Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

1,8-Naphthalimide derivatives: New leads against dynamin I GTPase activity

Mohammed K. Abdel-Hamid, Kylie A. Macgregor, Luke R. Odell, Ngoc Chau, Anna Mariana, Ainslie Whiting, Phillip J Robinson and Adam McCluskey

Supplementary Data

1. Figure S1. Clustering of the 1,8-naphthalimide scaffold (stick representation) at the GTP binding pocket of dynI (ribbon representation)
2. Calculated Ligand Efficiencies and related physicochemical properties of key napthaladyn and other dynamin inhibitor compounds.
3. ^{1}H and ^{13}C NMR spectra of key analogues

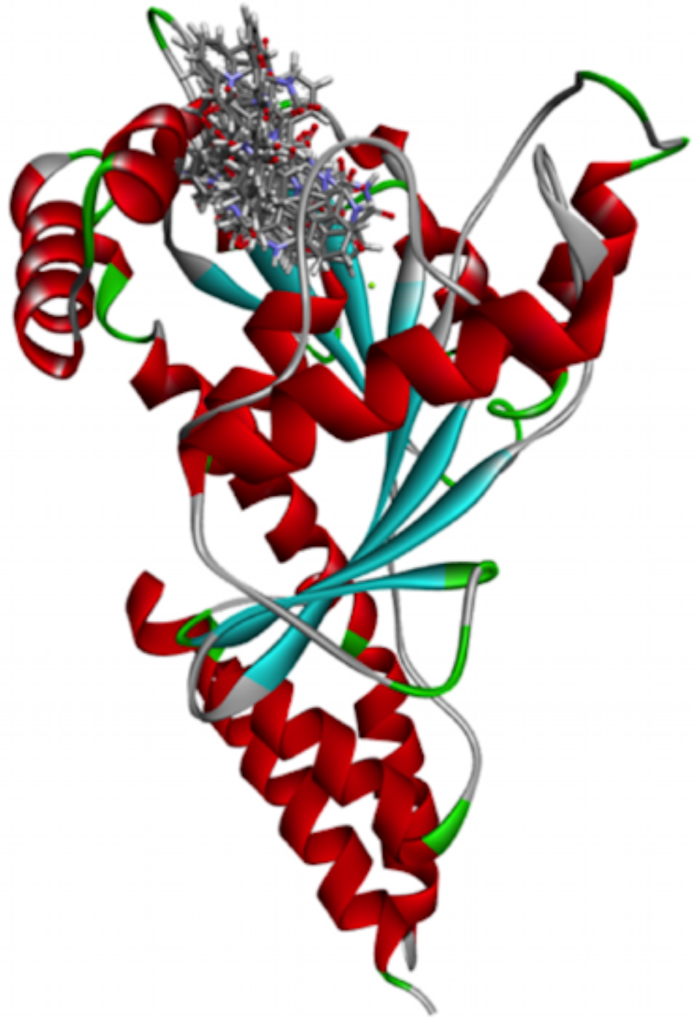
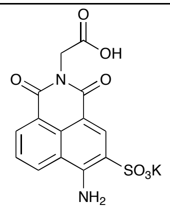
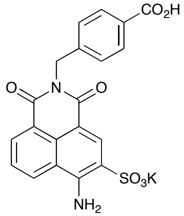
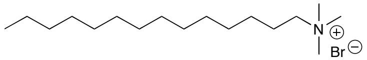
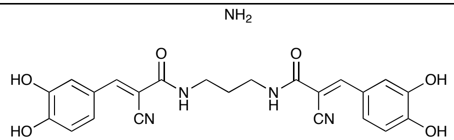
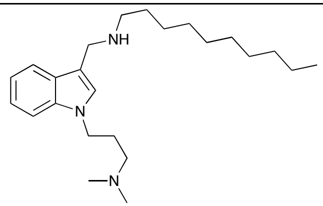
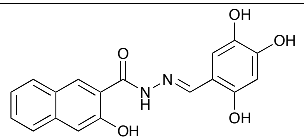
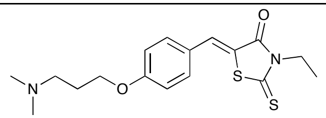
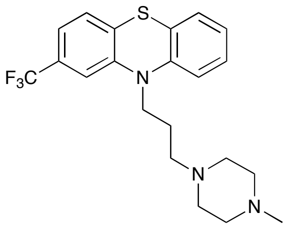
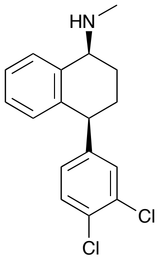


Figure S1. Clustering of the 1,8-naphthalimide scaffold (stick representation) at the GTP binding pocket of dynI (ribbon representation)

Table S1. Calculated ligand efficiencies and related physicochemical properties of key napthaladyn and other dynamin inhibitor compounds. The values cLogP and PSA were calculated using the Osiris Molecular Property Explorer (http://www.organic-chemistry.org/prog/peo/).

Compound Class	**Structure**	**MW**	**HAC**	**cLogP***	**PSA (Å^2)**	**HBA**	**HBD**	**IC_{50} (μM)**	**Ligand Efficiency**	**Ref**
Napthaladyn 23		388.39	25	-1.59	163.4	7	4	19.1	0.20	This work
Napthaladyn 29		464.49	31	0.18	163.4	7	4	18.5	0.16	This work
MiTMAB		336.39	19	2.79	-	-	-	3.1	0.31	1
Bis-T-22		464.45	35	1.47	186.7	8	6	1.7	0.16	2
Dynole 2-24		408.58	30	5.23	20.2	2	1	0.56	0.23	3
Dyngo-4a		338.31	25	3.01	122.3	6	5	0.35	0.26	4

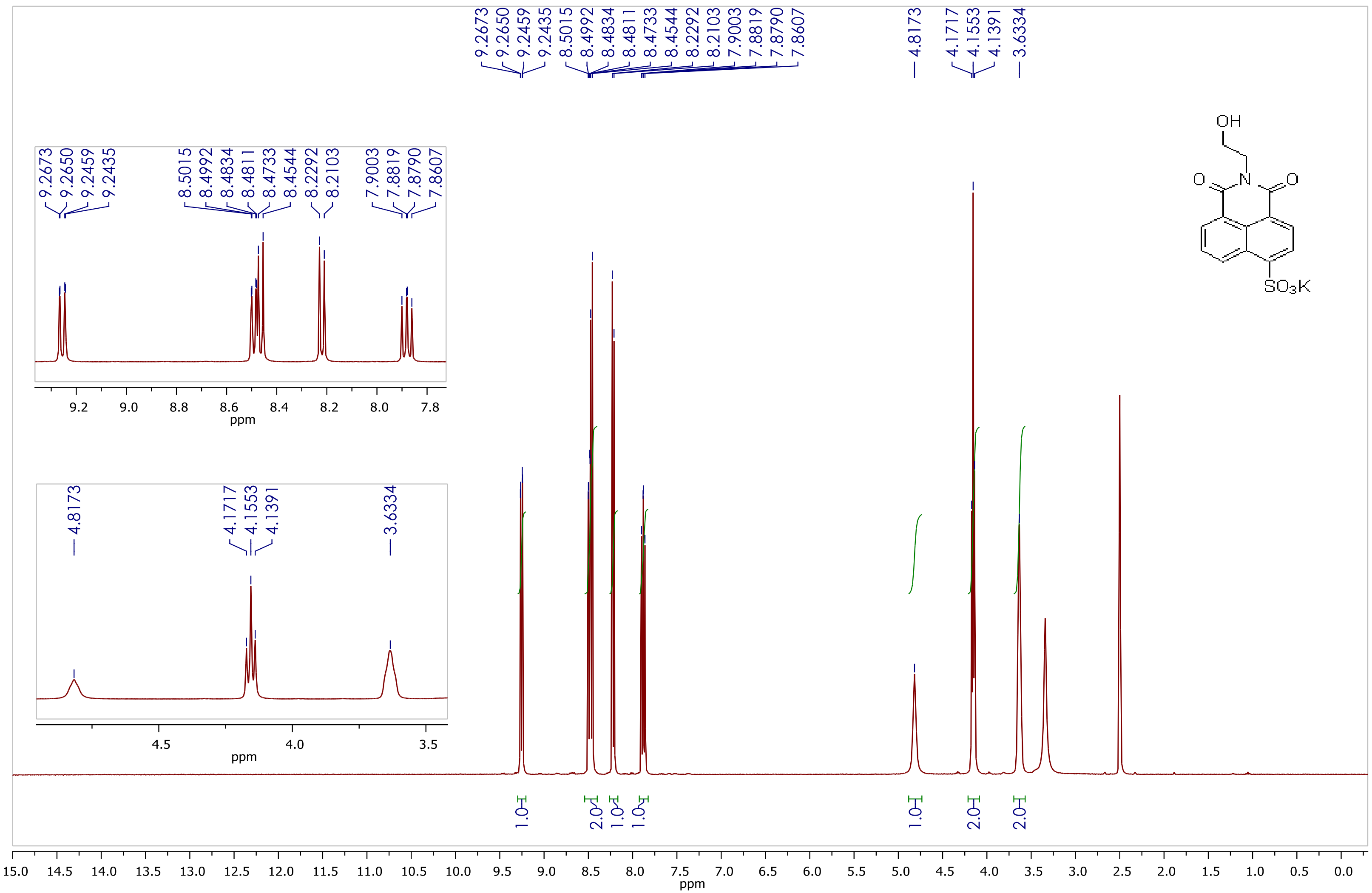
Rhodadyn C10		350.0	23	1.89	90.17	5	0	7.0	0.22	5
Anti-psychotic - Trifluoperazine		407.50	28	4.93	35.02	3	0	2.6	0.20	6
SSRI - Seralin		306.23	20	4.2	12.03	1	1	7.3	0.26	7

* Calculated as the SO_3H analogue;

References:

