Support Information for

Copper-catalyzed synthesis of pyrazolyl pyrazolo[5,1-*a*]isoquinoline derivatives from 2-*gem*-dipyrazolylvinylbromobenzenes

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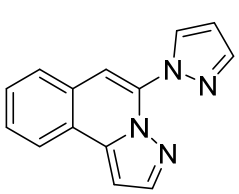
Experimental Section

General Information. Under otherwise noted, materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} and visualized using UV light. Column chromatography was performed with silica gel (mesh 300-400). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 500 MHz spectrometer in $CDCl_3$ with Me_4Si as an internal standard. Data were reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet), coupling constant in Herts (Hz) and integration. IR spectra were recorded on an FT-IR spectrometer, and only major peaks are reported in cm^{-1}. HRMS and mass data were recorded by ESI on a TOF mass spectrometer.

General procedure for the synthesis of pyrazolyl pyrazolo[5,1-*a*]isoquinoline. To a mixture of 1,1-dipyrazolyl alkene (0.5 mmol), L-Threonine (20 mol%) and NaOH (2.0 eq.) in DMSO (5 mL) was added CuCl (10 mol%). The resulting mixture was stirred at 90ºC under N_2. After completion**,** the reaction mixture was cooled to room temperature, added water and extracted with CH_2Cl_2 (3×15 mL). The organic phase was dried over anhydrous Na_2SO_4. The mixture was evaporated under vacuum, and the residue was purified by flash chromatography with petroleum ether and ethyl acetate as the eluent to give the pure product.

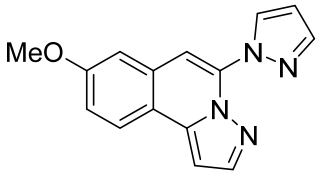
5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2a)**.



Yellow solid, 92% yield; mp 109.4-110.7 ^{o}C; IR (KBr, cm^{-1}) 1638, 1616, 1445, 1384, 1096, 905, 744; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, J = 2.6 Hz, 1H), 8.14-8.16 (m, 1H), 8.07 (d, J = 2.2 Hz, 1H), 7.87 (d, J = 1.5 Hz, 1H), 7.82-7.79 (m, 1H), 7.62-7.58 (m, 2H), 7.50 (s, 1H), 7.15 (d, J = 2.2 Hz, 1H), 6.60 (dd, J = 2.6, 1.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7,

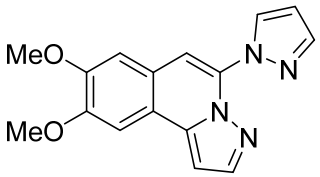
141.3, 140.3, 133.8, 132.6, 128.9, 128.4, 127.5, 127.4, 123.5, 123.0, 107.3, 105.3, 98.5. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{11}N_4$ 235.0984, found 235.0985.

8-methoxy-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2b)**.



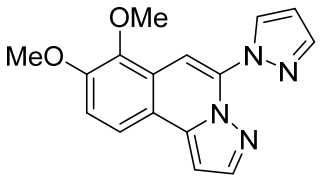
White solid, yield: 62%; mp 112.6-113.7 °C; IR (KBr, cm^{-1}) 1649, 1616, 1453, 1234, 1097, 867, 734; ^1H NMR (500 MHz, $CDCl_3$) δ 8.85 (d, J = 2.6 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 1.6 Hz, 1H), 7.43 (s, 1H), 7.19 (dd, J = 8.8, 2.5 Hz, 1H), 7.16 (d, J = 2.5 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 6.59 (dd, J = 2.6, 1.6 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 141.7, 141.4, 140.4, 134.1, 132.6, 130.6, 125.1, 117.5, 117.2, 108.2, 107.3, 104.8, 97.3, 55.5. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{13}N_4O$ 265.1089, found 265.1091.

8,9-dimethoxy-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2c)**.



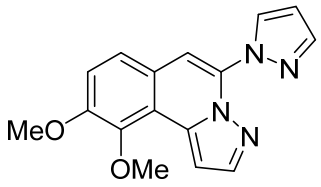
Yellow solid, yield 64%; mp 196.5-198.2 °C; IR (KBr, cm^{-1}) 1638, 1616, 1384, 1162, 1090, 638; ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, J = 2.5 Hz, 1H), 8.02 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 1.4 Hz, 1H), 7.43 (s, 1H), 7.39 (s, 1H), 7.14 (s, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 2.5, 1.4 Hz, 1H), 4.07 (s, 3H), 4.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 149.9, 141.5, 141.2, 139.9, 132.6, 132.4, 123.6, 117.5, 107.6, 107.1, 105.1, 104.1, 96.9, 56.1, 56.0. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{15}N_4O_2$ 295.1195, found 295.1193.

7,8-dimethoxy-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2d)**.



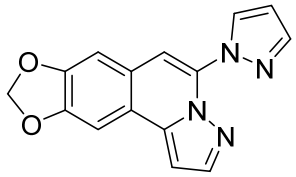
Yellow solid, yield 60%; mp 118 °C; IR (KBr, cm^{-1}) 1638, 1487, 1086, 1276, 762; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (d, J = 2.5 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.88 (d, J = 1.5 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.72 (s, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 2.5, 1.5 Hz 1H), 4.01 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 144.0, 141.8, 141.4, 140.2, 134.0, 132.6, 124.6, 119.5, 118.0, 114.2, 107.3, 100.3, 97.9, 61.4, 56.4. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{15}N_4O_2$ 295.1195, found 295.1195.

9,10-dimethoxy-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2e)**.



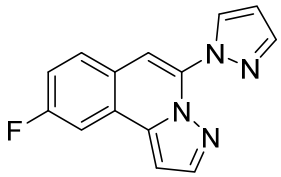
White solid, yield 61%; mp 110-111 °C; IR (KBr, cm^{-1}) 1637, 1080, 617; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 2.5 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 2.1 Hz, 1H), 7.35 (s, 1H), 7.27 (d, J =8.7 Hz, 1H) 6.58 (dd, J = 2.5, 1.5 Hz 1H), 4.06 (s, 3H), 4.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 144.0, 141.5, 141.3, 136.7, 132.6, 132.4, 123.8, 123.4, 118.7, 114.4, 107.1, 105.7, 103.3, 60.0, 56.4. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{15}N_4O_2$ 295.1195, found 295.1196.

***5-(1H-pyrazol-1-yl)-[1,3]dioxolo[4,5-g]pyrazolo[5,1-a]isoquinoline* (2f)**.



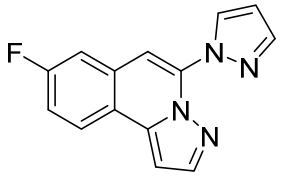
Yellow solid, yield 63%; mp 183.5-185.7 °C; IR (KBr, cm^{-1}) 1637, 1617, 1384, 1160, 938; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, J = 2.5 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.40 (s, 1H), 7.34 (s, 1H), 7.08 (s, 1H), 6.92 (d, J = 2.2 Hz, 1H), 6.58 (dd, J = 2.5, 1.5 Hz, 1H), 6.08 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.9, 148.4, 141.6, 141.2, 140.1, 132.7, 132.5, 124.9, 118.8, 107.2, 105.2, 101.8, 101.7, 97.2. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{15}H_{11}N_4O_2$ 279.0882, found 279.0885.

***9-fluoro-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline* (2g)**.



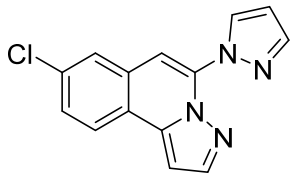
White solid, yield 70%; mp 158.4-159.9 °C; IR (KBr, cm^{-1}) 1637, 1617, 1384, 1092, 855; ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (d, J = 2.5 Hz, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.77-7.74 (m, 2H), 7.46 (s, 1H), 7.33-7.29 (m, 1H), 7.09 (d, J = 2.1 Hz, 1H), 6.60 (dd, J = 2.5, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.69 (d, J = 248.6 Hz), 141.8, 141,3, 139.53 (d, J = 4.4 Hz), 132.3, 132.6, 129.75 (d, J = 8.7 Hz), 125.42 (d, J = 1.8 Hz), 124.31 (d, J = 9.6 Hz), 117.27 (d, J = 23.6 Hz), 108.89 (d, J = 23.1 Hz), 107.4, 104.7, 99.1. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{10}FN_4$ 253.0889, found 253.0888.

***8-fluoro-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline* (2h)**.



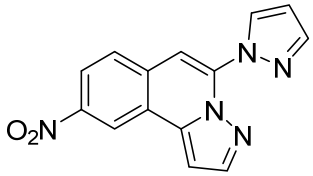
White solid, yield: 65%; mp 178.9-180.0 °C; IR (KBr, cm^{-1}) 1638, 1617, 1449, 1384, 1096, 874, 745; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 2.5 Hz, 1H), 8.10 (dd, J = 8.8, 5.3 Hz,1H), 8.06 (d, J = 2.1 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.45 (s, 1H), 7.42 (dd, J = 9.2, 2.4 Hz, 1H), 7.30 (td, J = 8.8, 2.4 Hz, 1H), 7.07 (d, J = 2.1 Hz, 1H), 6.60 (dd, J = 2.5,1.3 Hz,1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3 (d, J = 247.1 Hz), 141.9, 141.5, 140.0, 134.6, 132.7, 130.7 (d, J = 9.4 Hz), 125.8 (d, J = 9.1 Hz), 119.5 (d, J = 2.0 Hz), 116.2 (d, J = 24.0 Hz), 112.2 (d, J = 21.9 Hz), 107.5, 104.0(d, J = 3.4 Hz), 98.2. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{10}FN_4$ 253.0889, found 253.0886

8-chloro-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2i)**.



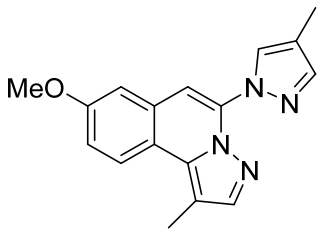
Yellow solid, yield 98%; mp 200.7-202.3 °C; IR (KBr, cm^{-1}) 1649, 1617, 1555, 1443, 1382, 1090, 917, 746; ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.07 (d, J = 1.2 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.52 (dd, J = 8.6, 2.0 Hz, 1H), 7.43 (s, 1H), 7.11 (d, J = 1.2 Hz, 1H), 6.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.0, 141.6, 139.9, 134.7, 134.3, 132.8, 130.2, 127.9, 126.5, 125.0, 121.2, 107.6, 103.7, 98.8. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{10}ClN_4$ 269.0594, found 269.0589.

9-nitro-5-(1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2j)**.



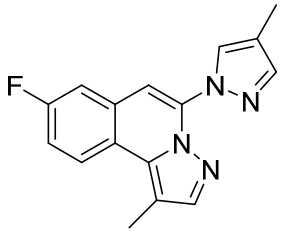
Yellow solid, yield 55%; mp 202-204 °C; IR (KBr, cm^{-1}) 1635, 1384, 1084; ^1H NMR (500 MHz, $CDCl_3$) δ 8.99 (d, J = 2.6 Hz, 1H), 8.71 (d, J = 2.1 Hz, 1H), 8.39 (dd, J = 8.8, 2.2 Hz, 1H), 8.28 (d, J = 8.8 Hz, 1H), 8.18 (d, J = 2.2 Hz, 1H), 7.91 (d, J = 1.4 Hz, 1H), 7.69 (s, 1H), 7.32 (d, J = 2.1 Hz, 1H), 6.64 (dd, J = 2.6, 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 142.0, 139.3, 135.5, 132.9, 129.2, 126.5, 124.8, 123.1, 121.5, 118.2, 108.0, 104.0, 100.9. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{14}H_{10}N_5O_2$ 280.0834, found 280.0836.

8-methoxy-1-methyl-5-(4-methyl-1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2k)**.



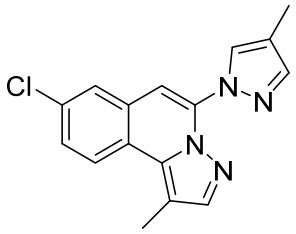
Yellow solid, yield: 71%; mp 112 °C; IR (KBr, cm^{-1}) 1638, 1615, 1384, 1104, 607; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 7.83 (s, 1H), 7.66 (s, 1H), 7.29 (s, 1H), 7.18 (dd, J =8.8, 2.6 Hz, 1H), 7.16 (d, J =2.6 Hz, 1H) , 3.92 (s, 3H), 2.63 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.8, 142.6, 142.5, 136.4, 134,4, 131.0, 130.8, 124.7, 118.7, 117.7, 116.6, 109.2, 108.6, 104.2, 55.4, 11.6, 9.1. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{17}H_{17}N_4O$ 293.1402, found 293.1401.

8-fluoro-1-methyl-5-(4-methyl-1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2l)**.



