ELECTRONIC SUPPLEMENTARY INFORMATION

Stereodivergent Synthesis of 5-Aminopipecolic Acids and Application in the Preparation of a Cyclic RGD Peptidomimetic as a Nanomolar $\alpha_V\beta_3$ Integrin Ligand

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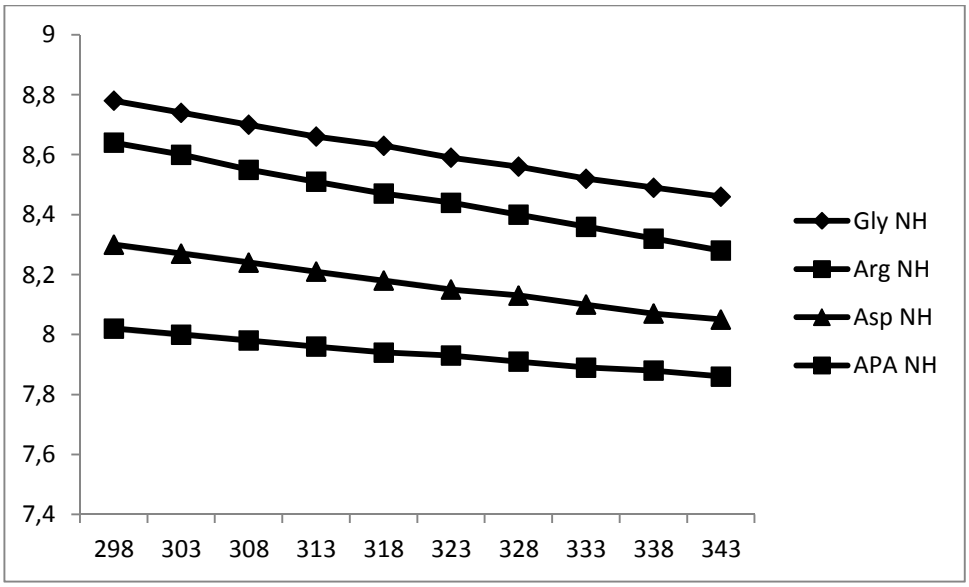
CONTENT



Gly NH = -7.6 ppb/K
Arg NH = -8.00 ppb/K
Asp NH = -5.56 ppb/K
5-APA NH = -3.56 ppb/K

Figure S1. Temperature coefficient values (ppb/K) for compound **22**

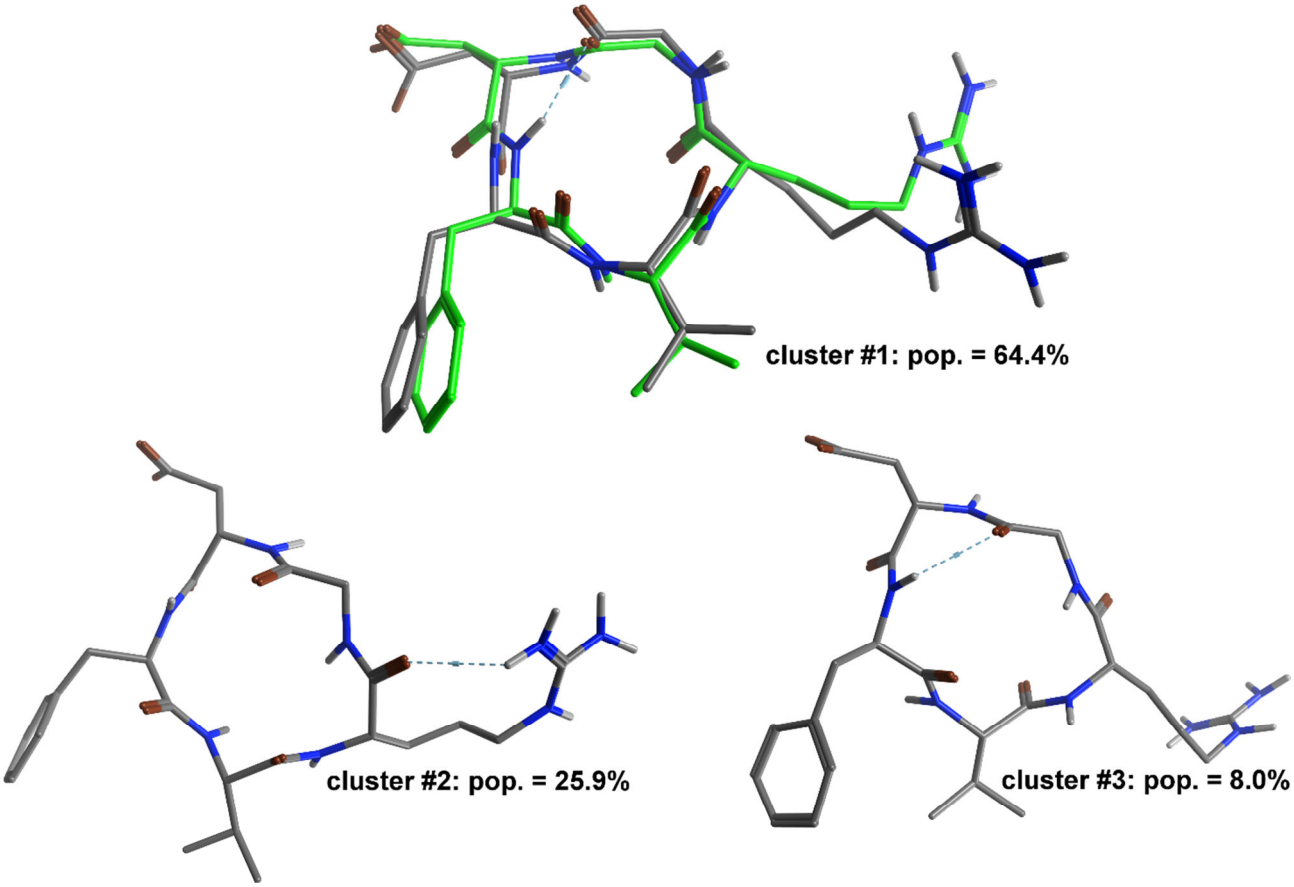
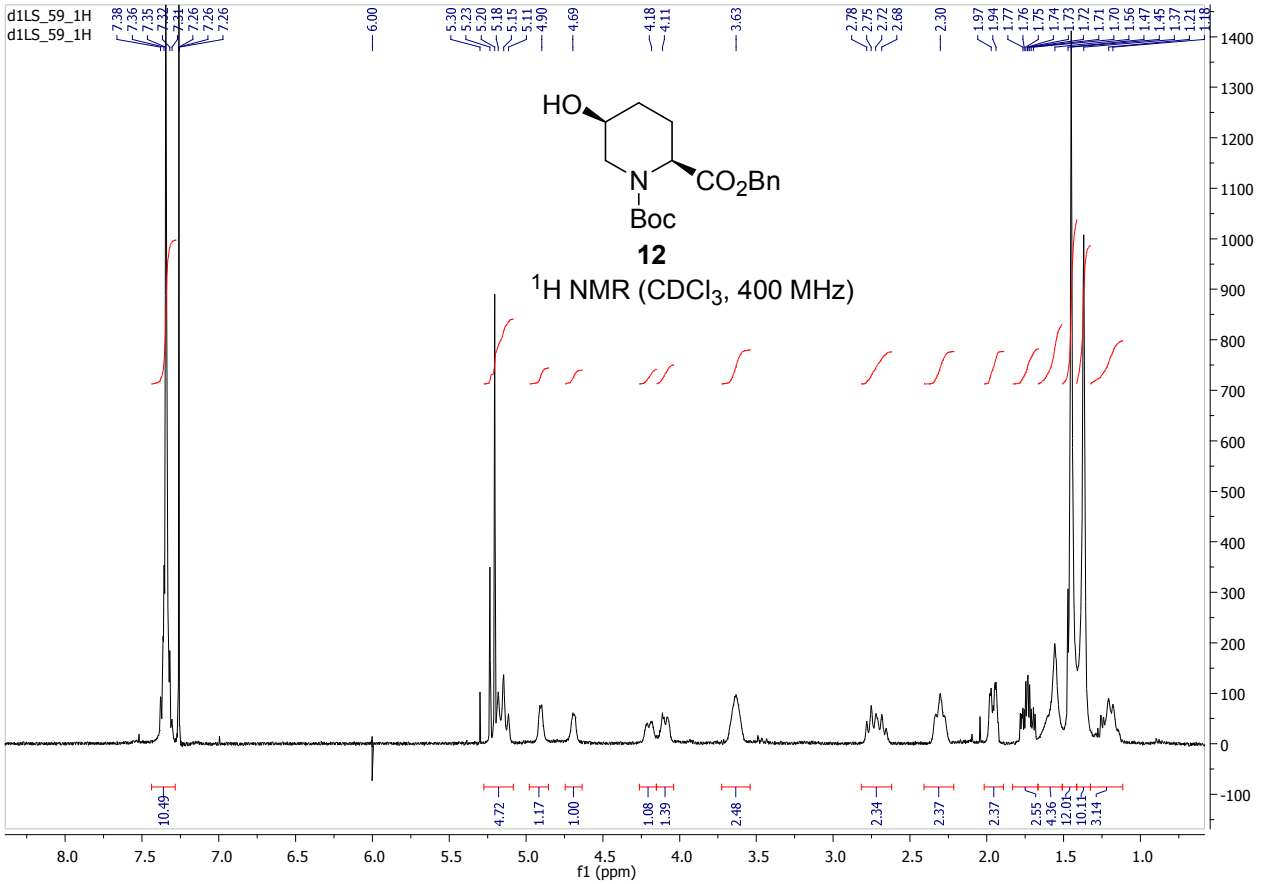


Figure S2. Principal conformations and cluster populations obtained from REMD simulations of Cilengitide, followed by cluster analysis of the final 50 ns of the 400 ns trajectory, obtained at 300 K. The binding conformation obtained from the co-crystallization of Cilengitide and $\alpha_V\beta_3$ integrin receptor is reported for comparison (green carbon atoms). The representative conformation of the principal cluster perfectly matches the X-ray structure. The main difference between the crystallographic geometry and representative conformation of cluster #2 is at the Arg-C=O and Gly-NH, that point at opposite directions, compared to X-ray. Concerning cluster #3, the main difference is observed at the MVA-C=O and Arg-NH, pointing at opposite direction respect to the X-ray geometry.

Table S1. Chemical shift values (500 MHz, 8 mM solution in D_2O/H_2O 1:9) for cyclic peptidomimetic **22**, temperature coefficients and NOE correlations. Two rotamers in a 1.4:1 ratio.

