Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Iron-Mediated Site-Selective Oxidative C-H/C-H Cross Coupling of Aryl Radical with Quinones: Synthesis of β-secretase -1 Inhibitor B and Related Arylated Quinones

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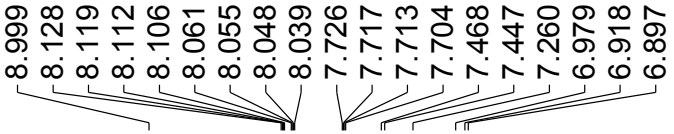
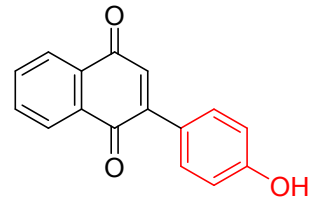
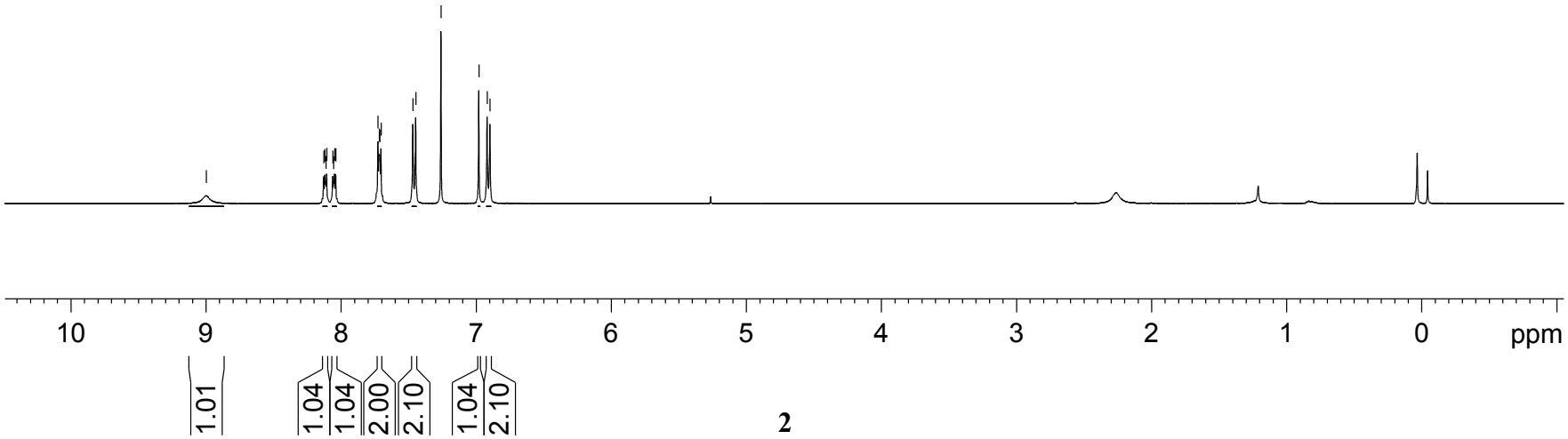
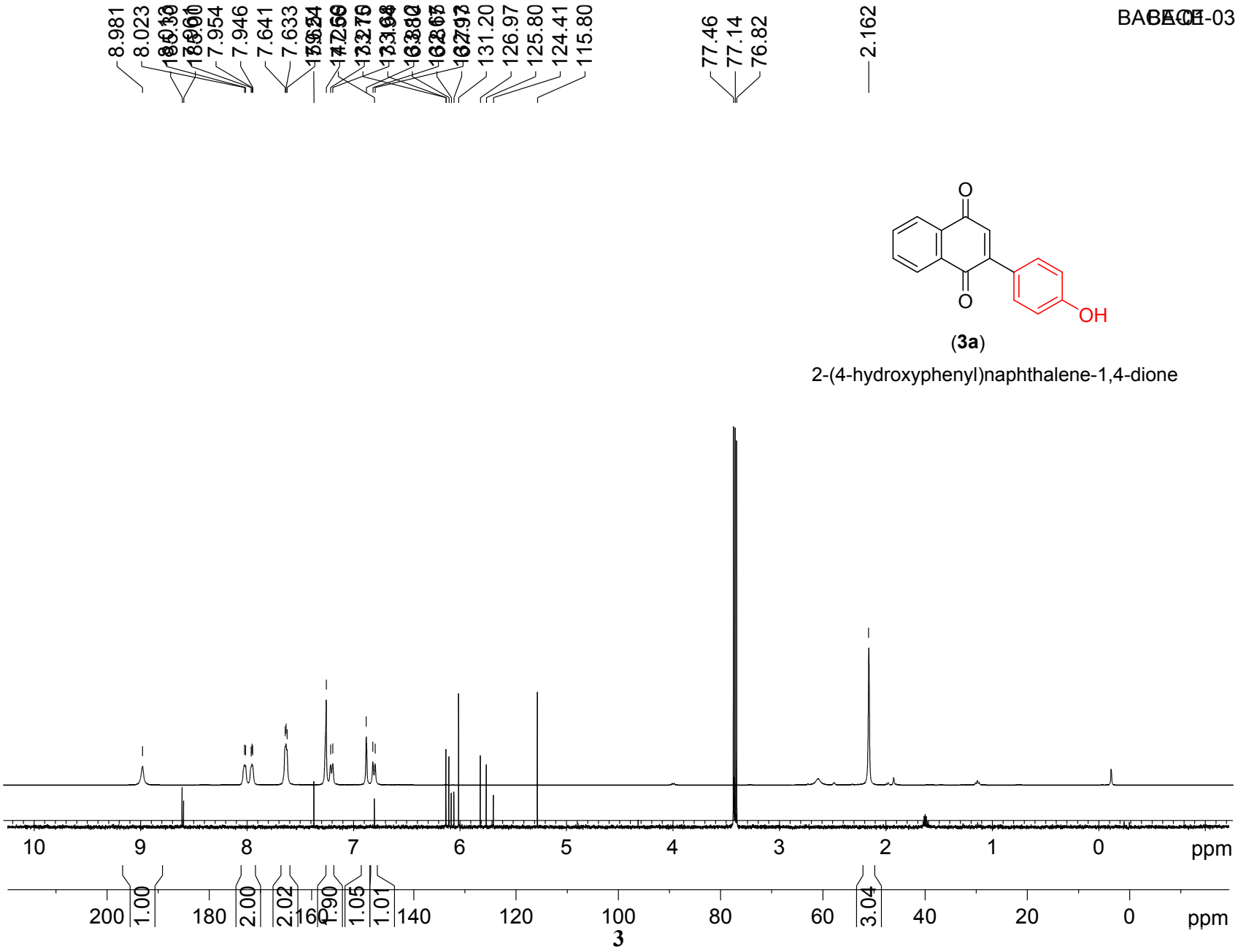




(**3a**)

2-(4-hydroxyphenyl)naphthalene-1,4-dione



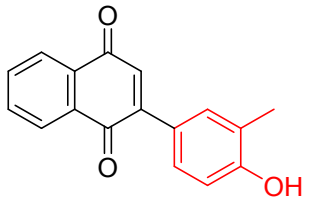


(**3a**)

2-(4-hydroxyphenyl)naphthalene-1,4-dione

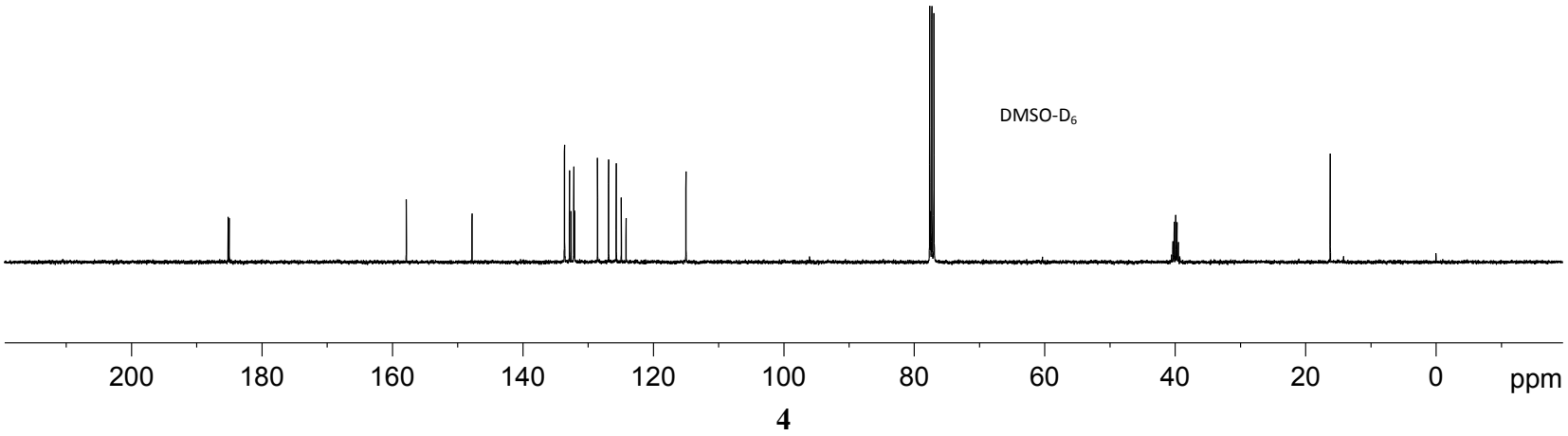
BACE-03

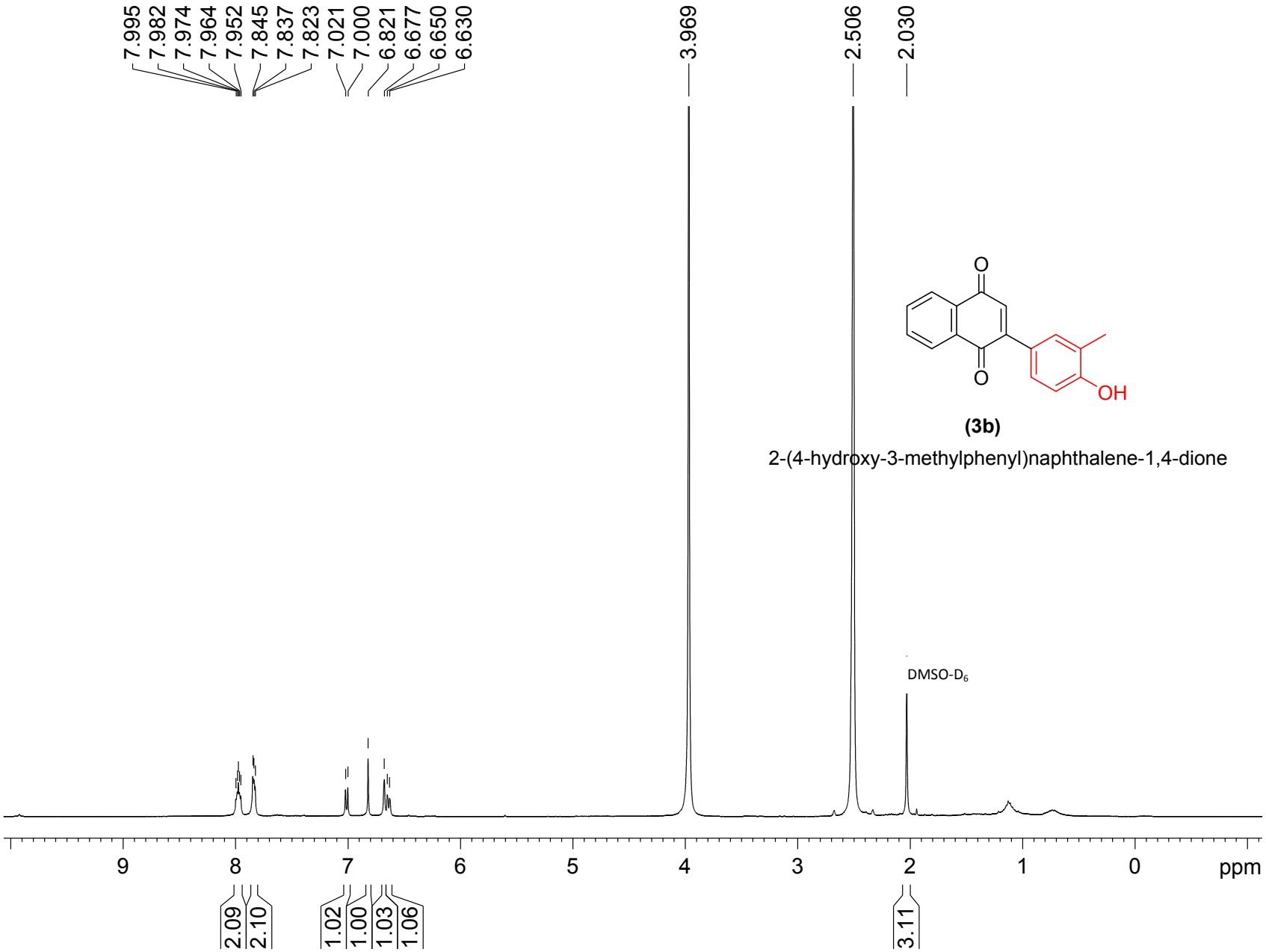
185.18
185.01
157.86
147.78
133.61
133.59
132.85
132.62
132.18
132.06
128.54
126.85
125.67
124.90
124.17
114.98
77.60
77.28
76.96
16.21



(3b)

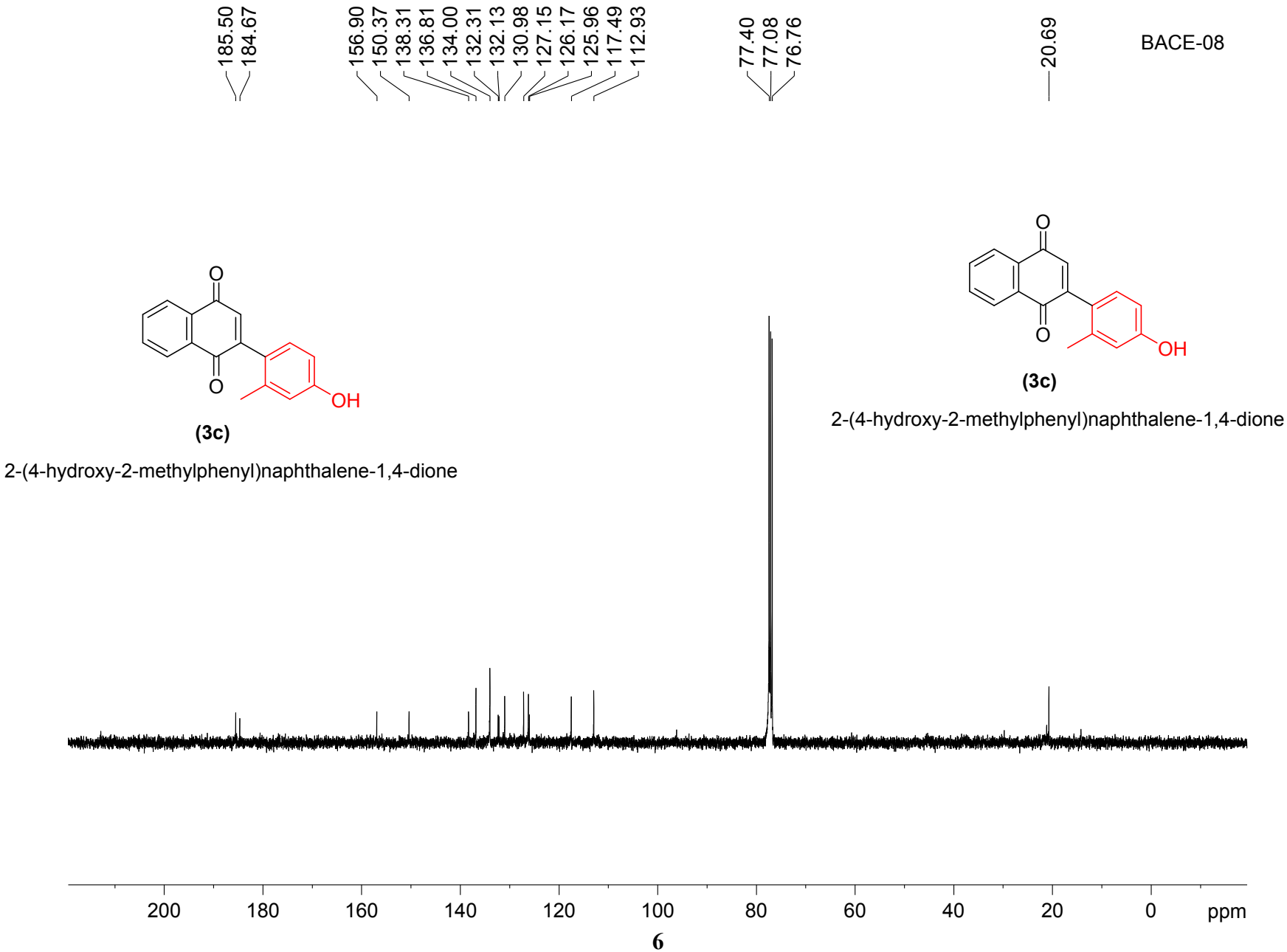
2-(4-hydroxy-3-methylphenyl)naphthalene-1,4-dione



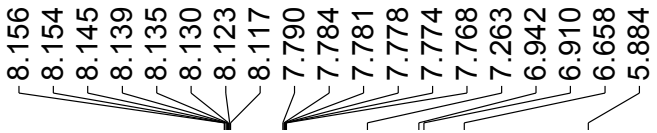


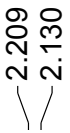
(3b)

