Supporting Information

Discovery of Orally Bioavailable Chromone Derivatives as Potent and Selective BRD4 Inhibitors: Scaffolding Hopping, Optimization and Pharmacological Evaluation

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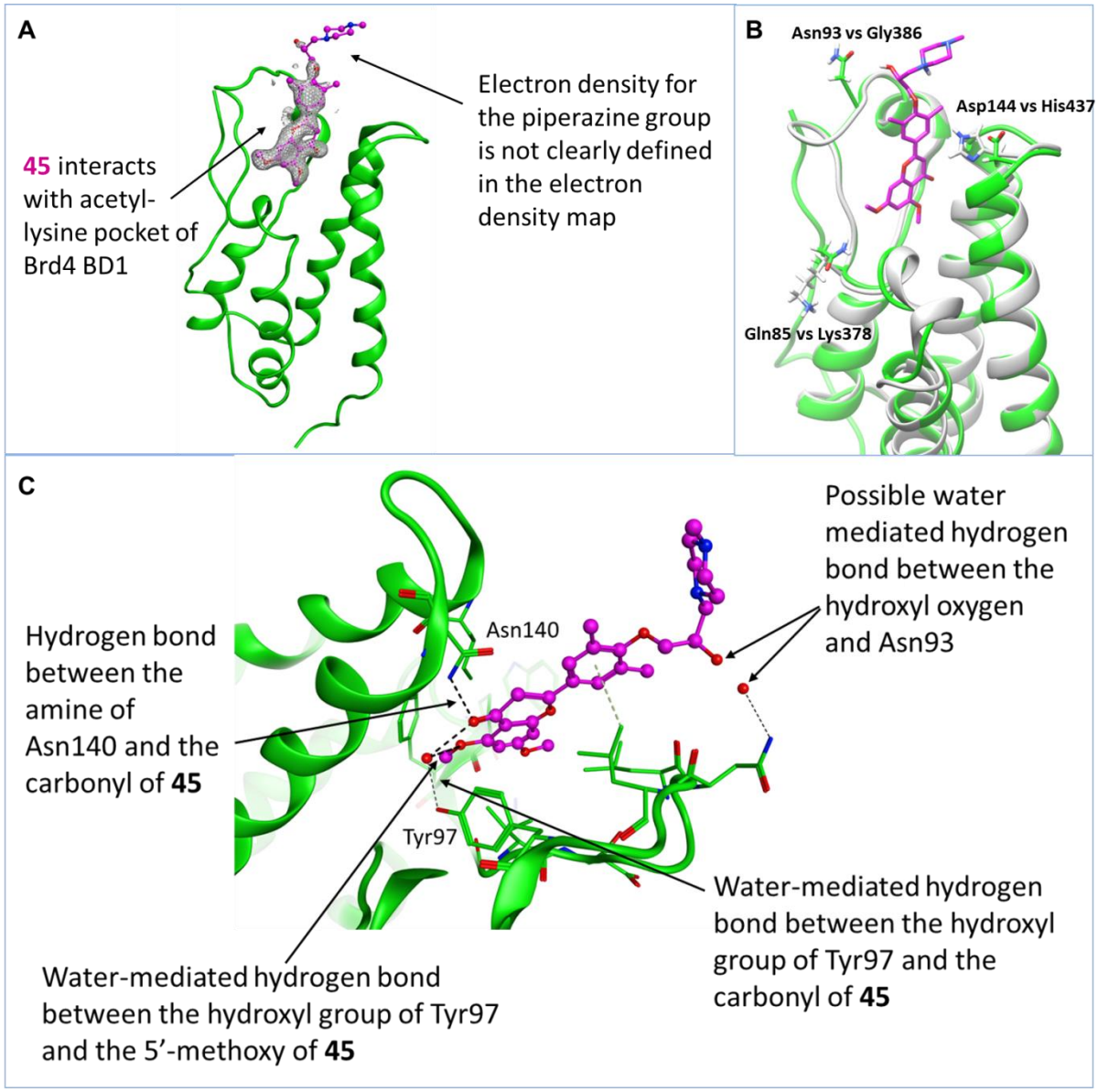


Figure S1. A) Crystal structure of **45** with BRD4 BD1 as ribbon diagram. Compound **45** occupying the Acetyl-lysine pocket of the bromodomain is shown with the ball and stick representation. The binding mode of **45** is unambiguously defined by the electron density in the crystal structure for the 5,7-dimethoxy-2-(3-methylphenyl)-4*H*-chromen-4-one part of the compound but the piperazine region is not clearly defined by the electron density suggesting this region adopts multiple conformations. The unbiased omit FoFcWT map for the compound, contoured at 3σ is

shown as a grey mesh. Compound **45** (pink) is depicted using ball and stick representation. B) Overlay and comparison of BRD4 BD1 (in green) and BRD4 BD2 (light gray, PDB code: 6C7Q). Different residues (Asn93 vs Gly386, Gln85 vs Lys378 and Asp144 vs His437) around the binding pocket are highlighted. C) Interaction network for **45** interacting with BRD4 BD1.

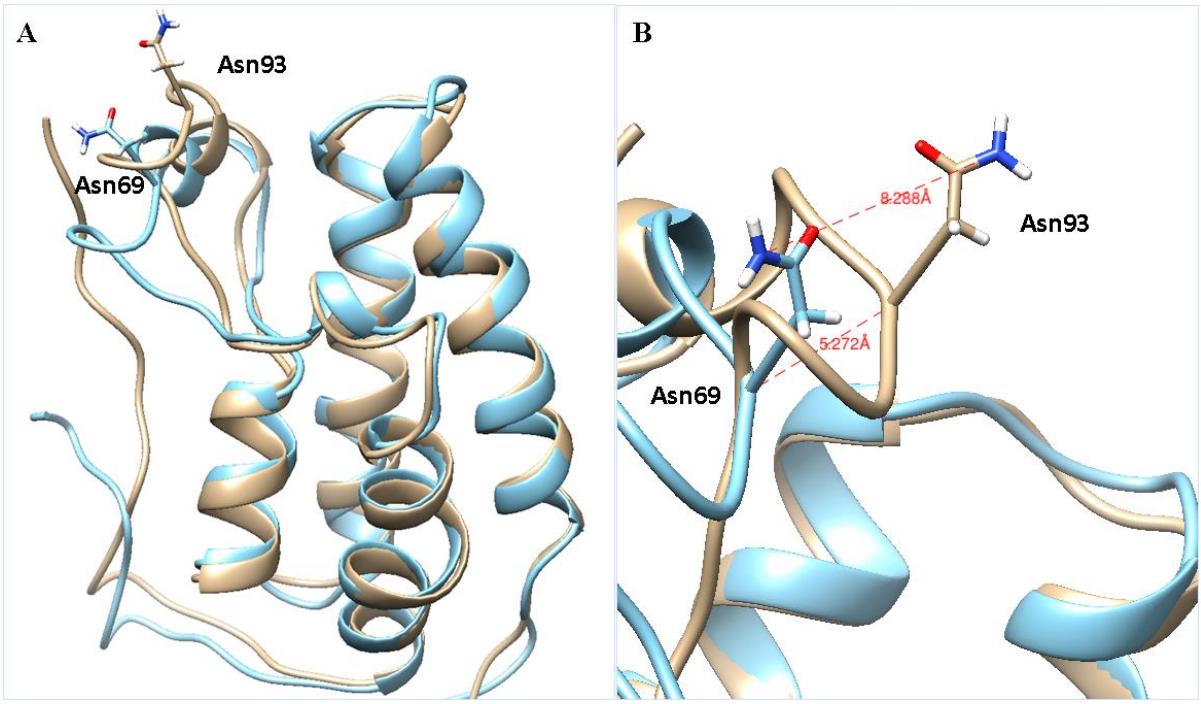


Figure S2. Superimposition of BRD4 BD1 (in tan, PDB code: 4MR4) and BRD3 BD1 (in light blue, PDB code: 2L5E). A) The helices of BRD4 BD1 and BRD3 BD1 are overlaid very well, while the loops especially ZA loop are far away from each other. B) The distances between the equivalent residues Asn93 and Asn69 were provided to highlight the ZA loop shift.

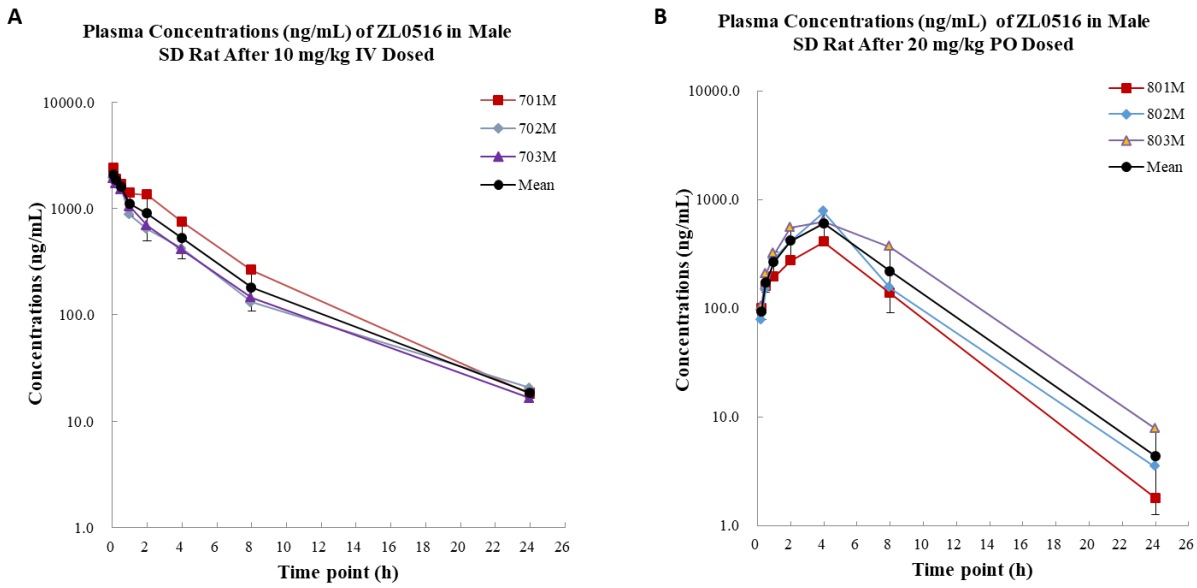


Figure S3. Plasma concentration curves of compound **45** in male SD rats after either IV or PO administration.

Table S1. BROMO*scan*™ Profiling of Compound 45.

Targets	Inhibition (%) @10 μM[a]
ATAD2A	8
BAZ2A	7
BRD1	42
CECR2	38
CREBBP	4
EP300	11
PCAF	64
SMARCA4	0
TAF1L(2)	29

[a]The compound(s) were screened at the concentration(s) requested, and results for primary screen binding interactions are reported as inhibitory rate (%) by calculating with '1-%Ctrl', where lower numbers indicate weaker hits in the matrix.

Assay principle: https://www.discoverx.com/technologies-platforms/competitive-binding-technology/bromoscan-technology-platform.

Table S2. NIMH Psychoactive Drug Screening Program (PDSP) for Compound 45.

Targets	Inhibition (%) @10 μM [a]
5-HT1A	3.6
5-HT1B	47.3
5-HT1D	-1.1
5-HT1E	4.9
5-HT2A	19.5
5-HT2B	64.7
5-HT2C	40
5-HT3	3.7
5-HT5A	14.1
5-HT6	-3.8
5-HT7	6.6
Alpha1A	-6.8
Alpha1B	33.4
Alpha1D	1.9
Alpha2A	36.2
Alpha2B	29.7
Alpha2C	17.3
Beta1	-2.5
Beta2	1.5
Beta3	37.8
BZP Rat Brain Site	39.7

D1	15.0
D2	-6.3
D3	-8.4
D4	12.0
D5	27.6
DAT	19.2
DOR	-3.3
H2	40.0
H4	-0.2
KOR	-6.1
M1	23.7
M2	9.7
M3	9.8
M4	9.4
M5	43.2
MOR	25.8
NET	17.9
PBR	24.9
SERT	25.4
Sigma	69.3

[a]Data represent mean % inhibition (N = 4 determinations) for compound tested at receptor subtypes. Significant inhibition is considered > 50%. In cases where negative inhibition (-) is seen, this represents a stimulation of binding.

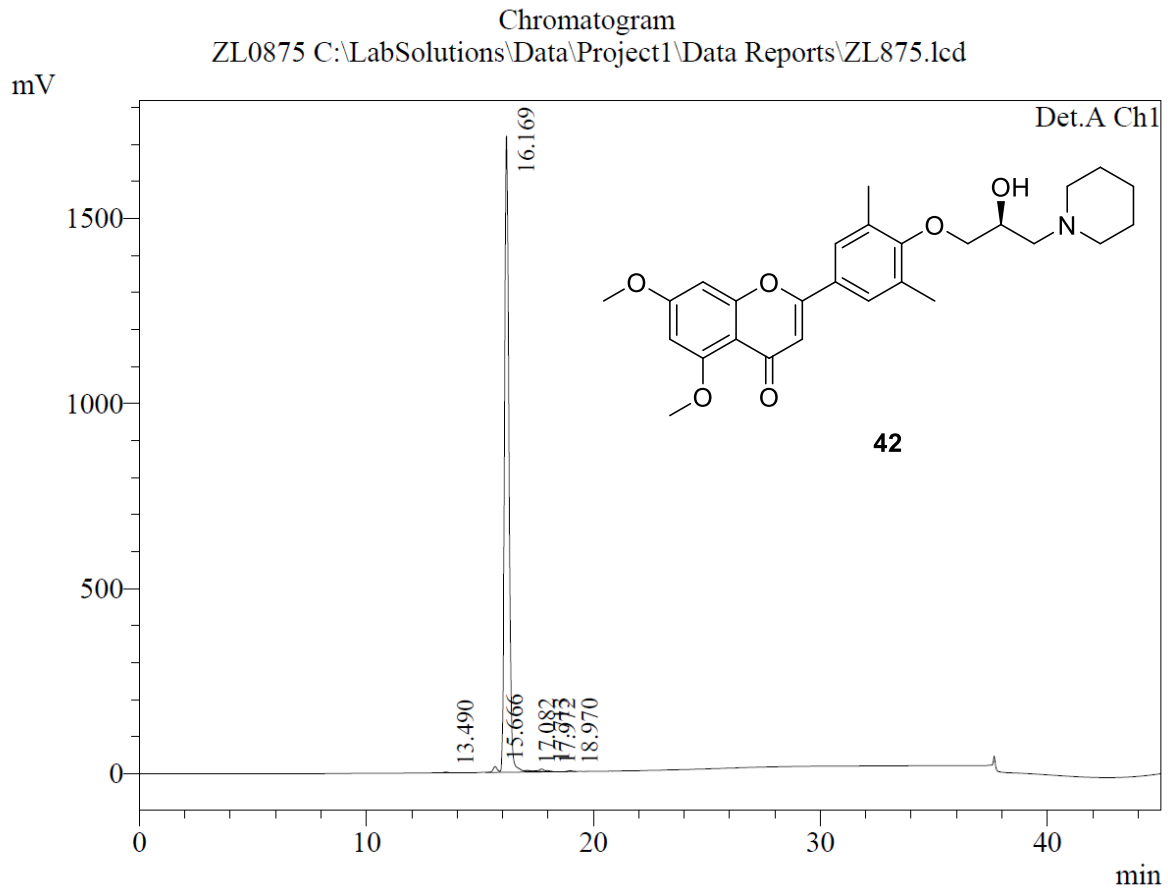
Table S3. Data Collection and Refinement Statistics for the Crystal Analysis of BRD4 Inhibitor 45 Co-complexed with Human BRD4 BD1.

	Brd4_BD1: **45**
Wavelength (nm)	1.541
Resolution range (Å)	26.87 - 2.0 (2.072 - 2.000)
Space group	P 2_1 2_1 2_1
Unit cell	37.0037 44.4639 78.1768 90 90 90
Total reflections	69104 (5312)
Unique reflections	9130 (844)
Multiplicity	7.6 (6.3)
Completeness (%)	99.40 (94.73)
Mean I/sigma(I)	7.06 (2.10)
Wilson B-factor	15.39
R-merge	0.2234 (0.8107)
R-meas	0.24 (0.8832)
R-pim	0.08587 (0.3397)
CC1/2	0.99 (0.673)
CC*	0.997 (0.897)
Reflections used in refinement	9128 (845)
Reflections used for R-free	912 (85)
R-work	0.1820 (0.2179)
R-free	0.2590 (0.2901)
CC(work)	0.959 (0.824)
CC(free)	0.907 (0.683)
Number of non-hydrogen atoms	1269
macromolecules	1056
ligands	55
solvent	158
Protein residues	126
RMS(bonds)	0.007
RMS(angles)	1.01

Ramachandran favored (%)	99.19
Ramachandran allowed (%)	0.81
Ramachandran outliers (%)	0.00
Rotamer outliers (%)	0.00
Clashscore	5.02
Average B-factor	16.94
macromolecules	15.43
ligands	30.17
solvent	22.47
	Brd4_BD1:ZL0516

*Statistics for the highest-resolution shell are shown in parentheses.

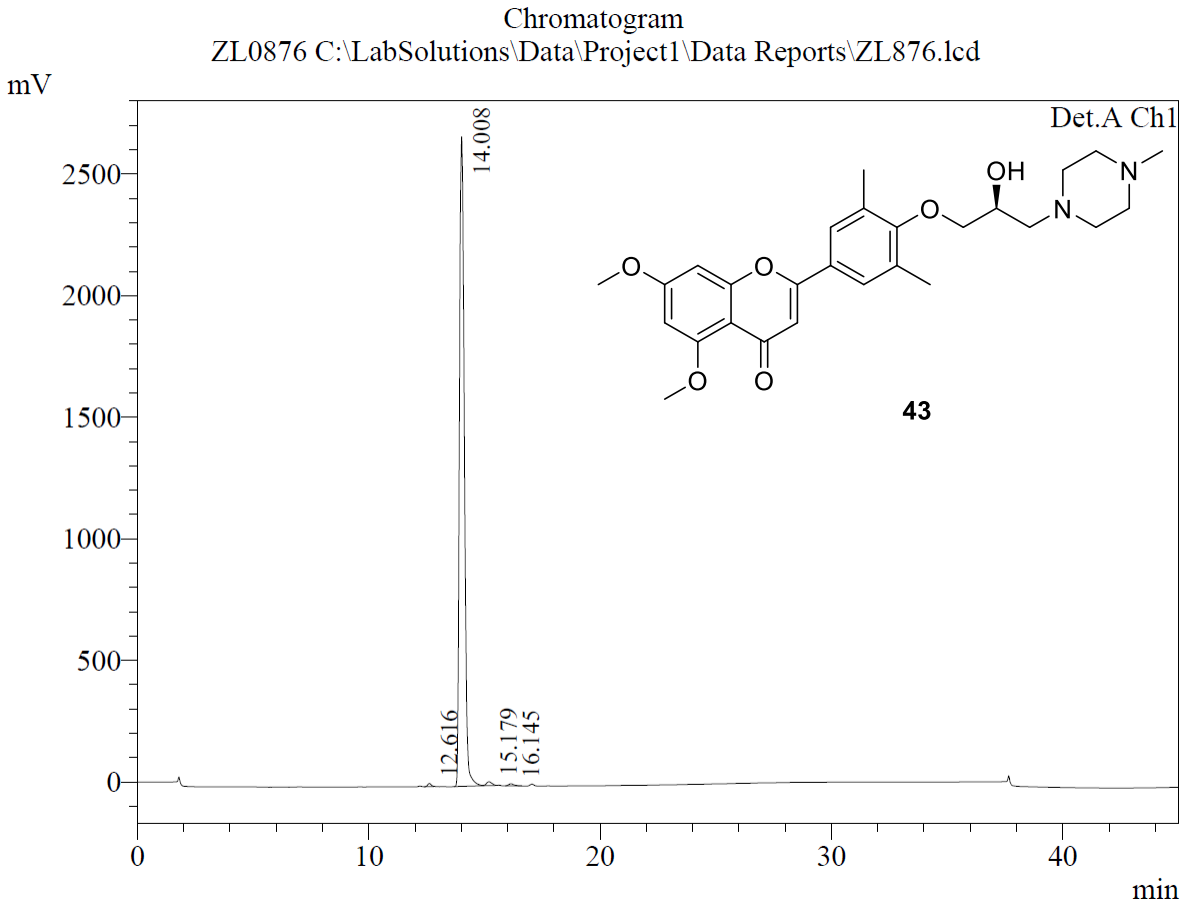
Copies of representative HPLC



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	13.490	30679	0.129	0.138
2	15.666	211791	0.892	0.901
3	16.169	23299507	98.182	98.179
4	17.082	19131	0.081	0.119
5	17.713	103290	0.435	0.382
6	17.972	28171	0.119	0.138
7	18.970	38285	0.161	0.143
Total		23730853	100.000	100.000



PeakTable

Detector A Ch1 254nm

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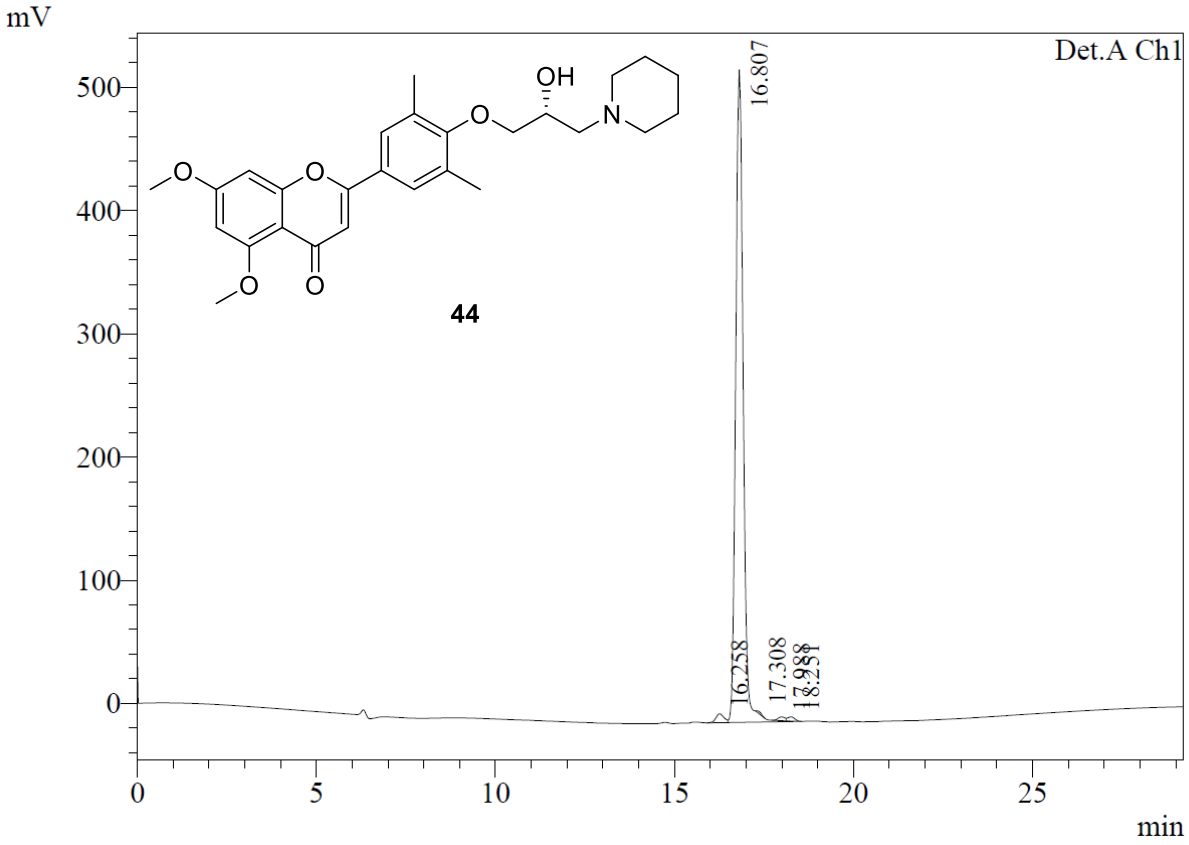
1	12.616	135711	0.340	0.472
2	14.008	39380087	98.630	98.613
3	15.179	268696	0.673	0.601
4	16.145	142411	0.357	0.315
Total		39926904	100.000	100.000

