Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Design, Synthesis, and Biological Evaluation of Novel Nicotinamide Derivatives as Potential Histone Deacetylase-3 Inhibitors.

Mohamed M.S. Hamoud,[a,#] Sravani Pulya,[b,#] Nermine A. Osman,[a] Yamini Bobde,[b] Abdalla E. A. Hassan,[c,d] Hanan A. Abdel-Fattah,[a] Balaram Ghosh,[b,*] Amany M. Ghanim.[a,*]

[a] *Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Zagazig University, Zagazig 44519, Egypt.*
[b] *Department of Pharmacy, BITS-Pilani, Hyderabad Campus, Shamirpet, Hyderabad, India, 500078.*
[c] *Applied Nucleic Acids Research Center, Zagazig University, Egypt.*
[d] *Department of Chemistry, Faculty of Science, Zagazig University, Zagazig 44519, Egypt.*

# Equal contribution, * Corresponding authors:
Amany M Ghanim; email ID; amanyghanim@yahoo.com or amanygh@zu.edu.eg and Balaram Ghosh; email ID: balaram@hyderabad.bits-pilani.ac.in

In vitro antiproliferative assay

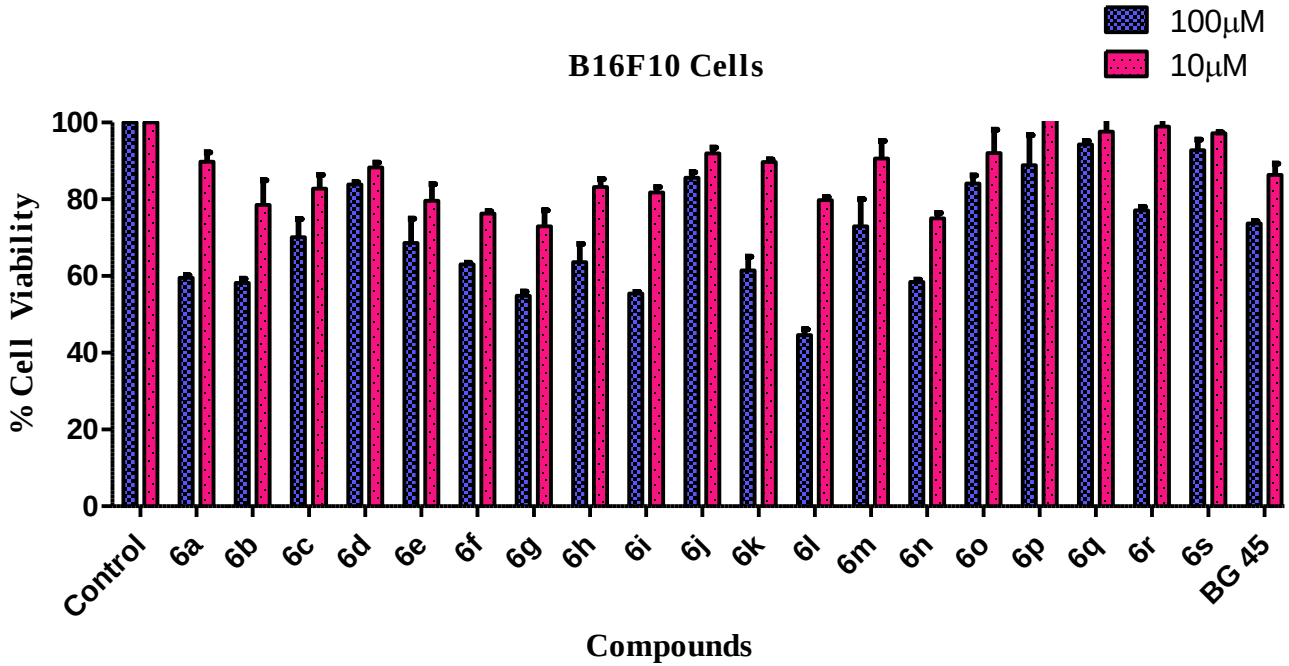


Fig. S1: Anticancer activity of the synthesized compounds in murine melanoma cells (B16F10). Cells were treated with compounds at 100µM and 10µM in triplicate for 72 hours. Cell viability was measured by MTT reagent. Data represents mean ± SD (n=2).

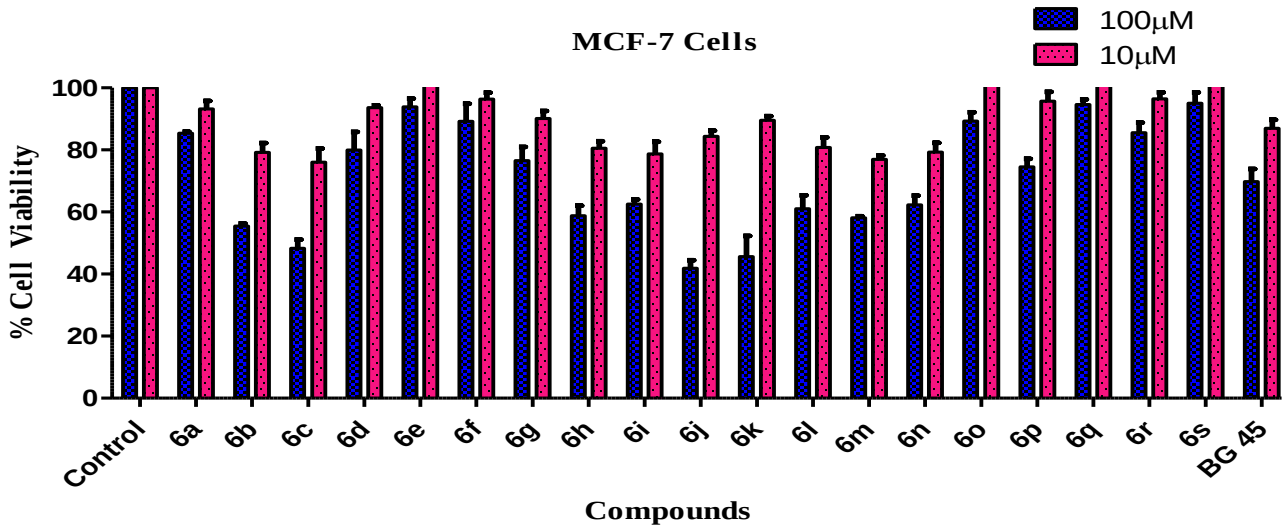


Fig. S2: Anticancer activity of the synthesized compounds in breast cancer cell line (MCF-7). Cells were treated with compounds at 100µM and 10µM in triplicate for 72 hours. Cell viability was measured by MTT reagent. Data represents mean ± SD (n=2).

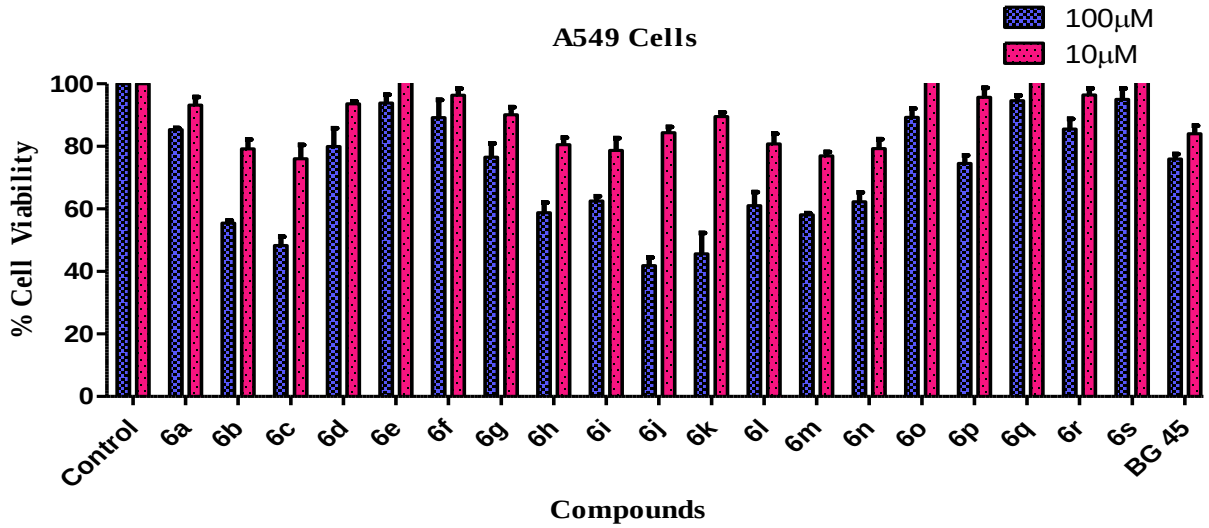
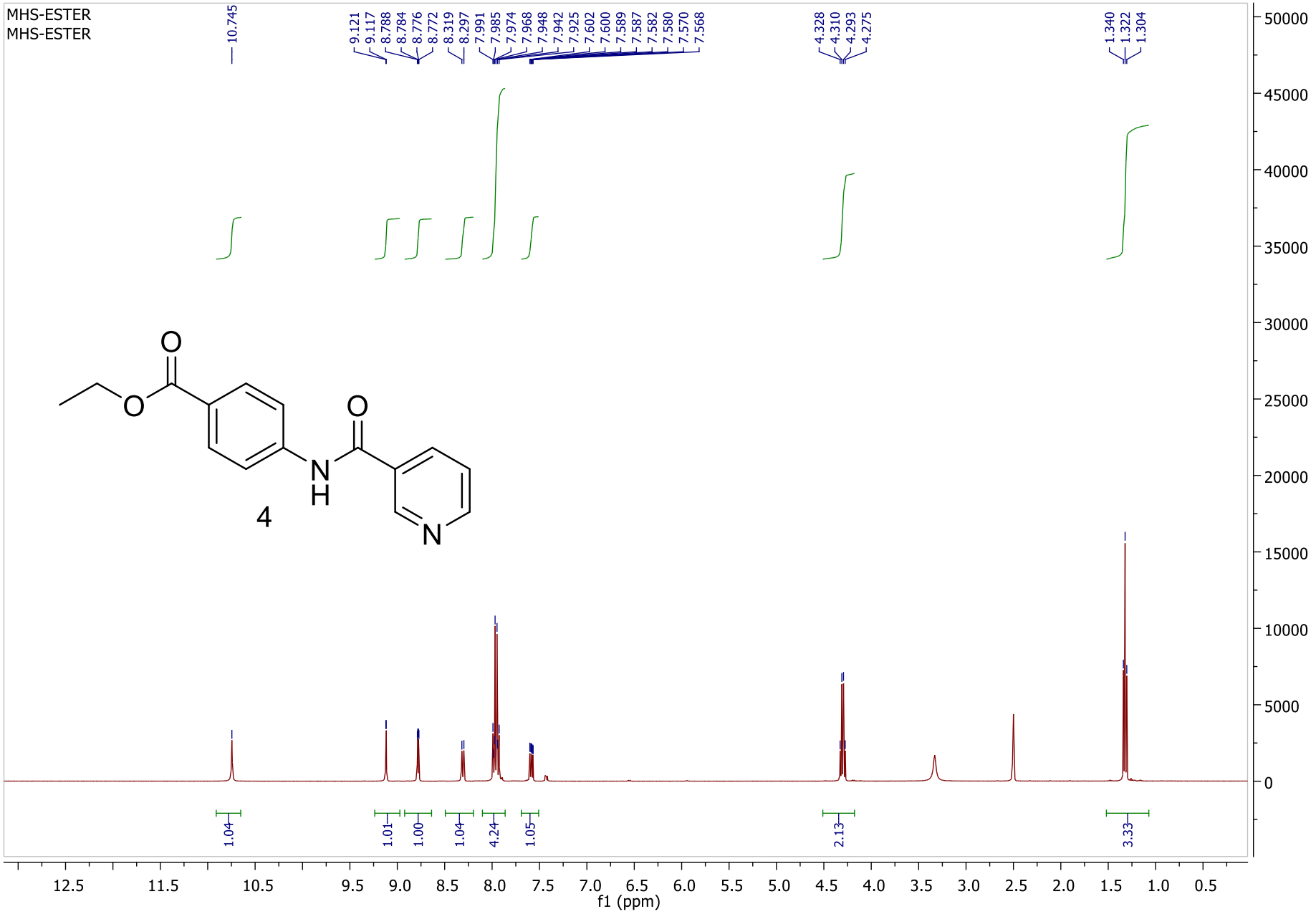
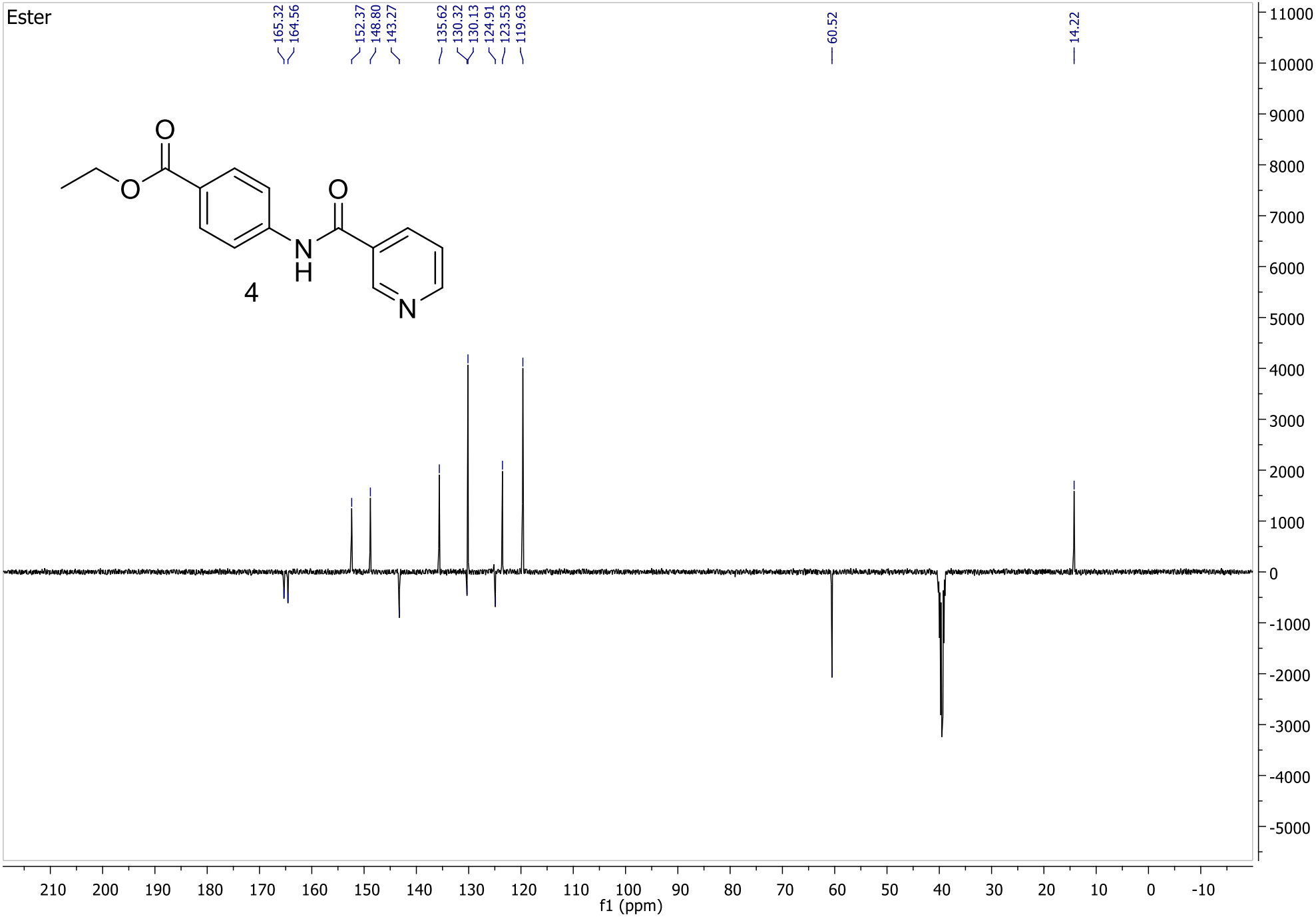


Fig. S3: Anticancer activity of the synthesized compounds in lung cancer cell line (A549). Cells were treated with compounds at 100µM and 10µM in triplicate for 72 hours. Cell viability was measured by MTT reagent. Data represents mean ± SD (n=2).

Supplementary material for ^{1}H NMR, ^{13}C NMR for target compounds

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152.37
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143.27
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130.32
130.13
124.91
123.53
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60.52
14.22
O
O
O
N
H
N
4
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
-5000
210
200
190
180
170
160
150
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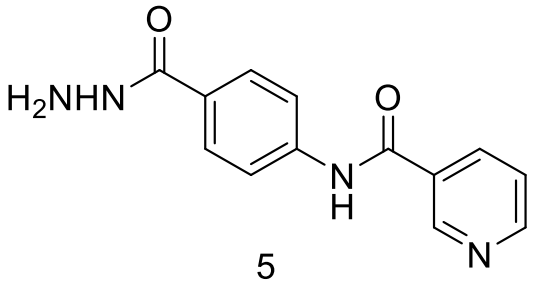
20
10
0
-10
f1 (ppm)

Hydrazide


O
H2NHN
O
N
H
N

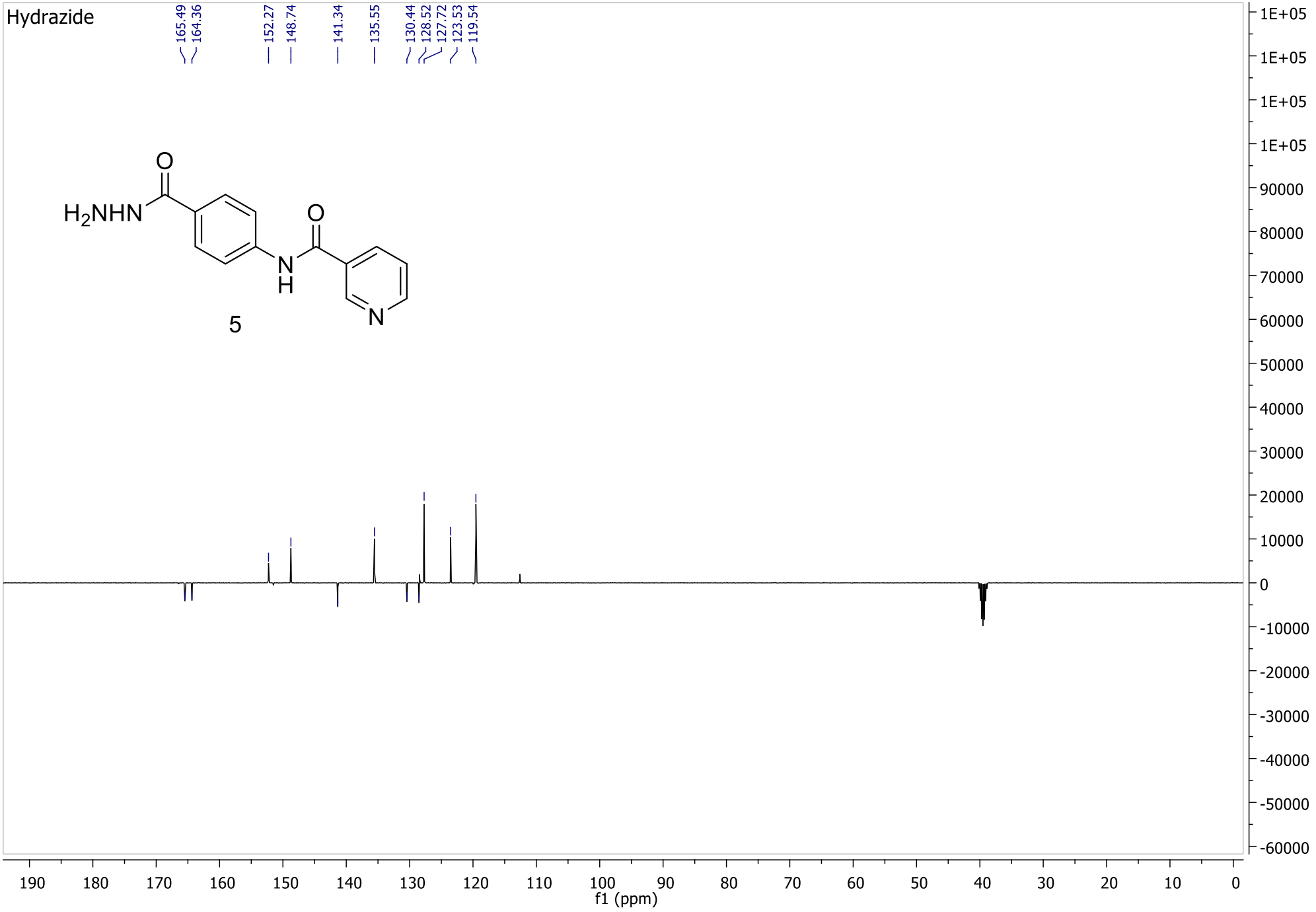
5

10.62
9.70
9.12
9.11
8.78
8.77
8.77
8.31
8.29
7.89
7.85
7.81
7.62
7.59
7.58
7.57
7.56
4.46
1.01
1.00
1.01
0.95
1.00
4.02
1.07
2.18
f1 (ppm)

Hydrazide

O
H2NHN
O
N
H
N

5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1E+05
1E+05
1E+05
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
-20000
-30000
-40000
-50000
-60000
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180
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30
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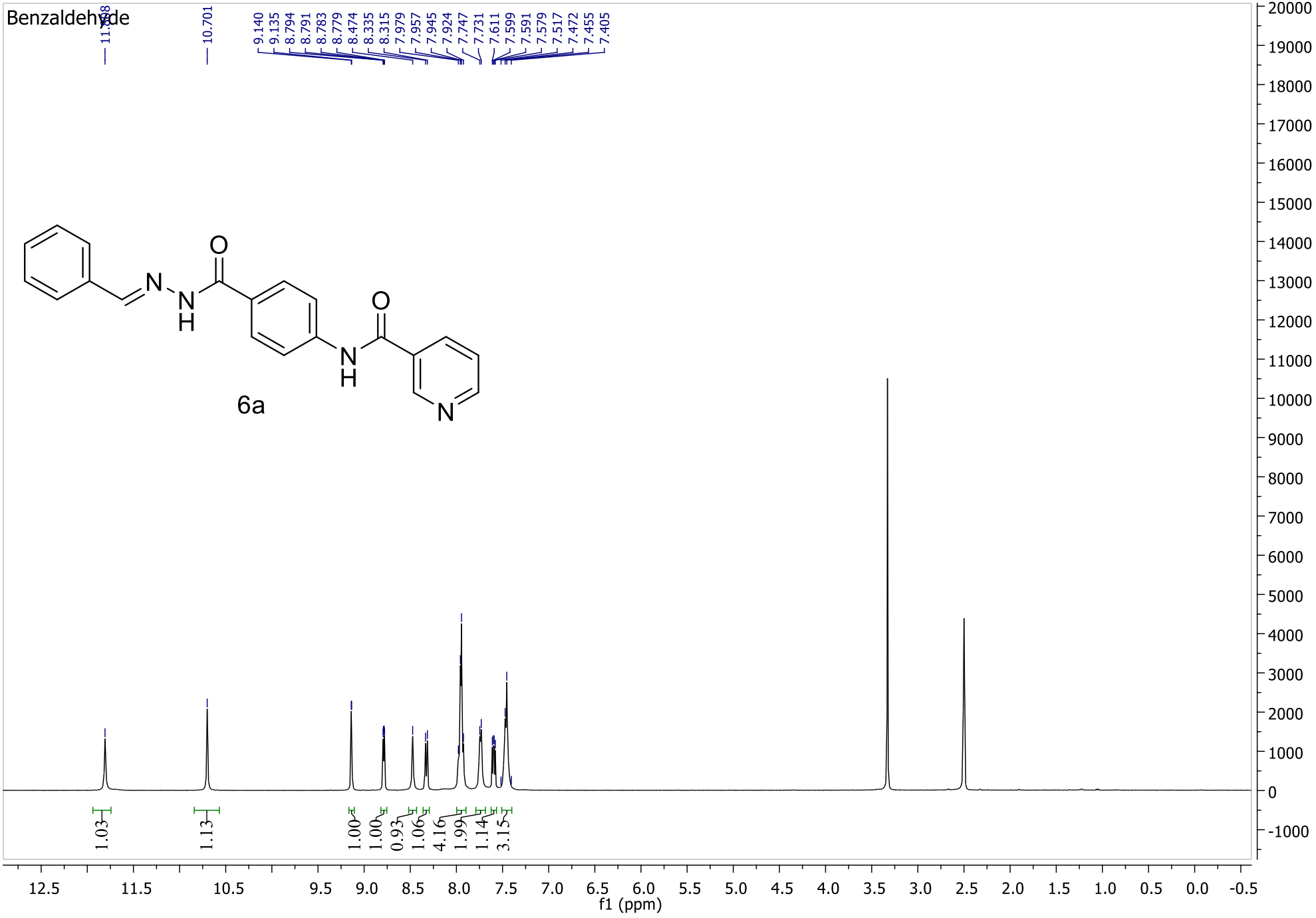
10
0
f1 (ppm)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8.783
8.779
8.474
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7.979
7.957
7.945
7.924
7.747
7.731
7.611
7.599
7.591
7.579
7.517
7.472
7.455
7.405
O
N
N
H
O
N
H
N
6a
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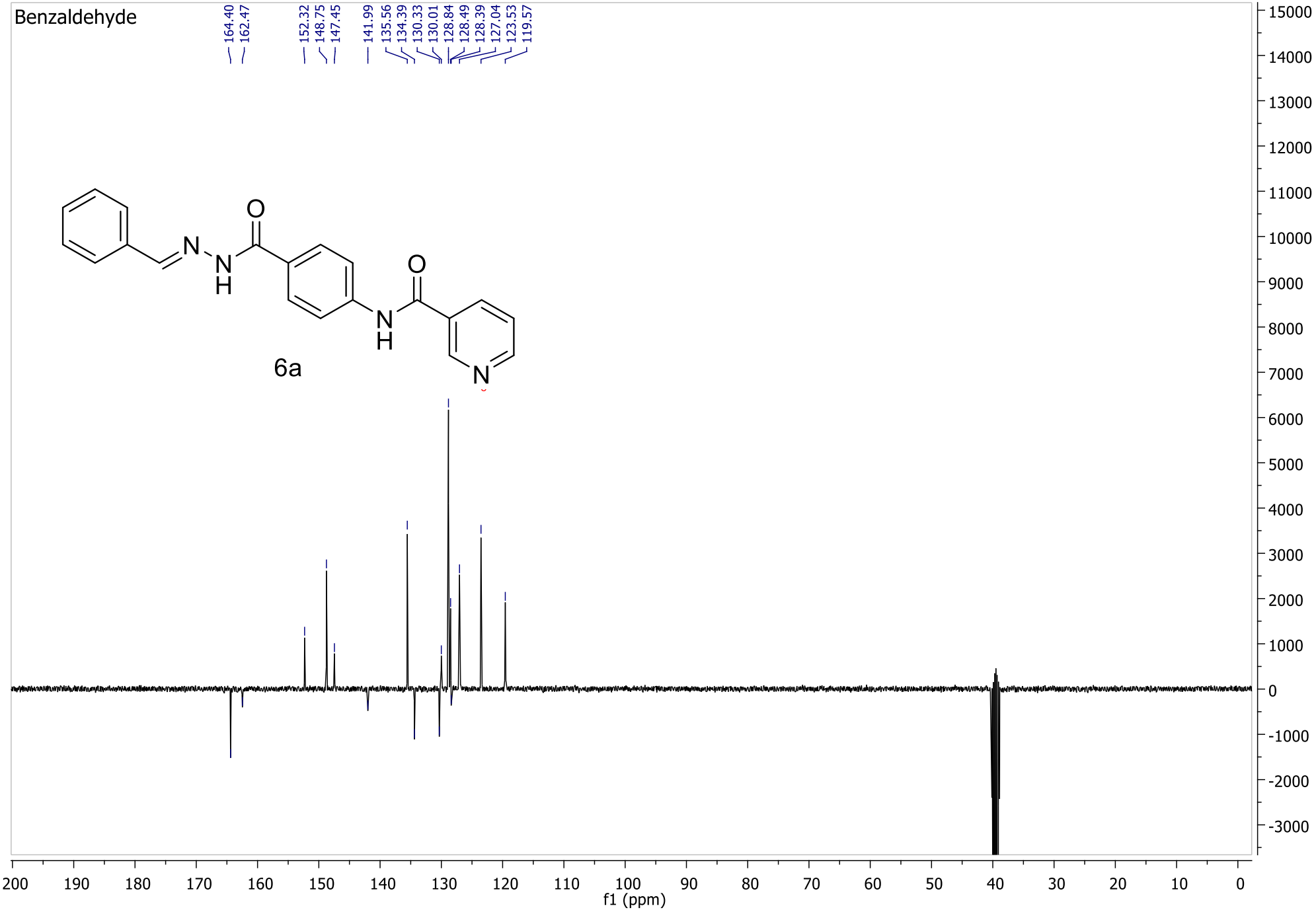
4.16
1.99
1.14
3.15
f1 (ppm)


Benzaldehyde
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147.45
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135.56
134.39
130.33
130.01
128.84
128.49
128.39
127.04
123.53
119.57
O
N
N
H
O
N
H
N
6a
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
200
190
180
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50
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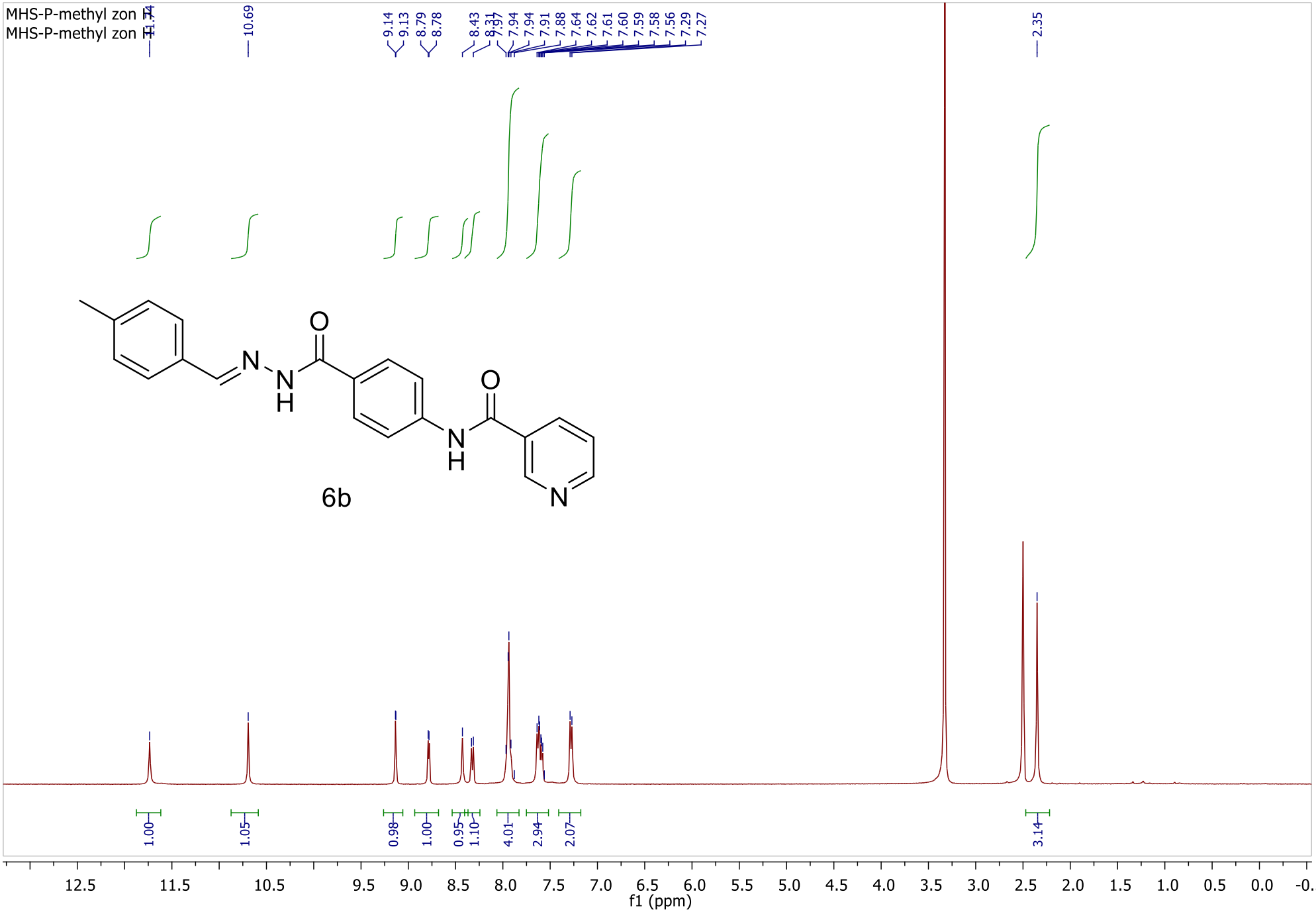
10
0
f1 (ppm)


MHS-P-methyl zon H
MHS-P-methyl zon H
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10.69
9.14
9.13
8.79
8.78
8.43
8.31
7.97
7.94
7.94
7.91
7.88
7.64
7.62
7.61
7.60
7.59
7.58
7.56
7.29
7.27
2.35
O
N
N
H
O
N
H
N
6b
1.00
1.05
0.98
1.00
0.95
1.10
4.01
2.94
2.07
3.14
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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0.5
0.0
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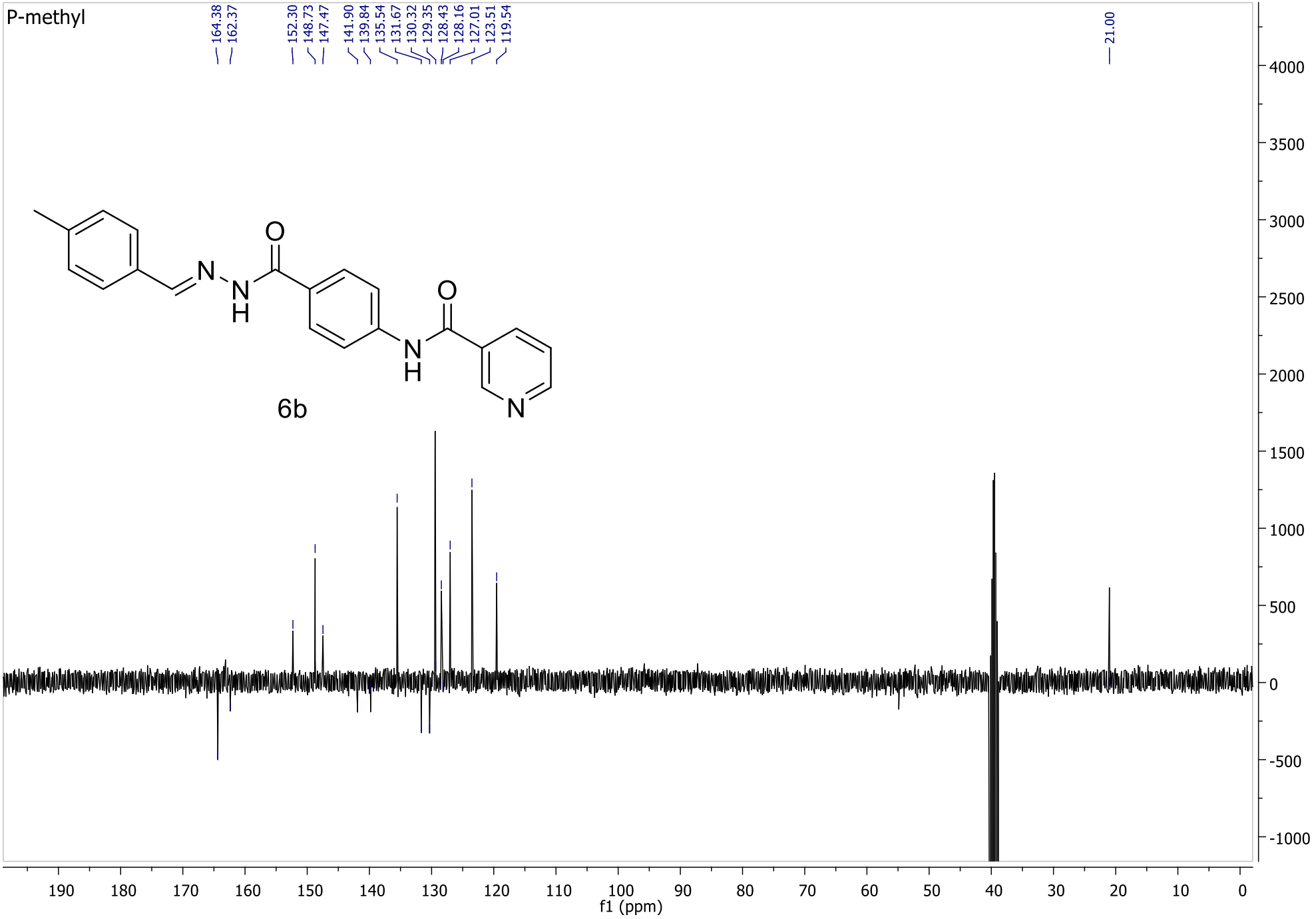
f1 (ppm)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147.47
141.90
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135.54
131.67
130.32
129.35
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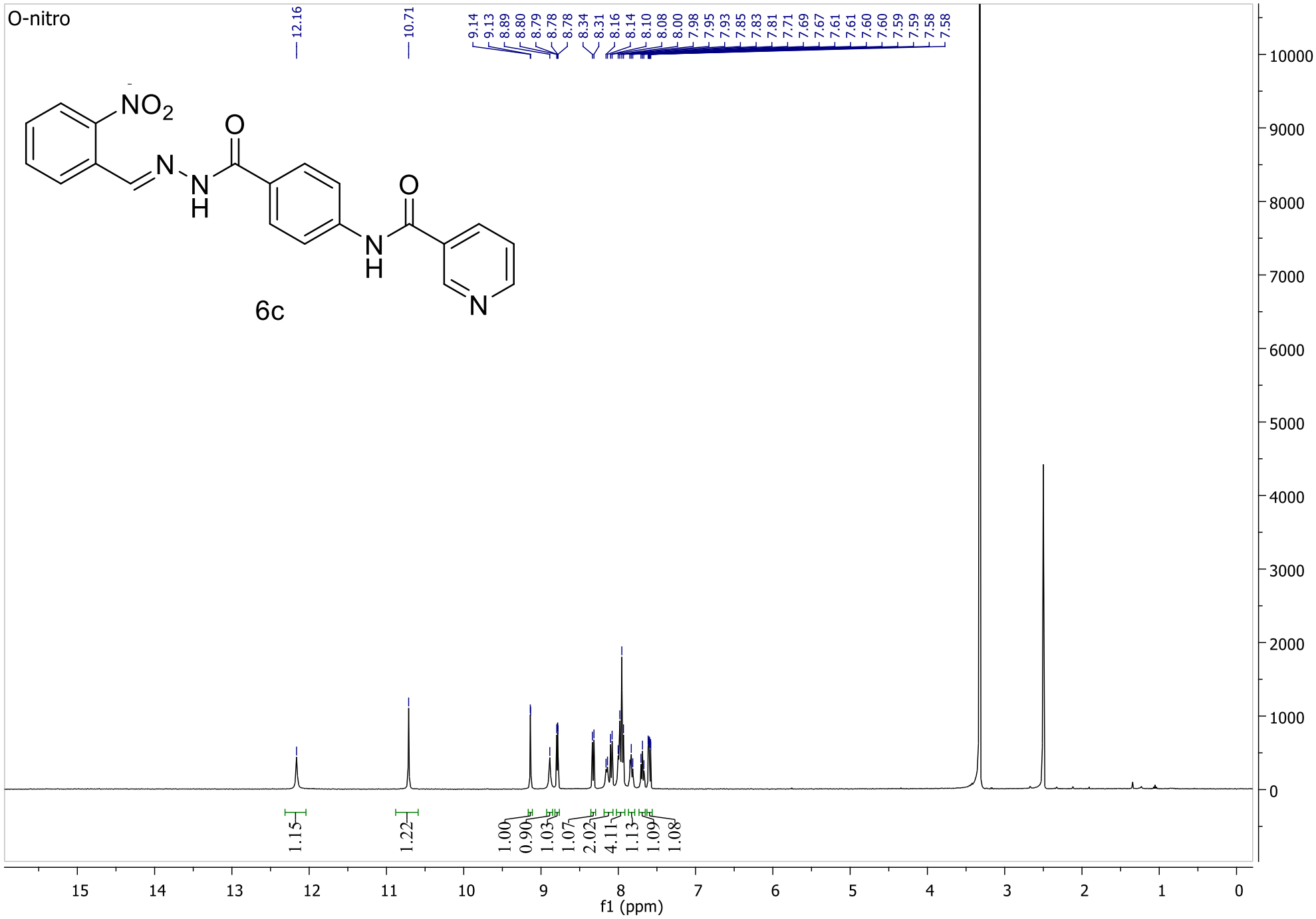
128.16
127.01
123.51
119.54
21.00
O
N
N
H
O
N
H
N
6b
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)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10.71
9.14
9.13
8.89
8.80
8.79
8.78
8.78
8.34
8.31
8.16
8.14
8.10
8.08
8.00
7.98
7.95
7.93
7.85
7.83
7.81
7.71
7.69
7.67
7.61
7.61
7.60
7.60
7.59
7.59
7.58
7.58
NO2
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N
N
H
O
N
H
N
6c
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
1.15
1.22
1.00
0.90
1.03
1.07
2.02
4.11
1.13
1.09
1.08
15
14
13
12
11
10
9
8
7
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5
4
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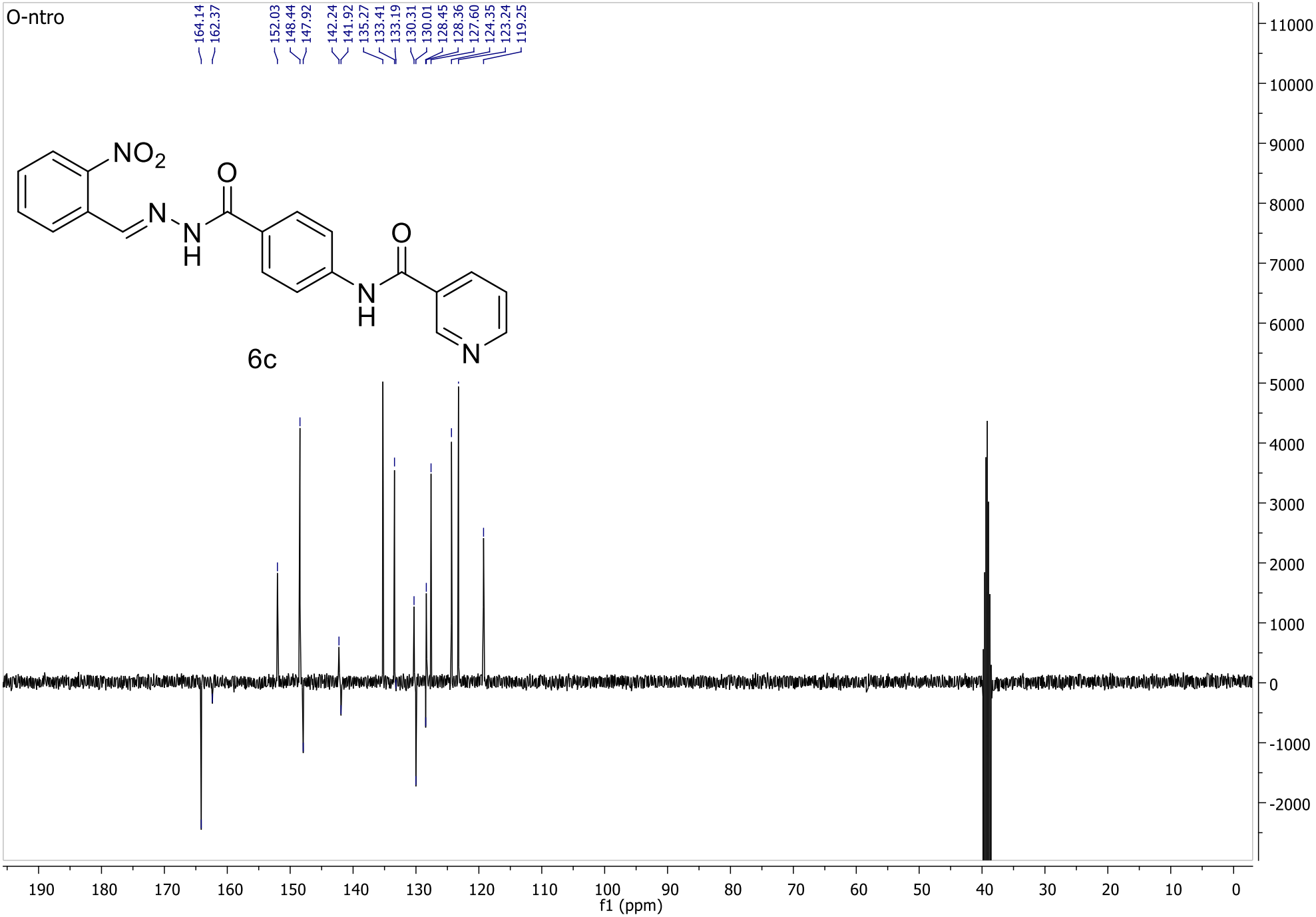
f1 (ppm)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148.44
147.92
142.24
141.92
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133.41
133.19
130.31
130.01
128.45
128.36
127.60
124.35
123.24
119.25
NO2
O
N
N
H
O
N
H
N
6c
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
190
180
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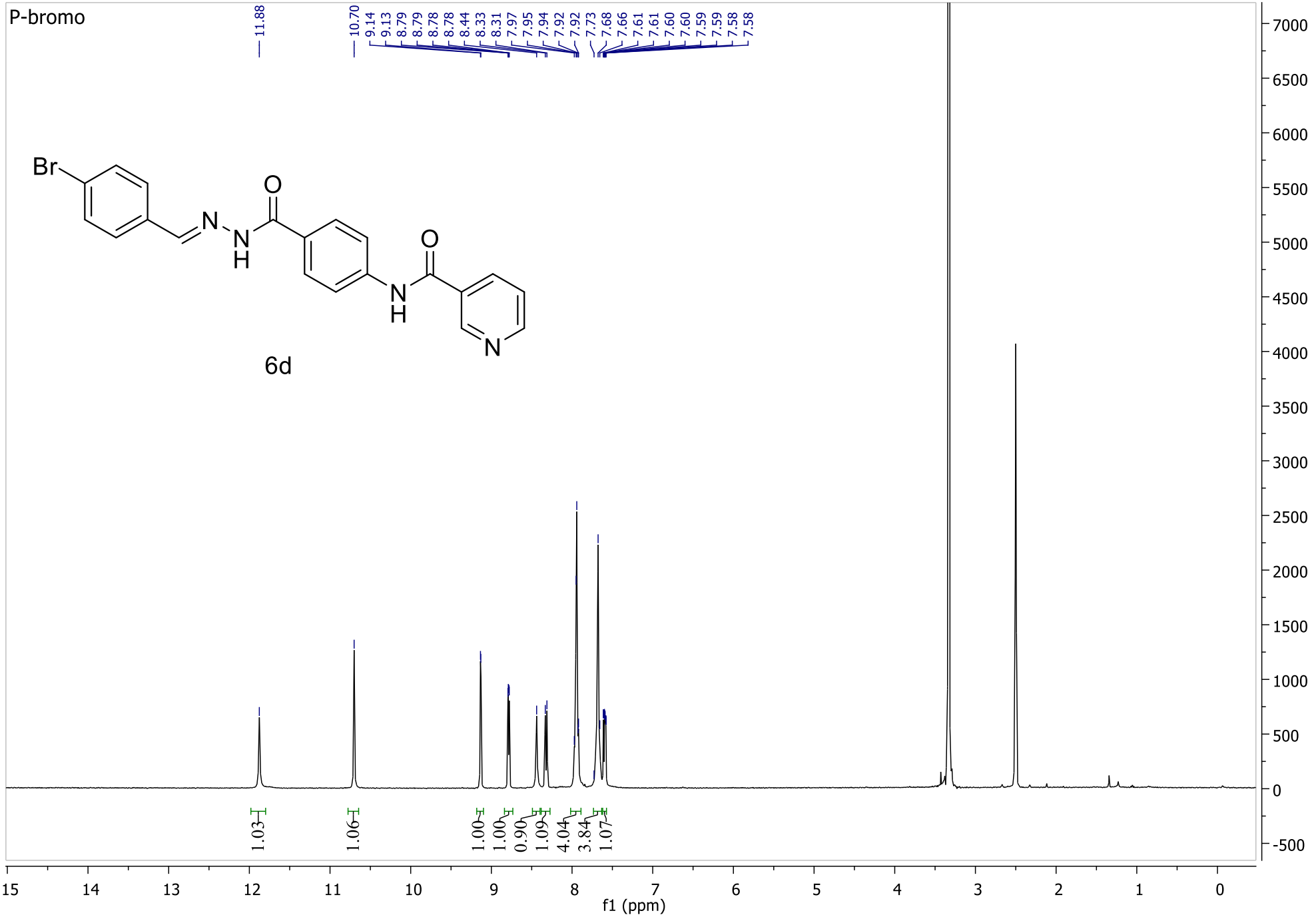
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10.70
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8.79
8.79
8.78
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8.44
8.33
8.31
7.97
7.95
7.94
7.92
7.92
7.73
7.68
7.66
7.61
7.61
7.60
7.60
7.59
7.59
7.58
7.58
Br
O
N
N
H
O
N
H
N
6d
1.03
1.06
1.00
1.00
0.90
1.09
4.04
3.84
1.07
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
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9
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5
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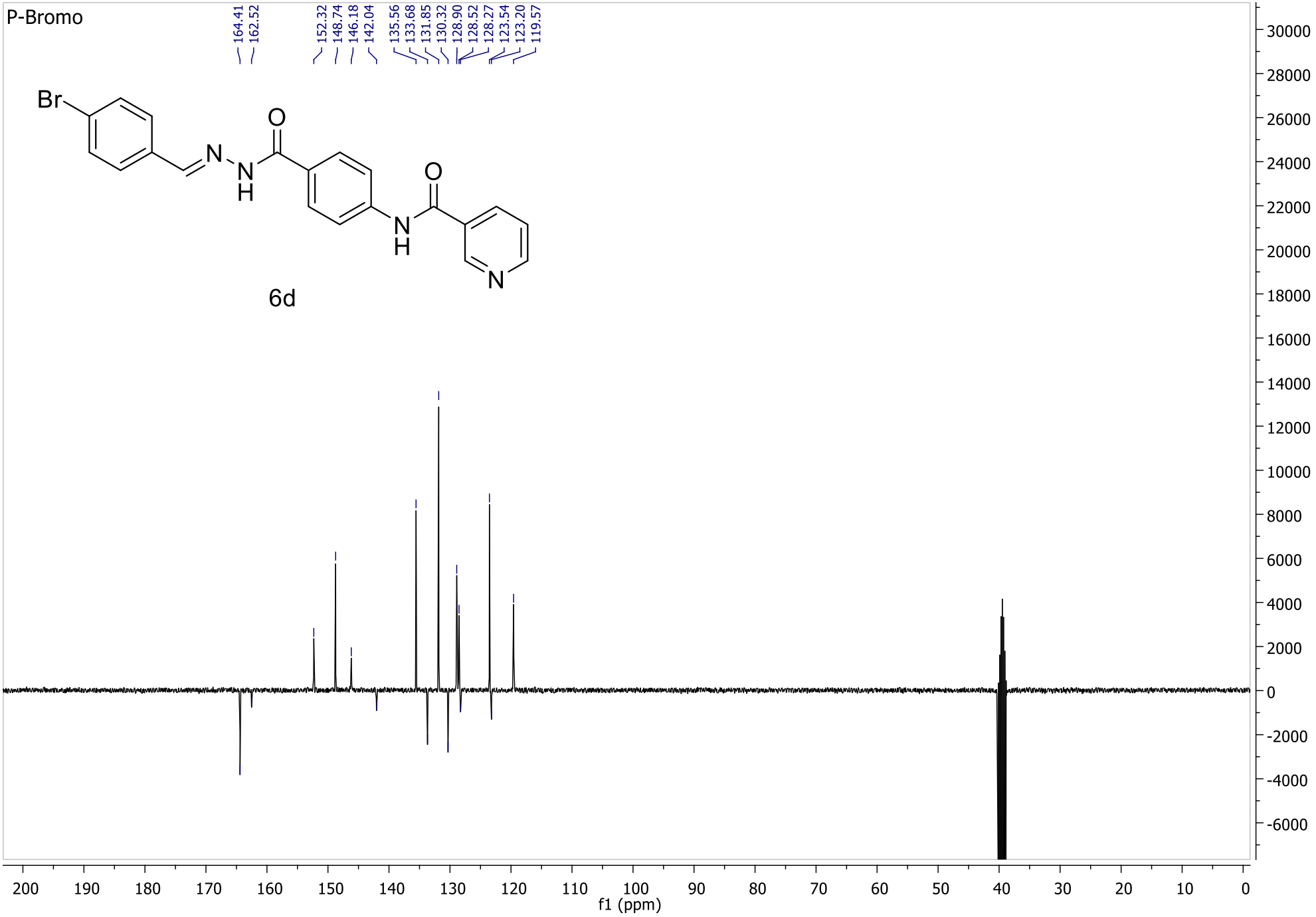
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146.18
142.04
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130.32
128.90
128.52
128.27
123.54
123.20
119.57
Br
O
N
N
H
O
N
H
N
6d
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
-6000
200
190
180
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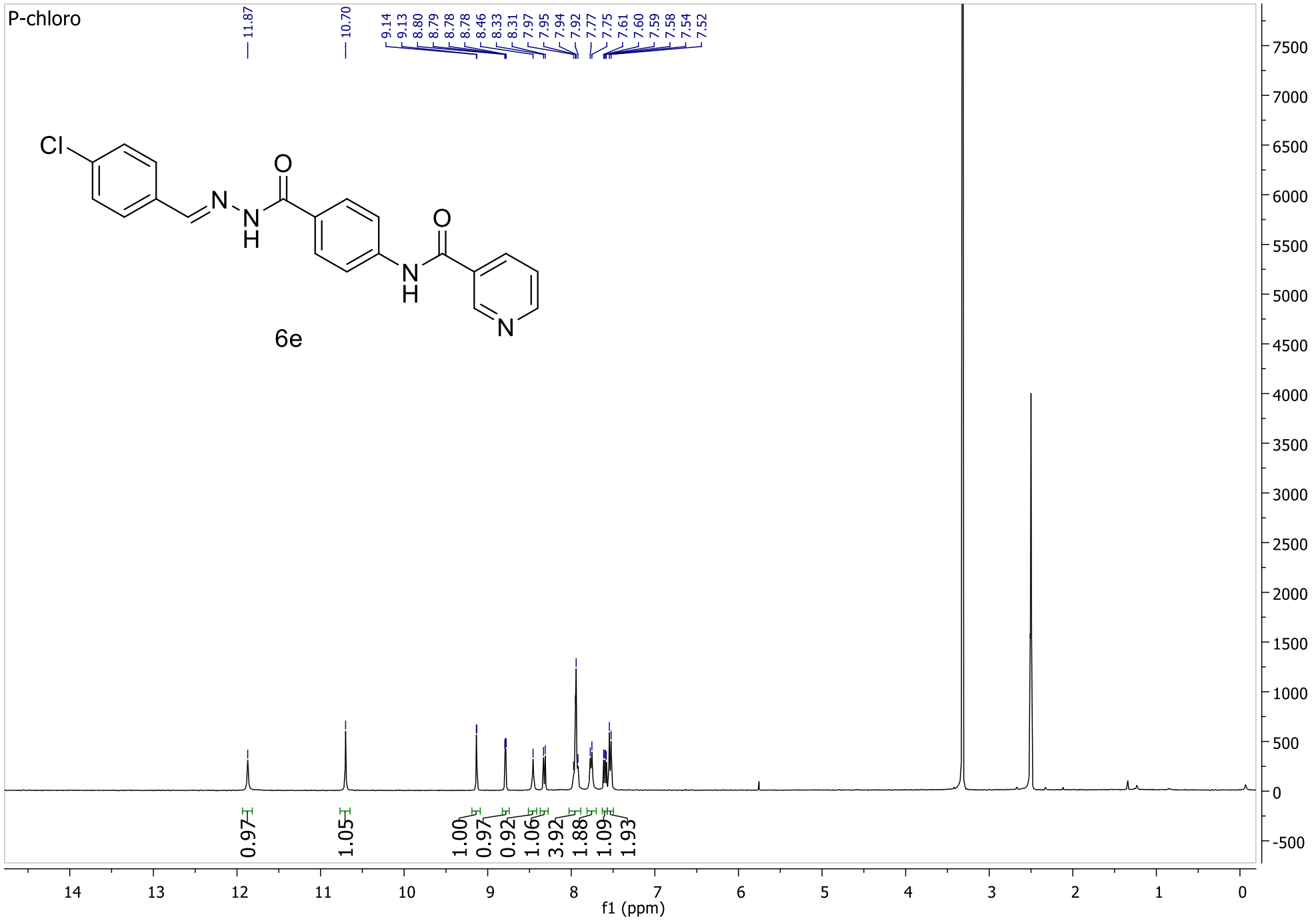
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7.97
7.95
7.94
7.92
7.77
7.75
7.61
7.60
7.59
7.58
7.54
7.52
Cl
O
N
N
H
O
N
H
N
6e
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1.09
1.93
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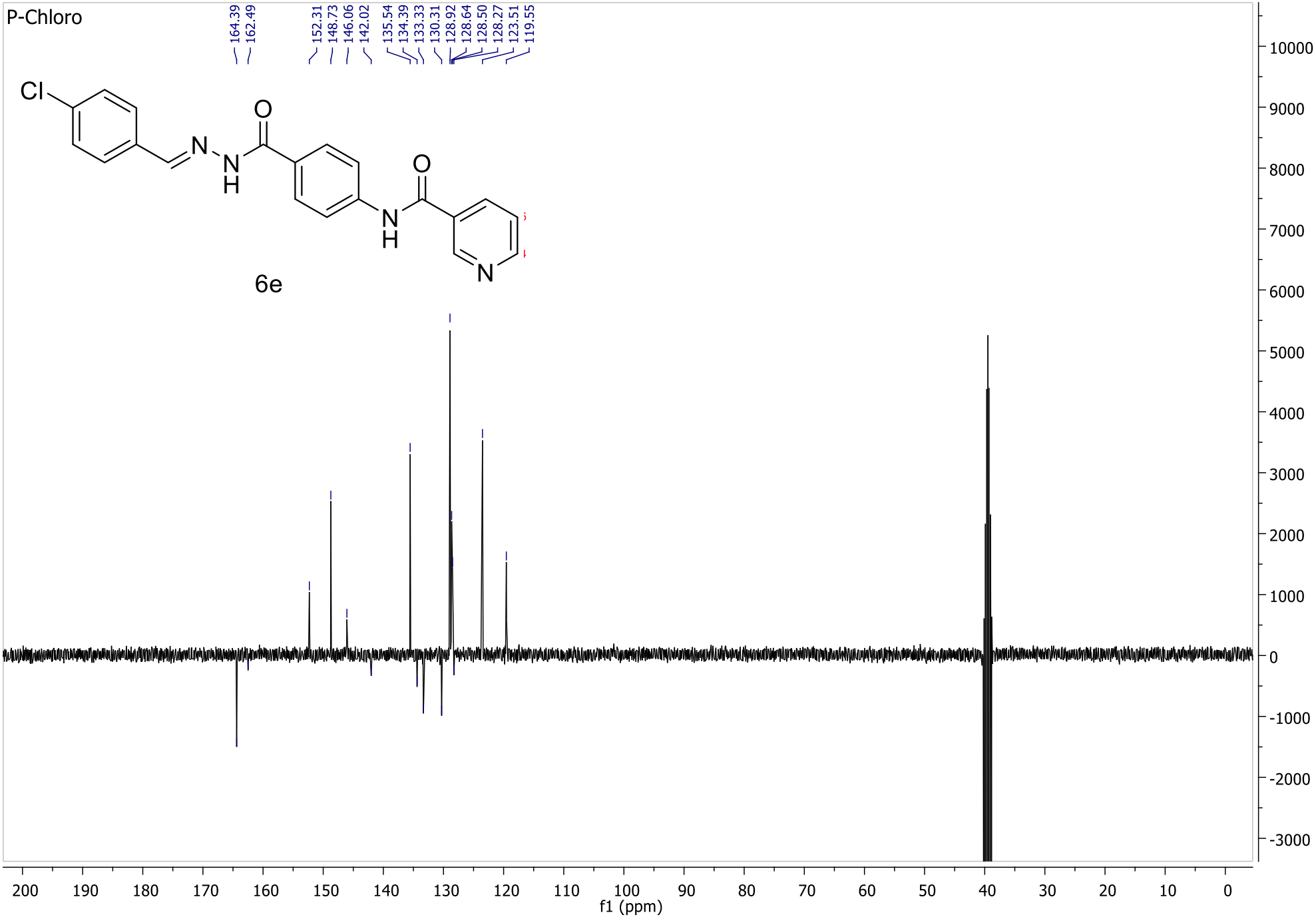
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142.02
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128.64
128.50
128.27
123.51
119.55
Cl
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O
N
H
N
6e
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4000
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1000
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-3000
200
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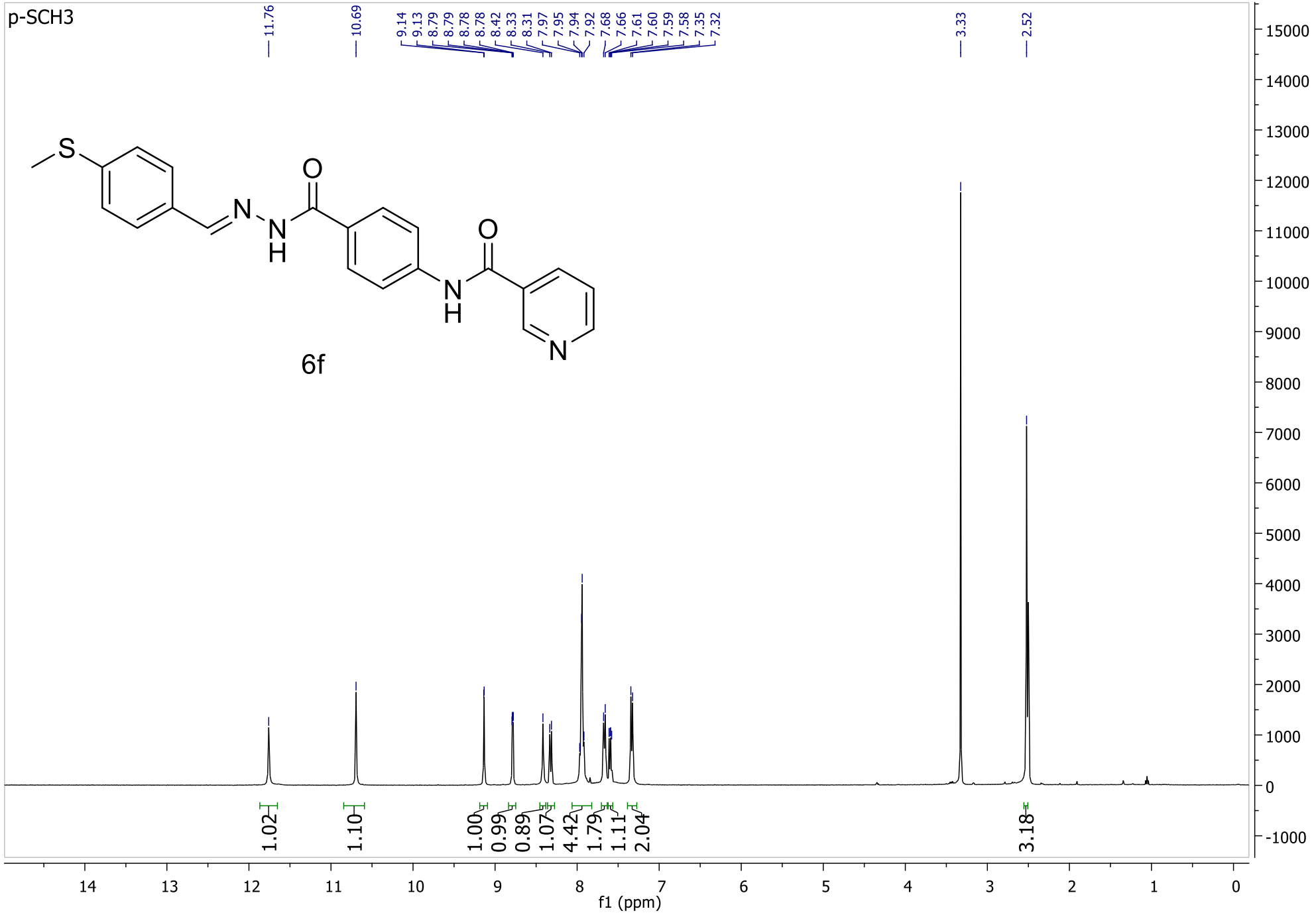
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7.95
7.94
7.92
7.68
7.66
7.61
7.60
7.59
7.58
7.35
7.32
3.33
2.52
S
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N
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H
O
N
H
N
6f
1.02
1.10
1.00
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0.89
1.07
4.42
1.79
1.11
2.04
3.18
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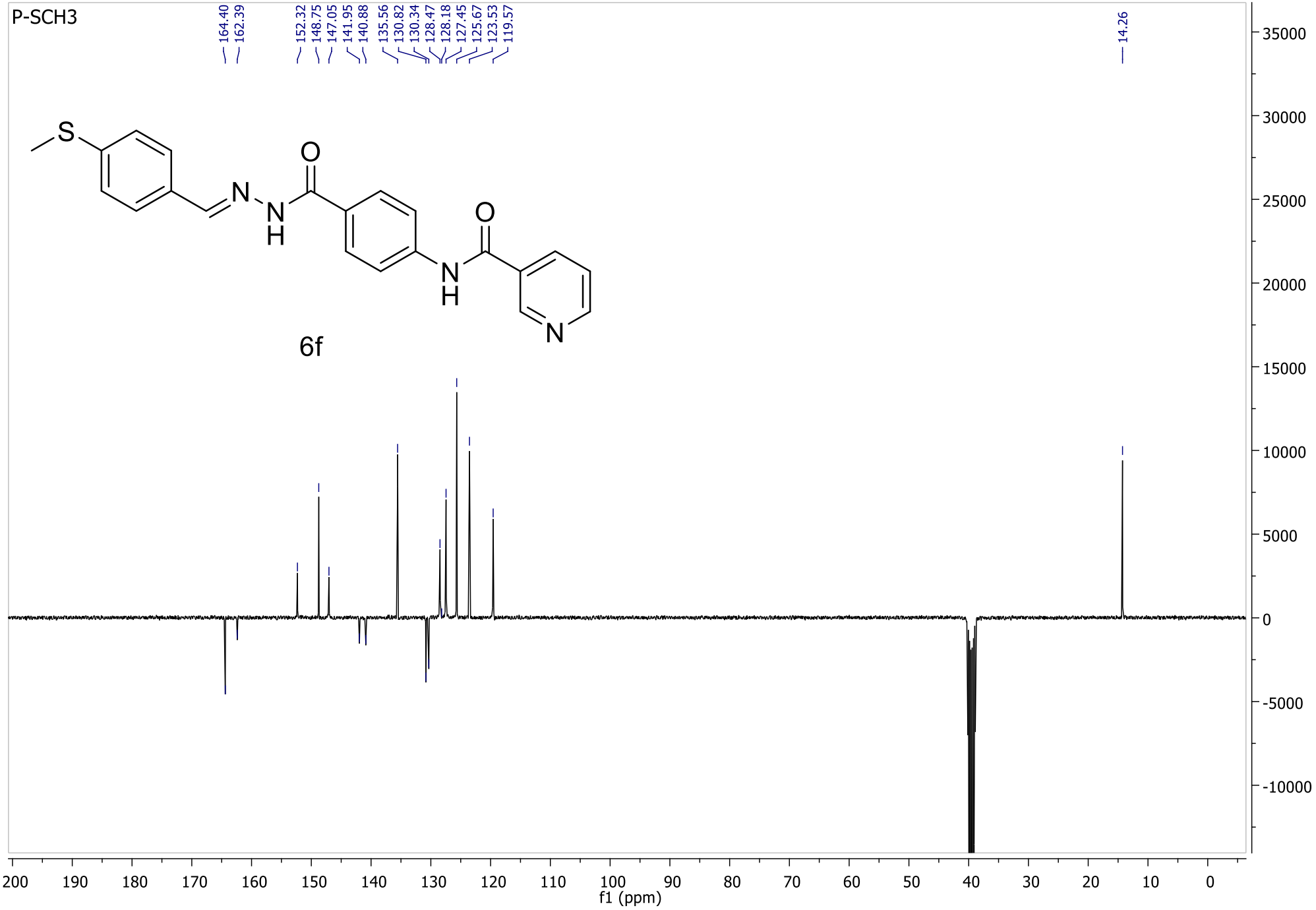
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128.18
127.45
125.67
123.53
119.57
14.26
S
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H
O
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N
H
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6f
35000
30000
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-10000
200
190
180
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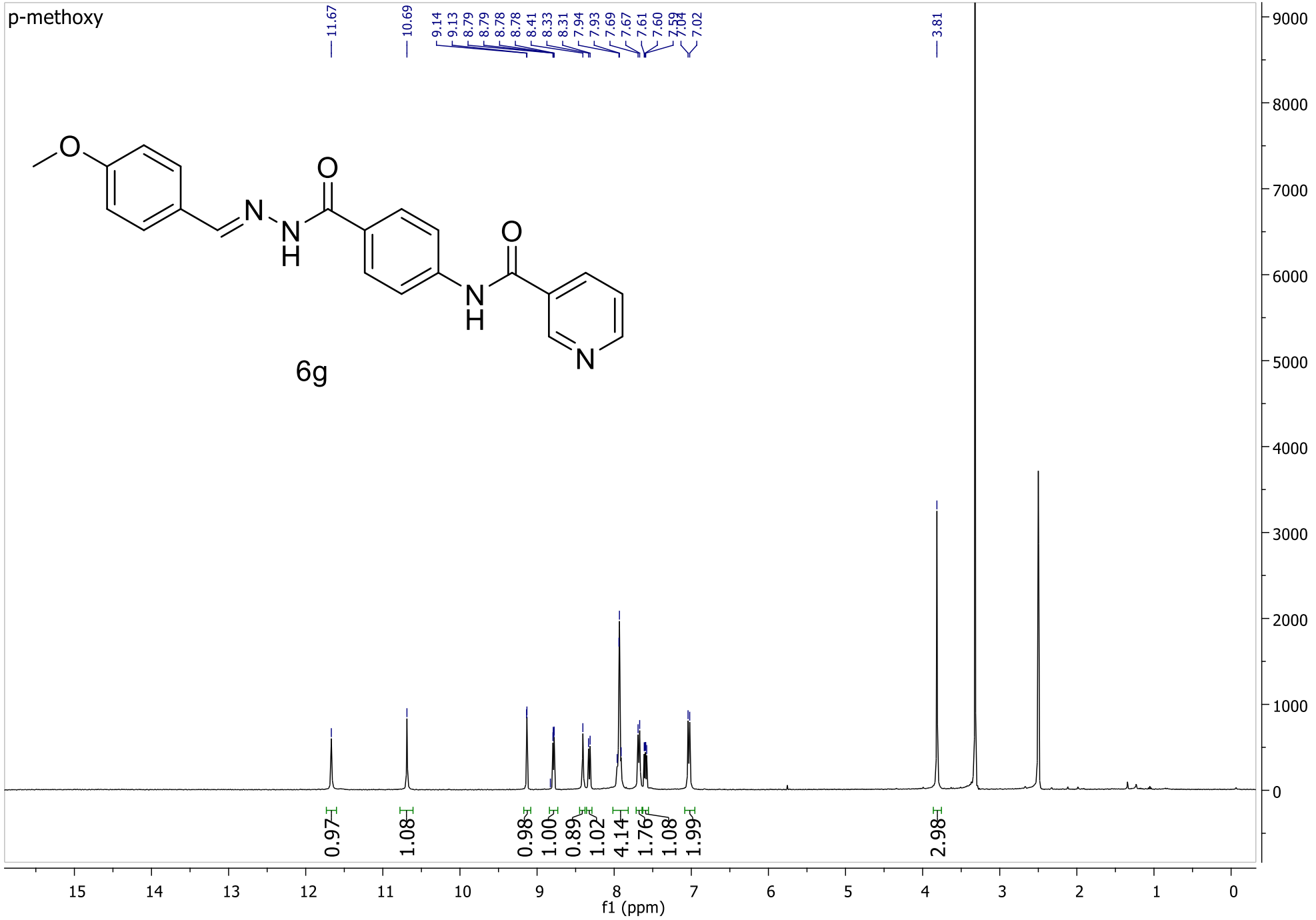
f1 (ppm)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8.41
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7.94
7.93
7.69
7.67
7.61
7.60
7.59
7.04
7.02
3.81
O
N
H
O
N
H
O
N
6g
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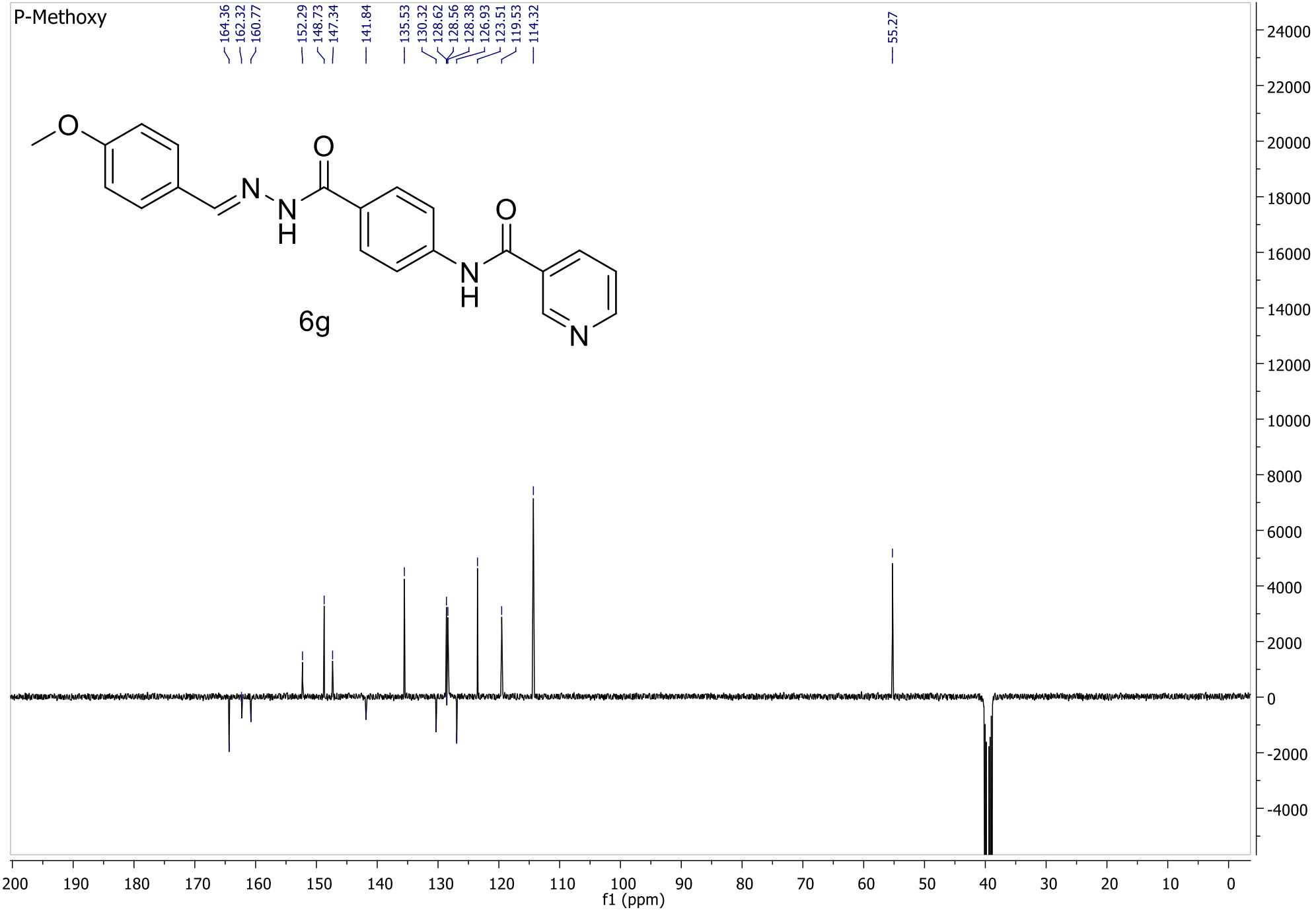
1.99
2.98
f1 (ppm)


P-Methoxy
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160.77
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141.84
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130.32
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128.38
126.93
123.51
119.53
114.32
55.27
O
N
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H
O
O
N
H
N
6g
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
-4000
200
190
180
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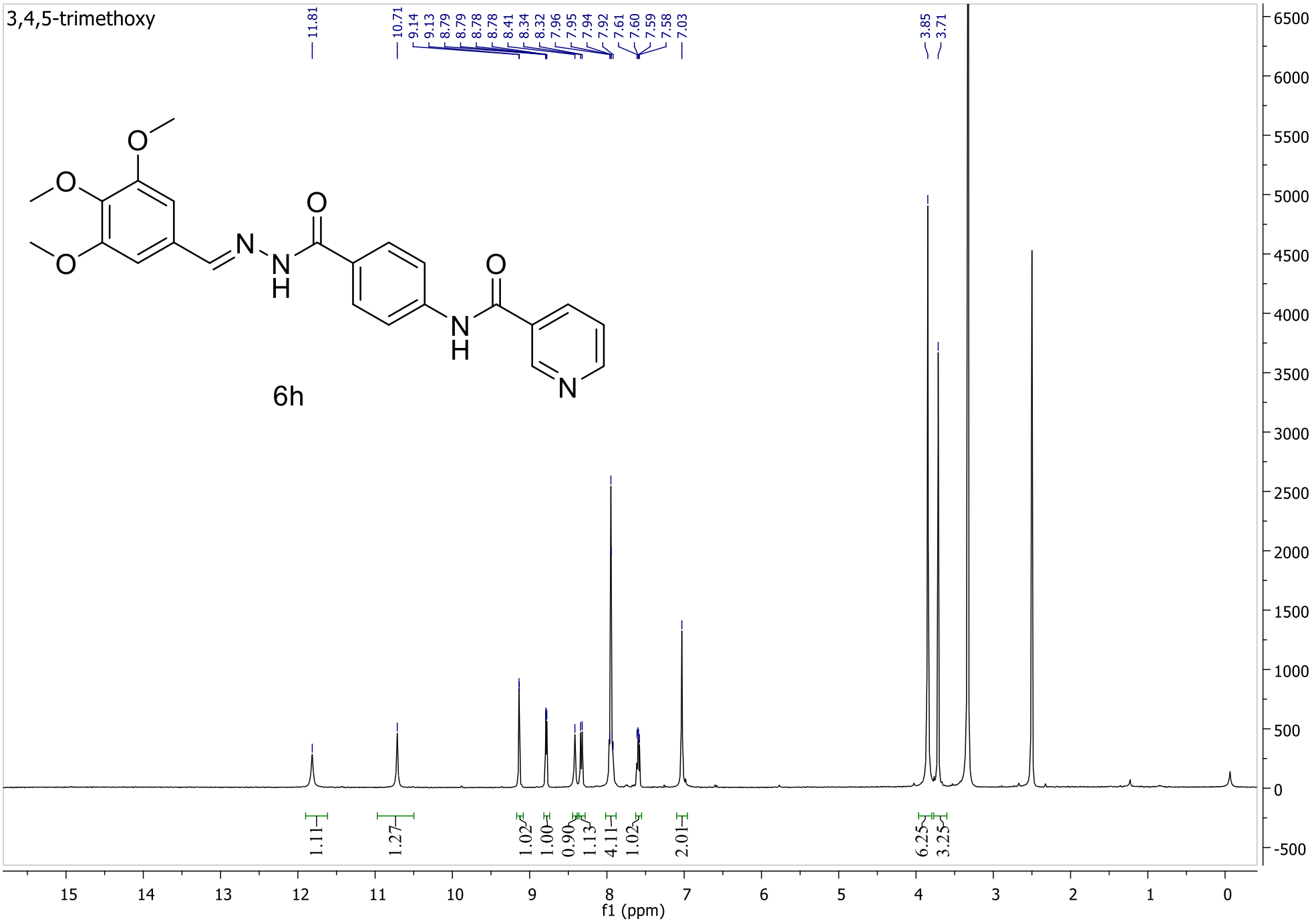
f1 (ppm)


3,4,5-trimethoxy
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9.14
9.13
8.79
8.79
8.78
8.78
8.41
8.34
8.32
7.96
7.95
7.94
7.92
7.61
7.60
7.59
7.58
7.03
3.85
3.71
6h
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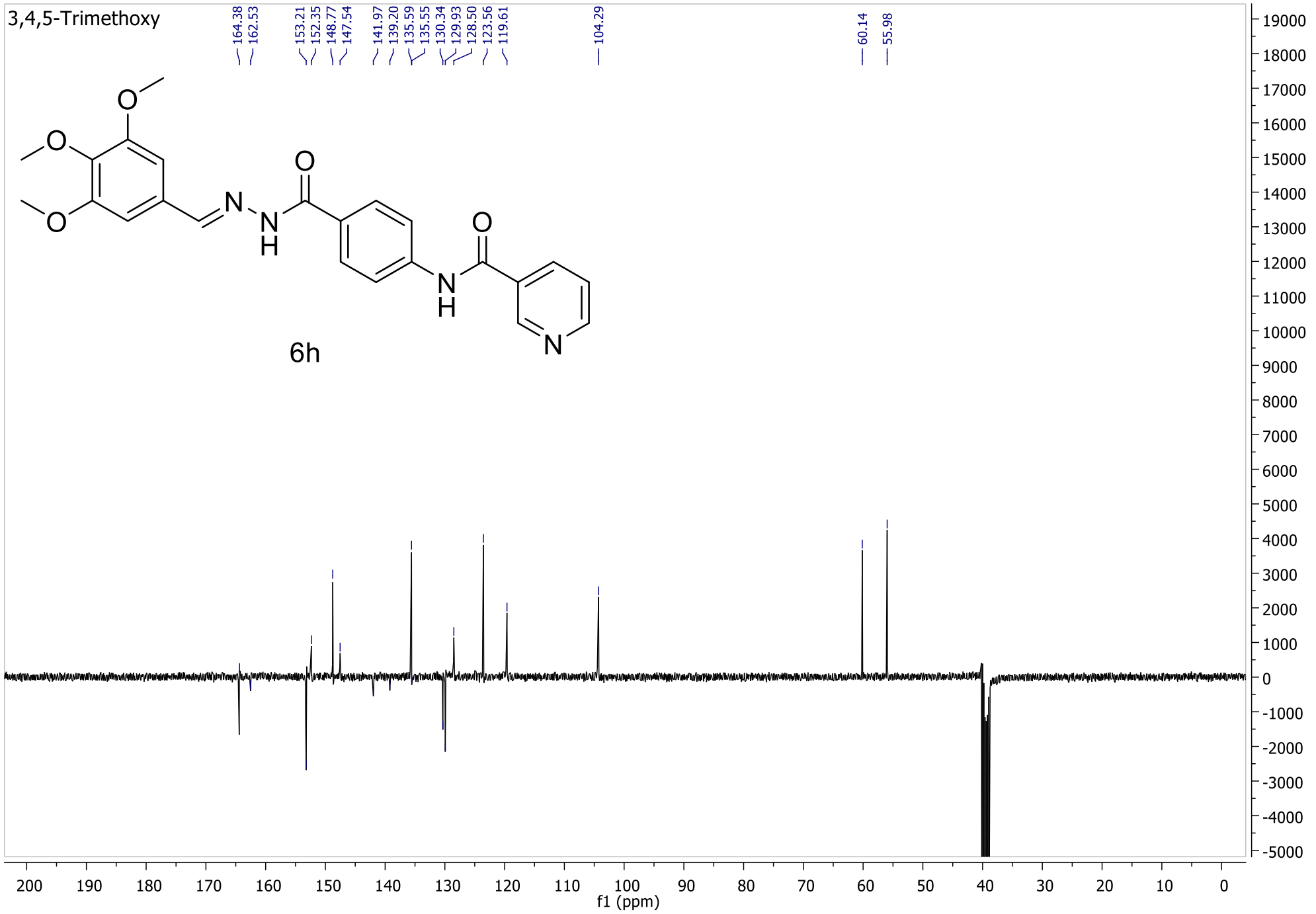
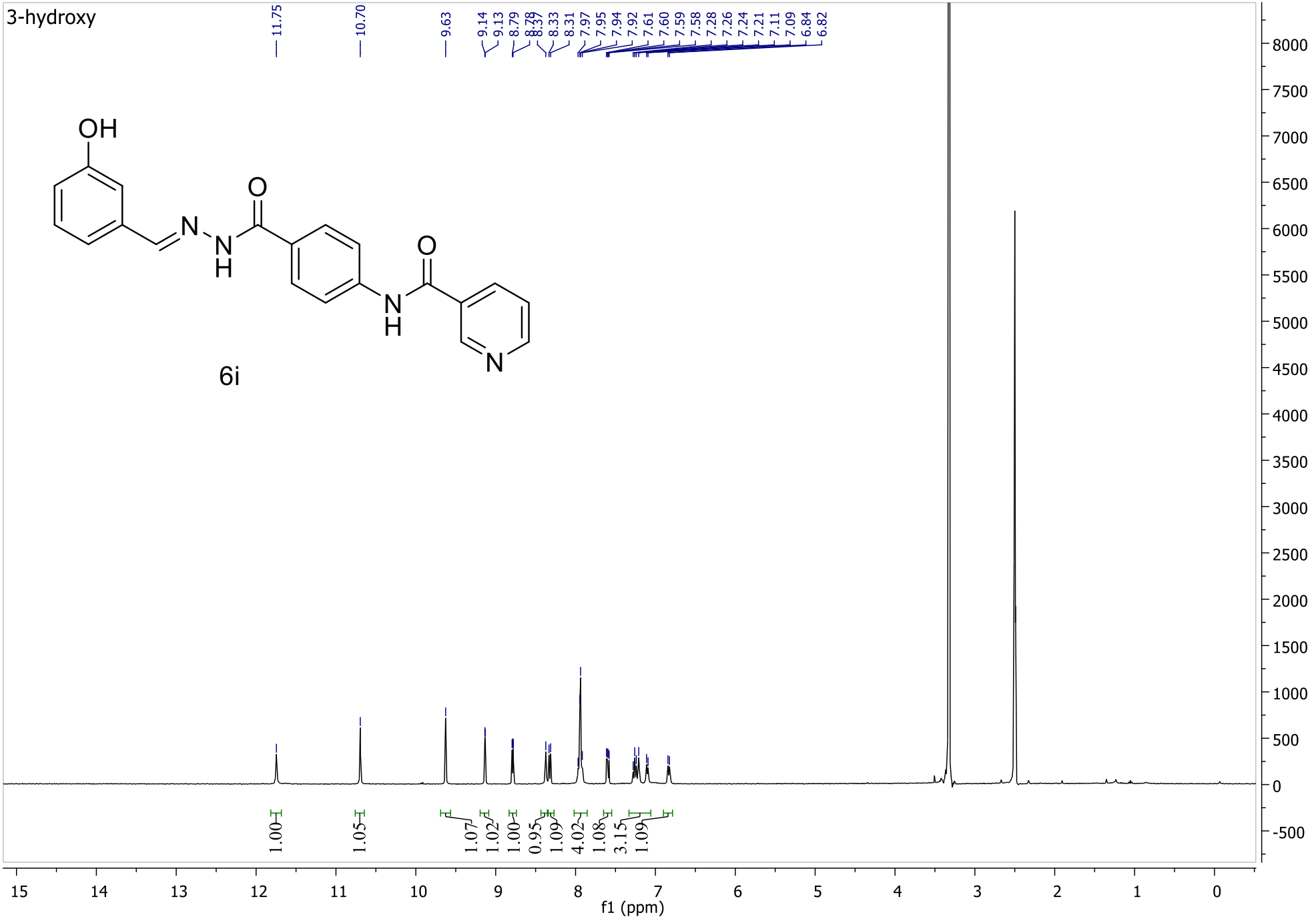
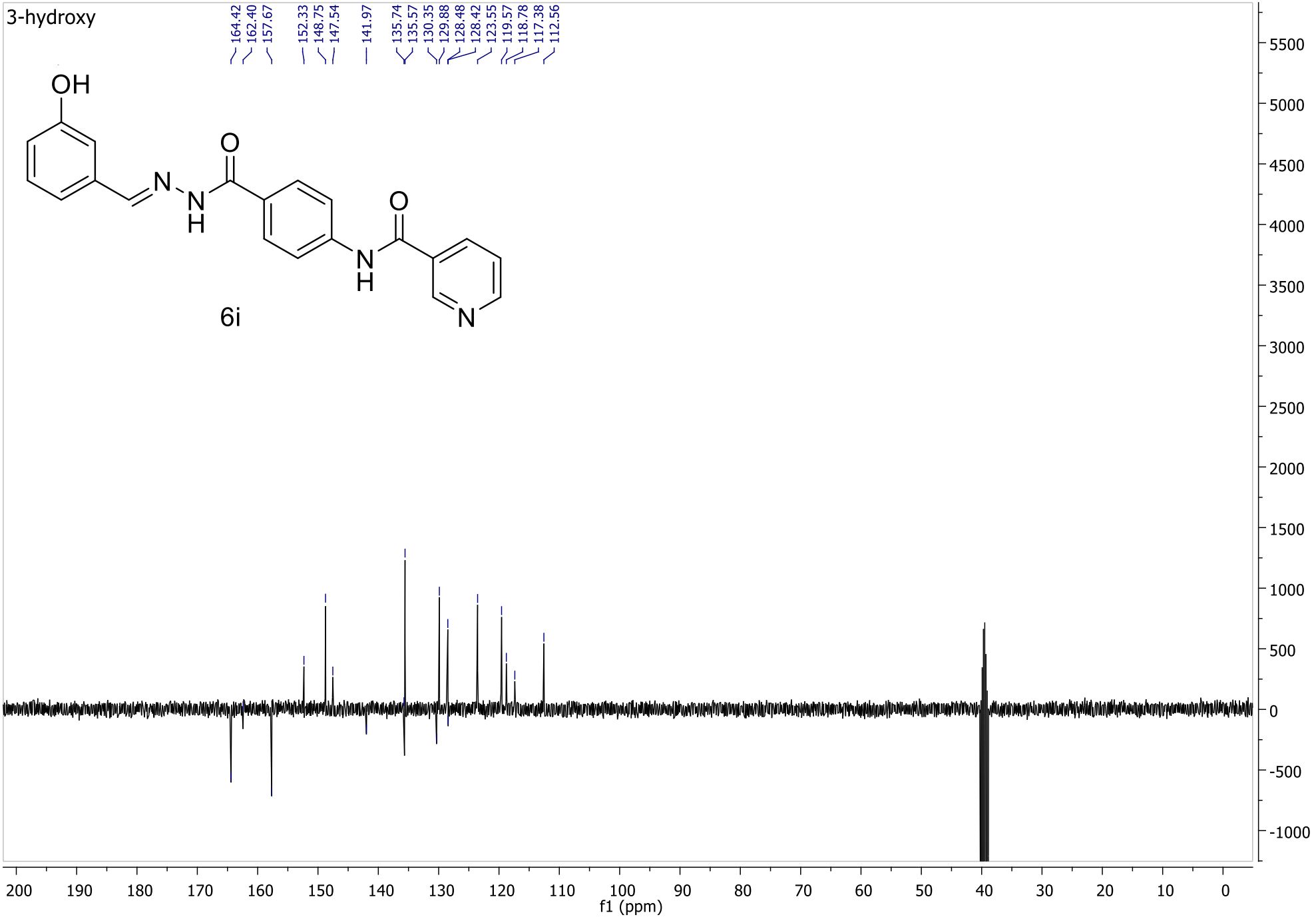
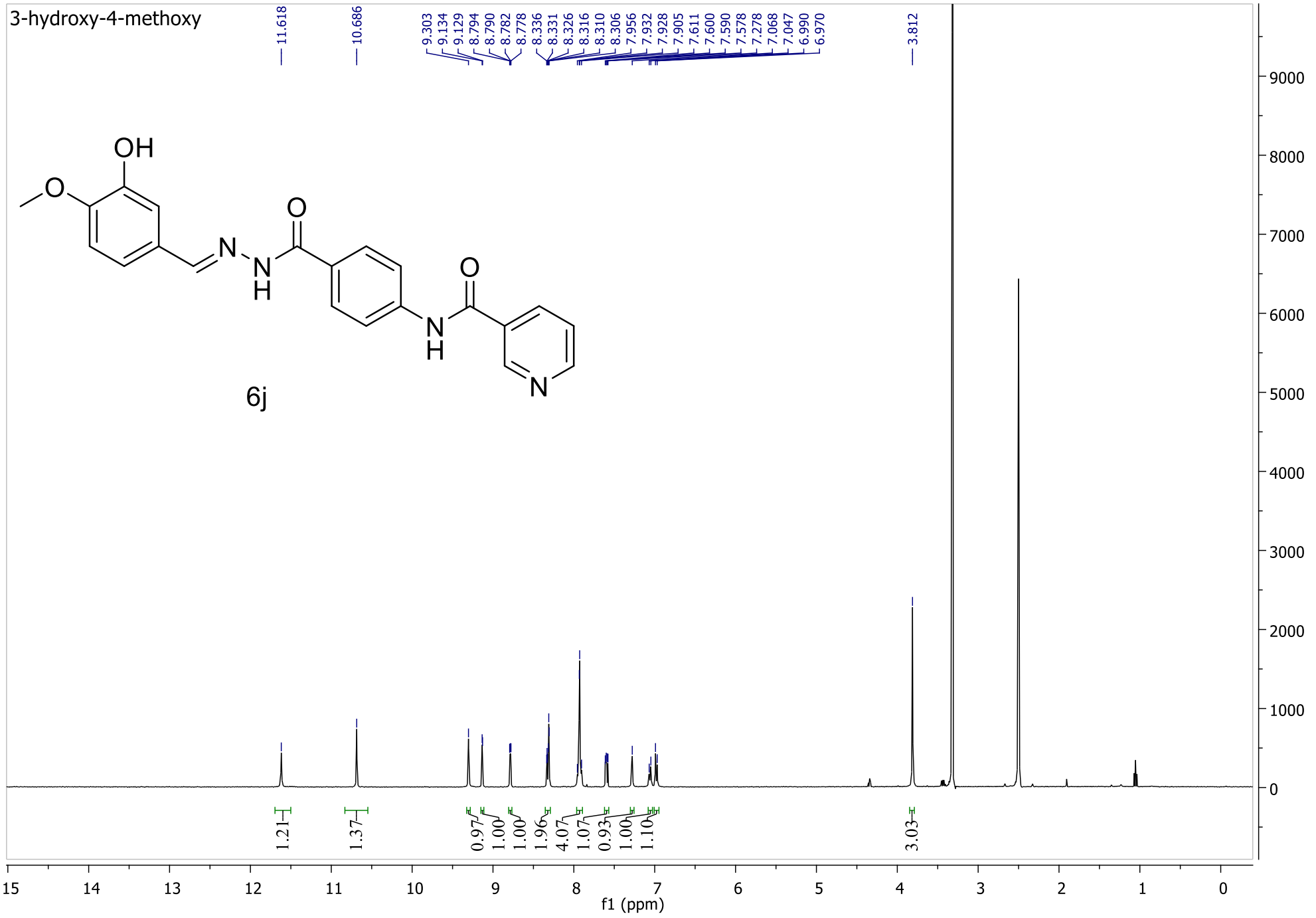
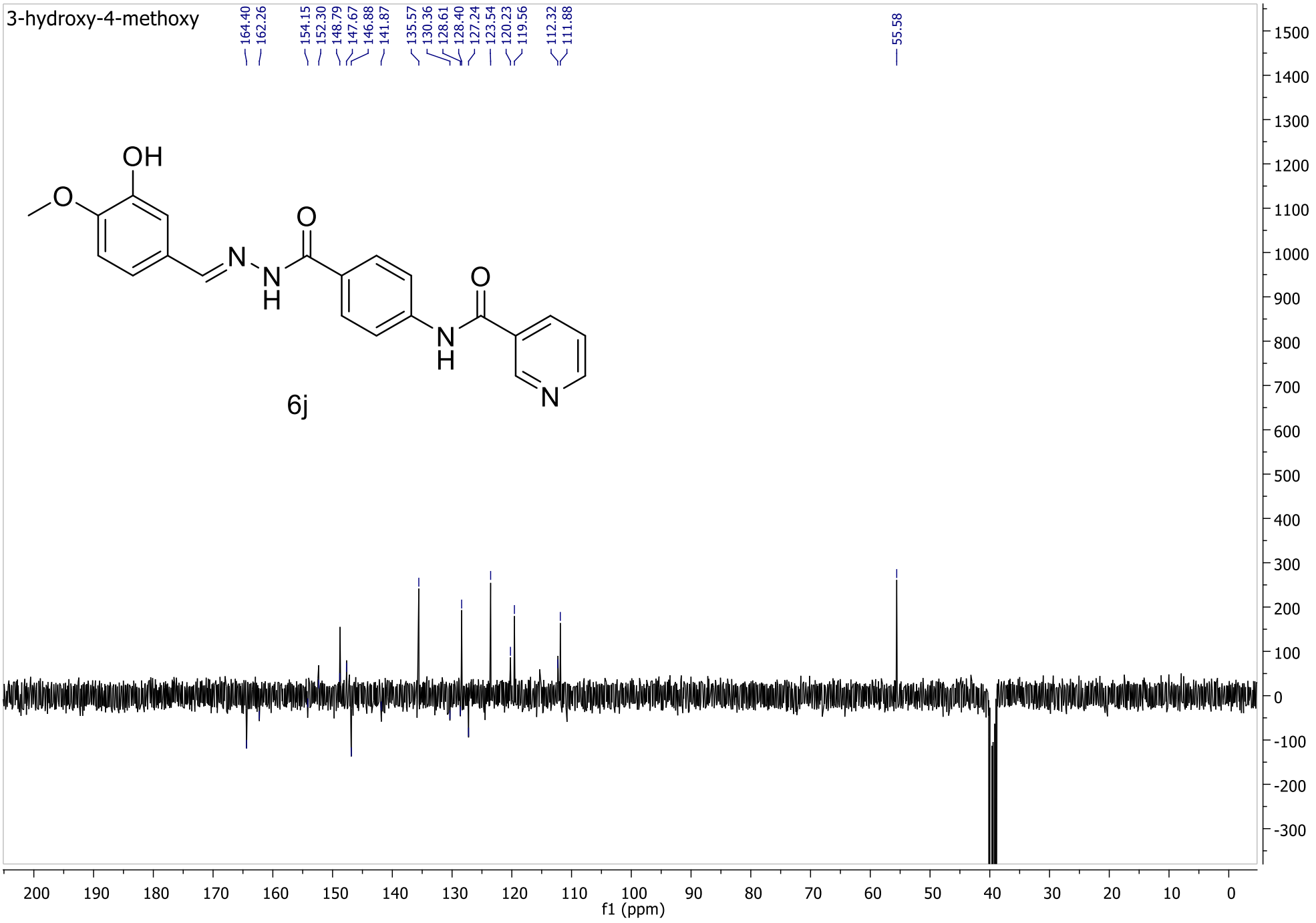
4.11
1.02
2.01
6.25
3.25
f1 (ppm)

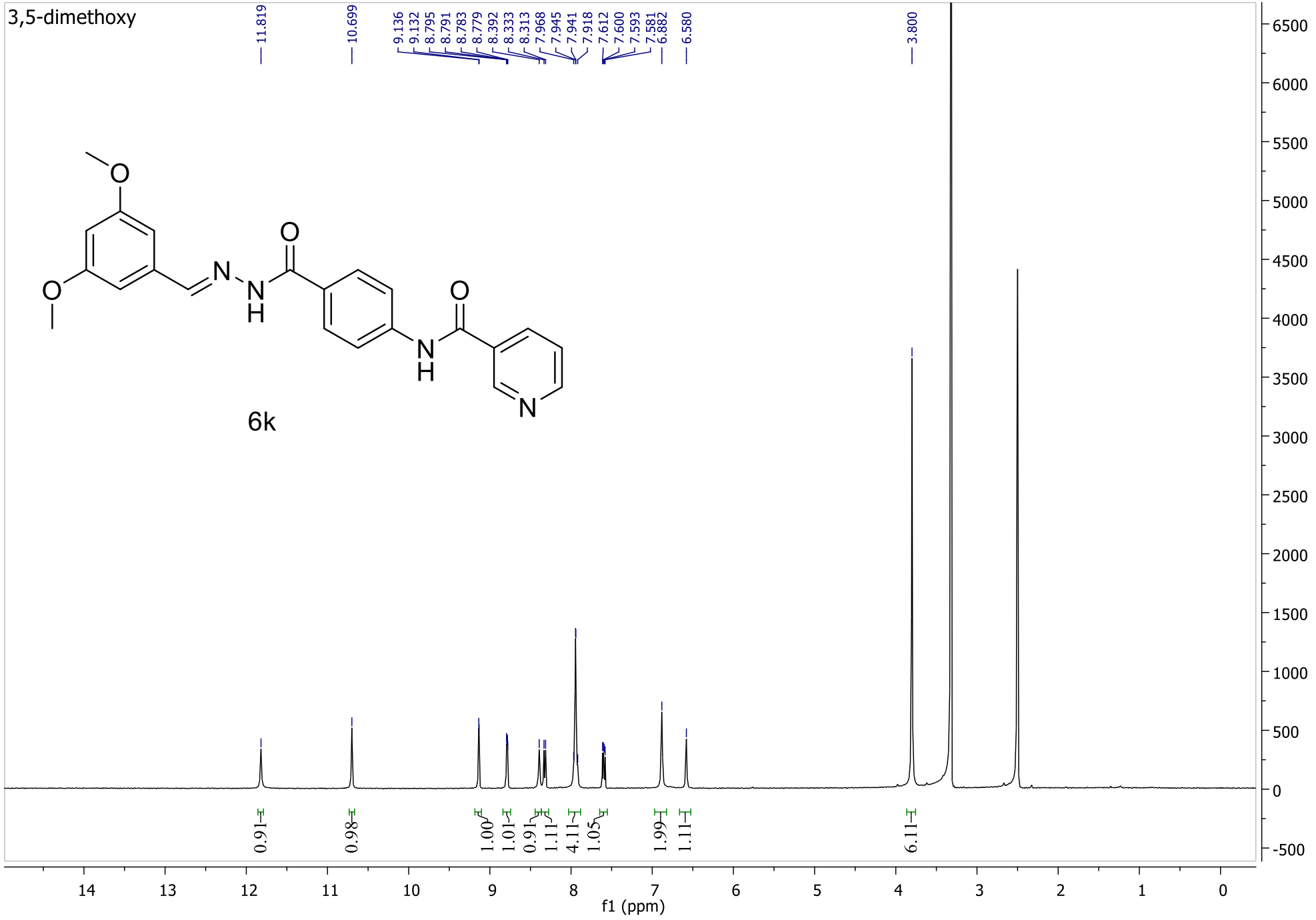

3,4,5-Trimethoxy
164.38
162.53
153.21
152.35
148.77
147.54
141.97
139.20
135.59
135.55
130.34
129.93
128.50
123.56
119.61
104.29
60.14
55.98
6h
f1 (ppm)

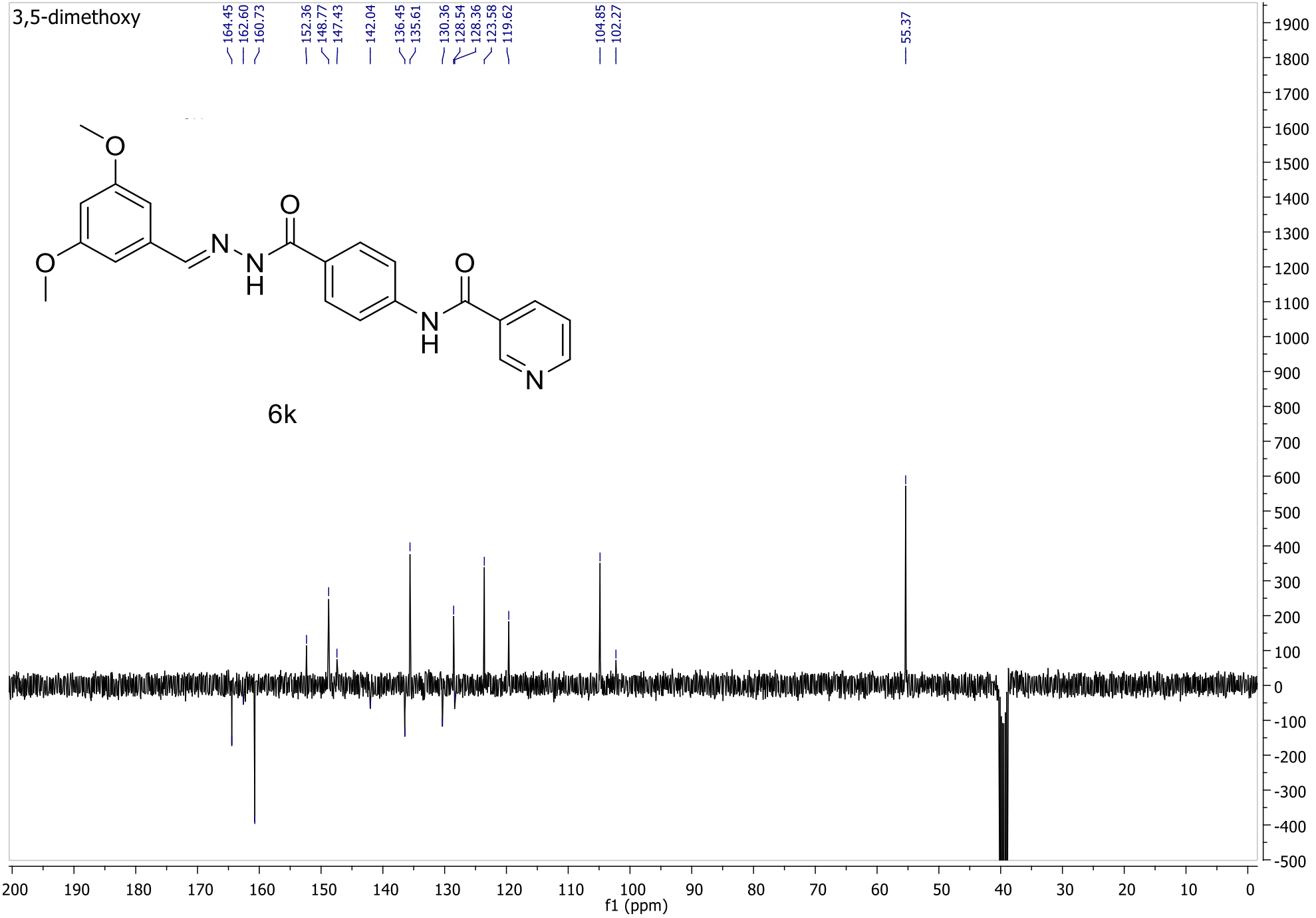

3-hydroxy
11.75
10.70
9.63
9.14
9.13
8.79
8.78
8.37
8.33
8.31
7.97
7.95
7.94
7.92
7.61
7.60
7.59
7.58
7.28
7.26
7.24
7.21
7.11
7.09
6.84
6.82
OH
O
N
N
H
O
N
H
N
6i
1.00
1.05
1.07
1.02
1.00
0.95
1.09
4.02
1.08
3.15
1.09
f1 (ppm)

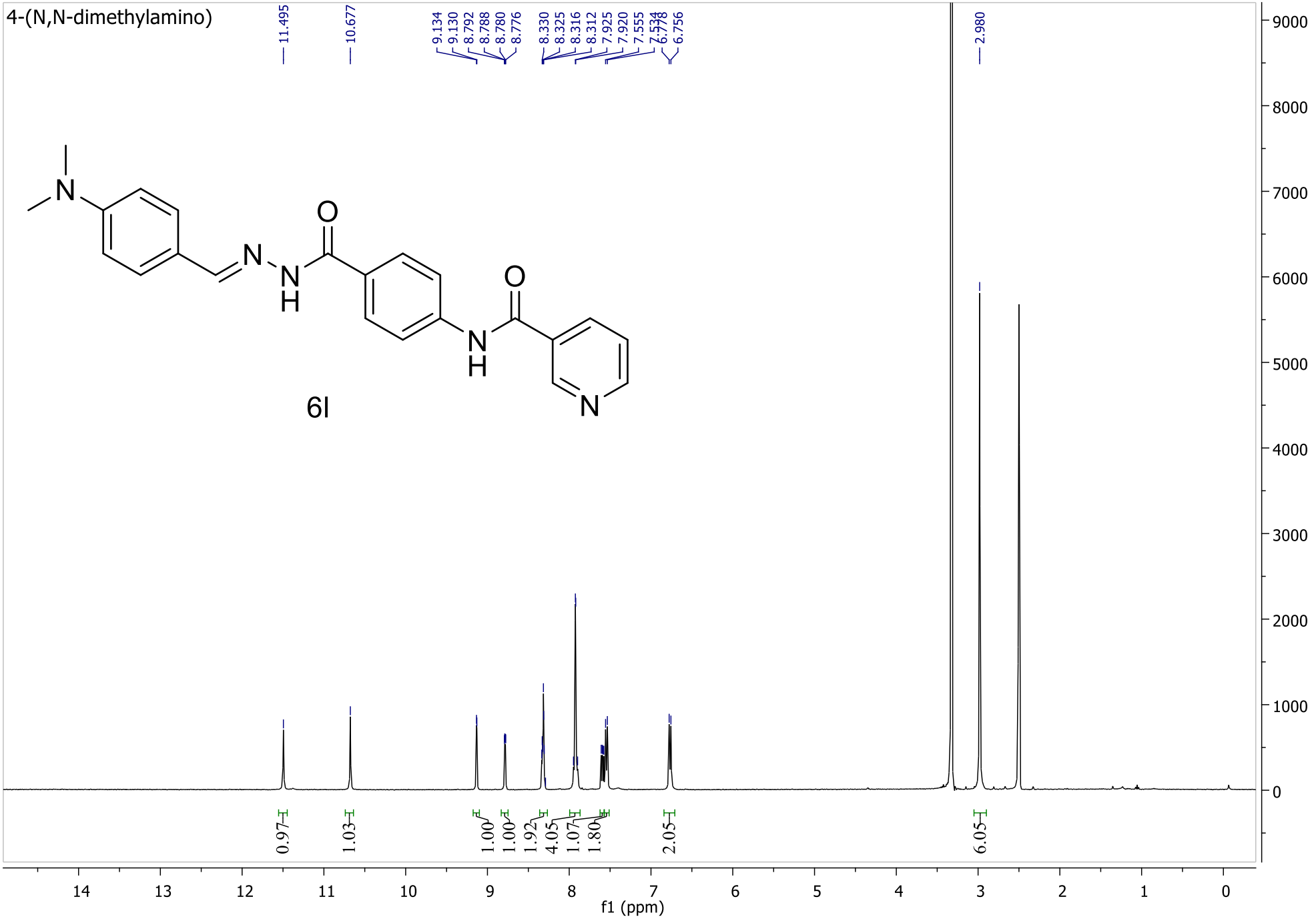

3-hydroxy
164.42
162.40
157.67
152.33
148.75
147.54
141.97
135.74
135.57
130.35
129.88
128.48
128.42
123.55
119.57
118.78
117.38
112.56
OH
O
N
N
H
O
N
H
N
6i
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

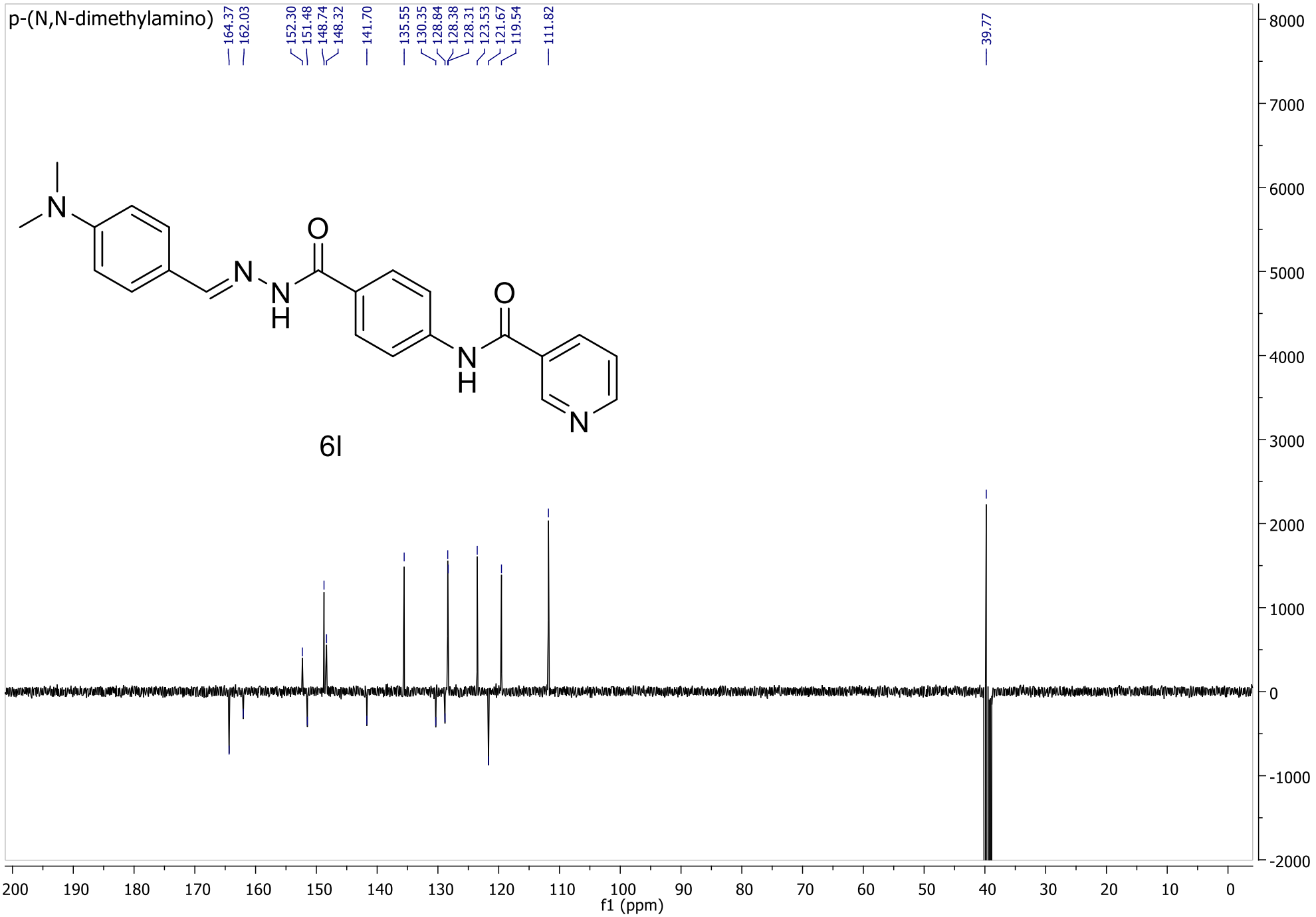

3-hydroxy-4-methoxy
11.618
10.686
9.303
9.134
9.129
8.794
8.790
8.782
8.778
8.336
8.331
8.326
8.316
8.310
8.306
7.956
7.932
7.928
7.905
7.611
7.600
7.590
7.578
7.278
7.068
7.047
6.990
6.970
3.812
OH
O
N
N
H
O
O
N
H
N
6j
1.21
1.37
0.97
1.00
1.00
1.96
4.07
1.07
0.93
1.00
1.10
3.03
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

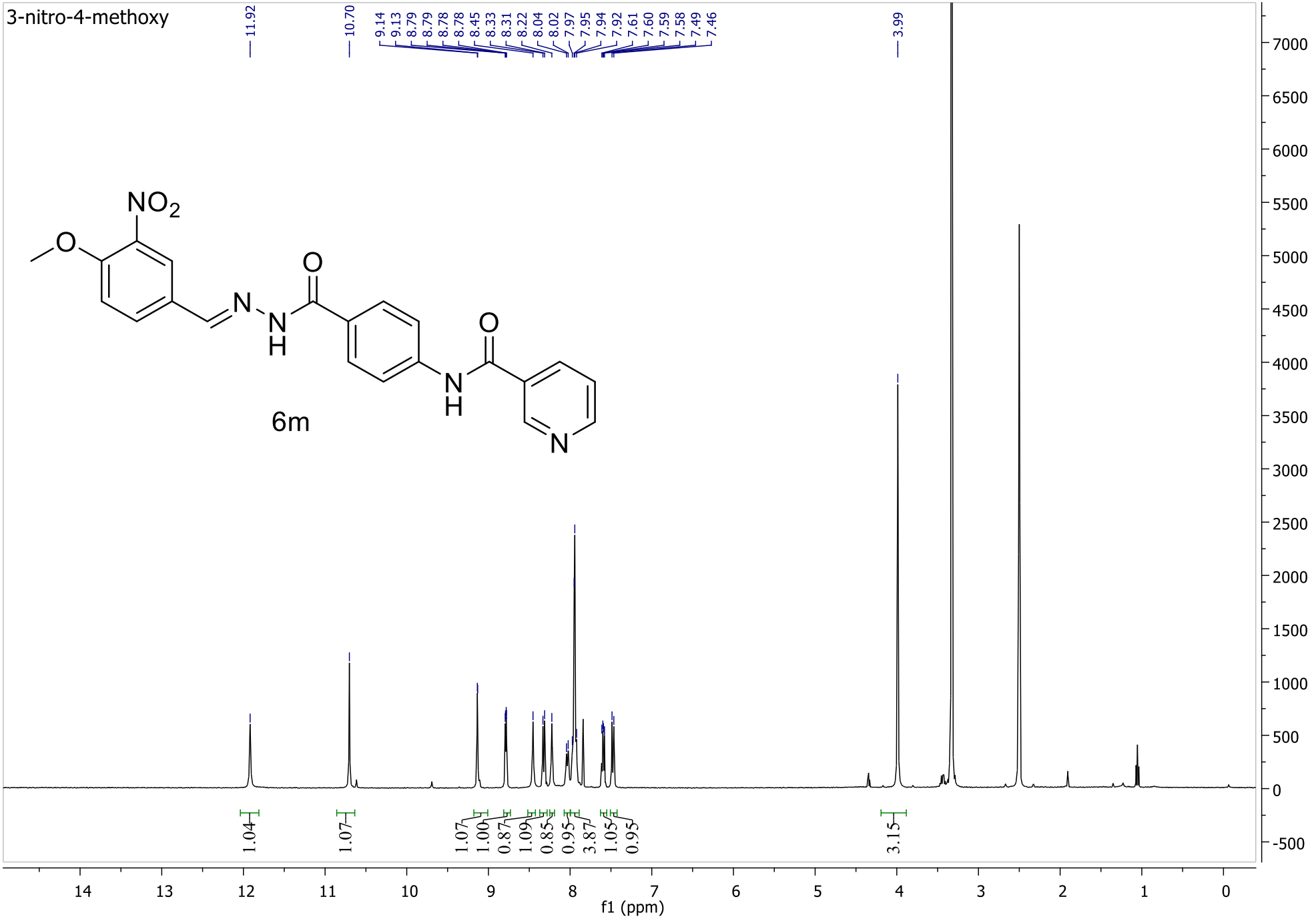

3-hydroxy-4-methoxy
164.40
162.26
154.15
152.30
148.79
147.67
146.88
141.87
135.57
130.36
128.61
128.40
127.24
123.54
120.23
119.56
112.32
111.88
55.58
OH
O
N
N
H
O
O
N
H
N
6j
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-300
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

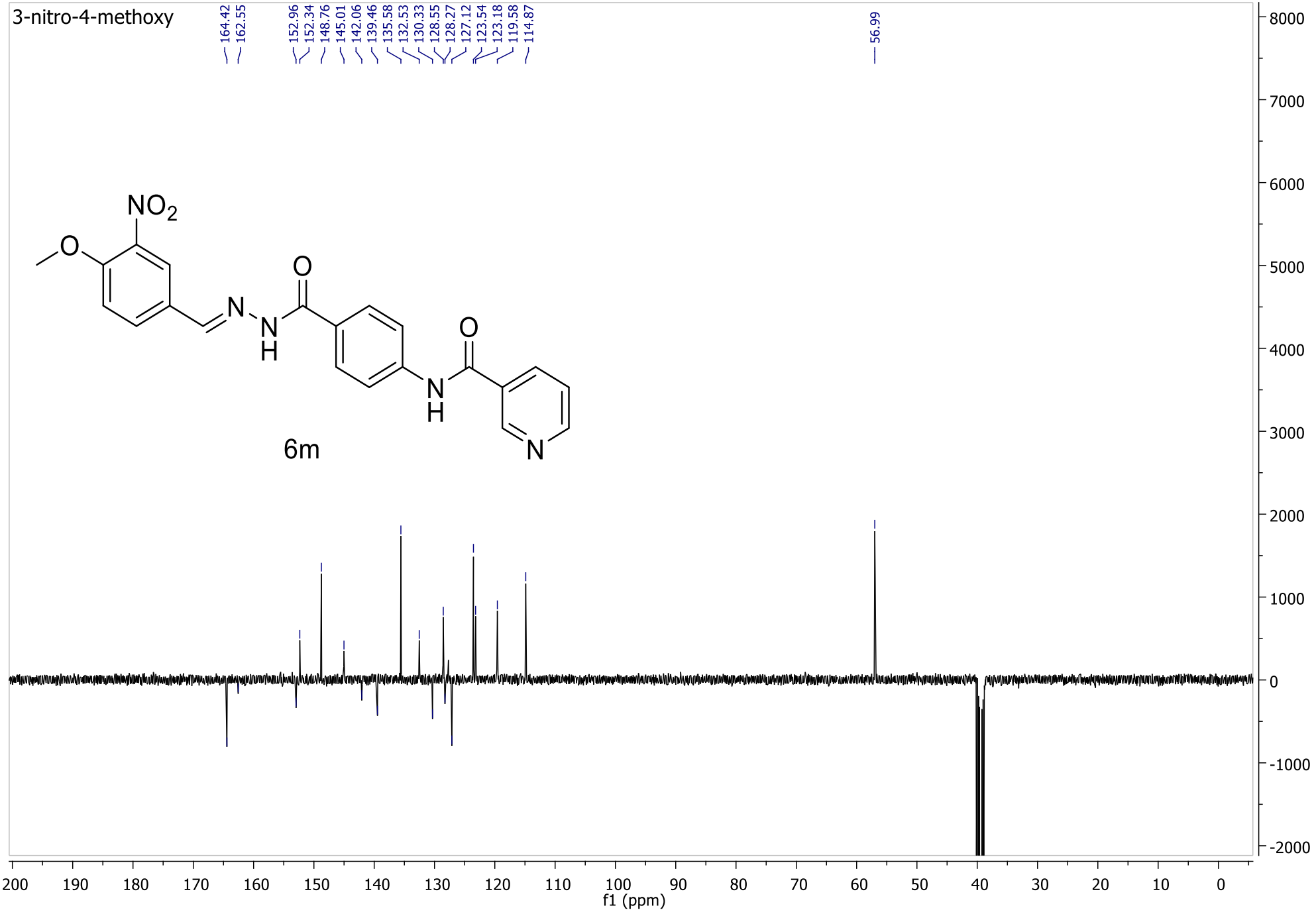

3,5-dimethoxy
11.819
10.699
9.136
9.132
8.795
8.791
8.783
8.779
8.392
8.333
8.313
7.968
7.945
7.941
7.918
7.612
7.600
7.593
7.581
6.882
6.580
3.800
6k
0.91
0.98
1.00
1.01
0.91
1.11
4.11
1.05
1.99
1.11
6.11
f1 (ppm)

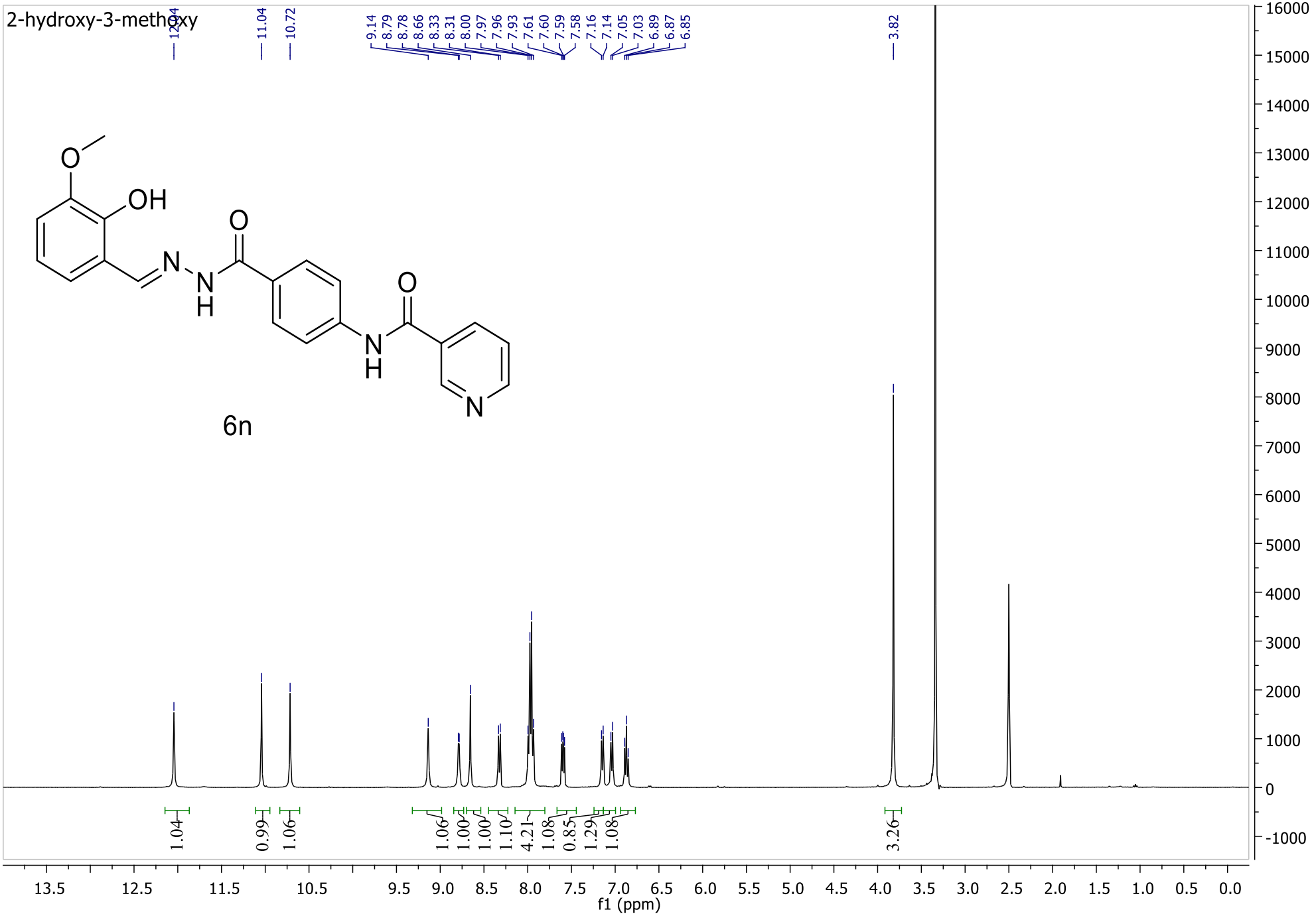

3,5-dimethoxy
164.45
162.60
160.73
152.36
148.77
147.43
142.04
136.45
135.61
130.36
128.54
128.36
123.58
119.62
104.85
102.27
55.37
O
O
N
N
H
O
N
H
O
N
6k
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
-300
-400
-500
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

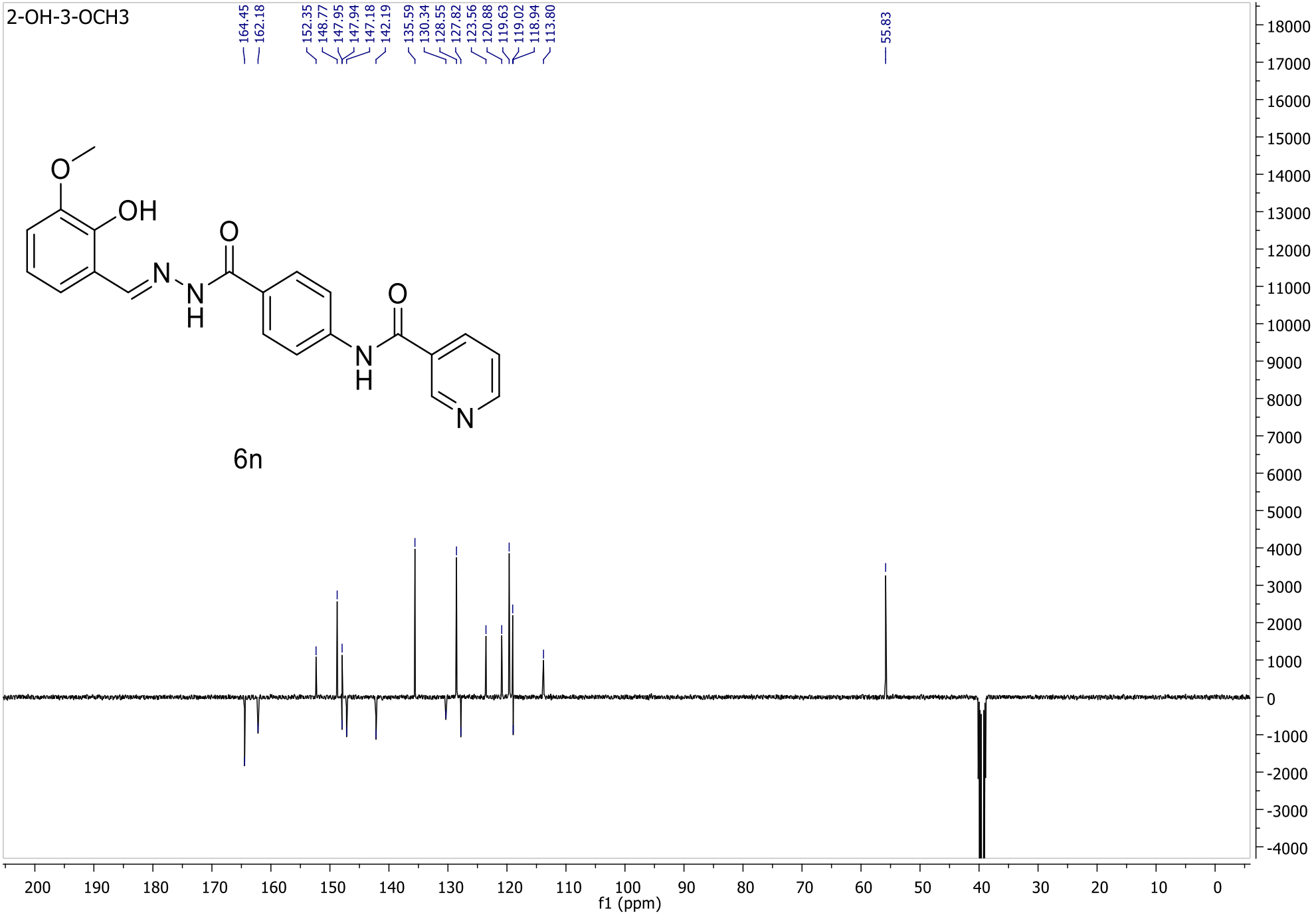

4-(N,N-dimethylamino)
11.495
10.677
9.134
9.130
8.792
8.788
8.780
8.776
8.330
8.325
8.316
8.312
7.925
7.920
7.555
7.534
6.778
6.756
2.980
6l
0.97
1.03
1.00
1.00
1.92
4.05
1.07
1.80
2.05
6.05
f1 (ppm)

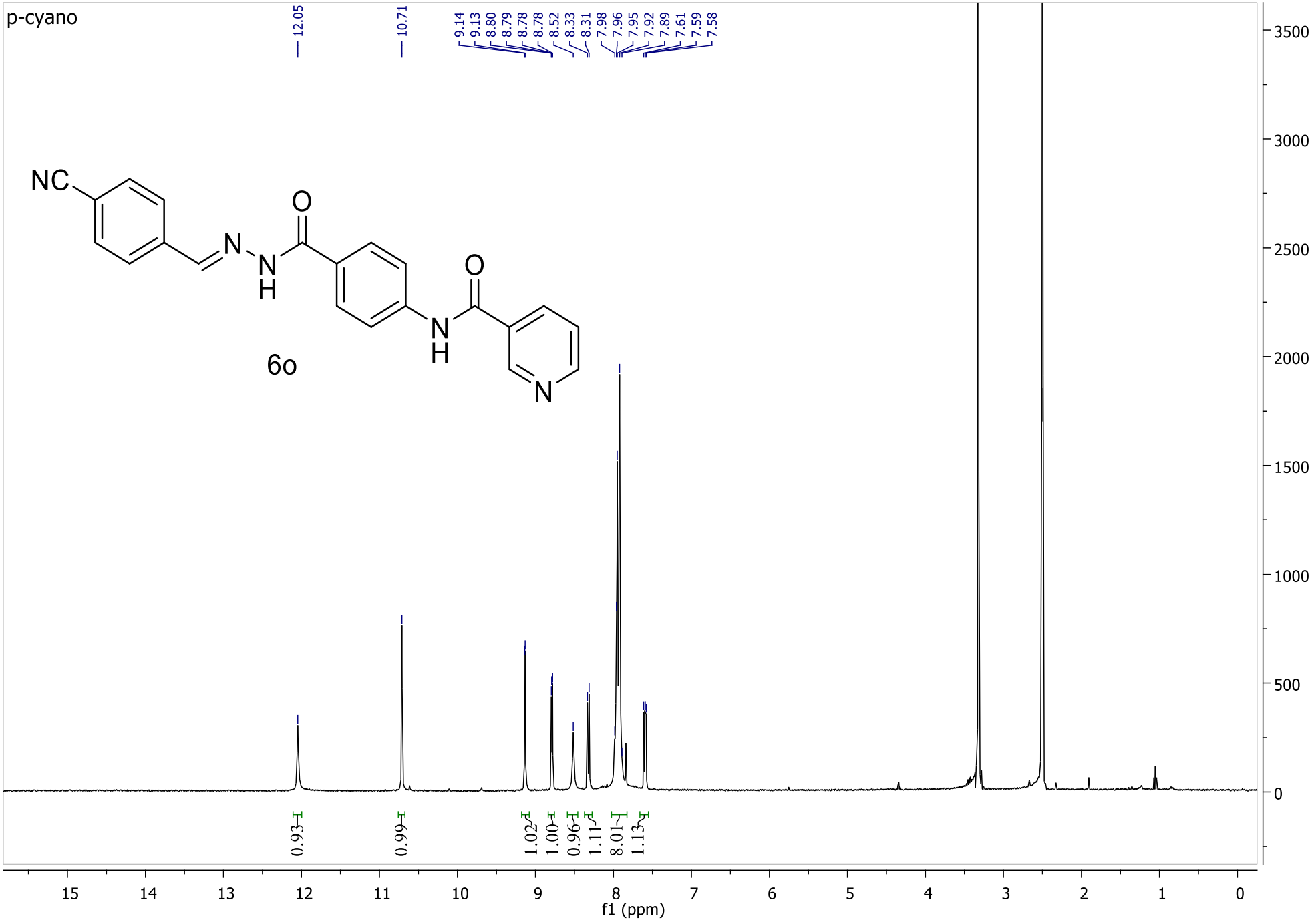

p-(N,N-dimethylamino)
164.37
162.03
152.30
151.48
148.74
148.32
141.70
135.55
130.35
128.84
128.38
128.31
123.53
121.67
119.54
111.82
39.77
6l
f1 (ppm)

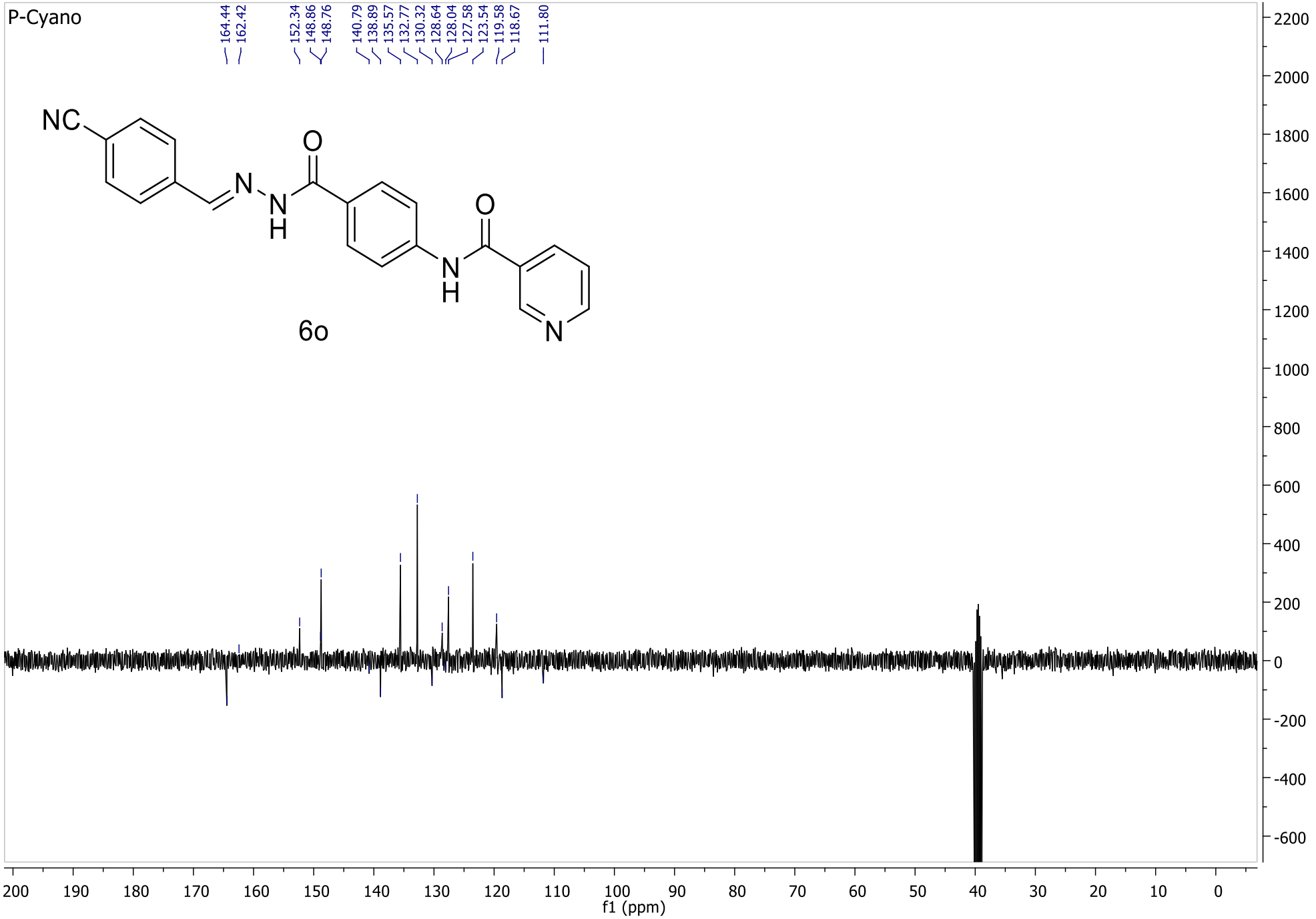

3-nitro-4-methoxy
11.92
10.70
9.14
9.13
8.79
8.79
8.78
8.78
8.45
8.33
8.31
8.22
8.04
8.02
7.97
7.95
7.94
7.92
7.61
7.60
7.59
7.58
7.49
7.46
3.99
NO2
O
N
N
H
O
O
N
H
N
6m
1.04
1.07
1.07
1.00
0.87
1.09
0.85
0.95
3.87
1.05
0.95
3.15
f1 (ppm)

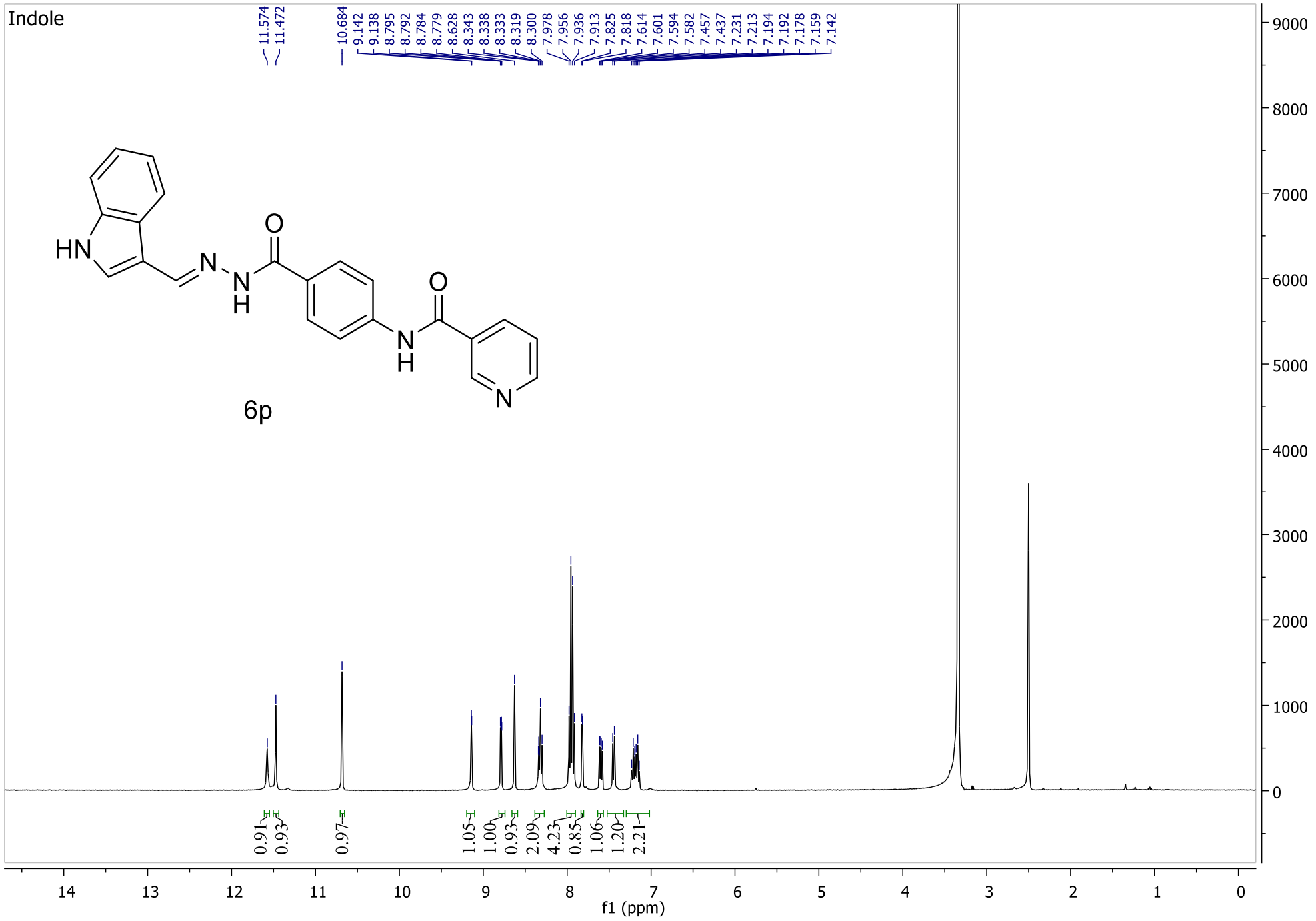

3-nitro-4-methoxy
164.42
162.55
152.96
152.34
148.76
145.01
142.06
139.46
135.58
132.53
130.33
128.55
128.27
127.12
123.54
123.18
119.58
114.87
56.99
NO2
O
N
N
H
O
O
N
H
N
6m
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

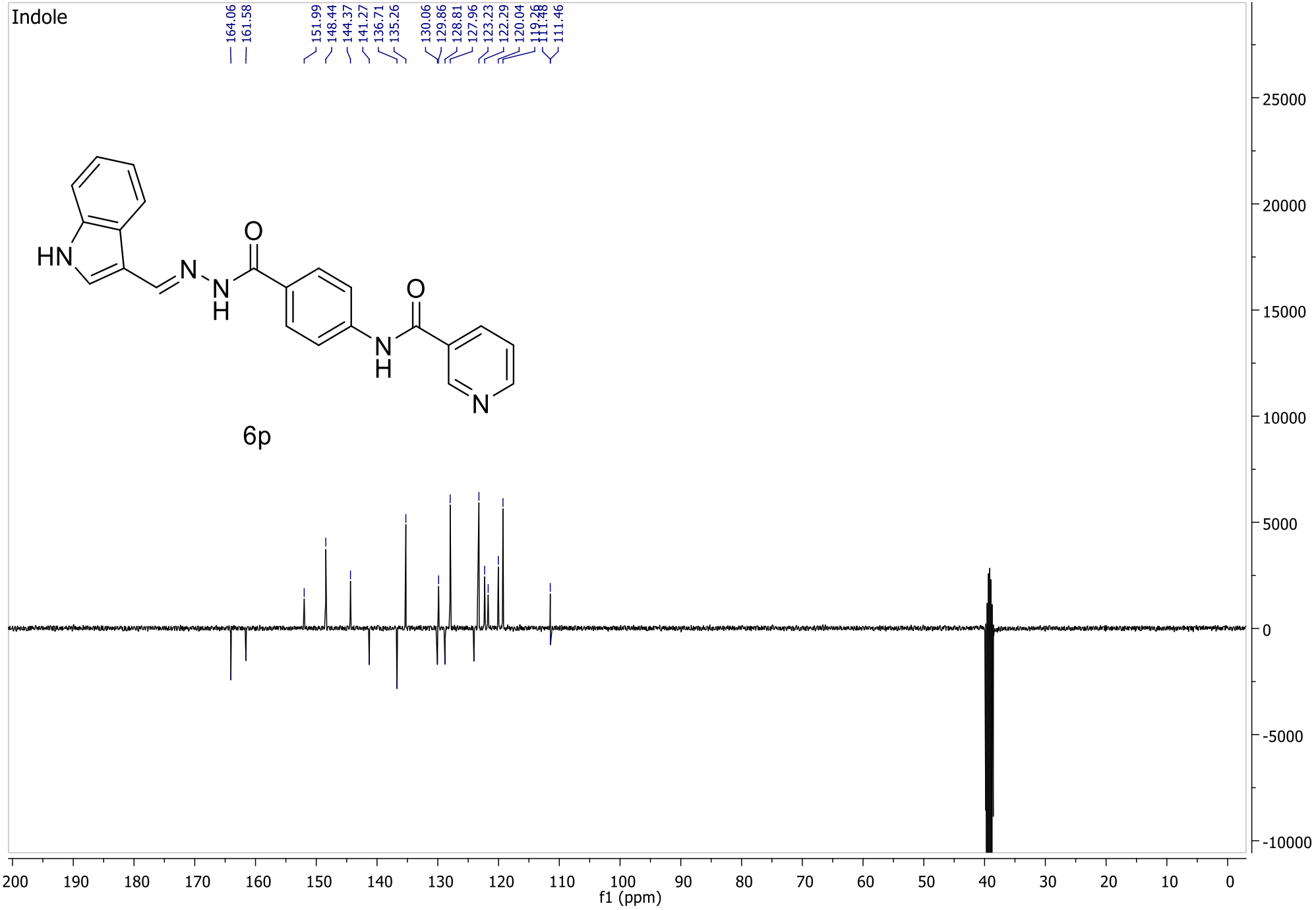

2-hydroxy-3-methoxy
12.04
11.04
10.72
9.14
8.79
8.78
8.66
8.33
8.31
8.00
7.97
7.96
7.93
7.61
7.60
7.59
7.58
7.16
7.14
7.05
7.03
6.89
6.87
6.85
3.82
O
OH
N
N
H
O
N
H
O
N
6n
1.04
0.99
1.06
1.06
1.00
1.00
1.10
4.21
1.08
0.85
1.29
1.08
3.26
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13.5
12.5
11.5
10.5
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)

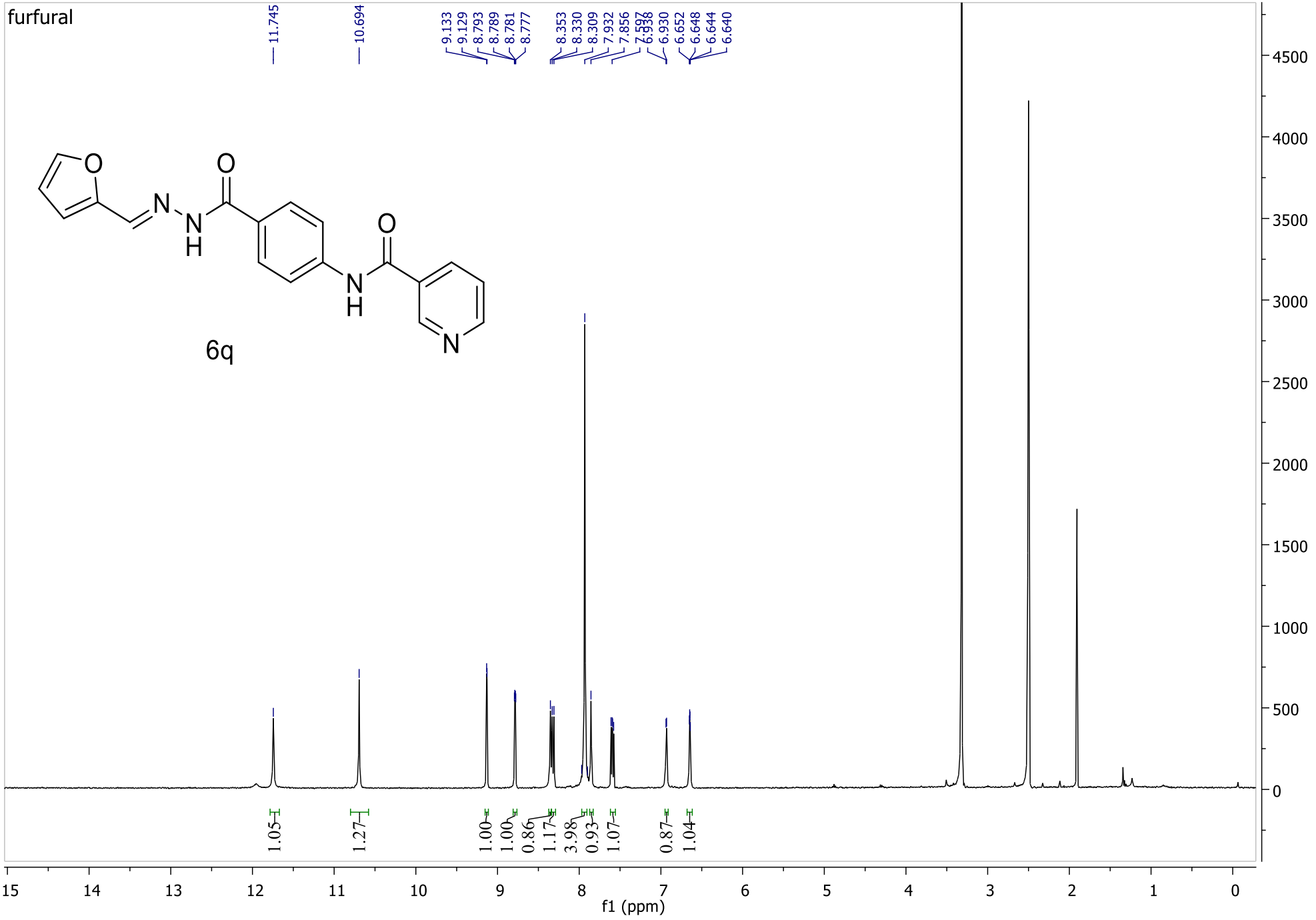

2-OH-3-OCH3
164.45
162.18
152.35
148.77
147.95
147.94
147.18
142.19
135.59
130.34
128.55
127.82
123.56
120.88
119.63
119.02
118.94
113.80
55.83
O
OH
O
N
N
H
O
N
H
N
6n
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


p-cyano
12.05
10.71
9.14
9.13
8.80
8.79
8.78
8.78
8.52
8.33
8.31
7.98
7.96
7.95
7.92
7.89
7.61
7.59
7.58
NC
O
N
N
H
O
N
H
N
6o
0.93
0.99
1.02
1.00
0.96
1.11
8.01
1.13
3500
3000
2500
2000
1500
1000
500
0
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


P-Cyano
164.44
162.42
152.34
148.86
148.76
140.79
138.89
135.57
132.77
130.32
128.64
128.04
127.58
123.54
119.58
118.67
111.80
NC
N
N
H
O
O
N
H
N
6o
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Indole
11.574
11.472
10.684
9.142
9.138
8.795
8.792
8.784
8.779
8.628
8.343
8.338
8.333
8.319
8.300
7.978
7.956
7.936
7.913
7.825
7.818
7.614
7.601
7.594
7.582
7.457
7.437
7.231
7.213
7.194
7.192
7.178
7.159
7.142
HN
N
N
H
O
O
N
H
N
6p
0.91
0.93
0.97
1.05
1.00
0.93
2.09
4.23
0.85
1.06
1.20
2.21
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

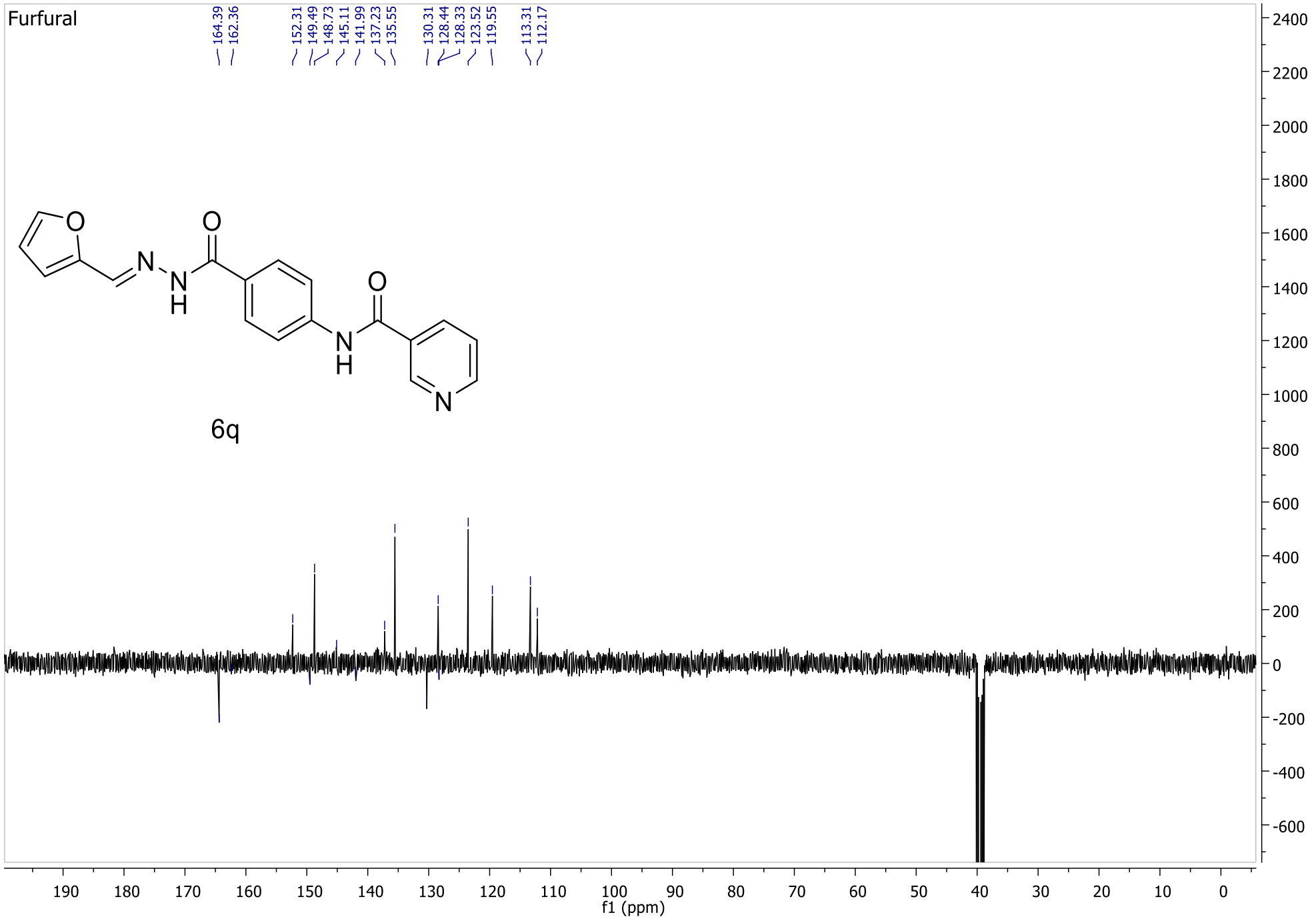

Indole
164.06
161.58
151.99
148.44
144.37
141.27
136.71
135.26
130.06
129.86
128.81
127.96
123.23
122.29
120.04
111.46
HN
N
N
H
O
O
N
H
N
6p
25000
20000
15000
10000
5000
0
-5000
-10000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

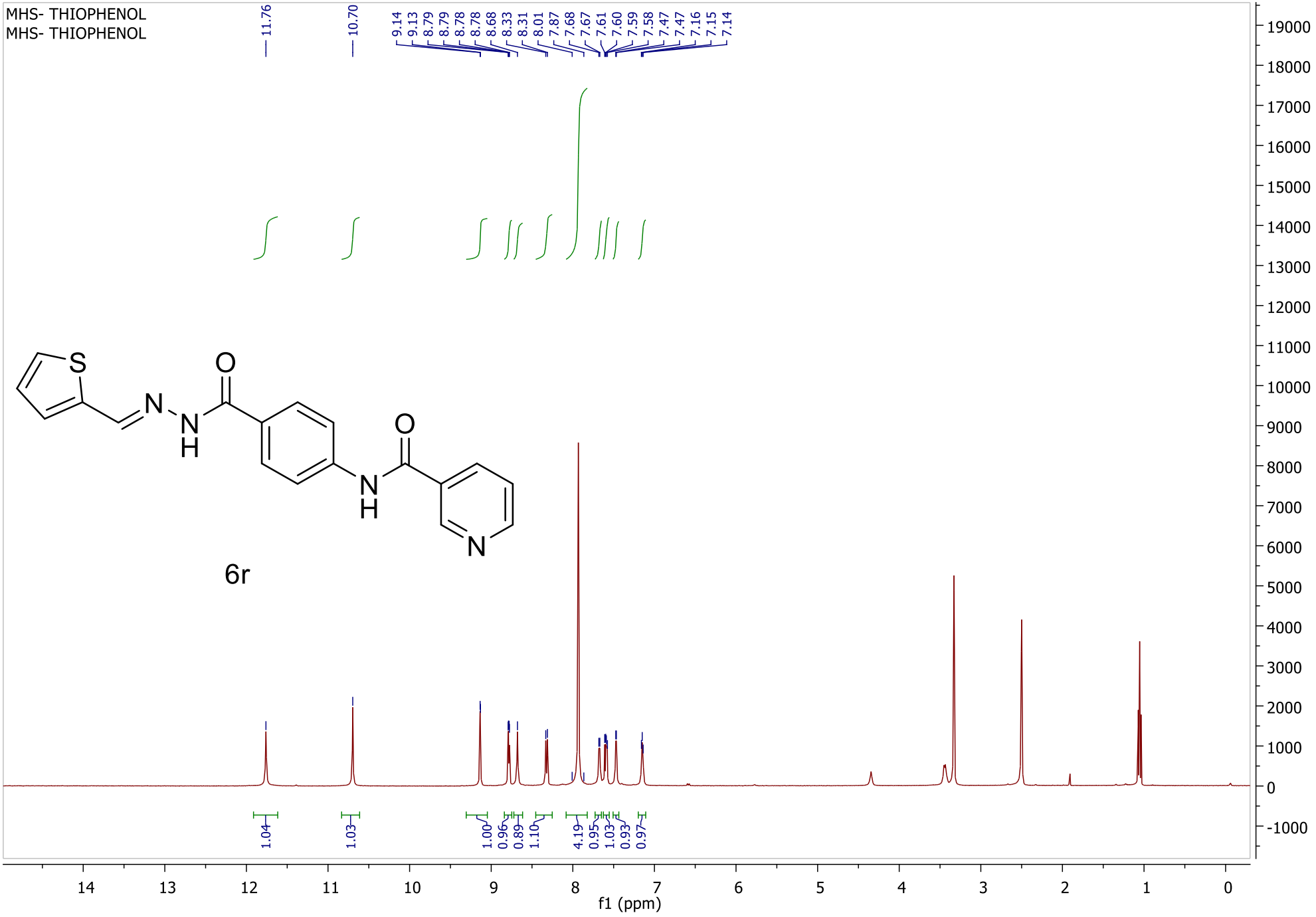

furfural
11.745
10.694
9.133
9.129
8.793
8.789
8.781
8.777
8.353
8.330
8.309
7.932
7.856
7.597
7.593
6.930
6.652
6.648
6.644
6.640
6q
1.05
1.27
1.00
1.00
0.86
1.17
3.98
0.93
1.07
0.87
1.04
f1 (ppm)

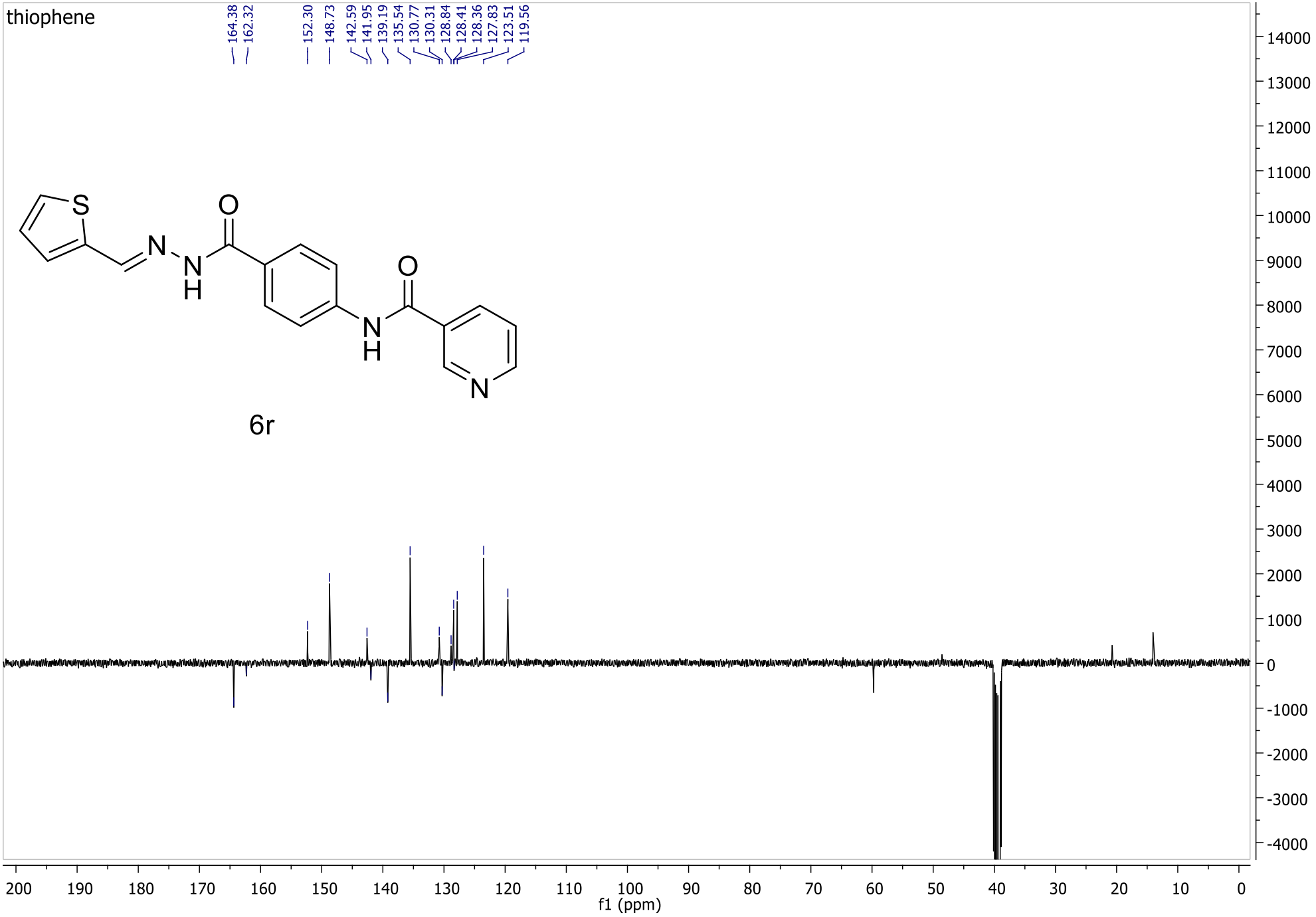
Furfural

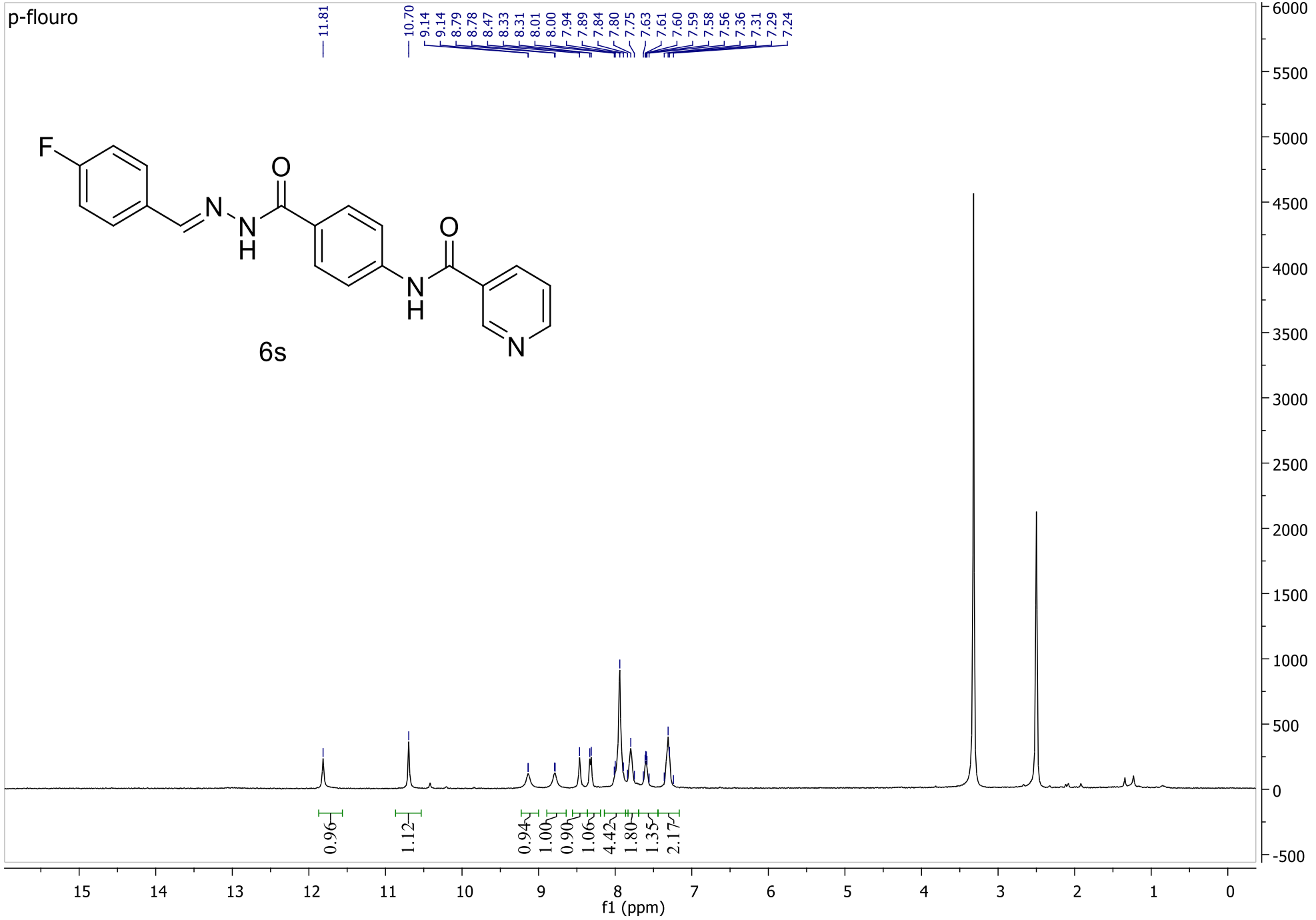
O
O
N
N
H
O
N
H
N

6q


164.39
162.36
152.31
149.49
148.73
145.11
141.99
137.23
135.55
130.31
128.44
128.33
123.52
119.55
113.31
112.17
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
-400
-600
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MHS- THIOPHENOL
MHS- THIOPHENOL
11.76
10.70
9.14
9.13
8.79
8.79
8.78
8.78
8.68
8.33
8.31
8.01
7.87
7.68
7.67
7.61
7.60
7.59
7.58
7.47
7.47
7.16
7.15
7.14
S
N
N
H
O
O
N
H
N
6r
1.04
1.03
1.00
0.96
0.89
1.10
4.19
0.95
1.03
0.93
0.97
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


thiophene
164.38
162.32
152.30
148.73
142.59
141.95
139.19
135.54
130.77
130.31
128.84
128.41
128.36
127.83
123.51
119.56
S
N
N
H
O
O
N
H
N
6r
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
-4000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


p-flouro
11.81
10.70
9.14
9.14
8.79
8.78
8.47
8.33
8.31
8.01
8.00
7.94
7.89
7.84
7.80
7.75
7.63
7.61
7.60
7.59
7.58
7.56
7.36
7.31
7.29
7.24
F
O
N
N
H
O
N
H
N
6s
0.96
1.12
0.94
1.00
0.90
1.06
4.42
1.80
1.35
2.17
f1 (ppm)

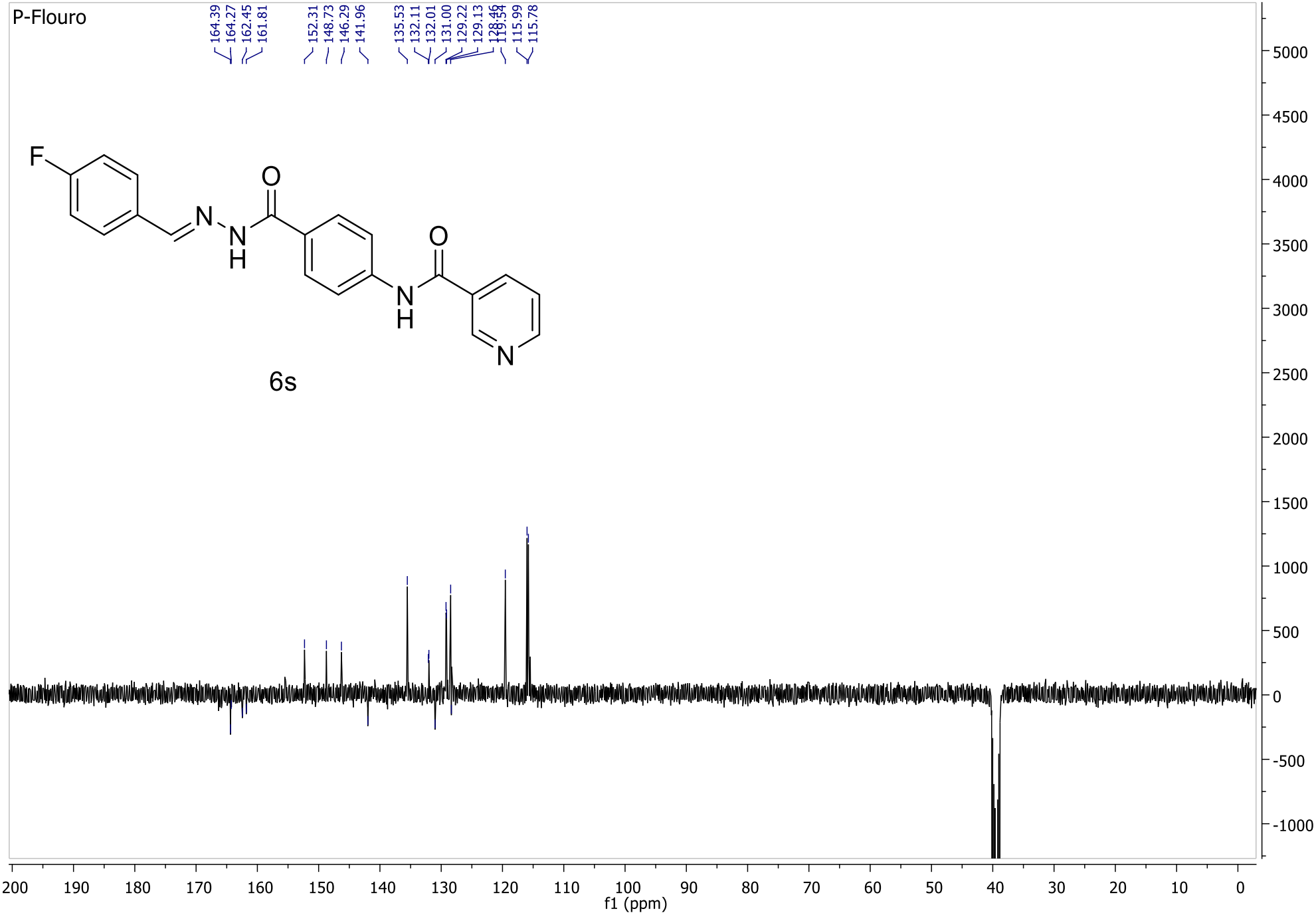

P-Flouro
164.39
164.27
162.45
161.81
152.31
148.73
146.29
141.96
135.53
132.11
132.01
131.00
129.22
129.13
128.46
119.54
115.99
115.78
F
O
N
N
H
O
N
H
N
6s
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
-1000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Table 1: Data from Molinspiration server illustrate lipinisk's rules of fives:

Code	Log p	M.WT	nON HBA	nOHNH HBD	LIPINSK'S VIOLATION	TPSA	%ABS	VOLUMES	NROTB
6a	2.75	344.37	6	2	0	83.45	80.21	308.74	5
6b	3.20	358.40	6	2	0	83.45	80.21	325.30	5
6c	2.66	389.37	9	2	0	129.28	64.40	332.07	6
6d	3.56	423.27	6	2	0	83.45	80.21	326.62	5
6e	3.43	378.82	6	2	0	83.45	80.21	322.27	5
6f	3.19	390.47	6	2	0	83.45	80.21	343.43	6
6g	2.81	374.40	7	2	0	92.69	77.02	334.28	6
6h	2.38	434.45	9	2	0	111.15	70.65	385.37	8
6i	2.25	360.37	7	3	0	103.68	73.23	316.75	5
6j	2.09	390.40	8	3	0	112.91	70.05	342.30	6
6k	2.79	404.43	8	2	0	101.92	73.84	359.83	7
6l	2.85	387.44	7	2	0	86.69	79.09	354.64	6
6m	2.70	419.40	10	2	0	138.51	61.21	357.62	7
6n	2.30	390.40	8	3	0	112.91	70.05	342.30	6
6o	2.51	369.38	7	2	0	107.24	72.00	325.60	5
6p	2.90	383.41	7	3	0	99.24	74.76	337.71	5
6q	2.01	334.33	7	2	0	96.59	75.68	290.30	5
6r	2.65	350.40	6	2	0	83.45	80.21	299.45	5
6s	2.92	362.36	6	2	0	83.45	80.21	313.67	5

Note. MWt = molecular weight; LogP = octanol/water partition coefficient; nOHNH = number of hydrogen bond donors; nON = number of hydrogen bond acceptors; nRotB = number of rotatable bonds; tPSA, topological polar surface area.
According to Lipinski's rule of five, compound is more likely to be easily absorbed if log P <5, M.WT <500, nON HBA <10, nOHNH HBD <5 and NROTB <10.
The bioavailability is acceptable for a drug with a TPSA value below 140‑150 $Å^2$ and NROTB less than or equal to 10.

The values of TPSA are used to calculate the percentage of oral absorption %ABS using the following equation:

%ABS= 109 - 0.345 TPSA

Table 2: Data from Molsoft software represent drug-likeness score and solubility

code	S (mg/kg) (drug H_2O solubility)	Drug-likeness model score
6a	4.82	0.91
6b	1.76	0.88
6c	3.38	-0.11
6d	0.42	1.03
6e	0.58	1.37
6f	0.52	0.85
6g	2.88	0.84
6h	9.02	1.03
6i	7.53	1.35
6j	6.47	0.78
6k	5.01	0.94
6l	2.54	0.63
6m	1.00	-0.14
6n	13.84	1.06
6o	1.32	0.71
6p	0.66	0.24
6q	34.90	1.15
6r	10.79	1.25
6s	1.54	1.20

Table 3: Results from Pre-ADMET software demonstrate the cell permeability and absorption bioavailability:

code	Caco2	MDCK	HIA	BBB	PPB
6a	21.49	21.30	94.32	0.03	98.24
6b	21.62	3.15	94.47	0.04	97.73
6c	20.96	19.65	92.52	0.06	97.07
6d	21.21	0.055	95.55	0.06	96.01
6e	20.95	2.38	95.06	0.05	92.67
6f	21.62	2.95	95.16	0.02	91.86
6g	21.97	12.44	94.47	0.02	93.45
6h	25.11	3.65	95.17	0.03	86.19
6i	21.13	25.16	91.46	0.05	91.98
6j	21.08	8.96	91.61	0.04	87.72
6k	23.40	15.20	94.77	0.02	90.75
6l	22.74	2.45	94.71	0.03	94.88
6m	19.15	7.19	91.05	0.05	97.07
6n	21.03	11.25	91.60	0.03	85.86
6o	21.14	14.38	94.96	0.01	98.43
6p	21.25	2.60	92.66	0.04	82.10
6q	21.10	17.28	94.14	0.01	90.84
6r	4.29	20.03	95.17	0.01	89.92
6s	21.44	8.78	94.33	0.03	92.71