Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Generation of 1-amino-isoquinoline-*N*-oxides via a tandem reaction of 2-alkynylbenzaldoxime with secondary amines in the presence of silver(I) and copper(I)

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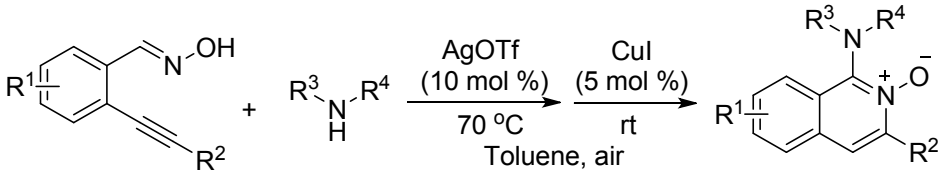
Supporting Information

1. General experimental methods (S2).
2. General experimental procedure and characterization data (S2-S7).
3. ^{1}H and ^{13}C NMR spectra of compound **3** (S8-S49).

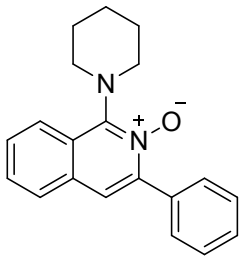
General experimental methods:

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr at 25–35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a micrOTOF II Instrument.

General experimental procedure for the synthesis of 1-amino-isoquinoline-N-oxides 3 through a tandem reaction of 2-alkynylbenzaldoximes 1 with amines 2 in the presence of silver(I) and copper(I)

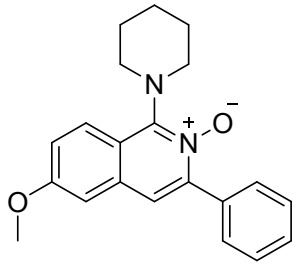


A mixture of silver triflate (0.02 mmol, 5.1 mg) and 2-alkynylbenzaldoxime **1a** (0.2 mmol) in toluene (1.0 mL) was stirred at 70 °C under N_2 for 2 hours. Piperidine **2a** (1.6 mmol), CuI (0.01mmol, 1.9 mg) and toluene (1.0 mL) were added subsequently. The reaction was stirred at 25 °C until completion of the reaction as indicated by TLC. Evaporation of the solvent followed by purification on silica gel afforded the corresponding product **3a**.



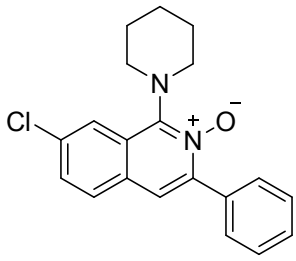
3-Phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3a**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 7.75 - 7.70 (m, 3H), 7.61 - 7.49 (m, 3H), 7.49 - 7.38 (m, 3H), 3.79 (s, 2H), 3.17 (s, 2H), 1.83 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 147.5, 133.8, 130.2, 129.9, 128.9, 128.2, 128.0, 127.5, 127.3, 126.9, 124.2, 120.8, 49.7, 26.6, 24.4; HRMS (ESI) calcd for $C_{20}H_{20}N_2O$: 305.1648 ($M + H^+$), found: 305.1663.



5-Methoxy-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3b**

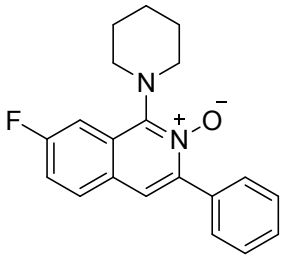
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.77 - 7.74 (m, 3H), 7.48 - 7.38 (m, 4H), 6.86 (d, *J* = 7.7 Hz, 1H), 3.97 (s, 3H), 3.72 (s, 2H), 3.16 (s, 2H), 1.79 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 150.9, 146.6, 134.2, 130.9, 129.9, 128.7, 128.6, 127.9, 122.3, 116.2, 115.6, 106.4, 55.7, 49.6, 26.5, 24.4; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_2$: 335.1754 ($M + H^+$), found: 335.1758.



7-Chloro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3c**

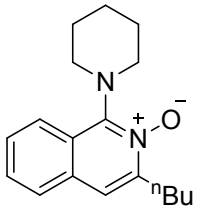
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.72 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.51 (s, 1H), 7.48 - 7.40 (m, 4H), 3.80 (s, 2H), 3.09 (s, 2H), 1.85 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.9, 134.3, 133.4, 130.9, 129.7,

129.1, 128.9, 128.5, 128.2, 128.1, 123.0, 120.6, 49.3, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O$: 339.1259 (M + H^+), found: 339.1256.



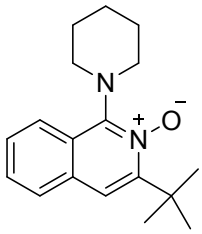
7-Fluoro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3d**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 10.3, 2.0 Hz, 1H), 7.73 - 7.70 (m, 3H), 7.54 (s, 1H), 7.48 - 7.40 (m, 3H), 7.31 - 7.26 (m, 1H), 3.78 (s, 2H), 3.08 (s, 2H), 1.84 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, $^1J_{CF}$ = 247.4 Hz), 150.7, 147.1, 133.5, 130.9, 129.8, 129.0, 128.8, 128.1, 127.0, 120.7, 118.2 (d, $^2J_{CF}$ = 25.4 Hz), 108.1 (d, $^2J_{CF}$ = 24.0 Hz), 49.2, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 (M + H^+), found: 323.1561.



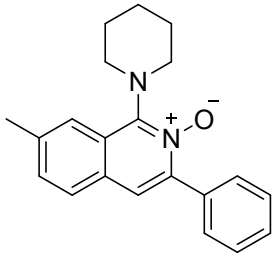
3-Butyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3e**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.12 (m, 1H), 7.66 - 7.64 (m, 1H), 7.50 - 7.48 (m, 2H), 7.33 (s, 1H), 3.75 (s, 2H), 3.10 (s, 1H), 3.03 - 2.95 (m, 2H), 2.17 (s, 1h), 1.78 - 1.72 (m, 8H), 1.54 - 1.45 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.8, 130.2, 128.0, 127.3, 126.2, 124.1, 117.9, 49.6, 30.4, 29.2, 26.6, 24.3, 22.7, 13.9; HRMS (ESI) calcd for $C_{18}H_{24}N_2O$: 285.1961 (M + H^+), found: 285.1952.



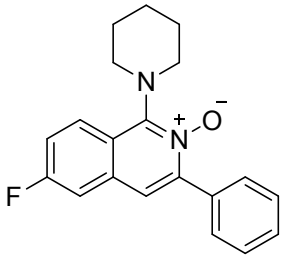
3-(*tert*-Butyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3f**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.51 - 7.43 (m, 3H), 3.63 (s, 2H), 3.11 (s, 2H), 1.84 - 1.75 (m, 6H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.9, 129.6, 127.5, 126.7, 123.5, 117.2, 49.1, 36.6, 28.3, 26.5, 24.3; HRMS (ESI) calcd for $C_{18}H_{24}N_2O$: 285.1961 ($M + H^+$), found: 285.1941.



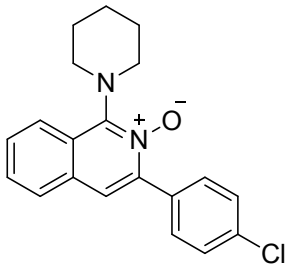
7-Methyl-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3g**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.74 (d, J = 6.7 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.48 - 7.40 (m, 4H), 7.36 (d, J = 8.1 Hz, 1H), 3.74 (s, 2H), 3.14 (s, 2H), 2.56 (s, 3H), 1.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.6, 138.3, 133.9, 130.9, 130.4, 129.8, 128.7, 127.9, 127.4, 126.8, 123.1, 120.7, 49.4, 26.5, 24.3, 22.2; HRMS (ESI) calcd for $C_{21}H_{22}N_2O$: 319.1805 ($M + H^+$), found: 319.1802.



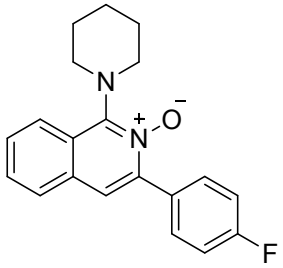
6-Fluoro-3-phenyl-1-(piperidin-1-yl)isoquinoline 2-oxide **3h**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 1H), 7.73 (d, J = 6.6 Hz, 2H), 7.48 - 7.41 (m, 4H), 7.33 - 7.29 (m, 2H), 3.72 (s, 2H), 3.13 (s, 2H), 1.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{CF}$ = 249.6 Hz), 151.2, 148.6, 133.5, 131.3, 129.7, 129.1, 128.0, 127.3 (d, $^3J_{CF}$ = 8.9 Hz), 124.4, 120.1 (d, $^4J_{CF}$ = 5.0 Hz), 118.3 (d, $^2J_{CF}$ = 24.9 Hz), 110.9 (d, $^2J_{CF}$ = 21.7 Hz), 49.5, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 ($M + H^+$), found: 323.1557.



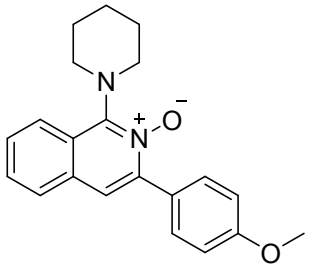
3-(4-Chlorophenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3i**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 1H), 7.72 - 7.69 (m, 3H), 7.60 - 7.50 (m, 3H), 7.42 (d, J = 8.5 Hz, 2H), 3.73 (s, 2H), 3.19 (s, 2H), 1.85 - 1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 146.2, 134.9, 132.2, 131.2, 130.2, 128.4, 128.3, 127.3, 126.9, 124.2, 120.7, 49.6, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}ClN_2O$: 339.1259 (M + H^+), found: 339.1258.



3-(4-Fluorophenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3j**

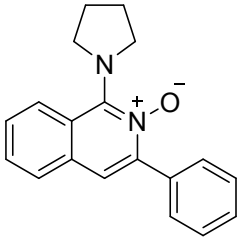
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.1 Hz, 1H), 7.76 -7.70 (m, 3H), 7.59 - 7.50 (m, 3H), 7.13 (t, J = 8.4 Hz, 2H), 3.73 (s, 2H), 3.19 (s, 2H), 1.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, $^1J_{CF}$ = 247.3 Hz), 151.2, 146.4, 131.9 (d, $^3J_{CF}$ = 8.2 Hz), 130.2, 129.8, 128.3 (d, $^3J_{CF}$ = 7.7 Hz), 127.2, 126.9, 124.2, 120.7, 115.0 (d, $^2J_{CF}$ = 21.6 Hz), 49.6, 26.5, 24.3; HRMS (ESI) calcd for $C_{20}H_{19}FN_2O$: 323.1554 (M + H^+), found: 323.1543.



3-(4-Methoxyphenyl)-1-(piperidin-1-yl)isoquinoline 2-oxide **3k**

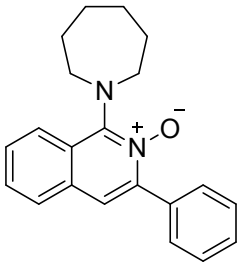
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.1 Hz, 1H), 7.73 - 7.68 (m, 3H), 7.59 - 7.48 (m, 3H), 6.98 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H), 3.73 (s, 2H), 3.17 (s, 2H), 1.84 -

1.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 151.1, 147.2, 131.3, 130.3, 128.1, 127.9, 127.0, 126.7, 126.1, 124.1, 120.4, 113.4, 55.4, 49.5, 26.6, 24.3; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_2$: 335.1754 ($M + H^+$), found: 335.1753.



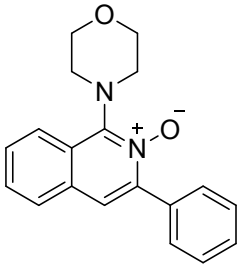
3-Phenyl-1-(pyrrolidin-1-yl)isoquinoline 2-oxide **3l**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.2 Hz, 1H), 7.75 - 7.71 (m, 3H), 7.57 - 7.52 (m, 3H), 7.50 - 7.41 (m, 3H), 3.64 -3.52 (m, 4H), 2.15 - 2.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 147.6, 133.9, 130.9, 129.9, 129.8, 128.9, 128.6, 128.2, 128.1, 126.7, 124.7, 120.9, 48.8, 26.5; HRMS (ESI) calcd for $C_{19}H_{18}N_2O$: 291.1492 ($M + H^+$), found: 291.1492.



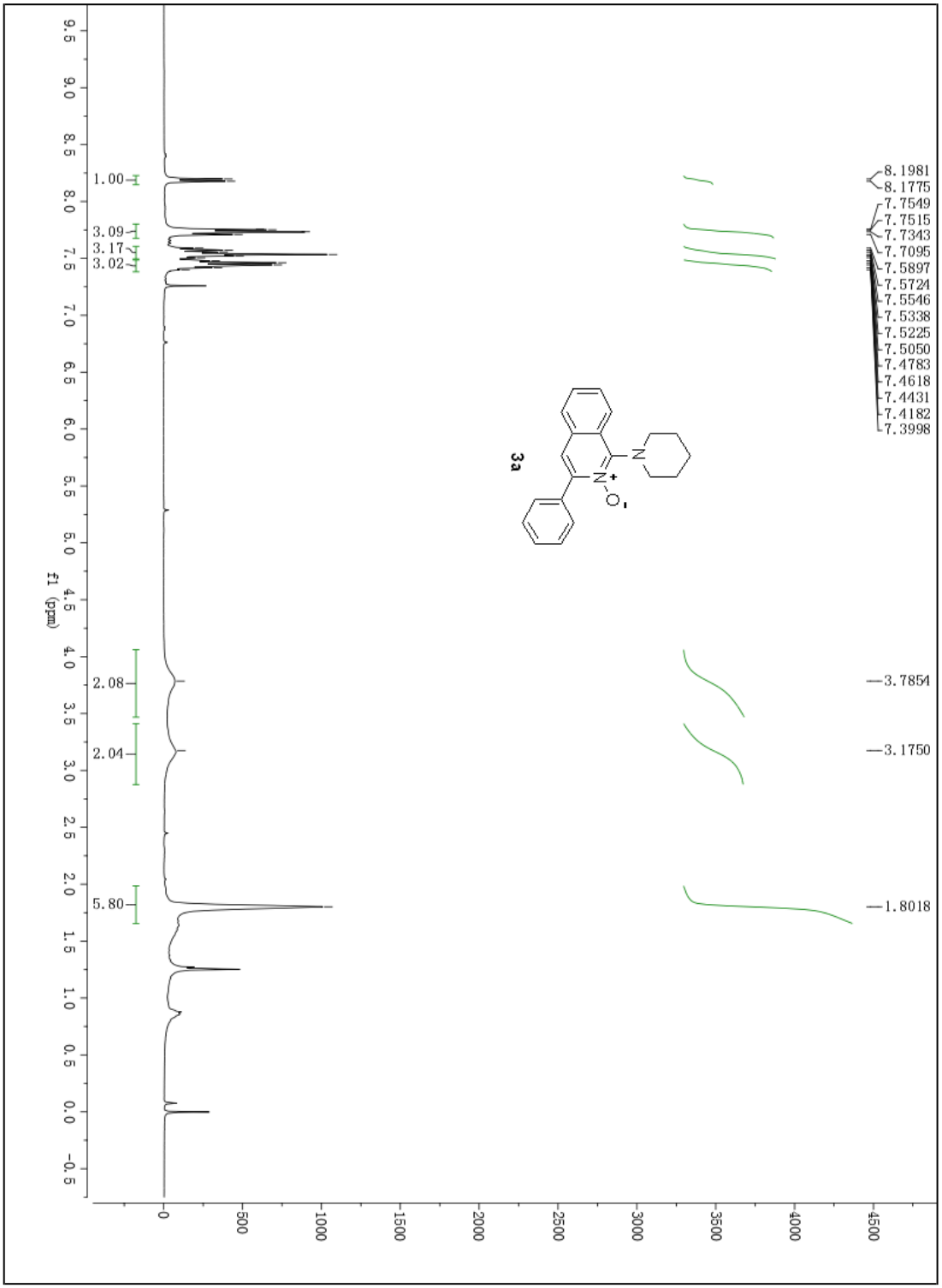
1-(Azepan-1-yl)-3-phenylisoquinoline 2-oxide **3m**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.3 Hz, 1H), 7.76 -7.72 (m, 3H), 7.60 – 7.57 (m, 2H), 7.54 -7.50 (m, 1H), 7.48 - 7.40 (m, 3H), 3.43 (s, 4H), 1.83 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 147.6, 133.7, 130.9, 130.1, 129.8, 128.9, 128.4, 128.2, 128.0, 126.8, 124.4, 121.4, 51.1, 30.5, 28.2; HRMS (ESI) calcd for $C_{21}H_{22}N_2O$: 319.1805 ($M + H^+$), found: 319.1803.



