"Supplementary Materials"

2-Hydroxy-5-(3,5,7-trihydroxy-4-oxo-4*H*-chromen-2-yl)phenyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylate: synthesis, *in silico* analysis and *in vitro* pharmacological evaluation

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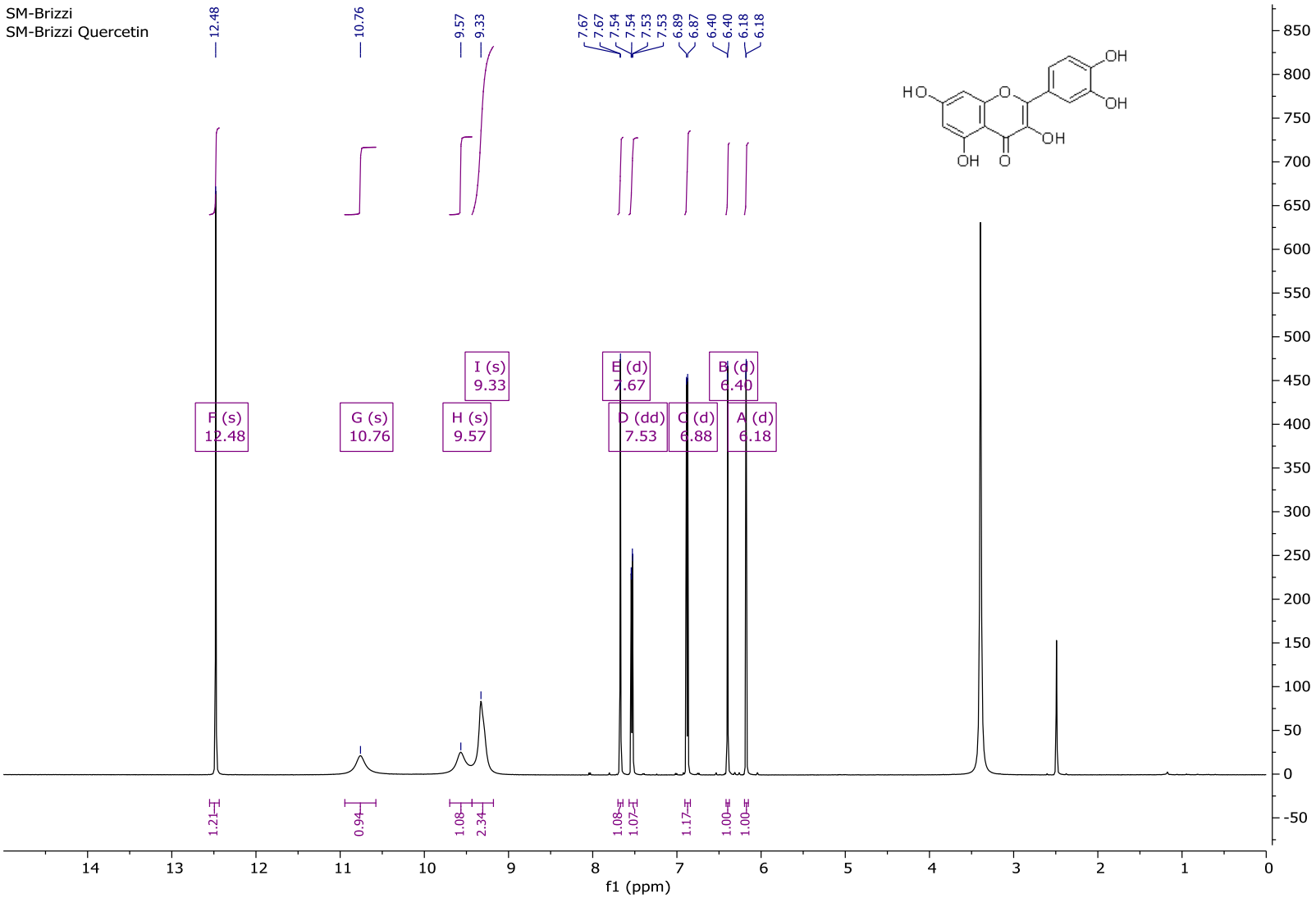
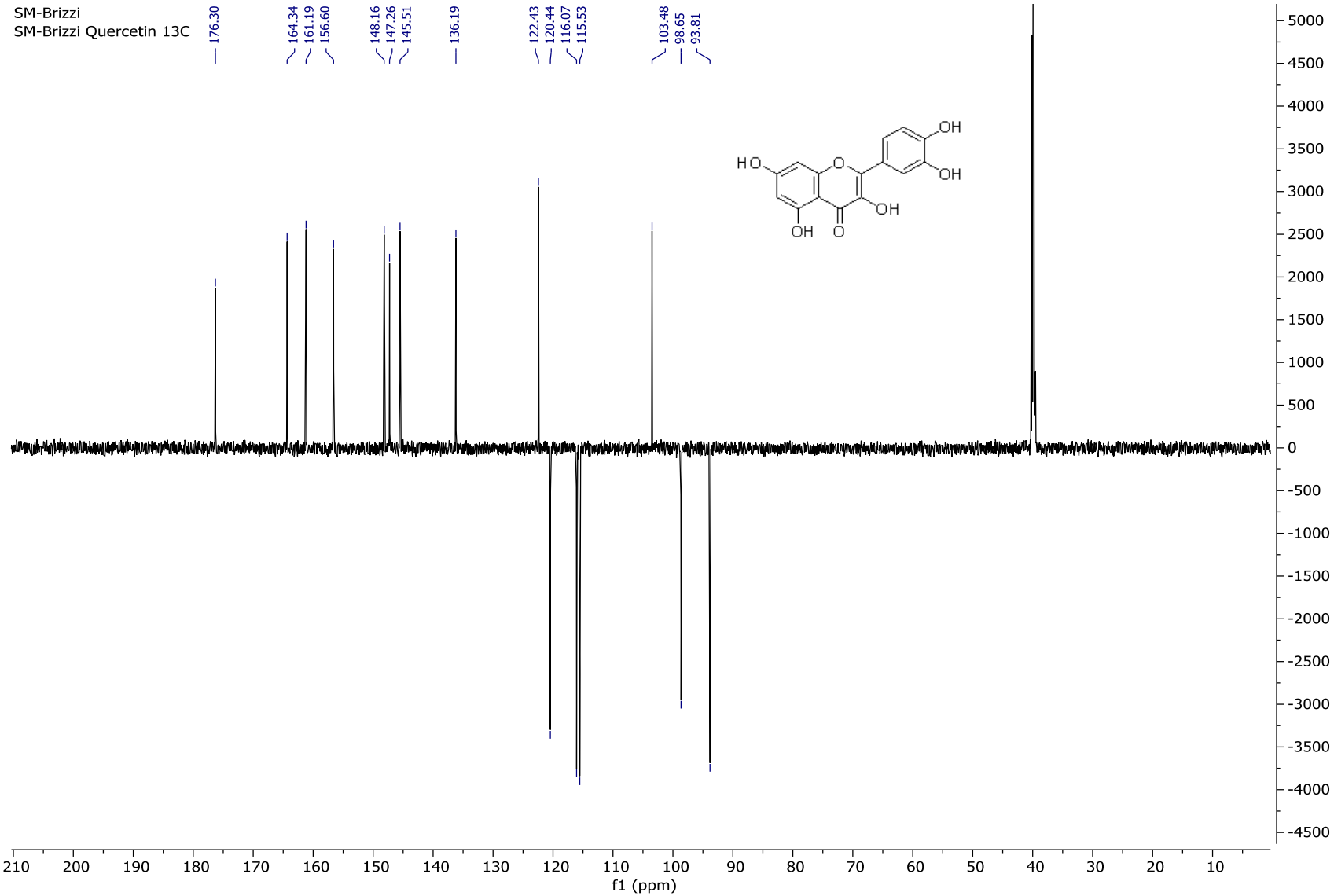
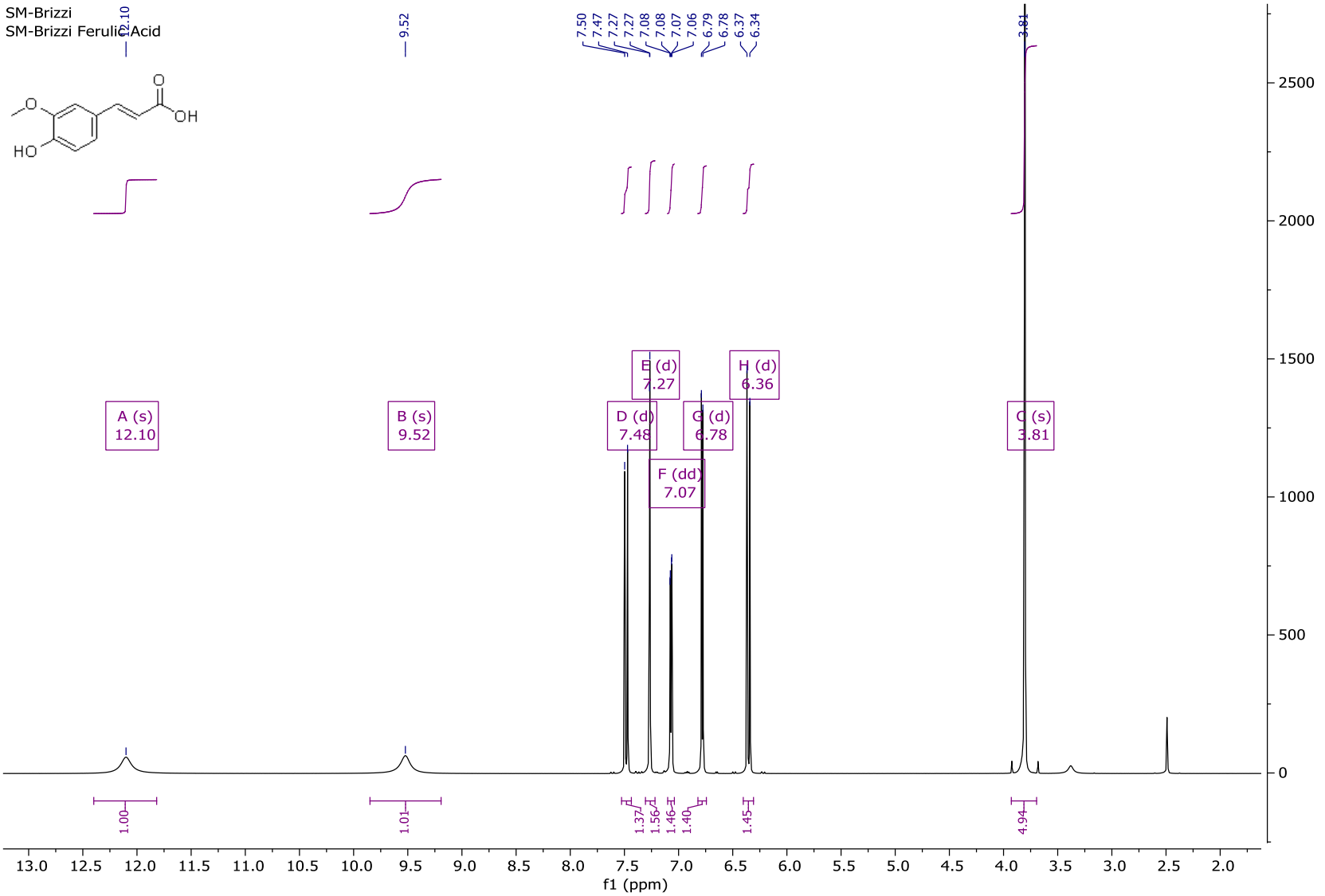


