Preparation of amides mediated by isopropylmagnesium bromide under continuous flow conditions.

Experimental.

The GC measurement was performed using a 6890 Series Gas Chromatograph (Agilent Technologies) system comprising a 7683 Series injector and autosampler, J&W HP-5MS column (20 m x 0.18 mm, 0.18 µm) from Agilent Technologies coupled to a 5973N MSD Mass Selective Detector (single quadrupole, Agilent Technologies). The MS detector was configured with an electronic impact ionization source / chemical ionization source (EI/CI). EI low-resolution mass spectra were acquired by scanning from 50 to 550 at a rate of 14.29 scan. The source temperature was maintained at 230°C. Helium was used as the nebulizer gas. Data acquisition was performed with Chemstation-Open Action software. Thin layer chromatography (TLC) was carried out on silica gel 60 F254 plates (Merck) using reagent grade solvents. Unless otherwise specified, reagents were obtained from commercial sources and used without further purification.

General flow procedure.

Two solutions, amine (1.5 equiv) in THF and isopropylmagnesium chloride lithium chloride complex solution 1.3 M in THF (3 equiv) were pumped at 0.1 mL/min (each one) using a syringe pump through Sigma-Aldrich microreactor. At the same time a third solution of ester (1 equiv) in THF was pumped at 0.2 mL/min with a second syringe pump and mixed with the previous solution in a Sigma-Aldrich microreactor and then pass through a coil of 5 mL (Rt= 14 min).The outlet solution was poured into HCl 1M and extracted with eter The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo to yield the product.

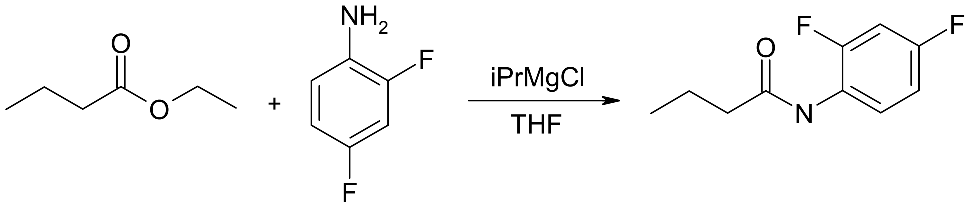
Work-up on-line.

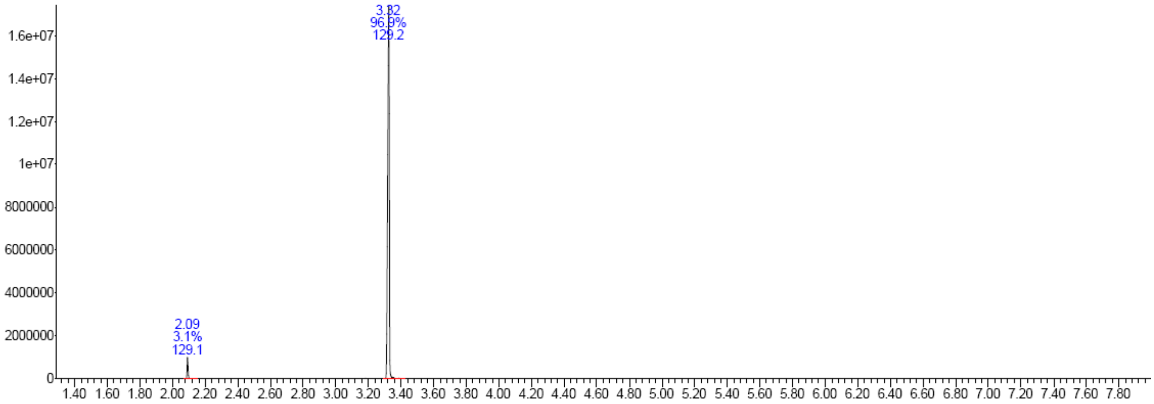
The output of the coil was then directed into a 10 mm diameter Omnifit column filled with Amberlyst A-15 (2 g). The solution collected was evaporated to dryness to yield the product.

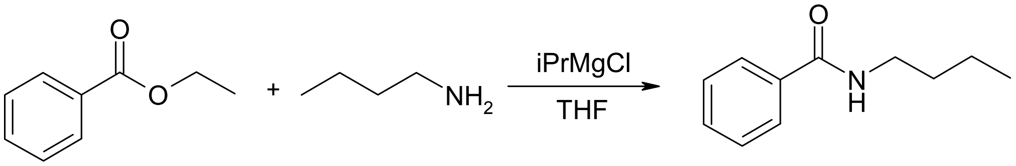
General batch procedure.

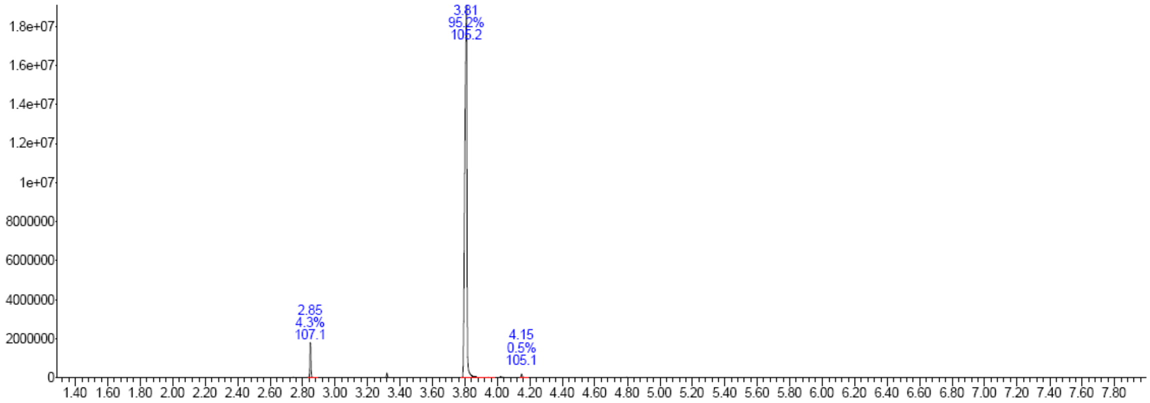
A solution of isopropylmagnesium chloride lithium chloride complex solution 1.3 M (3 equiv) in THF was added to a stirred solution of amine (1.5 equiv) in THF in a sealed tube under nitrogen at rt. The mixture was stirred for 1 hour. Then a solution of ester (1 equiv) in THF was added to the previous one at room temperature for 1 hour (at 14min the reaction was not completed). The mixture was quenched with HCl 1M and extracted with eter. The organic layer was separated, dried (MgSO4), filtered and the solvents evaporated in vacuo to yield the product.

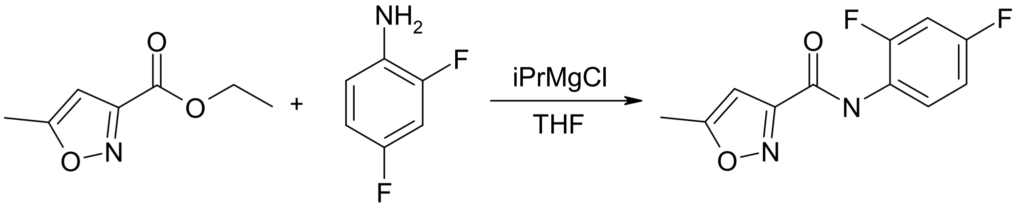
GCMS spectra of representative reactions crude.

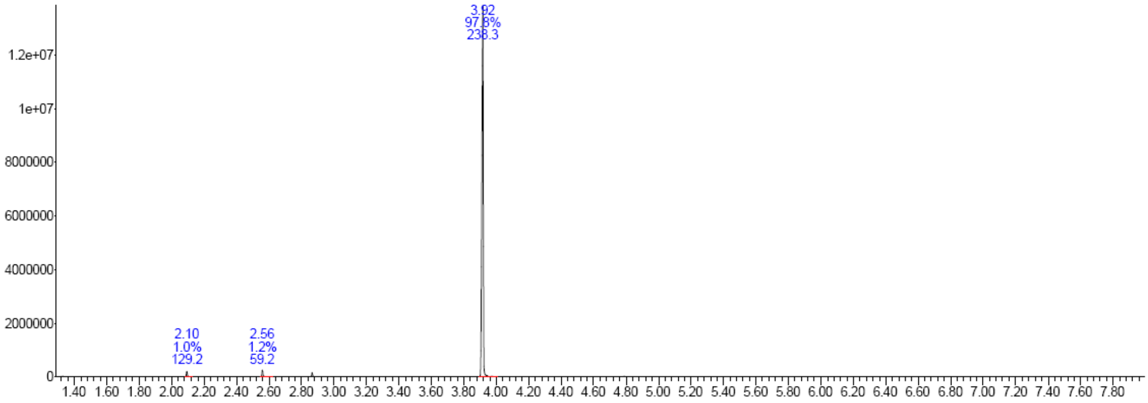




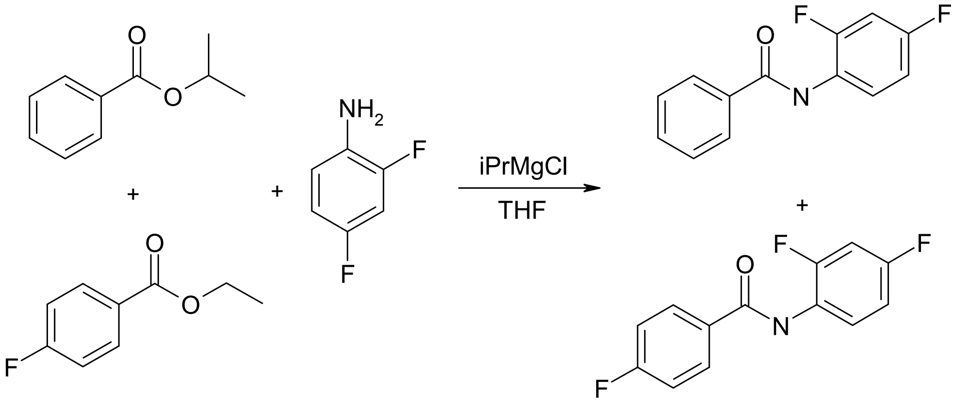





iPrMgCl
THF

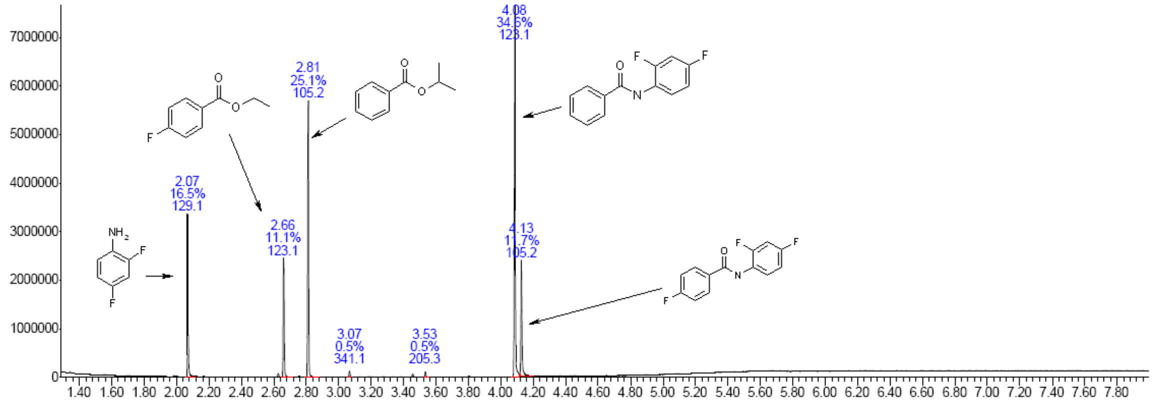

3.92
97.8%
238.3
2.10
1.0%
129.2
2.56
1.2%
59.2
1.2e+07
1e+07
8000000
6000000
4000000
2000000
0
1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00 3.20 3.40 3.60 3.80 4.00 4.20 4.40 4.60 4.80 5.00 5.20 5.40 5.60 5.80 6.00 6.20 6.40 6.60 6.80 7.00 7.20 7.40 7.60 7.80

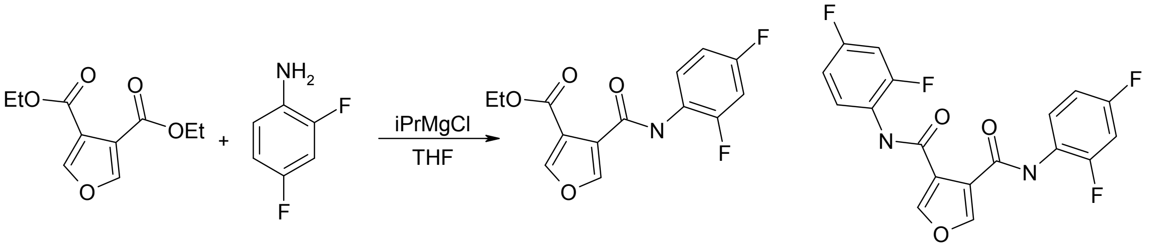
GCMS spectra of selectivy reactions.