White solid, yield 63%; mp 135-136 °C; IR (KBr, cm^{-1}) 1638, 1618, 1454, 1149, 966, 799; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.19 (dd, J = 9.0, 5.4 Hz, 1H), 7.84 (s, 1H), 7.65 (s, 1H), 7.37 (dd, J = 9.0, 2.6 Hz, 1H), 7.29-7.24 (m, 2H), 2.60 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.2 (d, J = 246.3 Hz), 142.8, 142.6, 135.8, 134.8, 131.1 (d, J = 9.3 Hz), 130.9, 125.2 (d, J = 8.6 Hz), 120.9 (d, J = 2.0 Hz), 117.9, 115.4 (d, J = 23.2 Hz), 112.1 (d, J = 21.8 Hz), 110.1, 103.2(d, J = 3.3 Hz), 11.6, 9.0. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{14}FN_4$ 281.1202, found 281.1204

8-chloro-1-methyl-5-(4-methyl-1H-pyrazol-1-yl)pyrazolo[5,1-a]isoquinoline **(2m)**.



White solid, yield 67%; mp 155-156 °C; IR (KBr, cm^{-1}) 1637, 1617, 1384, 1091, 922, 616; ^1H NMR (500 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.18 (d, J = 8.7 Hz, 1H), 7.88 (s, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.67 (s, 1H), 7.51 (dd, J = 8.7, 2.2 Hz, 1H), 7.28 (s, 1H), 2.64 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 142.7, 135.8, 134.8, 133.4, 130.9, 130.6, 127.4, 126.4, 124.5, 122.7, 118.0, 110.9, 103.2, 11.7, 9.1. HRMS (ESI) m/z $[M+H]^+$ Calcd for $C_{16}H_{14}ClN_4$ 297.0907, found 297.0909.

151009
qk20151006 CDCl3

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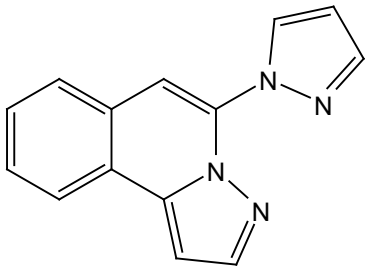

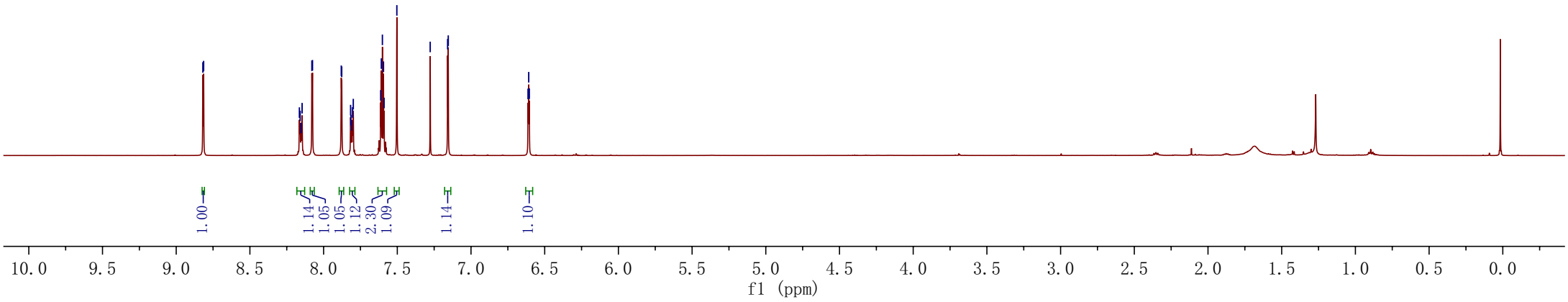

151010
qk20151006 CDCl3

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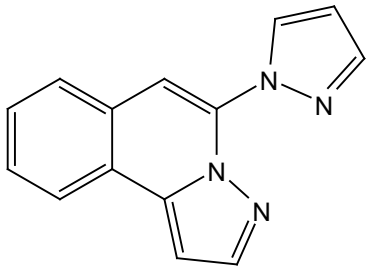

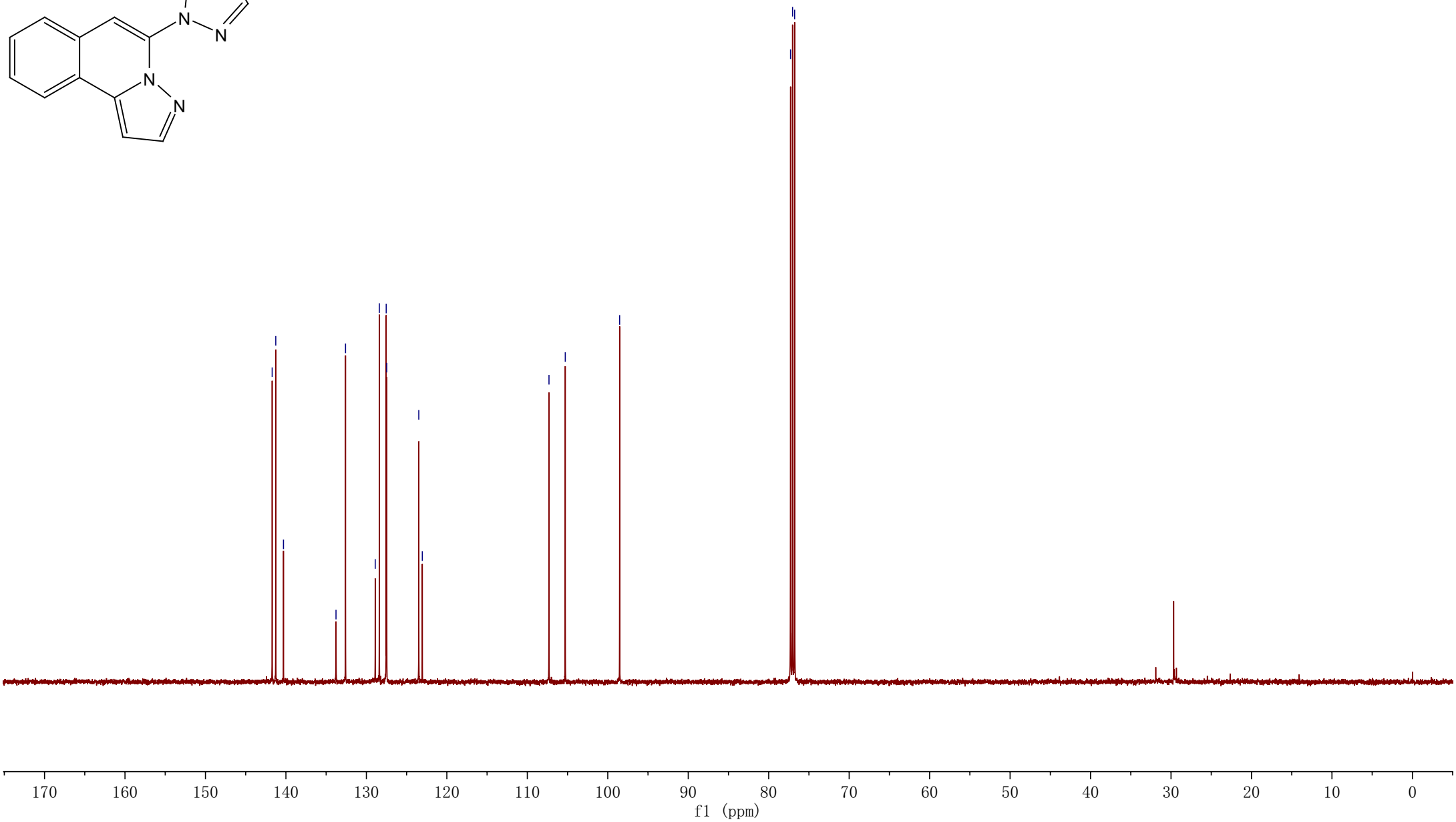

161121
qk20161117 CDCl3 1121

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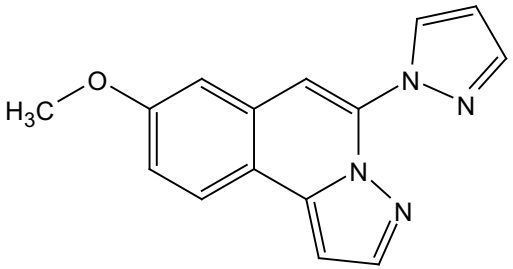

1.00
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0.98
0.99
1.02
1.06
1.05
1.06
1.03
3.19

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f1 (ppm)

161123
qk20161117 CDCl3 1123

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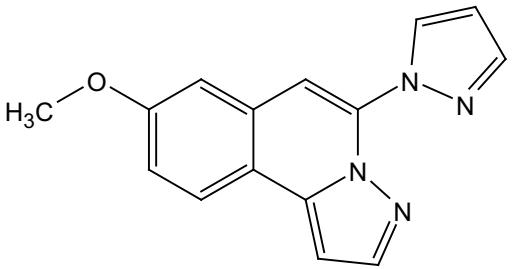
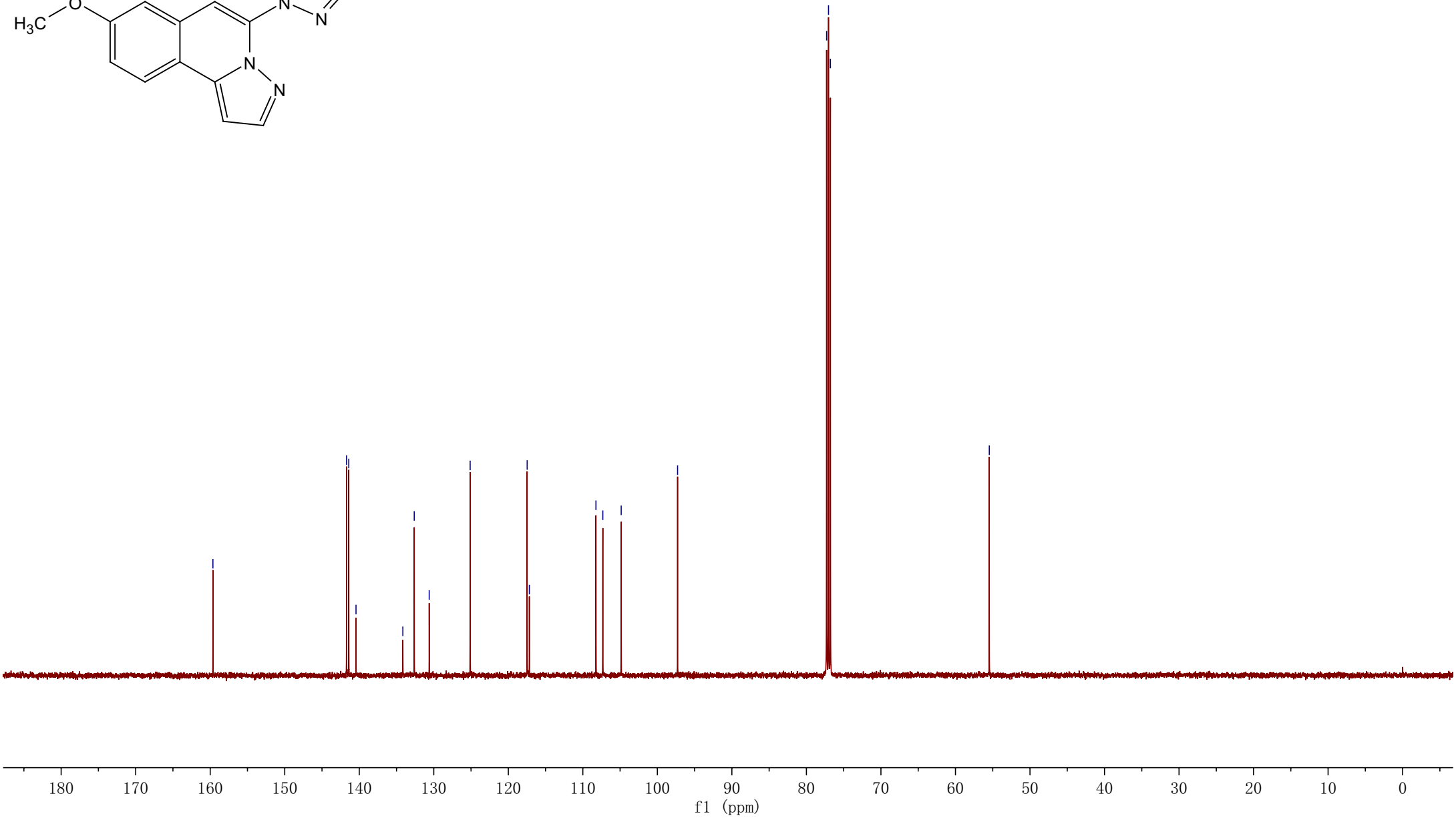
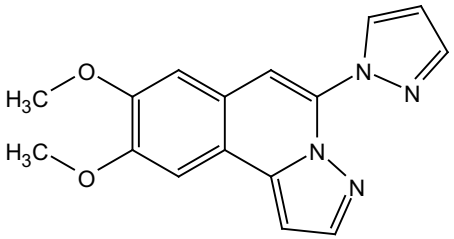
76.7810
55.4613





