Supporting Information

Turning Non-Selective Inhibitors of Type I Protein Arginine Methyltransferases into Potent and Selective Inhibitors of Protein Arginine Methyltransferase 4 through a Deconstruction-Reconstruction and Fragment Growing Approach

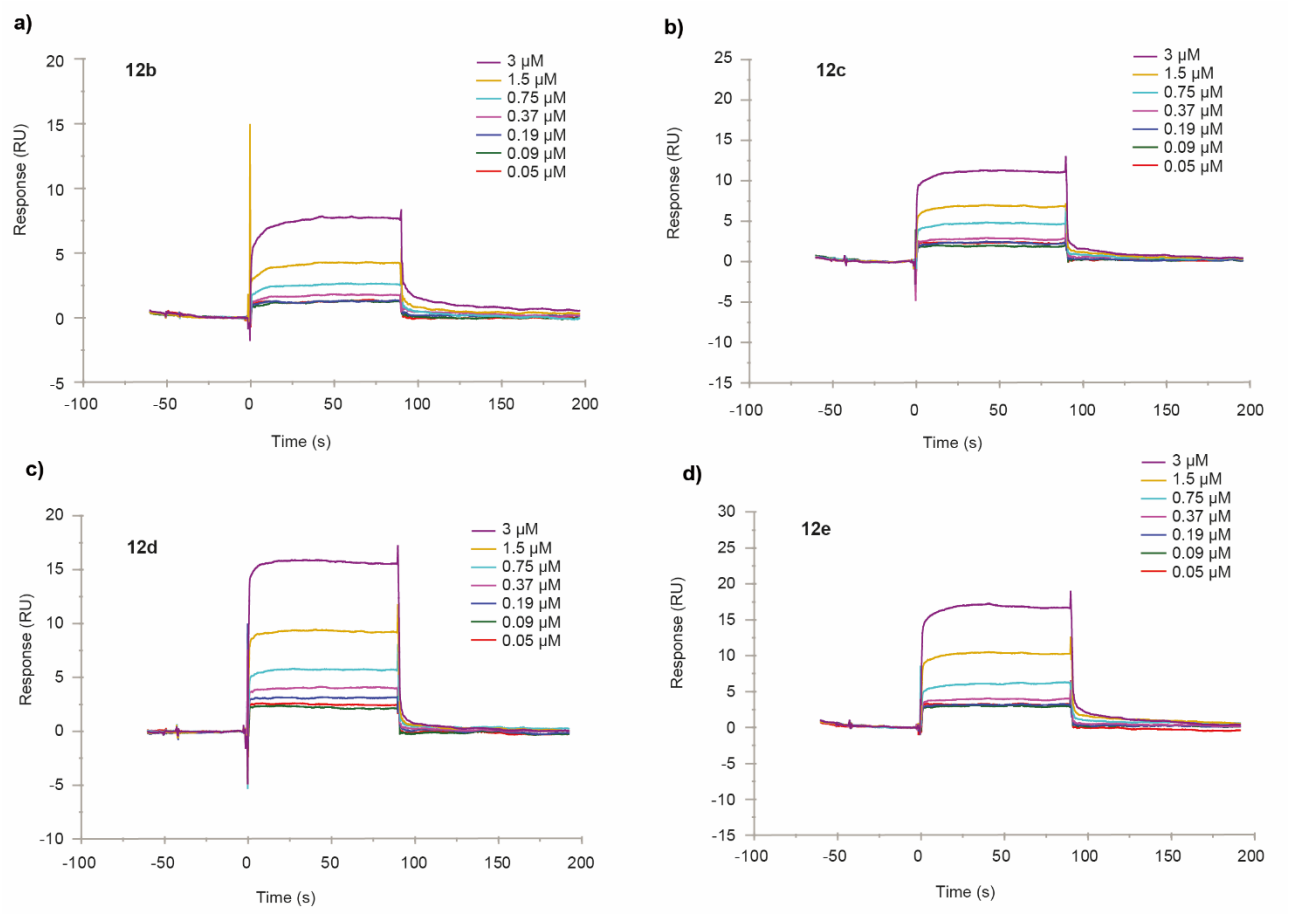
Giulia Iannelli,[‡,∫,‖] Ciro Milite,[‡,‖] Nils Marechal,[§] Vincent Cura,[§] Luc Bonnefond,[§] Nathalie-Troffer-Charlier,[§] Alessandra Feoli,[‡] Donatella Rescigno,[‡,†] Yalong Wang,[△] Alessandra Cipriano,[‡] Monica Viviano,[‡] Mark T. Bedford,[△] Jean Cavarelli,[,§] Sabrina Castellano,[*,‡] and Gianluca Sbardella[*,‡]*

[‡]Department of Pharmacy, Epigenetic Med Chem Lab, University of Salerno, via Giovanni Paolo II 132, I-84084 Fisciano (SA), Italy
[§] Department of Integrated Structural Biology, Institut de Génétique et de Biologie Moléculaire et Cellulaire, Illkirch, France; Centre National de la Recherche Scientifique, UMR7104, Illkirch, France; Institut National de la Santé et de la Recherche Médicale, U1258, Illkirch, France; Université de Strasbourg, Illkirch, France.
[∫]PhD Program in Drug Discovery and Development, University of Salerno, Via Giovanni Paolo II 132, I-84084 Fisciano (SA), Italy
[△] Department of Epigenetics and Molecular Carcinogenesis, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, United States

*J.C.: E-mail, cava@igbmc.fr; *S.C.: E-mail, scastellano@unisa.it; *G.S.: E-mail, gsbardella@unisa.it

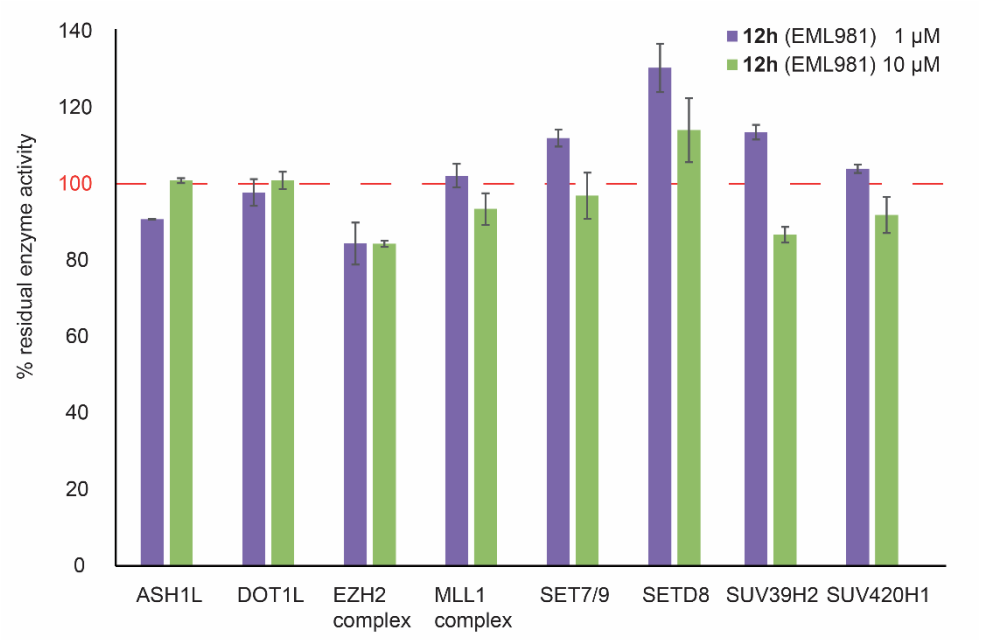
Table of Contents:

Figure S1. SPR interaction analysis of compounds **12b–e** binding to immobilized PRMT4**.**



Sensorgrams obtained from the SPR interaction analysis of compounds **12b–e** (panels a–d, respectively) binding to immobilized PRMT4. Each compound was injected at different concentrations (from 3 μM to 0.05 μM) with an association and a dissociation time of 90 sec, with a flow rate of 30 μL/min. The equilibrium dissociation constants (K_D) were derived from the ratio between kinetic dissociation (k_{off}) and association (k_{on}) constants.

Figure S2



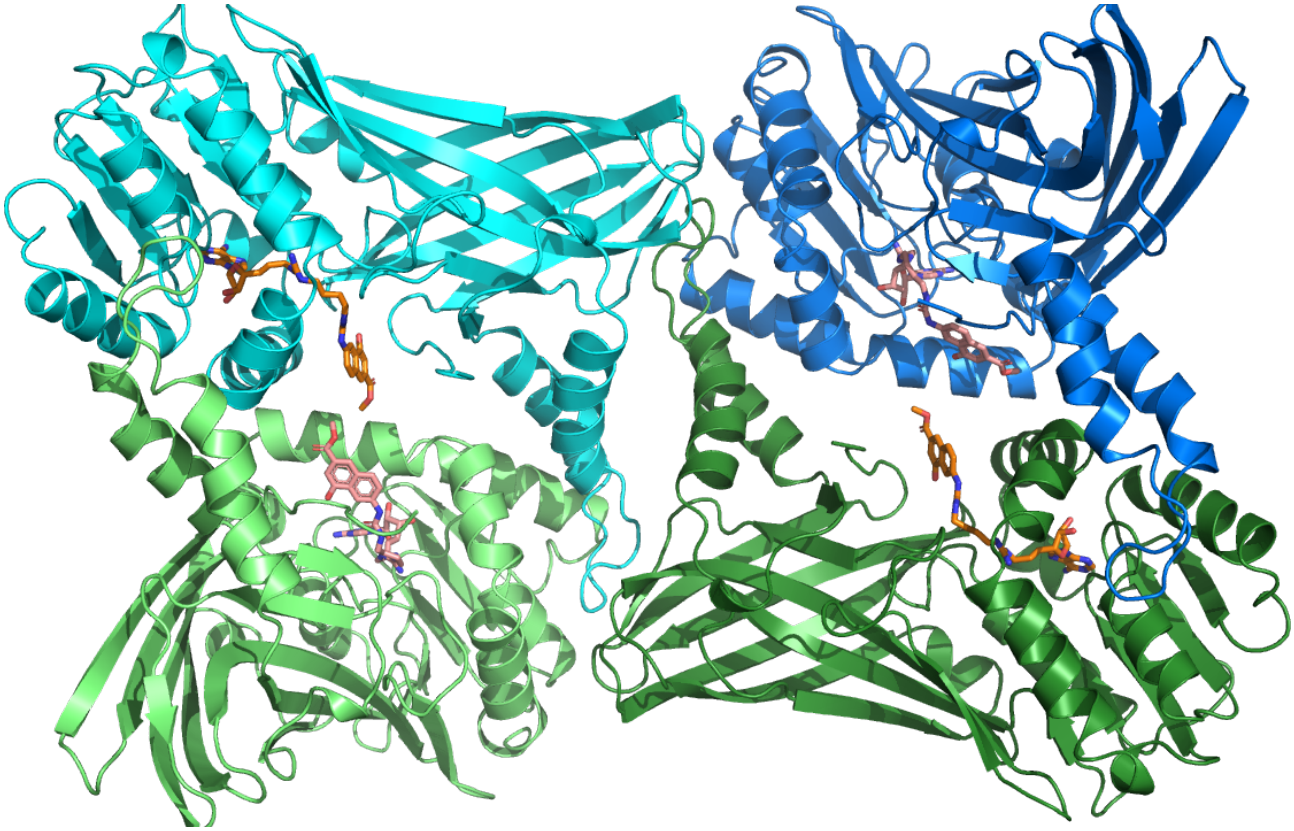
Inhibitory activity profiles of compound 12h towards ASH1L, DOT1L, EZH2, MLL1, SET7/9, SETD8, SUV39H2, and SUV420H1 at two different fixed concentrations (1 and 10 µM).

Table S1. Inhibitory activity values of compound **12h** against a panel of KMTs

	% enzyme residual activ. after treatment with 12h[a,b,]		**ref. cmpd. IC_{50}(µM)[b,c]**		
	1 µM	10 µM	SAH	chaet	ryuv
ASH1L	90.76±0.13	90.76±0.13	-	0.14	-
DOT1L	97.74±3.48	90.76±0.13	0.174	-	-
EZH2	84.39±5.51	90.76±0.13	18.8	-	-
G9a	101.54±1.67	90.76±0.13	1.19	-	-
MLL1	102.15±3.11	90.76±0.13	0.464	-	-
SET7/9	112.02±2.25	90.76±0.13	139	-	-
SETD8	130.39±6.36	90.76±0.13	-	-	0.186
SMYD3	72.83±0.68	90.76±0.13	18.7	-	-
SUV39H2	113.51±1.92	90.76±0.13	32.7	-	-
SUV420H1	104.00±1.13	90.76±0.13	46.5	-	-

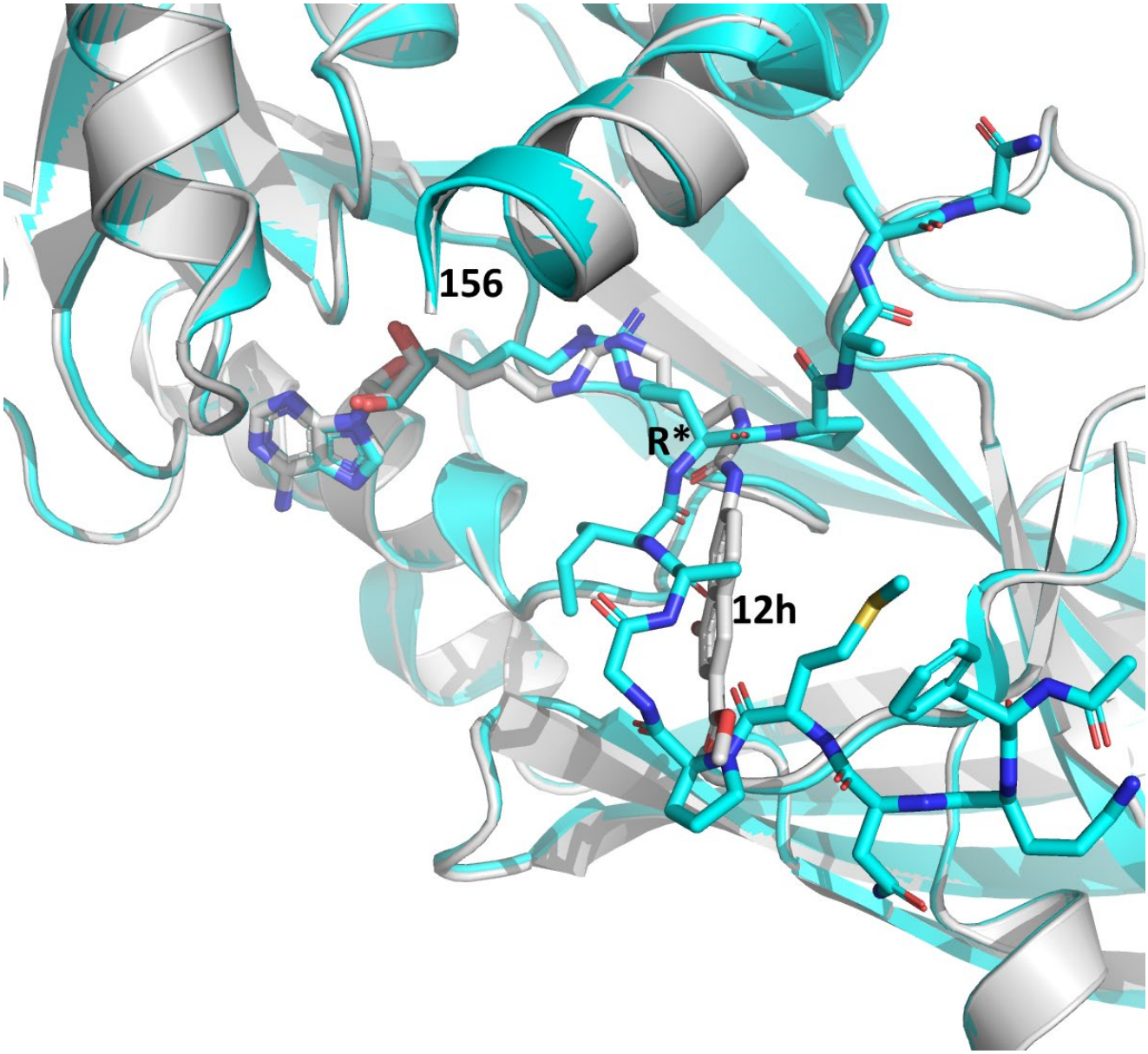
[a]Compounds were tested at 1 and 10 µM fixed concentrations; values obtained for each compound are mean ± SD determined for two separate experiments.in duplicate; [b]values were obtained in a radioisotope-based filter assay, using 0.05 mg/mL oligo nucleosomes (for ASH1L, MLL1 complex, SETD8, SUV420H1 and DOT1L), 0.05 mg/mL core histone (for EZH2 complex and SET7/9), or 5 µM histone H3 (for SUV39H2) as substrate and *S*-adenosyl-L-[methyl-^{3}H]methionine (1 µM) as methyl donor; [c]reference compounds were tested in 10-dose IC_{50} mode with 3-fold serial dilution starting at 100 µM; data were analyzed using Excel and GraphPad Prism 6.0 software (GraphPad Software Inc., San Diego, CA) for IC_{50} curve fits using sigmoidal dose *vs.* response - variable slope (four parameters) equations.

Figure S3.



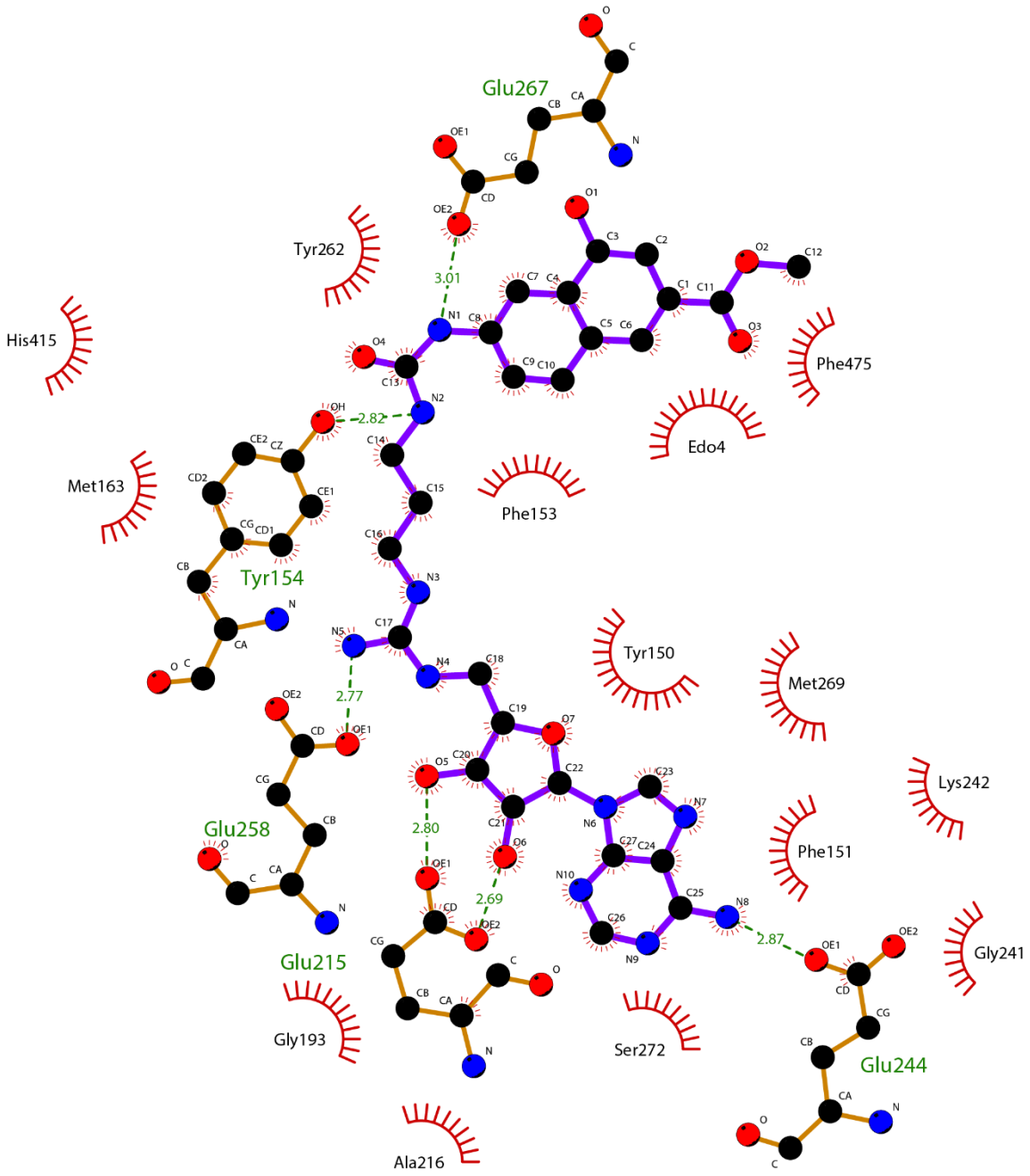
An overview of Tetramer of *mm*PRMT4 with compound **12h** (EML981) bound (PDB ID 7PUC). PRMT4 monomers within tetramer (dodger blue, cyan, light green, sea green) are represented as a cartoon. Compound **12h** (EML981) is represented as orange sticks. PRMT4 crystallized in the space group $P2_12_12$ which contains one copy of the PRMT4 tetramer in the asymmetric unit.

Figure S4.



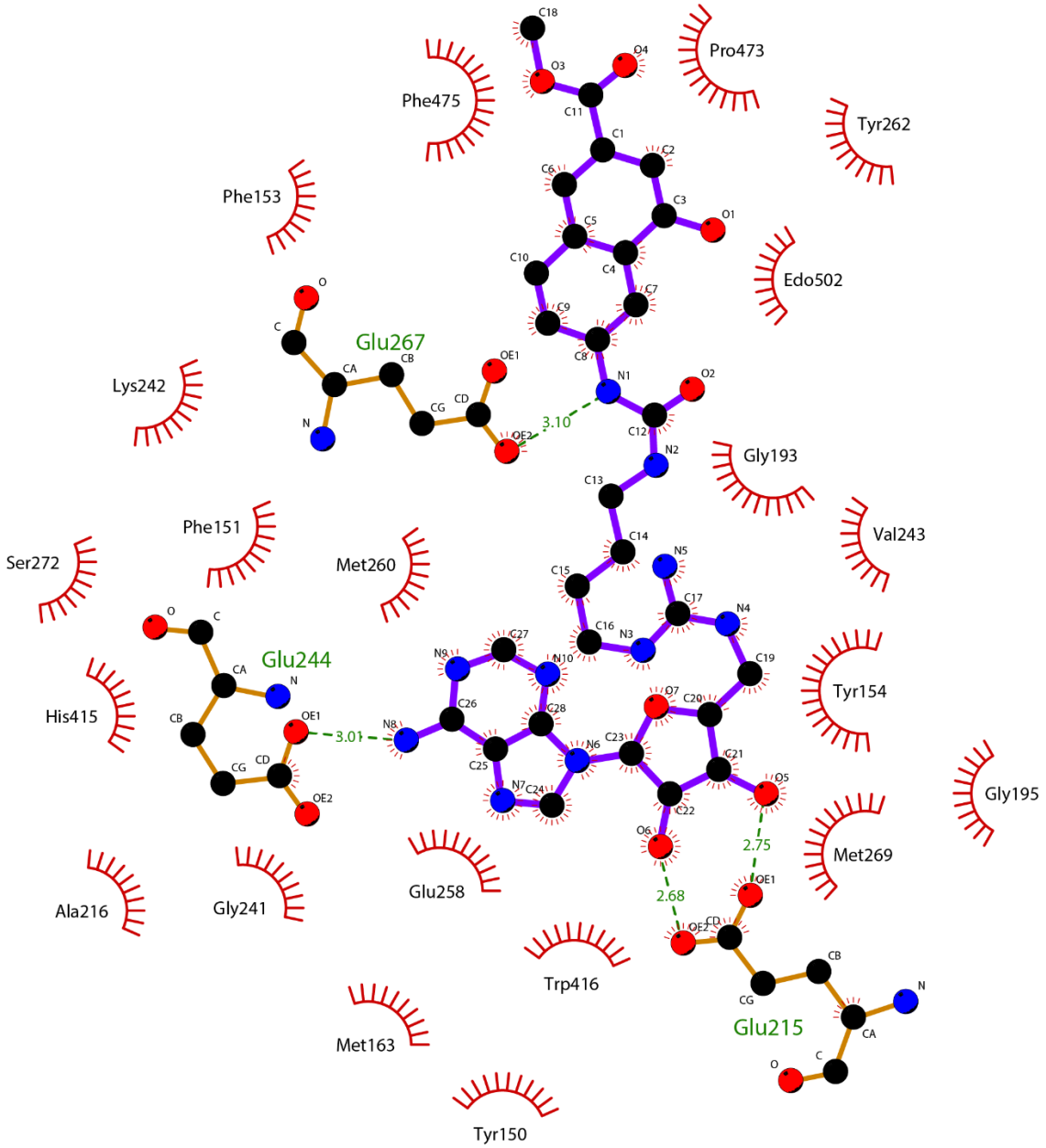
Superimposition of compound **12h** (grey sticks) bound to *mm*PRMT4 (represented as grey cartoon, PDB ID 7PUC) with a transition state mimic (cyan sticks) bound to *mm*PRMT4 (cyan cartoon, PDB ID 5LGP). R* represent the mimic of the arginine to be methylated. Superimposition is done on protein backbones. For clarity, the N-terminal helices of mmCARM1 are not shown.

Figure S5.



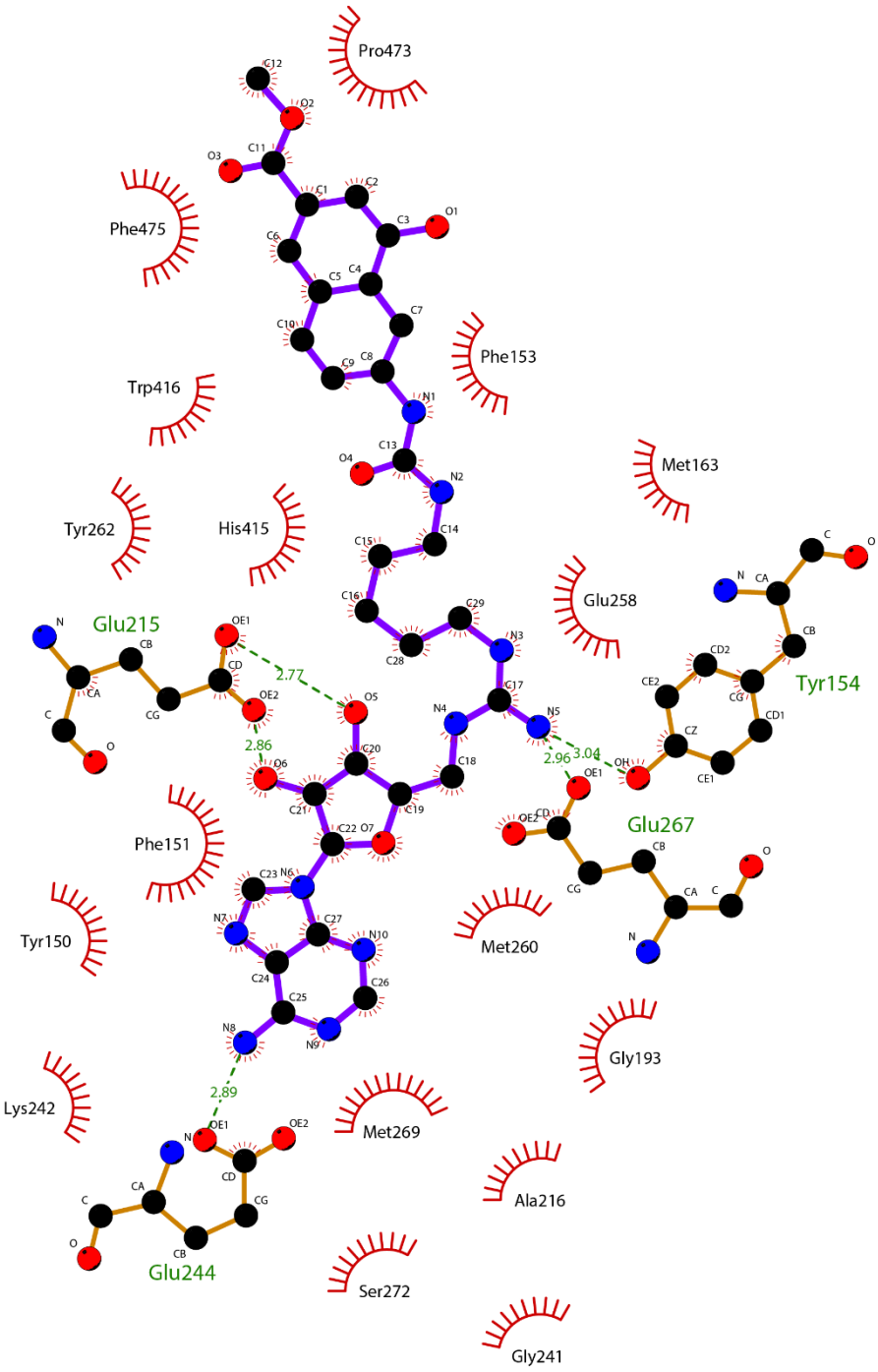
Flat representation done with LigPlot+ showing contacts between compound **12a** (EML734) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S6.



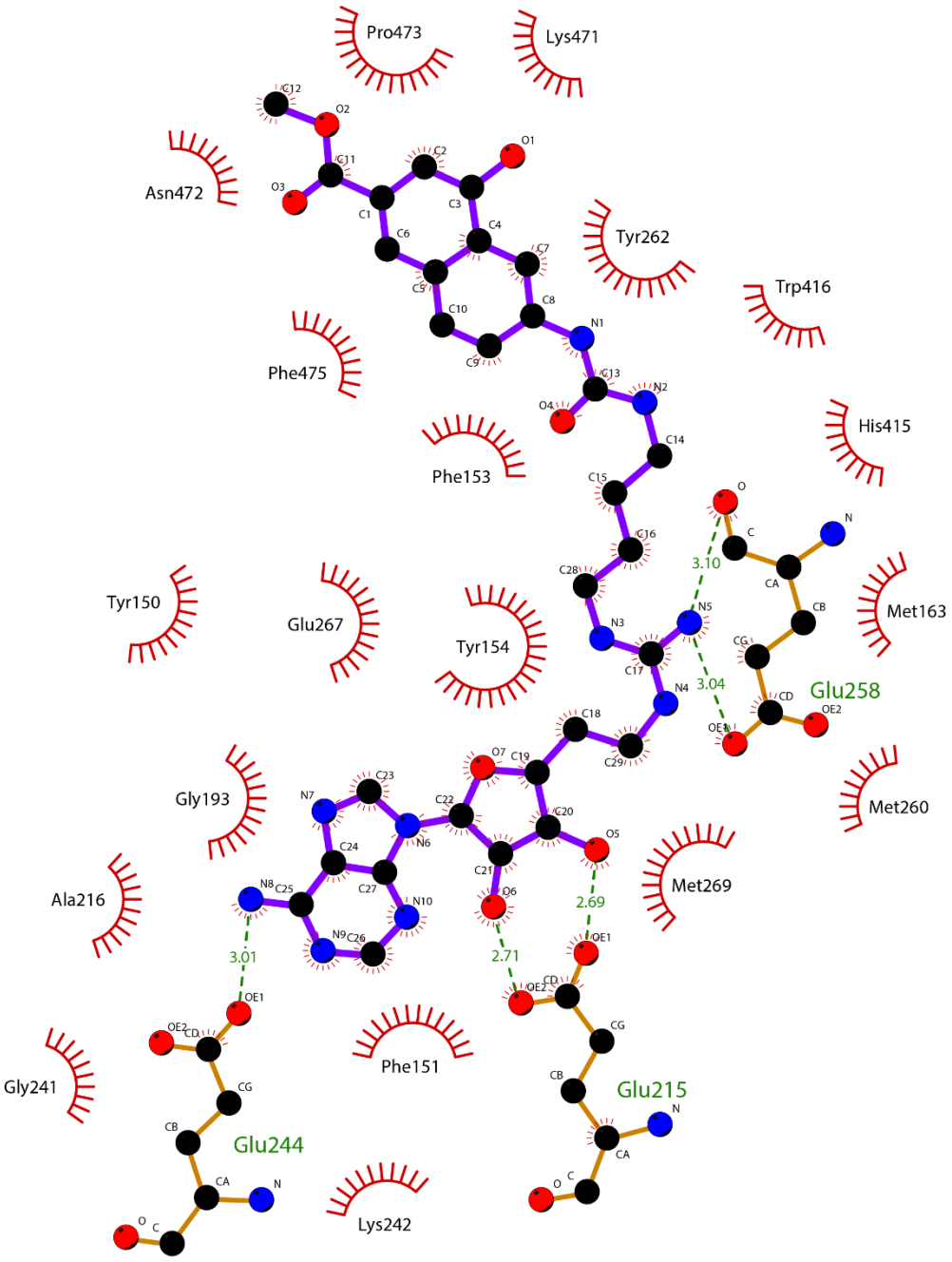
Flat representation done with LigPlot+ showing contacts between compound **12b** (EML709) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S7.



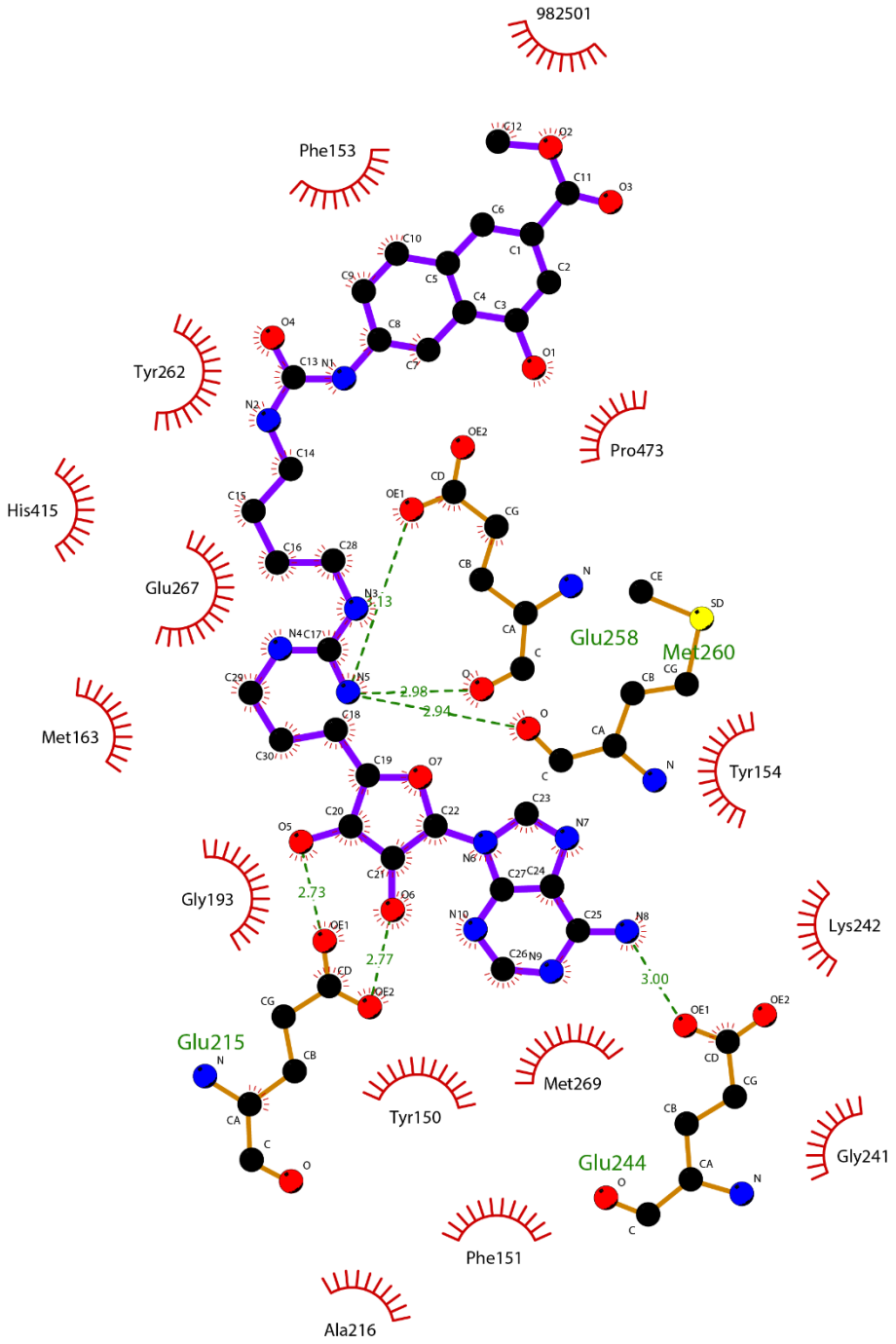
Flat representation done with LigPlot+ showing contacts between compound **12c** (EML736) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S8.



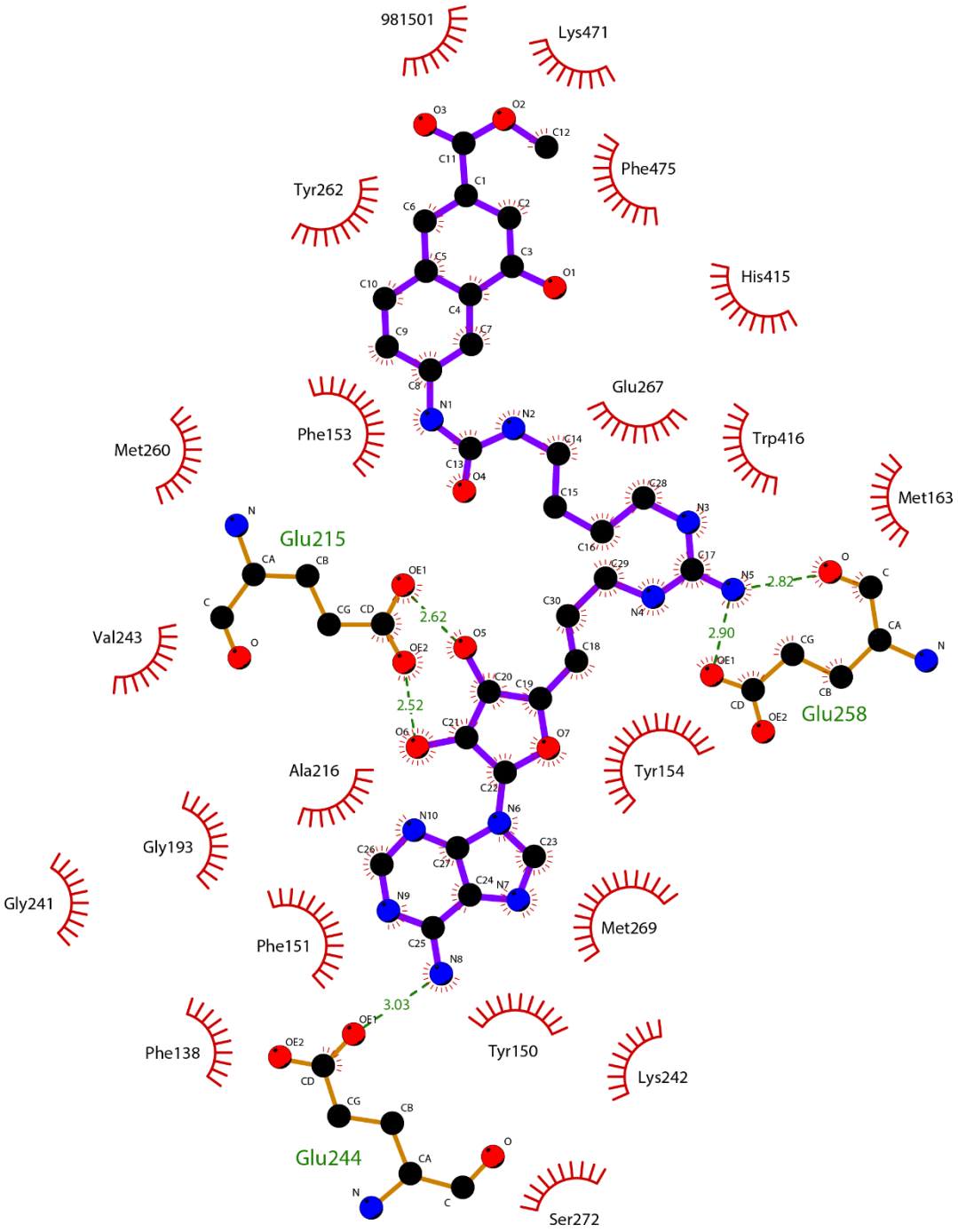
Flat representation done with LigPlot+ showing contacts between compound **12f** (EML980) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S9.



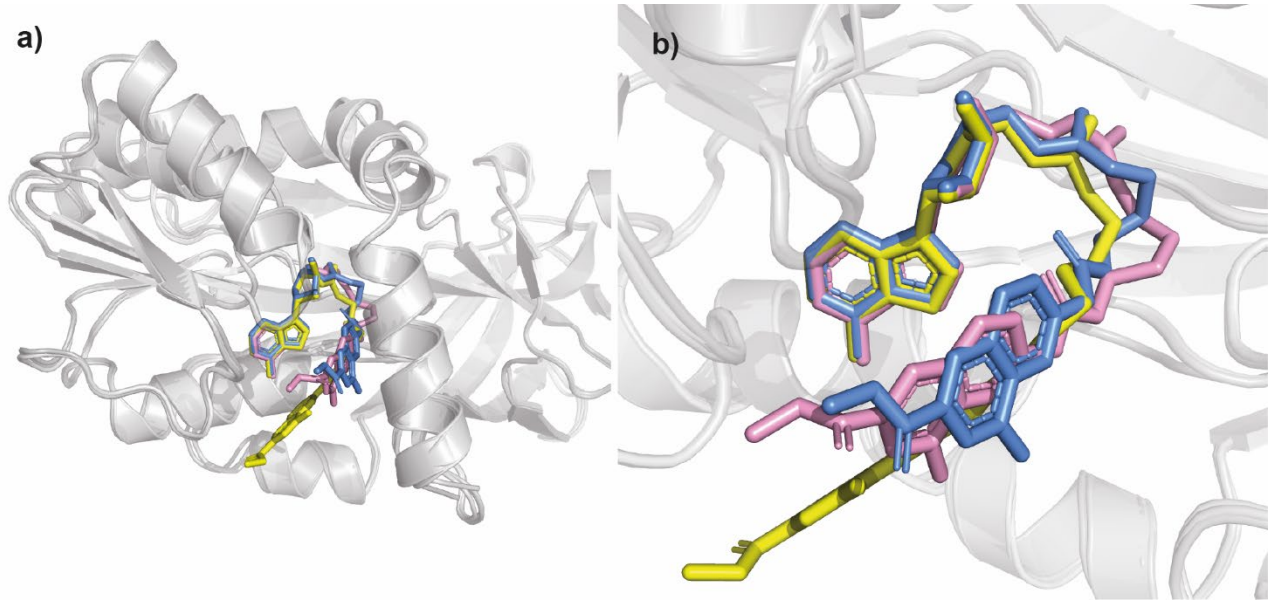
Flat representation done with LigPlot+ showing contacts between compound **12g** (EML982) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S10.



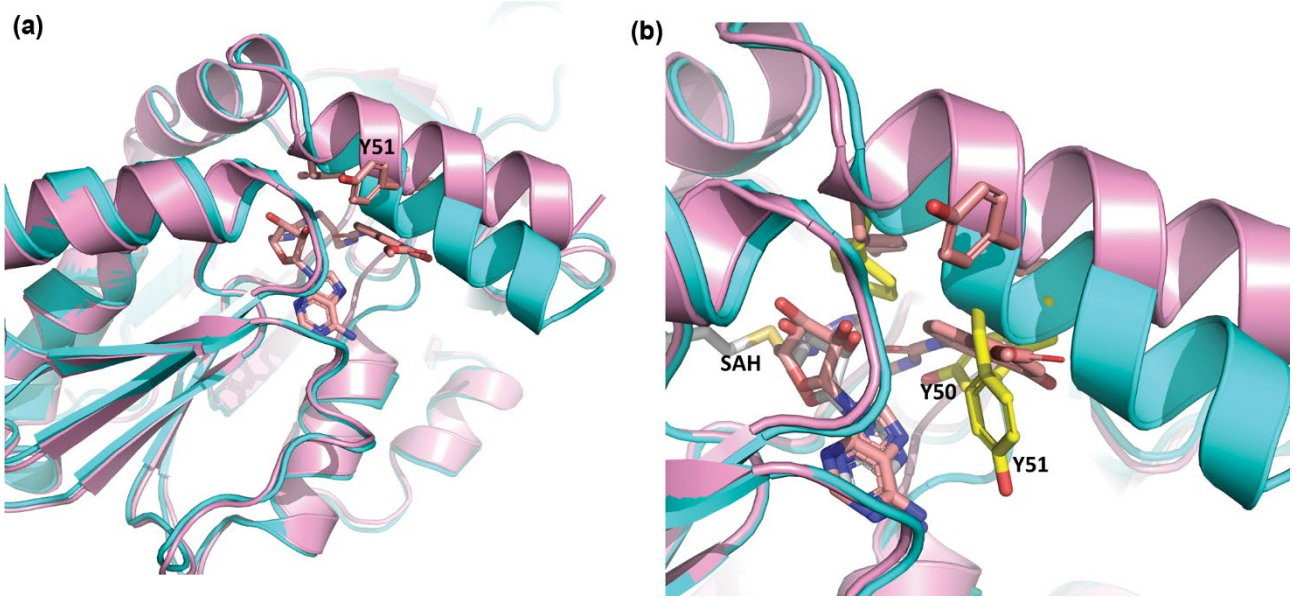
Flat representation done with LigPlot+ showing contacts between compound **12h** (EML981) and active site residues in PRMT4 (subunit B). Hydrogen bonds are shown as dotted lines. The spoked arcs represent protein residues making non-bonded (hydrophobic) contacts with compounds.