2-(4-hydroxy-3-methylphenyl)naphthalene-1,4-dione



(3c)
2-(4-hydroxy-2-methylphenyl)naphthalene-1,4-dione





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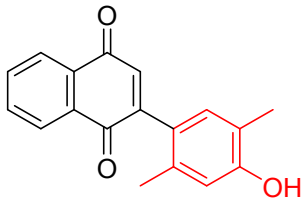
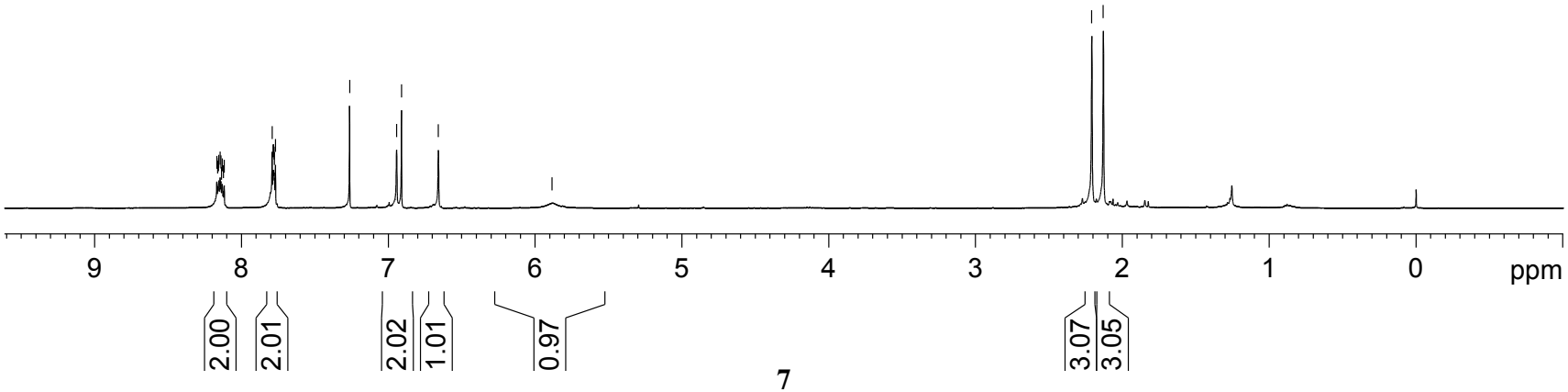
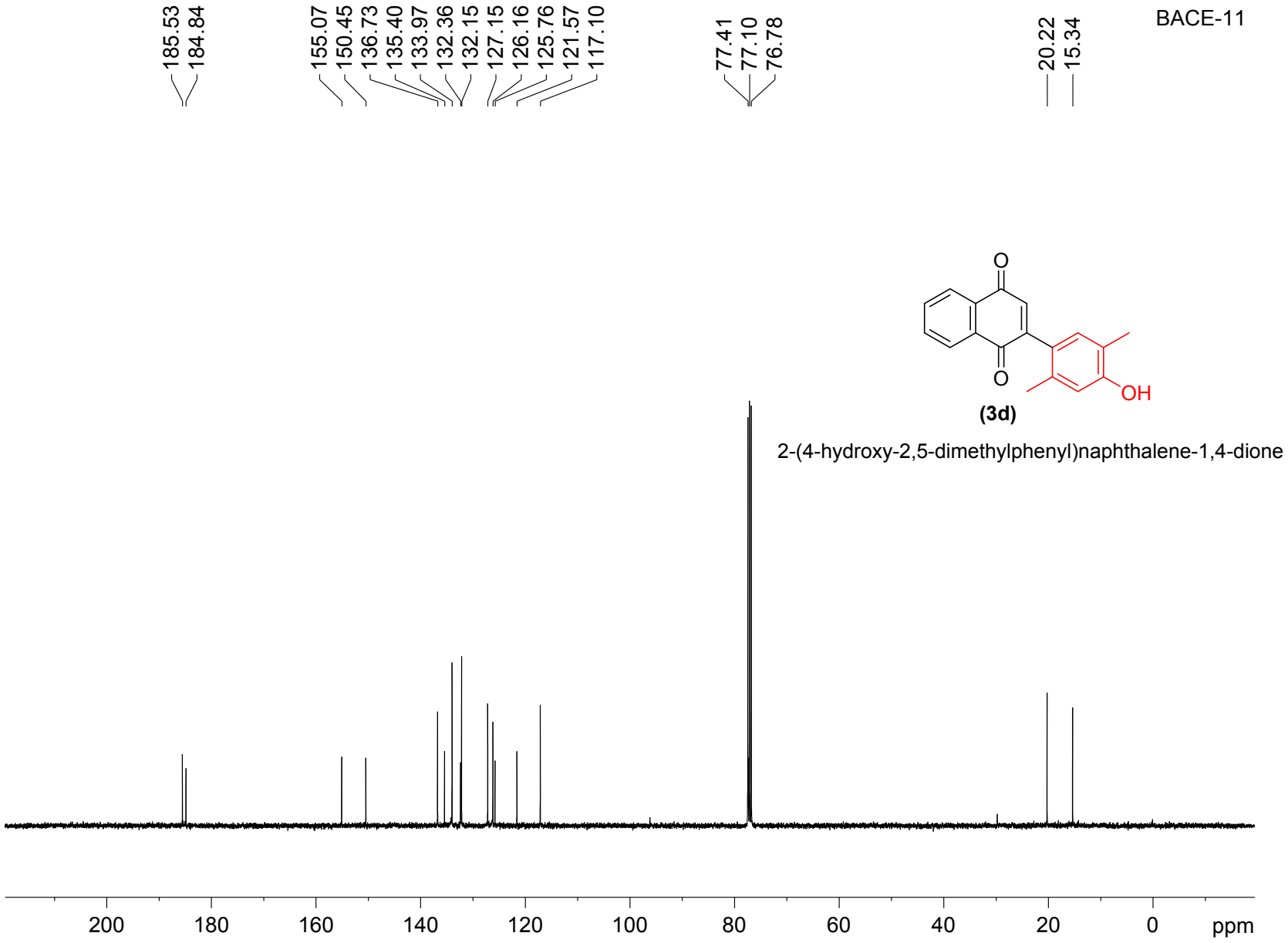


(3d)

2-(4-hydroxy-2,5-dimethylphenyl)naphthalene-1,4-dione

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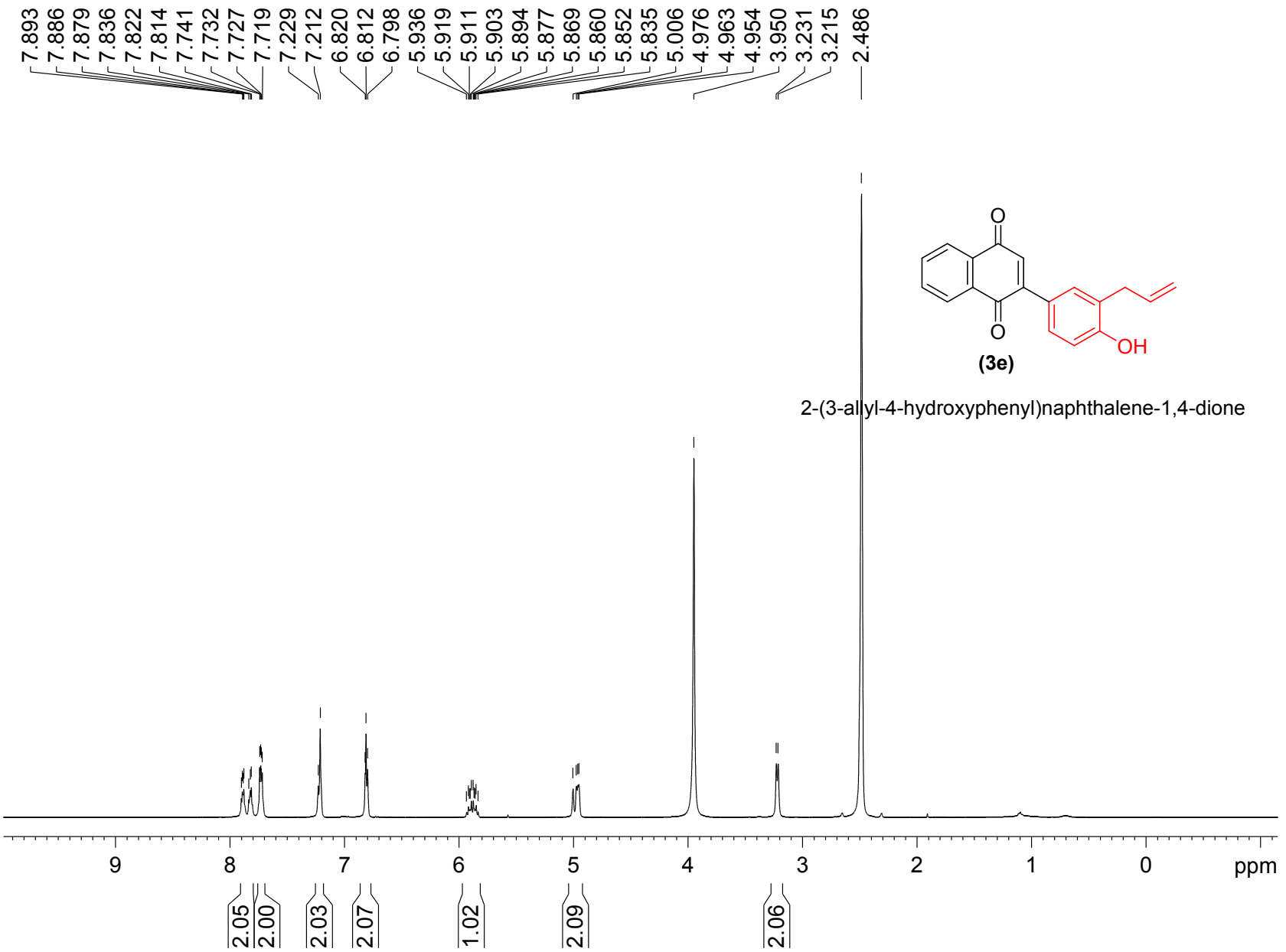
155.07
150.45
136.73
135.40
133.97
132.36
132.15
127.15
126.16
125.76
121.57
117.10
77.41
77.10
76.78
20.22
15.34
BACE-11
O
O
OH
(3d)
2-(4-hydroxy-2,5-dimethylphenyl)naphthalene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm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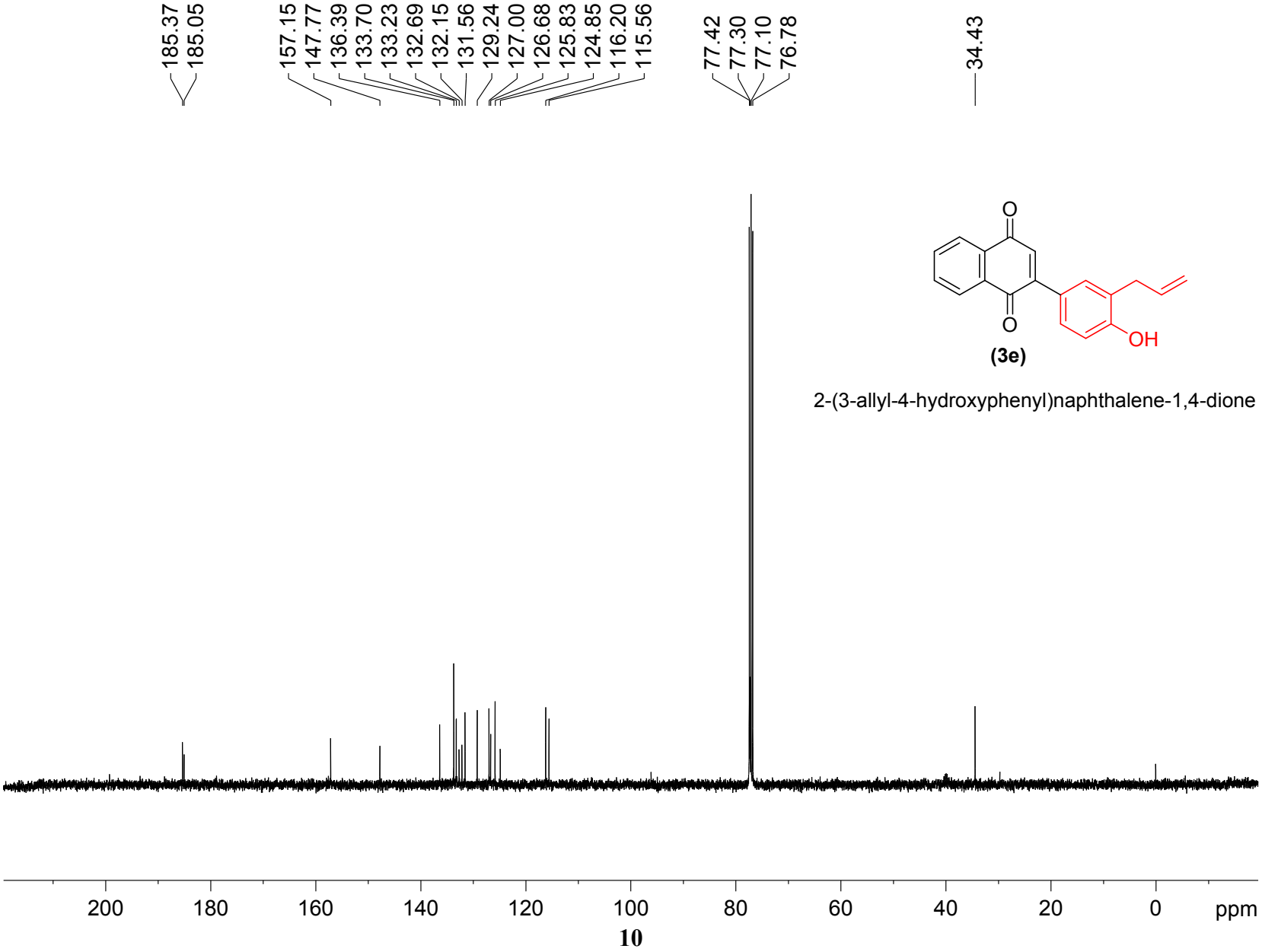
7.879
7.836
7.822
7.814
7.741
7.732
7.727
7.719
7.229
7.212
6.820
6.812
6.798
5.936
5.919
5.911
5.903
5.894
5.877
5.869
5.860
5.852
5.835
5.006
4.976
4.963
4.954
3.950
3.231
3.215
2.486
O
O
OH
(3e)
2-(3-allyl-4-hydroxyphenyl)naphthalene-1,4-dione
9
8
7
6
5
4
3
2
1
0
ppm
2.05
2.00
2.03
2.07
1.02
2.09
2.06

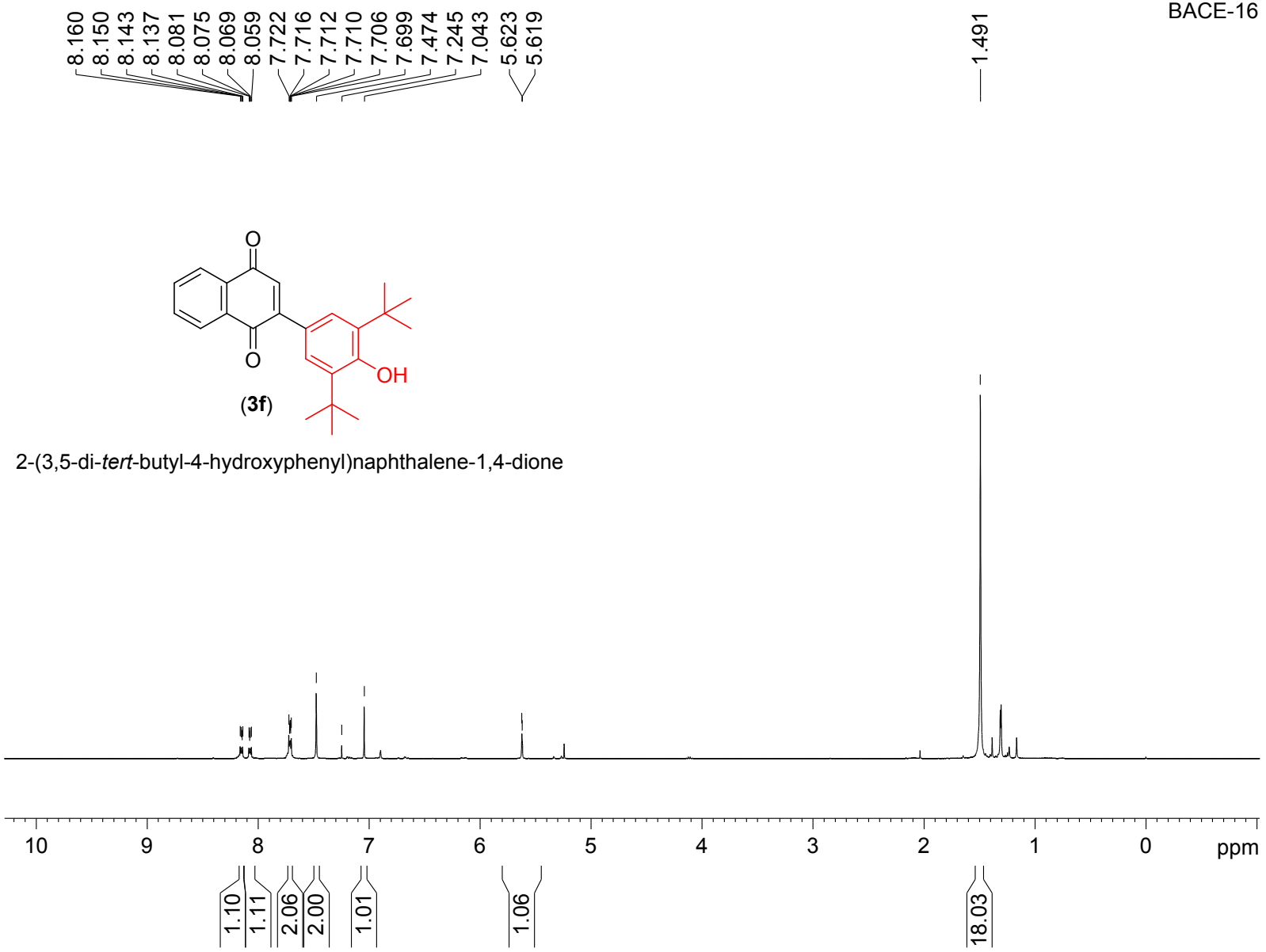
BACE-04



(3e)

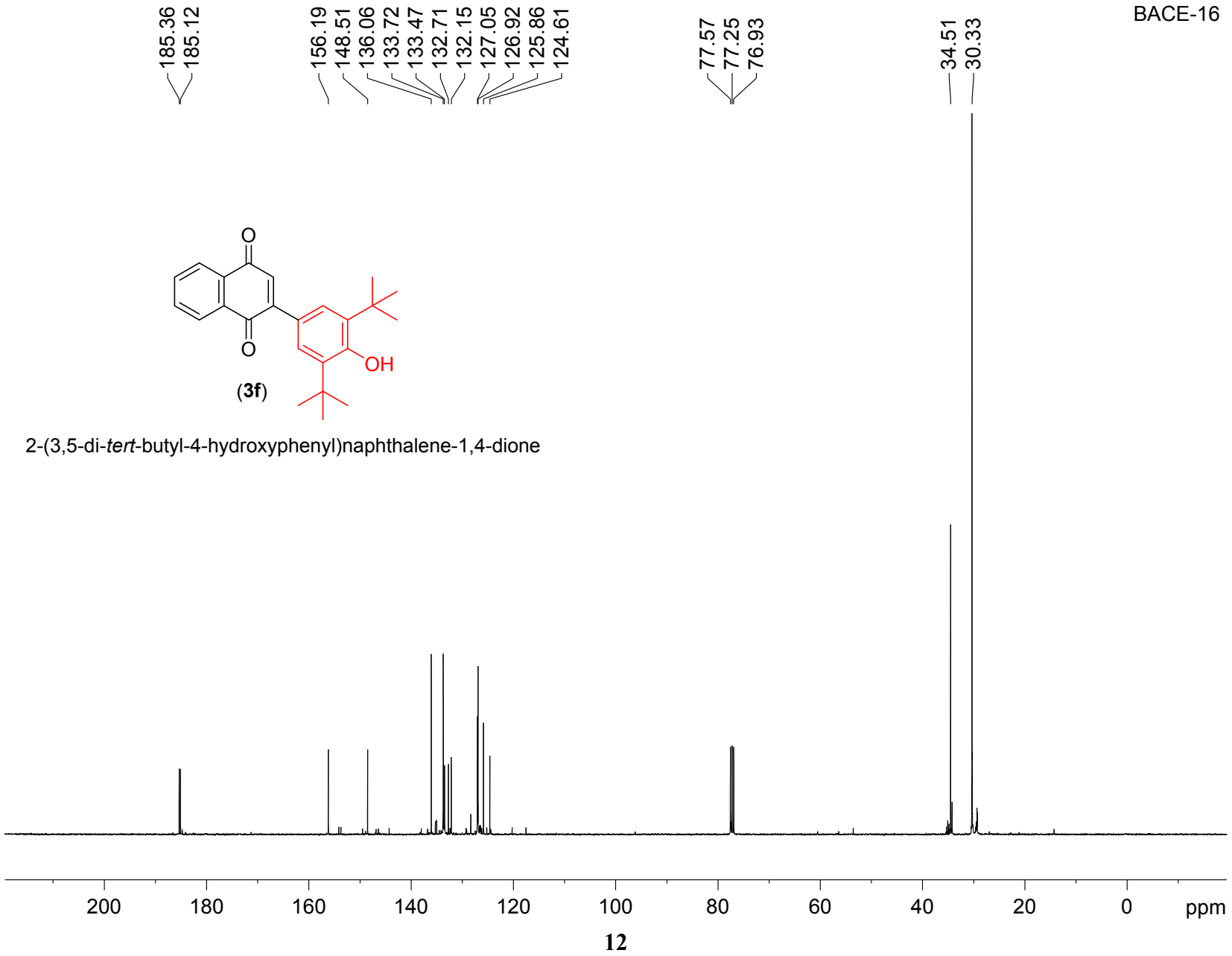
2-(3-allyl-4-hydroxyphenyl)naphthalene-1,4-dione

BACE-16



(**3f**)