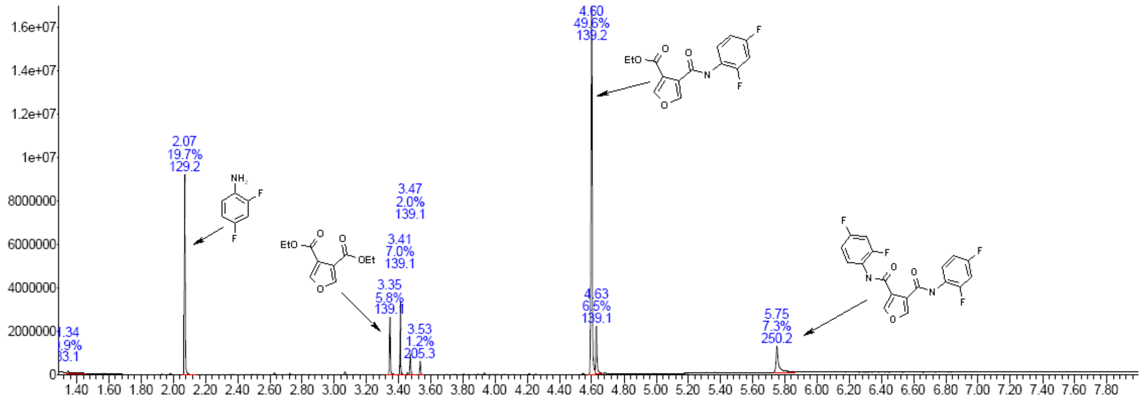
Flow reaction

Batch reaction

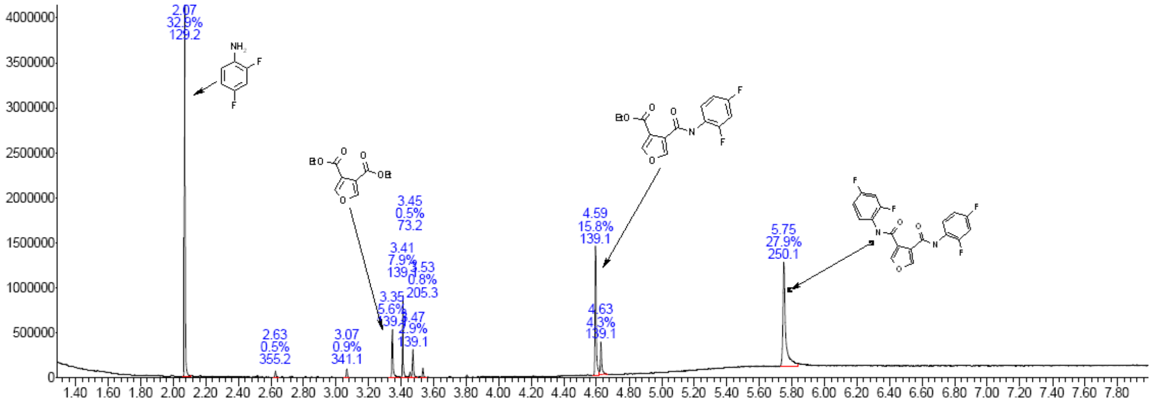


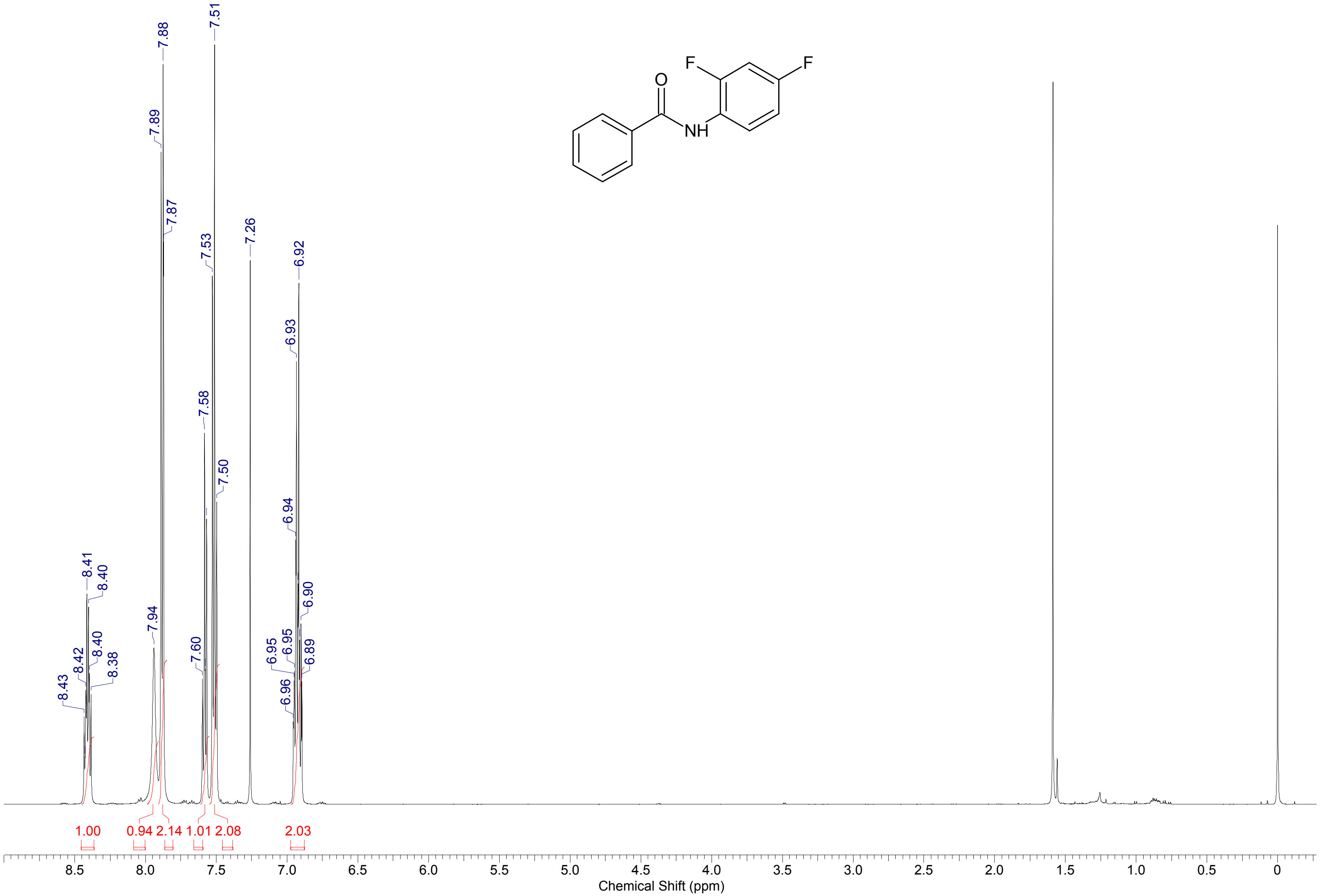


Flow reaction

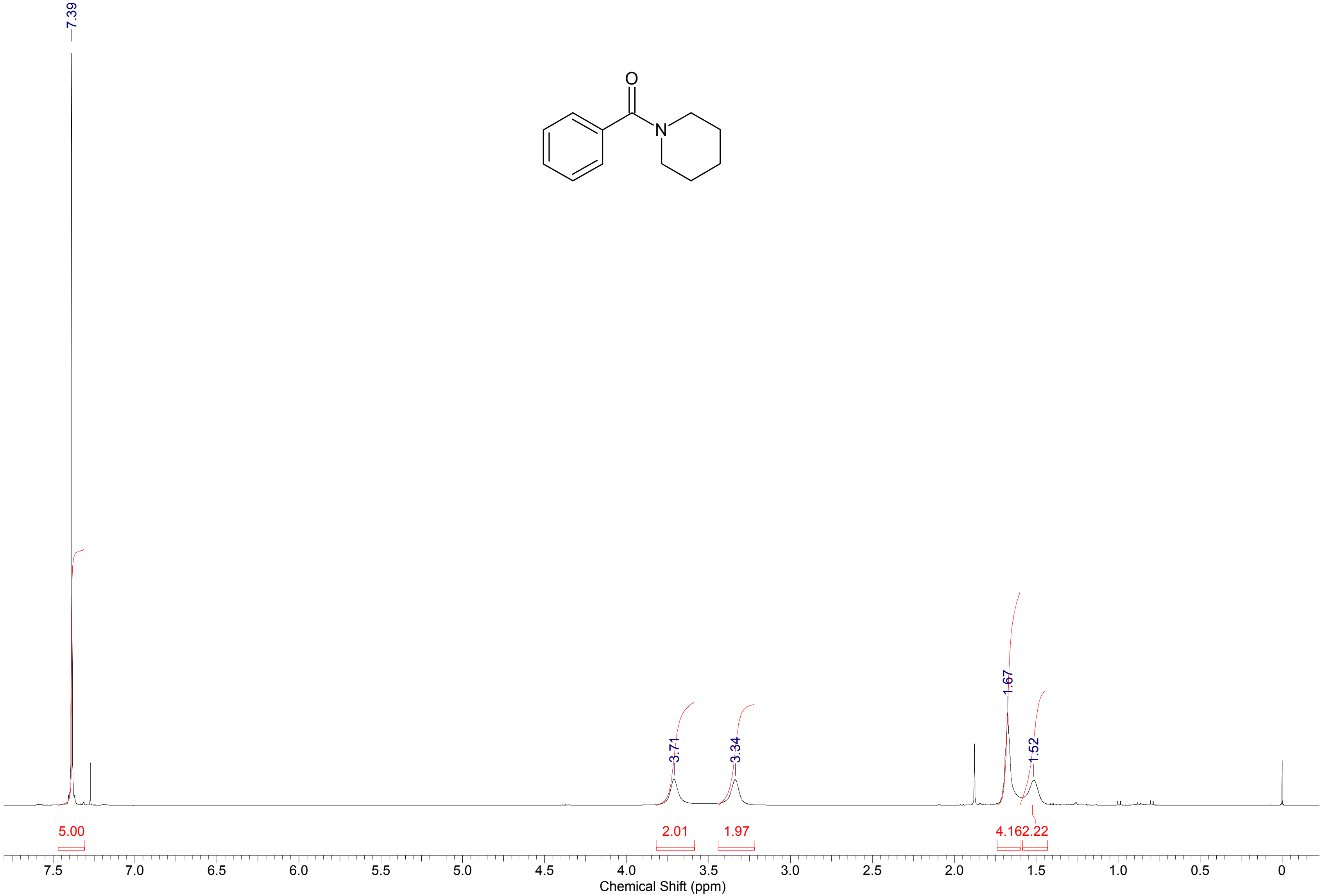


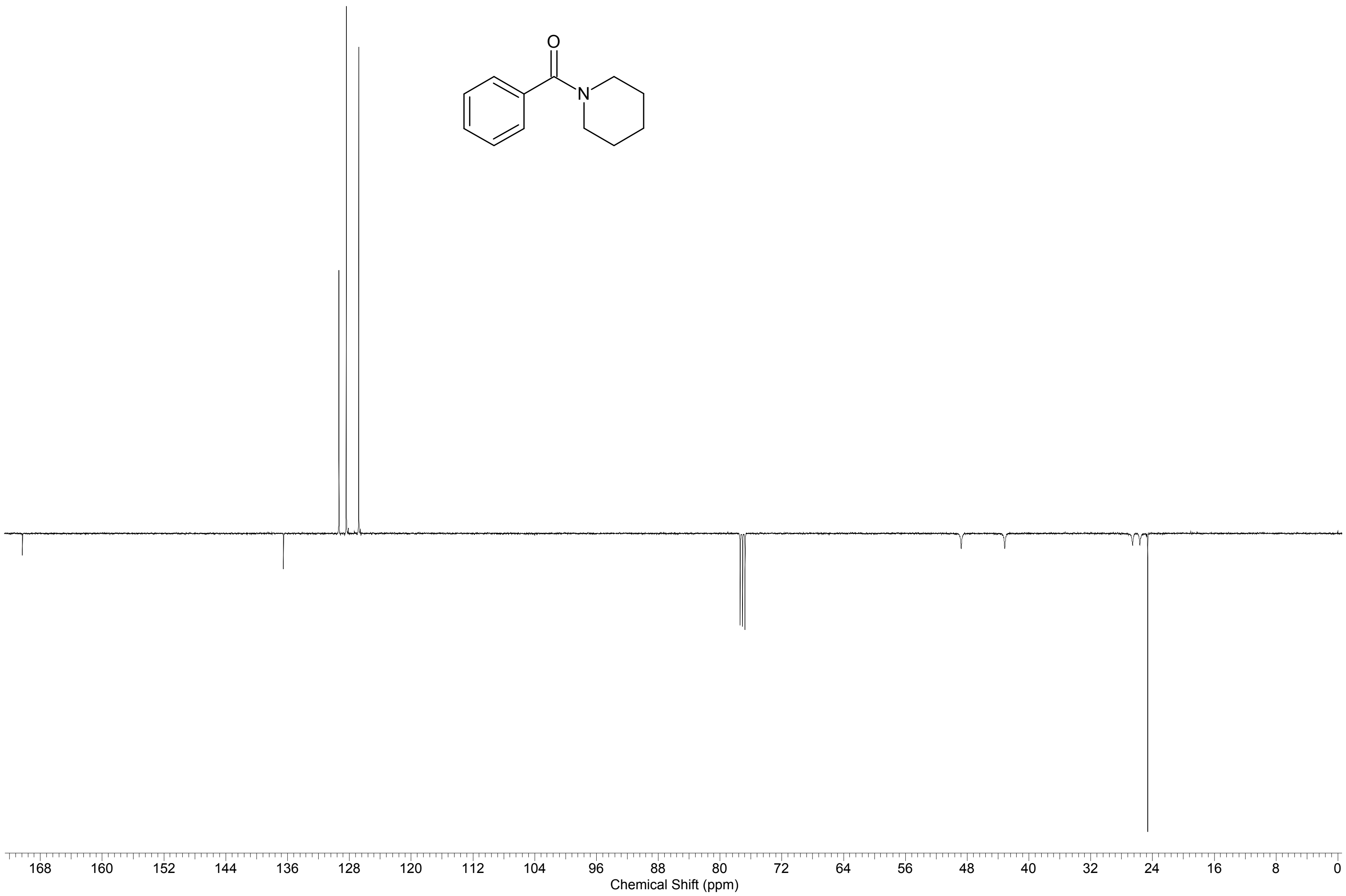
Batch reaction

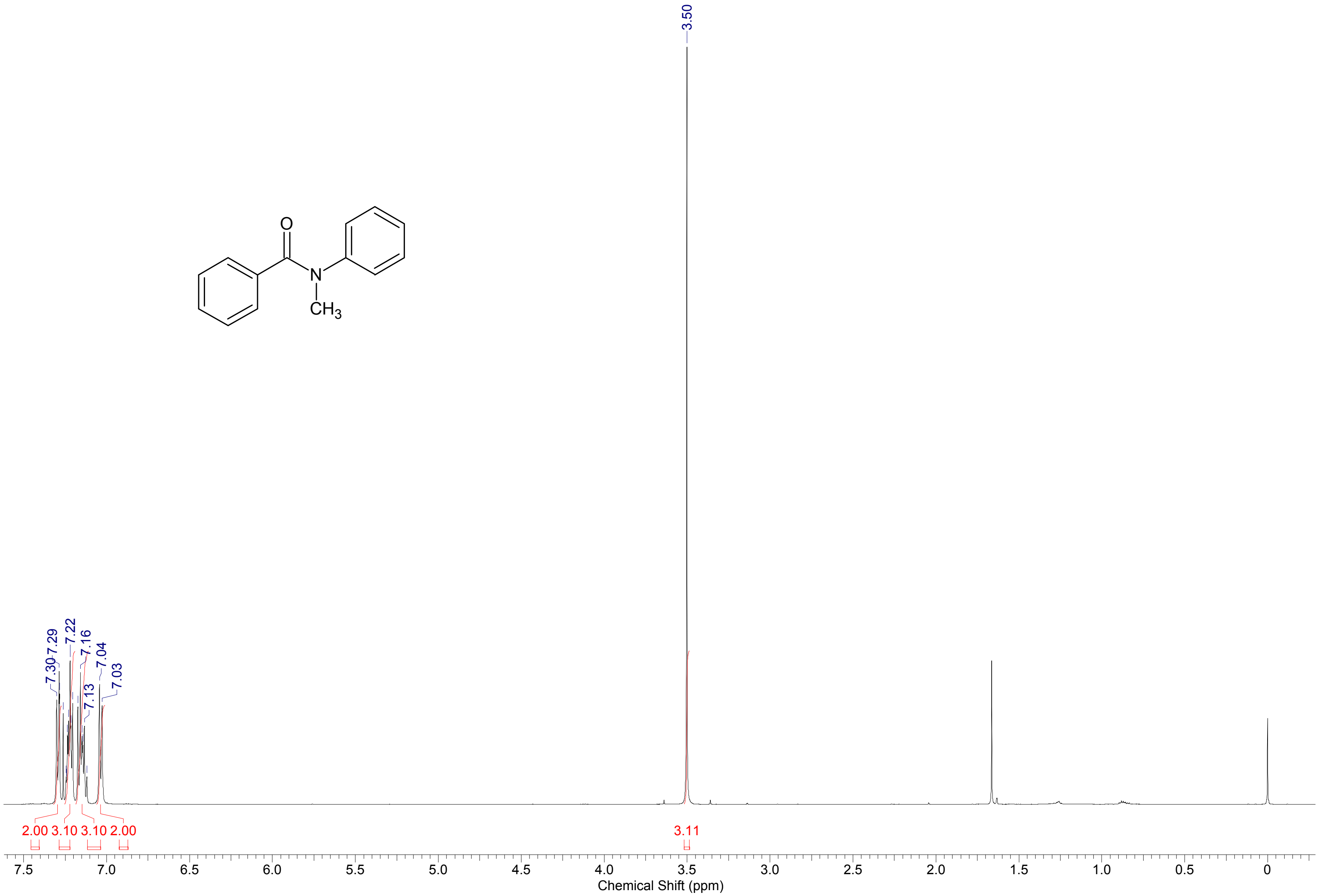



8.43
8.42
8.41
8.40
8.40
8.38
7.94
7.89
7.88
7.87
7.60
7.58
7.53
7.51
7.50
7.26
6.96
6.95
6.95
6.94
6.93
6.92
6.90
6.89
1.00
0.94
2.14
1.01
2.08
2.03
O
NH
F
F
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

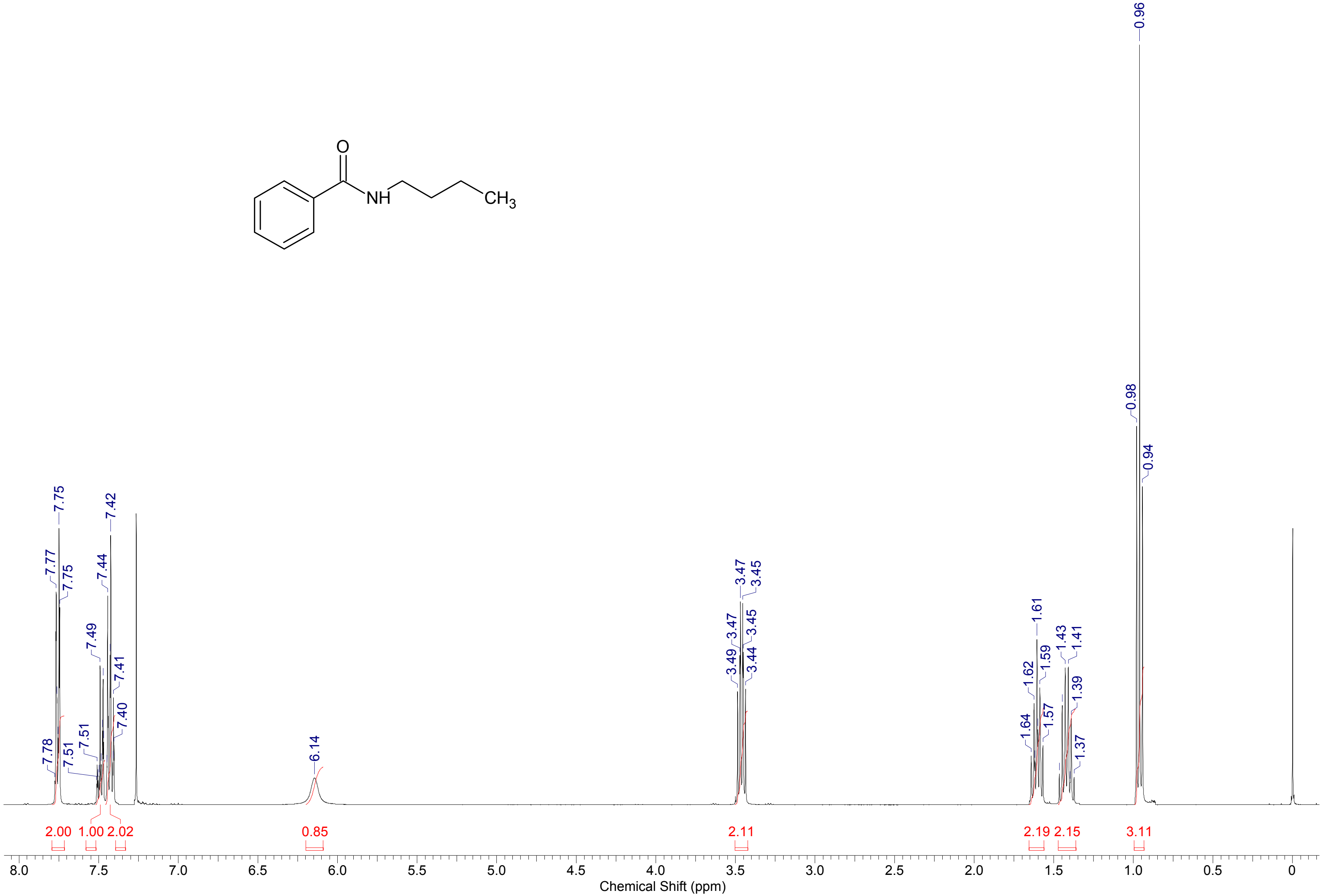

O
F
F
NH
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

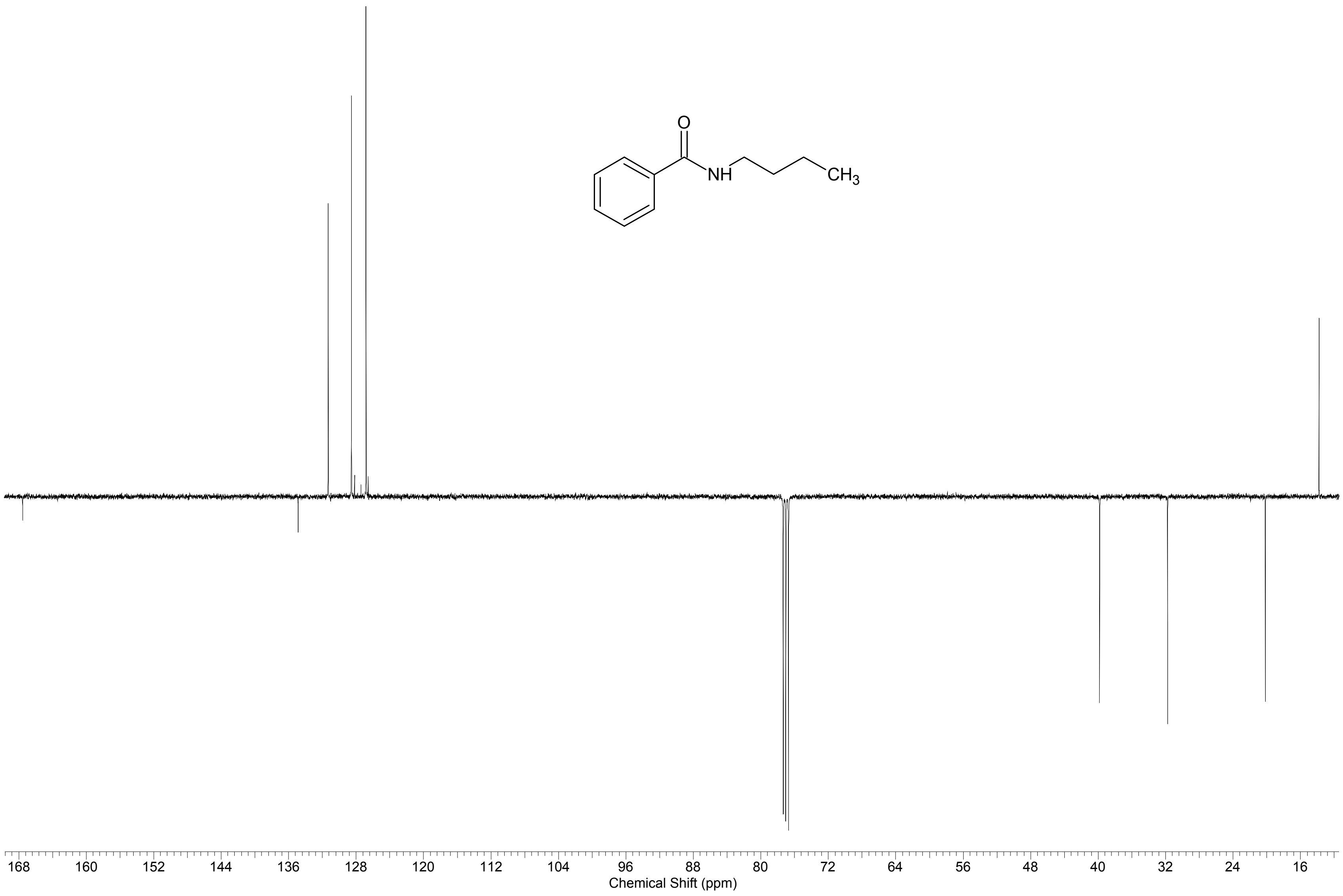

7.39
O
N
3.71
3.34
1.67
1.52
5.00
2.01
1.97
4.16
2.22
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

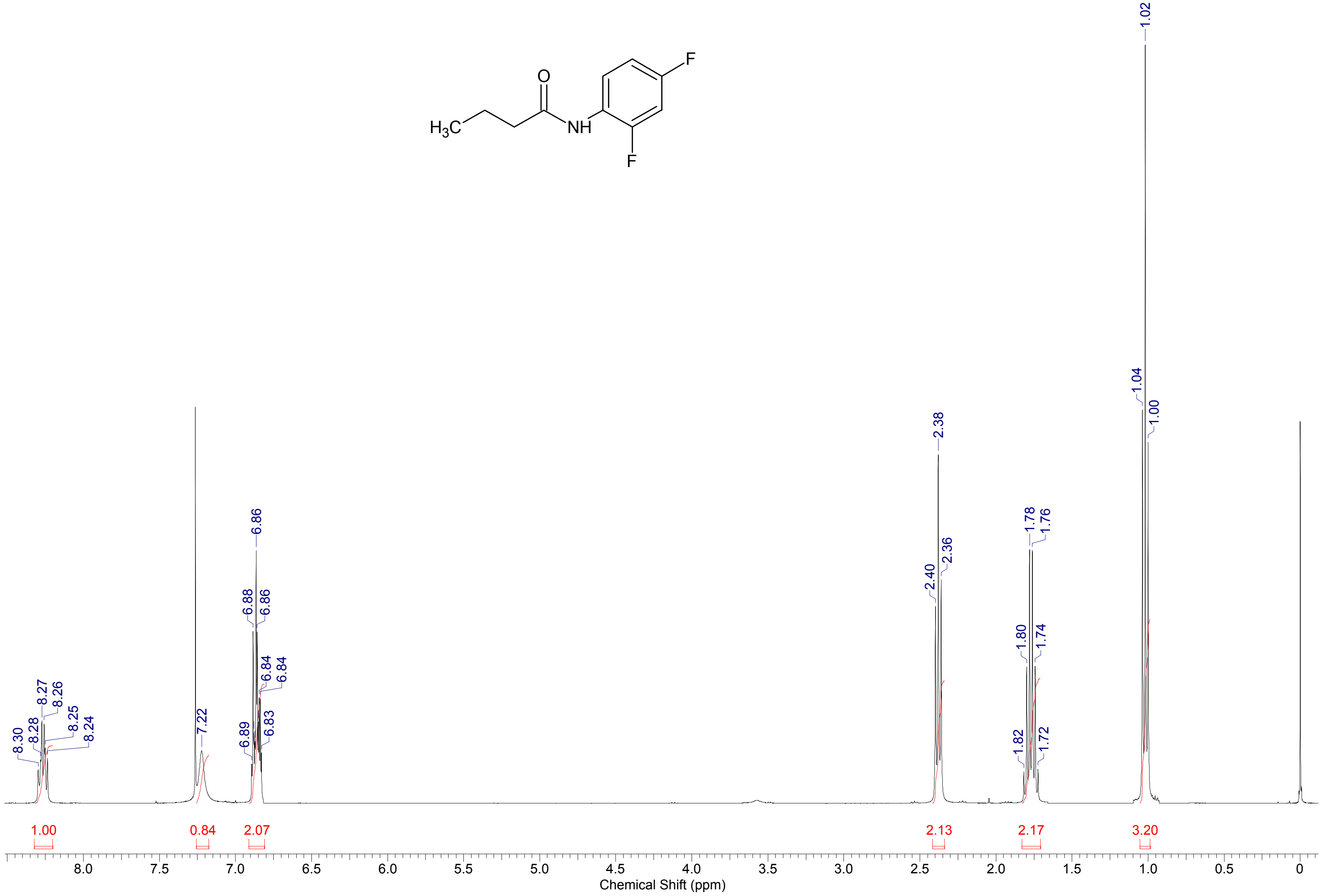

O
N
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

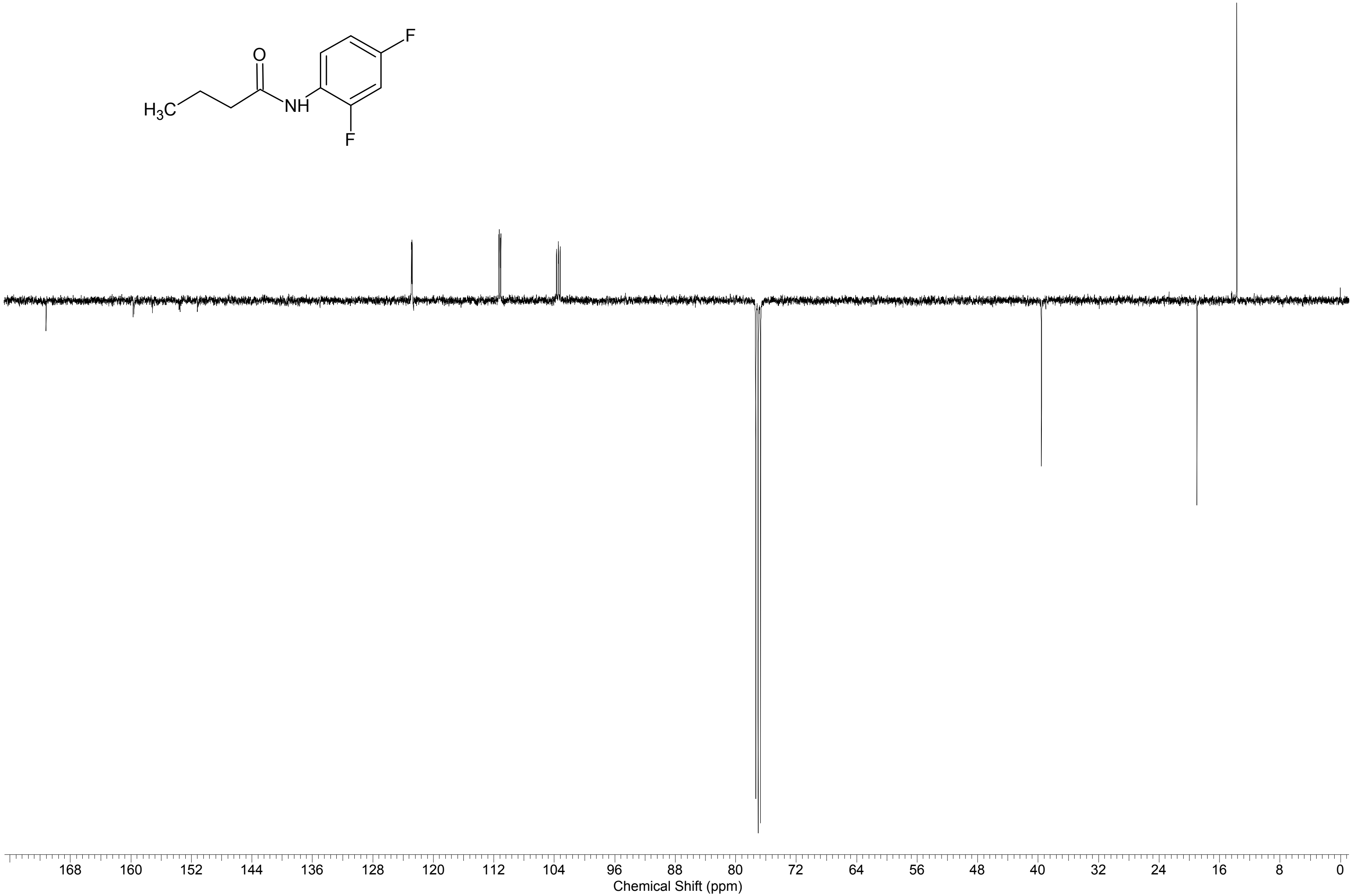

O
N
CH3
7.30
7.29
7.22
7.16
7.13
7.04
7.03
3.50
2.00
3.10
3.10
2.00
3.11
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

