Supporting Information for:

$FeCl_2$/TBAC efficiently catalyze the domino coupling reaction for constructing the indoline-fused tetrahydroisoquinolines

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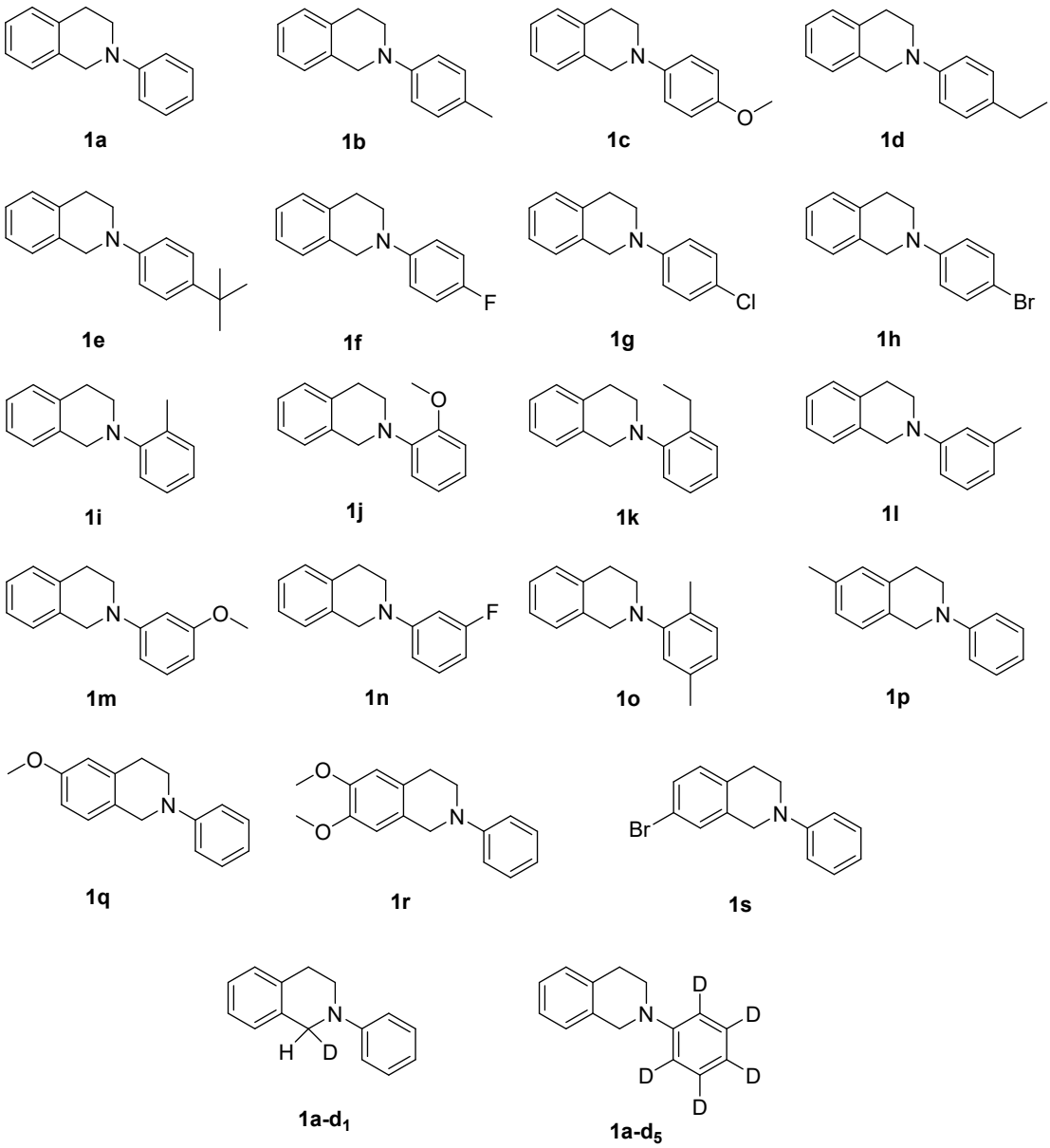
Experimental

Chemicals and reagents

All the reagents and solvents in the study were analytically pure and were all purchased from Energy or Aladdin and used as received. *N*-phenyl-1,2,3,4-tetrahydroisoquinoline and its derivatives were prepared from corresponding tetrahydroisoquinolines and aryl halides according to the reported method.[1] 1-Deutero-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a-*d*$_1$**) was synthesized according to reported method,[2] and the purity of **1a-*d*$_1$** was 92% according to ^{1}HNMR analysis. 2-(phenyl-d$_5$)-1,2,3,4-tetrahydroisoquinoline (**1a-*d*$_5$**) was synthesized according to the reported method using 1-bromobenzene-2,3,4,5,6-d$_5$ as the substrate, and the purity of **1a-*d*$_5$** was 99% according to GC-MS analysis. And other substrates (98%~99% purity) were also purchased from Energy or Aladdin and used as received.



Catalytic cascade coupling/cyclization reaction between N-phenyl-1,2,3,4-tetrahydroisoquinoline and malononitrile

Typically, a mixture of *N*-phenyl-1,2,3,4-tetrahydroquinoline (0.50 mmol), malononitrile (1.5 mmol), $FeCl_2$ (31.7 mg, 0.25 mmol), toluene (2 mL) and TBAC (tetrabutylammonium chloride) (6.9 mg, 0.025 mmol) in a carousel reaction tube (Figure S1) was magnetically stirred at 80 ℃ under an 1 atm of oxygen atmosphere. The reaction was monitored by TLC (thin-layer chromatography, petroleum ether/ethyl acetate (10:1, v/v)) and analyzed through a GC-MS (SHIMADZU, GCMS-QP2010

SE). After completion of the reaction, the reaction mixture was cooled. The conversion of the substrate and the selectivity of quinoline were obtained on the basis of the GC-MS analysis.

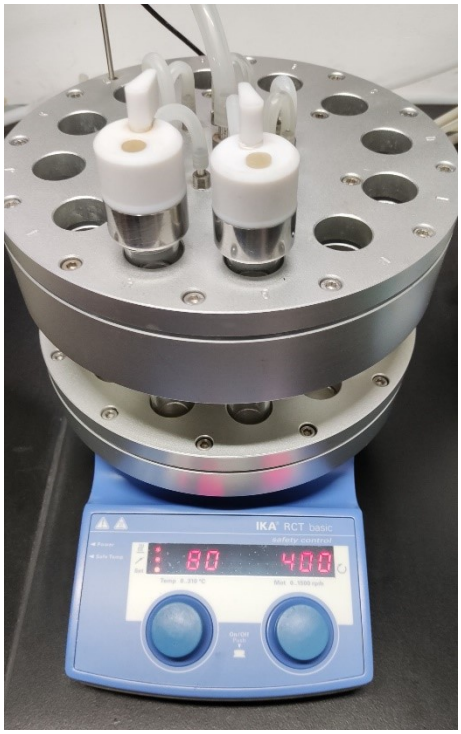


Fig. S1. The photographs of the reactor and the reaction.

Catalytic cascade coupling/cyclization reaction between N-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives and other nucleophiles

A mixture of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline derivative (0.50 mmol), nucleophile (1.5 mmol), $FeCl_2$ (31.7 mg, 0.25 mmol), toluene (2 mL) and TBAC (tetrabutylammonium chloride) (6.9mg, 0.025 mmol) in a carousel reaction tube was stirred at 80 ℃ under 1 am of oxygen. After the finish of the reaction monitored by TLC (thin-layer chromatography, petroleum ether/ethyl acetate 10:1 (v/v)), the mixture was cooled and purified using flash chromatography to give the corresponding product. NMR spectra were recorded on a Bruker ADVANCE NMR spectrometer. The melting point was analyzed on a OptiMelt Automated Melting Point System. Silica gel 60 F254 thin-layer chromatography plates (Sinopharm) was used for the thin-layer chromatography using petroleum ether/ethyl acetate (10:1, v/v) as the mobile phase.

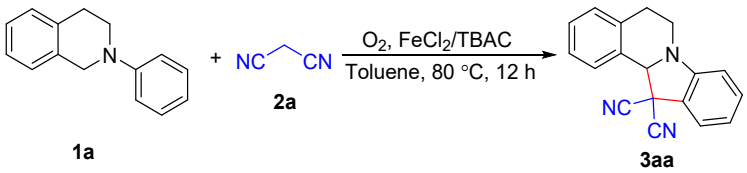
Electron paramagnetic resonance (EPR) experiments

X-band continuous-wave EPR spectra were obtained using a Bruker EMX Plus 6/1 spectrometer equipped with a dual-mode cavity (ER 4116DM). The solution of *N*-phenyl-1,2,3,4-tetrahydroisoquinoline derivative (0.50 mmol), malononitrile (1.5 mmol), $FeCl_2$ (31.7 mg, 0.25 mmol) and TBAC (6.9mg, 0.025 mmol) in toluene (2 mL) was stirred for 1 h at 80 ℃ and 100 μL of the solution was sampled in EPR tube, which were cooled 5 K prior to measurements. EPR analysis was carried out at low temperature on EPR spectrometer operated at 9.802 GHz. Typical spectrometer parameters are shown as follows, sweep width: 4000 G; center field: 3000 G; time constant: 10.24 ms; sweep time: 184.32 s; scan number: 5; modulation amplitude: 1.0 G; modulation frequency: 100 kHz; microwave power: 20.13 mW.

Larger scale reaction between N-phenyl-1,2,3,4-tetrahydroisoquinoline and malononitrile

A mixture of *N*-phenyl-1,2,3,4-tetrahydroquinoline (1.05 g, 5.0 mmol), malononitrile (15.0 mmol), $FeCl_2$ (0.32 g, 2.5 mmol), toluene (15 mL) in a 100 mL round-bottom flask was magnetically stirred at 80 ℃ under an 1 atm of oxygen atmosphere. The reaction was monitored by TLC (petroleum ether/ethyl acetate (10:1, v/v)). After completion of the reaction (12 h), the reaction

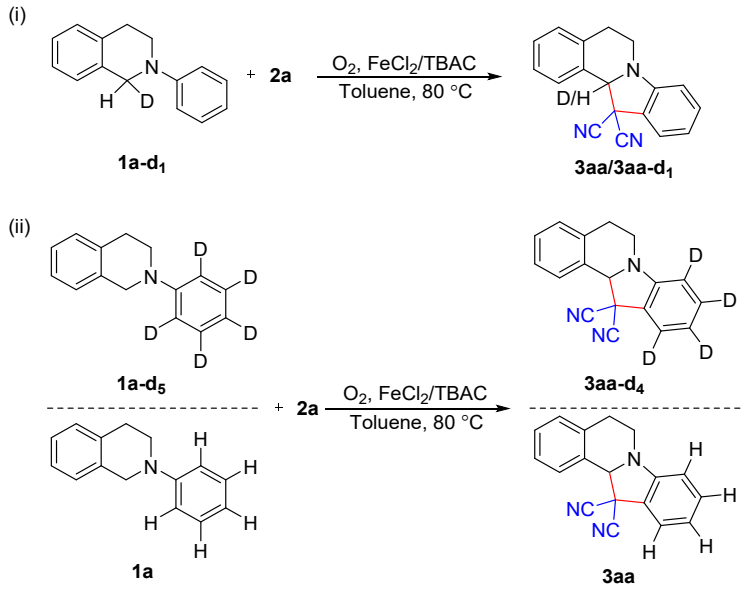
mixture was cooled and separated by filtration to remove the catalyst. The filtrate was purified using flash chromatography to give 1.06 g of **3aa** in a 78% yield (Scheme S1).



Scheme S1. Larger scale reaction.

Kinetic isotope effect studies

For the calculation of intramolecular isotopic value, the reaction was performed as described above except for the use of **1a-*d*$_1$** instead of **1a**. When **1a-*d*$_1$** was completely converted, Kinetic isotopic effects (KIE) values k_H/k_D were calculated based on the GC-MS analysis. On the other hand, for the calculation of intermolecular isotopic value, the reactions were performed as described above except for the use of the mixture of **1a-*d*$_5$** and **1a** as the substrates. When the substrates were completely converted, KIE values k_H/k_D were calculated based on the GC-MS analysis. For the calculation of KIE values, it was taken into account that substrates **1a-*d*$_1$** and **1a-*d*$_5$** were 92% and 99% pure, respectively.

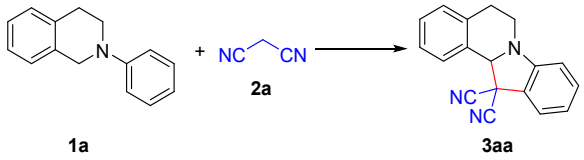


Scheme S2.

Optimization of the reaction conditions

The reaction between *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and malononitrile (**2a**) was selected as the model reaction to optimize the reaction conditions (Table S1). Initially, various iron salts were screened, and $FeCl_2$ gave the highest conversion and selectivity to **3aa** (Entries 1-6), while lower selectivity was observed for $FeCl_2·4H_2O$ with comparable conversion of 1a. These results indicated that water in the system affected the selectivity. Oxygenated product was confirmed to be the main by-product (**4a**). Then the solvent, the ratio of **2a**/**1a** and the reaction temperature were investigated in sequence. After the optimization, a 95.3% conversion with a good 92.9% selectivity to the **3aa** could be obtained with toluene as the solvent (Entry 12). To further investigate the reaction conditions, various additives have also been investigated, and TBAC could obviously improve the selectivity to **3aa**. Although TBAI could efficiently increase the conversion of **1a**, the selectivity to oxygenated product increased (Entry 23). Some chloro salts including NaCl and NH_4Cl, were also tested, and the best results was obtained in case of TBAC (Entry 21). Finally, an excellent 95.5% selectivity was observed with a >99% conversion when prolonging the reaction time to 12 h (Entry 33).

Table S1. Optimization of the reaction conditions.[a]



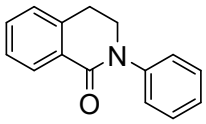
1a **3aa**

Entry	Catalyst	Solvent	Temp. /℃	**2a**/**1a**	Conv.[b]/%	Sel.[b]/%
1	$FeCl_2$	1,4-dioxane	80	3	85.5	91.8
2	$FeCl_2·4H_2O$	1,4-dioxane	80	3	82.6	72.3
3	$FeCl_3$	1,4-dioxane	80	3	39.9	91.2
4	$FeCl_3·6H_2O$	1,4-dioxane	80	3	78.2	72.0
5	$FeSO_4·7H_2O$	1,4-dioxane	80	3	trace	-
6	$Fe(NO_3)_3·7H_2O$	1,4-dioxane	80	3	trace	-
7	$FeCl_2$	DMF	80	3	80.1	30.6
8	$FeCl_2$	DMSO	80	3	>99	58.6
9	$FeCl_2$	H_2O	80	3	trace	-
10	$FeCl_2$	acetonitrile	80	3	86.1	50.4
11	$FeCl_2$	1,2-dichloroethane	80	3	83.4	83.3
12	$FeCl_2$	toluene	80	3	92.3	92.9
13	$FeCl_2$	benzotrifluoride	80	3	90.8	83.8
14	$FeCl_2$	dodecane	80	3	88.0	49.1
15	$FeCl_2$	toluene	80	1	78.9	87.7
16	$FeCl_2$	toluene	80	2	93.1	90.8
17	$FeCl_2$	toluene	80	4	94.4	91.2
18	$FeCl_2$	toluene	40	3	trace	-
19	$FeCl_2$	toluene	60	3	74.5	92.7
20	$FeCl_2$	toluene	100	3	>99	79.5
21[c]	$FeCl_2$/TBAC	toluene	80	3	95.7	95.8
22[c]	$FeCl_2$/TBAB	toluene	80	3	72.2	94.5
23[c]	$FeCl_2$/TBAI	toluene	80	3	>99	90.9
24[c]	$FeCl_2/Na_2CO_3$	toluene	80	3	94.4	87.0
25[c]	$FeCl_2/NaHCO_3$	toluene	80	3	91.4	87.9
26[c]	$FeCl_2/CH_3COOH$	toluene	80	3	63.8	87.2
27[c]	$FeCl_2/CF_3COOH$	toluene	80	3	80.5	88.3

continued

28[c]	$FeCl_2$/KOH	toluene	80	3	72.9	86.3
29[c]	$FeCl_2$/Cs_2CO_3	toluene	80	3	27.8	85.7
30[c]	$FeSO_4 \cdot 7H_2O$/TBAC	toluene	80	3	80.5	88.3
31[c]	$FeCl_2$/NaCl	toluene	80	3	27.8	85.7
32[c]	$FeCl_2$/NH_4Cl	toluene	80	3	80.5	88.3
33[c,d]	$FeCl_2$/TBAC	toluene	80	3	>99	95.5

[a] Reaction conditions: **1a** 0.5 mmol, catalyst 50 mol%, reaction time 10 h, solvent 2 mL, oxygen atmosphere. [b] Based on the GC-MS analysis, and the by-products were not quantified. [c] The amount of additive was 5 mol% of the substrate. [d] 12 h.



4a

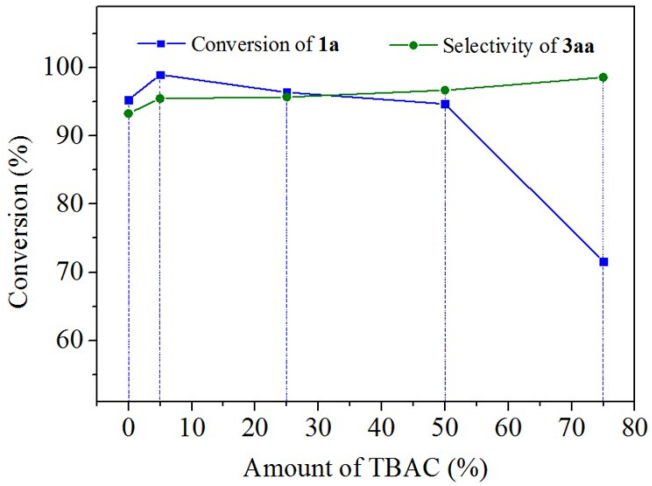
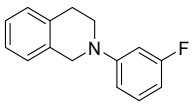
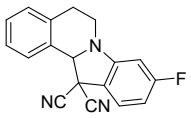
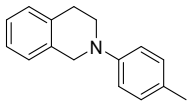
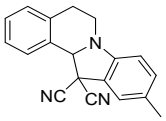
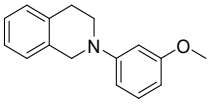
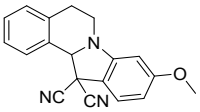
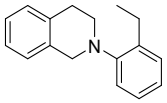
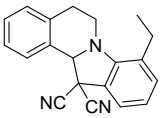
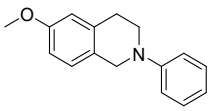
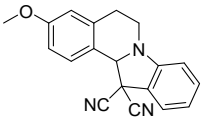


Fig. S2. Effect of the amount of TBAC on the reaction

Reaction conditions: **1a** 0.5 mmol, **2a** 1.5 mmol, $FeCl_2$ 50 mol%, toluene 2 mL, 12 h, oxygen atmosphere. The conversion and selectivity were calculated based on GC-MS analysis.

Table S2. The reaction results for some substrates with or without of TBAC.[a]

Entry	1	3	Yield (without of TBAC[b]) /%	Yield (with TBAC[b]) /%
1	 **1n**	 **3na**	23	62
2	 **1b**	 **3ba**	34	78
3	 **1m**	 **3ma**	52	72
4	 **1k**	 **3ka**	42	47
5	 **1q**	 **3qa**	38	78

[a] Reaction conditions: **1** 0.5 mmol, **2a** 1.5 mmol, $FeCl_2$ 50 mol%, 24 h, toluene 2 mL, oxygen atmosphere, TBAC 5 mol%.

[b] Based on the GC-MS analysis, and the by-products were not quantified.

