Metal-Free Methylation of Pyridine *N*-Oxides C–H Bond Using Peroxides

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Supporting Information

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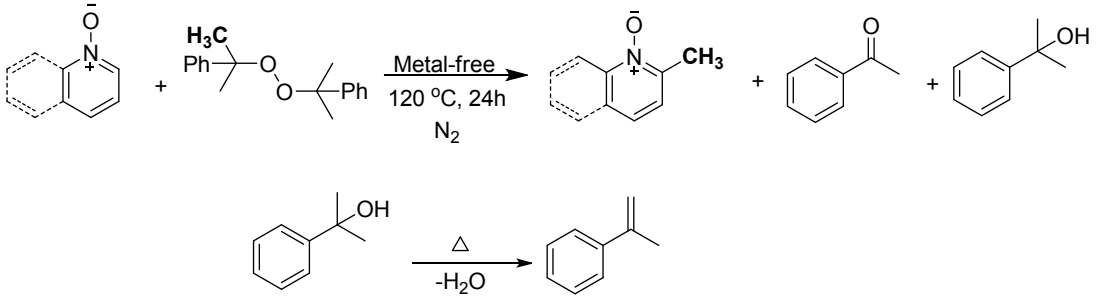
1. General Information

Unless otherwise noted, reagents and solvents were purchased and used directly without any further purification. Column chromatography were performed on silica gel 200-300 mesh. ^{1}H NMR and ^{13}C NMR spectra were registered on a Bruker Ascend^{TM} 400 spectrometer (Germany). ^{1}H NMR peaks were labeled as singlet (s), doublet (d), triplet (t), and multiplet (m). Chemical shifts were reported in units (ppm) referenced to 0.0 ppm of TMS in the ^{1}H spectrum and 77.0 ppm of $CDCl_3$ in the ^{13}C spectrum. All coupling constants were reported in Hertz (Hz). HRMS data were obtained on a Waters LCT Premierxe^{TM} (USA).

2. Preparation of Pyridine-N-Oxide Derivatives

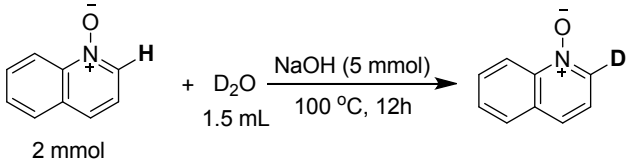
Under vigorous magnetic stirring, 3-Chloroperbenzoicacid (*m*CPBA) (345 mg, 2 mmol) in CH_2Cl_2 (5 mL) was dropped into solution of pyridine derivatives (2 mmol) in CH_2Cl_2 (5 mL) cooled to 0°C. After the completion of this course, the reaction mixture was allowed up to room temperature and stirred overnight. An aqueous solution of saturated $NaHCO_3$ was added to the mixture to neutralize residual *m*CPBA. The resulting mixture was extracted with CH_2Cl_2 (3x 10 mL). The organic phase were combined and washed with a saturated NaCl solution (3x 5 mL). The organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to give crude product, which was purified by column chromatography (silica gel 200-300 mesh, EtOAc: methanol (8:1) as eluent). The product was identified by ^{1}H-NMR and MS spectra and compared to the previous literature.

3. Methylation of Pyridine-*N*-Oxide Using peroxides



Pyridine-*N*-oxide (0.5 mmol), DCP (1 mmol, 2 equiv.) were charged into a 30-mL pressure tube sealed with rubber plugs. The reaction mixture was stirred at 120 °C for 24 h under nitrogen atmosphere. After the starting material was completely consumed (based on thin layer chromatography (TLC) monitoring, EtOAc: methanol as eluent), the reaction was cooled down to room temperature. The mixture was purified by column chromatography on silica gel(200-300 mesh) to afford desired products.

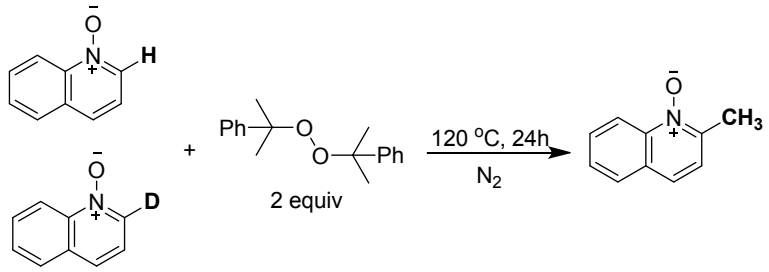
4. Preparation of 2-d_1-Quinoline-*N*-Oxide.



D_2O (1.5 mL), NaOH (200 mg, 5 mmol), quinoline-*N*-oxide (258 mg, 2.0 mmol) were weighed into 30-mL pressure tube sealed with rubber plugs. The reaction mixture was stirred at 100 ℃ for overnight. After cooling to room temperature, the mixture was then extracted with Chloroform (3 x 10 mL). The combined organic

phases were washed with saturated NaCl solution (3 x 5 mL), dried over MgSO4, and filtered. Chloroform was removed under reduced pressure to obtain the product. Deuterium incorporation was detected to be 91% by ^{1}H NMR in $CDCl_3$. Peak areas at 8.76 ppm and 8.53 ppm were compared to obtain the deuterium incorporation (see ^{1}H spectrum). Spectral data were consistent with related reports[1].

5. KIE Experiment



2-d1-quinoline-*N*-oxide and quinoline-*N*-oxide (1:1) (totally 0.5 mmol), DCP (1 mmol, 2 equiv) were added into pressure tube sealed with rubber plugs. The reaction mixture was stirred at 120 °C for 3 h under nitrogen atmosphere. After cooling to room temperature, residual starting material (mixture of 2-d_1-quinoline-*N*-oxide and quinoline-*N*-oxide) was recovered by column chromatography on silica gel (200-300 mesh), which was characterized by 1H NMR spectroscopy. Peak areas at 8.76 ppm and 8.53 ppm were compared to give nearly 1:1 ratio of 2-d_1-quinoline-*N*-oxide to quinoline-*N*-oxide in residual material[2].

6. References

[1] Sylvester, K. T.; Wu, K.; Doyle, A. G.; *J. Am. Chem. Soc.*, **2012**, *134*, 16967-16970.

[2] G. Li, C. Q. Jia, K. Sun, *Org. Lett.* **2013**, *15*, 5198-5201.

7. Data and Spectra of ^{1}H NMR and ^{13}C NMR

2-methylpyridine 1-oxide (3a)

3a was obtained as yellow oil**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.0 Hz, 1H), 7.31–7.23 (m, 1H), 7.17 (2H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.15, 139.42, 126.55, 125.67, 123.57, 17.81. HRMS (ESI) Calcd. For C_6H_8NO: $[M+H]^+$, 110.0606, Found: *m/z*. 110.0598

2,6-dimethylpyridine 1-oxide (4a)

4a was obtained as yellow oil**.**^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.3 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 2.53 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 149.07, 124.74, 123.96, 18.27. HRMS (ESI) Calcd. For $C_7H_{10}NO$: $[M+H]^+$, 124.0762, Found: *m/z*.

124.0758

2,4-dimethylpyridine 1-oxide (3b)

3b was obtained as yellow oil (27mg, 45%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.5 Hz, 1H), 7.08 (s, 1H), 6.96 (d, *J* = 5.9 Hz, 1H), 2.50 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.24, 138.69, 137.31, 127.17, 124.33, 77.40, 77.08, 76.76, 20.20, 17.71. HRMS (ESI) Calcd. For $C_7H_{10}NO$: $[M+H]^+$, 124.0762, Found: *m/z*. 124.0760

2,4,6-trimethylpyridine 1-oxide (4b)

4b was obtained as yellow oil (21mg, 31%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (s, 2H), 2.50 (s, 6H), 2.28 (s,3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 148.20, 124.75, 77.34, 77.03, 76.71, 20.19, 18.18.HRMS (ESI) Calcd. For $C_8H_{12}NO$: $[M+H]^+$, 138.0919, Found: *m/z*. 138.0909

4-methoxy-2-methylpyridine 1-oxide (3c)

3c was obtained as yellow oil (32mg, 47%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.2 Hz, 1H), 6.80 (s, 1H), 6.73 (m, 1H), 3.86 (s, 3H), 2.53 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.96, 150.02, 140.16, 111.63, 109.90, 55.97, 18.33.HRMS (ESI) Calcd. For $C_7H_{10}NO_2$: $[M+H]^+$, 140.0712, Found: *m/z*. 140.0704

4-methoxy-2,6-dimethylpyridine 1-oxide (4c)

4c was obtained as yellow oil (21mg, 28%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 2H), 3.82 (s, 3H), 2.53 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.72, 149.91, 109.73, 55.71, 18.77. HRMS (ESI) Calcd. For $C_8H_{12}NO_2$: $[M+H]^+$, 154.0868, Found: *m/z*. 154.0864

2-methyl-4-nitropyridine 1-oxide (3d)

3d was obtained as pale yellow solid (34mg, 44%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.1 Hz, 1H), 8.12 (d, *J* = 3.0 Hz, 1H), 7.97 (dd, *J* = 7.1, 3.1 Hz, 1H), 2.53 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 150.59, 141.68, 140.05, 120.66, 118.10, 18.01. HRMS (ESI) Calcd. For $C_6H_7N_2O_3$: $[M+H]^+$, 155.0457, Found: *m/z*. 155.0461

2,6-dimethyl-4-nitropyridine 1-oxide (4d)

4d was obtained as pale yellow solid (29mg, 35%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 2H), 2.52 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.33, 140.73, 117.92,

18.52. HRMS (ESI) Calcd. For $C_7H_9N_2O_3$: $[M+H]^+$, 169.0613, Found: *m/z*. 169.09610

2,3,6-trimethyl-4-nitropyridine 1-oxide (4e)

4e was obtained as pale yellow solid (75mg, 82%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 2.59 (s, 3H), 2.52 (d, *J* = 4.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.69, 147.33, 143.80, 126.61, 118.05, 18.21, 15.81, 14.95, HRMS (ESI) Calcd. For $C_8H_{11}N_2O_3$: $[M+H]^+$, 183.0770, Found: *m/z*. 183.0765

2-methylquinoline 1-oxide (3f)

3f was obtained as yellow oil (57mg, 72%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.71, 141.42, 130.21, 129.10, 127.96, 127.63, 125.16, 122.91, 119.36, 18.72. HRMS (ESI) Calcd. For $C_{10}H_{10}NO$: $[M+H]^+$, 160.0762, Found: *m/z*. 160.0751

2,8-dimethylquinoline 1-oxide (3g)

3g was obtained as yellow oil (59mg, 68%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.61 (m, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.27 (d, *J* = 4.8 Hz, 1H), 3.23 (s, 3H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.88, 141.54, 133.50, 133.19, 131.23, 127.15, 126.81, 125.57, 122.69, 25.20, 19.14. HRMS (ESI) Calcd. For $C_{11}H_{12}NO$: $[M+H]^+$, 174.0919, Found: *m/z*. 174.0911

2,6-dimethylquinoline 1-oxide (3h)

3h was obtained as yellow oil (58mg, 67%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 3H), 7.27 (s, 1H), 2.72 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.04, 137.79, 132.46, 126.90, 124.80, 122.94, 119.38, 21.29, 18.63.HRMS (ESI) Calcd. For $C_{11}H_{12}NO$: $[M+H]^+$, 174.0919, Found: *m/z*. 174.0708

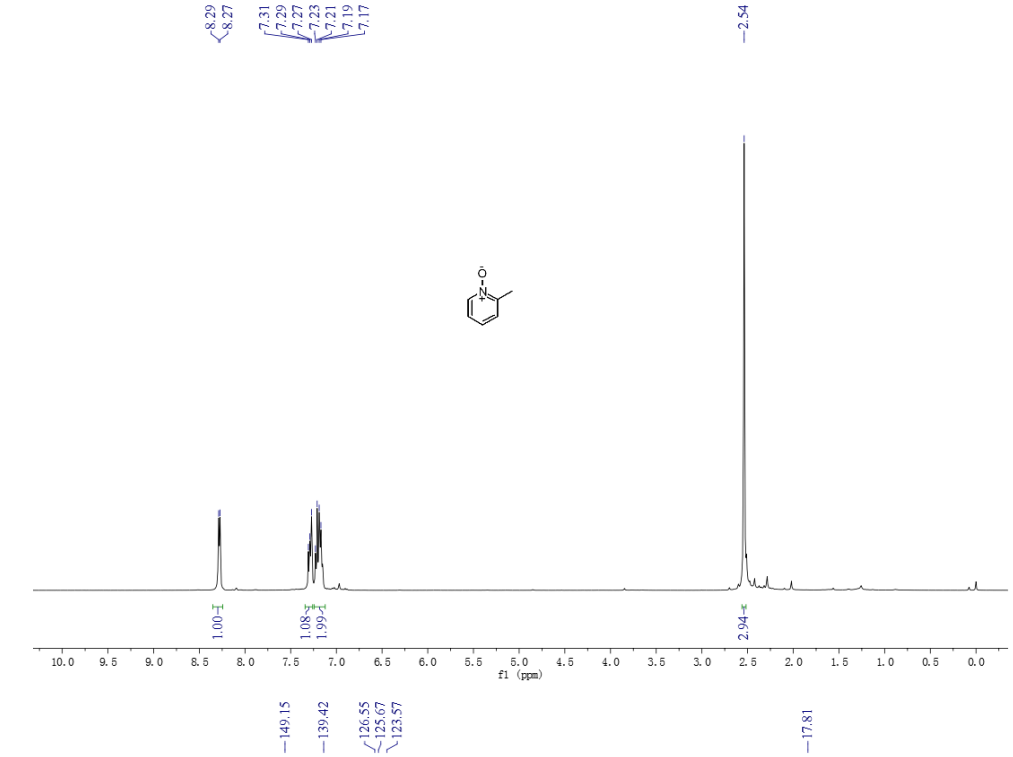
6-chloro-2-methylquinoline 1-oxide (3i)

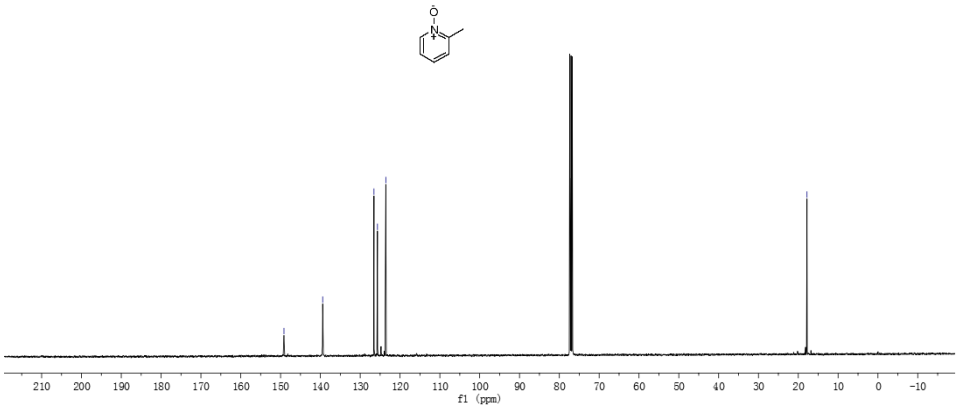
3i was obtained as yellow oil (52mg, 54%)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 9.3 Hz, 1H), 7.82 (s, 1H), 7.70 – 7.64 (m, 1H), 7.55 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.97, 140.16, 133.94, 130.92, 129.96, 126.65, 124.22, 123.72, 121.57, 18.67. HRMS (ESI) Calcd. For

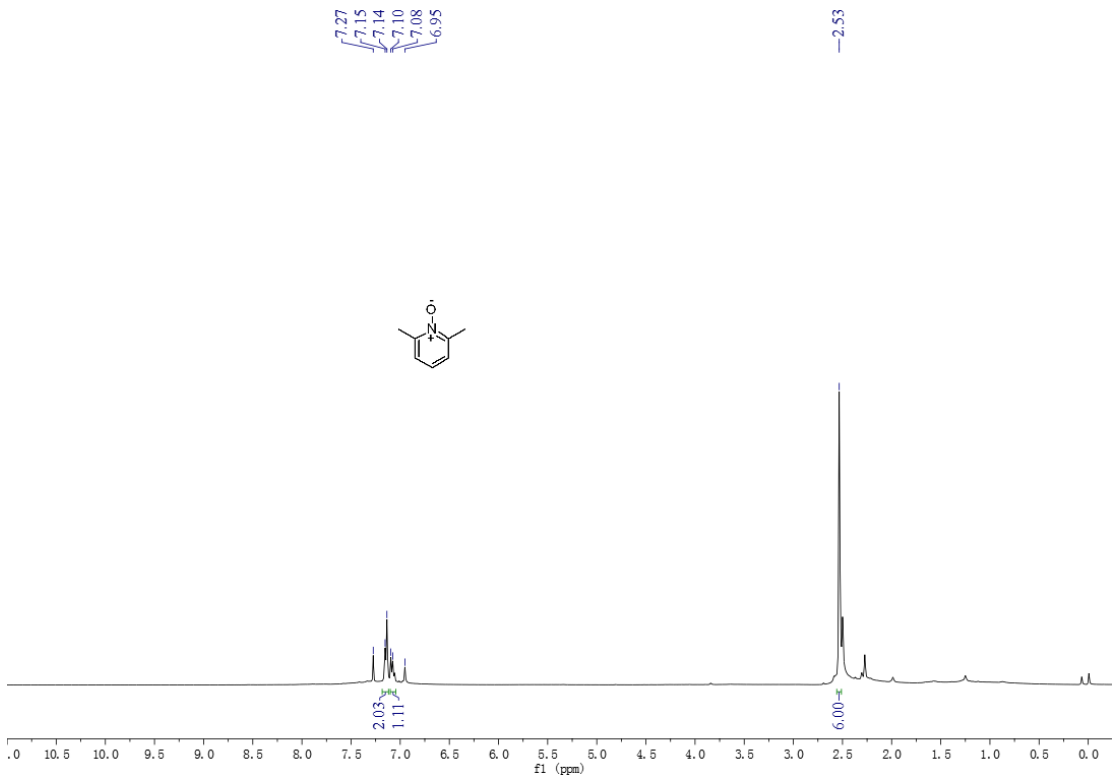
$C_{10}H_9ClNO$: $[M+H]^+$, 194.0373, Found: *m/z*. 194.0372

1-methylisoquinoline 2-oxide (3j)

3j was obtained as yellow oil (65mg, 82%)**.** ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 – 8.18 (m, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.71 – 7.63 (m, 1H), 7.63 – 7.52 (m, 2H), 2.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.58, 136.51 , 129.08, 128.91, 128.84, 128.37, 127.38, 124.02, 121.84, 12.91.HRMS (ESI) Calcd. For $C_{10}H_{10}NO$: $[M+H]^+$,160.0762 , Found: *m/z*. 160.0765



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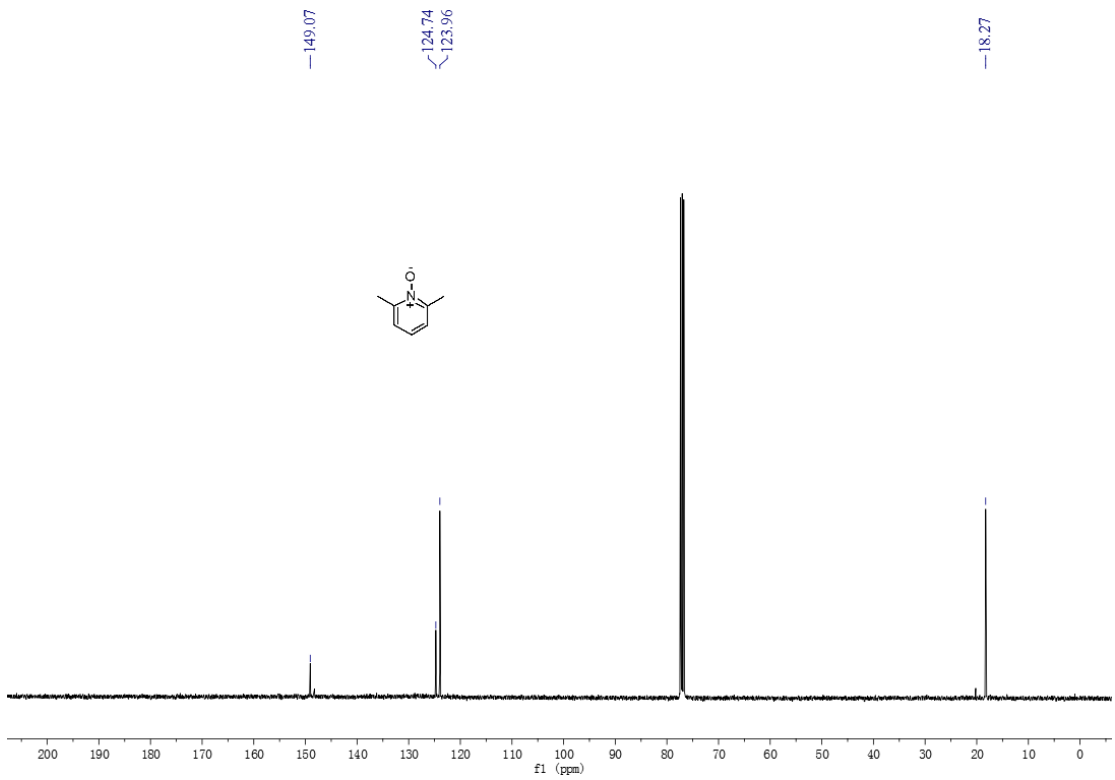
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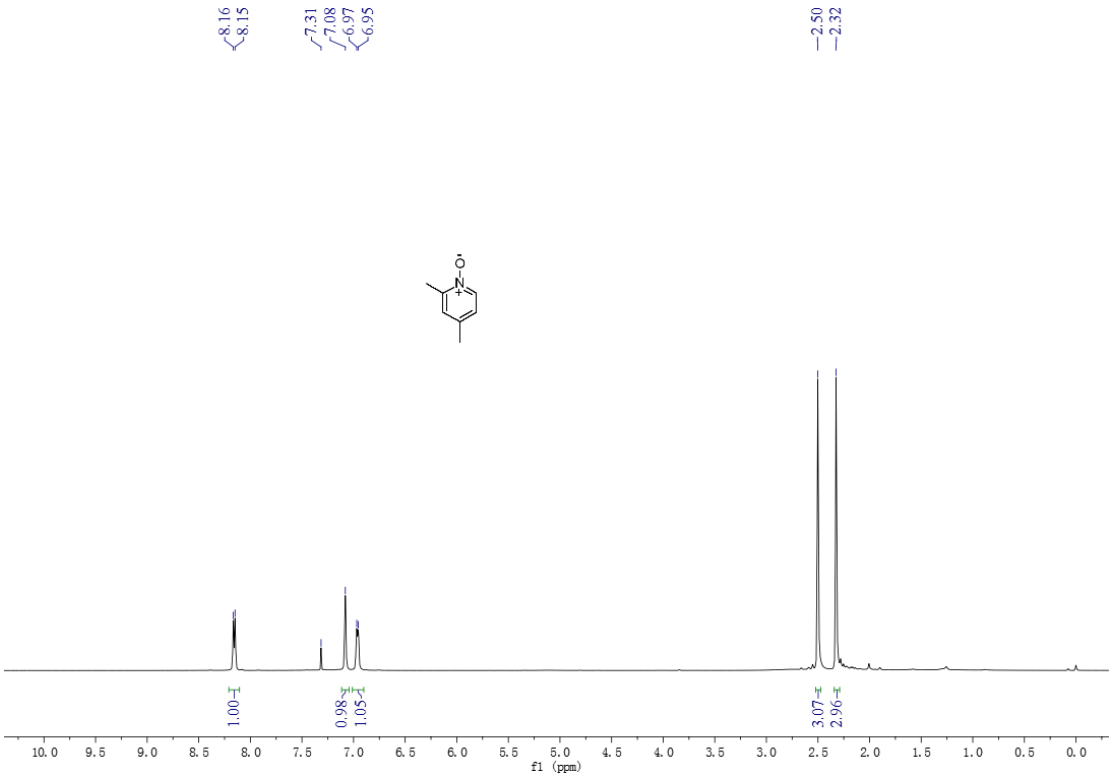
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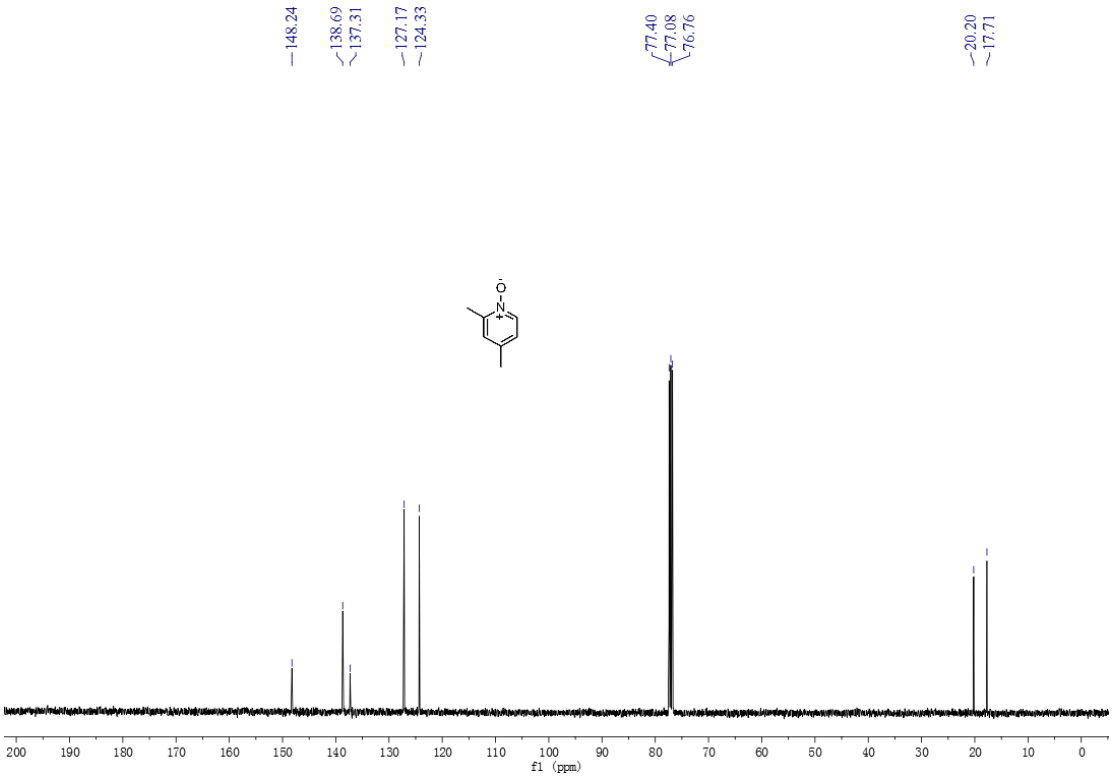
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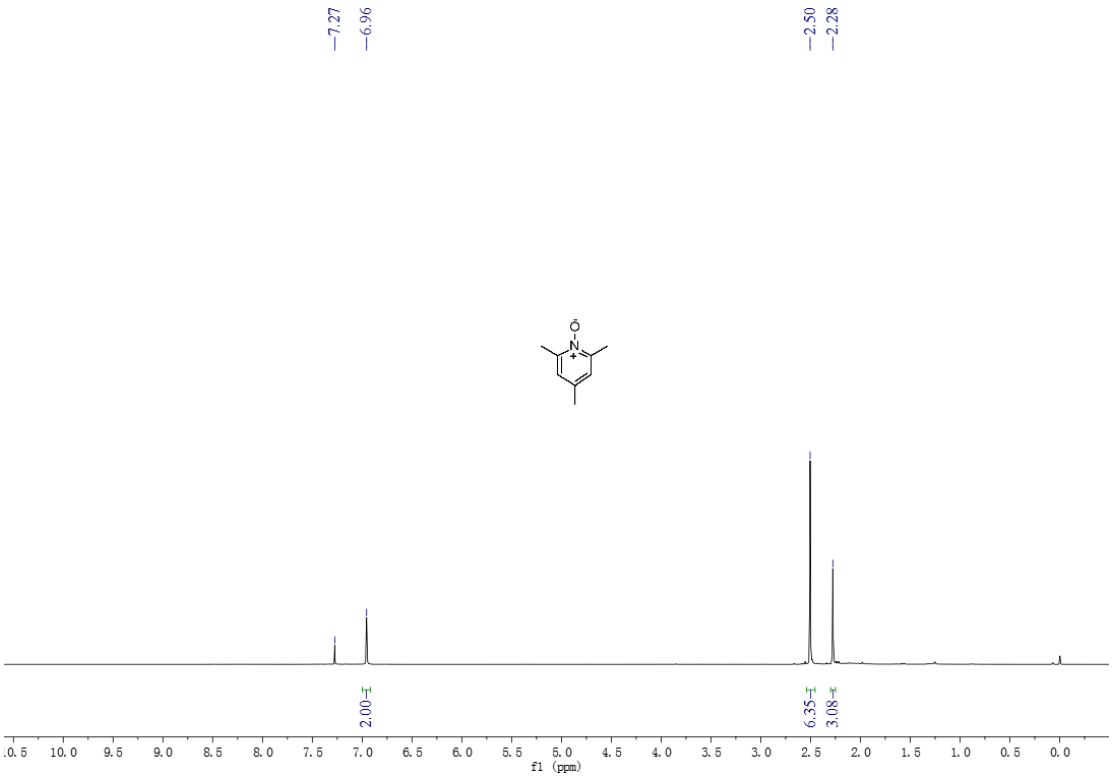
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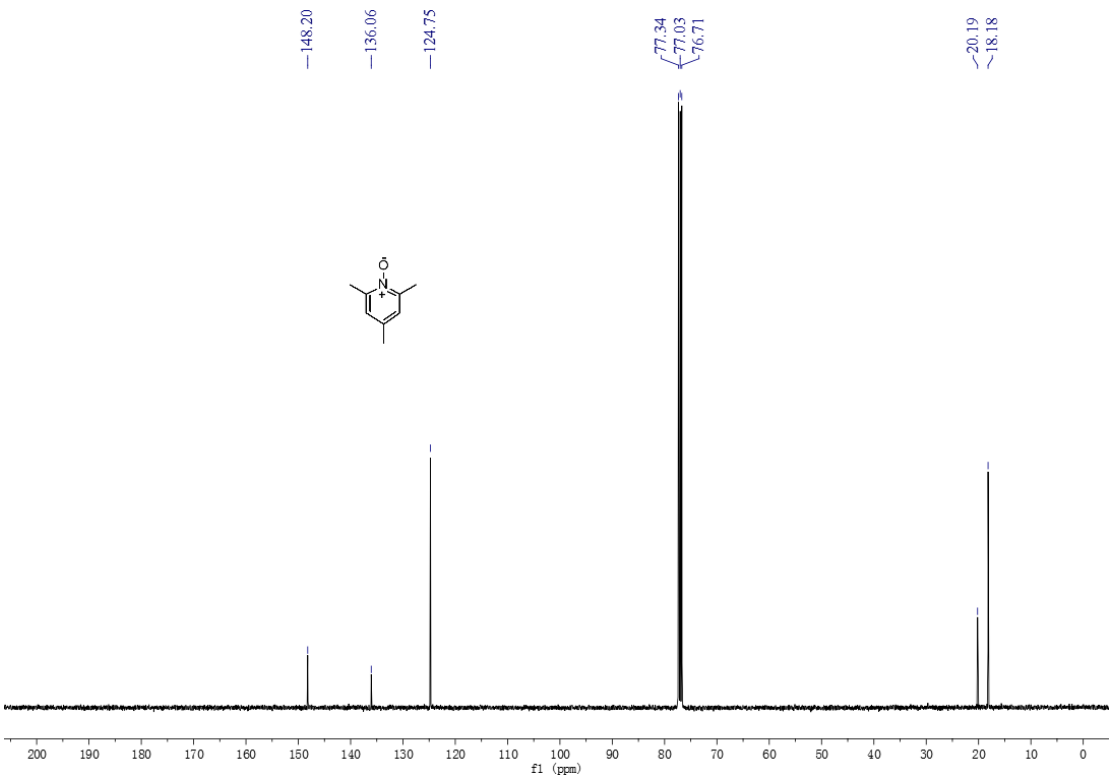
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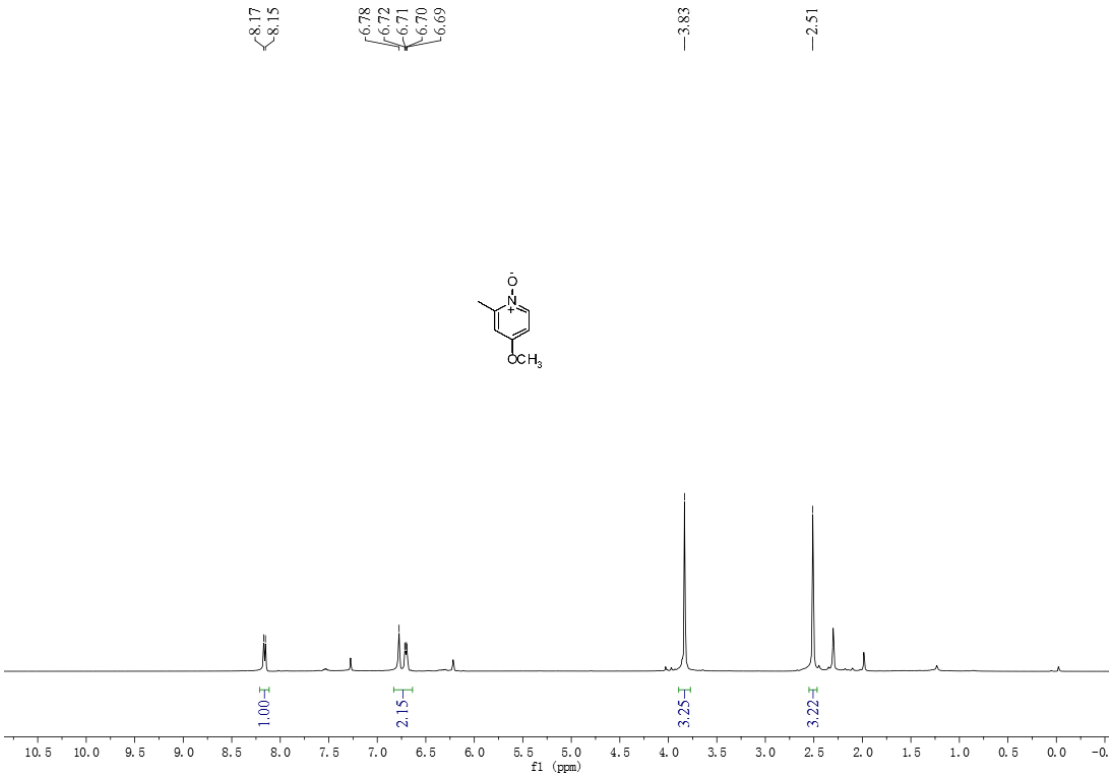
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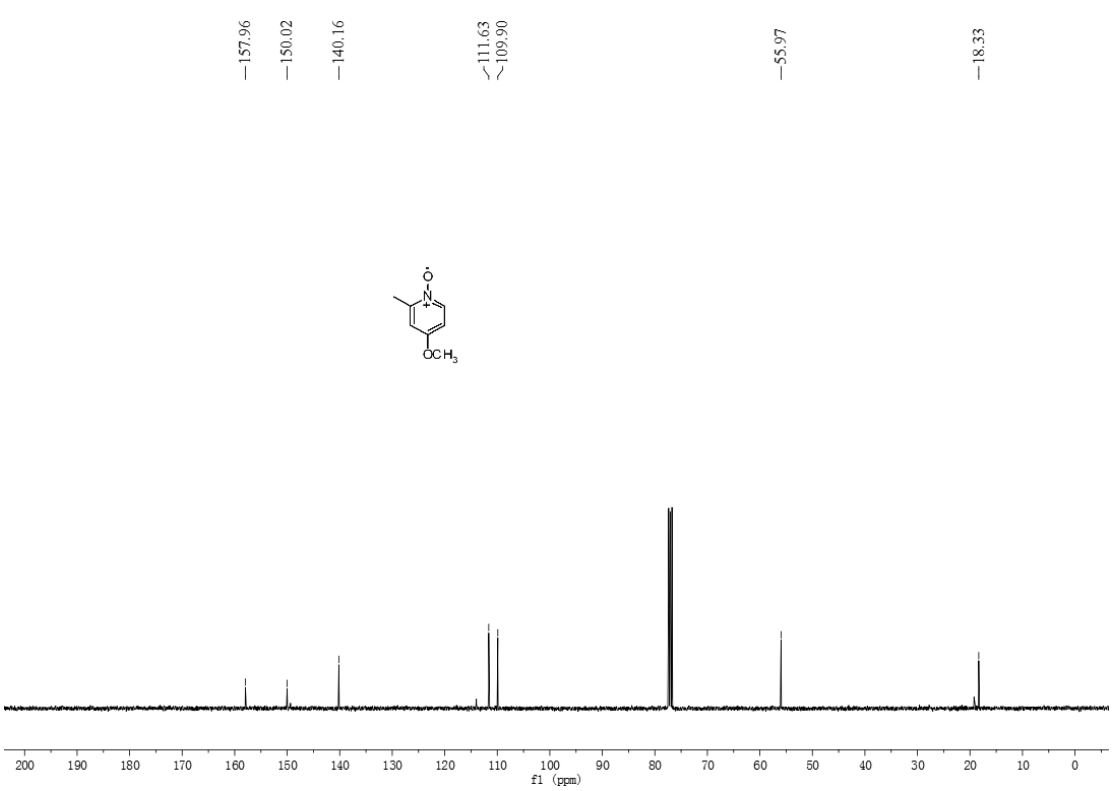
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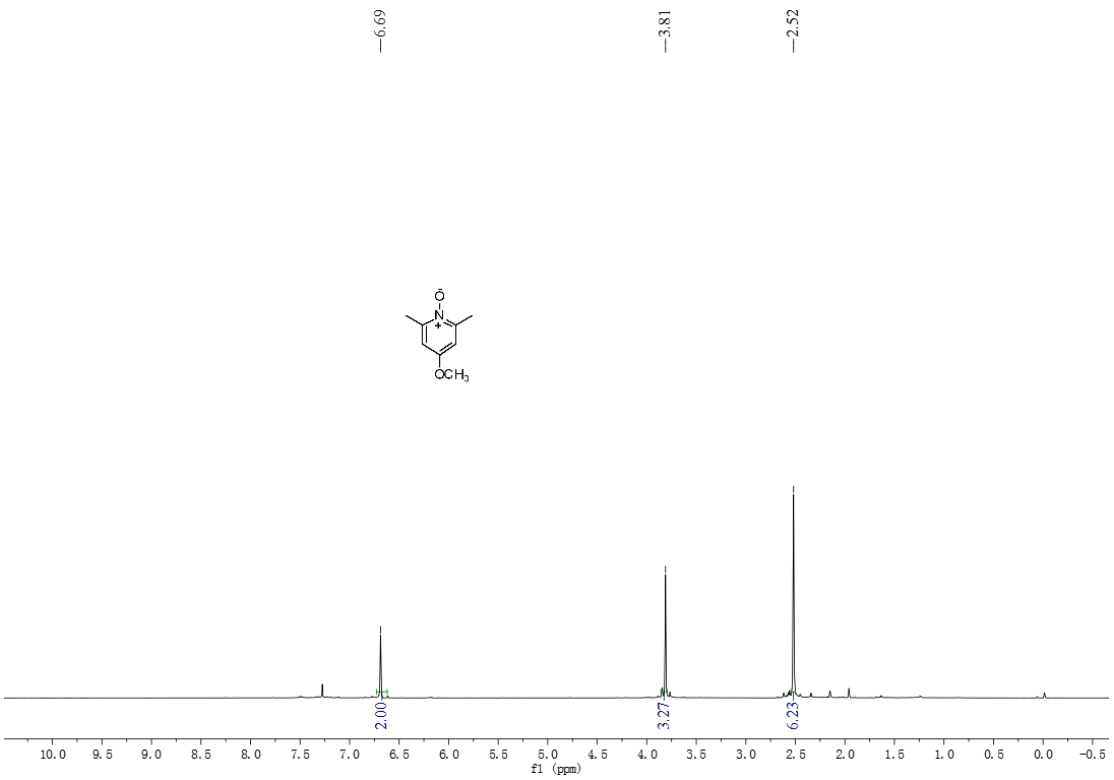
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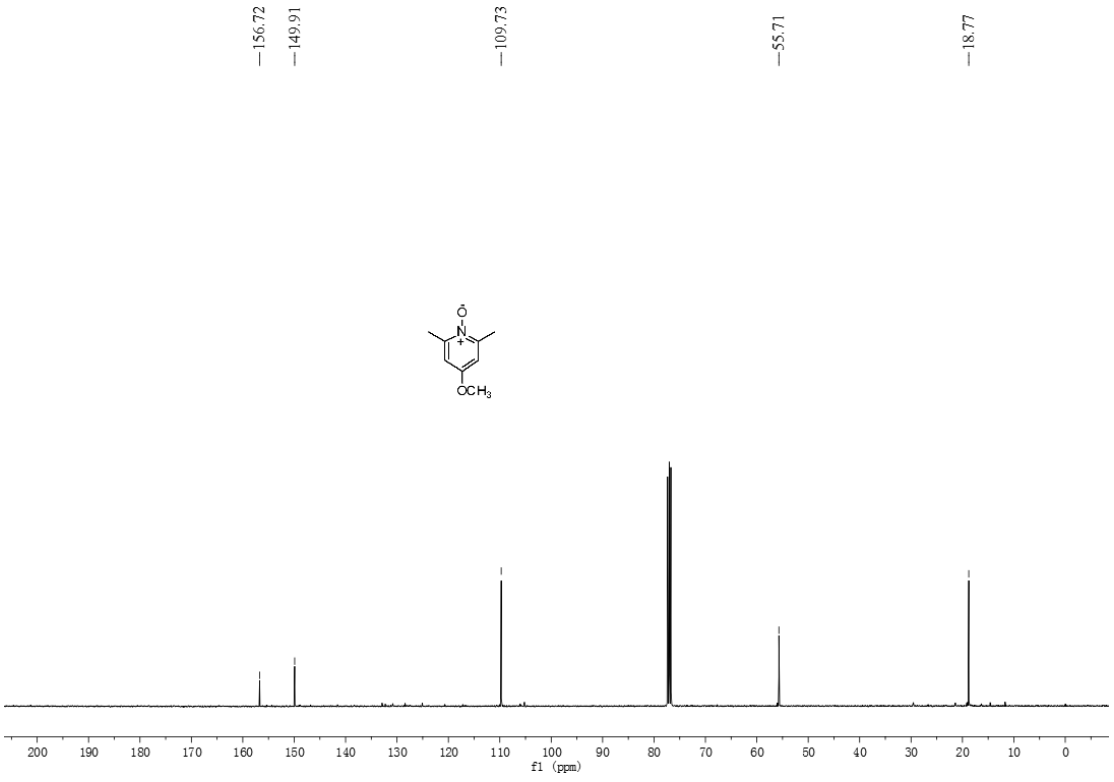
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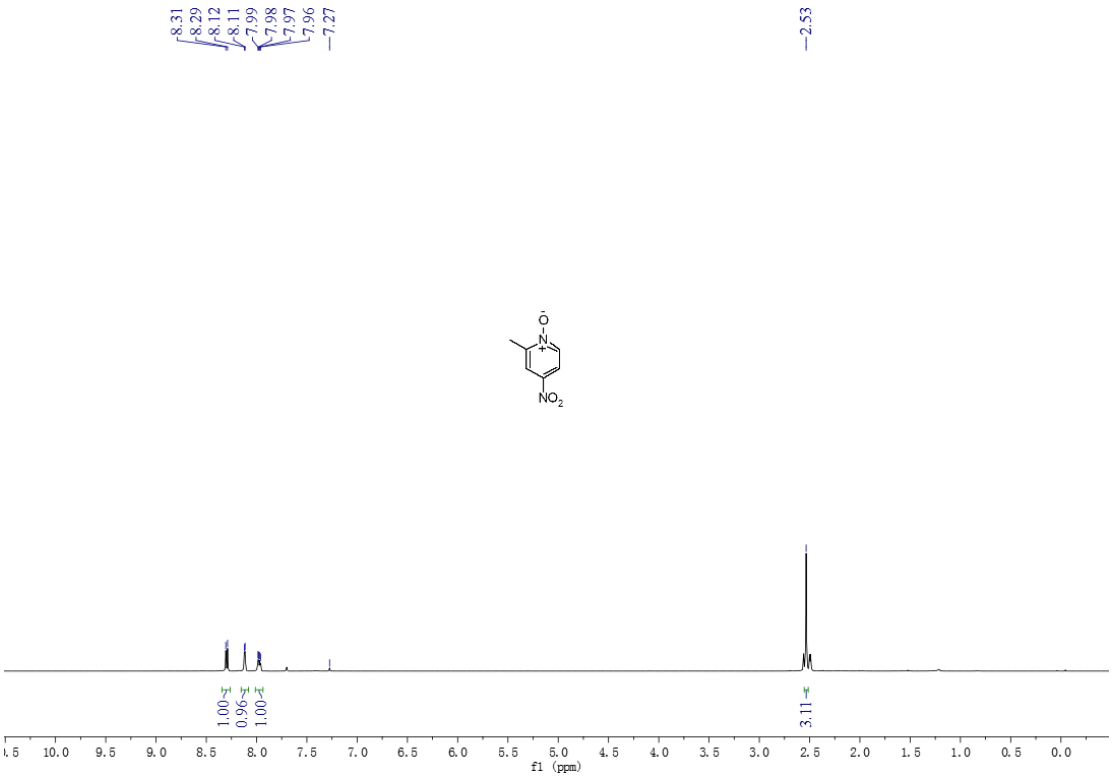
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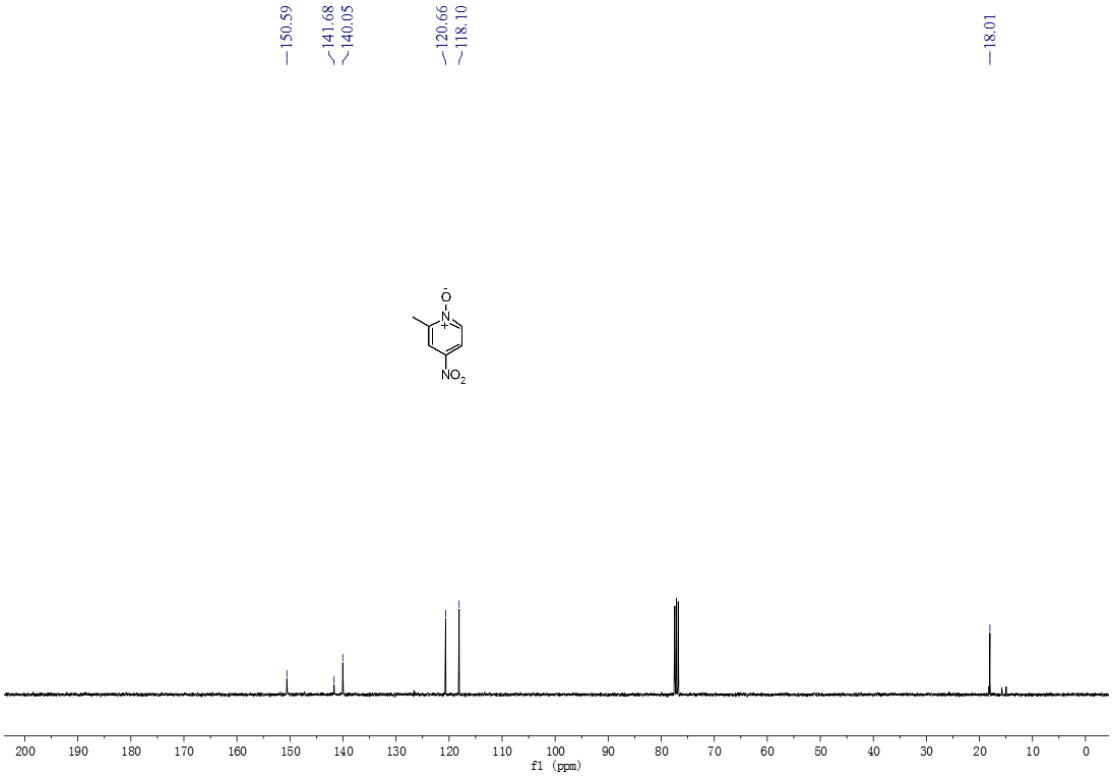
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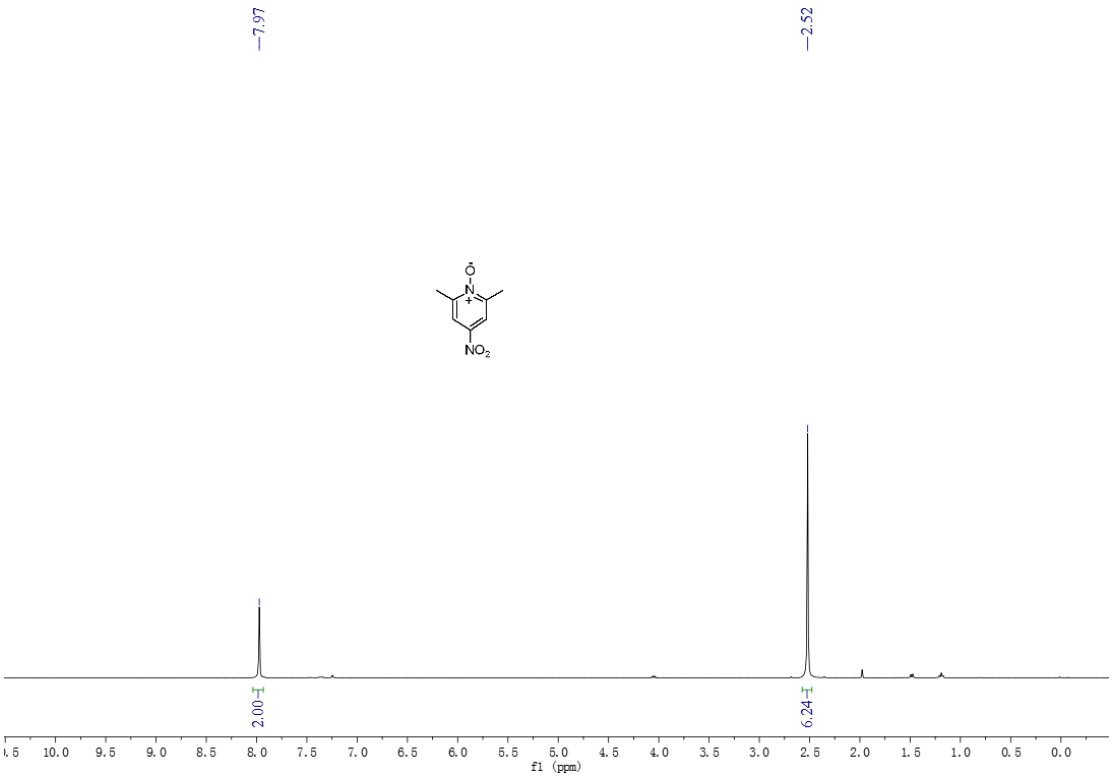
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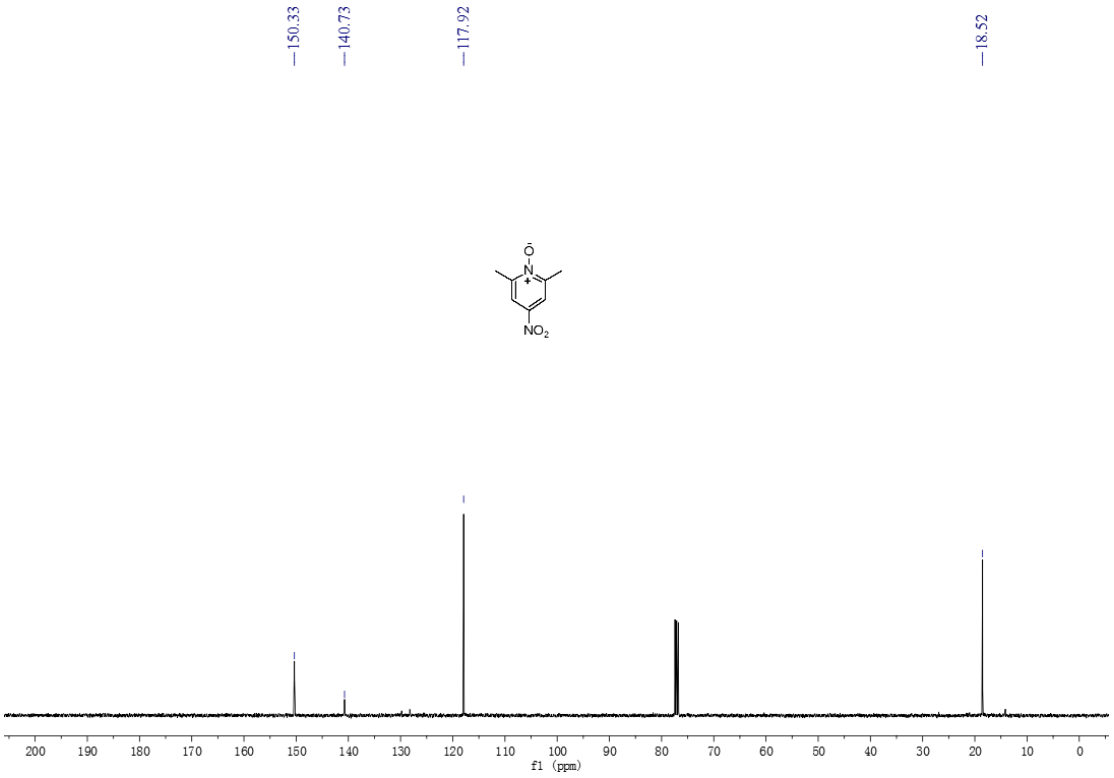
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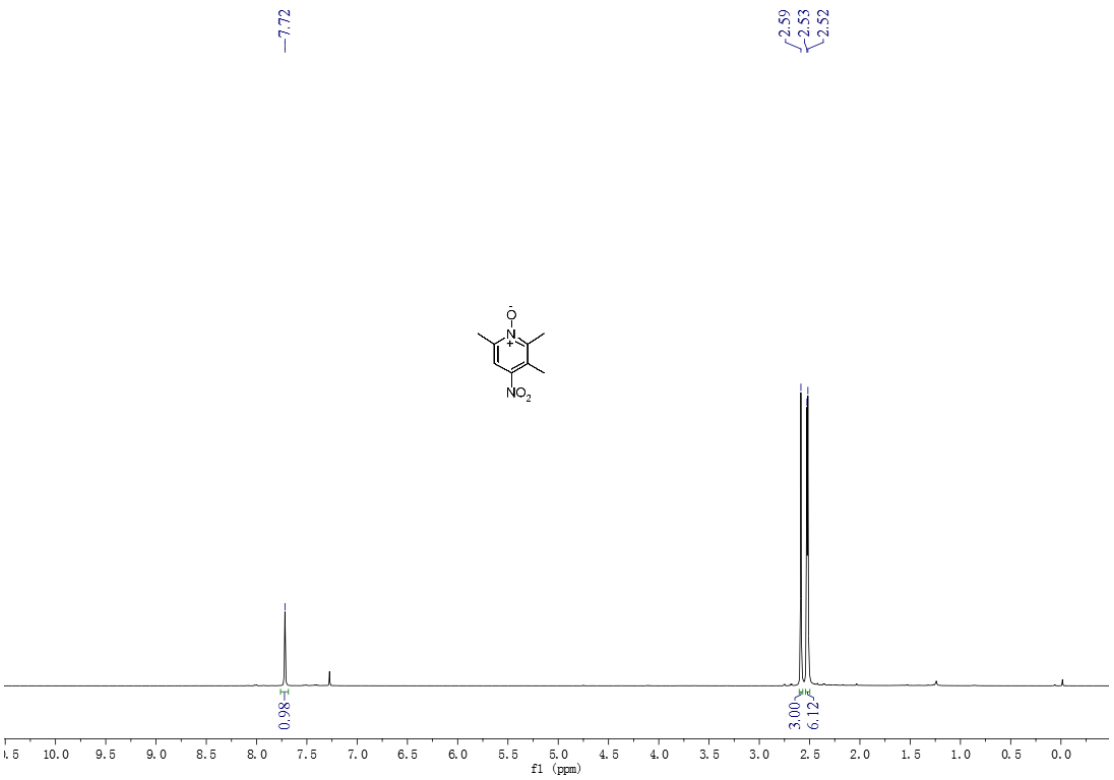
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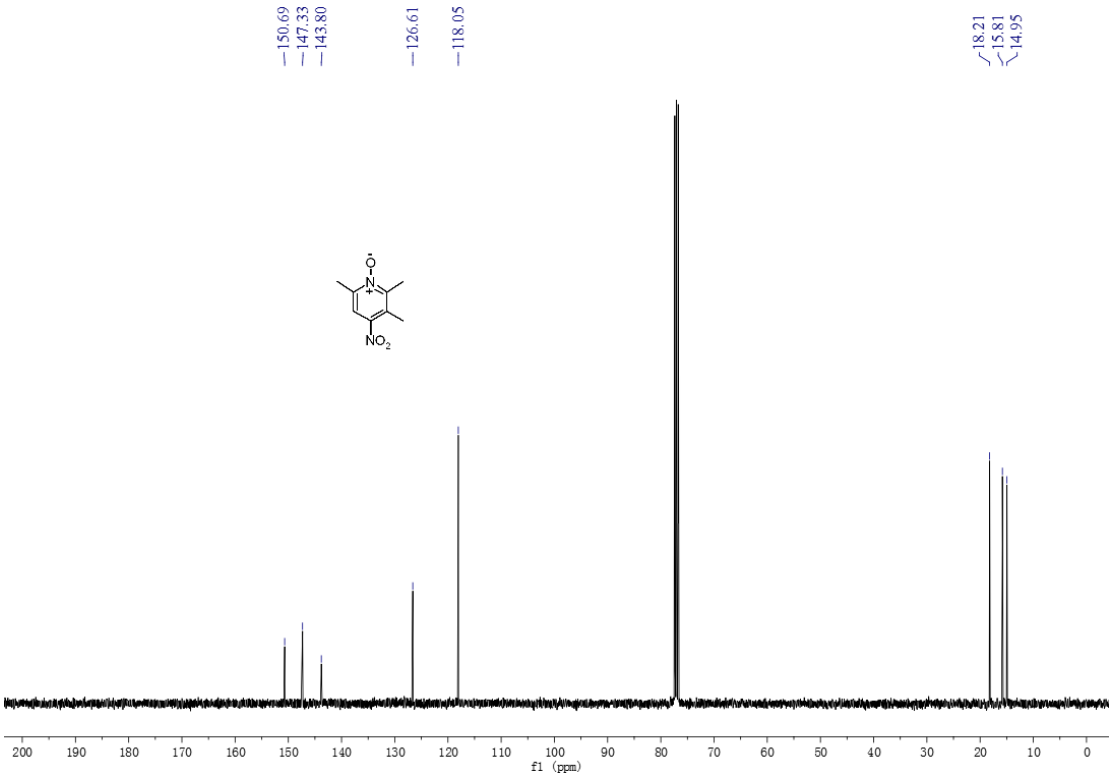
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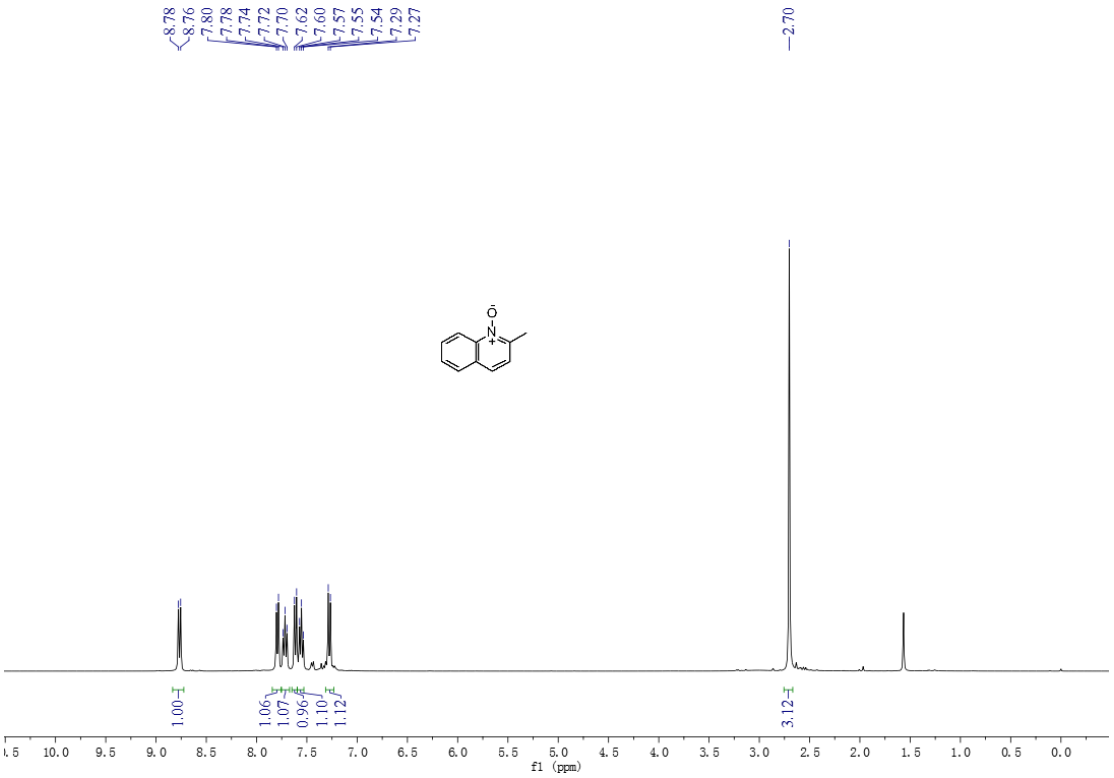
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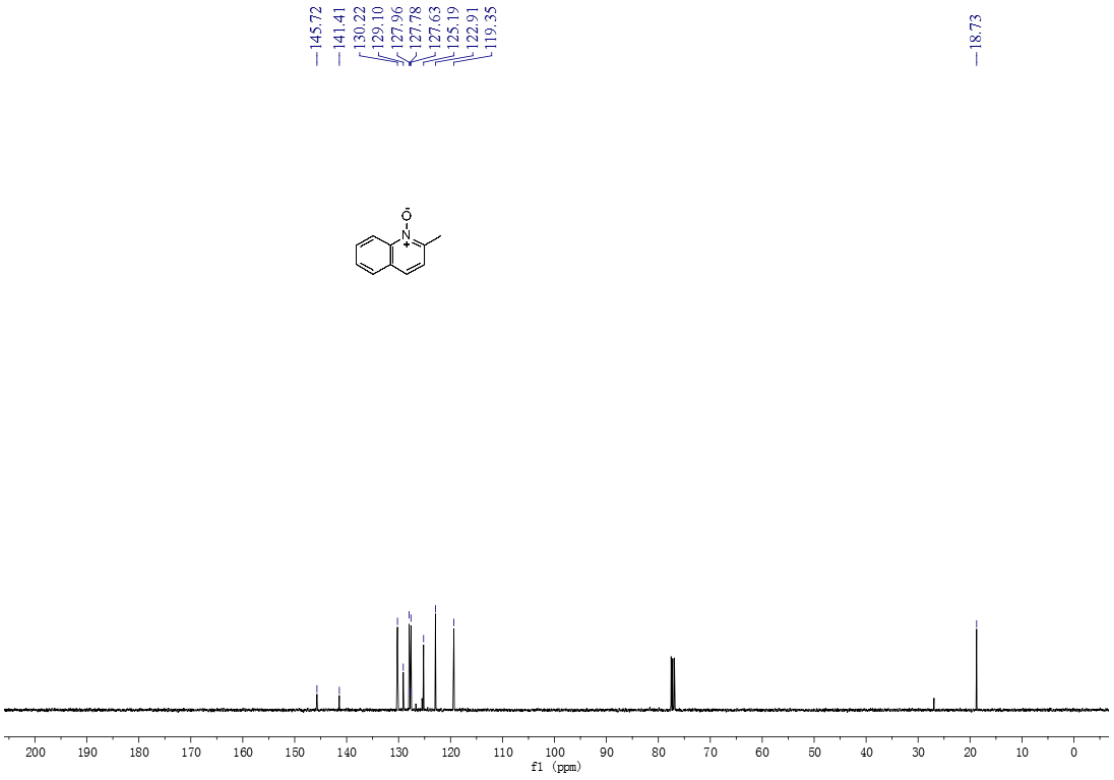
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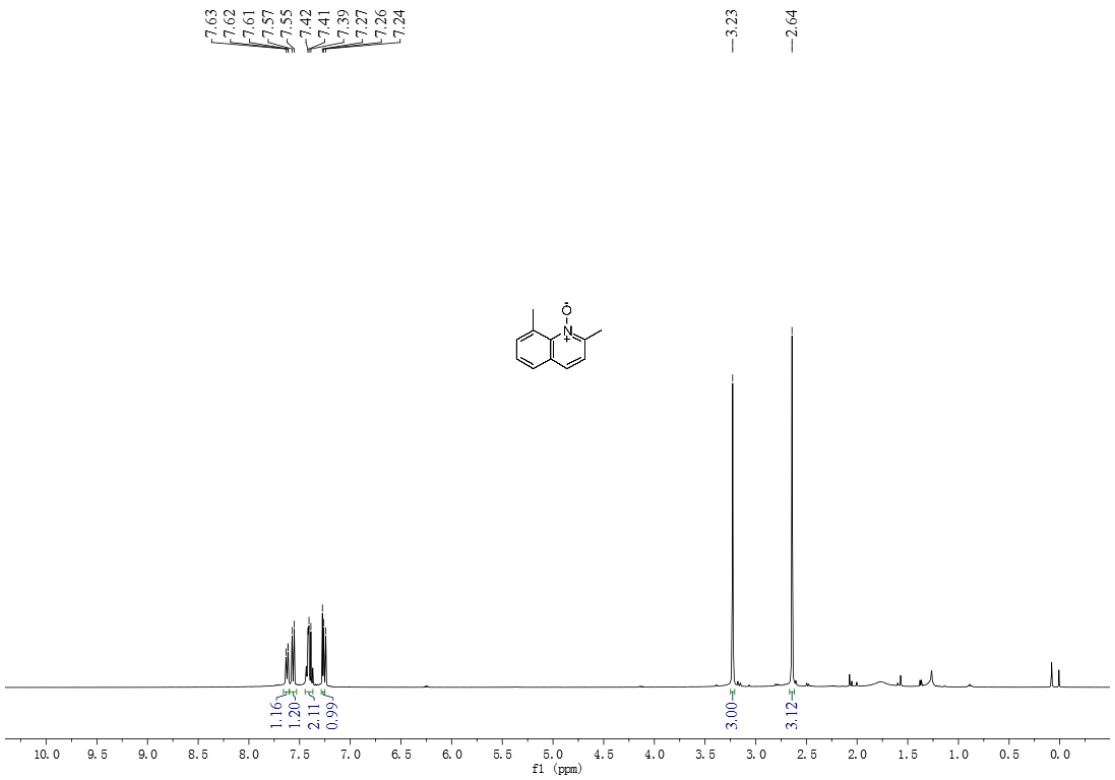
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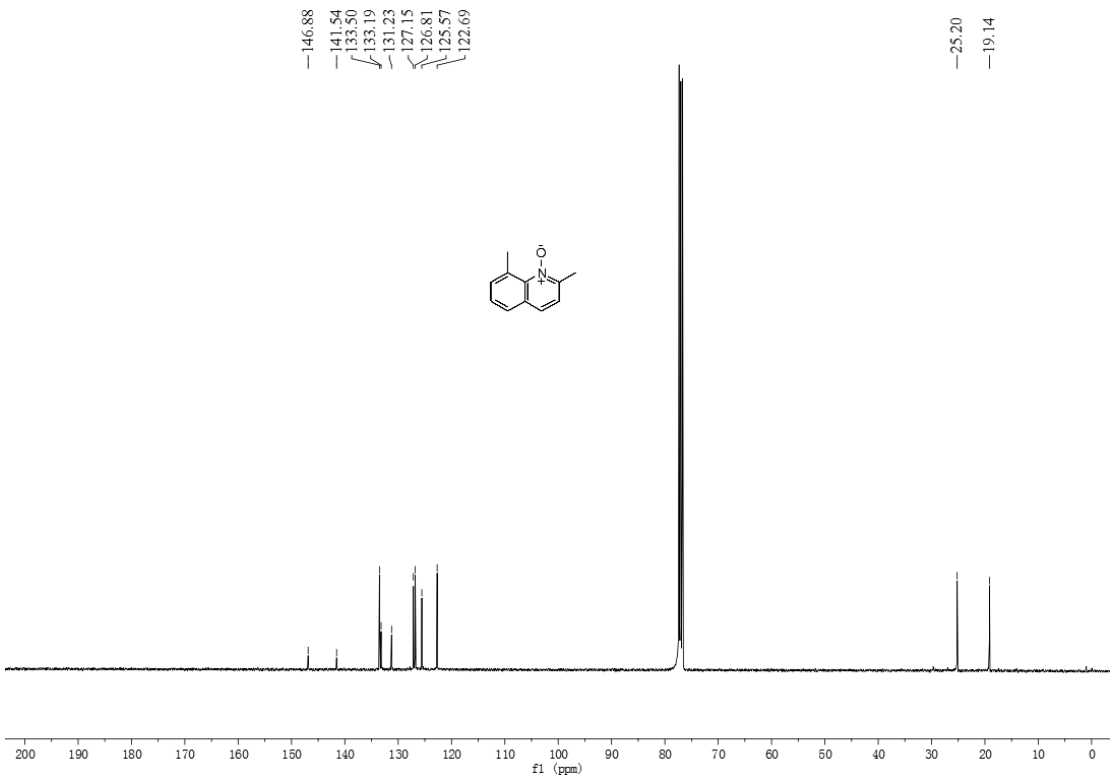
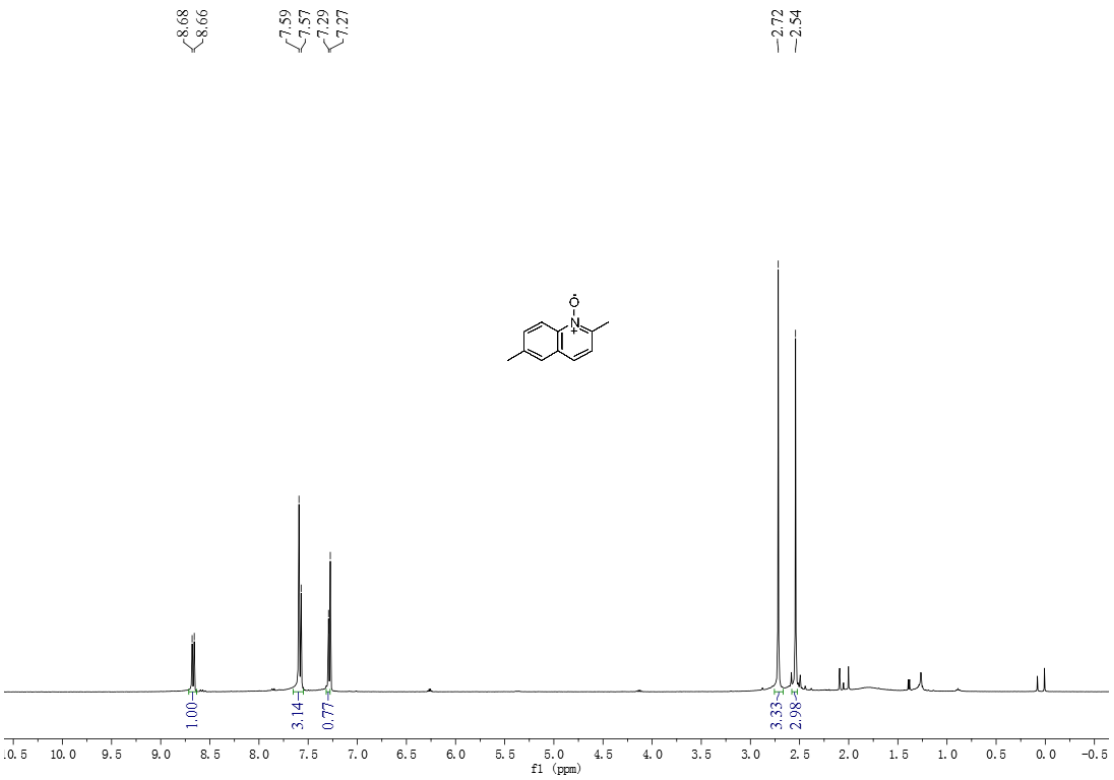
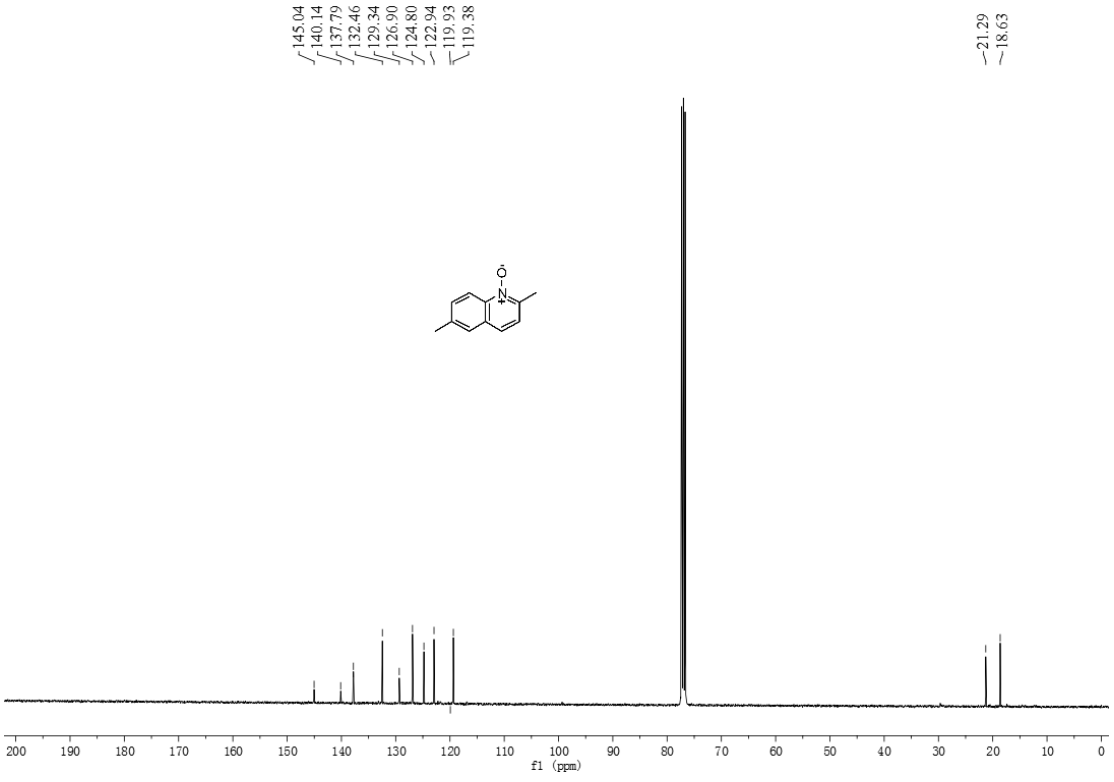
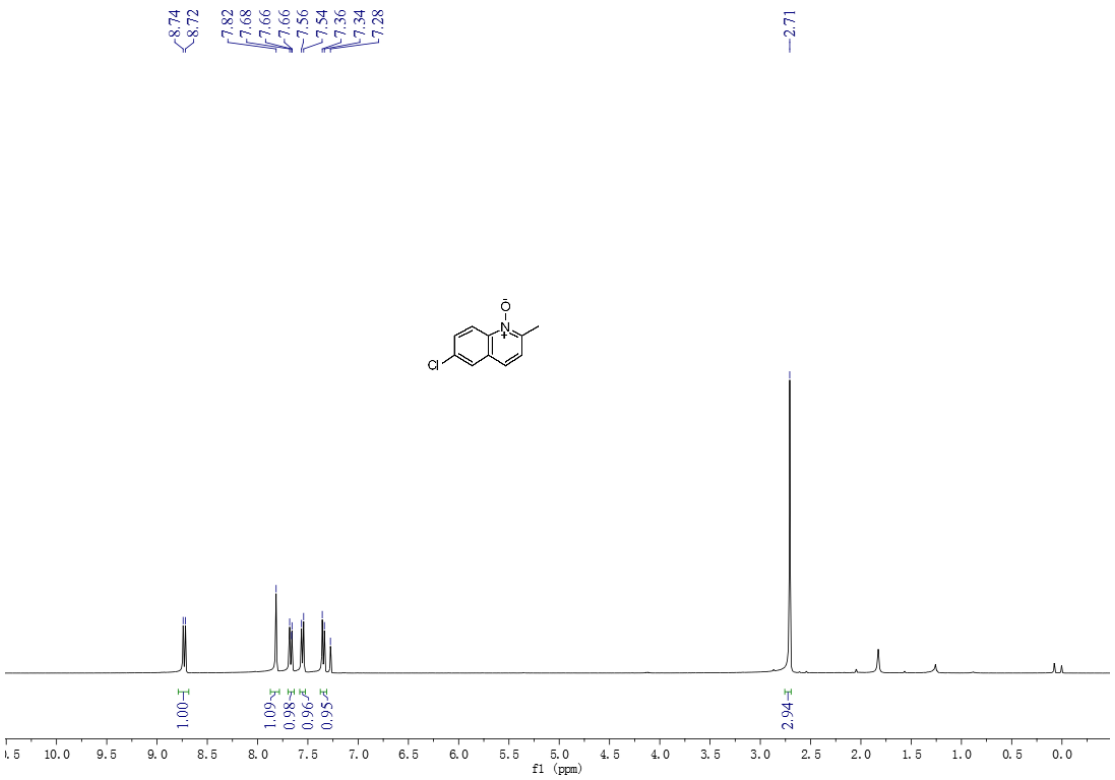
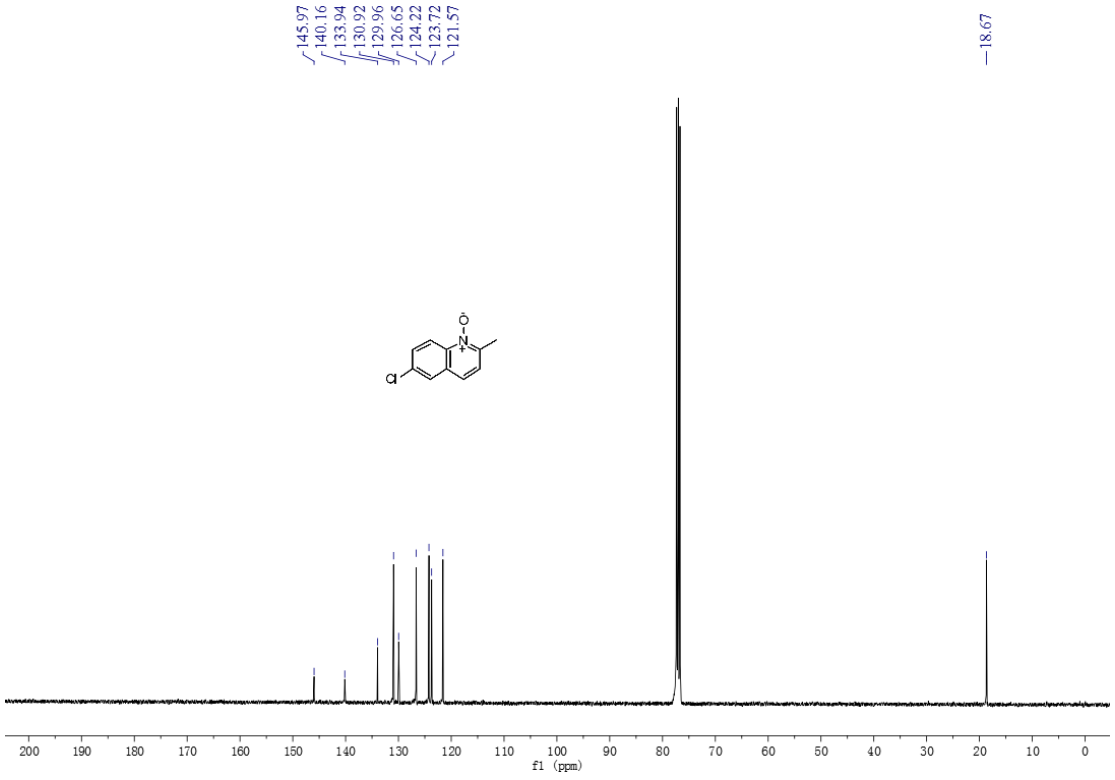
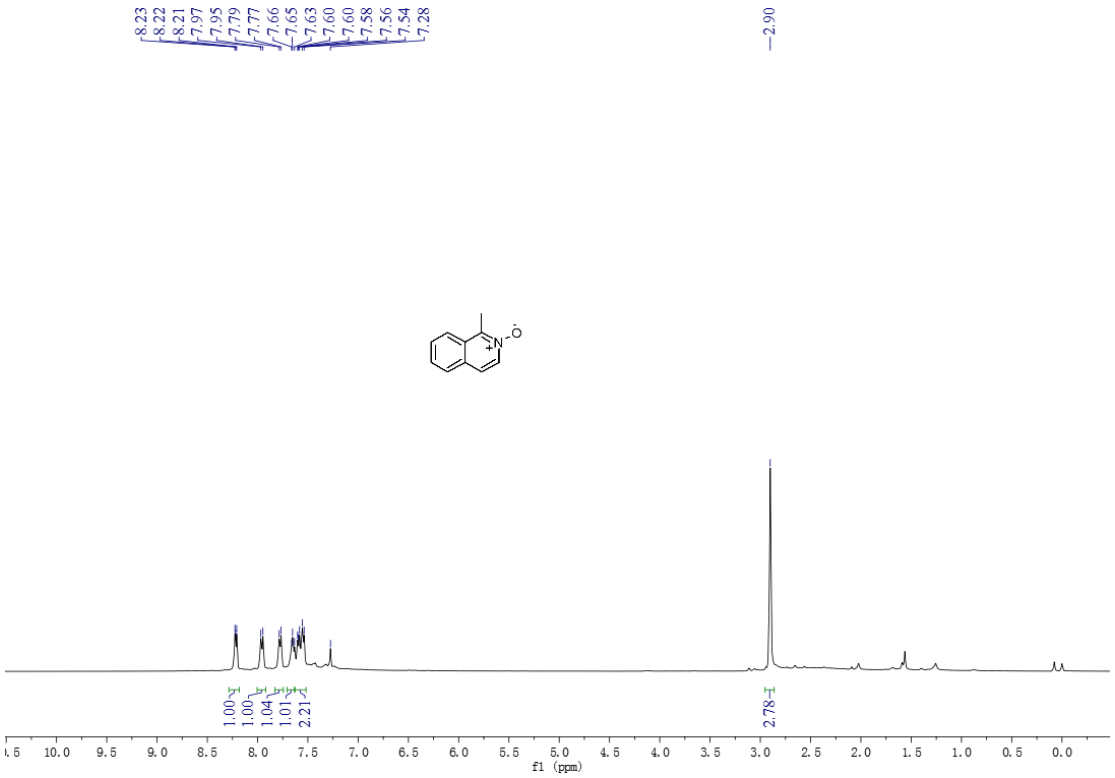

146.88
141.54
133.50
133.19
131.23
127.15
126.81
125.57
122.69
25.20
19.14
f1 (ppm)

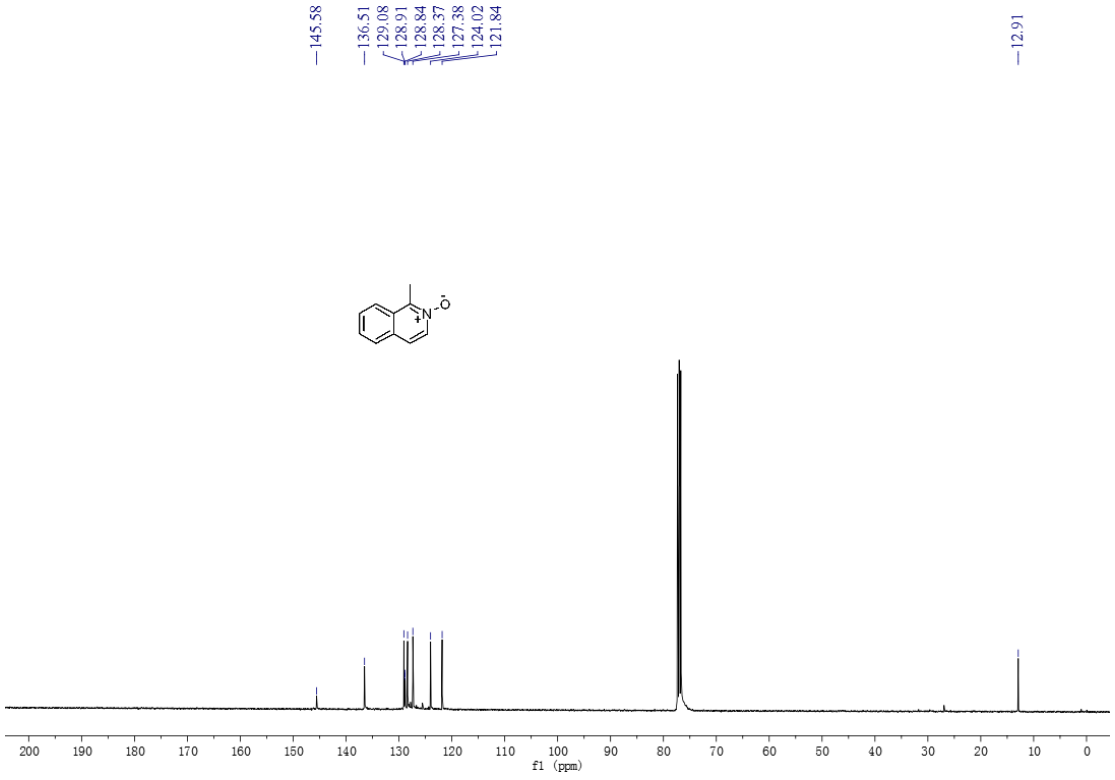

8.68
8.66
7.59
7.57
7.29
7.27
2.72
2.54
1.00
3.14
0.77
3.33
2.98
f1 (ppm)


145.04
140.14
137.79
132.46
129.34
126.90
124.80
122.94
119.93
119.38
21.29
18.63
f1 (ppm)


8.74
8.72
7.82
7.68
7.66
7.66
7.56
7.54
7.36
7.34
7.28
2.71
1.00
1.09
0.98
0.96
0.95
2.94
f1 (ppm)


145.97
140.16
133.94
130.92
129.96
126.65
124.22
123.72
121.57
18.67
f1 (ppm)


8.23
8.22
8.21
7.97
7.95
7.79
7.77
7.66
7.65
7.63
7.60
7.60
7.58
7.56
7.54
7.28
2.90
1.00
1.00
1.04
1.01
2.21
2.78
f1 (ppm)


145.58
136.51
129.08
128.91
128.84
128.37
127.38
124.02
121.84
12.91
f1 (ppm)