Chromatogram

ZL0513 C:\LabSolutions\Data\Project1\Data Reports\ZL0513_2.lcd



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	16.258	113599	1.425	1.324
2	16.807	7758250	97.294	97.285
3	17.308	14540	0.182	0.212
4	17.988	40701	0.510	0.563
5	18.251	46945	0.589	0.615
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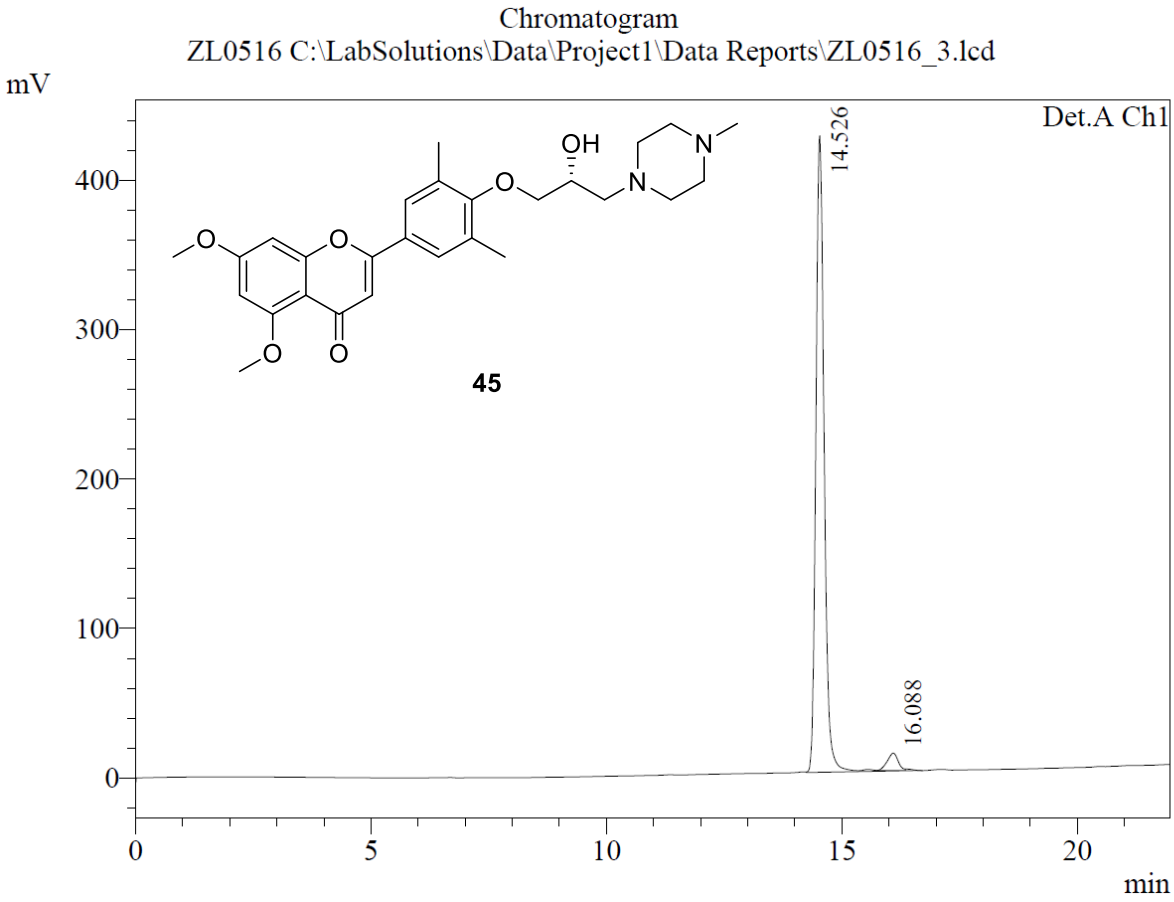

PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
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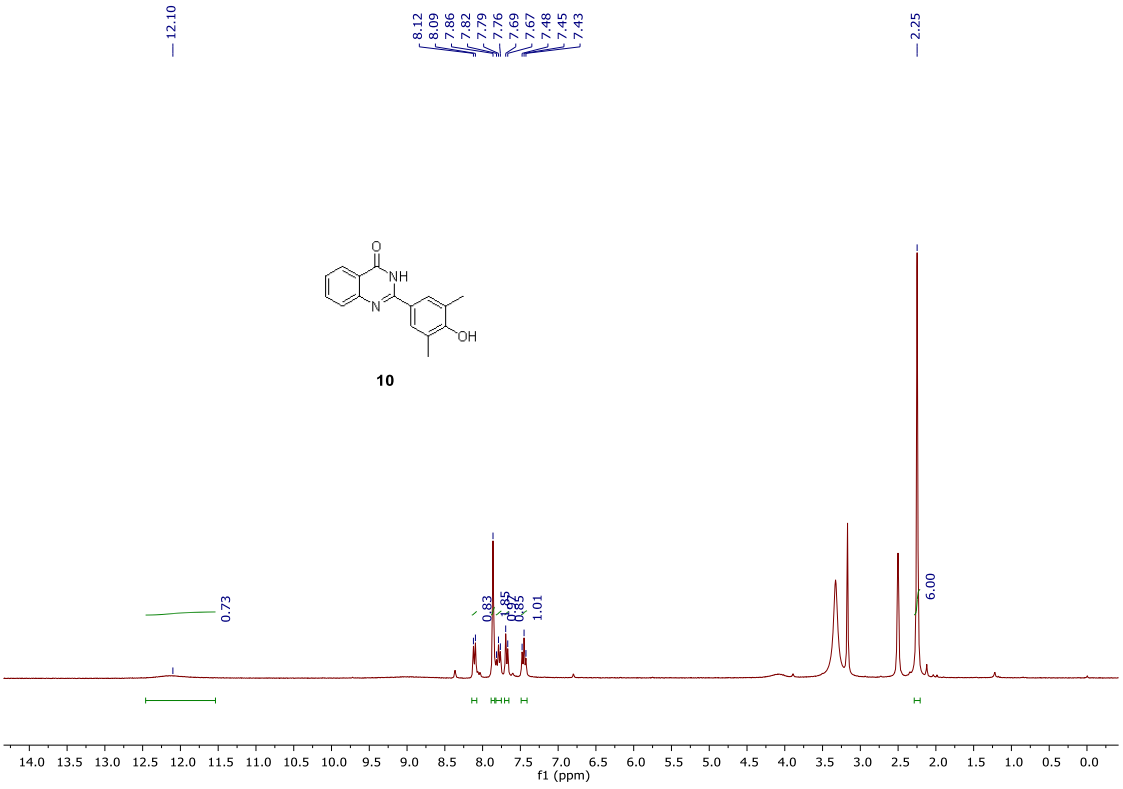
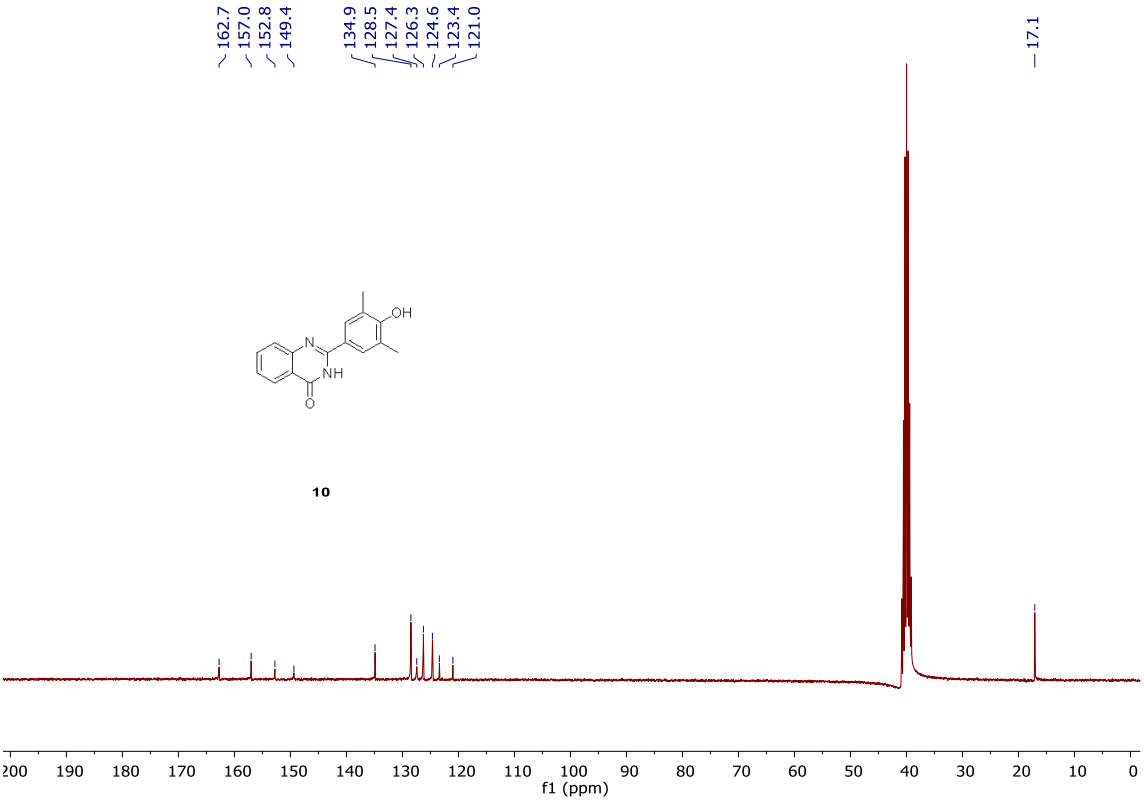
2	16.088	187015	3.473	2.656
Total		5384458	100.000	100.000

Copies of ^{1}H NMR and ^{13}C NMR

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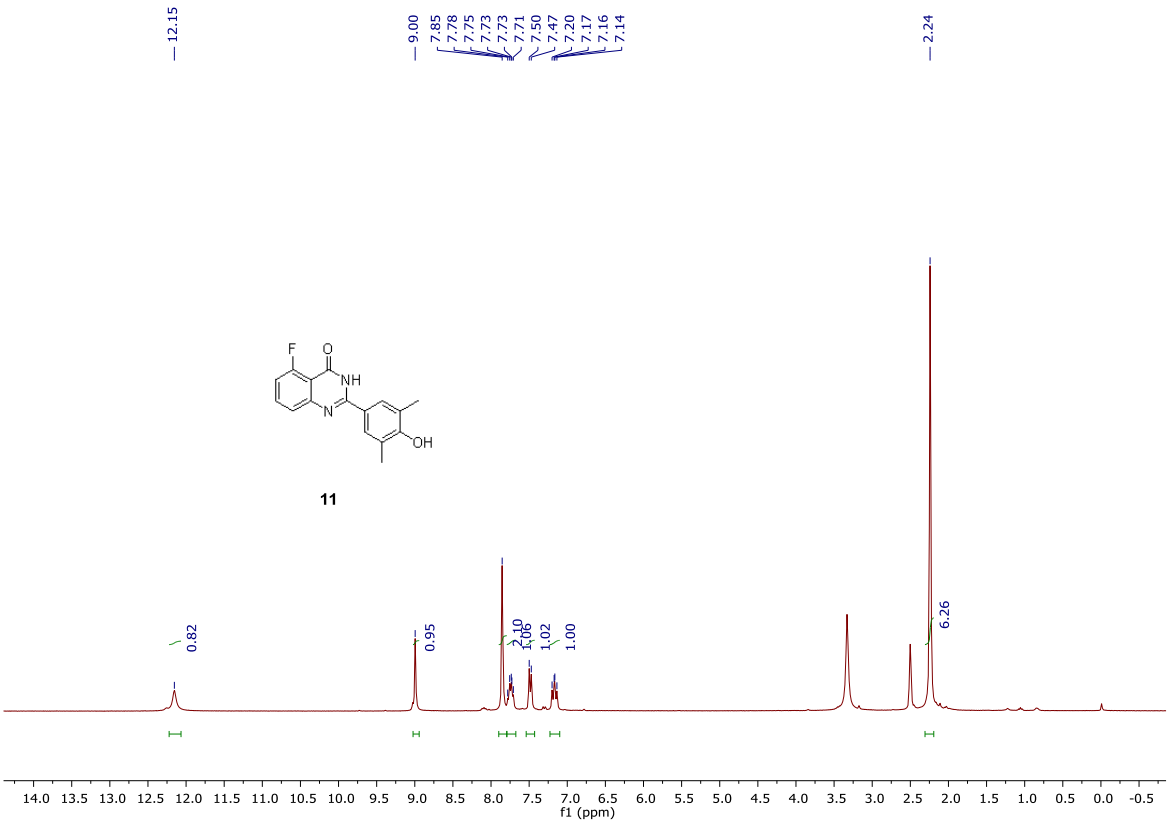
N
NH
O
f1 (ppm)

10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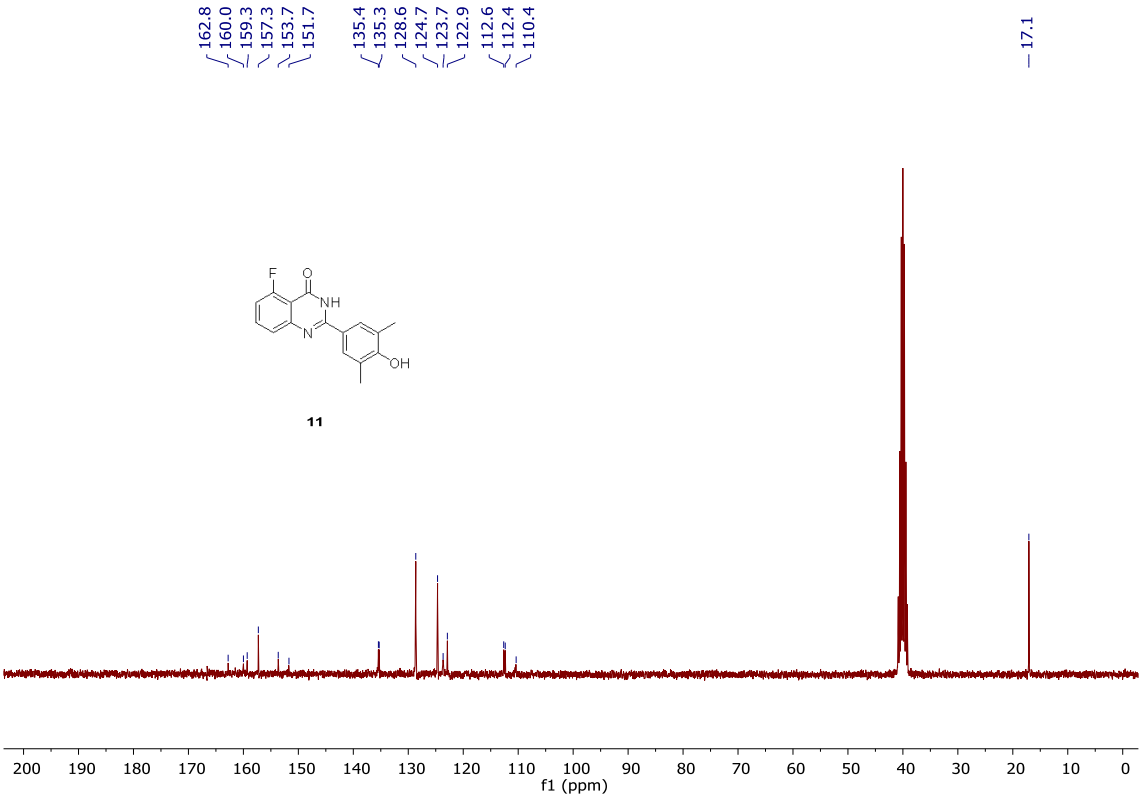
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f1 (ppm)

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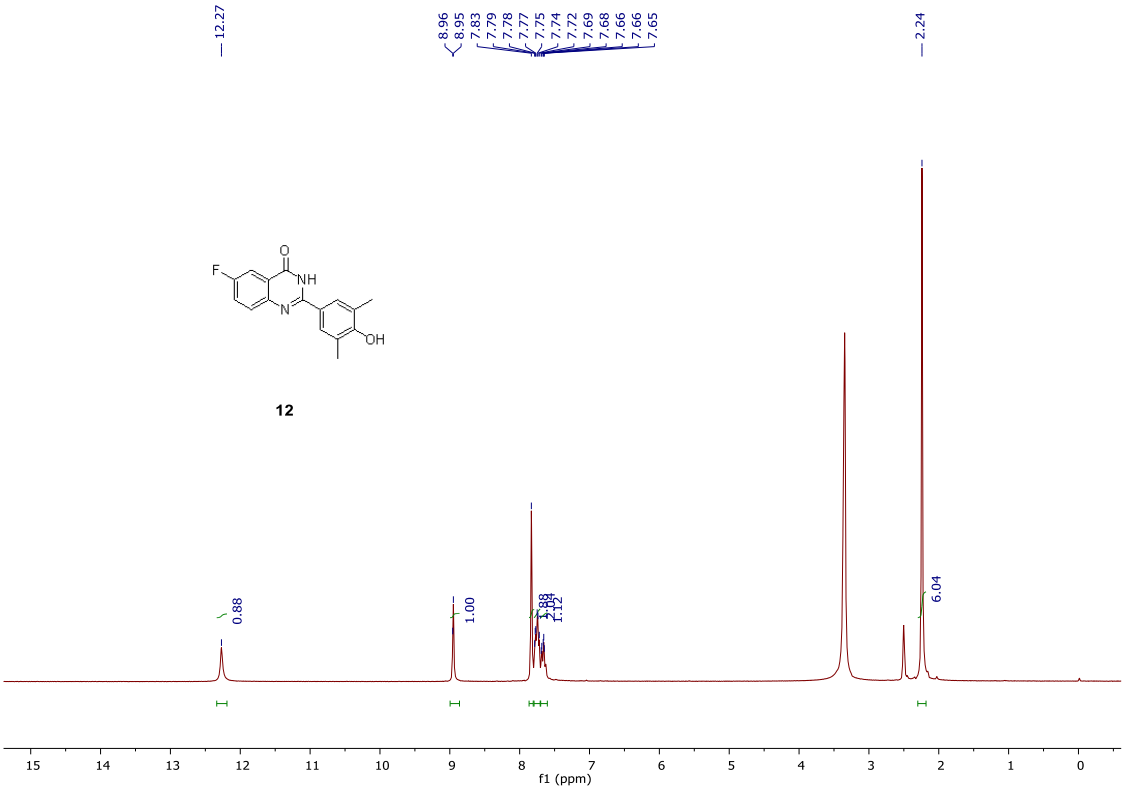
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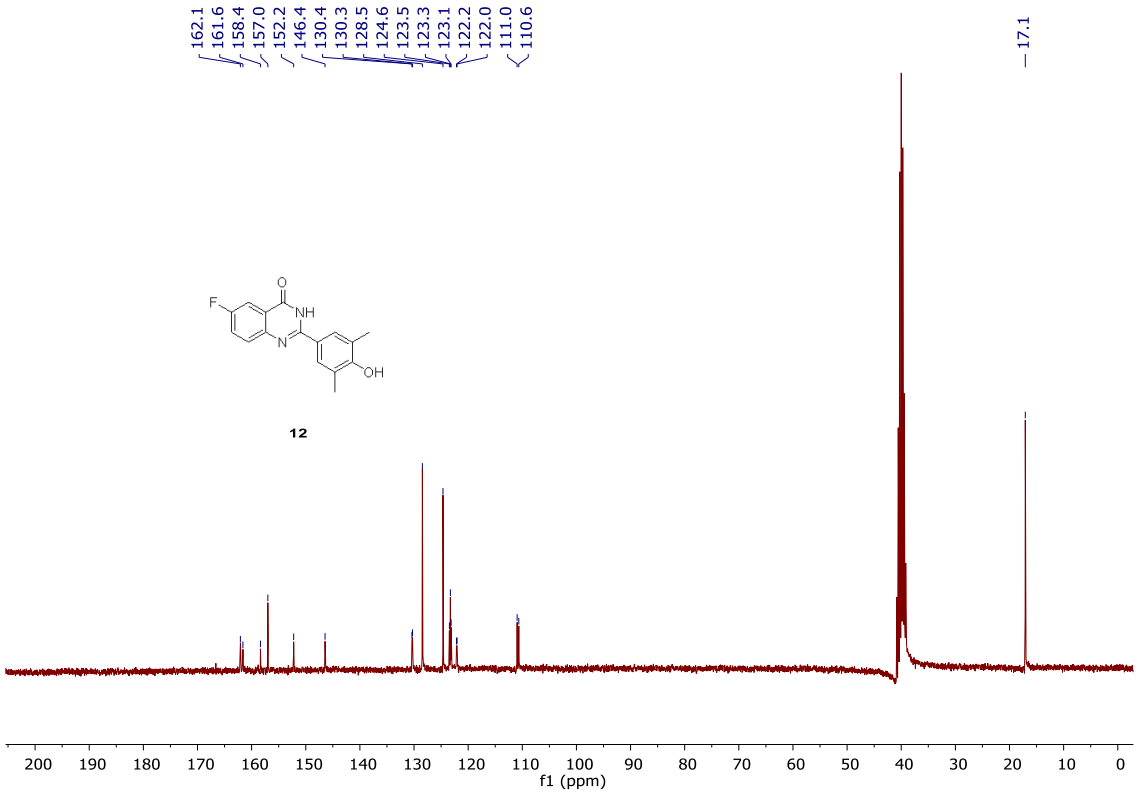
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122.2
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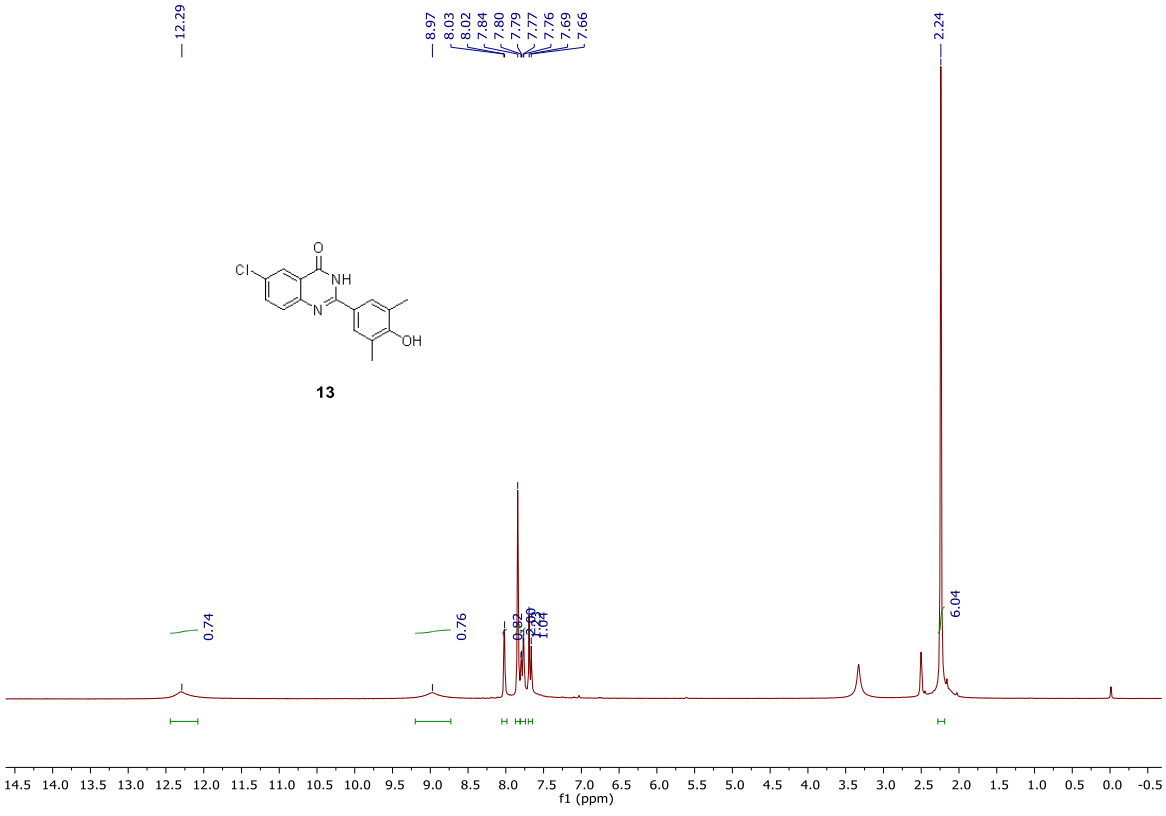
f1 (ppm)

