Facile synthesis and *in vitro* activity of N-substituted 1,2-benzisothiazol-3(2*H*)-ones against Dengue virus NS2BNS3 protease

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Supporting information

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Viability test for the compounds on Vero cells

To exclude any toxic side effects of the used compounds, cell survival and metabolism were measured by MTS Cell Viability Assay (Promega). Vero cells ($2x10^4$) were incubated with 30µM of the compounds solubilised in DMEM or DMSO. Wells with either DMEM alone or DMSO served as controls. The MTS Cell Viability Assay was performed according to the manufacturer's instructions in triplicates. After 72h, the substrate was added and cells were incubated for one additional hour. Then the absorbance was measured at 490 nm. Changes in the absorbance were compared to the solvent control (Figure S1). All compounds showed no cytotoxicity at 30µM.

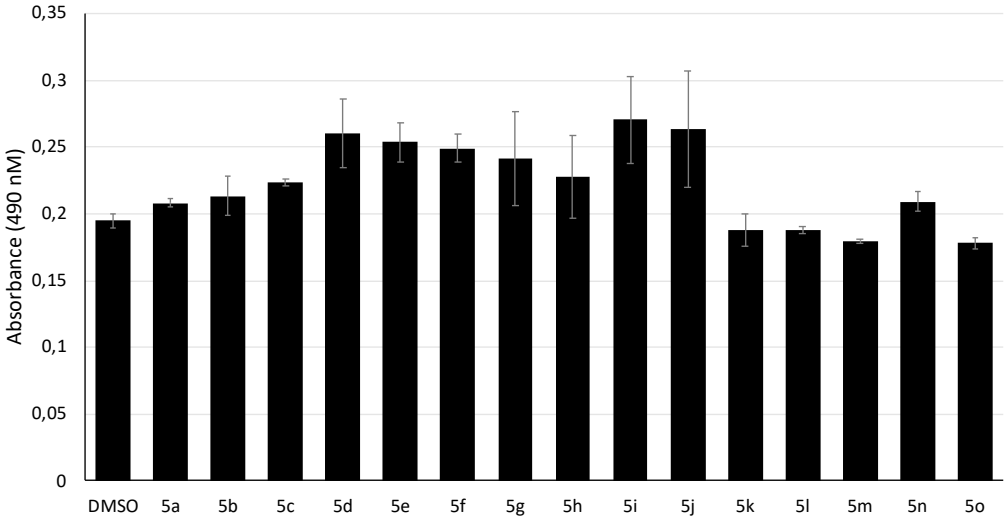
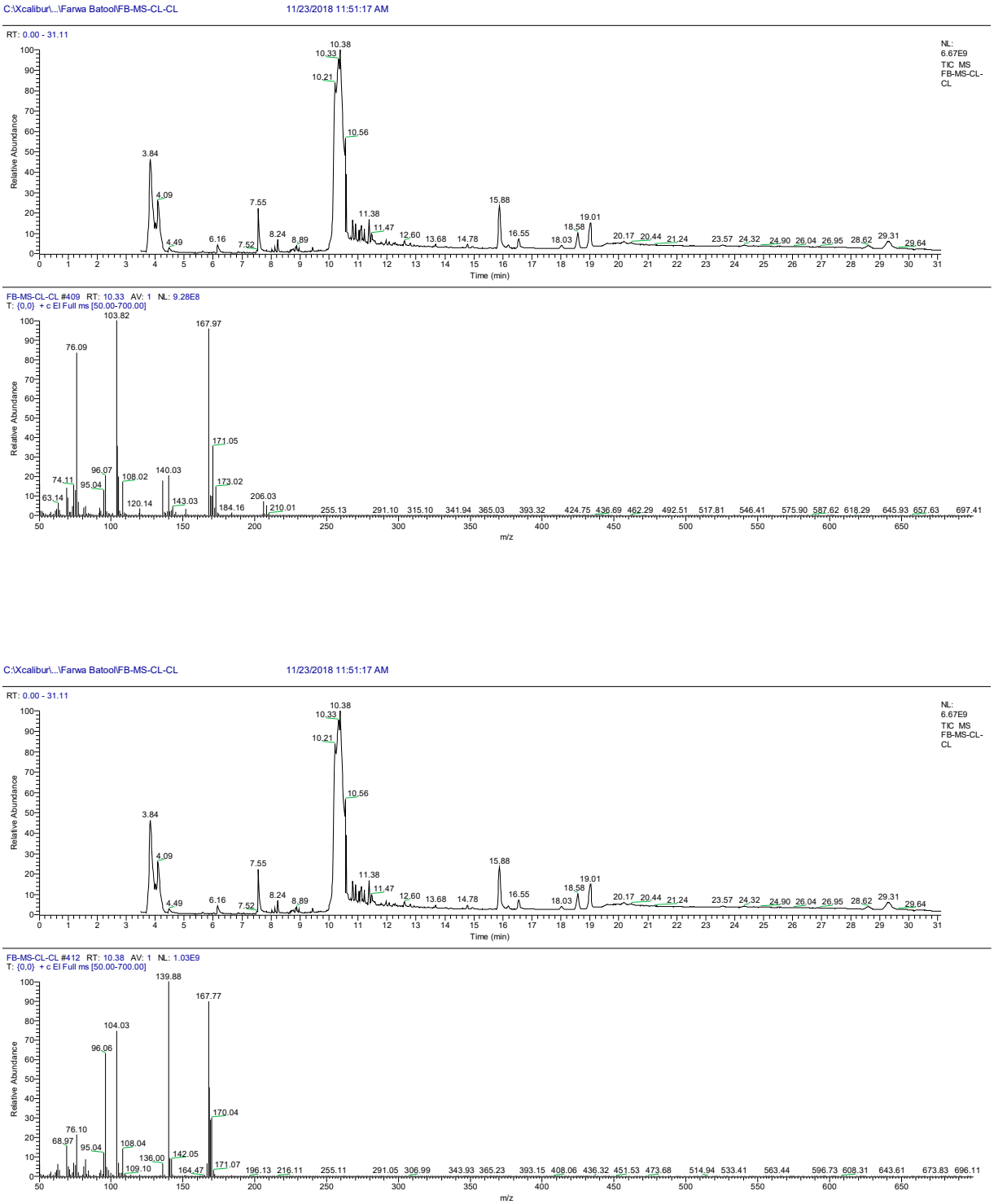


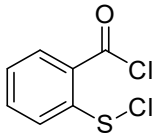
Figure S1: MTS viability assays with the compounds. Vero cells were incubated with the compounds at a concentration of 30µM for 72h. The MTS substrate was added and the cell were further incubated for 1 h. The absorbance was measured at 490nm.

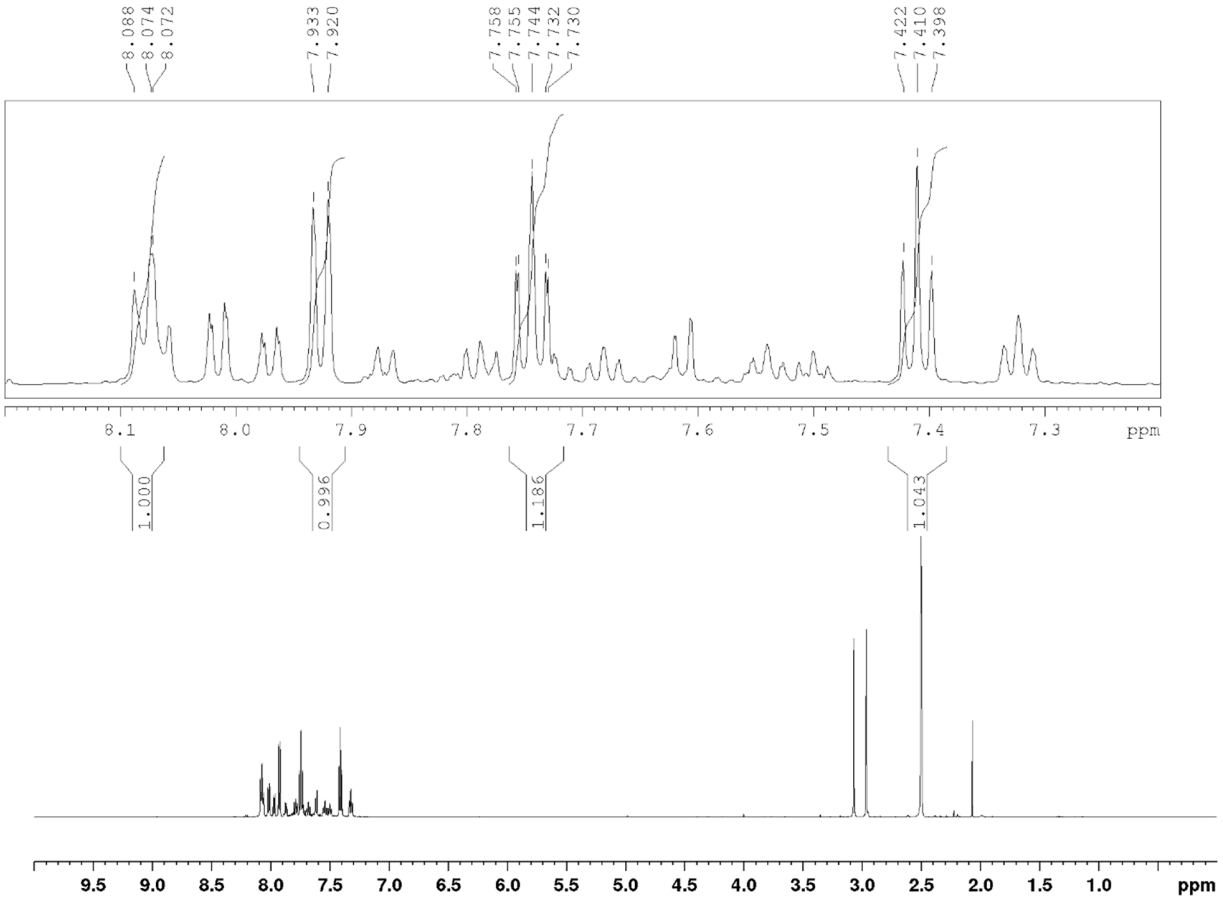
GC-MS of compounds **4** and **6**



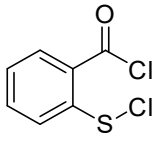
^{1}H & ^{13}C NMR Spectra of compounds **4** and **6**

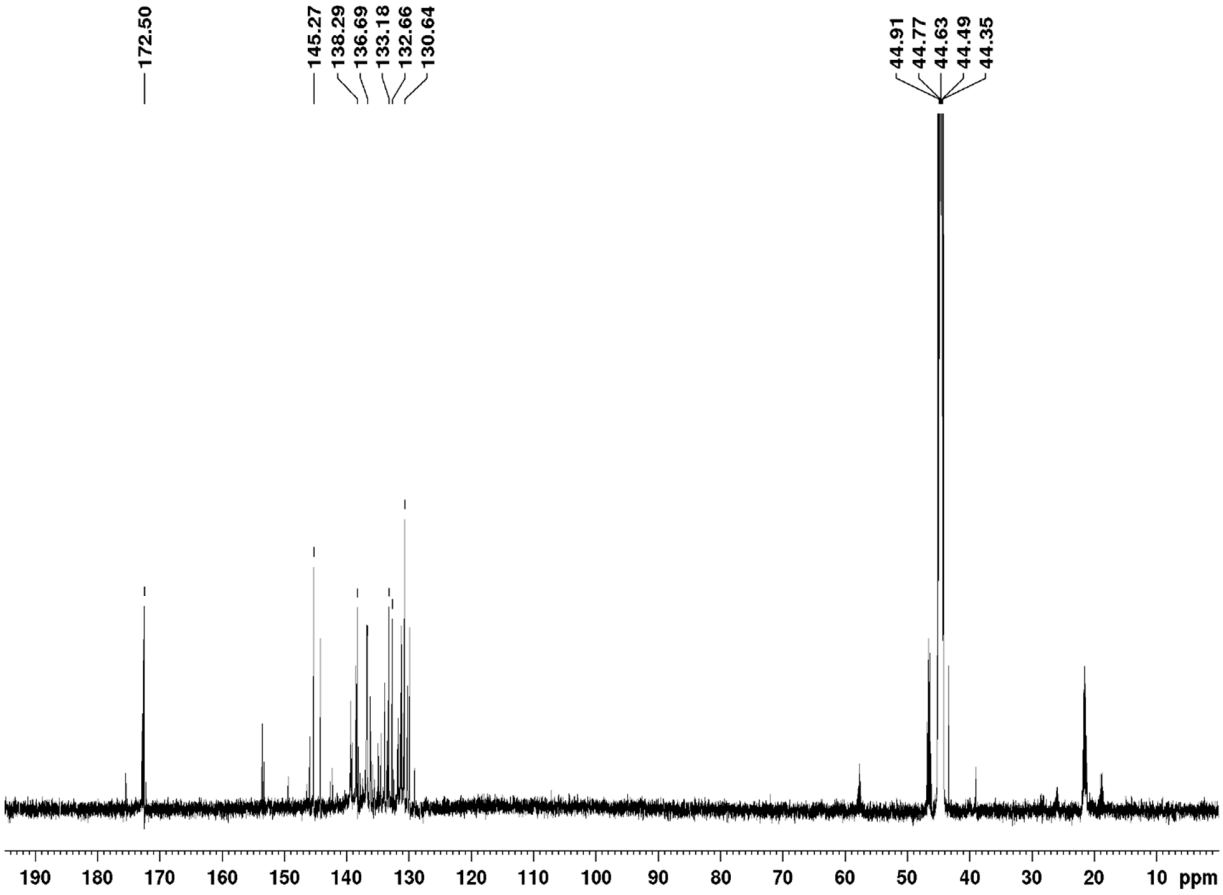
2-(Chlorosulfenyl)benzoyl chloride (4)



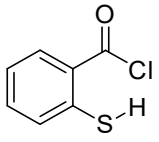


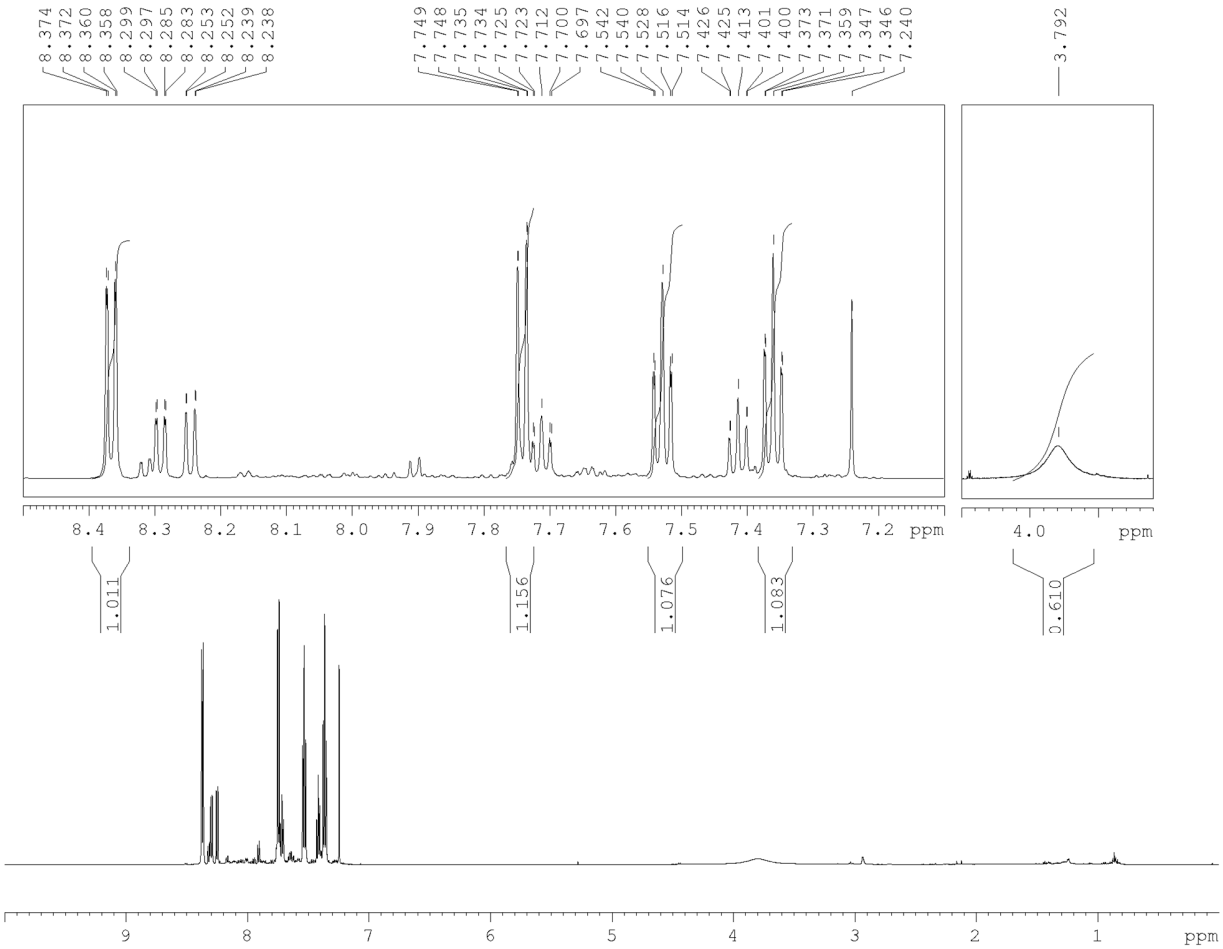
2-(Chlorosulfenyl)benzoyl chloride (4)