Proton	δ (ppm)	Carbon	δ (ppm)	$\Delta\delta/\Delta$T (ppb/ K)
2-H	4.55 (br s) and 4.50 (br s)	C2	53.7 and 53.8	
3-H	2.13-2.00 (m)	C3	23.5	
3-H'	2.13-2.00 (m)			
4-H (eq)	2.13-2.00 (m)	C4	22.7	
4-H' (ax)	1.21-1.11 (m)			
5-H	4.32-4.22 (m)	C5	42.6	
6-H (eq)	3.71 (d, *J* = 13.5 Hz) and 3.68 (d, *J* = 13.5 Hz)	C6	43.2 and 43.0	
6-H' (ax)	3.35 (dd, *J* = 14.0, 4.0 Hz) and 3.30 (dd, *J* = 14.0, 4.0 Hz)			
CO_2Me	3.61 (s) and 3.56 (s)	CO_2*Me*	53.2 and 53.1	
5-APA-NH	7.96 (d, *J* = 9.0 Hz) and 7.94 (d, *J* = 9.0 Hz)			-3.56
Asp CHα	4.58-4.52 (m)	Asp Cα	49.7 and 49.6	
Asp CHβ	2.84 (dd, *J* = 17.0, 7.0 Hz) and 2.83 (dd, *J* = 17.0, 7.0 Hz)	Asp Cβ	34.2 and 34.1	
Asp CHβ'	2.70 (dd, *J* = 17.0, 6.0 Hz)			
Asp N-H	8.23 (d, *J* = 8.5 Hz) and 8.22 (d, *J* = 8.5 Hz)			-5.56
Gly CHα (pro-*S*)	4.06-4.00 (m)	Gly Cα	43.9	
Gly CHα' (pro-*R*)	3.50 (dd, *J* = 15.0, 4.5 Hz)			
Gly N-H	8.73-8.66 (m, two overlying dds)			-7.6
Arg CHα	4.00-3.94 (m)	Arg Cα	55.7 and 55.6	
Arg CHβ and CHβ'	1.77-1.57 (m)	Arg Cβ	26.2 and 26.1	
Arg CHγ and CHγ'	1.77-1.57 (m) and 1.56-1.46 (m)	Arg Cγ	24.1	
Arg CHδ and CHδ'	3.17-3.11 (m)	Arg Cδ	40.2	
Arg N-H	8.56 (d, *J* = 12 Hz) and 8.55 (d, *J* = 12 Hz)			-8.0