12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2.00
1.04
6.04
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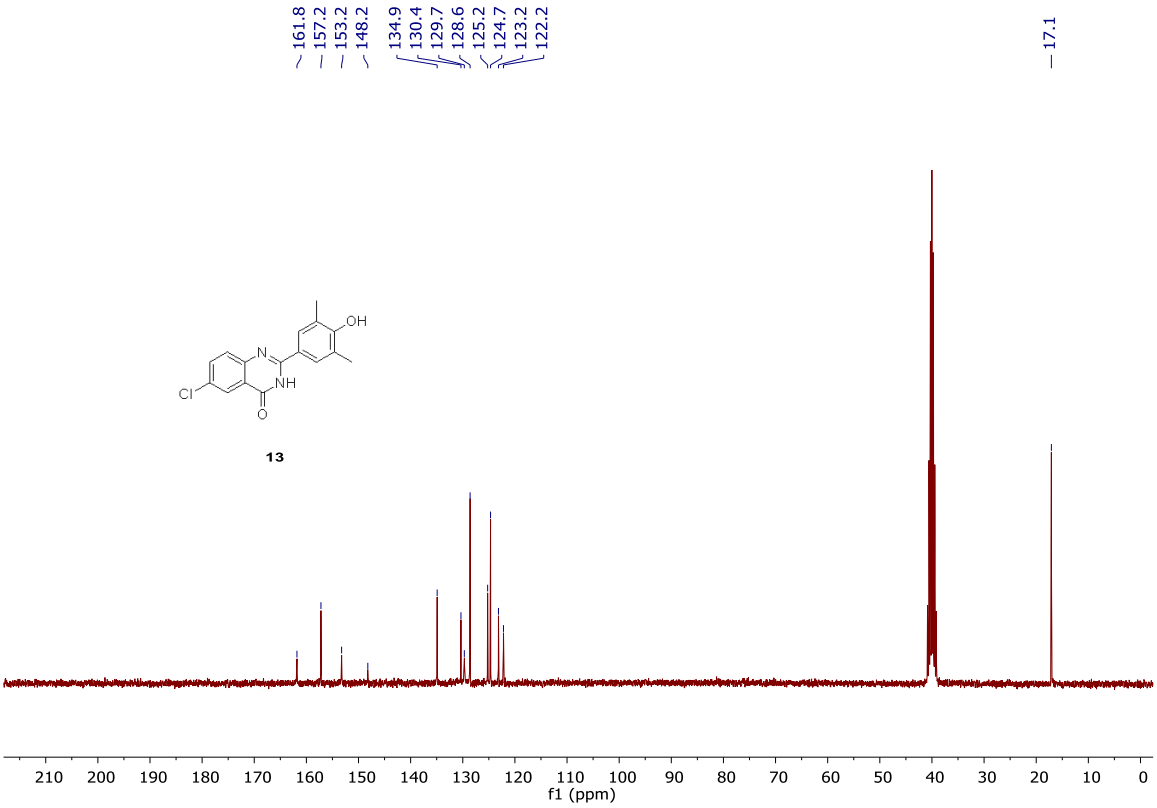
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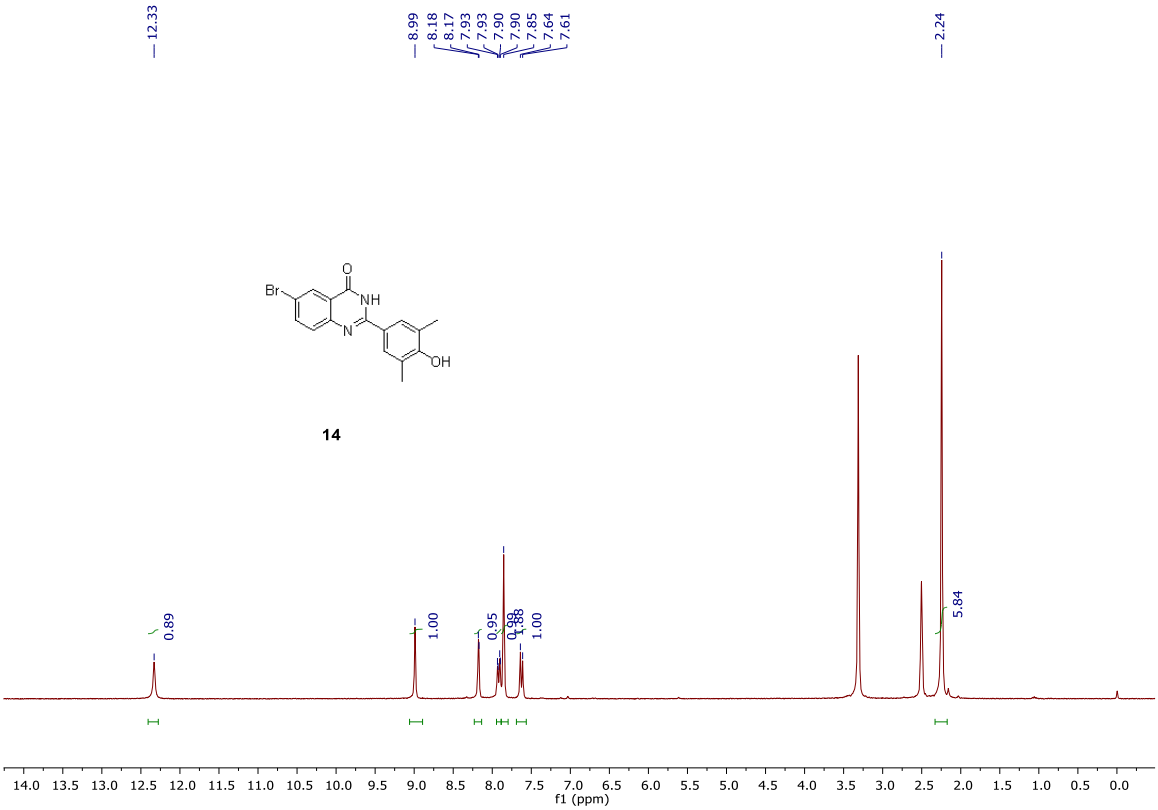
f1 (ppm)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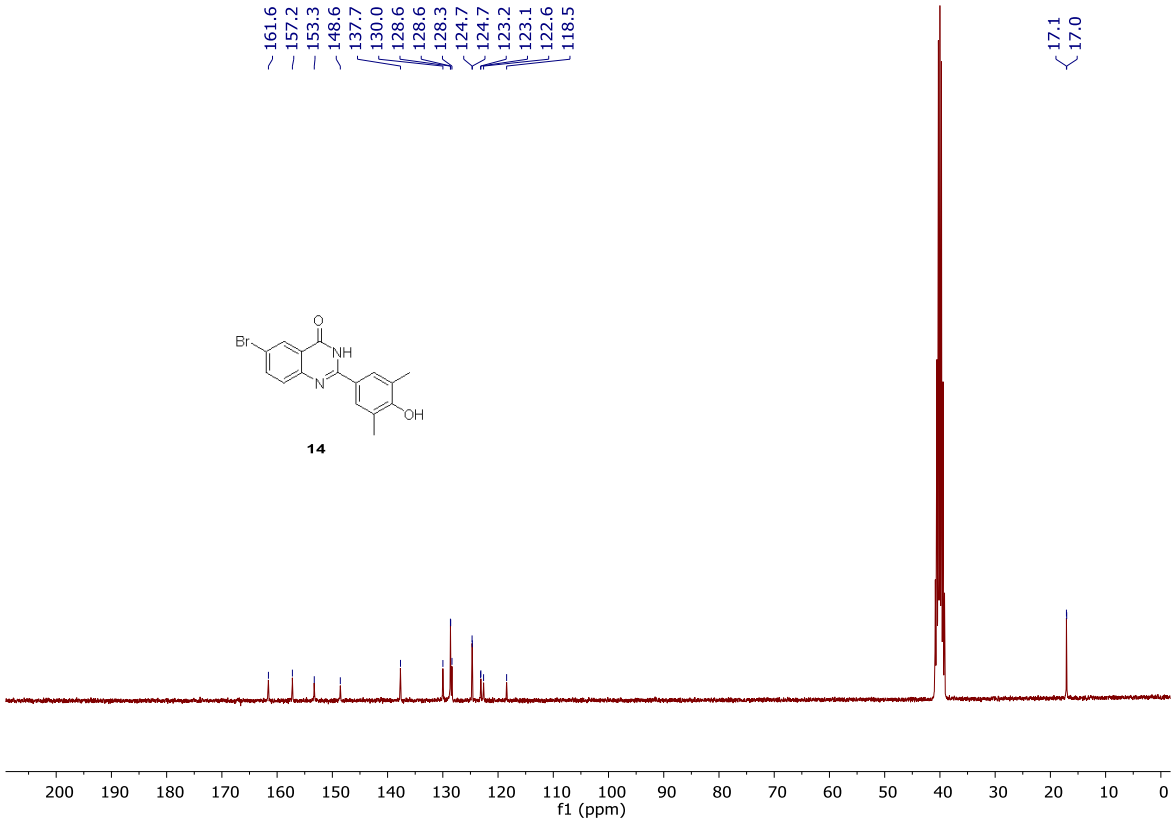
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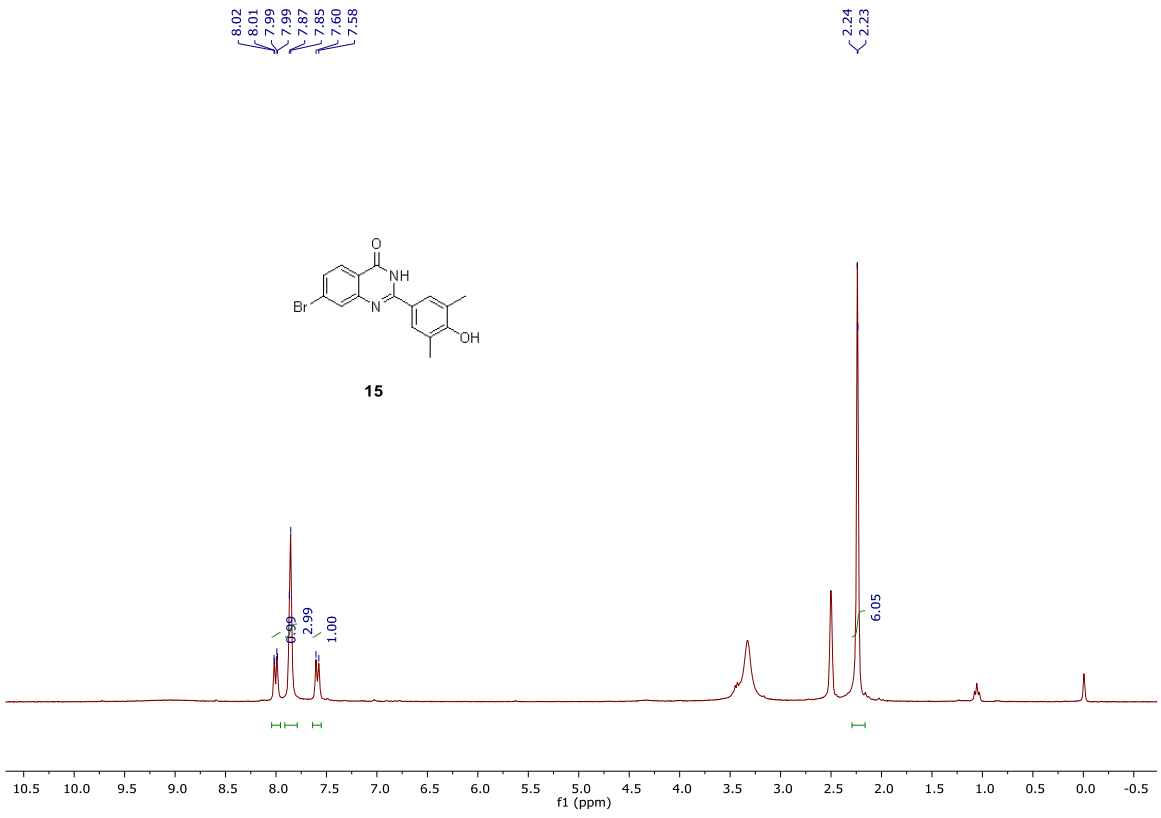
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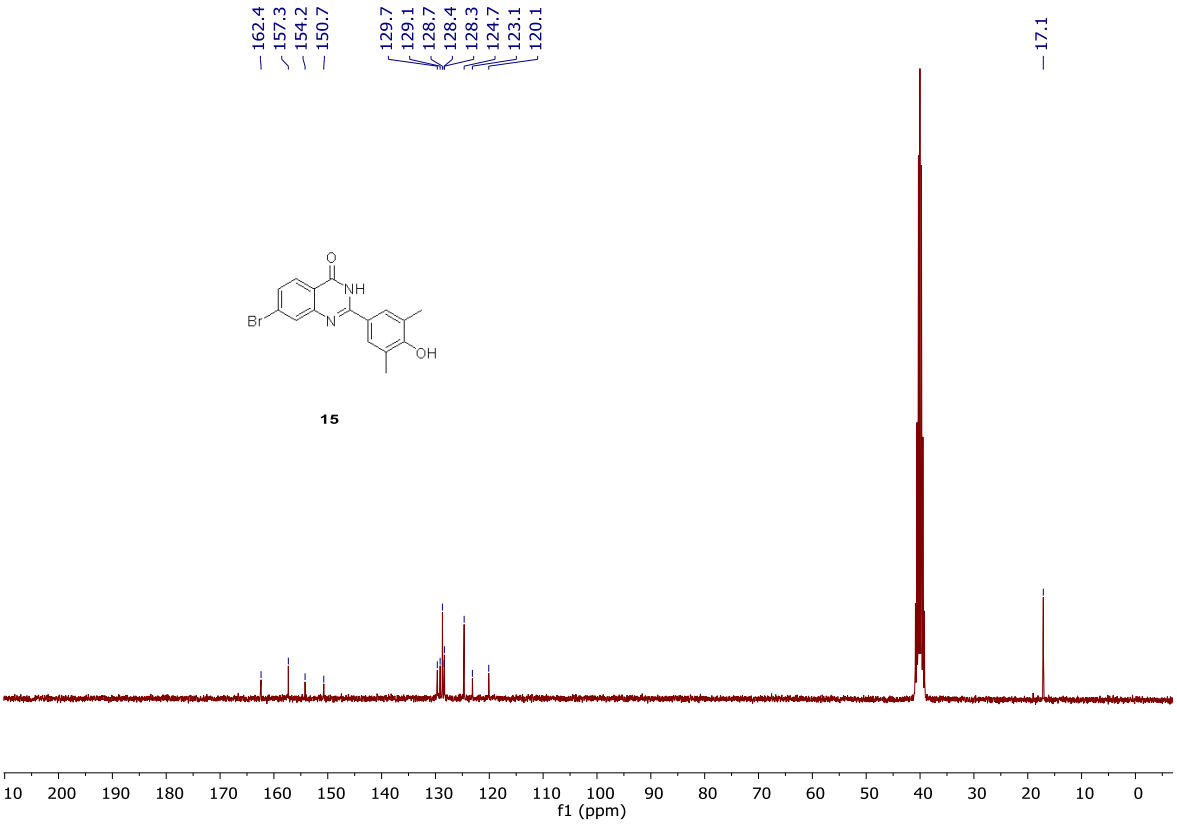
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f1 (ppm)

