

Supporting Information

A Radical-Promoted Site-Specific Cross Dehydrogenative Coupling of Heterocycles with Nitriles

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General Information

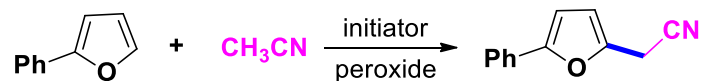
¹H and ¹³C NMR spectra were recorded on a Bruker advance III 400 spectrometer in CDCl₃ with TMS as internal standard. Mass spectra were determined on a Hewlett Packard 5988A spectrometer by direct inlet at 70 eV. High-resolution mass spectral analysis (HRMS) data were measured on a Bruker Apex II. Element analysis (EA) data were measured on a Vario EL. All products were identified by ¹H and ¹³C NMR, ¹⁹F NMR, ¹³⁵DEPT NMR, MS, HRMS. The starting materials were purchased from Energy Chemicals, Alfa Aesar, Acros Organics, J&K Chemicals, Adamas, or Aldrich and used without further purification.

Typical procedure

Reaction of Acetonitriles with heterocycles: A mixture of heterocycles (1 equiv, 0.20 mmol), acetonitriles (7 mL), CuCl (10 mol%, 0.02 mmol), and DCP (3 equiv, 0.60 mmol) was heated at 110 °C, 115 °C or 130 °C (the measured temperature of the oil bath) under nitrogen condition

for 12 h in a sealed tube (15 mL). After the reaction finished, the mixture was evaporated under vacuum and purified by column chromatography to afford the desired product.

Modification of the typical reaction conditions

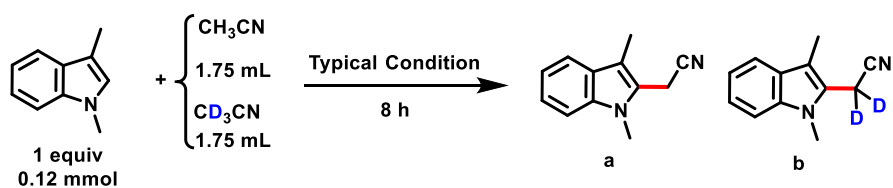


Entry	CH_3CN (mL)	Initiator (mol%)	Peroxide (equiv)	T (°C)	t (h)	Yield (%)
1	5	CuI(10)	DCP(3)	110	12	40
2	5	CuI (10)	DTBP(3)	110	12	Trace
3	5	CuI (10)	BPO(3)	110	12	Trace
4	5	CuI (10)	TBHP(3)	110	12	Trace
5	5	CuI(10)	TBPB(3)	110	12	39
6	5	CuI(10)	TBCP(3)	110	12	29
7	5	CuI(10)	DCP(1)	110	12	6
8	5	CuI(10)	DCP(2)	110	12	25
9	5	CuI(10)	DCP(4)	110	12	29
10	5	CuI(10)	DCP(5)	110	12	18
11	5	CuI(10)	DCP(3)	50	12	Trace
12	5	CuI(10)	DCP(3)	80	12	Trace
13	5	CuI(10)	DCP(3)	120	12	38
14	5	CuI(10)	DCP(3)	130	12	35
15	5	CuI(10)	DCP(3)	110	3	22
16	5	CuI(10)	DCP(3)	110	6	23
17	5	CuI(10)	DCP(3)	110	18	41
18	5	CuI(10)	DCP(3)	110	24	27
19	1	CuI(10)	DCP(3)	110	12	Trace
20	2	CuI(10)	DCP(3)	110	12	6
21	3	CuI(10)	DCP(3)	110	12	26
22	6	CuI(10)	DCP(3)	110	12	42
23	7	CuI(10)	DCP(3)	110	12	52
24	8	CuI(10)	DCP(3)	110	12	44
25	10	CuI(10)	DCP(3)	110	12	Trace
26	$\text{CH}_3\text{CN}(5)$ + <i>t</i> -Butanol(2)	CuI(10)	DCP(3)	110	12	30
27	7	$\text{CuF}_2(10)$	DCP(3)	110	12	46
28	7	$\text{Cu}(\text{OAc})_2(10)$	DCP(3)	110	12	27
29	7	CuBr(10)	DCP(3)	110	12	42
30	7	CuCl(10)	DCP(3)	110	12	53
31	7	CuCl(5)	DCP(3)	110	12	33
32	7	CuCl(20)	DCP(3)	110	12	18
33	7	CuCl(50)	DCP(3)	110	12	10

34	7	TBAI(10)	DCP(3)	110	12	5
35	7	Cu ₂ O(10)	DCP(3)	110	12	30
36	7	Cu(acac) ₂ (10)	DCP(3)	110	12	44
37	7	Cu(10)	DCP(3)	110	12	6
38	7	-	DCP(3)	110	12	Trace
39	7	CuSO ₄ ·5H ₂ O(10)	DCP(3)	110	12	42
40	7	CuO(10)	DCP(3)	110	12	Trace
41	7	CuCl ₂ ·2H ₂ O(10)	DCP(3)	110	12	43
42	7	NiCl ₂ ·2H ₂ O(10)	DCP(3)	110	12	40
43	7	FeCl ₂ (10)	DCP(3)	110	12	35
44	7	Co(acac) ₂ (10)	DCP(3)	110	12	5
45	7	Mn(OAc) ₂ (10)	DCP(3)	110	12	Trace
46	7	Cu(OTf) ₂ (10)	DCP(3)	110	12	8
47	7	TTF-OMe(10)	-	110	12	Trace
48	7	CuCl(10)	H ₂ O ₂ (3)	R.T.	12	Trace
49	7	FeCl ₂ (10)	H ₂ O ₂ (3)	R.T.	12	Trace
50	7	Ferrocene (10)	DCP(3)	110	12	26
51	7	CuNO ₃ (PPh ₃) ₂ (10)	DCP(3)	110	12	28
52	7	CuI(10)+TFA(20)	DCP(3)	110	12	22
53	7	CuI(10)+ 1,10-phen(20)	DCP(3)	110	12	Trace
54	7	CuI(10)+ TMEDA(20)	DCP(3)	110	12	Trace
55	7	AgNO ₃ (20)	K ₂ S ₂ O ₈ (3)	110	12	Trace
56	7	CuI(10)	DCP(3)	105	12	Trace
57	7	CuI(10)	DCP(3)	115	12	30
58	7	CuI(10)	DCP(3)	120	12	26
59	7	CuI(10)	DCP(3)	130	12	16
60	7	CuCl(10)	DCP(3)	105	12	Trace
61	7	CuCl(10)	DCP(3)	115	12	55
62	7	CuCl(10)	DCP(3)	120	12	28
63	7	KI(10)	DCP(3)	115	12	Trace
64	7	NaI(10)	DCP(3)	115	12	Trace

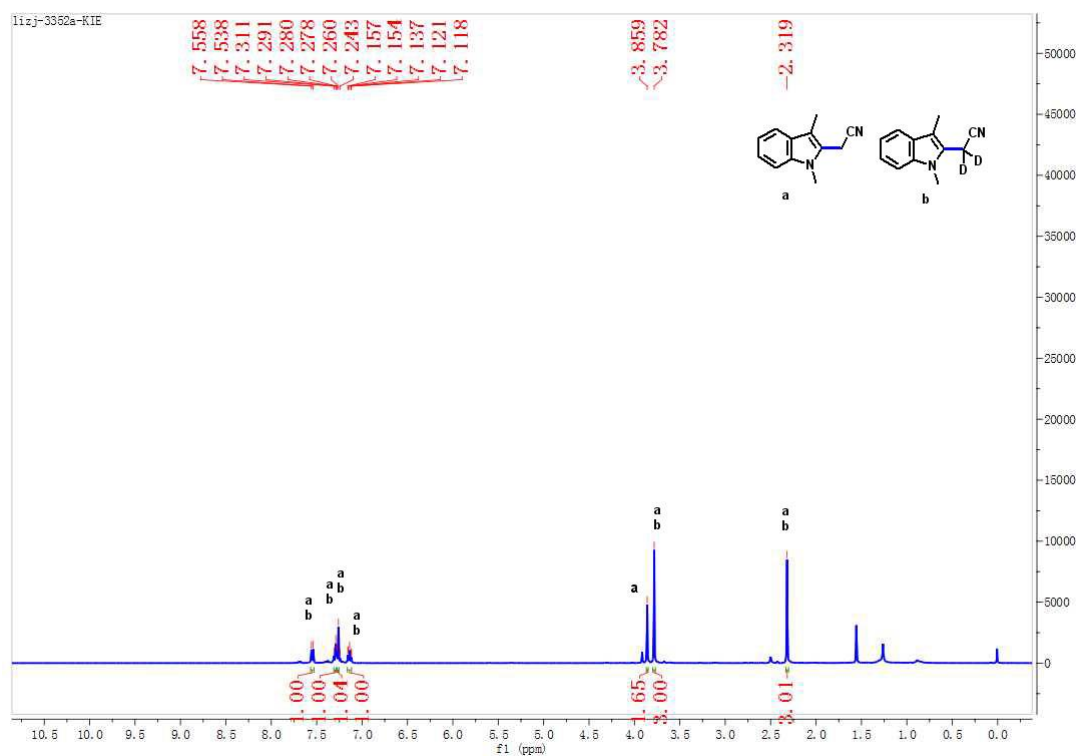
^a Reaction conditions: 2-phenylfuran (1 equiv, 0.20 mmol), acetonitrile as solvent, sealed tube, unless otherwise noted. ^b Isolated yields.

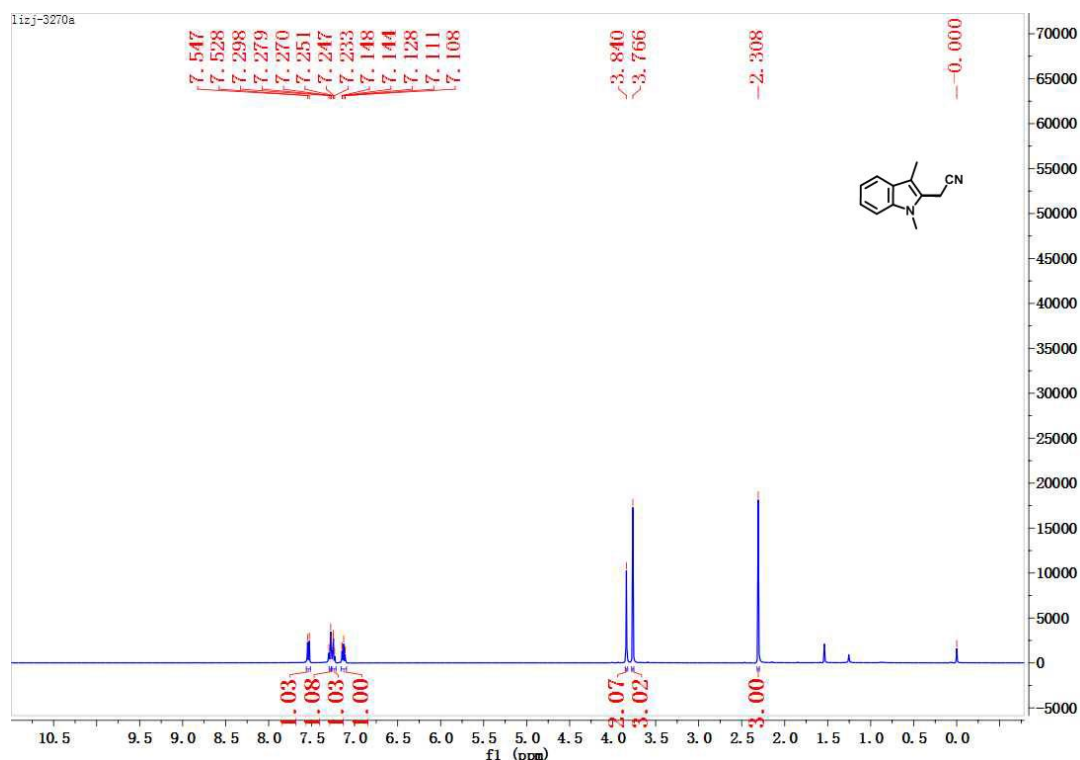
Competing Kinetic Isotope Effect (KIE) Experiment:



At low conversion (38%): $K_H/K_D = 4.7$.

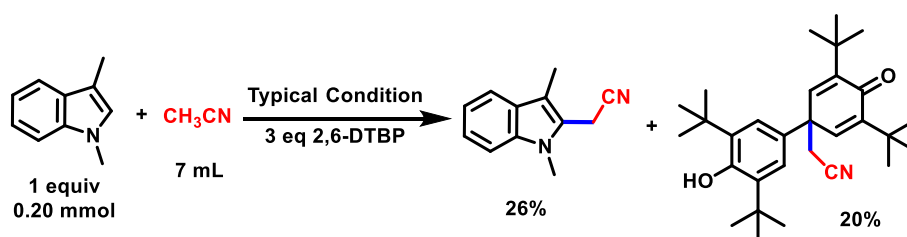
^1H NMR





Note: The value of k_H/k_D was calculated from the ^1H NMR spectra above which should be the mixture of compound **a** and **b** (the KIE scheme). The sum of the integral of **a** and **b** at chemical shift 3.78 was integrated as 3.00 (both **a** and **b** keep the same single bond hydrogen). Compound **a** has 2 hydrogen atoms at chemical shift 3.86, while **b** has no H atoms. The amount of **a** could be defined as 1.65, on the other hand, the sum of **a** and **b** is 2.00, so the amount of **b** is 0.35 ($2.00 - 1.65 = 0.35$). As a result, $k_H / k_D = 1.65 / 0.35 = 4.7$.

Radical trapping by addition of 2,6-DTBP:



Physical data and references for the following products:

All known compounds are determined by ^1H NMR, ^{13}C NMR and ^{19}F NMR, MS analysis and compared with which were cited in the following references, and the new compounds were further confirmed by HRMS and/or element analysis.

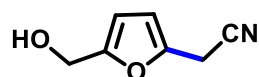
References:

1. M. E. Kurz, S. C. Lapin, K. Mariam, T. J. Hagen, X. Q. Qian, *J. Org. Chem.*, **1984**, 49, 2728.
2. J. Y. Merour, A. Buzas, *Synthetic Communications*, **1988**, 18, 2331.
3. M. Soledade, C. Pedras, D. P. O. Okinyo, *J Label Compd Radiopharm*, **2006**, 49, 33.
4. L. T. Pierce, M. M. Cahill, F. O. McCarthy, *Tetrahedron*, **2011**, 67, 4601.

Physical data for the following products:

1a. 2-(5-(hydroxymethyl)furan-2-yl)acetonitrile

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 2/1).



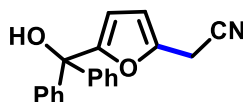
¹H NMR (400 MHz, CDCl₃): δ 6.29 (d, *J* = 3.2 Hz, 1H), 6.27 (d, *J* = 3.2 Hz, 1H), 4.59 (s, 2H), 3.76 (s, 2H), 1.79 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 154.7, 143.0, 115.3, 109.3, 109.0, 57.3, 17.6.

HRMS (ESI, *m/z*): Calculated for C₇H₁₁N₂O₂ (M+NH₄)⁺ 155.0815, found 155.0811.

1b. 2-(5-(hydroxydiphenylmethyl)furan-2-yl)acetonitrile

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1).



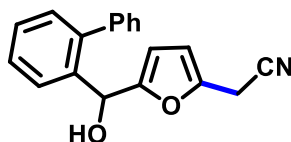
¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.29 (m, 10H), 6.29 (d, *J* = 2.8 Hz, 1H), 5.89 (d, *J* = 3.2 Hz, 1H), 3.75 (s, 2H), 3.04 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 158.6, 144.1, 143.3, 128.1, 127.8, 127.1, 115.3, 110.9, 109.0, 77.9, 17.7.

HRMS (ESI, *m/z*): Calculated for C₁₉H₁₅NO₂Na(M+Na)⁺ 312.0995, found 312.1001.

1c. 2-(5-([1,1'-biphenyl]-2-yl(hydroxy)methyl)furan-2-yl)acetonitrile

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1).



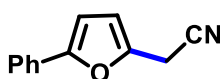
¹H NMR (400 MHz, CDCl₃): δ 7.70 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.41 – 7.36 (m, 4H), 7.29 – 7.24 (m, 3H), 6.25 (d, *J* = 3.2 Hz, 1H), 6.00 (d, *J* = 3.2 Hz, 1H), 5.82 (s, 1H), 3.72 (s, 2H), 2.27 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 156.9, 142.8, 141.1, 140.2, 137.7, 130.0, 129.2, 128.2, 128.1, 127.9, 127.4, 127.2, 115.4, 109.2, 109.1, 66.7, 17.6.

HRMS (ESI, *m/z*): Calculated for C₁₉H₁₉N₂O₂ (M+NH₄)⁺ 307.1441, found 307.1438.

1d. 2-(5-phenylfuran-2-yl)acetonitrile

A red solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1).



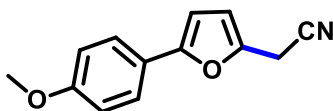
¹H NMR (400 MHz, CDCl₃): δ 7.65 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 6.61 (d, *J* = 3.2 Hz, 1H), 6.41 (d, *J* = 3.2 Hz, 1H), 3.84 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 154.6, 142.2, 130.1, 128.7, 127.8, 123.7, 115.4, 110.6, 105.9, 17.7.

HRMS (ESI, *m/z*): Calculated for C₁₂H₁₀NO (M+H)⁺ 184.0757, found 184.0760.

1e. 2-(5-(4-methoxyphenyl)furan-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1); m.p.: 93-95 °C.



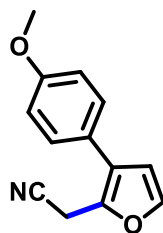
¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 3.2 Hz, 1H), 6.38 (d, *J* = 3.2 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 159.3, 154.7, 141.5, 125.2, 123.2, 114.2, 110.5, 104.3, 55.3, 17.7.

HRMS (ESI, *m/z*): Calculated for C₁₃H₁₂NO₂ (M+H)⁺ 214.0863, found 214.0861.

1f. 2-(4-(4-methoxyphenyl)furan-2-yl)acetonitrile

A colorless liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1).



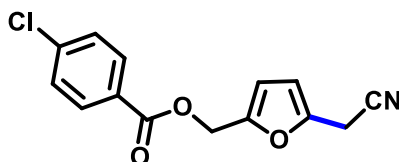
¹H NMR (400 MHz, CDCl₃): δ 7.43 (d, *J* = 1.6 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.51 (d, *J* = 2.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 159.1, 142.6, 137.5, 129.0, 124.4, 115.6, 114.4, 112.0, 55.3, 16.4.

HRMS (ESI, *m/z*): Calculated for C₁₃H₁₂NO₂ (M+H)⁺ 214.0863, found 214.0860.

1g. (5-(cyanomethyl)furan-2-yl)methyl 4-chlorobenzoate

A light yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1).



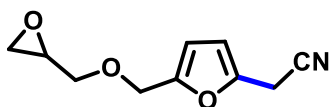
¹H NMR (400 MHz, CDCl₃): δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 3.2 Hz, 1H), 5.26 (s, 2H), 3.78 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 165.3, 150.1, 143.9, 139.7, 131.2, 128.8, 128.1, 112.2, 109.6, 58.4, 17.7.

HRMS (ESI, *m/z*): Calculated for C₁₄H₁₀ClNO₃Na(M+Na)⁺ 298.0241, found 298.0237.

1h. 2-(5-((oxiran-2-ylmethoxy)methyl)furan-2-yl)acetonitrile

A light yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 3/1).



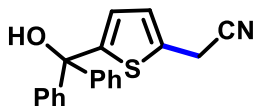
¹H NMR (400 MHz, CDCl₃): δ 6.30 (dd, *J* = 7.2, 3.2 Hz, 2H), 4.49 (q, *J* = 12.8 Hz, 2H), 3.78 (dd, *J* = 11.6, 2.8 Hz, 1H), 3.76 (s, 2H), 3.42 (dd, *J* = 11.6, 6.0 Hz, 1H), 3.16 (dq, *J* = 8.8, 2.8 Hz, 1H), 2.80 (t, *J* = 4.8 Hz, 1H), 2.61 (dd, *J* = 4.8, 2.8 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 152.1, 143.4, 115.3, 110.8, 109.2, 70.8, 64.9, 50.7, 44.2, 17.6.

HRMS (ESI, *m/z*): Calculated for C₁₀H₁₁NO₃Na(M+Na)⁺ 216.0631, found 216.0627.

1i. 2-(5-(hydroxydiphenylmethyl)thiophen-2-yl)acetonitrile

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1).



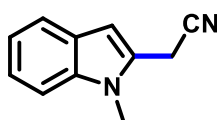
¹H NMR (400 MHz, CDCl₃): δ 7.36 – 7.31 (m, 10H), 6.91 (d, *J* = 3.6 Hz, 1H), 6.61 (d, *J* = 3.6 Hz, 1H), 3.85 (s, 2H), 2.95 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 153.0, 145.9, 131.0, 128.1, 127.8, 127.1, 126.8, 126.6, 116.7, 80.1, 18.8.

HRMS (ESI, *m/z*): Calculated for C₁₉H₁₅NOSNa(M+Na)⁺ 328.0767, found 328.0772.

2a. 2-(1-methyl-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 99-101 °C.



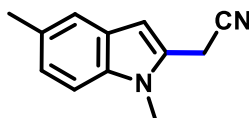
¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.16 – 7.12 (m, 1H), 6.54 (s, 1H), 3.89 (s, 2H), 3.76 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 137.9, 127.6, 127.1, 122.3, 120.7, 120.1, 116.0, 109.1, 102.3, 29.8, 16.7.

MS(EI): *m/z*(%): 170(100.0), 169(94.3), 144(39.0), 128(10.0), 115(13.6).

2b. 2-(1,5-dimethyl-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 110-112 °C.



¹H NMR (400 MHz, CDCl₃): δ 7.36 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.08 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.44 (s, 1H), 3.86 (s, 2H), 3.72 (s, 3H), 2.44 (s, 3H).

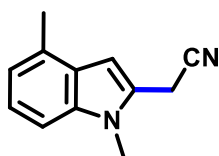
¹³C NMR (100 MHz, CDCl₃): δ 136.3, 129.4, 127.5, 127.3, 123.9, 120.3, 116.0, 108.8, 101.7, 29.8, 21.3, 16.7.

HRMS (ESI, *m/z*): Calculated for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1071.

2c. 2-(1,4-dimethyl-1H-indol-2-yl)acetonitrile

A light yellow solid after purification by flash column chromatography (petroleum ether/ethyl

acetate = 10/1); m.p.: 112-114 °C.



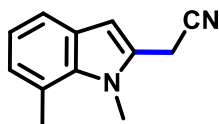
¹H NMR (400 MHz, CDCl₃): δ 7.19 – 7.14 (m, 2H), 6.94 (dd, *J* = 6.0, 1.2 Hz, 1H), 6.55 (s, 1H), 3.88 (s, 2H), 3.73 (s, 3H), 2.54 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 137.7, 130.2, 127.0, 122.4, 120.3, 116.0, 106.8, 100.8, 29.9, 18.6, 16.7.

HRMS (ESI, *m/z*): Calculated for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1070.

2d. 2-(1,7-dimethyl-1H-indol-2-yl)acetonitrile

A light yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 145-146 °C.



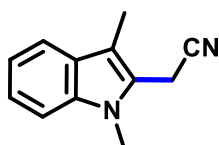
¹H NMR (400 MHz, CDCl₃): δ 7.41 (d, *J* = 8.0 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 7.2 Hz, 1H), 6.50 (s, 1H), 3.99 (s, 3H), 3.84 (s, 2H), 2.78 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 136.8, 128.0, 127.9, 125.4, 121.0, 120.2, 118.8, 116.1, 102.9, 32.9, 20.2, 17.0.

HRMS (ESI, *m/z*): Calculated for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1070.

2e. 2-(1,3-dimethyl-1H-indol-2-yl)acetonitrile

A red solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1); m.p.: 90-92 °C.



¹H NMR (400 MHz, CDCl₃): δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.25 – 7.23 (m, 1H), 7.15 – 7.11 (m, 1H), 3.84 (s, 2H), 3.77 (s, 3H), 2.31 (s, 3H).

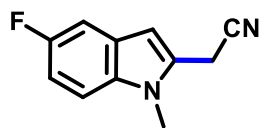
¹³C NMR (100 MHz, CDCl₃): δ 137.1, 127.6, 123.4, 122.5, 119.4, 118.9, 116.0, 109.8, 109.0, 29.9, 13.8, 8.8.

HRMS (ESI, *m/z*): Calculated for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1072.

2f. 2-(5-fluoro-1-methyl-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate =

5/1); m.p.: 101-103 °C.



¹H NMR (400 MHz, CDCl₃): δ 7.24 – 7.22 (m, 1H), 7.21 (t, *J* = 3.6 Hz, 1H), 7.00 (td, *J* = 9.2, 2.4 Hz, 1H), 6.49 (s, 1H), 3.87 (s, 2H), 3.74 (s, 3H).

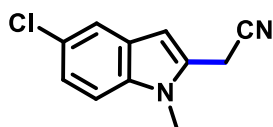
¹³C NMR (100 MHz, CDCl₃): δ 159.2, 156.9, 134.5, 129.2, 127.3, 127.2, 115.7, 110.8, 110.6, 109.9, 109.8, 105.6, 105.4, 102.2, 102.1, 30.1, 16.8.

¹⁹F NMR (376 MHz, CDCl₃): δ -124.27 (td, *J* = 9.4, 4.1 Hz, 1F).

HRMS (ESI, *m/z*): Calculated for C₁₁H₁₀FN₂ (*M*+H)⁺ 189.0823, found 189.0822.

2g. 2-(5-chloro-1-methyl-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1); m.p.: 118-120 °C.



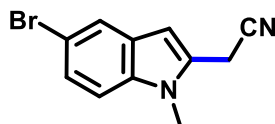
¹H NMR (400 MHz, CDCl₃): δ 7.54 – 7.53 (m, 1H), 7.23 – 7.18 (m, 2H), 6.47 (s, 1H), 3.87 (s, 2H), 3.73 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 136.3, 129.0, 128.0, 125.8, 122.6, 120.0, 115.6, 110.2, 101.9, 30.0, 16.7.

HRMS (ESI, *m/z*): Calculated for C₁₁H₁₀ClN₂ (*M*+H)⁺ 205.0527, found 205.0525.

2h. 2-(5-bromo-1-methyl-1H-indol-2-yl)acetonitrile

A red solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1); m.p.: 107-109 °C.



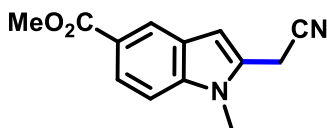
¹H NMR (400 MHz, CDCl₃): δ 7.70 (d, *J* = 1.6 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.17 (d, *J* = 8.8 Hz, 1H), 6.47 (s, 1H), 3.87 (s, 2H), 3.73 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 136.6, 128.9, 128.7, 125.2, 123.2, 115.6, 113.4, 110.7, 101.8, 30.0, 16.7.

HRMS (ESI, *m/z*): Calculated for C₁₁H₁₀BrN₂ (*M*+H)⁺ 249.0022, found 249.0019.

2i. methyl 2-(cyanomethyl)-1-methyl-1H-indole-5-carboxylate

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 3/1).



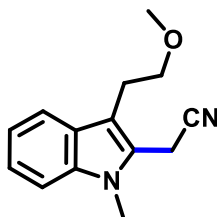
¹H NMR (400 MHz, CDCl₃): δ 8.34 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.64 (s, 1H), 3.93 (s, 3H), 3.91 (s, 2H), 3.79 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 167.9, 140.3, 129.2, 126.6, 123.7, 123.6, 122.3, 115.6, 108.9, 103.8, 51.9, 30.1, 16.8.

HRMS (ESI, *m/z*): Calculated for C₁₃H₁₃N₂O₂ (M+H)⁺ 229.0972, found 229.0975.

2j. 2-(3-(2-methoxyethyl)-1-methyl-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 85-87 °C.



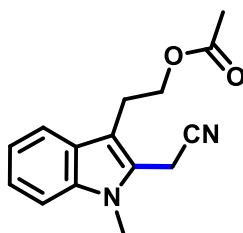
¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.15 – 7.11 (m, 1H), 3.92 (s, 2H), 3.78 (s, 3H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.32 (s, 3H), 2.99 (t, *J* = 6.4 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 137.0, 126.9, 125.2, 122.3, 119.5, 118.6, 116.4, 111.4, 109.2, 72.8, 58.8, 29.9, 25.0, 14.2.

HRMS (ESI, *m/z*): Calculated for C₁₄H₁₇N₂O (M+H)⁺ 229.1335, found 229.1334.

2k. 2-(2-(cyanomethyl)-1-methyl-1H-indol-3-yl)ethyl acetate

A red solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1); m.p.: 90-91 °C.



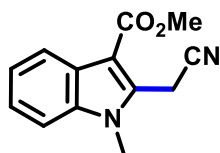
¹H NMR (400 MHz, CDCl₃): δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 6.8, 1.2 Hz, 1H), 7.18 – 7.14 (m, 1H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.91 (s, 2H), 3.81 (s, 3H), 3.08 (t, *J* = 6.8 Hz, 2H), 2.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 171.1, 137.2, 126.8, 124.9, 122.7, 119.8, 118.7, 116.0, 110.2, 109.3, 64.4, 30.0, 23.9, 21.0, 14.0.

HRMS (ESI, *m/z*): Calculated for C₁₅H₂₀N₃O₂ (M+NH₄)⁺ 274.1550, found 274.1549.

2l. methyl 2-(cyanomethyl)-1-methyl-1H-indole-3-carboxylate

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 2/1); m.p.: 128-130 °C.



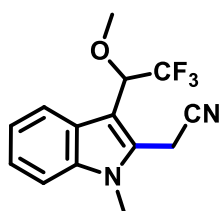
¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.31 – 7.28 (m, 1H), 4.57 (s, 2H), 3.97 (s, 3H), 3.86 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 165.7, 136.8, 134.6, 125.6, 123.7, 122.5, 122.2, 115.3, 109.6, 105.7, 51.3, 30.3, 14.3.

HRMS (ESI, *m/z*): Calculated for C₁₃H₁₃N₂O₂ (M+H)⁺ 229.0972, found 229.0969.

2m. 2-(1-methyl-3-(2,2,2-trifluoro-1-methoxyethyl)-1H-indol-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 123-125 °C.



¹H NMR (400 MHz, CDCl₃): δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.23 – 7.19 (m, 1H), 4.99 (q, *J* = 6.8 Hz, 1H), 4.22 (d, *J* = 18.0 Hz, 1H), 3.98 (d, *J* = 18.0 Hz, 1H), 3.85 (s, 3H), 3.50 (s, 3H).

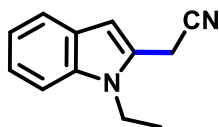
¹³C NMR (150 MHz, CDCl₃): δ 137.0, 127.2, 126.6, 124.3(d, *J* = 281.9 Hz), 123.1, 120.8, 118.7, 115.5, 109.6, 104.9, 75.6(q, *J* = 32.6 Hz), 58.5, 30.0, 14.3.

¹⁹F NMR (376 MHz, CDCl₃): δ -76.79 (s, 3F).

HRMS (ESI, m/z): Calculated for C₁₄H₁₄F₃N₂O (M+H)⁺ 283.1053, found 283.1058.

2n. 2-(1-ethyl-1H-indol-2-yl)acetonitrile

A yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1).



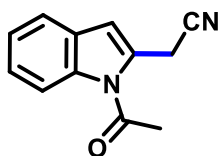
¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.15 – 7.11 (m, 1H), 6.54 (d, *J* = 0.8 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 3.88 (s, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 136.8, 127.4, 126.9, 122.3, 120.8, 120.1, 116.1, 109.3, 102.5, 38.3, 16.6, 15.2.

HRMS (ESI, m/z): Calculated for C₁₂H₁₃N₂ (M+H)⁺ 185.1073, found 185.1067.

2o. 2-(1-acetyl-1H-indol-2-yl)acetonitrile

A white solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1).



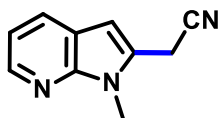
¹H NMR (400 MHz, CDCl₃): δ 7.66 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.32 – 7.28 (m, 1H), 6.83 (s, 1H), 4.23 (s, 2H), 2.84 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 170.3, 135.8, 130.8, 129.2, 124.8, 123.6, 121.5, 116.7, 114.1, 111.4, 27.4, 20.9.

HRMS (ESI, m/z): Calculated for C₁₂H₁₄N₃O (M+NH₄)⁺ 216.1131, found 216.1128.

2p. 2-(1-methyl-1H-pyrrolo[2,3-b]pyridin-2-yl)acetonitrile

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 3/1); m.p.: 100-103 °C.



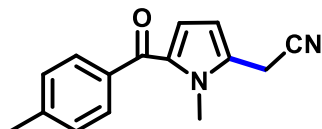
¹H NMR (400 MHz, CDCl₃): δ 8.34 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.08 (dd, *J* = 8.0, 4.8 Hz, 1H), 6.52 (s, 1H), 3.92 (s, 2H), 3.88 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 148.7, 143.4, 128.6, 128.5, 119.7, 116.4, 115.5, 100.1, 28.2, 17.0.

HRMS (ESI, m/z): Calculated for C₁₀H₁₀N₃ (M+H)⁺ 172.0869, found 172.0864.

2q. 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetonitrile

A red solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 100-102 °C.



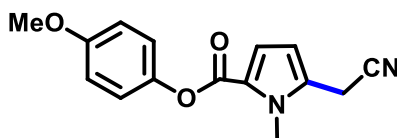
¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 4.4 Hz, 1H), 6.23 (d, *J* = 4.4 Hz, 1H), 3.98 (s, 3H), 3.77 (s, 2H), 2.43 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 186.1, 142.4, 136.7, 132.3, 129.5, 129.1, 128.8, 121.7, 115.4, 109.2, 33.1, 21.6, 16.5.

HRMS (ESI, m/z): Calculated for C₁₅H₁₅N₂O (M+H)⁺ 239.1179, found 239.1176.

2r. 4-methoxyphenyl 5-(cyanomethyl)-1-methyl-1H-pyrrole-2-carboxylate

A yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1); m.p.: 136-138 °C.



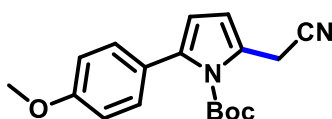
¹H NMR (400 MHz, CDCl₃): δ 7.15 (d, *J* = 4.0 Hz, 1H), 7.08 (d, *J* = 9.2 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.27 (d, *J* = 4.0 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.75 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 159.8, 157.2, 143.8, 128.5, 123.3, 122.6, 118.4, 115.4, 114.5, 109.5, 55.6, 32.7, 16.5.

HRMS (ESI, m/z): Calculated for C₁₅H₁₅N₂O₃ (M+H)⁺ 271.1077, found 271.1075.

2s. tert-butyl 2-(cyanomethyl)-5-(4-methoxyphenyl)-1H-pyrrole-1-carboxylate

A blue liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 10/1).



¹H NMR (400 MHz, CDCl₃): δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.30 (d, *J* = 3.6 Hz, 1H), 6.07 (d, *J* = 3.6 Hz, 1H), 4.00 (s, 2H), 3.83 (s, 3H), 1.28 (s,

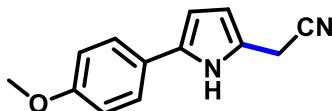
9H).

¹³C NMR (150 MHz, CDCl₃): δ 159.0, 149.7, 136.6, 130.0, 127.2, 123.8, 117.2, 113.2, 112.2, 110.0, 84.7, 55.4, 27.4, 19.2.

HRMS (ESI, m/z): Calculated for C₁₈H₂₁N₂O₃ (M+H)⁺ 313.1547, found 313.1548.

2s'. 2-(5-(4-methoxyphenyl)-1H-pyrrol-2-yl)acetonitrile

A red liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 5/1).



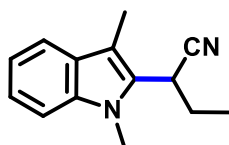
¹H NMR (400 MHz, CDCl₃): δ 8.35 (s, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 6.31 (t, *J* = 3.2 Hz, 1H), 6.16 (t, *J* = 3.2 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 2H).

¹³C NMR (150 MHz, CDCl₃): δ 158.6, 133.4, 125.3, 118.8, 116.9, 114.4, 110.0, 109.9, 105.5, 55.3, 17.1.

HRMS (ESI, m/z): Calculated for C₁₃H₁₃N₂O (M+H)⁺ 213.1022, found 213.1020.

2t. (S)-2-(1,3-dimethyl-1H-indol-2-yl)butanenitrile

A light yellow liquid after purification by flash column chromatography (petroleum ether/ethyl acetate = 20/1).



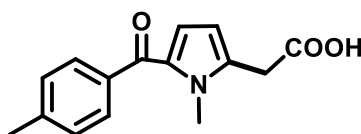
¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.24 (m, 1H), 7.16 – 7.12 (m, 1H), 4.07 (t, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H), 2.20 – 2.09 (m, 1H), 2.00 – 1.89 (m, 1H), 1.10 (t, *J* = 7.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 137.1, 127.9, 127.8, 122.4, 119.4, 119.2, 118.8, 109.5, 109.0, 30.5, 29.4, 27.1, 11.9, 8.9.

HRMS (ESI, m/z): Calculated for C₁₄H₁₇N₂ (M+H)⁺ 213.1386, found 213.1384.

Tolmetin. 2-(1-methyl-5-(4-methylbenzoyl)-1H-pyrrol-2-yl)acetic acid

A light yellow solid after purification by flash column chromatography (petroleum ether/ethyl acetate = 1/1); m.p.: 160-161 °C.

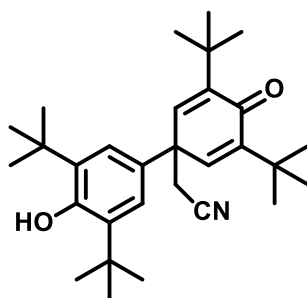


¹H NMR (400 MHz, CDCl₃): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 4.0 Hz, 1H), 6.13 (d, *J* = 4.0 Hz, 1H), 3.95 (s, 3H), 3.76 (s, 2H), 2.42 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 186.1, 174.7, 142.0, 137.1, 133.8, 131.5, 129.5, 128.7, 122.4, 109.7, 33.2, 32.5, 21.5.

HRMS (ESI, *m/z*): Calculated for C₁₅H₁₅NO₃Na (M+Na)⁺ 280.0944, found 280.0948.

2-(3,3',5,5'-tetra-*tert*-butyl-4'-hydroxy-4-oxo-1,4-dihydro-[1,1'-biphenyl]-1-yl)acetonitrile



¹H NMR (400 MHz, CDCl₃): δ 7.01 (s, 2H), 6.58 (s, 2H), 5.25 (s, 1H), 3.00 (s, 2H), 1.42 (s, 18H), 1.27 (s, 18H).

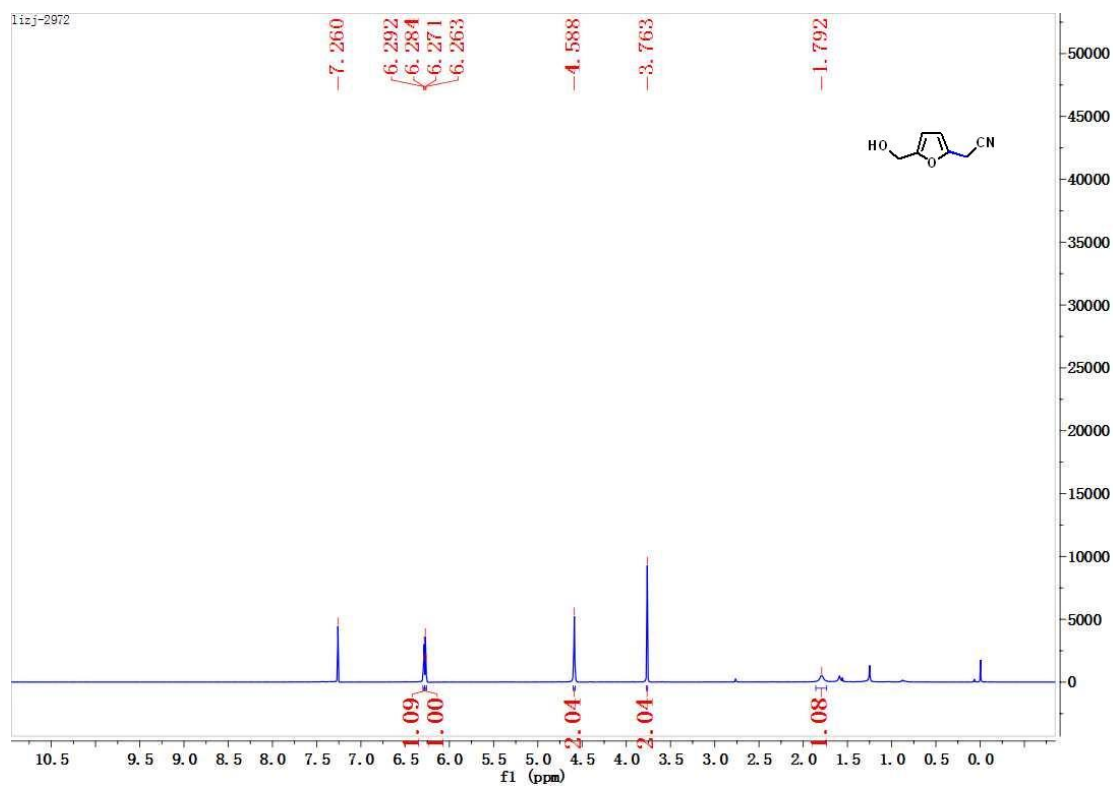
¹³C NMR (100 MHz, CDCl₃): δ 185.6, 153.3, 147.2, 142.1, 136.5, 128.8, 122.6, 116.4, 44.5, 35.0, 34.6, 30.1, 29.4, 27.5.

¹³⁵DEPT NMR (150 MHz, CDCl₃): δ 142.1, 122.5, 30.1, 29.4, 27.5.

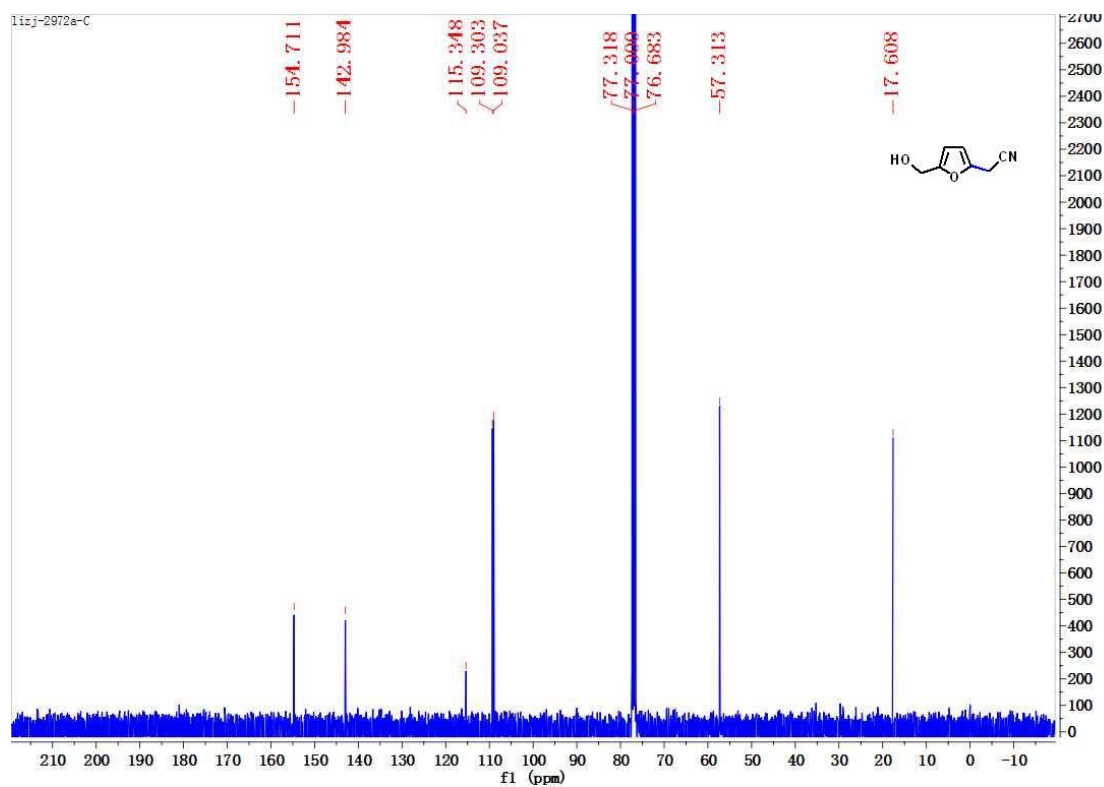
HRMS (ESI, *m/z*): Calculated for C₃₀H₄₃NO₂Na (M+Na)⁺ 472.3186, found 472.3173.

Copies of the ^1H NMR, ^{13}C NMR, ^{19}F NMR, $^{135}\text{DEPT}$

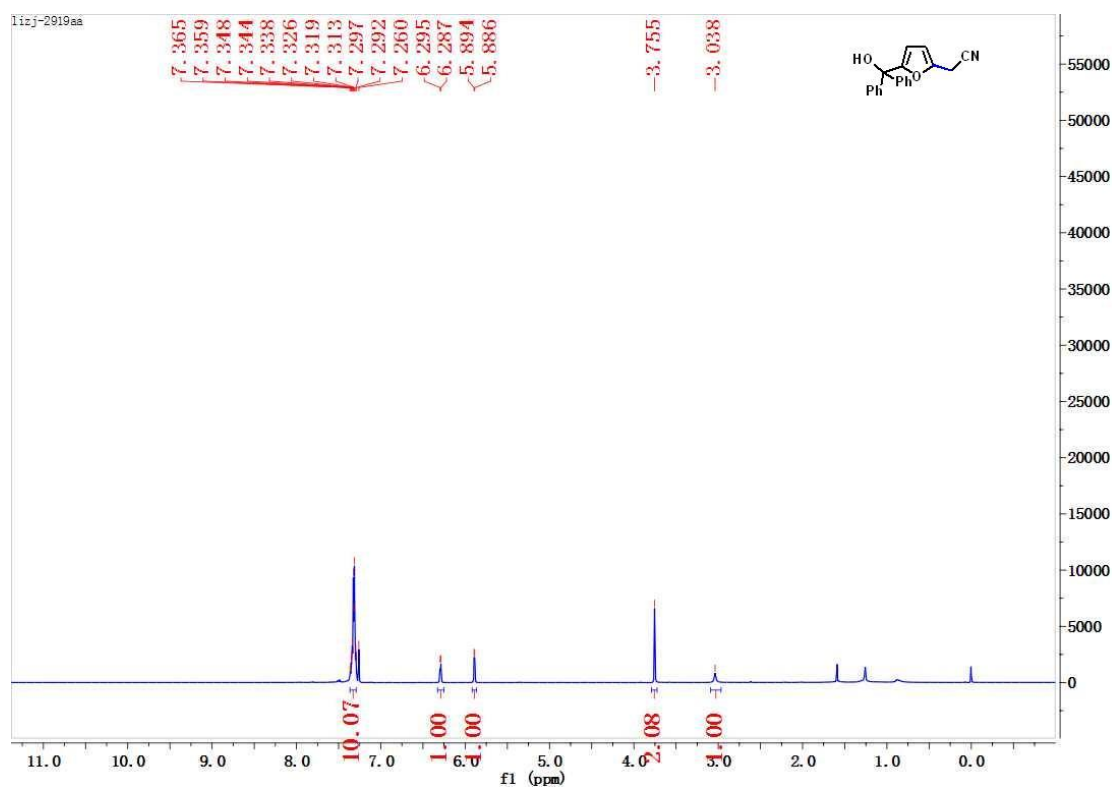
1a- ^1H NMR



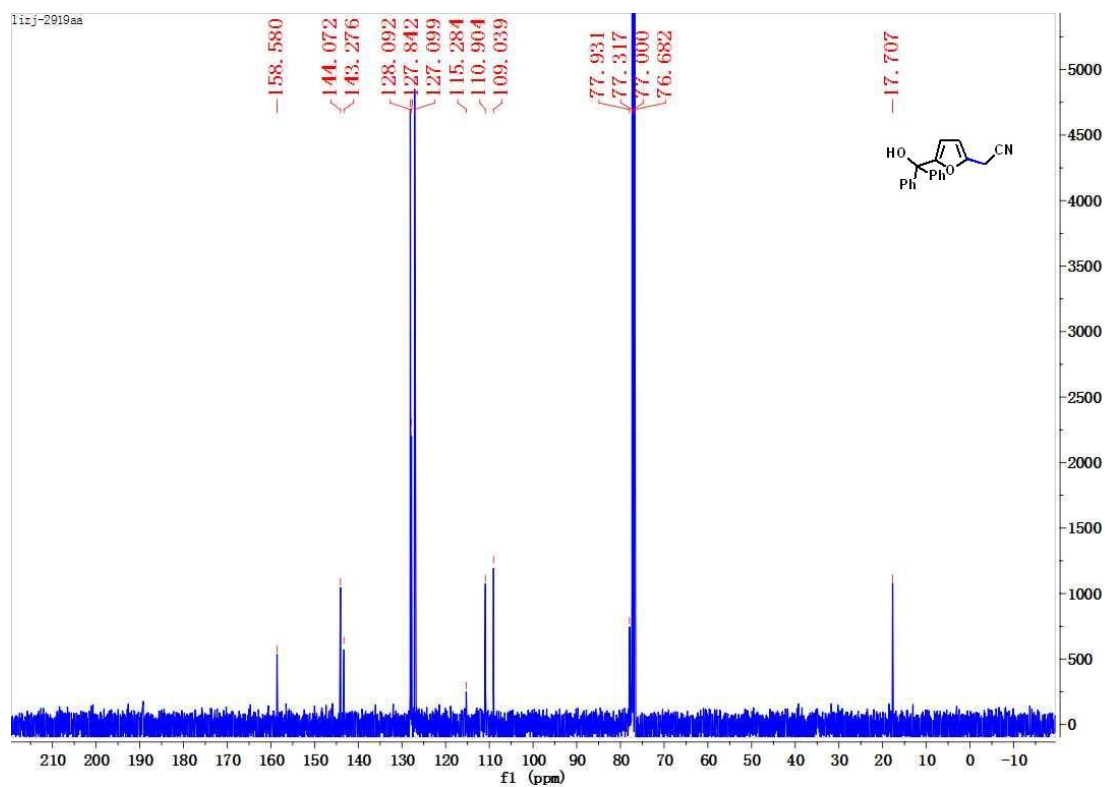
1a- ^{13}C NMR



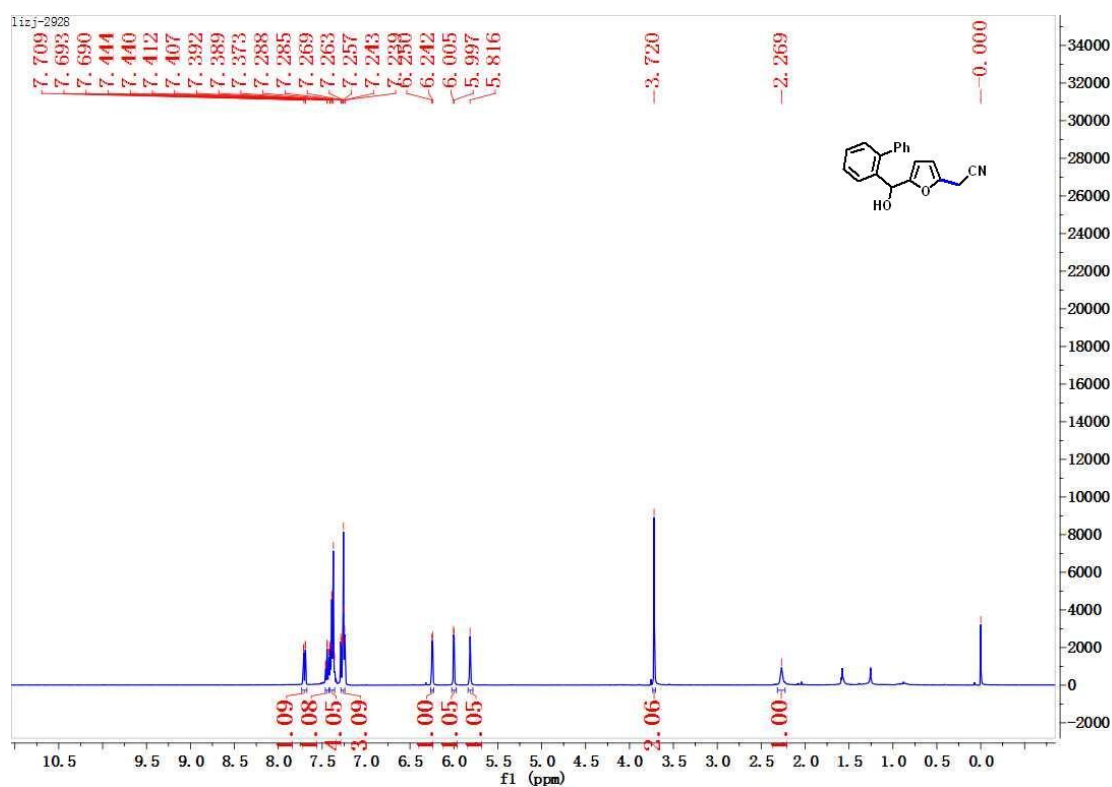
1b-¹H NMR



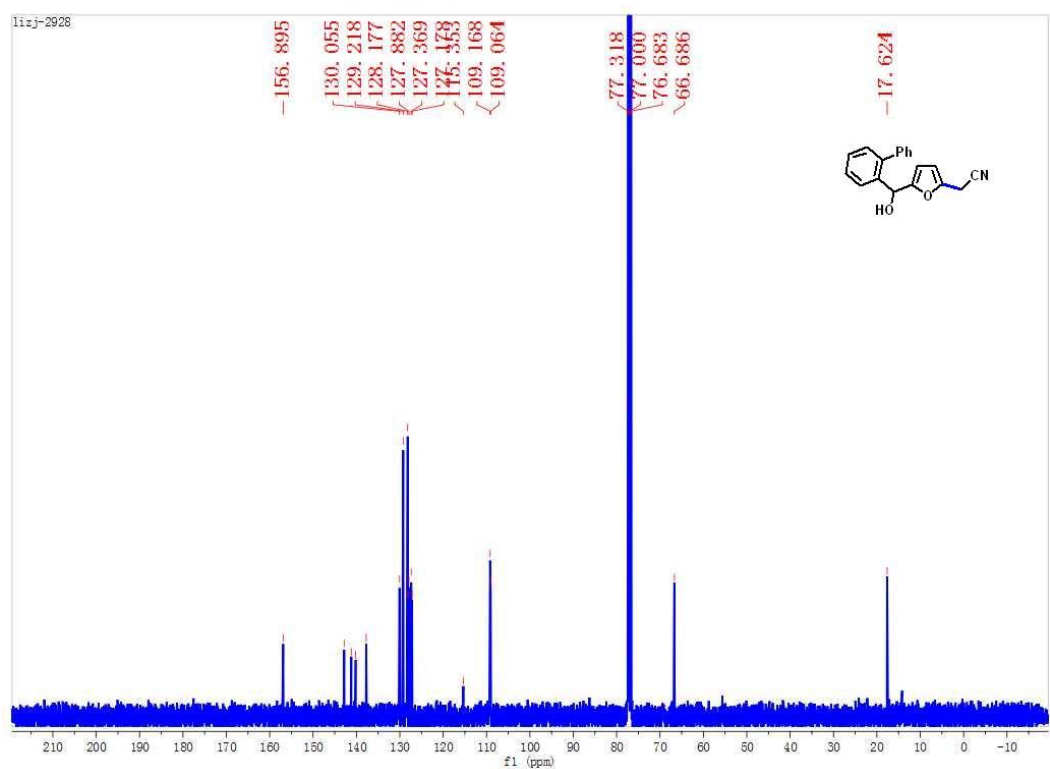
1b-¹³C NMR



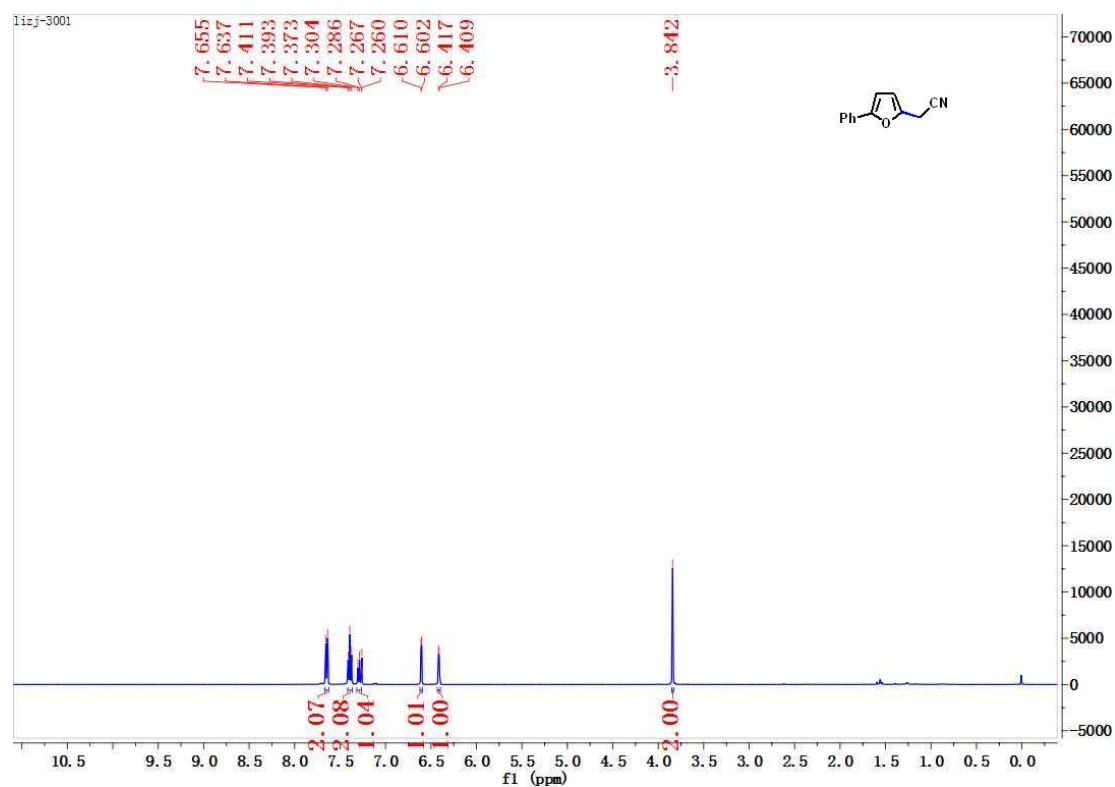
1c-¹H NMR



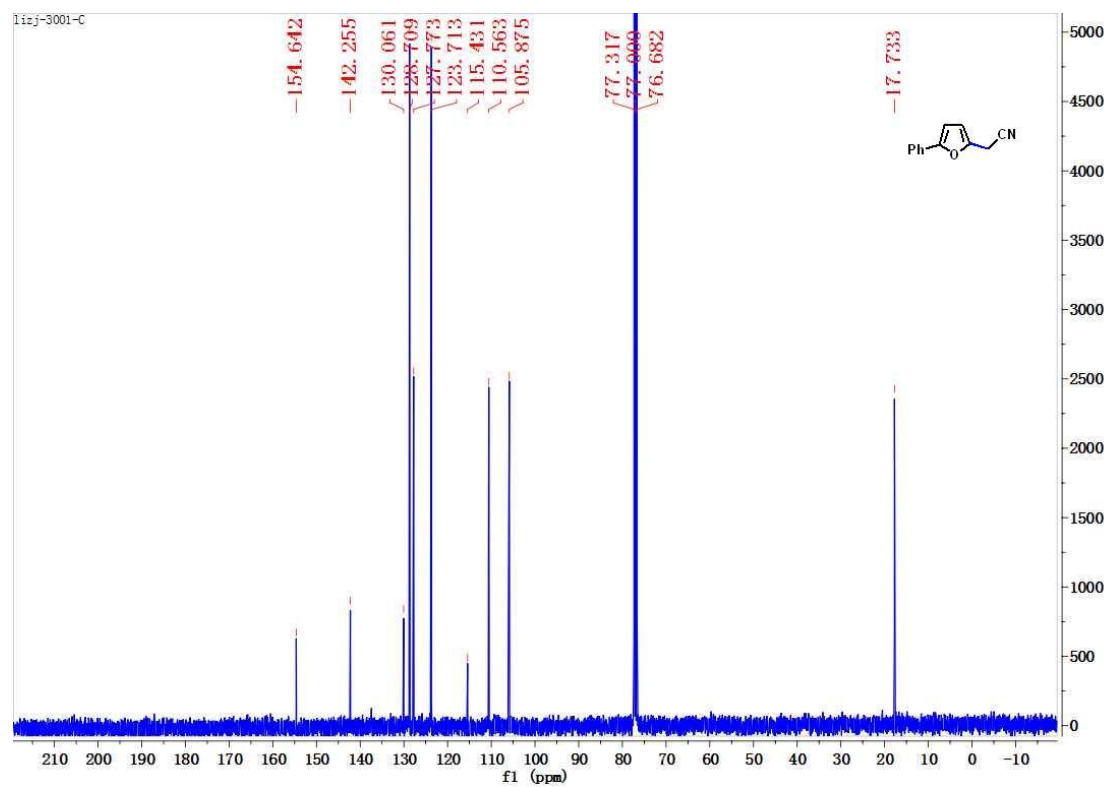
1c-¹³C NMR



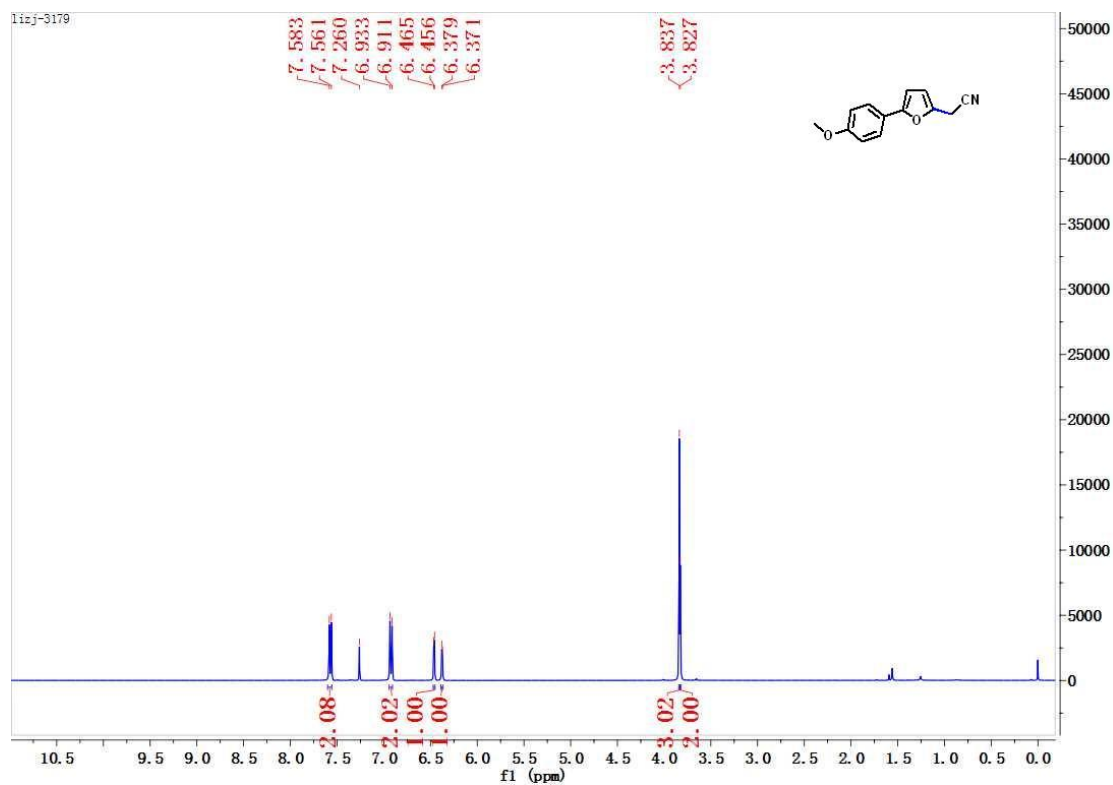
1d-¹H NMR



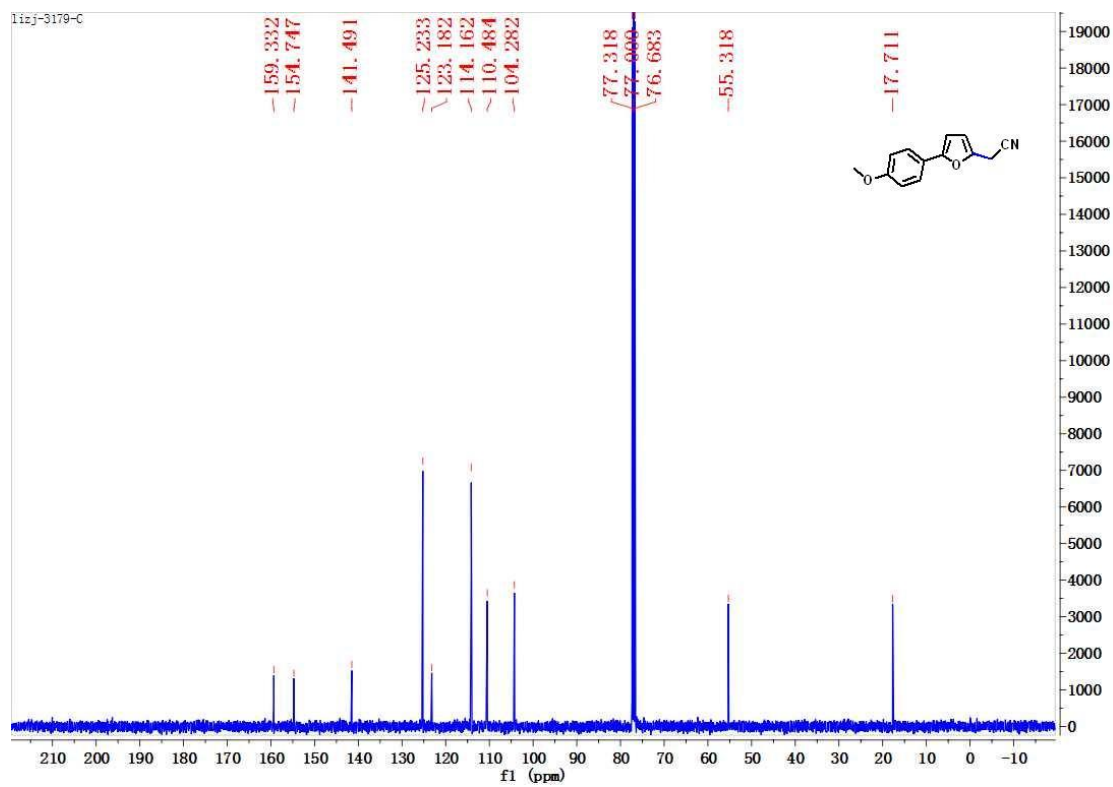
1d-¹³C NMR



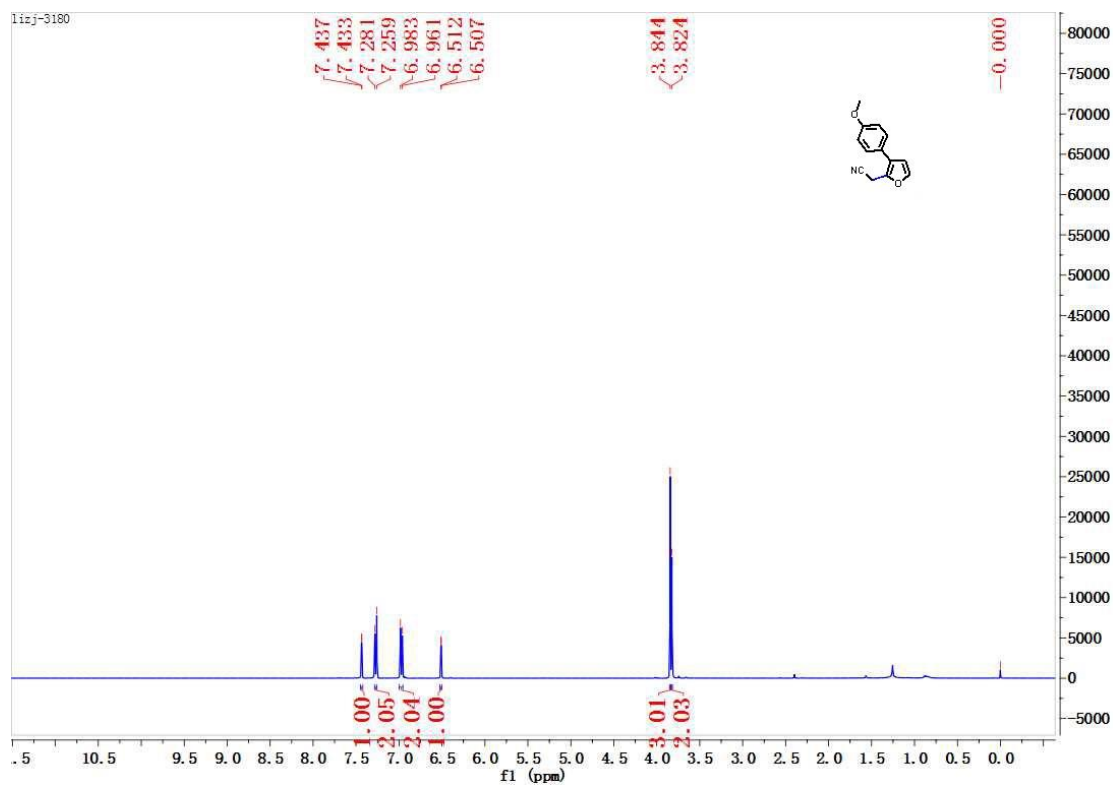
$1\text{e-}^1\text{H}$ NMR



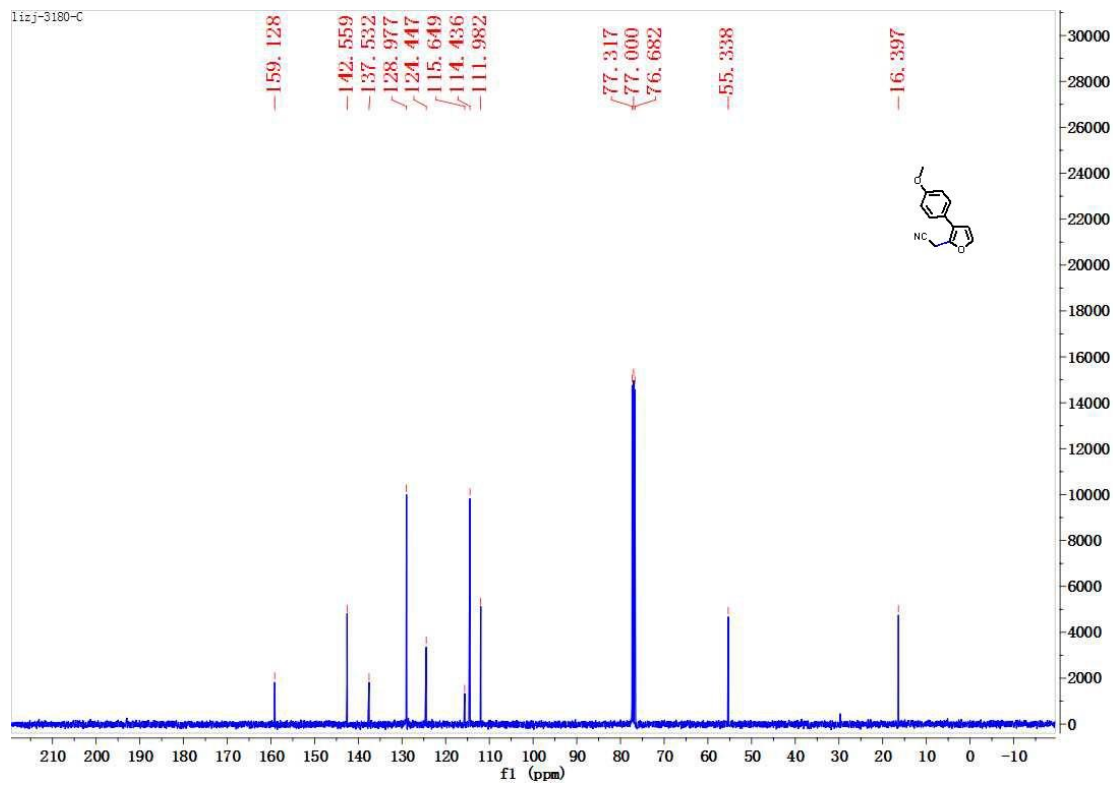
$1\text{e-}^{13}\text{C}$ NMR



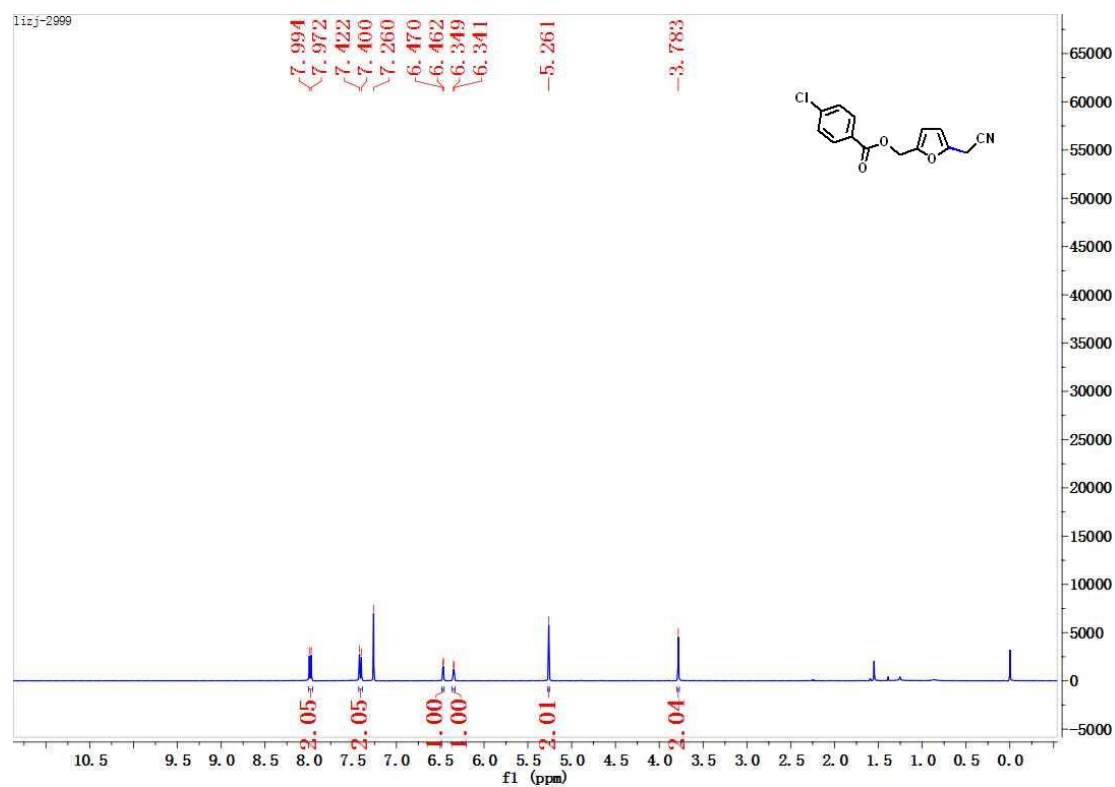
1f-¹H NMR



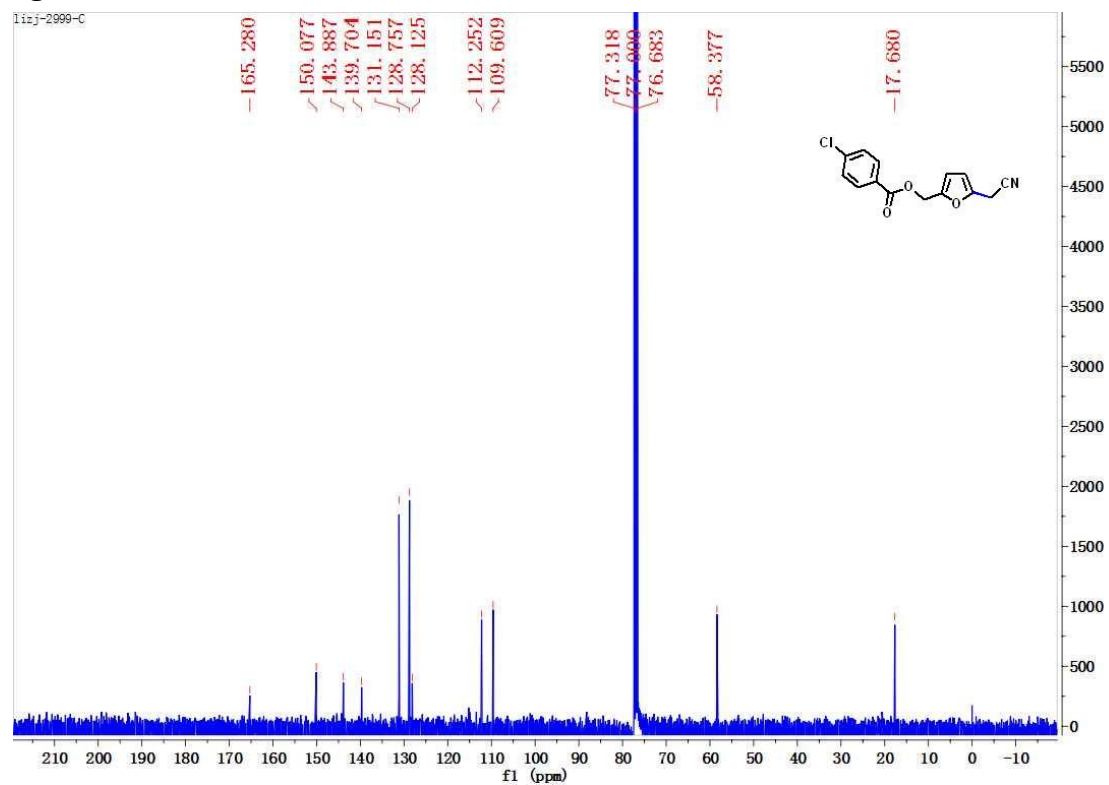
1f-¹³C NMR



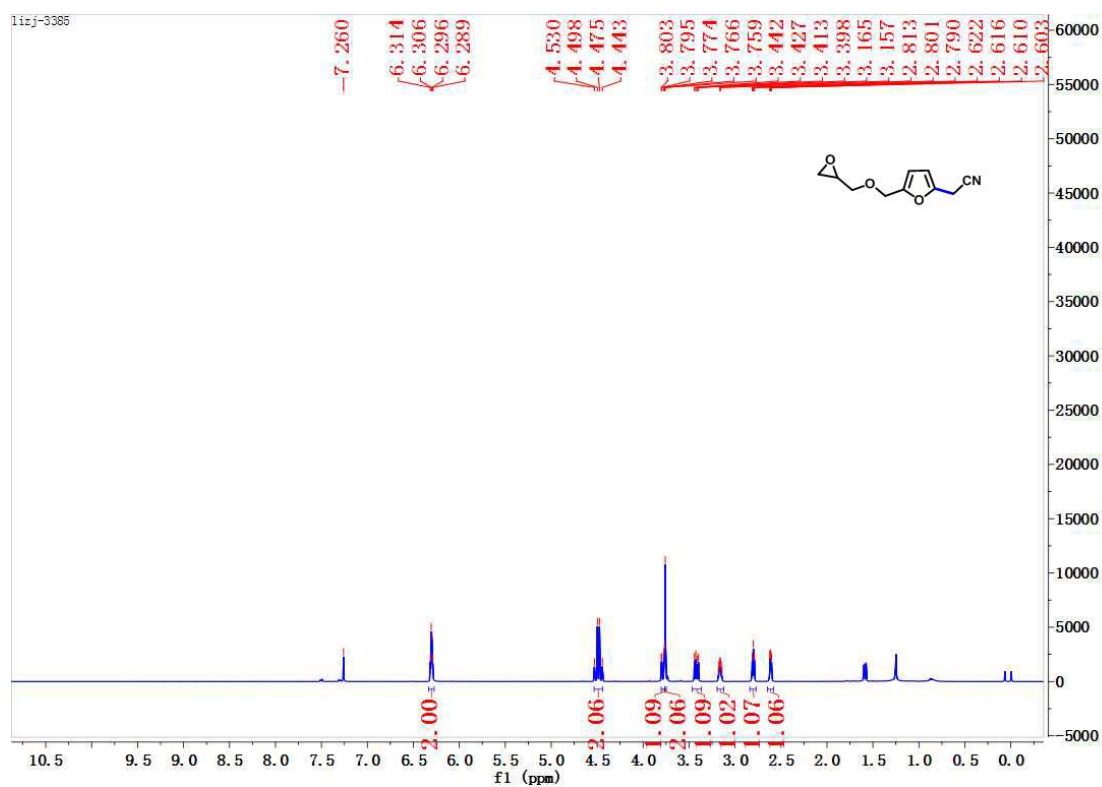
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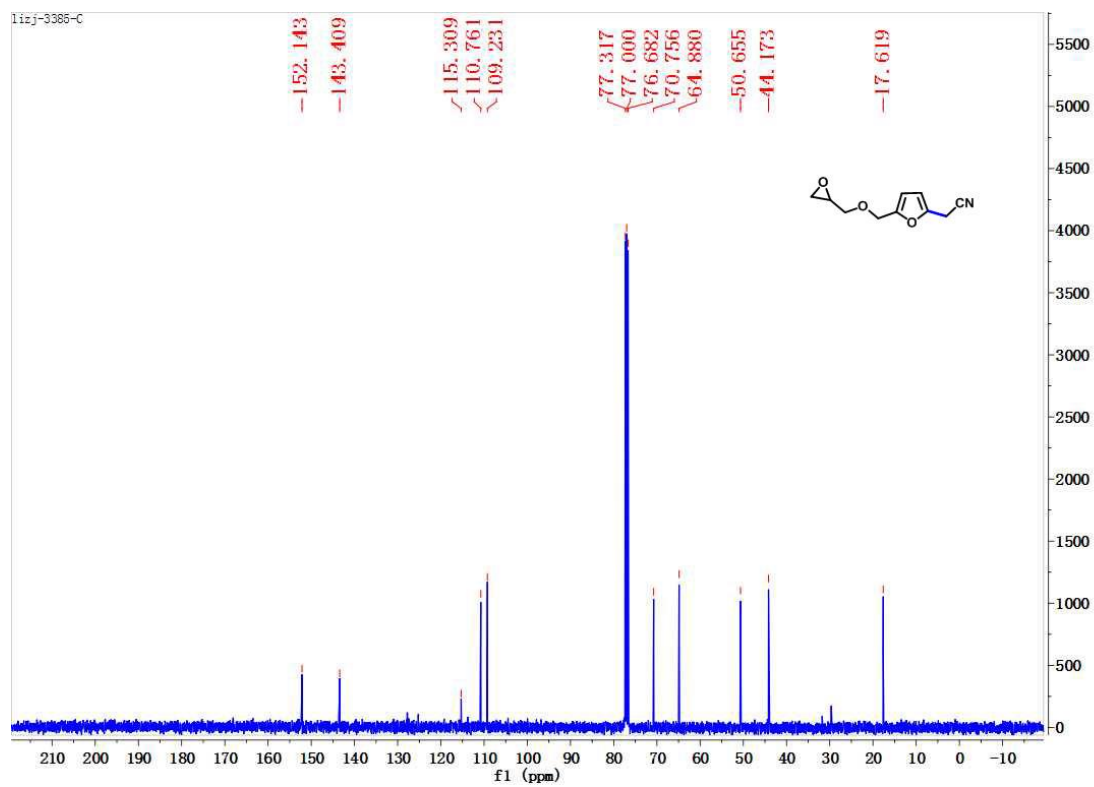
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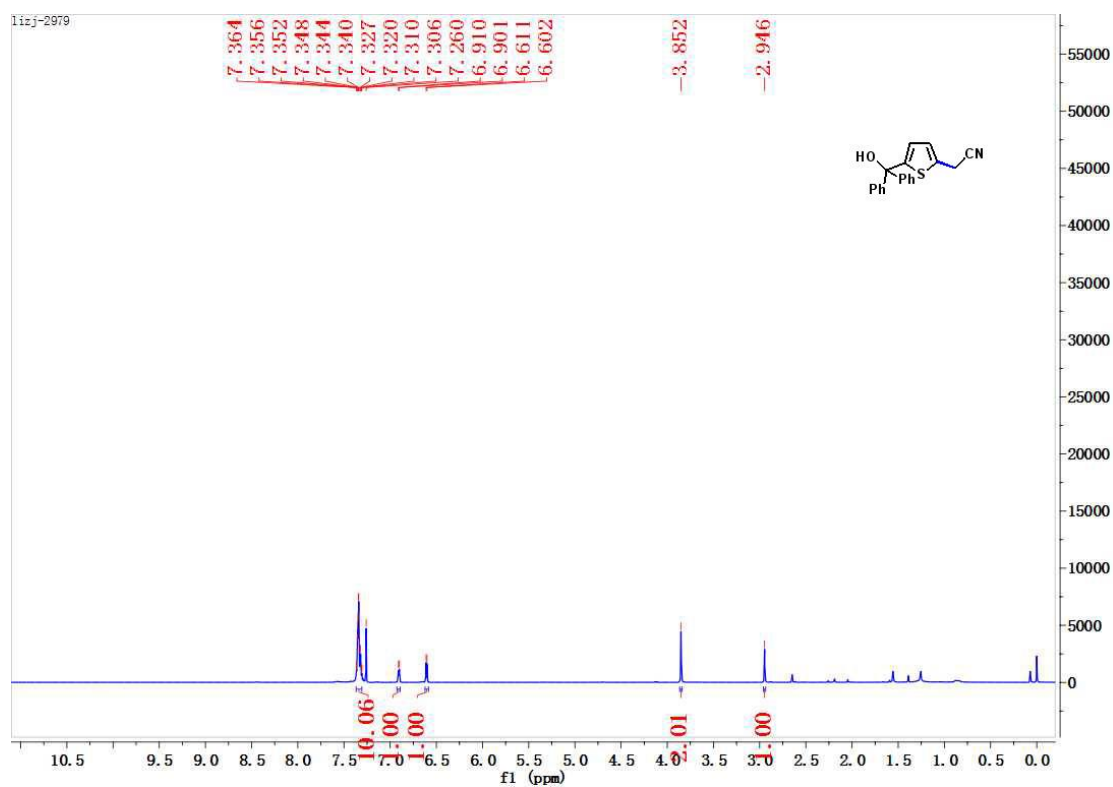
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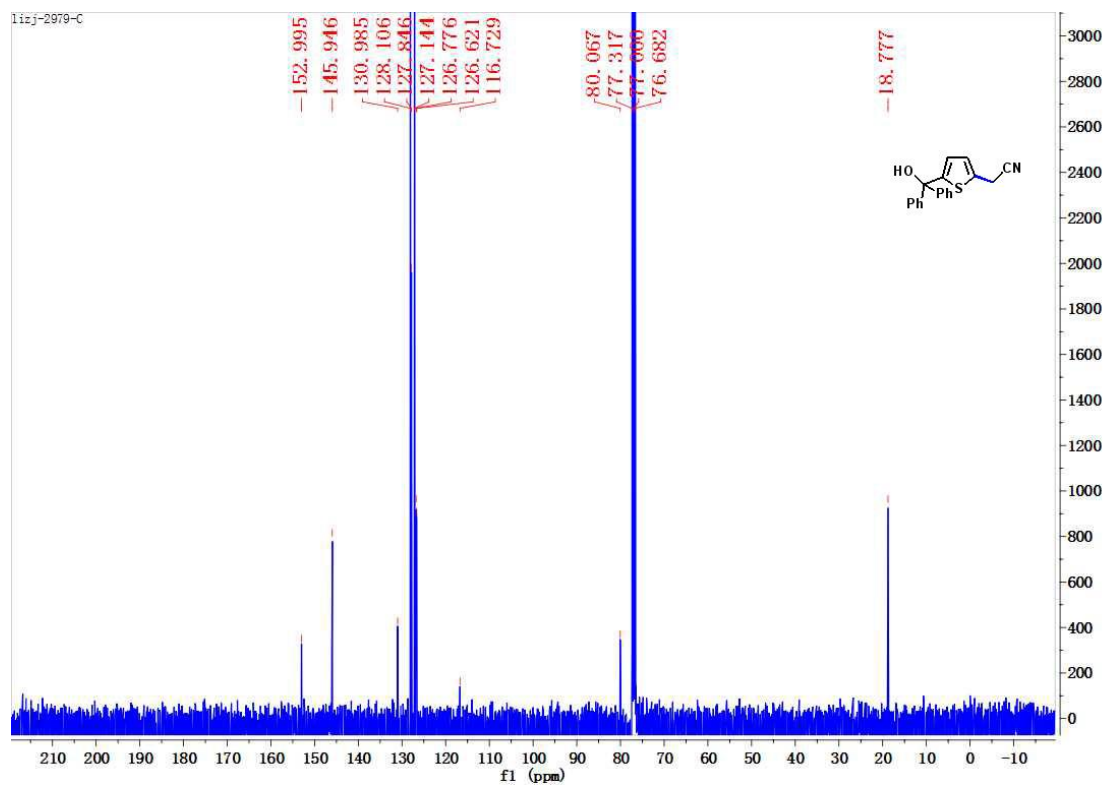
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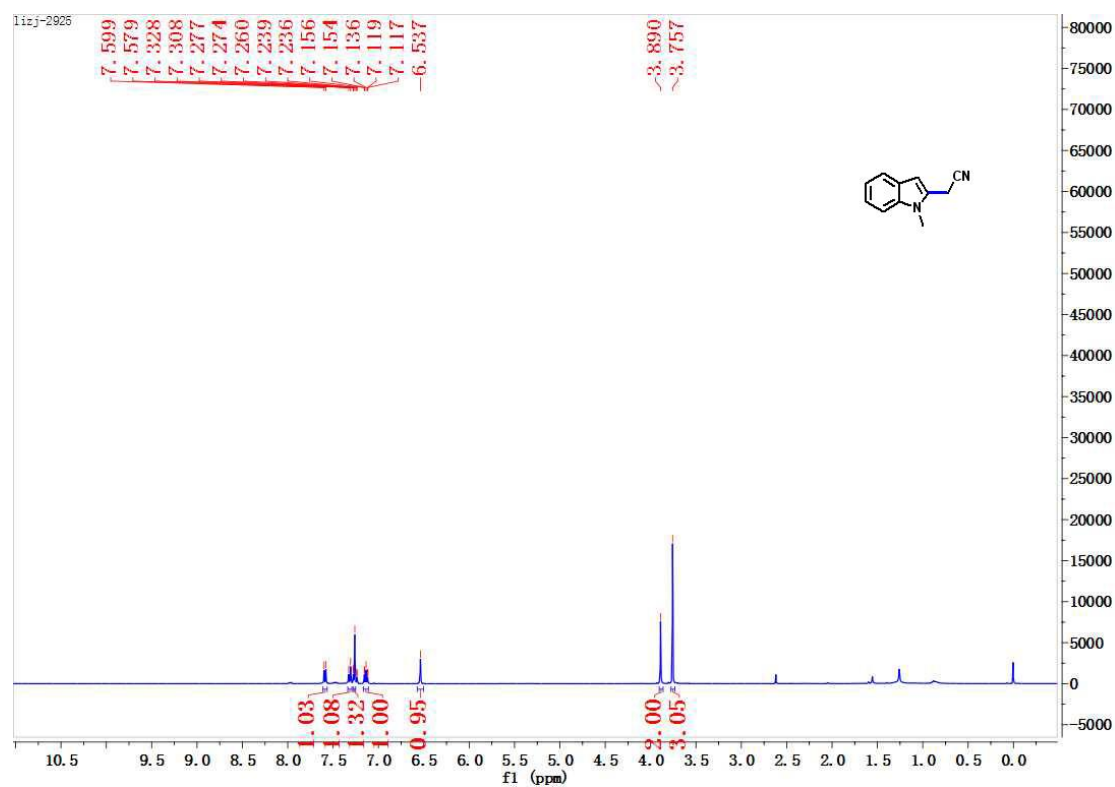
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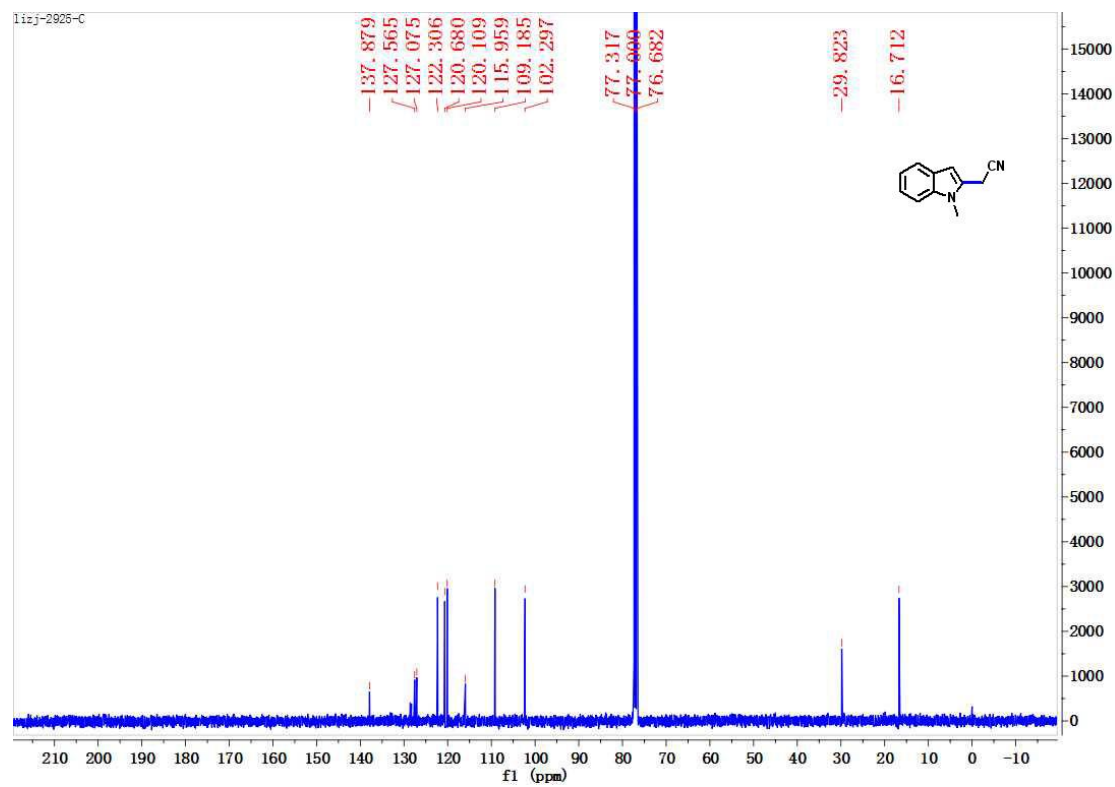
13C NMR



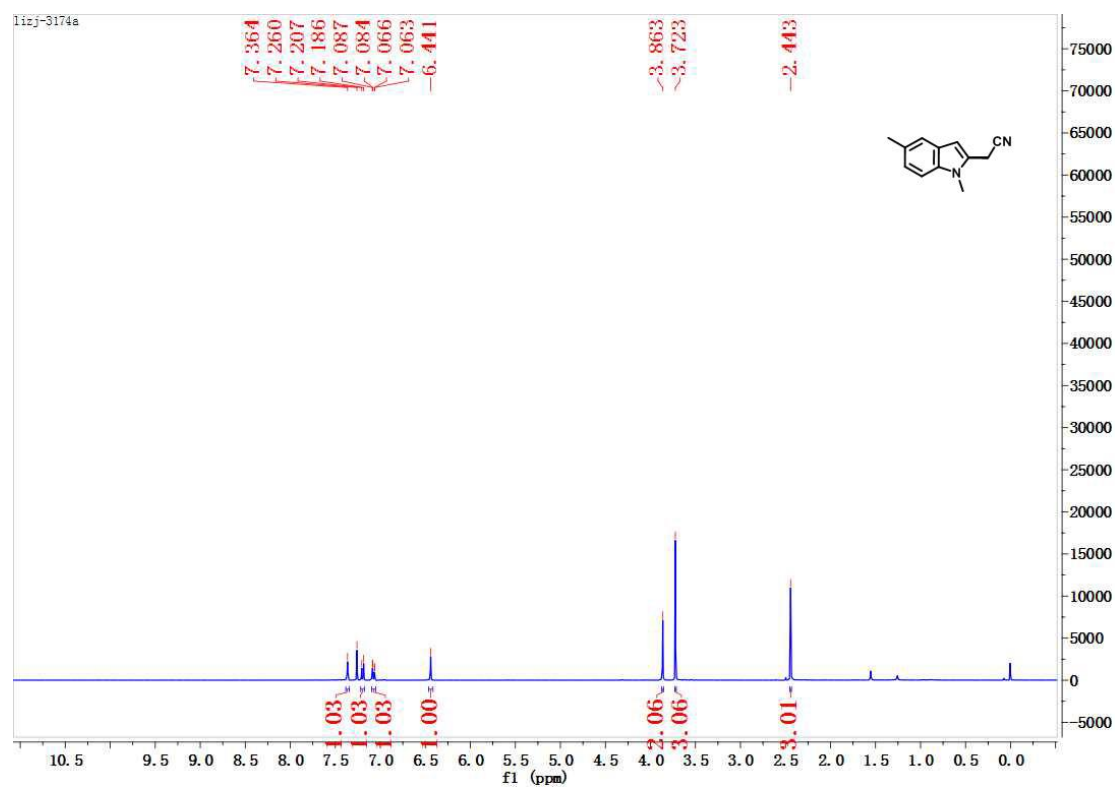
2a-¹H NMR



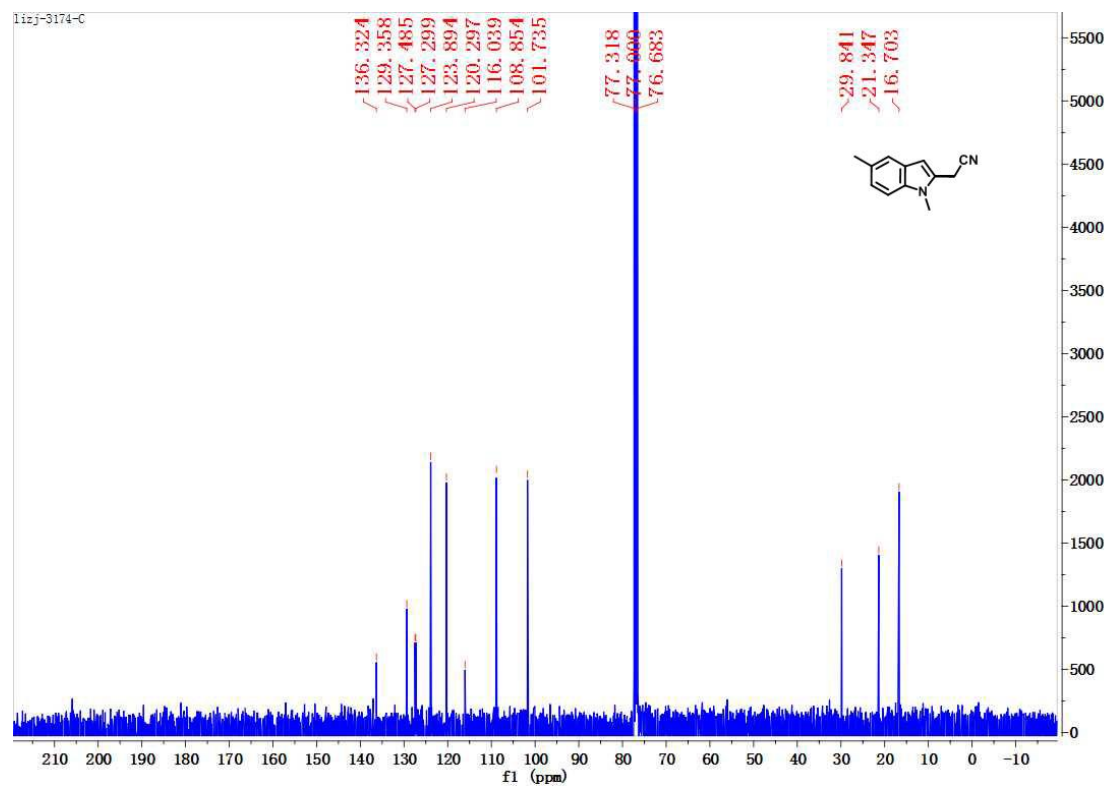
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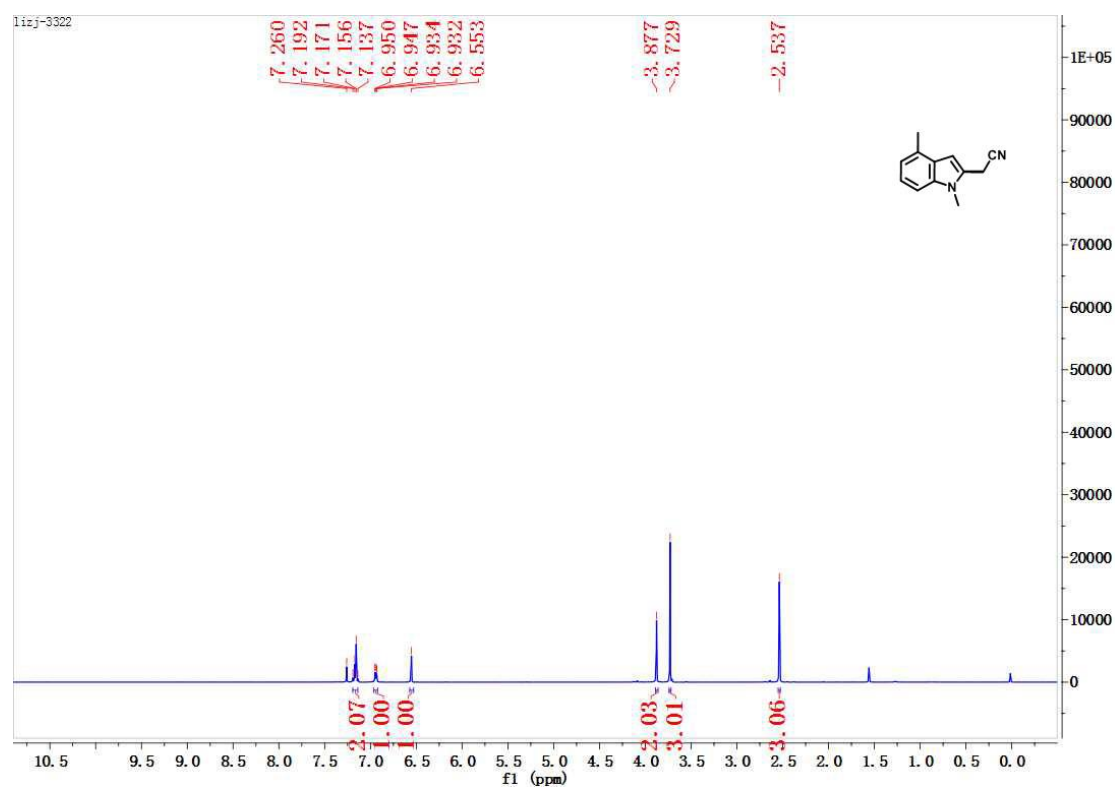
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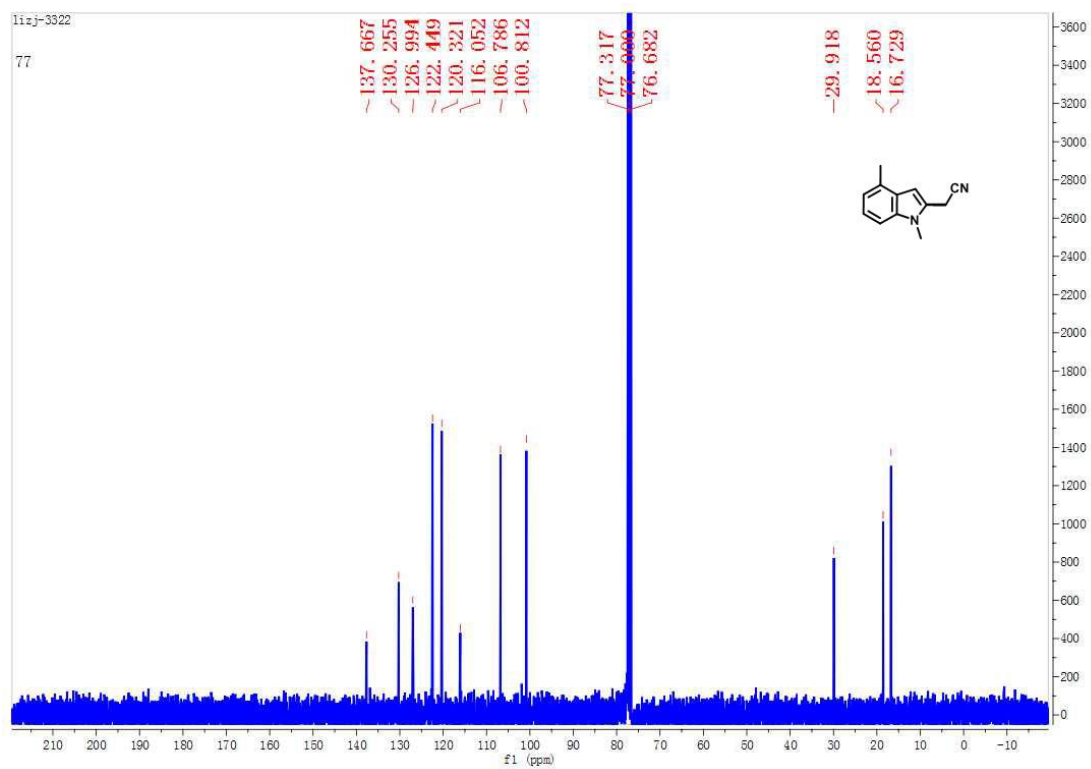
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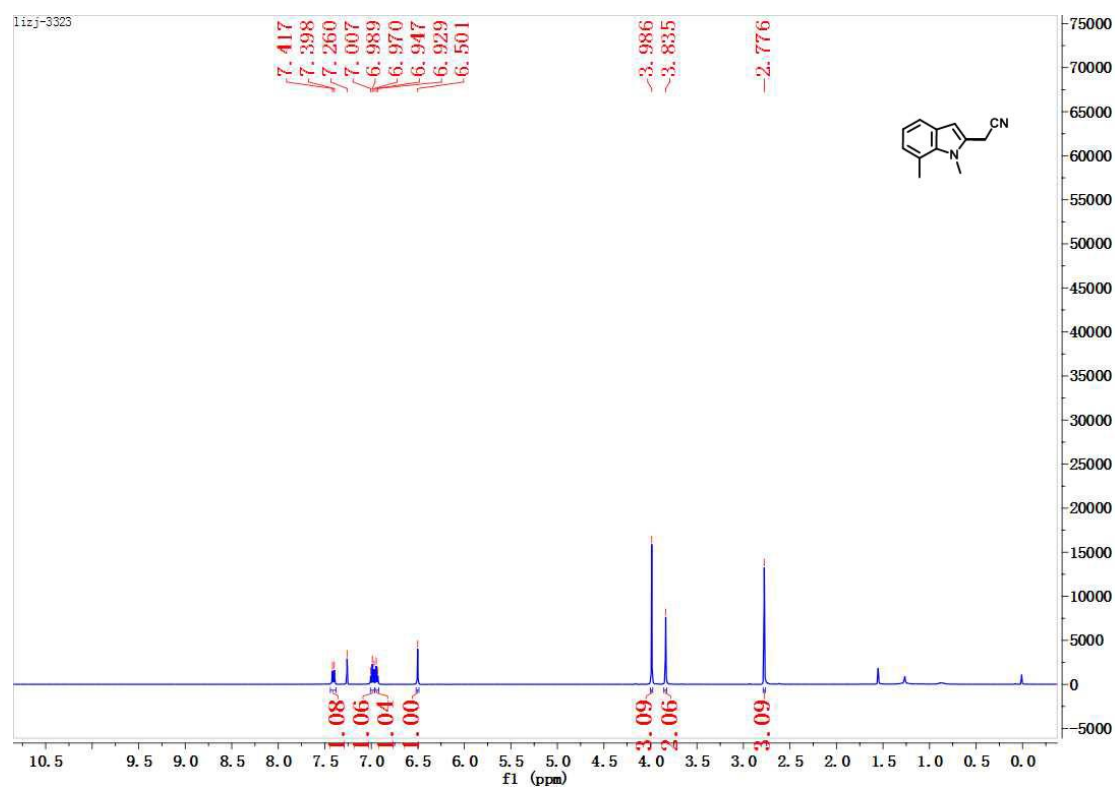
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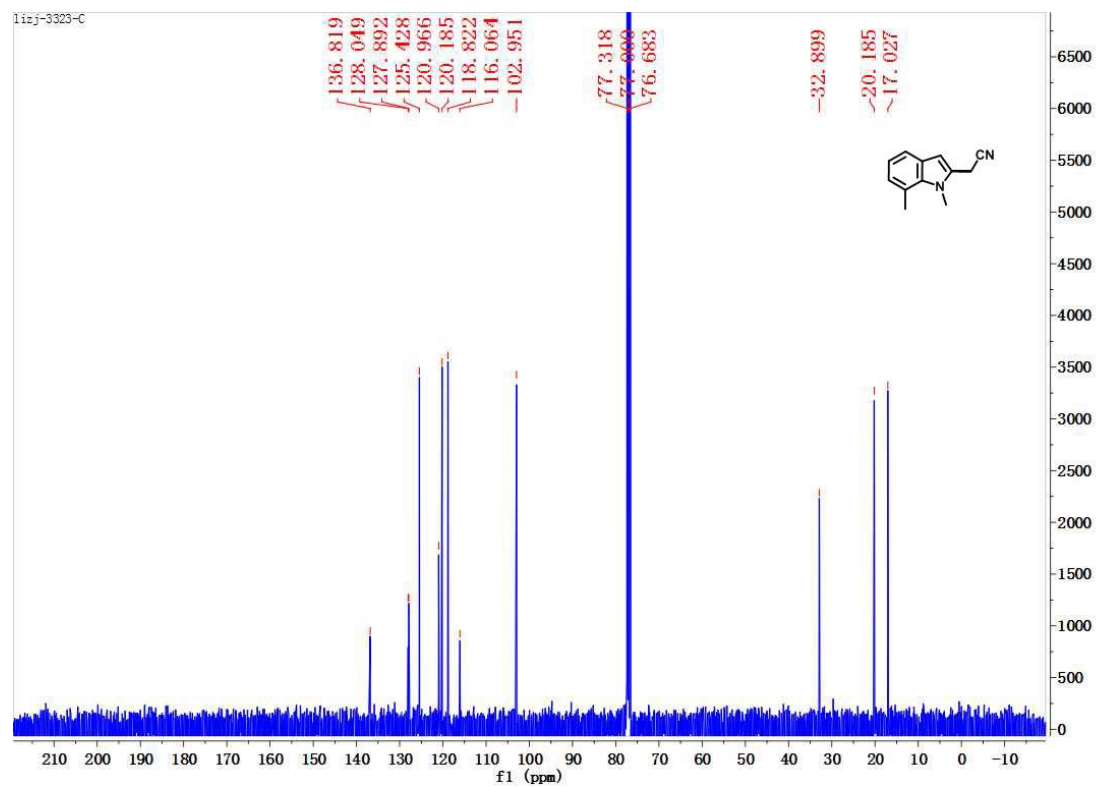
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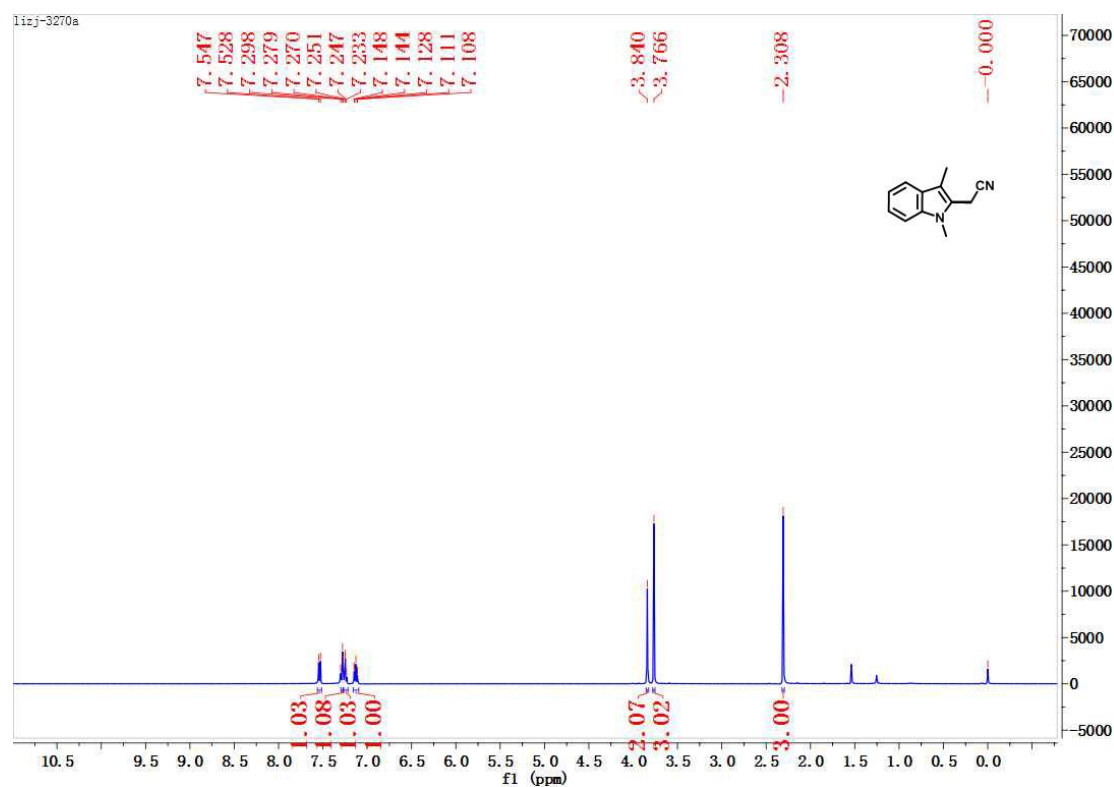
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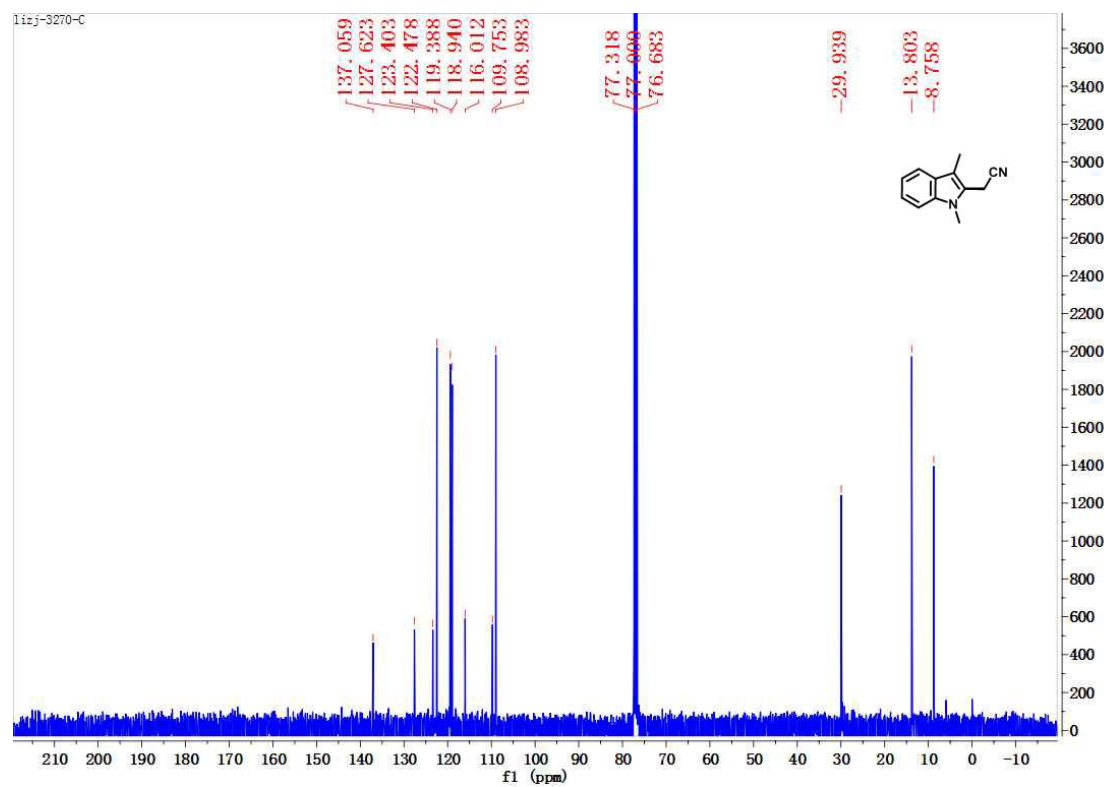
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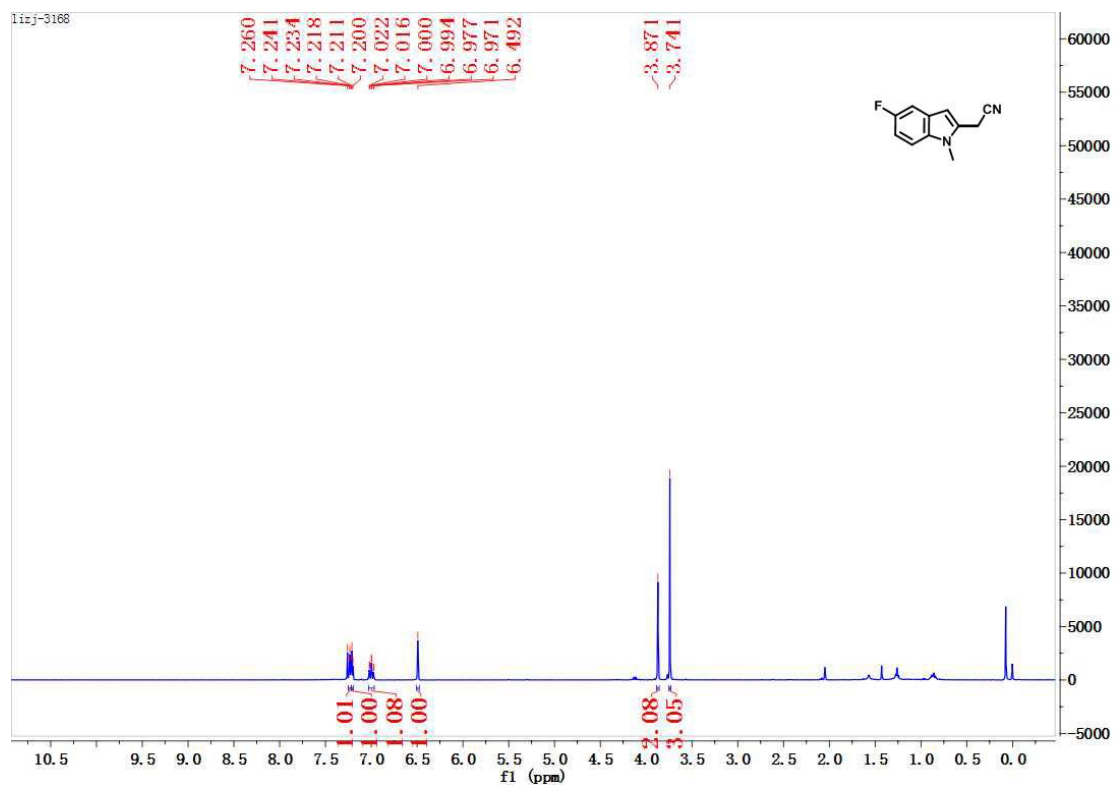
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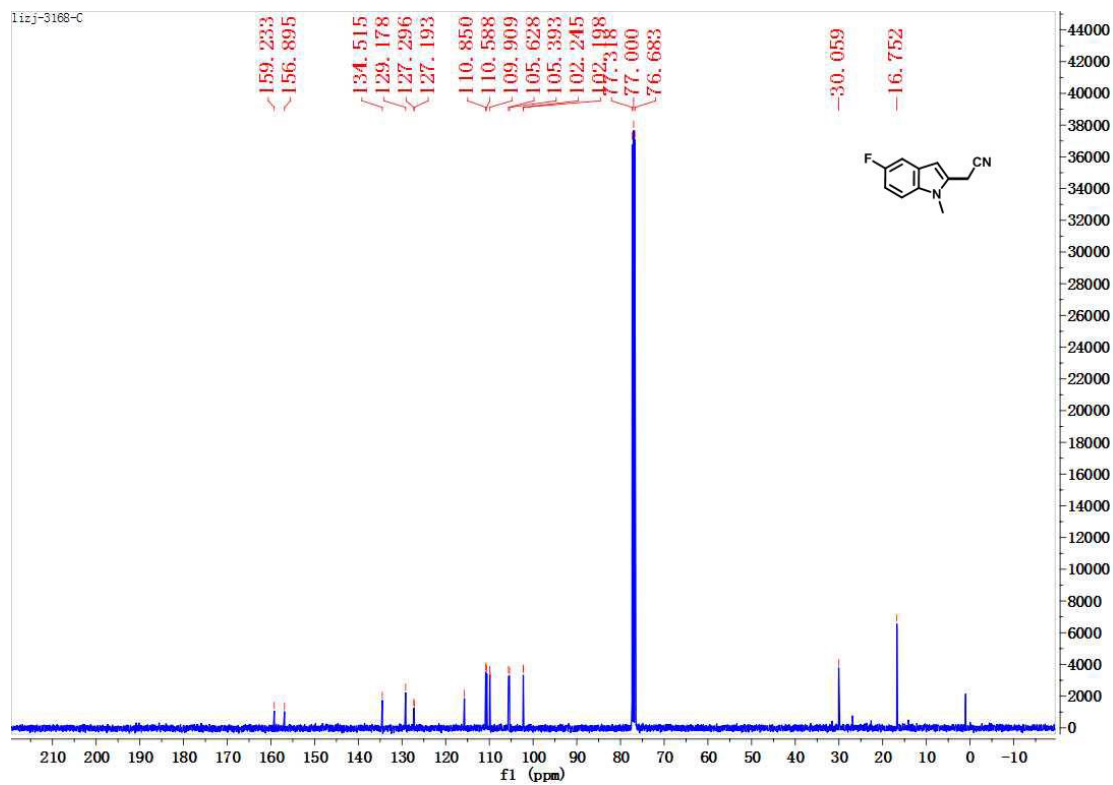
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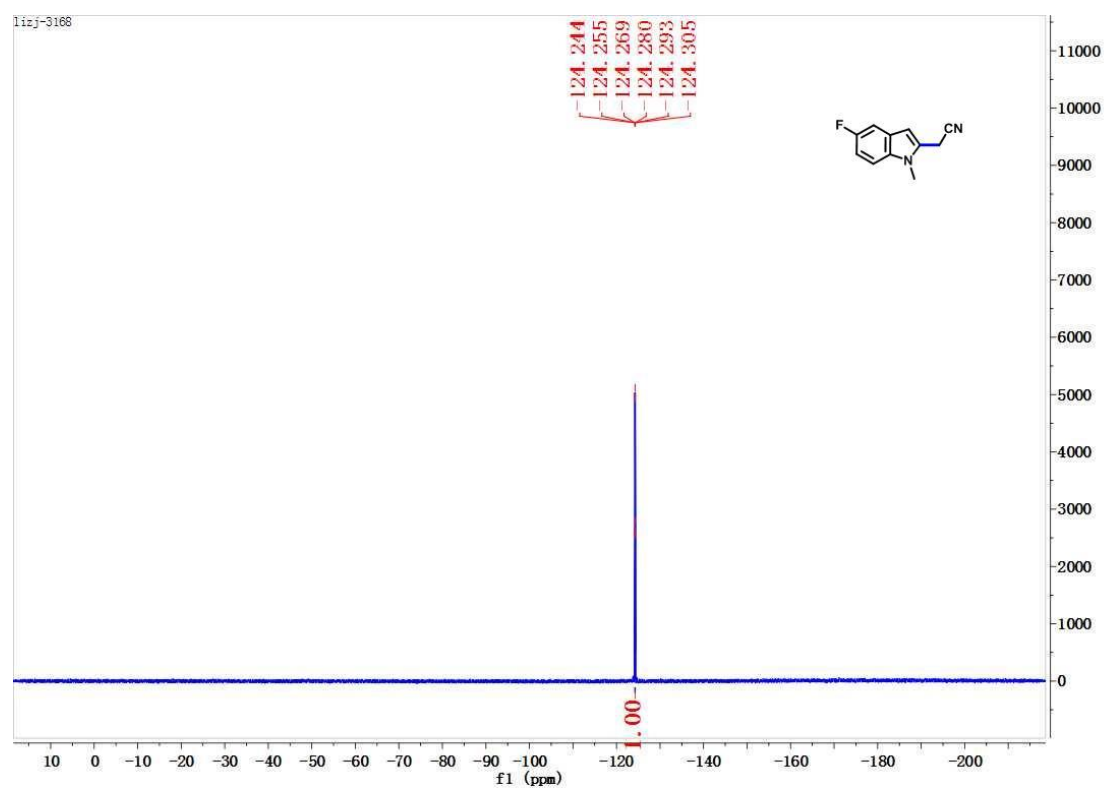
2f-¹H NMR



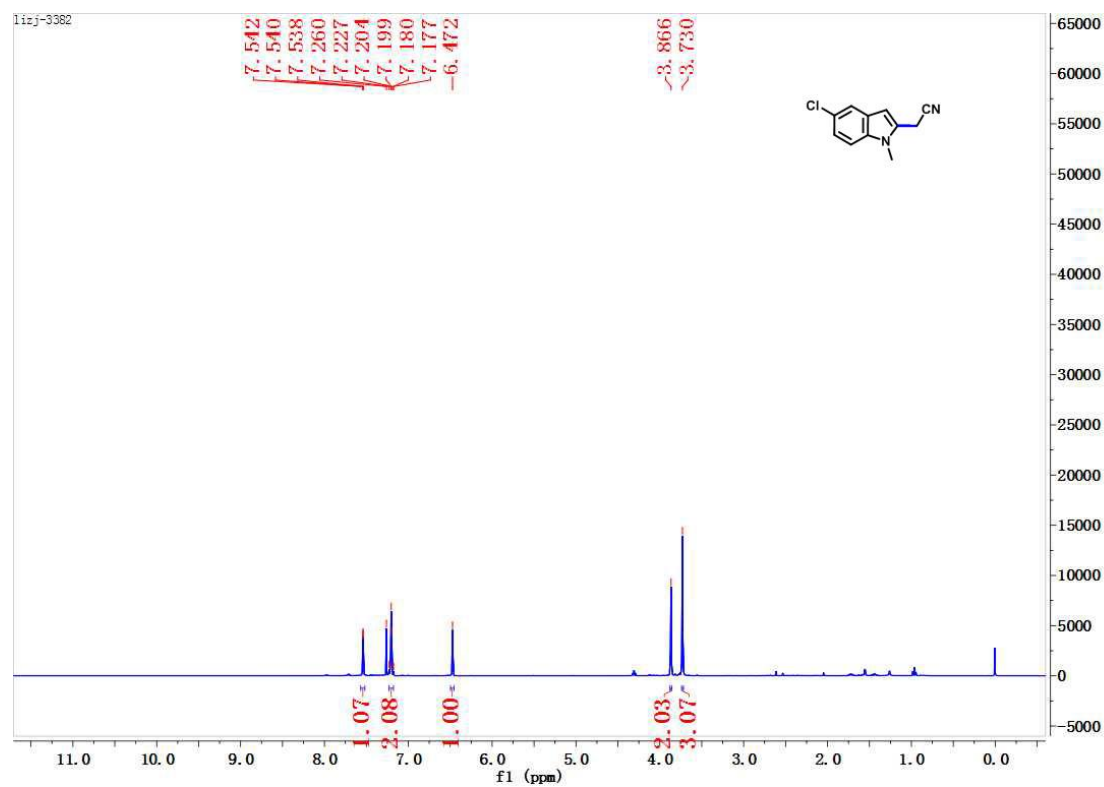
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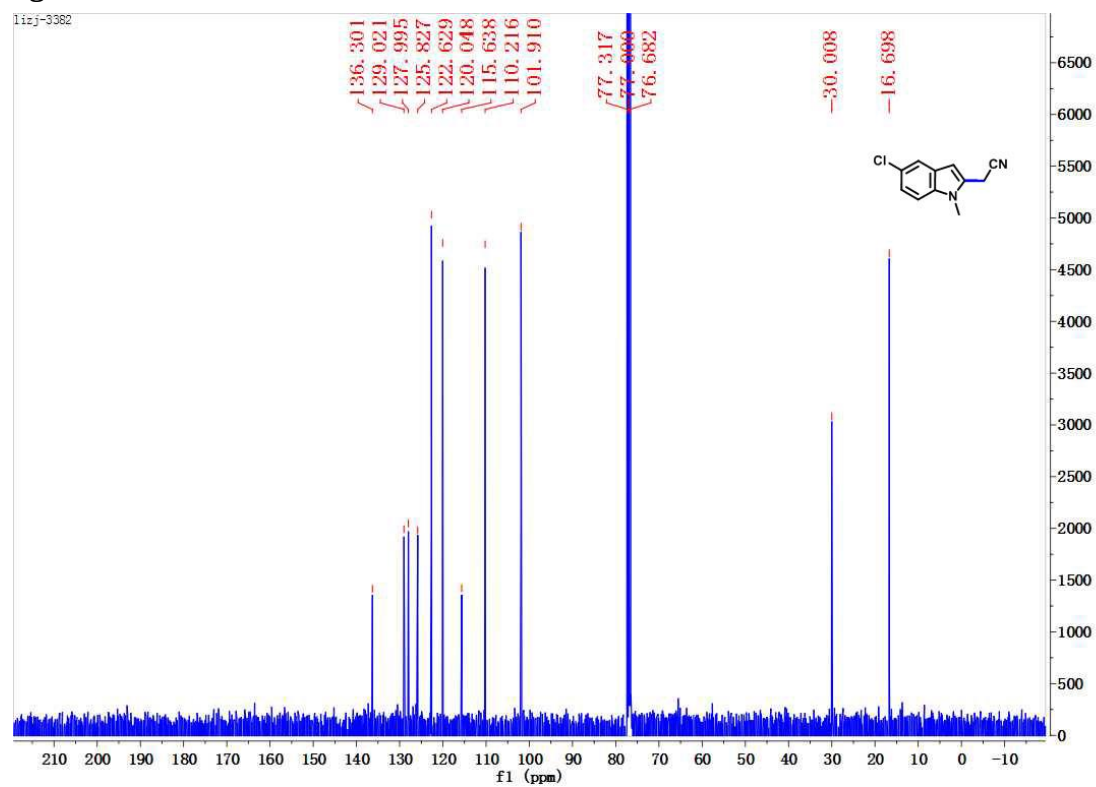
2f- ^{19}F NMR



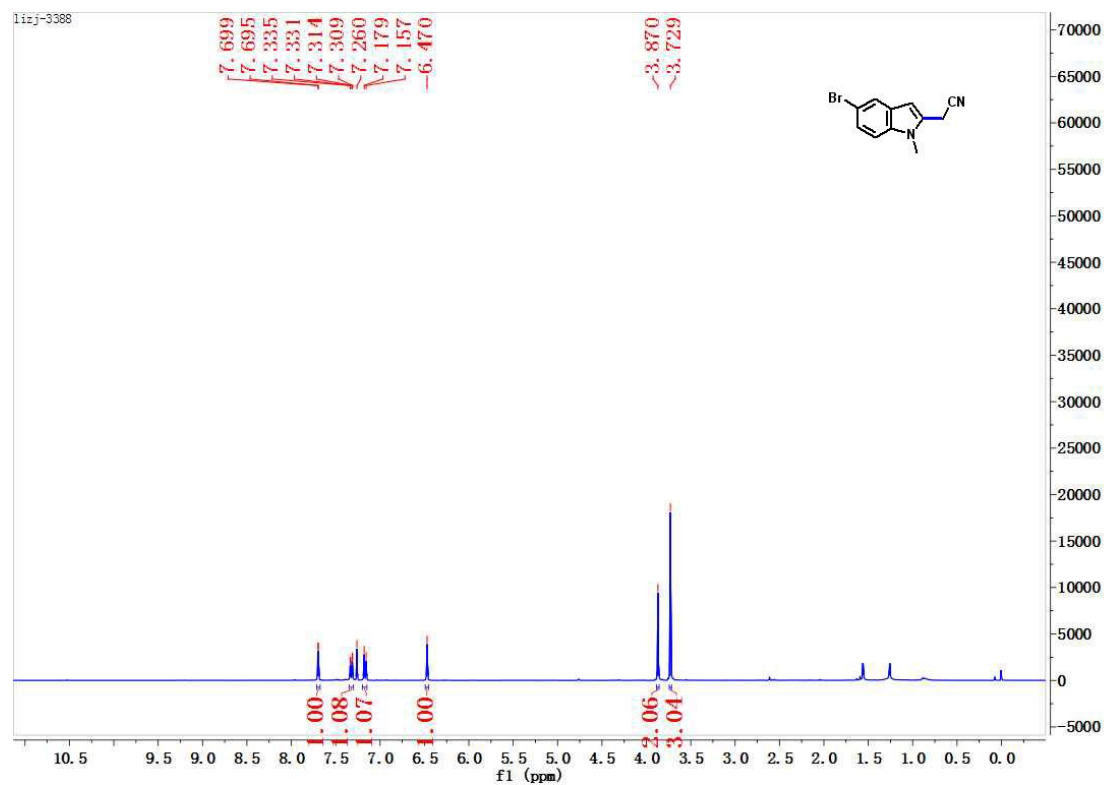
2g- ^1H NMR



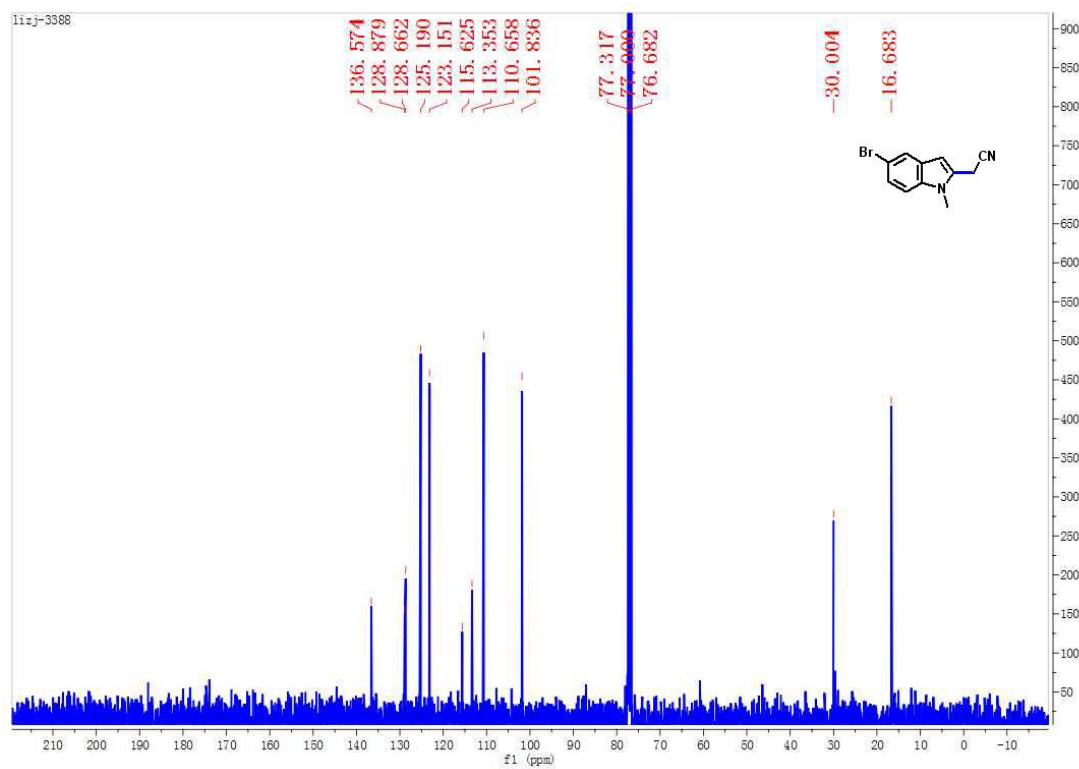
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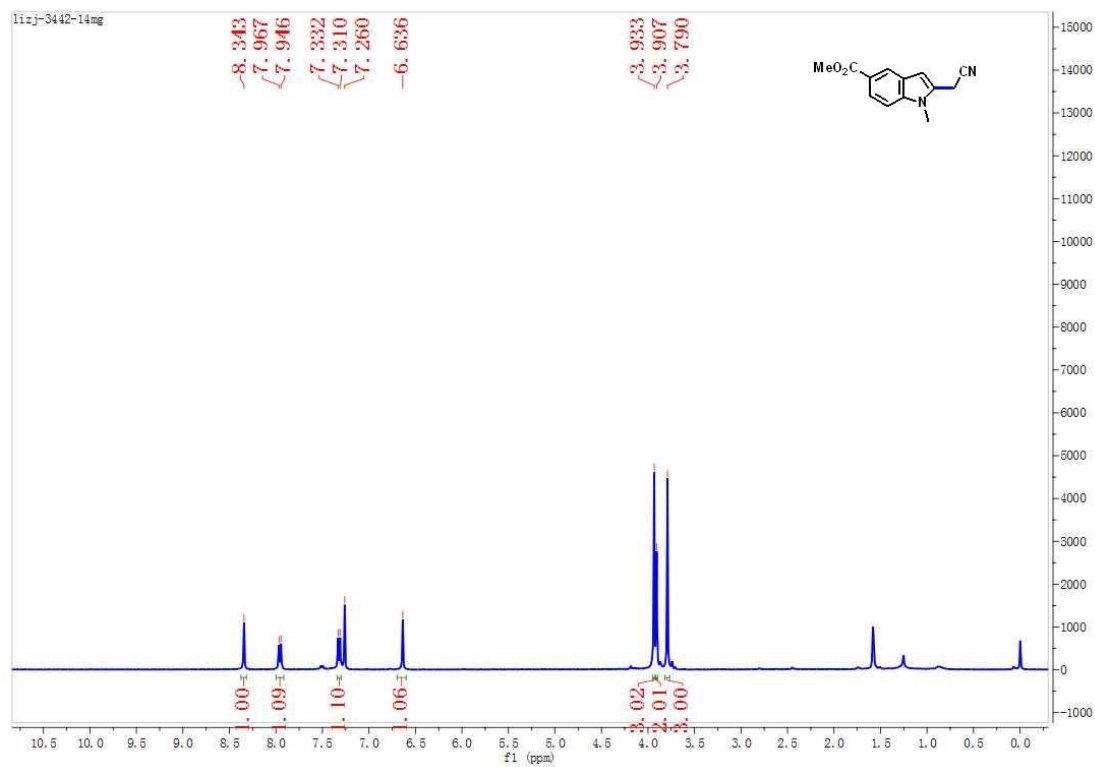
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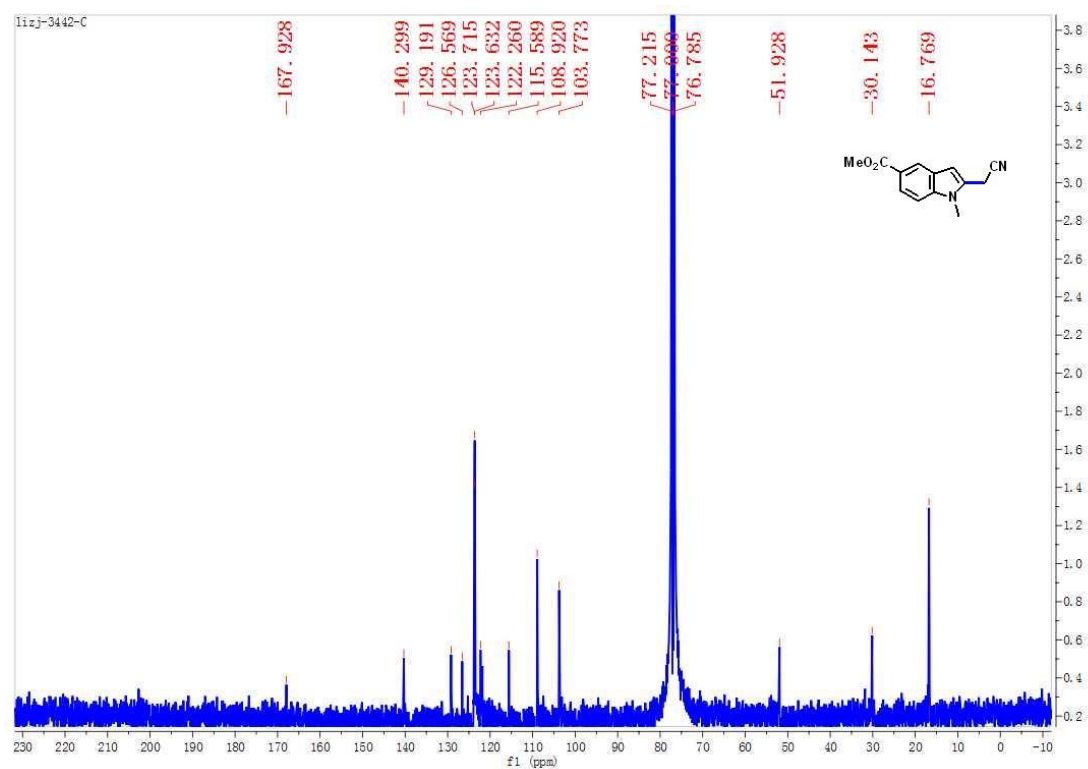
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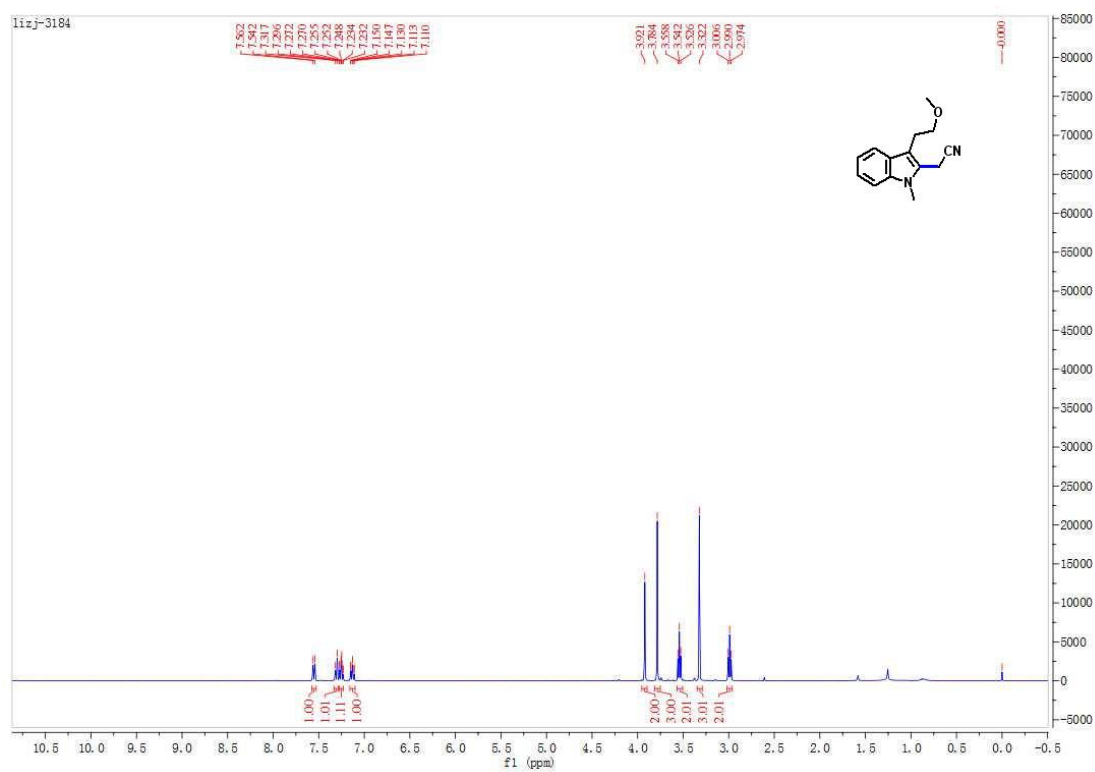
2i-¹H NMR



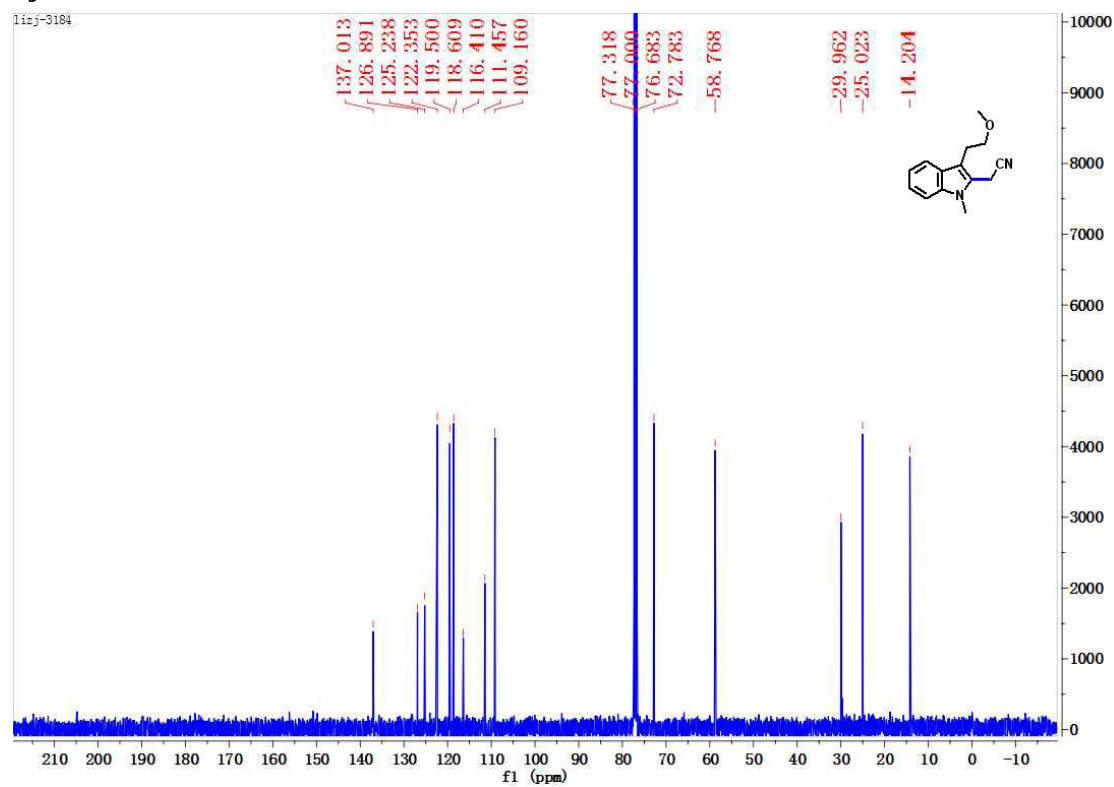
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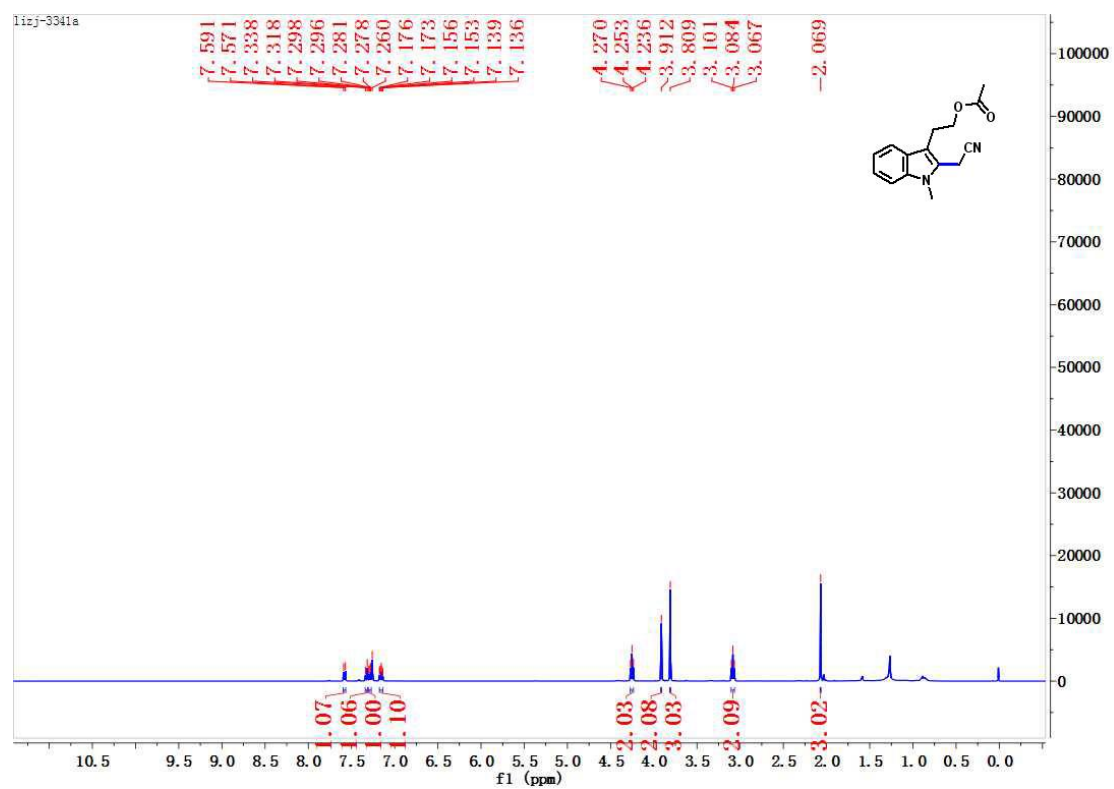
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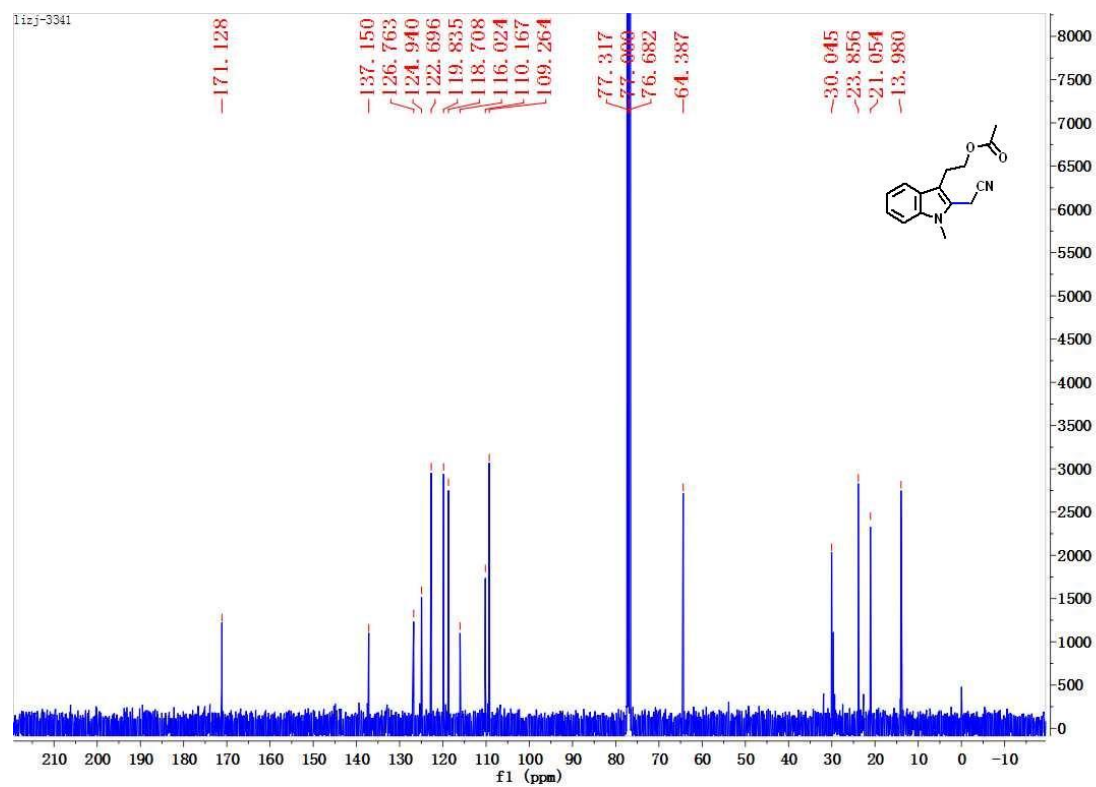
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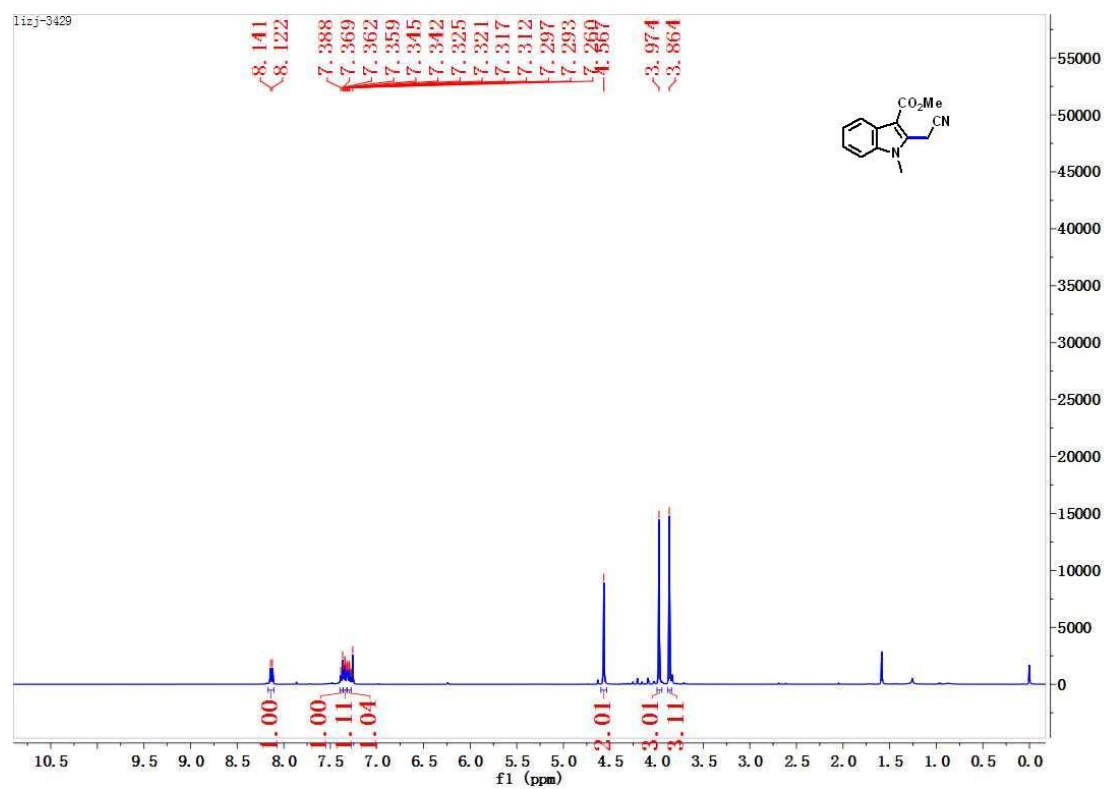
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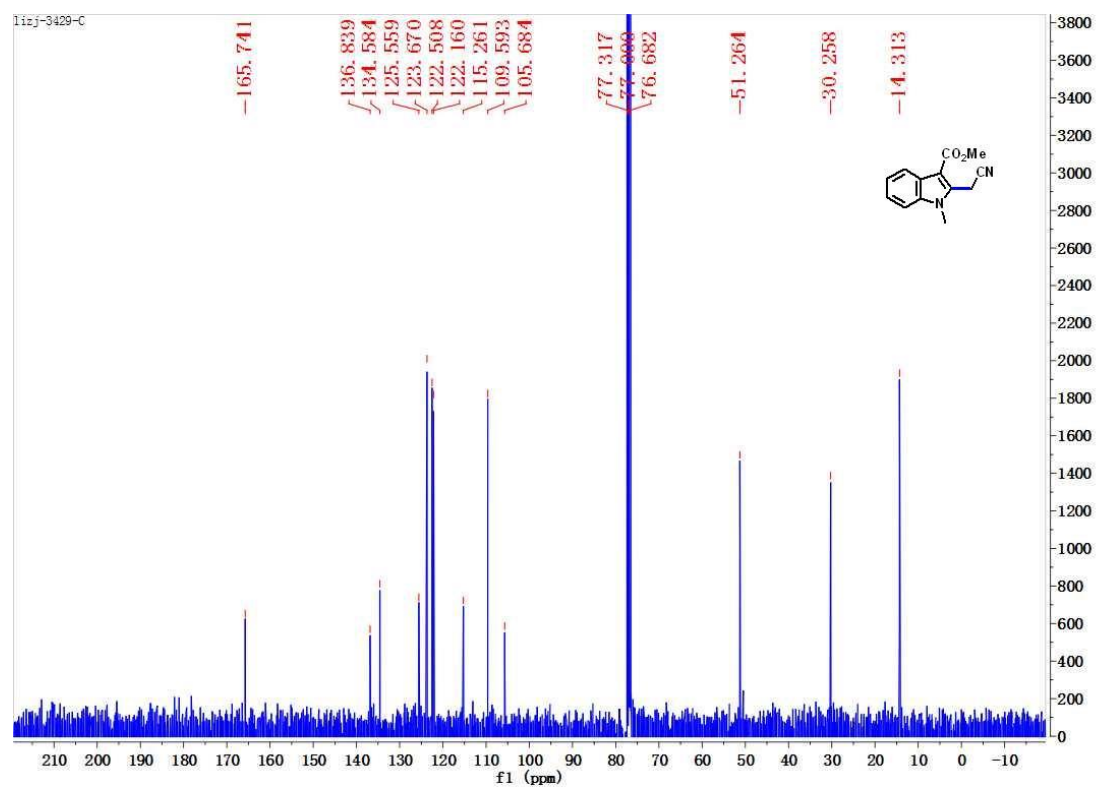
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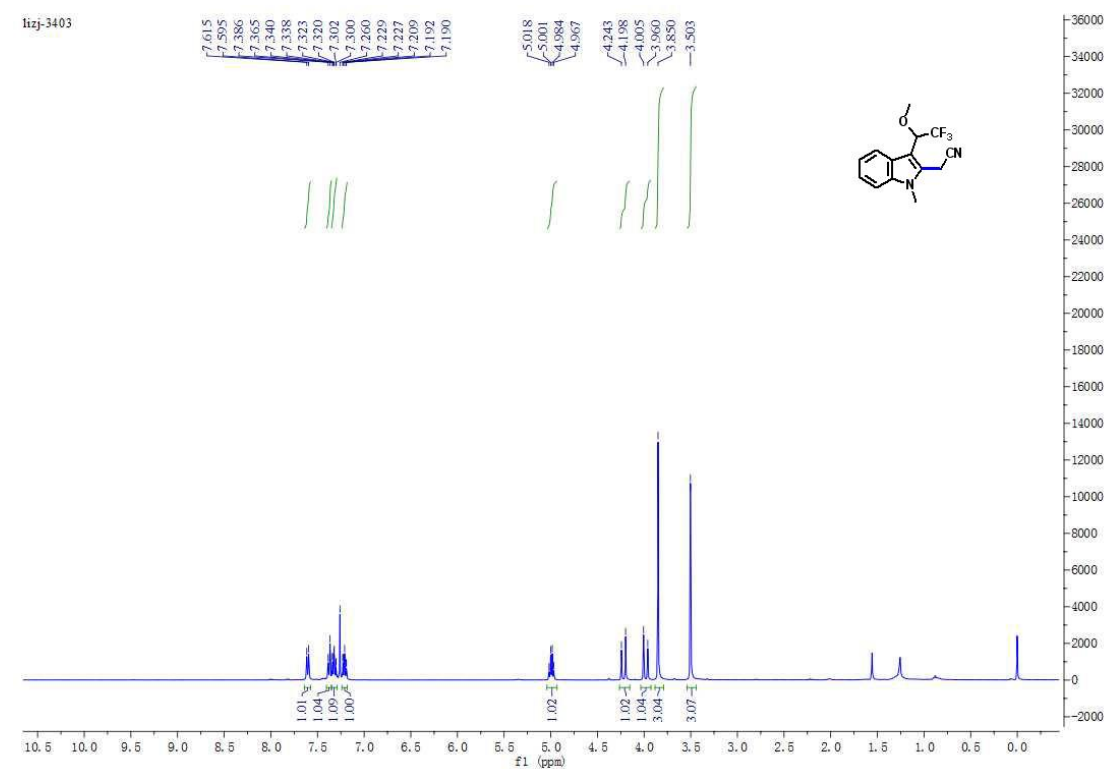
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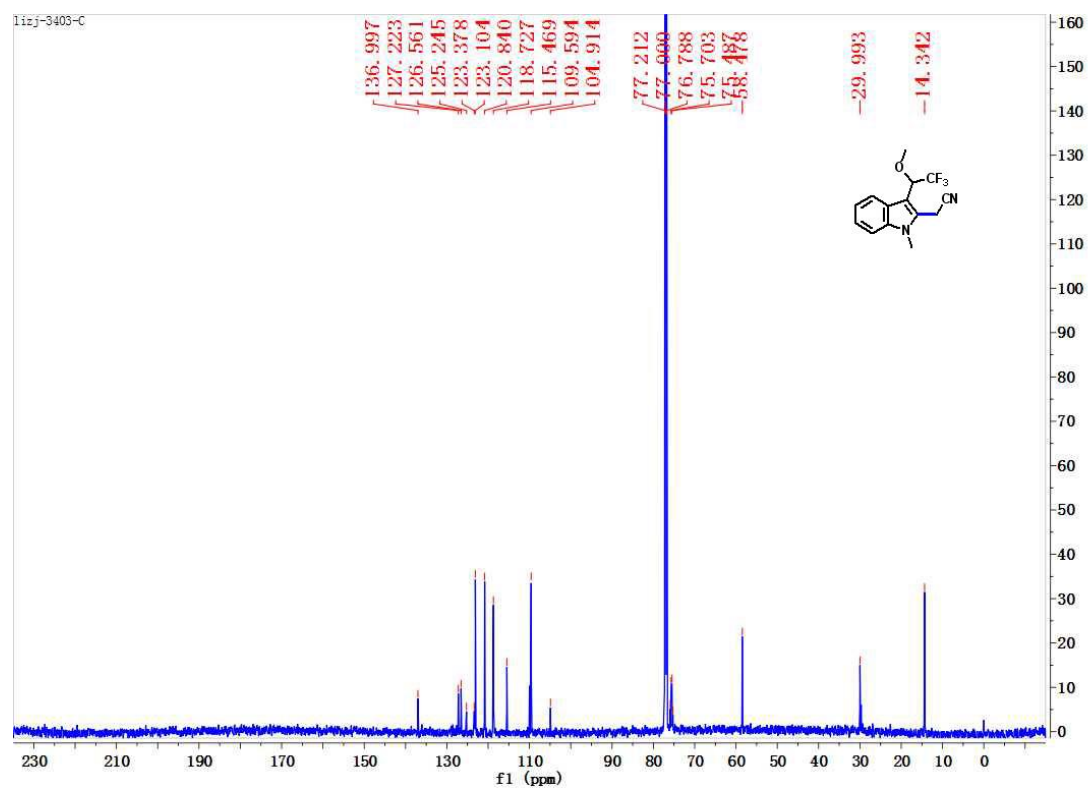
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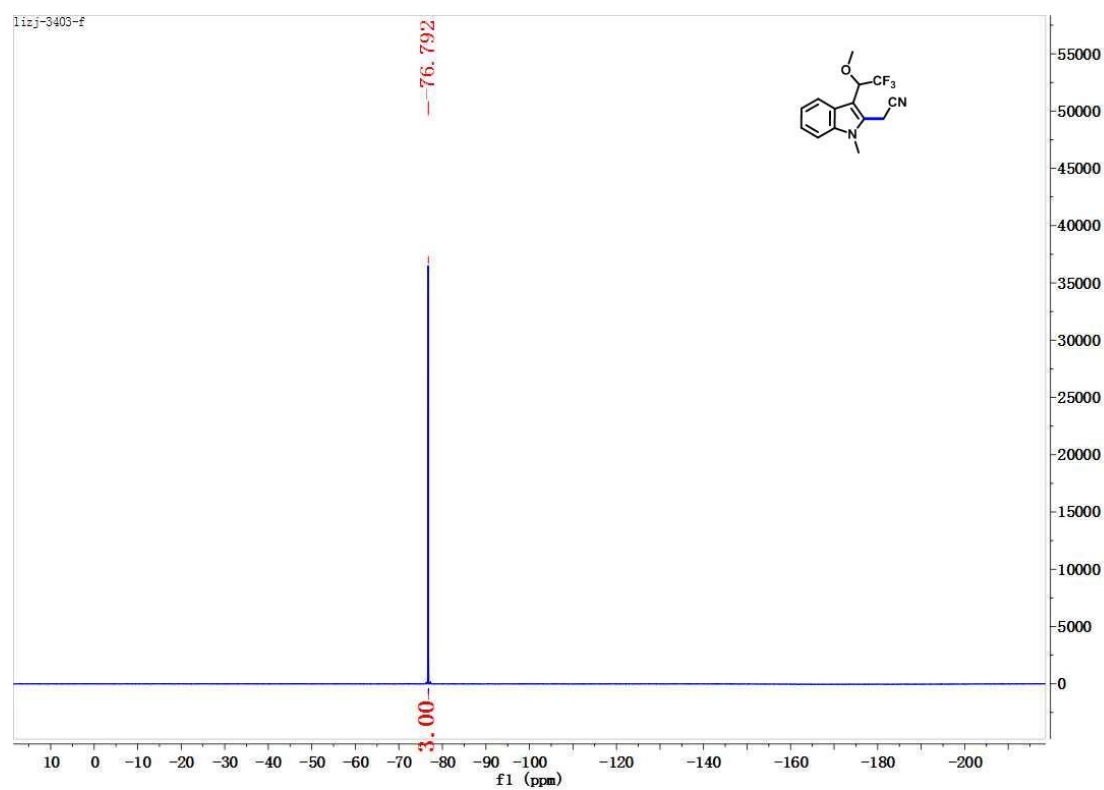
2m-¹H NMR



