Electronic Supplementary Information

5-(Thiophen-2-yl)isoxazoles as novel anti-breast cancer agents targeting ER$_\alpha$: Synthesis, *in vitro* biological evaluation, *in silico* studies, and molecular dynamics simulation

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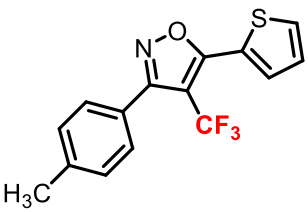
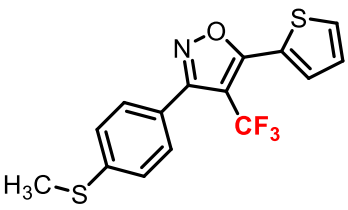
1. Analytical data for all the newly synthesized target molecules (TTI-1 to TTI-3 and TTI-5 to TTI-15).

5-(Thiophen-2-yl)-3-(*p*-tolyl)-4-(trifluoromethyl)isoxazole (TTI-1)



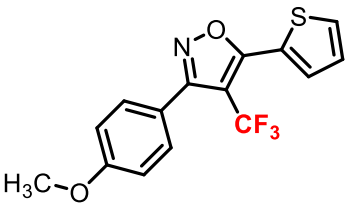
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 – 7.69 (m, 1H), 7.65 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.35 – 7.28 (m, 2H), 7.21 (dd, *J* = 5.1, 3.8 Hz, 1H), 2.44 (s, 3H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.16.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.33, 161.83, 140.48, 131.00, 130.97, 130.91, 129.28, 128.72, 128.11, 126.28, 125.71, 124.40, 123.05, 120.39, 117.72, 105.43, 105.05, 104.67, 104.29, 21.39. HRMS (ESI), m/z calcd for $C_{15}H_{11}F_3NOS$ $[M + H]^+$: 310.0513; found: 310.0530.

3-(4-(Methylthio)phenyl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-2)



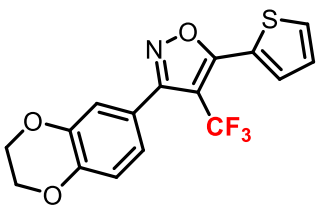
White solid; eluent, 5% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 3.5 Hz, 1H), 7.65 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.22 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.53 (s, 3H)..**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.16.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.49, 161.39, 141.93, 131.02, 129.12, 128.15, 126.20, 125.77, 123.55, 123.02, 120.35, 104.97, 77.00, 15.14. HRMS (ESI), m/z calcd for $C_{15}H_{11}F_3NOS_2$ $[M + H]^+$: 342.0234; found: 342.0240.

3-(4-Methoxyphenyl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-3)



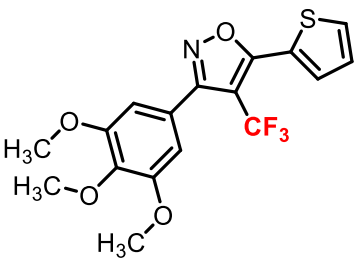
White solid; eluent, 2% EtOAc/hexane**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, J = 3.7 Hz, 1H), 7.64 (dd, J = 5.0, 1.0 Hz, 1H), 7.59 (d, J = 8.7 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.05 – 6.98 (m, 2H), 3.86 (s, 3H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.19.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.29, 161.49, 161.19, 130.97, 130.95, 130.87, 130.24, 128.08, 126.28, 125.74, 123.08, 120.42, 119.49, 117.75, 114.04, 104.92, 104.54, 77.00, 55.27. HRMS (ESI), m/z calcd for $C_{15}H_{11}F_3NO_2S$ $[M + H]^+$: 326.0463; found: 326.0410.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-5)



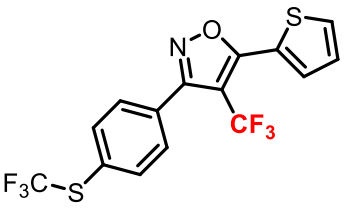
White solid; eluent, 5% EtOAc/hexane, **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (d, J = 3.8 Hz, 1H), 7.63 (dd, J = 5.1, 1.1 Hz, 1H), 7.22 – 7.15 (m, 2H), 7.13 – 7.10 (m, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.32 – 4.27 (m, 4H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.18. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.32, 161.29, 145.47, 143.51, 131.02, 130.99, 130.91, 128.09, 126.28, 125.68, 123.01, 122.20, 120.35, 120.28, 118.01, 117.52, 104.95, 104.57, 77.00, 64.45, 64.23. HRMS (ESI), m/z calcd for $C_{16}H_{11}F_3NO_3S$ $[M + H]^+$: 354.0412; found: 354.0452.

5-(Thiophen-2-yl)-4-(trifluoromethyl)-3-(3,4,5-trimethoxyphenyl)isoxazole (TTI-6)



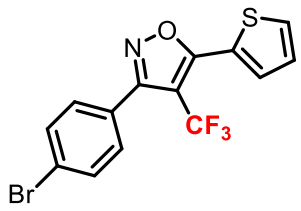
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.70 (d, J = 3.8 Hz, 1H), 7.66 (dd, J = 5.1, 1.1 Hz, 1H), 7.22 (dd, J = 5.0, 3.8 Hz, 1H), 6.86 (s, 2H), 3.91 (s, 3H), 3.90 (s, 6H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.05.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.54, 161.74, 153.32, 139.79, 131.19, 131.13, 128.20, 126.15, 123.04, 122.46, 120.37, 106.19, 105.02, 60.97, 56.21. HRMS (ESI), m/z calcd for $C_{17}H_{15}F_3NO_4S$ $[M + H]^+$: 386.0674; found: 386.0690.

5-(Thiophen-2-yl)-4-(trifluoromethyl)-3-(4-((trifluoromethyl)thio)phenyl)isoxazole (TTI-7)



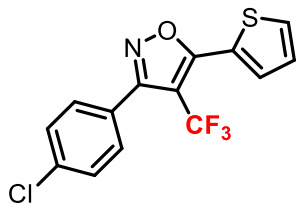
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.79 (d, J = 8.2 Hz, 2H), 7.73 (d, J = 3.8 Hz, 1H), 7.73 – 7.63 (m, 3H), 7.23 (dd, J = 5.0, 3.8 Hz, 1H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -42.10, -54.11. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.90, 160.75, 150.18, 136.09, 131.37, 130.90, 129.91, 128.28, 127.84, 127.11, 125.88, 122.88, 120.21, 104.59, 77.00. HRMS (ESI), m/z calcd for $C_{15}H_8F_6NOS_2$ $[M + H]^+$: 395.9951; found: 395.9898.

3-(4-Bromophenyl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-8)



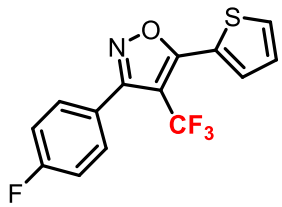
White solid; eluent, 4% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$** δ 7.73 – 7.70 (m, 1H), 7.67 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.22 (dd, *J* = 5.1, 3.8 Hz, 1H)..**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.13. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.76, 160.98, 132.91, 131.93, 131.26, 130.45, 128.26, 126.33, 126.01, 125.61, 125.56, 125.03, 122.95, 120.28, 104.96, 104.57. HRMS (ESI), m/z calcd for $C_{14}H_8BrF_3NOS$ $[M + H]^+$: 373.9462; found: 373.9400.

3-(4-Chlorophenyl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-9)



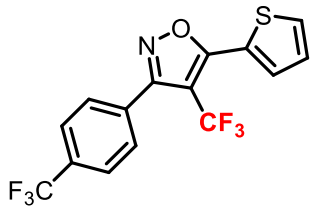
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.74 – 7.70 (m, 1H), 7.67 (d, J = 5.1 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.7 Hz, 2H), 7.22 (dd, J = 5.1, 3.8 Hz, 1H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.15.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.74, 160.92, 136.73, 131.25, 130.24, 128.97, 128.25, 126.04, 125.86, 125.63, 122.97, 120.30, 117.64, 105.69, 105.37, 104.98, 104.60, 104.22. HRMS (ESI), m/z calcd for $C_{14}H_8ClF_3NOS$ $[M + H]^+$: 329.9967; found: 329.9967.

3-(4-Fluorophenyl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-10)



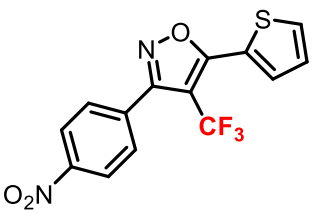
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.72 (d, J = 3.8 Hz, 1H), 7.67 (dd, J = 5.1, 1.1 Hz, 1H), 7.62 (dd, J = 8.5, 5.3 Hz, 2H), 7.23 – 7.16 (m, 3H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.20, -109.99. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.61, 165.29, 162.80, 160.99, 131.15, 130.98, 130.89, 128.20, 126.08, 123.45, 122.97, 120.30, 115.95, 115.73, 77.00. HRMS (ESI), m/z calcd for $C_{14}H_8F_4NOS$ $[M + H]^+$: 314.0263; found: 314.0240.

5-(Thiophen-2-yl)-4-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)isoxazole (TTI-11)



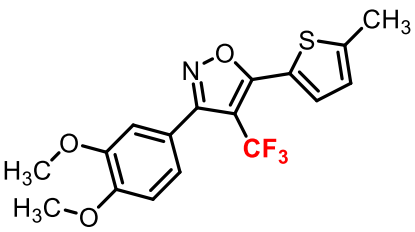
White solid; eluent, 2% EtOAc/hexane**. ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.76 (s, 4H), 7.74 (d, J = 3.7 Hz, 1H), 7.69 (dd, J = 5.0, 0.6 Hz, 1H), 7.24 (dd, J = 4.9, 4.0 Hz, 1H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.11, -62.96. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.89, 160.75, 132.54, 132.22, 131.40, 131.01, 129.41, 128.30, 125.86, 125.62, 125.58, 125.10, 122.87, 122.39, 120.21, 104.64, 77.00. HRMS (ESI), m/z calcd for $C_{15}H_8F_6NOS$ $[M + H]^+$: 364.0231; found: 364.0260.

5-(Thiophen-2-yl)-4-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)isoxazole (TTI-12)



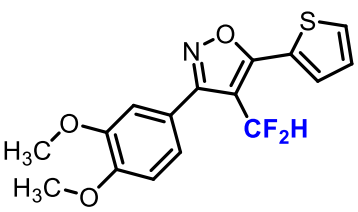
Pale yellow solid; eluent, 5% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.40 – 8.33 (m, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 3.8 Hz, 1H), 7.70 (dd, J = 5.1, 1.1 Hz, 1H), 7.26 – 7.23 (m, 1H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.05.**^{13}C NMR (101 MHz, $CDCl_3$)** δ 166.22, 160.13, 149.10, 133.69, 131.68, 131.56, 130.12, 128.41, 127.52, 125.63, 124.34, 123.81, 122.81, 120.14, 77.03. HRMS (ESI), m/z calcd for $C_{14}H_8F_3N_2O_3S$ $[M + H]^+$: 341.0208; found: 341.0222.

3-(3,4-Dimethoxyphenyl)-5-(5-methylthiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-13)



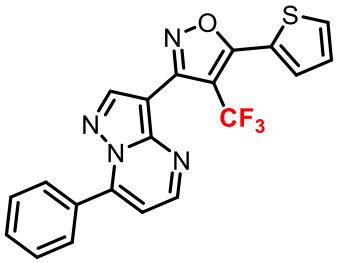
White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 3.7 Hz, 1H), 7.20 (d, *J* = 8.3 Hz, 1H), 7.15 (d, *J* = 1.8 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 6.86 (dd, *J* = 3.7, 1.0 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 2.57 (s, 3H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -54.10. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.53, 161.48, 150.67, 149.88, 148.85, 146.93, 146.56, 131.35, 126.89, 126.67, 123.72, 123.17, 121.83, 120.51, 119.77, 113.64, 111.72, 110.94, 109.15, 104.10, 103.72, 77.00, 55.91, 15.38. HRMS (ESI), m/z calcd for $C_{17}H_{15}F_3NO_3S$ $[M + H]^+$: 370.0725; found: 370.0760.

4-(Difluoromethyl)-3-(3,4-dimethoxyphenyl)-5-(thiophen-2-yl)isoxazole (TTI-14)



White solid; eluent, 2% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.69 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.64 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.30 (s, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 53.7 Hz, 1H), 3.95 (s, 3H), 3.95 (s, 3H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -108.17. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.18, 161.91, 150.83, 149.20, 130.44, 130.28, 128.26, 126.85, 121.68, 119.93, 112.64, 111.53, 111.18, 110.31, 107.99, 77.00, 55.97. HRMS (ESI), m/z calcd for $C_{16}H_{14}F_2NO_3S$ $[M + H]^+$: 338.0662; found: 338.0650.

3-(7-Phenylpyrazolo[1,5-*a*]pyrimidin-3-yl)-5-(thiophen-2-yl)-4-(trifluoromethyl)isoxazole (TTI-15)



Light yellow solid; eluent, 10% EtOAc/hexane. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.74 (d, J = 4.3 Hz, 1H), 8.46 (d, J = 0.7 Hz, 1H), 8.15 – 7.96 (m, 2H), 7.73 (d, J = 3.6 Hz, 1H), 7.65 (dd, J = 5.1, 1.1 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.22 (dd, J = 5.0, 3.8 Hz, 1H), 7.07 (d, J = 4.3 Hz, 1H).**^{19}F NMR (377 MHz, $CDCl_3$)** δ -55.00. **^{13}C NMR (101 MHz, $CDCl_3$)** δ 165.37, 153.78, 151.21, 147.77, 147.53, 144.55, 131.47, 131.02, 130.96, 130.34, 129.37, 128.80, 128.10, 126.22, 123.10, 120.44, 108.68, 105.45, 105.07, 97.82, 77.00. HRMS (ESI), m/z calcd for $C_{20}H_{12}F_3N_4OS$ $[M + H]^+$: **413.0684;** found: **413.0653.**

2. HPLC data of TTI-6

Table S1: Optimized chromatographic conditions in HPLC for **TTI-6**.

HPLC: Optimized chromatographic conditions (RS4)	
Column	Shim-pack GIST C_{18} (4.6 mm× 150 mm, 5 µm)
Mobile phase	Isocratic - Methanol: Water (80%: 20%)
Injection volume	10 µL
Run time	15 min
Flow rate	1 mL/min
Column temp	40°C
Retention time	6.77 min

Chromatogram

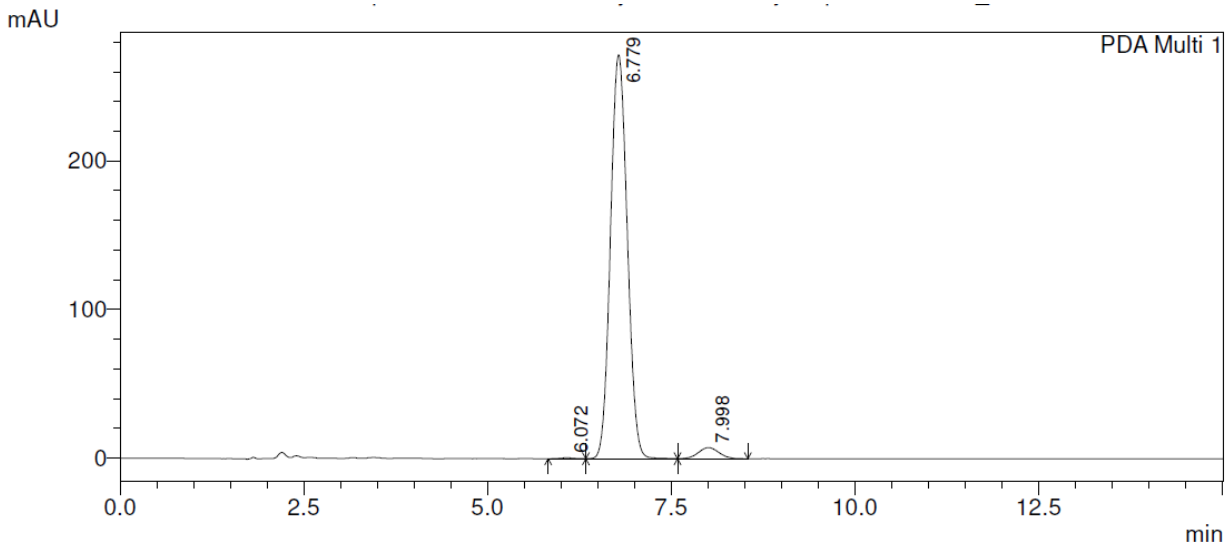


Figure S1. HPLC chromatogram of TTI-6.

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	6.072	7979	531	0.178	0.190
2	6.779	4329849	271955	96.599	97.161
3	7.998	144449	7416	3.223	2.650
Total		4482277	279903	100.000	100.000

3. 3D interaction diagram

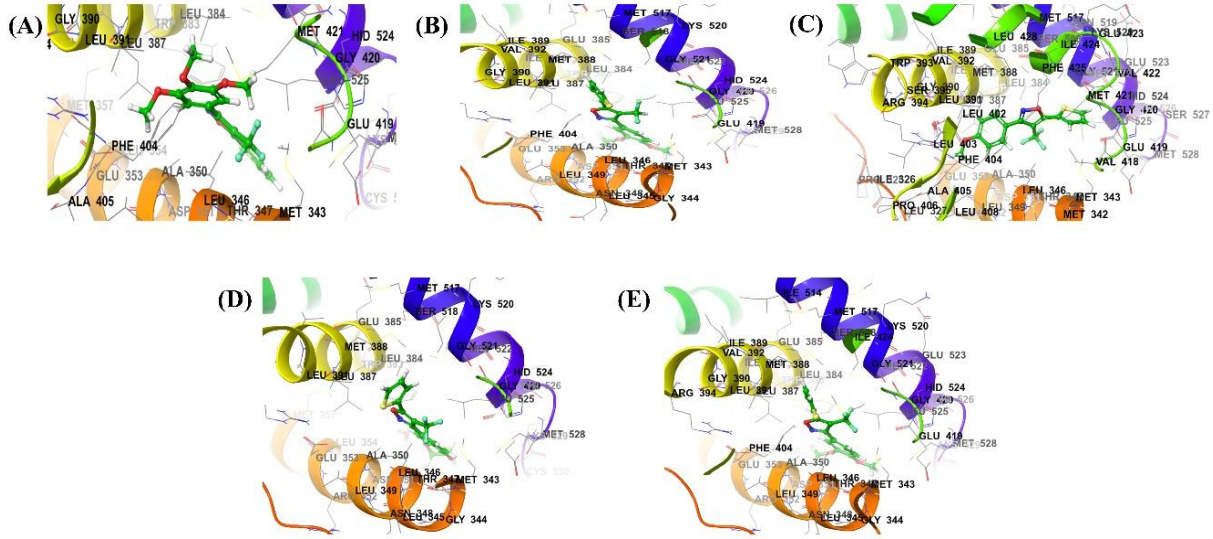


Figure S2. 3D interaction diagram of – (A) **TTI-6**, (B) **TTI-14**, (C) **TTI-3**, (D) **TTI-5**, and (E) **TTI-4** with HERα [PDB ID: 3ERT].

4. 2D interacting diagram.

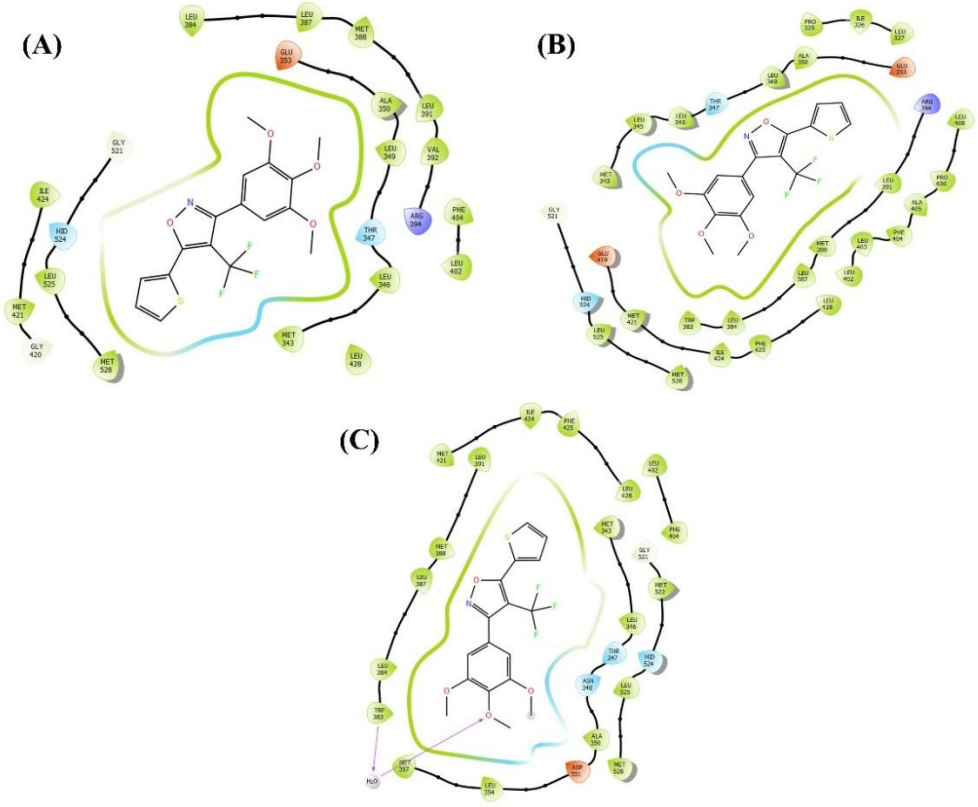


Figure S3. 2D interaction diagram of IFD of **TTI-6** in top three poses with HERα [PDB ID: 3ERT].

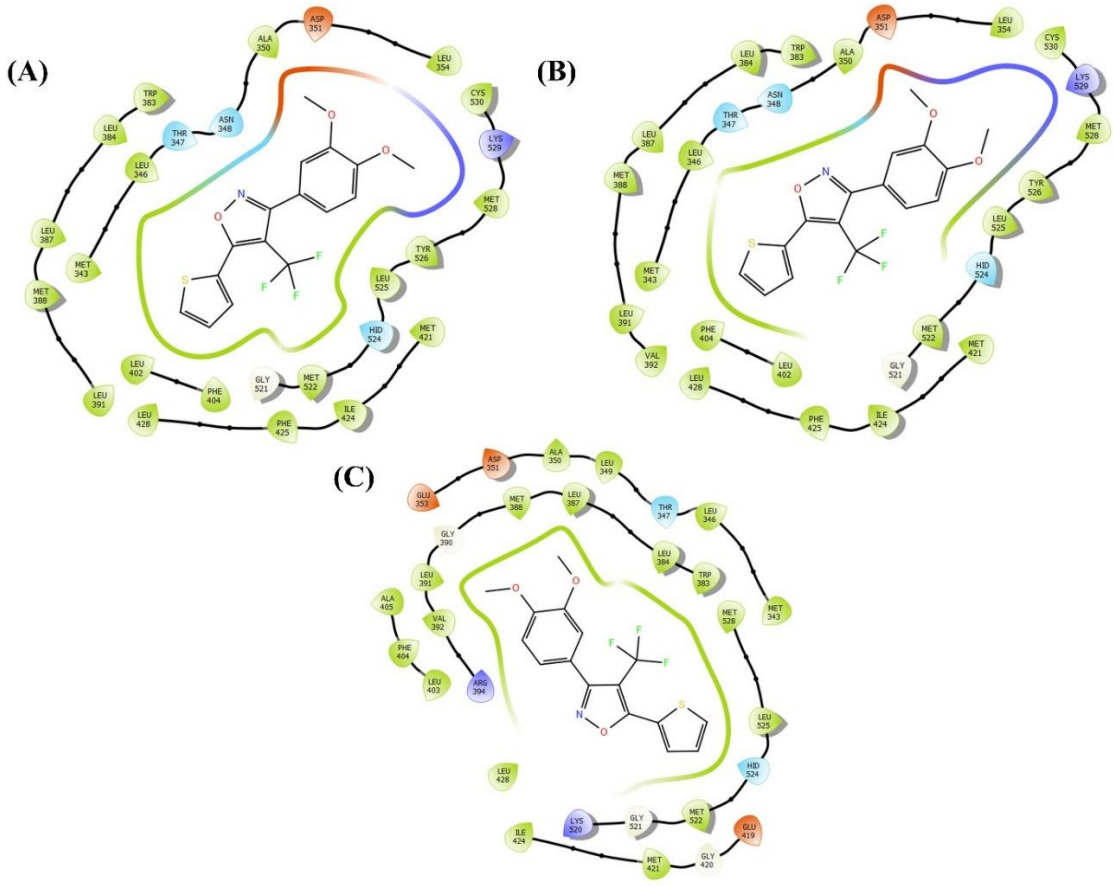


Figure S4. 2D interaction diagram of IFD of **TTI-4** in top three poses with HERα [PDB ID: 3ERT].