1-Morpholino-3-phenylisoquinoline 2-oxide **3n**

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.75 -7.72 (m, 3H), 7.61 - 7.54 (m, 3H), 7.50 - 7.43 (m, 3H), 3.96 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 147.5, 133.5, 130.9, 130.2, 129.7, 129.0, 128.5, 128.4, 128.1, 127.1, 123.8, 121.3, 67.9, 48.5; HRMS (ESI) calcd for $C_{19}H_{18}N_2O_2$: 307.1441 ($M + H^+$), found: 307.1447.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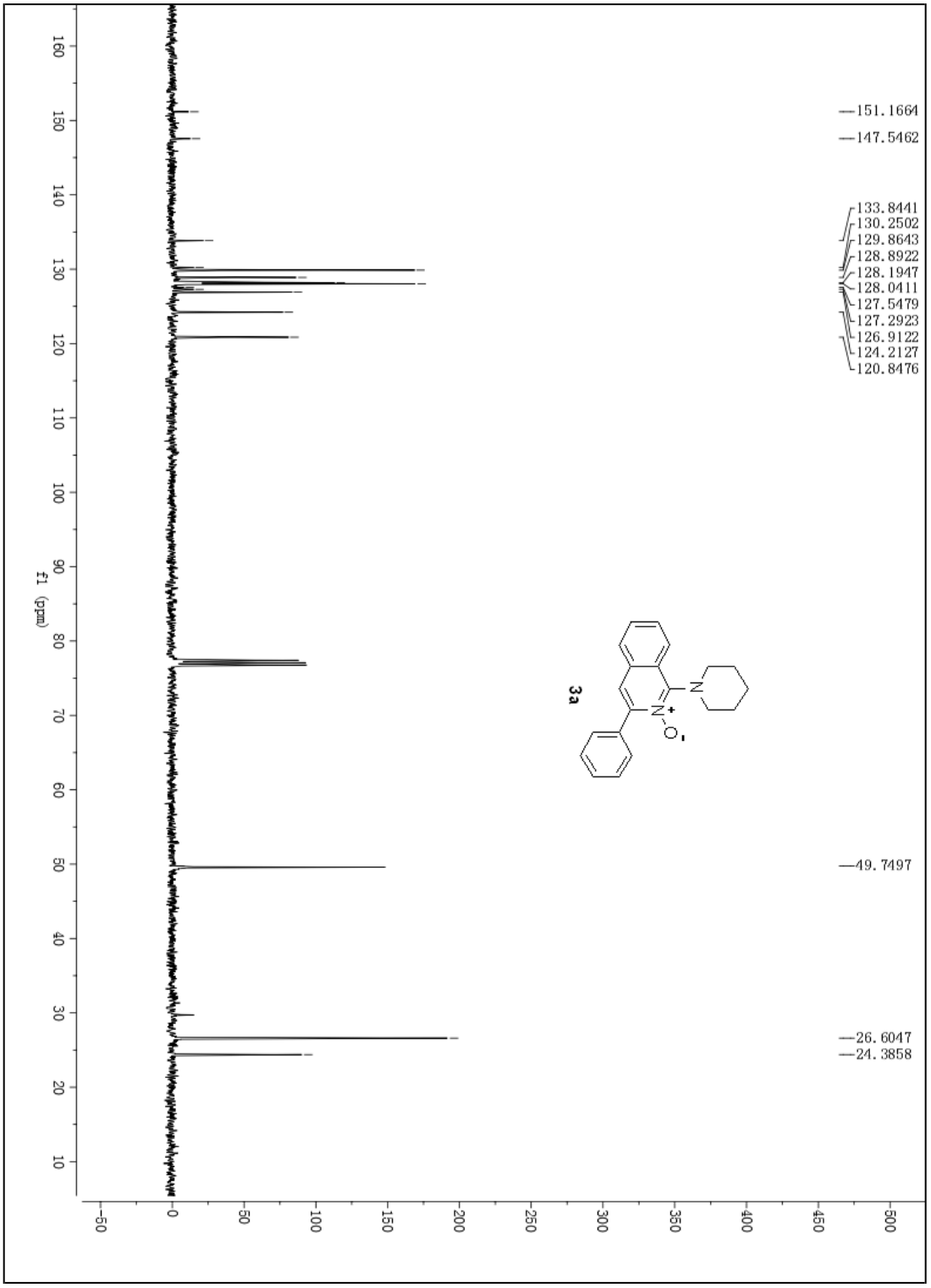
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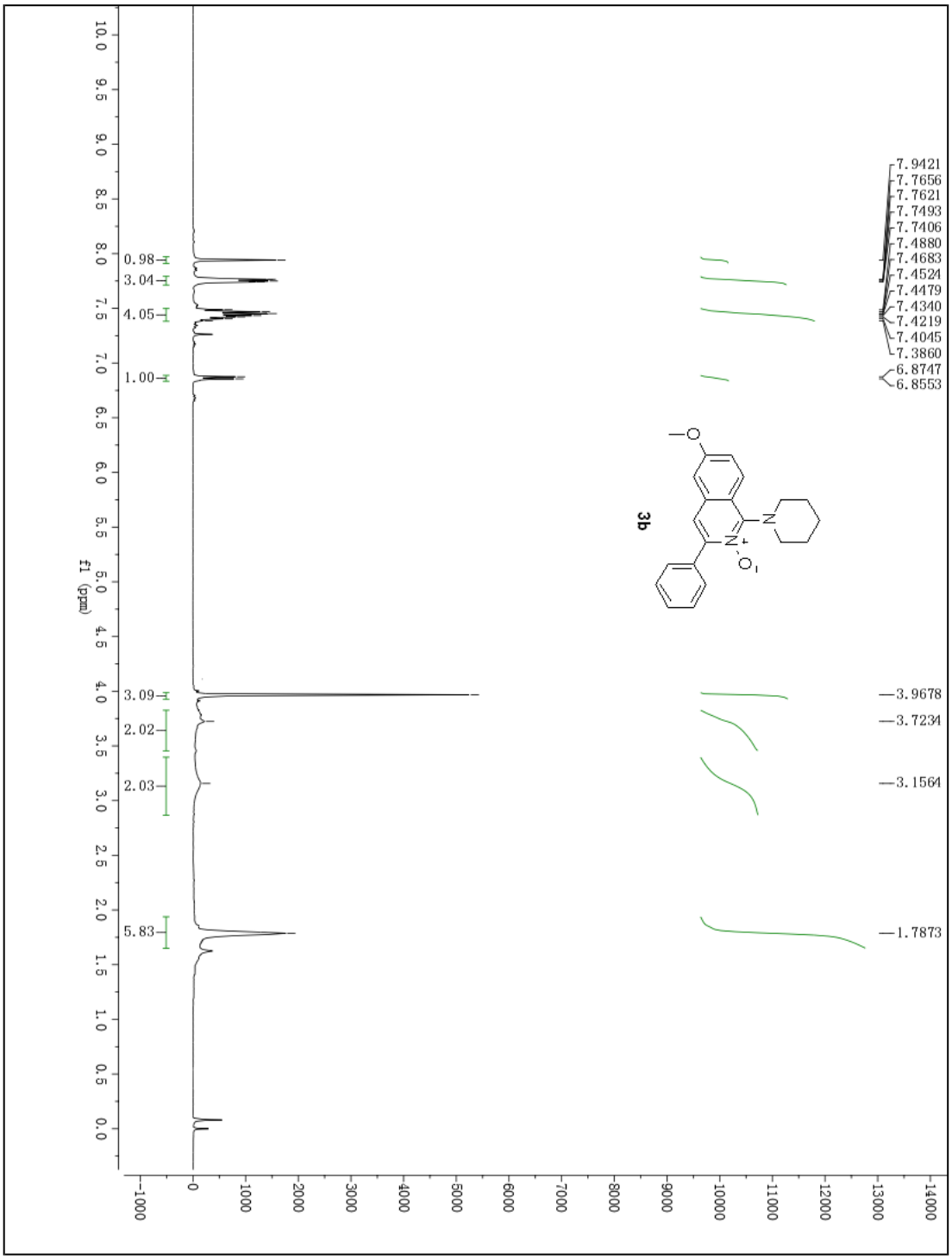
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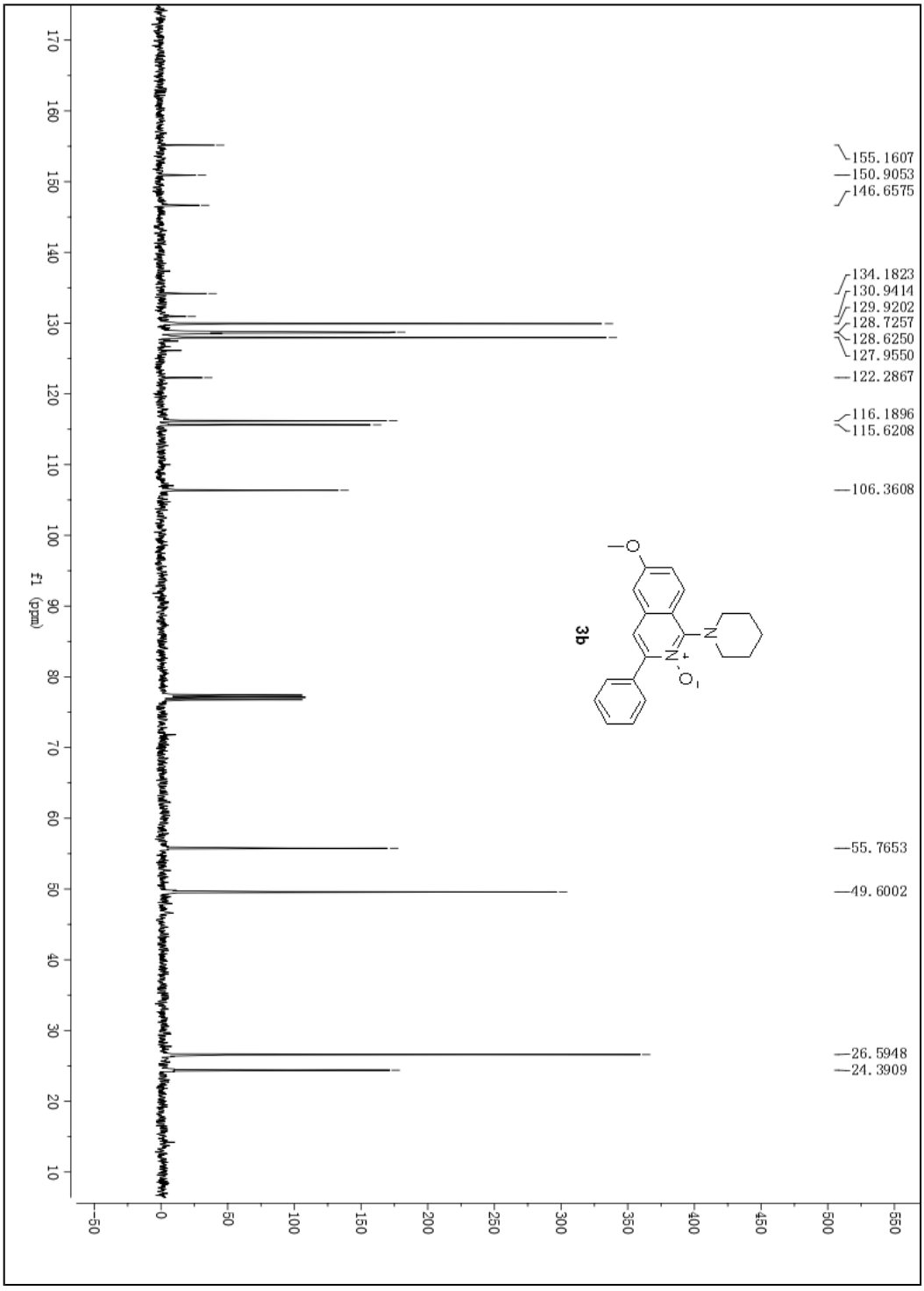
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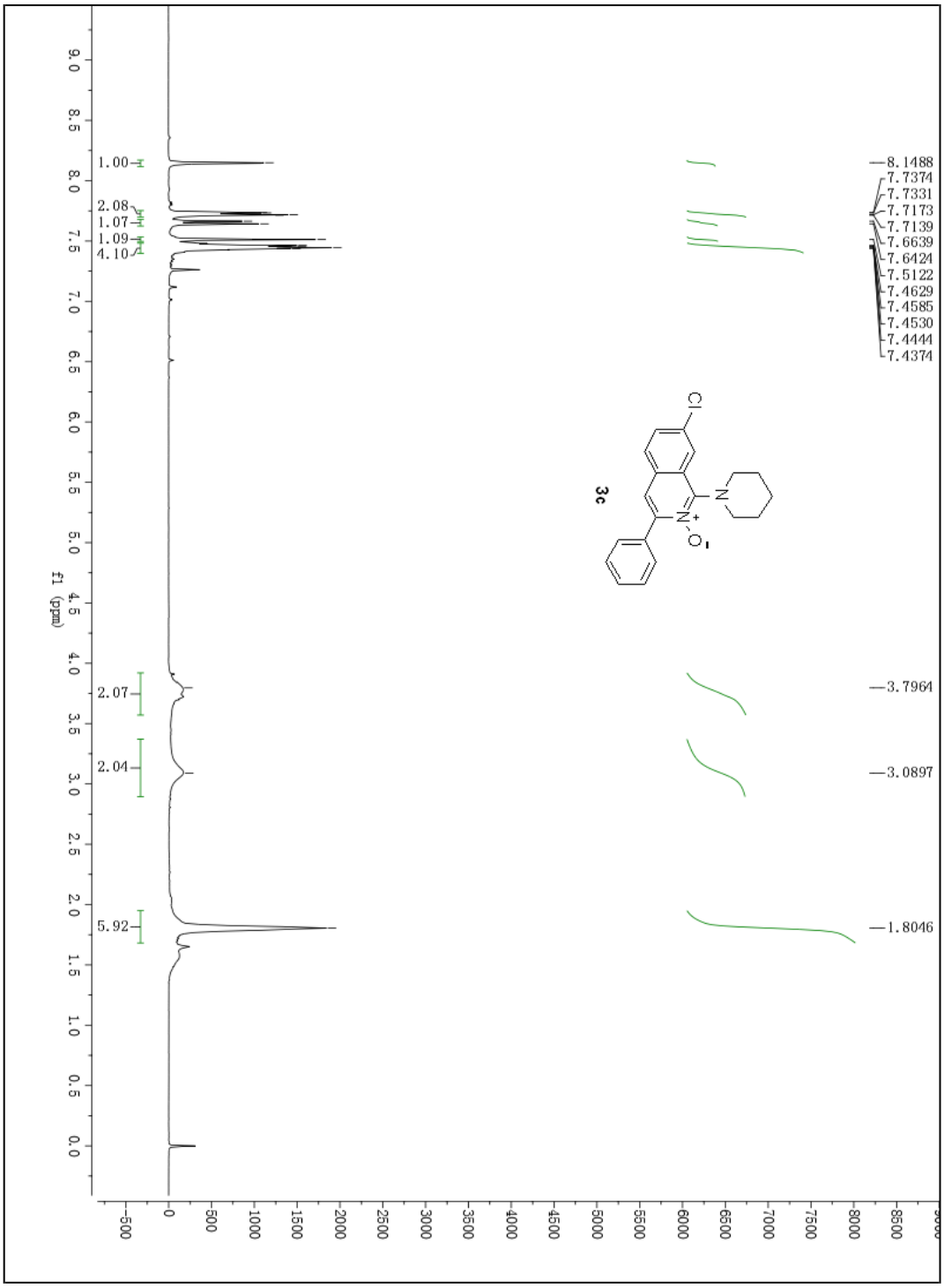
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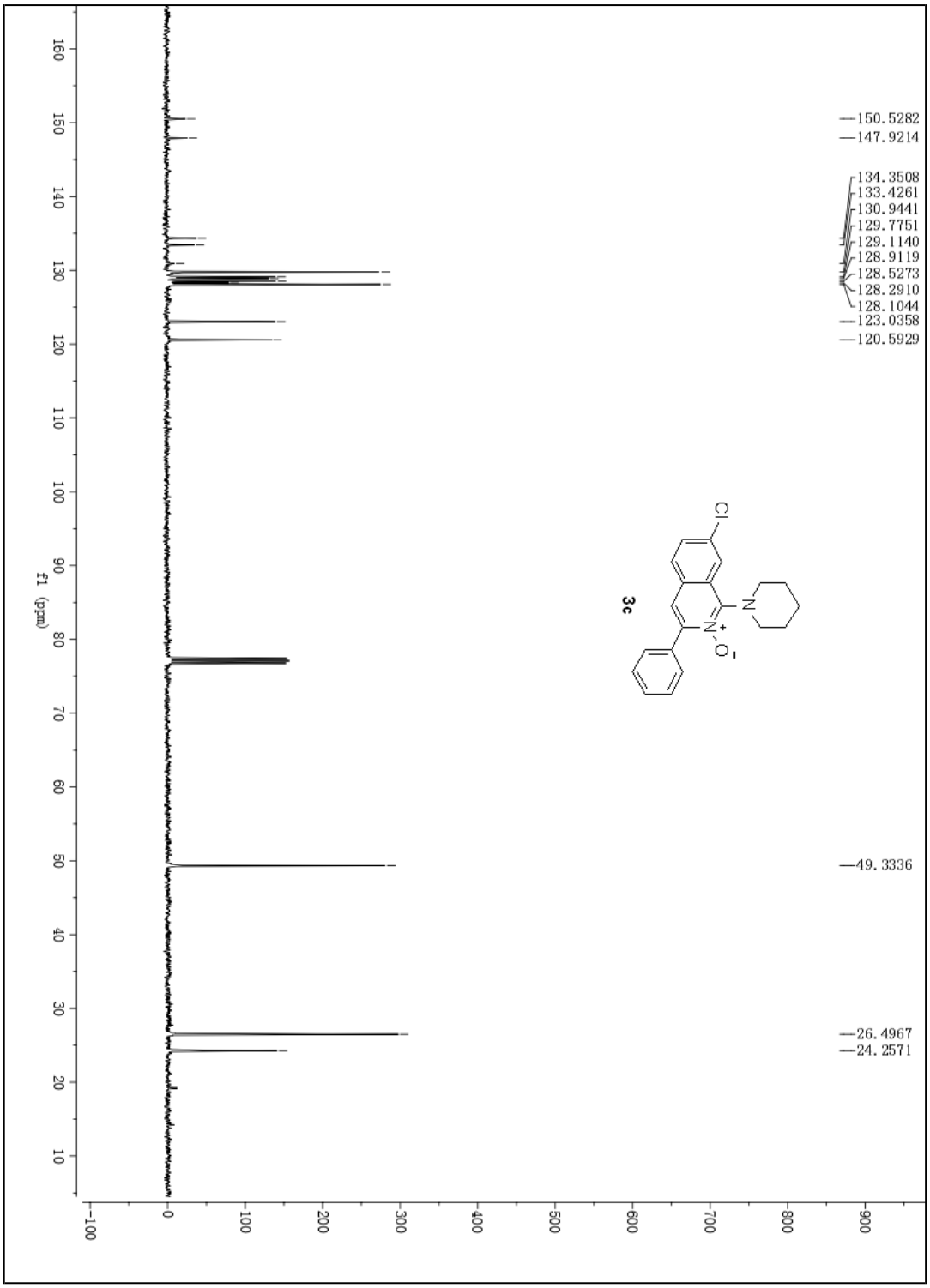
