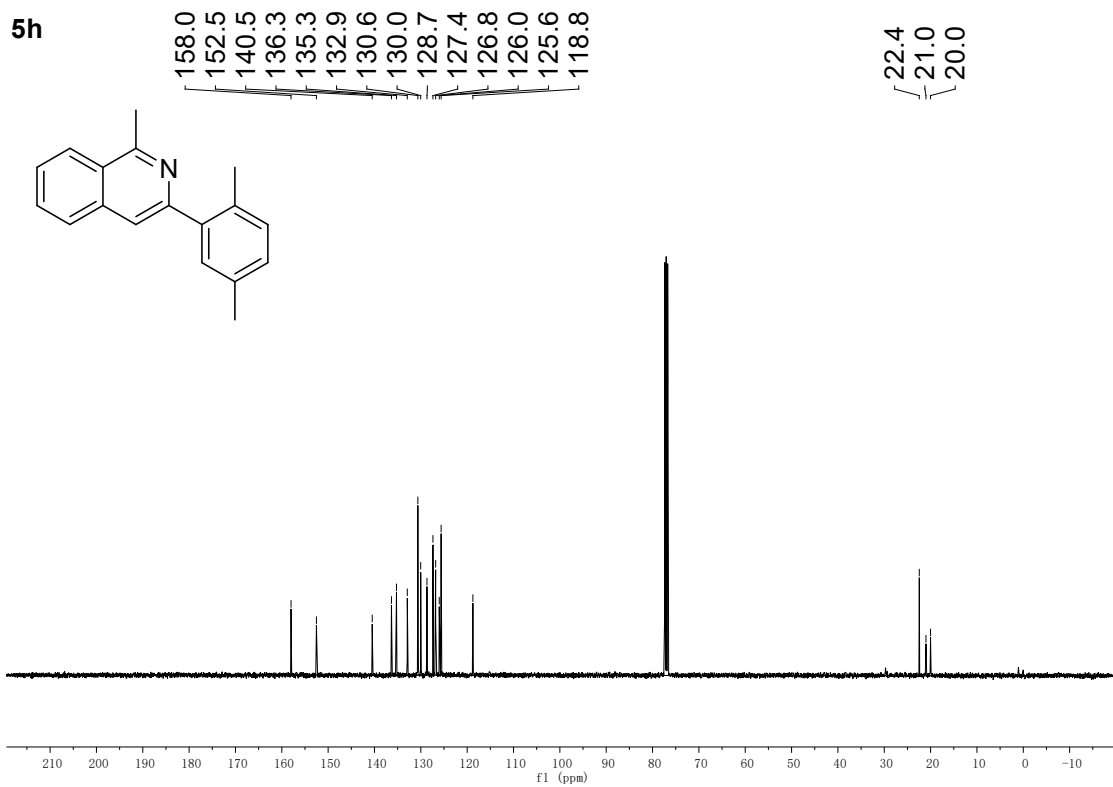
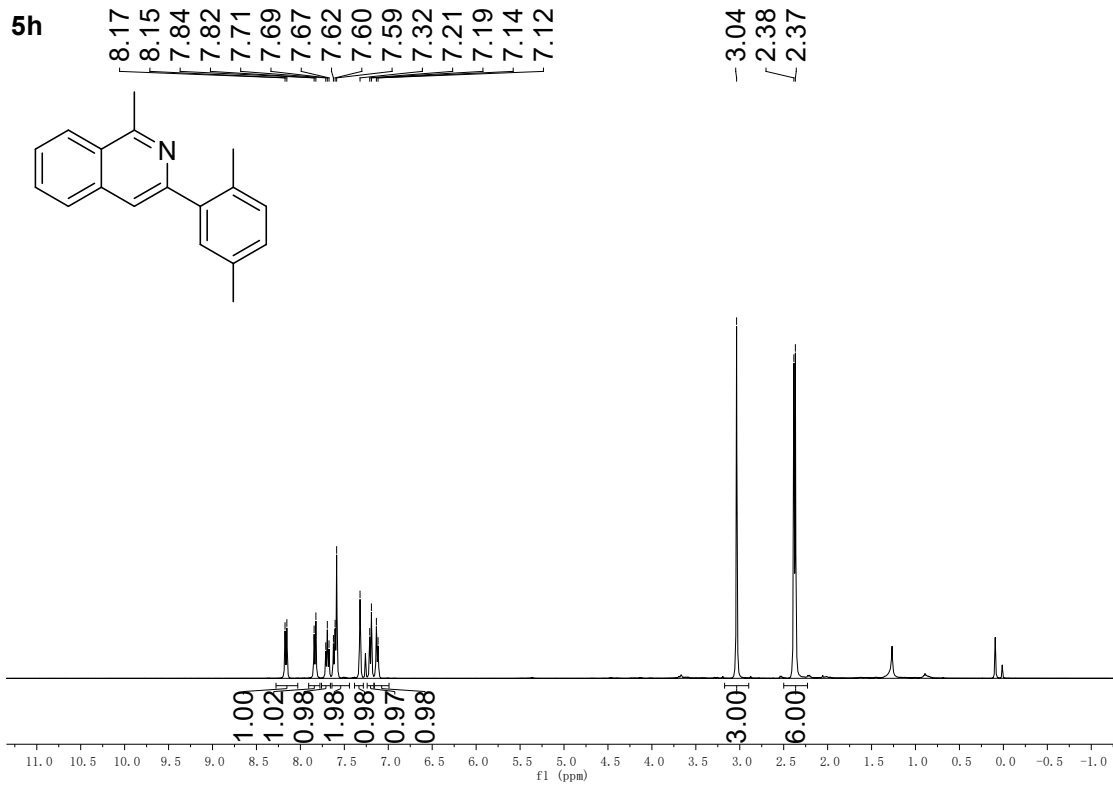
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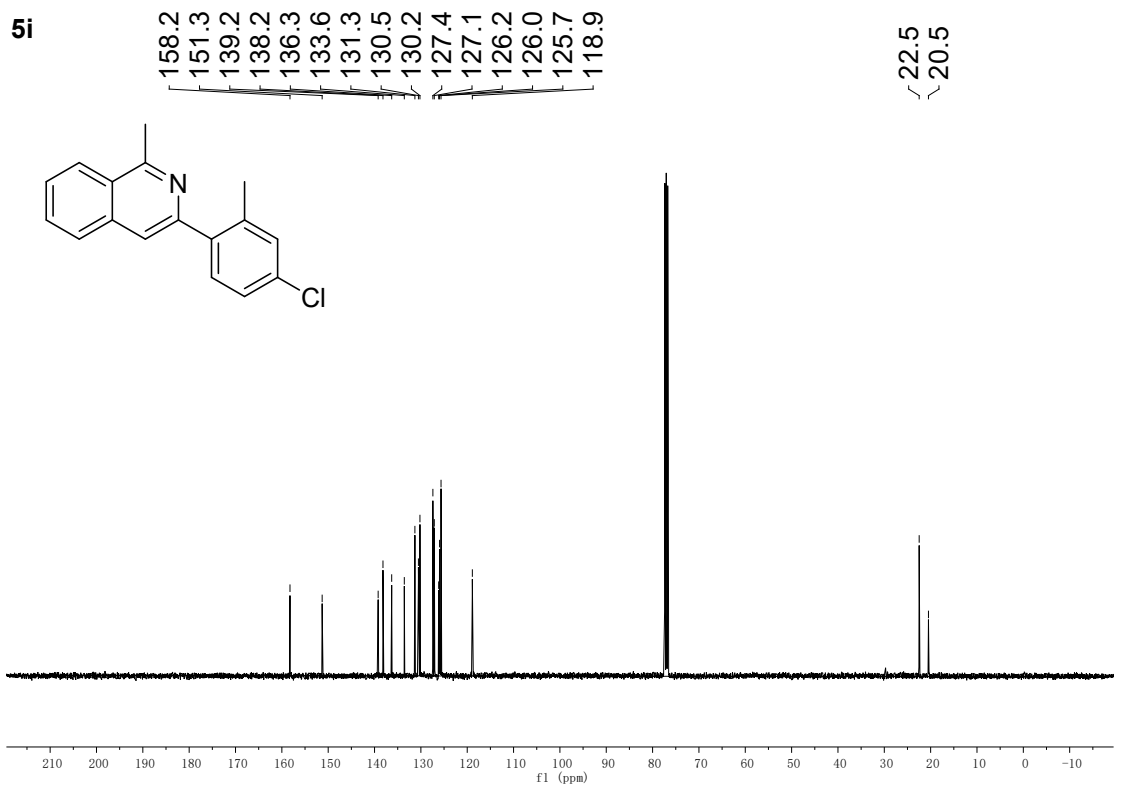