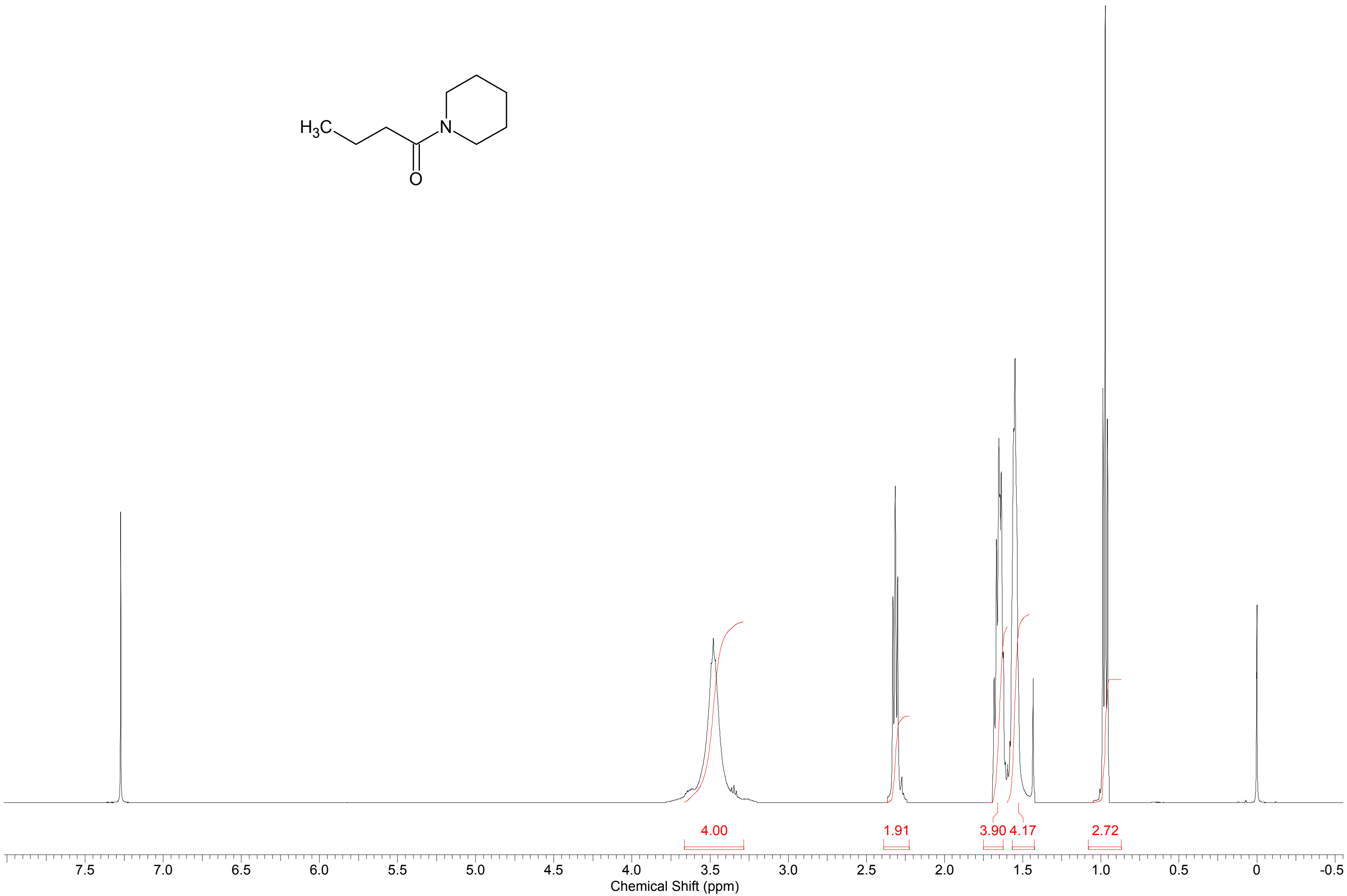

O
N
CH3
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

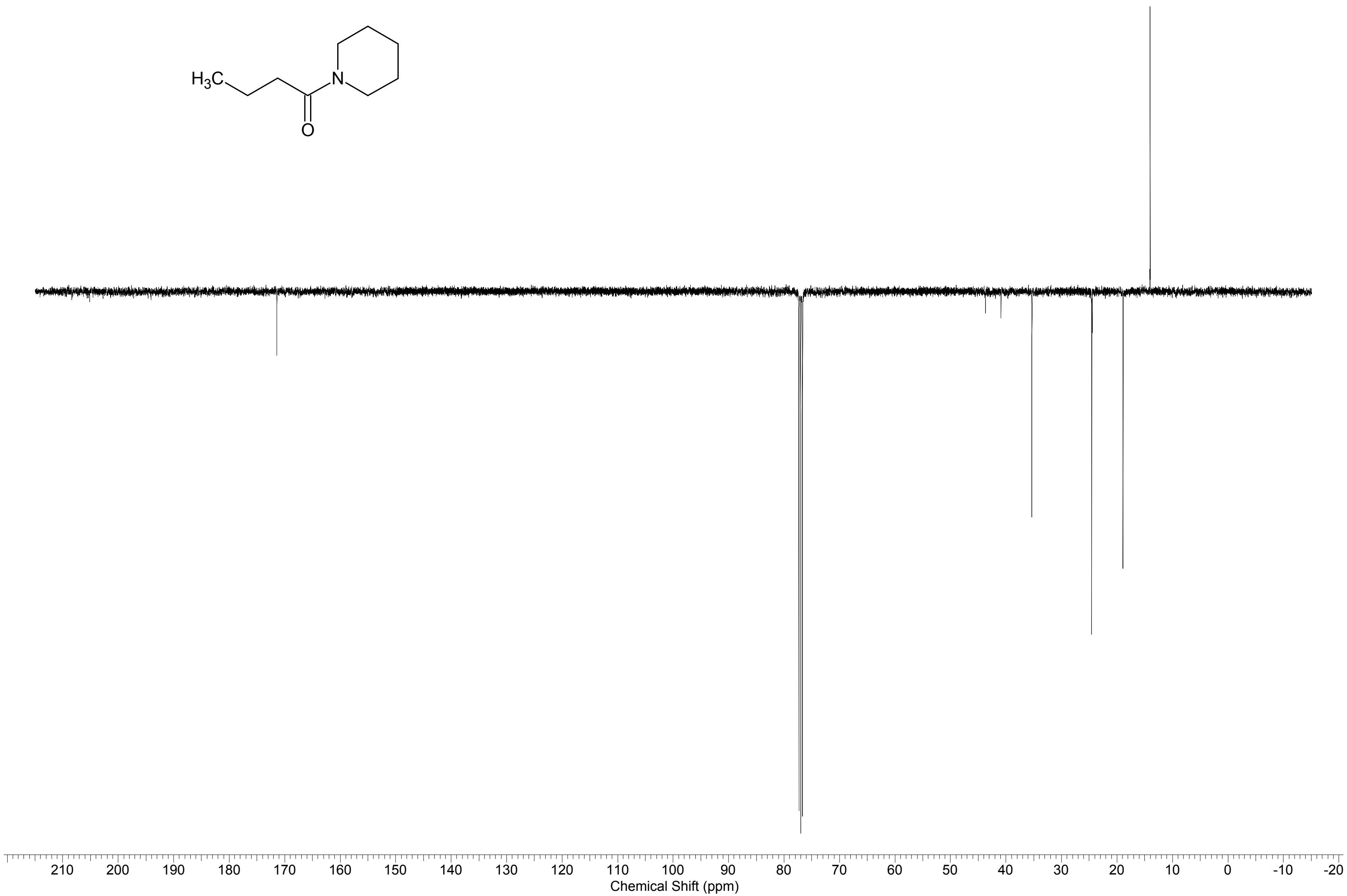

O
NH
CH3
7.78
7.77
7.75
7.75
7.51
7.51
7.49
7.44
7.42
7.41
7.40
6.14
3.49
3.47
3.47
3.45
3.45
3.44
1.64
1.62
1.61
1.59
1.57
1.43
1.41
1.39
1.37
0.98
0.96
0.94
2.00
1.00
2.02
0.85
2.11
2.19
2.15
3.11
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

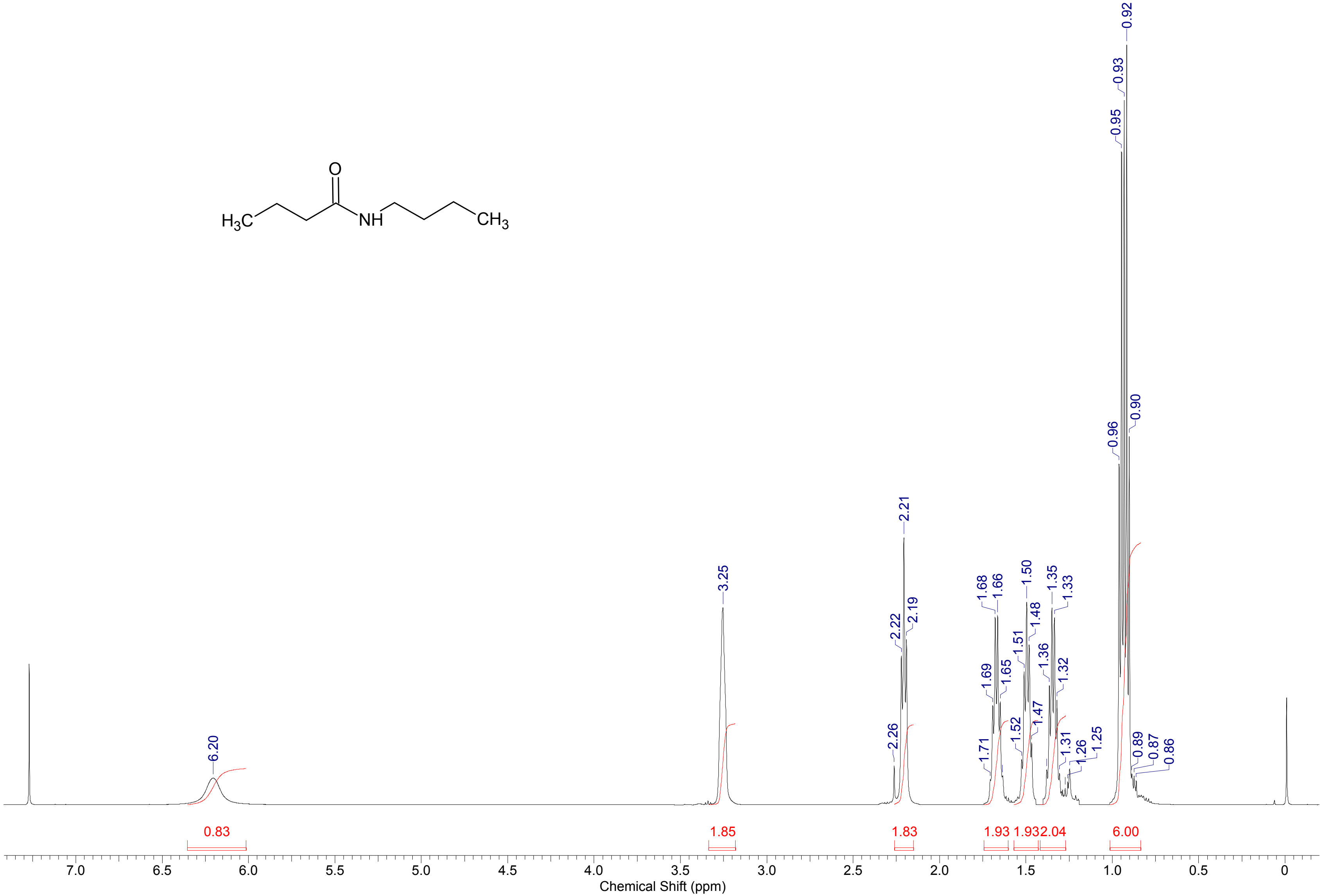

O
NH
CH_3
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

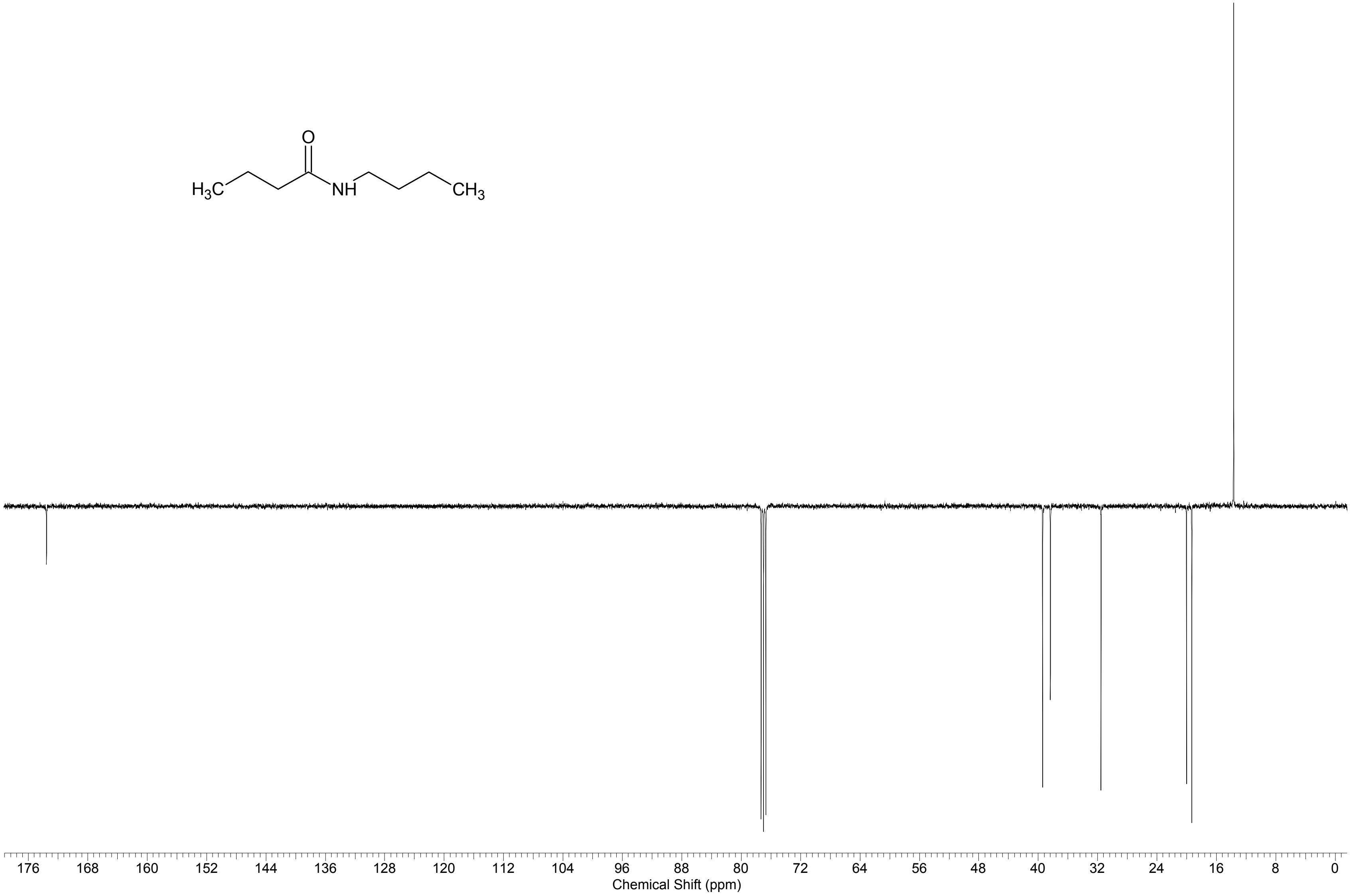

O
F
F
H_3C
NH
8.30
8.28
8.27
8.26
8.25
8.24
7.22
6.89
6.88
6.86
6.86
6.84
6.84
6.83
2.40
2.38
2.36
1.82
1.80
1.78
1.76
1.74
1.72
1.04
1.02
1.00
1.00
0.84
2.07
2.13
2.17
3.20
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

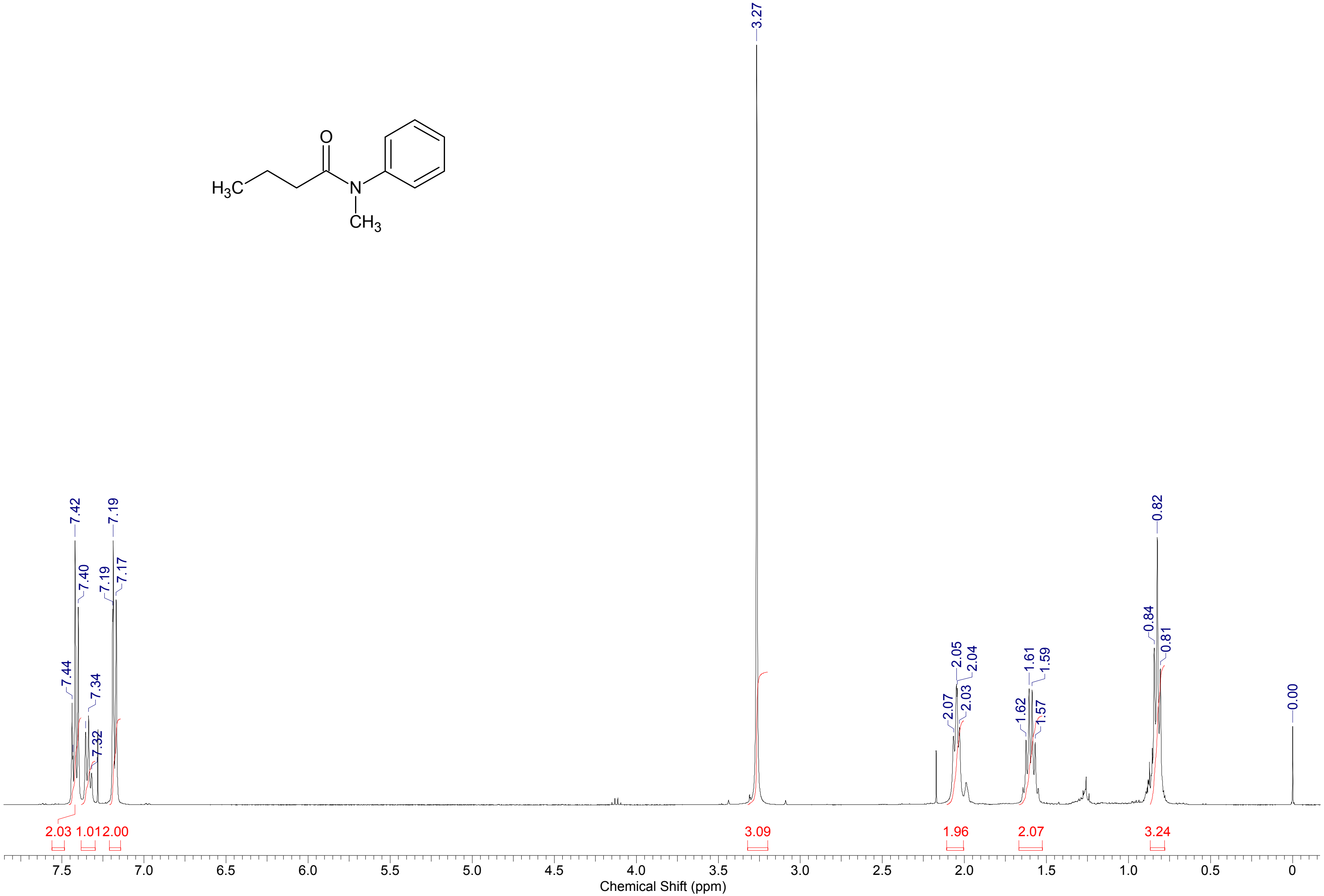

O
NH
F
F
H3C
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


H$_3$C
N
O
4.00
1.91
3.90
4.17
2.72
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
-0.5
Chemical Shift (ppm)

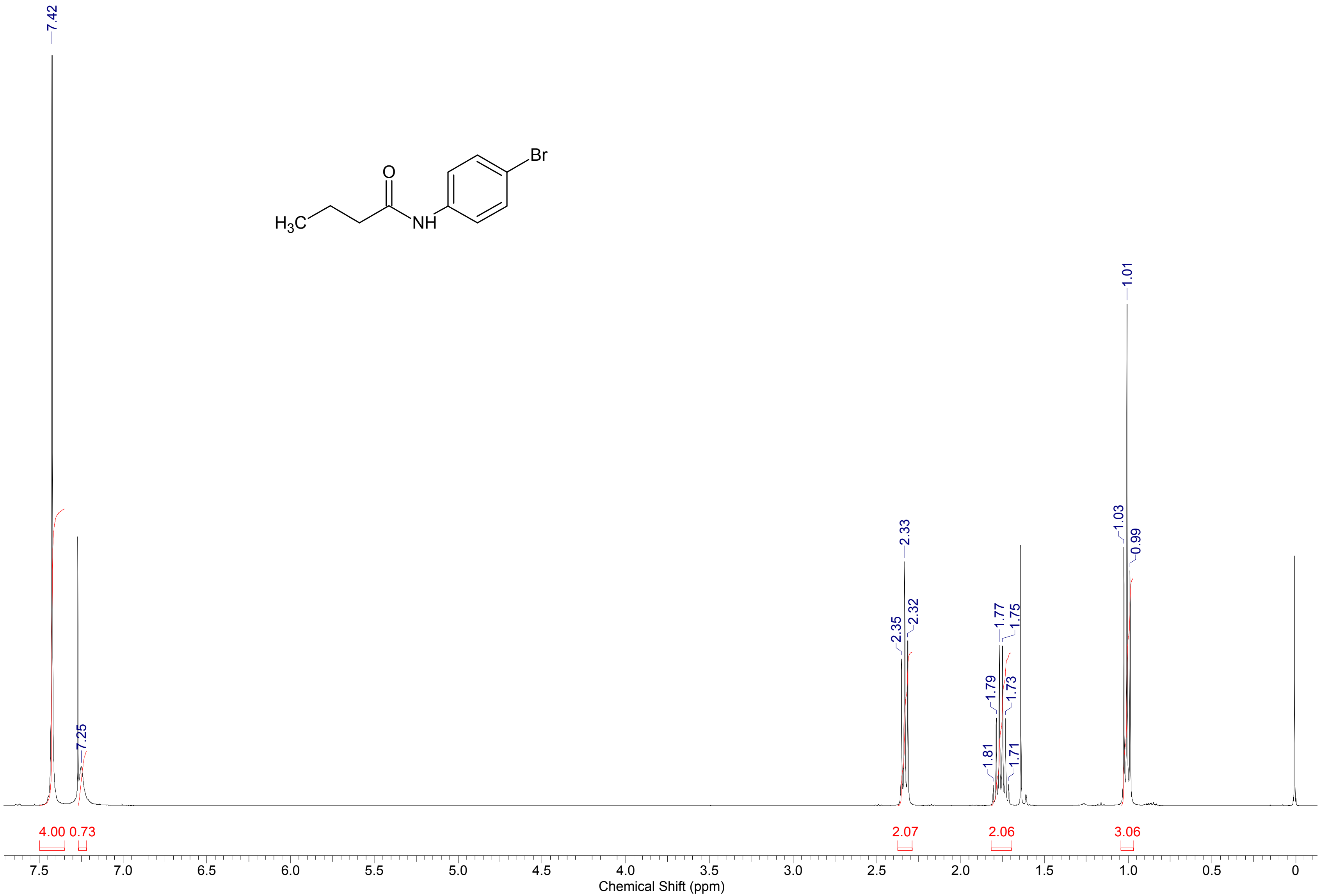

H3C
N
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
Chemical Shift (ppm)

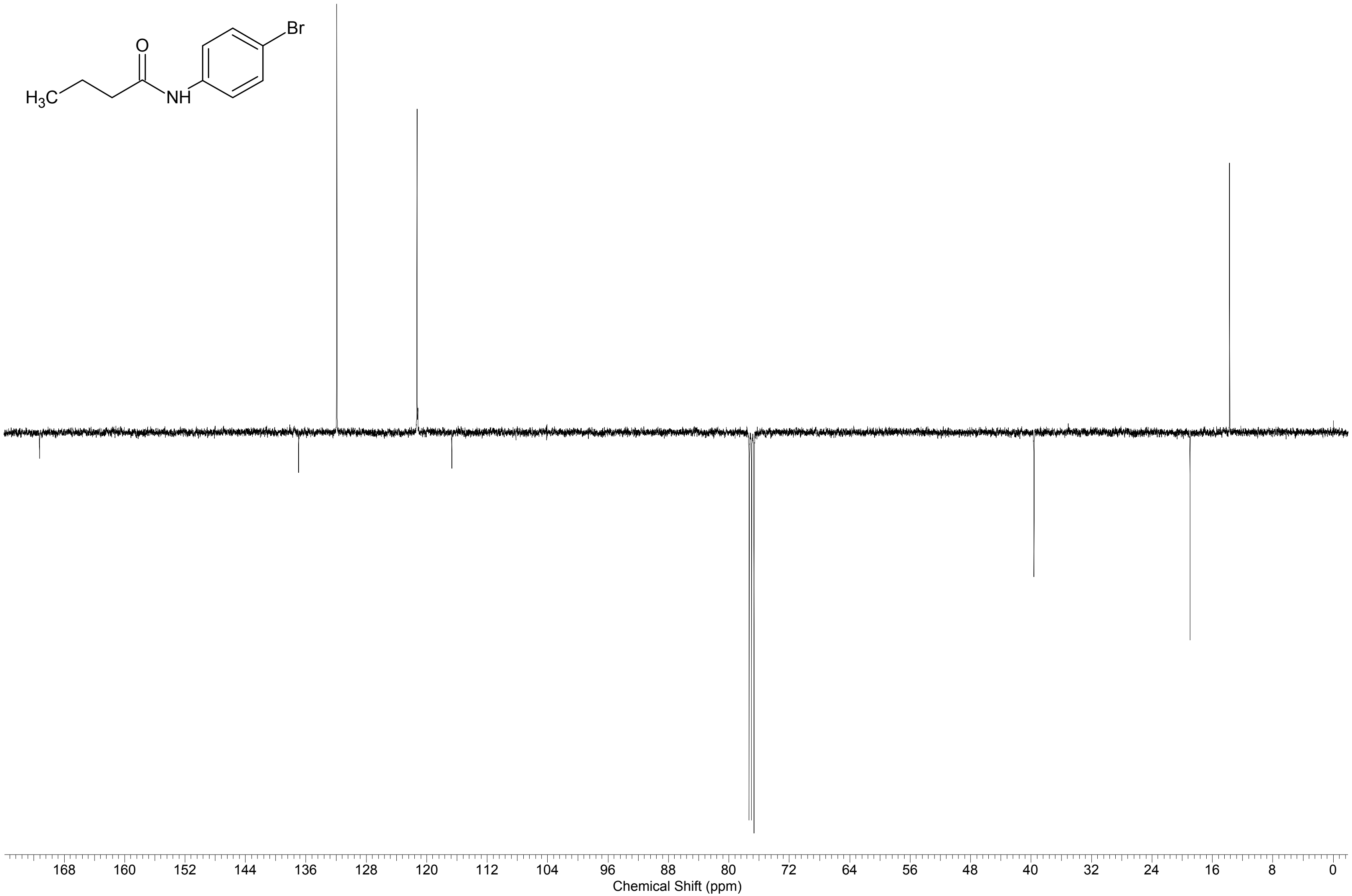

O
H_3C
NH
CH_3
6.20
3.25
2.26
2.22
2.21
2.19
1.71
1.69
1.68
1.66
1.65
1.52
1.51
1.50
1.48
1.47
1.36
1.35
1.33
1.32
1.31
1.26
1.25
0.96
0.95
0.93
0.92
0.90
0.89
0.87
0.86
0.83
1.85
1.83
1.93
1.93
2.04
6.00
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

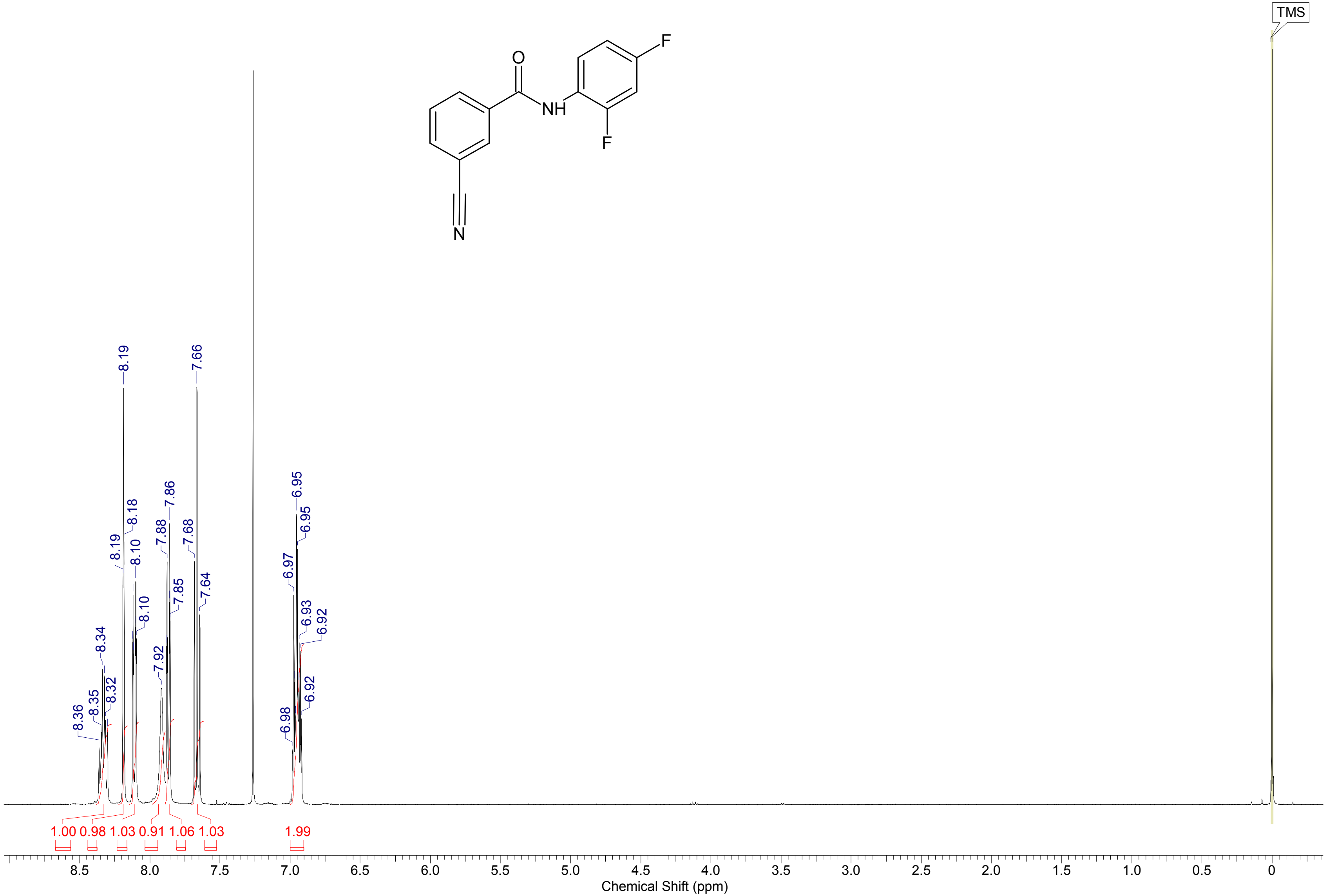

O
H_3C
NH
CH_3
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

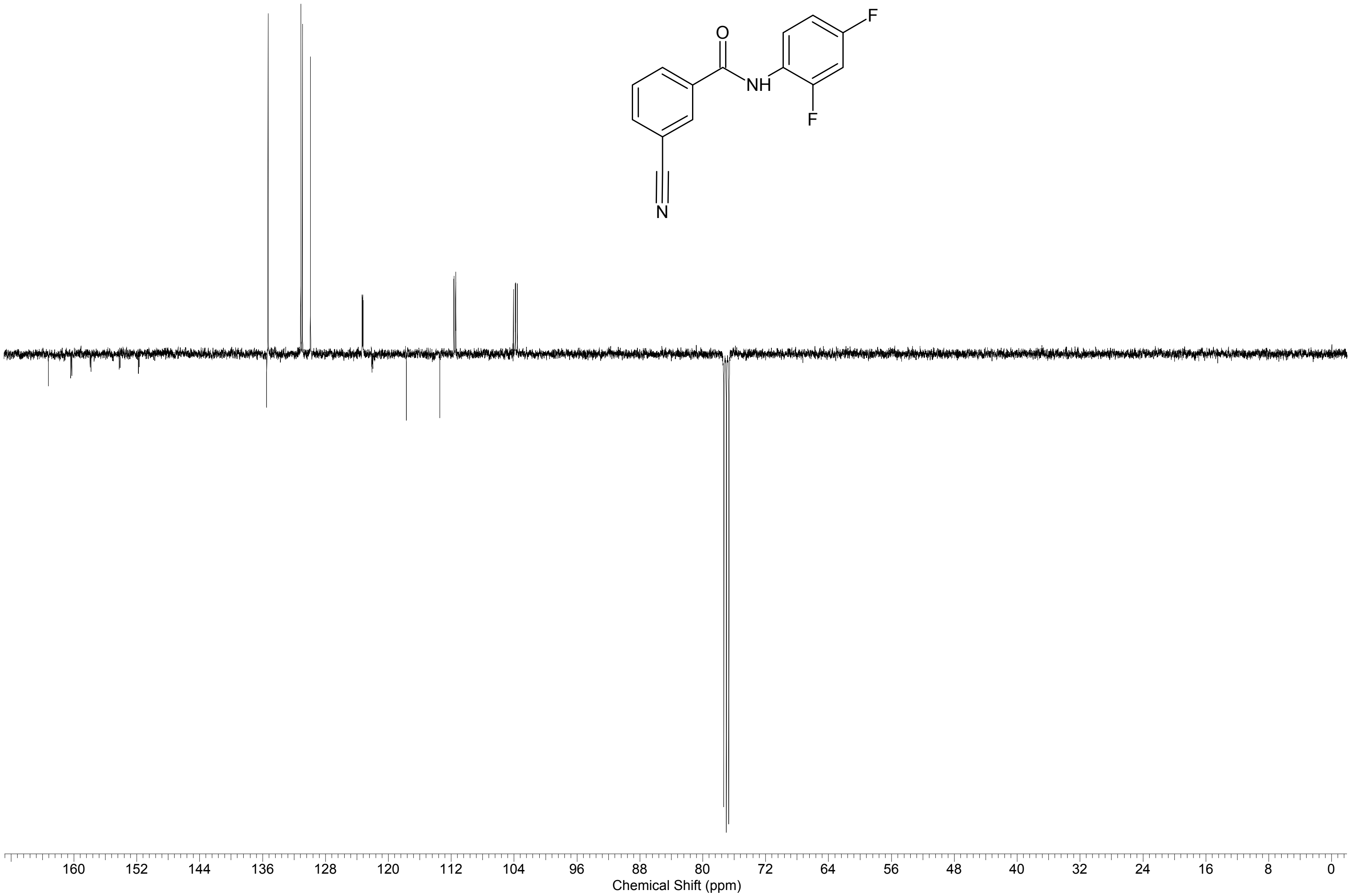

O
H_3C
N
CH_3
7.44
7.42
7.40
7.34
7.32
7.19
7.19
7.17
3.27
2.07
2.05
2.04
2.03
1.62
1.61
1.59
1.57
0.84
0.82
0.81
0.00
2.03
1.01
2.00
3.09
1.96
2.07
3.24
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

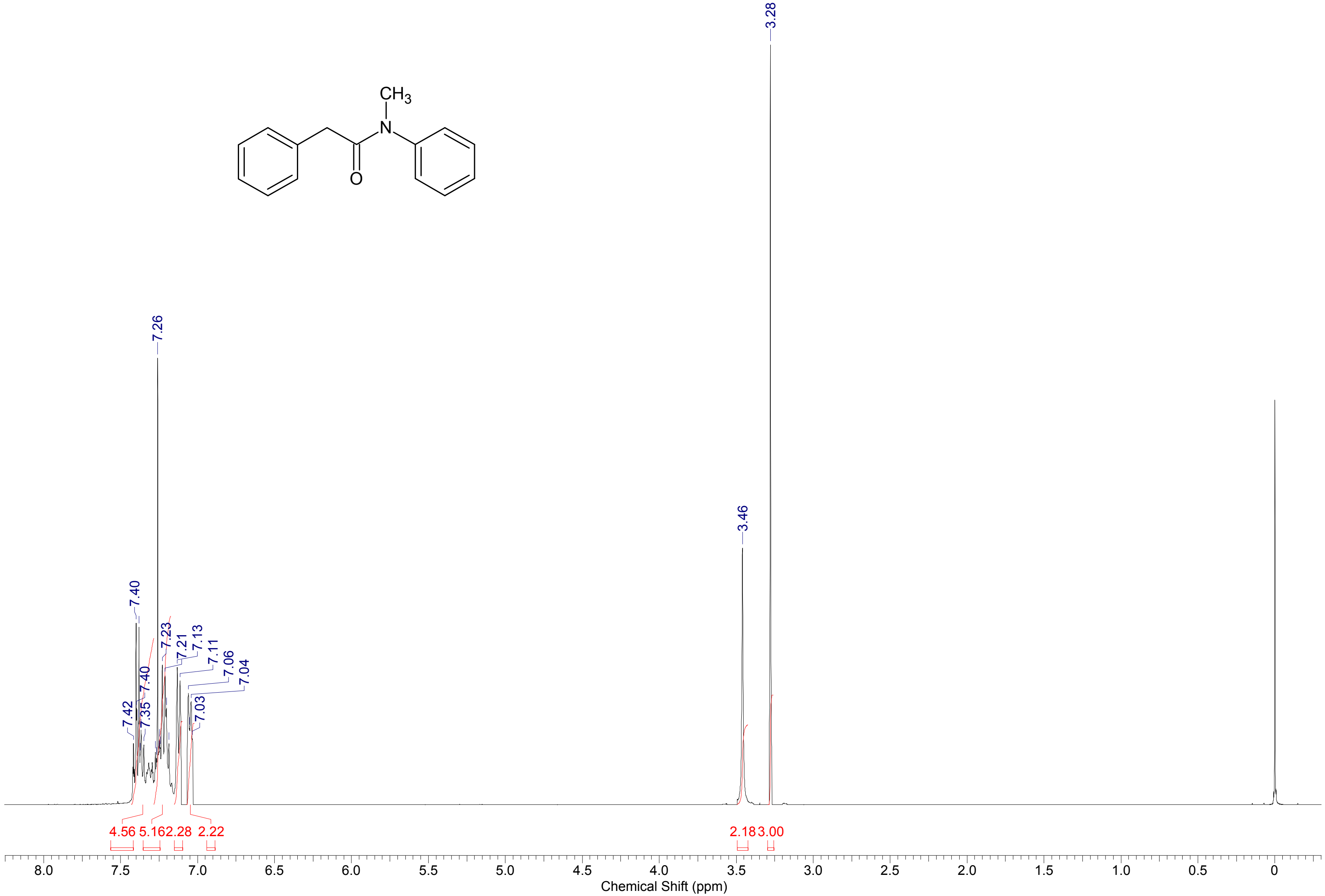

O
H3C
N
CH3
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

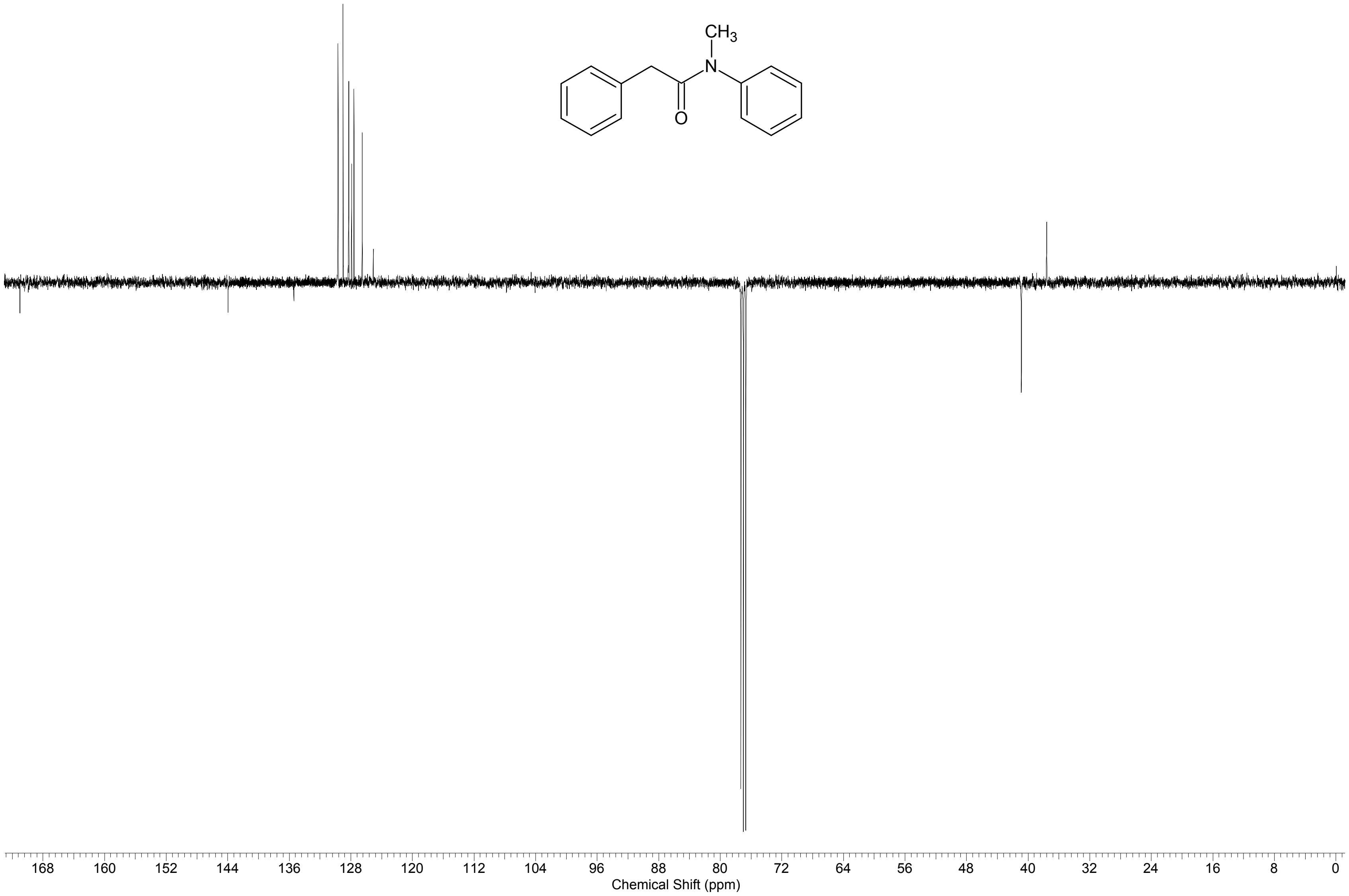

7.42
7.25
2.35
2.33
2.32
1.81
1.79
1.77
1.75
1.73
1.71
1.03
1.01
0.99
4.00
0.73
2.07
2.06
3.06
Br
O
H_3C
NH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


