Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supplementary Information

Synthesis and evaluation of immunomodulating properties of the mono- and dimannosylated adamantane-containing desmuramyl dipeptides

Marija Paurević,[a] Aleksandra Maršavelski,[b] Siniša Ivanković, [c] Ranko Stojković[c] and Rosana Ribić*[d]

‡To whom correspondence should be addressed: Tel: +358 42 493 306; e-mail: rosana.ribic@unin.hr

Table S1. Gibbs energy of binding of mono-mannosylated compound **7**

$E_{VDWAALS}$ / kcalmol^{-1}	E_{el} / kcalmol^{-1}	EGB / kcalmol^{-1}	E_{surf} / kcalmol^{-1}	ΔH_{gas} / kcalmol^{-1}	ΔH_{solv} / kcalmol^{-1}	ΔH_{bind} + Std. Err. of Mean / kcalmol^{-1}	$T\Delta S$ / kcalmol^{-1}	ΔG_{bind} / kcalmol^{-1}
	Complex compound 7 – pocket 1							
-65.0	15.3	6.7	-9.3	-49.7	-2.6	-52.3±0.5	-26.6± 2.5	**-25.7**
-65.4	22.7	0.3	-8.6	-42.7	-8.3	-51.0±0.3	-27.7±2.2	**-23.3**
-68.4	12.3	9.4	-9.3	-56.1	0.1	-56.0±0.4	-27.9± 2.3	**-28.1**
							average	**-25.7**
	Complex compound 7 – pocket 2a							
-37.7	56.5	-41.7	-5.4	18.8	-47.1	-28.3±0.3	-28.1± 1.4	**-0.2**
-33.1	57.3	-47.5	-5.3	24.2	-52.8	-28.6±0.3	-28.5±3.4	**-0.1**
-43.7	60.1	-44.9	-6.0	16.5	-50.9	-34.5±0.6	-33.4±1.9	**-1.1**
							average	**-0.4**
	Complex compound 7 – pocket 2b							
-32.7	-61.0	72.8	-5.1	-93.7	67.7	-26.0±0.4	-27.7± 2.3	**1.8**
-32.1	-49.9	63.4	-5.8	-81.9	57.6	-24.3 ±3.2	-27.0±3.3	**2.7**
-38.2	-43.3	62.3	-5.0	-81.4	57.3	-24.1±1.0	-27.0±4.2	**2.9**
							average	**2.4**

Table S2. Gibbs energy of binding of di-mannosylated compoud **11**

$E_{VDWAALS}$ / kcalmol^{-1}	E_{el} / kcalmol^{-1}	EGB / kcalmol^{-1}	E_{surf} / kcalmol^{-1}	ΔH_{gas} / kcalmol^{-1}	ΔH_{solv} / kcalmol^{-1}	ΔH_{bind} + Std. Err. of Mean / kcalmol^{-1}	$T\Delta S$ / kcalmol^{-1}	ΔG_{bind} / kcalmol^{-1}
Complex compound 11 – pocket 1								
-108.1	-3.6	48.8	-14.4	-111.7	34.3	-77.7 ± 0.4	-43.7 ± 2.6	**-33.6**
-100.4	-26.3	60.5	-13.6	-126.7	46.9	-79.7 ± 0.3	-42.9 ± 2.7	**-36.8**
-96.1	-20.8	45.5	-13.5	-116.9	32.0	-84.9 ± 0.3	-47.3 ± 2.7	**-37.6**
							average	**-36.0**
Complex compound 11 – pocket 2a								
-65.6	-46.9	64.1	-9.8	-112.5	54.3	-58.8 ± 0.7	-39.7 ± 2.9	**-18.5**
-64.1	-11.5	29.6	-8.8	-75.7	20.8	-54.9 ± 0.3	-38.7 ± 2.1	**-16.2**
-64.7	-12.5	31.3	-9.6	-77.2	21.7	-55.5 ± 0.4	-35.6 ± 2.5	**-19.9**
							average	**-18.2**
Complex compound 11 – pocket 2b								
-63.1	16.6	7.4	-8.8	-46.6	-1.4	-48.0 ± 0.5	-32.9 ± 1.5	**-15.0**
-67.5	10.1	19.5	-9.5	-57.4	10.0	-47.4 ± 0.2	-34.9 ± 2.9	**-12.5**
-65.9	19.8	5.5	-9.1	-46.1	-3.6	-49.7 ± 0.7	-31.9 ± 2.5	**-17.8**
							average	**-15.1**

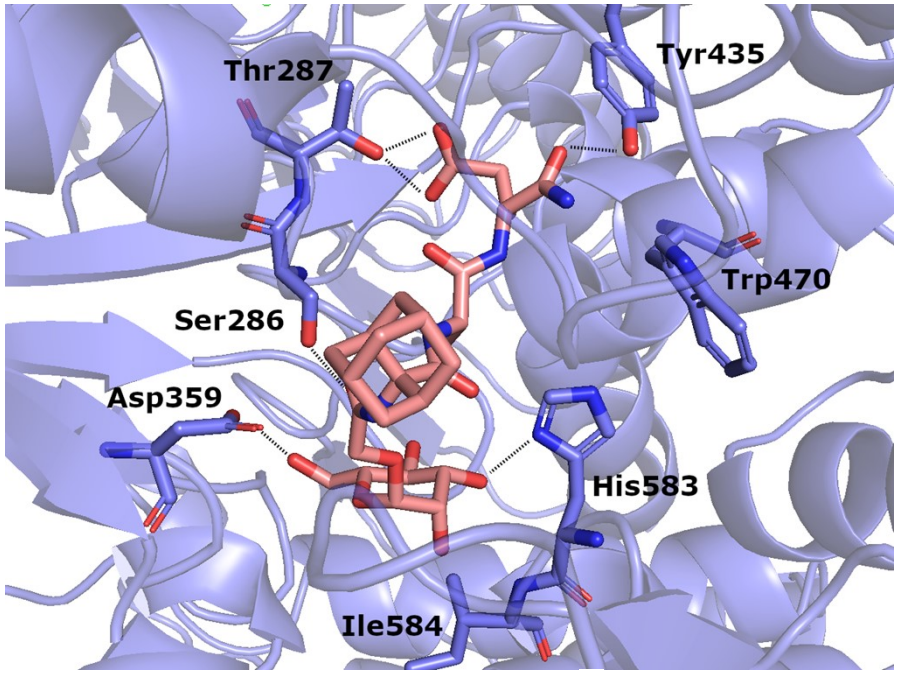


Figure S1. Mono-mannostylated compound **7** in binding pocket 1

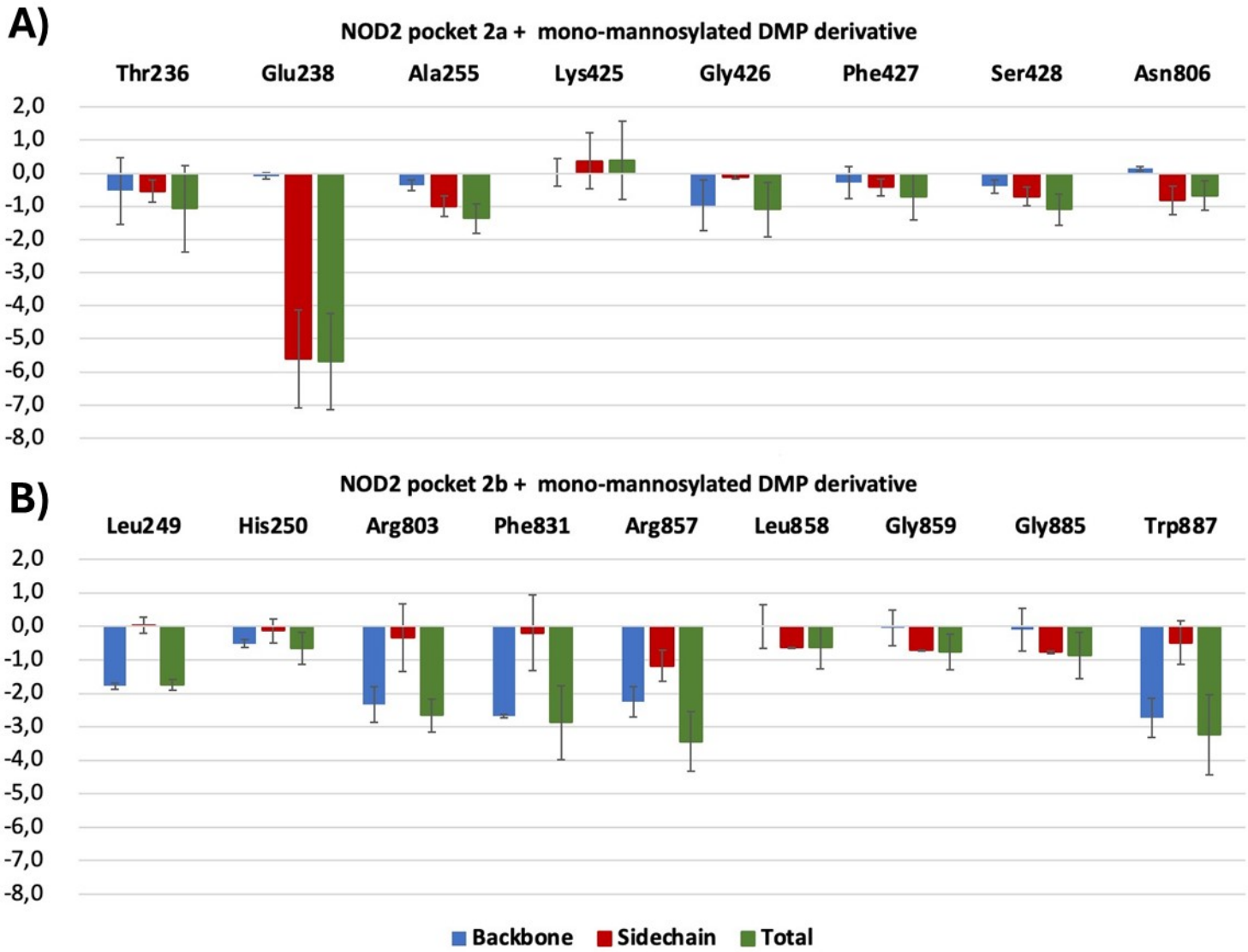


Figure S2. Per residue enthalpy decomposition for mono-mannosylated compound **7** in binding pocket 2a (A) and 2b (B) of NOD2