150415
YDP150413b CDCL3



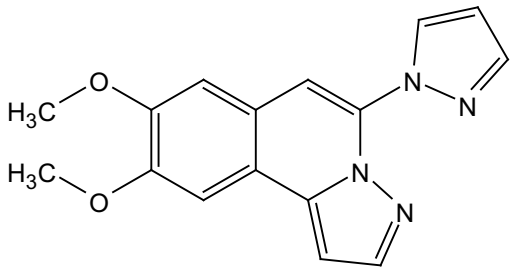
8.7553
8.7503
8.0323
8.0282
7.8561
7.8532
7.4377
7.3911
7.1405
6.9839
6.9796
6.5951
6.5911
6.5868
4.0734
4.0115
1.6791

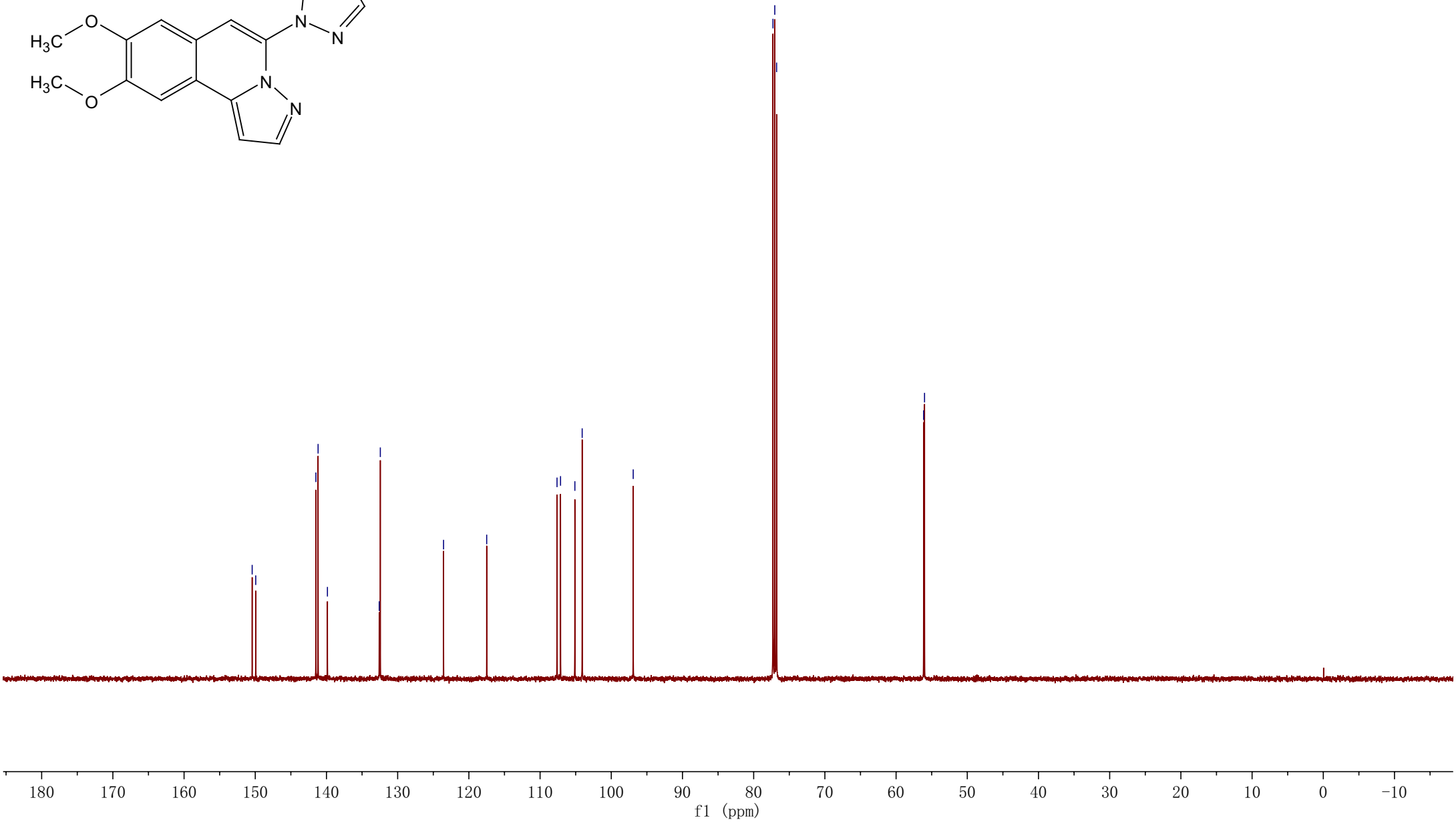
1.00
1.03
1.01
1.09
1.05
1.10
1.07
1.02
3.19
3.17

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

160921
qk20160912 CDCl3 0921

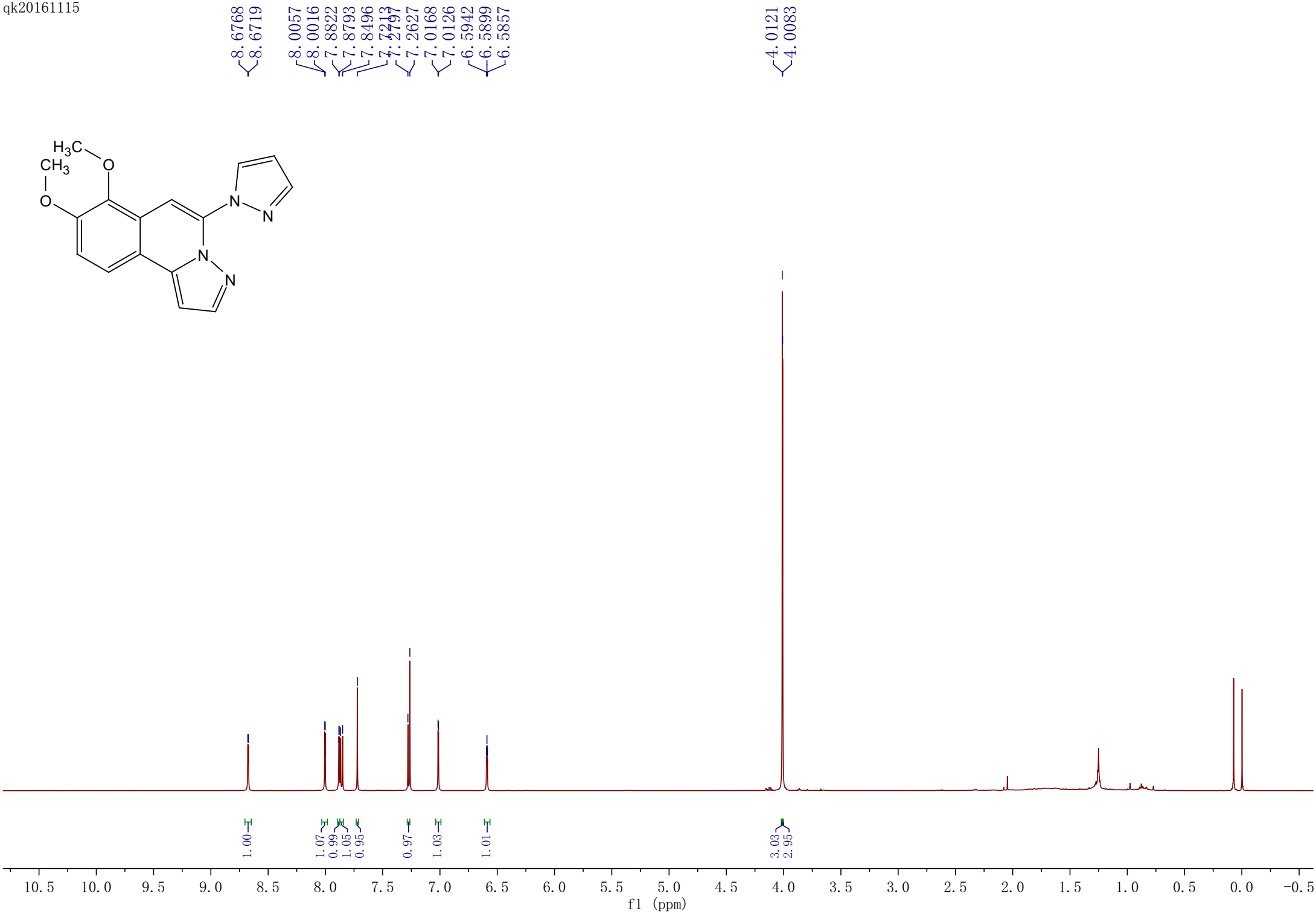
150.4341
149.9336
141.4865
141.1757
139.8647
132.5908
132.4358
123.5555
117.4978
107.6188
107.1265
105.1133
104.0866
96.9190
77.2907
77.0354
76.7817
56.1312
56.0033