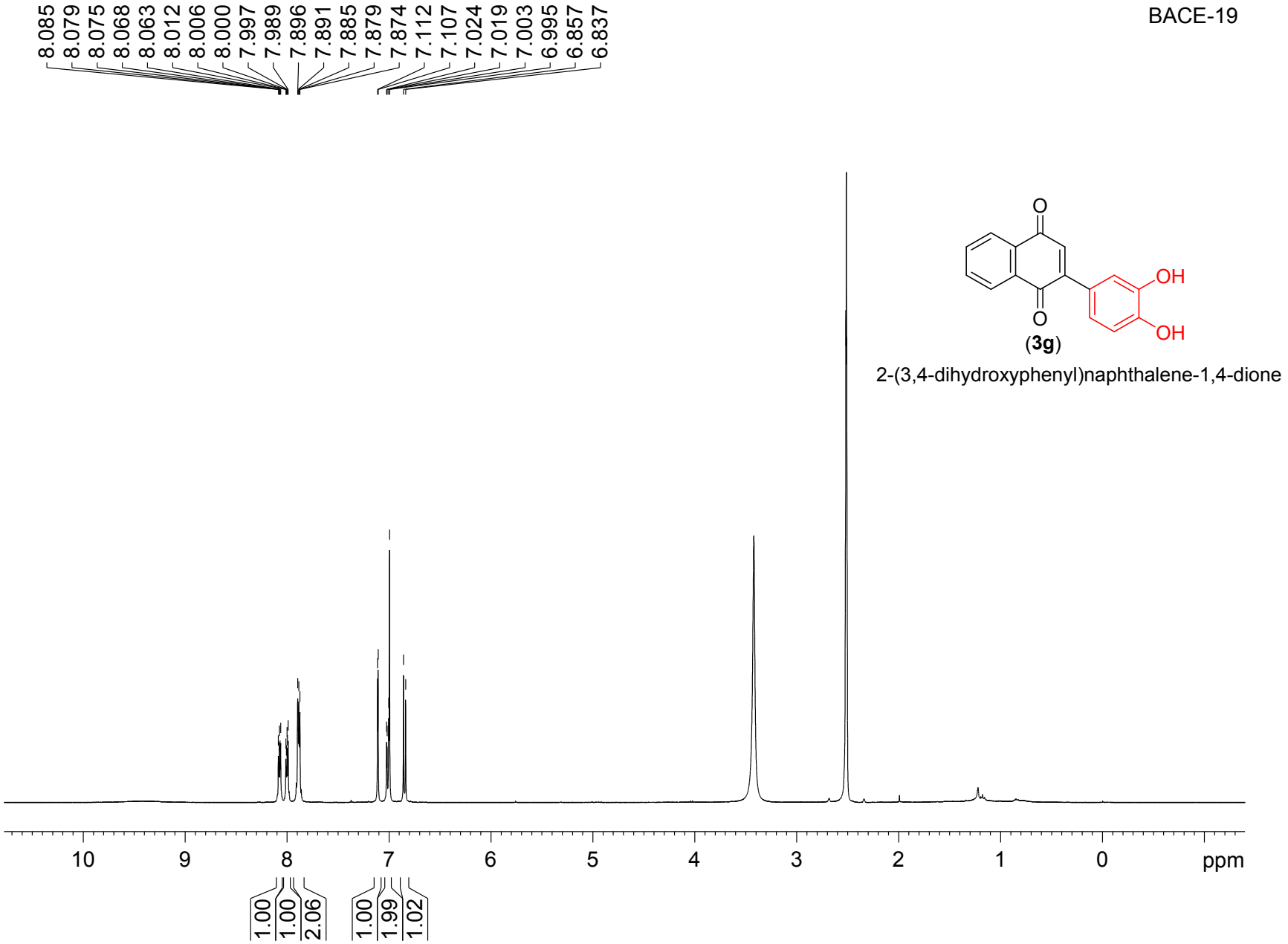
2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)naphthalene-1,4-dione



(**3f**)

2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)naphthalene-1,4-dione

BACE-19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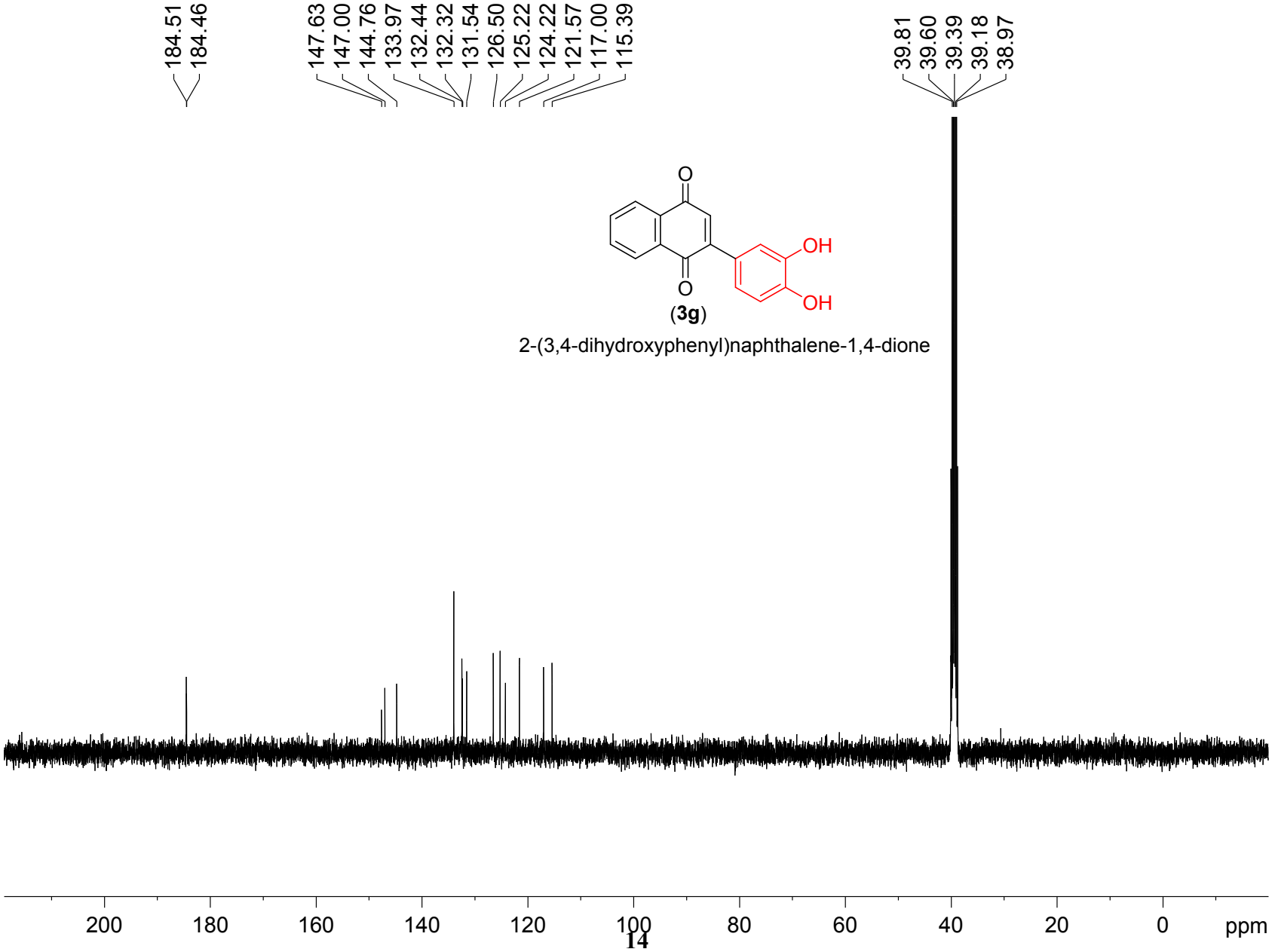
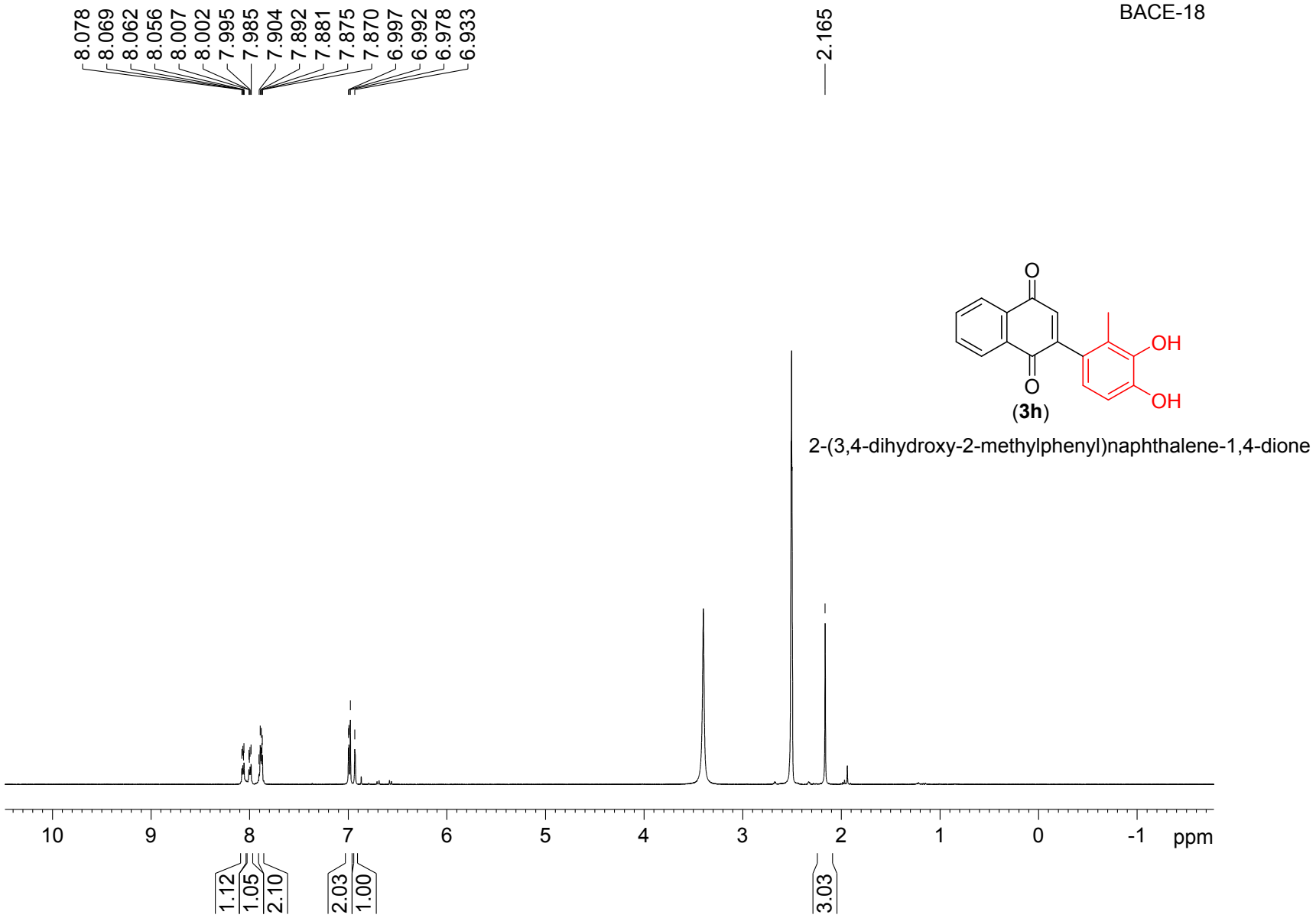
8.079
8.075
8.068
8.063
8.012
8.006
8.000
7.997
7.989
7.896
7.891
7.885
7.879
7.874
7.112
7.107
7.024
7.019
7.003
6.995
6.857
6.837
O
O
OH
OH
(3g)
2-(3,4-dihydroxyphenyl)naphthalene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.00
2.06
1.00
1.99
1.02

BACE-19



(**3g**)

2-(3,4-dihydroxyphenyl)naphthalene-1,4-dione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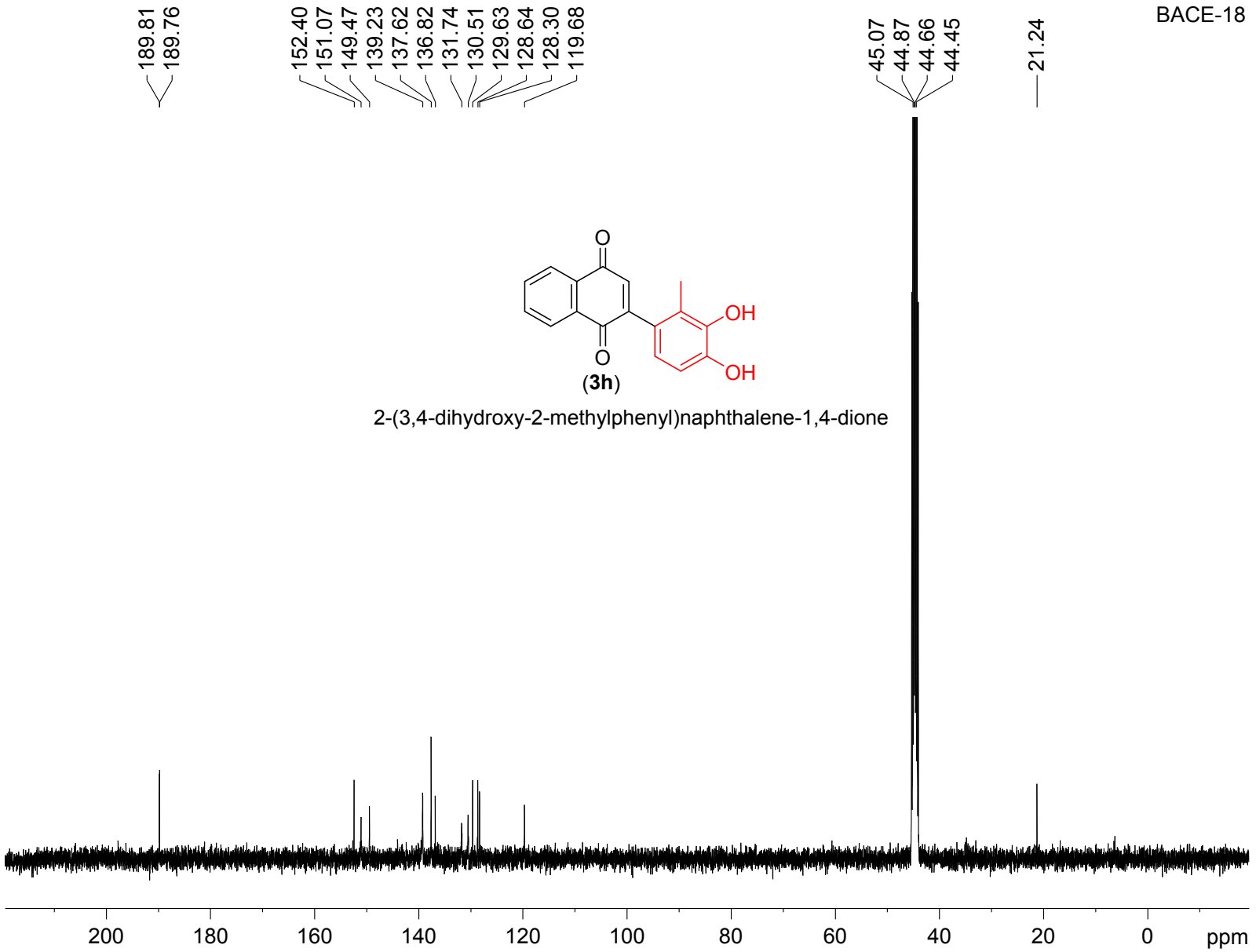
8.069
8.062
8.056
8.007
8.002
7.995
7.985
7.904
7.892
7.881
7.875
7.870
6.997
6.992
6.978
6.933
2.165
BACE-18
O
O
OH
OH
(3h)
2-(3,4-dihydroxy-2-methylphenyl)naphthalene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.12
1.05
2.10
2.03
1.00
3.03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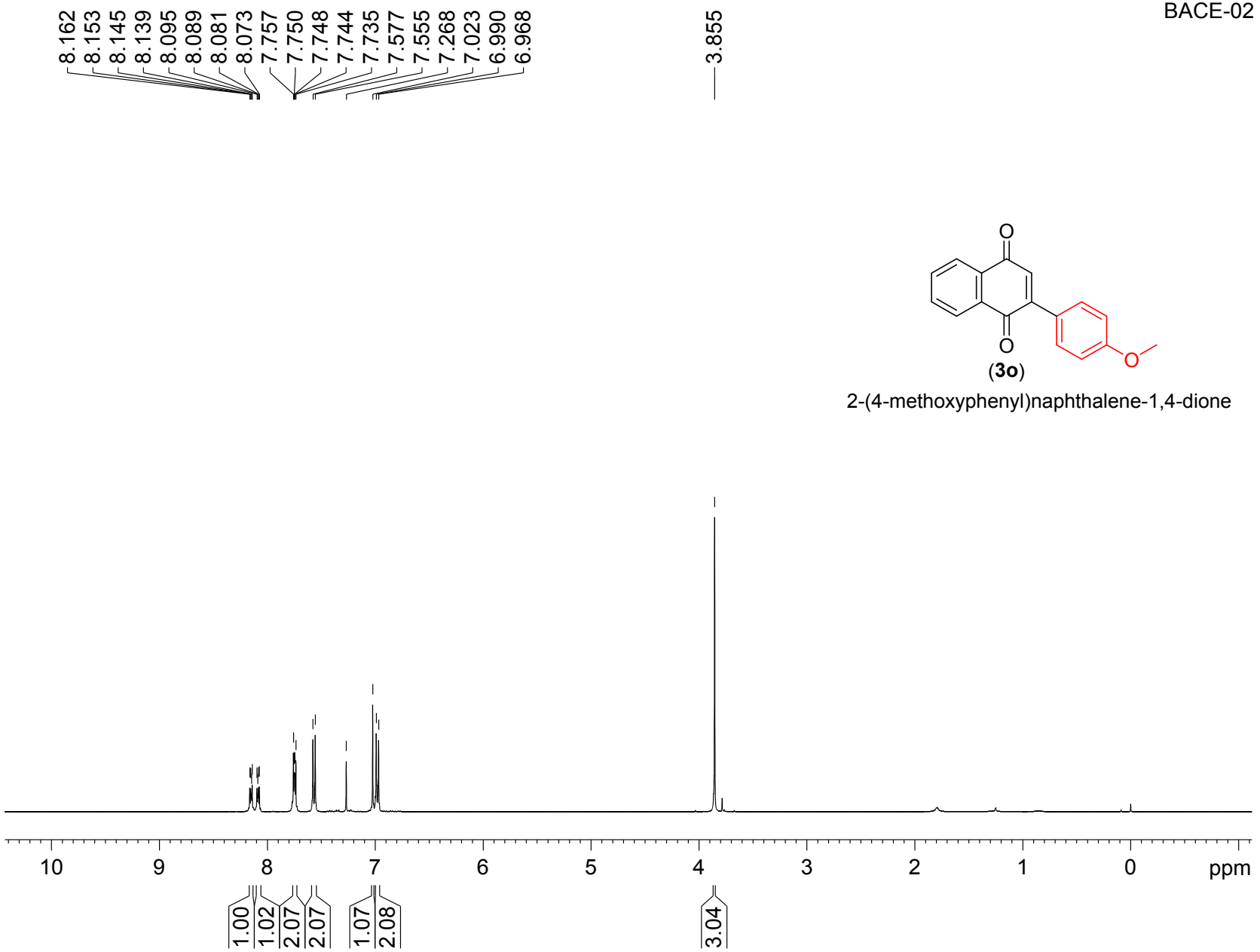
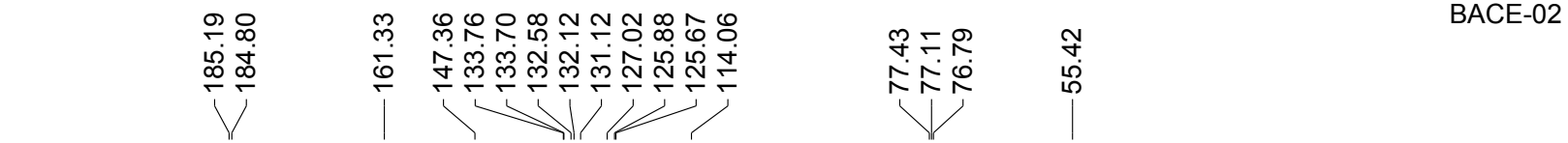
189.81
189.76
152.40
151.07
149.47
139.23
137.62
136.82
131.74
130.51
129.63
128.64
128.30
119.68
45.07
44.87
44.66
44.45
21.24
O
O
OH
OH
(3h)
2-(3,4-dihydroxy-2-methylphenyl)naphthalene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