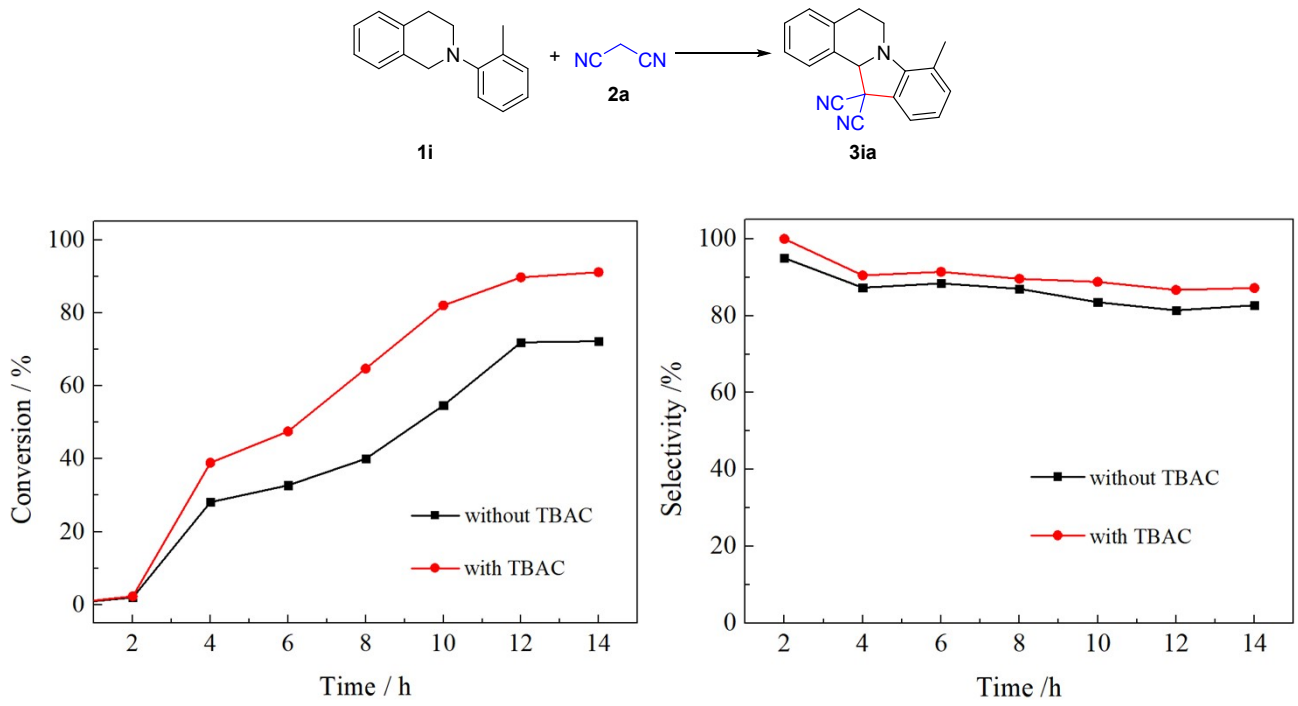


Fig. S3. The catalytic results between **1i** and **2a** with or without TBAC

Reaction conditions: **1i** 0.5 mmol, **2a** 1.5 mmol, $FeCl_2$ 50 mol%, toluene 2 mL, oxygen atmosphere, TBAC 5 mol%. The conversion and selectivity were calculated based on the GC-MS analysis.

ESI-MS spectra of iminium intermediate

To demonstrate the possibility of the formation of iminium intermediate, the reaction was performed in the presence of $FeCl_2$ without a nucleophile, and the filtrate was analyzed by MS with ESI ion source (Finnigan TSQ Quantum Mass Spectrometer). The iminum could be obviously observed at 208.1 (Fig. S4).

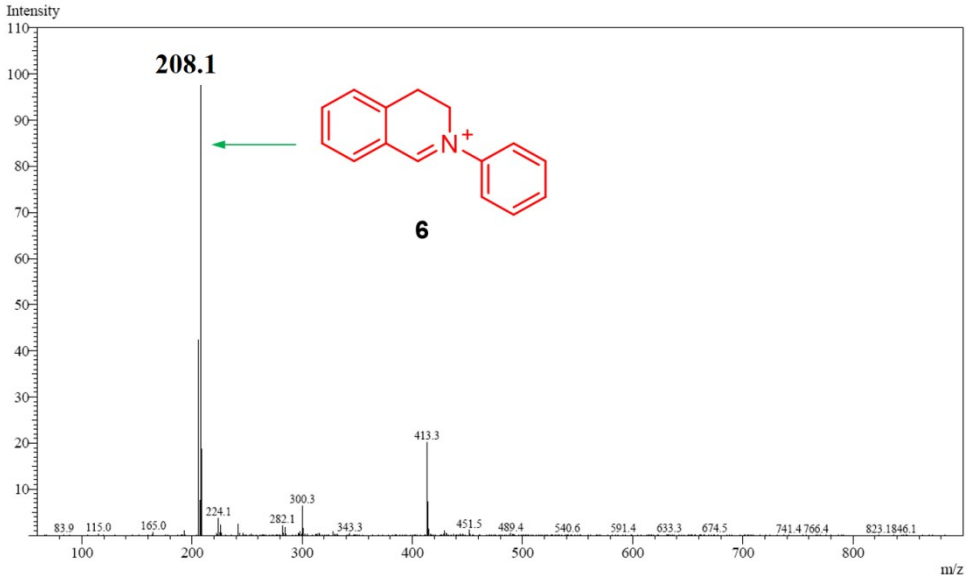
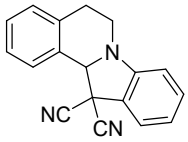
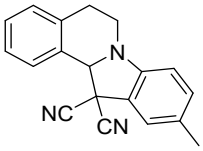


Fig. S4. The MS-ESI spectra for the possible iminium intermediate.

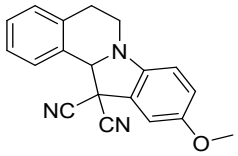
Spectrometric data for the products:



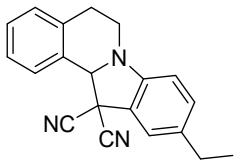
5,12a-Dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3aa**): White solid, mp. 60.5 – 62.0 ºC. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 – 7.56 (m, 1H), 7.51 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.42 – 7.32 (m, 3H), 7.29 – 7.24 (m, 1H), 6.93 (td, *J* = 7.6, 0.8 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.20 (s, 1H), 3.93 – 3.78 (m, 1H), 3.28 – 3.12 (m, 2H), 2.96 – 2.82 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 135.6, 132.2, 129.8, 129.7, 129.0, 127.3, 125.6, 125.0, 122.0, 120.5, 115.1, 112.2, 109.6, 77.5, 77.1, 76.6, 72.0, 42.6, 42.5, 28.8. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{13}N_3$ $[M+H]^+$ 272.1182, found 272.1179.



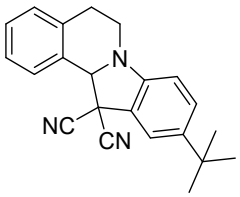
10-Methyl-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ba**): Orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.29 – 7.26 (m, 2H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.33 (s, 1H), 3.84 (ddd, *J* = 12.0, 5.6, 2.4 Hz, 1H), 3.29 – 3.22 (m, 1H), 3.17 (ddd, *J* = 16.6, 11.1, 5.7 Hz, 1H), 2.94 – 2.87 (m, 1H), 2.59 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.7, 135.7, 132.7, 130.8, 129.9, 129.6, 128.9, 127.2, 125.6, 125.3, 122.4, 115.3, 112.4, 110.2, 72.3, 43.3, 42.7, 28.8, 20.8. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$ 286.1339, found 286.1332.



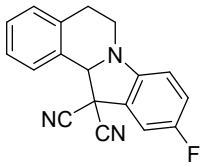
10-Methoxy-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ca**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 1H), 7.37 (ddd, *J* = 21.1, 16.0, 7.7 Hz, 3H), 7.29 (s, 1H), 6.45 (d, *J* = 8.3 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 3.99 (s, 3H), 3.83 (ddd, *J* = 12.3, 5.7, 2.4 Hz, 1H), 3.27 (td, *J* = 11.8, 3.6 Hz, 1H), 3.14 (ddd, *J* = 16.6, 11.3, 5.7 Hz, 1H), 2.88 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.0, 151.5, 135.7, 133.8, 130.0, 129.5, 128.9, 127.3, 125.9, 114.9, 111.8, 107.7, 103.0, 102.5, 72.2, 56.0, 43.1, 40.8, 28.9. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3O$ $[M+H]^+$ 302.1288, found 302.1281.



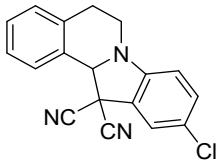
10-ethyl-5,12a-dihydroindolo[2,1-a]isoquinoline-12,12(6H)-dicarbonitrile (**3da**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 1H), 7.47 – 7.32 (m, 3H), 7.32 – 7.28 (m, 1H), 6.80 (ddd, *J* = 27.5, 14.3, 4.6 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 5.26 (d, *J* = 44.0 Hz, 1H), 3.93 – 3.81 (m, 1H), 3.29 – 3.13 (m, 2H), 3.02 – 2.89 (m, 2H), 2.72 – 2.65 (m, 1H), 1.42 (d, *J* = 7.5 Hz, 1H), 1.29 (q, *J* = 7.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 142.5, 135.8, 132.3, 131.6, 130.0, 129.6, 128.9, 127.3, 127.2, 127.2, 125.7 , 125.6, 125.6, 124.7, 124.2, 120.5, 120.4, 115.5, 112.1, 110.2, 109.3, 107.3, 72.3, 71.9, 43.2, 42.9, 42.6, 29.4, 28.9, 28.8, 28.8, 24.9, 15.6, 14.1. **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{17}N_3$ $[M+H]^+$ 300.1495, found 300.1491.



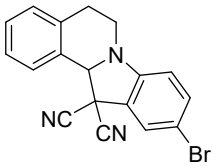
10-(*tert*-Butyl)-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ea**): Red-brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 – 7.60 (m, 1H), 7.64 – 7.61 (m, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.29 (s, 1H), 6.76 (d, *J* = 8.4 Hz, 1H), 5.22 (s, 1H), 3.87 – 3.81 (m, 1H), 3.27 – 3.16 (m, 2H), 2.95 – 2.89 (m, 1H), 1.36 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.6, 144.6, 135.7, 129.9, 129.6, 129.2, 128.9, 127.2, 125.7, 122.0, 121.6, 115.3, 112.5, 109.8, 72.4, 43.2, 42.9, 34.6, 31.5, 28.8. **HRMS** (ESI-TOF) Calcd. for $C_{22}H_{21}N_3$ $[M+H]^+$ 328.1808, found 328.1803.



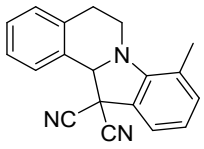
10-Fluoro-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3fa**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 1H), 7.41 (pd, *J* = 7.4, 1.7 Hz, 2H), 7.31 (dd, *J* = 7.1, 2.5 Hz, 2H), 7.14 (td, *J* = 8.7, 2.6 Hz, 1H), 6.77 (dd, *J* = 8.7, 4.0 Hz, 1H), 5.26 (s, 1H), 3.80 (ddd, *J* = 7.5, 5.0, 2.9 Hz, 1H), 3.22 (dtd, *J* = 16.2, 10.7, 4.6 Hz, 2H), 2.97 – 2.91 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.2, 156.3, 146.4, 135.5, 129.7, 129.5, 129.1, 127.3, 125.6, 123.1 (d, $J_{C\text{-}F}$ = 8.4 Hz), 119.2-119.0 (d, $J_{C\text{-}F}$ = 23.4 Hz), 114.6, 112.7-112.5 (d, $J_{C\text{-}F}$ = 26.0 Hz), 111.0 (d, $J_{C\text{-}F}$ = 7.8 Hz), 72.6, 43.4, 28.7. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{12}FN_3$ $[M+H]^+$ 290.1088, found 290.1079.



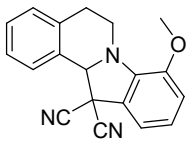
10-Chloro-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ga**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.61 – 7.57 (m, 1H), 7.52 (d, *J* = 1.9 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.36 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.32 – 7.28 (m, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 5.27 (s, 1H), 3.87 – 3.82 (m, 1H), 3.29 – 3.16 (m, 2H), 2.95 – 2.90 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.2, 135.4, 132.3, 129.7, 129.3, 127.4, 125.6, 125.0, 123.1, 114.5, 111.7, 110.5, 72.1, 42.5, 28.7. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{12}ClN_3$ $[M+H]^+$ 306.0793, found 306.0786.



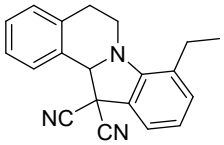
10-Bromo-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ha**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.9 Hz, 1H), 7.60 – 7.57 (m, 1H), 7.49 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.31 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.27 (s, 1H), 3.87 – 3.82 (m, 1H), 3.29 – 3.16 (m, 2H), 2.95 – 2.89 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 148.5, 135.4, 135.1, 129.7, 129.2, 127.9, 127.4, 125.6, 123.5, 114.4, 111.6, 110.9, 72.0, 42.5, 28.7. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{12}BrN_3$ $[M+H]^+$ 350.0287, found 350.0282.



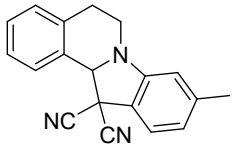
8-Methyl-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ia**): Yellow solid, mp. 126.5 – 141.5 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.2 Hz, 1H), 7.50 – 7.37 (m, 3H), 7.30 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.33 (s, 1H), 3.84 (ddd, *J* = 12.0, 5.7, 2.4 Hz, 1H), 3.29 – 3.23 (m, 1H), 3.17 (ddd, *J* = 16.7, 11.4, 5.7 Hz, 1H), 2.93 – 2.88 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.1, 136.6, 135.7, 132.1, 129.9, 129.6, 128.9, 127.3, 125.7, 122.5, 115.1, 111.7, 107.5, 71.8, 43.0, 42.0, 28.8, 18.2. **HRMS** (ESI-TOF): Calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$ 286.1339, found 286.1332.



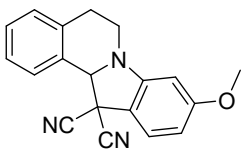
8-Methoxy-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ja**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 1H), 7.43 – 7.28 (m, 4H), 6.45 (d, *J* = 8.3 Hz, 1H), 6.40 (d, *J* = 8.0 Hz, 1H), 5.37 (s, 1H), 3.99 (s, 3H), 3.83 (ddd, *J* = 12.3, 5.8, 2.4 Hz, 1H), 3.30 – 3.24 (m, 1H), 3.14 (ddd, *J* = 16.5, 11.3, 5.7 Hz, 1H), 2.88 (dt, *J* = 16.0, 2.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.0, 151.5, 133.8, 129.5, 128.9, 127.3, 125.8, 114.9, 111.9, 107.6, 103.0, 102.5, 72.2, 56.0, 43.1, 40.8, 28.9. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3O$ $[M+H]^+$ 302.1288, found 302.1288.



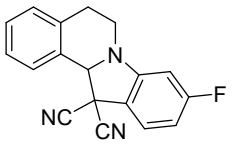
8-Ethyl-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ka**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 – 7.61 (m, 1H), 7.48 – 7.34 (m, 3H), 7.32 – 7.28 (m, 1H), 6.84 – 6.78 (m, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.26 (d, *J* = 44.1 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.29 – 3.13 (m, 2H), 3.00 – 2.88 (m, 2H), 2.70 (q, *J* = 7.6 Hz, 1H), 1.43 (t, *J* = 7.6 Hz, 2H), 1.31 (d, *J* = 7.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.0, 149.8, 149.3, 142.5, 135.8, 135.7, 132.3, 130.0, 129.9, 128.9, 128.9, 127.2, 127.2, 125.7, 124.7, 120.5, 120.4, 119.5, 119.4, 115.5, 115.2, 112.4, 112.1, 109.3, 107.3, 72.3, 71.9, 42.9, 42.6, 29.4, 28.9, 24.9, 15.6, 14.1. **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{17}N_3$ $[M+H]^+$ 300.1495, found 300.1485.



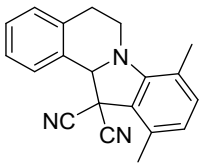
9-methyl-5,12a-dihydroindolo[2,1-a]isoquinoline-12,12(6H)-dicarbonitrile (**3la**): Yellow solid, mp. 127.8-129.1 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.41 (dd, *J* = 7.9, 6.2 Hz, 3H), 7.30 (s, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.33 (s, 1H), 3.84 (ddd, *J* = 11.9, 5.7, 2.4 Hz, 2H), 3.27 (dd, *J* = 11.4, 3.7 Hz, 1H), 2.92 (s, 1H), 2.59 (s, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 150.1, 136.6, 135.8, 132.1, 130.0, 129.6, 128.9, 127.3, 125.7, 122.5, 115.1, 111.7, 107.5, 71.8, 43.0, 42.0, 28.8, 18.2. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$ 286.1339, found 286.1334.



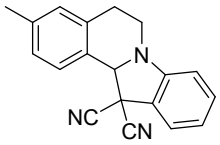
9-methoxy-5,12a-dihydroindolo[2,1-a]isoquinoline-12,12(6H)-dicarbonitrile (**3ma**): Orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 – 7.59 (m, 1H), 7.40 (ddd, *J* = 9.1, 7.9, 4.9 Hz, 3H), 7.29 (t, *J* = 3.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.31 (d, *J* = 2.3 Hz, 1H), 5.24 (s, 1H), 3.86 – 3.83 (m, 4H), 3.27 – 3.16 (m, 2H), 2.91 (dd, *J* = 12.6, 1.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.5, 151.0, 129.6, 128.9, 127.2, 125.7, 125.5, 115.2, 113.9, 112.5, 105.4, 96.2, 72.4, 55.7, 42.4, 42.2, 28.8. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3O$ $[M+H]^+$ 302.1288, found 302.1284.



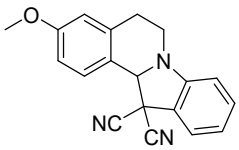
9-fluoro-5,12a-dihydroindolo[2,1-a]isoquinoline-12,12(6H)-dicarbonitrile (**3na**): Orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.0 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.30 (d, *J* = 7.0 Hz, 1H), 6.63 (t, *J* = 8.6 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 5.41 (s, 1H), 3.88 (ddd, *J* = 12.3, 5.8, 2.1 Hz, 1H), 3.34 – 3.27 (m, 1H), 3.18 (ddd, *J* = 16.8, 11.4, 5.7 Hz, 1H), 2.91 (d, *J* = 15.9 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 135.5, 134.4 (d, J_{C-F} = 9.1 Hz), 129.7, 129.2 (d, J_{C-F} = 6.0 Hz), 127.5, 125.7, 113.9, 111.0, 107.3, 107.3-107.2 (d, J_{C-F} = 19.1 Hz), 105.2, 72.3, 42.7, 29.7, 28.8. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{12}FN_3$ $[M+H]^+$ 290.1088, found 290.1085.



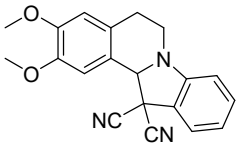
8,11-Dimethyl-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3oa**): White solid, mp. 146.8 – 148.0ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 1H), 7.44 – 7.40 (m, 2H), 7.35 – 7.32 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 5.49 (s, 1H), 3.44 (dt, *J* = 11.4, 4.5 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.14 (ddd, *J* = 14.7, 10.0, 4.4 Hz, 1H), 2.94 (dt, *J* = 15.8, 3.8 Hz, 1H), 2.59 (s, 3H), 2.37 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 152.3, 135.7, 133.9, 133.6, 129.7, 129.1, 129.0, 127.4, 126.7, 126.6, 125.7, 125.2, 115.9, 113.0, 71.7, 46.3, 43.8, 29.8, 18.3, 17.3. **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{17}N_3$ $[M+H]^+$ 300.1495, found 300.1491.