5. Docking Scores of TTI-3, TTI-4, TTI-5, TTI-6, and TTI-14.

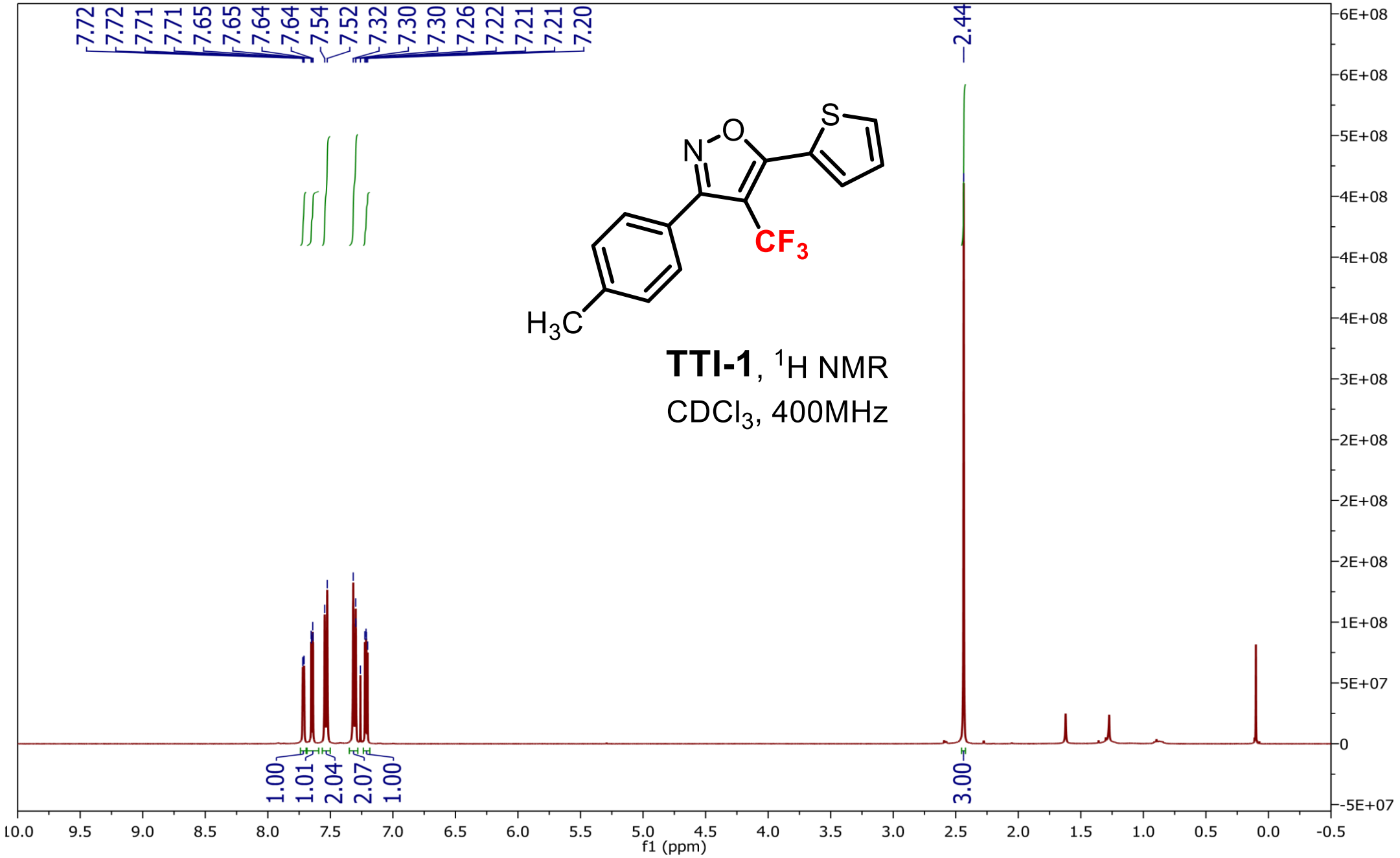
Compounds	Docking score XP	Docking score SP	Mean	SD
3	-7.029	-6.901	-6.965	0.090
4	-7.870	-7.072	-7.471	0.564
5	-6.307	-4.969	-5.638	0.946
6	-9.366	-7.416	-8.391	1.378
14	-7.591	-7.021	-7.306	0.403

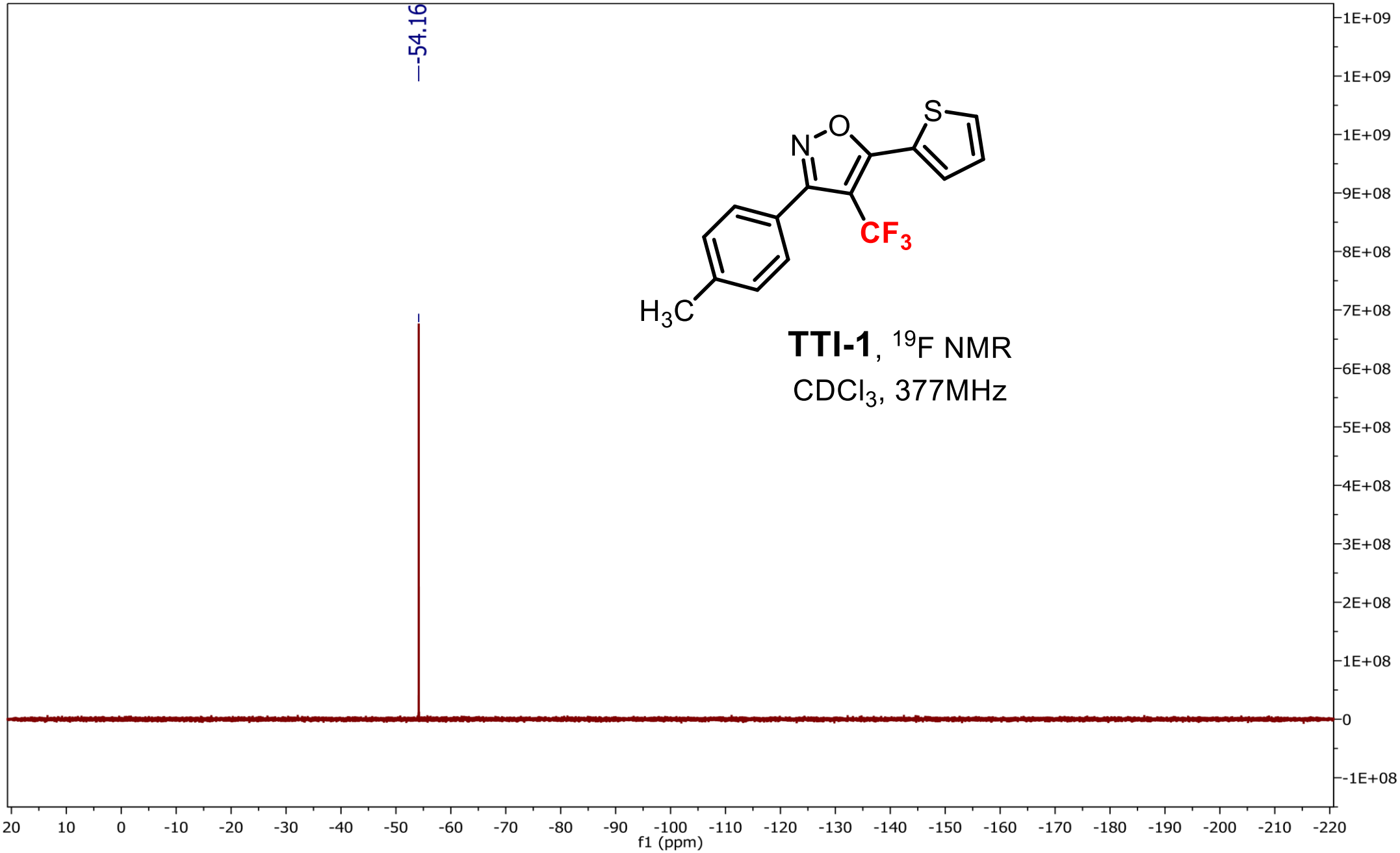
Table S2. The docking scores of –**TTI-3, TTI-4, TTI-5, TTI-6**, and **TTI-14** in two different modes – XP and SP, with their mean and standard deviation (SD).

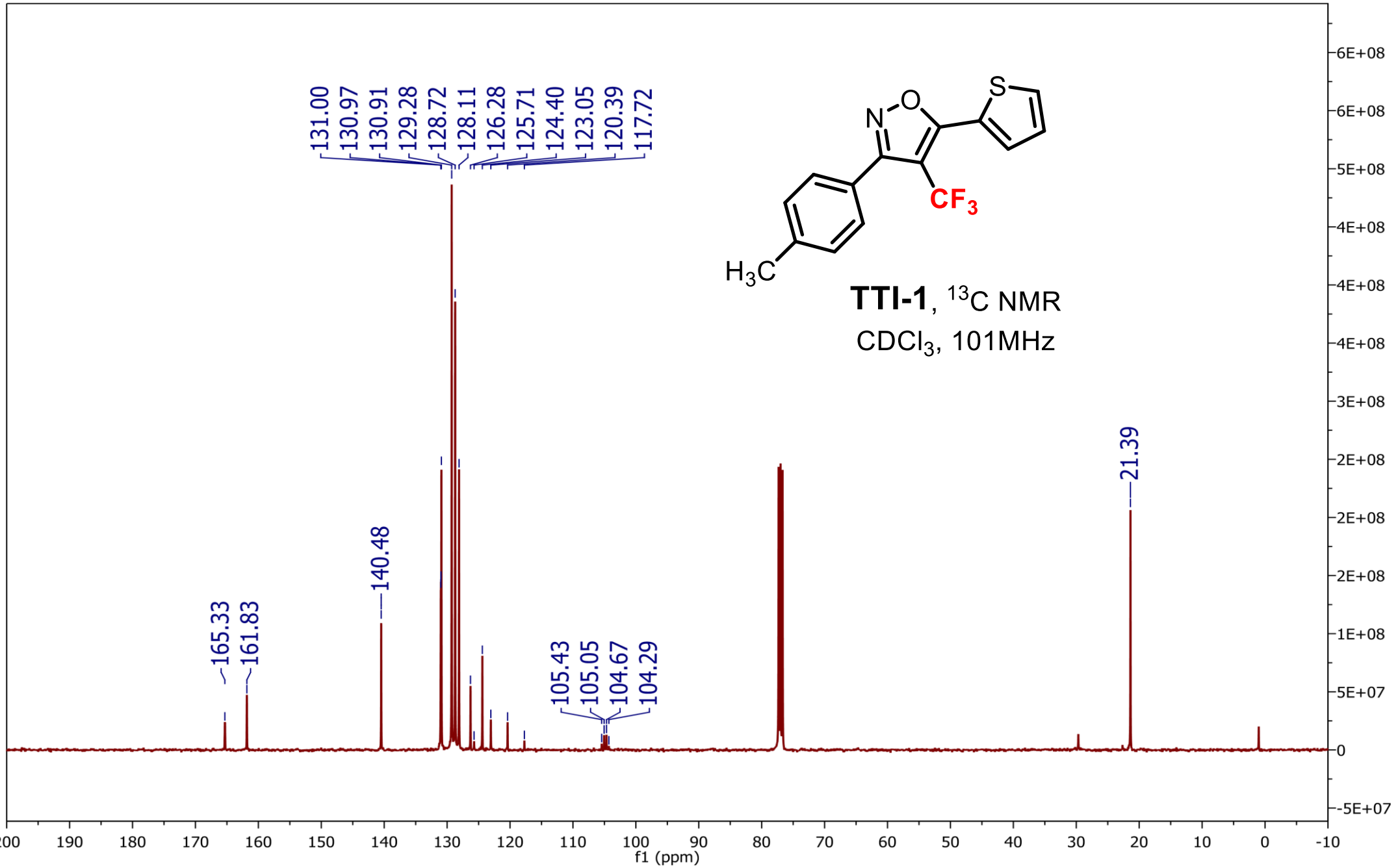
6. Toxicity analysis of TTI-6 compared with TTI-4.

Compounds	AMES toxicity	Max. tolerated dose (human) [log mg/kg/day]	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50) [mol/kg]	Oral Rat Chronic Toxicity (LOAEL) [log mg/kg_bw/day]	Hepatotoxicity	Skin Sensitization	*T.Pyriformis* toxicity [log µg/L]	Minnow toxicity [log mM]
TTI-6	No	0.729	No	No	2.819	0.532	Yes	No	0.369	-1.271
TTI-4	No	0.606	No	No	2.798	0.667	Yes	No	0.414	-1.235

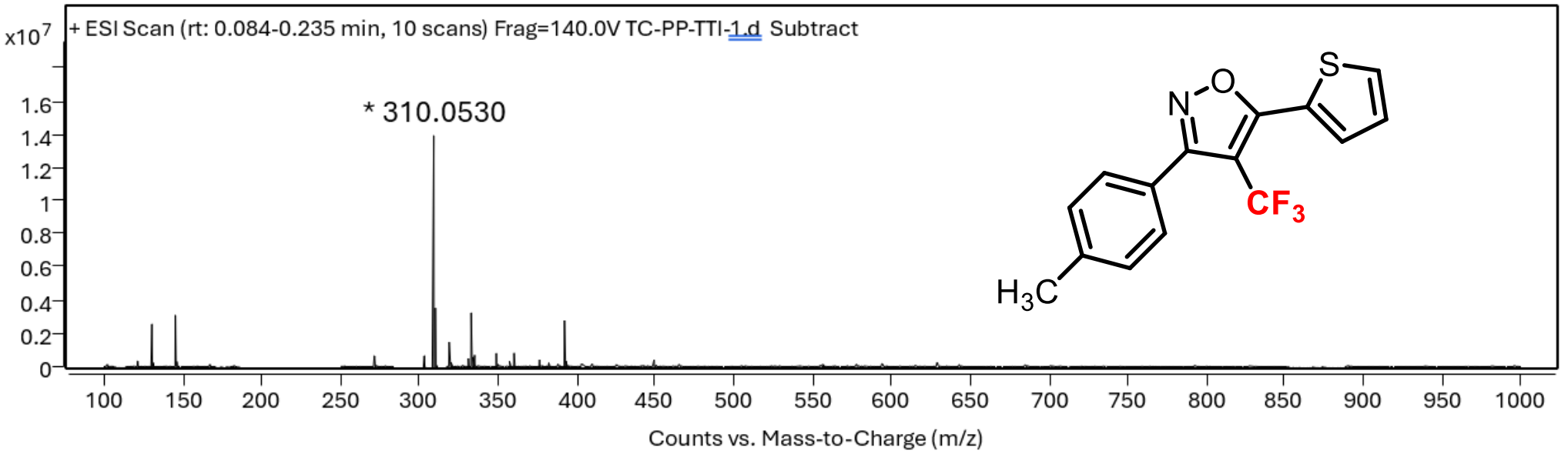
Table S3. Toxicity analysis of **TTI-6** compared with **TTI-4**.

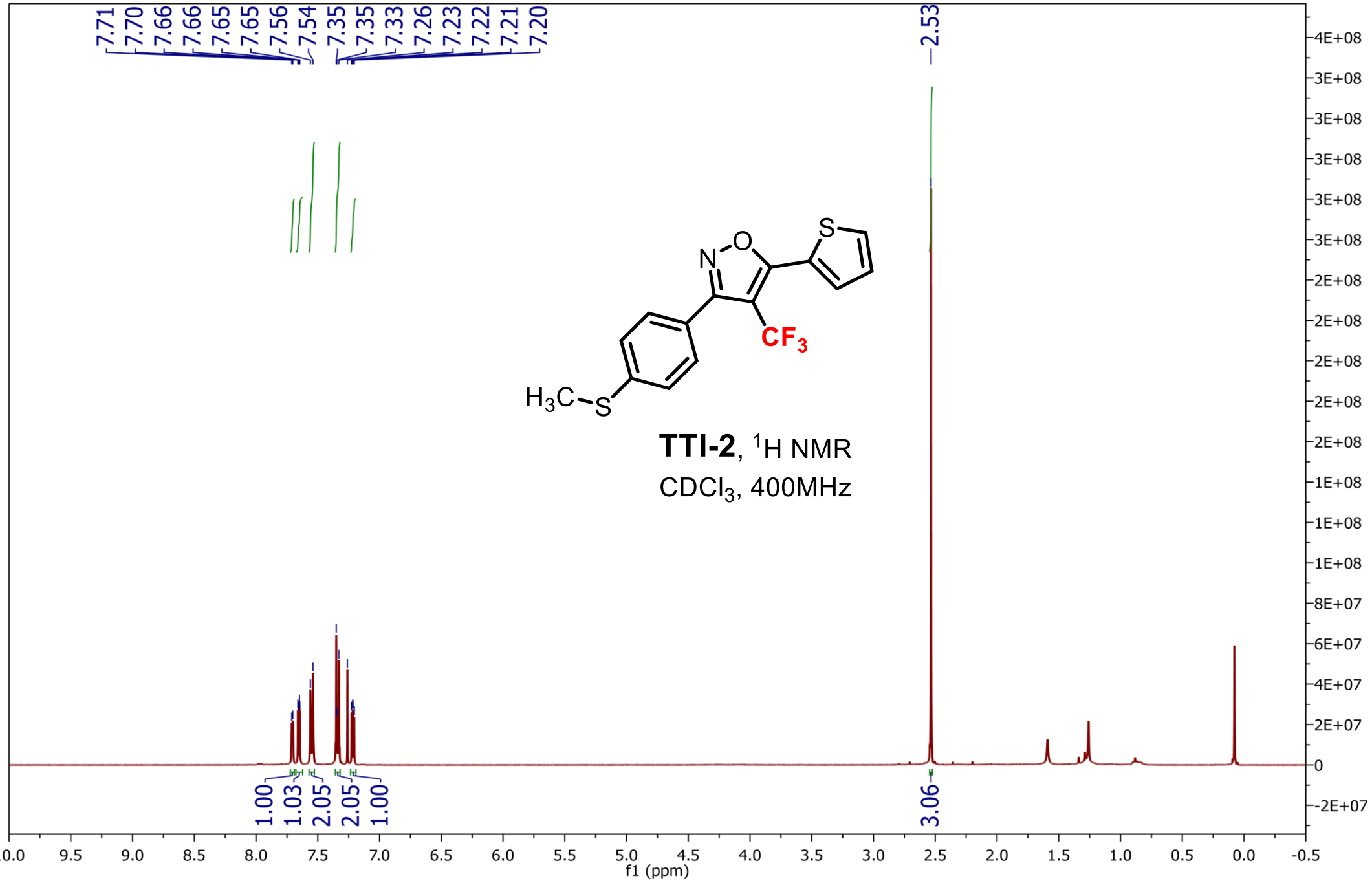

7.72
7.72
7.71
7.71
7.65
7.65
7.64
7.64
7.54
7.52
7.32
7.30
7.30
7.26
7.22
7.21
7.21
7.20
2.44
S
O
N
CF3
H3C
TTI-1, 1H NMR
CDCl3, 400MHz
1.00
1.01
2.04
2.07
1.00
3.00
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

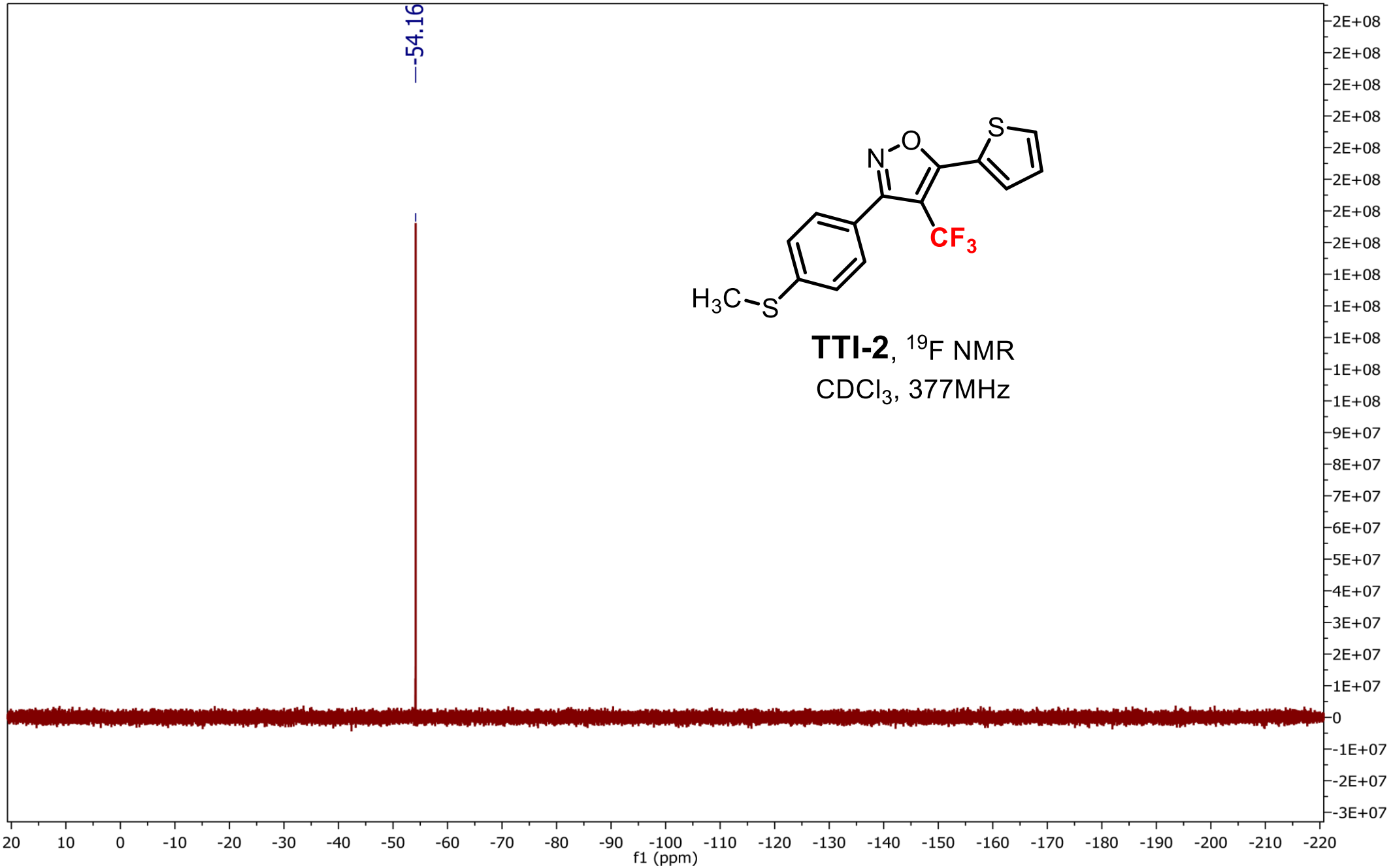

-54.16
S
O
N
CF3
H3C
TTI-1, 19F NMR
CDCl3, 377MHz
1E+09
1E+09
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

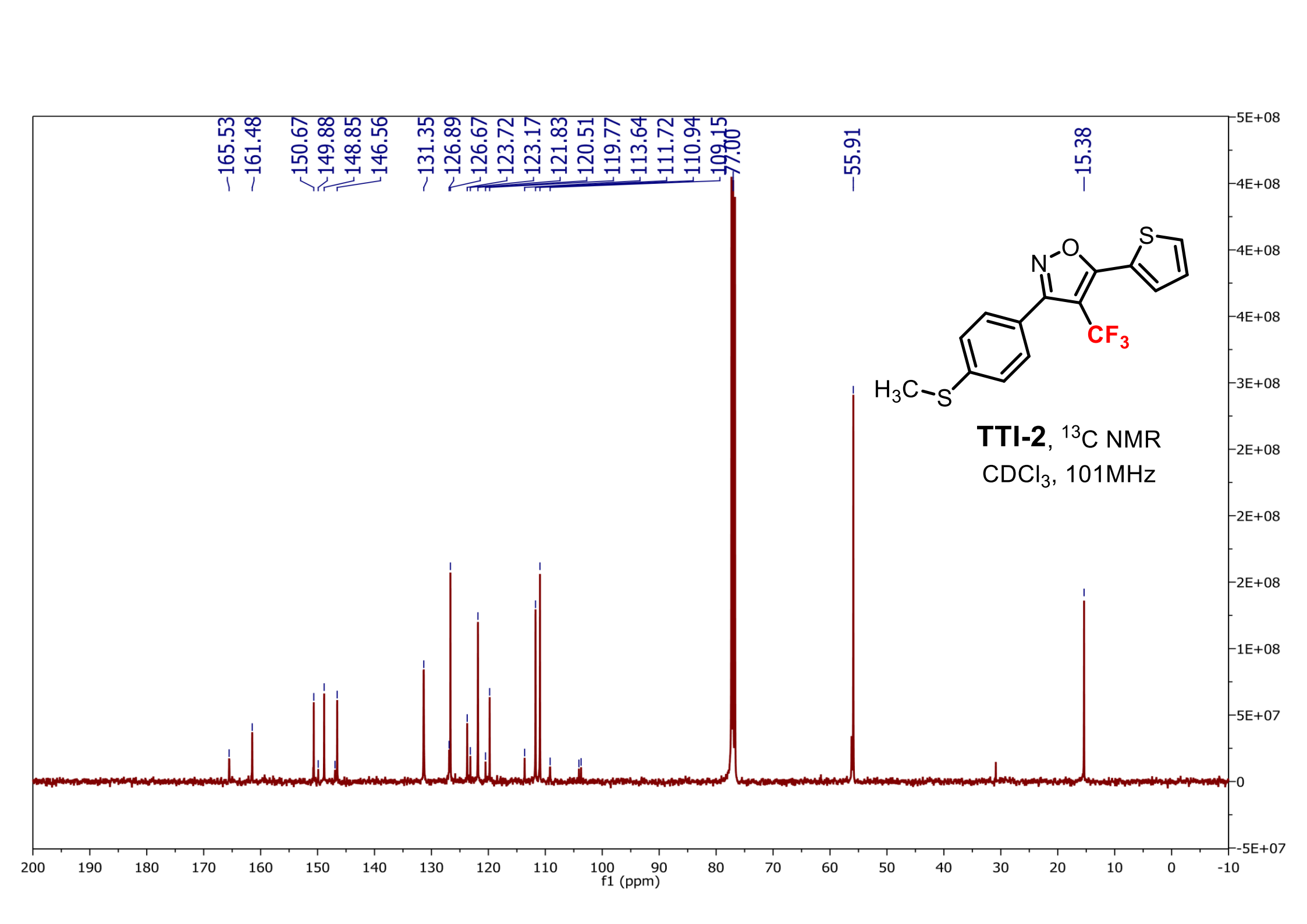

131.00
130.97
130.91
129.28
128.72
128.11
126.28
125.71
124.40
123.05
120.39
117.72
165.33
161.83
140.48
105.43
105.05
104.67
104.29
21.39
S
O
N
CF3
H3C
TTI-1, 13C NMR
CDCl3, 101MHz
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

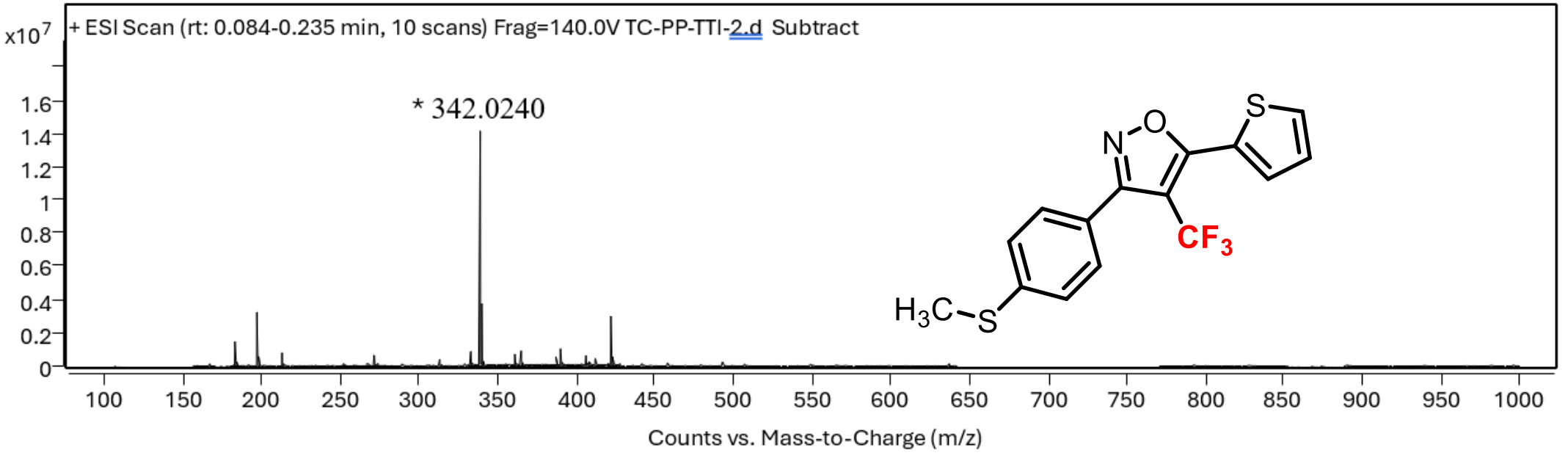


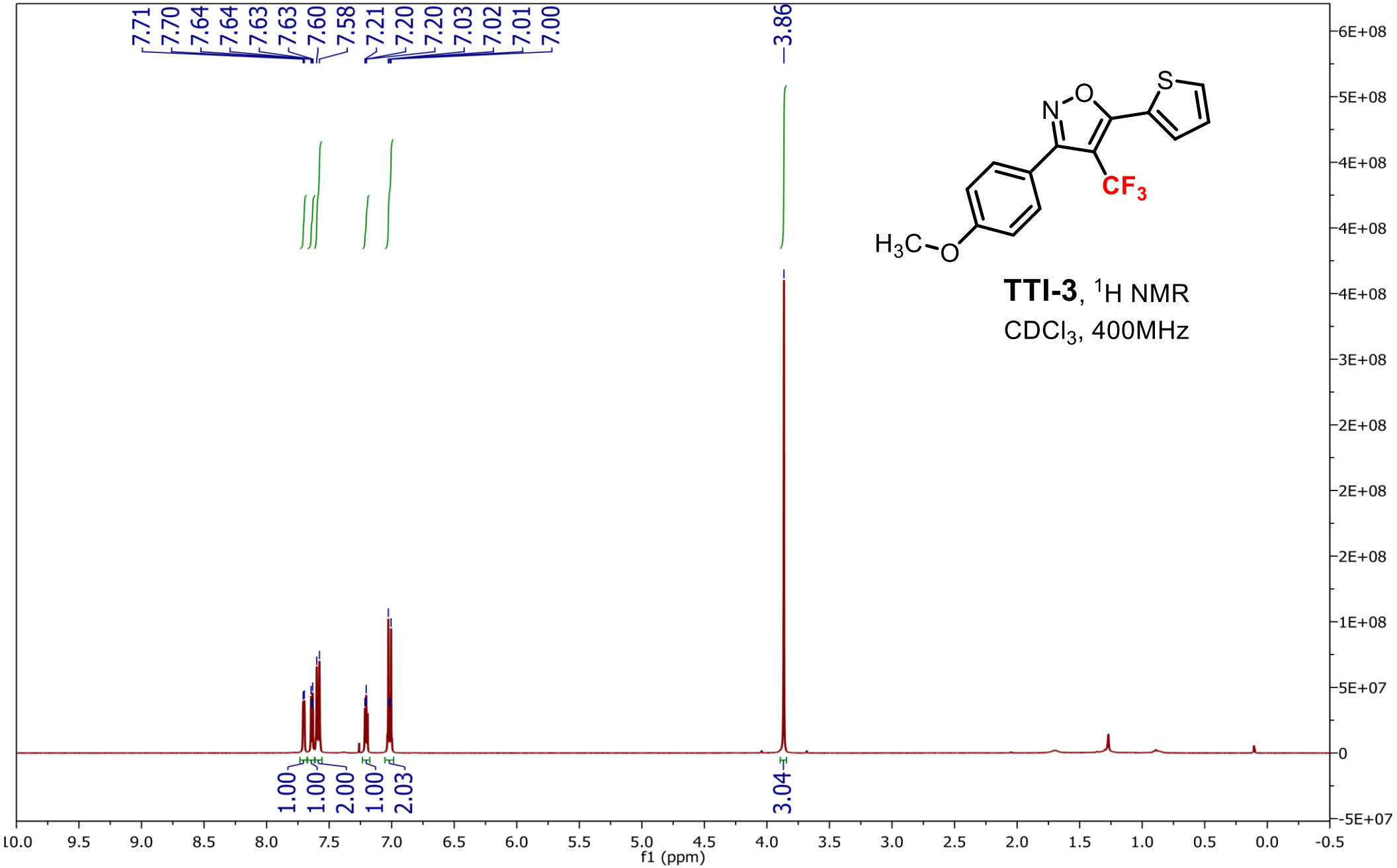

7.71
7.70
7.66
7.66
7.65
7.65
7.56
7.54
7.35
7.35
7.33
7.26
7.23
7.22
7.21
7.20
2.53
S
N
O
CF3
H3C
S
TTI-2, 1H NMR
CDCl3, 400MHz
1.00
1.03
2.05
2.05
1.00
3.06
4E+08
3E+08
3E+08
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
10.0
9.5
9.0
8.5
8.0
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)