Figure S11.



Structures of the complexes of PRMT6 and compounds **12a**, **12c**, and **12f** (PDB ID 7NUD, 7NUE, 7P2R, respectively). (a) Superimposition of compound **12a** (cornflower blue sticks) bound to subunit A of *mm*PRMT6, compound **12c** (yellow sticks) bound to subunit A of *mm*PRMT6, compound **12f** (pink sticks) bound to subunit A of *mm*PRMT6. Superimposition is done on protein backbones. Protein subunits are shown as cartoons colored in different shades of grey; (b) close-up view of bound compound conformations. For clarity, the N-terminal helices of *mm*PRMT6 (residues 42–56) are not shown.

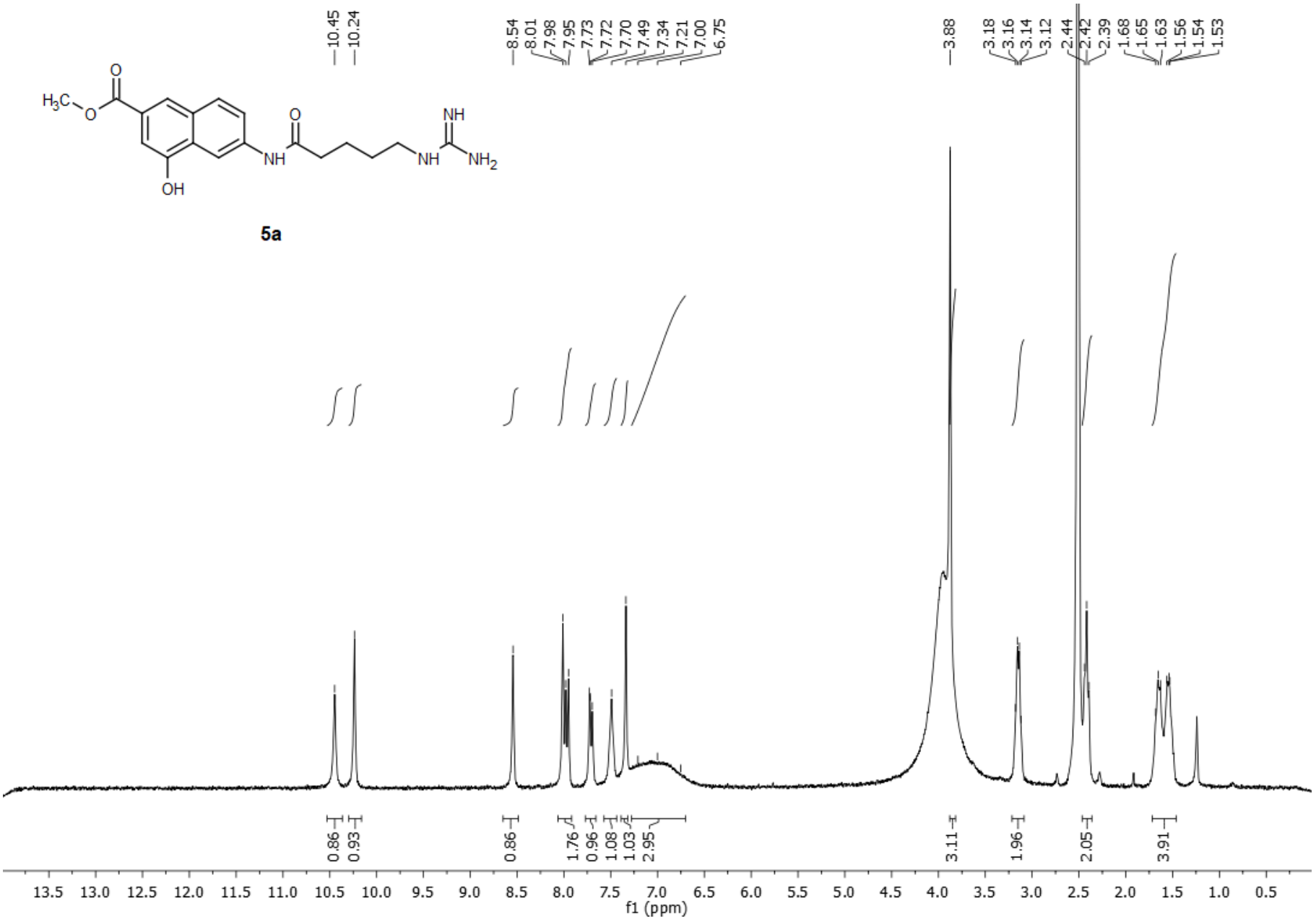
Figure S12.



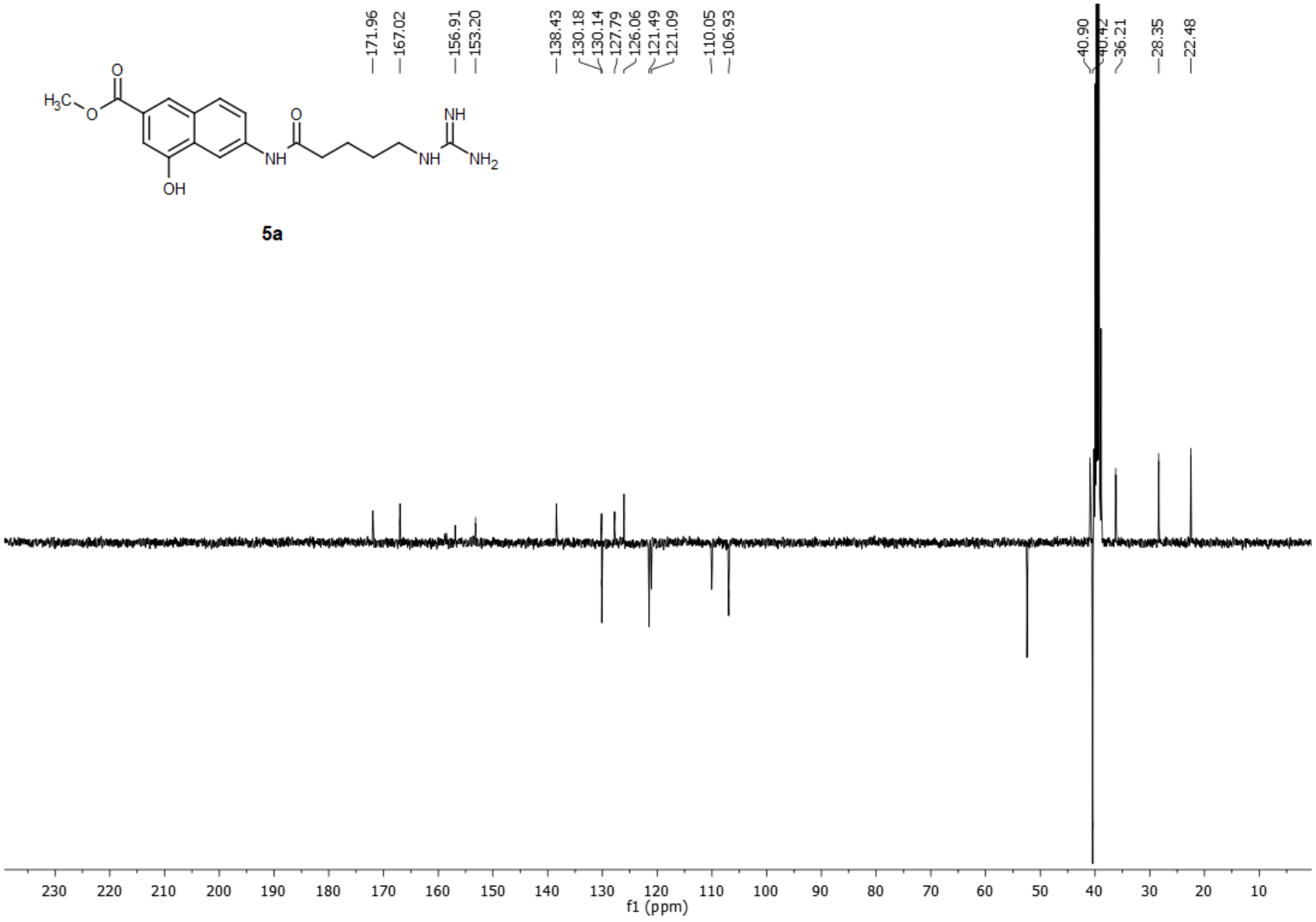
Conformational changes of PRMT6 alpha-X helix containing the motif I (Y50-Y51-X-X-Y54) (a) Superimposition of the structures of compound **12a** (EML734) bound to PRMT6 (pink cartoon, PDB ID 7NUD) and of the PRMT6/SAH complex (PDB ID 5FQN, cyan cartoon). Y51 of motif I and **12a** are shown as sticks. (B) Close-up view displaying also Y50, Y51 (yellow sticks) and SAH molecule (grey sticks) as seen in PRMT6/SAH structure.

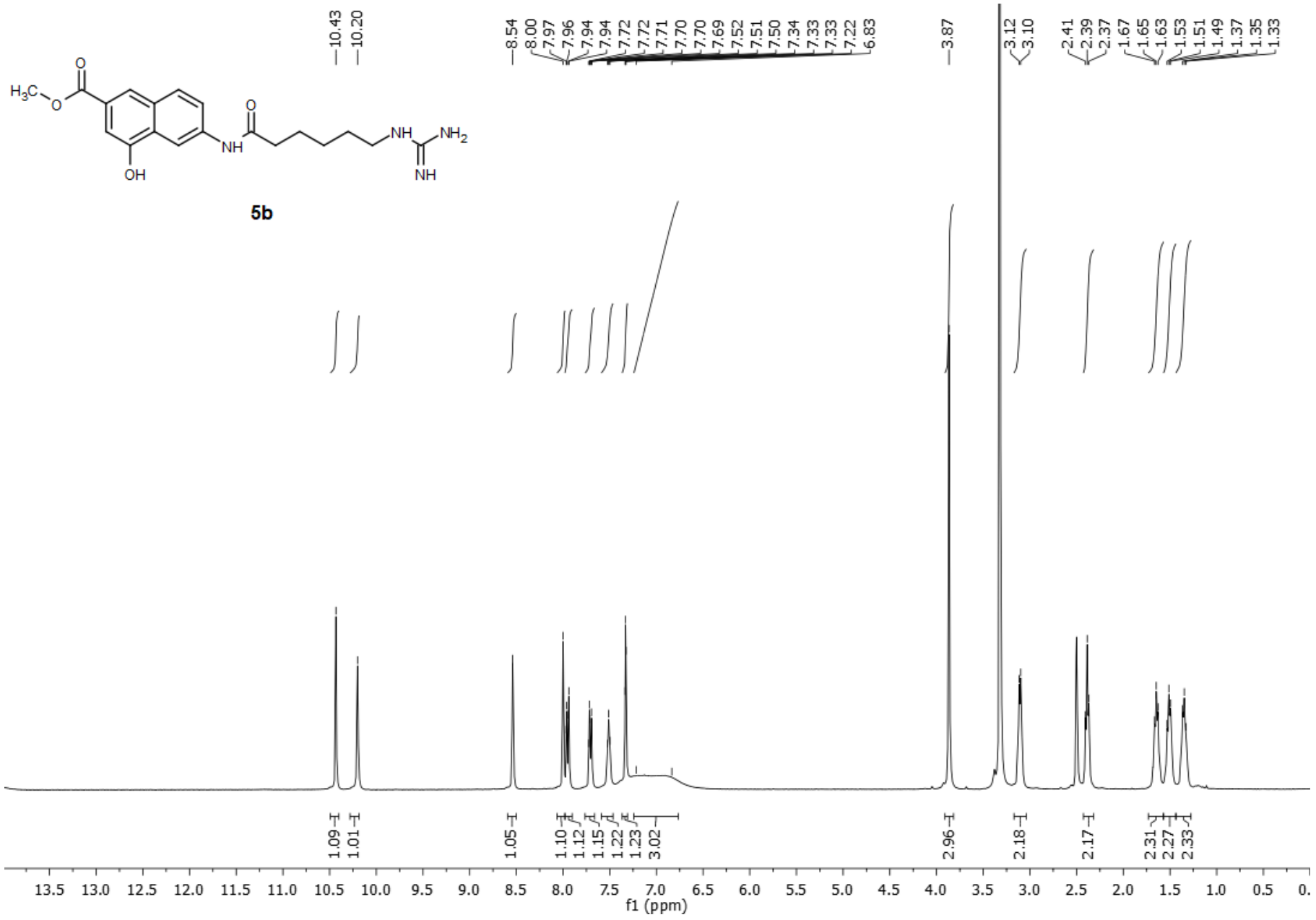
Table S2. Permeability values of compounds **12f–h**

#	PAMPA P_{app} (cm/s)
12f	0.55×10^{-7}
12g	0.39×10^{-7}
12h	0.38×10^{-7}
propranolol	60×10^{-7}
furosemide	0.34×10^{-7}

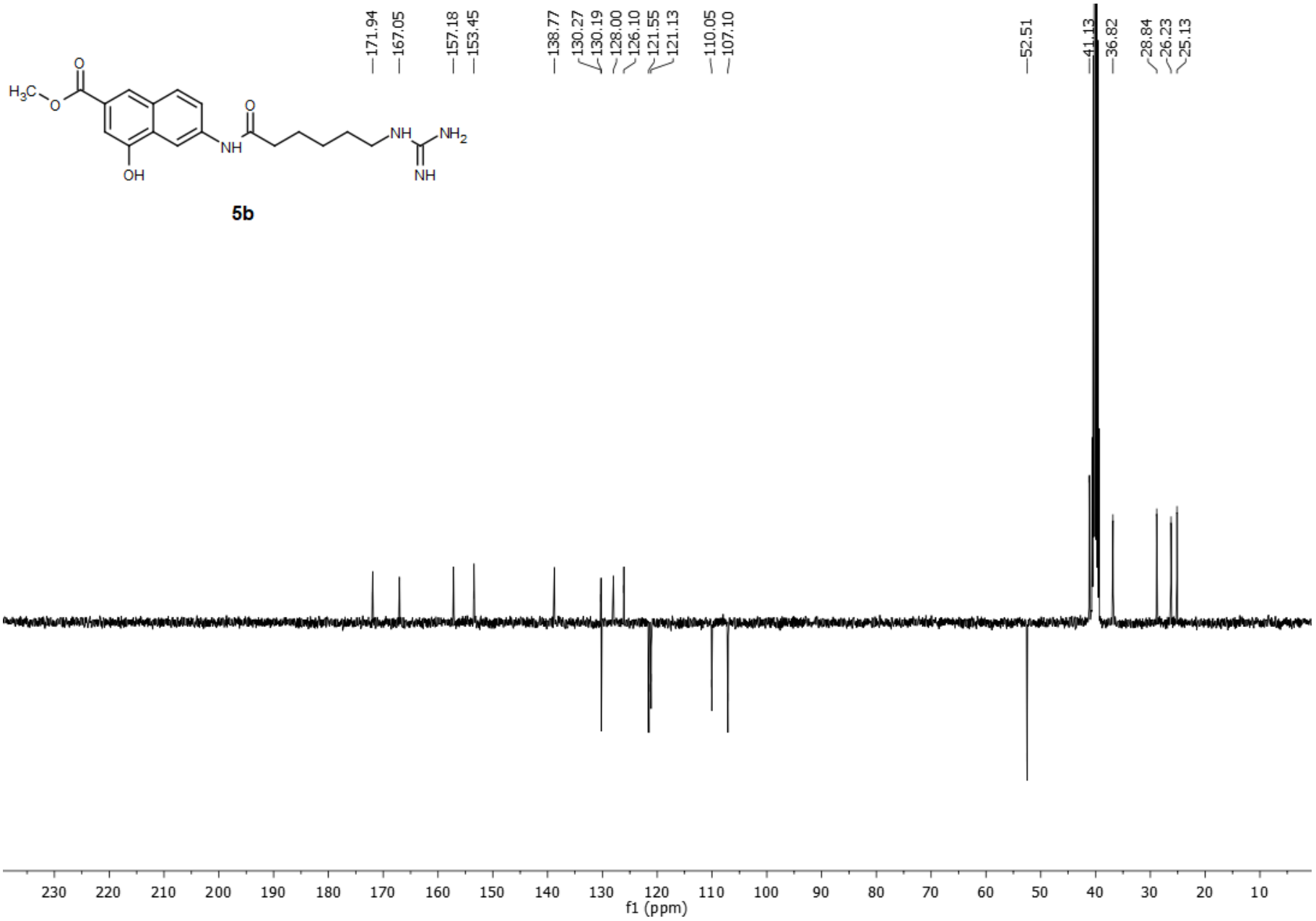

10.45
10.24
8.54
8.01
7.98
7.95
7.73
7.72
7.70
7.49
7.34
7.21
7.00
6.75
3.88
3.18
3.16
3.14
3.12
2.44
2.42
2.39
1.68
1.65
1.63
1.56
1.54
1.53
0.86
0.93
0.86
1.76
0.96
1.08
1.03
2.95
3.11
1.96
2.05
3.91
f1 (ppm)

5a

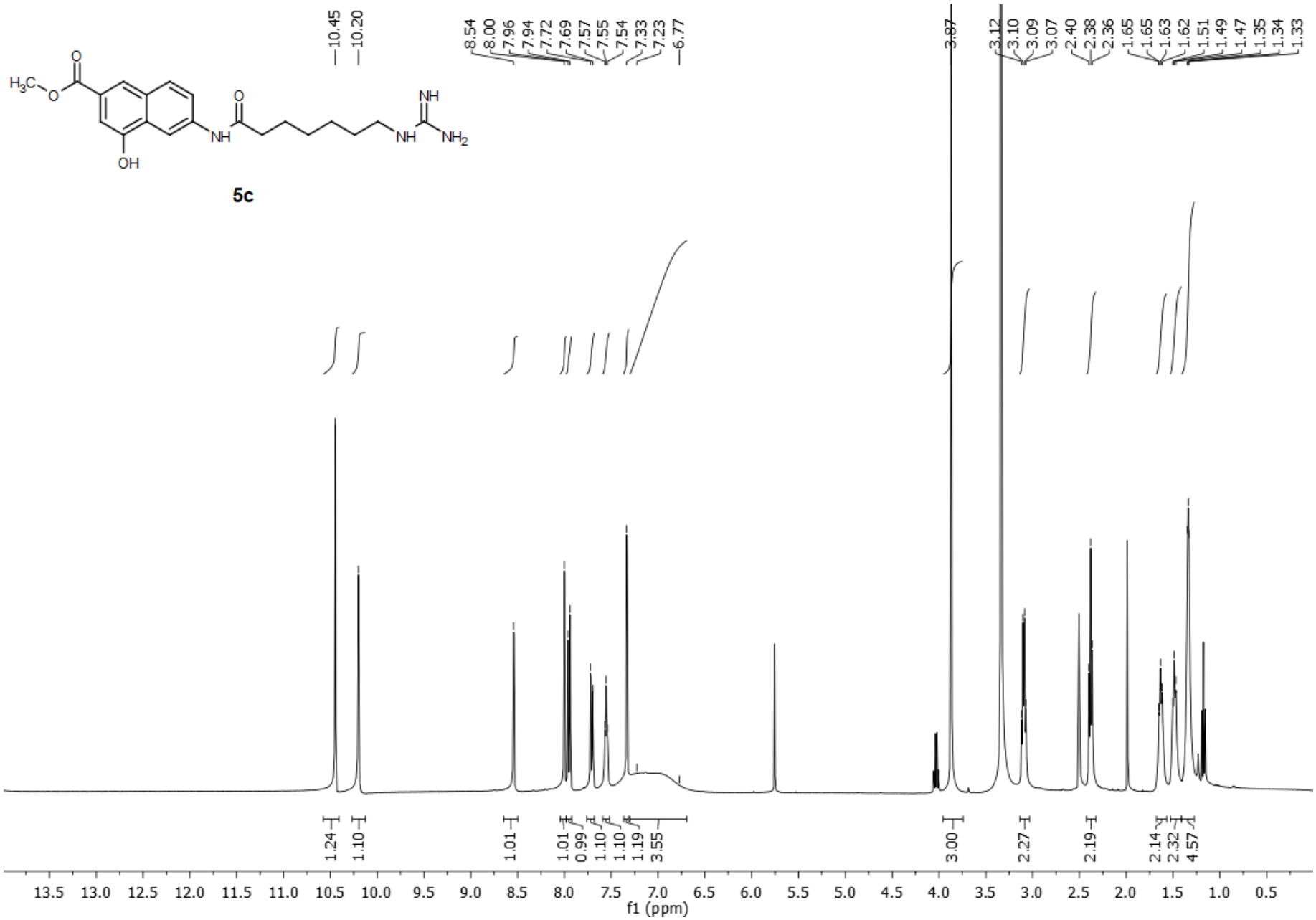

171.96
167.02
156.91
153.20
138.43
130.18
130.14
127.79
126.06
121.49
121.09
110.05
106.93
40.90
40.42
36.21
28.35
22.48
O
H3C
O
O
NH
NH
NH
NH2
OH
5a
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


10.43
10.20
8.54
8.00
7.97
7.96
7.94
7.94
7.72
7.72
7.71
7.70
7.70
7.69
7.52
7.51
7.50
7.34
7.33
7.33
7.22
6.83
3.87
3.12
3.10
2.41
2.39
2.37
1.67
1.65
1.63
1.53
1.51
1.49
1.37
1.35
1.33
1.09
1.01
1.05
1.10
1.12
1.15
1.22
1.23
3.02
2.96
2.18
2.17
2.31
2.27
2.33
f1 (ppm)

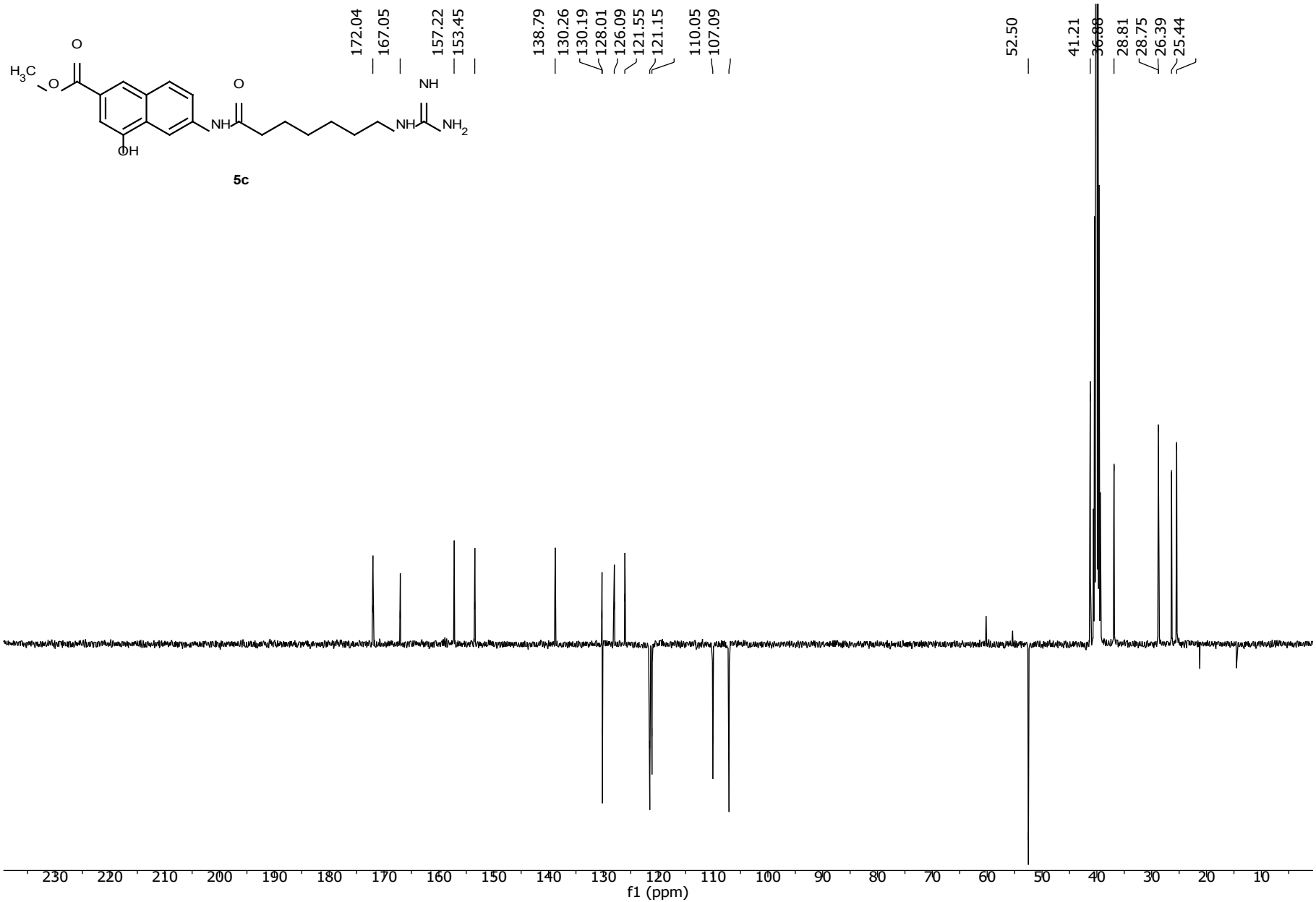
5b

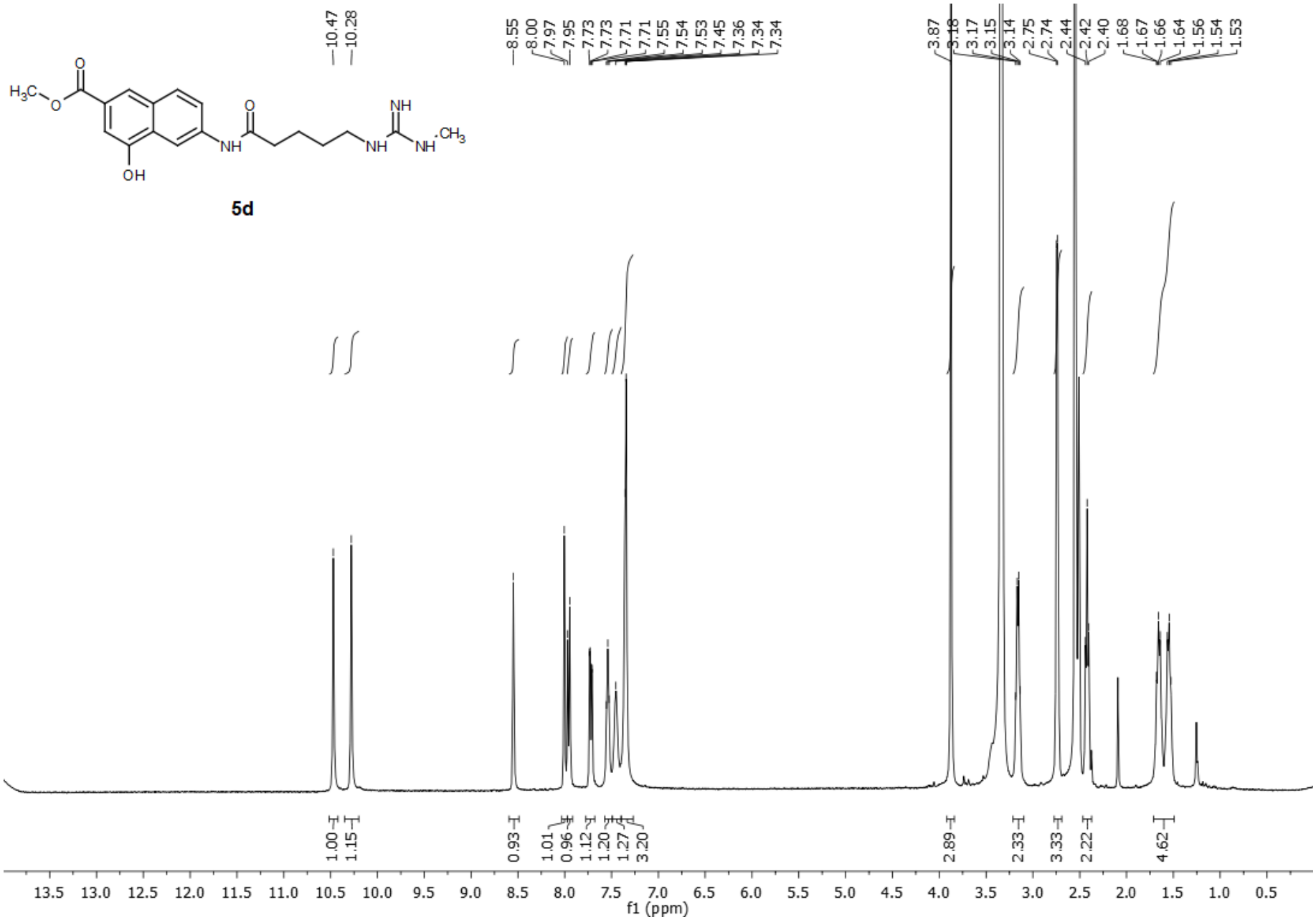

171.94
167.05
157.18
153.45
138.77
130.27
130.19
128.00
126.10
121.55
121.13
110.05
107.10
52.51
41.13
36.82
28.84
26.23
25.13
O
H3C
O
O
NH
NH
NH2
NH
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

5b

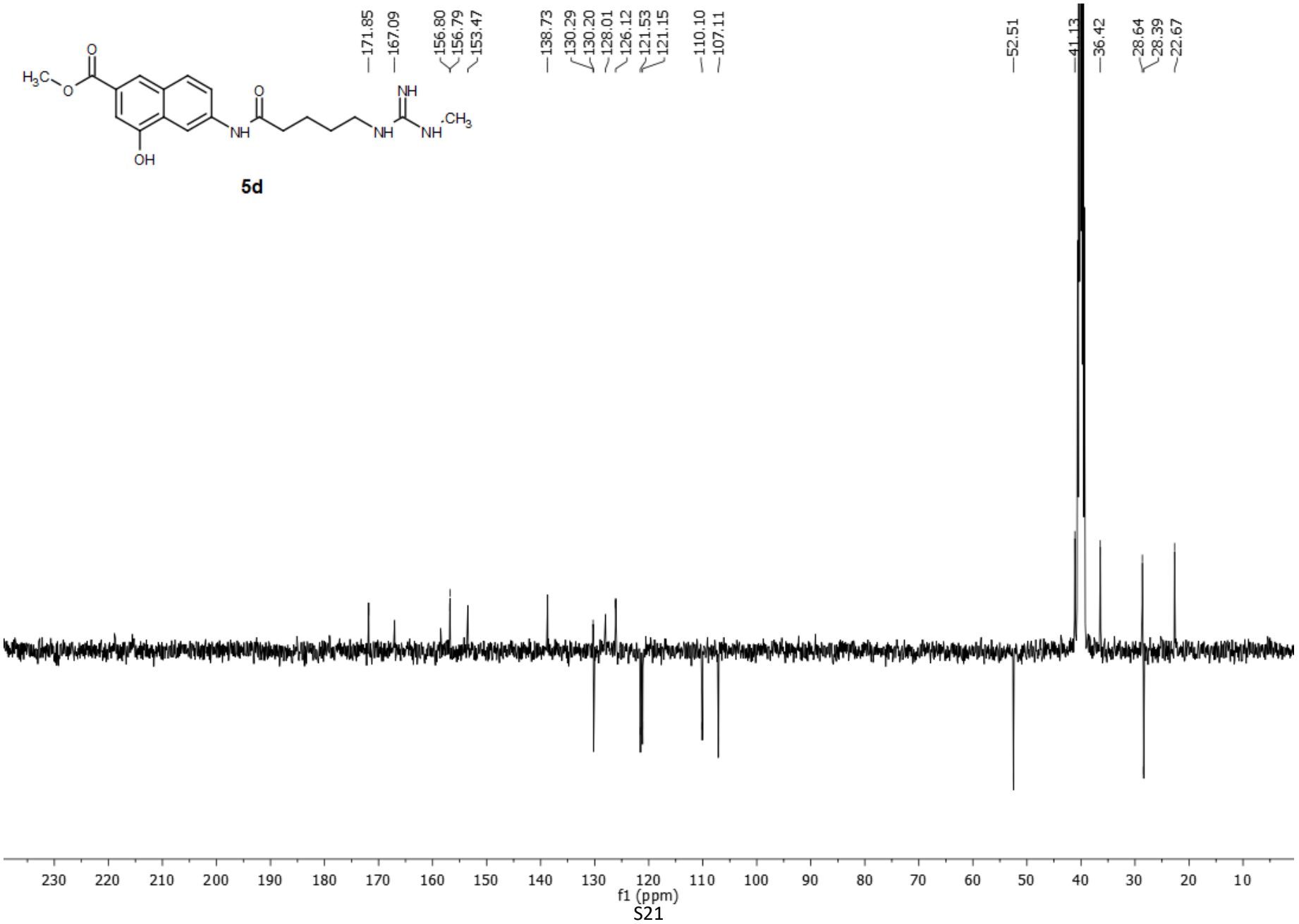

10.45
10.20
8.54
8.00
7.96
7.94
7.72
7.69
7.57
7.55
7.54
7.33
7.23
6.77
3.87
3.12
3.10
3.09
3.07
2.40
2.38
2.36
1.65
1.65
1.63
1.62
1.51
1.49
1.47
1.35
1.34
1.33
1.24
1.10
1.01
1.01
0.99
1.10
1.10
1.19
3.55
3.00
2.27
2.19
2.14
2.32
4.57
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 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
f1 (ppm)

5c

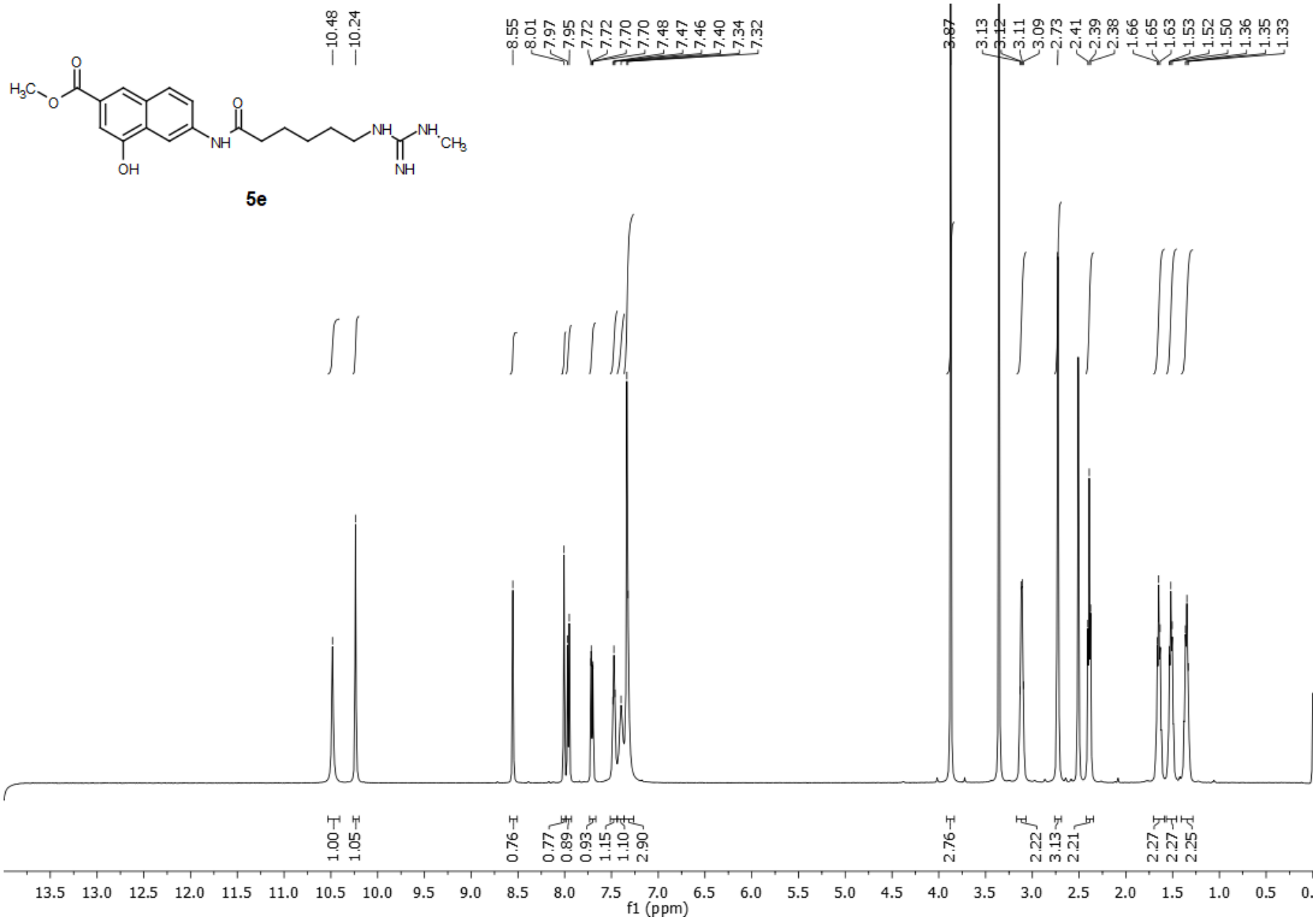

172.04
167.05
157.22
153.45
138.79
130.26
130.19
128.01
126.09
121.55
121.15
110.05
107.09
52.50
41.21
36.88
28.81
28.75
26.39
25.44
O
H3C
O
O
NH
NH
NH
NH2
OH
5c
f1 (ppm)


10.47
10.28
8.55
8.00
7.97
7.95
7.73
7.73
7.71
7.71
7.55
7.54
7.53
7.45
7.36
7.34
7.34
3.87
3.18
3.17
3.15
3.14
2.75
2.74
2.44
2.42
2.40
1.68
1.67
1.66
1.64
1.56
1.54
1.53
1.00
1.15
0.93
1.01
0.96
1.12
1.20
1.27
3.20
2.89
2.33
3.33
2.22
4.62
f1 (ppm)

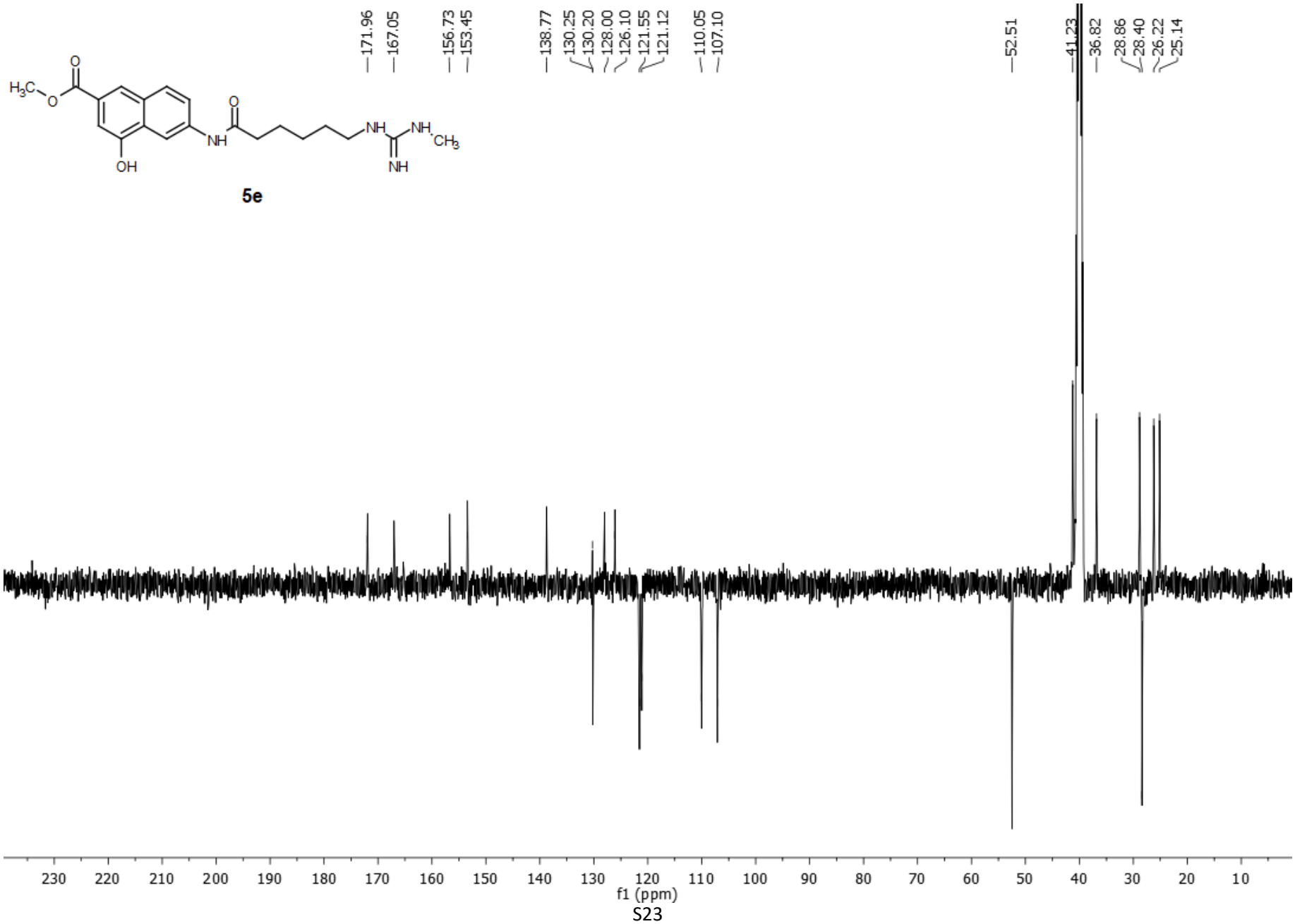
5d

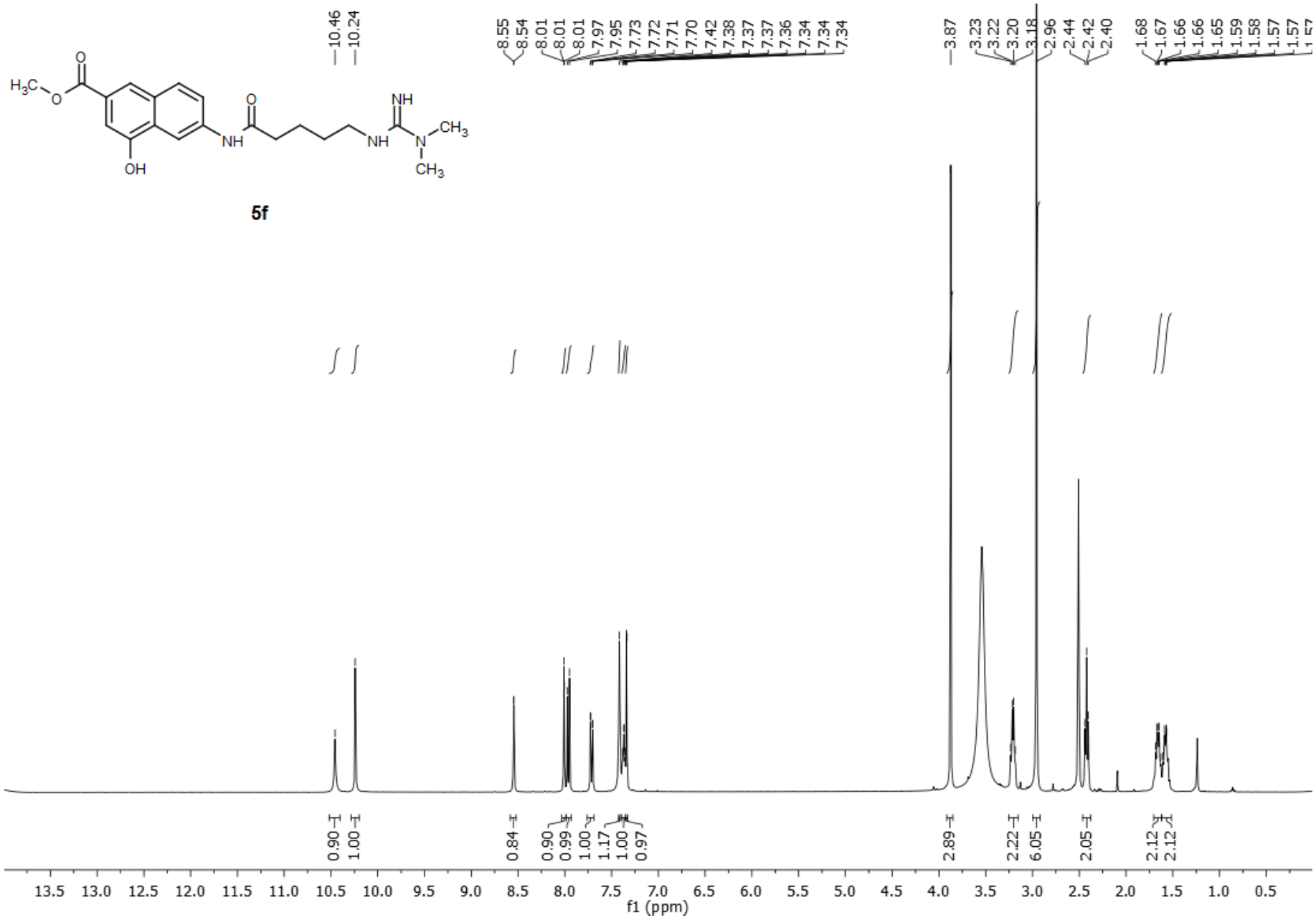

171.85
167.09
156.80
156.79
153.47
138.73
130.29
130.20
128.01
126.12
121.53
121.15
110.10
107.11
52.51
41.13
36.42
28.64
28.39
22.67
O
H3C
O
O
NH
NH
NH
NH
CH3
OH
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