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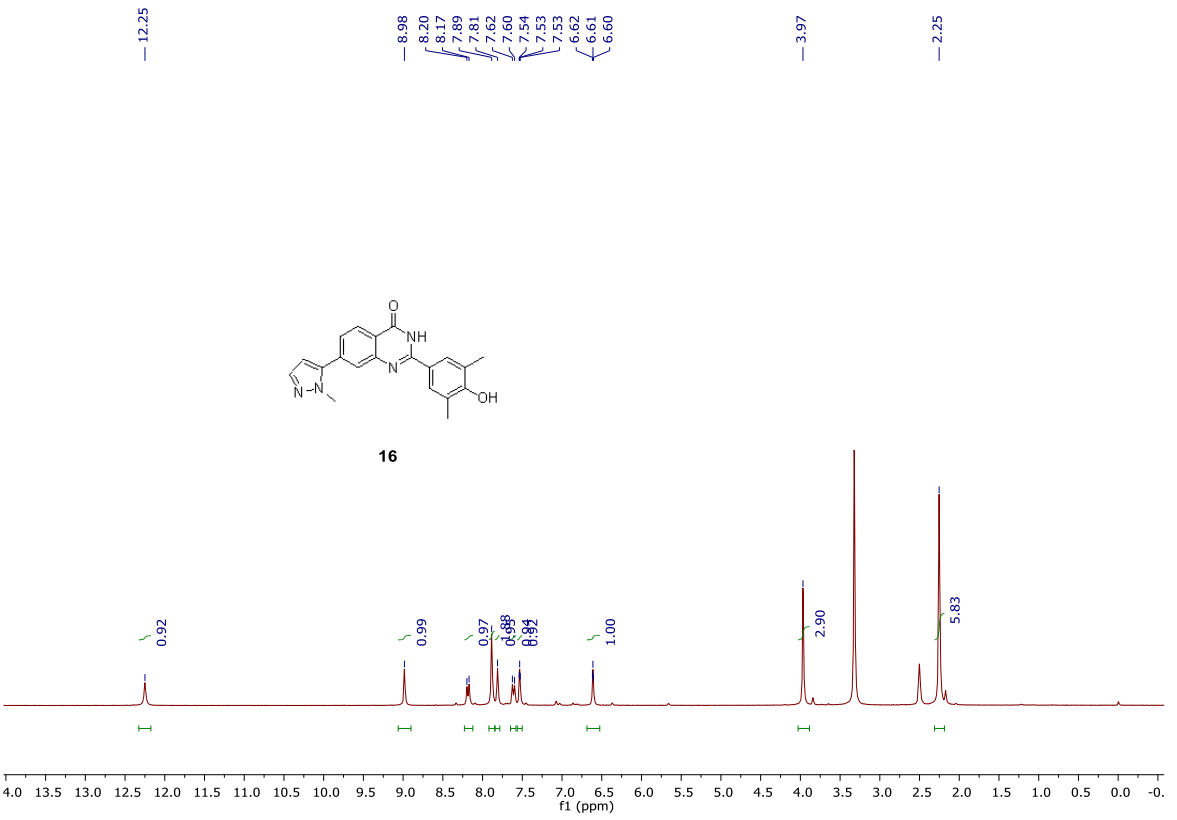
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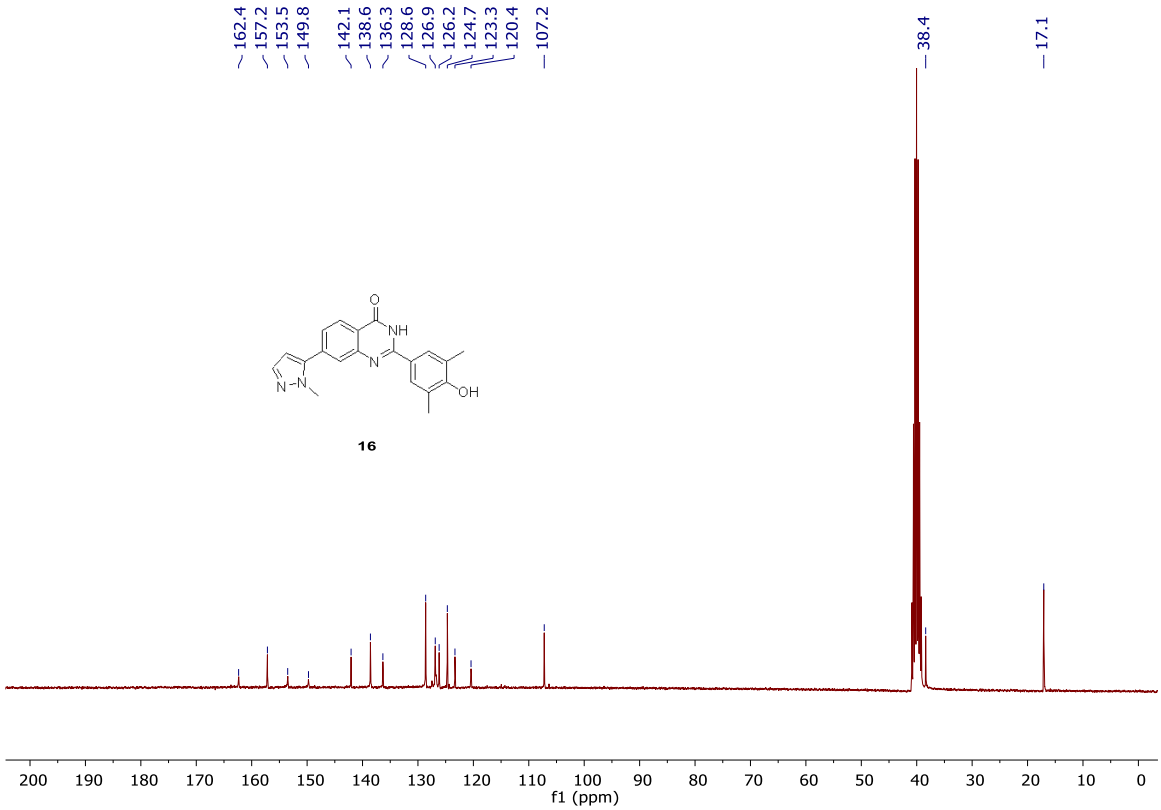
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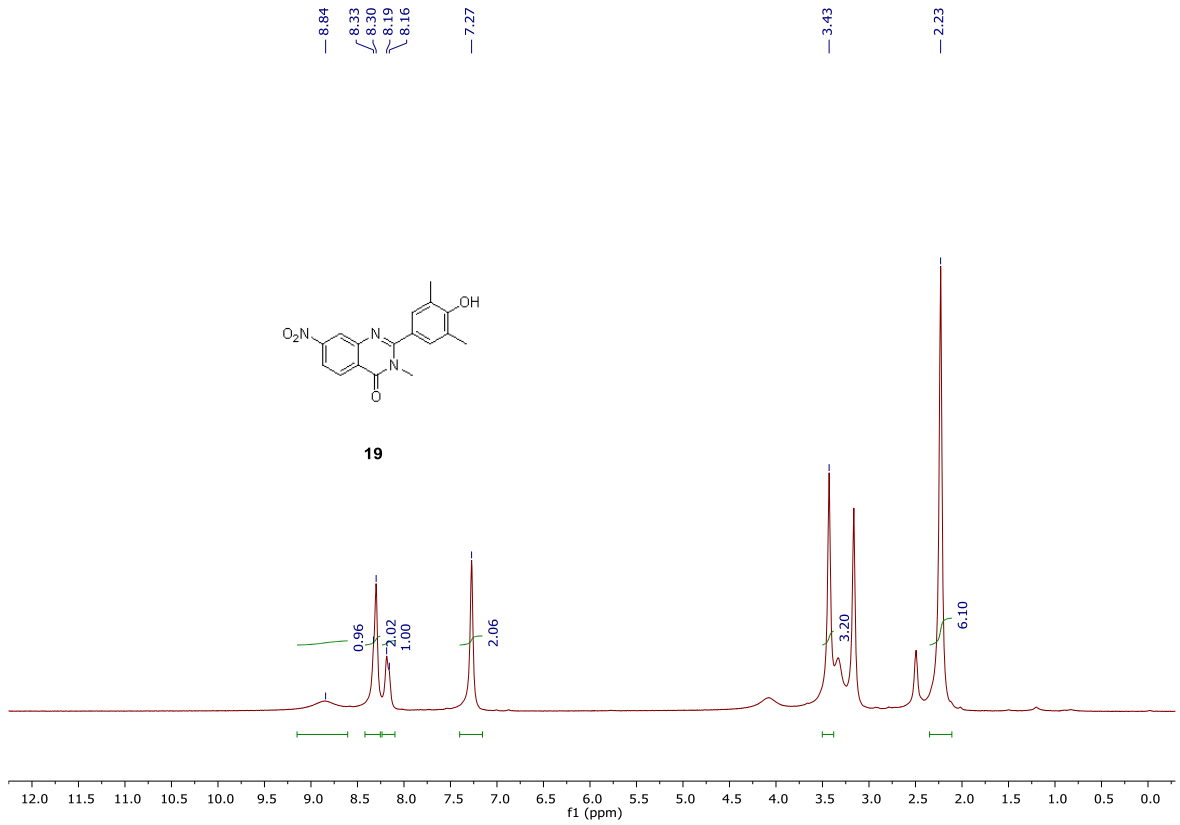
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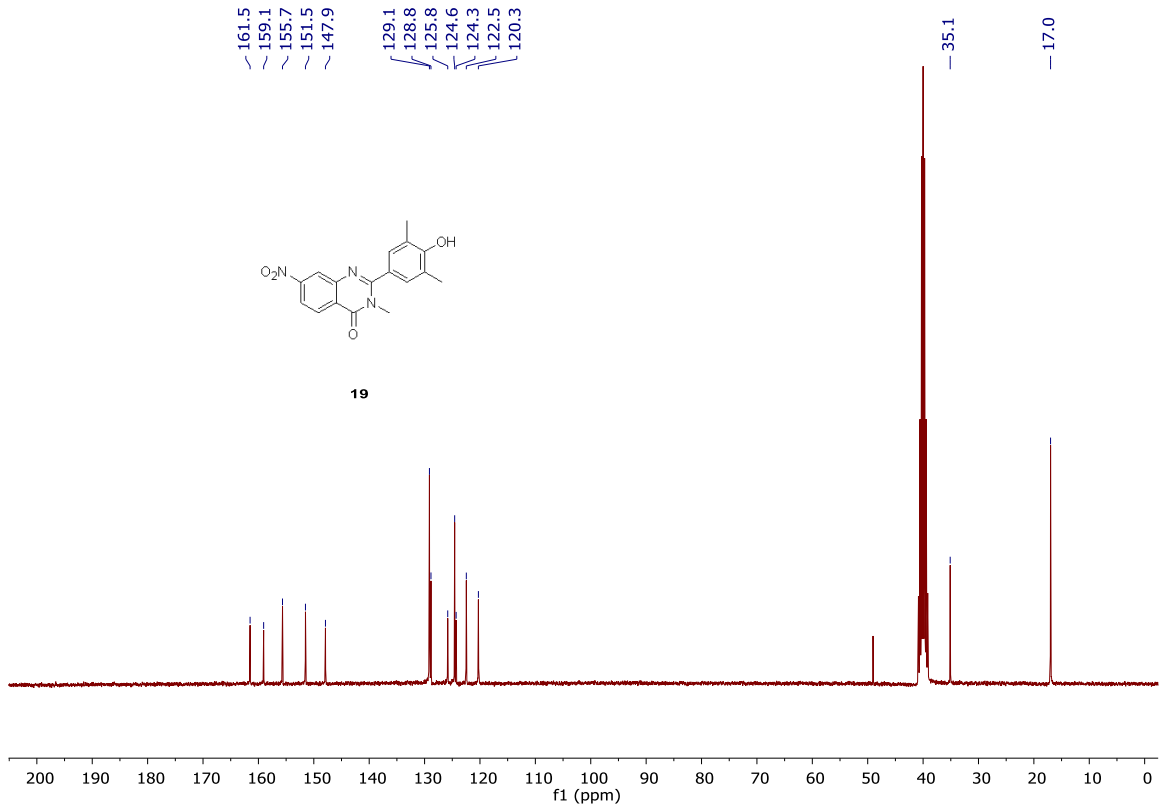
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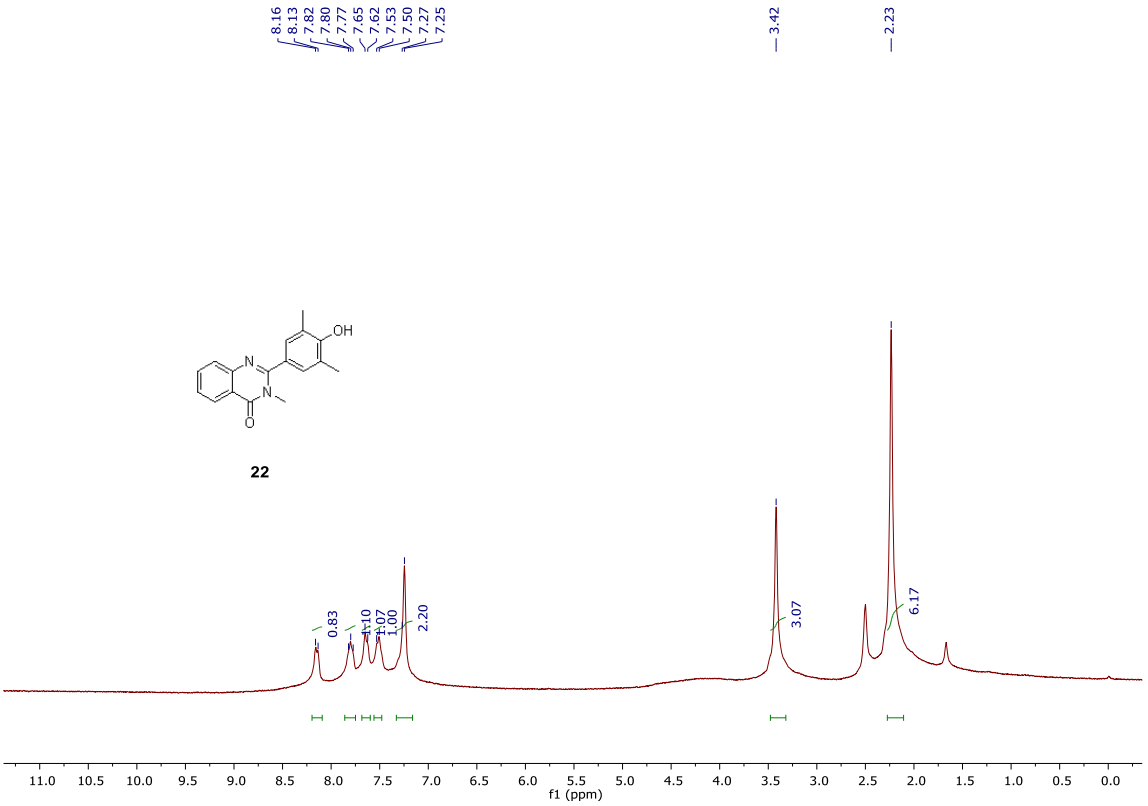
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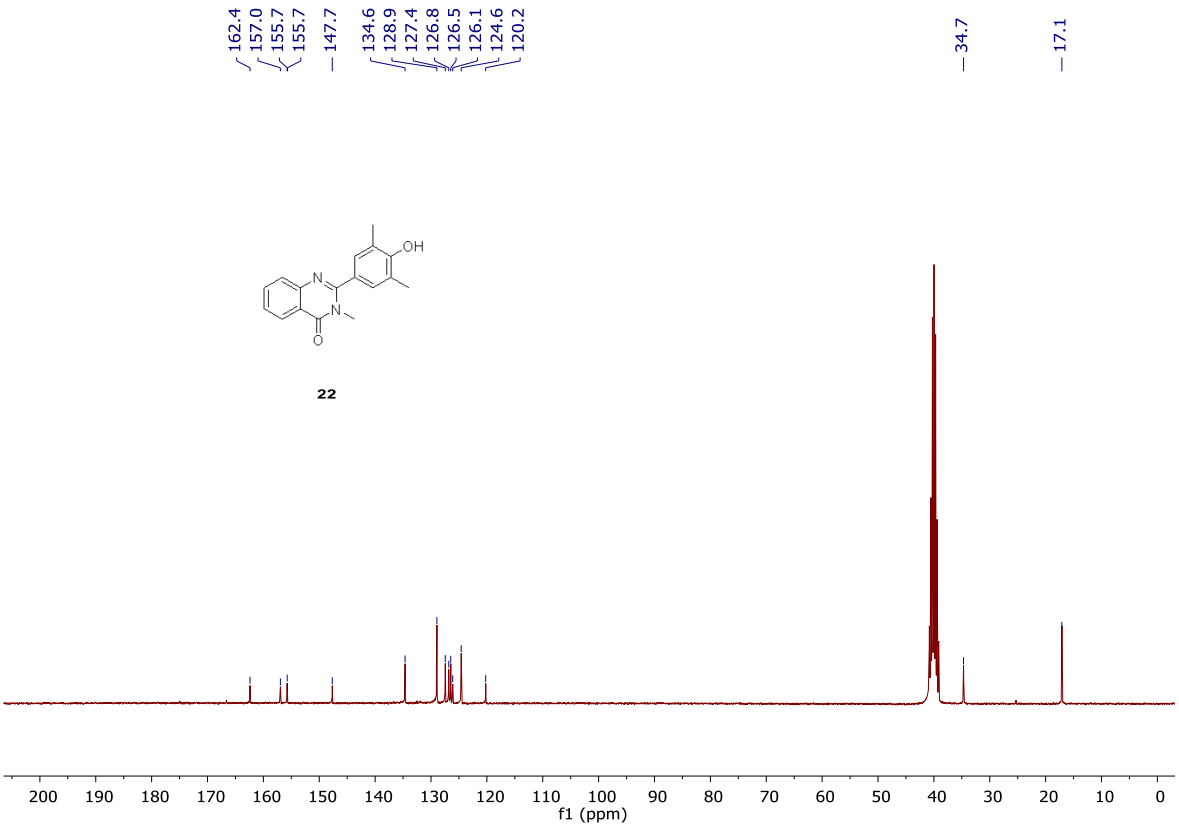
f1 (ppm)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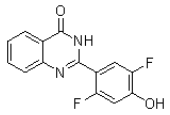
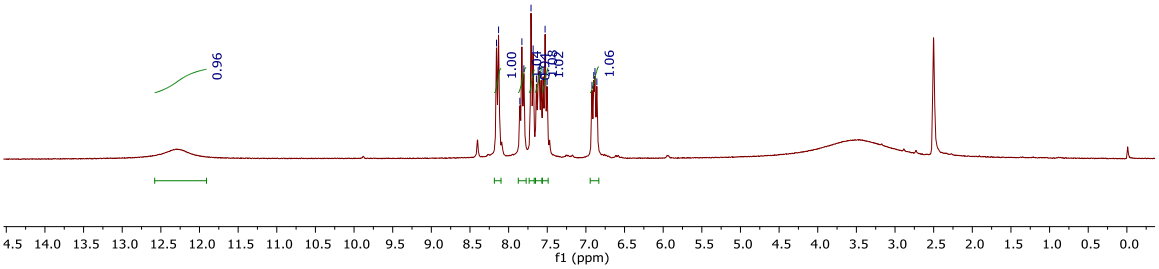
120.2
34.7
17.1
OH
N
N
O
22
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

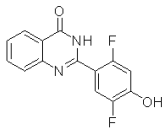

8.16
8.13
7.85
7.83
7.80
7.71
7.68
7.64
7.62
7.60
7.58
7.55
7.53
7.50
6.92
6.90
6.88
6.86


O
NH
N
F
F
OH

24

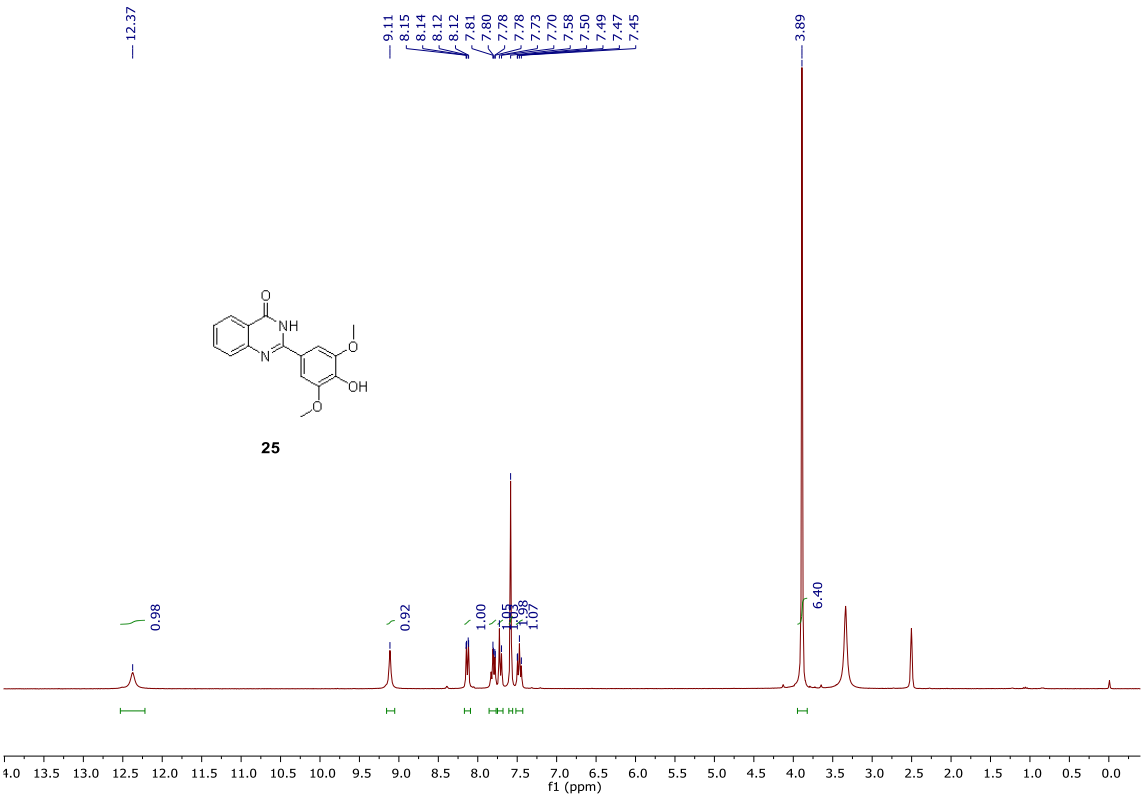

0.96
1.00
1.06
4.5 14.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

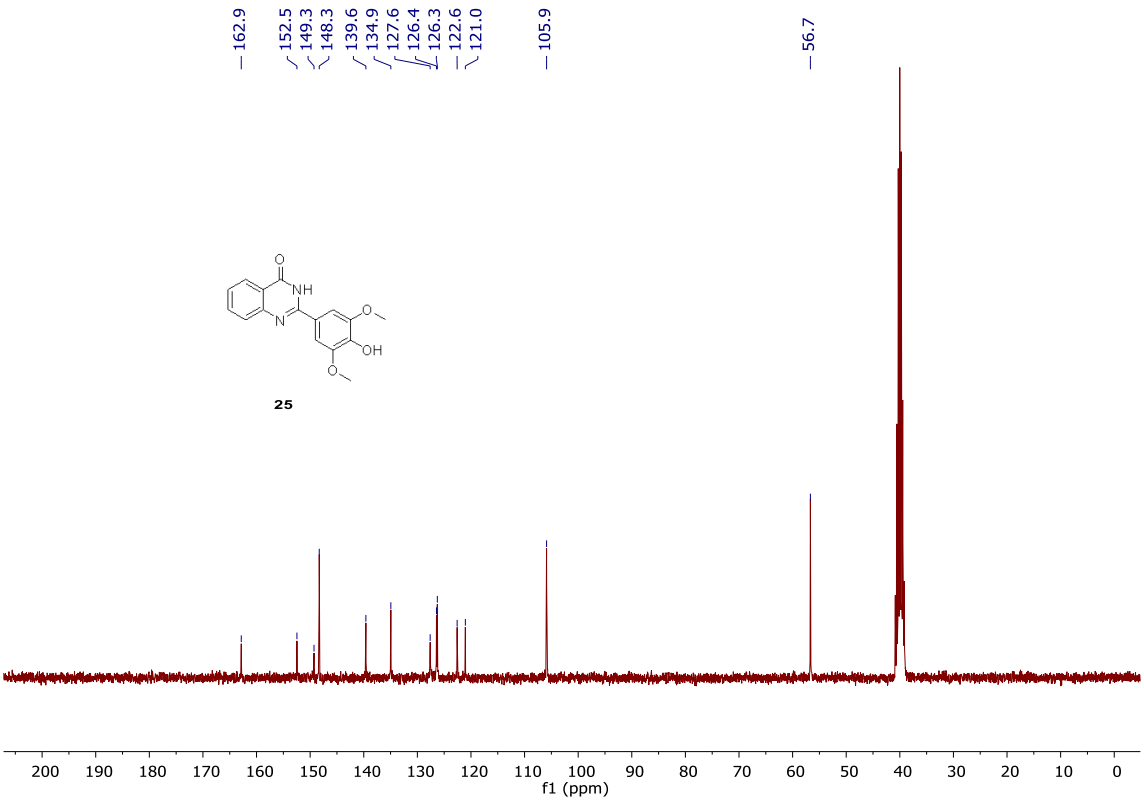

162.0
158.3
155.0
149.5
149.2
149.1
146.3
143.3
134.9
127.7
127.2
126.3
121.4
117.8
117.5
117.5
112.5
112.4
106.0
105.6

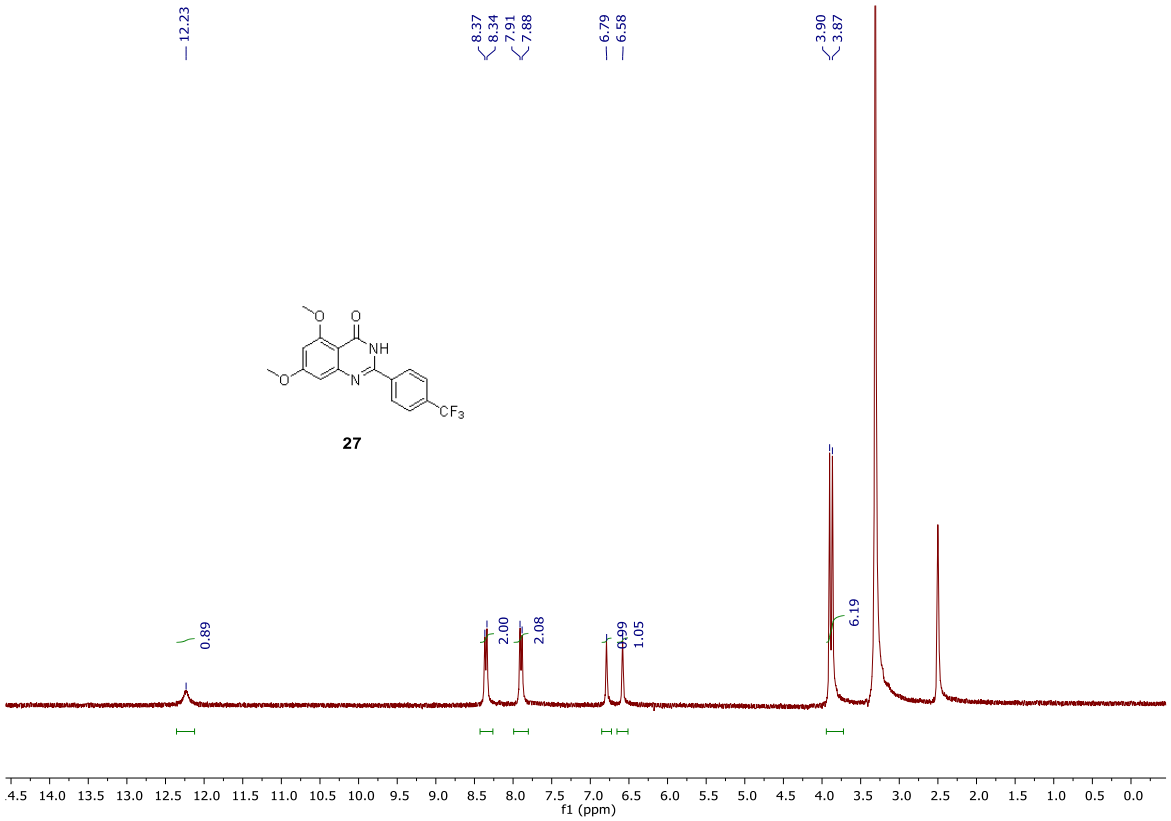

O
NH
F
N
OH
F

24

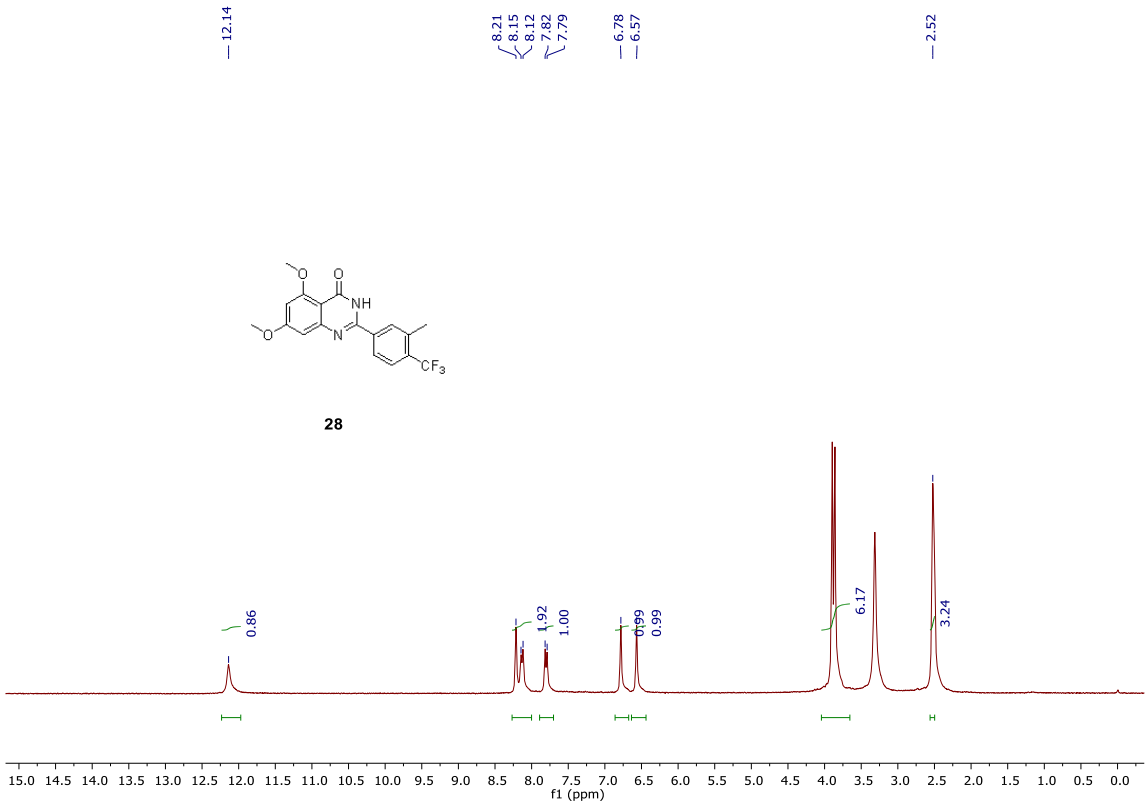
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