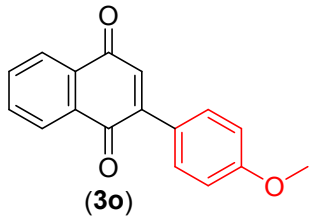


(**3o**)

2-(4-methoxyphenyl)naphthalene-1,4-dione

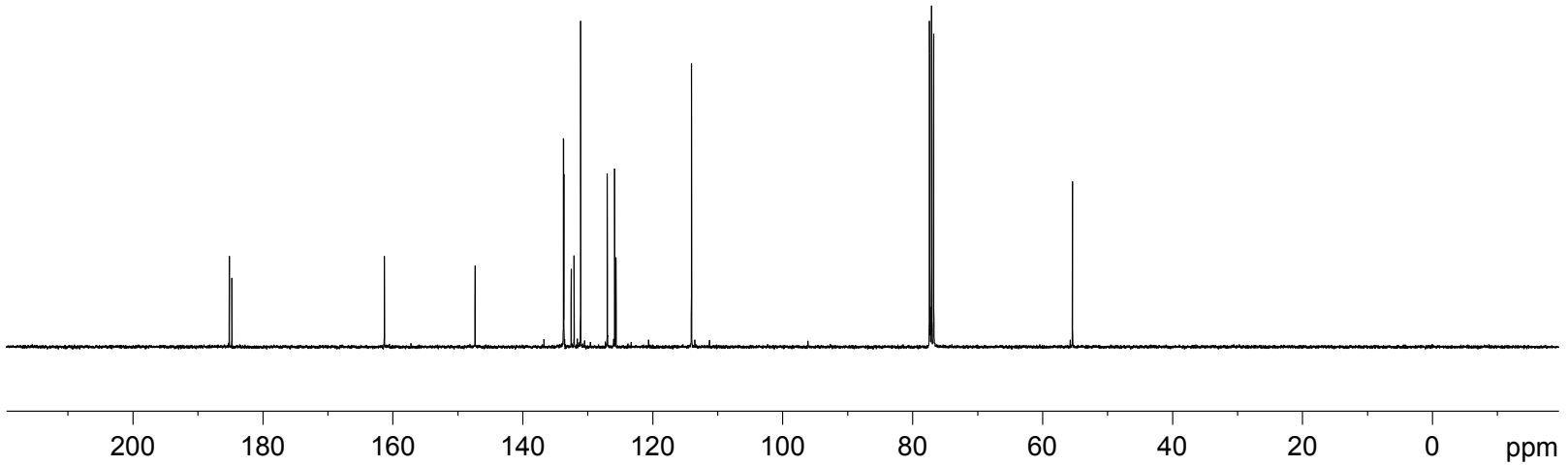
BACE-02





(**3o**)

2-(4-methoxyphenyl)naphthalene-1,4-dione



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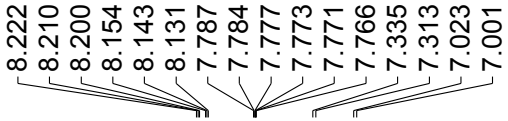
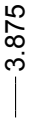
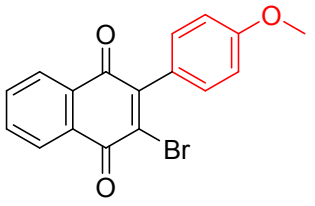
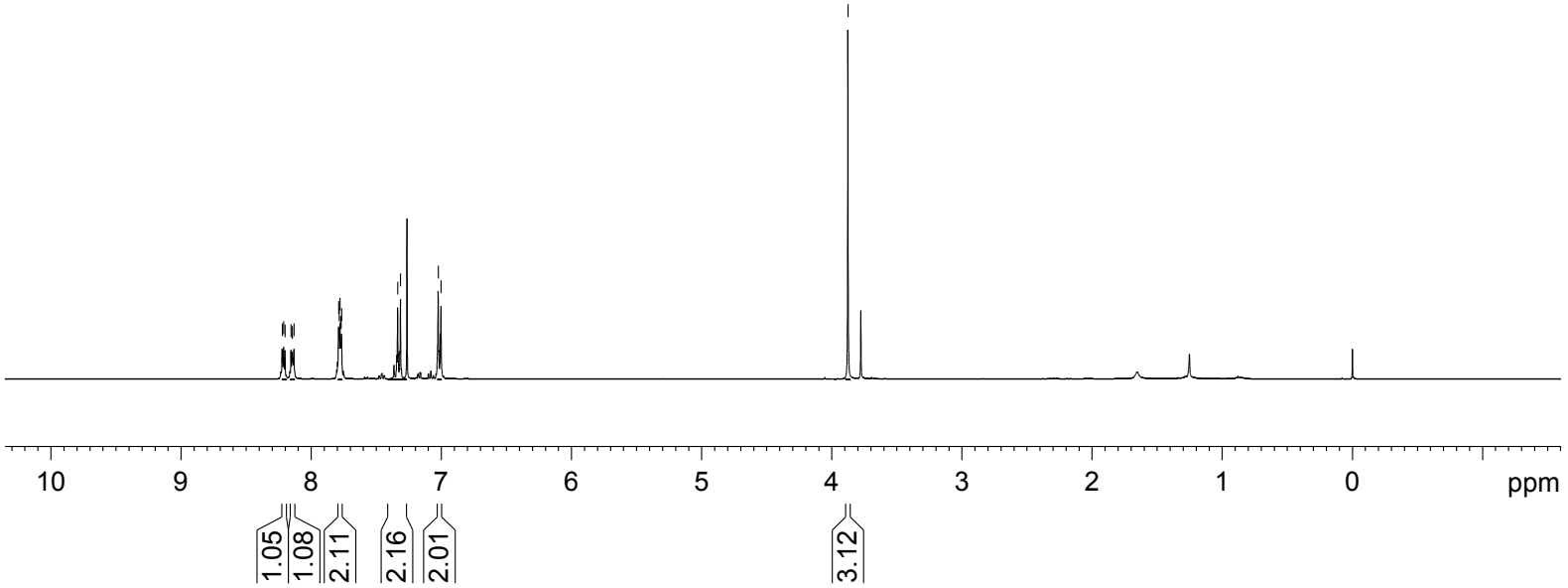


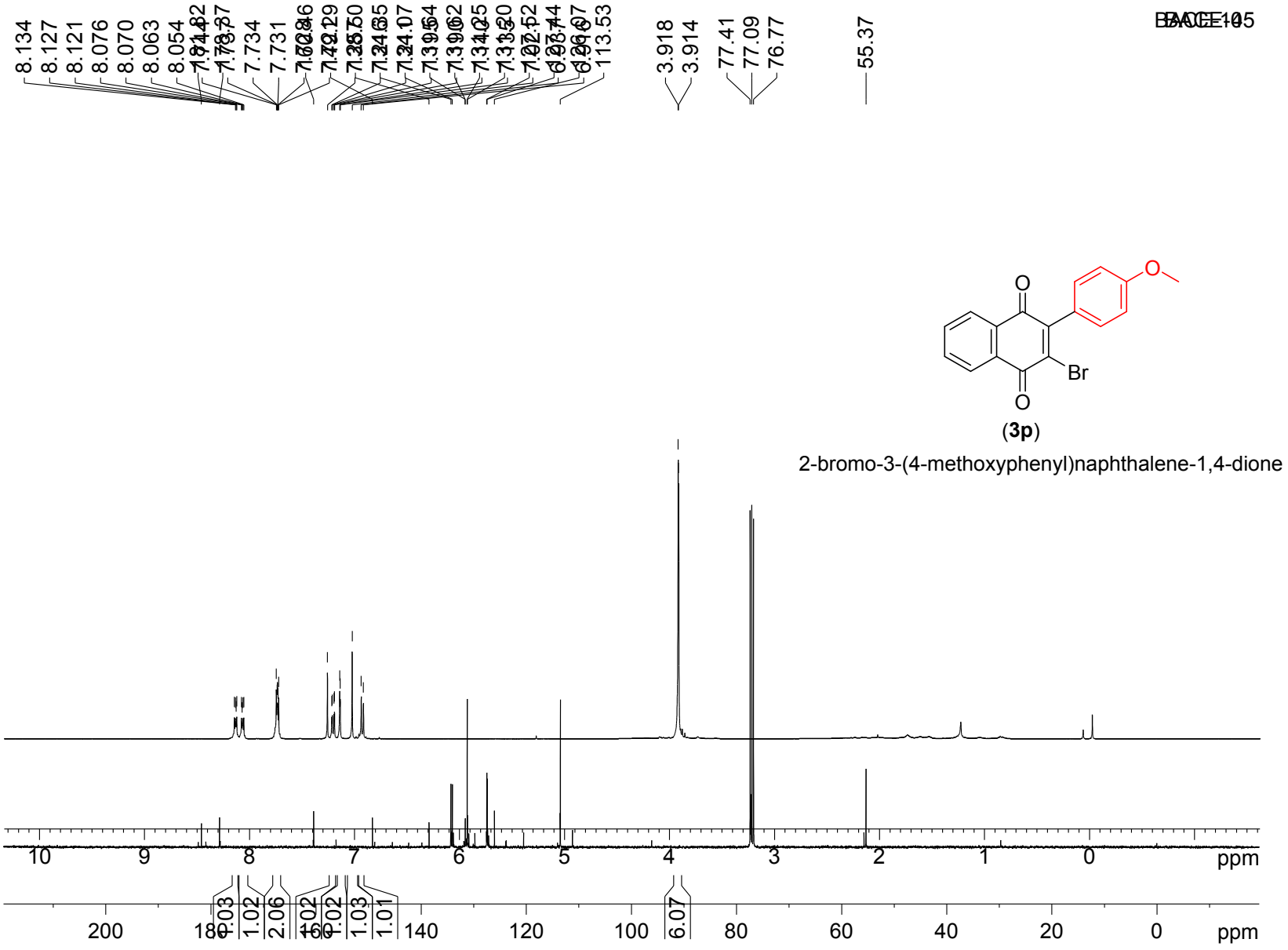




(**3p**)

2-bromo-3-(4-methoxyphenyl)naphthalene-1,4-dione

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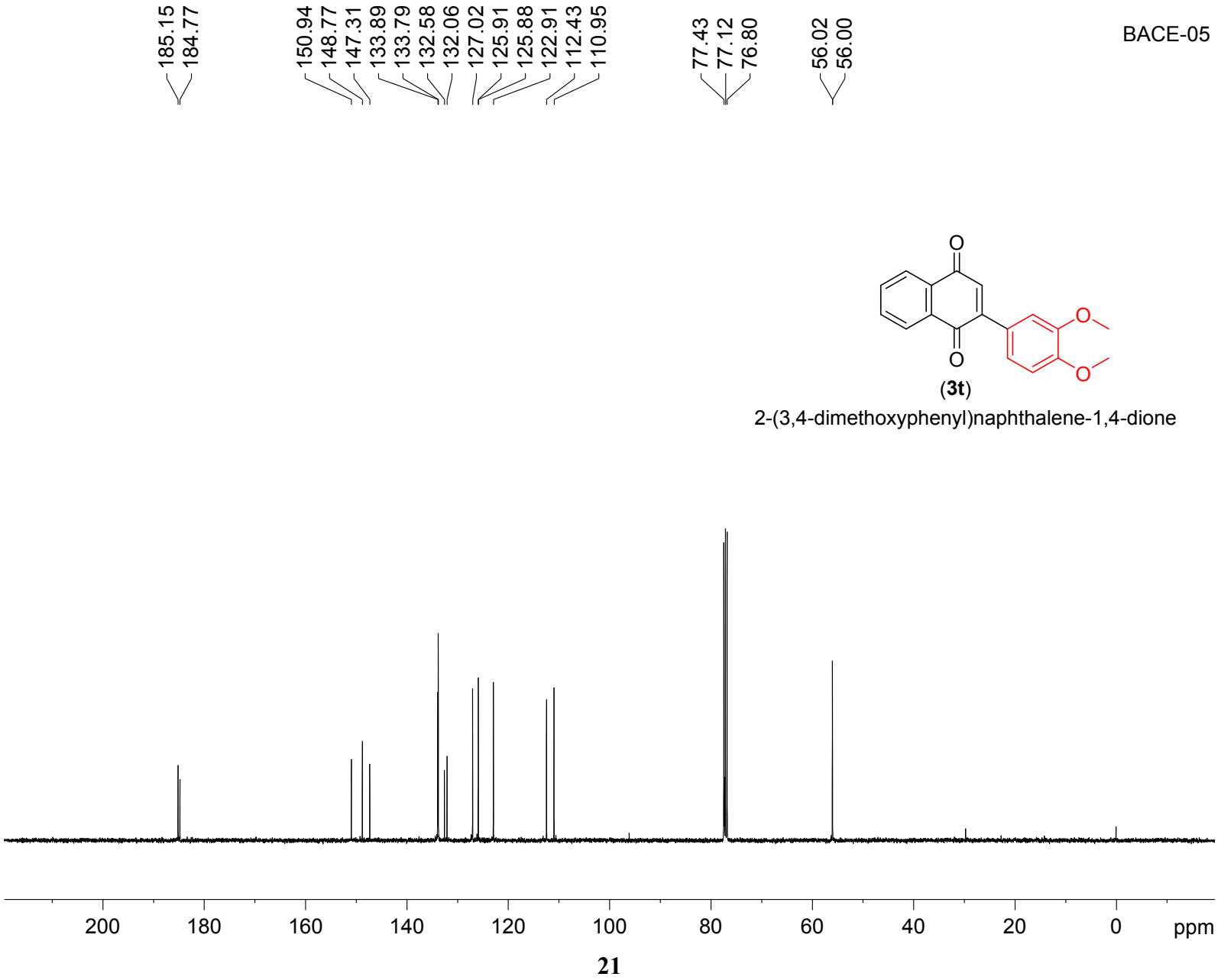
8.127
8.121
8.076
8.070
8.063
8.054
7.734
7.731
113.53
3.918
3.914
77.41
77.09
76.77
55.37
O
O
O
Br
(3p)
2-bromo-3-(4-methoxyphenyl)naphthalene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
1.03
1.02
2.06
1.02
1.02
1.03
1.01
6.07
200
180
160
140
120
100
80
60
40
20
0
ppm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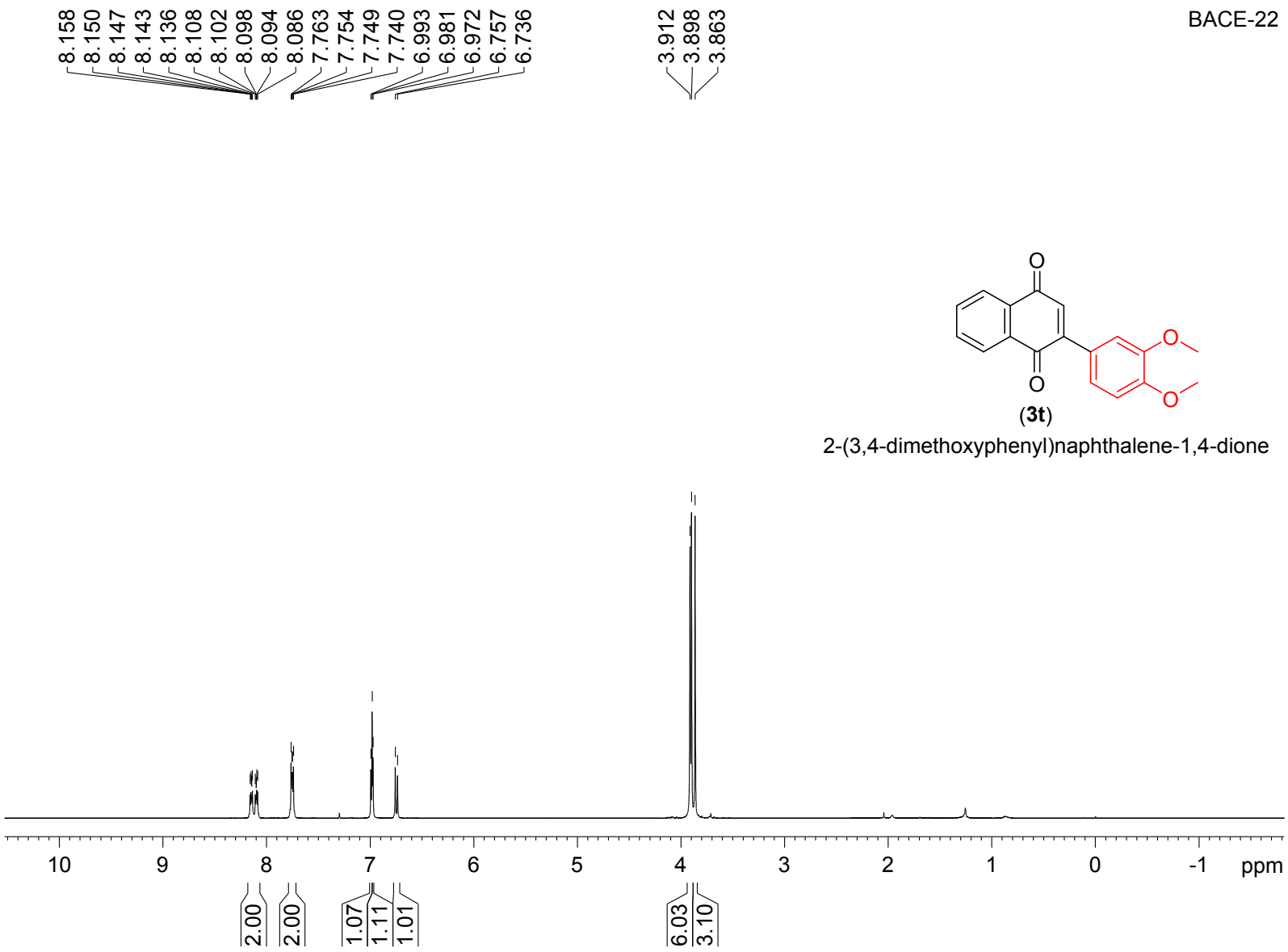
184.77
150.94
148.77
147.31
133.89
133.79
132.58
132.06
127.02
125.91
125.88
122.91
112.43
110.95
77.43
77.12
76.80
56.02
56.00
BACE-05
O
O
O
O
(3t)
2-(3,4-dimethoxyphenyl)naphthalene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm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8.147
8.143
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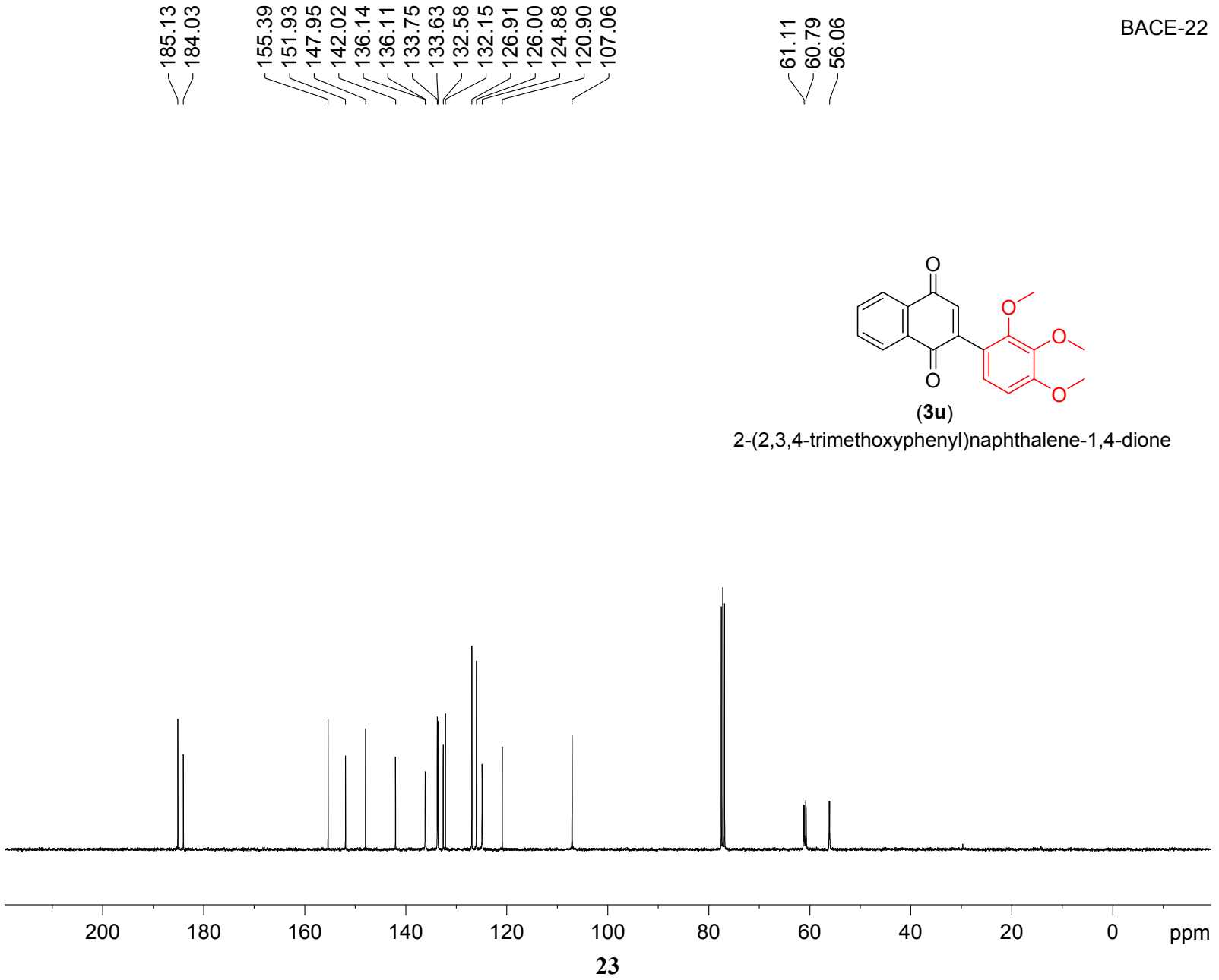
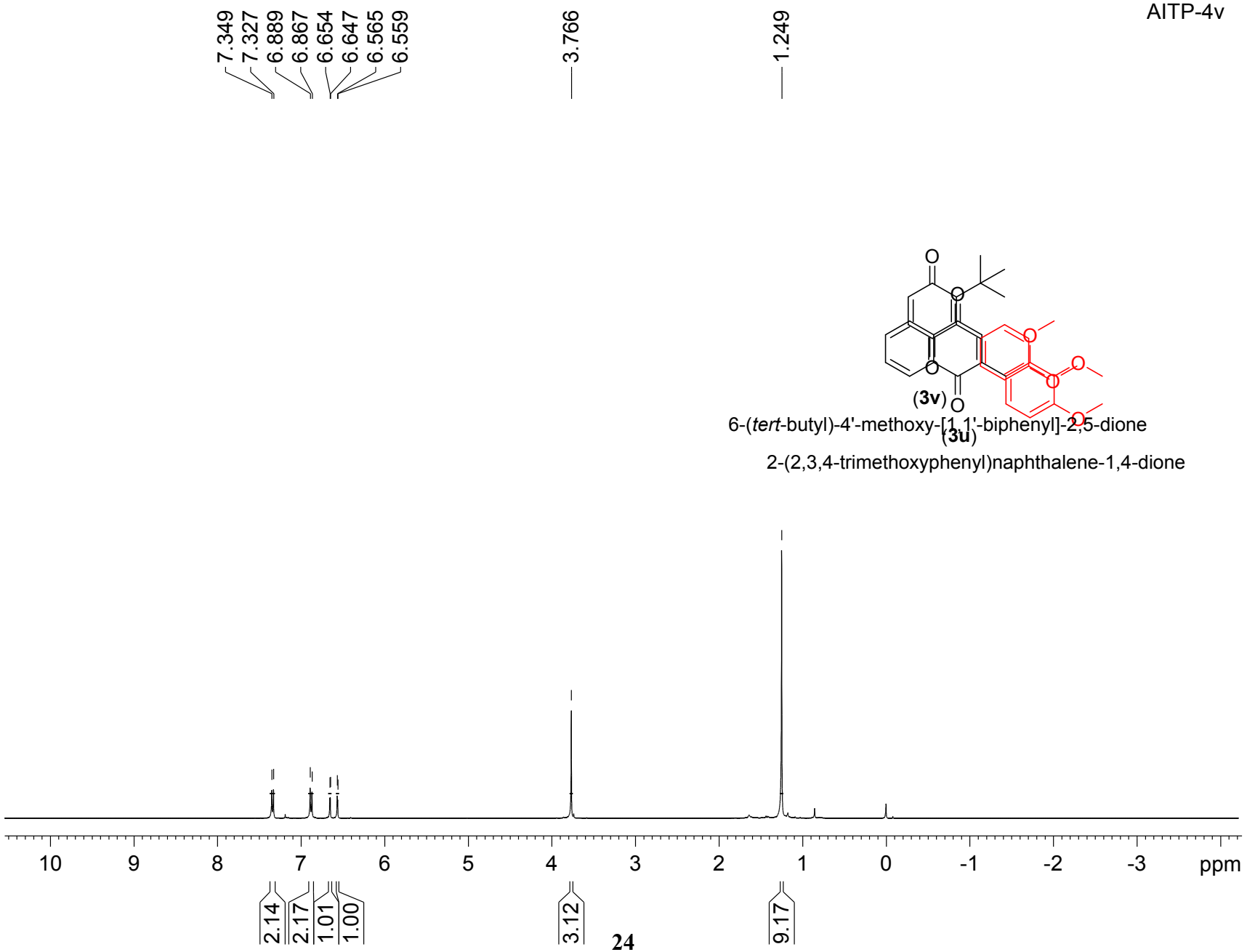
8.108
8.102
8.098
8.094
8.086
7.763
7.754
7.749
7.740
6.993
6.981
6.972
6.757
6.736
3.912
3.898
3.863
BACE-22
O
O
O
O
(3t)
2-(3,4-dimethoxyphenyl)naphthalene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
2.00
2.00
1.07
1.11
1.01
6.03
3.10