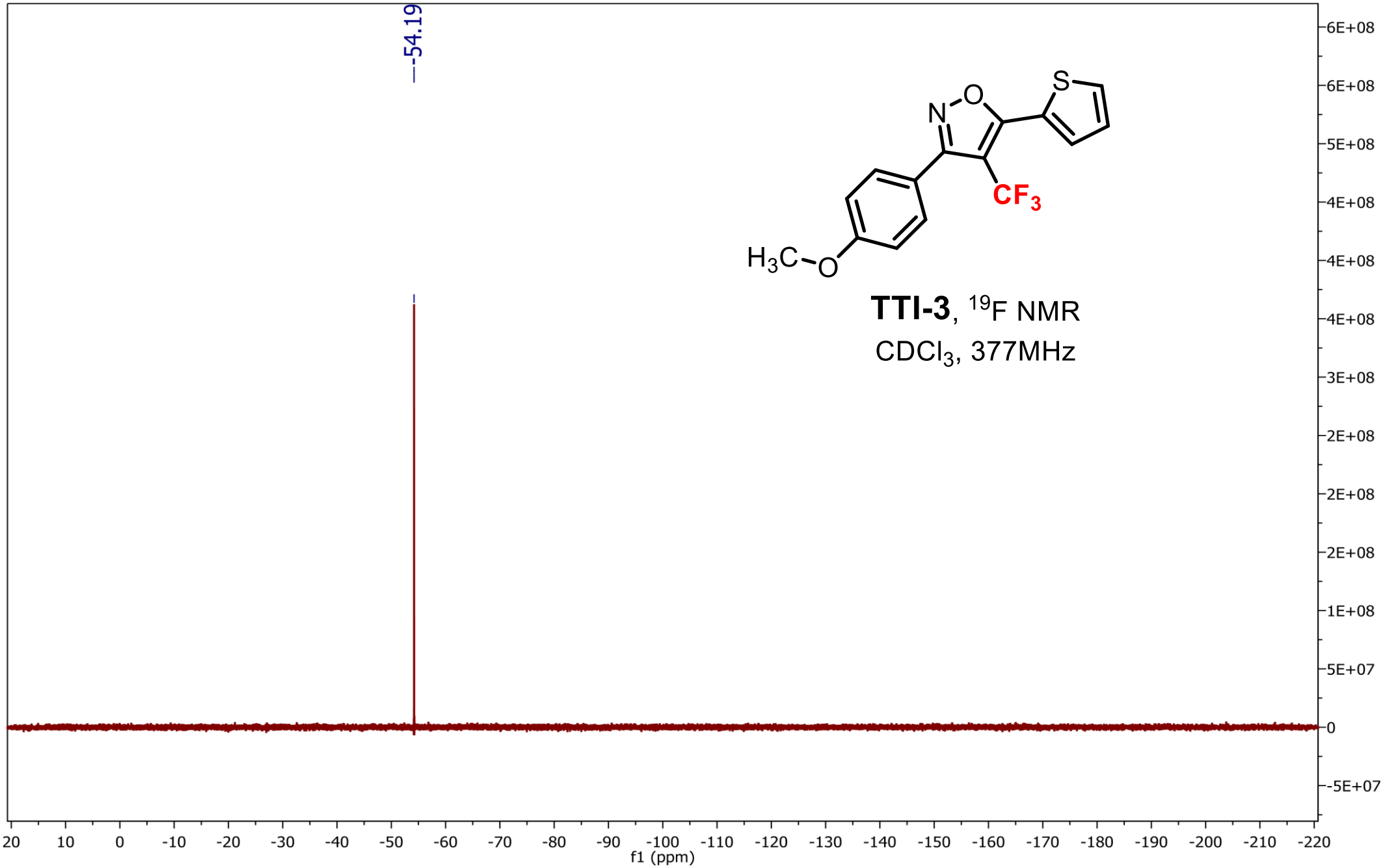

-54.16
S
N
O
CF3
H3C
S
TTI-2, 19F NMR
CDCl3, 377MHz
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
1E+08
1E+08
1E+08
9E+07
8E+07
7E+07
6E+07
5E+07
4E+07
3E+07
2E+07
1E+07
0
-1E+07
-2E+07
-3E+07
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
-220
f1 (ppm)

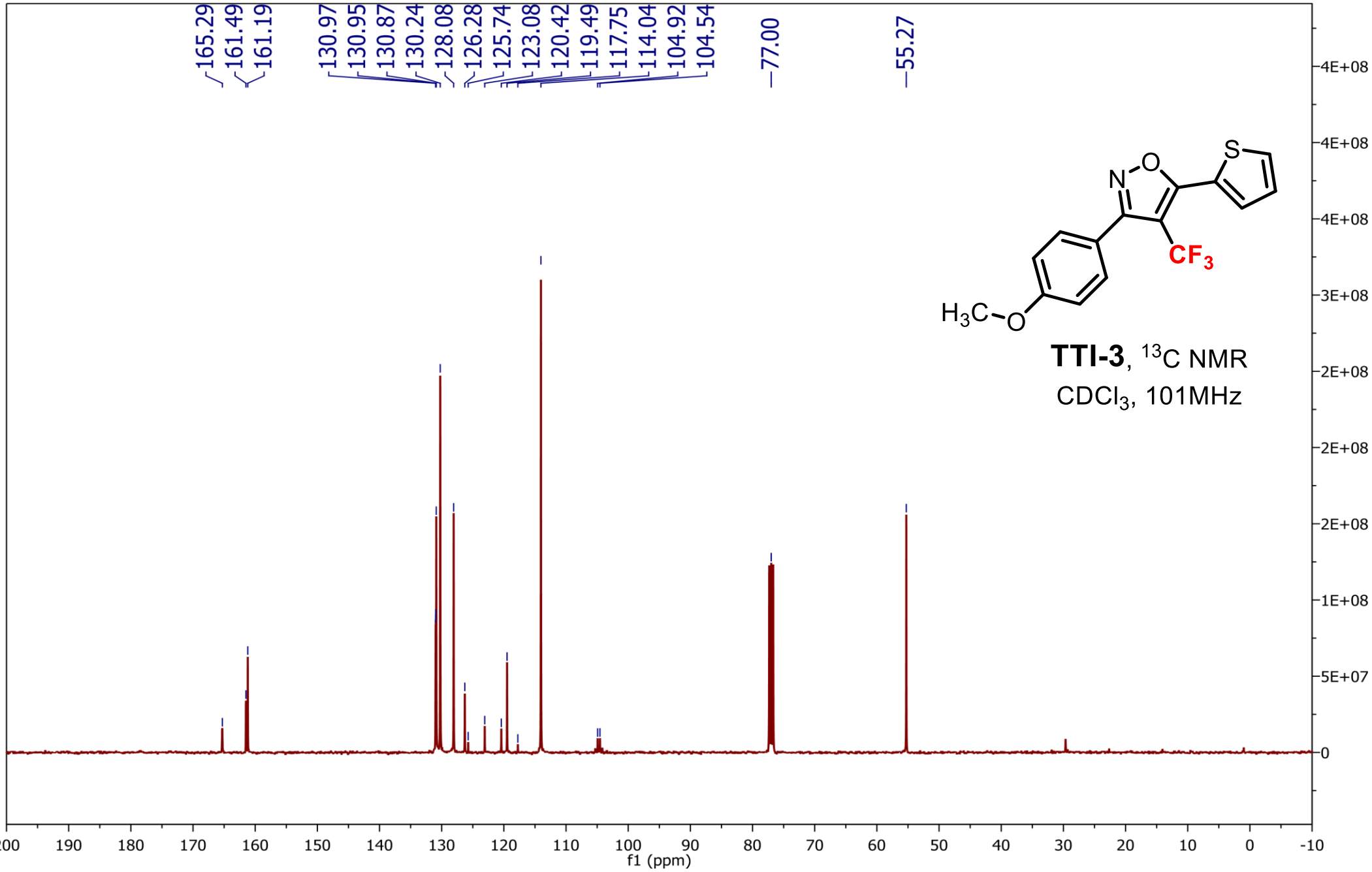

165.53
161.48
150.67
149.88
148.85
146.56
131.35
126.89
126.67
123.72
123.17
121.83
120.51
119.77
113.64
111.72
110.94
109.15
77.00
55.91
15.38
TTI-2, 13C NMR
CDCl3, 101MHz
CF3
H3C
S
N
O
S
f1 (ppm)

Spectrum Plot Report

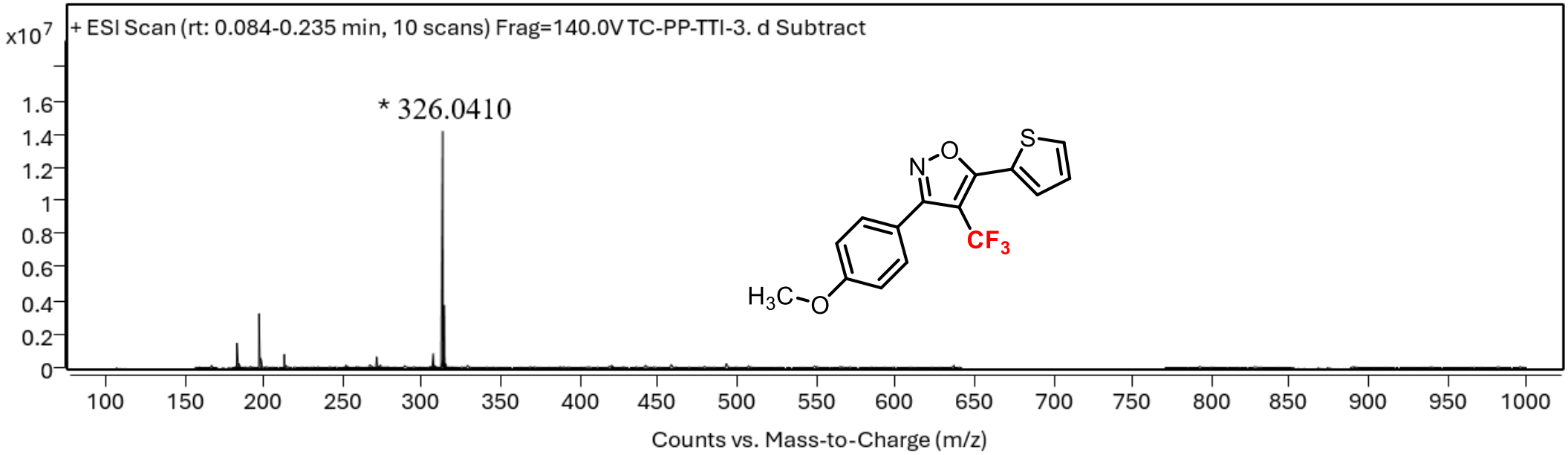


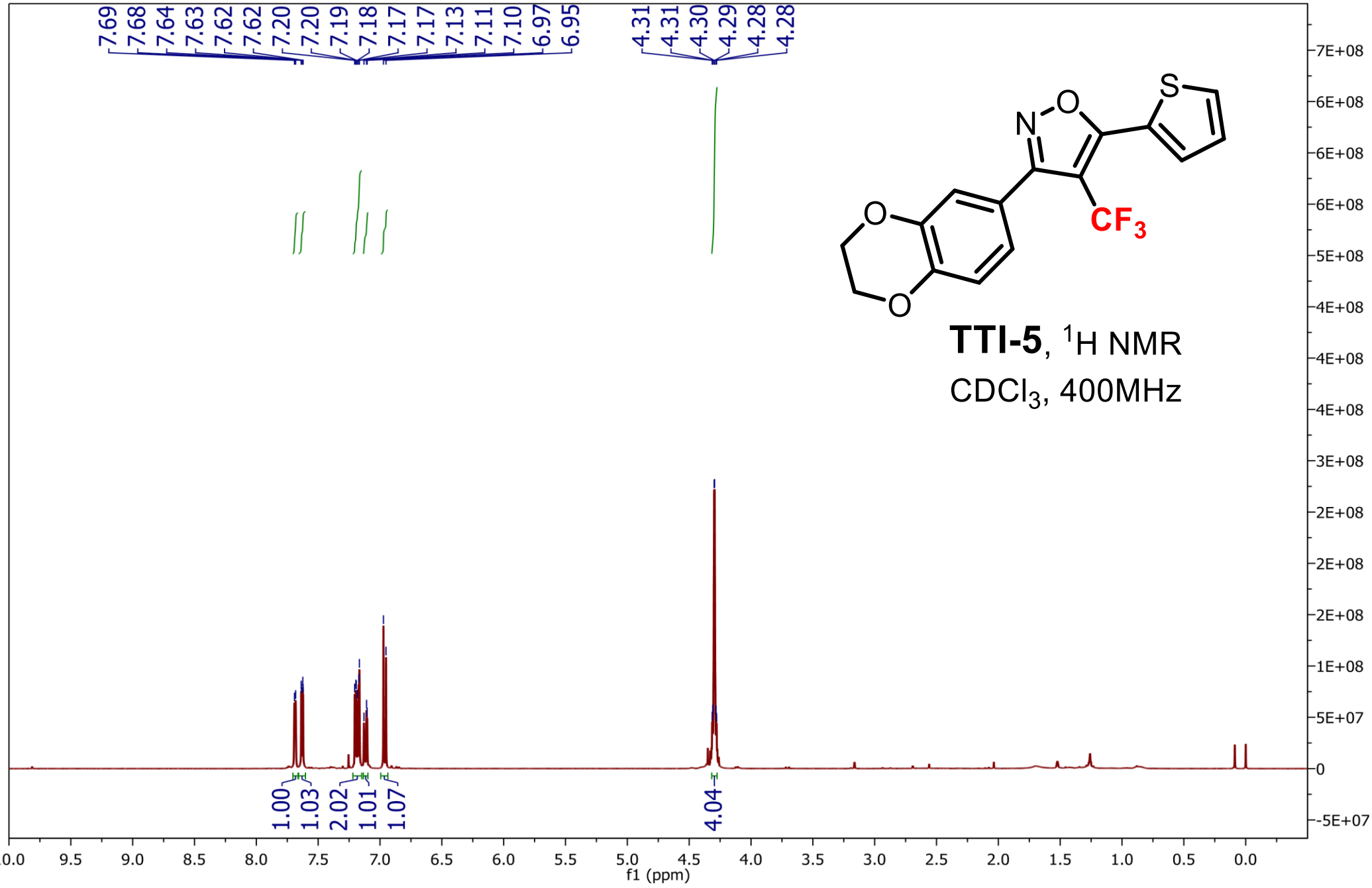

7.71
7.70
7.64
7.64
7.63
7.63
7.60
7.58
7.21
7.20
7.20
7.03
7.02
7.01
7.00
3.86
1.00
1.00
2.00
1.00
2.03
3.04
S
N
O
CF3
H3C
O
TTI-3, 1H NMR
CDCl3, 400MHz
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

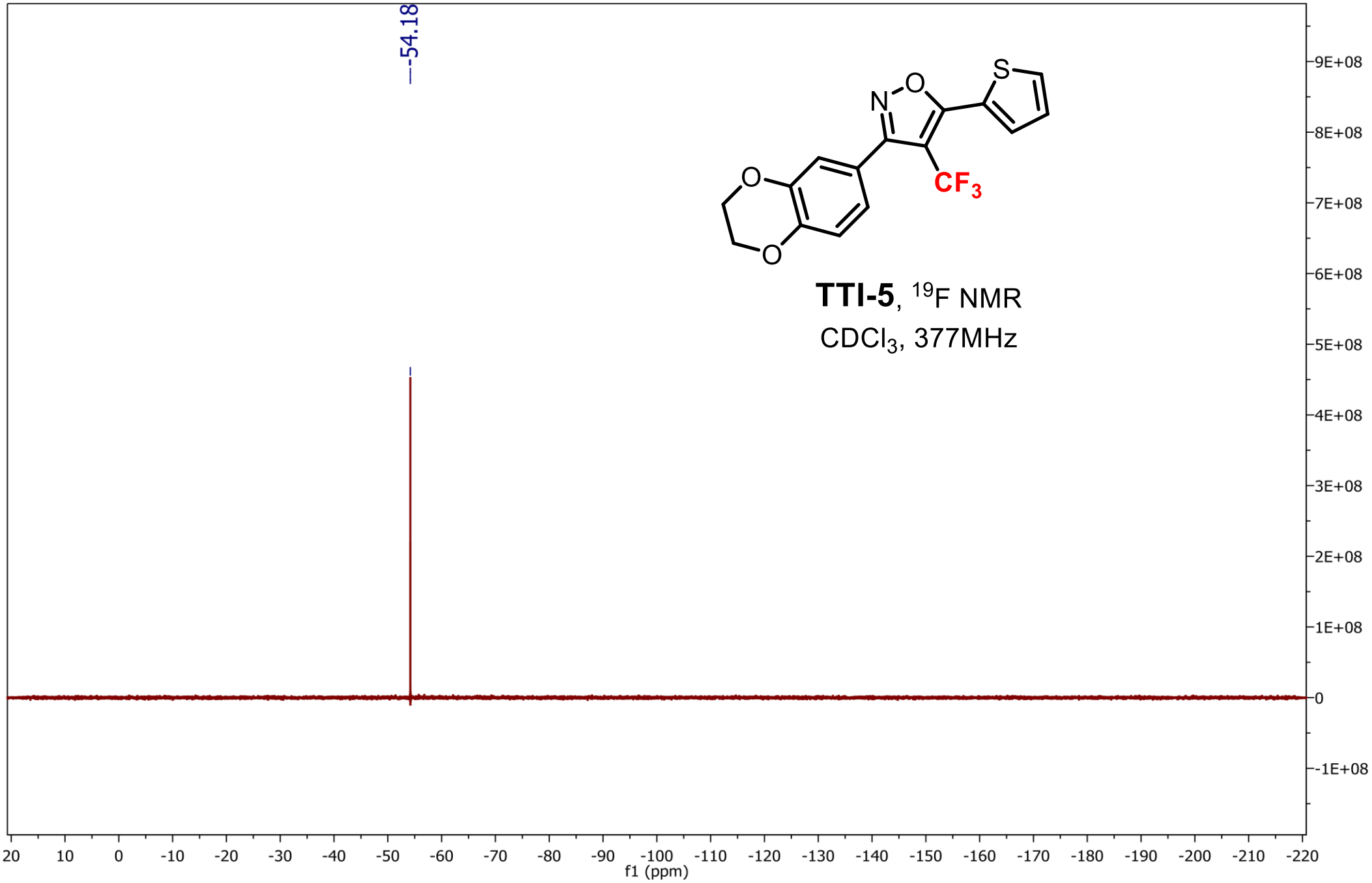

-54.19
S
O
N
CF3
H3C
O
TTI-3, 19F NMR
CDCl3, 377MHz
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

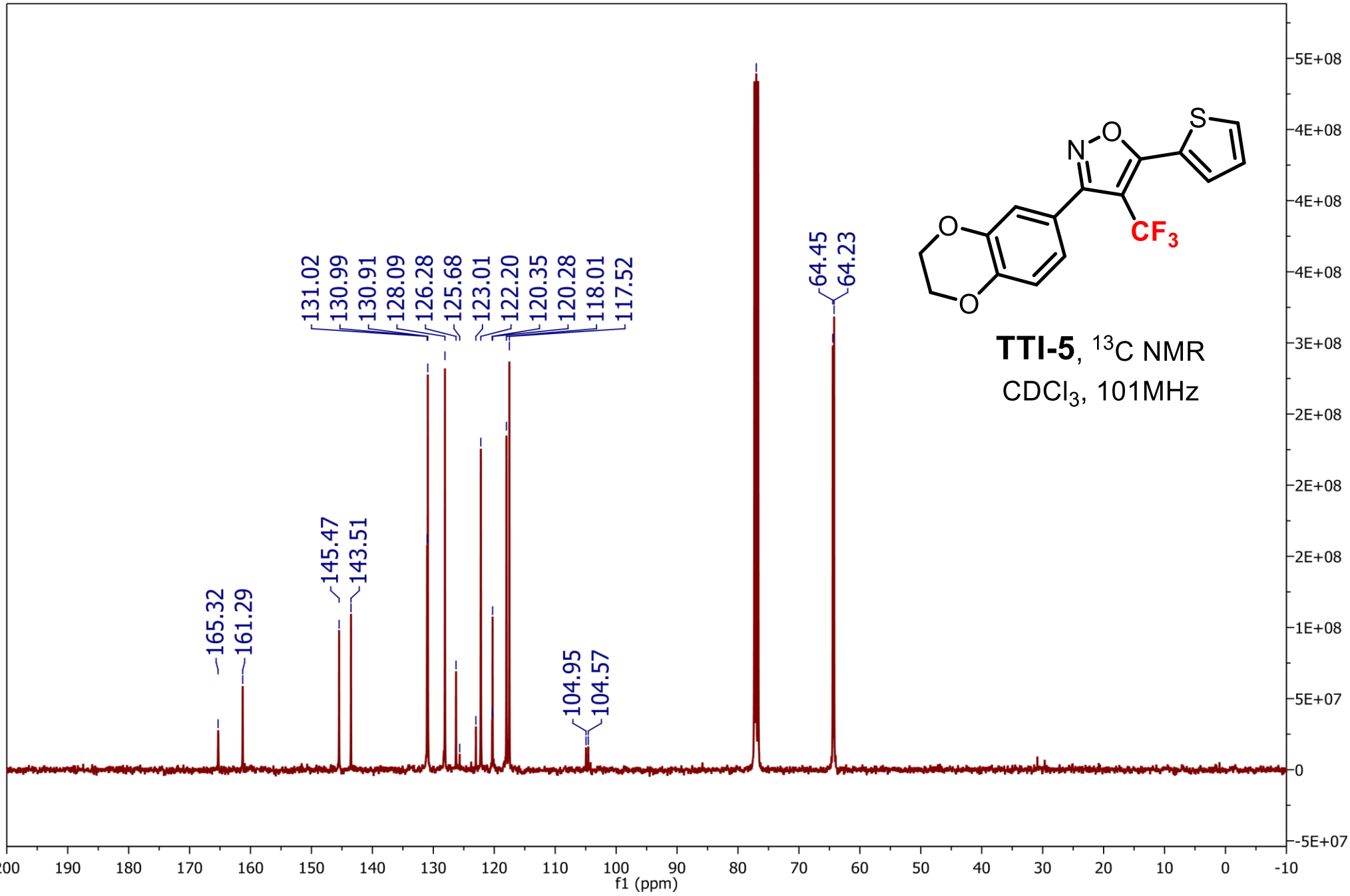

165.29
161.49
161.19
130.97
130.95
130.87
130.24
128.08
126.28
125.74
123.08
120.42
119.49
117.75
114.04
104.92
104.54
77.00
55.27
S
O
N
CF3
H3C
O
TTI-3, 13C NMR
CDCl3, 101MHz
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

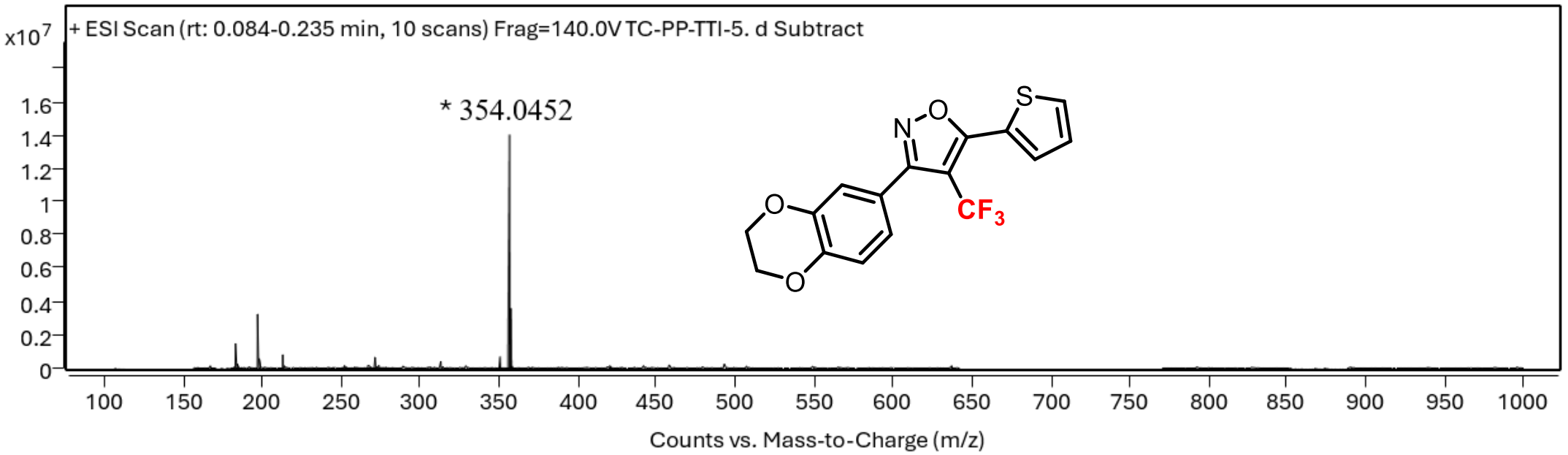


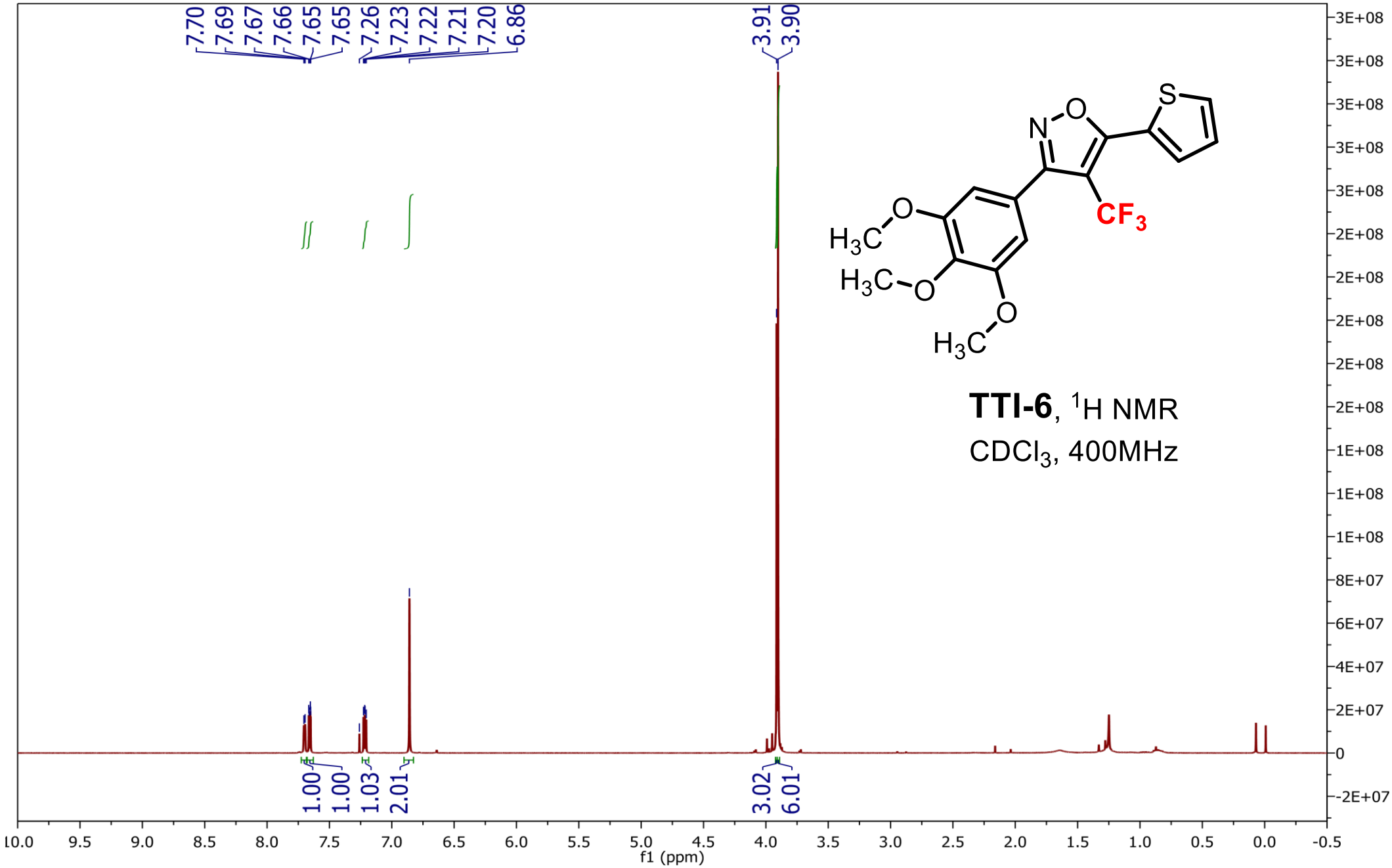

7.69
7.68
7.64
7.63
7.62
7.62
7.20
7.20
7.19
7.18
7.17
7.17
7.13
7.11
7.10
6.97
6.95
4.31
4.31
4.30
4.29
4.28
4.28
1.00
1.03
2.02
1.01
1.07
4.04
f1 (ppm)
O
N
O
S
O
O
CF3
TTI-5, 1H NMR
CDCl3, 400MHz

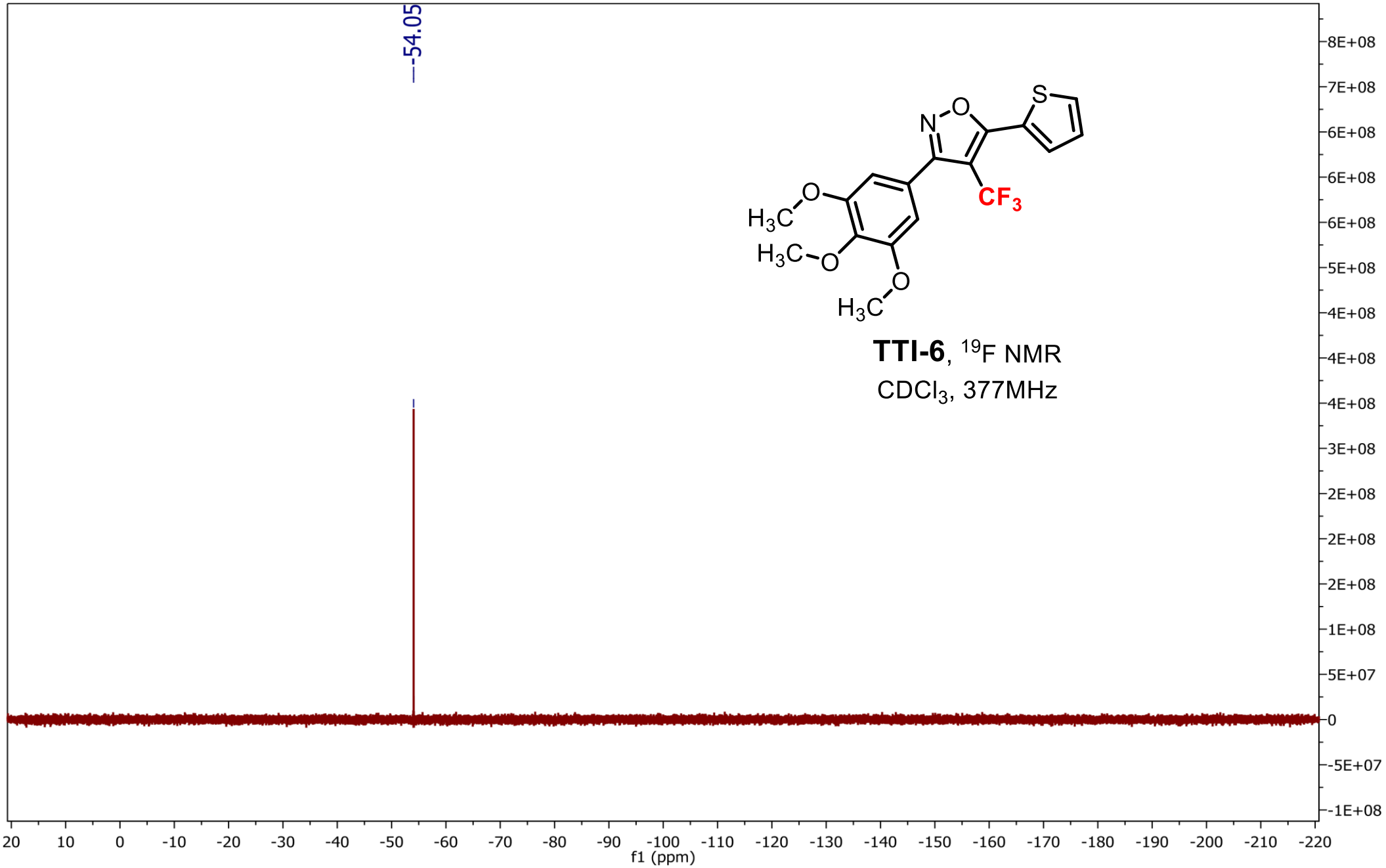

-54.18
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)
O
N
O
S
O
O
CF3
TTI-5, 19F NMR
CDCl3, 377MHz

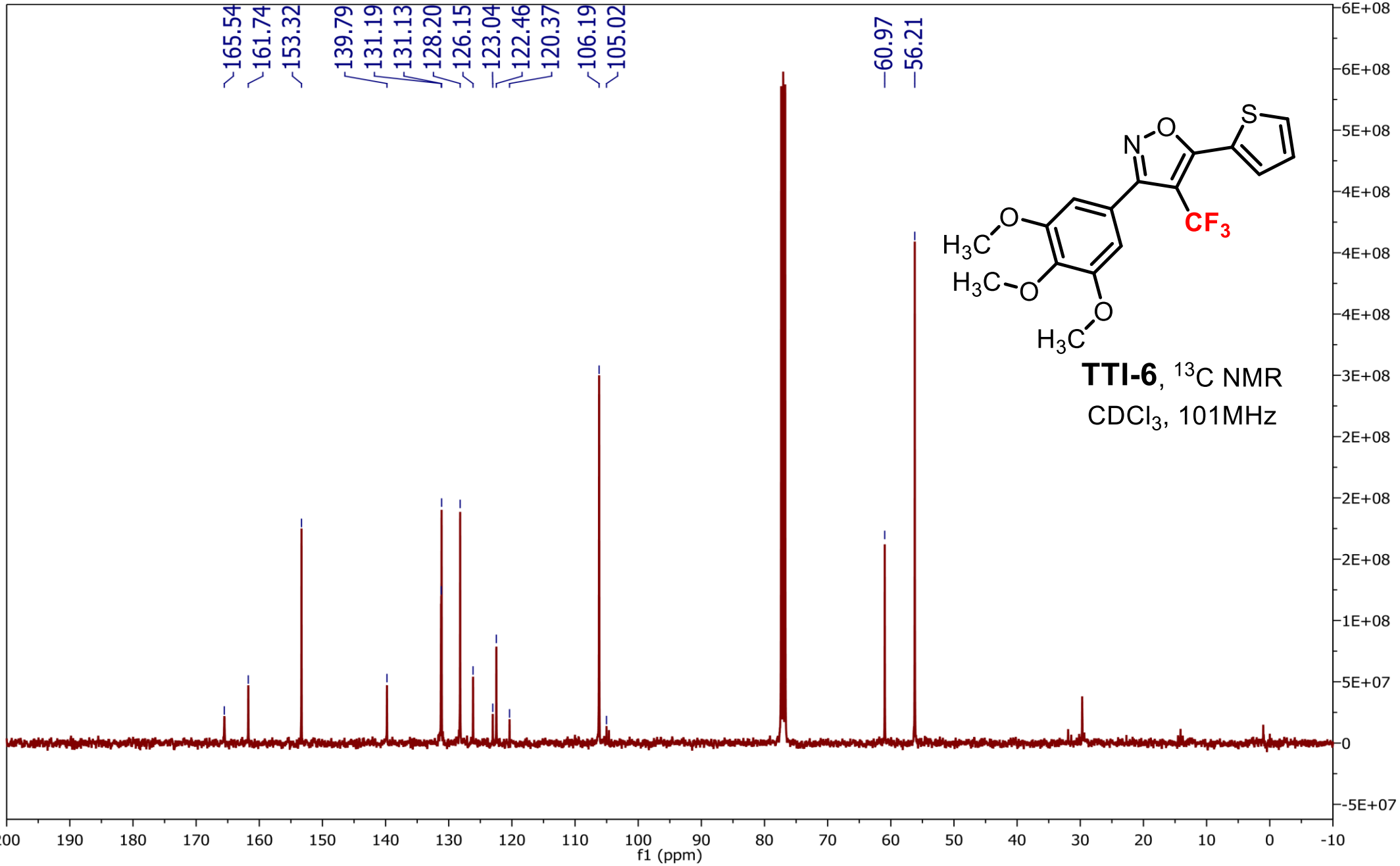

131.02
130.99
130.91
128.09
126.28
125.68
123.01
122.20
120.35
120.28
118.01
117.52
165.32
161.29
145.47
143.51
104.95
104.57
64.45
64.23
O
N
O
S
O
O
CF3
TTI-5, 13C NMR
CDCl3, 101MHz
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report




7.70
7.69
7.67
7.66
7.65
7.65
7.26
7.23
7.22
7.21
7.20
6.86
3.91
3.90
1.00
1.00
1.03
2.01
3.02
6.01
f1 (ppm)
TTI-6, 1H NMR
CDCl3, 400MHz


-54.05
S
N
O
CF3
H3C
O
H3C
O
H3C
O
TTI-6, 19F NMR
CDCl3, 377MHz
8E+08
7E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
-1E+08
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


165.54
161.74
153.32
139.79
131.19
131.13
128.20
126.15
123.04
122.46
120.37
106.19
105.02
60.97
56.21
S
N
O
CF3
H3C
O
H3C
O
H3C
O
TTI-6, 13C NMR
CDCl3, 101MHz
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

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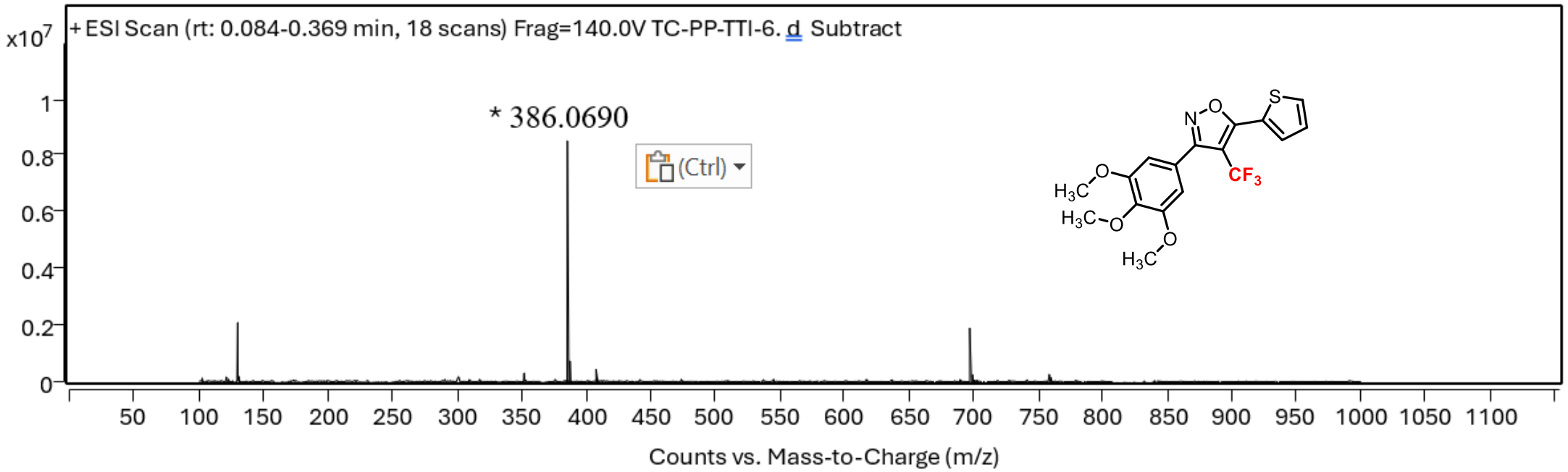
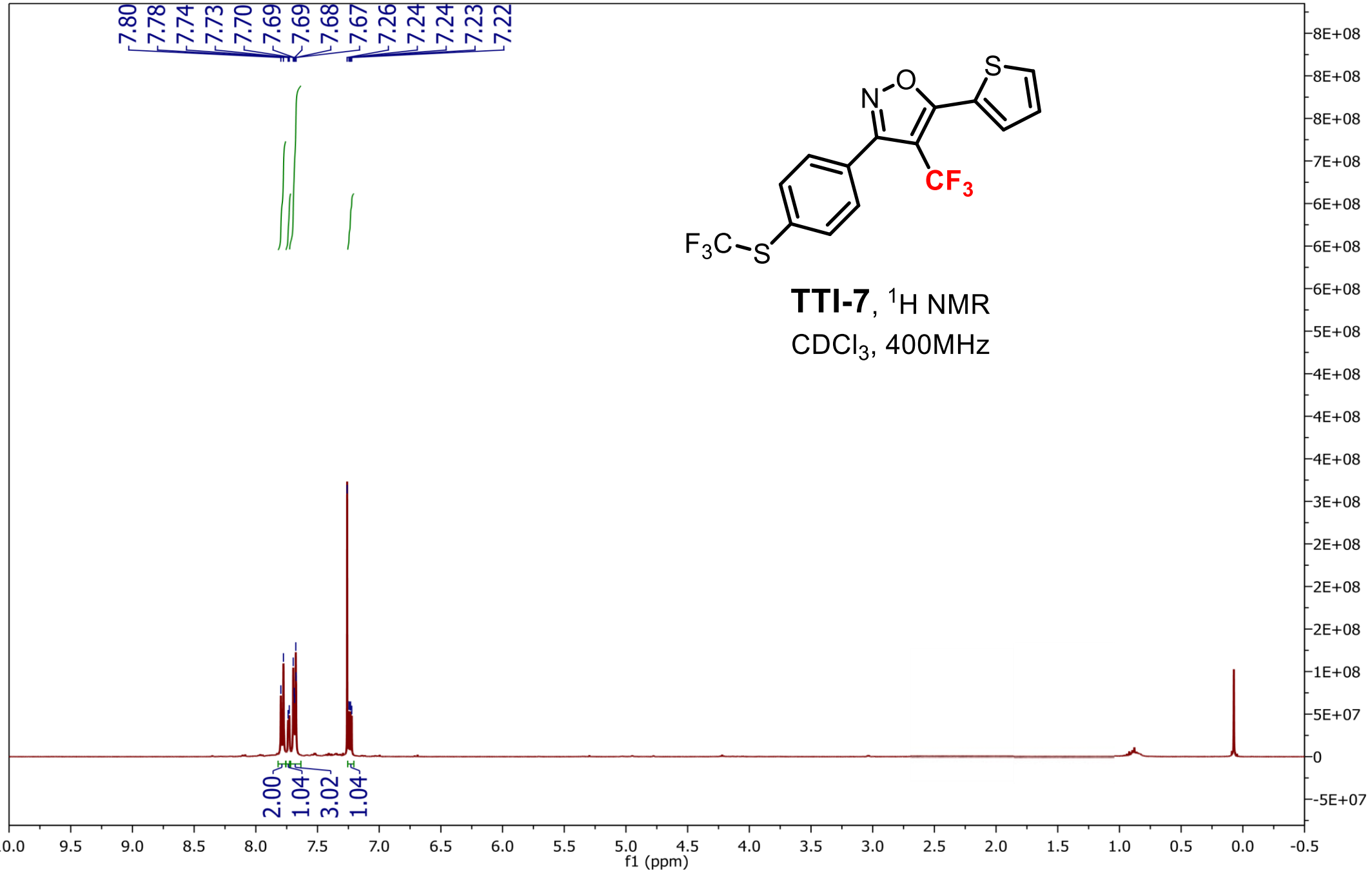
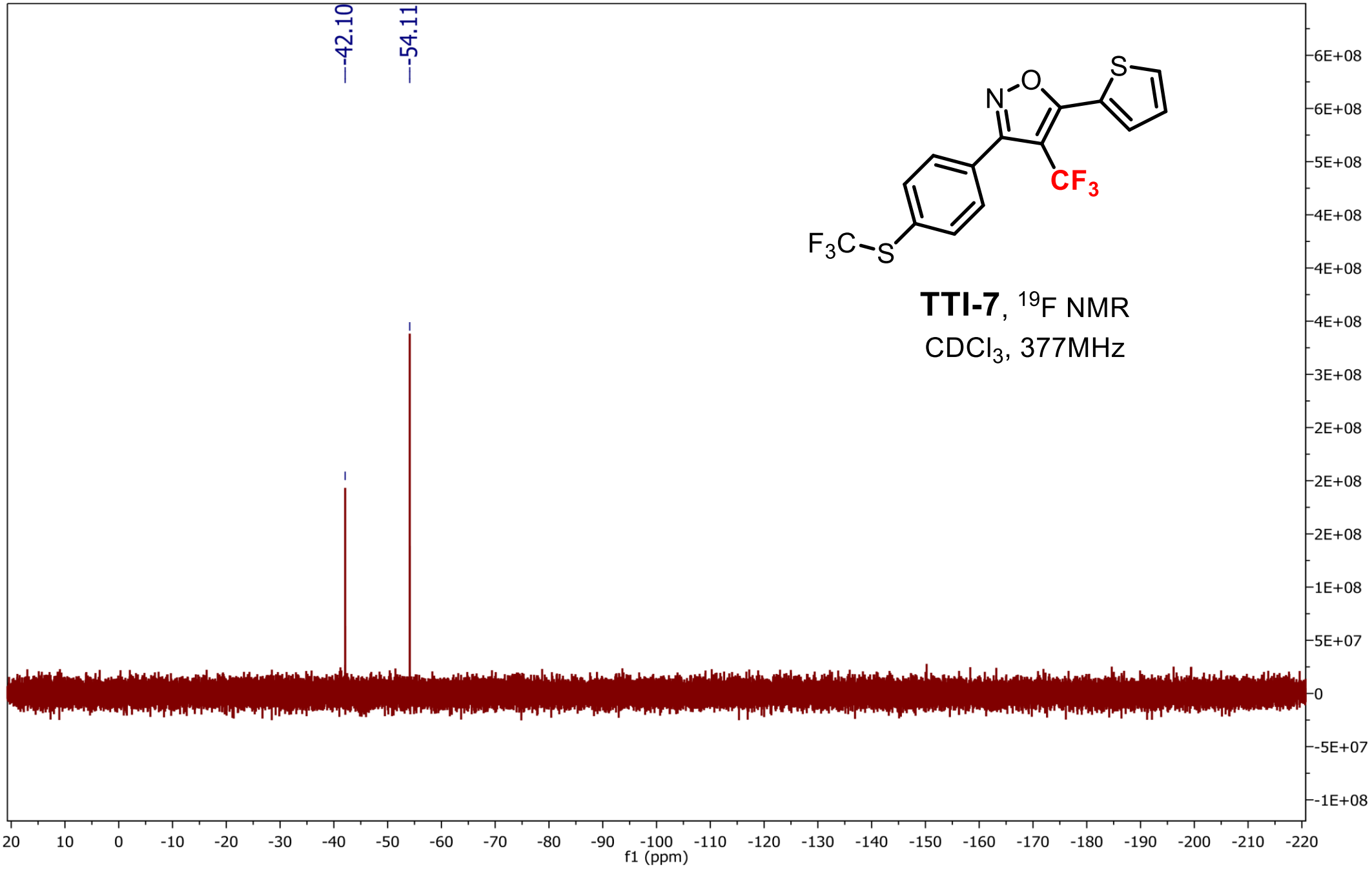
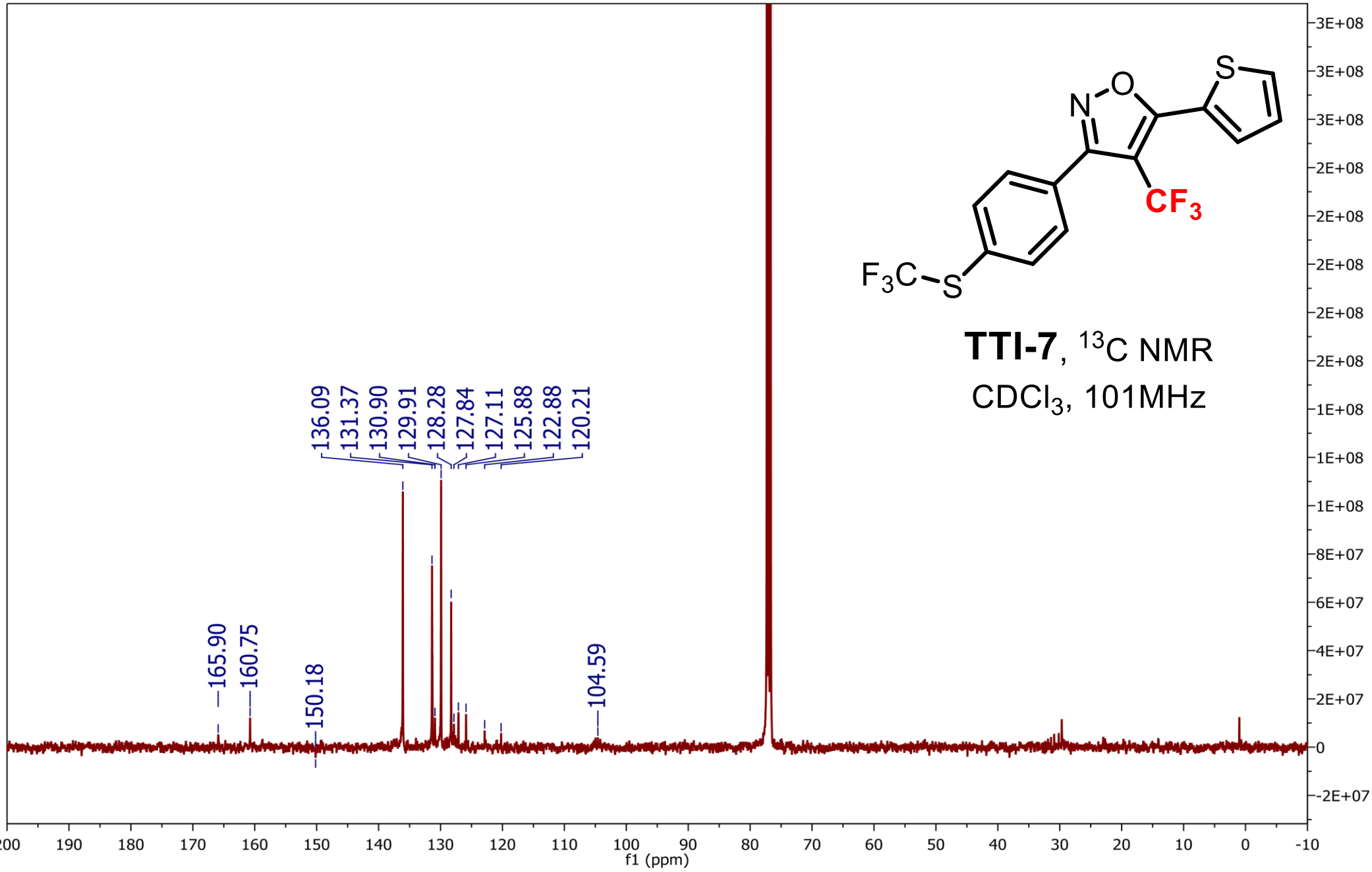



7.80
7.78
7.74
7.73
7.70
7.69
7.69
7.68
7.67
7.26
7.24
7.24
7.23
7.22
S
N
O
CF3
F3C
S
TTI-7, 1H NMR
CDCl3, 400MHz
2.00
1.04
3.02
1.04
f1 (ppm)


-42.10
-54.11
S
O
N
CF3
F3C
S
TTI-7, 19F NMR
CDCl3, 377MHz
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
-1E+08
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)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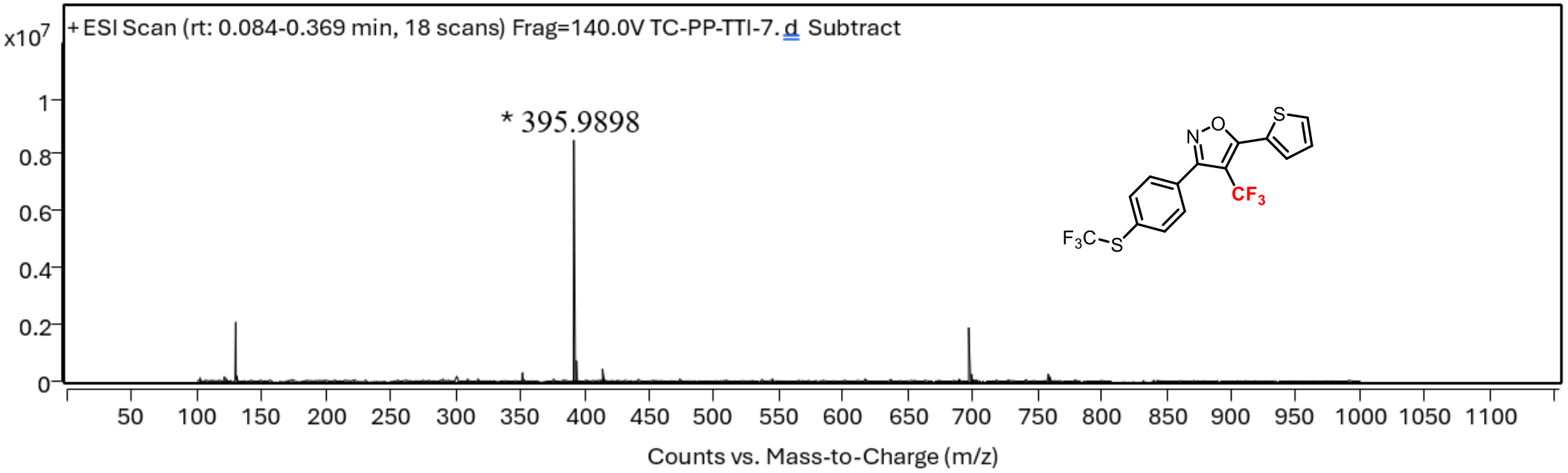
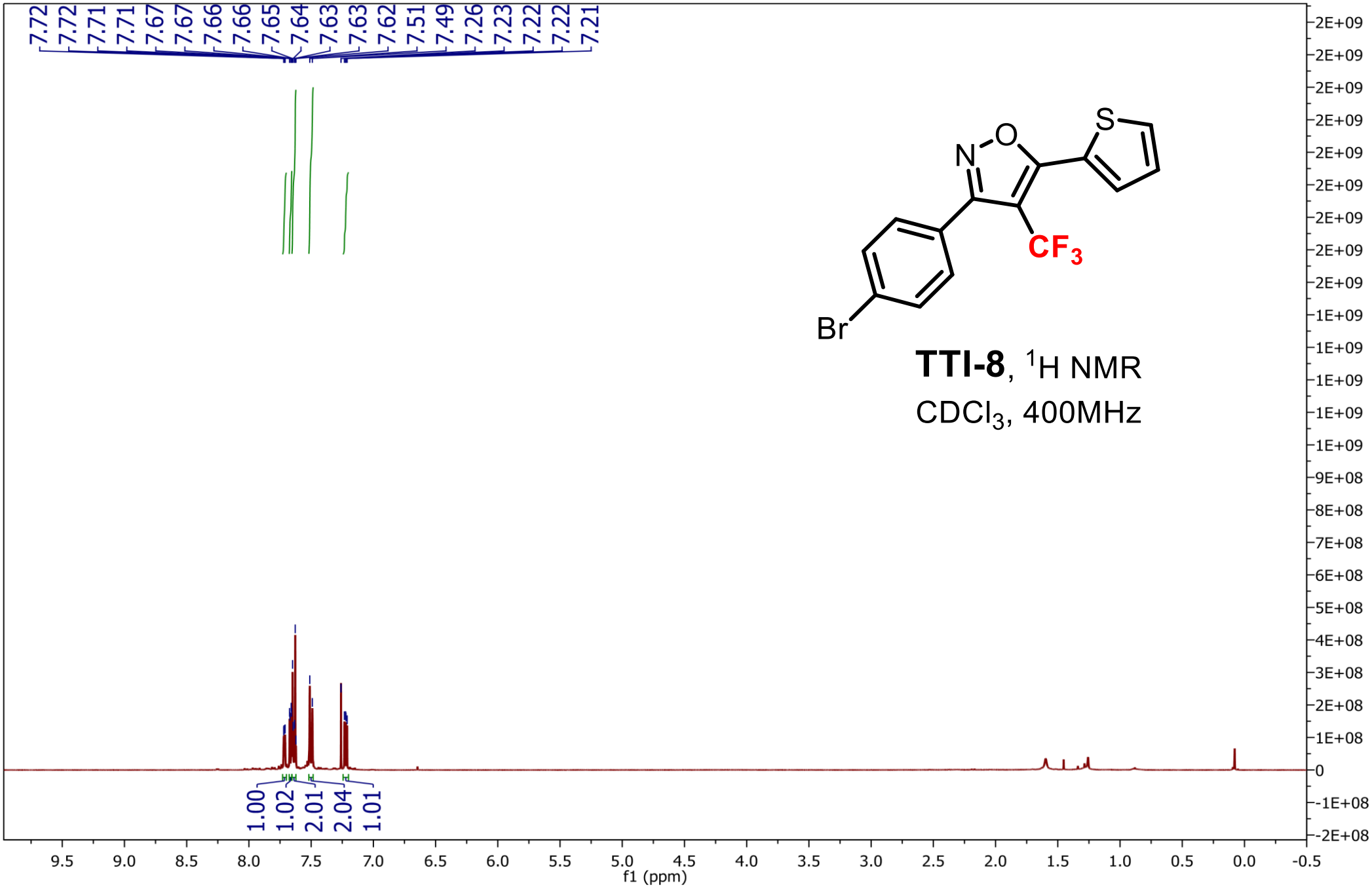
131.37
130.90
129.91
128.28
127.84
127.11
125.88
122.88
120.21
165.90
160.75
150.18
104.59
f1 (ppm)
TTI-7, 13C NMR
CDCl3, 101MHz
F3C
S
N
O
S
CF3

Spectrum Plot Report

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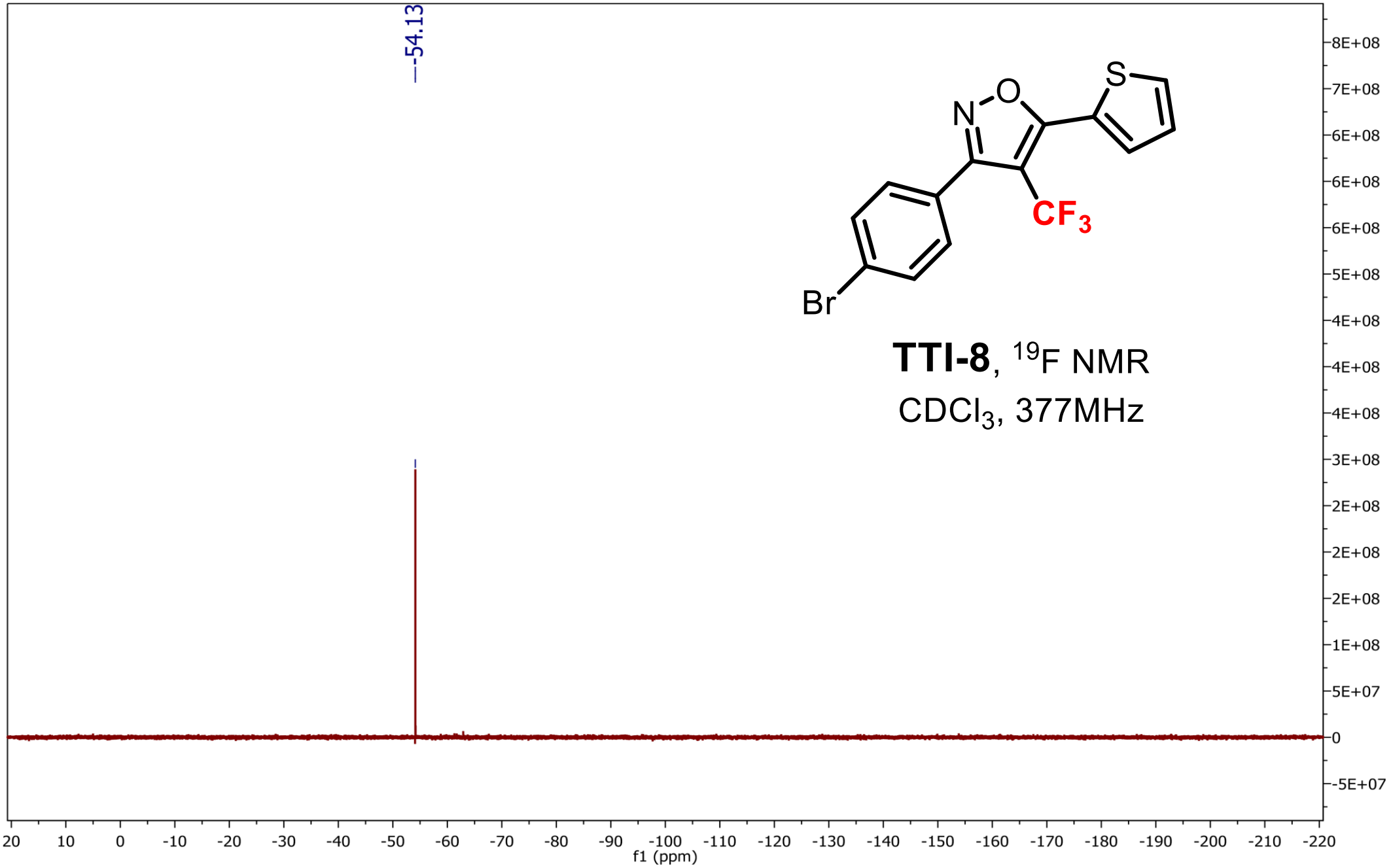
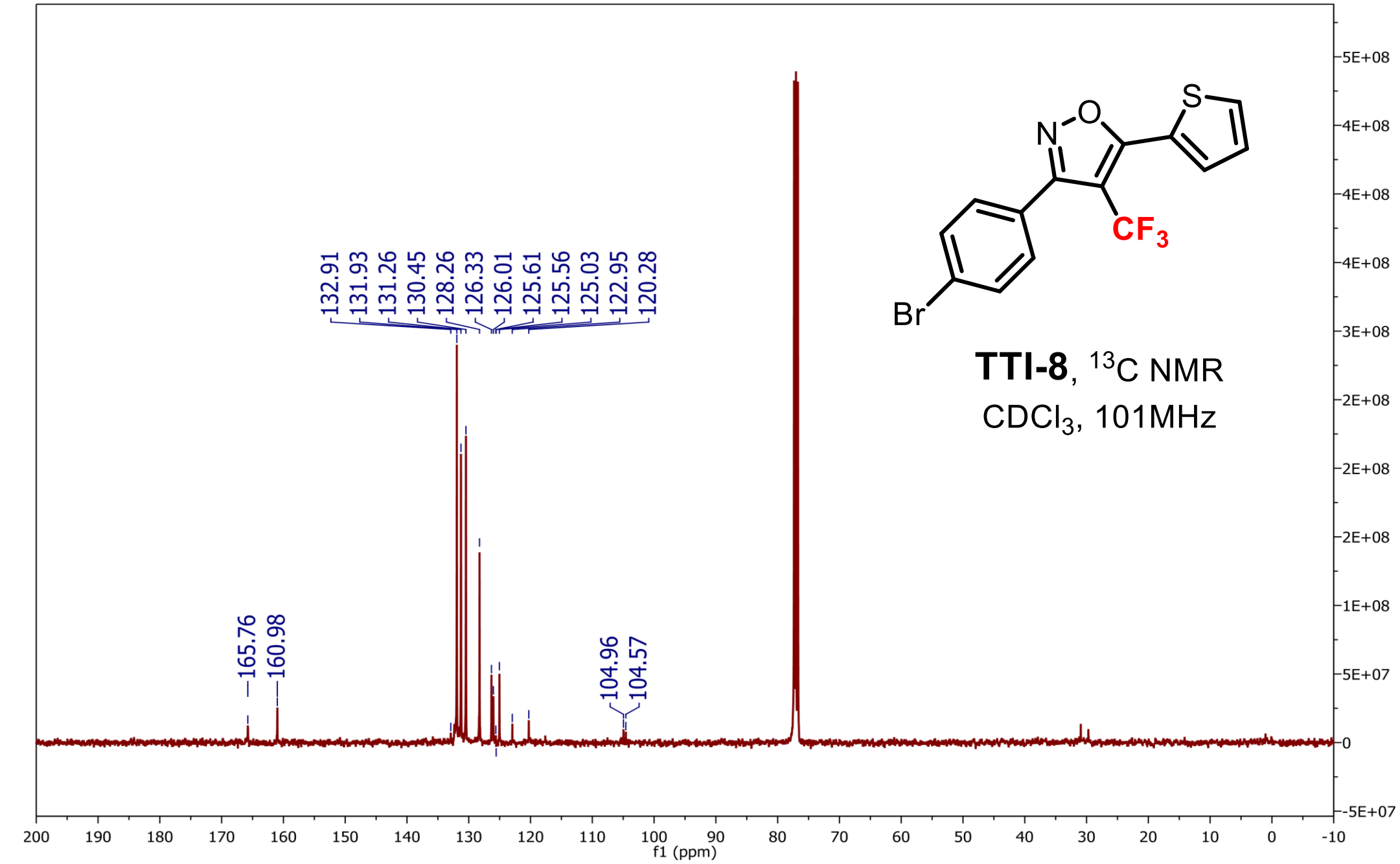
7.72
7.71
7.71
7.67
7.67
7.66
7.66
7.65
7.64
7.63
7.63
7.62
7.51
7.49
7.26
7.23
7.22
7.22
7.21
N
O
S
CF3
Br
TTI-8, 1H NMR
CDCl3, 400MHz
1.00
1.02
2.01
2.04
1.01
f1 (ppm)


-54.13
S
O
N
CF3
Br
TTI-8, 19F NMR
CDCl3, 377MHz
8E+08
7E+08
6E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


132.91
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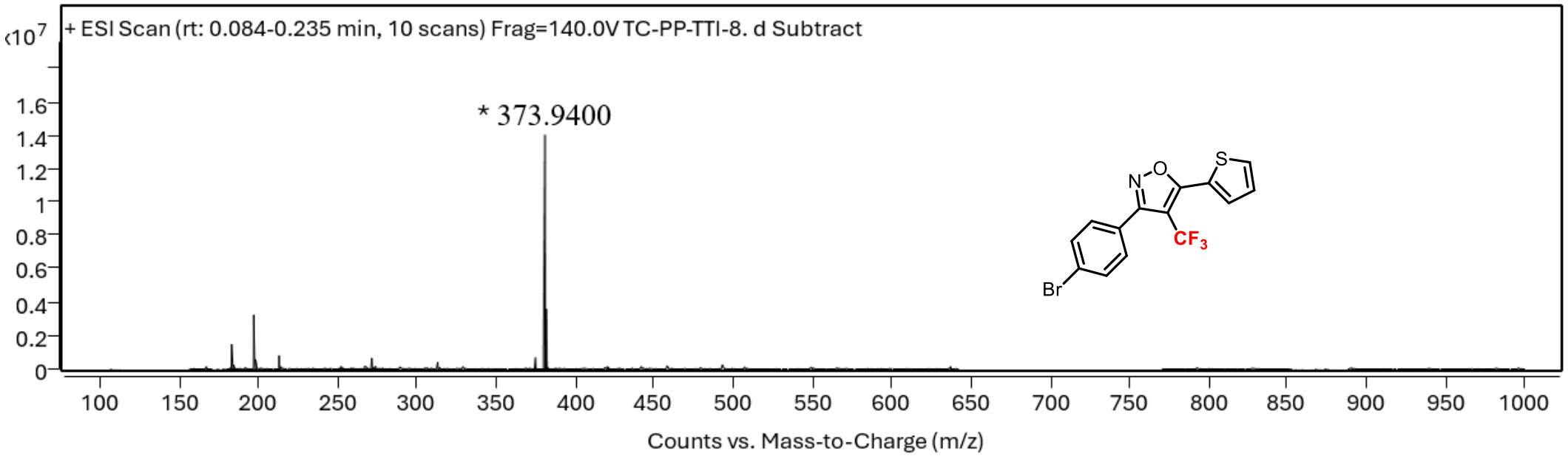
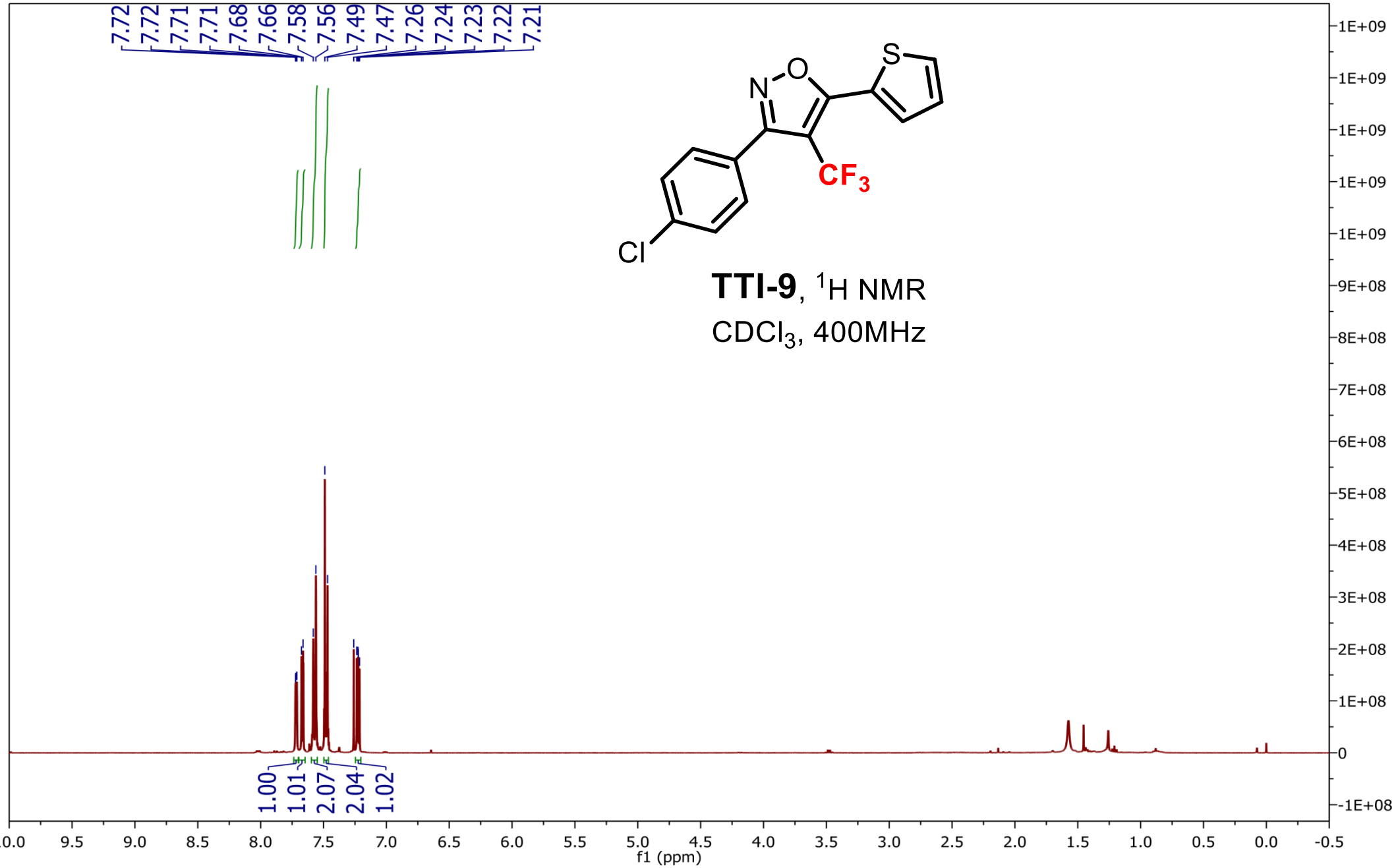
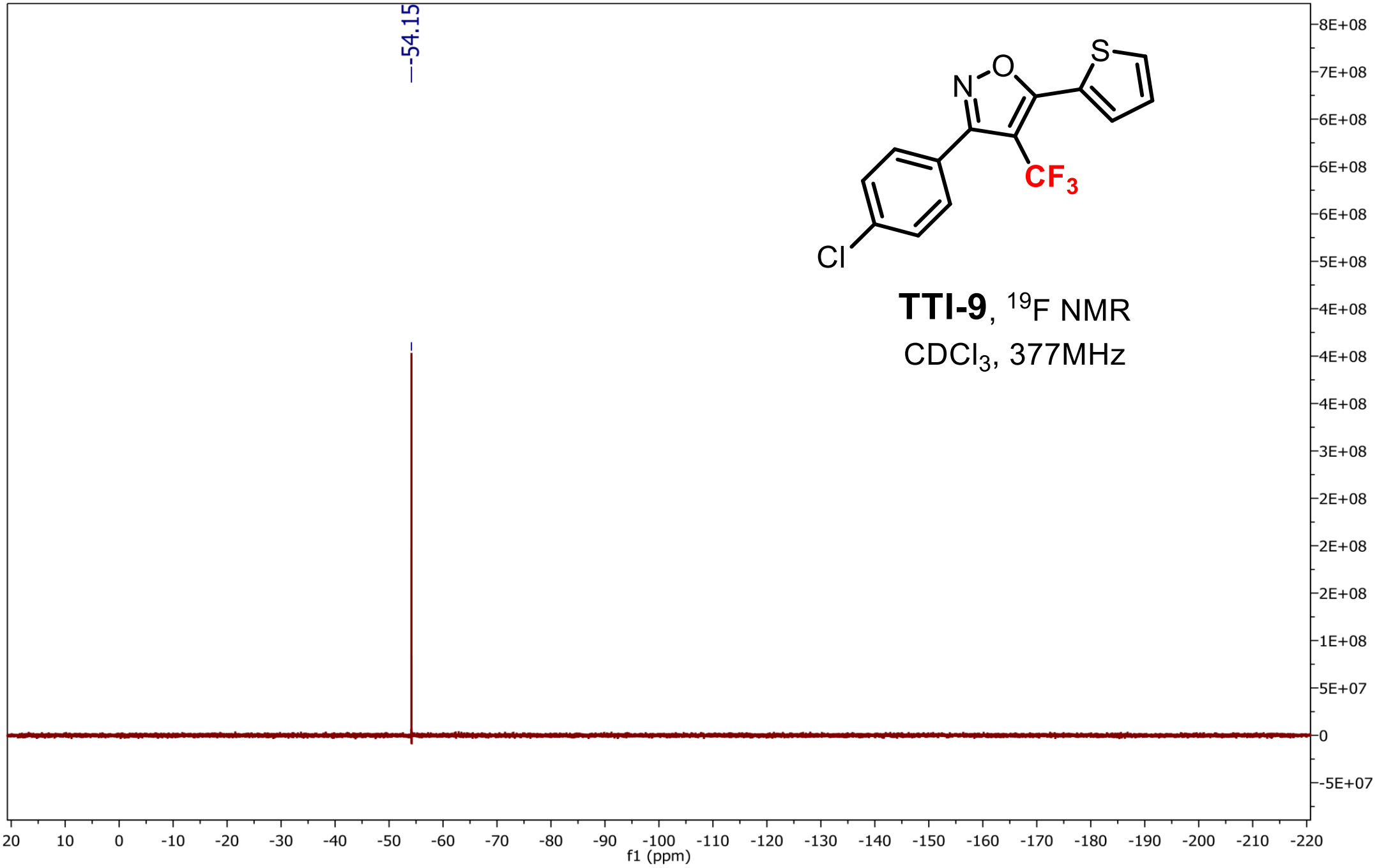
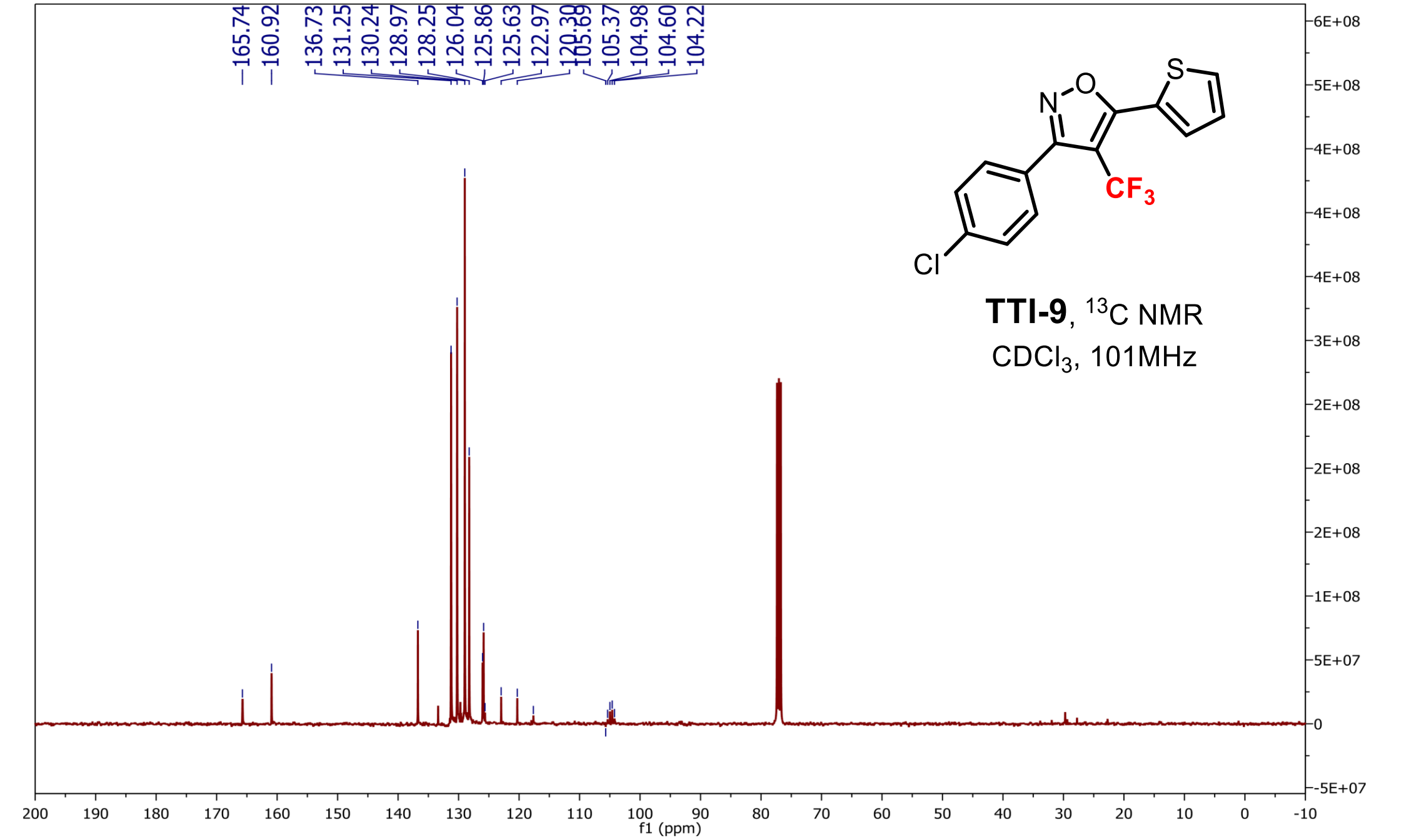
131.26
130.45
128.26
126.33
126.01
125.61
125.56
125.03
122.95
120.28
165.76
160.98
104.96
104.57
N
O
S
Br
CF3
TTI-8, 13C NMR
CDCl3, 101MHz
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report




7.72
7.72
7.71
7.71
7.68
7.66
7.58
7.56
7.49
7.47
7.26
7.24
7.23
7.22
7.21
N
O
S
CF3
Cl
TTI-9, 1H NMR
CDCl3, 400MHz
1.00
1.01
2.07
2.04
1.02
f1 (ppm)


-54.15
S
O
N
CF3
Cl
TTI-9, 19F NMR
CDCl3, 377MHz
8E+08
7E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)


165.74
160.92
136.73
131.25
130.24
128.97
128.25
126.04
125.86
125.63
122.97
120.30
105.89
105.37
104.98
104.60
104.22
O
N
S
CF3
Cl
TTI-9, 13C NMR
CDCl3, 101MHz
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