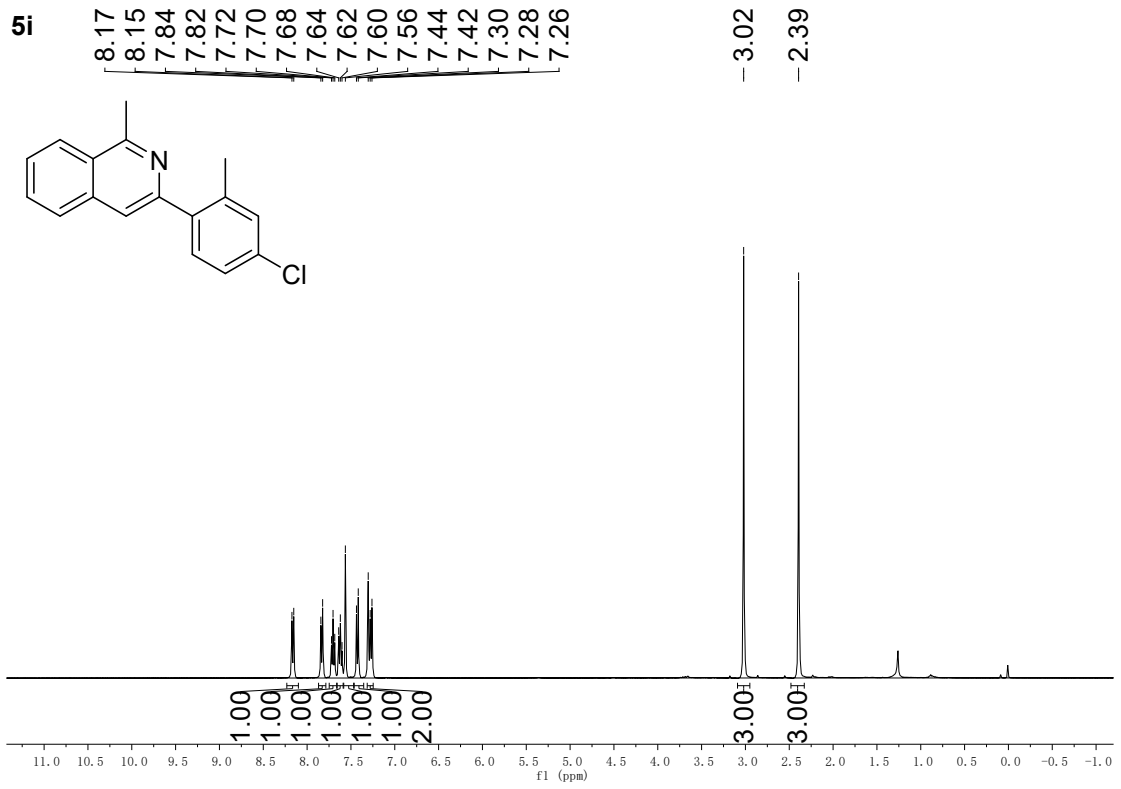




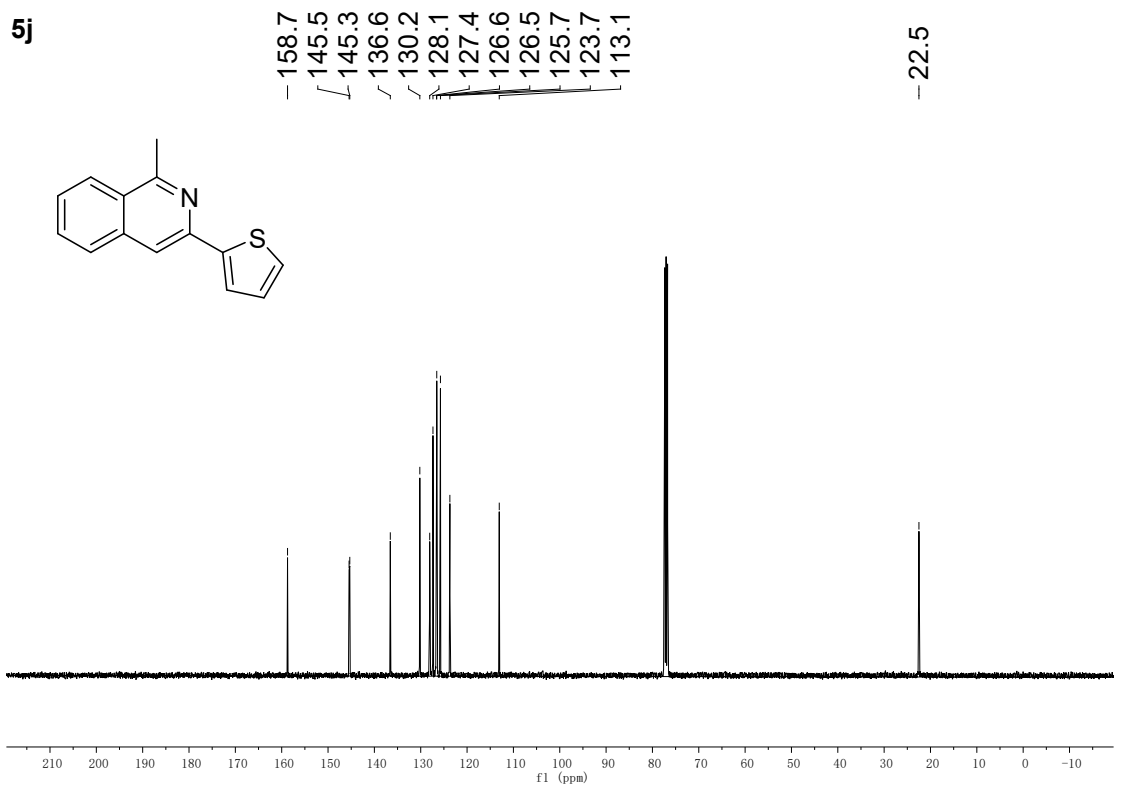
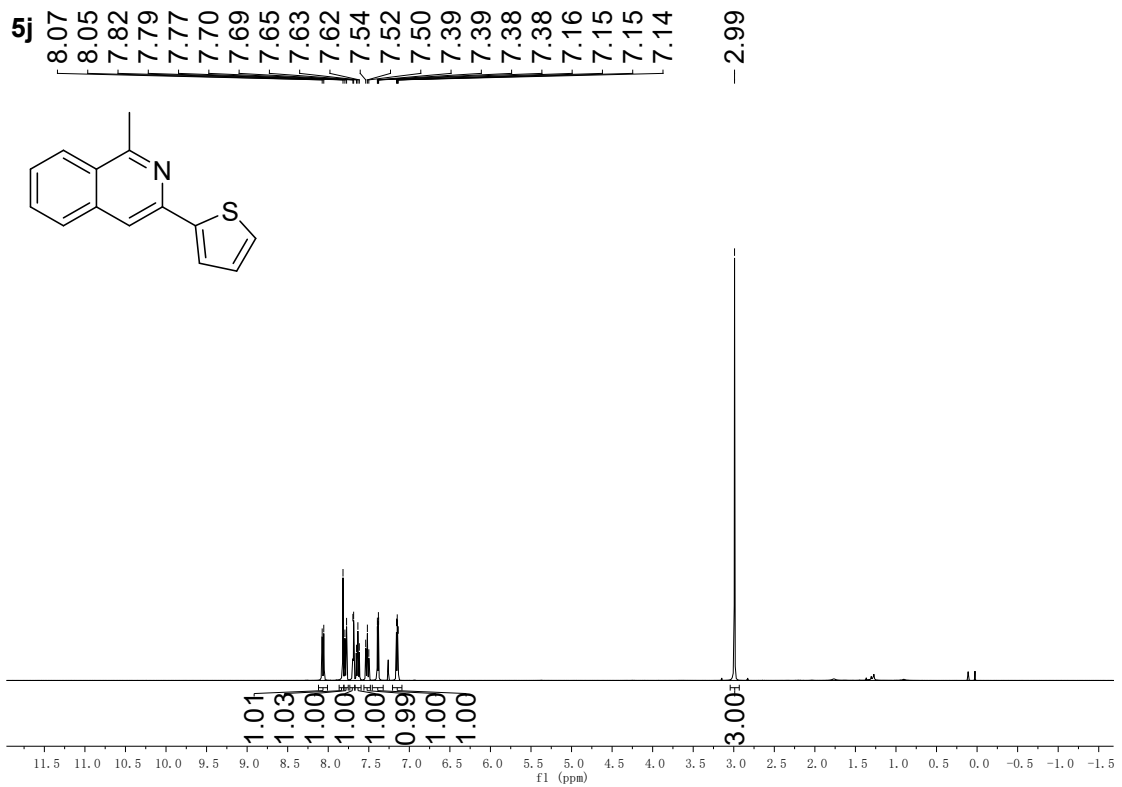


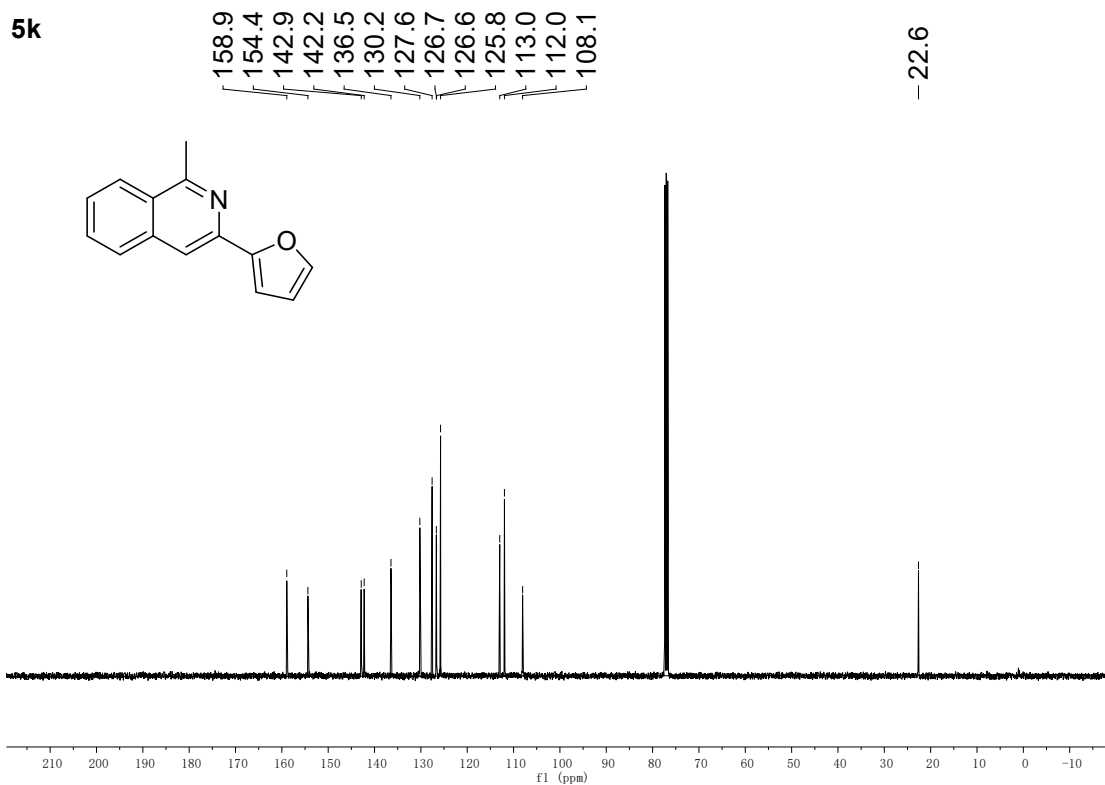