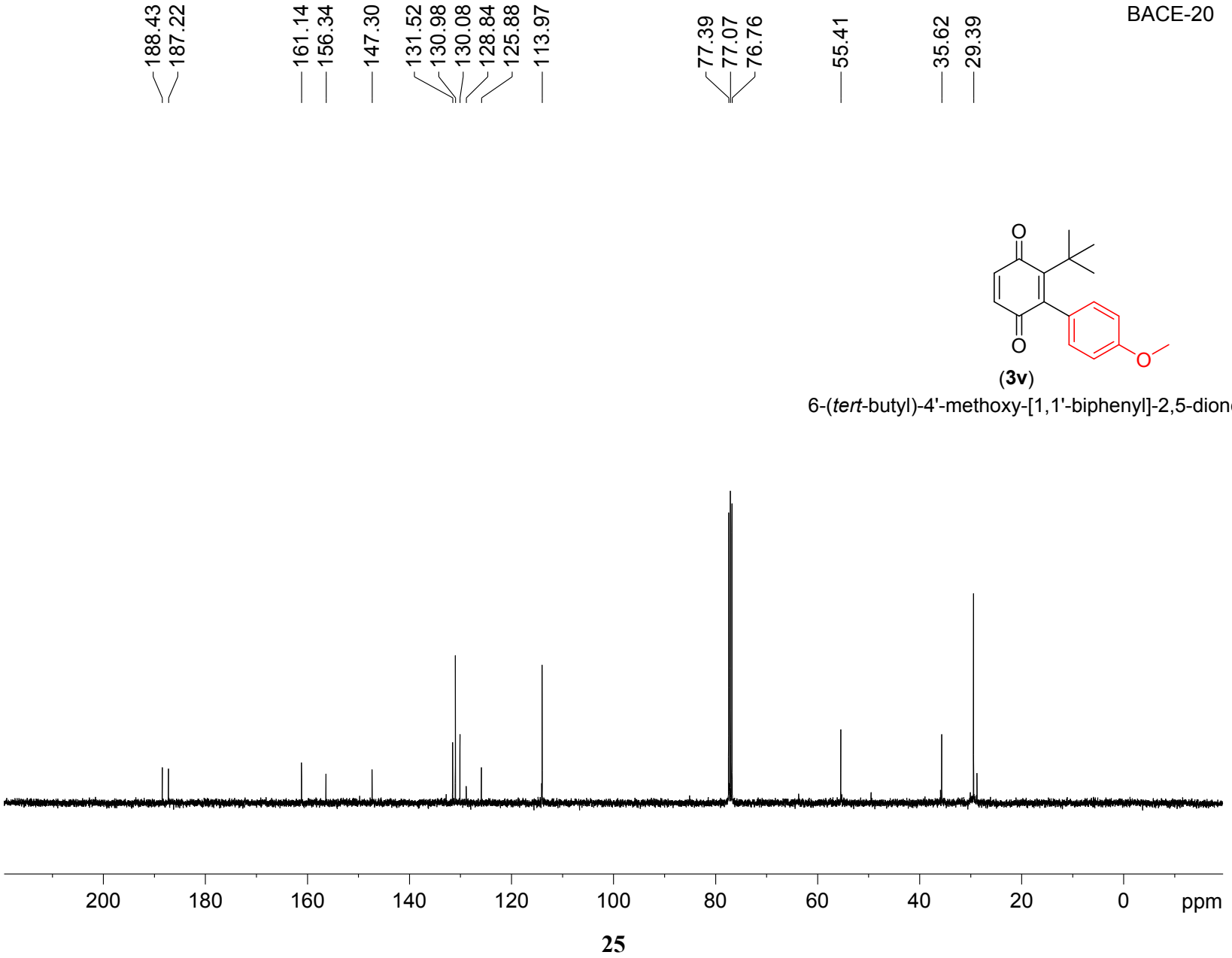

185.13
184.03
155.39
151.93
147.95
142.02
136.14
136.11
133.75
133.63
132.58
132.15
126.91
126.00
124.88
120.90
107.06
61.11
60.79
56.06
BACE-22
O
O
O
O
O
(3u)
2-(2,3,4-trimethoxyphenyl)naphthalene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

AITP-4v



(**3v**) 6-(*tert*-butyl)-4'-methoxy-[1,1'-biphenyl]-2,5-dione

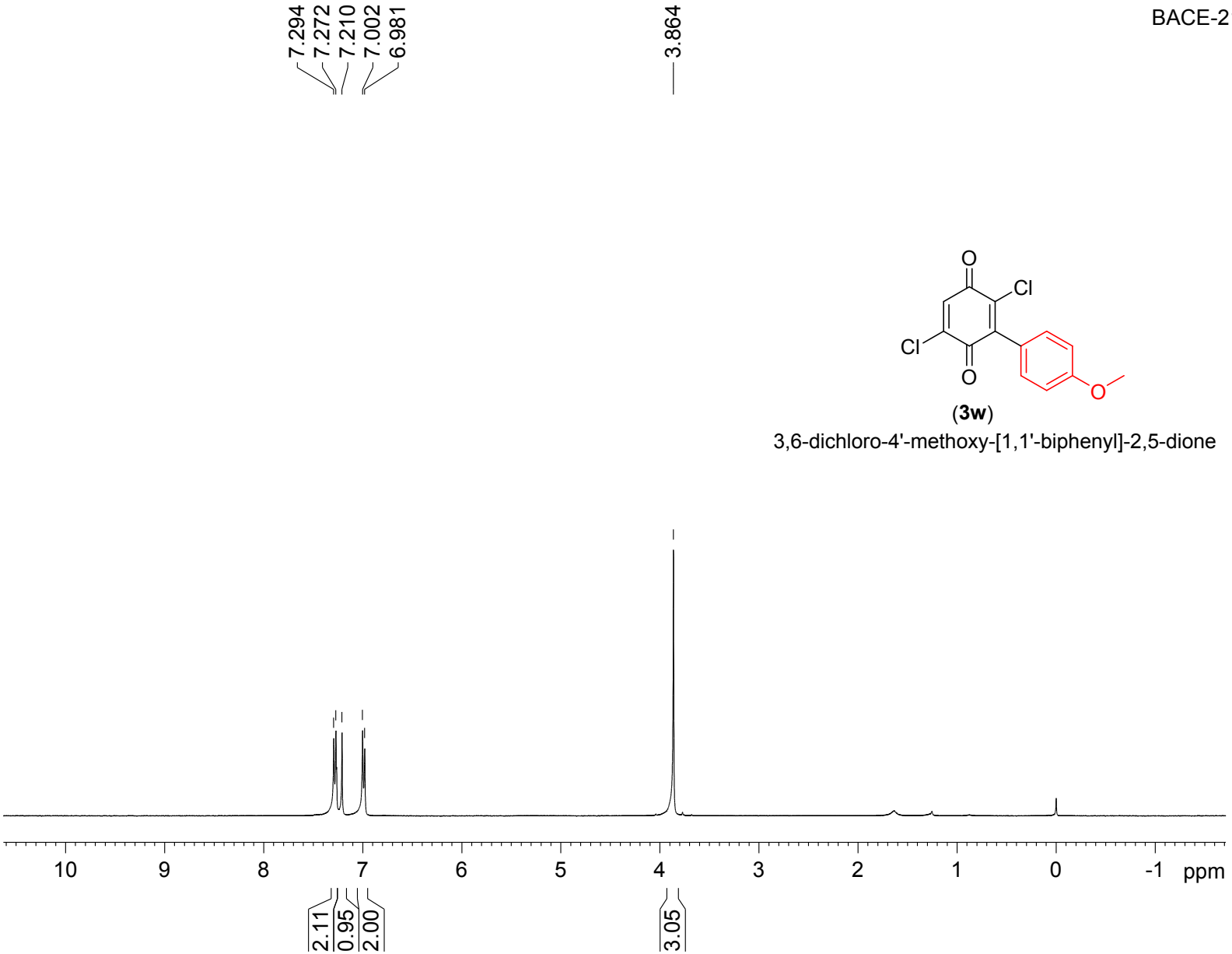
(**3u**) 2-(2,3,4-trimethoxyphenyl)naphthalene-1,4-dione



(**3v**)

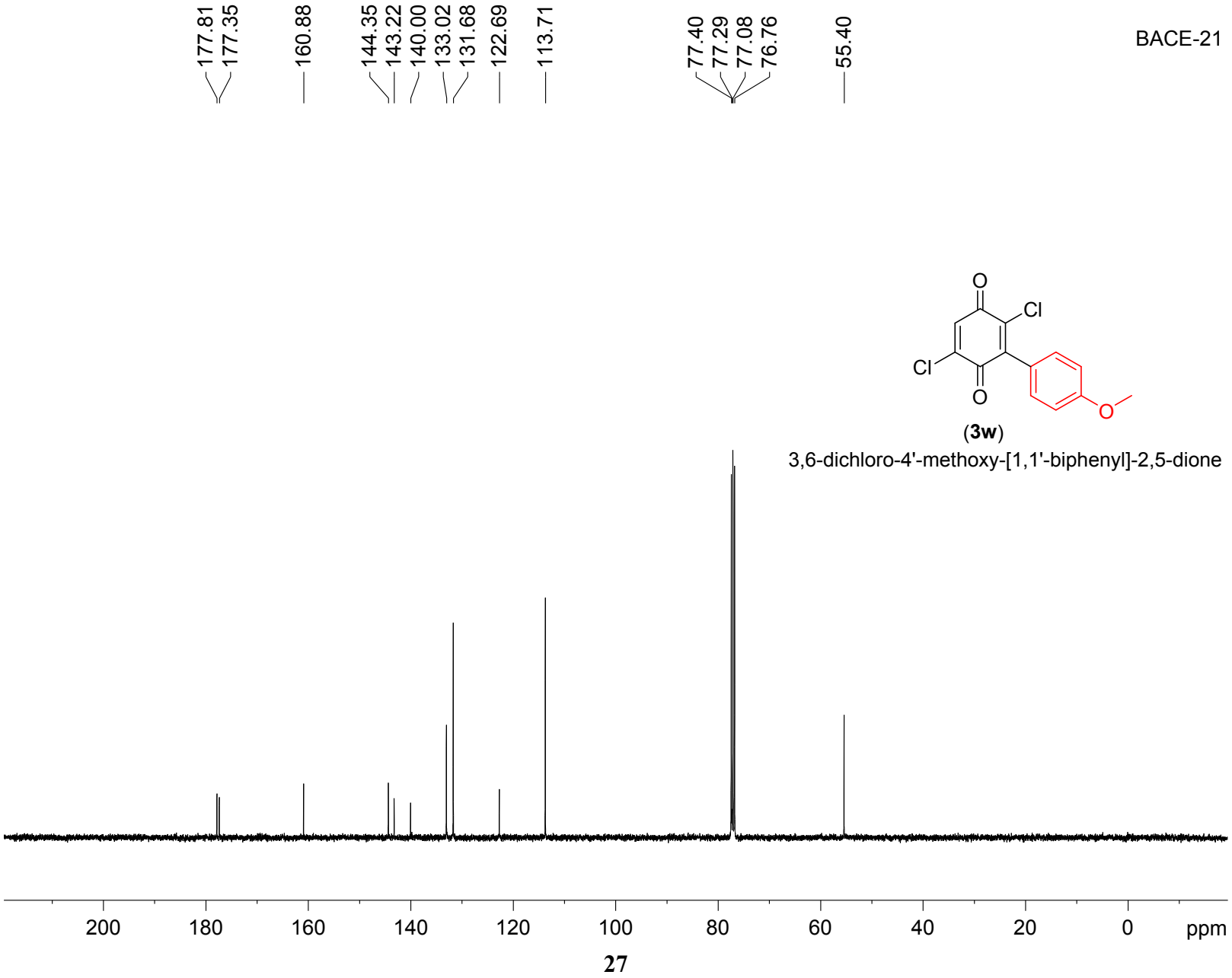
6-(*tert*-butyl)-4'-methoxy-[1,1'-biphenyl]-2,5-dione