12.37
9.11
8.15
8.14
8.12
8.12
7.81
7.80
7.78
7.78
7.73
7.70
7.58
7.50
7.49
7.47
7.45
3.89
O
NH
N
O
OH
O
25
0.98
0.92
1.00
1.05
1.08
1.07
6.40
f1 (ppm)

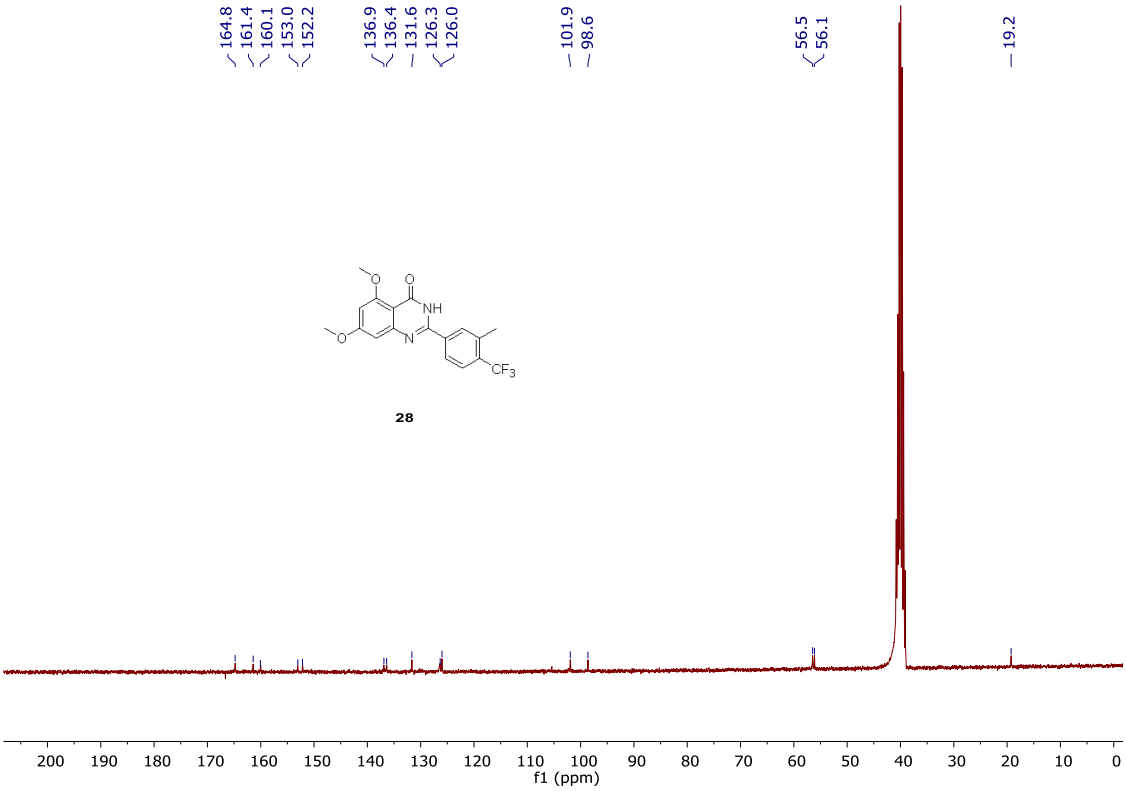

162.9
152.5
149.3
148.3
139.6
134.9
127.6
126.4
126.3
122.6
121.0
105.9
56.7
O
NH
N
O
OH
O
25
f1 (ppm)


12.23
8.37
8.34
7.91
7.88
6.79
6.58
3.90
3.87
0.89
2.00
2.08
0.99
1.05
6.19
f1 (ppm)

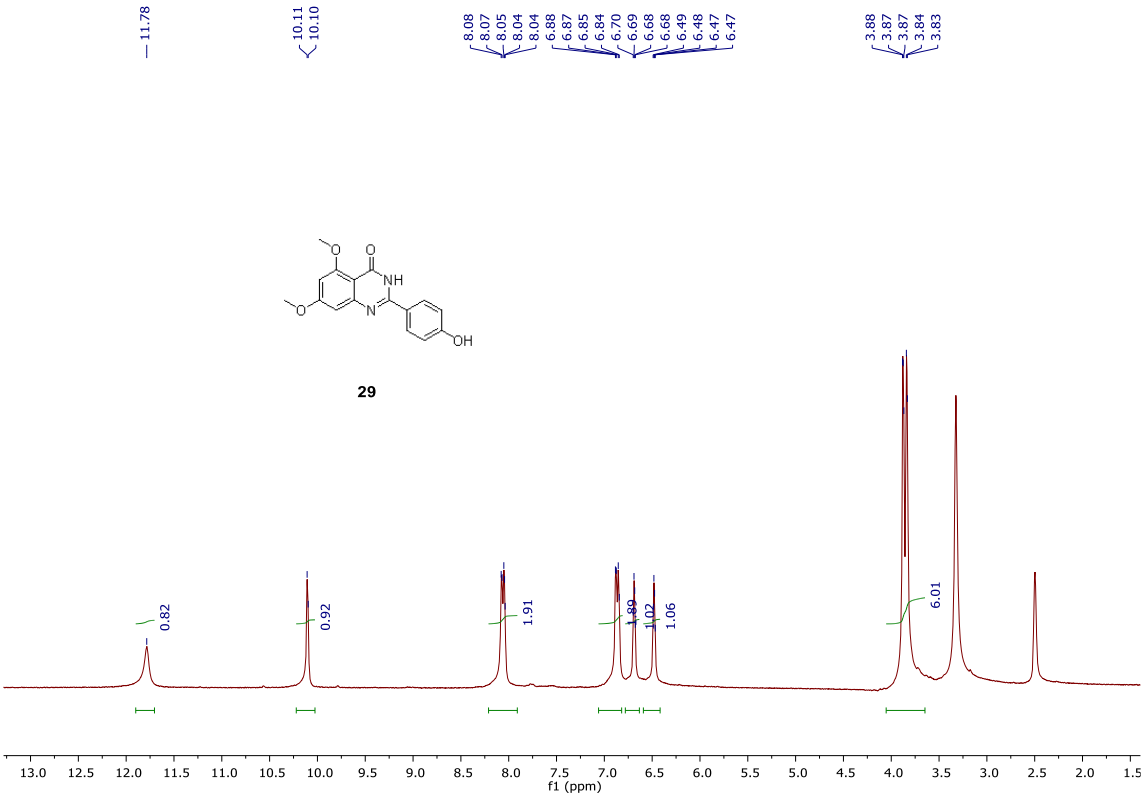
27


12.14
8.21
8.15
8.12
7.82
7.79
6.78
6.57
2.52
0.86
1.92
1.00
0.99
0.99
6.17
3.24
f1 (ppm)

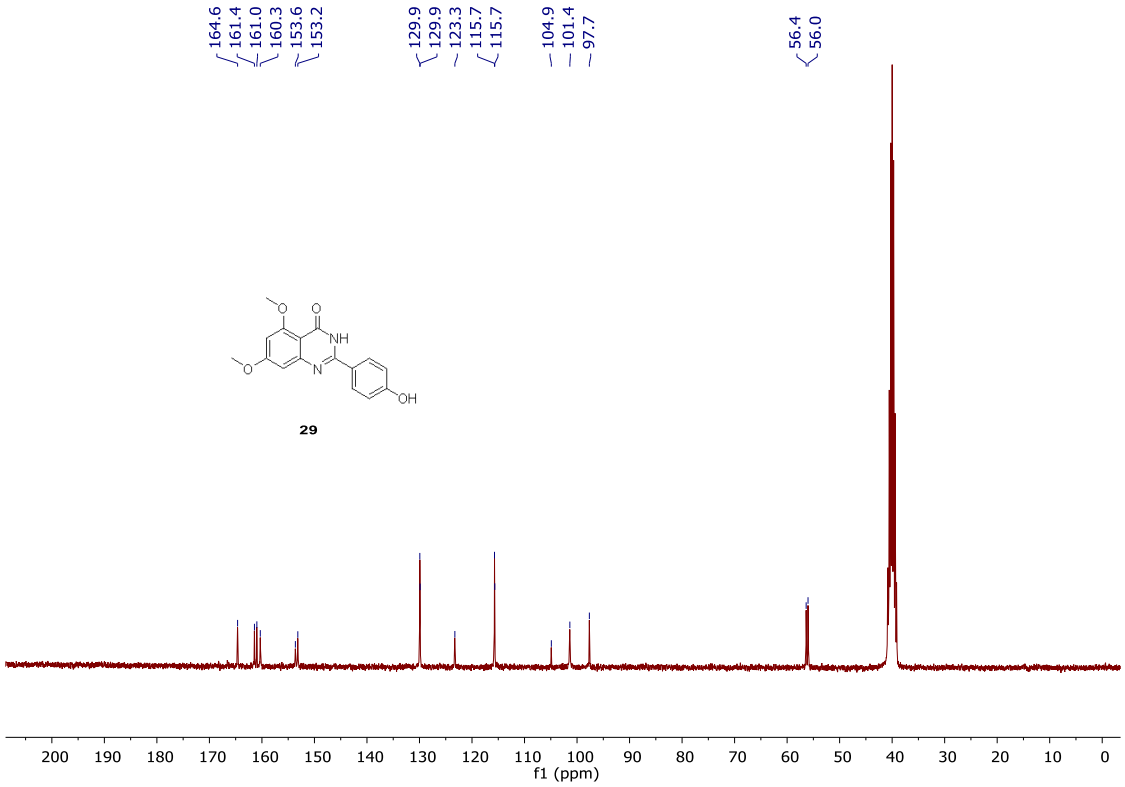
28


164.8
161.4
160.1
153.0
152.2
136.9
136.4
131.6
126.3
126.0
101.9
98.6
56.5
56.1
19.2
O
O
NH
N
O
CF3
f1 (ppm)

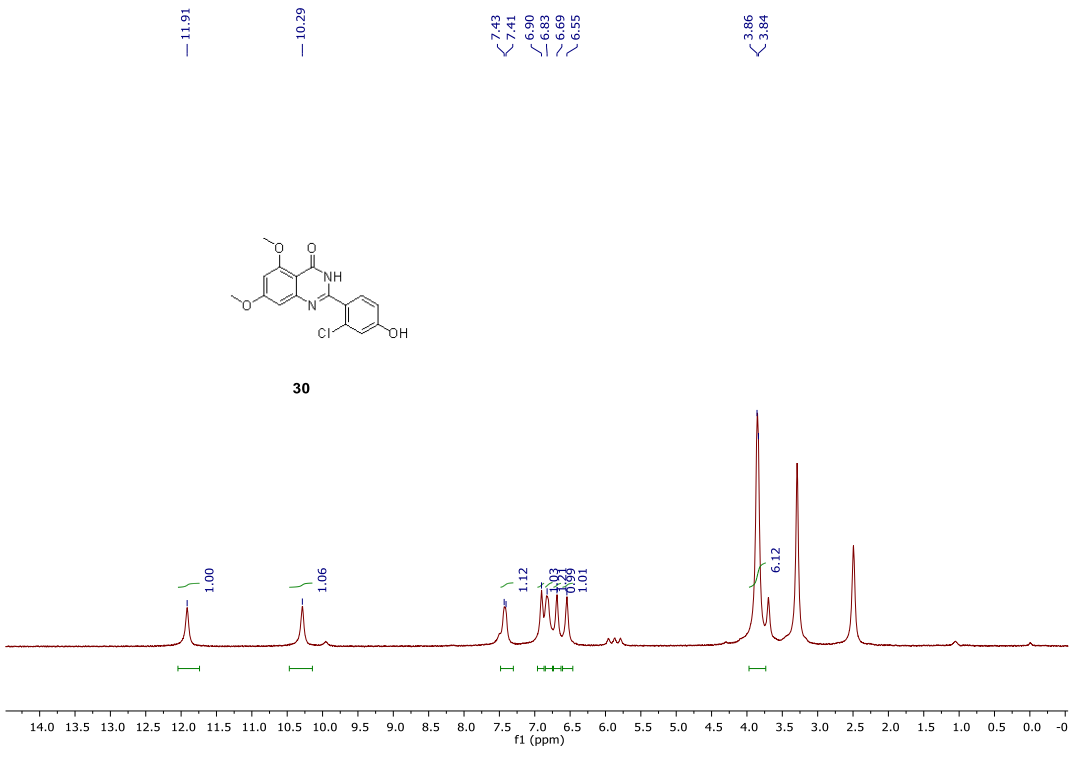
28


11.78
10.11
10.10
8.08
8.07
8.05
8.04
8.04
6.88
6.87
6.85
6.84
6.70
6.69
6.68
6.68
6.49
6.48
6.47
6.47
3.88
3.87
3.87
3.84
3.83
O
O
NH
N
O
OH
0.82
0.92
1.91
1.89
1.02
1.06
6.01
f1 (ppm)

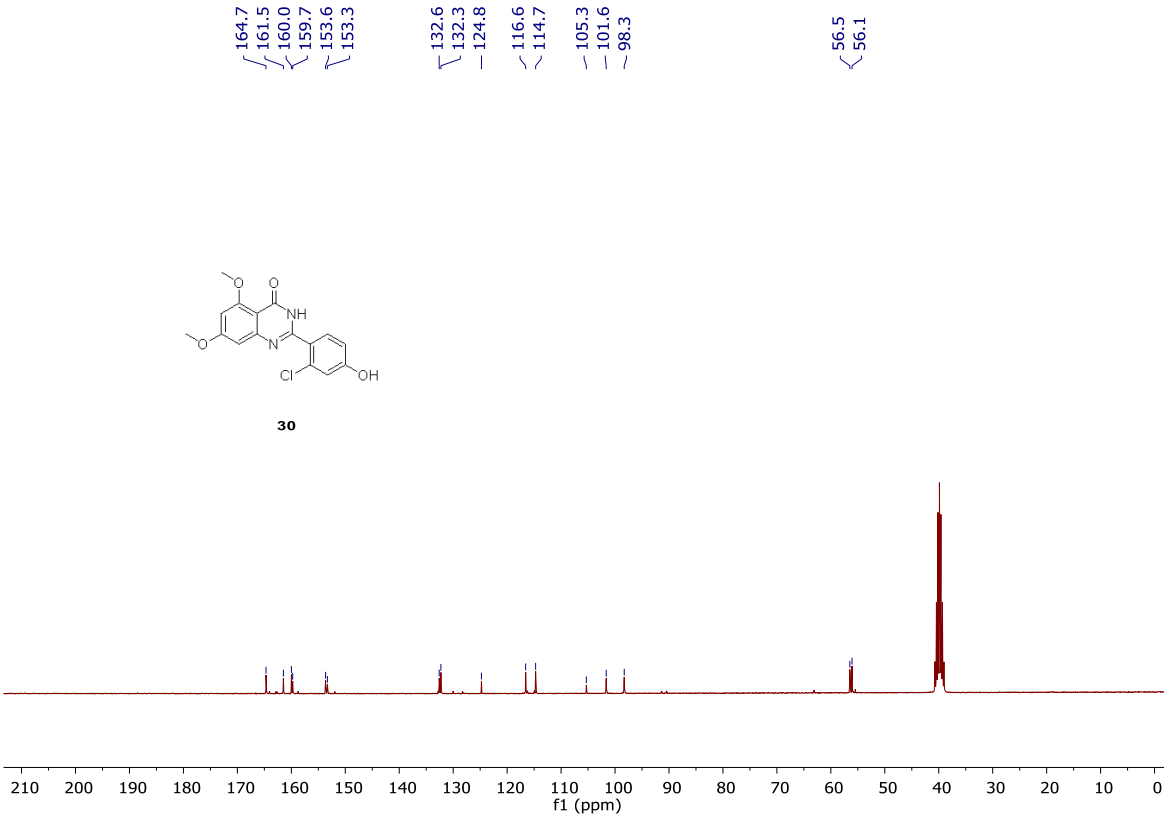
29


164.6
161.4
161.0
160.3
153.6
153.2
129.9
129.9
123.3
115.7
115.7
104.9
101.4
97.7
56.4
56.0
NH
N
OH
f1 (ppm)

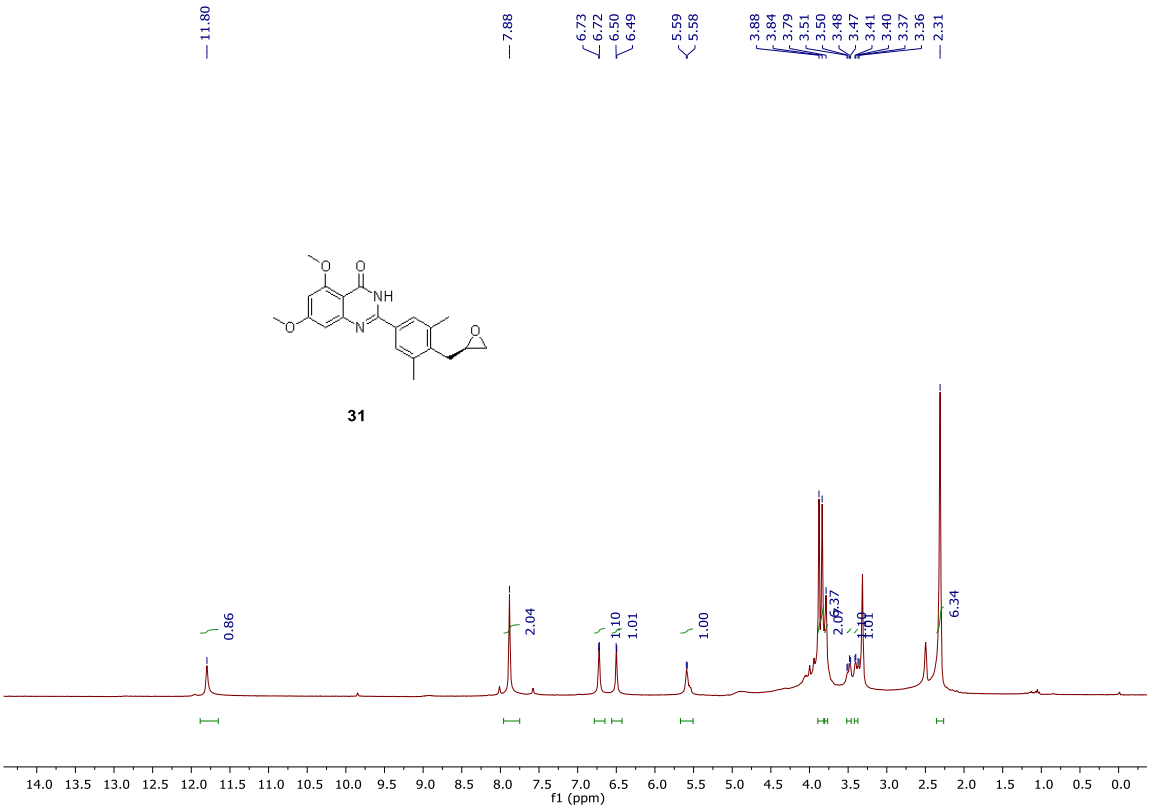
29


11.91
10.29
7.43
7.41
6.90
6.83
6.69
6.55
3.86
3.84
NH
N
Cl
OH
1.00
1.06
1.12
1.03
1.01
6.12
f1 (ppm)

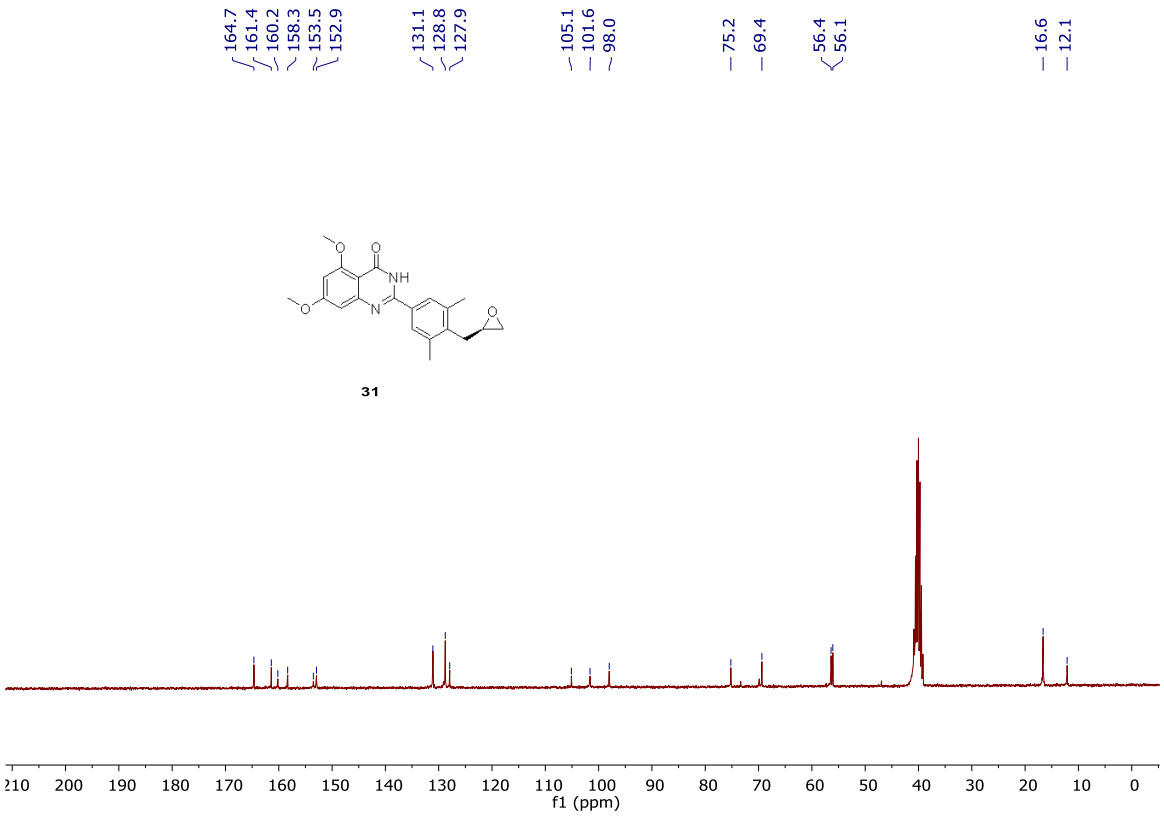
30

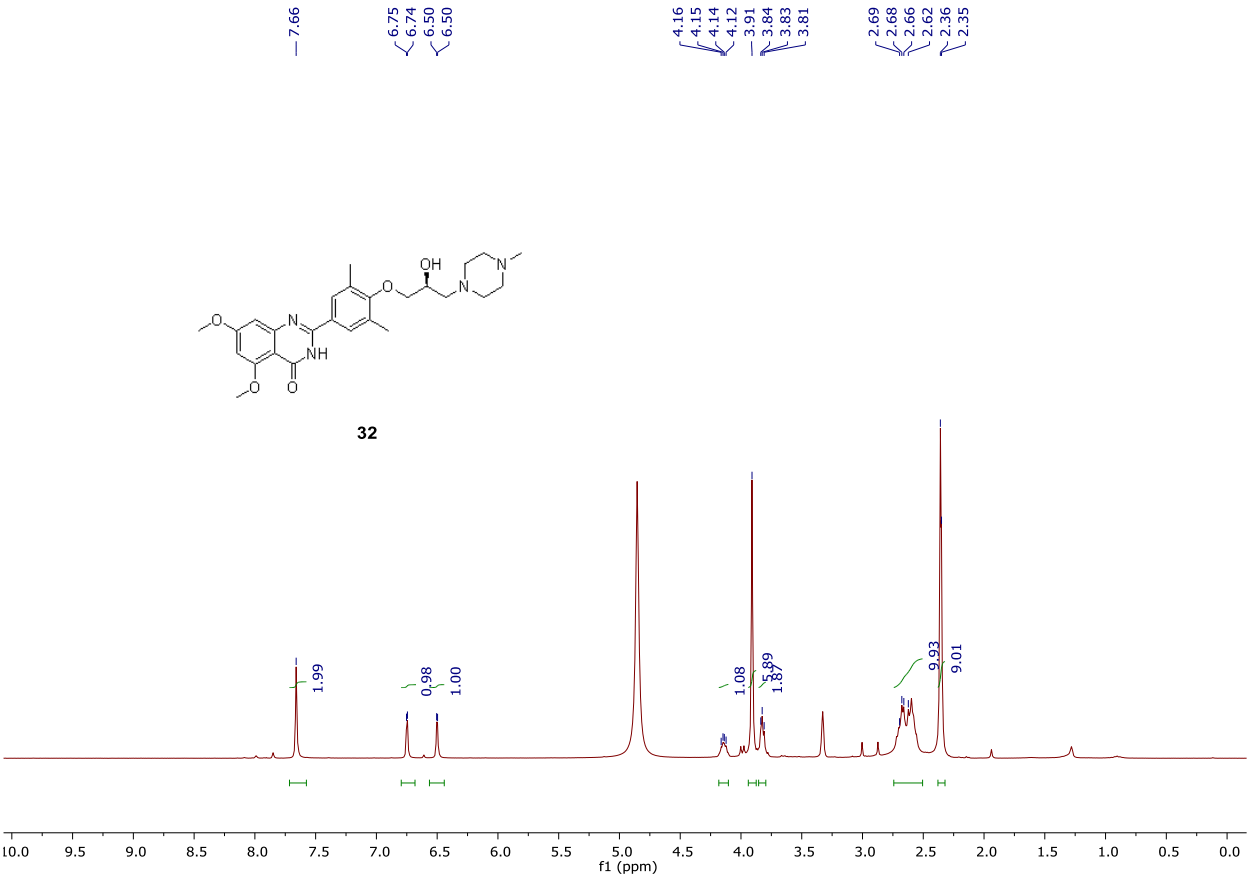

164.7
161.5
160.0
159.7
153.6
153.3
132.6
132.3
124.8
116.6
114.7
105.3
101.6
98.3
56.5
56.1
O
O
NH
N
O
Cl
OH
f1 (ppm)