Arg N-H (guanidinium)	7.11 (t, *J* = 6.0 Hz)			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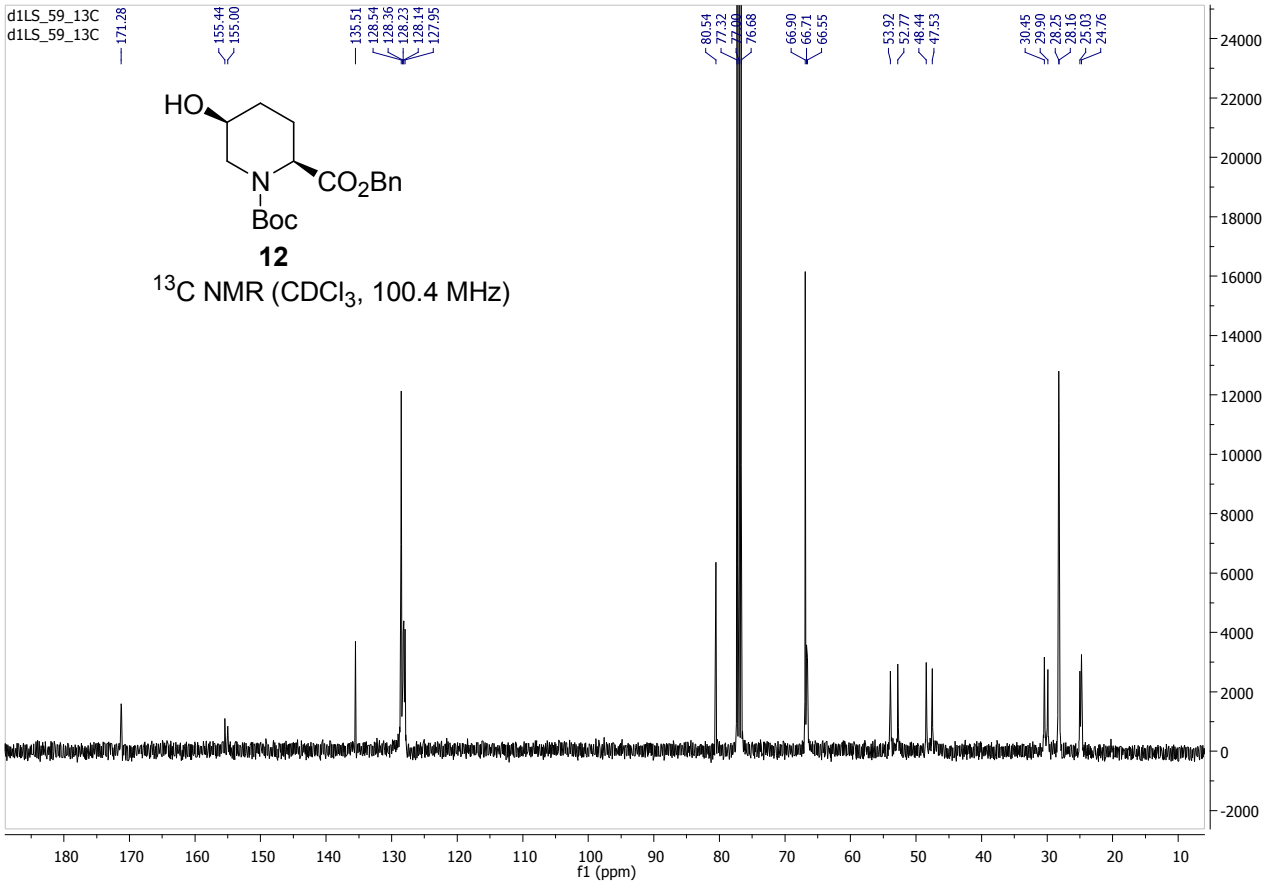
d1LS_59_1H
HO
N
CO2Bn
Boc
12
1H NMR (CDCl3, 400 MHz)
f1 (ppm)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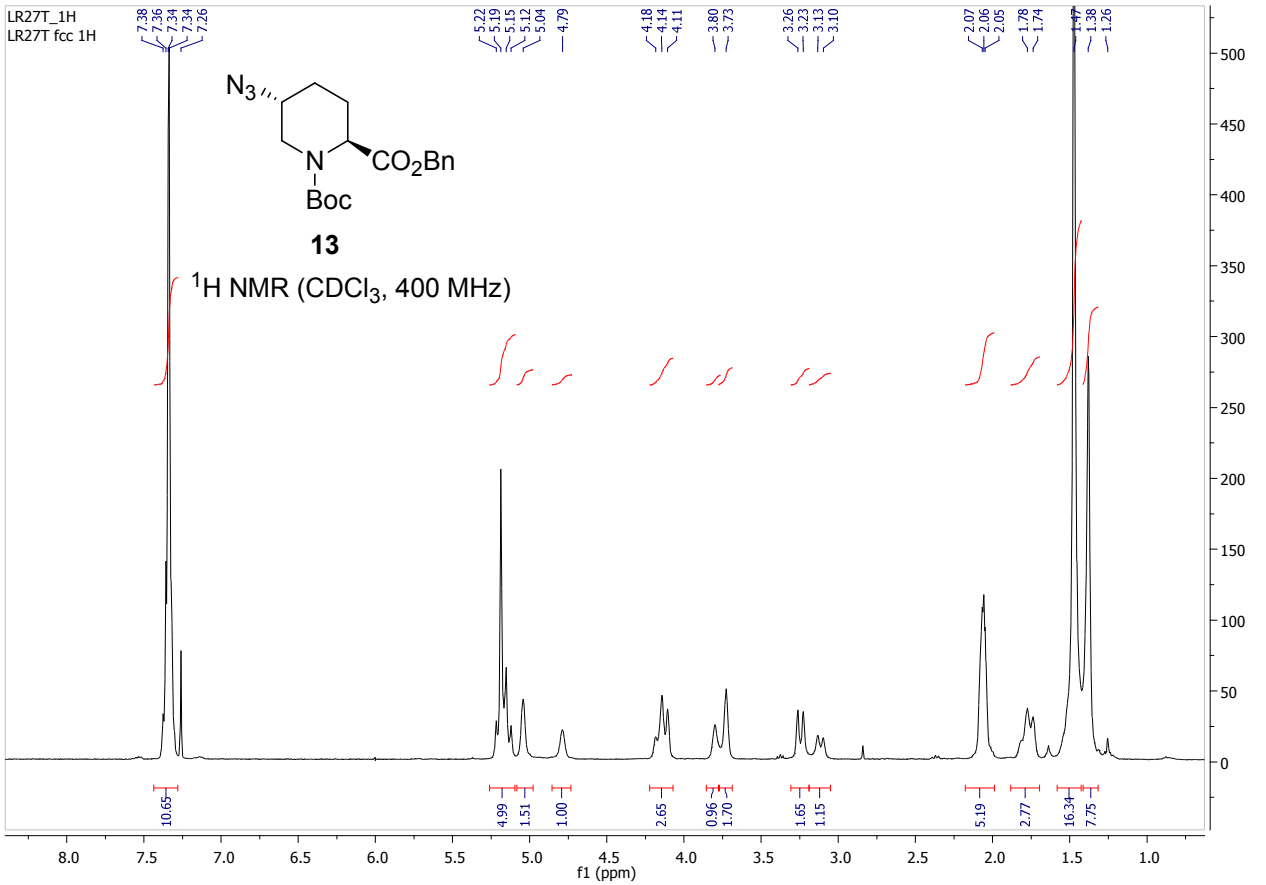
d1LS_59_13C
HO
N
CO2Bn
Boc
12
13C NMR (CDCl3, 100.4 MHz)
f1 (ppm)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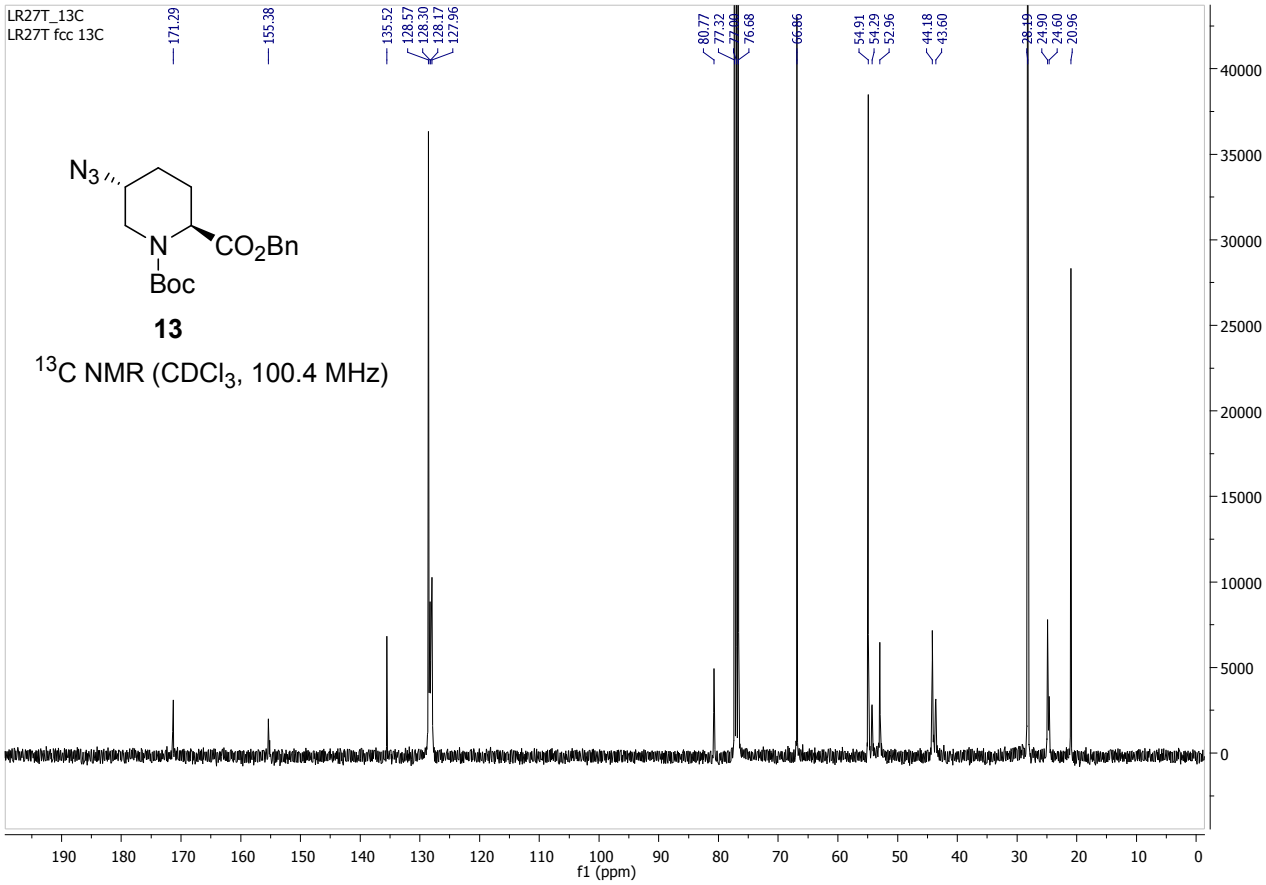
N3
N
CO2Bn
Boc
13
1H NMR (CDCl3, 400 MHz)
f1 (ppm)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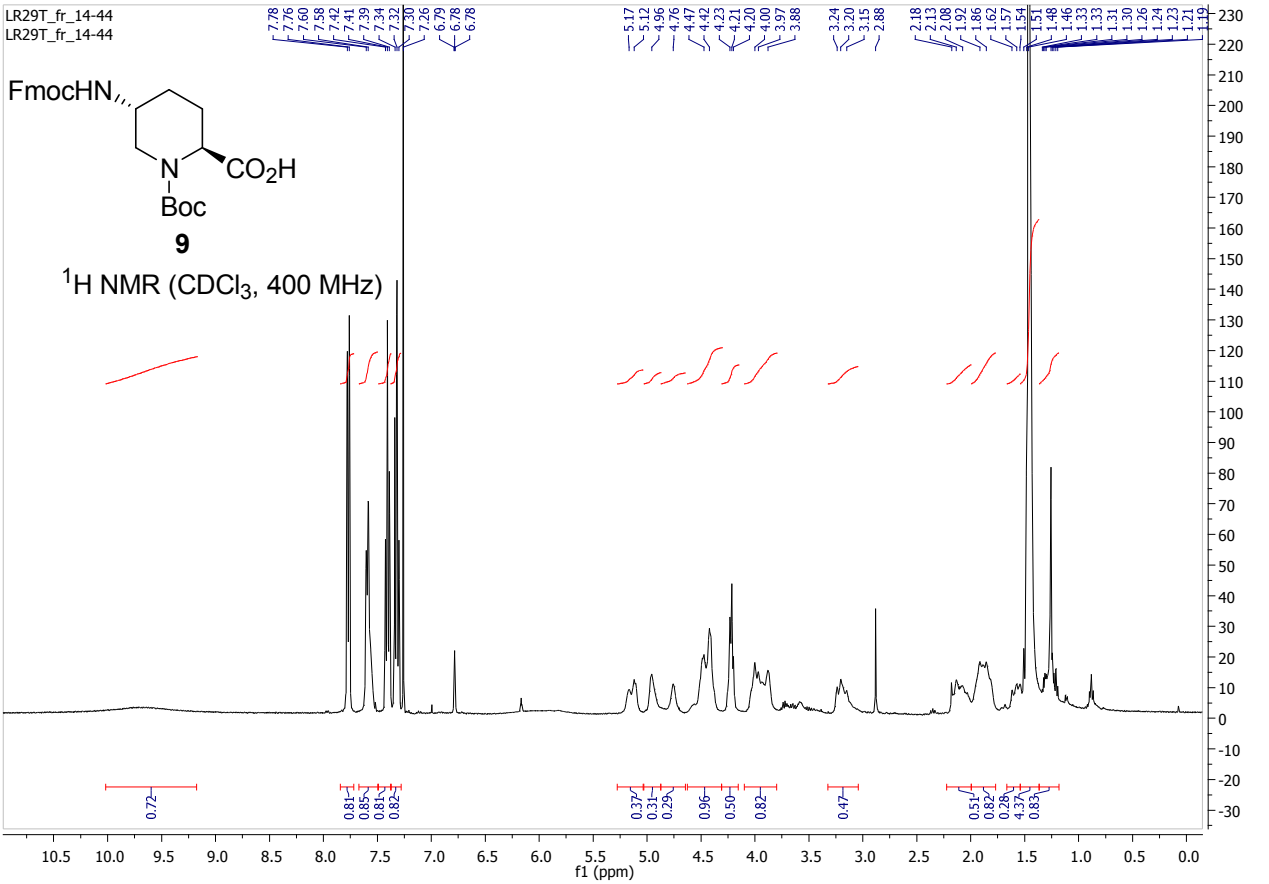
LR27T fcc 13C
N3
N
CO2Bn
Boc
13
13C NMR (CDCl3, 100.4 MHz)
f1 (ppm)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LR29T_fr_14-44
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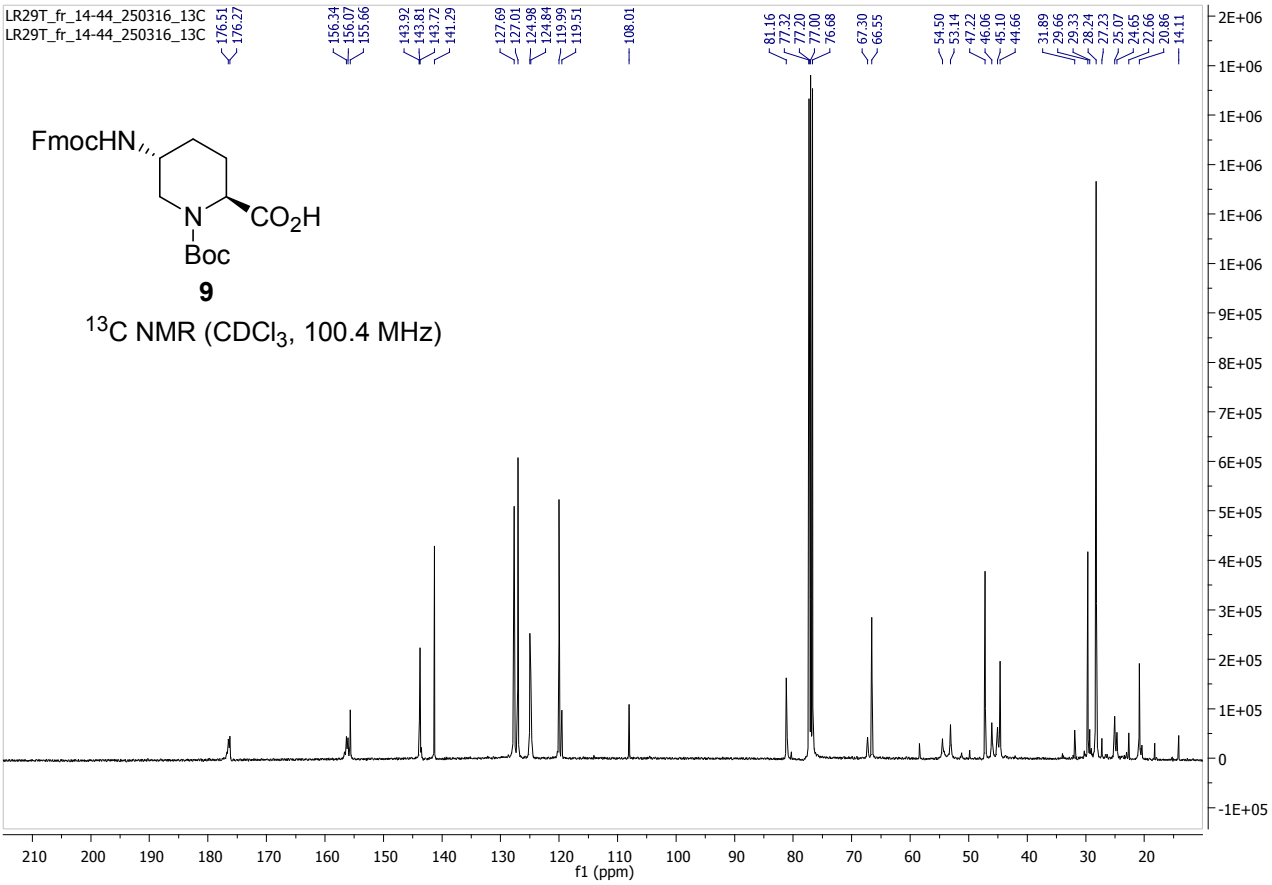
N
Boc
CO2H
9
1H NMR (CDCl3, 400 MHz)
f1 (ppm)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Boc
CO2H
9
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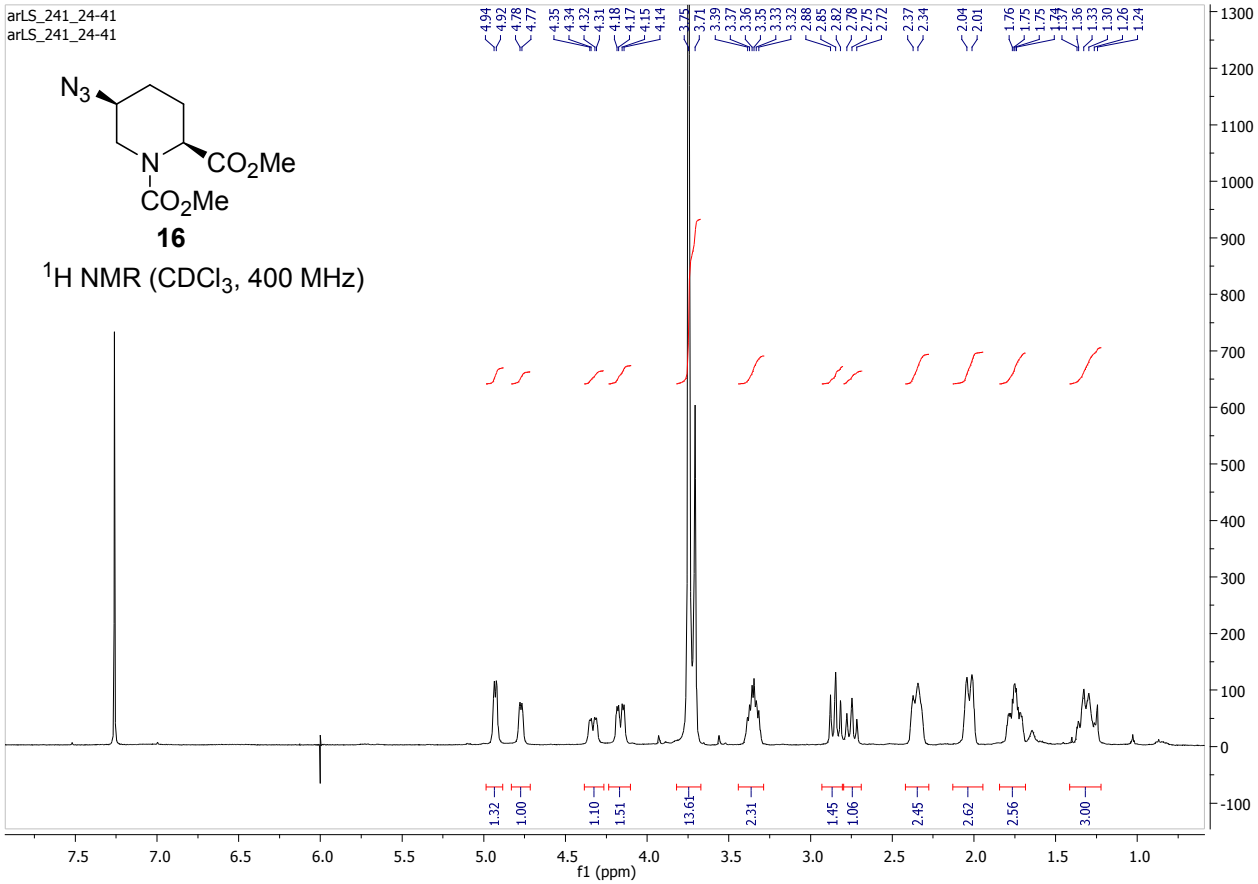
f1 (ppm)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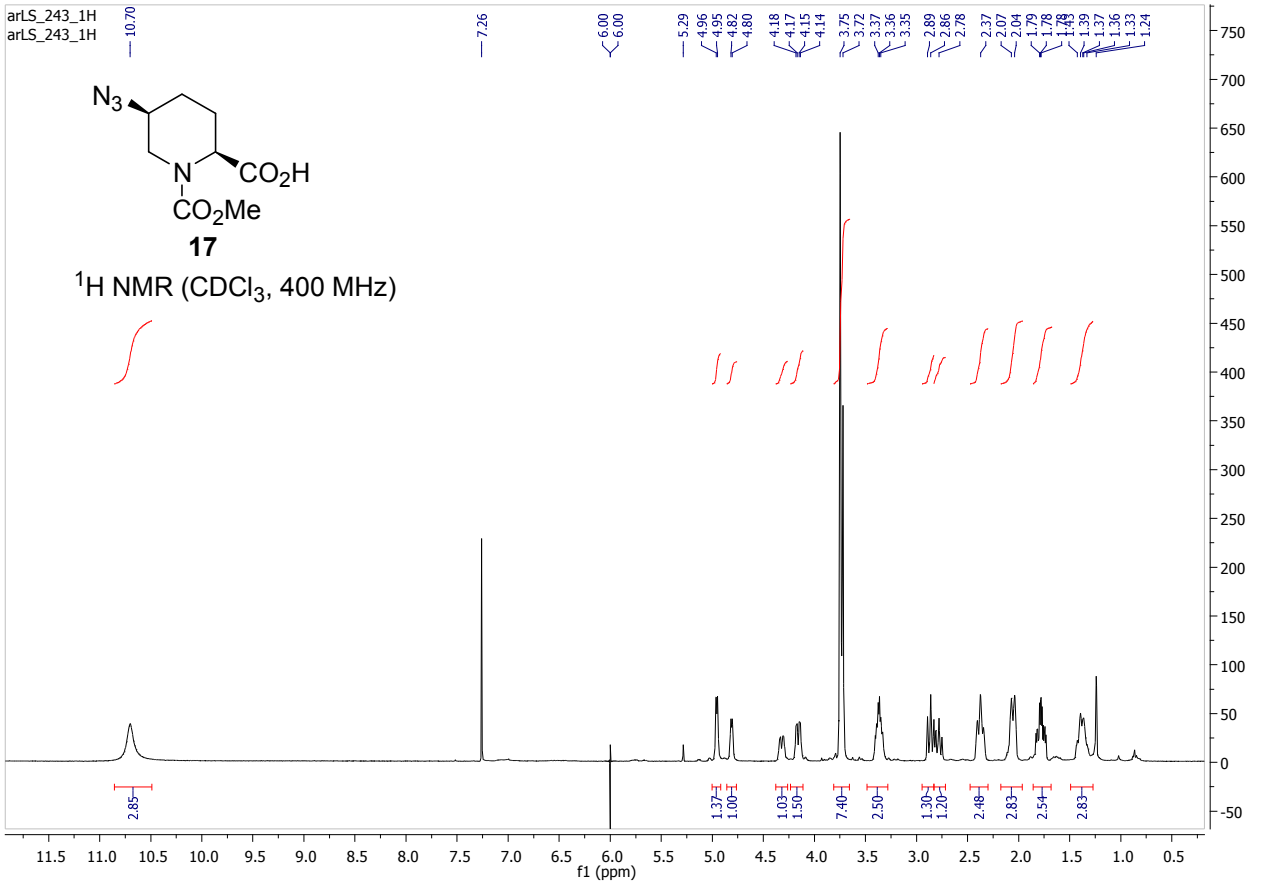
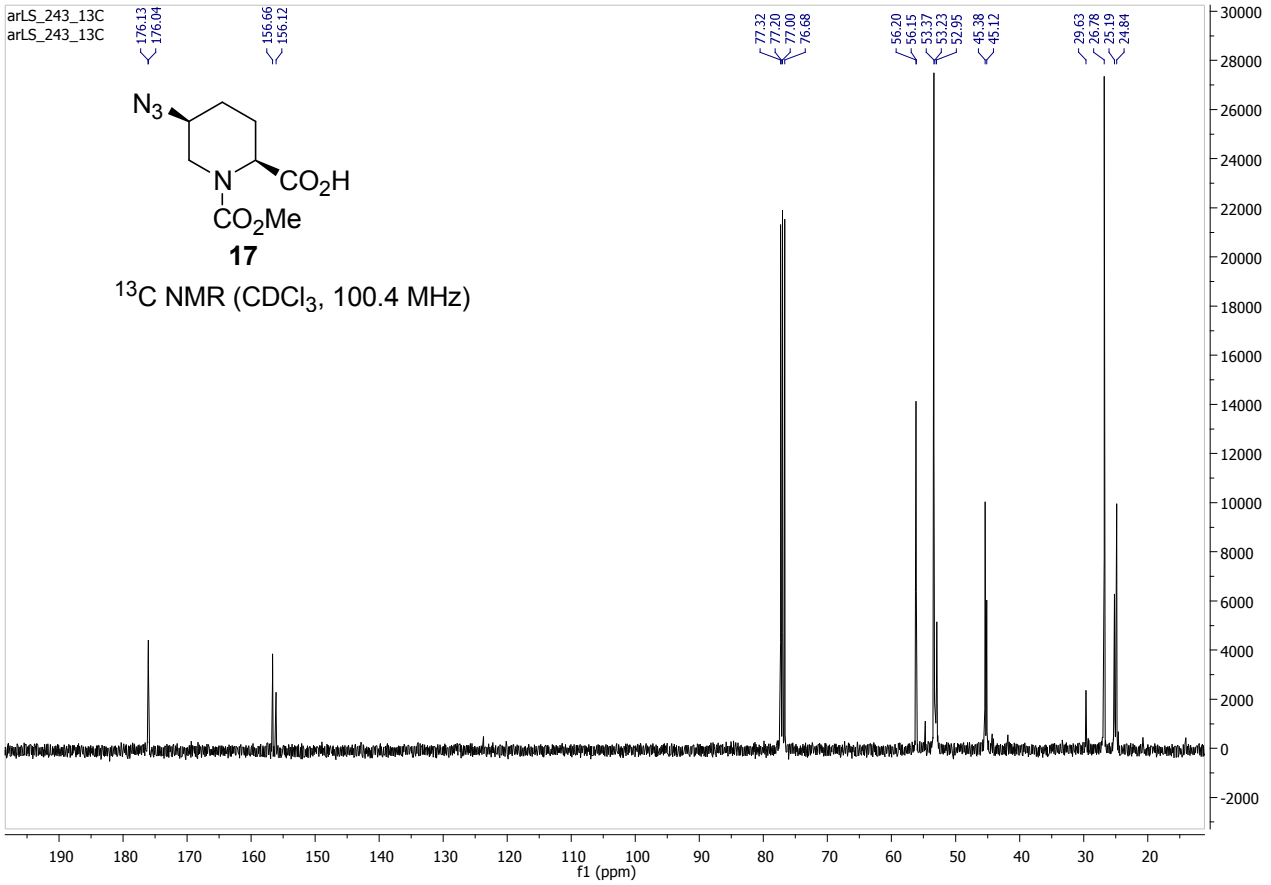
arLS_241_24-41
N3
N
CO2Me
CO2Me
16
1H NMR (CDCl3, 400 MHz)
f1 (ppm)


arLS_243_1H
arLS_243_1H
10.70
7.26
6.00
6.00
5.29
4.96
4.95
4.82
4.80
4.18
4.17
4.15
4.14
3.75
3.72
3.37
3.36
3.35
2.89
2.86
2.78
2.37
2.07
2.04
1.79
1.78
1.39
1.37
1.36
1.33
1.24
N3
N
CO2H
CO2Me
17
1H NMR (CDCl3, 400 MHz)
2.85
1.37
1.00
1.03
1.50
7.40
2.50
1.30
1.20
2.48
2.83
2.54
2.83
f1 (ppm)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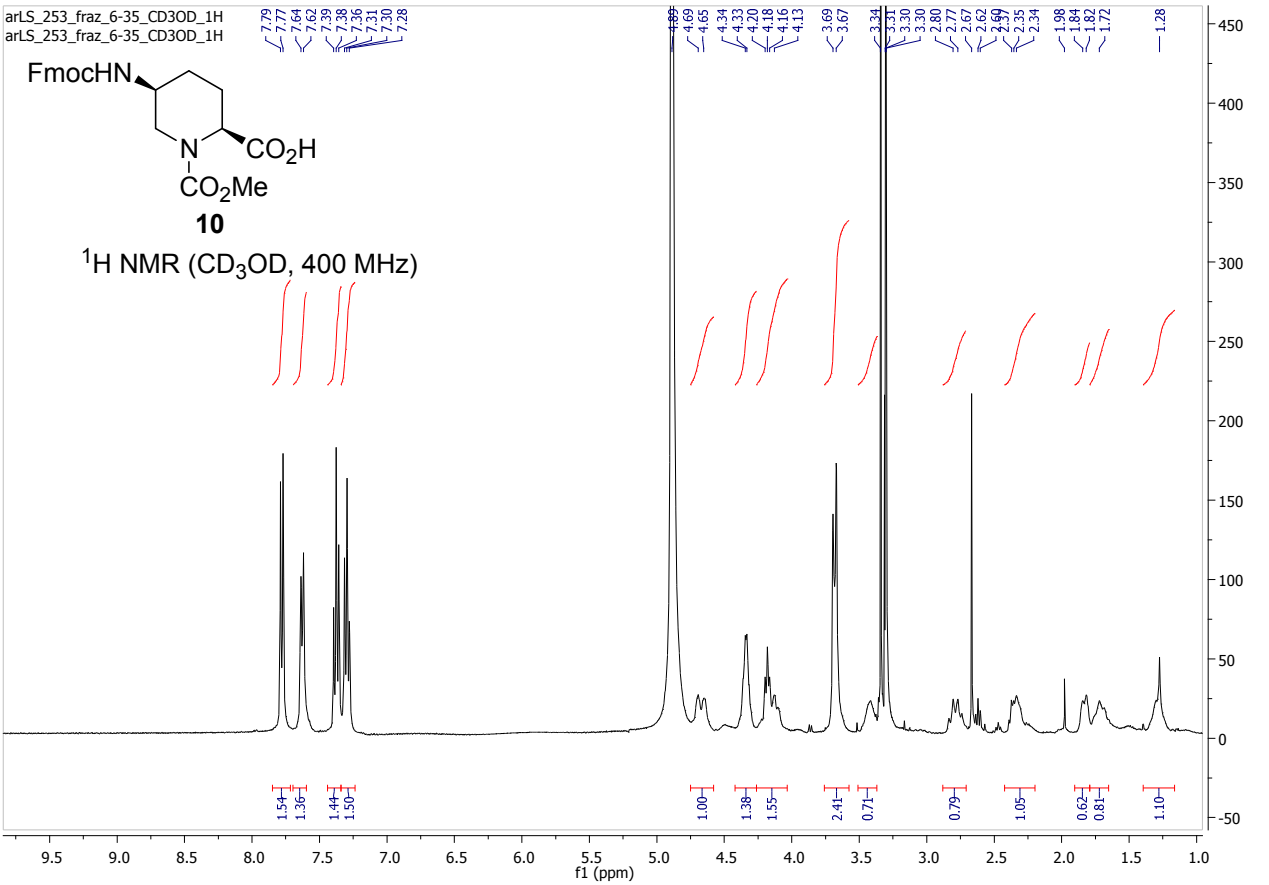
arLS_243_13C
176.13
176.04
156.66
156.12
77.32
77.20
77.00
76.68
56.20
56.15
53.37
53.23
52.95
45.38
45.12
29.63
26.78
25.19
24.84
N3
N
CO2H
CO2Me
17
13C NMR (CDCl3, 100.4 MHz)
f1 (ppm)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N
CO2H
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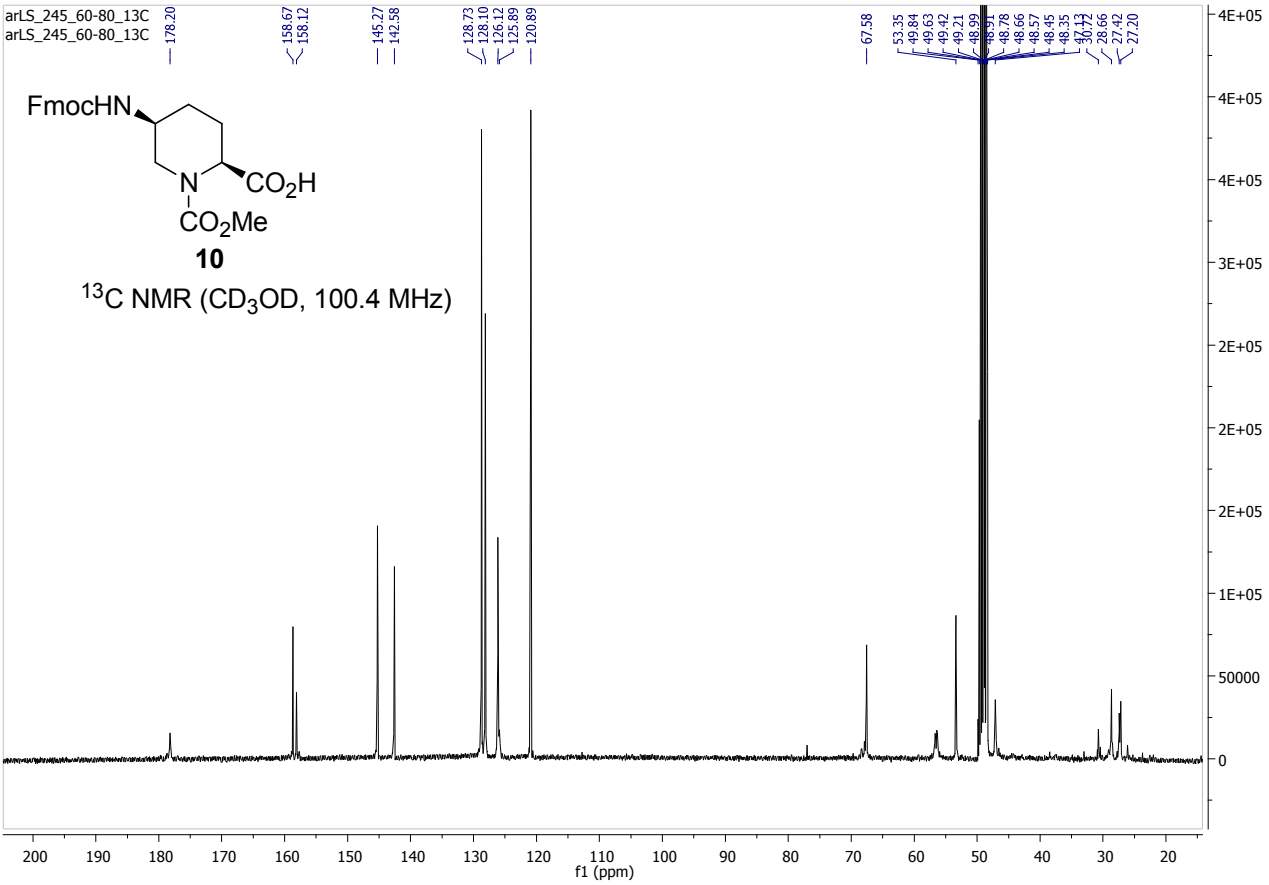
10
1H NMR (CD3OD, 400 MHz)
f1 (ppm)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CO2H
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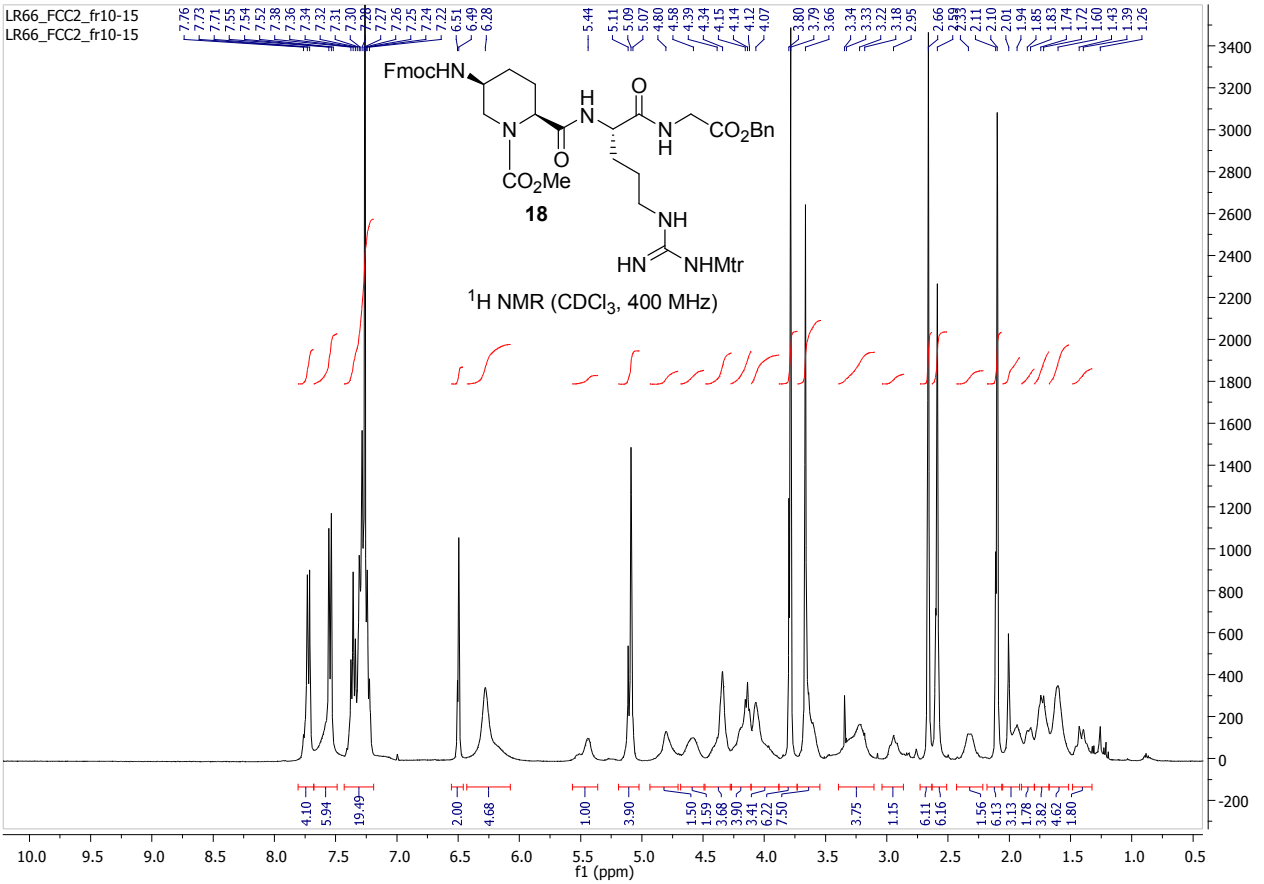
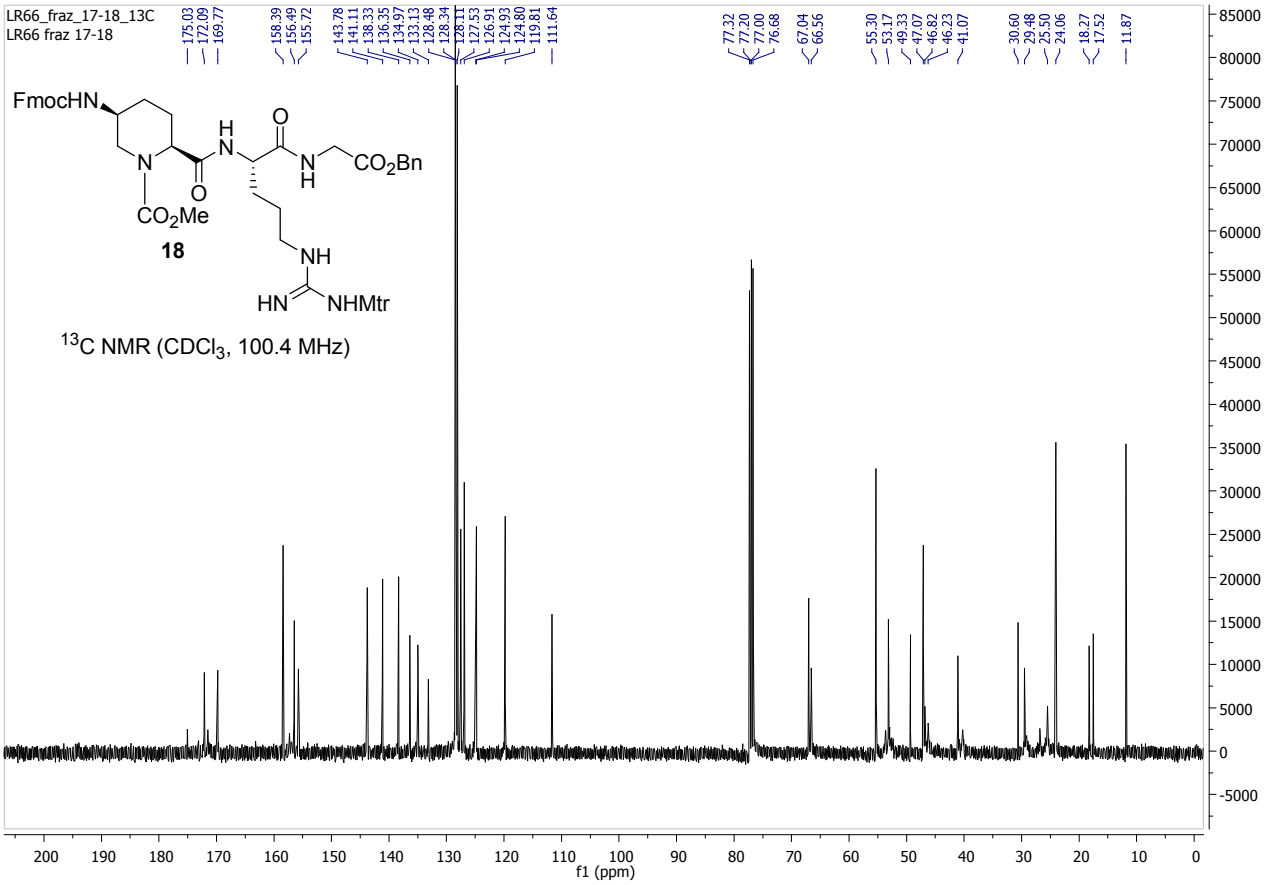
f1 (ppm)


LR66_FCC2_fr10-15
LR66_FCC2_fr10-15
FmocHN
CO2Me
18
CO2Bn
NH
HN
NHMtr
1H NMR (CDCl3, 400 MHz)
f1 (ppm)


LR66_fraz_17-18_13C
LR66 fraz 17-18
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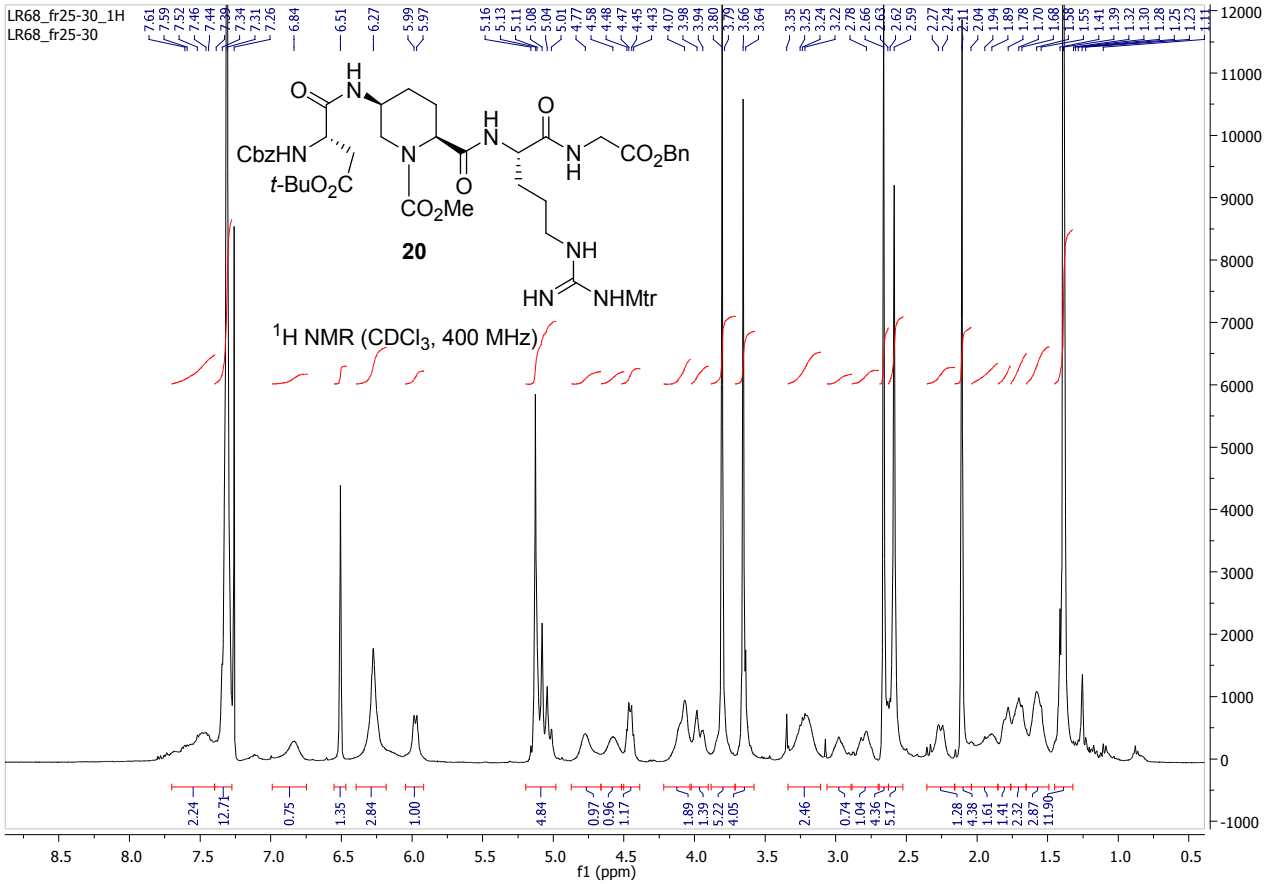
CO2Me
18
CO2Bn
NH
HN
NHMtr
13C NMR (CDCl3, 100.4 MHz)
f1 (ppm)


LR68_fr25-30_1H
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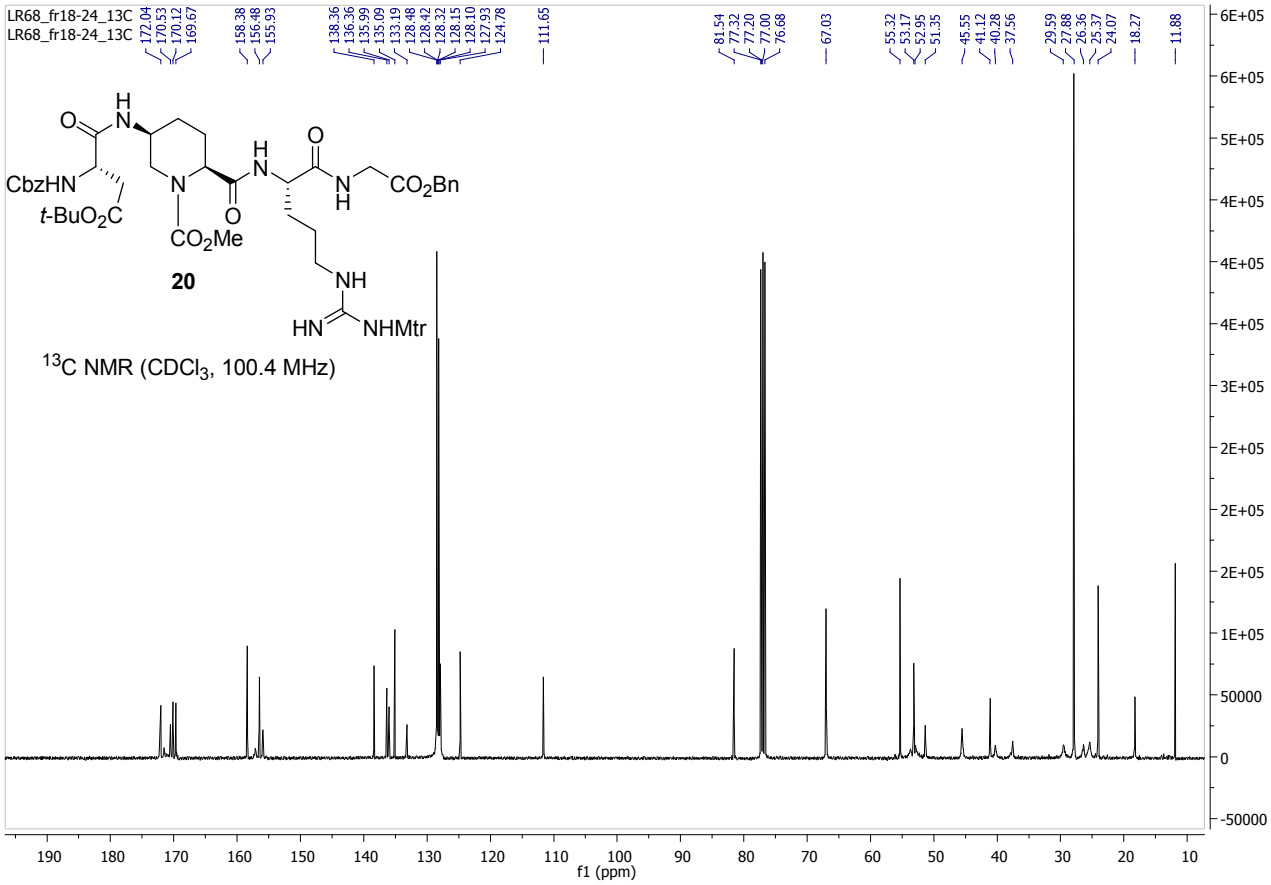
20
^{1}H NMR ($CDCl_3$, 400 MHz)
f1 (ppm)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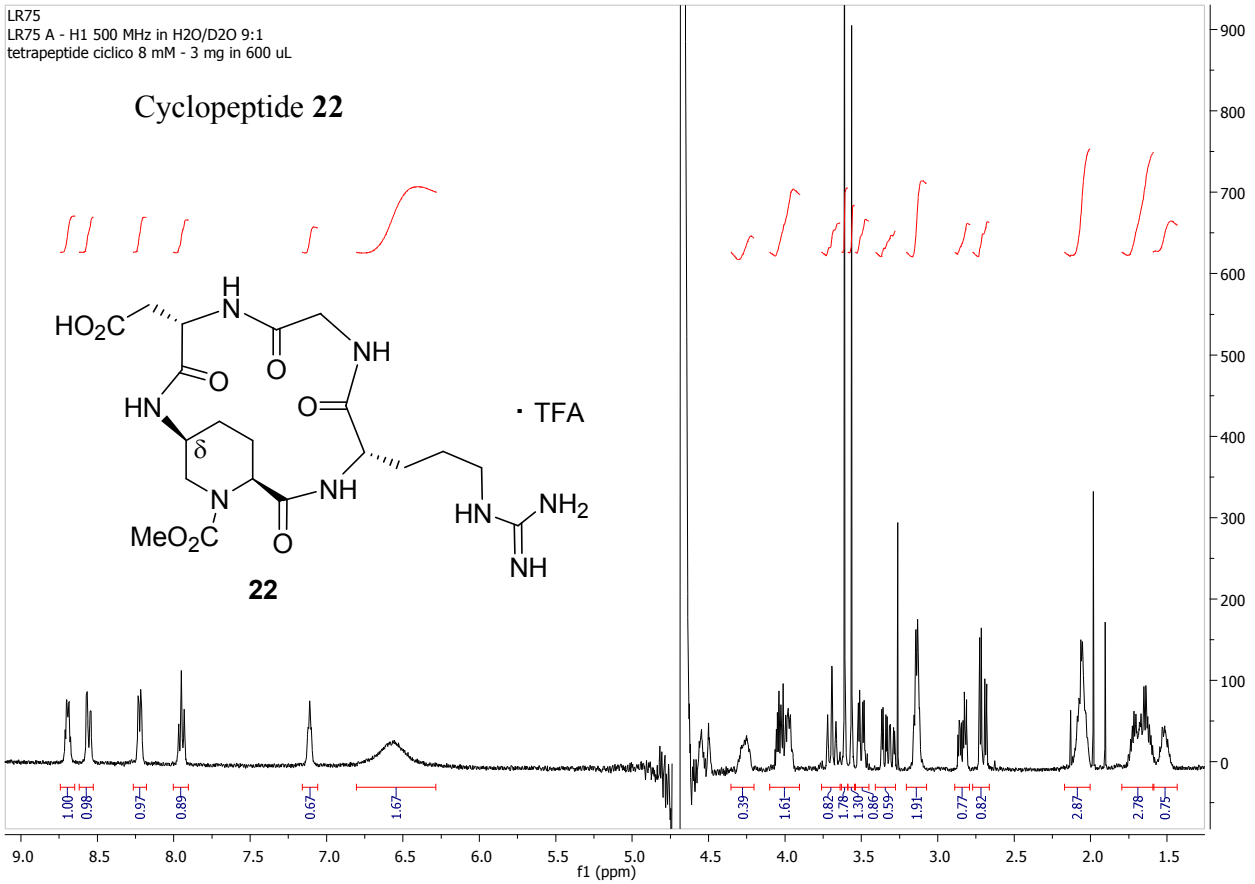
LR68_fr18-24_13C
20
^{13}C NMR ($CDCl_3$, 100.4 MHz)
f1 (ppm)