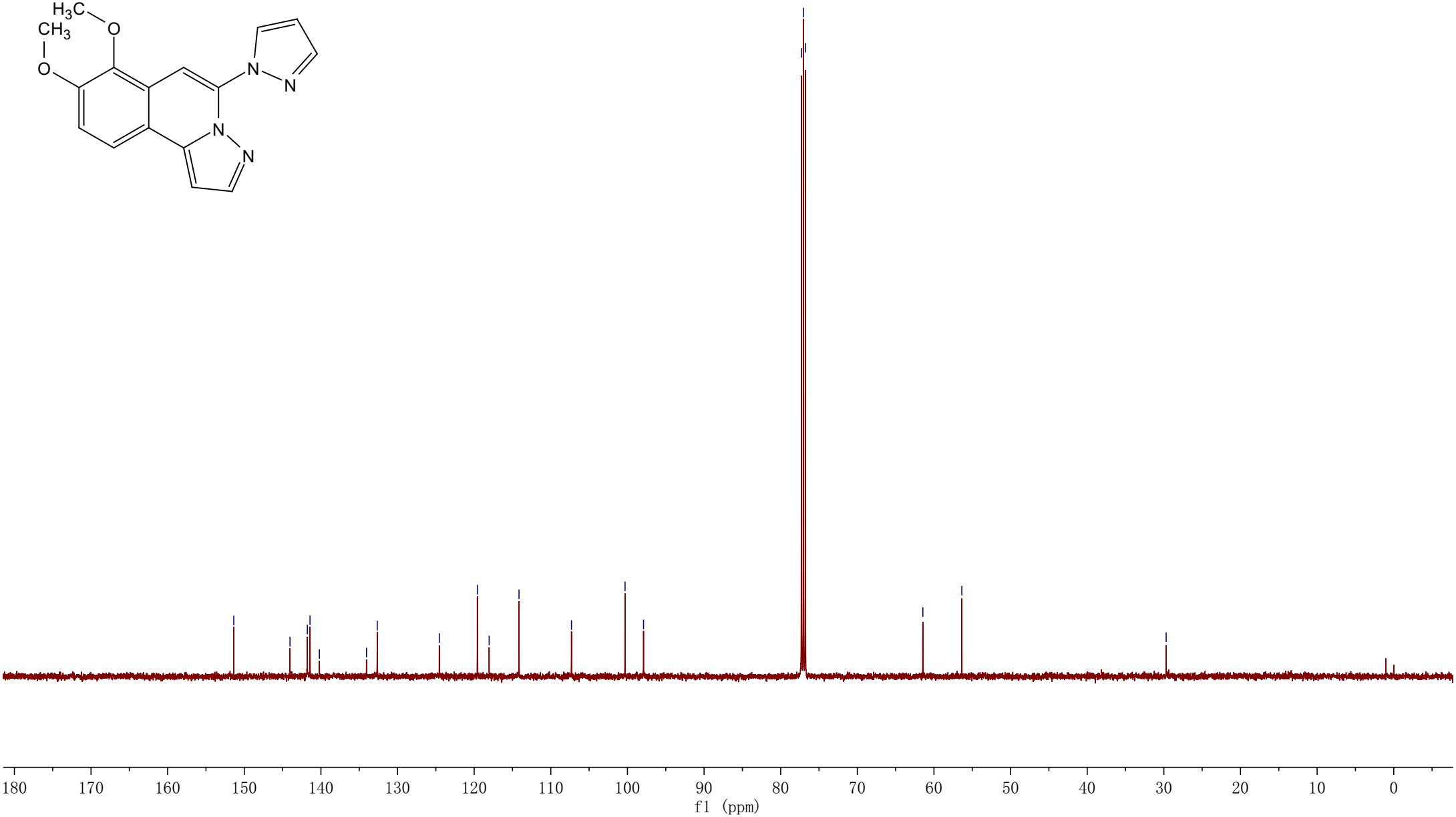
qk20161115

H3C
CH3
O
O
N
N
N
N

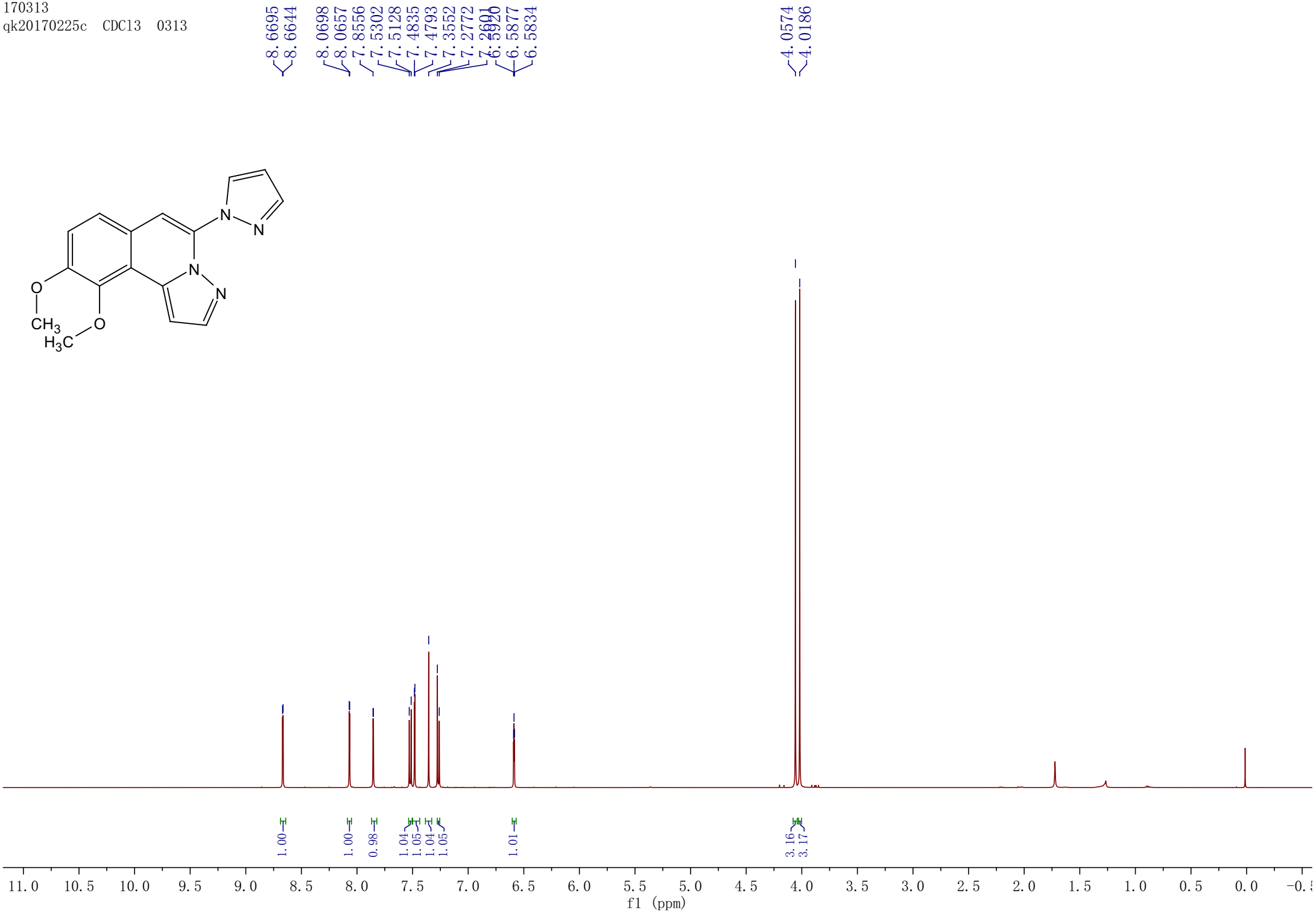

8.6768
8.6719
8.0057
8.0016
7.8822
7.8793
7.8496
7.7213
7.2797
7.2627
7.0168
7.0126
6.5942
6.5899
6.5857
4.0121
4.0083
1.00
1.07
0.99
1.05
0.95
0.97
1.03
1.01
3.03
2.95
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

170313
qk20161115 CDCl3 0313

151.3708
144.0354
141.7715
141.4249
140.2050
134.0470
132.6461
124.5505
119.5851
118.0476
114.1509
107.3034
100.3099
97.8996
77.2893
77.0345
76.7798
61.4484
56.3634
29.6991

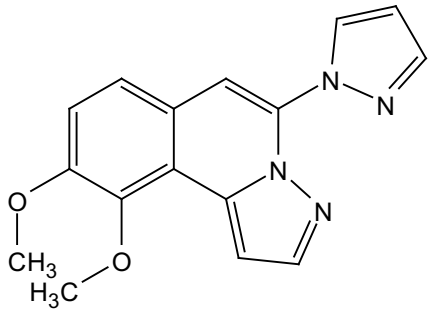


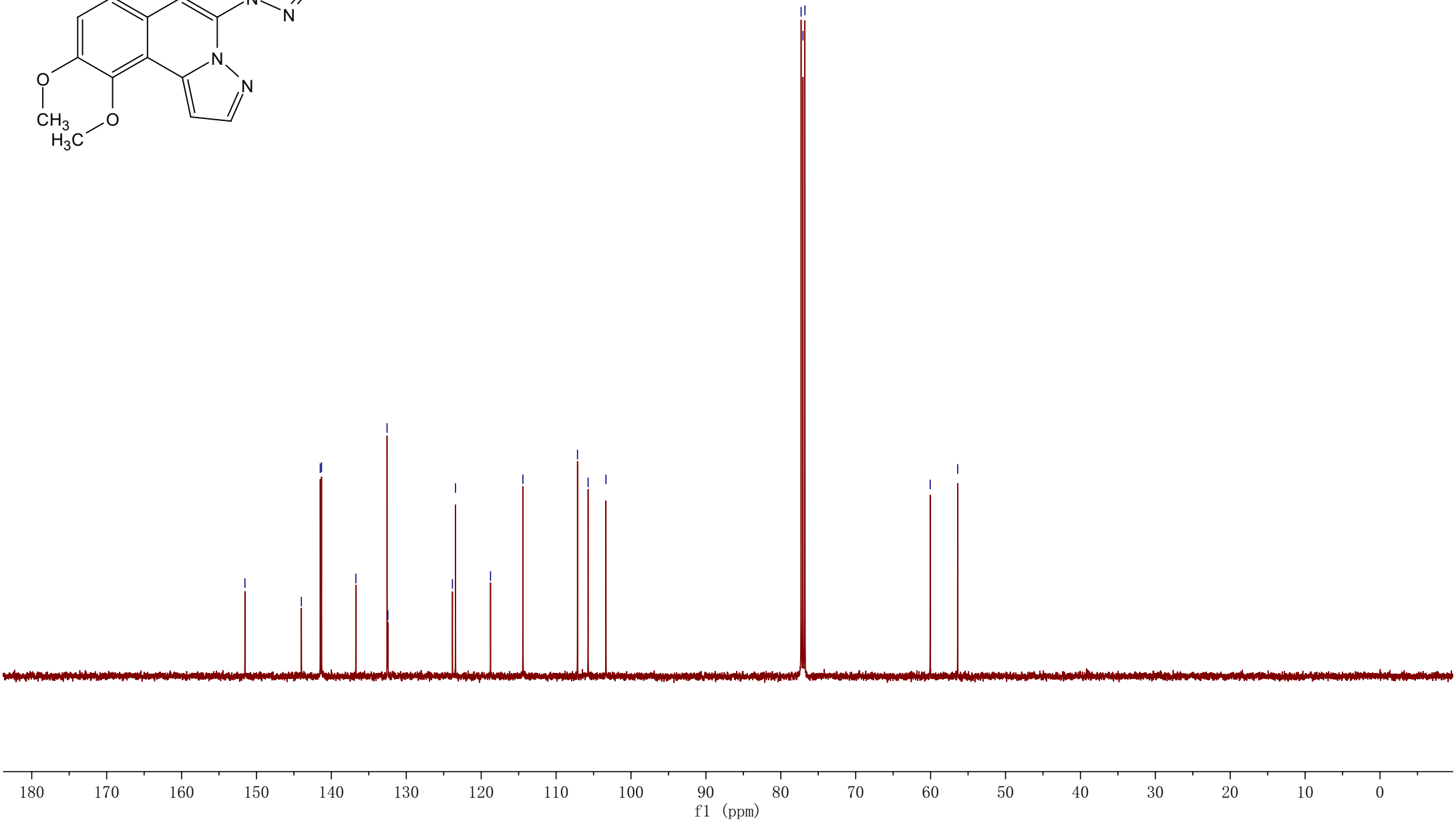
170313
qk20170225c CDC13 0313



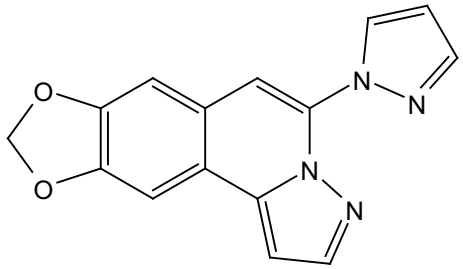
170321
qk20170225c CDC13 0321

151.54
144.00
141.48
141.31
136.73
132.57
132.46
123.84
123.43
118.75
114.43
107.14
105.73
103.34
77.29
77.03
76.78
60.06
56.39