2-Mercaptobenzoyl chloride (6)





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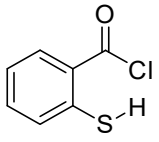
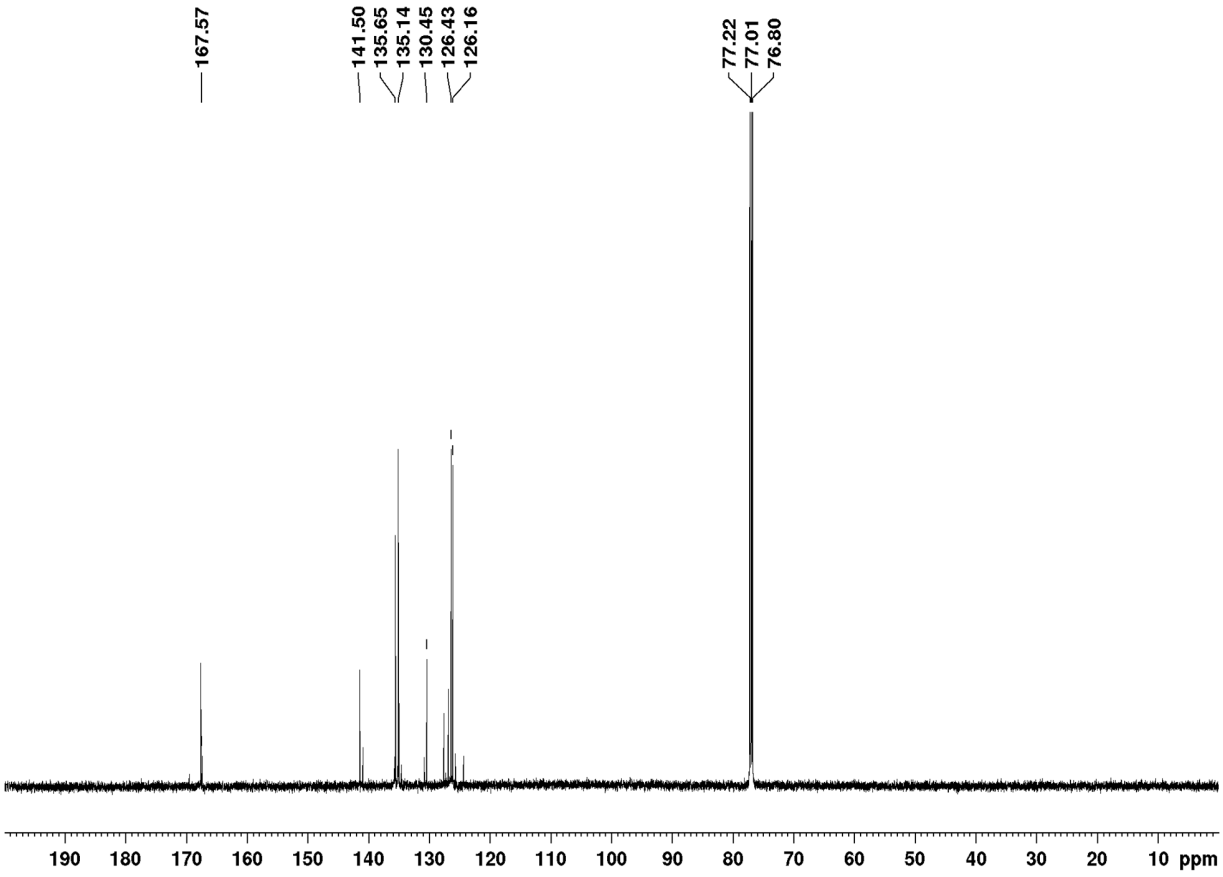
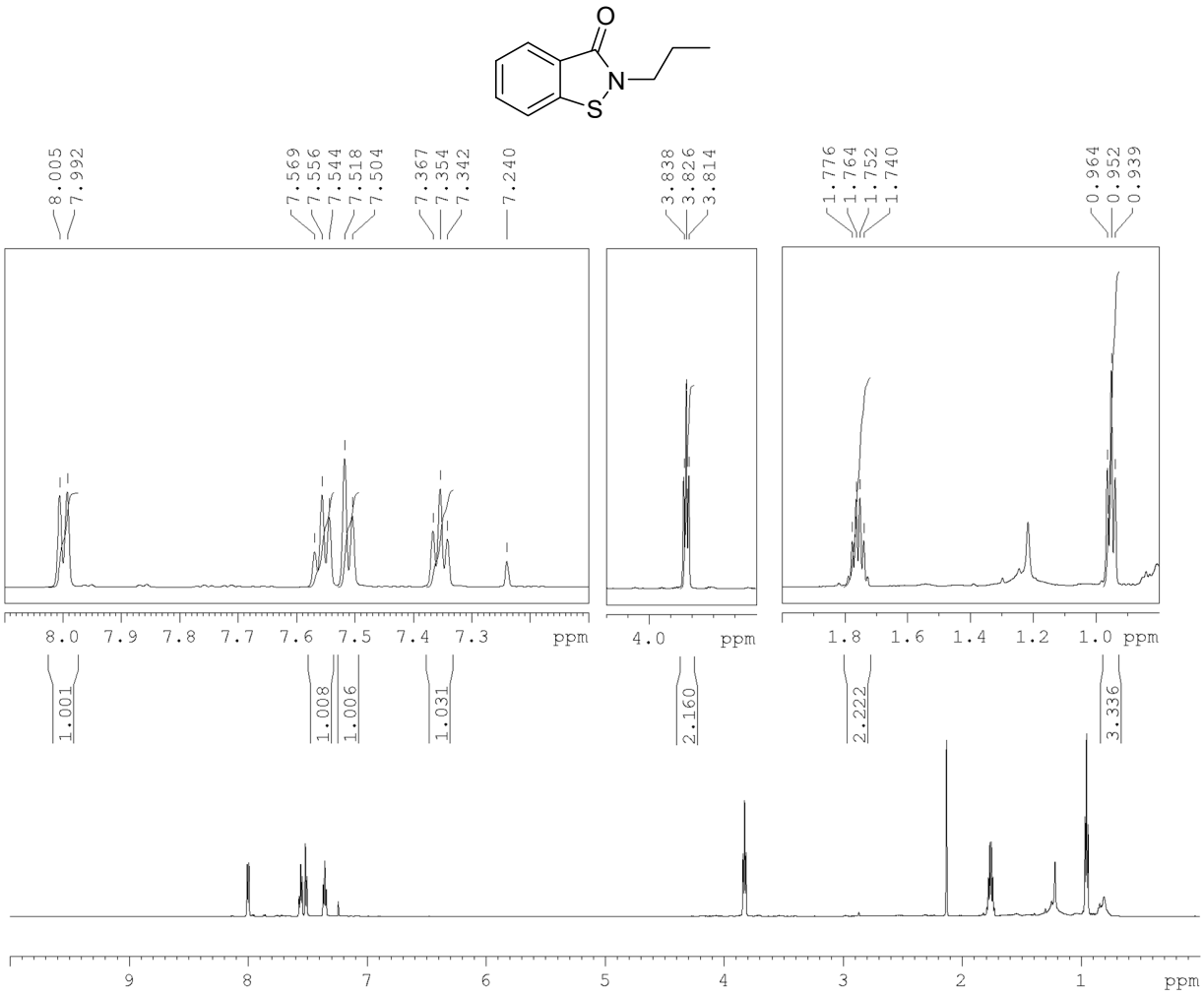
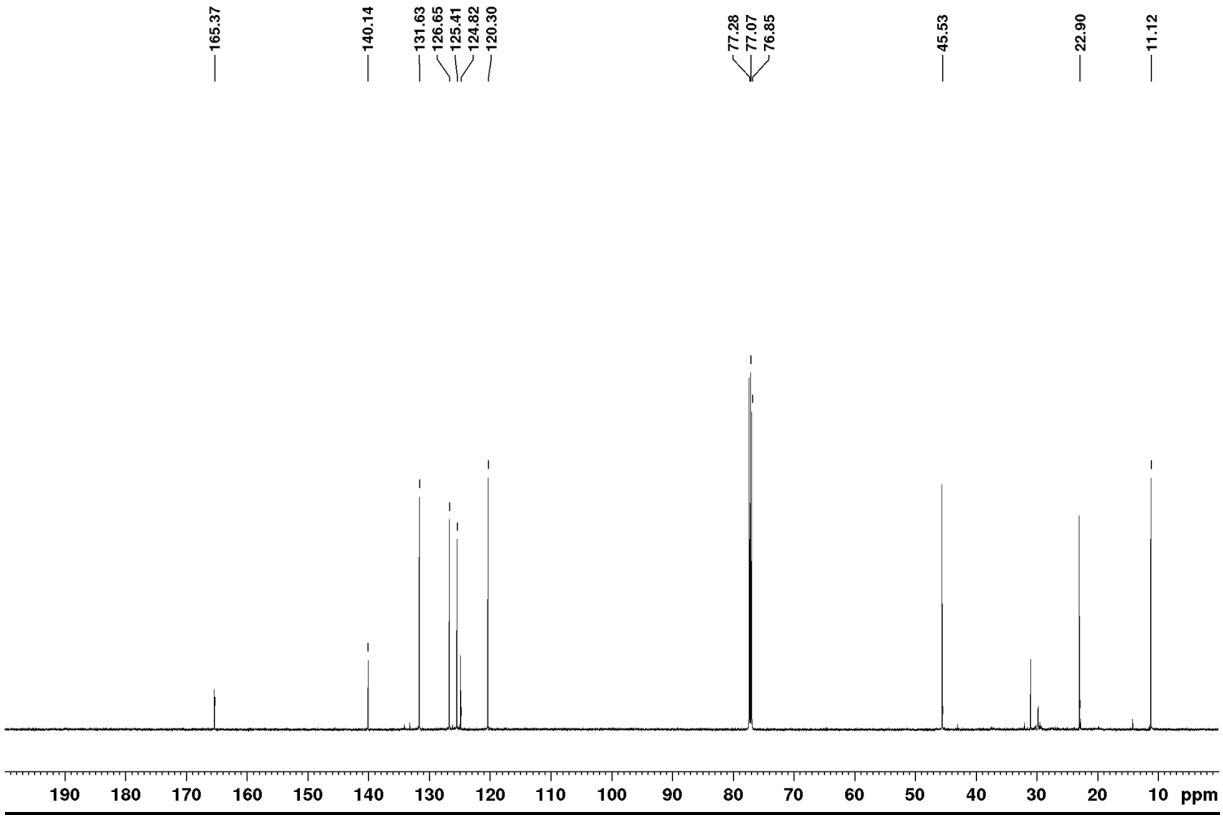




^{1}H & ^{13}C NMR Spectra of 1,2-benzisothiazol-3(2*H*)-ones

(5a)

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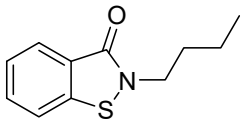
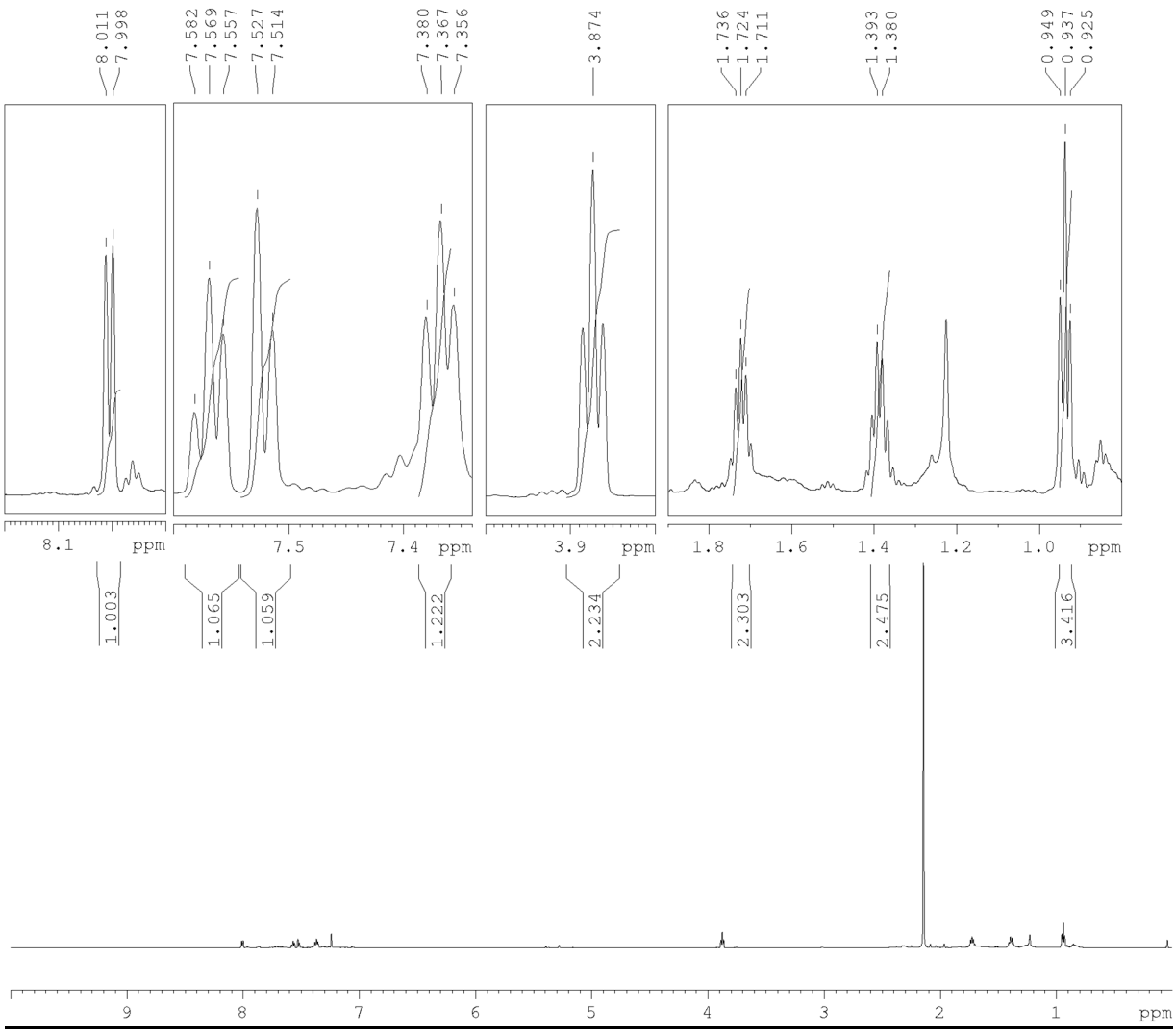
131.63
126.65
125.41
124.82
120.30
77.28
77.07
76.85
45.53
22.90
11.12
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(5b)