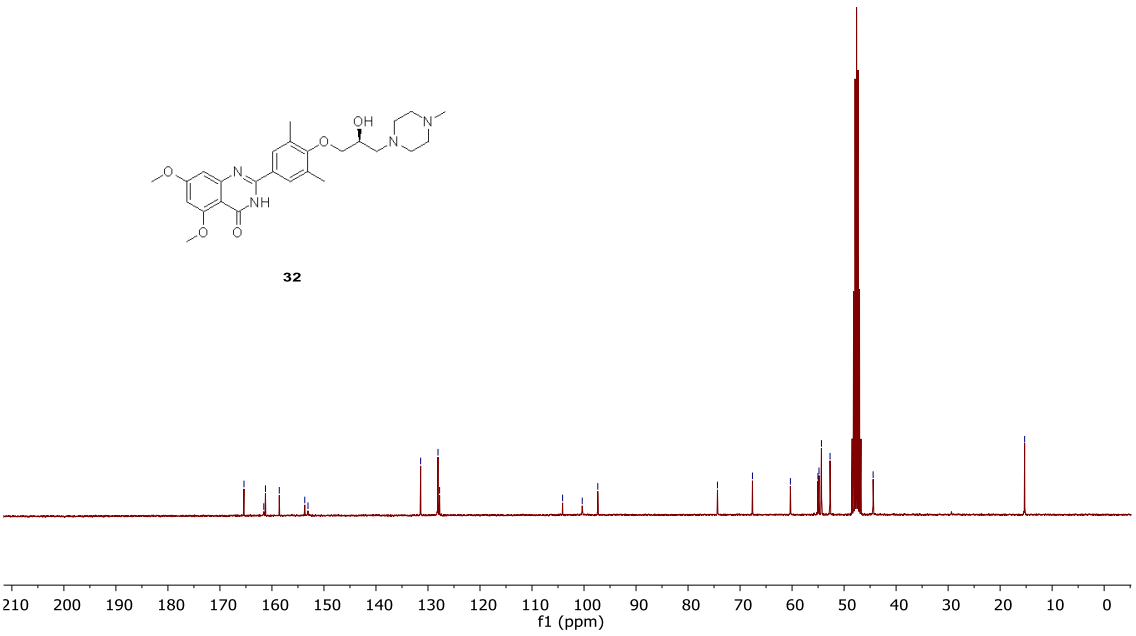
30

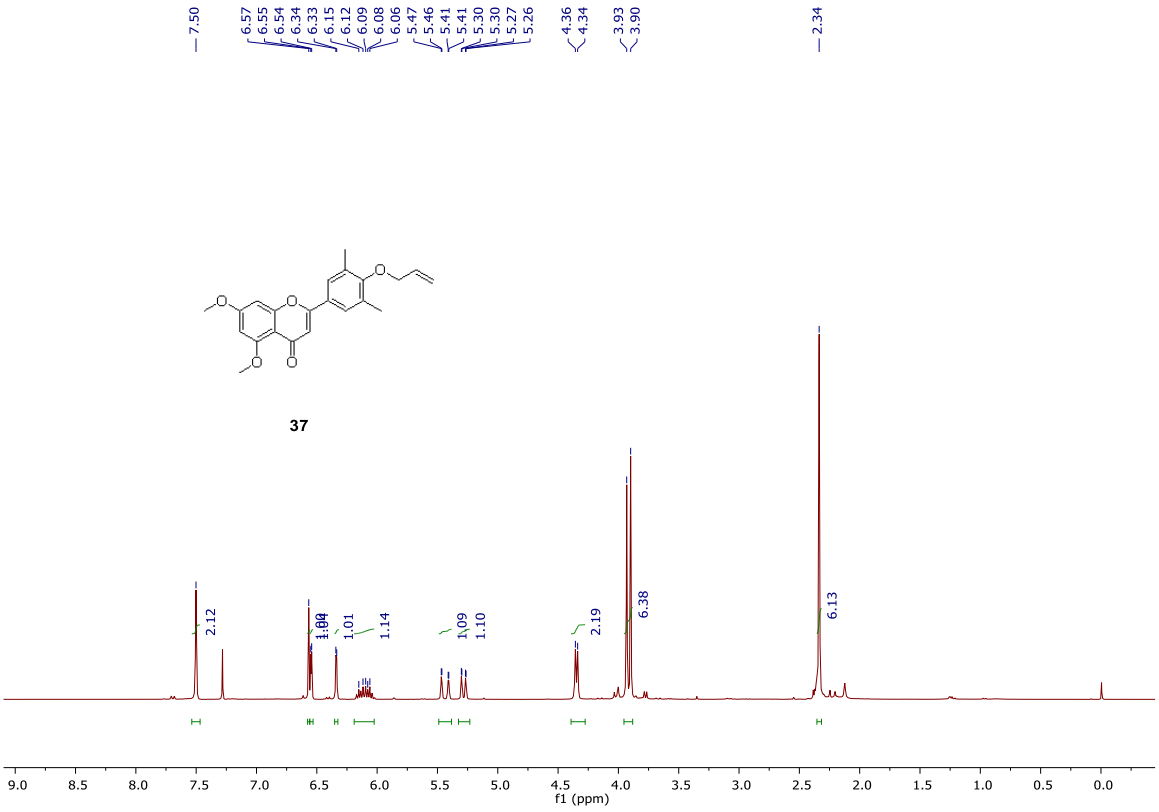

11.80
7.88
6.73
6.72
6.50
6.49
5.59
5.58
3.88
3.84
3.79
3.51
3.50
3.48
3.47
3.41
3.40
3.37
3.36
2.31
O
O
NH
N
O
0.86
2.04
1.10
1.01
1.00
2.09
2.07
1.01
6.34
f1 (ppm)

31

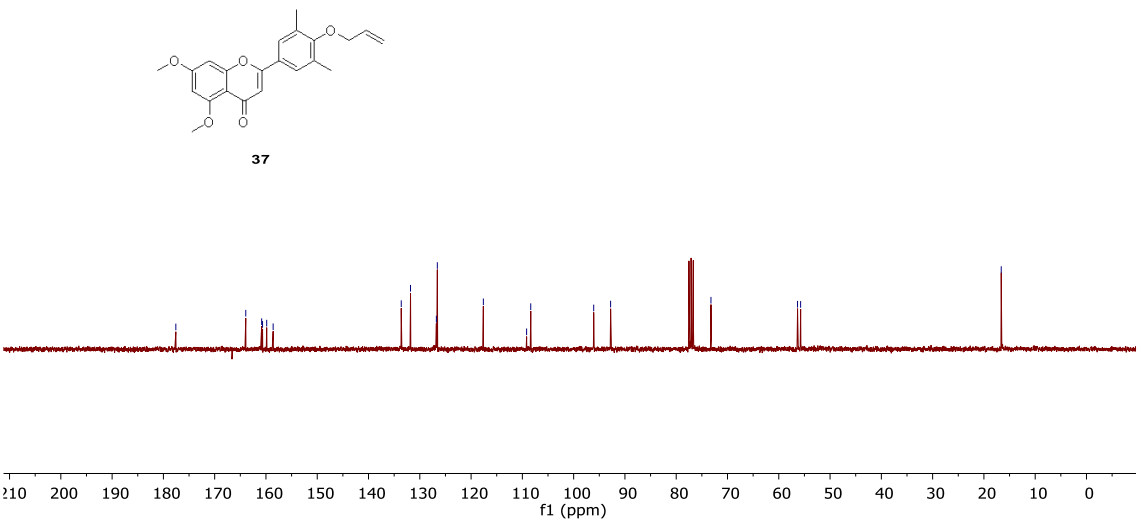

164.7
161.4
160.2
158.3
153.5
152.9
131.1
128.8
127.9
105.1
101.6
98.0
75.2
69.4
56.4
56.1
16.6
12.1
O
NH
N
O
O
31
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


7.66
6.75
6.74
6.50
6.50
4.16
4.15
4.14
4.12
3.91
3.84
3.83
3.81
2.69
2.68
2.66
2.62
2.36
2.35
OH
N
O
N
NH
O
O
32
1.99
0.98
1.00
1.08
1.89
1.87
9.93
9.01
f1 (ppm)

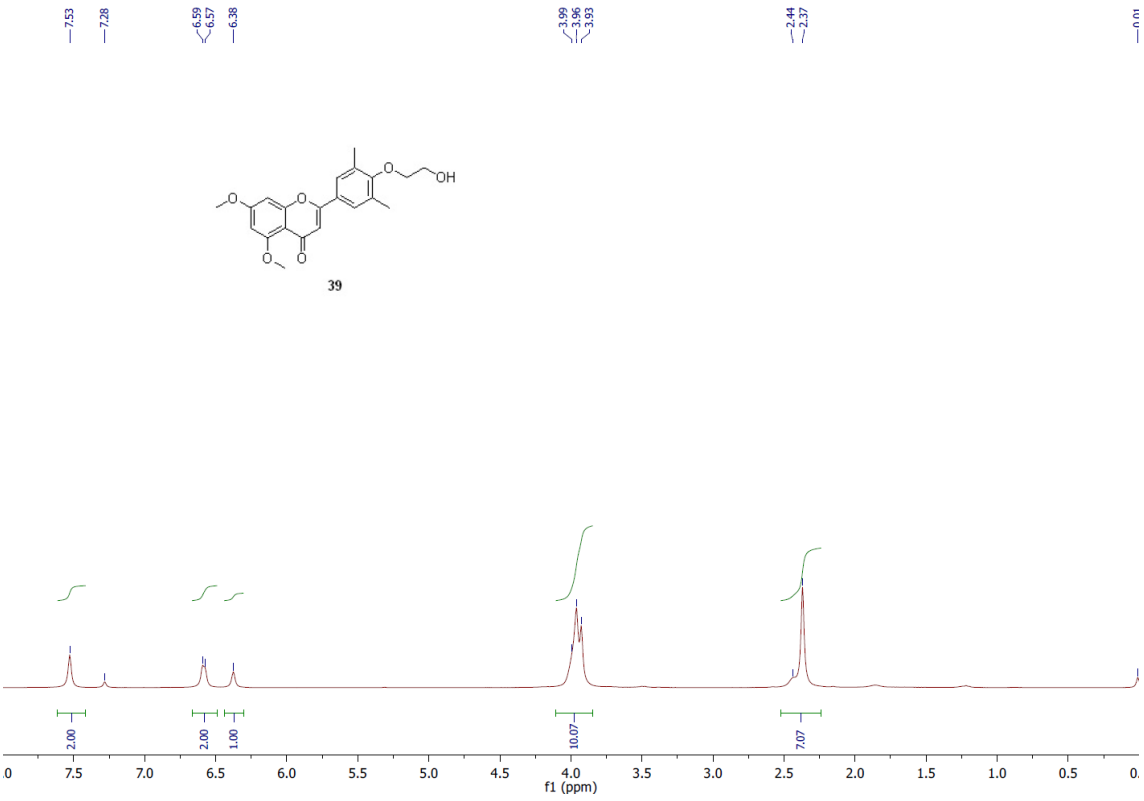

165.4
161.6
161.2
158.6
153.7
153.1
131.4
128.1
127.8
104.1
100.3
97.4
74.3
67.6
60.3
55.0
54.8
54.4
52.7
44.4
15.3
OH
N
O
N
NH
O
O
32
f1 (ppm)

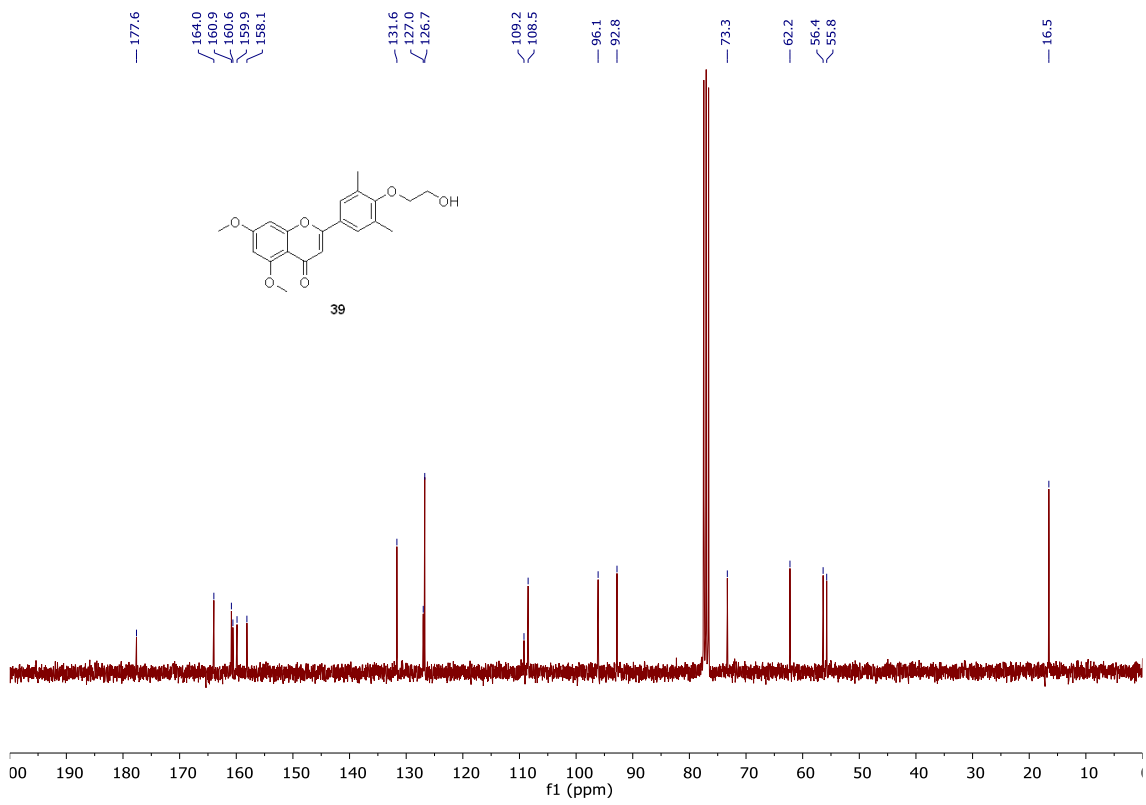

7.50
6.57
6.55
6.54
6.34
6.33
6.15
6.12
6.09
6.08
6.06
5.47
5.46
5.41
5.41
5.30
5.30
5.27
5.26
4.36
4.34
3.93
3.90
2.34
2.12
1.01
1.14
1.09
1.10
2.19
6.38
6.13
f1 (ppm)

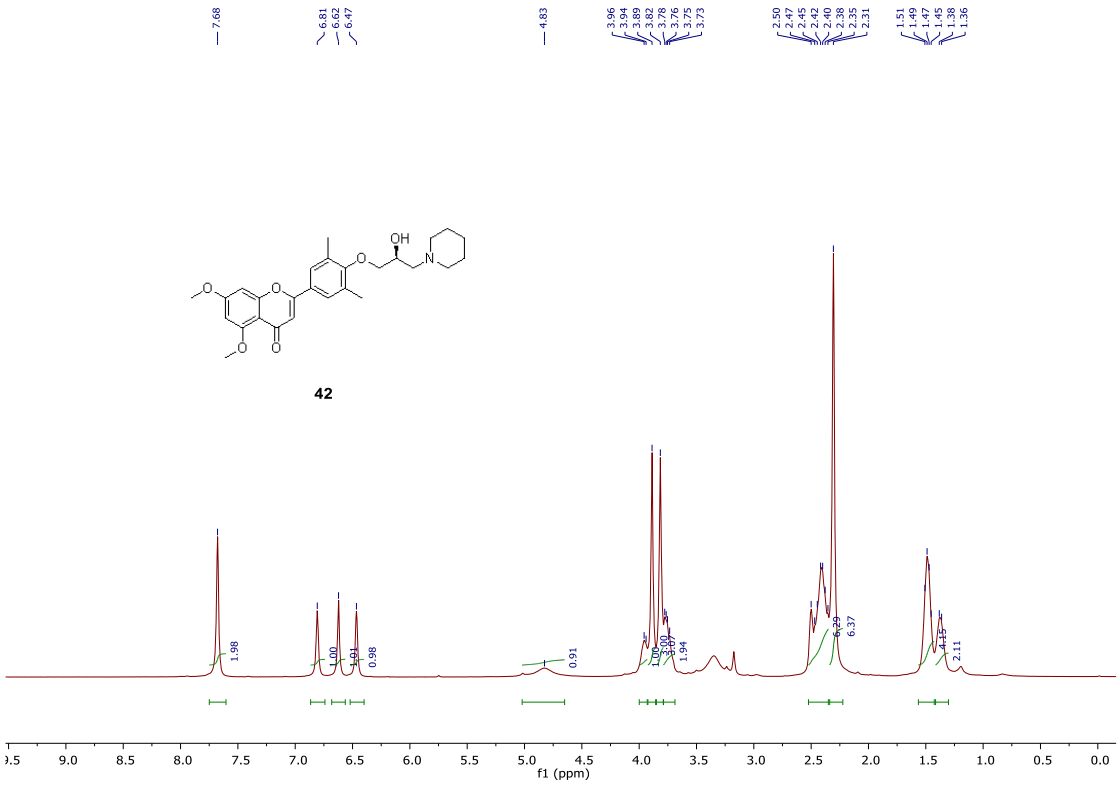
37

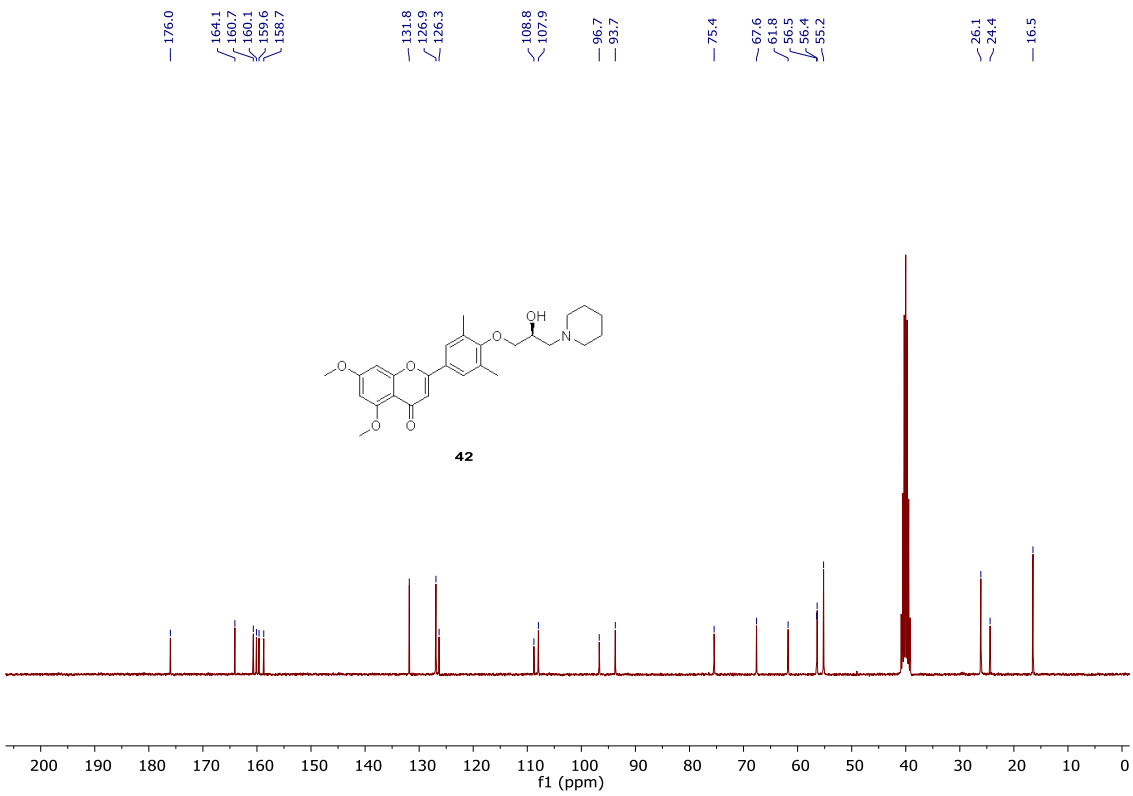

177.6
163.9
160.8
160.7
159.9
158.6
133.6
131.8
126.8
126.6
117.6
109.2
108.4
96.1
92.8
73.2
56.3
55.7
16.6
f1 (ppm)