5d

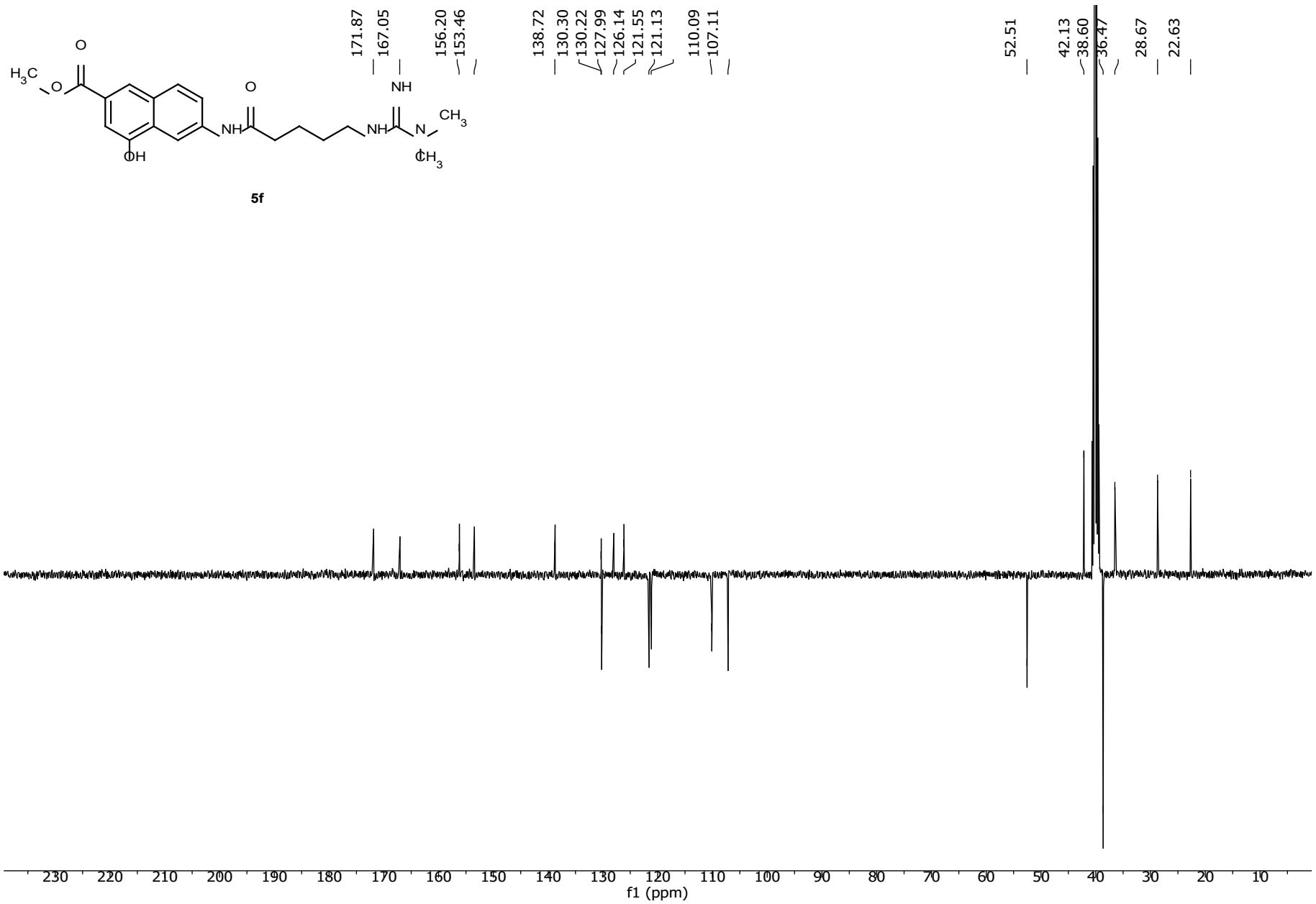

10.48
10.24
8.55
8.01
7.97
7.95
7.72
7.72
7.70
7.70
7.48
7.47
7.46
7.40
7.34
7.32
3.87
3.13
3.12
3.11
3.09
2.73
2.41
2.39
2.38
1.66
1.65
1.63
1.53
1.52
1.50
1.36
1.35
1.33
1.00
1.05
0.76
0.77
0.89
0.93
1.15
1.10
2.90
2.76
2.22
3.13
2.21
2.27
2.27
2.25
f1 (ppm)

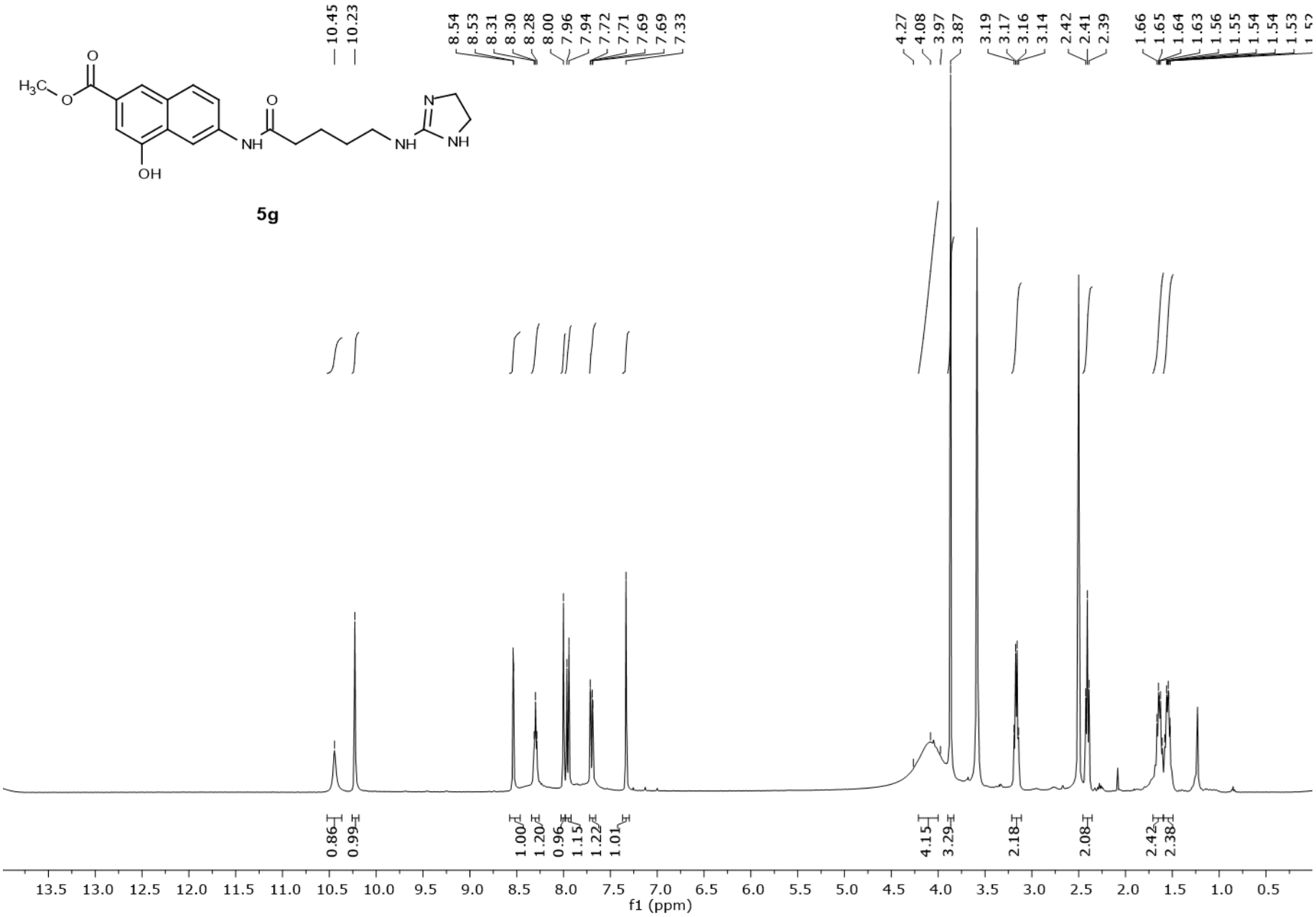
5e


171.96
167.05
156.73
153.45
138.77
130.25
130.20
128.00
126.10
121.55
121.12
110.05
107.10
52.51
41.23
36.82
28.86
28.40
26.22
25.14
O
H3C
O
O
NH
OH
NH
NH
NH
CH3
NH
5e
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)

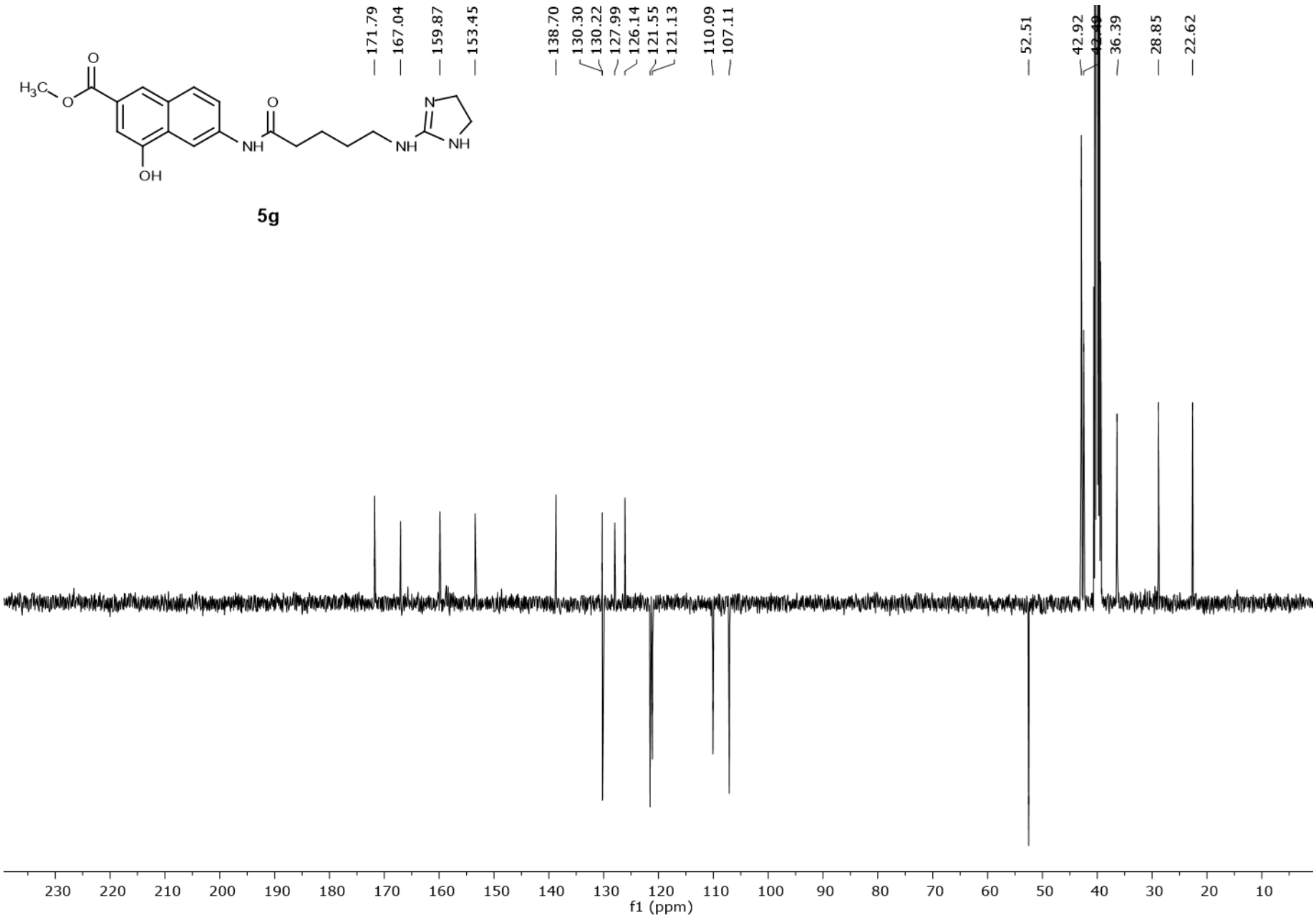

10.46
10.24
8.55
8.54
8.01
8.01
8.01
7.97
7.95
7.73
7.72
7.71
7.70
7.42
7.38
7.37
7.37
7.36
7.34
7.34
7.34
3.87
3.23
3.22
3.20
3.18
2.96
2.44
2.42
2.40
1.68
1.67
1.66
1.66
1.65
1.59
1.58
1.57
1.57
0.90
1.00
0.84
0.90
0.99
1.00
1.17
1.00
0.97
2.89
2.22
6.05
2.05
2.12
2.12
f1 (ppm)

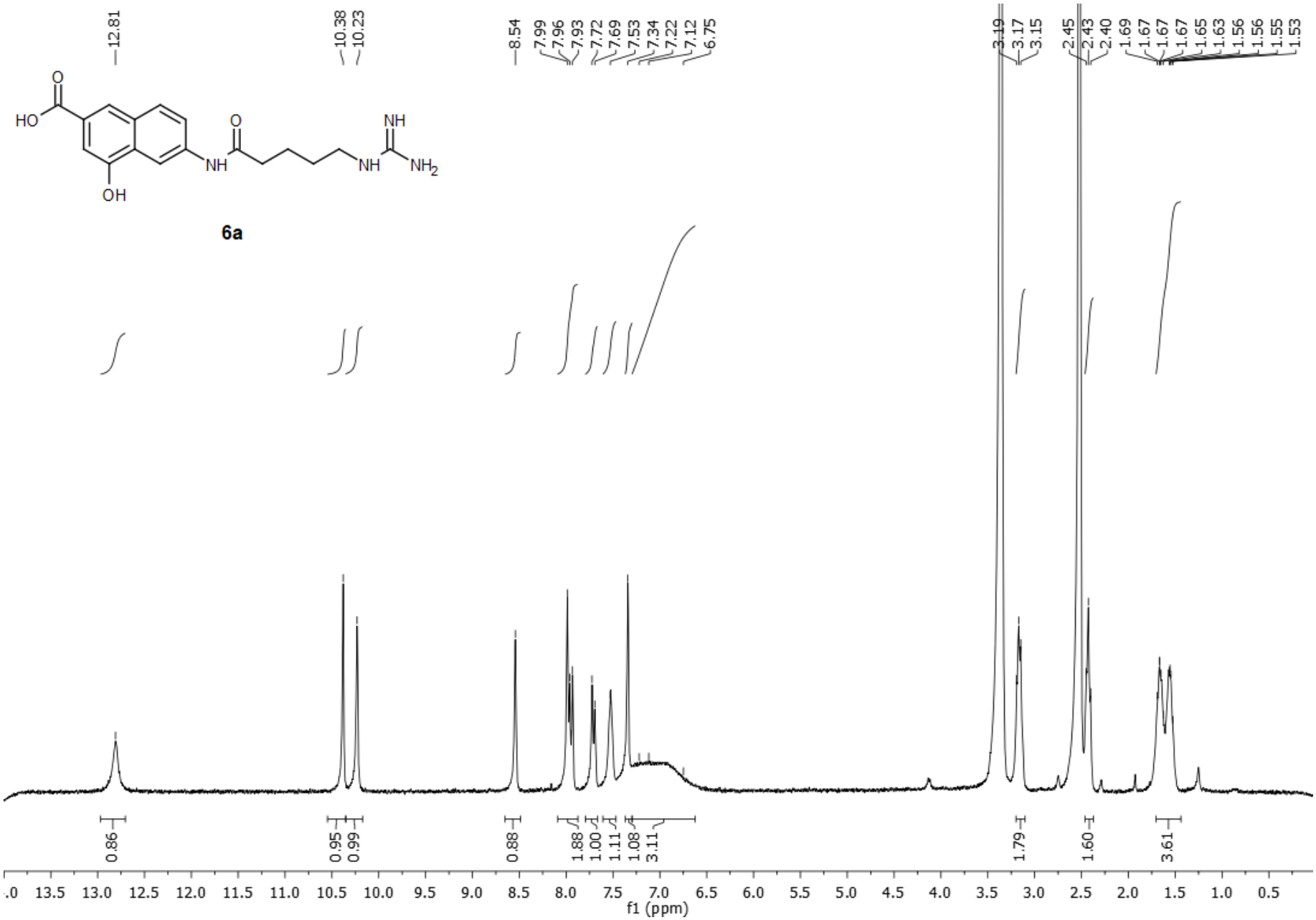
5f

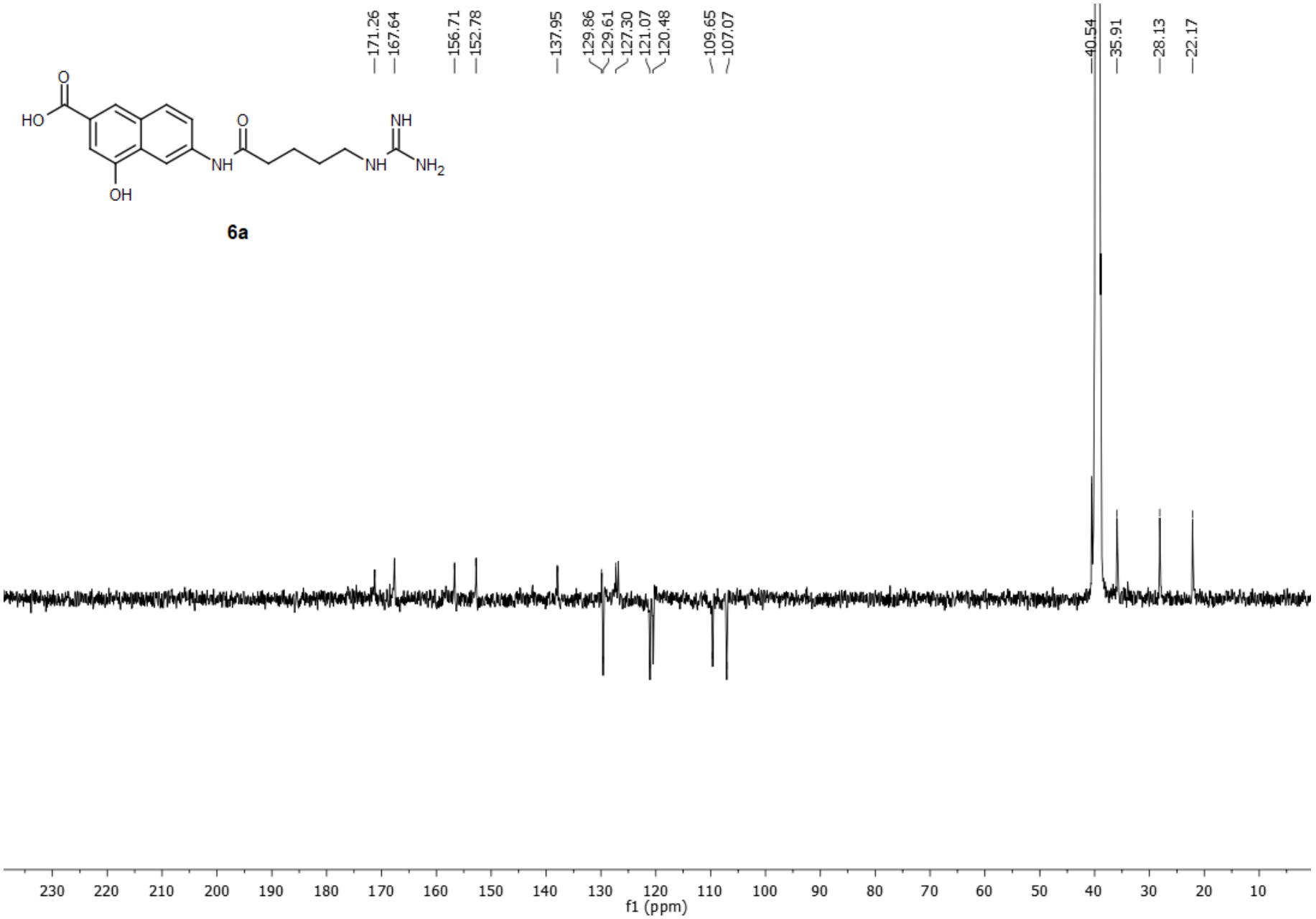

171.87
167.05
156.20
153.46
138.72
130.30
130.22
127.99
126.14
121.55
121.13
110.09
107.11
52.51
42.13
38.60
36.47
28.67
22.63
O
H3C
O
O
NH
NH
NH
N
CH3
CH3
OH
5f
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

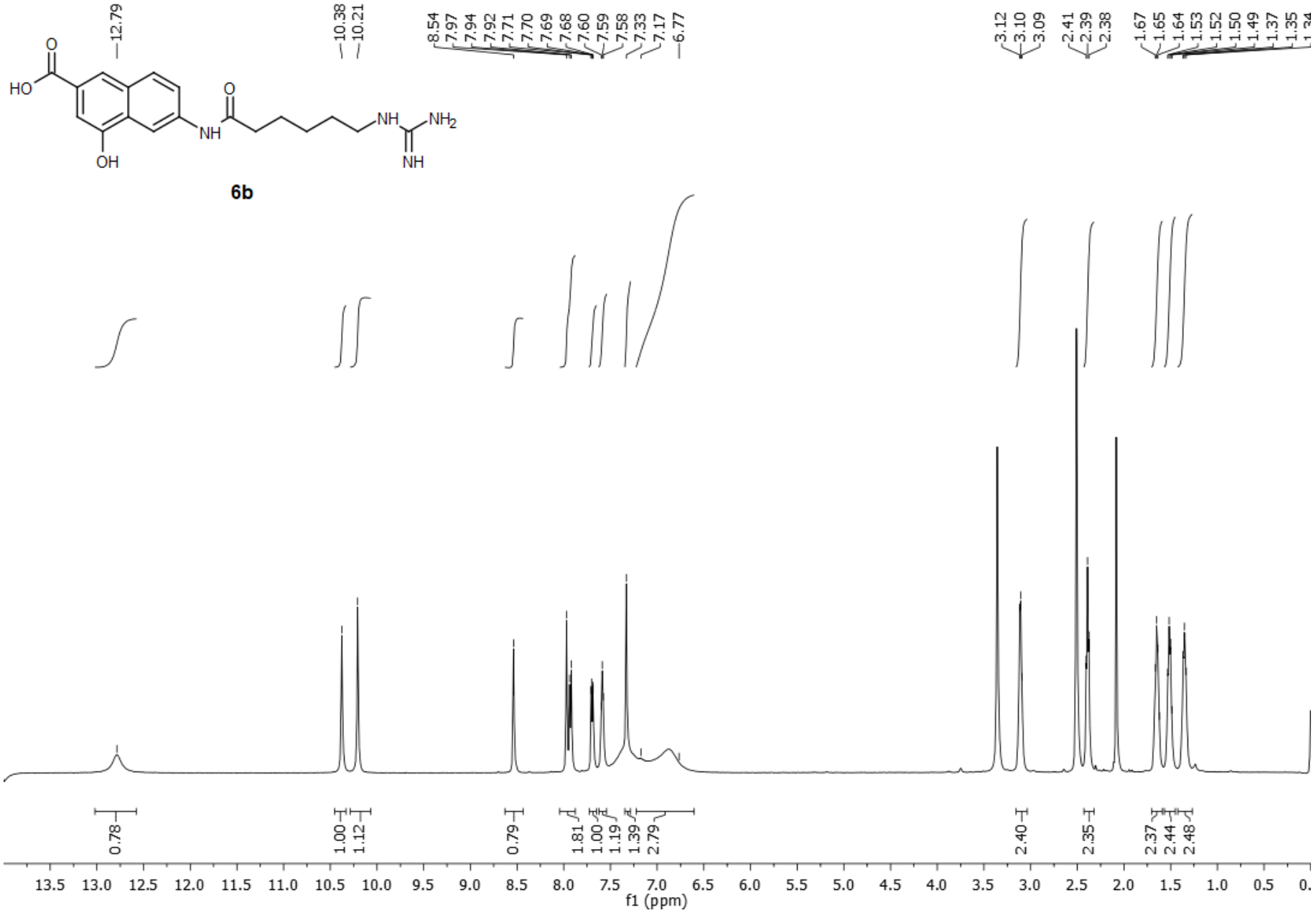

10.45
10.23
8.54
8.53
8.31
8.30
8.28
8.00
7.96
7.94
7.72
7.71
7.69
7.69
7.33
4.27
4.08
3.97
3.87
3.19
3.17
3.16
3.14
2.42
2.41
2.39
1.66
1.65
1.64
1.63
1.56
1.55
1.54
1.54
1.53
0.86
0.99
1.00
1.20
0.96
1.15
1.22
1.01
4.15
3.29
2.18
2.08
2.42
2.38
f1 (ppm)

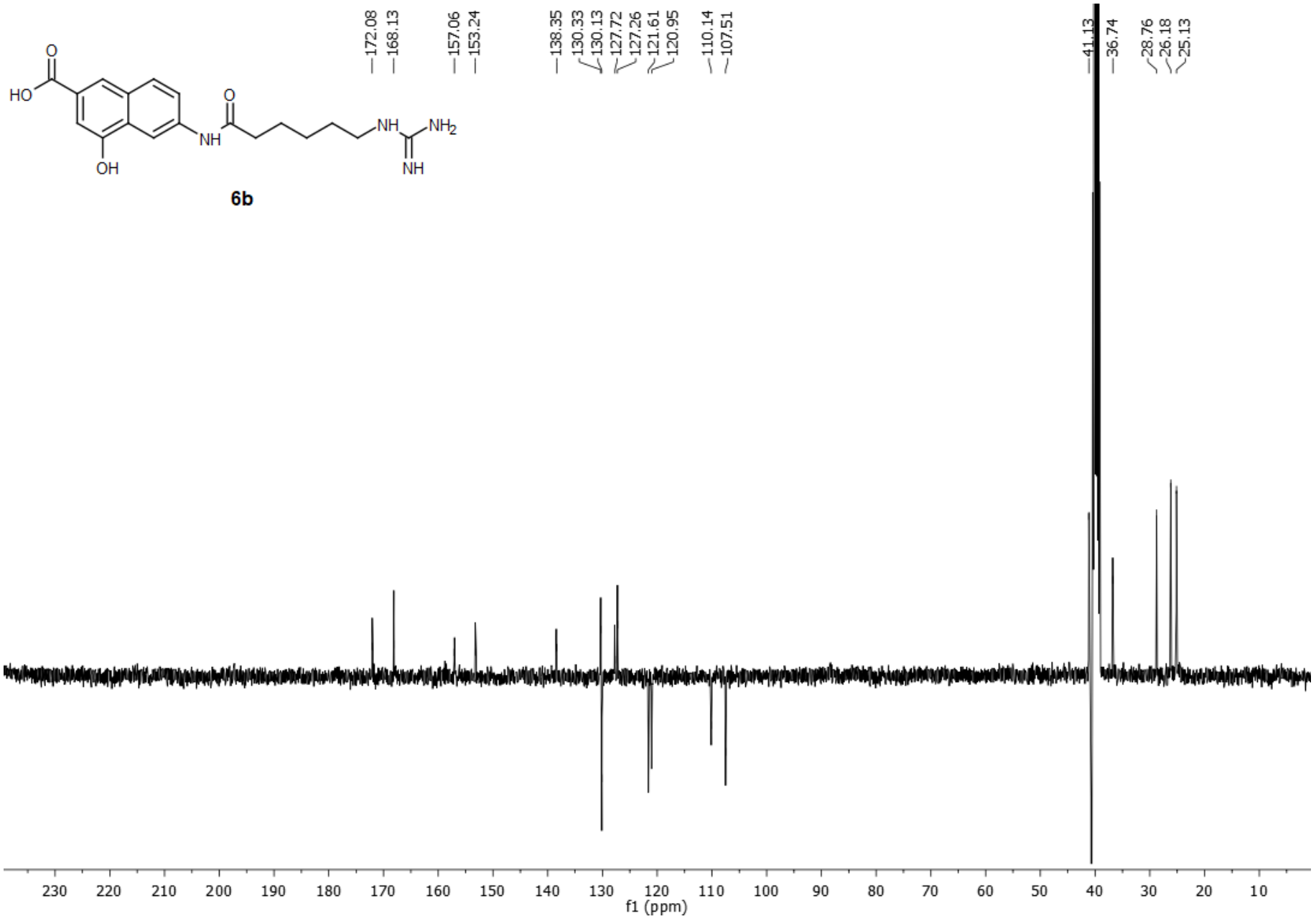
5g


171.79
167.04
159.87
153.45
138.70
130.30
130.22
127.99
126.14
121.55
121.13
110.09
107.11
52.51
42.92
42.48
36.39
28.85
22.62
O
H3C
O
O
NH
NH
N
NH
OH
5g
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)

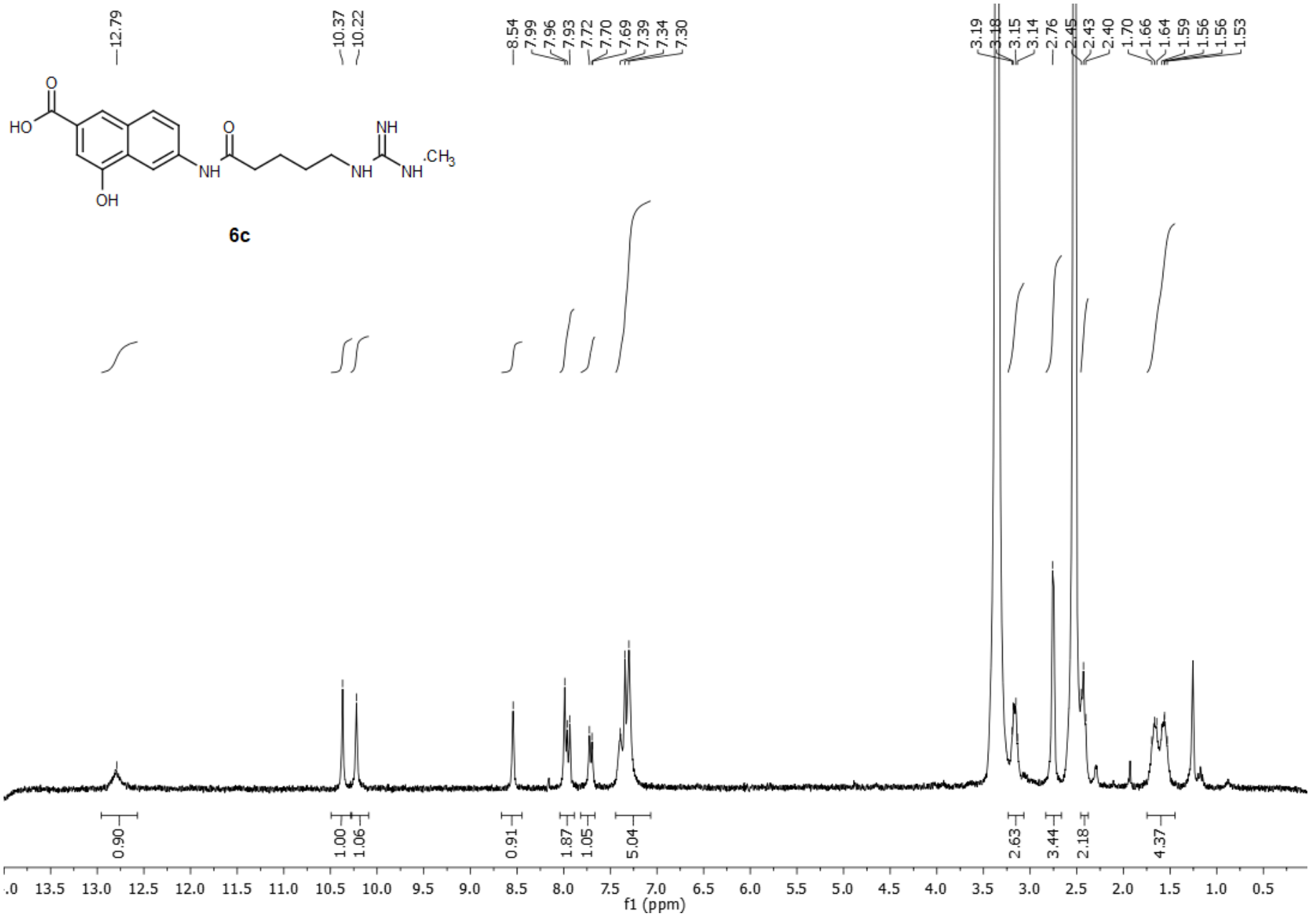

12.81
10.38
10.23
8.54
7.99
7.96
7.93
7.72
7.69
7.53
7.34
7.22
7.12
6.75
3.19
3.17
3.15
2.45
2.43
2.40
1.69
1.67
1.67
1.67
1.65
1.63
1.56
1.56
1.55
1.53
HO
O
NH
O
NH
NH
NH2
OH
6a
0.86
0.95
0.99
0.88
1.88
1.00
1.11
1.08
3.11
1.79
1.60
3.61
f1 (ppm)

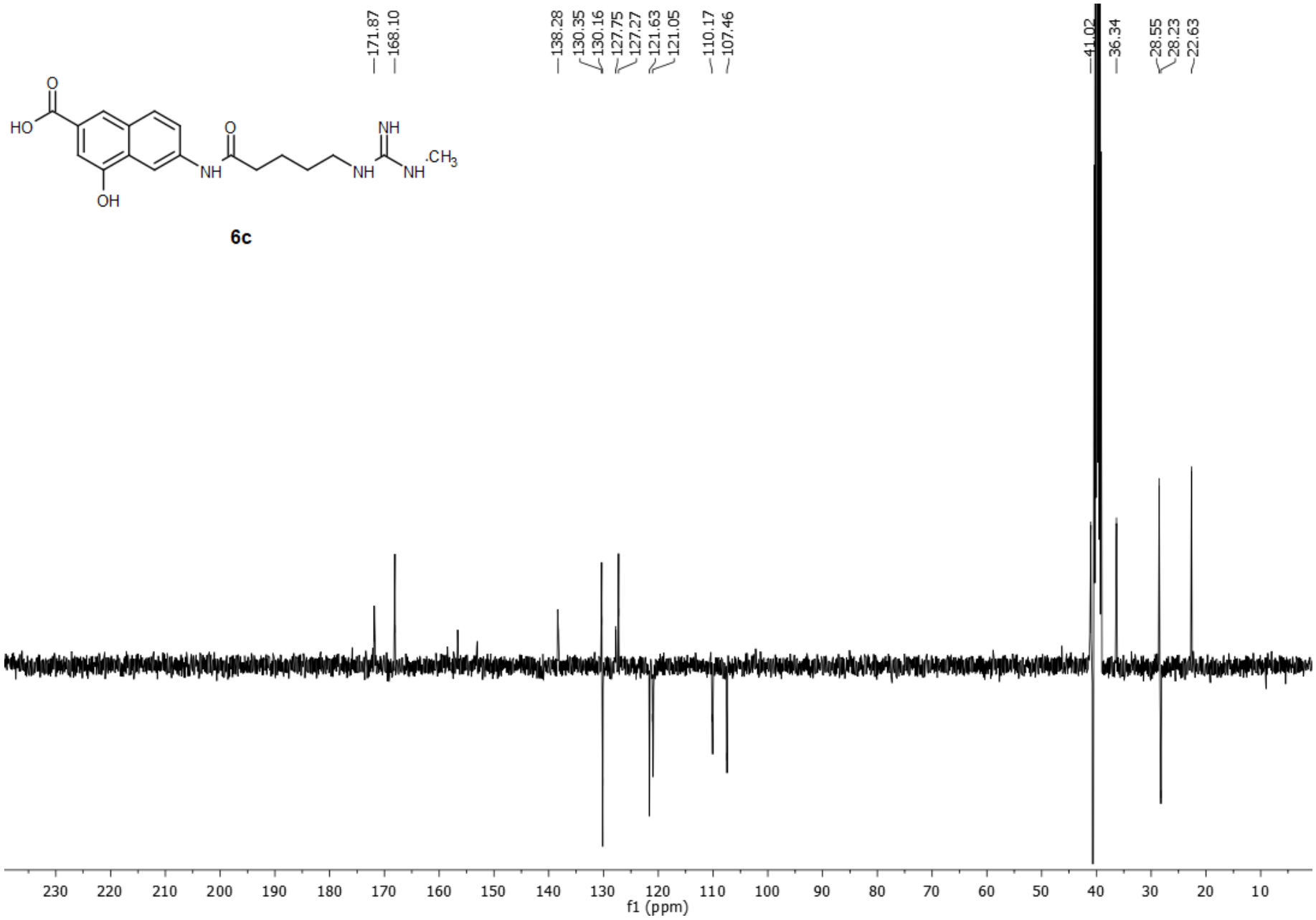

171.26
167.64
156.71
152.78
137.95
129.86
129.61
127.30
121.07
120.48
109.65
107.07
40.54
35.91
28.13
22.17
HO
O
OH
NH
O
NH
NH
NH2
6a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


12.79
10.38
10.21
8.54
7.97
7.94
7.92
7.71
7.70
7.69
7.68
7.60
7.59
7.58
7.33
7.17
6.77
3.12
3.10
3.09
2.41
2.39
2.38
1.67
1.65
1.64
1.53
1.52
1.50
1.49
1.37
1.35
HO
O
NH
O
NH
NH2
NH
OH
6b
0.78
1.00
1.12
0.79
1.81
1.00
1.19
1.39
2.79
2.40
2.35
2.37
2.44
2.48
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.
f1 (ppm)

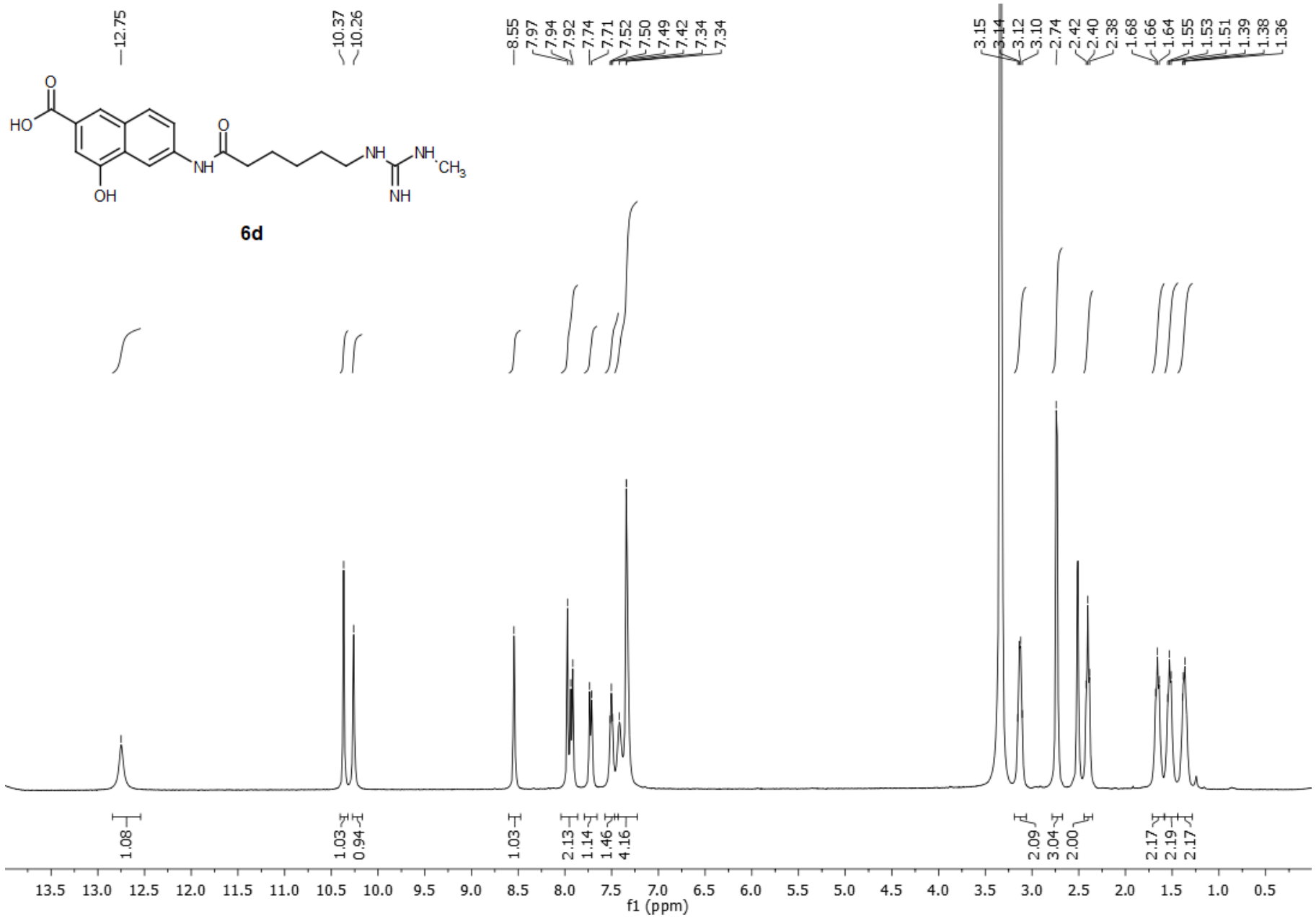

HO
O
OH
NH
O
NH
NH
NH2
172.08
168.13
157.06
153.24
138.35
130.33
130.13
127.72
127.26
121.61
120.95
110.14
107.51
41.13
36.74
28.76
26.18
25.13
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

6b

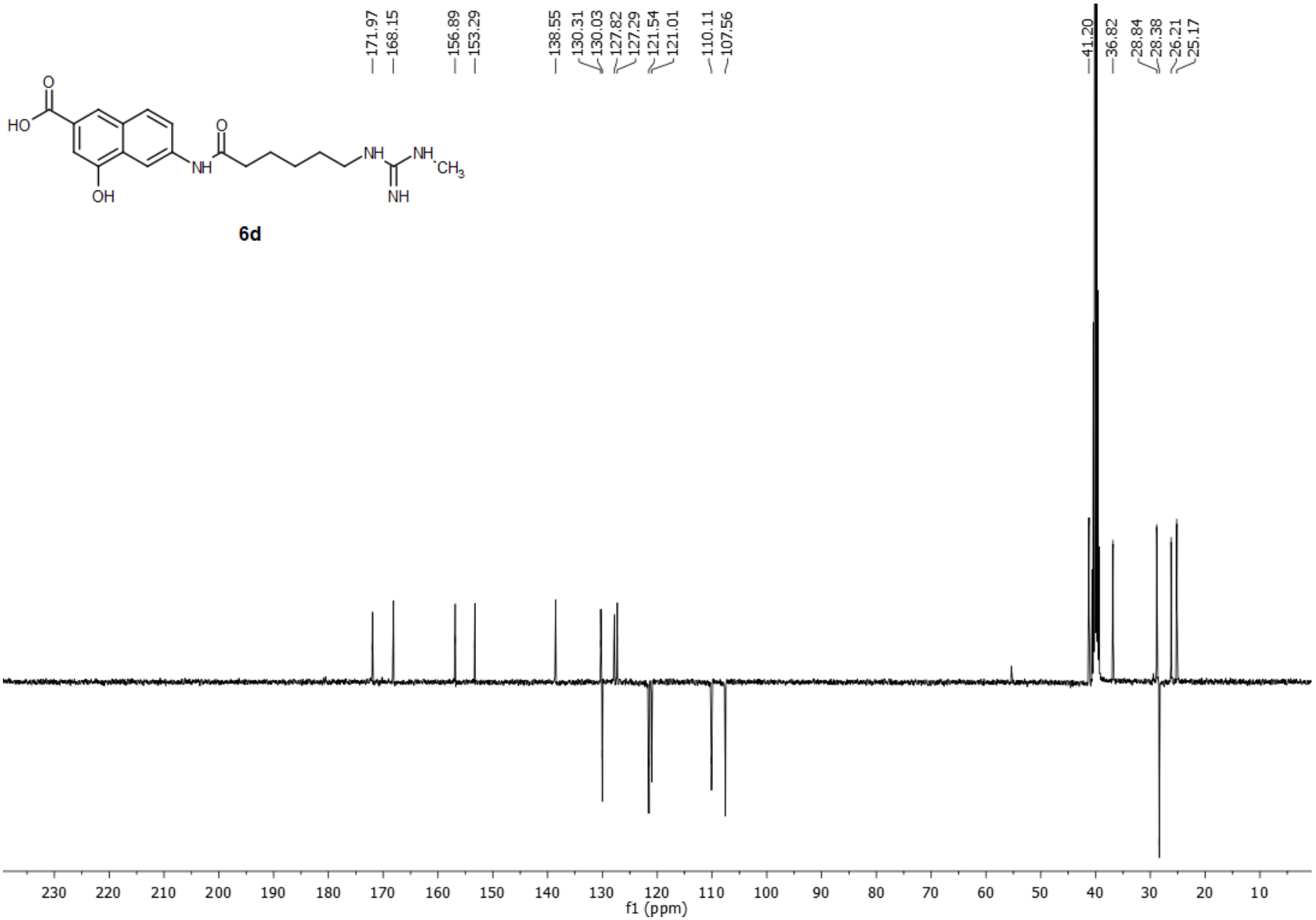

12.79
10.37
10.22
8.54
7.99
7.96
7.93
7.72
7.70
7.69
7.39
7.34
7.30
3.19
3.18
3.15
3.14
2.76
2.45
2.43
2.40
1.70
1.66
1.64
1.59
1.56
1.56
1.53
HO
O
OH
NH
O
NH
NH
NH
CH3
6c
0.90
1.00
1.06
0.91
1.87
1.05
5.04
2.63
3.44
2.18
4.37
f1 (ppm)


171.87
168.10
138.28
130.35
130.16
127.75
127.27
121.63
121.05
110.17
107.46
41.02
36.34
28.55
28.23
22.63
HO
O
OH
NH
O
NH
NH
NH
.CH3
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)

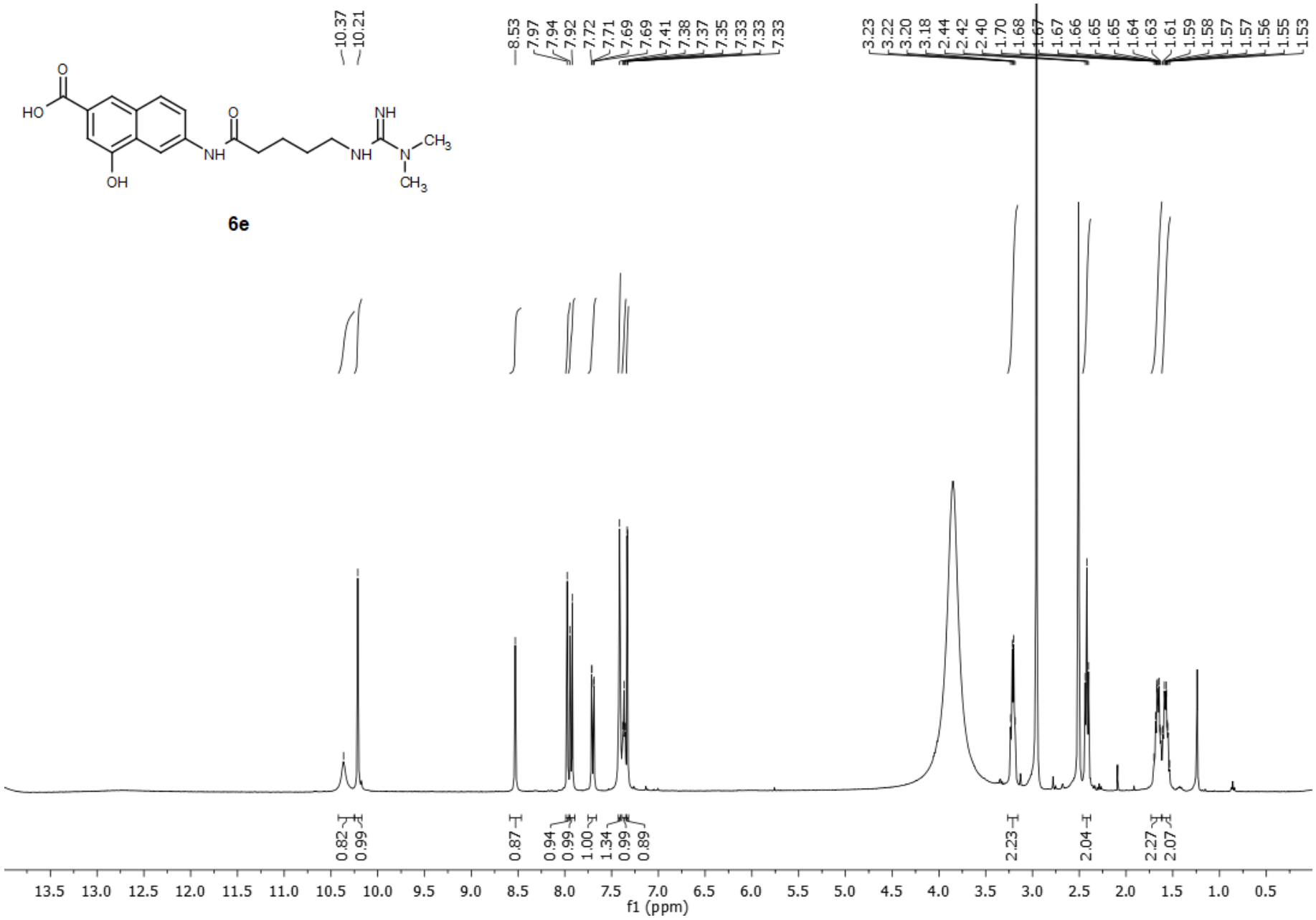
6c

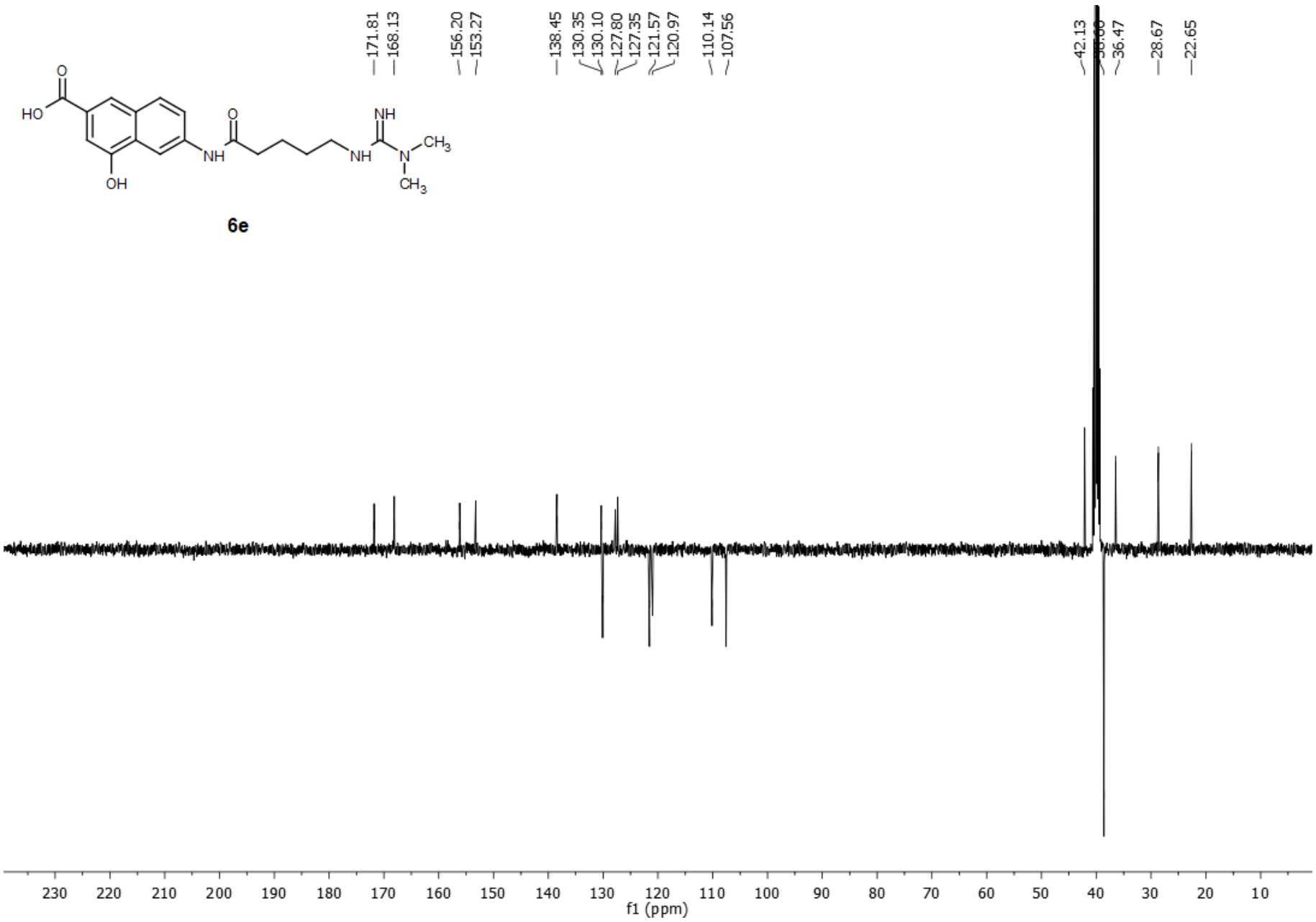

12.75
10.37
10.26
8.55
7.97
7.94
7.92
7.74
7.71
7.52
7.50
7.49
7.42
7.34
7.34
3.15
3.14
3.12
3.10
2.74
2.42
2.40
2.38
1.68
1.66
1.64
1.55
1.53
1.51
1.39
1.38
1.36
HO
O
OH
NH
O
NH
NH
CH3
NH
1.08
1.03
0.94
1.03
2.13
1.14
1.46
4.16
2.09
3.04
2.00
2.17
2.19
2.17
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 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
f1 (ppm)

6d

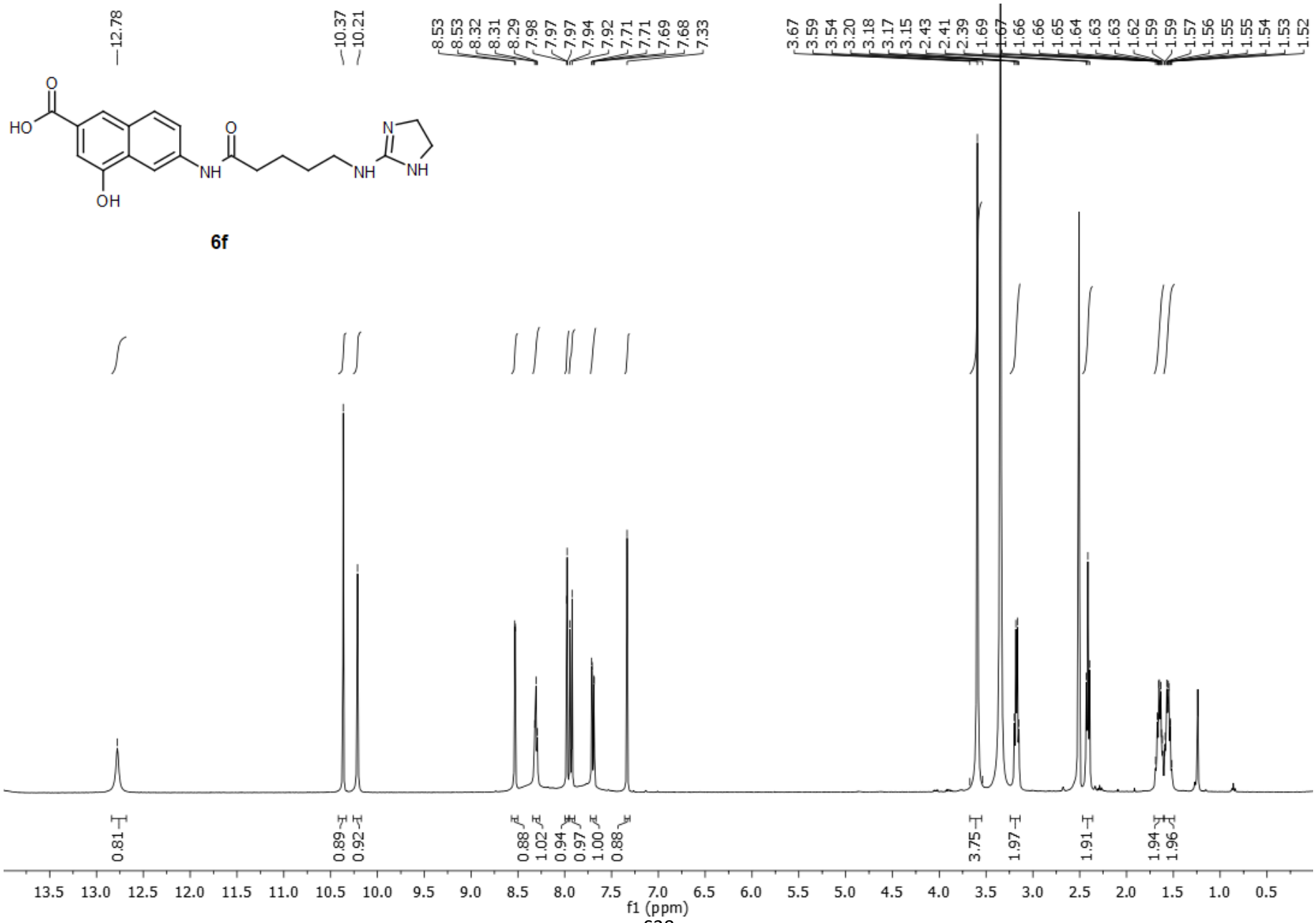

171.97
168.15
156.89
153.29
138.55
130.31
130.03
127.82
127.29
121.54
121.01
110.11
107.56
41.20
36.82
28.84
28.38
26.21
25.17
HO
O
OH
NH
O
NH
NH
NH
CH3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

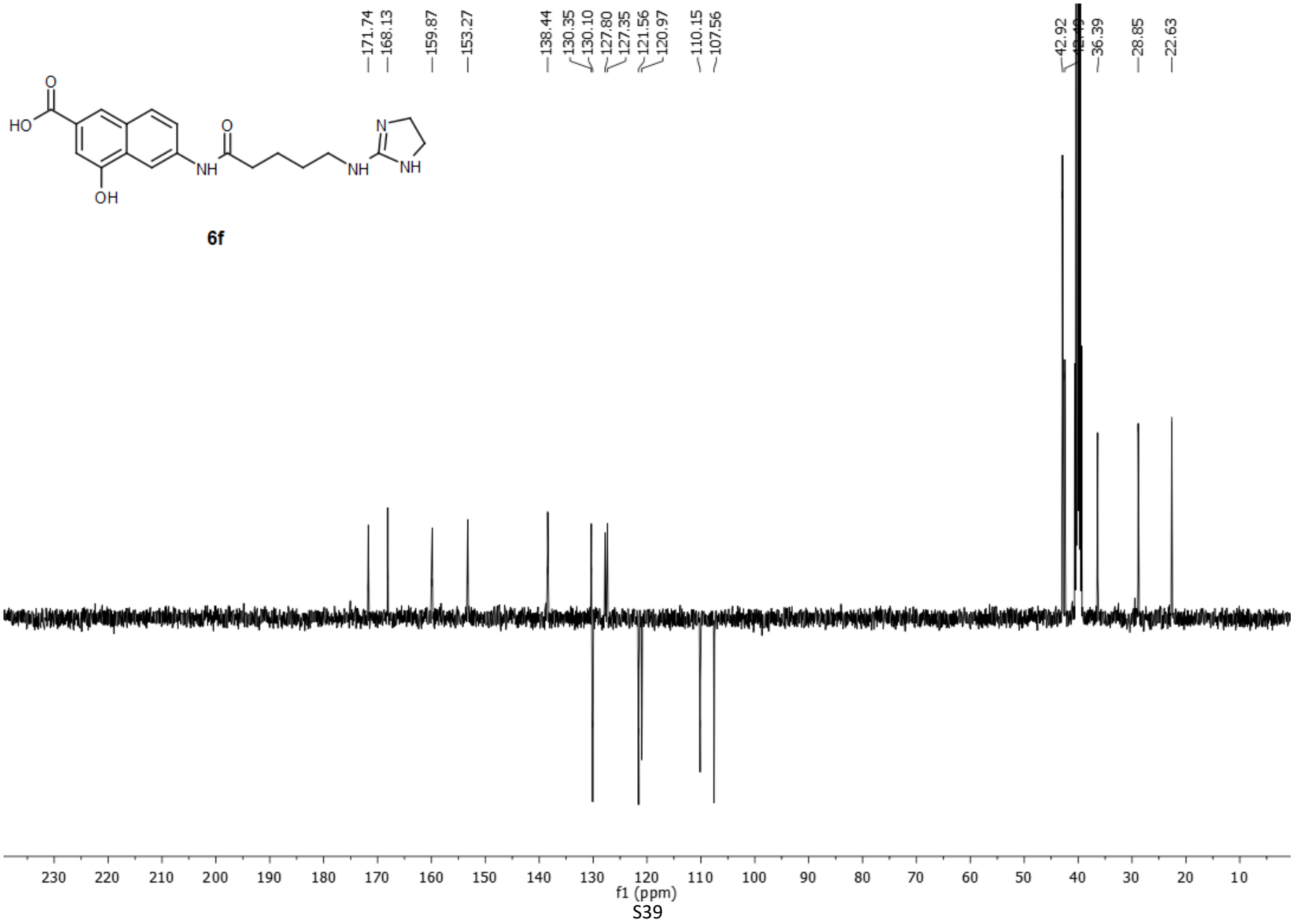
6d

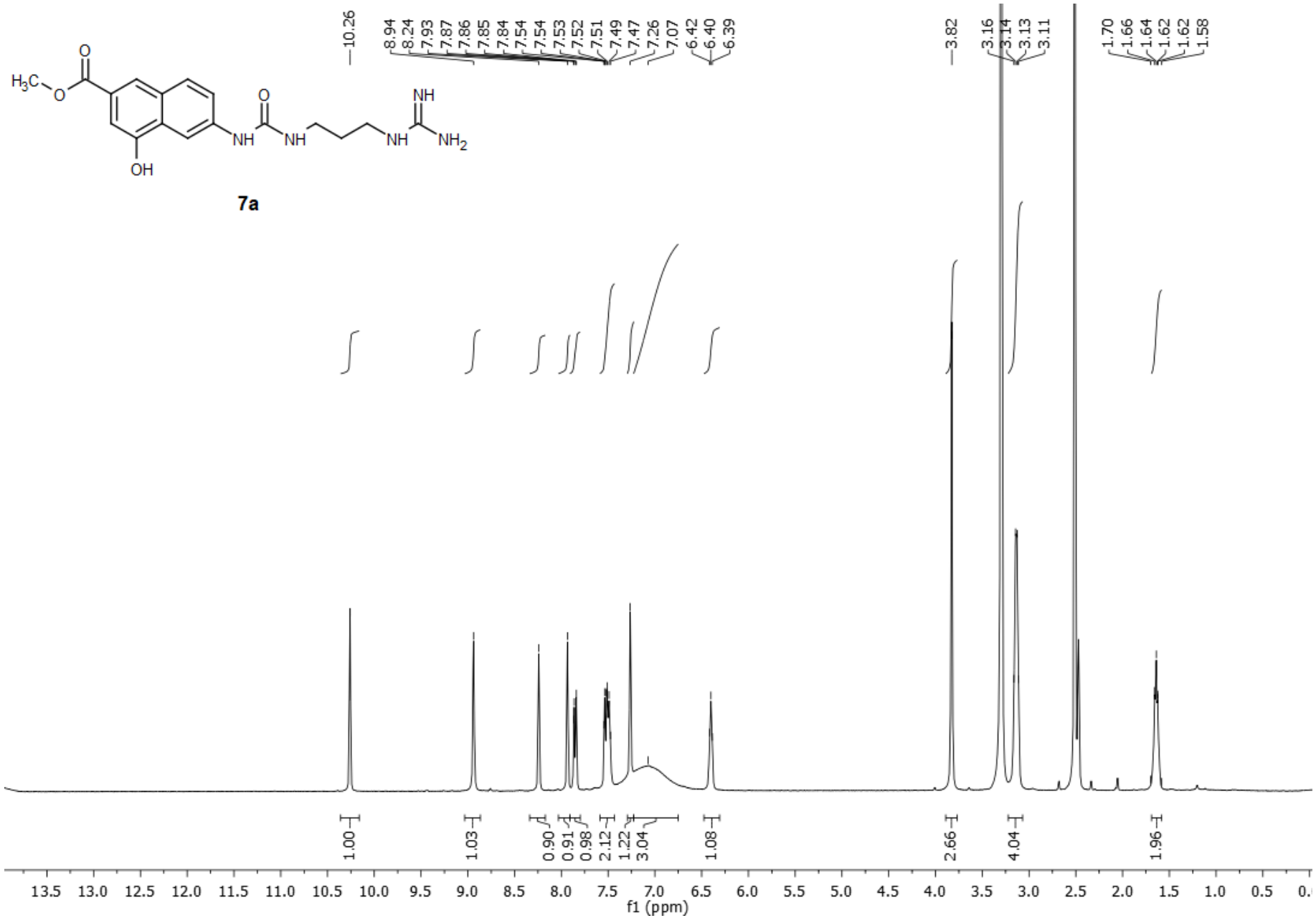

10.37
10.21
8.53
7.97
7.94
7.92
7.72
7.71
7.69
7.69
7.41
7.38
7.37
7.35
7.33
7.33
7.33
3.23
3.22
3.20
3.18
2.44
2.42
2.40
1.70
1.68
1.67
1.67
1.66
1.65
1.65
1.64
1.63
1.61
1.59
1.58
1.57
1.57
1.56
1.55
1.53
HO
O
O
NH
NH
NH
N
CH3
CH3
OH
6e
0.82
0.99
0.87
0.94
0.99
1.00
1.34
0.99
0.89
2.23
2.04
2.27
2.07
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
f1 (ppm)


171.81
168.13
156.20
153.27
138.45
130.35
130.10
127.80
127.35
121.57
120.97
110.14
107.56
42.13
36.47
28.67
22.65
HO
O
OH
NH
O
NH
NH
N
CH3
CH3
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)

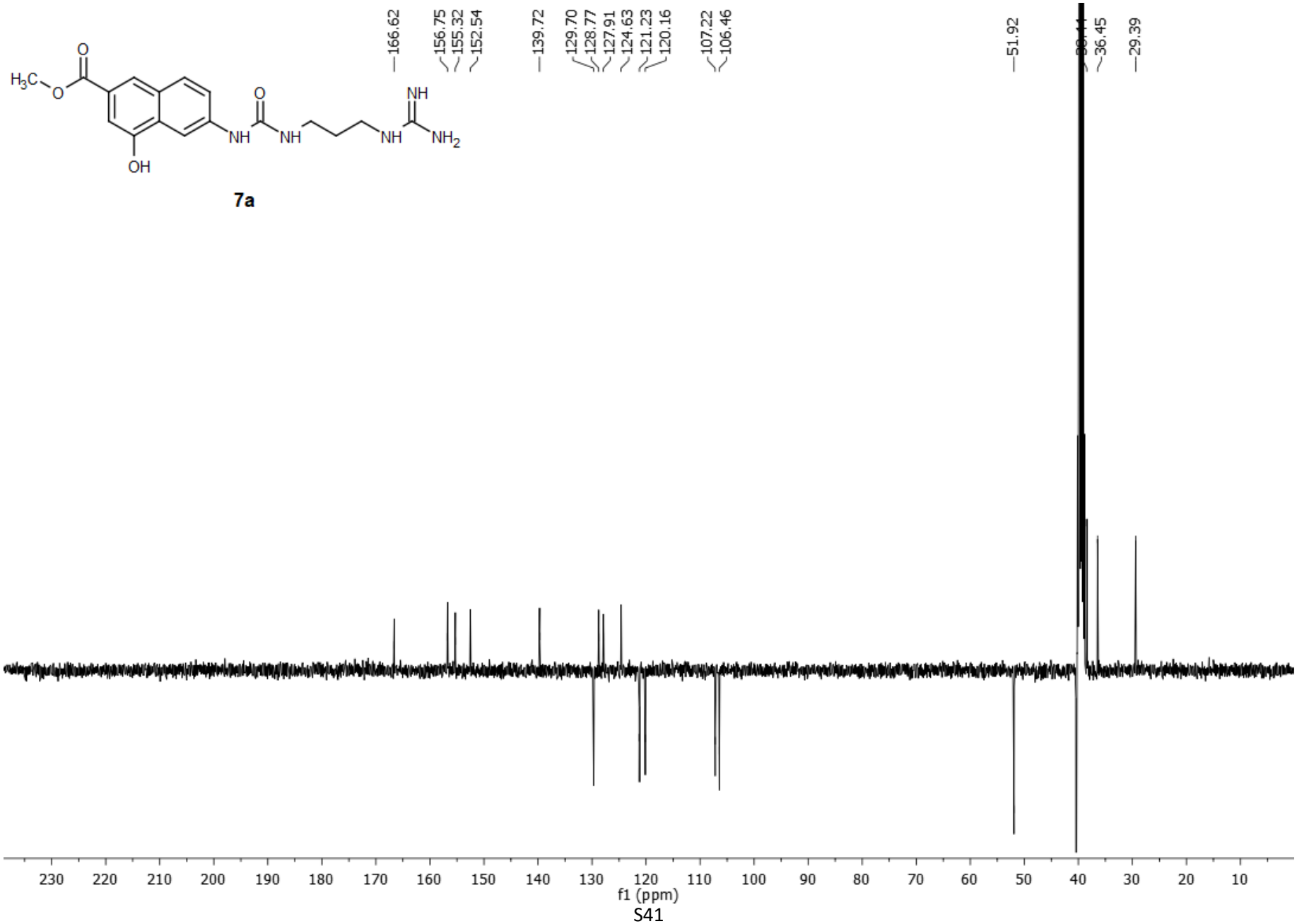
6e

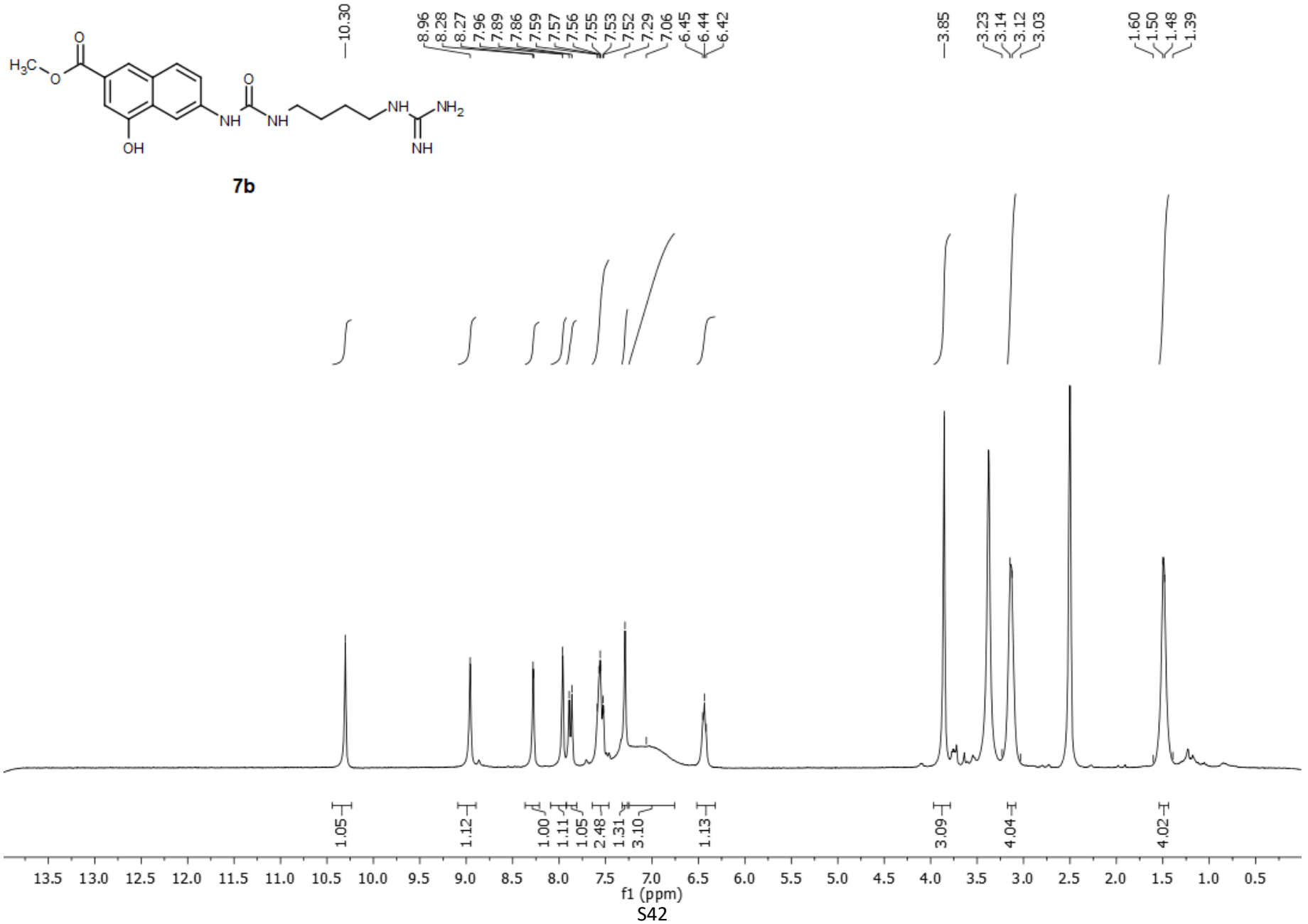

12.78
10.37
10.21
8.53
8.53
8.32
8.31
8.29
7.98
7.97
7.97
7.94
7.92
7.71
7.71
7.69
7.68
7.33
3.67
3.59
3.54
3.20
3.18
3.17
3.15
2.43
2.41
2.39
1.69
1.67
1.66
1.66
1.65
1.64
1.63
1.63
1.62
1.59
1.59
1.57
1.56
1.55
1.55
1.54
1.53
1.52
HO
O
NH
O
N
NH
NH
OH
6f
0.81
0.89
0.92
0.88
1.02
0.94
0.97
1.00
0.88
3.75
1.97
1.91
1.94
1.96
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
f1 (ppm)


171.74
168.13
159.87
153.27
138.44
130.35
130.10
127.80
127.35
121.56
120.97
110.15
107.56
42.92
36.39
28.85
22.63
HO
O
OH
NH
O
NH
N
NH
6f
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)

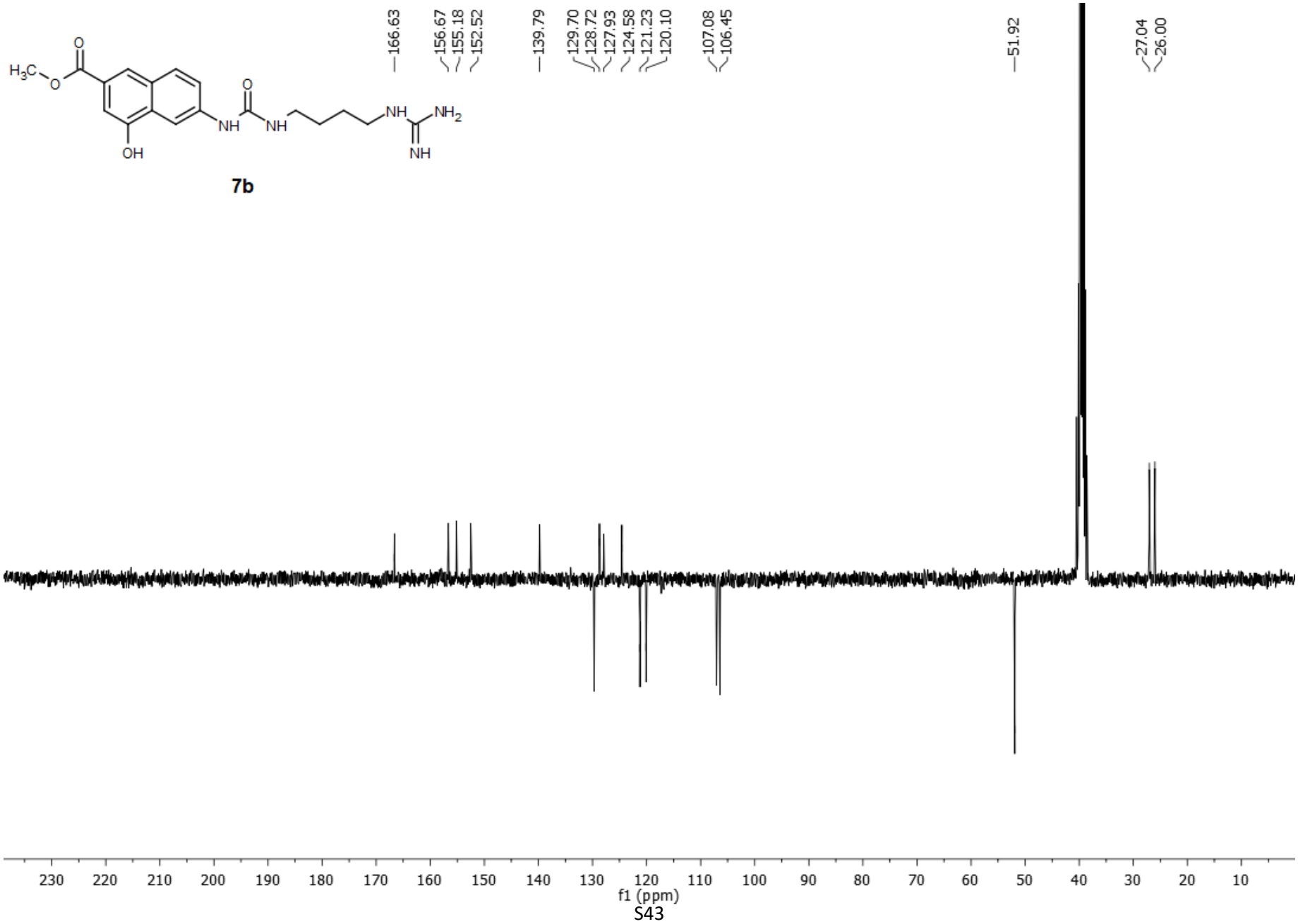

10.26
8.94
8.24
7.93
7.87
7.86
7.85
7.84
7.54
7.54
7.53
7.52
7.51
7.49
7.47
7.26
7.07
6.42
6.40
6.39
3.82
3.16
3.14
3.13
3.11
1.70
1.66
1.64
1.62
1.62
1.58
1.00
1.03
0.90
0.91
0.98
2.12
1.22
3.04
1.08
2.66
4.04
1.96
f1 (ppm)

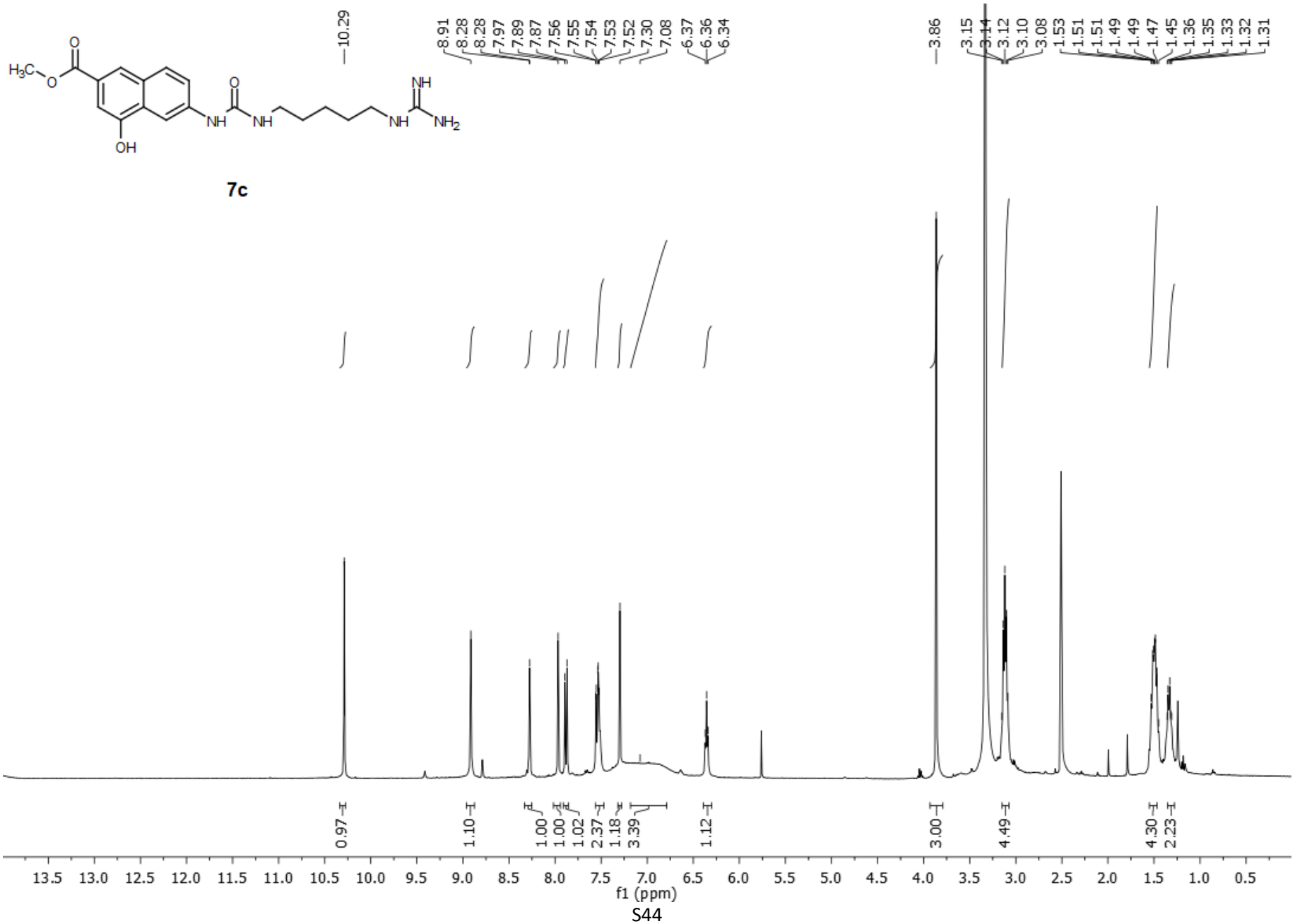
7a


166.62
156.75
155.32
152.54
139.72
129.70
128.77
127.91
124.63
121.23
120.16
107.22
106.46
51.92
39.41
36.45
29.39
O
H3C
O
O
NH
NH
NH
NH
NH2
OH
7a
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)

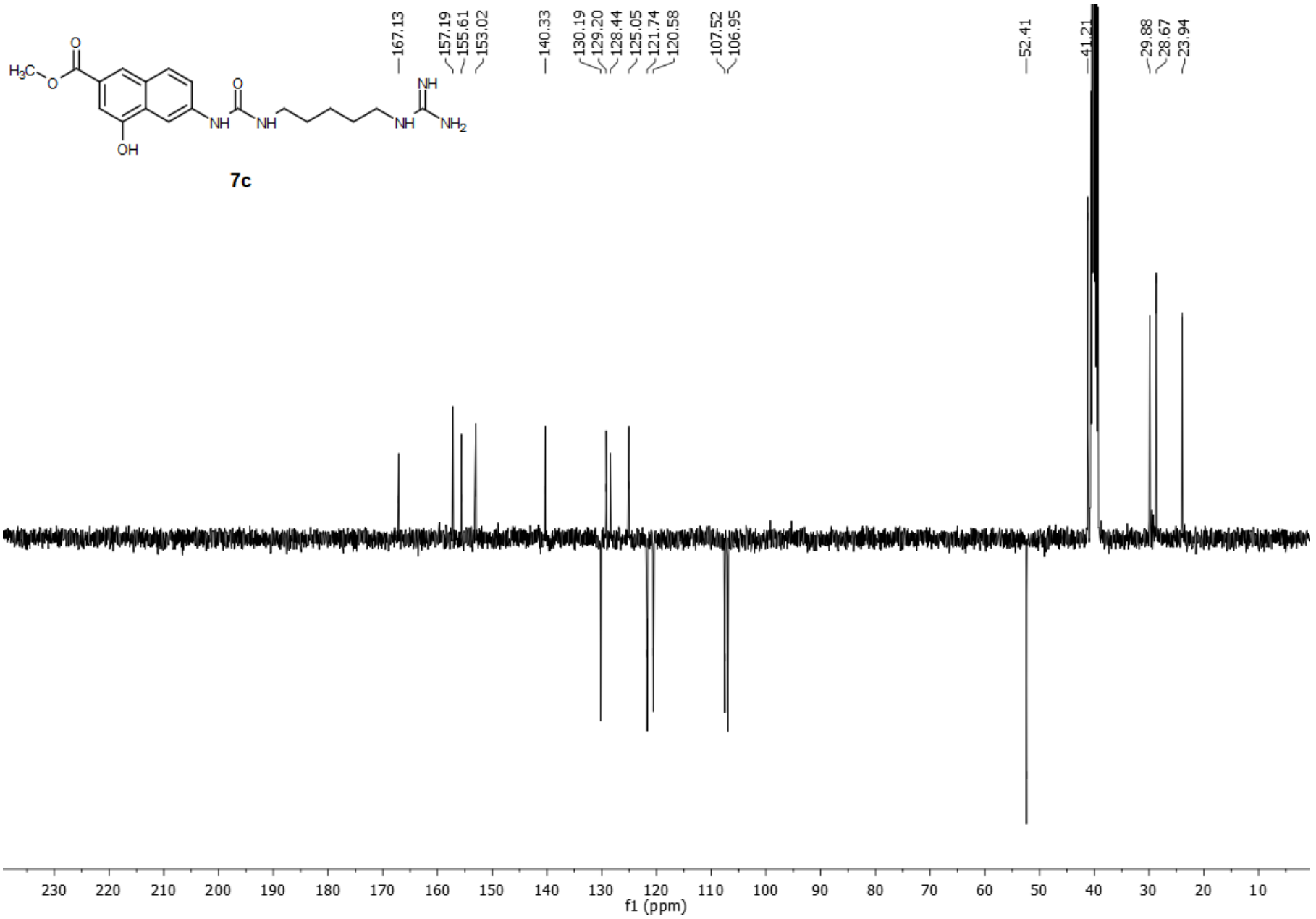

10.30
8.96
8.28
8.27
7.96
7.89
7.86
7.59
7.57
7.56
7.55
7.53
7.52
7.29
7.06
6.45
6.44
6.42
3.85
3.23
3.14
3.12
3.03
1.60
1.50
1.48
1.39
1.05
1.12
1.00
1.11
1.05
2.48
1.31
3.10
1.13
3.09
4.04
4.02
f1 (ppm)

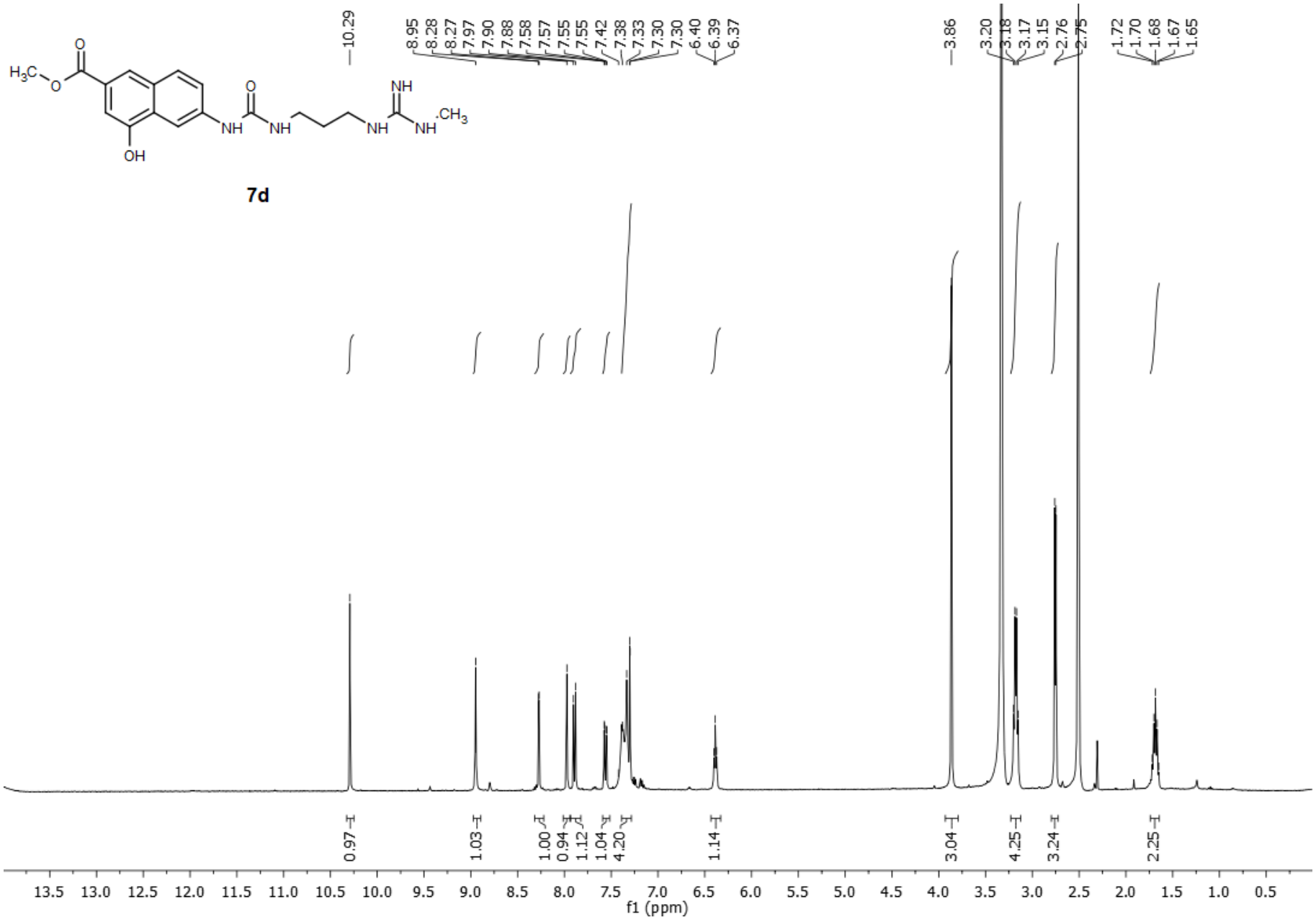
7b


166.63
156.67
155.18
152.52
139.79
129.70
128.72
127.93
124.58
121.23
120.10
107.08
106.45
51.92
27.04
26.00
O
H3C
O
O
NH
NH
NH
NH2
NH
OH
7b
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)