O-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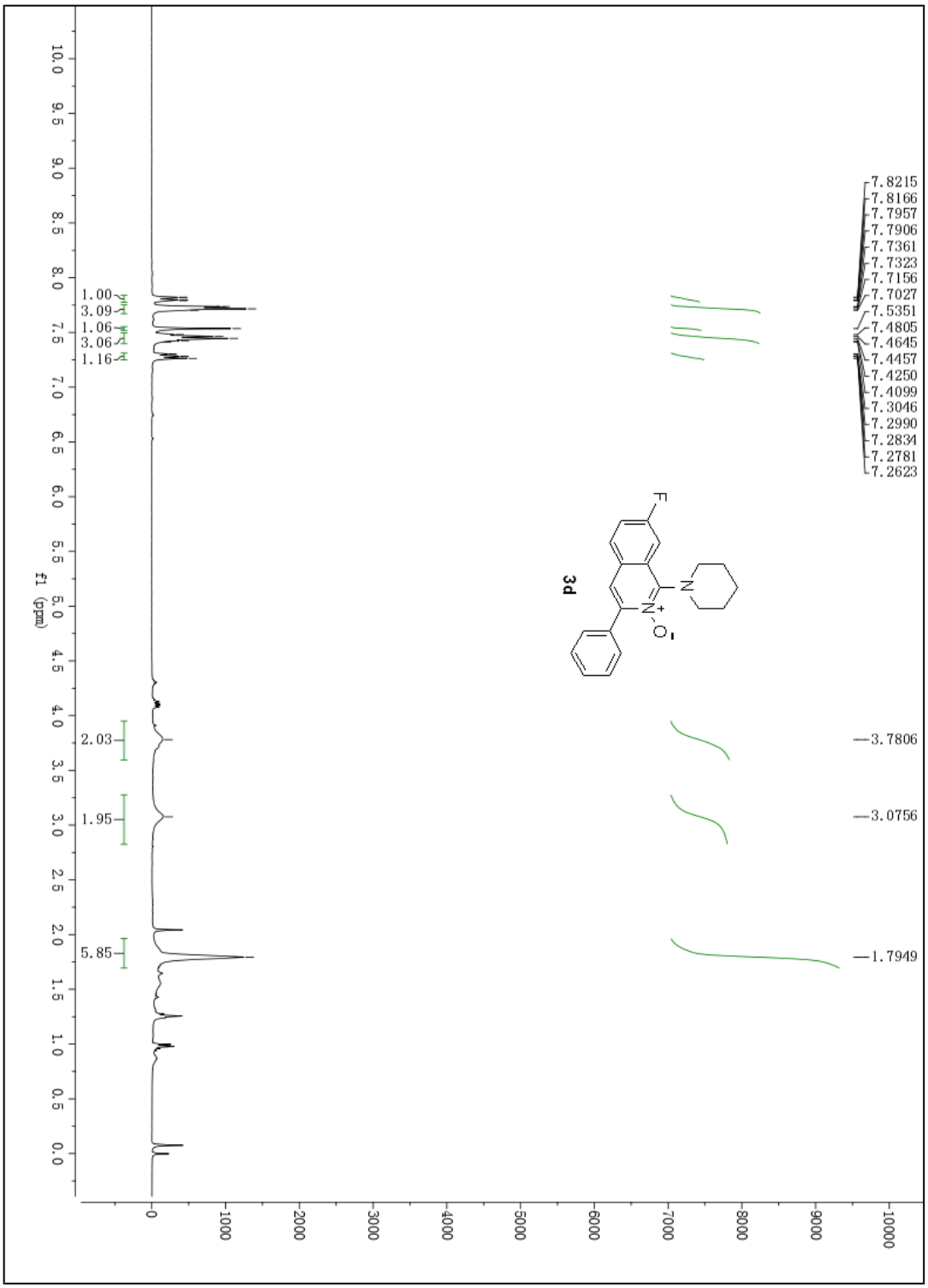
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7.7156
7.7027
7.5351
7.4805
7.4645
7.4457
7.4250
7.4099
7.3046
7.2990
7.2834
7.2781
7.2623
1.00
3.09
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1.16
2.03
1.95
5.85
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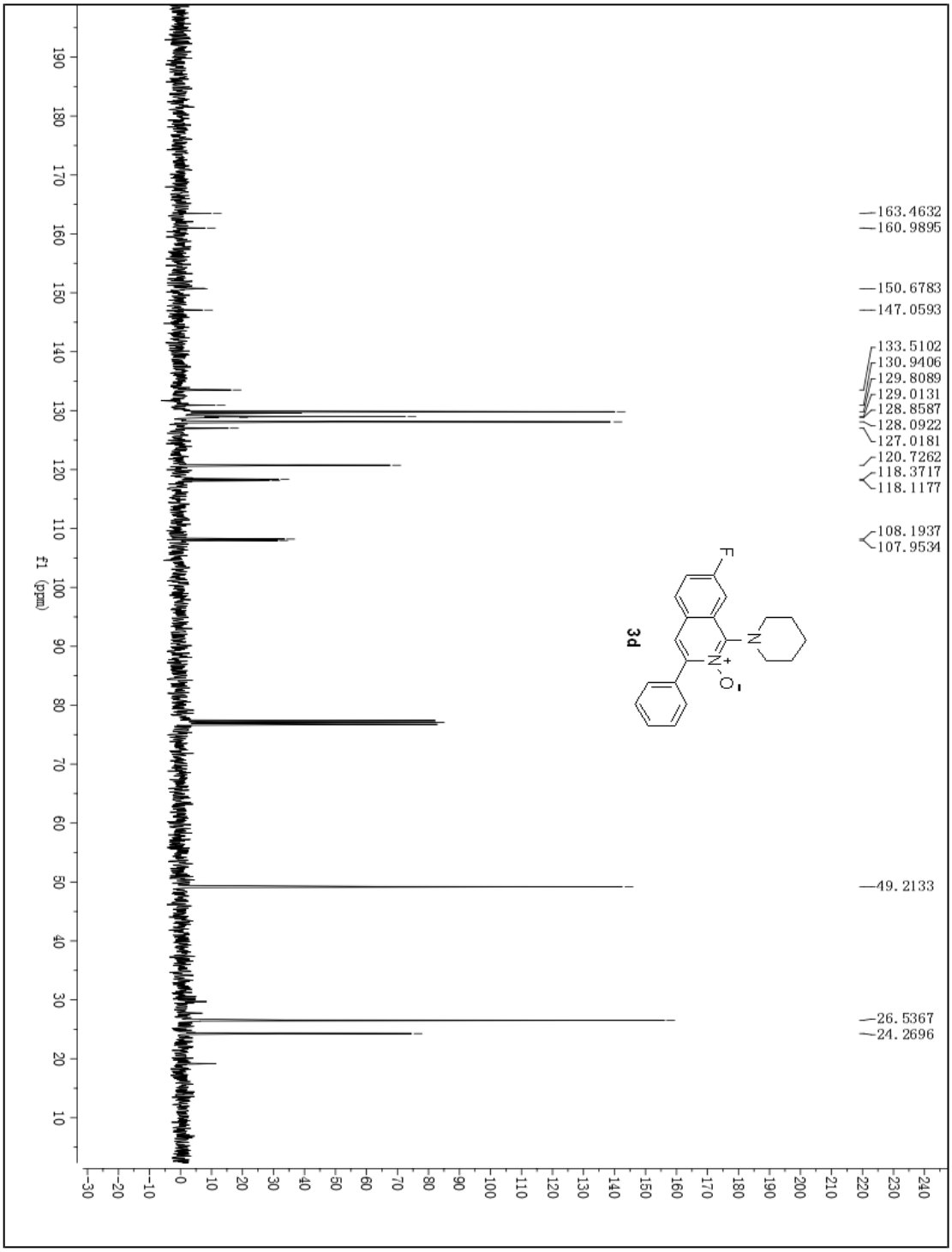
3.0756
1.7949
3d
f1 (ppm)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129.8089
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128.8587
128.0922
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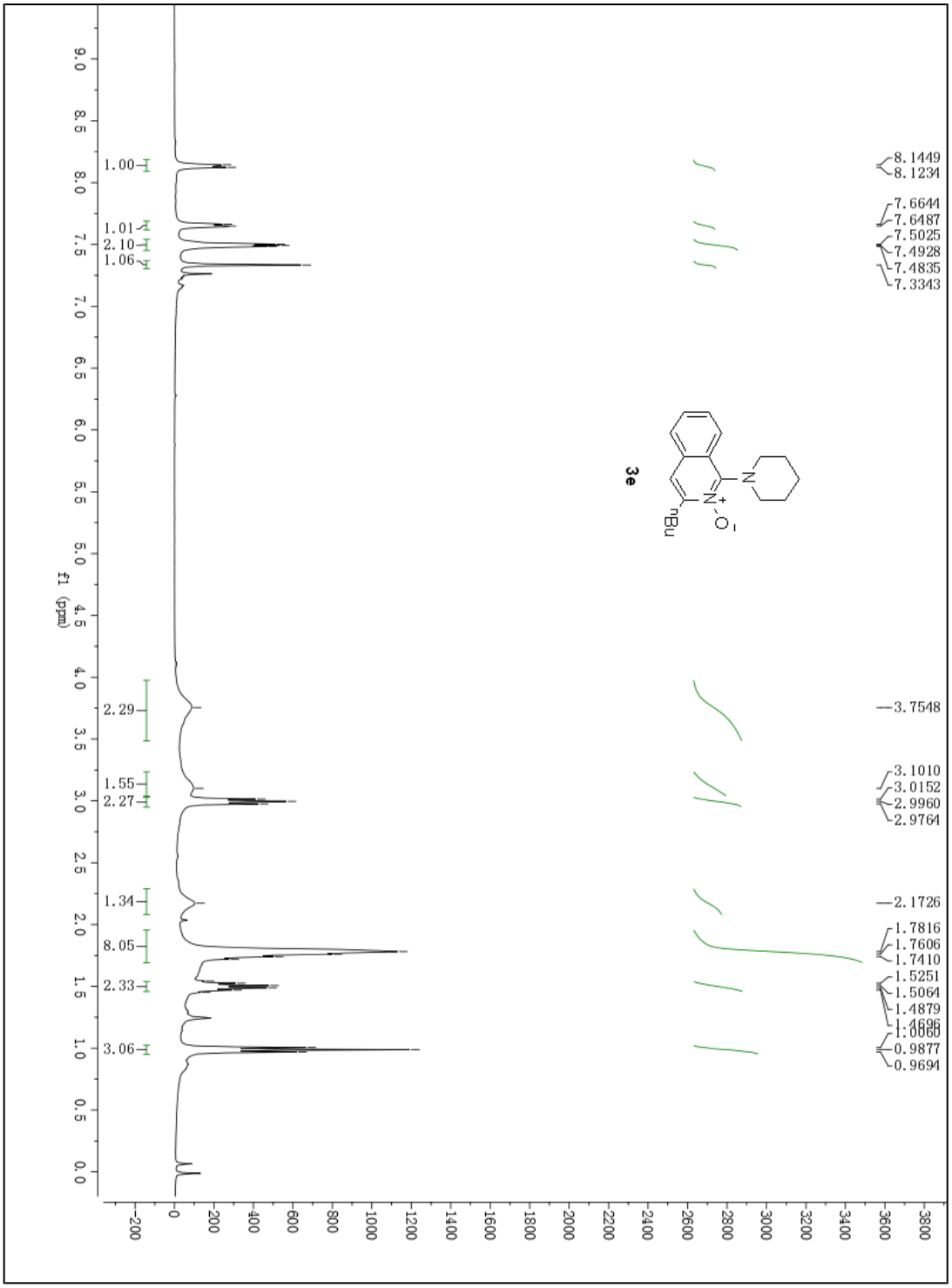
118.3717
118.1177
108.1937
107.9534
49.2133
26.5367
24.2696
3d
f1 (ppm)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f1 (ppm)
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2.29