O
N
S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7.582
7.569
7.557
7.527
7.514
7.380
7.367
7.356
3.874
1.736
1.724
1.711
1.393
1.380
0.949
0.937
0.925
8.1
ppm
7.5
7.4
ppm
3.9
ppm
1.8
1.6
1.4
1.2
1.0
ppm
1.003
1.065
1.059
1.222
2.234
2.303
2.475
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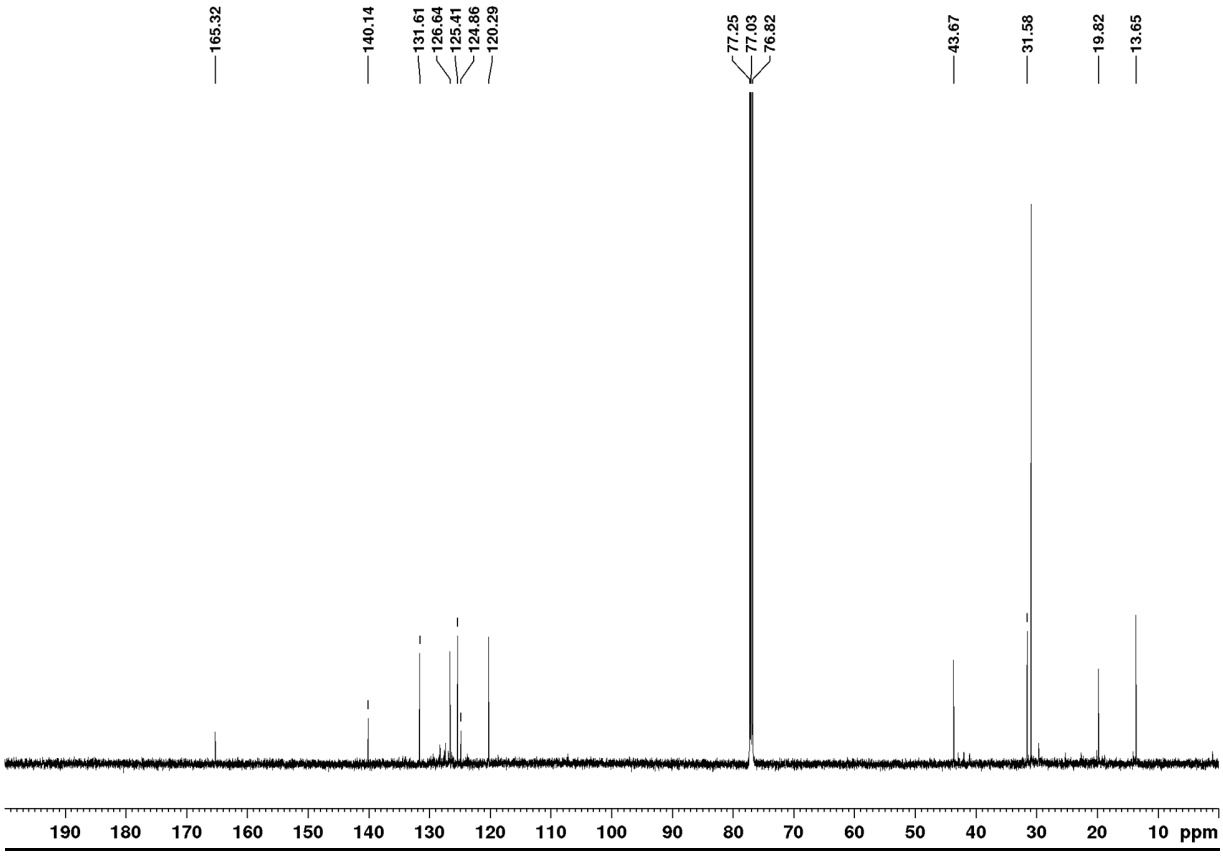
9
8
7
6
5
4
3
2
1
ppm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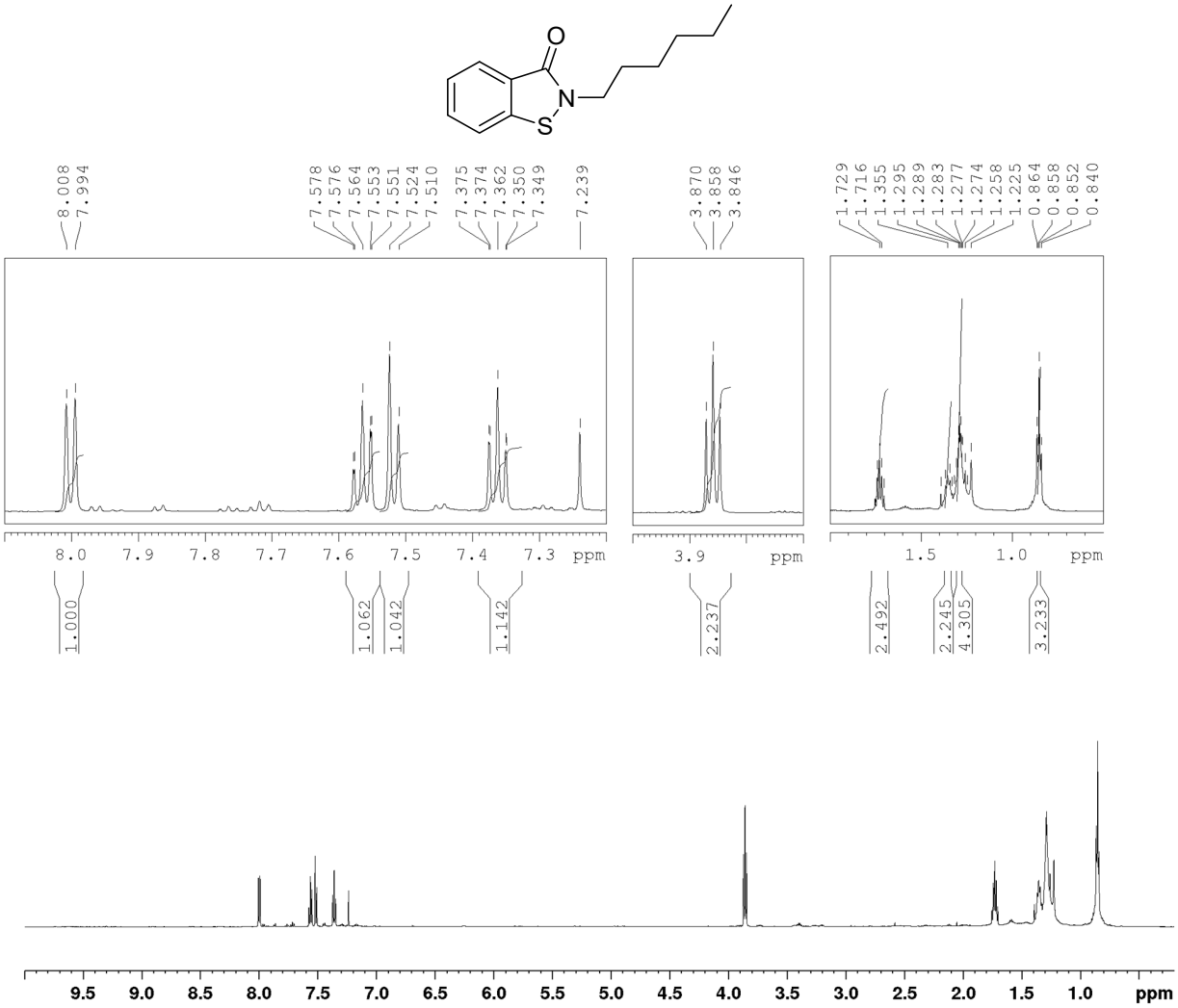
140.14
131.61
126.64
125.41
124.86
120.29
77.25
77.03
76.82
43.67
31.58
19.82
13.65
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(5c)


O
N
S
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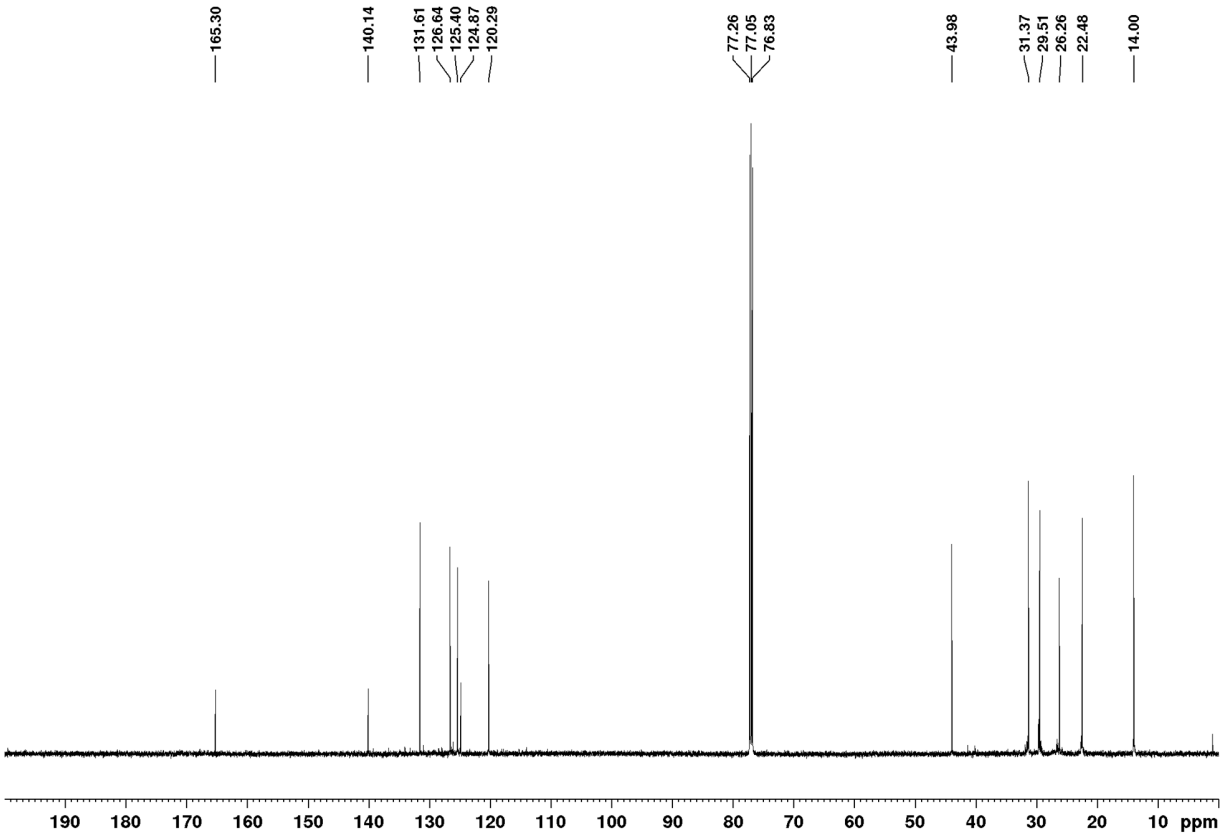
7.994
7.578
7.576
7.564
7.553
7.551
7.524
7.510
7.375
7.374
7.362
7.350
7.349
7.239
3.870
3.858
3.846
1.729
1.716
1.355
1.295
1.289
1.283
1.277
1.274
1.258
1.225
0.864
0.858
0.852
0.840
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
ppm
3.9
ppm
1.5
1.0
ppm
1.000
1.062
1.042
1.142
2.237
2.492
2.245
4.305
3.233
9.5
9.0
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
ppm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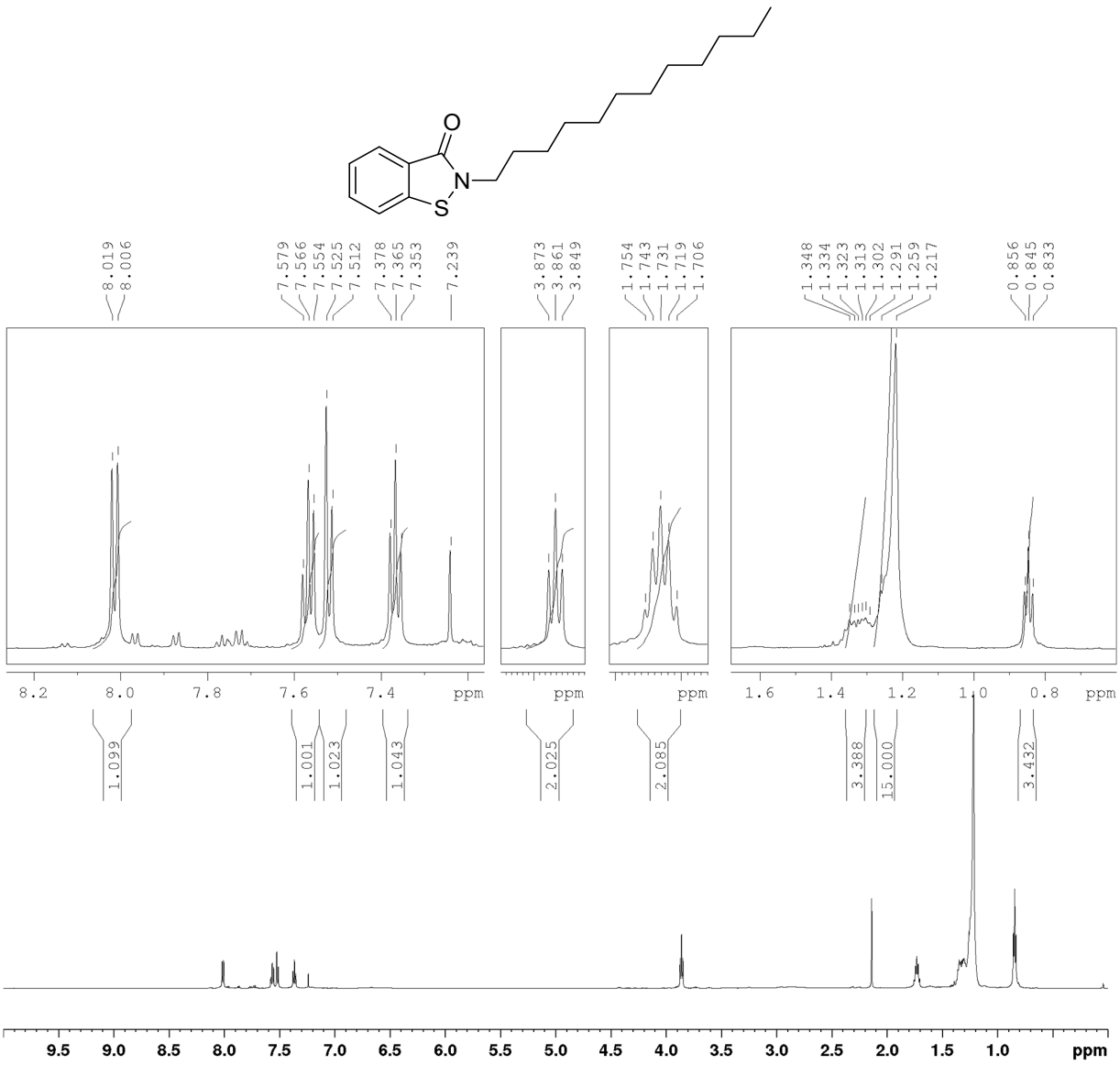
140.14
131.61
126.64
125.40
124.87
120.29
77.26
77.05
76.83
43.98
31.37
29.51
26.26
22.48
14.00
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(5d)


