Supplementary Data

Novel 2-substituted-benzimidazole-6-sulfonamides as carbonic anhydrase inhibitors: synthesis, biological evaluation against isoforms I, II, IX and XII and molecular docking studies

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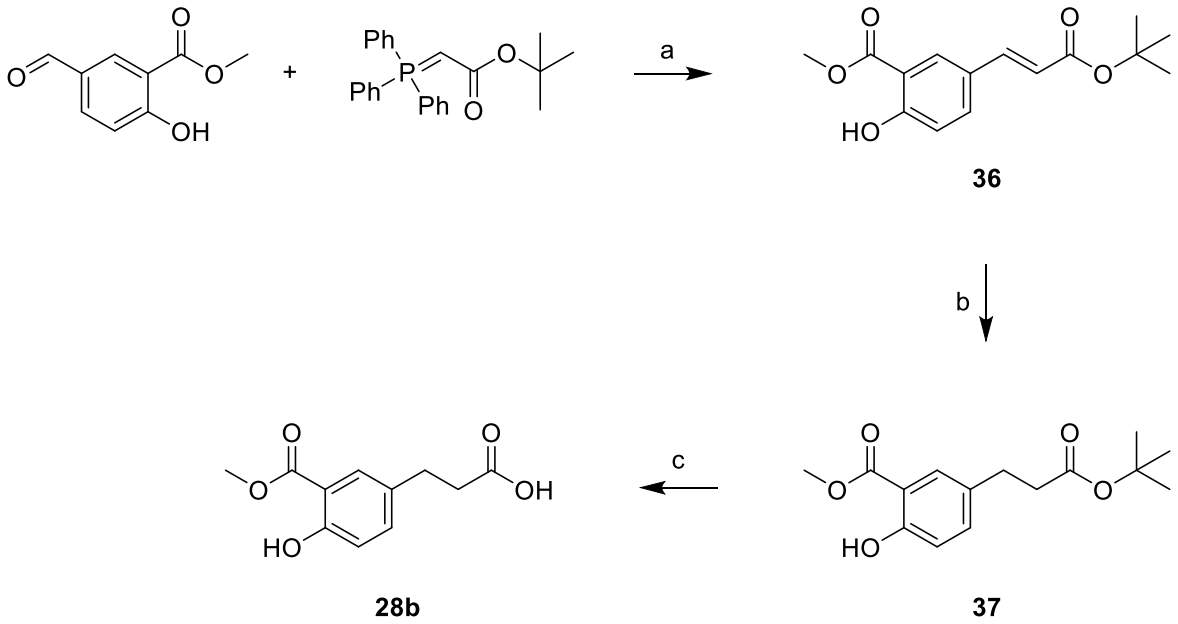
Table of Contents:

Preparation of *3-(4-Hydroxy-3-(methoxycarbonyl)phenyl)propanoic acid* (28b)



(a) Toluene, 18 h (98%); (b) ammonium formate, Pd/C 10 %, MeOH, reflux, 4 h (98%); (c) DCM/TFA (9:1), r.t. 3 h (99%).

*Methyl (E)-5-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)-2-hydroxybenzoate (**36**)*

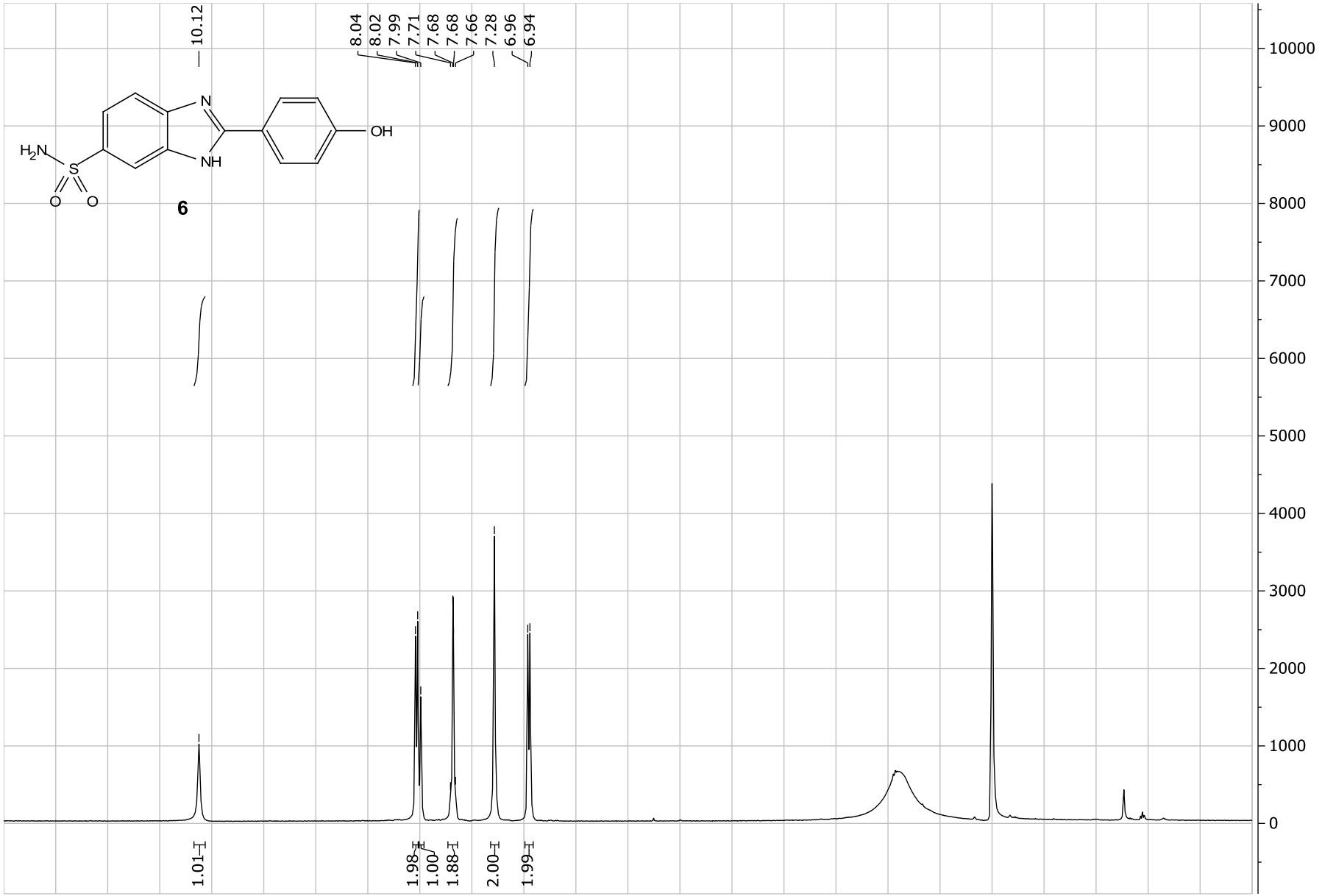
To a suspension of methyl 5-formyl-2-hydroxybenzoate (400 mg, 2.22 mmol) in 25 mL of toluene, tert-butyl(triphenylphosphoranylidene)acetate (1.67 g, 4.44 mmol) was added and the resulting mixture was stirred at room temperature for 18h. Solvent was evaporated and the crude material was purified by silica gel chromatography (DCM/EtOAc, 9/1) yielding **36** as a white solid (605 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.00 (d, J = 2.3 Hz, 1H), 7.63 (dd, J = 8.7, 2.3 Hz, 1H), 7.51 (d, J = 15.9 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.27 (d, J = 16.0 Hz, 1H), 3.98 (s, 3H), 1.53 (s, 9H). ESI m/z: 279 $[M+H]^+$.

*Methyl 5-(3-(tert-butoxy)-3-oxopropyl)-2-hydroxybenzoate (**37**)*

To a stirred suspension of **36** (550 mg, 1.97 mmol) in 120 mL of MeOH, ammonium formate (1.24 g, 19.7 mmol) and palladium on carbon 10 % wt. (36 mg) were added. The resulting mixture was heated at reflux for 4 h. After cooling, the mixture was filtered, and the solvent evaporated under reduced pressure. The crude material was taken up with 100 mL of water and extracted with EtOAc (3 x 60 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and evaporated. The product, obtained as a white solid (540 mg, 98%), was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.69 (d, 1H, J = 1.5 Hz), 7.33 (d, J = 8.5 Hz, 2H), 6.93 (dd, J = 8.5, 1.5 Hz, 1H), 3.96 (s, 3H), 2.87 (t, J = 7.5 Hz, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.44 (s, 9H). ESI m/z: 281 $[M+H]^+$.