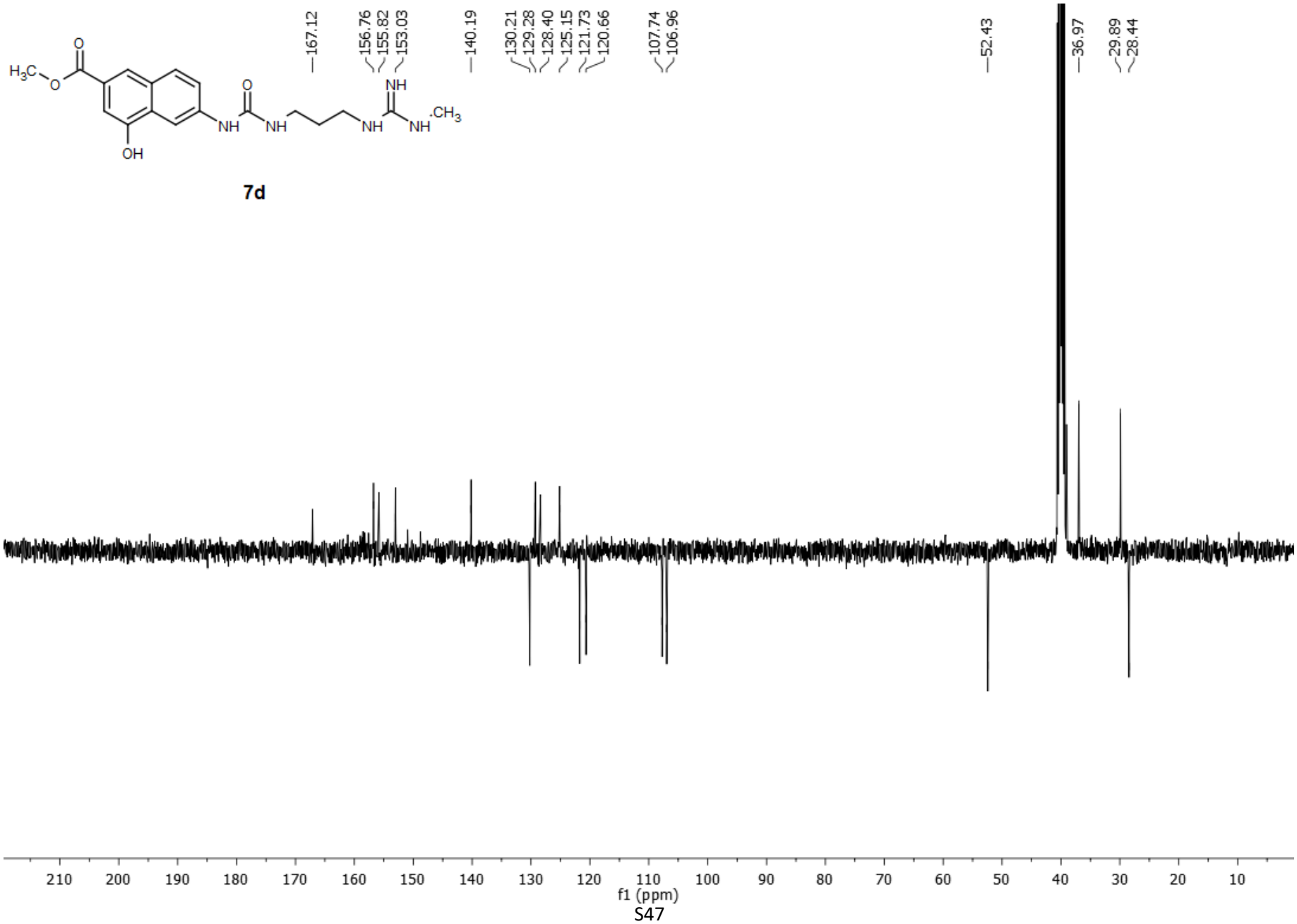

10.29
8.91
8.28
8.28
7.97
7.89
7.87
7.56
7.55
7.54
7.53
7.52
7.30
7.08
6.37
6.36
6.34
3.86
3.15
3.14
3.12
3.10
3.08
1.53
1.51
1.51
1.49
1.49
1.47
1.45
1.36
1.35
1.33
1.32
1.31
0.97
1.10
1.00
1.00
1.02
2.37
1.18
3.39
1.12
3.00
4.49
4.30
2.23
f1 (ppm)

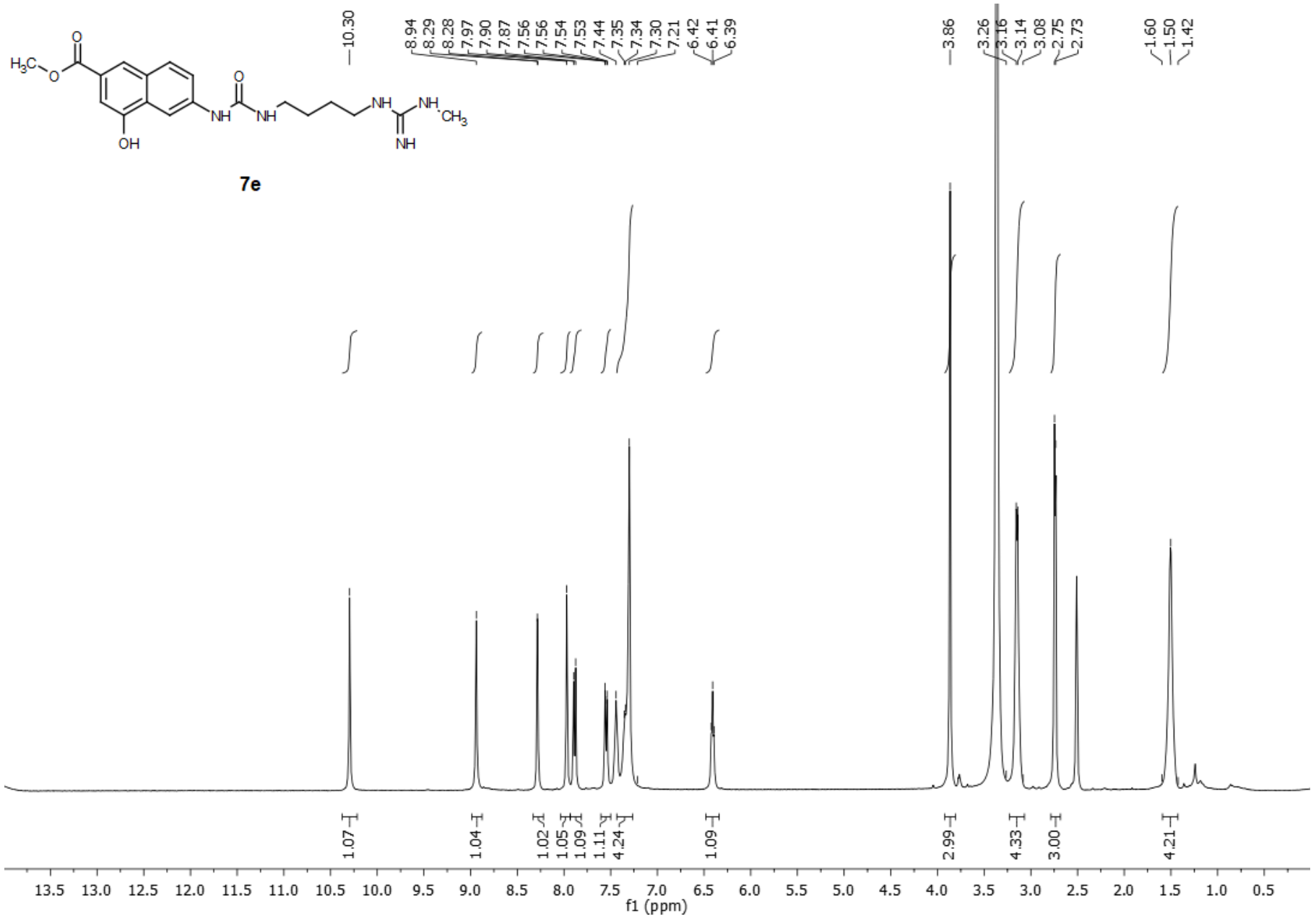
7c


167.13
157.19
155.61
153.02
140.33
130.19
129.20
128.44
125.05
121.74
120.58
107.52
106.95
52.41
41.21
29.88
28.67
23.94
O
H3C
O
O
NH
NH
NH
NH
NH2
OH
7c
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)

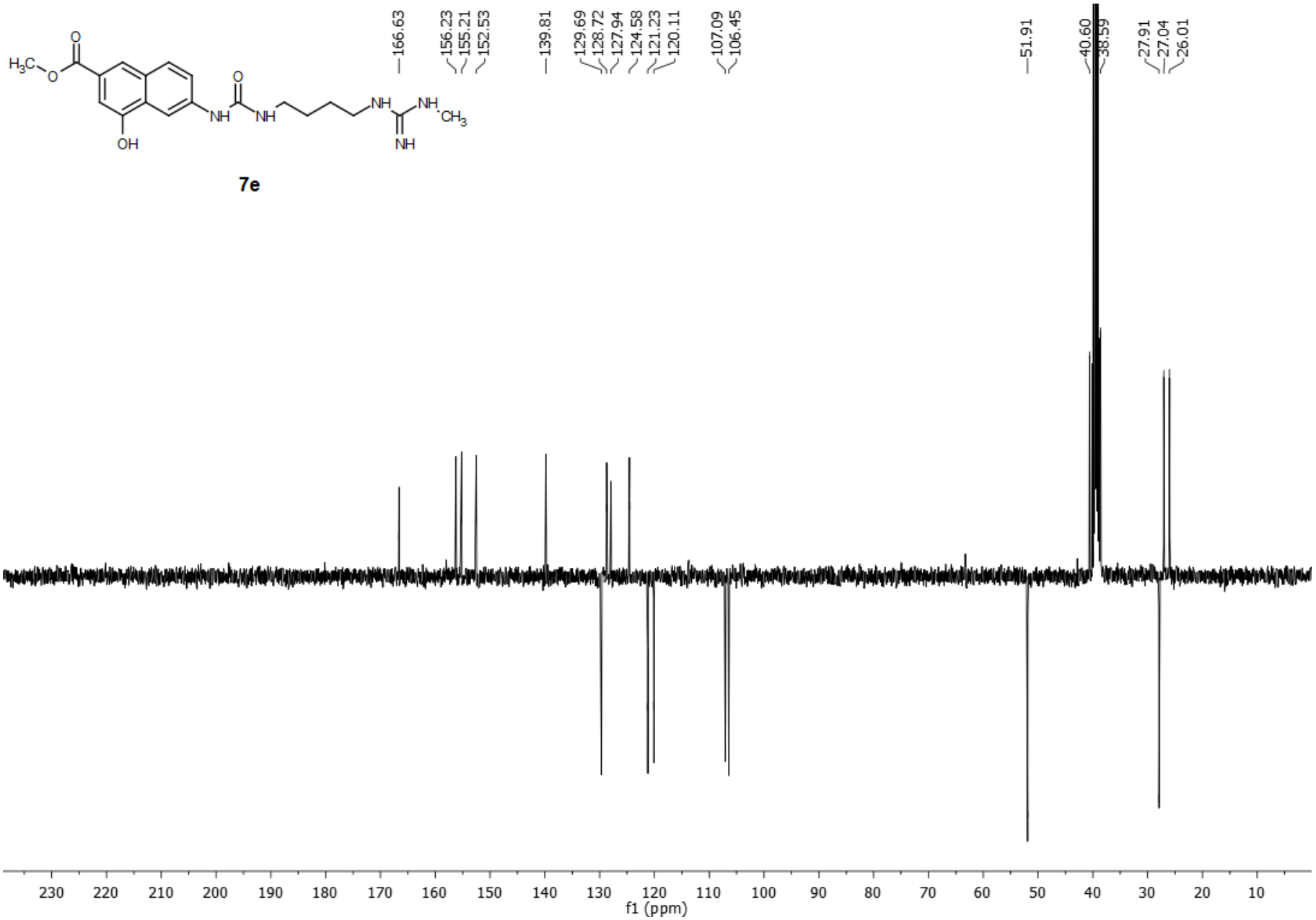

10.29
8.95
8.28
8.27
7.97
7.90
7.88
7.58
7.57
7.55
7.55
7.42
7.38
7.33
7.30
7.30
6.40
6.39
6.37
3.86
3.20
3.18
3.17
3.15
2.76
2.75
1.72
1.70
1.68
1.67
1.65
0.97
1.03
1.00
0.94
1.12
1.04
4.20
1.14
3.04
4.25
3.24
2.25
f1 (ppm)

7d

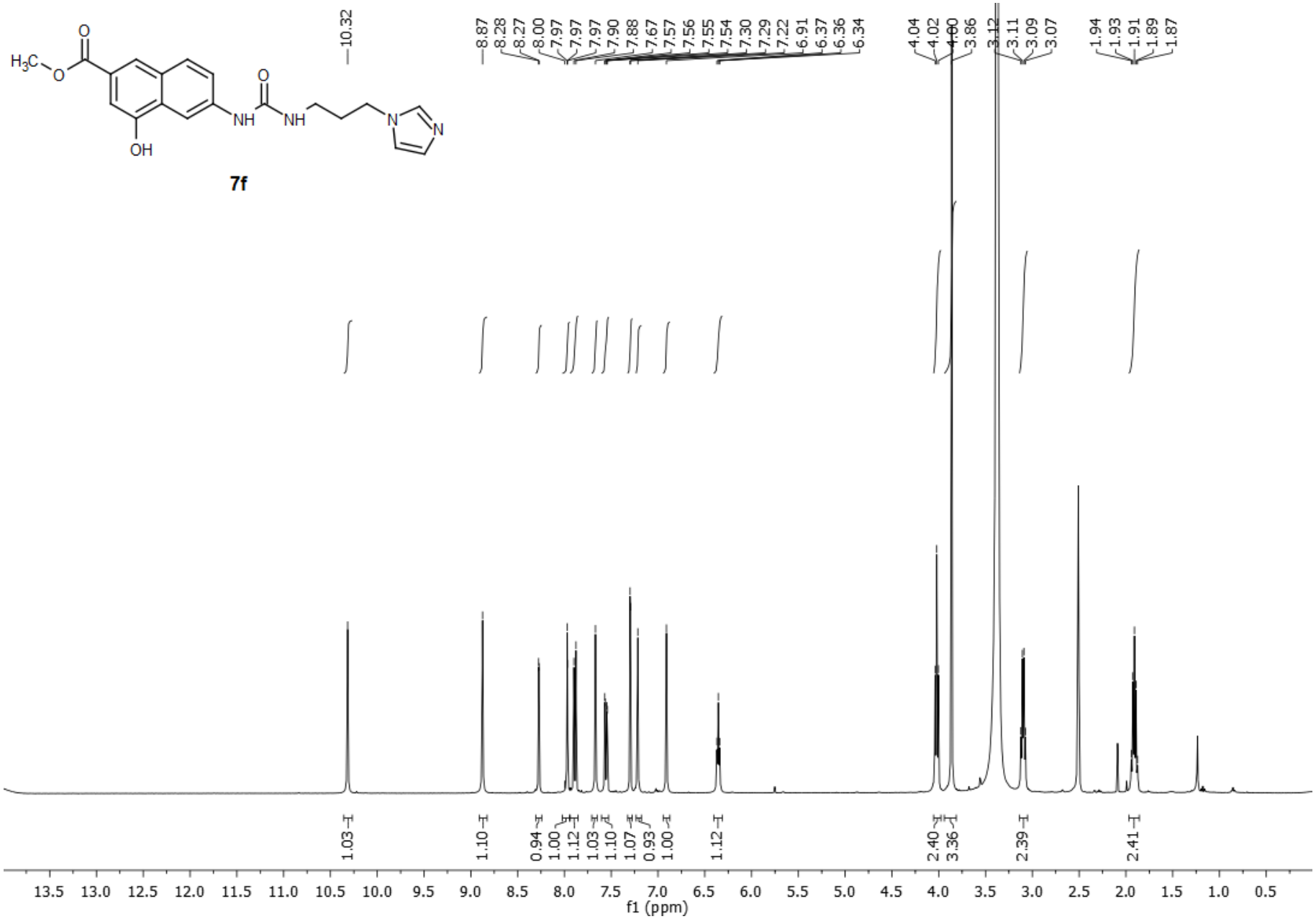

167.12
156.76
155.82
153.03
140.19
130.21
129.28
128.40
125.15
121.73
120.66
107.74
106.96
52.43
36.97
29.89
28.44
H3C
O
O
O
NH
NH
NH
NH
NH
CH3
OH
7d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


10.30
8.94
8.29
8.28
7.97
7.90
7.87
7.56
7.56
7.54
7.53
7.44
7.35
7.34
7.30
7.21
6.42
6.41
6.39
3.86
3.26
3.16
3.14
3.08
2.75
2.73
1.60
1.50
1.42
1.07
1.04
1.02
1.05
1.09
1.11
4.24
1.09
2.99
4.33
3.00
4.21
f1 (ppm)

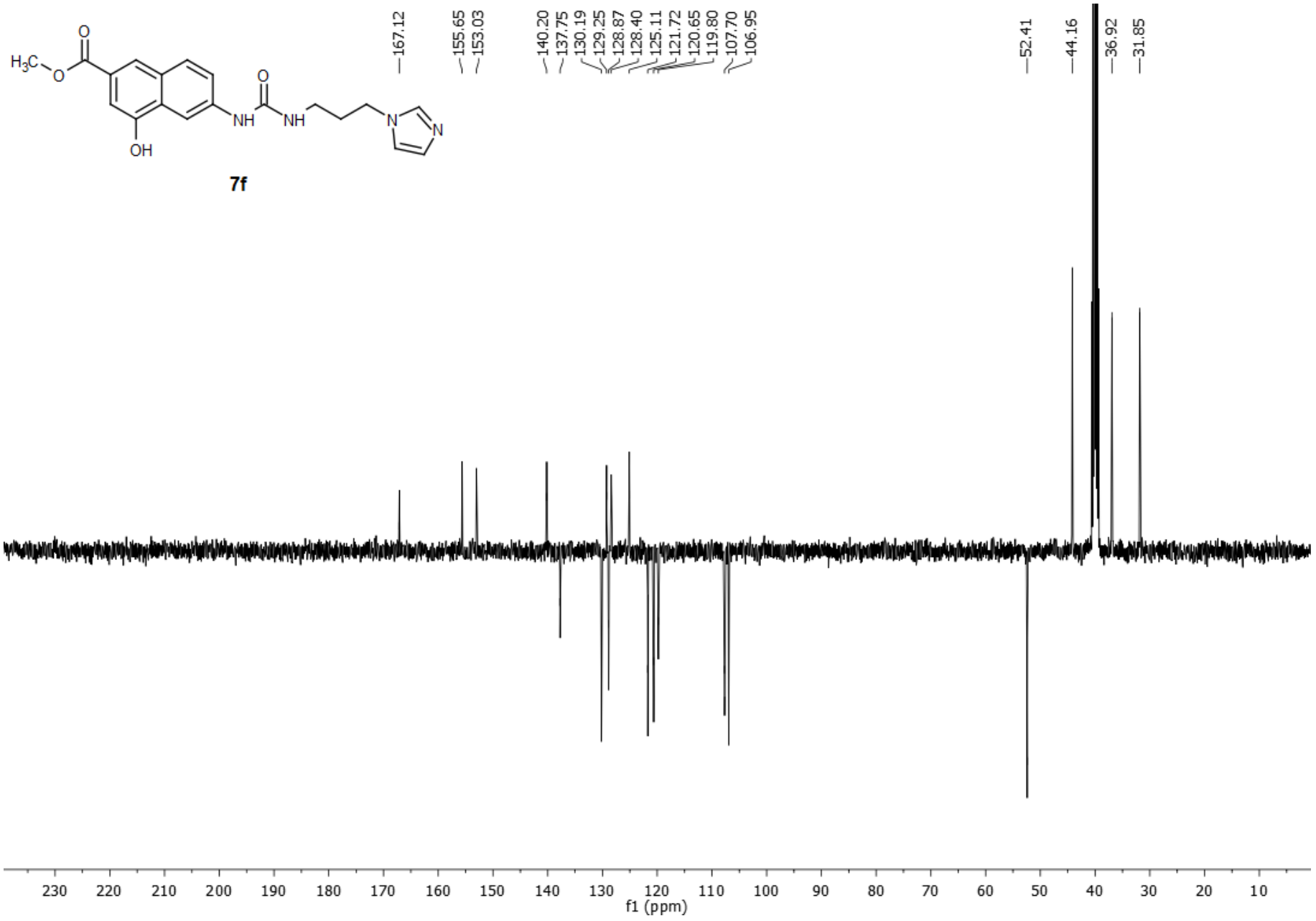
7e

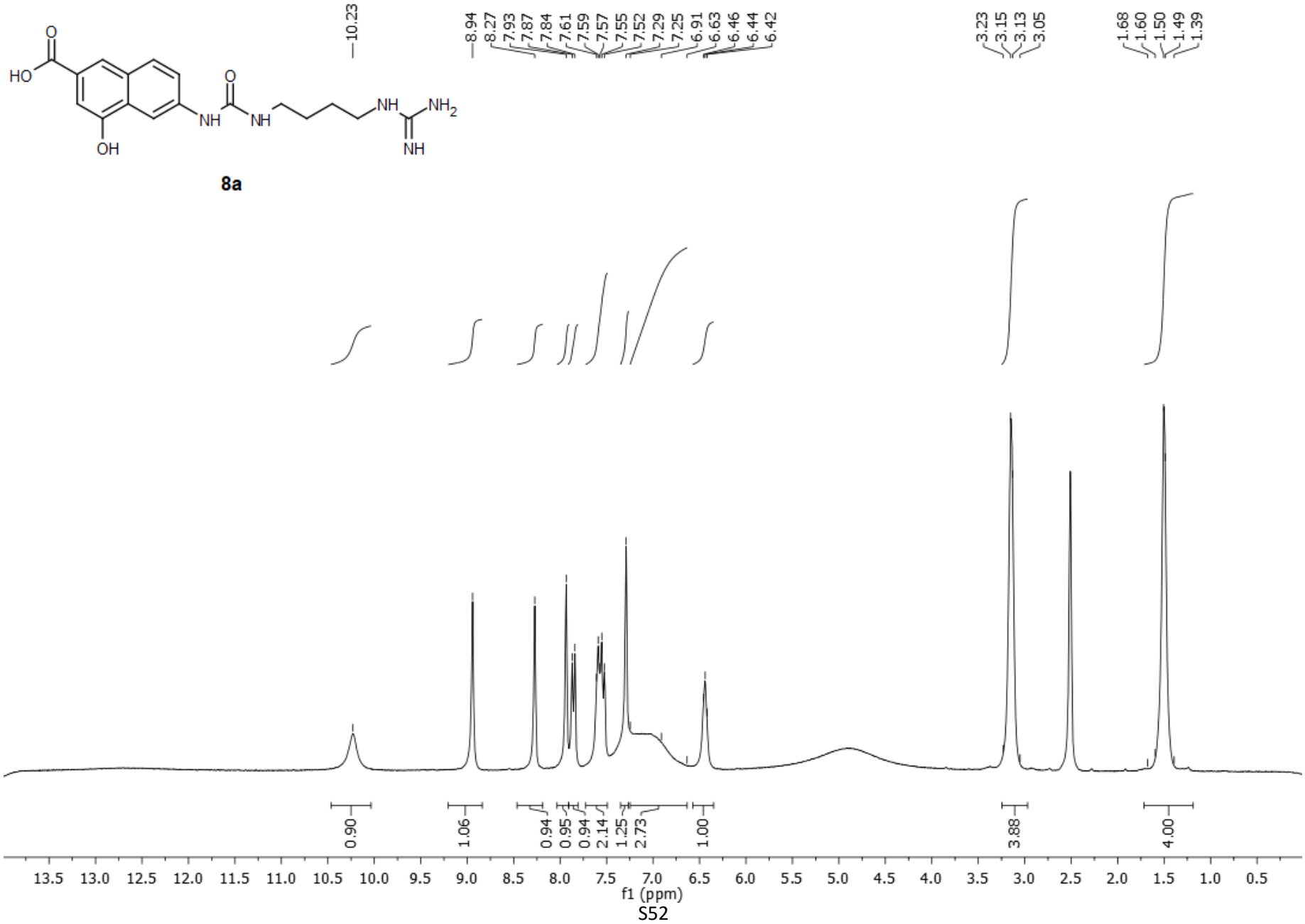

166.63
156.23
155.21
152.53
139.81
129.69
128.72
127.94
124.58
121.23
120.11
107.09
106.45
51.91
40.60
38.59
27.91
27.04
26.01
O
H3C
O
O
NH
NH
NH
NH
CH3
OH
NH
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

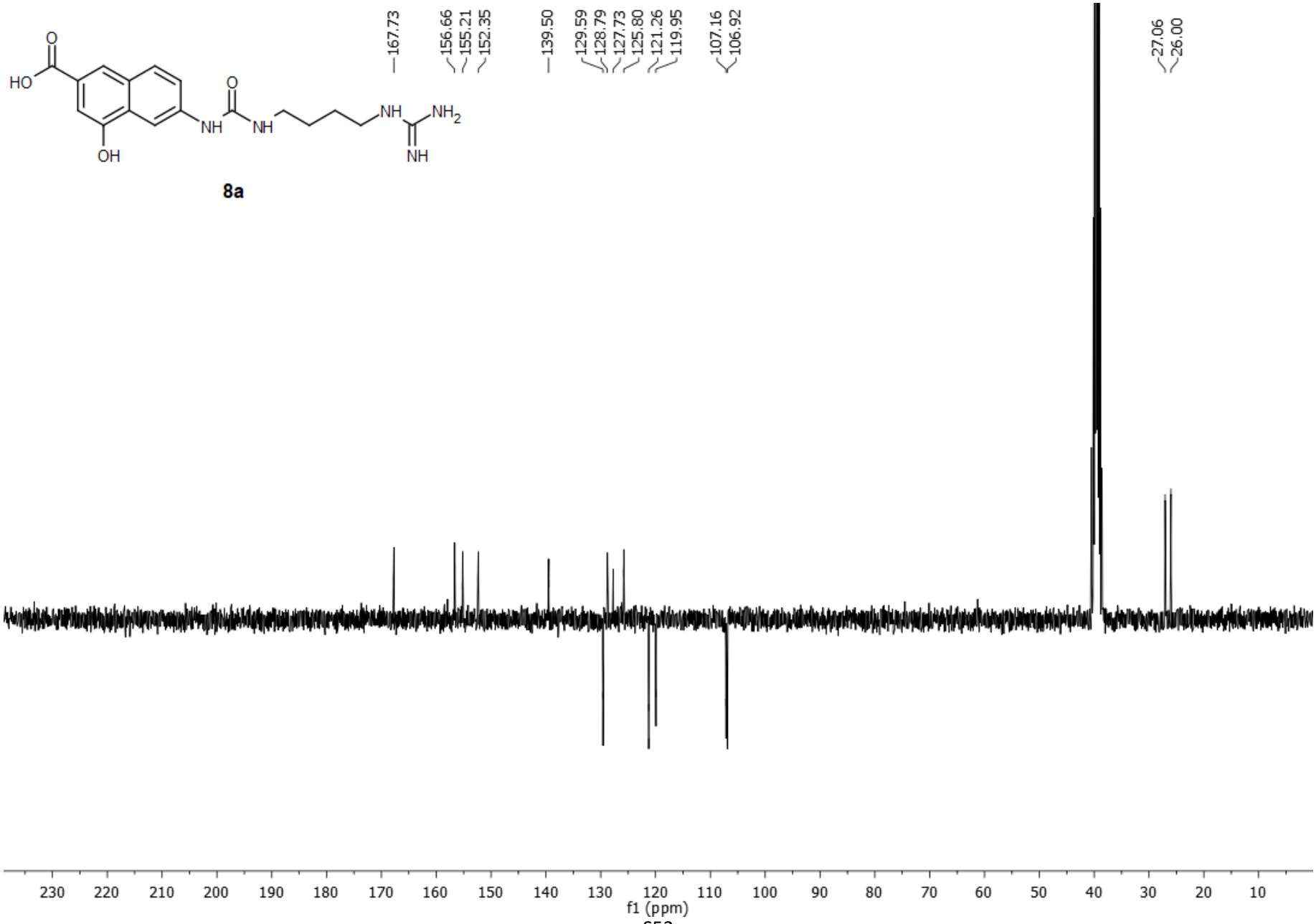
7e

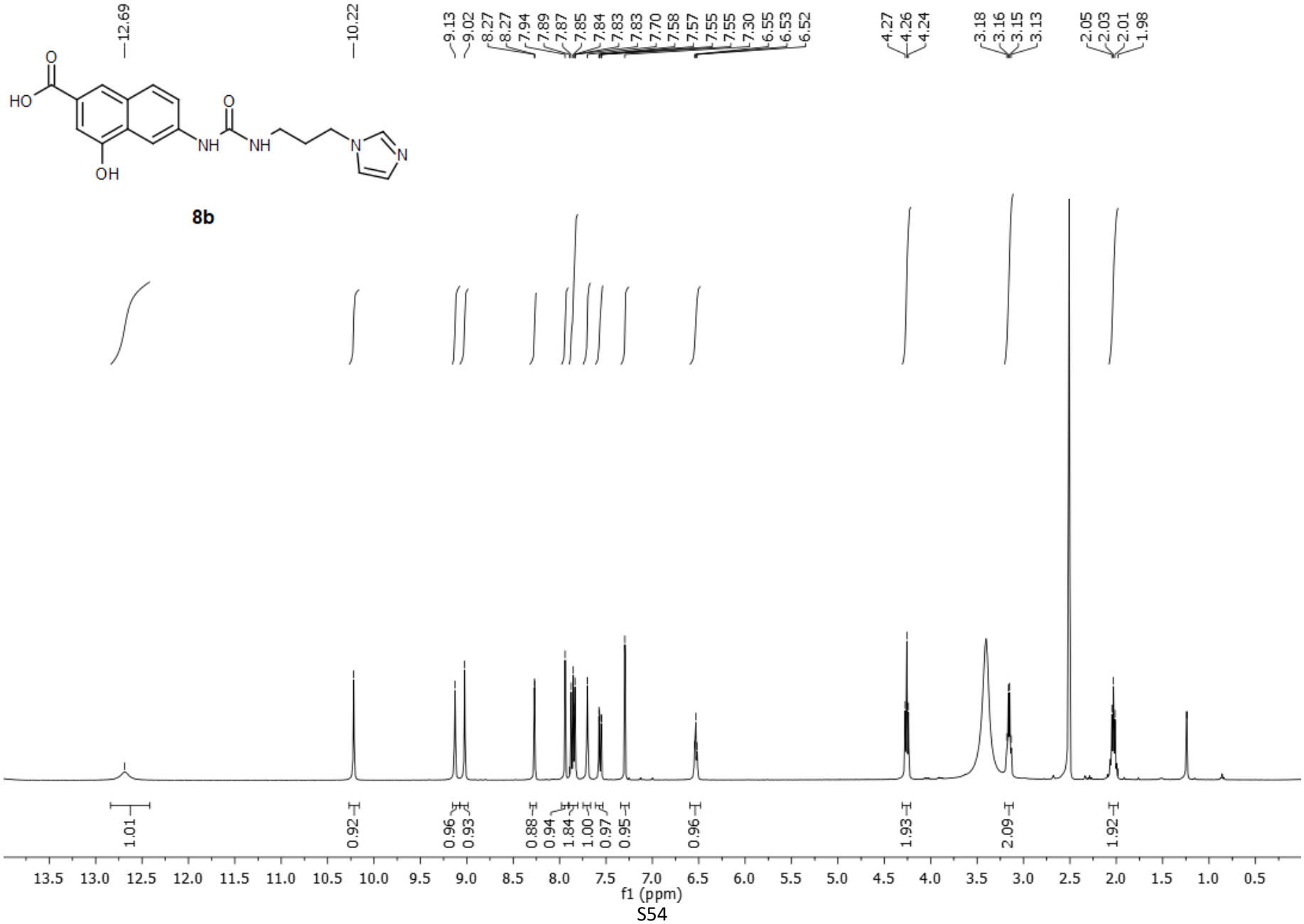

10.32
8.87
8.28
8.27
8.00
7.97
7.97
7.97
7.90
7.88
7.67
7.57
7.56
7.55
7.54
7.30
7.29
7.22
6.91
6.37
6.36
6.34
4.04
4.02
4.00
3.86
3.12
3.11
3.09
3.07
1.94
1.93
1.91
1.89
1.87
1.03
1.10
0.94
1.00
1.12
1.03
1.10
1.07
0.93
1.00
1.12
2.40
3.36
2.39
2.41
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 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
f1 (ppm)

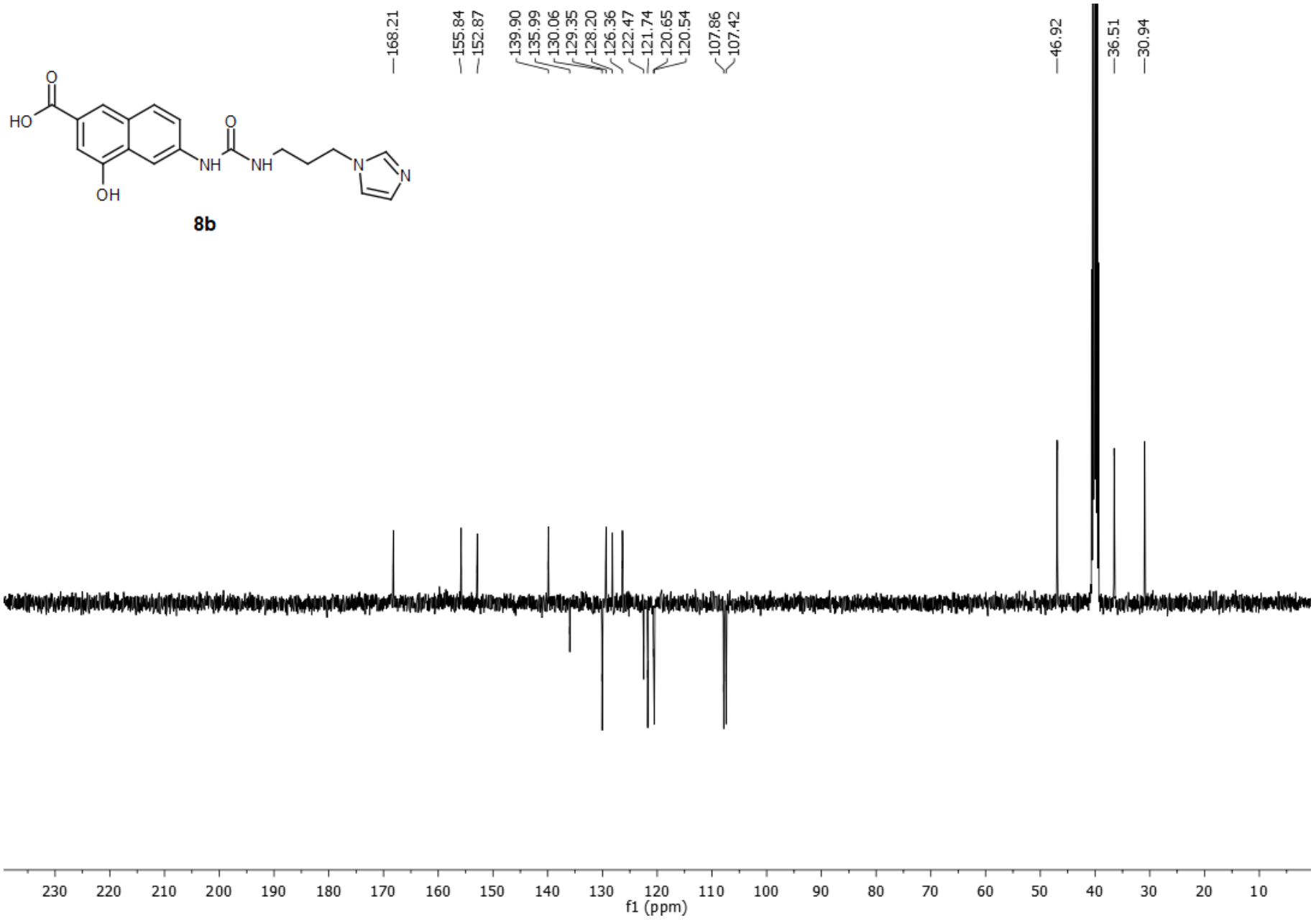
7f

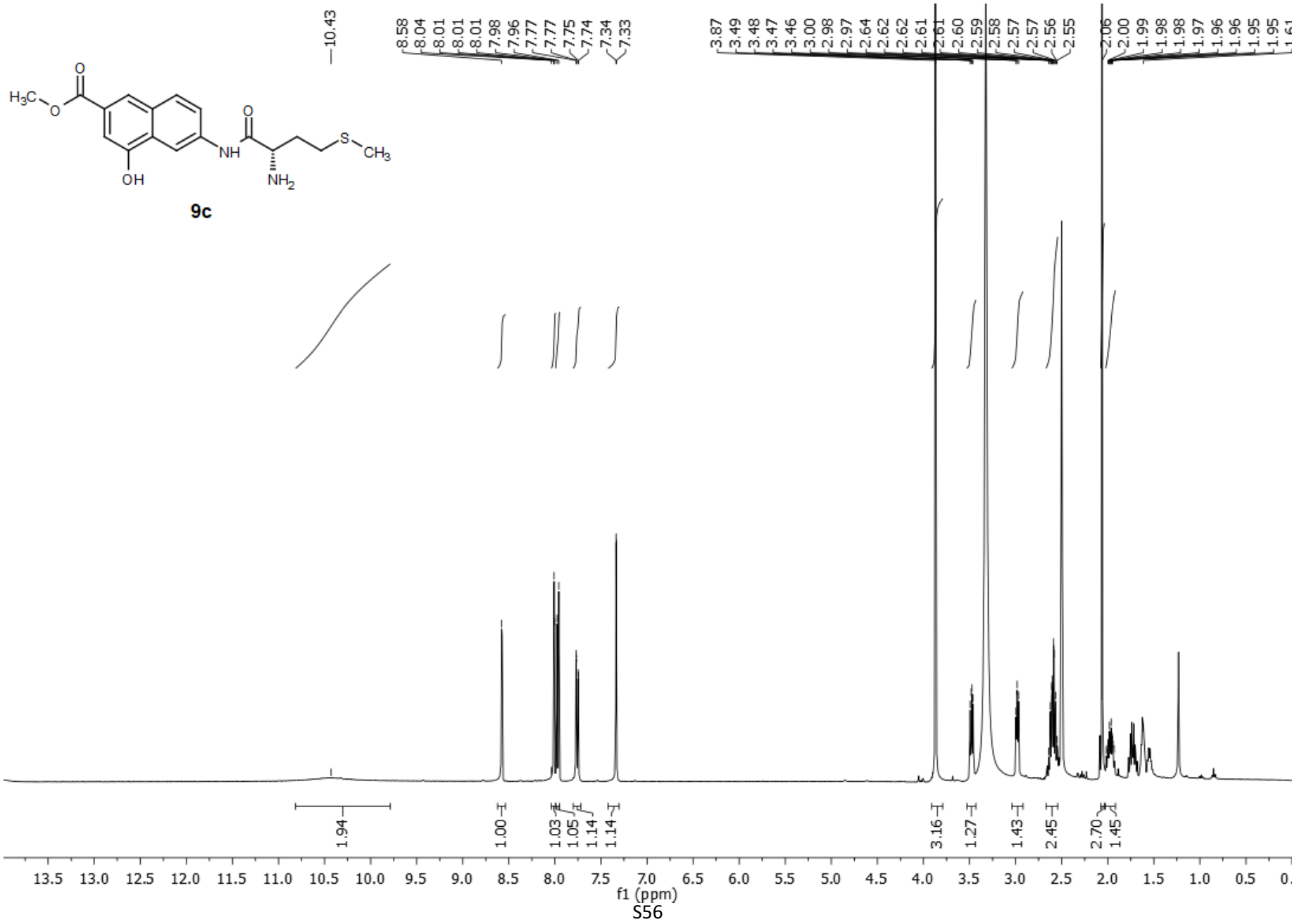

H3C
O
O
OH
NH
O
NH
N
N
7f
167.12
155.65
153.03
140.20
137.75
130.19
129.25
128.87
128.40
125.11
121.72
120.65
119.80
107.70
106.95
52.41
44.16
36.92
31.85
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


10.23
8.94
8.27
7.93
7.87
7.84
7.61
7.59
7.57
7.55
7.52
7.29
7.25
6.91
6.63
6.46
6.44
6.42
3.23
3.15
3.13
3.05
1.68
1.60
1.50
1.49
1.39
HO
O
NH
O
NH
NH
NH2
NH
OH
8a
0.90
1.06
0.94
0.95
0.94
2.14
1.25
2.73
1.00
3.88
4.00
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
f1 (ppm)

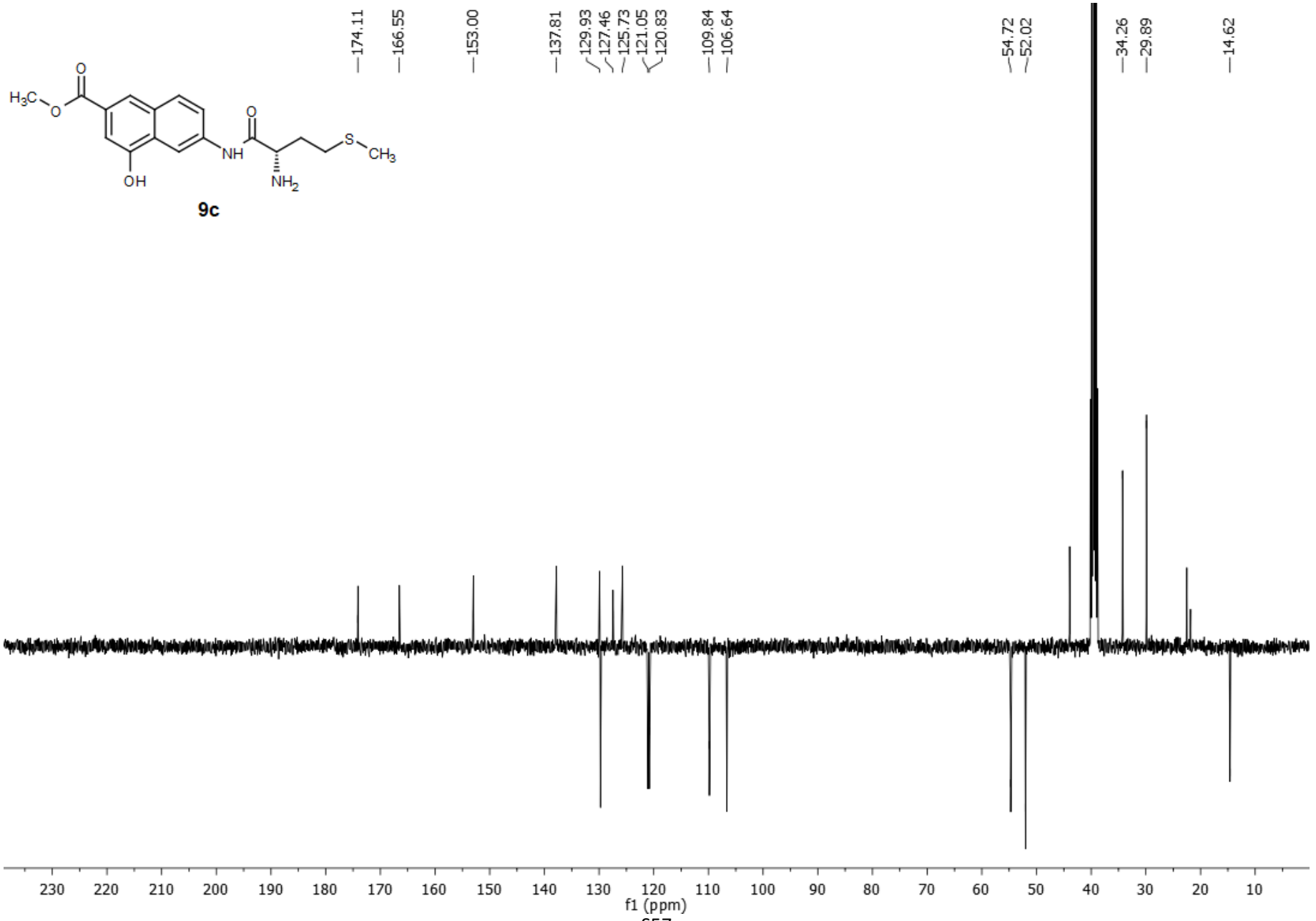

HO
O
OH
NH
O
NH
NH
NH
NH2
NH
8a
167.73
156.66
155.21
152.35
139.50
129.59
128.79
127.73
125.80
121.26
119.95
107.16
106.92
27.06
26.00
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

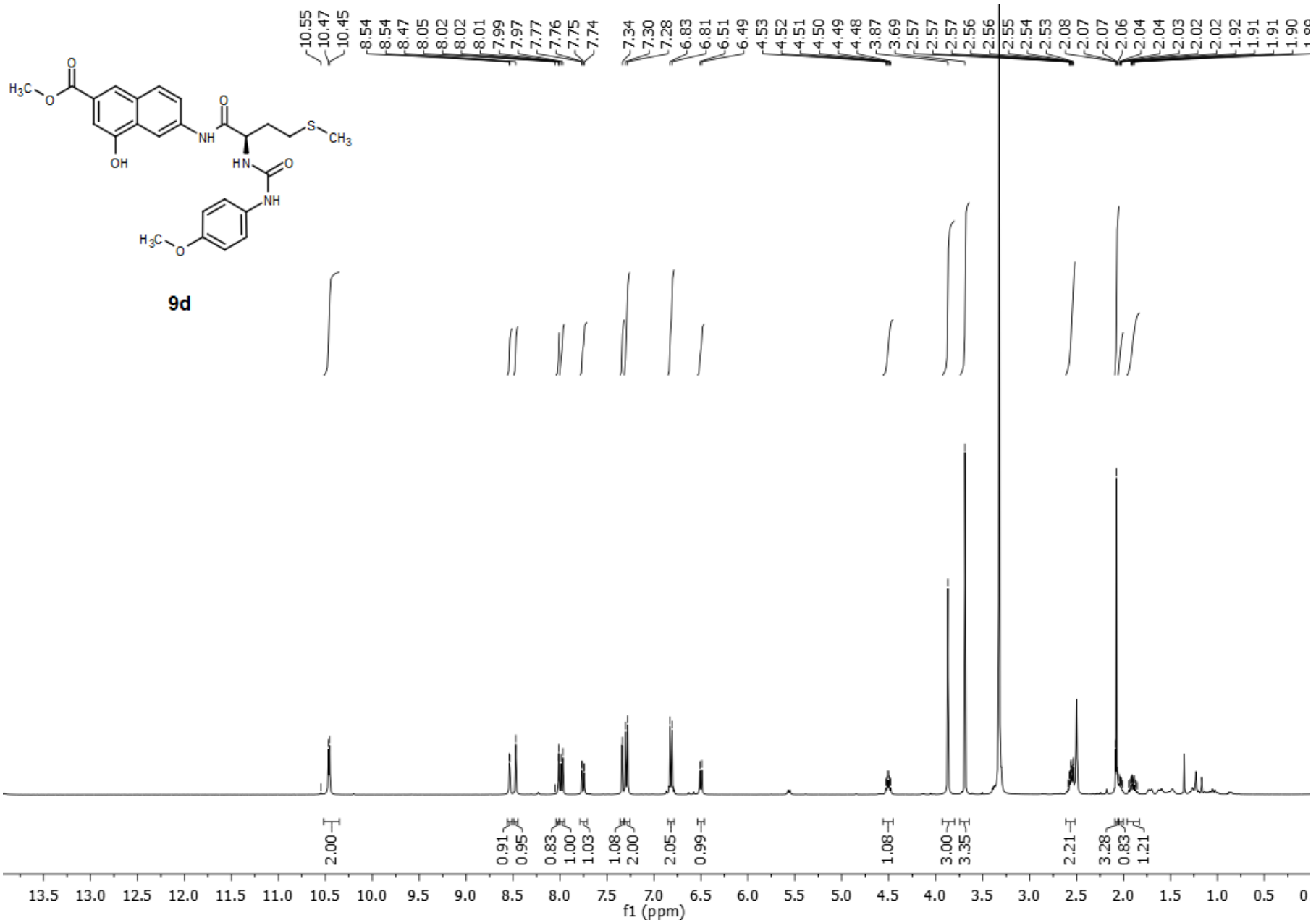

12.69
10.22
9.13
9.02
8.27
8.27
7.94
7.89
7.87
7.85
7.84
7.83
7.83
7.70
7.58
7.57
7.55
7.55
7.30
6.55
6.53
6.52
4.27
4.26
4.24
3.18
3.16
3.15
3.13
2.05
2.03
2.01
1.98
HO
O
NH
O
NH
N
N
OH
8b
1.01
0.92
0.96
0.93
0.88
0.94
1.84
1.00
0.97
0.95
0.96
1.93
2.09
1.92
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 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
f1 (ppm)