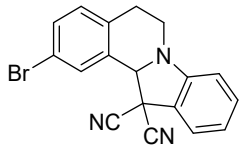
3-Methyl-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3pa**): Yellow solid, mp. 121.5 – 134.0 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 17.7, 7.7 Hz, 2H), 7.39 (dd, *J* = 11.3, 4.2 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.11 (s, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 5.22 (s, 1H), 3.90 – 3.85 (m, 1H), 3.20 (dtd, *J* = 16.6, 11.3, 4.6 Hz, 2H), 2.87 (d, *J* = 15.6 Hz, 1H), 2.40 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 138.8, 135.5, 132.2, 130.2, 128.1, 126.8, 125.5, 125.0, 122.0, 120.4, 115.1, 112.3, 109.6, 72.0, 42.8, 42.6, 28.7, 21.3. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3$ $[M+H]^+$ 286.1339, found 286.1332.



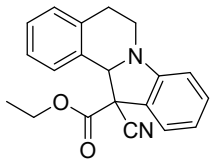
3-Methoxy-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3qa**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.39 (t, *J* = 7.7 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.80 (dd, *J* = 10.7, 5.2 Hz, 2H), 5.21 (s, 1H), 3.87 – 3.84 (m, 4H), 3.26 – 3.13 (m, 2H), 2.90 – 2.83 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.7, 149.6, 137.3, 132.2, 126.9, 125.0, 122.0, 120.5, 115.2, 114.6, 113.2, 112.4, 109.7, 71.9, 55.3, 43.0, 42.5, 29.1. **HRMS** (ESI-TOF) Calcd. for $C_{19}H_{15}N_3O$ $[M+H]^+$ 302.1288, found 302.285.



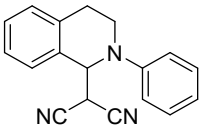
2,3-Dimethoxy-5,12a-dihydroindolo[2,1-*a*]isoquinoline-12,12(6*H*)-dicarbonitrile (**3ra**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 1H), 7.39 (td, *J* = 7.8, 1.1 Hz, 1H), 7.05 (s, 1H), 6.95 (td, *J* = 7.6, 0.7 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.74 (s, 1H), 5.23 (s, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.86 (ddd, *J* = 12.1, 5.7, 2.2 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.13 (ddd, *J* = 16.8, 11.2, 5.7 Hz, 1H), 2.80 (d, *J* = 15.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 149.3, 148.2, 132.2, 128.3, 125.0, 121.8, 121.3, 120.4, 115.3, 112.4, 112.0, 109.7, 108.8, 108.1, 71.9, 56.1, 43.1, 42.5, 28.3. **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{17}N_3O_2$ $[M+H]^+$ 332.1394, found 332.1394.



2-bromo-5,12a-dihydroindolo[2,1-a]isoquinoline-12,12(6H)-dicarbonitrile (**3sa**): Red-brown oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.55 – 7.47 (m, 2H), 7.42 – 7.35 (m, 1H), 7.16 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 5.16 (s, 1H), 3.91 – 3.82 (m, 1H), 3.13 (ddd, *J* = 27.0, 12.2, 4.4 Hz, 2H), 2.86 (d, *J* = 15.3 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 149.6, 138.8, 135.5, 132.2, 130.2, 128.1, 126.8, 125.5, 124.9, 122.0, 120.4, 115.1, 112.3, 109.6, 72.0, 42.8, 42.6, 28.7, 21.3. **HRMS** (ESI-TOF) Calcd. for $C_{18}H_{12}BrN_3$ $[M+H]^+$ 350.0287, found 350.0283.



Ethyl 12-cyano-5,6,12,12a-tetrahydroindolo[2,1-*a*]isoquinoline-12-carboxylate (**3ab**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 7.17 – 7.14 (m, 1H), 7.11 (dd, *J* = 6.7, 1.8 Hz, 2H), 6.72 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 2H), 4.40 (s, 1H), 3.38 (d, *J* = 17.1 Hz, 1H), 3.33 – 3.27 (m, 2H), 3.02 (d, *J* = 17.1 Hz, 1H), 1.28 (s, 3H), 0.89 (dt, *J* = 19.0, 6.6 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.7, 142.2, 142.1, 135.8, 134.9, 132.3, 129.2, 128.5, 128.1, 126.6, 123.4, 123.2, 119.0, 114.7, 57.0, 54.7, 34.6, 34.3, 29.7. **HRMS** (ESI-TOF) Calcd. for $C_{20}H_{18}N_2O_2$ $[M+H]^+$ 319.1441, found 319.1436.



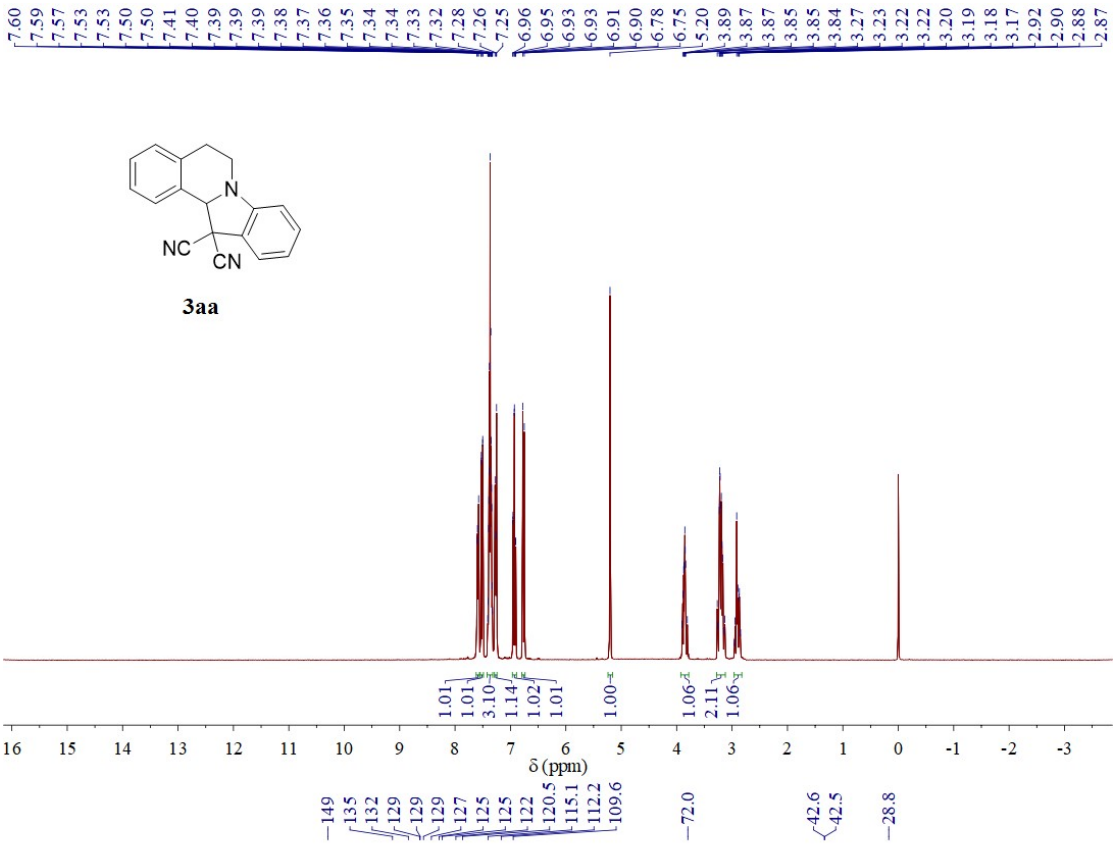
5,6-Dihydroindolo[2,1-*a*]isoquinoline-12-carbonitrile (**4aa**): Yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.3 Hz, 1H), 7.43 – 7.31 (m, 5H), 7.03 (dd, *J* = 15.0, 7.7 Hz, 3H), 5.41 (d, *J* = 4.7 Hz, 1H), 4.24 (d, *J* = 4.7 Hz, 1H), 3.84 (ddd, *J* = 12.3, 7.4, 5.0 Hz, 1H), 3.59 – 3.53 (m, 1H), 3.22 – 3.15 (m, 1H), 3.13 – 3.05 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.8, 135.2, 133.1, 129.9, 128.7, 128.4, 127.9, 126.3, 125.7, 123.9, 122.4, 119.5, 117.4, 109.9, 80.6, 40.4, 28.7. **HRMS** (ESI-TOF) Calcd for $C_{18}H_{15}N_3$ $[M+H]^+$ 274.1339, found 274.1335.

References

[1] L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, *Org. Lett.* **2003**, *5*, 3515–3517.

[2] E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325.

