Supporting Information

Multi-targeted Imidazoles: Potential Therapeutic Leads for Alzheimer's and Other Neurodegenerative Diseases

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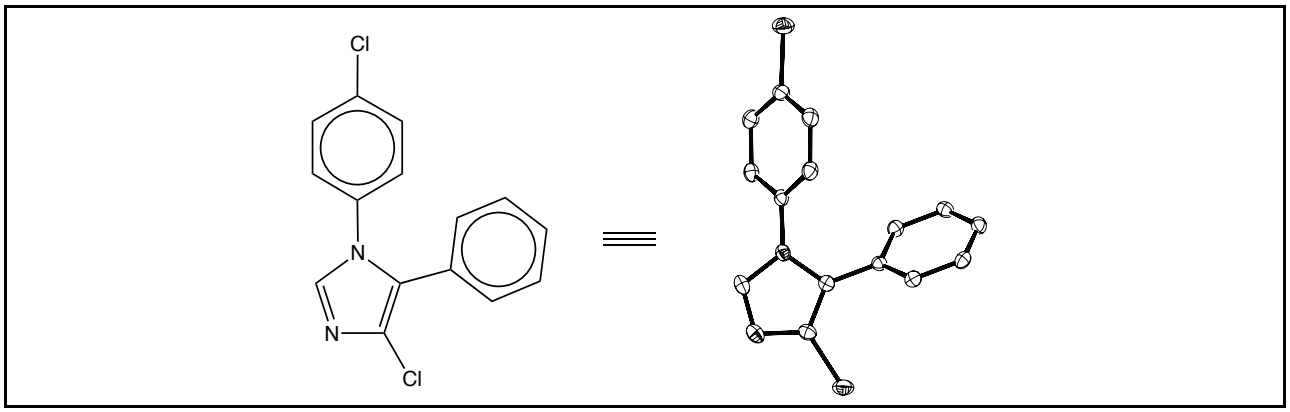
The structure of COX-1 was prepared from the X-ray structure available in the Protein Data Bank database (PDB code: 3KK6). Using Autodock 4.2, water molecules, ligand and hydrogens were removed, while polar hydrogens and Gasteiger charges were added. The structure was converted in .pdbqt format.

Compounds were built and minimized with the MMFF94 force field using Chem3D (CambridgeSoft), saved in .mol2 format and converted in .pdbqt format using Autodock 4.2. Autodock Vina software was used for docking calculation.[1] In the configuration files we set a grid of 20 (*x*), 30 (*y*), 35 (*z*) and centered at -32.085 (*x*), 43.871 (*y*) and -5.222 (*z*) corresponding to the active site. Docking results were analyzed and docking poses were selected following the conformation and binding affinity results.

[1] Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading Trott, Oleg; Olson, Arthur J. *Journal of Computational Chemistry*, *31*(2), 455-461

X-ray Structure Determination of 1436 (compound 98) - CCDC 1529316



Compound 1436x, $C_{15}H_{10}Cl_2N_2$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd and 00l: l=odd) with a=8.0987(4)Å, b=9.6131(4)Å, c=17.2587(8)Å, V=1343.65(11)Å^3, Z=4, and d_{calc}=1.429 g/cm$_3$. X-ray intensity data were collected on a Bruker APEXII [1] CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073Å) at a temperature of 100K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 4191 frames were collected with a crystal to detector distance of 59.9 mm, rotation widths of 0.5° and exposures of 10 seconds:

scan type	2θ	ω	ϕ	χ	Frames
ϕ	32.00	44.52	349.55	-24.38	739
ϕ	-28.00	348.53	335.02	-55.24	669
ω	37.00	1.45	201.14	-31.86	308
ω	37.00	335.50	316.23	-20.60	350
ϕ	39.50	166.34	331.87	-58.65	739
ϕ	-35.50	197.88	22.47	48.96	739
ω	39.50	123.67	224.27	-99.82	184
ω	39.50	359.79	317.07	99.72	72
ω	-30.50	311.87	203.97	-93.68	124
ω	37.00	324.24	181.66	91.29	139
ω	-38.00	306.44	63.99	-90.90	128

Rotation frames were integrated using SAINT [2], producing a listing of unaveraged F^2 and $\sigma(F^2)$ values. A total of 34619 reflections were measured over the ranges $4.72 \le 2\theta \le 54.956°$, $-10 \le h \le 10$, $-12 \le k \le 12$, $-22 \le l \le 22$ yielding 3093 unique reflections (R_{int} = 0.0167). The intensity data were corrected for

Lorentz and polarization effects and for absorption using SADABS [3] (minimum and maximum transmission 0.7019, 0.7456). The structure was solved by direct methods - SHELXS-97 [4]. Refinement was by full-matrix least squares based on F^2 using SHELXL-2014 [5]. All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0288P)^2 + 0.3254P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0197 and wR2=0.0539 for 3020 observed reflections for which $F > 4\sigma(F)$ and R1=0.0204 and wR2=0.0546 and GOF =1.072 for all 3093 unique, non-zero reflections and 172 variables. The maximum Δ/σ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.21 and -0.15 e/Å^3.

Table 1. lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables 2. and 3. Anisotropic thermal parameters are in Table 4. Tables 5. and 6. list bond distances and bond angles. Figure 1. is an ORTEP representation of the molecule with 50% probability thermal ellipsoids displayed.

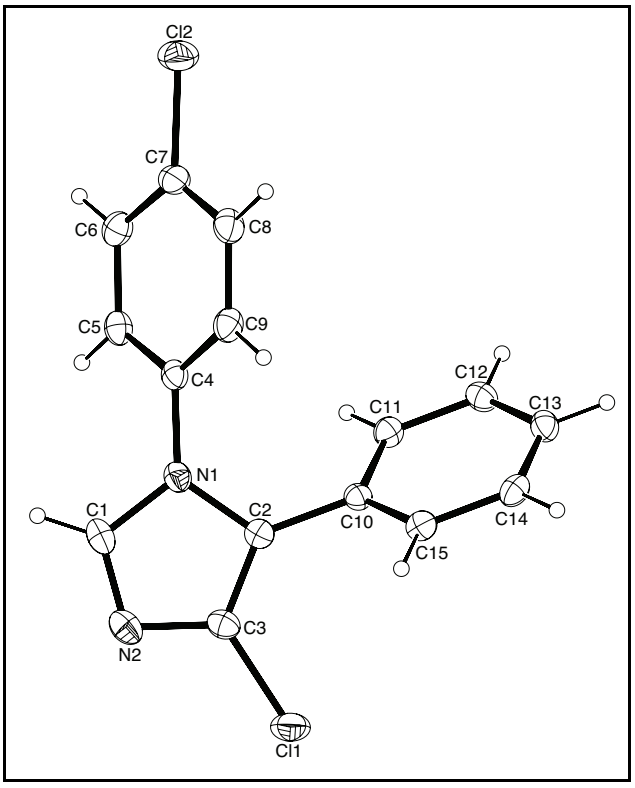


Figure 1. ORTEP drawing of the title compound with 50% thermal ellipsoids.

Table 1. Summary of Structure Determination of Compound 1436

Empirical formula	$C_{15}H_{10}Cl_2N_2$
Formula weight	289.15
Temperature/K	100
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a	8.0987(4)Å
b	9.6131(4)Å
c	17.2587(8)Å
Volume	1343.65(11)$Å^3$
Z	4
d_{calc}	1.429 g/cm^3
μ	0.469 mm^{-1}
F(000)	592.0
Crystal size, mm	0.38 × 0.25 × 0.13
2θ range for data collection	4.72 - 54.956°
Index ranges	$-10 \le h \le 10$, $-12 \le k \le 12$, $-22 \le l \le 22$
Reflections collected	34619
Independent reflections	3093[R(int) = 0.0167]
Data/restraints/parameters	3093/0/172
Goodness-of-fit on F^2	1.072
Final R indexes [I>=2σ (I)]	R_1 = 0.0197, wR_2 = 0.0539
Final R indexes [all data]	R_1 = 0.0204, wR_2 = 0.0546
Largest diff. peak/hole	0.21/-0.15 $eÅ^{-3}$
Flack parameter	0.019(7)

Table 2 . Refined Positional Parameters for Compound 1436

Atom	*x*	*y*	*z*	U(eq)
Cl1	0.09107(5)	0.70615(4)	0.33214(2)	0.02712(10)
Cl2	1.09986(5)	0.20840(5)	0.40390(2)	0.03140(11)
N1	0.47760(16)	0.52924(13)	0.41620(7)	0.0174(3)
N2	0.27362(18)	0.66304(14)	0.46030(8)	0.0228(3)
C1	0.4113(2)	0.59712(16)	0.47801(9)	0.0211(3)
C2	0.37380(18)	0.55263(15)	0.35335(8)	0.0169(3)
C3	0.25187(19)	0.63474(16)	0.38344(9)	0.0196(3)
C4	0.62683(19)	0.44939(15)	0.41620(8)	0.0170(3)
C5	0.7695(2)	0.50647(16)	0.44722(9)	0.0192(3)
C6	0.9153(2)	0.43018(16)	0.44545(9)	0.0213(3)
C7	0.9144(2)	0.29927(16)	0.41118(9)	0.0216(3)
C8	0.7721(2)	0.24107(17)	0.38158(10)	0.0241(3)
C9	0.6256(2)	0.31601(16)	0.38482(9)	0.0214(3)
C10	0.40238(19)	0.49792(14)	0.27482(8)	0.0159(3)
C11	0.55152(18)	0.52238(16)	0.23666(9)	0.0183(3)
C12	0.57762(19)	0.46838(15)	0.16287(8)	0.0196(3)
C13	0.4549(2)	0.39032(16)	0.12695(9)	0.0197(3)
C14	0.30663(19)	0.36612(15)	0.16454(9)	0.0196(3)
C15	0.27985(19)	0.41918(15)	0.23853(9)	0.0182(3)

Table 3 . Positional Parameters for Hydrogens in Compound 1436

Atom	*x*	*y*	*z*	U(eq)
H1	0.458	0.597	0.5272	0.028
H5	0.7677	0.5949	0.469	0.026
H6	1.0118	0.4661	0.4668	0.028
H8	0.7741	0.1527	0.3597	0.032
H9	0.5279	0.2776	0.3663	0.028
H11	0.6335	0.5748	0.2606	0.024
H12	0.6772	0.4845	0.1375	0.026
H13	0.4725	0.3543	0.0776	0.026
H14	0.2246	0.3142	0.1403	0.026
H15	0.1804	0.4022	0.2638	0.024

Table 4 . Refined Thermal Parameters (U's) for Compound 1436

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	0.01982(17)	0.03064(19)	0.0309(2)	0.00261(16)	0.00326(15)	0.00733(17)
Cl2	0.0306(2)	0.0347(2)	0.0289(2)	0.00907(17)	0.00530(17)	0.0145(2)
N1	0.0210(6)	0.0155(6)	0.0157(6)	-0.0012(5)	0.0007(5)	-0.0001(5)
N2	0.0259(7)	0.0211(6)	0.0213(6)	-0.0012(5)	0.0069(5)	-0.0008(5)
C1	0.0276(8)	0.0197(7)	0.0161(6)	-0.0024(5)	0.0045(6)	-0.0015(7)
C2	0.0174(7)	0.0160(6)	0.0174(6)	0.0012(5)	0.0012(5)	-0.0012(5)
C3	0.0182(7)	0.0190(7)	0.0215(7)	0.0005(6)	0.0039(6)	0.0006(6)
C4	0.0218(7)	0.0155(6)	0.0137(6)	0.0014(5)	0.0007(5)	0.0008(5)
C5	0.0252(7)	0.0163(7)	0.0161(7)	-0.0003(5)	0.0002(6)	-0.0027(6)
C6	0.0222(7)	0.0229(7)	0.0187(7)	0.0032(6)	-0.0010(6)	-0.0027(6)
C7	0.0249(7)	0.0220(7)	0.0180(6)	0.0049(6)	0.0022(6)	0.0069(7)
C8	0.0351(9)	0.0166(7)	0.0206(7)	-0.0021(6)	-0.0030(7)	0.0042(6)
C9	0.0270(8)	0.0168(7)	0.0204(7)	-0.0019(6)	-0.0048(6)	-0.0007(6)
C10	0.0174(6)	0.0145(6)	0.0159(6)	0.0007(5)	0.0004(6)	0.0017(5)
C11	0.0181(7)	0.0175(7)	0.0192(7)	-0.0010(6)	-0.0012(6)	-0.0017(5)
C12	0.0186(7)	0.0204(7)	0.0196(7)	0.0002(6)	0.0040(6)	0.0006(6)
C13	0.0257(8)	0.0168(7)	0.0165(7)	-0.0009(5)	-0.0004(6)	0.0025(6)
C14	0.0206(7)	0.0182(7)	0.0201(7)	0.0005(6)	-0.0058(6)	-0.0017(6)
C15	0.0172(6)	0.0186(7)	0.0189(7)	0.0029(6)	0.0005(6)	-0.0011(5)

Table 5 . Bond Distances in Compound 1436, Å

Cl1-C3	1.7178(16)	Cl2-C7	1.7419(16)	N1-C1	1.3608(19)
N1-C2	1.3906(19)	N1-C4	1.4318(19)	N2-C1	1.319(2)
N2-C3	1.366(2)	C2-C3	1.367(2)	C2-C10	1.4721(19)
C4-C5	1.387(2)	C4-C9	1.392(2)	C5-C6	1.390(2)
C6-C7	1.391(2)	C7-C8	1.380(2)	C8-C9	1.389(2)
C10-C11	1.396(2)	C10-C15	1.396(2)	C11-C12	1.392(2)
C12-C13	1.391(2)	C13-C14	1.385(2)	C14-C15	1.392(2)

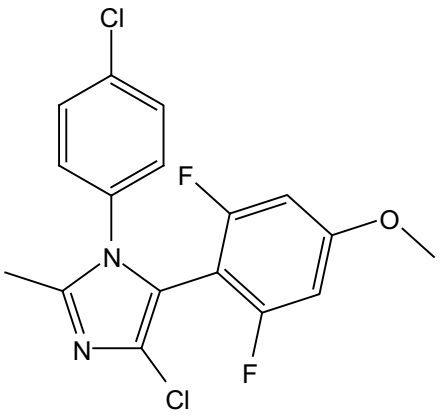
Table 6 . Bond Angles in Compound 1436, °

C1-N1-C2	107.19(13)	C1-N1-C4	126.15(13)	C2-N1-C4	126.66(12)
C1-N2-C3	103.80(13)	N2-C1-N1	112.48(14)	N1-C2-C10	124.42(13)
C3-C2-N1	103.52(13)	C3-C2-C10	132.05(14)	N2-C3-Cl1	121.25(12)
N2-C3-C2	113.01(14)	C2-C3-Cl1	125.64(12)	C5-C4-N1	119.43(13)
C5-C4-C9	121.38(14)	C9-C4-N1	119.19(14)	C4-C5-C6	119.38(14)
C5-C6-C7	118.83(15)	C6-C7-Cl2	118.69(13)	C8-C7-Cl2	119.37(12)
C8-C7-C6	121.93(15)	C7-C8-C9	119.24(14)	C8-C9-C4	119.16(15)
C11-C10-C2	120.68(13)	C11-C10-C15	119.65(13)	C15-C10-C2	119.66(14)
C12-C11-C10	120.03(13)	C13-C12-C11	120.04(14)	C14-C13-C12	120.09(14)
C13-C14-C15	120.23(14)	C14-C15-C10	119.96(14)		

This report has been created with Olex2 [6], compiled on 2016.02.19 svn.r3266 for OlexSys.

Reference

[1] APEX2 2014.11-0
[2] SAINT v8.34A
[3] SADABS v2014/5
[4] SHELXS-97
[5] SHELXL-2014/7
[6] Olex2 (Dolomanov et al., 2009)


Cl
F
O
N
N
F
Cl

Compound 2

7.41
7.39
7.26 CDCl3
7.11
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6.40
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2.41
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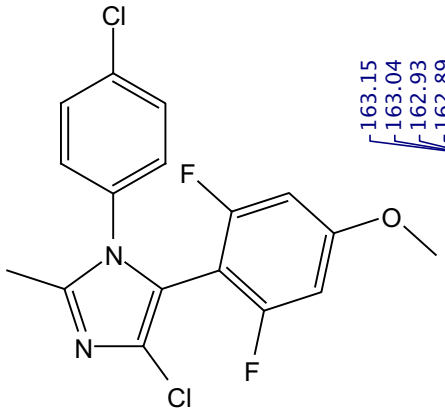
2.89
f1 (ppm)


Cl
F
O
N
N
F
Cl

Compound 2

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160.62
160.58
145.57
136.10
136.07
133.46
130.11
129.90
128.65
128.38
127.63
117.32
98.49
98.45
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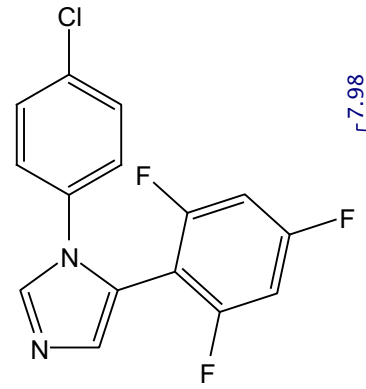
H grease
f1 (ppm)


Cl
F
F
N
N
F

Compound 25

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7.37
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7.36
7.35
7.26 CDCl3
7.13
7.12
7.12
7.11
7.10
7.10
7.09
6.71
6.70
6.70
6.69
6.69
6.68
6.68
6.67
6.66
6.66
6.66
6.65
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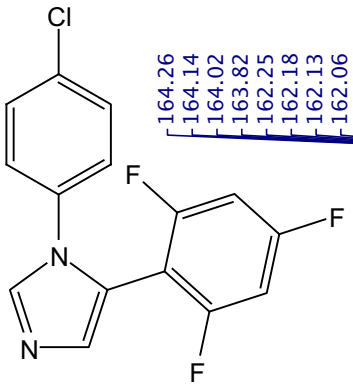
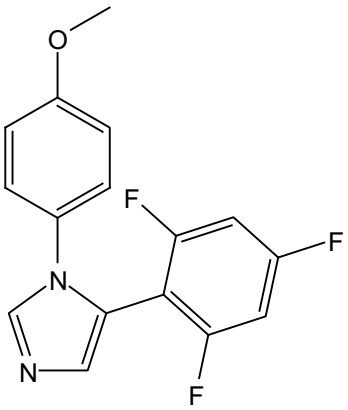
1.09
1.77
1.83
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)



Compound 25


O
F
F
N
N
F

Compound 26

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7.26 CDCl3
7.25
7.08
7.07
7.07
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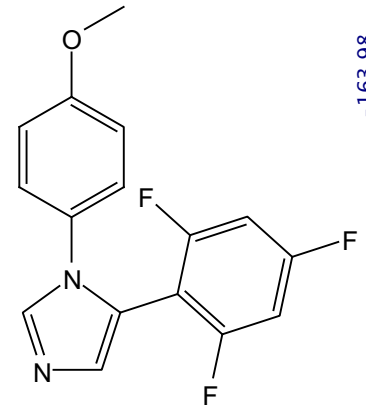
7.06
7.05
6.88
6.87
6.87
6.86
6.85
6.85
6.84
6.83
6.65
6.65
6.64
6.63
6.62
6.61
6.60
6.60
3.79
1.00
0.93
1.94
2.18
1.90
2.71
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
F
F
N
N
F

Compound 26

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162.11
161.84
161.79
161.75
161.69
160.18
160.12
160.08
160.02
159.50
139.30
131.76
129.26
126.20
119.50
114.58
114.32
104.26
104.16
104.13
104.05
104.00
100.82
100.78
100.65
100.62
100.49
100.45
77.16 CDCl3
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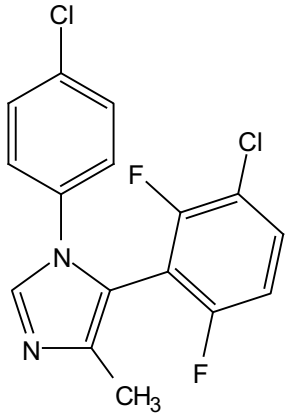
450
400
350
300
250
200
150
100
50
0
f1 (ppm)


Cl
Cl
F
N
N
F
CH3

Compound 29

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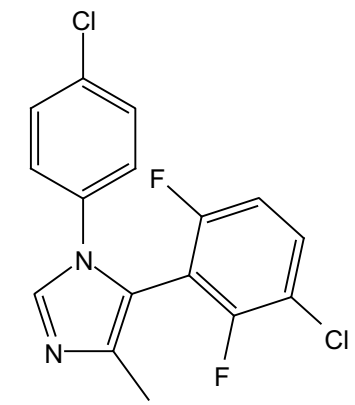
7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.32
7.32
7.31
7.31
7.30
7.29
7.26 CDCl3
7.06
7.06
7.05
7.05
7.04
7.03
7.03
6.86
6.86
6.85
6.84
6.84
6.84
6.83
6.82
2.20
1.00
0.99
2.02
2.05
1.00
2.93
f1 (ppm)



Compound 29

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157.84
157.80
156.90
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154.90
154.84
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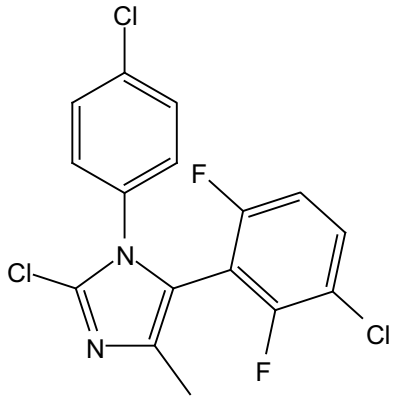
138.02
135.11
134.20
131.29
131.21
129.79
125.77
117.32
117.28
117.17
117.13
115.41
112.40
112.36
112.21
112.17
109.28
109.12
108.95

77.16 CDCl3

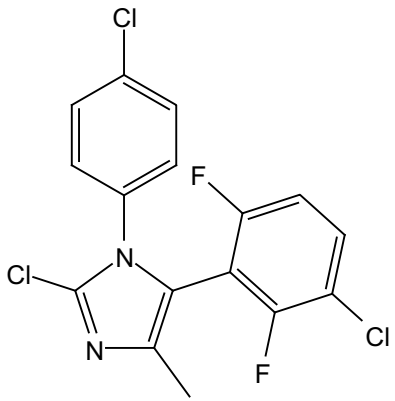
13.48

f1 (ppm)


Cl
F
N
Cl
N
Cl
F

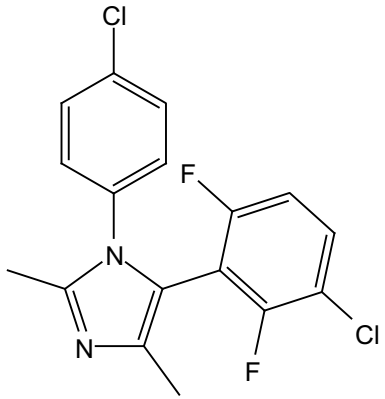
Compound 30

7.36
7.35
7.33
7.26 CDCl3
7.10
7.09
6.83
6.82
6.81
2.17
2.68
1.68
0.82
3.00
4000
3500
3000
2500
2000
1500
1000
500
0
f1 (ppm)


Cl
F
N
Cl
N
Cl
F

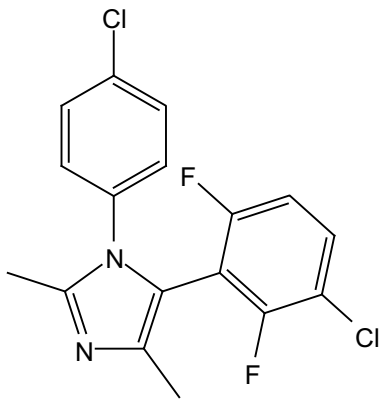
Compound 30

159.96
159.92
157.96
157.93
157.04
157.00
155.04
154.99
139.23
135.37
133.57
133.48
131.78
131.70
129.61
128.57
117.71
117.25
117.22
117.10
117.07
112.34
112.31
112.15
112.12
108.73
108.57
108.40
77.16 CDCl3
13.43
40
35
30
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
f1 (ppm)


Cl
F
N
N
Cl
F

Compound 31

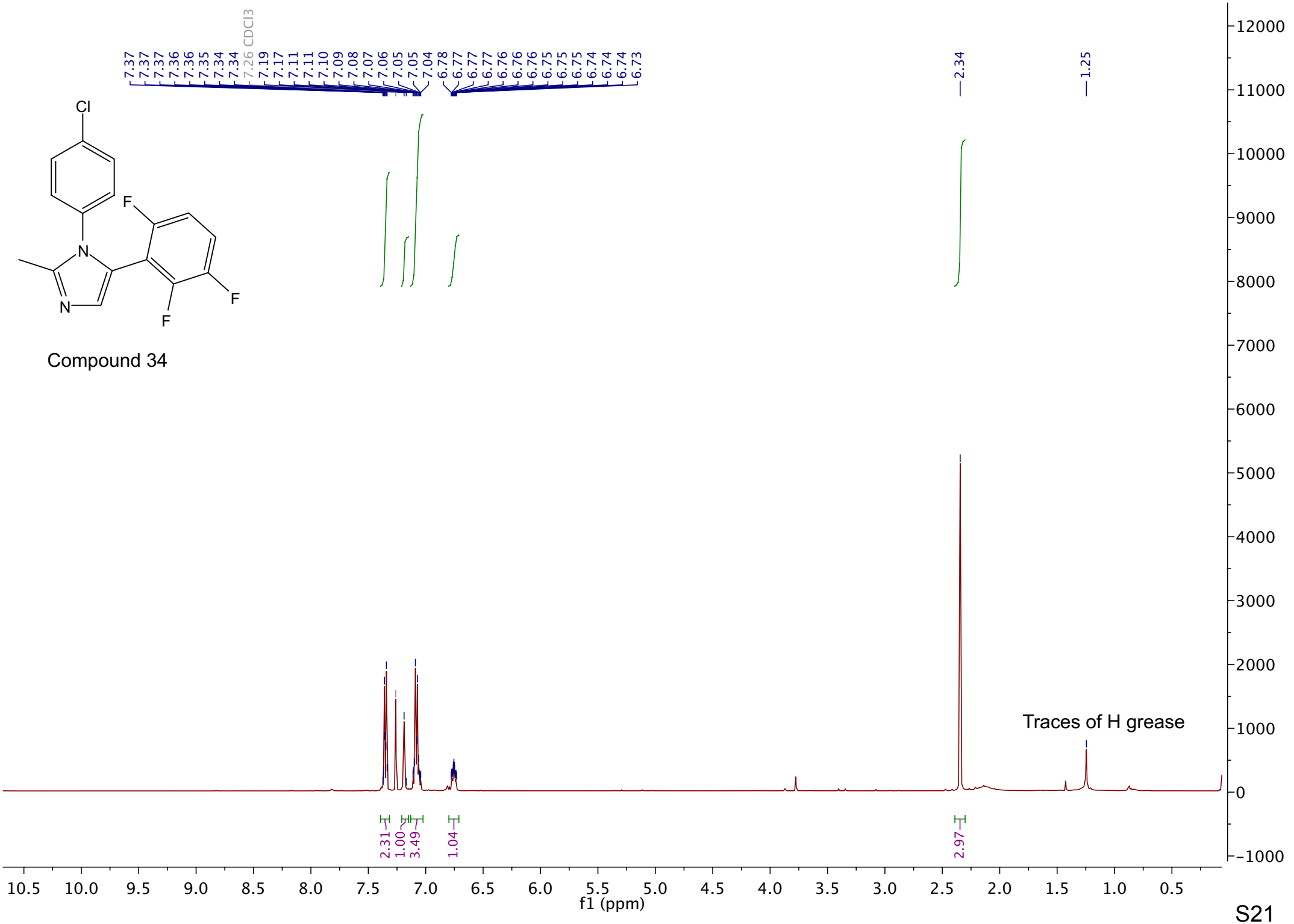
7.32
7.32
7.31
7.31
7.29
7.29
7.28
7.26 CDCl3
7.04
7.03
6.80
6.80
6.78
6.78
6.77
6.76
2.29
2.14
1.24
H grease
2.44
0.54
2.02
1.00
3.11
3.19
f1 (ppm)

