SUPPORTING INFORMATION

Electrophilic ring fluorination of 3,5-disubstituted pyrazoles: application to the formal synthesis of neprilysin inhibitor key intermediate

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1. General Information

a. Purification of solvents and reagents

All reactions were performed under an atmosphere of argon. Reaction vessels were oven-dried, cooled under vacuum and flushed with argon before use. THF and CH_2Cl_2 were dried over alumina columns in a solvent purification apparatus (Innovative Technologies PS-MD-5). Acetonitrile was distilled over CaH_2, stored over 4 Å molecular sieves (MS) and used without further purification. Every reagent was either purified following the methods described in the literature or used without further purification.

b. Chromatography

Reactions were monitored by thin layer chromatography (TLC) using commercial silica-gel plates (Merck 60 F254). Spots were detected with UV light (254 nm) and revealed with a $KMnO_4$ stain.[1] VWR Silica Gel 60 (40-63 μm) was employed for flash column chromatography.

c. NMR analyses

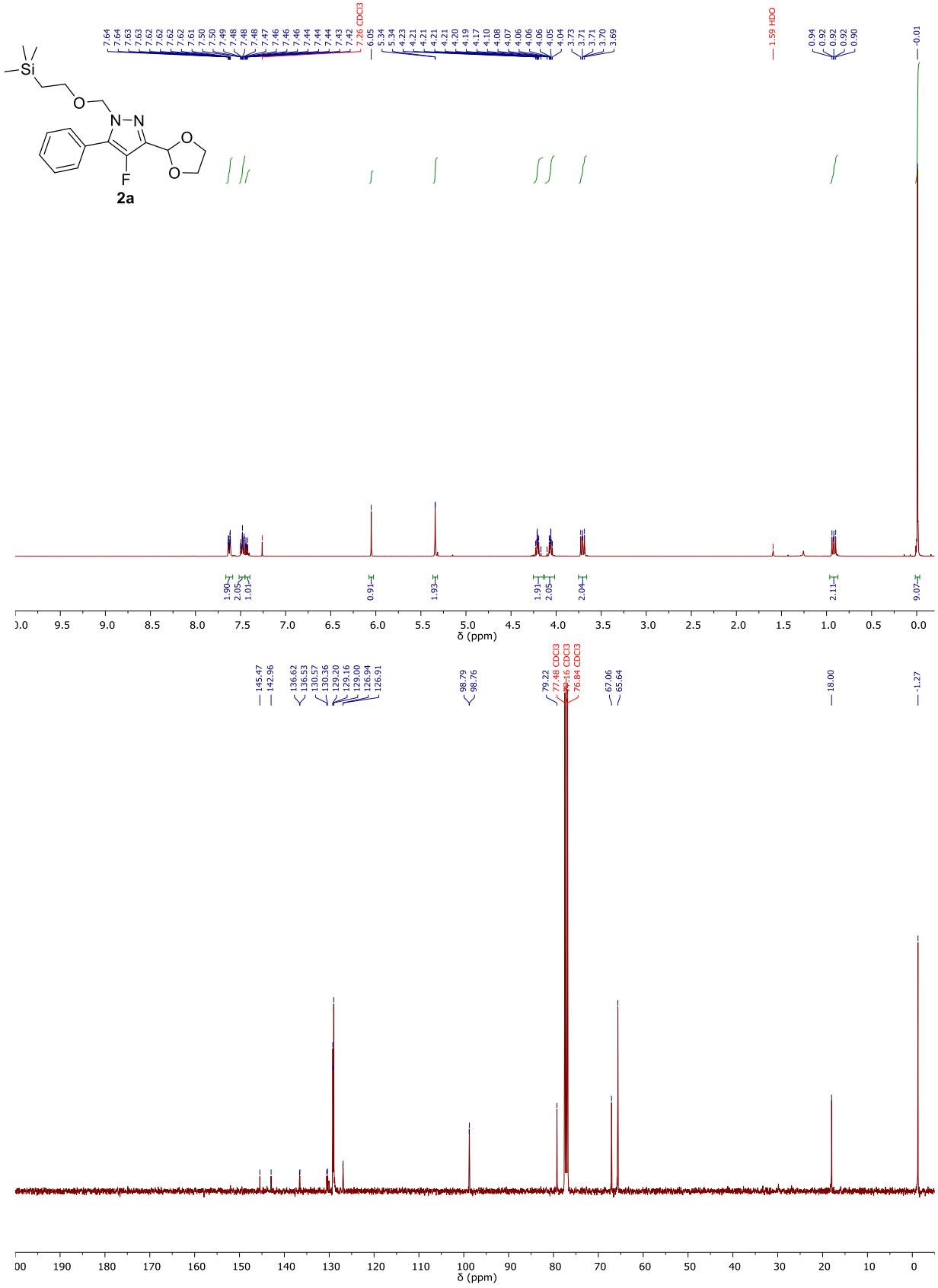
Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Bruker AVANCE 300 (300 MHz) or a Bruker AVANCE 400 (400 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to the residual protonated solvent (7.26 ppm for $CDCl_3$ and 2.05 ppm for acetone-d_6). Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, brs = broad singlet, brd = broad doublet. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Bruker AVANCE 300 (75 MHz) or a Bruker AVANCE 400 (100 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to the centre line of the triplet at 77.16 ppm for $CDCl_3$, the septet at 106.29 ppm for acetone-d_6. ^{13}C NMR experiments were routinely run with broadband decoupling. Fluorine nuclear magnetic resonance (^{19}F{^{1}H} NMR) spectra were recorded using a Bruker AVANCE 400 (376 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) and calibrated with $CFCl_3$ as external reference (0 ppm). NMR experiments were routinely run with broadband decoupling.

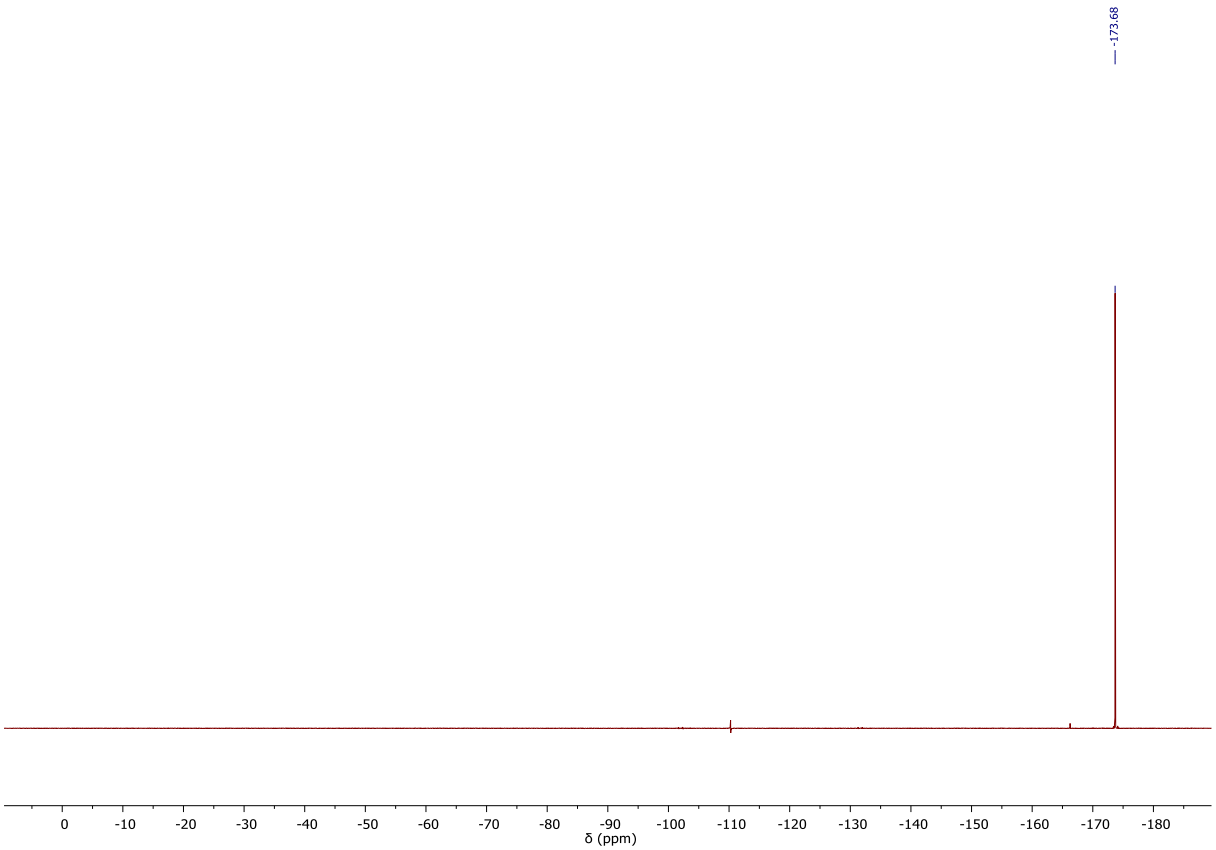
d. Mass and IR analyses

Mass spectra were measured by electrospray ionization and were recorded at Sorbonne University (Paris). Infrared spectra were measured on a FT-4500 spectrometer at ENSCP Chimie ParisTech.

[1] $KMnO_4$ stain: purple solution prepared with 1.5 g of potassium permanganate, 10 g of potassium carbonate and 150 mg of potassium hydroxide in 200 mL of water.