NMR spectra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CN
3aa
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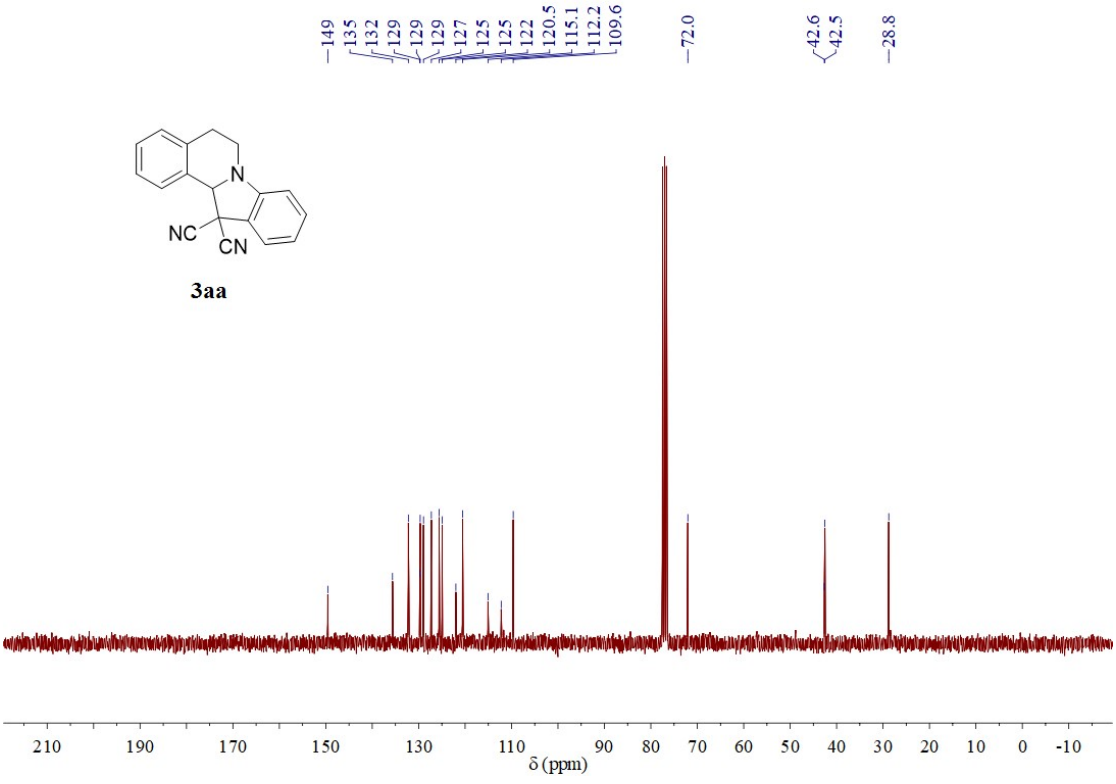
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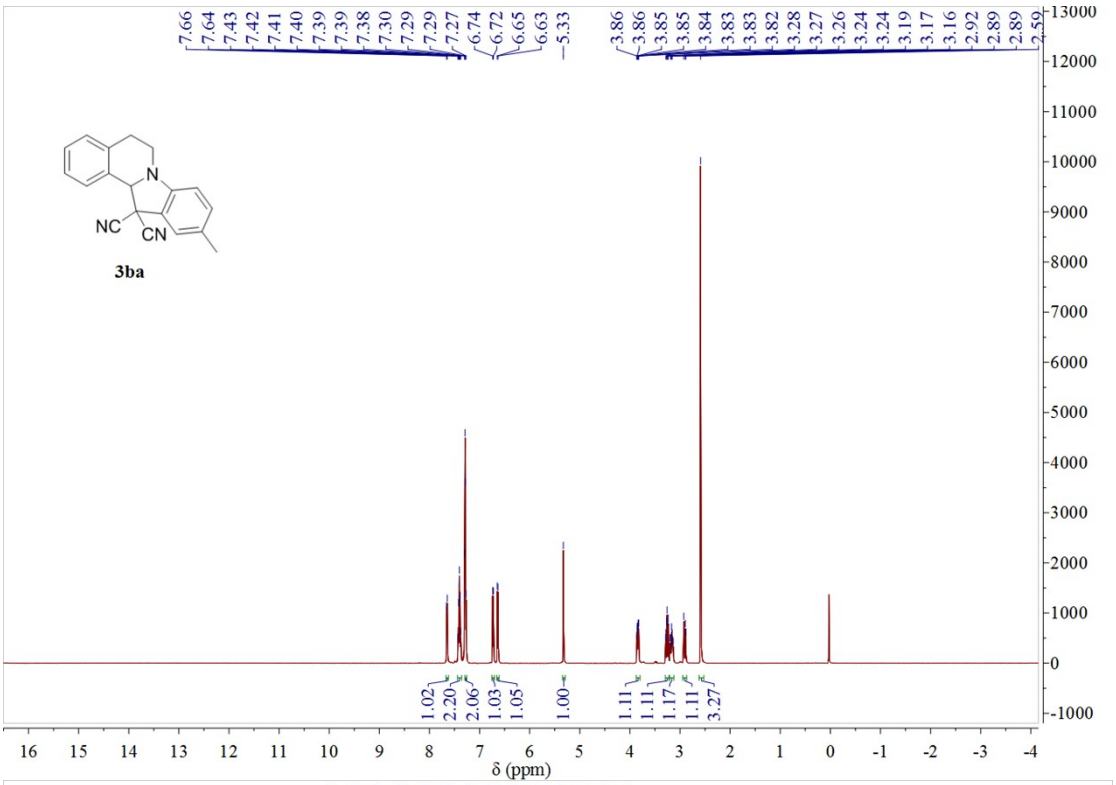
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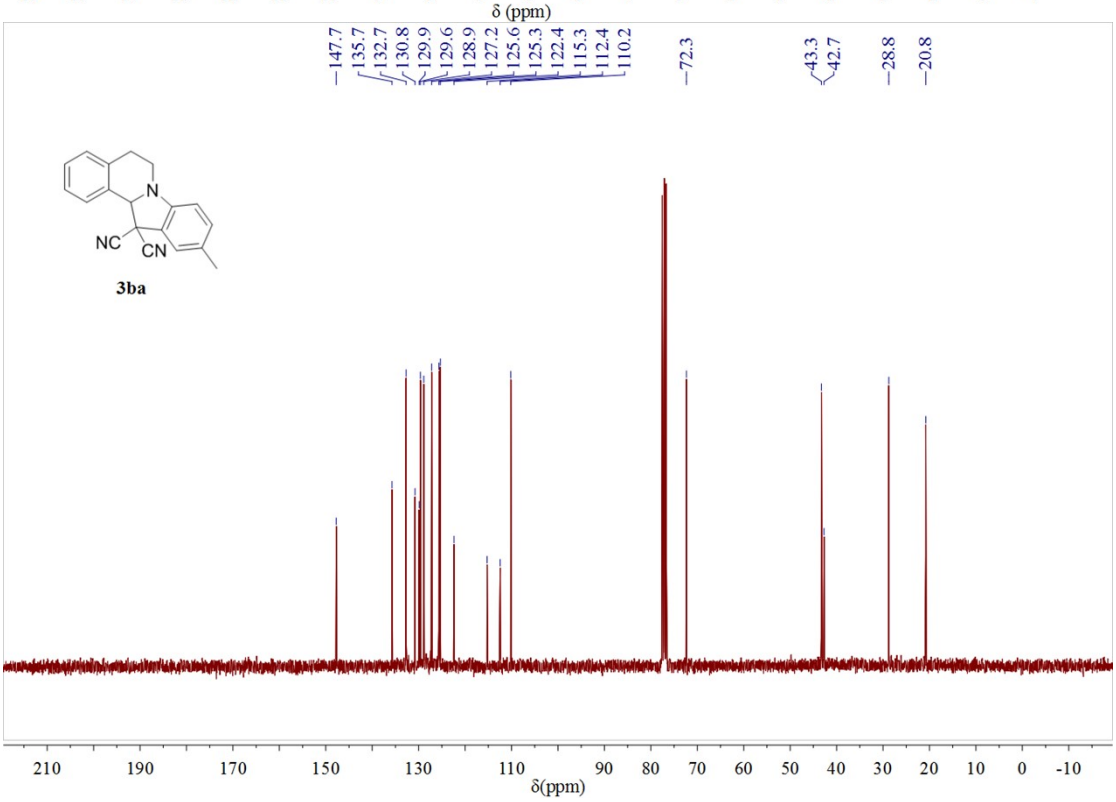
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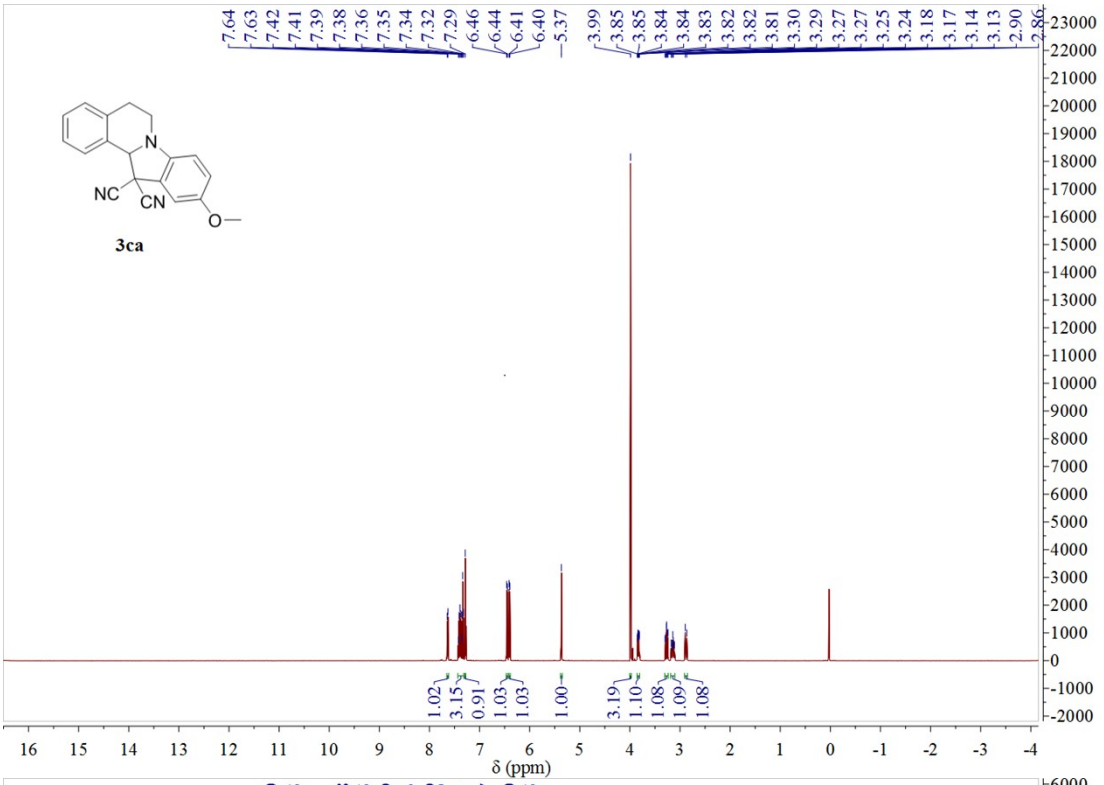
δ(ppm)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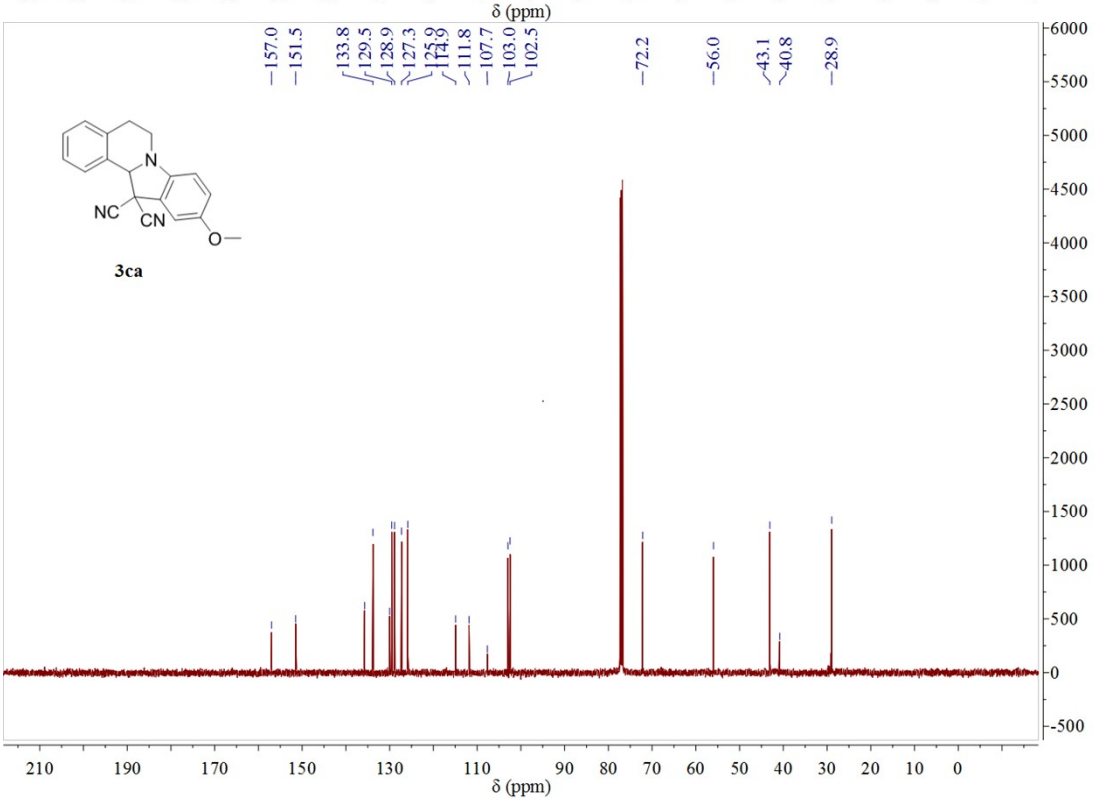
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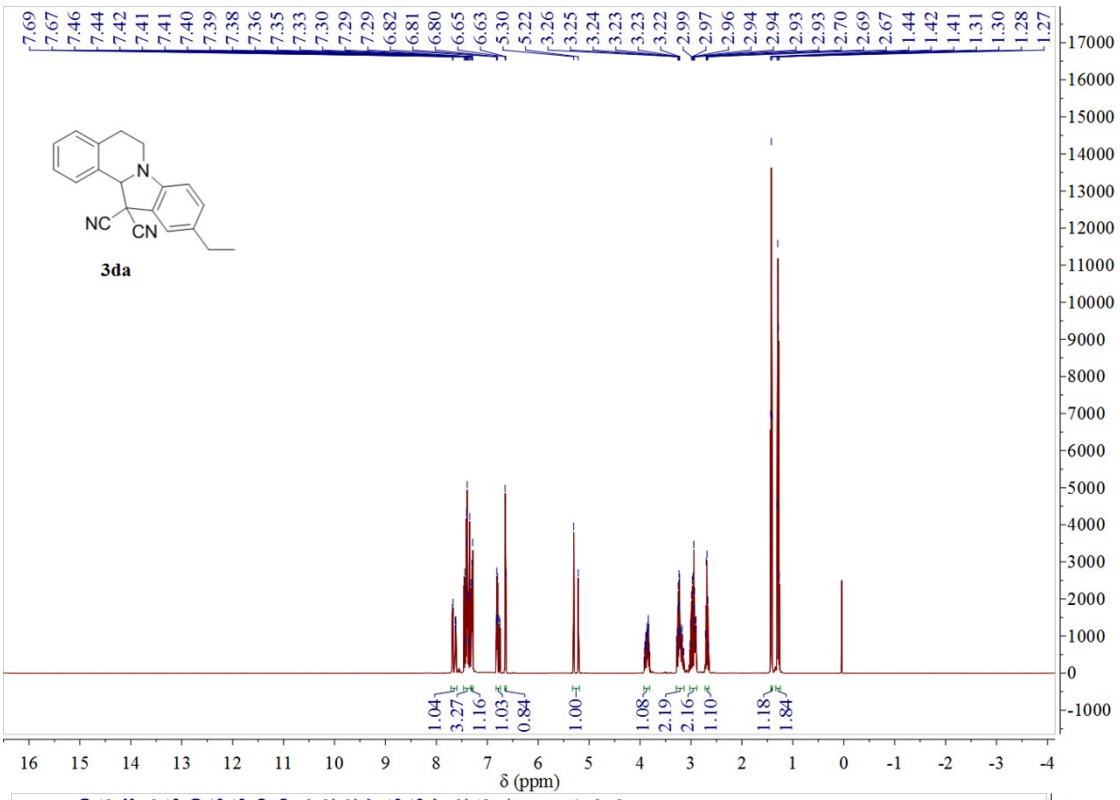
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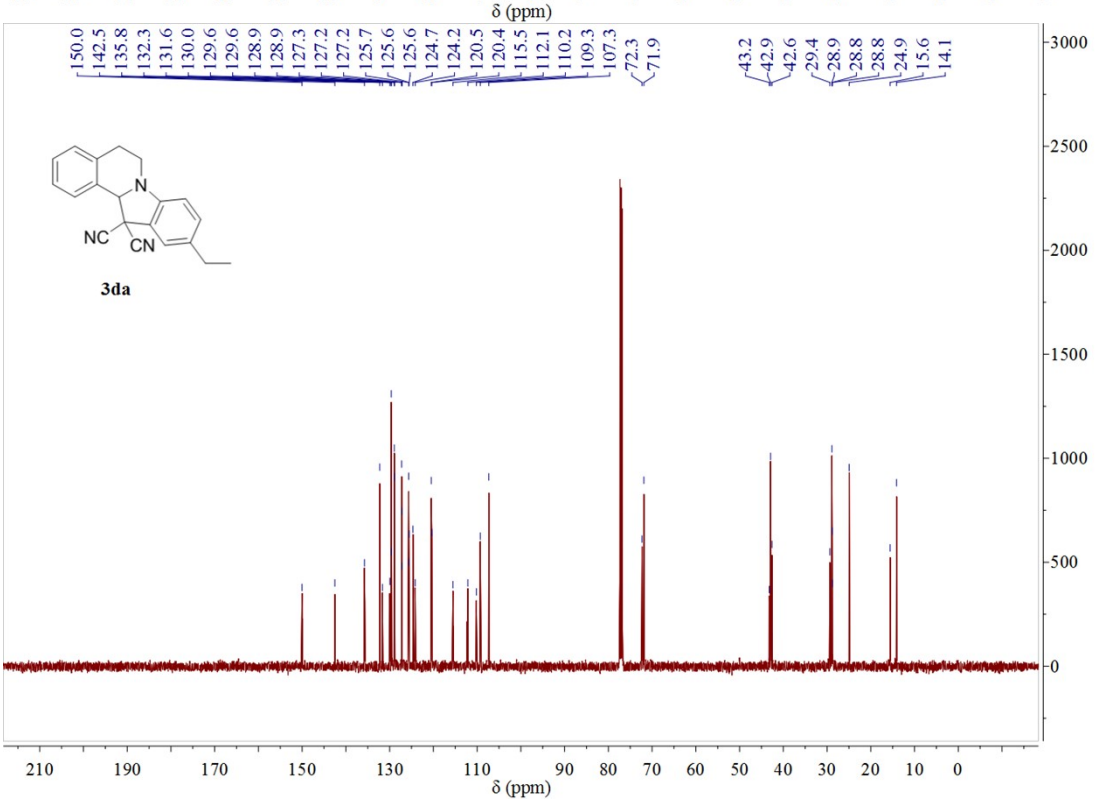
δ (ppm)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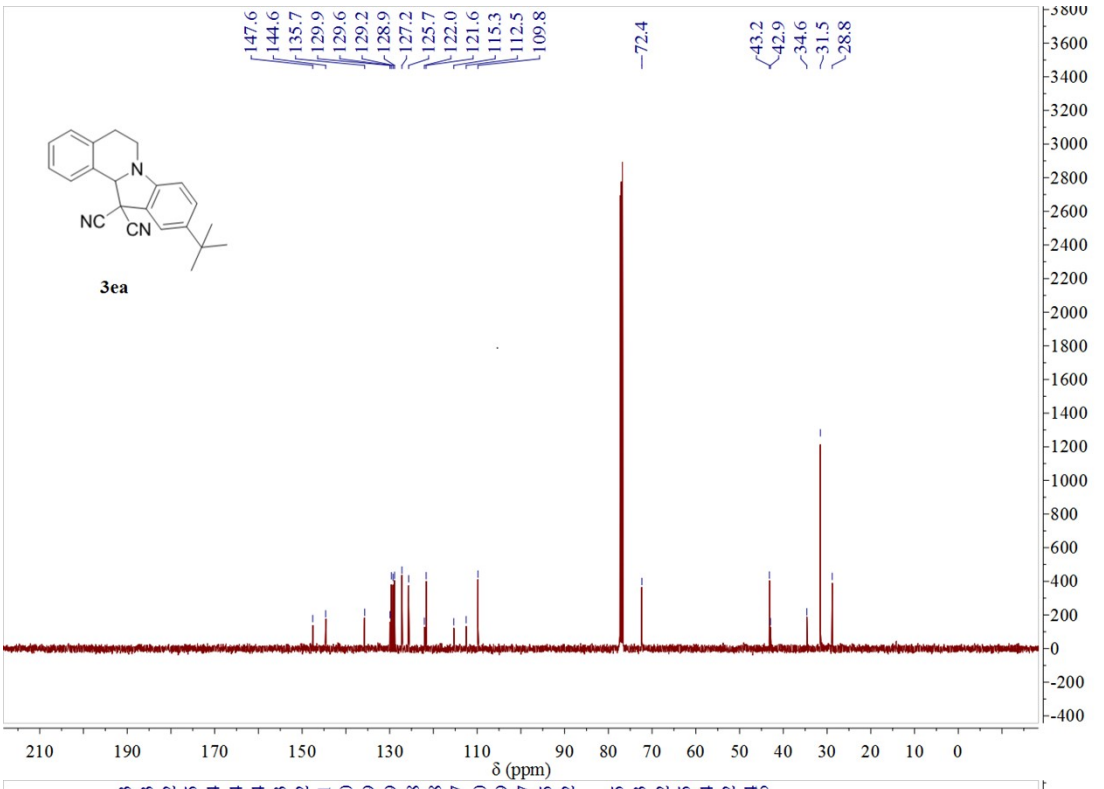
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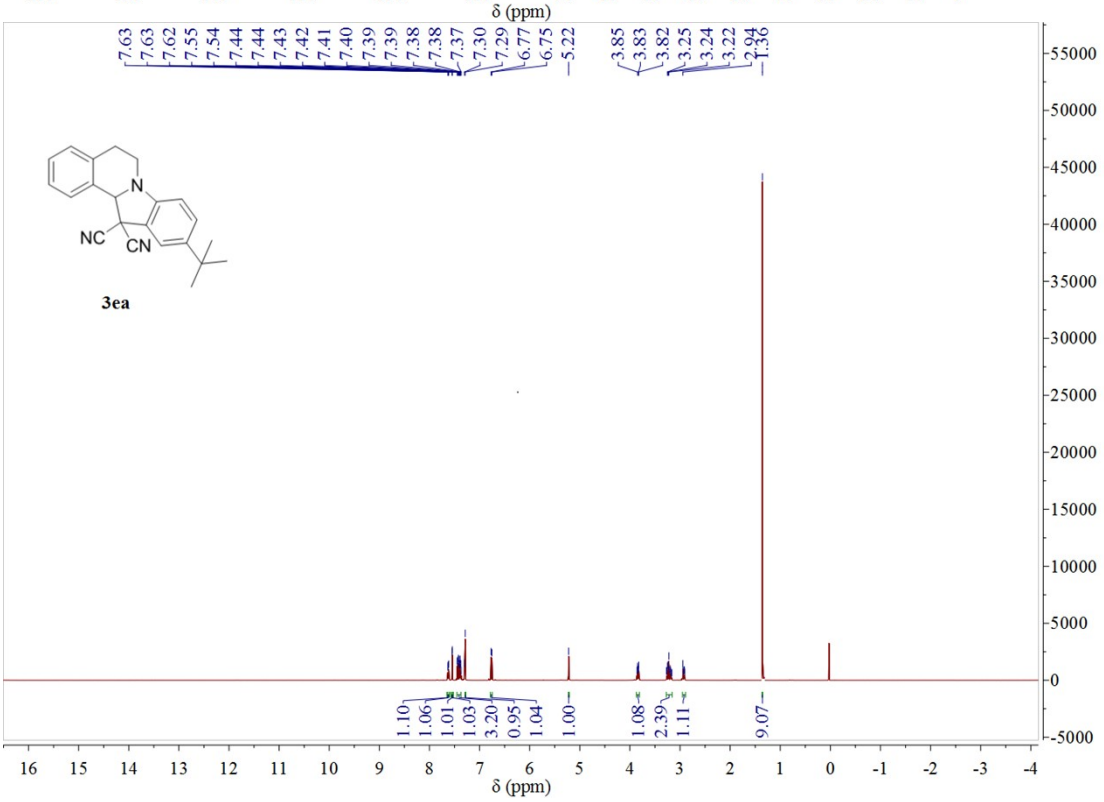
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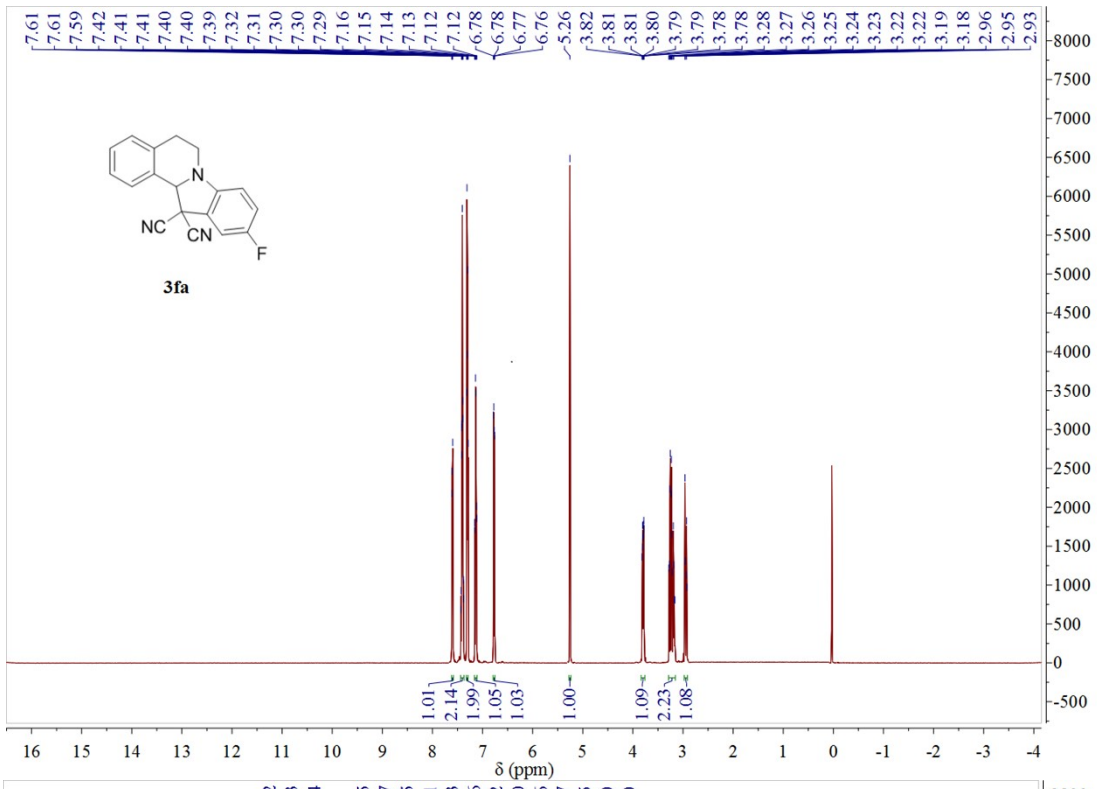
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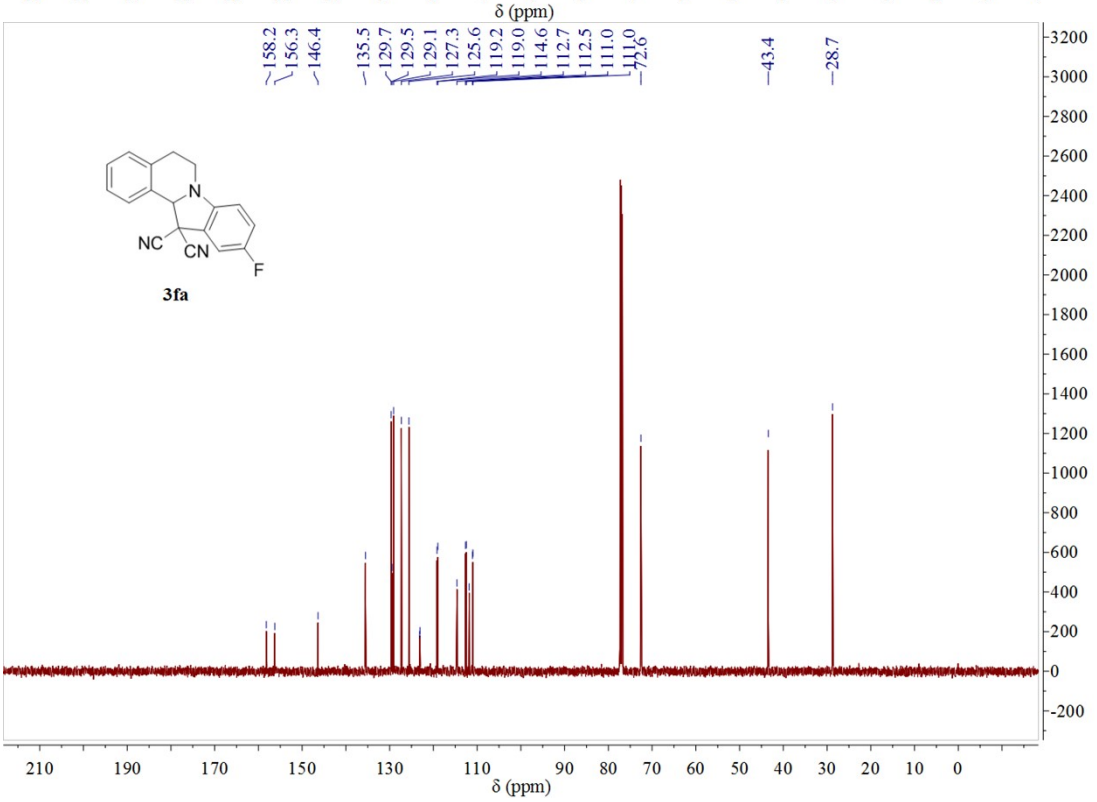
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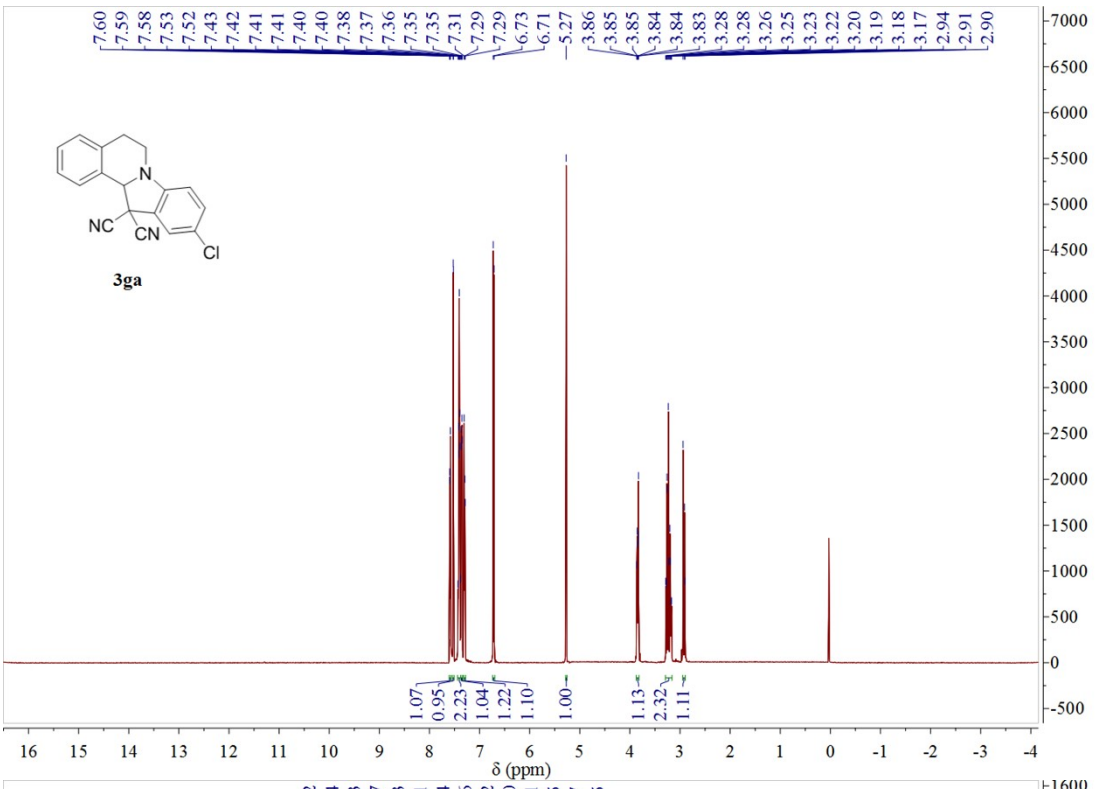
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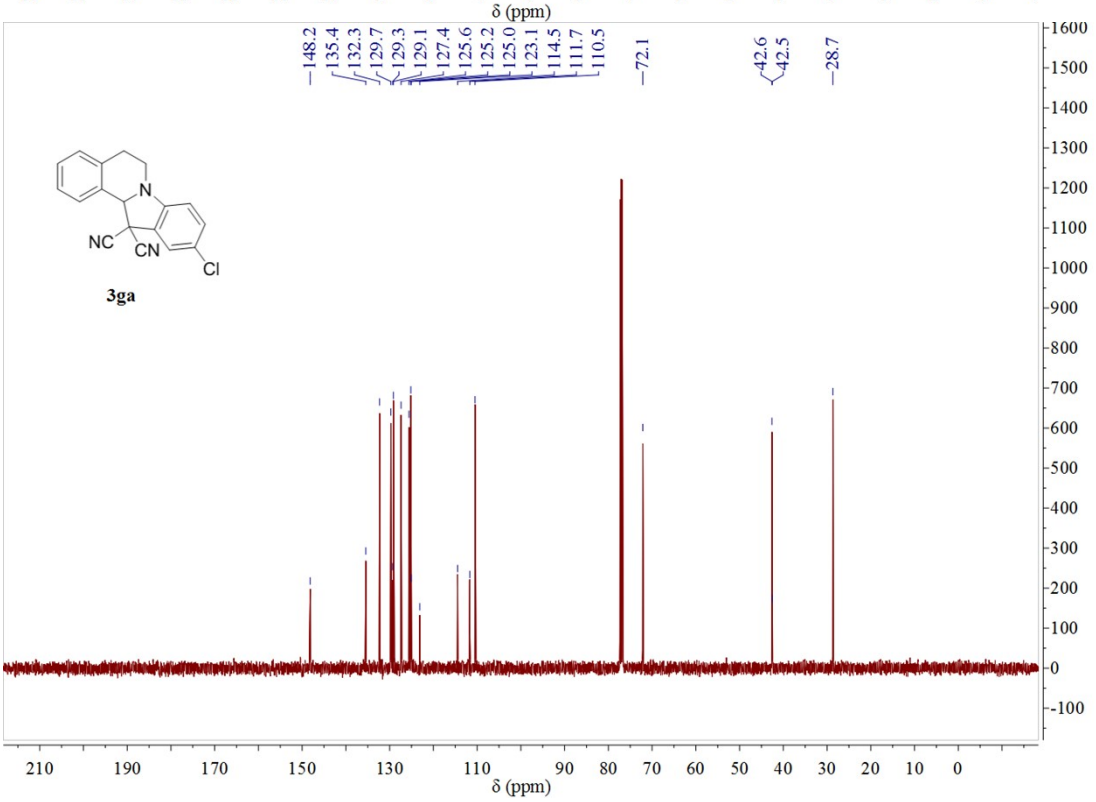
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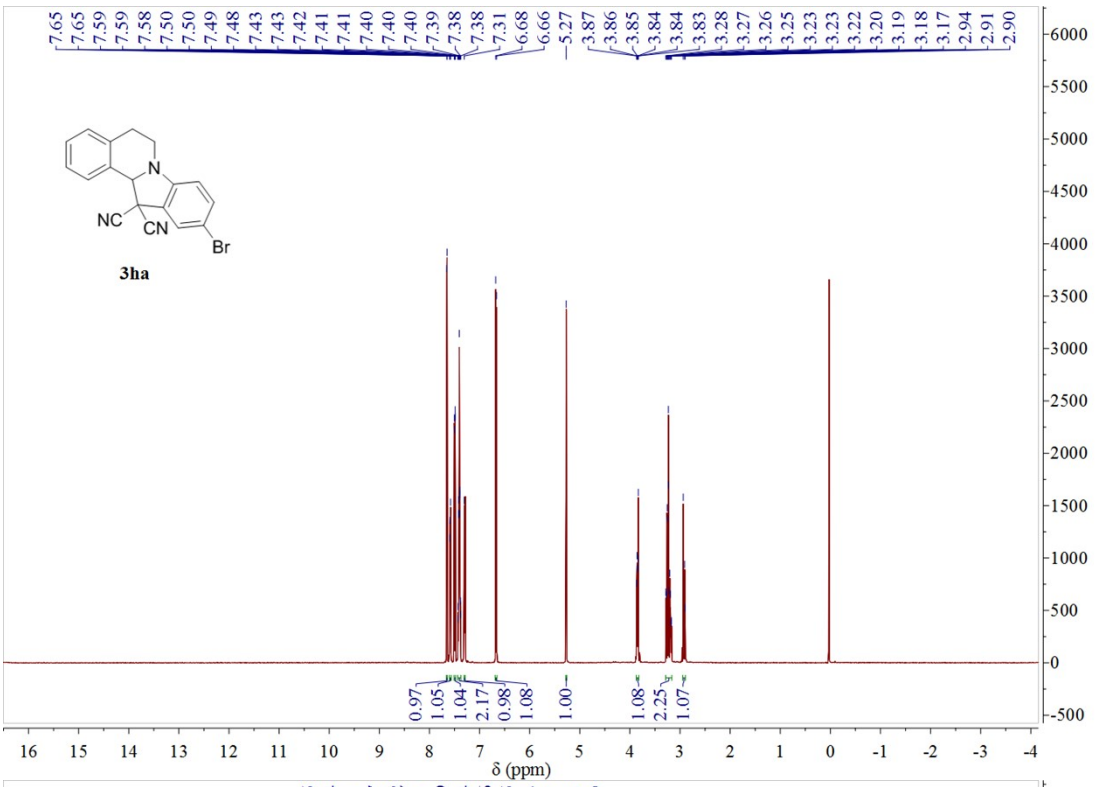
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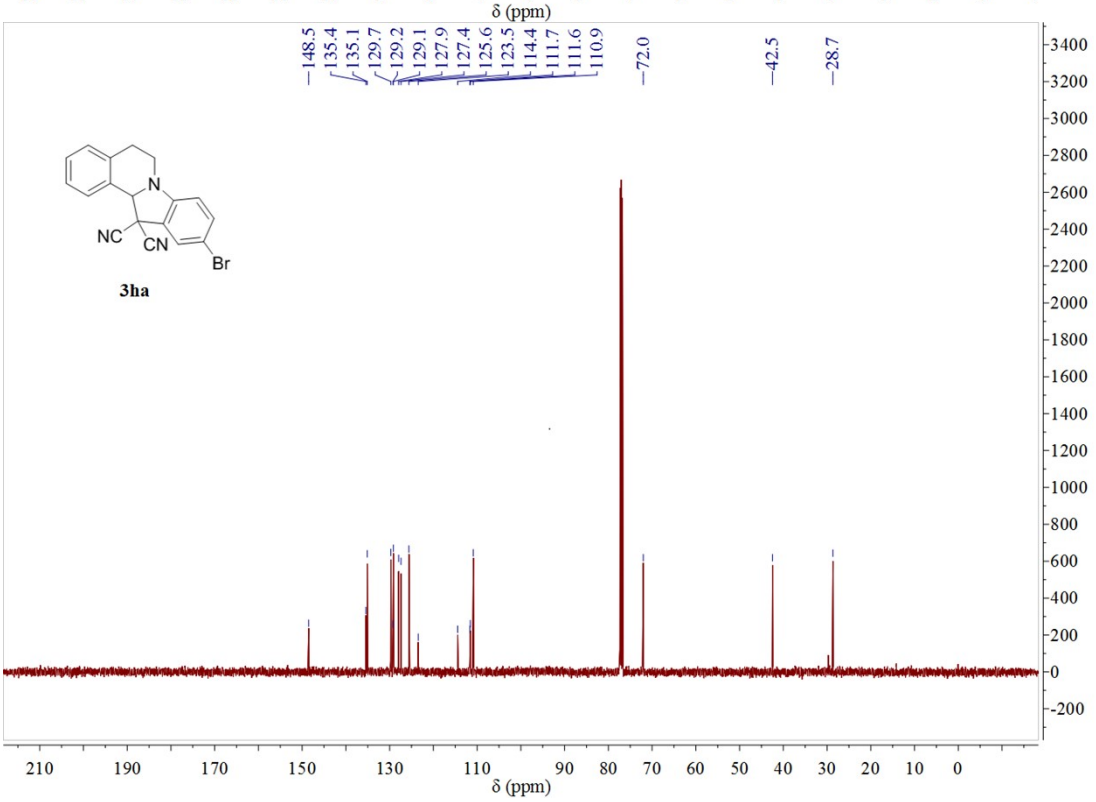
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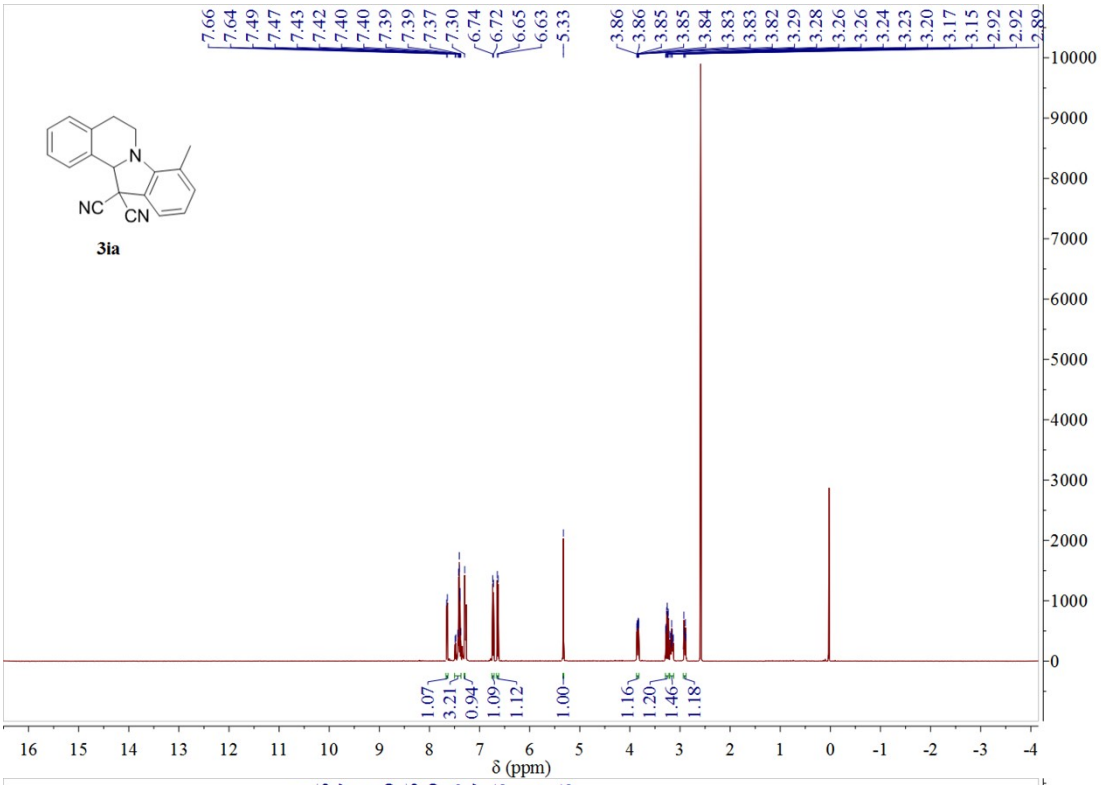
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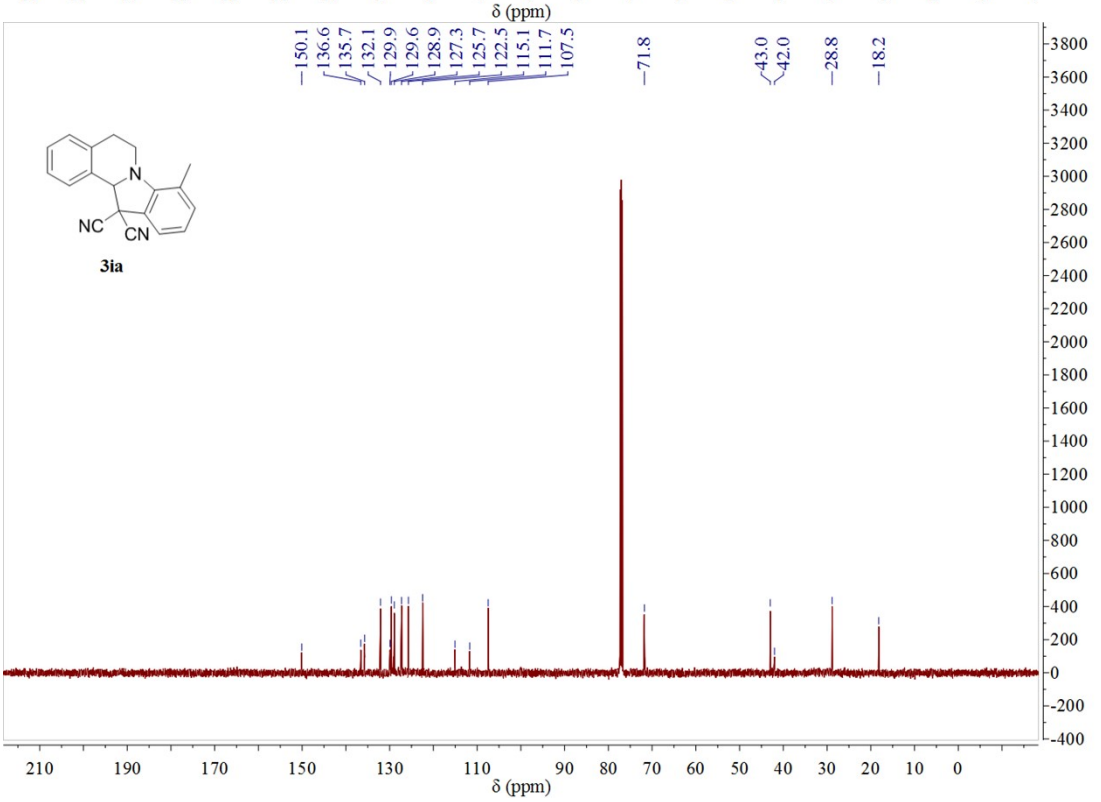
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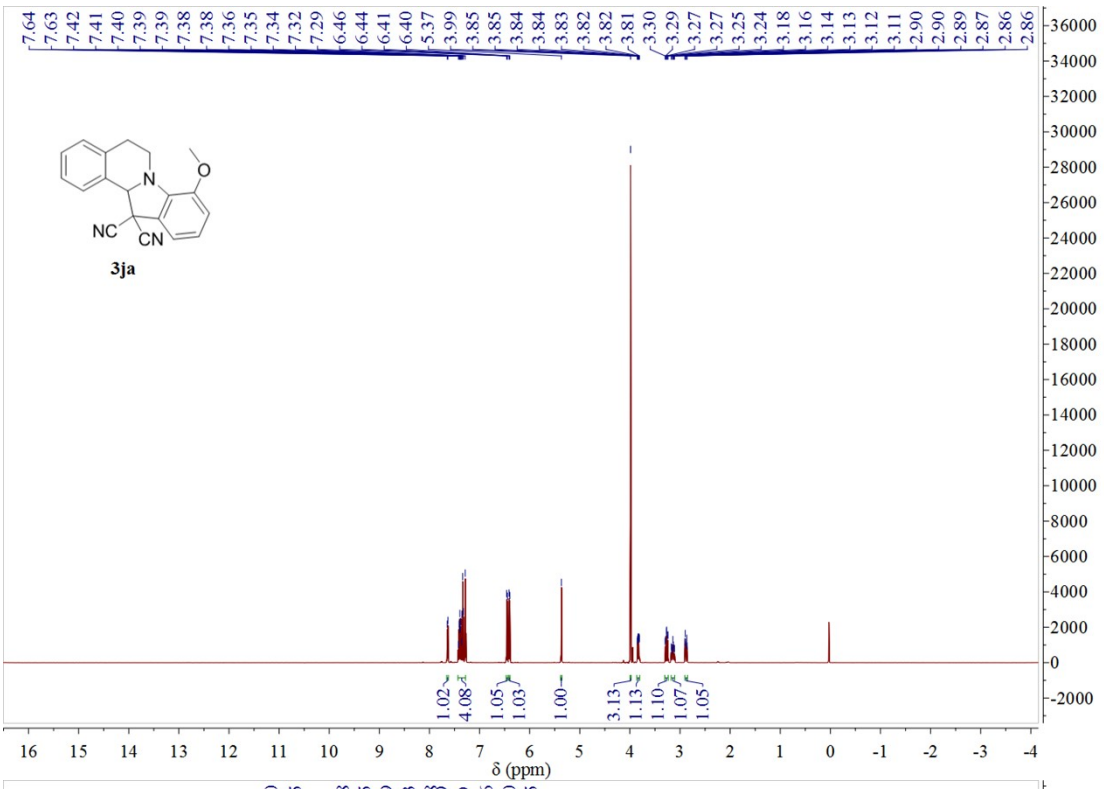
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O
NC
CN
3ja
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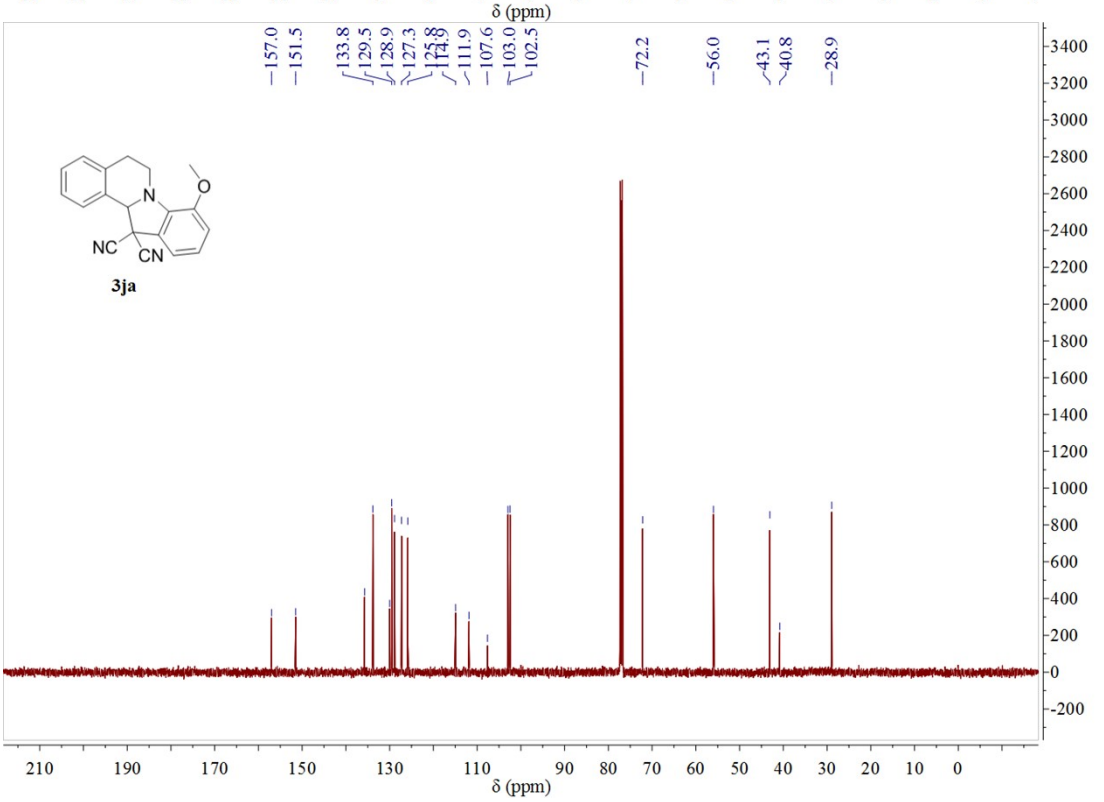
δ (ppm)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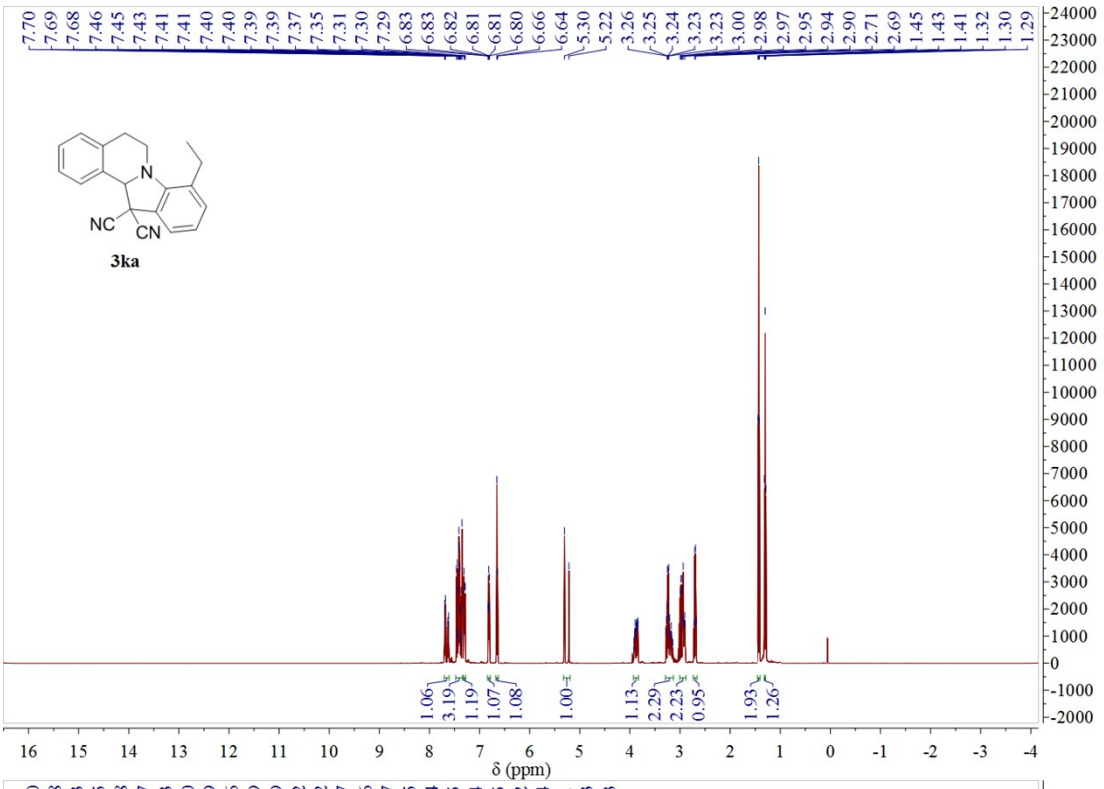
O
NC
CN
3ja
δ (ppm)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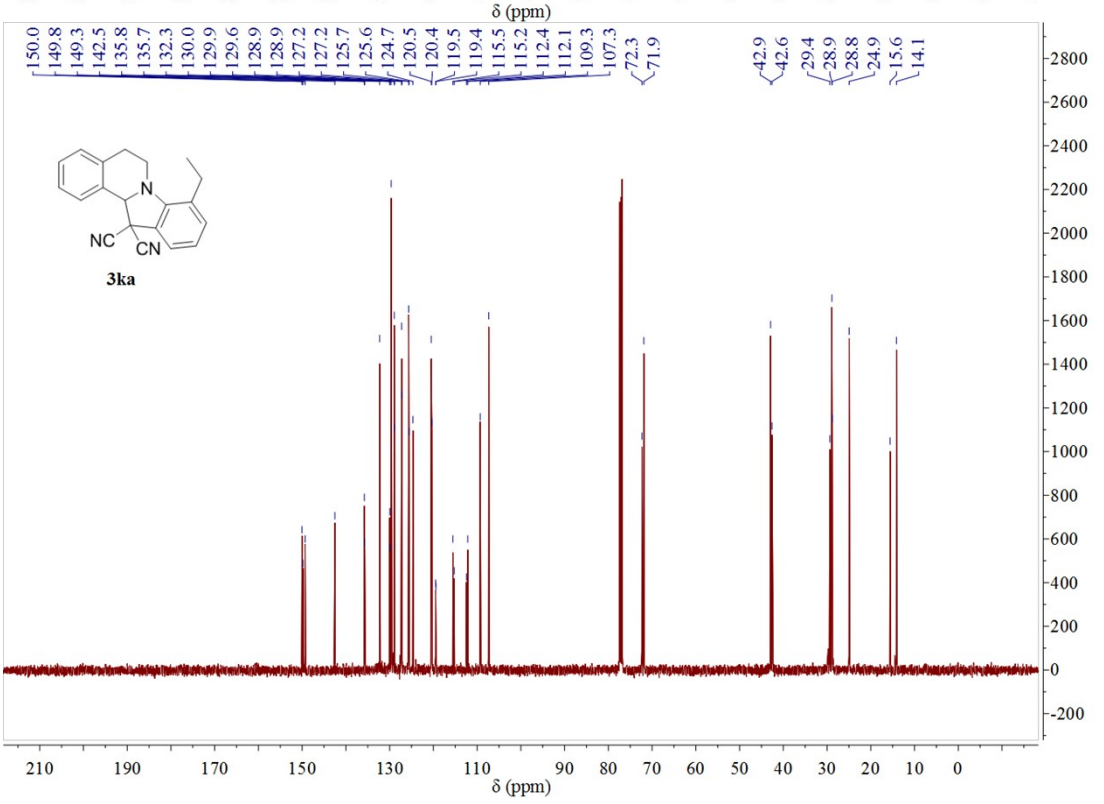
1.06 3.19 1.19 1.07 1.08 1.00 1.13 2.29 2.23 0.95 1.93 1.26
δ (ppm)
NC CN
3ka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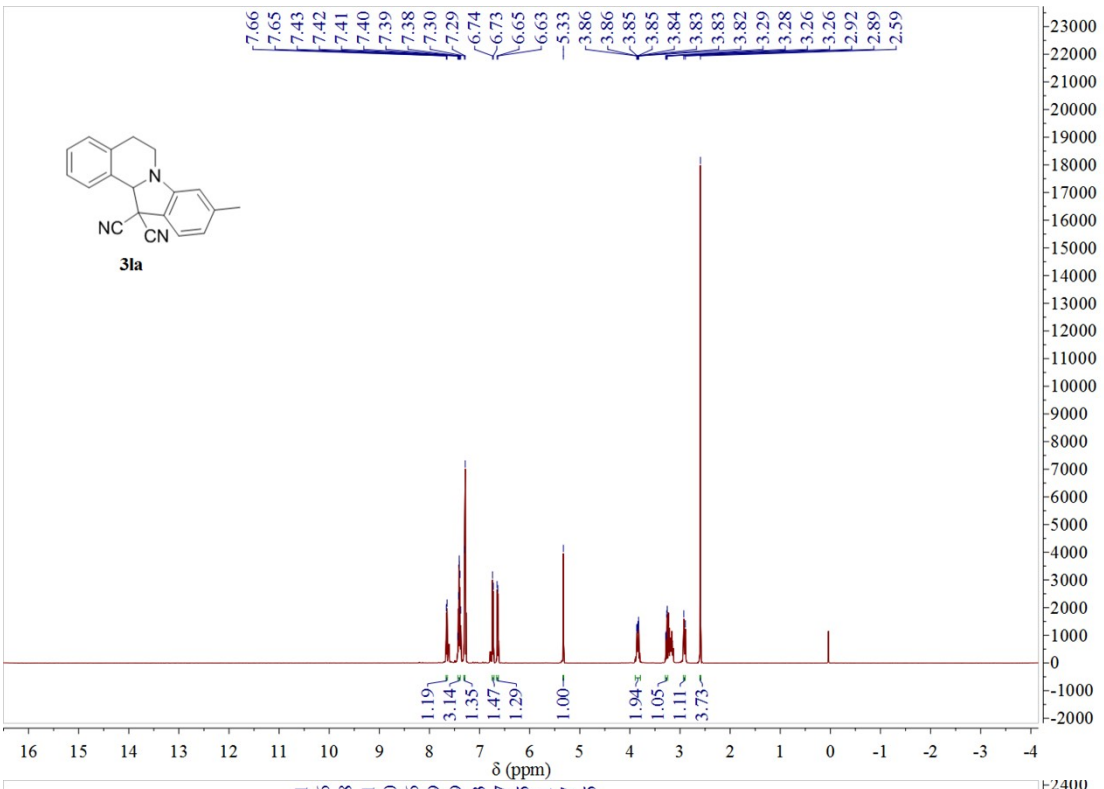
δ (ppm)
NC CN
3ka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7.65
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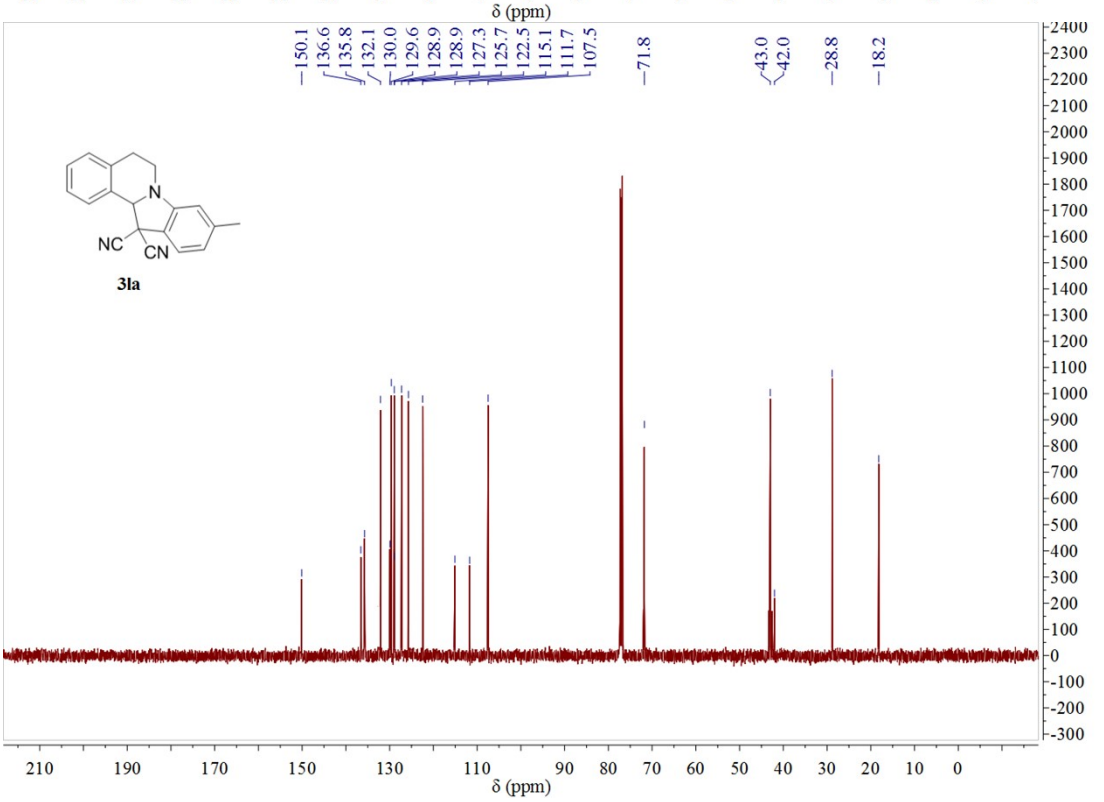
7.41
7.40
7.39
7.38
7.30
7.29
6.74
6.73
6.65
6.63
5.33
3.86
3.86
3.85
3.85
3.84
3.83
3.83
3.82
3.29
3.28
3.26
3.26
2.92
2.89
2.59
1.19
3.14
1.35
1.47
1.29
1.00
1.94
1.05
1.11
3.73
δ (ppm)
NC
CN
3la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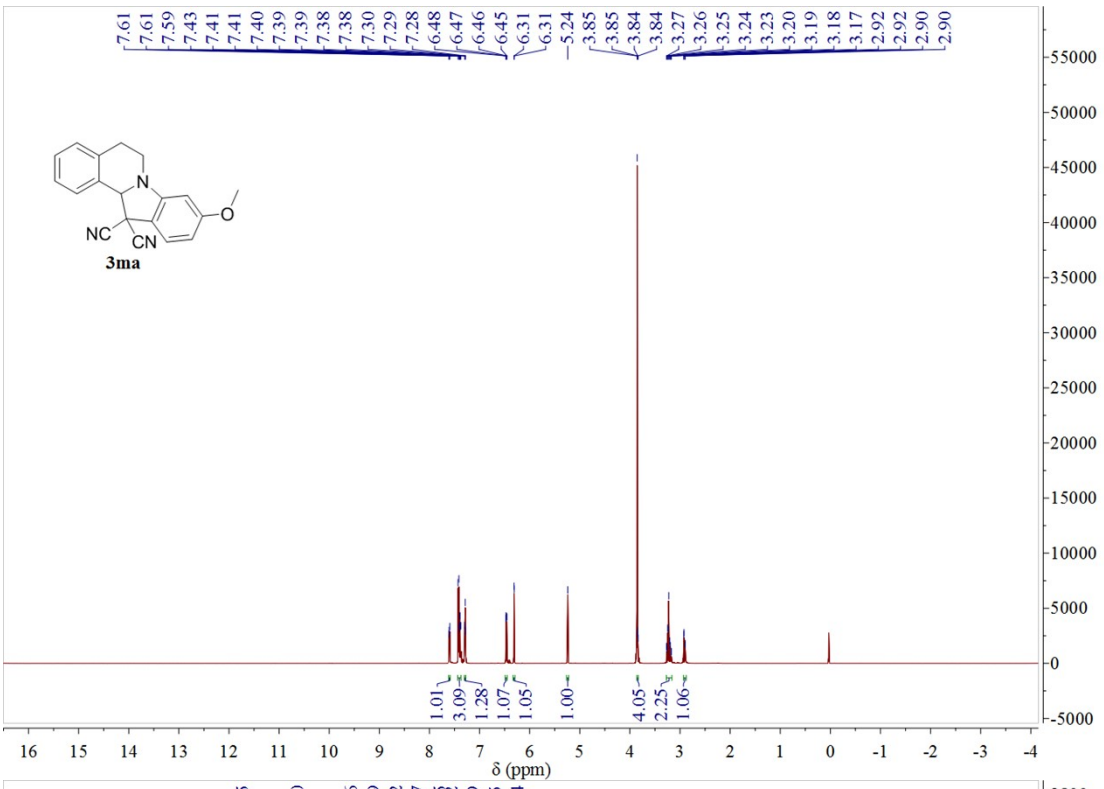
136.6
135.8
132.1
130.0
129.6
128.9
128.9
127.3
125.7
122.5
115.1
111.7
107.5
71.8
43.0
42.0
28.8
18.2
δ (ppm)
NC
CN
3la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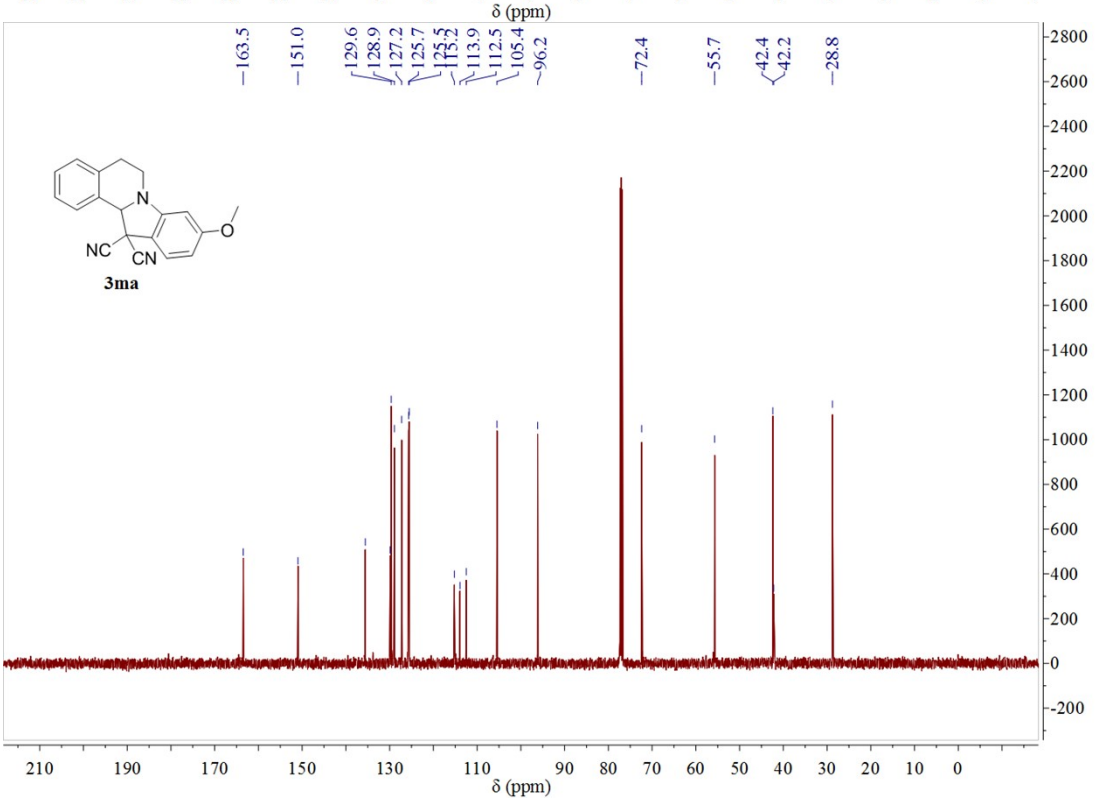
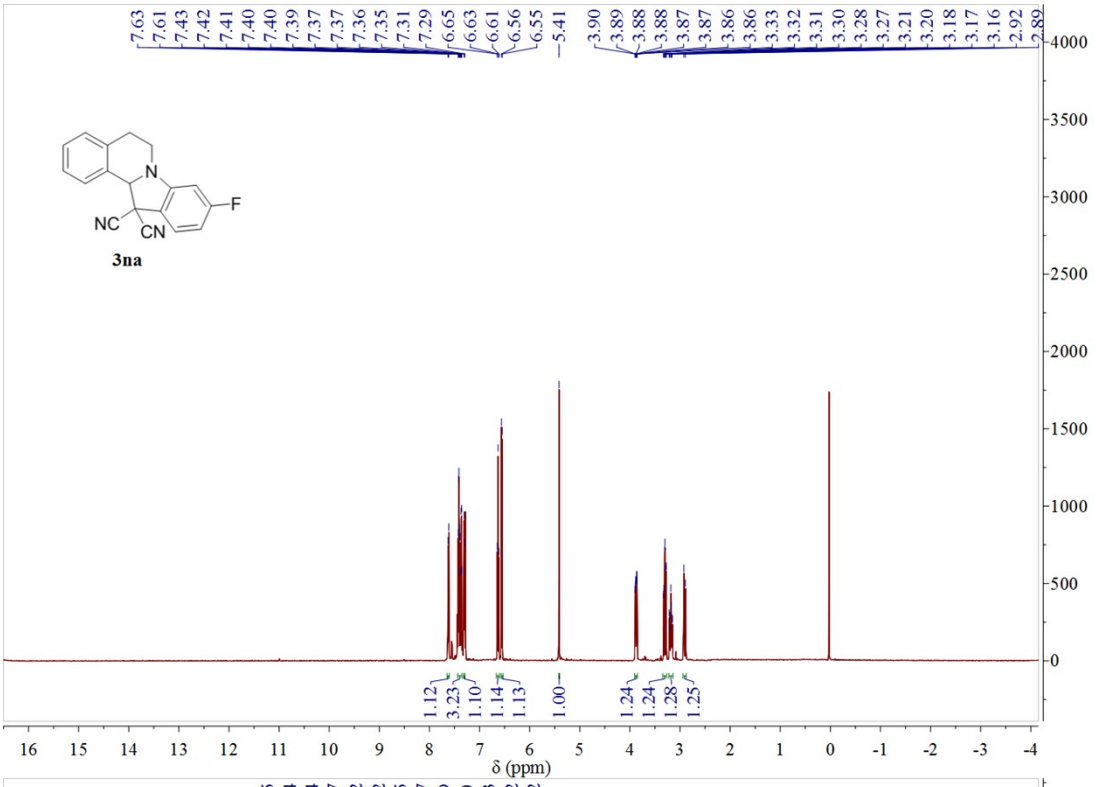
7.59
7.43
7.41
7.41
7.40
7.39
7.39
7.38
7.38
7.30
7.29
7.28
6.48
6.47
6.46
6.45
6.31
6.31
5.24
3.85
3.85
3.84
3.84
3.27
3.26
3.25
3.24
3.23
3.20
3.19
3.18
3.17
2.92
2.92
2.90
2.90
2.90
N
O
NC
CN
3ma
1.01
3.09
1.28
1.07
1.05
1.00
4.05
2.25
1.06
δ (ppm)