1.55
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1.34
8.05
2.33
3.06
8.1449
8.1234
7.6644
7.6487
7.5025
7.4928
7.4835
7.3343
3.7548
3.1010
3.0152
2.9960
2.9764
2.1726
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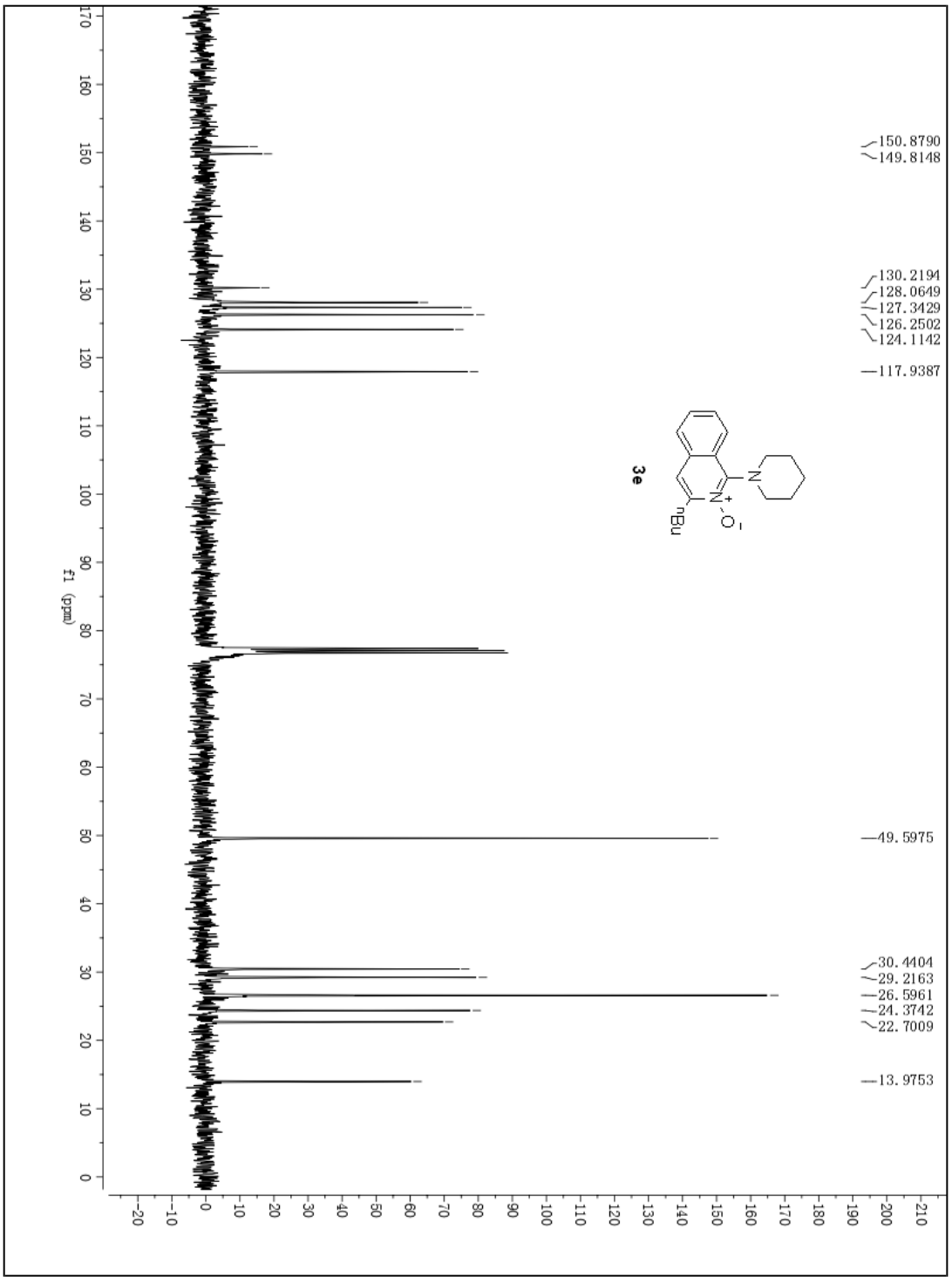
1.7410
1.5251
1.5064
1.4879
1.4696
1.0060
0.9877
0.9694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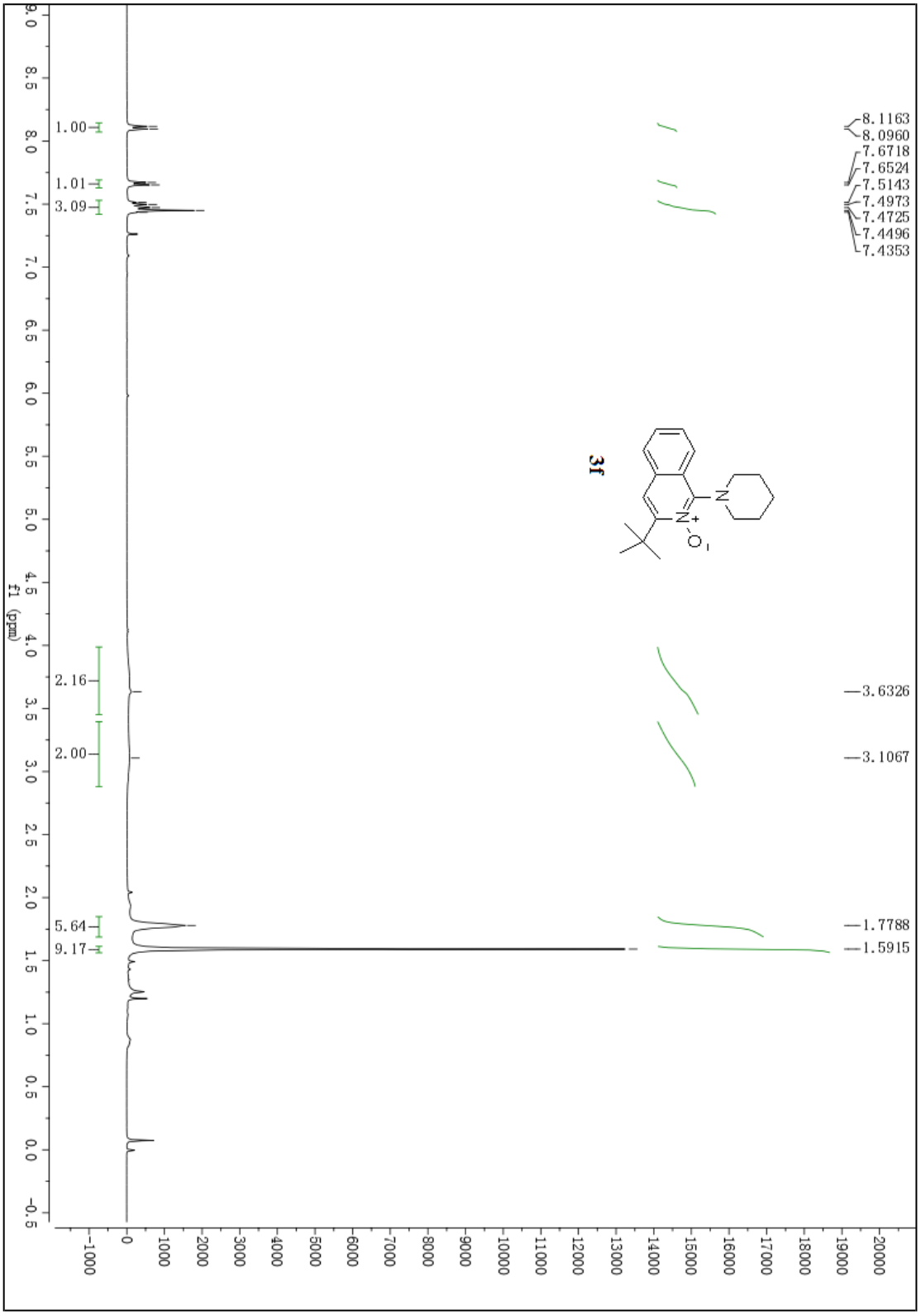
30.4404
29.2163
26.5961
24.3742
22.7009
13.9753
3e
nBu
f1 (ppm)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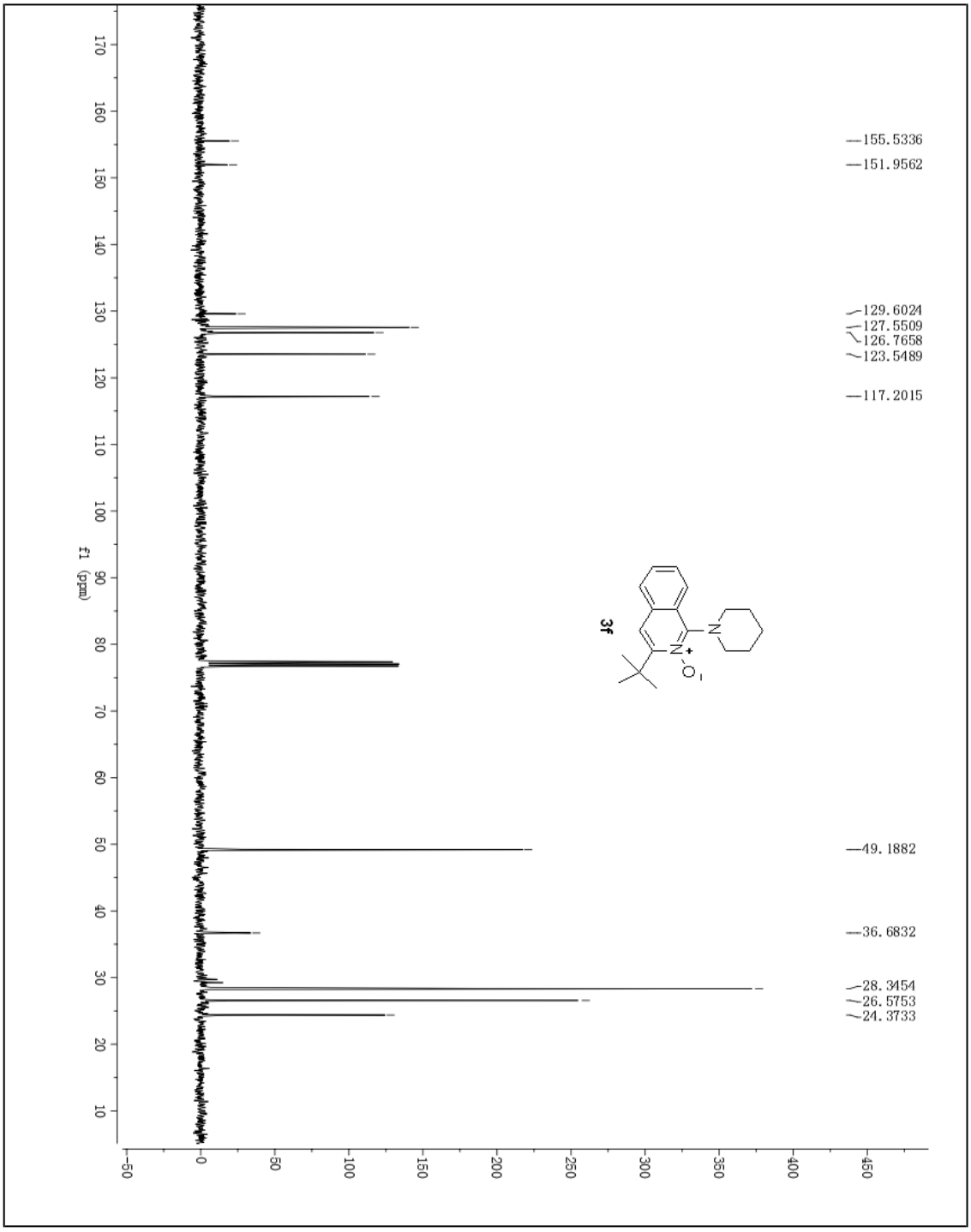
7.6524
7.5143
7.4973
7.4725
7.4496
7.4353
3.6326
3.1067
1.7788
1.5915
1.00
1.01
3.09
2.16
2.00
5.64
9.17
f1 (ppm)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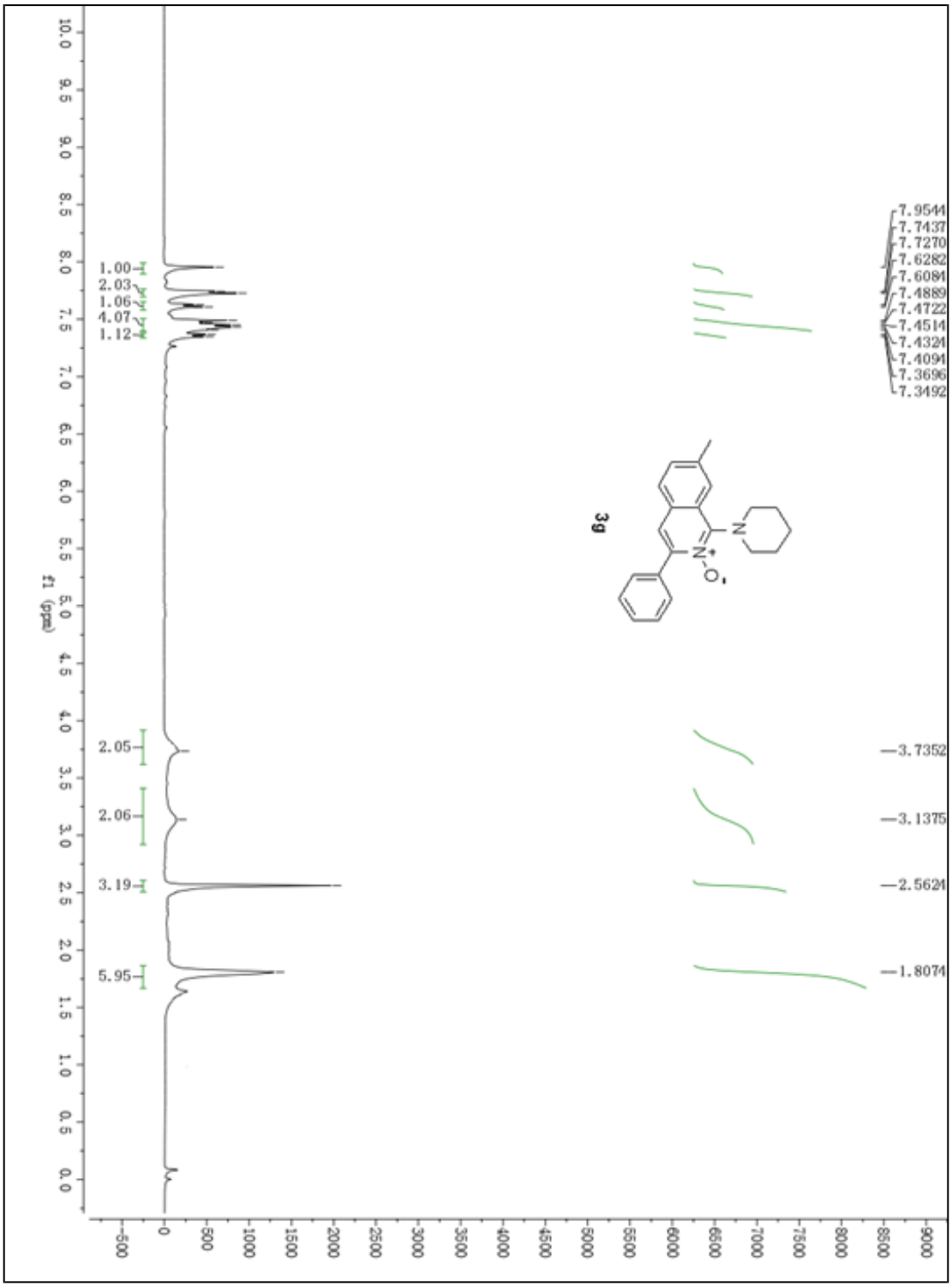
127.5509
126.7658
123.5489
117.2015
49.1882
36.6832
28.3454