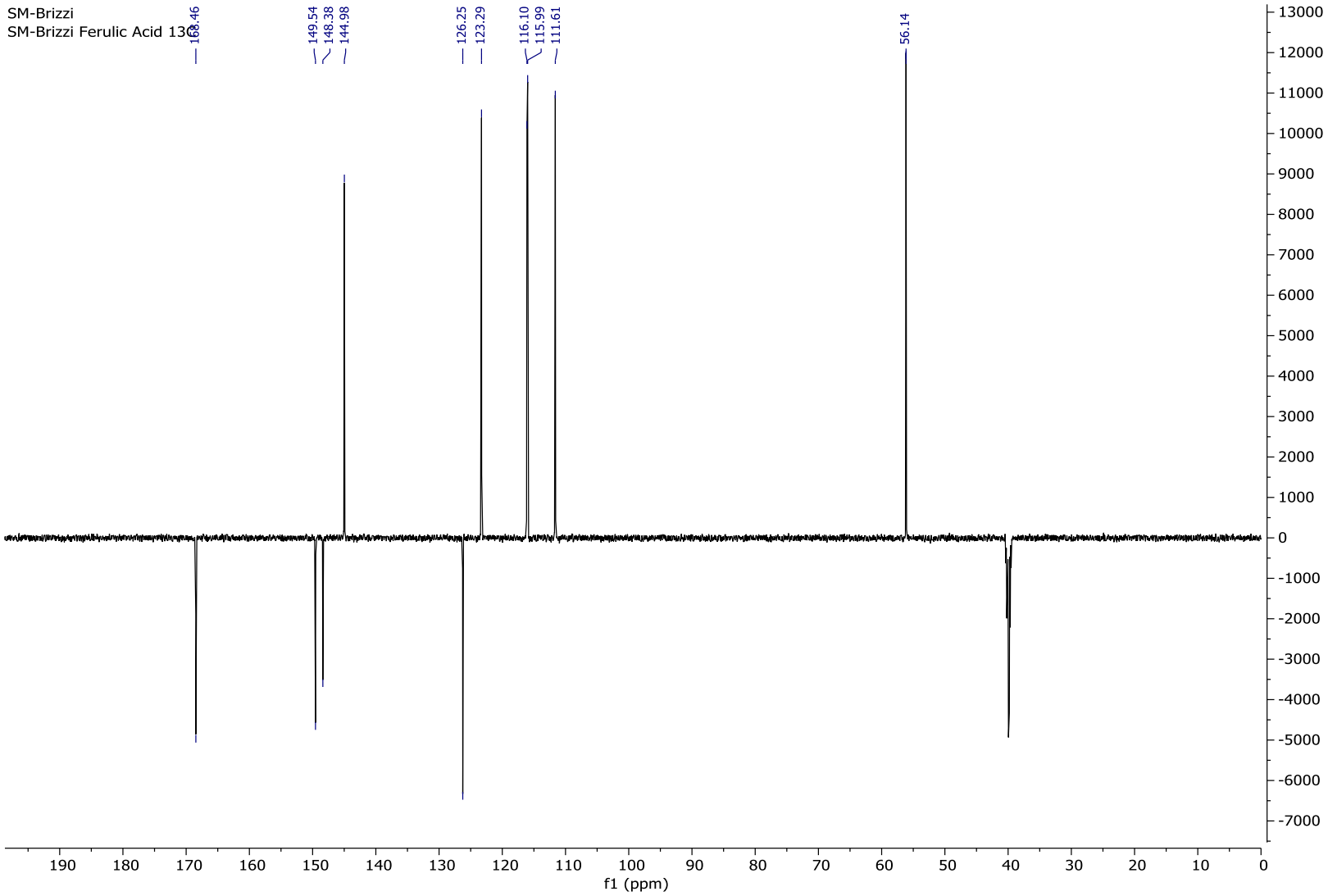
^{1}H-NMR (600 MHz, DMSO-d_6) δ: 12.48 (s, 1H, OH in 5), 10.76 (br s, 1H, OH in 3), 9.57 (br s, 1H, OH in 7), 9.33 (br s, 2H, OH in 3’ and 4’), 7.67 (d, J = 2.1 Hz, 1H, H in 2’), 7.53 (dd, J = 8.5 Hz, 2.1 Hz, H in 6’), 6.88 (d, J = 8.5 Hz, 1H, H in 5’), 6.40 (d, J = 2.0 Hz, 1H, H in 8), 6.18 (d, J = 1.8 Hz, 1H, H in 6).



^{13}C-NMR (151 MHz, DMSO-d_6) δ: 173.3 (C=O), 164.3 (C in 7), 161.2 (C in 5), 156.6 (C in 8a), 148.2 (C in 4'), 147.3 (C in 2), 145.5 (C in 3'), 136.2 (C in 3), 122.4 (C in 1'), 120.4 (C in 6'), 116.1 (C in 5'), 115.5 (C in 2'), 103.5 (C in 4a), 98.65 (C in 6), 93.8 (C in 8).

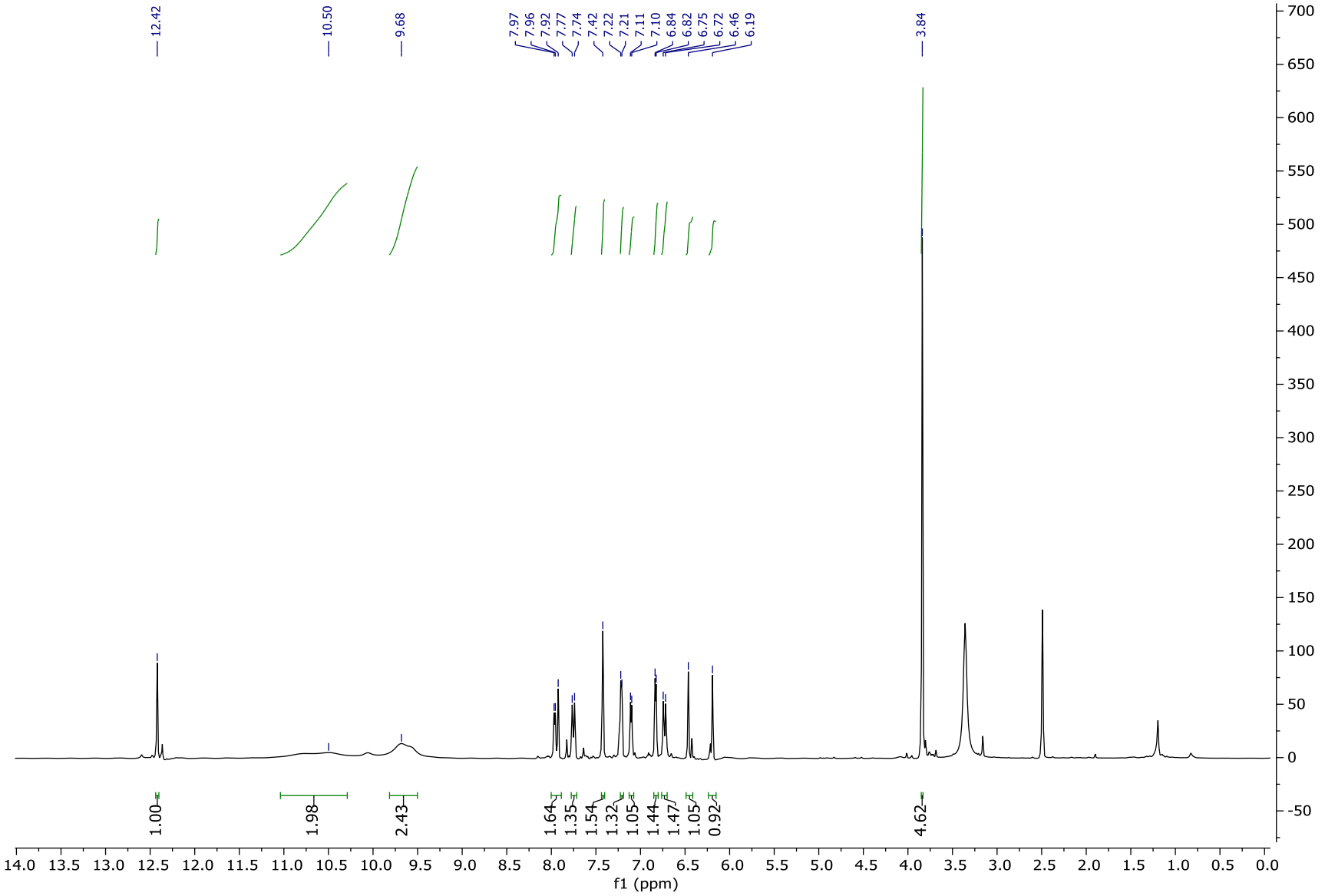


^{1}H-NMR (600 MHz, DMSO-d_6) δ: 12.10 (br s, 1H, COOH), 9.52 (br s, 1H, OH in 4'), 7.48 (d, J = 15.9 Hz, 1H, -CH=*CH*-Ar), 7.27 (d, J = 1.8 Hz, 1H, H in 2'), 7.07 (dd, J = 8.2 Hz, 1.8 Hz, H in 6'), 6.78 (d, J = 8.1 Hz, 1H, H in 5'), 6.36 (d, J = 15.9 Hz, 1H, CO-*CH*=CH-Ar), 3.81 (s, 3H, OCH_3).



^{13}C-NMR (151 MHz, DMSO-d_6) δ: 168.5 (C=O), 149.5 (C in 4'), 148.4 (C in 3'), 145.0 (-CH=*CH*-Ar), 126.2 (C in 1'), 123.3 (C in 6'), 116.1 (CO-*CH*=CH-Ar), 116.0 (C in 5'), 111.6 (C in 2'), 56.1 (OCH_3).

Compd.**1**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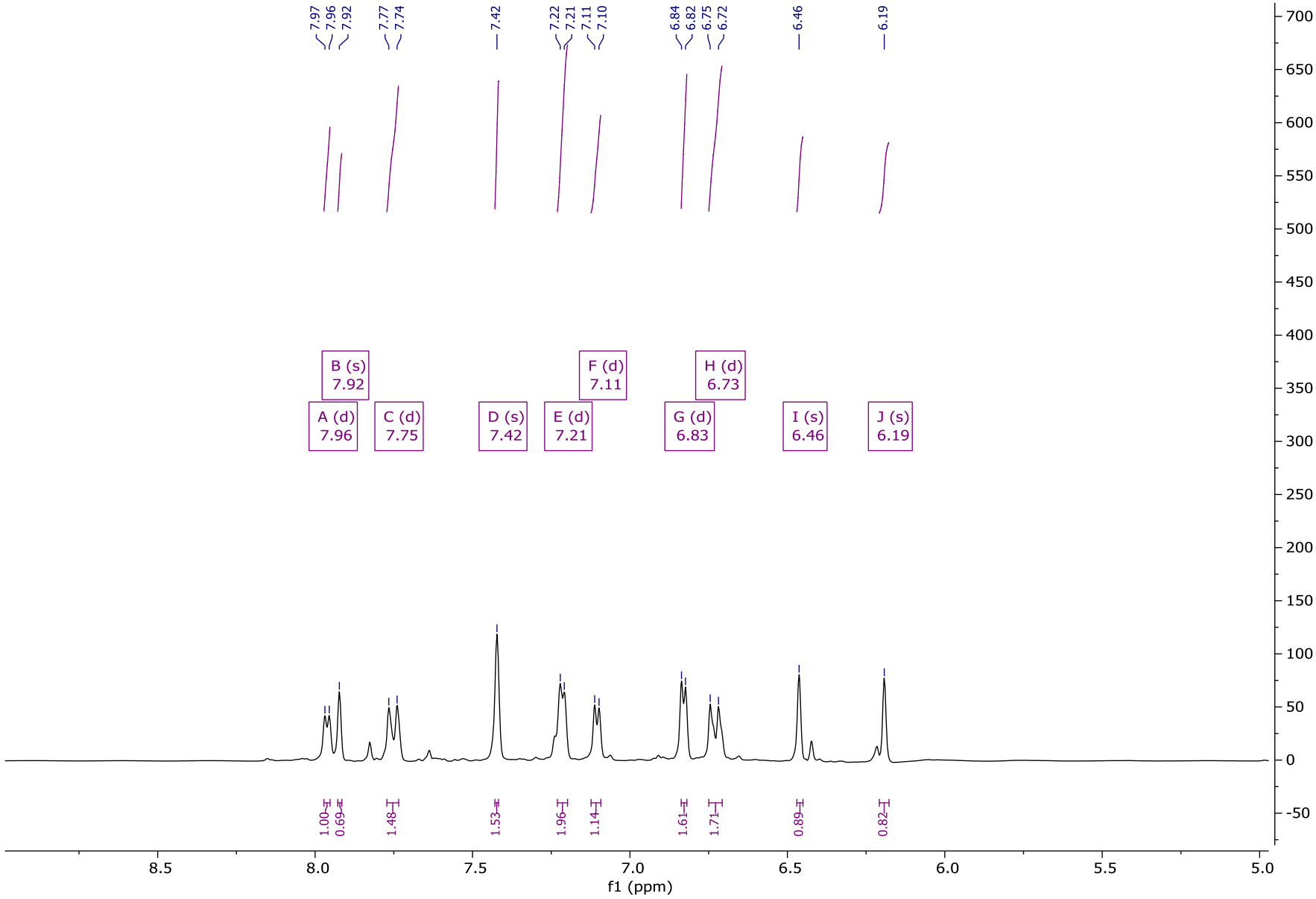
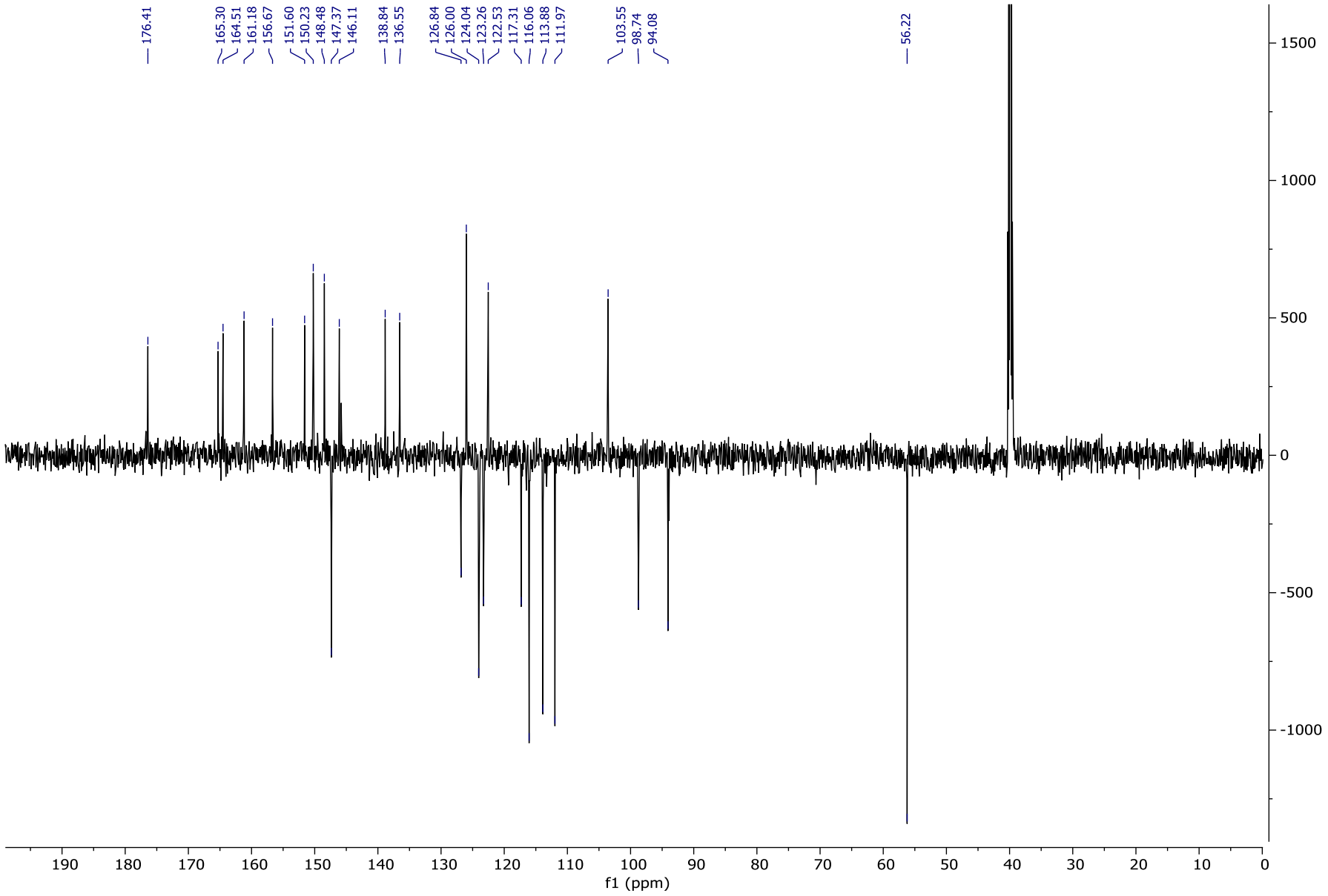
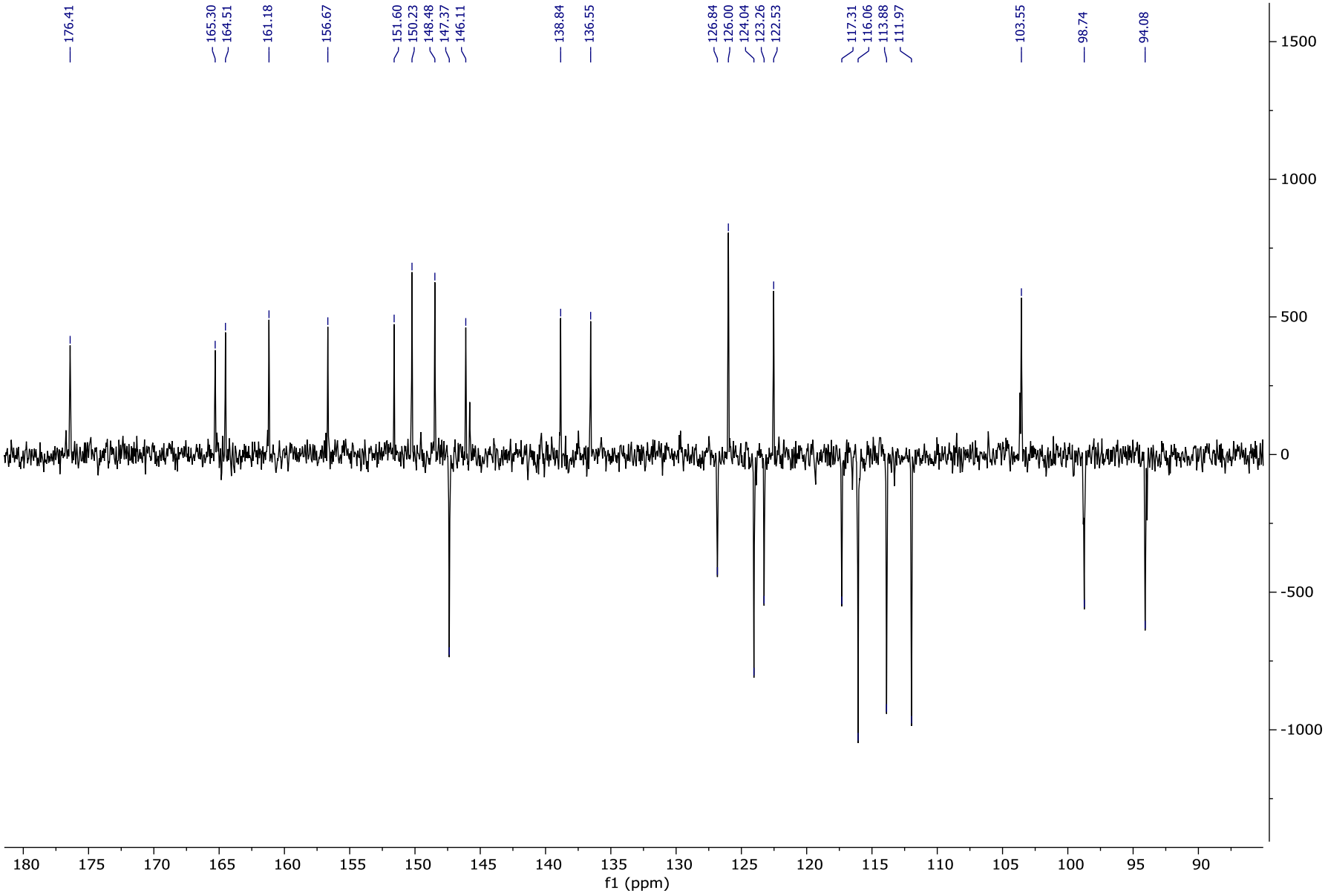
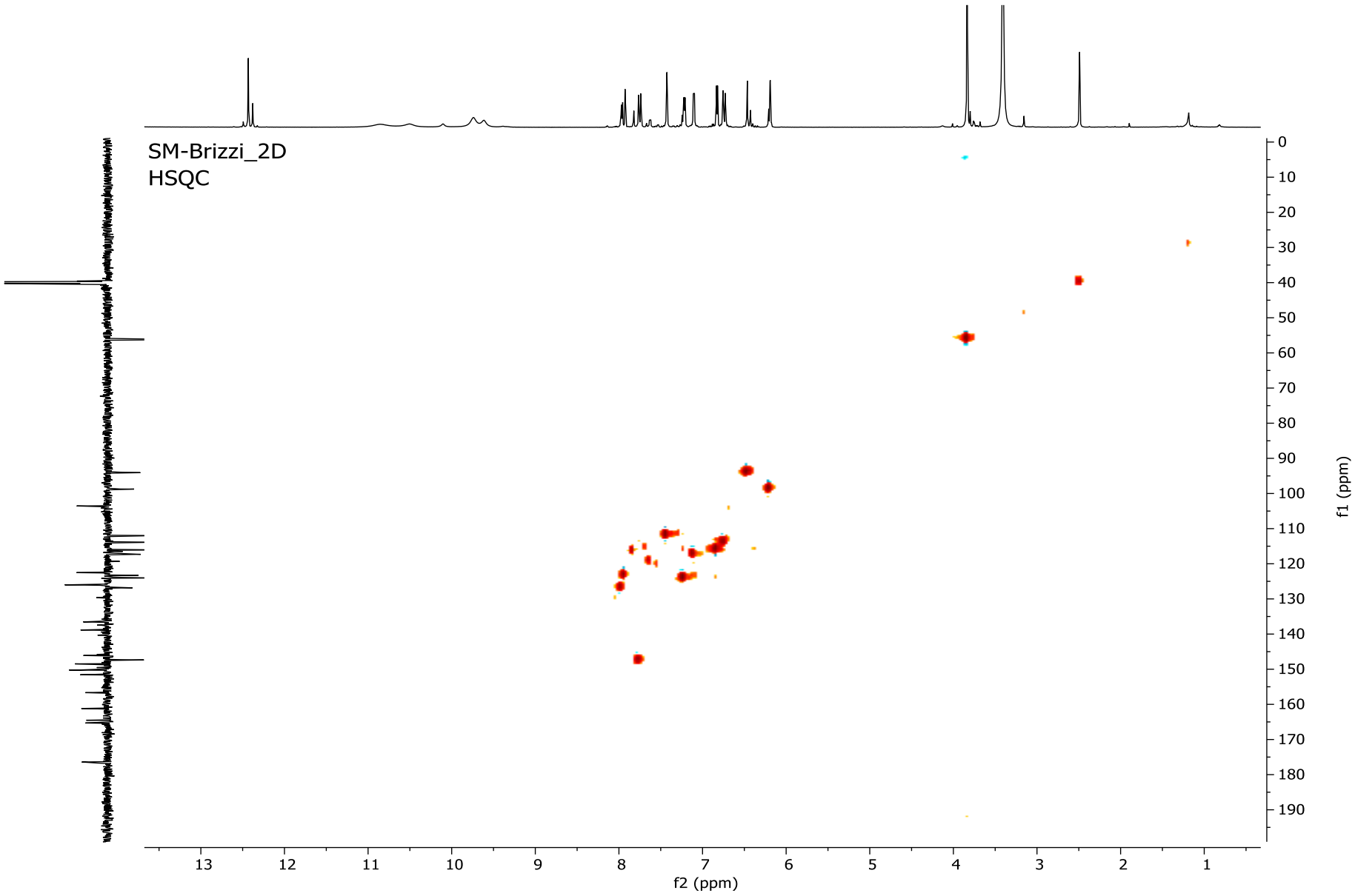
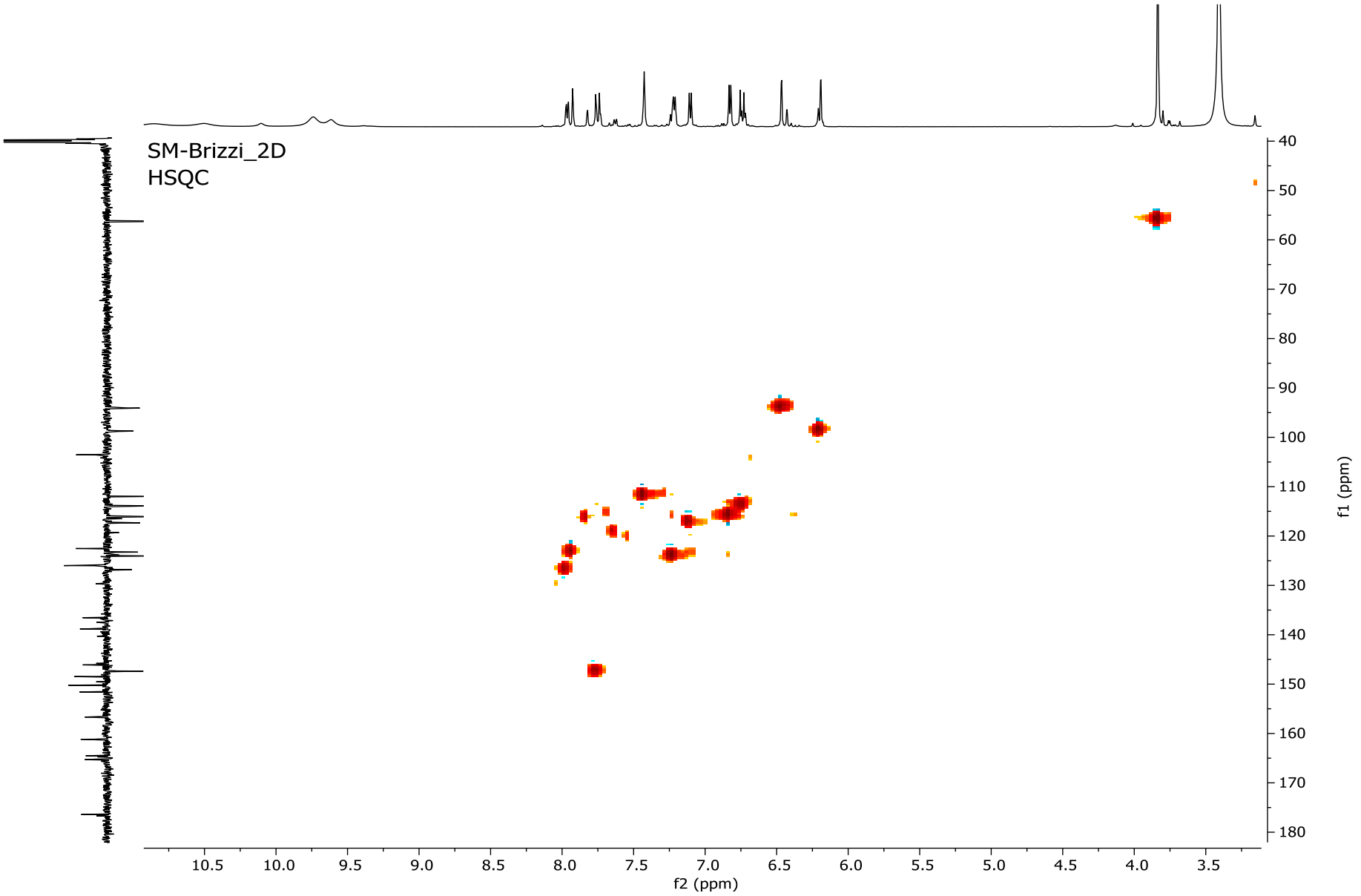
9.68
7.97
7.96
7.92
7.77
7.74
7.42
7.22
7.21
7.11
7.10
6.84
6.82
6.75
6.72
6.46
6.19
3.84
1.00
1.98
2.43
1.64
1.35
1.54
1.32
1.05
1.44
1.47
1.05
0.92
4.62
f1 (ppm)

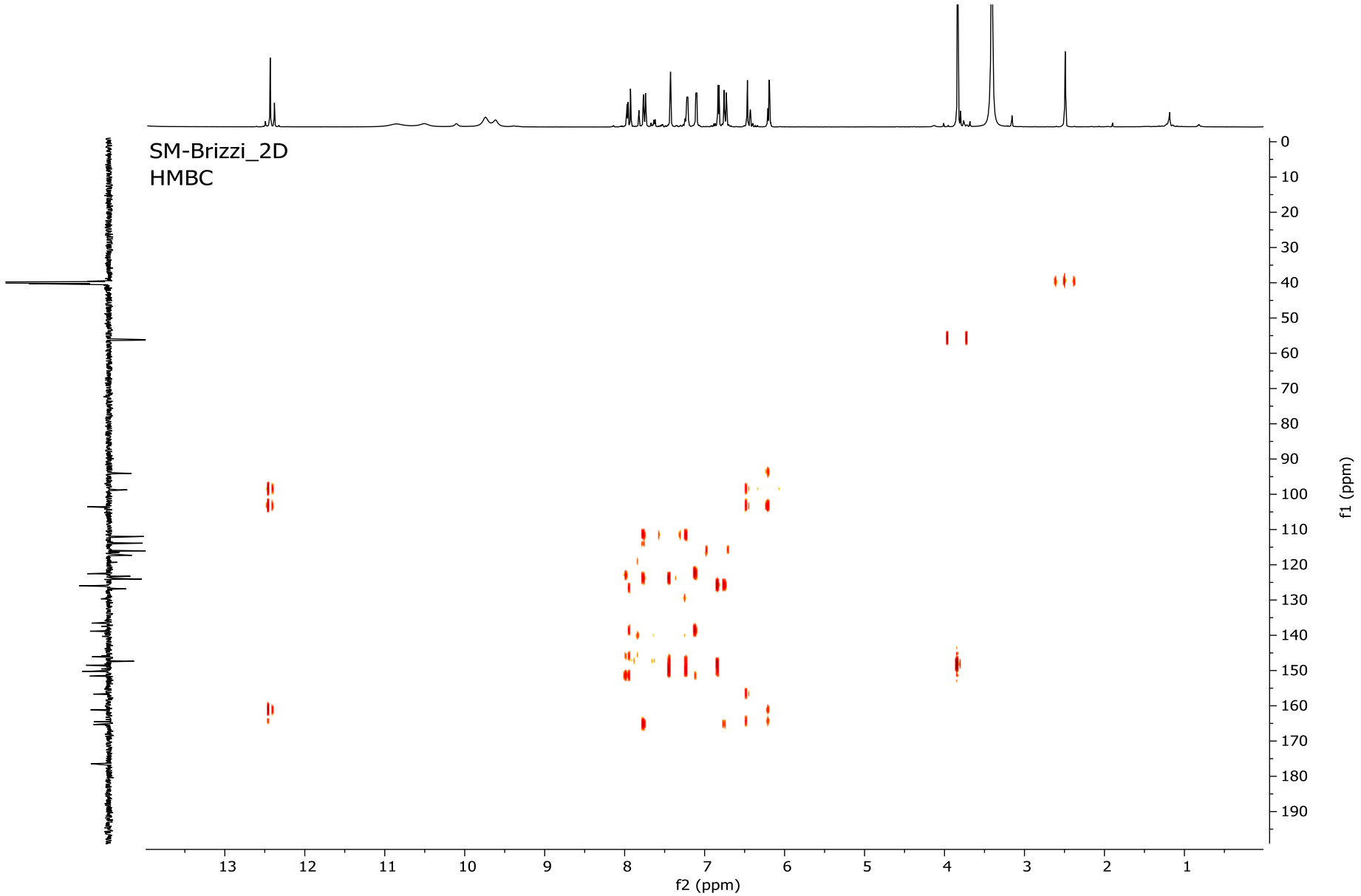

7.97
7.96
7.92
7.77
7.74
7.42
7.22
7.21
7.11
7.10
6.84
6.82
6.75
6.72
6.46
6.19
B (s)
7.92
F (d)
7.11
H (d)
6.73
A (d)
7.96
C (d)
7.75
D (s)
7.42
E (d)
7.21
G (d)
6.83
I (s)
6.46
J (s)
6.19
1.00
0.69
1.48
1.53
1.96
1.14
1.61
1.71
0.89
0.82
f1 (ppm)


176.41
165.30
164.51
161.18
156.67
151.60
150.23
148.48
147.37
146.11
138.84
136.55
126.84
126.00
124.04
123.26
122.53
117.31
116.06
113.88
111.97
103.55
98.74
94.08
56.22
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)


176.41
165.30
164.51
161.18
156.67
151.60
150.23
148.48
147.37
146.11
138.84
136.55
126.84
126.00
124.04
123.26
122.53
117.31
116.06
113.88
111.97
103.55
98.74
94.08
1500
1000
500
0
-500
-1000
180
175
170
165
160
155
150
145
140
135
130
125
120
115
110
105
100
95
90
f1 (ppm)


SM-Brizzi_2D
HSQC
f2 (ppm)
f1 (ppm)


SM-Brizzi_2D
HSQC
f2 (ppm)
f1 (ppm)
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
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180


SM-Brizzi_2D
HMBC
f2 (ppm)
f1 (ppm)

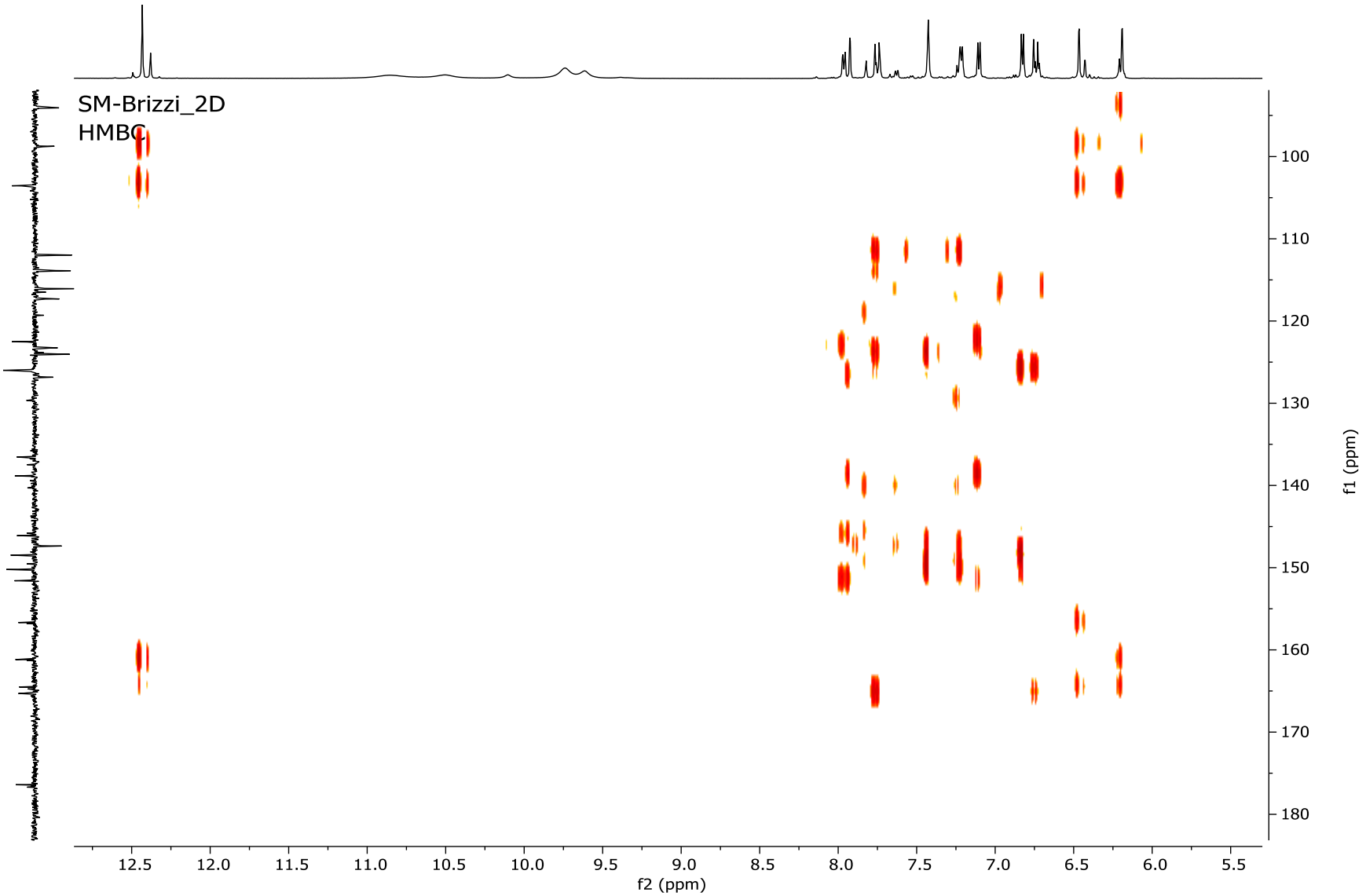

SM-Brizzi_2D
HMBC
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
f2 (ppm)
100
110
120
130
140
150
160
170
180
f1 (ppm)

Table S1. $K_{Ca}1.1$ channel-compounds **1** and **2** interaction network. The *consensus* binding residues are marked in bold.

Compound	Hydrophobic Interaction	Hydrogen bond	Π- Stacking	Π- Cationic	ΔG (Kcal/mol)
Compd. **1** (3'-*O*-feruloyl derivative)	Arg-395, **Tyr-402**, **Lys-458**, **Phe-461**,	**Lys-300**, **Tyr-402**, Tyr-467	**Tyr-398**, **Tyr-402**, Phe-461	Lys-458	-8,7
Compd. **2** (4'-*O*-feruloyl derivative)	Arg-395, **Tyr-402**, **Lys-458**, **Phe-461**, Glu-465	**Lys-300**, **Tyr-398**, **Tyr-402**, Glu-454, Phe-466, Tyr-467	**Tyr-398**	Lys-458	-9,1