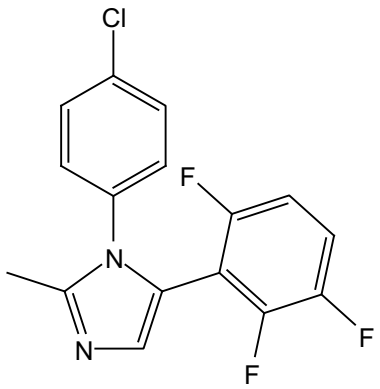


Compound 31

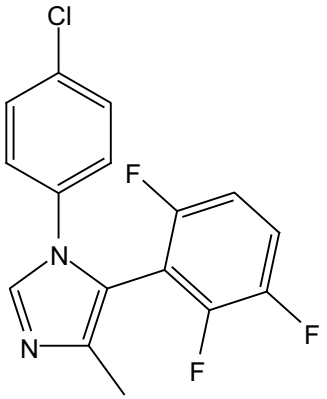
160.00
159.96
158.01
157.97
157.04
156.99
155.04
154.99
146.28
138.04
135.07
134.66
131.03
130.96
129.62
128.34
117.05
117.02
116.90
116.87
115.69
112.16
112.13
111.97
111.94
109.77
109.60
109.44
77.16 CDCl3
29.82
14.04
13.13
H grease

f1 (ppm)


7.37
7.37
7.37
7.36
7.36
7.35
7.34
7.34
7.26 CDCl3
7.19
7.17
7.11
7.11
7.10
7.09
7.08
7.07
7.06
7.05
7.05
7.04
6.78
6.77
6.77
6.76
6.76
6.76
6.75
6.75
6.75
6.74
6.74
6.74
6.73
2.34
1.25
Cl
F
N
N
F
F
Compound 34
Traces of H grease
2.31
1.00
3.49
1.04
2.97
f1 (ppm)

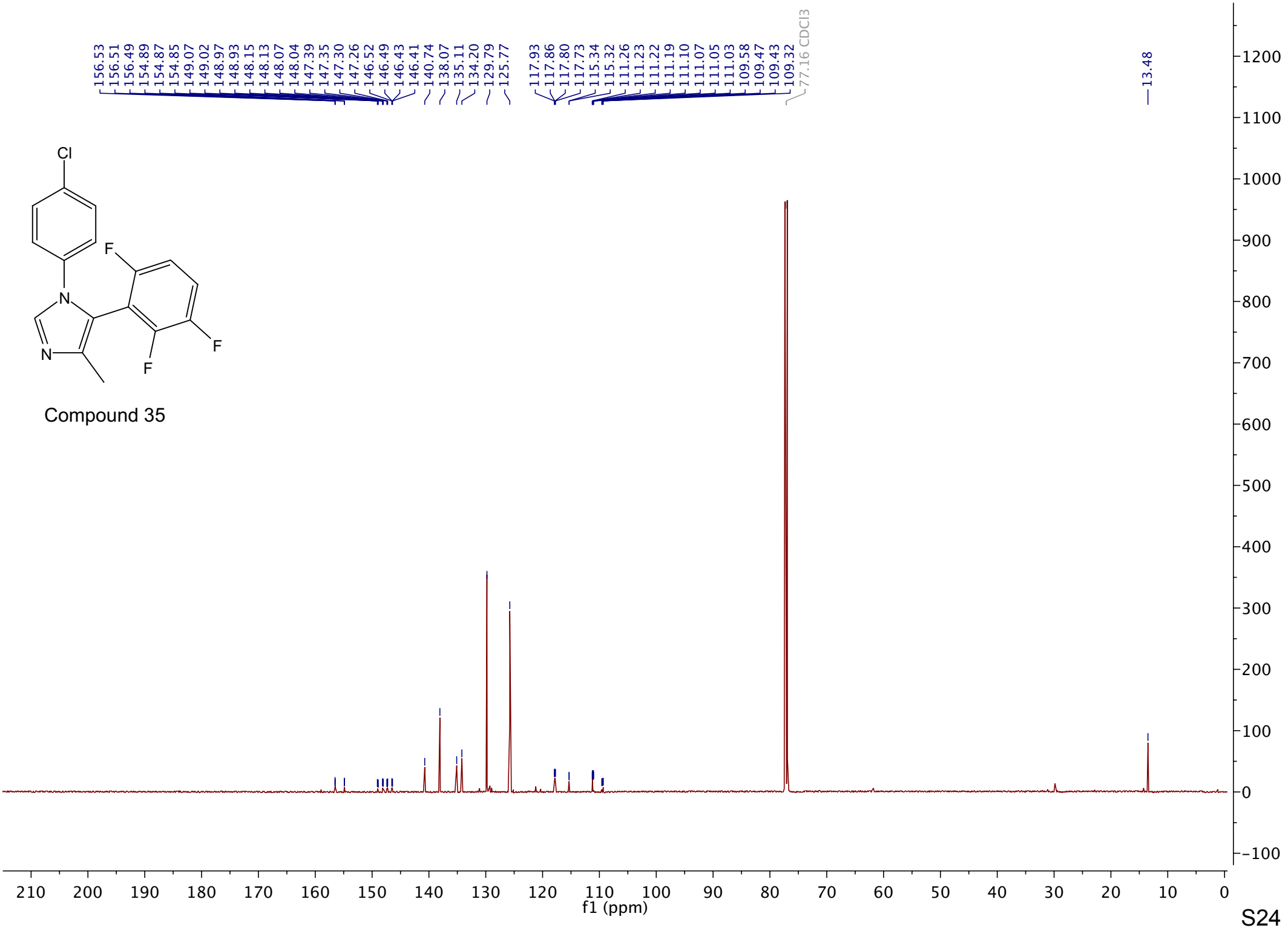


Compound 34

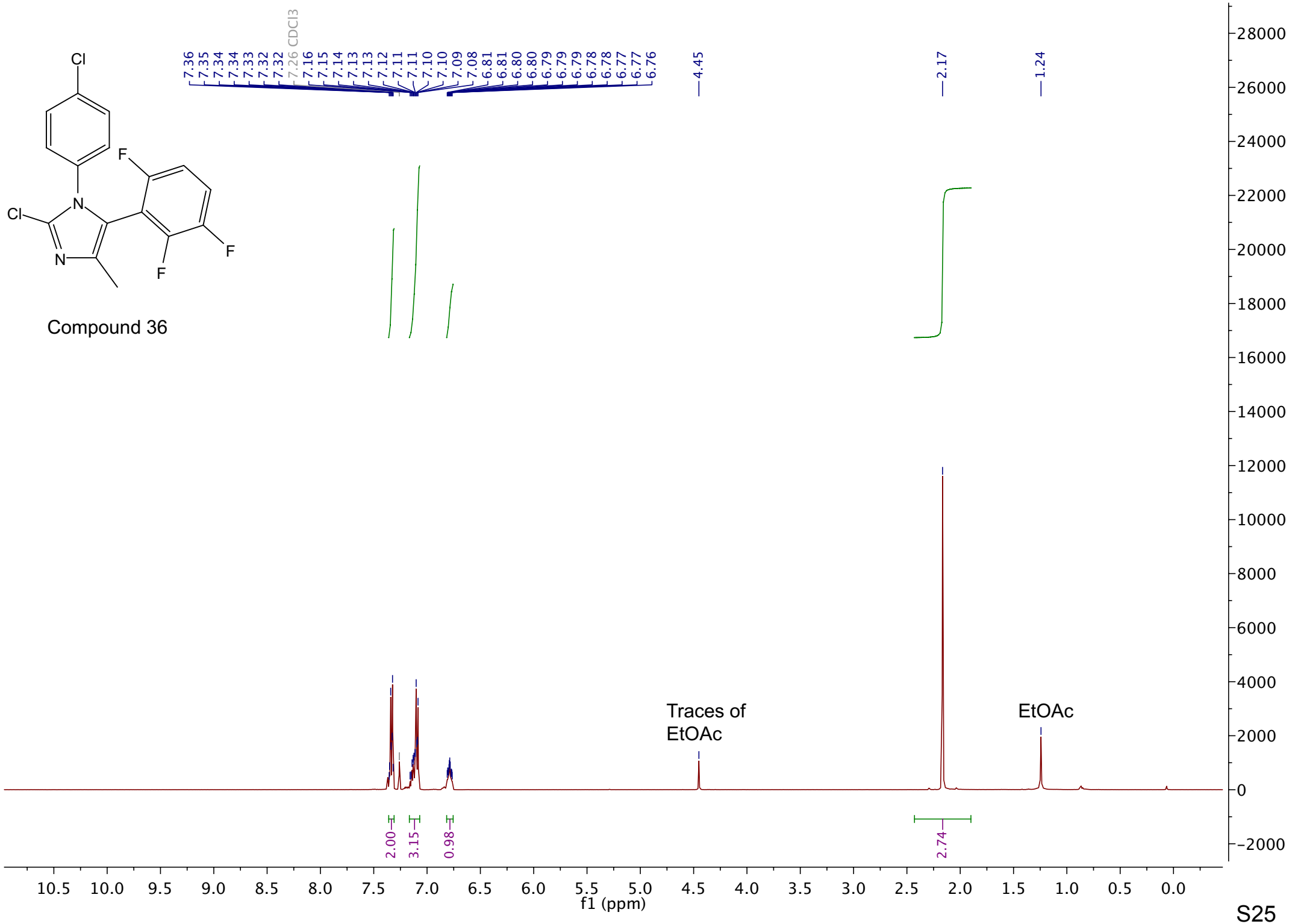

Cl
F
N
N
F
F

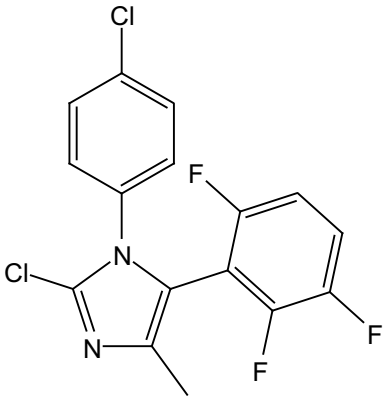
Compound 35

7.72
7.33
7.32
7.32
7.31
7.30
7.30
CDCl3
7.26
7.18
7.17
7.16
7.15
7.14
7.13
7.13
7.12
7.11
7.06
7.06
7.05
7.04
7.04
7.03
6.84
6.84
6.83
6.83
6.83
6.82
6.82
6.81
6.81
6.81
6.80
6.80
6.80
2.22
30000
25000
20000
15000
10000
5000
0
1.00
2.04
1.06
2.12
1.11
3.04
11.5
11.0
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)


156.53
156.51
156.49
154.89
154.87
154.85
149.07
149.02
148.97
148.93
148.15
148.13
148.07
148.04
147.39
147.35
147.30
147.26
146.52
146.49
146.43
146.41
140.74
138.07
135.11
134.20
129.79
125.77
117.93
117.86
117.80
117.73
115.34
115.32
111.26
111.23
111.22
111.19
111.10
111.07
111.05
111.03
109.58
109.47
109.43
109.32
77.16 CDCl3
13.48
Cl
F
N
N
F
F
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
−100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

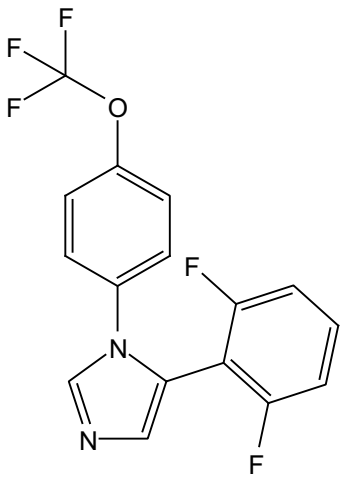
Compound 35


Cl
F
N
Cl
N
F
F
Compound 36
7.36
7.35
7.34
7.34
7.33
7.32
7.32
7.26 CDCl3
7.16
7.15
7.14
7.13
7.13
7.12
7.11
7.11
7.10
7.10
7.09
7.08
6.81
6.81
6.80
6.80
6.79
6.79
6.79
6.78
6.78
6.77
6.77
6.76
4.45
2.17
1.24
Traces of
EtOAc
EtOAc
2.00
3.15
0.98
2.74
f1 (ppm)


Cl
F
N
Cl
N
F
F

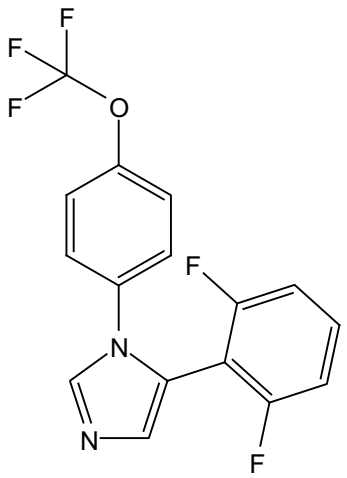
Compound 36

156.65
156.64
156.62
155.02
155.00
154.98
149.21
149.16
149.11
149.07
148.00
147.97
147.91
147.88
147.53
147.49
147.44
147.40
146.36
146.33
146.27
146.25
139.27
135.37
133.57
133.53
129.60
128.57
118.43
118.37
118.31
118.24
117.61
117.59
111.23
111.20
111.18
111.15
111.06
111.03
111.02
110.99
109.03
108.92
108.88
108.77
77.16 CDCl3
29.84
13.44
H grease
f1 (ppm)


F
F
F
O
F
N
N
F

Compound 42

8.20
7.51
7.50
7.48
7.46
7.44
7.36
7.34
7.32
7.17
7.15
7.14
3.34
2.50 DMSO-d6
1.00
1.10
2.03
2.31
1.00
2.19
f1 (ppm)

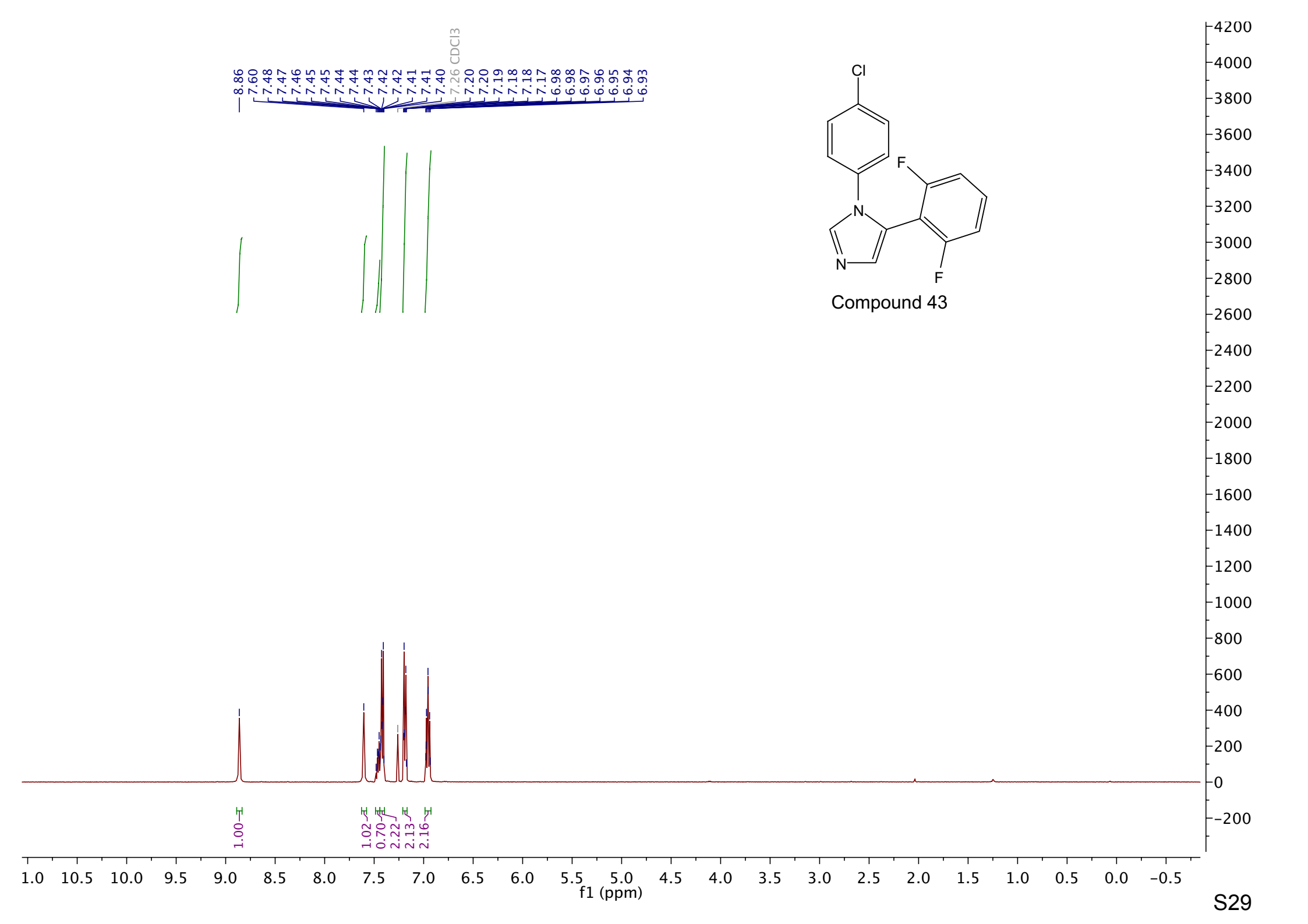


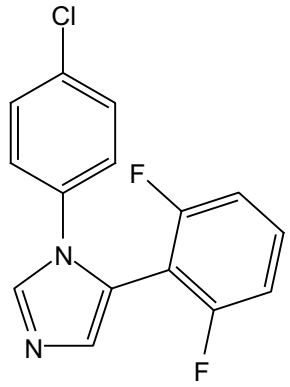
Compound 42

160.55
160.51
158.58
158.53
147.53
147.52
147.50
139.64
135.08
131.88
131.80
131.76
131.72
126.09
122.98
122.12
120.93
118.93
118.89
116.85
112.08
112.04
111.92
111.88
106.72
106.56
106.40

55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000

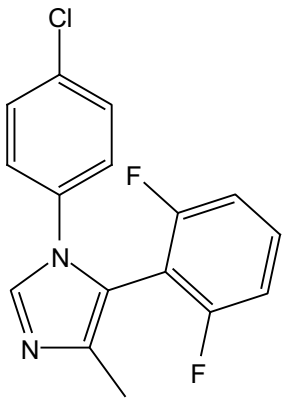
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.86
7.60
7.48
7.47
7.46
7.45
7.45
7.44
7.44
7.43
7.42
7.42
7.41
7.41
7.40
7.26 CDCl3
7.20
7.20
7.19
7.18
7.18
7.17
6.98
6.98
6.97
6.96
6.95
6.94
6.93
Cl
F
N
N
F
Compound 43
1.00
1.02
0.70
2.22
2.13
2.16
f1 (ppm)


Cl
F
N
N
F

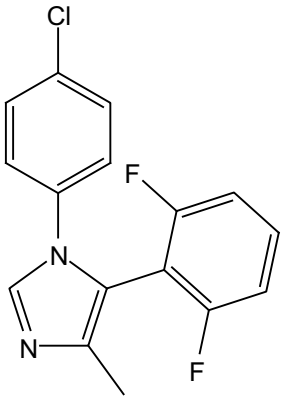
Compound 43

161.49
161.44
159.47
159.43
136.99
136.90
133.52
133.44
133.36
132.54
130.41
126.30
123.71
122.62
112.31
112.28
112.15
112.11
103.86
103.70
103.55
77.16 CDCl3
f1 (ppm)


Cl
F
N
N
F

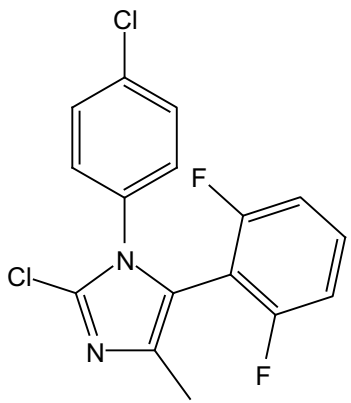
Compoun 44

7.73
7.72
7.71
7.34
7.32
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.28
7.27
7.26 CDCl3
7.06
7.05
7.05
7.04
7.03
7.03
6.91
6.90
6.89
6.89
6.88
6.88
6.87
6.87
6.86
6.86
6.85
2.21
1.00
0.72
2.33
2.14
2.14
2.92
f1 (ppm)


Cl
F
N
N
F

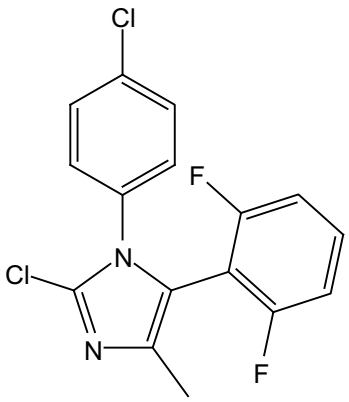
Compound 44

161.63
161.58
159.64
159.59
140.19
137.61
135.40
133.91
131.08
131.00
130.92
129.63
125.74
116.13
111.84
111.80
111.68
111.64
107.69
107.53
107.37
77.16 CDCl3
13.44
f1 (ppm)


Cl
F
Cl
N
N
F

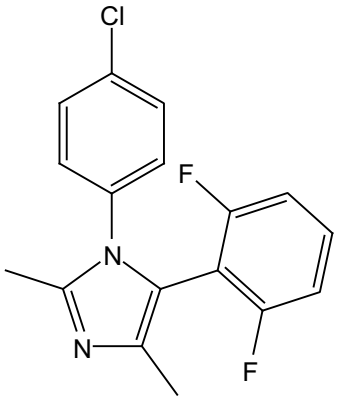
Compound 45

7.33
7.32
7.32
7.30
7.29
7.28
7.27
7.26 CDCl3
7.11
7.10
7.09
7.09
6.87
6.87
6.86
6.85
6.85
6.83
6.83
6.82
2.16
2.00
0.67
1.95
1.86
2.66
f1 (ppm)


Cl
F
N
Cl
N
F

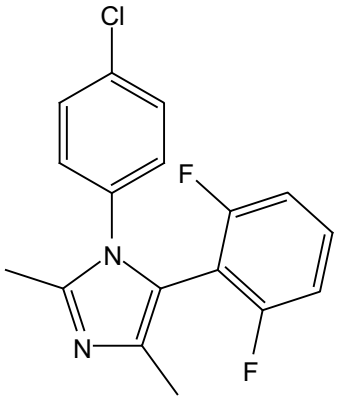
Compound 45

161.72
161.67
159.73
159.68
138.71
135.08
133.82
132.88
131.54
131.46
131.38
129.41
128.63
128.60
118.49
111.75
111.71
111.59
111.55
107.17
107.02
106.86
77.16 CDCl3
13.37
f1 (ppm)


Cl
F
N
N
F

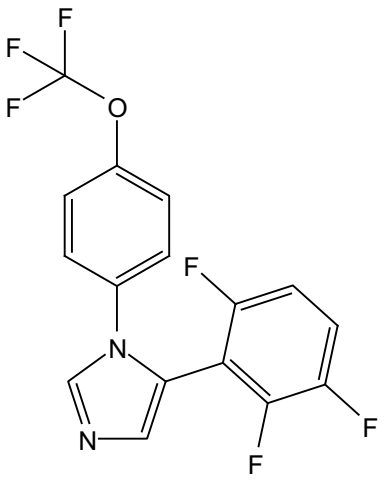
Compound 46

7.30
7.29
7.28
7.28
7.26 CDCl3
7.24
7.24
7.23
7.23
7.22
7.21
7.20
7.19
7.04
7.03
7.03
6.83
6.81
6.80
6.79
2.29
2.14
1.70
0.65
1.74
1.64
2.85
3.00
f1 (ppm)

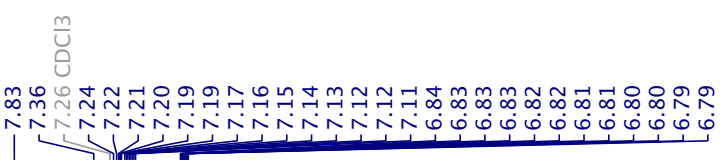

Cl
F
N
N
F

Compound 46

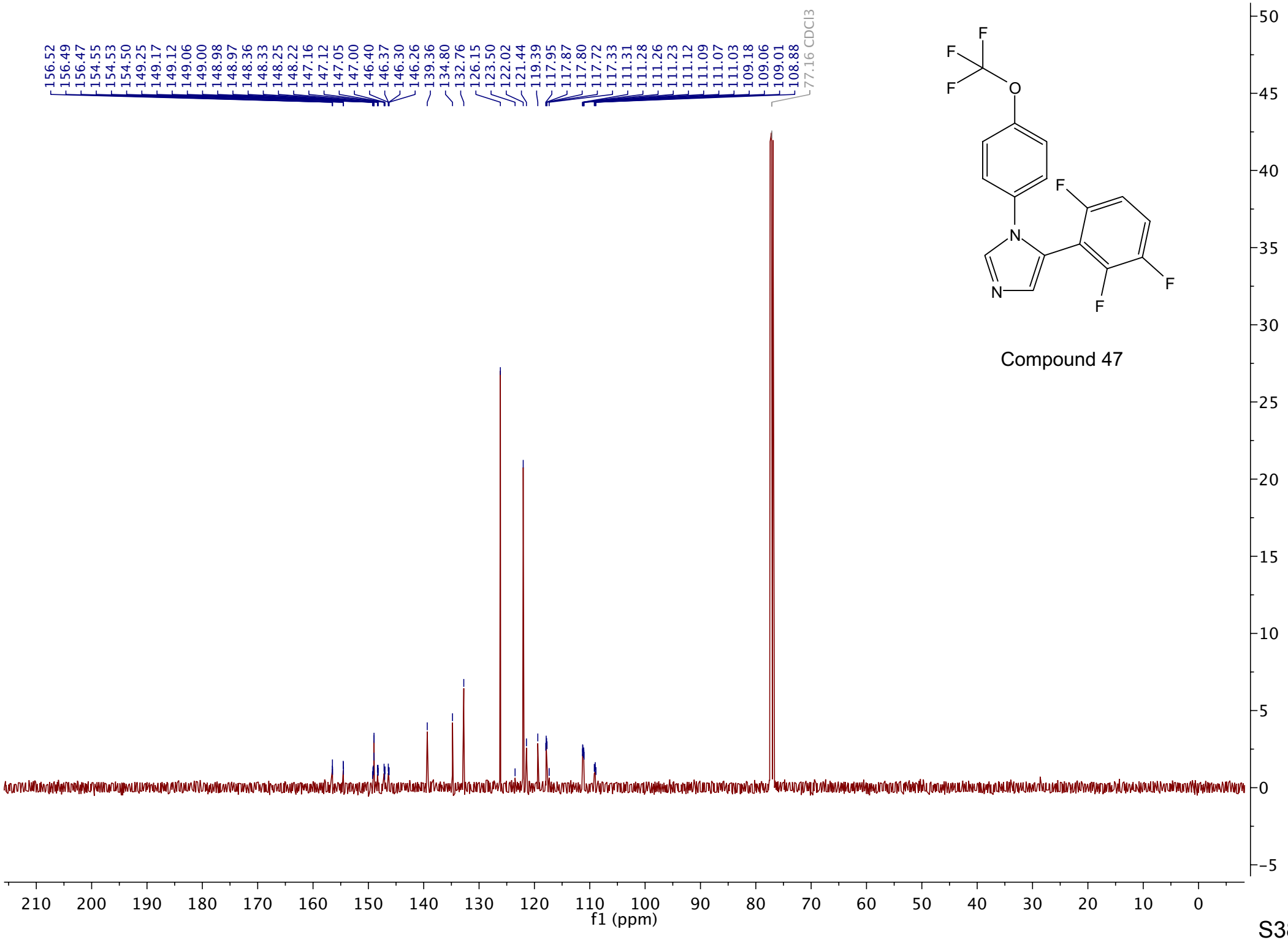
161.81
161.76
159.83
159.78
145.79
137.59
135.43
134.38
130.77
130.69
130.61
129.44
128.40
116.41
111.59
111.55
111.43
111.39
108.28
108.12
107.96
77.16 CDCl3
14.09
13.12
f1 (ppm)

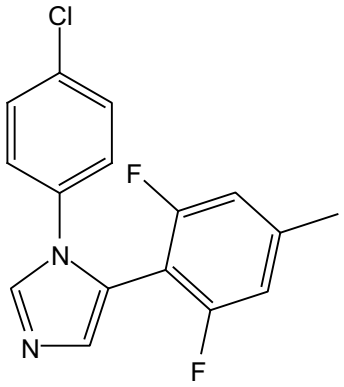

F
F
F
O
F
N
N
F
F
F

Compound 47


7.83
7.36
7.26 CDCl3
7.24
7.22
7.21
7.20
7.19
7.19
7.17
7.16
7.15
7.14
7.13
7.12
7.12
7.11
6.84
6.83
6.83
6.82
6.82
6.81
6.81
6.80
6.80
6.79
6.79

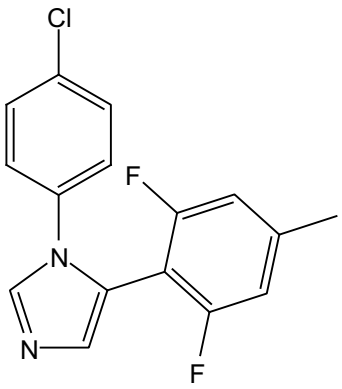
1.00
1.03
4.23
0.97
1.04
f1 (ppm)


156.52
156.49
156.47
154.55
154.53
154.50
149.25
149.17
149.12
149.06
149.00
148.98
148.97
148.36
148.33
148.25
148.22
147.16
147.12
147.05
147.00
146.40
146.37
146.30
146.26
139.36
134.80
132.76
126.15
123.50
122.02
121.44
119.39
117.95
117.87
117.80
117.72
117.33
111.31
111.28
111.26
111.23
111.12
111.09
111.07
111.03
109.18
109.06
109.01
108.88
77.16 CDCl3
F
F
F
O
N
N
F
F
F
Compound 47
50
45
40
35
30
25
20
15
10
5
0
−5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
N
F

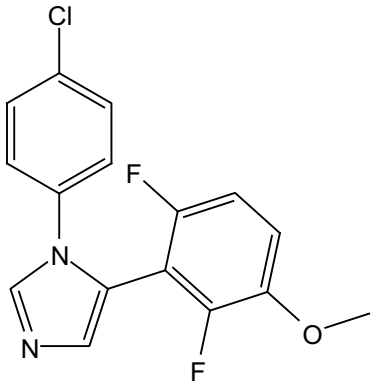
Compound 48

7.76
7.32
7.30
7.26 CDCl3
7.26
7.09
7.07
6.68
6.66
2.32
1.00
2.08
0.96
2.20
2.06
2.92
f1 (ppm)


Cl
F
N
N
F

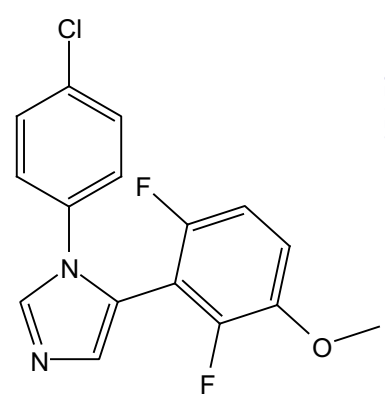
Compound 48

161.12
161.07
159.14
159.08
142.42
142.34
142.26
138.65
135.27
134.11
132.11
129.68
125.88
120.32
112.42
112.38
112.26
112.22
104.19
104.03
103.88
77.16 CDCl3
21.58
f1 (ppm)


Cl
F
N
N
F
O

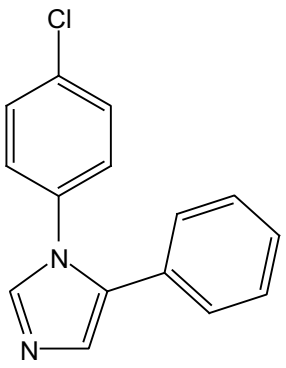
Compound 49

7.79
7.33
7.31
7.26 CDCl3
7.12
7.11
7.09
6.92
6.91
6.90
6.89
6.88
6.87
6.80
6.79
6.77
3.83
1.00
3.32
2.16
1.05
1.03
3.16
f1 (ppm)


Cl
F
N
N
O
F

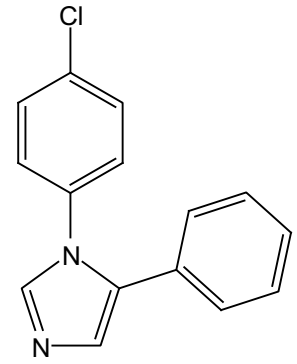
Compound 49

154.70
154.67
152.76
152.73
150.76
150.71
148.77
148.72
144.58
144.55
144.49
144.47
138.92
135.18
134.20
132.42
129.73
125.86
120.12
113.99
113.96
113.91
113.89
110.50
110.47
110.32
110.29
108.23
108.10
108.10
108.06
107.93
77.16 CDCl3
56.86
40
35
30
25
20
15
10
5
0
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

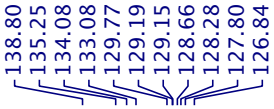

Cl
N
N

Compound 50

7.67
7.37
7.36
7.29
7.28
7.27
7.26 CDCl3
7.13
7.13
7.12
7.11
1.25
H grease
1.00
2.07
4.20
4.41
f1 (ppm)


Cl
N
N

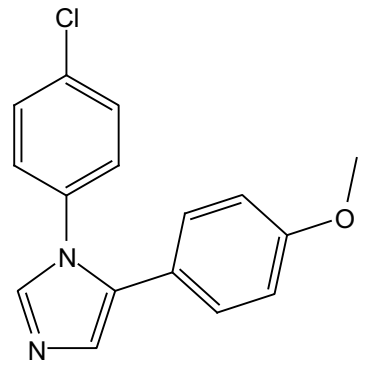
Compound 50


138.80
135.25
134.08
133.08
129.77
129.19
129.15
128.66
128.28
127.80
126.84

77.16 CDCl3

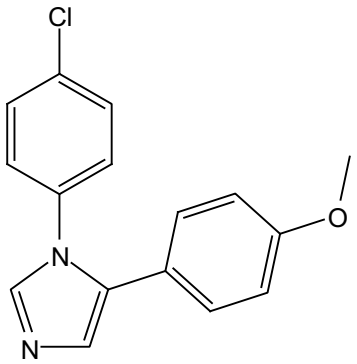
29.78

H grease
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
O
N
N

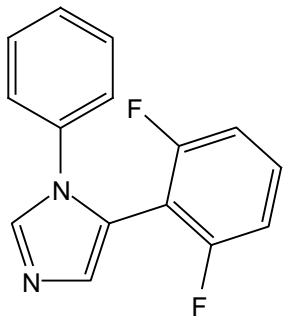
Compound 51

7.64
7.36
7.36
7.34
7.34
7.26 CDCl3
7.18
7.12
7.11
7.10
7.10
7.08
7.06
7.05
7.04
7.03
6.82
6.81
6.80
6.80
3.78
1.00
1.91
1.03
2.05
1.94
1.89
2.93
f1 (ppm)

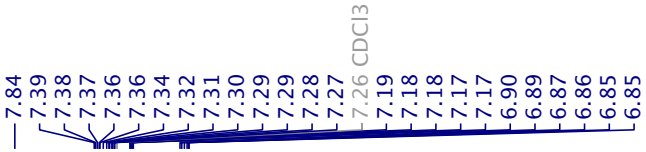

Cl
N
N
O

Compound 51

159.35
138.30
135.38
134.01
132.95
129.74
128.50
126.88
121.62
114.17
77.16 CDCl3
55.35
f1 (ppm)

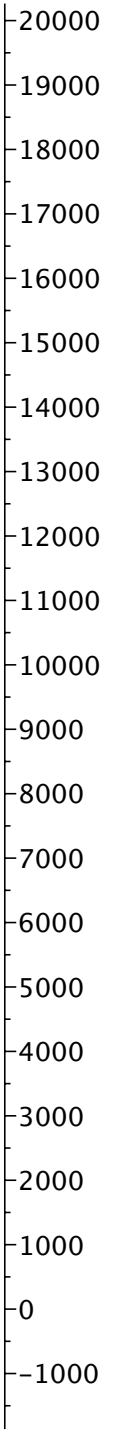

F
N
N
F

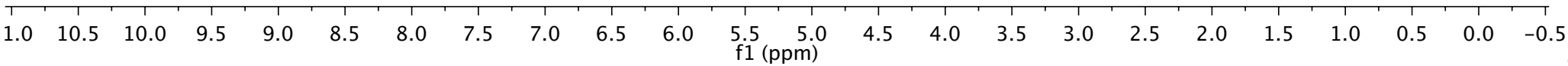
Compound 52

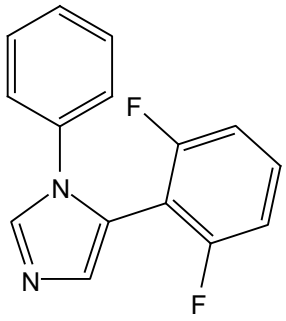

7.84
7.39
7.38
7.37
7.36
7.36
7.34
7.32
7.31
7.30
7.29
7.29
7.28
7.27
7.26 CDCl3
7.19
7.18
7.18
7.17
7.17
6.90
6.89
6.87
6.86
6.85
6.85


1.28


H grease
1.00
3.20
1.05
1.07
2.38
2.25


20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000


1.0
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)

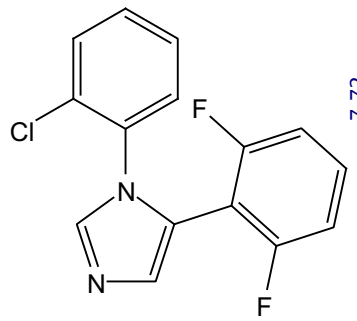


Compound 52

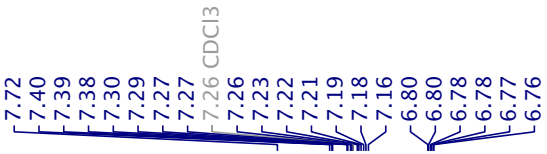
161.57
161.52
159.58
159.53
138.99
136.71
132.15
130.76
130.67
130.59
129.46
128.25
124.59
120.06
111.71
111.67
111.55
111.50
107.81
107.65
107.49
77.16 CDCl3
29.81

H grease

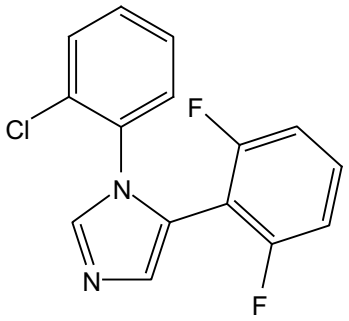
f1 (ppm)


Cl
F
N
N
F

Compound 53

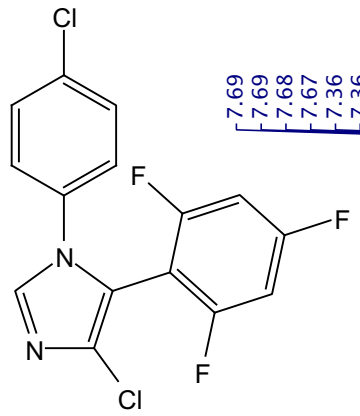

7.72
7.40
7.39
7.38
7.30
7.29
7.27
7.27
7.27 CDCl3
7.26
7.23
7.22
7.21
7.19
7.18
7.16
6.80
6.80
6.78
6.78
6.77
6.76

14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
1.27
0.95
1.78
3.19
2.00
11.5
11.0
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)

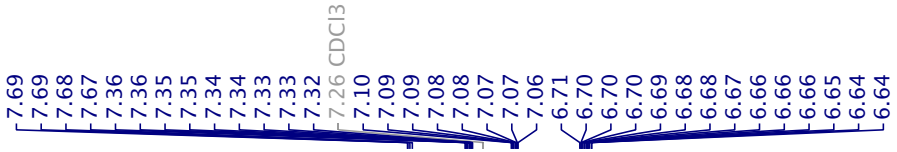

Cl
F
N
N
F

Compound 53

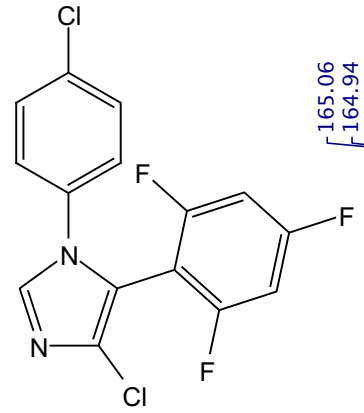
161.51
161.46
159.52
159.47
139.55
134.11
131.55
131.53
130.76
130.68
130.60
130.54
130.13
129.00
127.44
121.01
111.63
111.59
111.46
111.42
107.47
107.31
107.16
77.16 CDCl3
40
35
30
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
N
F
Cl

Compound 54

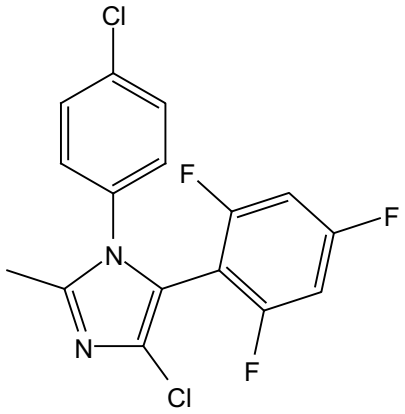

7.69
7.69
7.68
7.67
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.26 CDCl3
7.10
7.09
7.09
7.08
7.08
7.07
7.07
7.06
6.71
6.70
6.70
6.70
6.69
6.68
6.68
6.67
6.66
6.66
6.66
6.65
6.64
6.64

1.00
2.06
2.13
2.05
11.0
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
f1 (ppm)
25000
24000
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000


Cl
F
F
N
N
F
Cl

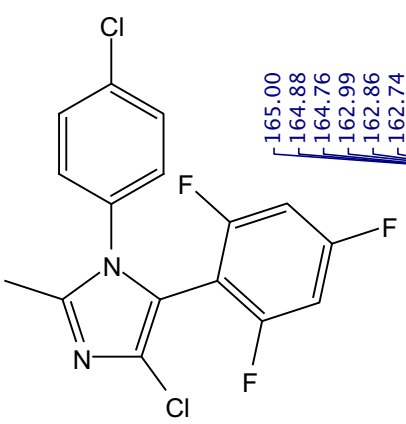
Compound 54

165.06
164.94
164.81
163.04
162.92
162.80
162.14
162.08
162.02
161.96
160.13
160.06
160.01
159.94
136.90
135.09
134.44
132.62
129.98
125.99
115.23
102.05
102.01
101.89
101.85
101.73
101.69
101.21
101.19
101.16
101.01
100.97
100.82
100.79
100.77
77.16 CDCl3
f1 (ppm)


Cl
F
F
N
N
F
Cl

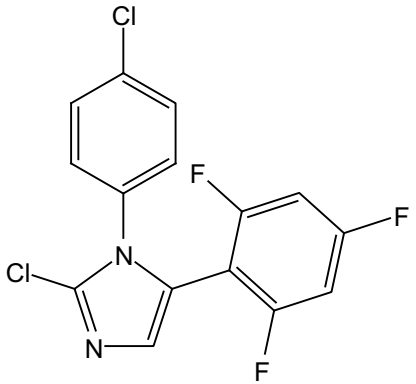
Compound 55

7.81
7.37
7.36
7.26 CDCl3
7.14
7.11
7.10
7.09
6.68
6.66
6.64
2.37
2.12
0.69
2.03
2.17
1.06
3.00
f1 (ppm)


Cl
F
F
N
N
Cl

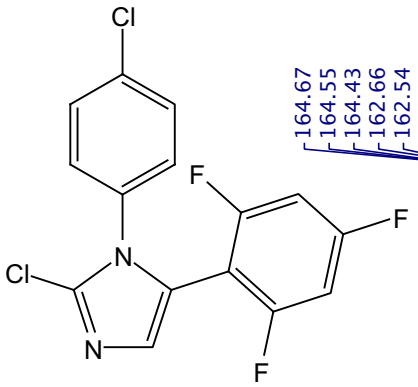
Compound 55

165.00
164.88
164.76
162.99
162.86
162.74
162.36
162.29
162.24
162.17
160.36
160.29
160.24
160.17
145.85
135.65
134.21
130.25
129.96
128.37
115.30
102.54
102.50
102.37
102.34
102.21
102.17
101.05
101.02
100.99
100.84
100.83
100.81
100.78
100.66
100.63
100.60
77.16 CDCl3
29.86
14.02
H grease
f1 (ppm)


Cl
F
F
N
Cl
N
F

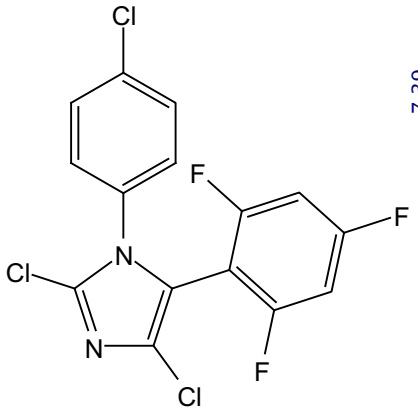
Compound 56

7.37
7.36
7.36
7.35
7.34
7.34
7.26 CDCl3
7.16
7.12
7.10
6.64
6.63
6.63
6.63
6.62
6.61
6.61
6.60
6.59
6.58
1.85
0.77
1.93
2.00
f1 (ppm)


Cl
F
F
N
Cl
N
F

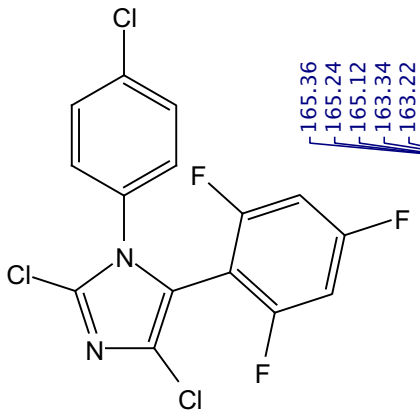
Compound 56

164.67
164.55
164.43
162.66
162.54
162.41
162.14
162.08
162.02
161.96
160.14
160.07
160.02
159.95
135.66
134.53
133.38
130.58
129.69
128.63
121.59
103.62
103.58
103.46
103.42
103.30
103.26
101.06
100.99
100.97
100.93
100.81
100.78
100.77
100.74
100.72
100.60
100.56
100.54
77.16 CDCl3
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
−5000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
Cl
N
F
Cl

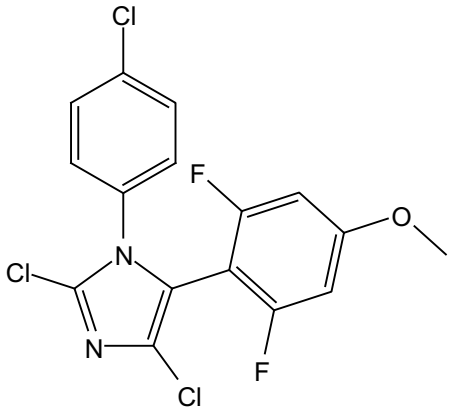
Compound 57

7.39
7.39
7.39
7.38
7.38
7.37
7.37
7.37
7.37
7.36
7.36
7.26 CDCl3
7.13
7.11
6.69
6.68
6.68
6.67
6.67
6.66
6.66
6.66
6.65
6.64
6.64
6.64
6.63
1.93
1.99
2.00
f1 (ppm)


Cl
F
F
N
Cl
N
Cl
F

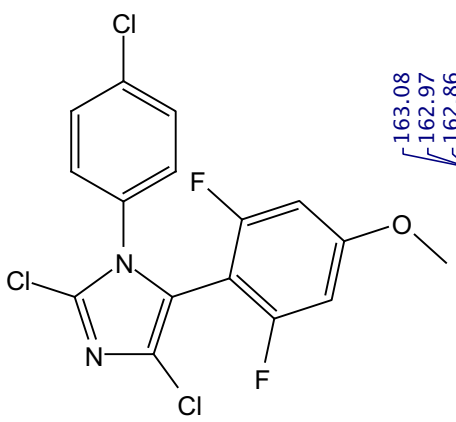
Compound 57

165.36
165.24
165.12
163.34
163.22
163.10
162.36
162.30
162.24
162.18
160.35
160.28
160.23
160.16
136.22
132.94
132.88
130.83
129.91
128.57
117.68
101.79
101.75
101.62
101.59
101.47
101.43
101.23
101.20
101.17
101.04
101.02
100.99
100.97
100.84
100.81
100.78
77.16 CDCl3
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
O
N
Cl
N
Cl
F

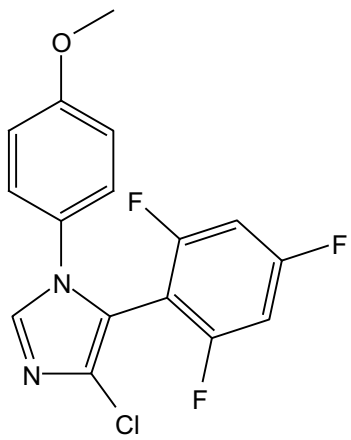
Compound 58

7.38
7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.26 CDCl3
7.13
7.12
6.43
6.42
6.42
6.42
6.40
6.40
6.39
3.78
1.66
1.86
1.76
3.00
f1 (ppm)


Cl
F
O
N
Cl
N
F
Cl

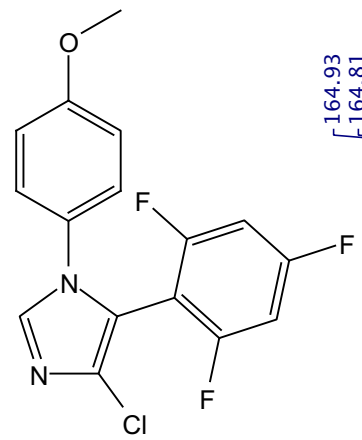
Compound 58

163.08
162.97
162.86
162.62
162.54
160.63
160.56
135.90
133.24
132.20
130.42
129.75
128.66
118.83
101.23
101.20
101.02
100.99
100.81
100.78
98.47
98.45
98.42
98.28
98.25
98.24
97.19
97.03
96.86
77.16 CDCl3
56.07
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
F
F
N
N
F
Cl

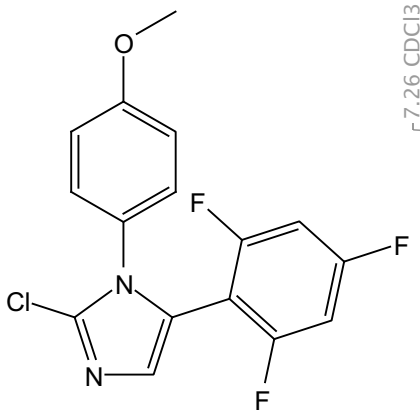
Compound 59

7.64
7.26 CDCl3
7.07
7.05
6.86
6.86
6.85
6.84
6.69
6.67
6.66
6.66
6.64
6.63
3.79
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
1.00
2.03
2.05
2.07
2.80
1.0 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)

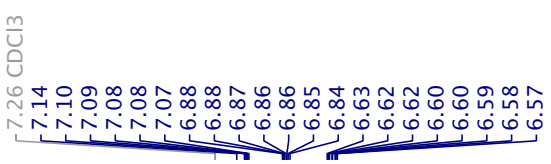

O
F
F
N
N
F
Cl

Compound 59

164.93
164.81
164.69
162.92
162.80
162.68
162.31
162.25
162.19
162.12
160.31
160.24
160.18
160.12
159.91
137.20
131.91
128.82
126.27
115.51
114.71
102.45
102.42
102.29
102.25
102.13
102.09
101.04
101.02
100.99
100.84
100.82
100.82
100.80
100.65
100.62
100.60
77.16 CDCl3
55.63
f1 (ppm)


O
F
F
N
Cl
N
F

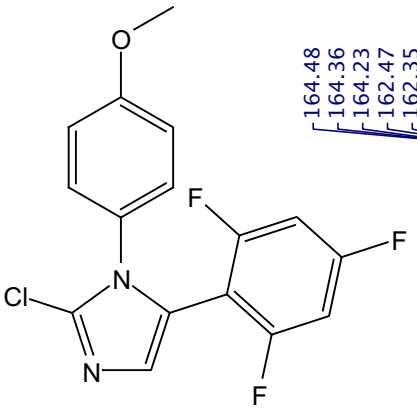
Compound 60


7.26 CDCl3
7.14
7.10
7.09
7.08
7.08
7.07
6.88
6.88
6.87
6.86
6.86
6.85
6.84
6.63
6.62
6.62
6.60
6.60
6.59
6.58
6.57

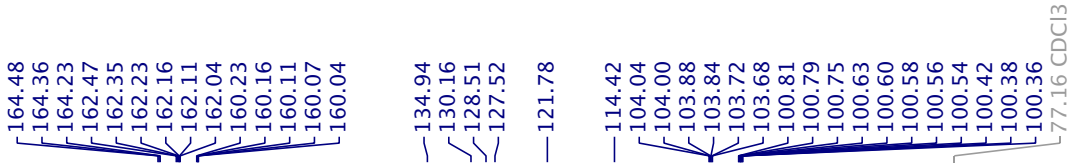

3.81
3.79

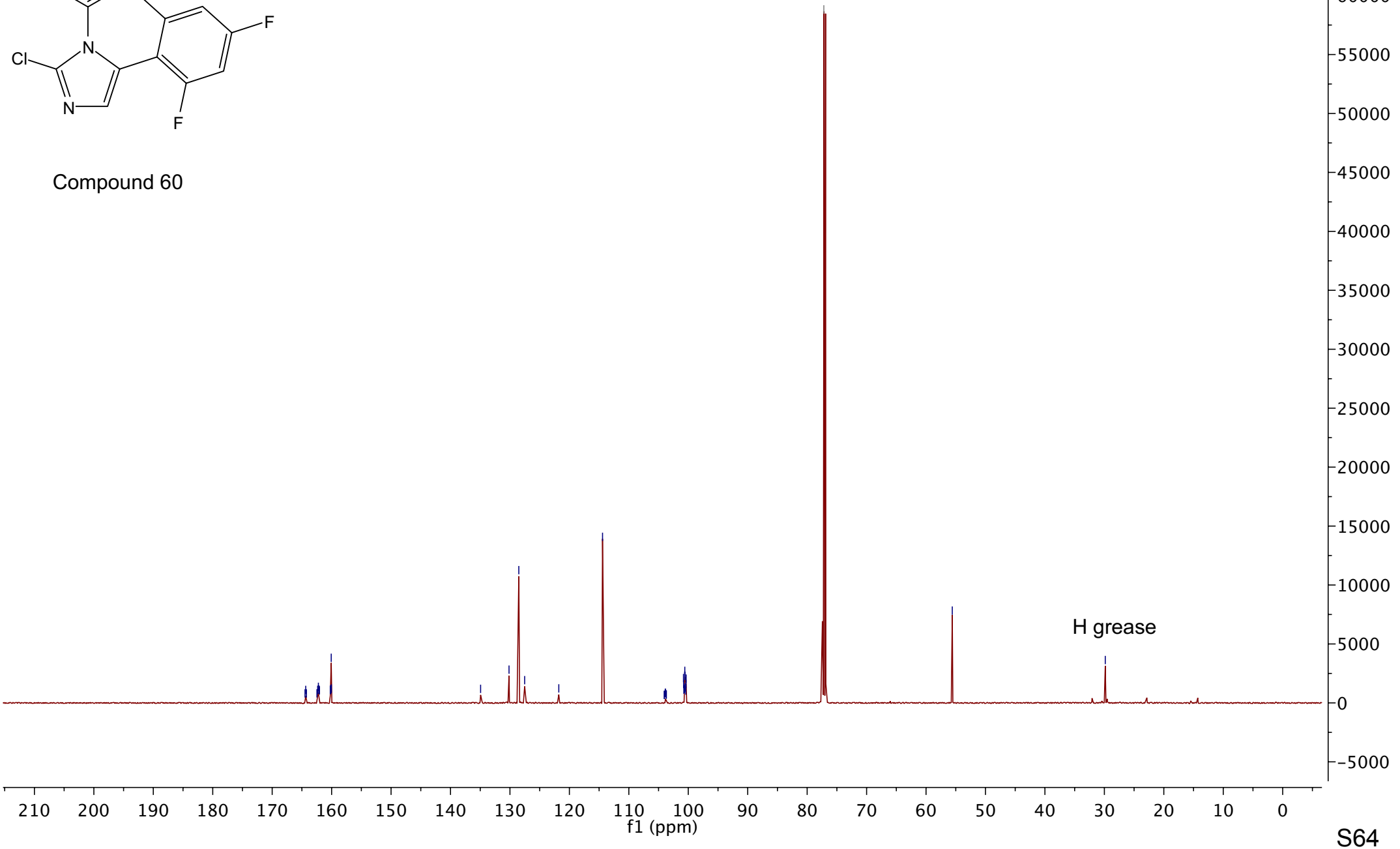

1.62
1.25

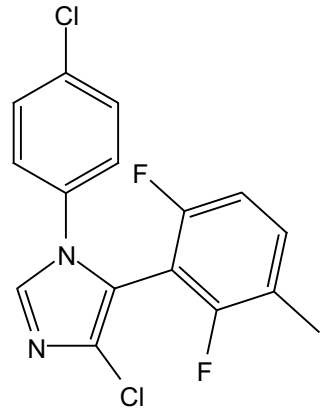
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Traces of H grease
Water
1.00
2.15
1.99
2.00
2.54
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


O
F
F
N
Cl
N
F

Compound 60

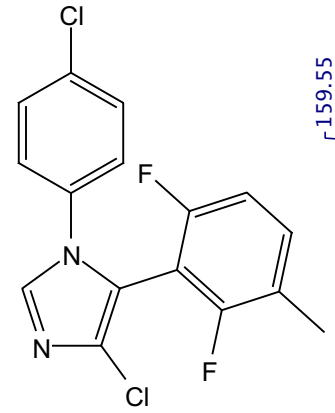

164.48
164.36
164.23
162.47
162.35
162.23
162.16
162.11
162.04
160.23
160.16
160.11
160.07
160.04
134.94
130.16
128.51
127.52
121.78
114.42
104.04
104.00
103.88
103.84
103.72
103.68
100.81
100.79
100.75
100.63
100.60
100.58
100.56
100.54
100.42
100.38
100.36
77.16 CDCl3
55.59
29.85


H grease
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
N
Cl
F

Compound 62

7.74
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.26 CDCl3
7.26
7.24
7.23
7.21
7.16
7.16
7.15
7.15
7.14
7.13
7.13
7.12
7.12
6.84
6.84
6.83
6.82
6.81
6.81
2.23
0.79
1.53
1.04
1.49
0.75
3.00
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
11.0
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
f1 (ppm)



Compound 62

159.55
159.51
159.46
159.41
157.57
157.53
157.47
157.42
136.49
134.58
134.56
133.27
133.21
133.19
133.13
131.96
129.69
125.74
121.12
121.09
120.98
120.95
116.38
111.05
111.02
110.88
110.85
104.69
104.53
104.37

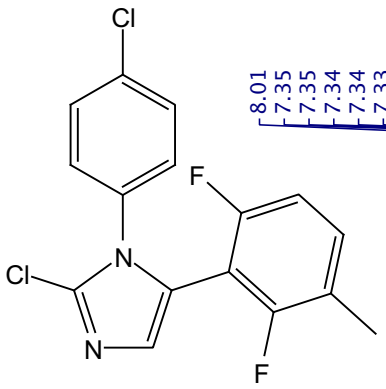
77.16 CDCl3

14.12
14.09

45
40
35
30
25
20
15
10
5
0

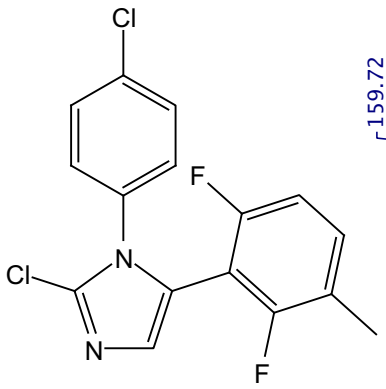
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)


Cl
F
N
Cl
N
F

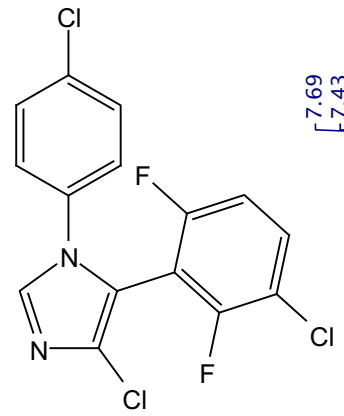
Compound 63

8.01
7.35
7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.26 CDCl3
7.16
7.14
7.13
7.13
7.12
7.11
7.11
7.10
7.09
7.08
6.73
6.73
6.72
6.71
6.70
6.70
2.95
2.87
2.15
1.24
DMF
DMF
H grease
2.08
1.00
3.12
0.96
4.13
f1 (ppm)


Cl
F
N
Cl
N
F

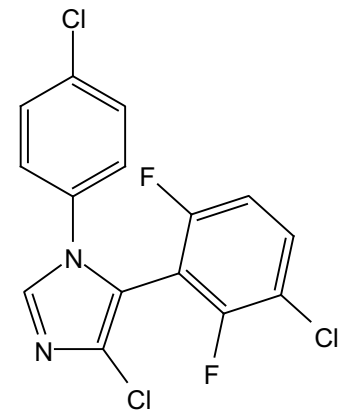
Compound 63

159.72
159.68
159.62
159.57
157.75
157.71
157.64
157.59
135.30
134.12
133.71
132.73
132.68
132.65
132.60
130.33
129.48
128.68
123.01
121.04
121.01
120.98
120.89
120.86
110.98
110.95
110.87
110.81
110.78
106.49
106.46
106.33
106.29
106.17
77.16 CDCl3
14.28
14.25
170000
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
N
Cl
F
Cl

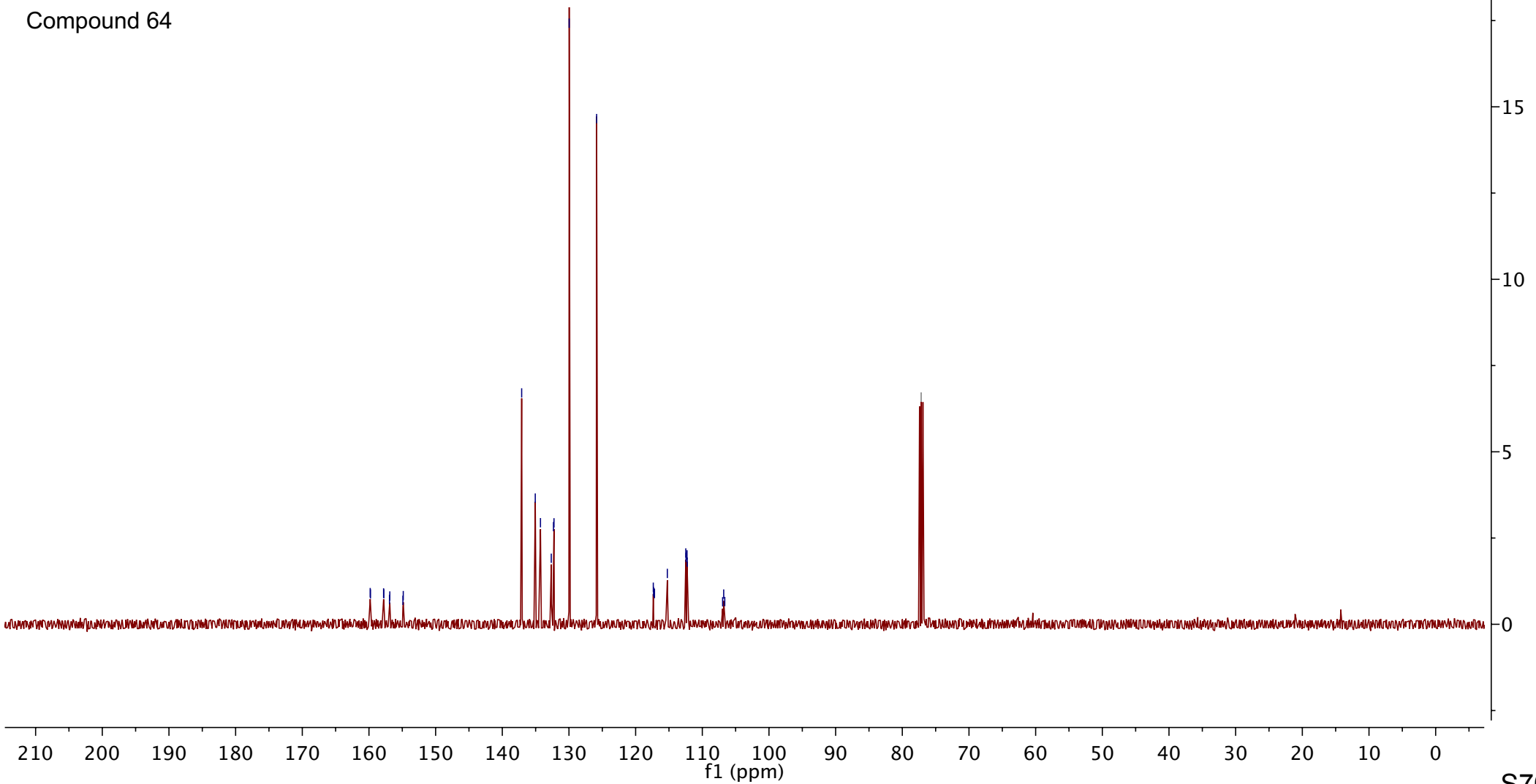
Compound 64

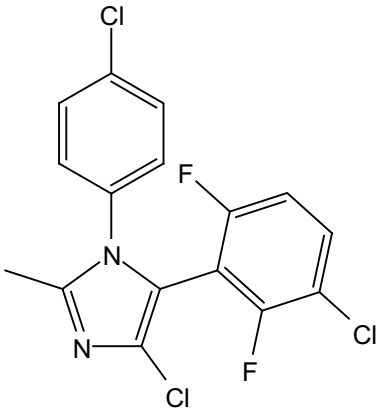
7.69
7.43
7.42
7.41
7.41
7.40
7.40
7.40
7.38
7.34
7.34
7.33
7.32
7.32
7.31
7.26 CDCl3
7.10
7.09
7.09
7.08
7.07
7.07
7.06
6.88
6.87
6.86
6.86
6.86
6.84
6.84
4.10
4.09
4.07
4.06
2.01
1.23
1.22
1.21
EtOAc
EtOAc
EtOAc
1.00
1.01
2.39
2.14
1.08
f1 (ppm)



Compound 64

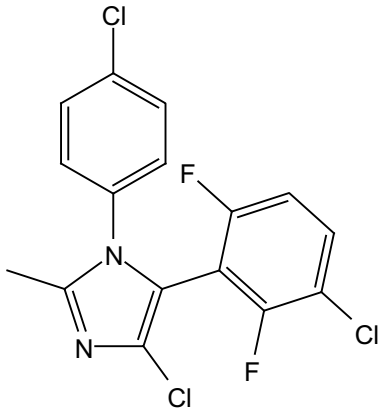
159.81
159.78
157.81
157.77
156.92
156.87
154.90
154.85
137.09
135.06
134.27
132.65
132.32
132.25
129.97
125.85
117.35
117.32
117.20
117.17
115.25
112.48
112.44
112.29
112.26
106.95
106.79
106.63
77.16 CDCl3




Cl
F
N
N
Cl
F
Cl

Compound 65

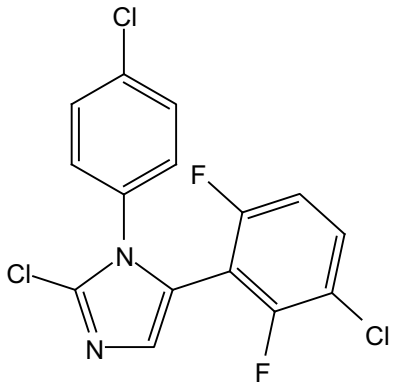
7.38
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.26 CDCl3
7.08
7.07
6.83
6.83
6.82
6.81
6.81
6.80
6.79
2.30
3.21
2.21
1.03
3.00
f1 (ppm)



Compound 65

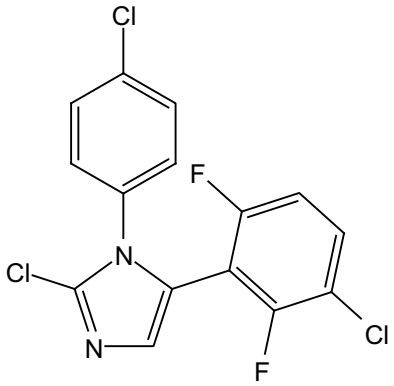
160.04
160.00
158.04
158.00
157.13
157.08
155.12
155.07
146.08
135.50
134.14
132.09
132.02
130.54
129.91
128.29
117.17
117.14
117.03
116.99
115.24
112.30
112.27
112.11
112.08
107.58
107.42
107.25
77.16 CDCl3
14.06

f1 (ppm)


Cl
F
N
Cl
N
Cl
F

Compound 66

7.37
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.33
7.32
7.26 CDCl3
7.20
7.14
7.14
7.13
7.13
7.12
7.11
7.11
6.83
6.82
6.82
6.81
6.80
6.80
6.80
6.79
6.78
4.12
4.11
4.10
4.08
2.03
1.25
1.24
1.23
EtOAc
EtOAc
EtOAc
3.05
0.86
2.02
1.00
f1 (ppm)



Compound 66

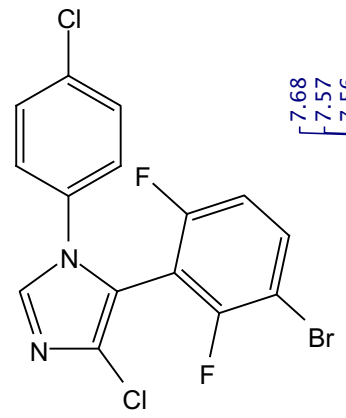
159.85
159.81
157.85
157.81
157.00
156.95
154.99
154.95
135.64
134.86
133.35
131.78
131.70
130.88
129.69
128.57
121.65
117.31
117.27
117.16
117.13
112.30
112.27
112.12
112.08
108.60
108.44
108.28

77.16 CDCl3

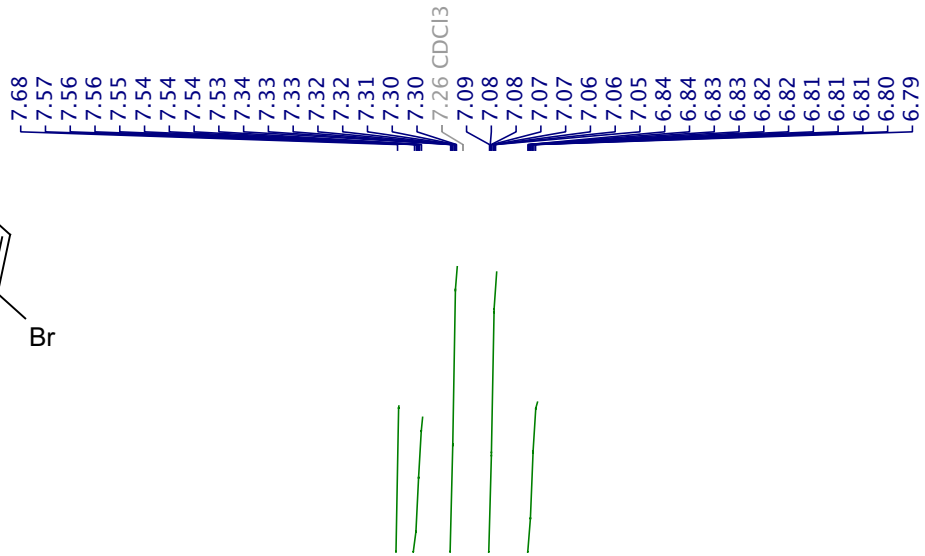
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000

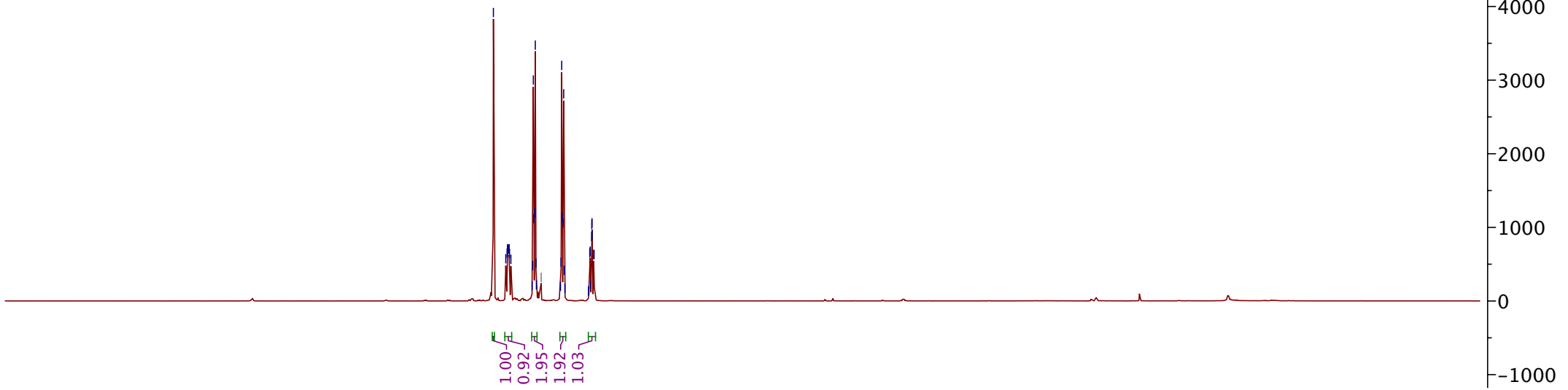
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

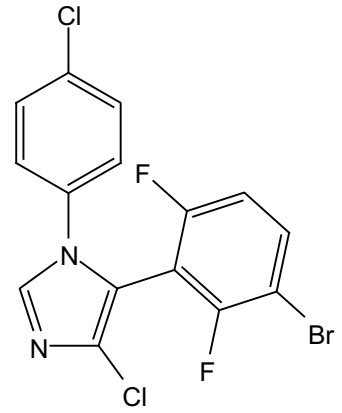

Cl
F
N
N
Br
F
Cl

Compound 67


7.68
7.57
7.56
7.56
7.55
7.54
7.54
7.54
7.53
7.34
7.33
7.33
7.32
7.32
7.31
7.30
7.30
7.26 CDCl3
7.09
7.08
7.08
7.07
7.07
7.06
7.06
7.05
6.84
6.84
6.83
6.83
6.82
6.82
6.81
6.81
6.81
6.80
6.79

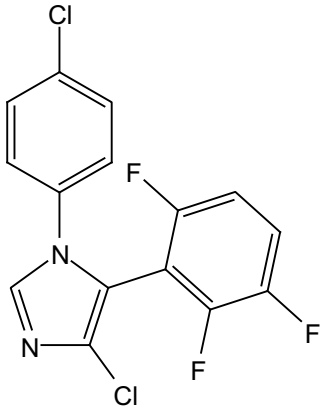

1.00
0.92
1.95
1.92
1.03

12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.5 11.0 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 -1.0
f1 (ppm)


Cl
F
N
N
Br
F
Cl

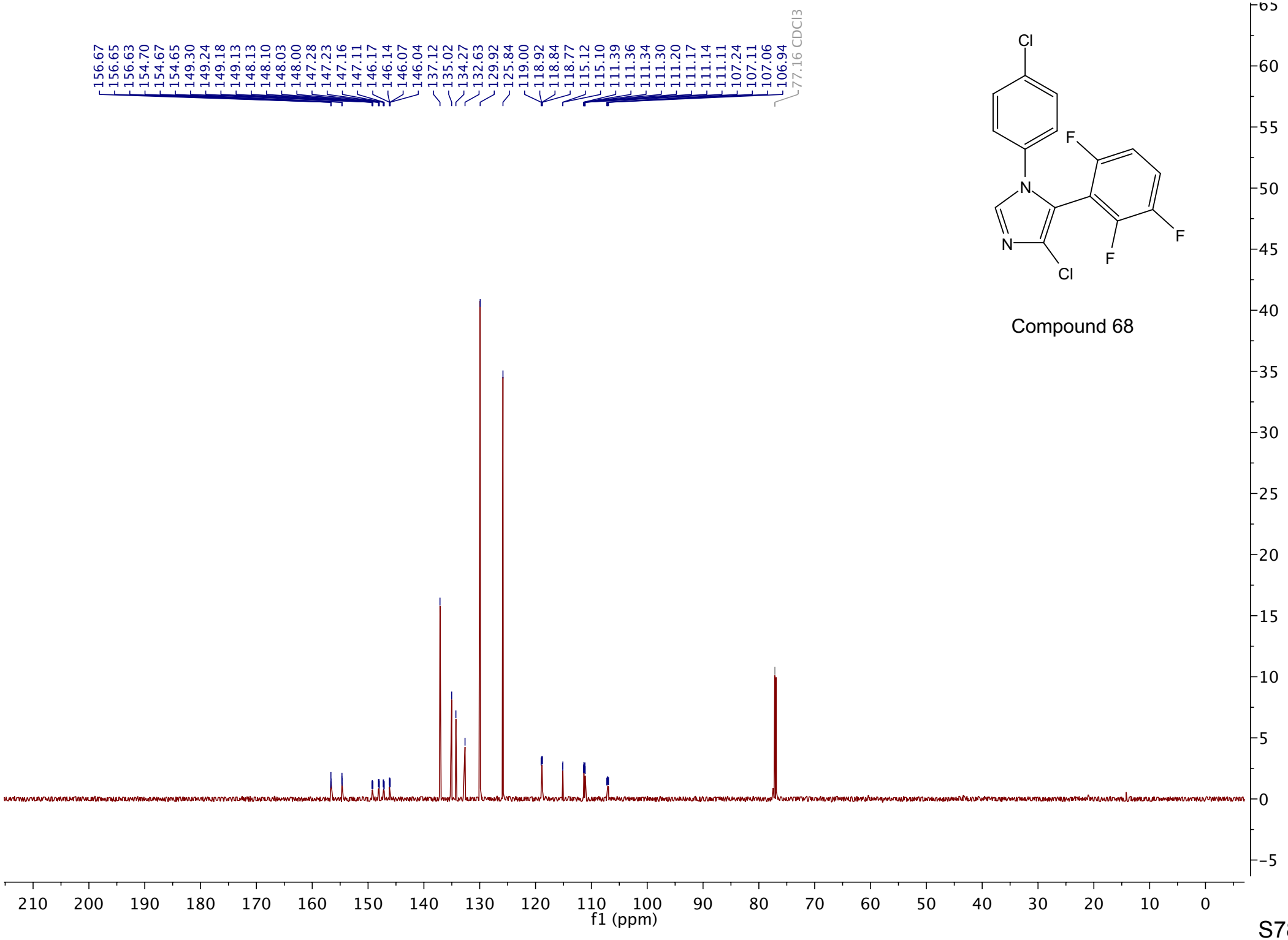
Compound 67

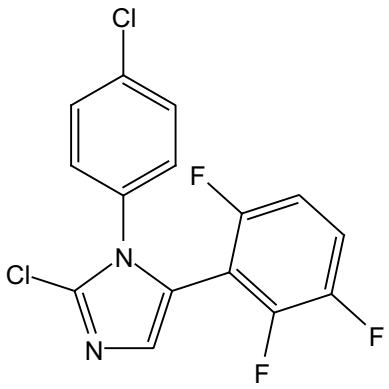
160.53
160.50
158.52
158.49
157.86
157.81
155.85
155.81
137.04
135.14
135.13
135.07
135.05
135.01
134.23
132.59
129.93
125.81
115.25
113.00
112.97
112.82
112.78
106.86
106.70
106.53
104.54
104.51
104.37
104.34
77.16 CDCl3
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
N
F
F
Cl

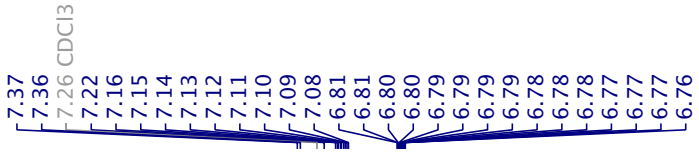
Compound 68

7.69
7.33
7.33
7.32
7.32
7.31
7.31
7.26 CDCl3
7.21
7.20
7.19
7.18
7.18
7.17
7.16
7.15
7.10
7.09
7.09
7.08
7.08
7.07
7.07
7.05
6.85
6.84
6.84
6.84
6.83
6.83
6.83
6.82
6.82
6.82
6.82
6.81
6.81
6.81
6.80
1.00
2.15
1.03
2.16
1.09
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.0
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
f1 (ppm)

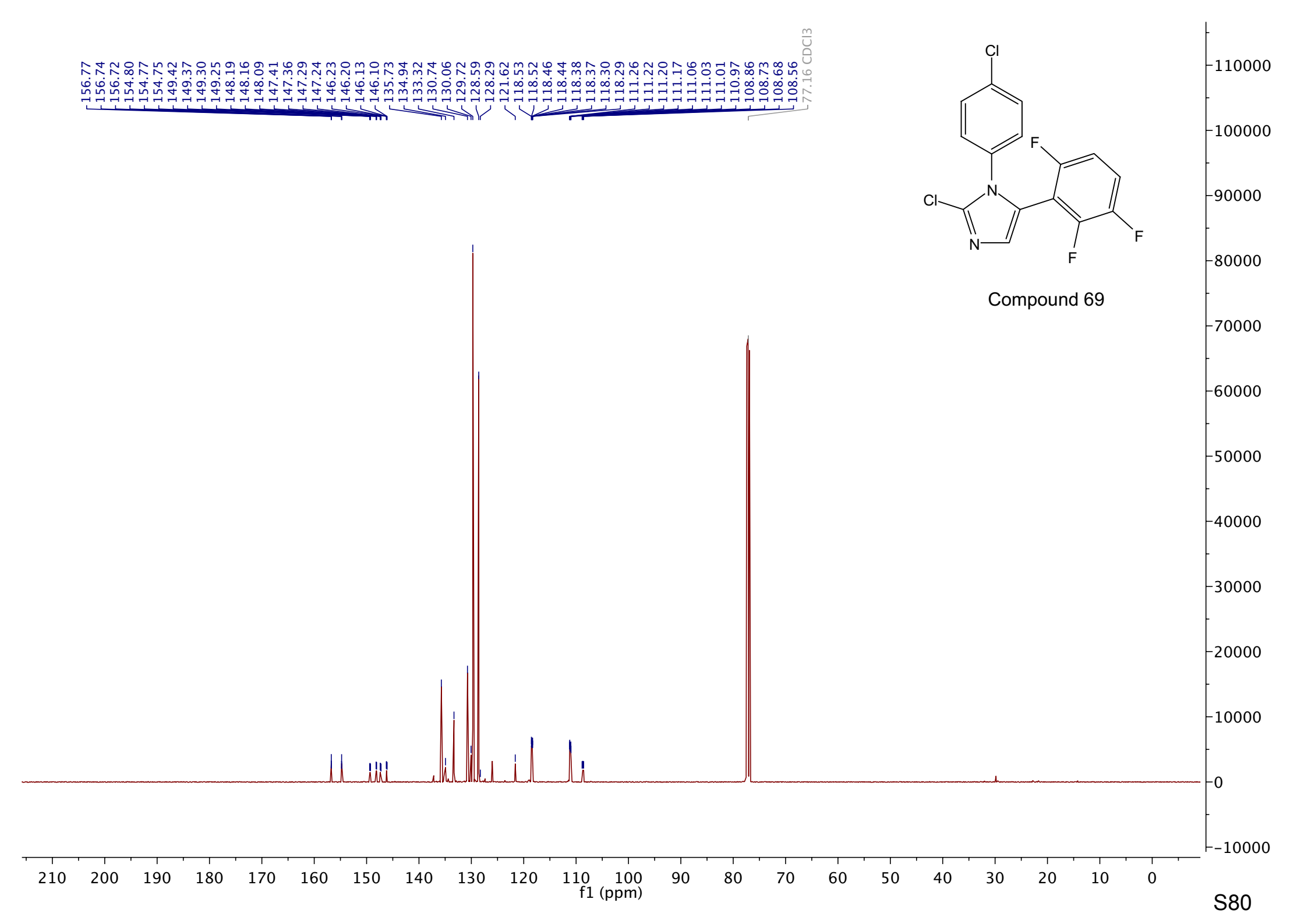

156.67
156.65
156.63
154.70
154.67
154.65
149.30
149.24
149.18
149.13
148.13
148.10
148.03
148.00
147.28
147.23
147.16
147.11
146.17
146.14
146.07
146.04
137.12
135.02
134.27
132.63
129.92
125.84
119.00
118.92
118.84
118.77
115.12
115.10
111.39
111.36
111.34
111.30
111.20
111.17
111.14
111.11
107.24
107.11
107.06
106.94
77.16 CDCl3
Cl
F
N
N
F
F
Cl
Compound 68
f1 (ppm)

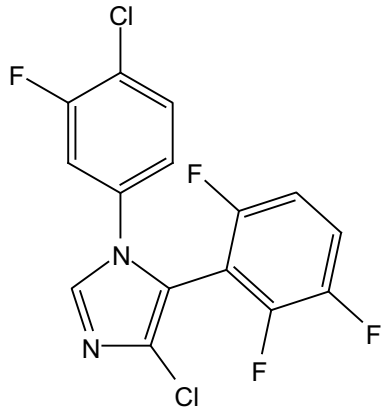

Cl
F
N
Cl
N
F
F

Compound 69


7.37
7.36
7.26 CDCl3
7.22
7.16
7.15
7.14
7.13
7.12
7.11
7.10
7.09
7.08
6.81
6.81
6.80
6.80
6.79
6.79
6.79
6.79
6.78
6.78
6.78
6.77
6.77
6.77
6.76

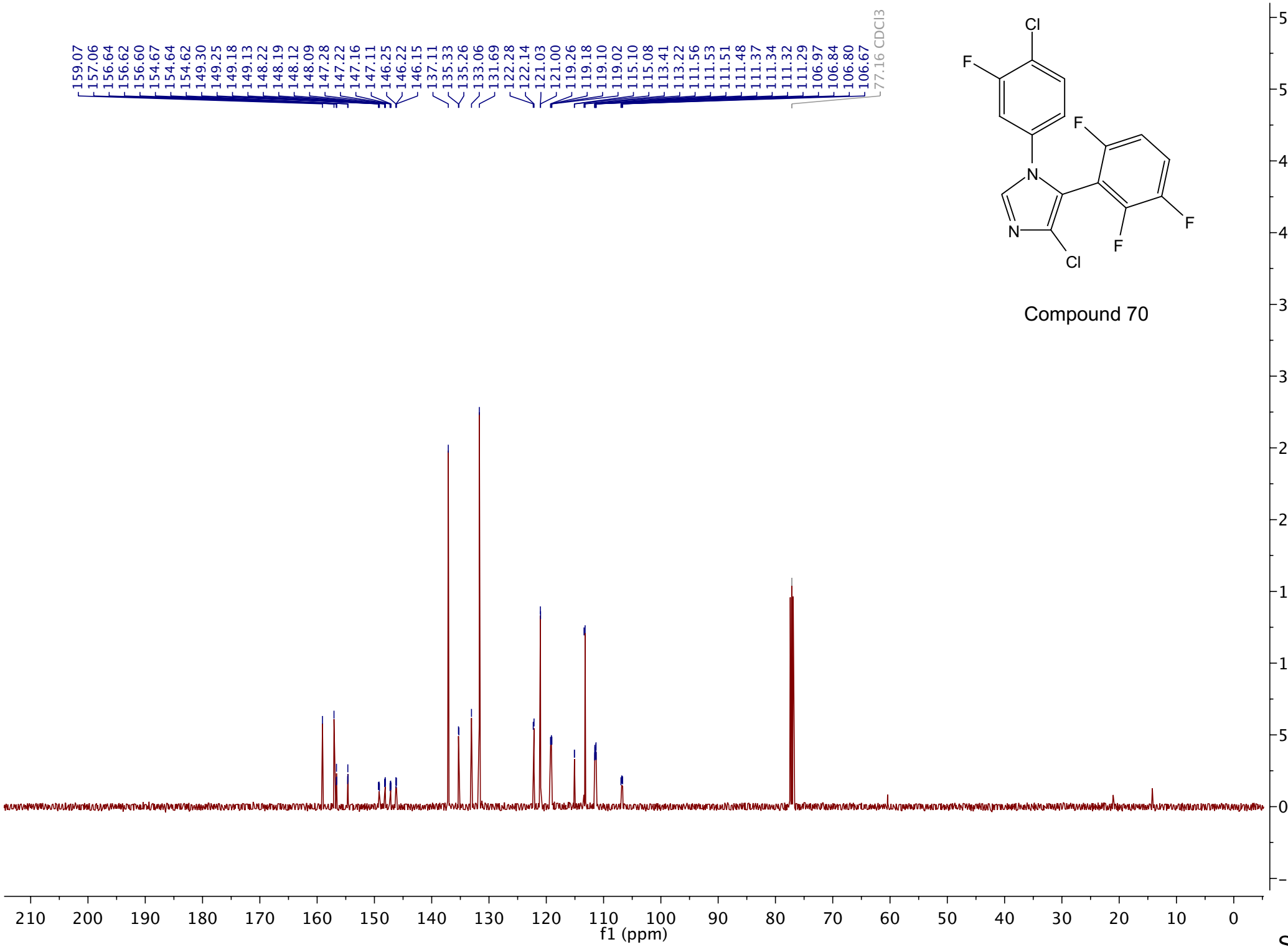
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
2.42
1.00
3.40
1.10
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

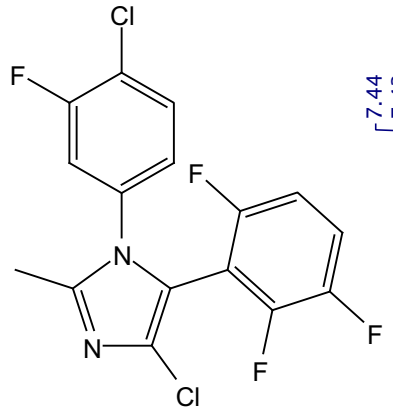

156.77
156.74
156.72
154.80
154.77
154.75
149.42
149.37
149.30
149.25
148.19
148.16
148.09
147.41
147.36
147.29
147.24
146.23
146.20
146.13
146.10
135.73
134.94
133.32
130.74
130.06
129.72
128.59
128.29
121.62
118.53
118.52
118.46
118.44
118.38
118.37
118.30
118.29
111.26
111.22
111.20
111.17
111.06
111.03
111.01
110.97
108.86
108.73
108.68
108.56
77.16 CDCl3
Cl
F
N
Cl
N
F
F
Compound 69
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
−10000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
N
F
F
Cl

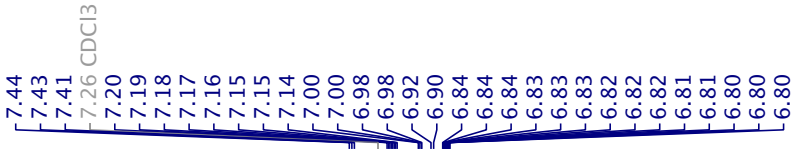
Compound 70

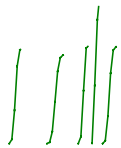
7.72
7.42
7.40
7.39
7.26 CDCl3
7.25
7.24
7.23
7.22
7.21
7.20
7.20
7.19
7.00
6.99
6.98
6.98
6.92
6.92
6.92
6.92
6.91
6.90
6.90
6.90
6.89
6.88
6.88
6.88
6.87
6.87
6.86
6.86
6.86
6.85
6.85
6.85
6.84
4.10
4.09
4.07
4.06
2.00
1.23
1.22
1.20
EtOAc
EtOAc
EtOAc
1.00
1.10
0.88
0.91
0.97
0.69
f1 (ppm)

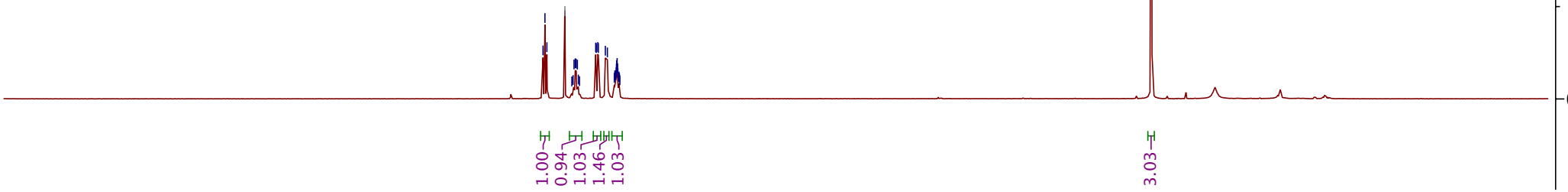

159.07
157.06
156.64
156.62
156.60
154.67
154.64
154.62
149.30
149.25
149.18
149.13
148.22
148.19
148.12
148.09
147.28
147.22
147.16
147.11
146.25
146.22
146.15
137.11
135.33
135.26
133.06
131.69
122.28
122.14
121.03
121.00
119.26
119.18
119.10
119.02
115.10
115.08
113.41
113.22
111.56
111.53
111.51
111.48
111.37
111.34
111.32
111.29
106.97
106.84
106.80
106.67
77.16 CDCl3
Cl
F
F
N
N
Cl
F
F
Compound 70
55
50
45
40
35
30
25
20
15
10
5
0
−5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
N
F
F
Cl

Compound 71

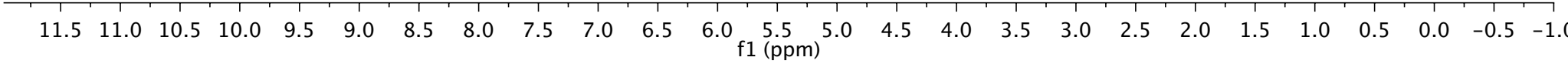

7.44
7.43
7.41
7.26 CDCl3
7.20
7.19
7.18
7.17
7.16
7.15
7.15
7.14
7.00
7.00
6.98
6.98
6.92
6.90
6.84
6.84
6.84
6.83
6.83
6.82
6.82
6.82
6.81
6.81
6.80
6.80
6.80

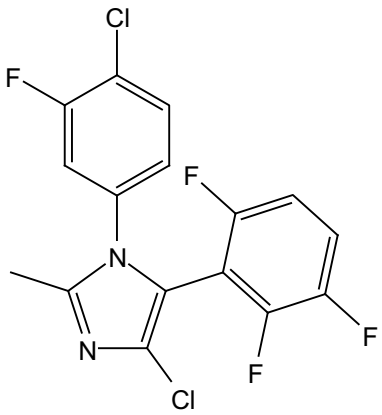




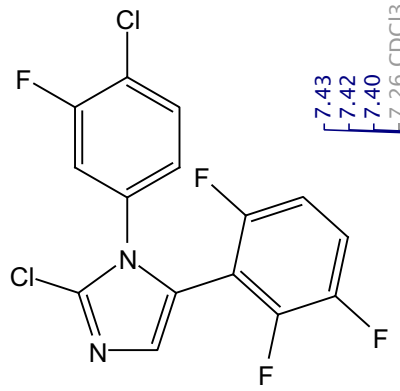
1.00
0.94
1.03
1.46
1.03

3.03


11.5
11.0
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
-1.0
f1 (ppm)

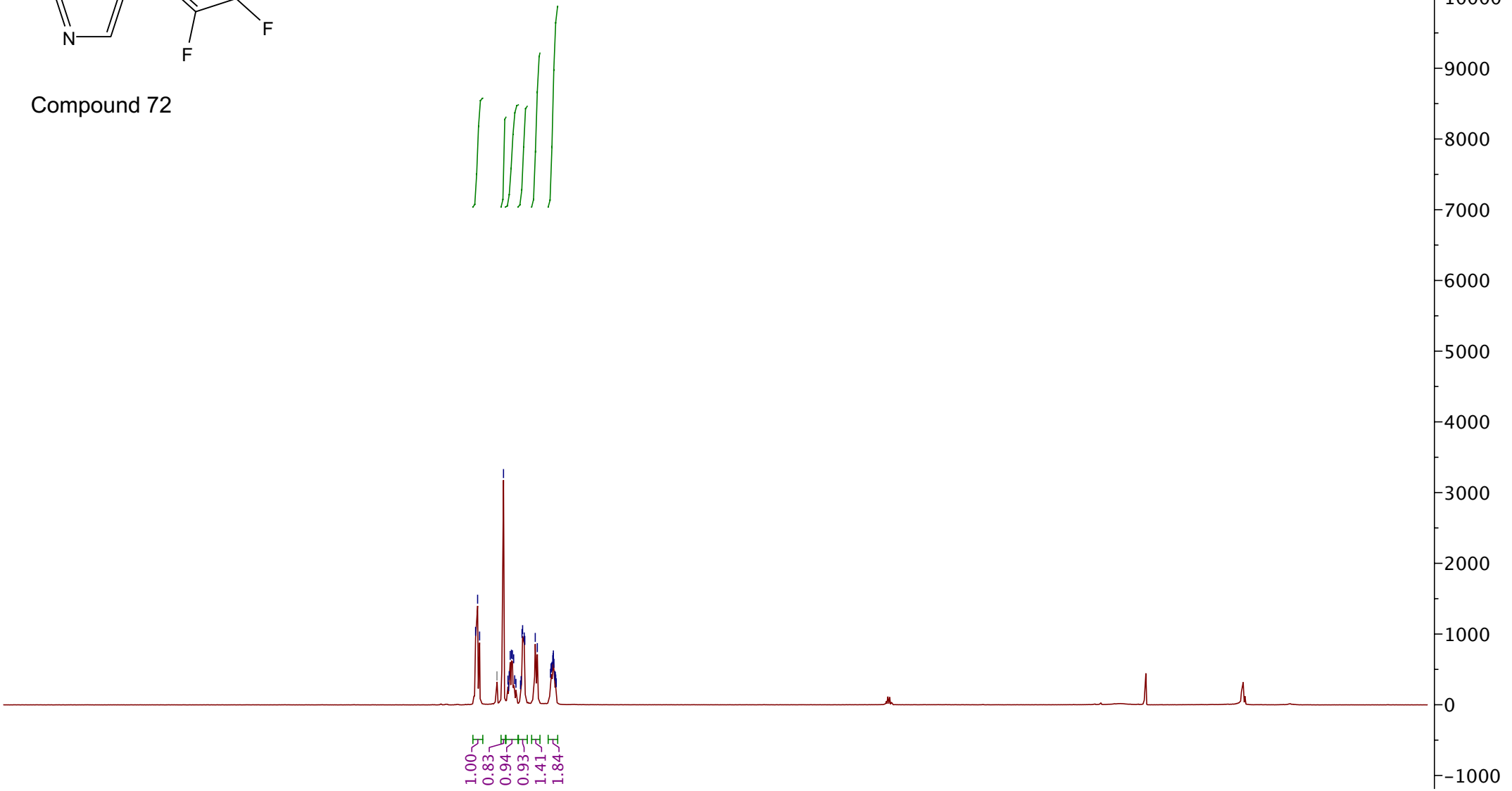


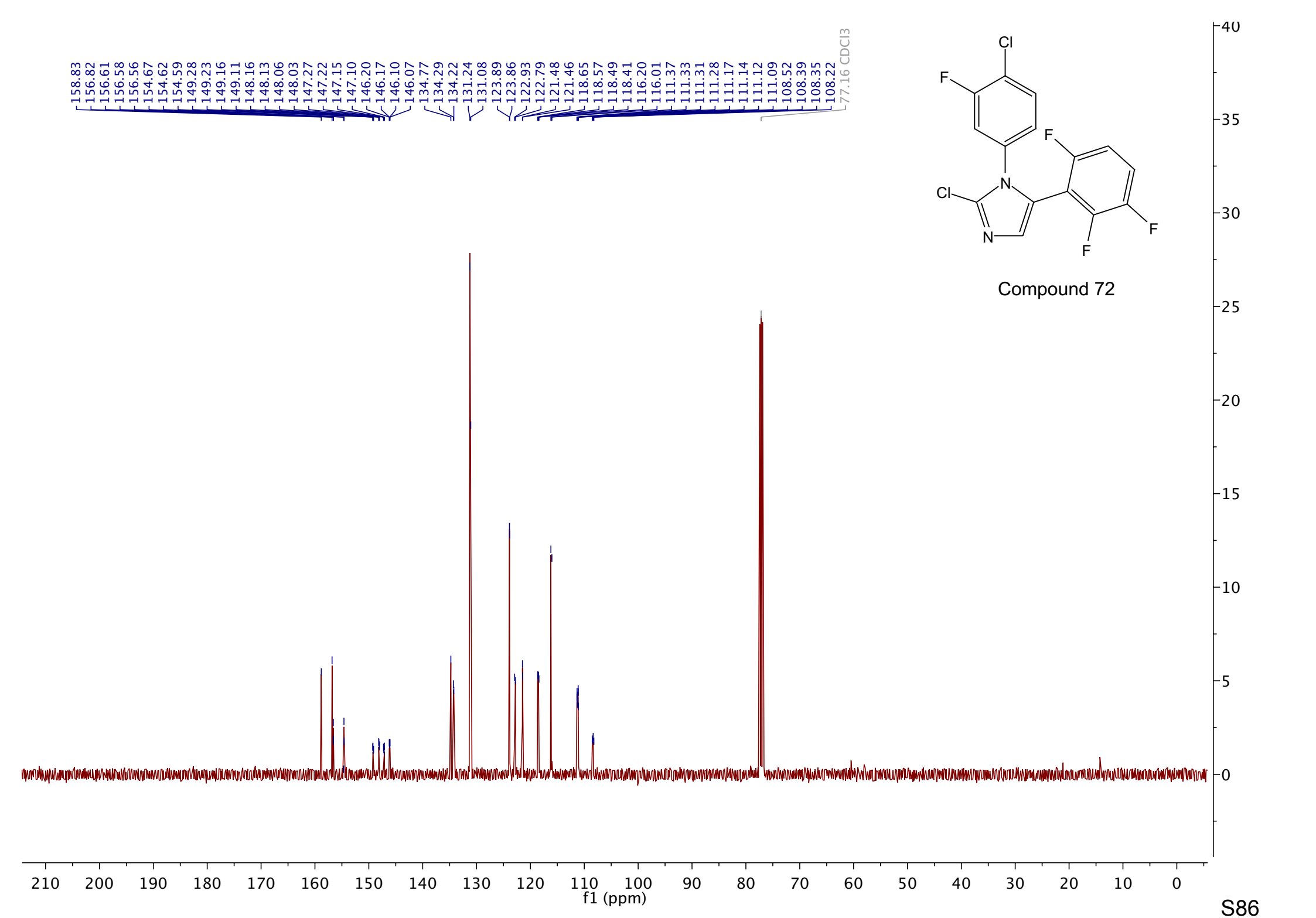
Compound 71

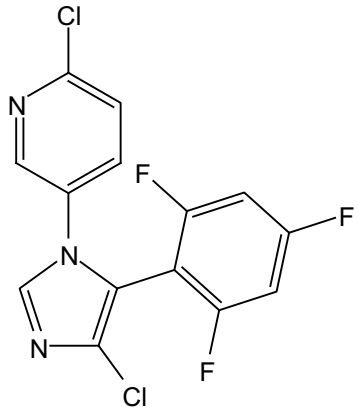

Cl
F
F
N
Cl
N
F
F

Compound 72


7.43
7.42
7.40
7.26 CDCl3
7.21
7.17
7.17
7.16
7.15
7.14
7.14
7.13
7.12
7.11
7.07
7.07
7.06
7.05
7.04
7.04
6.95
6.93
6.83
6.82
6.82
6.82
6.81
6.81
6.80
6.80
6.79
6.79
6.78

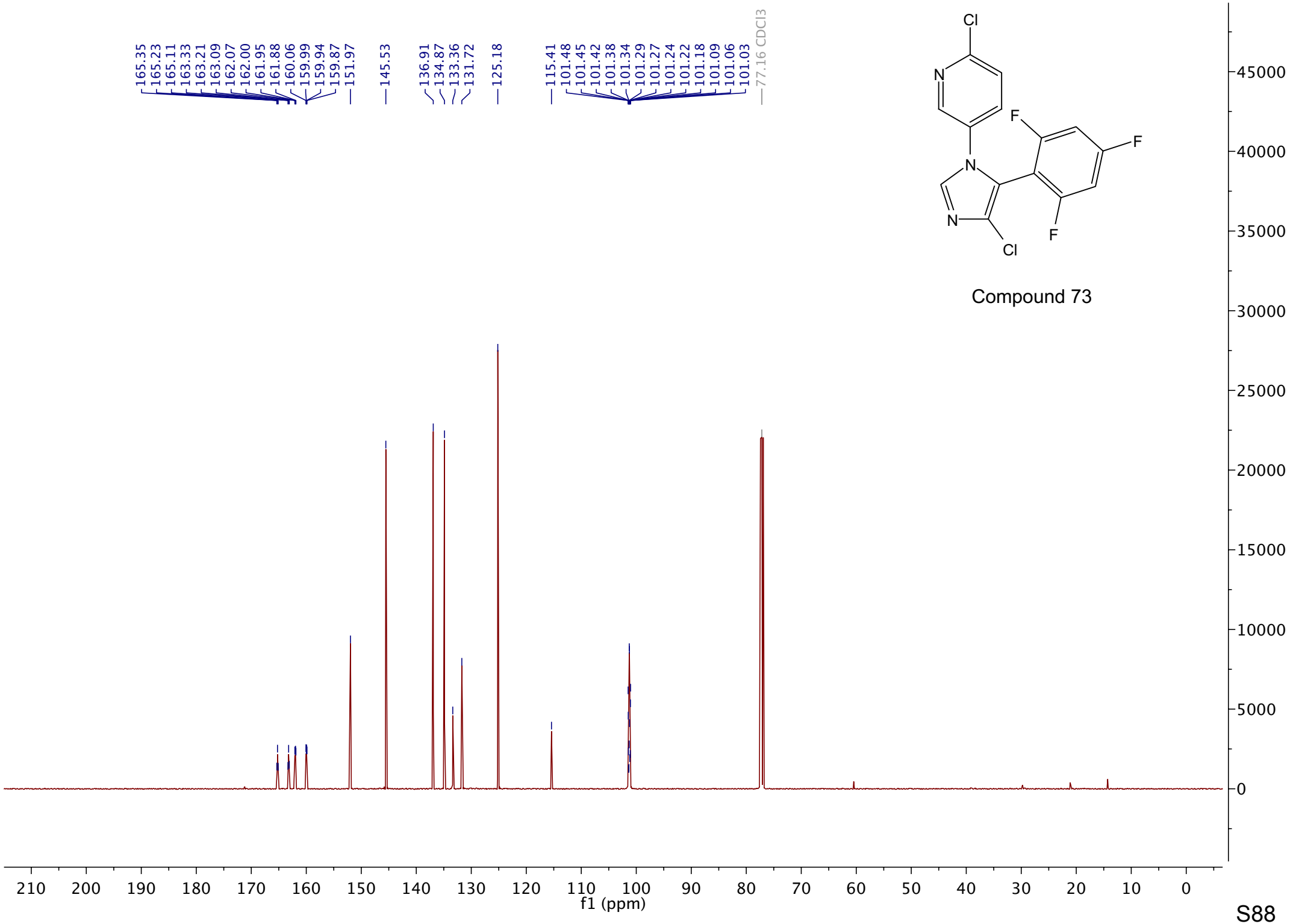

1.00
0.83
0.94
0.93
1.41
1.84
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

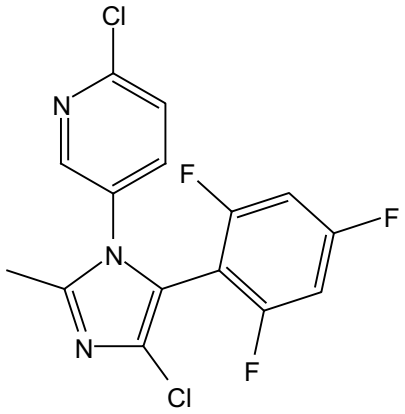

158.83
156.82
156.61
156.58
156.56
154.67
154.62
154.59
149.28
149.23
149.16
149.11
148.16
148.13
148.06
148.03
147.27
147.22
147.15
147.10
146.20
146.17
146.10
146.07
134.77
134.29
134.22
131.24
131.08
123.89
123.86
122.93
122.79
121.48
121.46
118.65
118.57
118.49
118.41
116.20
116.01
111.37
111.33
111.31
111.28
111.17
111.14
111.12
111.09
108.52
108.39
108.35
108.22
77.16 CDCl3
Cl
F
F
N
Cl
N
F
F
Compound 72
40
35
30
25
20
15
10
5
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
N
F
F
N
N
F
Cl

Compound 73

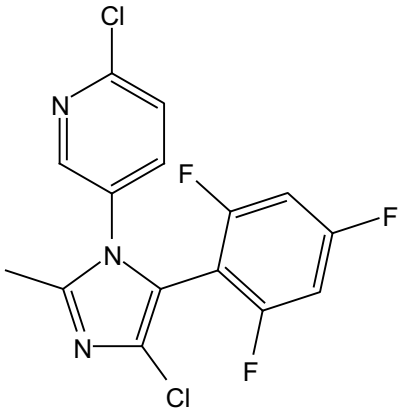
8.24
8.23
7.70
7.48
7.48
7.47
7.46
7.38
7.36
7.26 CDCl3
6.72
6.70
6.69
0.87
1.00
1.31
1.14
2.20
f1 (ppm)


165.35
165.23
165.11
163.33
163.21
163.09
162.07
162.00
161.95
161.88
160.06
159.99
159.94
159.87
151.97
145.53
136.91
134.87
133.36
131.72
125.18
115.41
101.48
101.45
101.42
101.38
101.34
101.29
101.27
101.24
101.22
101.18
101.09
101.06
101.03
77.16 CDCl3
Cl
N
F
F
N
F
N
Cl
Compound 73
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

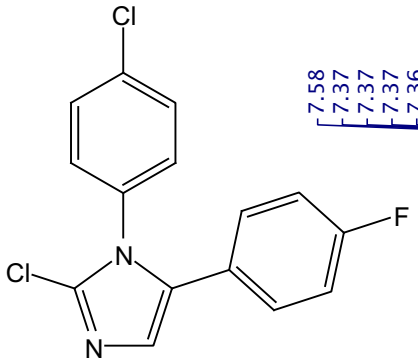

Cl
N
F
F
N
N
F
Cl

Compound 74

8.24
8.24
7.49
7.49
7.48
7.47
7.42
7.41
7.26 CDCl3
6.69
6.68
6.66
2.38
1.00
1.37
0.91
2.02
2.02
f1 (ppm)

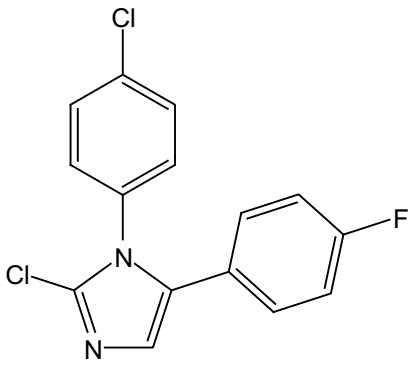


Compound 74


Cl
N
Cl
N
F

Compound 75

7.58
7.37
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.34
7.33
7.33
7.32
7.32
7.31
7.31
7.31
7.31
7.30
CDCl3
7.26
7.20
7.20
7.20
7.19
7.19
7.19
7.18
7.07
7.05
1.64
1.25
0.73
4.00
2.31
1.75
f1 (ppm)



Compound 75

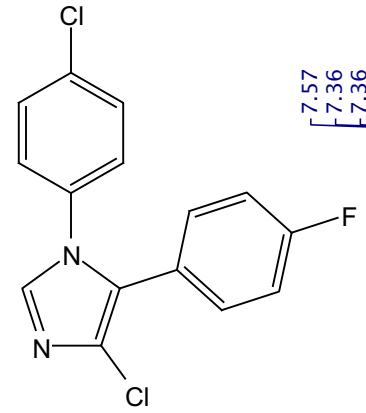
163.64
161.66
135.77
135.75
135.01
134.79
134.58
131.73
131.67
130.05
129.94
129.81
128.66
128.49
127.38
126.69
126.66
116.02
115.84

77.16 CDCl3

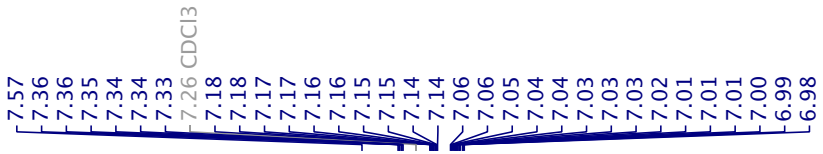
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

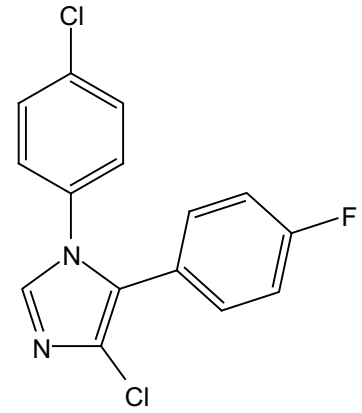
f1 (ppm)


Cl
F
N
N
Cl

Compound 76

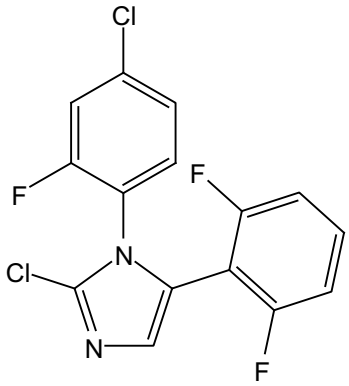

7.57
7.36
7.36
7.35
7.34
7.34
7.33
7.26 CDCl3
7.18
7.18
7.17
7.17
7.16
7.16
7.15
7.15
7.14
7.14
7.06
7.06
7.05
7.04
7.04
7.03
7.03
7.03
7.02
7.01
7.01
7.01
7.00
6.99
6.98

10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.87
2.00
2.03
4.00
11.0
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
f1 (ppm)

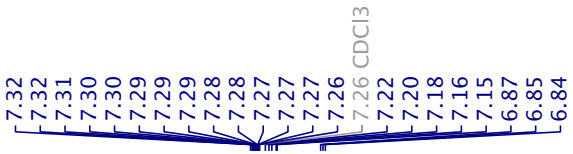

Cl
F
N
N
Cl

Compound 76

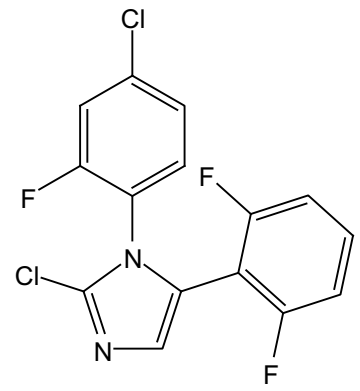
163.58
161.59
135.74
134.75
134.72
131.69
131.63
129.99
129.33
126.66
126.23
123.41
123.38
115.96
115.78
77.16 CDCl3
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
Cl
N
F

Compound 77


7.32
7.32
7.31
7.30
7.30
7.29
7.29
7.29
7.28
7.28
7.27
7.27
7.27
7.26
CDCl3
7.26
7.22
7.20
7.18
7.16
7.15
6.87
6.85
6.84

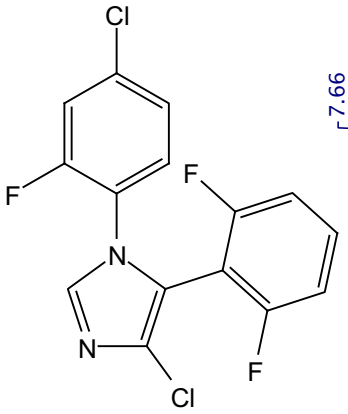
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
0.75
0.57
0.96
2.00
1.52
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


Cl
F
F
N
Cl
N
F

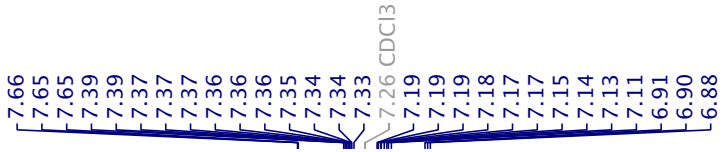
Compound 77


161.62
161.58
159.62
159.57
158.40
156.35
136.82
136.74
134.86
131.61
131.52
131.44
130.79
130.32
125.13
125.10
122.95
121.79
121.69
117.82
117.64
111.79
111.75
111.63
106.65
106.50
106.34

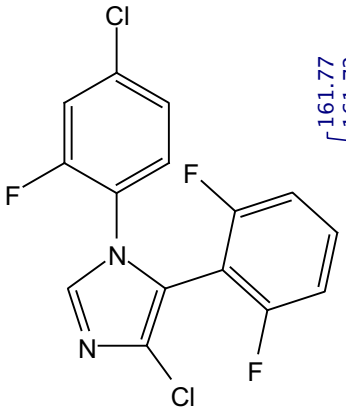
77.16 CDCl3
42000
40000
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
−2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
F
N
N
Cl
F

Compound 78

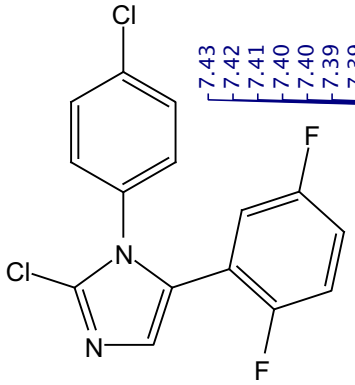

7.66
7.65
7.65
7.39
7.39
7.37
7.37
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.33
7.26 CDCl3
7.19
7.19
7.19
7.18
7.17
7.17
7.15
7.14
7.13
7.11
6.91
6.90
6.88

0.88
0.93
0.95
2.39
2.00
11.0
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
f1 (ppm)
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
−500

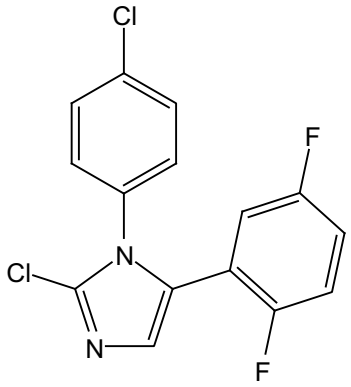

Cl
F
F
N
N
Cl
F

Compound 78

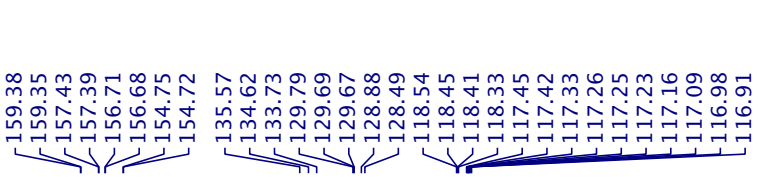
161.77
161.72
159.76
159.71
157.40
155.36
137.49
136.20
136.13
132.21
132.18
132.13
132.05
128.61
125.36
125.32
122.74
122.65
117.96
117.78
116.89
111.90
111.86
111.74
111.70
105.19
105.04
104.88
77.16 CDCl3
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



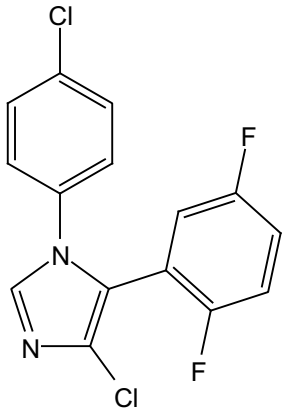
Compound 79


Cl
F
N
Cl
N
F

Compound 79

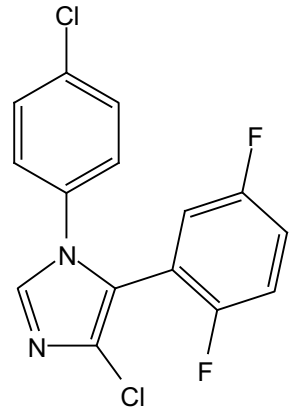

159.38
159.35
157.43
157.39
156.71
156.68
154.75
154.72
135.57
134.62
133.73
129.79
129.69
129.67
128.88
128.49
118.54
118.45
118.41
118.33
117.45
117.42
117.33
117.26
117.25
117.23
117.16
117.09
116.98
116.91
77.16 CDCl3

85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
N
F
Cl

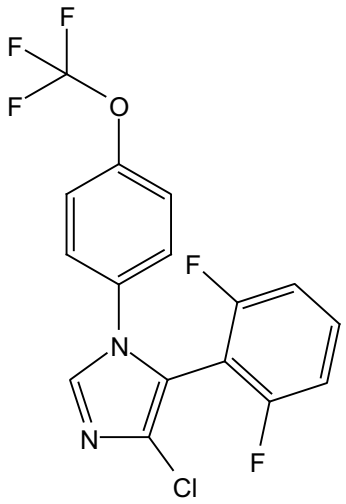
Compound 80

7.64
7.36
7.35
7.35
7.34
7.33
7.33
7.26 CDCl3
7.10
7.10
7.09
7.09
7.08
7.08
7.07
7.07
7.06
7.06
7.05
7.05
7.04
7.03
7.03
6.98
6.97
6.96
6.95
6.94
6.94
1.00
1.88
4.02
0.91
f1 (ppm)

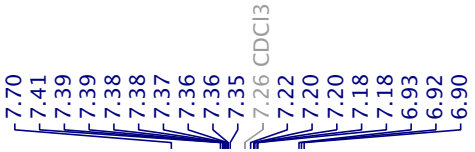

Cl
F
N
N
F
Cl

Compound 80

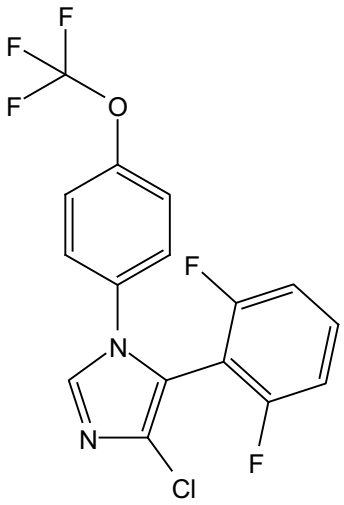
159.46
159.44
157.52
157.50
156.76
156.74
154.80
154.78
136.41
134.84
134.79
131.12
129.97
129.80
129.45
127.34
125.83
123.07
121.05
118.72
118.69
118.52
118.50
118.07
118.00
117.88
117.81
117.49
117.42
117.30
117.23
117.01
116.94
116.87
116.80
77.16 CDCl3
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


F
F
F
O
F
N
N
Cl
F

Compound 81

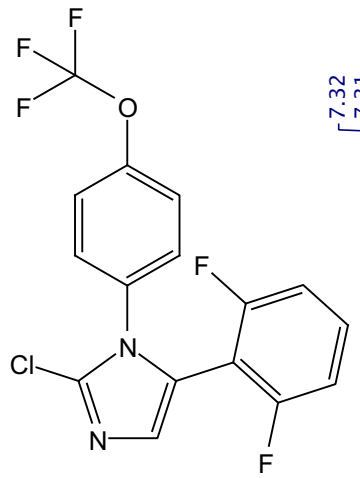

7.70
7.41
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.35
7.26 CDCl3
7.22
7.20
7.20
7.18
7.18
6.93
6.92
6.90

0.91
1.00
3.91
2.30
11.0
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)
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
−200

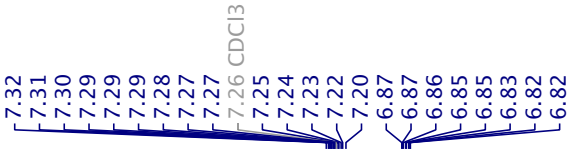

F
F
F
O
F
N
N
Cl
F

Compound 81

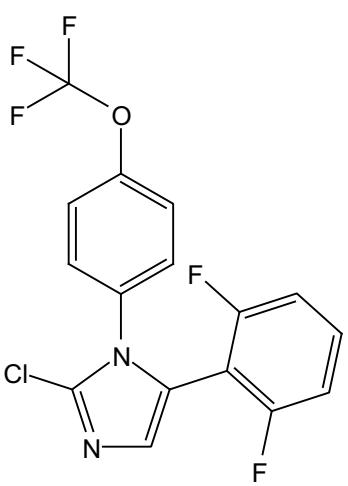
161.74
161.69
159.73
159.69
149.20
149.18
136.84
134.52
132.53
132.28
132.20
132.12
126.25
123.30
122.01
121.42
119.36
117.47
116.18
111.98
111.94
111.82
111.78
105.48
105.32
105.16
77.16 CDCl3
f1 (ppm)


F
F
F
O
F
N
Cl
N
F

Compound 82


7.32
7.31
7.30
7.29
7.29
7.29
7.28
7.27
7.27
7.26 CDCl3
7.25
7.24
7.23
7.22
7.20
6.87
6.87
6.86
6.85
6.85
6.83
6.82
6.82

4000
3500
3000
2500
2000
1500
1000
500
0
-500
1.00
3.60
1.13
1.99
11.0
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)

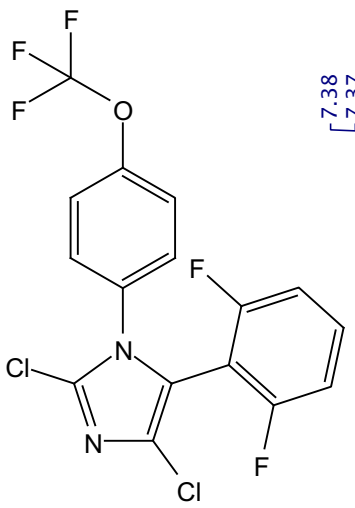


Compound 82

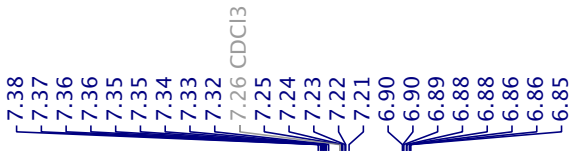
171.35
161.44
161.40
159.77
159.73
149.68
149.50
149.48
149.47
134.36
133.35
131.64
131.57
131.50
130.53
128.96
122.96
122.52
121.41
121.24
119.53
117.81
111.75
111.72
111.61
111.58
106.97
106.84
106.71
77.16 CDCl3
60.57
21.23
14.35

EtOAc
EtOAc
Traces of EtOAc

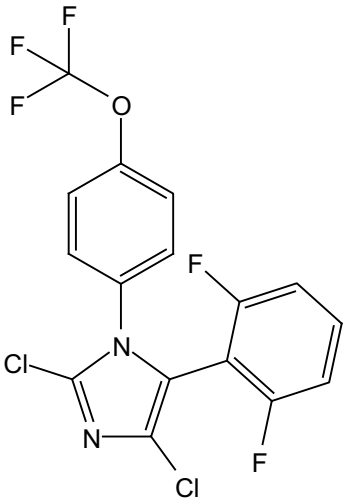
f1 (ppm)


F
F
F
O
F
N
Cl
N
F
Cl

Compound 83

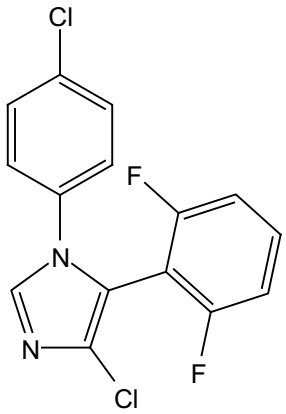

7.38
7.37
7.36
7.35
7.35
7.34
7.33
7.32
7.26 CDCl3
7.25
7.24
7.23
7.22
7.21
6.90
6.90
6.89
6.88
6.88
6.86
6.86
6.85

1.00
3.89
2.05
f1 (ppm)


F
F
F
O
F
N
Cl
N
Cl
F

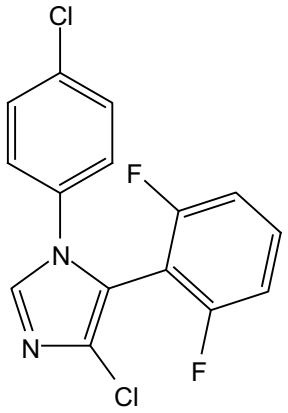
Compound 83

161.60
161.56
159.92
159.89
149.81
149.80
132.76
132.68
132.65
132.61
132.54
130.50
128.96
122.92
121.55
121.20
119.48
118.60
117.77
111.89
111.86
111.75
111.72
105.06
104.93
104.80
77.16 CDCl3
29.85
H grease
f1 (ppm)


Cl
F
N
N
Cl
F

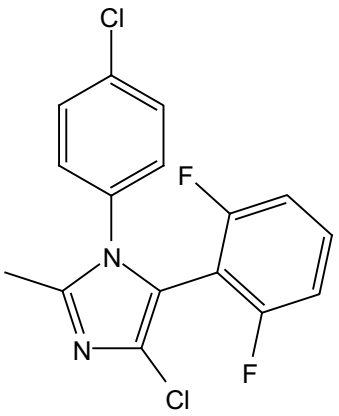
Compound 84

7.69
7.40
7.38
7.37
7.35
7.34
7.32
7.26 CDCl3
7.09
7.08
6.92
6.91
6.89
1.00
1.06
2.50
2.46
2.38
f1 (ppm)


Cl
F
N
N
Cl
F

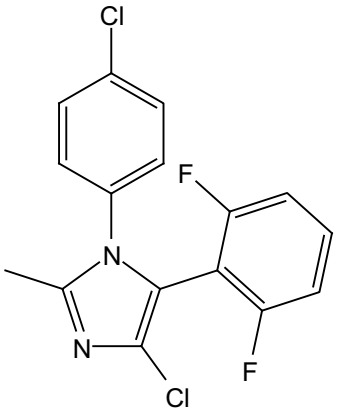
Compound 84

161.53
161.49
159.86
159.82
136.75
134.89
134.65
132.40
132.18
132.12
132.05
129.91
125.93
116.10
111.96
111.93
111.82
111.79
105.49
105.36
105.23
77.16 CDCl3
f1 (ppm)


Cl
F
N
N
Cl
F

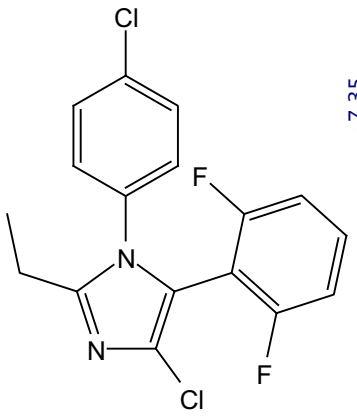
Compound 85

7.36
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.31
7.30
7.30
7.29
7.28
7.27
7.26 CDCl3
7.09
7.09
7.07
6.88
6.87
6.87
6.85
6.85
6.84
2.31
1.59
1.25
water
Traces of H grease
2.38
0.66
2.00
2.00
3.15
f1 (ppm)


Cl
F
N
N
Cl
F

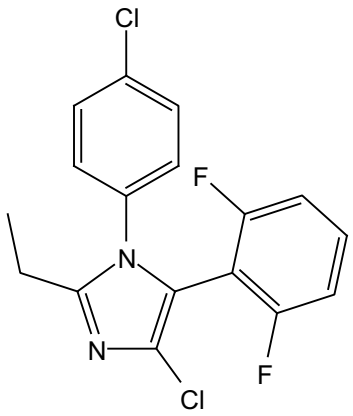
Compound 85

161.84
161.80
159.86
159.80
145.60
135.23
134.48
131.88
131.79
131.71
130.20
129.75
128.37
116.02
111.73
111.69
111.57
111.53
106.10
105.96
105.82
77.16 CDCl3
29.84
14.13
H grease
f1 (ppm)


Cl
F
N
N
Cl
F

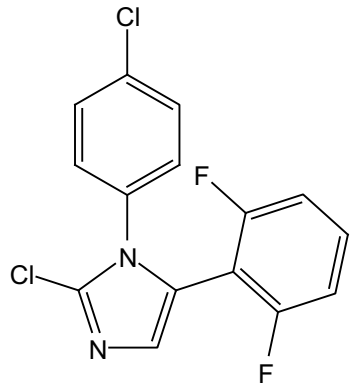
Compound 86

7.35
7.34
7.34
7.33
7.32
7.32
7.31
7.31
7.30
7.29
7.29
7.28
7.28
7.26
7.26 CDCl3
7.10
7.08
7.08
6.87
6.87
6.86
6.85
6.84
6.83
6.82
6.81
2.60
2.58
2.57
2.55
1.64
1.27
1.26
1.24
1.09
Water
Traces of
H grease
1.43
0.51
1.56
1.60
1.68
3.50
f1 (ppm)

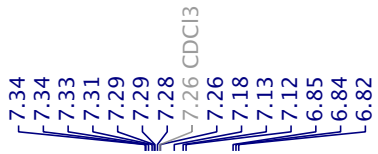

Cl
F
N
N
F
Cl

Compound 86

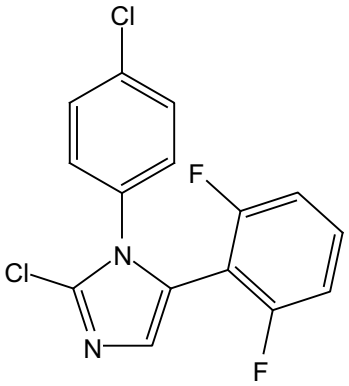
161.89
161.84
159.89
159.84
150.43
135.27
134.34
131.85
131.77
131.69
130.33
129.71
128.59
115.90
111.72
111.68
111.52
111.52
106.12
105.96
105.80
77.16 CDCl3
29.85
21.16
12.21
H grease
f1 (ppm)


Cl
F
N
Cl
N
F

Compound 87

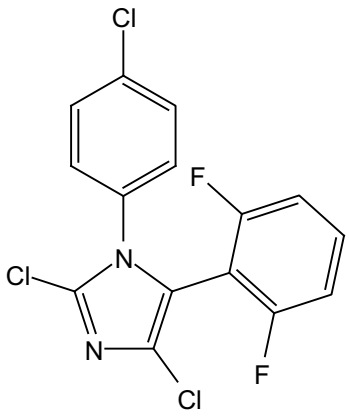

7.34
7.34
7.33
7.31
7.29
7.29
7.28
7.26 CDCl3
7.26
7.18
7.13
7.12
6.85
6.84
6.82

2.36
1.28
1.00
2.35
2.37
f1 (ppm)


Cl
F
N
Cl
N
F

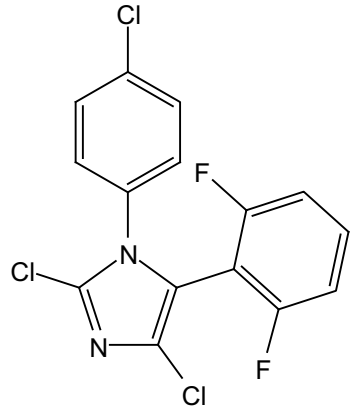
Compound 87

161.36
161.31
159.36
159.31
135.10
134.03
133.32
131.32
131.24
131.15
130.21
129.27
128.36
122.21
111.49
111.45
111.33
111.29
106.80
106.64
106.49
77.16 CDCl3
10
9
8
7
6
5
4
3
2
1
0
−1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
F
N
Cl
N
F
Cl

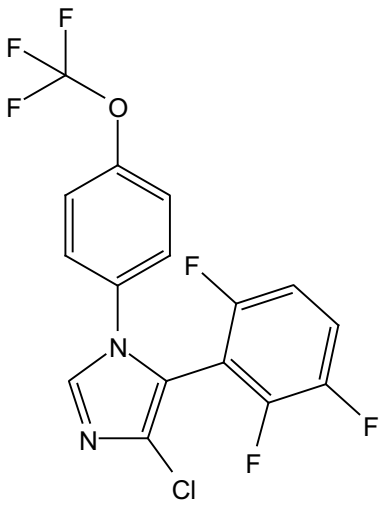
Compound 88

7.36
7.36
7.34
7.26 CDCl3
7.14
7.12
6.89
6.88
6.86
1.58
1.25
H grease
Water
3.17
2.00
2.04
f1 (ppm)

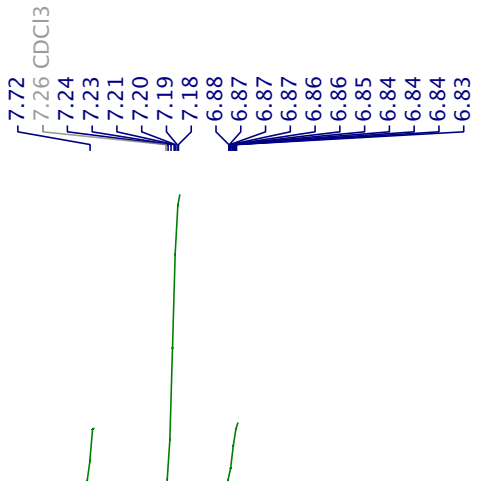

Cl
F
N
Cl
N
F
Cl

Compound 88

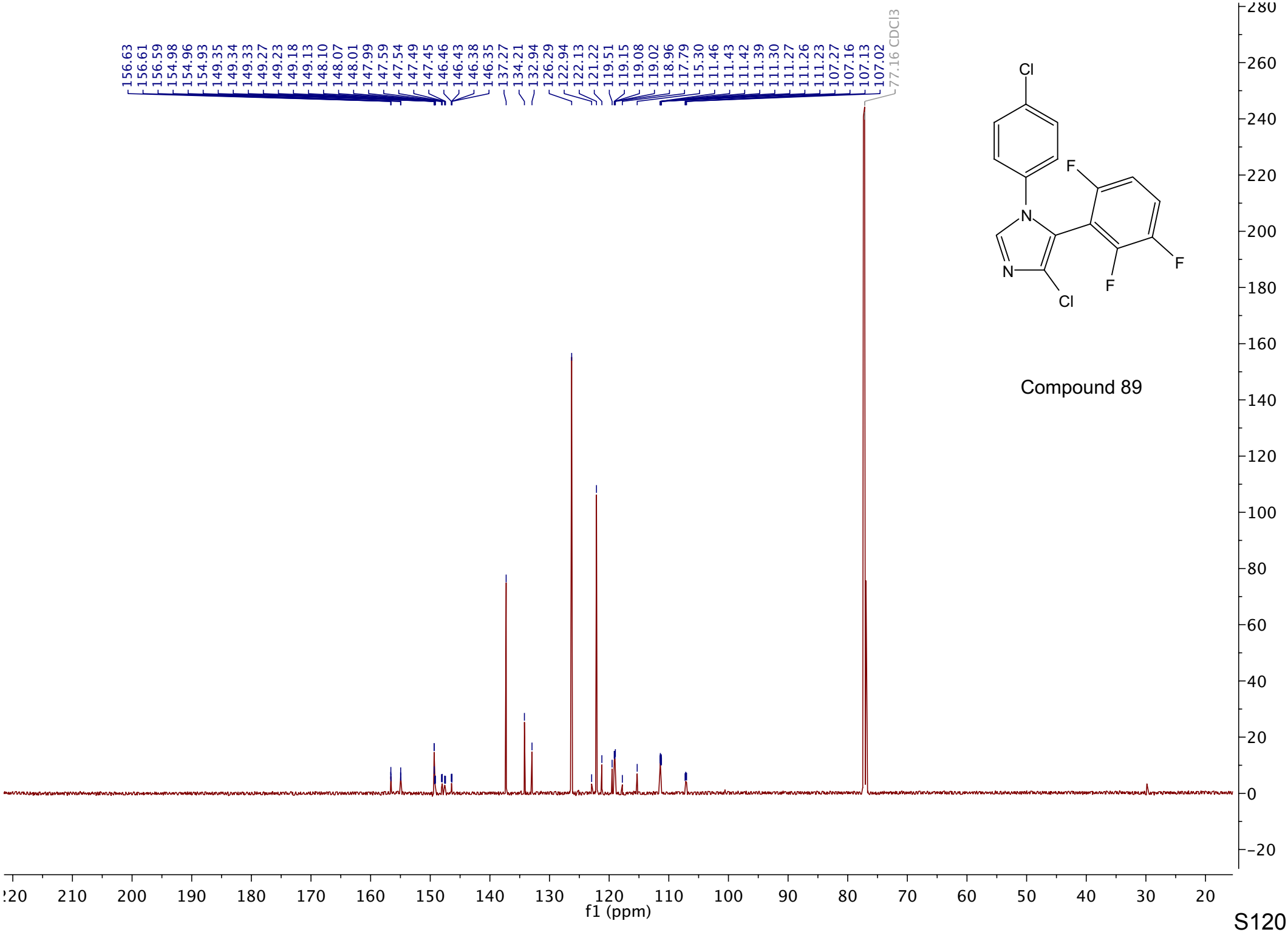
161.61
161.57
159.93
159.90
135.94
133.03
132.60
132.59
132.54
132.47
130.43
129.75
128.57
118.55
111.90
111.87
111.76
111.73
105.13
105.00
104.87
77.16 CDCl3
29.85
H grease
f1 (ppm)

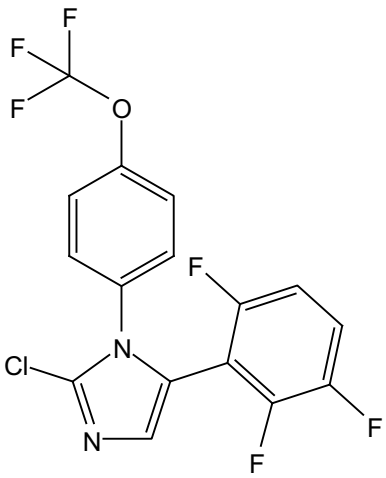

F
F
F
O
F
N
N
Cl
F
F

Compound 89

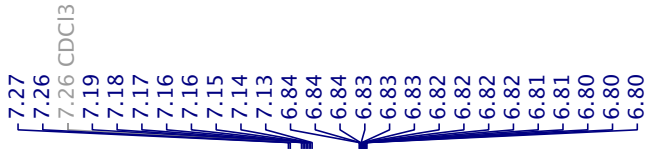

7.72
7.26 CDCl3
7.24
7.23
7.21
7.20
7.19
7.18
6.88
6.87
6.87
6.87
6.86
6.86
6.85
6.84
6.84
6.84
6.83

1.00
5.51
1.10
11.0
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)
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200

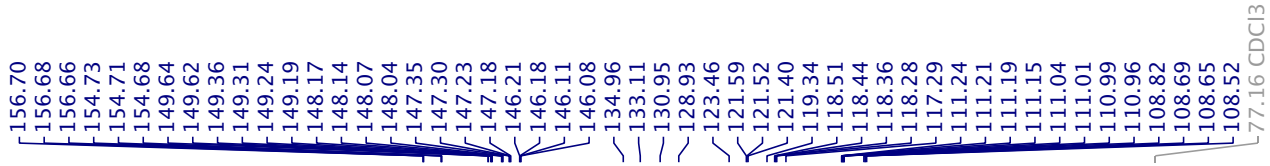

156.63
156.61
156.59
154.98
154.96
154.93
149.35
149.34
149.33
149.27
149.23
149.18
149.13
148.10
148.07
148.01
147.99
147.59
147.54
147.49
147.45
146.46
146.43
146.38
146.35
137.27
134.21
132.94
126.29
122.94
122.13
121.22
119.51
119.15
119.08
119.02
118.96
117.79
115.30
111.46
111.43
111.42
111.39
111.30
111.27
111.26
111.23
107.27
107.16
107.13
107.02
77.16 CDCl3
Cl
F
N
N
F
F
Cl
Compound 89
f1 (ppm)

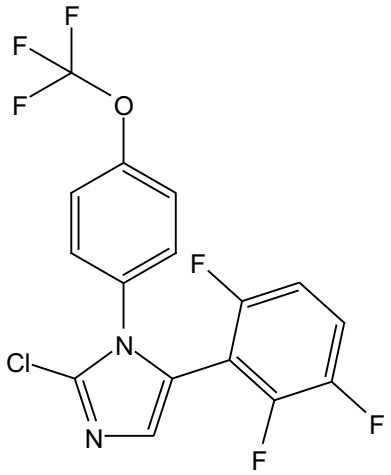

F
F
F
O
F
N
Cl
N
F
F

Compound 90

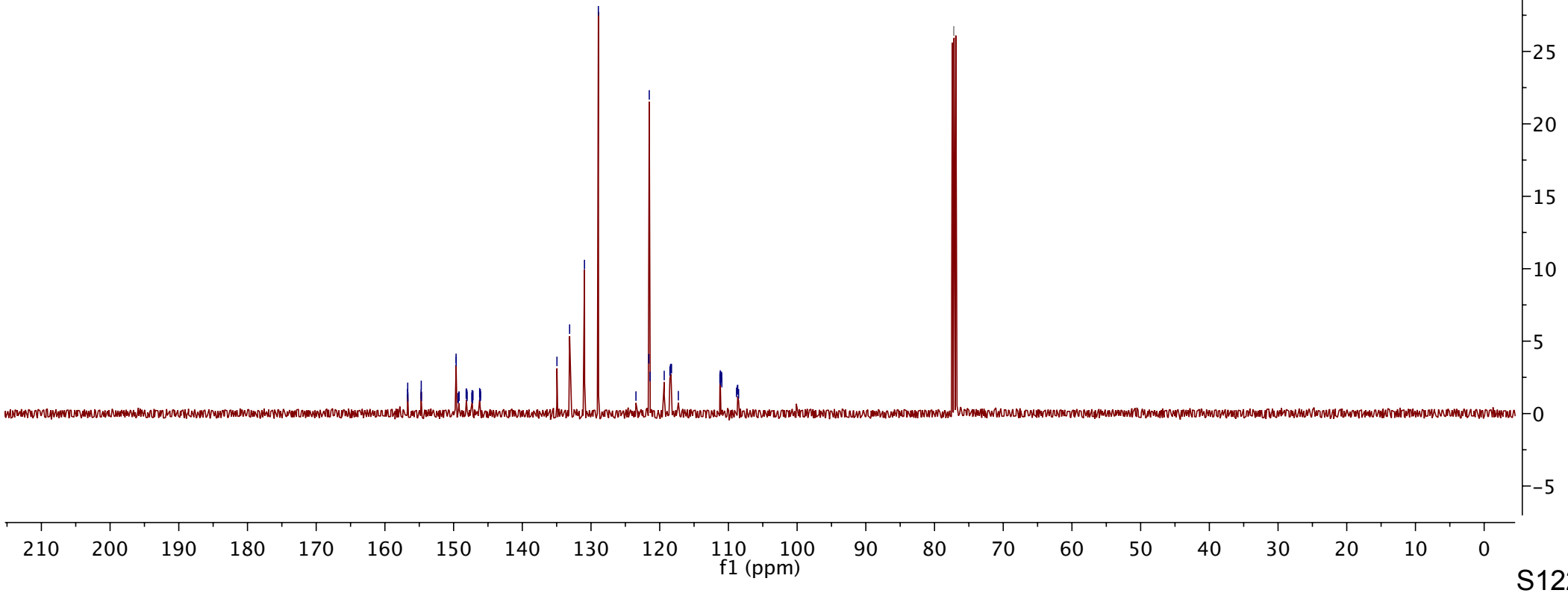

7.27
7.26
7.26 CDCl3
7.19
7.18
7.17
7.16
7.16
7.15
7.14
7.13
6.84
6.84
6.84
6.83
6.83
6.83
6.82
6.82
6.82
6.82
6.81
6.81
6.80
6.80
6.80

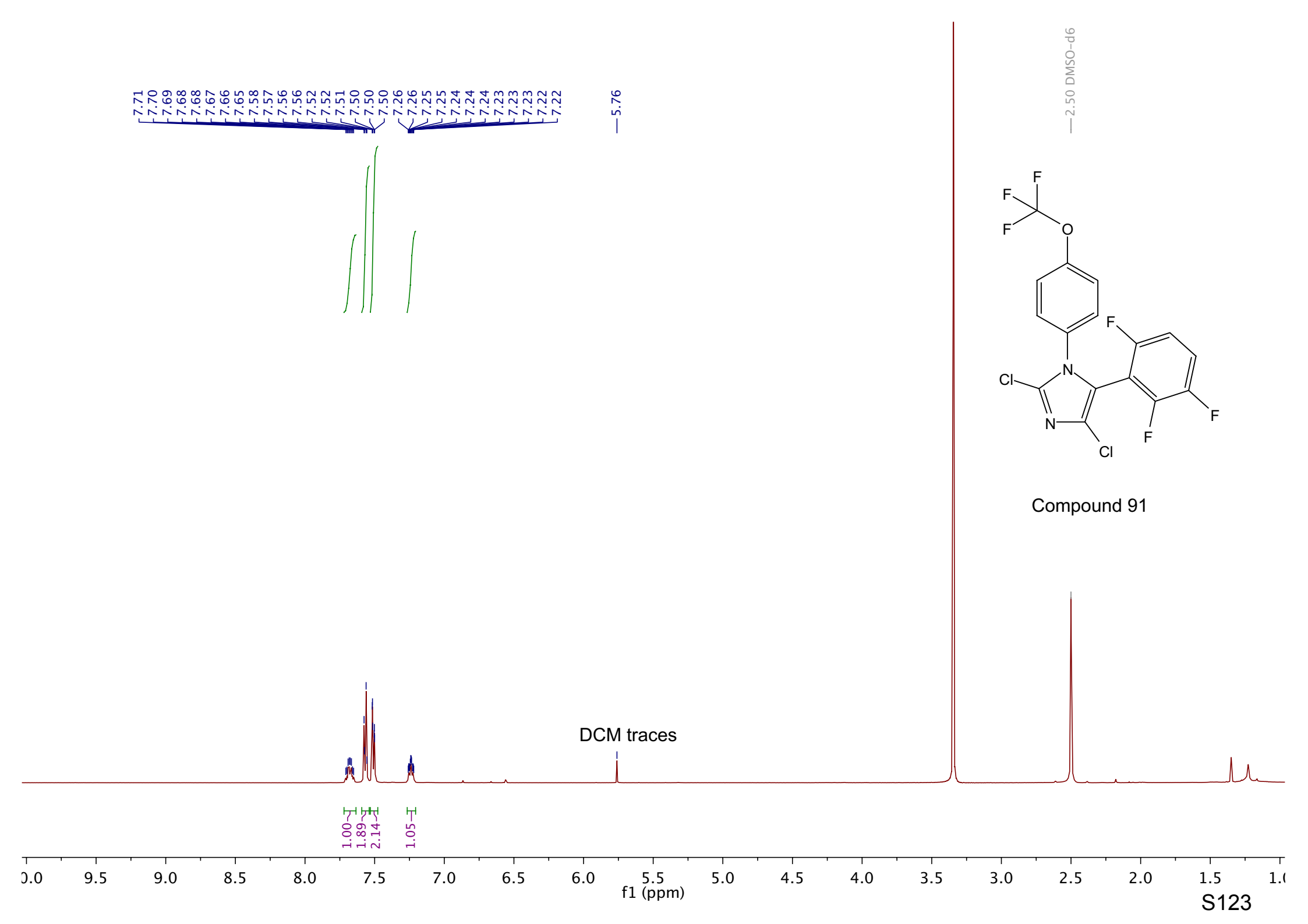
4.76
0.93
1.00
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500

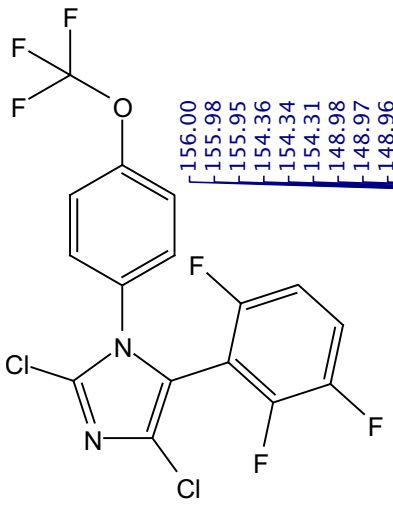

156.70
156.68
156.66
154.73
154.71
154.68
149.64
149.62
149.36
149.31
149.24
149.19
148.17
148.14
148.07
148.04
147.35
147.30
147.23
147.18
146.21
146.18
146.11
146.08
134.96
133.11
130.95
128.93
123.46
121.59
121.52
121.40
119.34
118.51
118.44
118.36
118.28
117.29
111.24
111.21
111.19
111.15
111.04
111.01
110.99
110.96
108.82
108.69
108.65
108.52
77.16 CDCl3


F
F
F
O
F
N
Cl
N
F
F
F

Compound 90


65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.71
7.70
7.69
7.68
7.68
7.67
7.66
7.65
7.58
7.57
7.56
7.56
7.52
7.52
7.51
7.50
7.50
7.50
7.26
7.26
7.25
7.25
7.24
7.24
7.24
7.23
7.23
7.23
7.22
7.22
5.76
2.50 DMSO-d6
F
F
F
O
F
N
Cl
N
Cl
F
F
F
Compound 91
DCM traces
1.00
1.89
2.14
1.05
f1 (ppm)



Compound 91

156.00
155.98
155.95
154.36
154.34
154.31
148.98
148.97
148.96
148.94
148.21
148.16
148.11
148.06
147.18
147.15
147.09
147.06
146.53
146.49
146.43
146.39
145.56
145.53
145.47
145.45
133.01
132.51
129.62
129.15
122.43
122.11
120.76
120.73
120.69
120.63
120.56
119.55
119.02
117.31
112.39
112.36
112.34
112.31
112.23
112.20
112.18
112.15
105.74
105.63
105.59
105.48

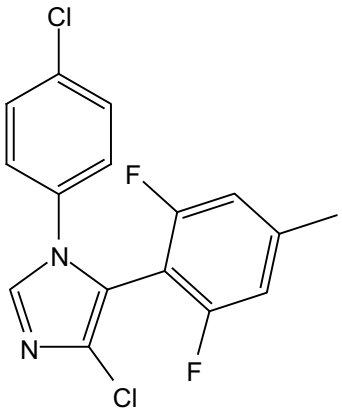
54.97

39.52 DMSO-d6

DCM traces

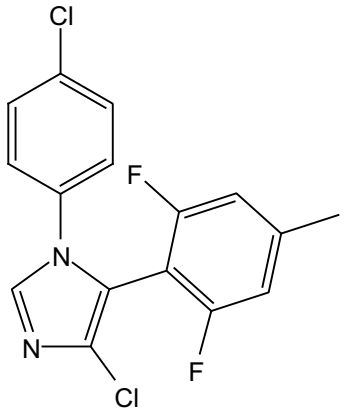
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

f1 (ppm)


Cl
F
N
N
Cl
F

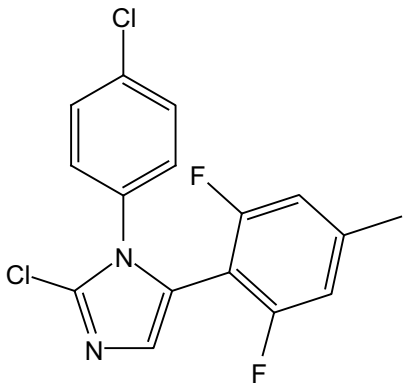
Compound 92

7.67
7.34
7.33
7.32
7.32
7.31
7.26 CDCl3
7.09
7.09
7.08
7.08
7.07
6.72
6.71
2.35
1.00
2.44
2.49
2.39
2.94
f1 (ppm)


Cl
F
N
N
F
Cl

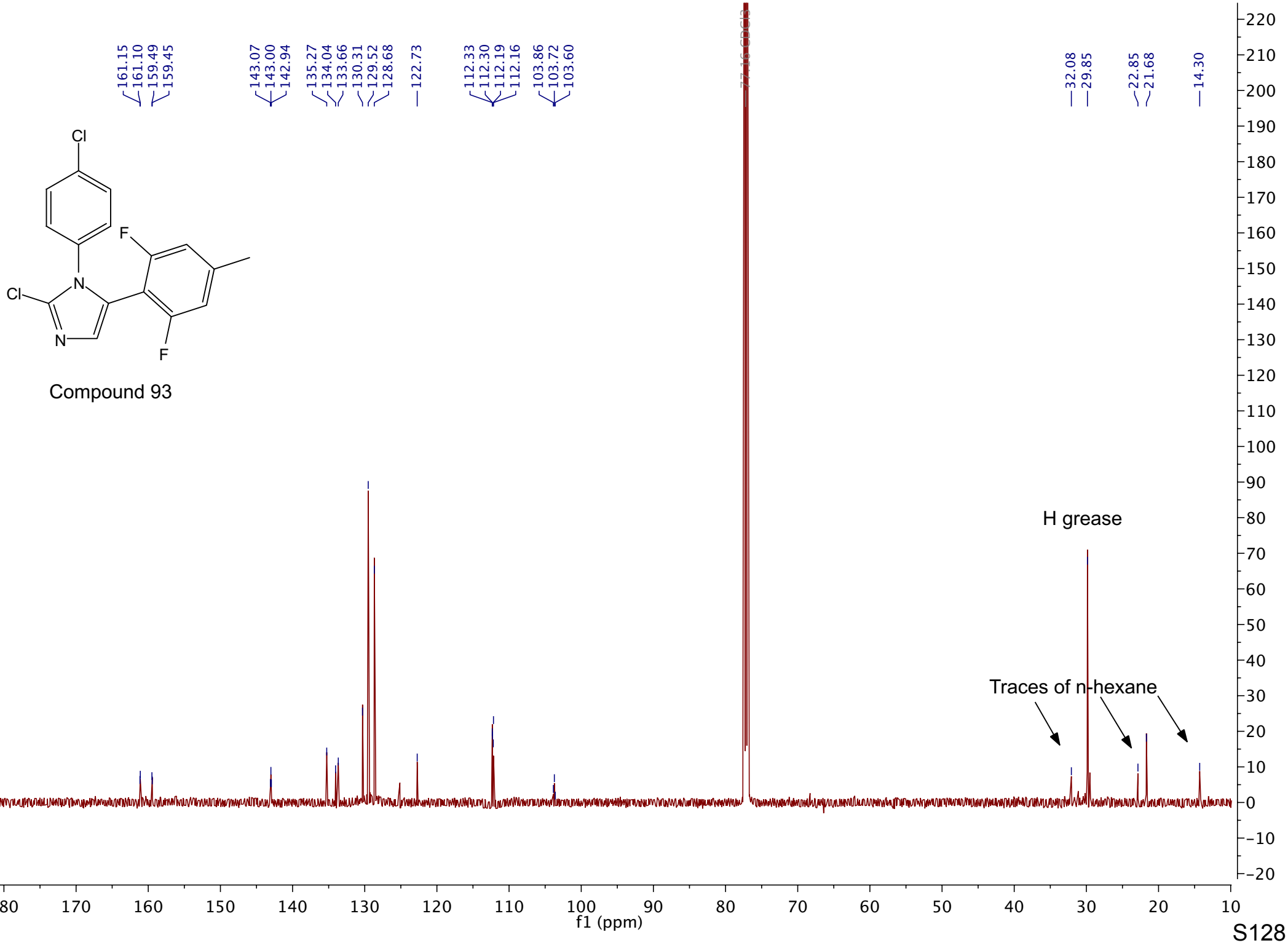
Compound 92

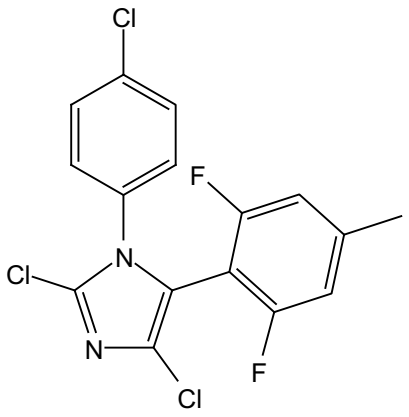
161.39
161.34
159.40
159.34
143.76
143.68
143.60
136.56
134.77
134.75
132.25
129.86
125.96
116.31
112.56
112.52
112.40
112.37
102.32
102.16
102.01
77.16 CDCl3
21.74
f1 (ppm)


Cl
F
N
Cl
N
F

Compound 93

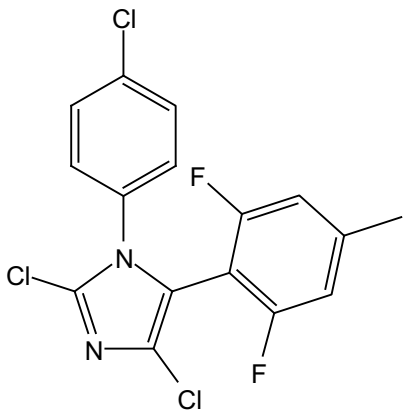
7.36
7.35
7.35
7.34
7.34
7.34
7.33
7.26 CDCl3
7.15
7.15
7.14
7.13
7.12
7.12
6.66
6.64
2.31
1.59
1.25
0.07
Water
Traces of
H grease
2.02
3.00
2.07
2.55
f1 (ppm)


161.15
161.10
159.49
159.45
143.07
143.00
142.94
135.27
134.04
133.66
130.31
129.52
128.68
122.73
112.33
112.30
112.19
112.16
103.86
103.72
103.60
77.16 CDCl3
32.08
29.85
22.85
21.68
14.30
Cl
F
N
Cl
N
F
Compound 93
H grease
Traces of n-hexane
f1 (ppm)


Cl
F
N
Cl
N
F
Cl

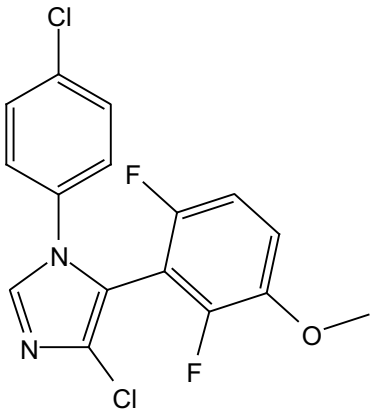
Compound 94

7.36
7.34
7.26 CDCl3
7.13
7.12
6.69
6.67
2.35
2.33
1.25
Traces of
H grease
2.00
1.98
1.90
2.79
f1 (ppm)


Cl
F
N
Cl
N
F
Cl

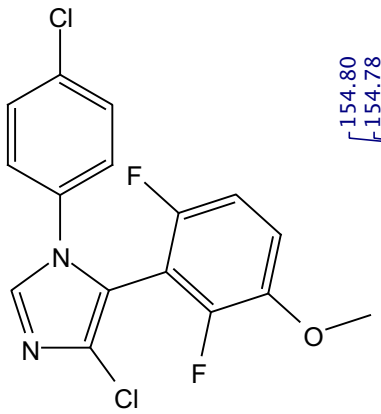
Compound 94

161.48
161.43
159.48
159.43
144.25
144.18
144.10
135.85
133.15
132.32
130.31
129.72
128.61
118.80
112.50
112.47
112.34
112.31
102.00
101.83
101.67
77.41
77.36
77.16
76.91
29.85
21.79
H grease
f1 (ppm)


Cl
F
N
N
O
F
Cl

Compound 95

7.67
7.32
7.32
7.31
7.26 CDCl3
7.09
7.08
6.98
6.97
6.96
6.95
6.94
6.93
6.83
6.83
6.81
6.81
6.79
6.79
3.86
3.83
1.00
2.19
2.20
1.07
1.05
3.20
f1 (ppm)



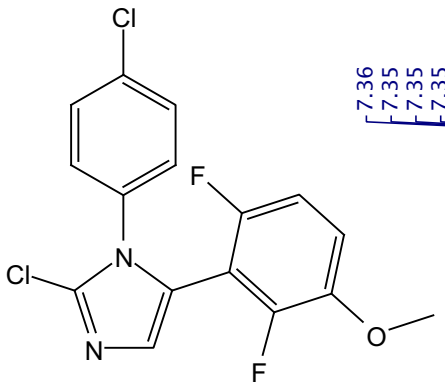
Compound 95

154.80
154.78
152.86
152.83
150.95
150.90
148.95
148.90
144.55
144.53
144.46
144.44
136.77
134.84
134.59
132.37
129.88
125.92
116.10
115.01
114.98
114.92
114.91
110.63
110.60
110.45
110.42
106.28
106.15
106.12
105.98

77.16 CDCl3

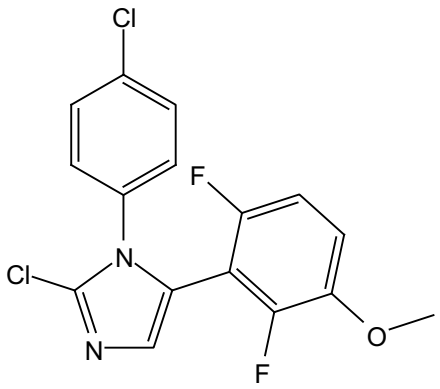
56.81

f1 (ppm)


Cl
F
N
Cl
N
O
F

Compound 96

7.36
7.35
7.35
7.35
7.34
7.34
7.33
7.33
7.26 CDCl3
7.18
7.14
7.13
7.13
6.91
6.90
6.89
6.88
6.87
6.86
6.78
6.77
6.77
6.76
6.75
6.74
6.74
6.74
3.82
1.67
1.25
Water
H grease
1.92
1.06
2.01
0.97
0.96
3.05
f1 (ppm)



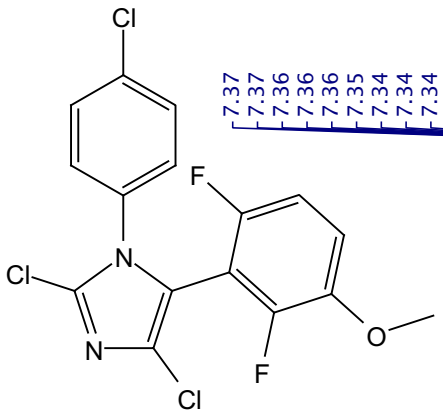
Compound 96

154.67
154.65
153.06
153.03
150.78
150.74
149.11
149.07
144.42
144.40
144.35
144.33
135.36
134.38
133.55
130.48
129.57
128.66
122.51
114.44
114.42
114.38
114.36
110.43
110.40
110.27
110.24
107.83
107.72
107.69
107.58
77.16 CDCl3
56.84
29.85

H grease

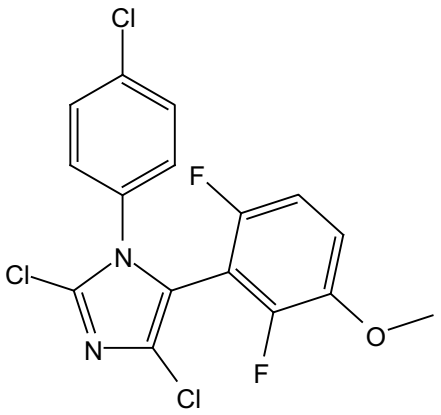
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Cl
F
N
Cl
N
O
F
Cl

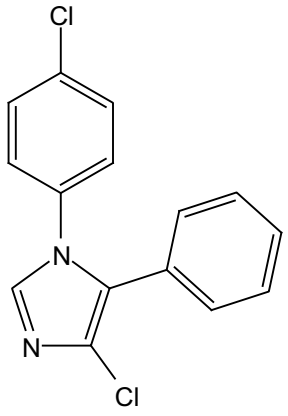
Compound 97

7.37
7.37
7.36
7.36
7.36
7.35
7.34
7.34
7.34
7.34
7.26 CDCl3
7.15
7.14
7.14
7.13
7.13
7.12
7.12
6.96
6.95
6.94
6.94
6.93
6.92
6.81
6.80
6.80
6.79
6.79
6.79
6.79
6.78
6.78
6.77
3.83
1.25
H grease
1.67
1.72
0.93
0.93
3.00
f1 (ppm)


Cl
F
N
Cl
N
O
F
Cl

Compound 97

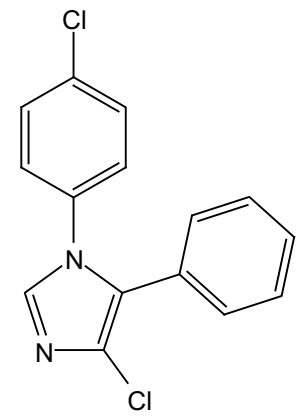
154.77
154.74
153.14
153.12
150.97
150.94
149.30
149.26
144.50
144.48
144.43
144.40
135.95
133.06
132.65
130.49
129.78
128.61
118.59
115.47
115.45
115.40
115.38
110.60
110.57
110.45
110.42
105.96
105.85
105.82
105.71
77.16 CDCl3
56.88
29.85
H grease
f1 (ppm)


Cl
N
N
Cl

Compound 98

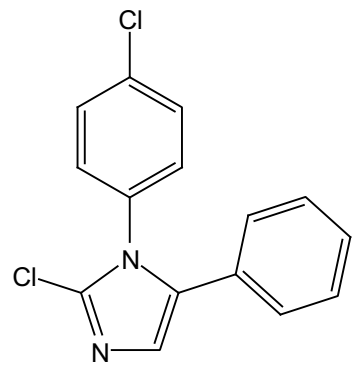

7.58
7.35
7.34
7.34
7.33
7.33
7.32
7.31
7.30
7.30
7.26 CDCl3
7.20
7.19
7.19
7.18
7.18
7.07
7.07
7.06
7.05
7.05
7.04

0.91
5.11
2.00
2.02
f1 (ppm)


Cl
N
N
Cl

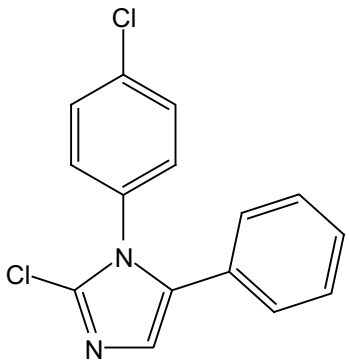
Compound 98

135.72
134.91
134.49
129.89
129.75
129.24
128.62
128.44
127.28
127.09
126.61
77.16 CDCl3
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
−2
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Cl
N
Cl
N

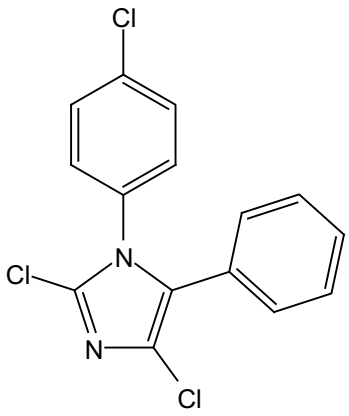
Compound 99

7.43
7.42
7.42
7.41
7.40
7.40
7.26 CDCl3
7.25
7.25
7.24
7.18
7.16
7.16
7.15
7.14
7.08
7.07
7.06
7.06
7.05
1.57
1.25
Water
H grease
1.89
3.40
2.83
1.94
f1 (ppm)

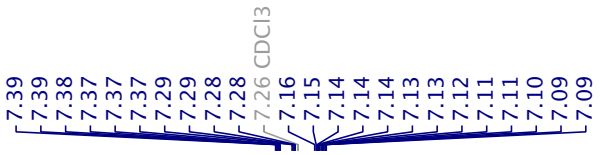

Cl
N
Cl
N

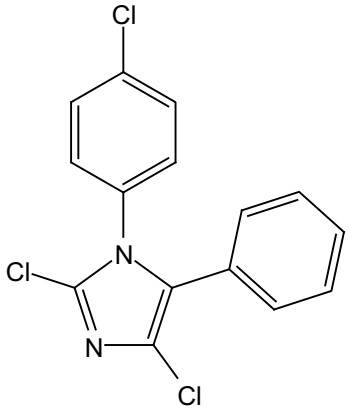
Compound 99

135.32
134.09
133.77
129.85
129.37
128.95
128.76
128.12
127.94
127.21
125.13
77.37
77.16 CDCl3
32.08
29.85
22.86
14.30
H grease
Traces of n-hexane
f1 (ppm)

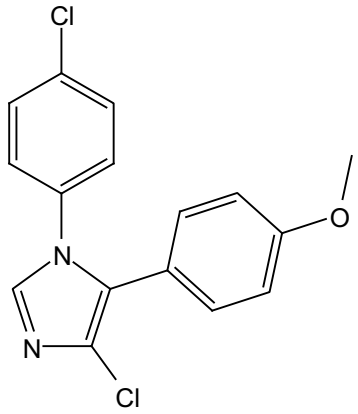


Compound 100

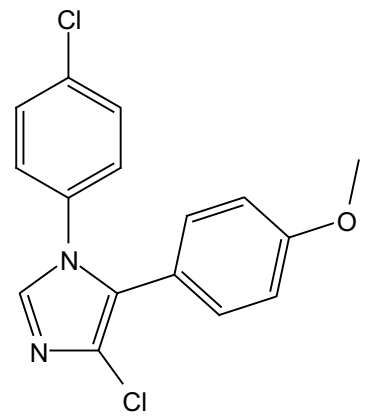




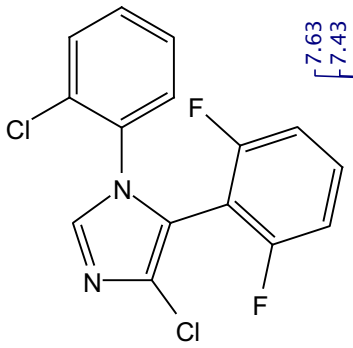
Compound 100



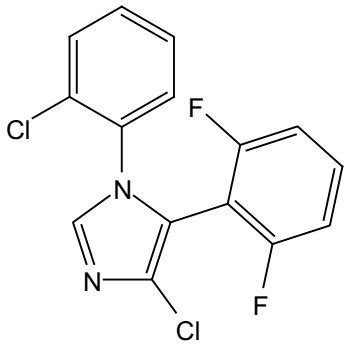
Compound 101



Compound 101



Compound 102



Compound 102

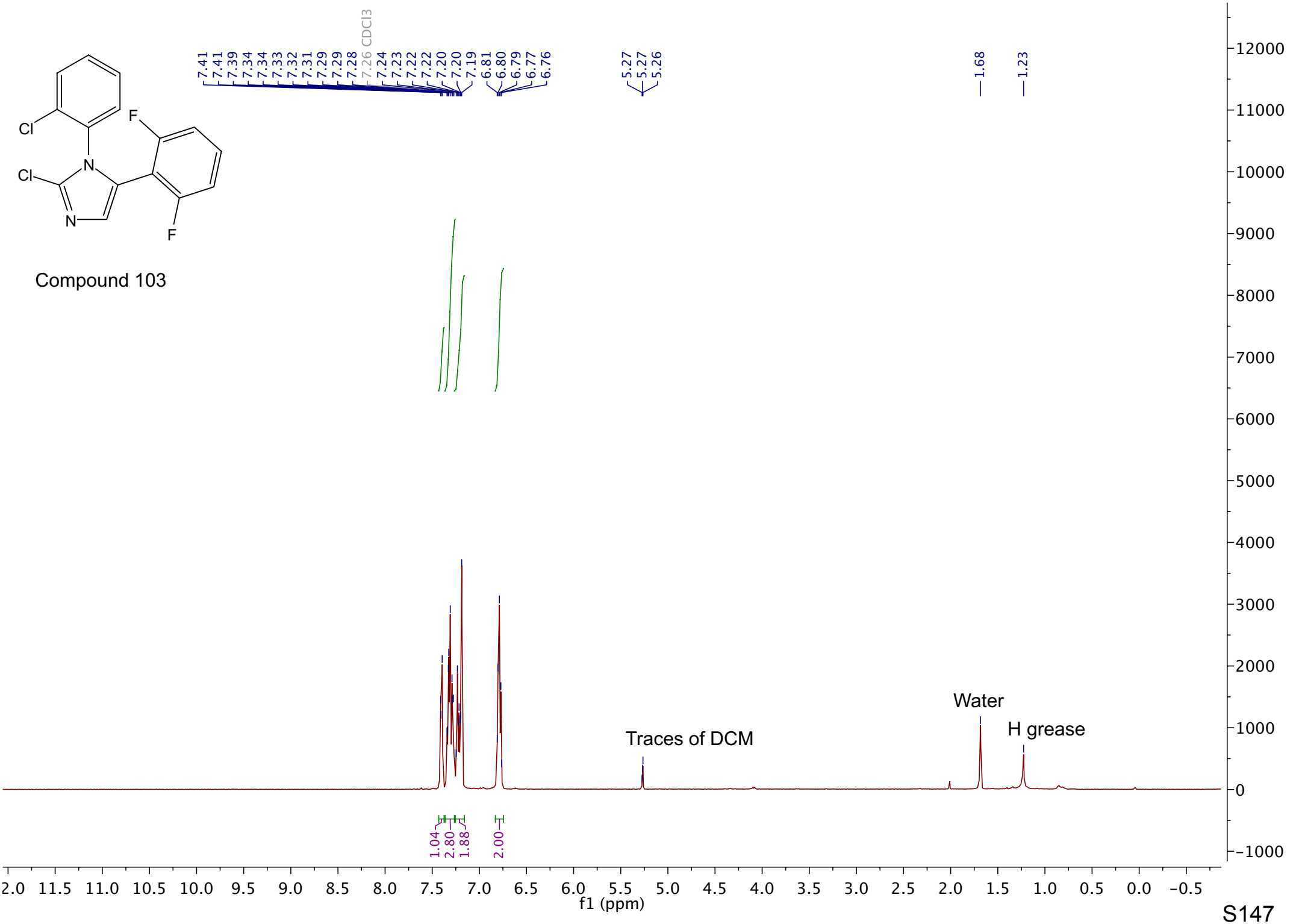
161.80
161.75
159.79
159.74
137.58
133.55
131.96
131.88
131.80
131.70
131.67
130.73
130.61
129.10
127.60
117.02
111.74
111.71
111.57
111.54
105.51
105.35
105.20

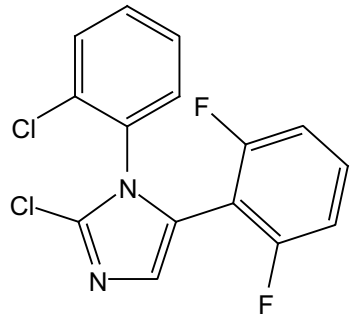
77.16 CDCl3

29.82

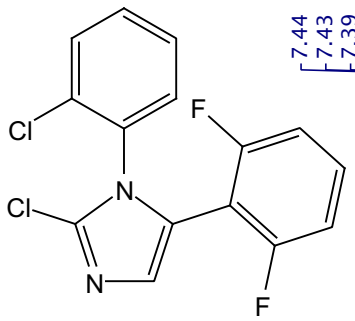
H grease

f1 (ppm)

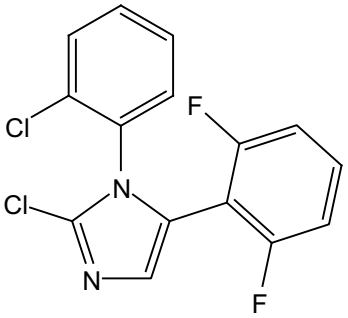

Cl
F
Cl
N
N
F
Compound 103
7.41
7.41
7.39
7.34
7.34
7.33
7.32
7.31
7.29
7.29
7.28
7.26 CDCl3
7.24
7.23
7.22
7.22
7.20
7.20
7.19
6.81
6.80
6.79
6.77
6.76
5.27
5.27
5.26
1.68
1.23
Traces of DCM
Water
H grease
1.04
2.80
1.88
2.00
f1 (ppm)



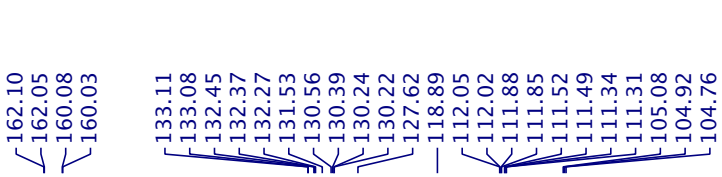
Compound 103



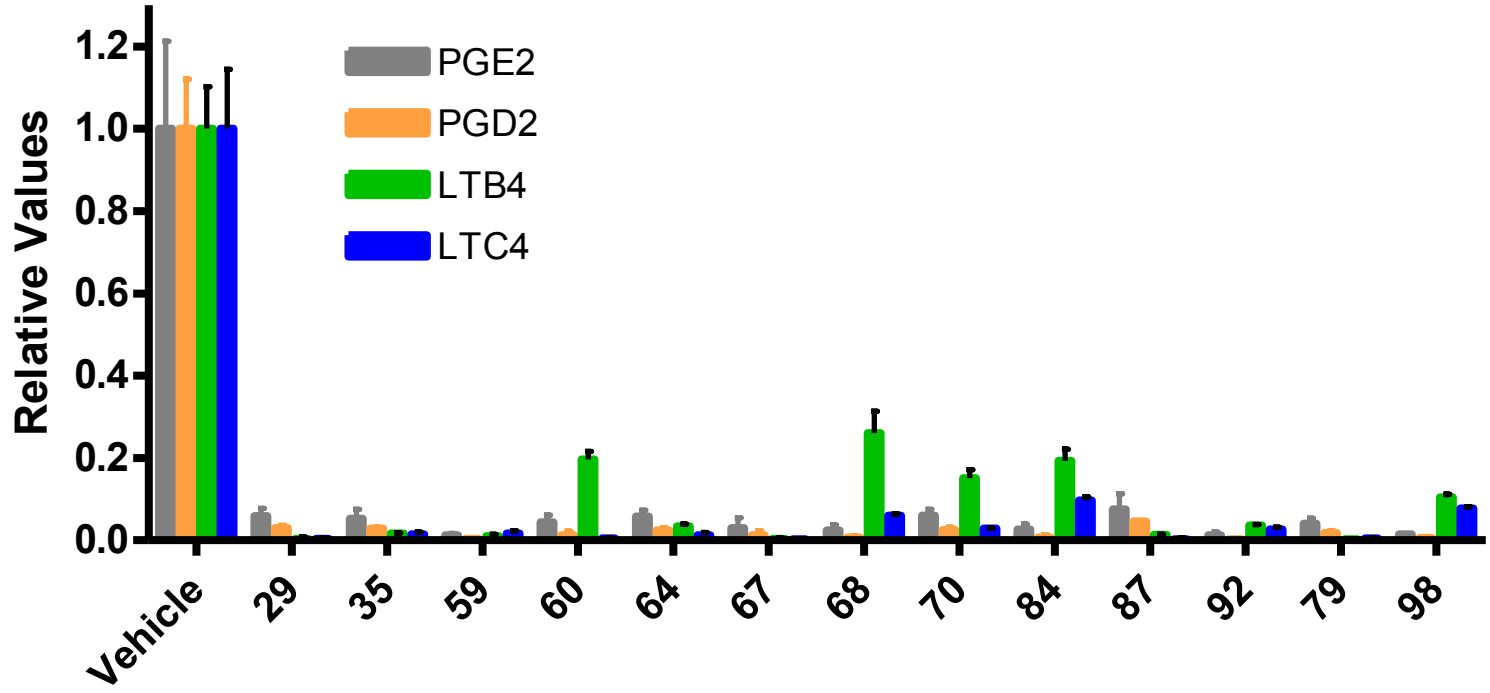
Compound 104



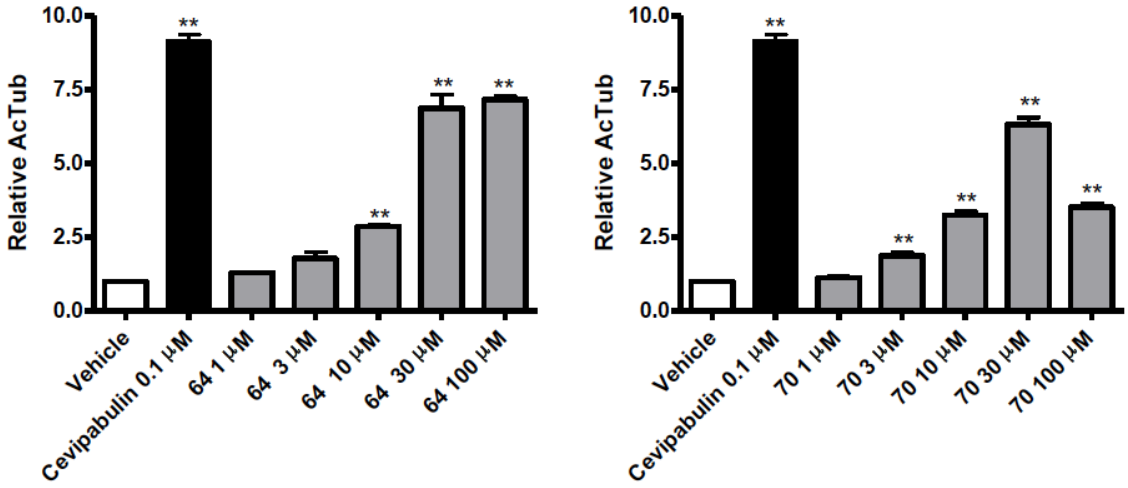
Compound 104



Supplemental Figure 1



Analysis of Table 2 compounds for their ability to reduce multiple COX and 5-LOX products. The compounds listed in Table 2 were tested at 50 µM in the RBL-1 assay, and COX-derived PGE2 and PGE2, as well as 5-LOX-derived LTB4 and LTC4, were assessed by LC-MS/MS. All compounds caused appreciable inhibition of all of the measured eicosanoids.



Supplemental Figure 2. Concentration response of compounds 64 and 70 in the QBI293 AcTub assay. Compounds **64** and **70** underwent concentration-response testing in triplicate in the QBI cell acetyl tubulin (AcTub) assay from 1-100 μM and the increase in AcTub/μg of cellular homogenate relative to vehicle-treated cells is graphed. The triazolopyrimidine, cevipabulin,[1] was tested at 0.1 μM as a positive control. Error bars represent standard error of the mean. **, $p<0.01$ relative to vehicle-treated cells as determined by one-way ANOVA and Dunnett's multiple comparison test.

Whereas **64** demonstrated a maximal activity that plateaued at 30 μM, a bell-shaped concentration-response was observed at high concentrations with **70,** such that a greater increase of AcTub was seen at 30 μM than 100 μM, as has been observed at lower concentrations for other imidazole and triazolopyprimidine examples (**58**, **71**, **108** in Table 1).

[1] Zhang N, et al. J. Med. Chem. 2007, *50*, 319-327.