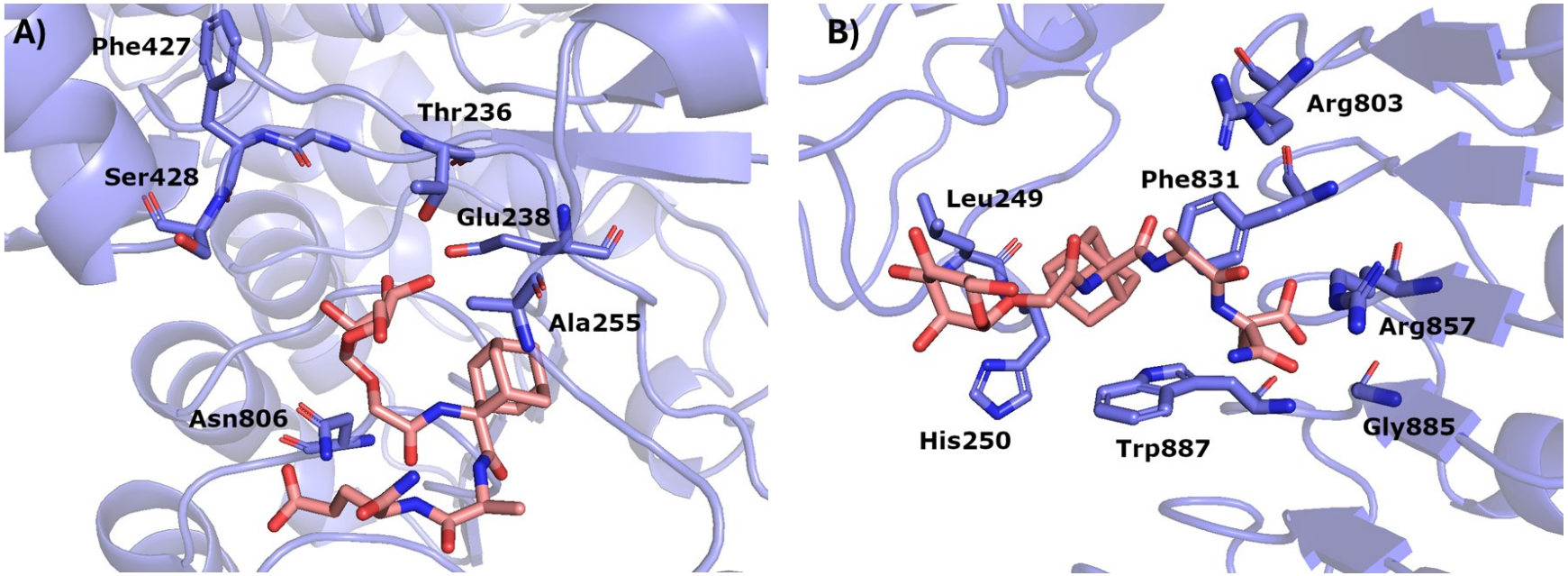


Figure S3. Mono-mannosylated compound **7** in binding pocket 2a (A) and pocket 2b (B) of NOD2

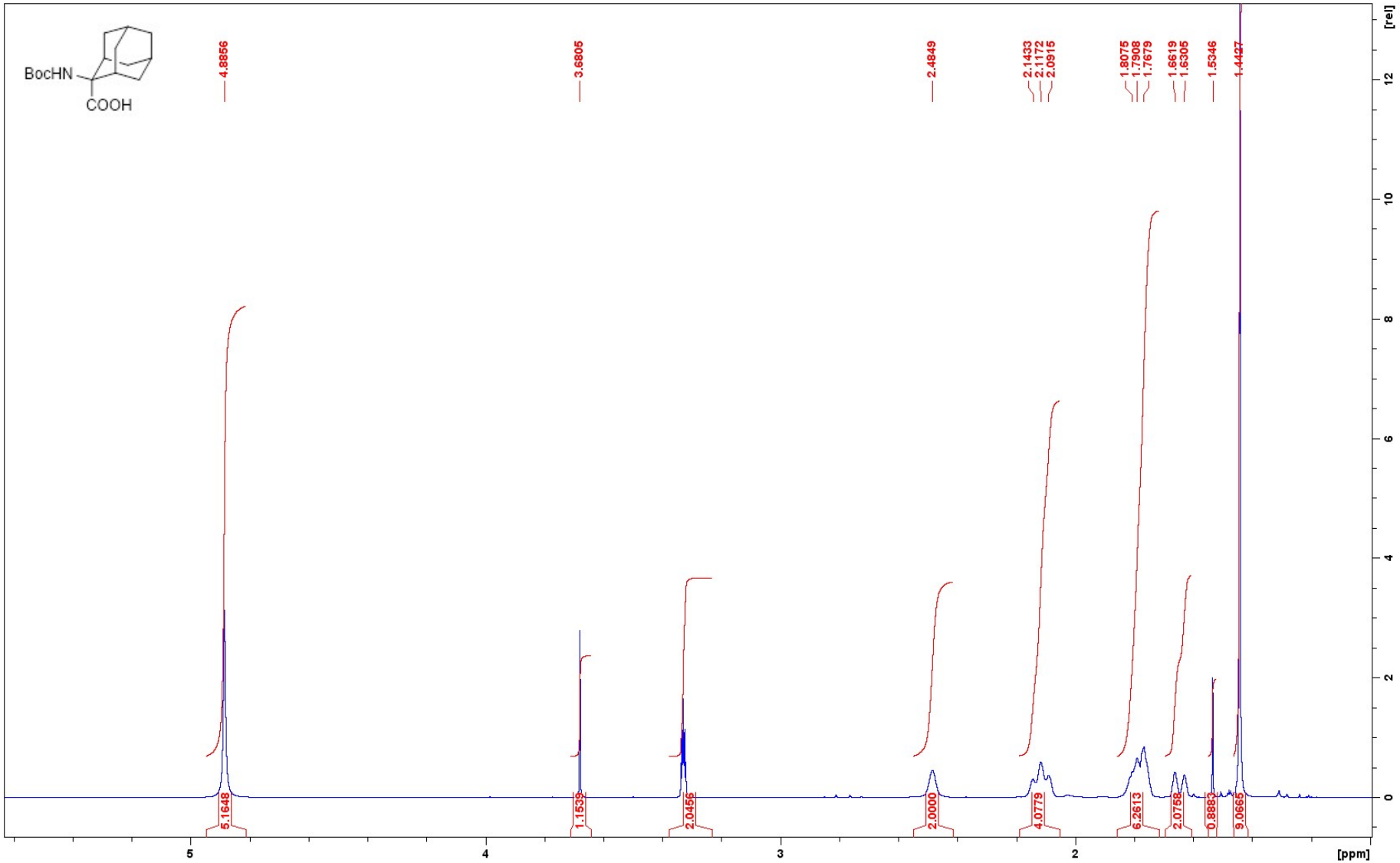


Figure S4. ^{1}H NMR spectrum of *N*-(*tert*-butoxycarbonyl)-2-aminoadamantane-2-carboxylic acid **1** (CD_3OD, 400 MHz)

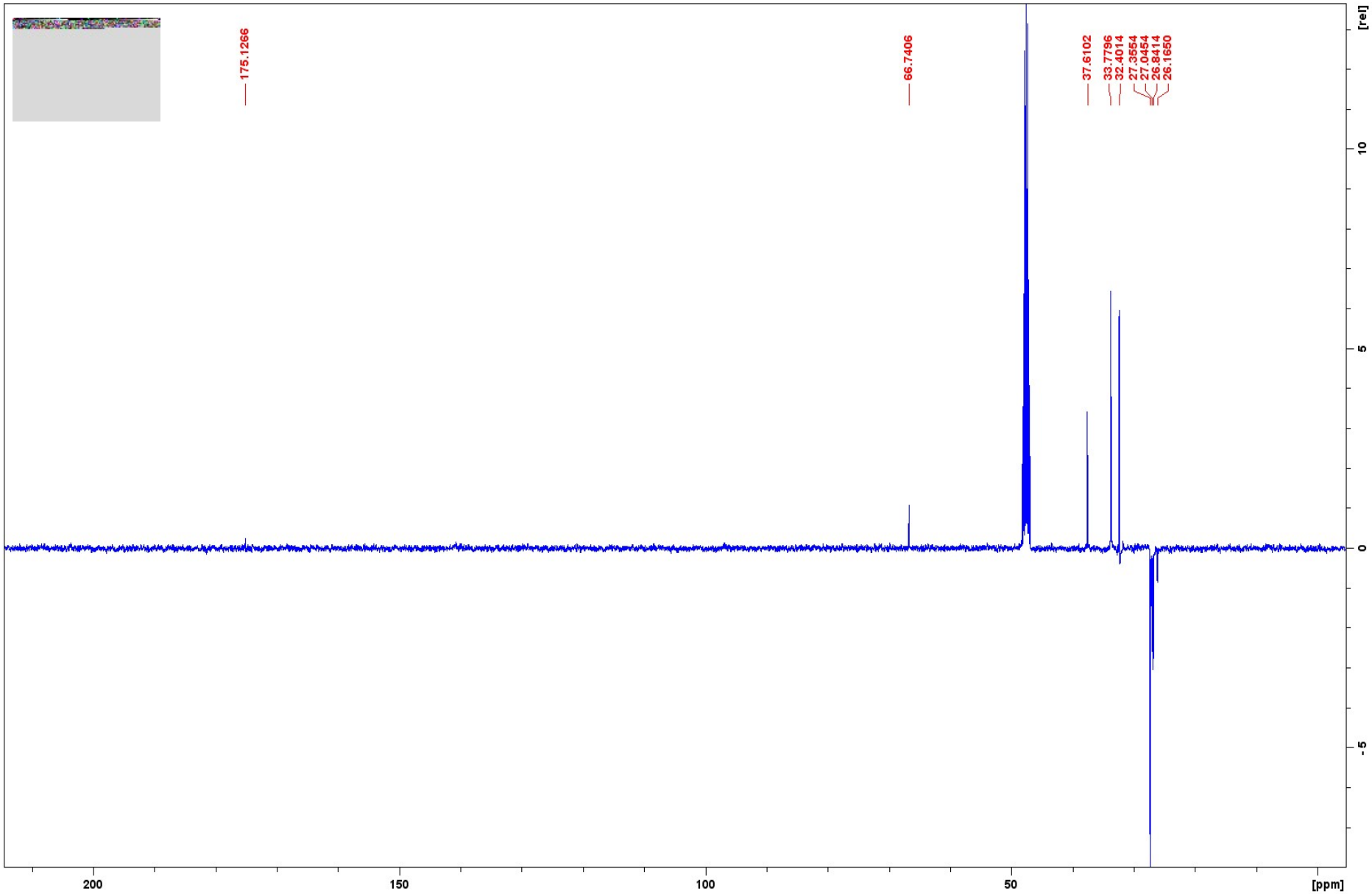


Figure S5. ^{13}C NMR spectrum of *N*-(*tert*-butoxycarbonyl)-2-aminoadamantane-2-carboxylic acid **1** (CD_3OD, 100 MHz)