163.5
151.0
129.6
128.9
127.2
125.7
113.9
112.5
105.4
96.2
72.4
55.7
42.4
42.2
28.8
N
O
NC
CN
3ma
δ (ppm)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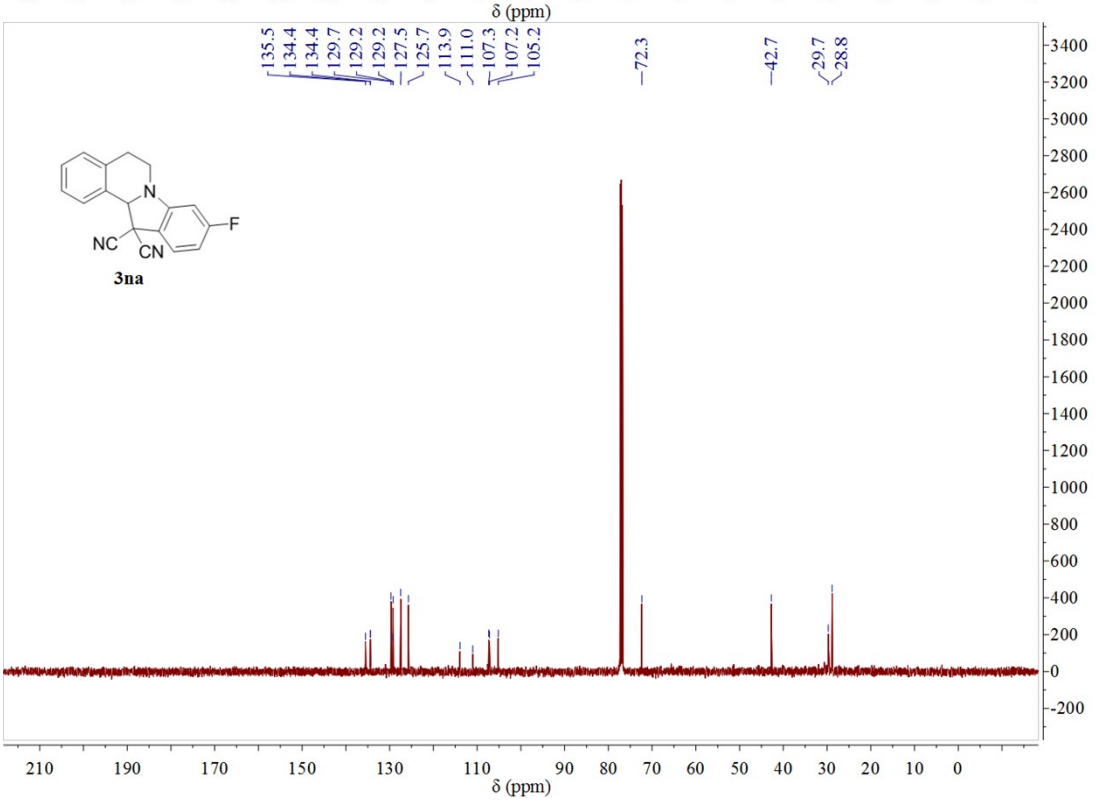
7.61
7.43
7.42
7.41
7.40
7.40
7.39
7.37
7.37
7.36
7.35
7.31
7.29
6.65
6.63
6.61
6.56
6.55
5.41
3.90
3.89
3.88
3.88
3.87
3.87
3.86
3.86
3.33
3.32
3.31
3.30
3.28
3.27
3.21
3.20
3.18
3.17
3.16
2.92
2.89
N
F
NC
CN
3na
1.12
3.23
1.10
1.14
1.13
1.00
1.24
1.24
1.28
1.25
δ (ppm)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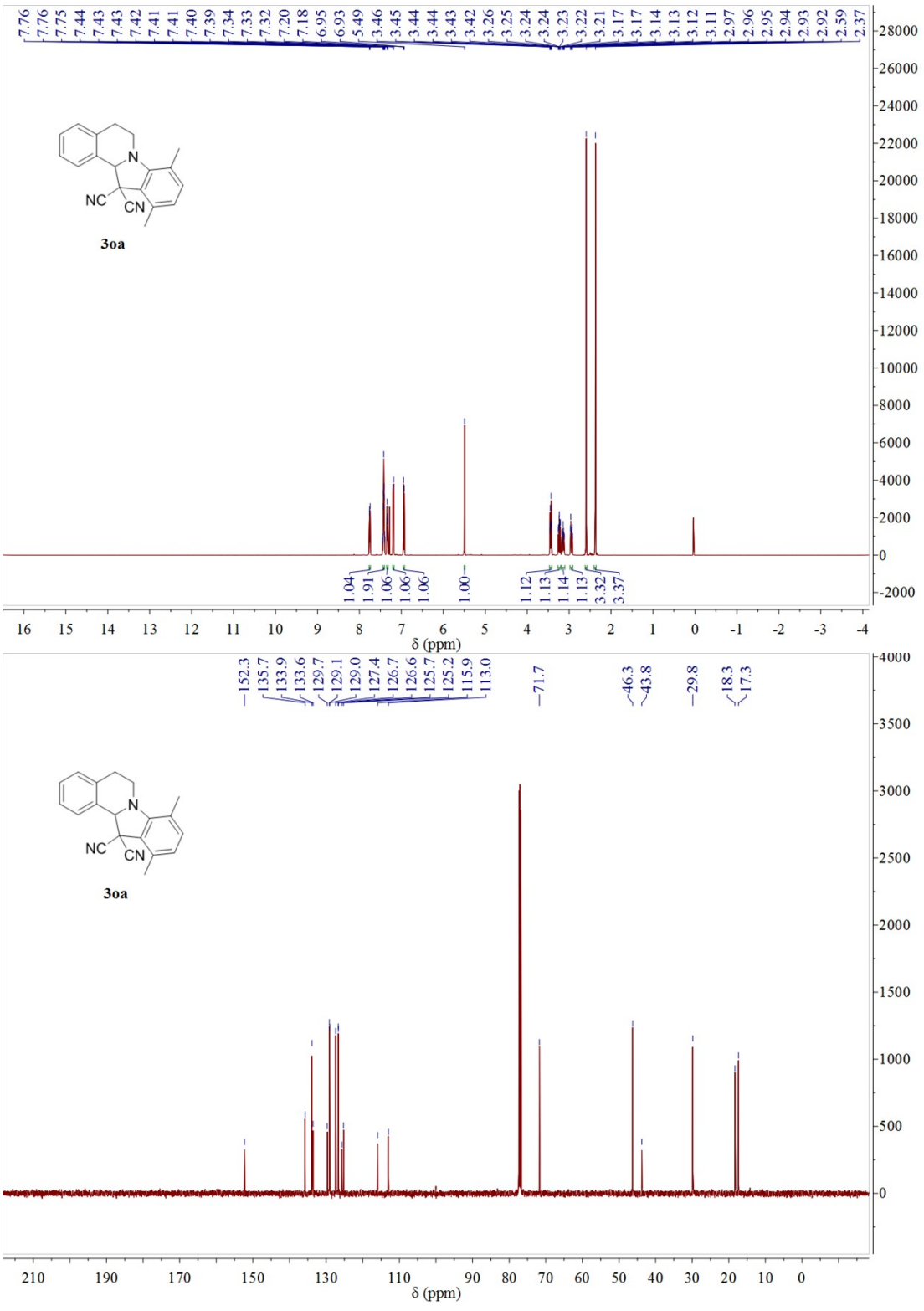
134.4
134.4
129.7
129.2
129.2
127.5
125.7
113.9
111.0
107.3
107.2
105.2
72.3
42.7
29.7
28.8
N
F
NC
CN
3na
δ (ppm)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7.75
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7.43
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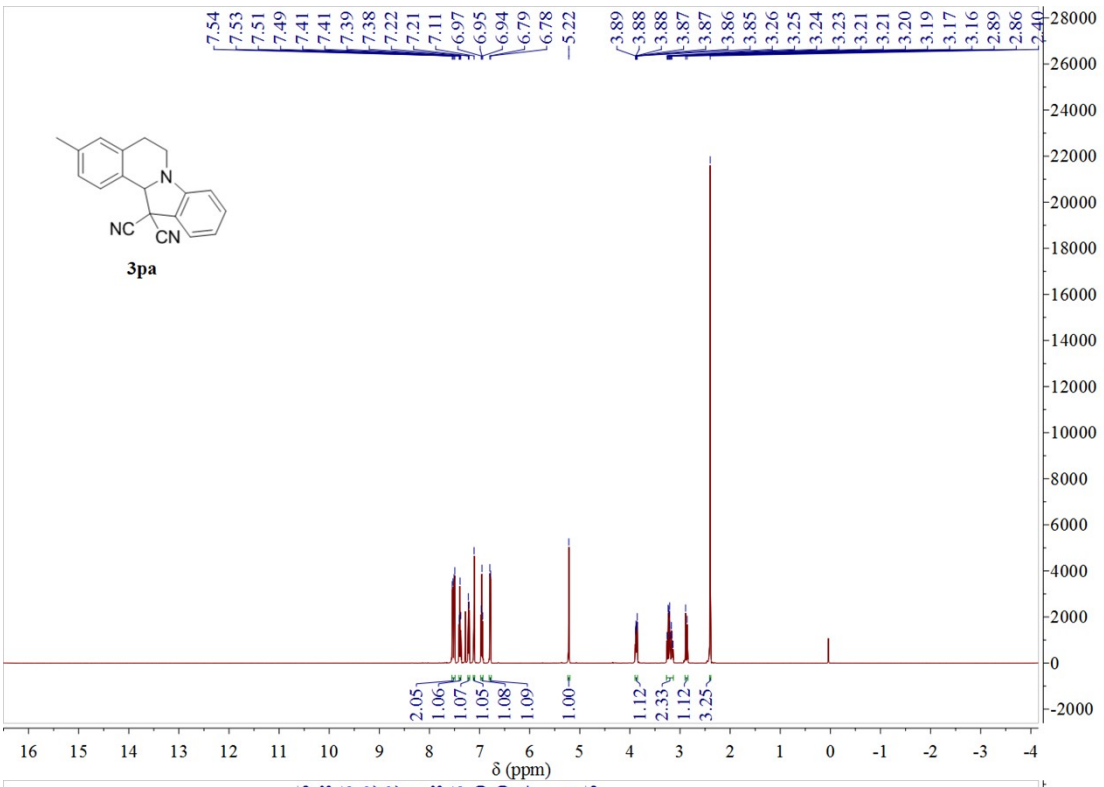
7.41
7.41
7.40
7.39
7.34
7.33
7.32
7.20
7.18
6.95
6.93
5.49
3.46
3.45
3.44
3.44
3.43
3.42
3.26
3.25
3.24
3.24
3.23
3.22
3.21
3.17
3.17
3.14
3.13
3.12
3.11
2.97
2.96
2.95
2.94
2.93
2.92
2.59
2.37
N
NC
CN
3oa
1.04
1.91
1.06
1.06
1.06
1.00
1.12
1.13
1.14
1.13
3.32
3.37
δ (ppm)
152.3
135.7
133.9
133.6
129.7
129.1
129.0
127.4
126.7
126.6
125.7
125.2
115.9
113.0
71.7
46.3
43.8
29.8
18.3
17.3
N
NC
CN
3oa
δ (ppm)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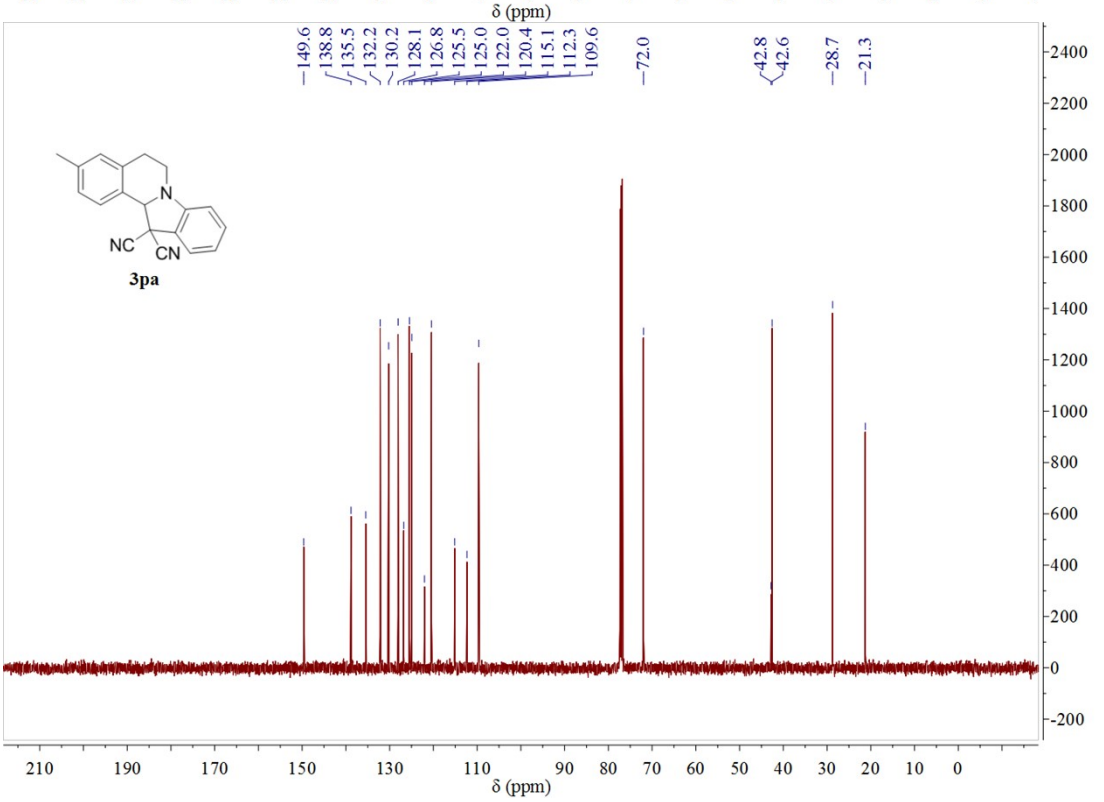
7.41
7.39
7.38
7.22
7.21
7.11
6.97
6.95
6.94
6.79
6.78
5.22
3.89
3.88
3.88
3.87
3.87
3.86
3.85
3.26
3.25
3.24
3.23
3.21
3.21
3.20
3.19
3.17
3.16
2.89
2.86
2.40
N
NC
CN
3pa
2.05
1.06
1.07
1.05
1.08
1.09
1.00
1.12
2.33
1.12
3.25
δ (ppm)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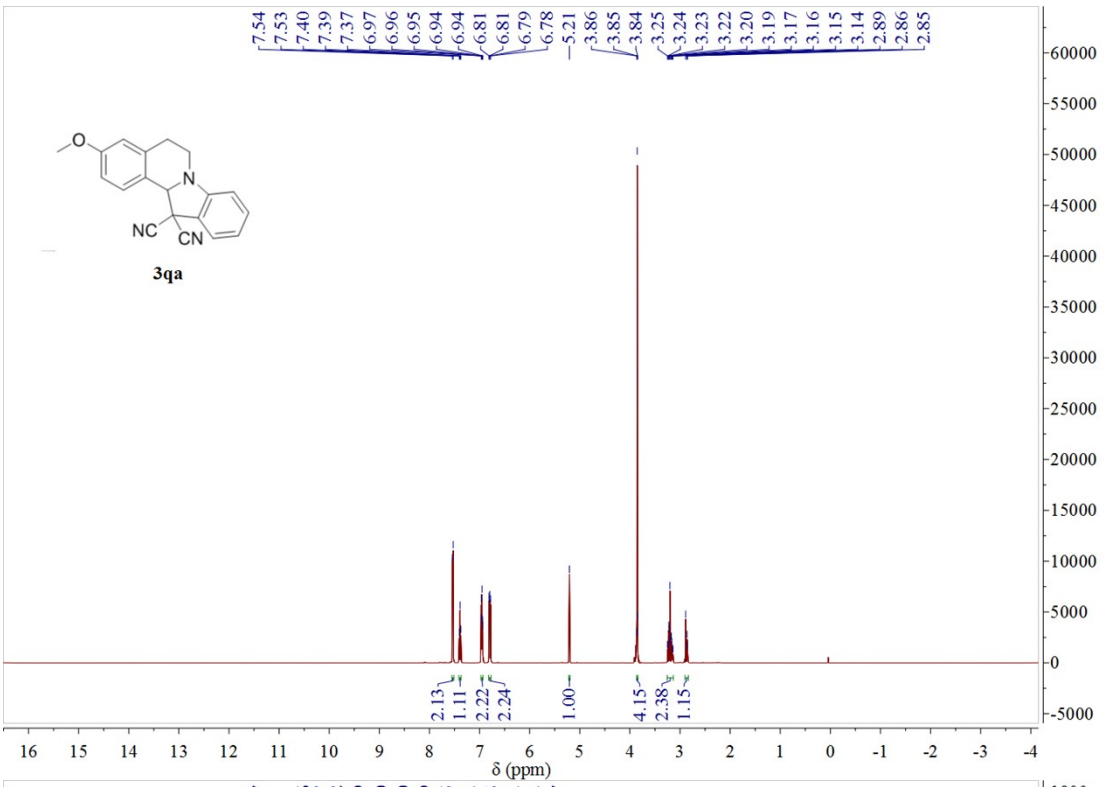
135.5
132.2
130.2
128.1
126.8
125.5
125.0
122.0
120.4
115.1
112.3
109.6
72.0
42.8
42.6
28.7
21.3
N
NC
CN
3pa
δ (ppm)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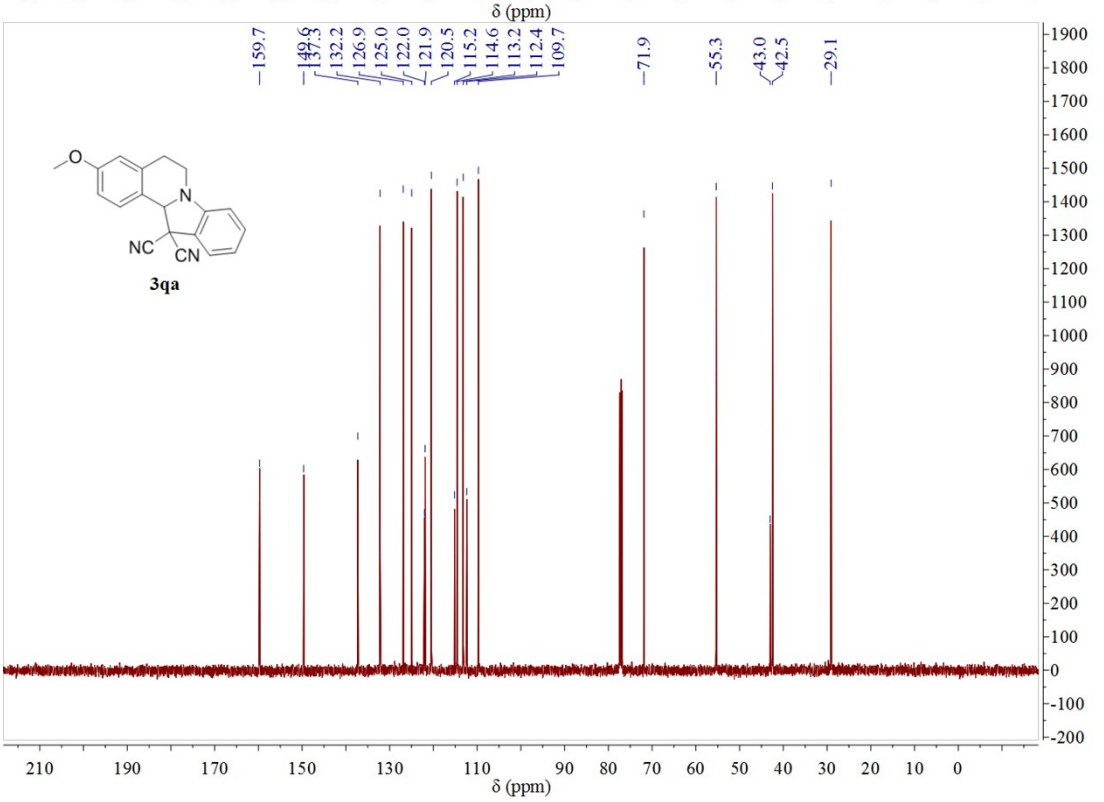
7.40
7.39
7.37
6.97
6.96
6.95
6.94
6.94
6.81
6.81
6.79
6.78
5.21
3.86
3.85
3.84
3.25
3.24
3.23
3.22
3.20
3.19
3.17
3.16
3.15
3.14
2.89
2.86
2.85
O
N
NC
CN
3qa
2.13
1.11
2.22
2.24
1.00
4.15
2.38
1.15
δ (ppm)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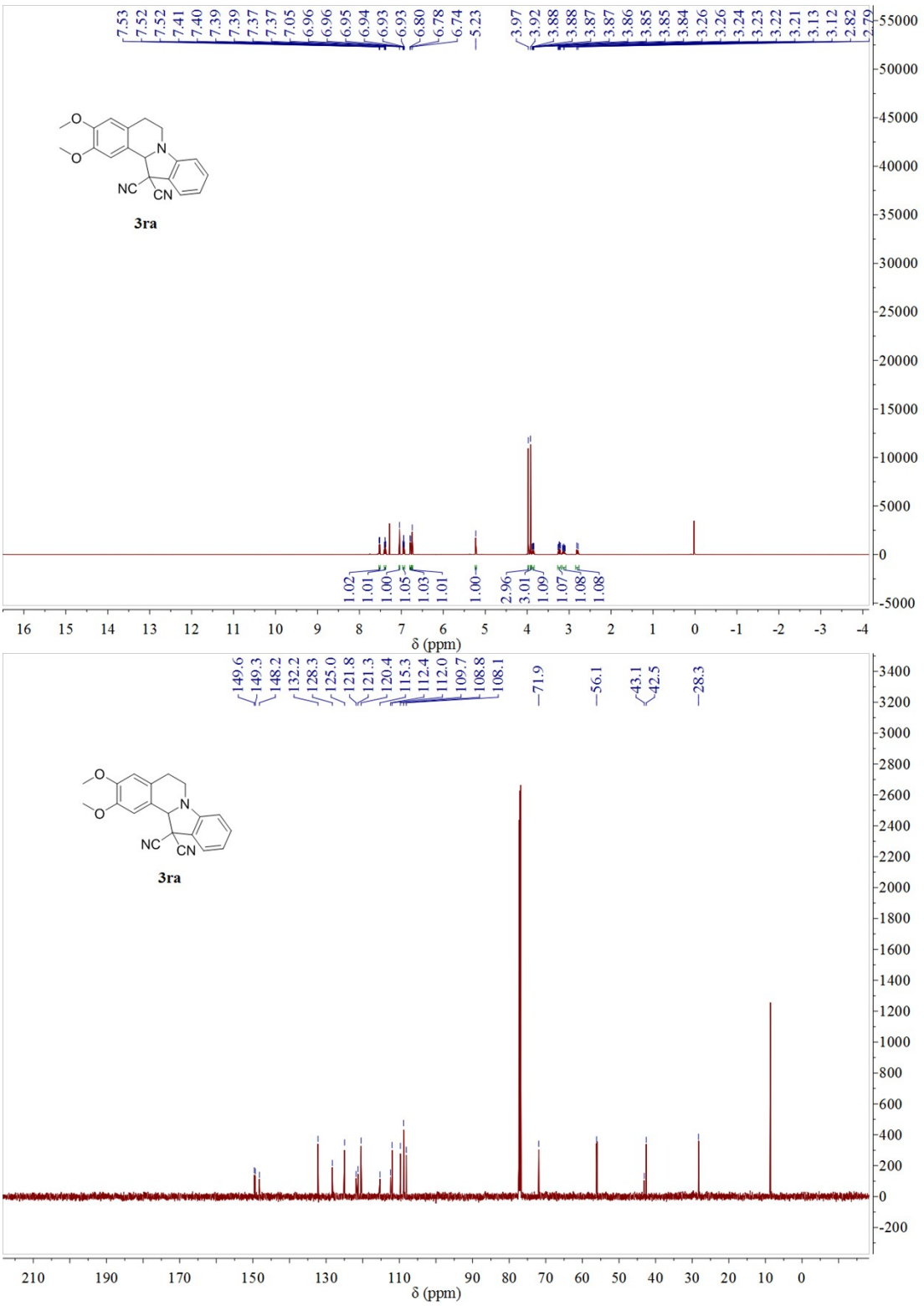
149.6
137.3
132.2
126.9
125.0
122.0
121.9
120.5
115.2
114.6
113.2
112.4
109.7
71.9
55.3
43.0
42.5
29.1
O
N
NC
CN
3qa
δ (ppm)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7.37
7.37
7.05
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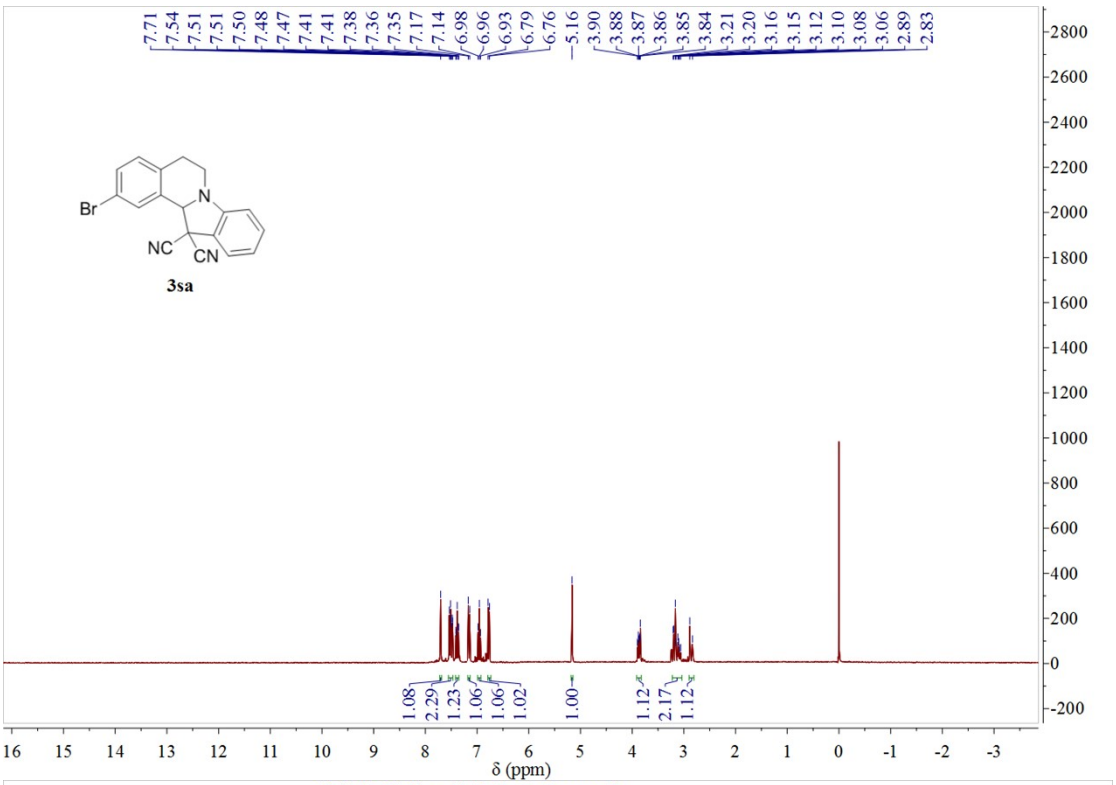
6.96
6.95
6.94
6.93
6.93
6.80
6.78
6.74
5.23
3.97
3.92
3.88
3.88
3.87
3.87
3.86
3.85
3.85
3.84
3.26
3.24
3.23
3.22
3.21
3.13
3.12
2.82
2.79
O
O
N
NC
CN
3ra
1.02
1.01
1.00
1.05
1.03
1.01
1.00
2.96
3.01
1.09
1.07
1.08
1.08
δ (ppm)
149.6
149.3
148.2
132.2
128.3
125.0
121.8
121.3
120.4
115.3
112.4
112.0
109.7
108.8
108.1
71.9
56.1
43.1
42.5
28.3
δ (ppm)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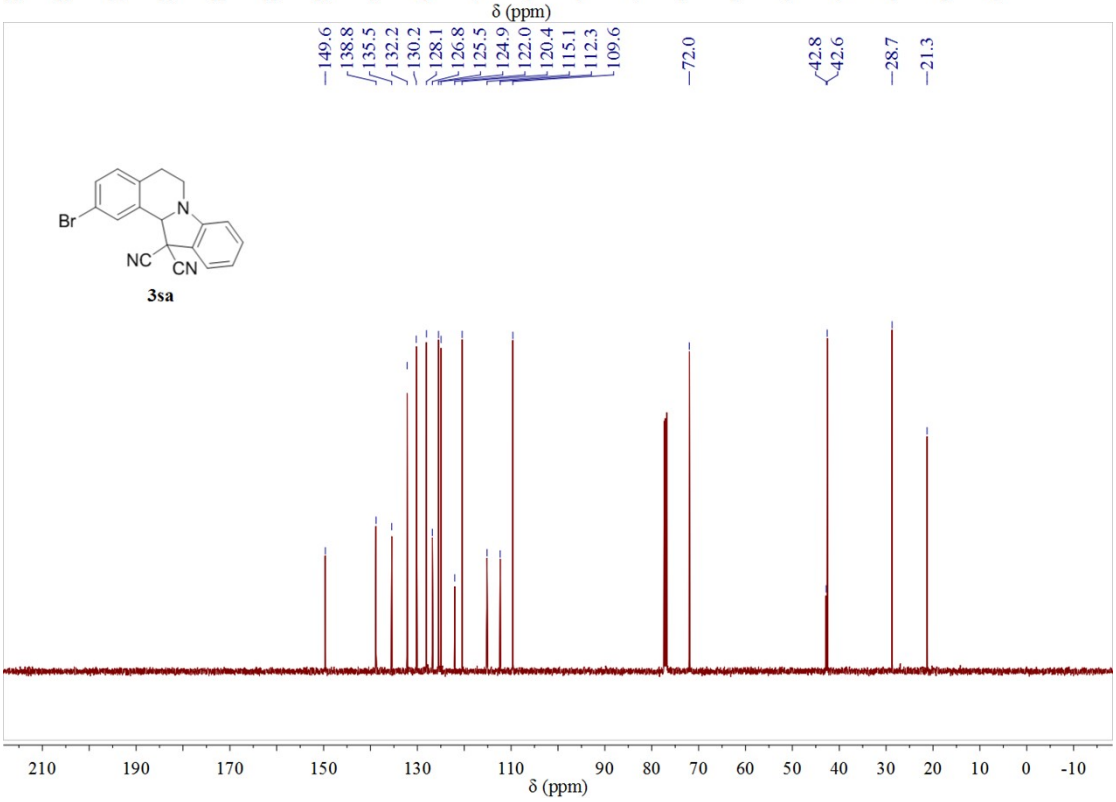
7.35
7.17
7.14
6.98
6.96
6.93
6.79
6.76
5.16
3.90
3.88
3.87
3.86
3.85
3.84
3.21
3.20
3.16
3.15
3.12
3.10
3.08
3.06
2.89
2.83
Br
N
NC
CN
3sa
1.08
2.29
1.23
1.06
1.06
1.02
1.00
1.12
2.17
1.12
δ (ppm)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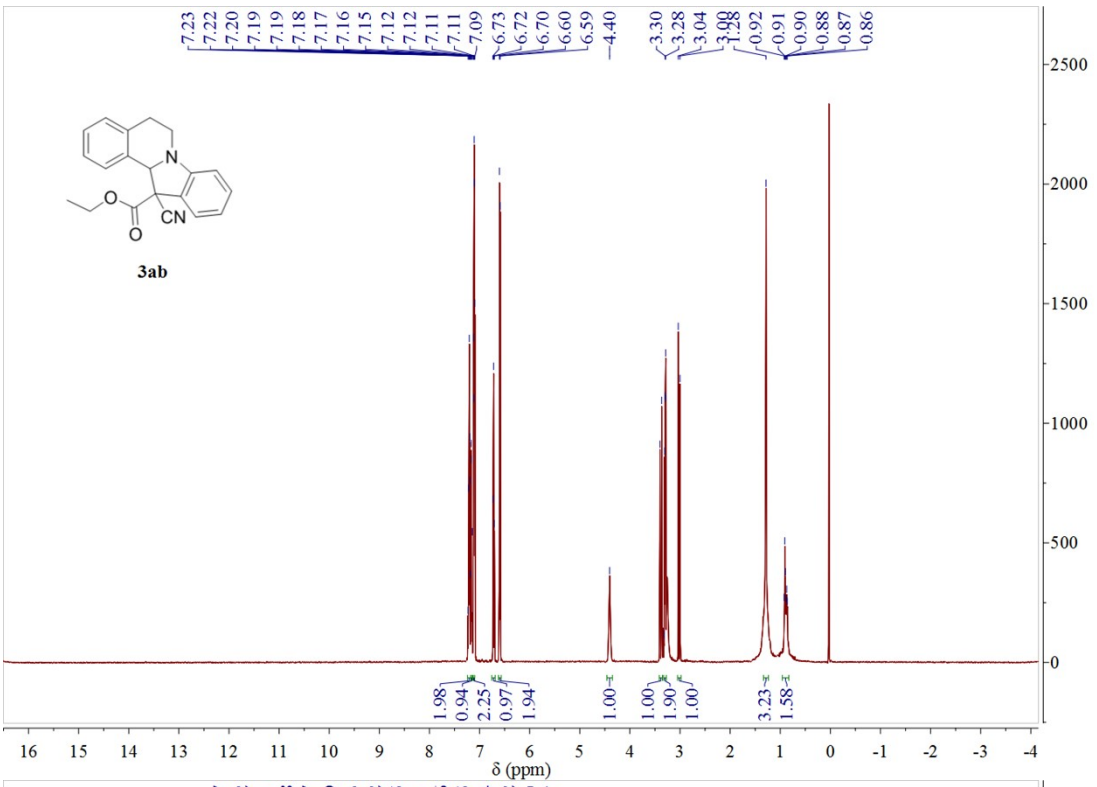
135.5
132.2
130.2
128.1
126.8
125.5
124.9
122.0
120.4
115.1
112.3
109.6
72.0
42.8
42.6
28.7
21.3
Br
N
NC
CN
3sa
δ (ppm)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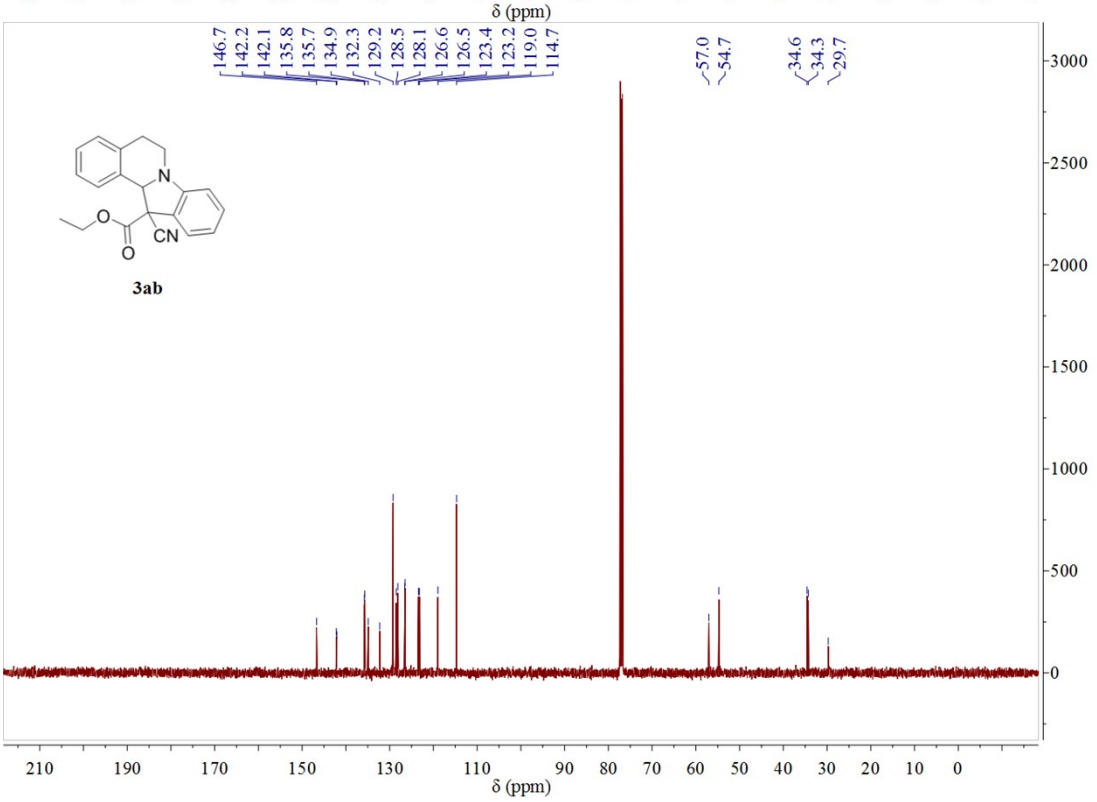
7.19
7.18
7.17
7.16
7.15
7.12
7.12
7.11
7.11
7.09
6.73
6.72
6.70
6.60
6.59
4.40
3.30
3.28
3.04
3.00
1.28
0.92
0.91
0.90
0.88
0.87
0.86
N
O
O
CN
3ab
1.98
0.94
2.25
0.97
1.94
1.00
1.00
1.90
1.00
3.23
1.58
δ (ppm)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142.2
142.1
135.8
135.7
134.9
132.3
129.2
128.5
128.1
126.6
126.5
123.4
123.2
119.0
114.7
57.0
54.7
34.6
34.3
29.7
N
O
O
CN
3ab
δ (ppm)