1. T. A. Hill, L. R. Odell, A. Quan, G. Ferguson, P. J. Robinson, A. McCluskey. Long chain amines and long chain ammonium salts as novel inhibitors of dynamin GTPase activity. *Bioorg. Med. Chem. Lett.*, 2004, **14**, 3275-3278
2. T. Hill, L. R. Odell, J. K. Edwards, M. E. Graham, A. B. McGeachie, J. Rusak, A. Quan, R. Abagyan, J. L. Scott, P. J. Robinson, A. McCluskey. Small molecule inhibitors of dynamin I GTPase activity: development of dimeric tyrphostins. *J. Med. Chem.*, 2005, **48**, 7781-7788
3. C. P. Gordon, B. Venn-Brown, M. J. Robertson, K. A. Young, N. Chau, A. Quan, P. J. Robinson, A. McCluskey. Development of second generation indole based dynamin GTPase inhibitors. *J. Med. Chem.*, 2013, **56**, 46-59.
4. A. McCluskey, J. A. Daniel, G. Hadzic, N. Chau, E. L. Clayton, A. Mariana, A. Whiting, J. Lloyd, A. Quan, L. Moshkanbaryans, S. Perera, M. Chircop, A. B. McGeachie, M. T. Howes, R. G. Parton, M. Campbell, J. A. Sakoff, X. Wang, J. –Y. Sun, M. J. Robertson, F. M. Deane, T. H. Nguyen, F. A. Meunier, M. A. Cousin, P. J. Robinson. Building a better dynasore: The dyngos potently inhibit dynamin and endocytosis. *Traffic* 2013, **14**, 1272-1289
5. M. J. Robertson, G. Hadzic, J. Ambrus, D. Y. Pome, E. Hyde, A. Whiting, A. Mariana, L. von Kleist, N. Chau, V. Haucke, P. J. Robinson, A. McCluskey. The *rhodadyns*[TM] – novel inhibitors of dynamin GTPase. *ACS Med. Chem. Lett.*, **2012**, *3*, 352-356

6. J. A. Daniel, N. Ngoc Chau, A. Whiting, L. von Kleist, P. Maamary, M. K. Abdel-Hamid, V. Haucke, A. McCluskey, P. J. Robinson. Phenothiazine-derived antipsychotic drugs inhibit dynamin and clathrin-mediated endocytosis. *Traffic*, **2015**, **14***,* 1272-1289.
7. M. Otomo, K. Takahashi, H. Miyoshi, K. Osada, H. Nakashima, N. Yamagichi. Some Selective Serotonin Reuptake Inhibitors Inhibit Dynamin I Guanosine Triphosphatase (GTPase), Biol. Pharm. Bull. 2008, **31**, 1489-1495.



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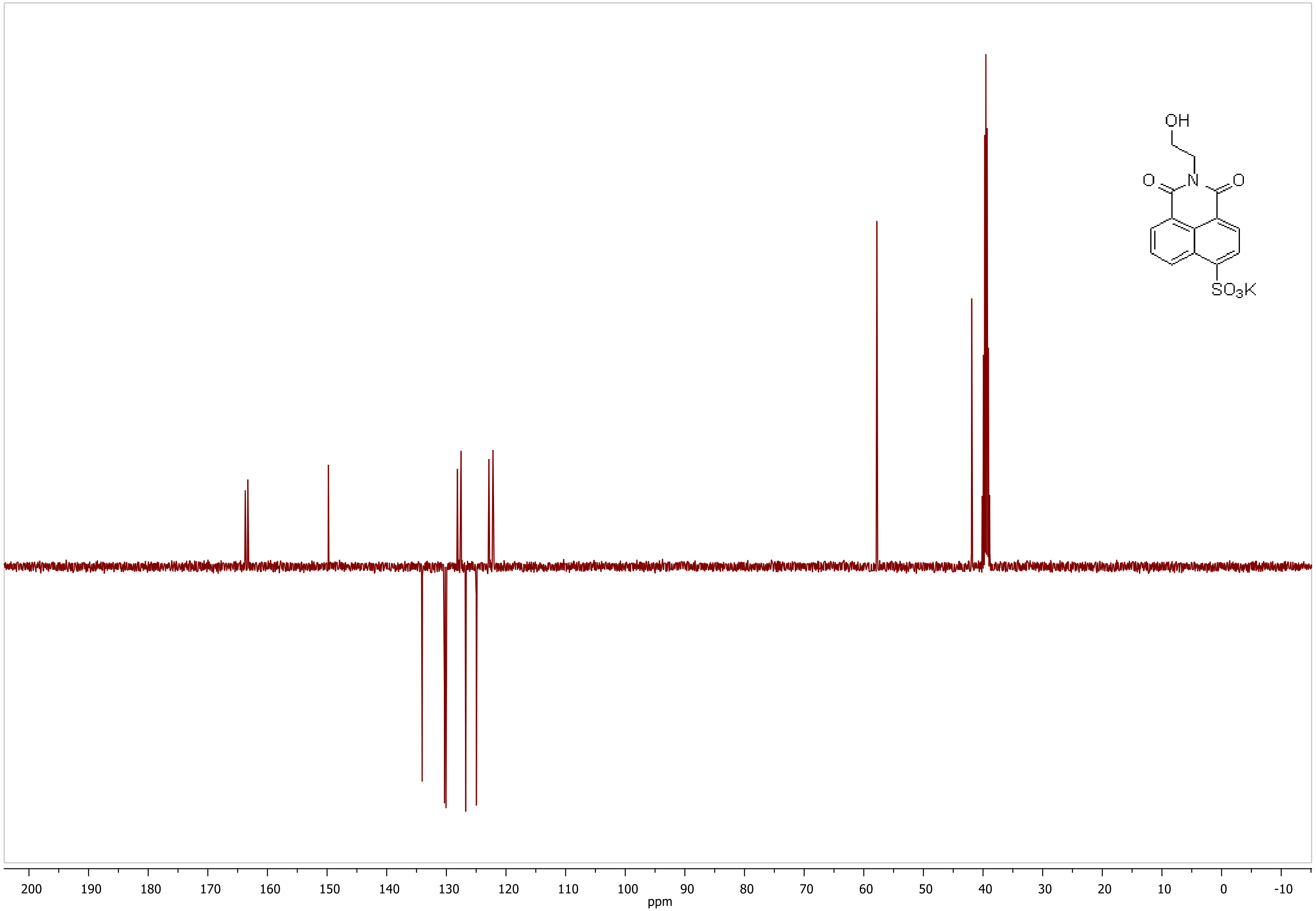
9.2650
9.2459
9.2435
8.5015
8.4992
8.4834
8.4811
8.4733
8.4544
8.2292
8.2103
7.9003
7.8819
7.8790
7.8607
4.8173
4.1717
4.1553
4.1391
3.6334
OH
O
N
O
SO3K
1.0
2.0
1.0
1.0
1.0
2.0
2.0
ppm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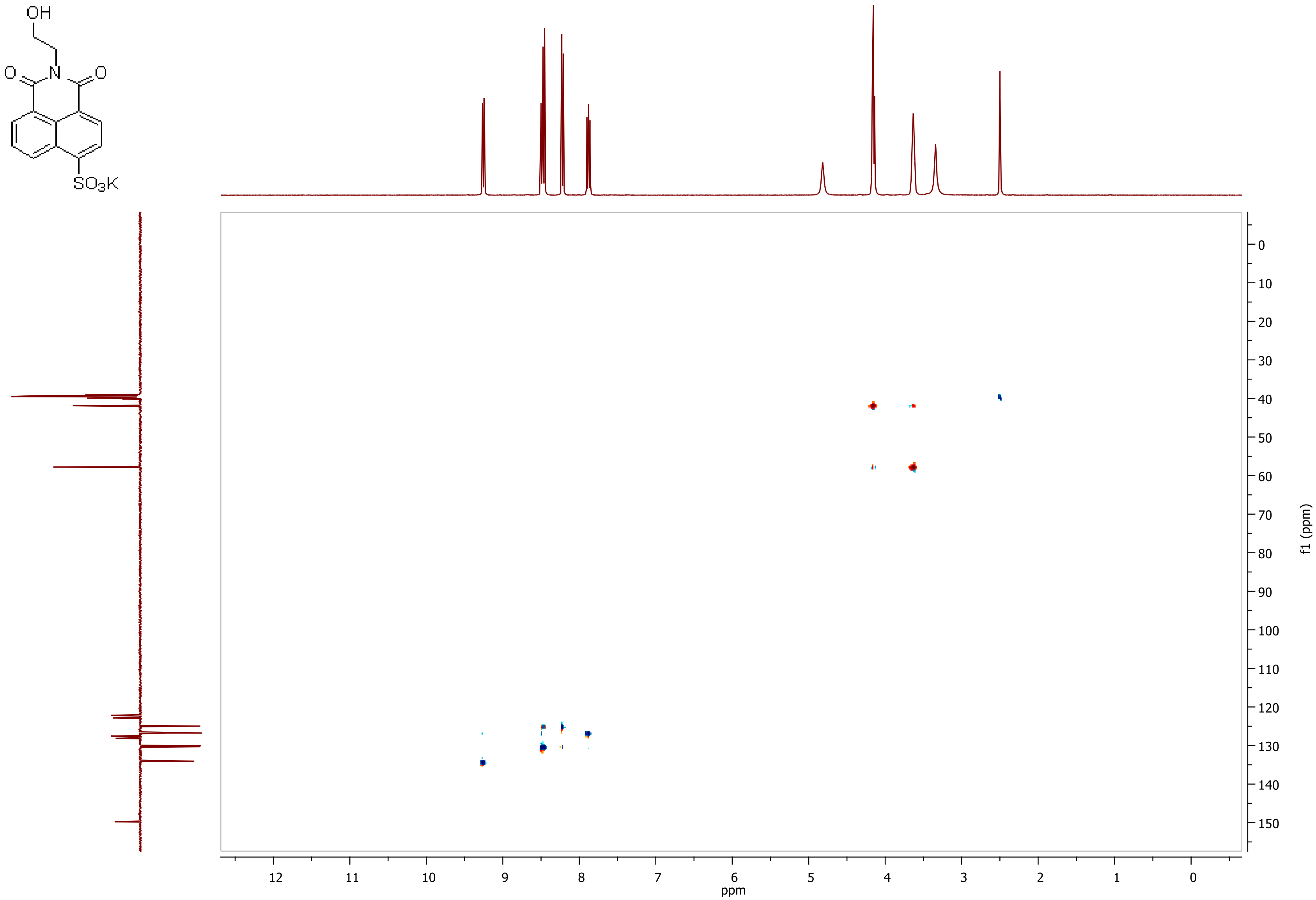
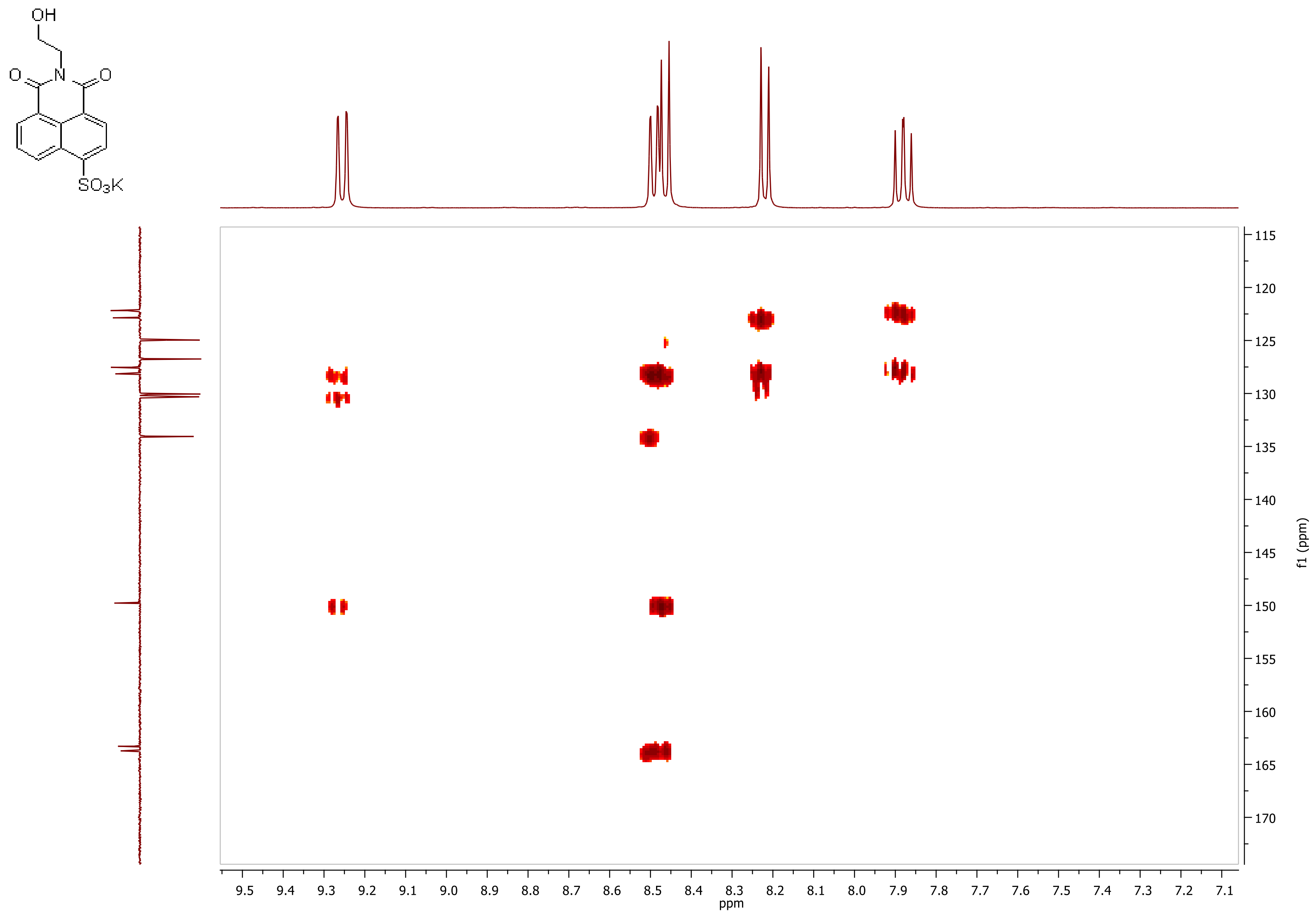
O
N
O
SO3K
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