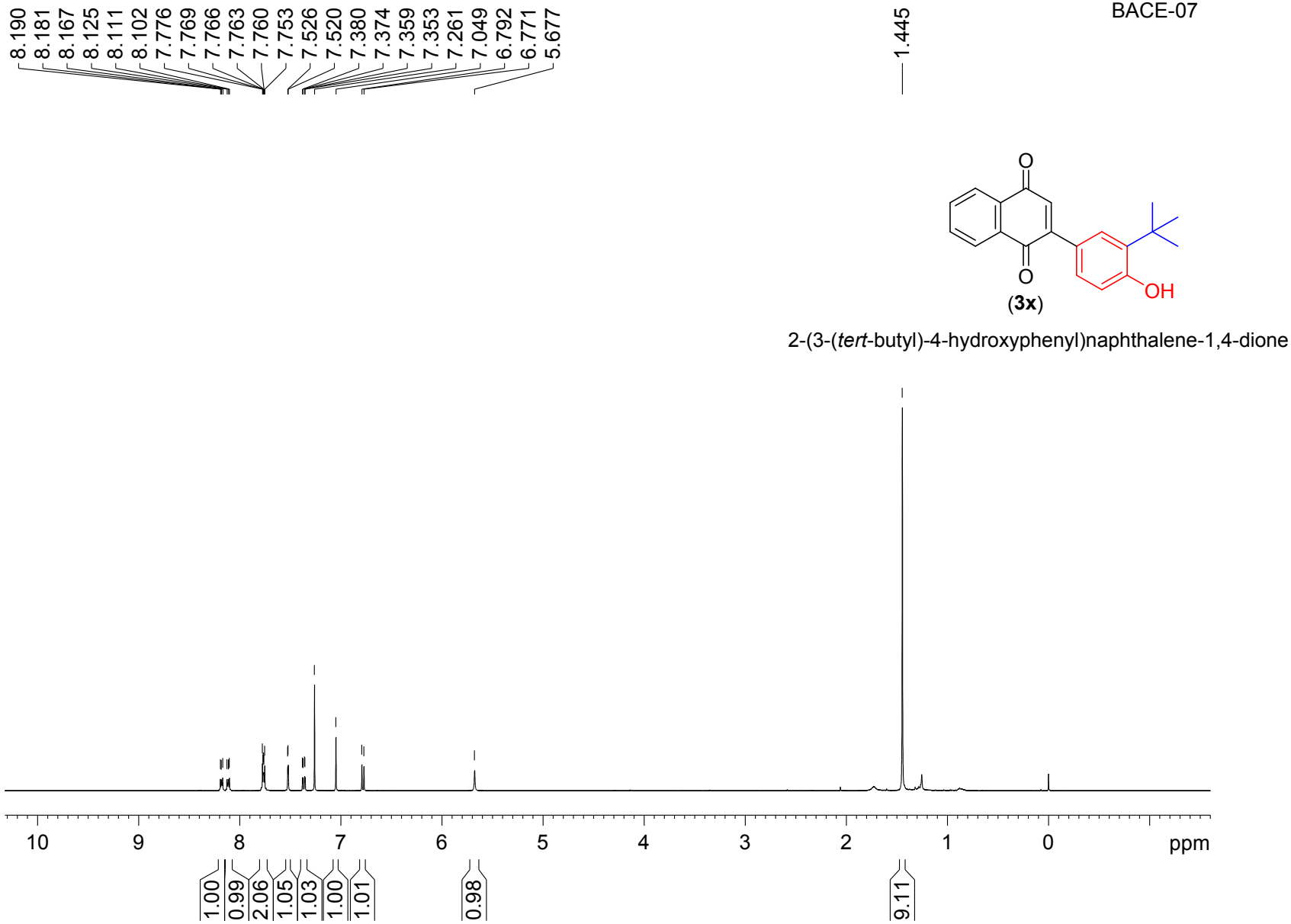
BACE-21

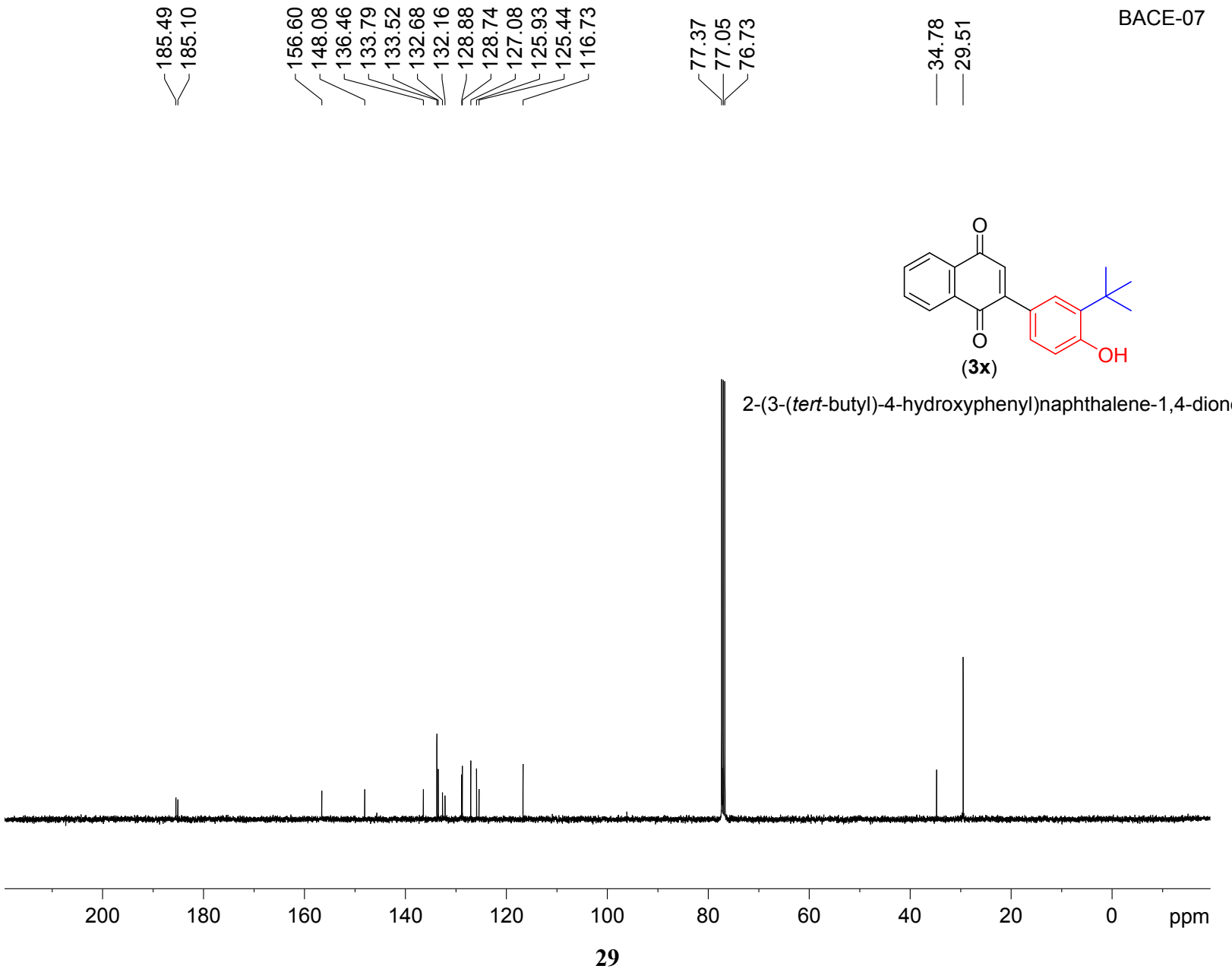


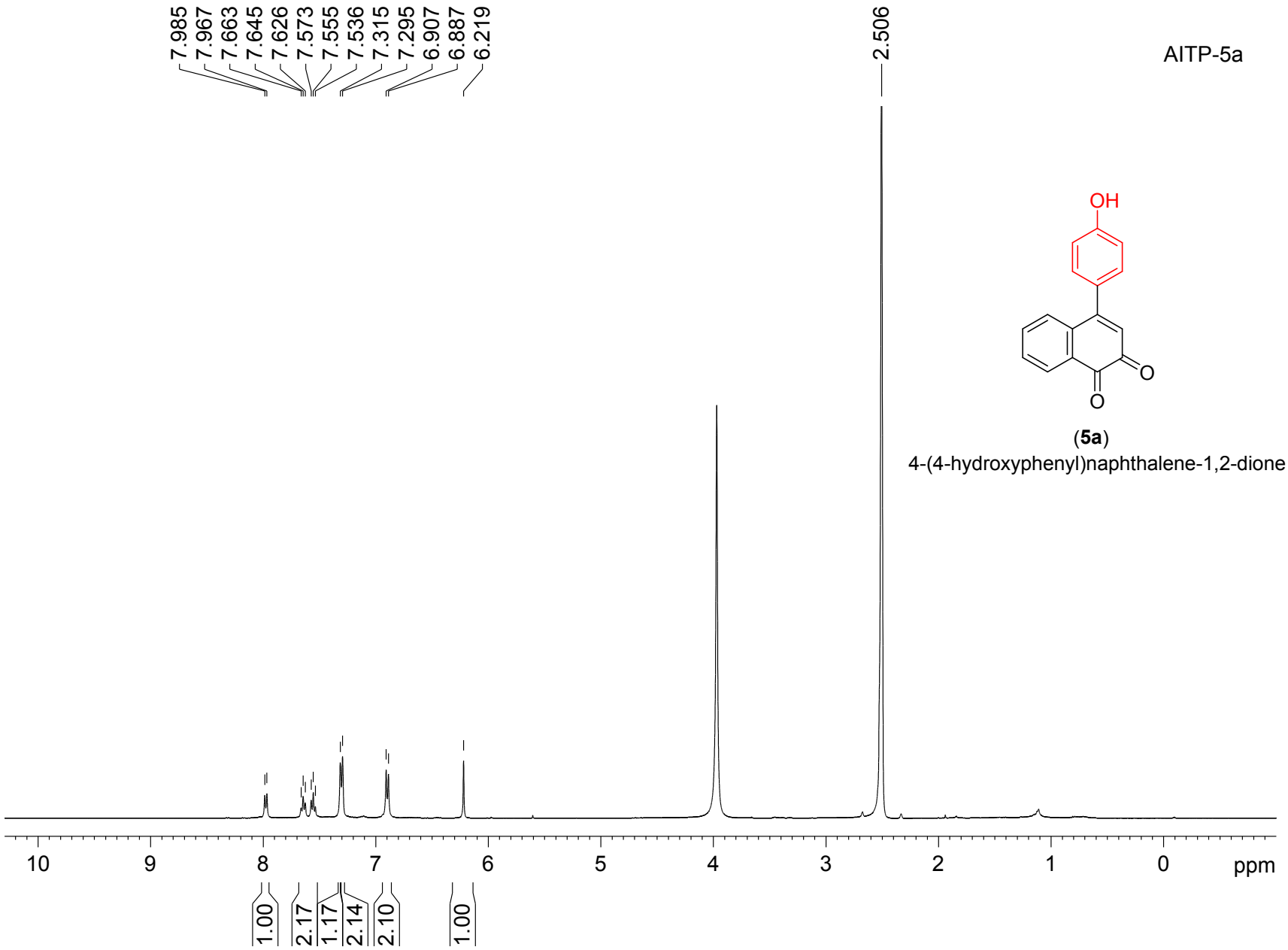
(**3w**)

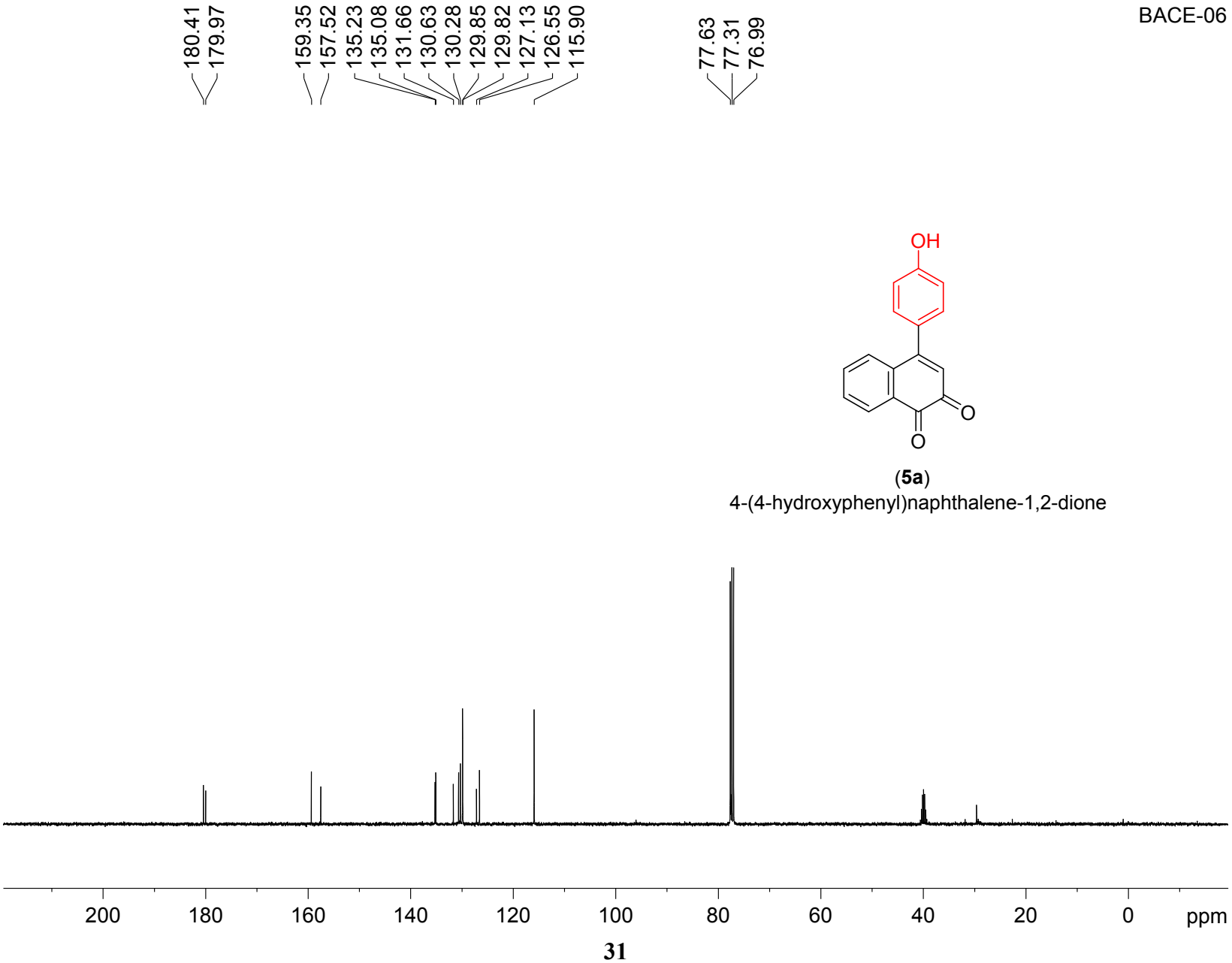
3,6-dichloro-4'-methoxy-[1,1'-biphenyl]-2,5-dione


177.81
177.35
160.88
144.35
143.22
140.00
133.02
131.68
122.69
113.71
77.40
77.29
77.08
76.76
55.40
BACE-21
O
Cl
Cl
O
O
(3w)
3,6-dichloro-4'-methoxy-[1,1'-biphenyl]-2,5-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

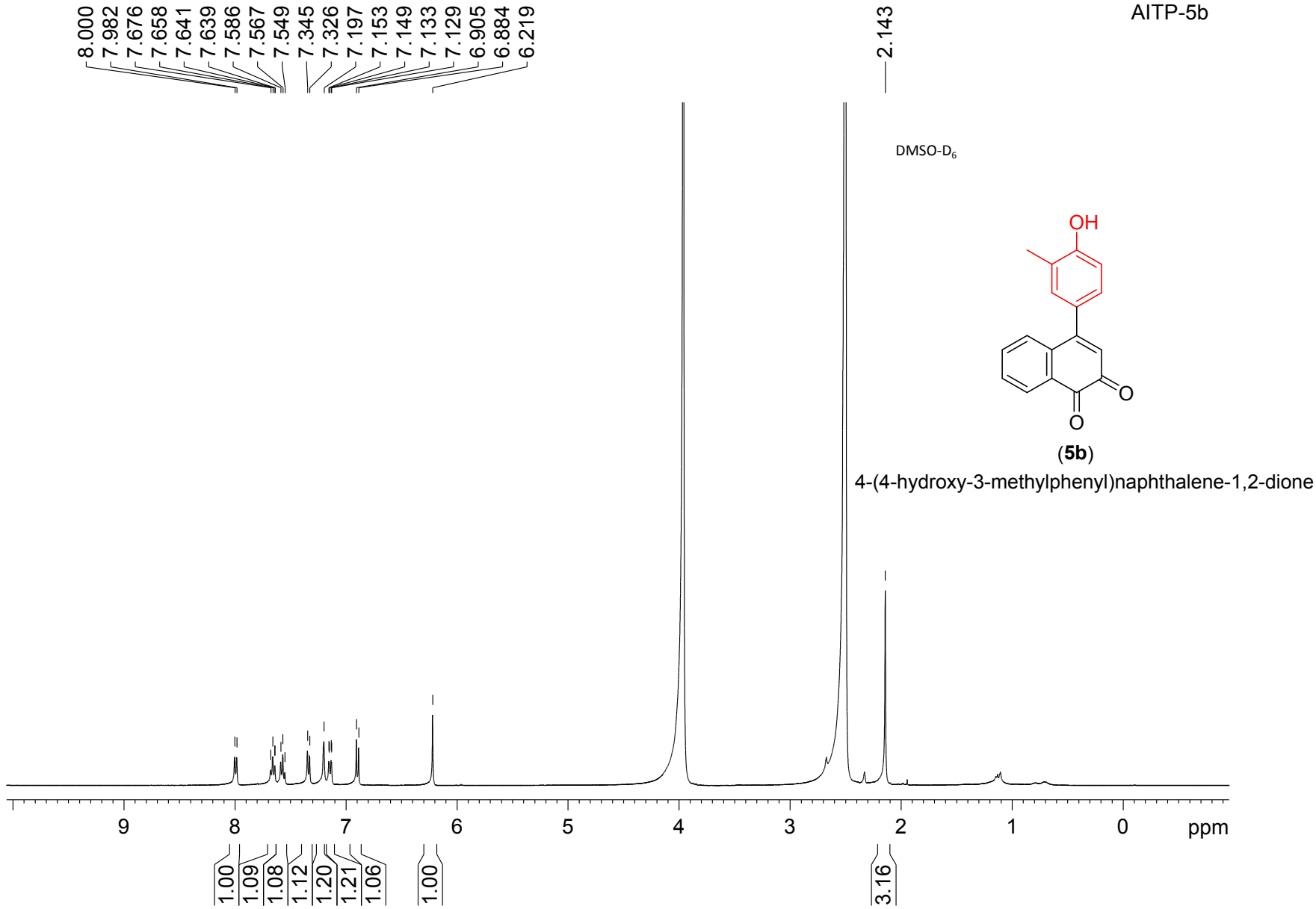

8.190
8.181
8.167
8.125
8.111
8.102
7.776
7.769
7.766
7.763
7.760
7.753
7.526
7.520
7.380
7.374
7.359
7.353
7.261
7.049
6.792
6.771
5.677
1.445
BACE-07
O
O
OH
(3x)
2-(3-(tert-butyl)-4-hydroxyphenyl)naphthalene-1,4-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.99
2.06
1.05
1.03
1.00
1.01
0.98
9.11


185.49
185.10
156.60
148.08
136.46
133.79
133.52
132.68
132.16
128.88
128.74
127.08
125.93
125.44
116.73
77.37
77.05
76.73
34.78
29.51
BACE-07
O
O
OH
(3x)
2-(3-(tert-butyl)-4-hydroxyphenyl)naphthalene-1,4-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

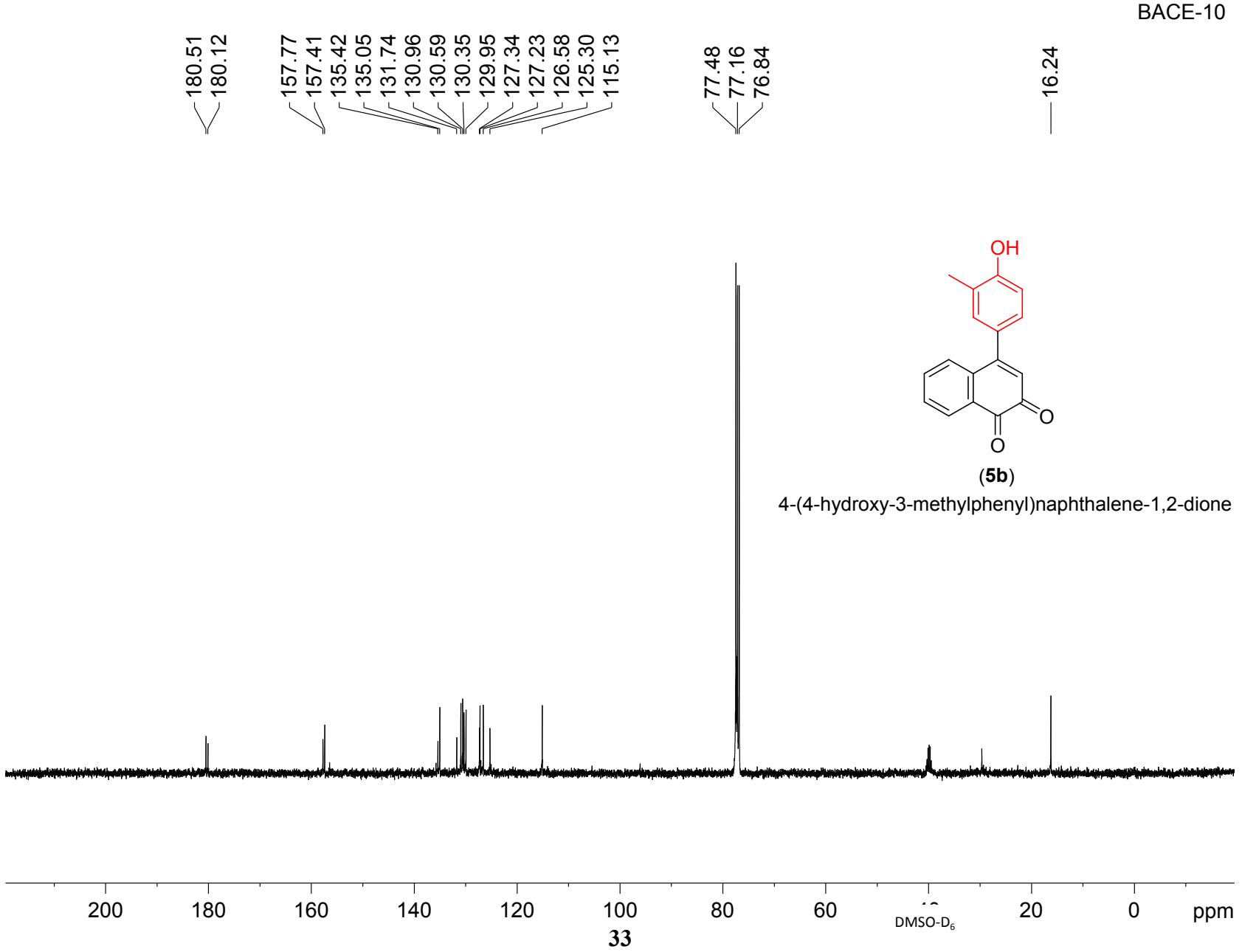

7.985
7.967
7.663
7.645
7.626
7.573
7.555
7.536
7.315
7.295
6.907
6.887
6.219
2.506
AITP-5a
OH
O
O
(5a)
4-(4-hydroxyphenyl)naphthalene-1,2-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.17
1.17
2.14
2.10
1.00