2. Preparation of 4-fluoropyrazoles – NMR spectra

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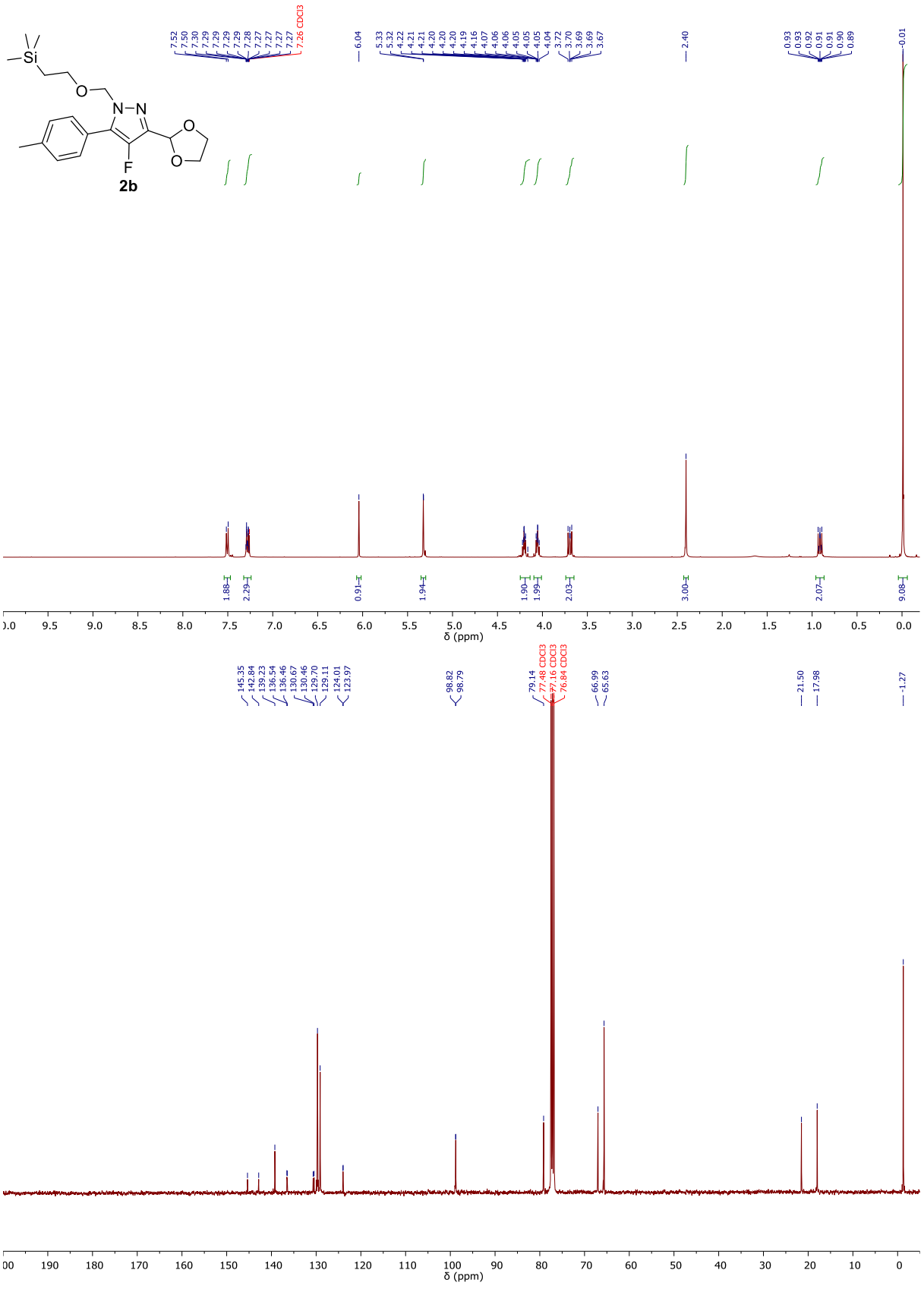
δ (ppm)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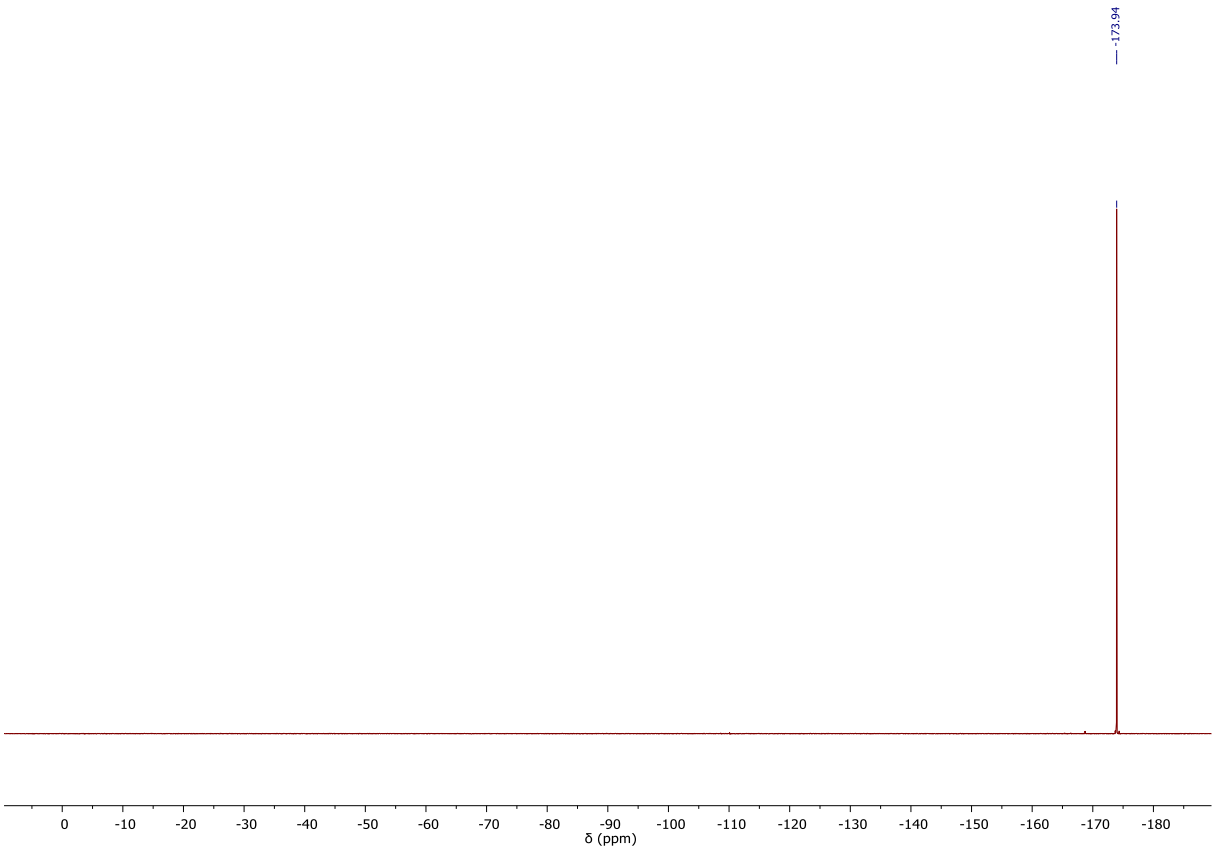
δ (ppm)
δ (ppm)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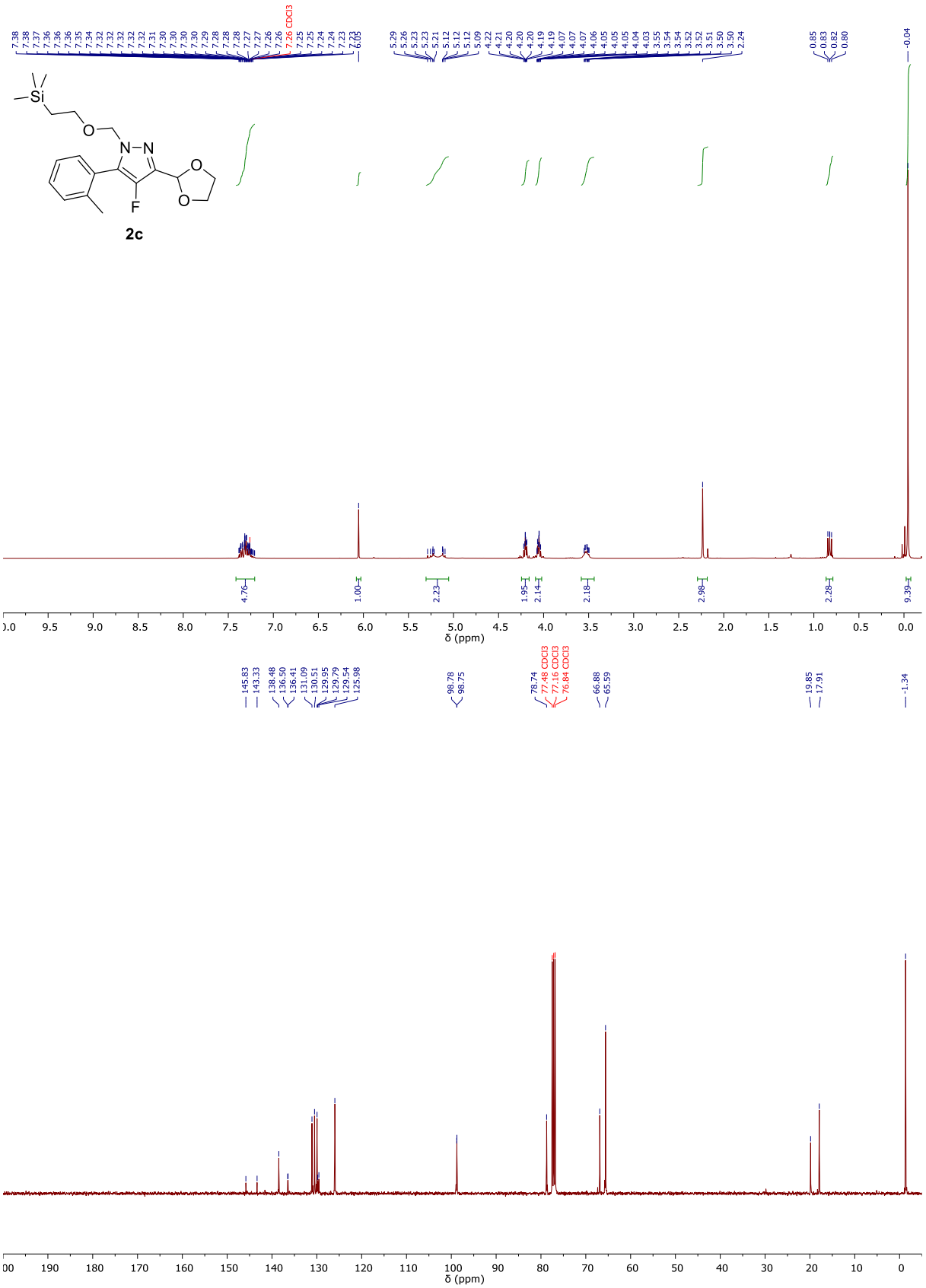
-180
δ (ppm)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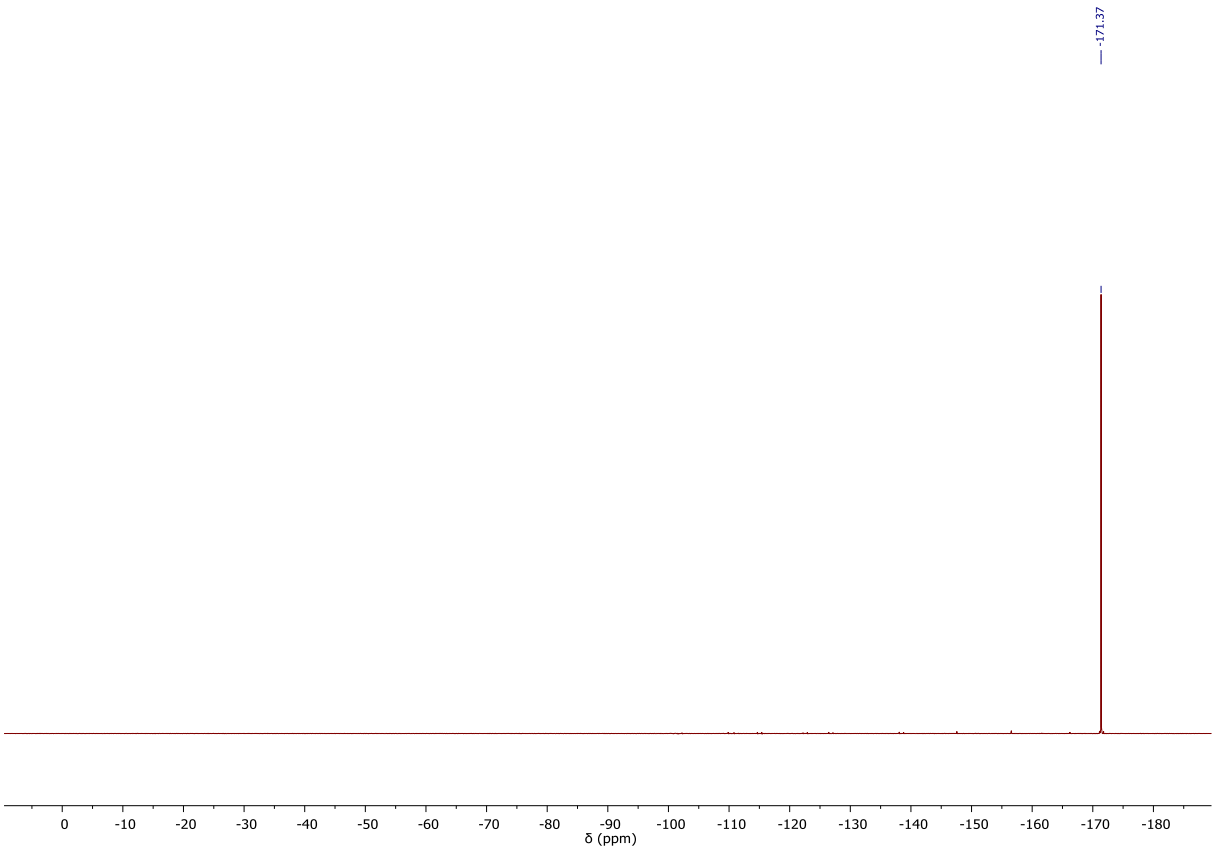
O
F
2c
δ (ppm)
δ (ppm)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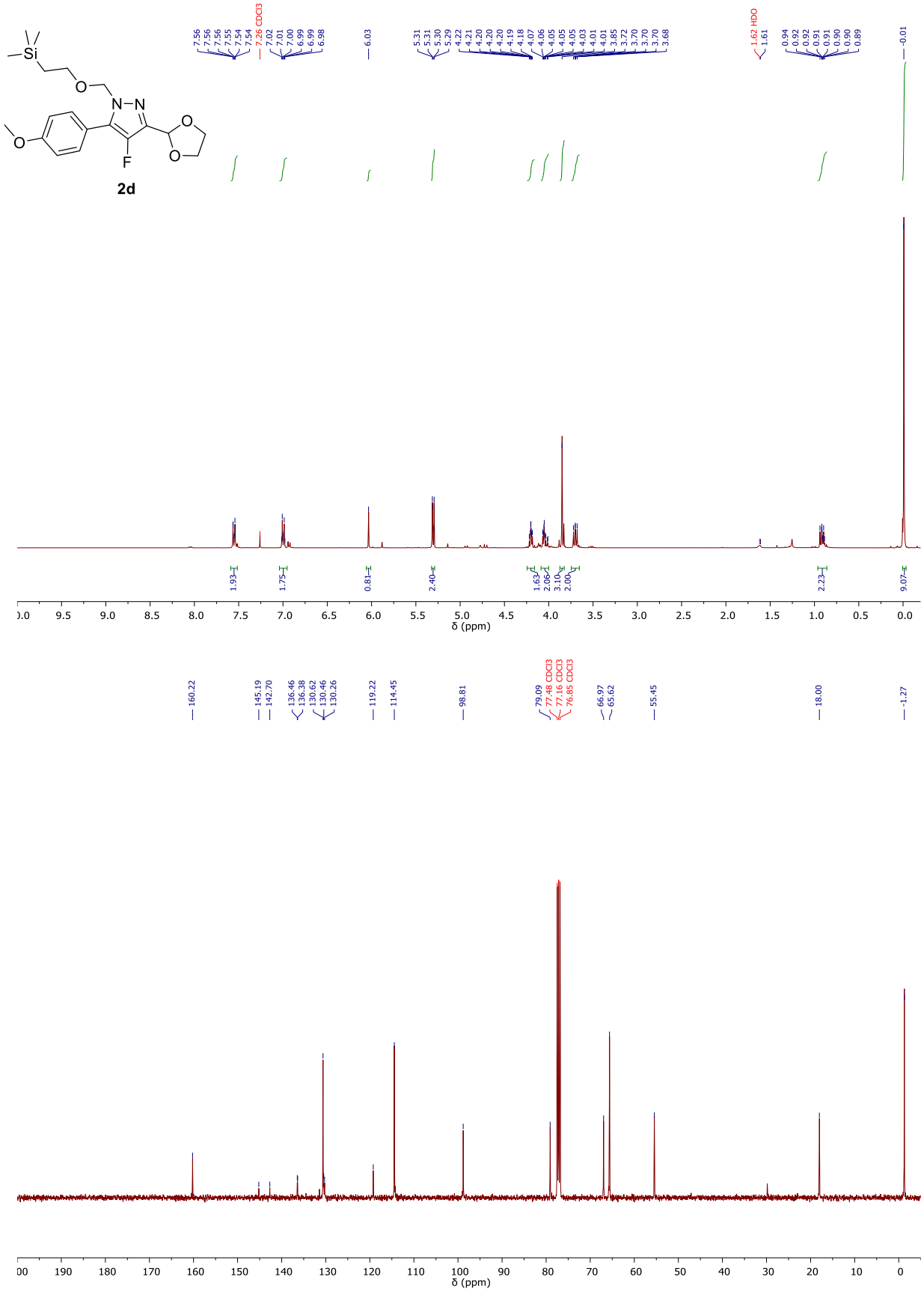
-170
-180
δ (ppm)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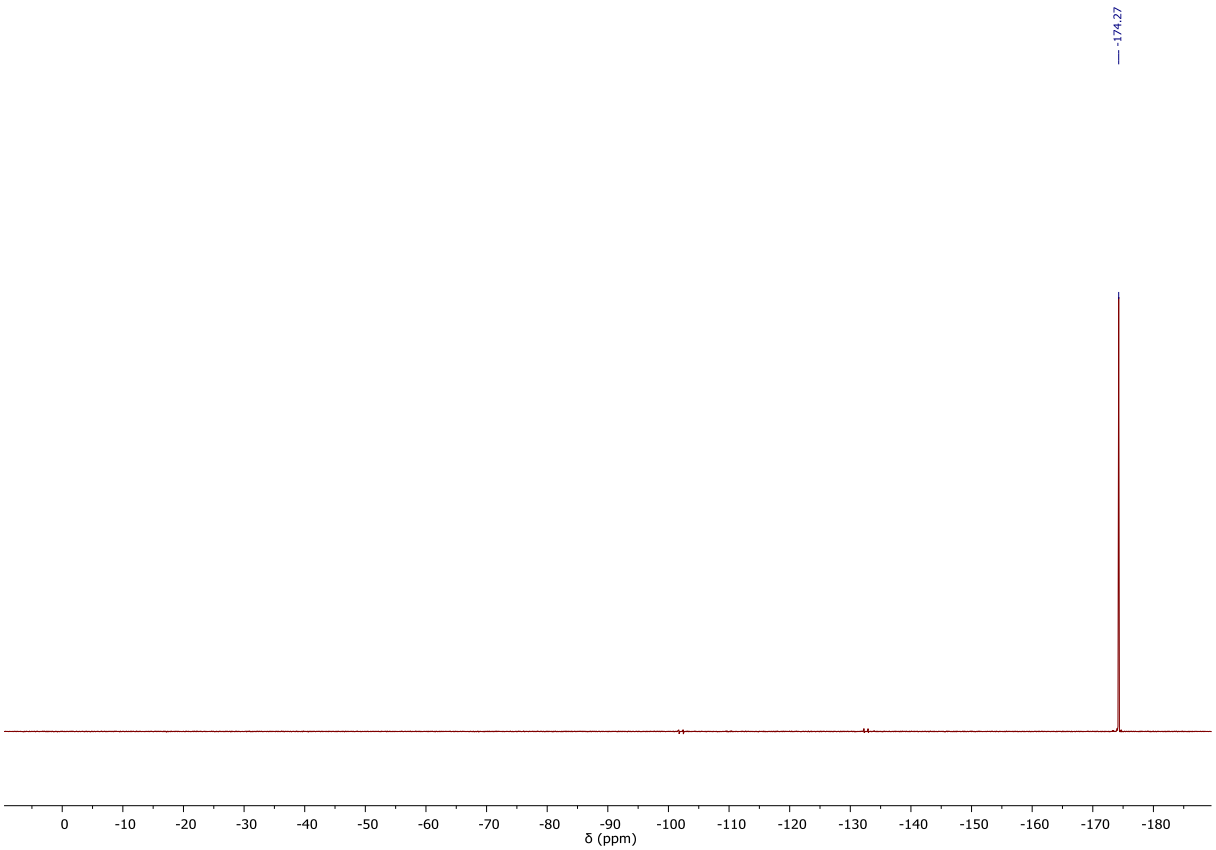
δ (ppm)
δ (ppm)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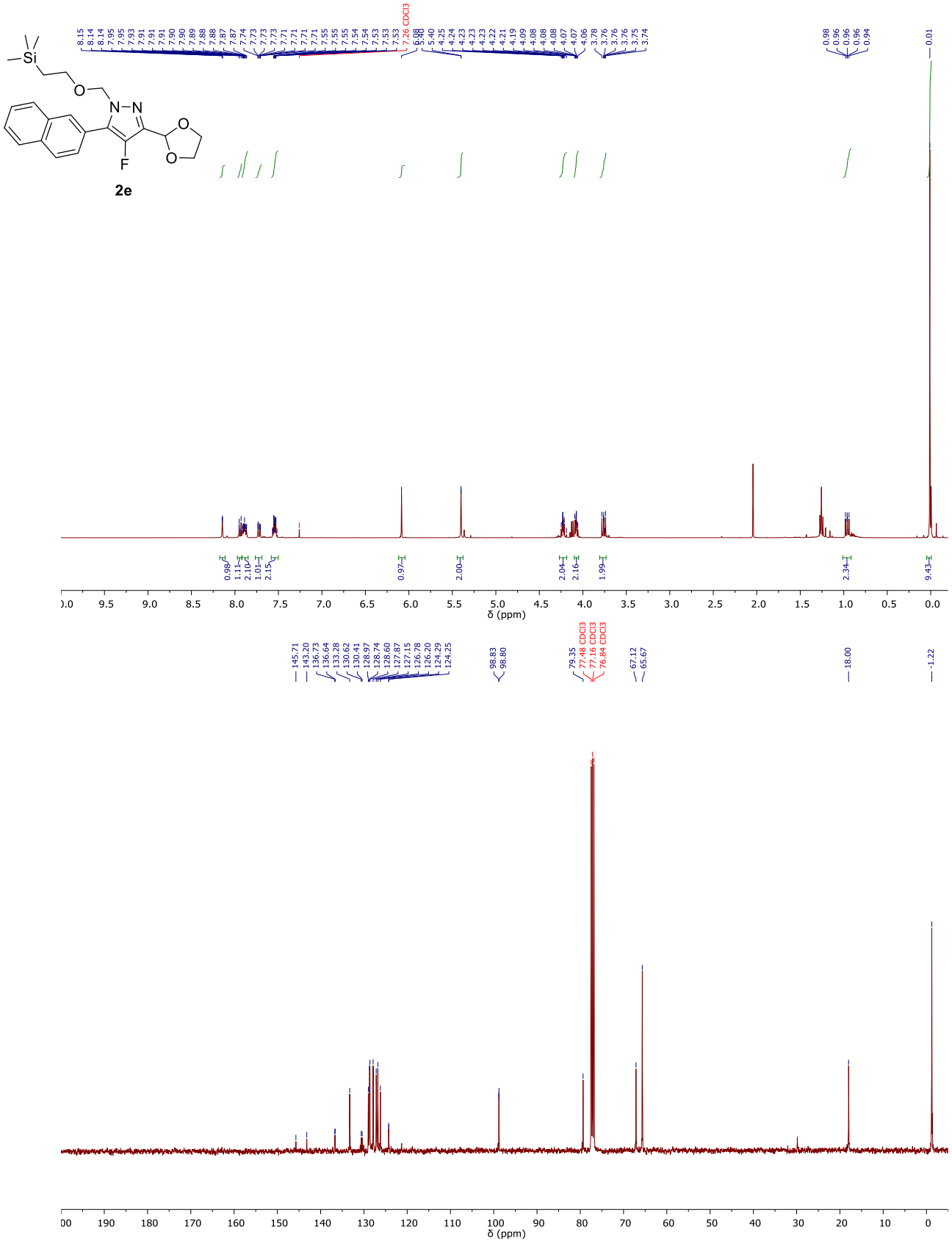
-170
-180
δ (ppm)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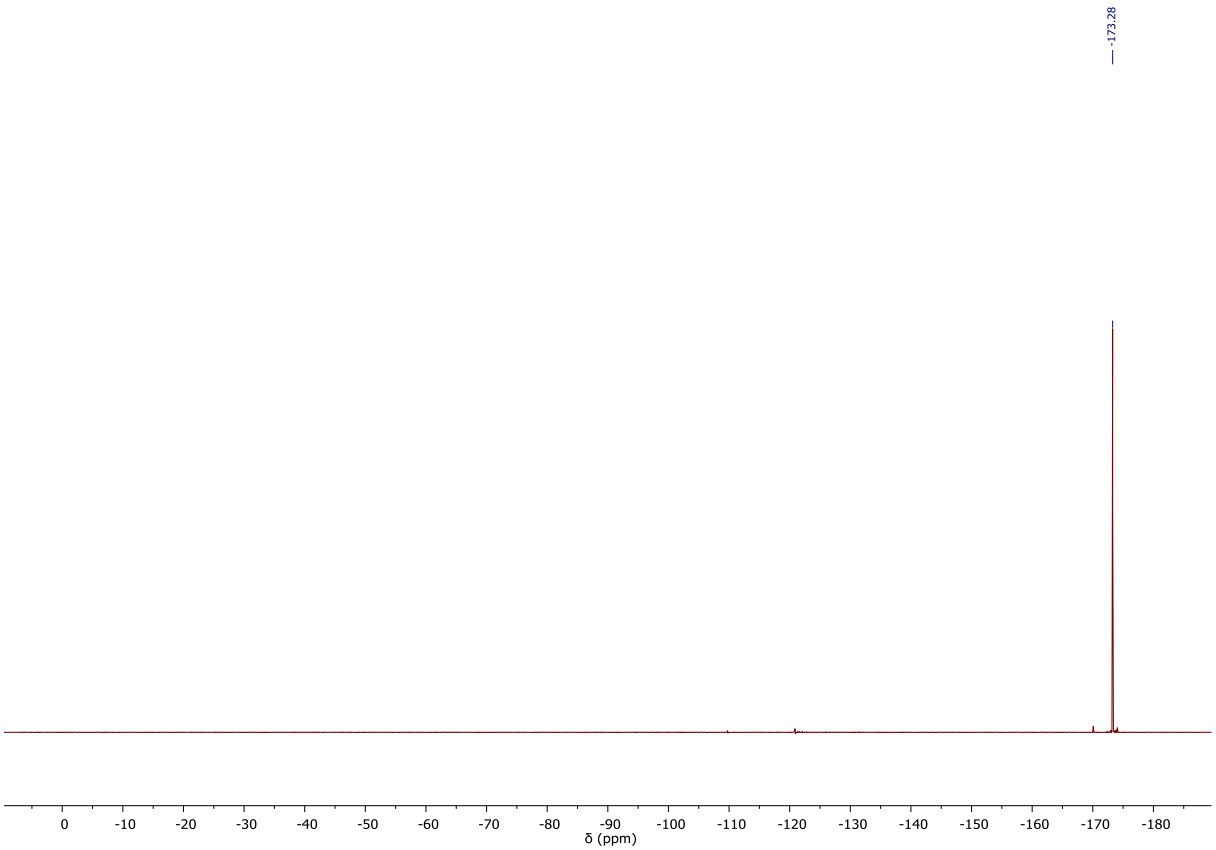
O
F
2e
δ (ppm)
δ (ppm)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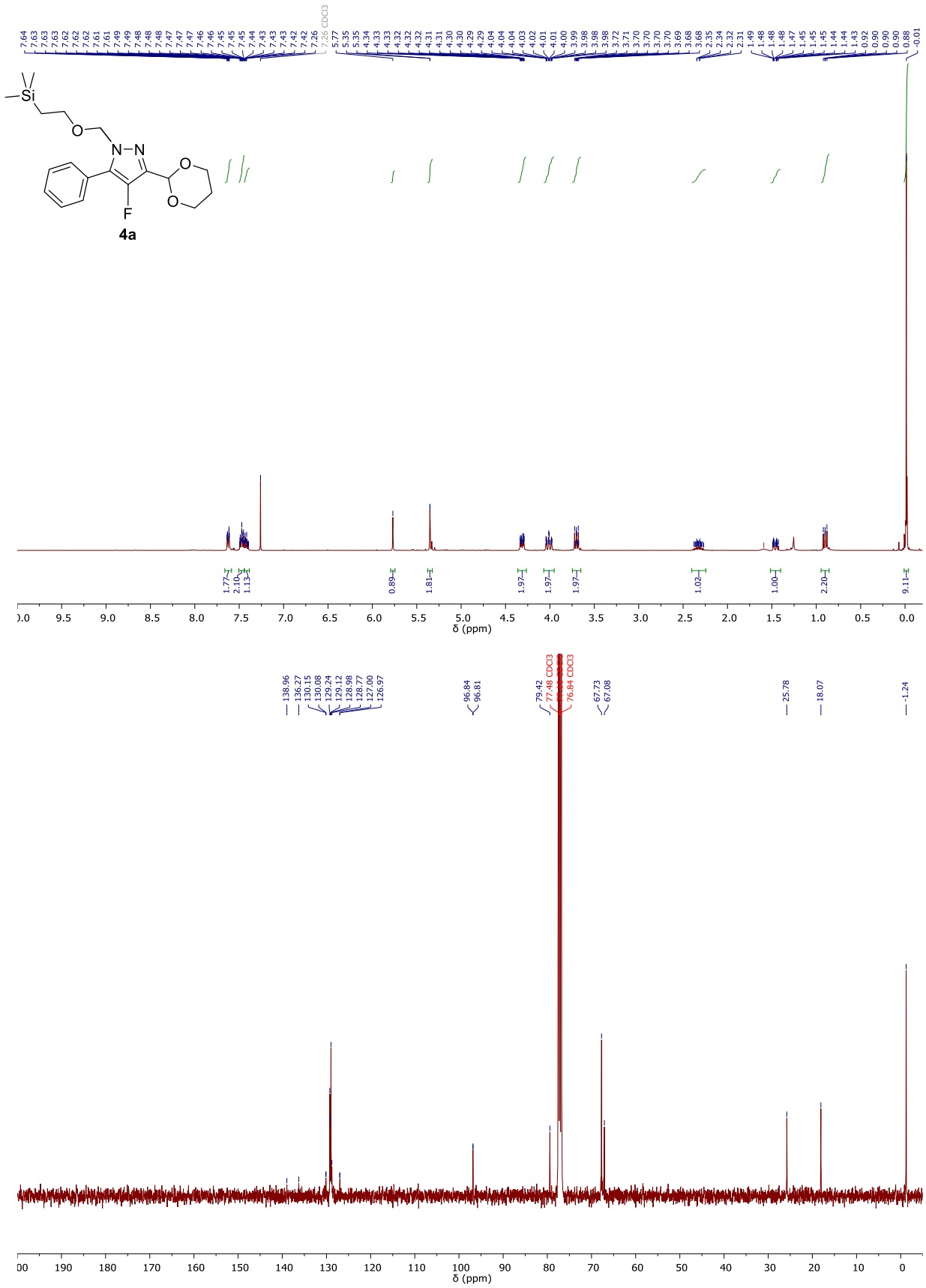
δ (ppm)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O
F
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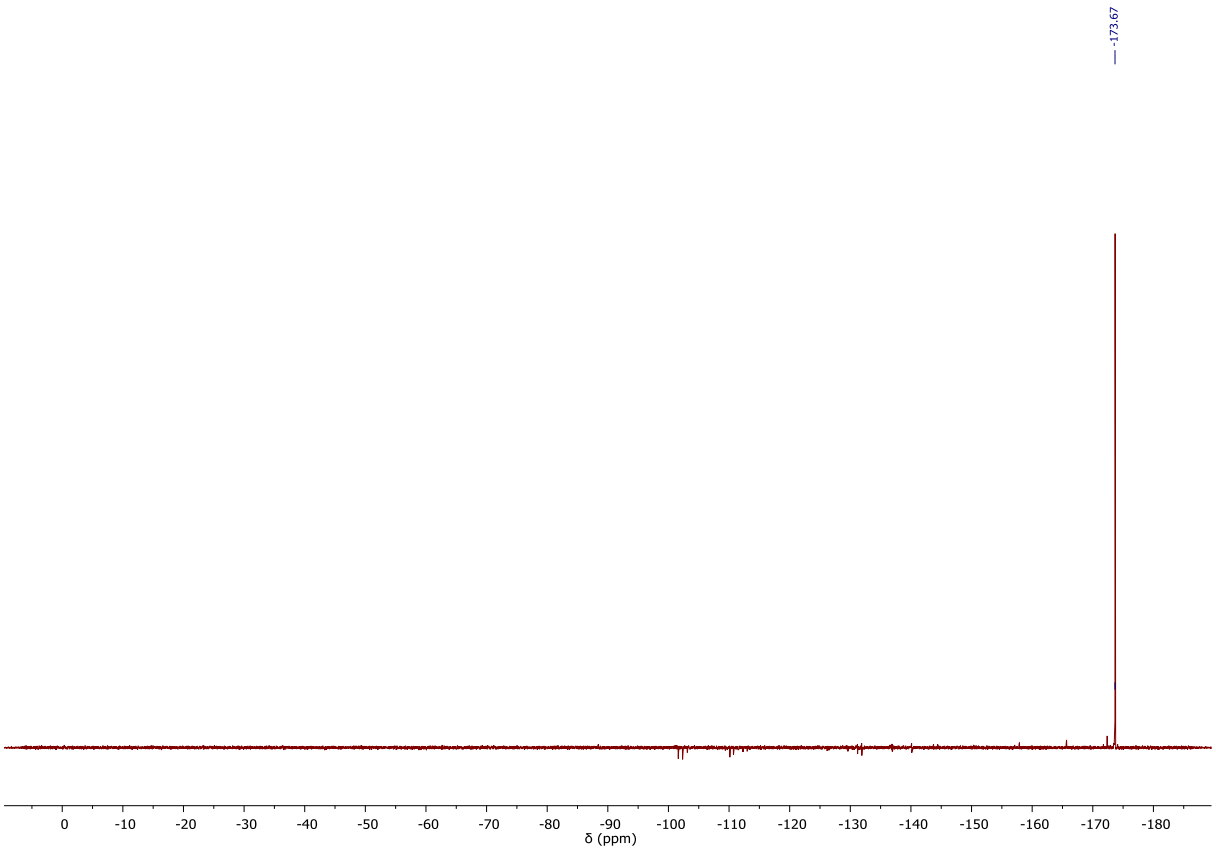
δ (ppm)
δ (ppm)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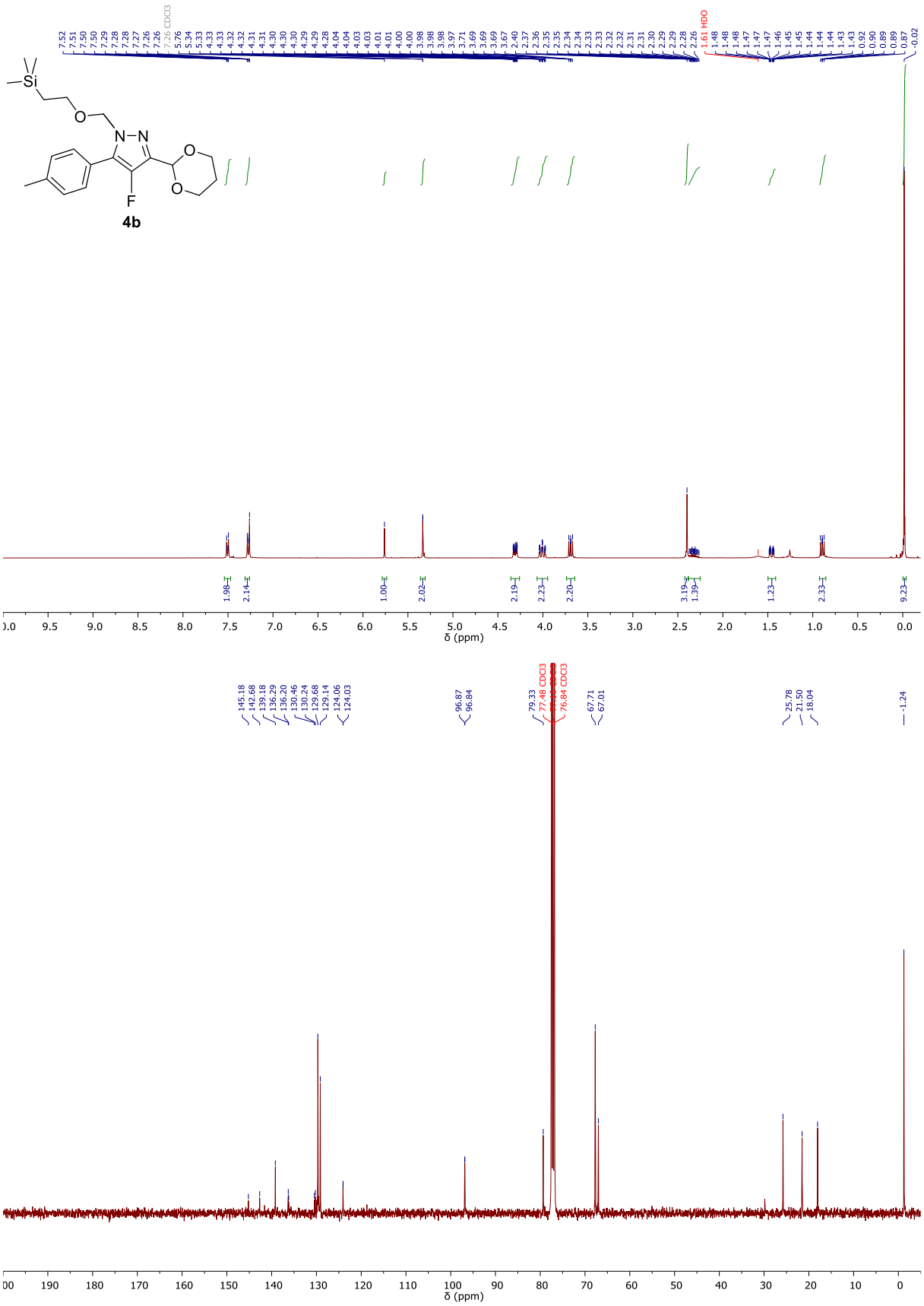
δ (ppm)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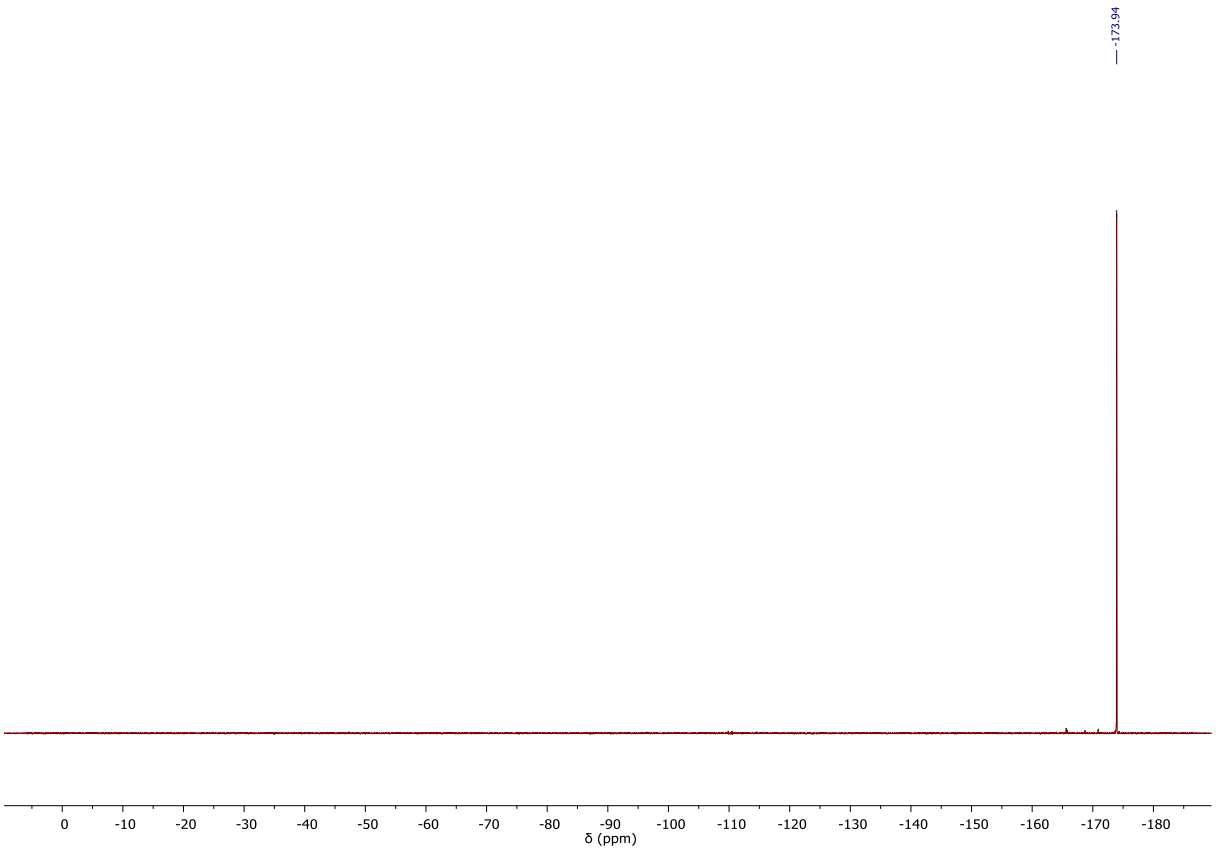
δ (ppm)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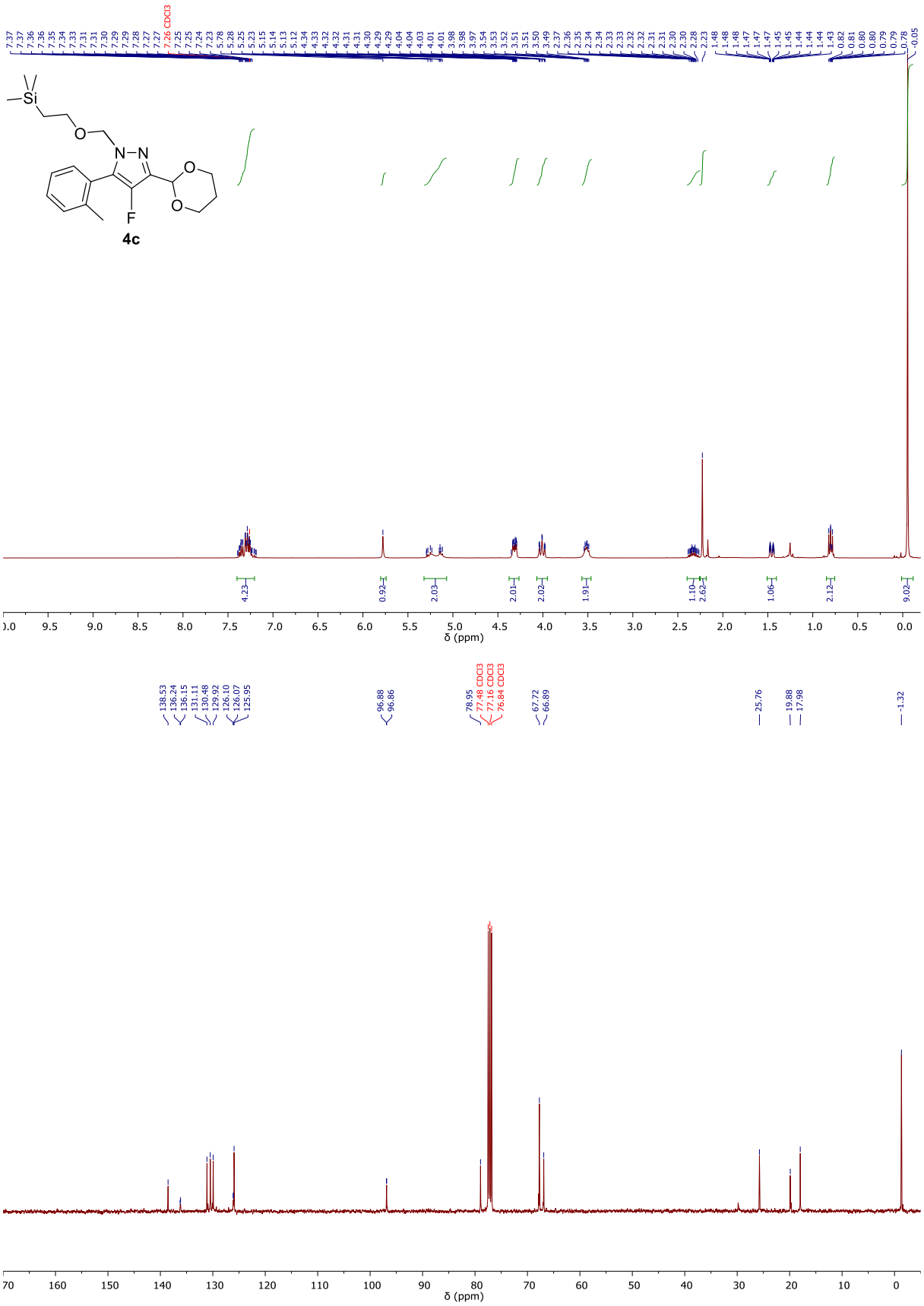
-170
-180
δ (ppm)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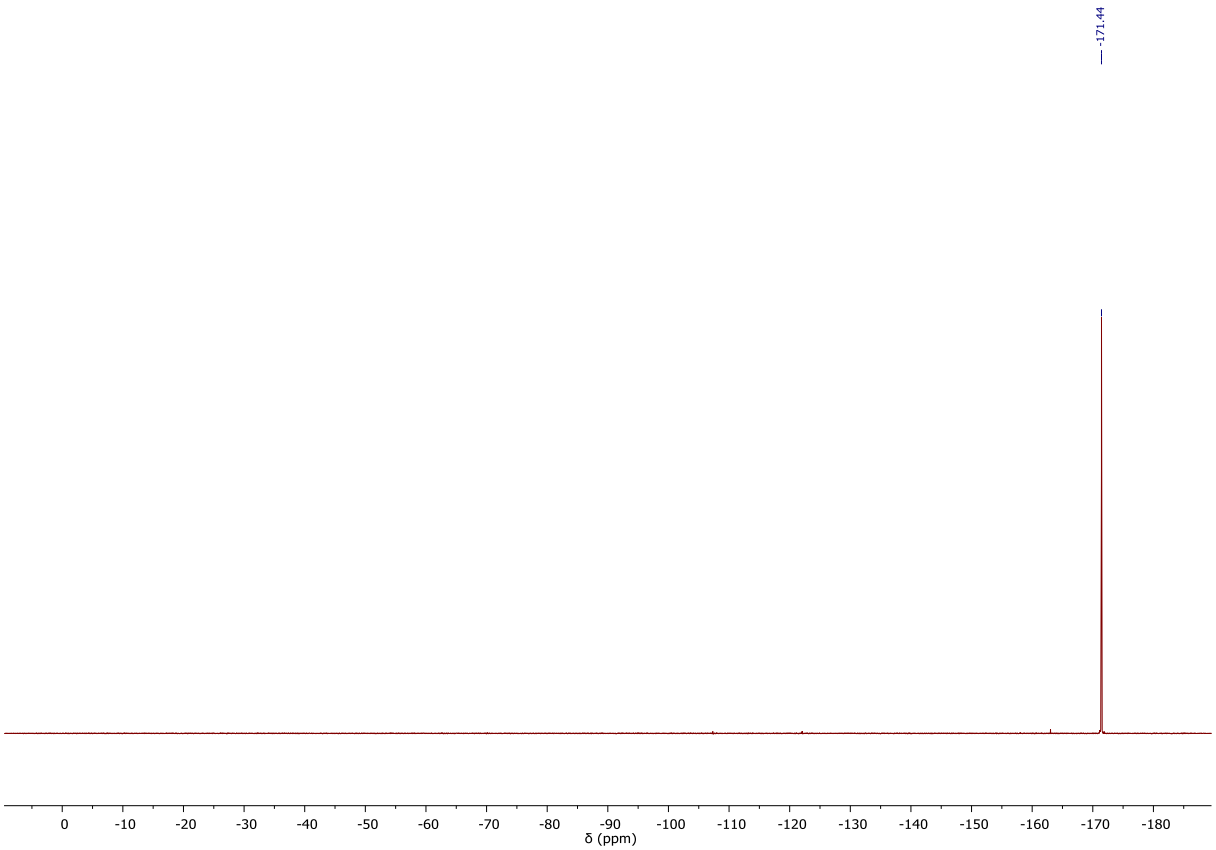
δ (ppm)
δ (ppm)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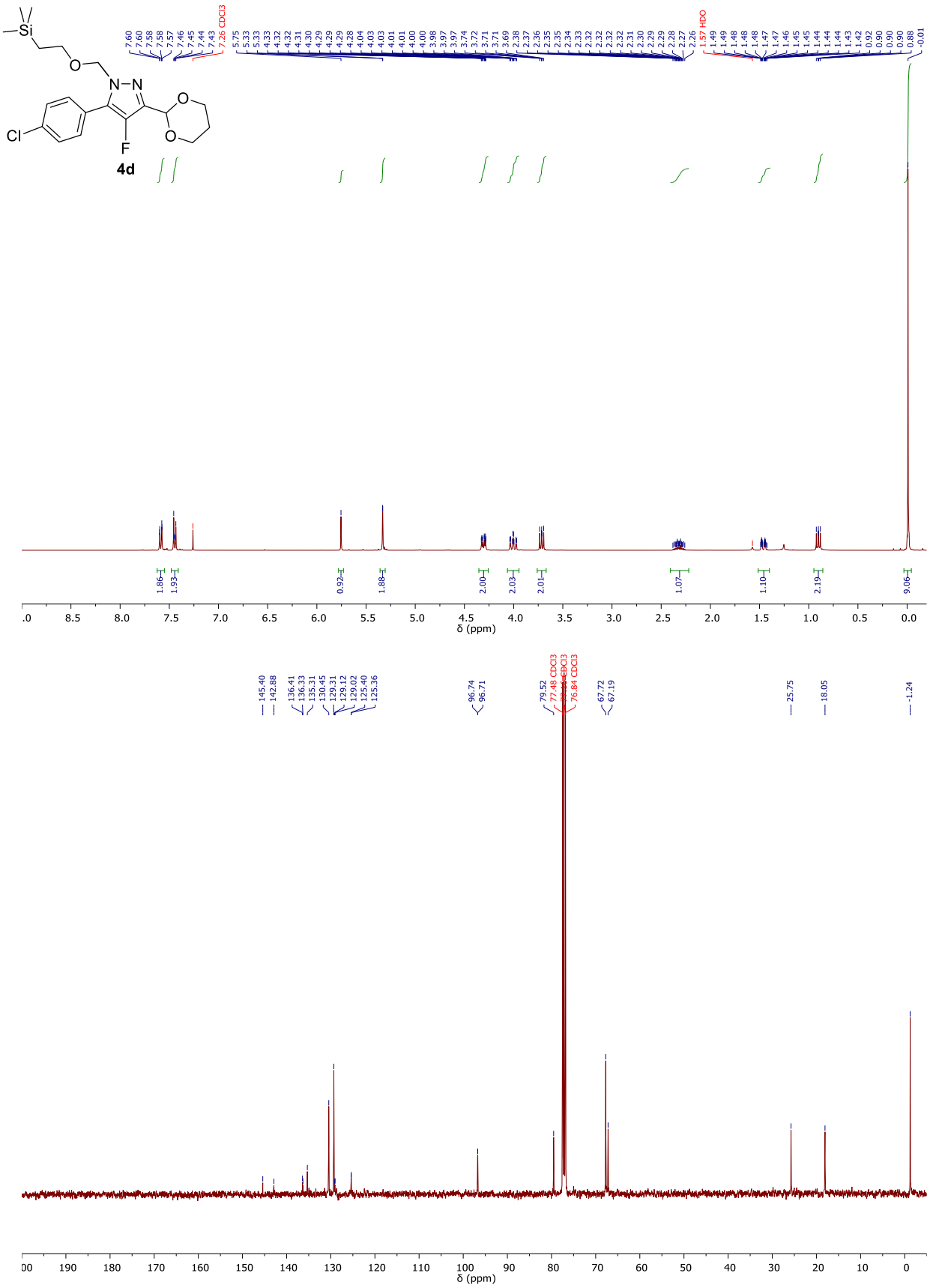
δ (ppm)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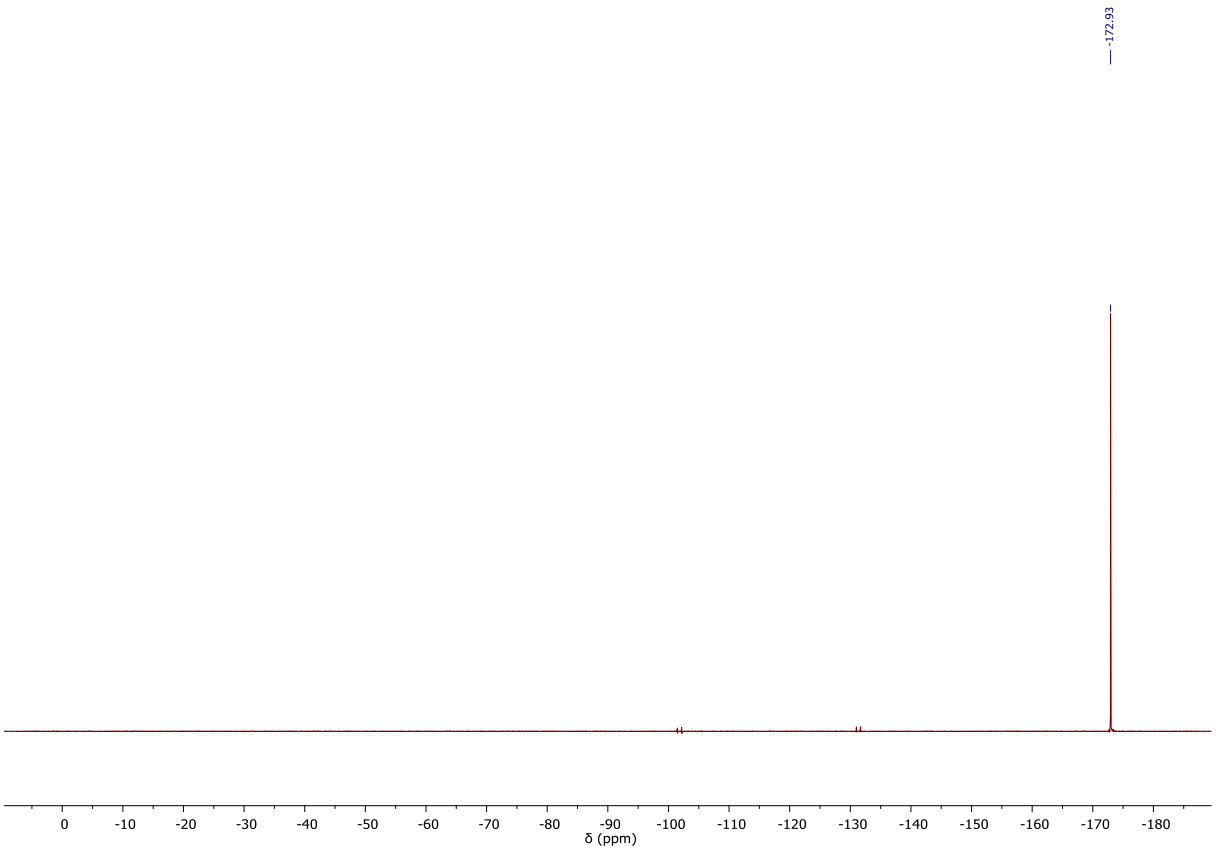
δ (ppm)
δ (ppm)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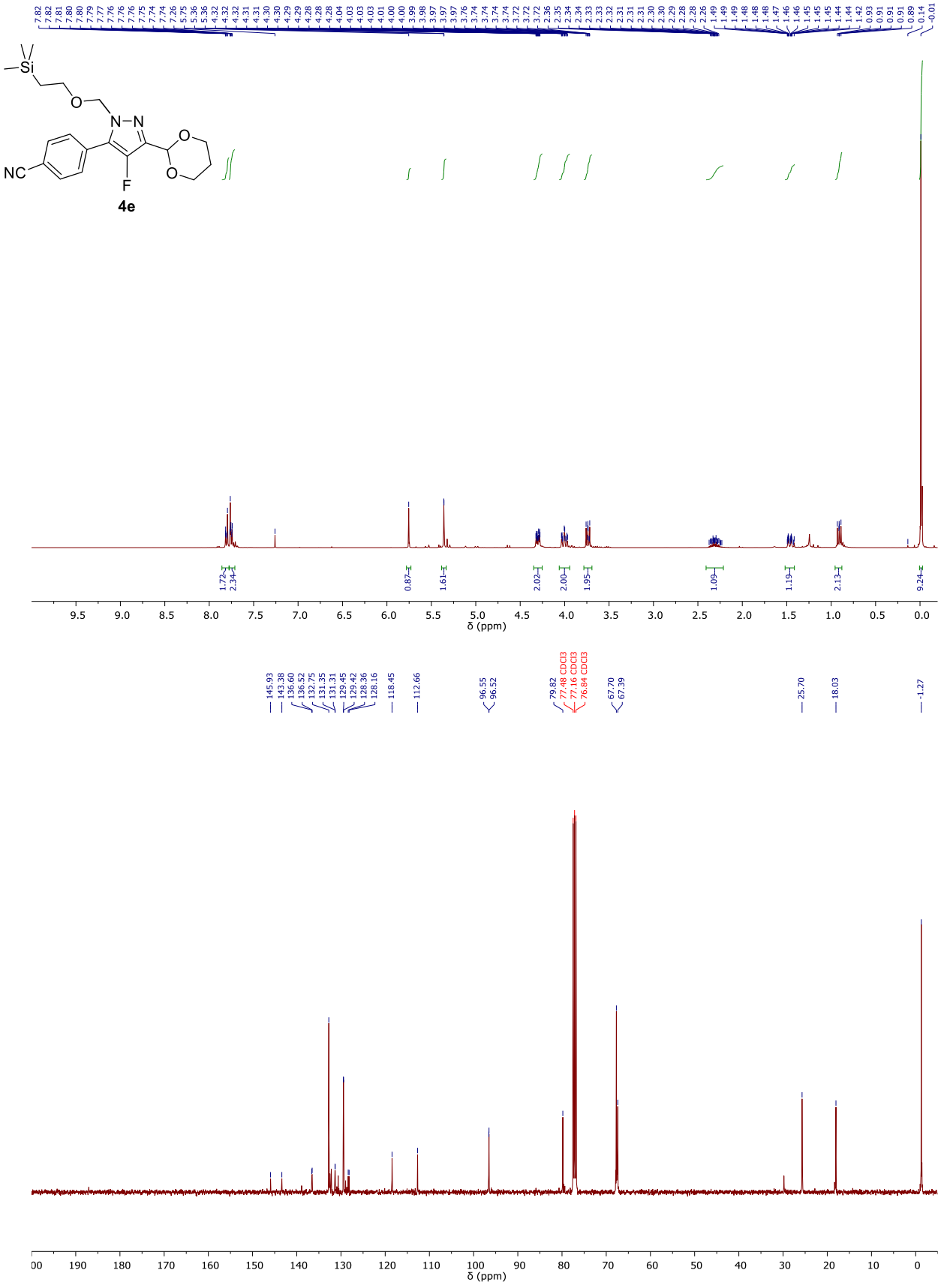
-170
-180
δ (ppm)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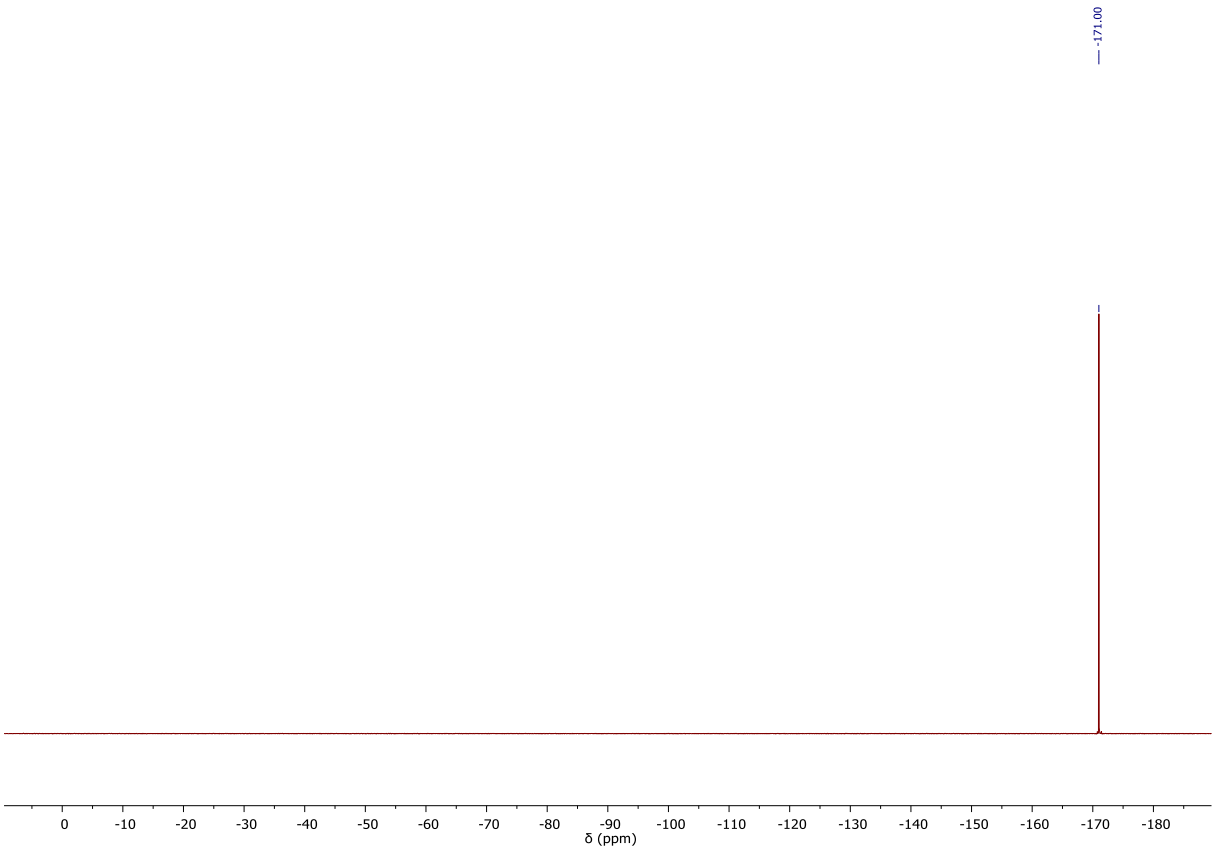
O
O
NC
F
4e
δ (ppm)
δ (ppm)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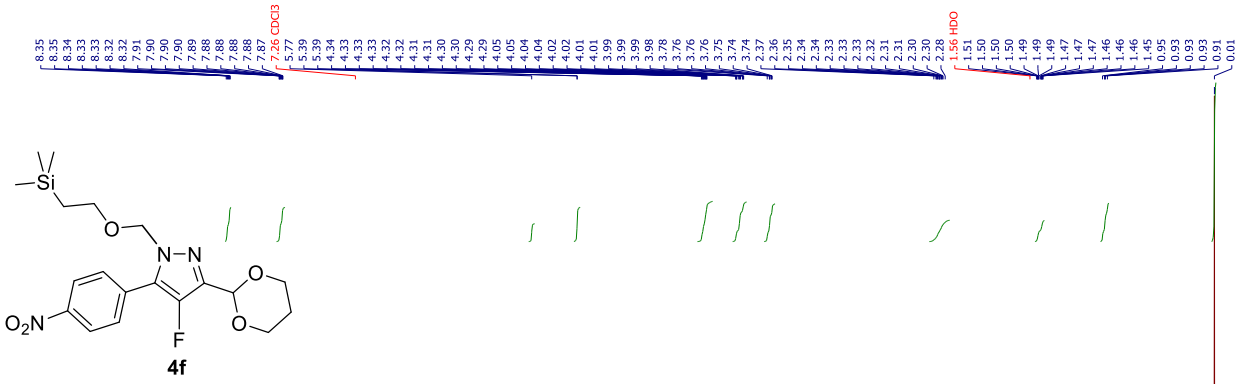
δ (ppm)