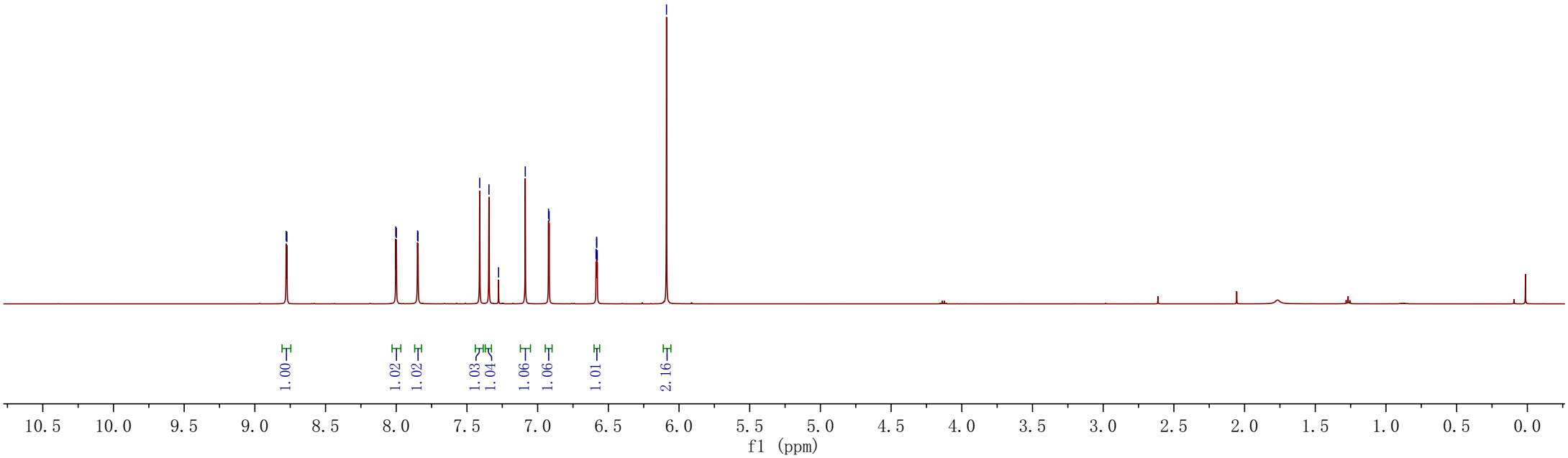




170220
qk20170116-b CDCl3 0220

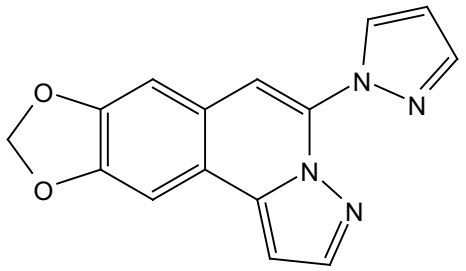


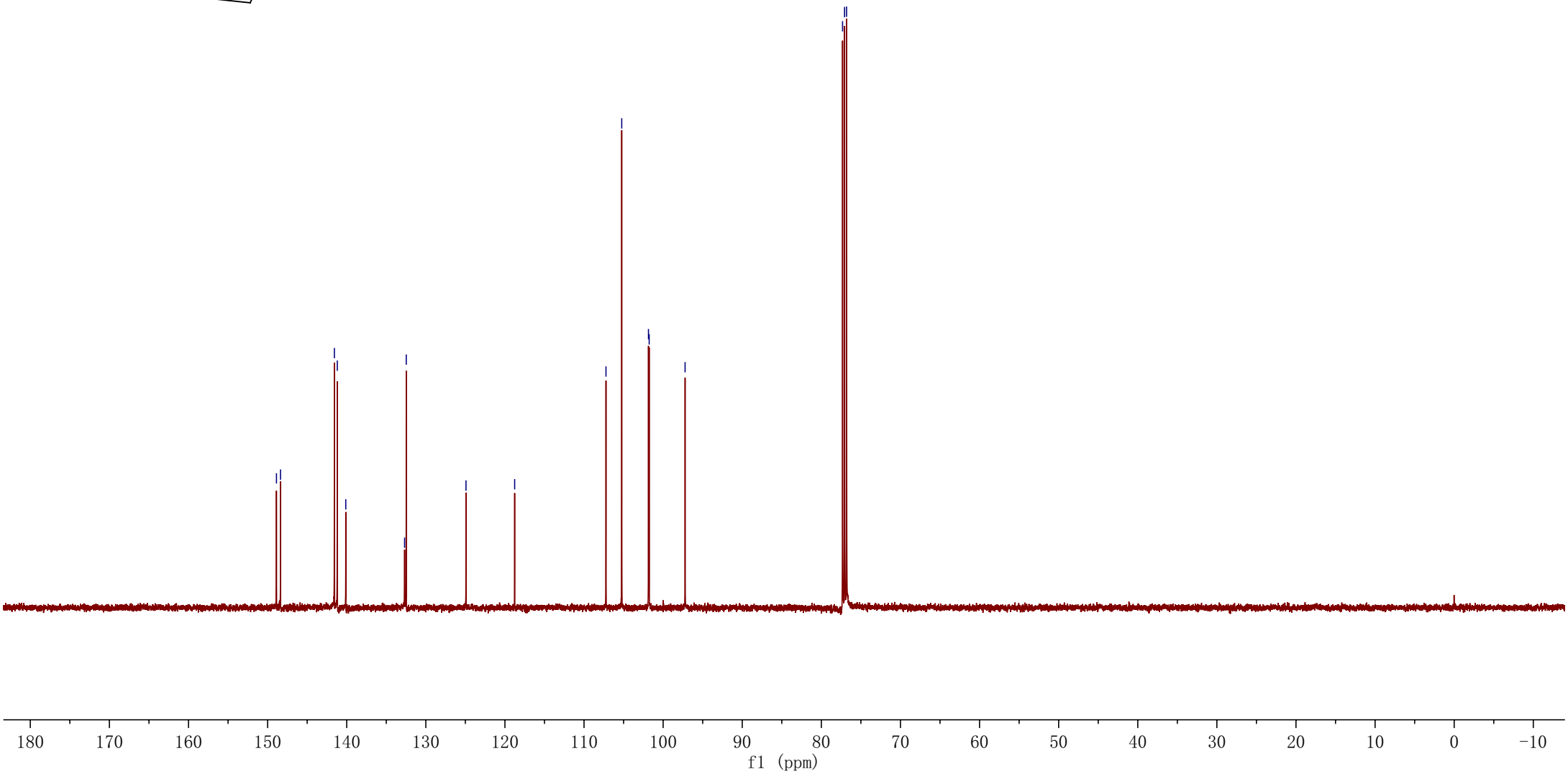
8.7784
8.7735
8.0033
7.9990
7.8495
7.8465
7.4098
7.3443
7.0875
6.9230
6.9187
6.5868
6.5830
6.5822
6.0885



4h
qk20170116-b CDCl3 0222

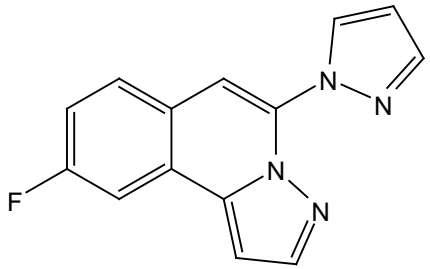
148.8803
148.3677
141.5578
141.1919
140.1178
132.6836
132.4727
124.9213
118.7686
107.2245
105.2337
101.8548
101.7634
97.2248
77.3188
77.0645
76.8103

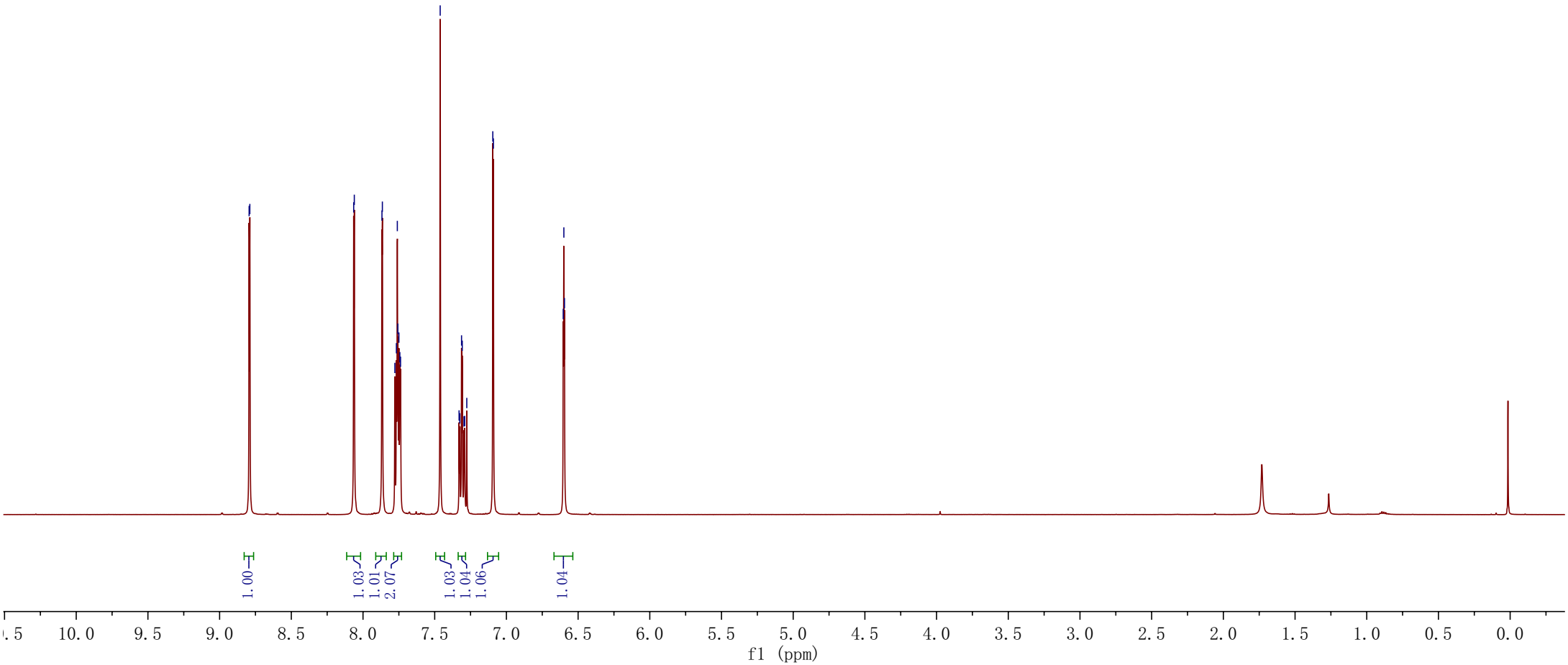




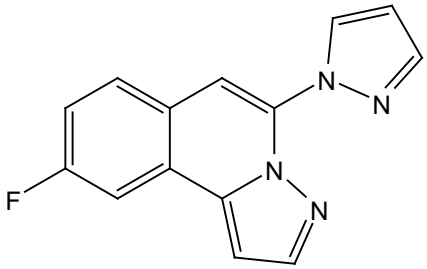
161201
qk20161128-1 CDCl3 1201

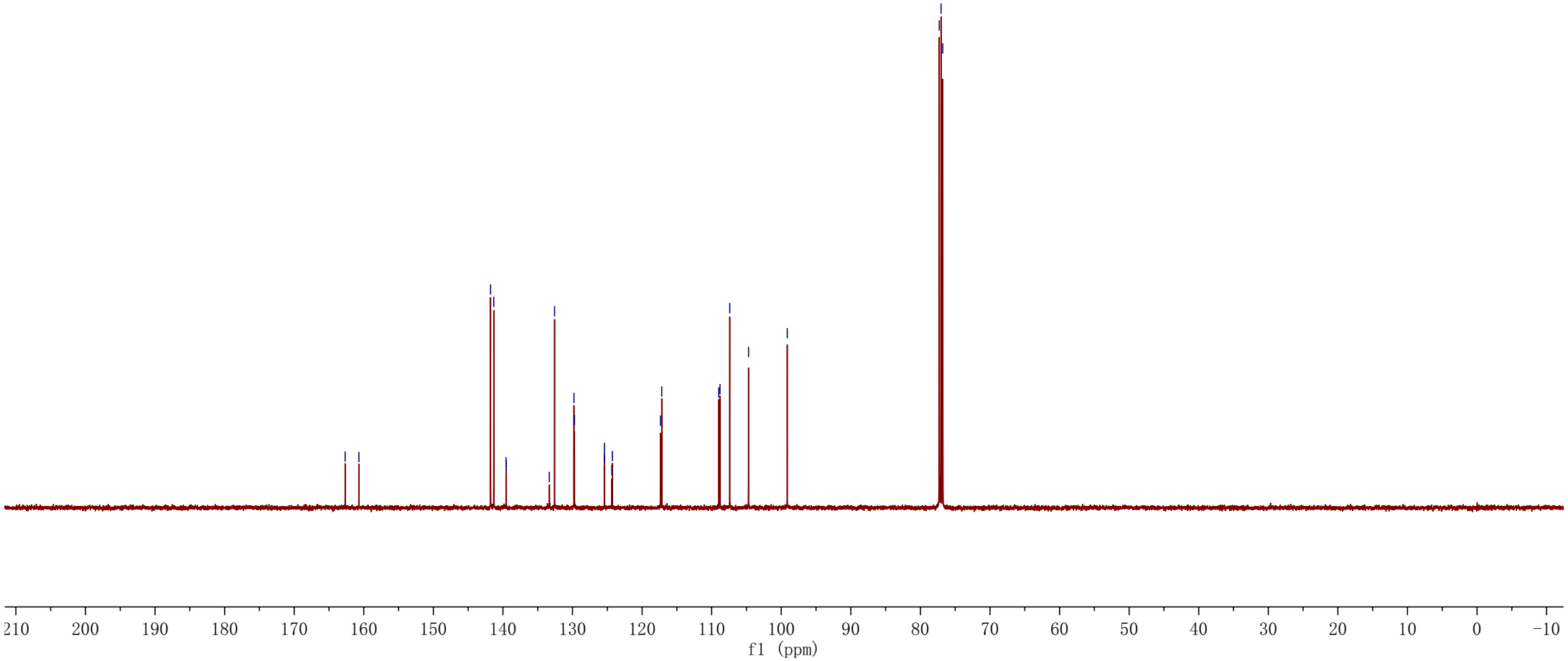
8.7943
8.7892
8.0649
8.0607
7.8678
7.8650
7.7607
7.7569
7.7497
7.4618
7.3128
7.3078
7.0949
7.0906
7.0835
6.5992
6.5952



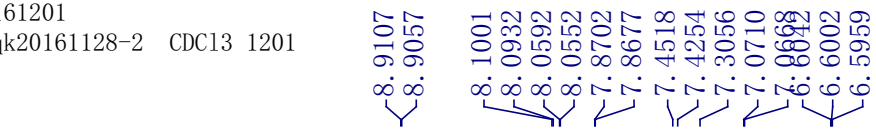


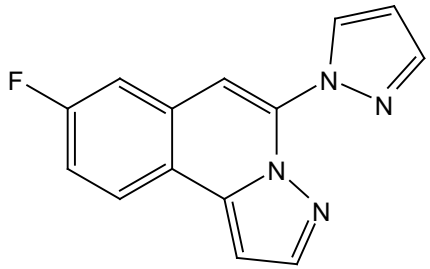
161205
qk20161128-1 CDCl3 1205

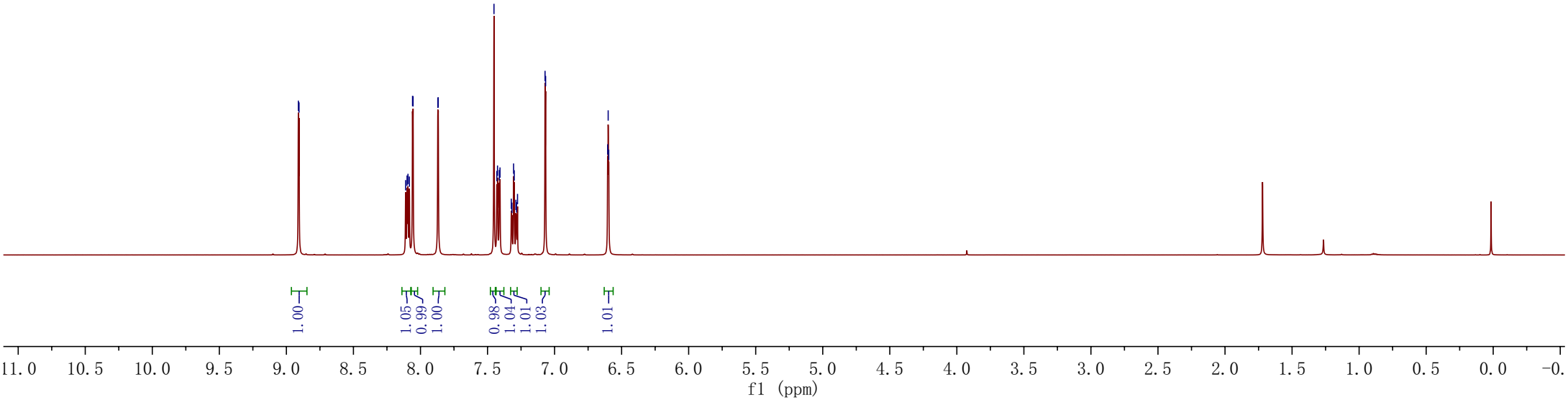




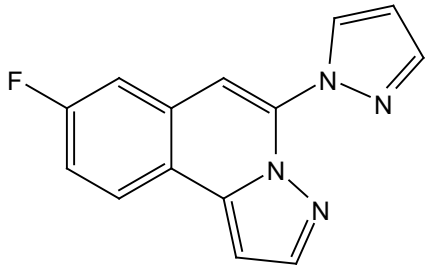
161201
qk20161128-2 CDCl3 1201

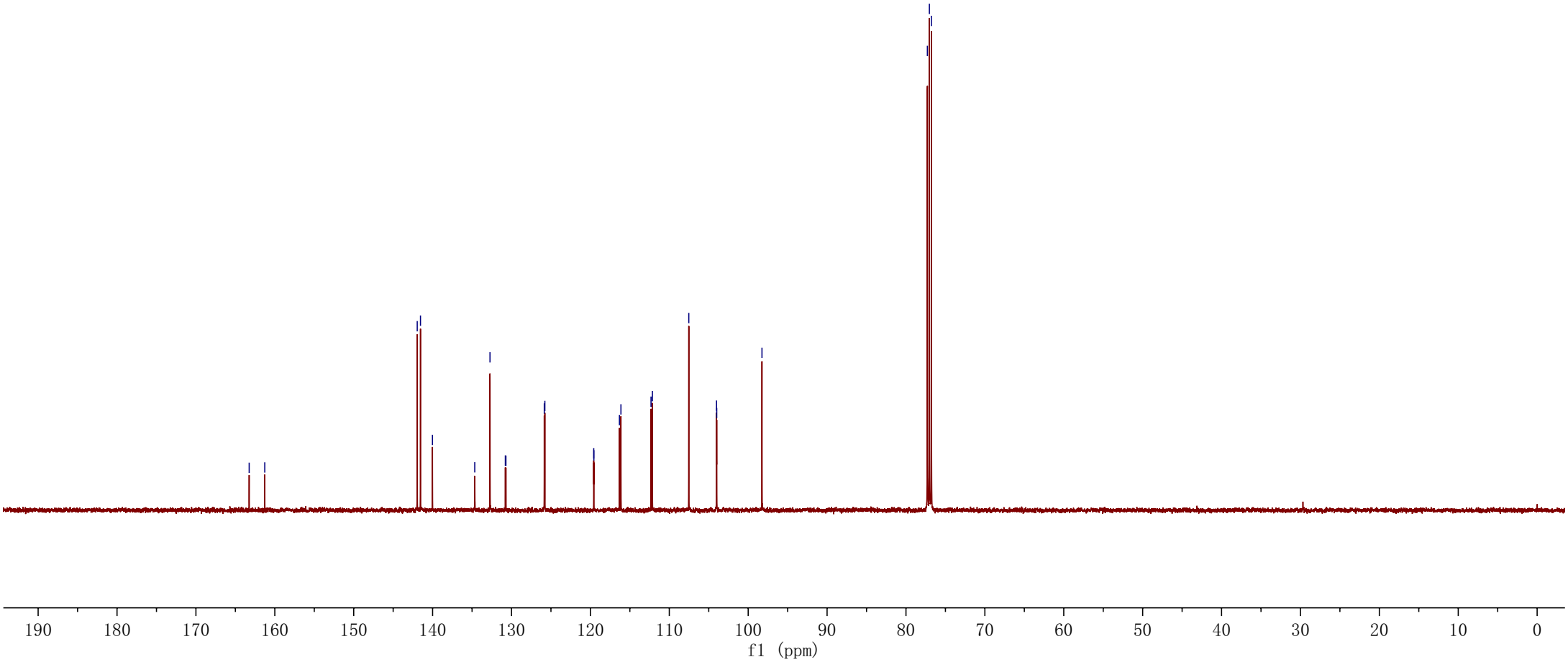






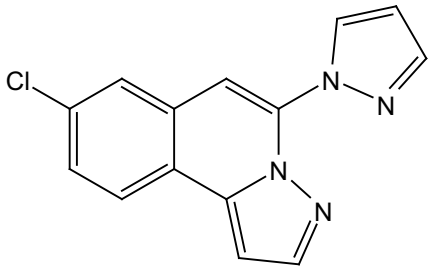
161205
qk20161128-2 CDCl3 1205

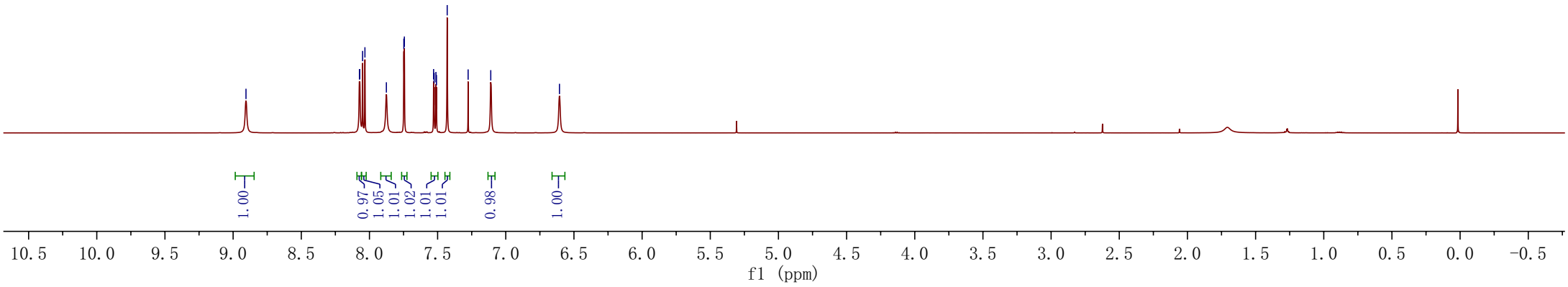




161114
qk20161108 CDCl3 1114

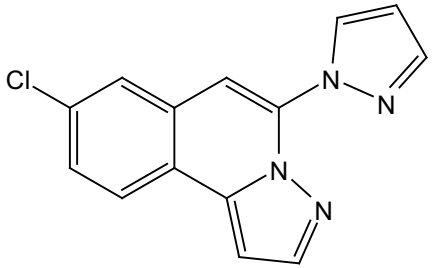
8.9056
8.0734
8.0709
8.0503
8.0332
7.7477
7.7439
7.5295
7.5255
7.5123
7.5085
7.4297
7.2762
7.1102
6.6062

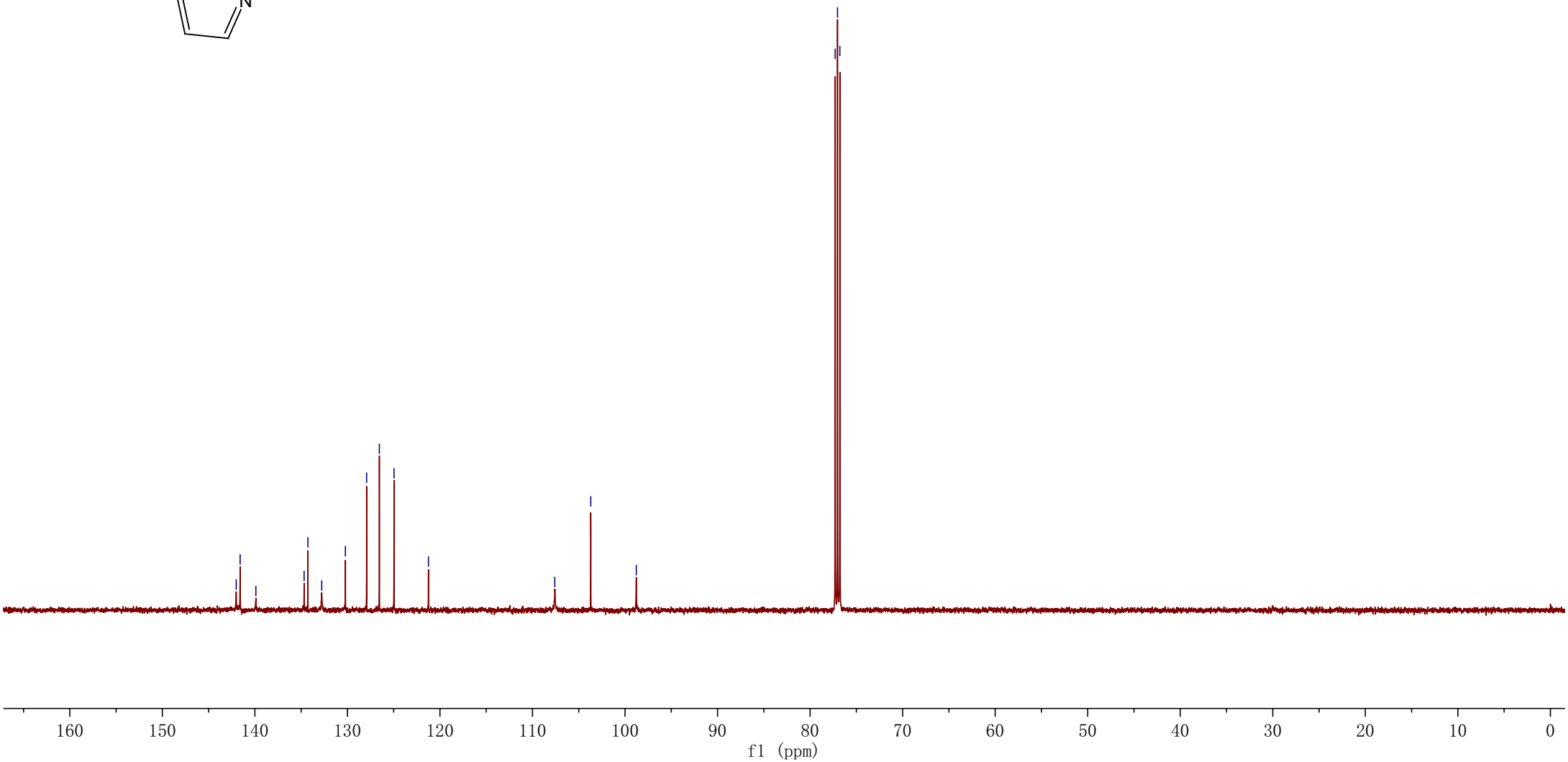




161116
qk20161108 CDCl3 1116

142.0188
141.5943
139.8939
134.6802
134.2697
132.7776
130.2170
127.9240
126.5464
124.9659
121.2449
107.5931
103.7014
98.7841
77.2932
77.0384
76.7836





170317
qk20170314c CDCl3 0317

8.9974
8.9921
8.7161
8.7119
8.4089
8.4046
8.3912
8.3869
8.2981
8.2804
8.1895
8.1852
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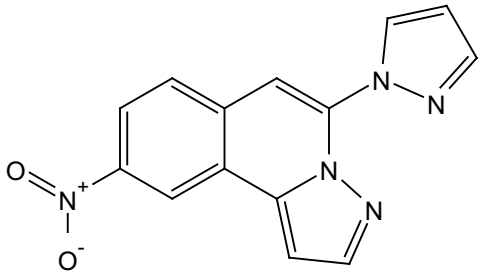
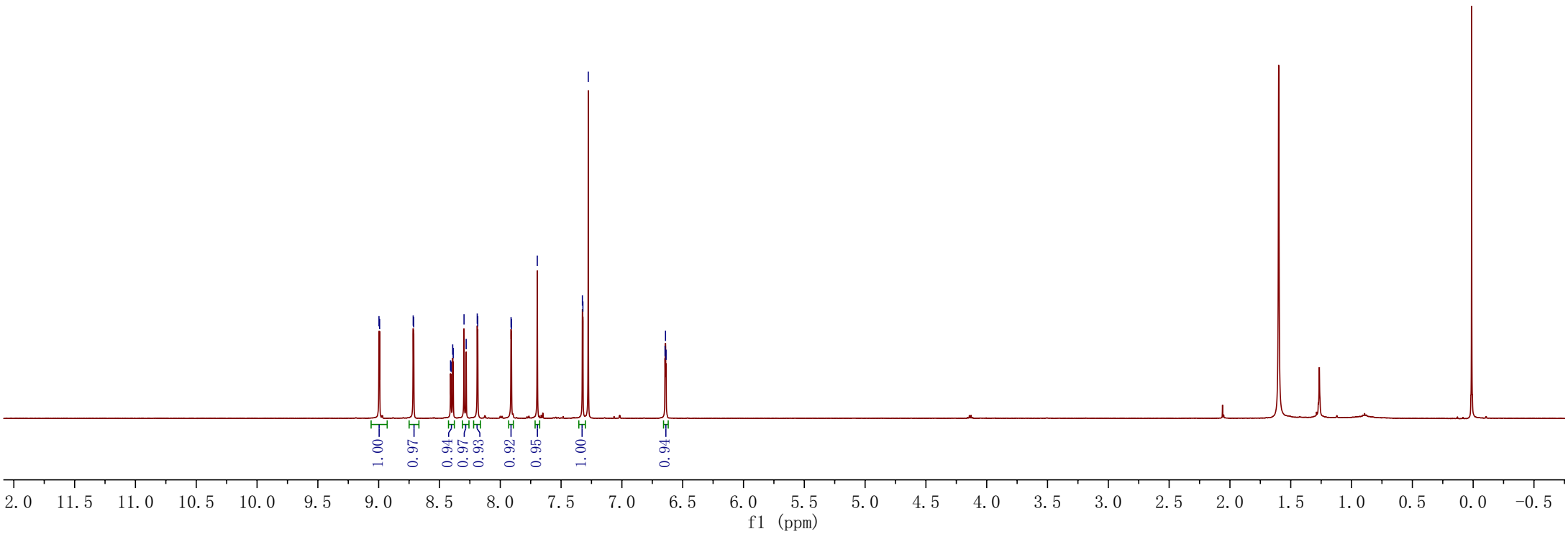
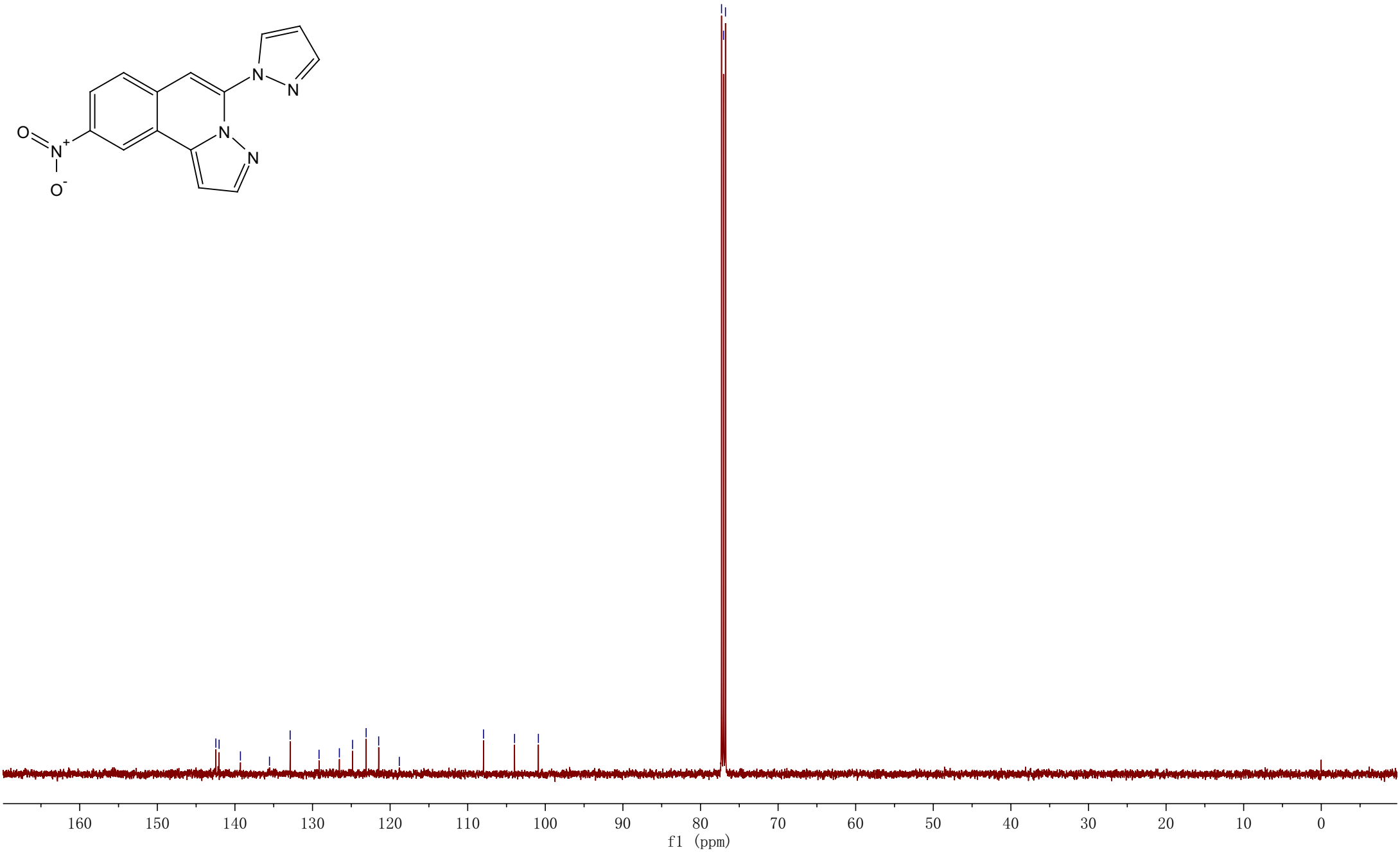
7.9087
7.6957
7.3248
7.3206
7.2763
6.6453
6.6413
6.6367



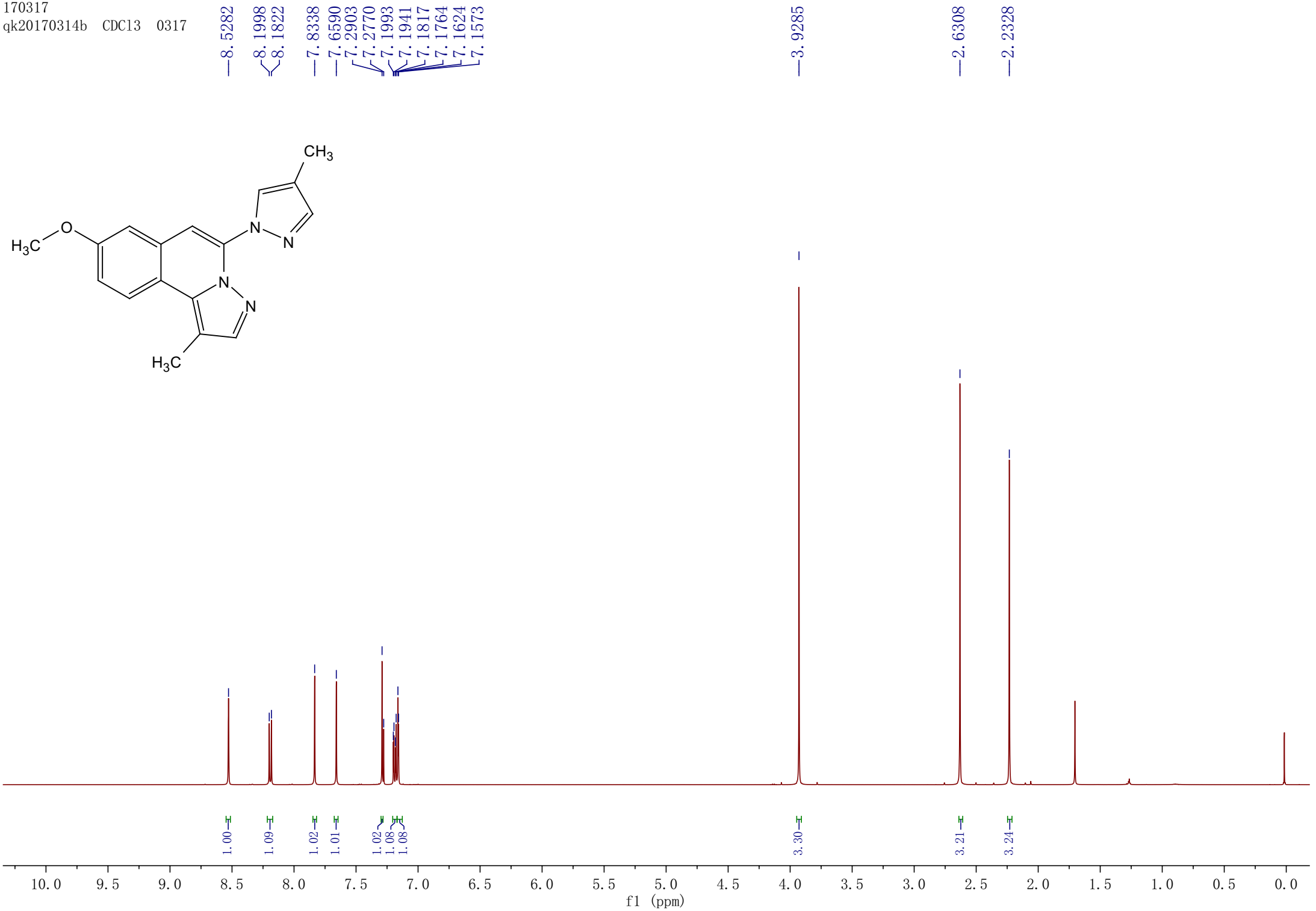


170321
qk20170314c CDCl3 0321

142.46
142.04
139.29
135.55
132.88
129.16
126.54
124.84
123.09
121.47
118.82
107.96
103.96
100.89
77.29
77.03
76.78