O
N
S
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8.006
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7.566
7.554
7.525
7.512
7.378
7.365
7.353
7.239
3.873
3.861
3.849
1.754
1.743
1.731
1.719
1.706
1.348
1.334
1.323
1.313
1.302
1.291
1.259
1.217
0.856
0.845
0.833
8.2
8.0
7.8
7.6
7.4
ppm
1.6
1.4
1.2
1.0
0.8
1.099
1.001
1.023
1.043
2.025
2.085
3.388
15.000
3.432
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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3.0
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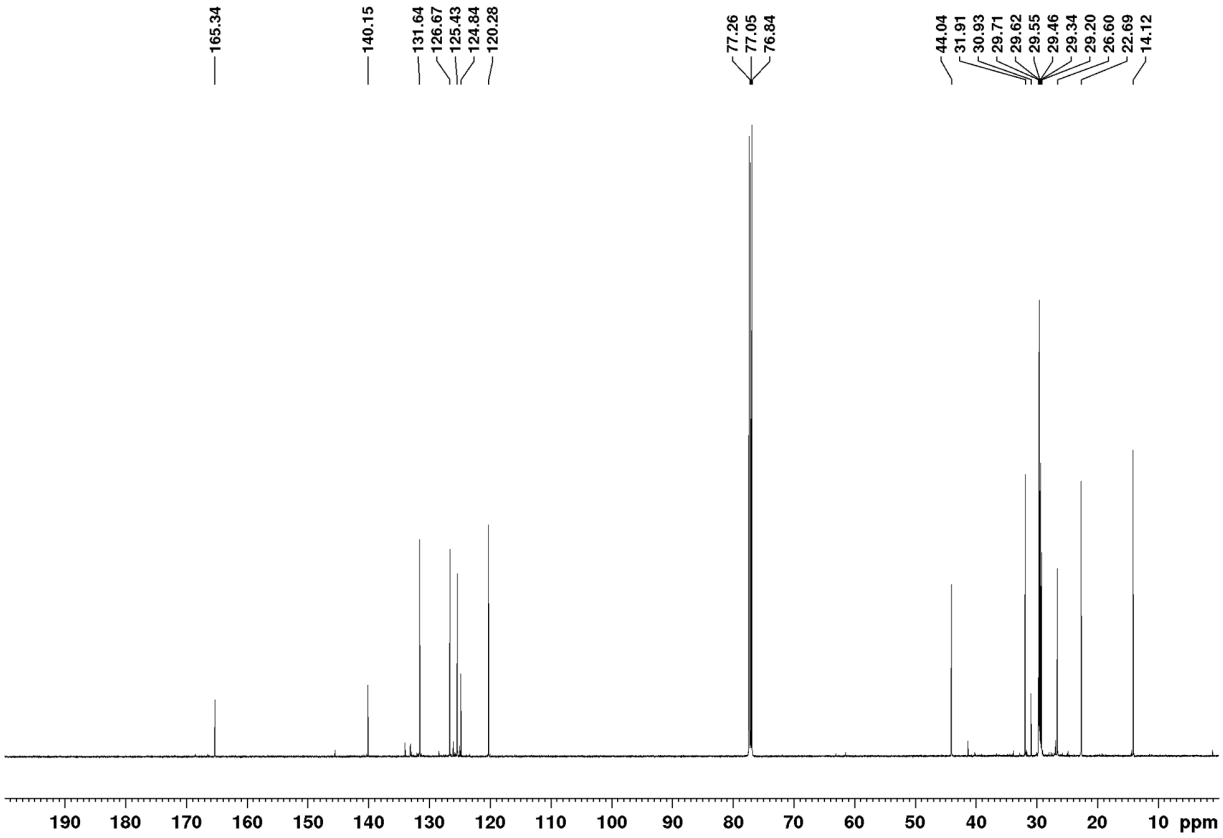
1.0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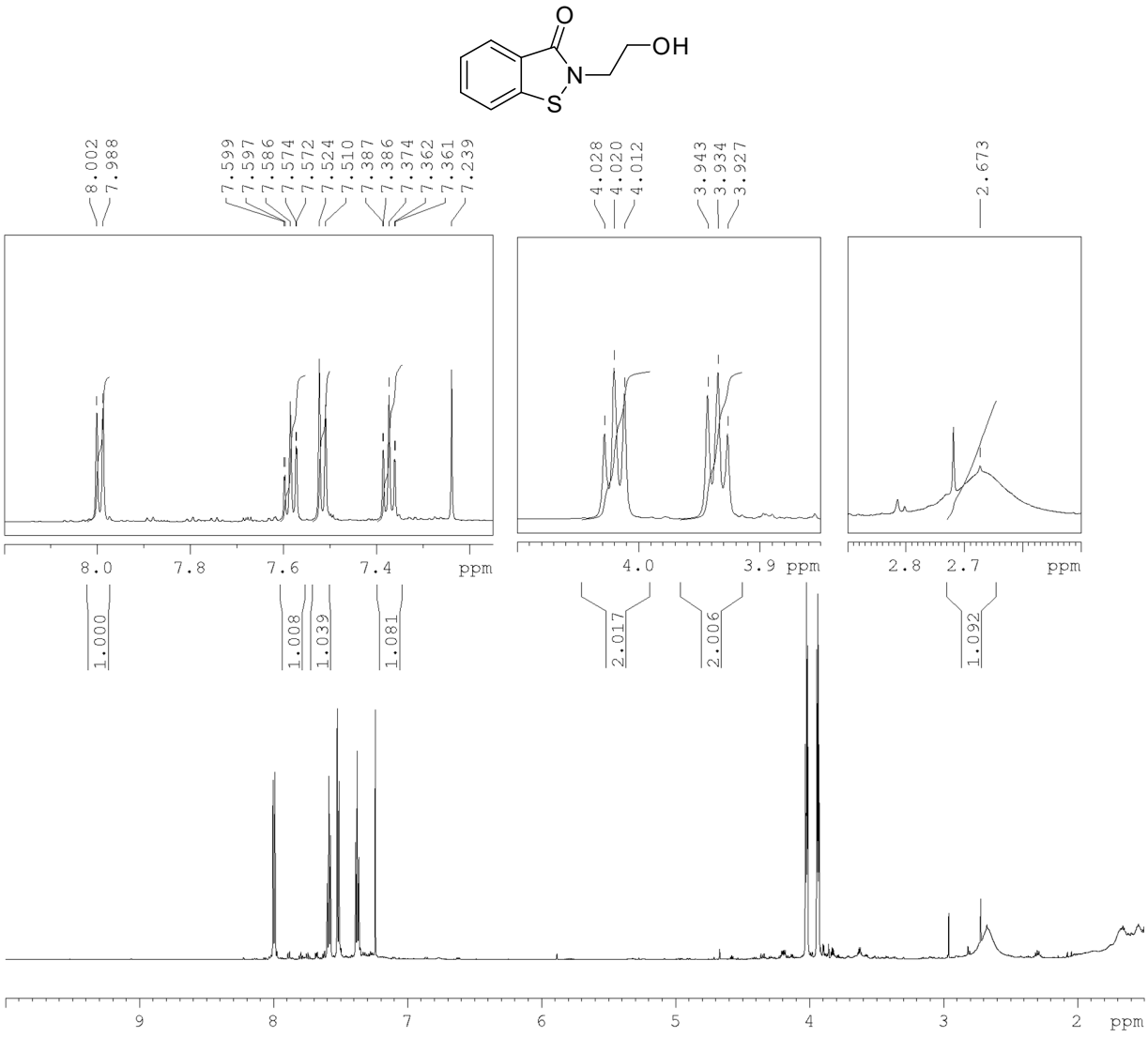
131.64
126.67
125.43
124.84
120.28
77.26
77.05
76.84
44.04
31.91
30.93
29.71
29.62
29.55
29.46
29.34
29.20
26.60
22.69
14.12
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(5e)


O
OH
N
S
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7.988
7.599
7.597
7.586
7.574
7.572
7.524
7.510
7.387
7.386
7.374
7.362
7.361
7.239
4.028
4.020
4.012
3.943
3.934
3.927
2.673
8.0
7.8
7.6
7.4
ppm
4.0
3.9 ppm
2.8
2.7
ppm
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1.081
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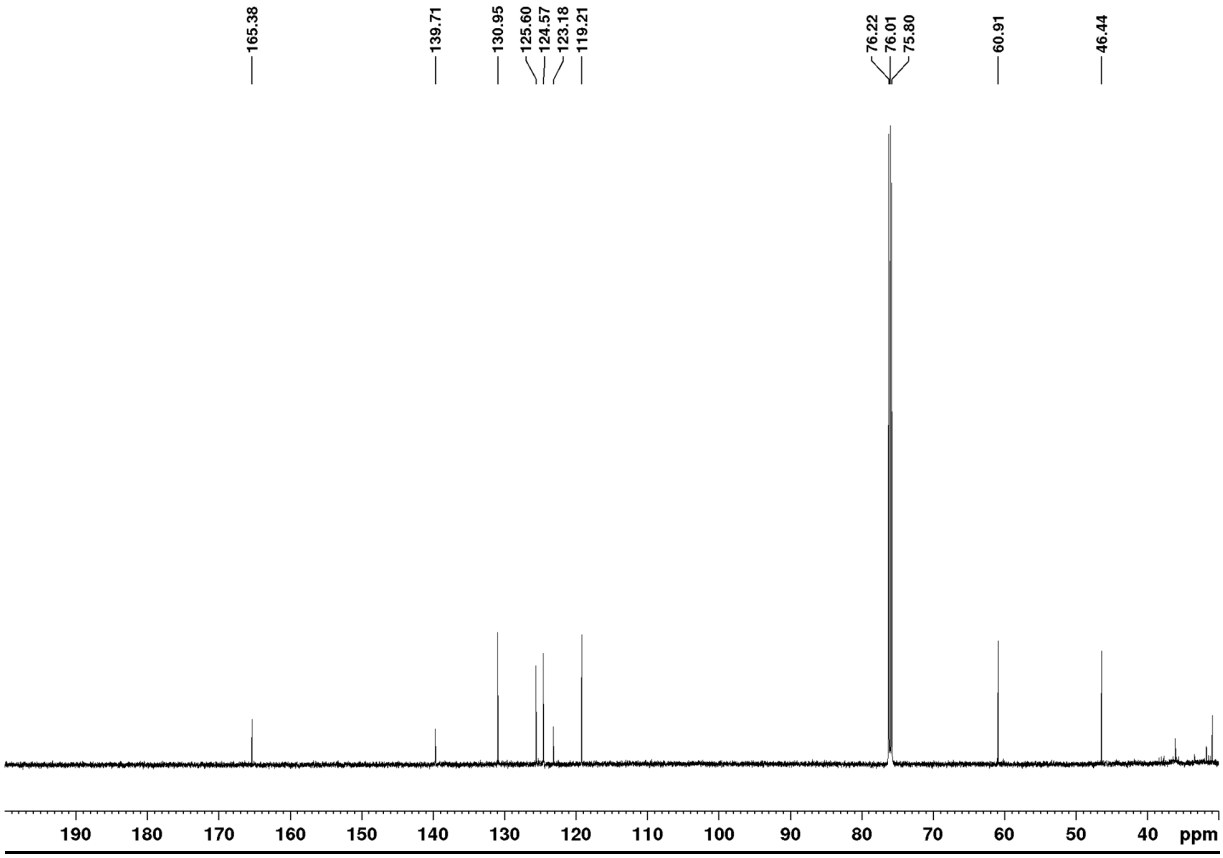
2.006
1.092
9
8
7
6
5
4
3
2
ppm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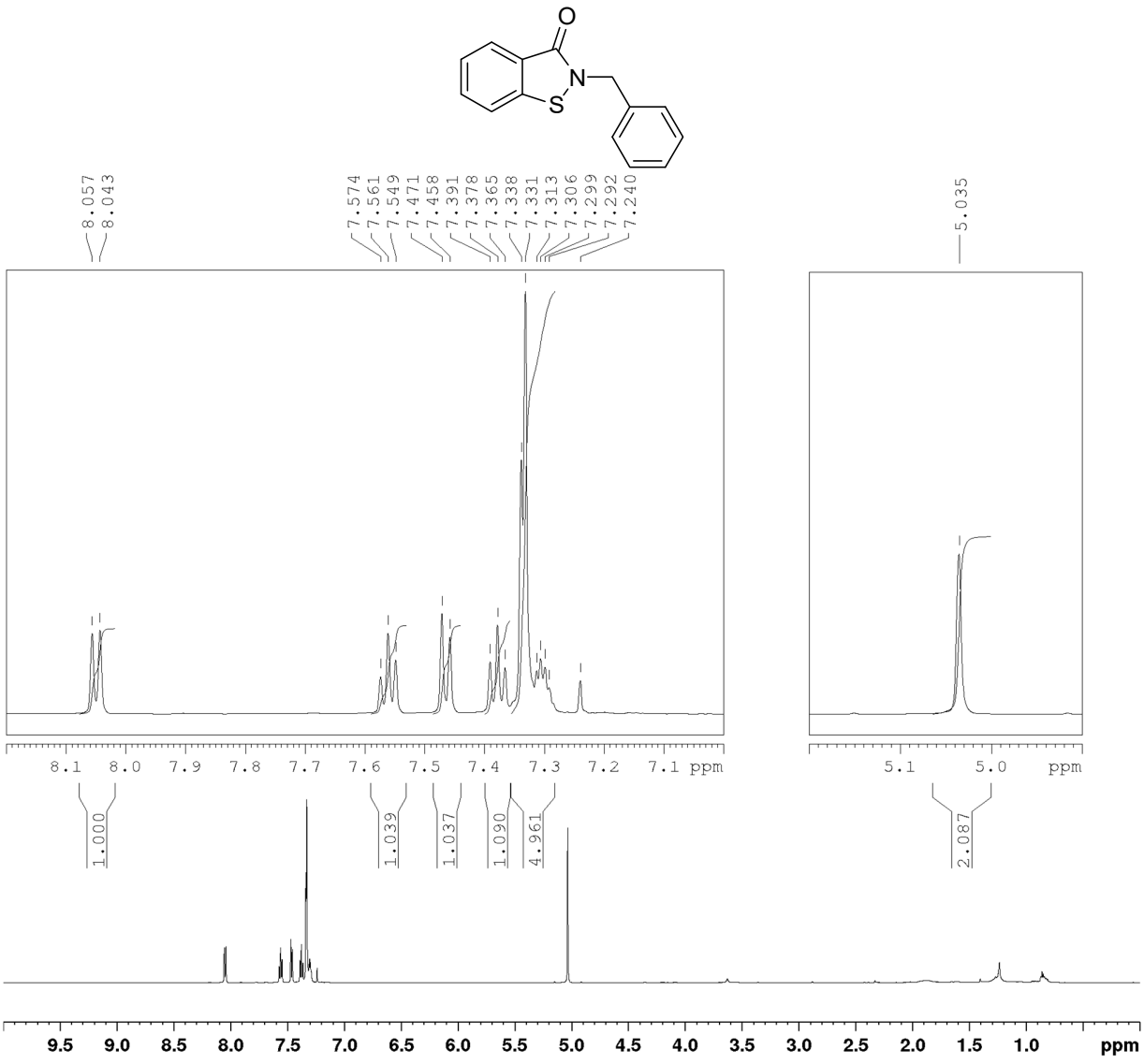
130.95
125.60
124.57
123.18
119.21
76.22
76.01
75.80
60.91
46.44
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

(5f)


O
N
S
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8.043
7.574
7.561
7.549
7.471
7.458
7.391
7.378
7.365
7.338
7.331
7.313
7.306
7.299
7.292
7.240
5.035
8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 ppm
5.1 5.0 ppm
1.000
1.039
1.037
1.090
4.961
2.087
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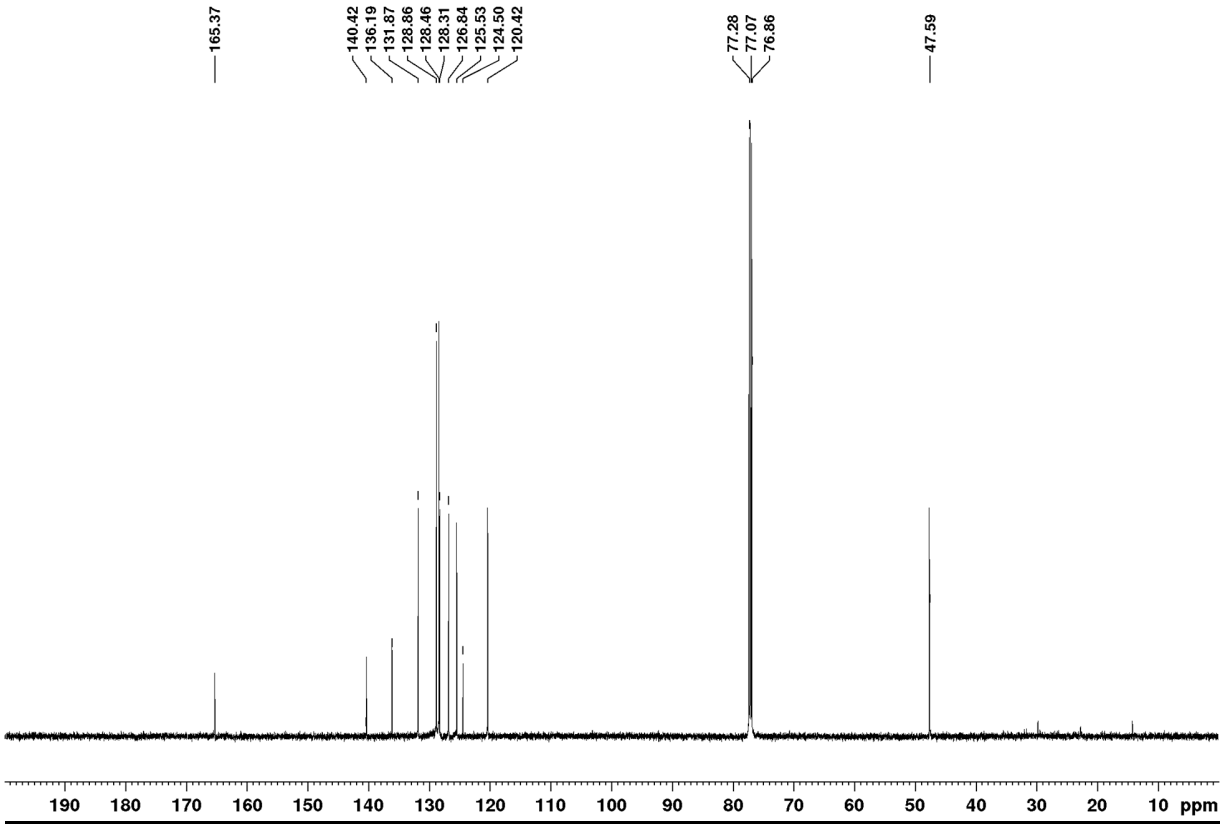
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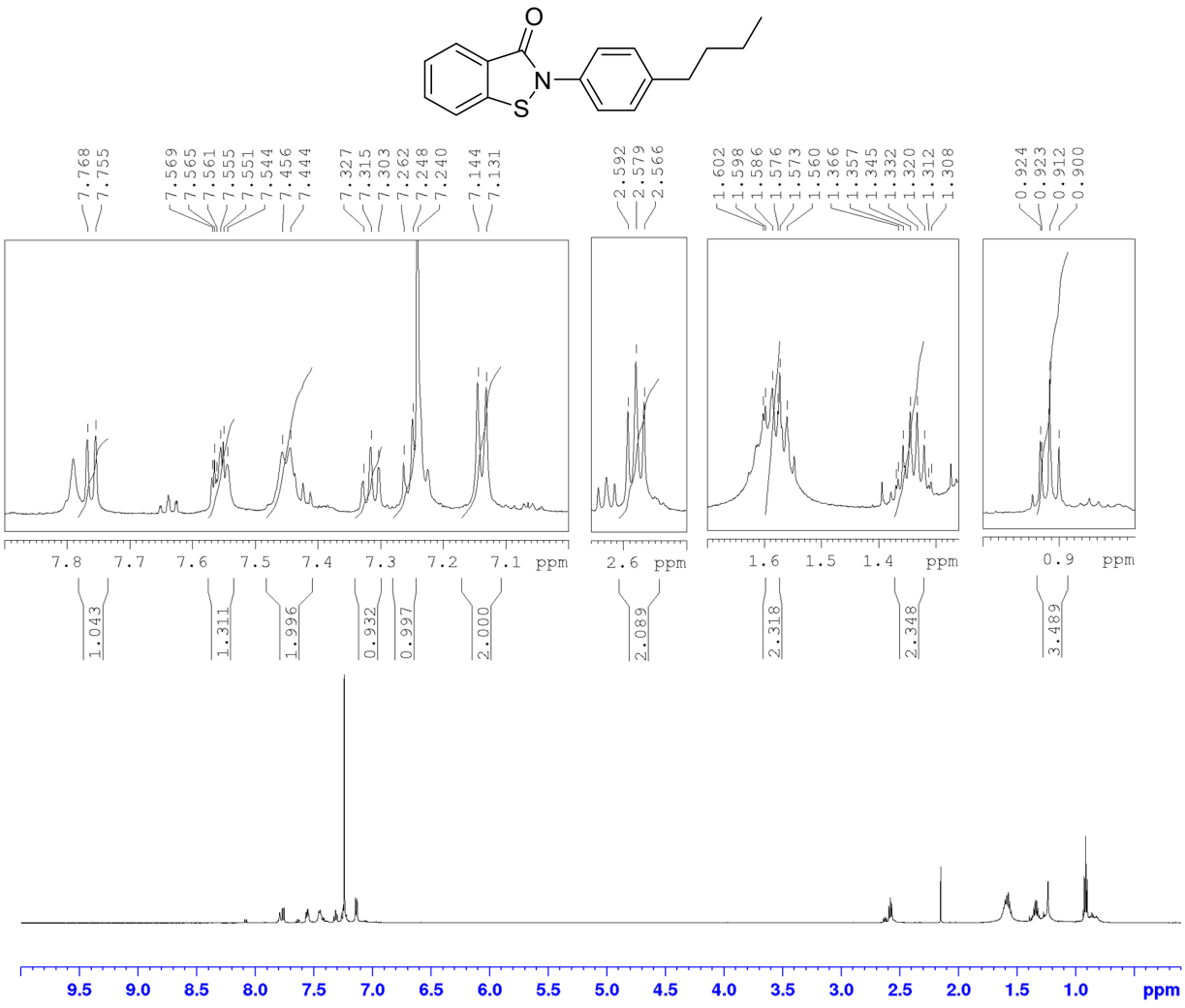
136.19
131.87
128.86
128.46
128.31
126.84
125.53
124.50
120.42
77.28
77.07
76.86
47.59
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