Si
O
N–N
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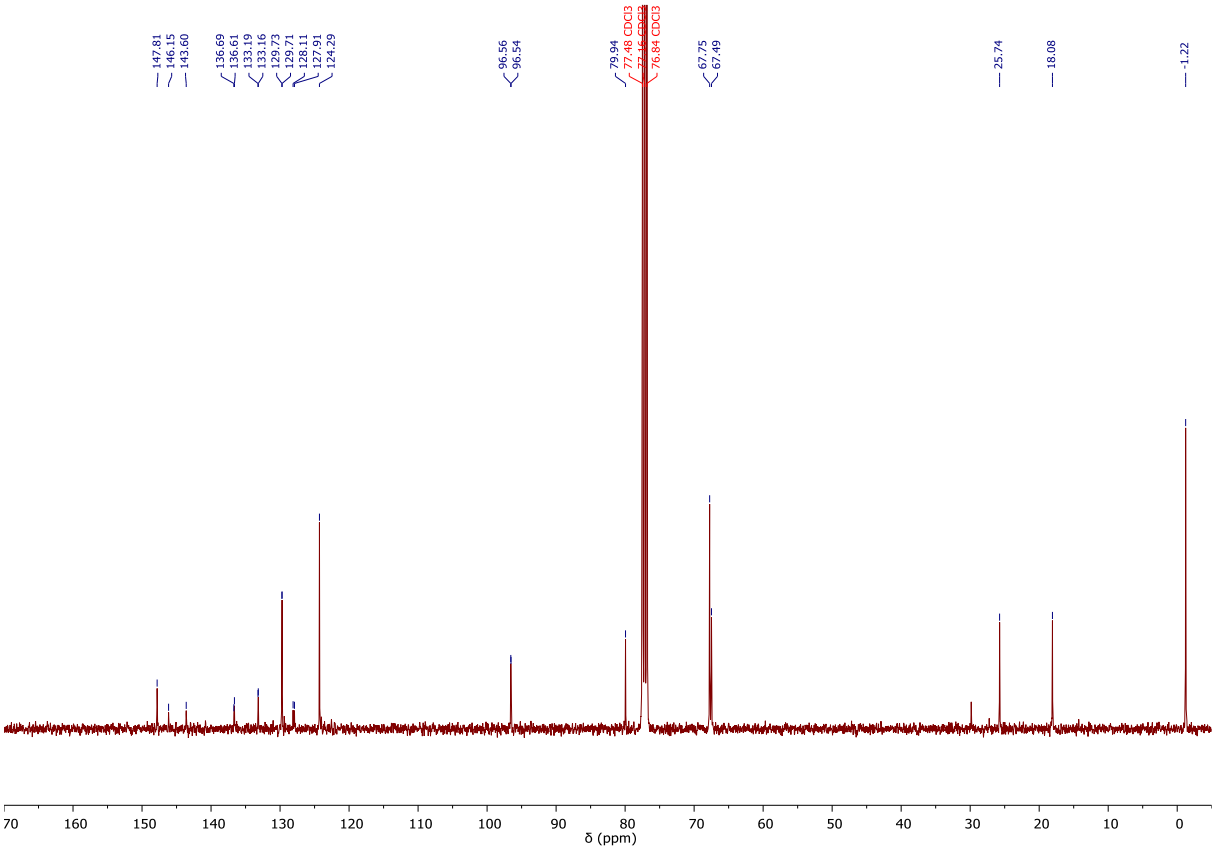
O
O_2N
F

