

# **Cu-Catalyzed Synthesis of 3-Formyl imidazo[1,2-a]pyridines and Imidazo[1,2-a]pyrimidines by Employing Ethyl Tertiary Amines as Carbon Sources**

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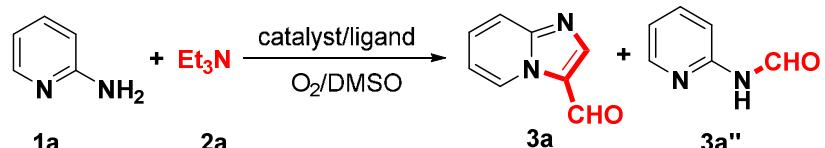
## 1. General information

All chemicals were purchased from Adamas Reagent, energy chemical company, J&K Scientific Ltd, Bide Pharmatech Ltd and Tansoole.  $\text{CH}_3\text{CN}$  was dried by  $\text{CaH}$  prior to use. Unless otherwise stated, all experiments were conducted in a sealed tube under air atmosphere. Reactions were monitored by TLC or GC-MS analysis. Flash column chromatography was performed over silica gel (200-300 mesh).

$^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker Avance 500 spectrometer (500 MHz  $^1\text{H}$ , 125 MHz  $^{13}\text{C}$ ) at room temperature. Chemical shifts were reported in ppm on the scale relative to  $\text{CDCl}_3$  ( $\delta = 7.26$  for  $^1\text{H}$ -NMR,  $\delta = 77.00$  for  $^{13}\text{C}$ -NMR) as an internal reference. High resolution mass spectra were recorded using a Thermo Fisher Scientific LTQ FT Ultra or Waters Micromass GCT Premier instrument. Coupling constants ( $J$ ) were reported in Hertz (Hz).

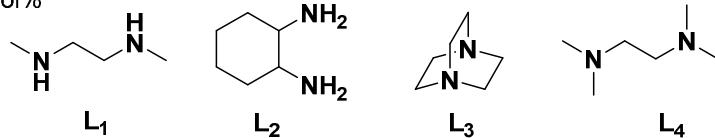
## 2. Optimization of the reaction conditions

### 2.1. Optimization of the reaction conditions for 3a

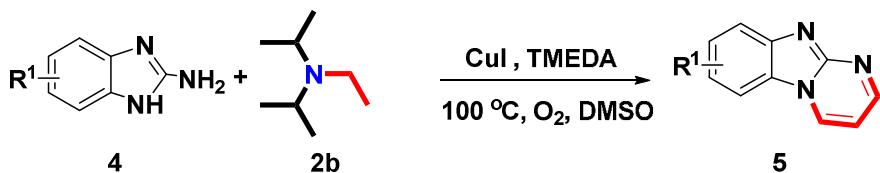


entry	catalyst	temp/°C	Ligand	(yield of 3a) <sup>a</sup>	(yield of 3a'') <sup>a</sup>
1	CuI	130	L <sub>1</sub>	20%	10%
2	CuBr	130	L <sub>1</sub>	Trace	trace
3	Cu(OAc) <sub>2</sub>	130	L <sub>1</sub>	N.D.	N.D.
4	Pd(OAc) <sub>2</sub>	130	L <sub>1</sub>	N.D.	N.D.
5	CuI	60	L <sub>1</sub>	N.D.	N.D.
6	CuI	80	L <sub>1</sub>	25%	49%
7	CuI	100	L <sub>1</sub>	41%	33%
8	CuI	120	L <sub>1</sub>	32%	10%
9	CuI	150	L <sub>1</sub>	25%	trace
10	CuI	100	L <sub>1</sub>	63%	22%
11	CuI	100	L <sub>2</sub>	48%	20%
12	CuI	100	L <sub>3</sub>	10%	trace
13	CuI	100	L <sub>4</sub>	66%	23%
14 <sup>b</sup>	CuI	100	L <sub>4</sub>	58%	32%
15 <sup>c</sup>	CuI	100	L <sub>4</sub>	56%	25%
16 <sup>d</sup>	CuI	100	L <sub>4</sub>	47%	12%
17 <sup>e</sup>	CuI	100	L <sub>4</sub>	16%	9%

Reaction conditions: **1a** (0.5 mmol), **2a** (2.5 equiv), catalyst (20 mol%), Ligand (40 mol%), DMSO (1 mL), under O<sub>2</sub>, 24 h. <sup>a</sup> Isolated yield. <sup>b</sup> CuI 40 mol%. <sup>c</sup> TMEDA 20 mol%. <sup>d</sup> TMEDA 60 mol%. <sup>e</sup> TMEDA 100 mol%



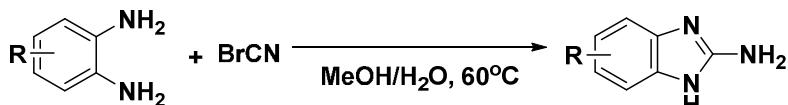
## 2.2. Optimization of the reaction conditions for 5a



entry	conditions	yield ( % )
1	without change	30
2	using DMF instead of DMSO	32
3	using toluene instead of DMSO	trace
4	using THF instead of DMSO	45
5	using 1,4-Dioxane instead of DMSO	55
6	using CH3CN instead of DMSO	75

Reaction conditions: 4a (0.5 mmol), 2b (2.5 equiv), CuI (20 mol%), TMEDA (40 mol%), solvent (1 mL), at 100 °C, under O<sub>2</sub>, 24 h.

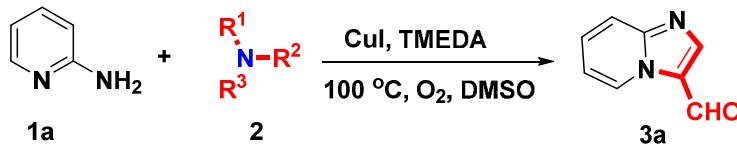
## 3. General Procedure for the Synthesis of 2-Aminobenzimidazole<sup>[1]</sup>



To a solution of *o*-phenylenediamine (540 mg, 5 mmol) in 1:1 mixture of MeOH (30 mL) and water (30 mL) was added CNBr (1590 mg, 15 mmol). The reaction mixture was stirred for 3 h at 60 °C. The reaction mixture was cooled to room temperature, the MeOH was removed under reduced pressure, and the remaining mixture was basified with 1.0 M aq. NaOH (to pH = 8.0) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated under reduced pressure, and the crude material was purified by silica gel column chromatography (MeOH/CH<sub>2</sub>Cl<sub>2</sub>=20:1) to obtain the compound as a white solid (109 mg, 82%).

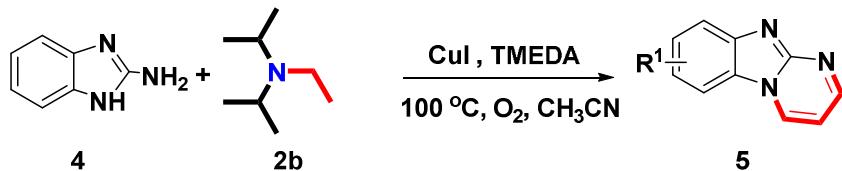
## 4. Typical procedures

### 4.1. Typical procedures for the synthesis of 3a



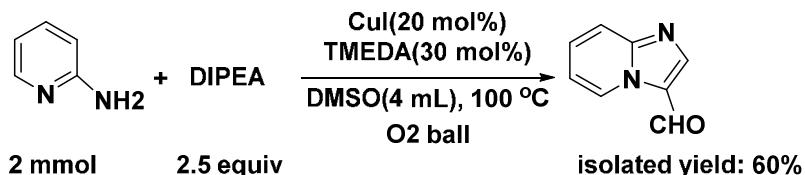
In a 25 mL reaction tube was charged with 2-aminopyridine (47 mg, 0.5 mmol), CuI (19 mg, 0.1 mmol), and DMSO (2 mL). Then TMEDA (30  $\mu$ L, 0.2 mmol) and DIPEA (220  $\mu$ L, 1.1 mmol) were added. The reaction mixture was stirred at 100 °C (oil bath) under O<sub>2</sub> for 24 hours. After the completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (10 mL). The filtrate was poured into water(15 mL) and extracted with ethylacetate (3  $\times$  5 mL). The combined organic phase was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel (petroleum ether/EtOAc= 1:2) to afford **3a** as a white solid

### 4.2. Typical procedures for the synthesis of 5a:



In a 25 mL reaction tube was charged with 1H-benzo[d]imidazol-2-amine (67 mg, 0.5 mmol), CuI (19 mg, 0.1 mmol), and CH<sub>3</sub>CN (2 mL). Then TMEDA (30  $\mu$ L, 0.2 mmol) and DIPEA (220  $\mu$ L, 1.1 mmol) were added. The reaction mixture was stirred at 100 °C (oil bath) under O<sub>2</sub> for 24 hours. After the completion of the reaction, the mixture was cooled to room temperature, then concentrated under reduced pressure. The residue was purified by silica gel (dichloromethane:EtOAc= 1:1) to afford **5a** as a yellow solid.

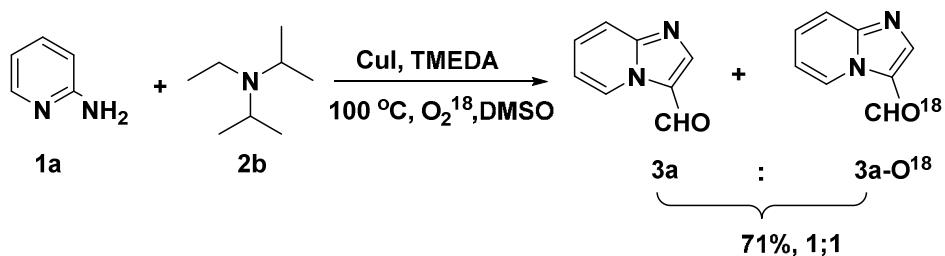
### 4.3. Typical procedures for scaling up 3a:



In a 50 mL reaction tube was charged with 2-aminopyridine (188 mg, 2 mmol), CuI (76 mg, 0.4 mmol), and DMSO (4 mL). Then TMEDA (120  $\mu$ L, 0.8 mmol) and DIPEA (880  $\mu$ L, 4.4 mmol) were added. The reaction mixture was stirred at 100 °C

(oil bath) under  $O_2$  ball for 24 hours. After the completion of the reaction, the mixture was cooled to room temperature, diluted with ethyl acetate (50 mL). The filtrate was poured into water (50 mL) and extracted with ethylacetate ( $3 \times 30$  mL). The combined organic phase was dried over  $Na_2SO_4$  and concentrated under reduced pressure. The residue was purified by silica gel (petroleum ether/EtOAc= 1:2) to afford **3a** as a white solid (175mg, 60%).

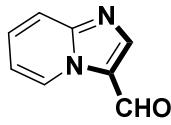
#### 4.4. Typical procedures for the synthesis of **3a** at $O_2^{18}$ :



To an oven dried screw-cap reaction tube equipped with a magnetic stir bar, 2-aminopyridine (47 mg, 0.5 mmol), CuI (19 mg, 0.1 mmol), the reaction tube was sealed with rubber-septum, then evacuated and backfilled with nitrogen after repeated a total of three times then evacuated the reaction tube and backfilled with  $O_2^{18}$ . TMEDA (30  $\mu$ L, 0.2 mmol) and DIPEA (220  $\mu$ L, 1.1 mmol) anhydrous DMSO (2 mL) were added sequentially via syringe. The reaction mixture was stirred at 100 °C (oil bath) for 24 hours. After the completion of the reaction, the mixture was cooled to room temperature. **3a** was obtained in 71% yield with 1:1 ratio of **3a** and **3a-O<sup>18</sup>** (detected by GC-MS).

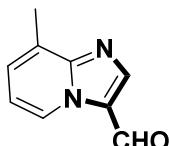
## 5. Characterization data for products

### Imidazo[1,2-a]pyridine-3-carbaldehyde (3a)( CAS: 6188-43-8)<sup>2</sup>



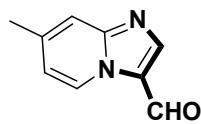
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (52 mg, 71%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.92 (s, 1H), 9.46 (td, *J* = 6.8, 1.1 Hz, 1H), 8.30 (s, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.59 – 7.47 (m, 1H), 7.11 (td, *J* = 6.9, 0.9 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 178.0, 149.4, 146.9, 130.2, 128.8, 125.0, 117.9, 115.6.

### 8-Methyl-Imidazo[1,2-a]pyridine-3-carbaldehyde (3b)(CAS: 175878-16-7)<sup>2</sup>



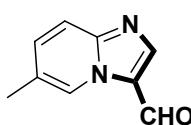
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (60 mg, 75%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.92 (s, 1H), 9.38 – 9.26 (m, 1H), 8.28 (s, 1H), 7.38 – 7.29 (m, 1H), 7.02 (t, *J* = 6.9 Hz, 1H), 2.66 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 178.0, 149.6, 1463, 129.2, 127.9, 126.5, 125.4, 115.6, 16.9.

### 7-Methyl-Imidazo[1,2-a]pyridine-3-carbaldehyde (3c) (CAS: 30384-94-2)<sup>2</sup>



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (48 mg, 60%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.86 (s, 1H), 9.32 (d, *J* = 6.9 Hz, 1H), 8.24 (s, 1H), 7.62 – 7.46 (m, 1H), 6.95 (dd, *J* = 6.9, 1.5 Hz, 1H), 2.48 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 177.4, 161.9, 152.11, 147.9, 129.5, 125.0, 109.8, 96.3, 56.3.

### 6-Methylimidazo[1,2-a]pyridine-3-carbaldehyde (3d) (CAS: 933752-89-7)<sup>2</sup>

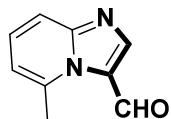


The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (56 mg, 70%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 9.88 (s, 1H),

9.28 (s, 1H), 8.24 (s, 1H), 7.67 (d,  $J = 9.1$  Hz, 1H), 7.39 (dd,  $J = 9.1, 1.7$  Hz, 1H), 2.40 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.8, 148.4, 146.8, 133.1, 126.7, 125.8, 124.8, 117.0, 18.3.

**5-Methylimidazo[1,2-a]pyridine-3-carbaldehyde (3e) (CAS:**

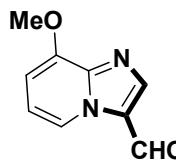
**178488-37-4)<sup>2</sup>**



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (40 mg, 51%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.88 (s, 1H), 8.39 (s, 1H), 7.64 (d, 1H), 7.45 (dd,  $J = 8.9, 7.1$  Hz, 1H), 6.88 (d,  $J = 7.0$  Hz, 1H), 2.96 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  176.0, 152.0, 149.8, 140.2, 130.2, 128.3, 116.4, 115.8, 23.2.