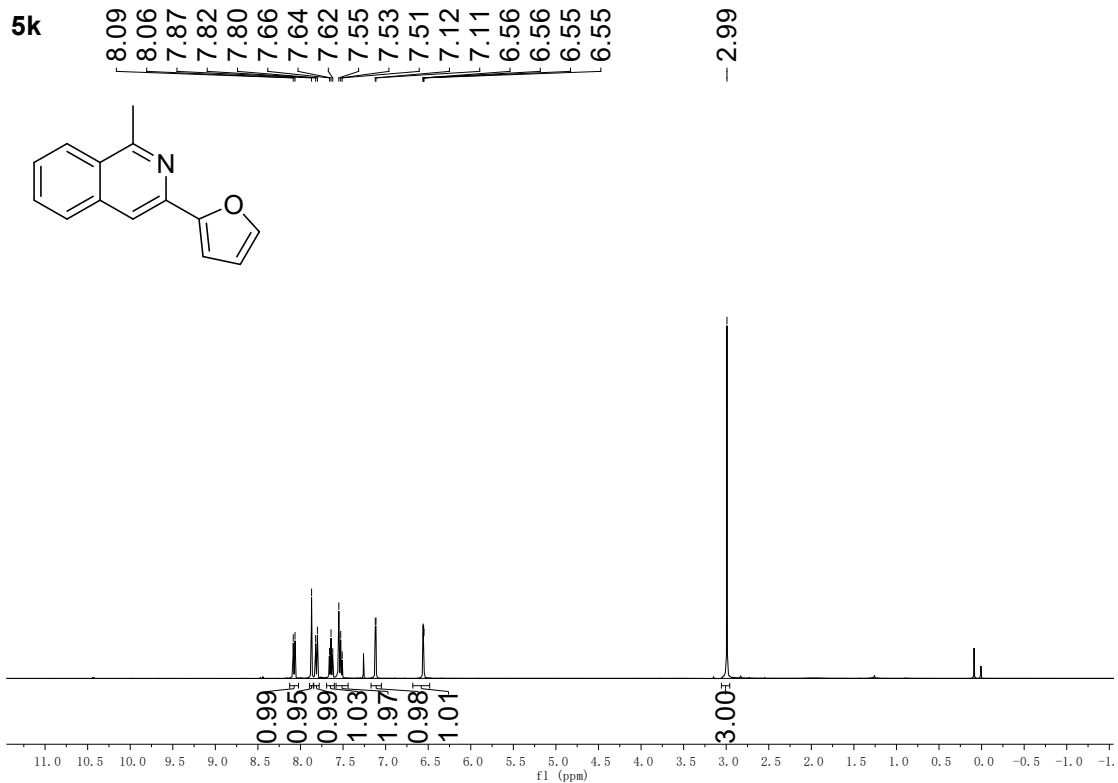




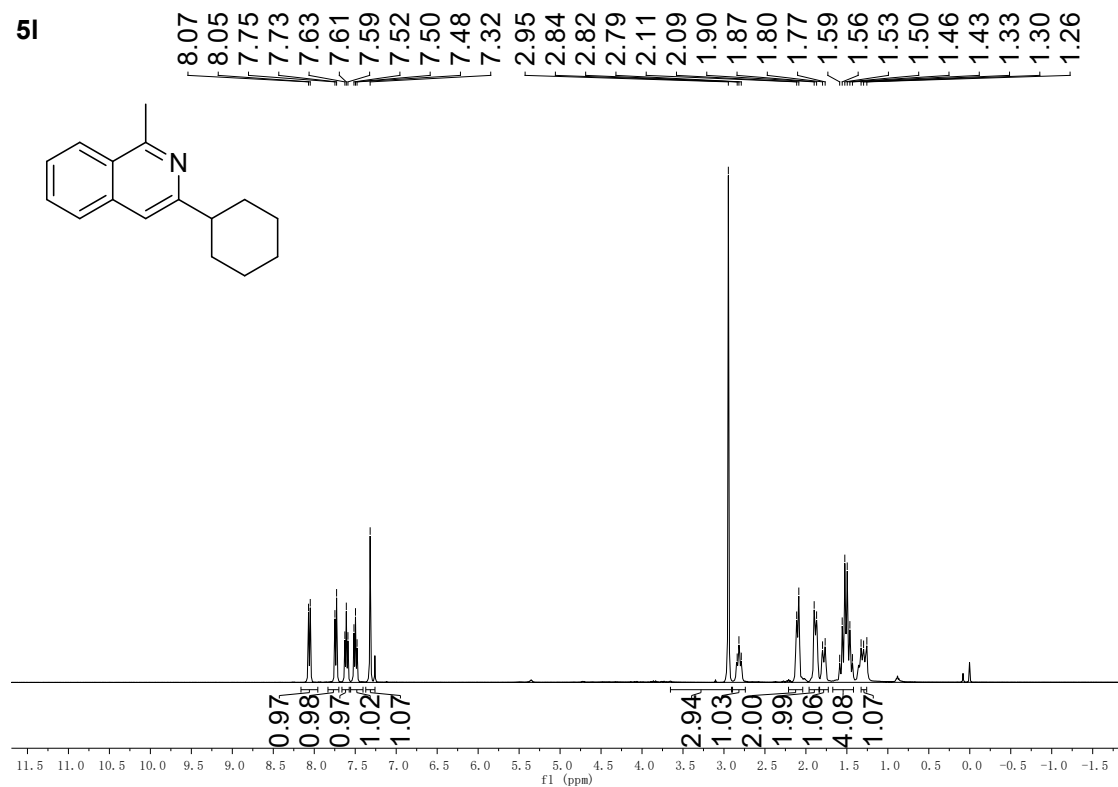




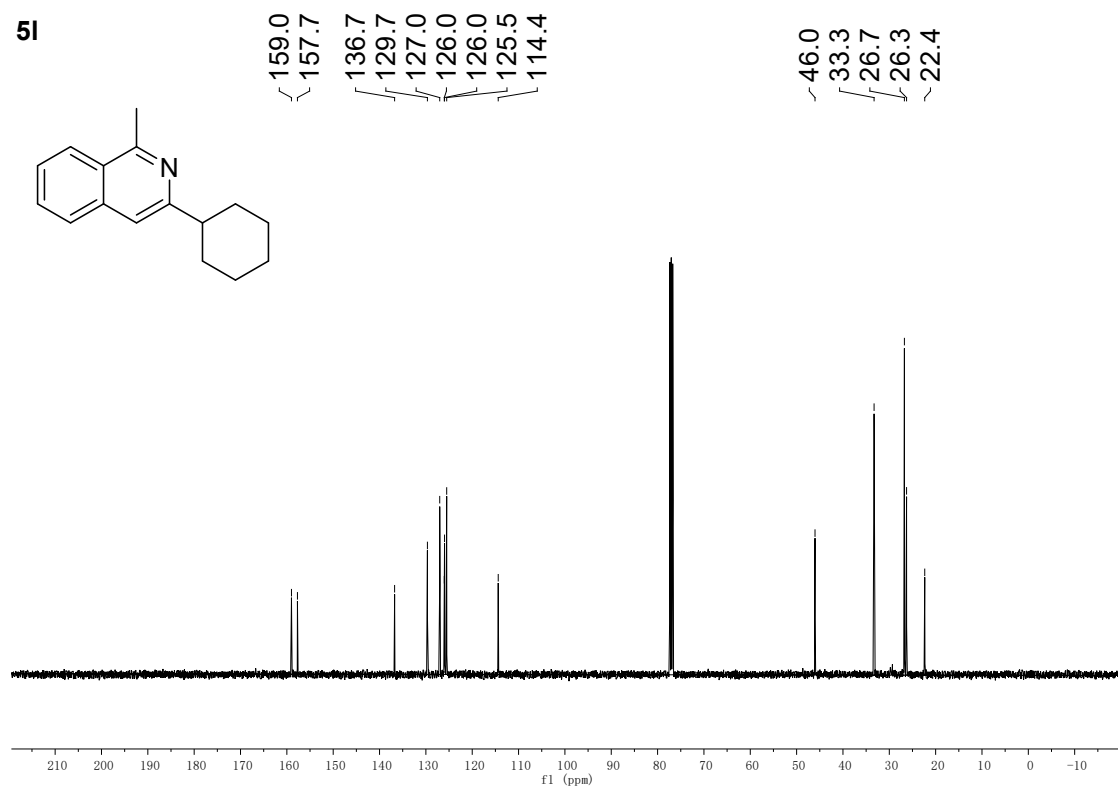




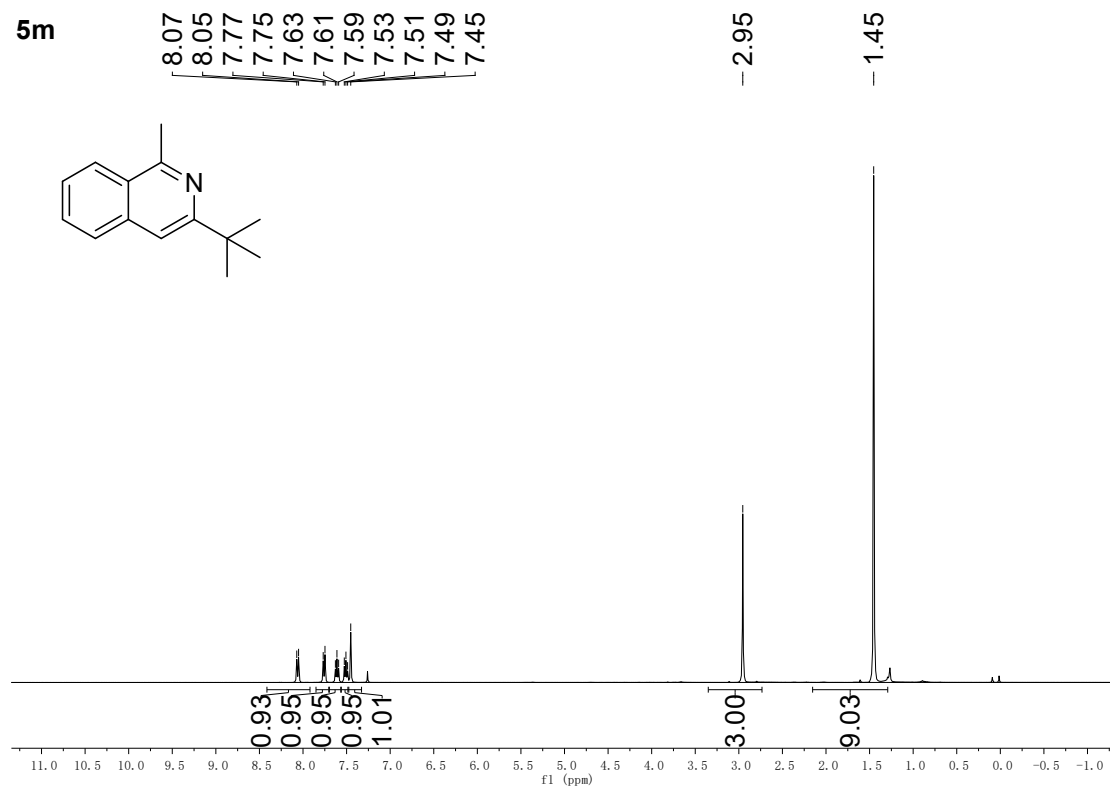