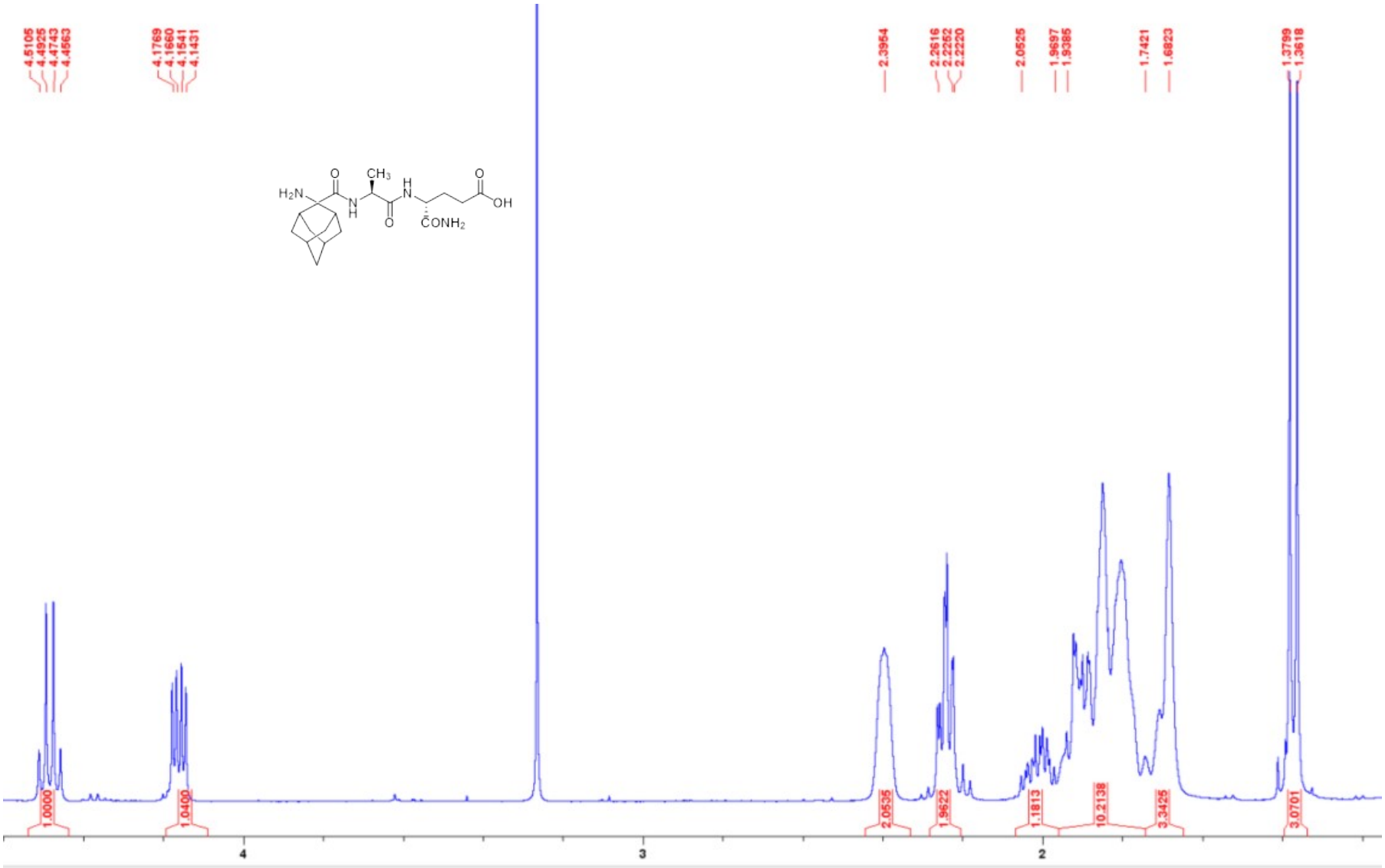
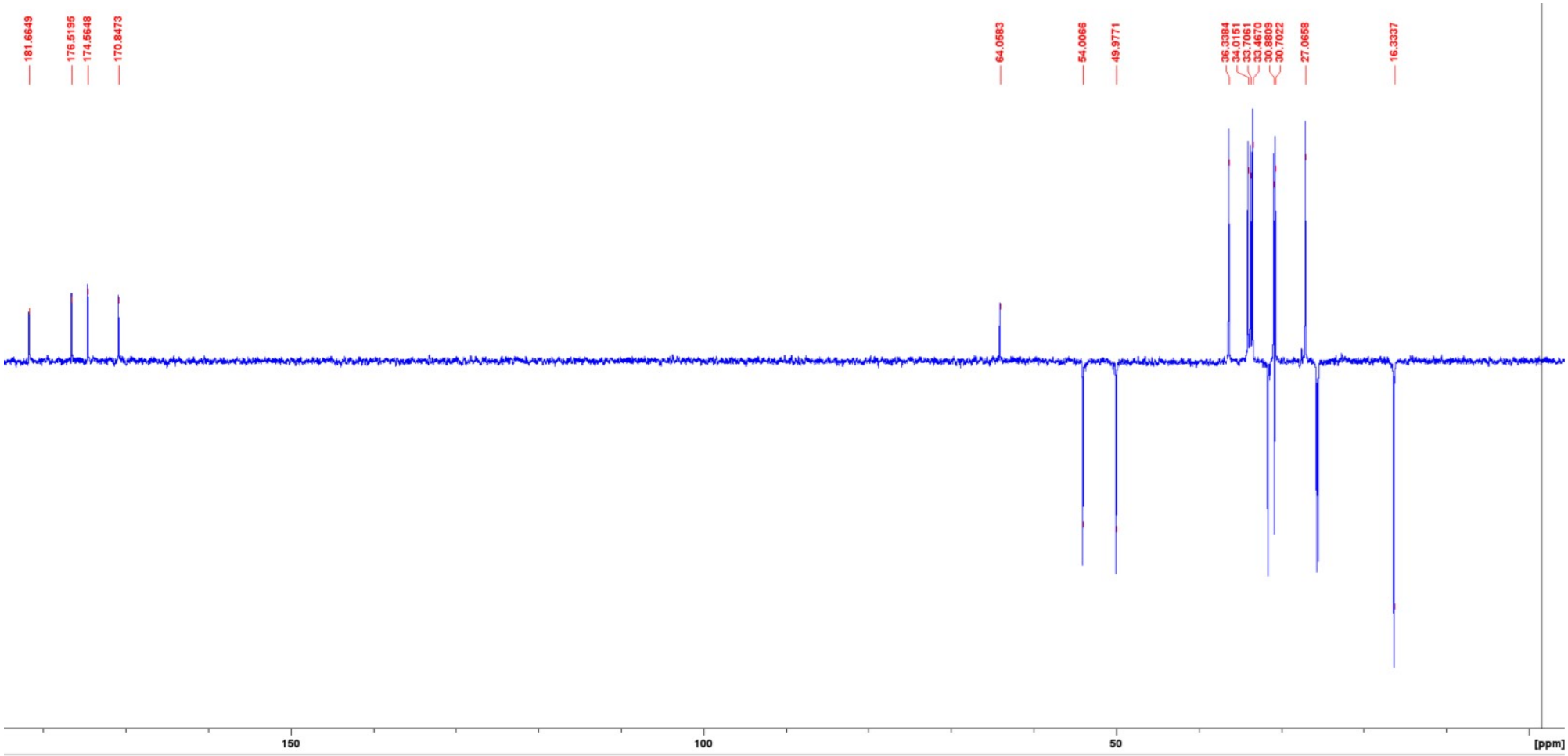


Figure S6. ^{1}H NMR spectrum of 4-{2-[(2-aminoadamantane-2-carbonyl)amino]propionylamino}-4-carbamoylbutanoic acid **4** (D_2O, 400 MHz)

a)


181.6649
176.5195
174.5648
170.8473
64.0583
54.0066
49.9771
36.3384
34.0151
33.7061
33.4670
30.8809
30.7022
27.0658
16.3337
150
100
50
[ppm]

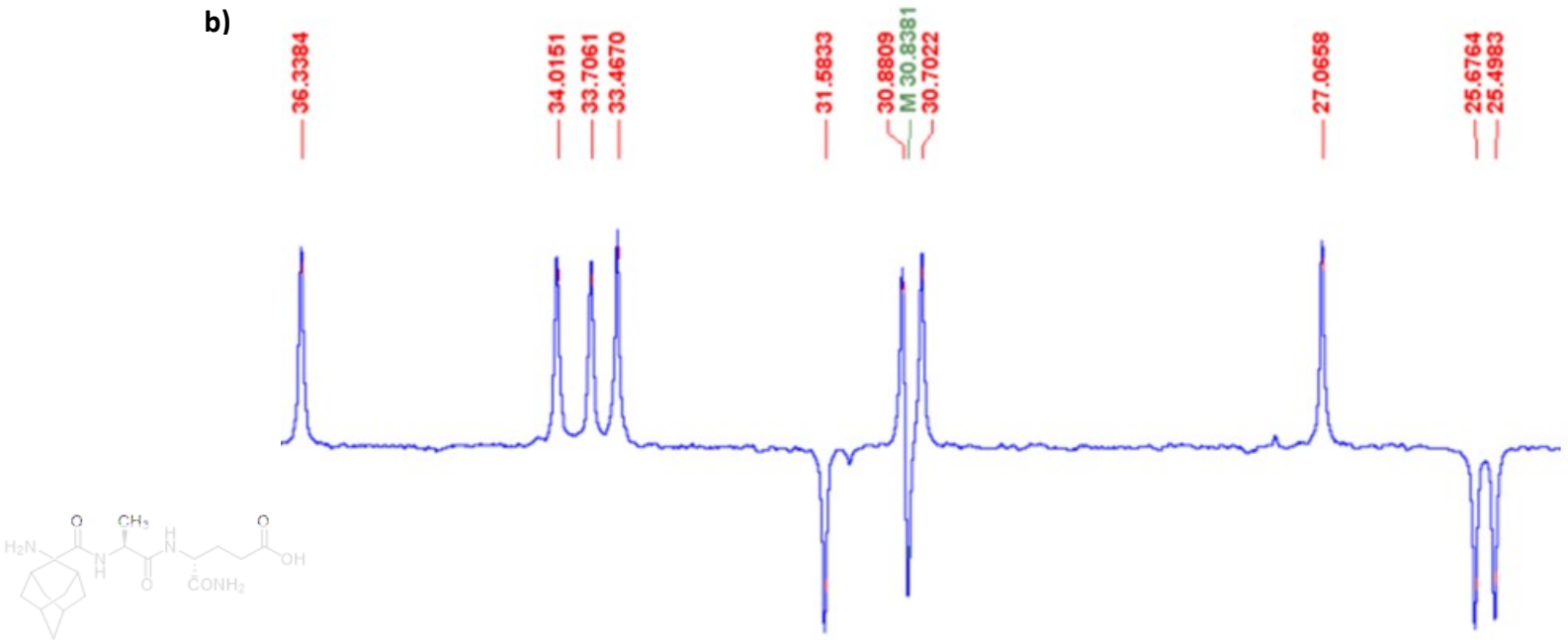


Figure S7. ^{13}C NMR spectrum of 4-{2-[(2-aminoadamantane-2-carbonyl)amino]propionylamino}-4-carbamoylbutanoic acid **4** (D_2O, 100 MHz); a) full spectrum, b) enlarged region between 36.34 and 25.50 ppm.