(5g)


O
N
S
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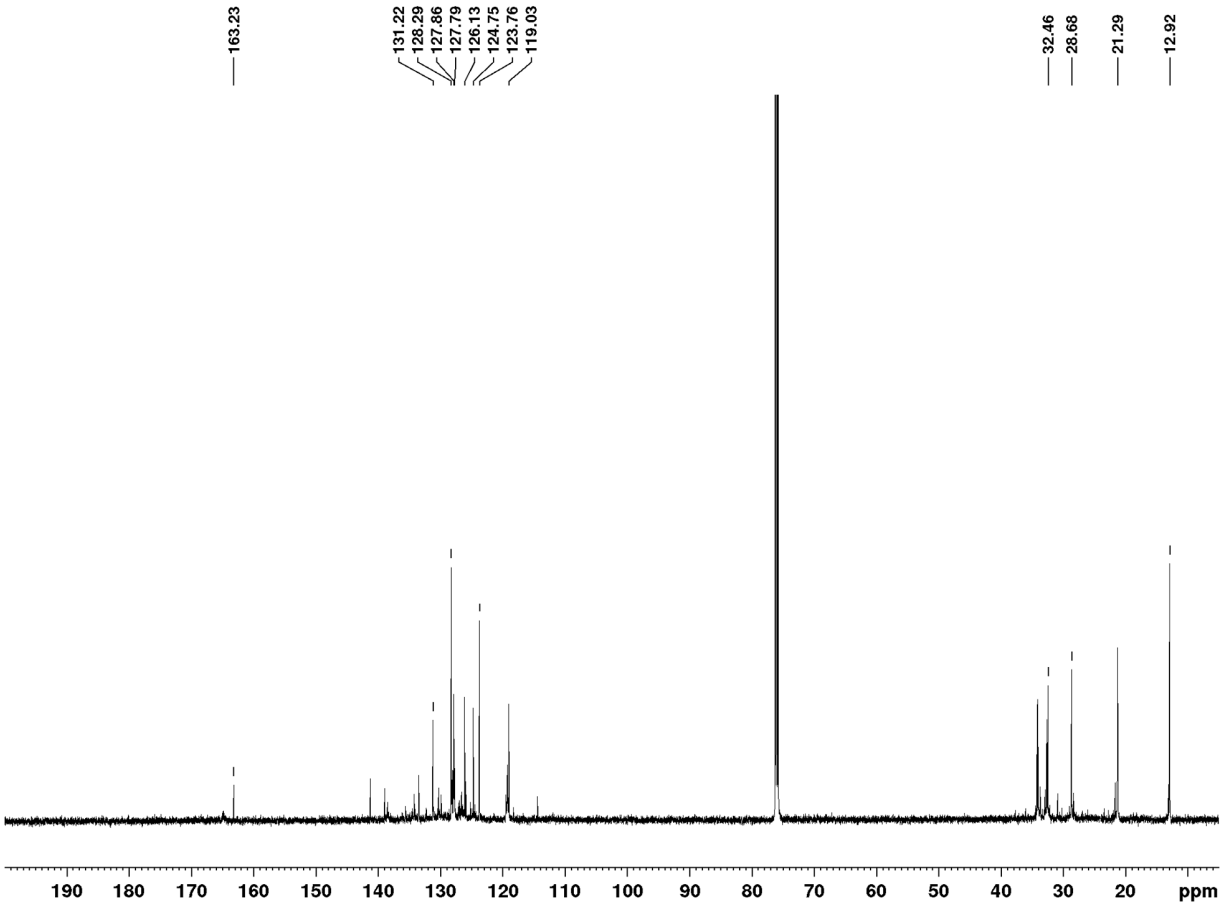
7.569
7.565
7.561
7.555
7.551
7.544
7.456
7.444
7.327
7.315
7.303
7.262
7.248
7.240
7.144
7.131
2.592
2.579
2.566
1.602
1.598
1.586
1.576
1.573
1.560
1.366
1.357
1.345
1.332
1.320
1.312
1.308
0.924
0.923
0.912
0.900
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
ppm
2.6
ppm
1.6
1.5
1.4
ppm
0.9
ppm
1.043
1.311
1.996
0.932
0.997
2.000
2.089
2.318
2.348
3.489
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
ppm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127.86
127.79
126.13
124.75
123.76
119.03
32.46
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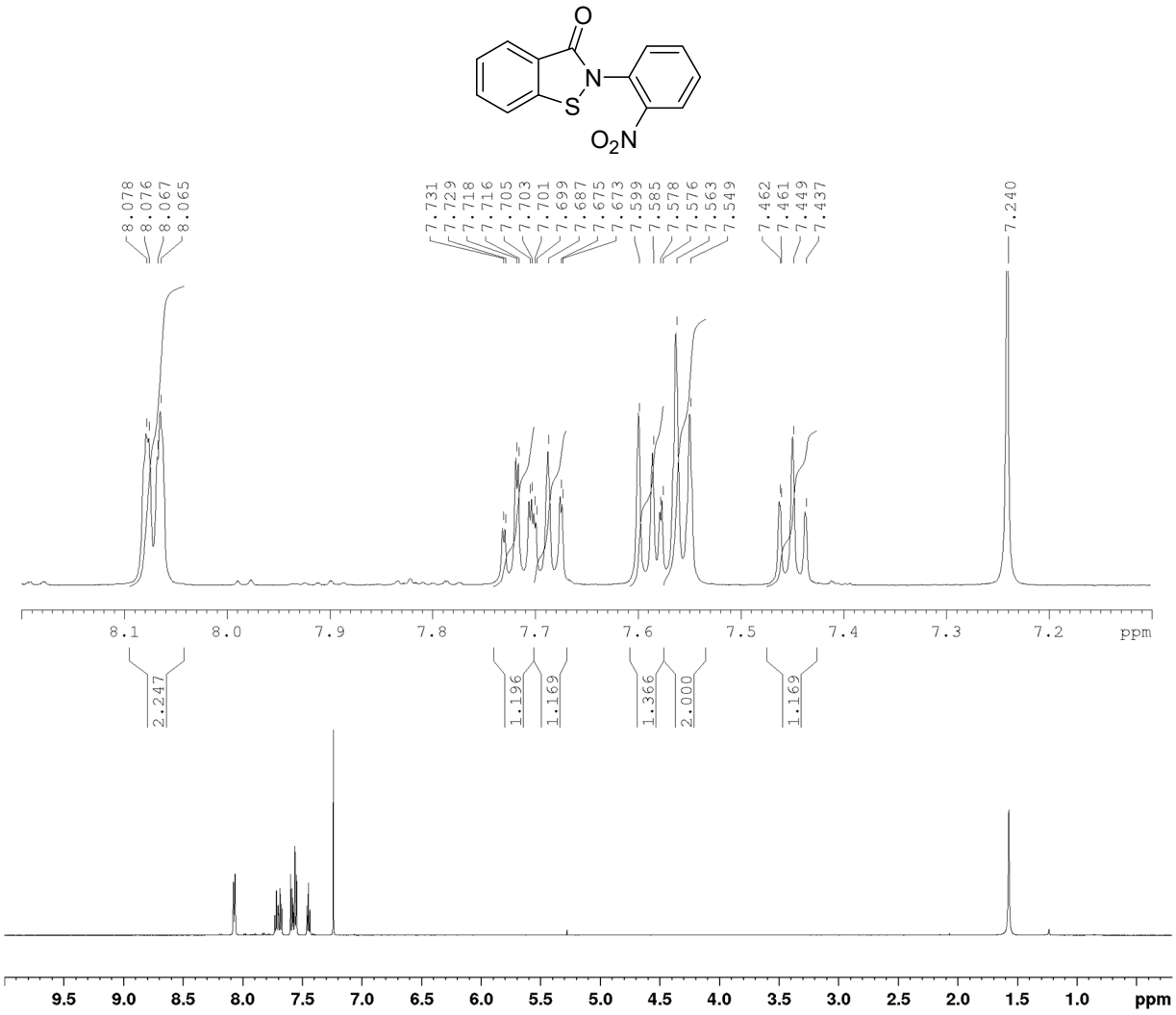
21.29
12.92
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

(5h)


O
N
S
O_2N
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8.076
8.067
8.065
7.731
7.729
7.718
7.716
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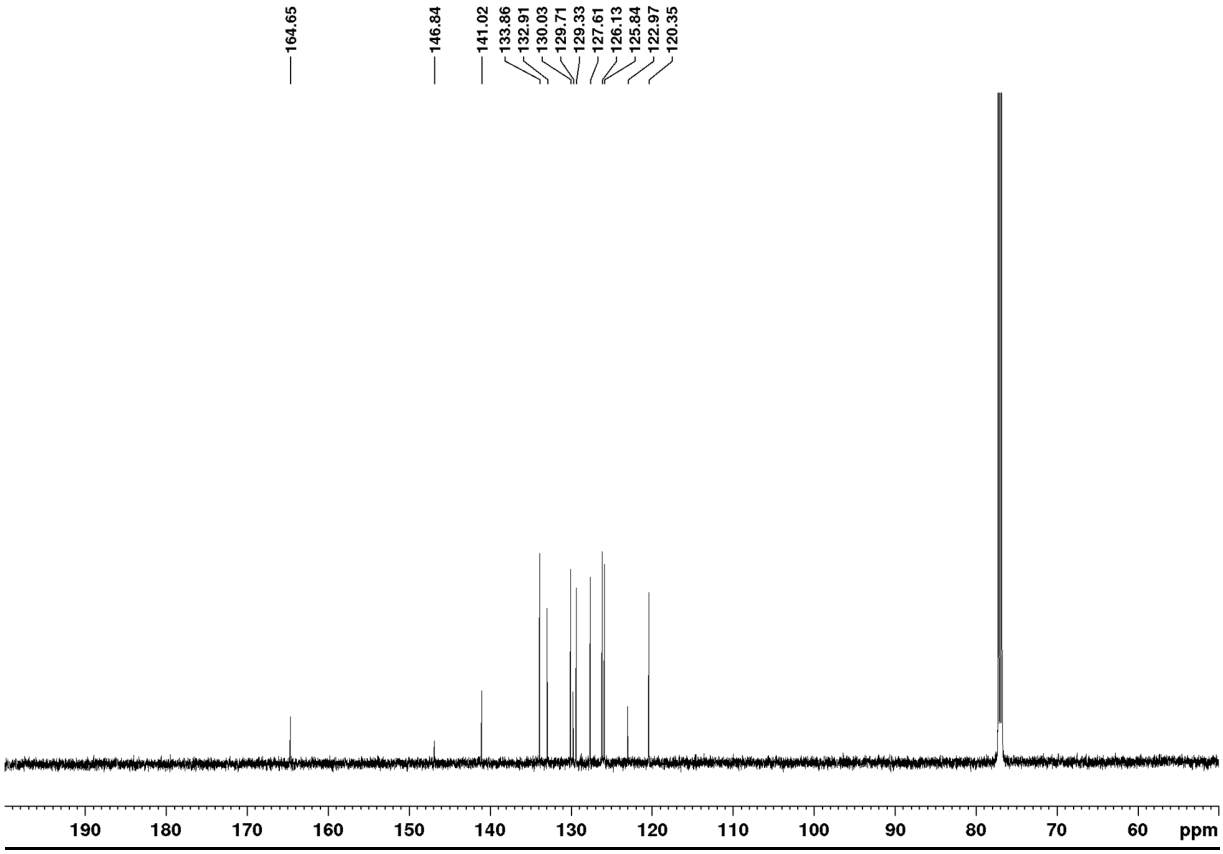
7.703
7.701
7.699
7.687
7.675
7.673
7.599
7.585
7.578
7.576
7.563
7.549
7.462
7.461
7.449
7.437
7.240
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
ppm
2.247
1.196
1.169
1.366
2.000
1.169
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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146.84
141.02
133.86
132.91
130.03
129.71
129.33
127.61
126.13
125.84
122.97
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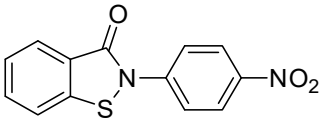
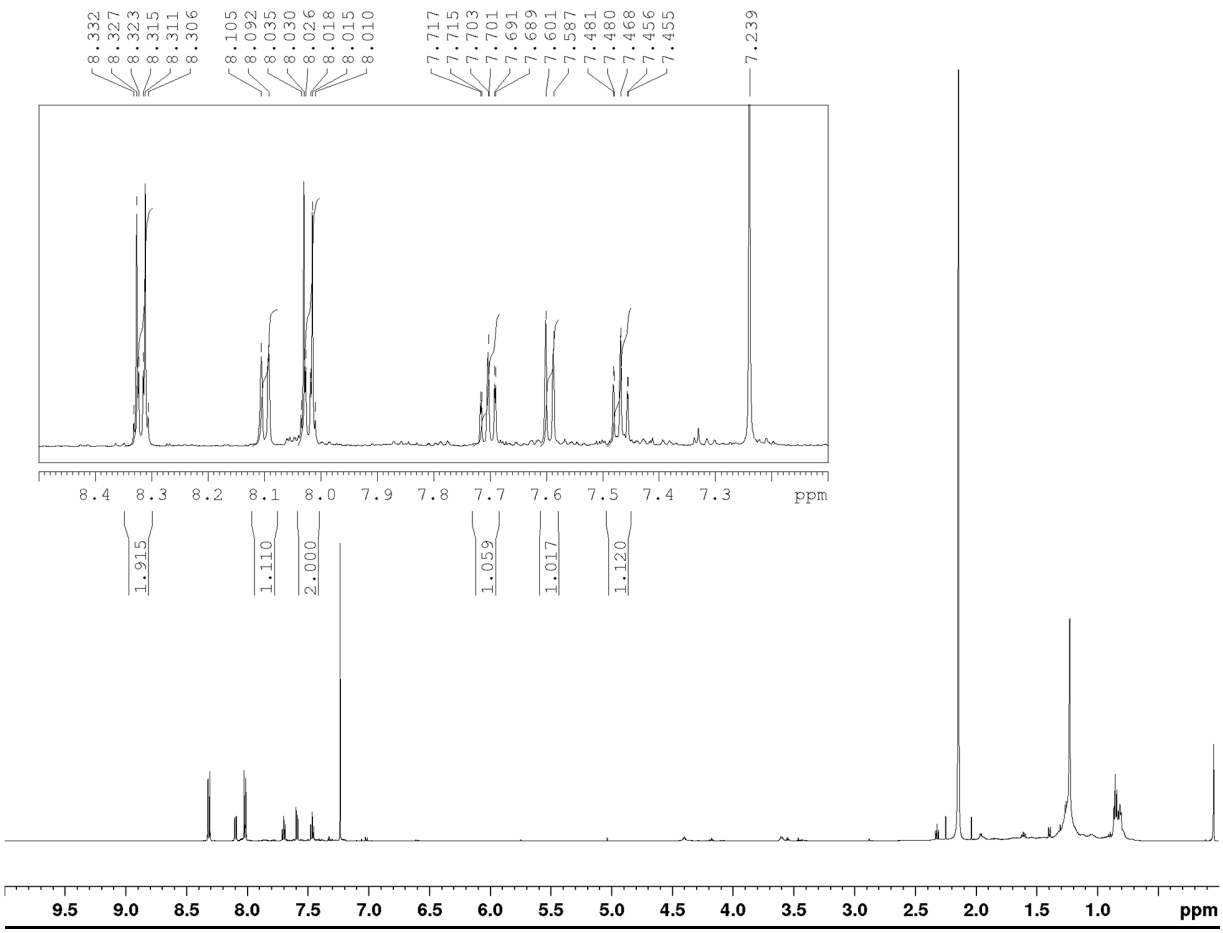
120
110
100
90
80
70
60
ppm