Br
O
H_3C
NH
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

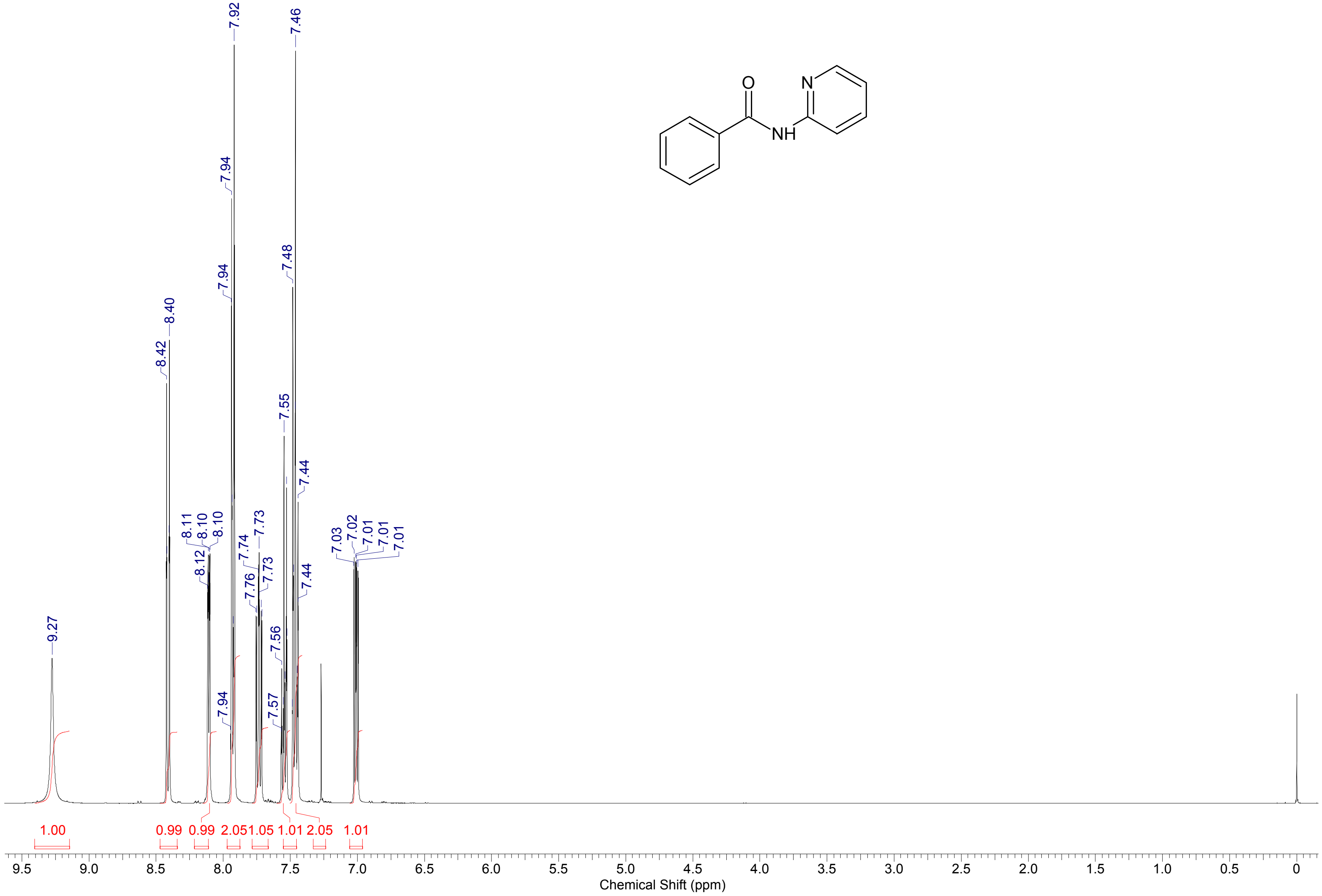

O
NH
F
F
N
TMS
8.36
8.35
8.34
8.32
8.19
8.19
8.18
8.10
8.10
7.92
7.88
7.86
7.85
7.68
7.66
7.64
6.98
6.97
6.95
6.95
6.93
6.92
6.92
1.00
0.98
1.03
0.91
1.06
1.03
1.99
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)


O
NH
F
F
N
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

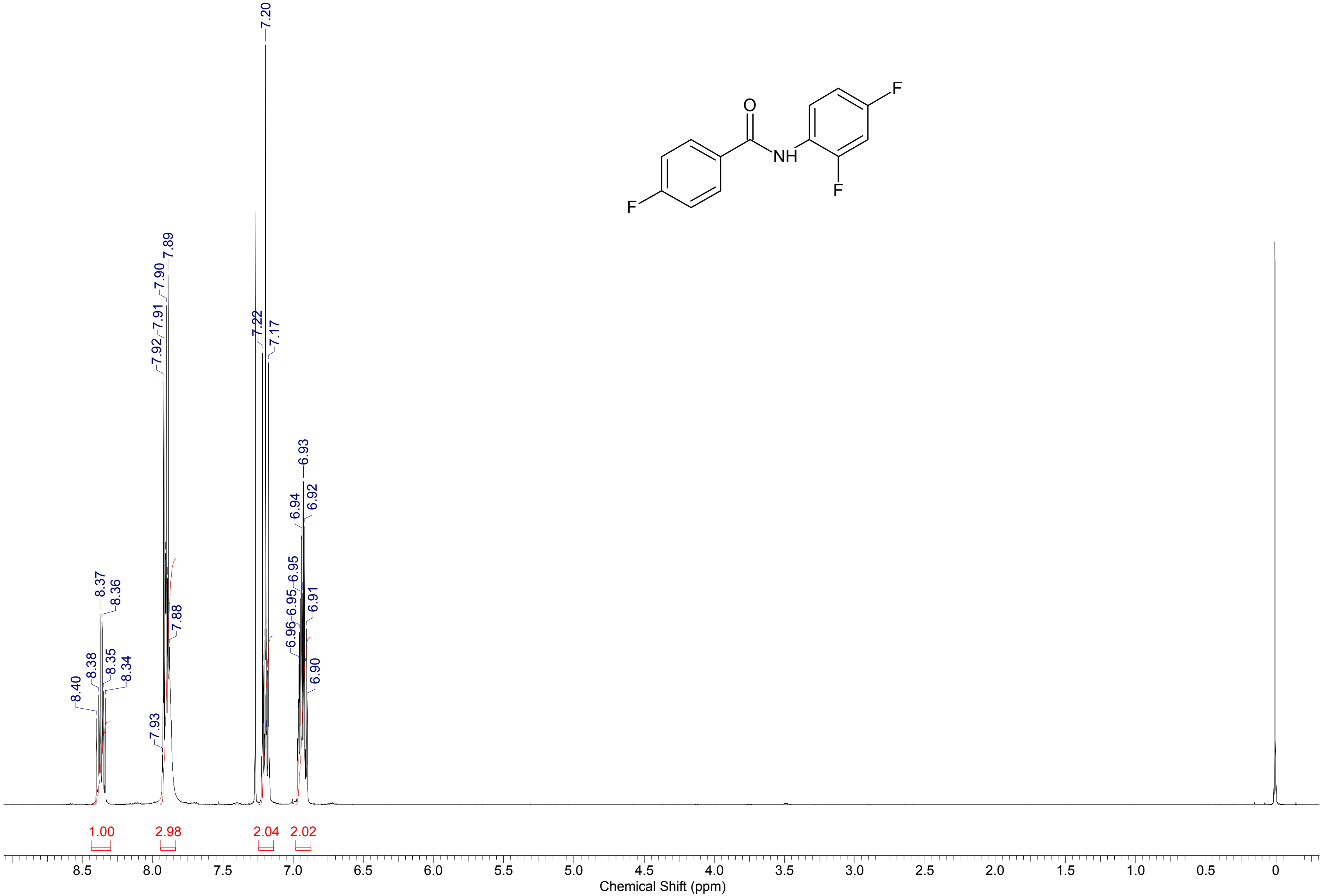

CH3
N
O
3.28
7.26
3.46
7.40
7.23
7.21
7.13
7.11
7.06
7.04
7.40
7.42
7.35
7.03
4.56
5.16
2.28
2.22
2.18
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

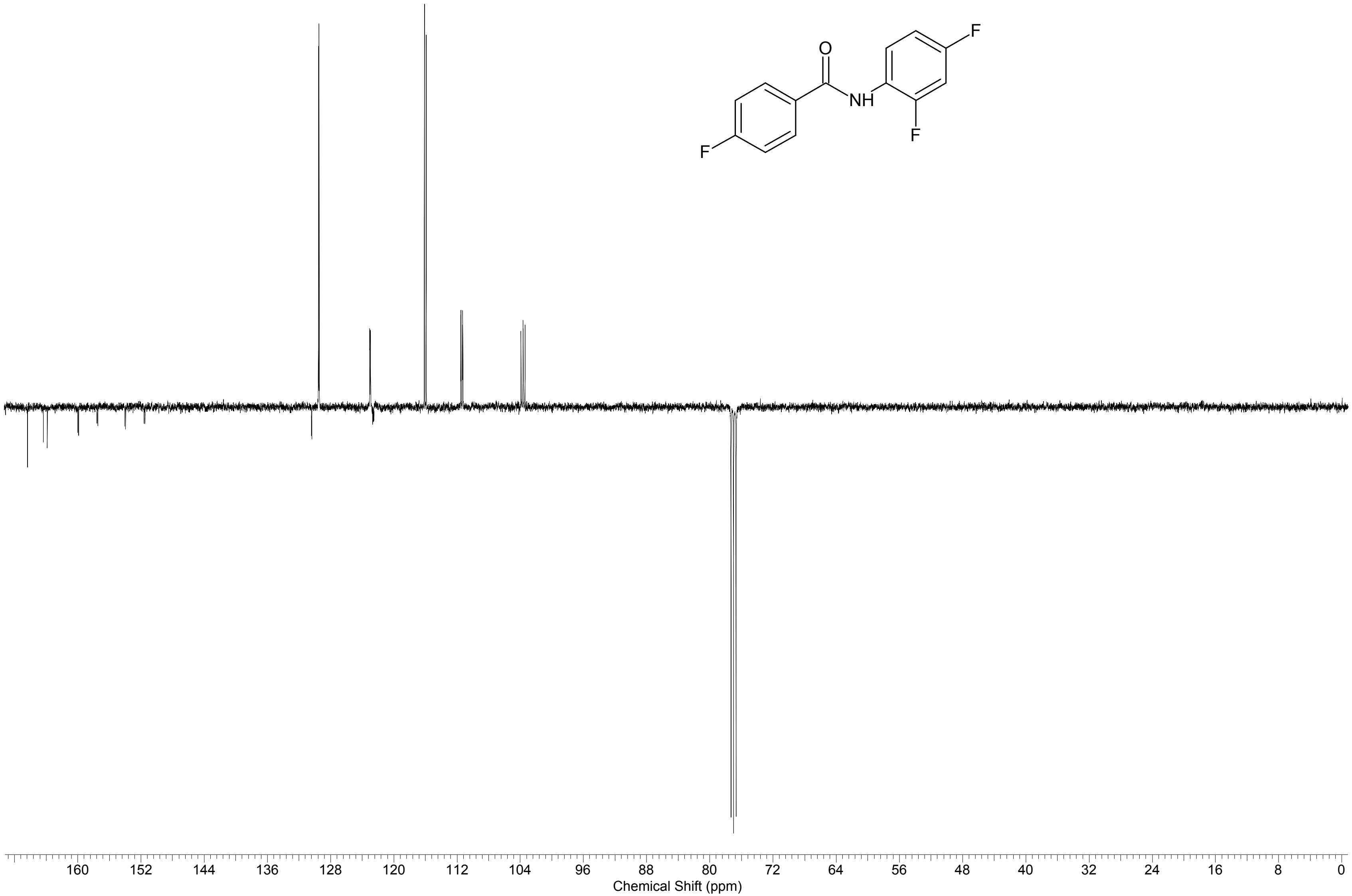

CH3
N
O
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

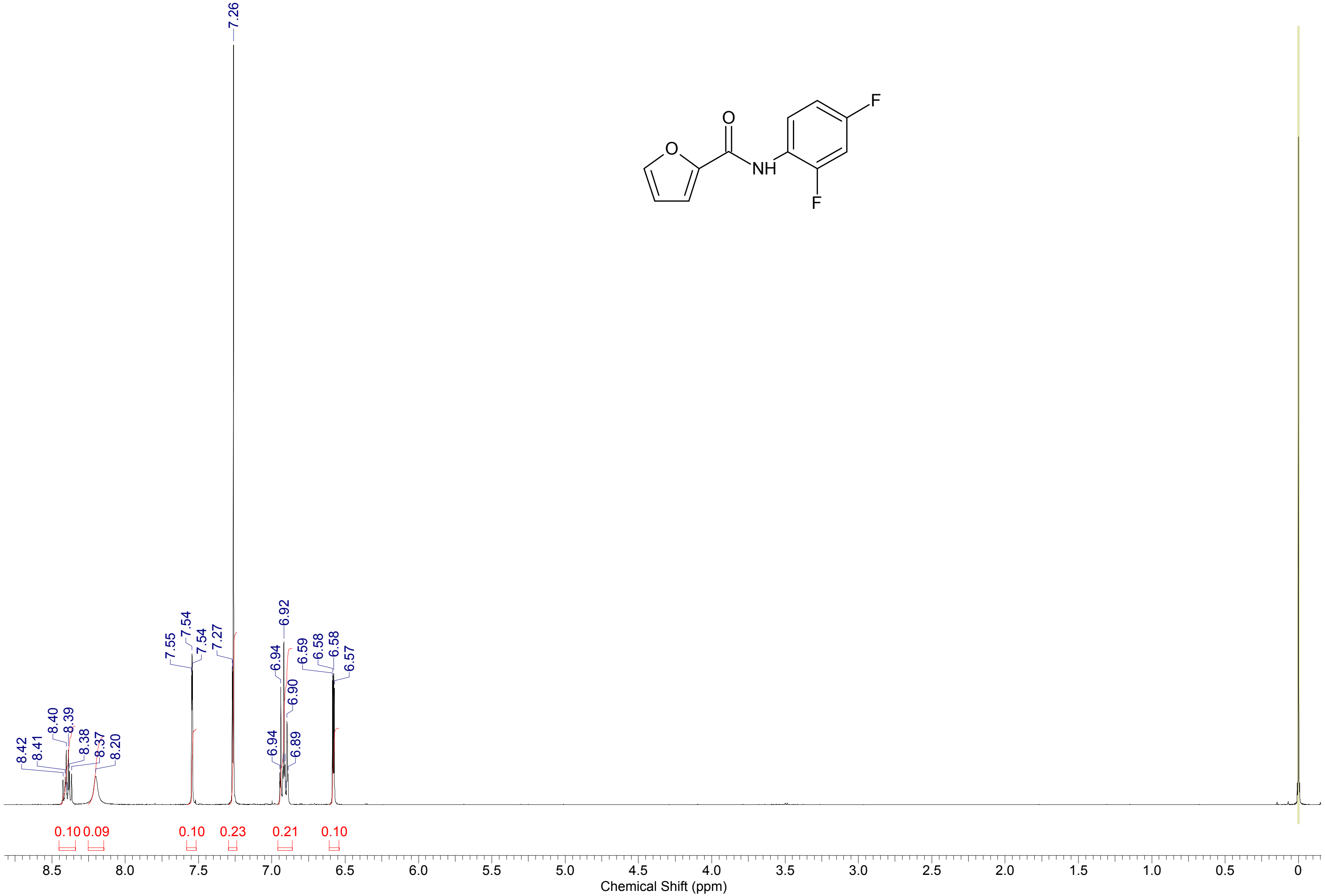
Electronic Supplementary Material (ESI) for Green Chemistry

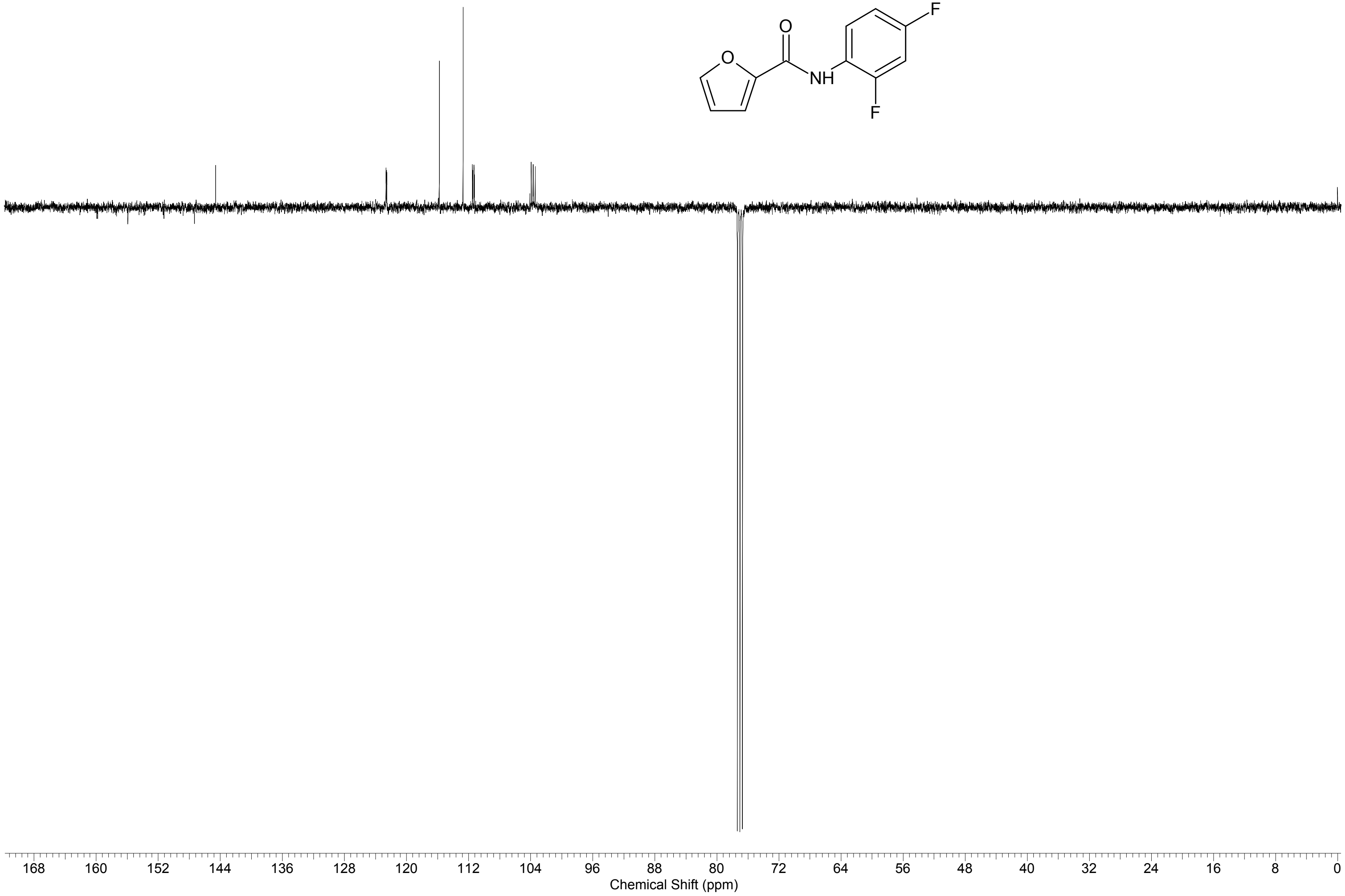


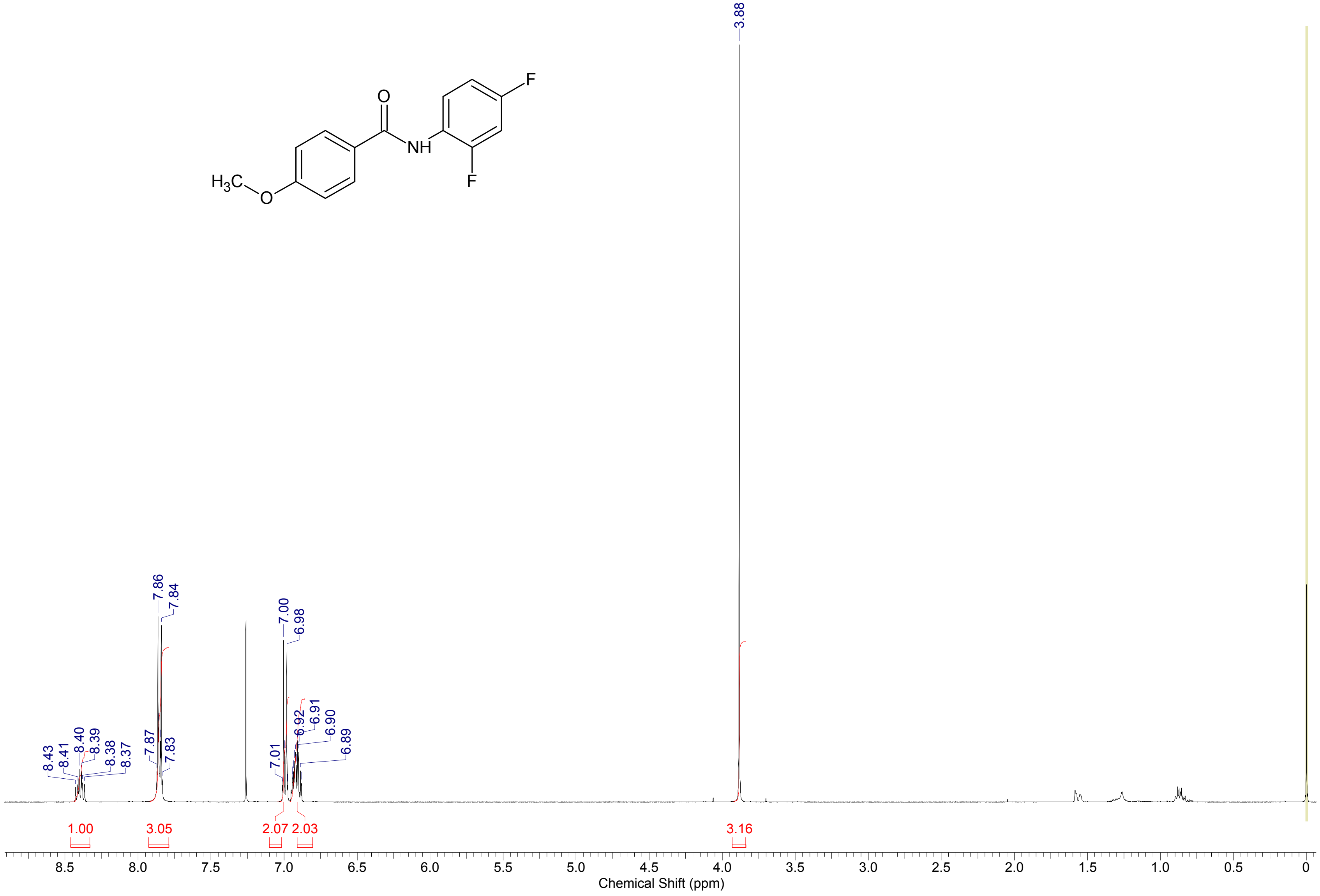

NH
N
O
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


O
NH
F
F
F
8.40
8.38
8.37
8.36
8.35
8.34
7.93
7.92
7.91
7.90
7.89
7.88
7.22
7.20
7.17
6.96
6.95
6.95
6.94
6.93
6.92
6.91
6.90
1.00
2.98
2.04
2.02
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
Chemical Shift (ppm)

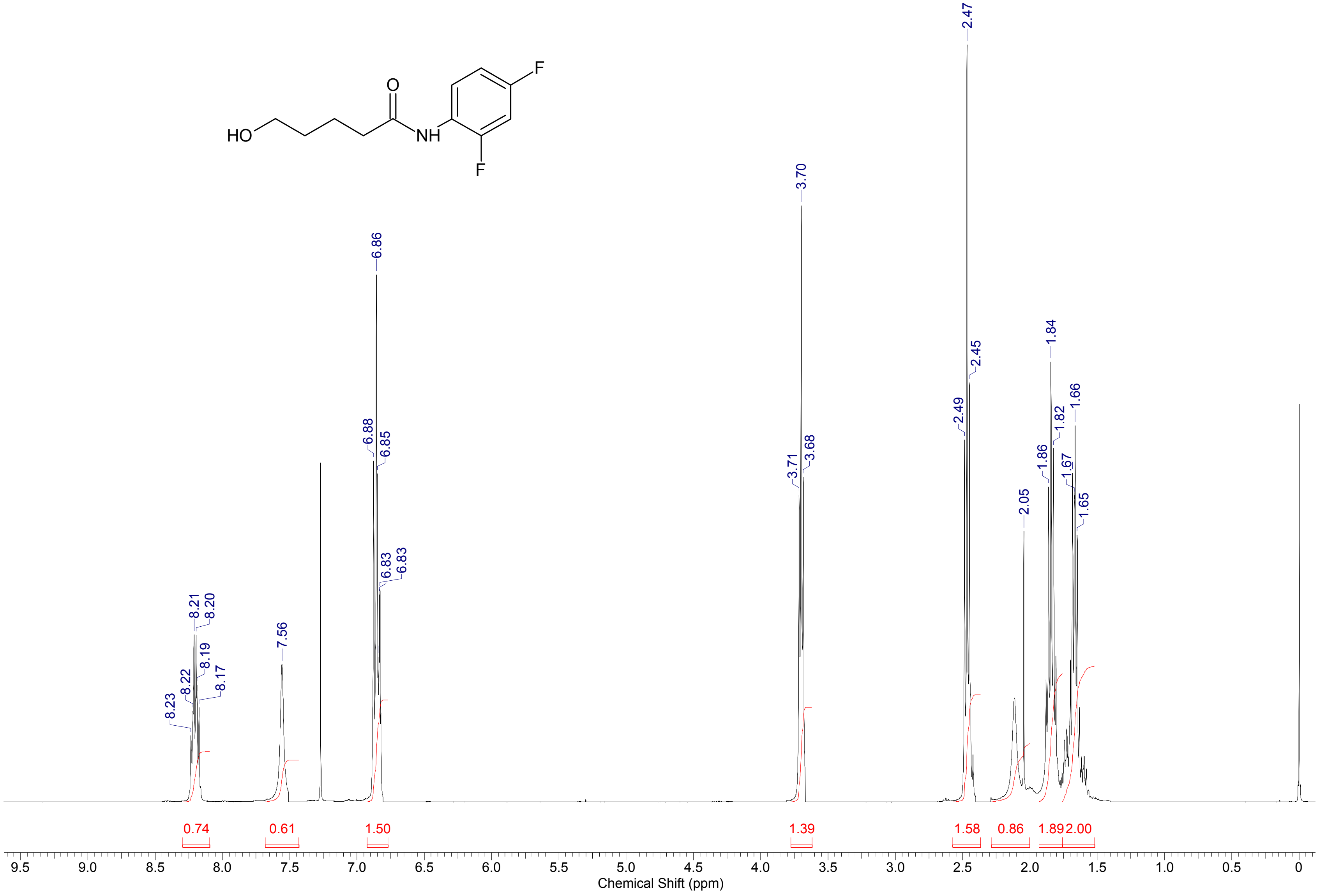

O
NH
F
F
F
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


7.26
8.42
8.41
8.40
8.39
8.38
8.37
8.20
7.55
7.54
7.54
7.27
6.94
6.92
6.94
6.90
6.89
6.59
6.58
6.58
6.57
0.10
0.09
0.10
0.23
0.21
0.10
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
Chemical Shift (ppm)
O
O
NH
F
F

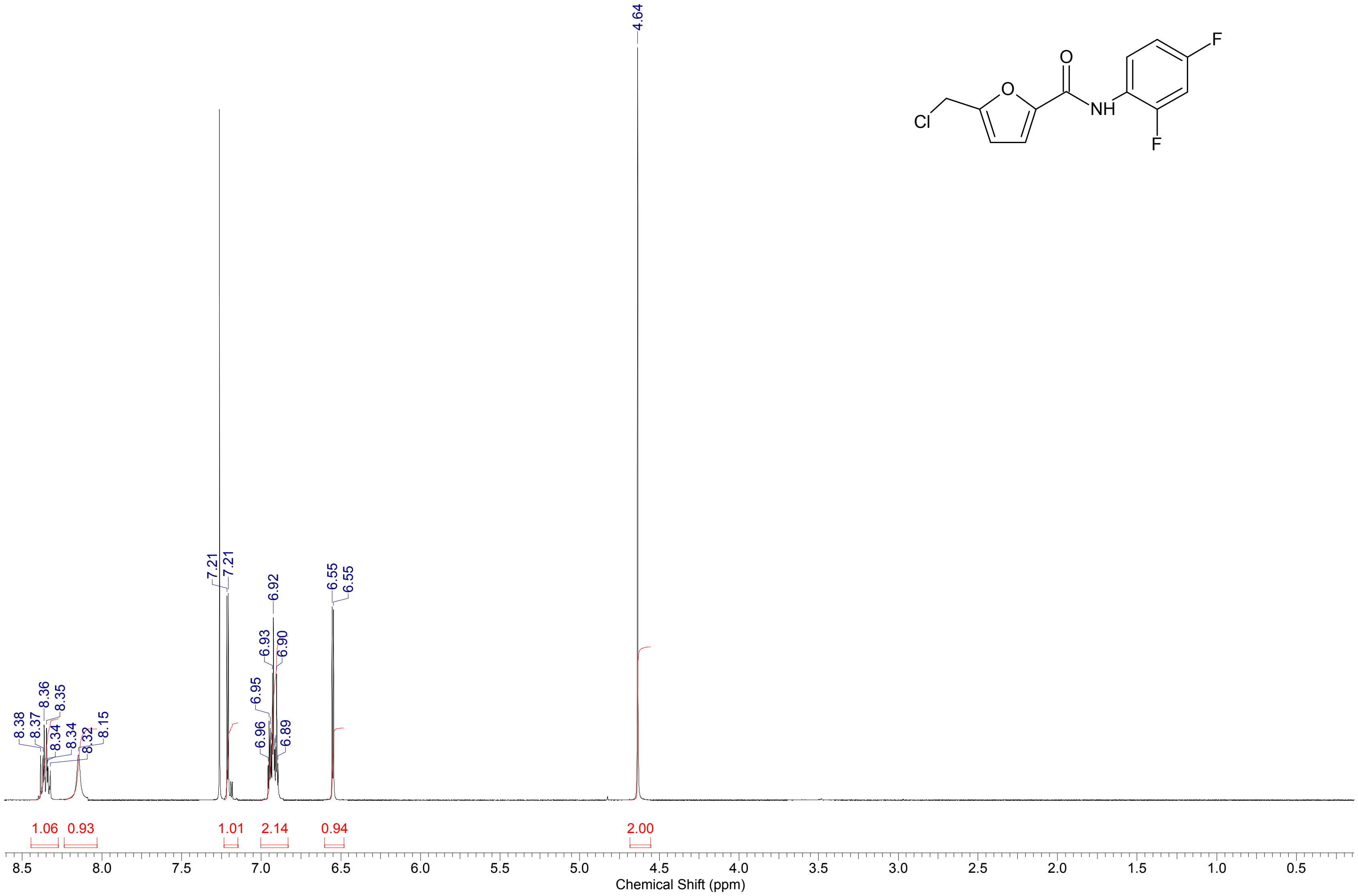

O
NH
F
F
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

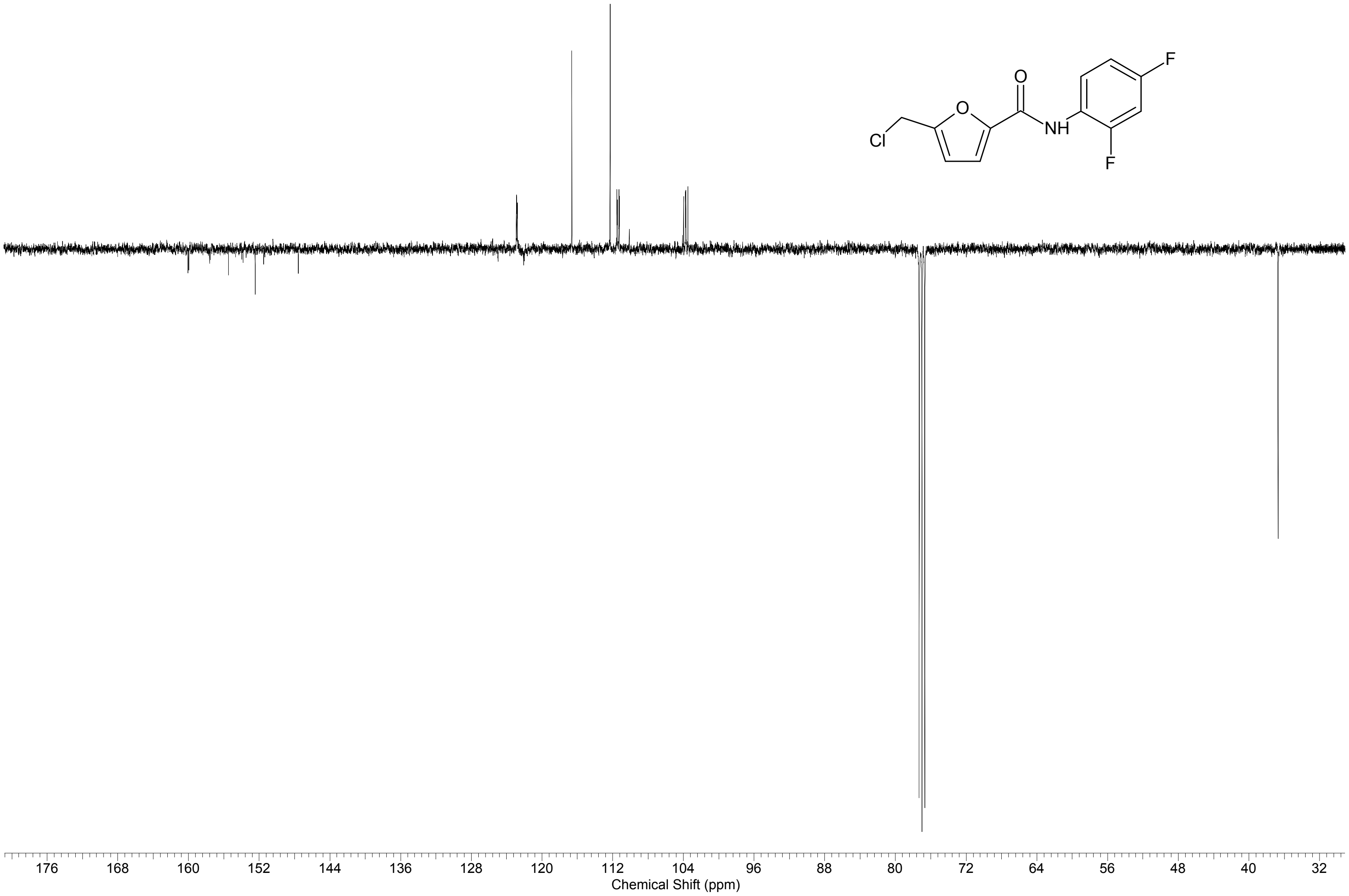

H3C
O
O
NH
F
F
3.88
7.86
7.84
7.00
6.98
8.43
8.41
8.40
8.39
8.38
8.37
7.87
7.83
7.01
6.92
6.91
6.90
6.89
1.00
3.05
2.07
2.03
3.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

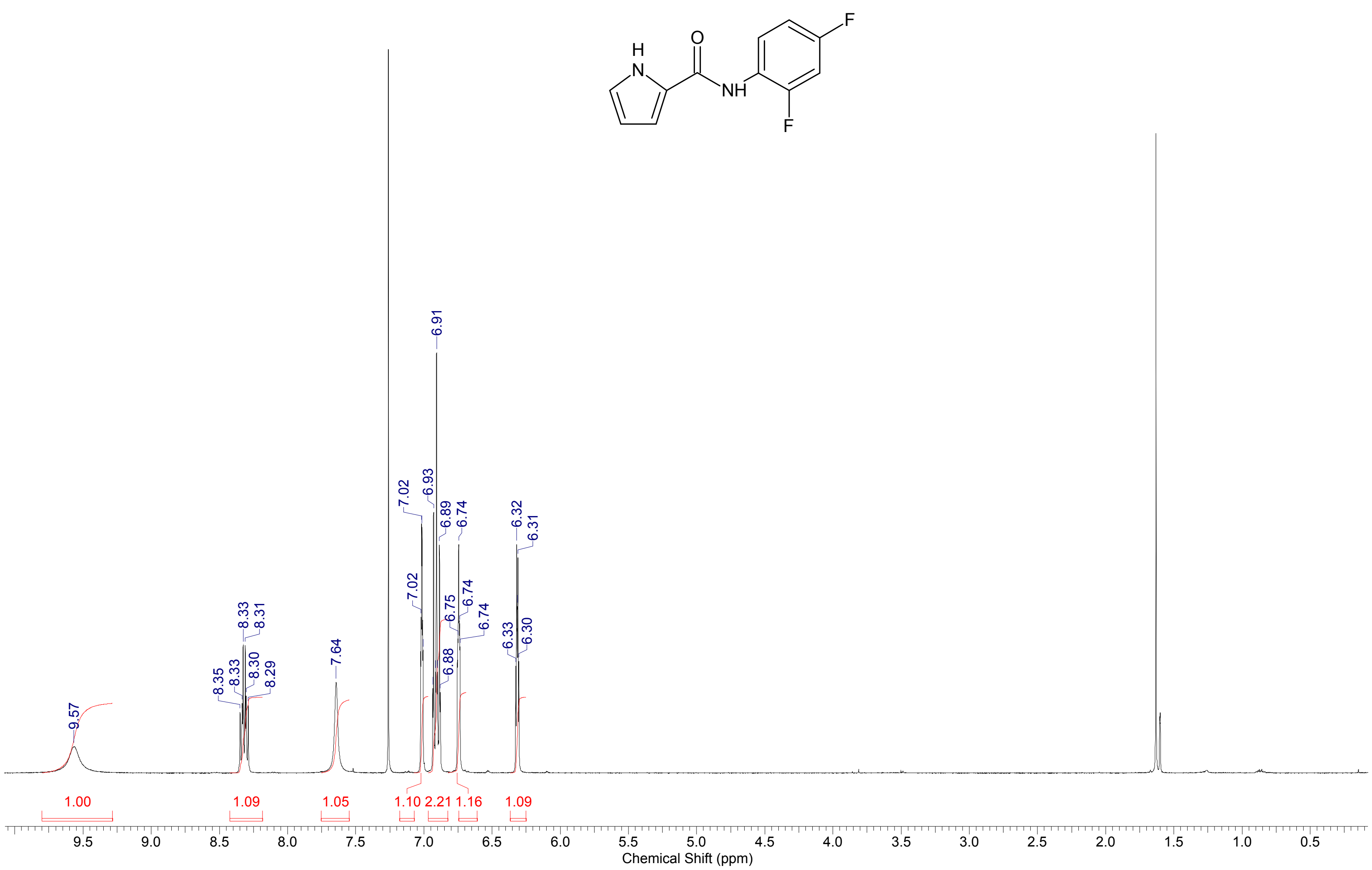

H3C
O
O
NH
F
F
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

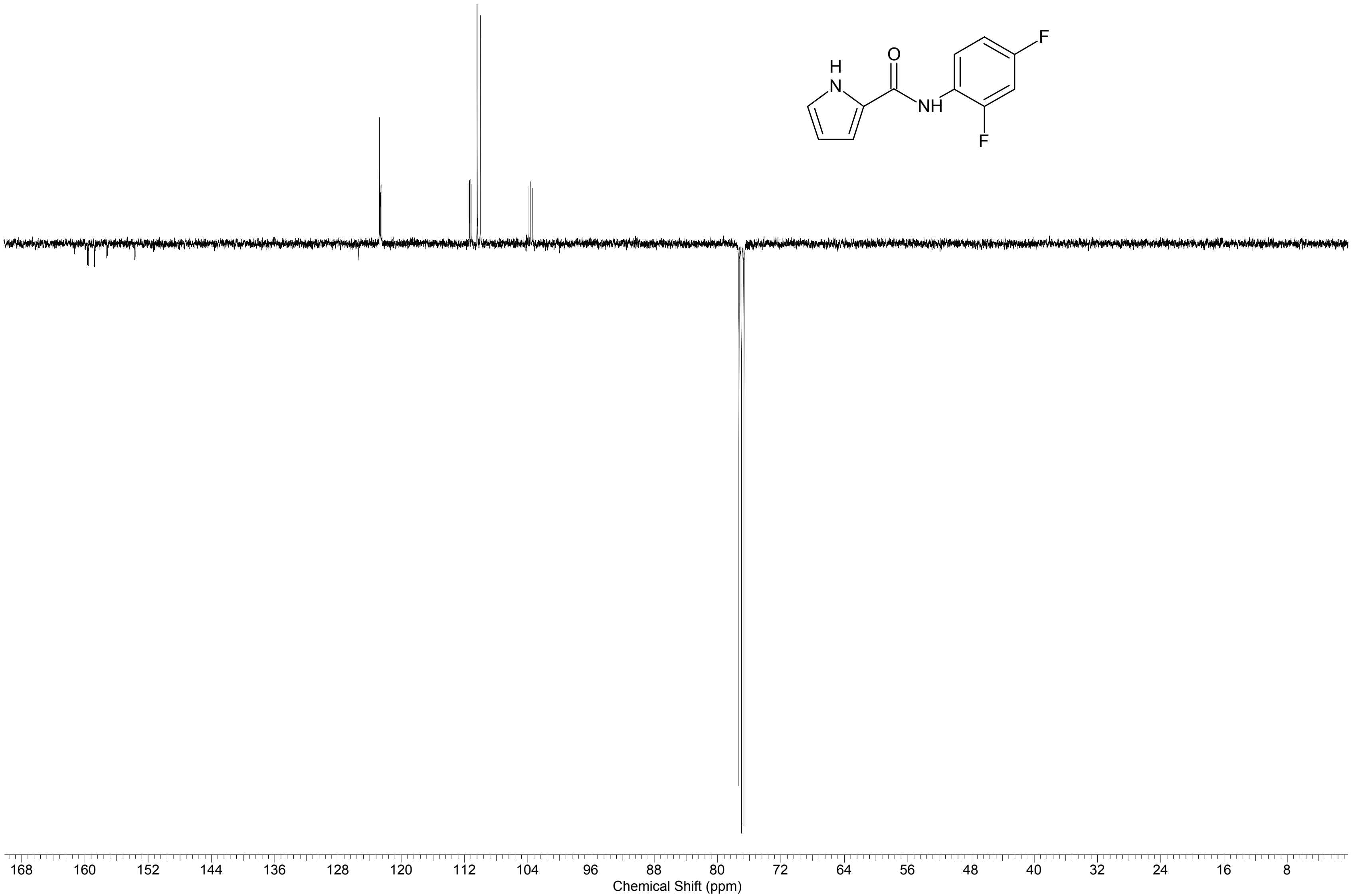

HO
O
NH
F
F
2.47
3.70
6.86
1.84
2.45
1.66
2.49
1.82
6.88
6.85
1.86
1.67
3.71
3.68
2.05
1.65
6.83
6.83
8.21
8.20
7.56
8.19
8.22
8.17
8.23
0.74
0.61
1.50
1.39
1.58
0.86
1.89
2.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

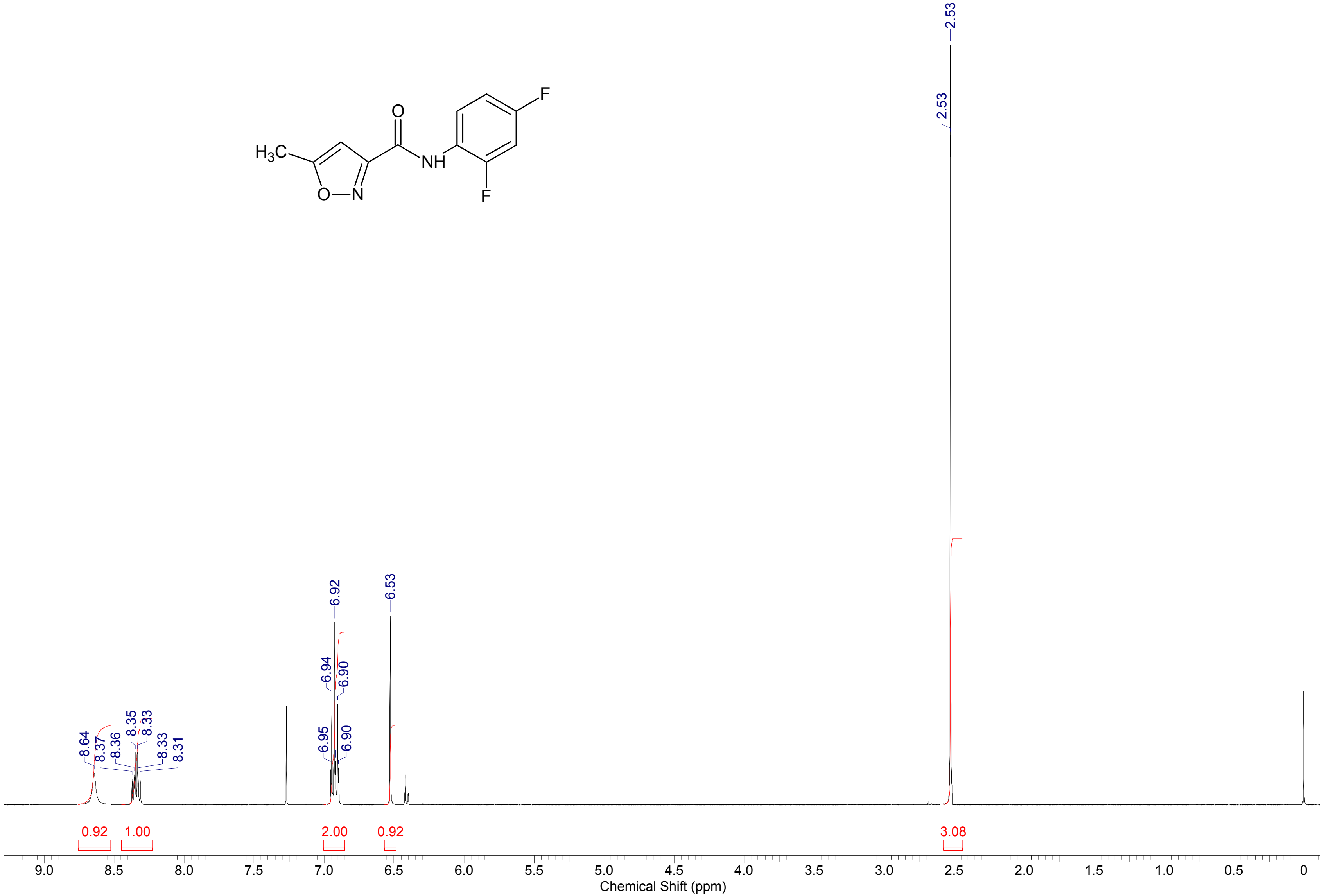

HO
O
NH
F
F
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


4.64
Cl
O
O
NH
F
F
7.21
7.21
6.92
6.93
6.90
6.95
6.96
6.89
6.55
6.55
8.38
8.37
8.36
8.35
8.34
8.34
8.32
8.15
1.06
0.93
1.01
2.14
0.94
2.00
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
Chemical Shift (ppm)

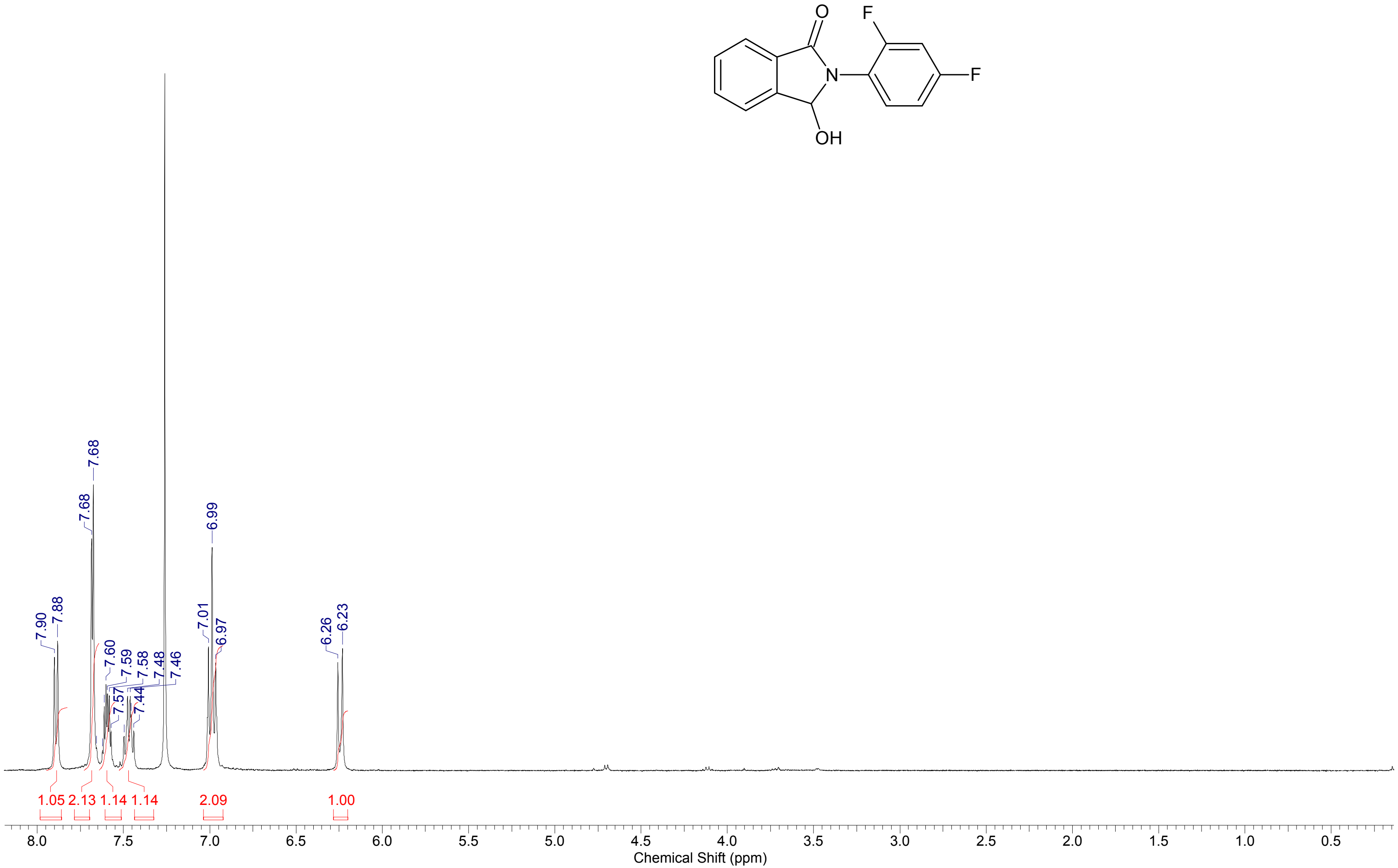

O
F
O
NH
Cl
F
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
Chemical Shift (ppm)

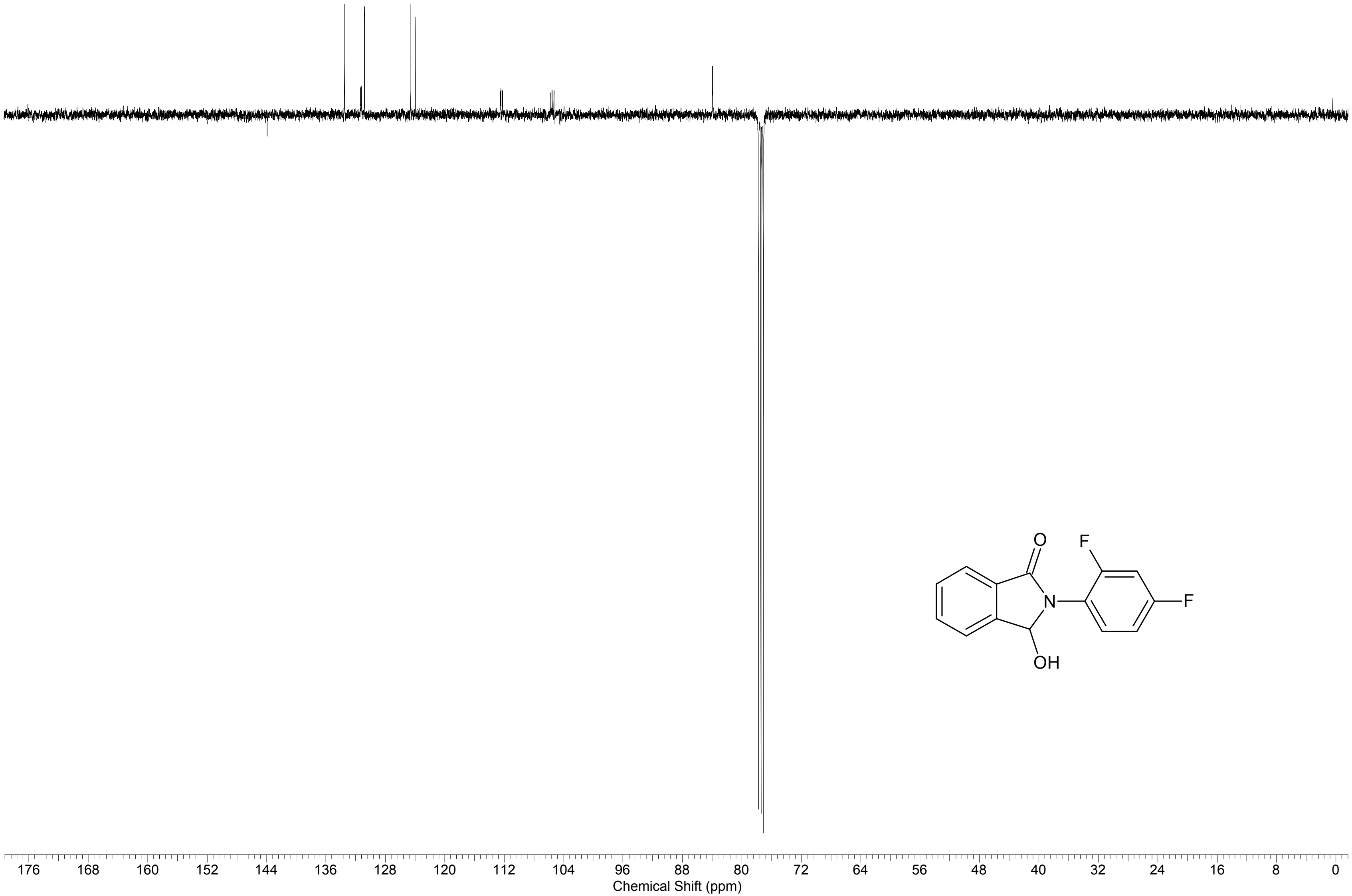

H
N
O
NH
F
F
9.57
8.35
8.33
8.33
8.31
8.30
8.29
7.64
7.02
7.02
6.93
6.91
6.89
6.88
6.75
6.74
6.74
6.74
6.33
6.32
6.31
6.30
1.00
1.09
1.05
1.10
2.21
1.16
1.09
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

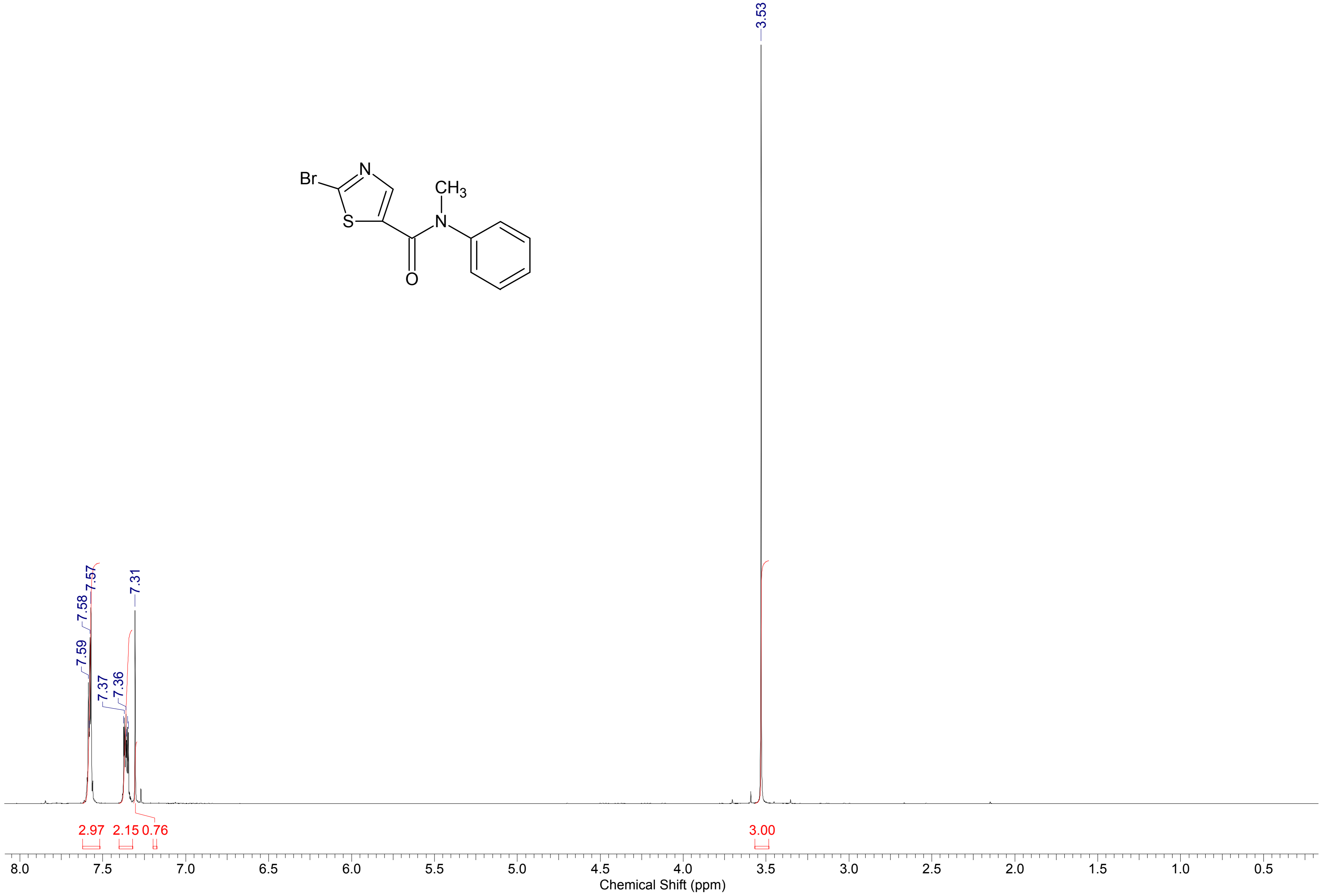

H
N
O
NH
F
F
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
Chemical Shift (ppm)

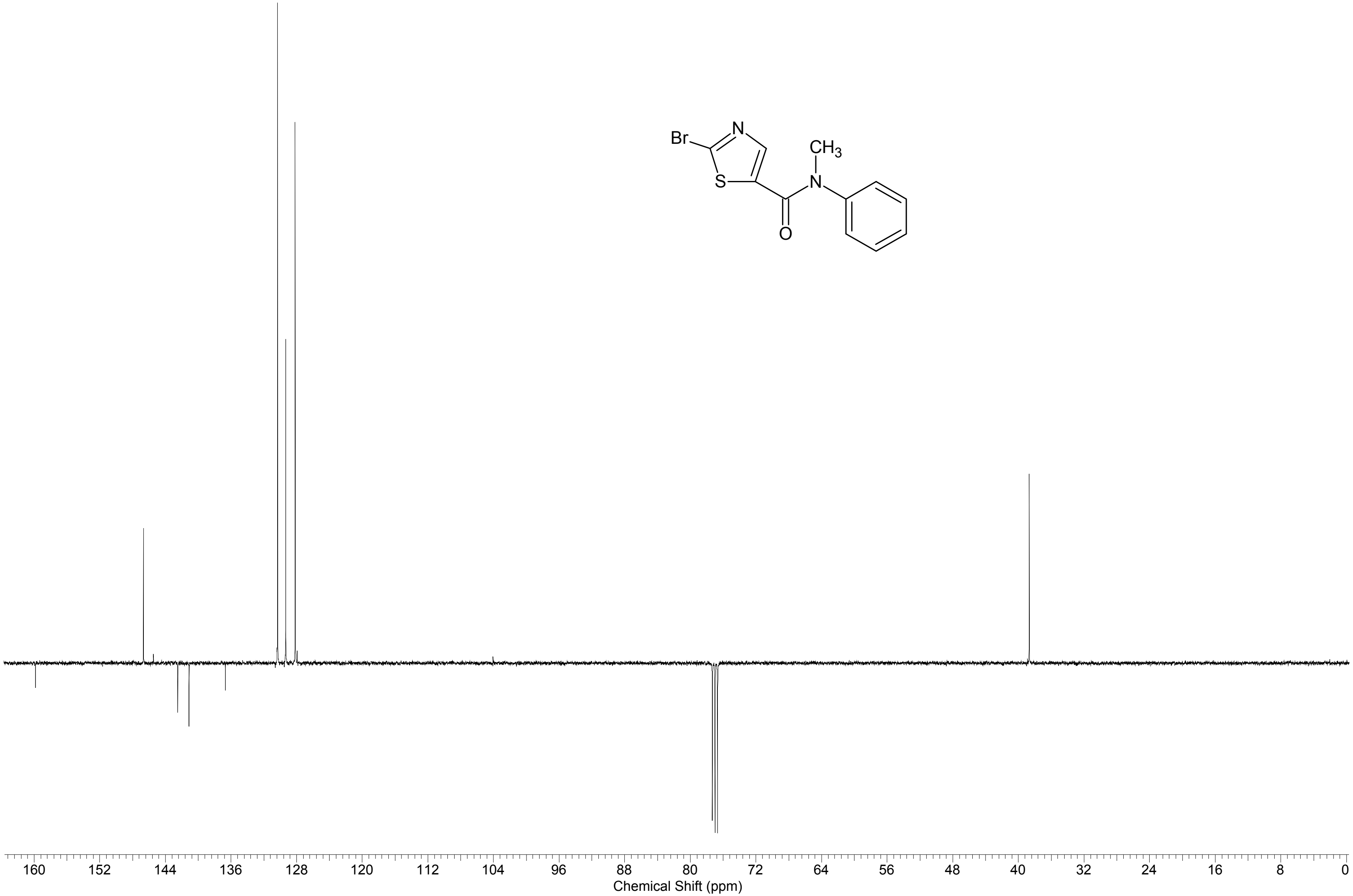

H3C
O
NH
F
F
O—N
2.53
2.53
8.64
8.37
8.36
8.35
8.33
8.33
8.31
6.95
6.94
6.92
6.90
6.90
6.53
0.92
1.00
2.00
0.92
3.08
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

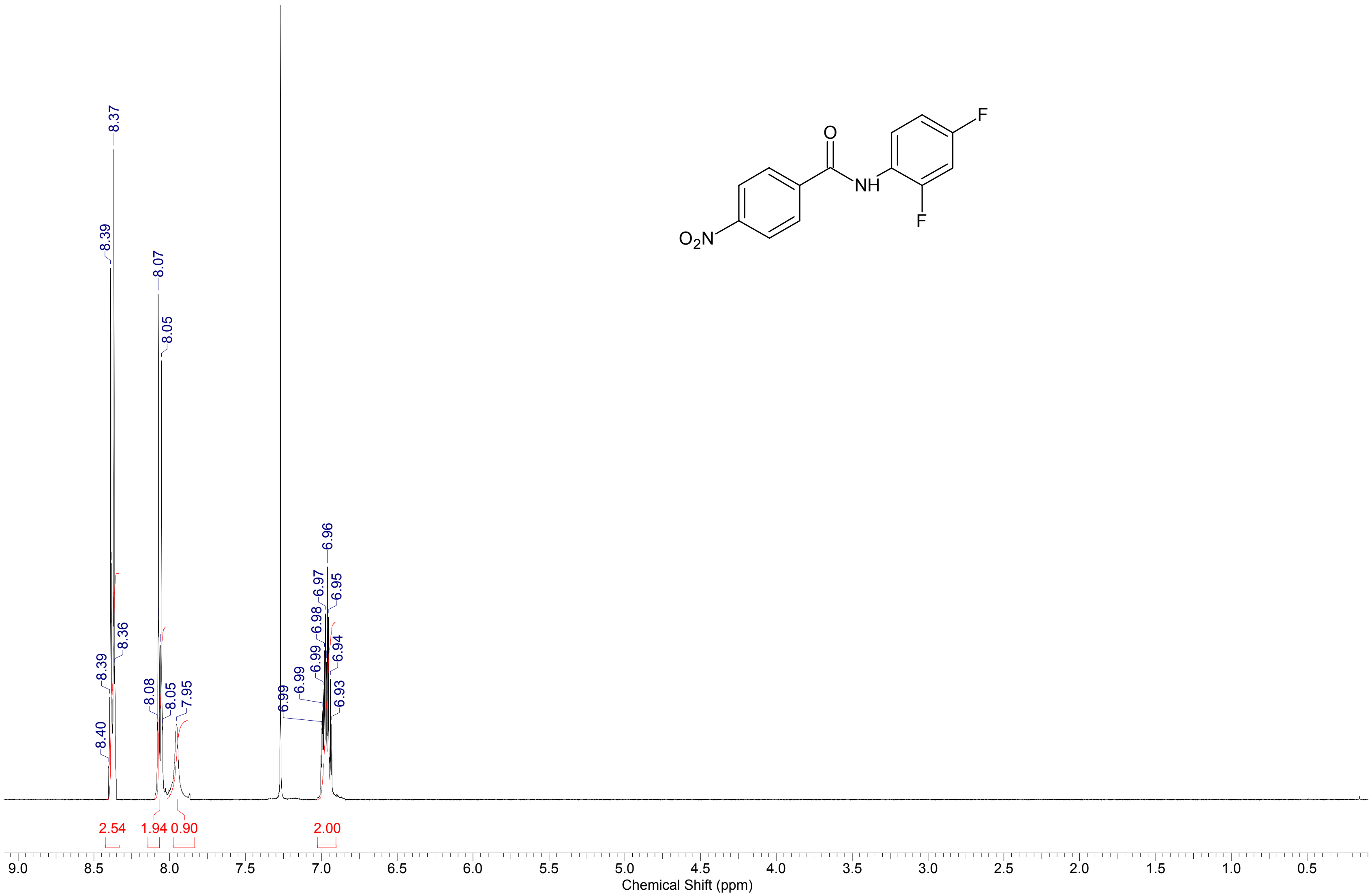

H3C
O
NH
F
F
O
N
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

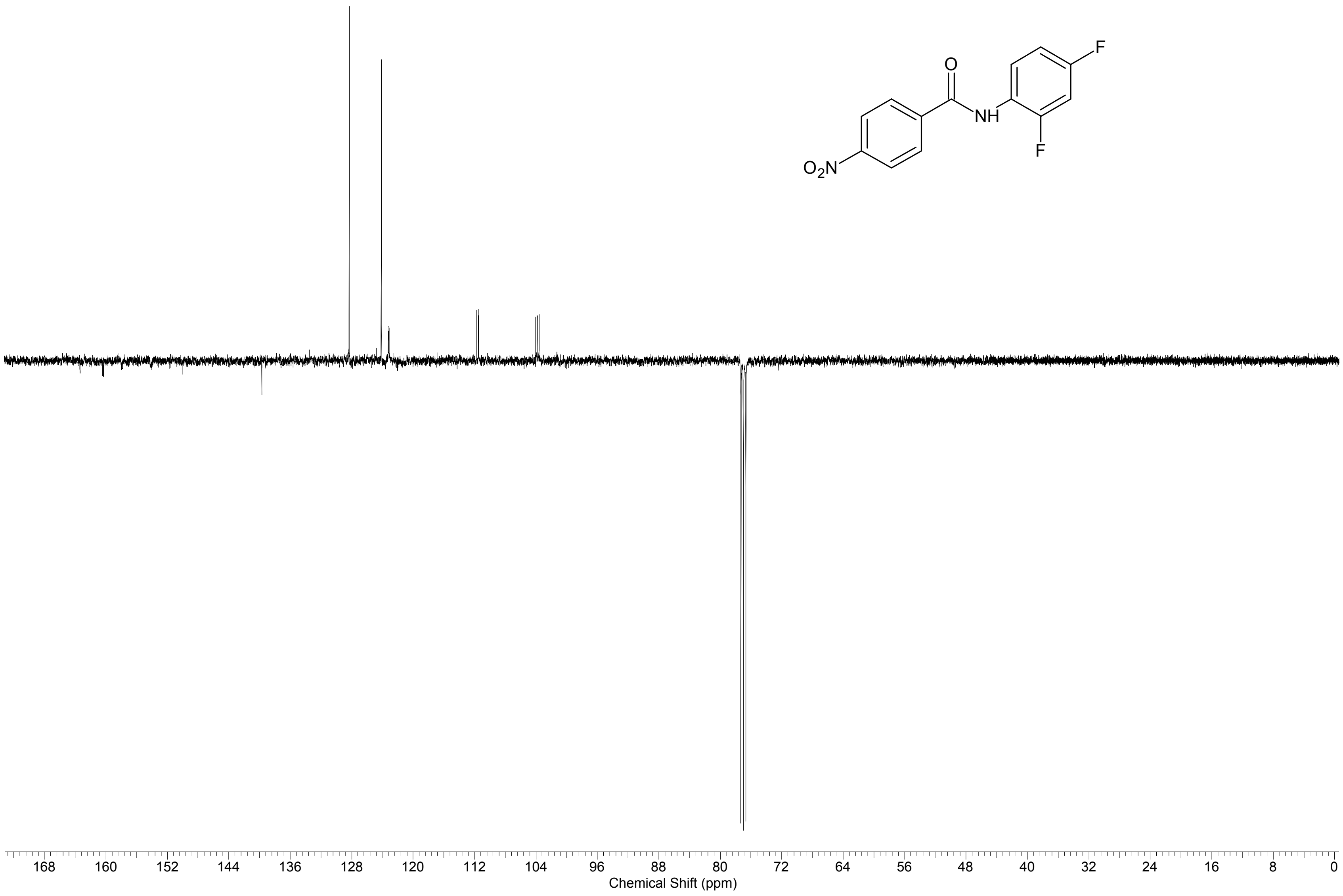

O
F
N
F
OH
7.90
7.88
7.68
7.68
7.60
7.59
7.58
7.57
7.48
7.46
7.44
7.01
6.99
6.97
6.26
6.23
1.05
2.13
1.14
1.14
2.09
1.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

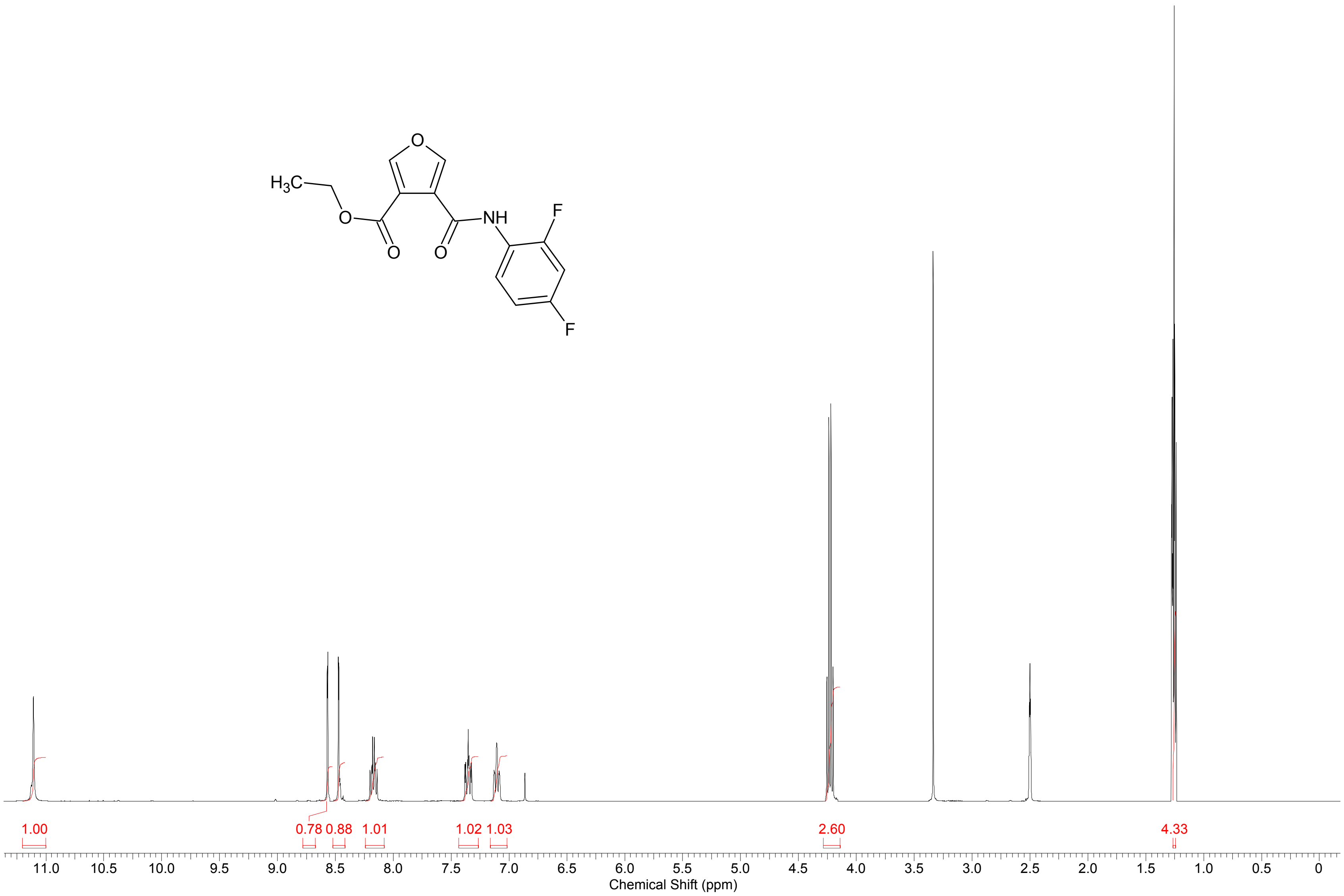

O
F
N
F
OH
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

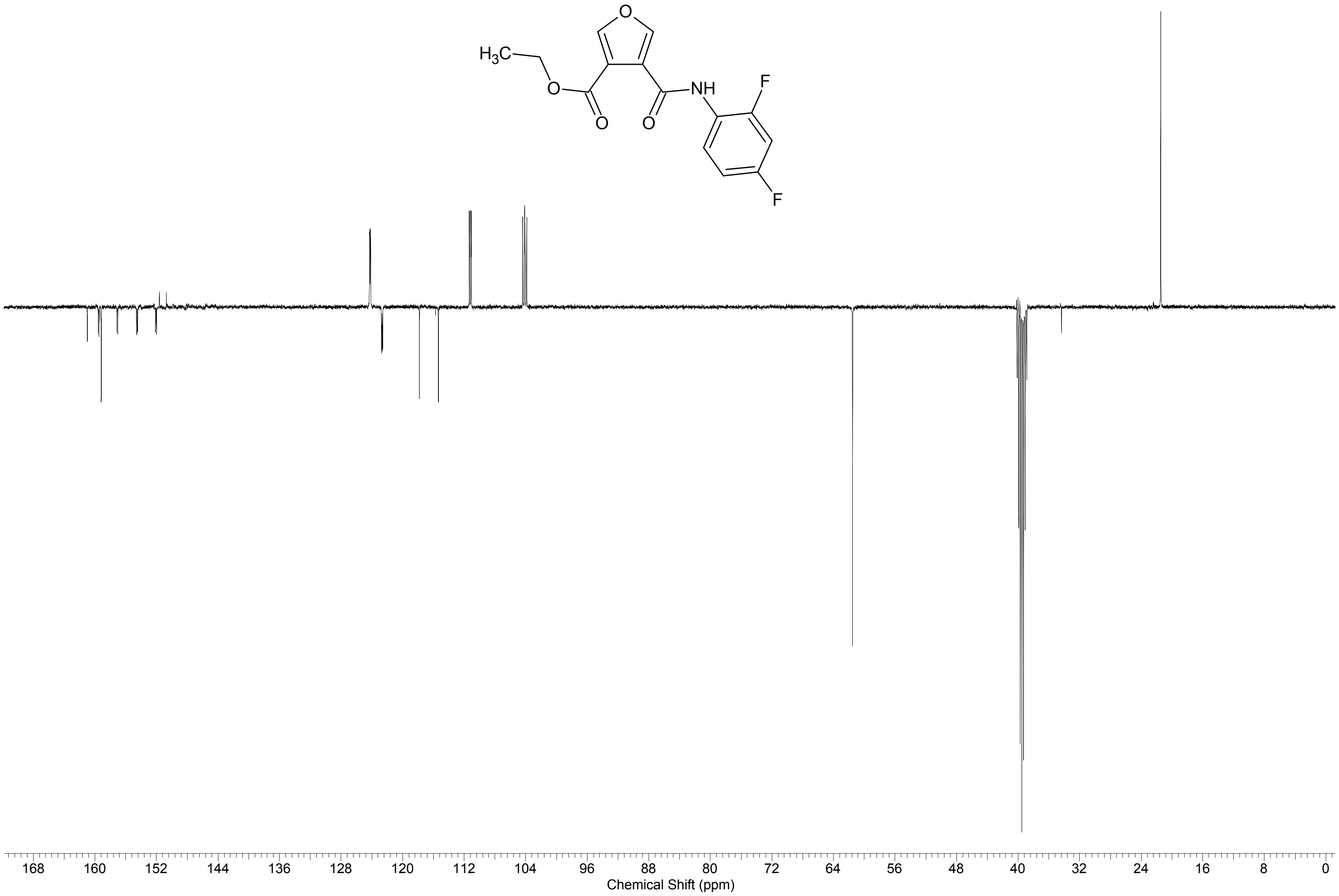

Br
N
S
CH3
N
O
3.53
7.59
7.58
7.57
7.37
7.36
7.31
2.97
2.15
0.76
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)

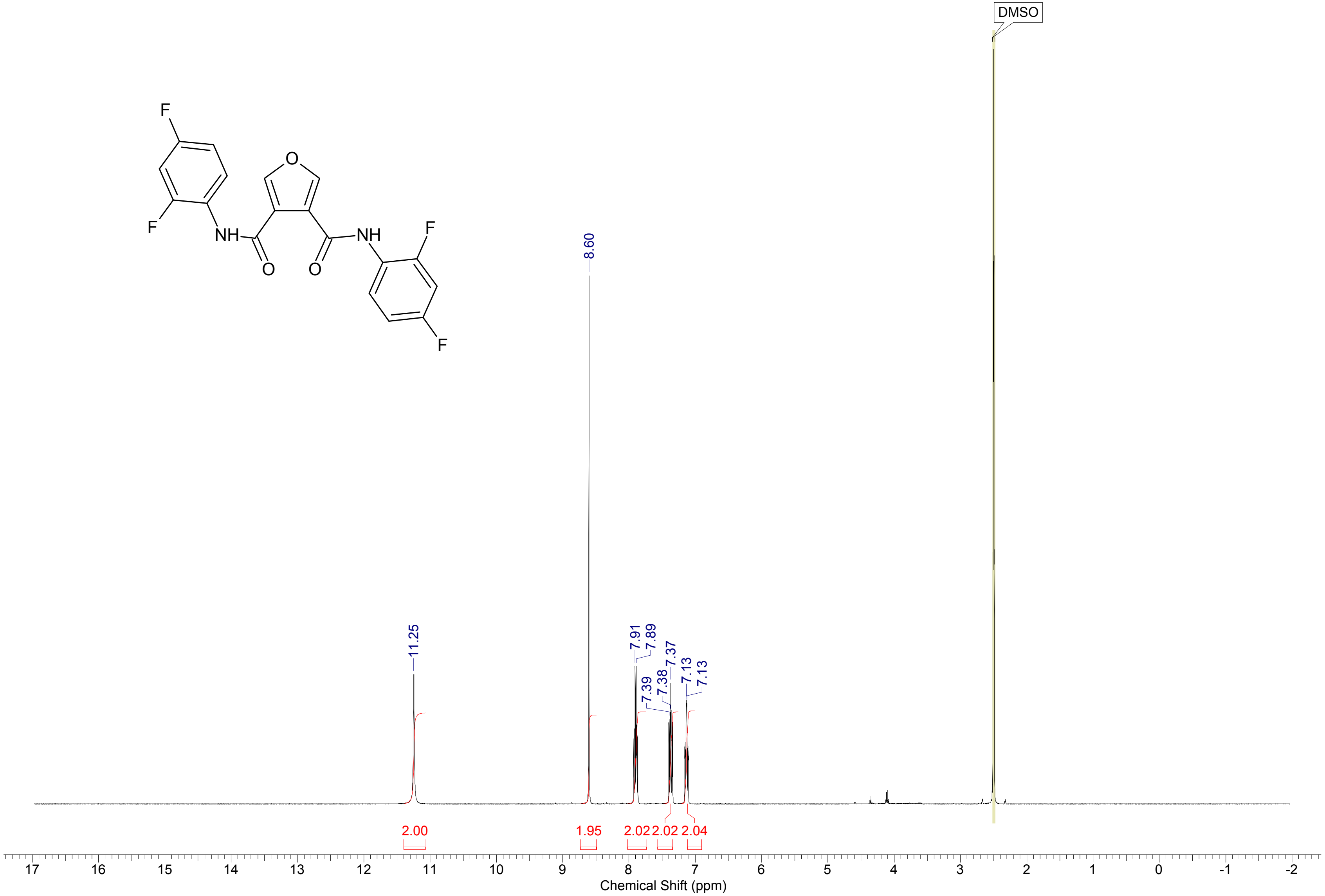

Br
N
S
CH3
N
O
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

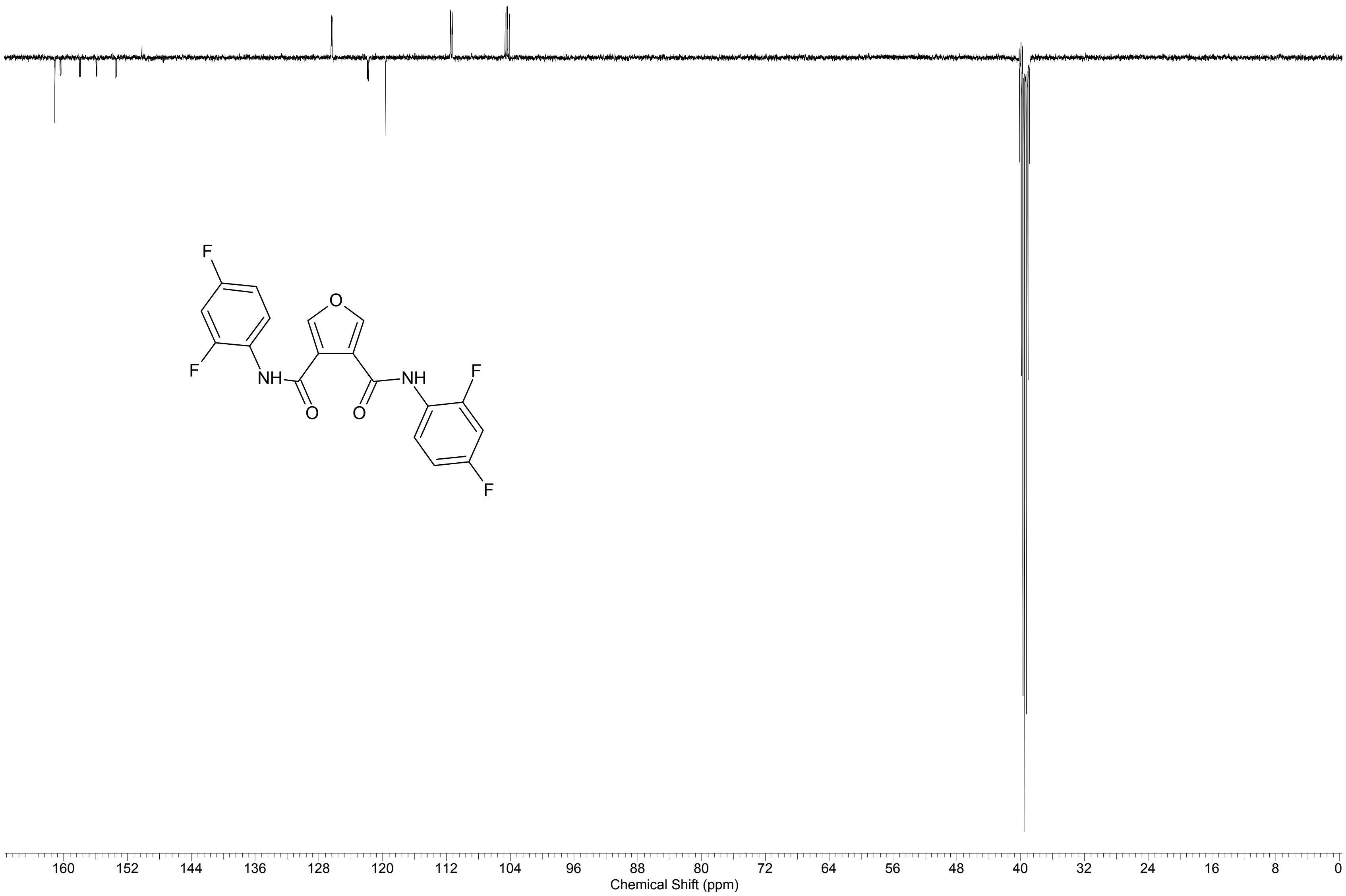

O
NH
F
F
O_2N
8.37
8.39
8.07
8.05
8.36
8.39
8.40
8.08
8.05
7.95
6.96
6.97
6.95
6.98
6.99
6.99
6.99
6.94
6.93
2.54
1.94
0.90
2.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Chemical Shift (ppm)


O
NH
F
F
O2N
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


O
H_3C
O
O
O
NH
F
F
1.00
0.78
0.88
1.01
1.02
1.03
2.60
4.33
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
Chemical Shift (ppm)


O
H$_3$C
O
NH
F
O
O
F
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)


F
F
NH
O
O
O
NH
F
F
DMSO
11.25
8.60
7.91
7.89
7.39
7.38
7.37
7.13
7.13
2.00
1.95
2.02
2.02
2.04
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
Chemical Shift (ppm)


F
F
O
NH
O
O
NH
F
F
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)