LR75
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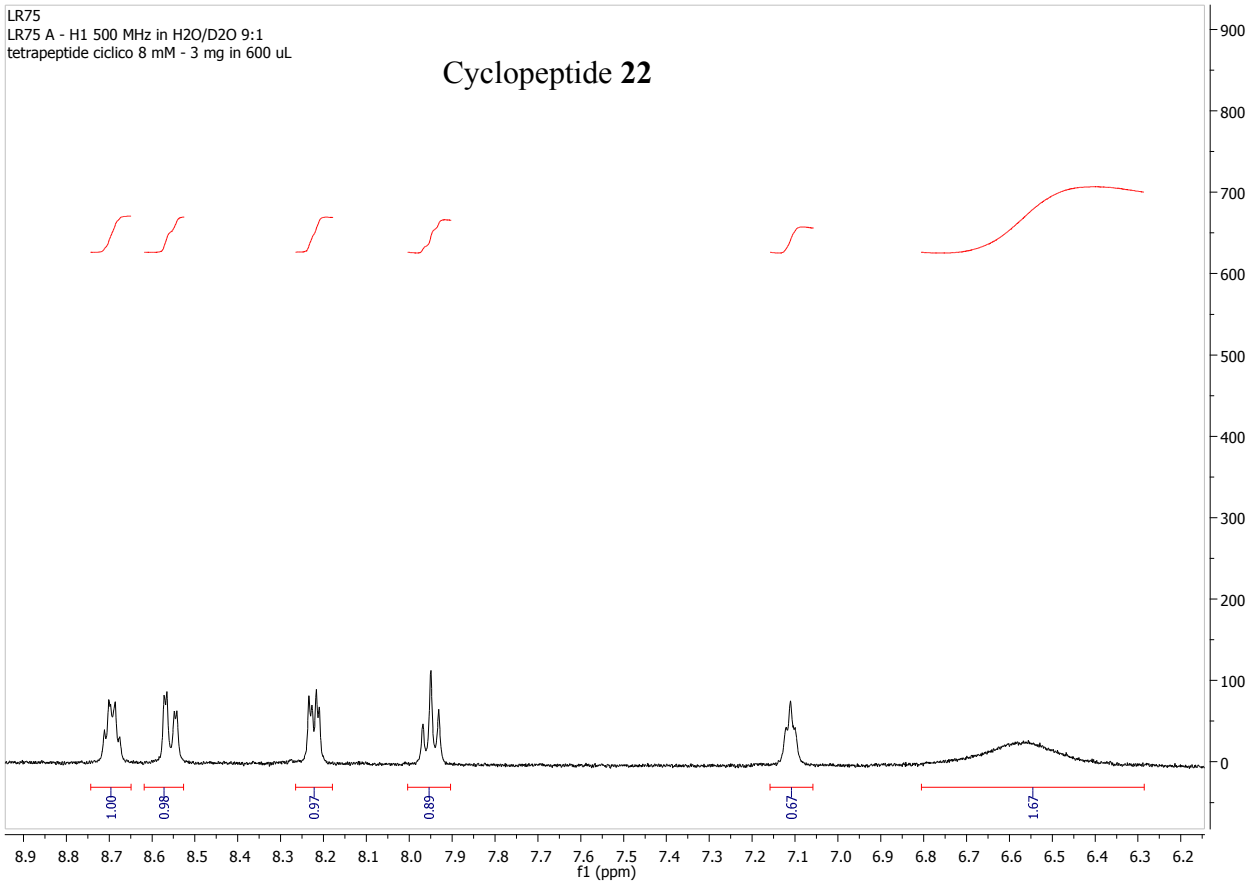
tetrapeptide ciclico 8 mM - 3 mg in 600 uL
Cyclopeptide 22
HO2C
MeO2C
HN
NH
NH2
· TFA
δ
22
1.00
0.98
0.97
0.89
0.67
1.67
0.39
1.61
0.82
1.78
1.30
0.86
0.59
1.91
0.77
0.82
2.87
2.78
0.75
f1 (ppm)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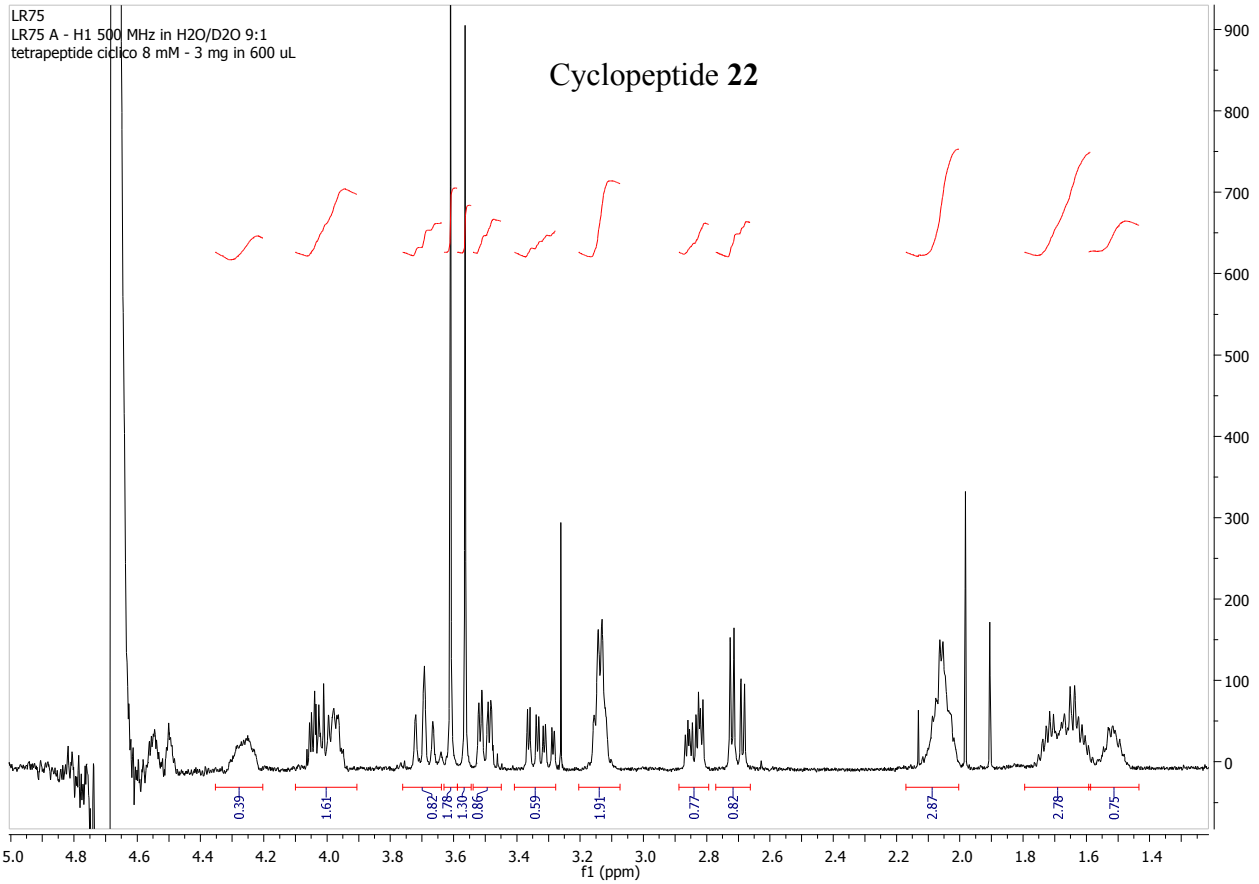
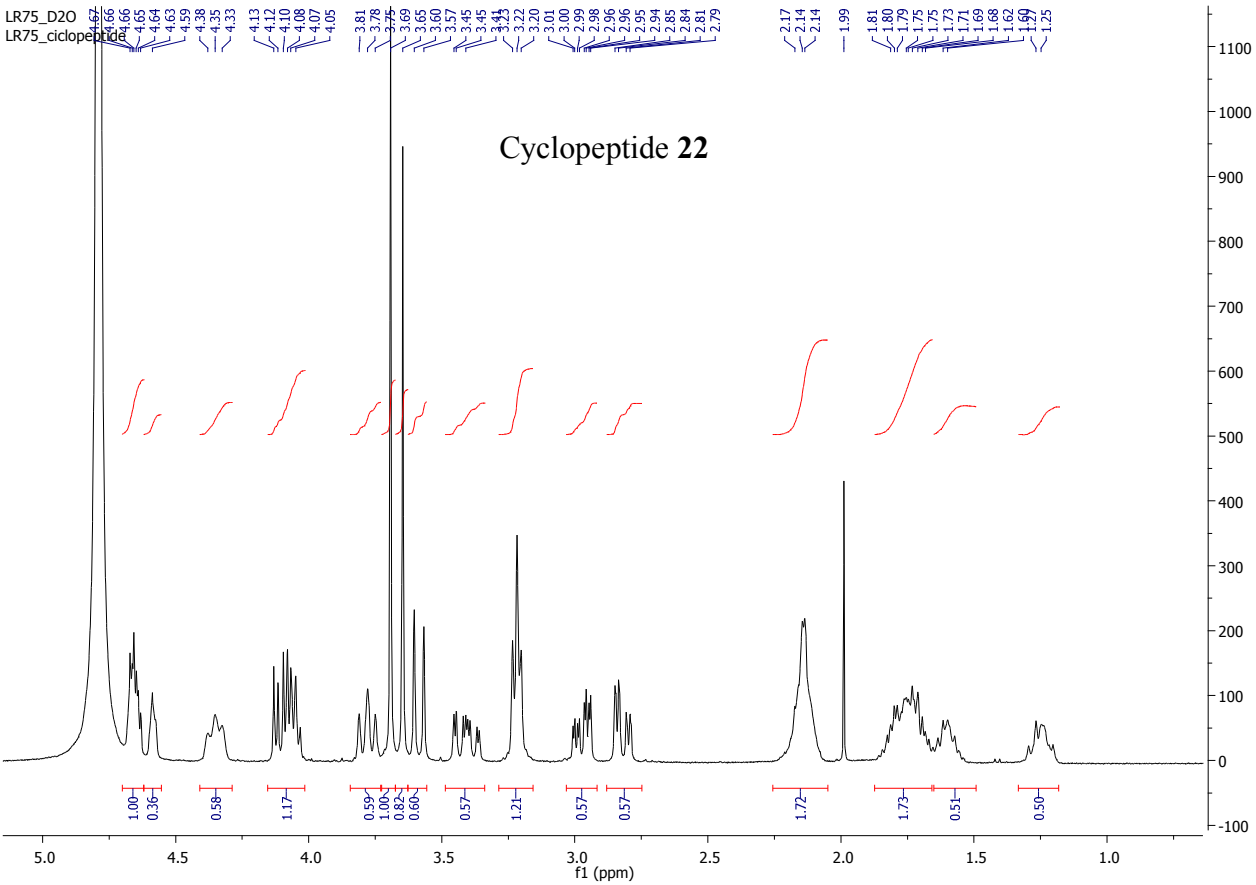
LR75 A - H1 500 MHz in H2O/D2O 9:1
tetrapeptide ciclico 8 mM - 3 mg in 600 uL
Cyclopeptide 22
1.00
0.98
0.97
0.89
0.67
1.67
f1 (ppm)


LR75
LR75 A - H1 500 MHz in H2O/D2O 9:1
tetrapeptide ciclico 8 mM - 3 mg in 600 uL
Cyclopeptide 22
0.39
1.61
0.82
1.78
1.30
0.86
0.59
1.91
0.77
0.82
2.87
2.78
0.75
f1 (ppm)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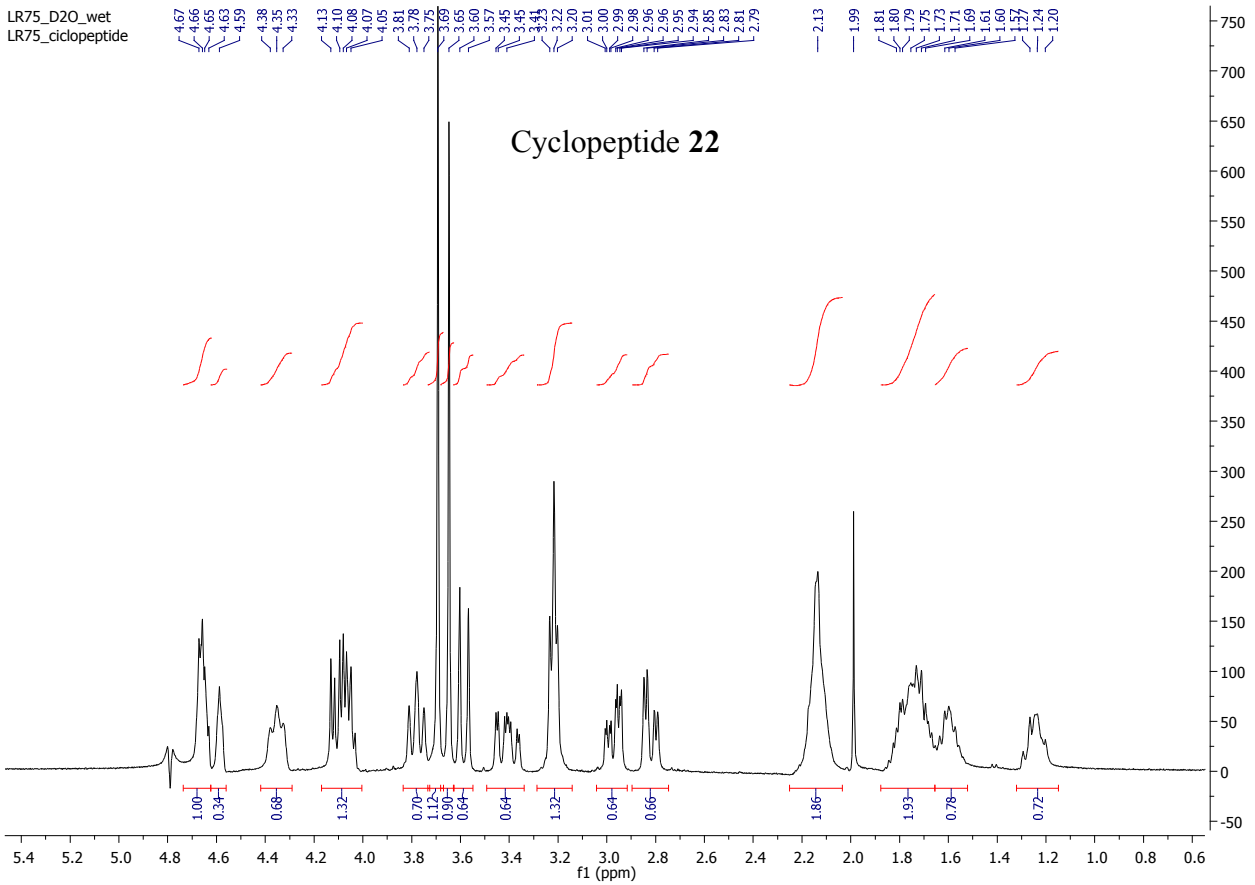
Cyclopeptide **22**
f1 (ppm)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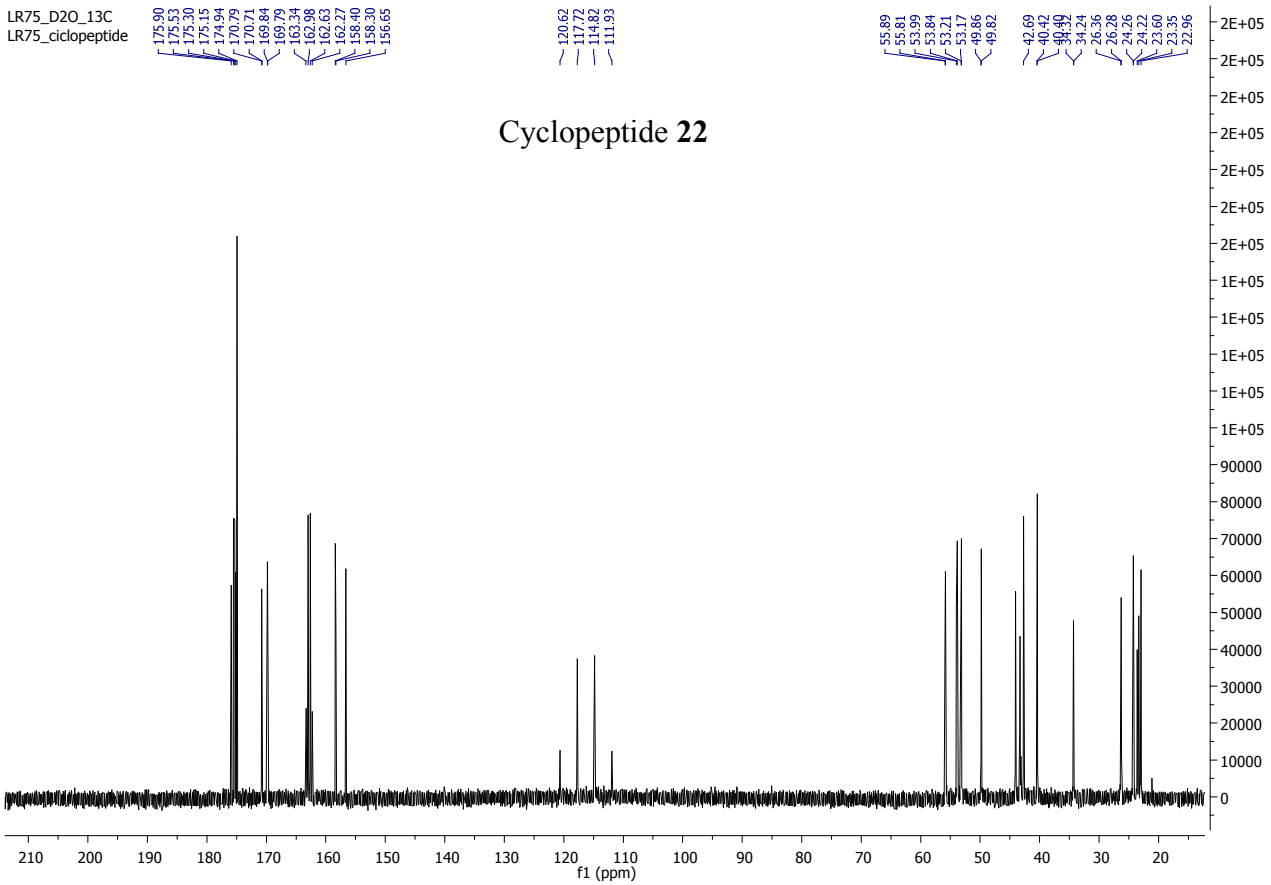
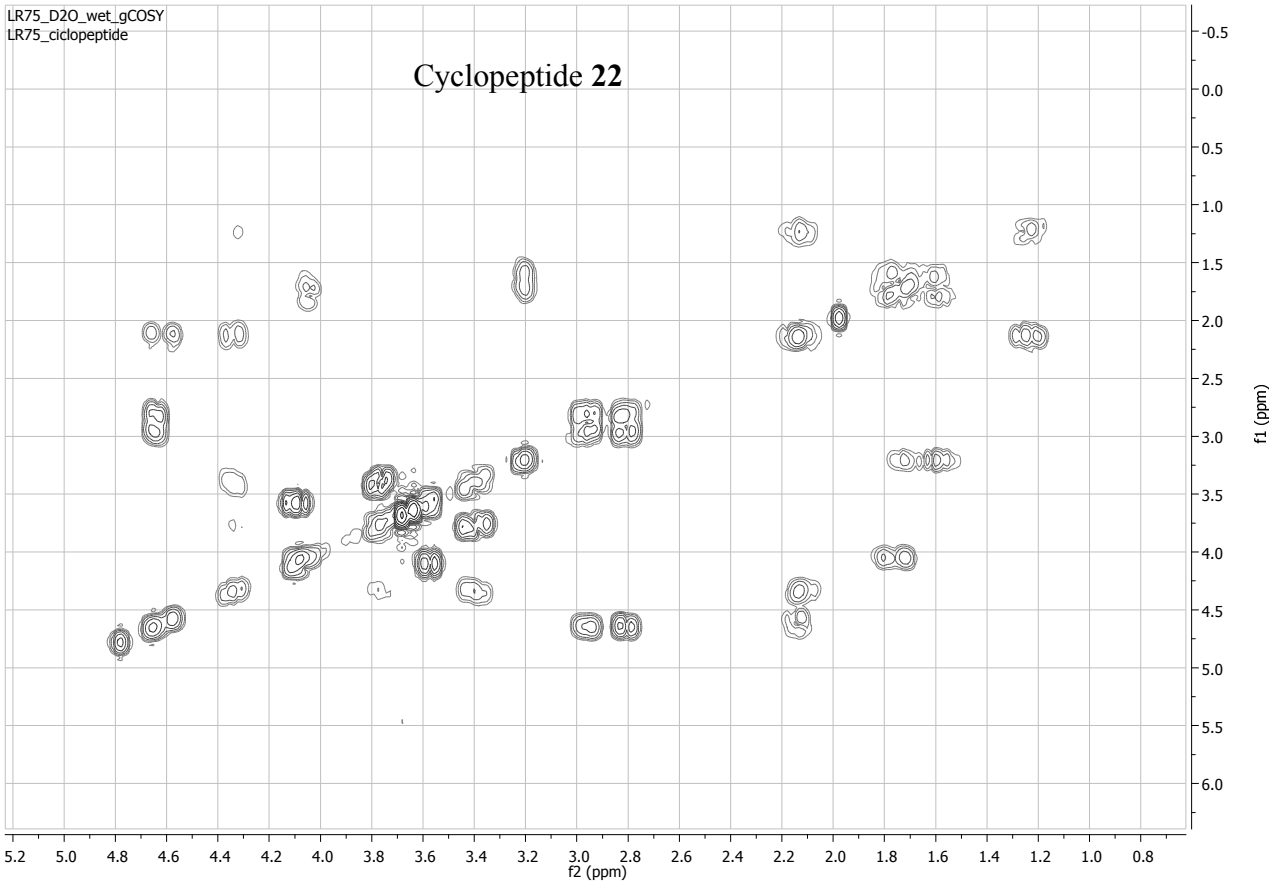
LR75_ciclopeptide
Cyclopeptide 22
f1 (ppm)



Cyclopeptide **22**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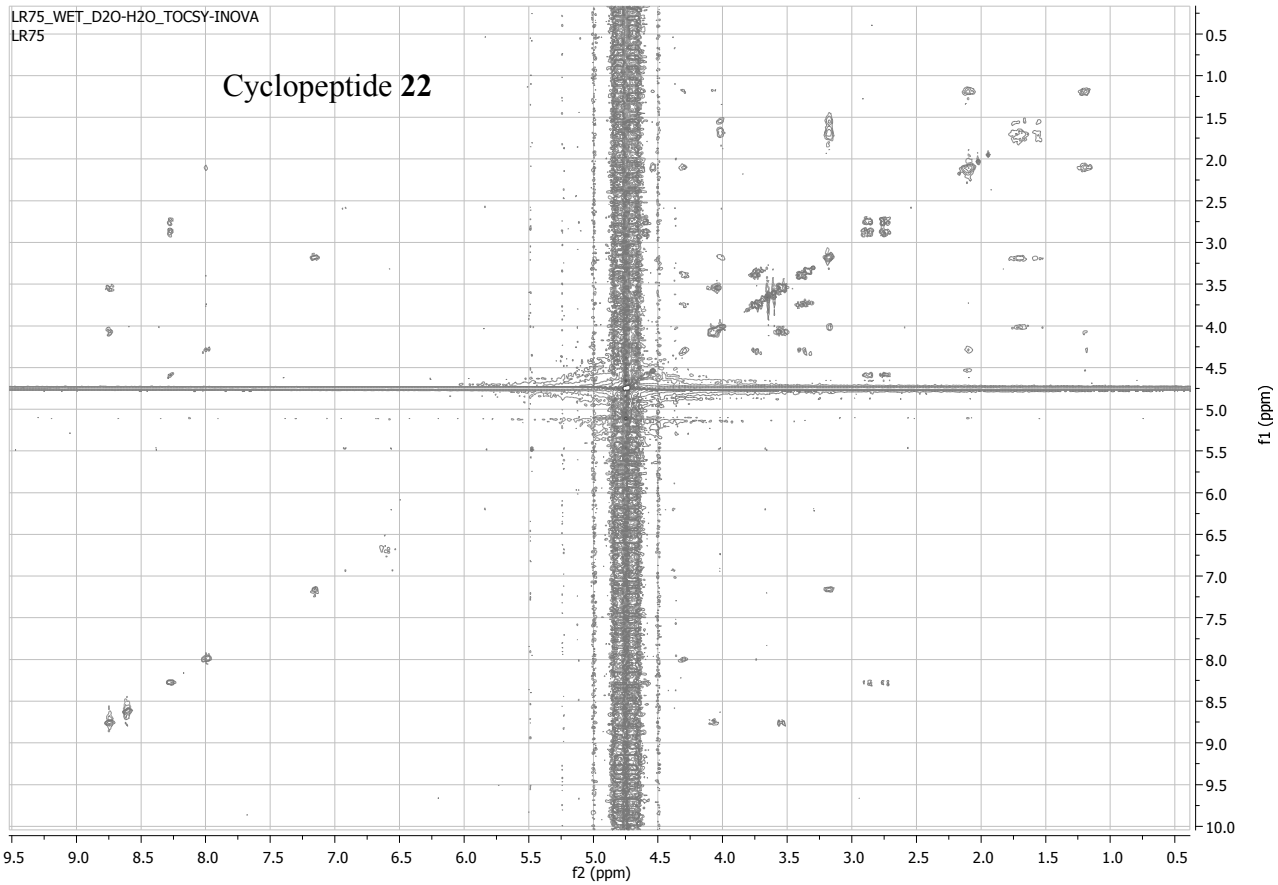
LR75_ciclopeptide
Cyclopeptide **22**
f2 (ppm)
f1 (ppm)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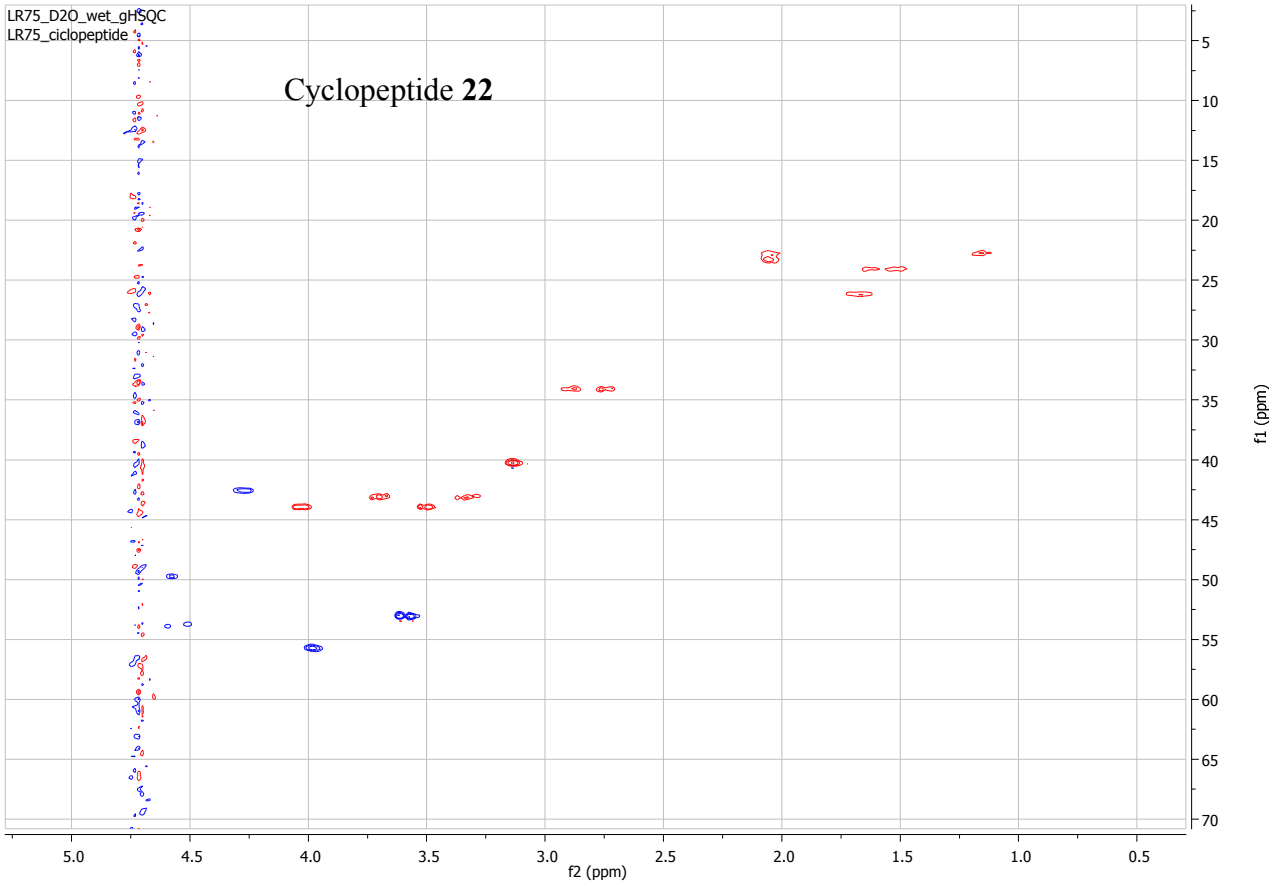
LR75
Cyclopeptide **22**
f2 (ppm)
f1 (ppm)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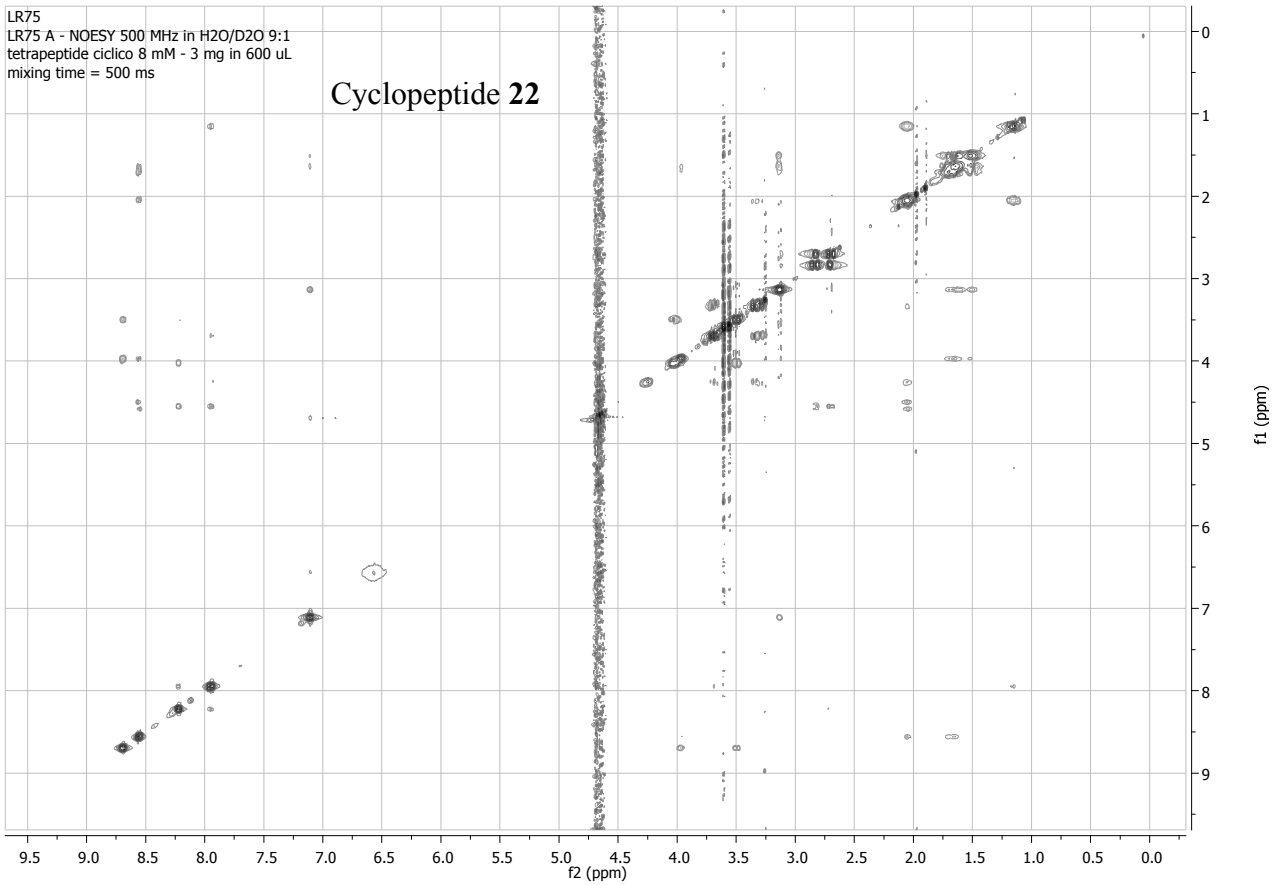
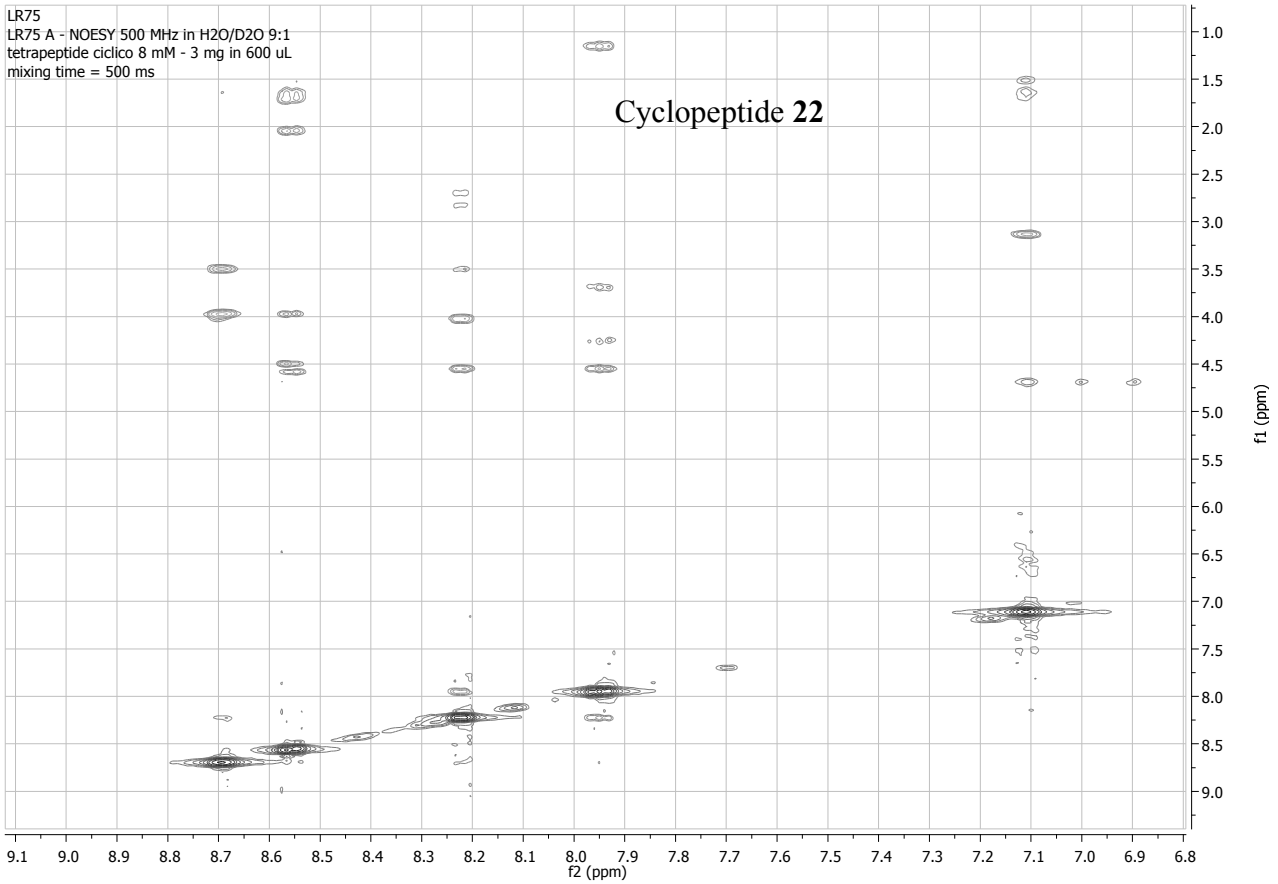
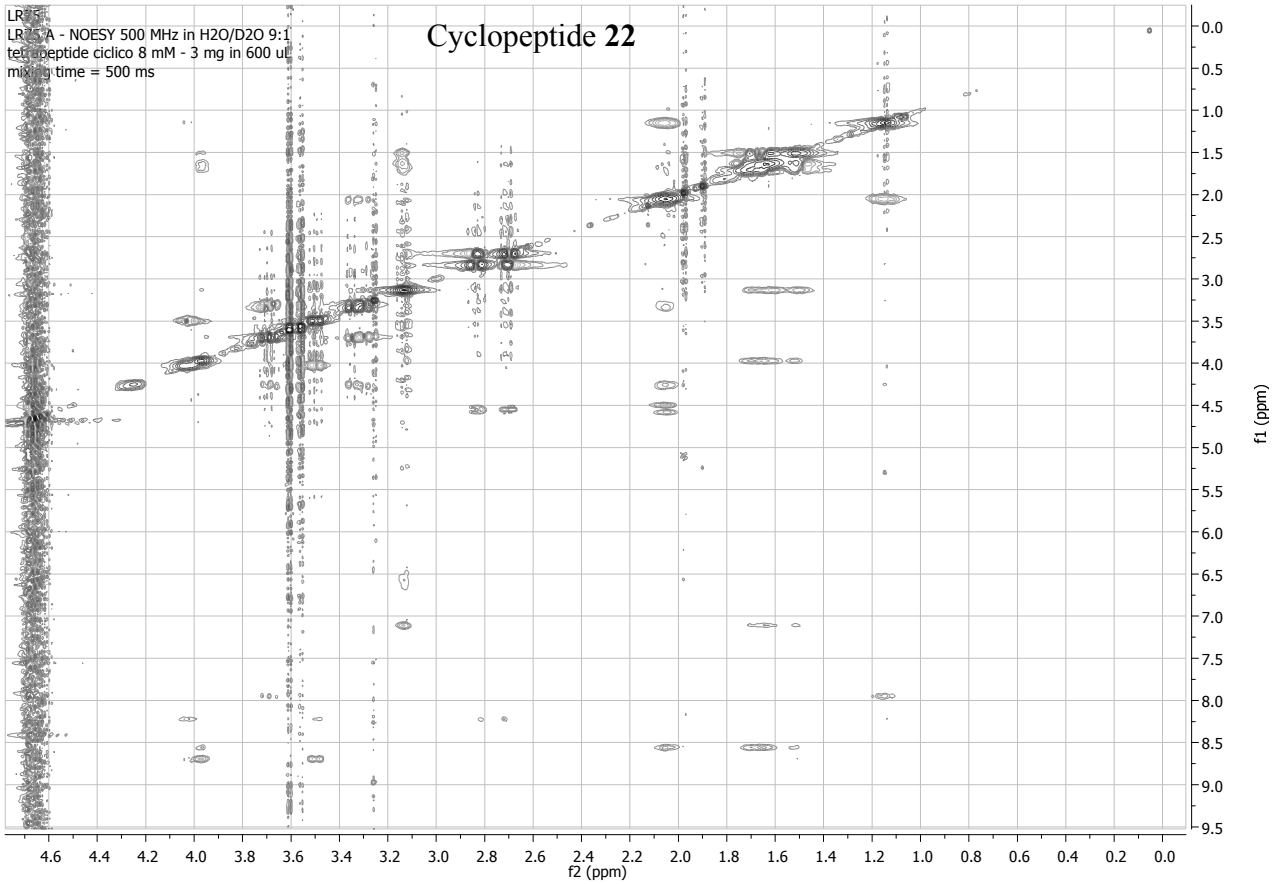
LR75_ciclopeptide
Cyclopeptide **22**
f1 (ppm)
f2 (ppm)


LR75
LR75 A - NOESY 500 MHz in H2O/D2O 9:1
tetrapeptide ciclico 8 mM - 3 mg in 600 uL
mixing time = 500 ms
Cyclopeptide **22**
f2 (ppm)
f1 (ppm)


LR75
LR75 A - NOESY 500 MHz in H2O/D2O 9:1
tetrapeptide ciclico 8 mM - 3 mg in 600 uL
mixing time = 500 ms
Cyclopeptide 22
f2 (ppm)
f1 (ppm)


LR75
LR75 A - NOESY 500 MHz in H2O/D2O 9:1
tetrapeptide ciclico 8 mM - 3 mg in 600 ul
mixing time = 500 ms
Cyclopeptide 22
f2 (ppm)
f1 (ppm)