26.5753
24.3733
3f
f1 (ppm)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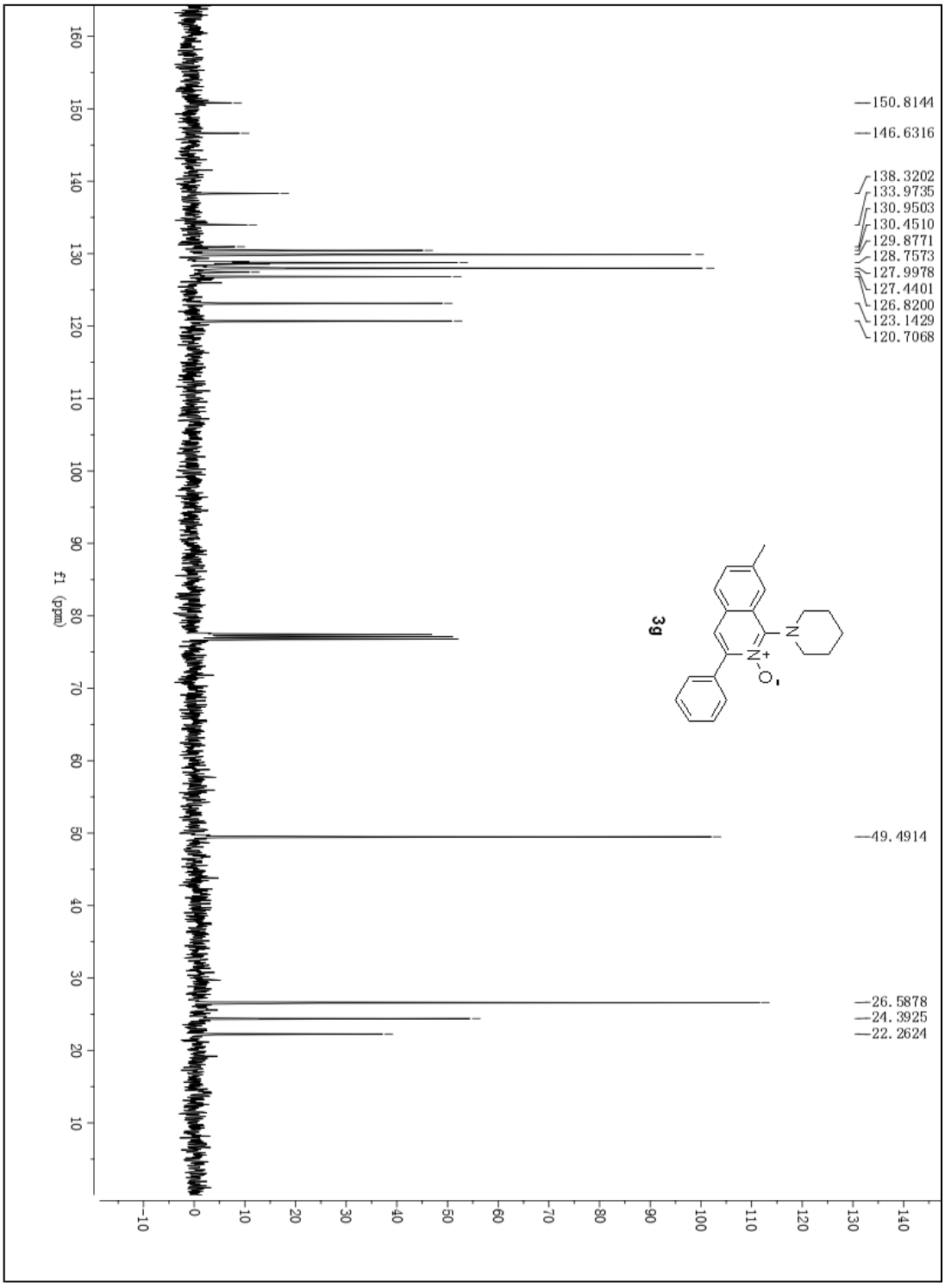
7.7437
7.7270
7.6282
7.6081
7.4889
7.4722
7.4514
7.4321
7.4091
7.3696
7.3492
1.00
2.03
1.06
4.07
1.12
2.05
2.06
3.19
5.95
3.7352
3.1375
2.5621
1.8071
3g
f1 (ppm)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130.9503
130.4510
129.8771
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127.9978
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123.1429
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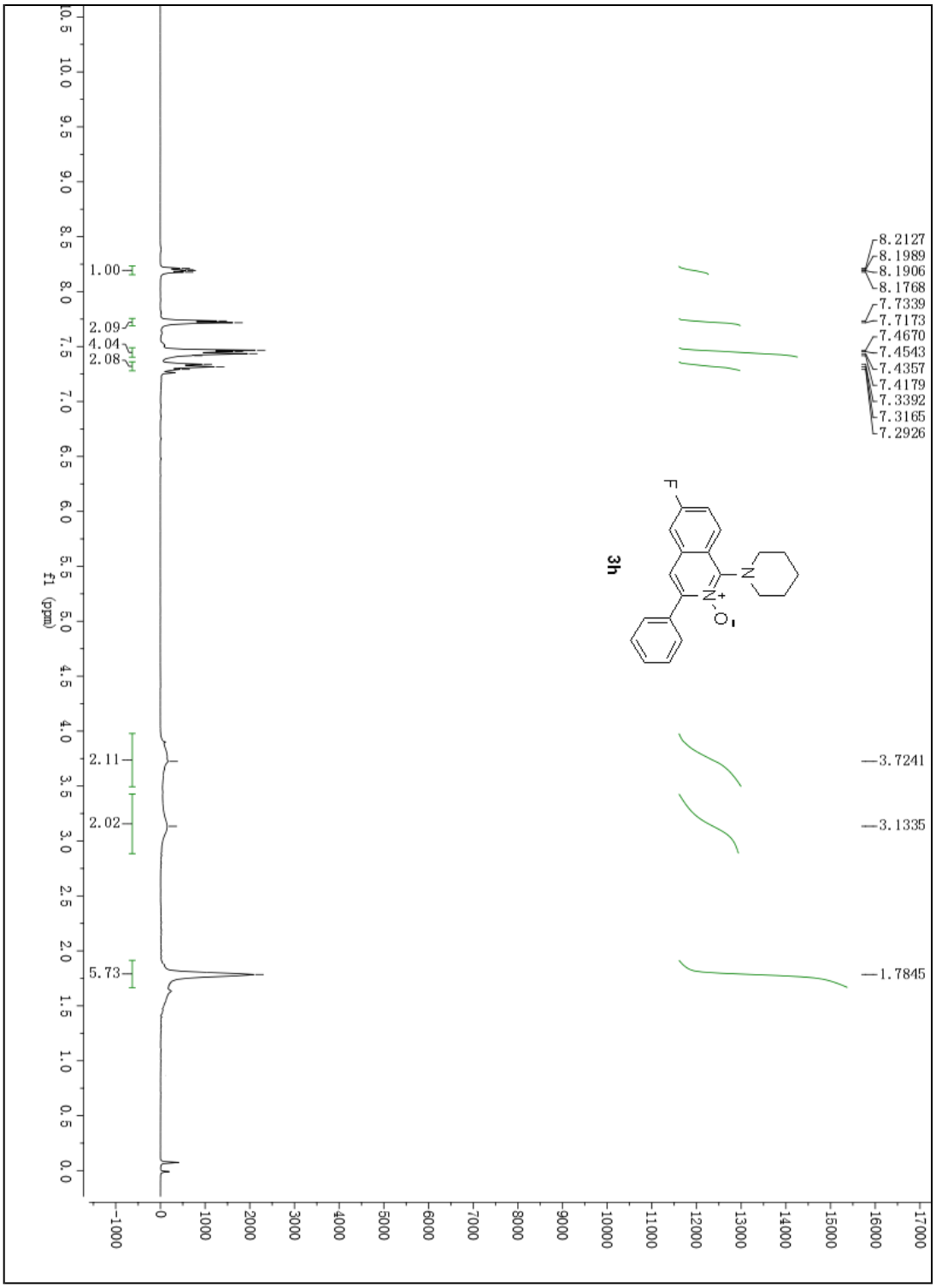
49.4914
26.5878
24.3925
22.2624
3g
f1 (ppm)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8.1989
8.1906
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7.4670
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7.4357
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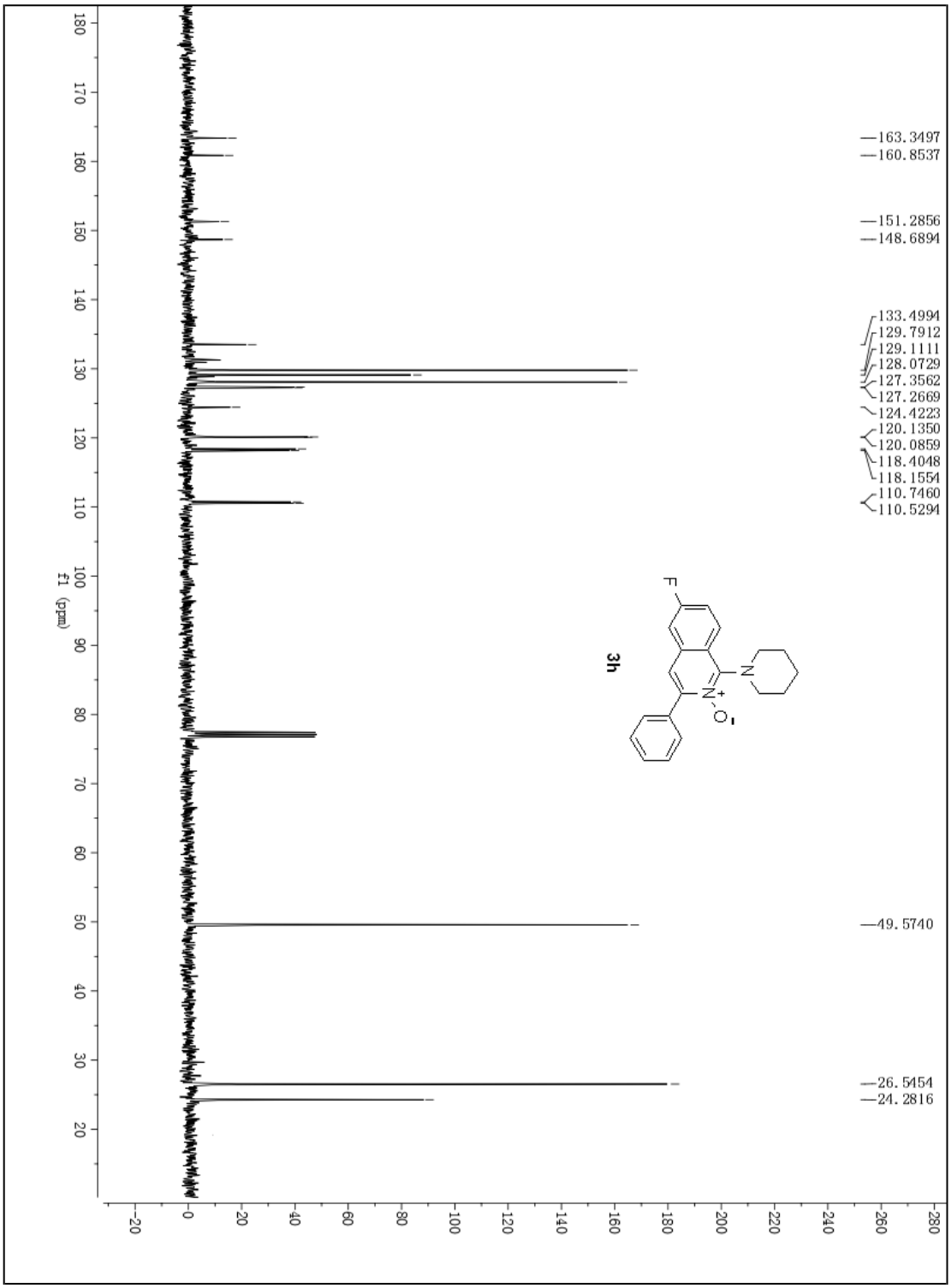