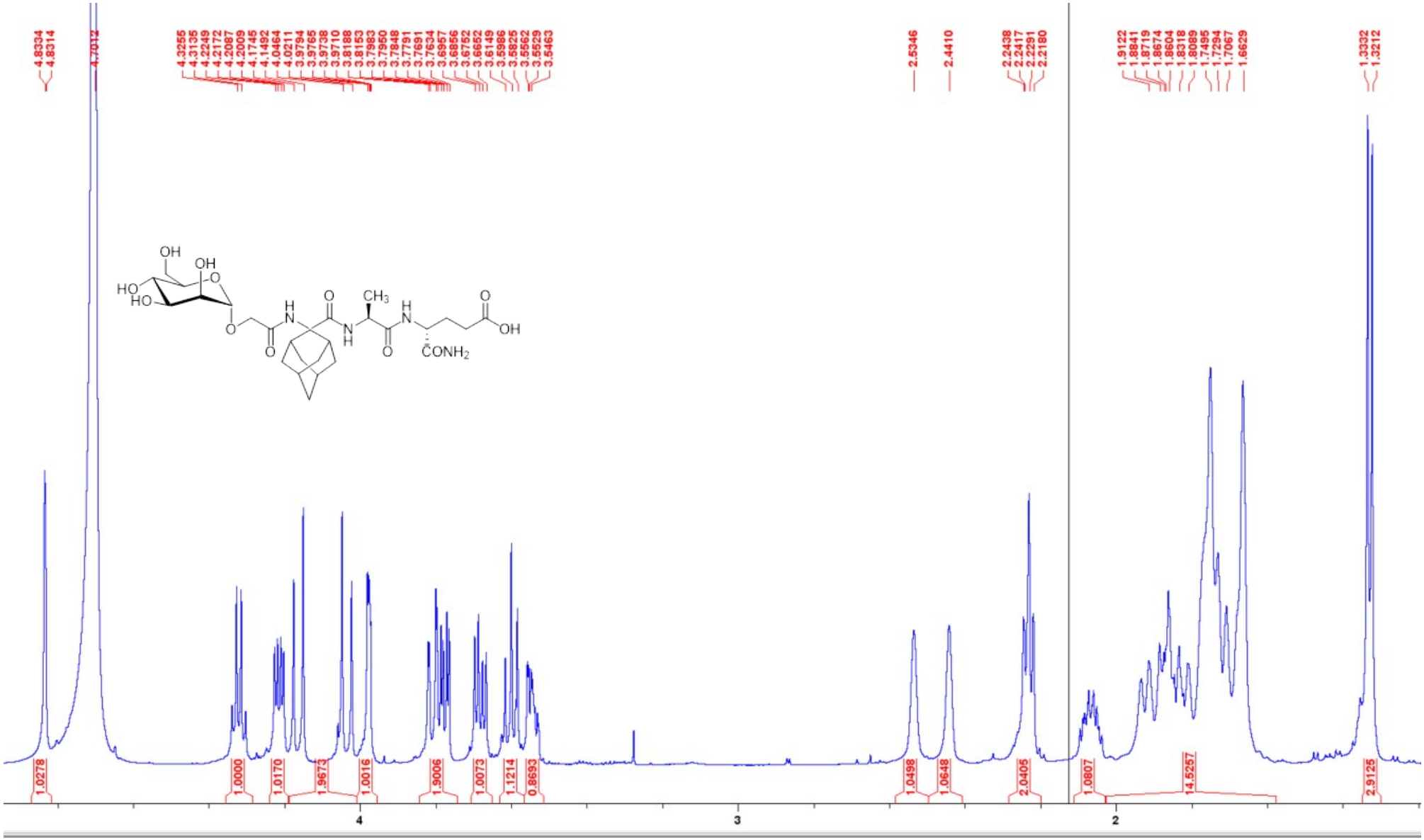
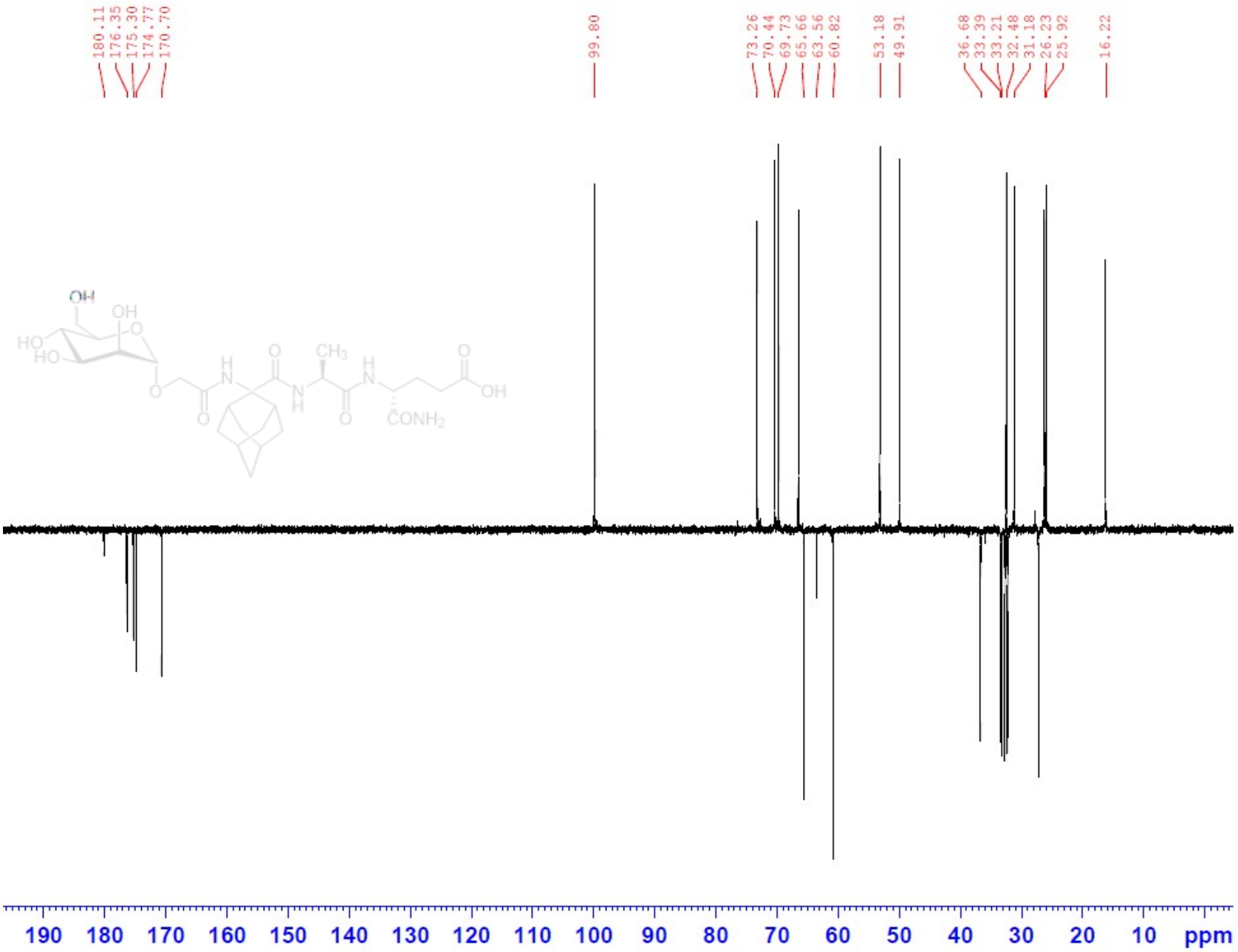
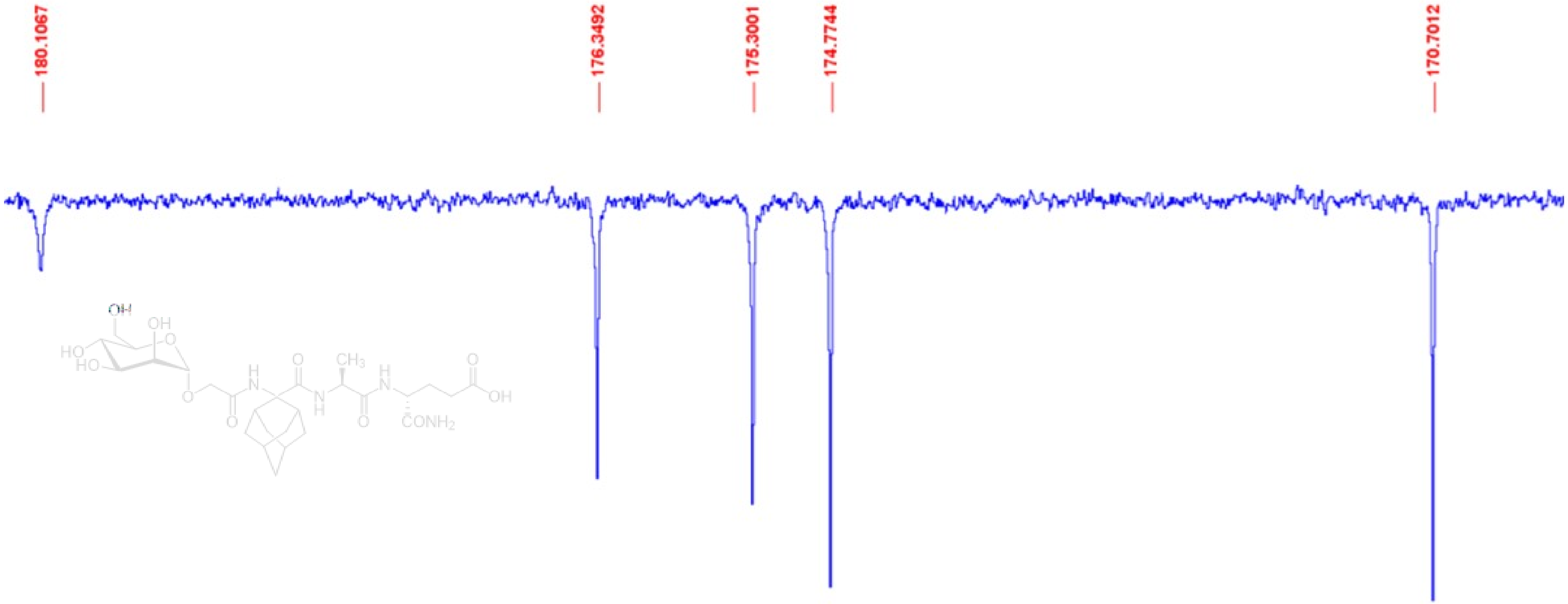


Figure S8. ^{1}H NMR spectrum of 4-{2-[([2-(α-D-mannopyranosyloxy)ethanol]-aminoadamantane-2-carbonyl)amino]-propionylamino}-4-carbamoylbutanoic acid **7** (D_2O, 400 MHz)