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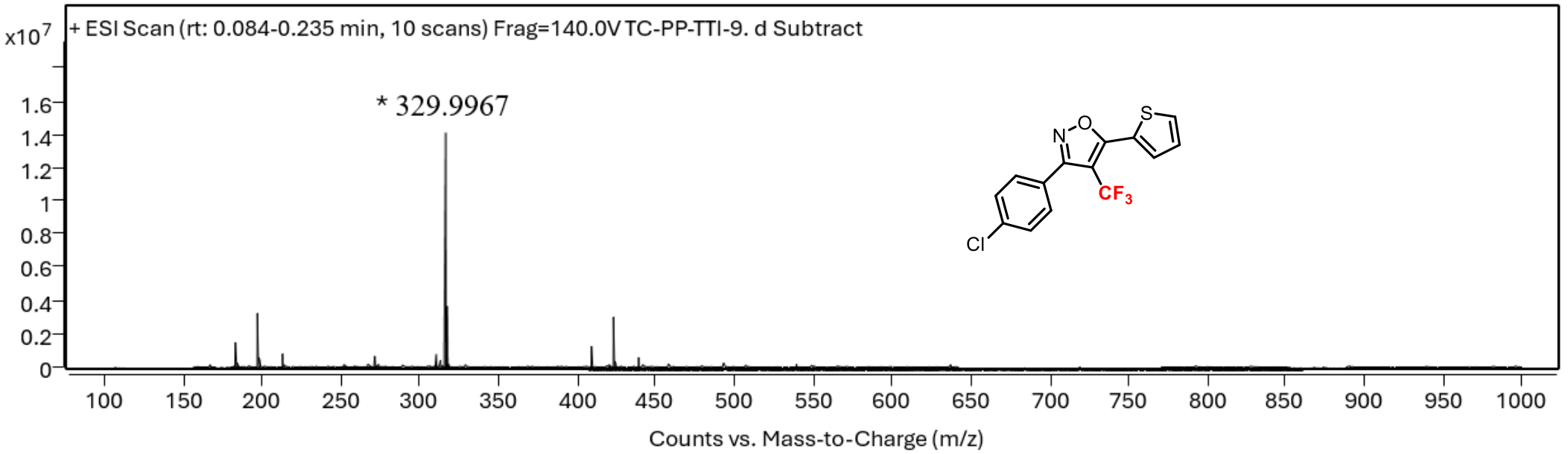
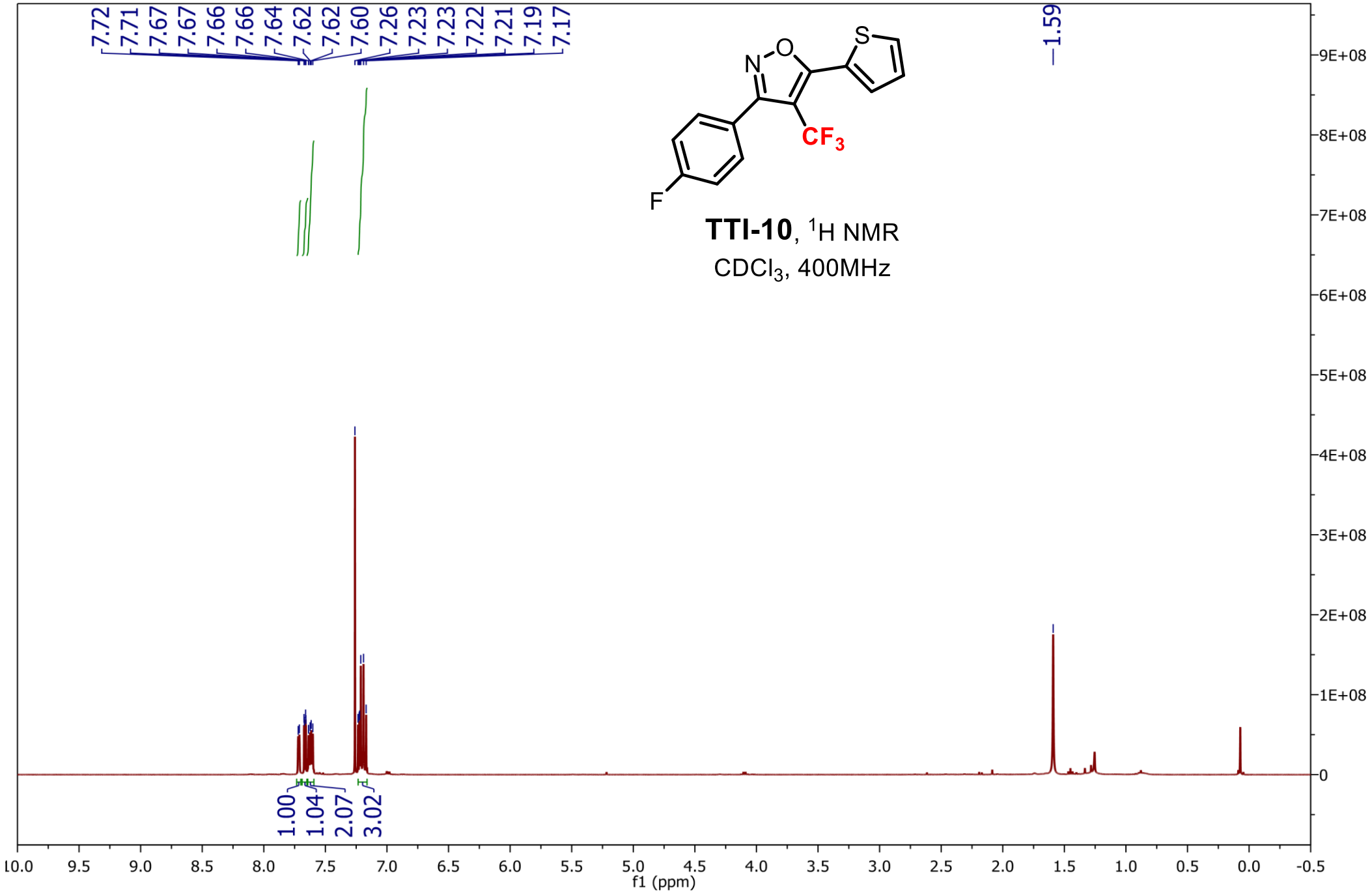
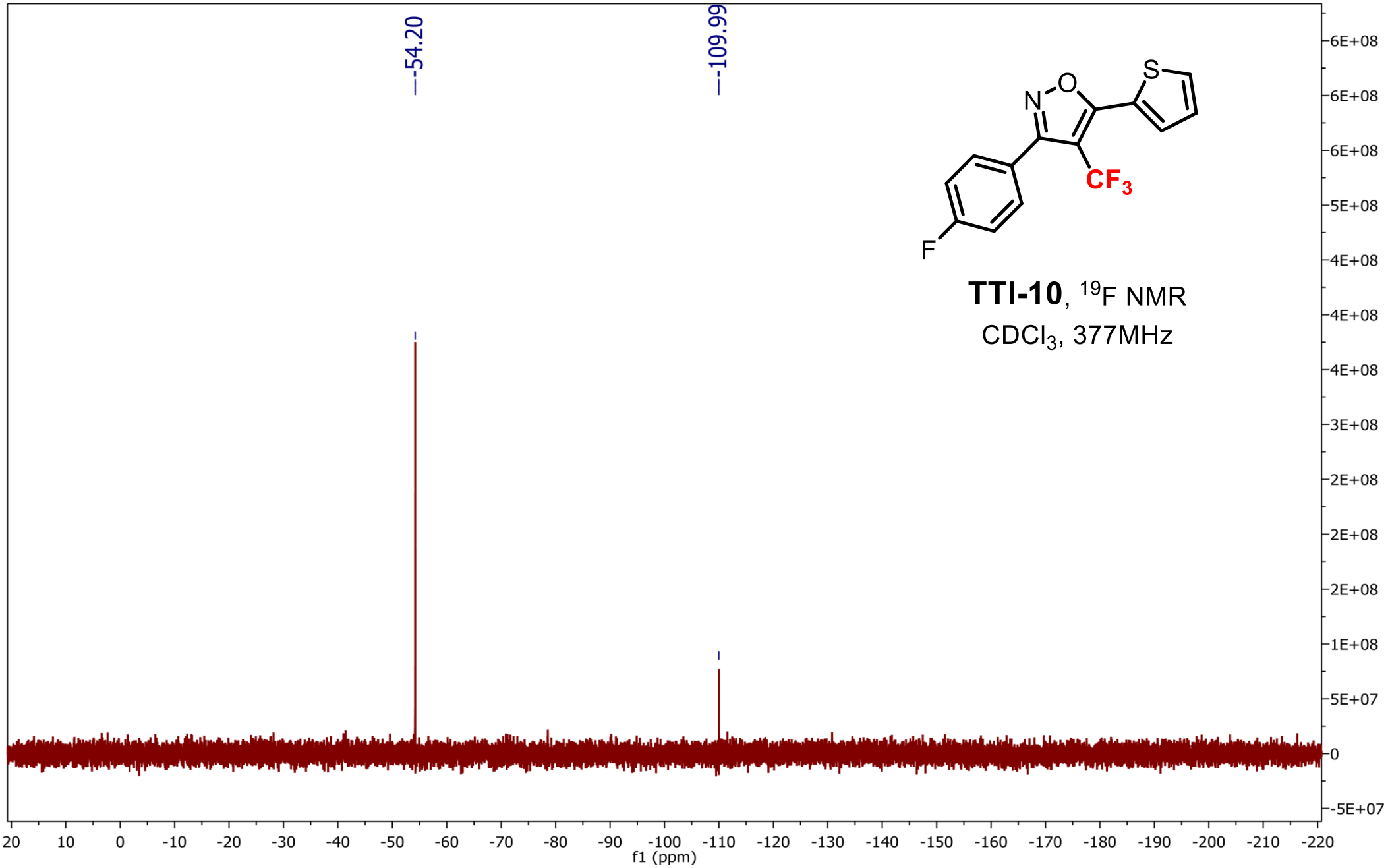
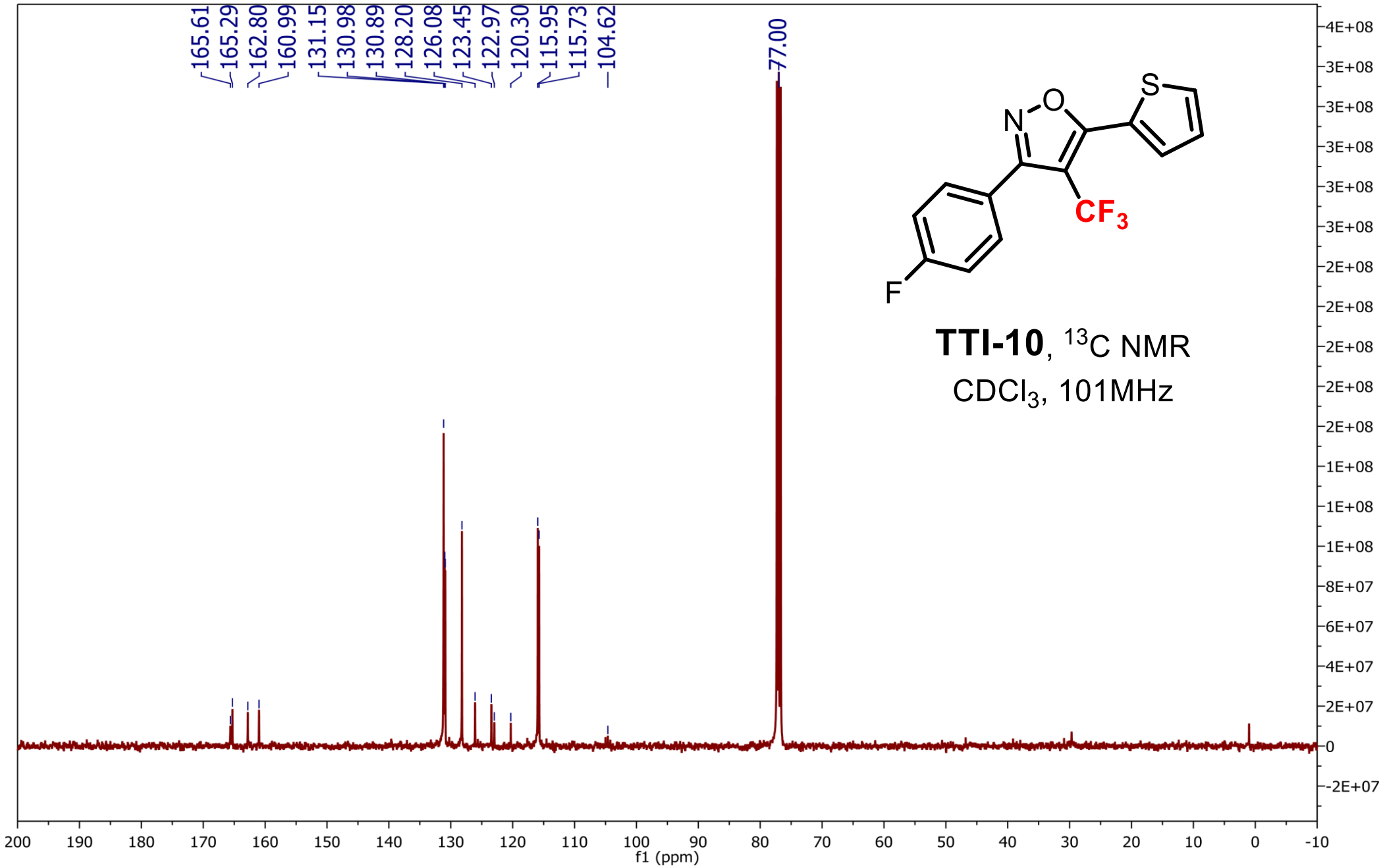
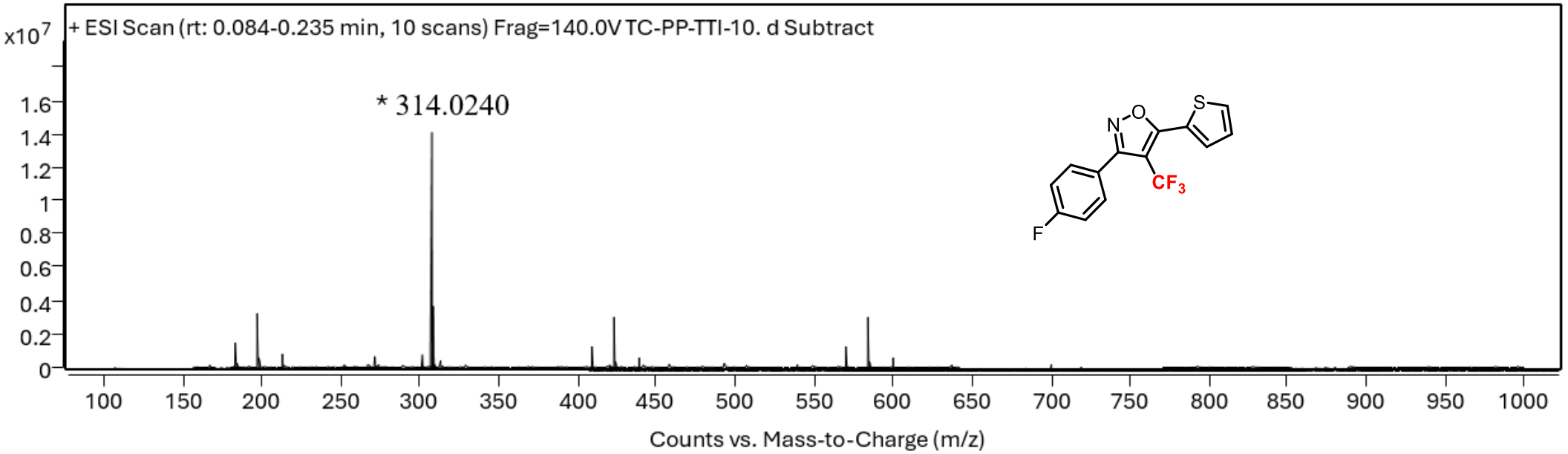


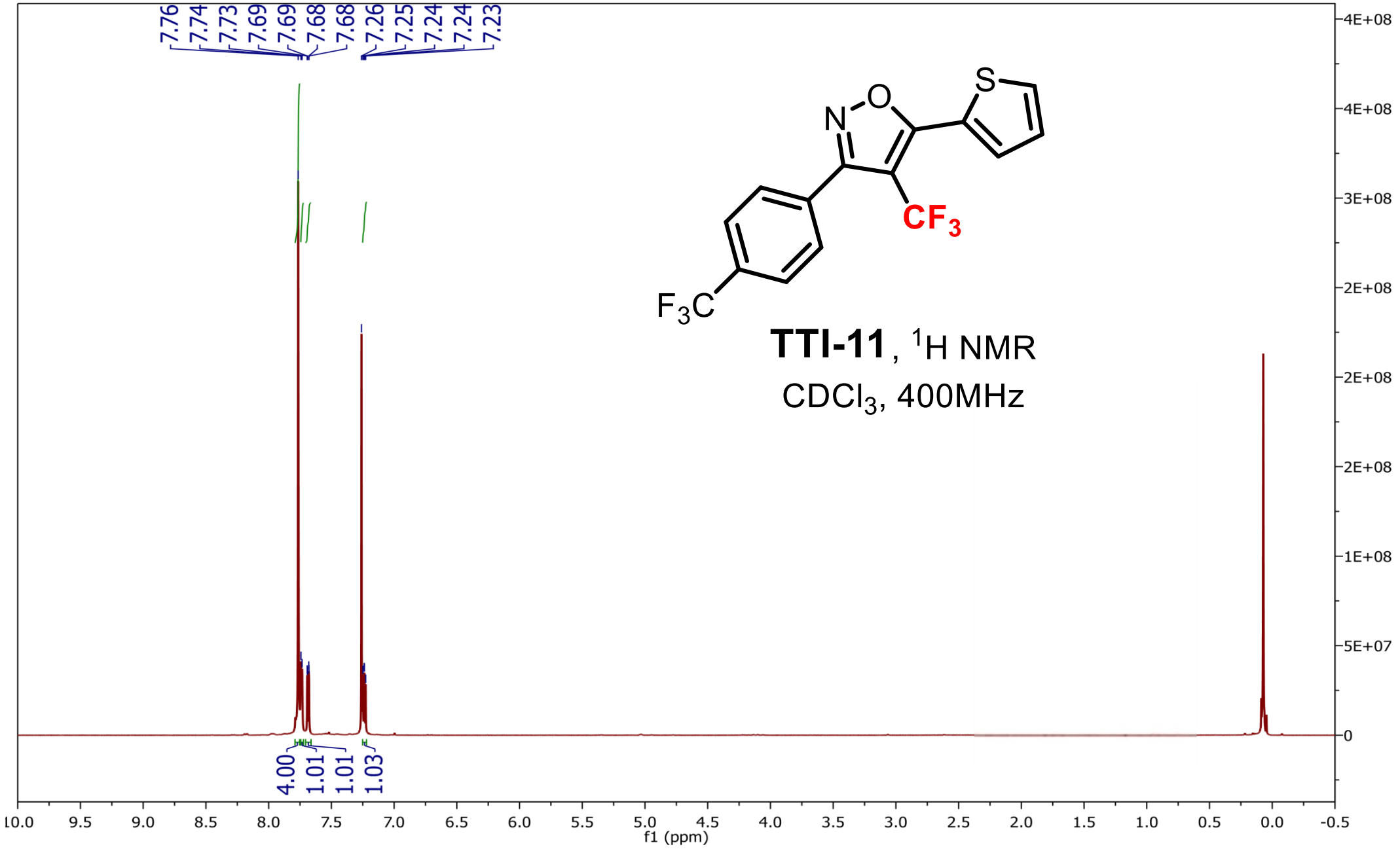

7.72
7.71
7.67
7.67
7.66
7.66
7.64
7.62
7.62
7.60
7.26
7.23
7.23
7.22
7.21
7.19
7.17
1.59
N
O
S
F
CF3
TTI-10, 1H NMR
CDCl3, 400MHz
1.00
1.04
2.07
3.02
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

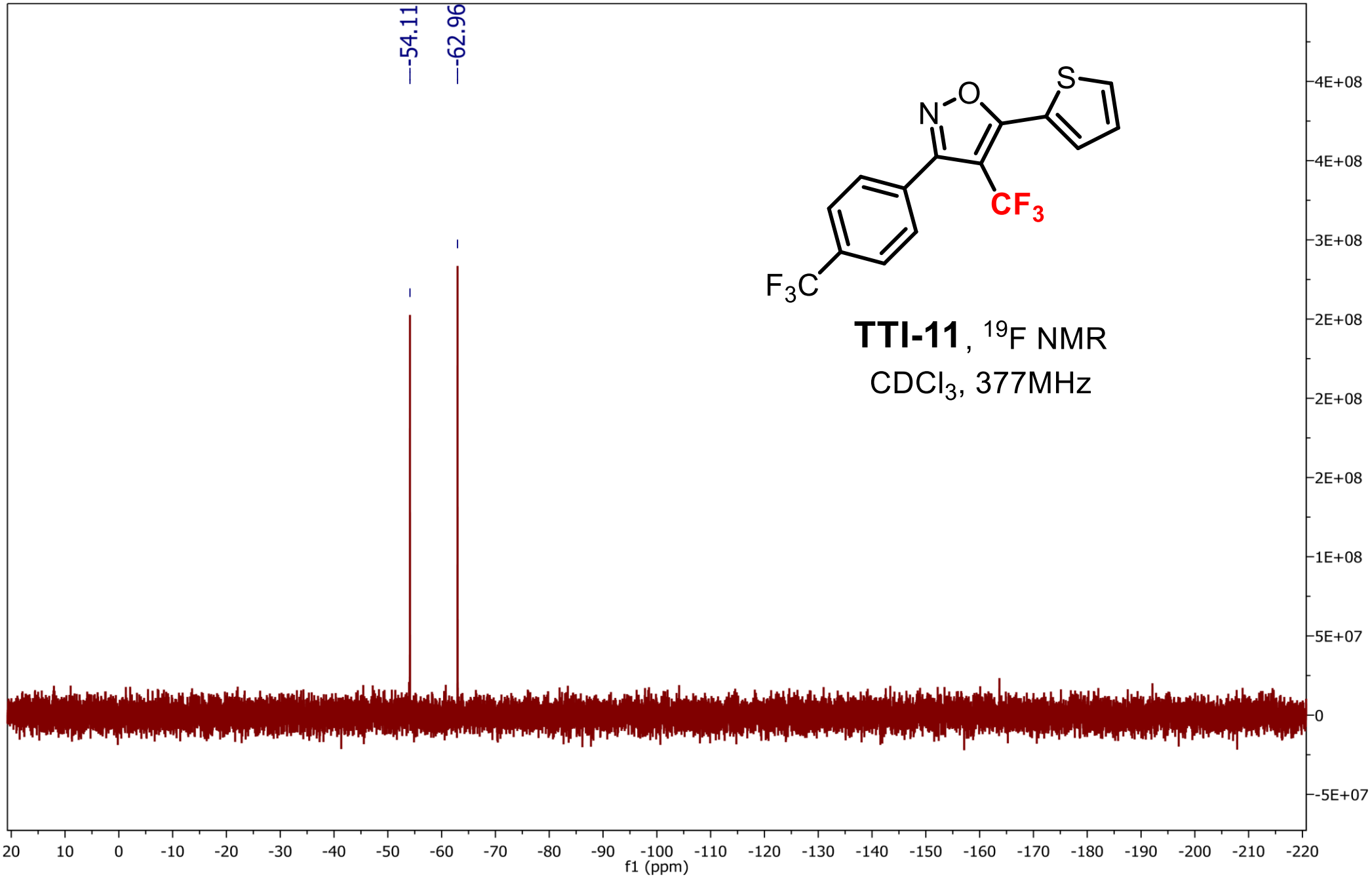

-54.20
-109.99
S
O
N
CF3
F
TTI-10, 19F NMR
CDCl3, 377MHz
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

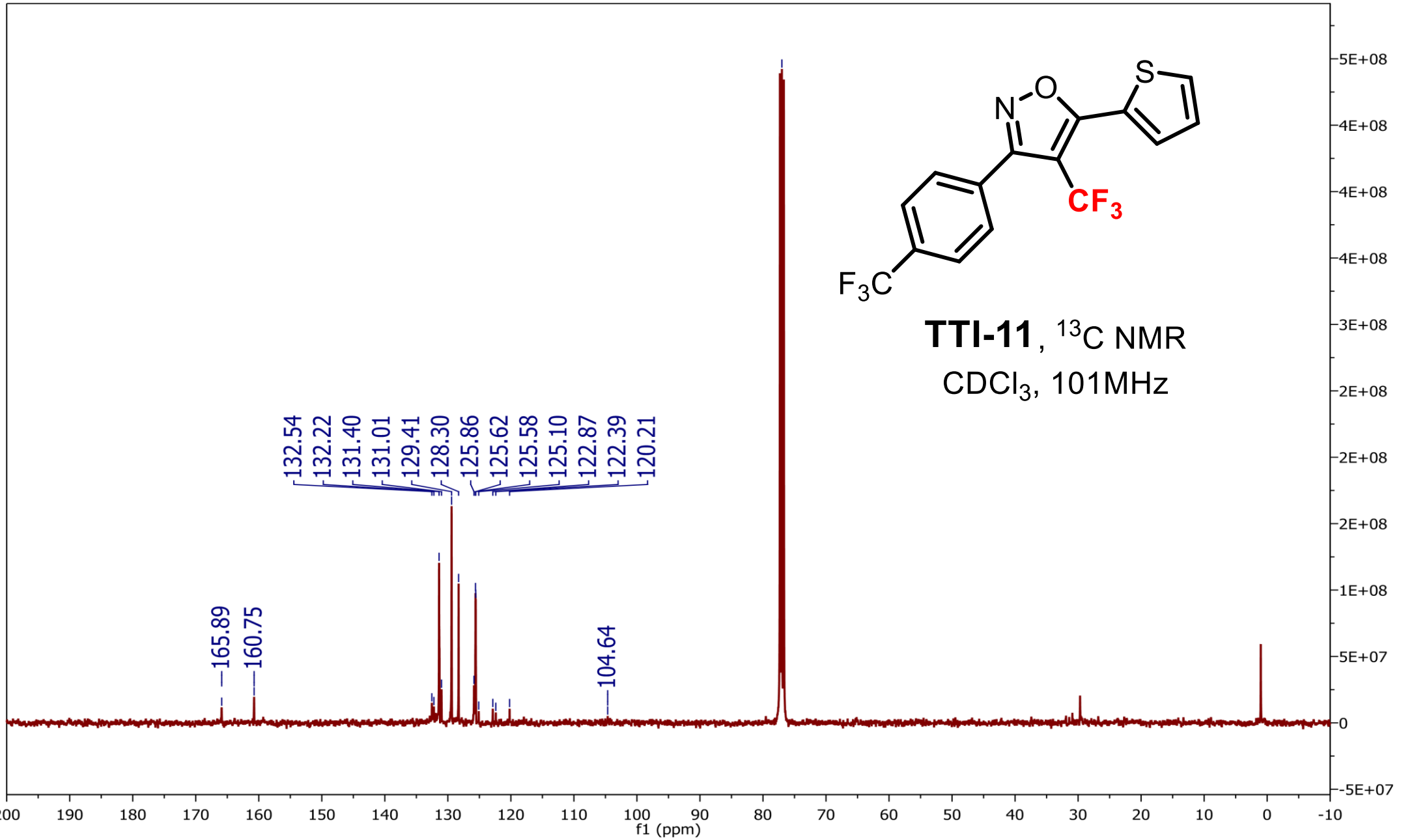

165.61
165.29
162.80
160.99
131.15
130.98
130.89
128.20
126.08
123.45
122.97
120.30
115.95
115.73
104.62
77.00
S
O
N
CF3
F
TTI-10, 13C NMR
CDCl3, 101MHz
4E+08
3E+08
2E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

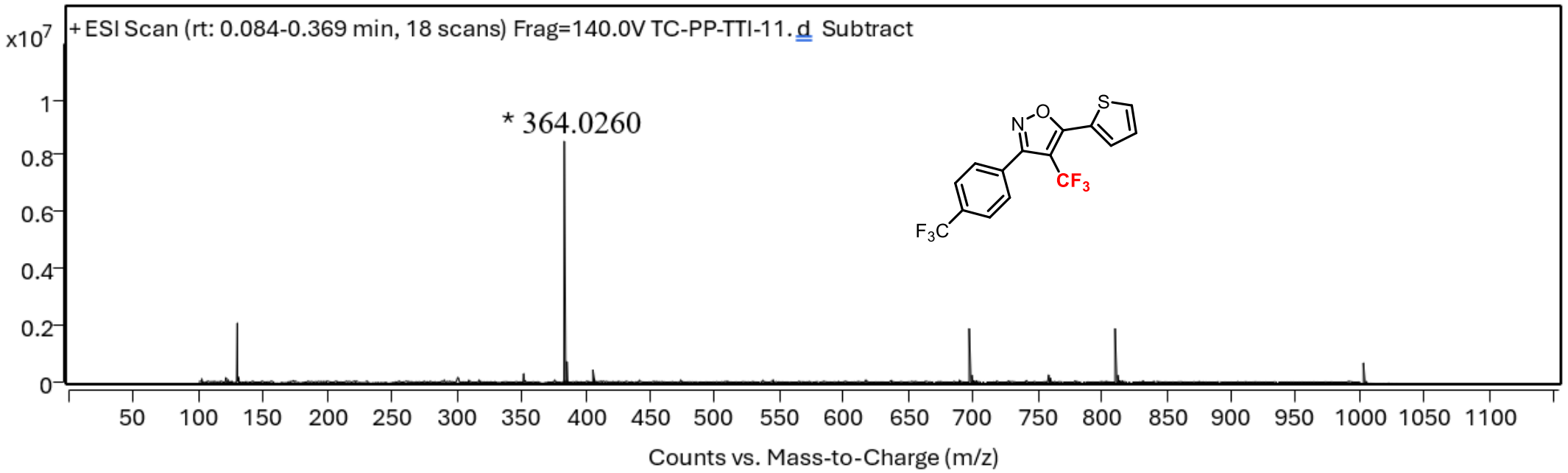


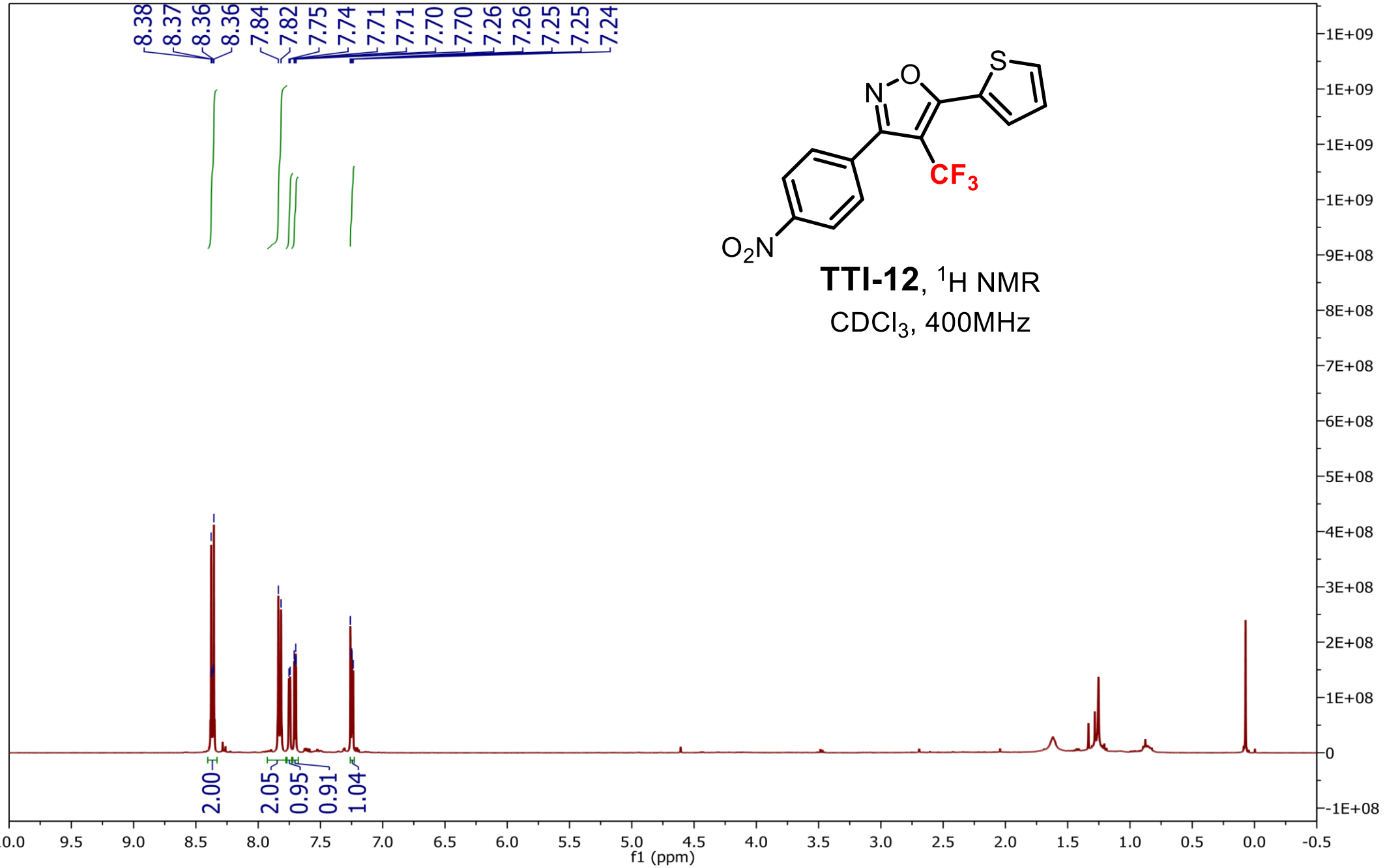

7.76
7.74
7.73
7.69
7.69
7.68
7.68
7.26
7.25
7.24
7.24
7.23
4.00
1.01
1.01
1.03
f1 (ppm)
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
N
O
S
CF3
F3C
TTI-11, 1H NMR
CDCl3, 400MHz

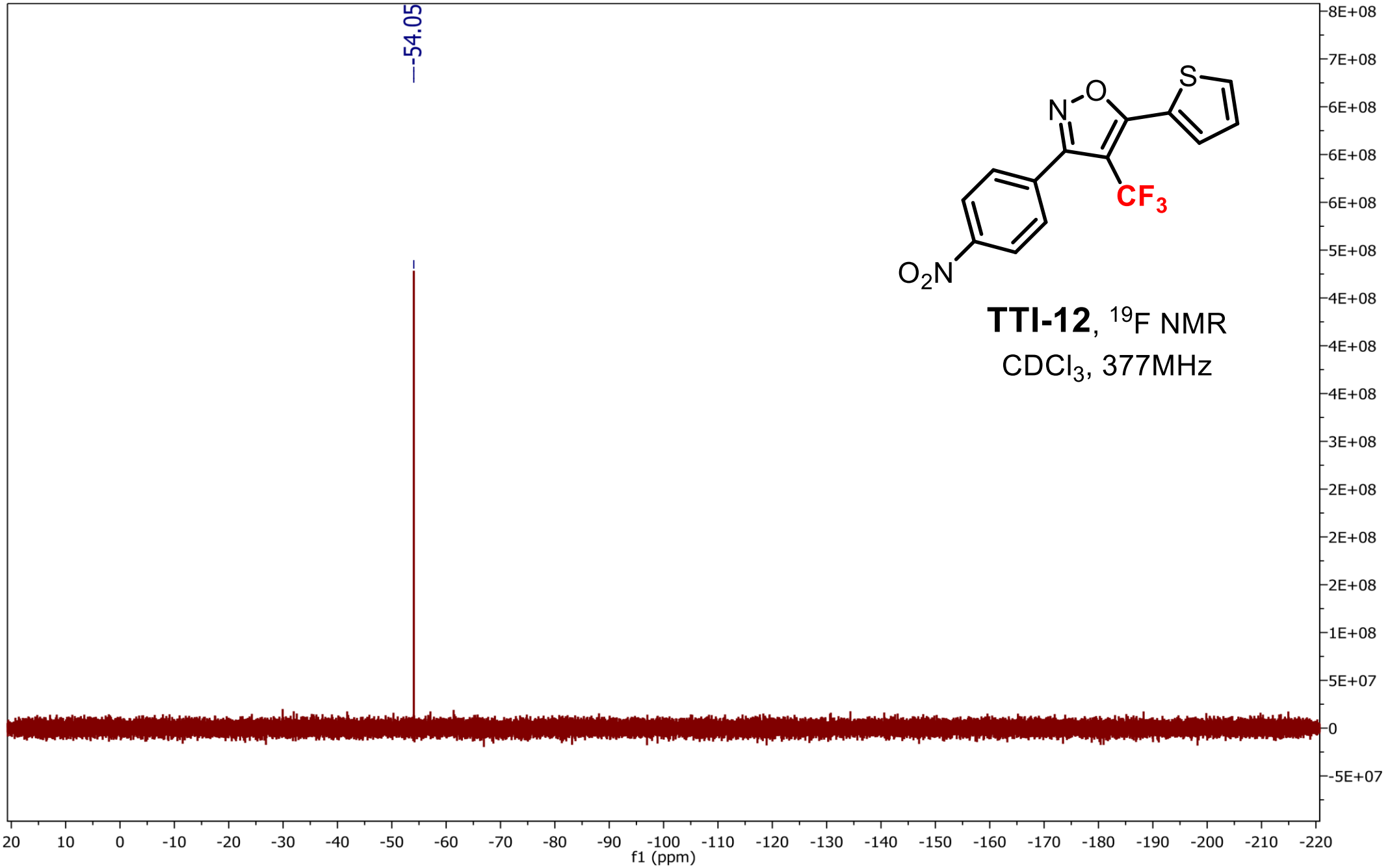

-54.11
-62.96
S
O
N
CF3
F3C
TTI-11, 19F NMR
CDCl3, 377MHz
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

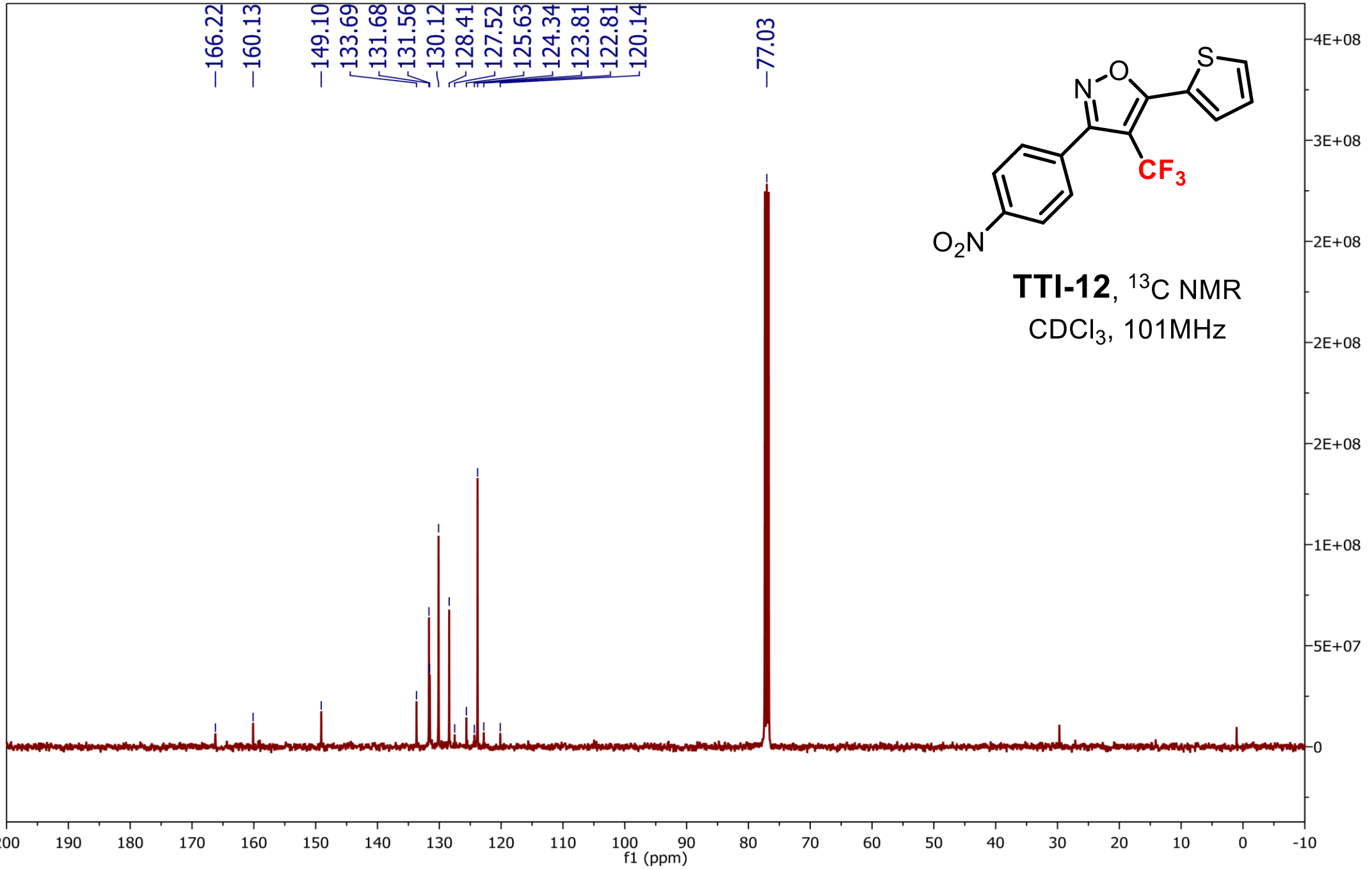

TTI-11, 13C NMR
CDCl3, 101MHz
F3C
CF3
N
O
S
132.54
132.22
131.40
131.01
129.41
128.30
125.86
125.62
125.58
125.10
122.87
122.39
120.21
165.89
160.75
104.64
f1 (ppm)

Spectrum Plot Report

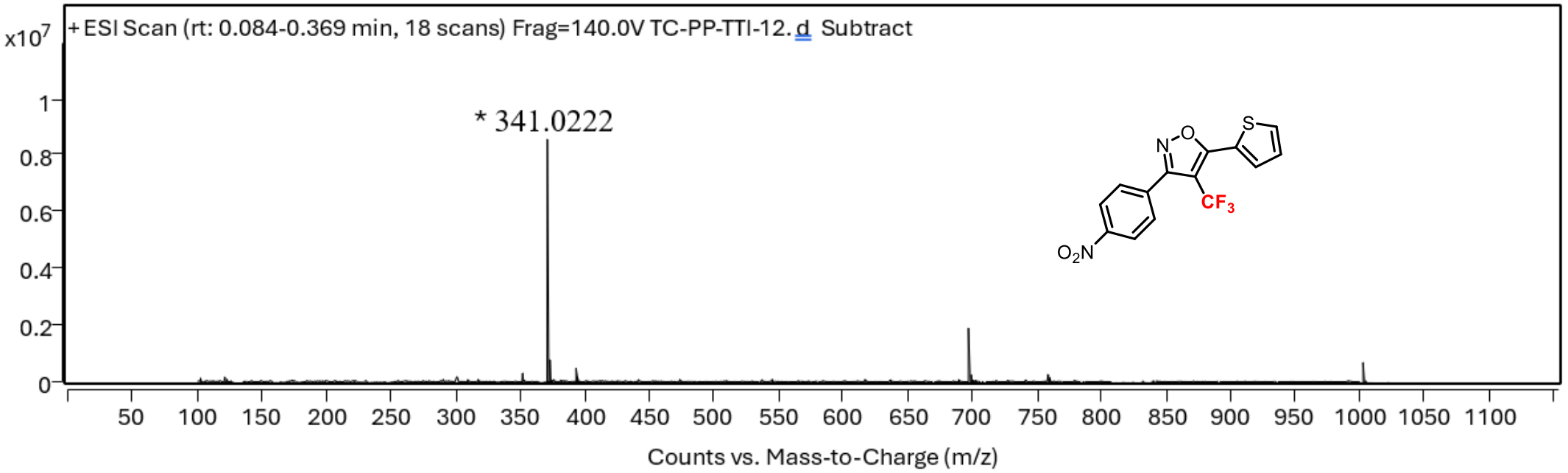


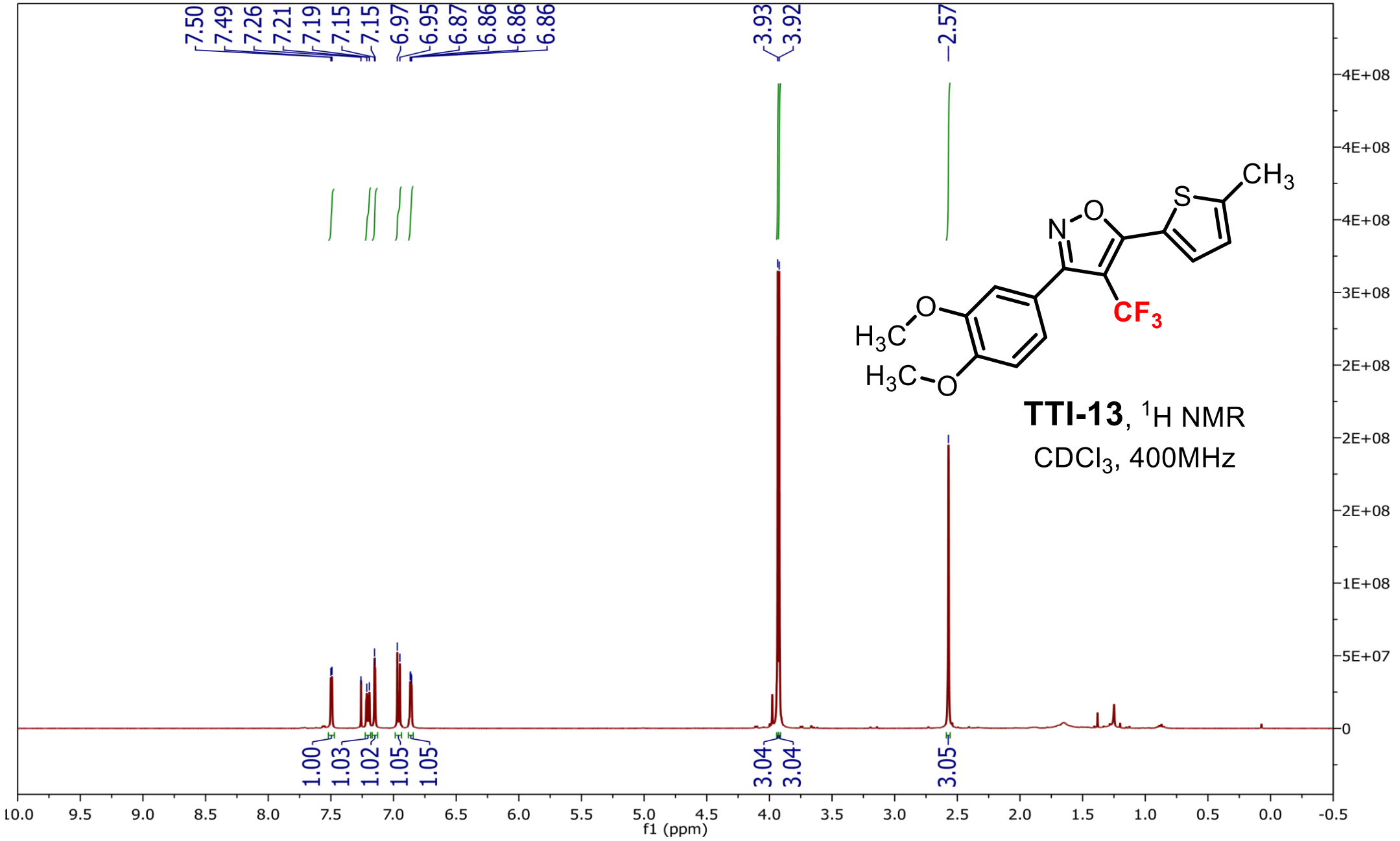

8.38
8.37
8.36
8.36
7.84
7.82
7.75
7.74
7.71
7.71
7.70
7.70
7.26
7.26
7.25
7.25
7.24
S
O
N
CF3
O2N
TTI-12, 1H NMR
CDCl3, 400MHz
2.00
2.05
0.95
0.91
1.04
f1 (ppm)

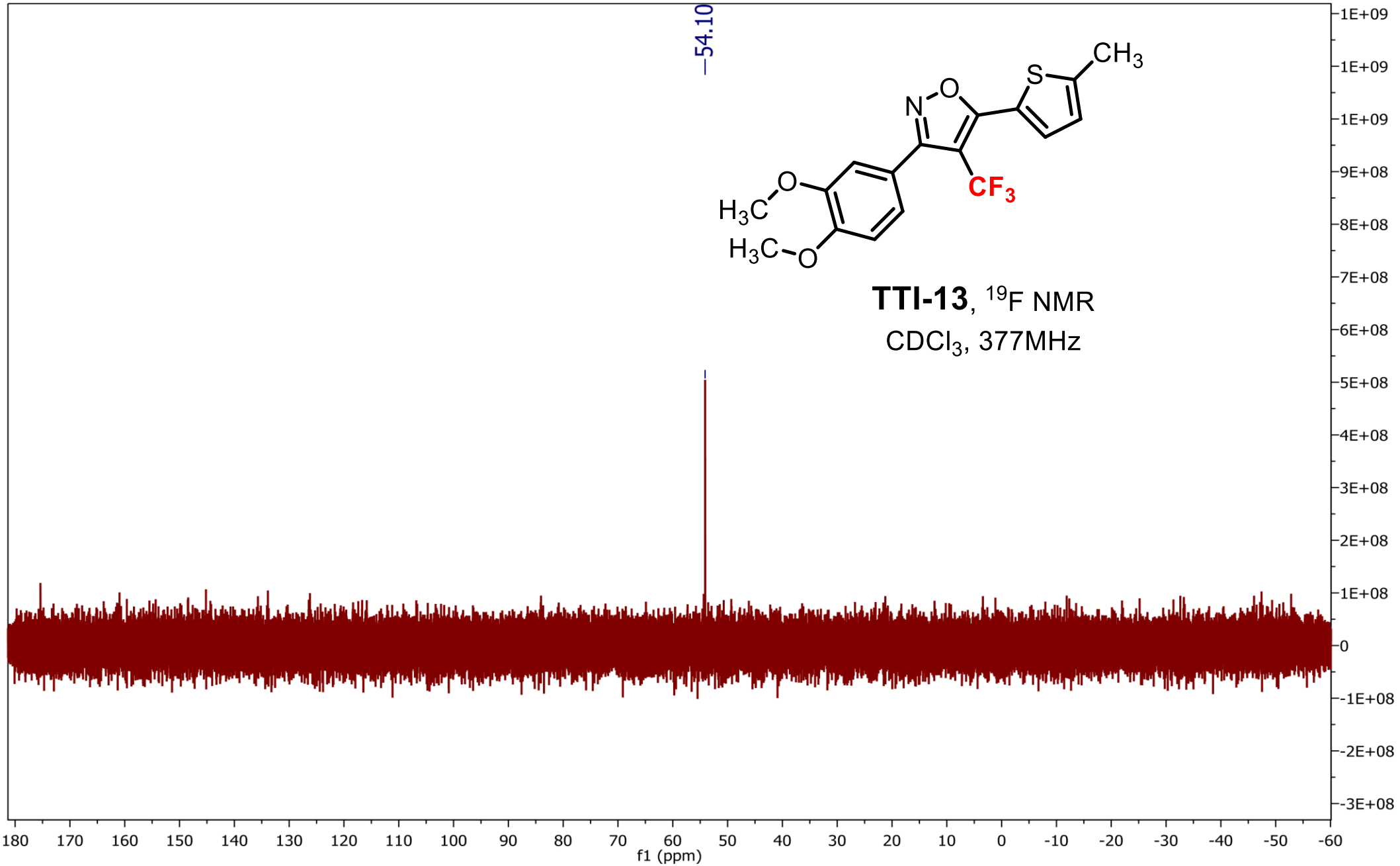

-54.05
S
N
O
CF3
O2N
TTI-12, 19F NMR
CDCl3, 377MHz
8E+08
7E+08
6E+08
6E+08
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

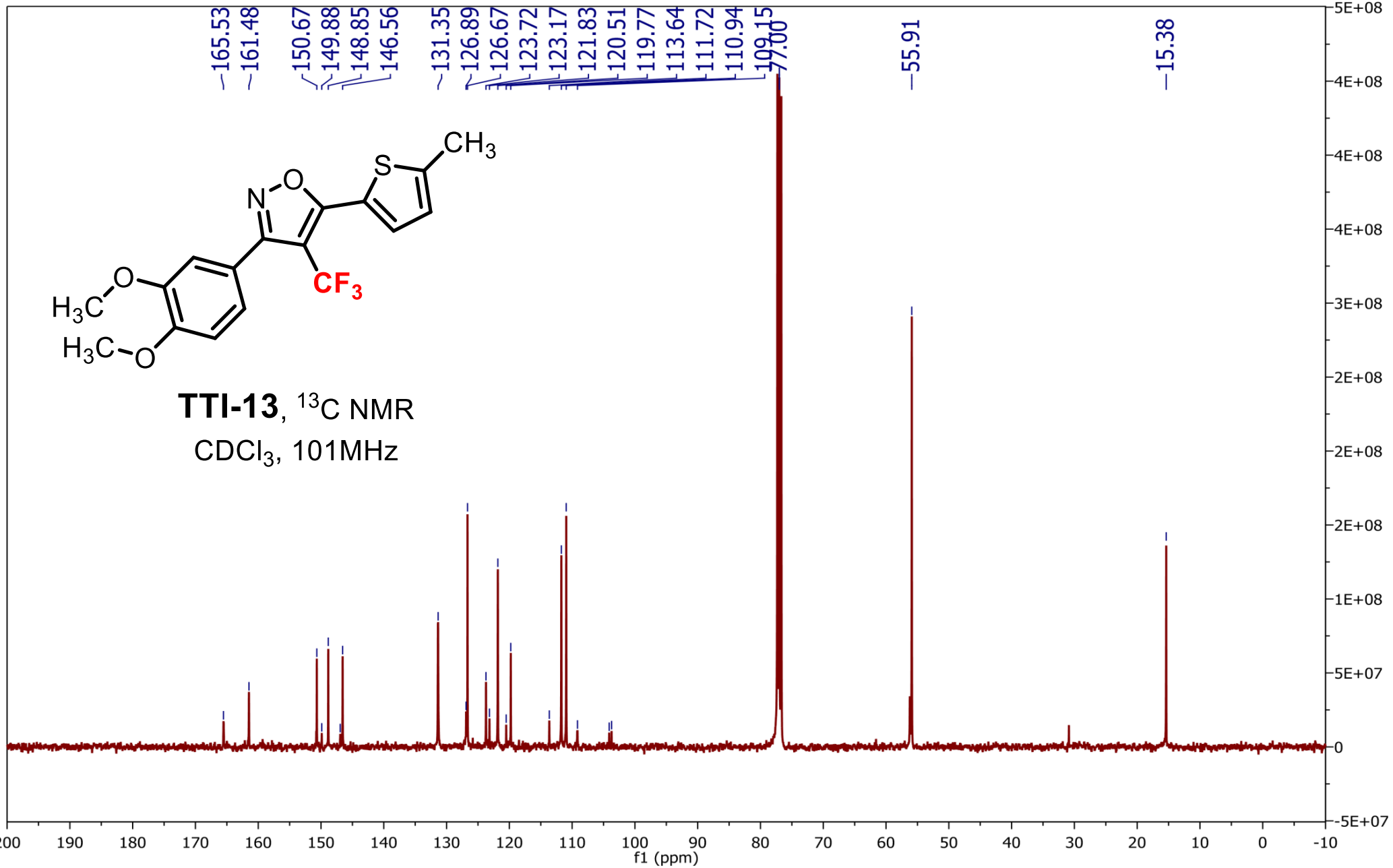

166.22
160.13
149.10
133.69
131.68
131.56
130.12
128.41
127.52
125.63
124.34
123.81
122.81
120.14
77.03
O
N
S
CF3
O2N
TTI-12, 13C NMR
CDCl3, 101MHz
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Spectrum Plot Report




7.50
7.49
7.26
7.21
7.19
7.15
7.15
6.97
6.95
6.87
6.86
6.86
6.86
3.93
3.92
2.57
1.00
1.03
1.02
1.05
1.05
3.04
3.04
3.05
f1 (ppm)
4E+08
3E+08
2E+08
1E+08
5E+07
0
CH3
S
N
O
CF3
H3C
O
H3C
O
TTI-13, 1H NMR
CDCl3, 400MHz


-54.10
CH3
S
N
O
CF3
H3C
O
H3C
O
TTI-13, 19F NMR
CDCl3, 377MHz
1E+09
1E+09
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
-2E+08
-3E+08
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60
f1 (ppm)


165.53
161.48
150.67
149.88
148.85
146.56
131.35
126.89
126.67
123.72
123.17
121.83
120.51
119.77
113.64
111.72
110.94
109.15
77.00
55.91
15.38
CH3
S
N
O
CF3
H3C
O
H3C
O
TTI-13, 13C NMR
CDCl3, 101MHz
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report

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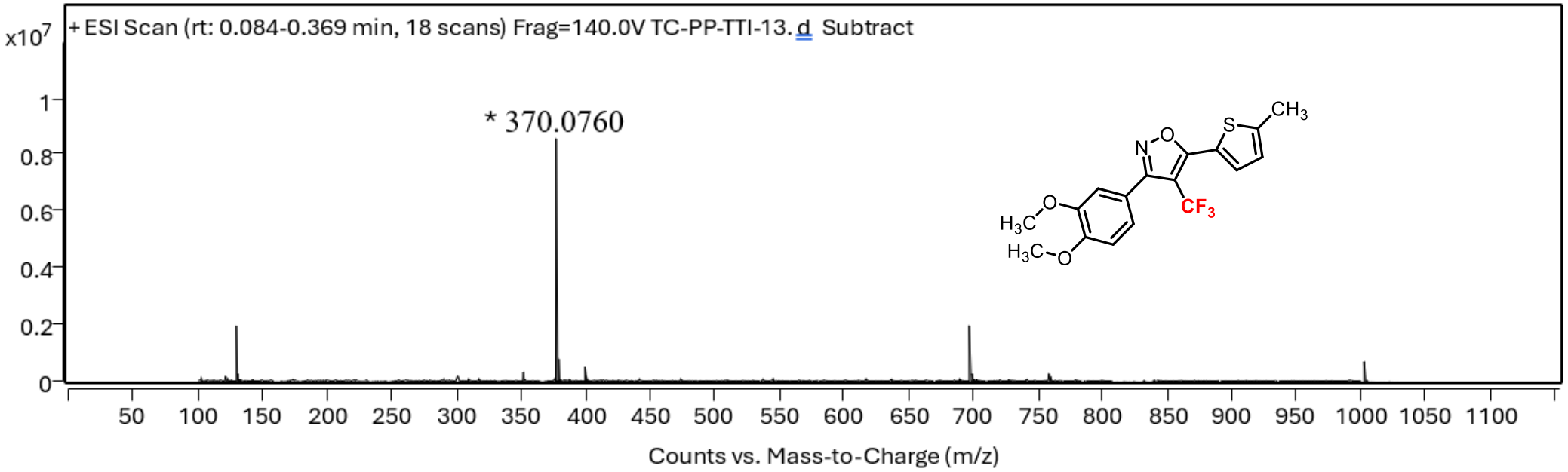
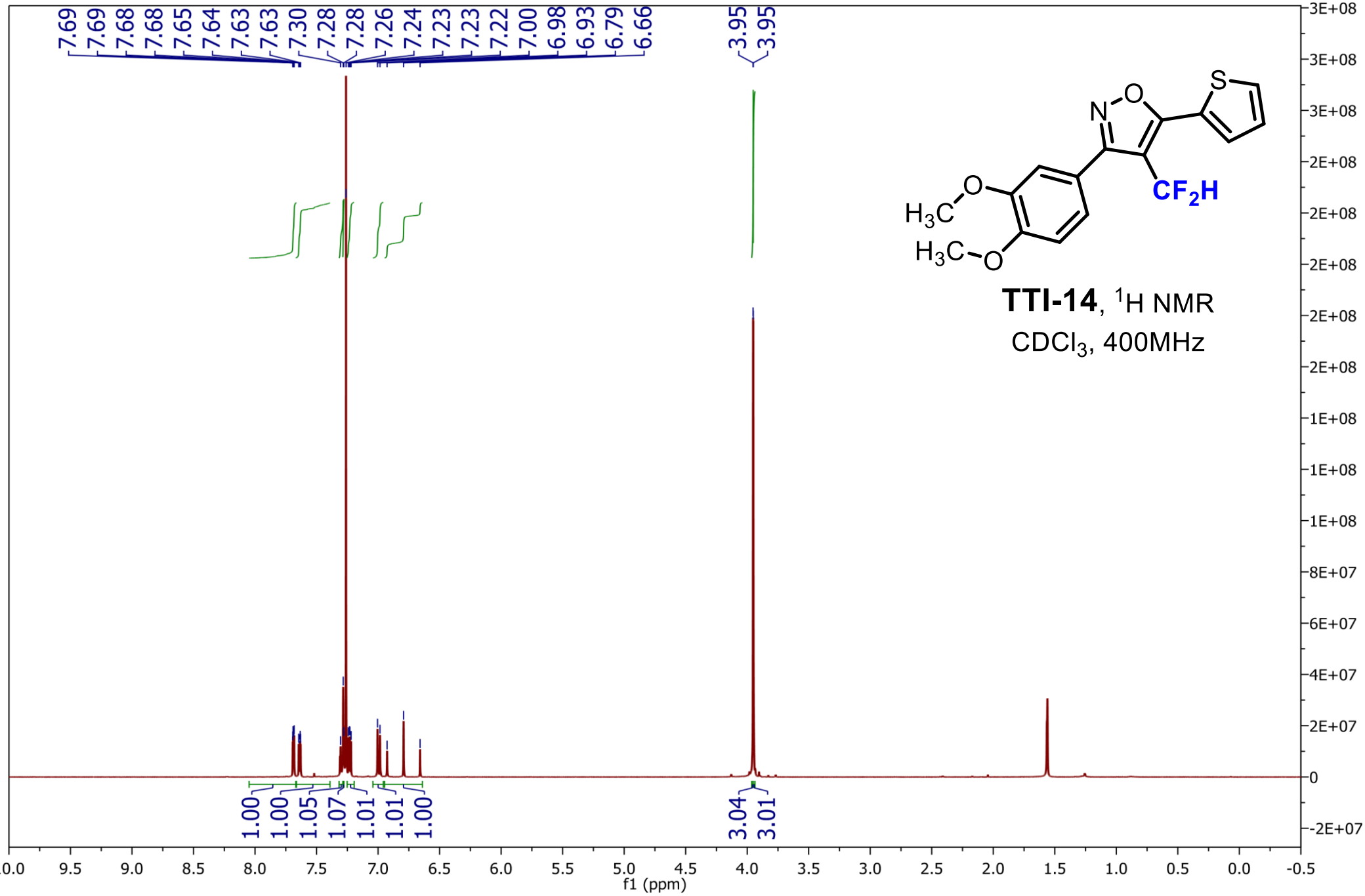
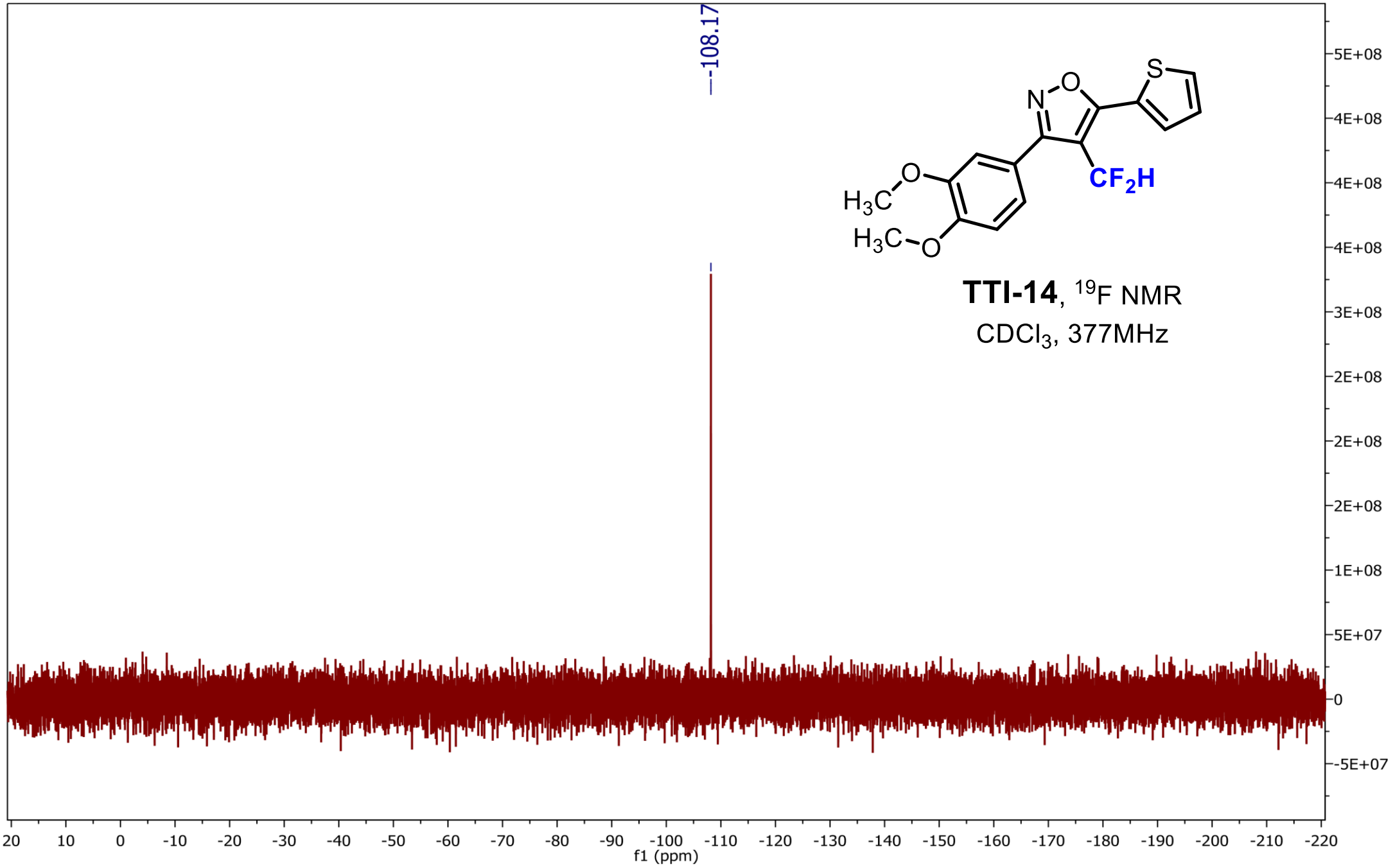
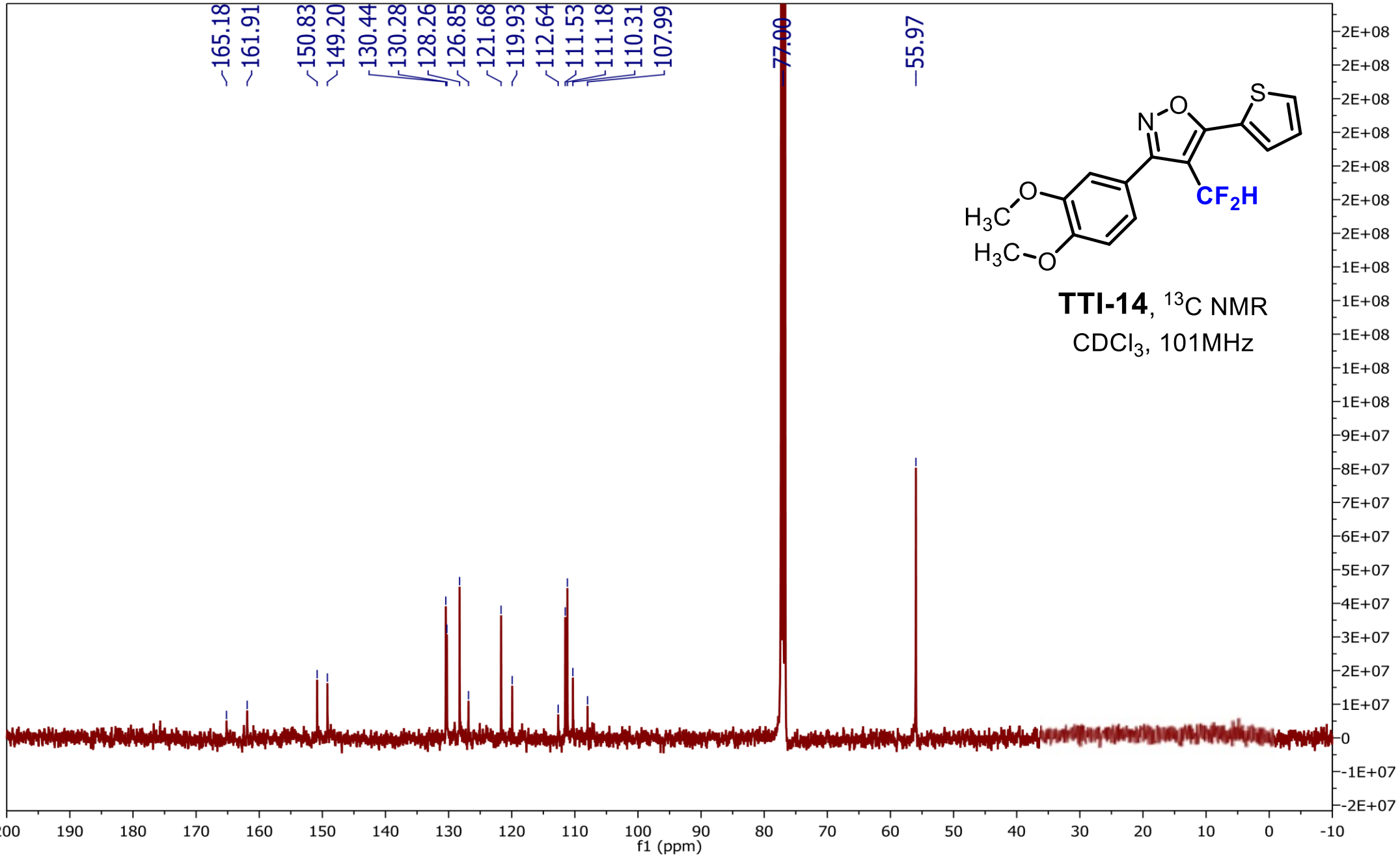
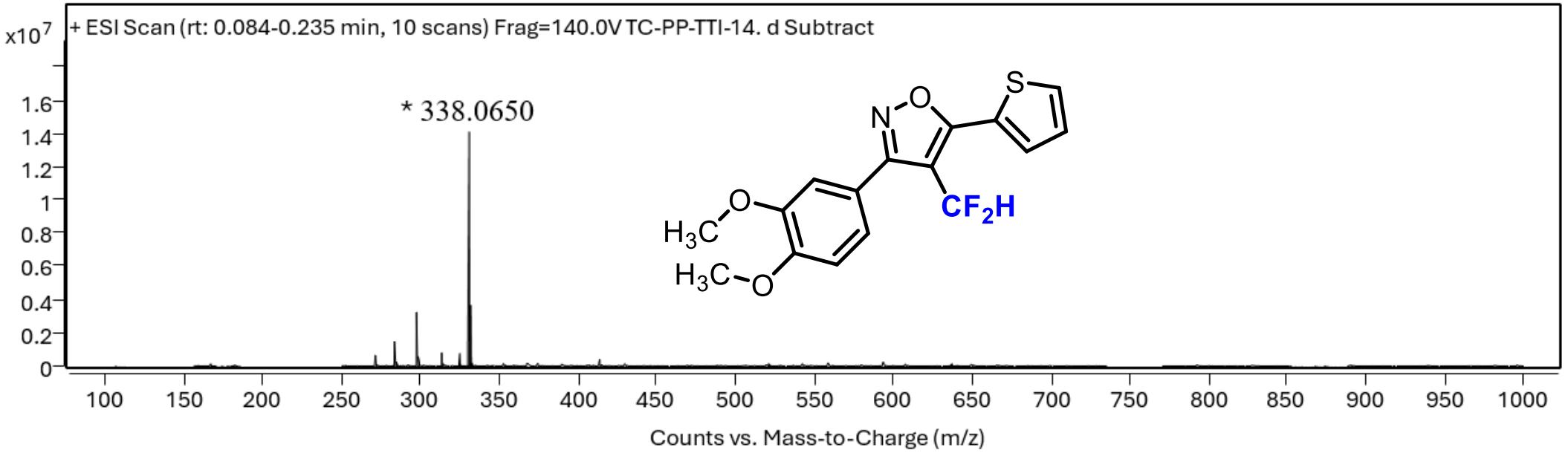


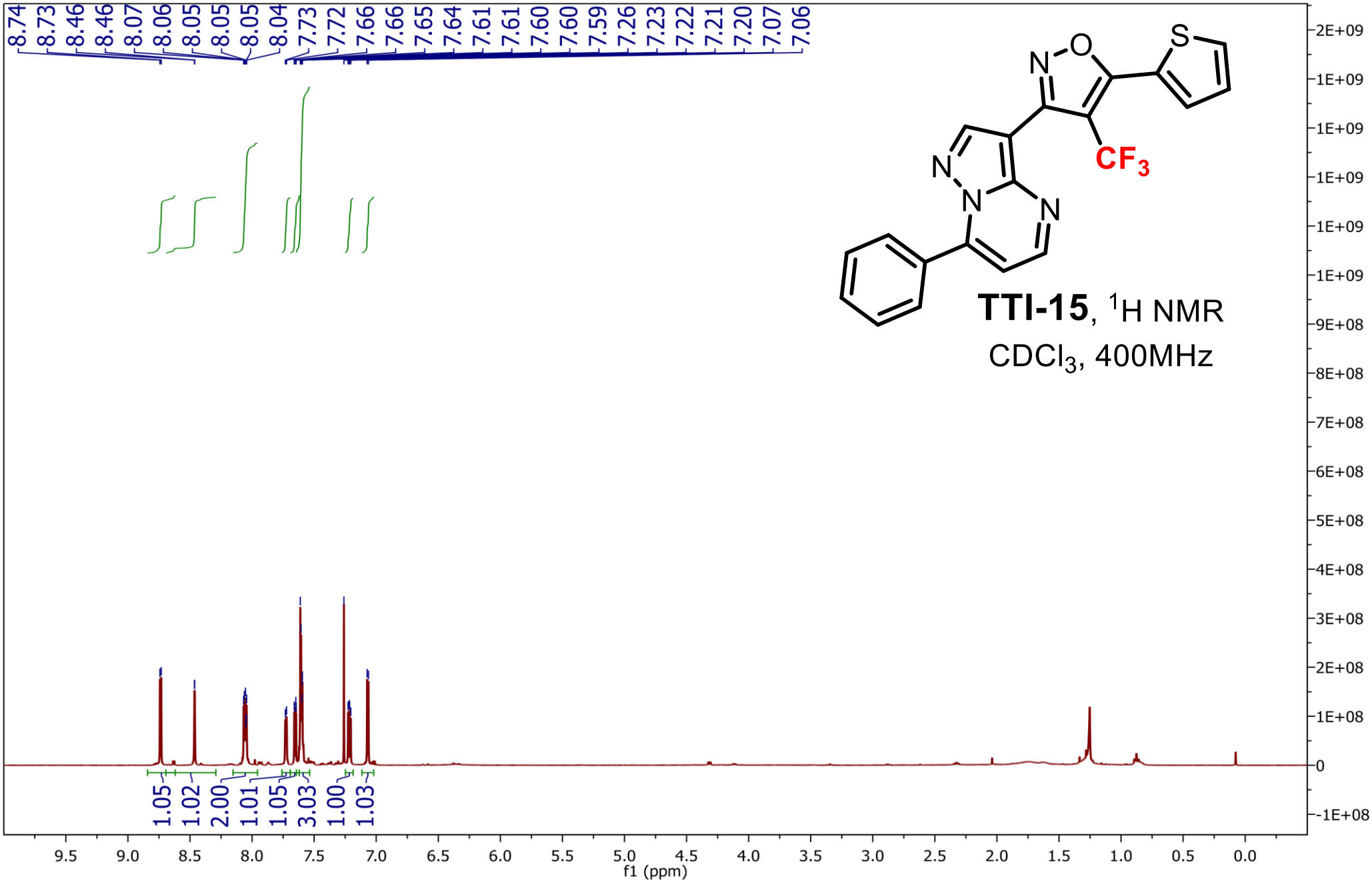

7.69
7.69
7.68
7.68
7.65
7.64
7.63
7.63
7.30
7.28
7.28
7.26
7.24
7.23
7.23
7.22
7.00
6.98
6.93
6.79
6.66
3.95
3.95
1.00
1.00
1.05
1.07
1.01
1.01
1.00
3.04
3.01
f1 (ppm)
TTI-14, 1H NMR
CDCl3, 400MHz

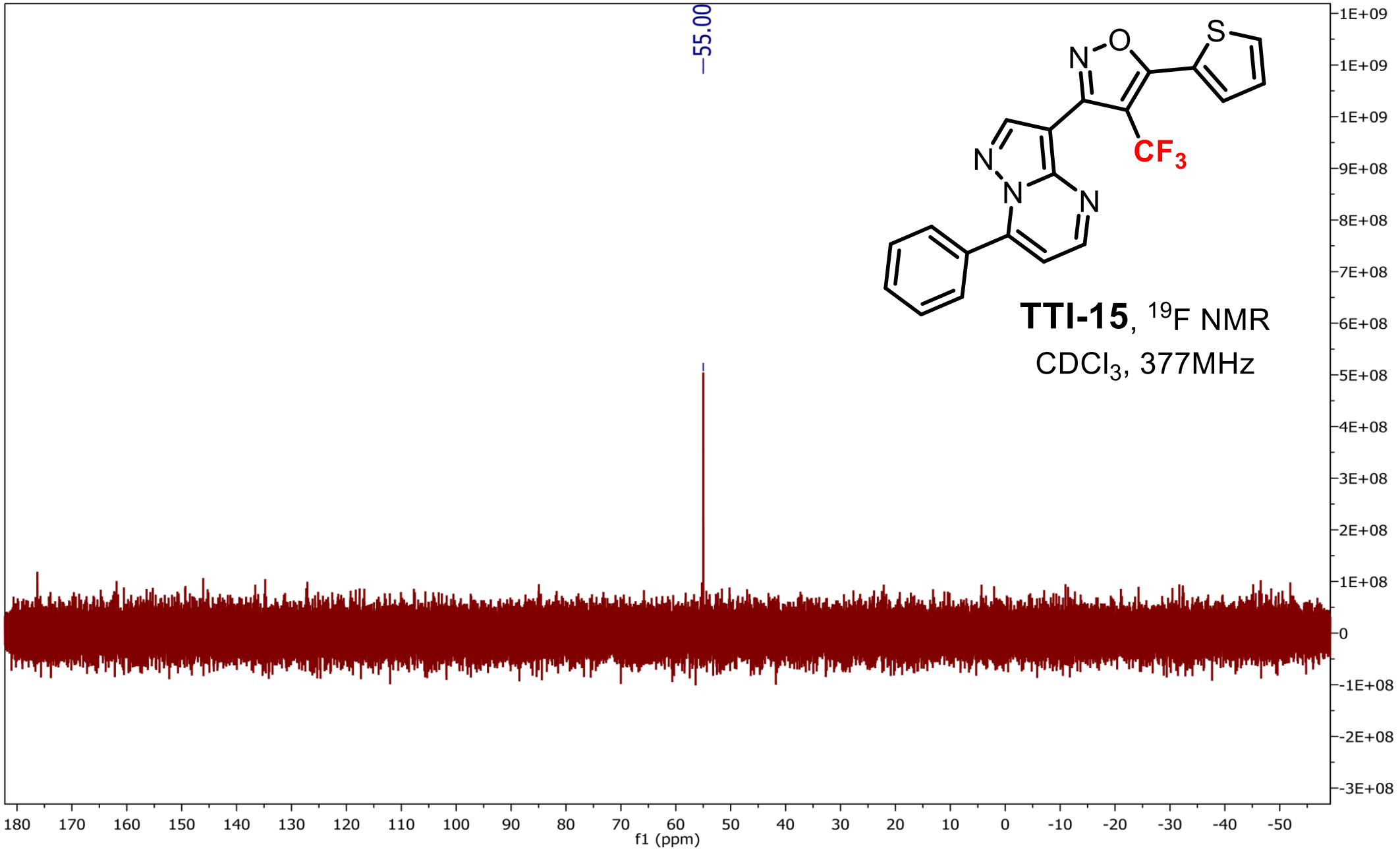

-108.17
TTI-14, 19F NMR
CDCl3, 377MHz
f1 (ppm)

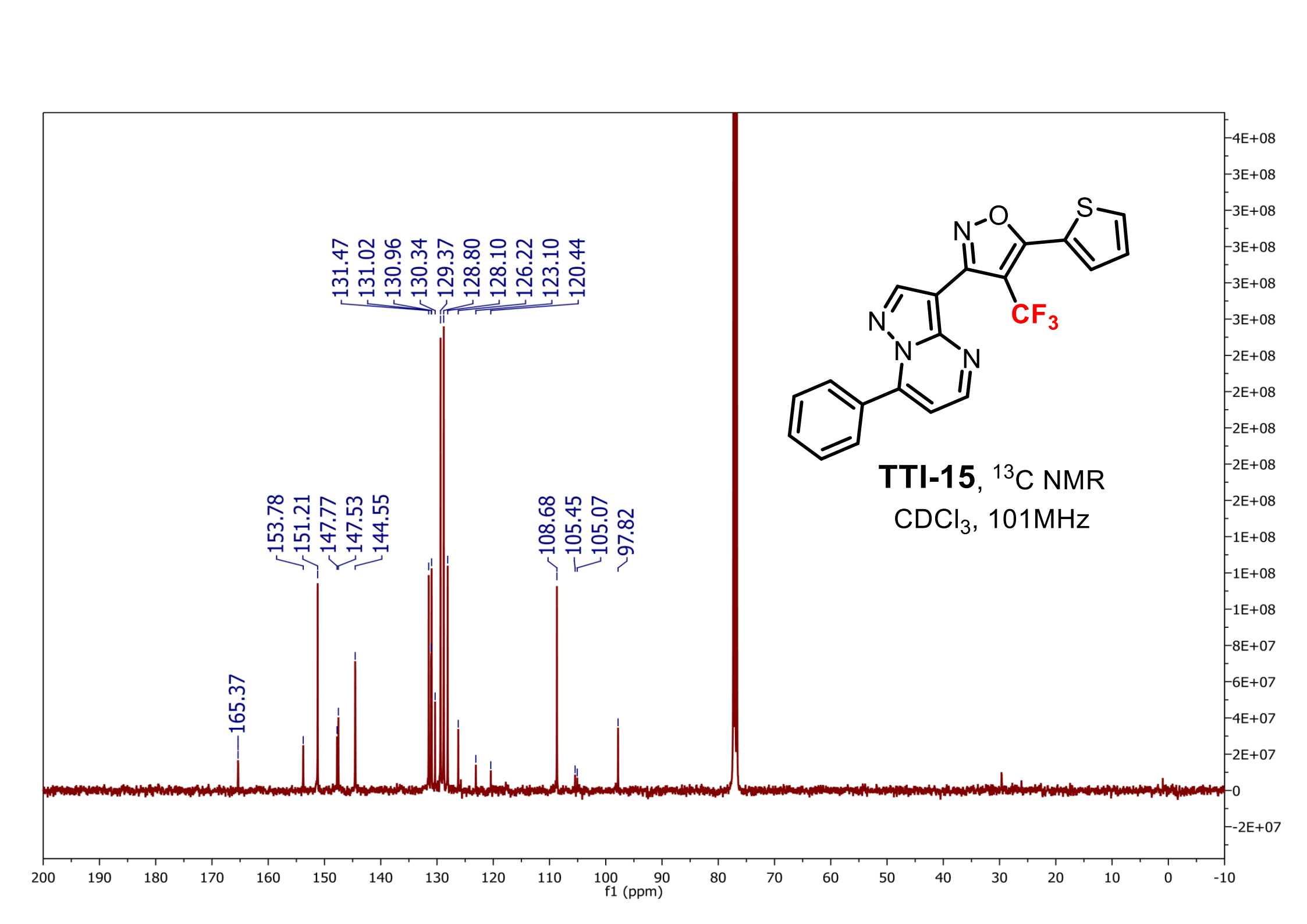

165.18
161.91
150.83
149.20
130.44
130.28
128.26
126.85
121.68
119.93
112.64
111.53
111.18
110.31
107.99
77.00
55.97
S
O
N
O
CF2H
H3C
O
H3C
O
TTI-14, 13C NMR
CDCl3, 101MHz
f1 (ppm)

Spectrum Plot Report




8.74
8.73
8.46
8.46
8.07
8.06
8.05
8.05
8.05
8.04
7.73
7.72
7.66
7.66
7.65
7.64
7.61
7.61
7.60
7.60
7.59
7.26
7.23
7.22
7.21
7.20
7.07
7.06
1.05
1.02
2.00
1.01
1.05
3.03
1.00
1.03
f1 (ppm)
TTI-15, 1H NMR
CDCl3, 400MHz
CF3


-55.00
1E+09
1E+09
1E+09
9E+08
8E+08
7E+08
6E+08
5E+08
4E+08
3E+08
2E+08
1E+08
0
-1E+08
-2E+08
-3E+08
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50
f1 (ppm)
N
O
S
N
N
N
CF3
TTI-15, 19F NMR
CDCl3, 377MHz


131.47
131.02
130.96
130.34
129.37
128.80
128.10
126.22
123.10
120.44
153.78
151.21
147.77
147.53
144.55
108.68
105.45
105.07
97.82
165.37
N
O
S
N
N
N
CF3
TTI-15, 13C NMR
CDCl3, 101MHz
4E+08
3E+08
3E+08
3E+08
3E+08
3E+08
2E+08
2E+08
2E+08
2E+08
2E+08
2E+08
1E+08
1E+08
1E+08
8E+07
6E+07
4E+07
2E+07
0
-2E+07
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

Spectrum Plot Report