7.3392
7.3165
7.2926
1.00
2.09
4.04
2.08
2.11
2.02
5.73
3.7241
3.1335
1.7845
3h
F
N
N+
O-
f1 (ppm)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124.4223
120.1350
120.0859
118.4048
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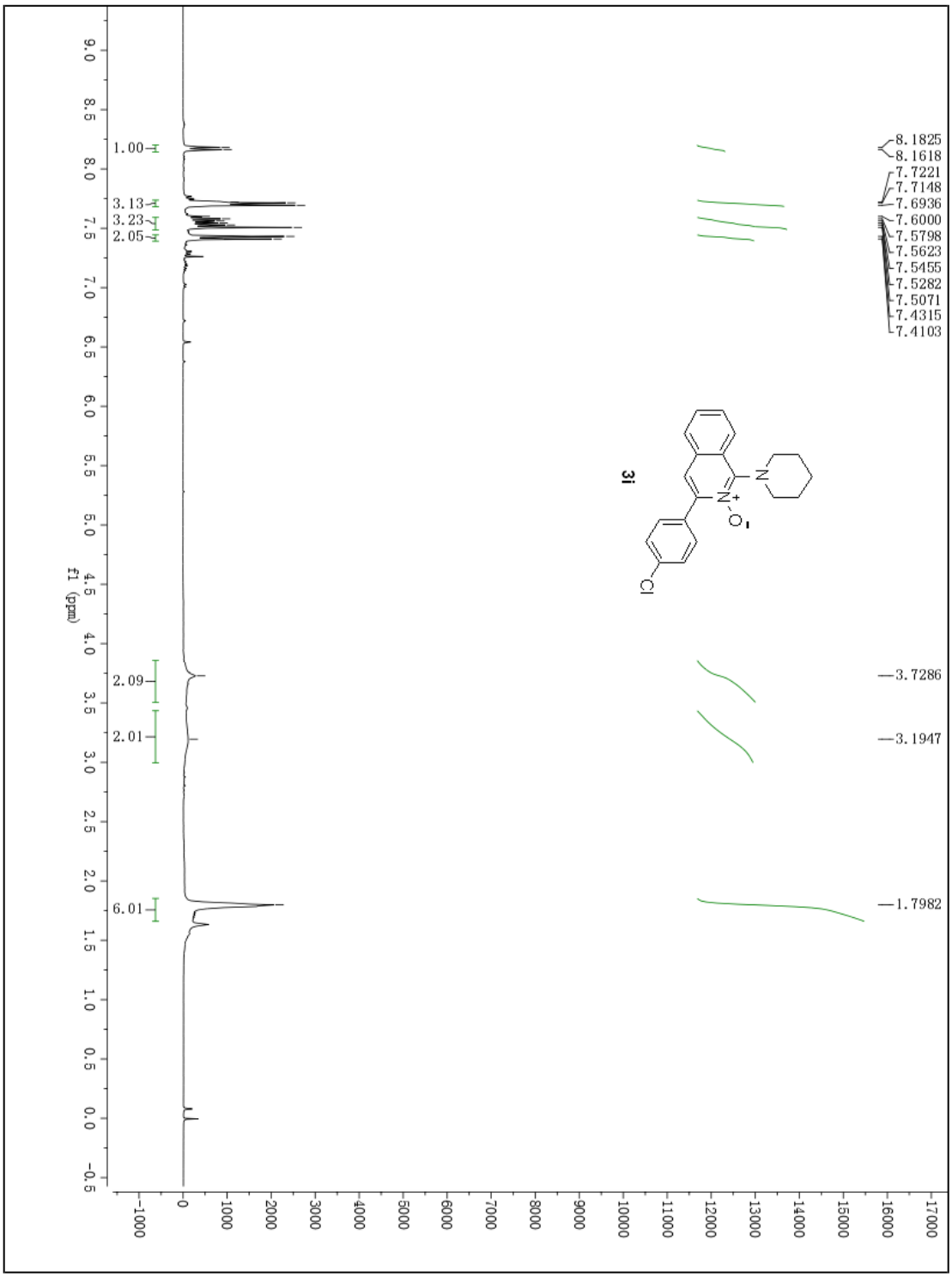
110.5294
49.5740
26.5454
24.2816
3h
F
N
N+
O-
f1 (ppm)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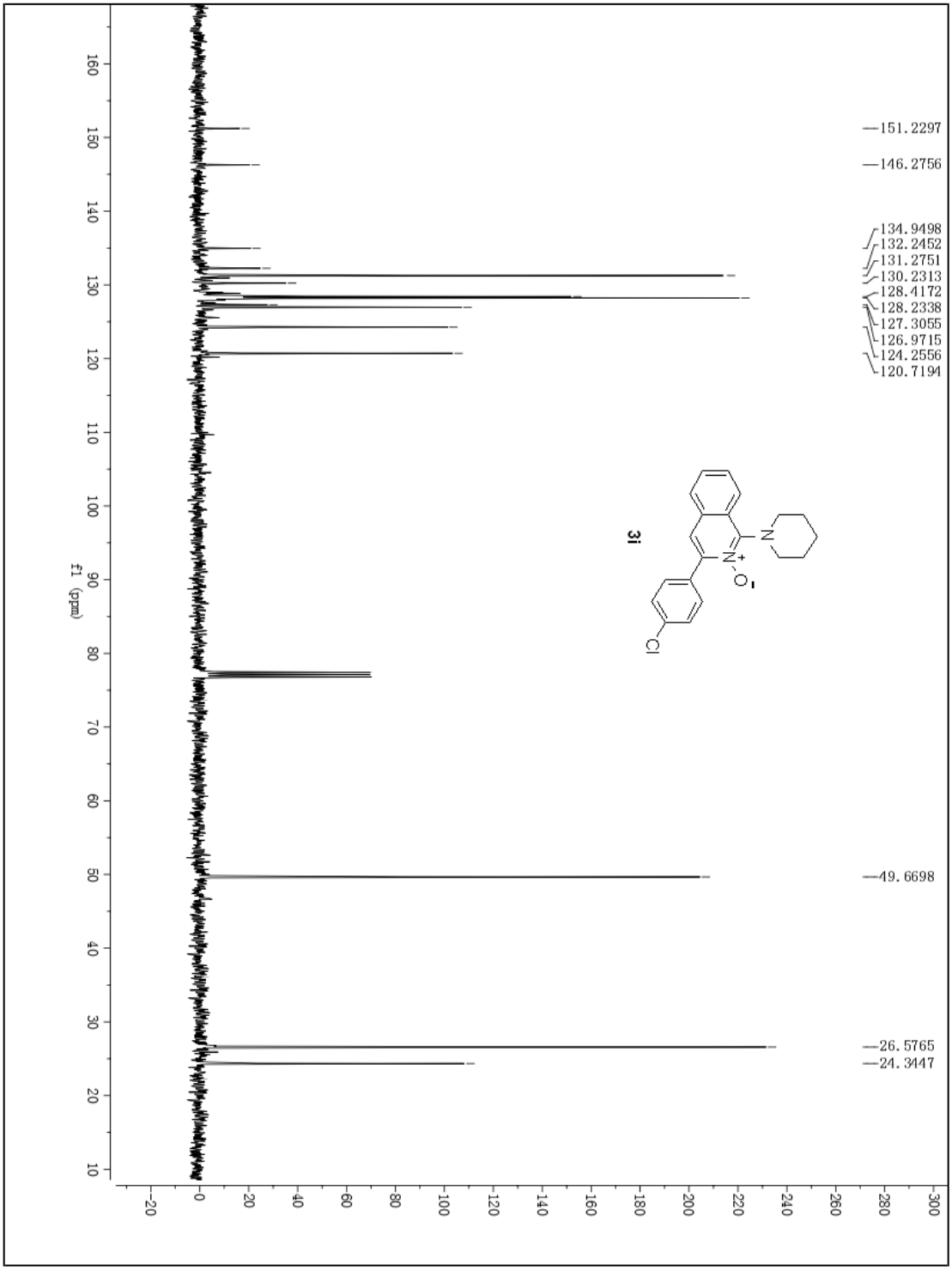
7.7148
7.6936
7.6000
7.5798
7.5623
7.5455
7.5282
7.5071
7.4315
7.4103
1.00
3.13
3.23
2.05
2.09
2.01
6.01
3.7286
3.1947
1.7982
3i
Cl
f1 (ppm)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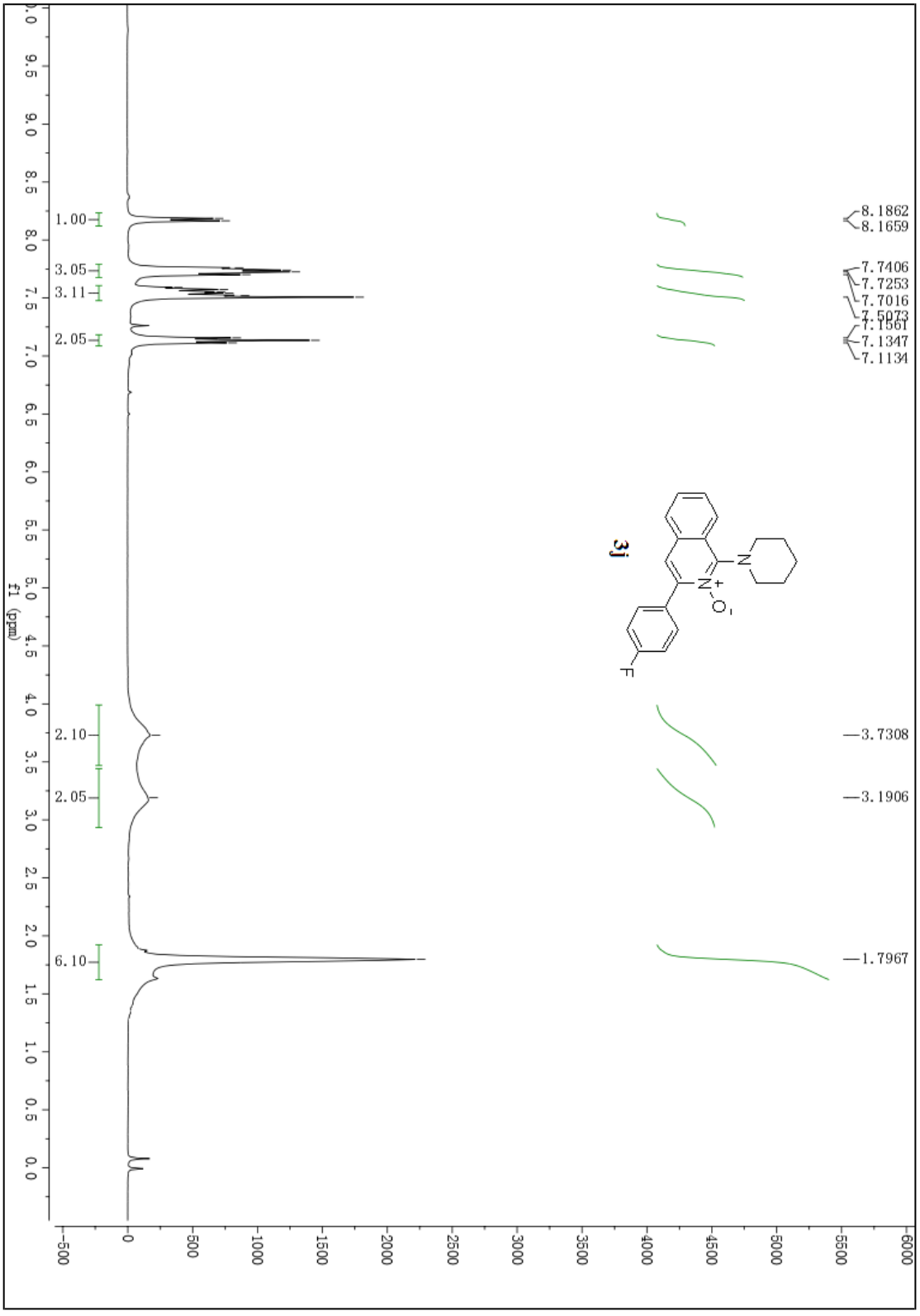
120.7194
49.6698
26.5765
24.3447
3i
Cl
f1 (ppm)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2.05
2.10
2.05
6.10
8.1862
8.1659
7.7406
7.7253
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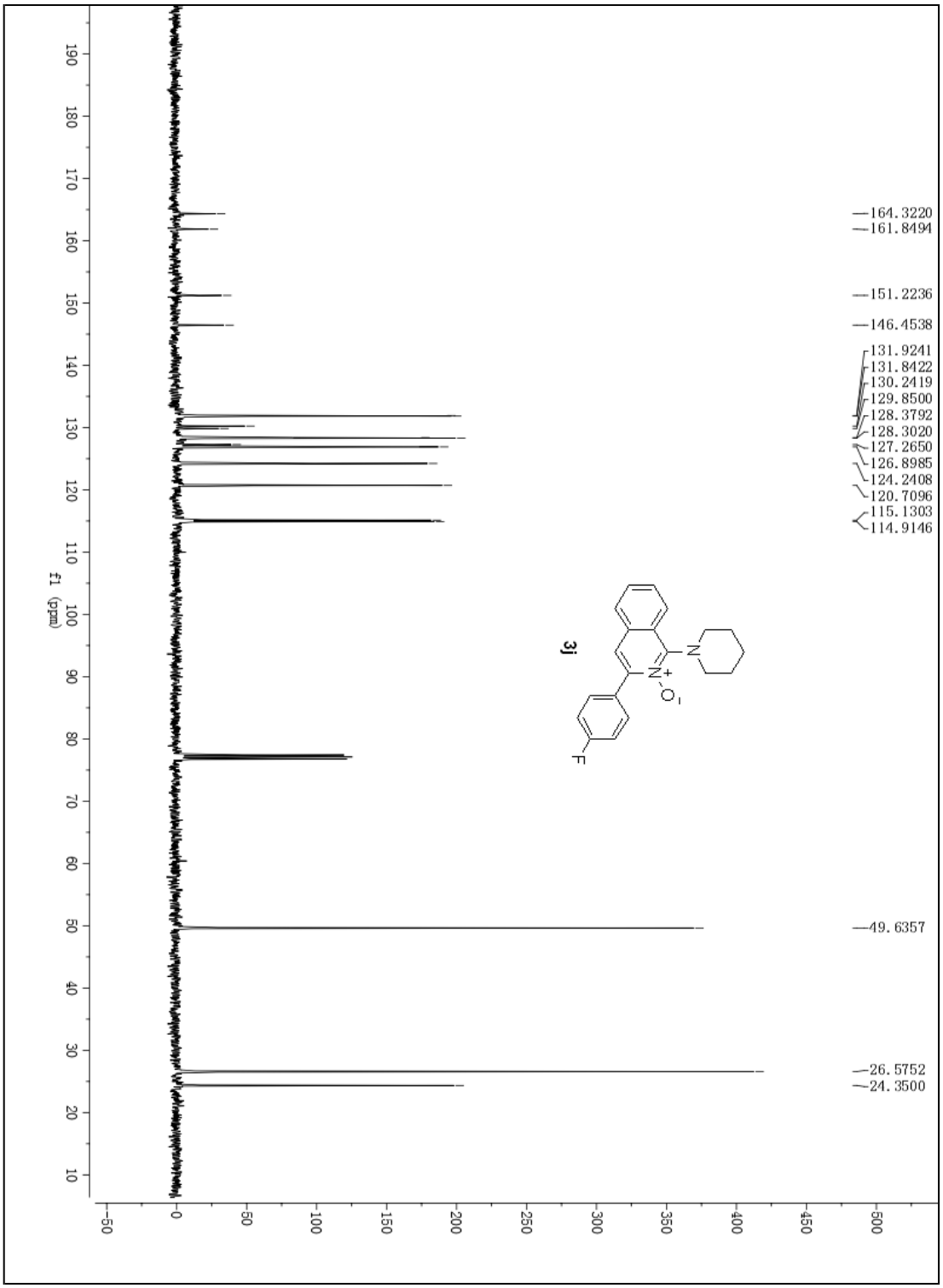
7.1134
3.7308
3.1906
1.7967
3j
f1 (ppm)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127.2650
126.8985
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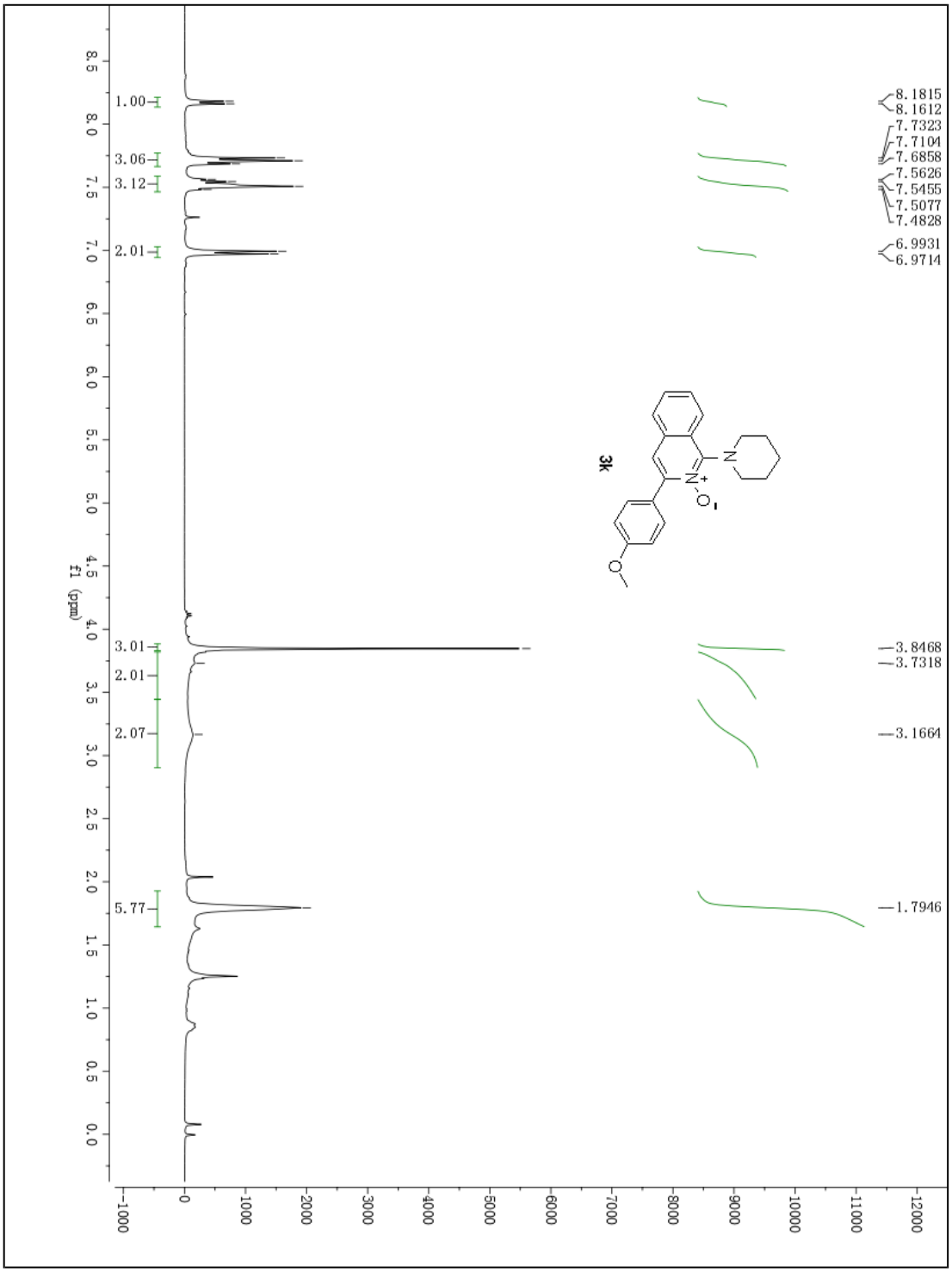
115.1303
114.9146
49.6357
26.5752
24.3500
3j
f1 (ppm)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7.5626
7.5455
7.5077
7.4828
6.9931
6.9714
3.8468
3.7318
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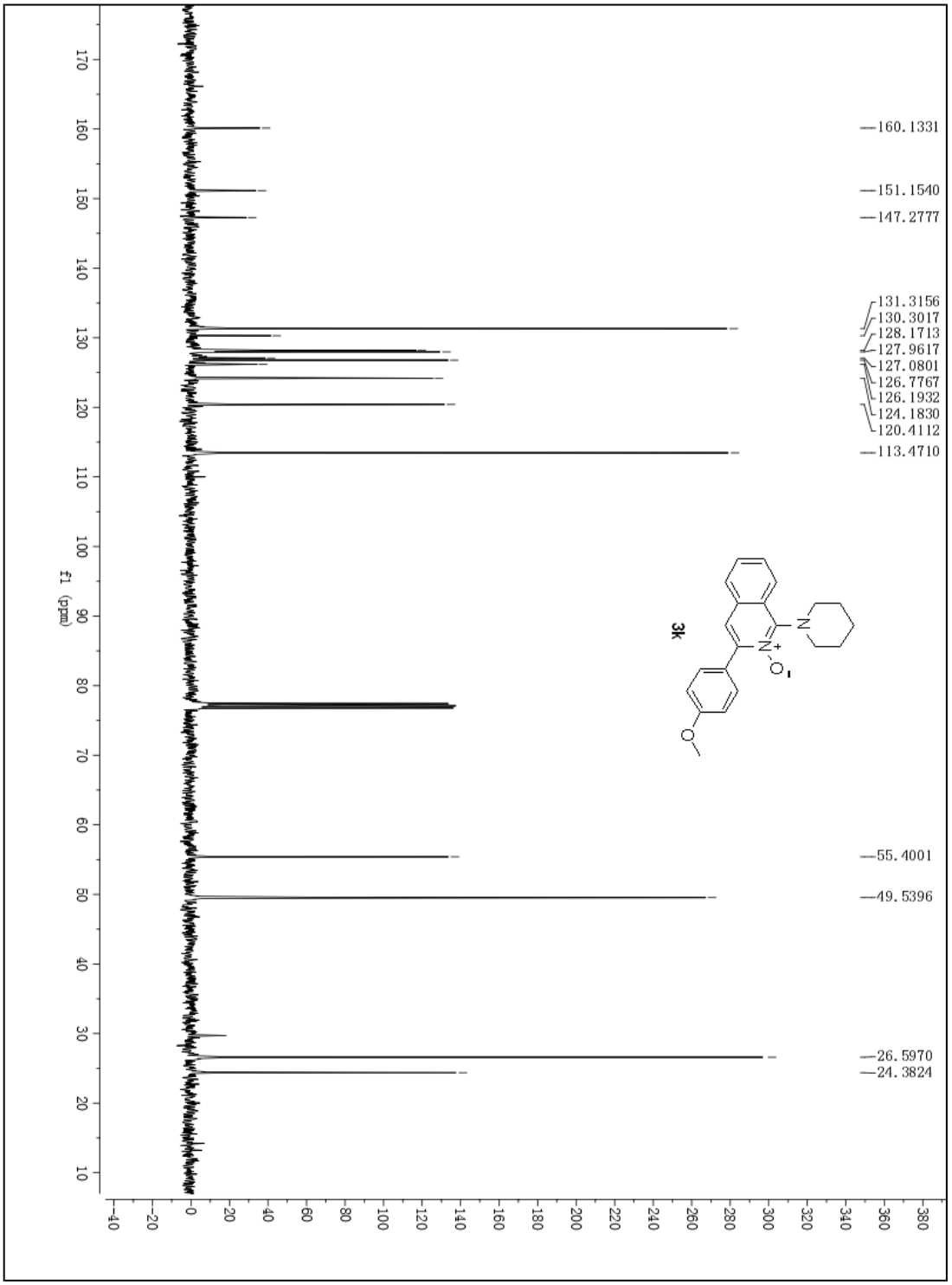
1.7946
1.00
3.06
3.12
2.01
3.01
2.01
2.07
5.77
3k
f1 (ppm)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127.9617
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126.7767
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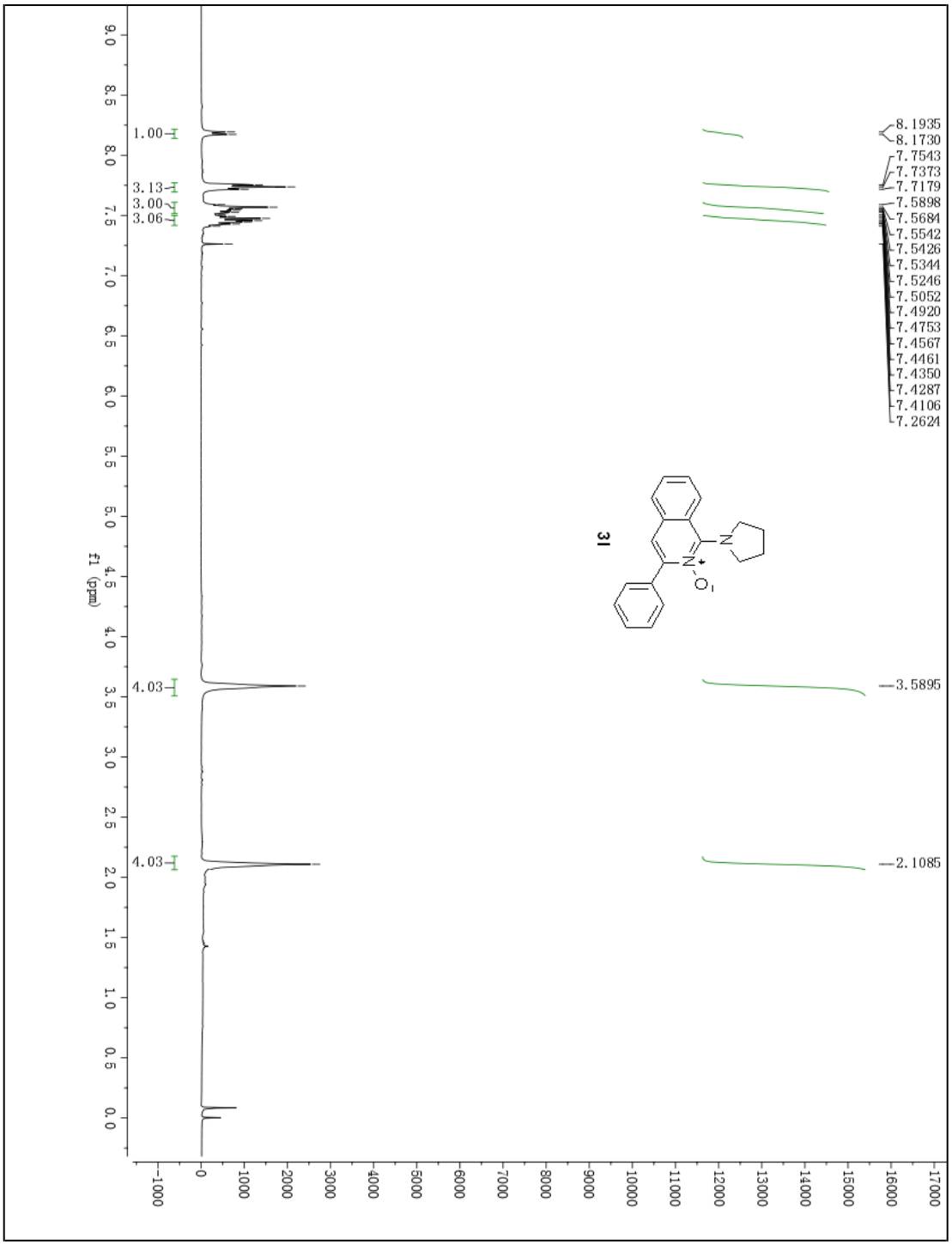
26.5970
24.3824
3k
f1 (ppm)


f1 (ppm)
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3.13
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4.03
4.03
8.1935
8.1730
7.7543
7.7373
7.7179
7.5898
7.5684
7.5542
7.5426
7.5344
7.5246
7.5052
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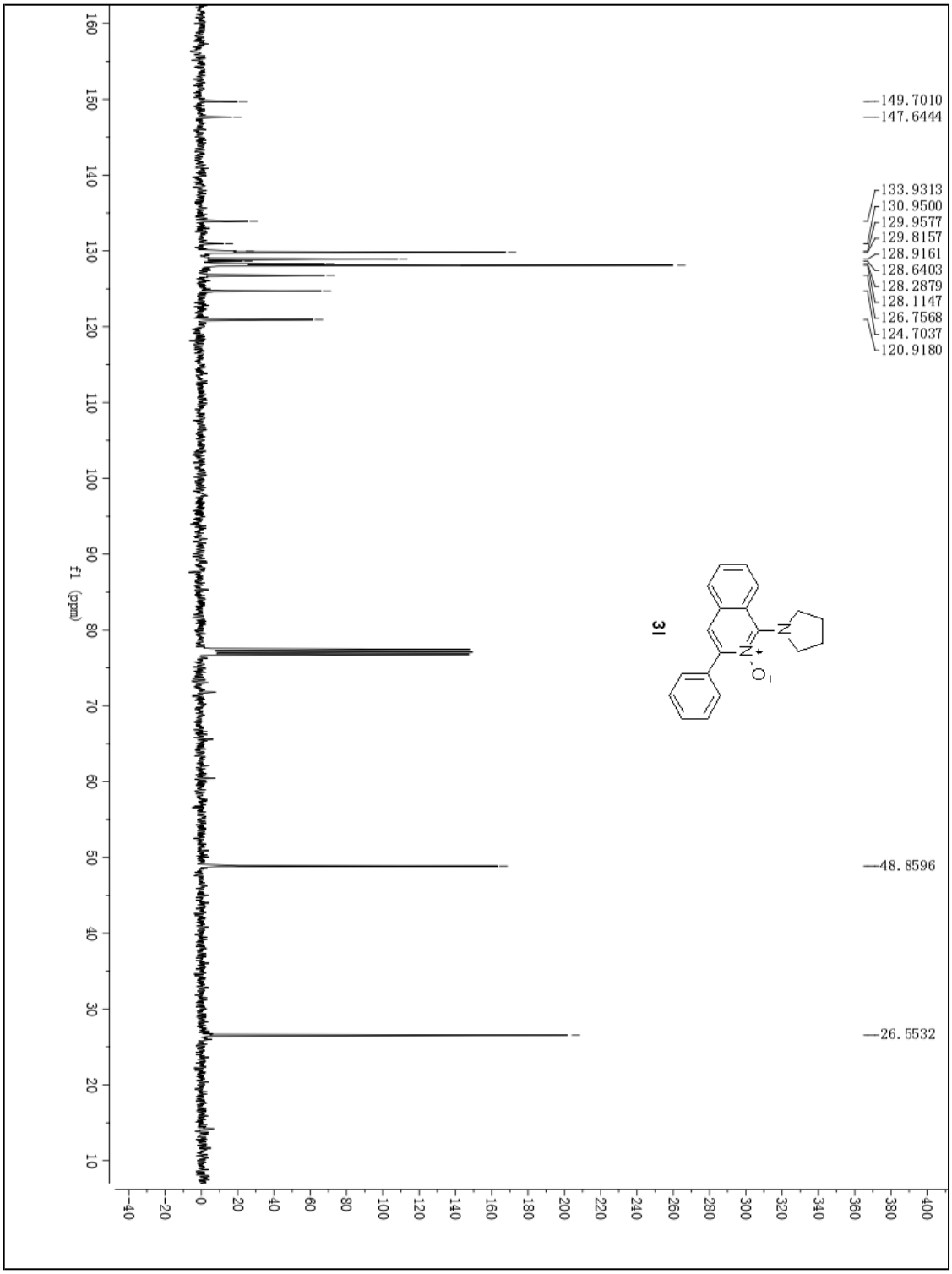
7.2624
3.5895
2.1085
31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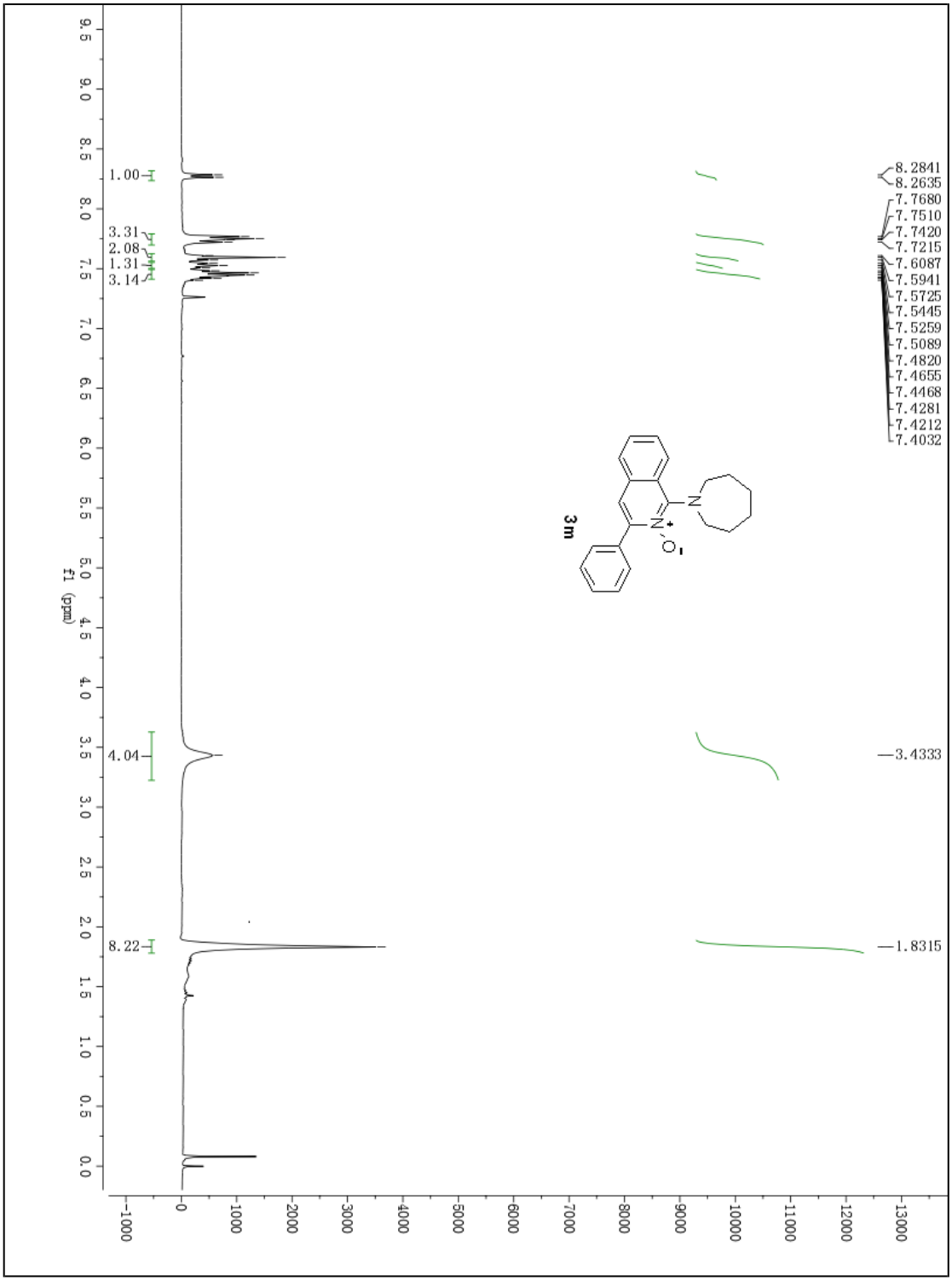
48.8596
26.5532
3l
f1 (ppm)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7.4212
7.4032
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2.08
1.31
3.14
4.04
8.22
3.4333
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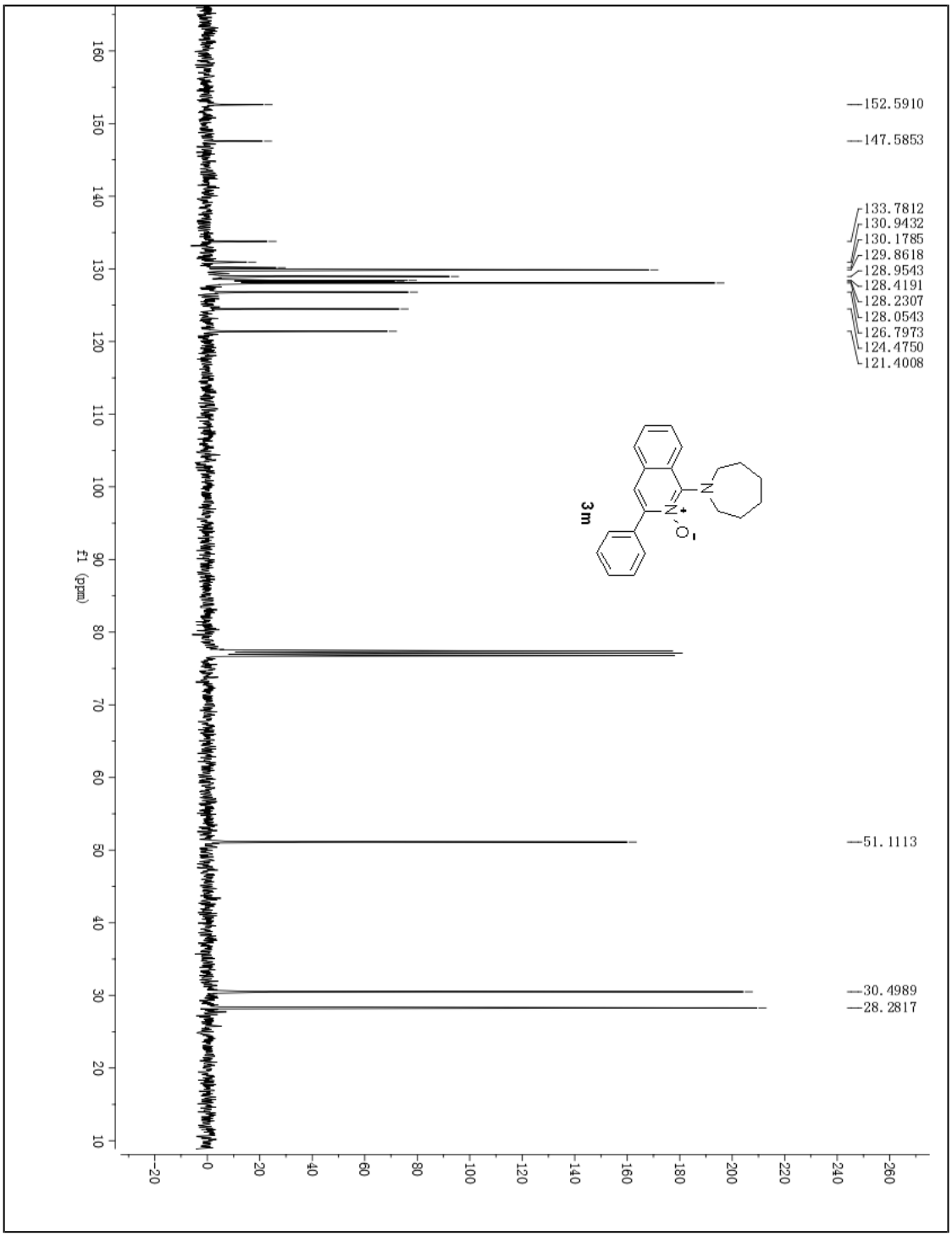
f1 (ppm)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30.4989
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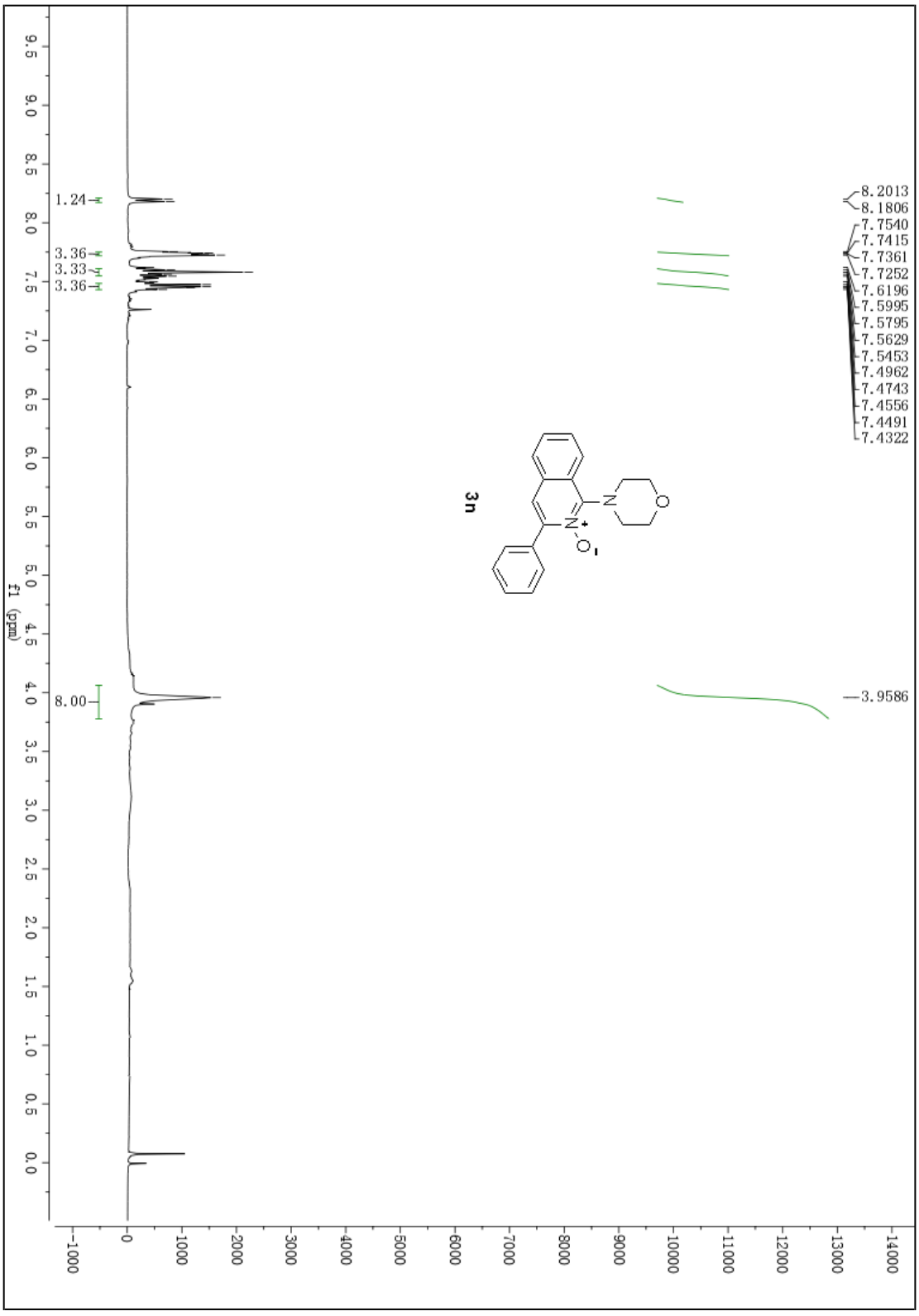
3m
f1 (ppm)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7.7252
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7.5995
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7.4743
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7.4491
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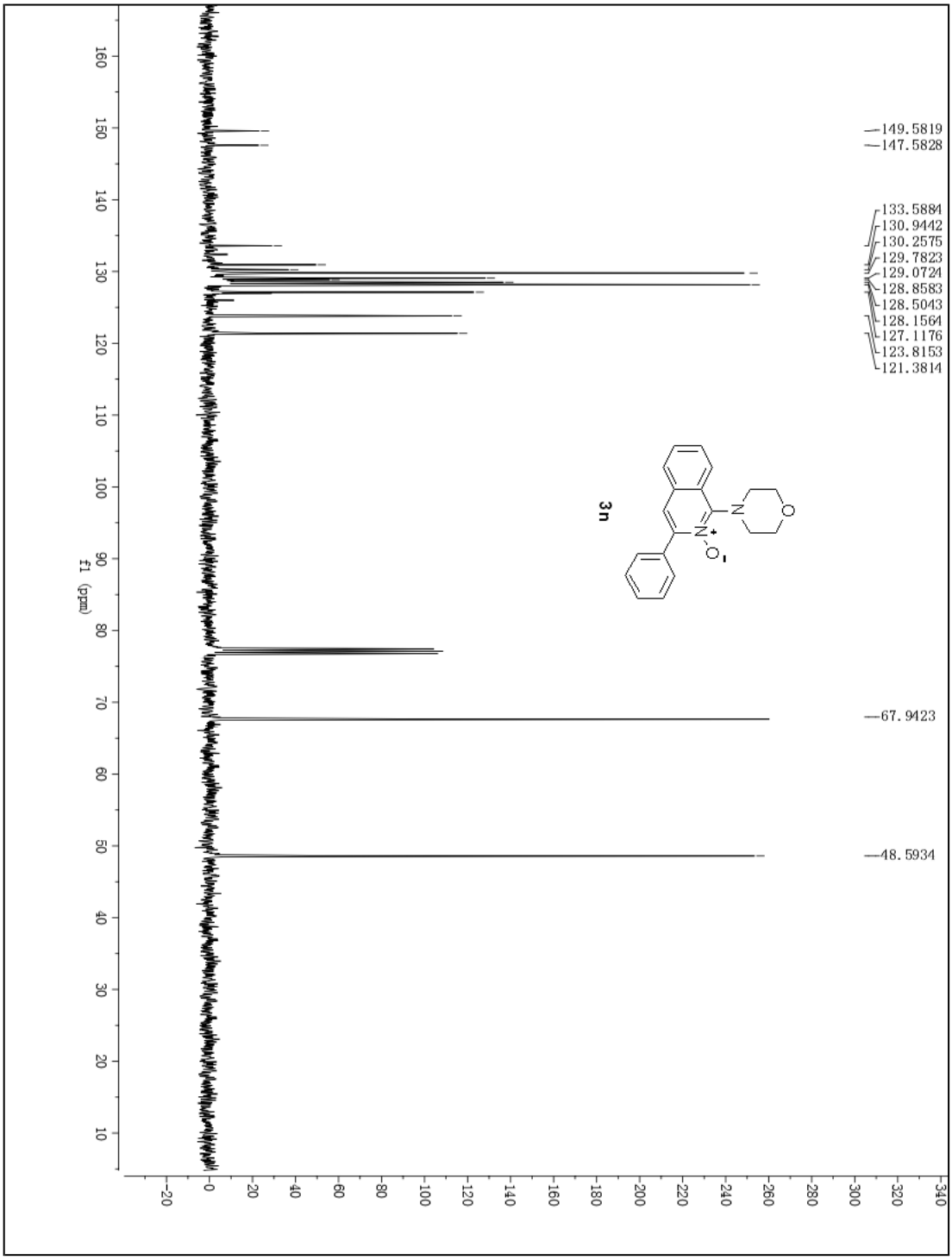
3n
f1 (ppm)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123.8153
121.3814
67.9423
48.5934
3n
f1 (ppm)