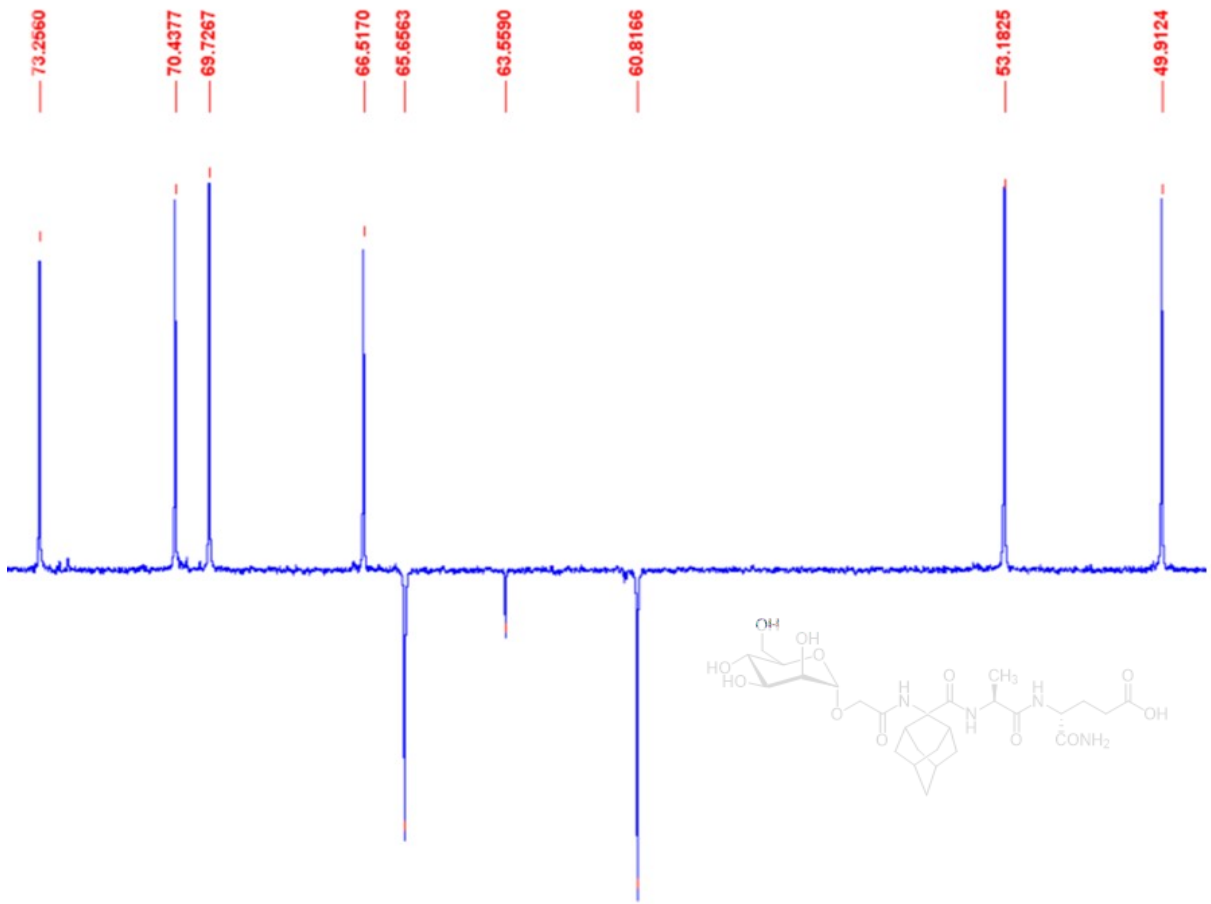
a)


180.11
176.35
175.30
174.77
170.70
99.80
73.26
70.44
69.73
65.66
63.56
60.82
53.18
49.91
36.68
33.39
33.21
32.48
31.18
26.23
25.92
16.22
OH
OH
HO
HO
O
O
H
N
O
CH3
N
H
O
H
N
O
OH
O
CONH2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

b)



c)


73.2560
70.4377
69.7267
66.5170
65.6563
63.5590
60.8166
53.1825
49.9124
OH
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H
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CH3
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H
O
H
N
O
OH
O
CONH2

d)

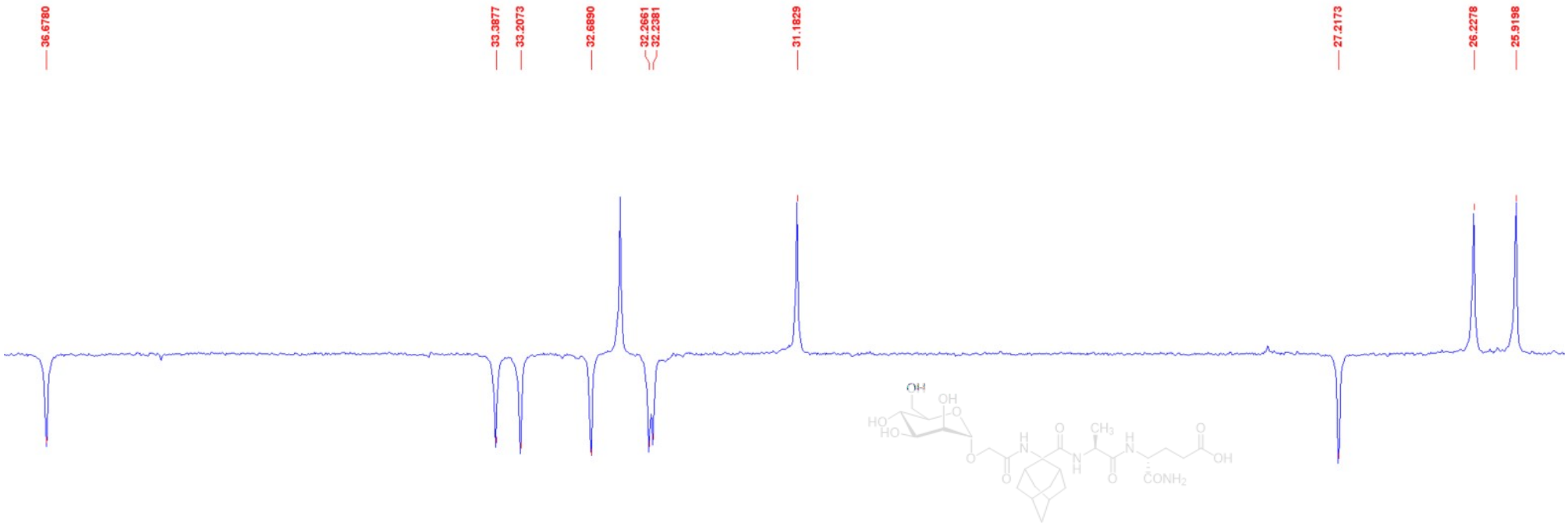


Figure S9. ^{13}C NMR spectrum of 4-{2-[([2-(α-D-mannopyranosyloxy)ethanol]-aminoadamantane-2-carbonyl)amino]-propionylamino}-4-carbamoylbutanoic acid **7** (D_2O, 100 MHz); a) full spectrum and enlarged regions between b) 180.11 and 170.70 ppm, c) 73.26 and 49.91 ppm and d) 36.68-25.92 ppm.

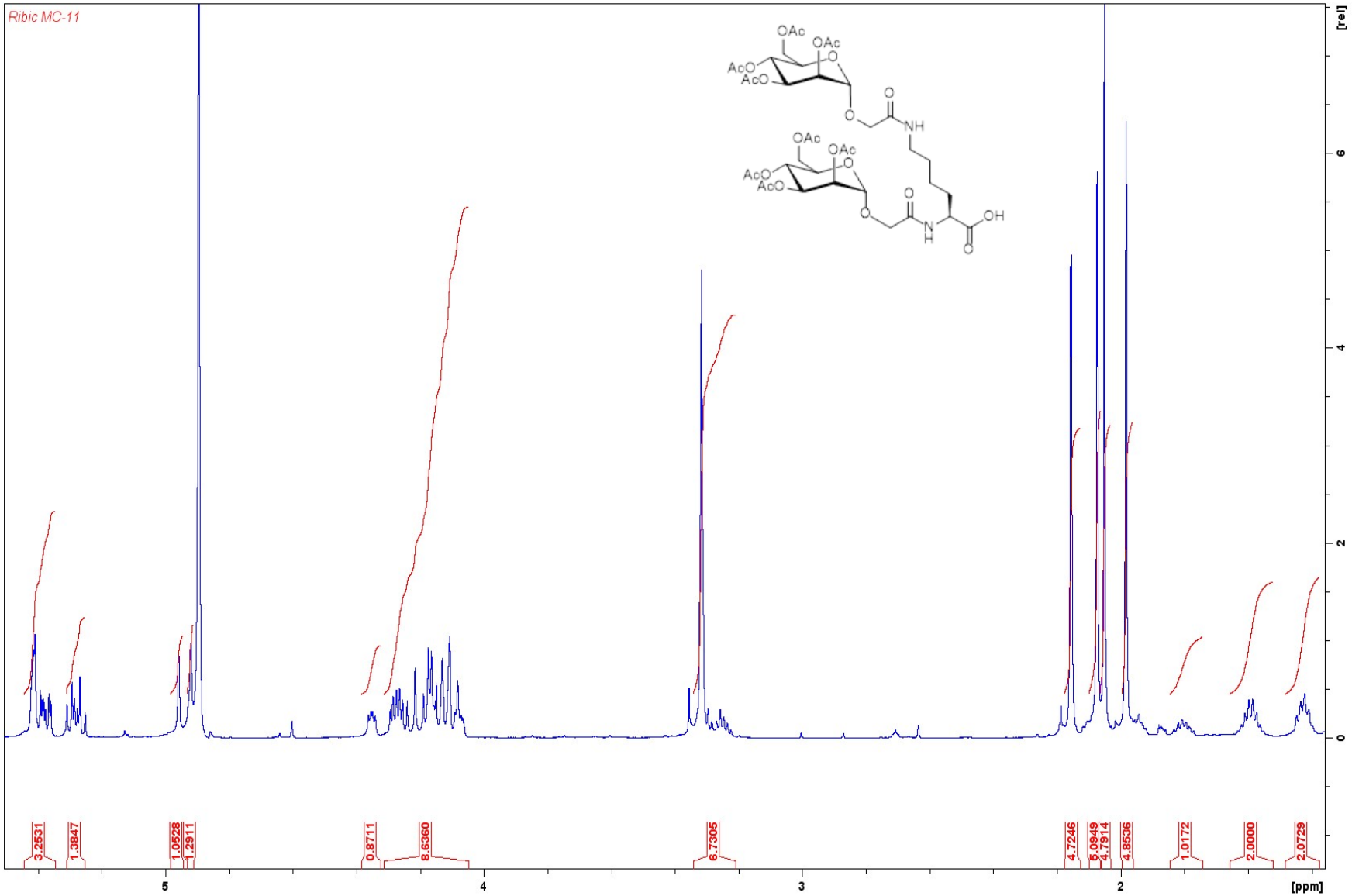
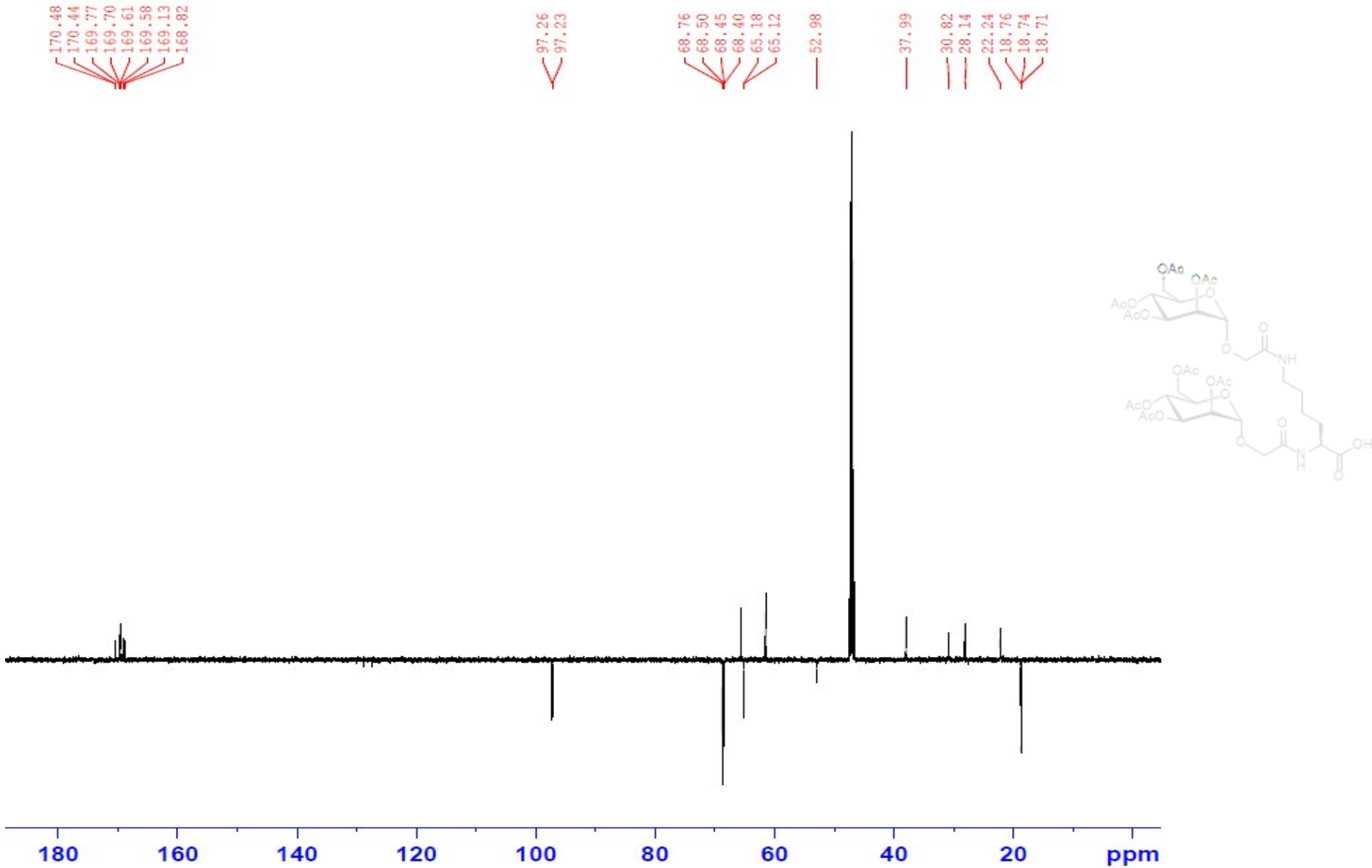
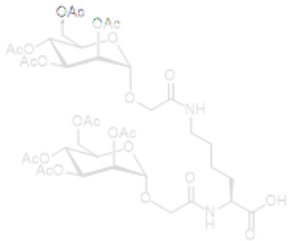


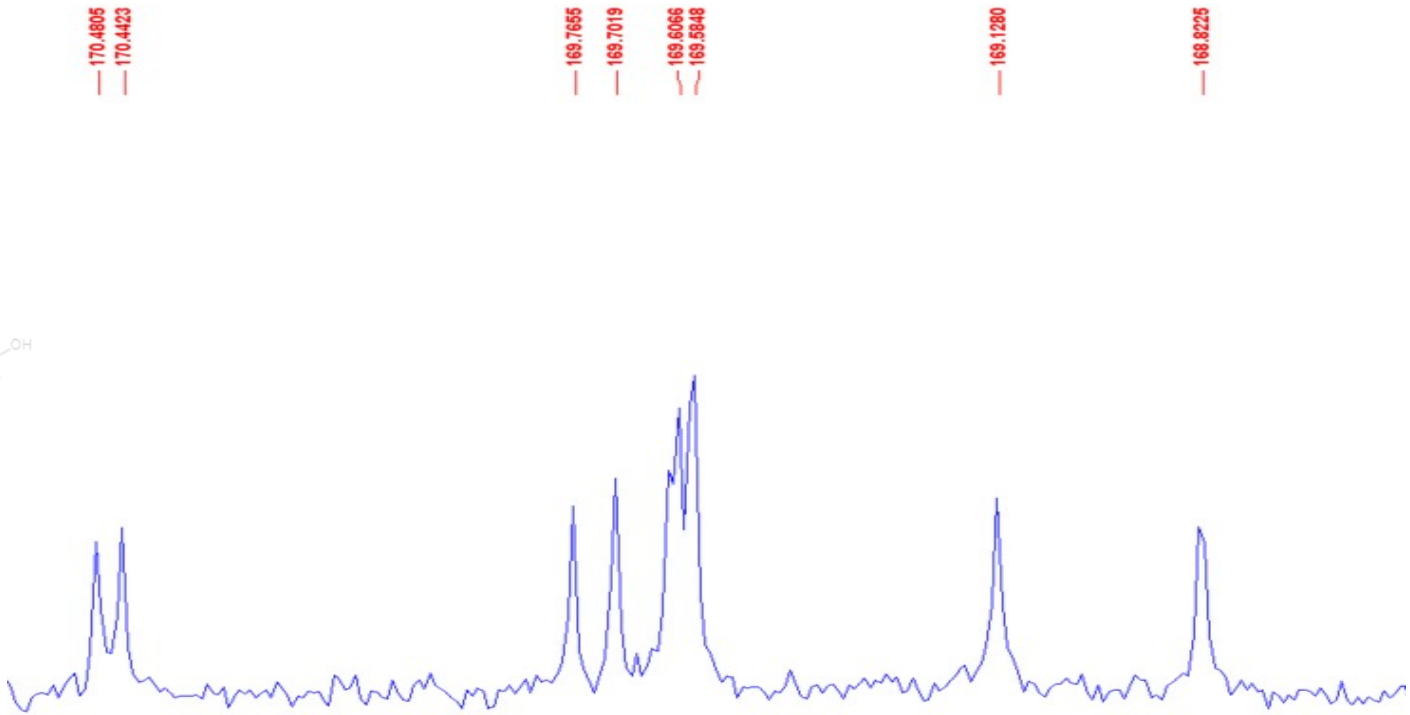
Figure S10. ^{1}H NMR spectrum of (2*S*)-2,6-di[2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)-acetylamino]hexanoic acid **9** (CD_3OD, 400 MHz)

a)

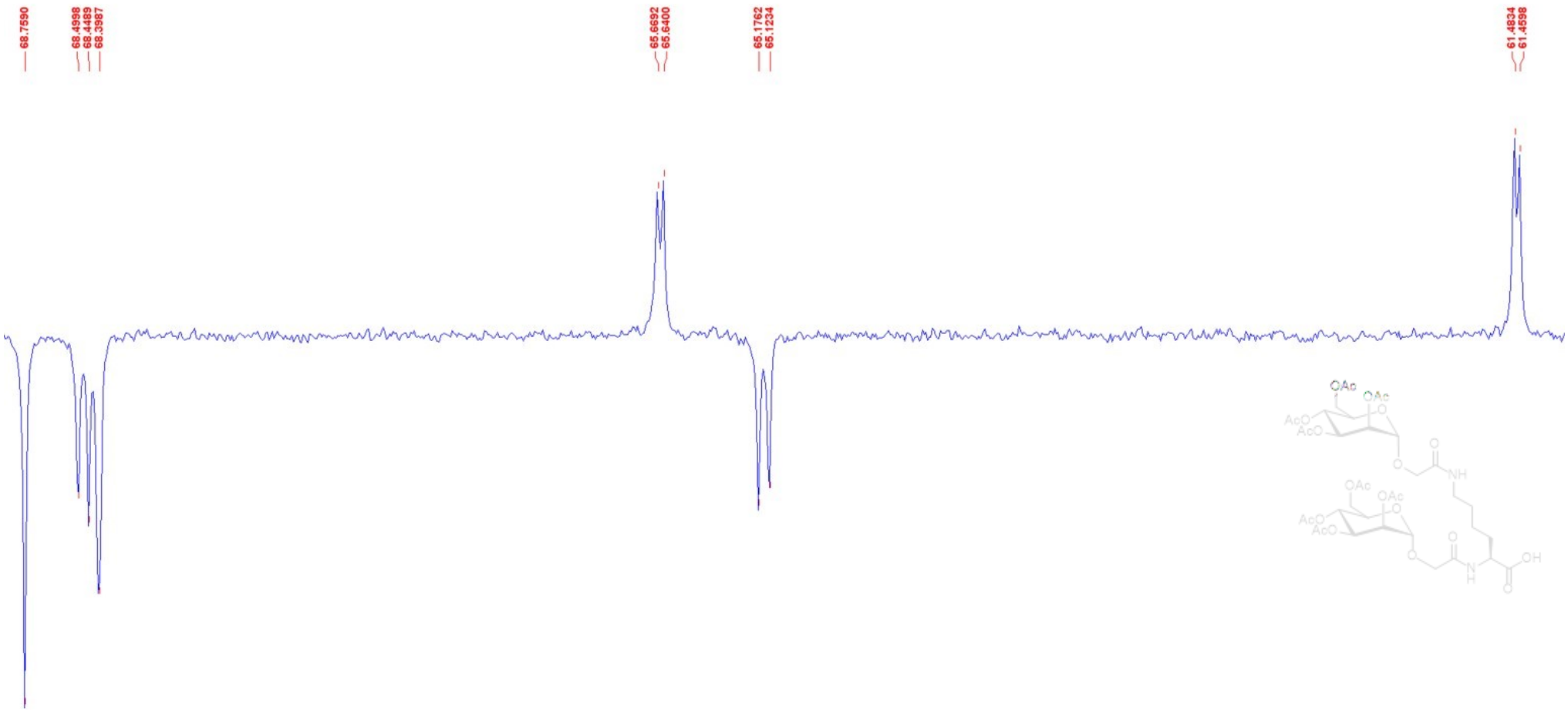

170.48
170.44
169.77
169.70
169.61
169.58
169.13
168.82
97.26
97.23
68.76
68.50
68.45
68.40
65.18
65.12
52.98
37.99
30.82
28.14
22.24
18.76
18.74
18.71
180
160
140
120
100
80
60
40
20
ppm

b)


OAc
OAc
AcO
AcO
O
NH
OAc
OAc
AcO
AcO
O
O
N
H
OH
O


170.4805
170.4423
169.7655
169.7019
169.6066
169.5848
169.1280
168.8225

c)


68.7590
68.4998
68.4489
68.3987
65.6692
65.6400
65.1762
65.1234
61.4834
61.4598
OAc
OAc
AcO
AcO
NH
OAc
OAc
AcO
AcO
OH

d)

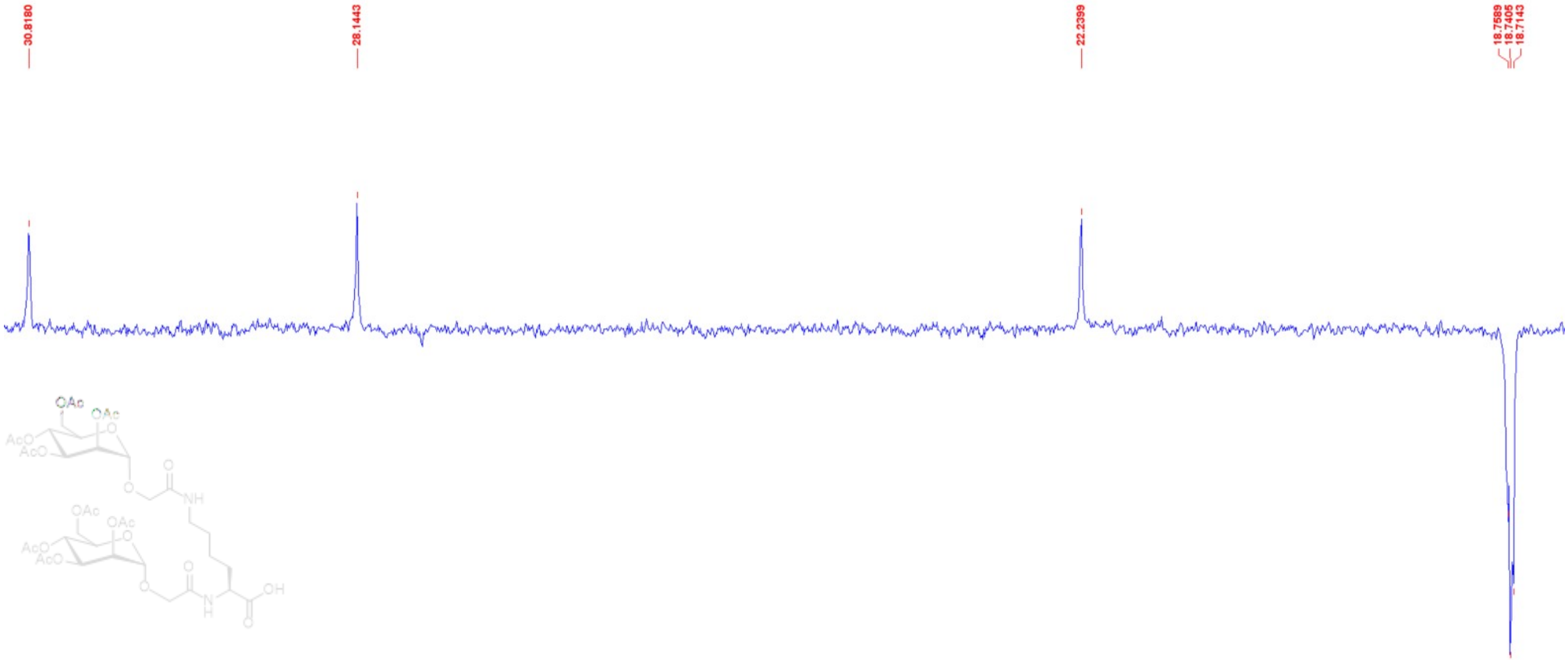


Figure S11. ^{13}C NMR spectrum of (2*S*)-2,6-di[2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)-acetylamino]hexanoic acid **9** (CD_3OD, 100 MHz) ; a) full spectrum, and enlarged regions between b) 170.48 and 168.82 ppm, c) 68.76 and 61.46 ppm and d) 30.82-18.71 ppm.

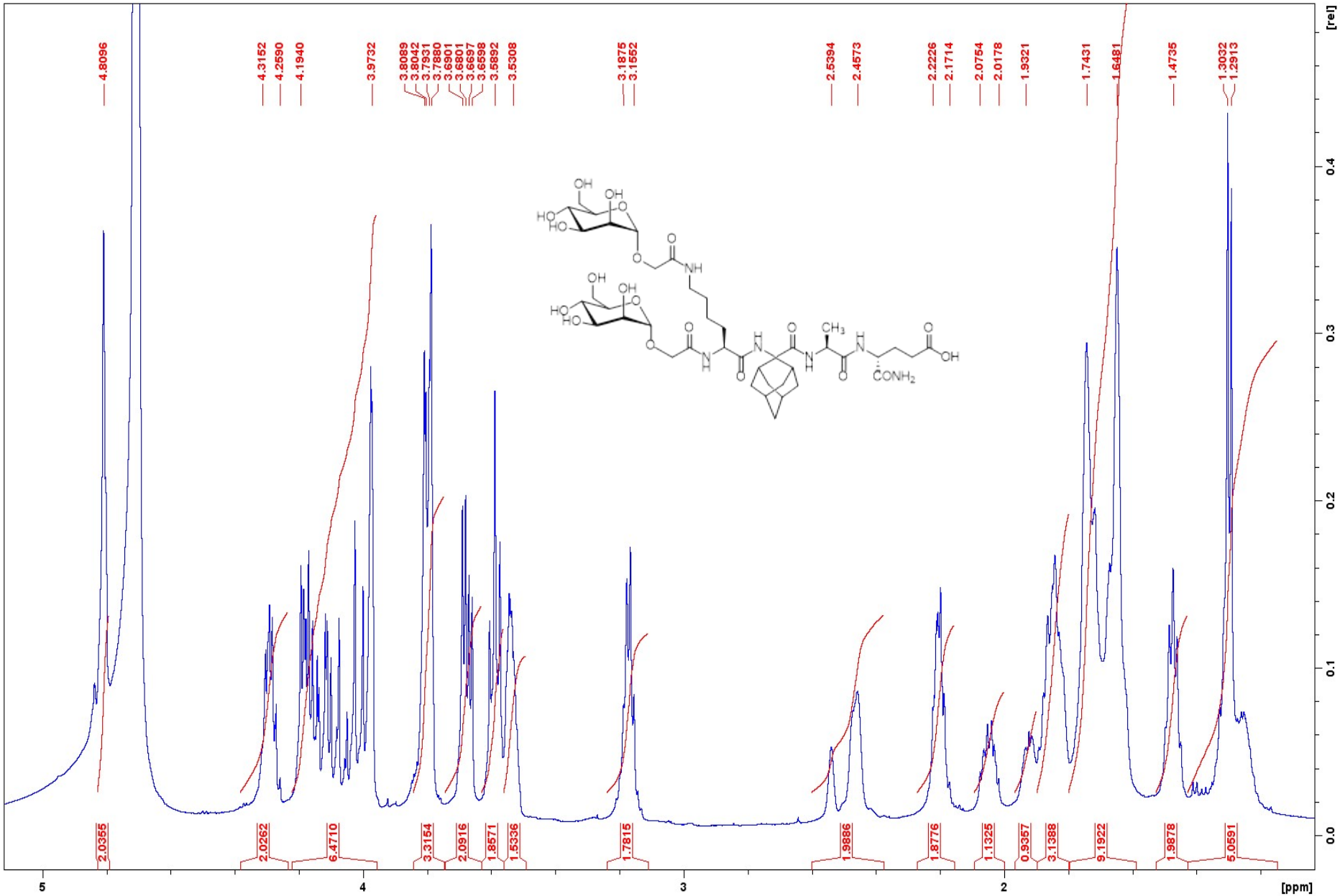
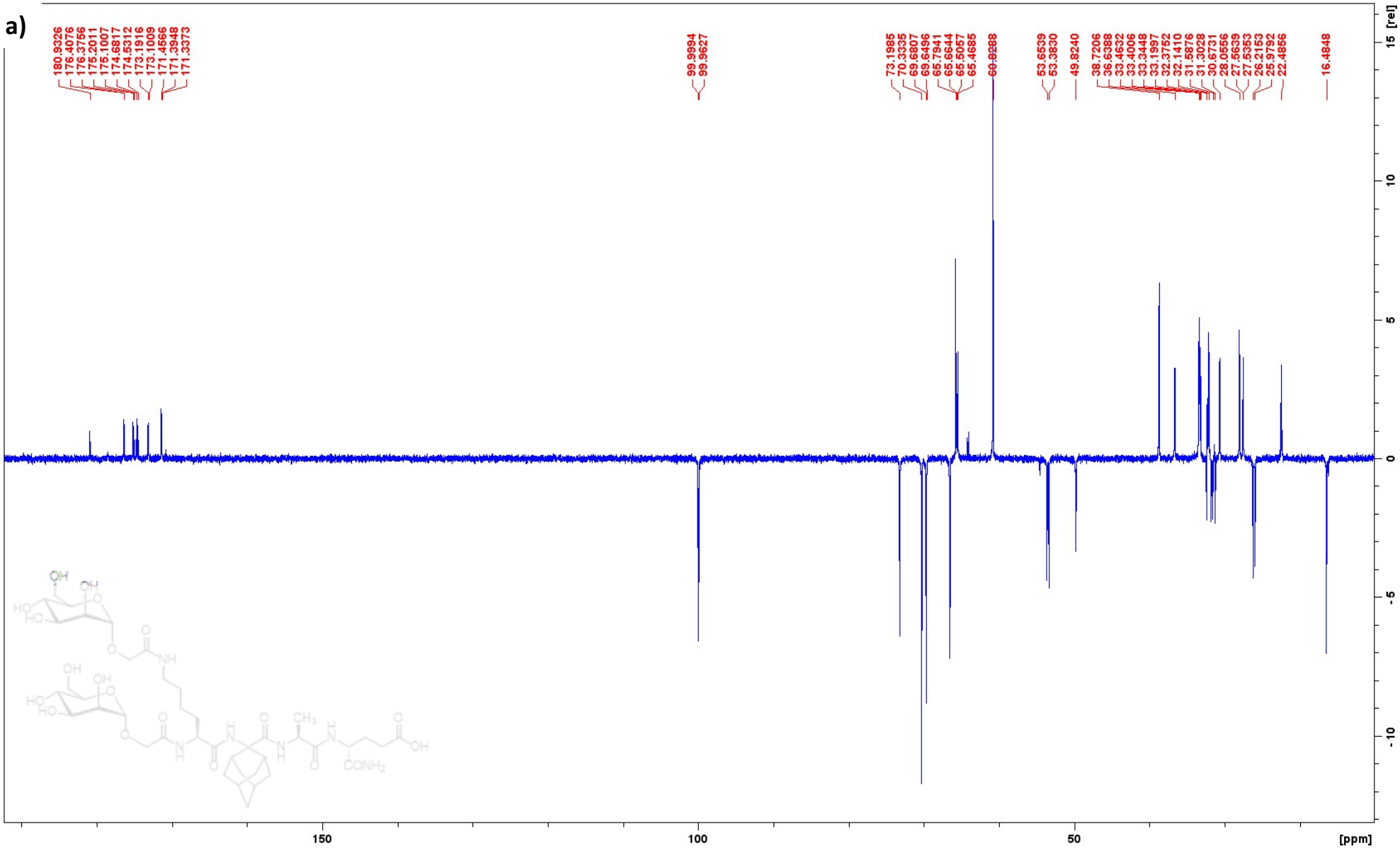
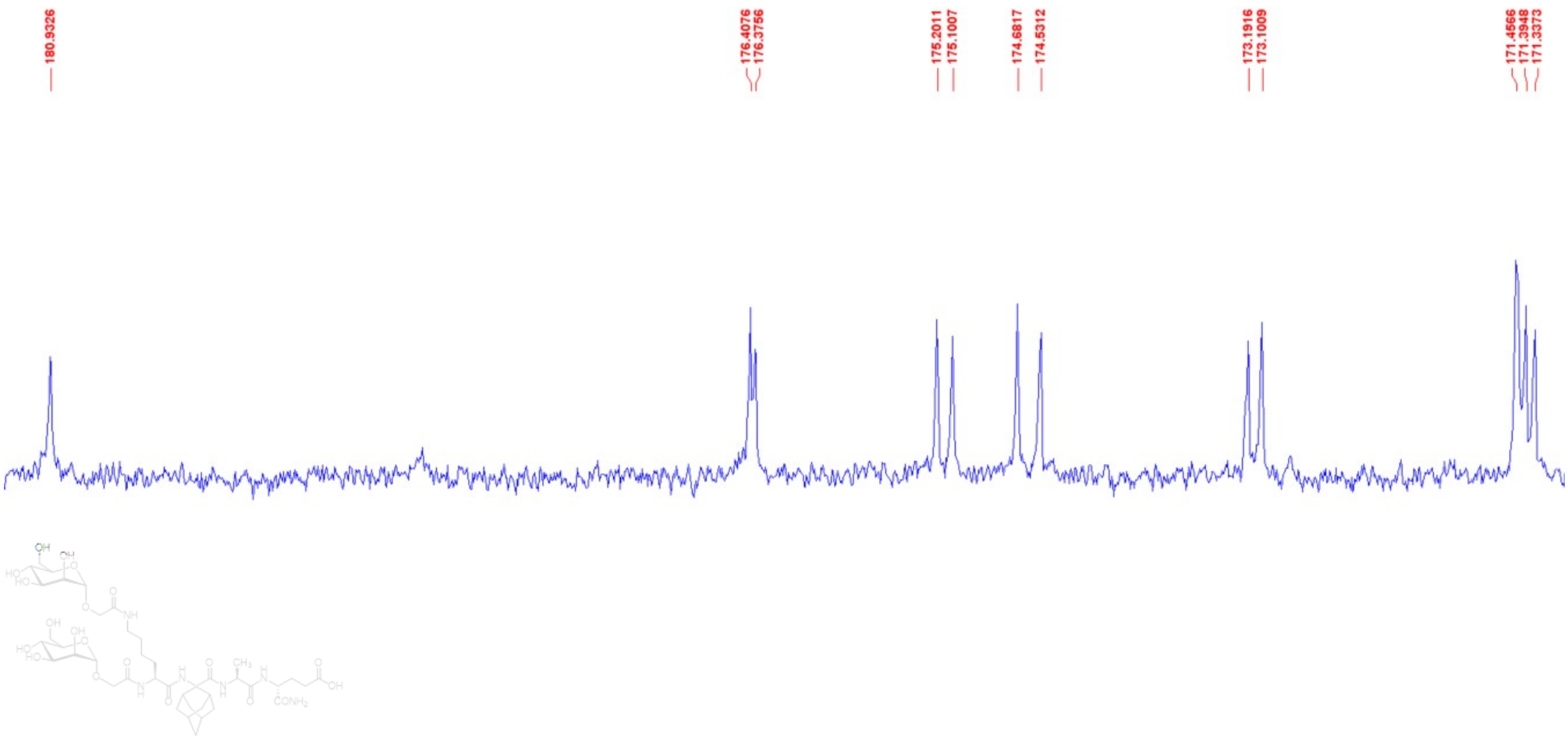


Figure S12. ^{1}H NMR spectrum of 4-{2-[([(2*S*)-2,6-di{2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)acetylamino}hexanoyl]aminoadamantane-2-carbonyl)amino]propionylamino}4-carbamoylbutanoic acid **11** (D_2O, 400 MHz)

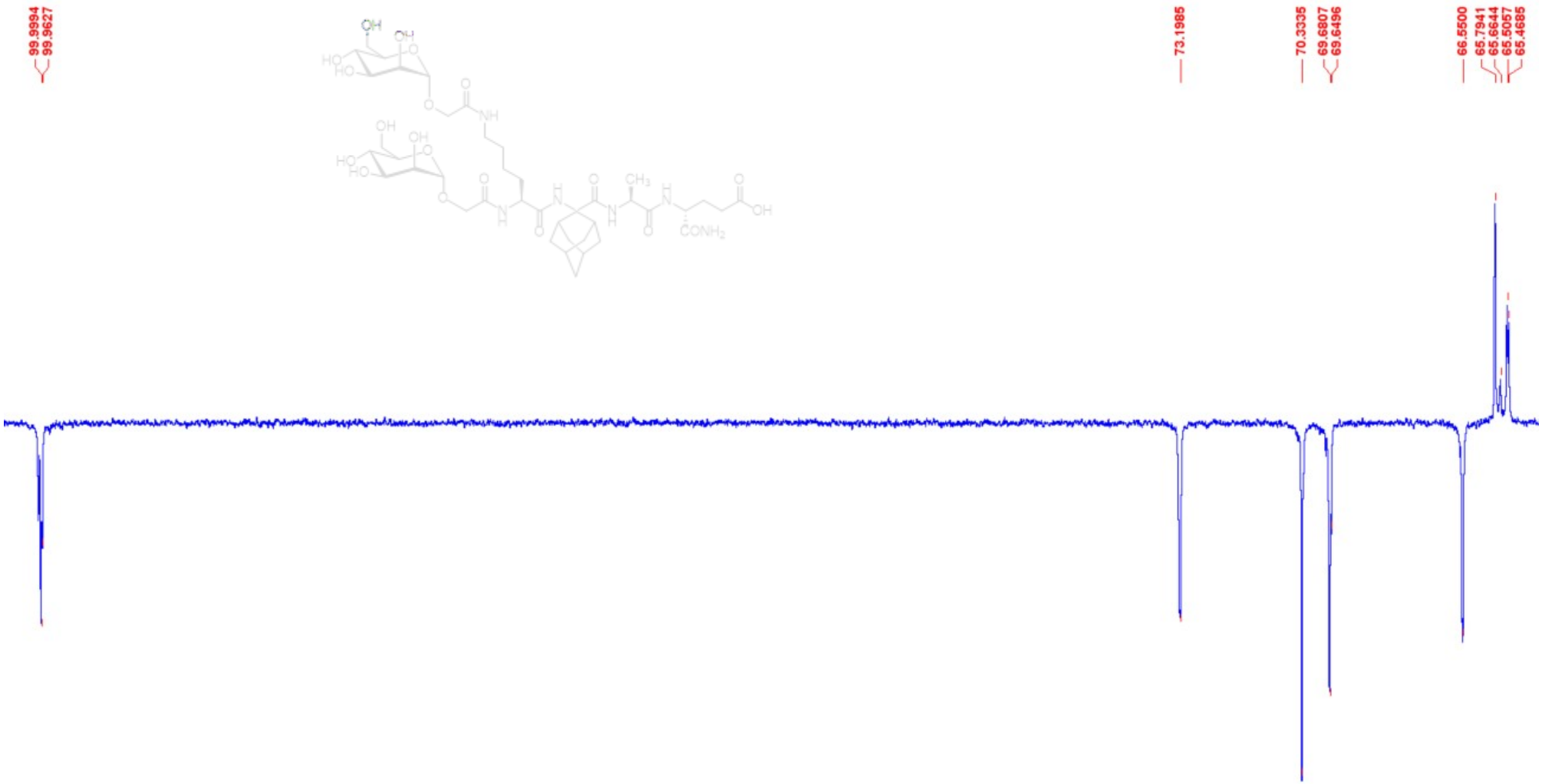
a)


180.9326
176.4076
176.3756
175.2011
175.1007
174.6817
174.5312
173.1916
173.1009
171.4566
171.3948
171.3373
99.9994
99.9627
73.1985
70.3335
69.6807
69.6496
65.7941
65.6644
65.5057
65.4685
60.8288
53.6539
53.3830
49.8240
38.7206
36.6388
33.4632
33.4006
33.3448
33.1997
32.3752
32.1410
31.5876
31.3028
30.6731
28.0556
27.5639
27.5353
26.2153
25.9792
22.4856
16.4848
15 [rel]
10
5
0
-5
-10
150
100
50
[ppm]

b)


180.9326
176.4076
176.3756
175.2011
175.1007
174.6817
174.5312
173.1916
173.1009
171.4566
171.3948
171.3373

c)


99.9994
99.9627
73.1985
70.3335
69.6807
69.6496
66.5500
65.7941
65.6644
65.5057
65.4685

d)

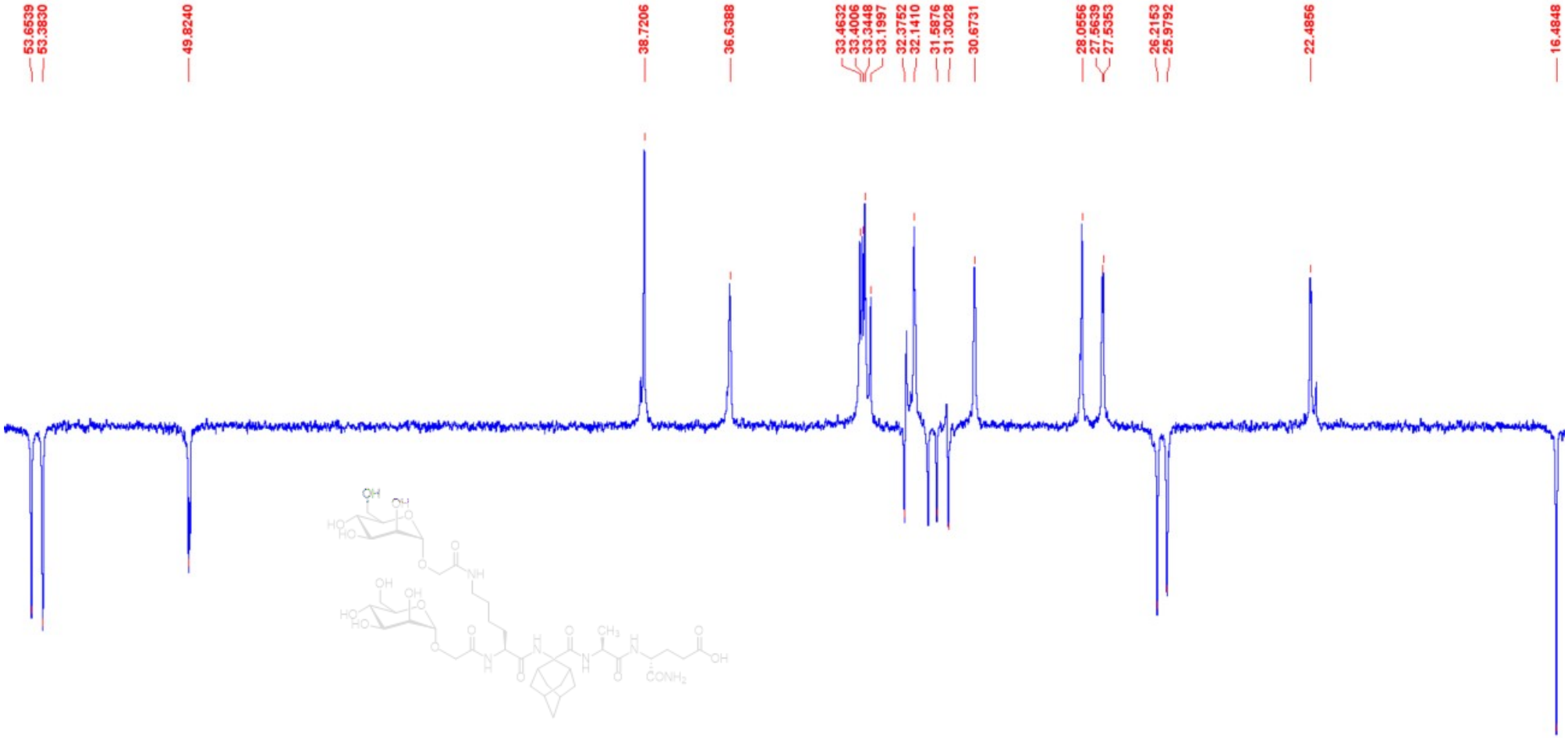


Figure S13. ^{13}C NMR spectrum of 4-{2-[([(2*S*)-2,6-di{2-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)acetylamino}hexanoyl]aminoadamantane-2-carbonyl)amino]propionylamino}4-carbamoylbutanoic acid **11** (D_2O, 100 MHz) ; a) full spectrum and enlarged regions between b) 180.93 and 171.33 ppm, c) 100.00 and 65.47 ppm and d) 53.65-16.48 ppm