4f

7.26 CDCl3
1.56 HDO
δ (ppm)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96.54
79.94
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77.16 CDCl3
76.84 CDCl3
67.75
67.49
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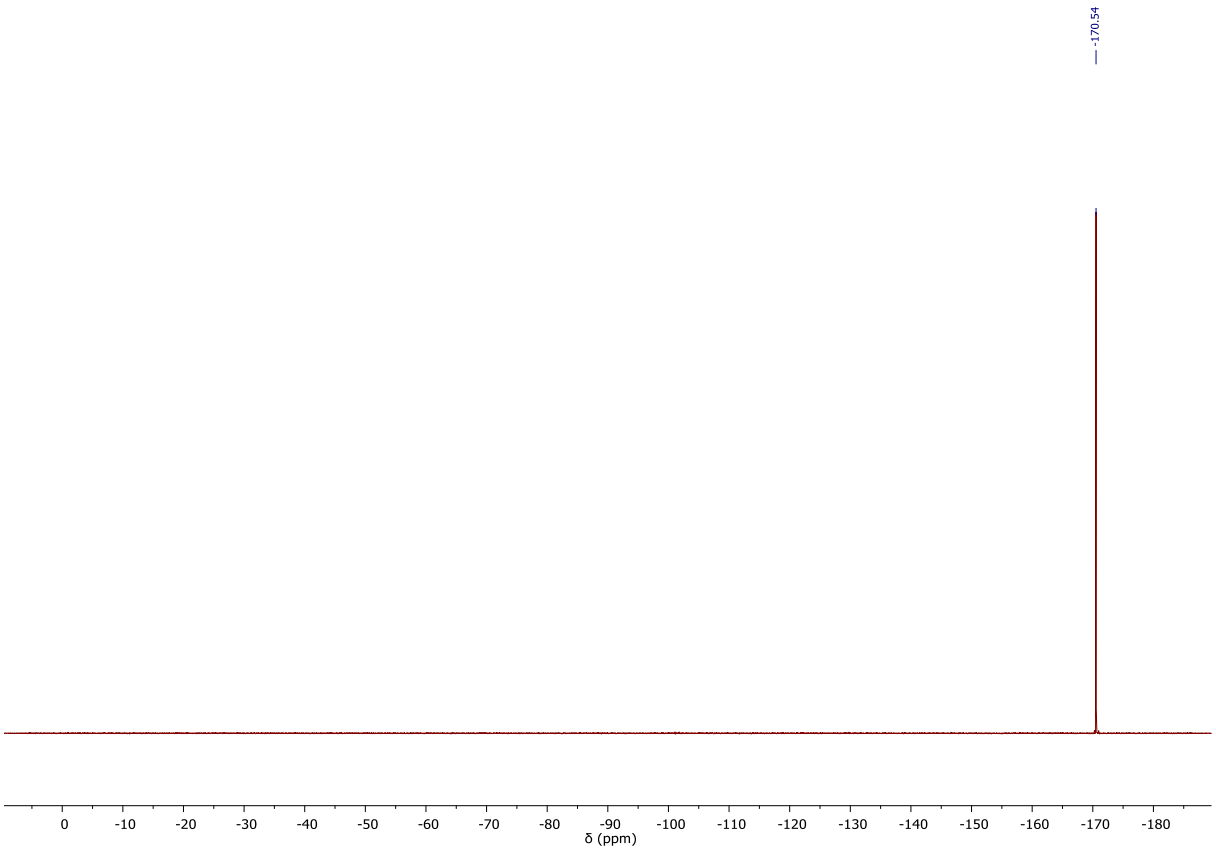
18.08
-1.22
δ (ppm)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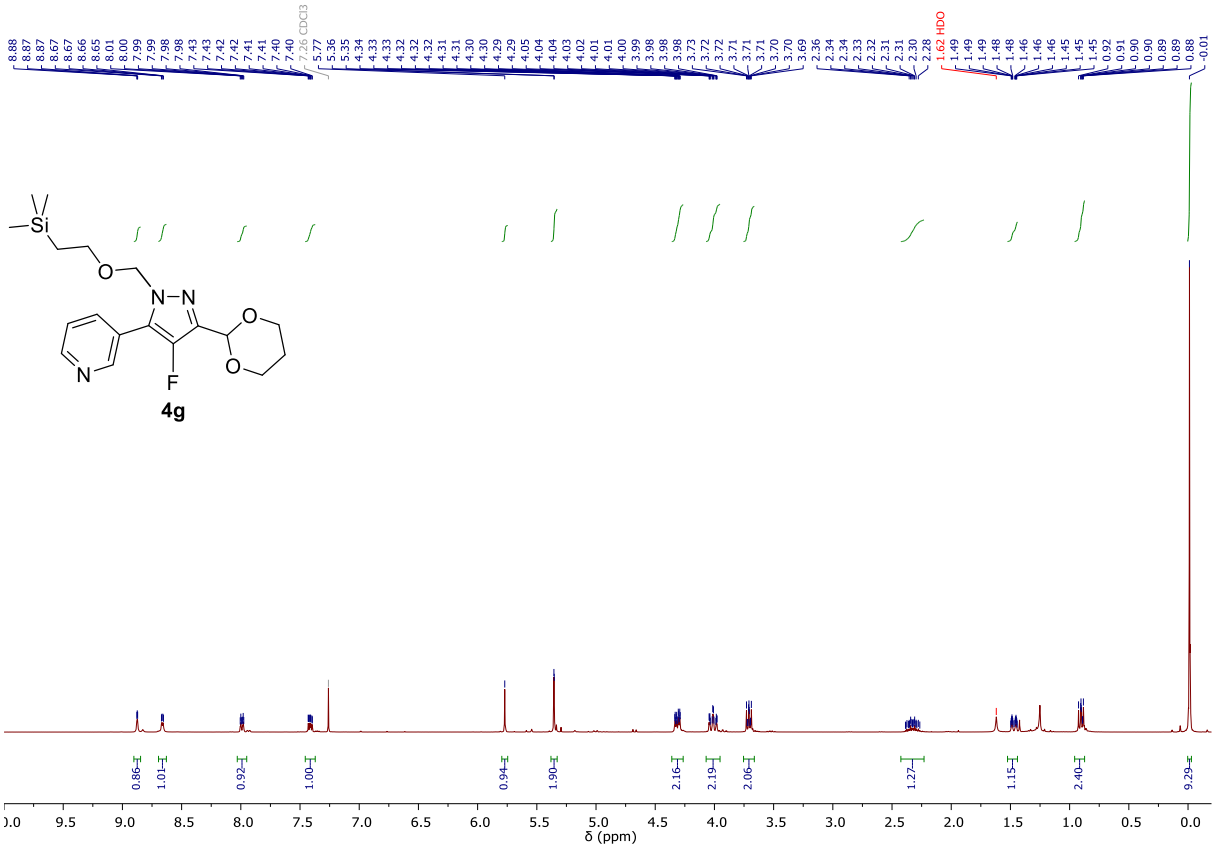
δ (ppm)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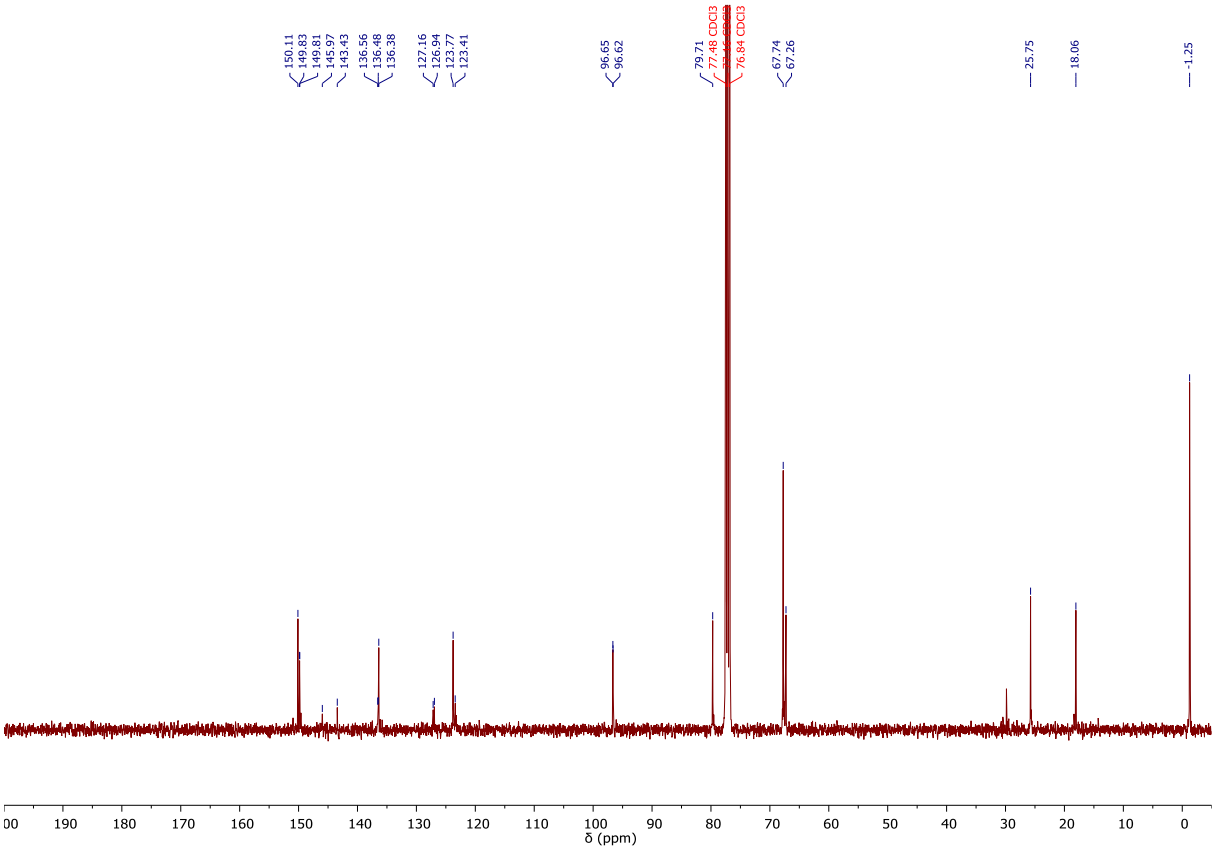
0.86 1.01 0.92 1.00 0.94 1.90 2.16 2.19 2.06 1.27 1.15 2.40 9.29
δ (ppm)

Si
O
N–N
O
O
N
F

4g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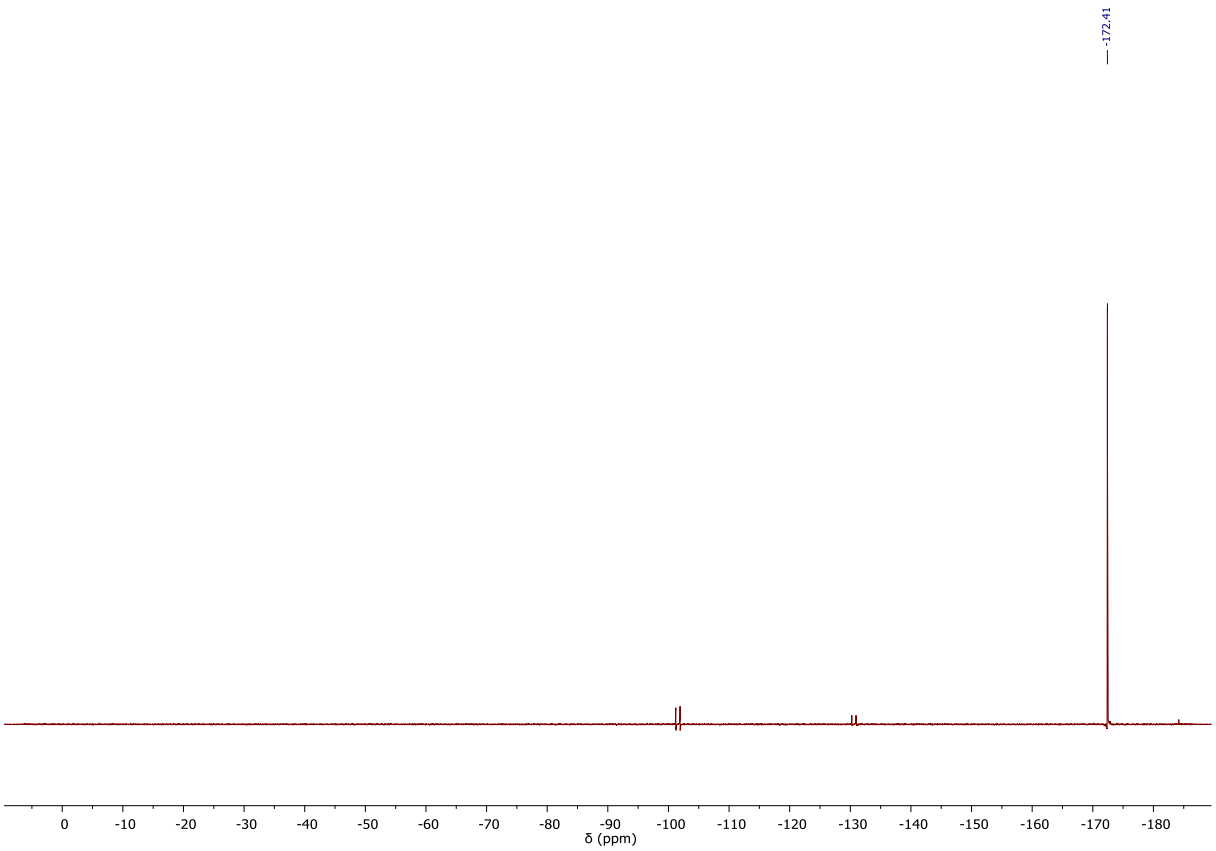
δ (ppm)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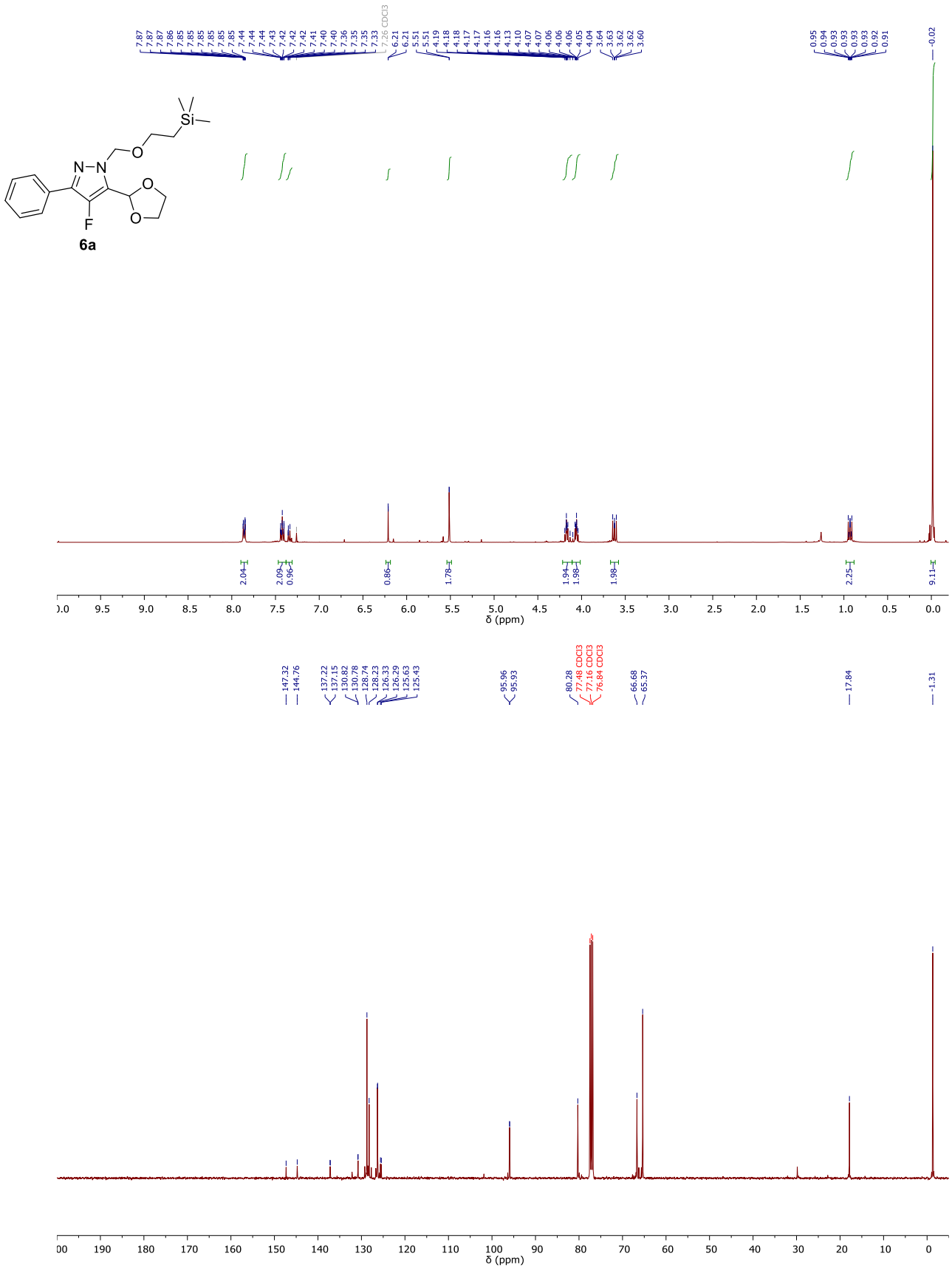
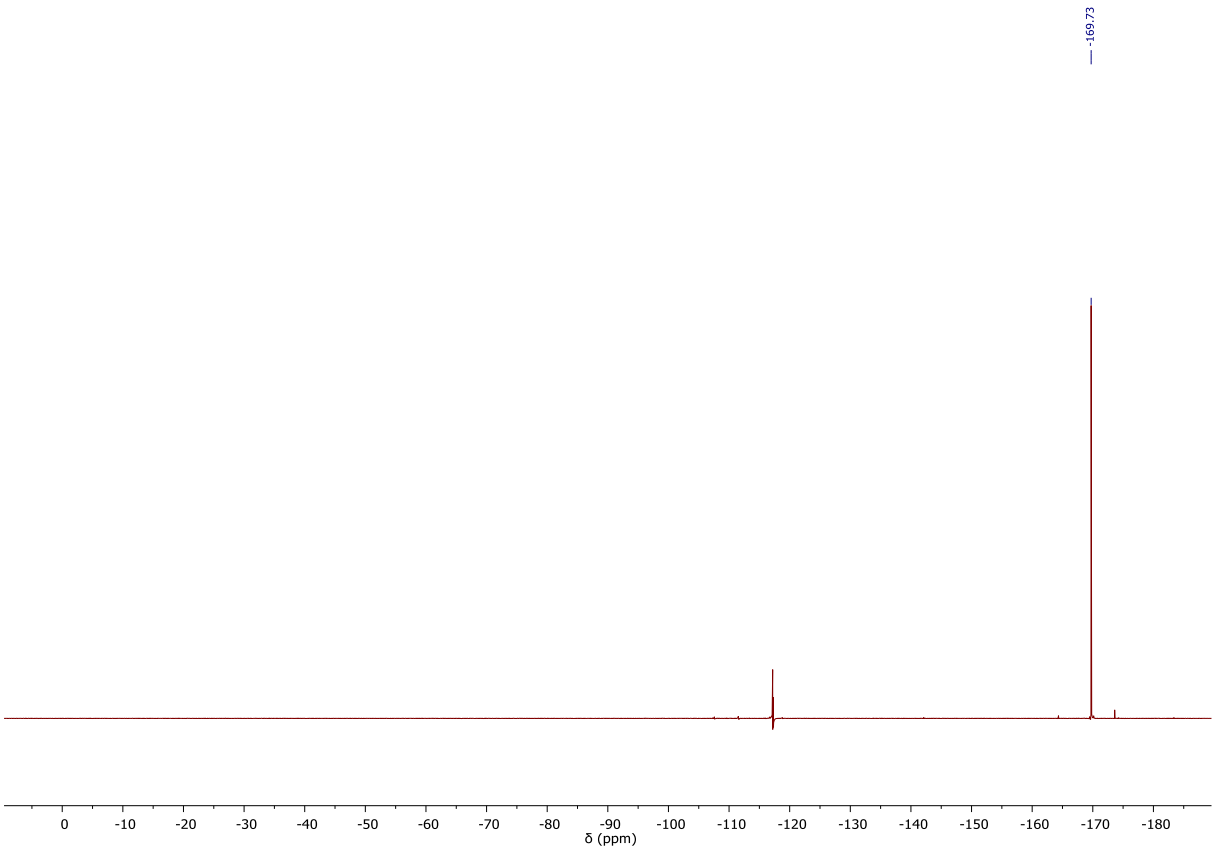
-180
δ (ppm)


6a
δ (ppm)
δ (ppm)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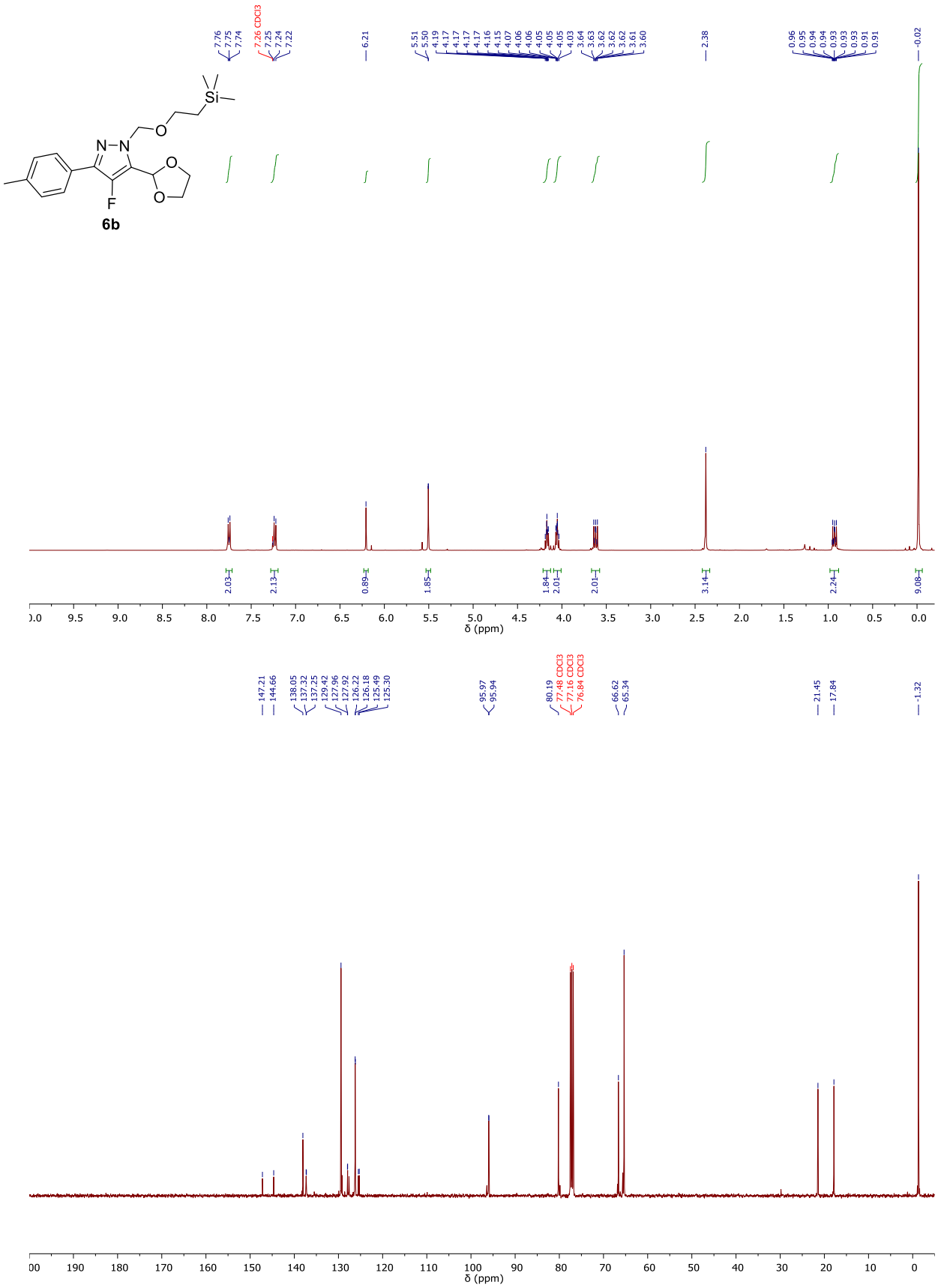
δ (ppm)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5.50
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4.17
4.17
4.17
4.16
4.15
4.07
4.06
4.06
4.05
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4.05
4.03
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3.62
3.62
3.62
3.61
3.60
2.38
0.96
0.95
0.94
0.94
0.93
0.93
0.93
0.91
0.91
-0.02
Si
O
N–N
O
O
F
6b
2.03
2.13
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1.85
1.84
2.01
2.01
3.14
2.24
9.08
δ (ppm)
147.21
144.66
138.05
137.32
137.25
129.42
127.96
127.92
126.22
126.18
125.49
125.30
95.97
95.94
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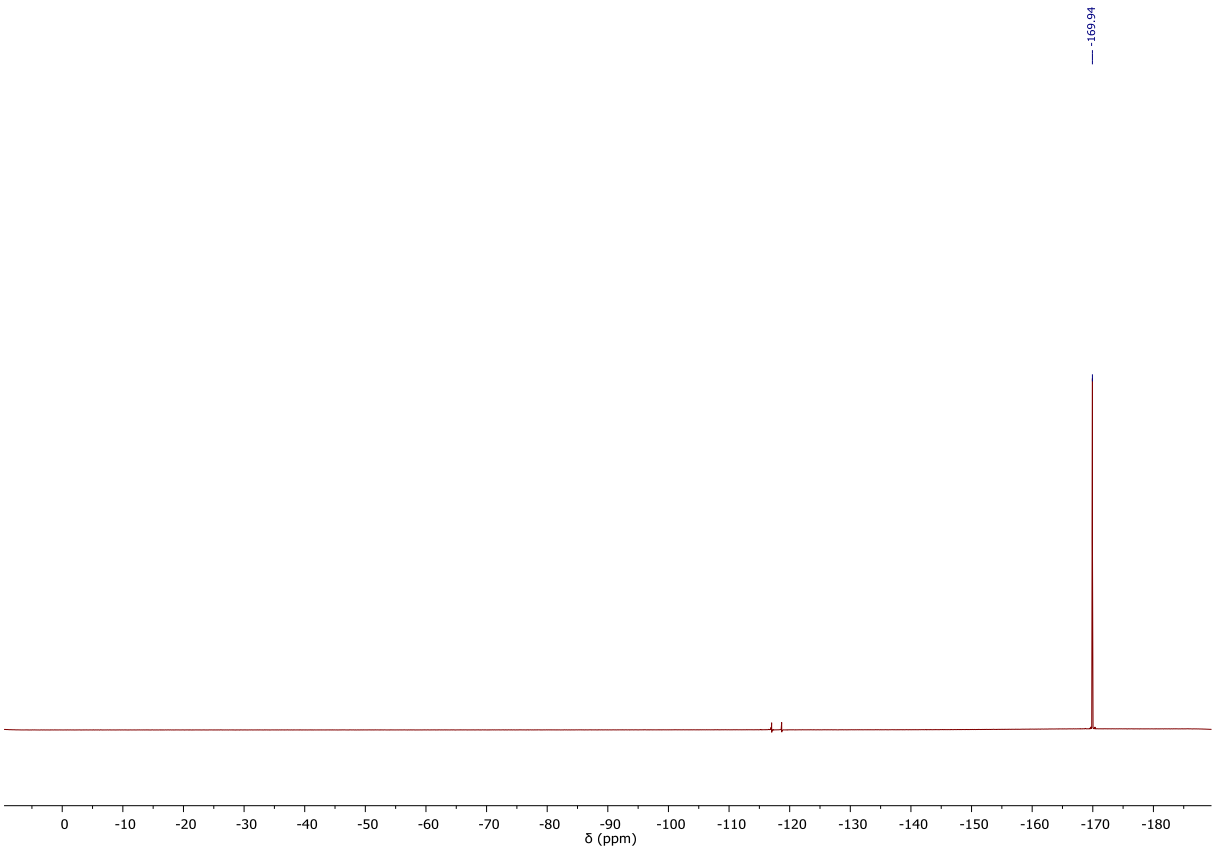
δ (ppm)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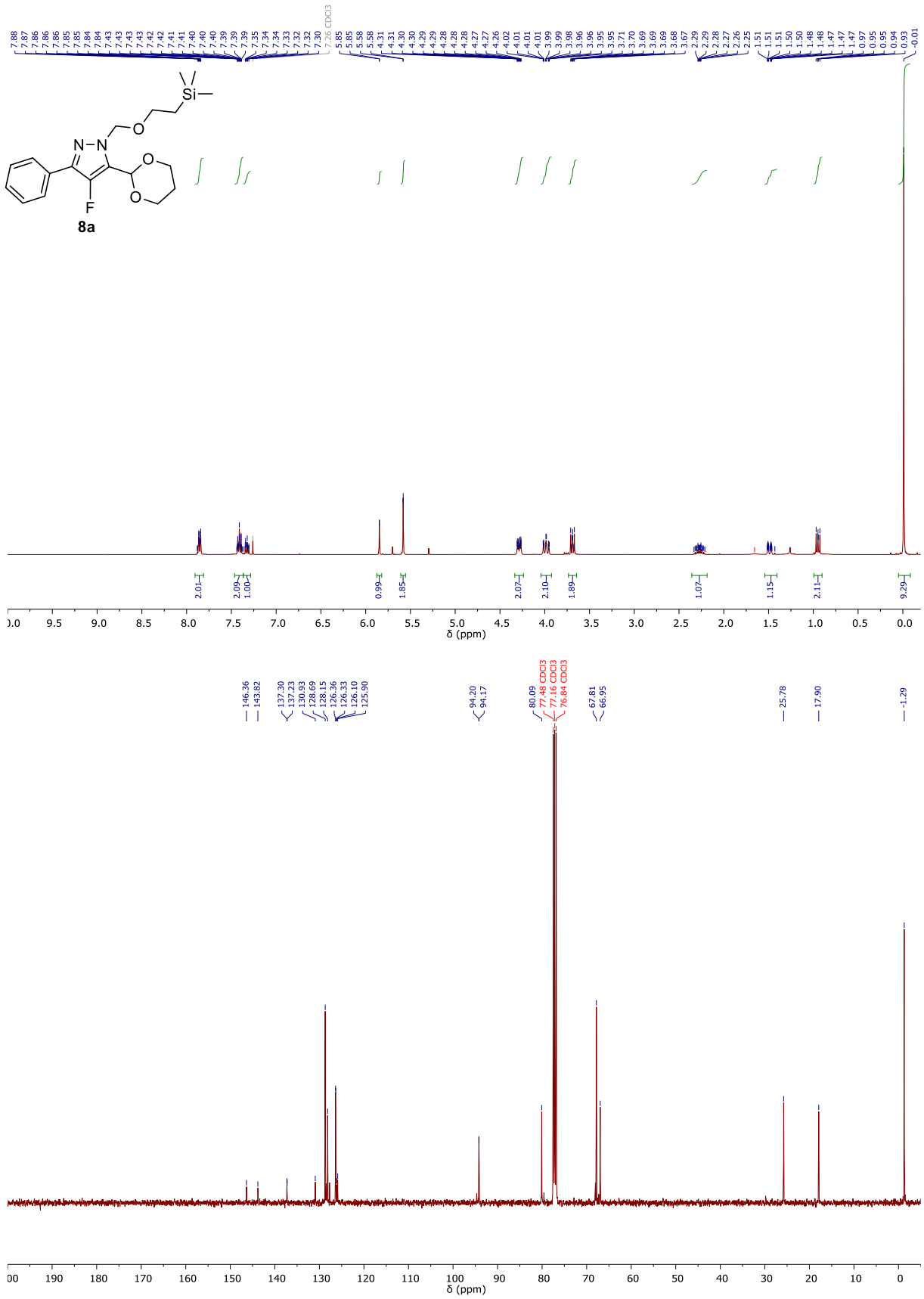
δ (ppm)


Si
O
N–N
O
O
F
8a
δ (ppm)
δ (ppm)


-170.71
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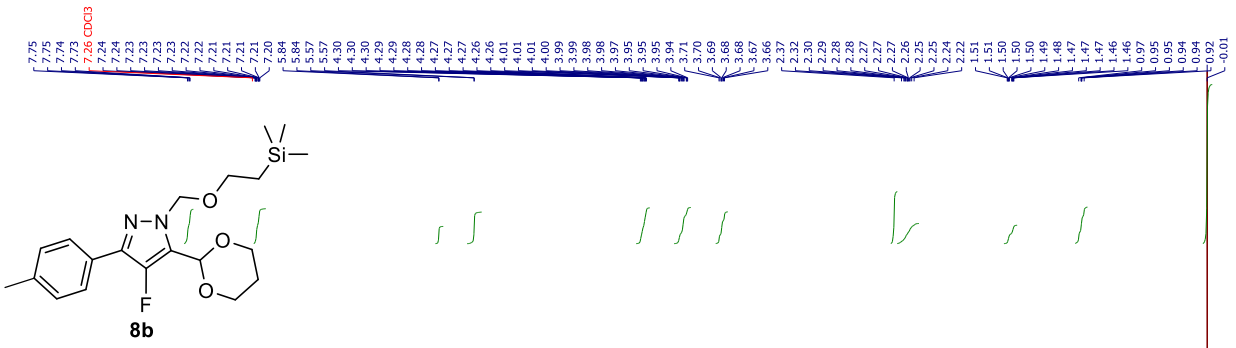
-170
-180
δ (ppm)



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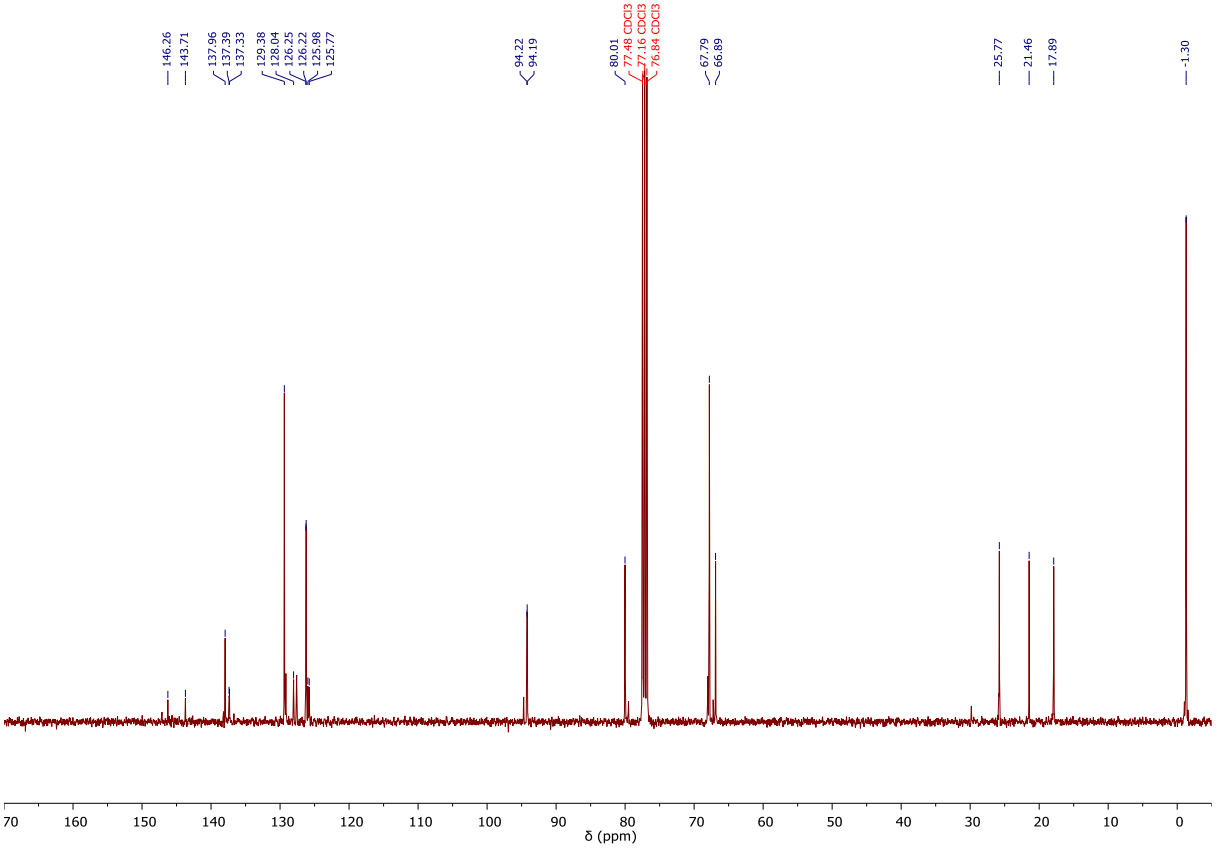


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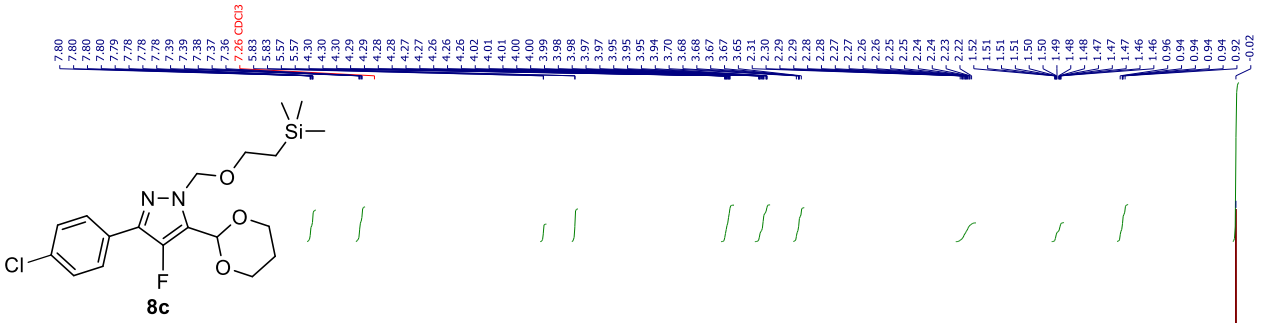
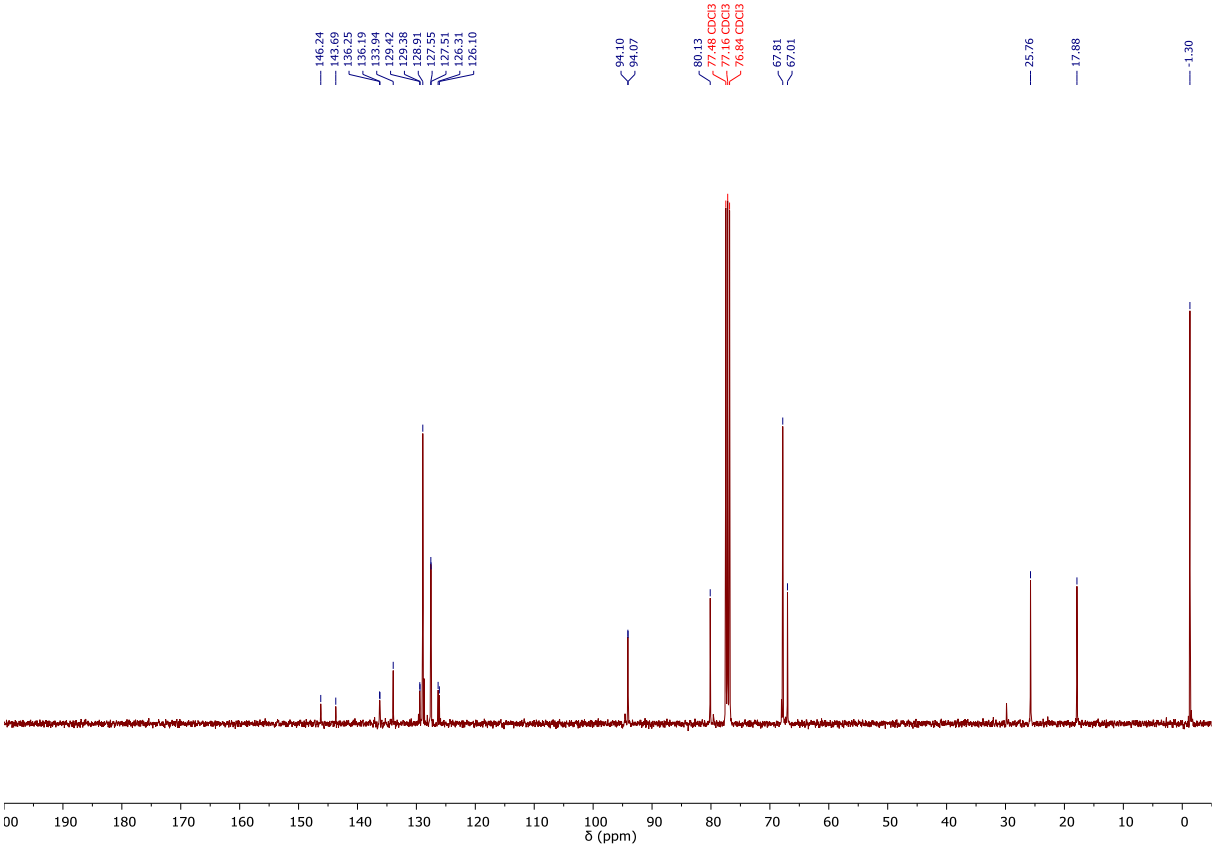
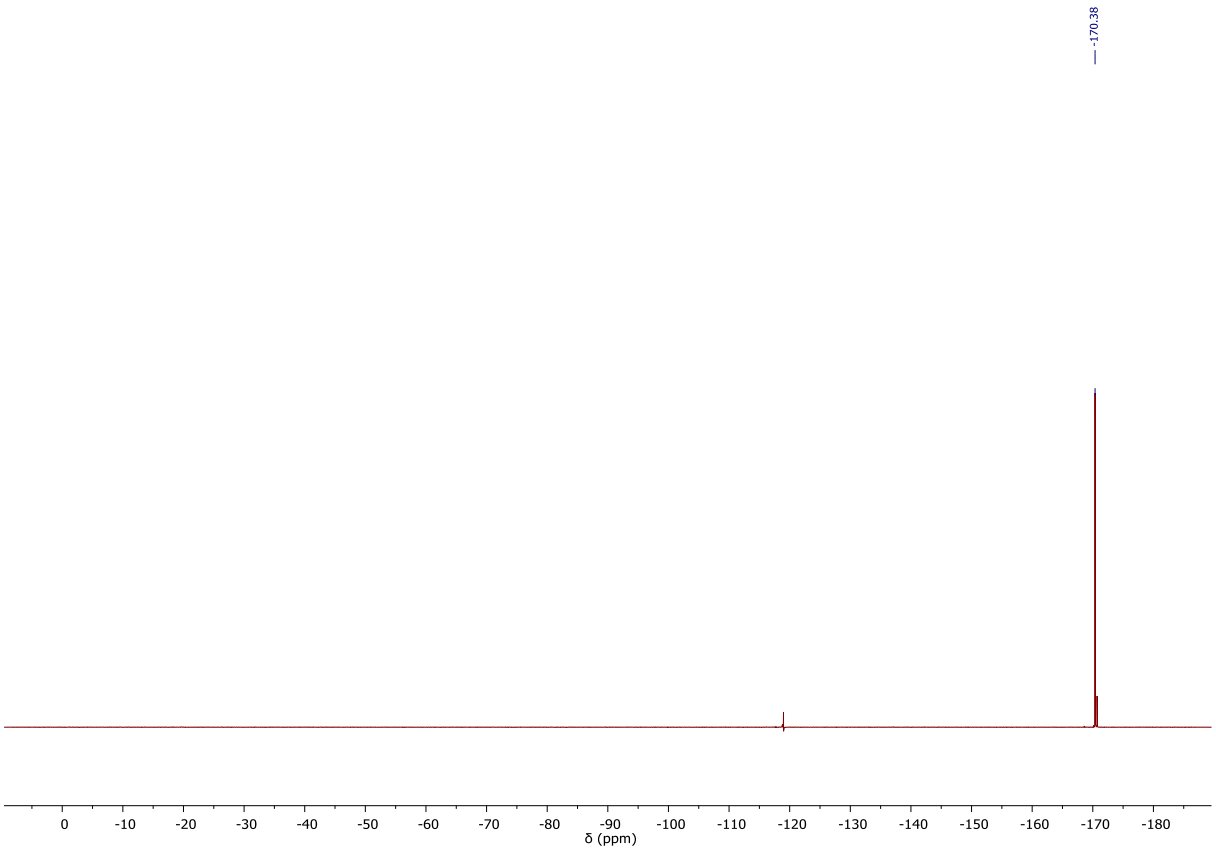
-170
-180
δ (ppm)

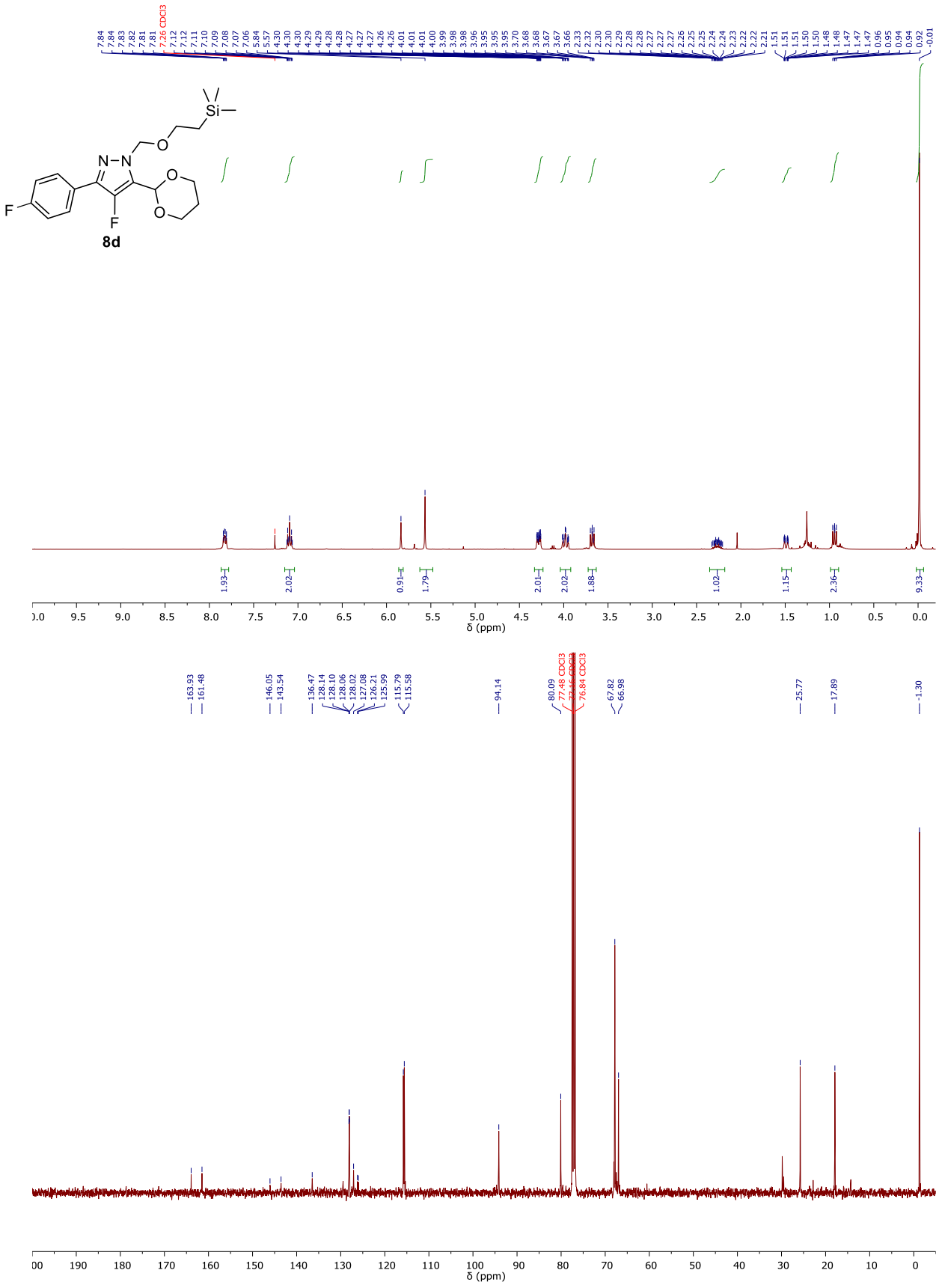

Si
O
N–N
O
O
Cl
F

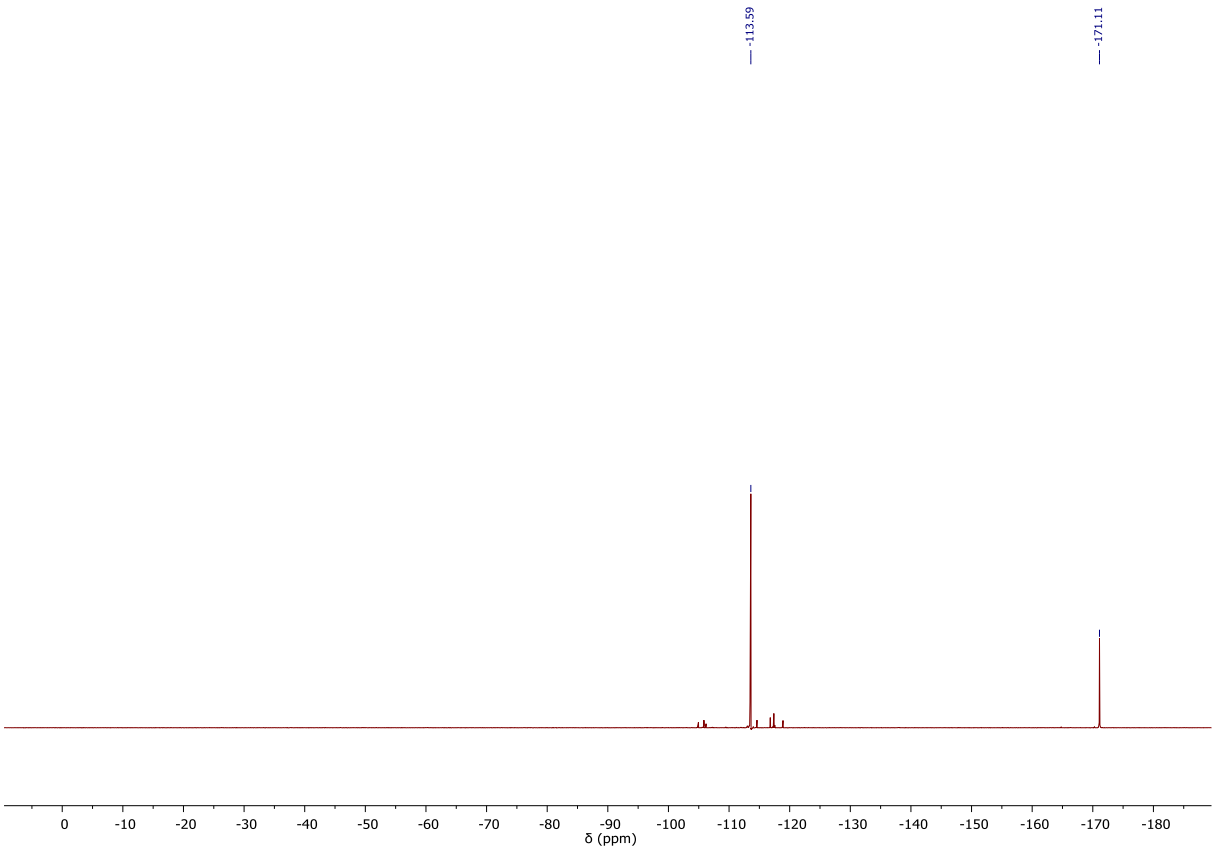
8c

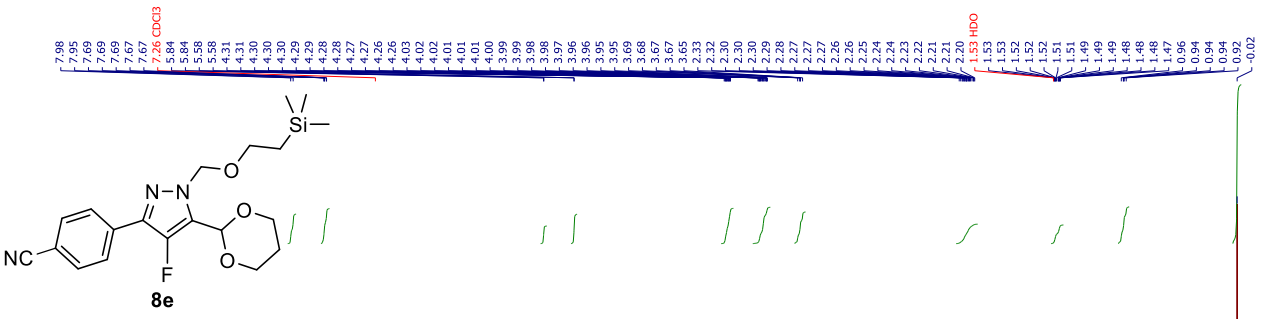
7.80 7.80 7.80 7.80 7.79 7.78 7.78 7.78 7.39 7.39 7.38 7.37 7.36 7.26 CDCl3 5.83 5.57 4.30 4.30 4.29 4.29 4.28 4.28 4.27 4.27 4.26 4.26 4.26 4.02 4.01 4.01 4.00 4.00 3.99 3.98 3.98 3.97 3.97 3.95 3.95 3.95 3.94 3.70 3.68 3.68 3.67 3.67 3.65 2.31 2.30 2.29 2.29 2.28 2.28 2.27 2.27 2.26 2.26 2.25 2.25 2.24 2.24 2.23 2.22 1.52 1.51 1.51 1.51 1.50 1.50 1.49 1.48 1.48 1.47 1.47 1.47 1.46 1.46 0.96 0.94 0.94 0.94 0.92 -0.02
1.80 1.98 1.00 1.86 2.07 2.09 1.93 1.06 1.08 2.12 9.02
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
δ (ppm)


146.24 143.69 136.25 136.19 133.94 129.42 129.38 128.91 127.55 126.31 126.10
94.10 94.07
80.13 77.48 CDCl3 77.16 CDCl3 76.84 CDCl3
67.81 67.01
25.76
17.88
-1.30
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)

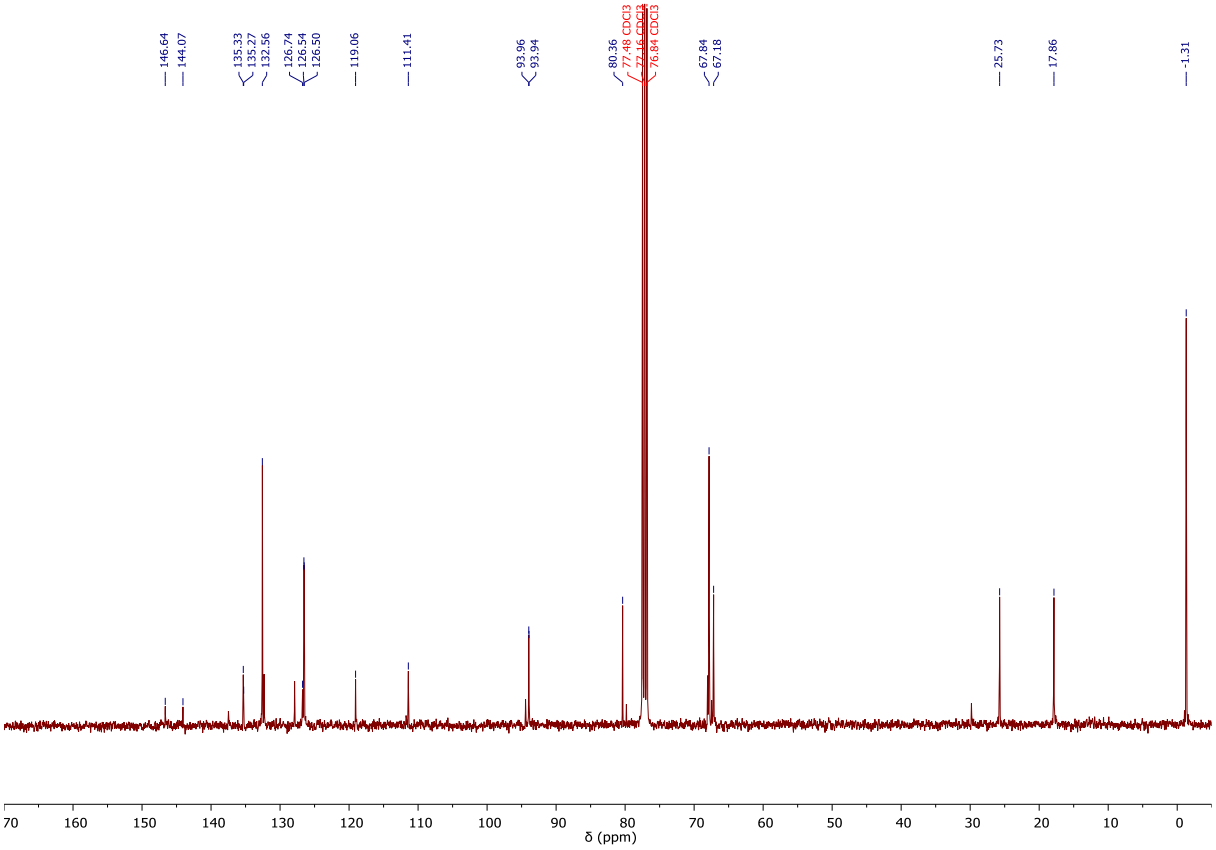

-170.38
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)

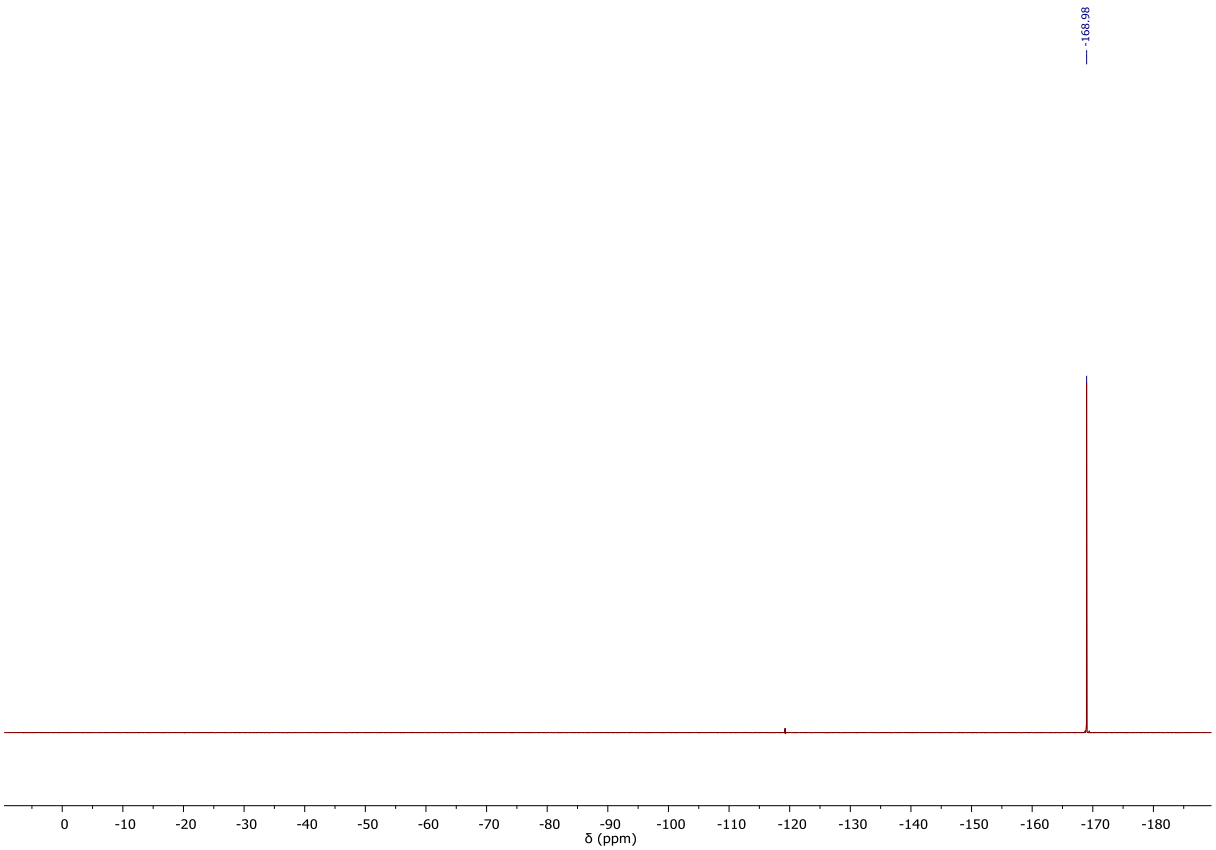

7.84
7.84
7.83
7.82
7.81
7.81
7.26 CDCl3
7.12
7.12
7.11
7.10
7.09
7.08
7.07
7.06
5.84
5.57
4.30
4.30
4.29
4.29
4.28
4.28
4.27
4.27
4.27
4.26
4.26
4.01
4.01
4.01
4.00
3.99
3.98
3.98
3.96
3.95
3.95
3.95
3.70
3.68
3.68
3.67
3.67
3.66
2.33
2.32
2.30
2.30
2.29
2.28
2.28
2.27
2.27
2.26
2.25
2.25
2.24
2.24
2.23
2.22
2.22
2.21
1.51
1.51
1.51
1.50
1.50
1.48
1.47
1.47
1.47
0.96
0.95
0.94
0.94
0.92
-0.01
Si
O
N–N
O
O
F
F
8d
1.93
2.02
0.91
1.79
2.01
2.02
1.88
1.02
1.15
2.36
9.33
δ (ppm)
163.93
161.48
146.05
143.54
136.47
128.14
128.10
128.06
128.02
127.08
126.21
125.99
115.79
115.58
94.14
80.09
77.46 CDCl3
76.84 CDCl3
67.82
66.98
25.77
17.89
-1.30
δ (ppm)

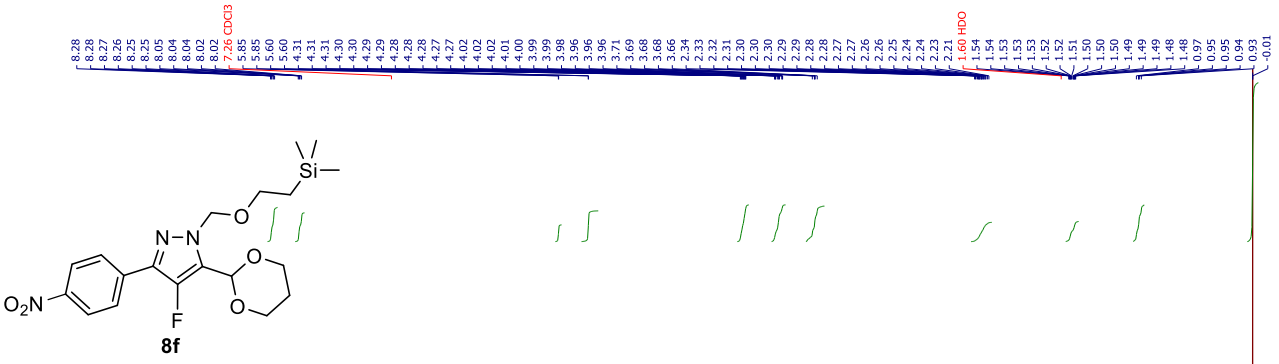

-113.59
-171.11
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)


NC
F
N–N
O
O
O
Si
8e

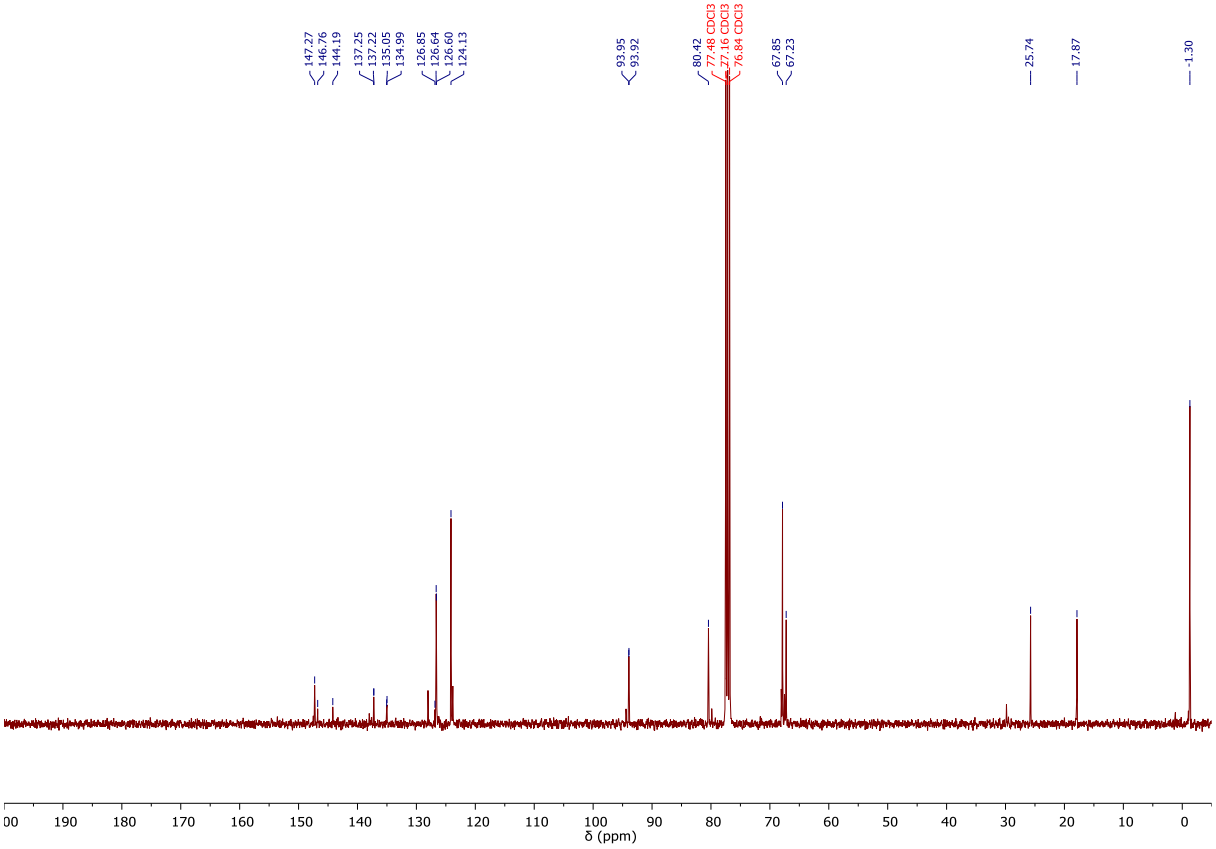
δ (ppm)

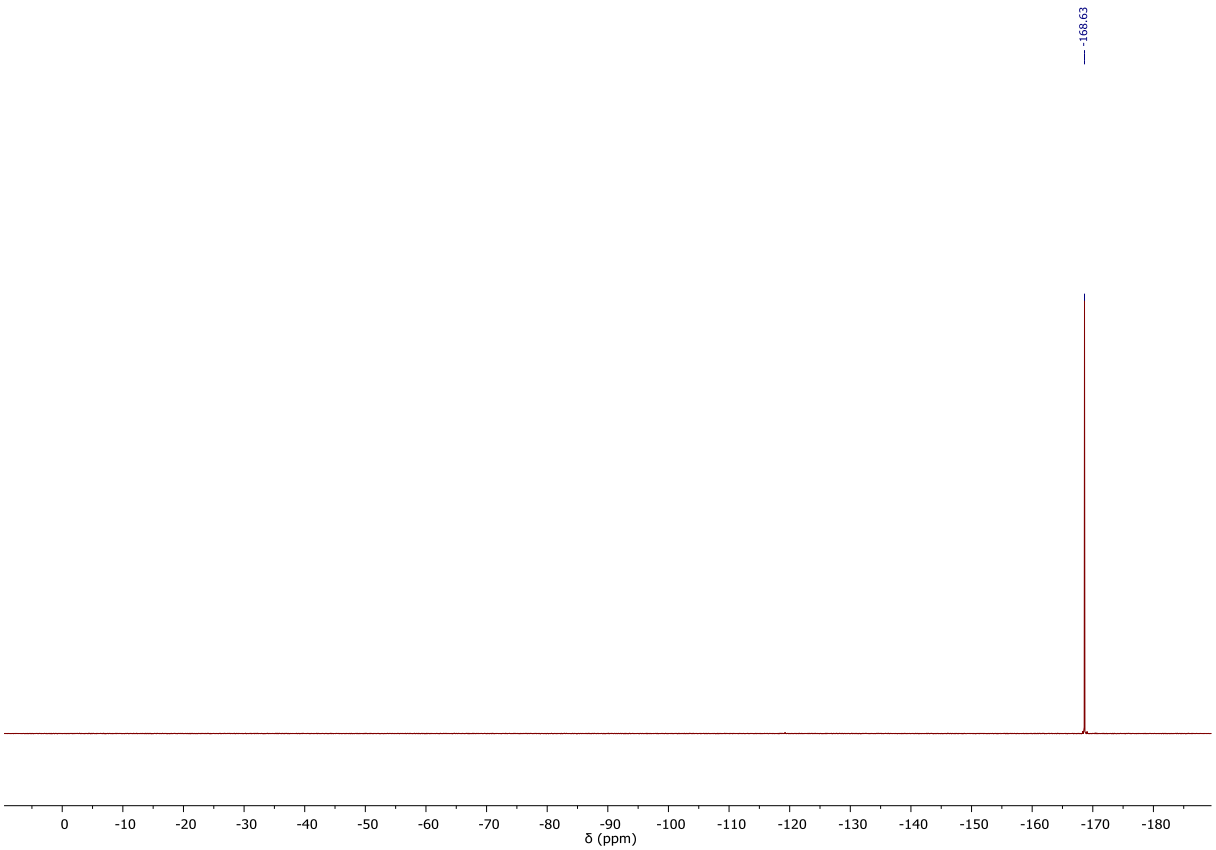

δ (ppm)


-168.98
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)

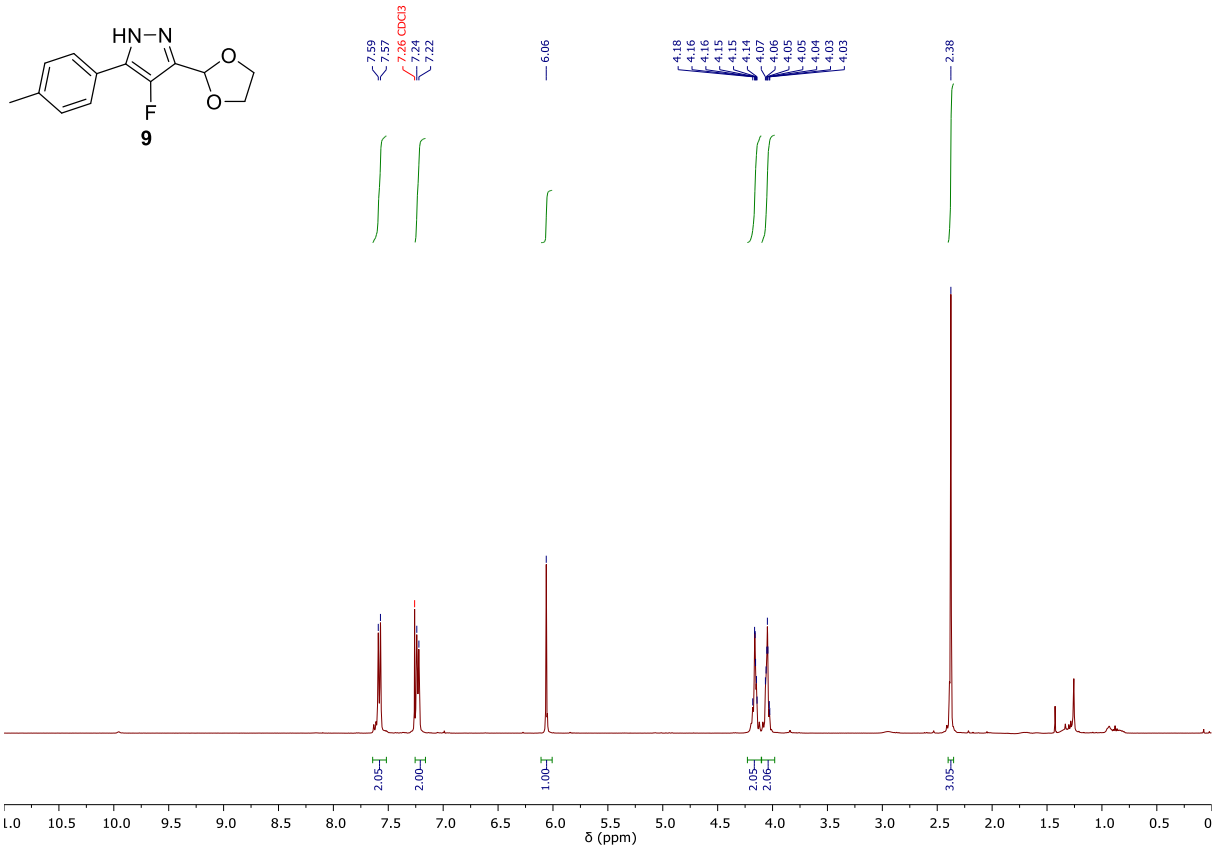


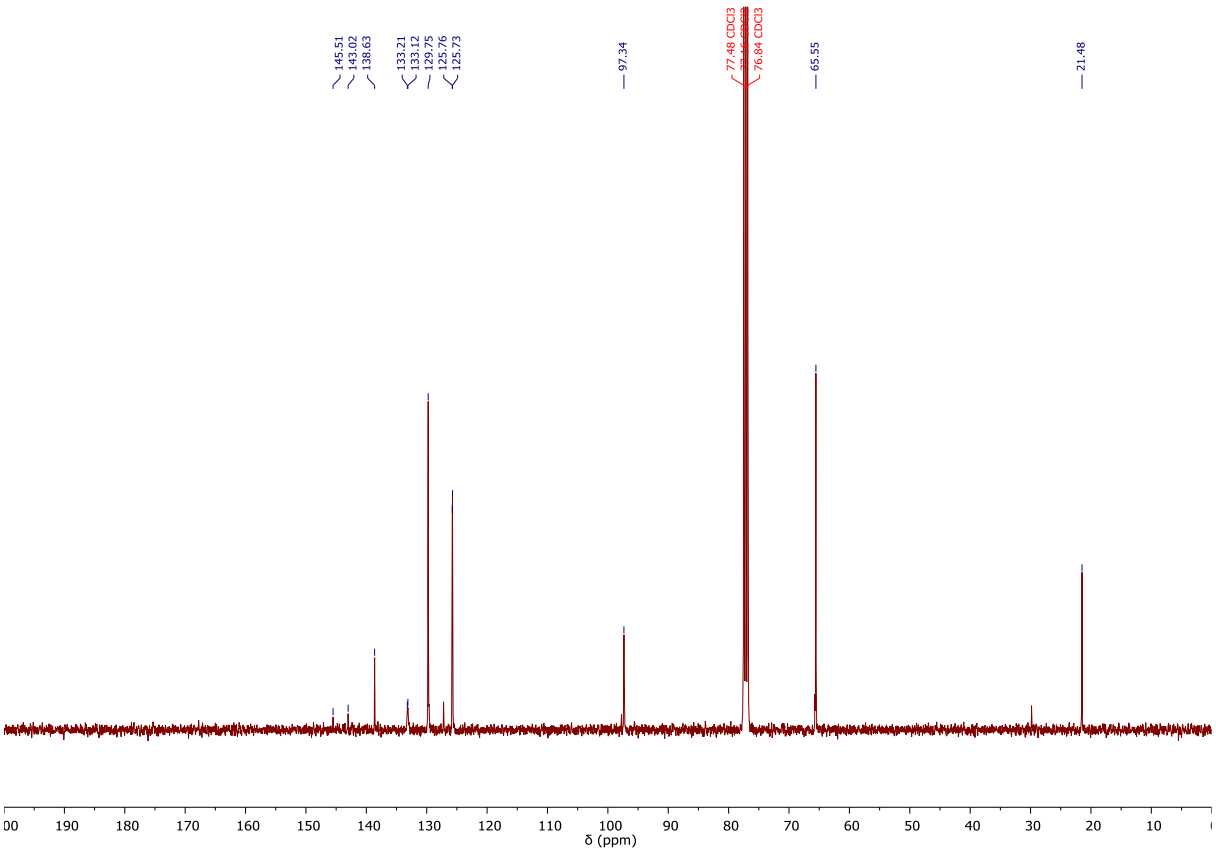
8f

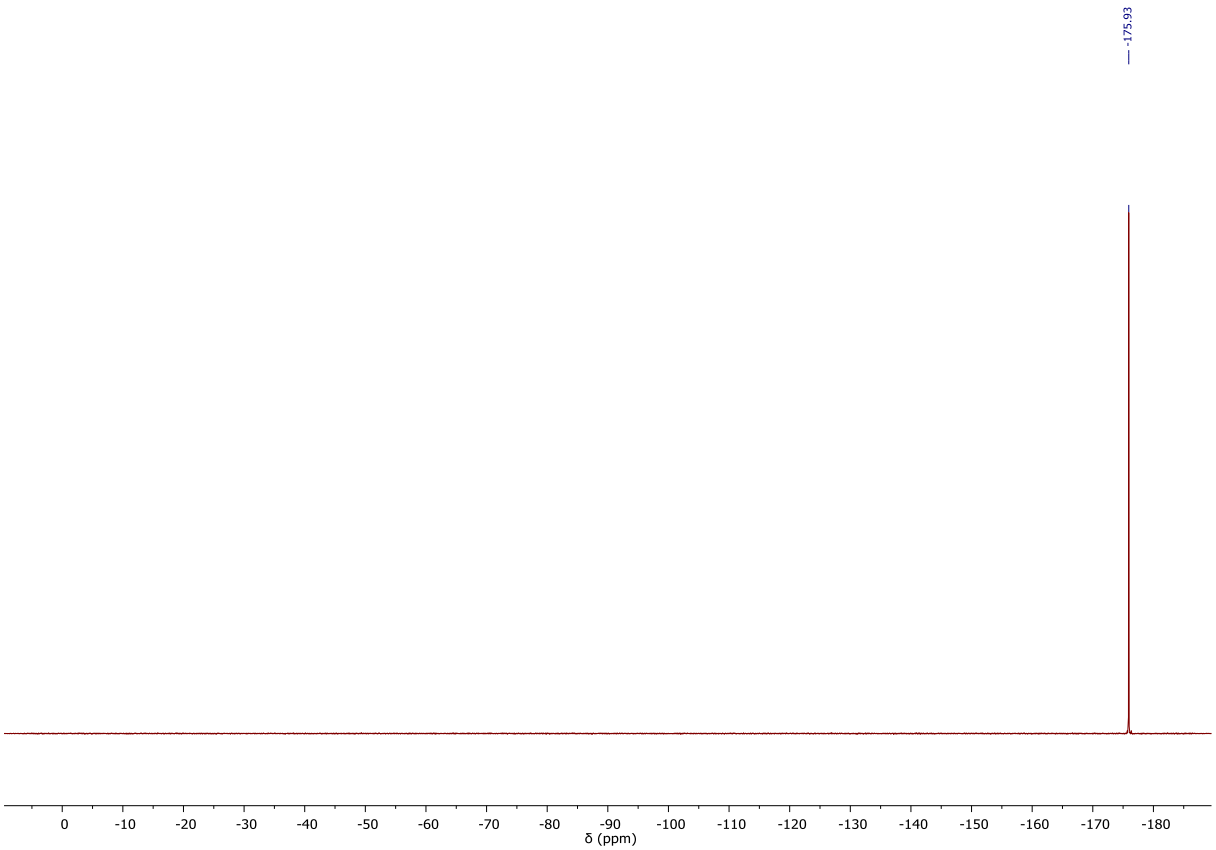


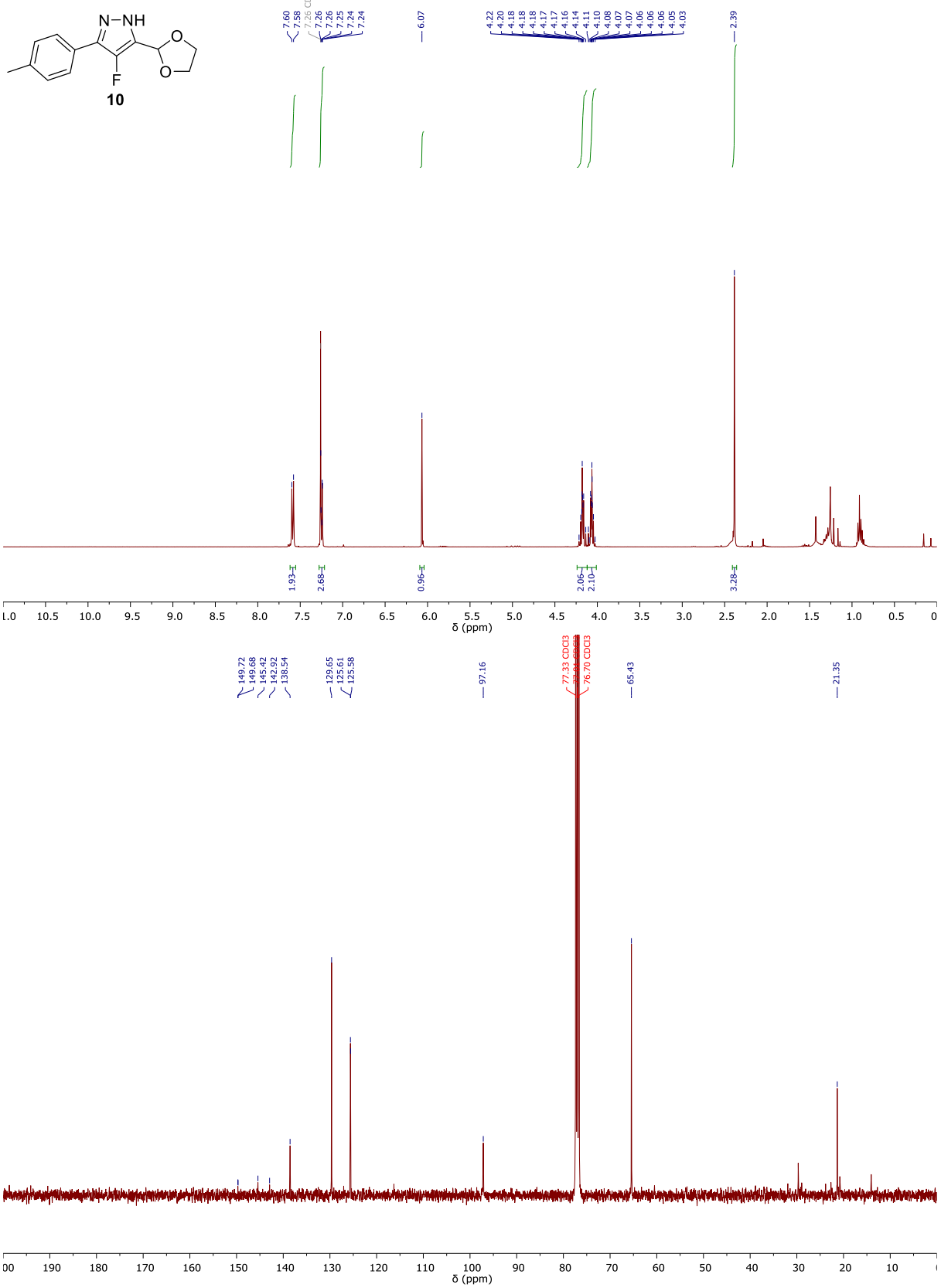

-168.63
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)

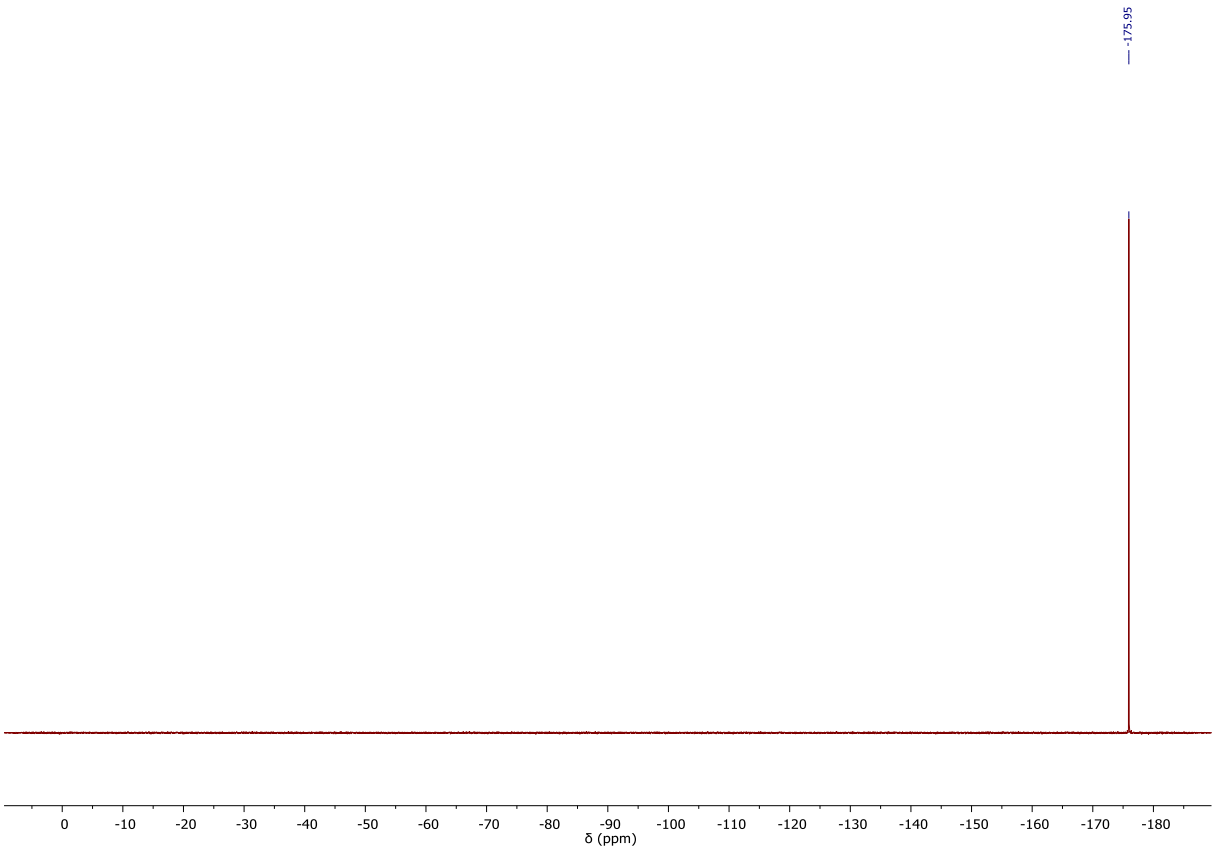
3. Selective deprotection of the SEM-group – NMR spectra



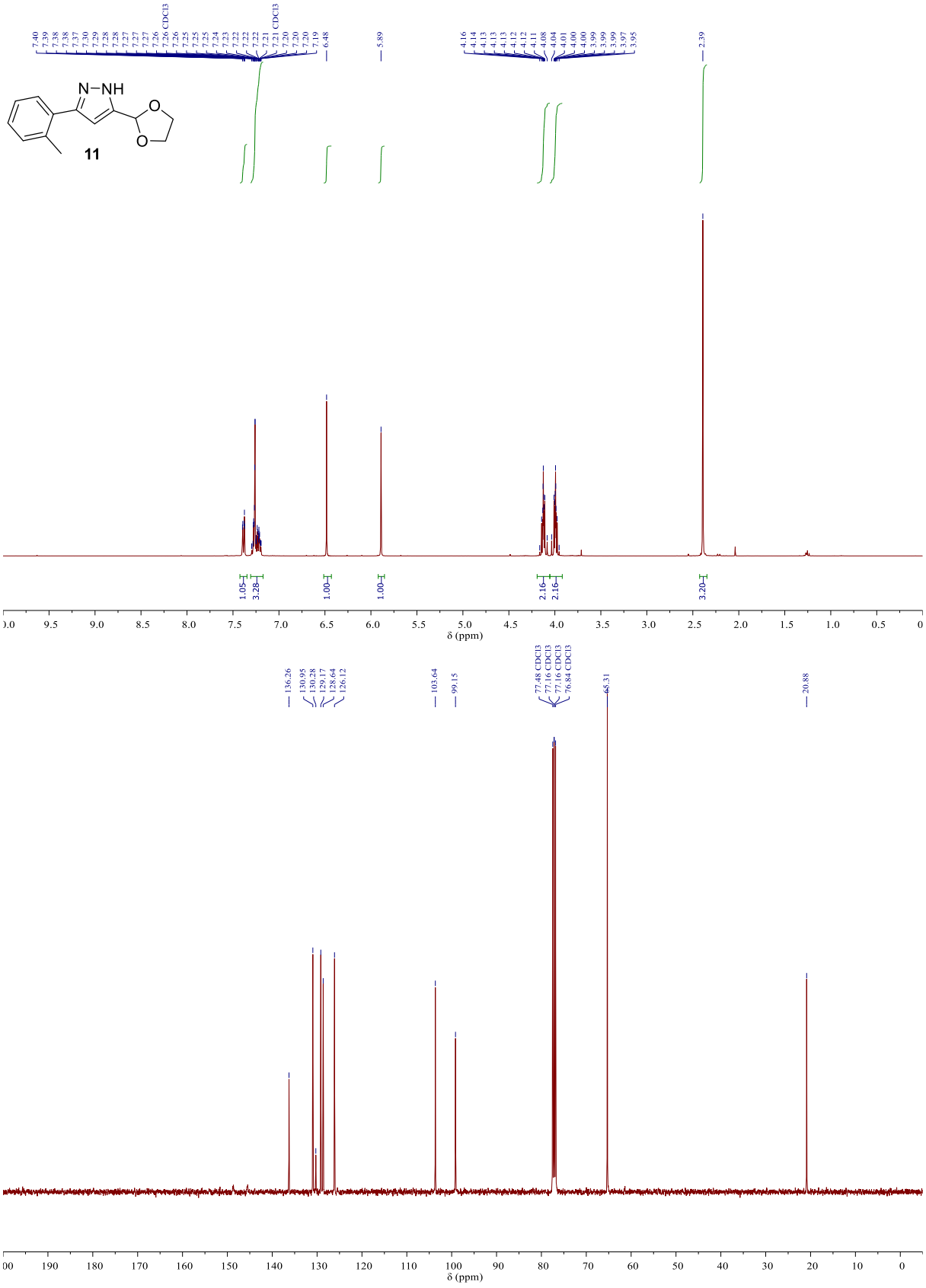


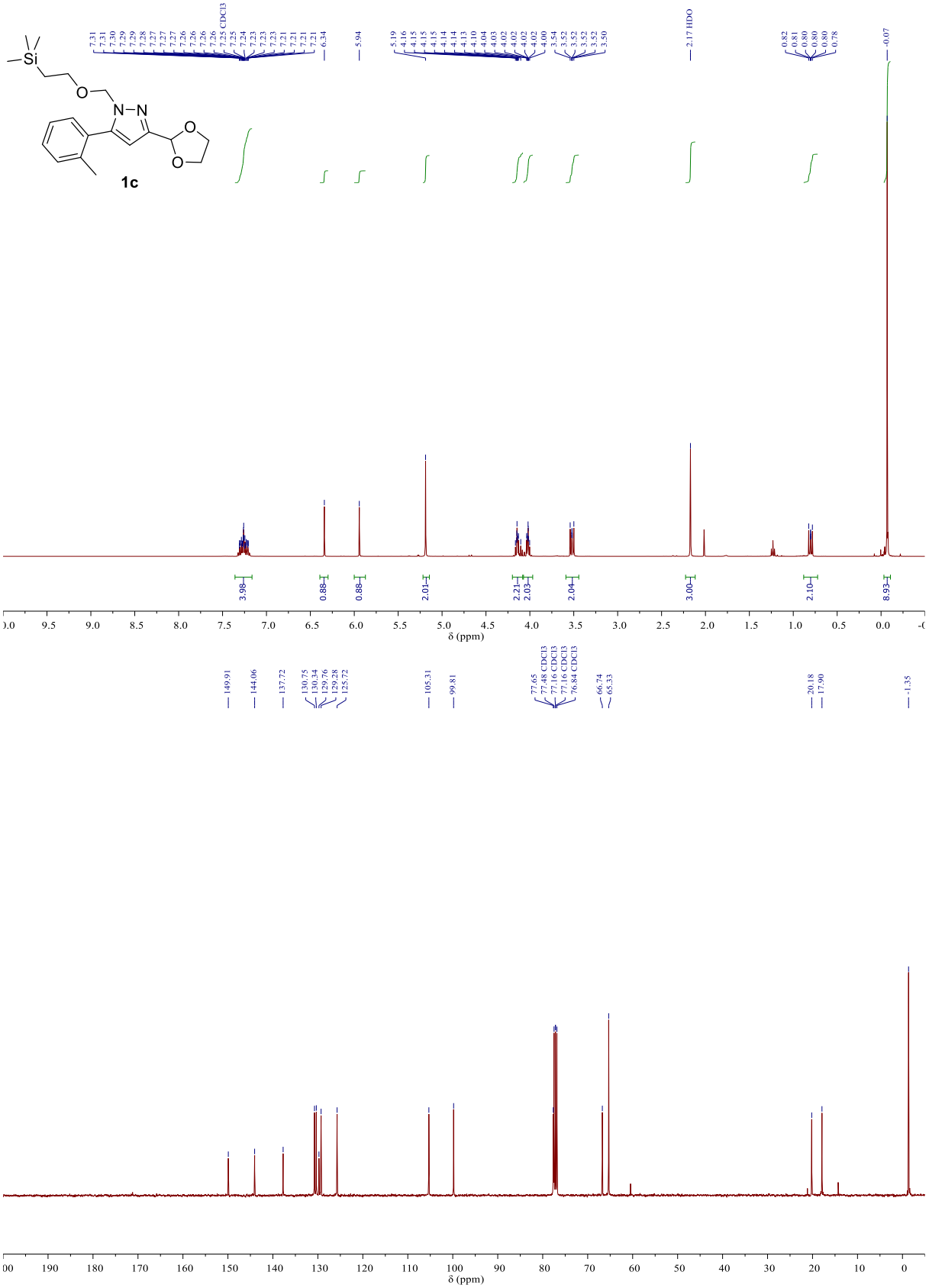

-175.93
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)

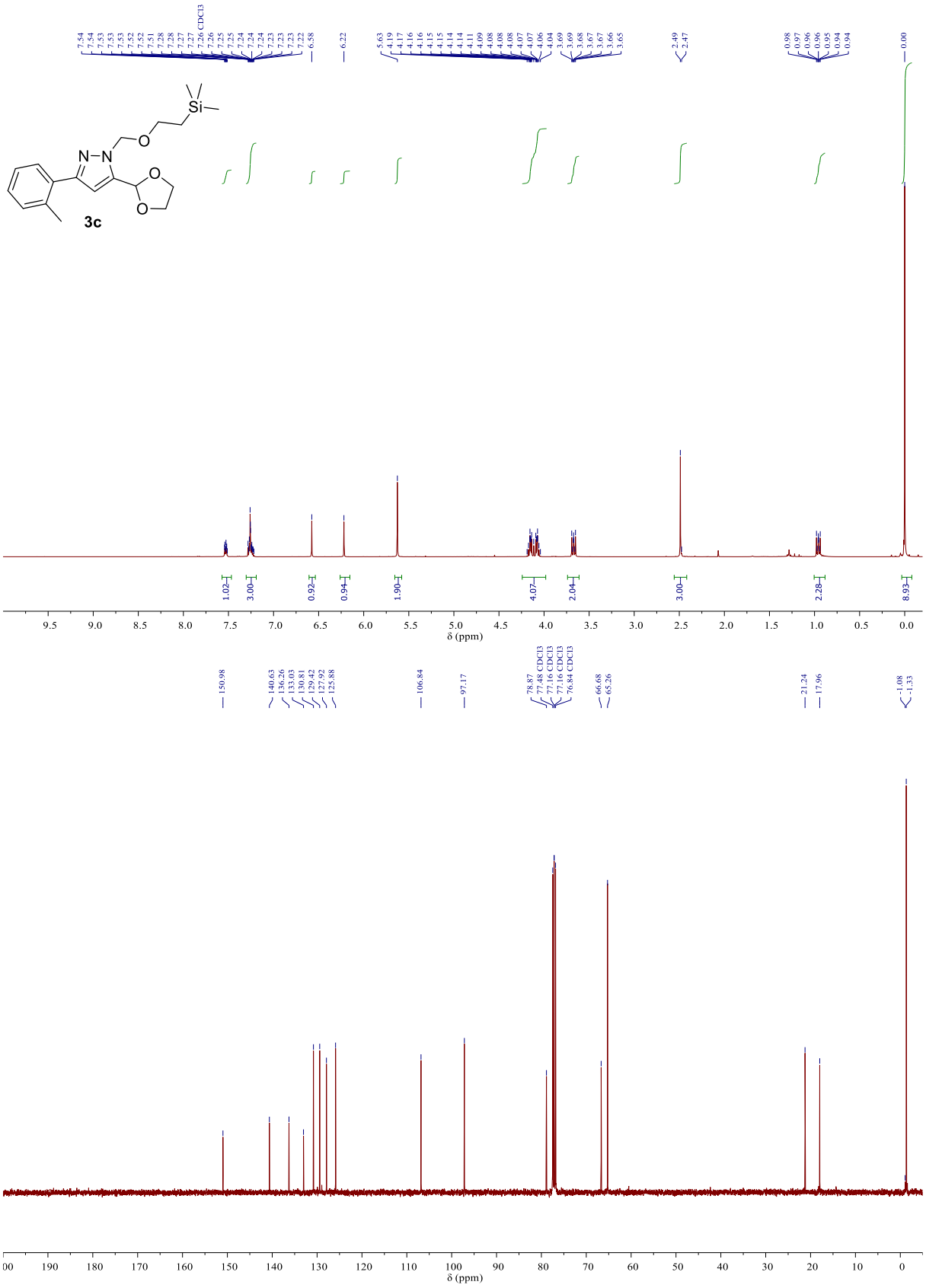

N–NH
O
O
F
10
7.60
7.58
7.26 CDCl3
7.26
7.26
7.25
7.24
7.24
6.07
4.22
4.20
4.18
4.18
4.18
4.17
4.17
4.16
4.14
4.11
4.10
4.08
4.07
4.07
4.06
4.06
4.06
4.05
4.03
2.39
1.93
2.68
0.96
2.06
2.10
3.28
δ (ppm)
149.72
149.68
145.42
142.92
138.54
129.65
125.61
125.58
97.16
77.33 CDCl3
76.70 CDCl3
65.43
21.35
δ (ppm)

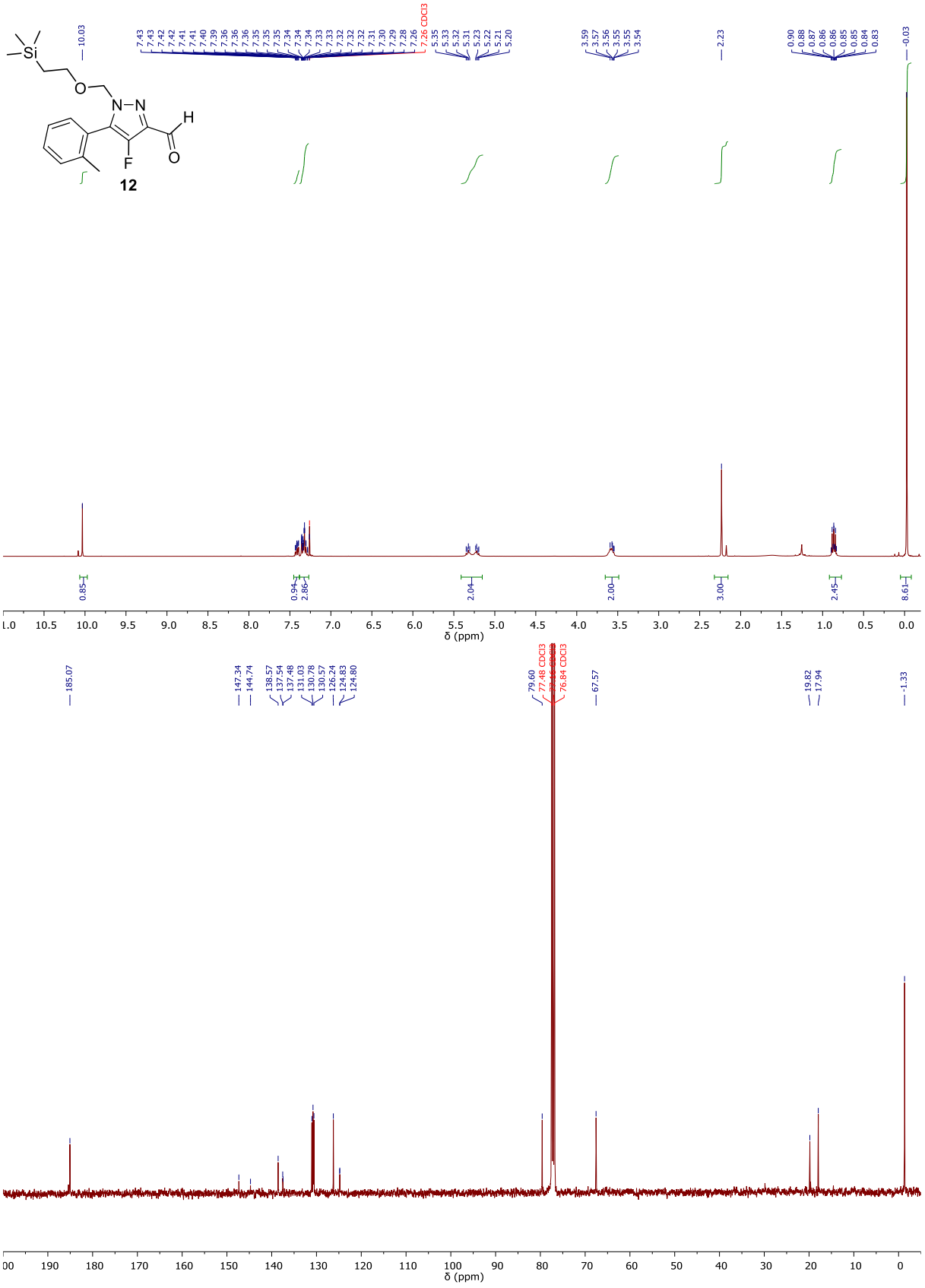

-175.95
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)

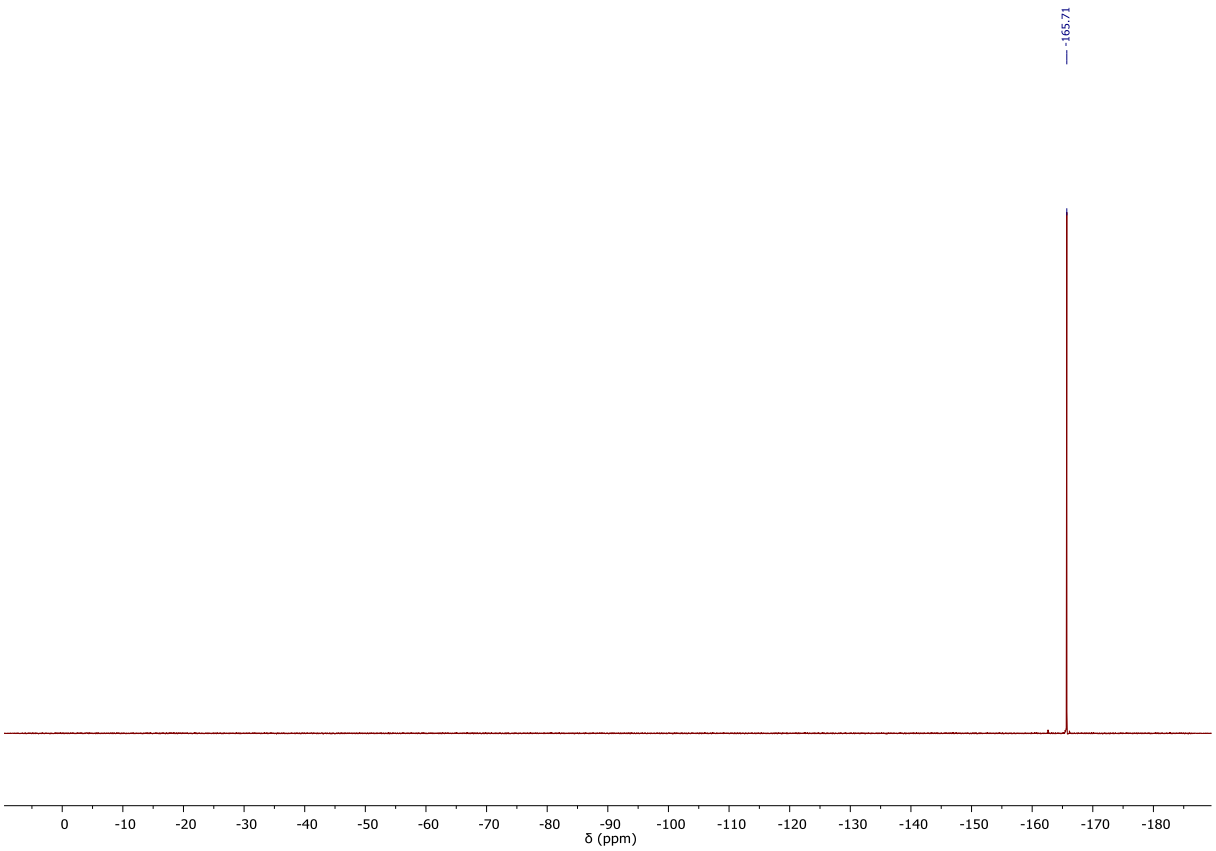
4. Formal synthesis of neprilysin inhibitor key intermediate – NMR spectra

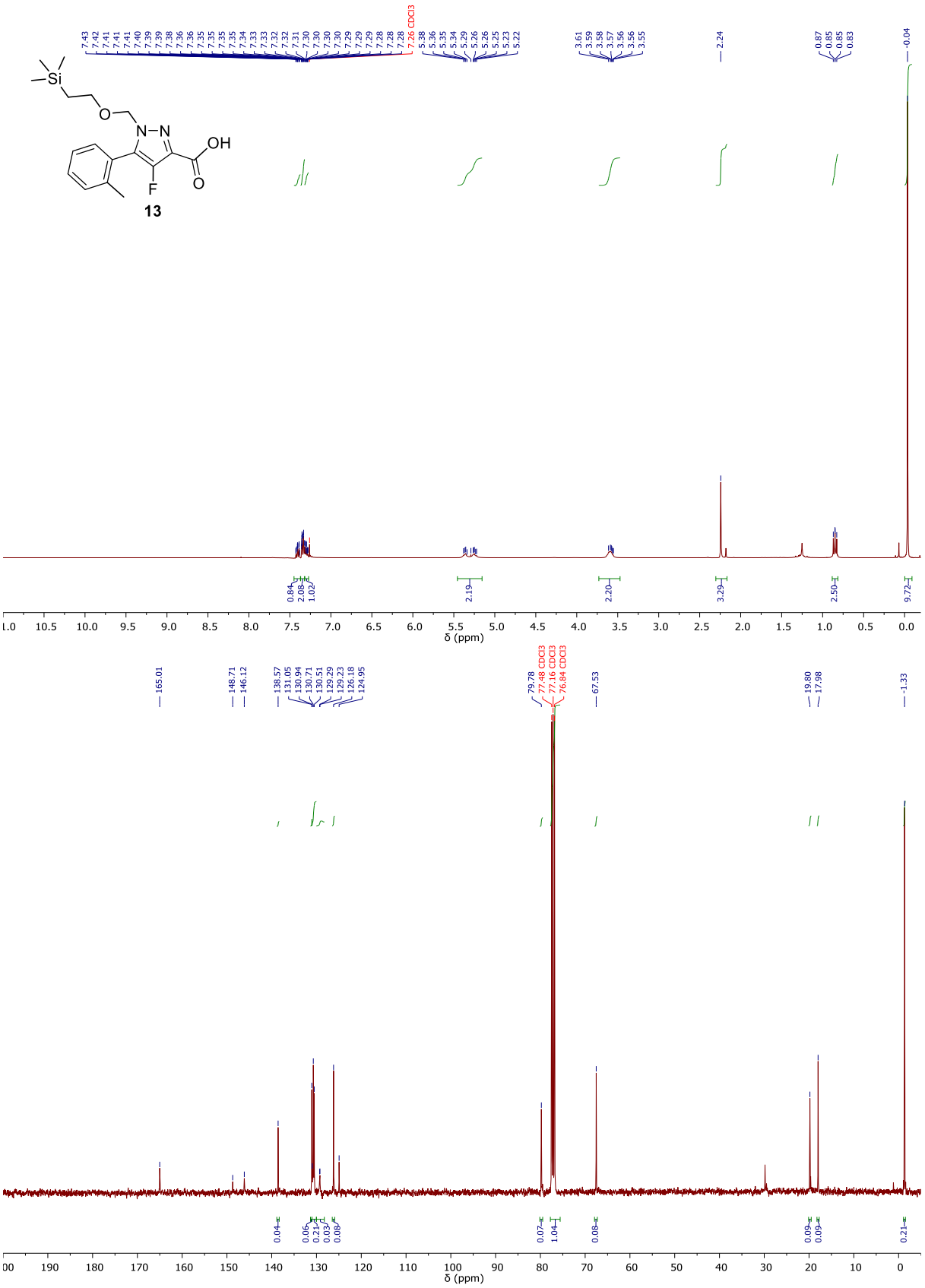


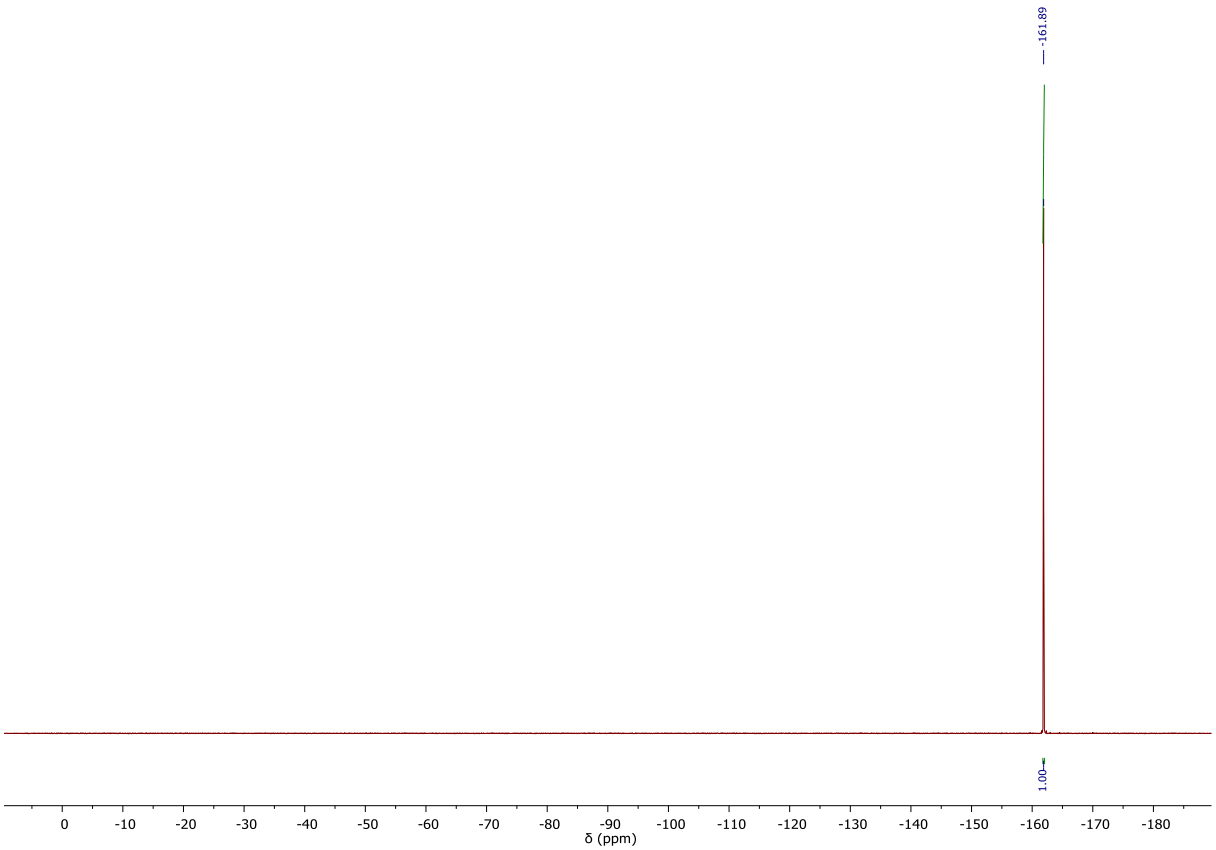

1c
δ (ppm)
δ (ppm)


7.54 7.54 7.53 7.53 7.53 7.52 7.52 7.51 7.28 7.28 7.27 7.27 7.26 CDCl3 7.26 7.25 7.25 7.24 7.24 7.24 7.23 7.23 7.23 7.22 6.58 6.22 5.63 4.19 4.17 4.16 4.16 4.15 4.15 4.14 4.14 4.11 4.09 4.08 4.08 4.08 4.07 4.07 4.06 4.04 3.69 3.69 3.68 3.67 3.67 3.66 3.65 2.49 2.47 0.98 0.97 0.96 0.96 0.95 0.94 0.94 0.00
Si
N–N
O
O
O
3c
1.02 3.00 0.92 0.94 1.90 4.07 2.04 3.00 2.28 8.93
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
δ (ppm)
150.98 140.63 136.26 133.03 130.81 129.42 127.92 125.88 106.84 97.17 78.87 77.48 CDCl3 77.16 CDCl3 77.16 CDCl3 76.84 CDCl3 66.68 65.26 21.24 17.96 -1.08 -1.33
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
δ (ppm)


Si
O
N–N
H
O
F
12
δ (ppm)
δ (ppm)


-165.71
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)


13
δ (ppm)
δ (ppm)


-161.89
1.00
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
δ (ppm)