Supporting Information

Discovery of Novel Adenosine Receptor Agonists that Exhibit Subtype Selectivity

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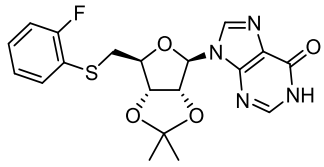
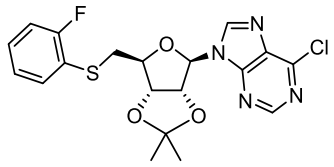
I. Synthesis of intermediates

5'-(2-Fluorophenylthio)-5'-deoxy-2',3'-*O*-isopropylideneinosine (28).



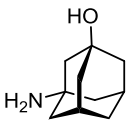
2-Fluorothiophenol (0.86 mL, 8.06 mmol) was added to anhydrous DMF (25 mL). Sodium hydride (60% oil dispersion, 0.26 g, 6.51 mmol) was added in portions at 0 ºC and stirred for 3 h at room temperature. Chloride **27** (0.56 g, 1.71 mmol) was added in anhydrous DMF (10 mL) and stirred overnight. The solvent was removed *in vacuo* and the resultant residue was dissolved in DCM (20 mL). The organic phase was washed with water (2 x 50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (methanol/DCM, 1–2%) to give **28** (0.34 g, 48% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.43 (1H, br s, NH), 8.26 (1H, s, adenine H), 8.08 (1H, s, adenine H), 7.42 (1H, td, *J* 7.8, 1.7, Ar H), 7.31-7.10 (3H, m, 3 x Ar H), 6.14 (1H, d, *J* 2.3, 1'-H), 5.41 (1H, dd, *J* 6.1, 2.3, 2'-H), 5.0 (1H, dd, *J* 6.1, 2.8, 3'-H), 4.18 (1H, td, *J* 7.1, 2.8, 4'-H), 3.26 (2H, d, *J* 7.1, 5'-H_2), 1.48 (3H, s, CH_3), 1.30 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 158.9, 156.5, 147.6, 146.1, 139.1, 131.1, 128.6 (d, *J* 7.9), 125.0 (d, *J* 3.5), 124.7, 121.7 (d, *J* 17.2), 115.6 (d, *J* 21.9), 113.4, 89.3, 85.0, 83.5, 83.2, 34.3, 26.8, 25.1 (there is an additional quaternary aromatic peak in the ^{13}C NMR spectrum); ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.4; HRMS calculated for $C_{19}H_{20}O_4N_4FS$ $[MH]^+$ 419.1184, found 419.1188.

6-Chloro-6-deoxy-5'-(2-fluorophenylthio)-2',3'-*O*-isopropylidene-5'-deoxyinosine (29).



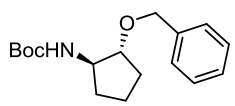
Intermediate **28** (0.12 g, 0.29 mmol) was dissolved in anhydrous DCM (10 mL). Anhydrous DMF (0.06 mL, 0.72 mmol) and thionyl chloride (0.11 mL, 1.44 mmol) were added and the reaction mixture was refluxed at 50 ºC for 5 h. The solution was allowed to cool to room temperature, diluted with DCM (100 mL) and washed thoroughly with saturated sodium hydrogen carbonate solution (2 x 50 mL), brine (2 x 50 mL) and water (3 x 100 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (methanol/DCM, 1–2%) to give chloride **29** (0.11, 88% yield) as a yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.84 (1H, s, adenine H), 8.81 (1H, s, adenine H), 7.38 (1H, td, *J* 7.7, 1.9, Ar H), 7.27-7.05 (3H, m, 3 x Ar H), 6.31 (1H, d, *J* 2.0, 1'-H), 5.56 (1H, dd, *J* 6.3, 2.0, 2'-H), 5.07 (1H, dd, *J* 6.3, 2.6, 3'-H), 4.28 (1H, td, *J* 7.1, 2.6, 4'-H), 3.26 (2H, d, *J* 7.1, 5'-H_2), 1.50 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.4, 159.0, 151.7, 151.0, 149.4, 146.2, 131.5, 131.3, 128.7 (d, *J* 8.0), 124.8 (d, *J* 3.6), 121.6, (d, *J* 17.2), 115.5 (d, *J* 22.0), 113.3, 90.1, 85.7, 83.3, 83.2, 34.3, 26.8, 25.1 (there is an additional quaternary aromatic peak in the ^{13}C NMR); ^{19}F NMR (376 MHz, DMSO-d_6) δ -110.3; HRMS (ESI) calculated for $C_{19}H_{19}O_3N_4ClFS$ $[MH]^+$ 437.0845, found 437.0847.

3-Amino-1-adamantanol[S1]



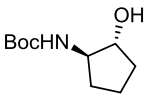
Sulfuric acid (97%, 10.3 mL) was cooled to 0 ºC and nitric acid (65%, 1 mL) was added dropwise and stirred for 5 min. Amantadine hydrochloride (1 g, 5.33 mmol) was added in small portions and stirred for 2 h at 0 ºC and then overnight at room temperature. The reaction mixture was again cooled to 0 ºC and ice water was added slowly and stirred for 30 min. Sodium hydroxide (3M aq. solution, 250 mL) was then added until the pH was alkaline. The reaction mixture was extracted with DCM (3 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 3-amino-1-adamantanol (0.64 g, 72% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 4.34 (1H, s, OH), 2.08 (2H, m, 2 x adamantyl H), 1.46-1.24 (14H, m, 12 x adamantyl H and NH_2); ^{13}C NMR (75 MHz, DMSO-d_6) δ 67.8, 54.0, 49.8, 44.9, 44.2, 34.9, 30.5; *m*/z (ES$^+$) 168 $(MH)^+$.

(1*R*, 2*R*)-2-Benzyloxycyclopentyl-(*tert*-butoxycarbonyl)amine[S2]



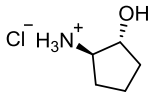
(1*R*,2*R*)-1-Amino-2-benzyloxycyclopentane (0.2 mL, 1.05 mmol) was dissolved in anhydrous THF (10 mL) and cooled to 0 ºC. Triethylamine (0.29 mL, 2.10 mmol) and Boc_2O (0.25 g, 1.16 mmol) were then added and stirred at room temperature overnight. Ethyl acetate (100 mL) was then added and the organic phase was washed with water (2 x 50 mL) and brine (50 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* to give a pale yellow solid, which was purified with column chromatography (methanol/DCM, 1%) to give the title compound (0.25 g, 84%) as a pale yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.39-7.22 (5H, m, 5 x phenyl H), 6.91 (1H, d, *J* 7.3, NH), 4.51 (2H, m, CH_2Ph), 3.82-3.66 (2H, m, 1- and 2-H), 1.98-1.73 (2H, m, 2 x cyclopentyl H), 1.68-1.50 (3H, m, 3 x cyclopentyl H), 1.47-1.32 (10H, m, -$(CH_3)_3$ and 1 x cyclopentyl H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.9, 138.9, 128.1, 127.3, 127.1, 84.5, 77.5, 69.8, 56.4, 30.1, 28.2, 21.3; *m*/z (ES$^+$) 314 $(MNa)^+$.

(1*R*,2*R*)-2-(*tert*-Butoxycarbonylamino)cyclopentanol[S3]



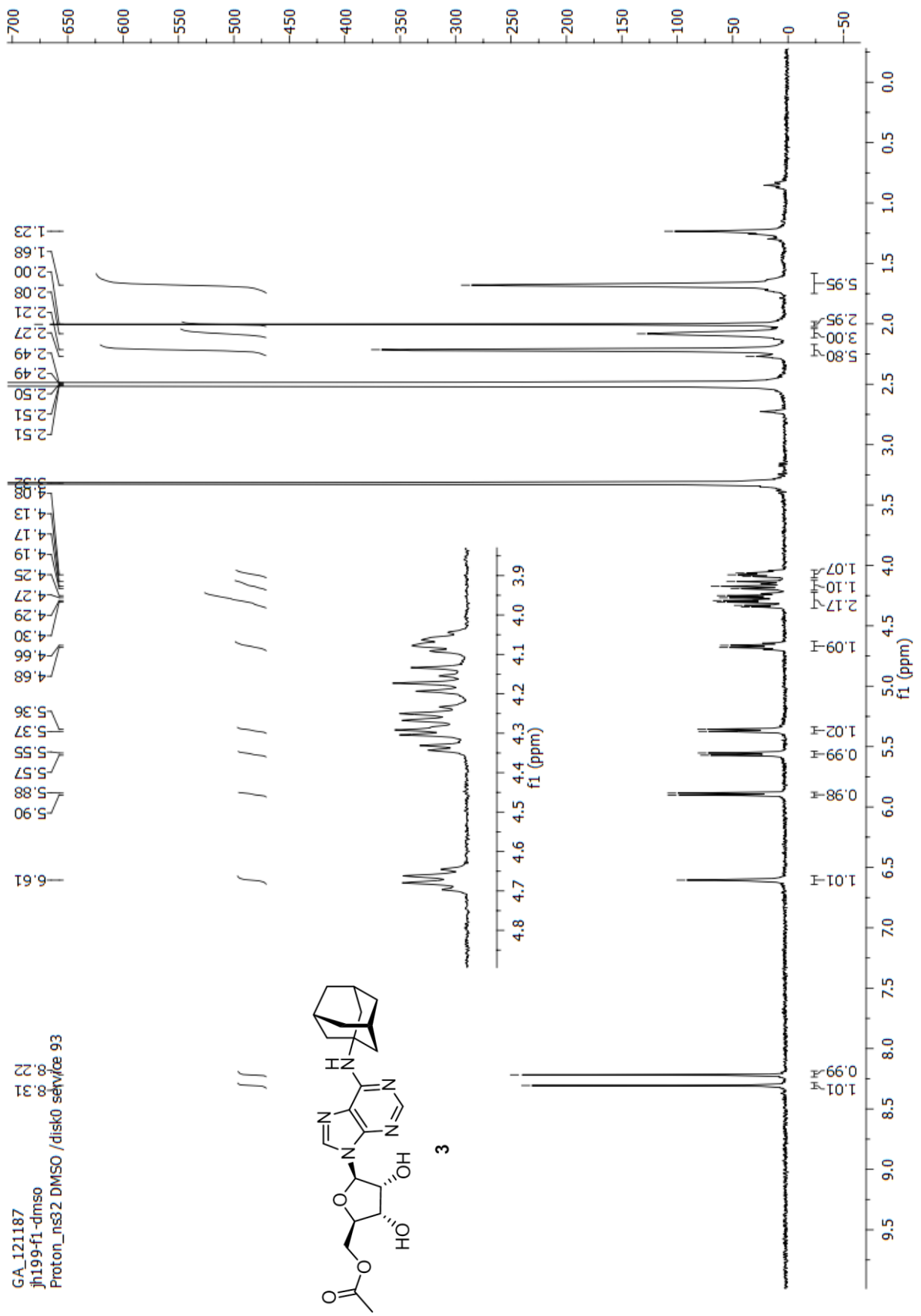
Fully protected cyclopentanol from above (0.25 g, 0.86 mmol) was dissolved in ethanol (20 mL). $Pd(OH)_2$/C (20 wt. %, 0.06 g) and cyclohexene (0.52 mL, 5.16 mmol) were then added and refluxed for 4 hours. The reaction mixture was allowed to cool to room temperature and filtered through celite. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (ethyl acetate/hexane, 50%) to give the title compound (0.20 g, 99% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54 (1H, m, NH), 5.42 (1H, d, *J* 4.3, OH), 4.60 (1H, m, 1-H), 4.32 (1H, m, 2-H), 2.76-2.51 (2H, m, 2 x cyclopentyl H), 2.45-2.31 (2H, m, 2 x cyclopentyl H), 2.28-2.08 (11H, m, 2 x cyclopentyl H and -$(CH_3)_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.2, 77.3, 32.0, 28.3, 20.3; *m*/z (ES$^+$) 224 $(MNa)^+$.

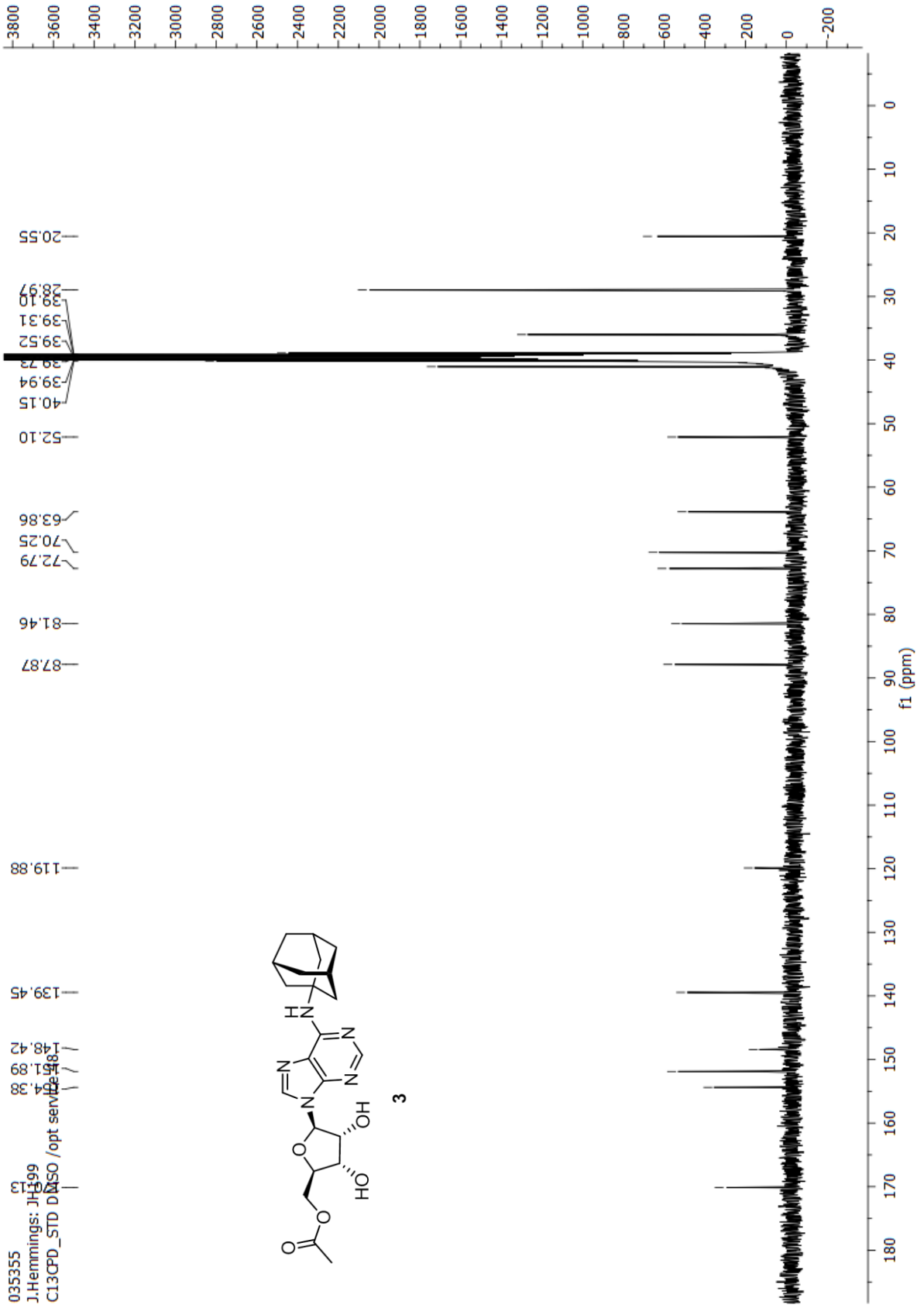
(1*R*,2*R*)-2-Aminocyclopentanol hydrochloride[S4]



The Boc-protected cyclopentanol from above (0.023 g, 0.11 mmol) was dissolved in 4M HCl in dioxane (0.51 mL, 2.01 mmol) and stirred at room temperature for 1.5 h. The solvent was removed *in vacuo* and the resultant solid was washed with diethyl ether to give the title compound (0.01 g, 99% yield) as a white solid as the HCl salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.99 (2H, br s, NH_2), 5.18 (1H, d, *J* 4.6, OH), 3.96 (1H, m, 1-H), 3.13 (1H, m, 2-H), 2.07-1.83 (2H, m, 2 x cyclopentyl H), 1.72-1.60 (2H, m, 2 x cyclopentyl H), 1.56-1.44 (2H, m, 2 x cyclopentyl H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 74.6, 57.9, 32.0, 27.6, 20.1; *m/*z (ES^+) 102 $(MH)^+$.

II. ^{1}H and ^{13}C NMR spectra for compounds

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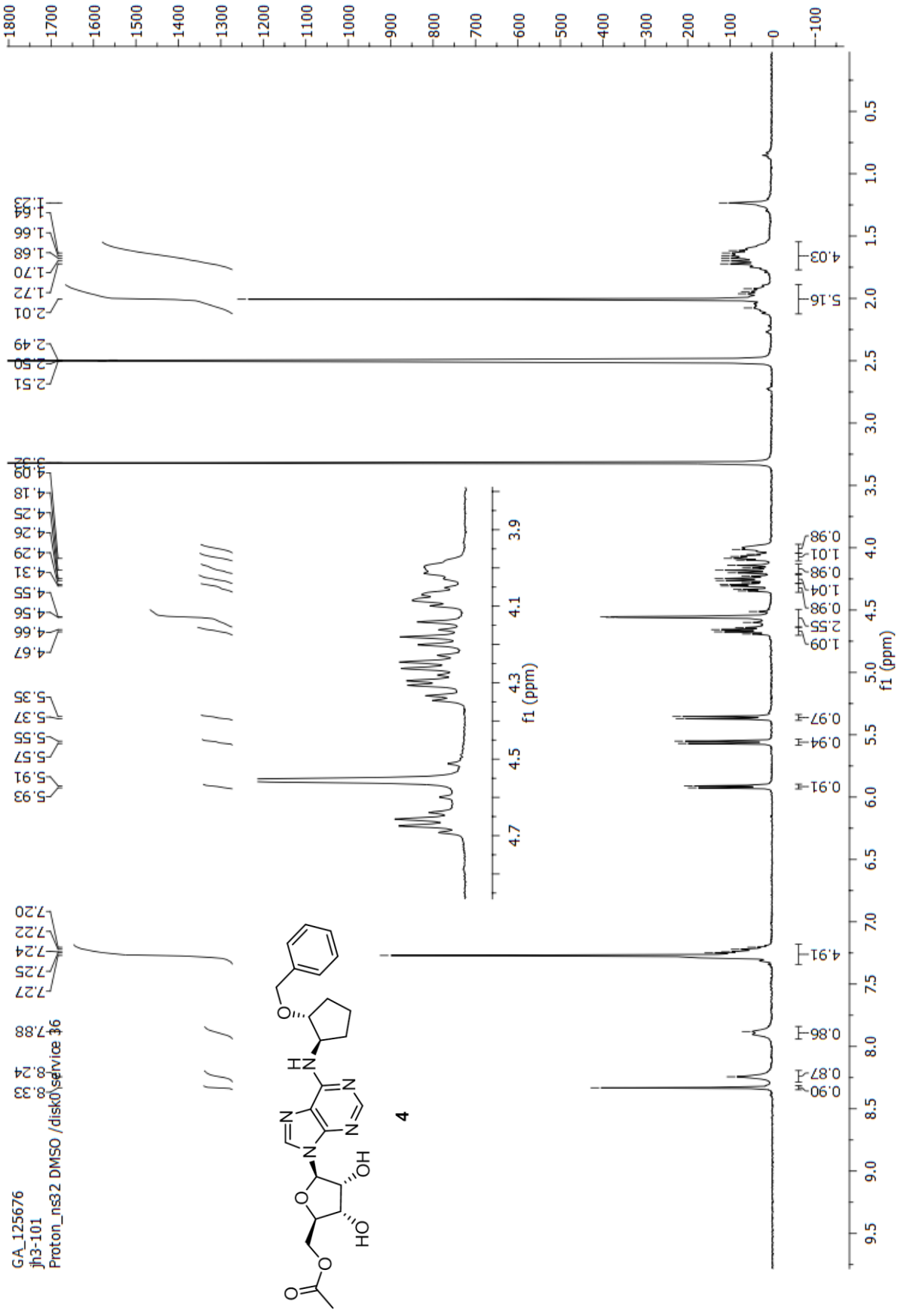
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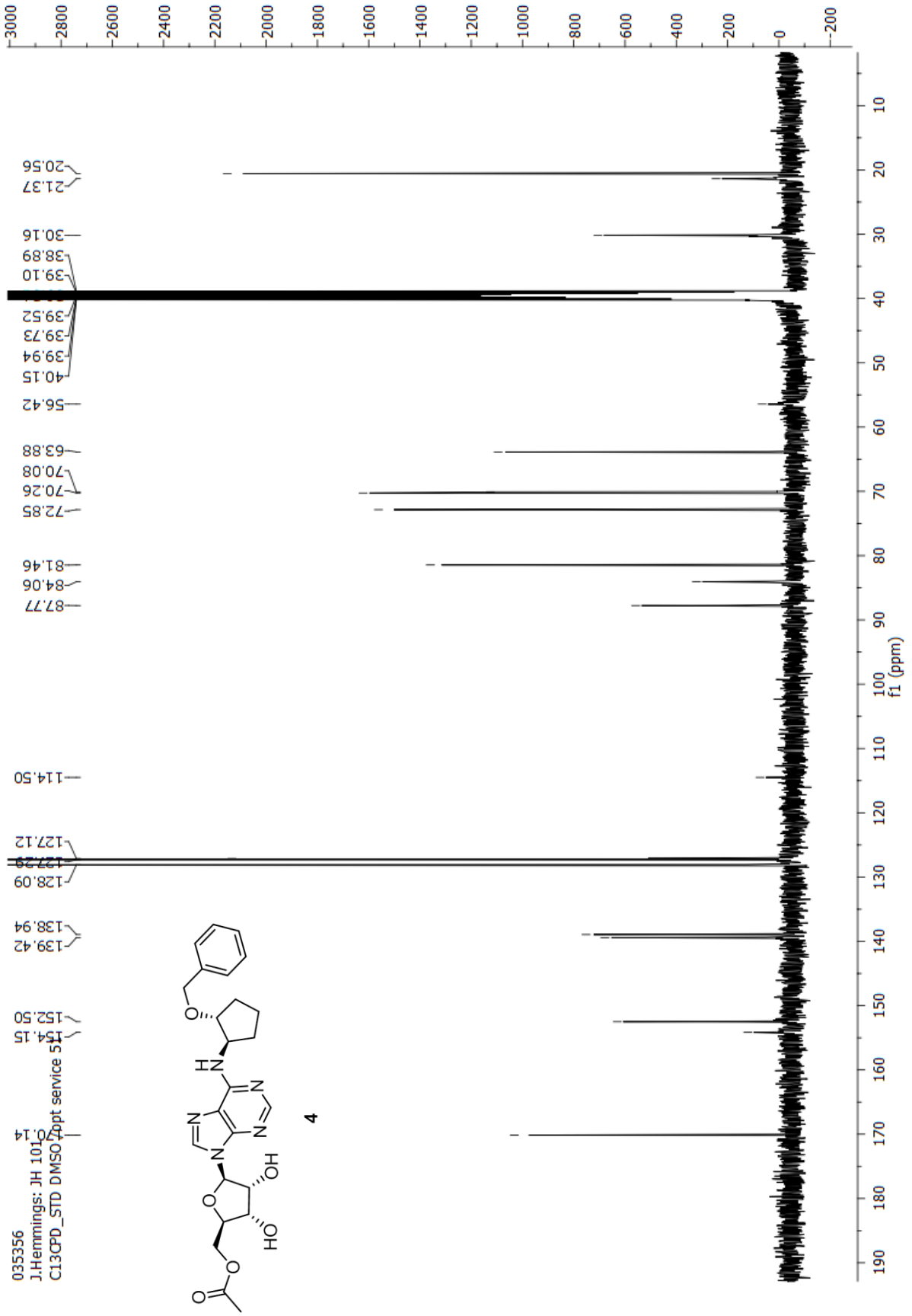
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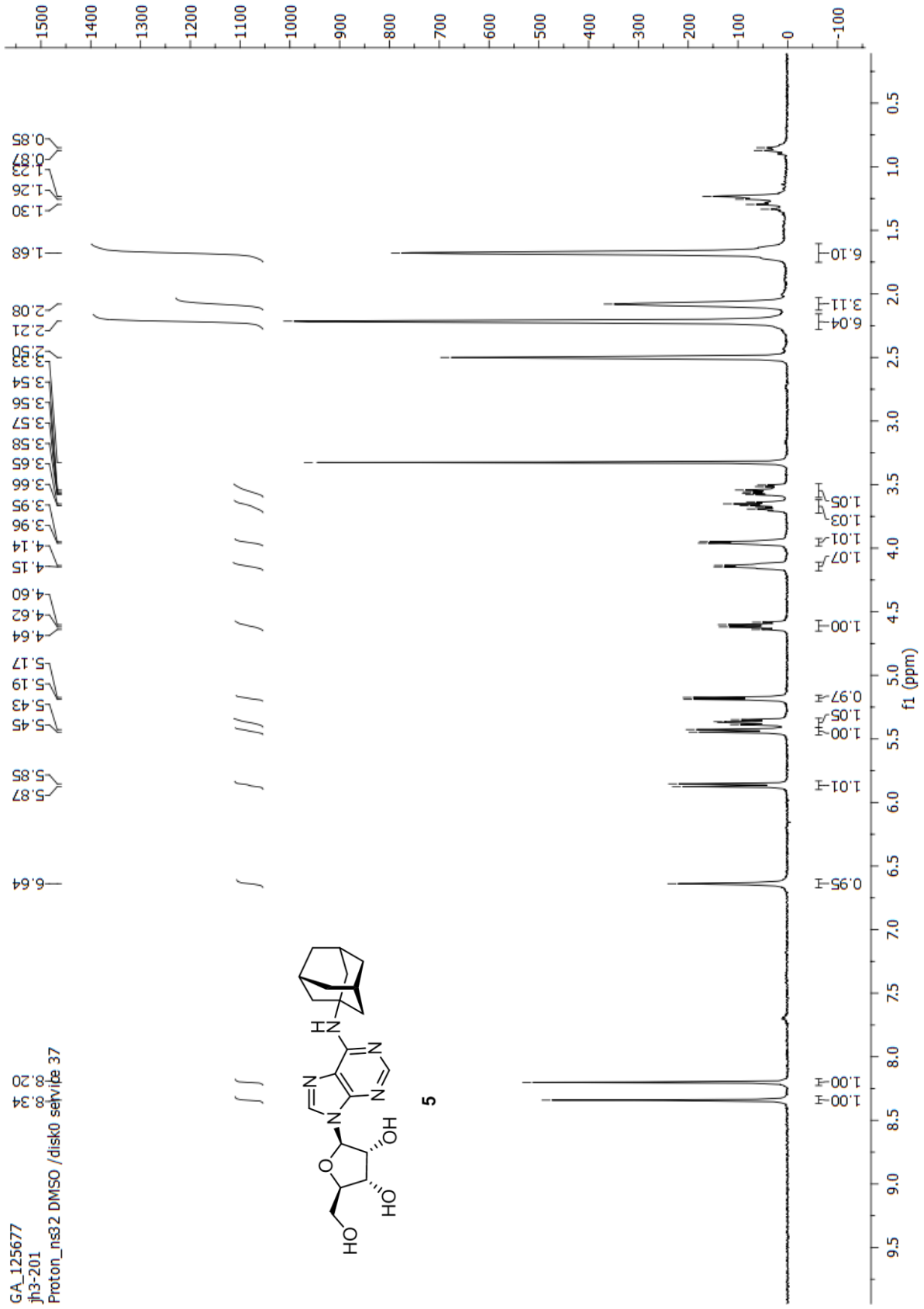
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3.66
3.65
3.58
3.57
3.56
3.54
2.33
2.21
2.08
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1.30
1.26
1.23
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0.85
6.64
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1.00
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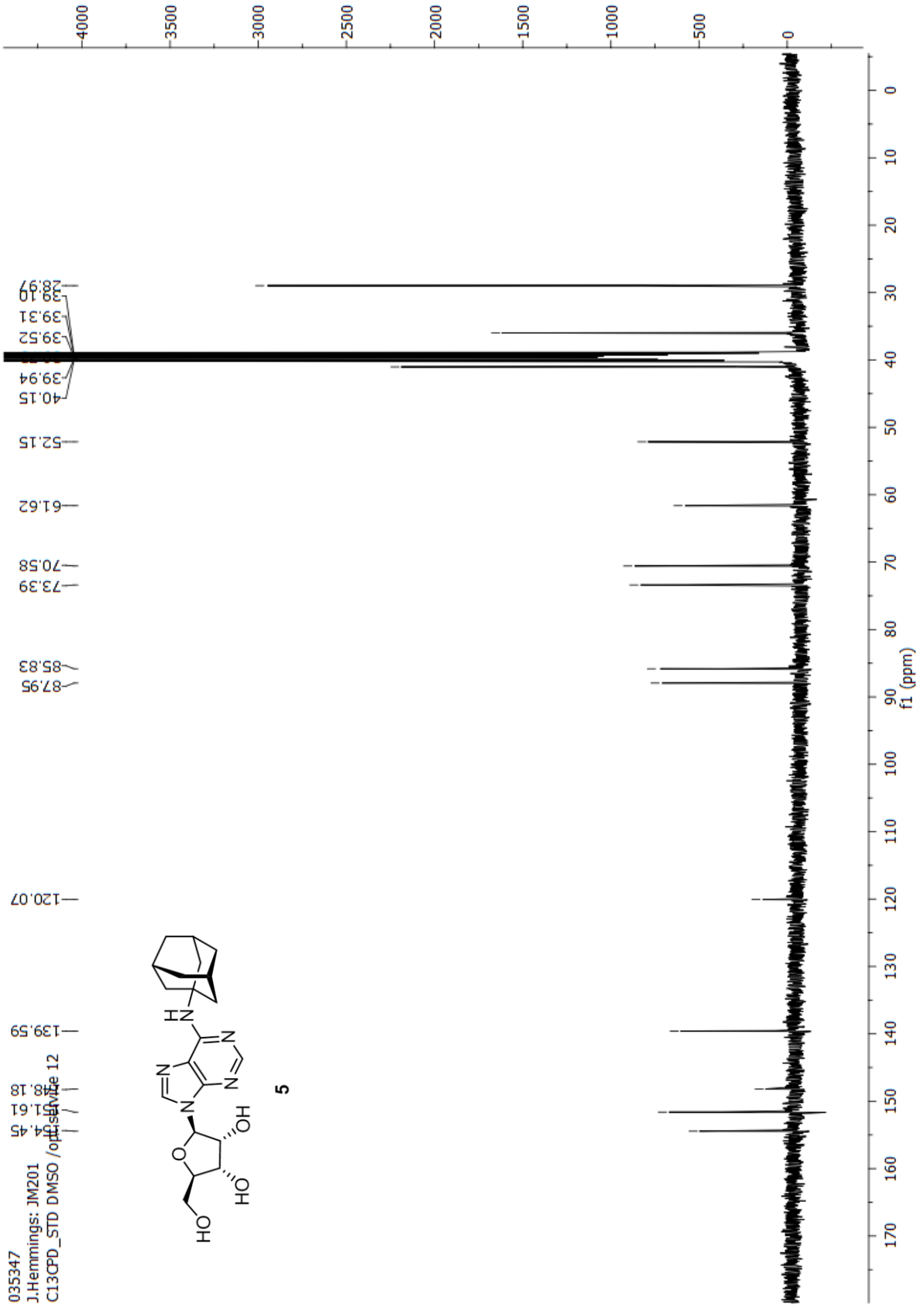
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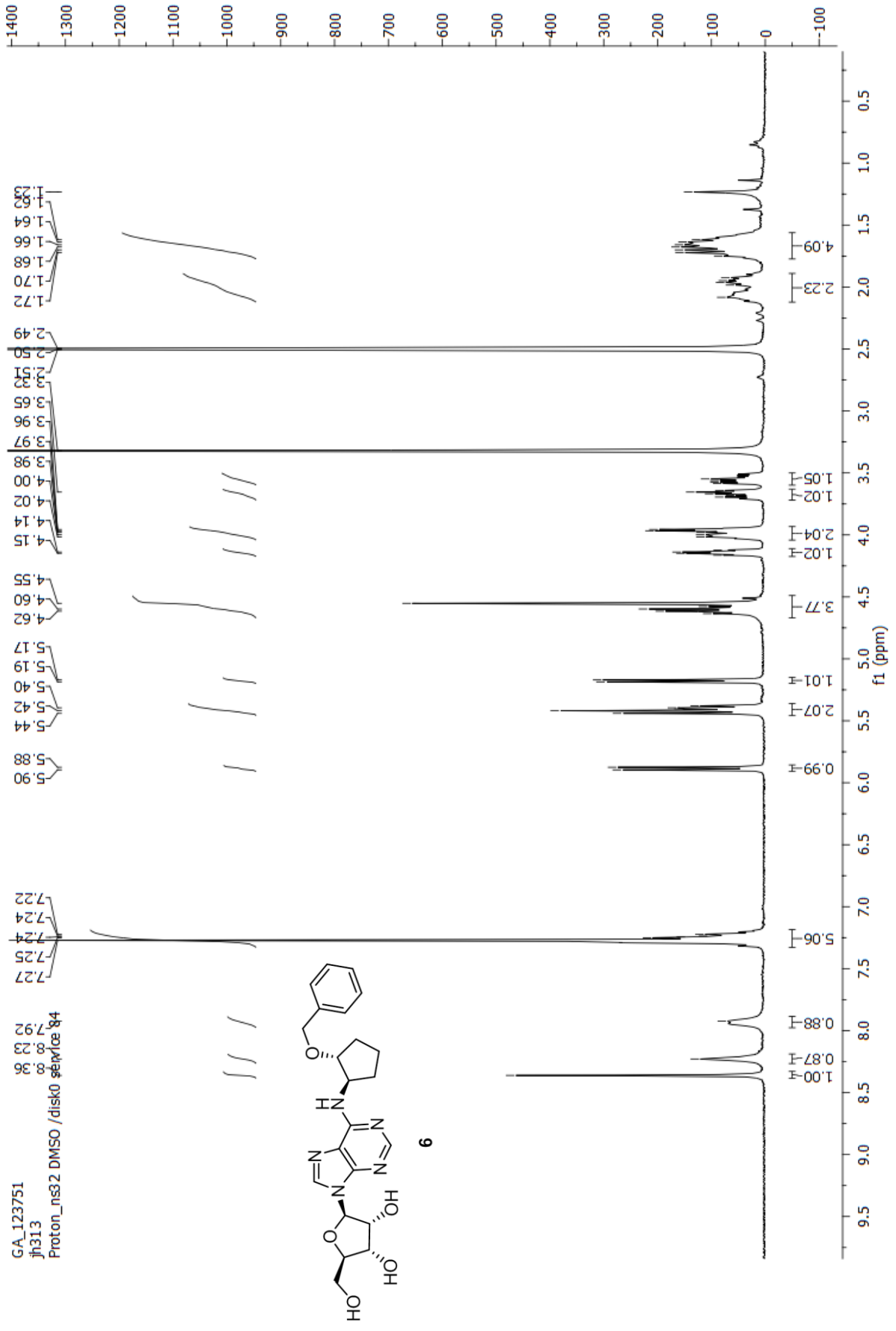
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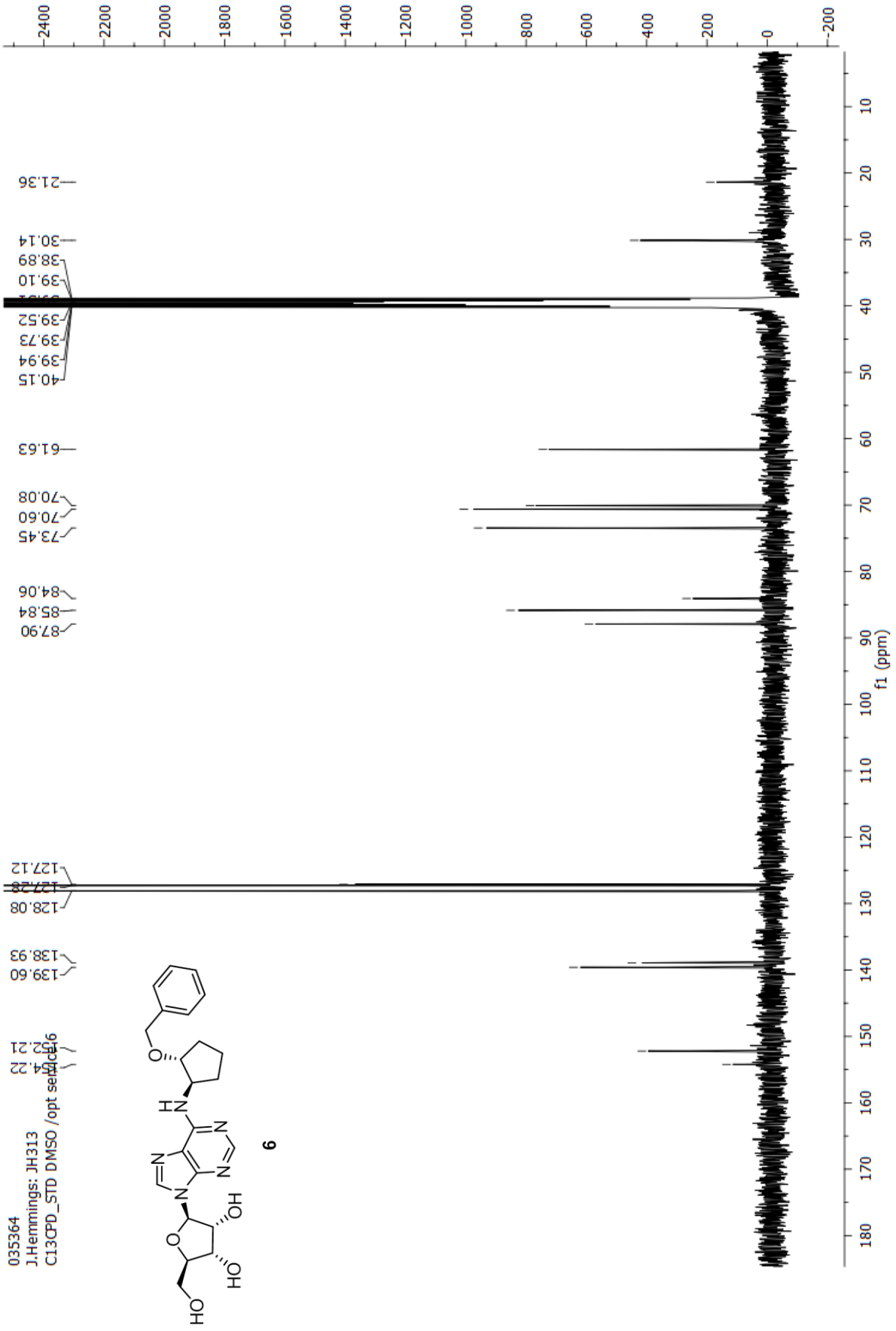
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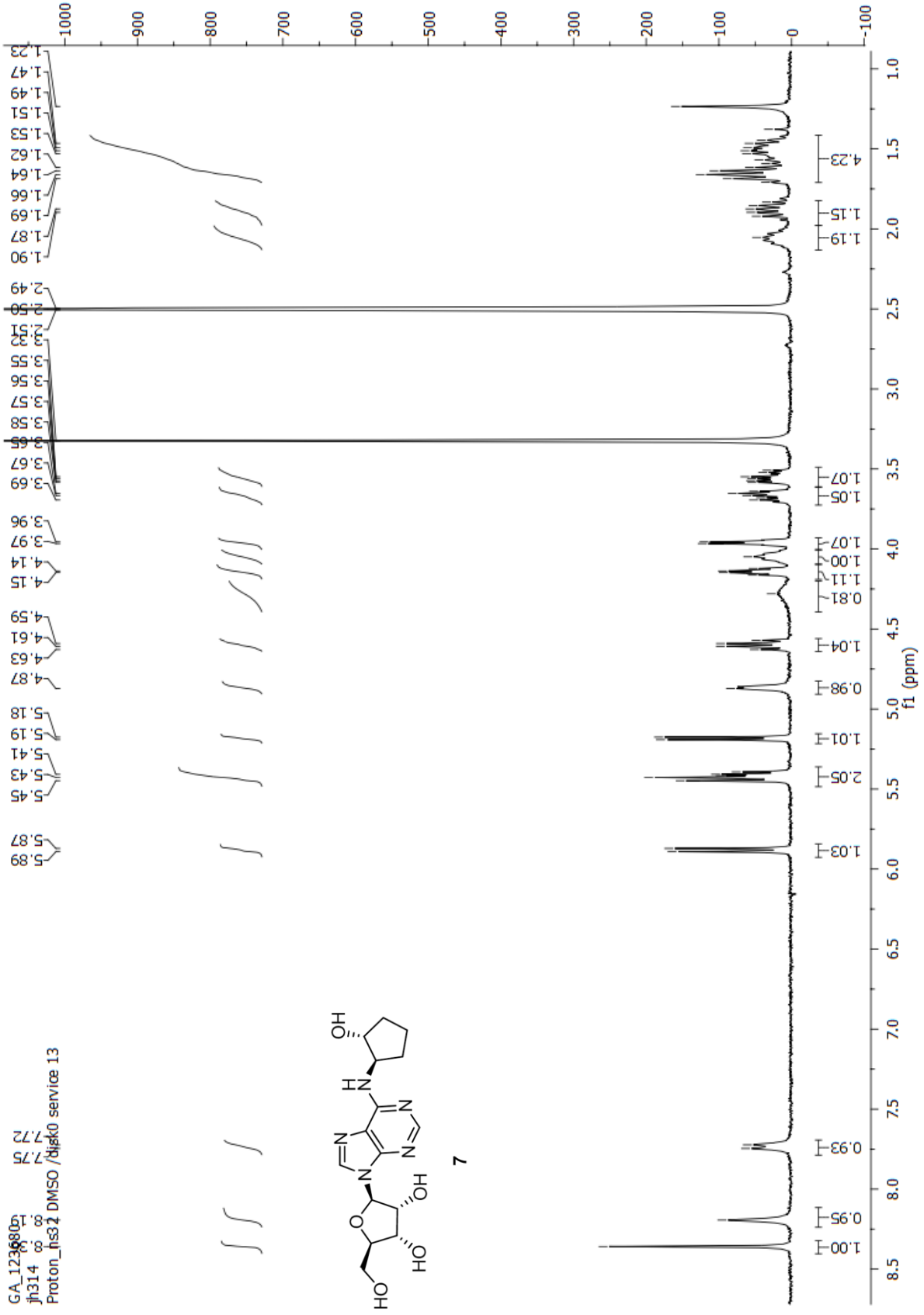

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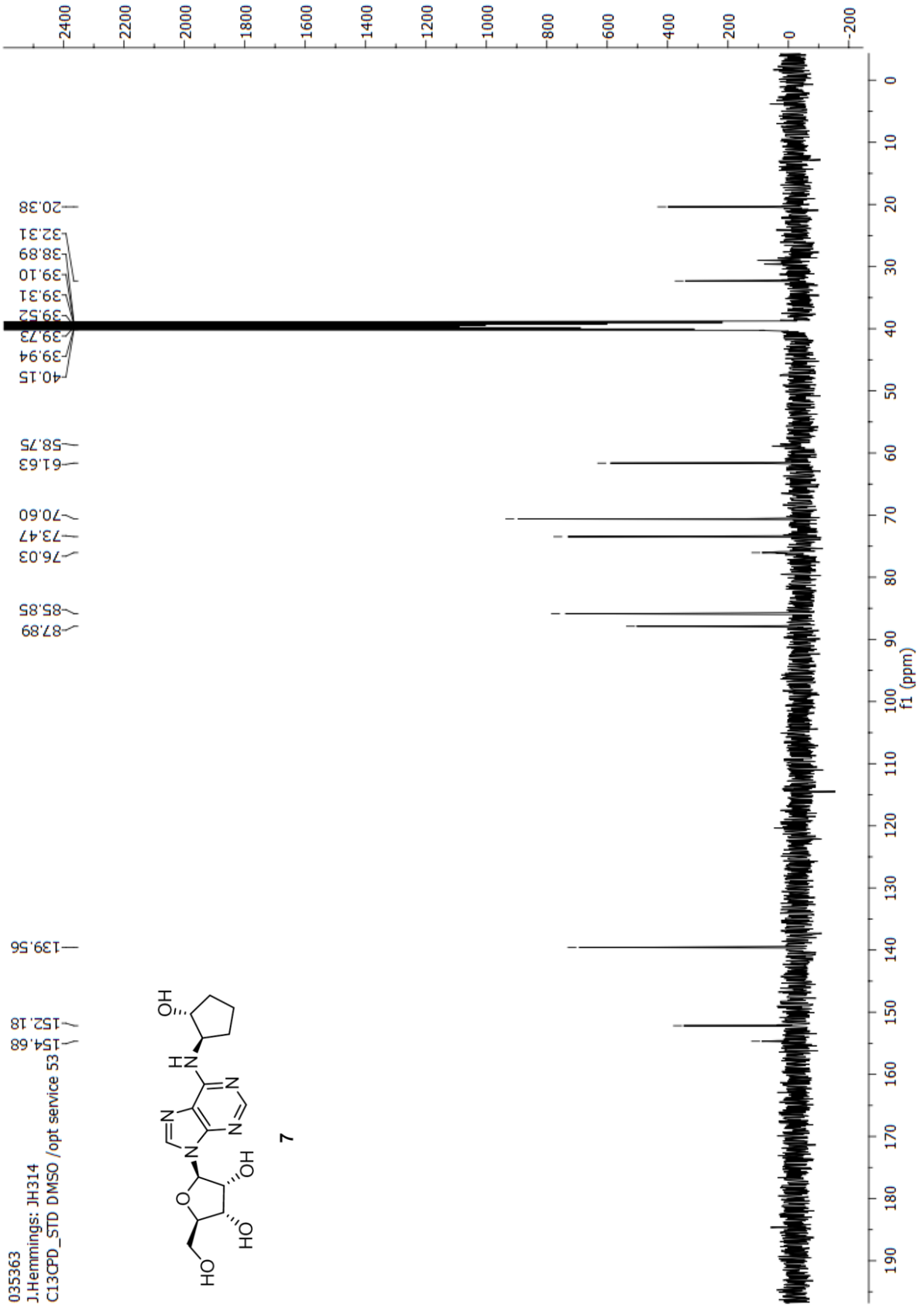
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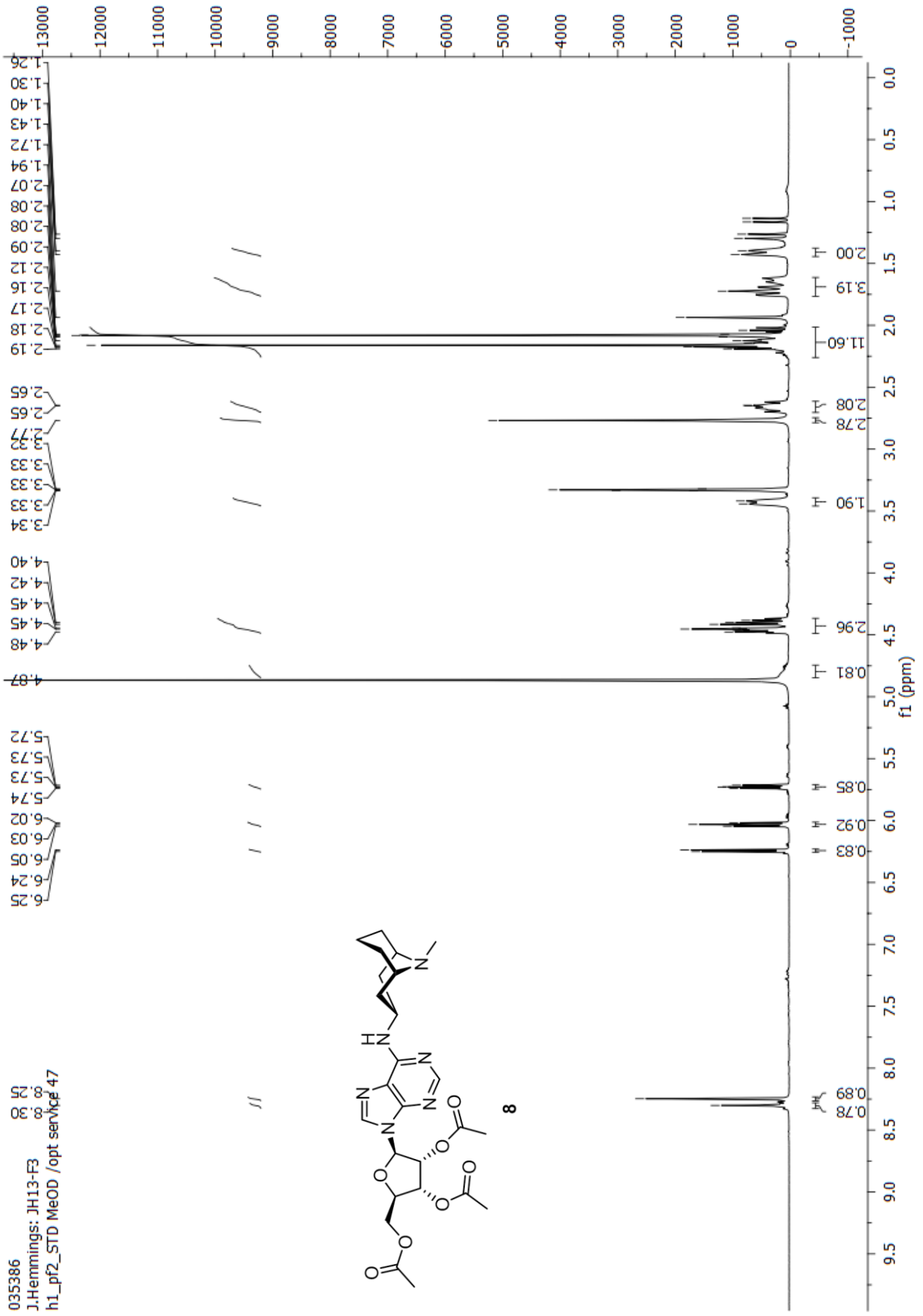
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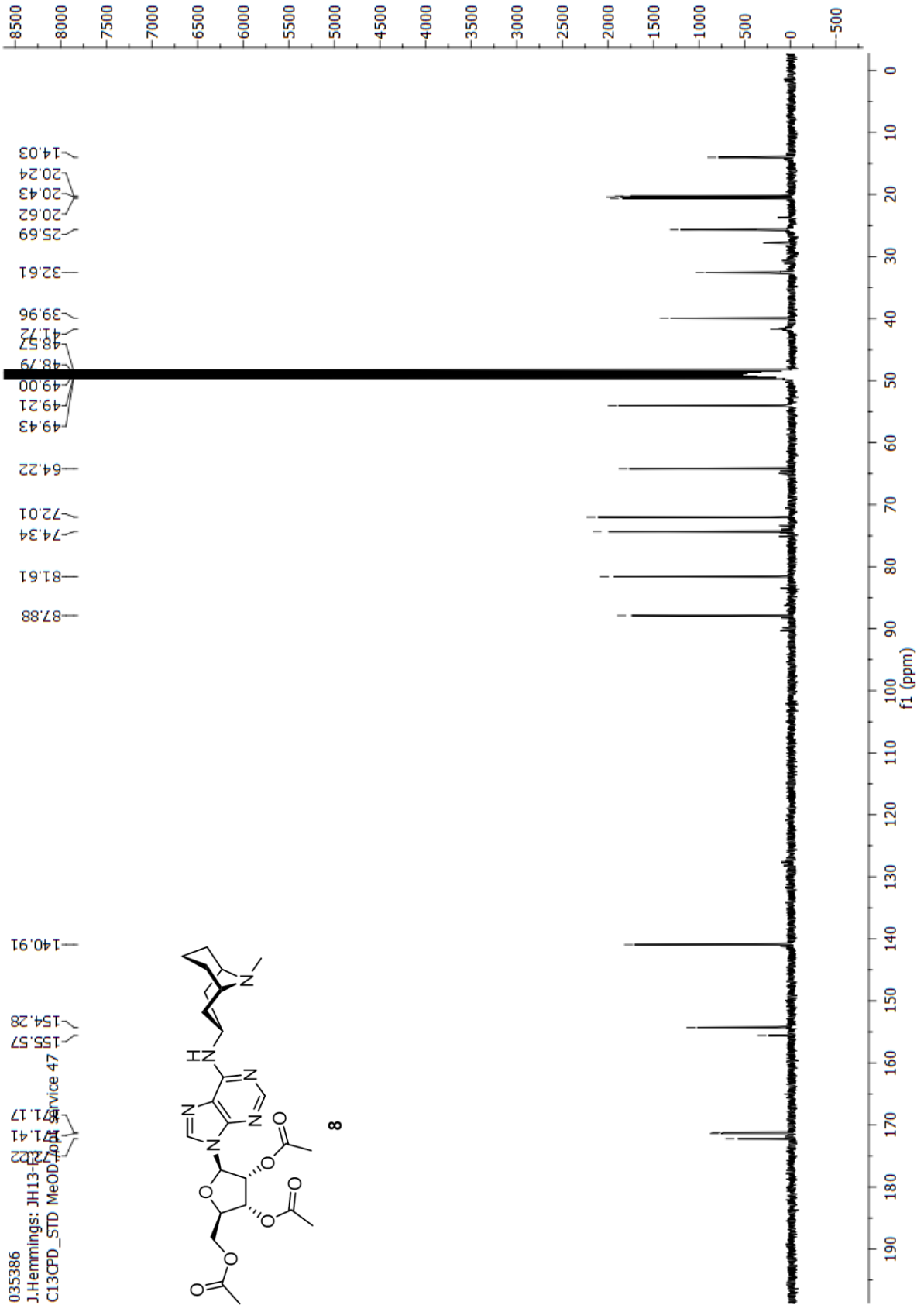
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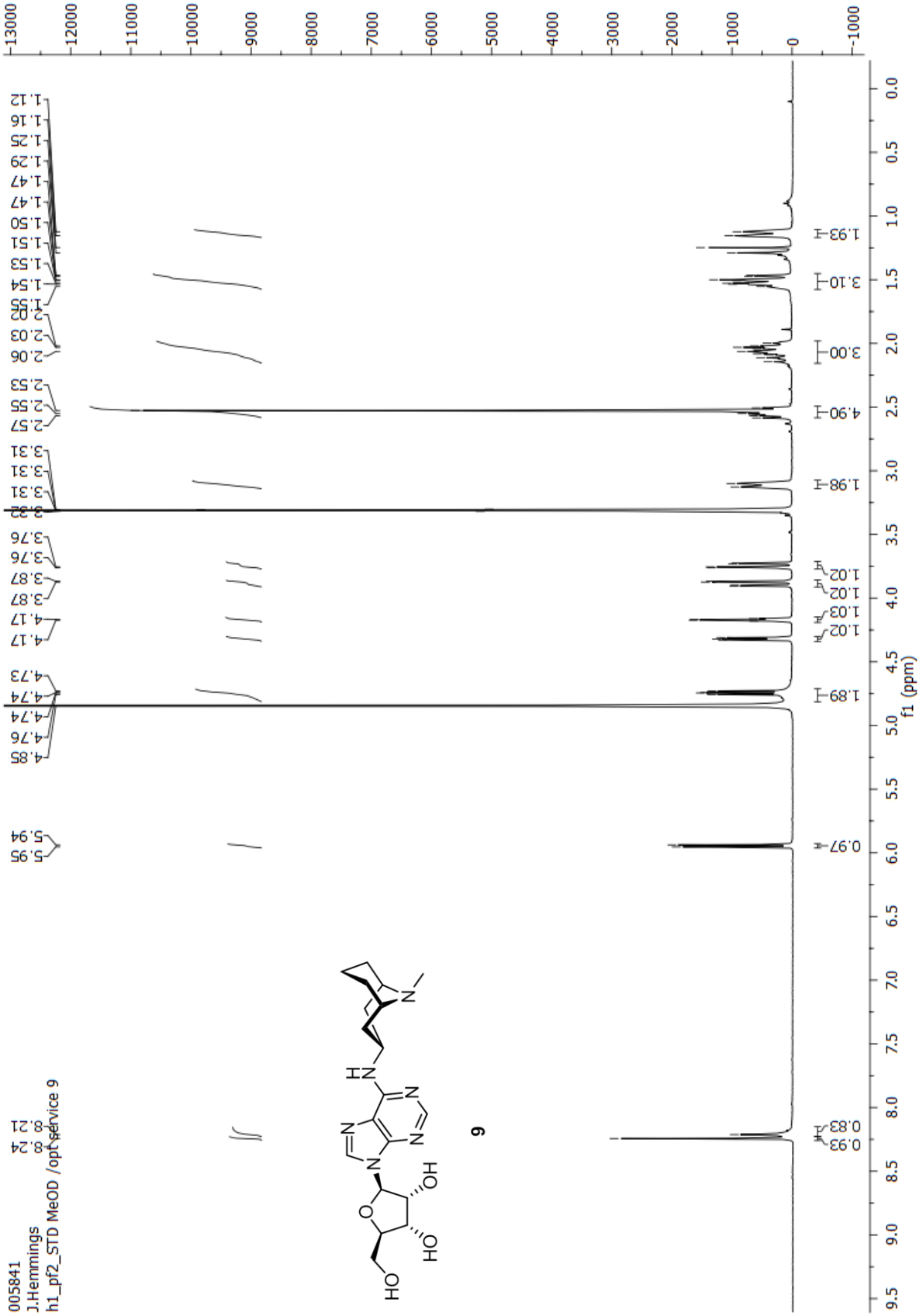
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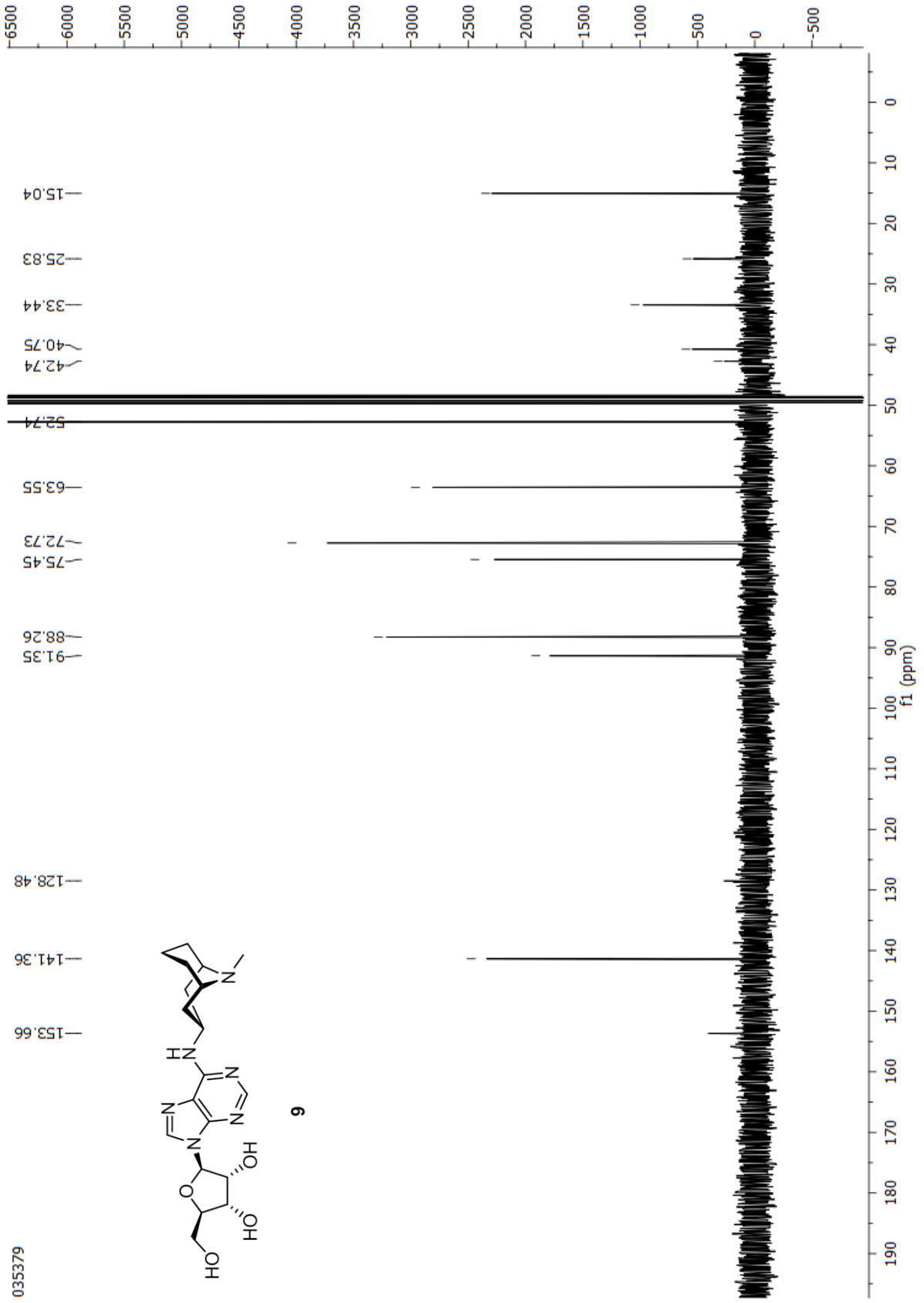
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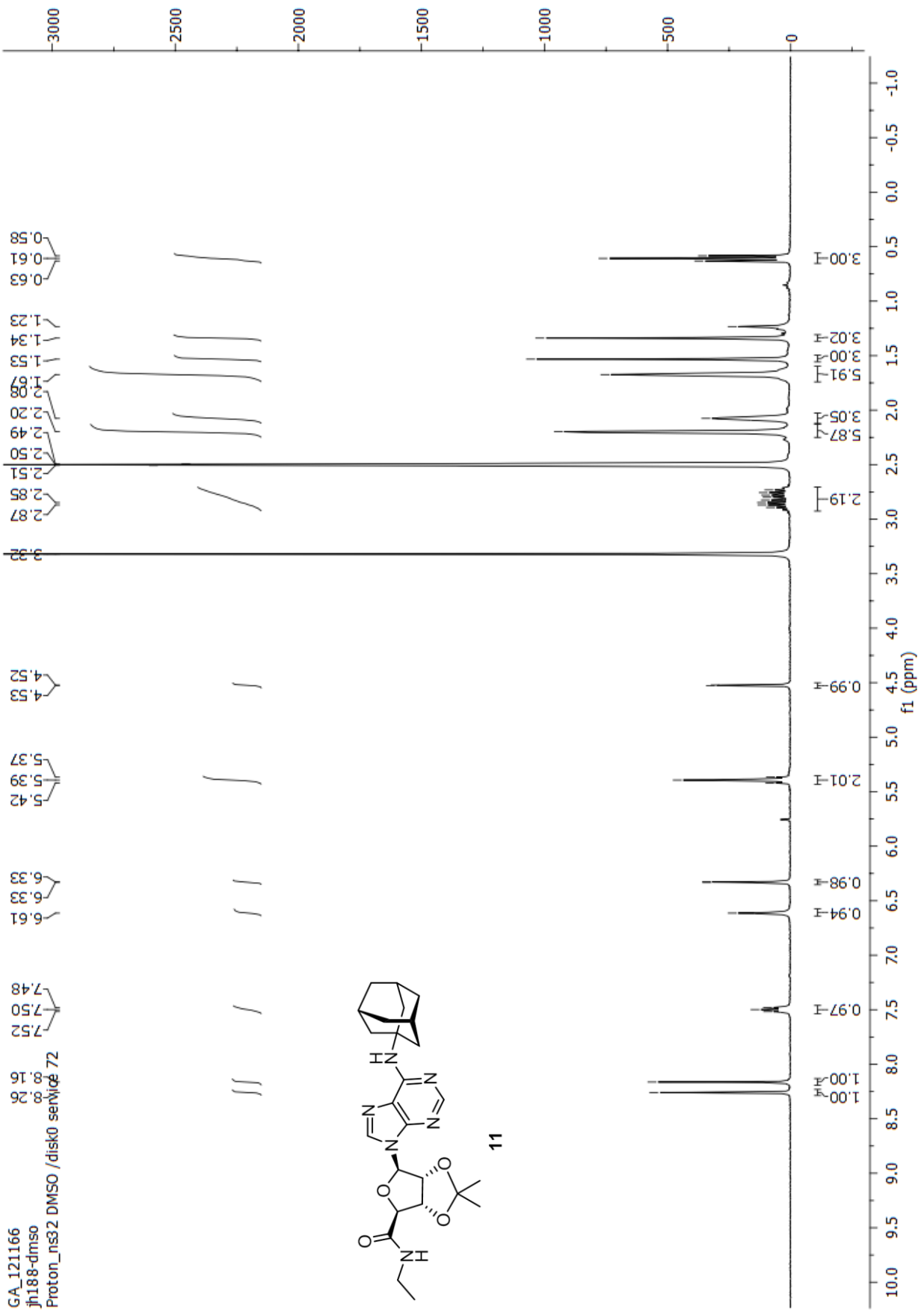
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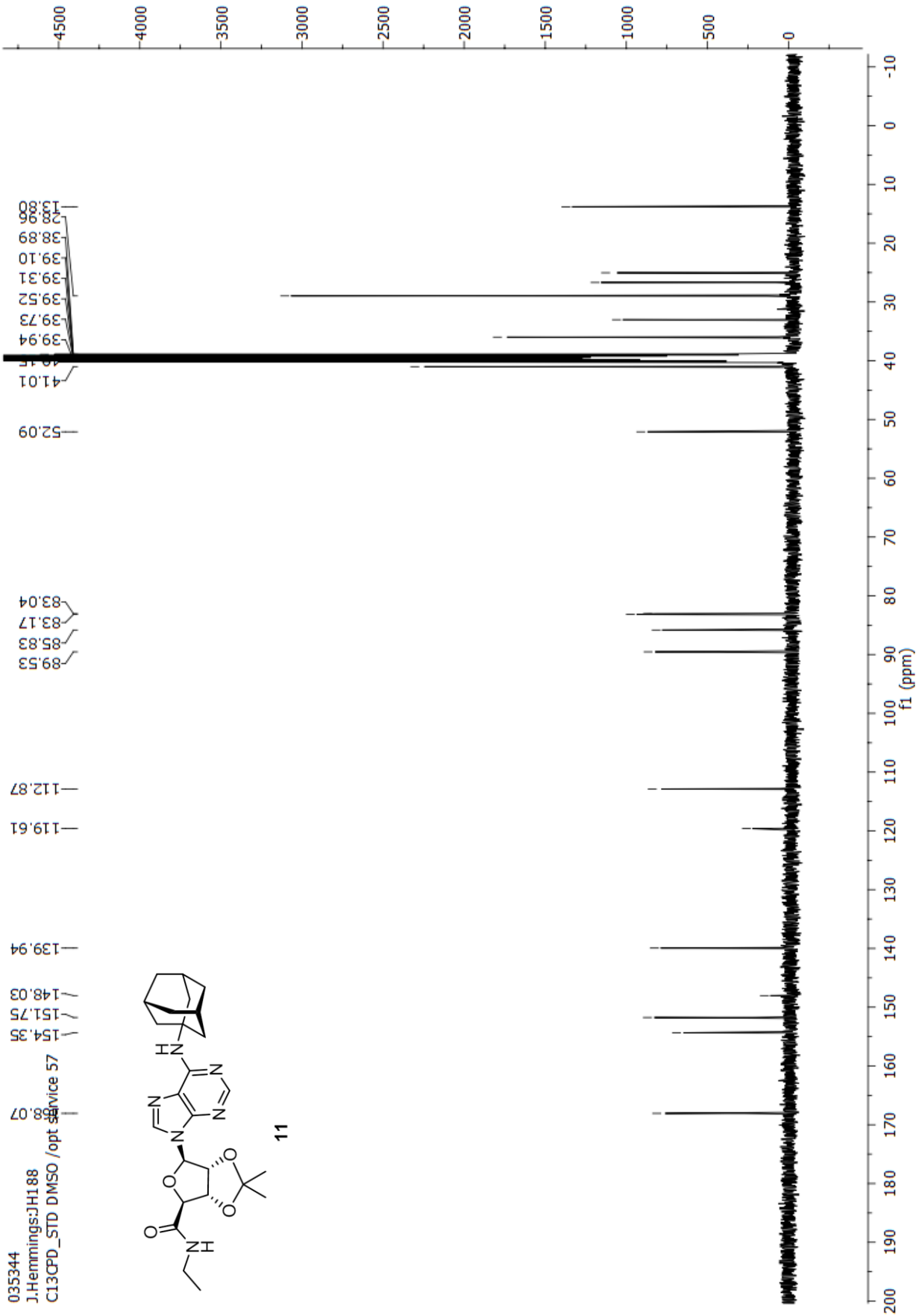
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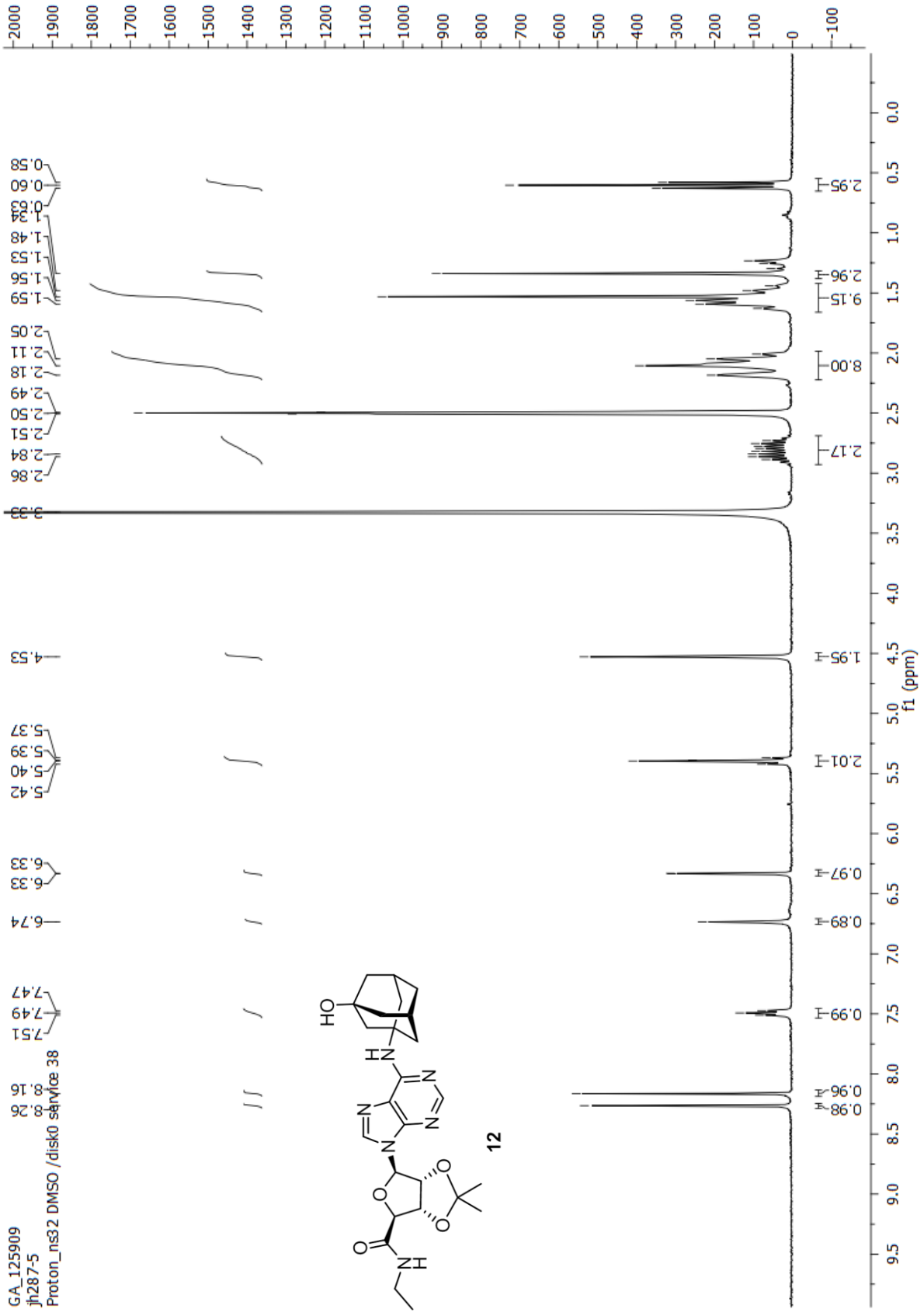
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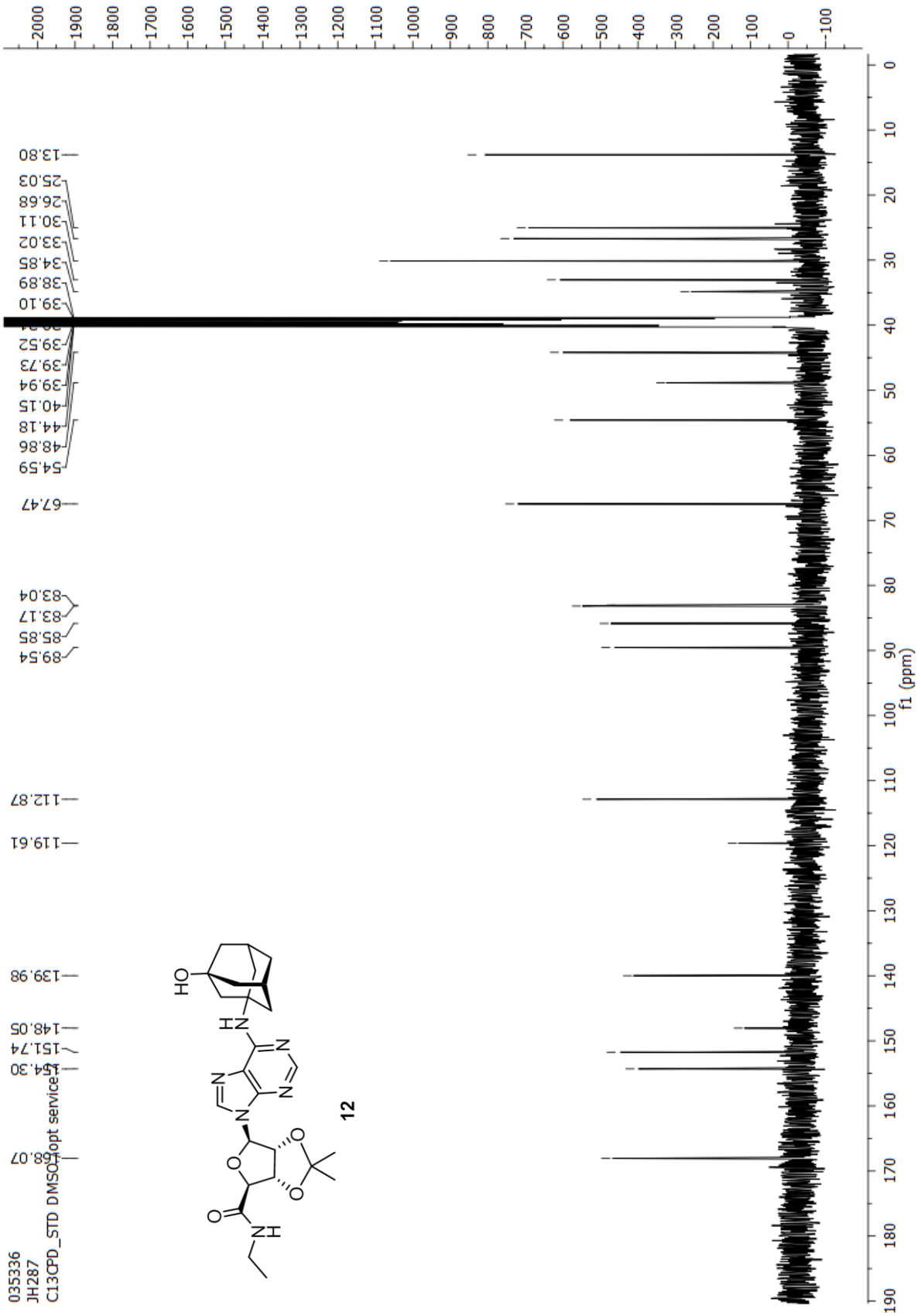
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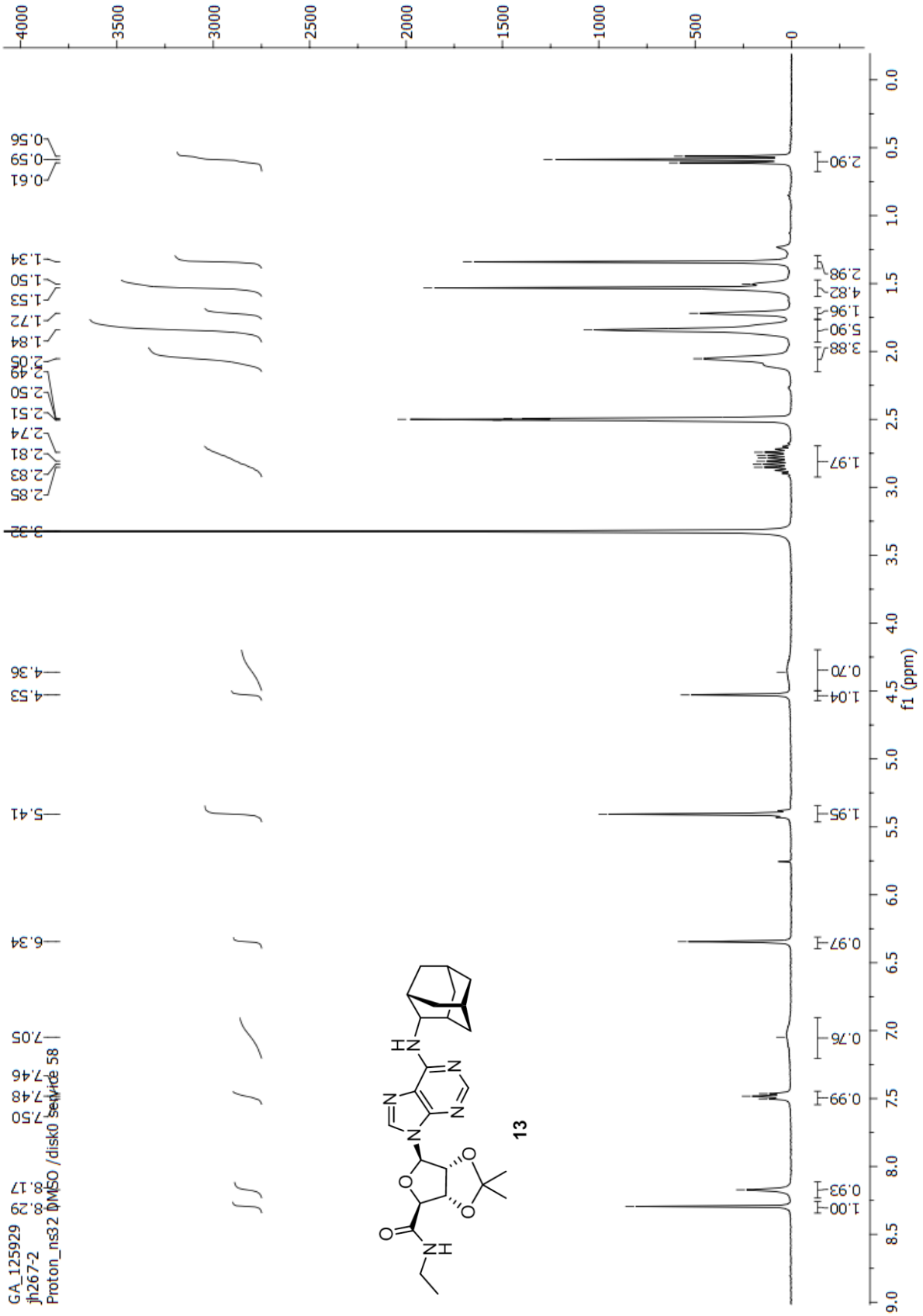
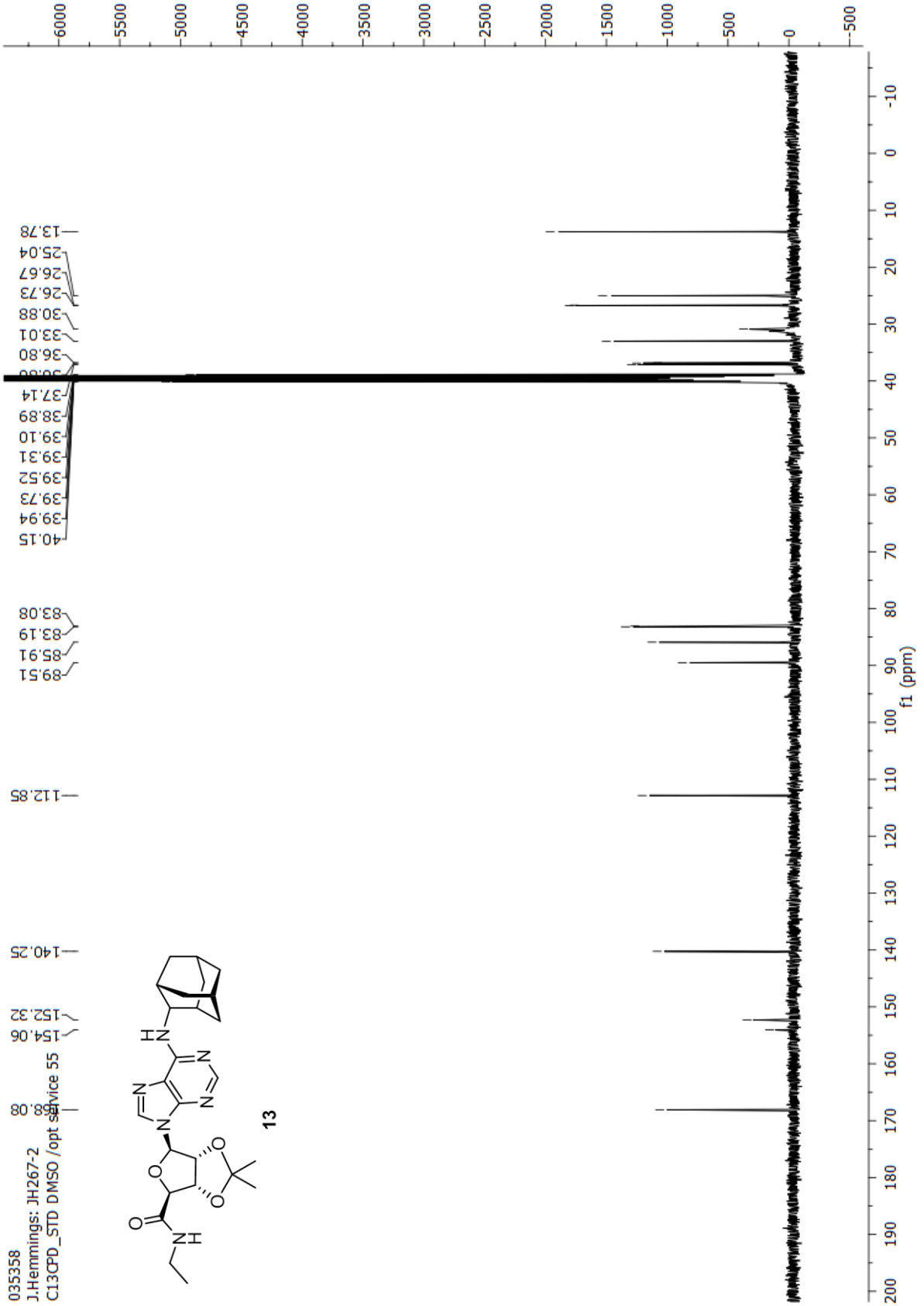
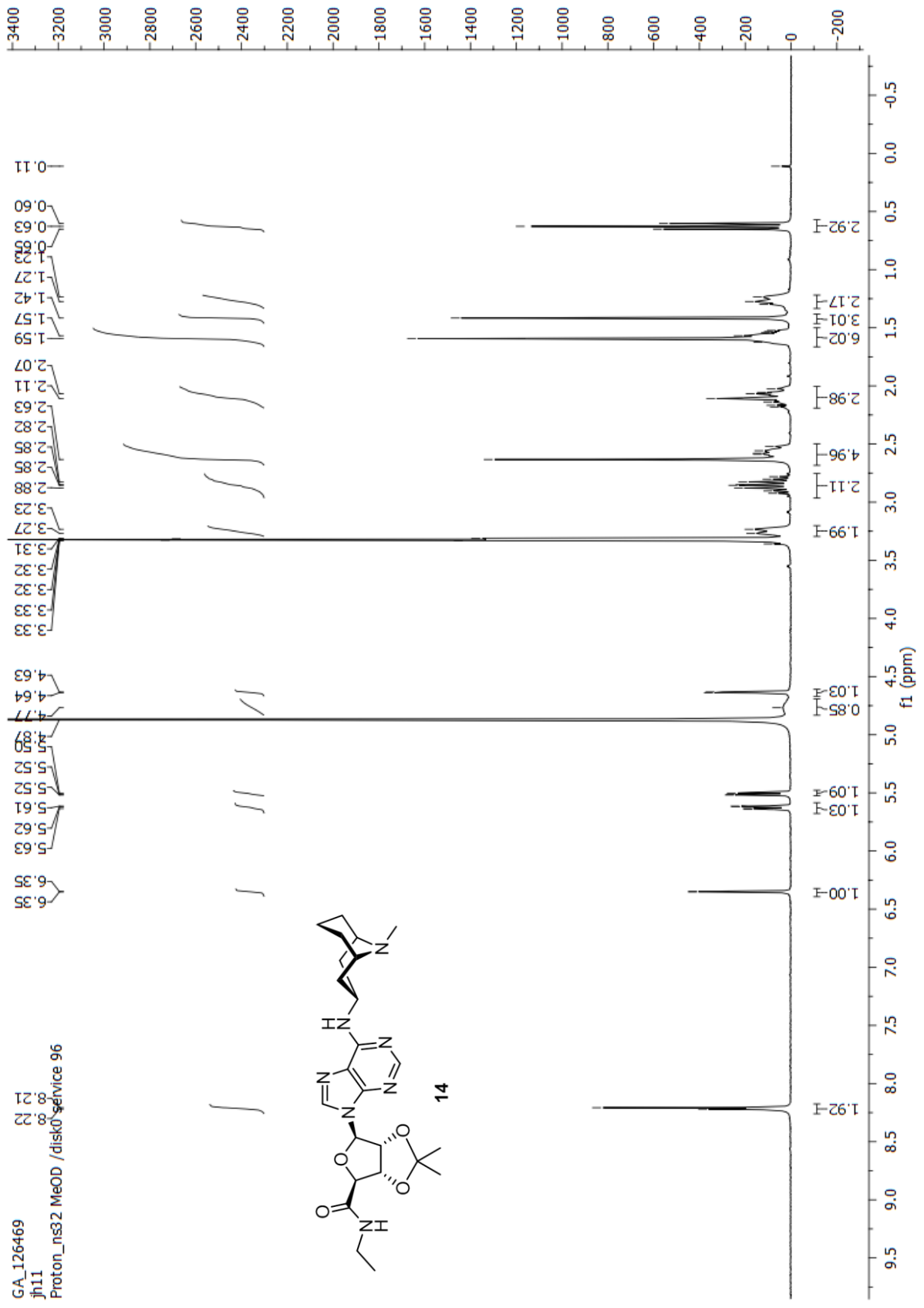
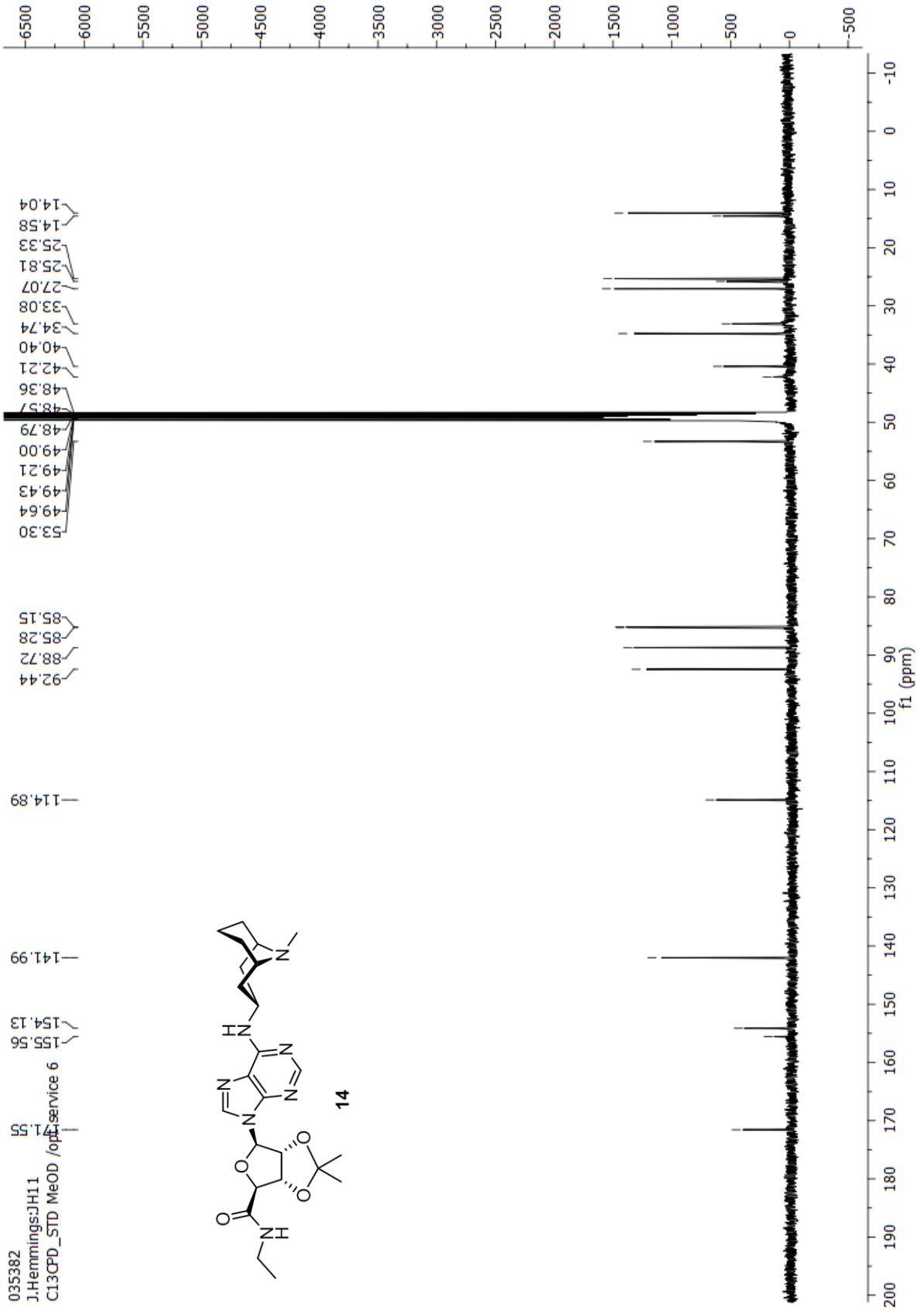
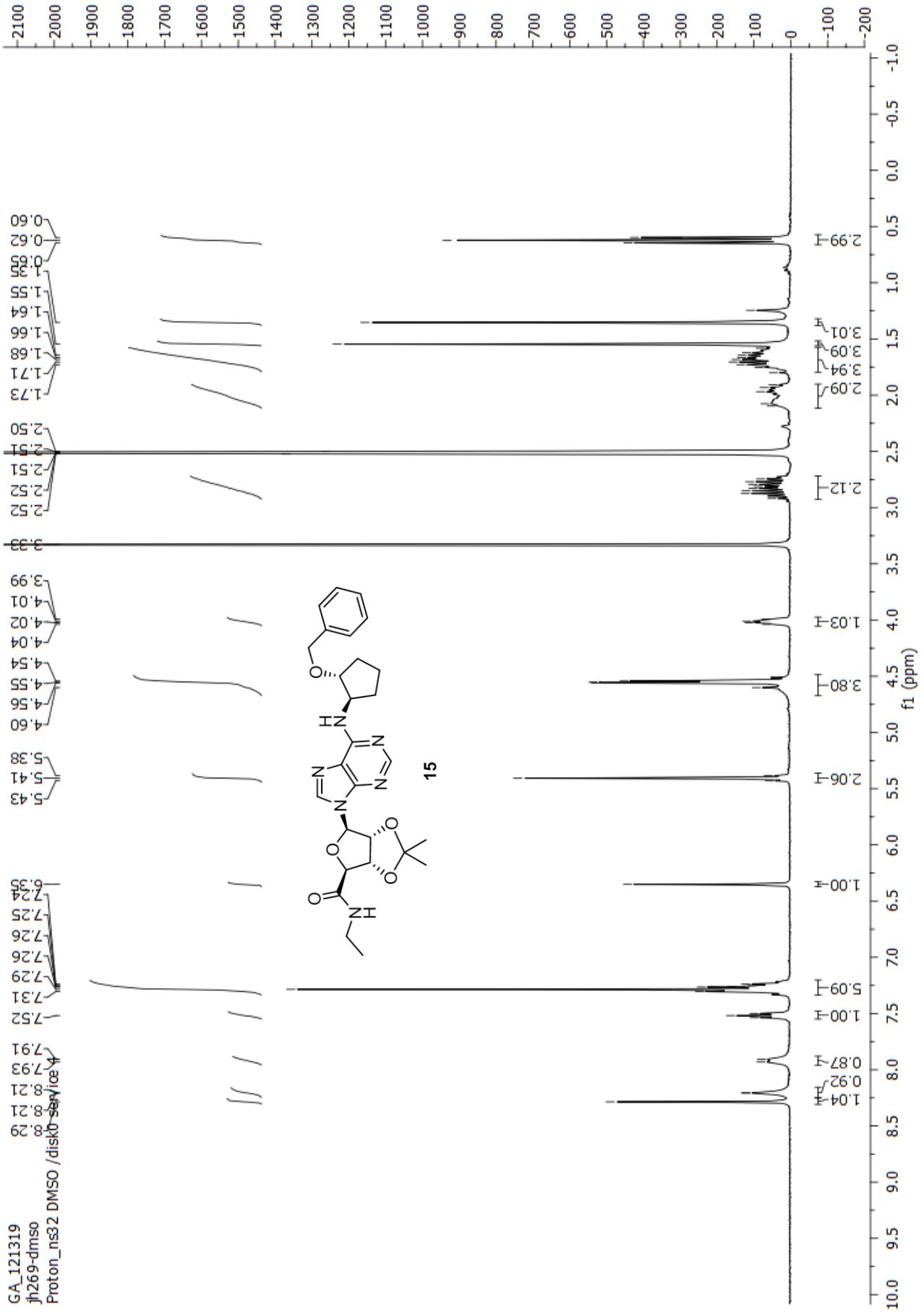
H
H

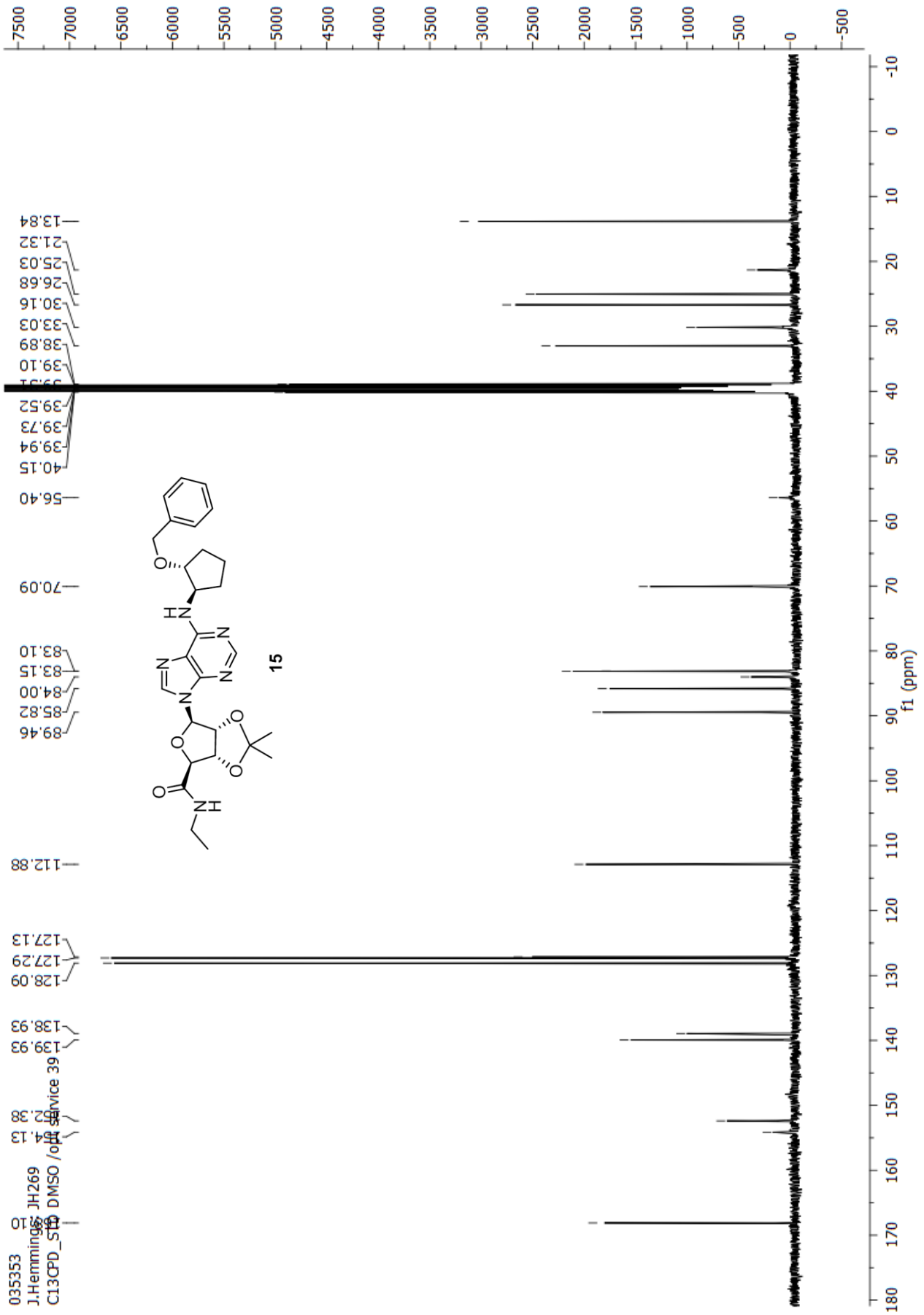

GA_125929
jh267-2
Proton_ns32 DMSO /disk0 service 58
8.29
8.17
7.50
7.48
7.46
7.05
6.34
5.41
4.53
4.36
3.32
2.85
2.83
2.81
2.74
2.51
2.50
2.49
2.05
1.84
1.72
1.53
1.50
1.34
0.61
0.59
0.56
2.90
2.98
4.82
1.96
5.90
3.88
1.97
0.70
1.04
1.95
0.97
0.76
0.99
0.93
1.00
13
f1 (ppm)

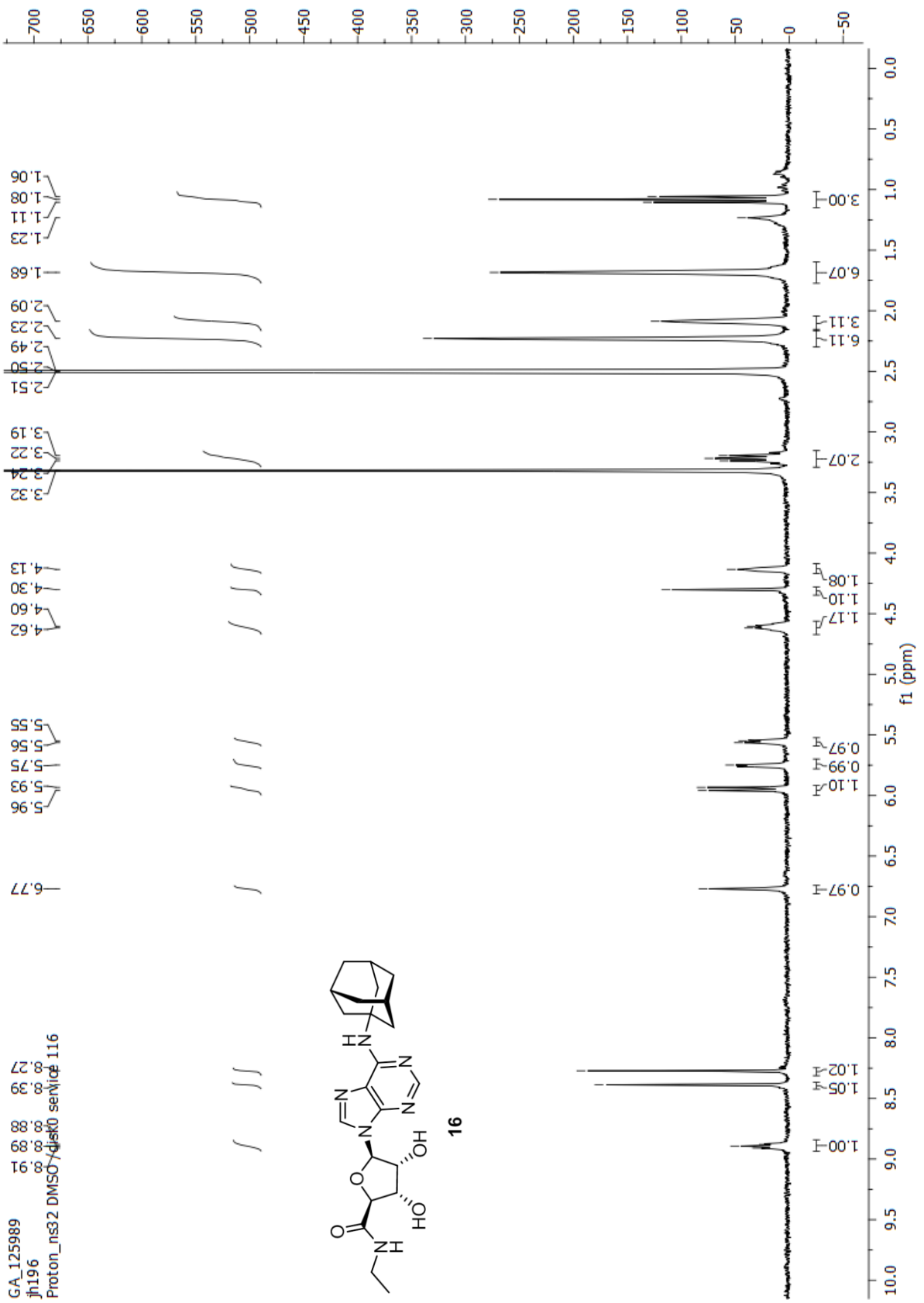

035358
J.Hemmings: JH267-2
C13CPD_STD DMSO /opt service 55
13
13.78
25.04
26.67
26.73
30.88
33.01
36.80
37.14
38.89
39.10
39.31
39.52
39.73
39.94
40.15
83.08
83.19
85.91
89.51
112.85
140.25
152.32
154.06
168.08
f1 (ppm)

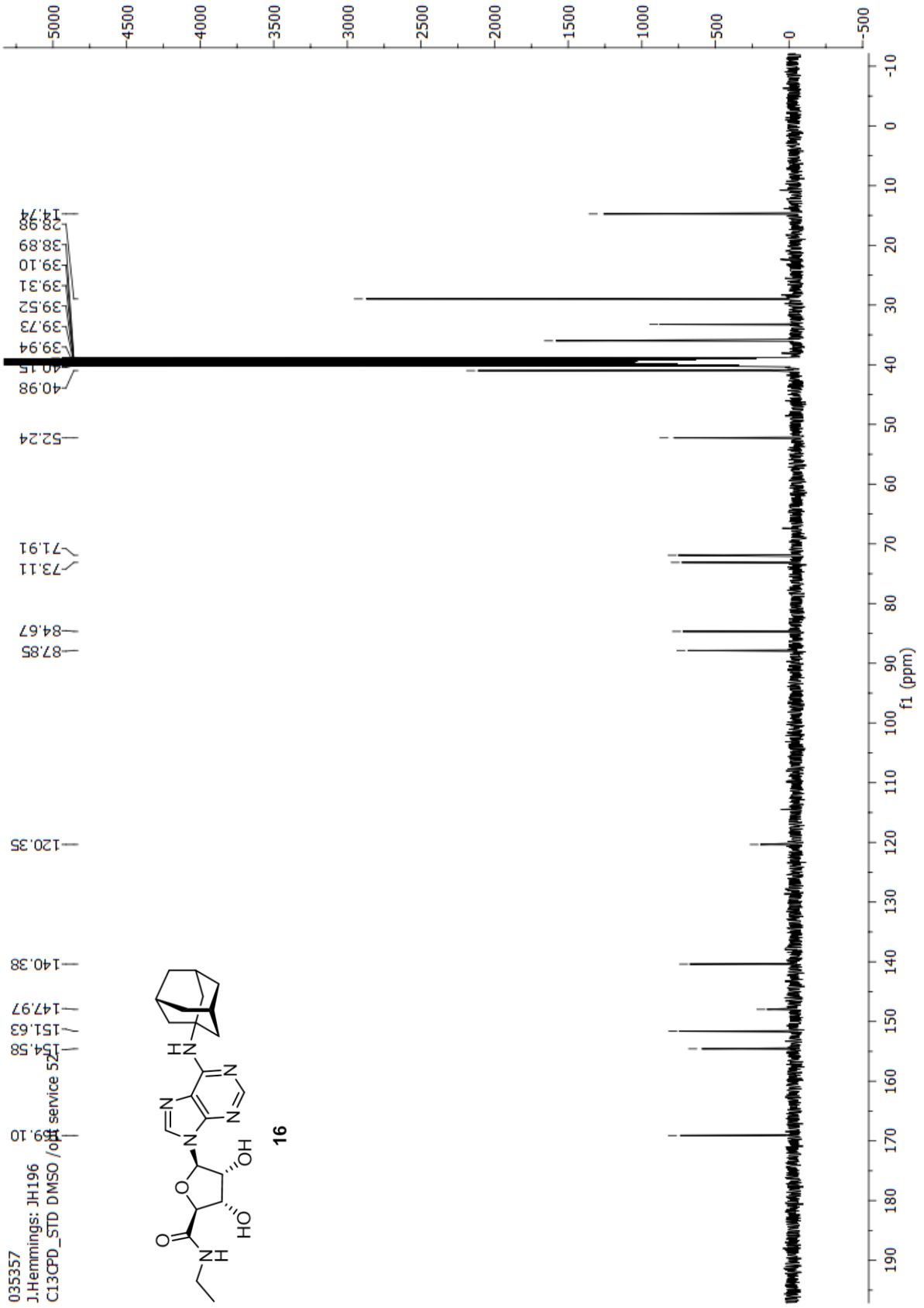

GA_126469
jh11
Proton_ns32 MeOD /disk0 service 96
14
f1 (ppm)

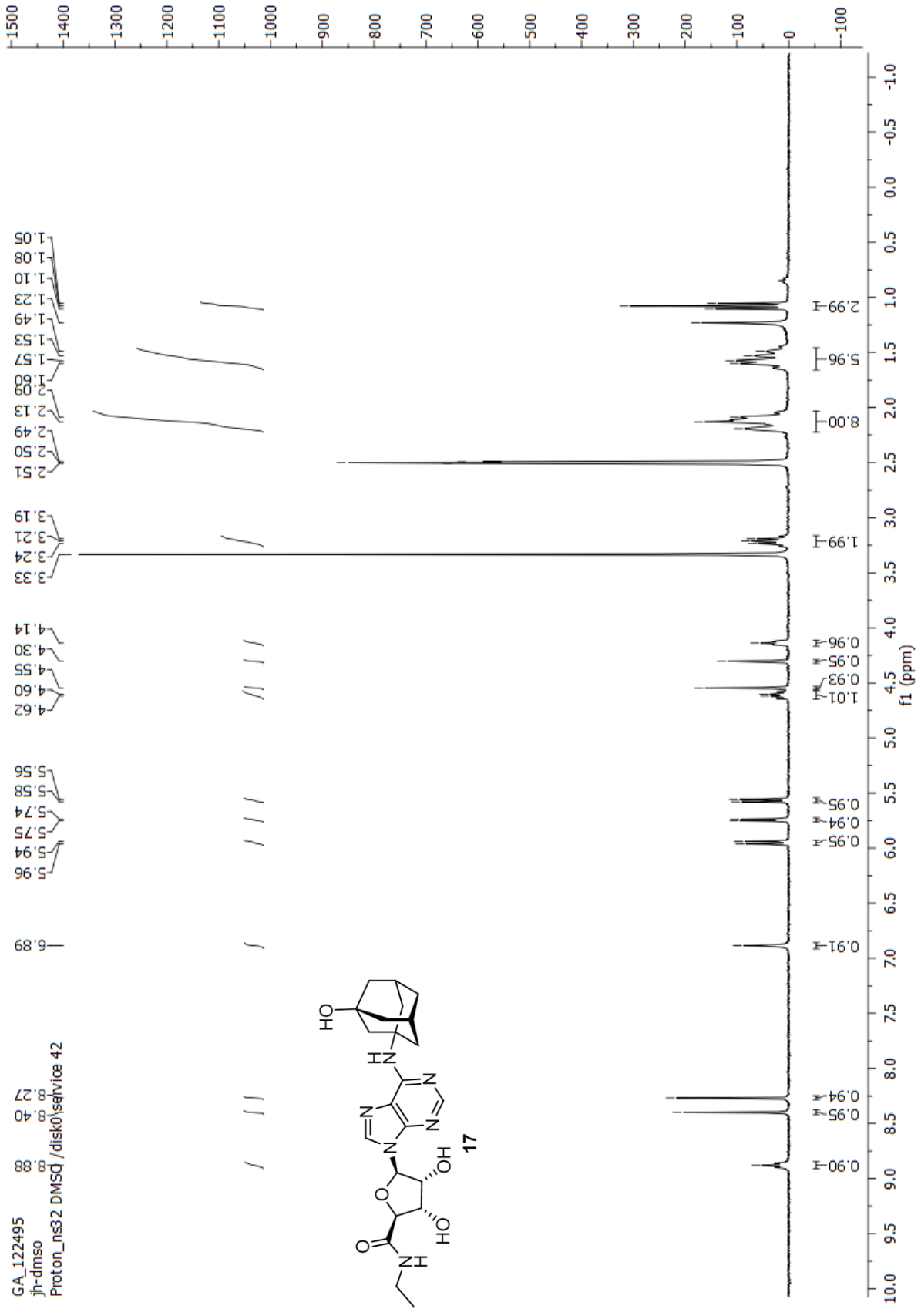

035382
J.Hemmings:JH11
C13CPD_STD MeOD /opt/service 6
14
f1 (ppm)

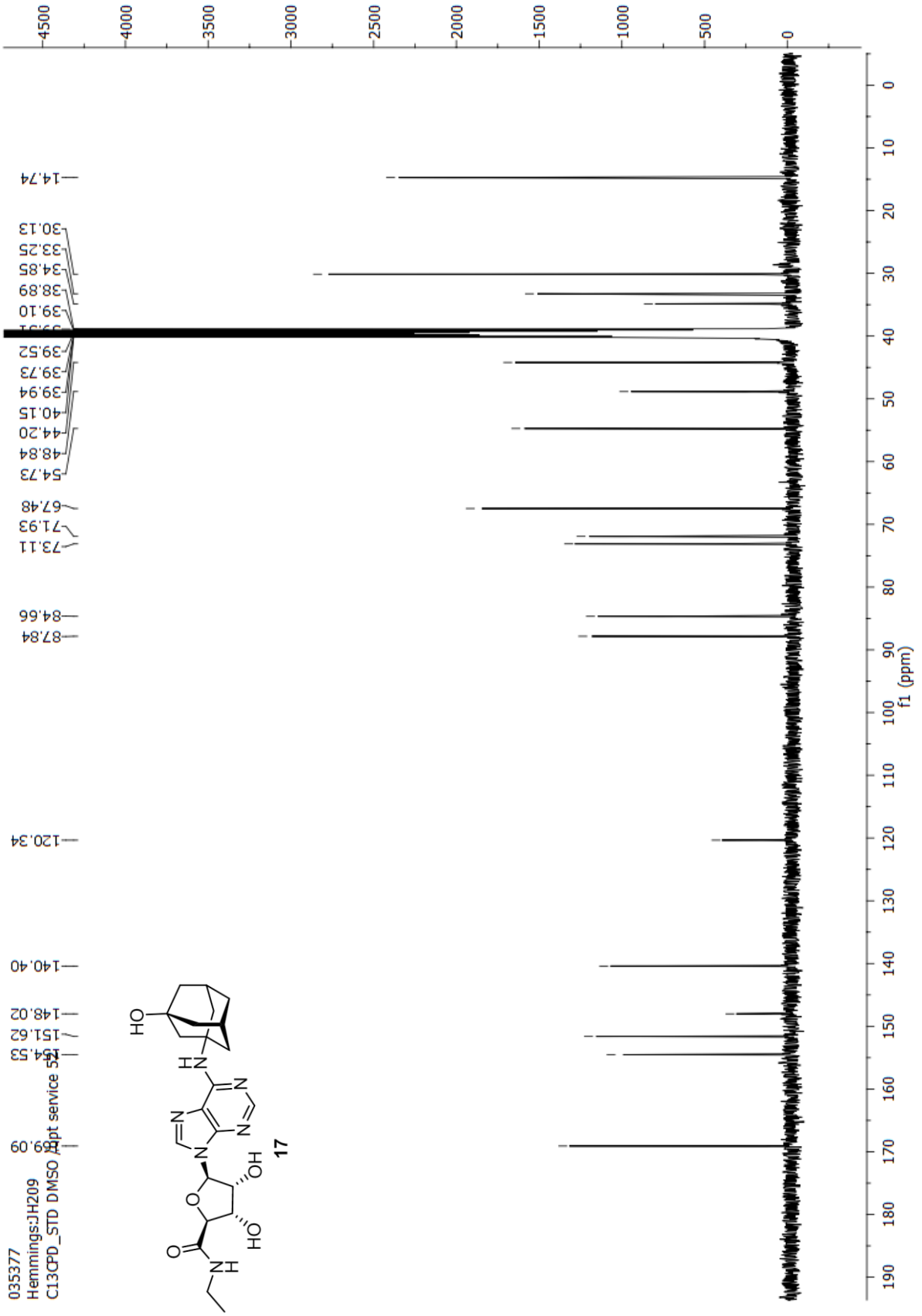

GA_121319
jh269-dmso
Proton_ns32 DMSO /disk0 service 4
15
f1 (ppm)

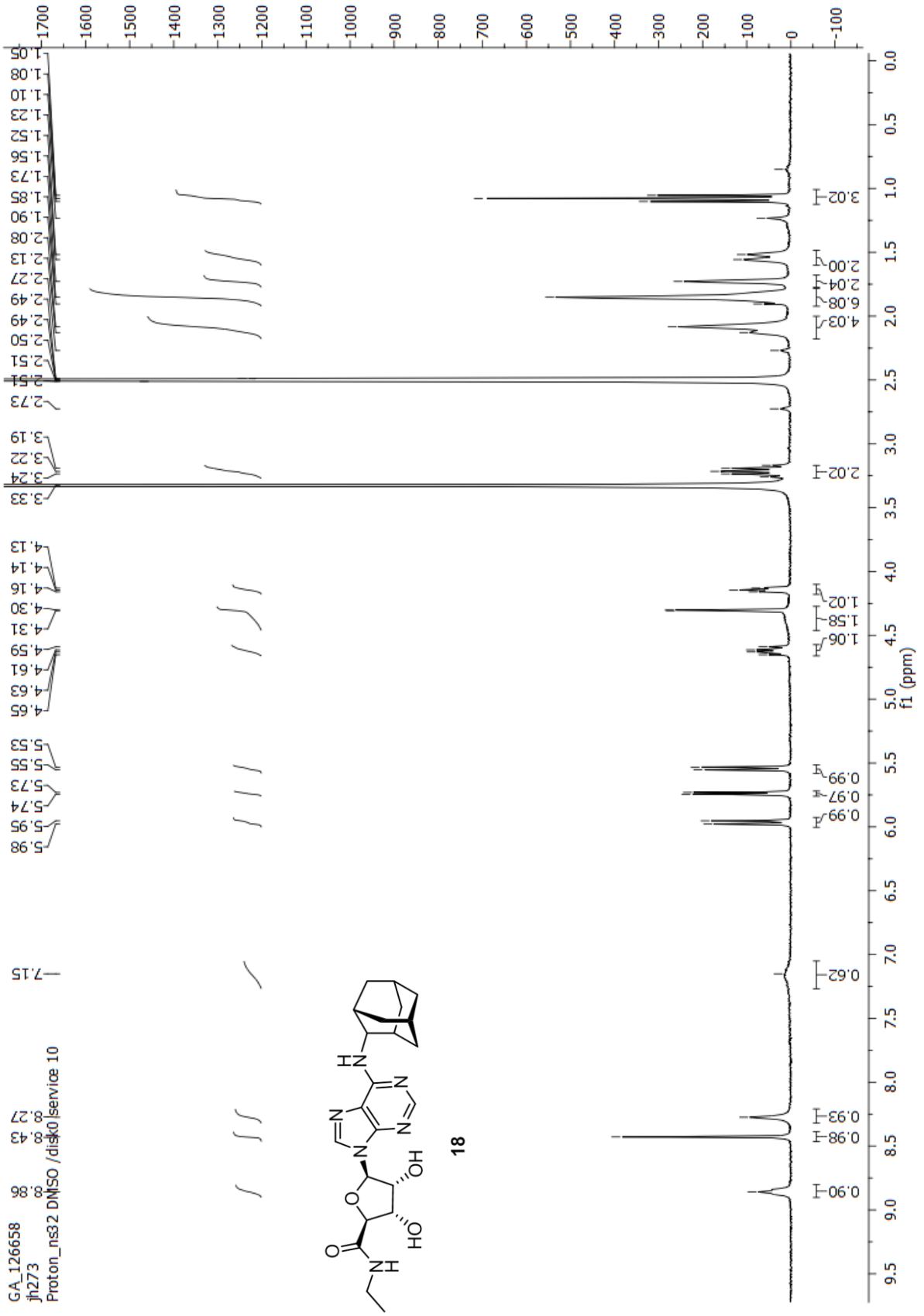

035353
J.Hemmingsen JH269
C13CPD_STD DMSO /old Service 39
13.84
21.32
25.03
26.68
30.16
33.03
38.89
39.10
39.31
39.52
39.73
39.94
40.15
56.40
70.09
83.10
83.15
84.00
85.82
89.46
112.88
127.13
127.29
128.09
138.93
139.93
152.38
154.13
168.10
15
f1 (ppm)

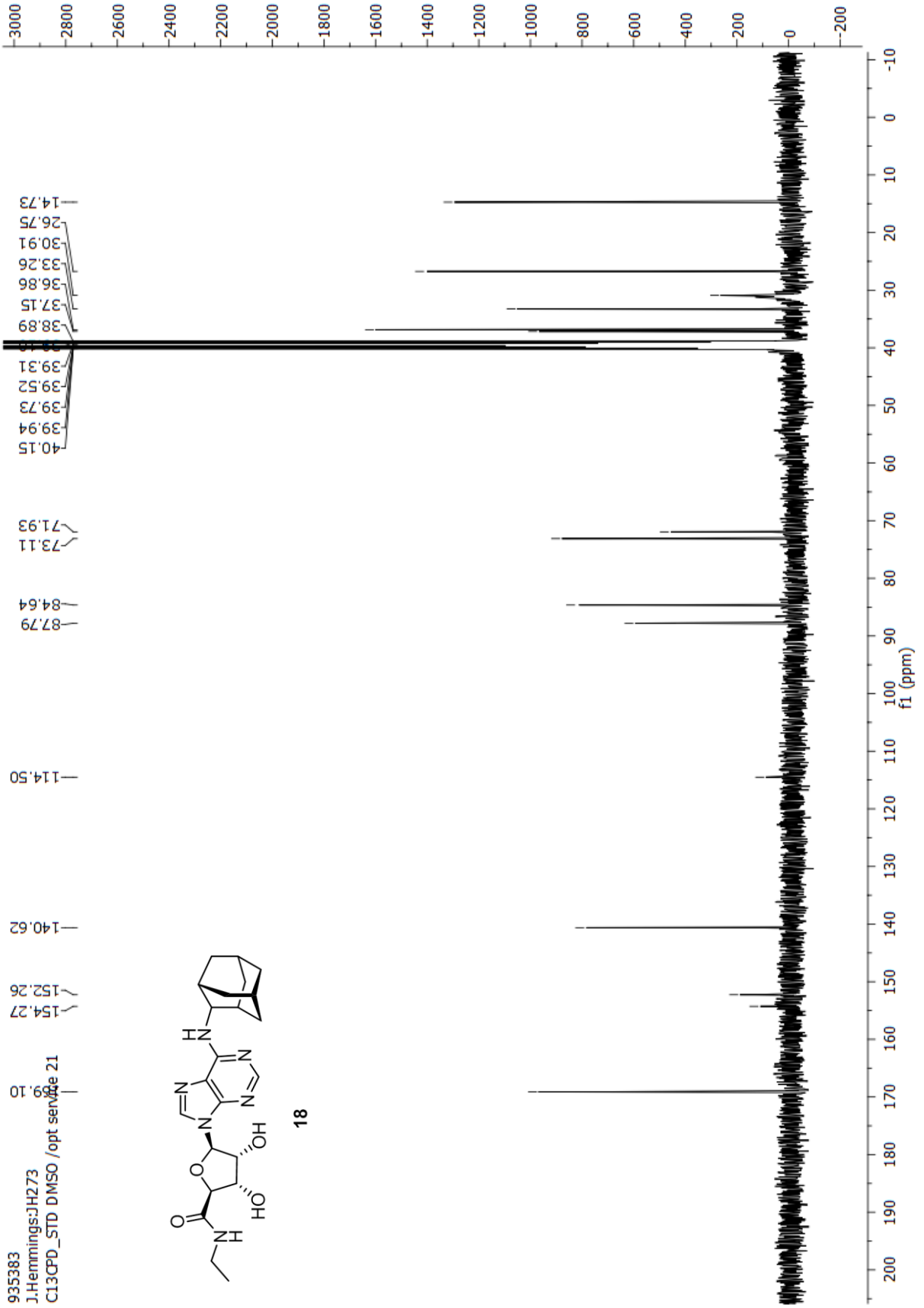

GA_125989
jh196
Proton_ns32 DMSO /disk0 service 116
16
f1 (ppm)

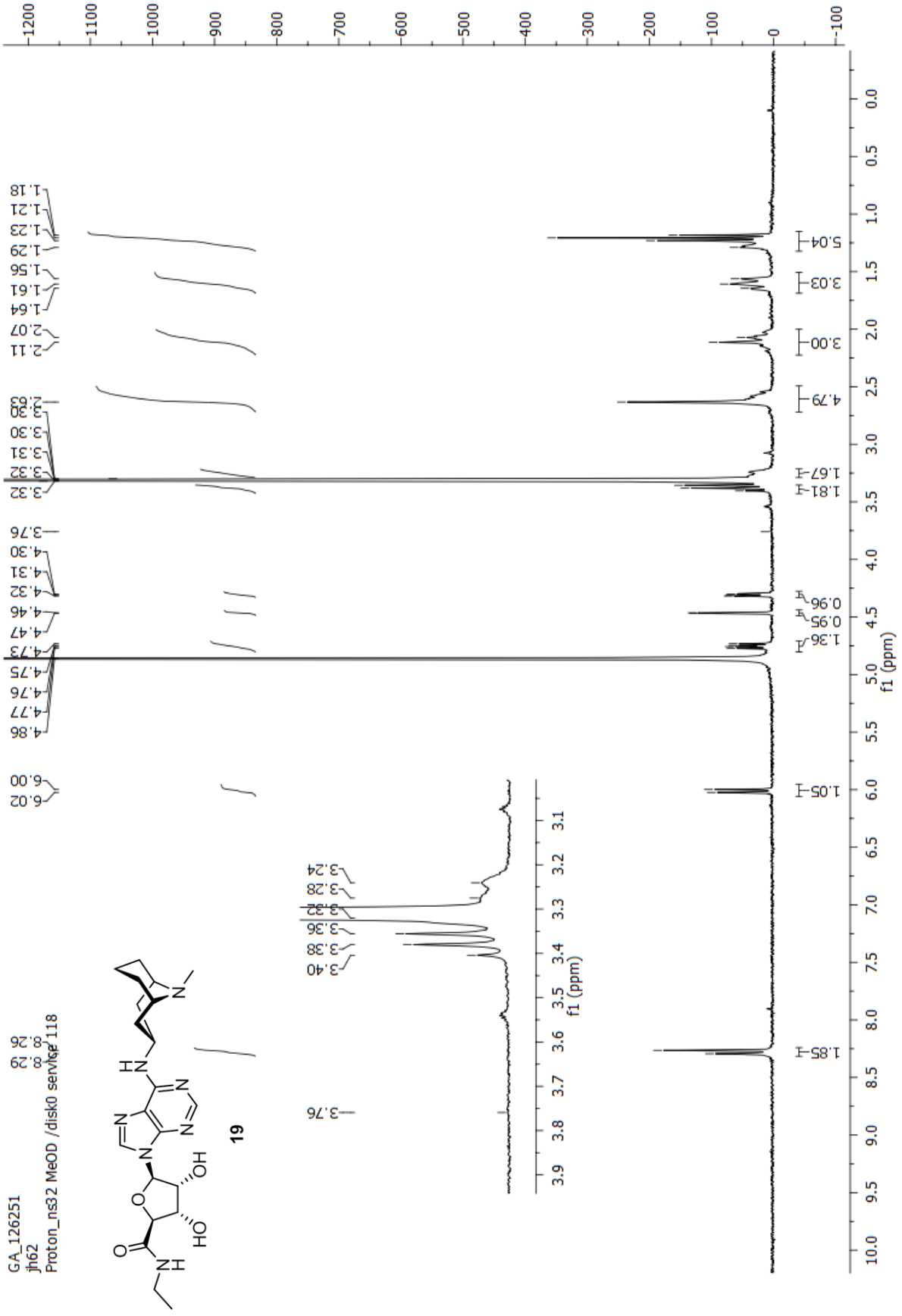

035357
J.Hemmings: JH196
C13CPD_STD DMSO /opt/topspin4.0.8/exp/stan/nmr/lists/pp/user service 5Z
14.74
28.98
38.89
39.10
39.31
39.52
39.73
39.94
40.15
40.98
52.24
71.91
73.11
84.67
87.85
120.35
140.38
147.97
151.63
154.58
189.10
16
f1 (ppm)

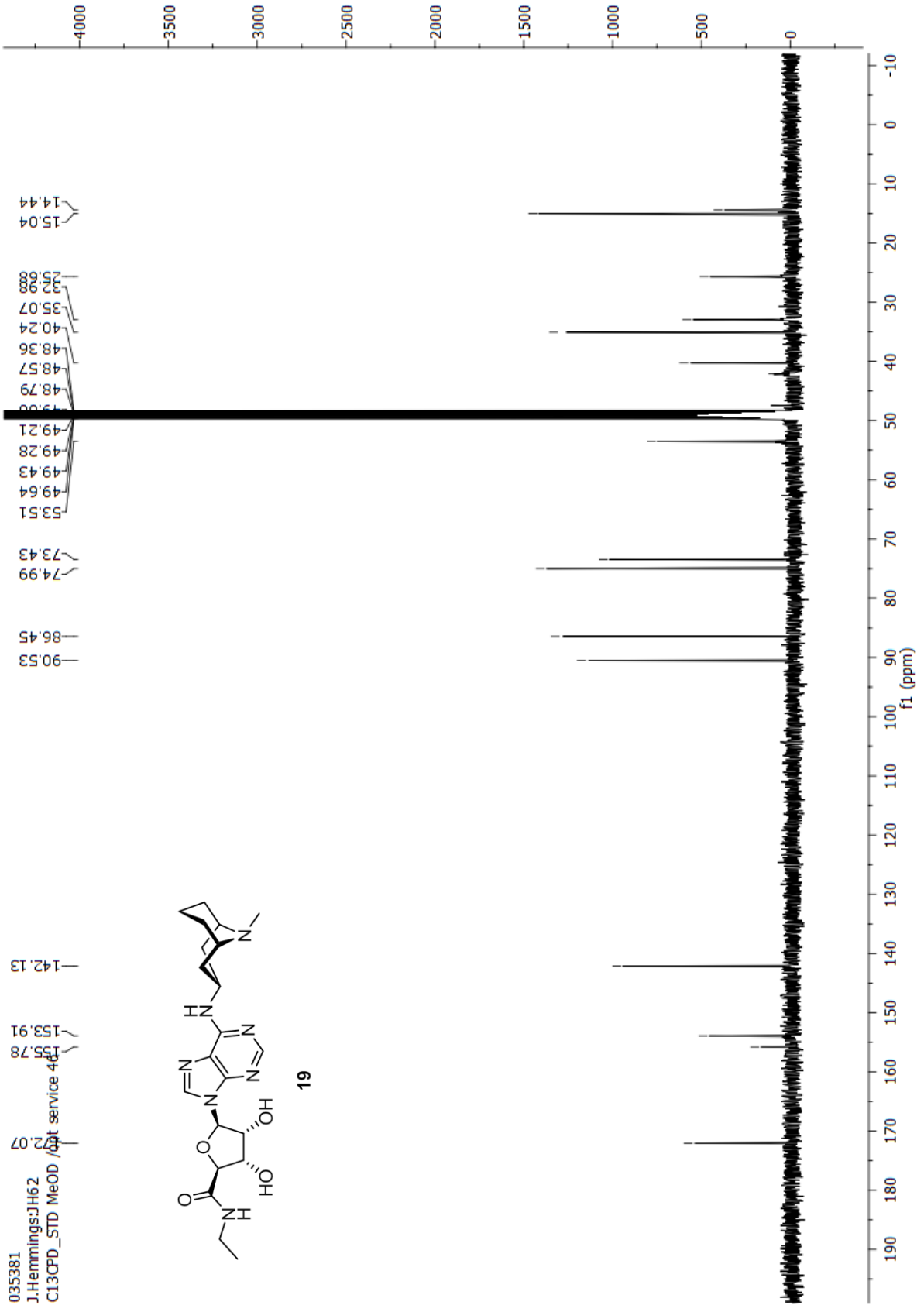

GA_122495
jh-dmso
Proton_ns32 DMSO /disk0\service 42
f1 (ppm)
17


035377
Hemmings:JH209
C13CPD_STD DMSO Appt service 52
14.74
30.13
33.25
34.85
38.89
39.10
39.52
39.73
39.94
40.15
44.20
48.84
54.73
67.48
71.93
73.11
84.66
87.84
120.34
140.40
148.02
151.62
154.53
159.09
HO
HO
OH
N
N
N
N
N
H
O
N
H
17
4500
4000
3500
3000
2500
2000
1500
1000
500
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
f1 (ppm)


GA_126658
jh273
Proton_ns32 DMSO /disk0 service 10
18
f1 (ppm)


935383
J.Hemmings:JH273
C13CPD_STD DMSO /opt servtime 21
14.73
26.75
30.91
33.26
36.86
37.15
38.89
39.31
39.52
39.73
39.94
40.15
71.93
73.11
84.64
87.79
114.50
140.62
152.26
154.27
169.10
18
f1 (ppm)


GA_126251
jh62
Proton_ns32 MeOD /disk0 servicе/118
19
f1 (ppm)


035381
J.Hemmings:JH62
C13CPD_STD MeOD /opt service 4d
14.44
15.04
25.68
32.98
35.07
40.24
48.36
48.57
48.79
49.00
49.21
49.28
49.43
49.64
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73.43
74.99
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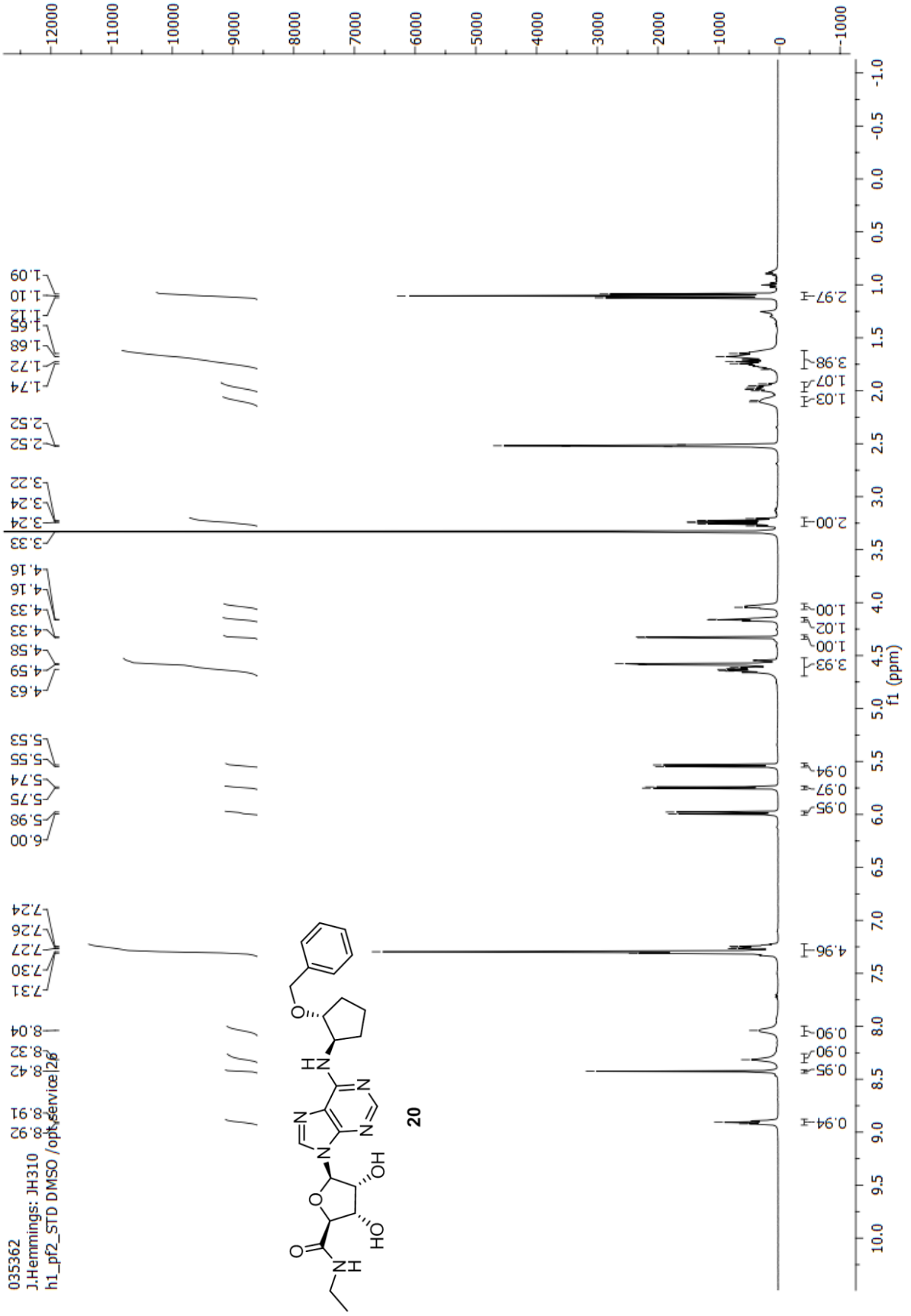
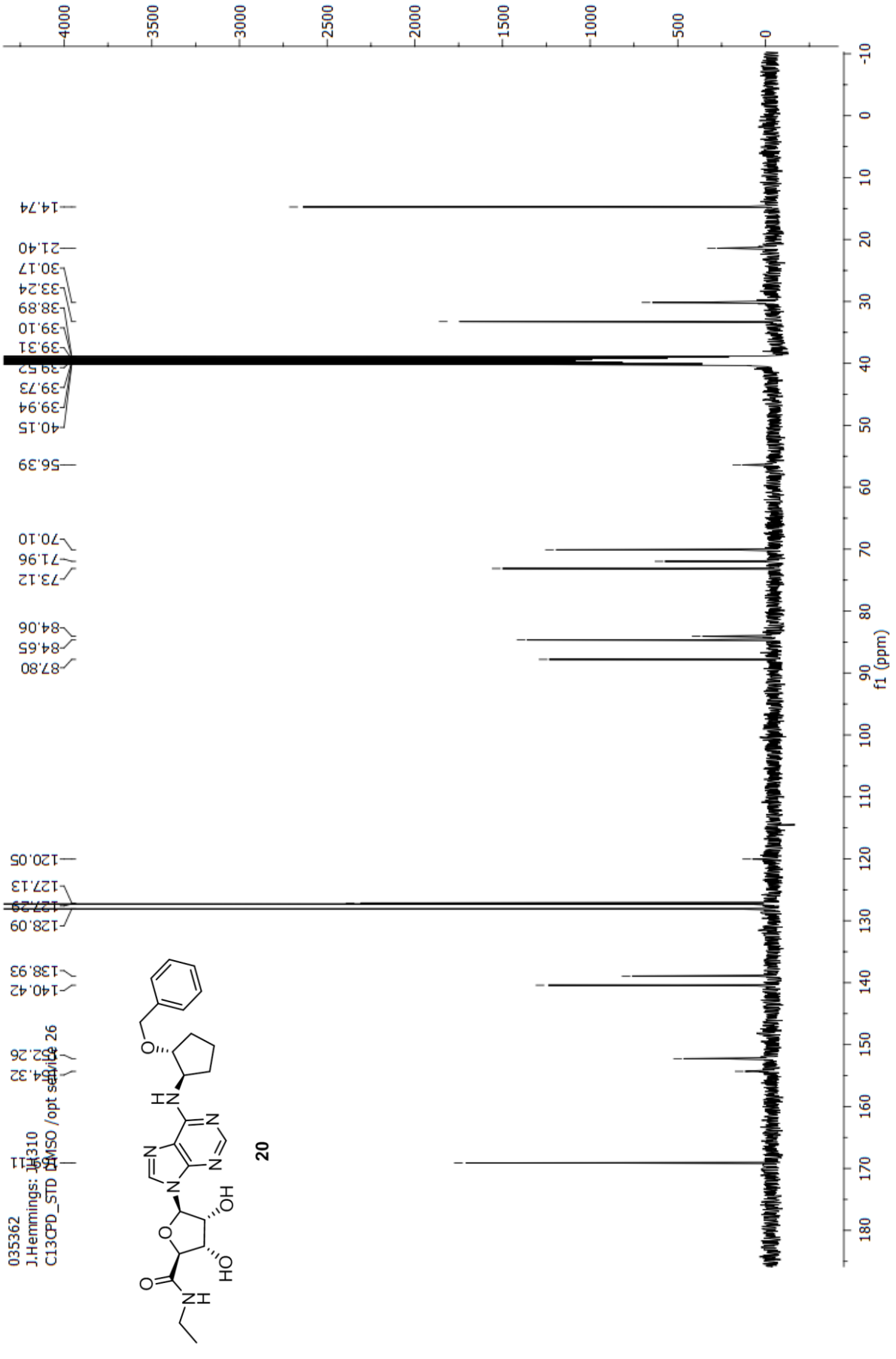
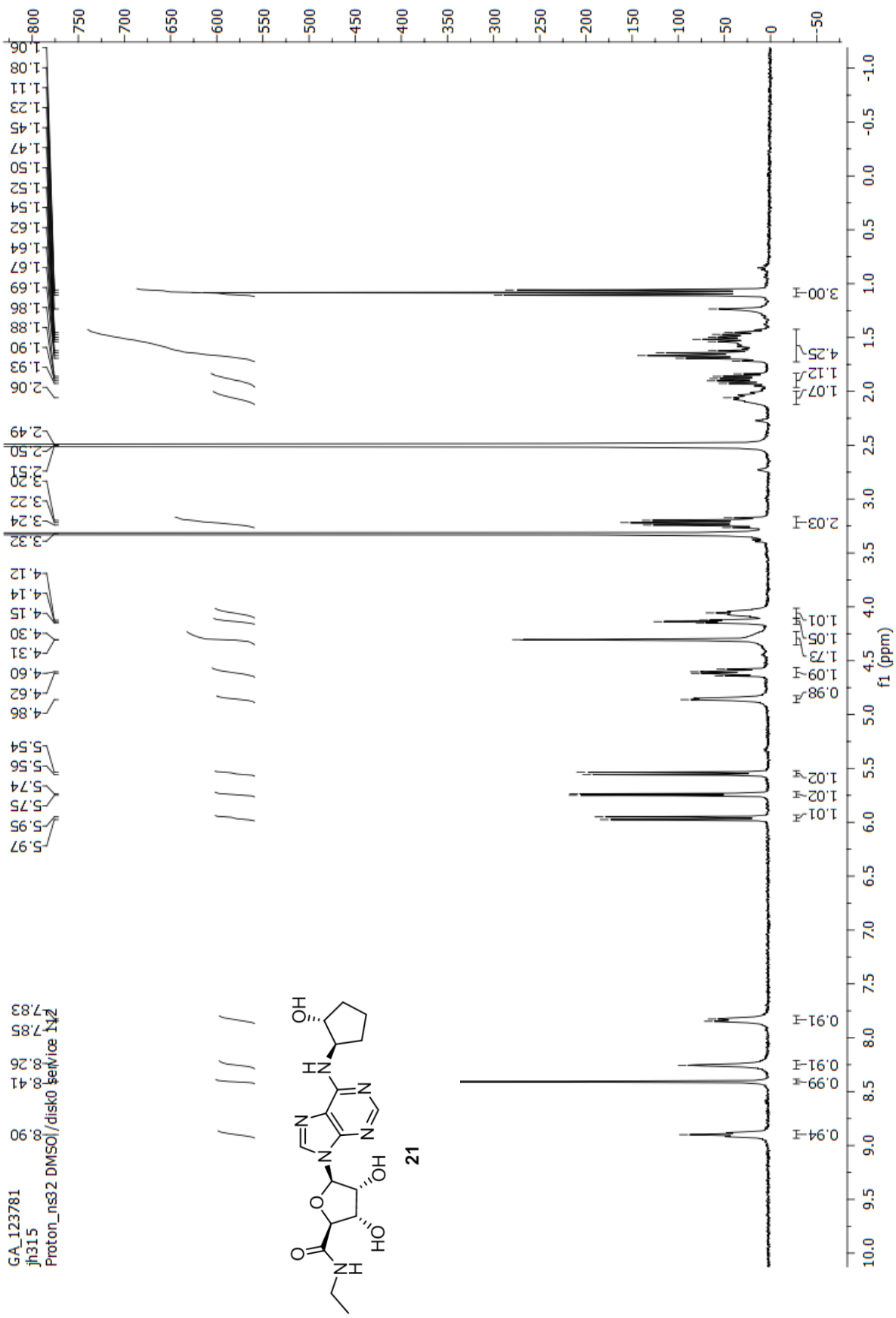
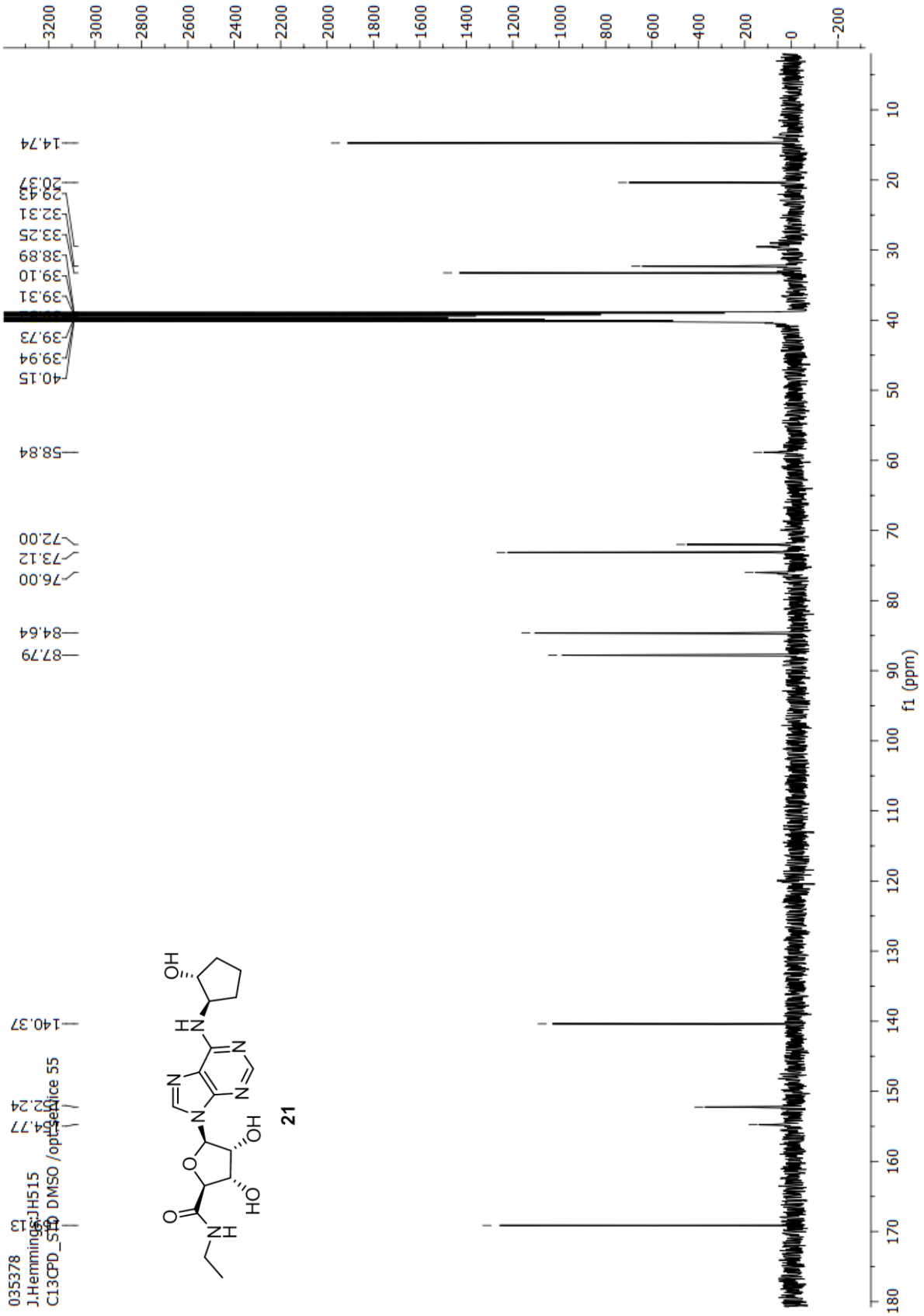
142.13
153.91
155.78
172.07
19
f1 (ppm)

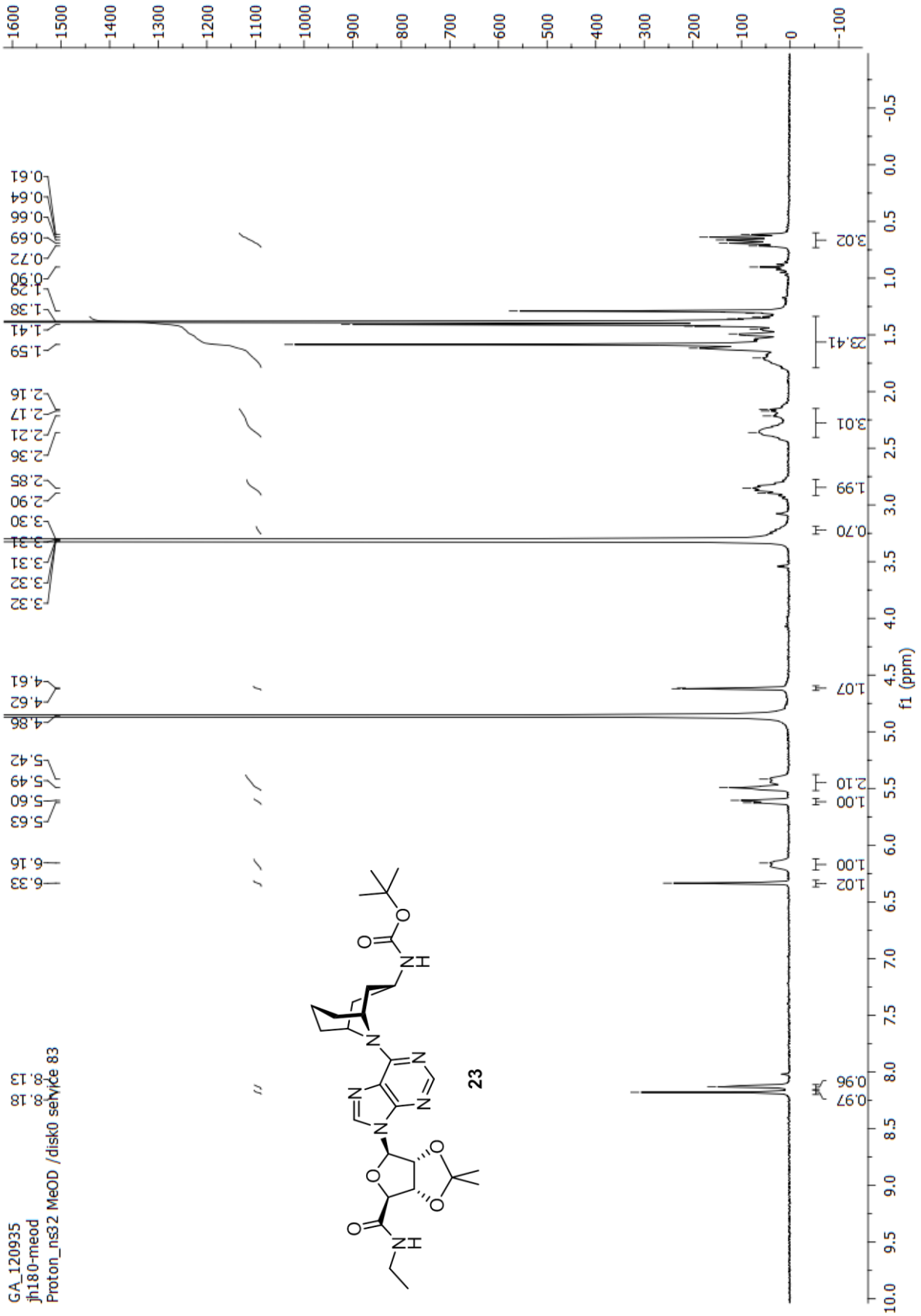

035362
J.Hemmings: JH310
h1_pf2_STD DMSO /opt/service/2
20
f1 (ppm)


035362
J.Hemmings: JH310
C13CPD_STD DMSO /opt sample 26
14.74
21.40
30.17
33.24
38.89
39.10
39.31
39.52
39.73
39.94
40.15
56.39
70.10
71.96
73.12
84.06
84.65
87.80
120.05
127.13
127.29
128.09
138.93
140.42
f1 (ppm)

20

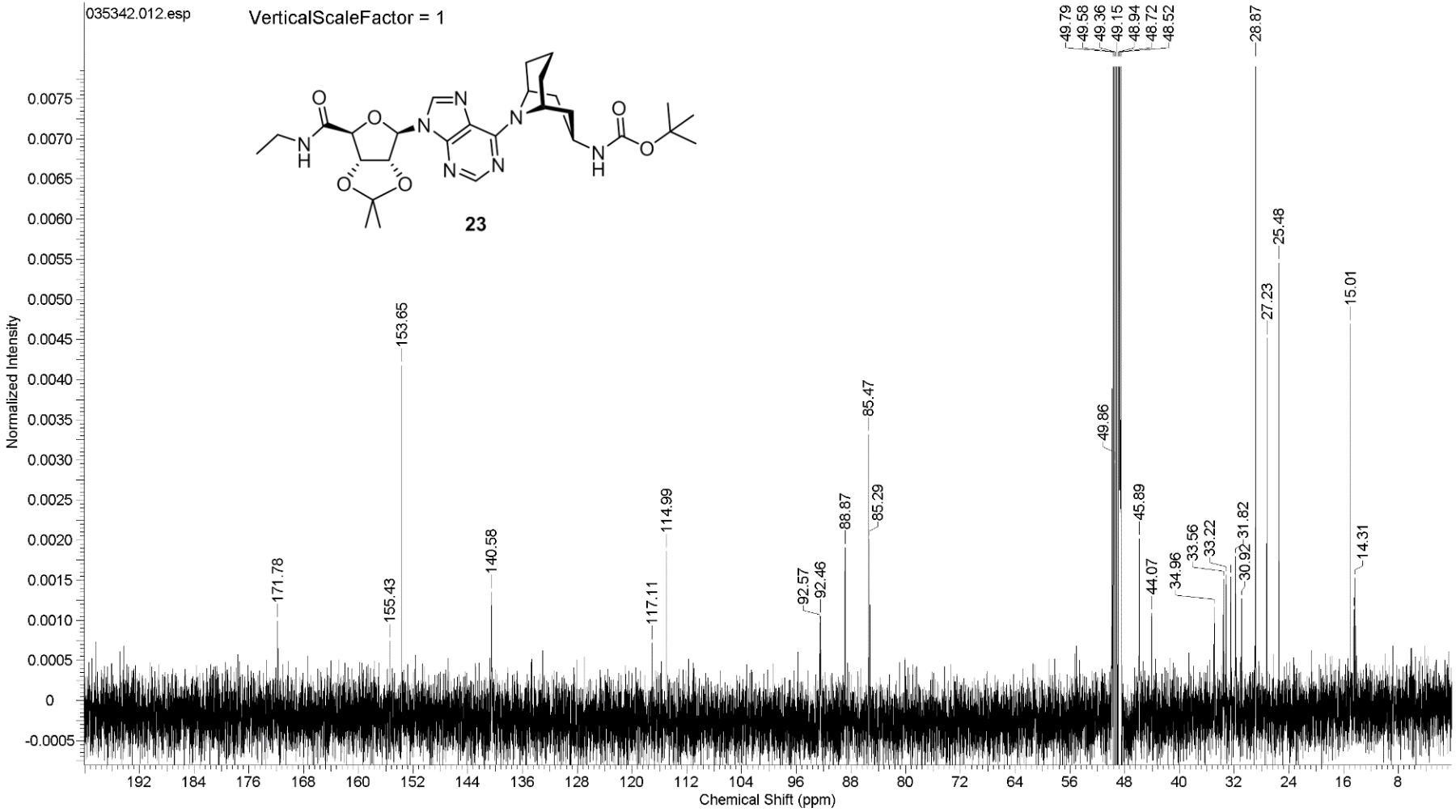

GA_123781
jh315
Proton_ns32 DMSO /disk0 service 1x7
f1 (ppm)
21

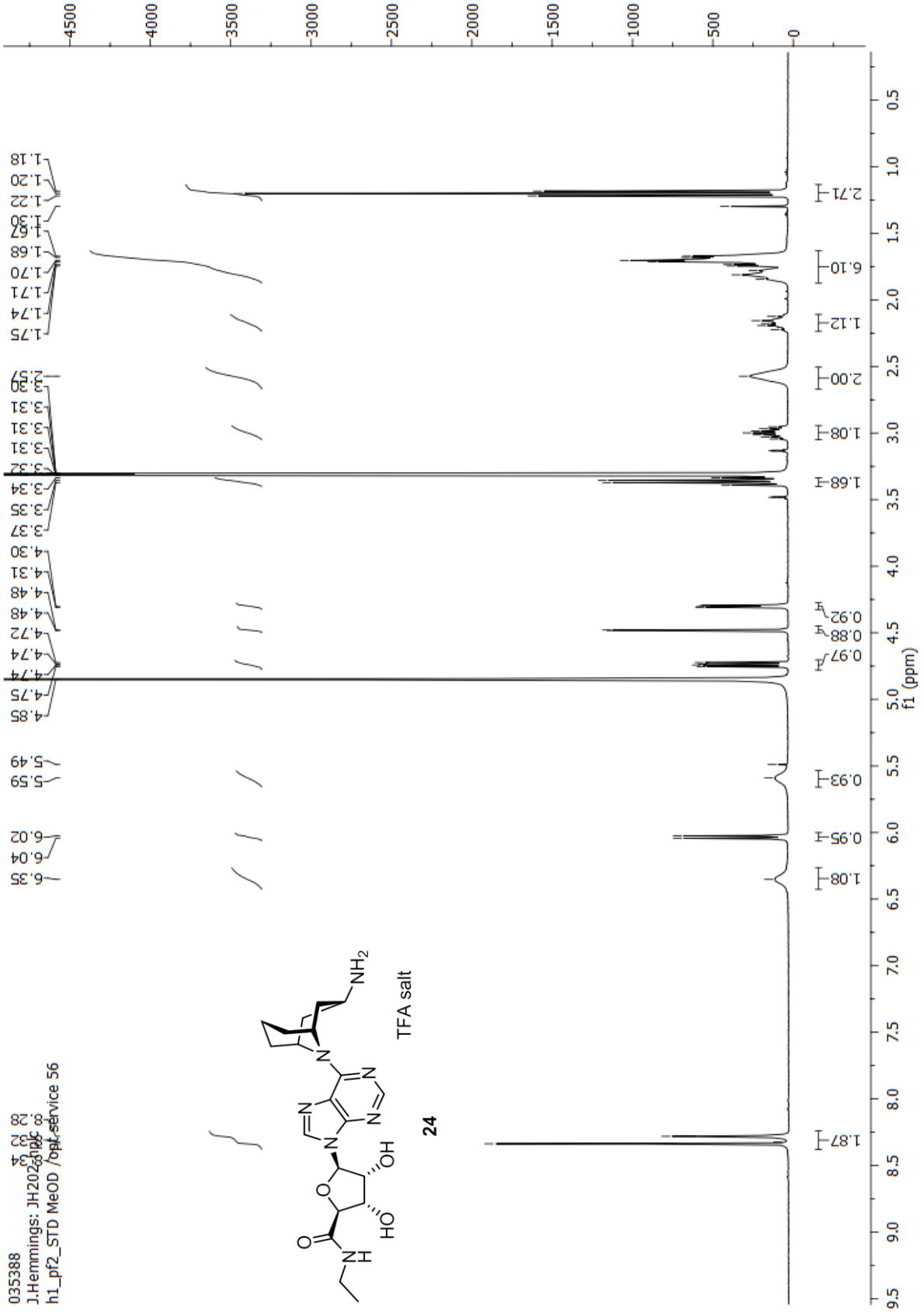

14.74
20.37
29.43
32.31
33.25
38.89
39.10
39.31
39.73
39.94
40.15
58.84
72.00
73.12
76.00
84.64
87.79
140.37
035378
J.Hemmingsen JH515
C13CPD_STD DMSO /opt/Service 55
f1 (ppm)
21

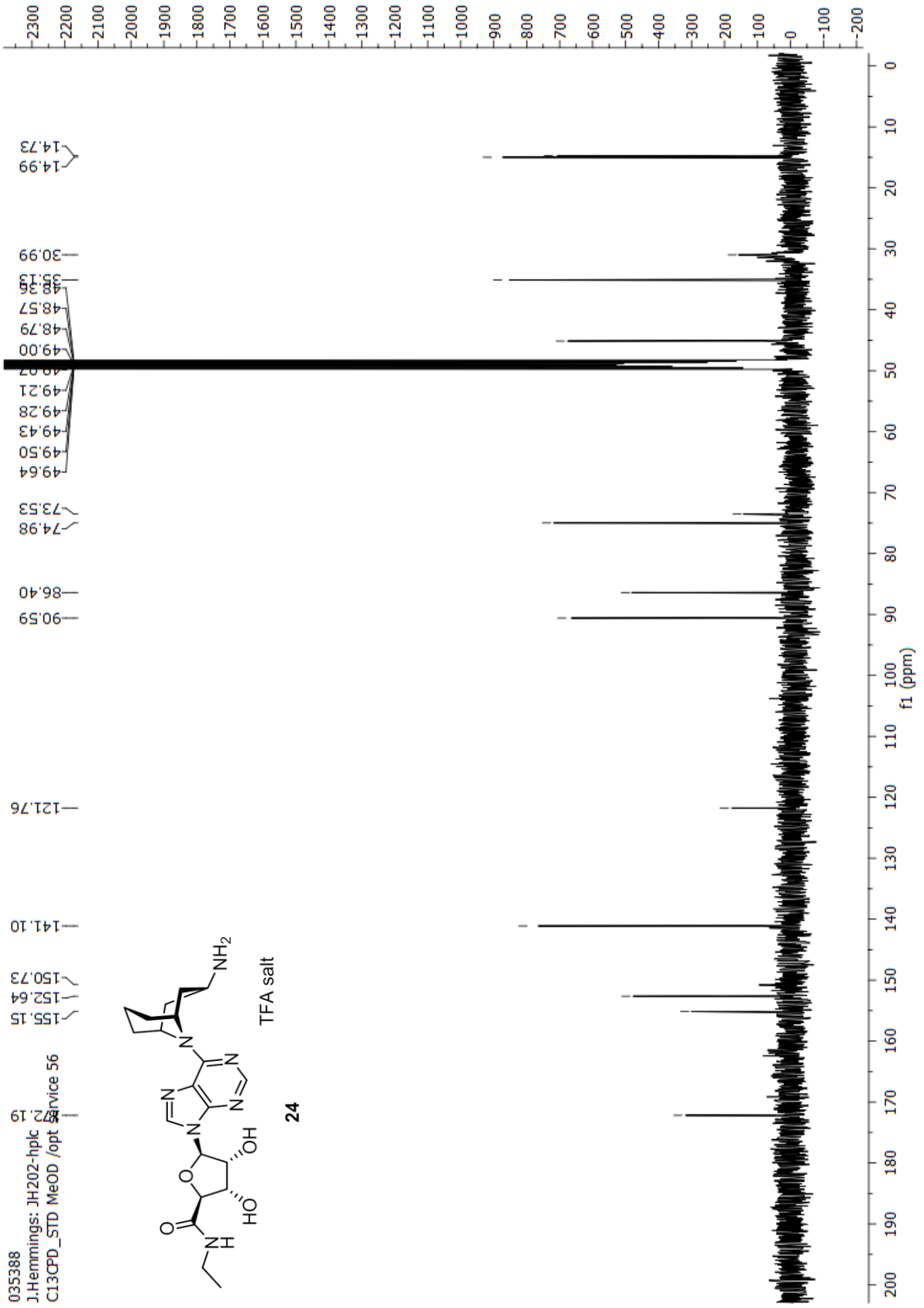

GA_120935
jh180-meod
Proton_ns32 MeOD /disk0 service 83
23
f1 (ppm)

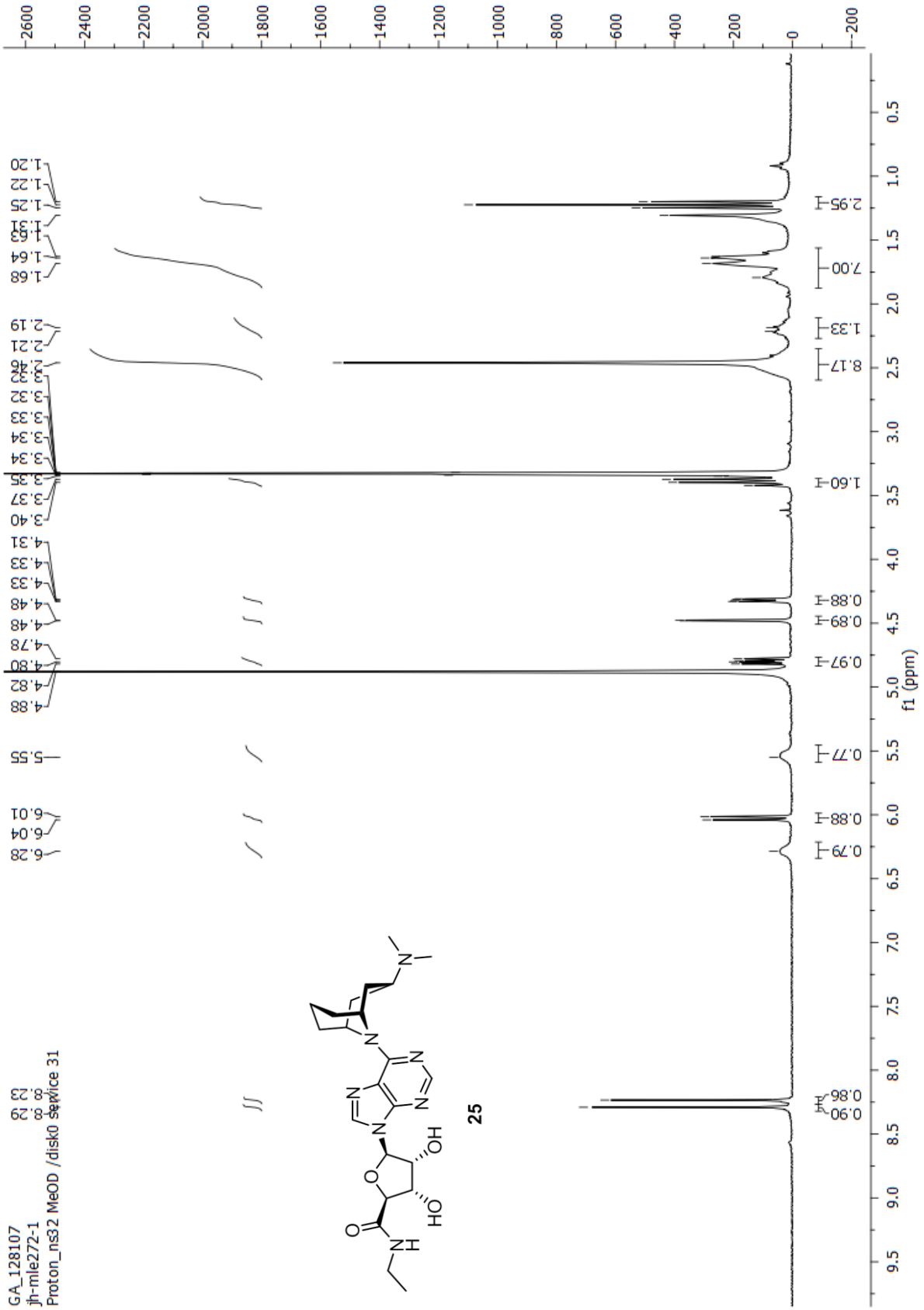
06/07/2015 21:51:43

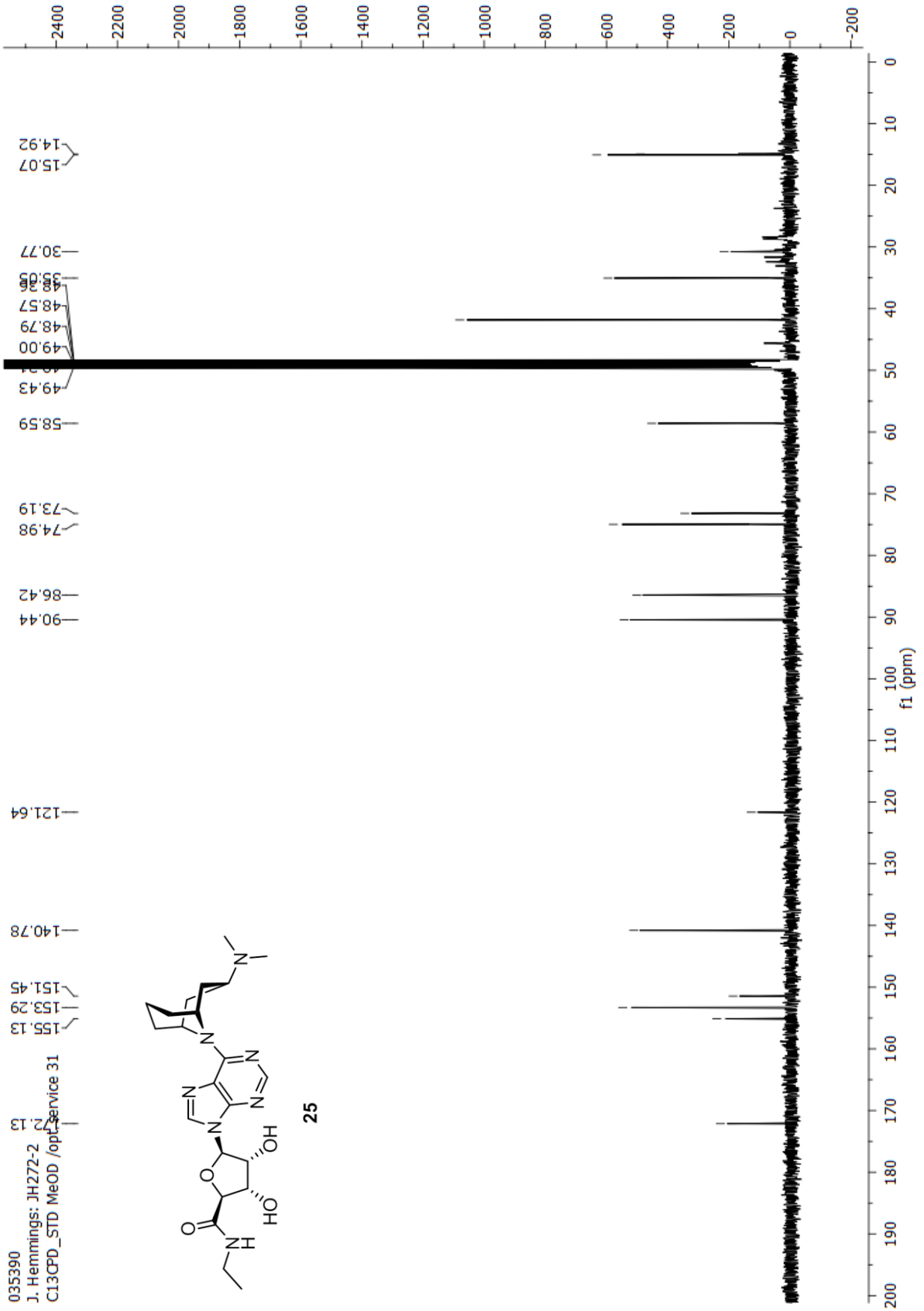
Acquisition Time (sec)	1.2059	***Comment***	J.Hemmings C13CPD_STD MeOD /opt service 40			***Date***	13 Sep 2014 11:14:40
Date Stamp	13 Sep 2014 11:14:40			***File Name***	G:\NMR data files\NMR Backup Jan 2015\NMR\035342\12\fid		
Frequency (MHz)	100.61	***Nucleus***	13C	***Number of Transients***	8192	***Origin***	avII400
Original Points Count	32768	***Owner***	nmr	***Points Count***	32768	***Pulse Sequence***	zgpg
Receiver Gain	203.00	***SW(cyclical) (Hz)***	27173.91	***Solvent***	METHANOL-d4	***Spectrum Offset (Hz)***	11726.5635
Spectrum Type	STANDARD	***Sweep Width (Hz)***	27173.08	***Temperature (degree C)***	26.660		

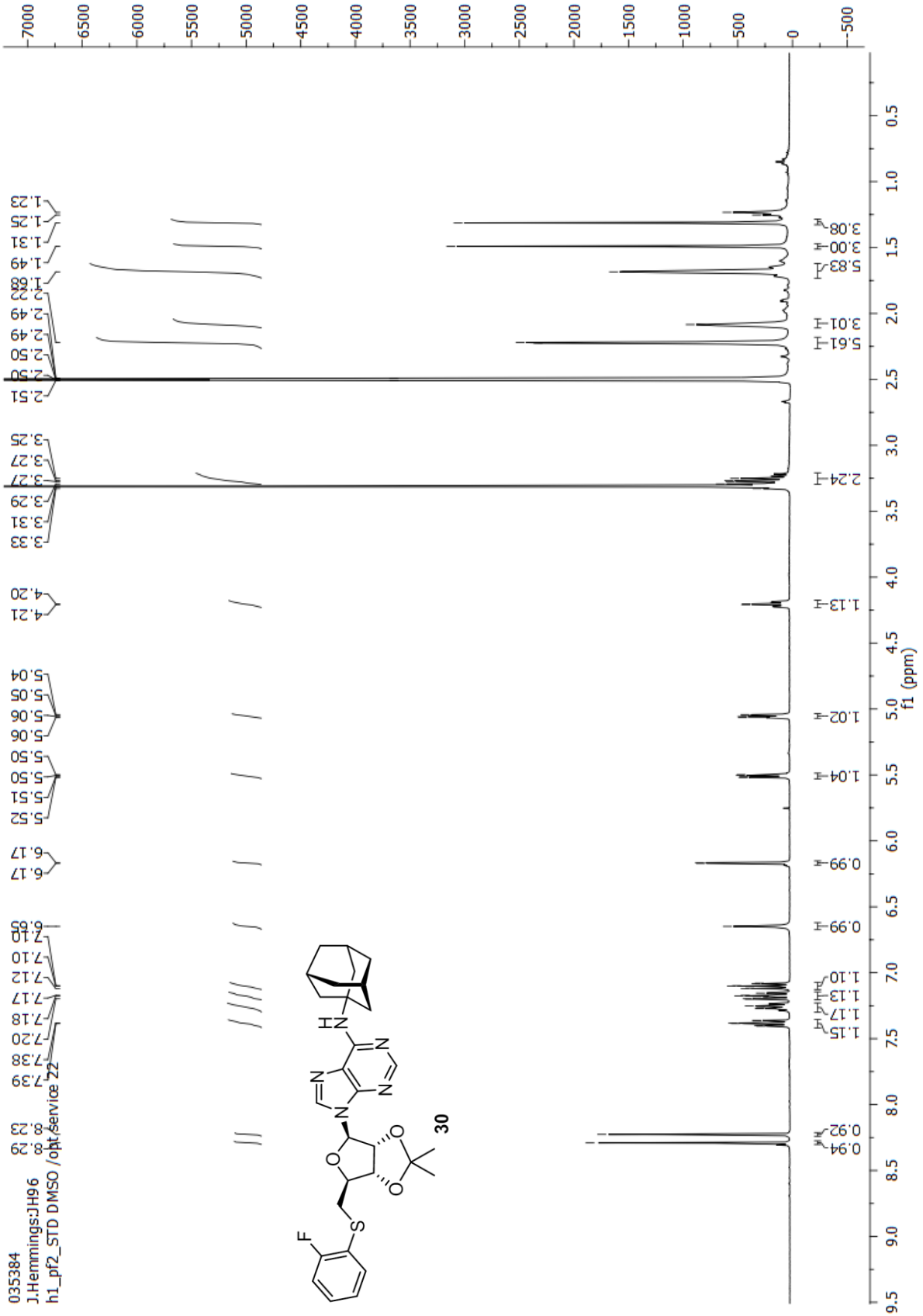


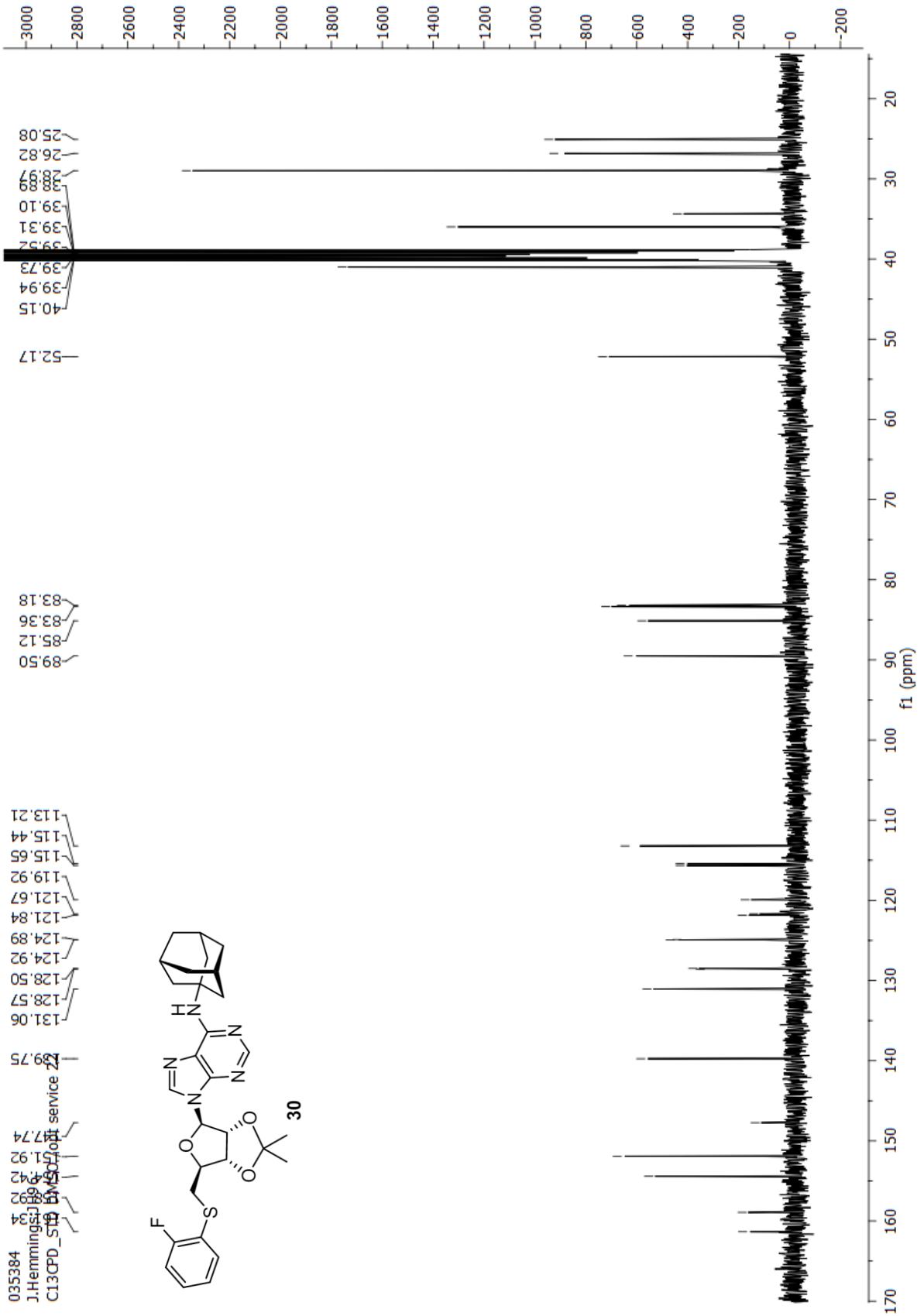

035388
J.Hemmings: JH202208
h1_pf2_STD MeOD /opt/service 56
TFA salt
24
f1 (ppm)

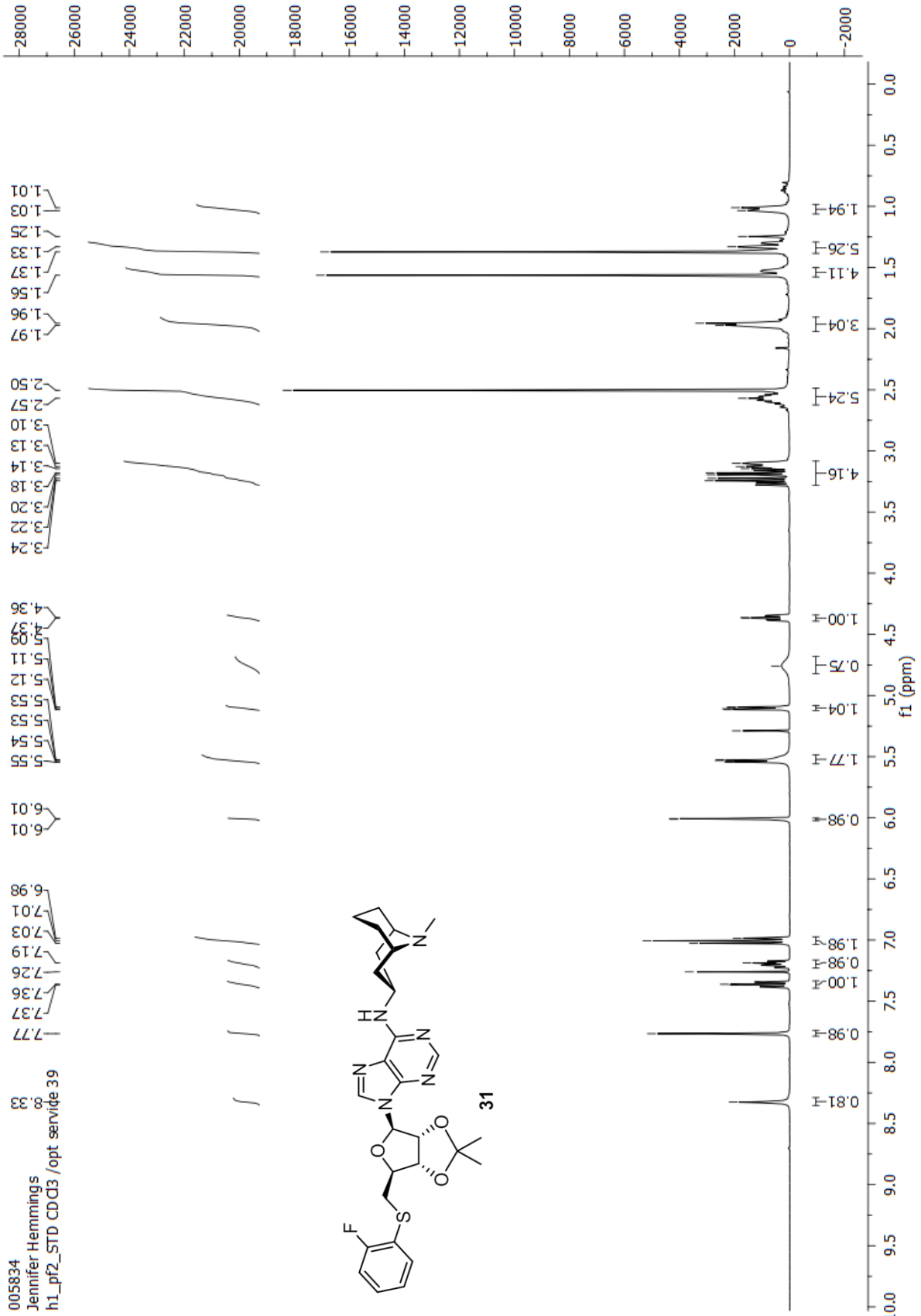

035388
J.Hemmings: JH202-hplc
C13CPD_STD MeOD /opt_Service 56
14.73
14.99
30.99
35.13
48.36
48.57
48.79
49.00
49.07
49.21
49.28
49.43
49.50
49.64
73.53
74.98
86.40
90.59
121.76
141.10
150.73
152.64
155.15
172.19
TFA salt
24
f1 (ppm)

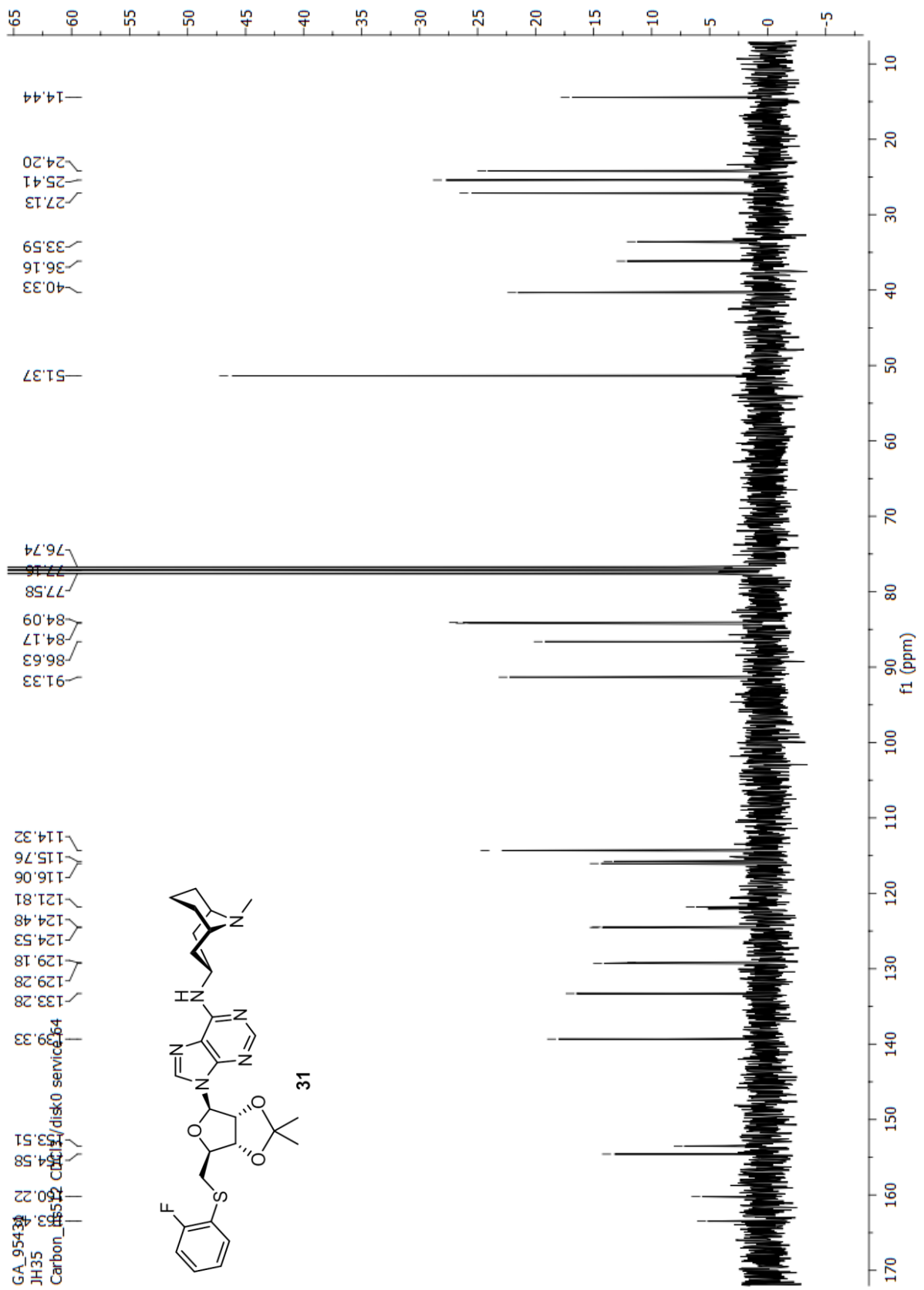

GA_128107
jh-mle272-1
Proton_ns32 MeOD /disk0 service 31
25

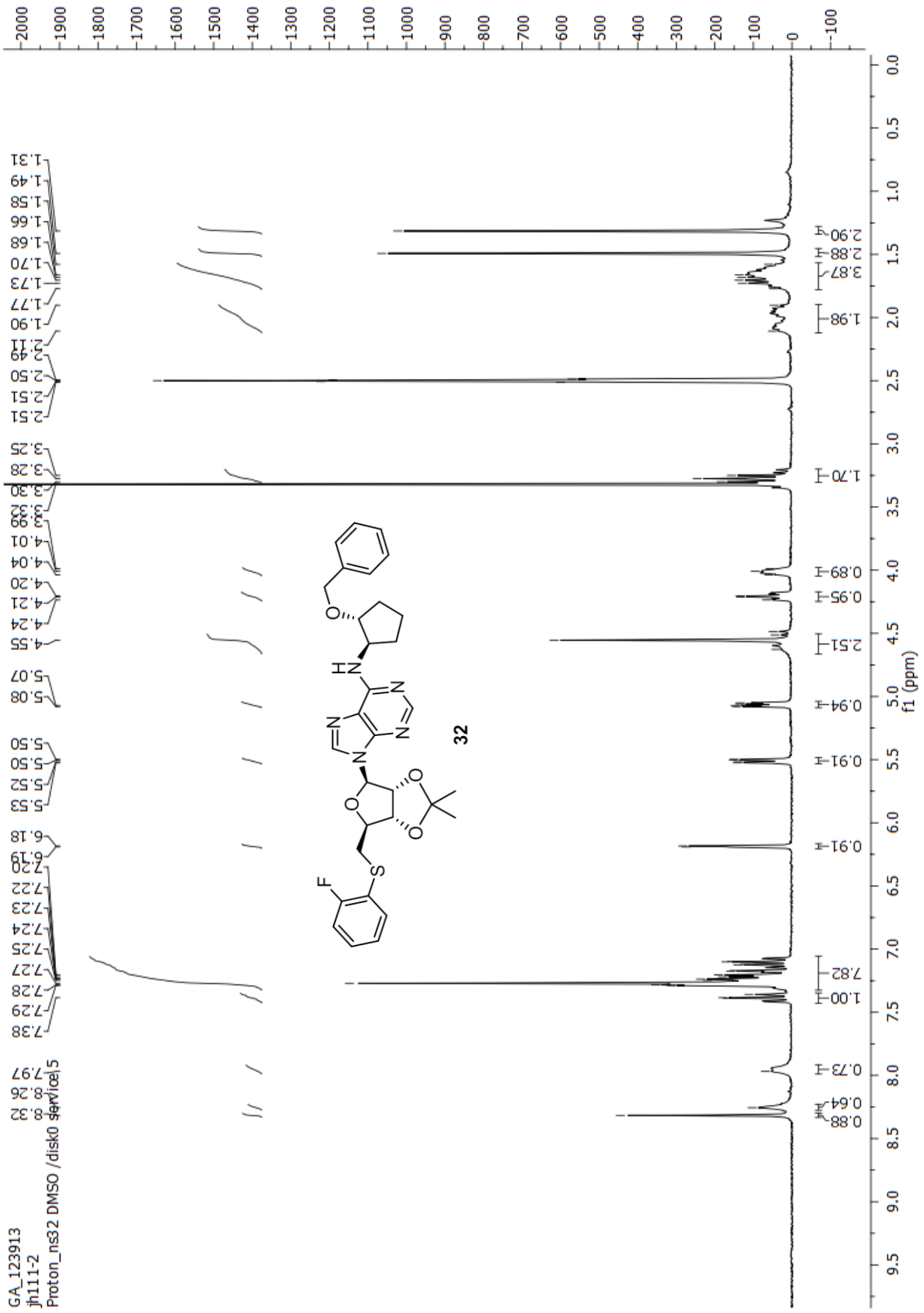

035390
J. Hemmings: JH272-2
C13CPD_STD MeOD /opt/service 31
14.92
15.07
30.77
35.05
48.36
48.57
48.79
49.00
49.31
49.43
58.59
73.19
74.98
86.42
90.44
121.64
140.78
151.45
153.29
155.13
172.13
f1 (ppm)
25

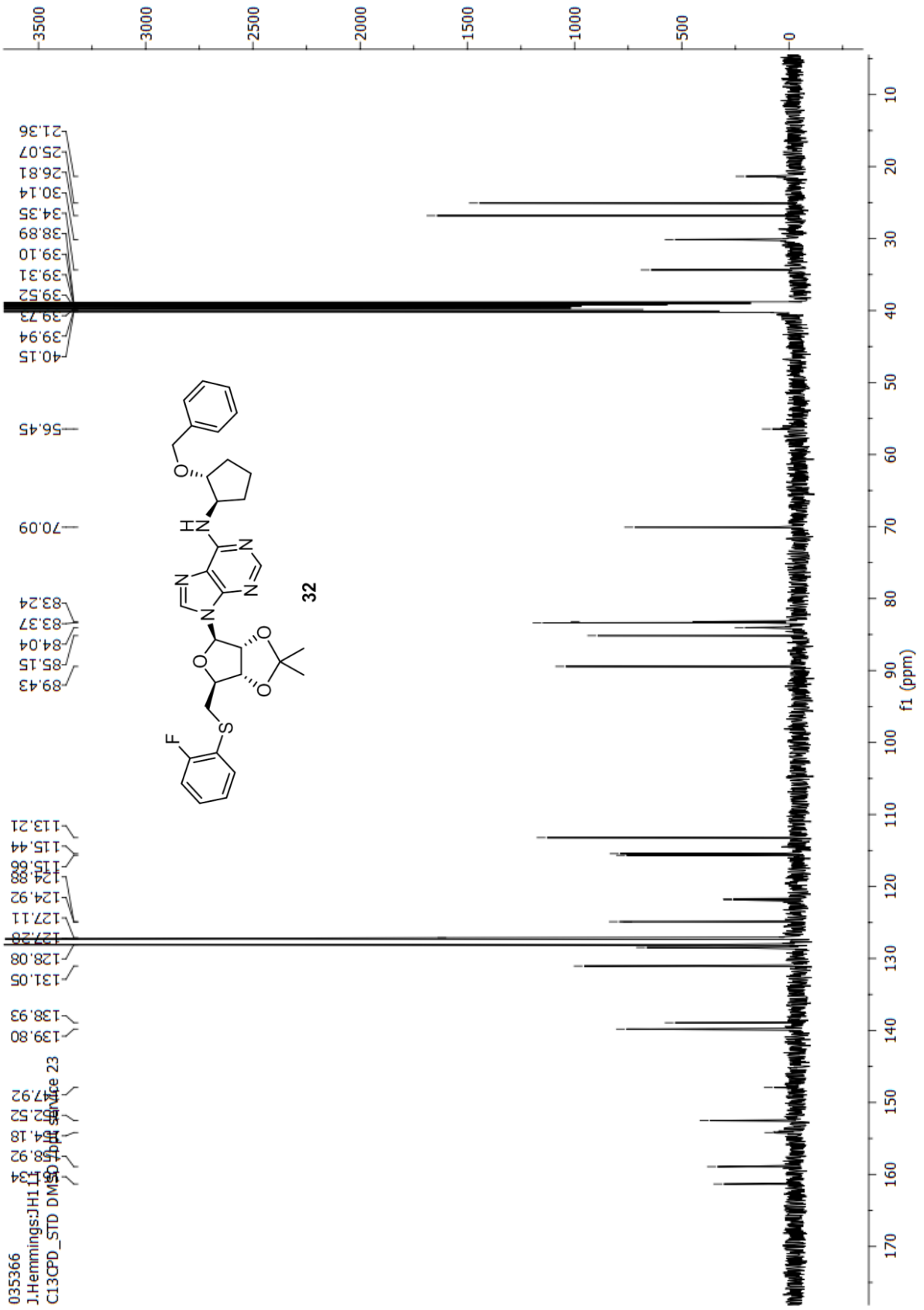

035384
J.Hemmings:JH96
h1_pf2_STD DMSO /opt/service 22
30
f1 (ppm)


035384
J.Hemmingsen
C13CPD_STD
f1 (ppm)
30


005834
Jennifer Hemmings
h1_pf2_STD CDCl3 /opt servide 39
31
f1 (ppm)


GA_95438
JH35
Carbon_18512 CDCl3 /disk0 service164
14.44
24.20
25.41
27.13
33.59
36.16
40.33
51.37
76.74
77.16
77.58
84.09
84.17
86.63
91.33
114.32
115.76
116.06
121.81
124.48
124.53
129.18
129.28
133.28
139.33
83.51
84.58
90.22
93.42
F
S
O
O
O
N
N
N
N
N
H
31
f1 (ppm)


GA_123913
jh111-2
Proton_ns32 DMSO /disk0 service 5
32
f1 (ppm)


035366
J.Hemmings:JH111_23
C13CPD_STD DMSO 1D pl sample 23
21.36
25.07
26.81
30.14
34.35
38.89
39.10
39.31
39.52
39.73
39.94
40.15
56.45
70.09
83.24
83.37
84.04
85.15
89.43
113.21
115.44
115.66
124.88
124.92
127.11
127.28
128.08
131.05
138.93
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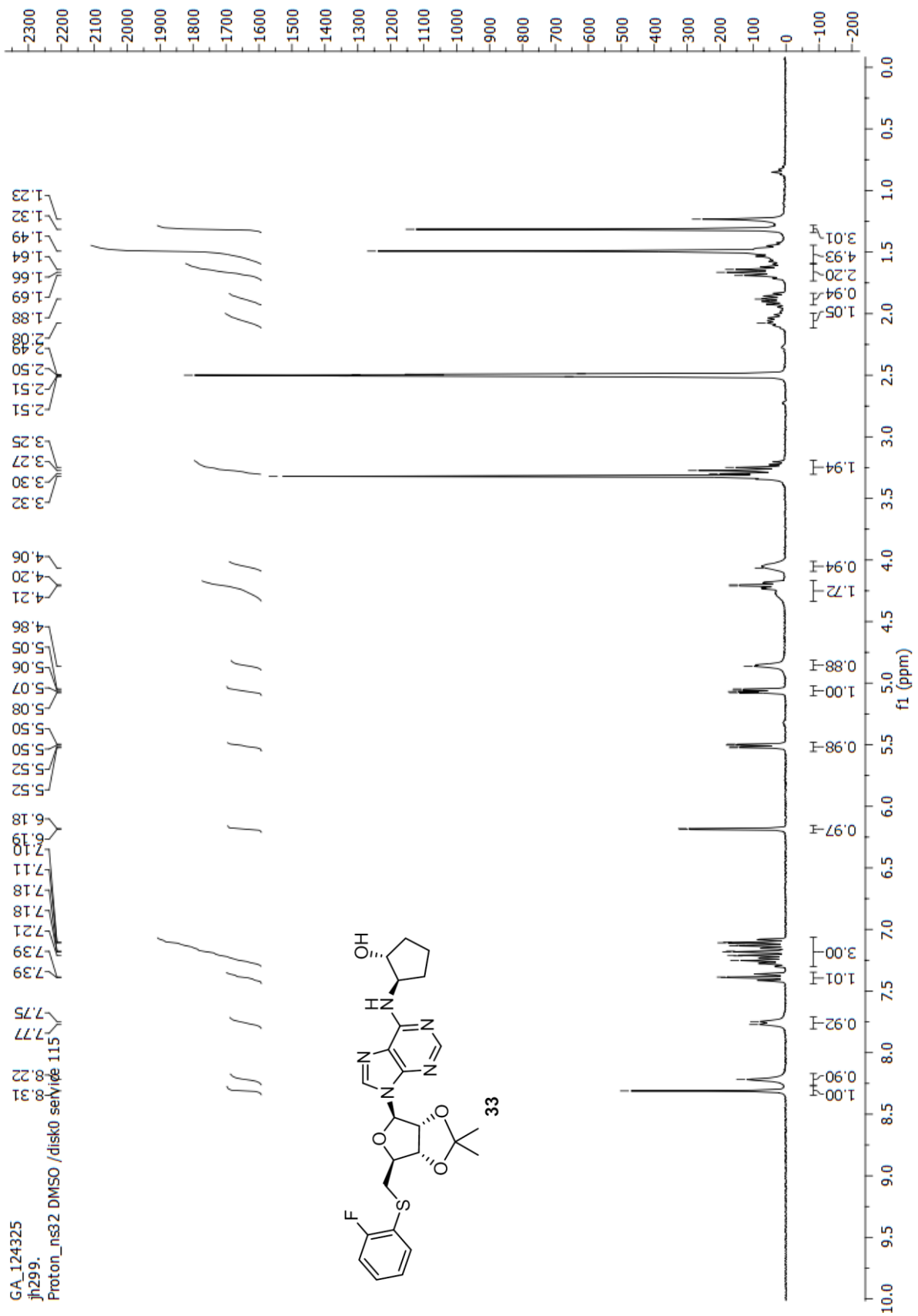
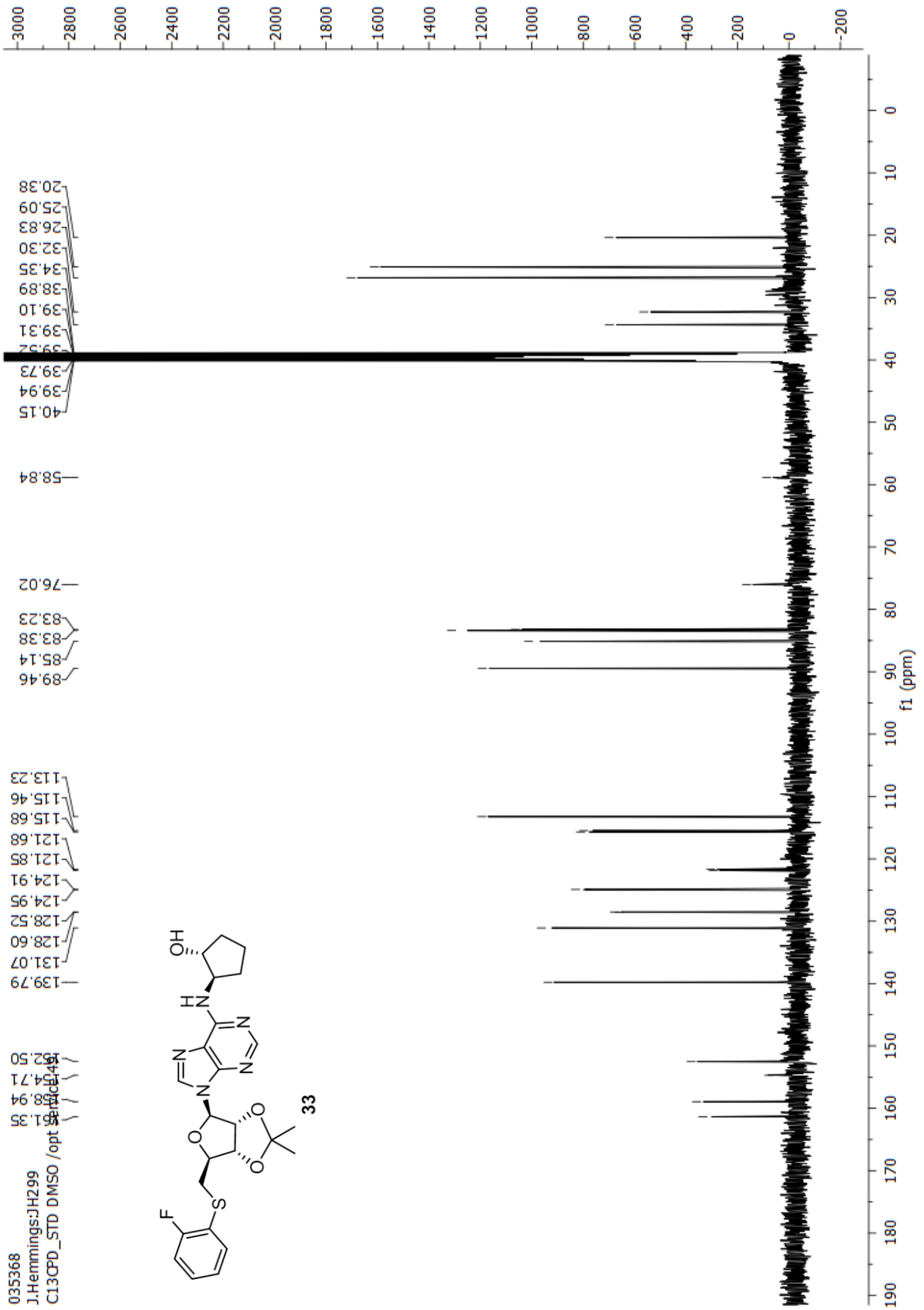
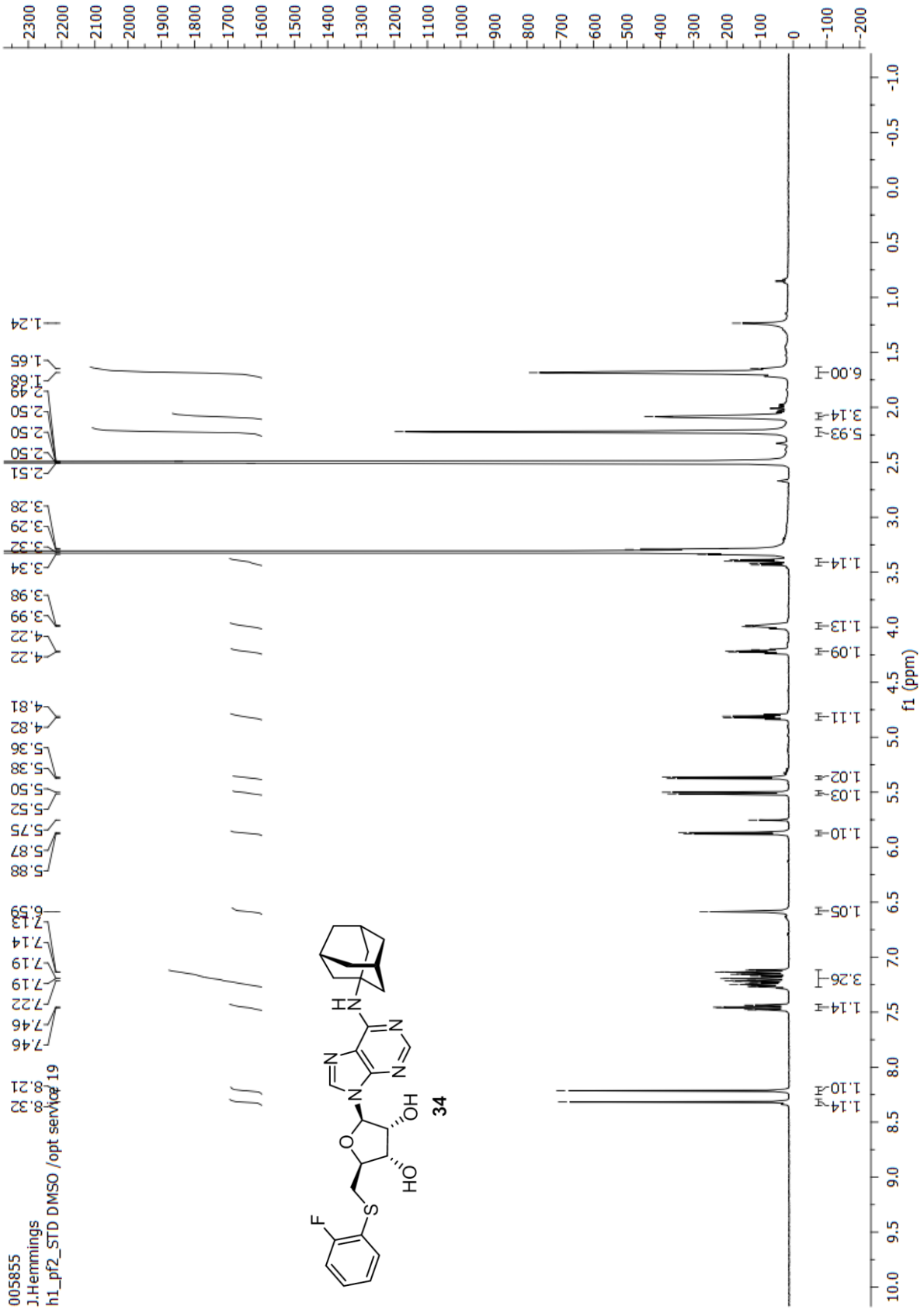
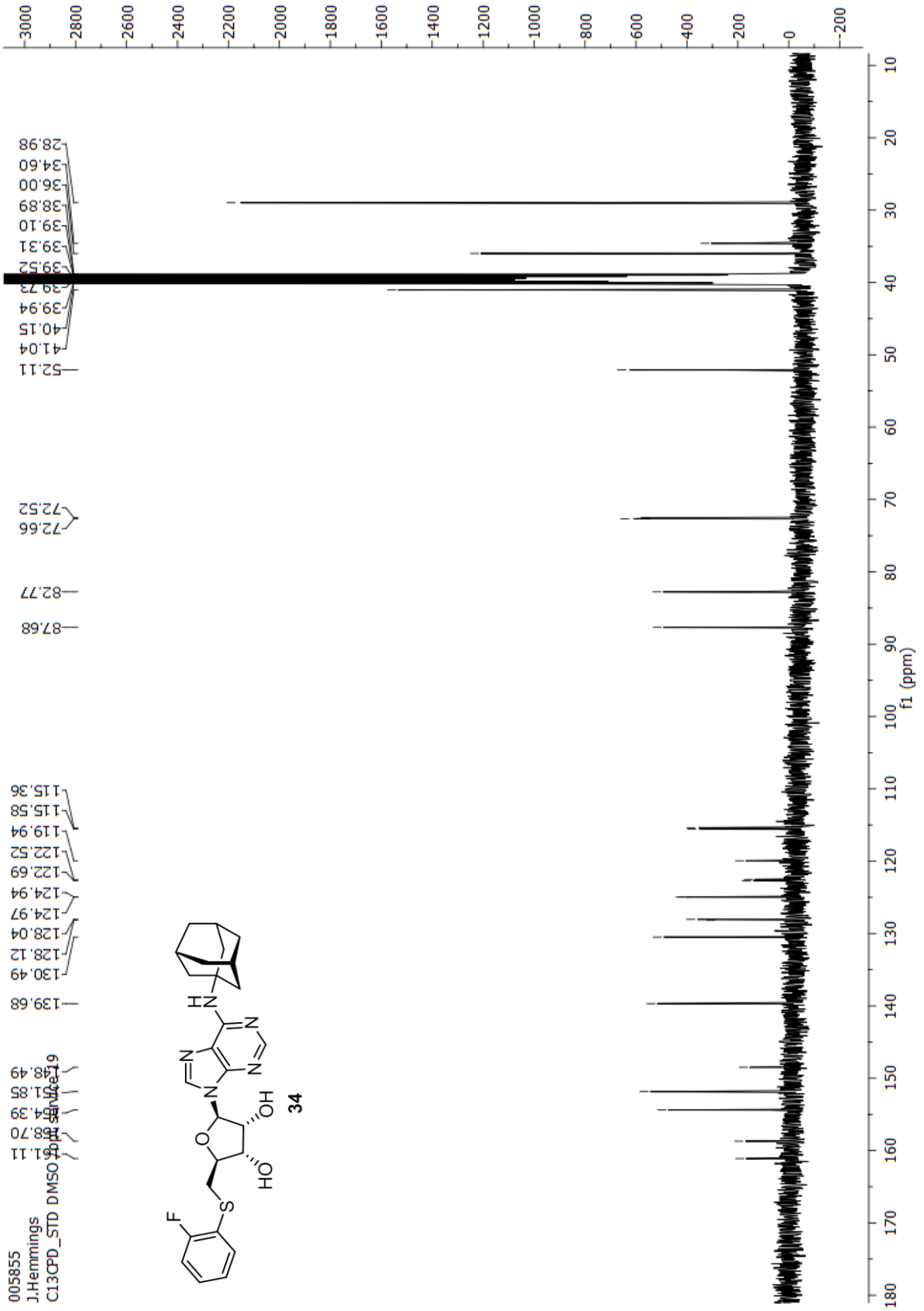
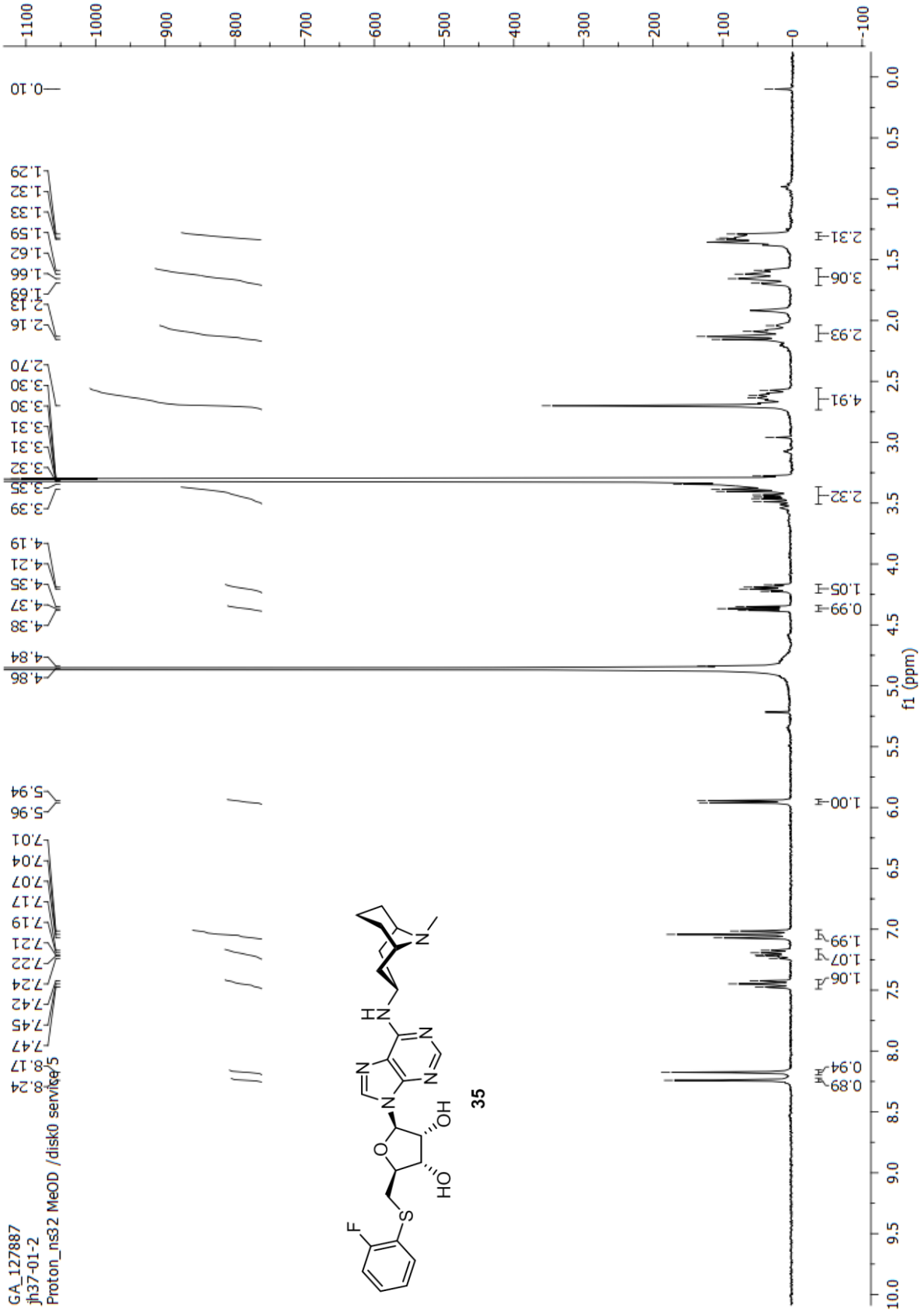
147.92
152.52
154.18
158.92
32
f1 (ppm)

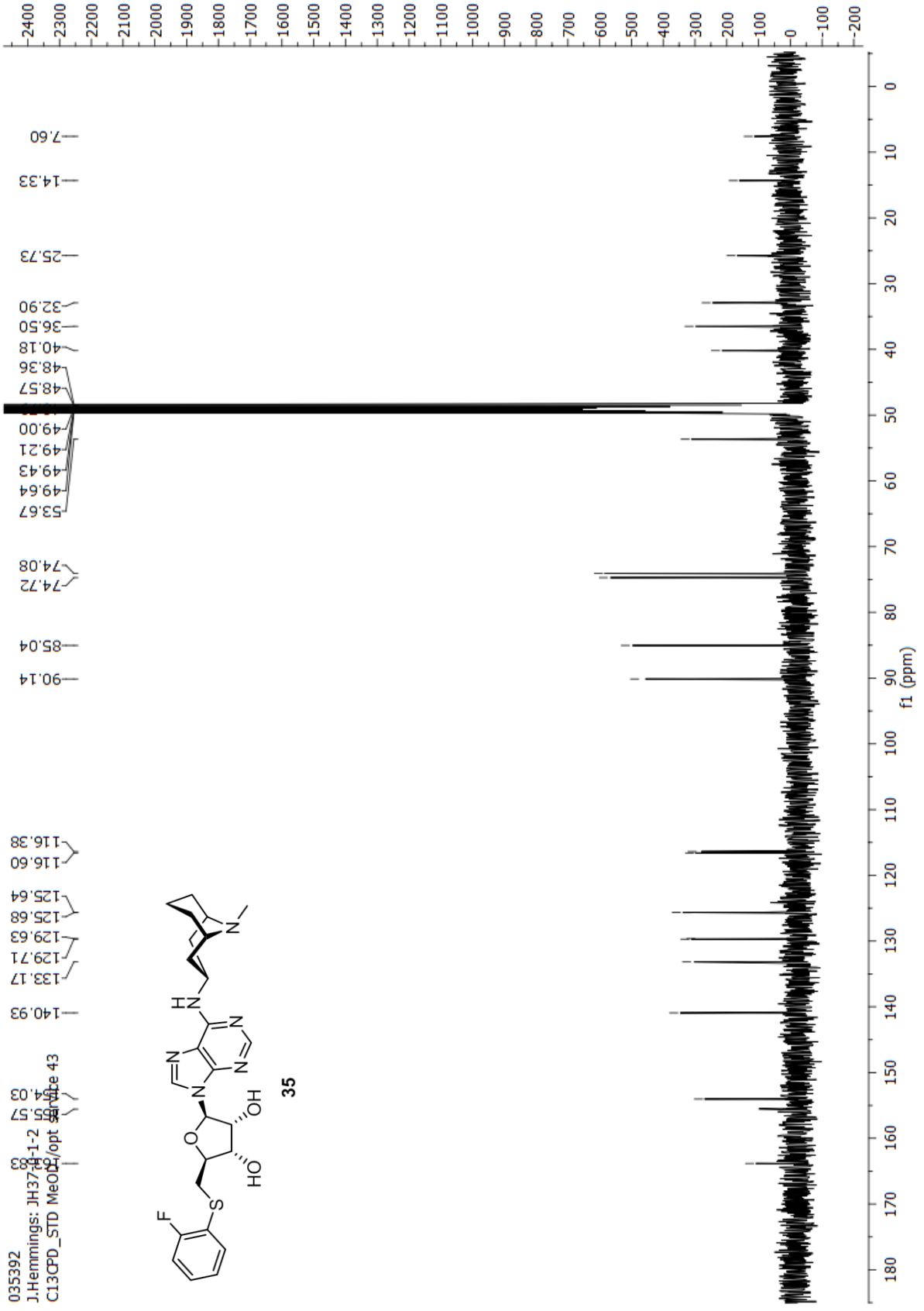

GA_124325
jh299.
Proton_ns32 DMSO /disk0 serVide 115
f1 (ppm)
33

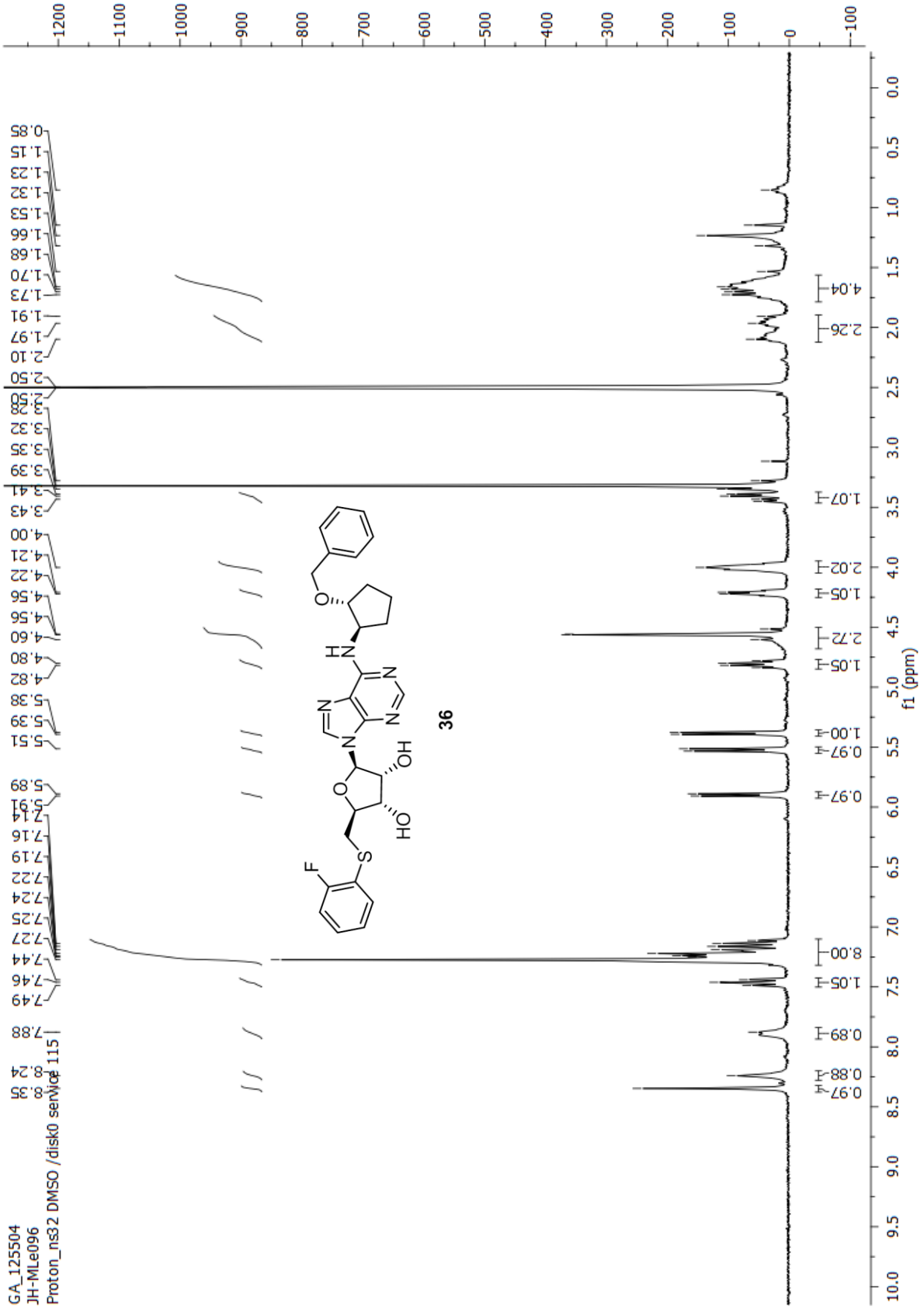

035368
J.Hemmings:JH299
C13CPD_STD DMSO /opt
20.38
25.09
26.83
32.30
34.35
38.89
39.10
39.31
39.52
39.73
39.94
40.15
58.84
76.02
83.23
83.38
85.14
89.46
113.23
115.46
115.68
121.68
121.85
124.91
124.95
128.52
128.60
131.07
139.79
f1 (ppm)
33

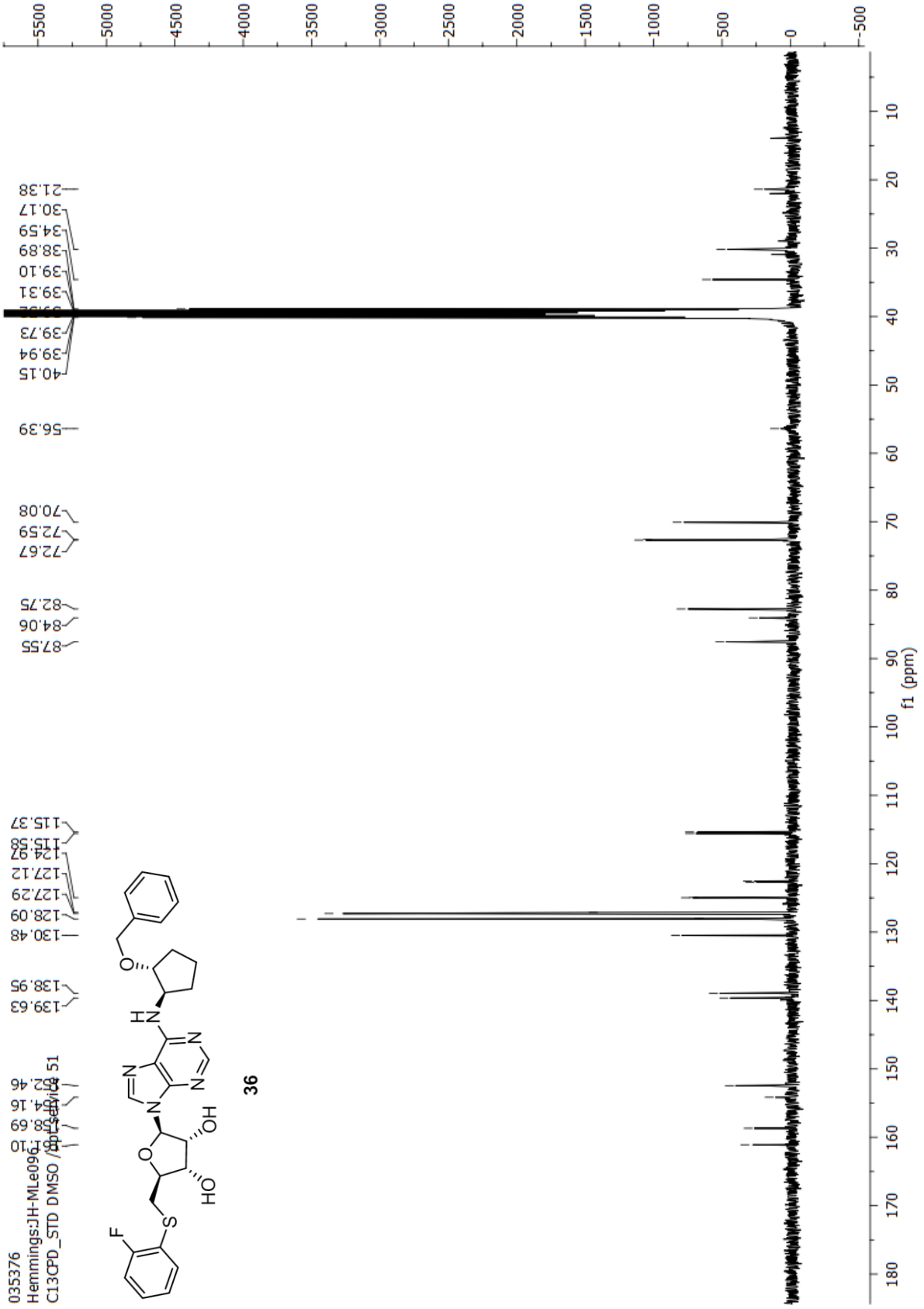

005855
J.Hemmings
h1_pf2_STD DMSO /opt service 19
f1 (ppm)
34

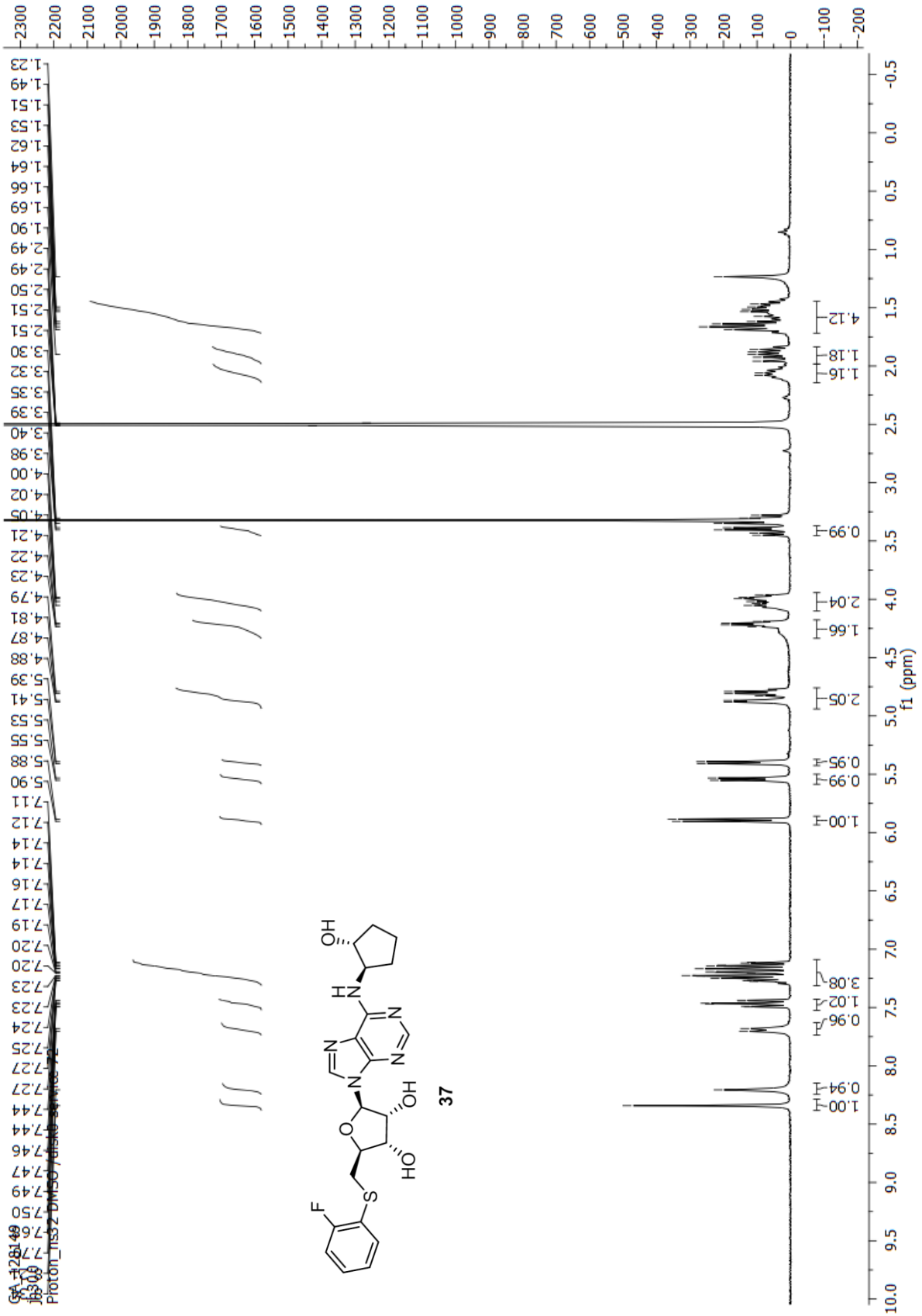

005855
J.Hemmings
C13CPD_STD DMSO 1Dpt sample19
161.11
158.70
154.39
151.85
148.49
139.68
130.49
128.12
128.04
124.97
124.94
122.69
122.52
119.94
115.58
115.36
87.68
82.77
72.66
72.52
52.11
41.04
40.15
39.94
39.73
39.52
39.31
39.10
38.89
36.00
34.60
28.98
34
f1 (ppm)

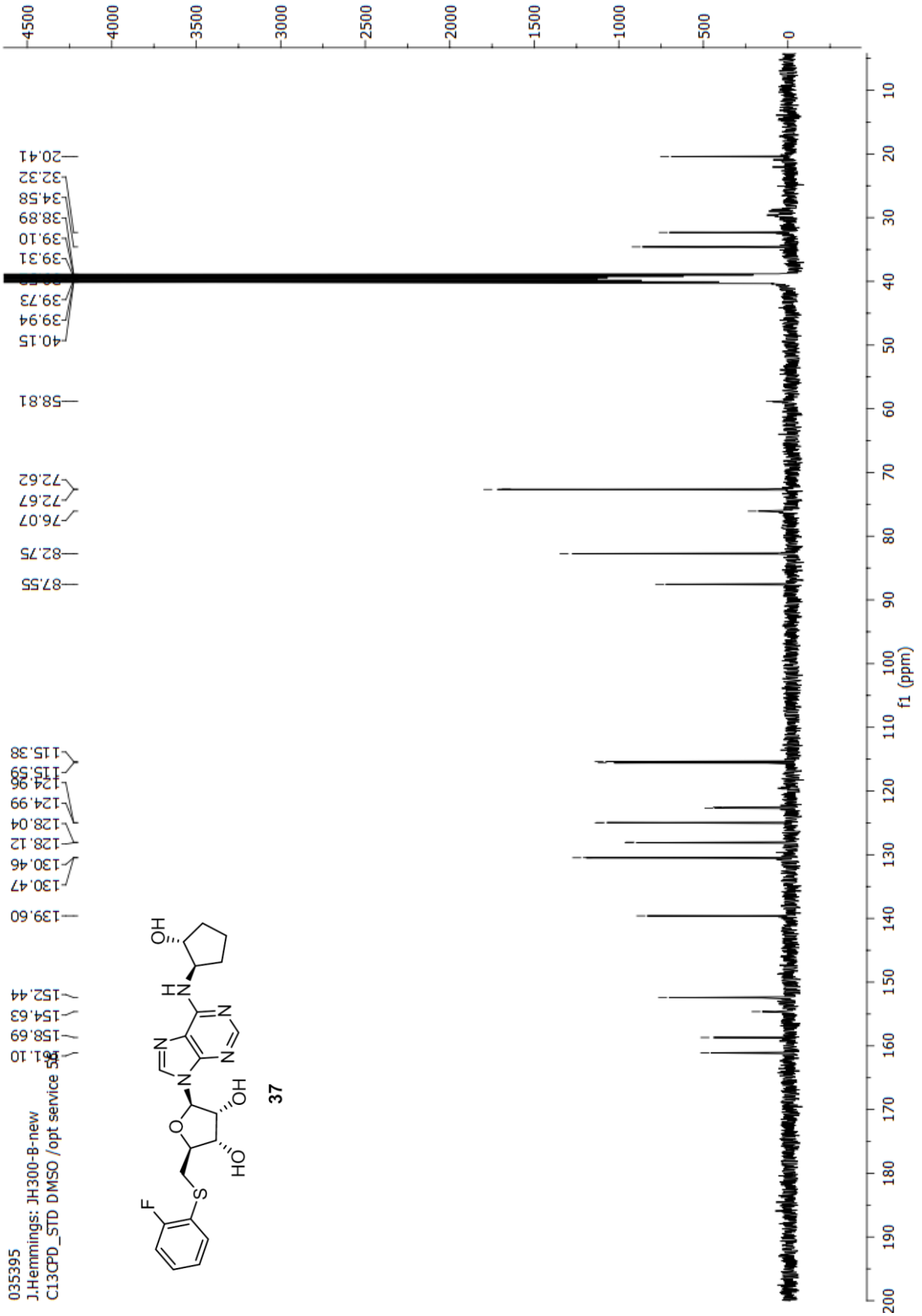

GA_127887
jh37-01-2
Proton_ns32 MeOD /disk0 servicev5
35


035392
J.Hemmings: JH374-1-2
C13CPD_STD MeOD2/opt
7,60
14,33
25,73
32,90
36,50
40,18
48,36
48,57
49,00
49,21
49,43
49,64
53,67
74,08
74,72
85,04
90,14
116,38
116,60
125,64
125,68
129,63
129,71
133,17
140,93
84,03
85,57
35
f1 (ppm)


GA_125504
JH-MLe096
Proton_ns32 DMSO /disk0 service 115
36
f1 (ppm)


035376
Hemmings:JH-MLe096_13C
C13CPD_STD DMSO /opt/topspin4
21.38
30.17
34.59
38.89
39.10
39.31
39.52
39.73
39.94
40.15
56.39
70.08
72.59
72.67
82.75
84.06
87.55
115.37
115.58
124.97
127.12
127.29
128.09
130.48
138.95
139.63
f1 (ppm)
36


37
f1 (ppm)


035395
J.Hemmings: JH300-B-new
C13CPD_STD DMSO /opt service 5
20.41
32.32
34.58
38.89
39.10
39.31
39.73
39.94
40.15
58.81
72.62
72.67
76.07
82.75
87.55
115.38
115.59
124.96
124.99
128.04
128.12
130.46
130.47
139.60
152.44
154.63
158.69
161.10
f1 (ppm)

37

III. Degree of purity for tested compounds

Table S1. Degree of purity for tested compounds.

Compound Number	Purity (%)	t_R (min)
5	99	2.66
6	98	2.30
7	99	1.46
9	99	1.41
16	99	3.06
17	94	2.18
18	99	2.69
19	99	1.62
20	98	2.59
21	99	2.21
24	99	1.80
25	99	1.87
34	-[a]	-[a]
35	99	2.24
36	99	3.14
37	95	2.35

[a] HPLC chromatogram could not be obtained. **34** is ≥95% pure according to ^{1}H, ^{13}C, ^{19}F NMR and HRMS (Δ = 0.8 ppm).

IV. A_3R in yeast

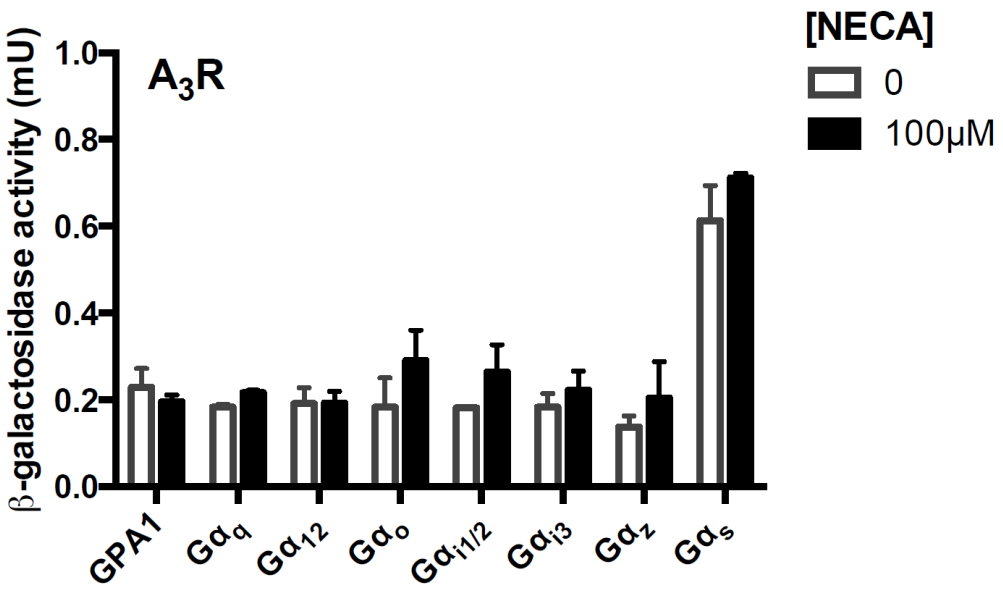


Figure S1. Non-functional coupling of the A_3R in yeast. Yeast strains expressing the human A_3R were stimulated with 0 or 100 μM NECA for 16 h and assayed for the activation of the *FUS1* > *lacZ* reporter gene as previously described.[15-17,19] β-galactosidase units (mU) are expressed as the ratio of *o*-nitrophenol product to cell density (determined colorimetrically; see *Experimental Section*). Data are mean of 5 independent experiments ± SEM.

V. Schild plot analysis for compounds 36 and 37

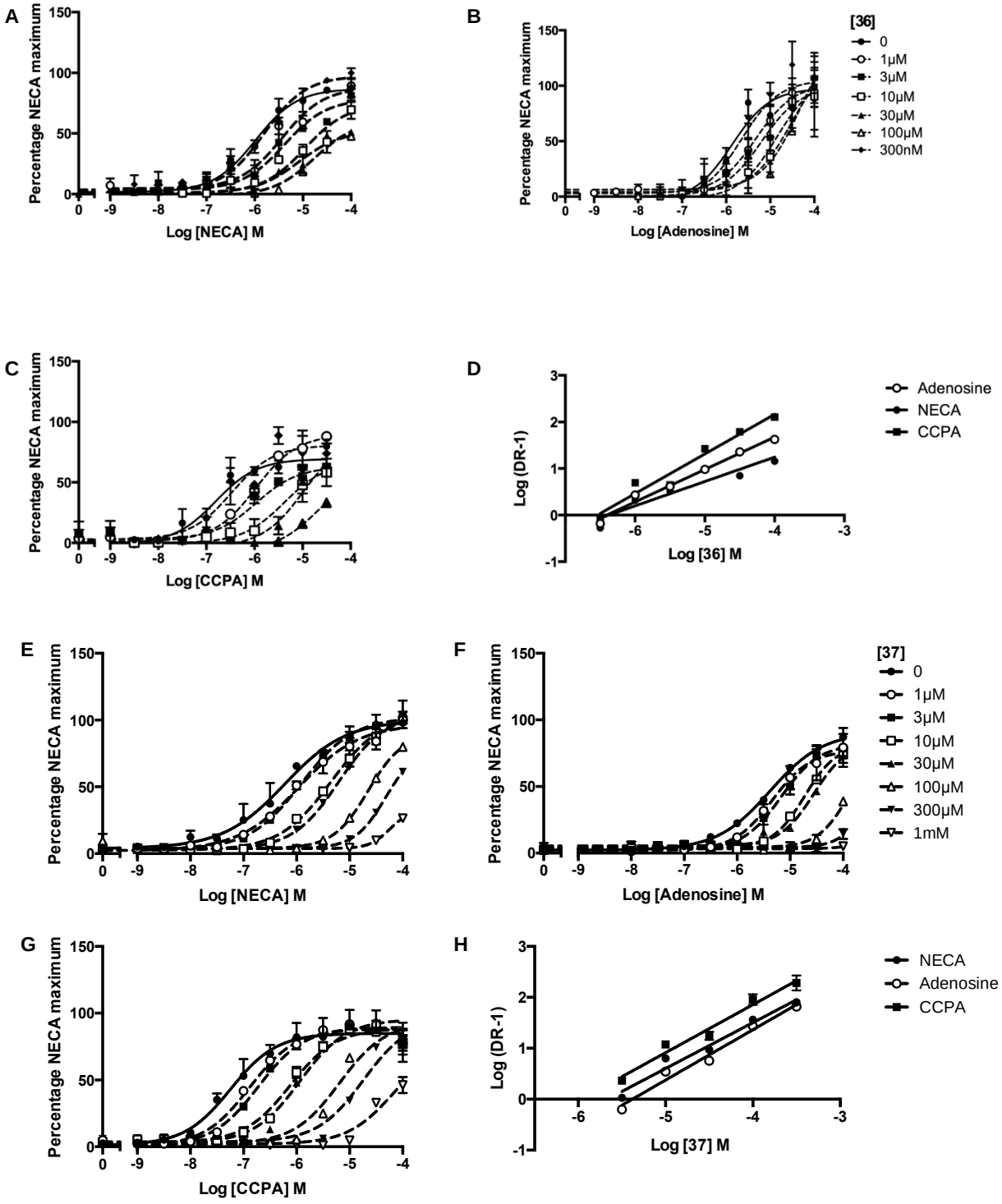


Figure S2. N^6-cyclopentyl congeners **36** and **37** (CVT-3619) are competitive antagonists of the A_1R. Yeast cells expressing the human A_1R were stimulated for 16 h with (A, E) NECA, (B, F) adenosine, (C, G) CCPA in the presence of the indicated concentrations of **36** (A-C) or **37** (E-G) and the extent of signaling quantified through activation of the *FUS1-lacZ* reporter gene. Data are expressed as the percentage of the maximum response achieved when cells were stimulated in the absence of **36** or **37** and are mean of 5 independent experiments ± SEM. (D, H) Schild regression lines obtained from the data in A-C (**36**) and E-G (**37**), respectively. In the double logarithmic plot, the DR-1 of each ligand was calculated from the data in A-C and E-G, respectively.

VI. Predicted binding poses for compounds 5-7, 17-21 and 34

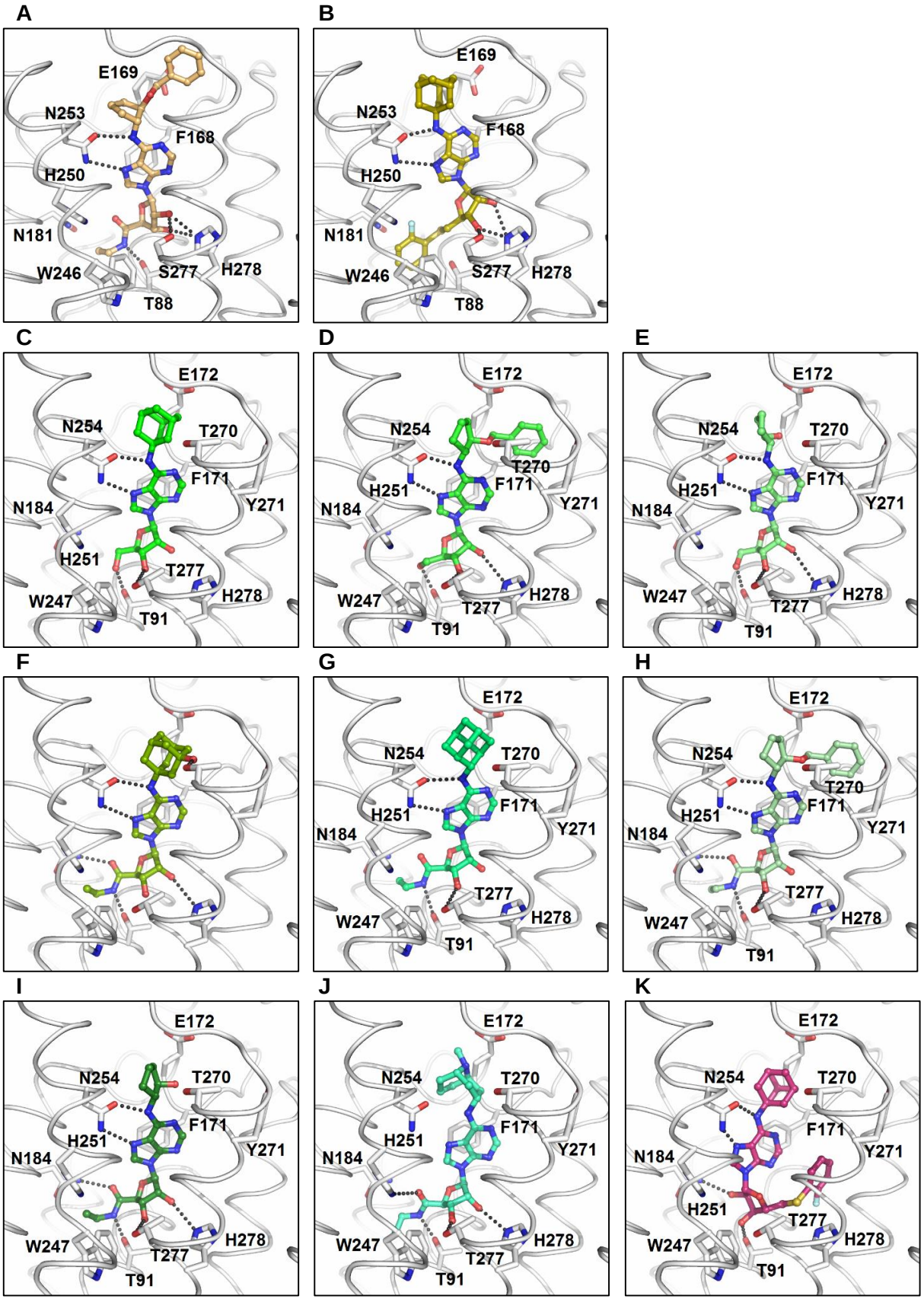


Figure S3. (left) Docking of N^6-substituted adenosine derivatives into the $A_{2A}R$ crystal structure (A,B) and into the A_1R homology model (C-K). Proposed binding poses for (A) **20** and (B) **34** in the $A_{2A}R$ crystal structure. Proposed binding poses for (C) **5**, (D) **6**, (E) **7**, (F) **17**, (G) **18**, (H) **20**, (I) **21**, (J) **19** and (K) **34** in the A_1R homology model. Black dotted lines represent potential hydrogen bonds. Compounds docked into $A_{2A}R$ crystal structure in brown shades, compounds that showed agonist activity at the A_1R (Table 1) are in green shades, compounds which exhibited activation at very high concentration in blue shade and compounds that failed to active the A_1R are shown in red shade. Numbering of residues in (A,B) according to P29274 (hA$_{2A}$R) and of homologous residues in (C-K) according to P30542 (hA$_1$R). Ballesteros-Weinstein (BW) numbering: T88 (A_{2A}), T91 (A_1): BW 3.36; F168 (A_{2A}), F171 (A_1): BW ECL2; E169 (A_{2A}), E172 (A_1): BW ECL2; N181 (A_{2A}), N184 (A_1): BW 5.42; W246 (A_{2A}), W247 (A_1): BW 6.48; H250 (A_{2A}), H251 (A_1): BW 6.52; N253 (A_{2A}), N254 (A_1): BW 6.55; T270 (A_1): BW 7.35; Y271 (A_{2A}), Y271 (A_1): BW 7.36; S277 (A_{2A}), T277 (A_1): BW 7.42; H278 (A_{2A}), H278 (A_1): BW 7.43.

VII. PSI-Coffee sequence alignment for A_1R homology modelling

```
3QAK 3   IMGSSVYITVELAIAVLAILGNVLVCWAVWLNSNLQNVTNYFVVSLAAADIAVGVLAIPF    62
hA1R 9   ---QAAYIGIEVLIALVSVPGNVLVIWAVKVNQALRDATFCFIVSLAVADVAVGALVIPL    65
               **  *  **     ***** ***  *  *   *  * **** ** *** * **

3QAK 63  AITISTGFCAACHGCLFIACFVLVLTQSSIFSLLAIAIDRYIAIRIPLRYNGLVTGTRAK   122
hA1R 66  AILINIGPQTYFHTCLMVACPVLILTQSSILALLAIAVDRYLRVKIPLRYKMVVTPRRAA   125
         ** *  *     * **  ** ** ******  ***** ***    *****   **  **

3QAK 123 GIIAICWVLSFAIGLTPMLGWNNCGQ---------GCGEGQVACLFEDVVPMNYMVYFNF   182
hA1R 126 VAIAGCWILSFVVGLTPMFGWNNLSAVERAWAANGSMGEPVIKCEFEKVISMEYMVYFNF   185
           ** ** ***  ***** ****             **    * ** *  * *******

3QAK 183 FACVLVPLLLMLGVYLRIFLAARRQL-----------RSTLQKEVHAAKSLAIIVGLFAL   244
hA1R 186 FVWVLPPLLLMVLIYLEVFYLIRKQLNKKVSASSGDPQKYYGKELKIAKSLALILFLFAL   245
         *  ** *****   **  *   * **                **   ***** *  ****

3QAK 245 CWLPLHIINCFTFFCPDCSHAPLWLMYLAIVLSHTNSVVNPFIYAYRIREFRQTFRKIIR   304
hA1R 246 SWLPLHILNCITLFCPSC-HKPSILTYIAIFLTHGNSAMNPIVYAFRIQKFRVTFLKIW-   303
          ****** ** * *** * * *  * * ** * * **  **  ** **  ** ** **
```

Figure S4. PSI-Coffee sequence alignment used for the construction of the human adenosine A_1R homology model. 3QAK: sequence of the human $A_{2A}R$ (accession no. P29274) from the agonist-bound crystal structure (PDB ID: 3QAK). hA1R: sequence of human A_1R (accession no. P30542). Identical residues are marked with an asterisk and highlighted with a grey background. Residues in bold are involved in ligand binding and discussed in the docking section (Figure 6).

VIII. Supplementary references

(S1) Slavik, R.; Herde, A. M.; Bieri, D.; Weber, M.; Schibli, R.; Krämer, S. D.; Ametamey, S. M.; Mu, L. Synthesis, radiolabeling and evaluation of novel 4-oxo quinoline derivatives as PET tracers for imaging cannabinoid type 2 receptor. *Eur. J. Med. Chem.* **2015**, *92*, 554-564.

(S2) Qiao, J. X.; Chang, C-H; Cheney, D. L.; Morin, P. E.; Wang, G. Z.; King, S. R.; Wang, T. C.; Rendina, A. R.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R.; Lam, P. Y. S. SAR and X-ray structures of enantiopure 1,2-*cis*-(1*R*,2*S*)-cyclopentyldiamine and cyclohexyldiamine derivatives as inhibitors of coagulation Factor Xa. *Bioorg. Med. Chem. Lett.* **2007**, 17, 4419-4427.

(S3) Friedrich, S. R.; Qiao, J. X.; Pinto, D. J.; Orwat, M. J.; Han, W. 1,1-Disubstituted cycloalkyl derivatives as factor Xa inhibitors. WO2003/99276 A1, **2003**.

(S4) Rouf, A.; Gupta, P.; Aga, M. A.; Kumar, B.; Parshad, R.; Taneja, S. C. *Tetrahedron Asymmetry* **2011**, *22*, 2134-2143.