(5i)


O
N
S
NO2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7.701
7.691
7.689
7.601
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7.480
7.468
7.456
7.455
7.239
8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 ppm
1.915
1.110
2.000
1.059
1.017
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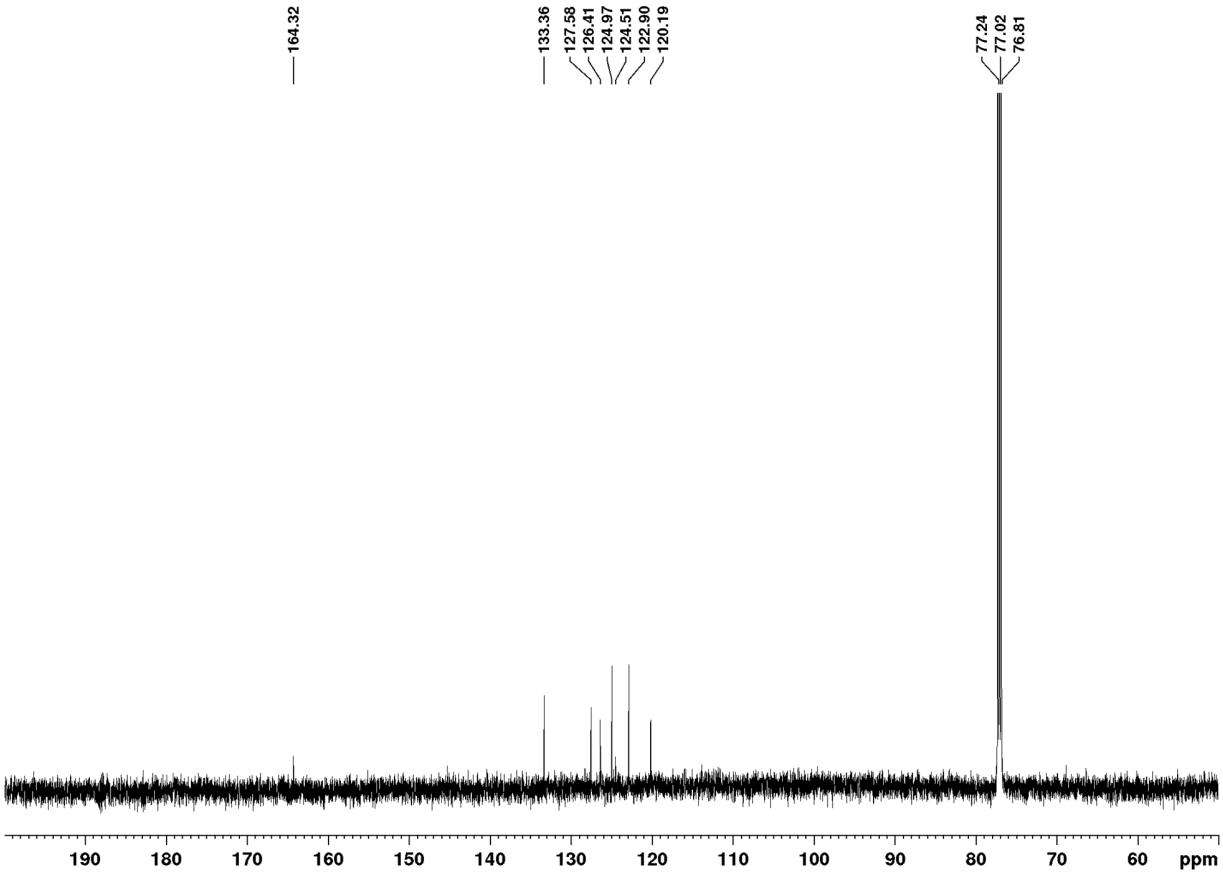
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm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133.36
127.58
126.41
124.97
124.51
122.90
120.19
77.24
77.02
76.81
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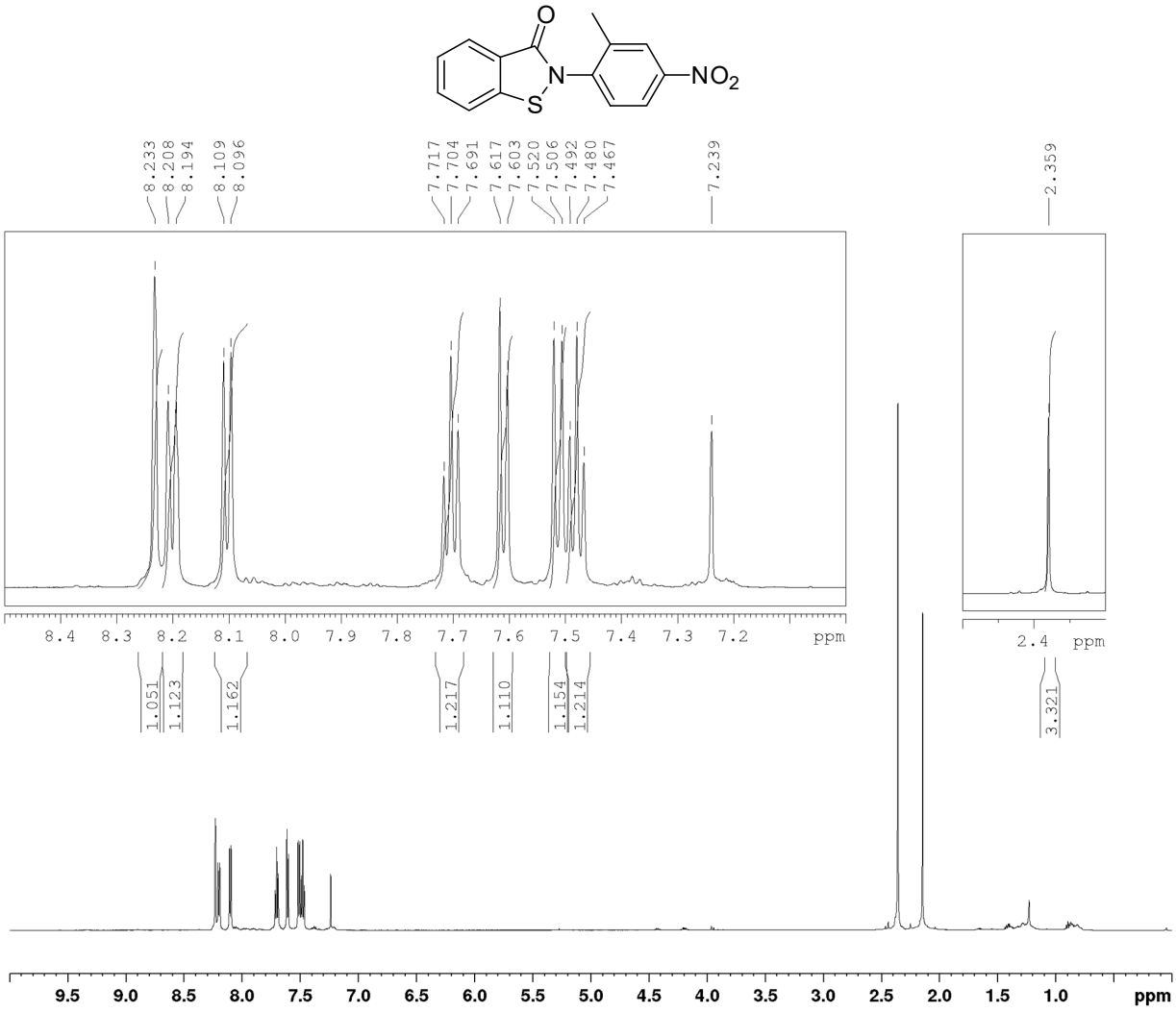
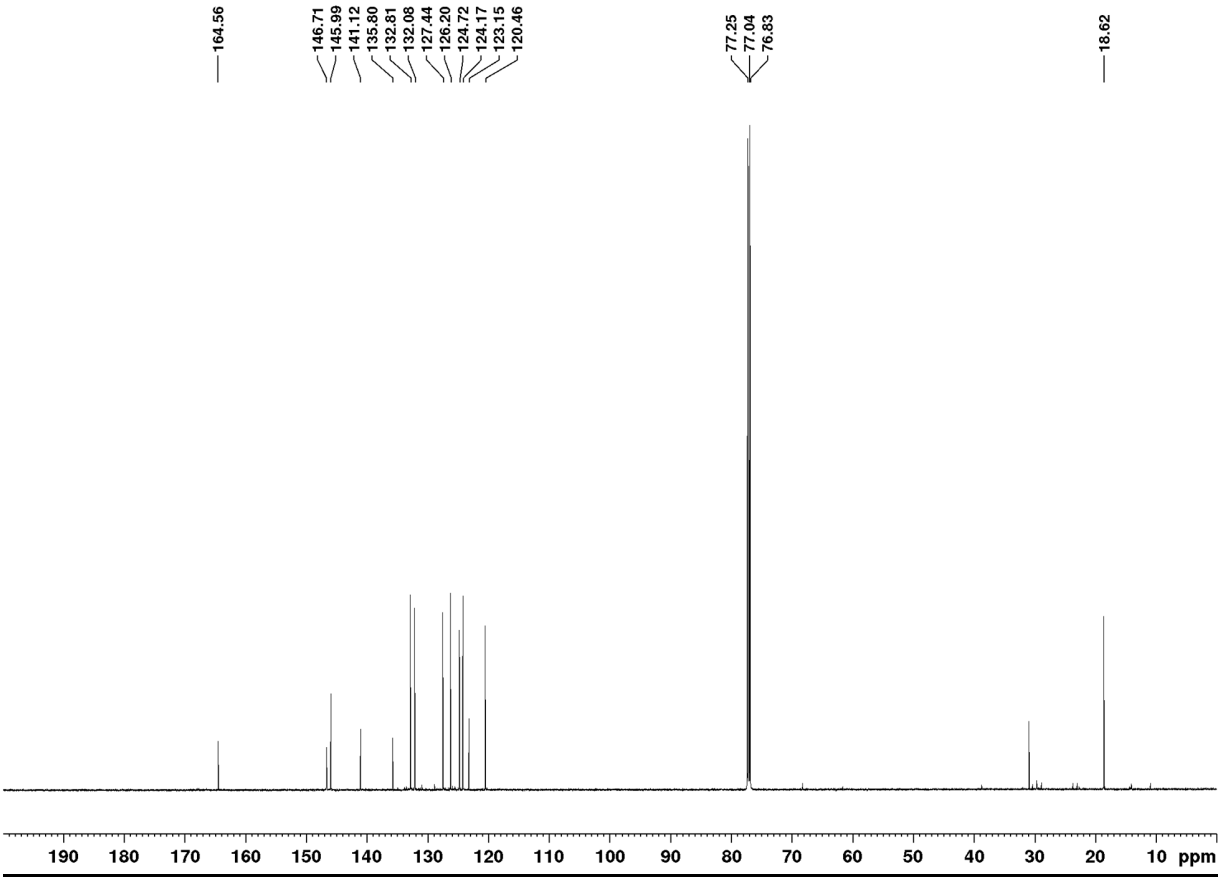
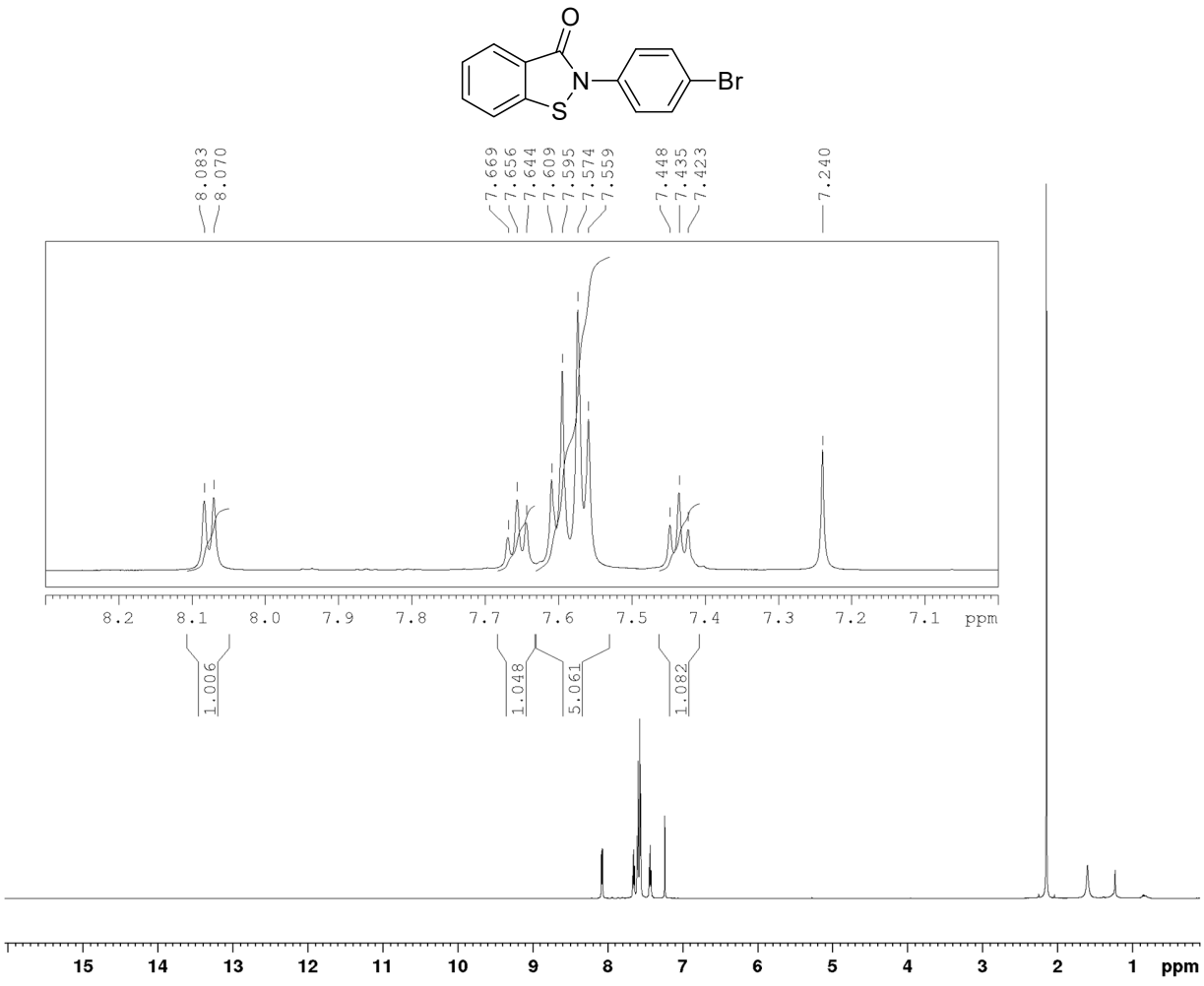
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

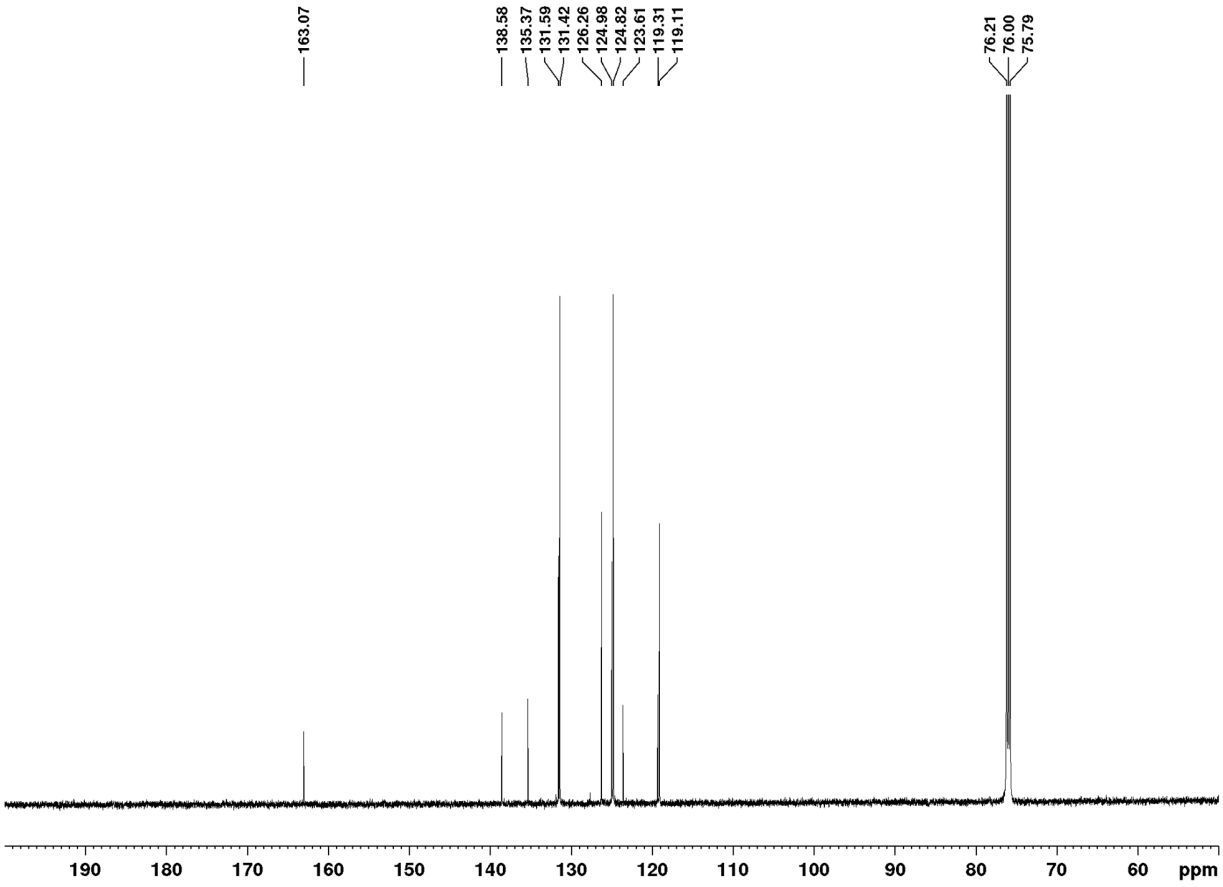
(5j)


O
N
S
NO2
8.233
8.208
8.194
8.109
8.096
7.717
7.704
7.691
7.617
7.603
7.520
7.506
7.492
7.480
7.467
7.239
2.359
8.4 8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 ppm
2.4 ppm
1.051
1.123
1.162
1.217
1.110
1.154
1.214
3.321
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 ppm

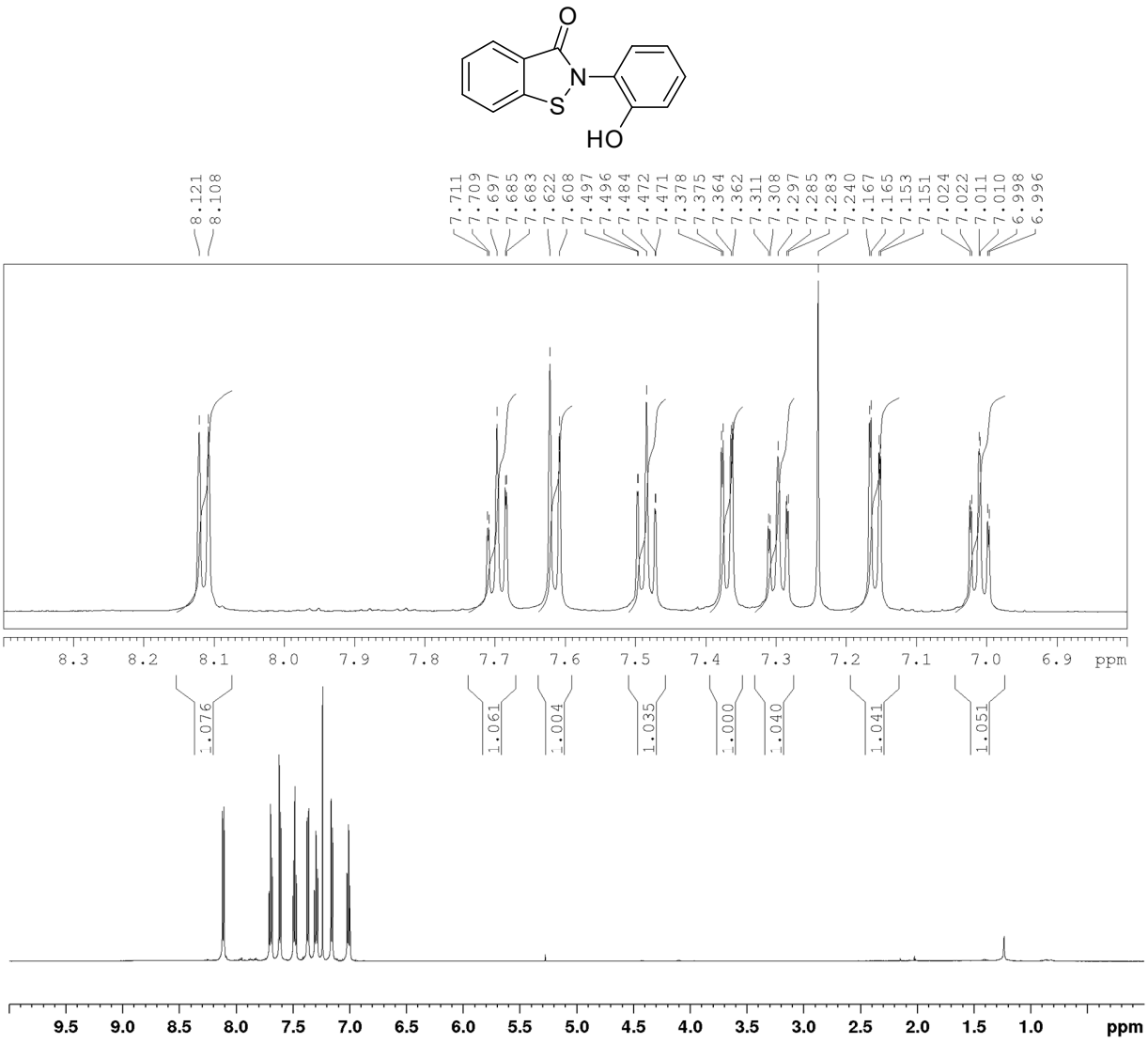

164.56
146.71
145.99
141.12
135.80
132.81
132.08
127.44
126.20
124.72
124.17
123.15
120.46
77.25
77.04
76.83
18.62
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

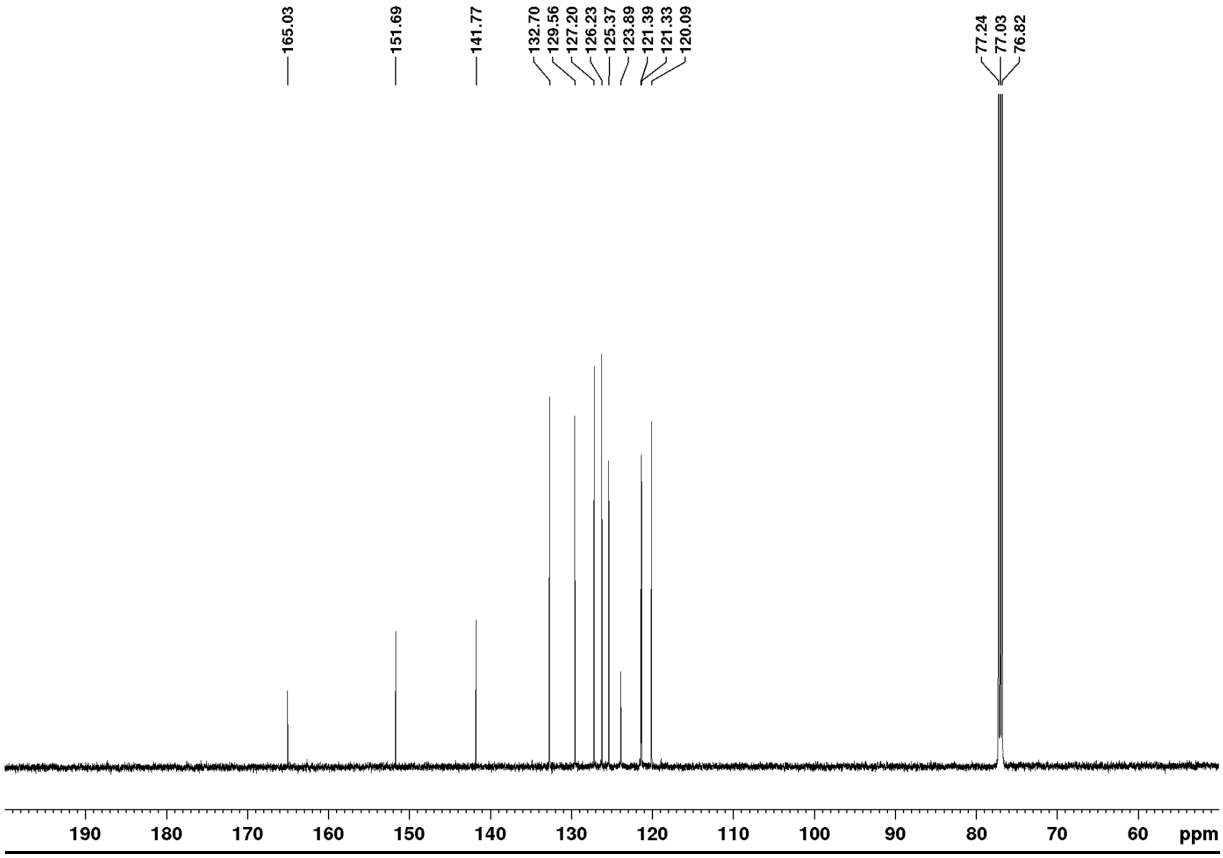
(5k)


O
N
S
Br
8.083
8.070
7.669
7.656
7.644
7.609
7.595
7.574
7.559
7.448
7.435
7.423
7.240
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
ppm
1.006
1.048
5.061
1.082
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

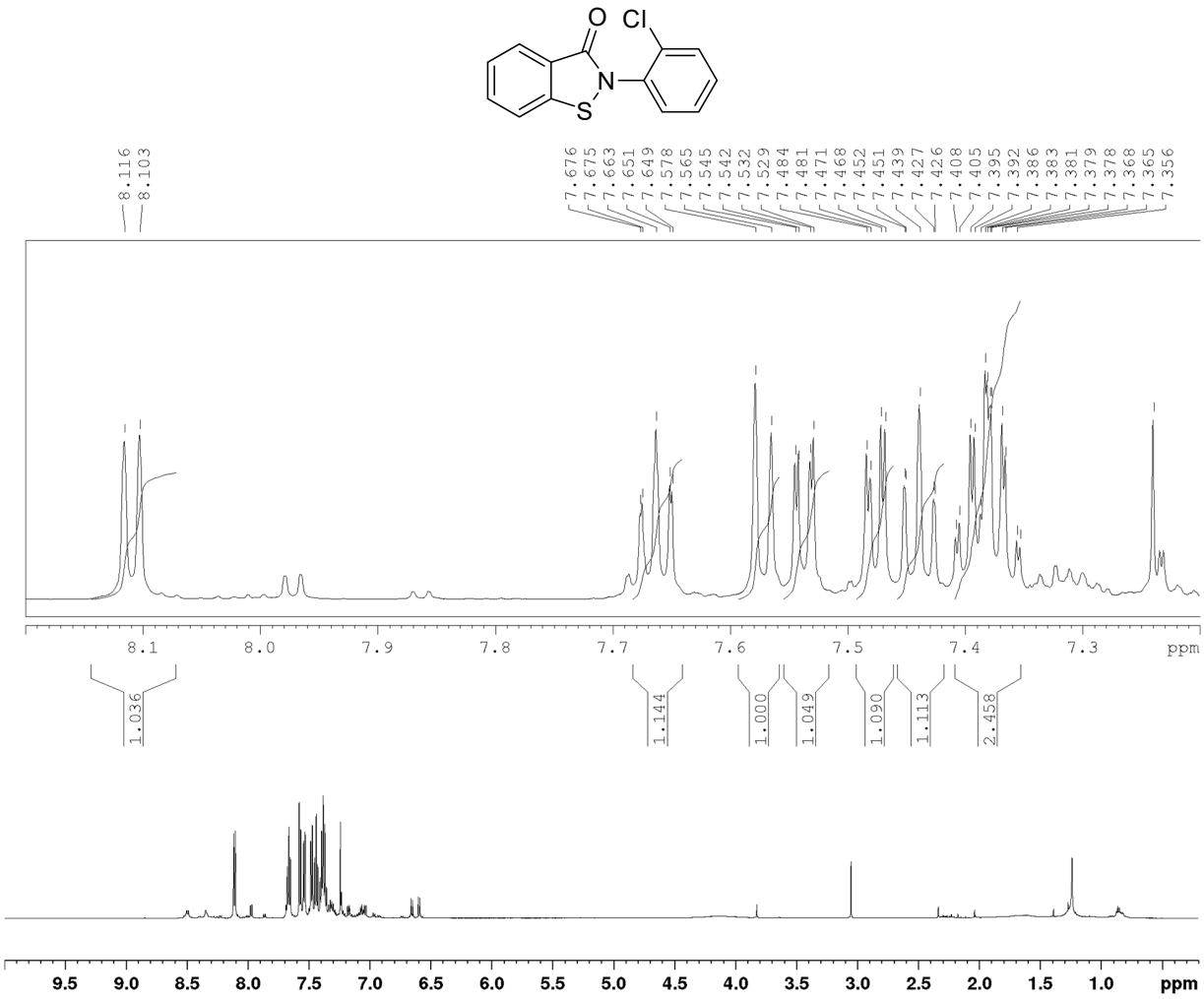

163.07
138.58
135.37
131.59
131.42
126.26
124.98
124.82
123.61
119.31
119.11
76.21
76.00
75.79
190
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

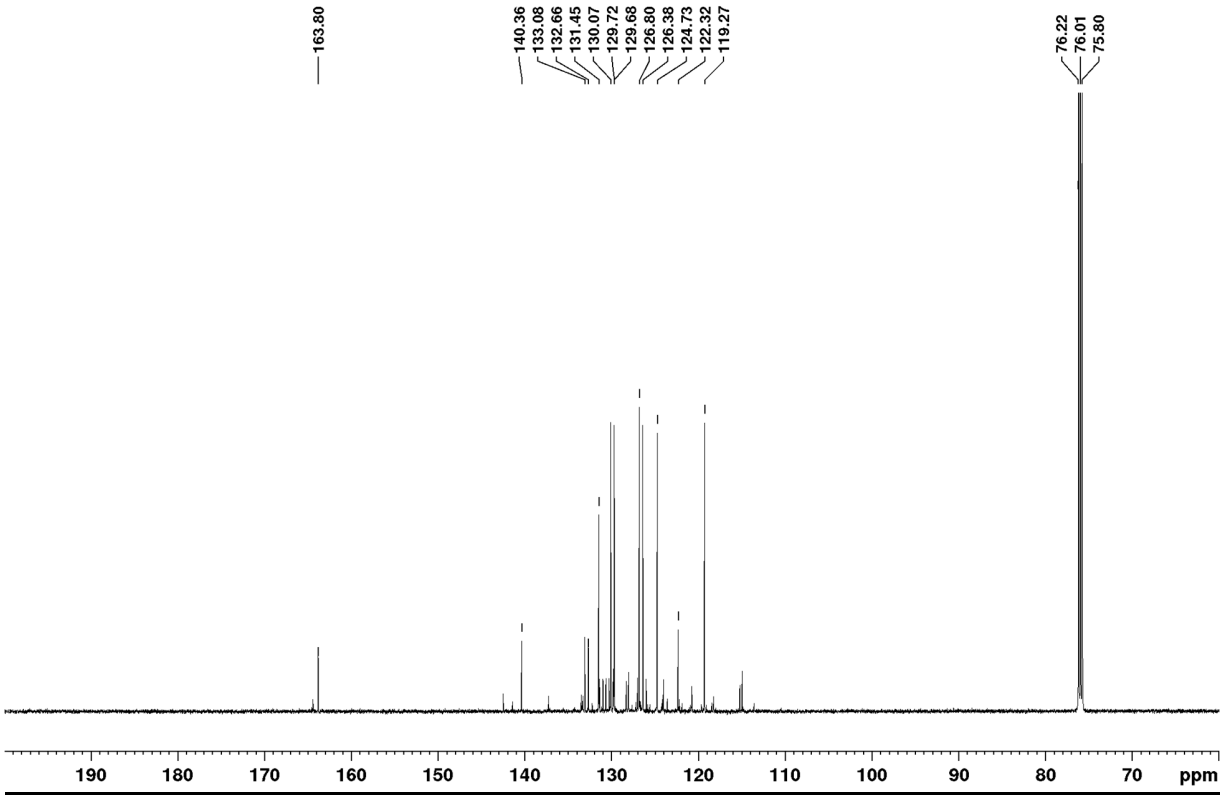
(5l)