170317
qk20170314b CDC13 0317



170321
qk20170314b CDC13 0321

158.84
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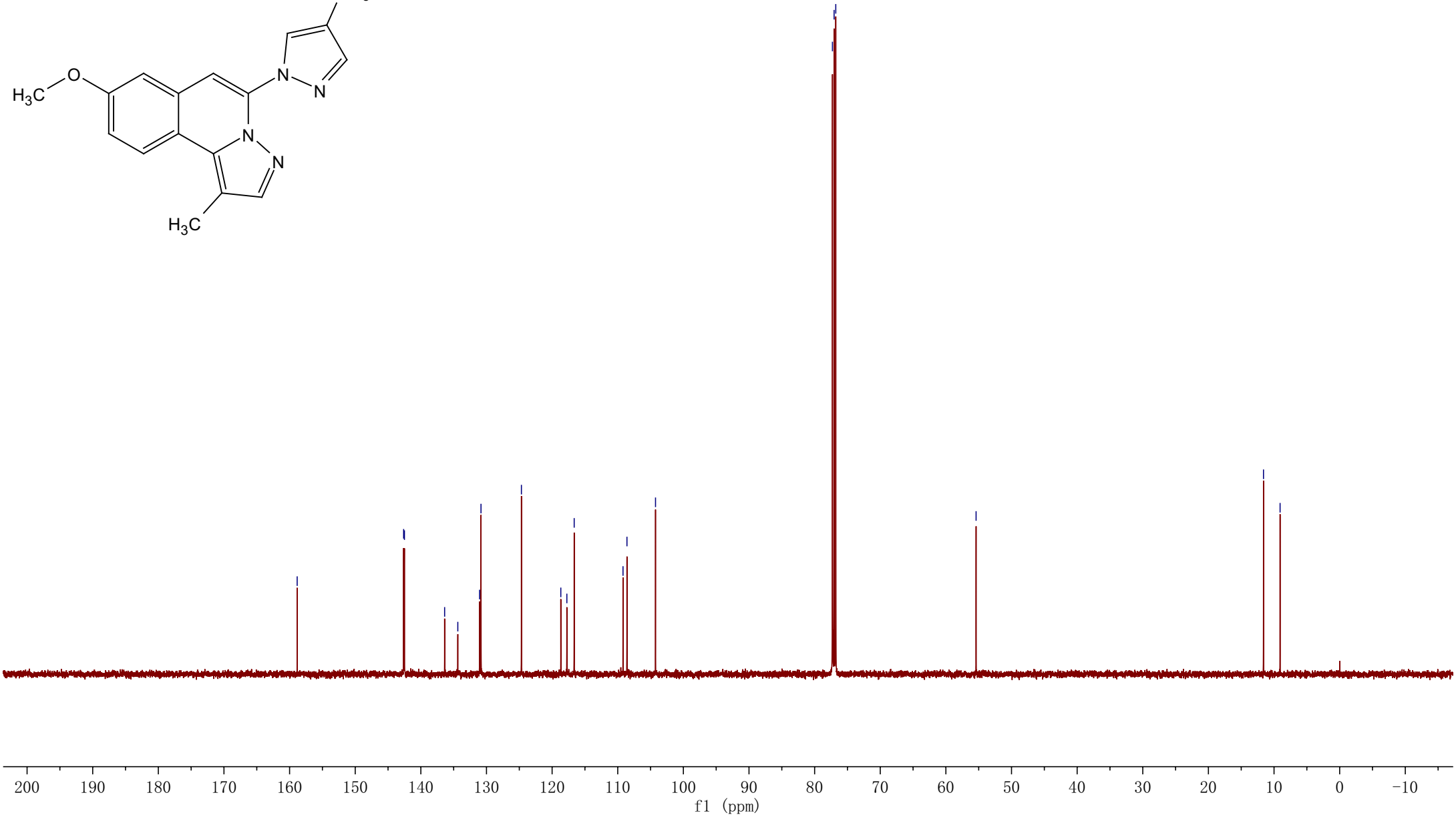
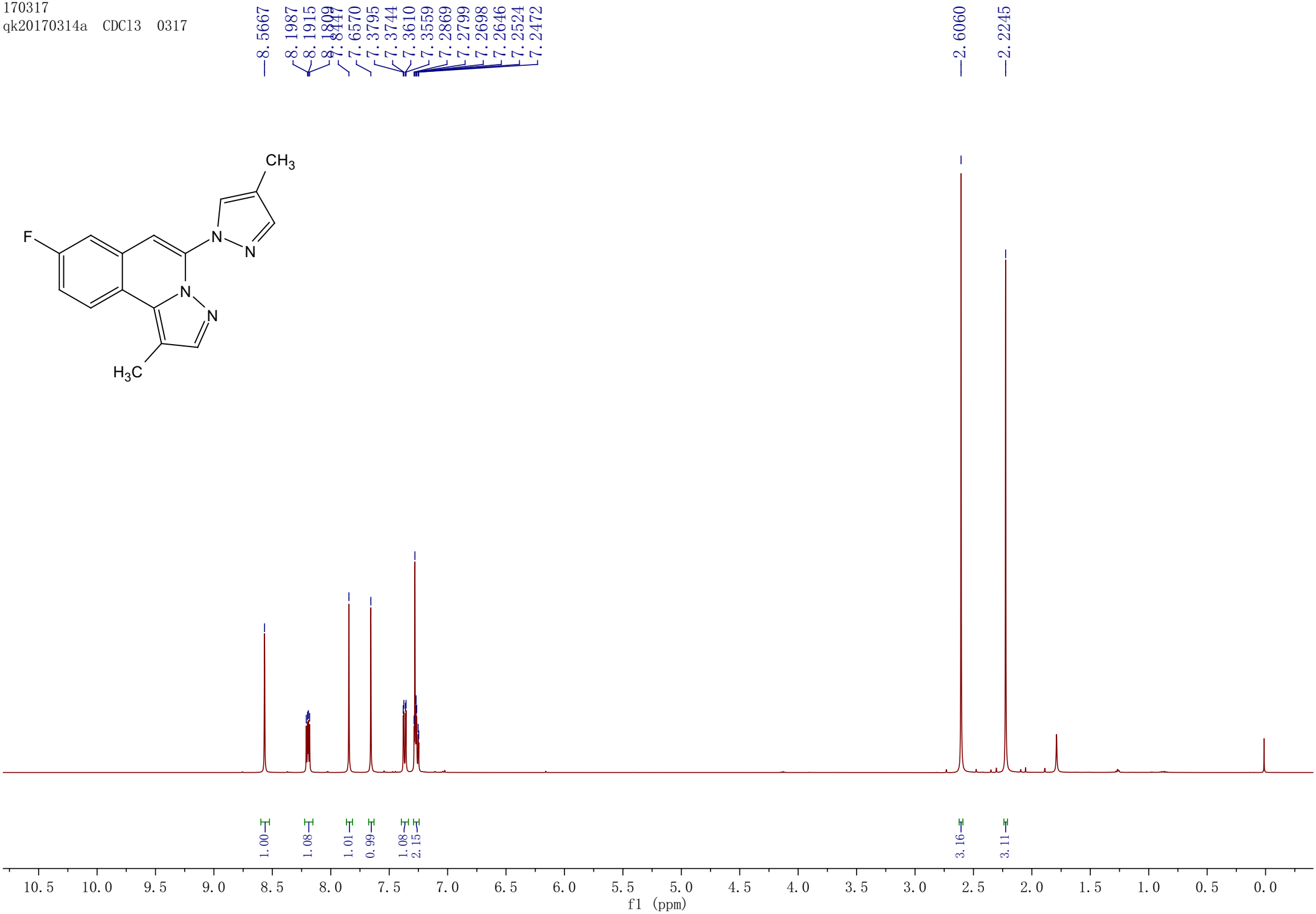
134.37
131.05
130.84
124.68
118.67
117.75
116.64
109.20
108.59
104.24
77.29
77.03
76.78
55.40
11.61
9.08



170317
qk20170314a CDCl3 0317



170321
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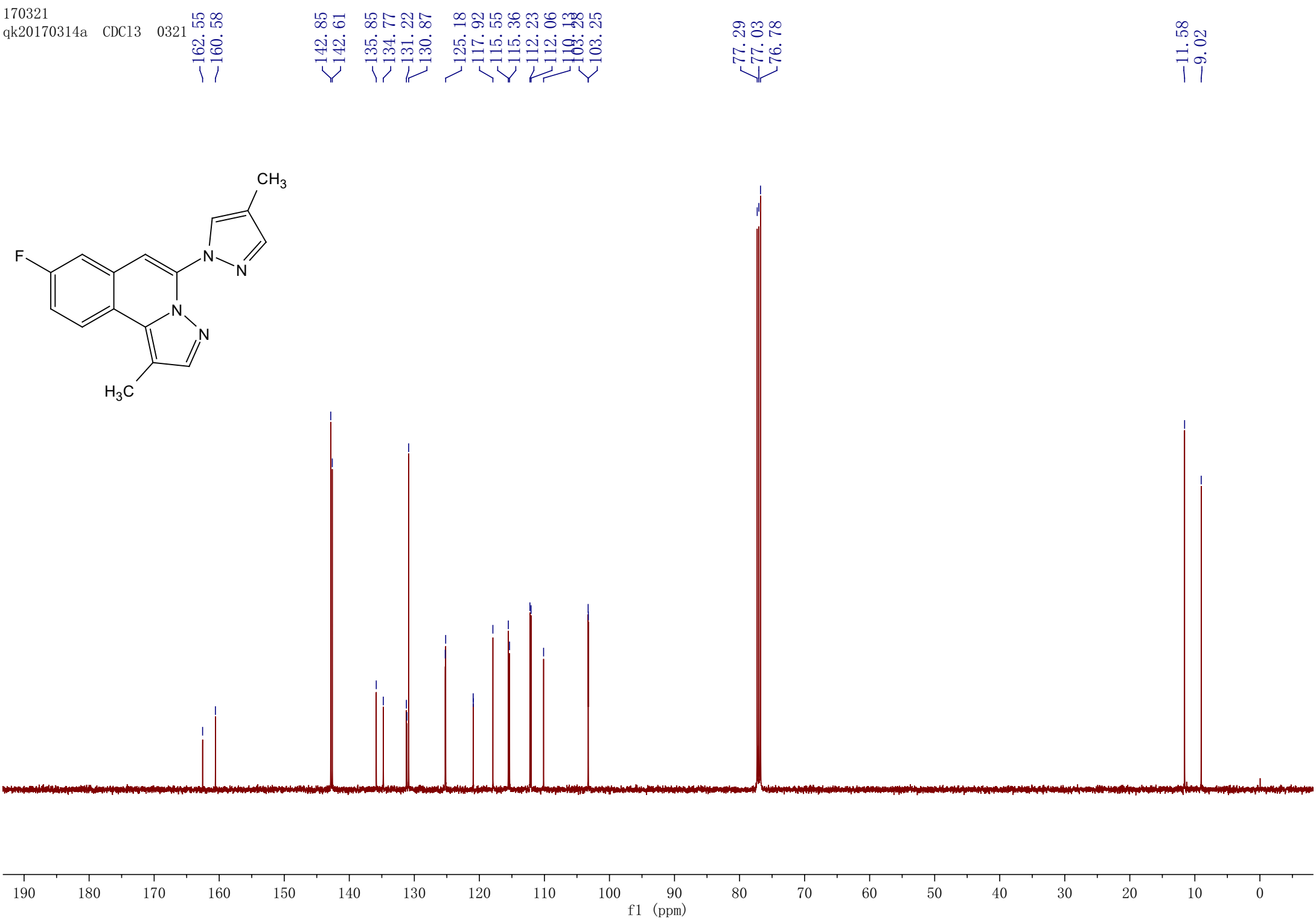
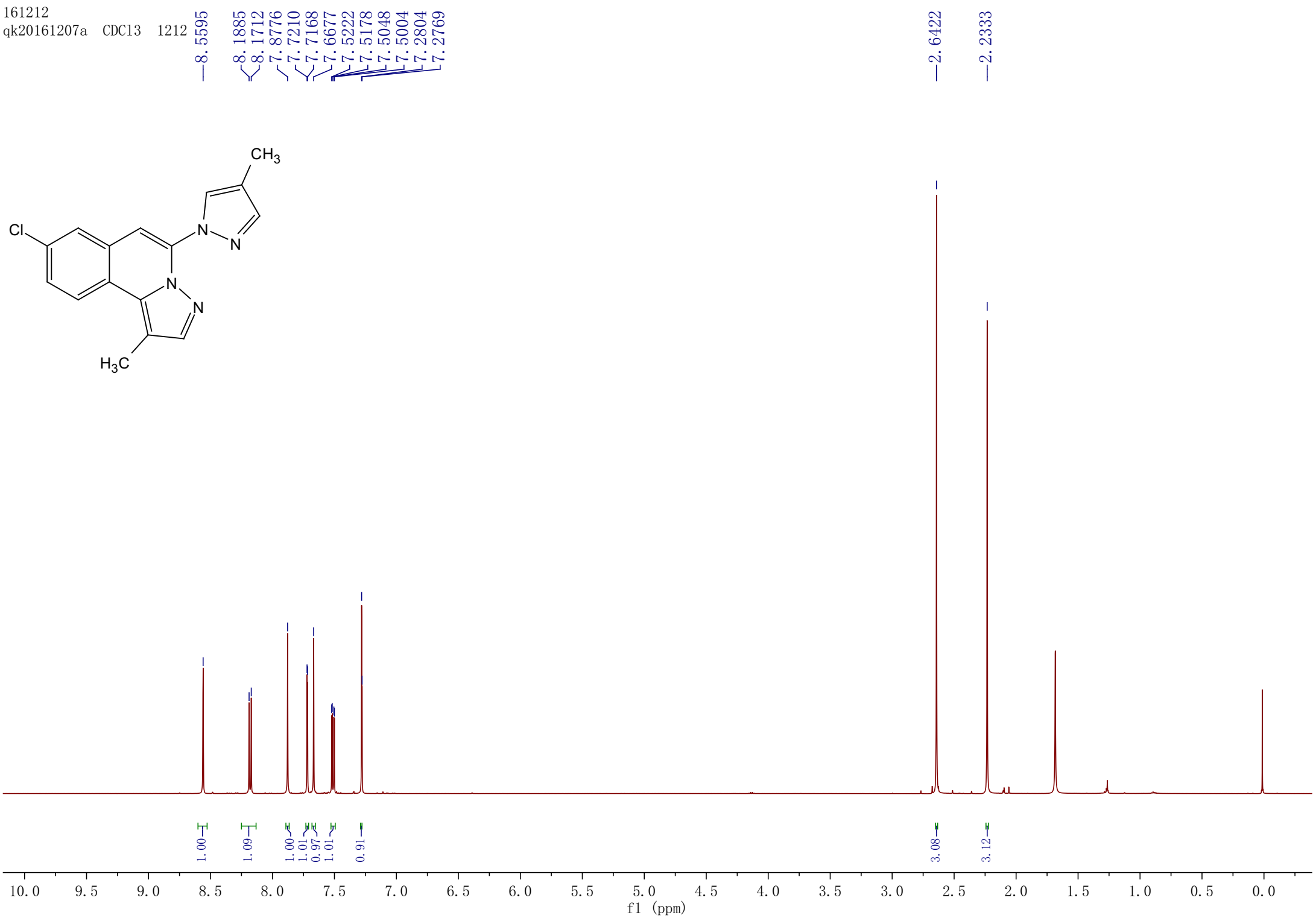


161212
qk20161207a CDCl3 1212



161214
qk20161207a CDCl3 1214

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133.3782
130.8875
130.6596
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124.4884
122.6837
118.0263
110.8698
103.1525
77.2937
77.0387
76.7842
11.6819
9.0807