*3-(4-Hydroxy-3-(methoxycarbonyl)phenyl)propanoic acid (**28b**)*

Compound **37** (500 mg, 1.78 mmol) was dissolved in a mixture of DCM/TFA (5 mL, 9/1) and the resulting solution was stirred at room temperature for 3 h. Solvent was evaporated yielding essentially pure **28b** (400 mg, 99%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.71 (s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 6.95 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H), 2.92 (t, J = 7.6 Hz, 2H), 2.68 (t, J = 7.6 Hz, 2H). ESI m/z: 225 $[M+H]^+$.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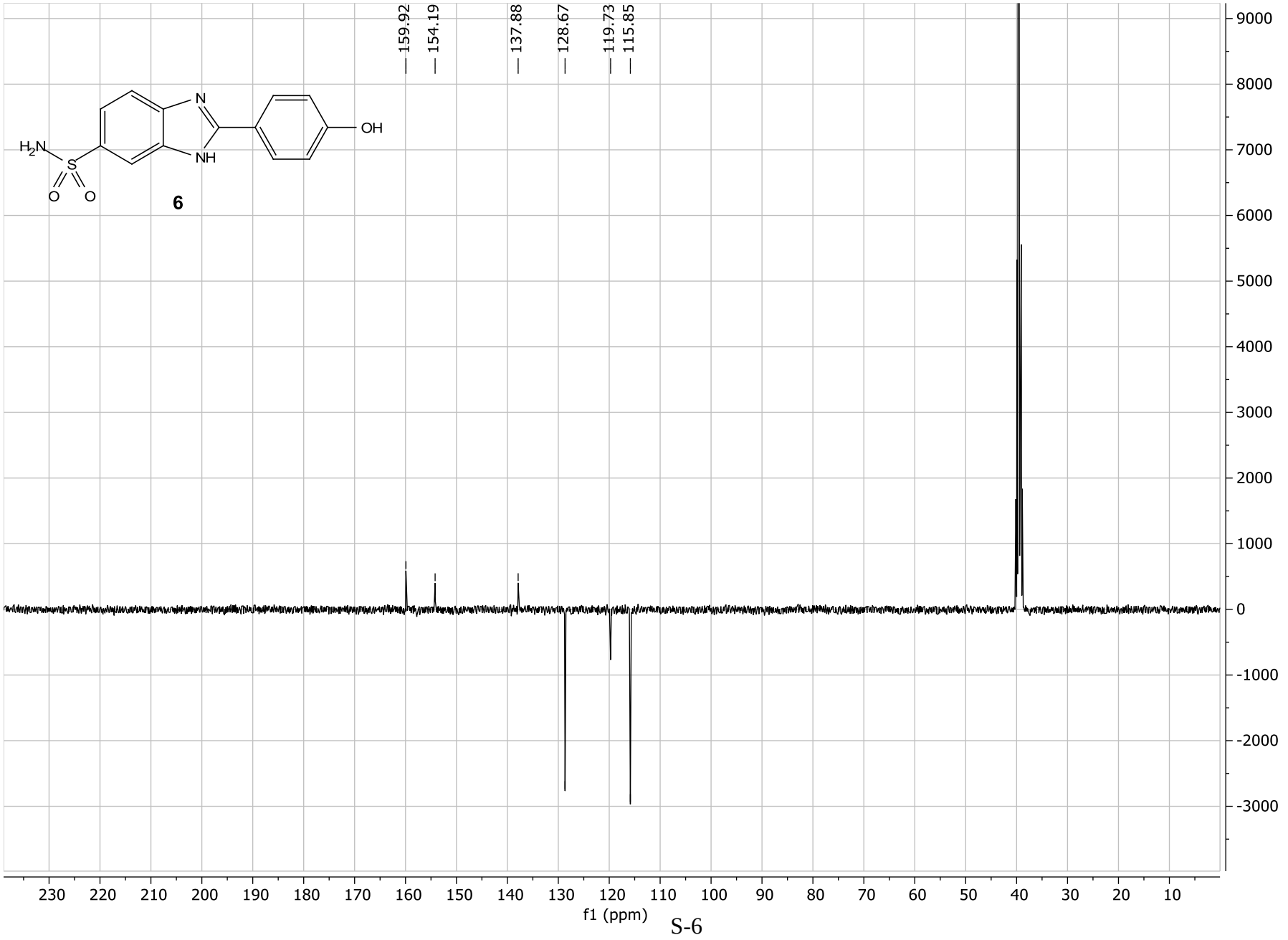
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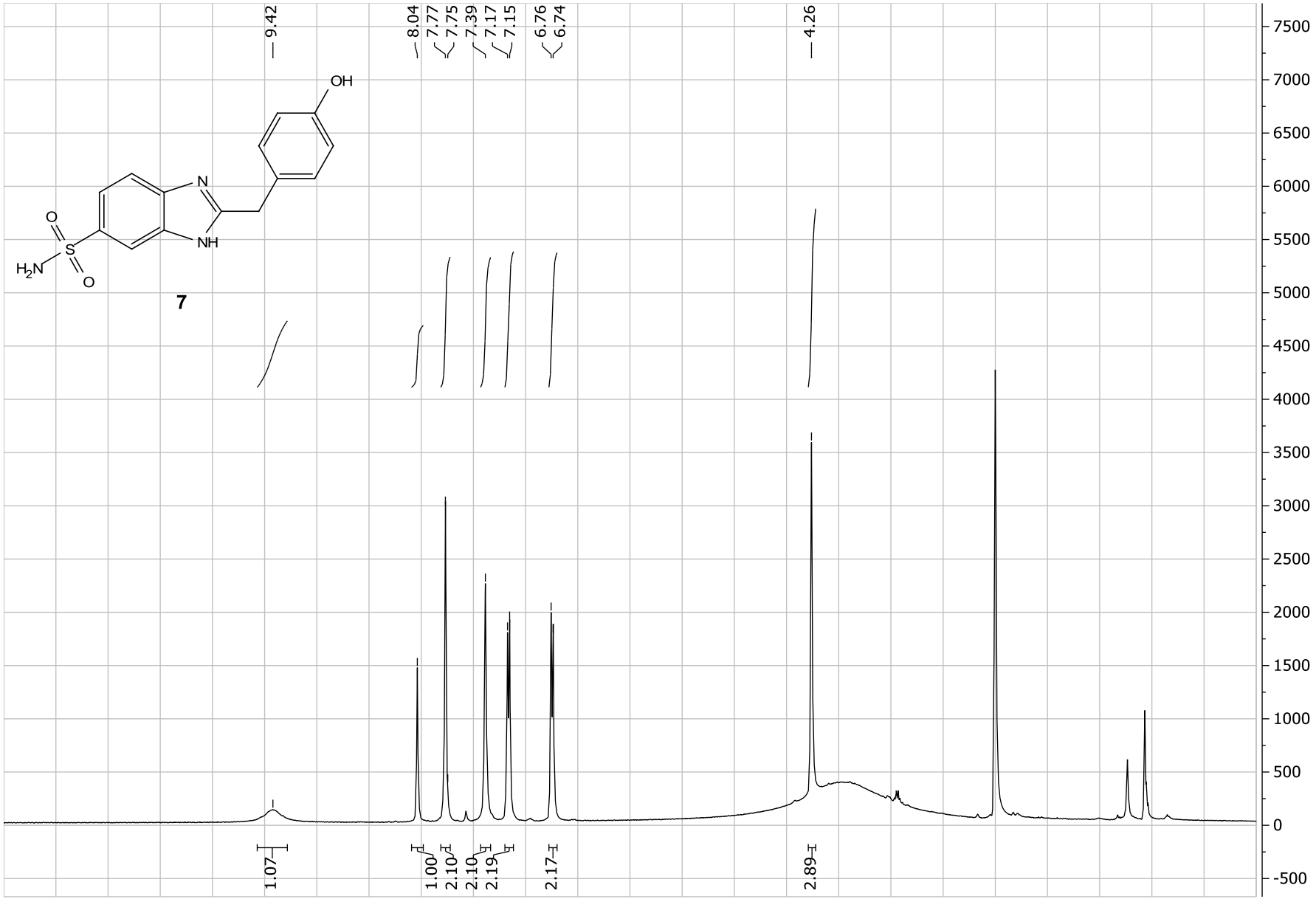
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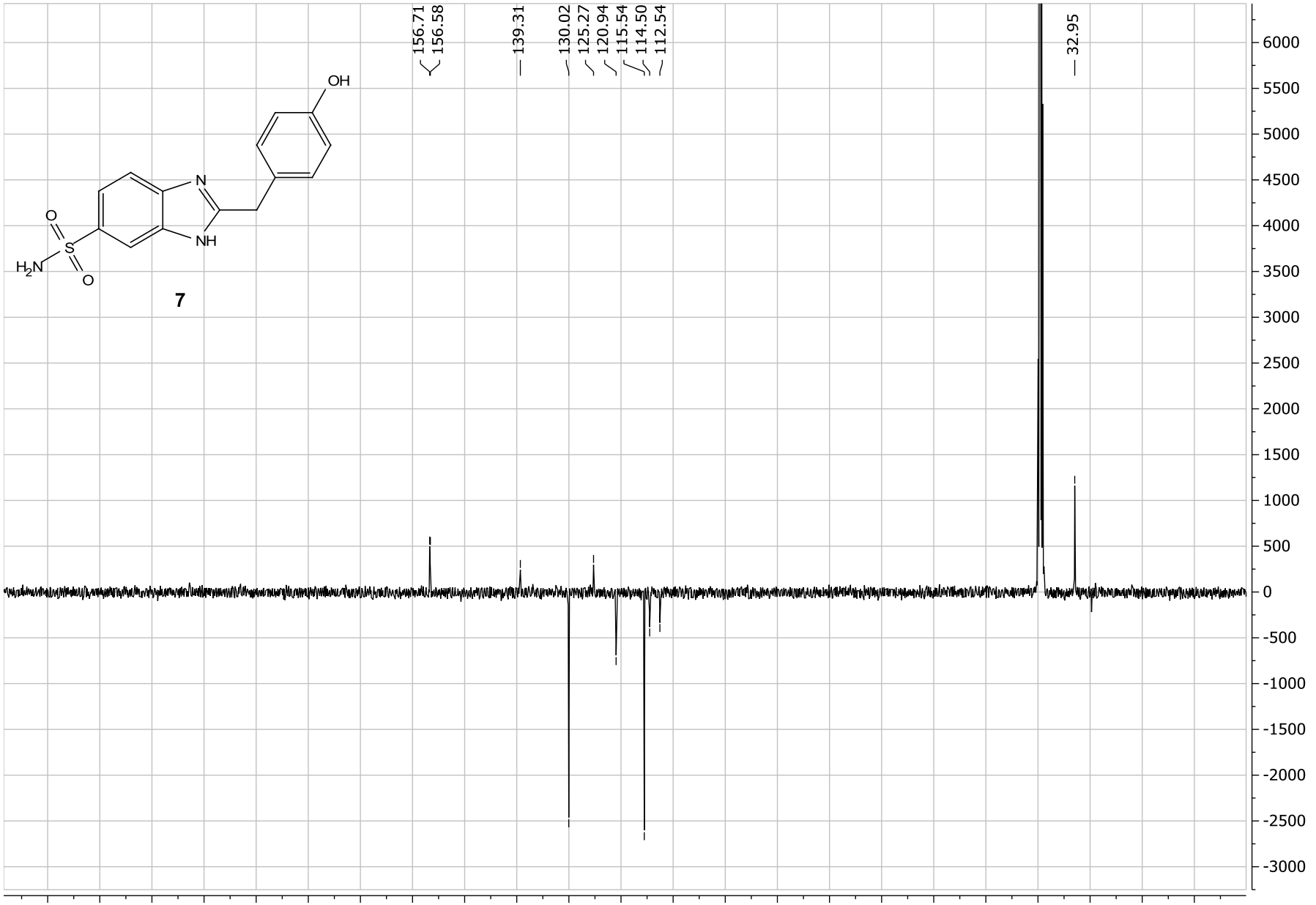
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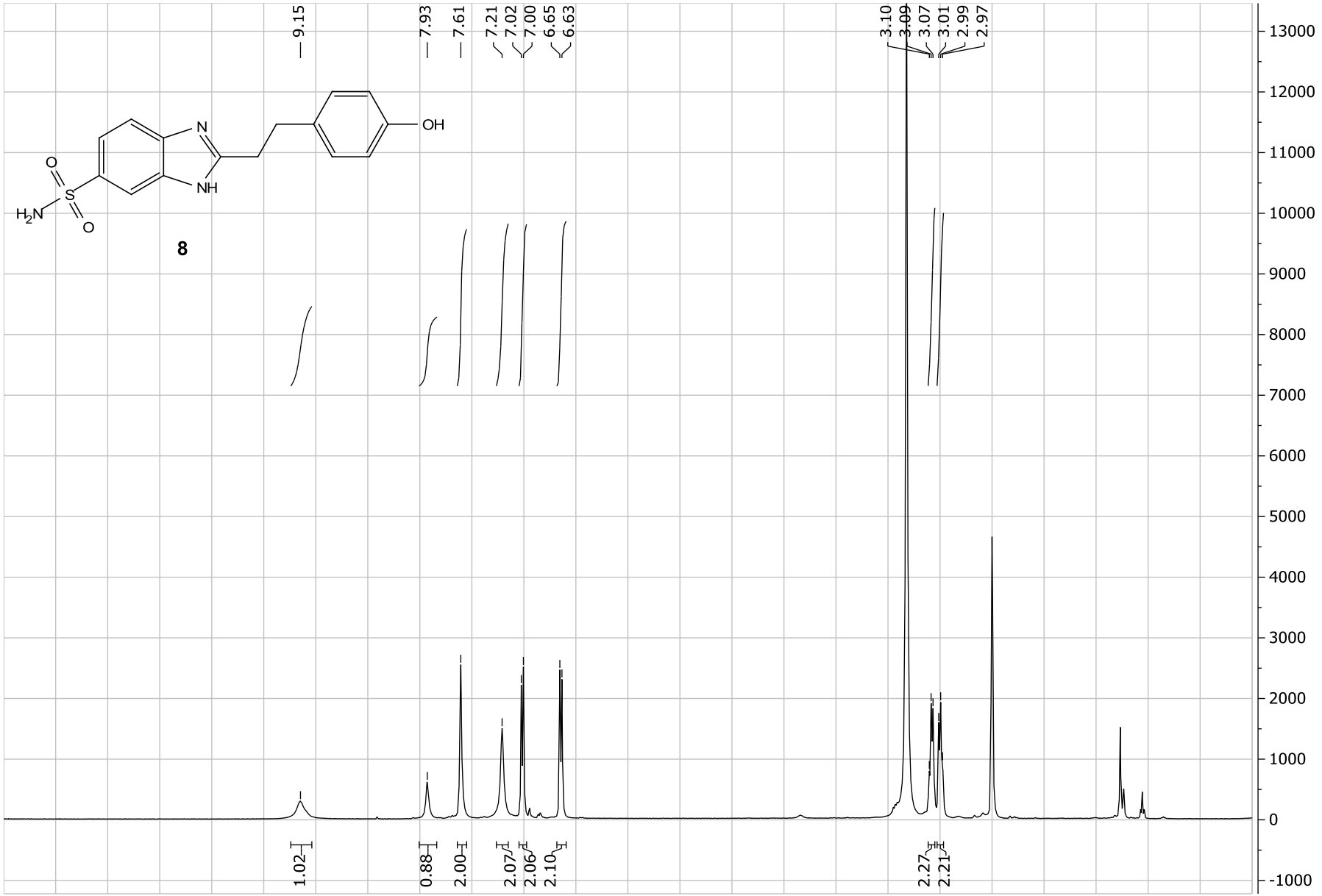
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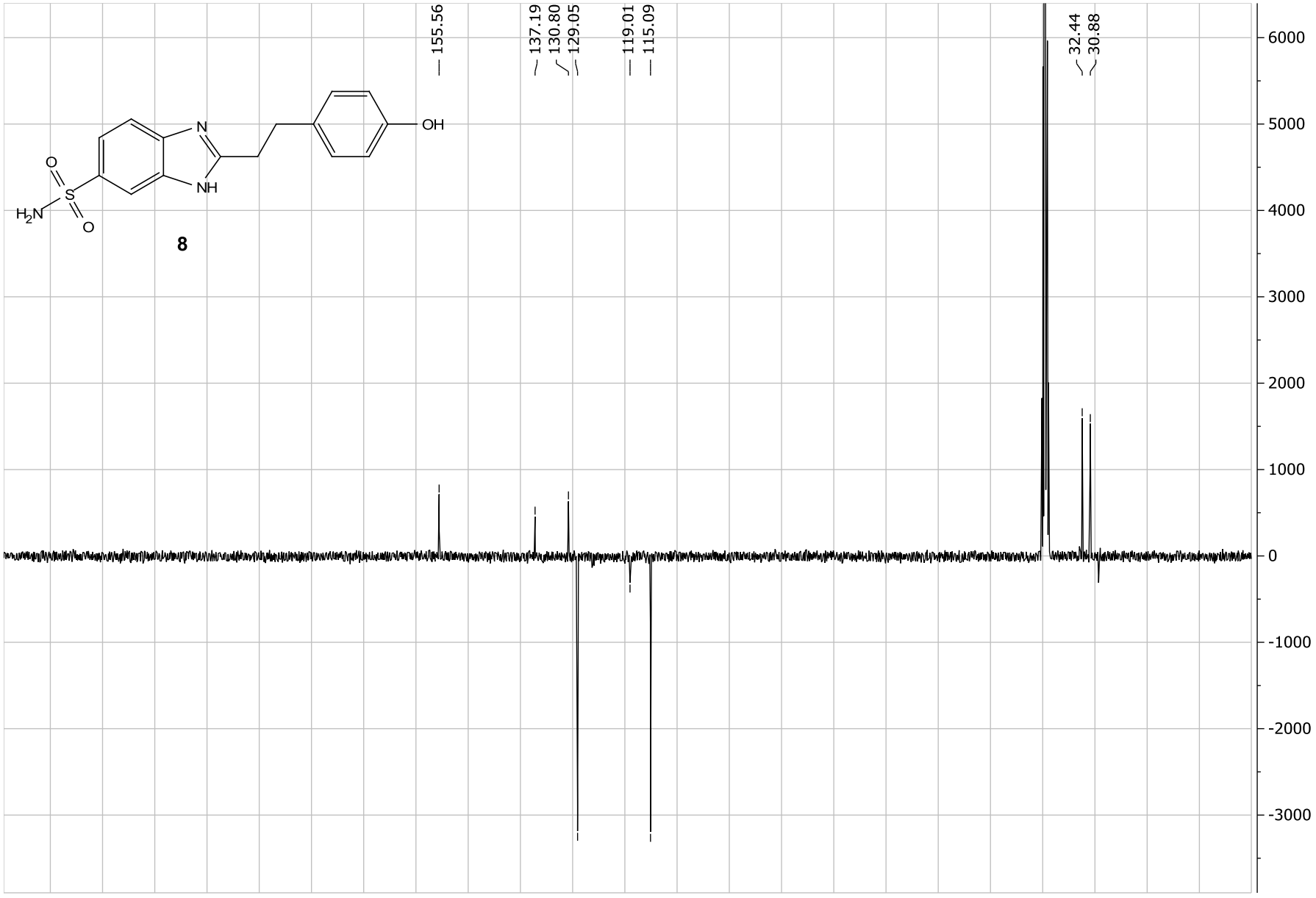
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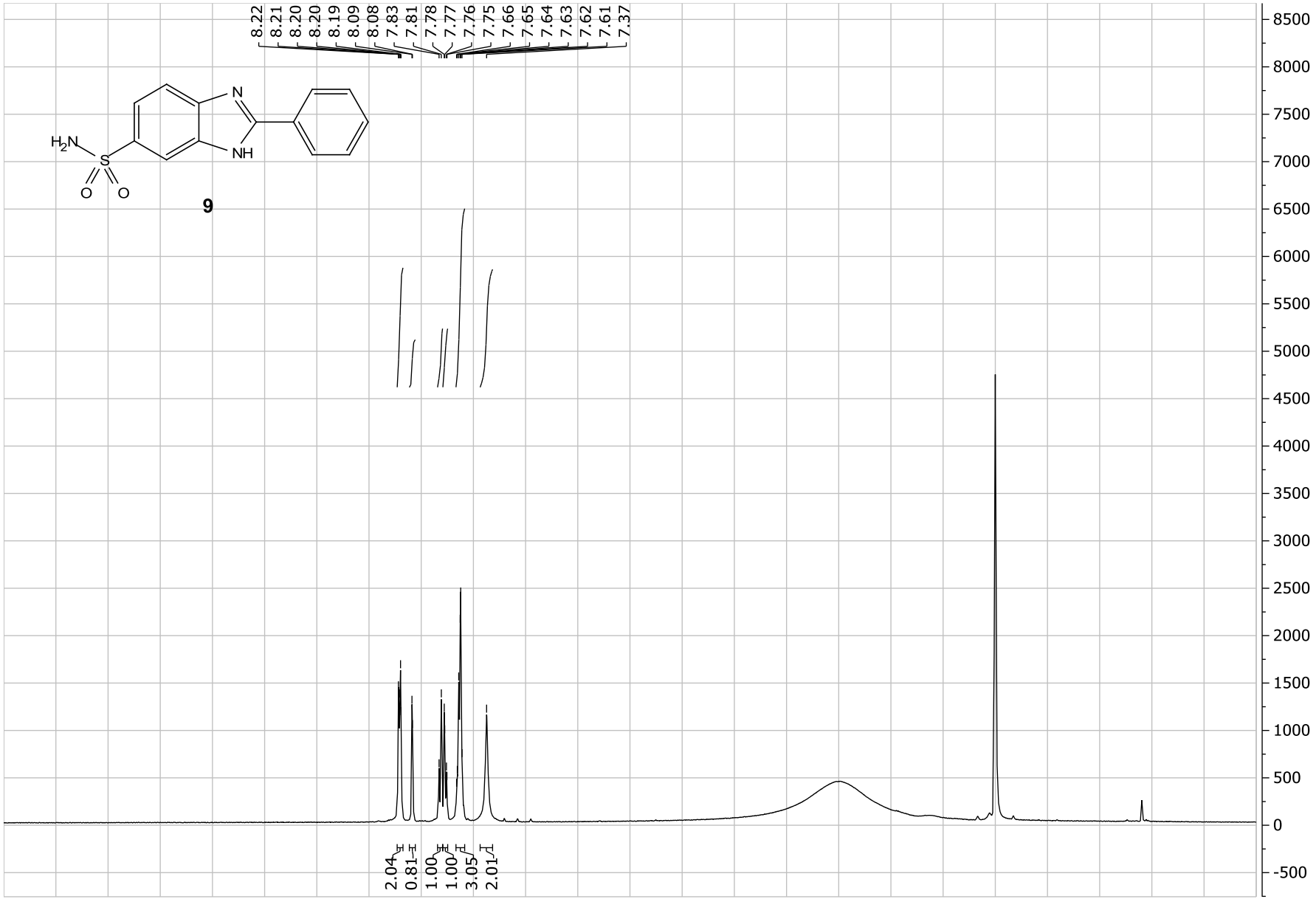
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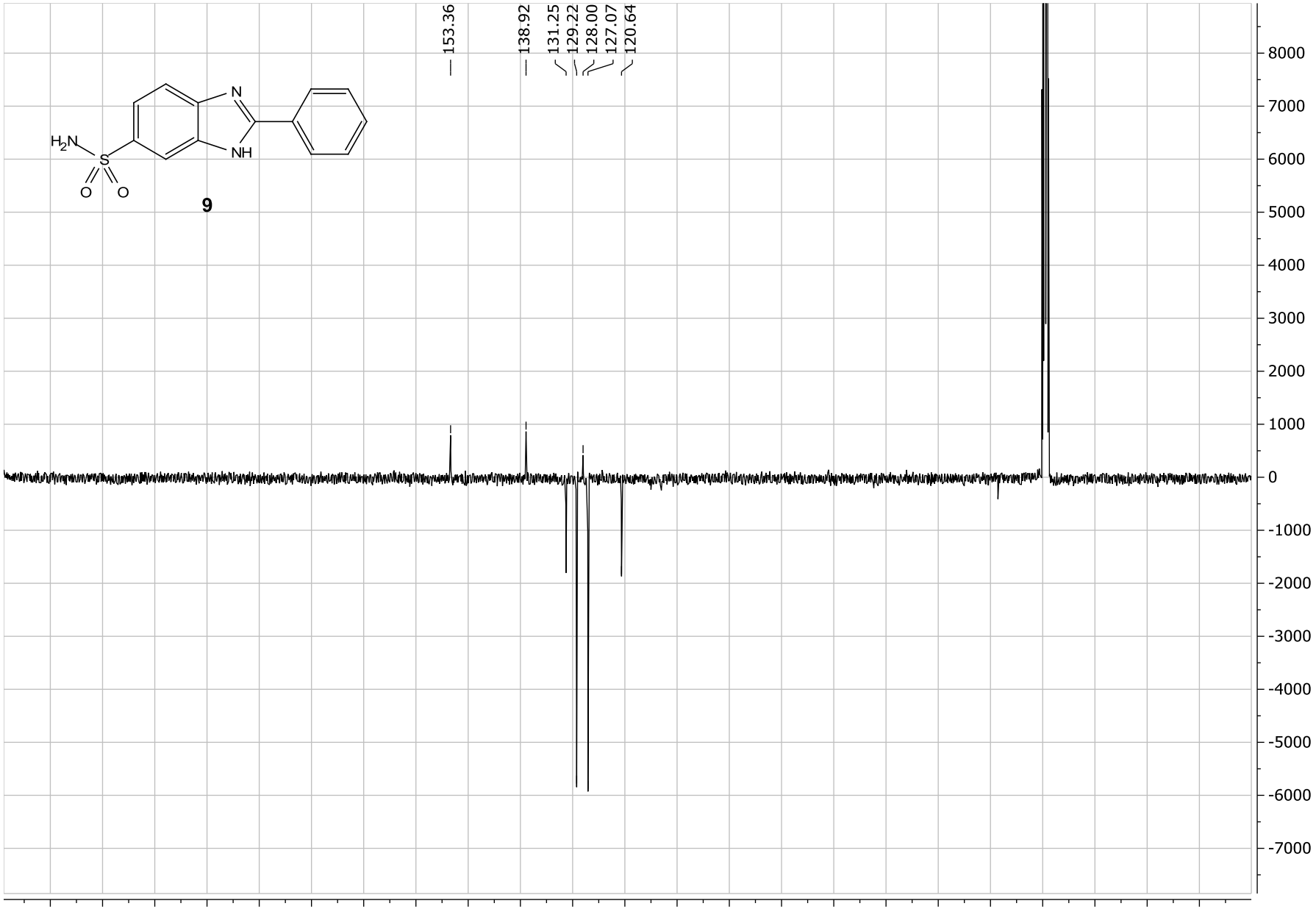
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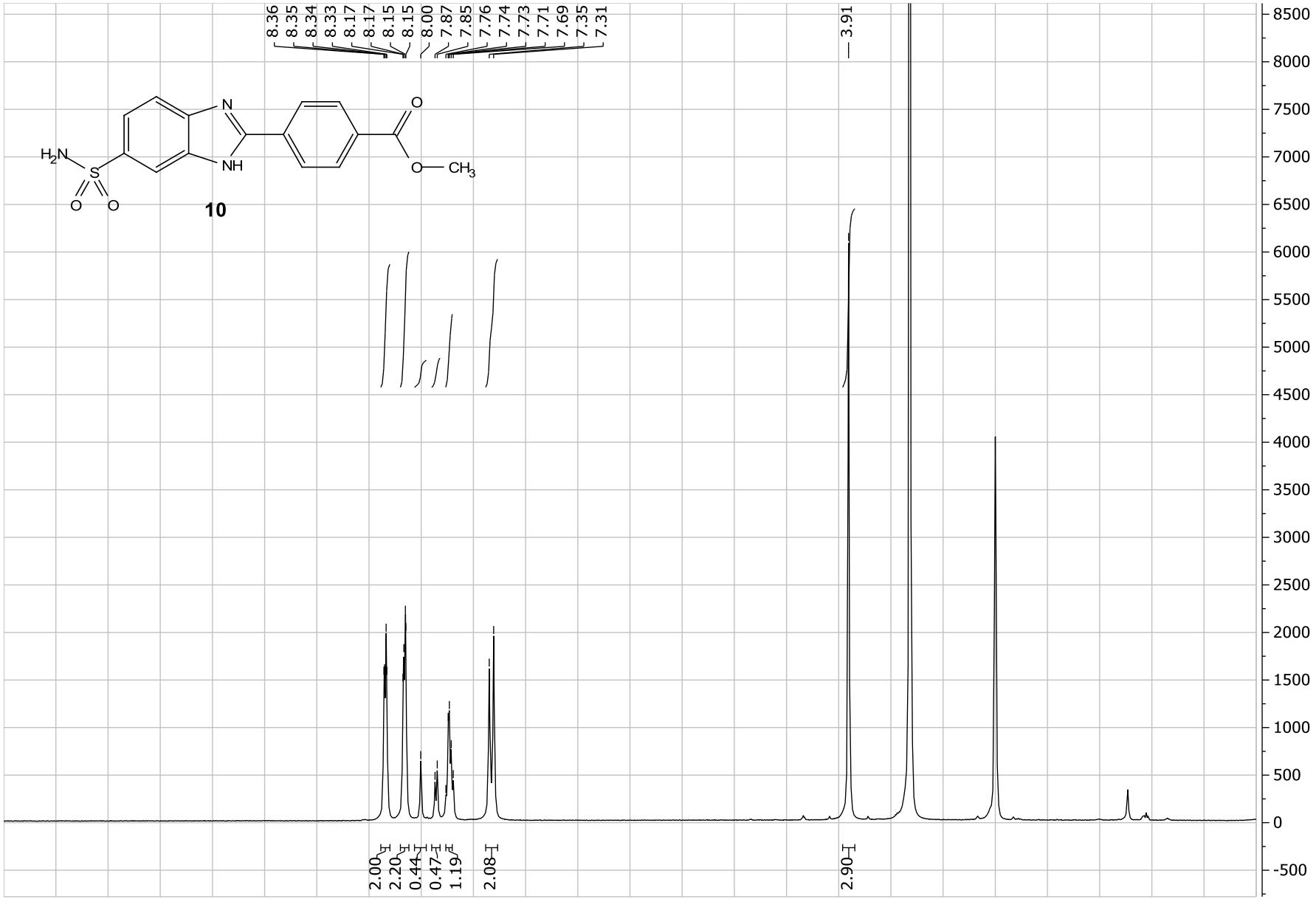
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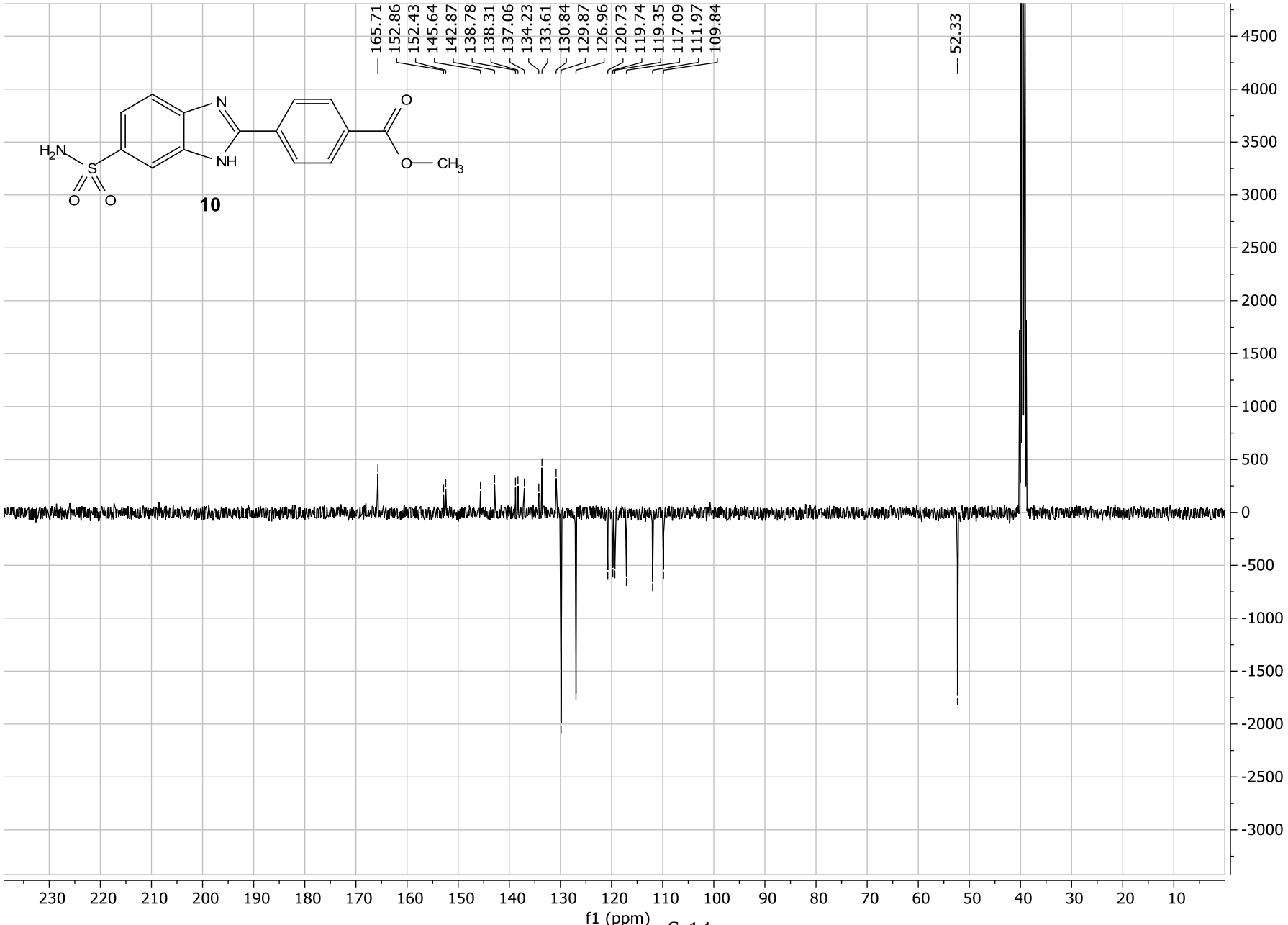
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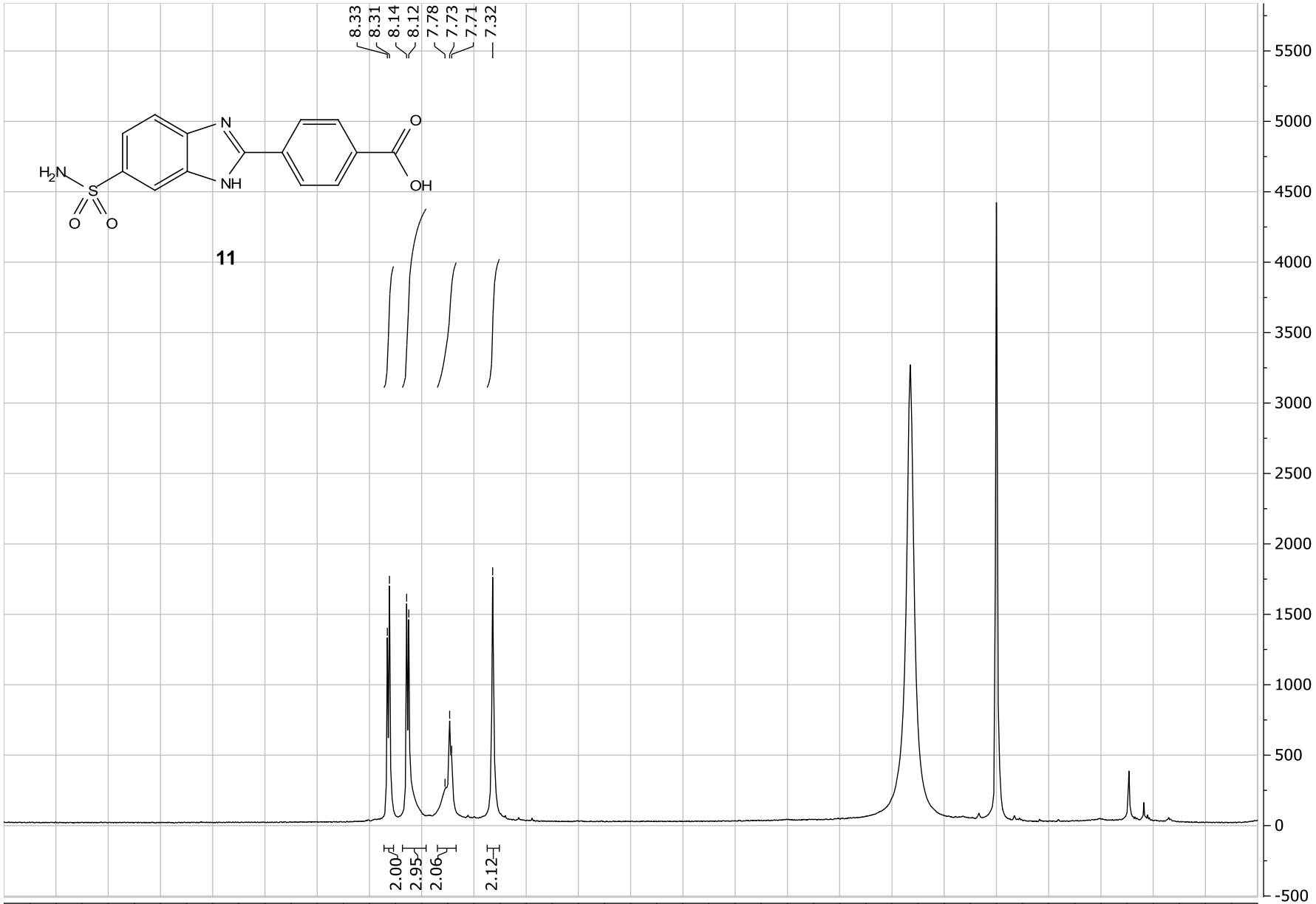
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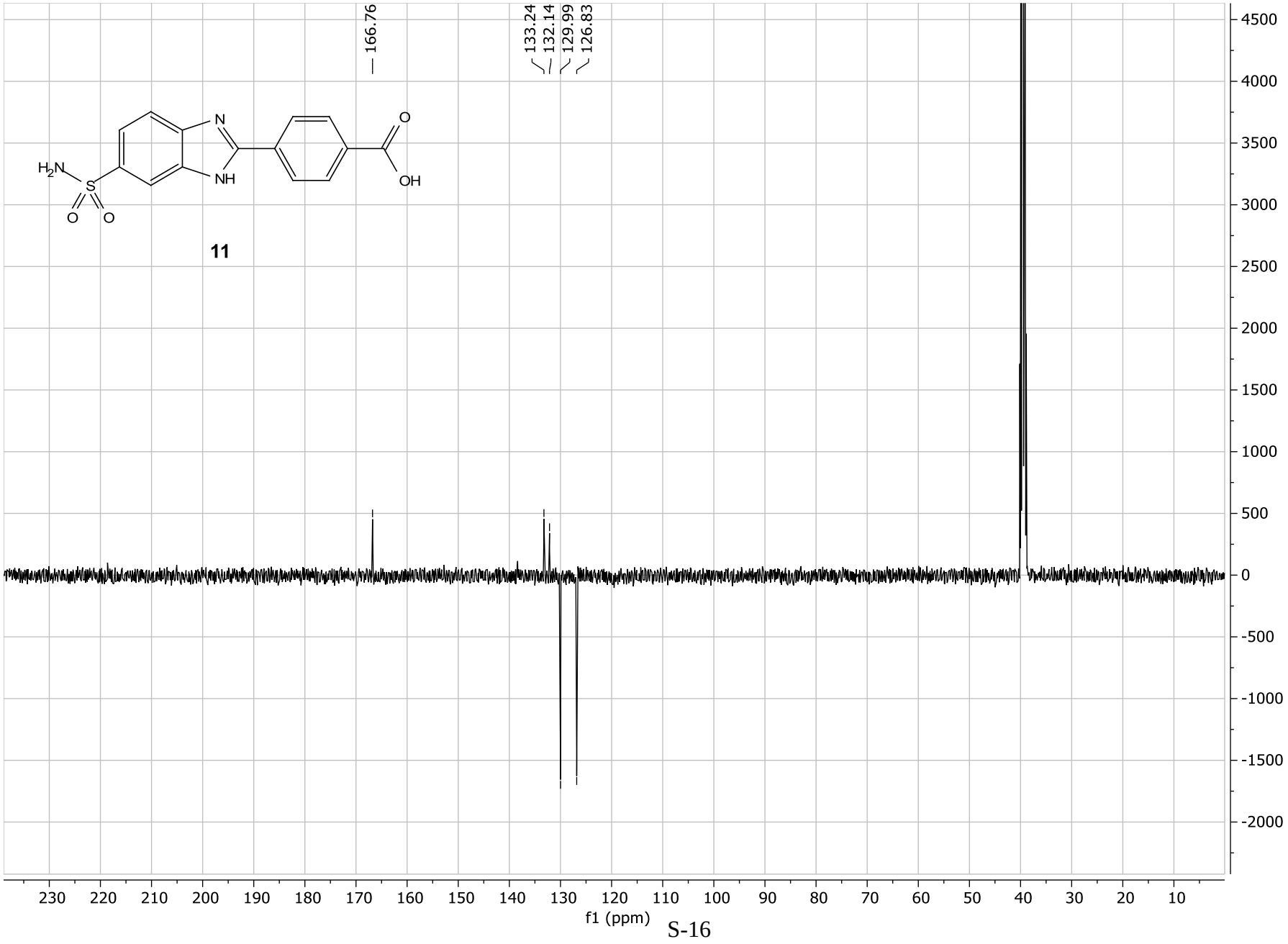
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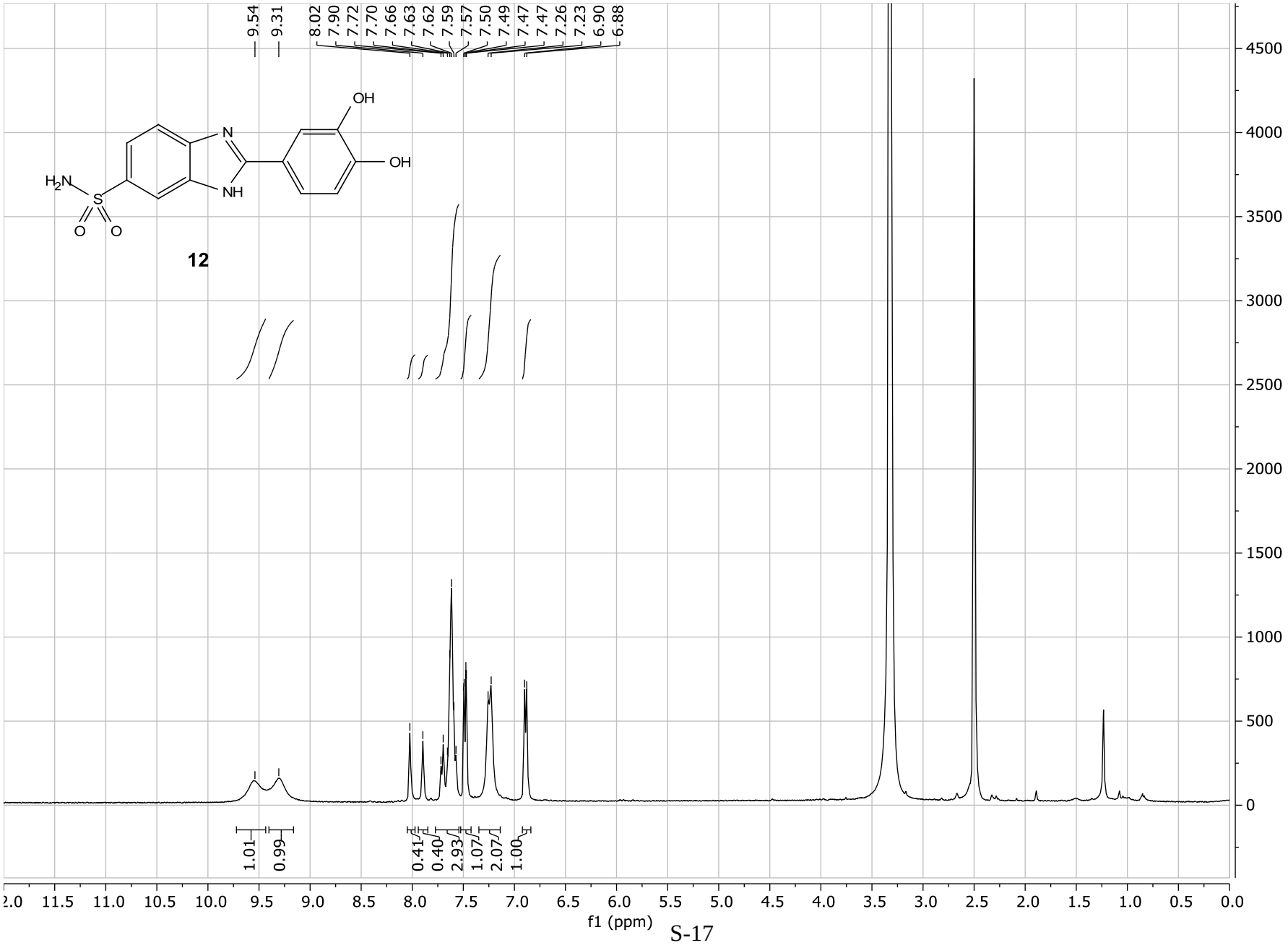
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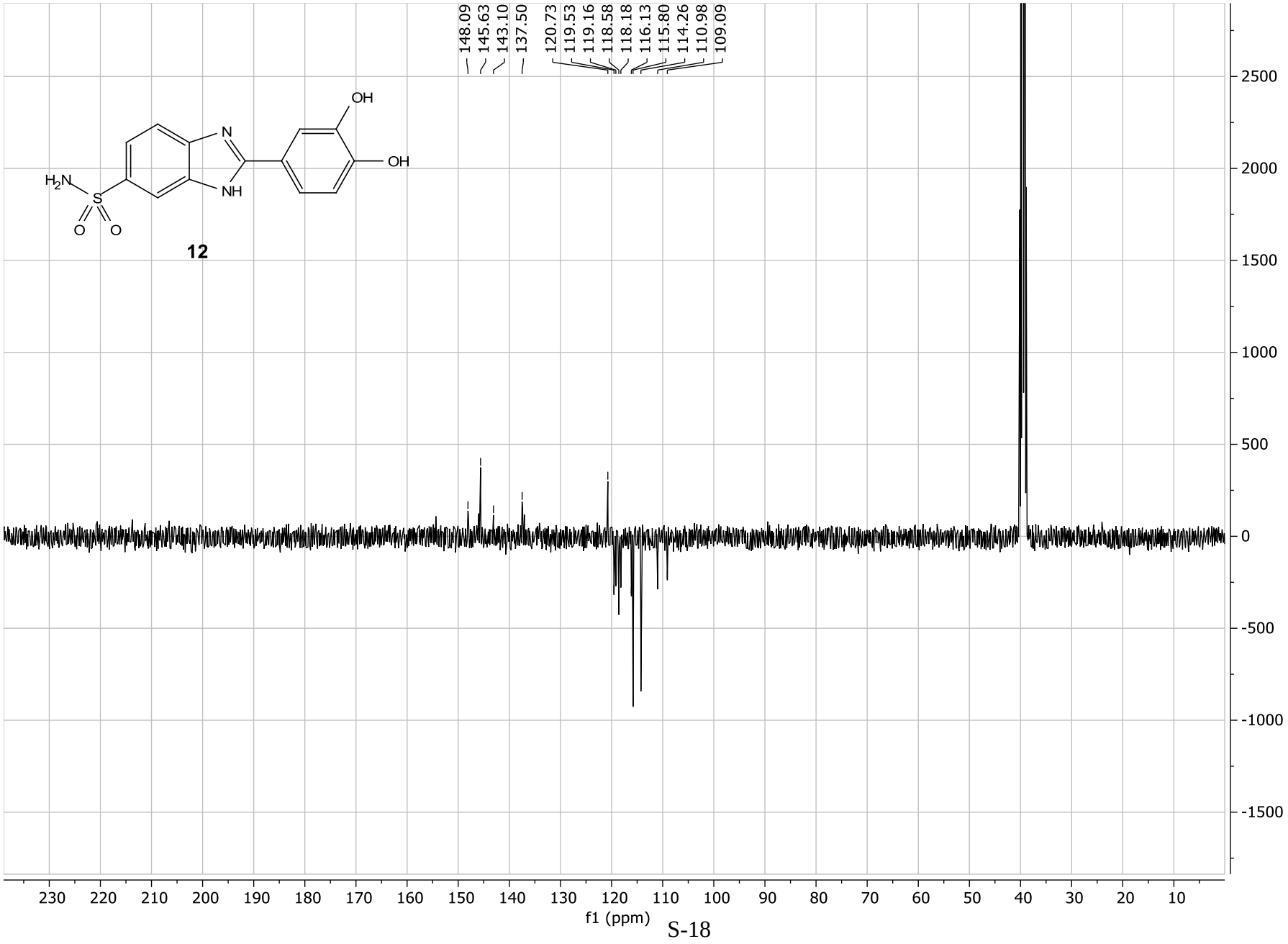
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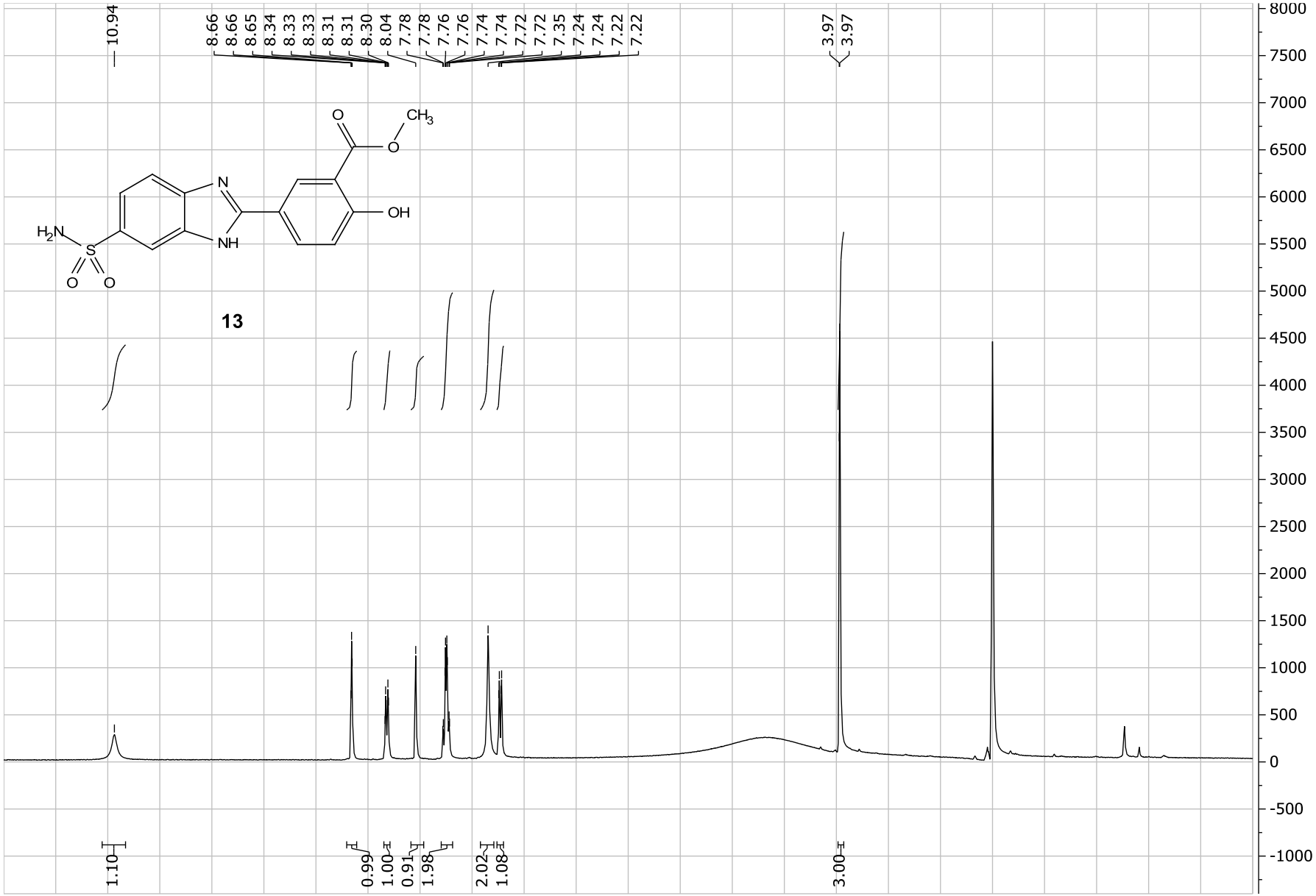
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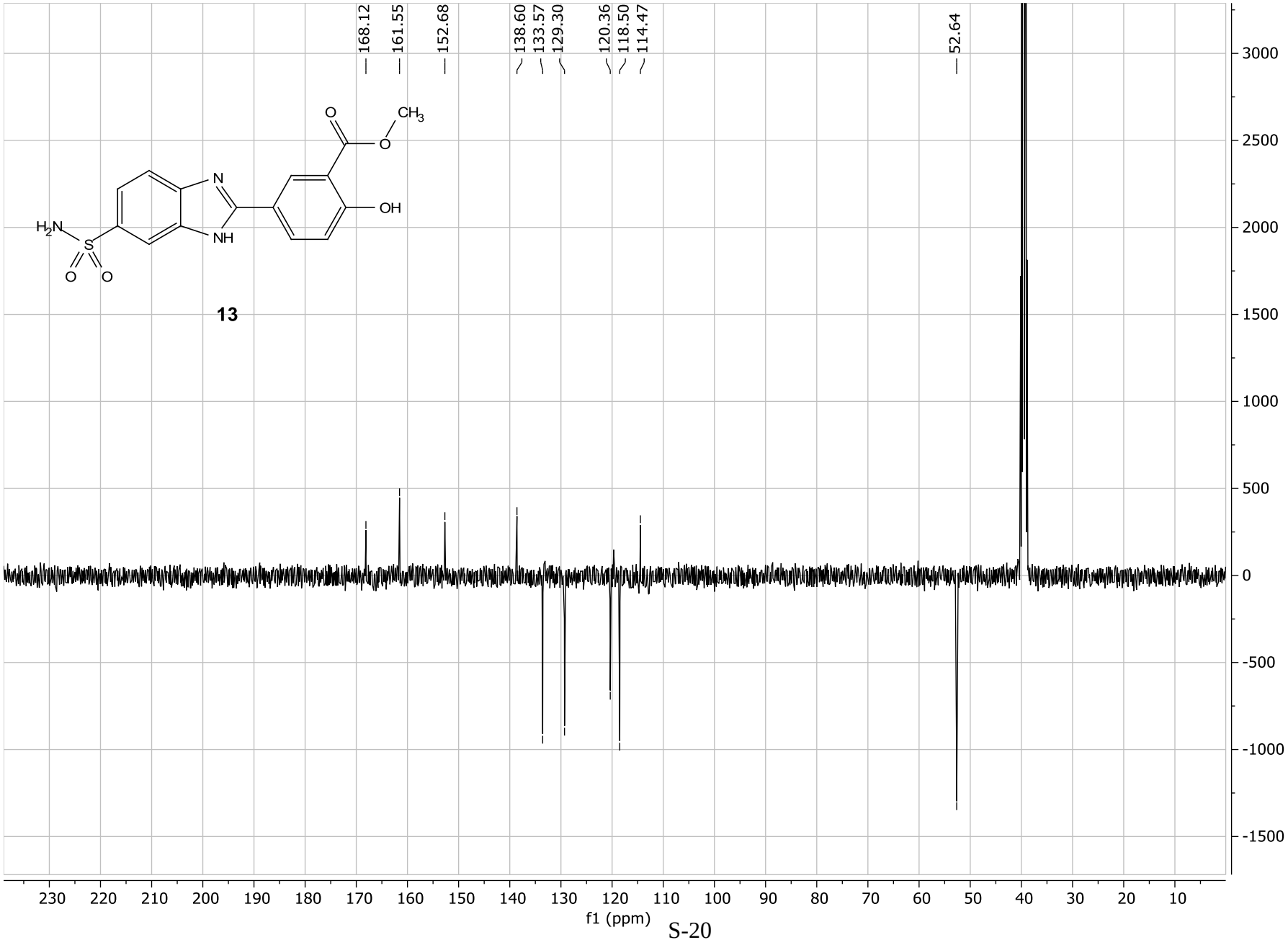
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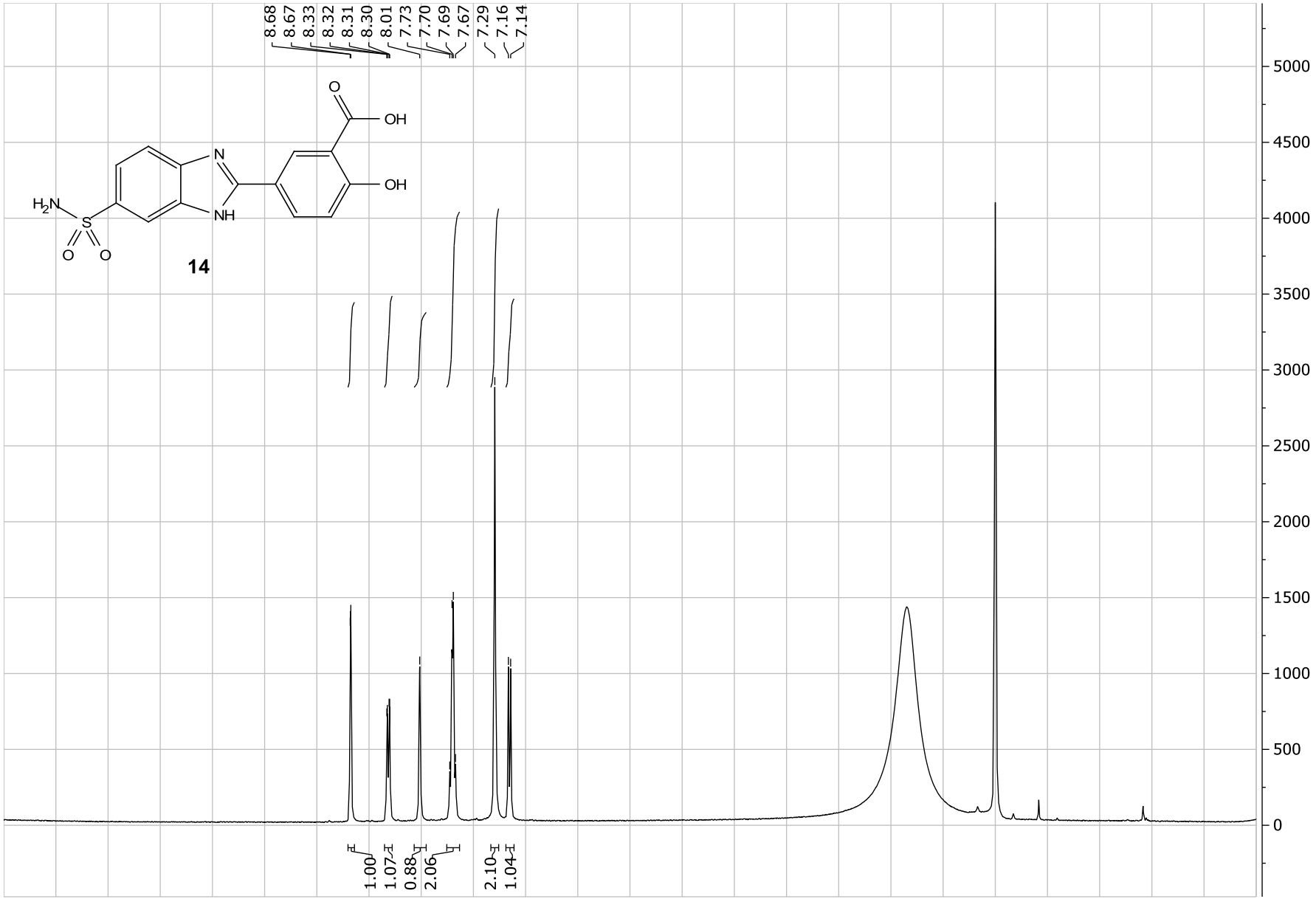
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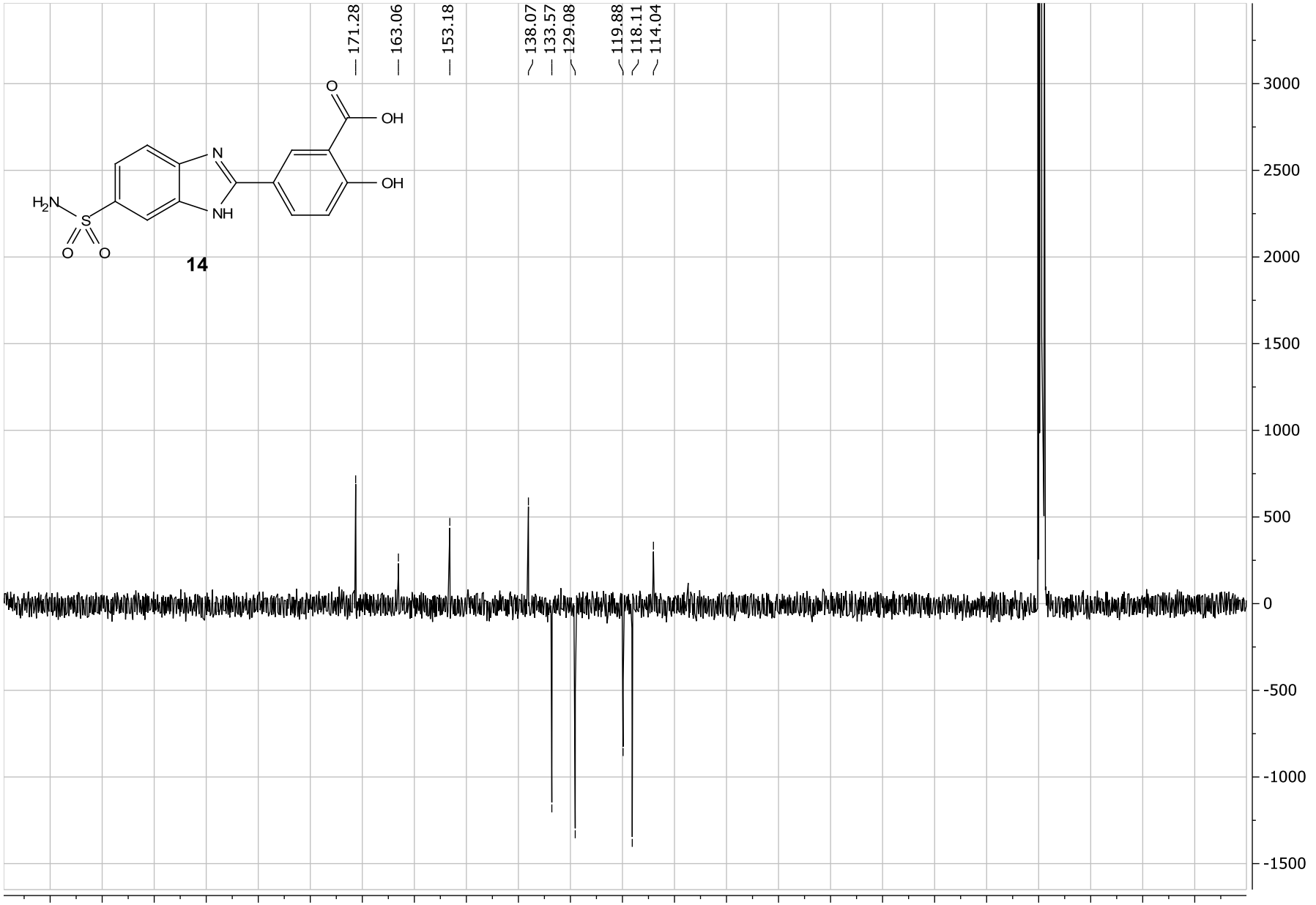
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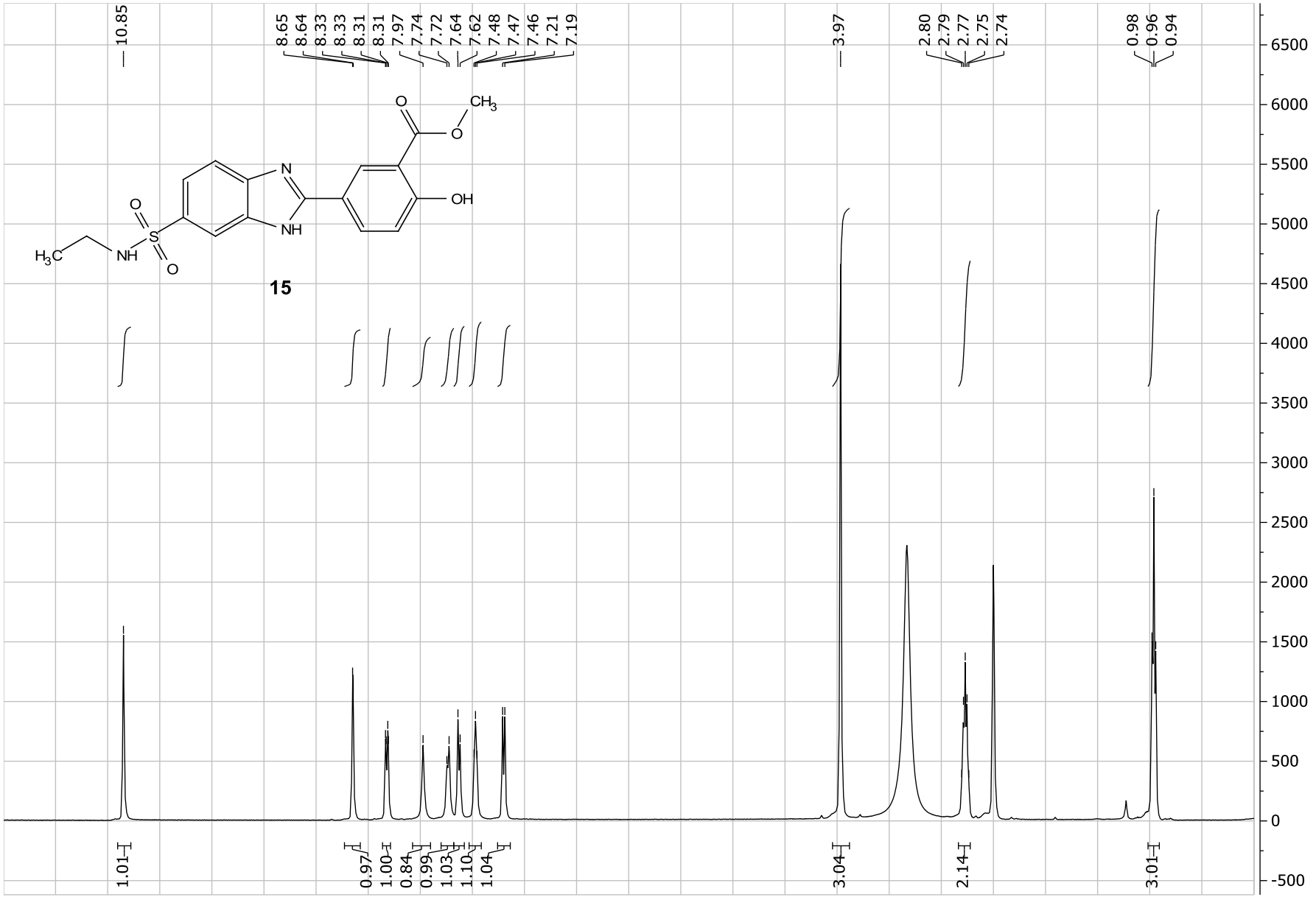
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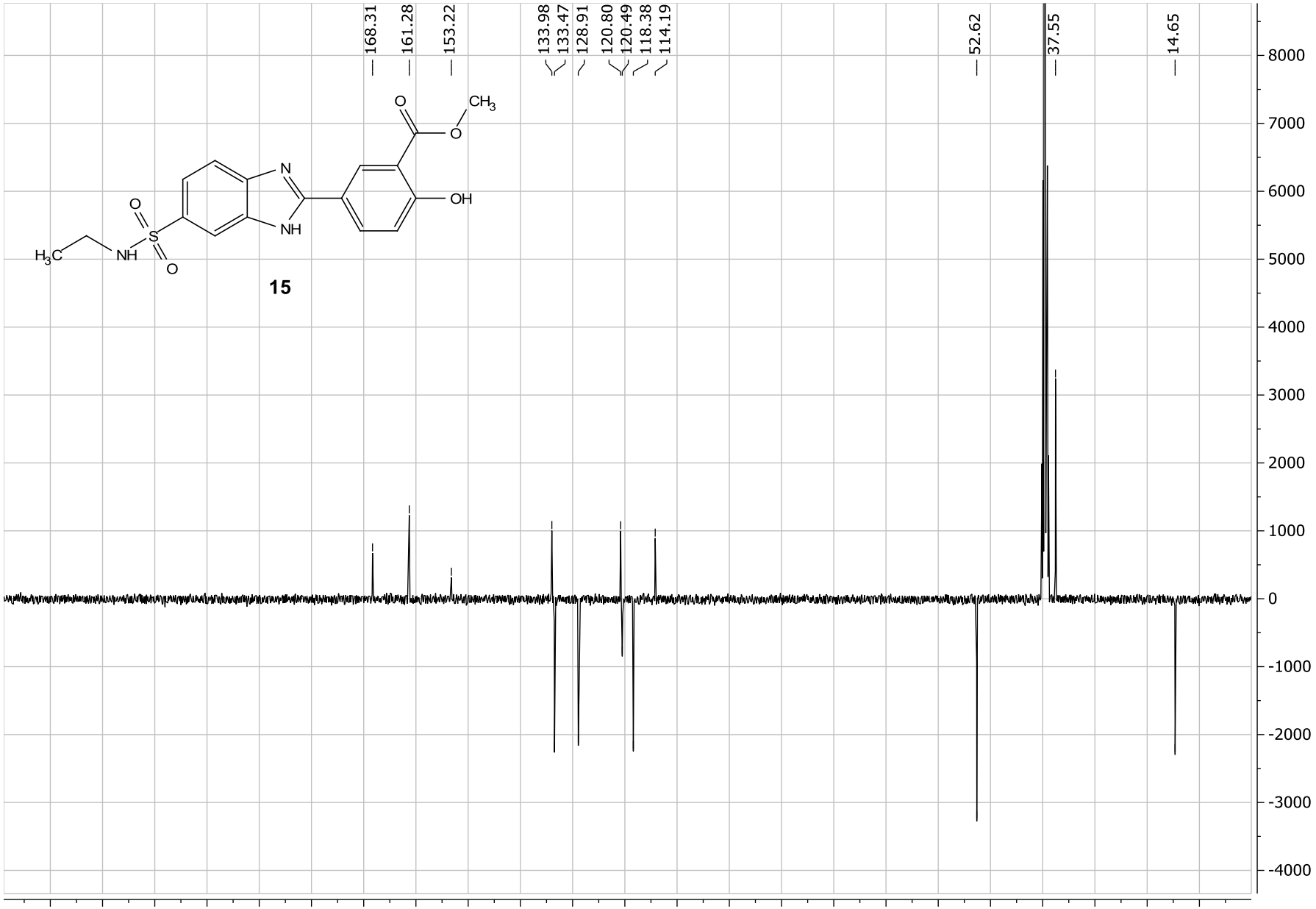
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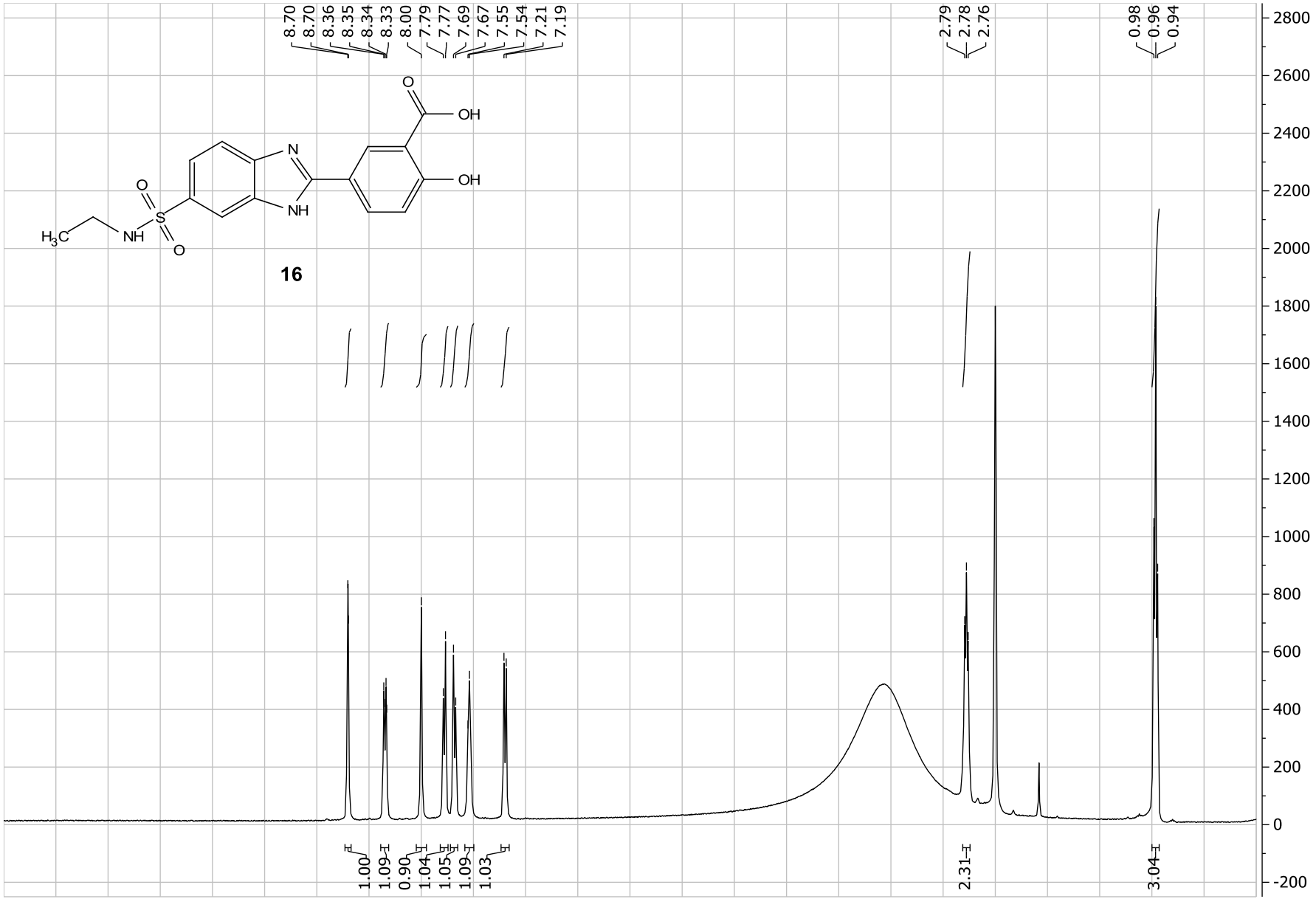
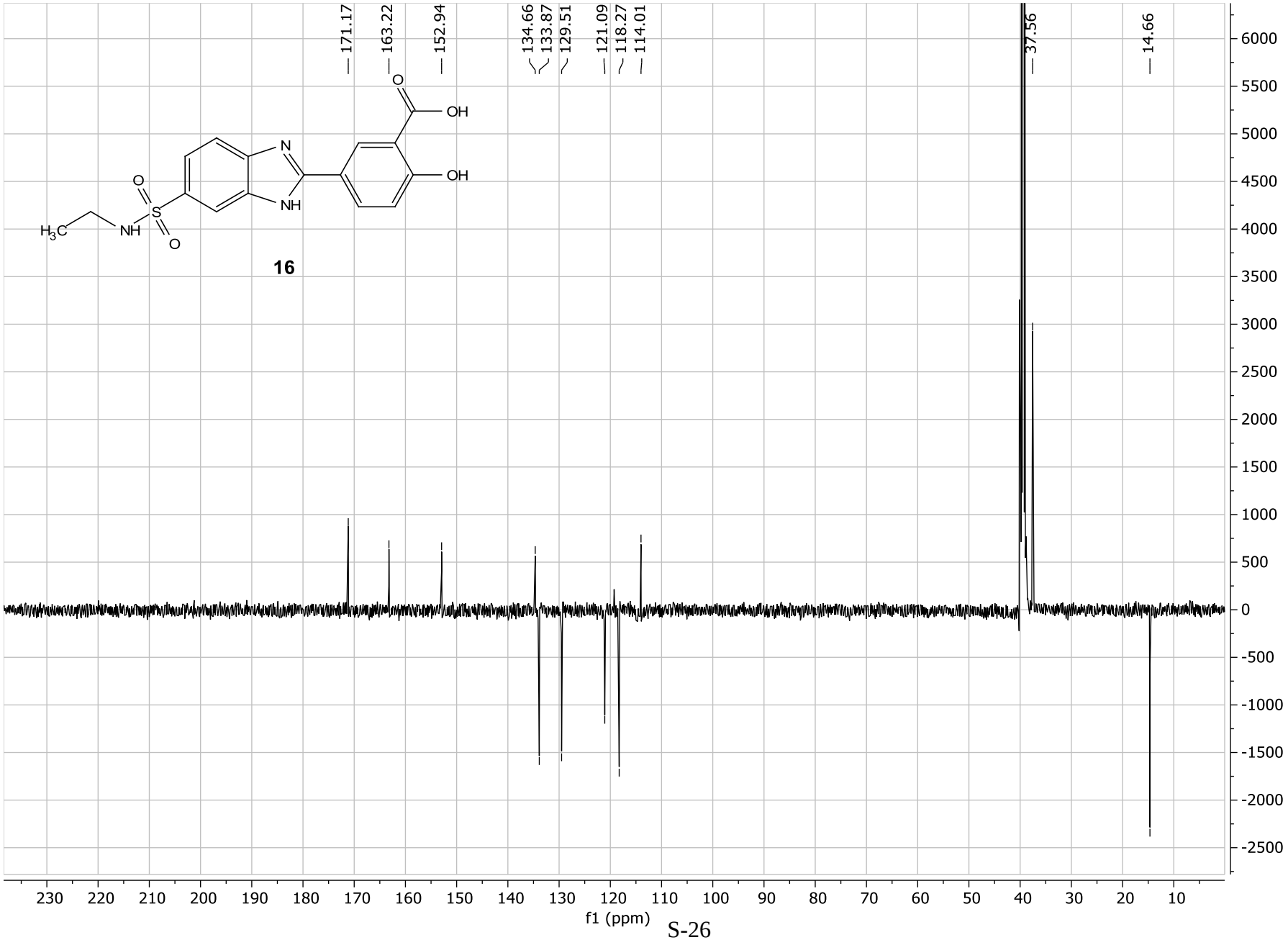
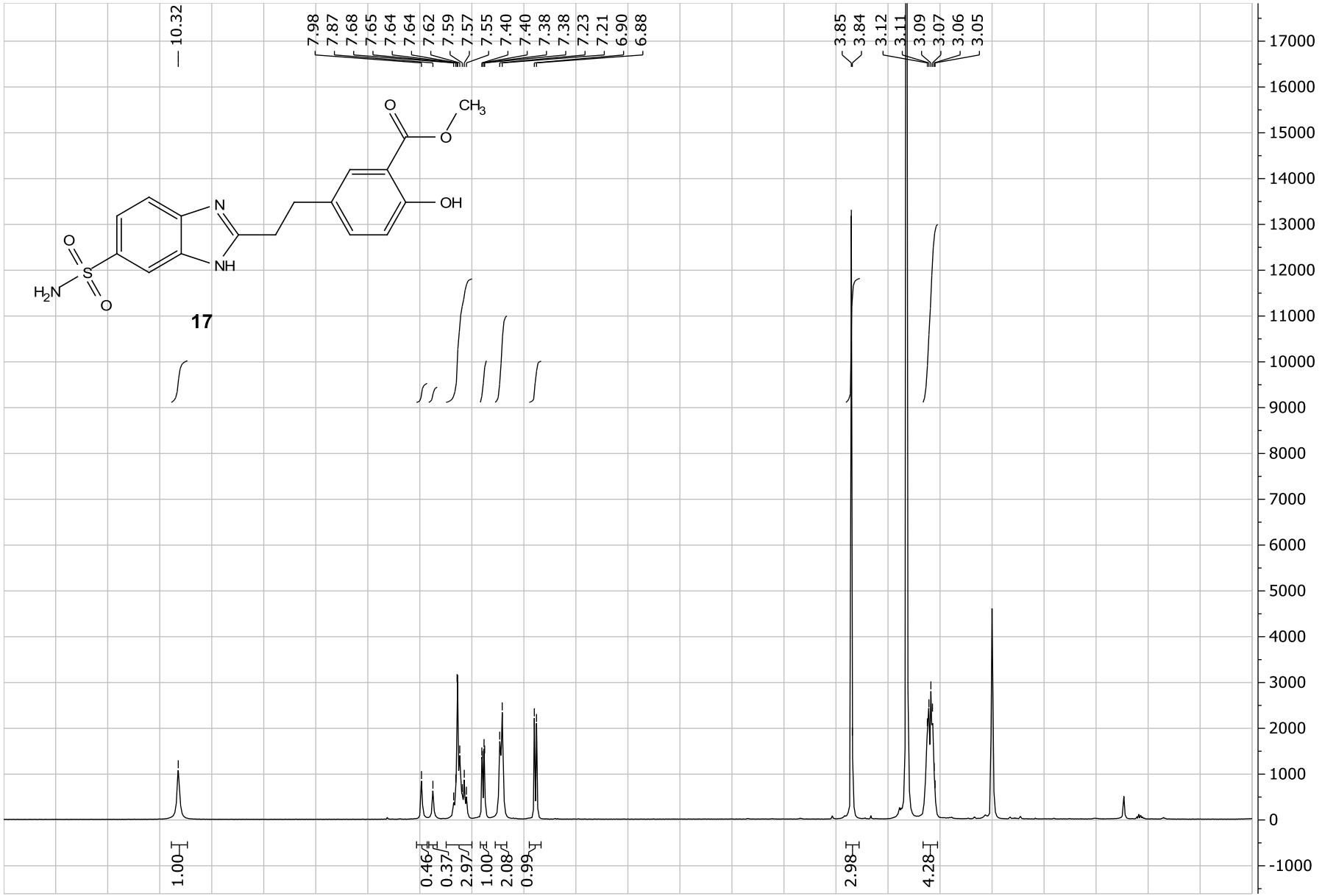
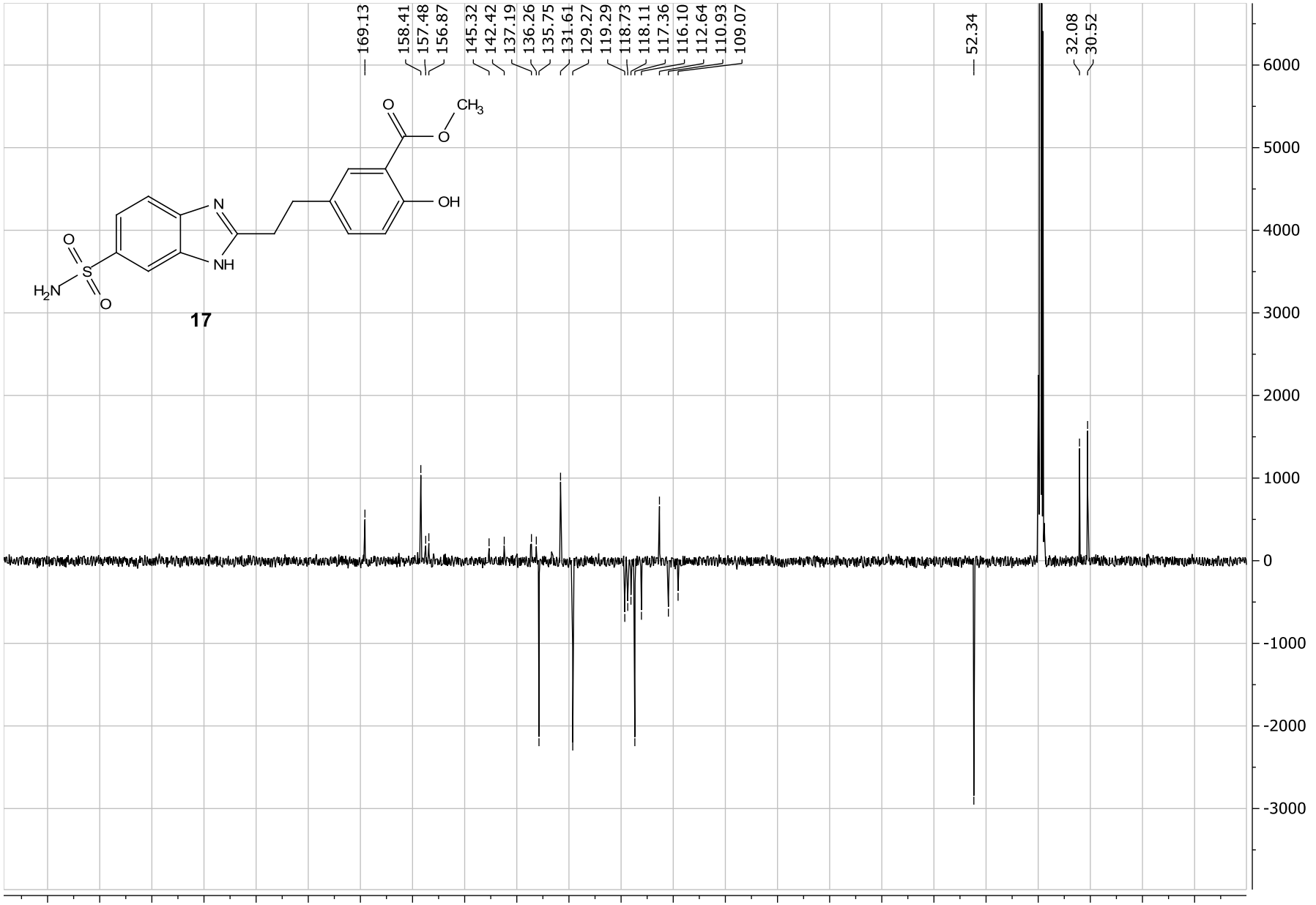
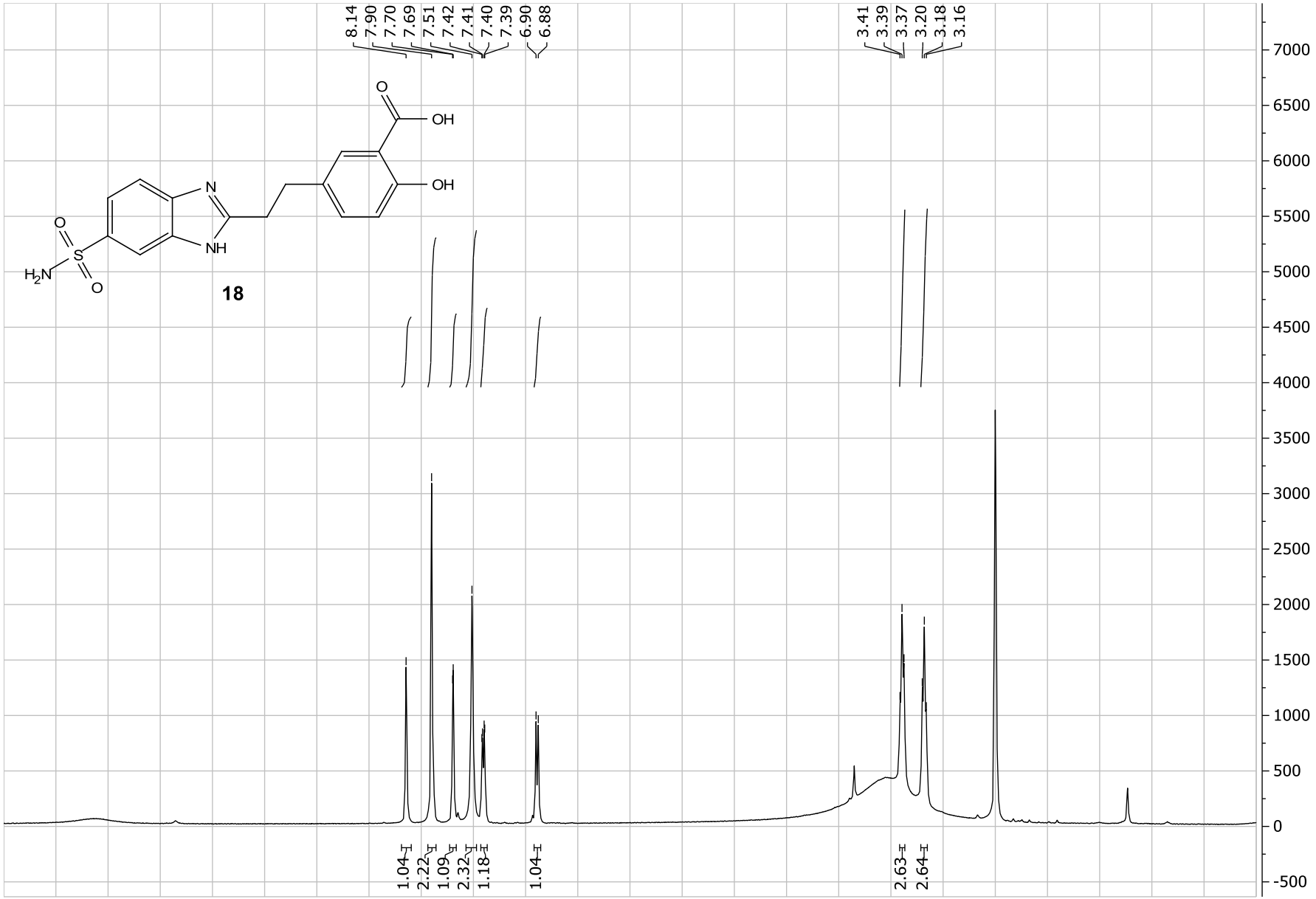
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

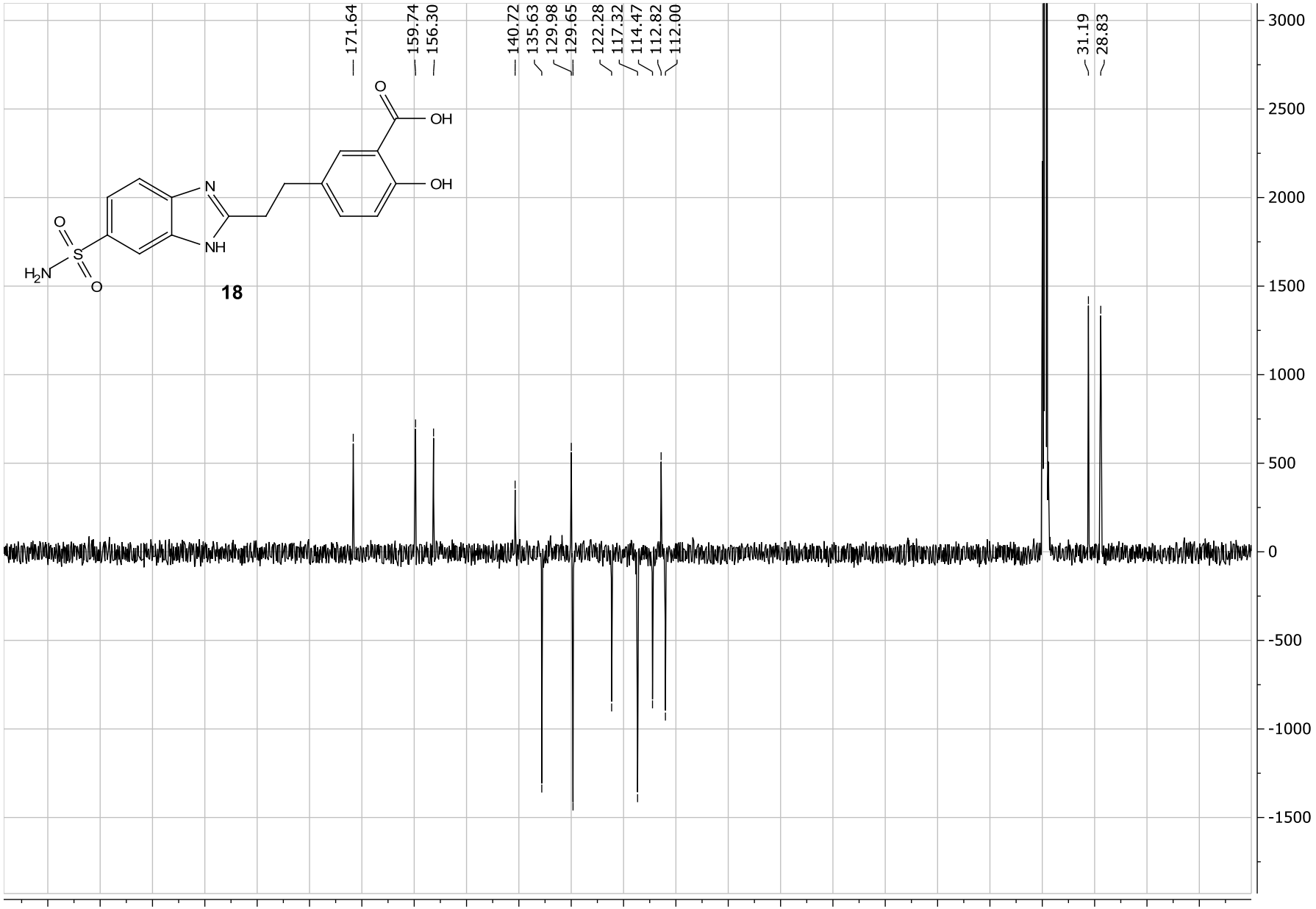

8.70
8.70
8.36
8.35
8.34
8.33
8.00
7.79
7.77
7.69
7.67
7.55
7.54
7.21
7.19
2.79
2.78
2.76
0.98
0.96
0.94
O
OH
OH
N
NH
O
S
O
NH
H3C
16
1.00
1.09
0.90
1.04
1.05
1.09
1.03
2.31
3.04
f1 (ppm)

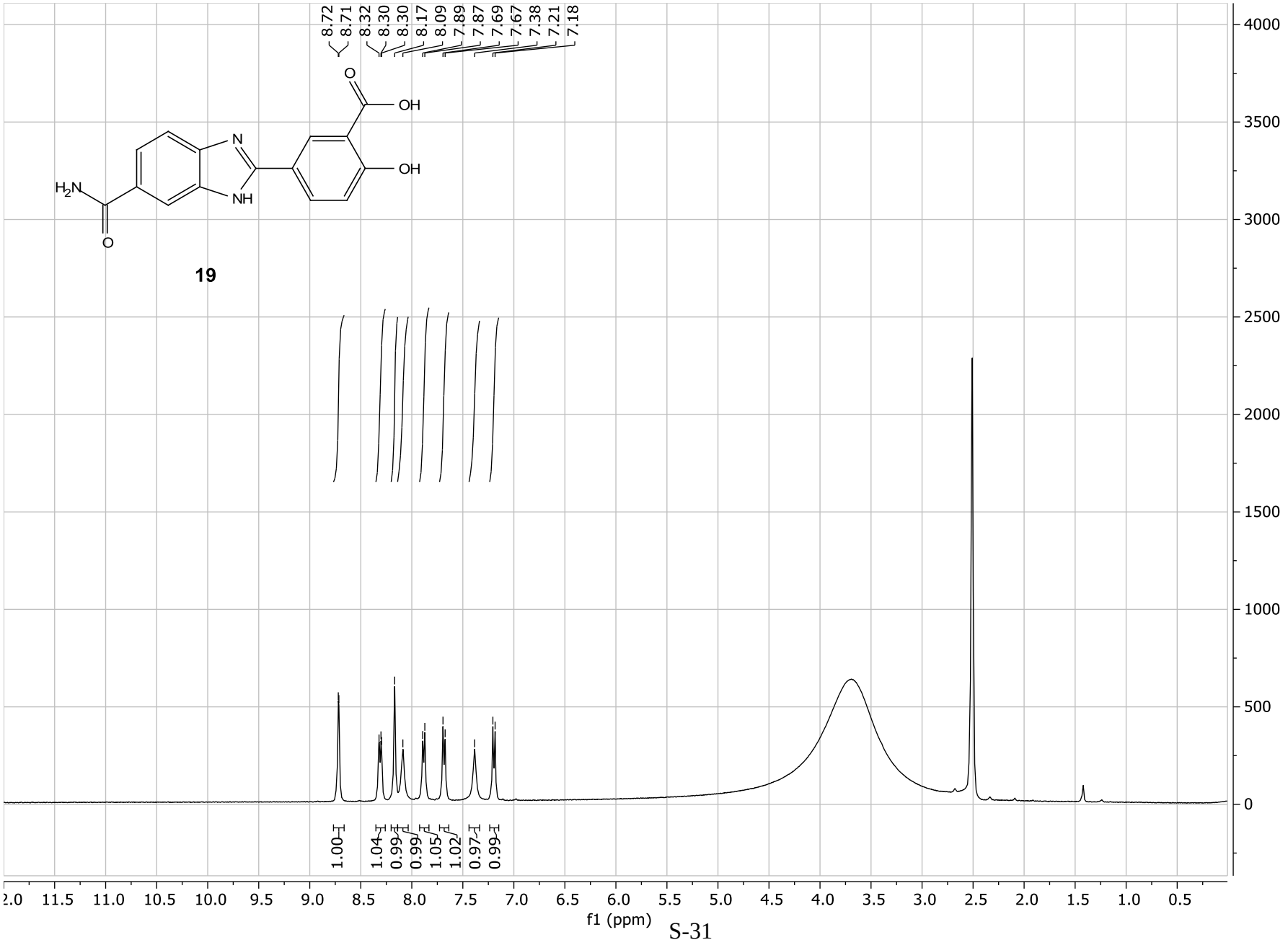

171.17
163.22
152.94
134.66
133.87
129.51
121.09
118.27
114.01
37.56
14.66
OH
OH
O
N
NH
S
NH
H_3C
16
f1 (ppm)

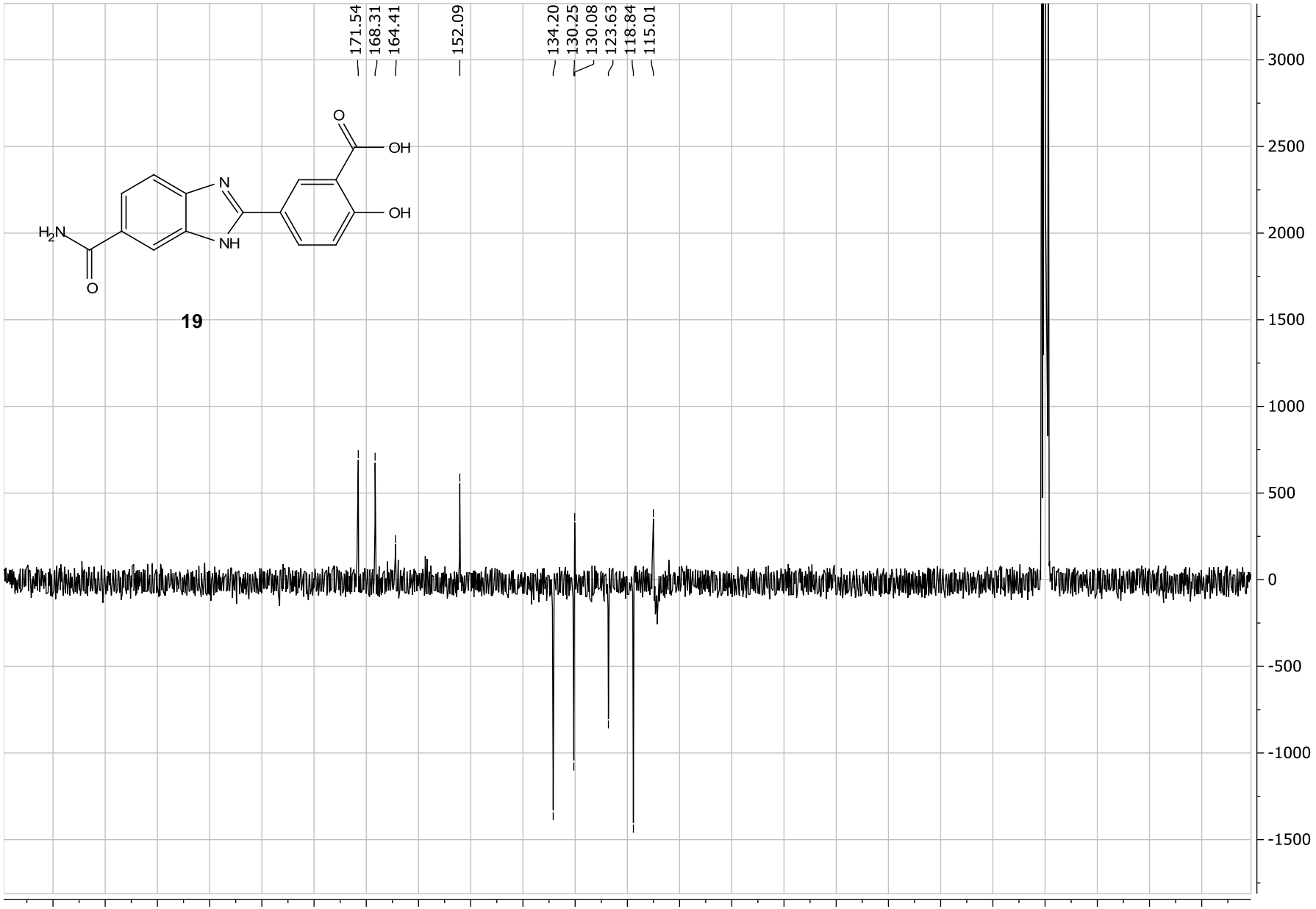

10.32
7.98
7.87
7.68
7.65
7.64
7.64
7.62
7.59
7.57
7.55
7.40
7.40
7.38
7.38
7.23
7.21
6.90
6.88
3.85
3.84
3.12
3.11
3.09
3.07
3.06
3.05
O
CH3
O
OH
N
NH
O
S
O
H2N
17
1.00
0.46
0.37
2.97
1.00
2.08
0.99
2.98
4.28
f1 (ppm)


169.13
158.41
157.48
156.87
145.32
142.42
137.19
136.26
135.75
131.61
129.27
119.29
118.73
118.11
117.36
116.10
112.64
110.93
109.07
52.34
32.08
30.52
O
CH3
O
OH
N
NH
O
S
O
H2N
17
6000
5000
4000
3000
2000
1000
0
-1000
-2000
-3000
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


8.14
7.90
7.70
7.69
7.51
7.42
7.41
7.40
7.39
6.90
6.88
3.41
3.39
3.37
3.20
3.18
3.16
O
OH
OH
N
NH
O
S
O
H2N
18
1.04
2.22
1.09
2.32
1.18
1.04
2.63
2.64
f1 (ppm)


171.64
159.74
156.30
140.72
135.63
129.98
129.65
122.28
117.32
114.47
112.82
112.00
31.19
28.83
OH
OH
O
N
NH
S
O
O
H2N
18
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


8.72
8.71
8.32
8.30
8.30
8.17
8.09
7.89
7.87
7.69
7.67
7.38
7.21
7.18
O
OH
OH
N
NH
H2N
O
19
1.00
1.04
0.99
0.99
1.05
1.02
0.97
0.99
4000
3500
3000
2500
2000
1500
1000
500
0
2.0
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
f1 (ppm)


171.54
168.31
164.41
152.09
134.20
130.25
130.08
123.63
118.84
115.01
O
OH
OH
N
NH
H2N
O
19
3000
2500
2000
1500
1000
500
0
-500
-1000
-1500
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)