**8-methoxyimidazo[1,2-a]pyridine-3-carbaldehyde (3f) (CAS:**

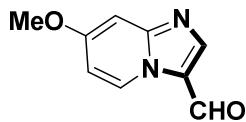
**1388026-13-8)<sup>3</sup>**



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (54 mg, 61%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.93 (s, 1H), 9.07 (d,  $J = 6.7$  Hz, 1H), 8.24 (s, 1H), 7.01 (t,  $J = 7.3$  Hz, 1H), 6.84 (d,  $J = 7.8$  Hz, 1H), 4.05 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.2, 148.9, 145.7, 143.5, 126.0, 121.3, 115.6, 106.8, 56.4.

**7-methoxyimidazo[1,2-a]pyridine-3-carbaldehyde (3g) (CAS:**

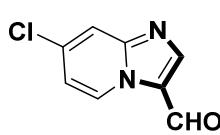
**896722-39-7)<sup>3</sup>**



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (58 mg, 66%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (s, 1H), 9.27 (d,  $J = 7.5$  Hz, 1H), 8.18 (s, 1H), 7.04 (d,  $J = 2.5$  Hz, 1H), 6.78 (dd,  $J = 7.5, 2.5$  Hz, 1H), 3.92 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.4, 161.9, 152.1, 147.9, 129.5, 125.0, 109.8, 96.3, 56.3.

**7-chloroimidazo[1,2-a]pyridine-3-carbaldehyde (3h) (CAS:**

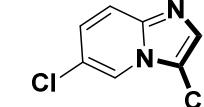
**1019020-44-0)<sup>4</sup>**



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (54 mg, 60%). white solid; 60% yield.  $^1\text{H}$  NMR (500

MHz,  $\text{CDCl}_3$ )  $\delta$  9.93 (s, 1H), 9.41 (dd,  $J = 7.2$  Hz, 9H), 8.30 (s, 1H), 7.79 (d,  $J = 1.5$  Hz, 1H), 7.11 (dd,  $J = 7.2, 2.0$  Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  177.8, 149.2, 147.1, 136.6, 128.6, 124.8, 116.9, 116.9.

**6-chloroimidazo[1,2-a]pyridine-3-carbaldehyde (3i) (CAS: 29096-59-1)<sup>4</sup>**

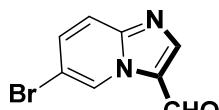


The reaction was performed by following the general procedure.

The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (45 mg, 50%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.09 (s, 1H), 9.31 (dt,  $J = 4.4, 1.5$  Hz, 2H), 8.43 (s, 1H), 8.25 (d,  $J = 4.4$  Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  179.3, 146.0, 144.4, 143.0, 133.3, 125.1, 120.9.

**6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde (3j) (CAS: 30384-96-4)**

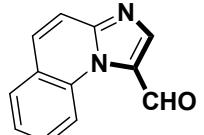
<sup>4</sup>



The reaction was performed by following the general procedure.

The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (56 mg, 52%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.95 (s, 1H), 9.62 – 9.55 (m, 1H), 8.32 (s, 1H), 7.74 (d,  $J = 9.5$  Hz, 1H), 7.53 (dd,  $J = 9.5, 2.1$  Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.2, 147.7, 146.9, 131.5, 126.8, 125.2, 124.0, 118.2.

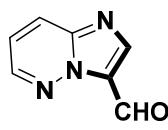
**imidazo[1,2-a]quinoline-1-carbaldehyde (3k) (CAS: 1889953-52-9)**



The reaction was performed by following the general procedure.

The residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (39 mg, 40%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.86 (s, 1H), 9.69 (d,  $J = 8.7$  Hz, 1H), 8.38 (s, 1H), 7.86 (s, 1H), 7.84 (s, 1H), 7.79 – 7.74 (m, 1H), 7.67 (d,  $J = 9.3$  Hz, 1H), 7.61 – 7.56 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  175.9, 152.5, 150.7, 134.3, 132.4, 130.0, 129.7, 128.8, 126.3, 124.6, 121.0, 116.8.

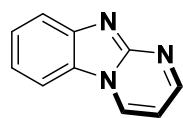
**imidazo[1,2-b]pyridazine-3-carbaldehyde (3l) (CAS: 154578-27-5)**



The reaction was performed by following the general procedure. The

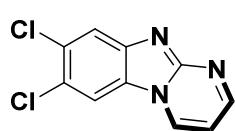
residue was purified by flash column chromatograph (silica gel, petroleum ether:AcOEt = 1:2, v/v) to give the product as a white solid (26 mg, 35%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.30 (s, 1H), 8.57 (dd,  $J = 4.4, 1.4$  Hz, 1H), 8.41 (s, 1H), 8.10 (dd,  $J = 9.2, 1.6$  Hz, 1H), 7.34 (dd,  $J = 9.2, 4.5$  Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  178.3, 144.6, 142.5, 141.8, 128.1, 126.7, 121.0.

### benzo[4,5]imidazo[1,2-a]pyrimidine (5a) (CAS: 245-55-6)<sup>5</sup>



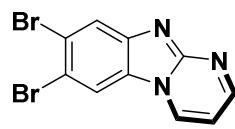
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (63 mg, 75%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.82 (s, 1H), 8.77 (s, 1H), 8.01 (d, *J* = 5.8 Hz, 1H), 7.90 (s, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.92 (dd, *J* = 6.6, 4.0 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 155.6, 150.5, 144.08, 144.06, 133.6, 126.7, 122.3, 120.6, 110.9, 106.8, 76.9.

### 7,8-dichlorobenzo[4,5]imidazo[1,2-a]pyrimidine (5b)



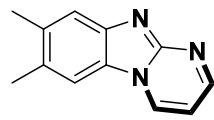
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (86 mg, 72%). <sup>1</sup>H NMR (500 MHz, Acetic acid-d4) δ 9.44 (d, *J* = 5.8 Hz, 1H), 9.22 (s, 1H), 8.54 (s, 1H), 8.35 (s, 1H), 7.53 – 7.45 (m, 1H). <sup>13</sup>C NMR (126 MHz, Acetic acid-d4) δ 158.2, 150.4, 140.3, 136.1, 131.2, 126.3, 119.8, 113.8, 111.7, 108.8. HRMS (ESI) calcd for C<sub>10</sub>H<sub>5</sub>N<sub>3</sub>Cl<sub>2</sub> (M+H)<sup>+</sup>: 236.9871; Found: 236.9870.

### 7,8-dibromobenzo[4,5]imidazo[1,2-a]pyrimidine (5c)



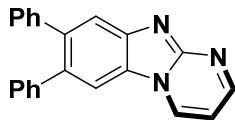
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (115 mg, 70%). <sup>1</sup>H NMR (500 MHz, Acetic acid-d4) δ 9.44 (dd, *J* = 6.8, 2.0 Hz, 1H), 9.25 (dd, *J* = 4.2, 2.0 Hz, 1H), 8.69 (s, 1H), 8.52 (s, 1H), 7.52 (dd, *J* = 6.8, 4.2 Hz, 1H). <sup>13</sup>C NMR (126 MHz, Acetic acid-d4) δ 158.4, 150.2, 141.3, 136.1, 126.5, 123.2, 122.7, 117.2, 116.8, 108.8. HRMS (DART) calcd for C<sub>10</sub>H<sub>5</sub>N<sub>3</sub>Br<sub>2</sub> (M+H)<sup>+</sup>: 325.8923 ; Found: 325.8920.

### 7,8-dimethylbenzo[4,5]imidazo[1,2-a]pyrimidine (5d)



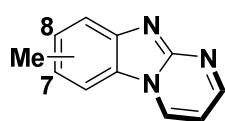
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (78 mg, 80%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.69 (s, 1H), 8.65 (s, 1H), 7.71 (s, 1H), 7.58 (s, 1H), 6.83 (dd, *J* = 6.3, 4.0 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ 154.5, 142.6, 136.4, 133.3, 132.0, 120.1, 110.7, 106.4, 20.8, 20.7. HRMS (EI) calcd for C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>(M)<sup>+</sup>: 197.0958; Found: 197.0960

### 7,8-diphenylbenzo[4,5]imidazo[1,2-a]pyrimidine (5e)



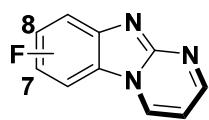
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (112 mg, 70%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.85 (d,  $J$  = 6.0 Hz, 1H), 8.80 (d,  $J$  = 1.5 Hz, 1H), 8.05 (s, 1H), 7.93 (s, 1H), 7.25 – 7.13 (m, 10H), 6.97 (dd,  $J$  = 6.1, 4.1 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  156.0, 151.1, 143.2, 141.7, 141.6, 140.7, 136.4, 133.8, 130.4, 130.4, 128.2, 128.1, 126.9, 126.9, 126.4, 121.9, 112.6, 107.3. HRMS (DART) calcd for  $\text{C}_{22}\text{H}_{16}\text{N}_3$  ( $\text{M}+\text{H}$ ) $^+$ : 322.1339; Found: 322.1335.

### Mixture of substituted on 7 or 8 position (5f)<sup>5</sup>



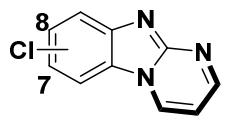
The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (74 mg, 81%).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ \_SPE)  $\delta$  9.17 (dd,  $J$  = 6.7, 1.8 Hz, 1H), 8.77 (dd,  $J$  = 4.0, 1.9 Hz, 1H), 7.88 (d,  $J$  = 8.0 Hz, 1H), 7.38 – 7.24 (m, 2H), 7.06 (dd,  $J$  = 6.7, 4.1 Hz, 1H), 2.66 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_3\text{OD}$ \_SPE)  $\delta$  157.4, 151.4, 143.4, 136.4, 130.4, 127.9, 123.4, 110.2, 108.5, 17.1.

### Mixture of substituted on 7 or 8 position (5g)



The reaction was performed by following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (70 mg, 75%).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.82 – 8.74 (m, 5H), 8.72 (dd,  $J$  = 6.8, 2.0 Hz, 1H), 7.93 (dd,  $J$  = 9.0, 4.7 Hz, 1H), 7.83 (dd,  $J$  = 8.9, 4.6 Hz, 2H), 7.61 (dd,  $J$  = 9.4, 2.3 Hz, 2H), 7.58 (dd,  $J$  = 7.9, 2.4 Hz, 1H), 7.32 (td,  $J$  = 9.3, 2.4 Hz, 1H), 7.13 (td,  $J$  = 9.0, 2.4 Hz, 2H), 6.95 (dd,  $J$  = 6.6, 4.2 Hz, 2H), 6.92 (dd,  $J$  = 6.8, 4.0 Hz, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  162.5, 160.5, 159.4, 157.5, 155.4, 155.3, 151.4, 145.0, 144.9, 140.3, 133.2, 133.2, 123.2, 121.6, 121.5, 115.5, 115.3, 111.7, 111.6, 111.06, 110.9, 106.9, 106.8, 105.9, 105.7, 99.9, 97.4, 97.2. HRMS (EI) calcd for  $\text{C}_{10}\text{H}_6\text{N}_3\text{F}$  ( $\text{M}$ ) $^+$ : 187.0544; Found: 187.0540

### Mixture of substituted on 7 or 8 position (5h)<sup>5</sup>



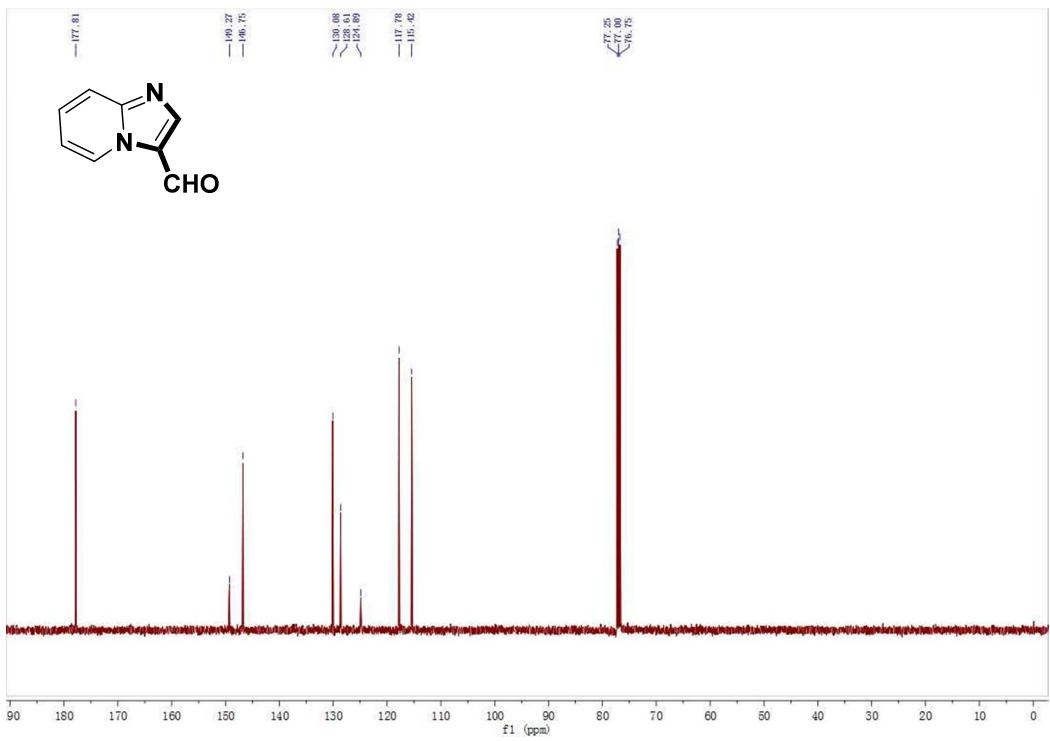
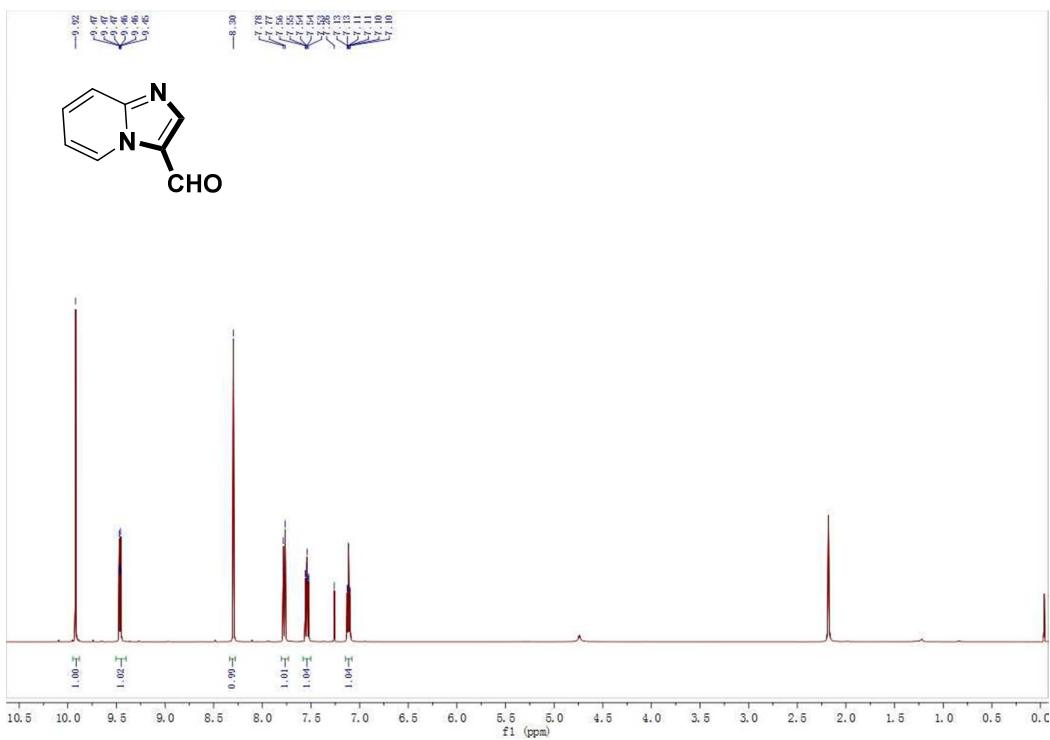
The reaction was performed following the general procedure. The residue was purified by flash column chromatograph (silica gel, dichloromethane:AcOEt = 1:1, v/v) to give the product as a yellow solid (79 mg, 78%).  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ \_SPE)  $\delta$  9.28 (ddd,  $J$  = 14.2, 6.8, 1.9 Hz, 1H), 8.87 – 8.79 (m, 1H), 8.25 (d,  $J$  = 1.8 Hz, 1H), 8.14 (d,  $J$  = 8.7 Hz, 1H), 7.80 (d,  $J$  = 8.6 Hz, 1H), 7.56 (dd,  $J$  = 8.7, 1.9 Hz, 1H), 7.42 (dd,  $J$  = 8.7, 1.7 Hz, 1H), 7.19 – 7.09 (m, 1H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CD}_3\text{OD}$ \_SPE)  $\delta$  158.5, 136.8, 136.8, 133.5, 128.8, 128.5, 123.8, 121.2, 119.5, 114.5, 113.4, 109.1, 109.0.

## 6. References

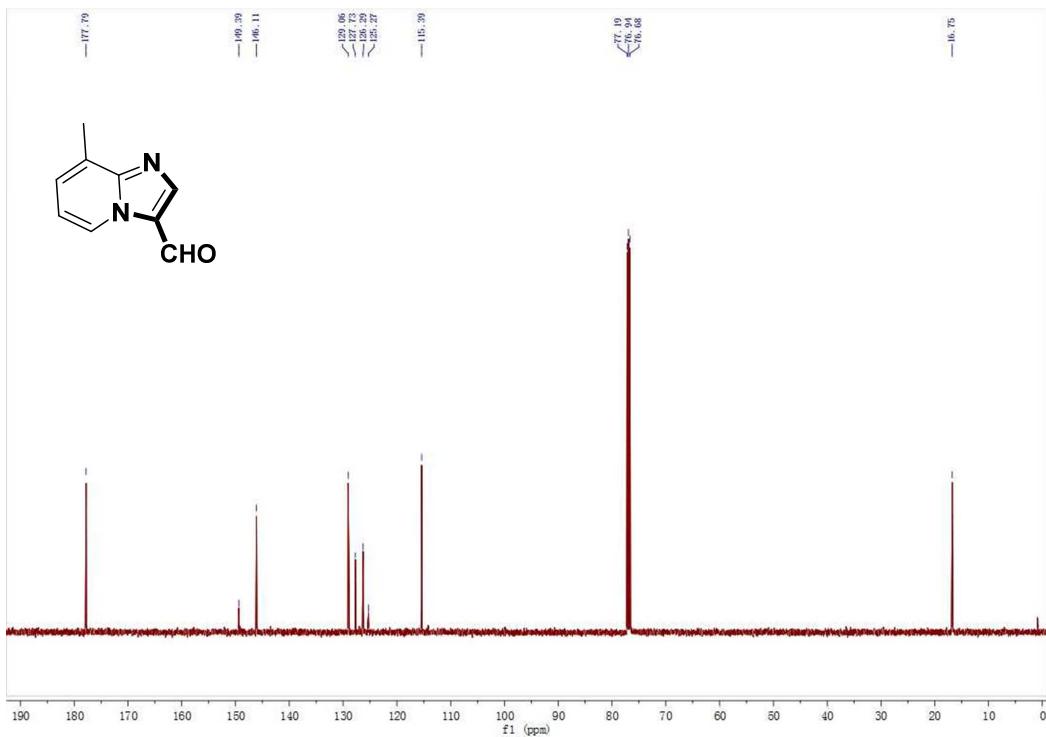
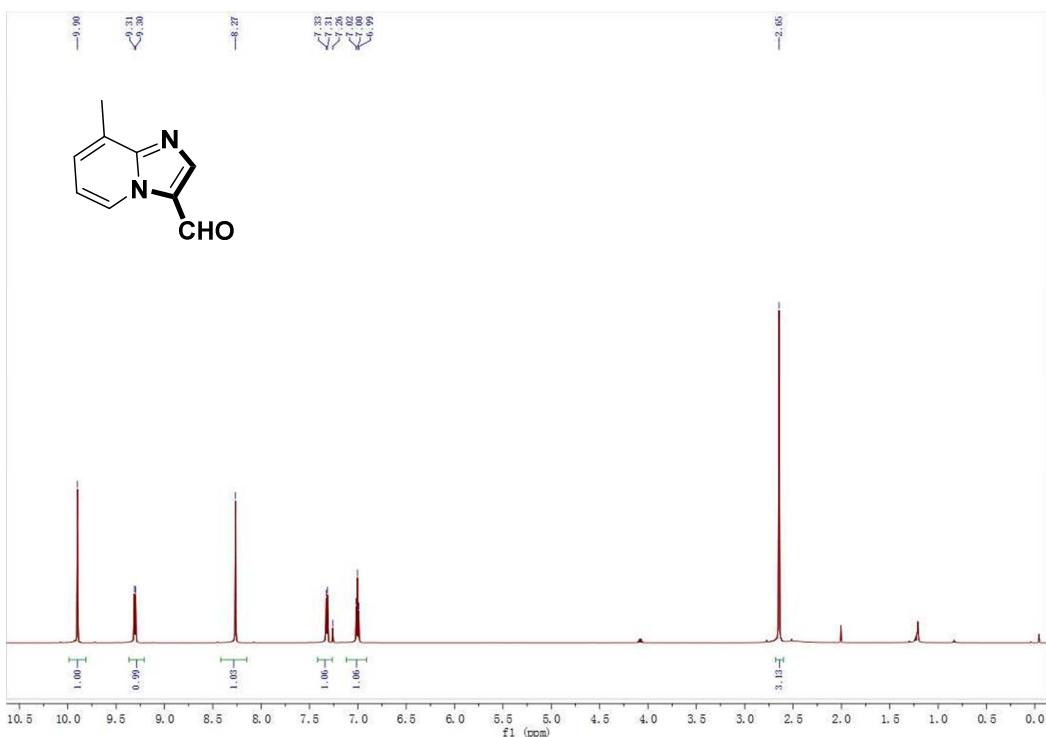
- 1) Beesu, M.; Malladi, S. S.; Fox, L. M.; Jones, C. D.; Dixit, A.; David, S. A. *J Med Chem* **2014**, *57*, 7325;
- 2) Cao, H.; Liu, X.; Liao, J.; Huang, J.; Qiu, H.; Chen, Q.; Chen, Y., *The Journal of organic chemistry* **2014**, *79* , 11209-11214.
- 3) Tung, Y. S.; Coumar, M. S.; Wu, Y. S.; Shiao, H. Y.; Chang, J. Y.; Liou, J. P.; Shukla, P.; Chang, C. W.; Chang, C. Y.; Kuo, C. C.; Yeh, T. K.; Lin, C. Y.; Wu, J. S.; Wu, S. Y.; Liao, C. C.; Hsieh, H. P. *J Med Chem* **2011**, *54* , 3076-3080.
- 4) Gao, G.-R.; Liu, J.-L.; Mei, D.-S.; Ding, J.; Meng, L.-H.; Duan, W.-H. *Chinese Chemical Letters* **2015**, *26* , 118-120;
- 5) Qian, G.; Liu, B.; Tan, Q.; Zhang, S.; Xu, B. *European Journal of Organic Chemistry* **2014**, *22* , 4837-4843;

## 7. NMR spectroscopic data

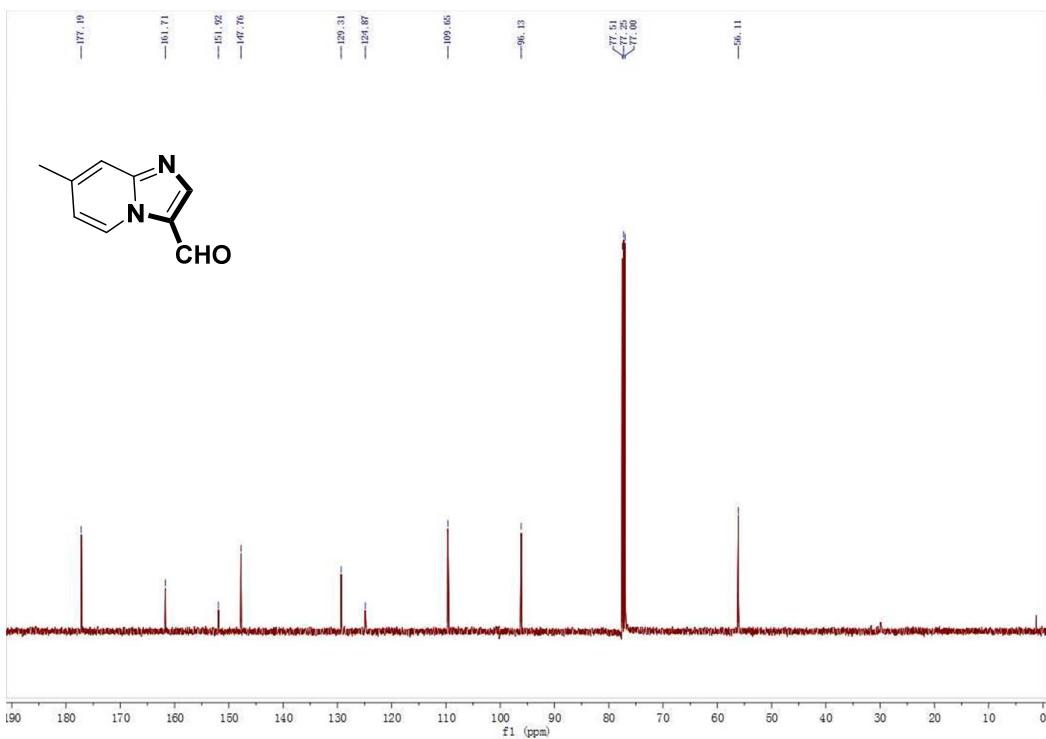
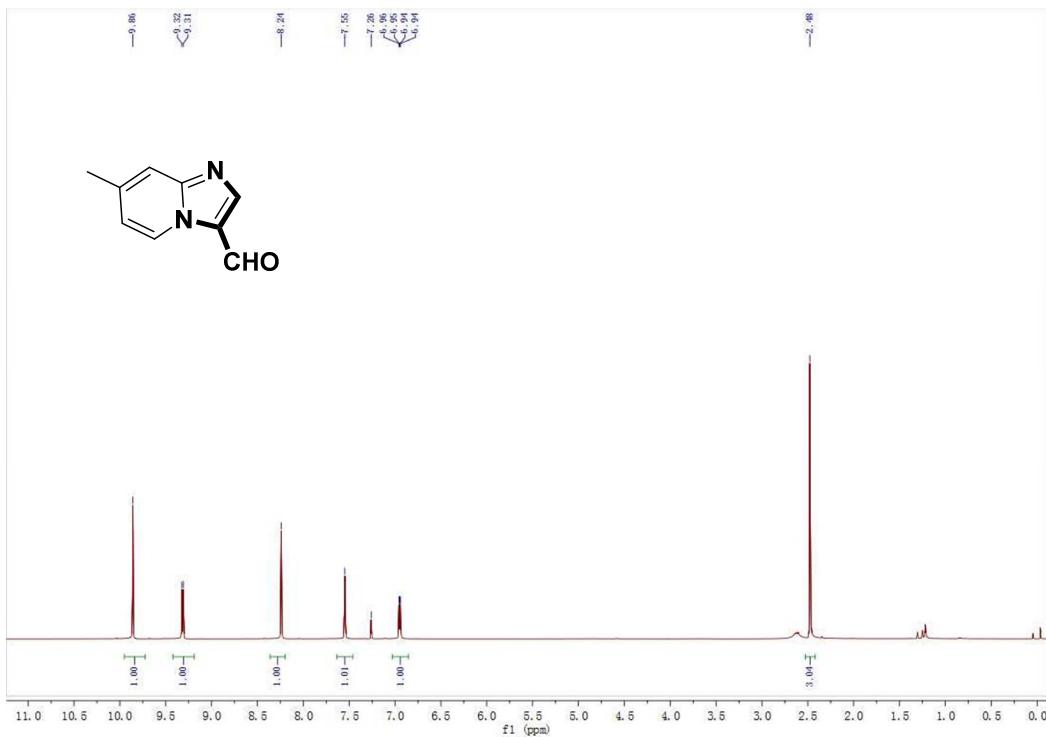
### Imidazo[1,2-a]pyridine-3-carbaldehyde 3a



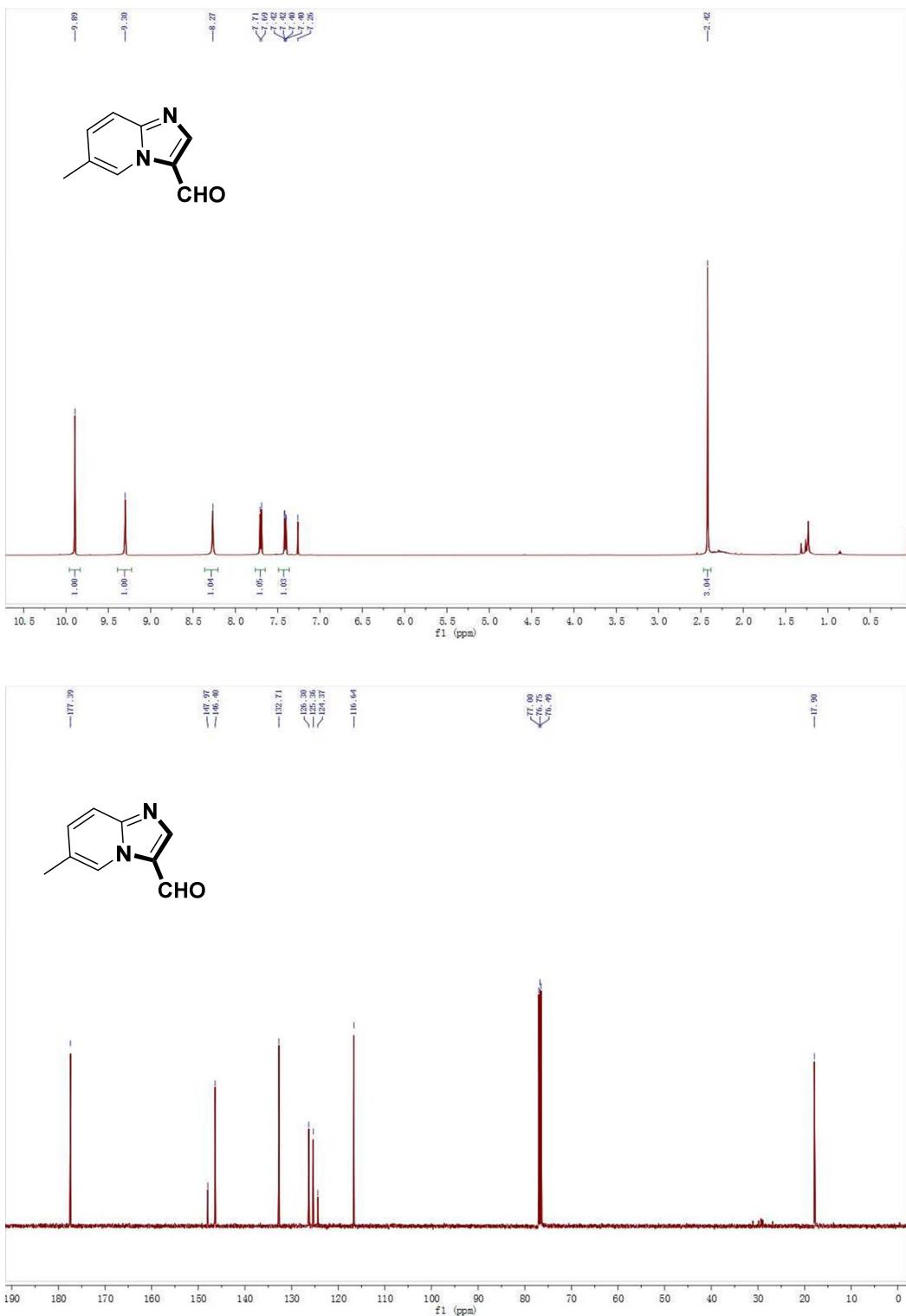
**8-Methyl-Imidazo[1,2-a]pyridine-3-carbaldehyde 3b**



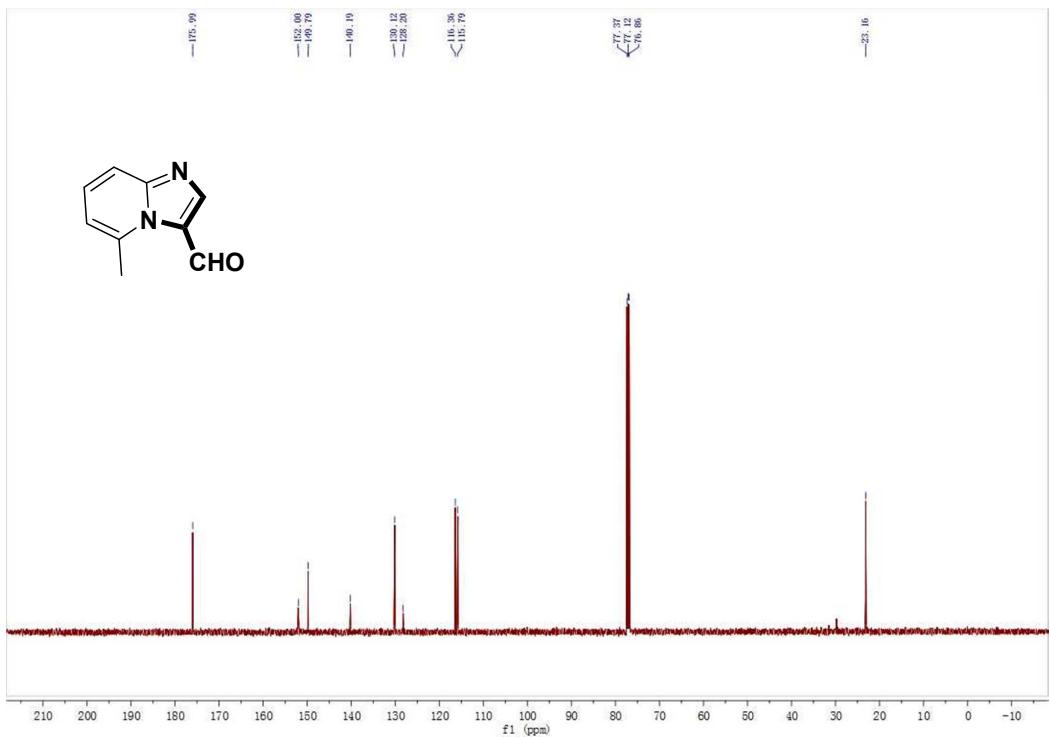
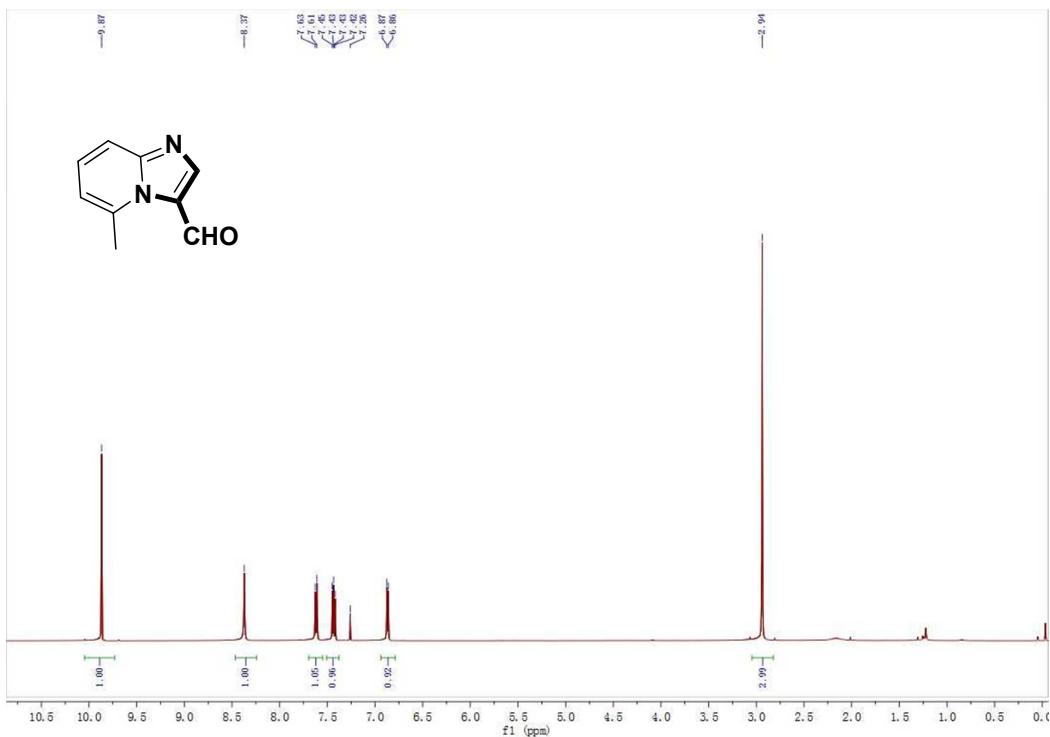
### 7-Methyl-Imidazo[1,2-a]pyridine-3-carbaldehyde 3c



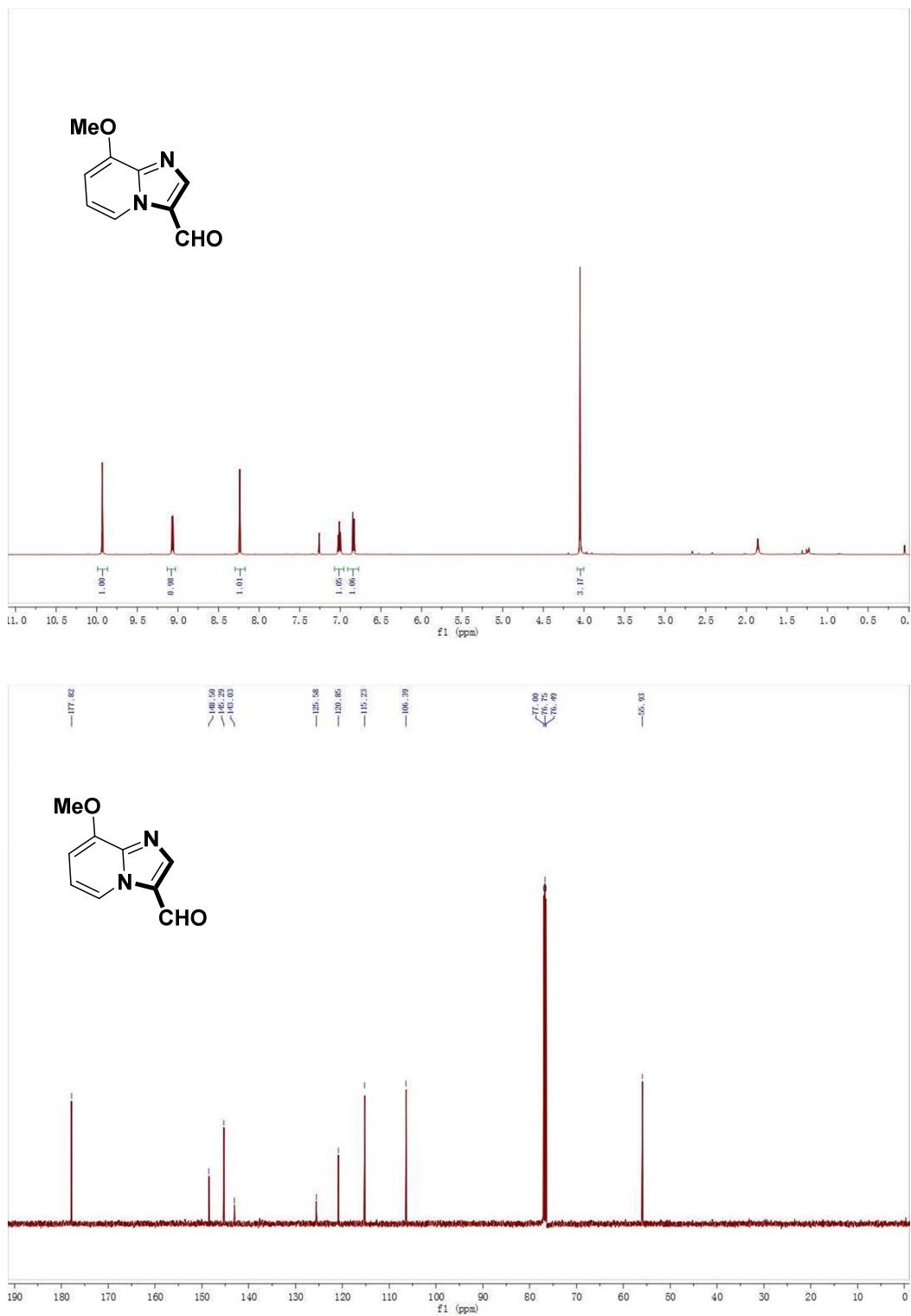
### 6-Methylimidazo[1,2-a]pyridine-3-carbaldehyde (3d)



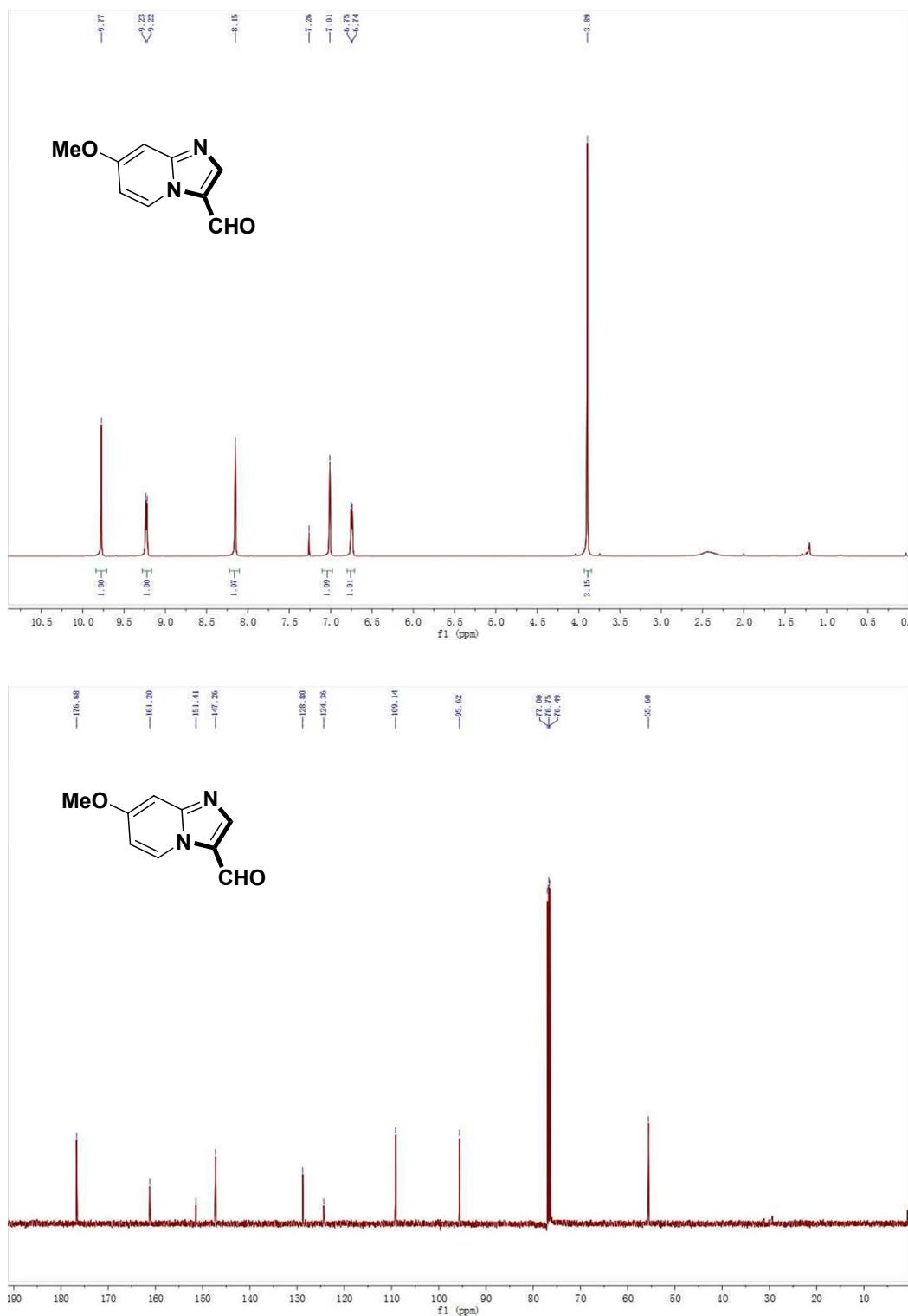
**5-Methylimidazo[1,2-a]pyridine-3-carbaldehyde (3e)**



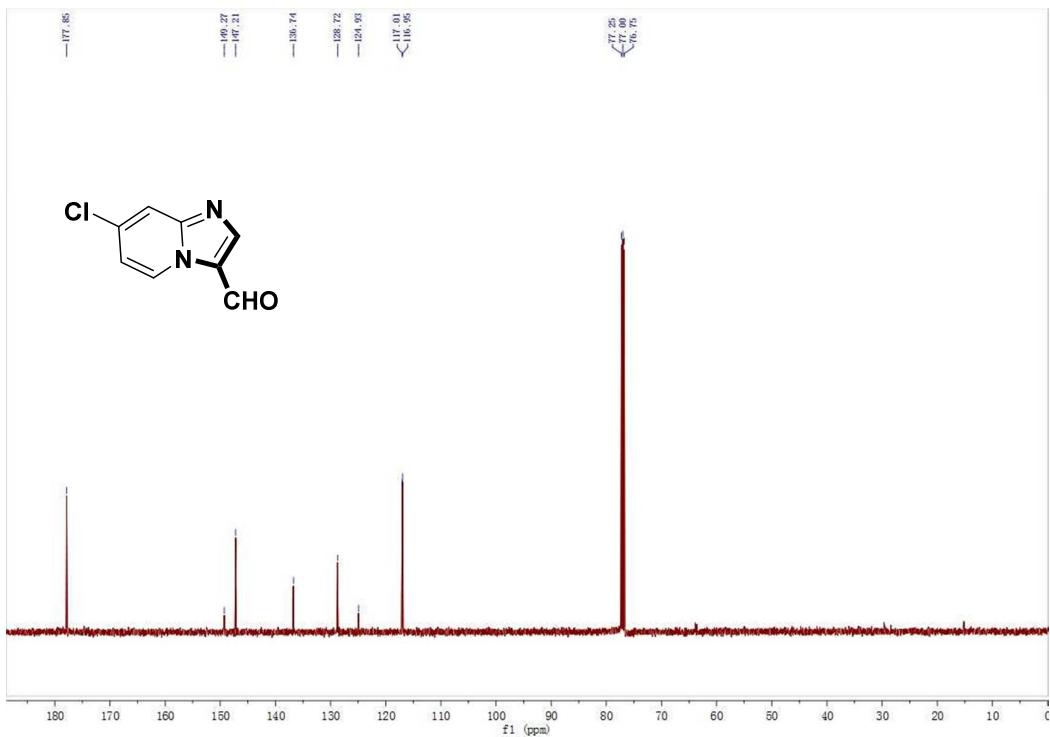
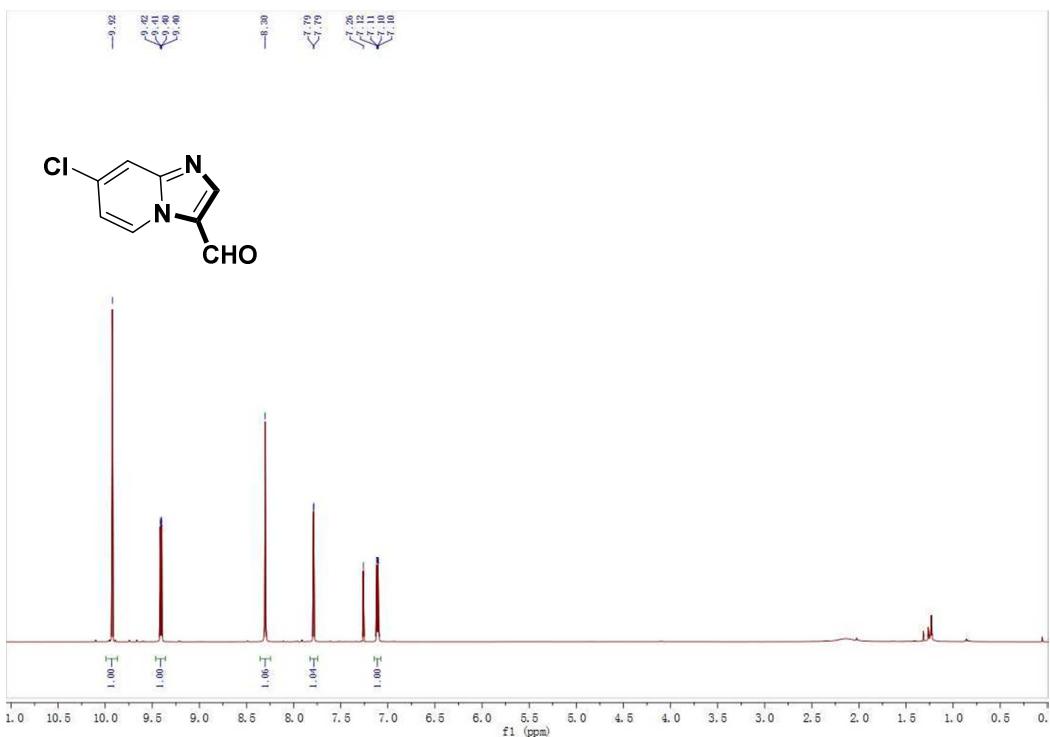
### 8-methoxyimidazo[1,2-a]pyridine-3-carbaldehyde (3f)



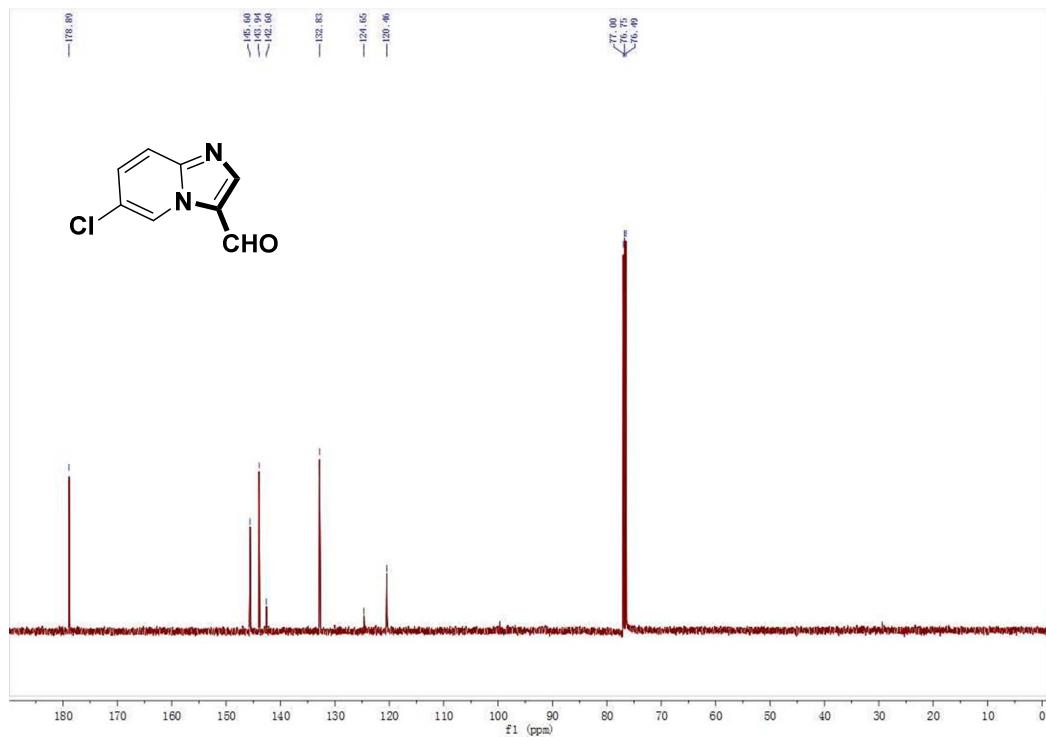
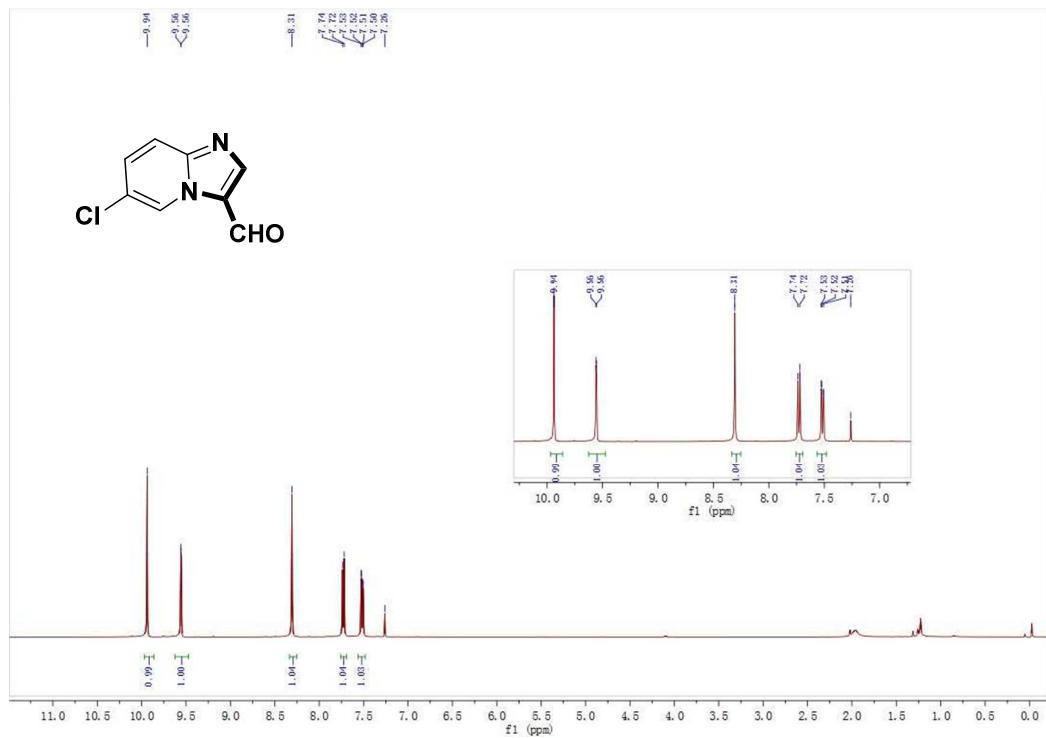
**7-methoxyimidazo[1,2-a]pyridine-3-carbaldehyde (3g)**



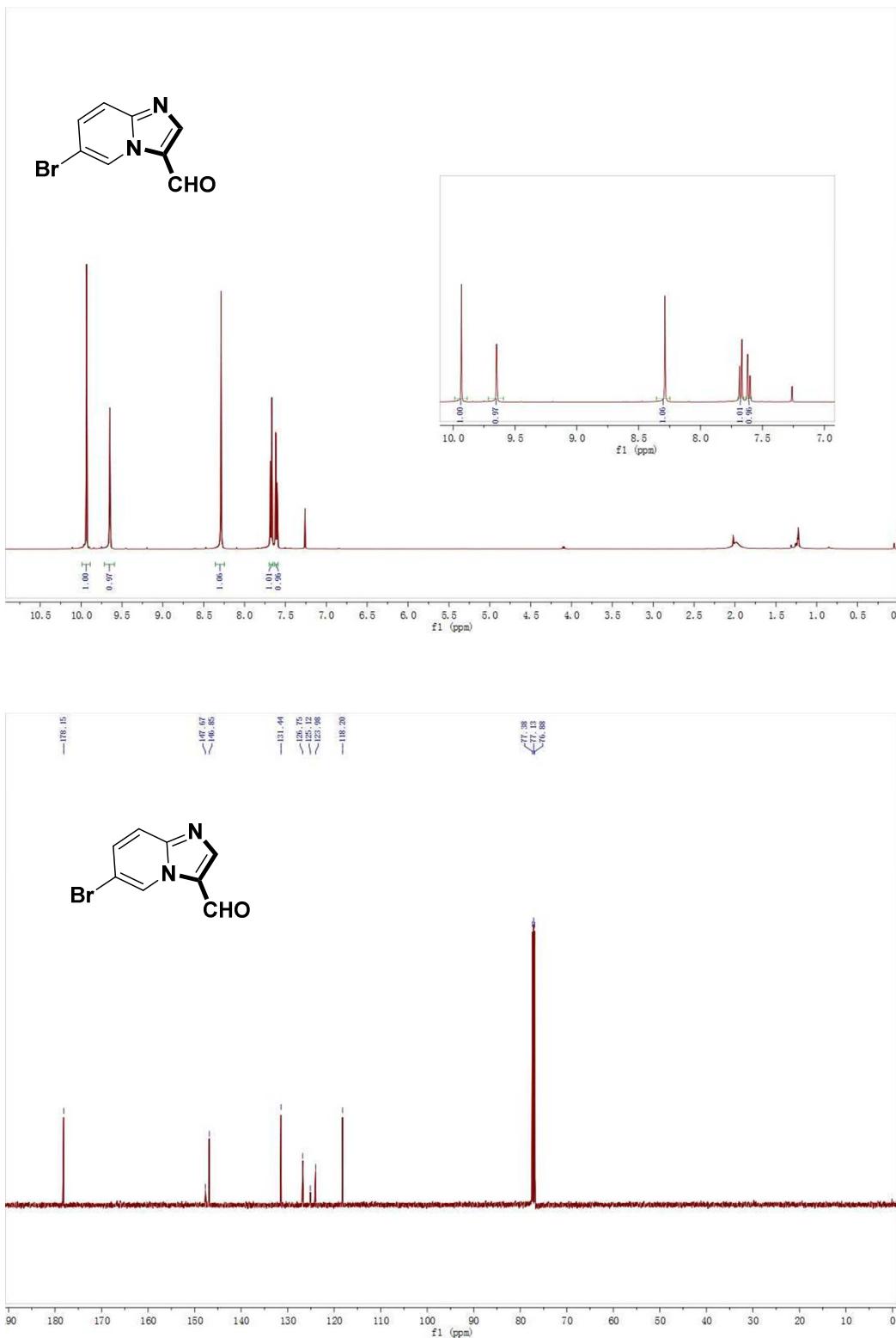
### 7-chloroimidazo[1,2-a]pyridine-3-carbaldehyde (3h)



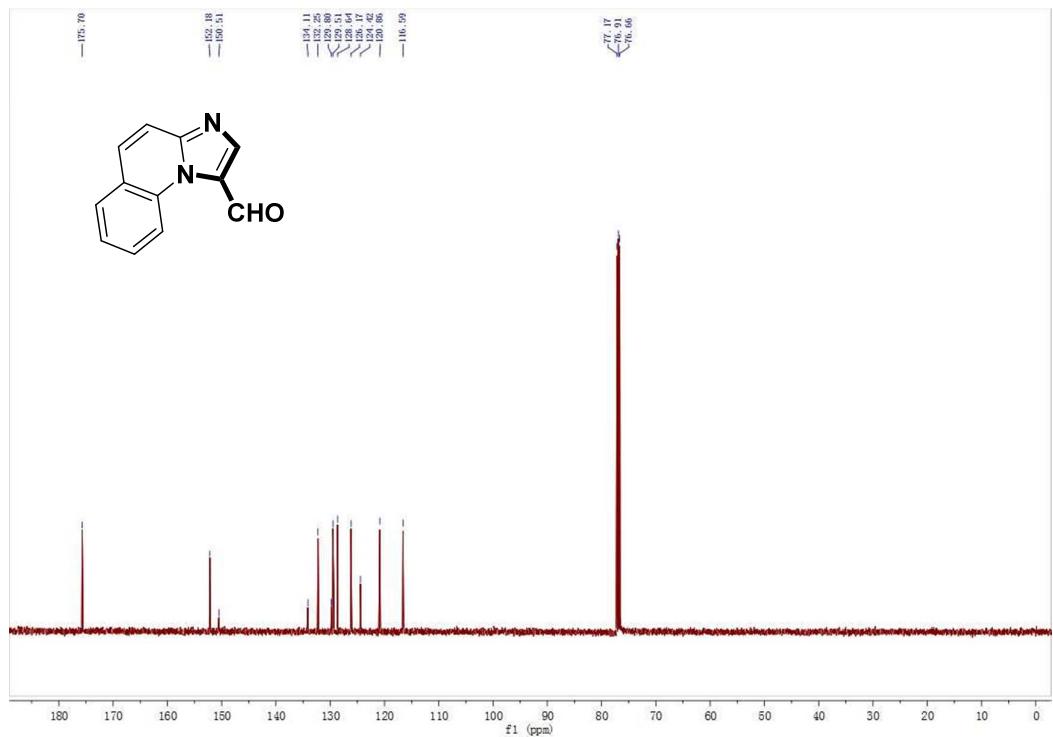
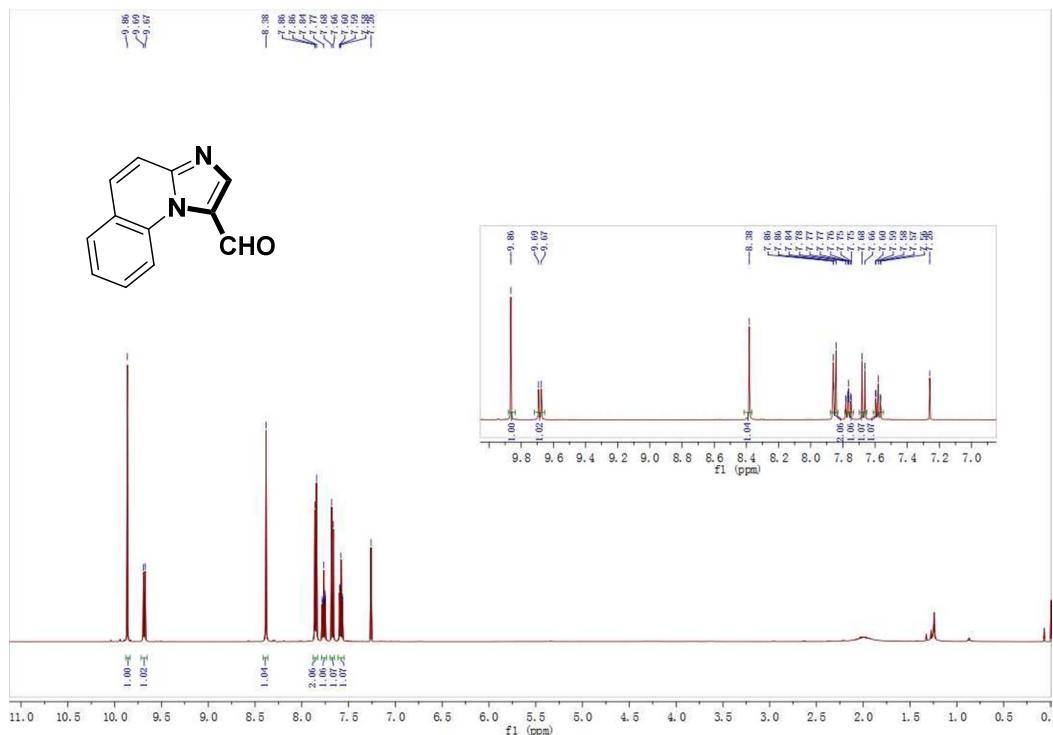
### 6-chloroimidazo[1,2-a]pyridine-3-carbaldehyde (3i)



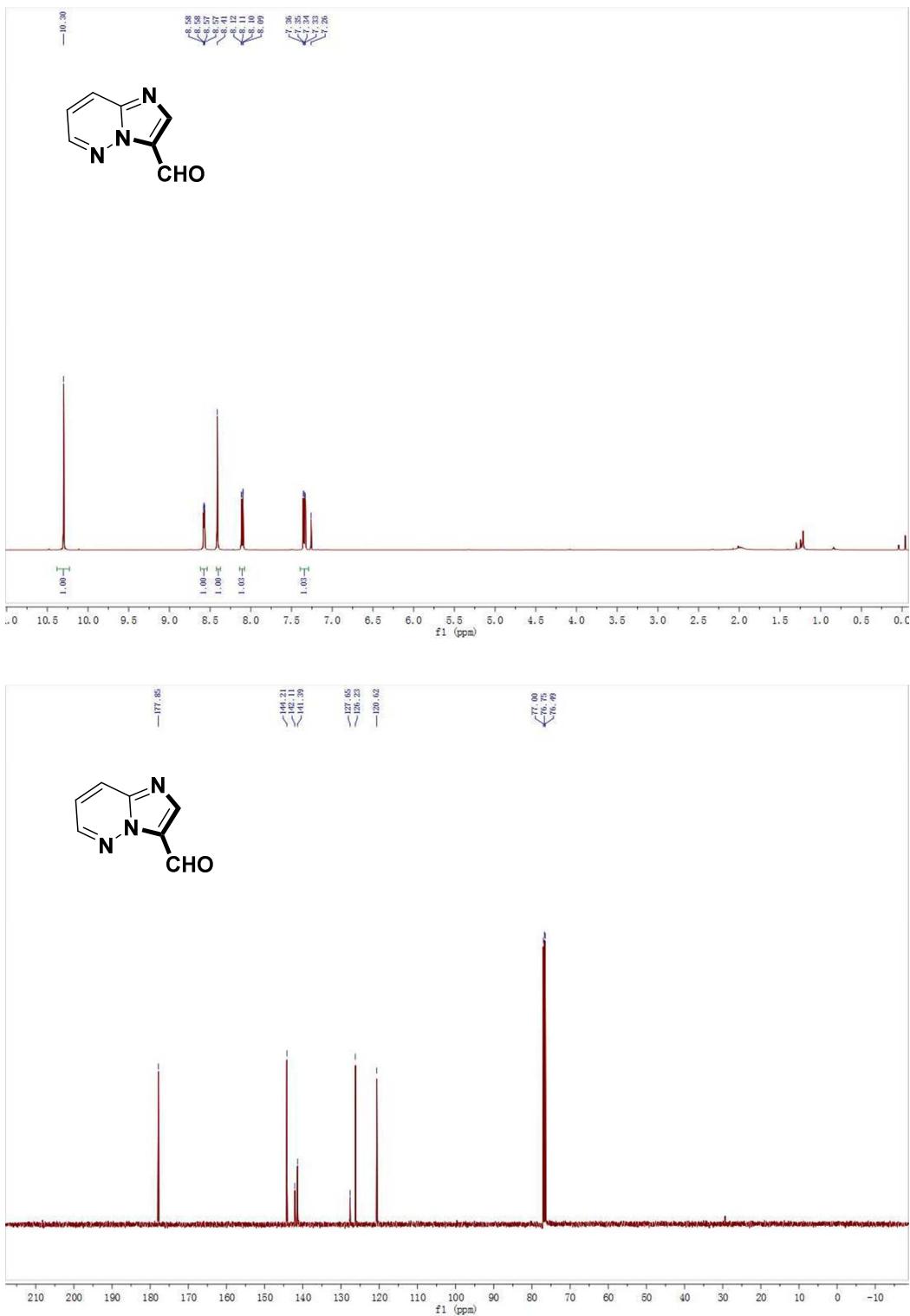
**6-bromoimidazo[1,2-a]pyridine-3-carbaldehyde (3j)**



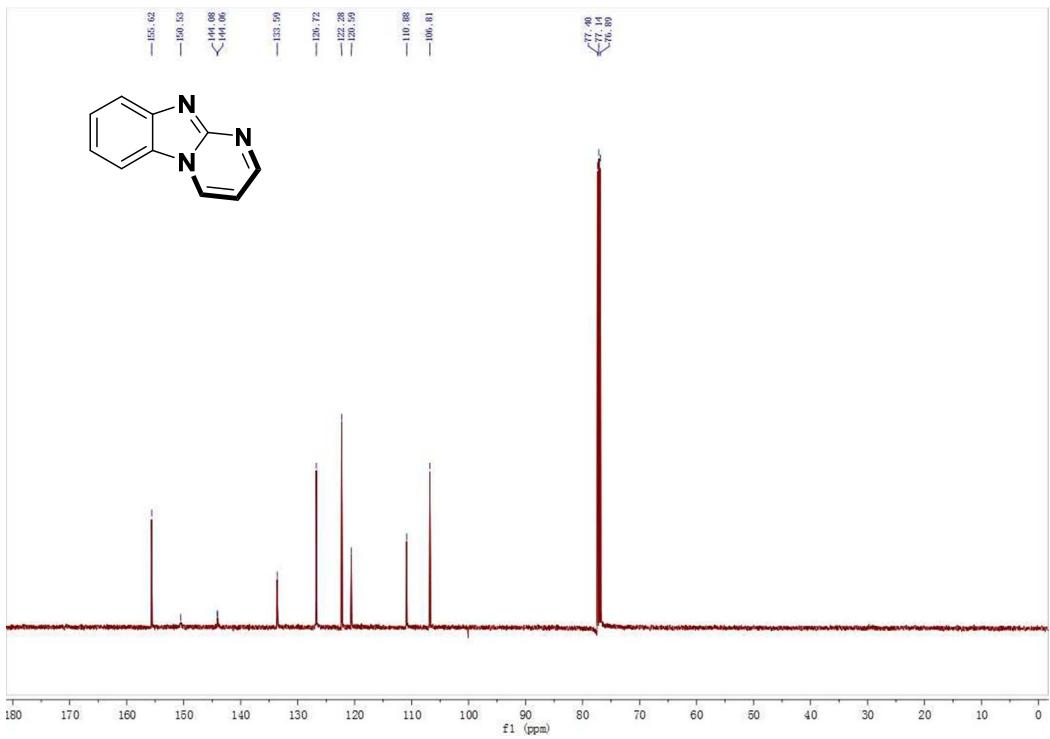
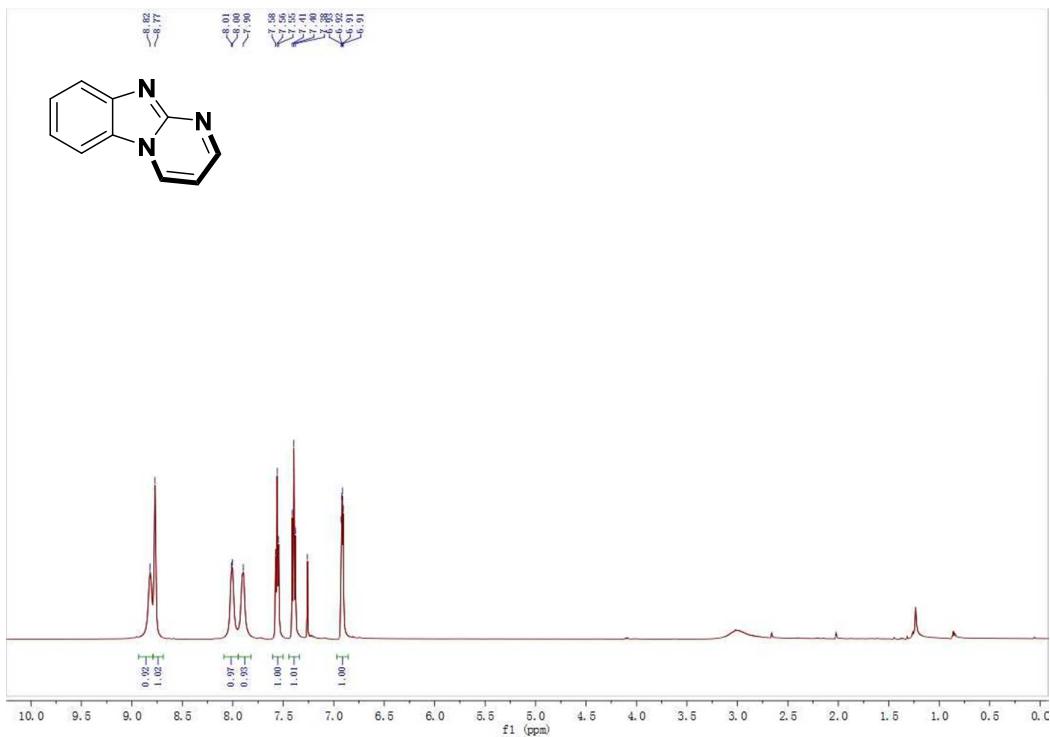
### imidazo[1,2-a]quinoline-1-carbaldehyde (3k)



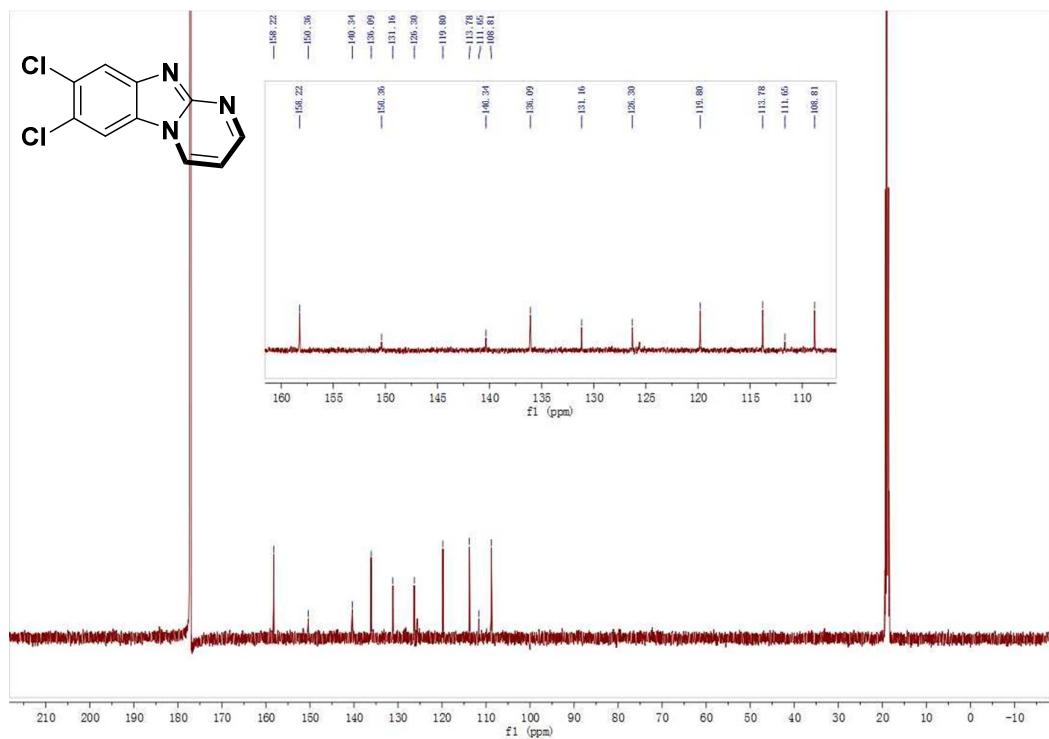
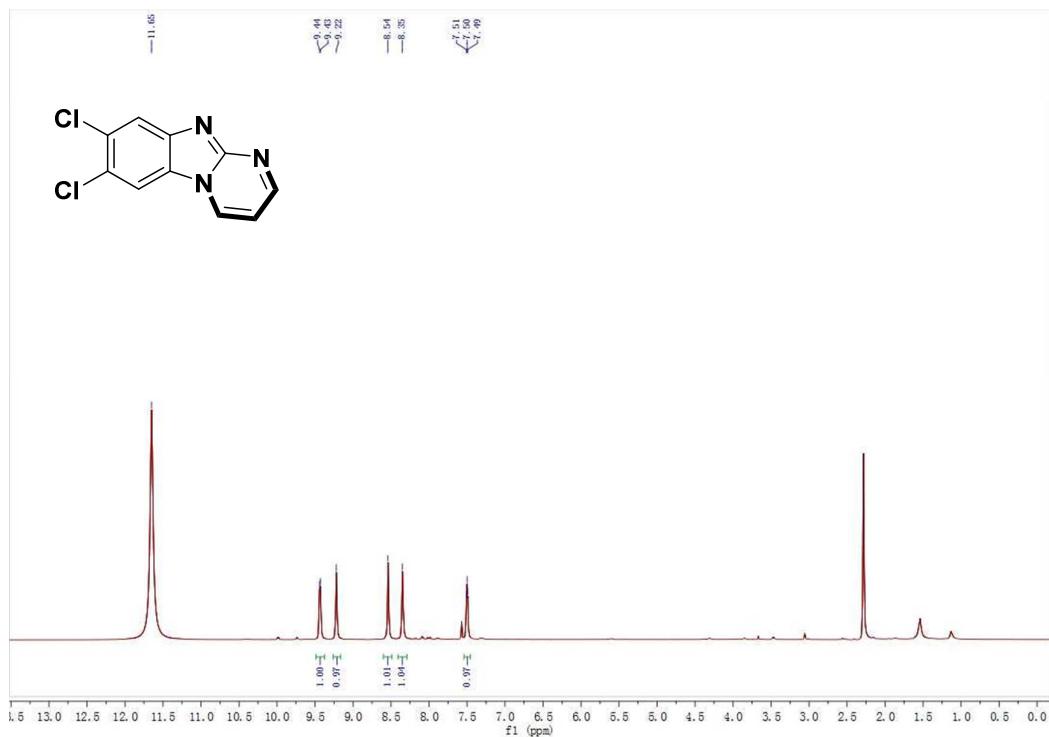
### imidazo[1,2-b]pyridazine-3-carbaldehyde (3l)



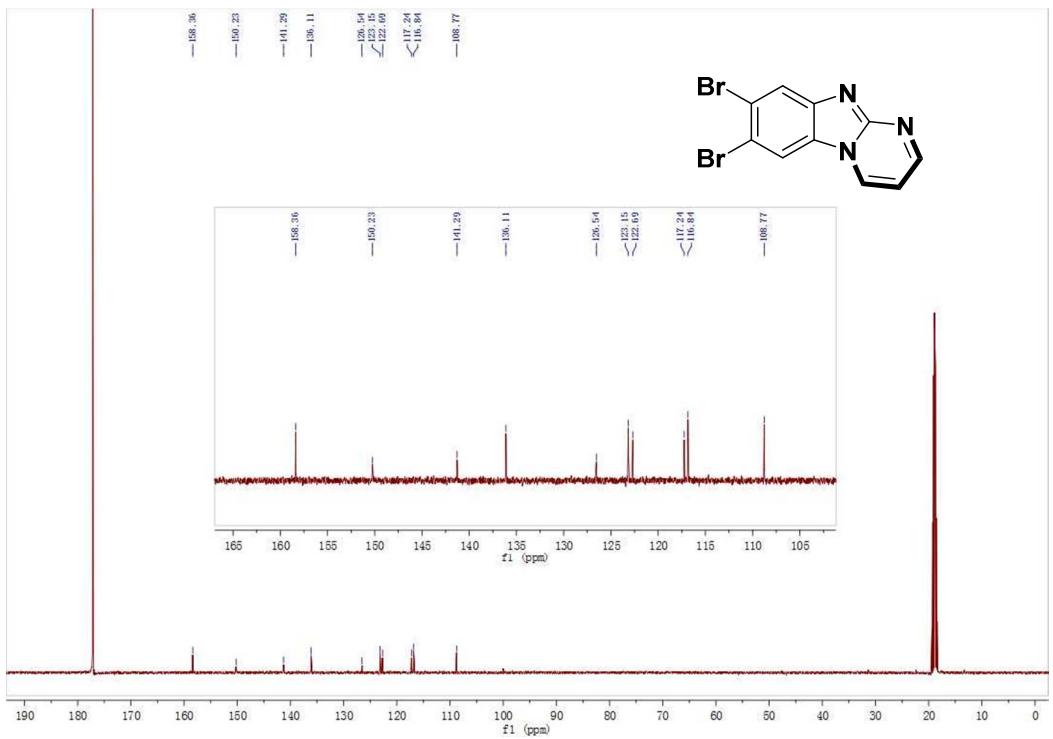
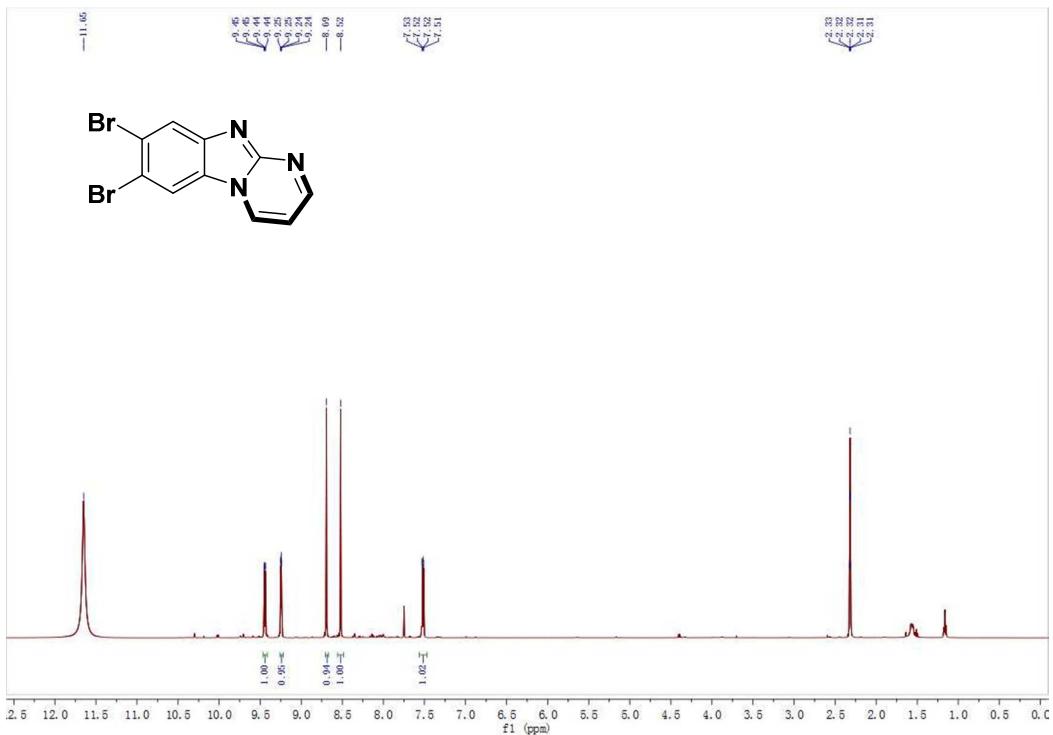
**benzo[4,5]imidazo[1,2-a]pyrimidine (5a)**



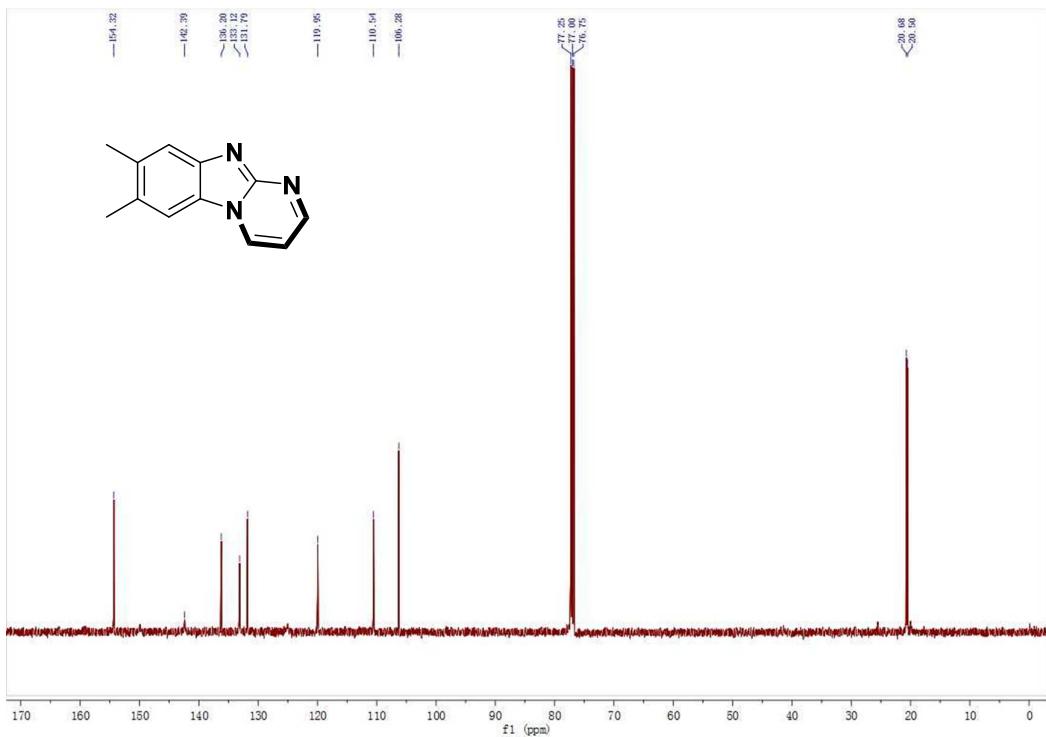
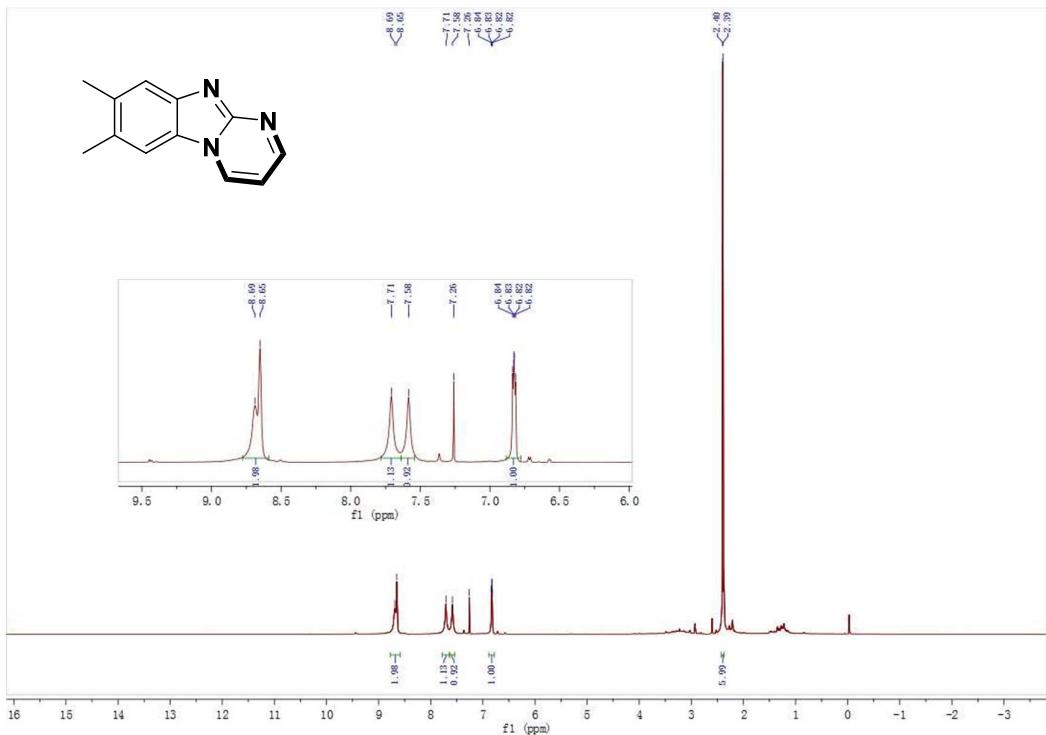
**7,8-dichlorobenzo[4,5]imidazo[1,2-a]pyrimidine (5b)**



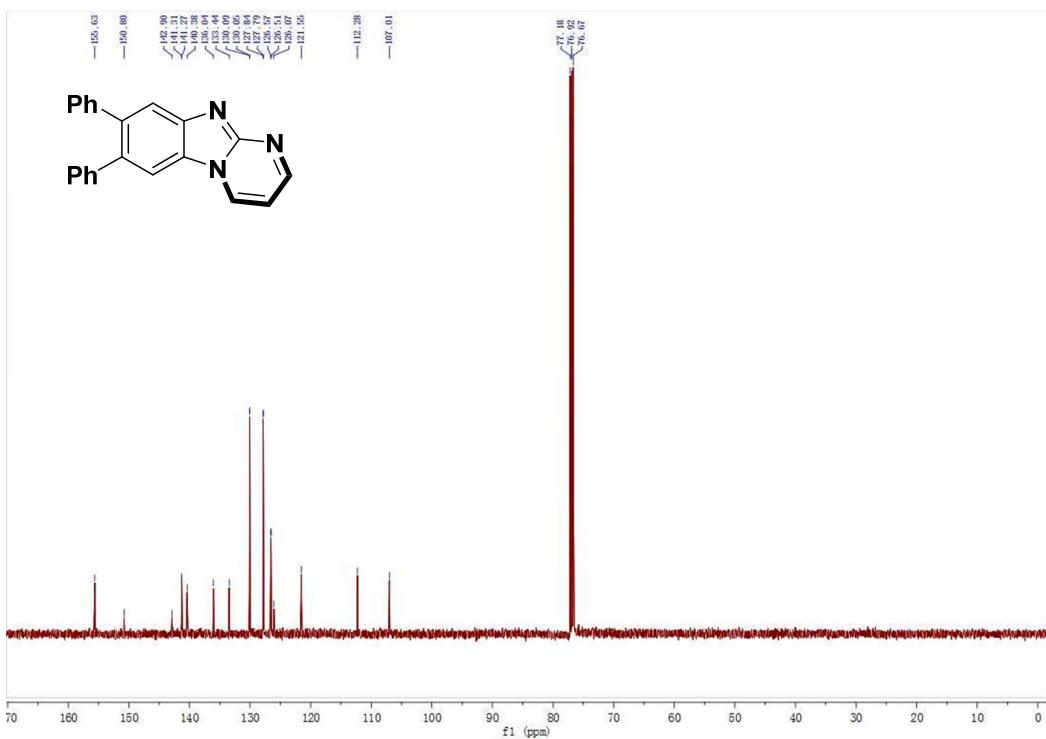
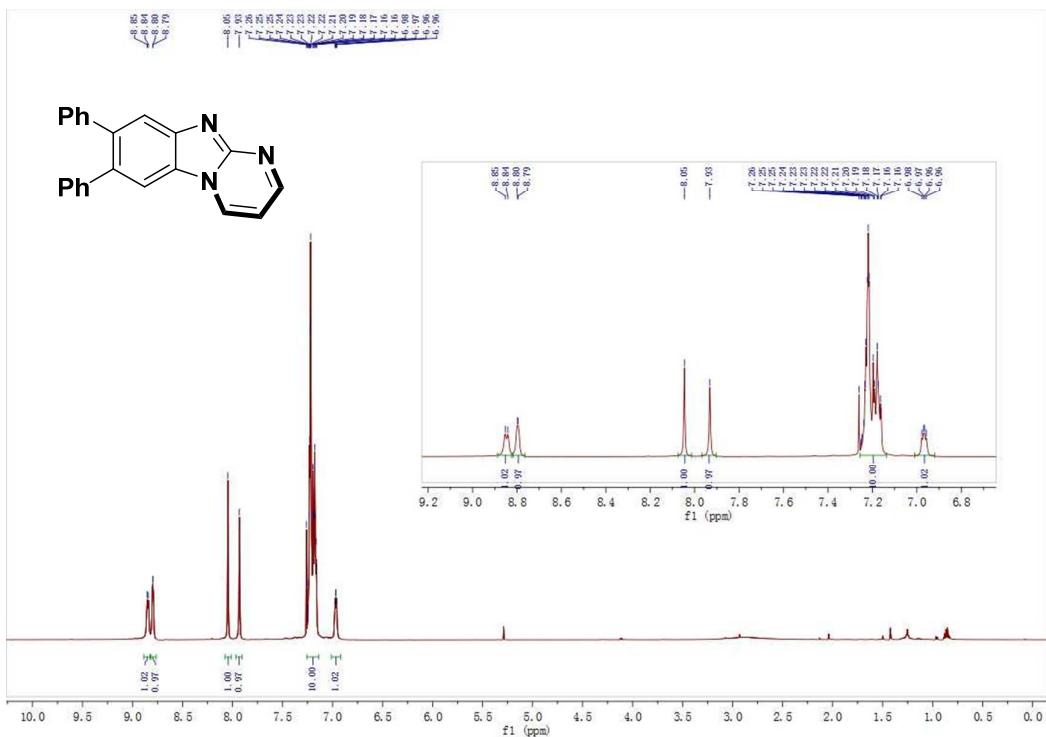
### 7,8-dibromobenzo[4,5]imidazo[1,2-a]pyrimidine (5c)



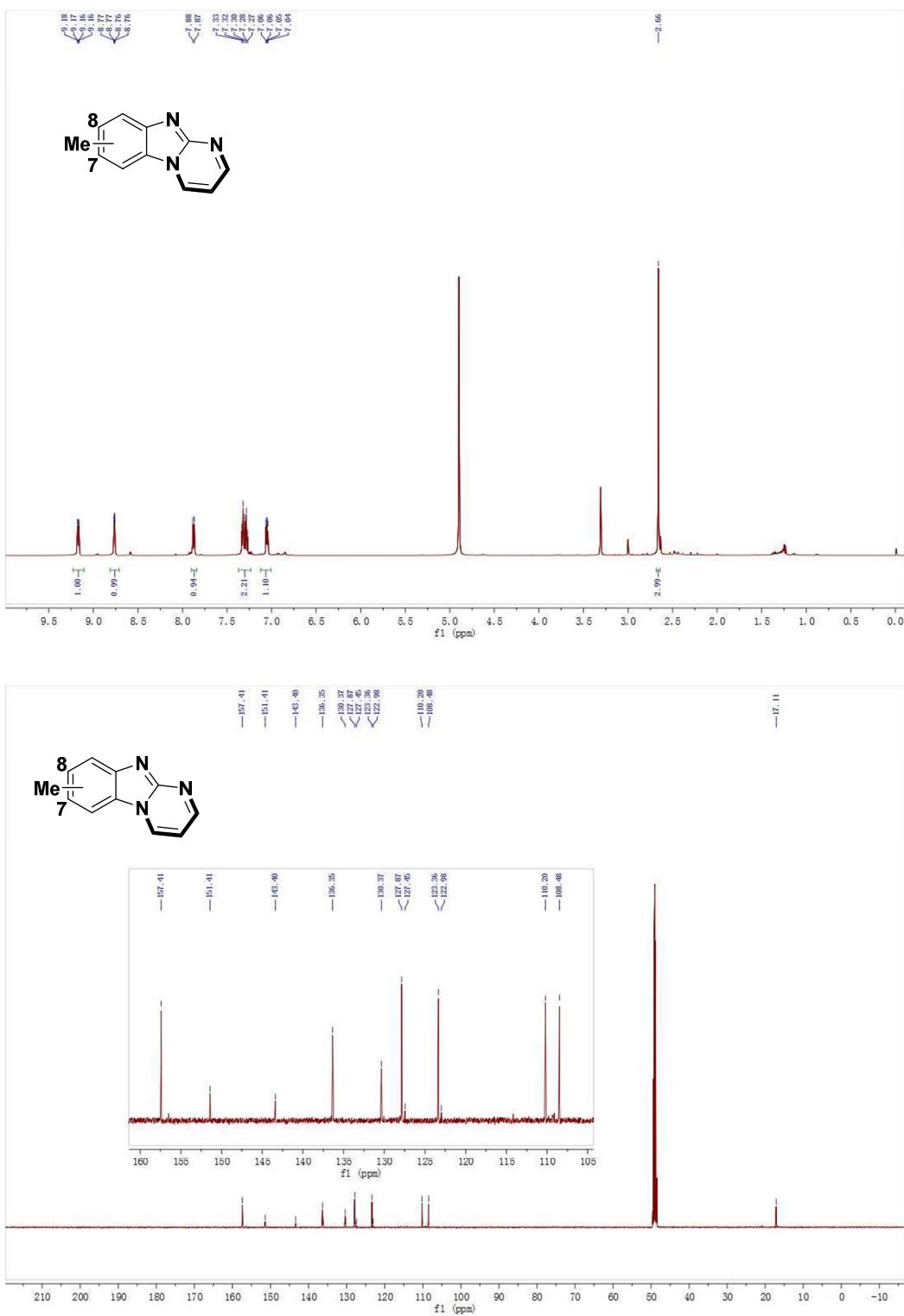
**7,8-dimethylbenzo[4,5]imidazo[1,2-a]pyrimidine (5d)**



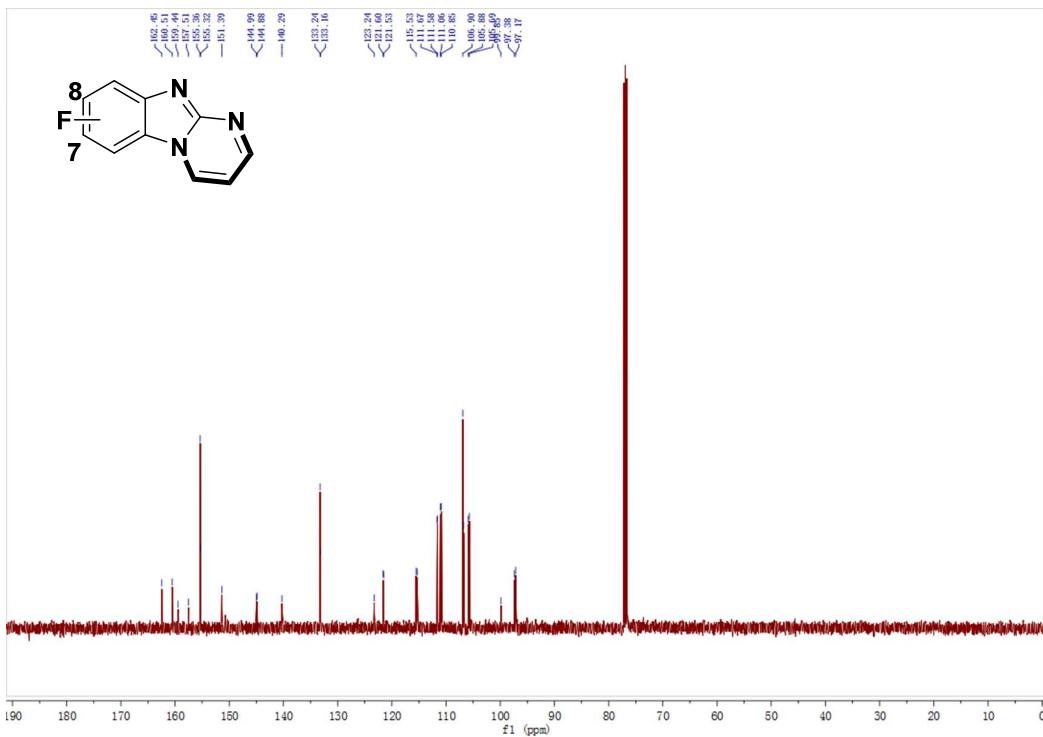
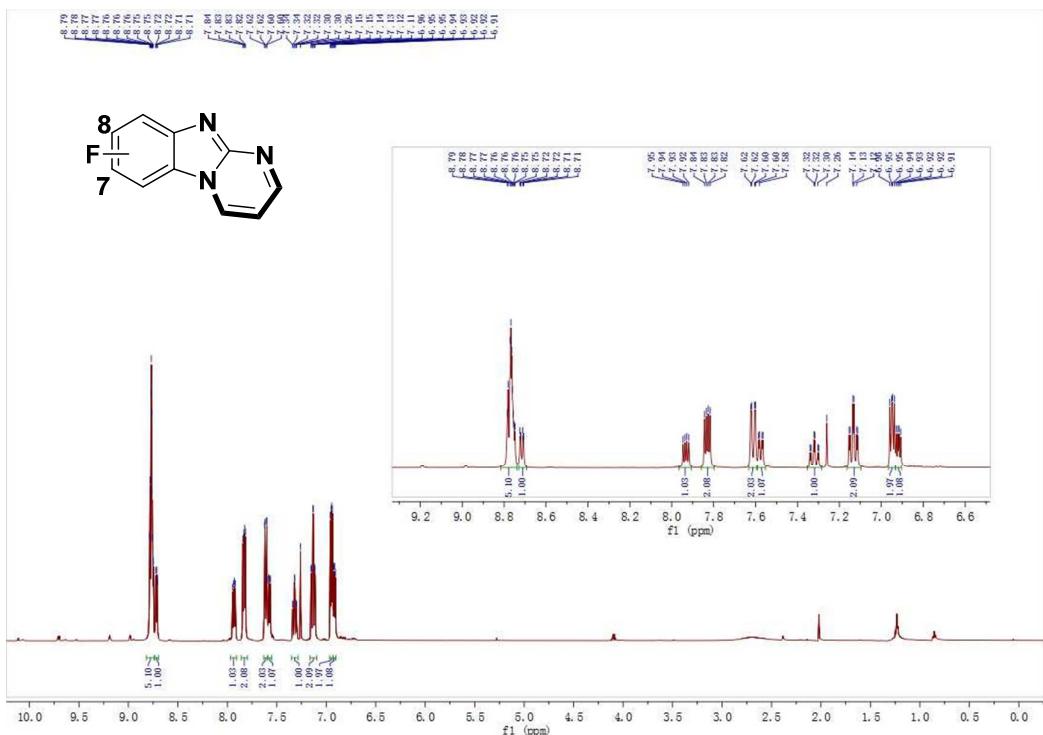
### 7,8-diphenylbenzo[4,5]imidazo[1,2-a]pyrimidine (5e)



### **Mixture of substituted on 7 or 8 position (5f)**



### Mixture of C7 or C8 of 5g



### Mixture of C7 or C8 of 5h