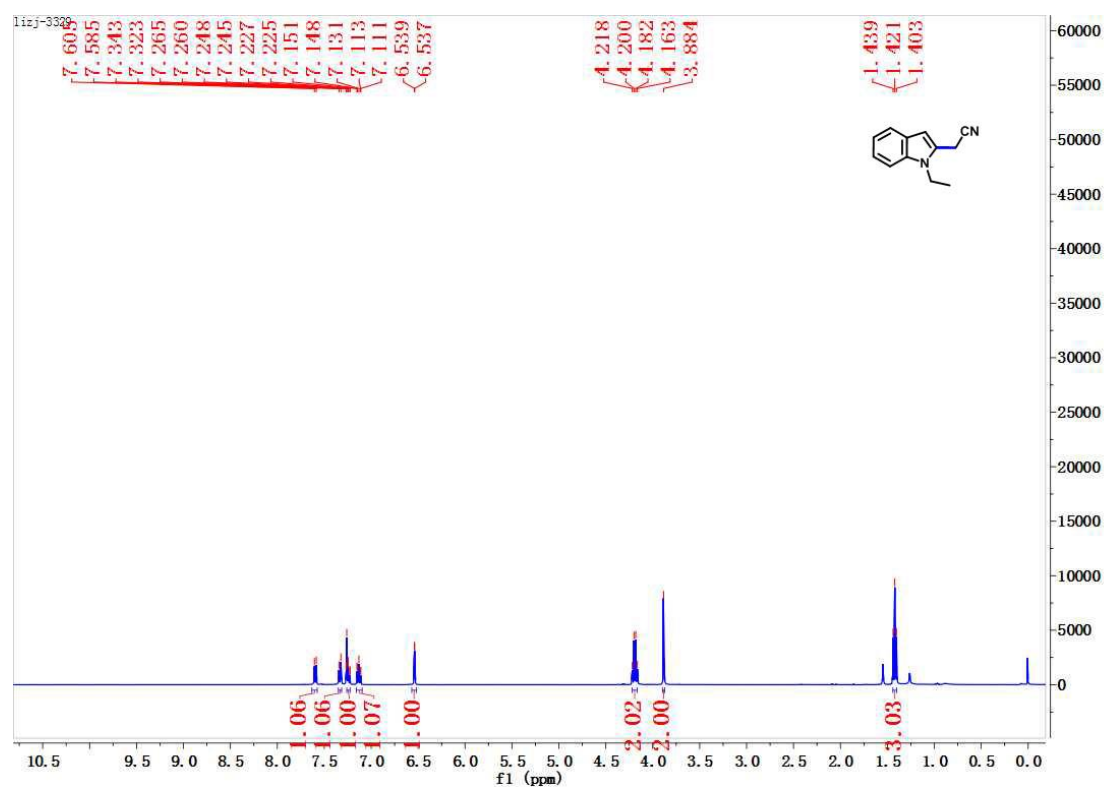
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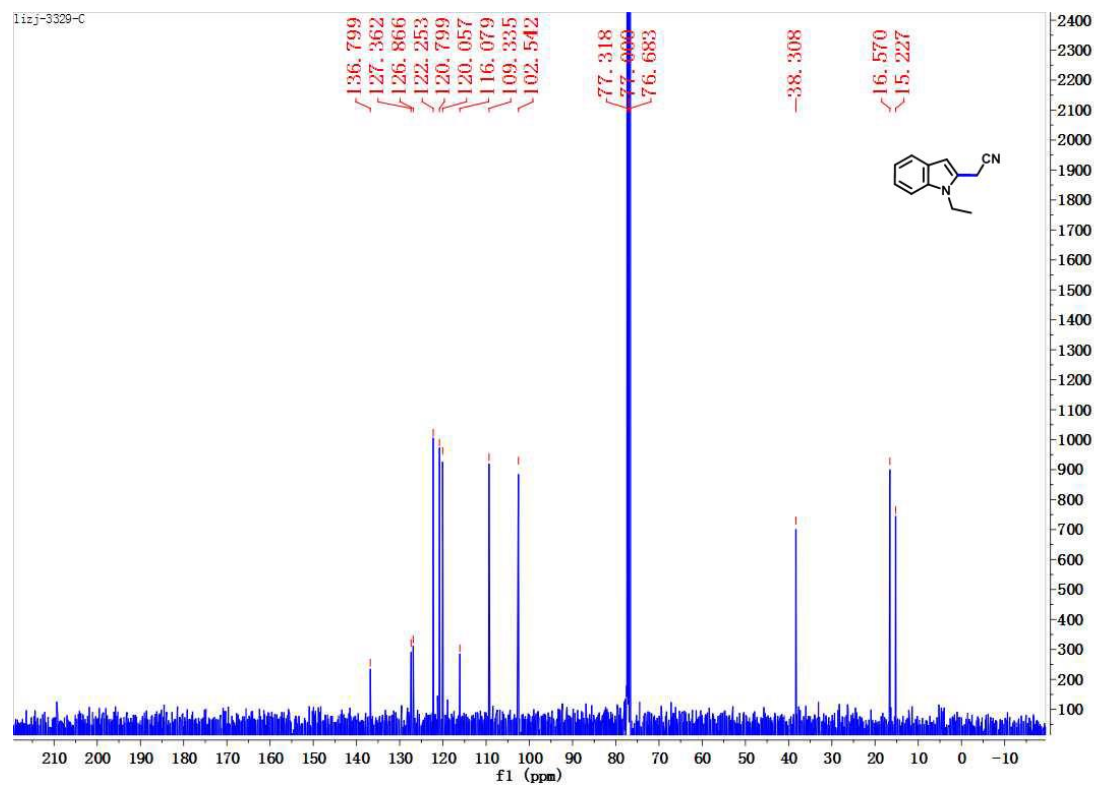
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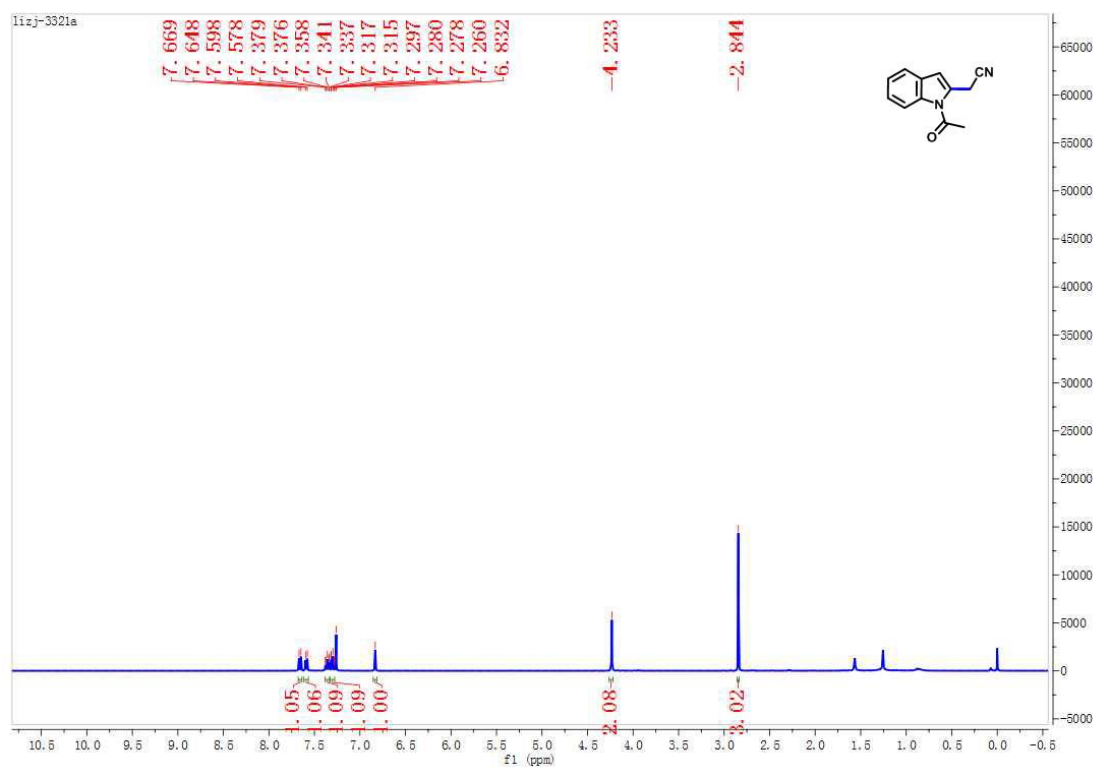
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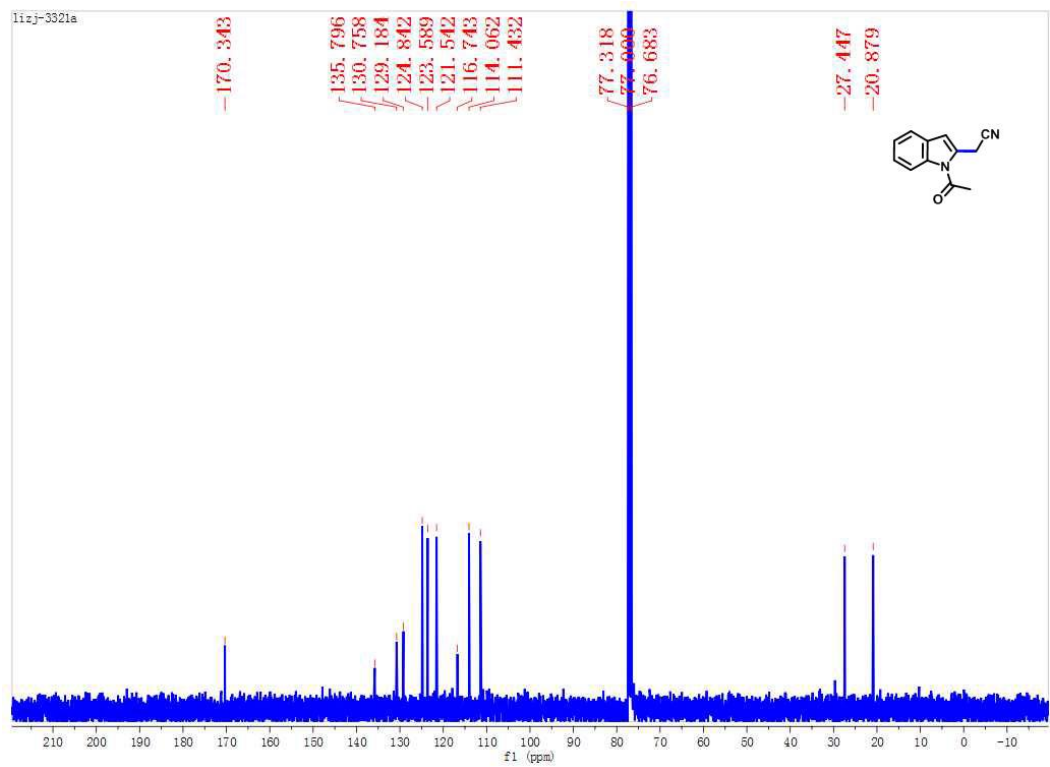
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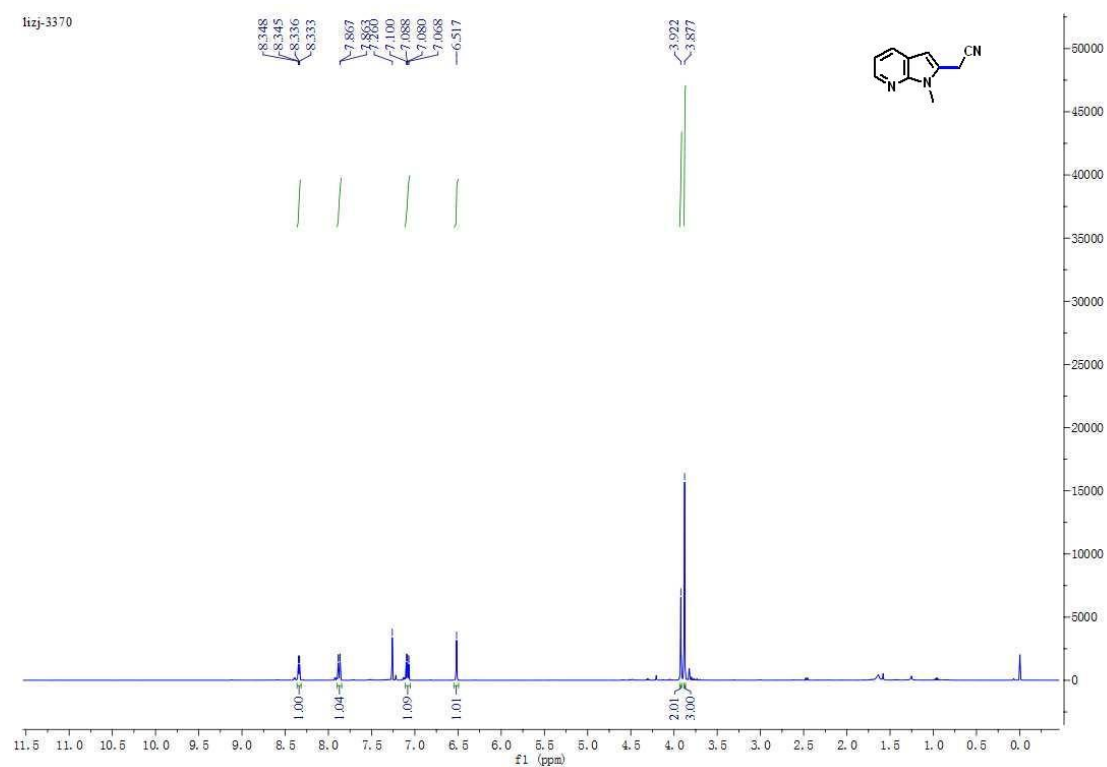
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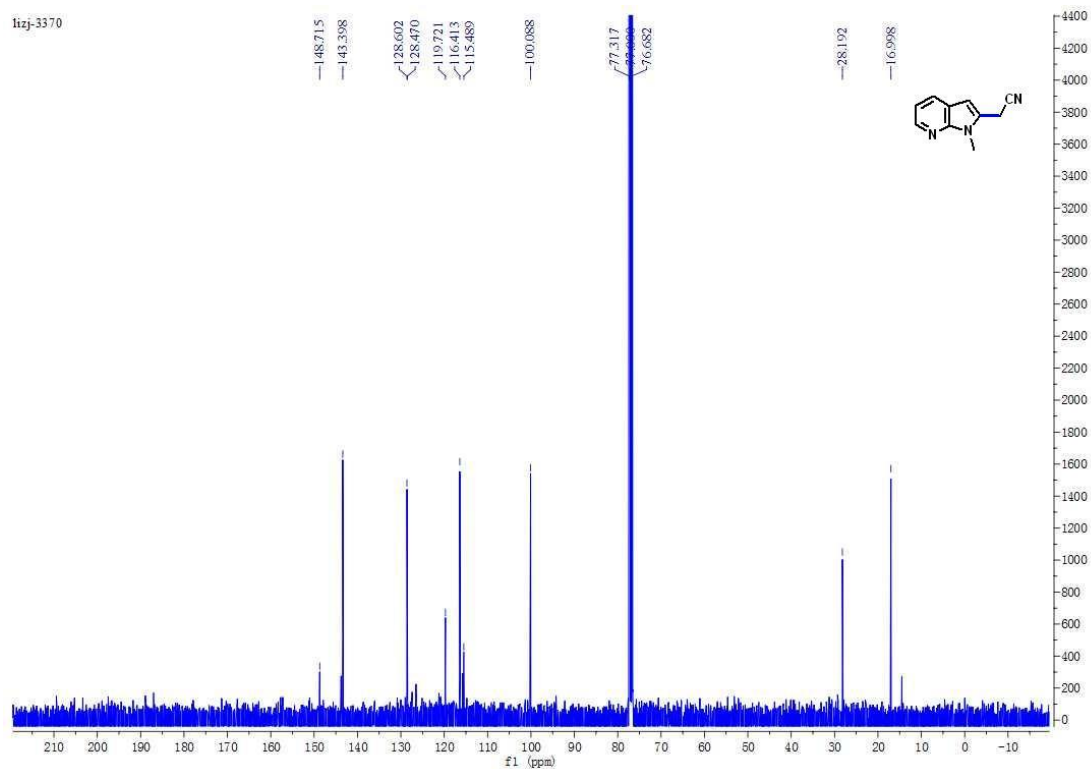
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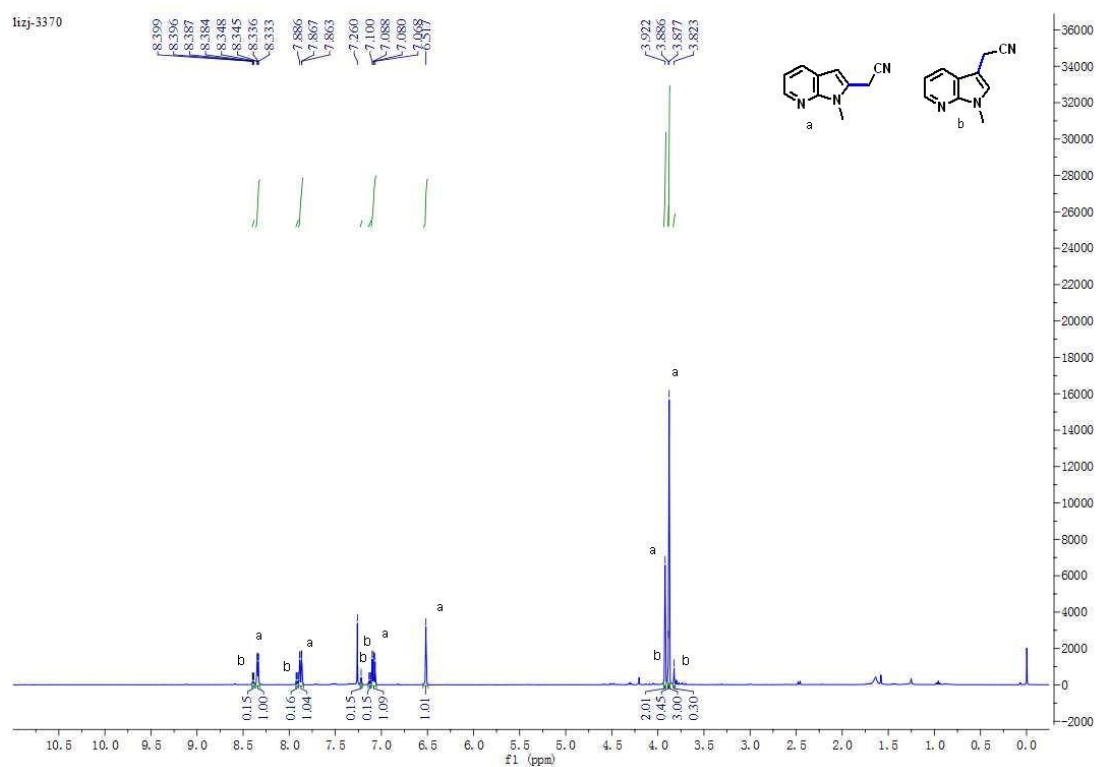
2p-¹H NMR



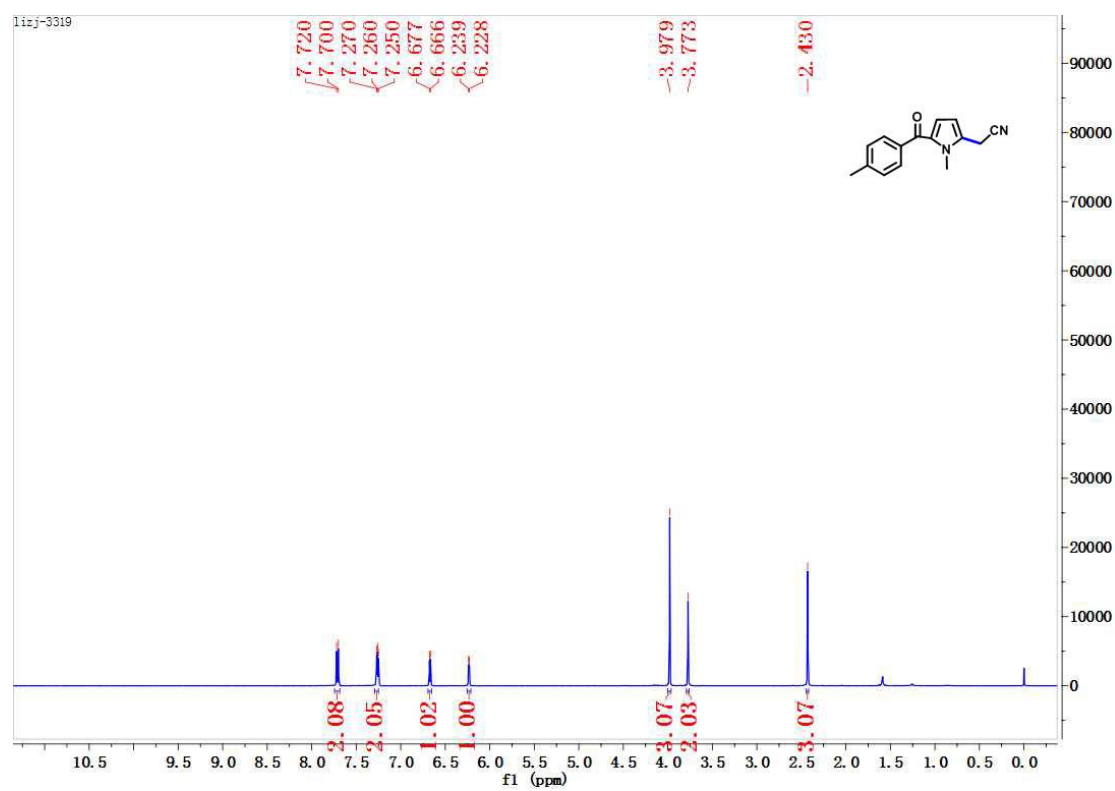
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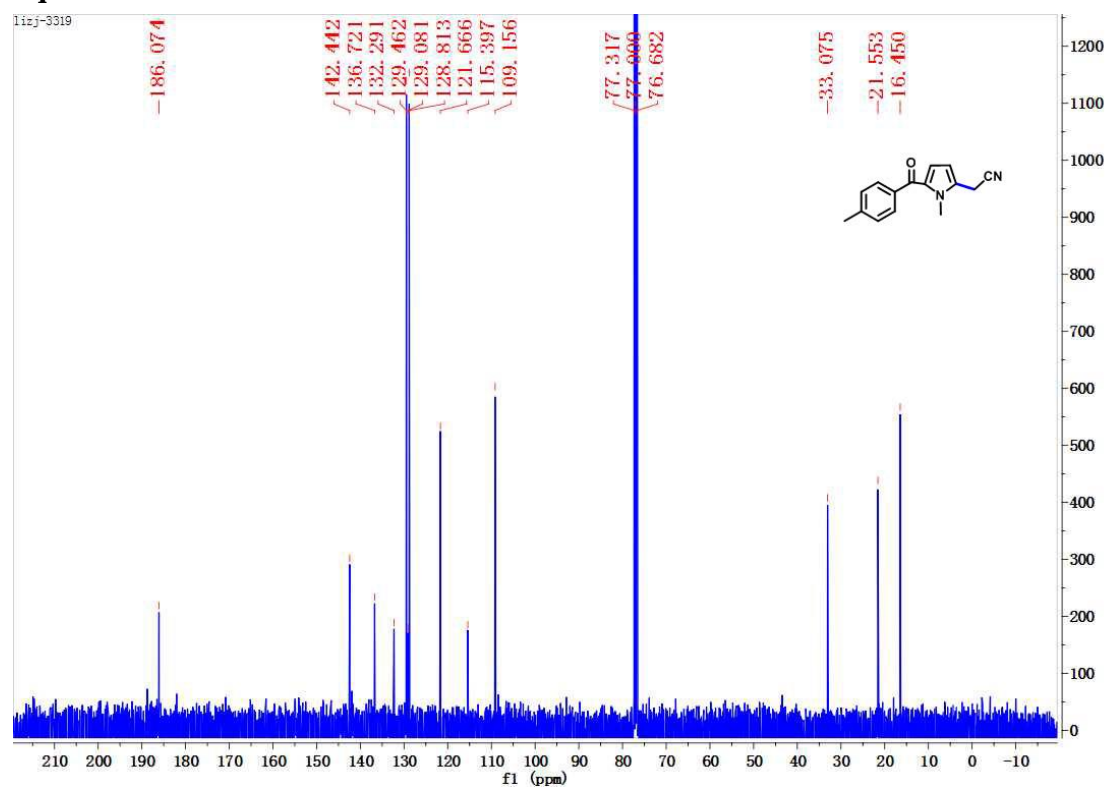
2p, 2p'-¹H NMR



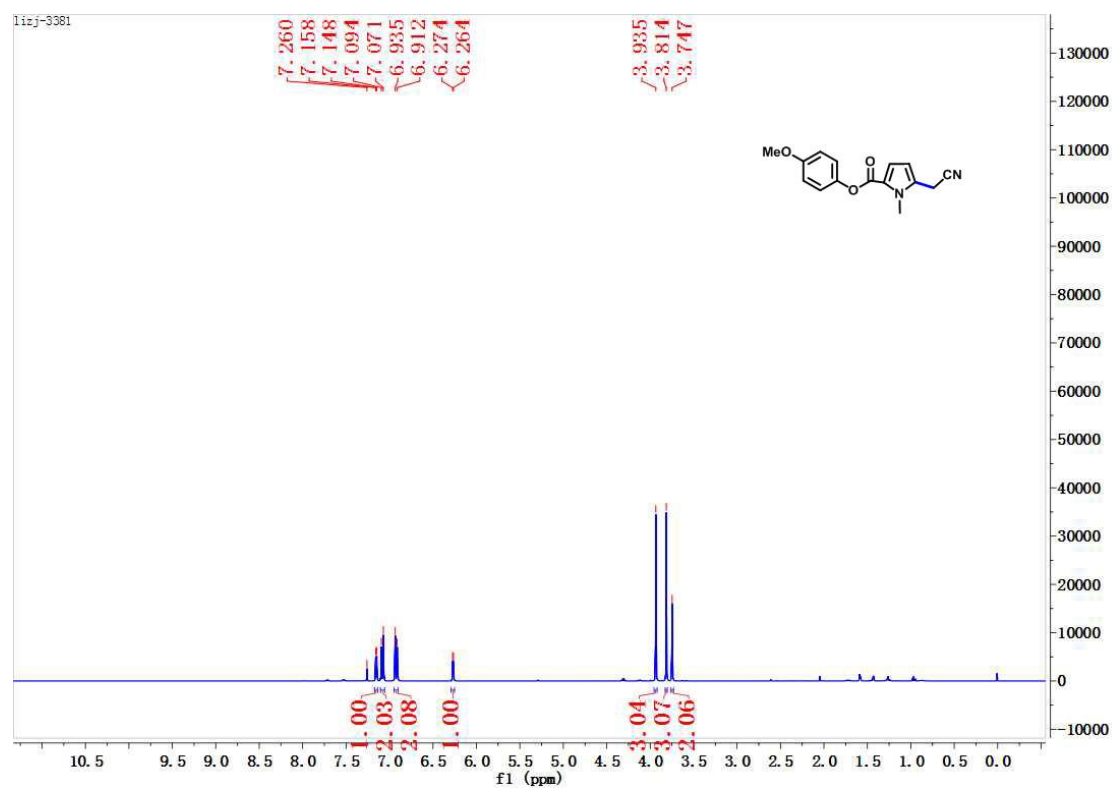
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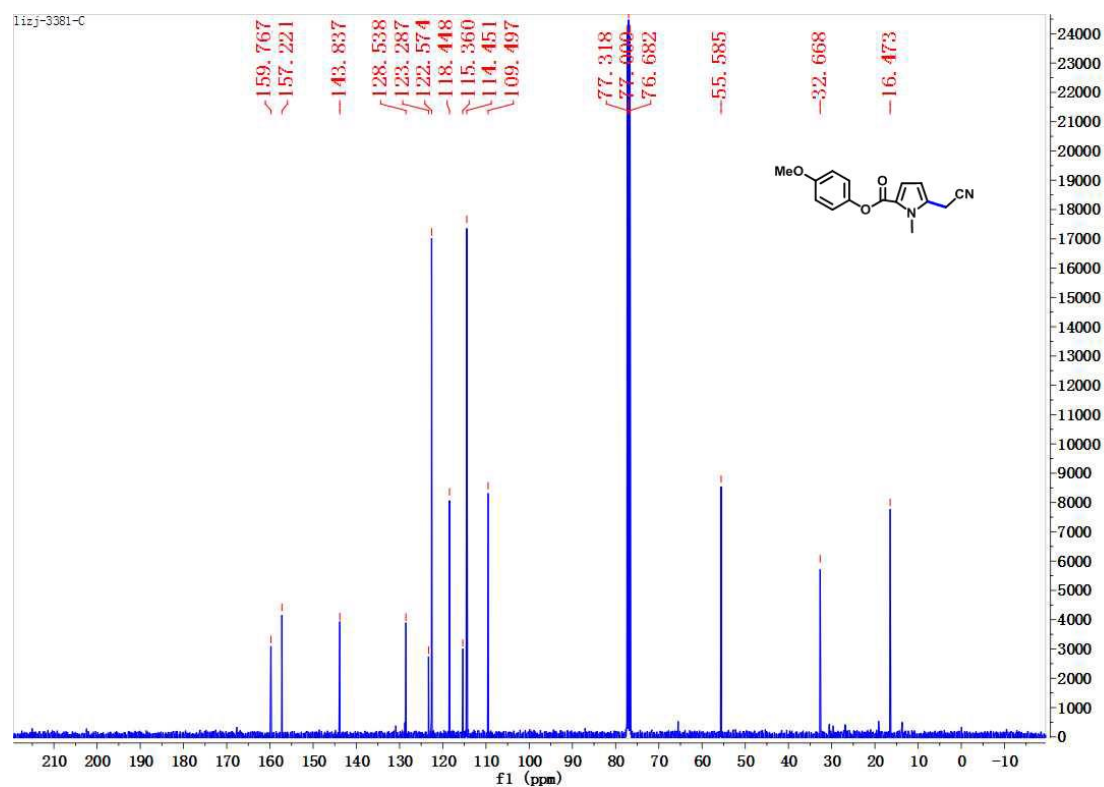
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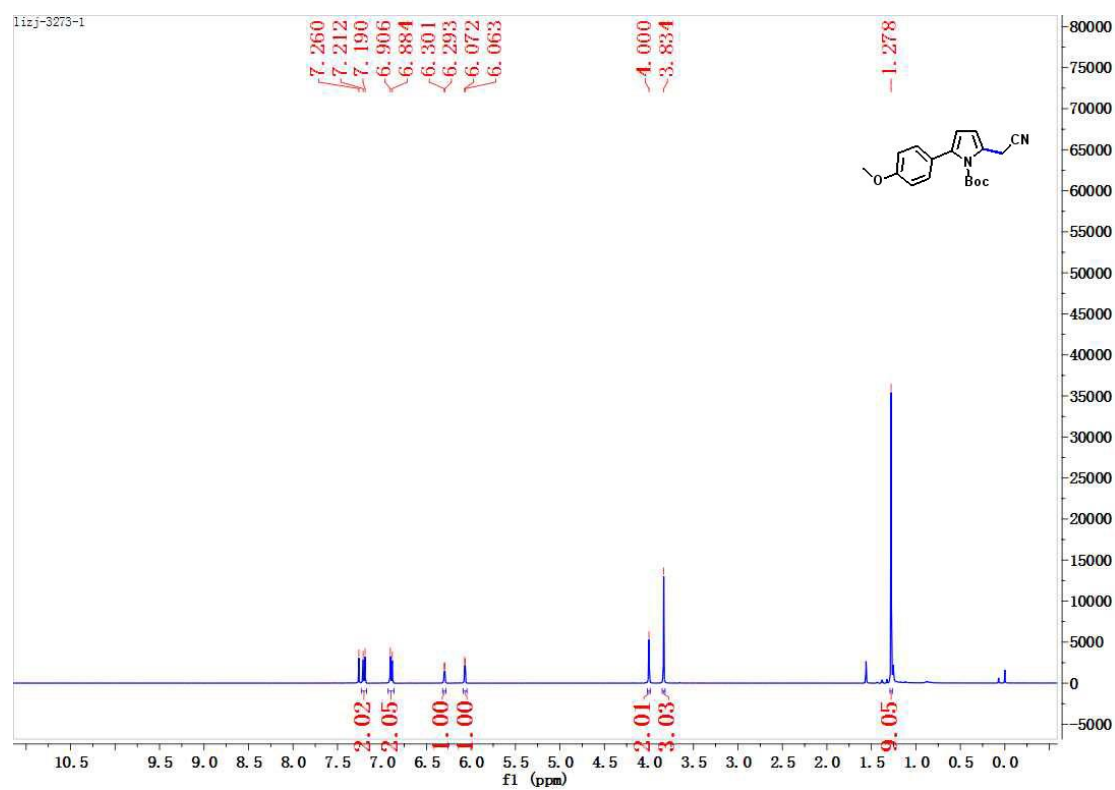
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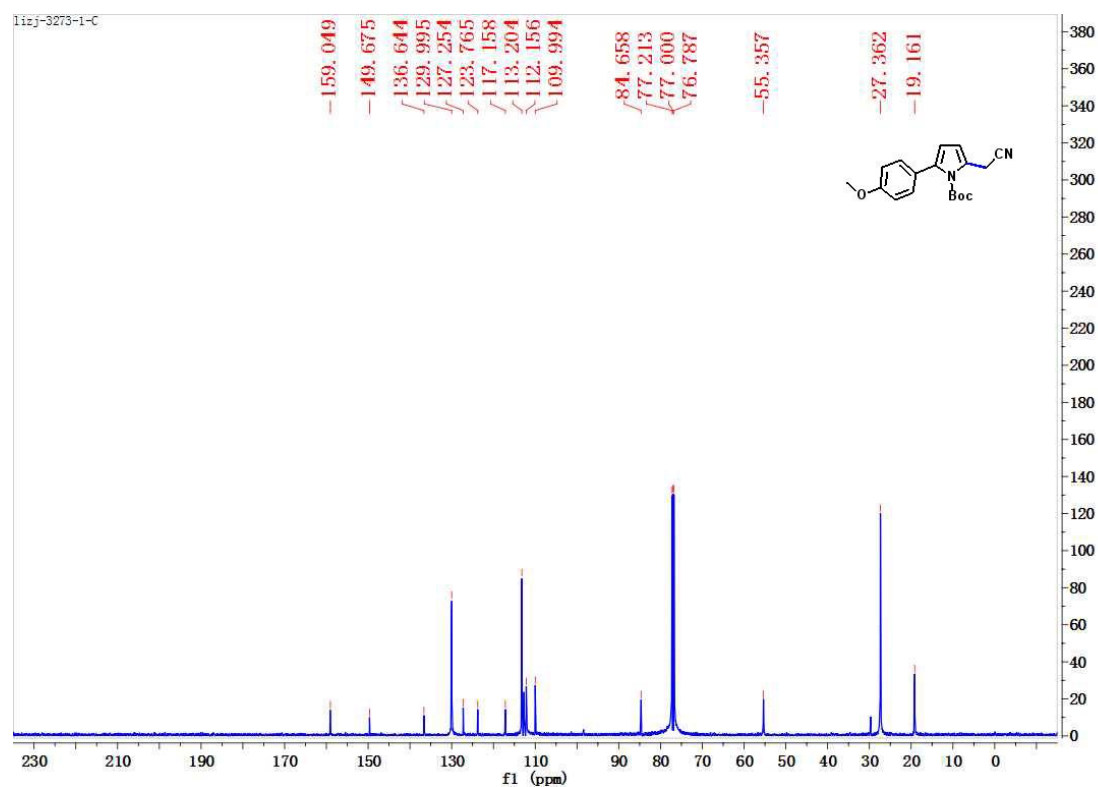
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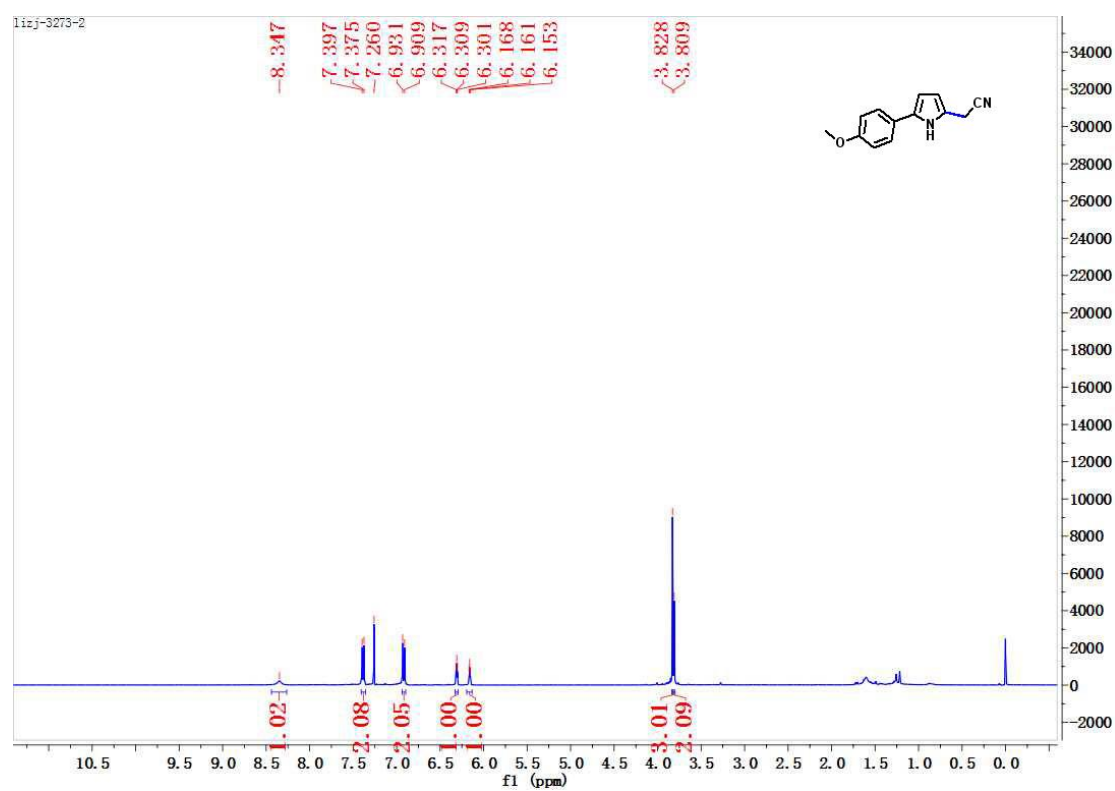
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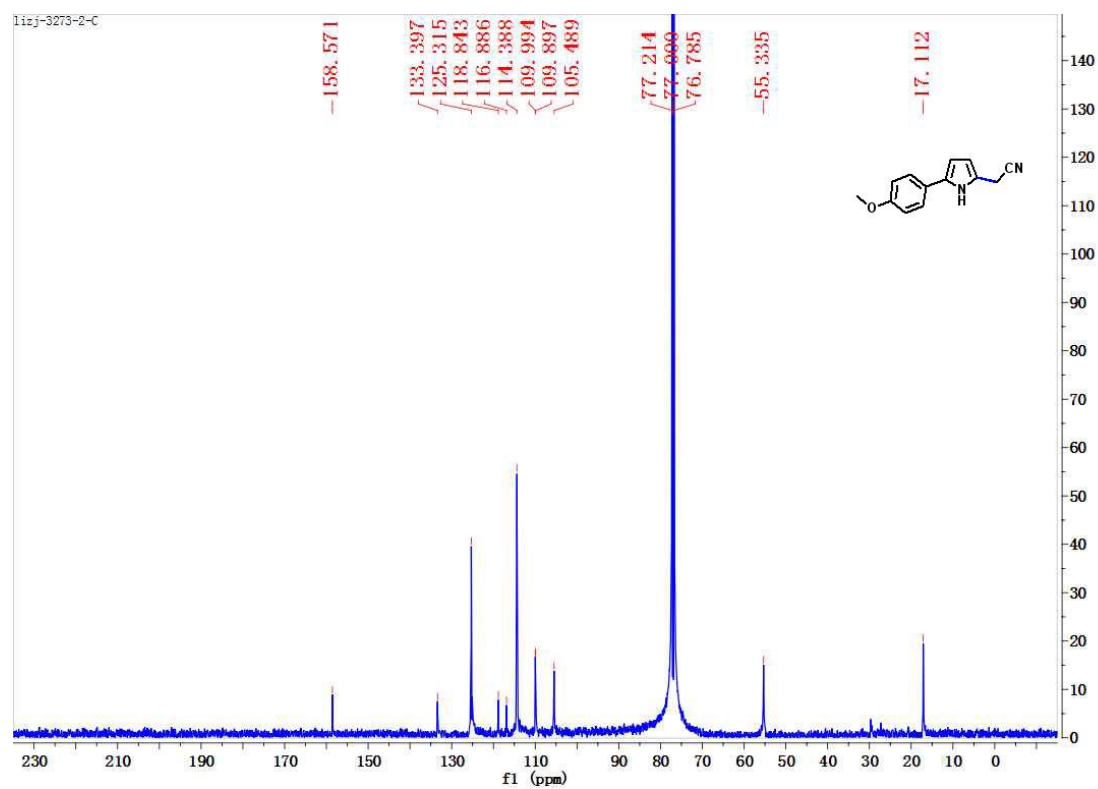
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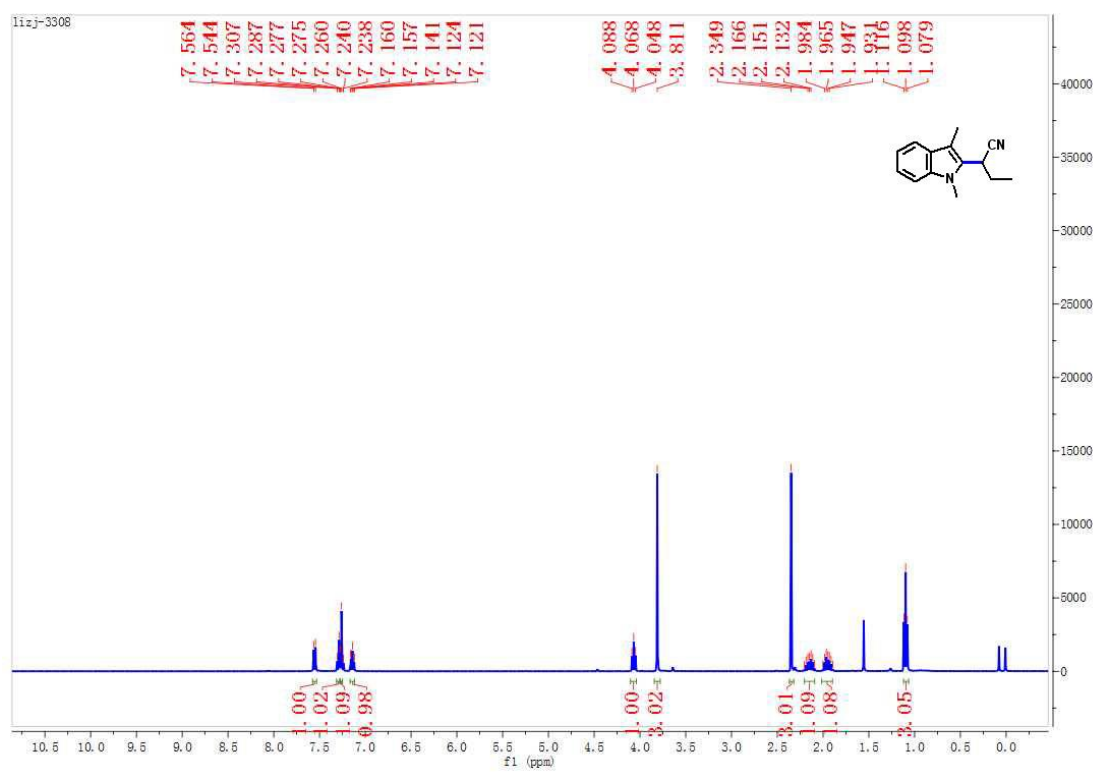
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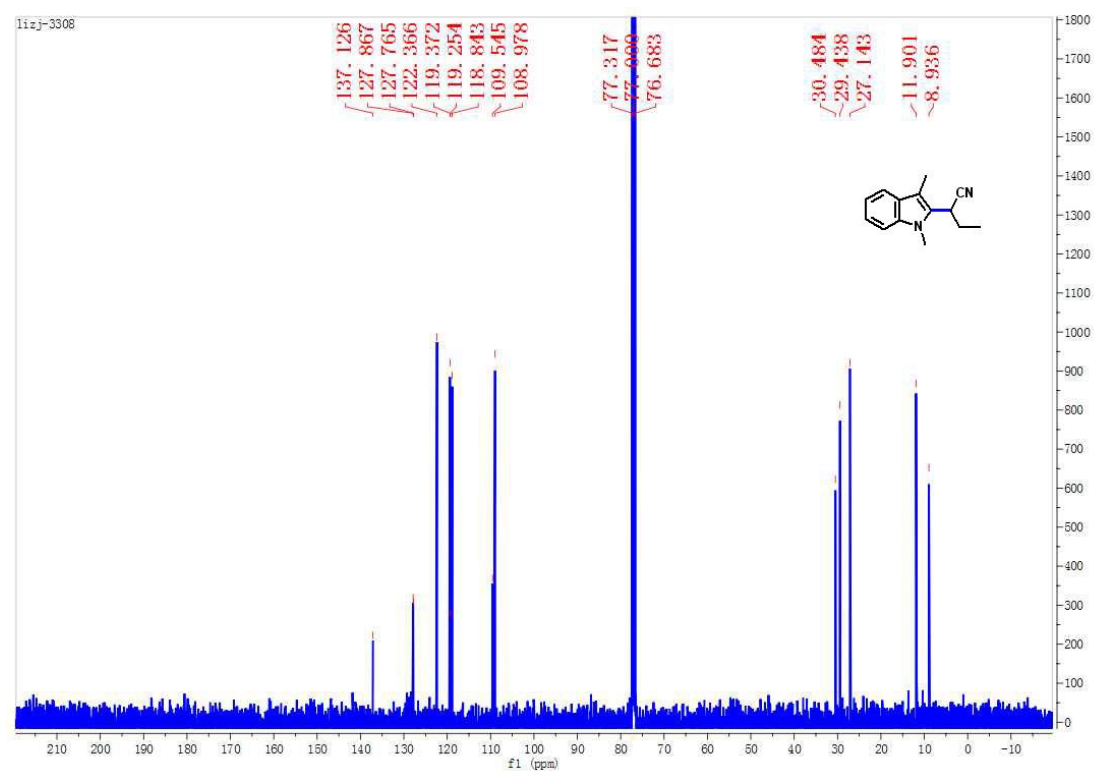
2s'-¹³C NMR



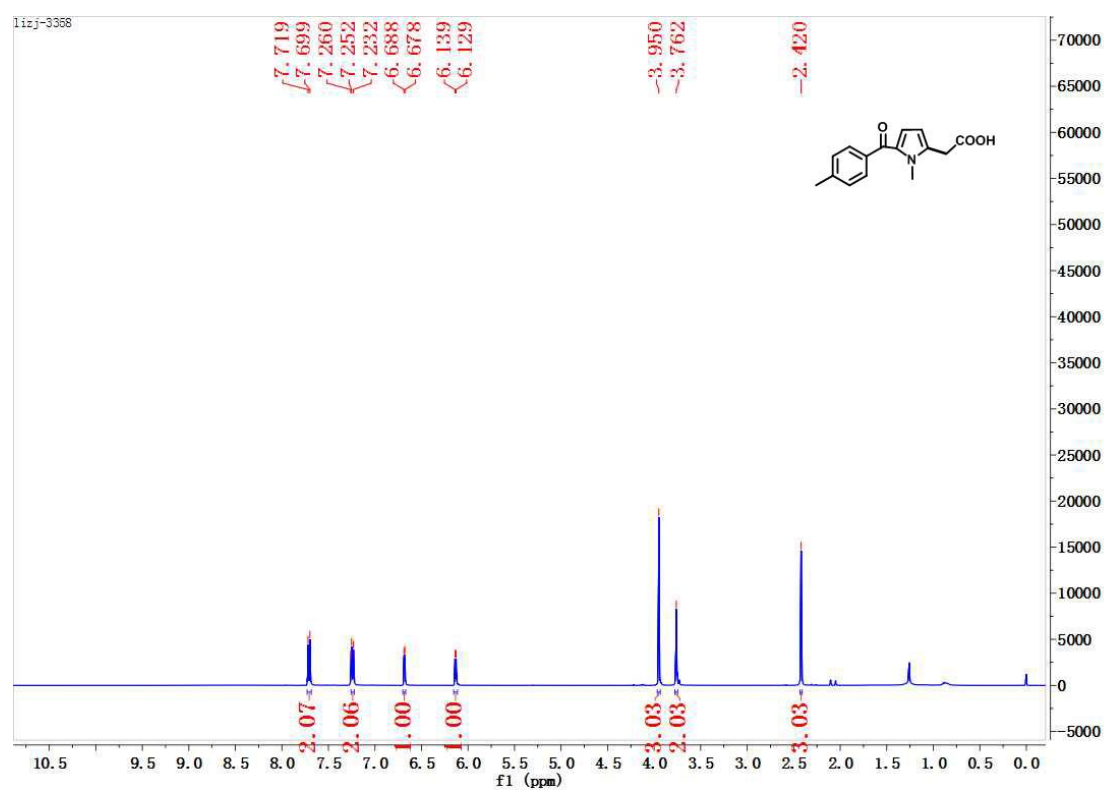
2t-¹H NMR



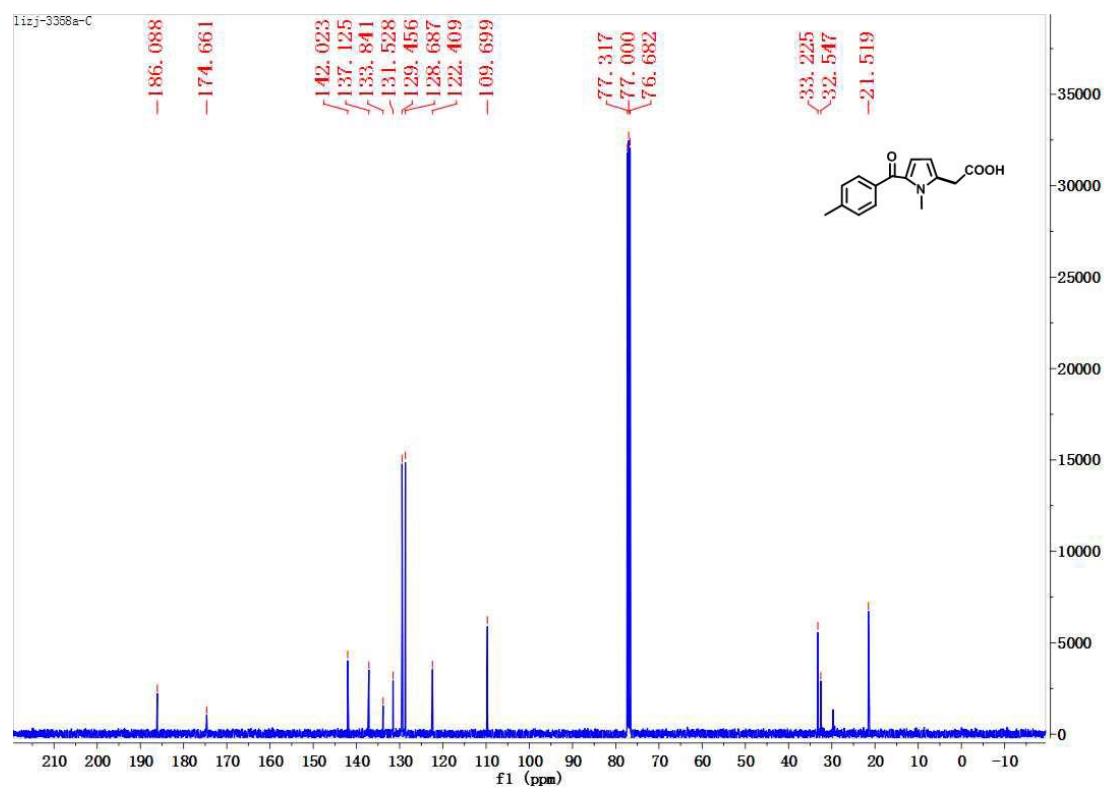
2t-¹³C NMR



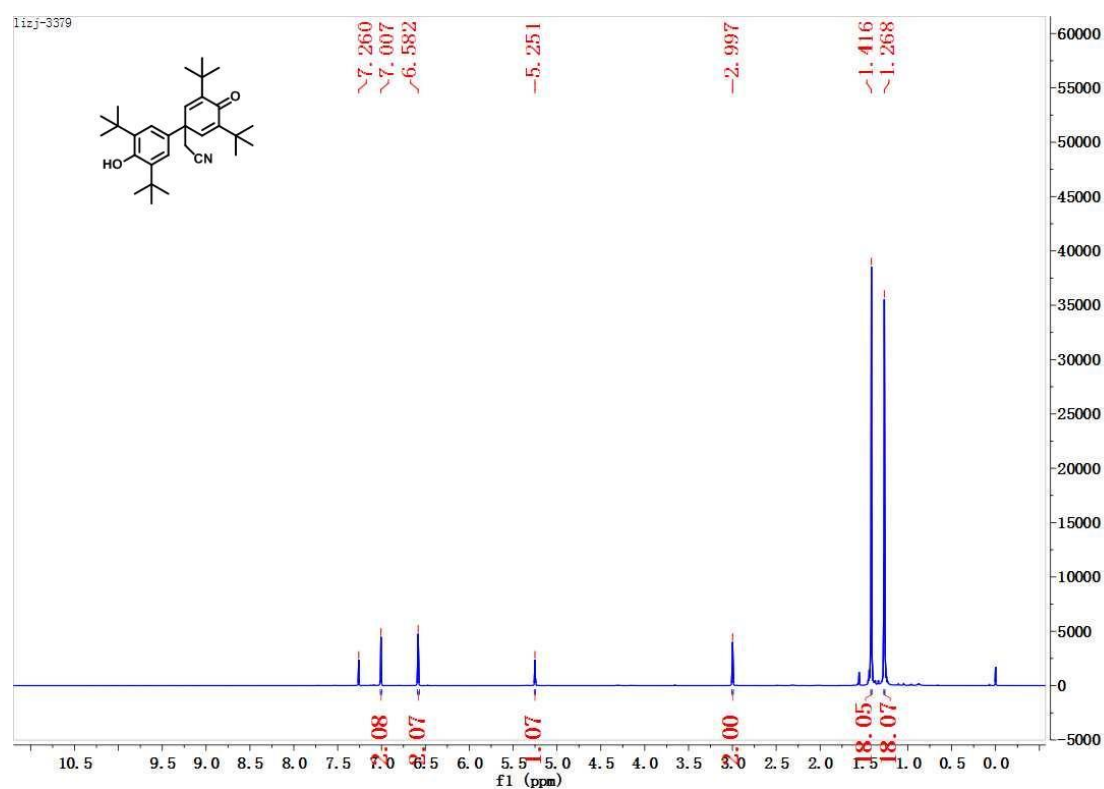
Tolmetin-¹H NMR



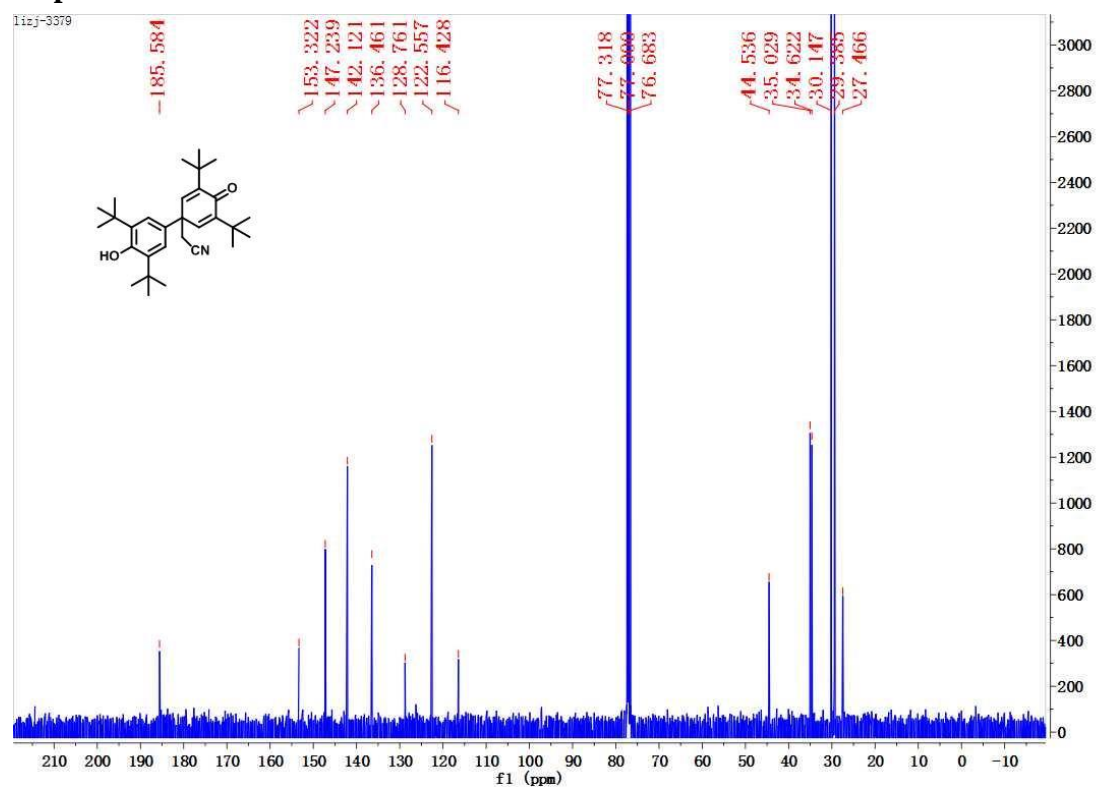
Tolmetin-¹³C NMR



trap-¹H NMR



trap-¹³C NMR



trap-¹³⁵DEPT