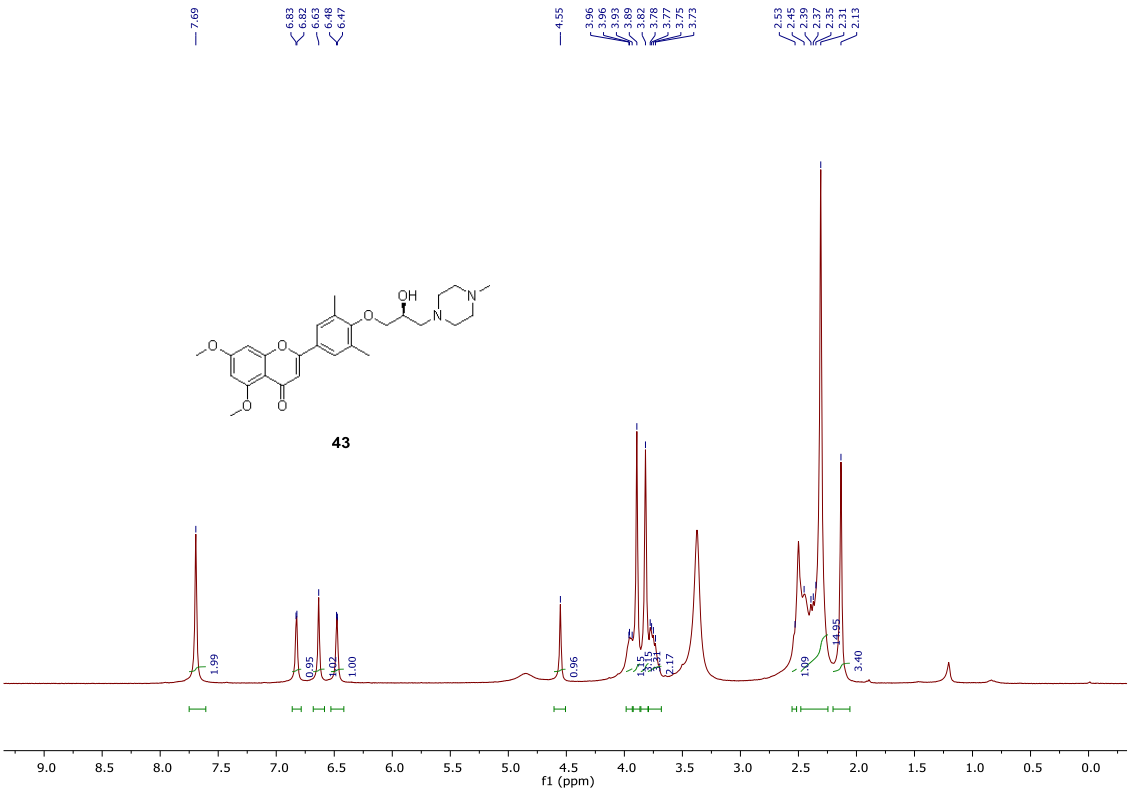
37

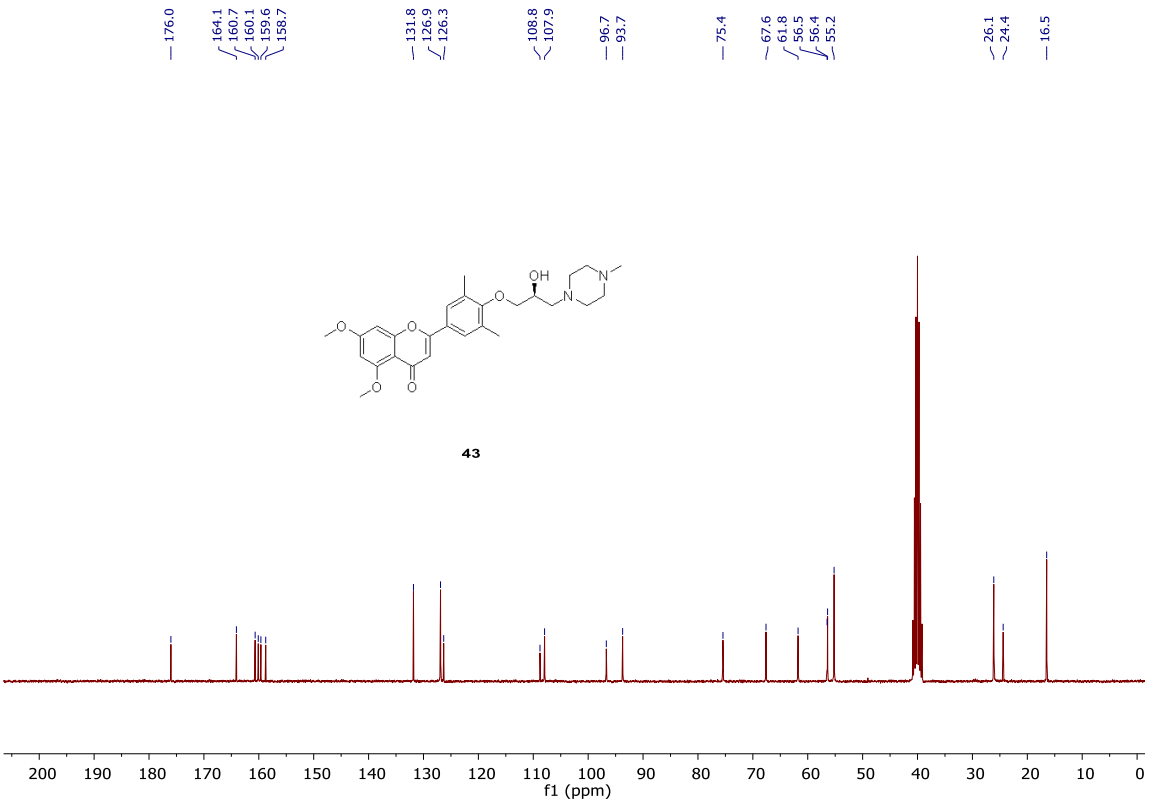

7.53
7.28
6.59
6.57
6.38
3.99
3.96
3.93
2.44
2.37
OH
39
2.00
2.00
1.00
10.07
7.07
f1 (ppm)

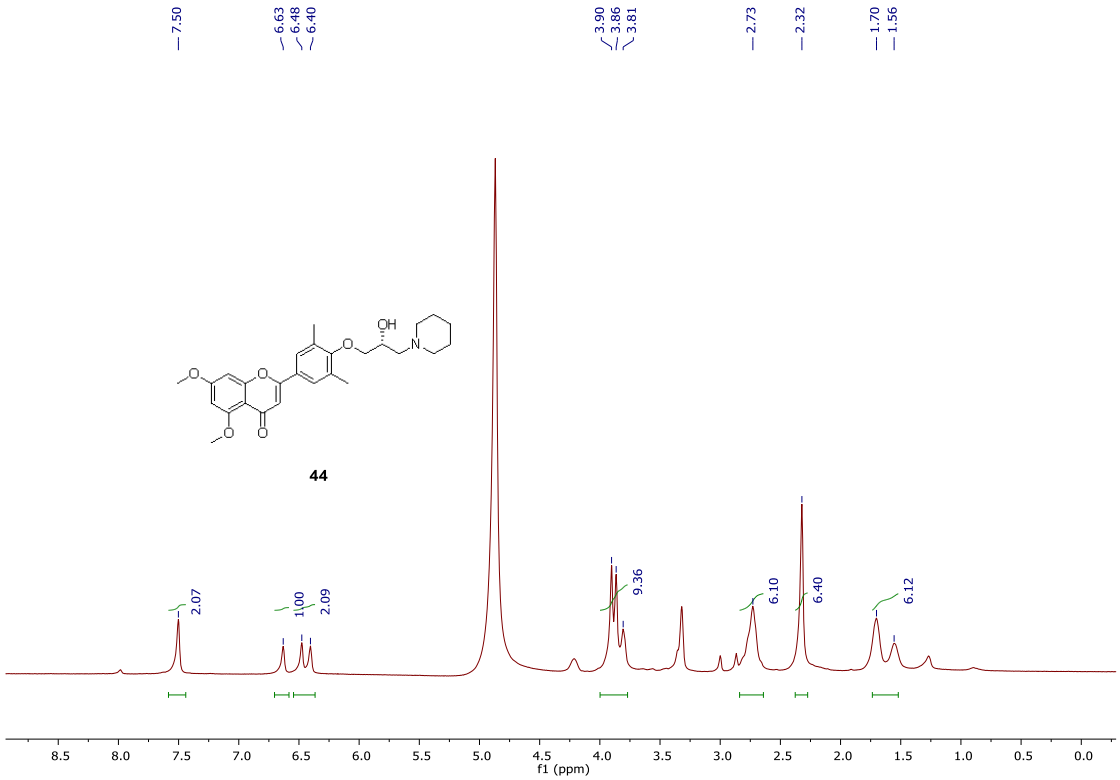

177.6
164.0
160.9
160.6
159.9
158.1
131.6
127.0
126.7
109.2
108.5
96.1
92.8
73.3
62.2
56.4
55.8
16.5
OH
39
f1 (ppm)

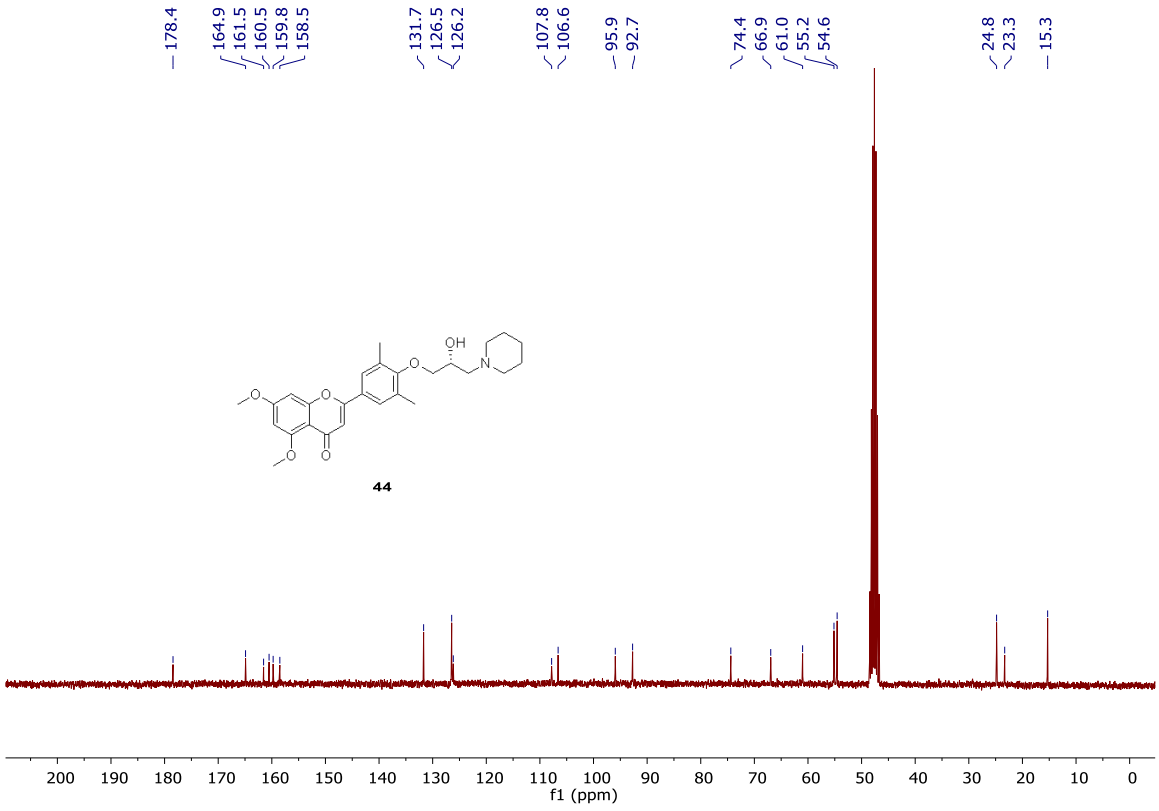

7.68
6.81
6.62
6.47
4.83
3.96
3.94
3.89
3.82
3.78
3.76
3.75
3.73
2.50
2.47
2.45
2.42
2.40
2.38
2.35
2.31
1.51
1.49
1.47
1.45
1.38
1.36
OH
N
O
O
O
O
42
1.98
1.00
1.01
0.98
0.91
1.00
3.07
1.94
6.89
6.37
4.15
2.11
f1 (ppm)

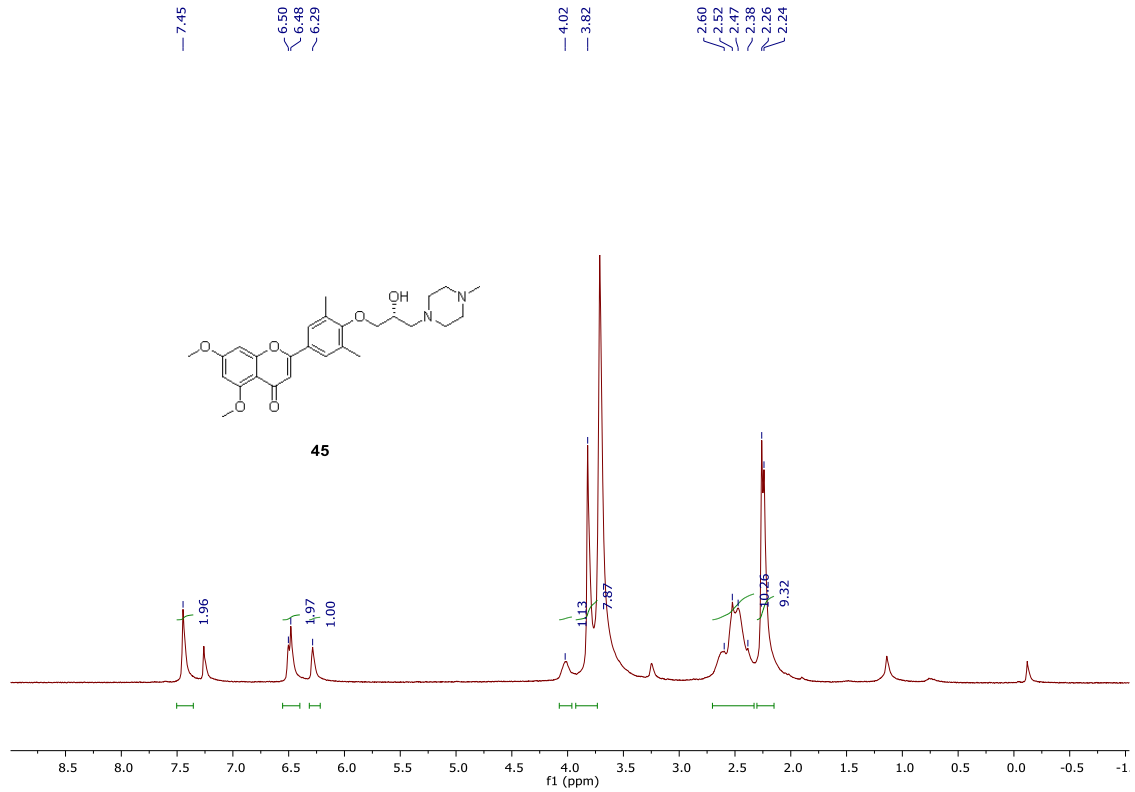

176.0
164.1
160.7
160.1
159.6
158.7
131.8
126.9
126.3
108.8
107.9
96.7
93.7
75.4
67.6
61.8
56.5
56.4
55.2
26.1
24.4
16.5
OH
N
O
O
O
O
42
f1 (ppm)

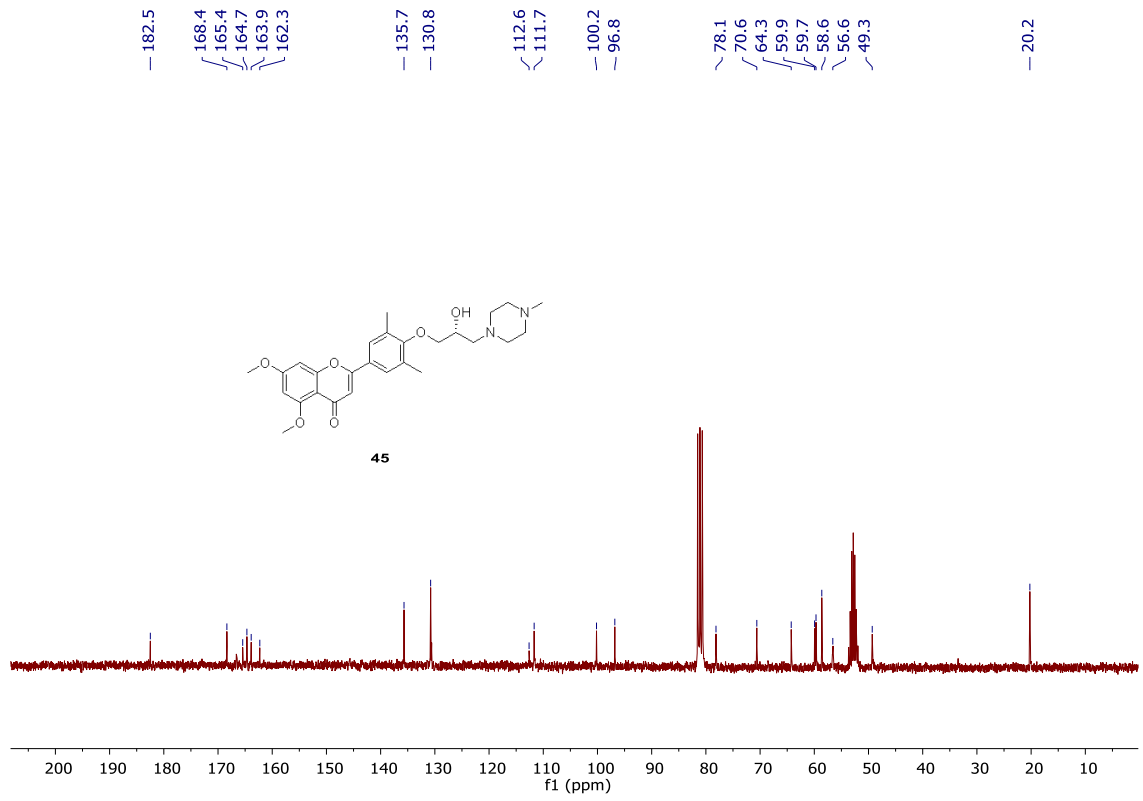

7.69
6.83
6.82
6.63
6.48
6.47
4.55
3.96
3.96
3.93
3.89
3.82
3.78
3.77
3.75
3.73
2.53
2.45
2.39
2.37
2.35
2.31
2.13
OH
N
O
O
O
O
43
1.99
0.95
1.02
1.00
0.96
3.15
3.13
3.11
2.17
1.00
14.95
3.40
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


176.0
164.1
160.7
160.1
159.6
158.7
131.8
126.9
126.3
108.8
107.9
96.7
93.7
75.4
67.6
61.8
56.5
56.4
55.2
26.1
24.4
16.5
OH
N
O
O
O
O
43
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.50
6.63
6.48
6.40
3.90
3.86
3.81
2.73
2.32
1.70
1.56
OH
N
O
O
O
O
44
2.07
1.00
2.09
9.36
6.10
6.40
6.12
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)


178.4
164.9
161.5
160.5
159.8
158.5
131.7
126.5
126.2
107.8
106.6
95.9
92.7
74.4
66.9
61.0
55.2
54.6
24.8
23.3
15.3
OH
N
O
O
O
O
44
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.45
6.50
6.48
6.29
4.02
3.82
2.60
2.52
2.47
2.38
2.26
2.24
OH
N
O
O
O
O
45
1.96
1.97
1.00
1.13
7.87
10.26
9.32
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
-1
f1 (ppm)


182.5
168.4
165.4
164.7
163.9
162.3
135.7
130.8
112.6
111.7
100.2
96.8
78.1
70.6
64.3
59.9
59.7
58.6
56.6
49.3
20.2
OH
N
O
O
O
O
45
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


7.42
7.41
6.55
6.55
6.41
6.35
6.34
4.16
4.15
4.14
4.12
3.88
3.84
3.81
3.81
3.80
3.79
3.77
3.75
3.74
3.72
3.69
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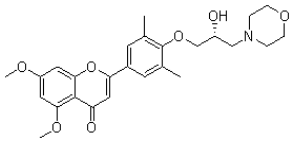
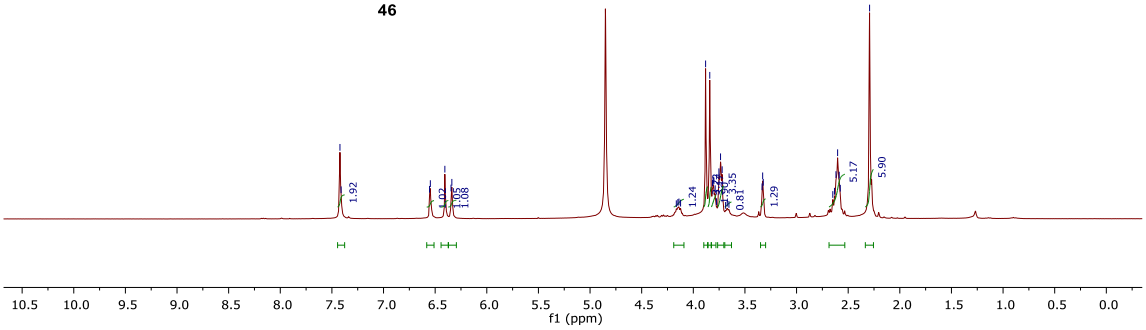
2.63
2.62
2.60
2.59
2.58
2.29


OH
O
O
O
O
O
O

46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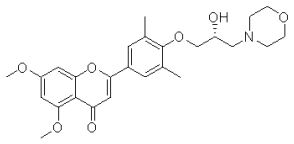
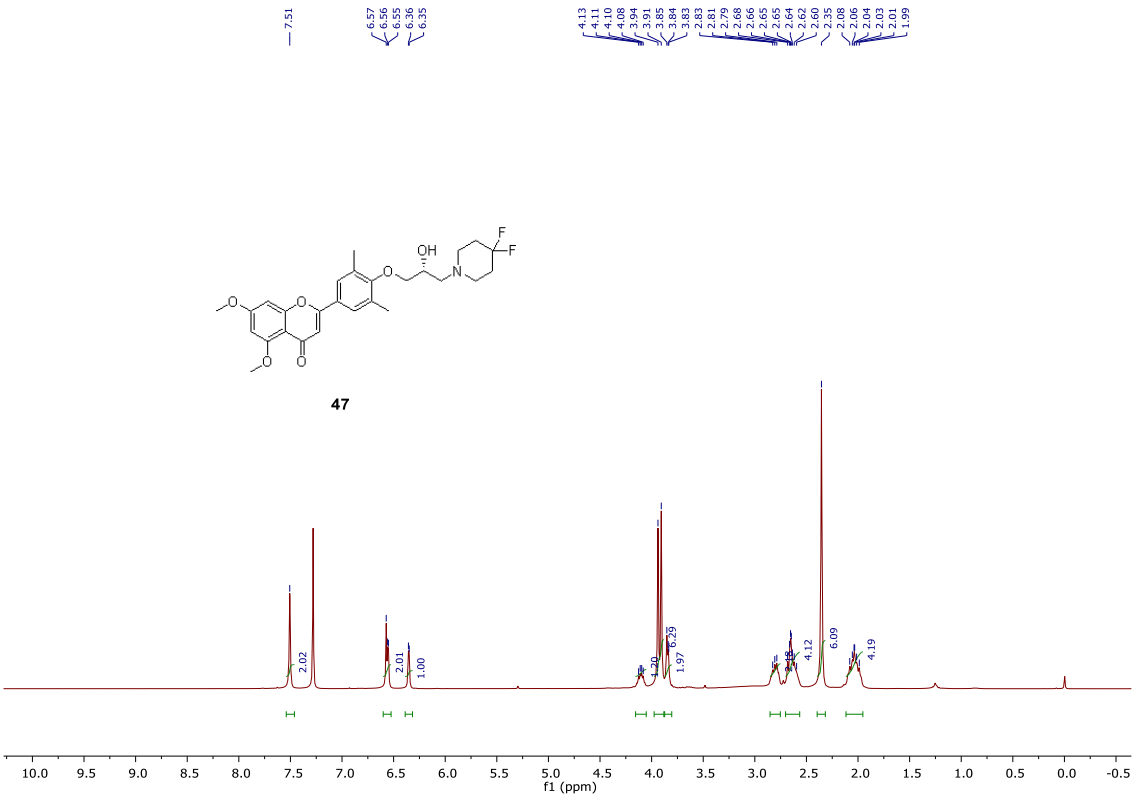
4.02
1.87
1.08
1.24
0.81
1.29
5.17
5.90
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.3
164.7
161.3
160.4
159.6
158.5
131.6
126.3
126.0
107.8
106.5
95.8
92.6
74.3
67.4
66.5
61.0
55.1
55.0
54.0
15.3


OH
O
O
O
O
O
O

46

200
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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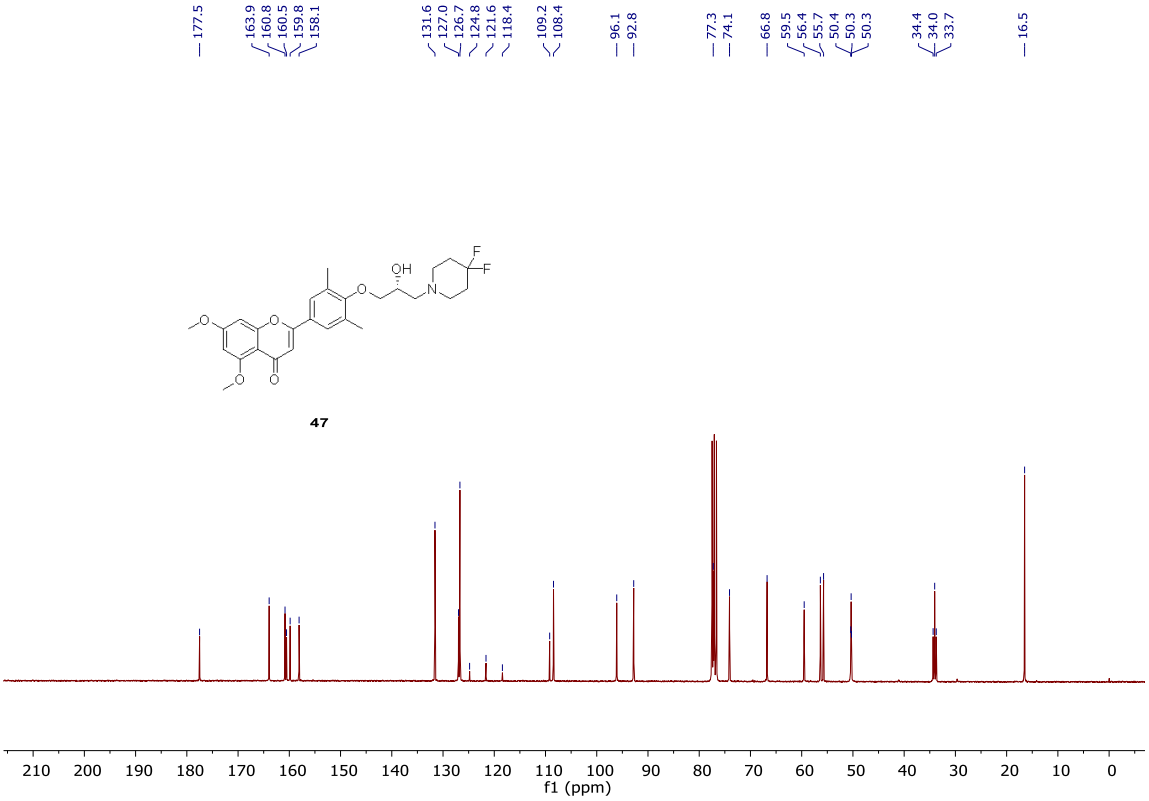
6.57
6.56
6.55
6.36
6.35
4.13
4.11
4.10
4.08
3.94
3.91
3.85
3.84
3.83
2.83
2.81
2.79
2.68
2.66
2.65
2.64
2.62
2.60
2.35
2.08
2.06
2.04
2.03
2.01
1.99
OH
F
F
N
O
O
O
O
47
2.02
2.01
1.00
1.02
1.97
6.29
4.12
6.09
4.19
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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160.8
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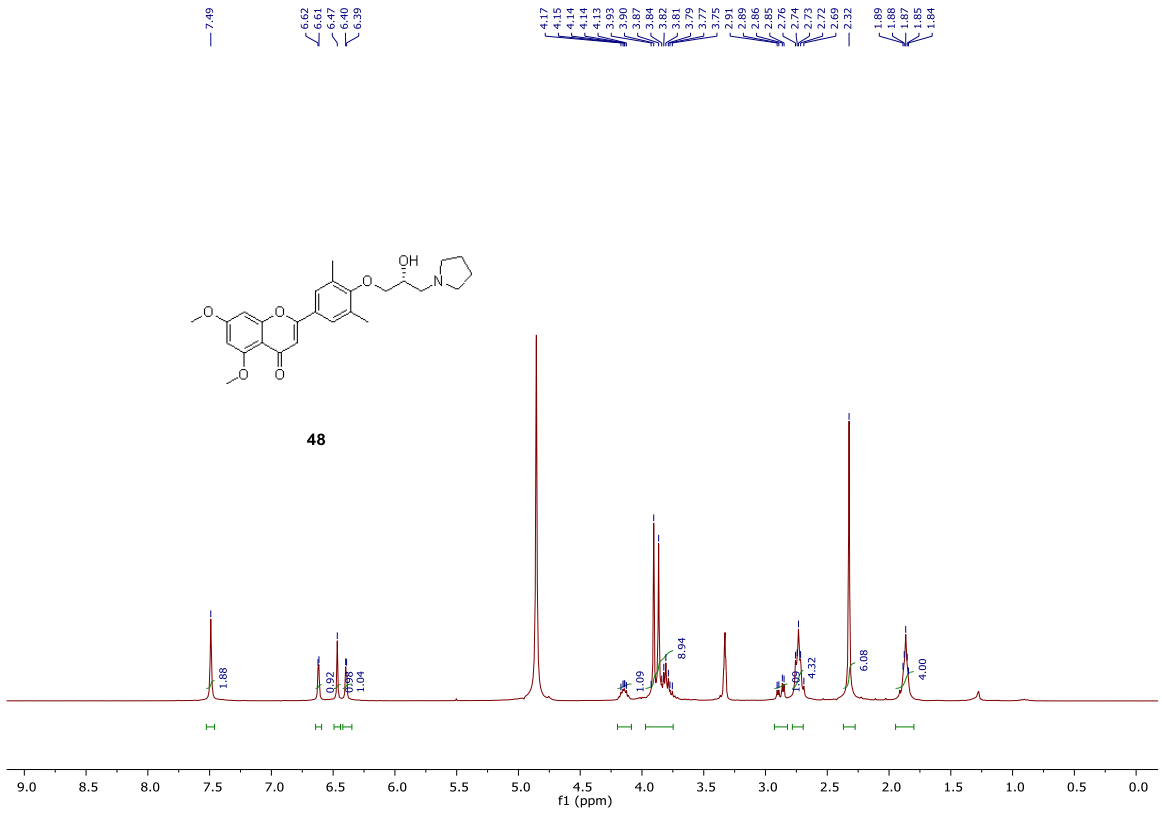
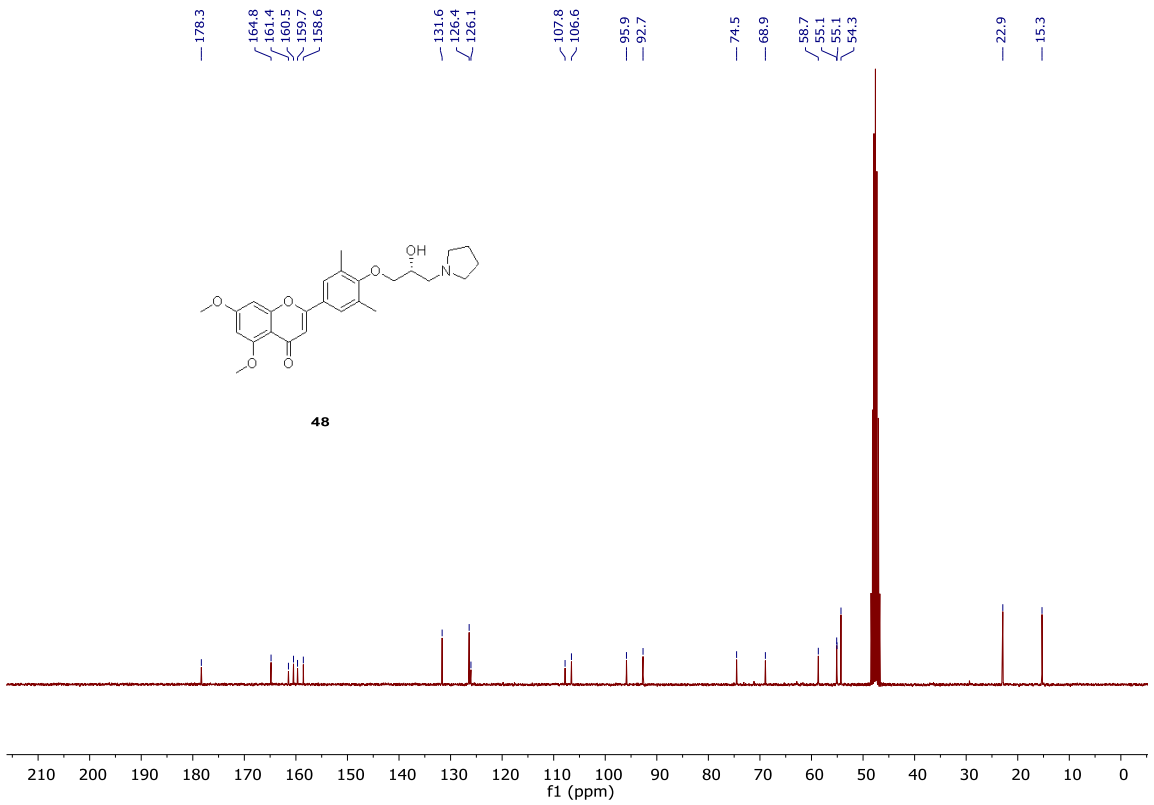
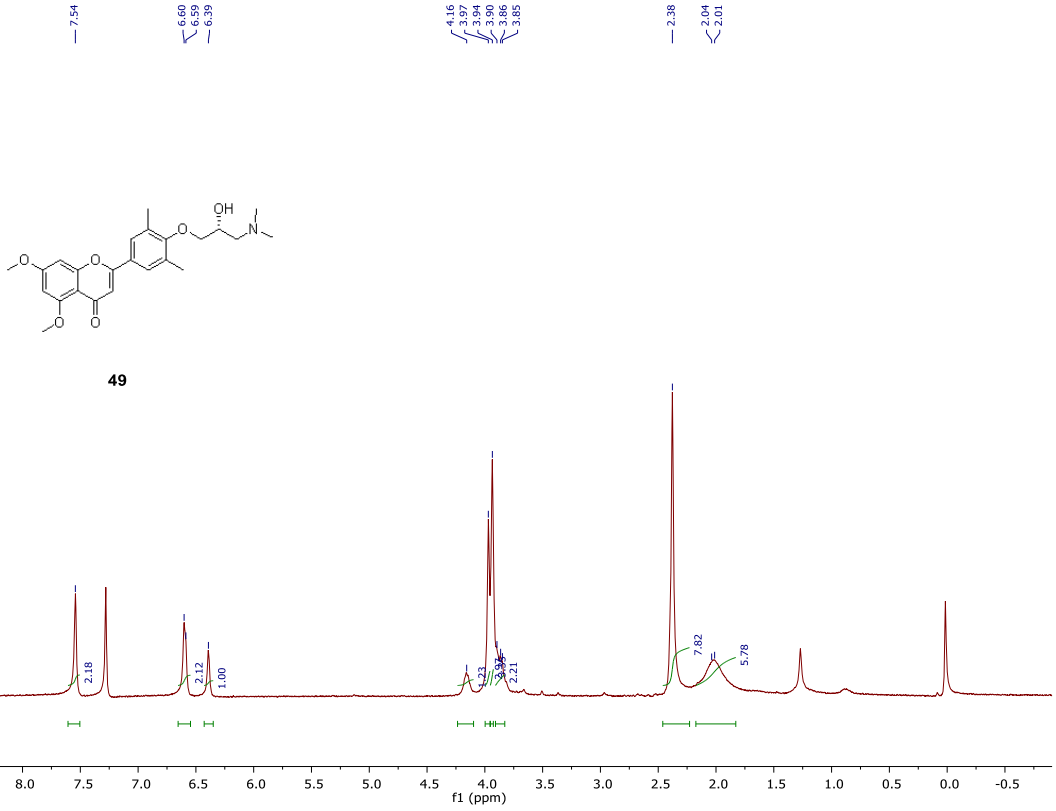
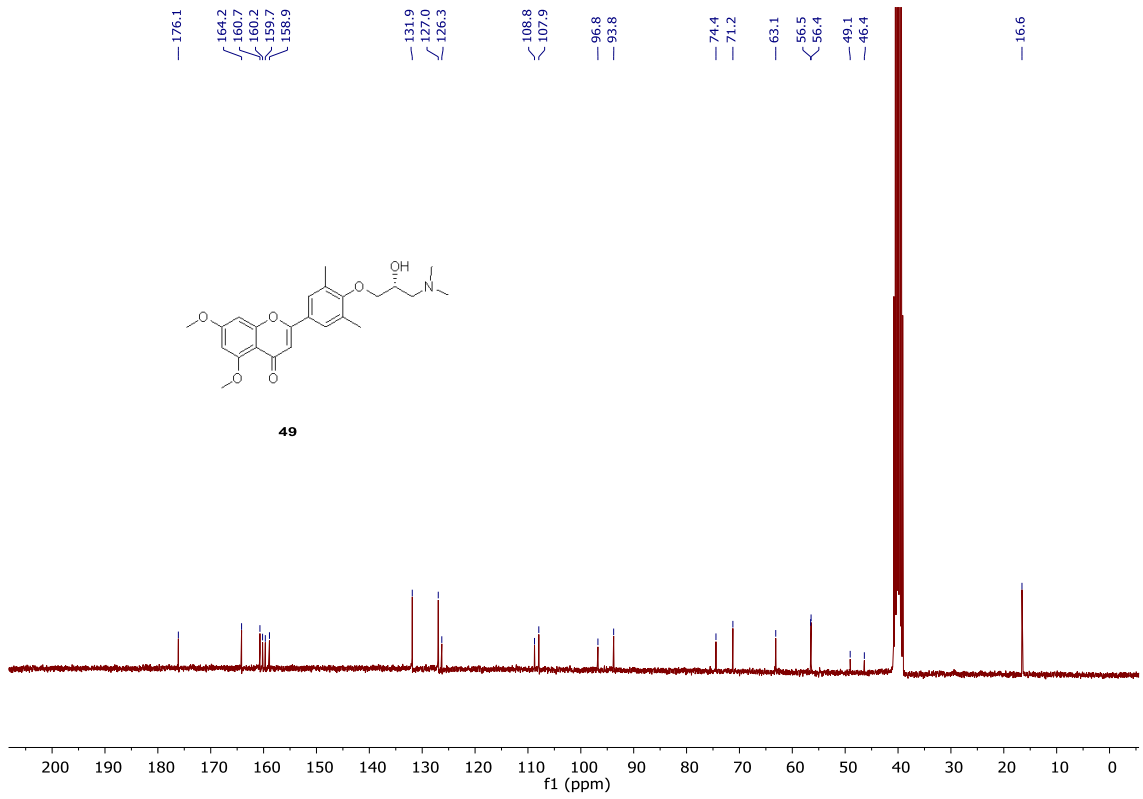
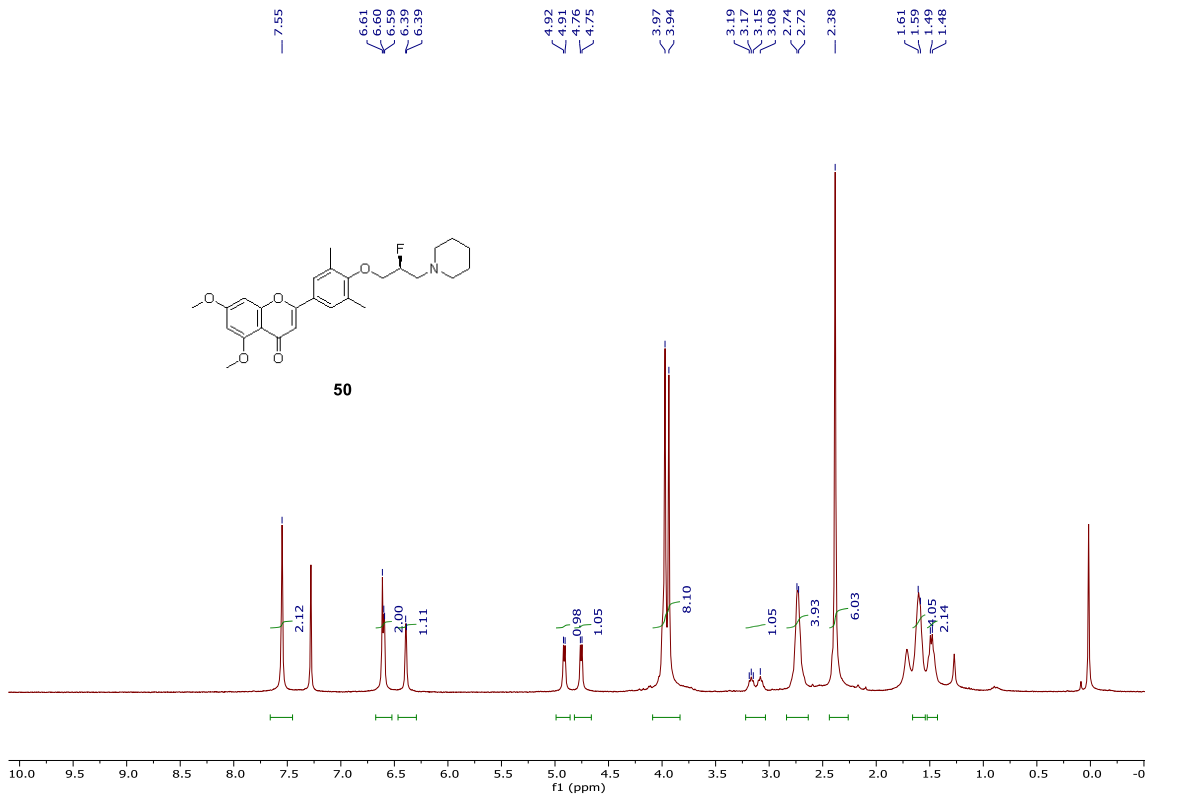
159.8
158.1
131.6
127.0
126.7
124.8
121.6
118.4
109.2
108.4
96.1
92.8
77.3
74.1
66.8
59.5
56.4
55.7
50.4
50.3
50.3
34.4
34.0
33.7
16.5
OH
F
F
N
O
O
O
O
47
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

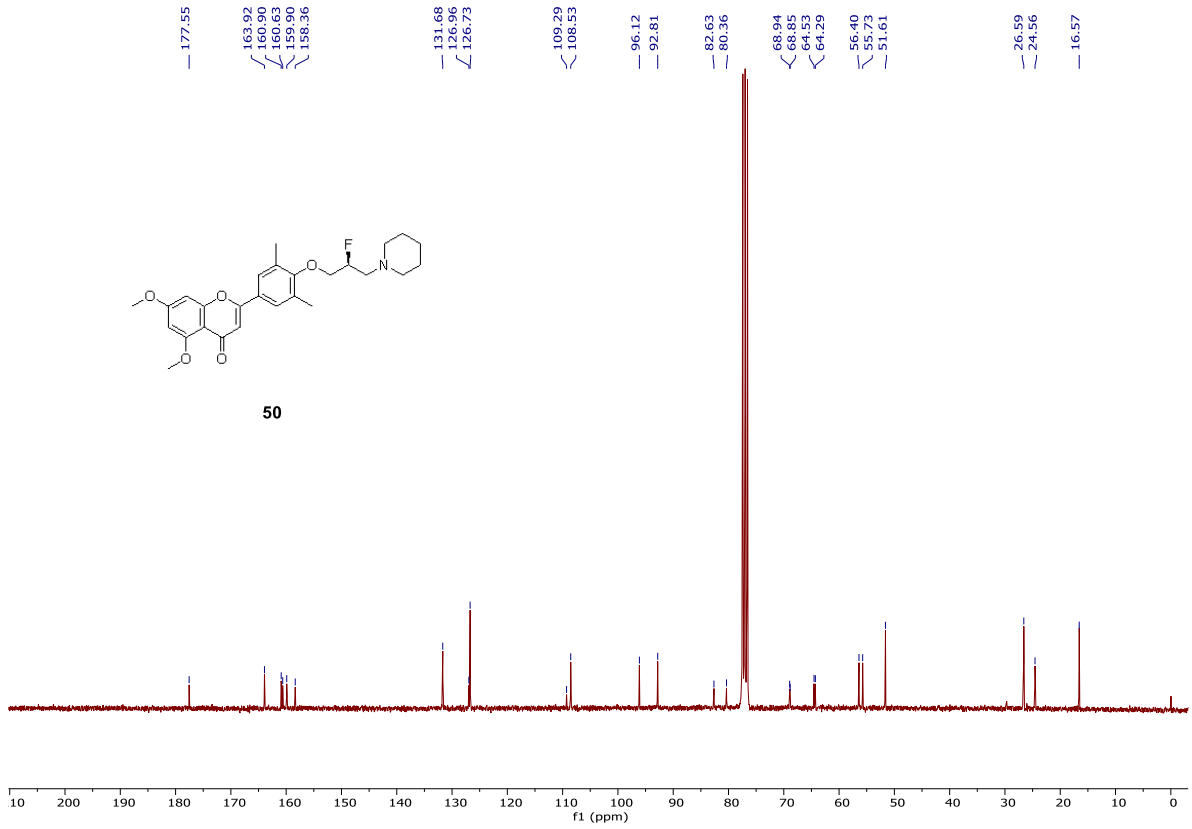

7.49
6.62
6.61
6.47
6.40
6.39
4.17
4.15
4.14
4.14
4.13
3.93
3.90
3.87
3.84
3.82
3.81
3.79
3.77
3.75
2.91
2.89
2.86
2.85
2.76
2.74
2.73
2.72
2.69
2.32
1.89
1.88
1.87
1.85
1.84
OH
O
N
O
O
O
O
48
1.88
0.92
0.98
1.04
1.09
8.94
1.99
4.32
6.08
4.00
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


178.3
164.8
161.4
160.5
159.7
158.6
131.6
126.4
126.1
107.8
106.6
95.9
92.7
74.5
68.9
58.7
55.1
55.1
54.3
22.9
15.3
OH
O
N
O
O
O
O
48
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.54
6.60
6.59
6.39
4.16
3.97
3.94
3.90
3.86
3.85
2.38
2.04
2.01
OH
N
O
O
O
O
49
2.18
2.12
1.00
2.23
2.21
7.82
5.78
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)


176.1
164.2
160.7
160.2
159.7
158.9
131.9
127.0
126.3
108.8
107.9
96.8
93.8
74.4
71.2
63.1
56.5
56.4
49.1
46.4
16.6
OH
N
O
O
O
O
49
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


7.55
6.61
6.60
6.59
6.39
6.39
4.92
4.91
4.76
4.75
3.97
3.94
3.19
3.17
3.15
3.08
2.74
2.72
2.38
1.61
1.59
1.49
1.48
F
O
N
O
O
O
O
50
2.12
2.00
1.11
0.98
1.05
8.10
1.05
3.93
6.03
4.05
2.14
f1 (ppm)


177.55
163.92
160.90
160.63
159.90
158.36
131.68
126.96
126.73
109.29
108.53
96.12
92.81
82.63
80.36
68.94
68.85
64.53
64.29
56.40
55.73
51.61
26.59
24.56
16.57
F
O
N
O
O
O
O
50
f1 (ppm)