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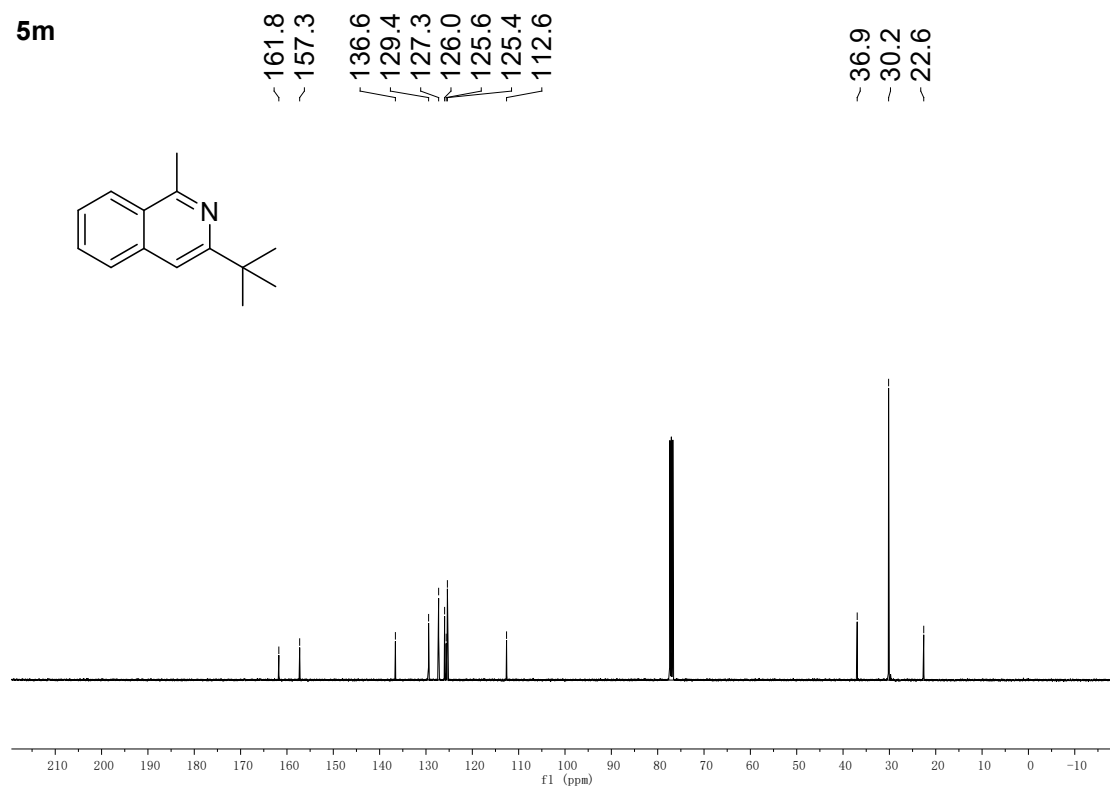
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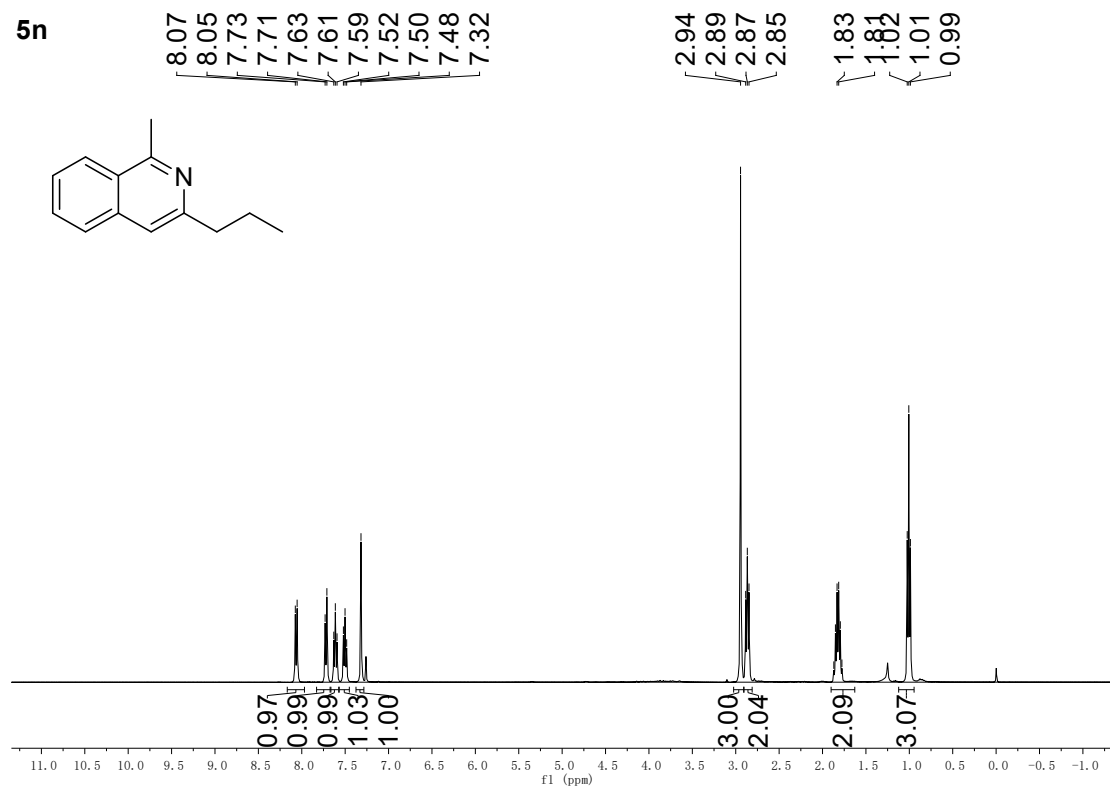
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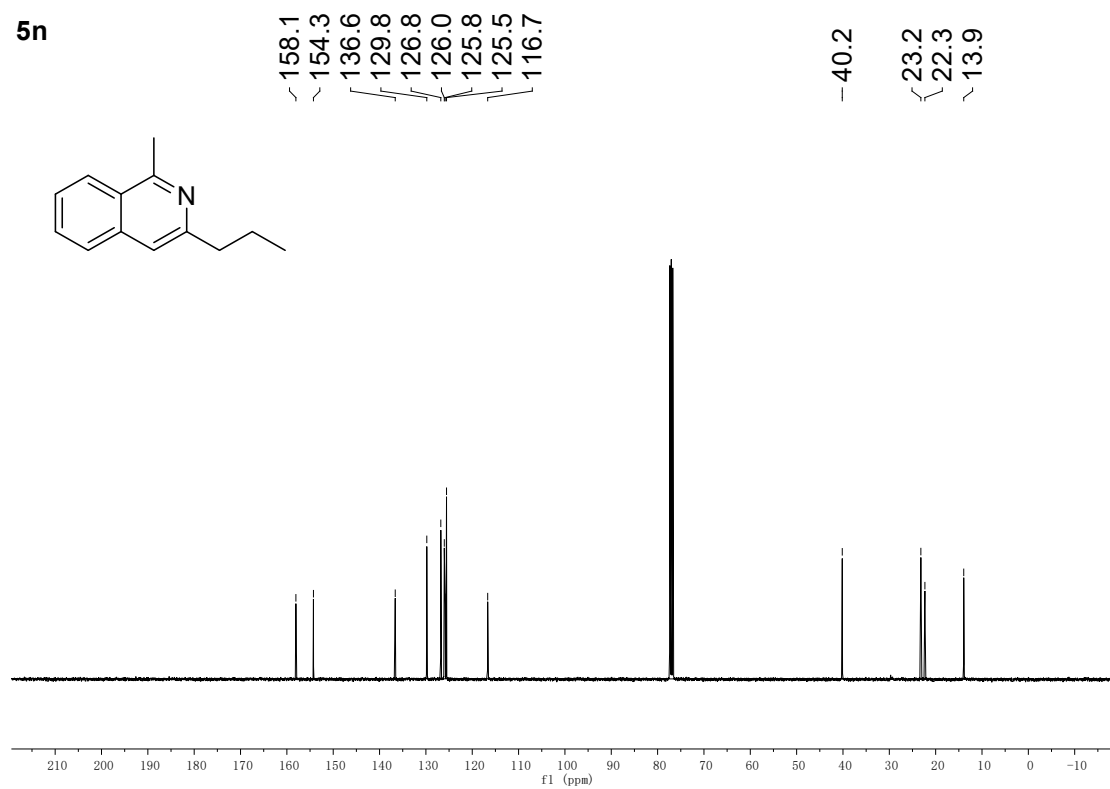
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5n

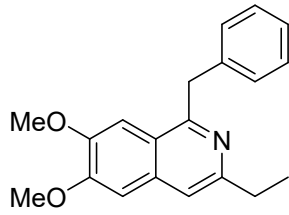


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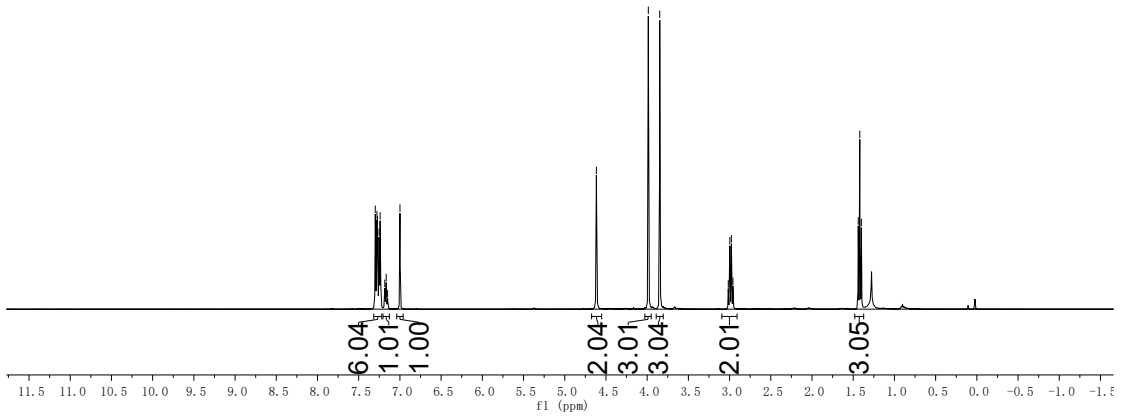


**Moxaverine**

7.30  
7.28  
7.27  
7.25  
7.24  
7.18  
7.17  
7.15  
7.00  
-4.62  
3.99  
3.85  
3.02  
3.00  
2.98  
2.96  
1.44  
1.42  
1.40

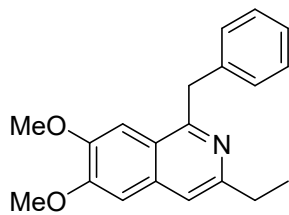


**Moxaverine**



**Moxaverine**

157.0  
154.6  
152.4  
149.1  
139.7  
134.3  
128.4  
126.1  
121.0  
115.5  
115.4  
104.8  
104.3  
55.8  
55.7  
42.6  
30.9  
-14.3



**Moxaverine**