(**5a**)
4-(4-hydroxyphenyl)naphthalene-1,2-dione

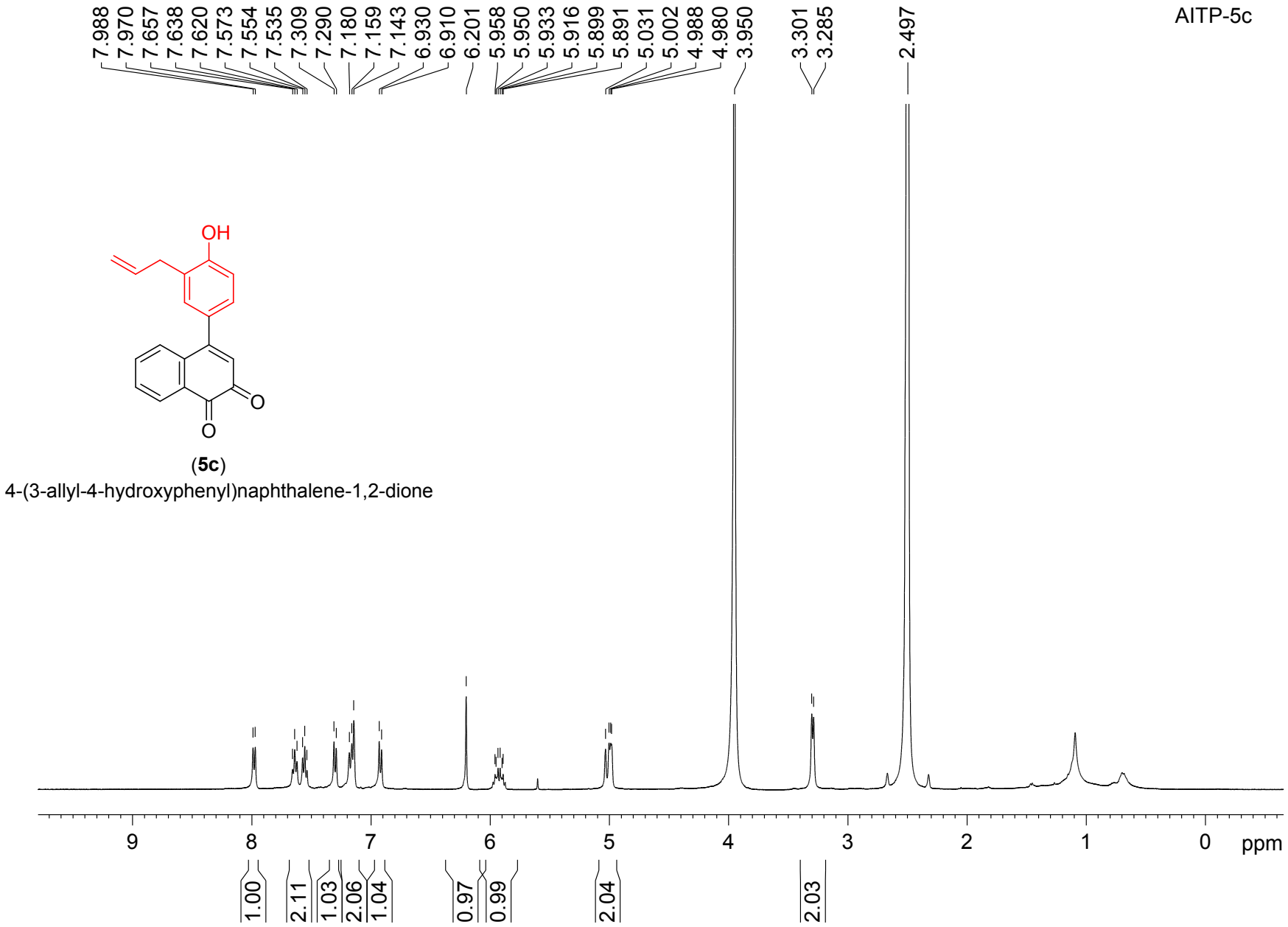

AITP-5b
8.000
7.982
7.676
7.658
7.641
7.639
7.586
7.567
7.549
7.345
7.326
7.197
7.153
7.149
7.133
7.129
6.905
6.884
6.219
2.143
DMSO-D6
OH
O
O
(5b)
4-(4-hydroxy-3-methylphenyl)naphthalene-1,2-dione
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.09
1.08
1.12
1.20
1.21
1.06
1.00
3.16

BACE-10

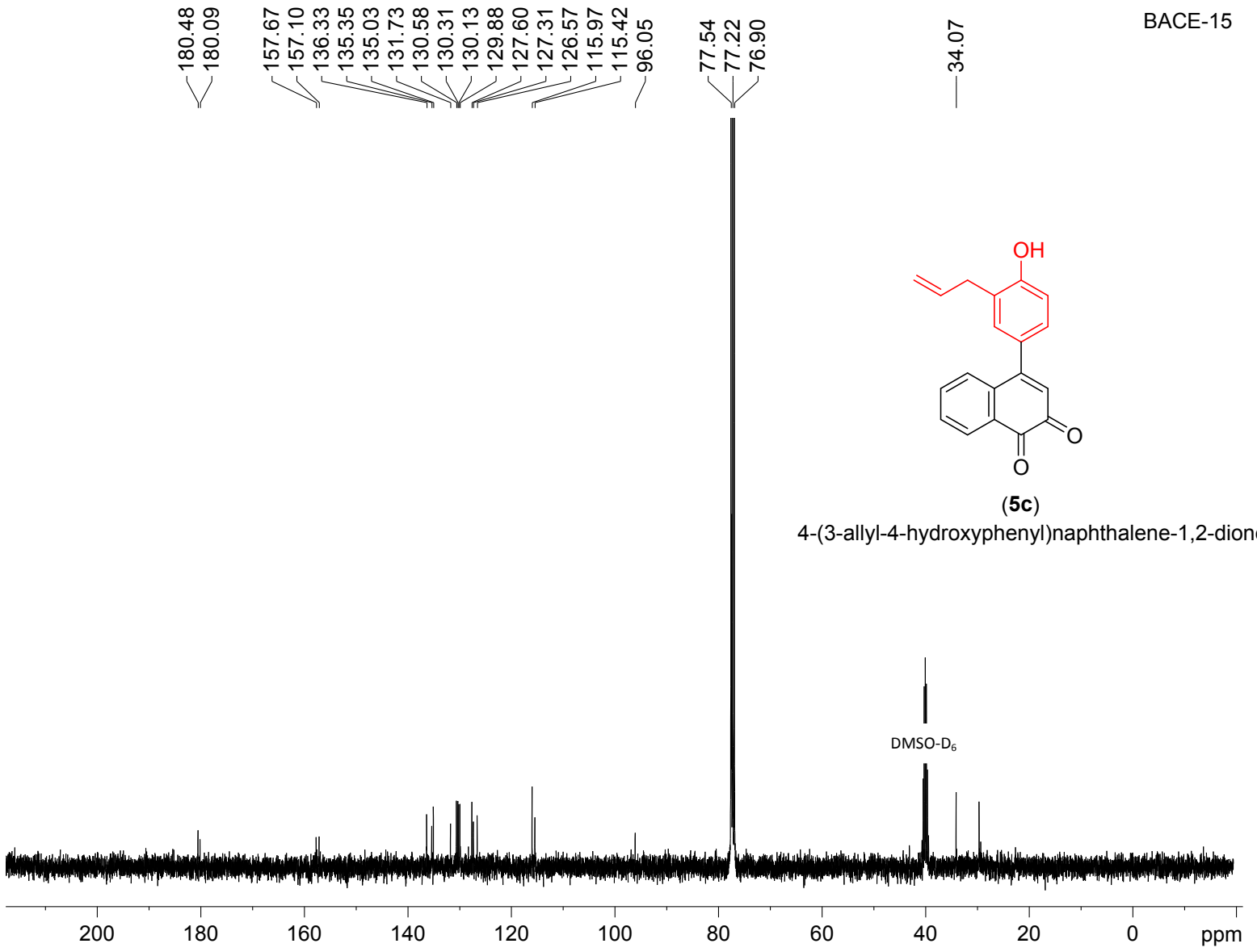


(**5b**)

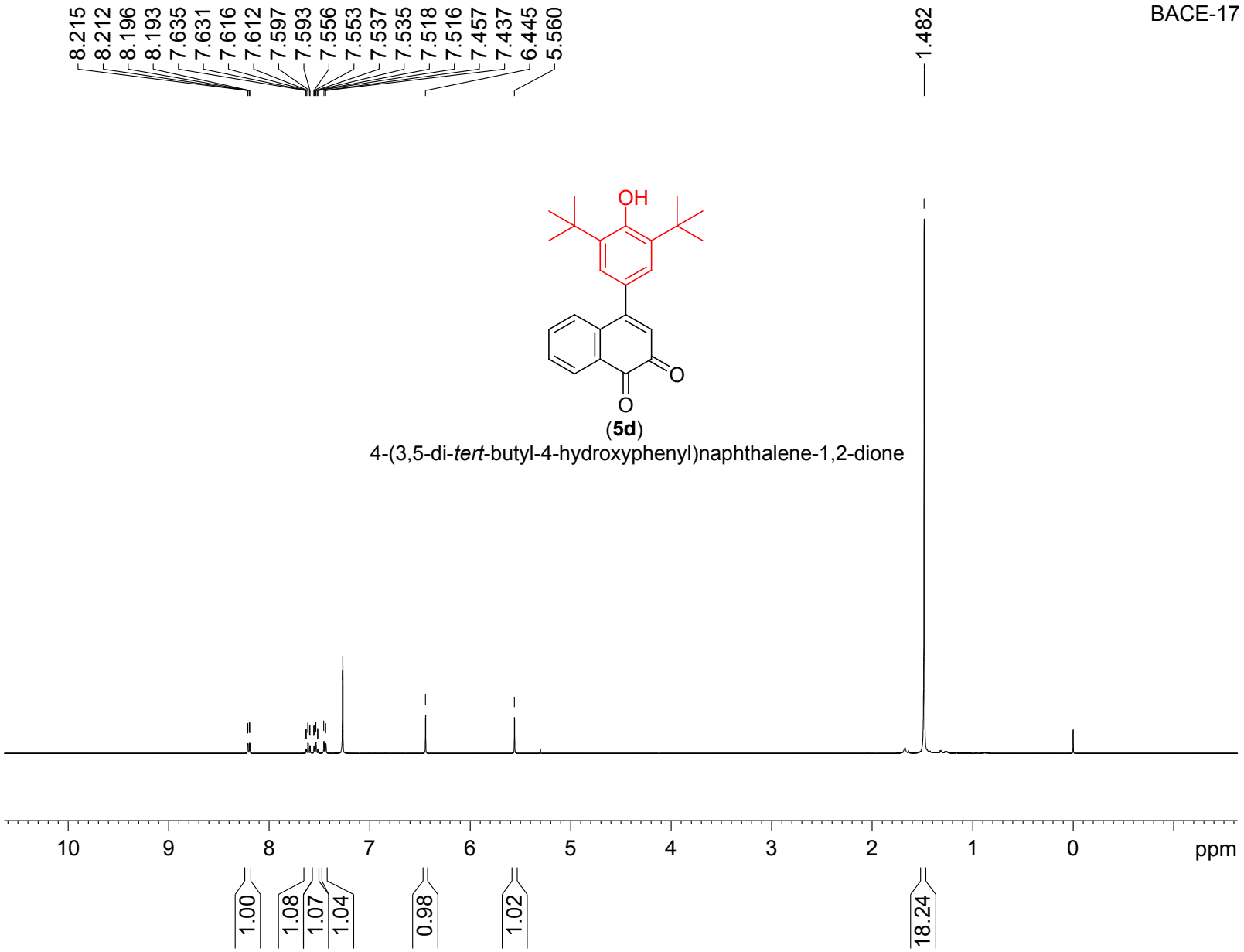
4-(4-hydroxy-3-methylphenyl)naphthalene-1,2-dione

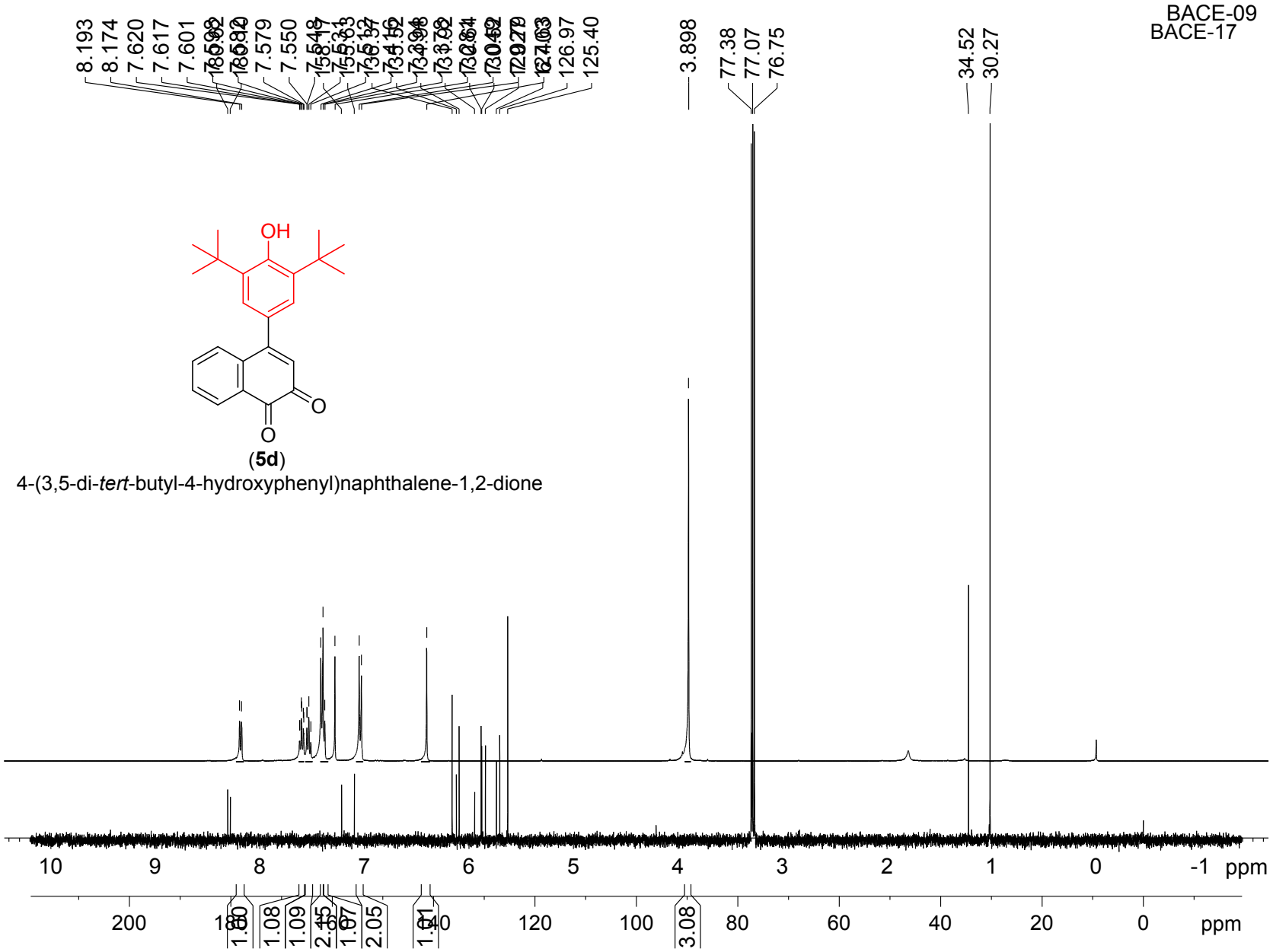


(**5c**)
4-(3-allyl-4-hydroxyphenyl)naphthalene-1,2-dione



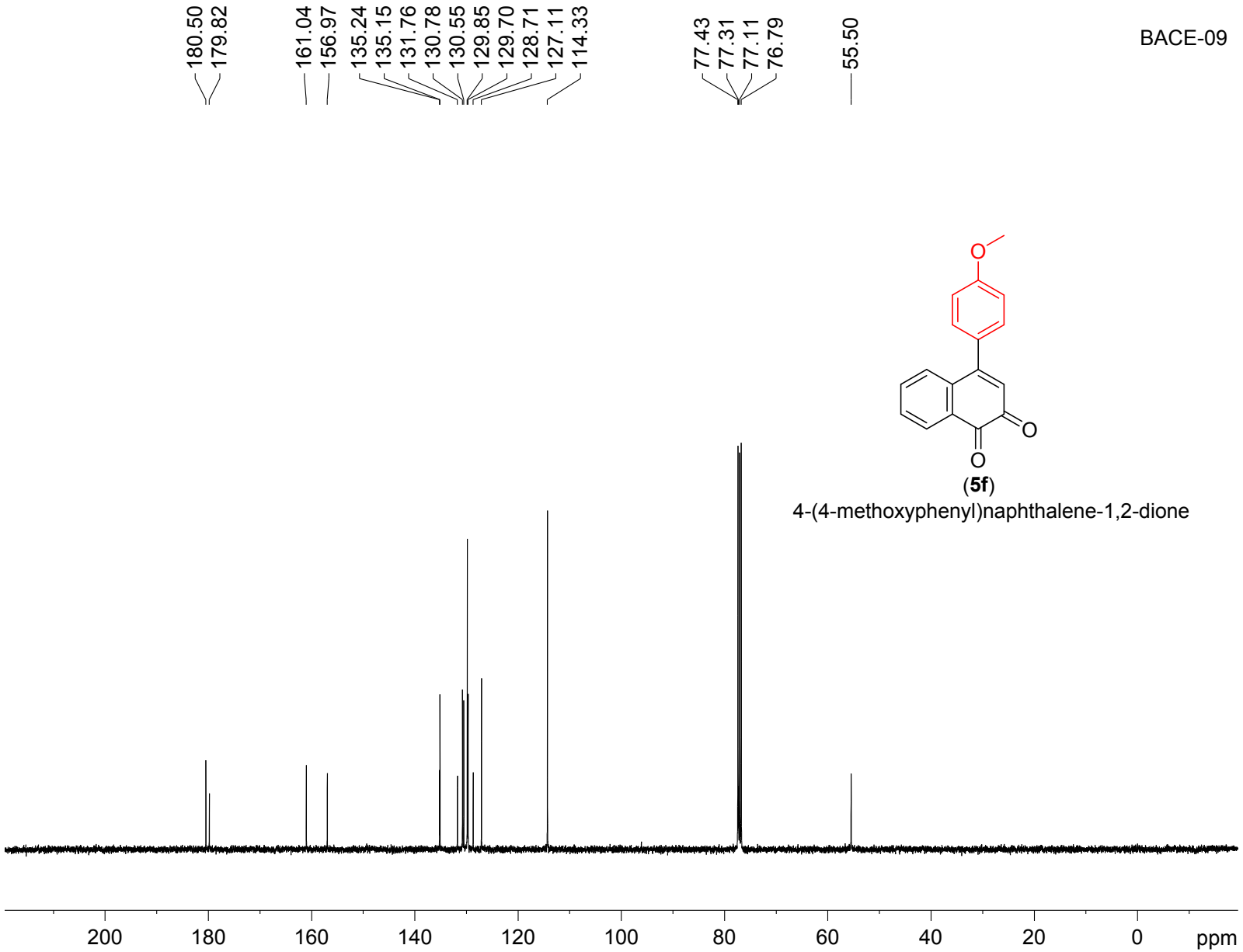
(**5c**)
4-(3-allyl-4-hydroxyphenyl)naphthalene-1,2-dione


BACE-17
8.215
8.212
8.196
8.193
7.635
7.631
7.616
7.612
7.597
7.593
7.556
7.553
7.537
7.535
7.518
7.516
7.457
7.437
6.445
5.560
1.482
OH
O
O
(5d)
4-(3,5-di-tert-butyl-4-hydroxyphenyl)naphthalene-1,2-dione
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.08
1.07
1.04
0.98
1.02
18.24

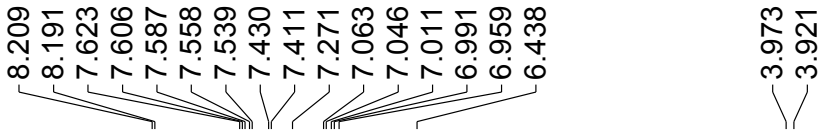


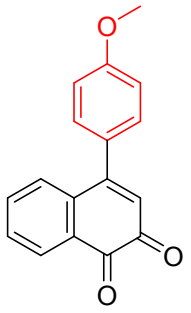
(**5d**)

4-(3,5-di-*tert*-butyl-4-hydroxyphenyl)naphthalene-1,2-dione


180.50
179.82
161.04
156.97
135.24
135.15
131.76
130.78
130.55
129.85
129.70
128.71
127.11
114.33
77.43
77.31
77.11
76.79
55.50
BACE-09
O
O
O
(5f)
4-(4-methoxyphenyl)naphthalene-1,2-dione
200
180
160
140
120
100
80
60
40
20
0
ppm

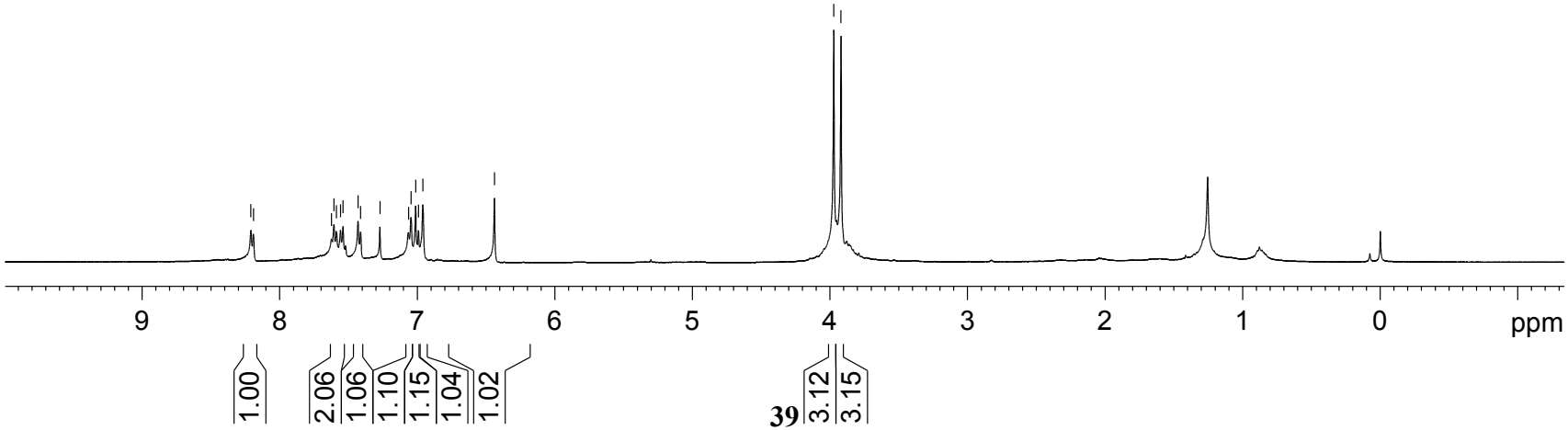
AITP-5g

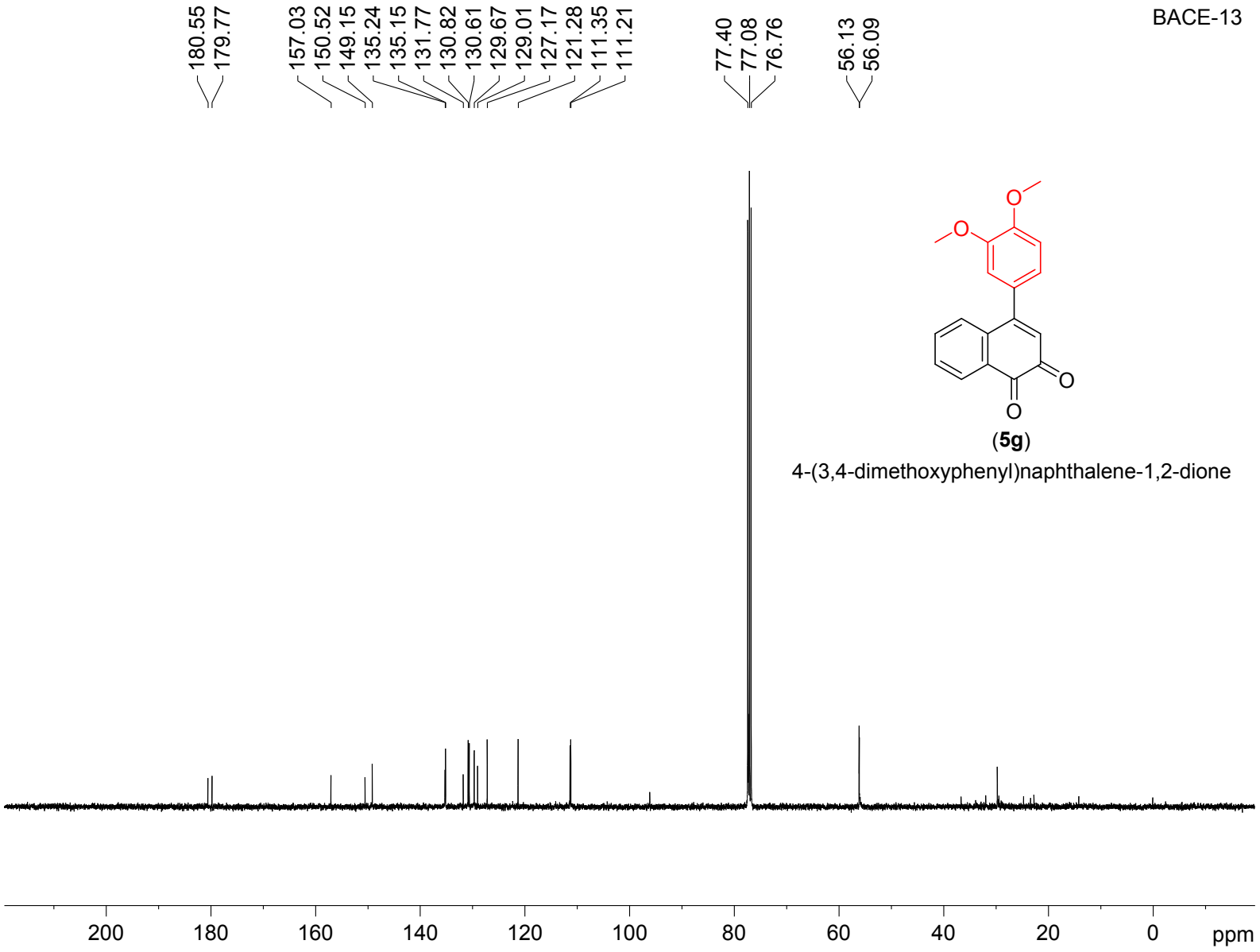


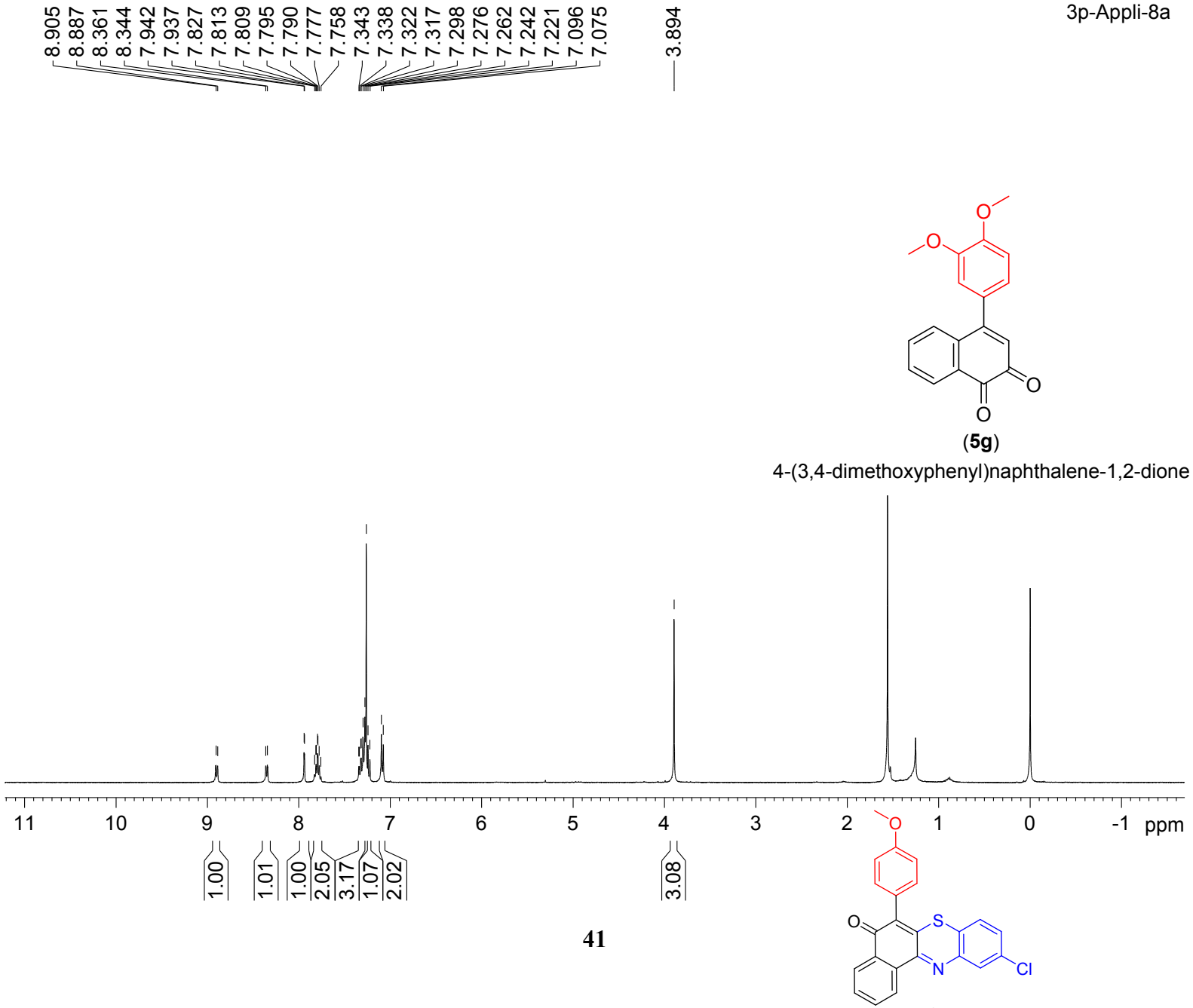


(**5f**)

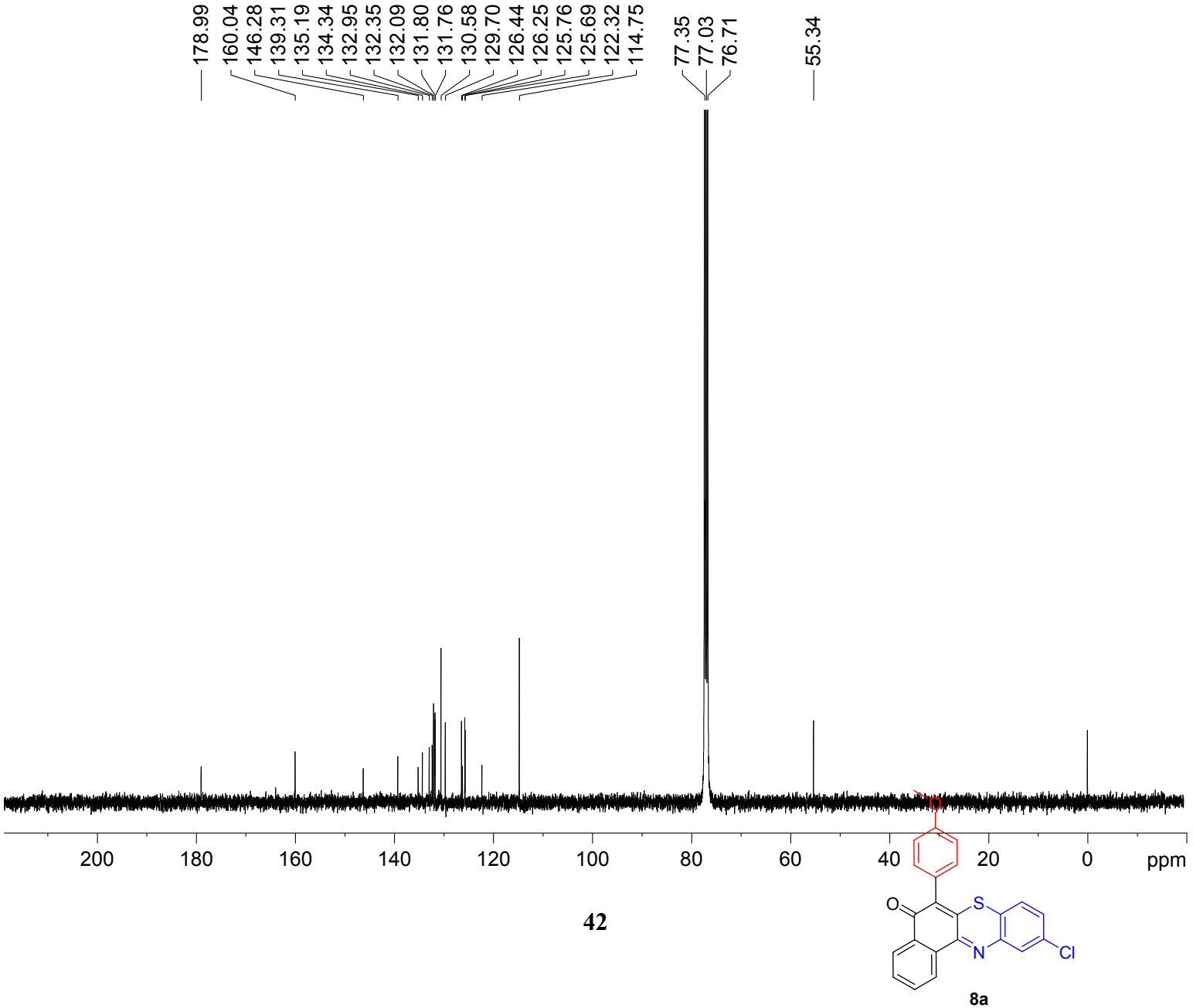
4-(4-methoxyphenyl)naphthalene-1,2-dione




180.55
179.77
157.03
150.52
149.15
135.24
135.15
131.77
130.82
130.61
129.67
129.01
127.17
121.28
111.35
111.21
77.40
77.08
76.76
56.13
56.09
BACE-13
O
O
O
O
(5g)
4-(3,4-dimethoxyphenyl)naphthalene-1,2-dione
200
180
160
140
120
100
80
60
40
20
0
ppm


8.905
8.887
8.361
8.344
7.942
7.937
7.827
7.813
7.809
7.795
7.790
7.777
7.758
7.343
7.338
7.322
7.317
7.298
7.276
7.262
7.242
7.221
7.096
7.075
3.894
3p-Appli-8a
O
O
O
O
(5g)
4-(3,4-dimethoxyphenyl)naphthalene-1,2-dione
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.00
1.01
1.00
2.05
3.17
1.07
2.02
3.08
O
S
N
Cl
8a
10-chloro-6-(4-methoxyphenyl)-5H-benzo[a]phenothiazin-5-one

3p-Appli-8a



8a

10-chloro-6-(4-methoxyphenyl)-5*H*-benzo[*a*]phenothiazin-5-one

6. ADME properties and molecular characterization of 8a

Computational methods are being used to filter and select compounds based on different molecular characteristics that are considered to be relevant to predict the drug-likeness of molecules. Without the aid of computational methods, the drug development process would be more time-consuming and less efficient, however, it is important to mention that the filtering rules employed by these methods are not absolute answers to the problem and that experimental confirmation is compulsory. A number of compounds fail during clinical phases due to poor pharmacokinetic and safety properties, therefore, the growing number of public and commercial *in silico* tools to predict ADMET (absorption, distribution, metabolism, excretion and toxicity) parameters is not surprising.

Pharmacokinetics and drug-likeness prediction for the synthesized compounds were also performed by online tool SwissADME[2a] of Swiss Institute of Bioinformatics (http://www.sib.swiss) was used to evaluate individual ADME behaviours of compound **8a**.[2b] 2D structural models were drawn in ChemBioDraw Ultra version 15.0 (Cambridge Software) and SMILES of **8a** was translated into molfile by online SMILES translator and structure file generator found in Online tool SwissADME. The analysis task was done to check whether the compound were inhibitor of isoforms of Cytochrome P450 (CYP) family such as CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4. In addition, pharmacokinetics (such as gastro intestinal absorption, P-glycoprotein and Blood brain barrier) and drug-likeness prediction such as Lipinski, Ghose and Veber rules and bioavailability score.[2c-e] The Lipinski, Ghose, Egan, Mugges and Veber rules were applied to assess druglikeness to predict whether a compound is likely to be a bioactive according to some important parameters such as molecular weight, Log *P*, number of HPA and HBD. The SwissADME tool used vector machine algorithm (SVM)[2f] with fastidiously cleaned large datasets of known inhibitors/non-inhibitors as well as substrates/non-substrates.

Table-1 Pharmacokinetic studies of compound 8a

Pharmacokinetics of 8a								
GI absorption	**BBB permeation**	**P-gp**	**Inhibition of cytochrome P450**					**Log *Kp***
			CYP1A2	*CYP2C19*	*CYP2C9*	*CYP3A4*	*CYP2D6*	
High	No	Yes	Yes	Yes	Yes	Yes	No	-4.73 cm/s

Table-2 Drug-likeness properties of compound **8a**

Drug-likeness of 8a							
Log *p*	**Log *s***	***Oral Bioavailability***					**Bioavailability**
		Lipinski	*Ghose*	*Veber*	*Egan*	*Mugge*	
3.69	-6.42	Yes	No	Yes	No	No	0.55

7. Reference

1. (a) D. Wang, B. Ge, S. Yang, H. Miao and Y. Ding. *Russ. J. Gen. Chem*, 2014, 84, 1615–1621.; (b) D. Wang, G. Bingyang, L. Liang, J. Shan and Y. Ding. *J. Org. Chem*., 2014, **79**, 8607.
2. (a) V. Zoete, A. Daina, C. Bovigny, O. Michielin. *J. Chem. Inf. Model*., 2016, **56,** 1399-1404. (b) A. Daina, O. Michielin, and V. Zoete., *Sci. Rep.,* 2017, **7**, 427-517. (c) C. Lipinski, F. Lombardo, B. Dominy, P. Feeney. *Adv. Drug. Deliv. Rev.,* 2011, **46**, 3-26., (d) A. K. Ghose, V.N. Viswanadhan, J. J. Wendoloski. *J. Comb. Chem.,* 1999, **1**, 55-68. (e)D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward. *J. Med. Chem.* 2002*,* **45**, 2615-2623., (f) C. Cortes and V. Vapnik. *Mach. Learn.*1995, **20**, 273-297.