OH
O
N
O
SO3K
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)



OH
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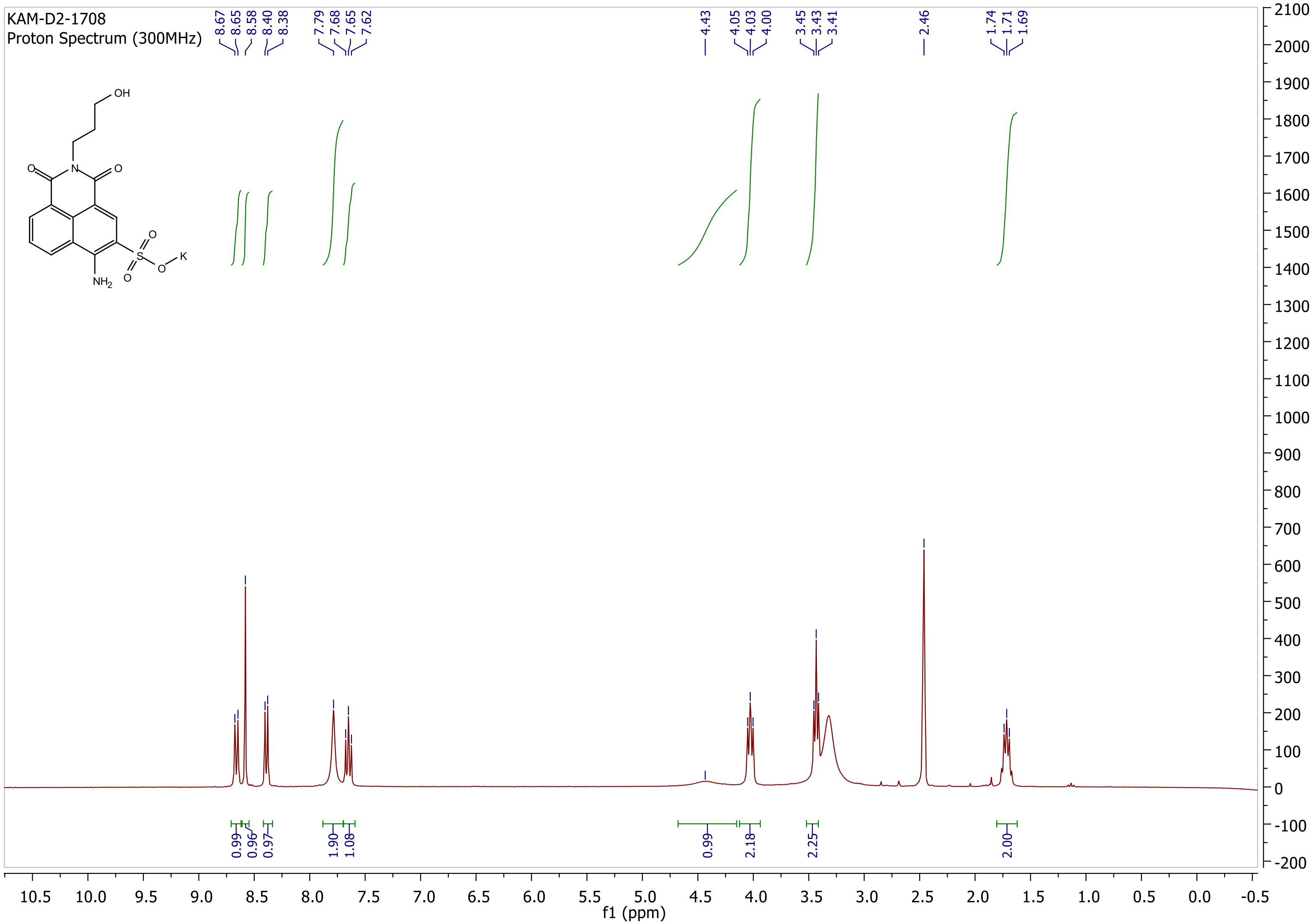
N
O
SO3K
9.5
9.4
9.3
9.2
9.1
9.0
8.9
8.8
8.7
8.6
8.5
8.4
8.3
8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
7.3
7.2
7.1
ppm
115
120
125
130
135
140
145
150
155
160
165
170
f1 (ppm)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Proton Spectrum (300MHz)
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8.65
8.58
8.40
8.38
7.79
7.68
7.65
7.62
4.43
4.05
4.03
4.00
3.45
3.43
3.41
2.46
1.74
1.71
1.69
OH
N
O
O
O
O
S
O
K
NH2
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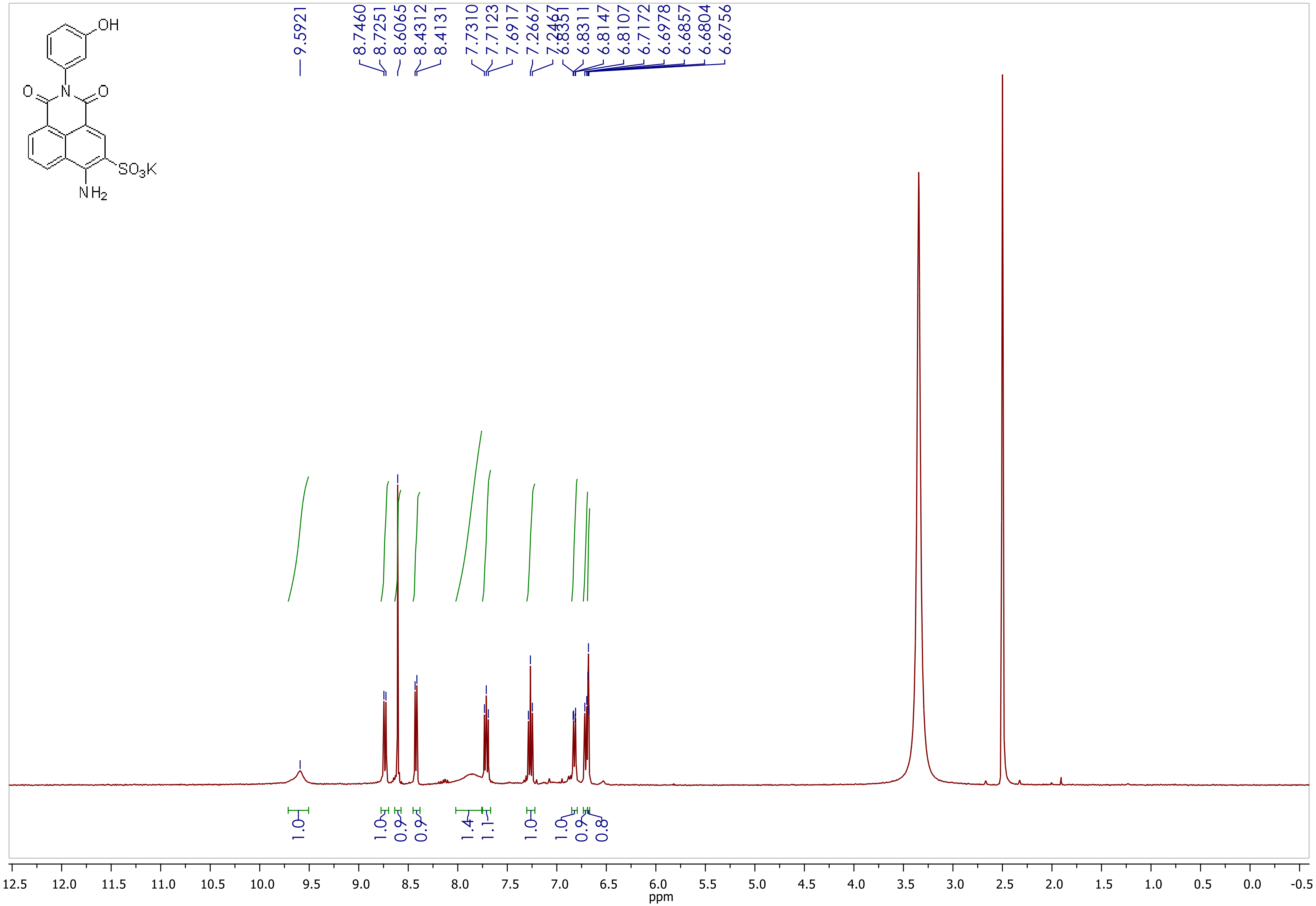
0.96
0.97
1.90
1.08
0.99
2.18
2.25
2.00
f1 (ppm)



OH
O
N
O
SO3K
NH2
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8.7251
8.6065
8.4312
8.4131
7.7310
7.7123
7.6917
7.2667
7.2467
6.8351
6.8311
6.8147
6.8107
6.7172
6.6978
6.6857
6.6804
6.6756
1.0
1.0
0.9
0.9
1.4
1.1
1.0
1.0
0.9
0.8
12.5
12.0
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
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3.0
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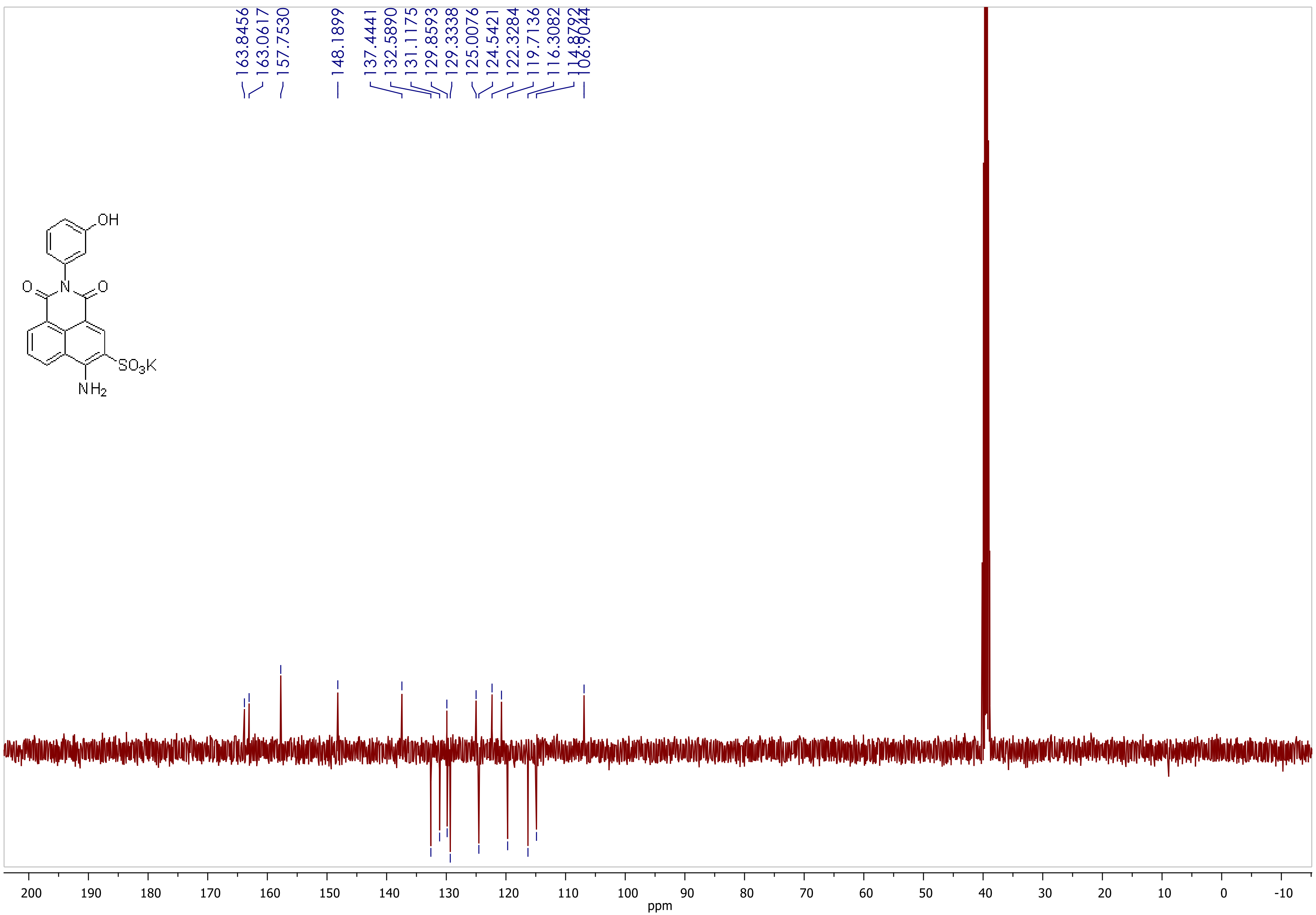
1.0
0.5
0.0
-0.5
ppm



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157.7530
148.1899
137.4441
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131.1175
129.8593
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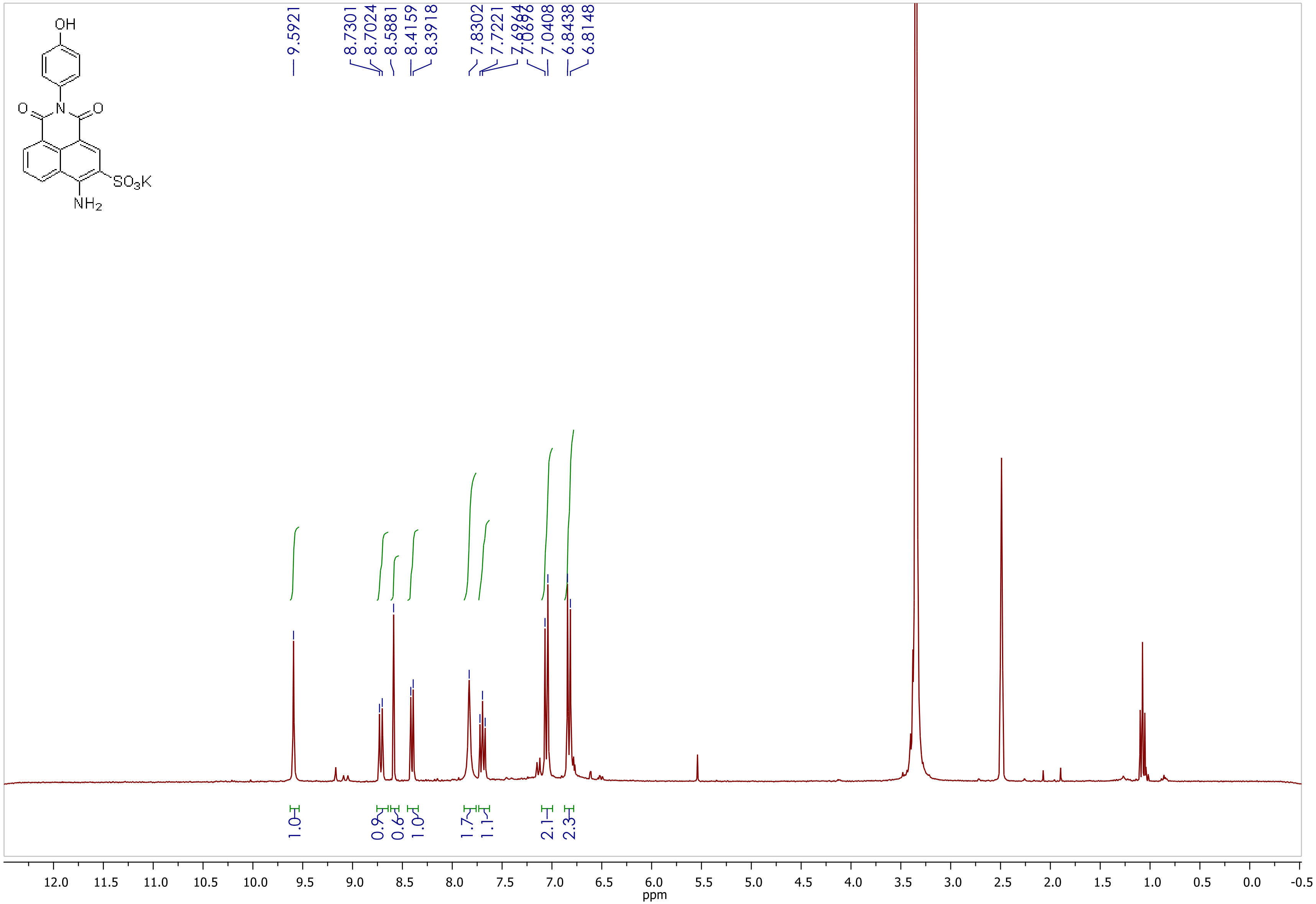
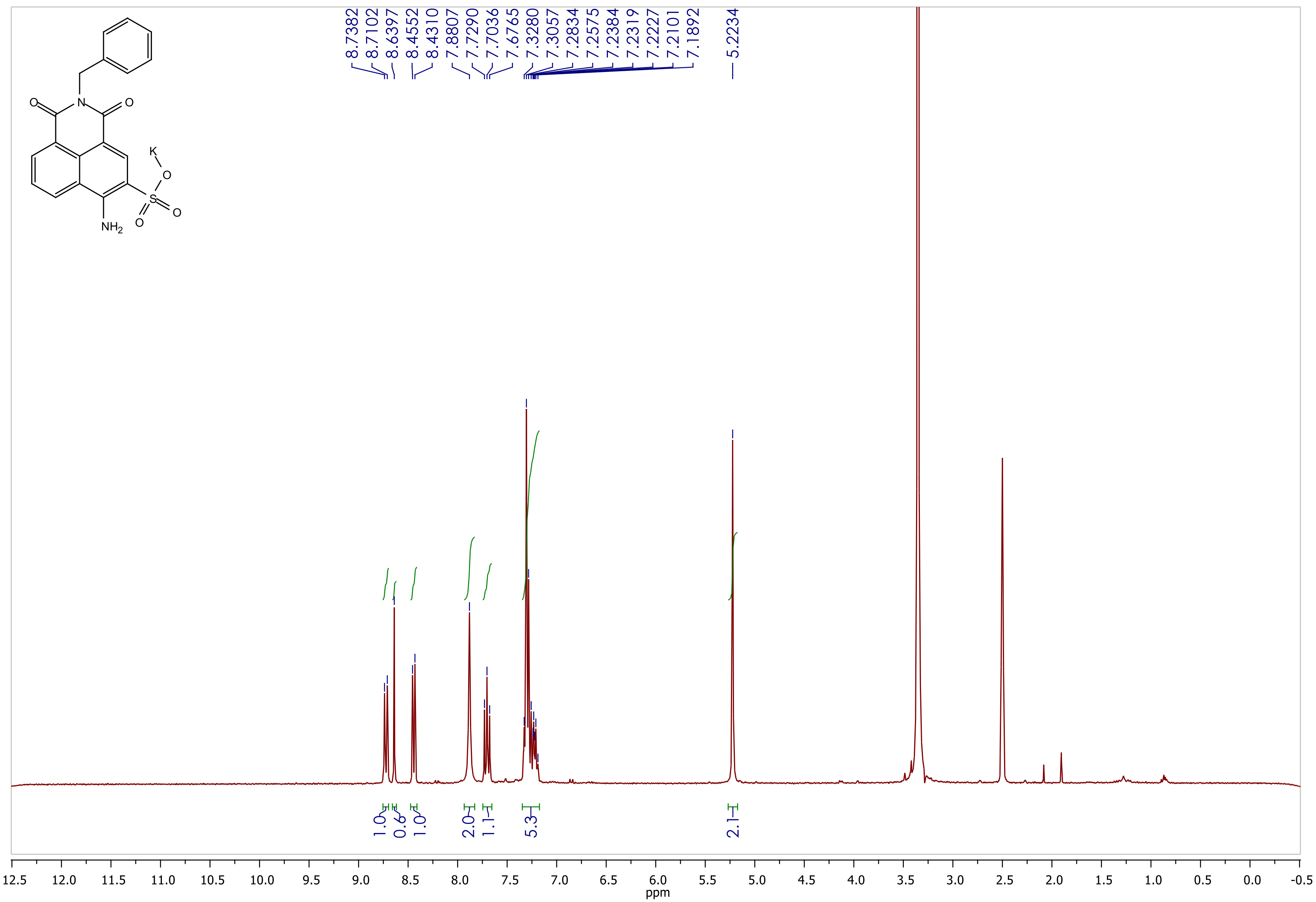
125.0076
124.5421
122.3284
119.7136
116.3082
114.8792
106.9044
OH
O
N
O
SO3K
NH2
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


OH
O
N
O
SO3K
NH2
9.5921
8.7301
8.7024
8.5881
8.4159
8.3918
7.8302
7.7221
7.6964
7.6696
7.0408
6.8438
6.8148
1.0
0.9
0.6
1.0
1.7
1.1
2.1
2.3
12.0
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
ppm



8.7382
8.7102
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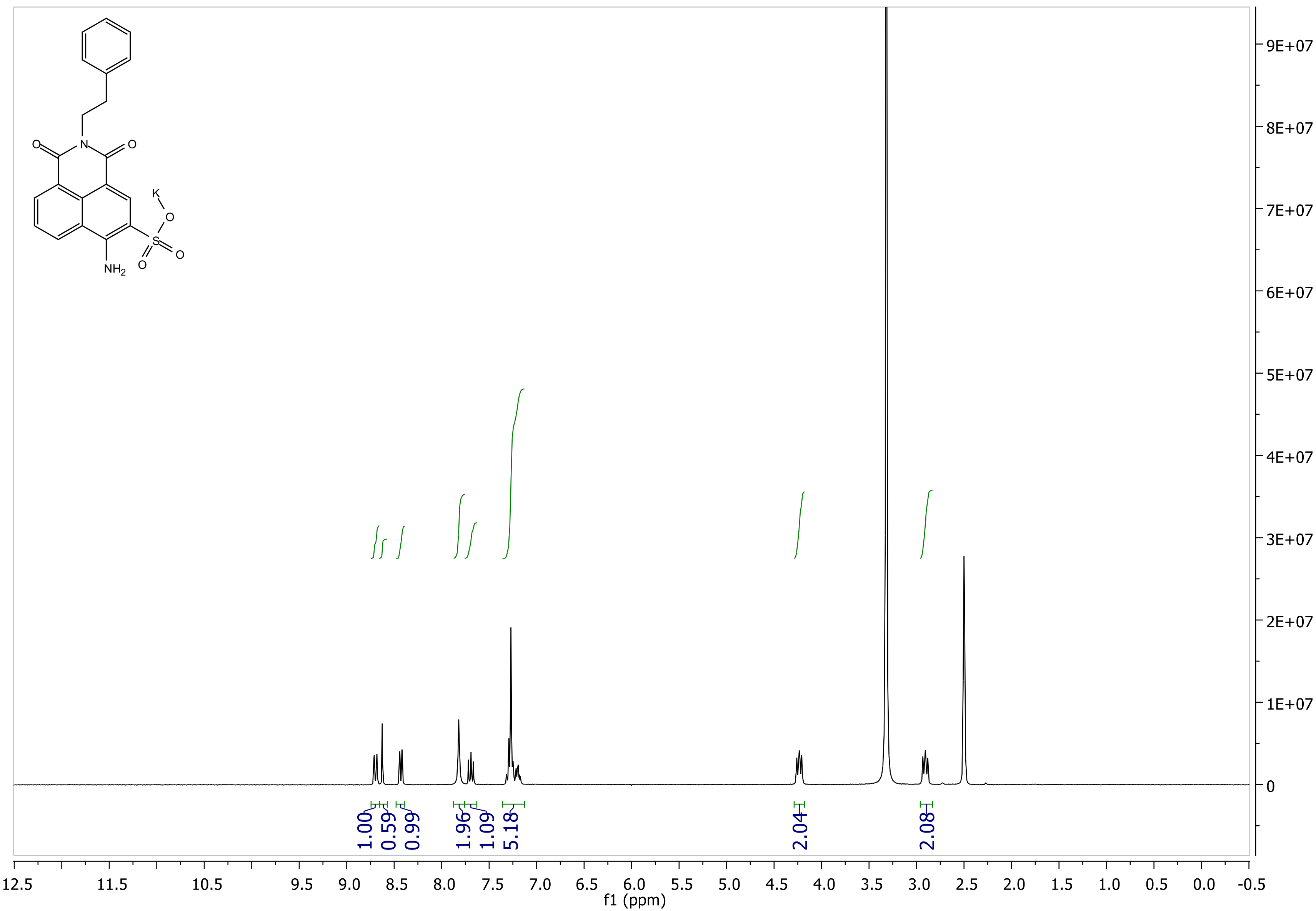
8.4552
8.4310
7.8807
7.7290
7.7036
7.6765
7.3280
7.3057
7.2834
7.2575
7.2384
7.2319
7.2227
7.2101
7.1892
5.2234
1.0
0.6
1.0
2.0
1.1
5.3
2.1
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
O
N
O
K
O
S
O
O
NH2



K
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S
O
O
N
O
O
NH2
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0.99
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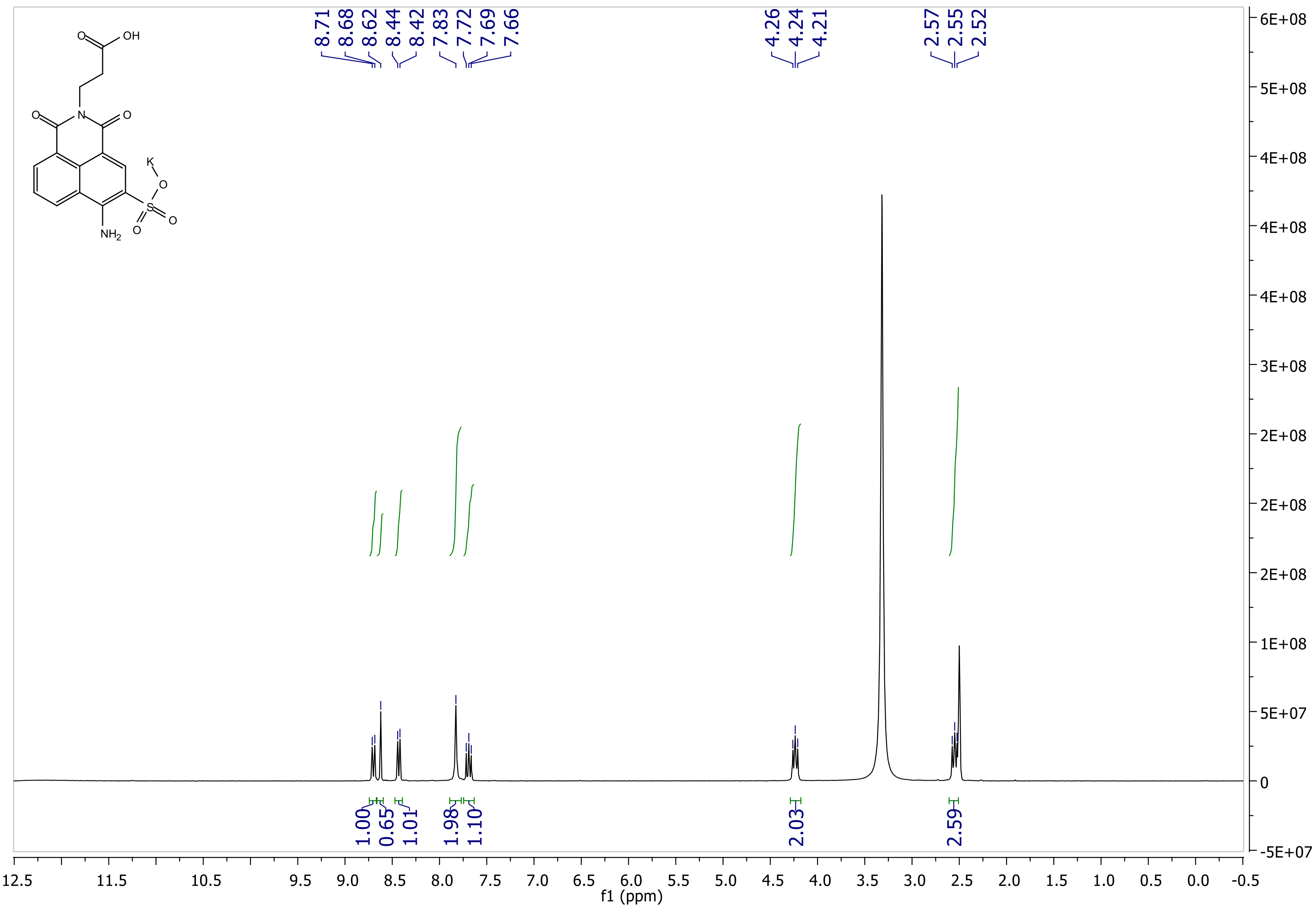
1.09
5.18
2.04
2.08
9E+07
8E+07
7E+07
6E+07
5E+07
4E+07
3E+07
2E+07
1E+07
0
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)



OH
O
N
O
O
K
O
S
O
O
NH2
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8.62
8.44
8.42
7.83
7.72
7.69
7.66
4.26
4.24
4.21
2.57
2.55
2.52
1.00
0.65
1.01
1.98
1.10
2.03
2.59
6E+08
5E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
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
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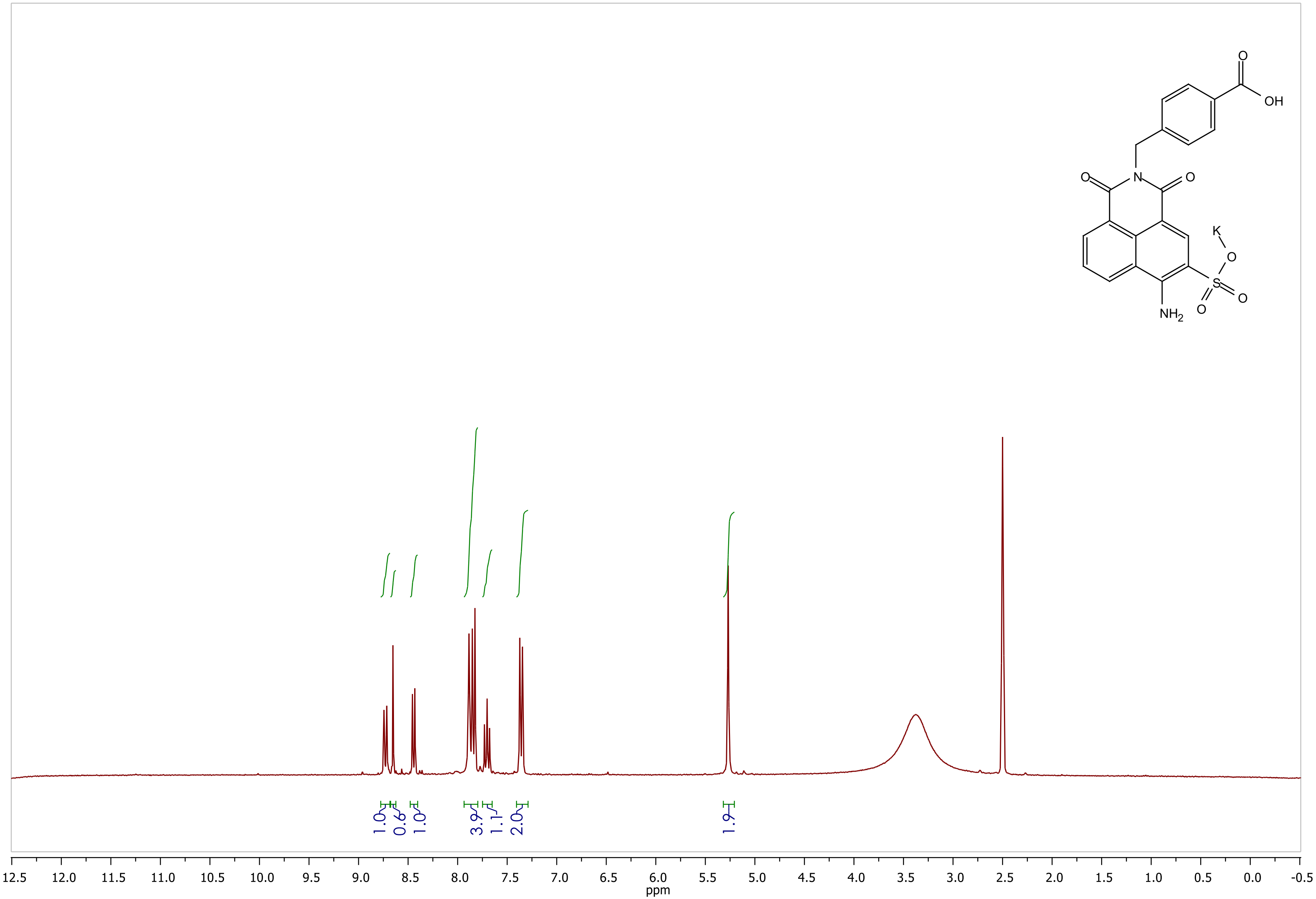
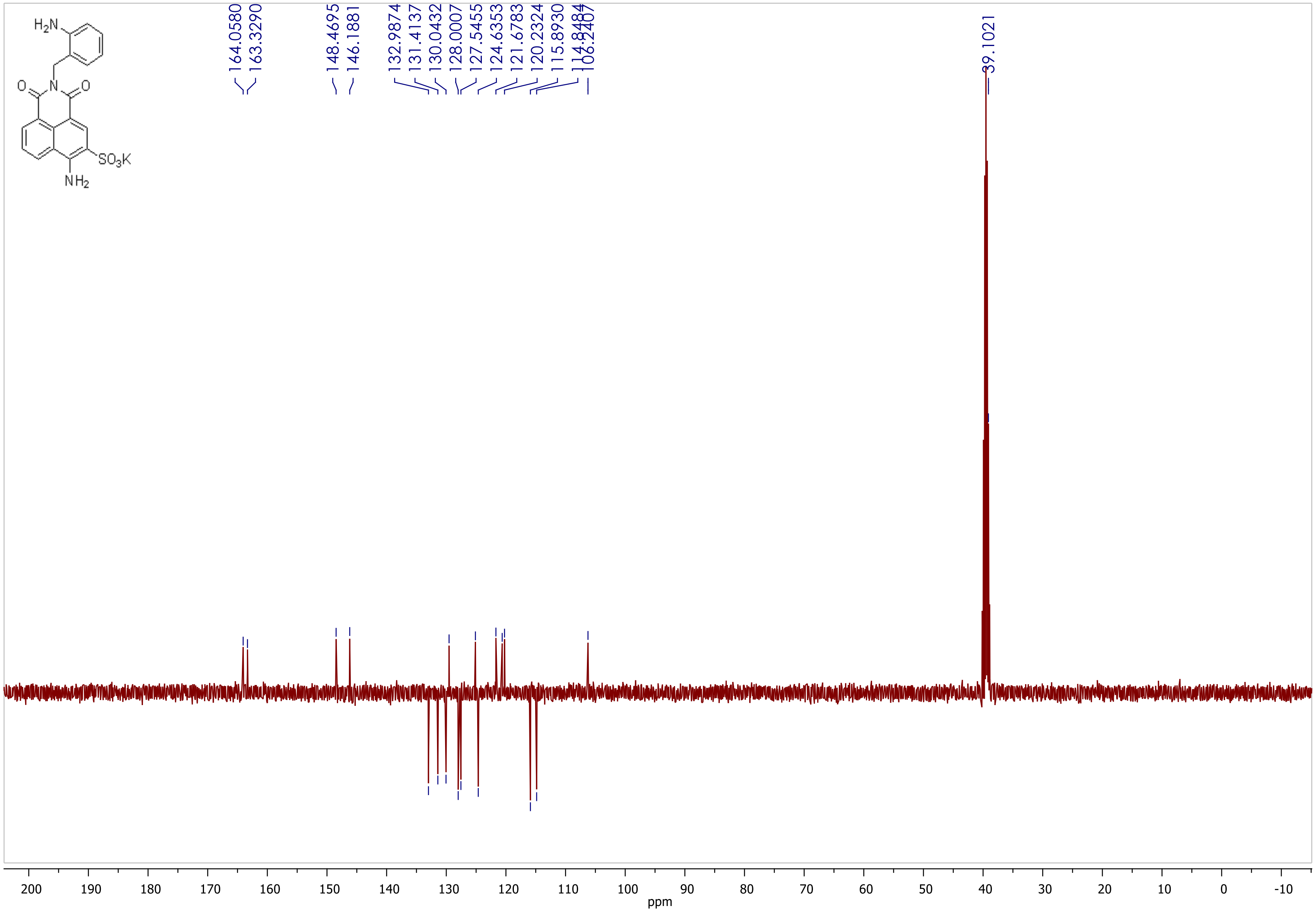
0.0
-0.5
f1 (ppm)



O
OH
O
N
O
K
O
S
O
O
NH2
1.0
0.6
1.0
3.9
1.1
2.0
1.9
12.5 12.0 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
ppm


H2N
O
N
O
SO3K
NH2
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163.3290
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130.0432
128.0007
127.5455
124.6353
121.6783
120.2324
115.8930
114.8484
106.2407
39.1021
200
190
180
170
160
150
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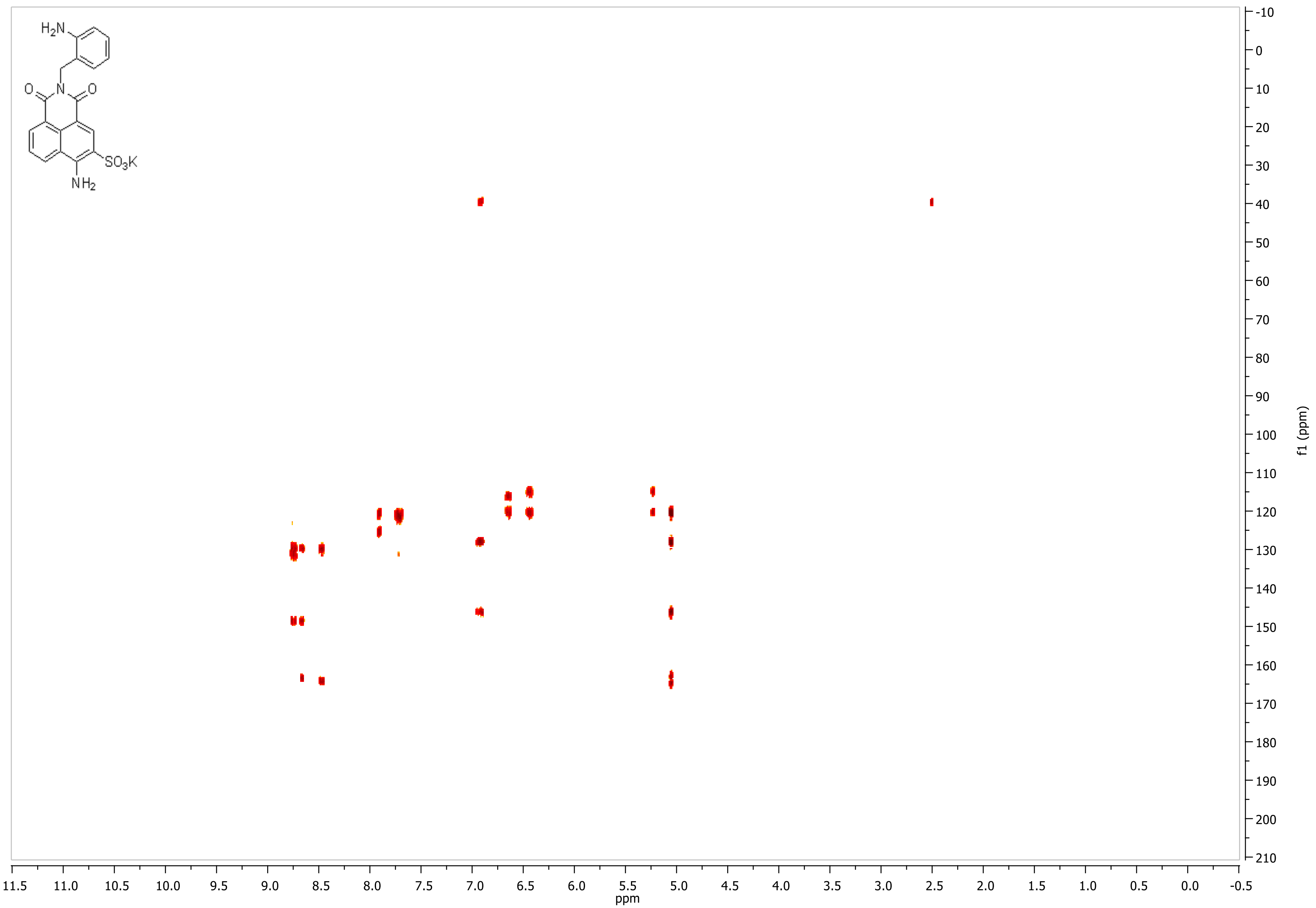
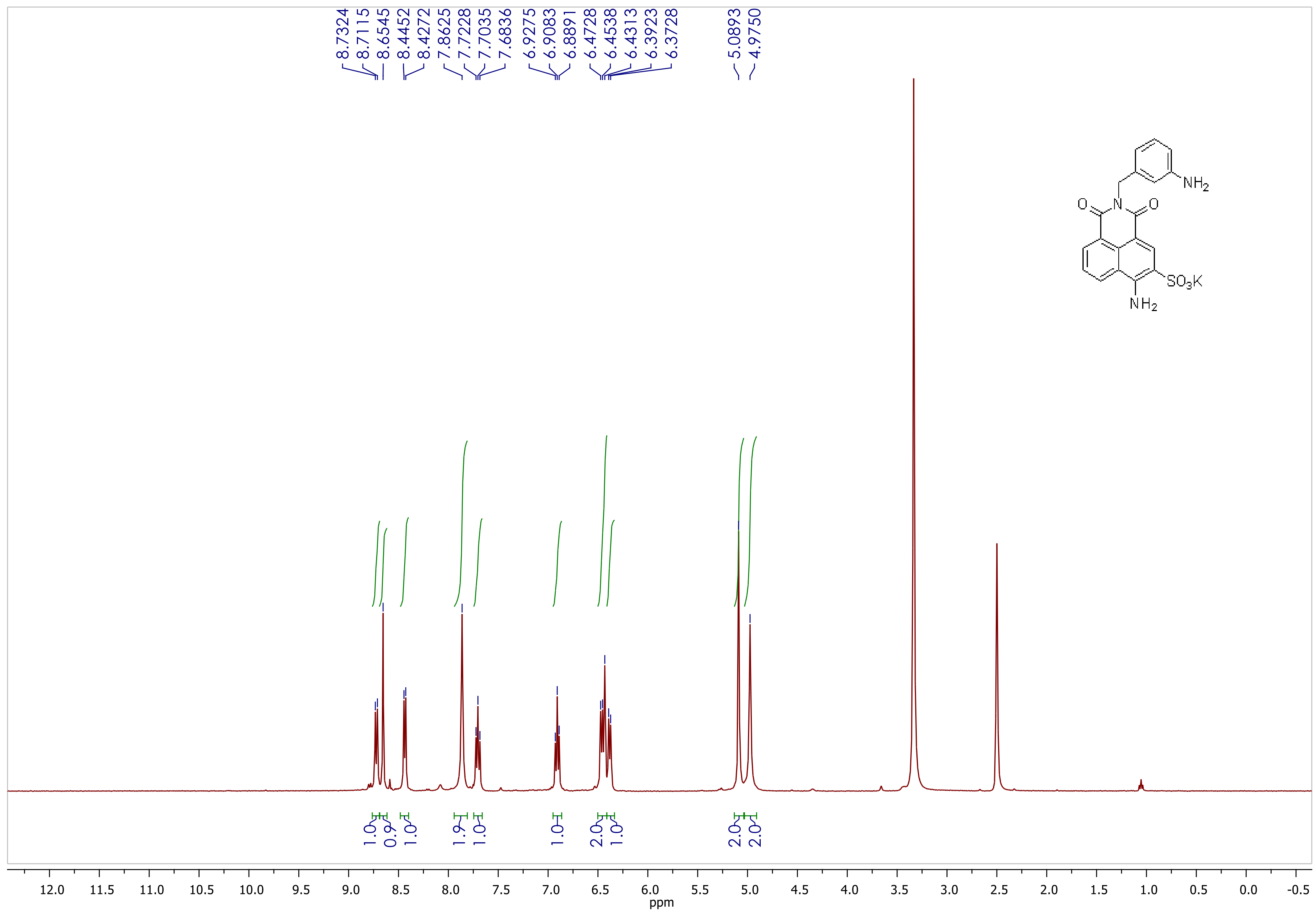
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm



H2N
O
N
O
SO3K
NH2
f1 (ppm)
ppm



8.7324
8.7115
8.6545
8.4452
8.4272
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7.7228
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7.6836
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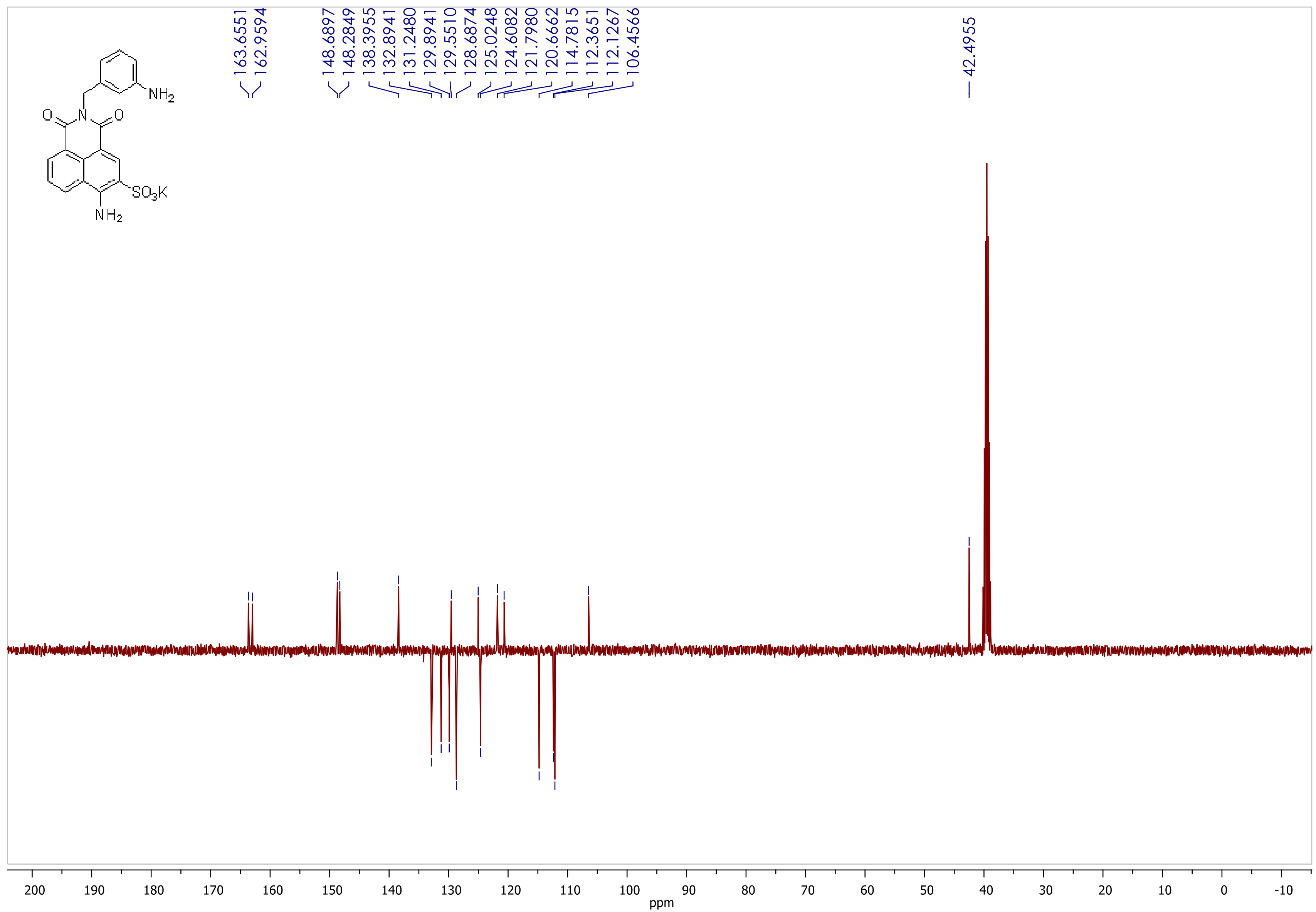
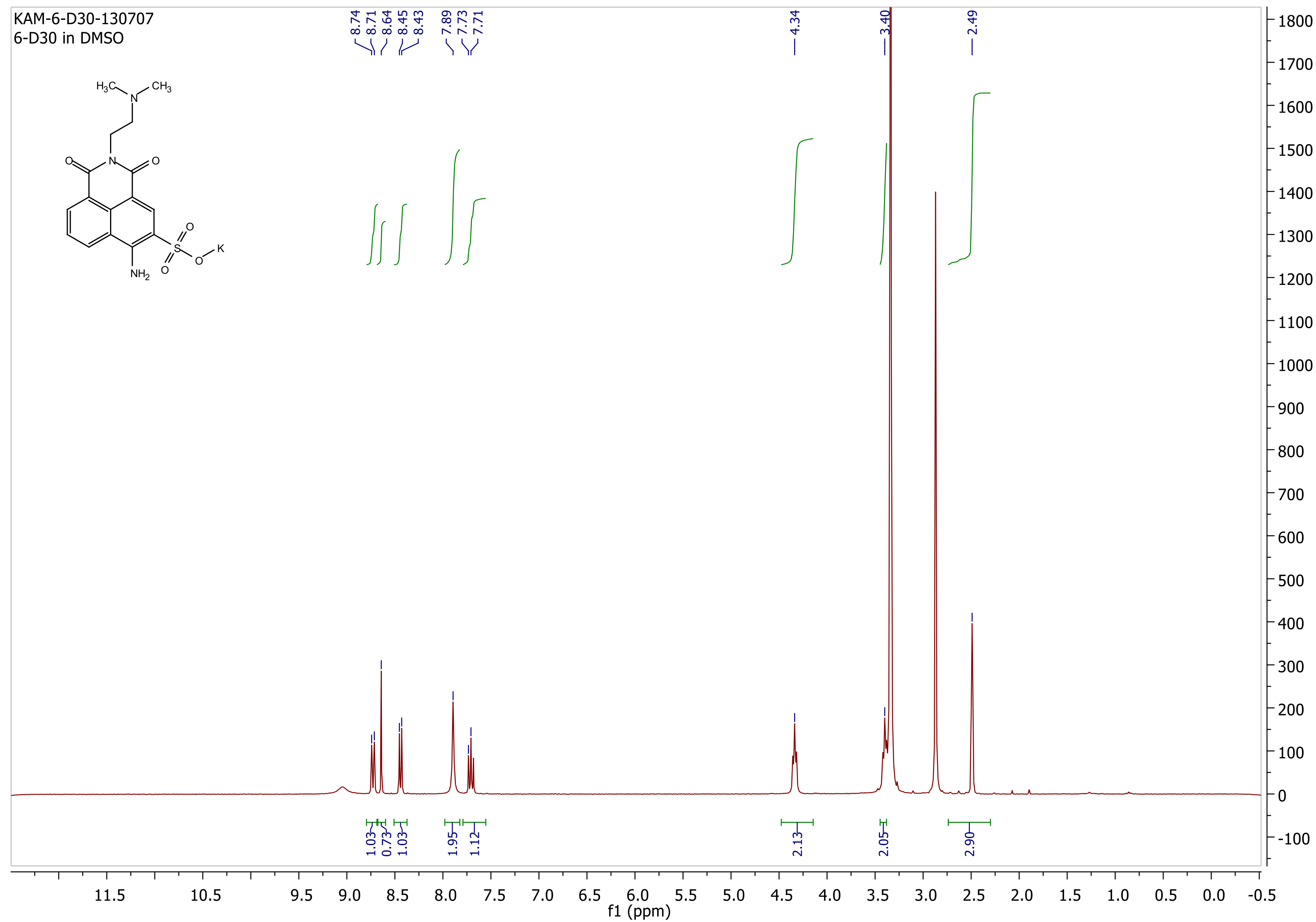
6.9083
6.8891
6.4728
6.4538
6.4313
6.3923
6.3728
5.0893
4.9750
1.0
0.9
1.0
1.9
1.0
1.0
2.0
1.0
2.0
2.0
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
NH2
O
N
O
SO3K
NH2



163.6551
162.9594
148.6897
148.2849
138.3955
132.8941
131.2480
129.8941
129.5510
128.6874
125.0248
124.6082
121.7980
120.6662
114.7815
112.3651
112.1267
106.4566
42.4955
NH2
O
N
O
SO3K
NH2
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
ppm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6-D30 in DMSO
H3C N CH3
O N O
S O O O K
NH2
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4.34
3.40
2.49
1.03 0.73 1.03 1.95 1.12
2.13
2.05
2.90
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 -0.5
f1 (ppm)
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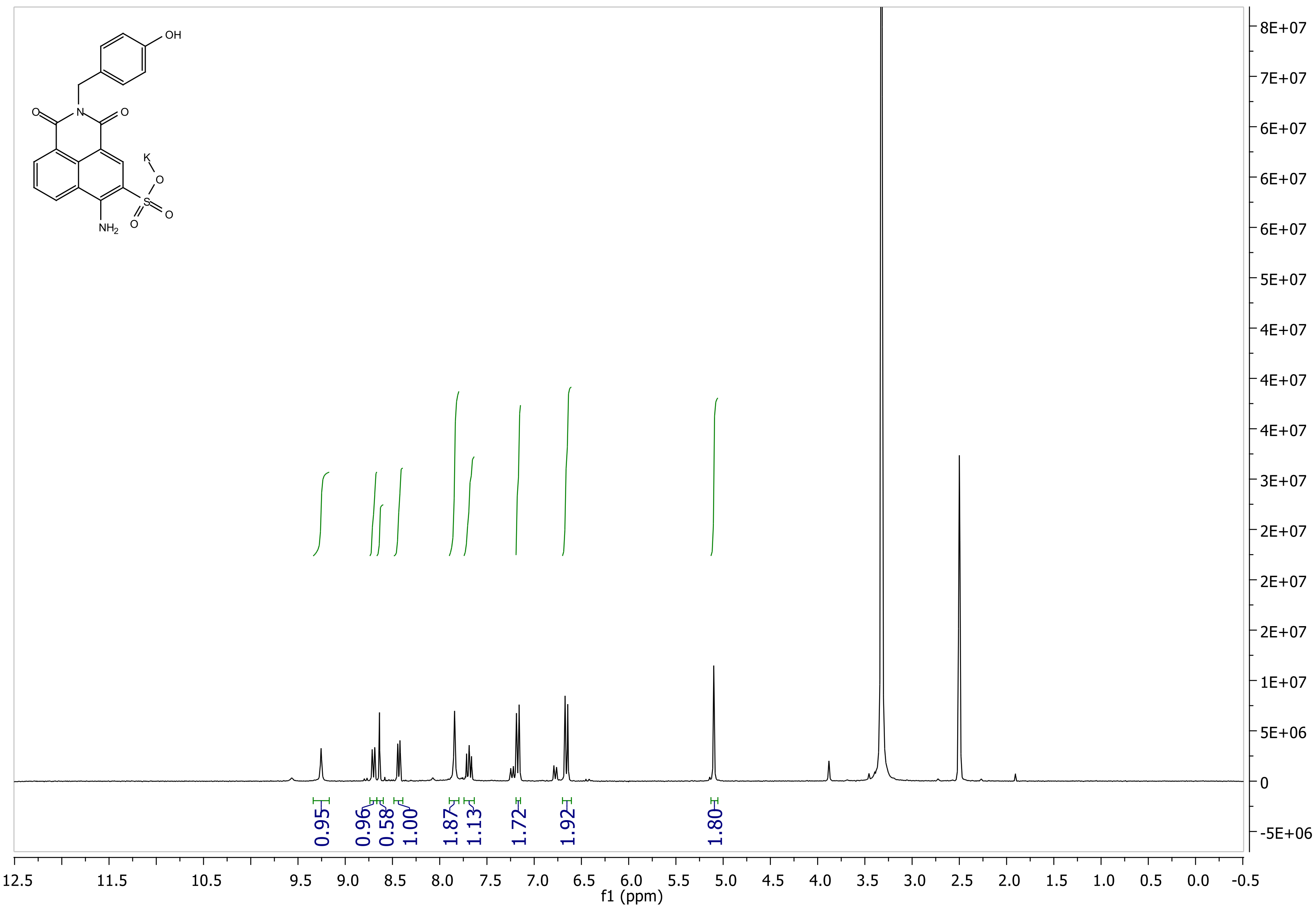

OH
O
N
O
K
O
S
O
O
NH2
0.95
0.96
0.58
1.00
1.87
1.13
1.72
1.92
1.80
8E+07
7E+07
6E+07
6E+07
6E+07
5E+07
4E+07
4E+07
4E+07
3E+07
2E+07
2E+07
2E+07
1E+07
5E+06
0
-5E+06
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)