168.21
155.84
152.87
139.90
135.99
130.06
129.35
128.20
126.36
122.47
121.74
120.65
120.54
107.86
107.42
46.92
36.51
30.94
HO
O
OH
NH
O
NH
N
N
8b
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)

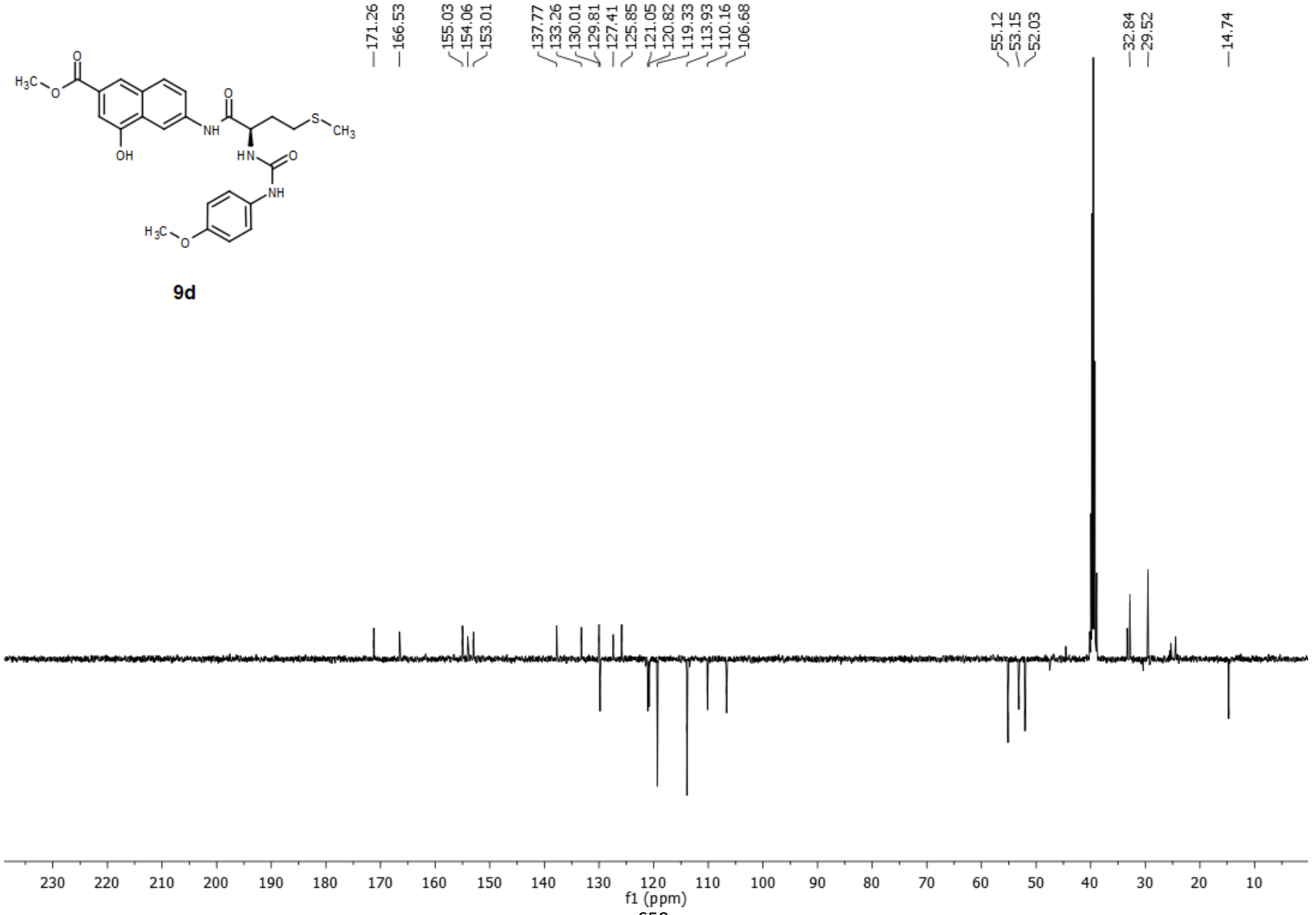

10.43
8.58
8.04
8.01
8.01
8.01
7.98
7.96
7.77
7.77
7.75
7.74
7.34
7.33
3.87
3.49
3.48
3.47
3.46
3.00
2.98
2.97
2.64
2.62
2.62
2.61
2.61
2.60
2.59
2.58
2.57
2.57
2.56
2.55
2.06
2.00
1.99
1.98
1.98
1.97
1.96
1.96
1.95
1.95
1.94
1.00
1.03
1.05
1.14
1.14
3.16
1.27
1.43
2.45
2.70
1.45
13.5 13.0 12.5 12.0 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
f1 (ppm)

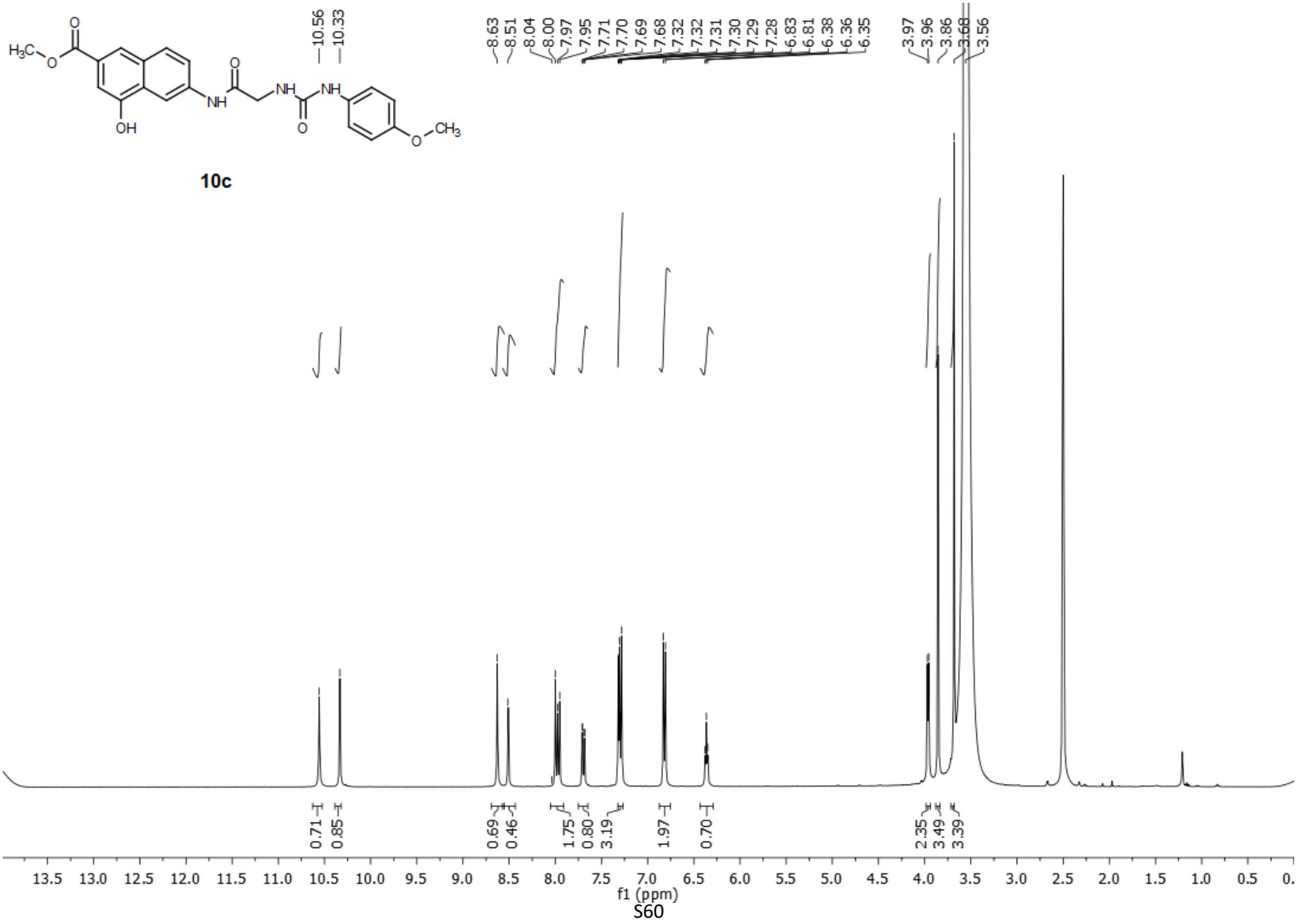
9c


174.11
166.55
153.00
137.81
129.93
127.46
125.73
121.05
120.83
109.84
106.64
54.72
52.02
34.26
29.89
14.62
H3C
O
O
O
NH
S
CH3
OH
NH2
9c
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)

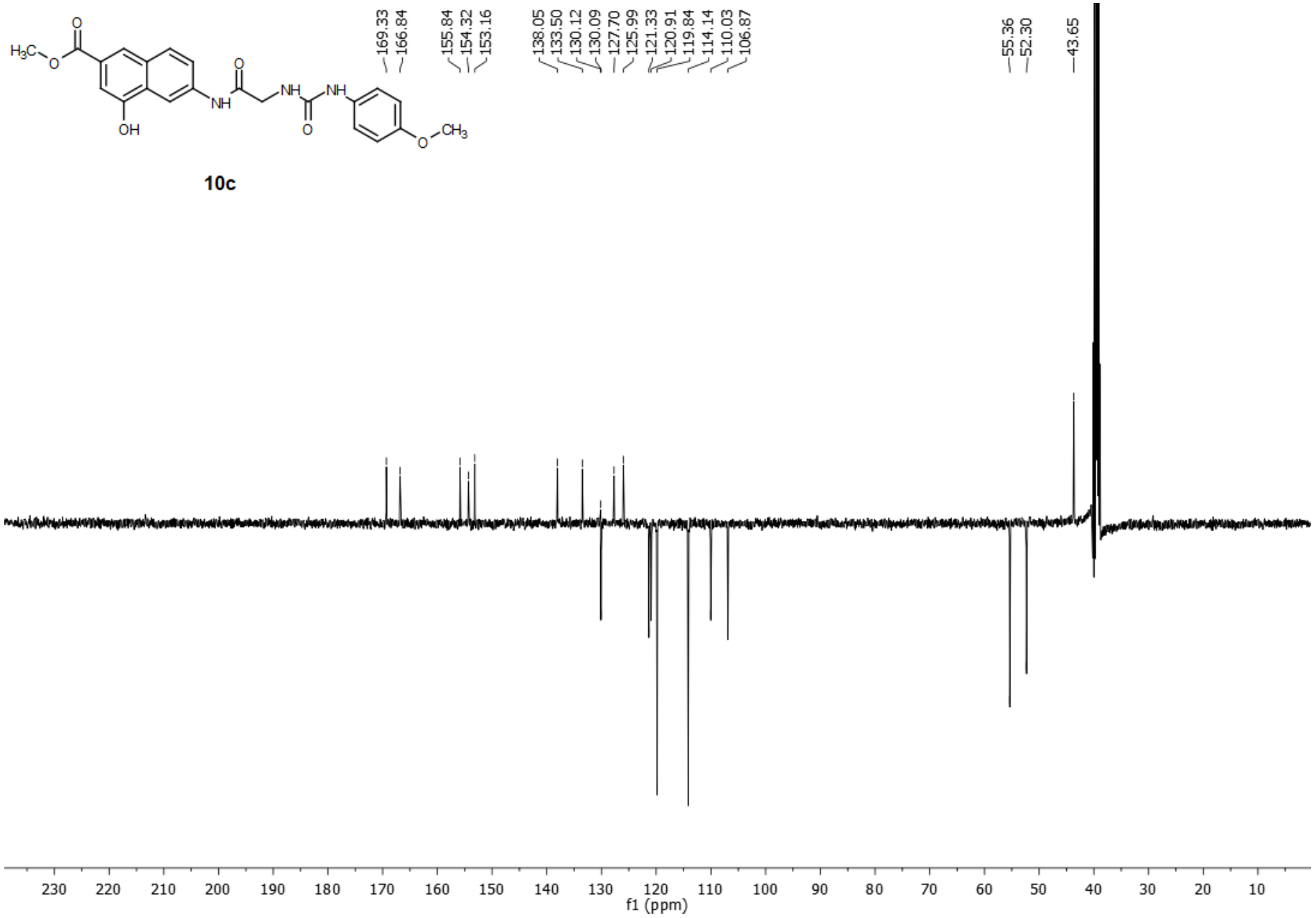

10.55
10.47
10.45
8.54
8.54
8.47
8.05
8.02
8.02
8.01
7.99
7.97
7.77
7.76
7.75
7.74
7.34
7.30
7.28
6.83
6.81
6.51
6.49
4.53
4.52
4.51
4.50
4.49
4.48
3.87
3.69
2.57
2.57
2.57
2.56
2.56
2.55
2.54
2.53
2.08
2.07
2.07
2.06
2.04
2.04
2.03
2.02
2.02
1.92
1.91
1.91
1.90
H3C
O
O
NH
O
S
CH3
OH
HN
O
NH
H3C
O
2.00
0.91
0.95
0.83
1.00
1.03
1.08
2.00
2.05
0.99
1.08
3.00
3.35
2.21
3.28
0.83
1.21
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
f1 (ppm)

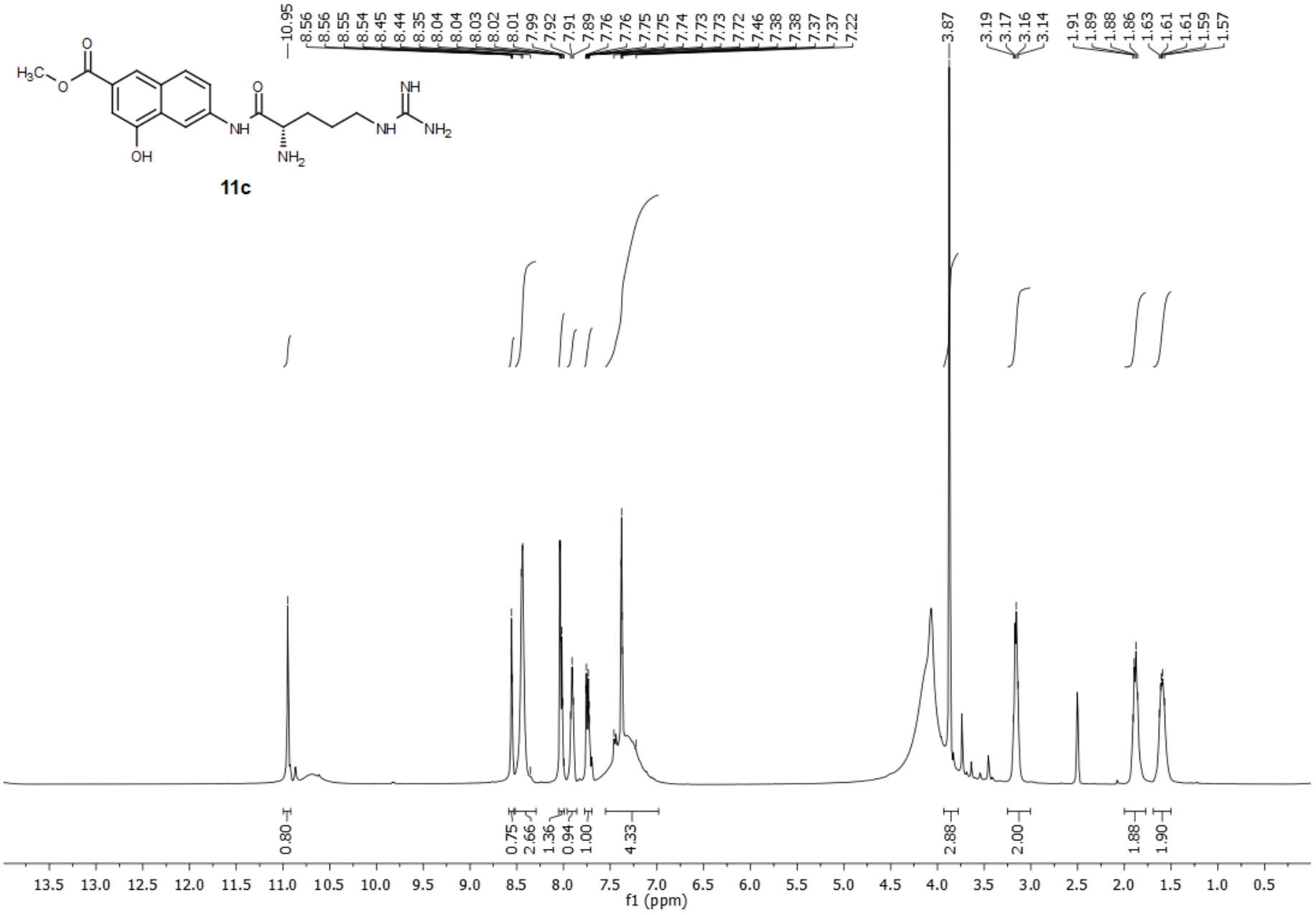
9d


171.26
166.53
155.03
154.06
153.01
137.77
133.26
130.01
129.81
127.41
125.85
121.05
120.82
119.33
113.93
110.16
106.68
55.12
53.15
52.03
32.84
29.52
14.74
9d
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)

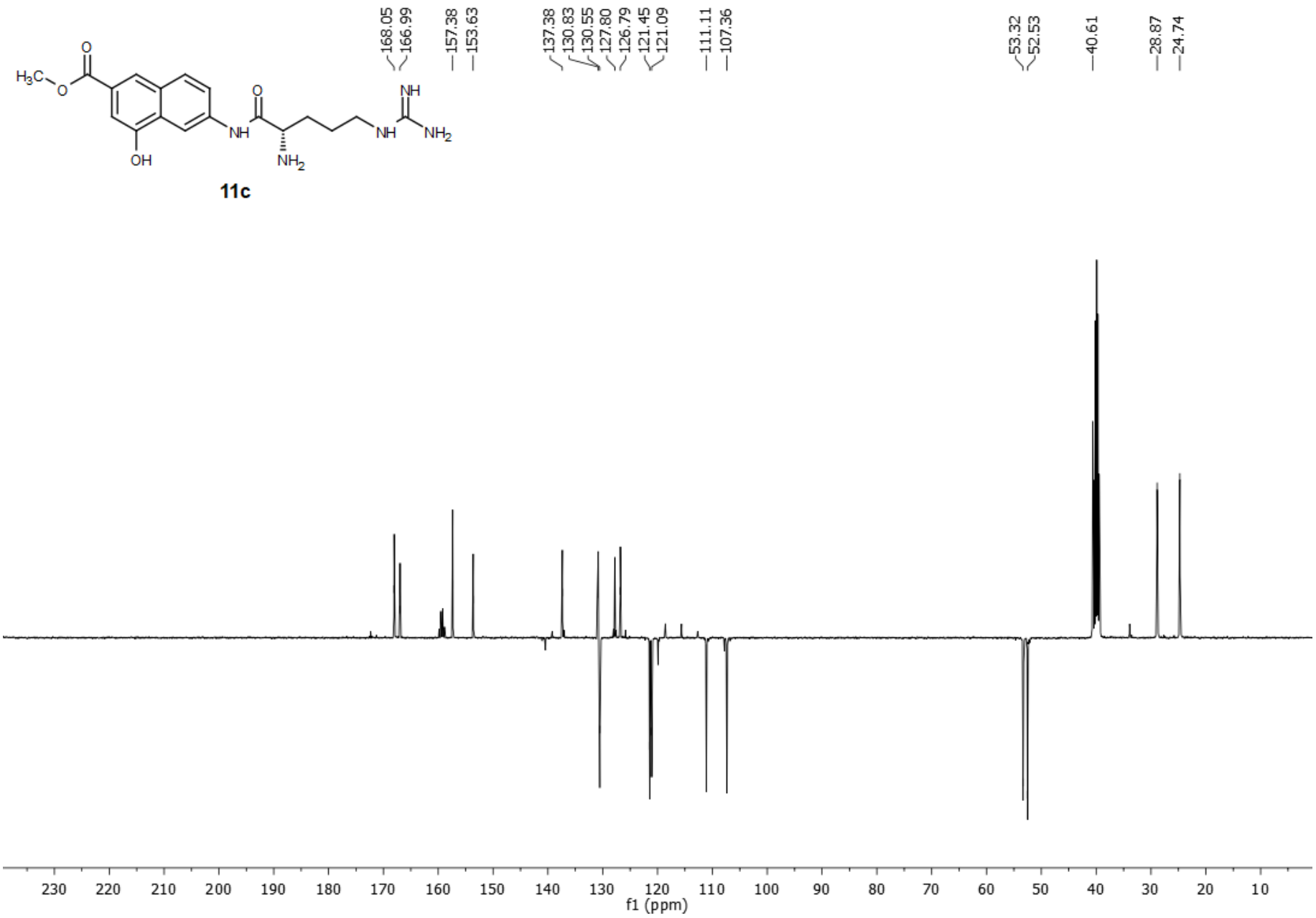

10.56
10.33
8.63
8.51
8.04
8.00
7.97
7.95
7.71
7.70
7.69
7.68
7.32
7.32
7.31
7.30
7.29
7.28
6.83
6.81
6.38
6.36
6.35
3.97
3.96
3.86
3.68
3.56
0.71
0.85
0.69
0.46
1.75
0.80
3.19
1.97
0.70
2.35
3.49
3.39
f1 (ppm)

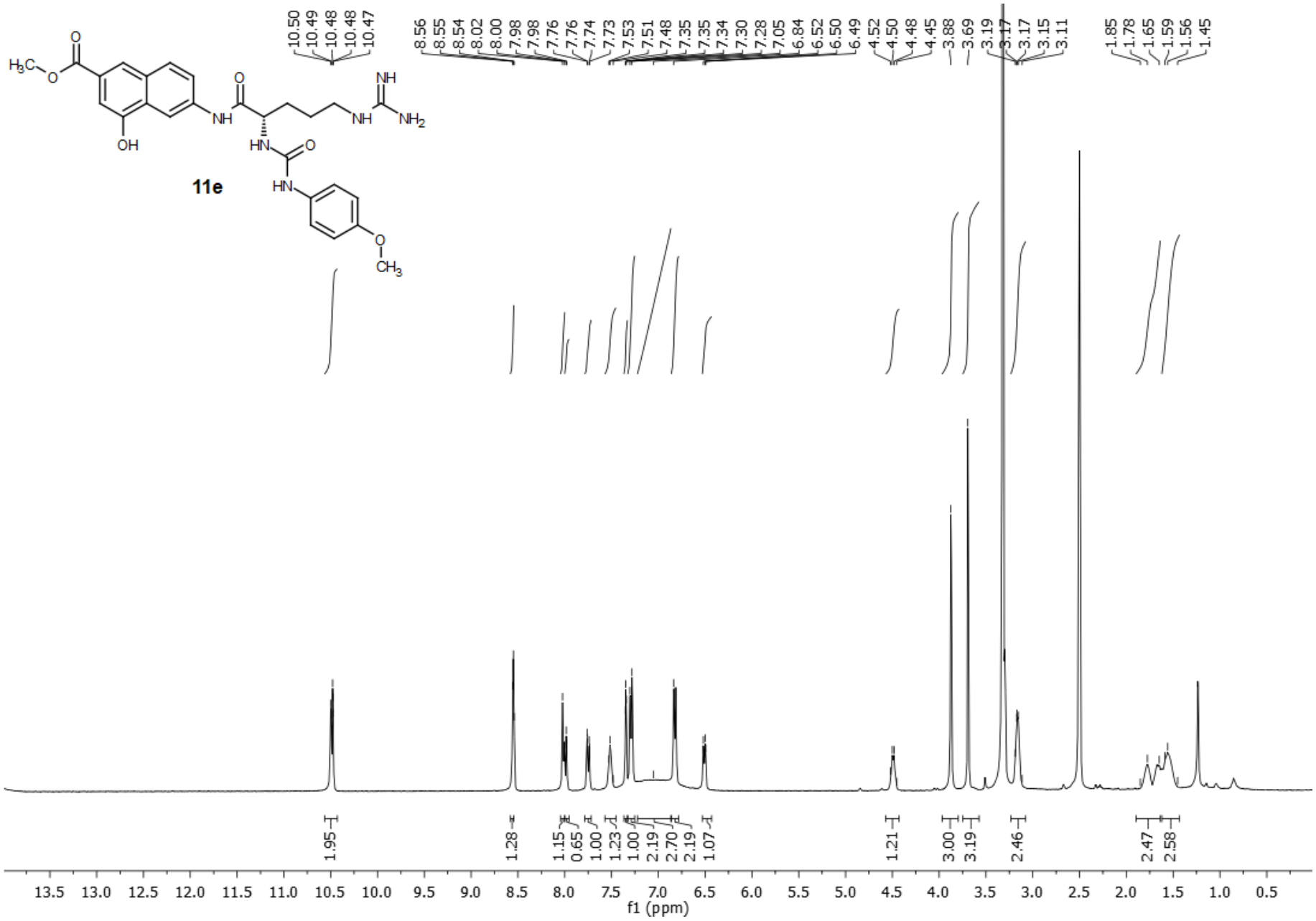
10c

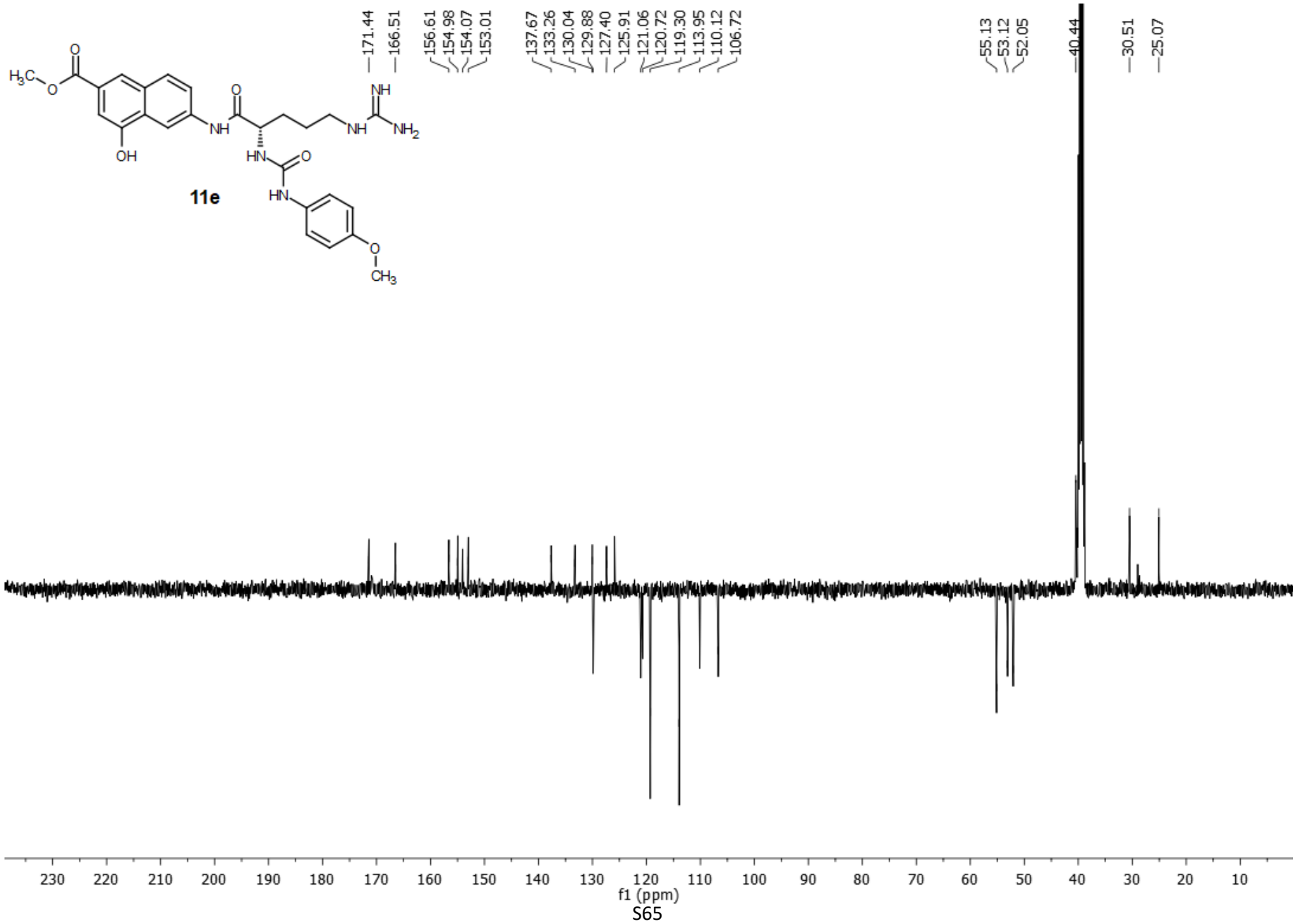

169.33
166.84
155.84
154.32
153.16
138.05
133.50
130.12
130.09
127.70
125.99
121.33
120.91
119.84
114.14
110.03
106.87
55.36
52.30
43.65
10c
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

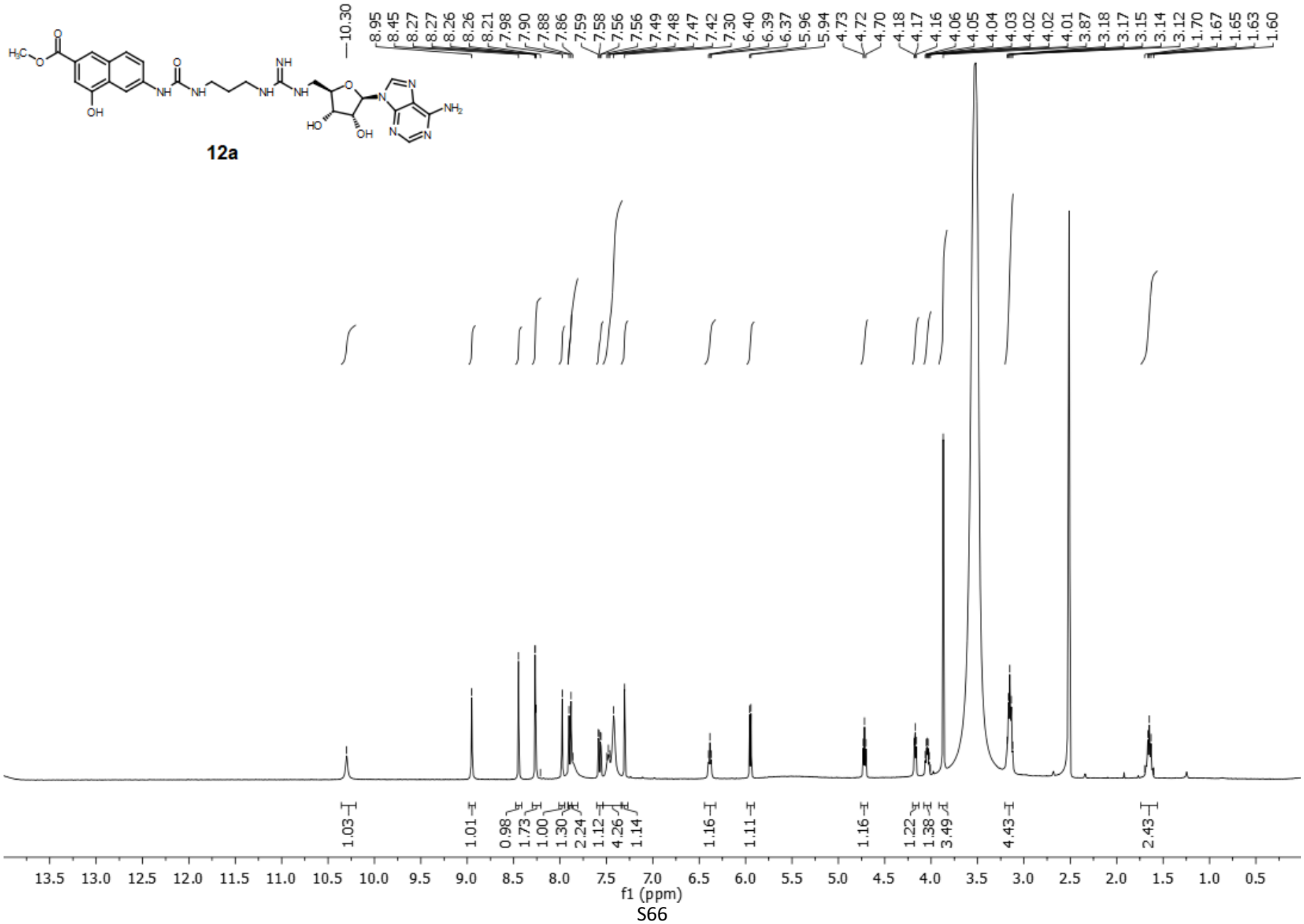

10.95
8.56
8.56
8.55
8.54
8.45
8.44
8.35
8.04
8.04
8.03
8.02
8.01
7.99
7.92
7.91
7.89
7.76
7.76
7.75
7.75
7.74
7.73
7.73
7.72
7.46
7.38
7.38
7.37
7.37
7.22
3.87
3.19
3.17
3.16
3.14
1.91
1.89
1.88
1.86
1.63
1.61
1.61
1.59
1.57
0.80
0.75
2.66
1.36
0.94
1.00
4.33
2.88
2.00
1.88
1.90
f1 (ppm)

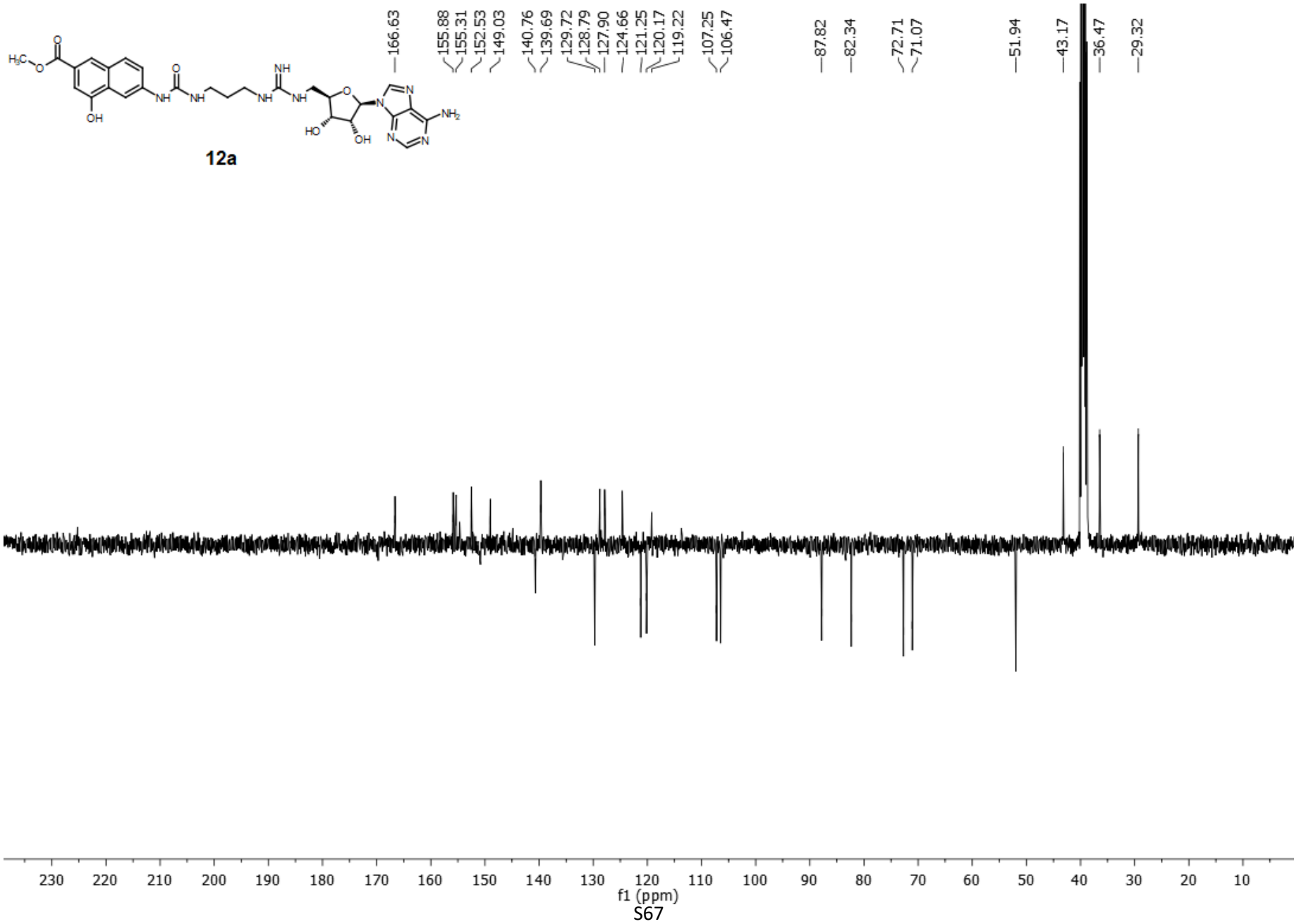
11c

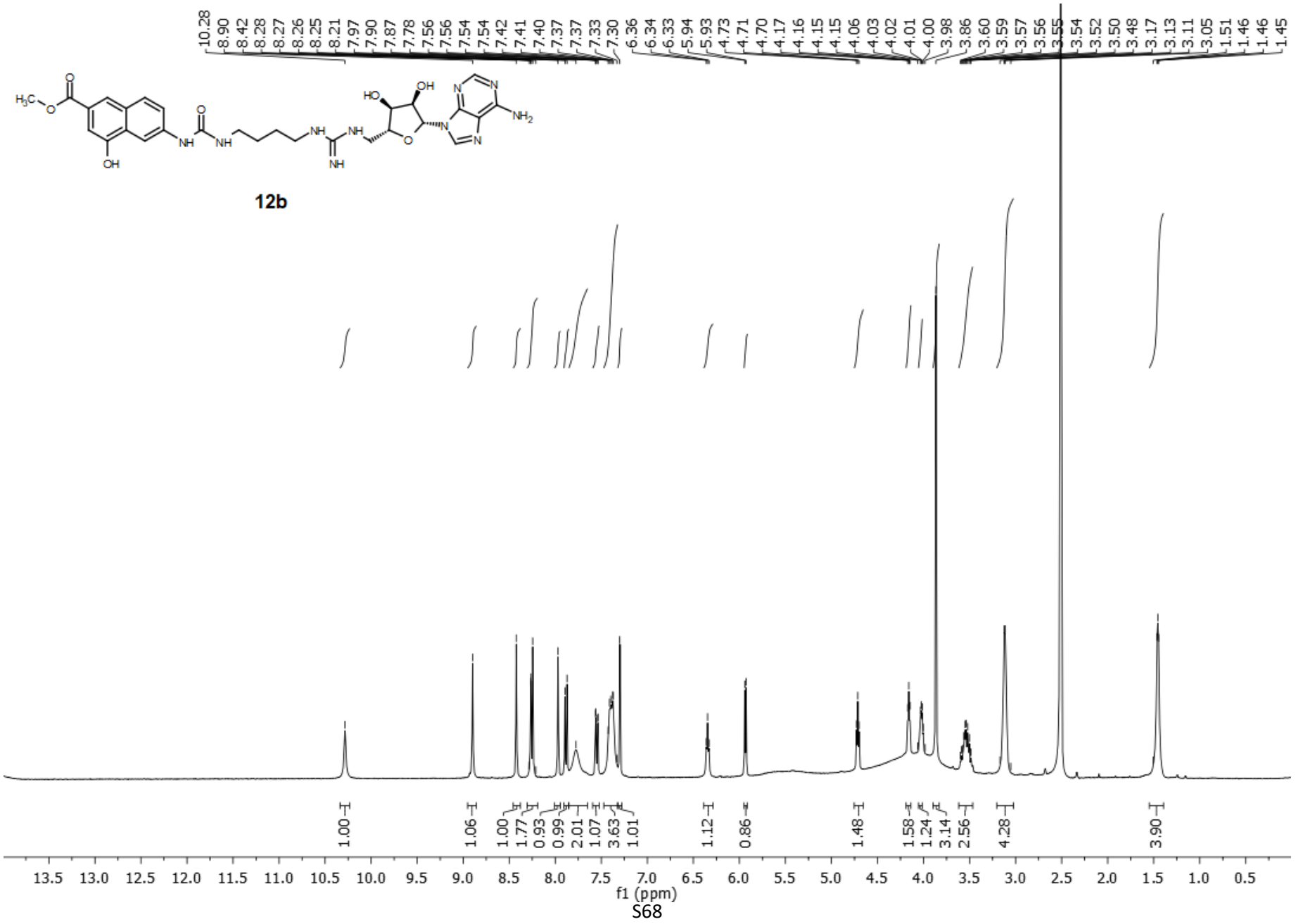

168.05
166.99
157.38
153.63
137.38
130.83
130.55
127.80
126.79
121.45
121.09
111.11
107.36
53.32
52.53
40.61
28.87
24.74
H3C
O
O
OH
NH
O
NH2
NH
NH
NH2
11c
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

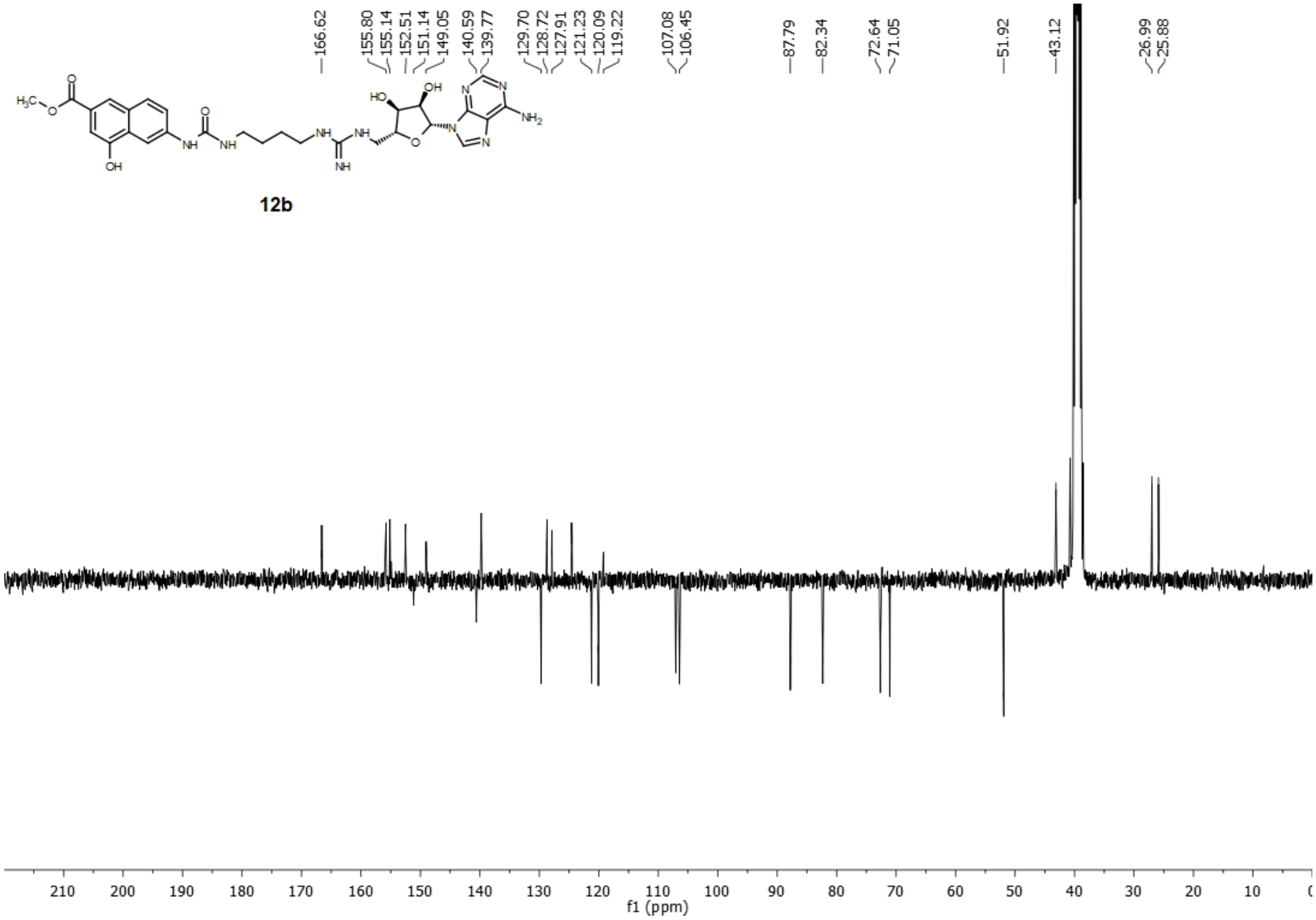

11e
10.50
10.49
10.48
10.48
10.47
8.56
8.55
8.54
8.02
8.00
7.98
7.98
7.76
7.76
7.74
7.73
7.53
7.51
7.48
7.35
7.35
7.34
7.30
7.28
7.05
6.84
6.52
6.50
6.49
4.52
4.50
4.48
4.45
3.88
3.69
3.19
3.17
3.17
3.15
3.11
1.85
1.78
1.65
1.59
1.56
1.45
1.95
1.28
1.15
0.65
1.00
1.23
1.00
2.19
2.70
2.19
1.07
1.21
3.00
3.19
2.46
2.47
2.58
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
f1 (ppm)

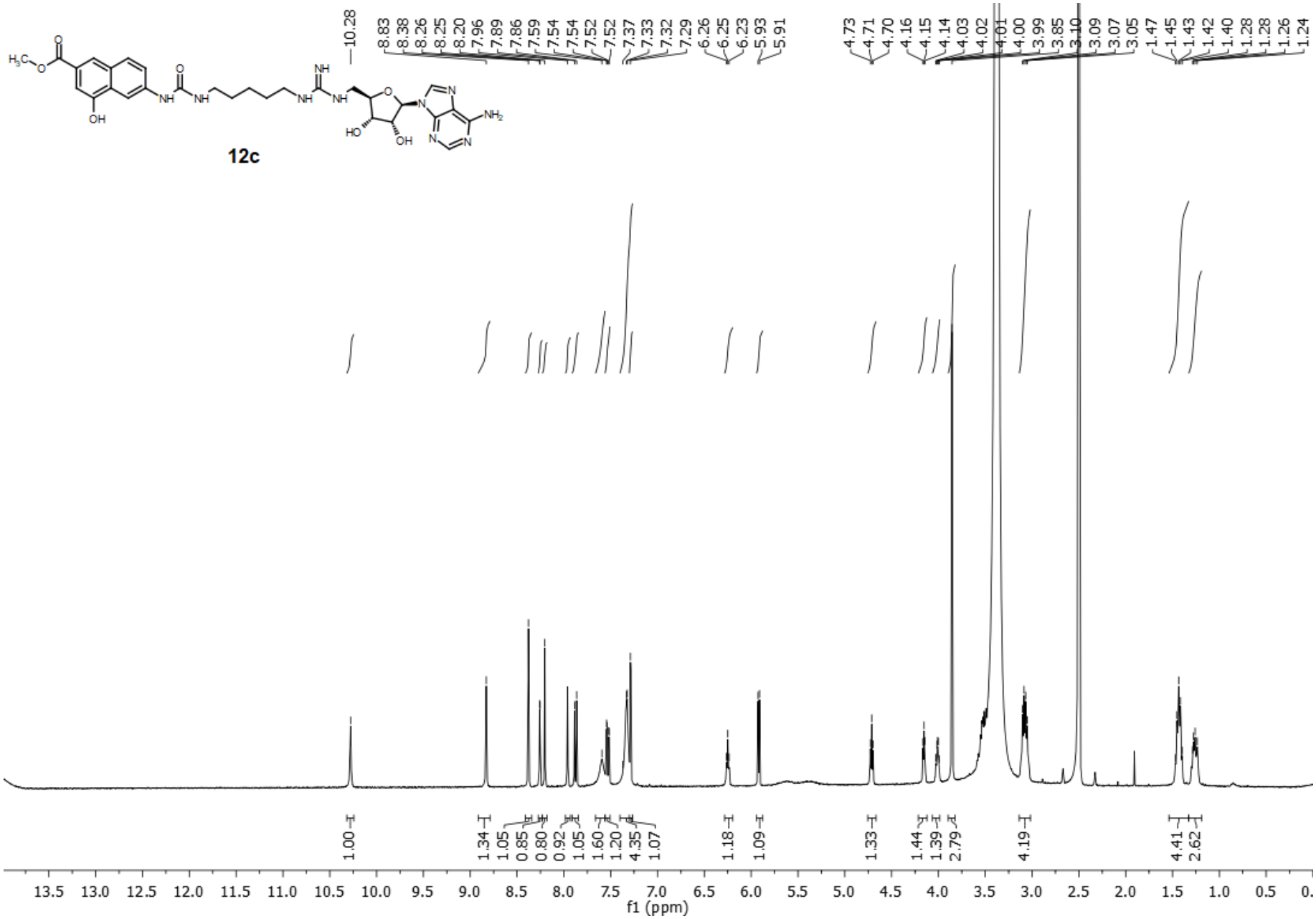

171.44
166.51
156.61
154.98
154.07
153.01
137.67
133.26
130.04
129.88
127.40
125.91
121.06
120.72
119.30
113.95
110.12
106.72
55.13
53.12
52.05
40.44
30.51
25.07
11e
f1 (ppm)

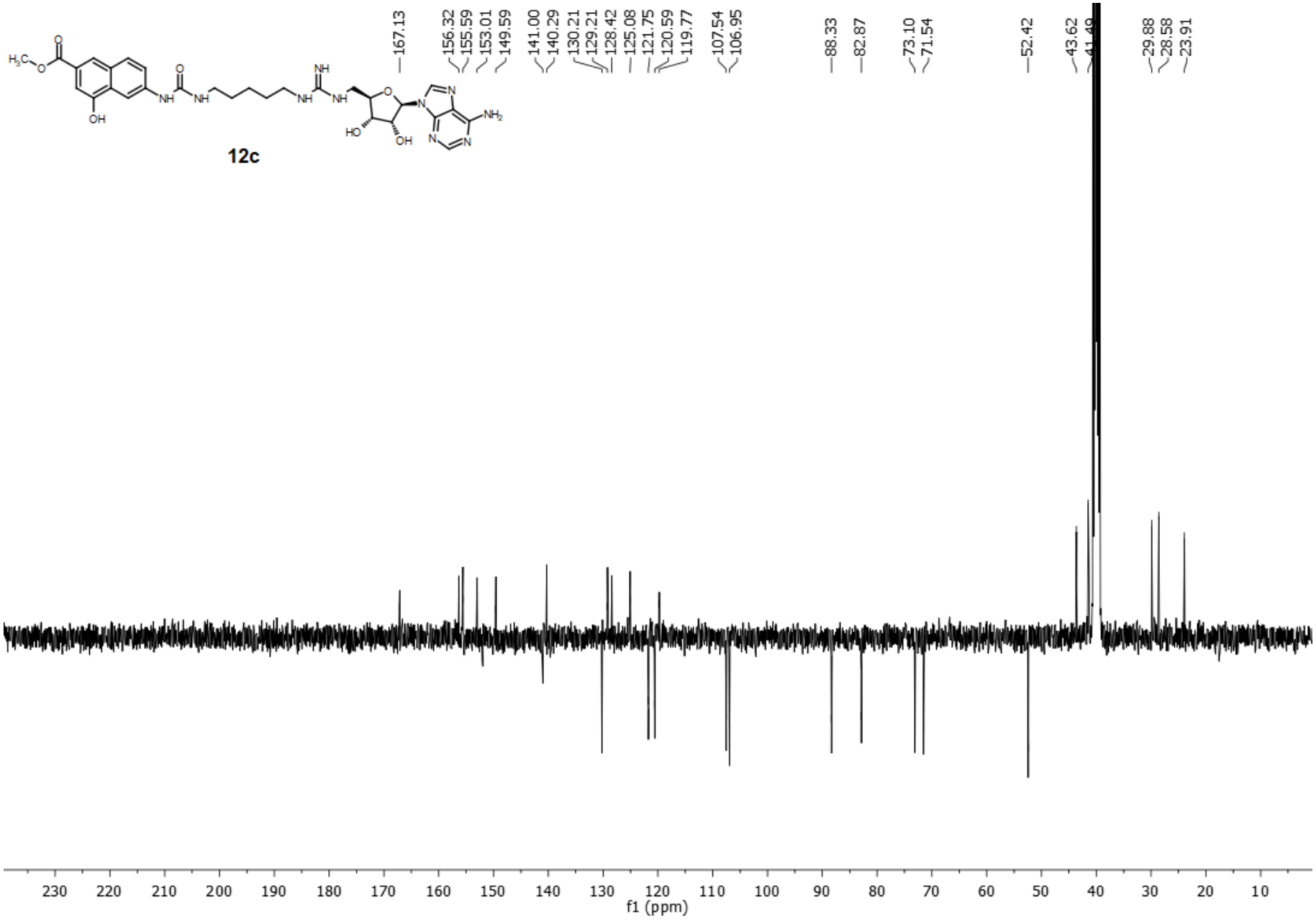

12a
10.30
8.95
8.45
8.27
8.27
8.26
8.26
8.21
7.98
7.90
7.88
7.86
7.59
7.58
7.56
7.56
7.49
7.48
7.47
7.42
7.30
6.40
6.39
6.37
5.96
5.94
4.73
4.72
4.70
4.18
4.17
4.16
4.06
4.05
4.04
4.03
4.02
4.02
4.01
3.87
3.18
3.17
3.15
3.14
3.12
1.70
1.67
1.65
1.63
1.60
1.03
1.01
0.98
1.73
1.00
1.30
2.24
1.12
4.26
1.14
1.16
1.11
1.16
1.22
1.38
3.49
4.43
2.43
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
f1 (ppm)

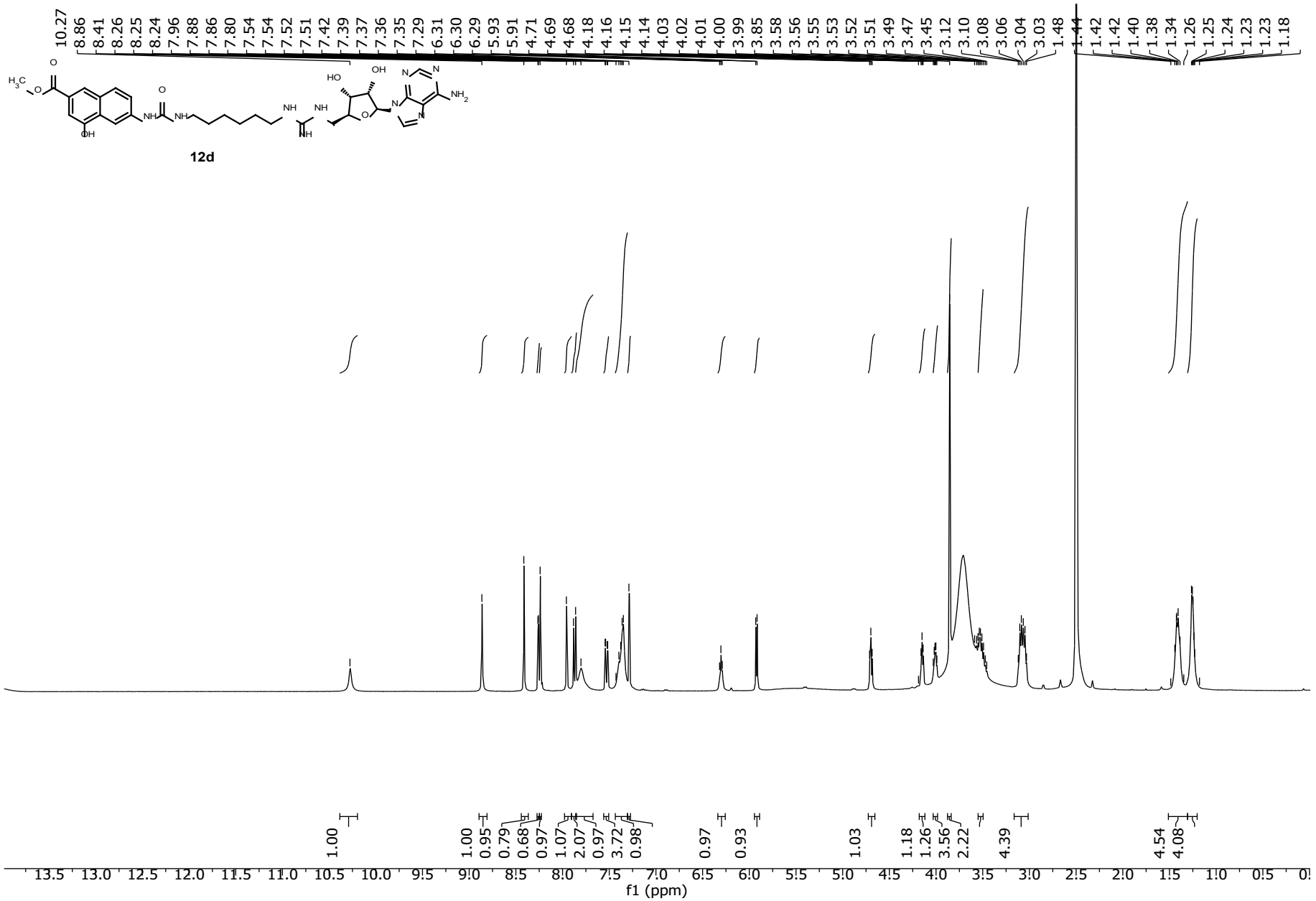

166.63
155.88
155.31
152.53
149.03
140.76
139.69
129.72
128.79
127.90
124.66
121.25
120.17
119.22
107.25
106.47
87.82
82.34
72.71
71.07
51.94
43.17
36.47
29.32
12a
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

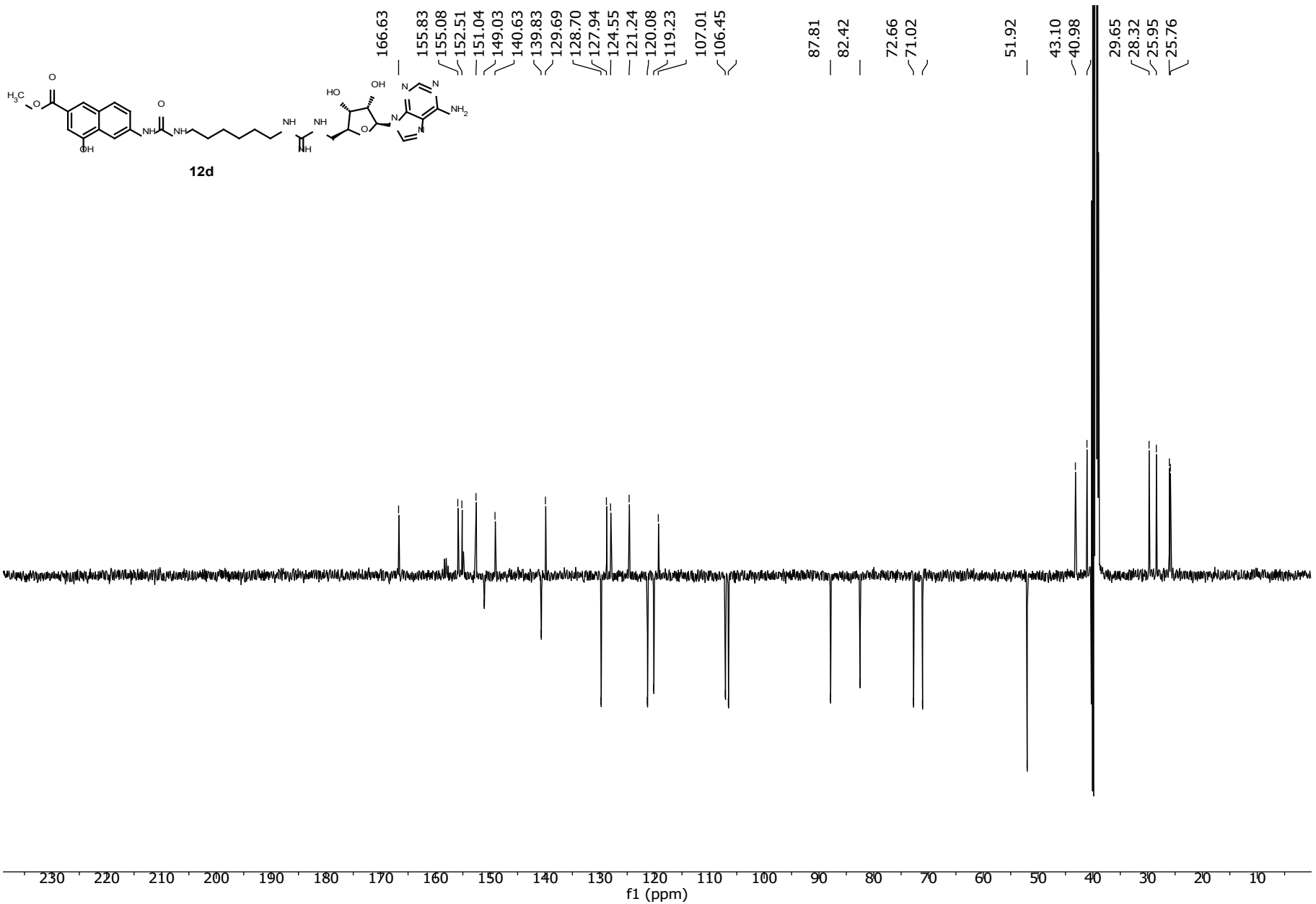

10.28
8.90
8.42
8.28
8.27
8.26
8.25
8.21
7.97
7.90
7.87
7.78
7.56
7.56
7.54
7.54
7.42
7.41
7.40
7.37
7.37
7.33
7.30
6.36
6.34
6.33
5.94
5.93
4.73
4.71
4.70
4.17
4.16
4.15
4.15
4.06
4.03
4.02
4.01
4.00
3.98
3.86
3.60
3.59
3.57
3.56
3.55
3.54
3.52
3.50
3.48
3.17
3.13
3.11
3.05
1.51
1.46
1.46
1.45
12b
1.00
1.06
1.00
1.77
0.93
0.99
2.01
1.07
3.63
1.01
1.12
0.86
1.48
1.58
1.24
3.14
2.56
4.28
3.90
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
f1 (ppm)

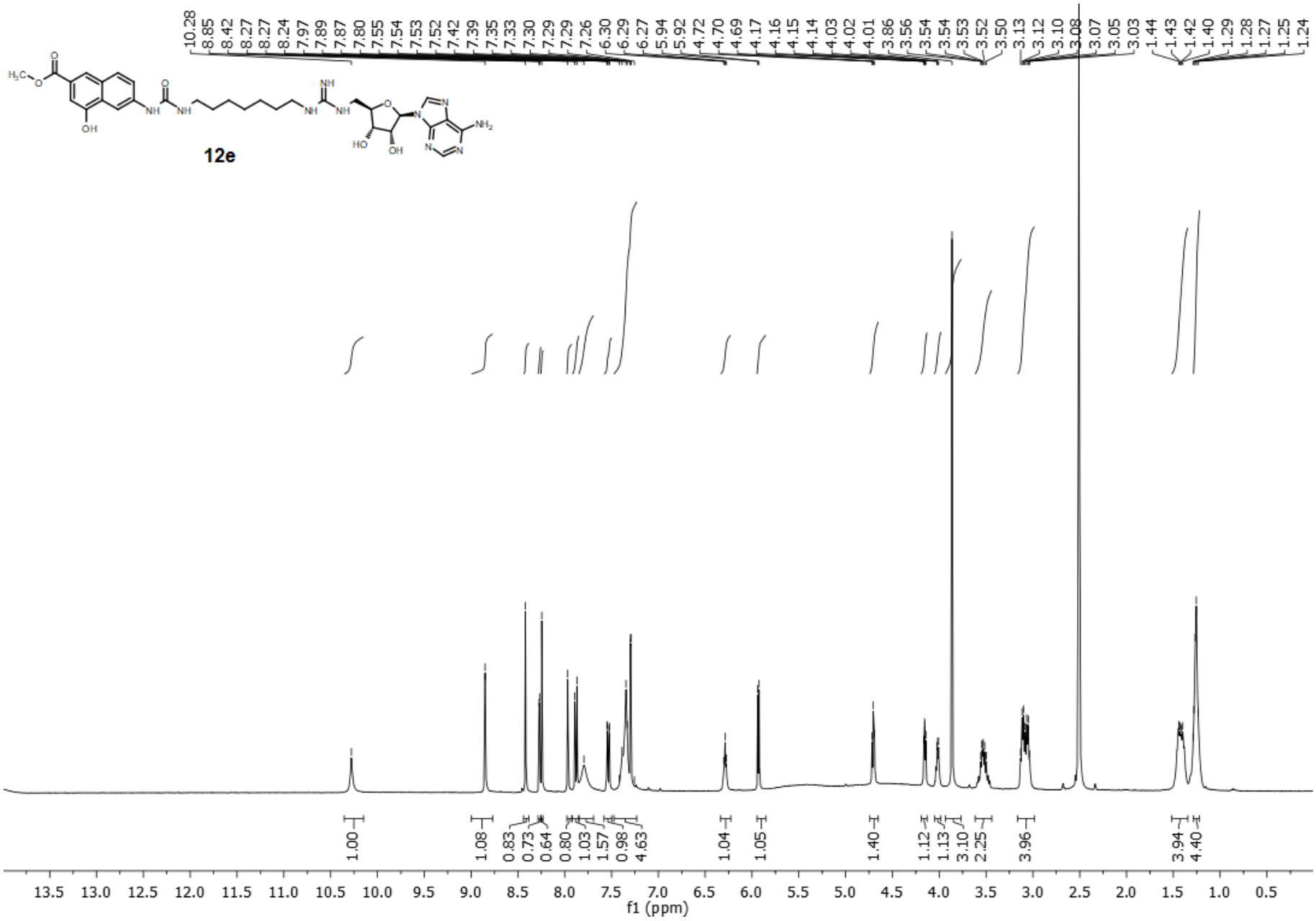

166.62
155.80
155.14
152.51
151.14
149.05
140.59
139.77
129.70
128.72
127.91
121.23
120.09
119.22
107.08
106.45
87.79
82.34
72.64
71.05
51.92
43.12
26.99
25.88
12b
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

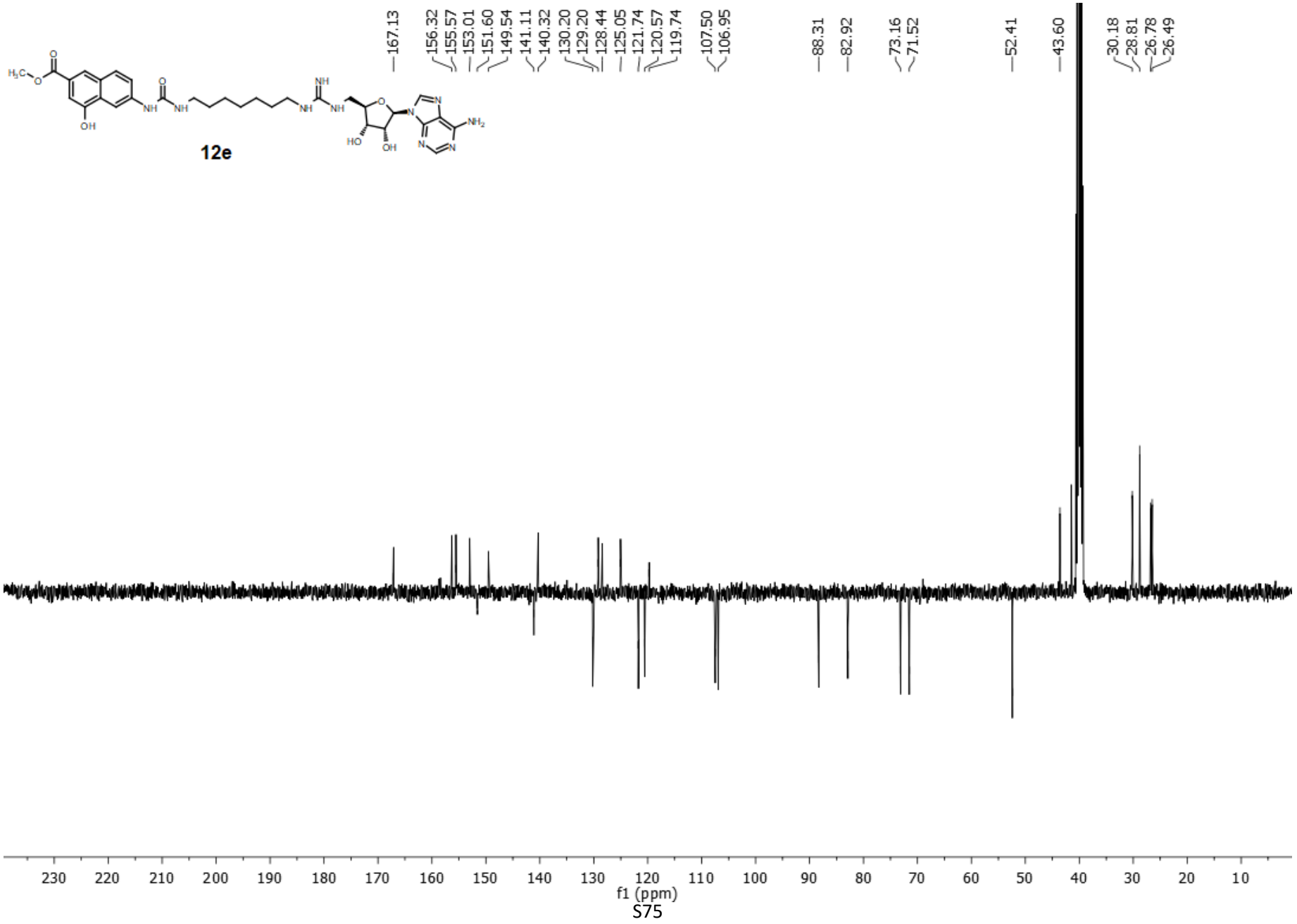

12c
10.28
8.83
8.38
8.26
8.25
8.20
7.96
7.89
7.86
7.59
7.54
7.54
7.52
7.52
7.37
7.33
7.32
7.29
6.26
6.25
6.23
5.93
5.91
4.73
4.71
4.70
4.16
4.15
4.14
4.03
4.02
4.01
4.00
3.99
3.85
3.10
3.09
3.07
3.05
1.47
1.45
1.43
1.42
1.40
1.28
1.28
1.26
1.24
1.00
1.34
1.05
0.85
0.80
0.92
1.05
1.60
1.20
4.35
1.07
1.18
1.09
1.33
1.44
1.39
2.79
4.19
4.41
2.62
f1 (ppm)

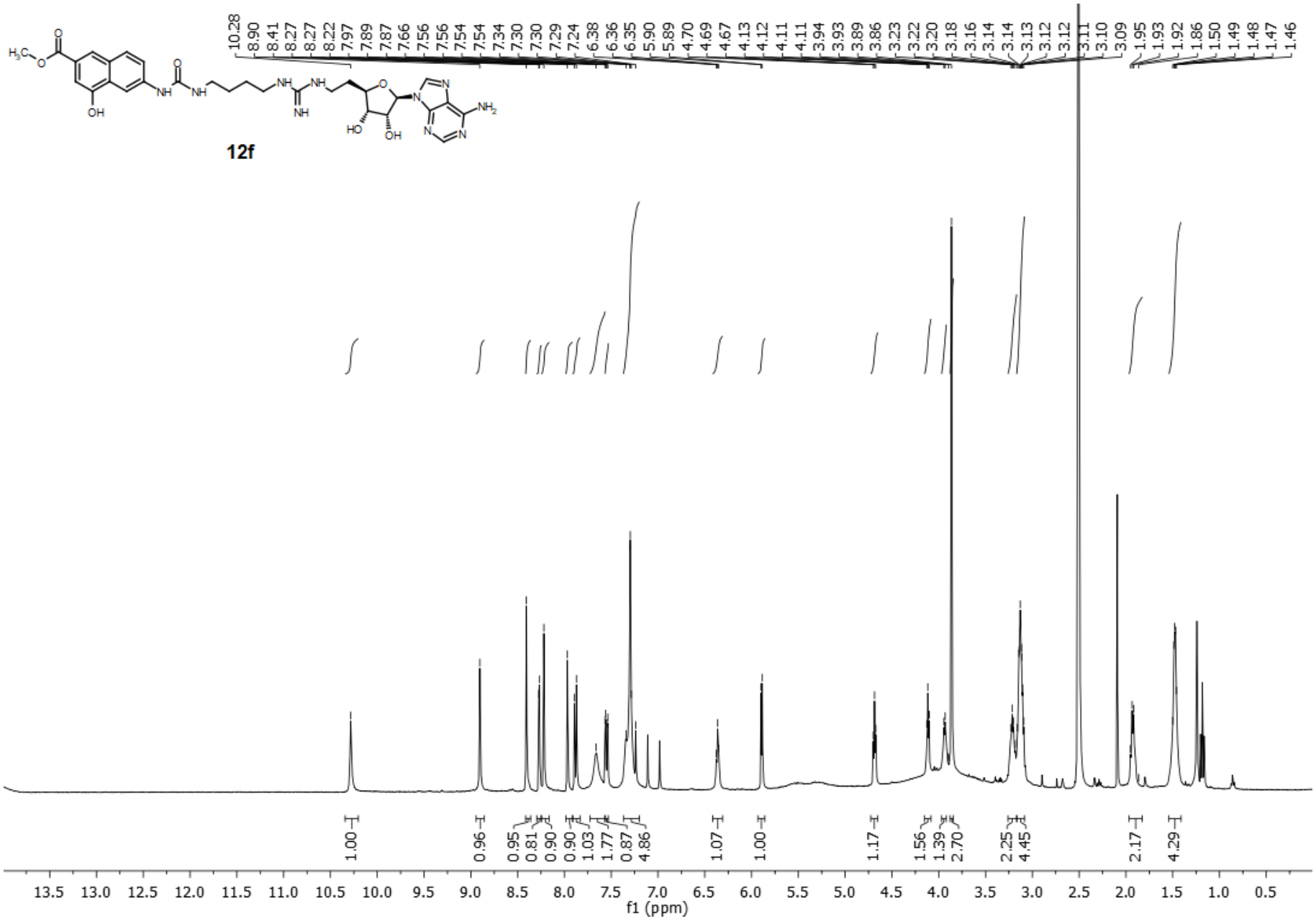

12c
167.13
156.32
155.59
153.01
149.59
141.00
140.29
130.21
129.21
128.42
125.08
121.75
120.59
119.77
107.54
106.95
88.33
82.87
73.10
71.54
52.42
43.62
41.49
29.88
28.58
23.91
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

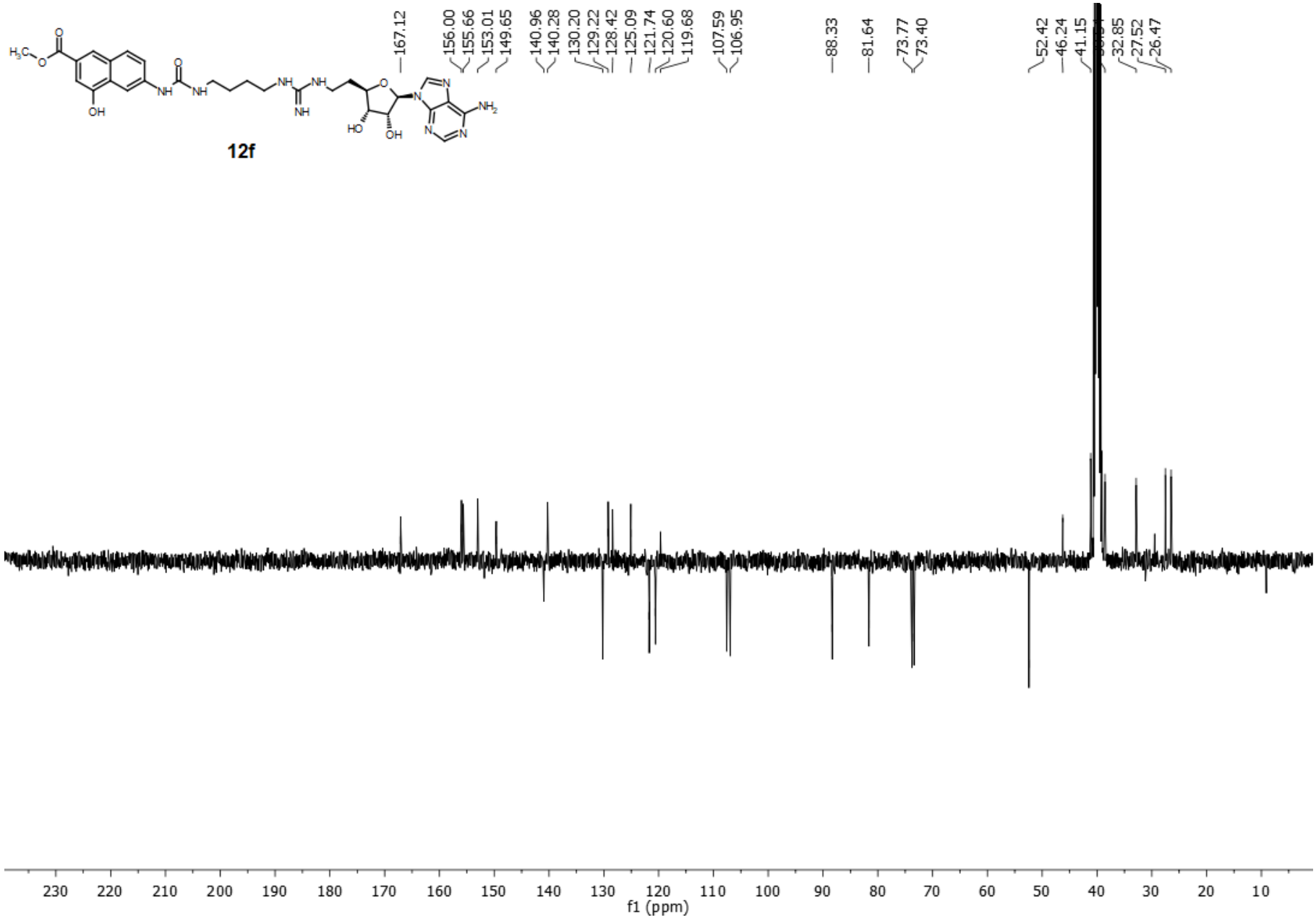

10.27
8.86
8.41
8.26
8.25
8.24
7.96
7.88
7.86
7.80
7.54
7.54
7.52
7.51
7.42
7.39
7.37
7.36
7.35
7.29
6.31
6.30
6.29
5.93
5.91
4.71
4.69
4.68
4.18
4.16
4.15
4.14
4.03
4.02
4.01
4.00
3.99
3.85
3.58
3.56
3.55
3.53
3.52
3.51
3.49
3.47
3.45
3.12
3.10
3.08
3.06
3.04
3.03
1.48
1.44
1.42
1.42
1.40
1.38
1.34
1.26
1.25
1.24
1.23
1.23
1.18
12d
1.00
1.00
0.95
0.79
0.68
0.97
1.07
2.07
0.97
3.72
0.98
0.97
0.93
1.03
1.18
1.26
3.56
2.22
4.39
4.54
4.08
f1 (ppm)

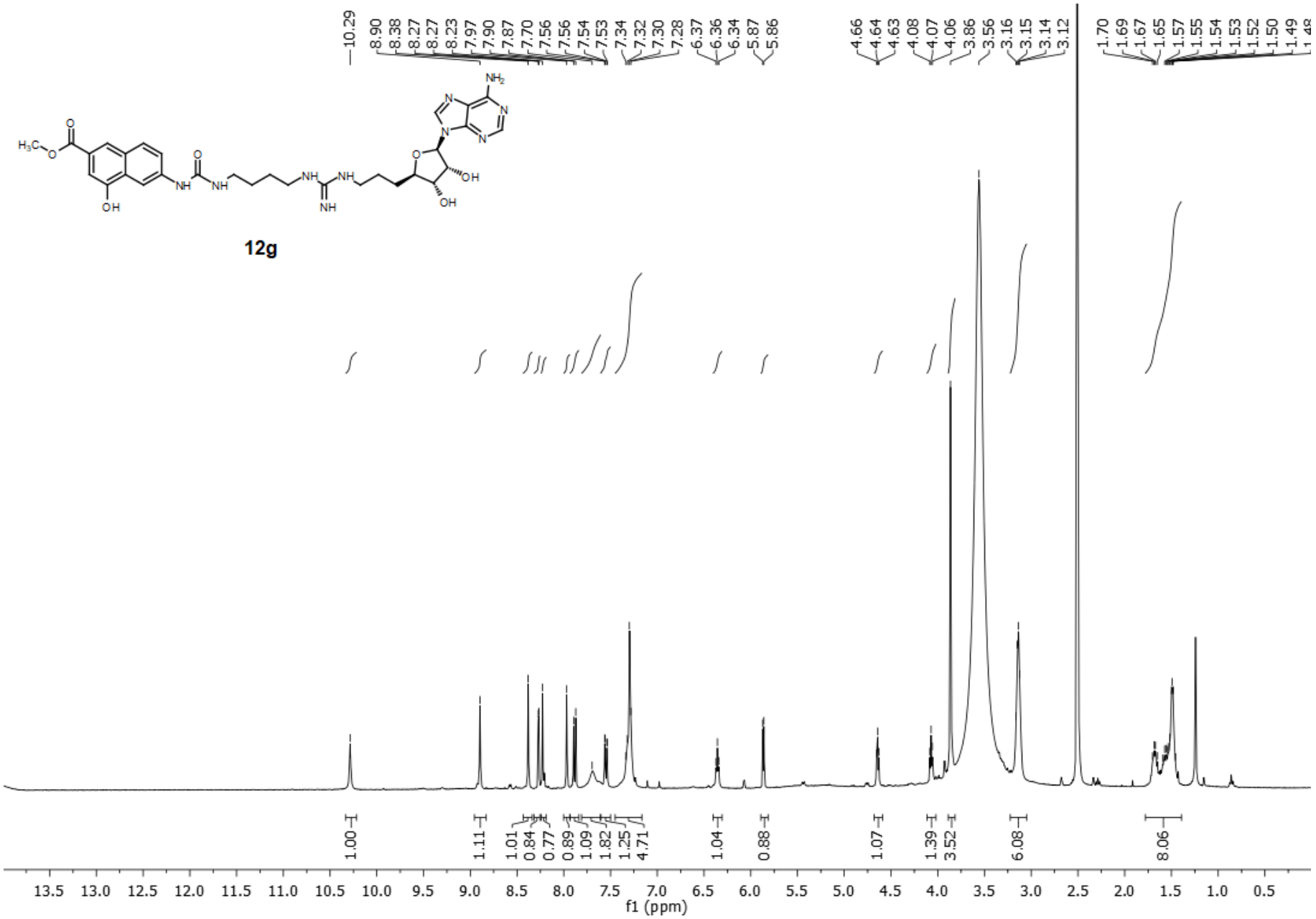

166.63
155.83
155.08
152.51
151.04
149.03
140.63
139.83
129.69
128.70
127.94
124.55
121.24
120.08
119.23
107.01
106.45
87.81
82.42
72.66
71.02
51.92
43.10
40.98
29.65
28.32
25.95
25.76
12d
f1 (ppm)


12e
10.28
8.85
8.42
8.27
8.27
8.24
7.97
7.89
7.87
7.80
7.55
7.54
7.53
7.52
7.42
7.39
7.35
7.33
7.30
7.29
7.29
7.26
6.30
6.29
6.27
5.94
5.92
4.72
4.70
4.69
4.17
4.16
4.15
4.14
4.03
4.02
4.01
3.86
3.56
3.54
3.54
3.53
3.52
3.50
3.13
3.12
3.10
3.08
3.07
3.05
3.03
1.44
1.43
1.42
1.40
1.29
1.28
1.27
1.25
1.24
1.00
1.08
0.83
0.73
0.64
0.80
1.03
1.57
0.98
4.63
1.04
1.05
1.40
1.12
1.13
3.10
2.25
3.96
3.94
4.40
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
f1 (ppm)

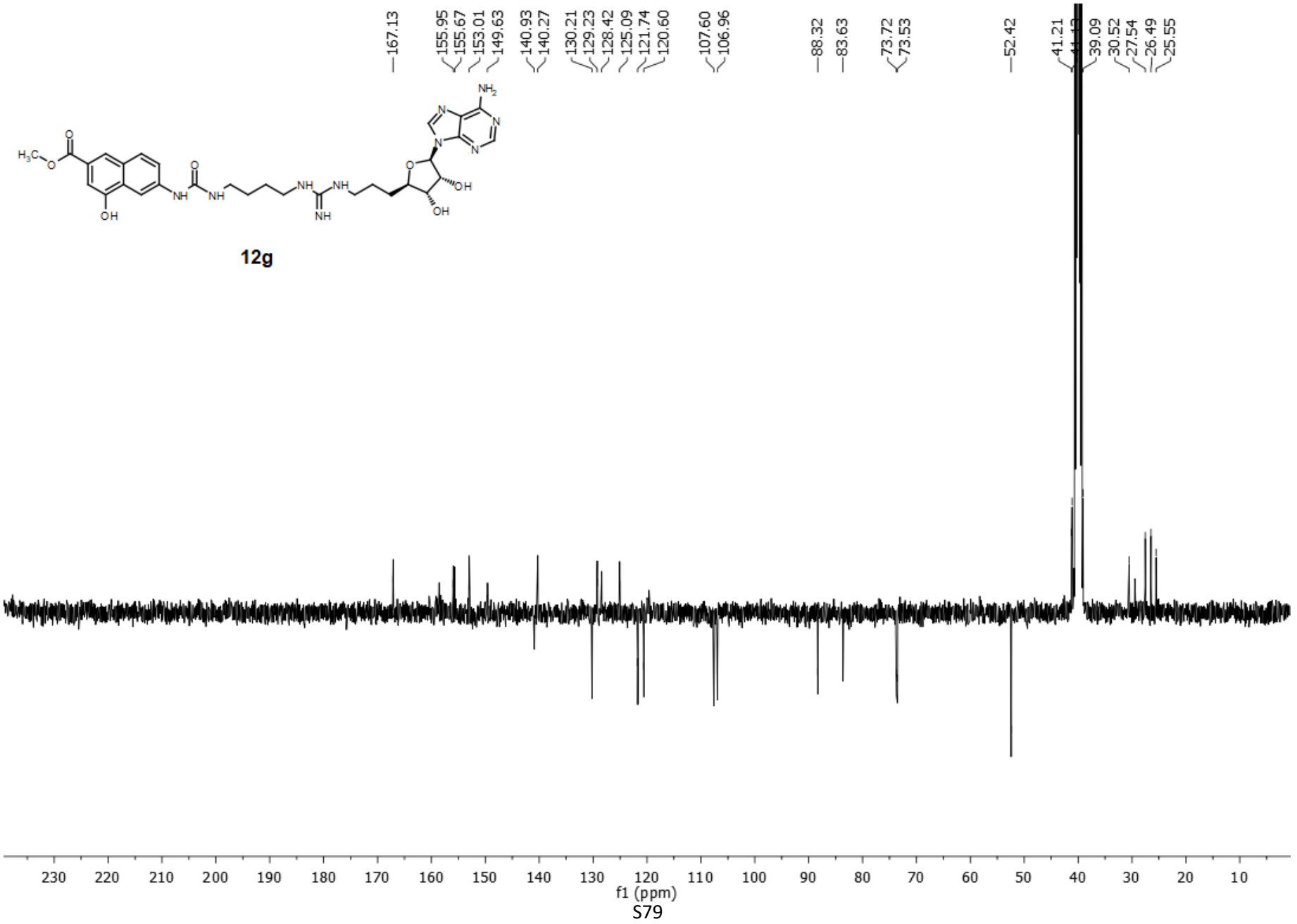

12e
167.13
156.32
155.57
153.01
151.60
149.54
141.11
140.32
130.20
129.20
128.44
125.05
121.74
120.57
119.74
107.50
106.95
88.31
82.92
73.16
71.52
52.41
43.60
30.18
28.81
26.78
26.49
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

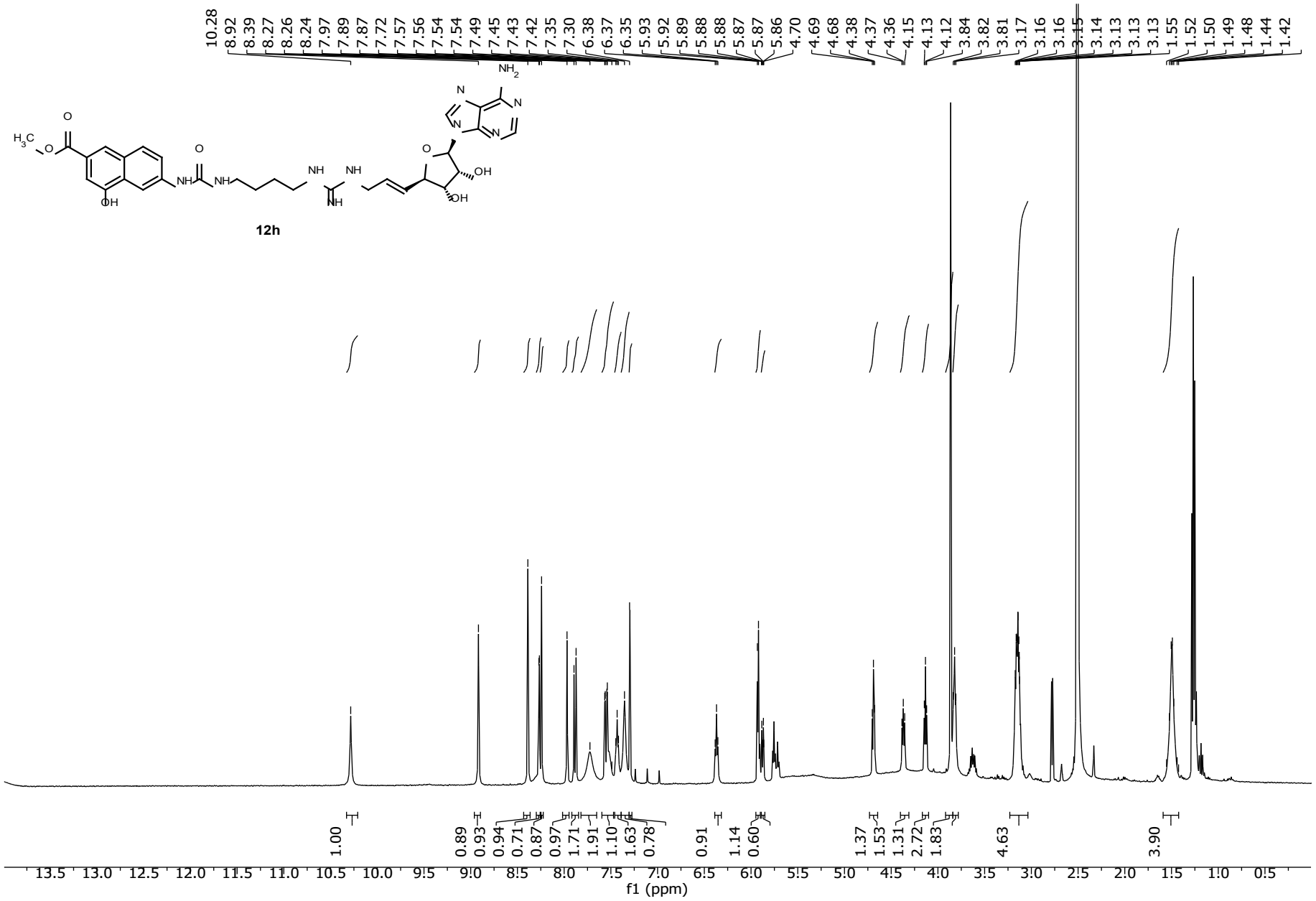

12f
10.28
8.90
8.41
8.27
8.27
8.22
7.97
7.89
7.87
7.66
7.56
7.56
7.54
7.54
7.34
7.30
7.30
7.29
7.24
6.38
6.36
6.35
5.90
5.89
4.70
4.69
4.67
4.13
4.12
4.11
4.11
3.94
3.93
3.89
3.86
3.23
3.22
3.20
3.18
3.16
3.14
3.14
3.13
3.12
3.12
3.11
3.10
3.09
1.95
1.93
1.92
1.86
1.50
1.49
1.48
1.47
1.46
1.00
0.96
0.95
0.81
0.90
0.90
1.03
1.77
0.87
4.86
1.07
1.00
1.17
1.56
1.39
2.70
2.25
4.45
2.17
4.29
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
f1 (ppm)

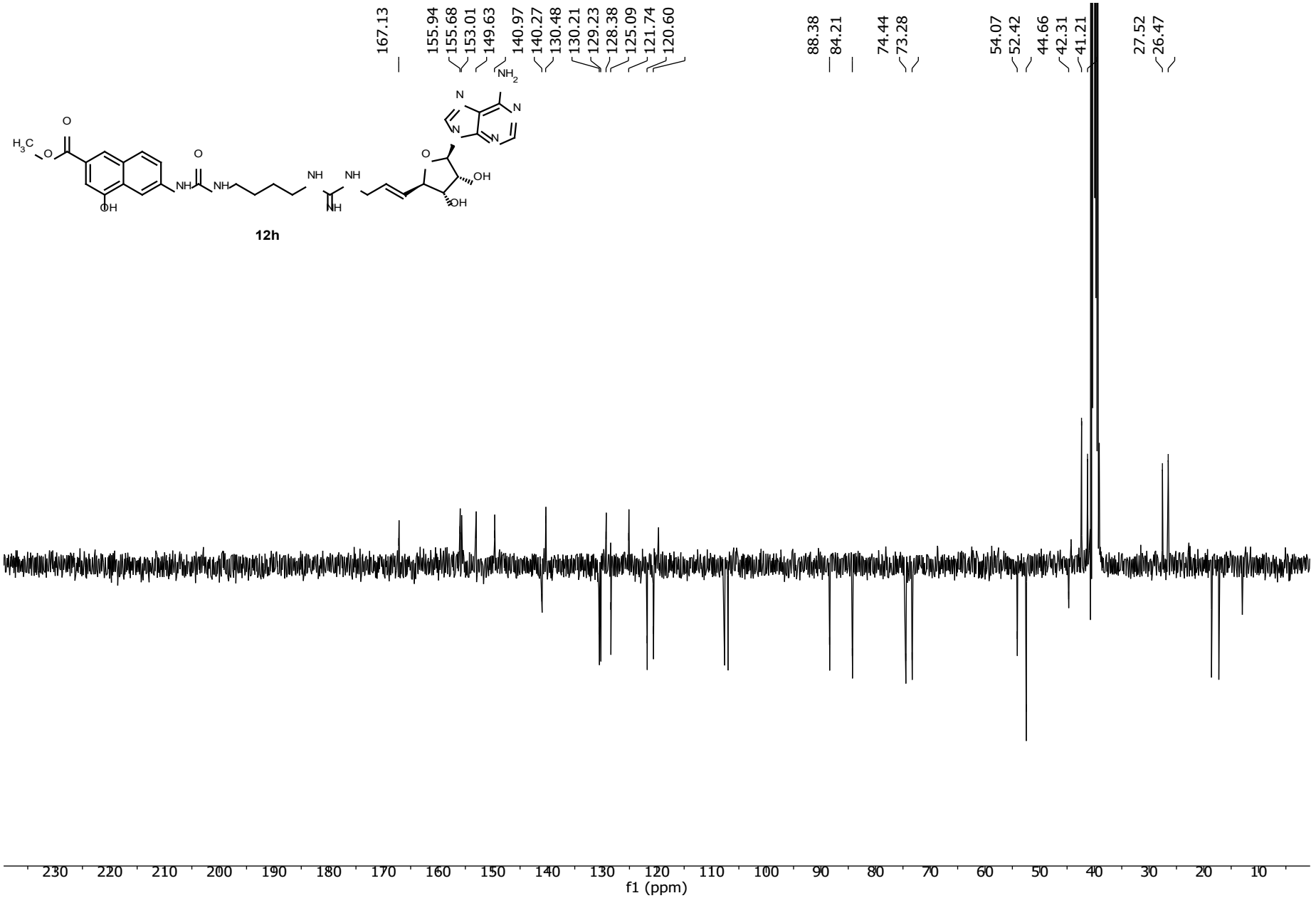

12f
167.12
156.00
155.66
153.01
149.65
140.96
140.28
130.20
129.22
128.42
125.09
121.74
120.60
119.68
107.59
106.95
88.33
81.64
73.77
73.40
52.42
46.24
41.15
32.85
27.52
26.47
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


10.29
8.90
8.38
8.27
8.27
8.23
7.97
7.90
7.87
7.70
7.56
7.56
7.54
7.53
7.34
7.32
7.30
7.28
6.37
6.36
6.34
5.87
5.86
4.66
4.64
4.63
4.08
4.07
4.06
3.86
3.56
3.16
3.15
3.14
3.12
1.70
1.69
1.67
1.65
1.57
1.55
1.54
1.53
1.52
1.50
1.49
1.00
1.11
1.01
0.84
0.77
0.89
1.09
1.82
1.25
4.71
1.04
0.88
1.07
1.39
3.52
6.08
8.06
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
f1 (ppm)

12g


167.13
155.95
155.67
153.01
149.63
140.93
140.27
130.21
129.23
128.42
125.09
121.74
120.60
107.60
106.96
88.32
83.63
73.72
73.53
52.42
41.21
39.09
30.52
27.54
26.49
25.55
12g
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)


10.28
8.92
8.39
8.27
8.26
8.24
7.97
7.89
7.87
7.72
7.57
7.56
7.54
7.54
7.49
7.45
7.43
7.42
7.35
7.30
6.38
6.37
6.35
5.93
5.92
5.89
5.88
5.88
5.87
5.87
5.86
4.70
4.69
4.68
4.38
4.37
4.36
4.15
4.13
4.12
3.84
3.82
3.81
3.17
3.16
3.16
3.15
3.14
3.13
3.13
3.13
1.55
1.52
1.50
1.49
1.48
1.44
1.42
12h
1.00
0.89
0.93
0.94
0.71
0.87
0.97
1.71
1.91
1.10
1.63
0.78
0.91
1.14
0.60
1.37
1.53
1.31
2.72
1.83
4.63
3.90
f1 (ppm)

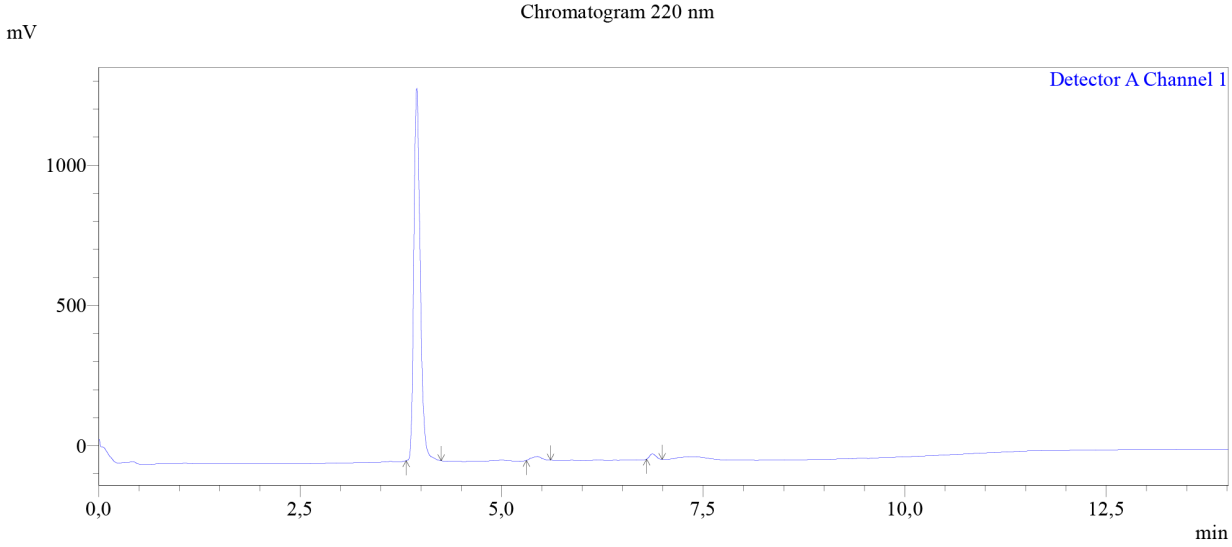

167.13
155.94
155.68
153.01
149.63
140.97
140.27
130.48
130.21
129.23
128.38
125.09
121.74
120.60
88.38
84.21
74.44
73.28
54.07
52.42
44.66
42.31
41.21
27.52
26.47
12h
f1 (ppm)

HPLC Traces of compound **12a**

SHIMADTZU HPLC ANALYSIS REPORT

Data File Name : EML734.lcd

Chromatogram 220 nm

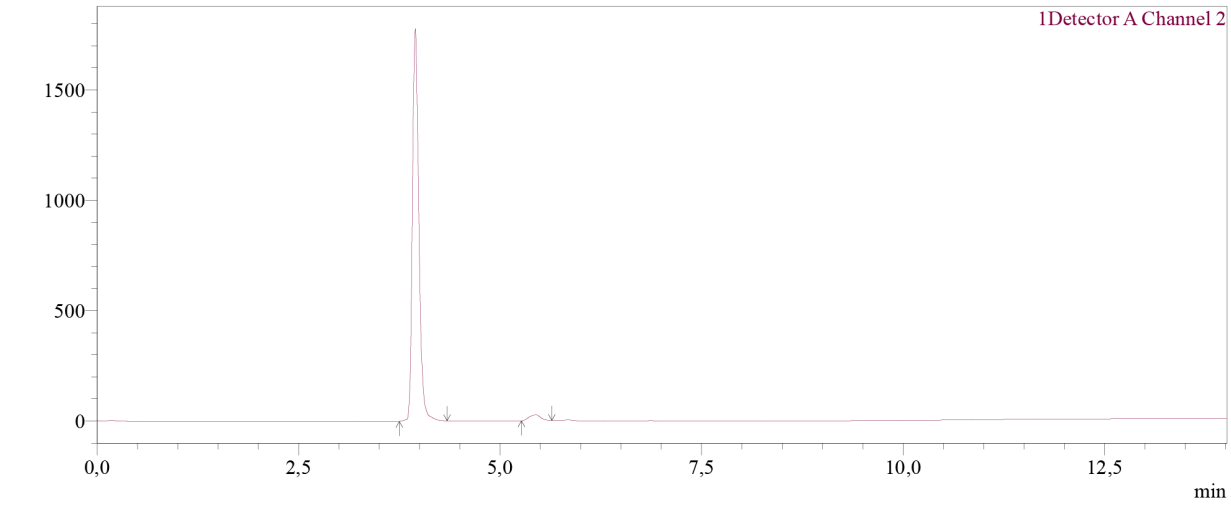


Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	3,942	1327058	7302685	97,122
2	5,436	13546	115682	1,539
3	6,867	18730	100711	1,339
Total		1359334	7519077	100,000

Chromatogram 254 nm



Peak Table

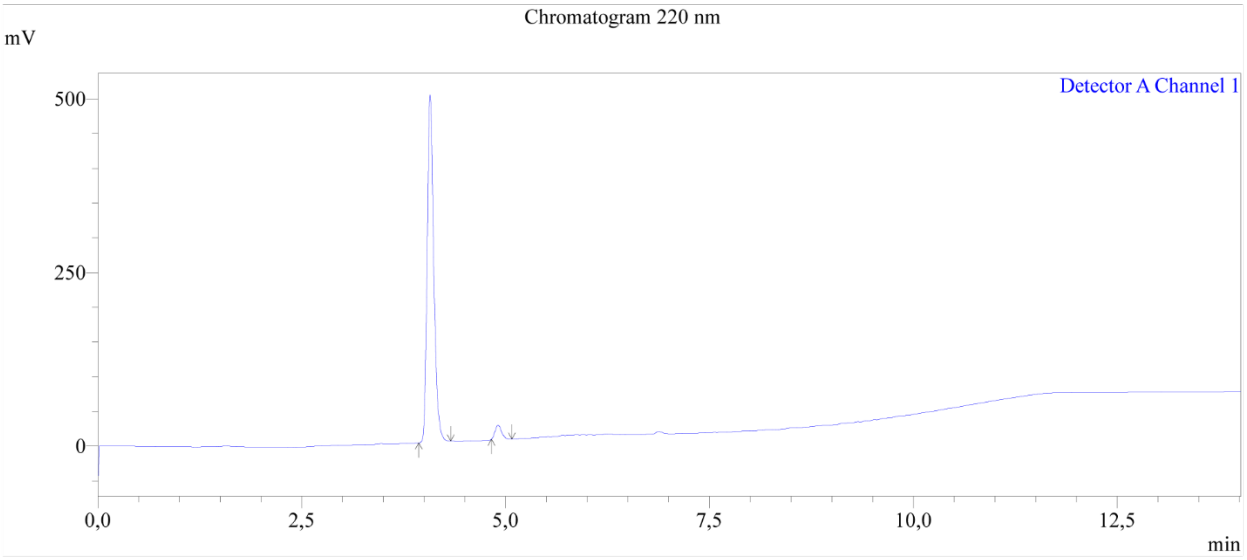
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	3,944	1779565	9879389	97,360
2	5,436	26906	267928	2,640
Total		1806471	10147317	100,000

HPLC Traces of compound **12b**

SHIMADTZU HPLC ANALYSIS REPORT

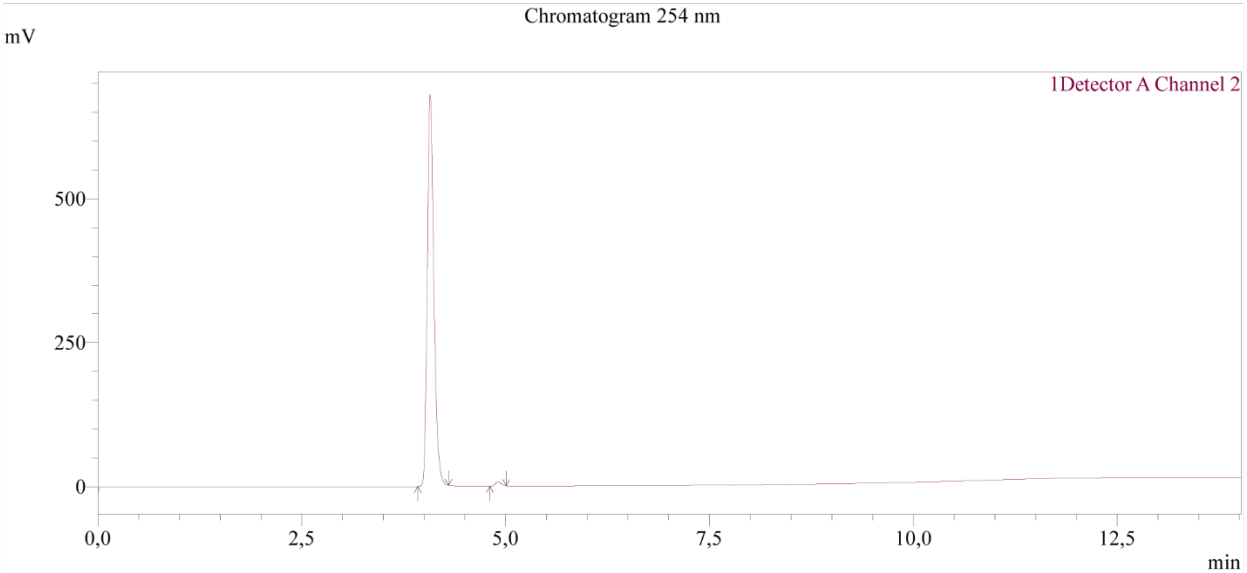
Data File Name : EML709.lcd



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	4,070	500641	2798814	96,212
2	4,903	20471	110182	3,788
Total		521112	2908996	100,000



Peak Table

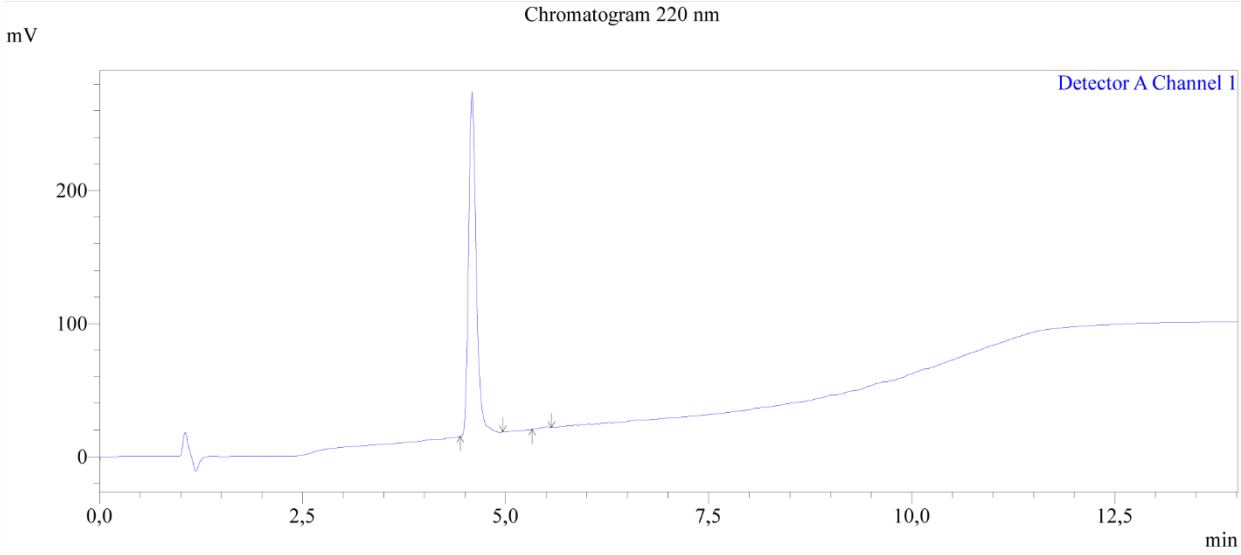
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4,072	680261	3785977	99,007
2	4,904	7129	37989	0,993
Total		687389	3823966	100,000

HPLC Traces of compound **12c**

SHIMADTZU HPLC ANALYSIS REPORT

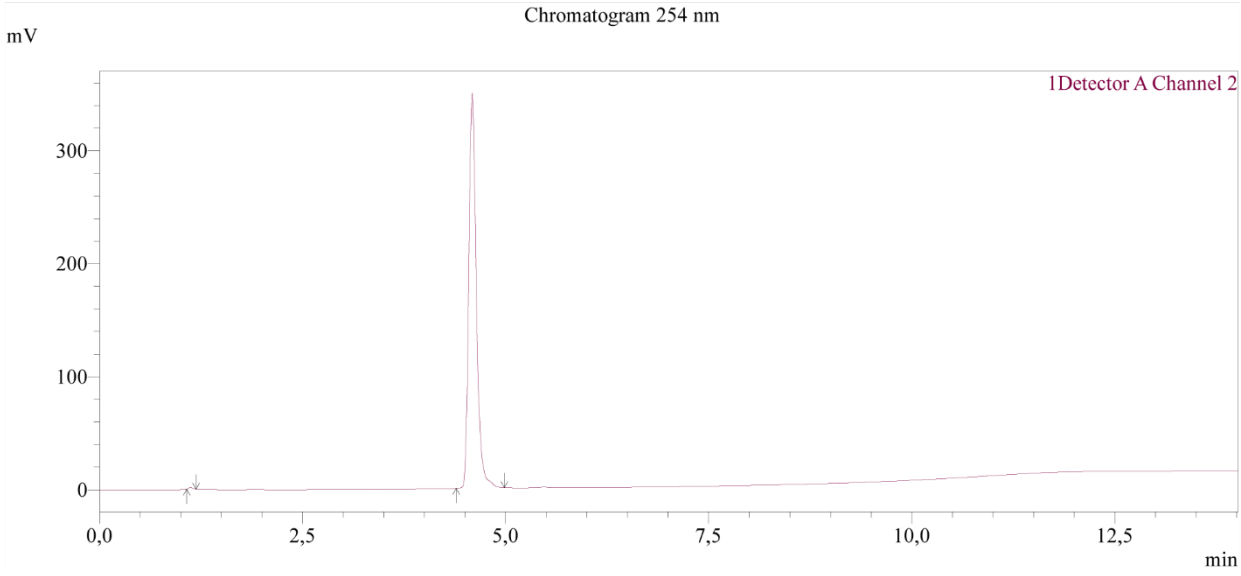
Data File Name : EML736.lcd



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	4,583	257927	1676431	99,666
2	5,504	827	5621	0,334
Total		258754	1682053	100,000



Peak Table

Detector A Channel 2 254nm

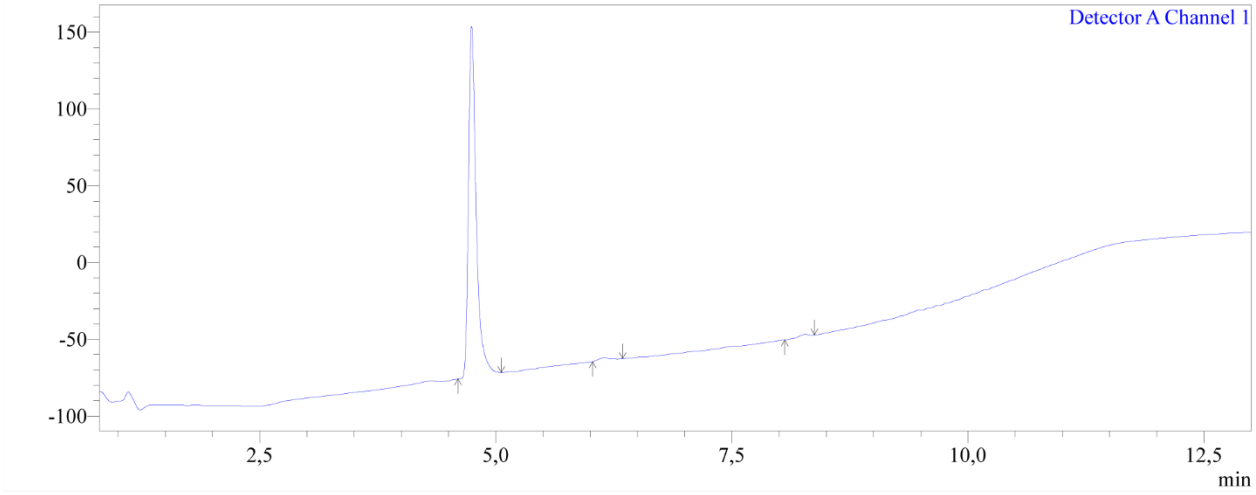
Peak#	Ret. Time	Height	Area	Area%
1	1,119	1623	5681	0,250
2	4,584	349363	2266847	99,750
Total		350986	2272528	100,000

HPLC Traces of compound **12d**

SHIMADTZU HPLC ANALYSIS REPORT

Data File Name : EML978.lcd

Chromatogram 220 nm

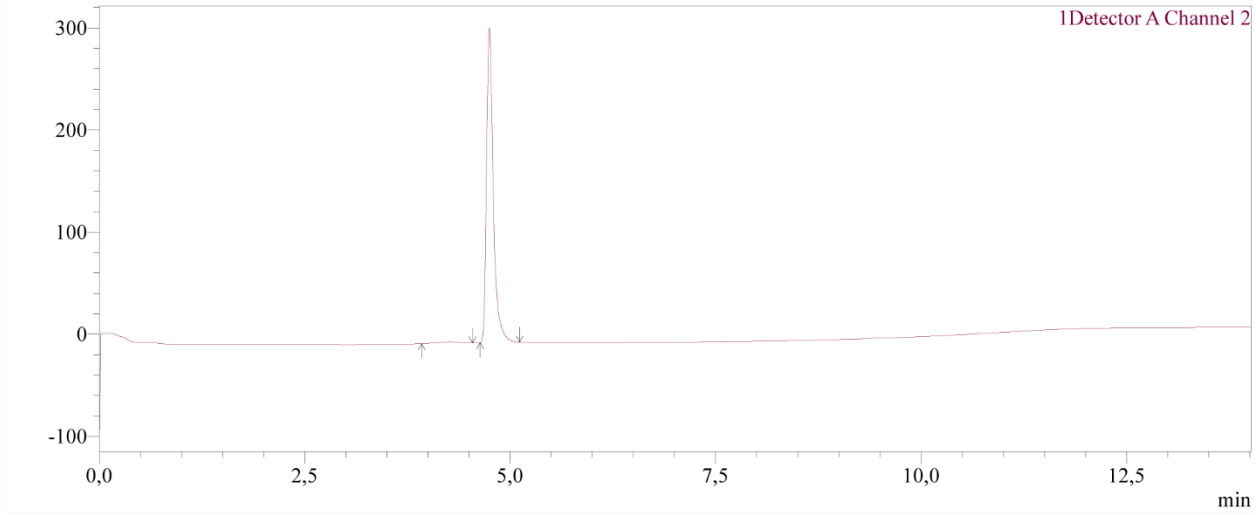


Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	4,741	228384	1302258	98,004
2	6,144	2091	15906	1,197
3	8,276	1545	10611	0,799
Total		232020	1328775	100,000

Chromatogram 254 nm



Peak Table

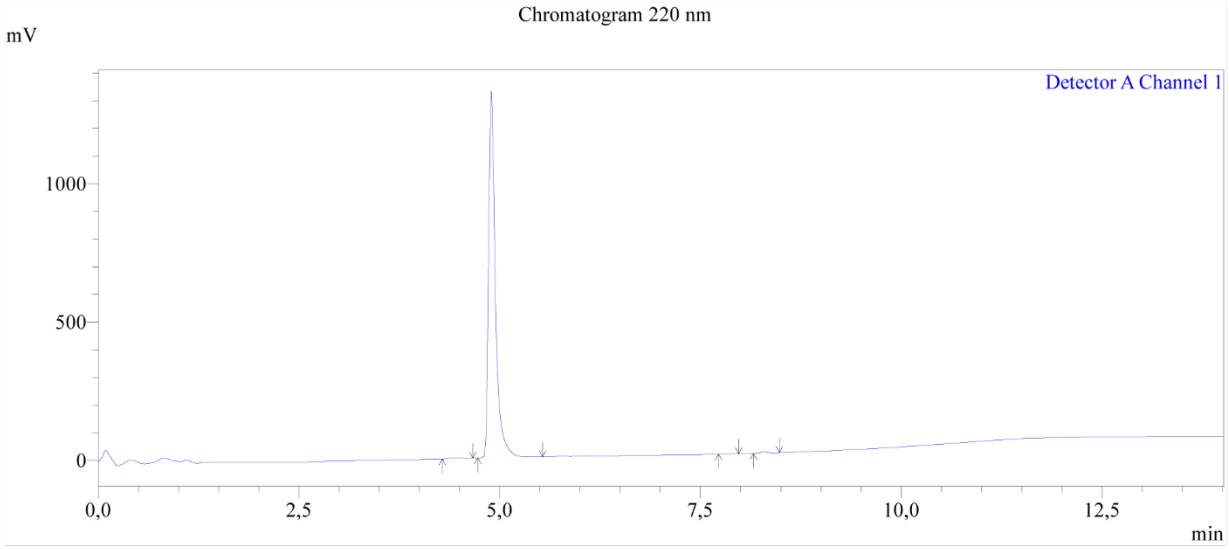
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4,279	1394	25406	1,420
2	4,742	307849	1764317	98,580
Total		309243	1789724	100,000

HPLC Traces of compound **12e**

SHIMADTZU HPLC ANALYSIS REPORT

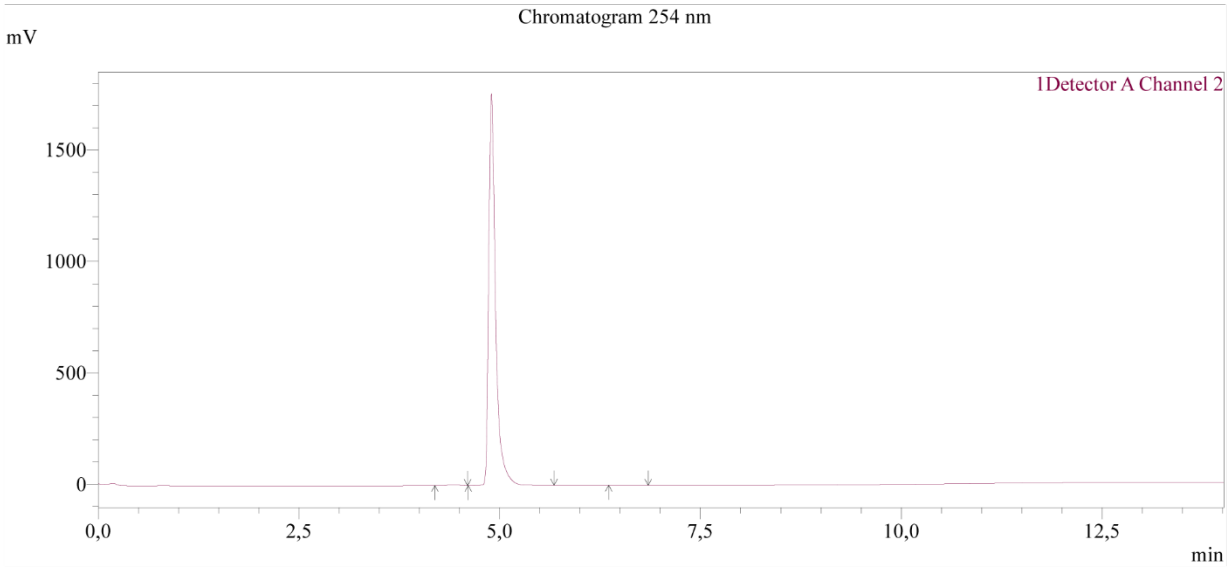
Data File Name : EML979.lcd



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	4,498	1748	24257	0,307
2	4,891	1323486	7832191	99,284
3	7,837	1580	10070	0,128
4	8,288	4020	22141	0,281
Total		1330834	7888660	100,000



Peak Table

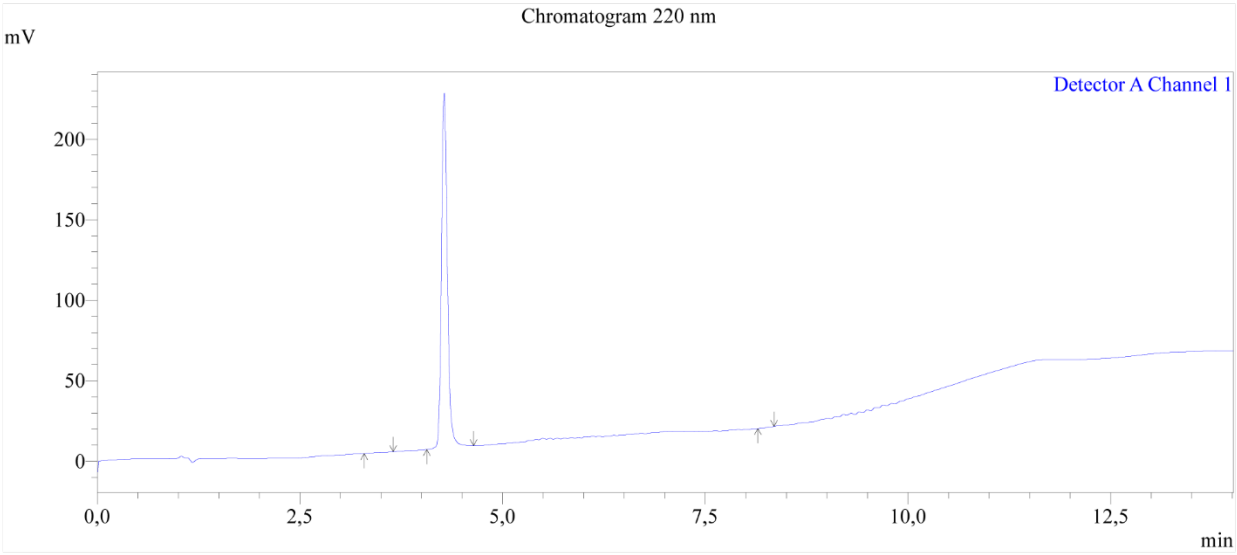
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4,388	3287	32127	0,305
2	4,893	1756030	10498271	99,596
3	6,666	1015	10413	0,099
Total		1760332	10540811	100,000

HPLC Traces of compound **12f**

SHIMADTZU HPLC ANALYSIS REPORT

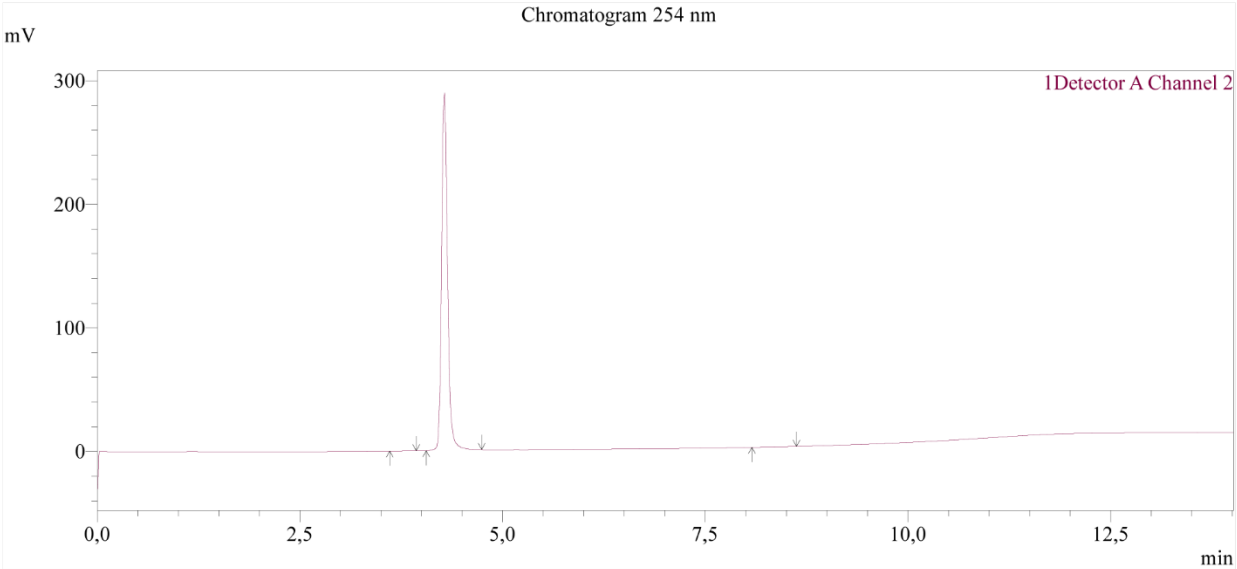
Data File Name : EML980.lcd



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	3,642	6	1594	0,142
2	4,275	220168	1117711	99,825
3	8,342	-58	366	0,033
Total		220116	1119671	100,000



Peak Table

Detector A Channel 2 254nm

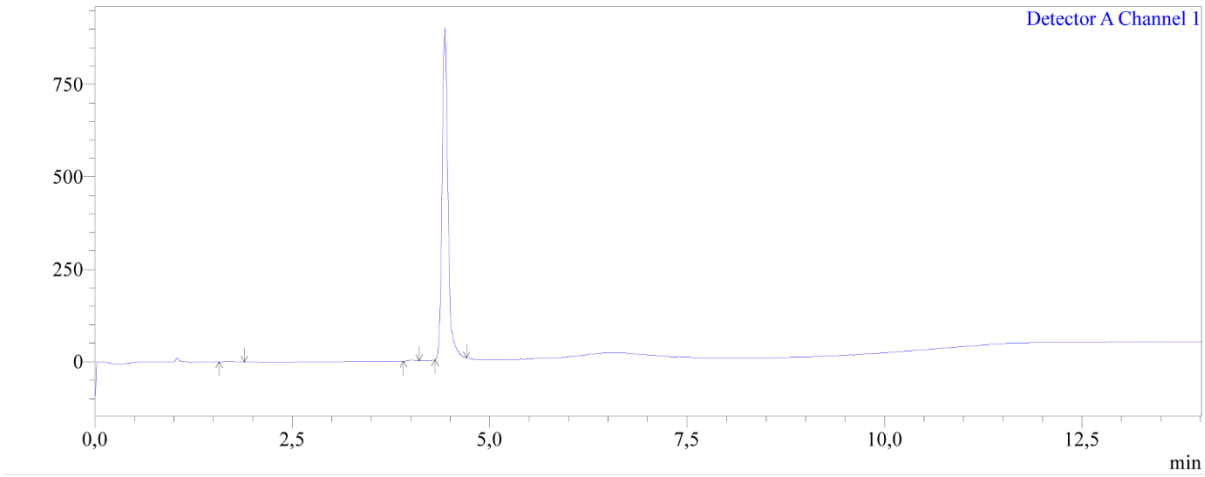
Peak#	Ret. Time	Height	Area	Area%
1	3,824	100	549	0,037
2	4,277	289360	1478164	99,992
3	8,617	-1	-431	-0,029
Total		289458	1478281	100,000

HPLC Traces of compound **12g**

SHIMADTZU HPLC ANALYSIS REPORT

Data File Name : EML982.lcd

Chromatogram 220 nm

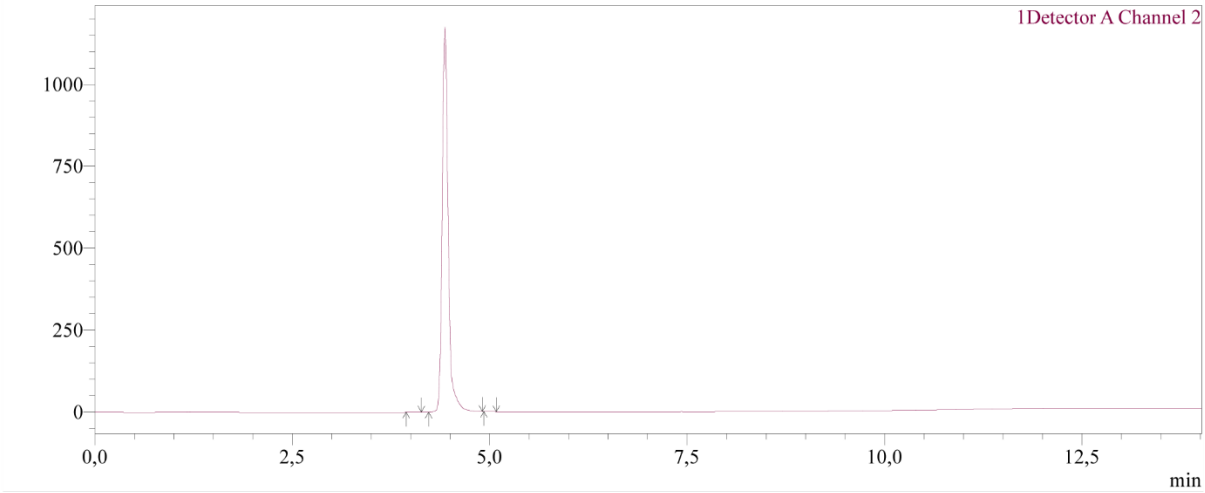


Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	1,676	1329	11757	0,251
2	4,014	1923	10936	0,234
3	4,428	897821	4655769	99,515
Total		901073	4678462	100,000

Chromatogram 254 nm



Peak Table

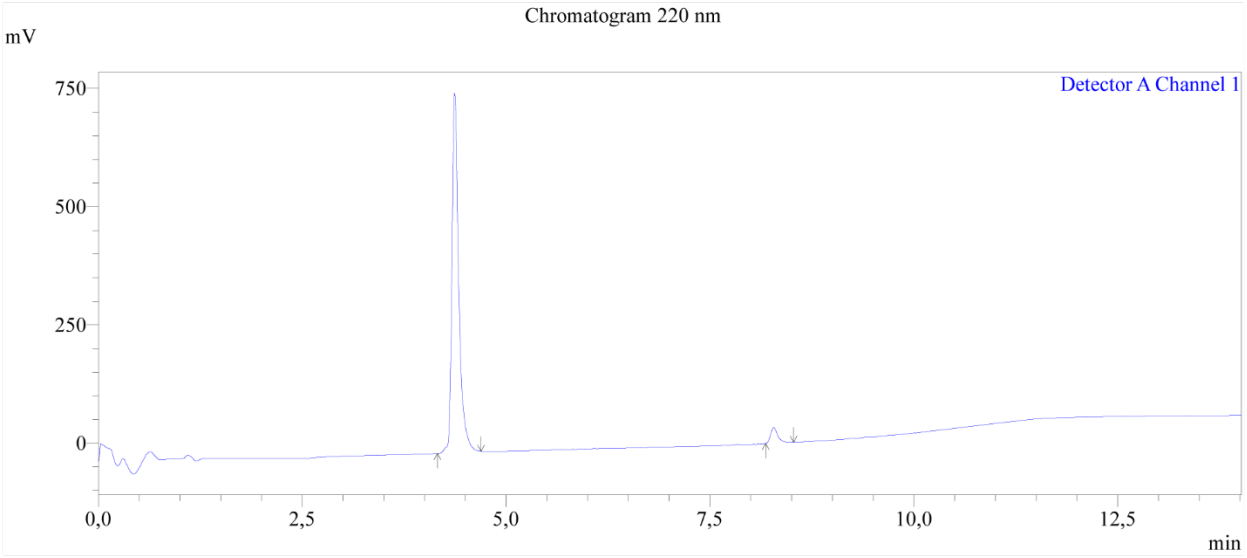
Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4,015	360	1989	0,032
2	4,429	1173656	6199655	99,937
3	4,979	401	1929	0,031
Total		1174417	6203574	100,000

HPLC Traces of compound **12h**

SHIMADTZU HPLC ANALYSIS REPORT

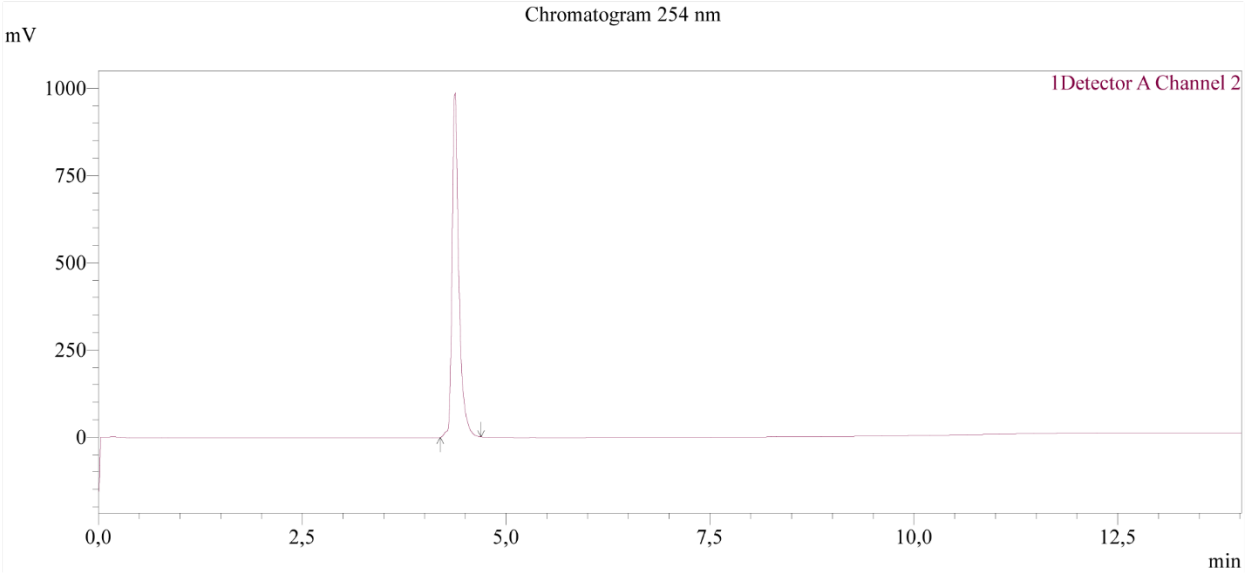
Data File Name : EML981.lcd



Peak Table

Detector A Channel 1 220nm

Peak#	Ret. Time	Height	Area	Area%
1	4,365	759645	4397472	95,647
2	8,277	33339	200112	4,353
Total		792985	4597584	100,000



Peak Table

Detector A Channel 2 254nm

Peak#	Ret. Time	Height	Area	Area%
1	4,368	986945	5700448	100,000
Total		986945	5700448	100,000