O
N
S
HO
8.121
8.108
7.711
7.709
7.697
7.685
7.683
7.622
7.608
7.497
7.496
7.484
7.472
7.471
7.378
7.375
7.364
7.362
7.311
7.308
7.297
7.285
7.283
7.240
7.167
7.165
7.153
7.151
7.024
7.022
7.011
7.010
6.998
6.996
8.3 8.2 8.1 8.0 7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 ppm
1.076
1.061
1.004
1.035
1.000
1.040
1.041
1.051
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 ppm

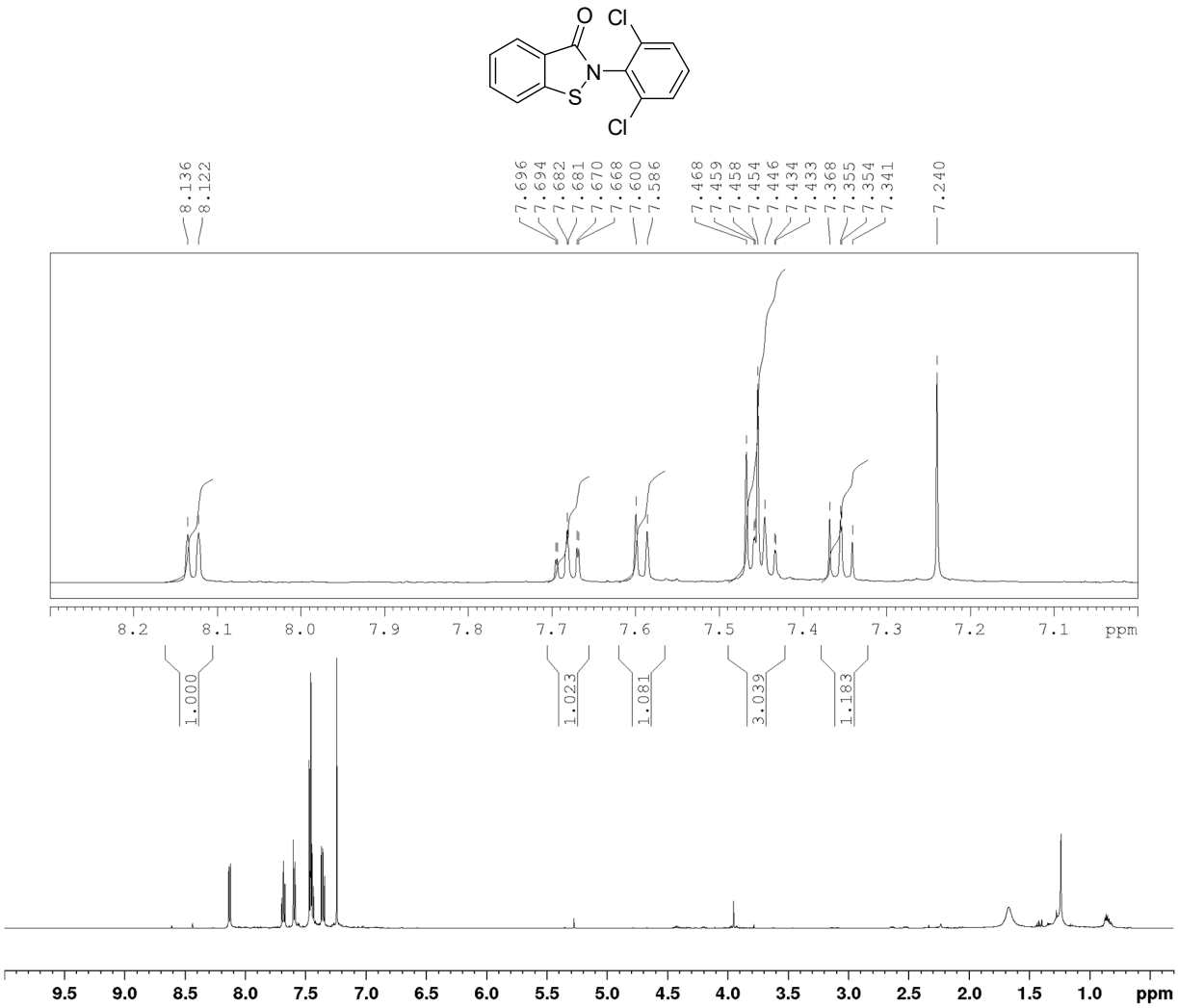

165.03
151.69
141.77
132.70
129.56
127.20
126.23
125.37
123.89
121.39
121.33
120.09
77.24
77.03
76.82
190
180
170
160
150
140
130
120
110
100
90
80
70
60
ppm

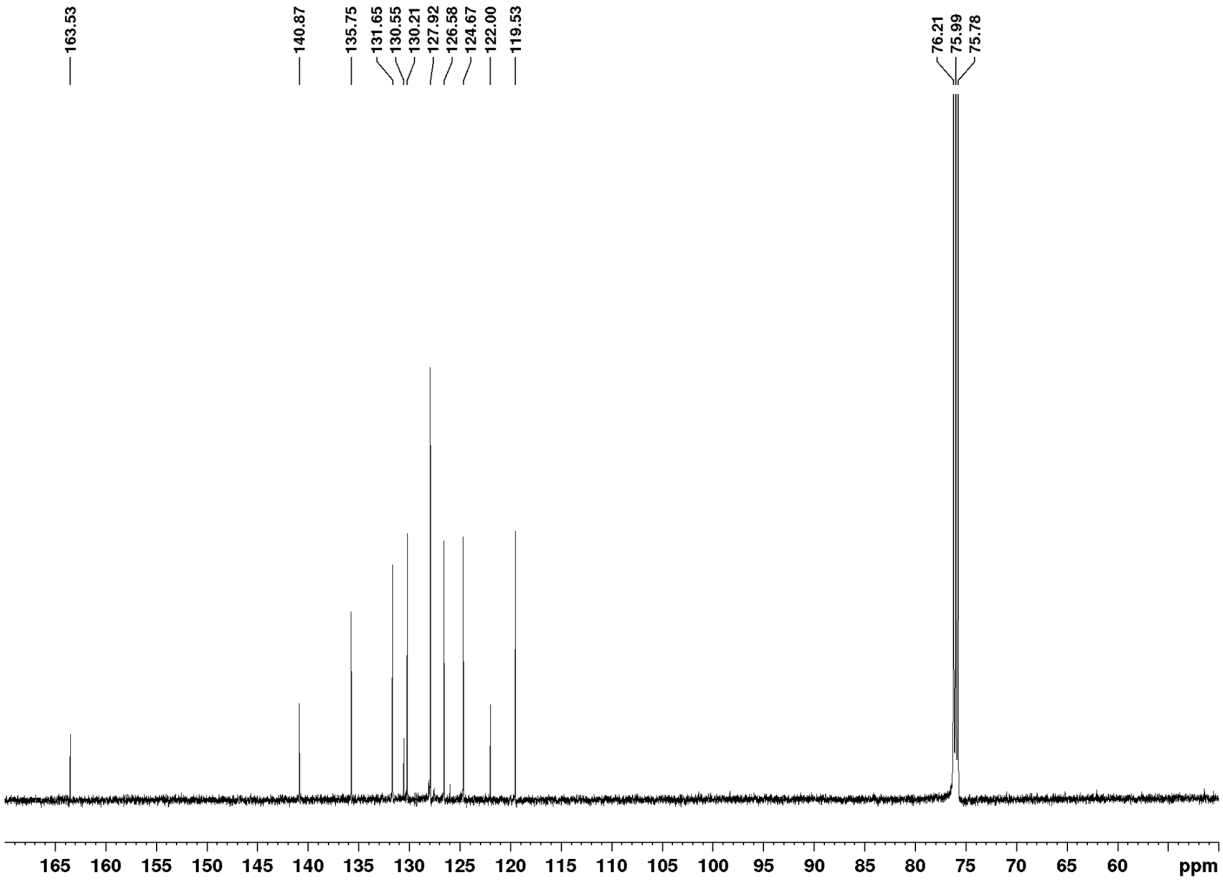
(5m)


O
Cl
N
S
8.116
8.103
7.676
7.675
7.663
7.651
7.649
7.578
7.565
7.545
7.542
7.532
7.529
7.484
7.481
7.471
7.468
7.452
7.451
7.439
7.427
7.426
7.408
7.405
7.395
7.392
7.386
7.383
7.381
7.379
7.378
7.368
7.365
7.356
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
ppm
1.036
1.144
1.000
1.049
1.090
1.113
2.458
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
ppm

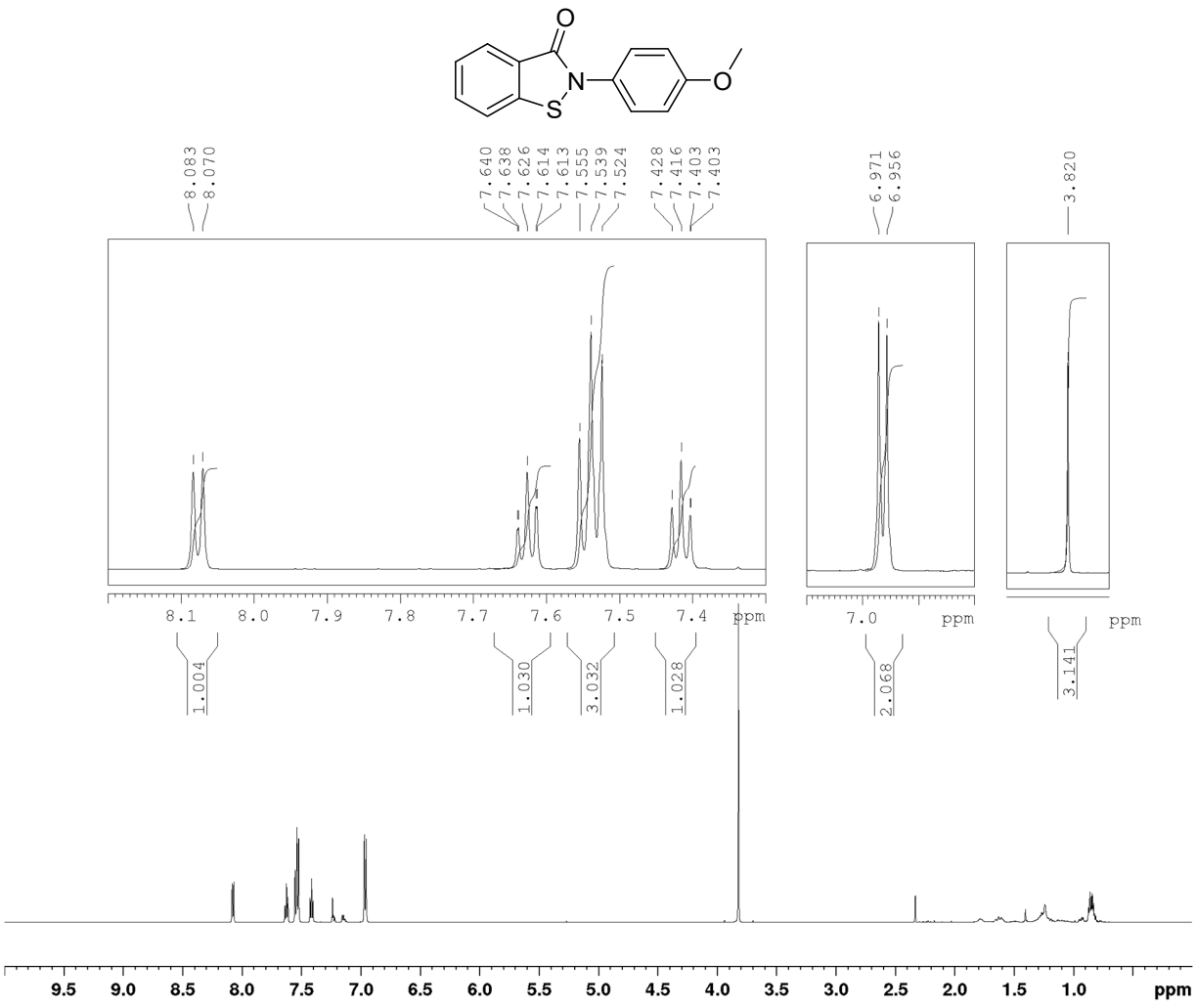

163.80
140.36
133.08
132.66
131.45
130.07
129.72
129.68
126.80
126.38
124.73
122.32
119.27
76.22
76.01
75.80
190
180
170
160
150
140
130
120
110
100
90
80
70
ppm

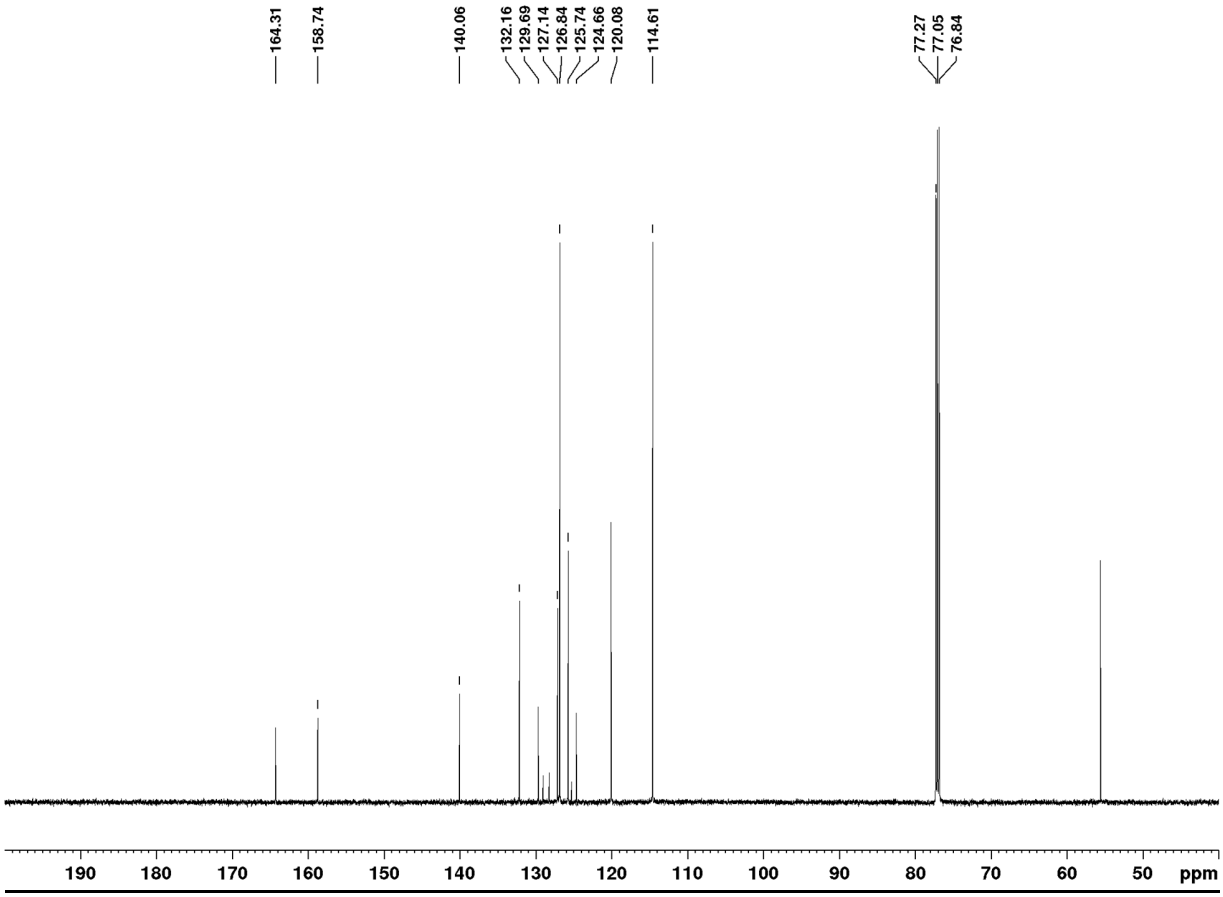
(5n)


O
Cl
N
S
Cl
8.136
8.122
7.696
7.694
7.682
7.681
7.670
7.668
7.600
7.586
7.468
7.459
7.458
7.454
7.446
7.434
7.433
7.368
7.355
7.354
7.341
7.240
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
ppm
1.000
1.023
1.081
3.039
1.183
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
ppm


163.53
140.87
135.75
131.65
130.55
130.21
127.92
126.58
124.67
122.00
119.53
76.21
75.99
75.78
165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 ppm

(5o)


O
N
S
O
8.083
8.070
7.640
7.638
7.626
7.614
7.613
7.555
7.539
7.524
7.428
7.416
7.403
7.403
6.971
6.956
3.820
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
ppm
7.0
ppm
ppm
1.004
1.030
3.032
1.028
2.068
3.141
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
ppm


164.31
158.74
140.06
132.16
129.69
127.14
126.84
125.74
124.66
120.08
114.61
77.27
77.05
76.84
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm