Table S1. Diffraction data and model refinement statistics

Protein / Ligand	M^{pro} with boceprevir	M^{pro} with telaprevir	M^{pro} with MG-78	M^{pro} with MG-131	EV-A71-3C^{pro} with MG-78	CVB3-3C^{pro} with MG-78
PDB entry	7NBR	7NBS	7QL8	7Z0P	7QUB	7QUW

Data collection statistics

	M^{pro} with boceprevir	M^{pro} with telaprevir	M^{pro} with MG-78	M^{pro} with MG-131	EV-A71-3C^{pro} with MG-78	CVB3-3C^{pro} with MG-78
X-ray source	DESY P11	DESY P11	DESY P11	DESY P11	DESY P11	DESY P11
Wavelength [Å]	1.0332	1.0332	1.0332	1.0332	1.0332	1.0332
V$_m$ [Å^3/Da]	2.02	2.10	2.27	2.32	2.32	2.22
Solvent content [%]	39.1	41.4	45.8	47.0	47.0	44.5
Space group	$C2$	$C2$	$P2_12_12$	$C2$	$P432$	$C2$

Unit cell dimensions [Å]	$a = 113.77$, $b = 53.37$, $c = 45.95$	$a = 109.69$, $b = 54.63$, $c = 48.28$	$a = 45.52$, $b = 64.04$, $c = 105.38$	a = 113.72, $b = 51.67$, $c = 45.45$	$a = b = c$ $= 122.34$	$a = 78.27$, $b = 64.29$, $c = 39.85$
Unit cell dimensions [º]	α = γ = 90, β = 101.83	α = γ = 90, β = 101.40	α = β = γ = 90	α = γ = 90, β = 103.33	α = β = γ = 90	α = γ = 90, β = 115.52
Resolution range [a] [Å]	48.13 - 2.40 (2.53 - 2.40)	48.70 - 1.70 (1.79 - 1.70)	41.79 - 1.80 (1.90 - 1.80)	46.81 – 2.52 (2.62 - 2.52)	43.25 - 2.07 (2.19 - 2.07)	35.95 - 1.65 (1.74 - 1.65)
Number of observations	71,648 (10,224)	206,145 (28,922)	195,279 (30,344)	168,983 (25,182)	771,011 (123,429)	141,834 (20,568)
Number of unique reflections	10,684 (1,563)	30,908 (4,476)	29,378 (4,548)	49,867 (7,839)	19,792 (3,098)	43,026 (6,281)
Completeness [%]	99.9 (100.0)	100.0 (100.0)	99.4 (97.0)	99.0 (98.3)	99.9 (99.8)	98.1 (98.0)
Mean I/σ(I)	15.6 (1.7)	15.6 (1.8)	18.9 (3.5)	16.2 (1.0)	14.4 (1.0)	15.4 (1.9)
Multiplicity	6.7 (6.5)	6.7 (6.5)	5.6 (6.6)	3.5 (3.6)	38.9 (39.8)	6.7 (6.8)

R_{merge} [b] [%]	0.093 (1.179)	0.073 (1.089)	0.042 (0.480)	0.040 (0.167)	0.043 (0.282)	0.047 (0.797)
R_{pim} [c] [%]	0.039 (0.496)	0.030 (0.462)	0.025 (0.297)	0.039 (0.156)	0.010 (0.063)	0.020 (0.326)
$CC_{1/2}$ [d]	0.999 (0.663)	0.999 (0.688)	0.991 (0.693)	0.990 (0.392)	0.999 (0.522)	0.999 (0.874)
Wilson B-factor [Å^2]	48	23	44	53	46	51

Refinement statistics

R_{cryst} [e] /R_{free} [f] [%]	18.5/26.4	21.3/26.7	23.4/30.0	20.3/28.9	19.1/21.8	21.9/27.9
r.m.s.d. in bond lengths [Å]	0.008	0.009	0.007	0.007	0.012	0.007
r.m.s.d. in bond angles [°]	1.9	1.7	1.8	1.6	1.7	1.6
Clashscore [g]	4	5	3	8	5	4

Average *B*-factor for protein atoms [Å^2]	58	29	55	47	45	53
Average *B*-factor for ligand atoms [Å^2]	51	25	51	40	38	66
Average *B*-factor for water molecules [Å^2]	49	35	51	37	46	57
Number of protein atoms	2320	2352	2331	2347	1413	1393
Number of ligand atoms	37	49	39	40	39	39
Number of water molecules	48	155	75	37	52	51

Ramachandran plot

Preferred regions [%]	93	97	93	88	93	92
Allowed regions [%]	6	2	6	10	6	8
Outlier regions [%]	1	1	1	2	1	0

a The highest resolution shell is shown in parantheses.

b $R_{merge} = \sum_{hkl} \sum_{i=1}^{n} |I_i(hkl) - \bar{I}(hkl)| / \sum_{hkl} \sum_{i=1}^{n} I_i(hkl)$

c $R_{pim} = \sum_{hkl} \sqrt{1/(n-1)} \sum_{i=1}^{n} |I_i(hkl) - \bar{I}(hkl)| / \sum_{hkl} \sum_{i=1}^{n} I_i(hkl)$ [34]

d $CC_{1/2}$ is the correlation coefficient determined by two random half data sets [35]

e $R_{cryst} = \sum_{hkl} |F_o(hkl) - F_c(hkl)| / \sum_{hkl} |F_o(hkl)|$

f R_{free} was calculated for a test set of reflections (5%) omitted from the refinement.

g Clashscore is defined as the number of clashes calculated for the model per 1000 atoms

(including hydrogens) of the model. Hydrogens were added by MolProbity [36]

Figure S1: Inhibitory activities of boceprevir-derived compounds vs. the SARS-CoV-2 M^{pro}

IC$_{50}$ of Boceprevir against SARS-CoV-2 M^{pro}

(a): IC$_{50}$ = 4.1 ± 0.9 μM

IC$_{50}$ of Telaprevir against SARS-CoV-2 M^{pro}

(b): IC$_{50}$ = 19.0 ± 9.8 μM

IC$_{50}$ of MG-78 against SARS-CoV-2 M^{pro}

(c): IC$_{50}$ = 13 ± 3 nM

IC$_{50}$ of MG-131 against SARS-CoV-2 M^{pro}

(d): IC$_{50}$ = 14 ± 3 nM

IC$_{50}$ of MG-78 against HCoV NL63

(e): IC$_{50}$ = 0.33 ± 0.07 μM

IC$_{50}$ of MG-78 against Enterovirus A71

(f): IC$_{50}$ = 6.7 ± 2.2 nM

IC$_{50}$ of MG-78 against Coxsackie virus B3 3C^{pro}

(g): IC$_{50}$ = 1.45 ± 0.40 μM

Figure S1. Inhibitory activities against the SARS-CoV-2 M^{pro} of boceprevir (a), telaprevir (b), MG-78 (c), and MG-131 (d); inhibitory activities of compound MG-78 against HCoV-NL63 M^{pro} (e), EV-A71 3C^{pro} (f), and CVB3 3C^{pro} (g). IC$_{50}$ values have been derived from FRET-based enzymatic assays described in the main text.

Figure S2. NMR spectra

NMR spectra of MG-78 and its intermediates

OH-amide major

^{1}H-NMR @ D$_3$COD

500 MHz, 298 K

Current Data Parameters
NAME   mag20_21813Fa_major
EXPNO   3
PROCNO   1

F2 - Acquisition Parameters
Date_   20210611
Time   2.01 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   zg30
TD   65536
SOLVENT   MeOD
NS   24
DS   2
SWH   10000.000 Hz
FIDRES   0.305176 Hz
AQ   3.2767999 sec
RG   205.77
DW   50.000 usec
DE   14.08 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1
SFO1   500.2830892 MHz
NUC1   1H
P0   2.97 usec
P1   8.90 usec
PLW1   25.00000000 W

F2 - Processing parameters
SI   65536
SF   500.2800094 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

OH-amide major

182.75
177.63
158.00
80.26
75.01
52.58
49.51
49.34
49.17
49.00
48.83
48.66
48.49
41.51
39.62
31.06
28.73
28.62

^{13}C-NMR @ D$_3$COD
126 MHz, 298 K

Structure labeled **3$_a$**: BocHN, OH, NH$_2$, O

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

OH-amide minor

^{1}H-NMR @ D$_3$COD
500 MHz, 298 K

Structure labeled **3$_b$**: BocHN, OH, NH$_2$, O

8 7 6 5 4 3 2 1 0 ppm

1.96 2.94 2.00 1.00 0.99 9.01

8

OH-amide minor

182.65
178.19
157.97
80.15
74.70
52.48
49.51
49.17
49.00
48.83
48.66
48.49
43.51
39.90
34.94
28.87
20.69

Current Data Parameters
NAME   mag20_21804Fm_minor
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20210609
Time   14.13 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   deptqgpsp
TD   65536
SOLVENT   MeOD
NS   360
DS   8
SWH   29761.904 Hz
FIDRES   0.908261 Hz
AQ   1.1010048 sec
RG   205.77
DW   16.800 usec
DE   6.50 usec
TE   298.0 K
CNST2   145.0000000
D1   2.00000000 sec
D2   0.00344828 sec
D12   0.00002000 sec
D16   0.00020000 sec
TD0   1
SFO1   125.8095952 MHz
NUC1   13C
P1   9.00 usec
P13   2000.00 usec
PLW0   0 W
PLW1   86.00000000 W
SPNAM[5]   Crp60comp.4
SPOAL5   0.500
SPOFFS5   0 Hz
SPW5   10.64299965 W
SFO2   500.2820011 MHz
NUC2   1H
CNST12   1.5000000
CPDPRG[2   waltz65
P0   13.38 usec
P3   8.92 usec
P4   17.84 usec
PCPD2   80.00 usec
PLW2   25.00300026 W
PLW12   0.31084999 W
GPNAM[1]   SMSQ10.100
GP21   31.00 %
GPNAM[2]   SMSQ10.100
GP22   31.00 %
GPNAM[3]   SMSQ10.100
GP23   31.00 %
P16   1000.00 usec

F2 - Processing parameters
SI   32768
SF   125.7953305 MHz
WDW   EM
SSB   0
LB   1.00 Hz
GB   0
PC   1.40

^{13}C-NMR @ D$_3$COD
126 MHz, 298 K

3$_b$

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10   ppm

HATU coupling

4.85
4.34
4.34
4.32
4.32
4.26
4.26
4.10
4.04
4.02
3.97
3.96
3.95
3.31
3.31
3.31
3.28
3.28
3.26
3.25
3.23
3.23
3.21
3.20
2.63
2.62
2.62
2.61
2.61
2.34
2.33
2.33
2.32
2.31
2.31
2.20
2.19
2.17
2.17
2.15
2.15
1.69
1.68
1.68
1.66
1.56
1.56
1.44
1.30
1.29
1.28
1.28
1.25
1.06
0.99

Current Data Parameters
NAME   mag20_21793Sm
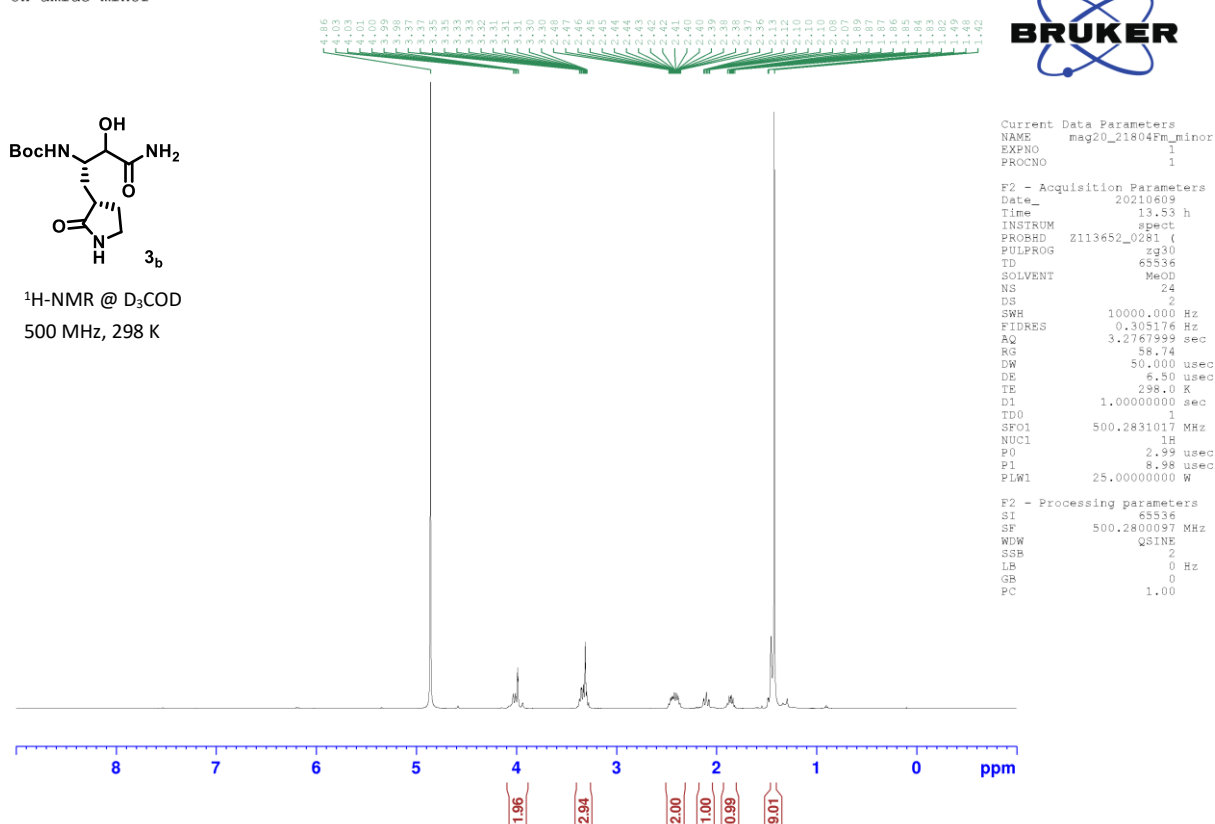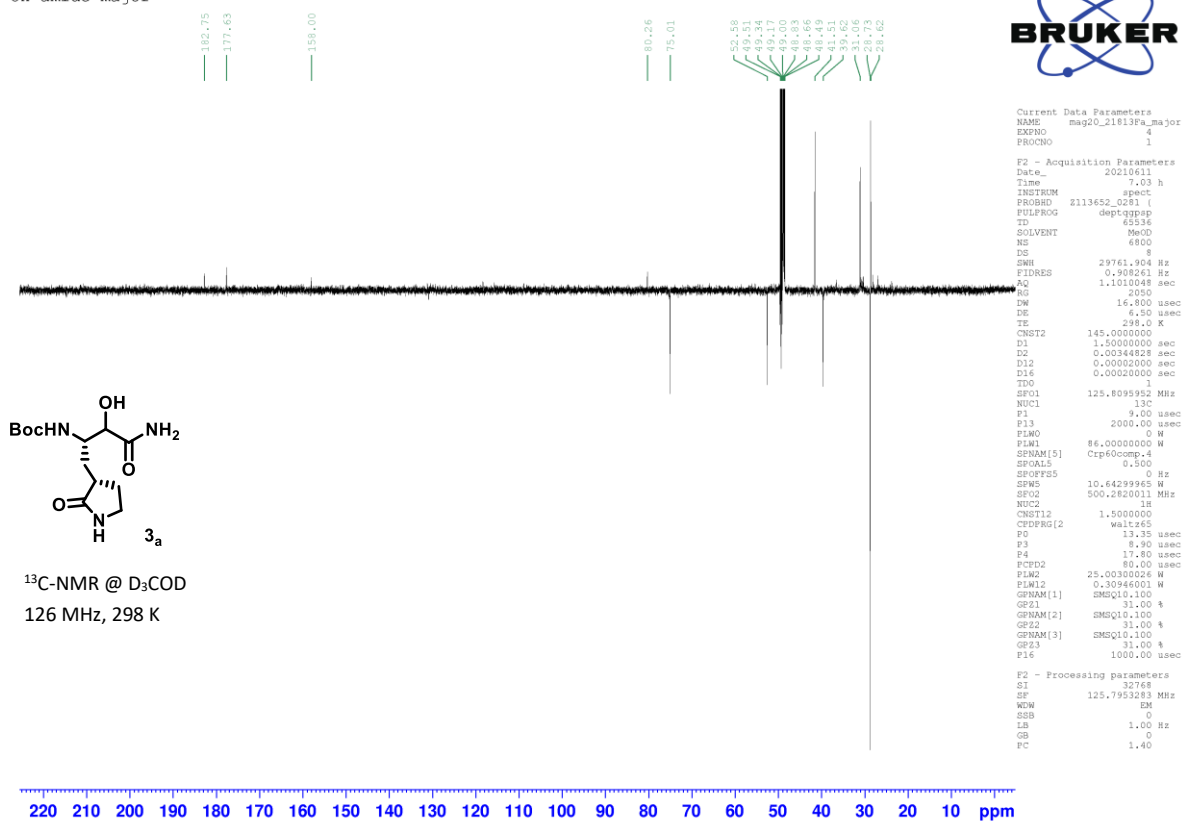EXPNO   1
PROCNO   1

F2 - Acquisition Parameters
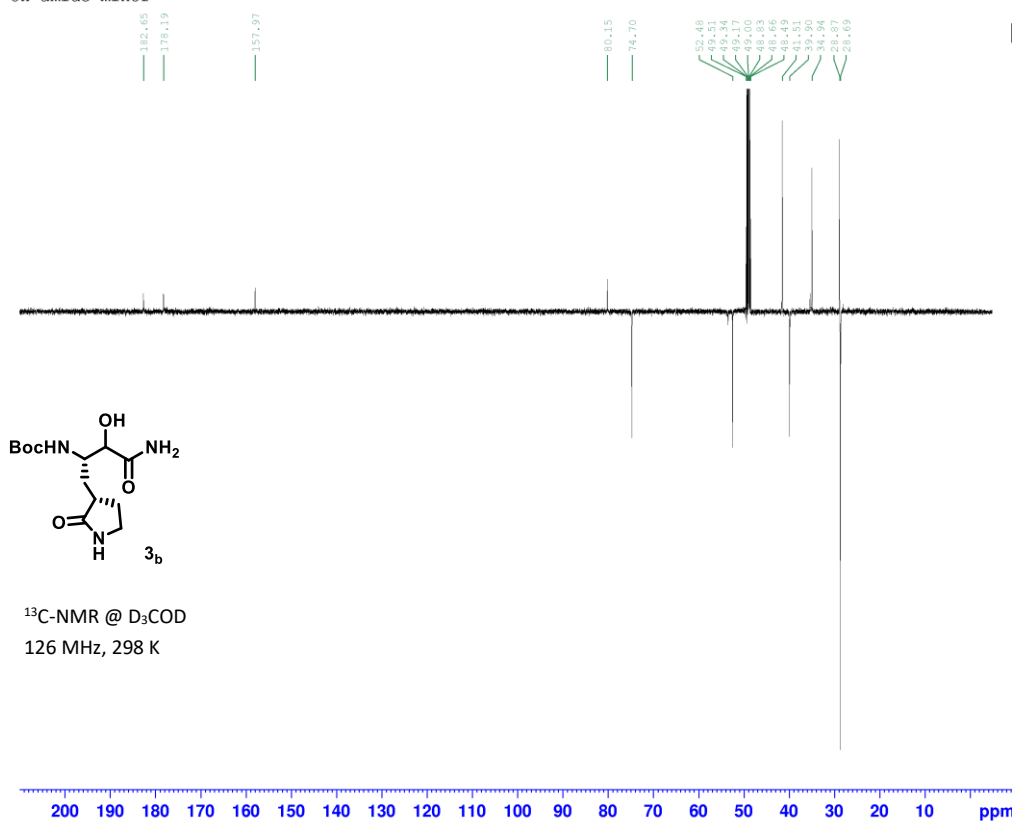Date_   20210609
Time   11.21 h
INSTRUM   spect
PROBHD   Z120187_0015 (
PULPROG   zg
TD   65536
SOLVENT   MeOD
NS   16
DS   2
SWH   14097.744 Hz
FIDRES   0.430229 Hz
AQ   2.3243434 sec
RG   17.76
DW   35.467 usec
DE   10.00 usec
TE   298.0 K
D1   5.00000000 sec
TD0   1
SFO1   700.4442000 MHz
NUC1   1H
P1   8.29 usec
PLW1   8.69999981 W

F2 - Processing parameters
SI   65536
SF   700.4400128 MHz
WDW   QSINE
SSB   2
LB   0 Hz
GB   0
PC   1.00

^{1}H-NMR @ D$_3$COD
700 MHz, 298 K

6

8   7   6   5   4   3   2   1   0   ppm

1.01 0.98 1.01 0.98 0.99   1.00 1.00   1.00 1.01 1.01   1.01 1.01 0.99 1.42 8.93 2.99 8.94 2.99

9

HATU coupling

182.81
177.51
173.79
173.38
159.72

74.72
62.06
50.86
50.95
50.71
49.24
49.12
49.00
48.86
48.64
41.42
39.19
35.78
32.32
30.65
30.95
29.25
28.92
27.04
26.54
20.35
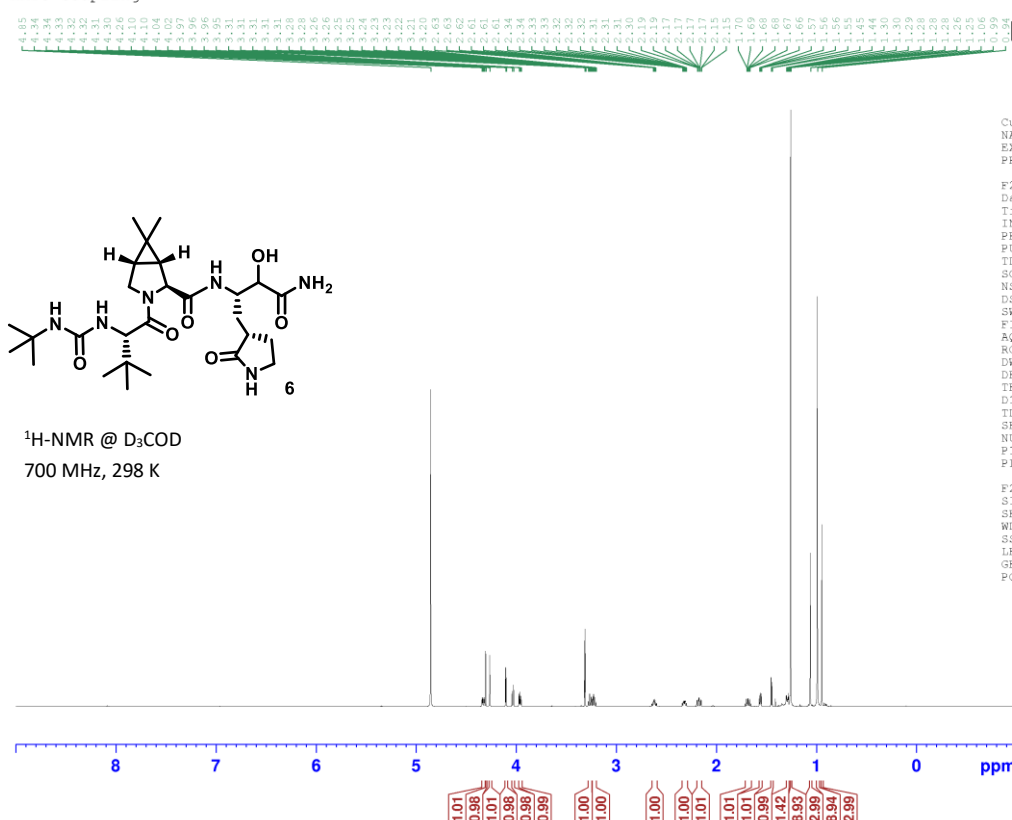11.19

Current Data Parameters
NAME   mag20_21793Sm
EXPNO   2
PROCNO   1

F2 - Acquisition Parameter
Date_   20210609
Time   11.38 h
INSTRUM   spect
PROBHD   Z120187_0015 (
PULPROG   zgpg30
TD   65356
SOLVENT   MeOD
NS   400
DS   4
SWH   43859.648 Hz
FIDRES   1.342177 Hz
AQ   0.7450584 se
RG   184.08
DW   11.400 us
DE   23.00 us
TE   298.0 K
D1   1.50000000 se
D11   0.03000000 se
TD0   1
SFO1   176.1447996 MH
NUC1   13C
P0   3.80 us
P1   11.40 us
PLW1   113.00000000 W
SFO2   700.4428018 MH
NUC2   1H
CPDPRG[2   waltz16
PCPD2   65.00 us
PLW2   8.69999981 W
PLW12   0.11583000 W
PLW13   0.04893700 W

F2 - Processing parameters
SI   32768
SF   176.1255309 MH
WDW   EM
SSB   0
LB   2.00 Hz
GB   0
PC   1.40

^{13}C-NMR @ D$_3$COD

176 MHz, 298 K

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10   ppm

MG-78

Current Data Parameters
NAME   MG_78
EXPNO   30
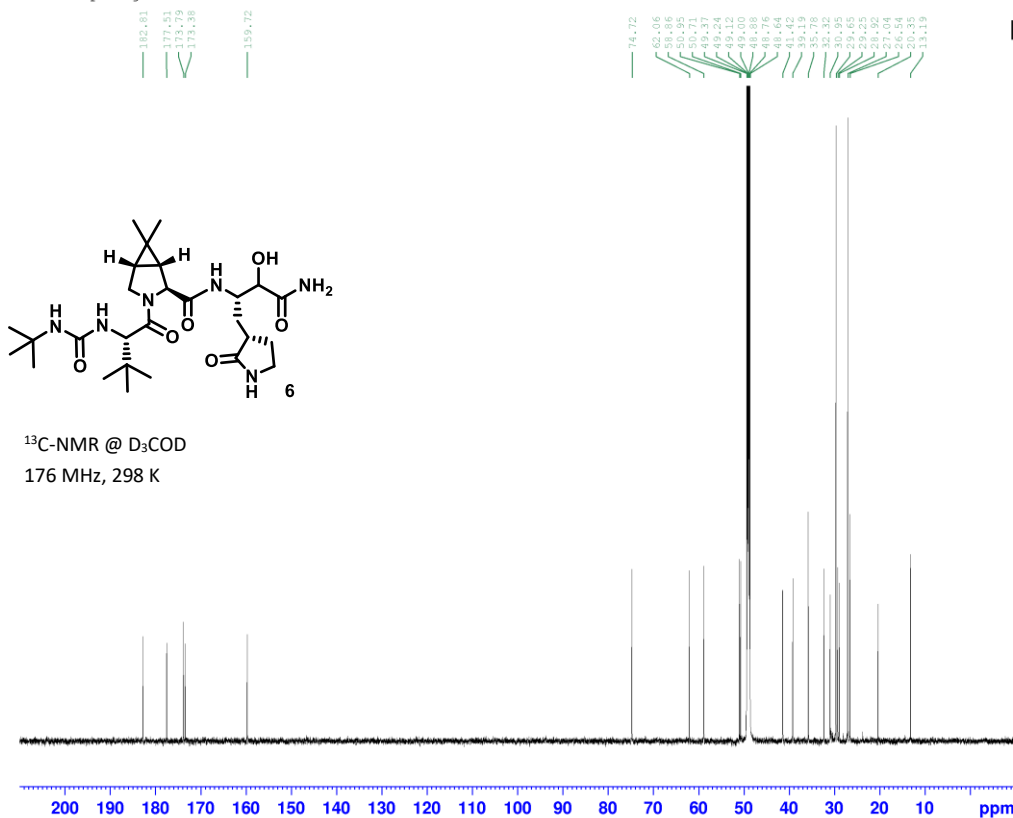PROCNO   1

F2 - Acquisition Parameters
Date_   20210719
Time   15.37 h
INSTRUM   spect
PROBHD   Z116098_0475 (
PULPROG   zg30
TD   65536
SOLVENT   DMSO
NS   32
DS   2
SWH   8012.820 Hz
FIDRES   0.244532 Hz
AQ   4.0894465 sec
RG   156.49
DW   62.400 usec
DE   6.50 usec
TE   298.1 K
D1   1.00000000 sec
TD0   1
SFO1   400.1524709 MHz
NUC1   1H
P0   3.33 usec
P1   10.00 usec
PLW1   16.62800026 W

F2 - Processing parameters
SI   65536
SF   400.1500032 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

MG-78

^{1}H-NMR @ DMSO-d6

^{1}H-NMR @ DMSO-d6

400 MHz, 298 K

8   7   6   5   4   3   2   1   0   ppm

0.84   0.93 0.91 0.78   1.06 1.00   0.94   1.00 2.01 1.04 1.08   1.10 1.92 0.96   1.06 0.88 1.84 1.05 1.01 9.08 2.92 8.88 2.97

MG-78

197.38

178.15
171.16
170.81

163.04
157.38

59.50
56.79
56.35
48.32
47.37
39.86
39.74
39.62
39.50
39.38
39.26
39.14
37.28
34.02
30.58
30.08
29.29
27.27
26.38
26.03
18.62
12.55

MG-78

13C-NMR @ DMSO-d6

176 MHz, 298 K

BRUKER

Current Data Parameters
NAME   mag20_219008m
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20210623
Time   9.57 h
INSTRUM   spect
PROBHD   Z120187_0015 (
PULPROG   deptqpsp
TD   65536
SOLVENT   DMSO
NS   4144
DS   8
SWH   42613.637 Hz
FIDRES   1.300465 Hz
AQ   0.7689557 sec
RG   184.08
DW   11.733 usec
DE   15.00 usec
TE   298.0 K
CNST2   145.0000000
D1   1.50000000 sec
D2   0.00344828 sec
D12   0.00002000 sec
D16   0.00020000 sec
TD0   1
SFO1   176.1442712 MHz
NUC1   13C
P1   11.40 usec
P13   2000.00 usec
PLW0   0 W
PLW1   113.00000000 W
SPNAM[5]   Crp80comp.4
SPOAL5   0.500
SPOFFS5   0 Hz
SPW5   29.91699982 W
SFO2   700.4428018 MHz
NUC2   1H
CNST12   1.5000000
CPDPRG[2   waltz65
P0   11.70 usec
P3   7.80 usec
P4   15.60 usec
PCPD2   65.00 usec
PLW2   8.70960045 W
PLW12   0.12542000 W
GPNAM[1]   SMSQ10.100
GP21   31.00 %
GPNAM[2]   SMSQ10.100
GP22   31.00 %
GPNAM[3]   SMSQ10.100
GP23   31.00 %
P16   1000.00 usec

F2 - Processing parameters
SI   32768
SF   176.1258642 MHz
WDW   EM
SSB   0
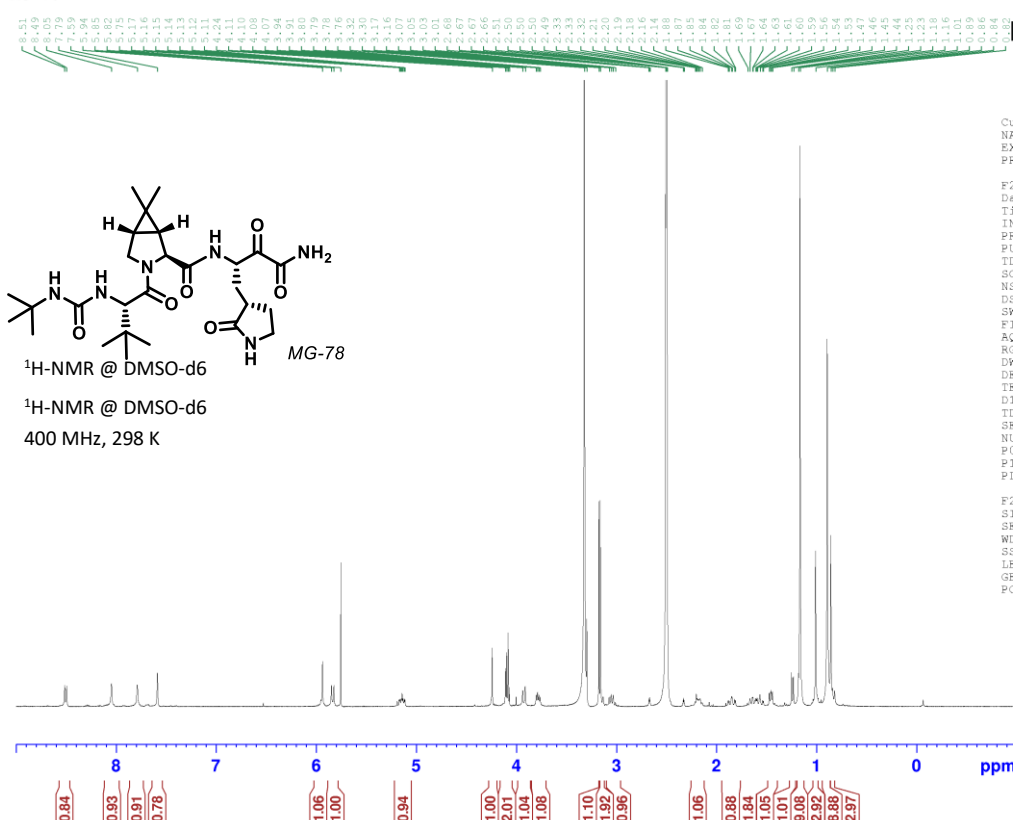LB   1.00 Hz
GB   0
PC   1.40

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10   ppm

NMR spectra of MG-131 and its intermediates

MG_126_DMSO

^{1}H-NMR @ DMSO-d6

700 MHz, 298 K

MG_126_DMSO

^{13}C-NMR @ DMSO-d6

176 MHz, 298 K

12

MG-128-II-Fr.23-35

¹H-NMR @ D₃COD
500 MHz, 298 K

Current Data Parameters
NAME   mag20_22659Fa
EXPNO   1
PROCNO   1

F2 - Acquisition Parameters
Date_   20210924
Time   12.42 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   zg30
TD   65536
SOLVENT   MeOD
NS   40
DS   2
SWH   10000.000 Hz
FIDRES   0.305176 Hz
AQ   3.2767999 sec
RG   63.14
DW   50.000 usec
DE   13.98 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1
SFO1   500.2830892 MHz
NUC1   1H
P0   3.17 usec
P1   9.50 usec
PLW1   25.00000000 W

F2 - Processing parameters
SI   65536
SF   500.2800096 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

MG-128-II-Fr.23-35

¹³C-NMR @ D₃COD
126 MHz, 298 K

Current Data Parameters
NAME   mag20_22659Fa
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20210924
Time   13.11 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   deptqgpsp
TD   65536
SOLVENT   MeOD
NS   512
DS   8
SWH   29761.904 Hz
FIDRES   0.908261 Hz
AQ   1.1010048 sec
RG   2050
DW   16.800 usec
DE   6.50 usec
TE   298.0 K
CNST2   145.0000000
D1   2.00000000 sec
D2   0.00344828 sec
D12   0.00002000 sec
D16   0.00020000 sec
TD0   1
SFO1   125.8095952 MHz
NUC1   13C
P1   9.00 usec
P13   2000.00 usec
PLW0   0 W
PLW1   86.00000000 W
GPNAM[5]   Crp60comp.4
SPOAL5   0.500
SPOFFS5   0 Hz
SPW5   10.64299965 W
SFO2   500.2820011 MHz
NUC2   1H
CNST12   1.5000000
CPDPRG[2   waltz65
P0   14.25 usec
P3   9.50 usec
P4   19.00 usec
PCPD2   80.00 usec
PLW2   25.00000000 W
PLW12   0.35253999 W
GPNAM[1]   SMSQ10.100
GP21   31.00 %
GPNAM[2]   SMSQ10.100
GP22   31.00 %
GPNAM[3]   SMSQ10.100
GP23   31.00 %
P16   1000.00 usec

F2 - Processing parameters
SI   32768
SF   125.7953309 MHz
WDW   EM
SSB   0
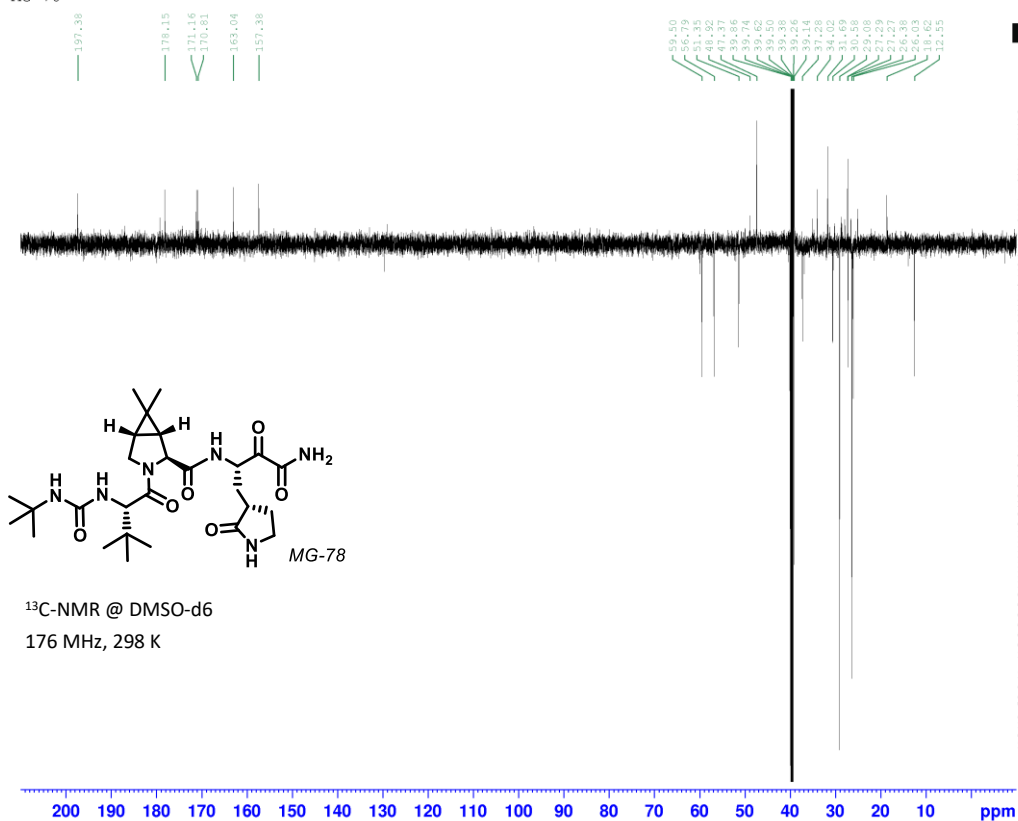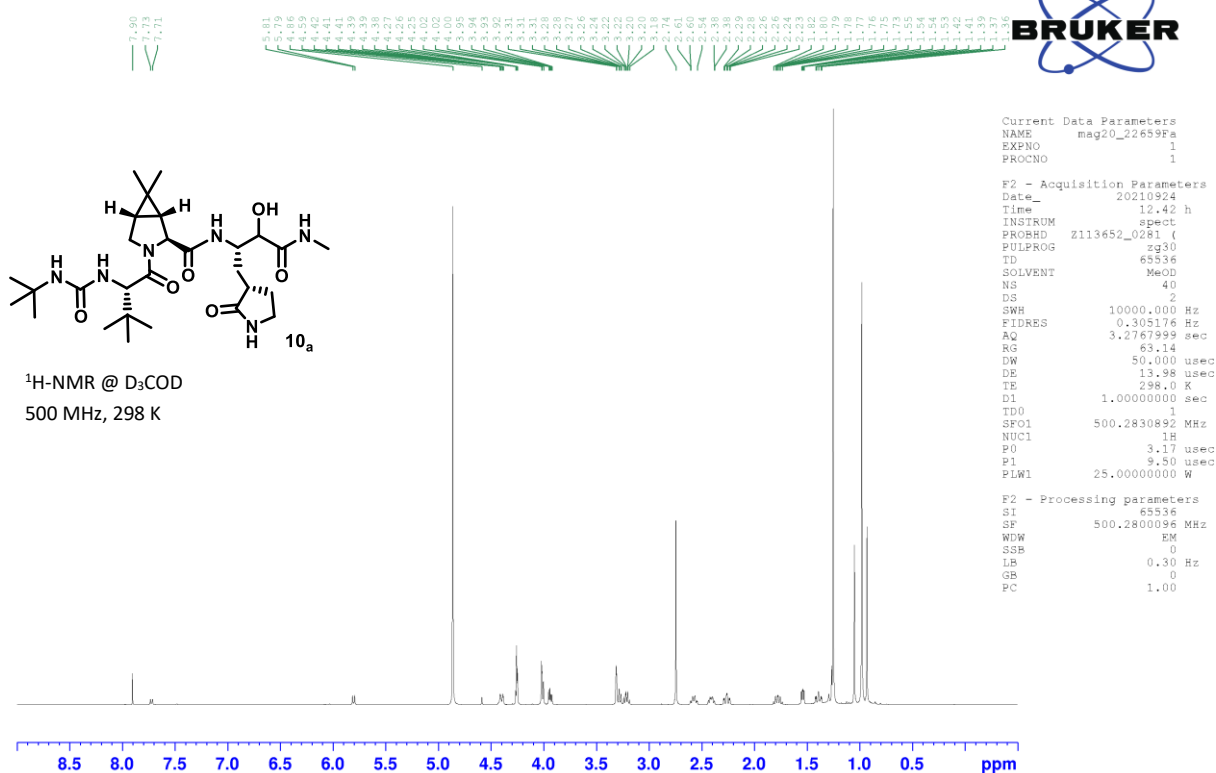LB   1.00 Hz
GB   0
PC   1.40

MG-131_Fr.13-31_DMP

BRUKER

¹H-NMR @ DMSO-d6

500 MHz, 298 K

MG-131

Current Data Parameters
NAME   MG_131
EXPNO   1
PROCNO   1

F2 - Acquisition Parameters
Date_   20211004
Time   12.18 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   zg30
TD   65536
SOLVENT   DMSO
NS   40
DS   2
SWH   10000.000 Hz
FIDRES   0.305176 Hz
AQ   3.2767999 sec
RG   224.28
DW   50.000 usec
DE   13.98 usec
TE   298.0 K
D1   1.00000000 sec
TD0   1
SFO1   500.2830892 MHz
NUC1   1H
P0   3.17 usec
P1   9.50 usec
PLW1   25.00000000 W

F2 - Processing parameters
SI   65536
SF   500.2800040 MHz
WDW   EM
SSB   0
LB   0.30 Hz
GB   0
PC   1.00

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   ppm

0.99 1.01   0.98   1.00 1.02   1.00   0.99 1.00 0.99 0.99   5.59 1.24 1.00   3.03   1.02 1.02 1.03 1.00 1.00 1.21 9.96   3.05 9.04 3.07

MG-131_Fr.13-31_DMP

BRUKER

Current Data Parameters
NAME   MG_131
EXPNO   2
PROCNO   1

F2 - Acquisition Parameters
Date_   20211004
Time   20.18 h
INSTRUM   spect
PROBHD   Z113652_0281 (
PULPROG   deptqgpsp
TD   65536
SOLVENT   DMSO
NS   4096
DS   8
SWH   29761.904 Hz
FIDRES   0.908261 Hz
AQ   1.1010048 sec
RG   2050
DW   16.800 usec
DE   6.50 usec
TE   298.0 K
CNST2   145.0000000
D1   2.00000000 sec
D2   0.00344828 sec
D12   0.00002000 sec
D16   0.00020000 sec
TD0   1
SFO1   125.8095952 MHz
NUC1   13C
P1   9.00 usec
P13   2000.00 usec
PLW0   0 W
PLW1   86.00000000 W
SPNAM[5]   Crp60comp.4
SPOAL5   0.500
SPOFFS5   0 Hz
SPW5   10.64299965 W
SFO2   500.2820011 MHz
NUC2   1H
CNST12   1.5000000
CPDPRG[2   waltz65
P0   14.25 usec
P3   9.50 usec
P4   19.00 usec
PCPD2   80.00 usec
PLW2   25.00000000 W
PLW12   0.35253999 W
GPNAM[1]   SMSQ10.100
GP21   31.00 %
GPNAM[2]   SMSQ10.100
GP22   31.00 %
GPNAM[3]   SMSQ10.100
GP23   31.00 %
P16   1000.00 usec

F2 - Processing parameters
SI   32768
SF   125.7955657 MHz
WDW   EM
SSB   0
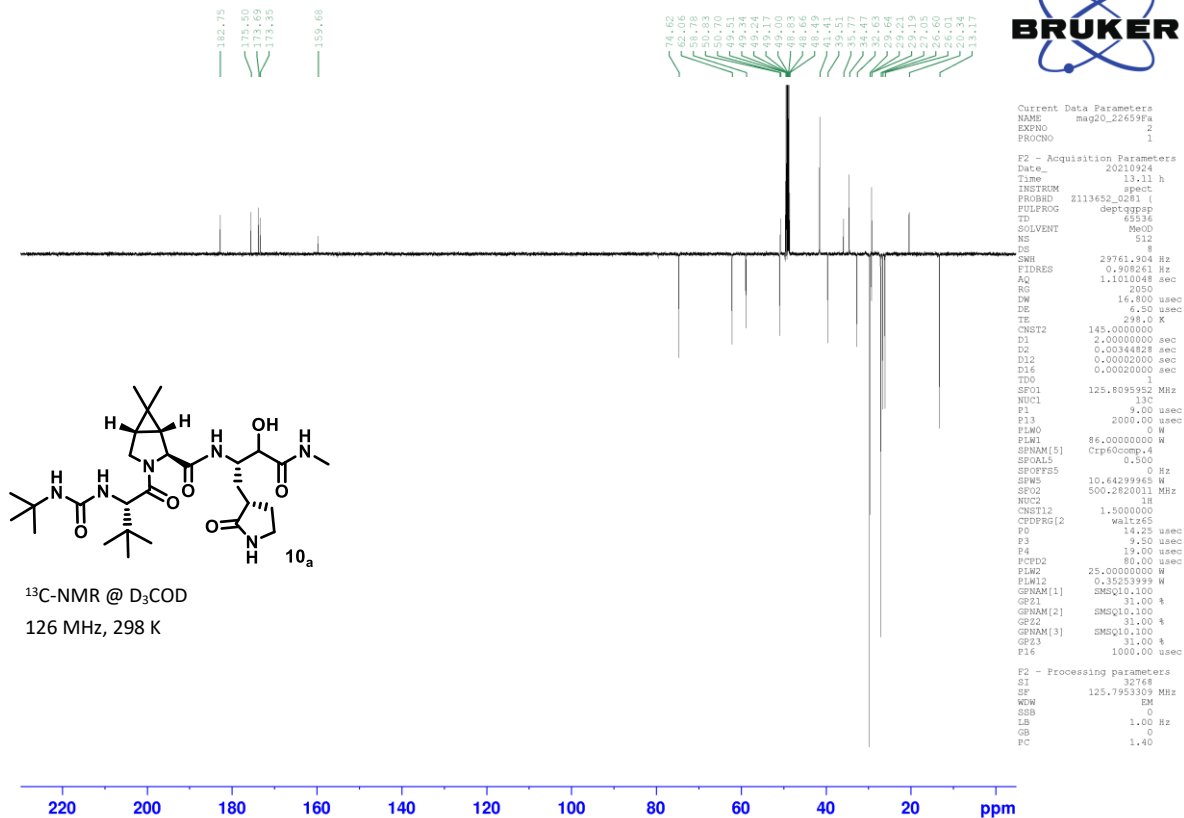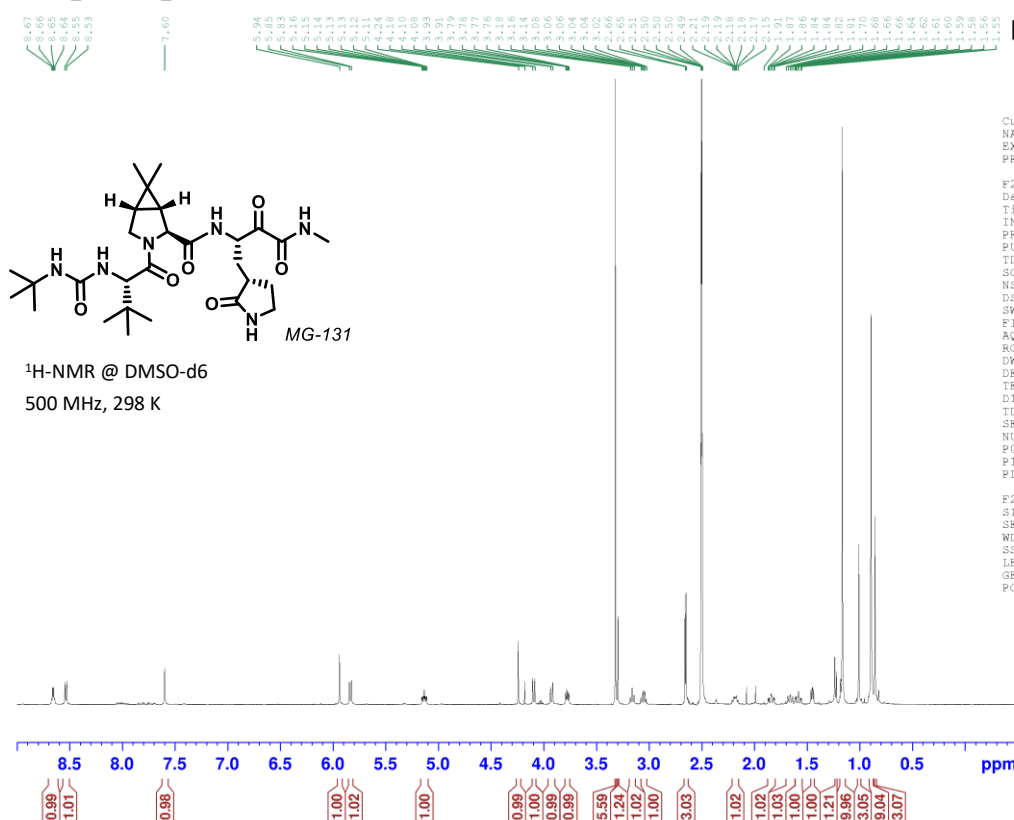LB   1.00 Hz
GB   0
PC   1.40

MG-131

¹³C-NMR @ DMSO-d6

126 MHz, 298 K

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm