

SUPPLEMENTARY MATERIAL

Cooperative Conformational Regulation in *N*-heterocyclic Fluoroalcohols

*Alpesh Ramanlal Patel and Fei Liu**

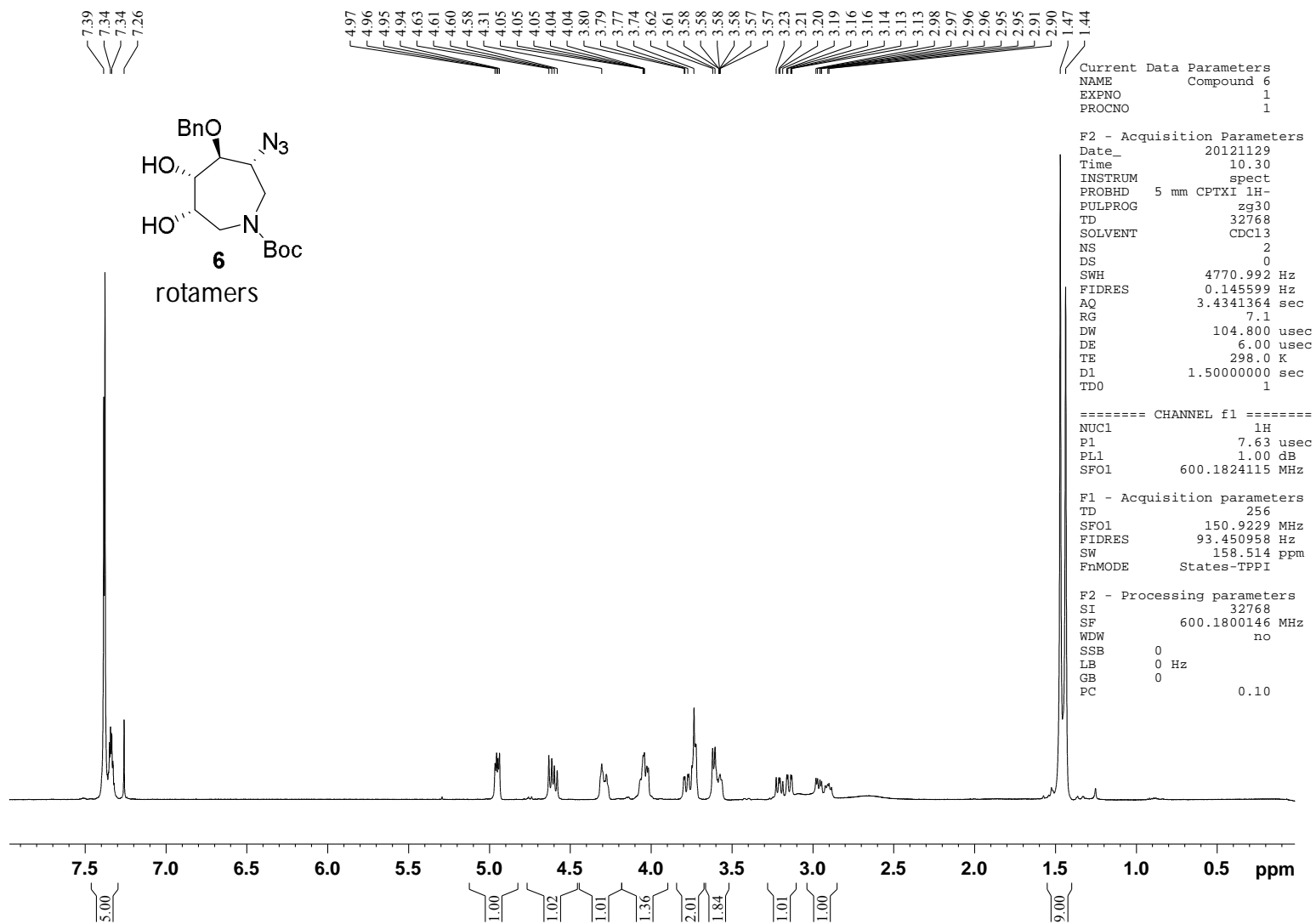
Department of Chemistry and Biomolecular Sciences, Macquarie University,
Sydney, NSW 2109, Australia.

*Email: fei.liu@mq.edu.au

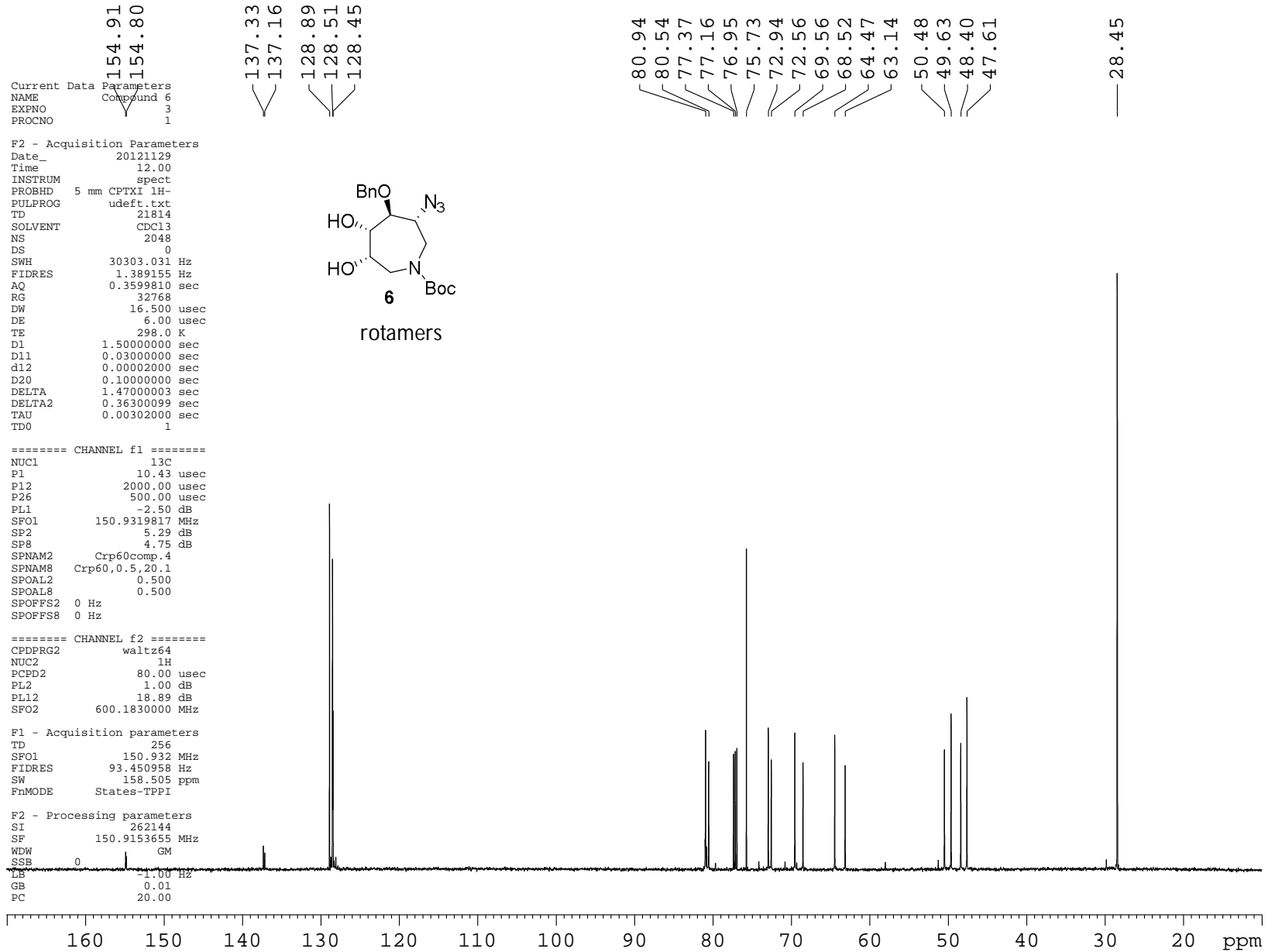
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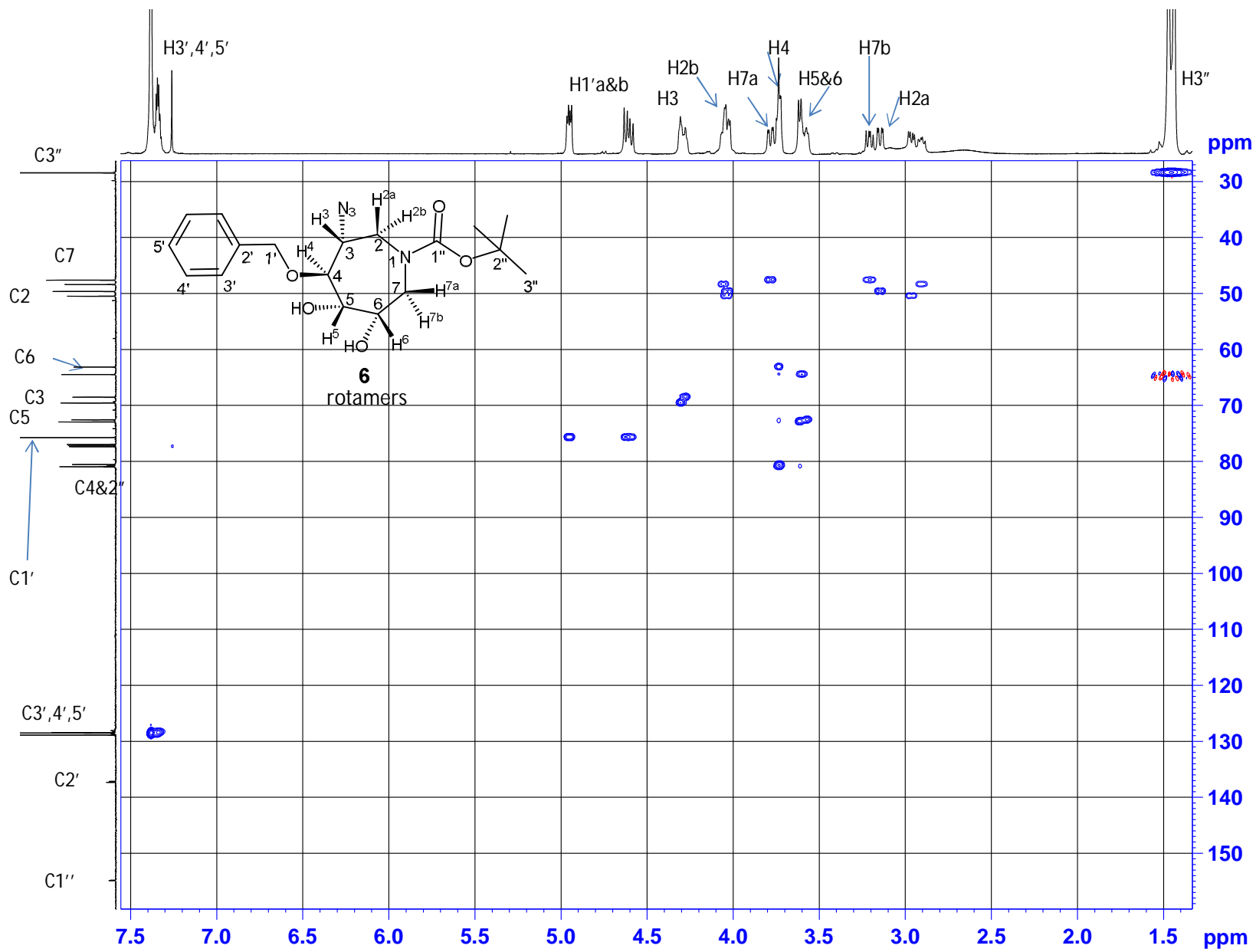
¹H NMR-6



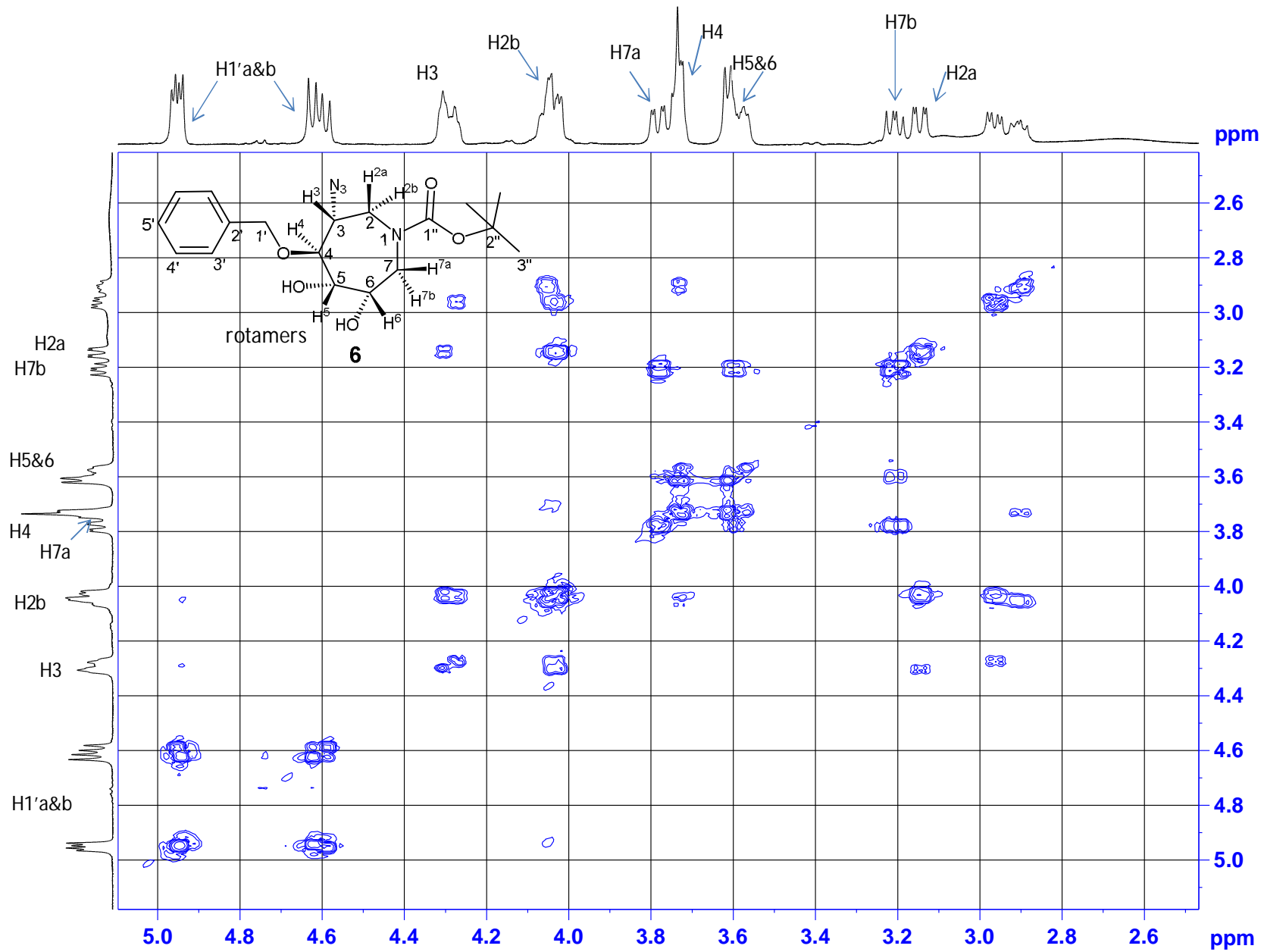
¹³C NMR-6



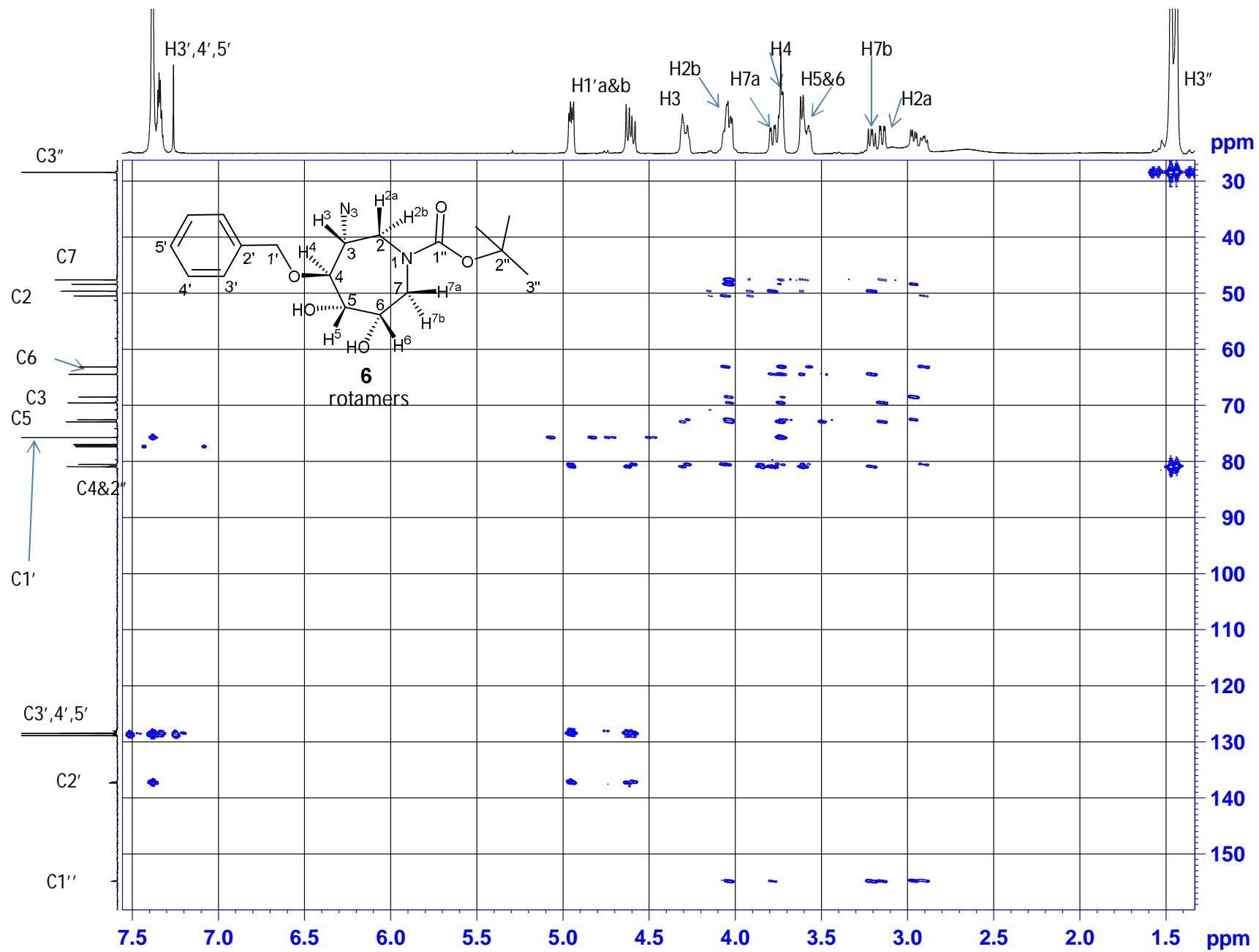
HSQC-6



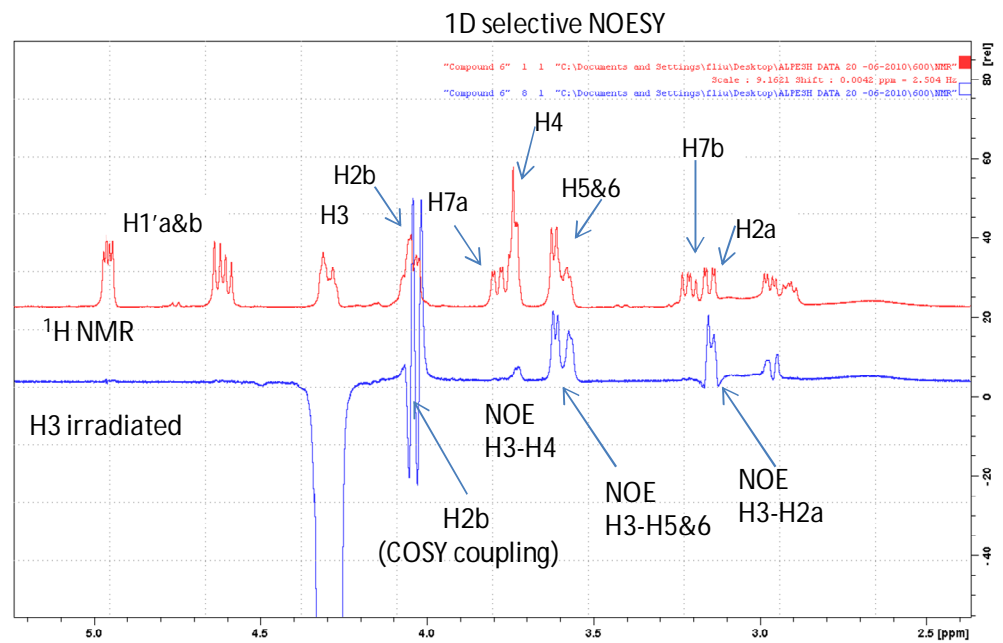
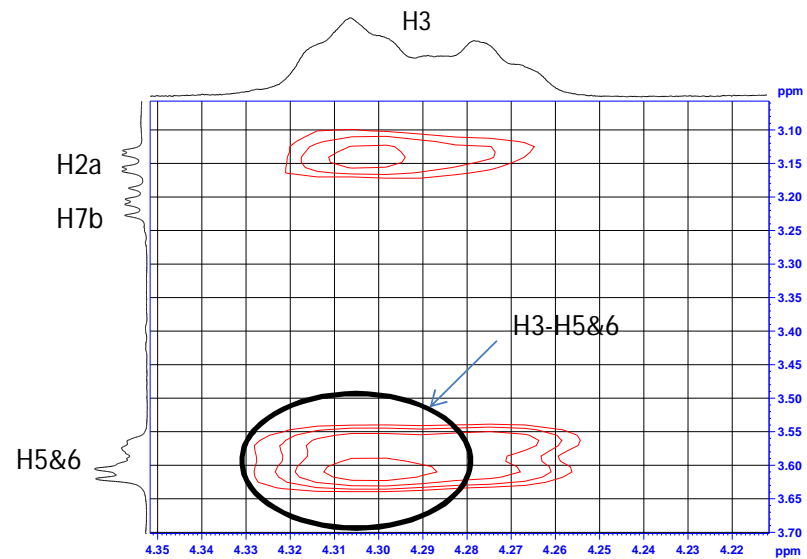
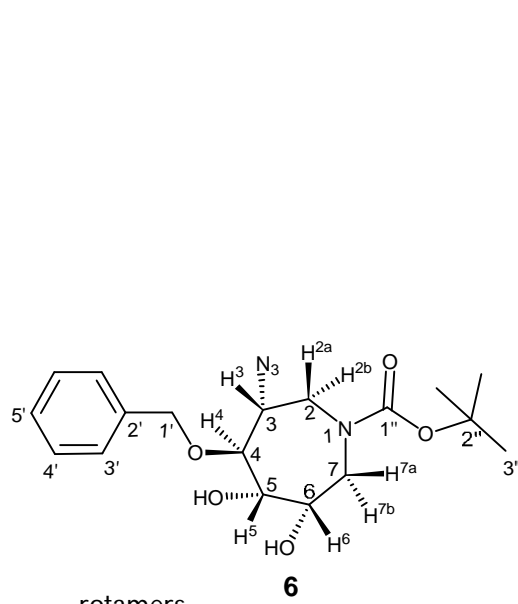
COSY-6



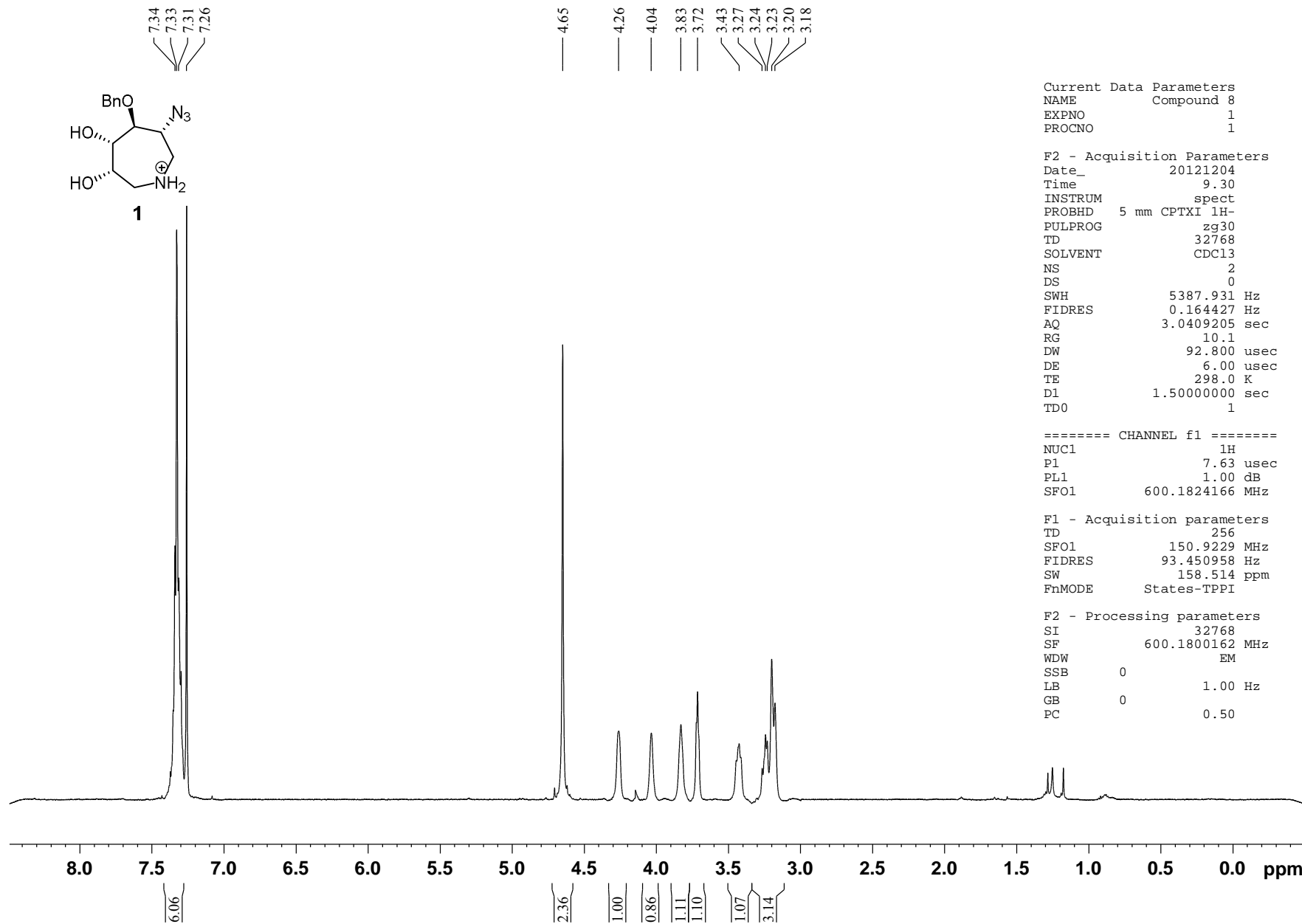
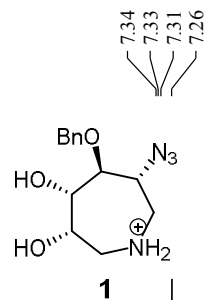
HMBC-6



NOESY-6



¹H NMR-1



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PROCNO 1

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PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 2
DS 0
SWH 5387.931 Hz
FIDRES 0.164427 Hz
AQ 3.0409205 sec
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DE 6.00 usec
TE 298.0 K
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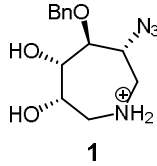
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FIDRES 93.450958 Hz
SW 158.514 ppm
FnMODE States-TPPI

F2 - Processing parameters
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SF 600.1800162 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.50

¹³C NMR-1

Current Data Parameters
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EXPNO 3
PROCNO 1

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FULPROG udef1.txt
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SOLVENT CDCl3
NS 15
DS 0
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FIDRES 1.389155 Hz
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RG 32768
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DE 6.00 usec
TE 298.0 K
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D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
DELTA2 0.36300099 sec
TAU 0.00302000 sec
TDO 1



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128.88
128.63
128.42

80.52
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76.95
74.55
73.92
65.99
59.85

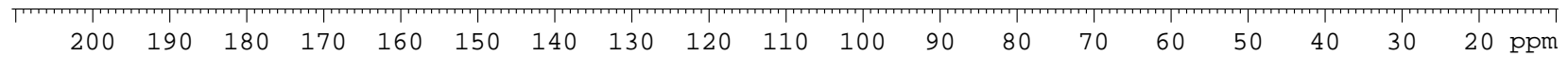
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45.06

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P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
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SPNAM8 Crp60,0.5,20.1
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SPOAL8 0.500
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SPOFFS8 0 Hz

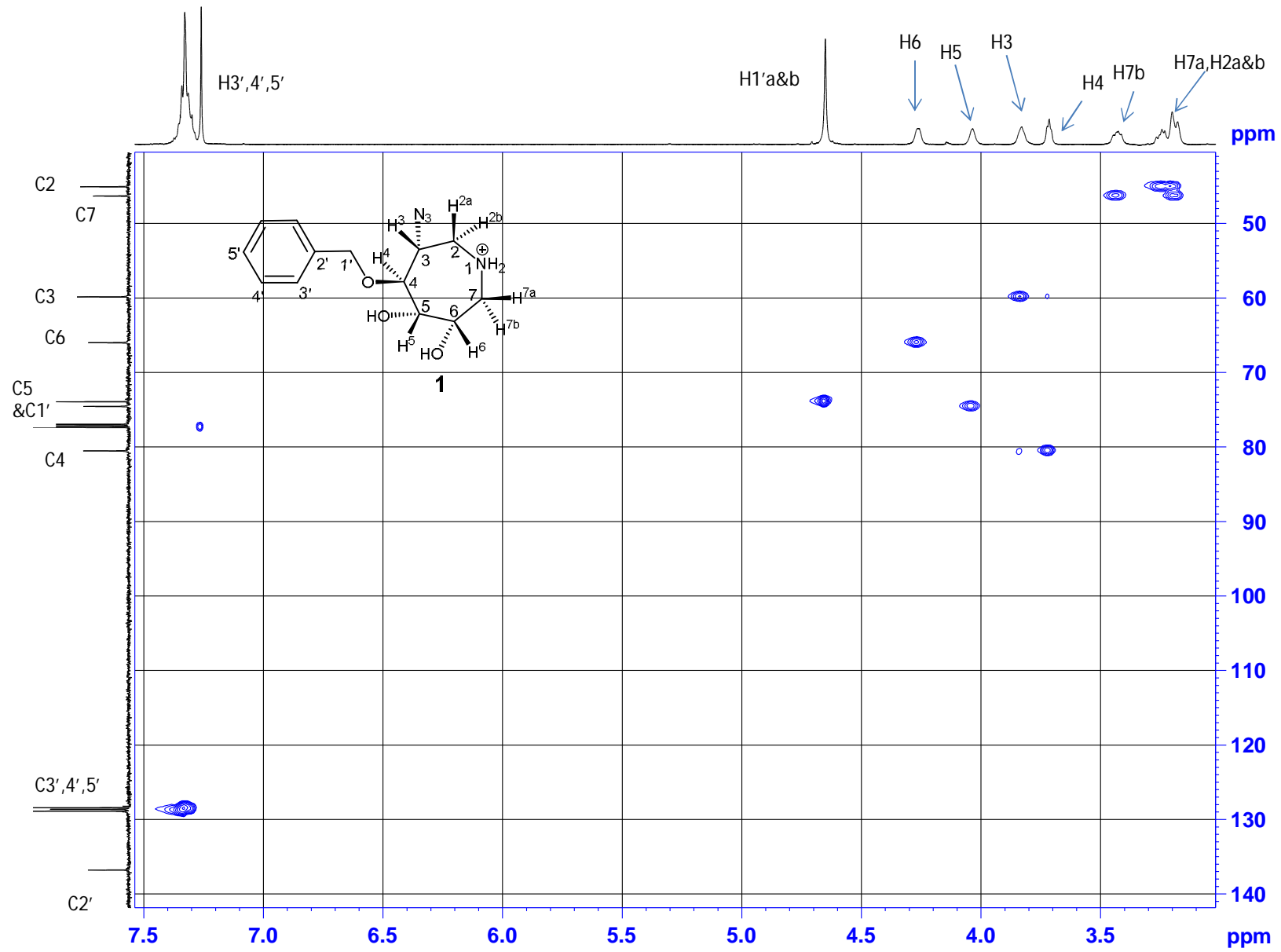
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NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
PL12 18.89 dB
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F1 - Acquisition parameters
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FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI

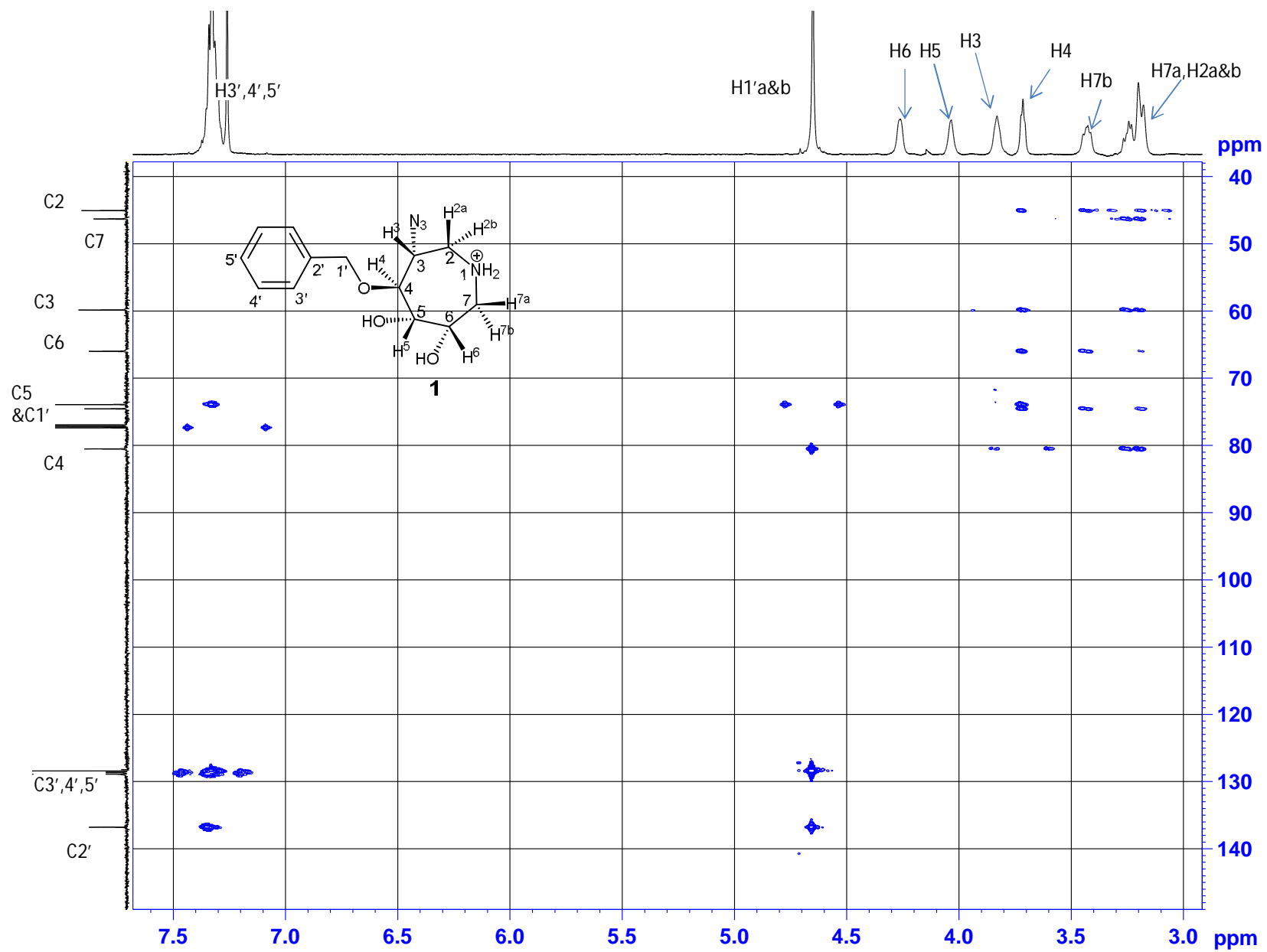
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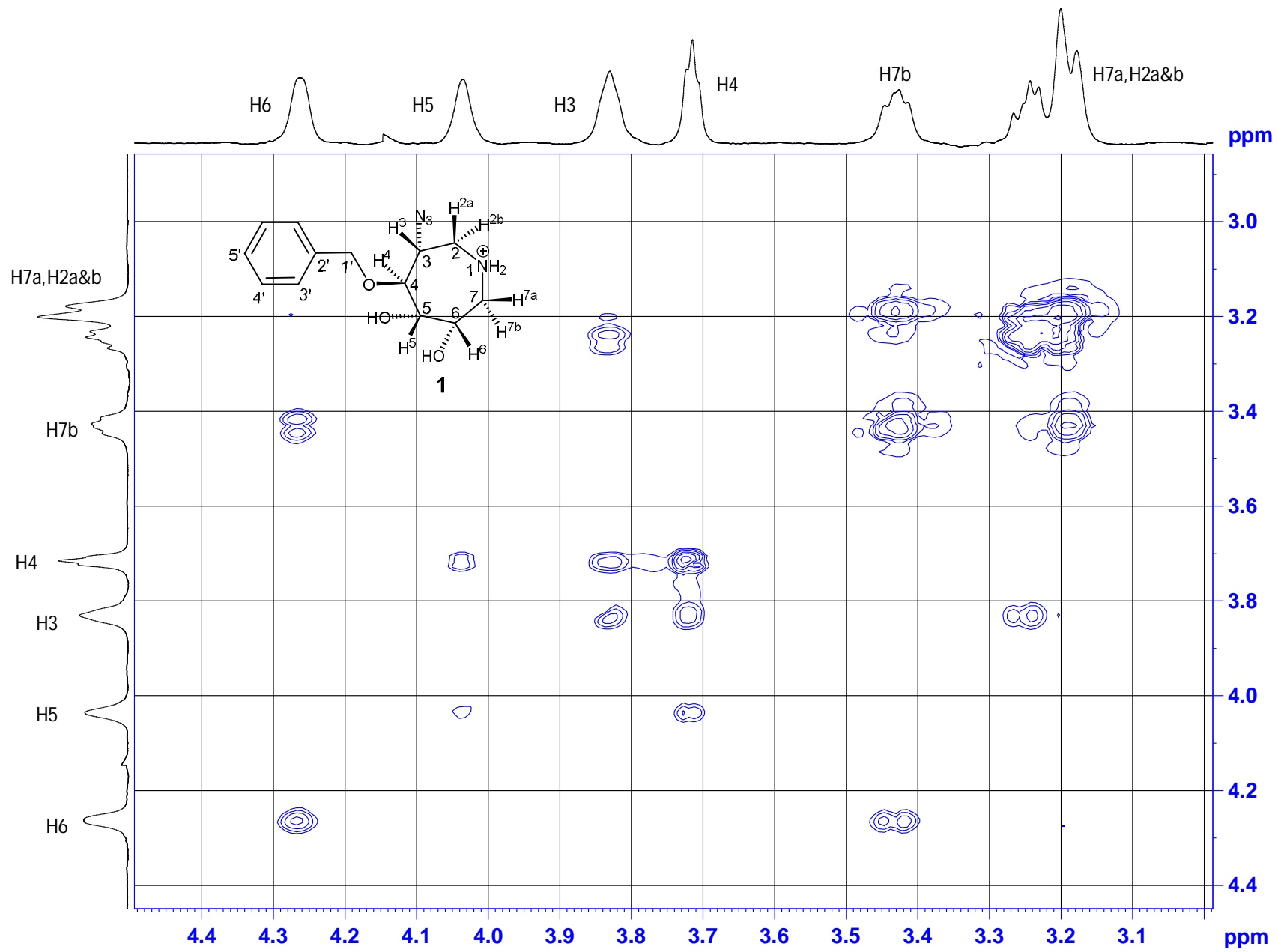
HSQC-1



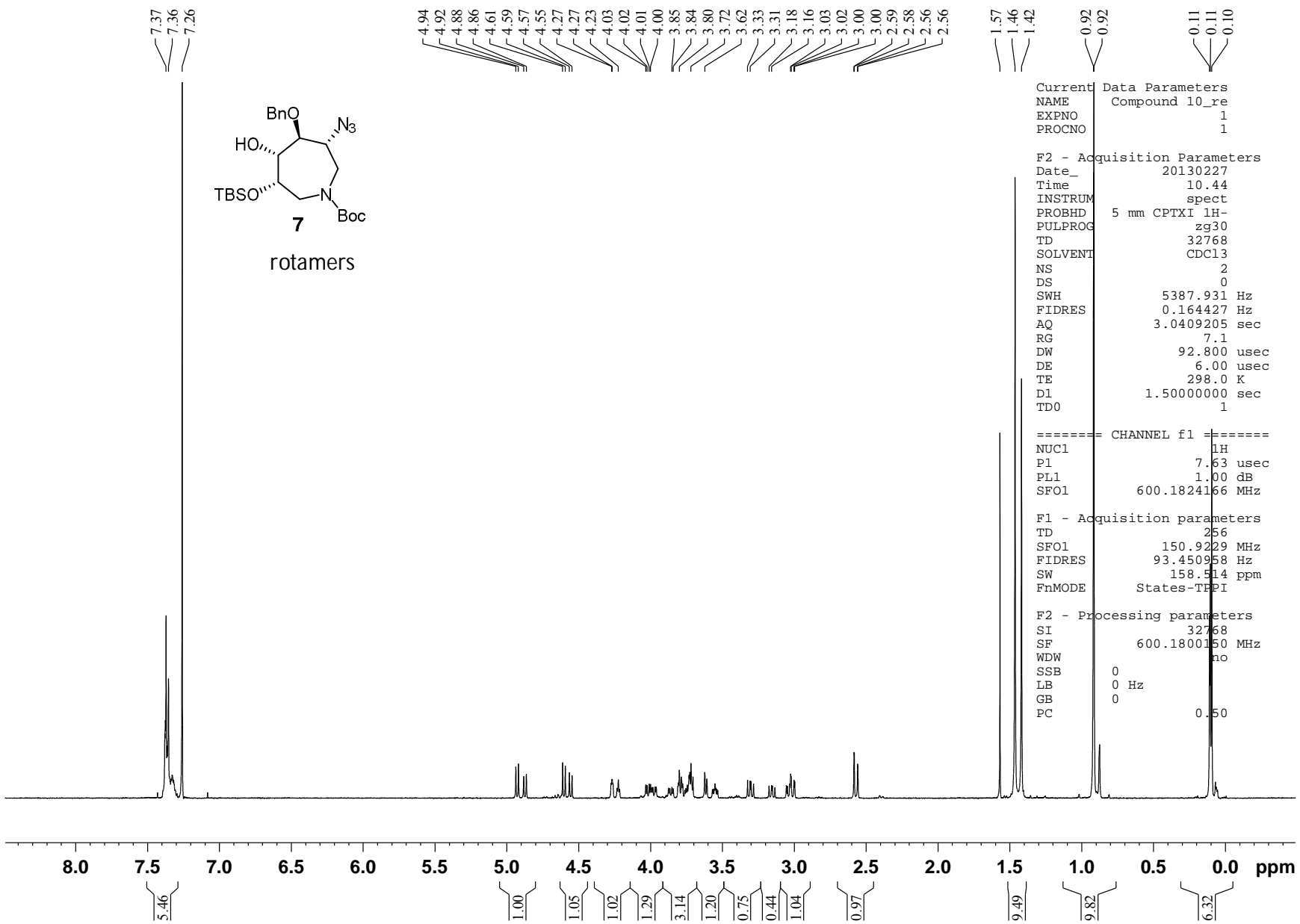
HMBC-1



COSY-1

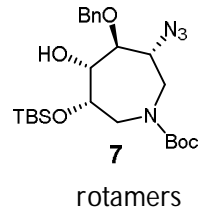


¹H NMR-7



¹³C NMR-7

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PROCNO 1
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SOLVENT CDCl3
NS 6144
DS 0
SNH 42372.883 Hz
FIDRES 1.942463 Hz
AQ 0.2574552 sec
RG 32768
DW 11.800 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
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TAU 0.00302000 sec
TDO 1
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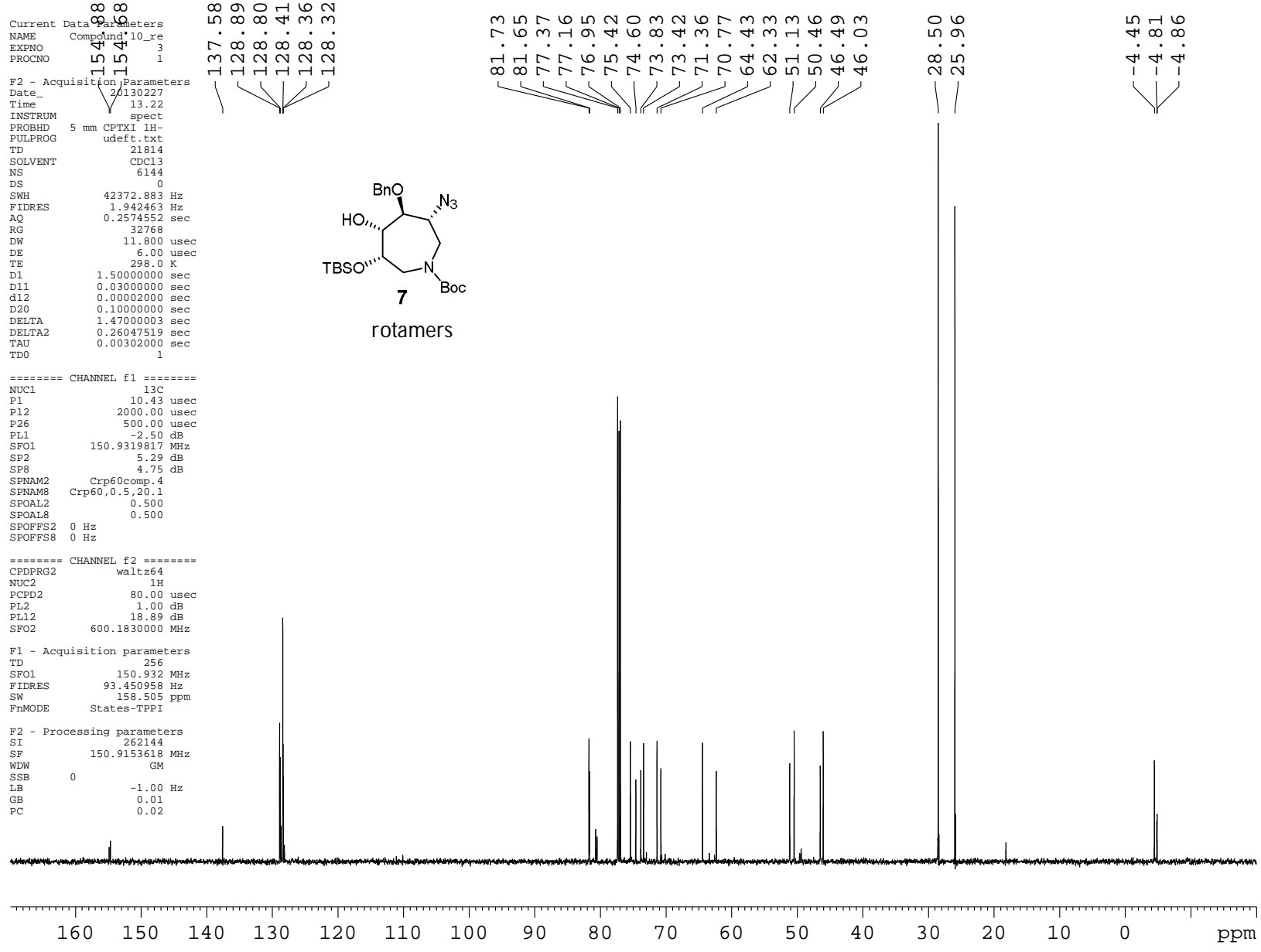


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NUC1 13C
P1 10.43 usec
P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
SPNAM2 Crp60comp.4
SPNAM8 Crp60,0.5,20.1
SPOAL2 0.500
SPOAL8 0.500
SPOFFS2 0 Hz
SPOFFS8 0 Hz

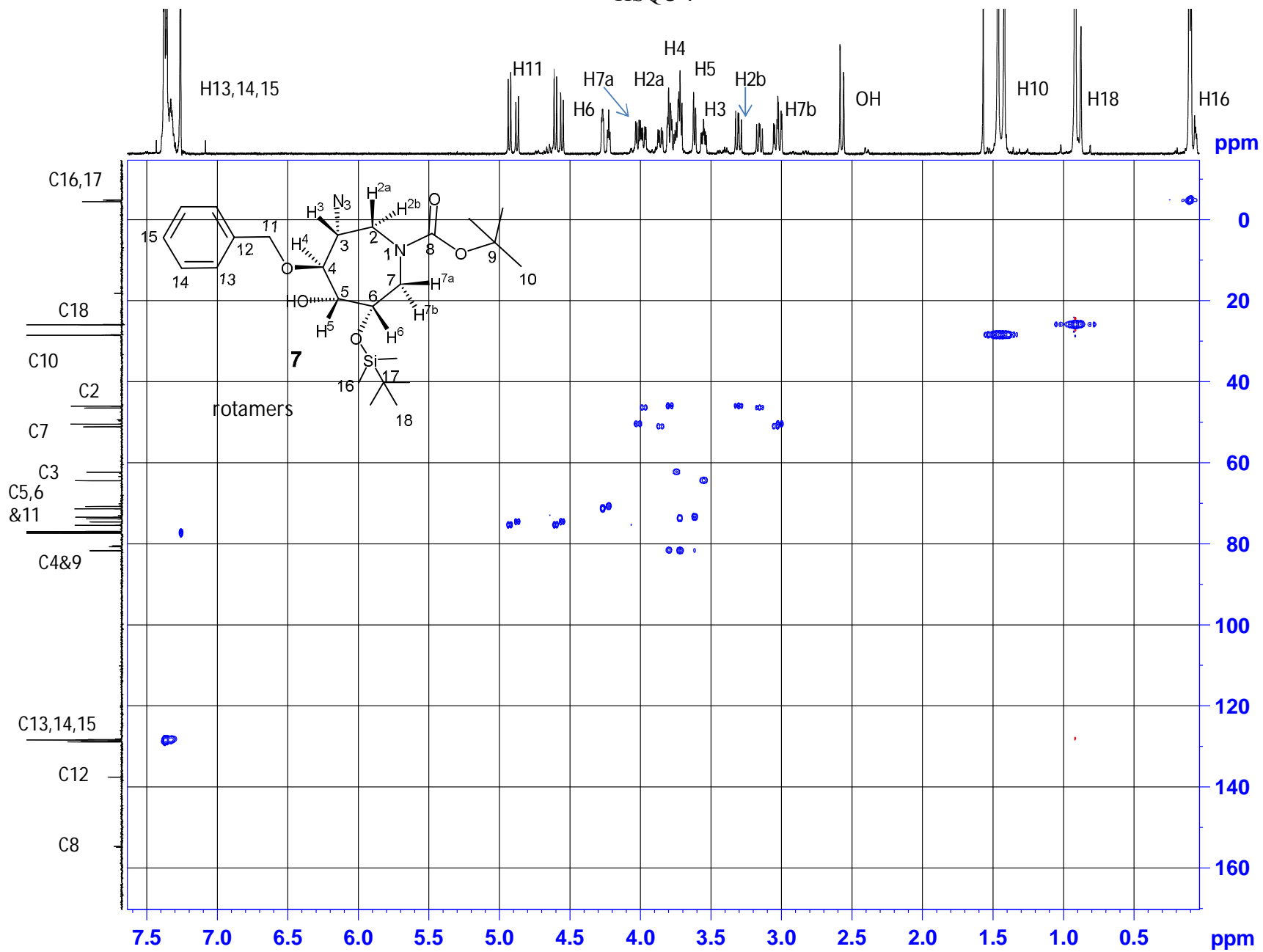
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NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
PL12 18.89 dB
SFO2 600.1830000 MHz

F1 - Acquisition parameters
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SFO1 150.932 MHz
FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI

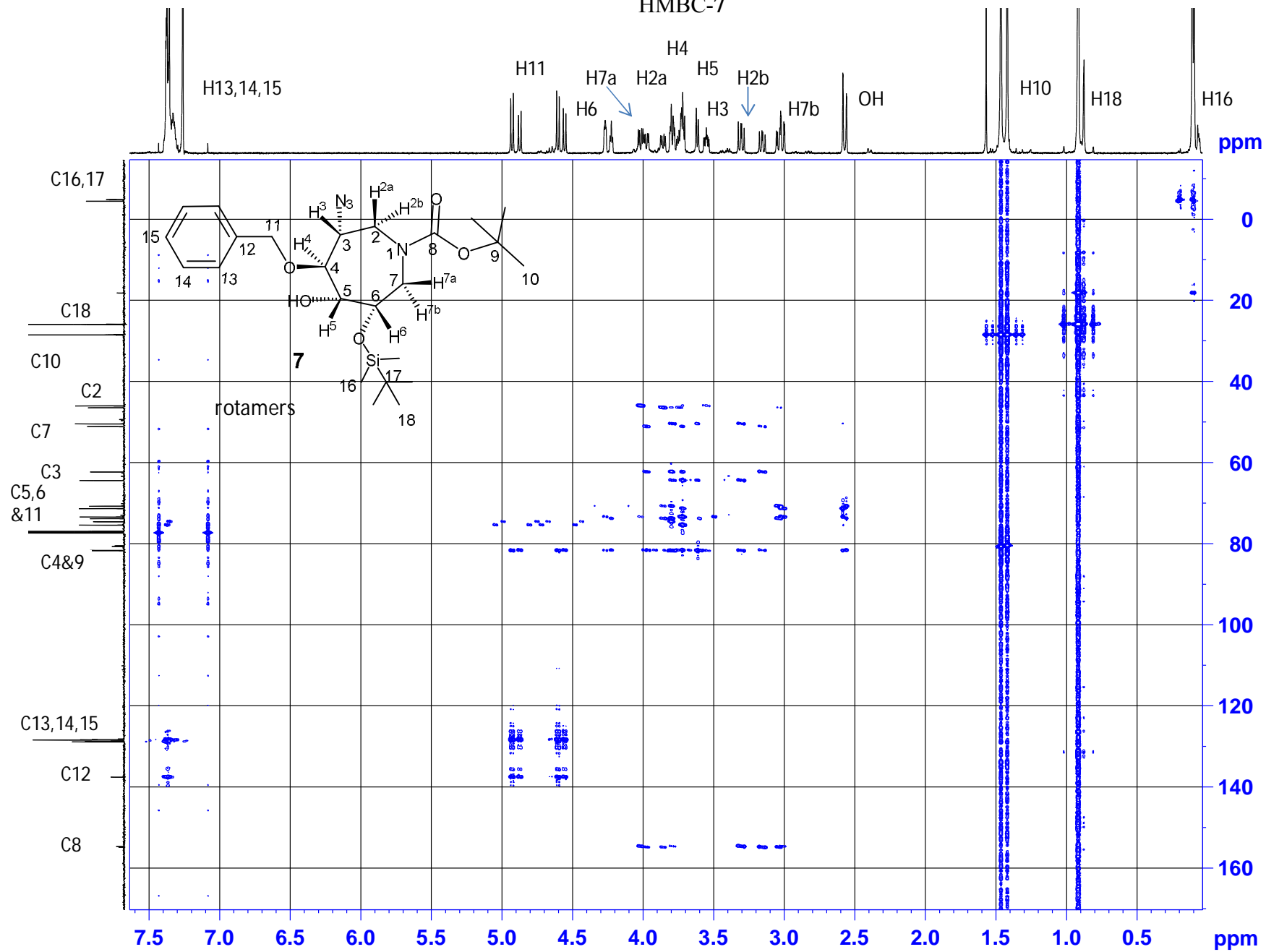
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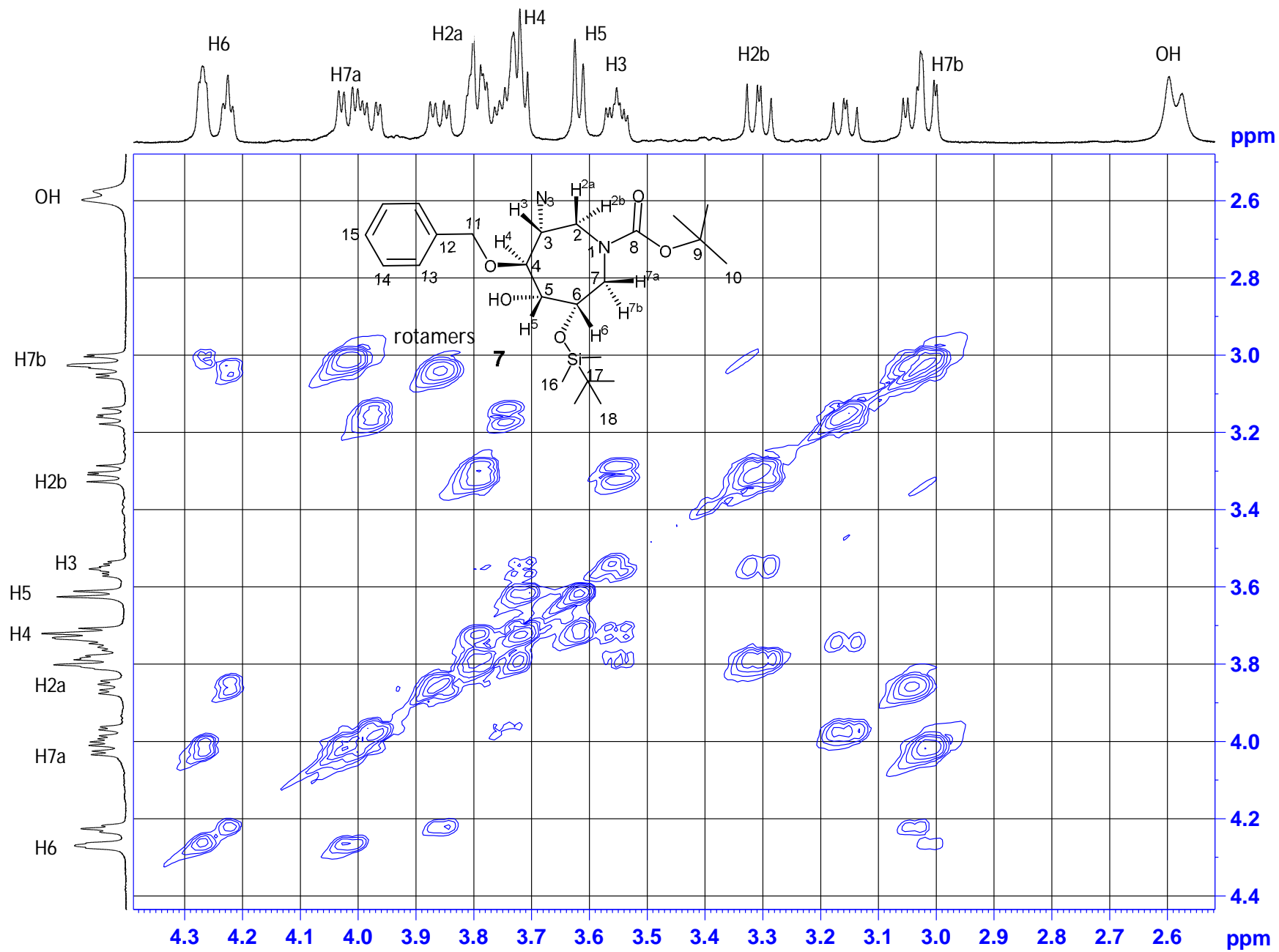
HSQC-7



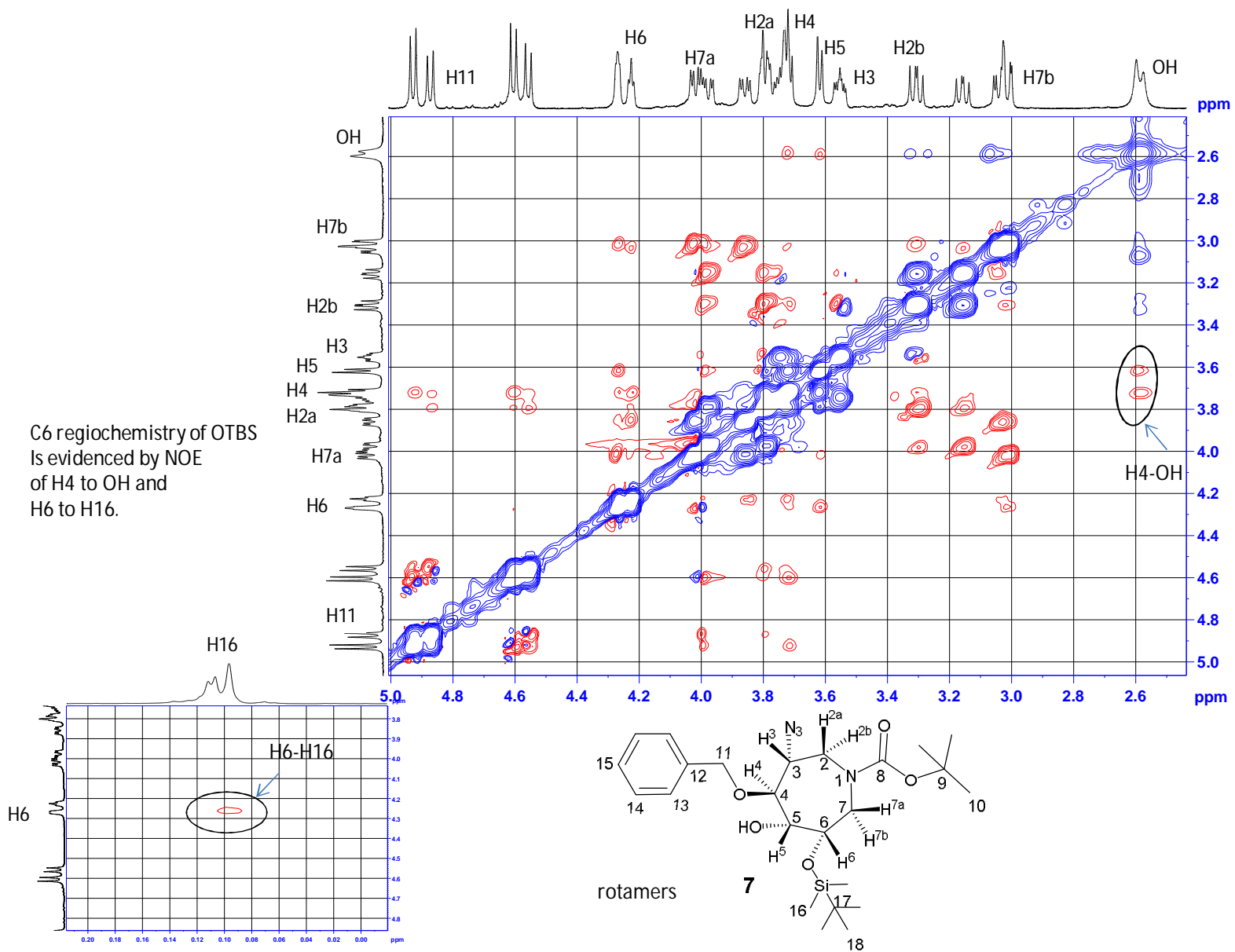
HMBC-7



COSY-7

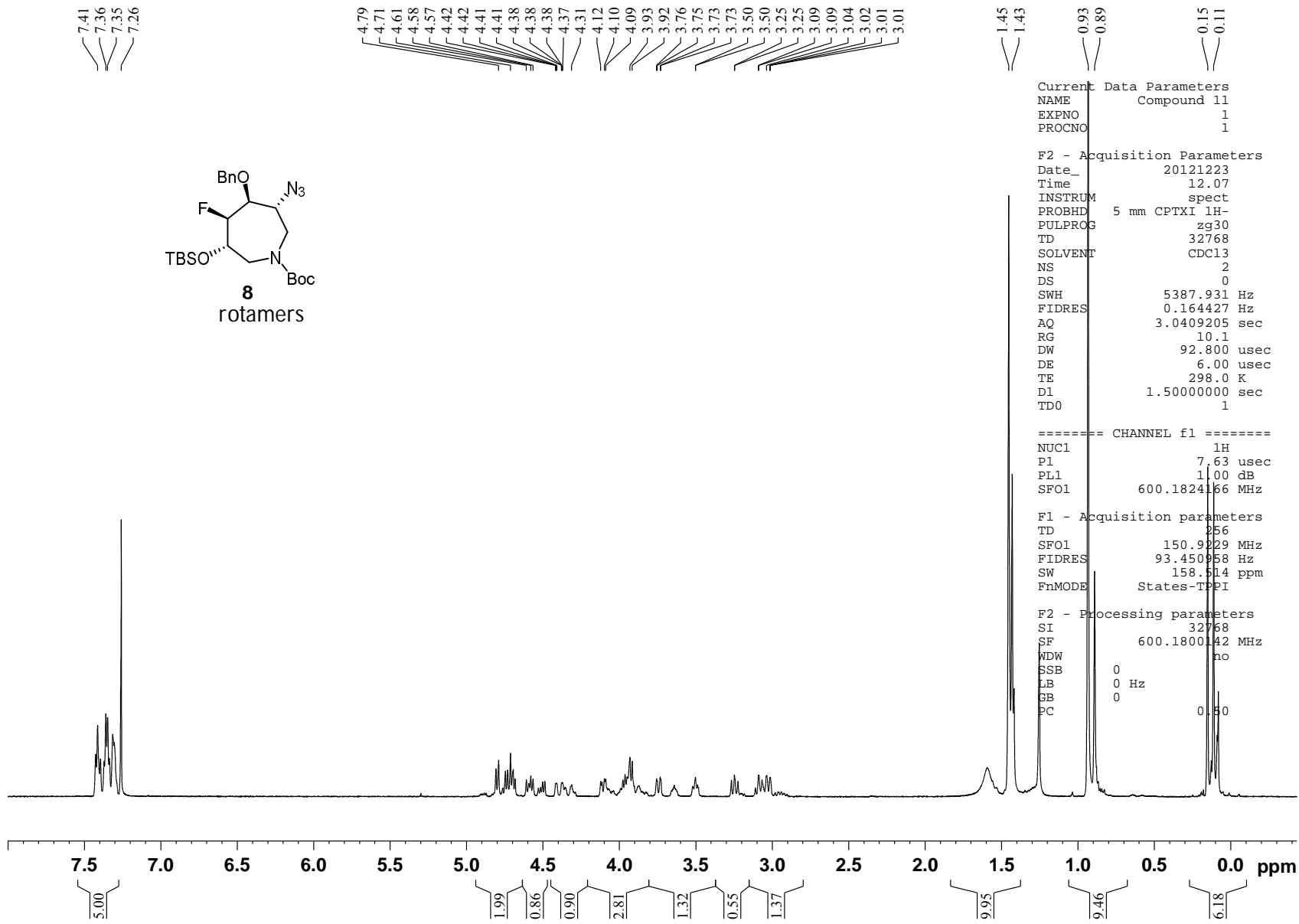


NOESY-7



C6 regiochemistry of OTBS
Is evidenced by NOE
of H4 to OH and
H6 to H16.

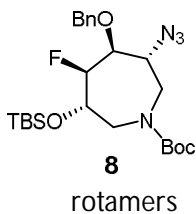
¹H NMR-8



¹³C NMR-8

Current Data Parameters
NAME Compound 11
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121223
Time 14.50
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PROBHD 5 mm CPTXI 1H-
PULPROG udeflt.txt
TD 21814
SOLVENT CDCl3
NS 4096
DS 0
SWH 42372.883 Hz
FIDRES 1.942463 Hz
AQ 0.2574552 sec
RG 32768
DW 11.800 usec
DE 6.00 usec
TE 298.0 K
D1 1.5000000 sec
D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
DELTA2 0.26047519 sec
TAU 0.00302000 sec
TD0 1

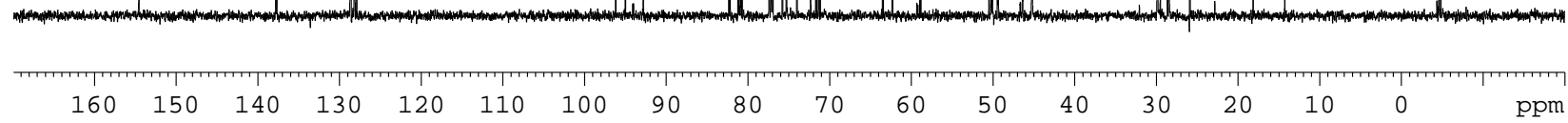
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137.68
128.69
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128.18



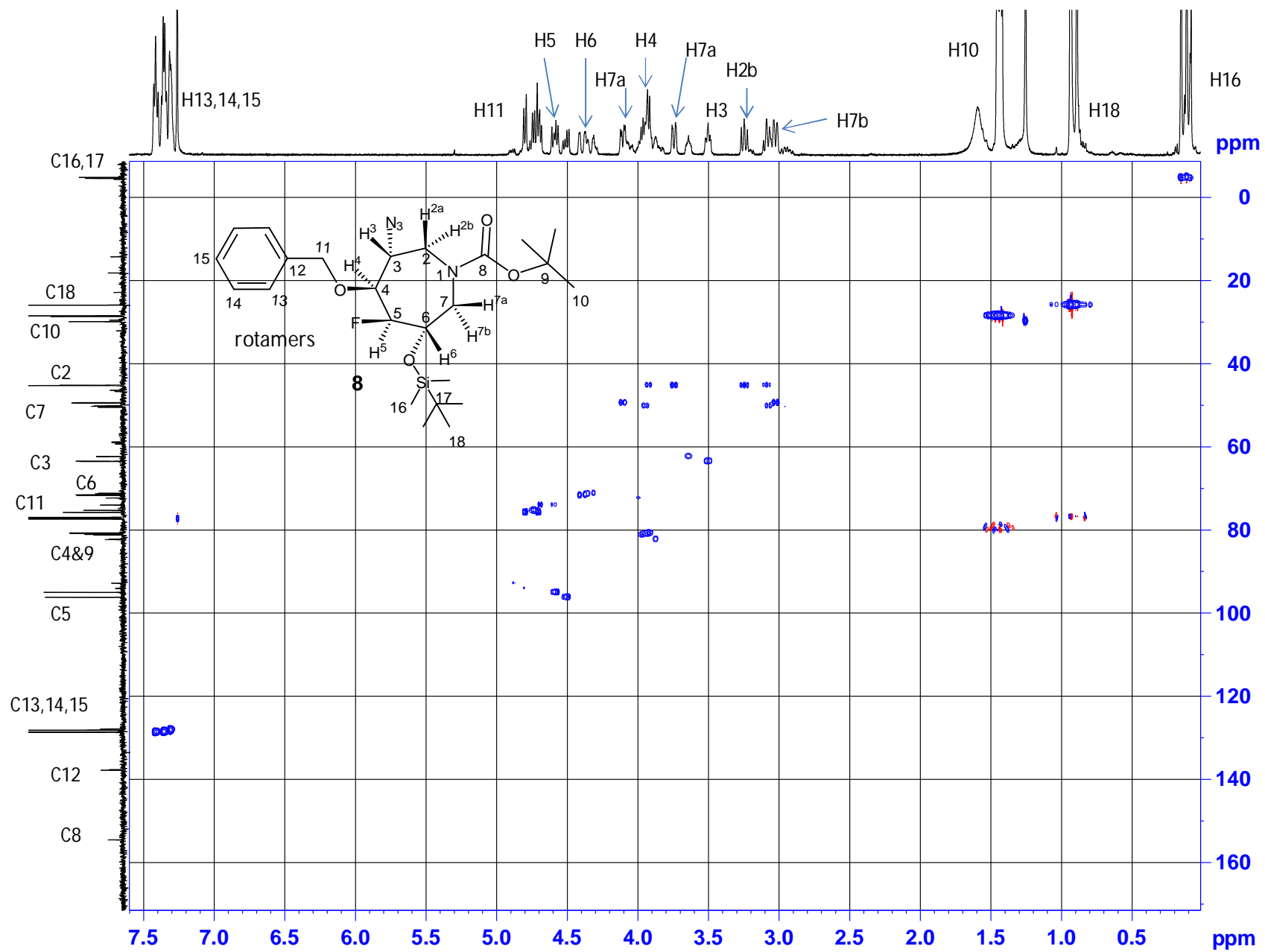
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95.00
81.20
81.06
80.83
80.71
77.37
77.16
76.95
75.76
75.27
71.68
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71.28
63.51
63.44
62.33
62.28
50.47
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28.63
28.46
25.89

-4.61
-4.84

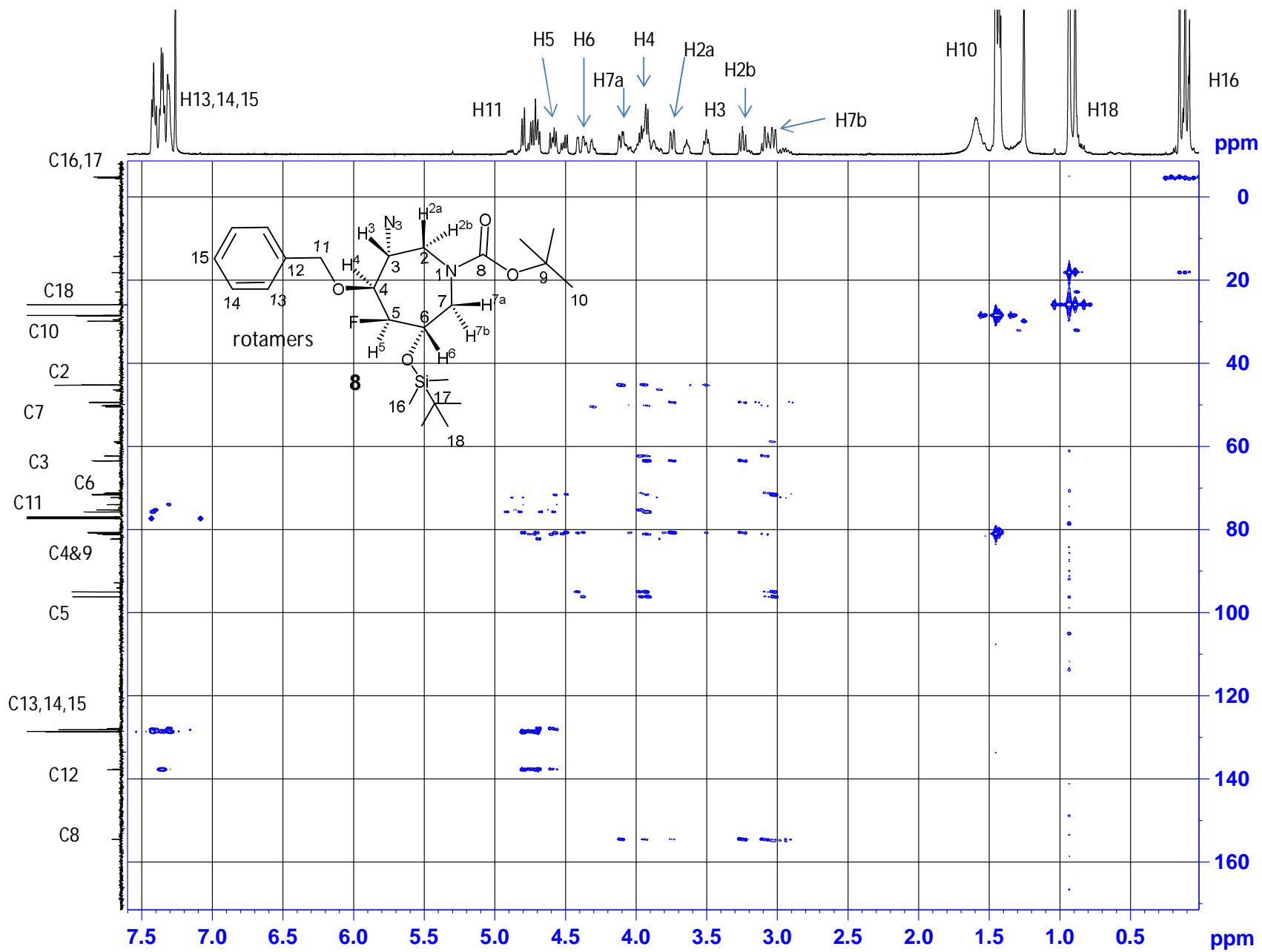
==== CHANNEL f1 =====
NUC1 13C
P1 10.43 usec
P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
SPNAM2 Crp60comp.4
SPNAM8 Crp60,0.5,20.1
SPOAL2 0.500
SPOAL8 0.500
SPOFFS2 0 Hz
SPOFFS8 0 Hz
==== CHANNEL f2 =====
CPDPRG2 waltz64
NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
PL12 18.89 dB
SFO2 600.1830000 MHz
F1 - Acquisition parameters
TD 256
SFO1 150.932 MHz
FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI
F2 - Processing parameters
SI 262144
SF 150.9153616 MHz
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SSB 0
LB -1.00 Hz
GB 0.01
PC 0.02



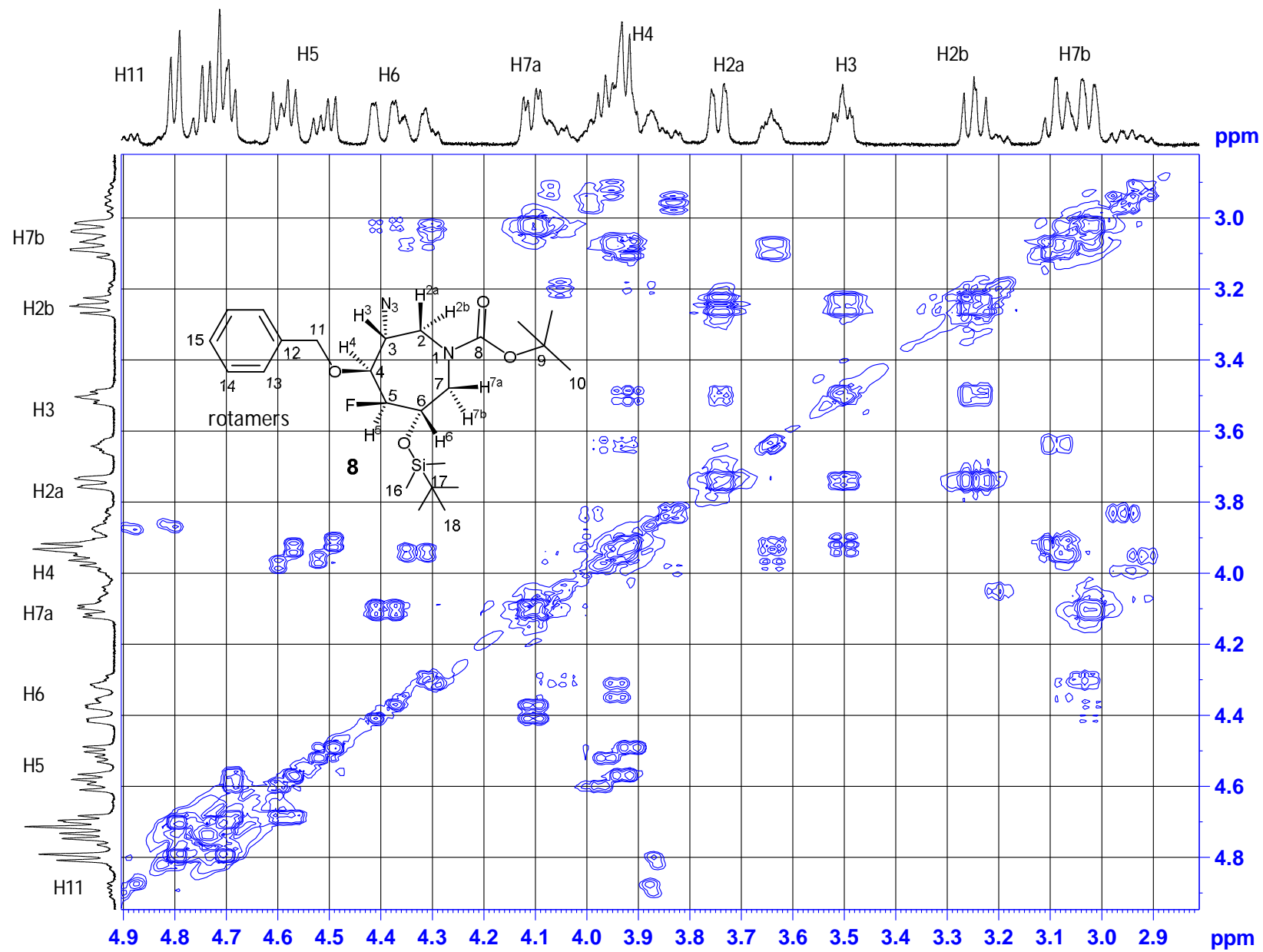
HSQC-8



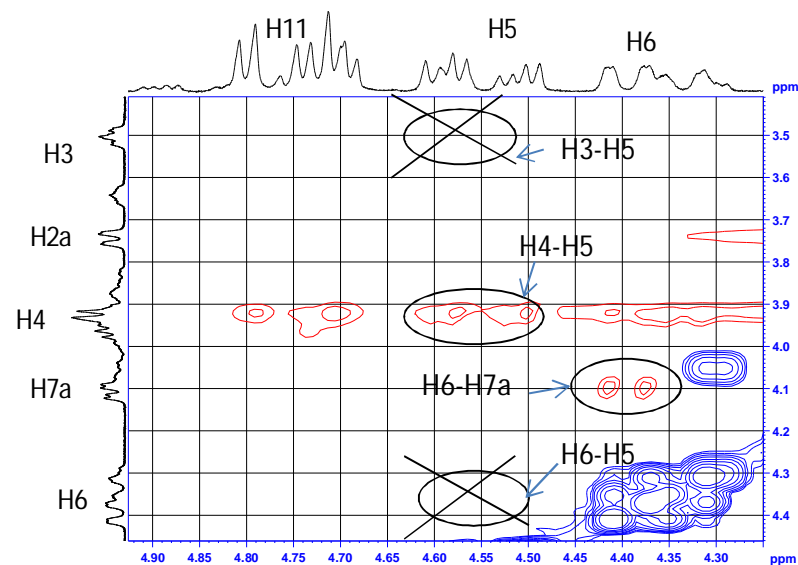
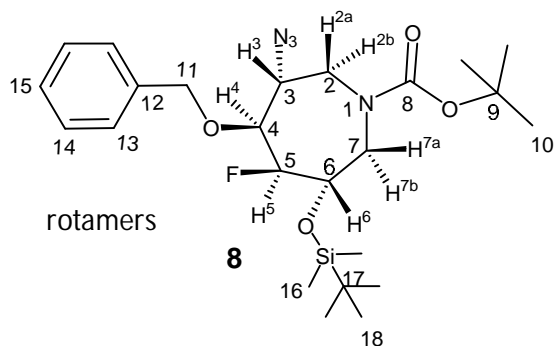
HMBC-8



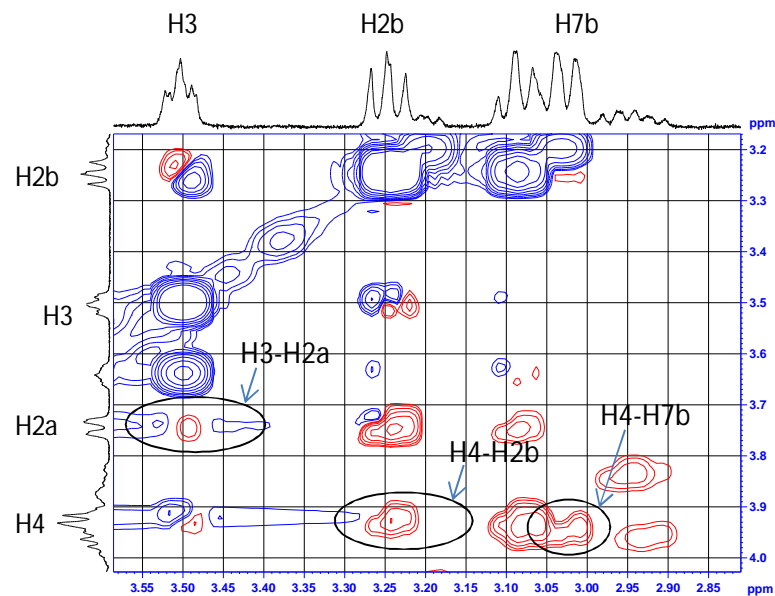
COSY-8



NOESY-8

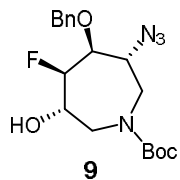


- ❑ C3, C4 and C6 are stereocentres with known stereochemistry and stereochemistry at C5 is of interest.
- ❑ H5 shows big NOE to H4 while no measurable NOE to H6 and H3 suggests H5 is *cis* to H4.
- ❑ H7a shows NOE to H6 while H7b shows NOE to H4 meaning H7a is *trans* and H7b is *cis* to H4.
- ❑ Moreover, H2b shows NOE to H4 and H3 shows NOE to H2a suggesting H2a is *trans* and H2b is *cis* to H4.
- ❑ Based on NOE data the absolute C5 stereochemistry is *S* (*cis* to C4 OBn).



¹H NMR-9

7.37
7.35
7.34
7.32
7.26



rotamers

4.79
4.77
4.71
4.63
4.61
4.14
4.14
4.02
4.01
4.00
3.97
3.97
3.96
3.96
3.95
3.94
3.41
3.40
3.38
3.38
3.25
3.25
3.23
3.22

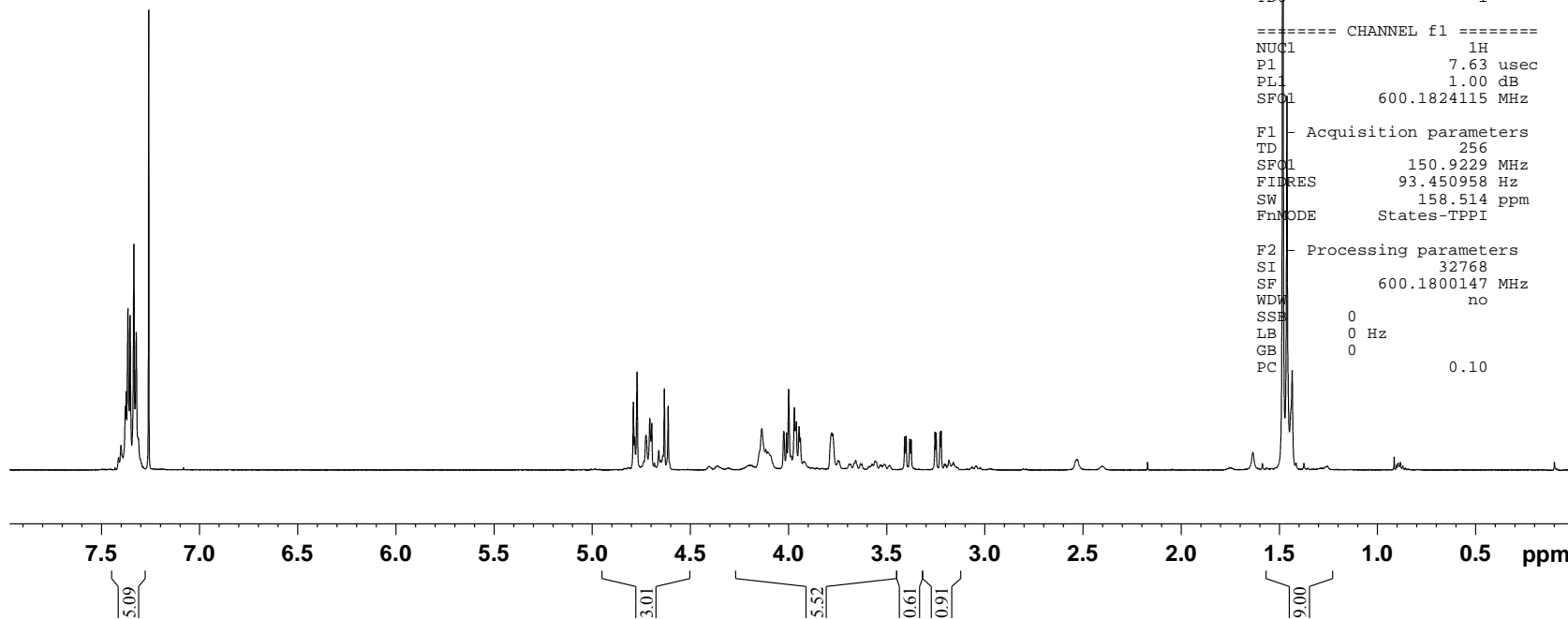
1.48
1.46

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PROCNO 1
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PULPROG zg30
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SOLVENT CDCl3
NS 4
DS 0
SWH 4770.992 Hz
FIDRES 0.145599 Hz
AQ 3.4341364 sec
RG 10.1
DW 104.800 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
TDO 1

==== CHANNEL f1 =====
NUC1 1H
P1 7.63 usec
PL1 1.00 dB
SF01 600.1824115 MHz

F1 - Acquisition parameters
TD 256
SF01 150.9229 MHz
FIDRES 93.450958 Hz
SW 158.514 ppm
FnMODE States-TPPI

F2 - Processing parameters
SI 32768
SF 600.1800147 MHz
WDW no
SSE 0
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GB 0
PC 0.10



¹³C NMR-9

Current Data Parameters
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EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
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Time 20.42
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PROBHD 5 mm CPTXI 1H-
PULPROG udeflt.txt
TD 21814
SOLVENT CDCl3
NS 4096
DS 0
SWH 30303.031 Hz
FIDRES 1.389155 Hz
AQ 0.3599810 sec
RG 32768
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
DELTA2 0.36300099 sec
TAU 0.00302000 sec
TDO 1

=====
CHANNEL f1
NUC1 13C
P1 10.43 usec
P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
SPNAM2 Crp60comp.4
SPNAM8 Crp60,0.5,20.1
SPOAL2 0.500
SPOAL8 0.500
SPOFFS2 0 Hz
SPOFFS8 0 Hz

=====
CHANNEL f2
CPDPRG2 waltz64
NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
FL12 18.89 dB
SFO2 600.1830000 MHz

F1 - Acquisition parameters
TD 256
SFO1 150.932 MHz
FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI

F2 - Processing parameters
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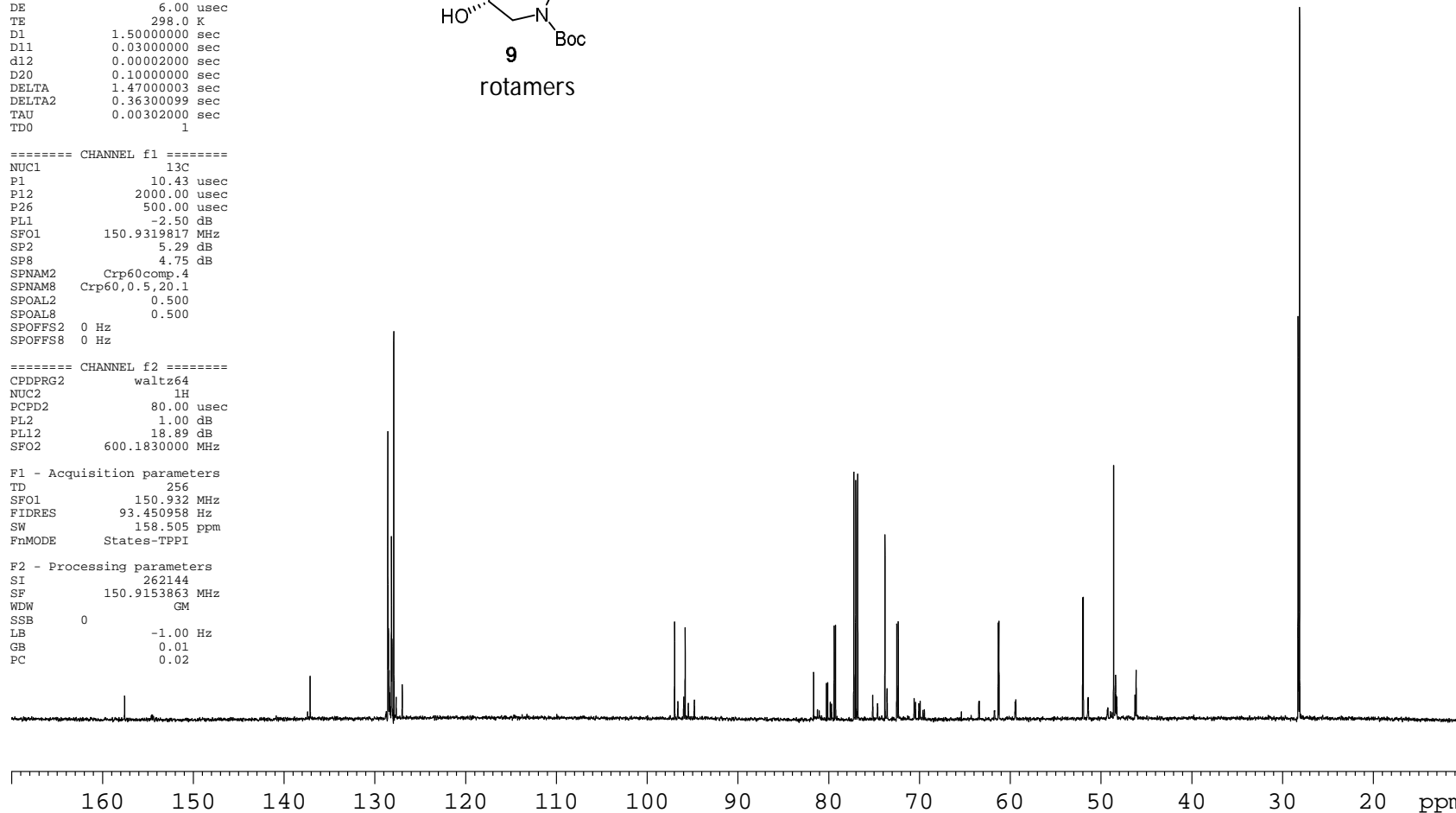
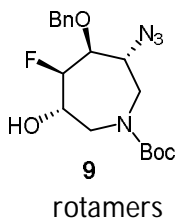
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96.97
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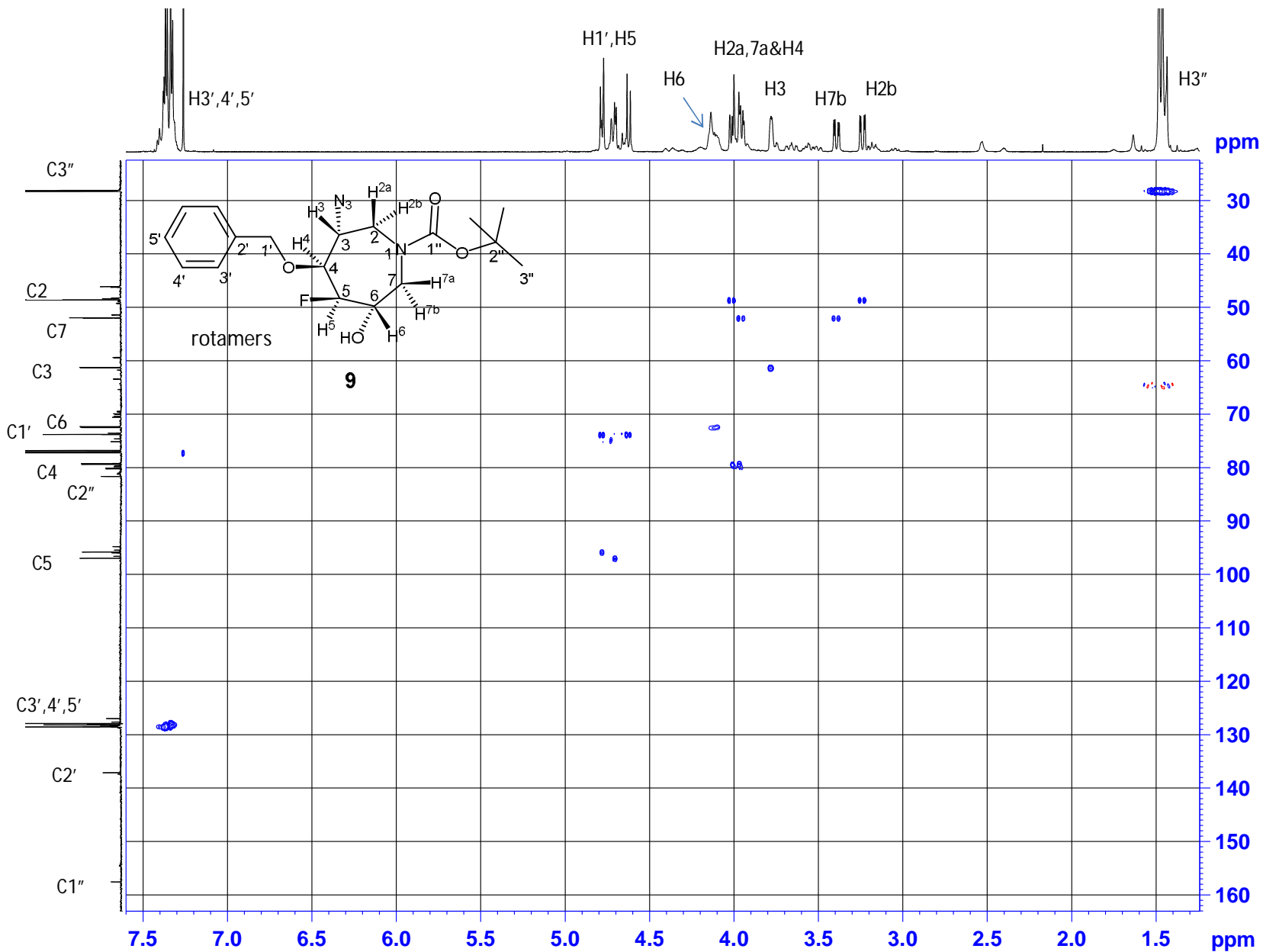
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79.39
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77.01
76.80
73.79
72.49
72.33
61.31
61.24

52.01
51.95
48.60

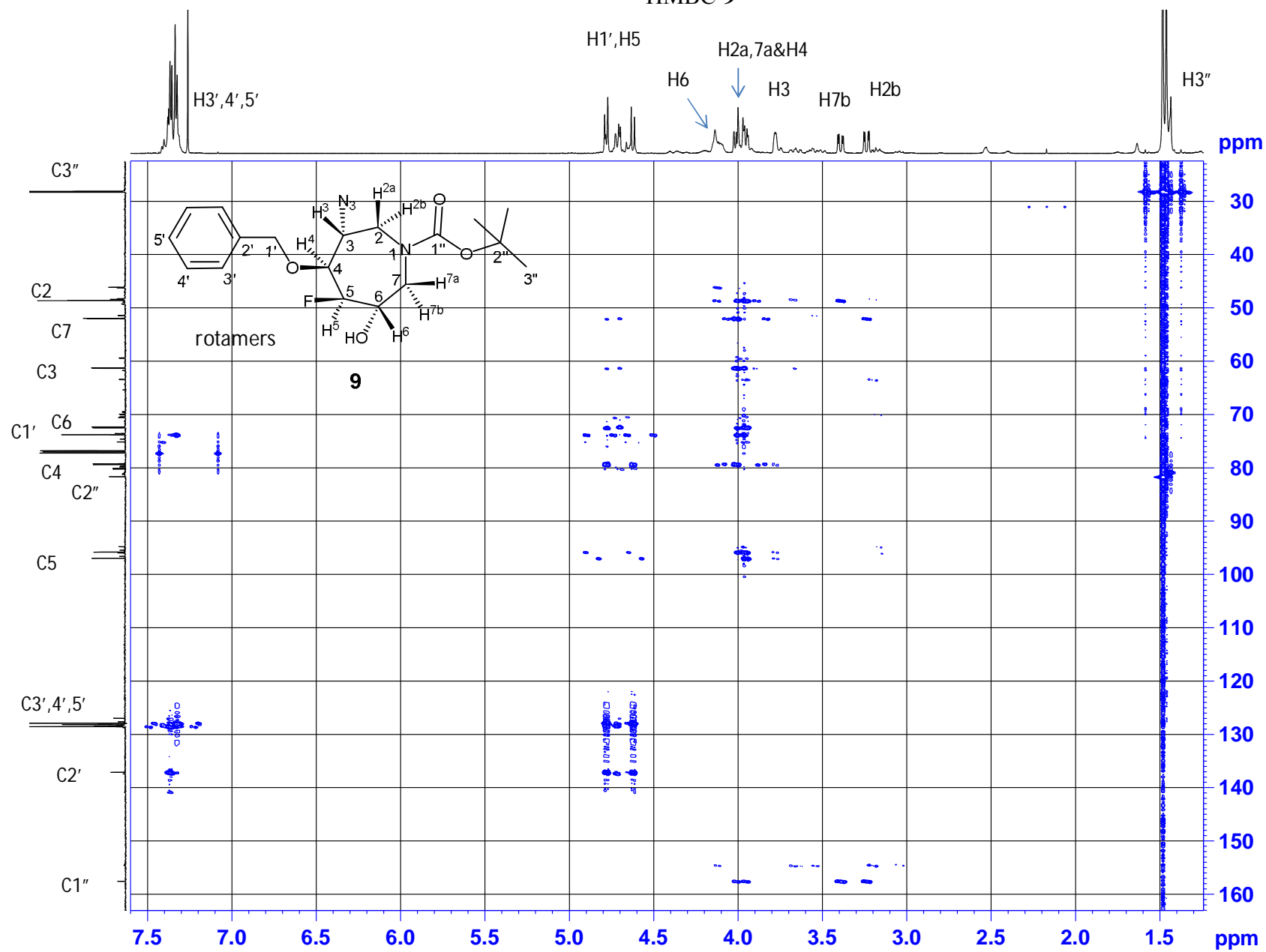
28.28
28.11



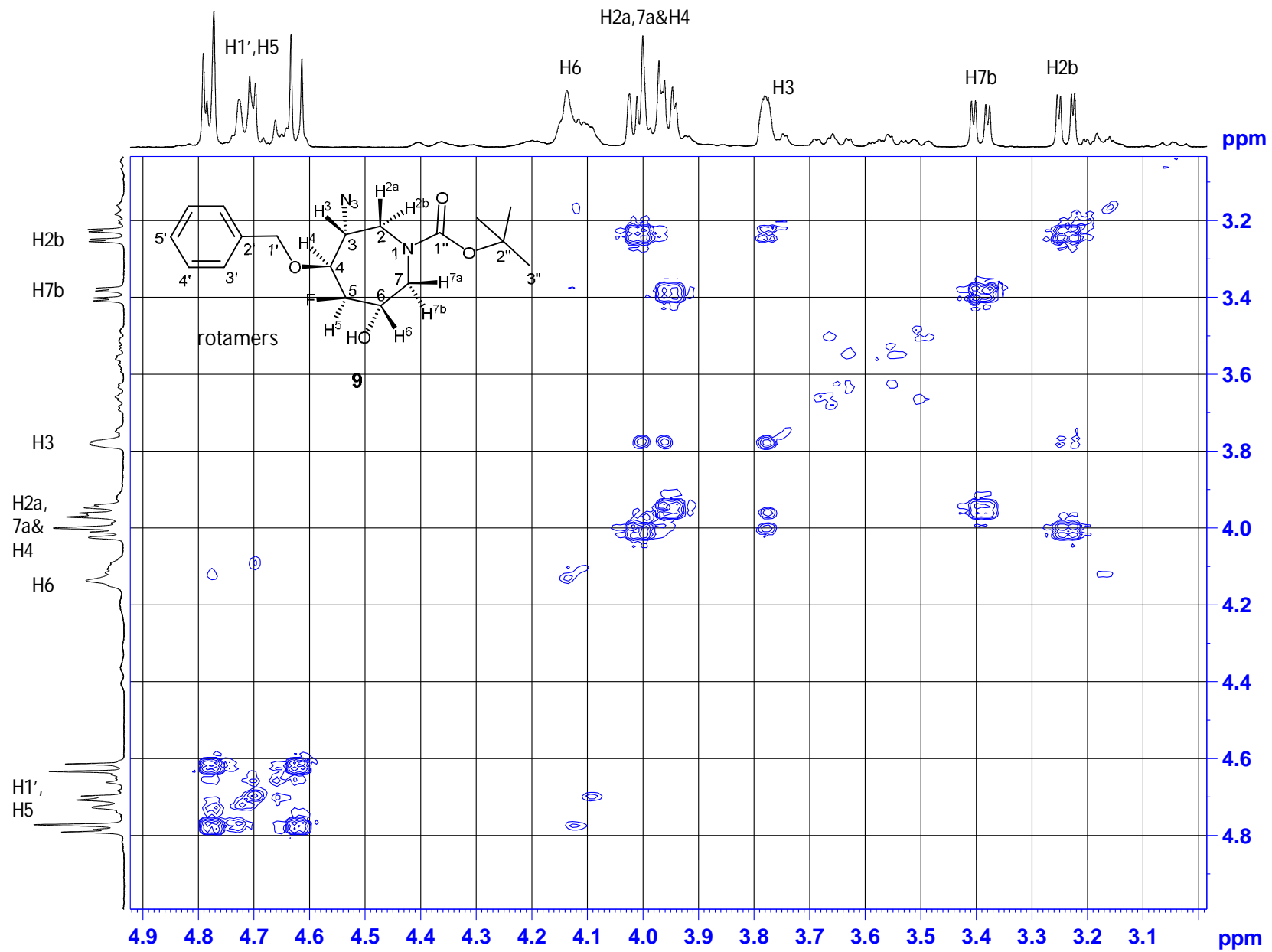
HSQC-9



HMBC-9



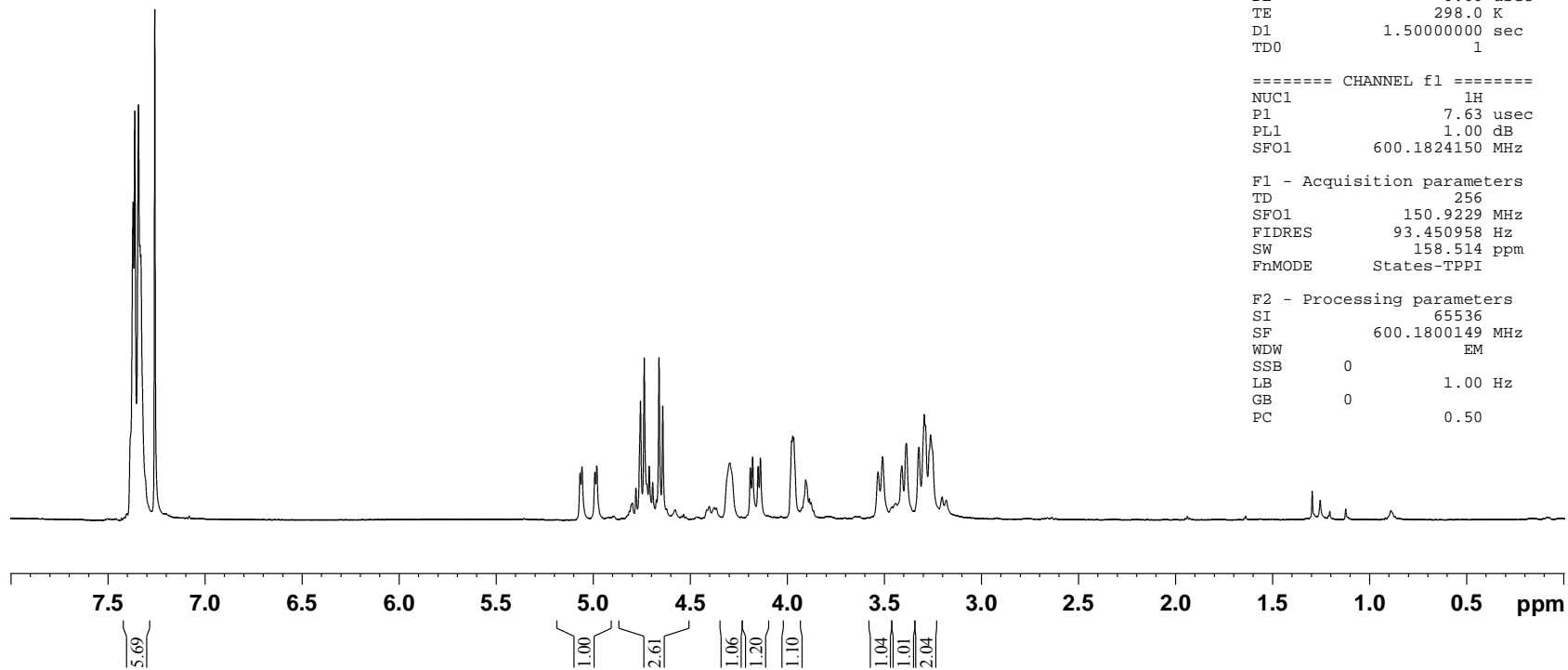
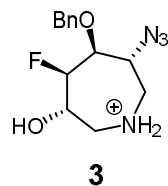
COSY-9



¹H NMR-3

7.37
7.36
7.34
7.34
7.33
7.26

5.07
5.06
4.99
4.98
4.78
4.76
4.74
4.72
4.71
4.69
4.66
4.64
4.30
4.19
4.18
4.15
4.14
3.98
3.97
3.91
3.53
3.51
3.41
3.39
3.32
3.29
3.26



Current Data Parameters
NAME arp704a_FOH spot1 salt
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130505
Time 11.38
INSTRUM spect
PROBHD 5 mm CPTXI 1H-
PULPROG zg30
TD 32768
SOLVENT CDC13
NS 2
DS 0
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4079220 sec
RG 11.3
DW 104.000 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
TD0 1

=====
CHANNEL f1
NUC1 1H
P1 7.63 usec
PL1 1.00 dB
SFO1 600.1824150 MHz

F1 - Acquisition parameters
TD 256
SFO1 150.9229 MHz
FIDRES 93.450958 Hz
SW 158.514 ppm
FnMODE States-TPPI

F2 - Processing parameters
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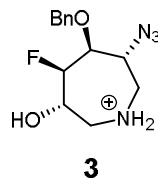
¹³C NMR-3

Current Data Parameters
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PROCNO 1

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Time 18.43
INSTRUM spect
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PULPROG zgpg
TD 66560
SOLVENT CDC13
NS 15172
DS 2
SWH 25125.629 Hz
FIDRES 0.377488 Hz
AQ 1.3245940 sec
RG 3649.1
DW 19.900 usec
DE 20.00 usec
TE 298.2 K
D1 2.00000000 sec
d11 0.03000000 sec
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TD0 1

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136.55
128.96
128.88
128.80
128.67
128.61
128.33

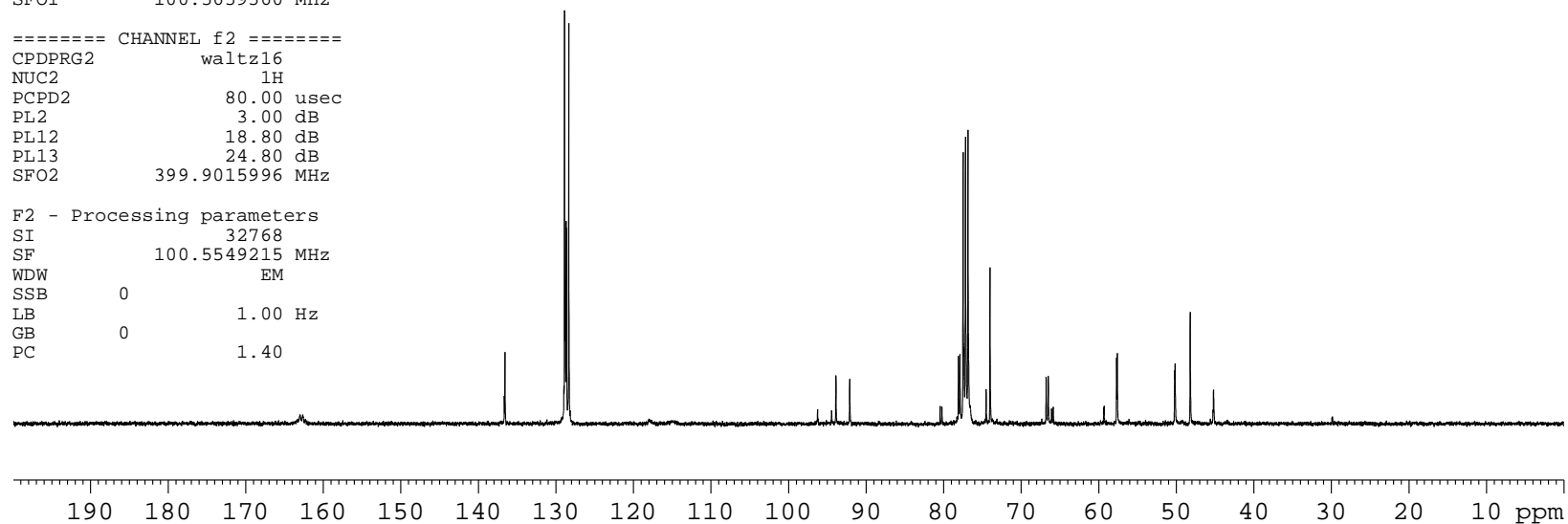
93.88
92.10
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77.88
77.48
77.36
77.16
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74.01
66.76
66.49
57.68
57.59
50.18
50.13
48.19



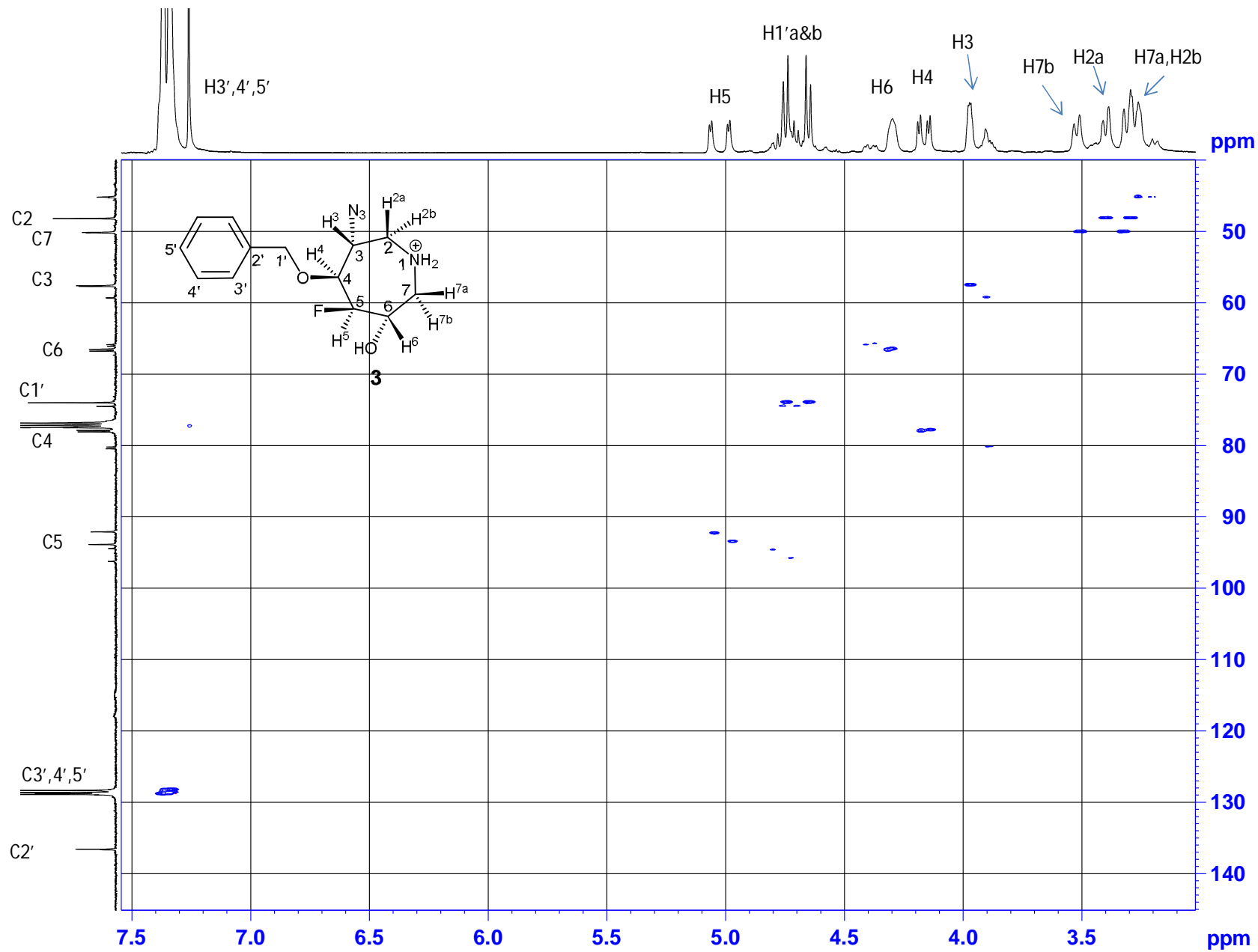
==== CHANNEL f1 =====
NUC1 13C
P1 12.00 usec
PL1 -0.50 dB
SFO1 100.5659560 MHz

==== CHANNEL f2 =====
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 3.00 dB
PL12 18.80 dB
PL13 24.80 dB
SFO2 399.9015996 MHz

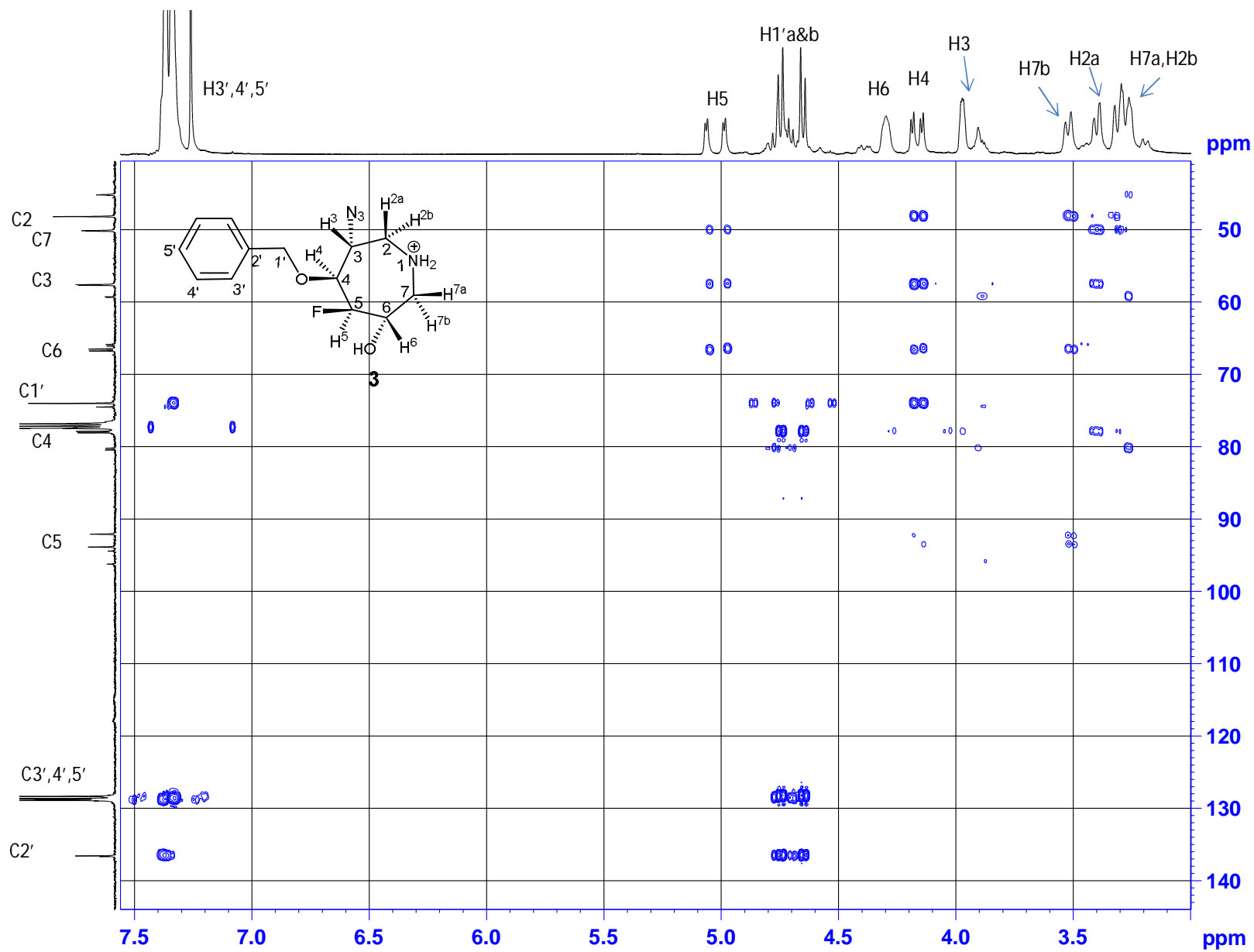
F2 - Processing parameters
SI 32768
SF 100.5549215 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40



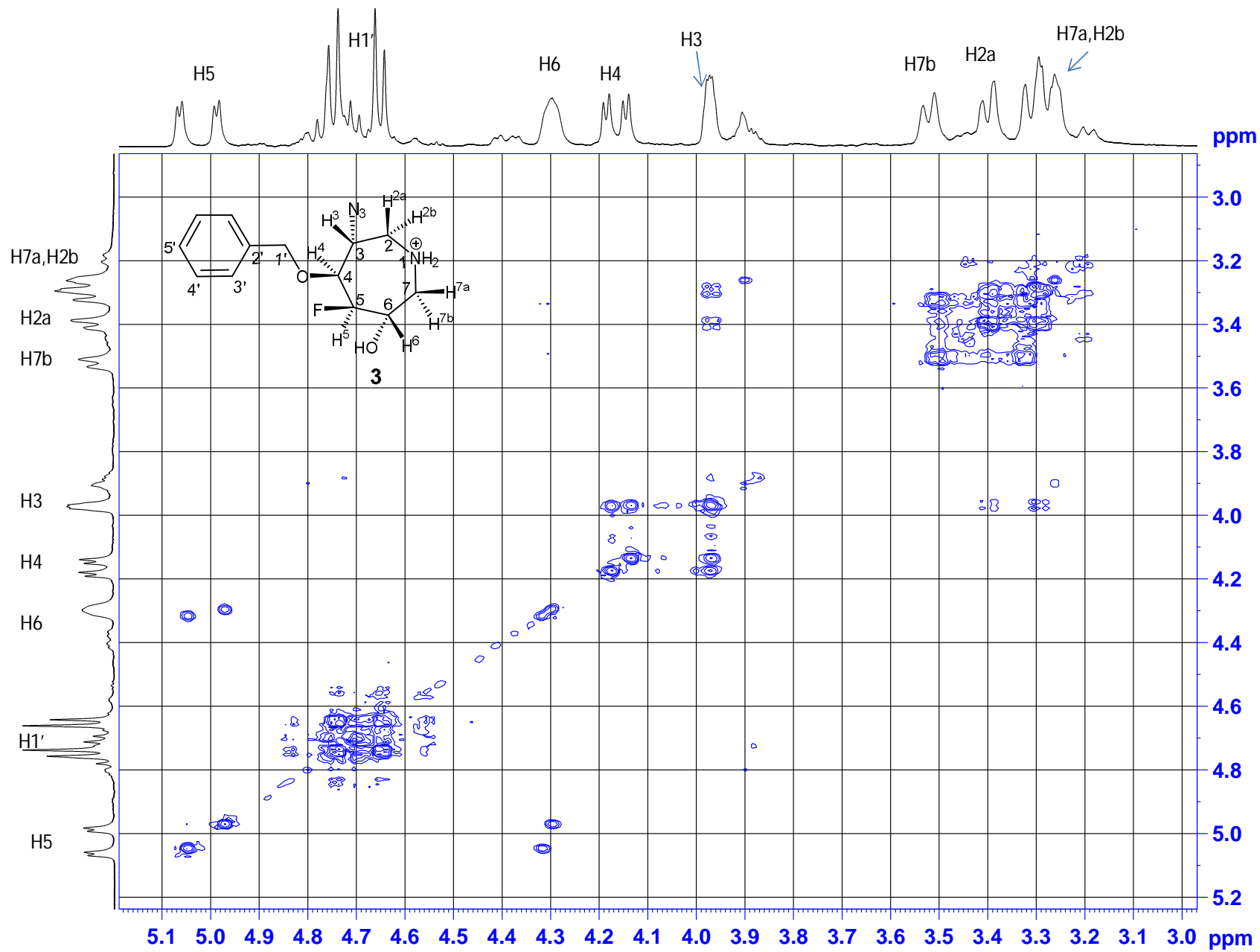
HSQC-3



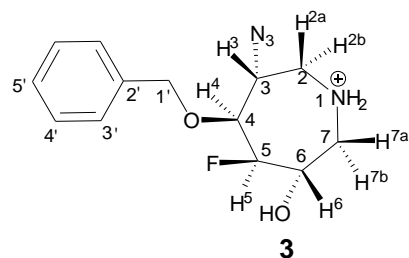
HMBC-3



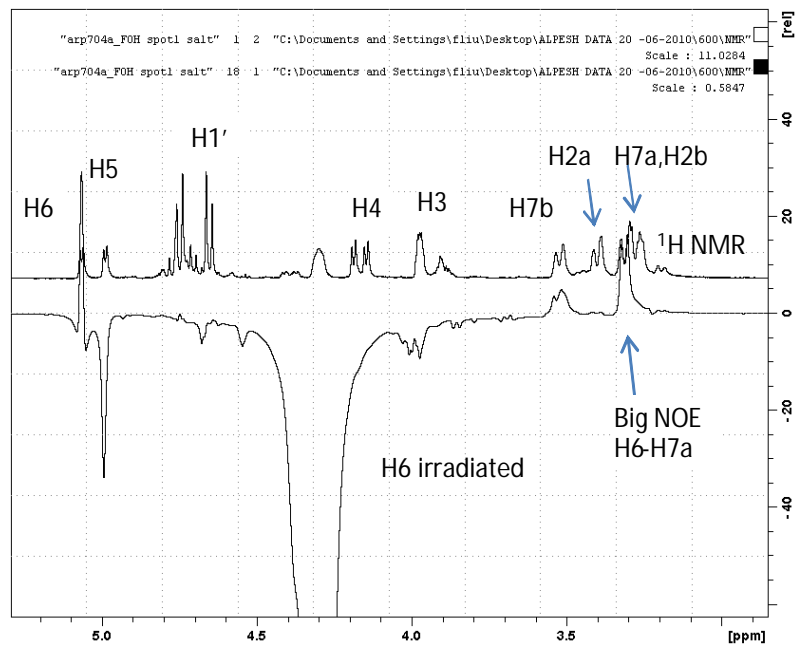
COSY-3



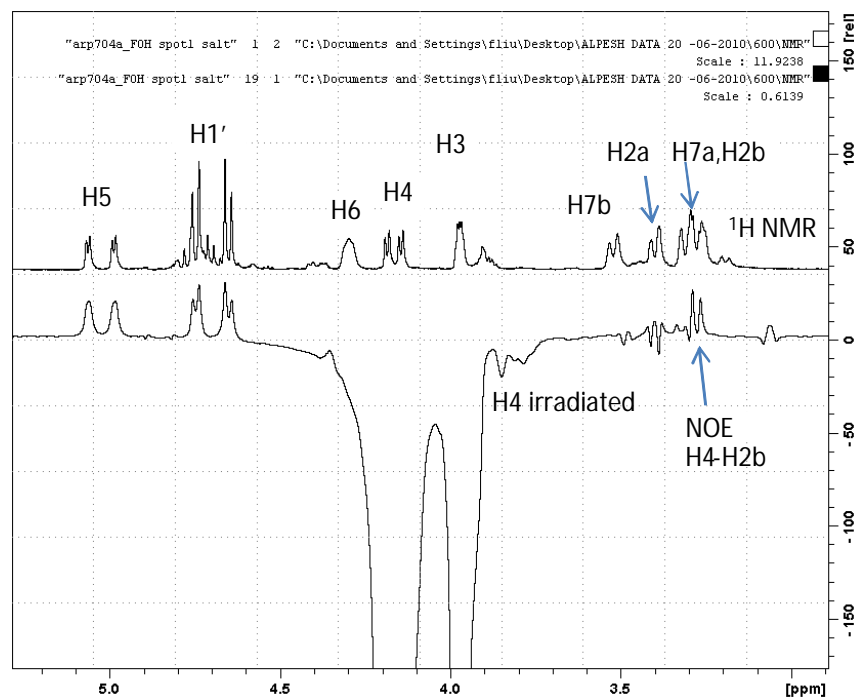
NOESY-3



1D selective NOESY

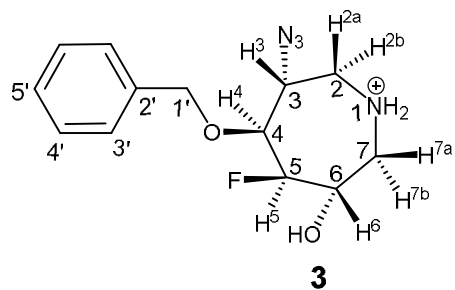


1D selective NOESY

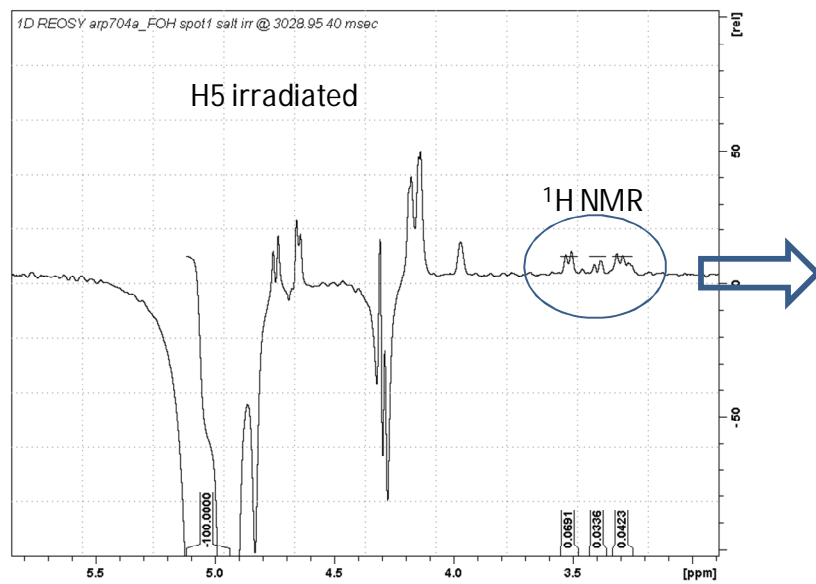


- Compound **3** has three stereocentres (C3, C4 and C6) having known absolute stereochemistry
- H4 shows NOE with H2b while no measurable NOE with H2a meaning H2b is *cis* and H2a is *trans* to H4.
- H6 shows significantly large NOE with H7a compared to H7b suggesting H7a is *cis* and H7b is *trans* to H6.
- H5 shows big NOE to H4 and small to H3 which leads to nowhere. However, quantitative 1D NOE of H5-H7b (7%) is almost double of H5-H7a NOE. Which clearly suggests H5 is *trans* to H4.
- J_{H5-H4} (1.4 Hz) and J_{H5-H6} (6.22 Hz) also support that H5 and H4 are *cis* while H5 and H6 are *trans*.

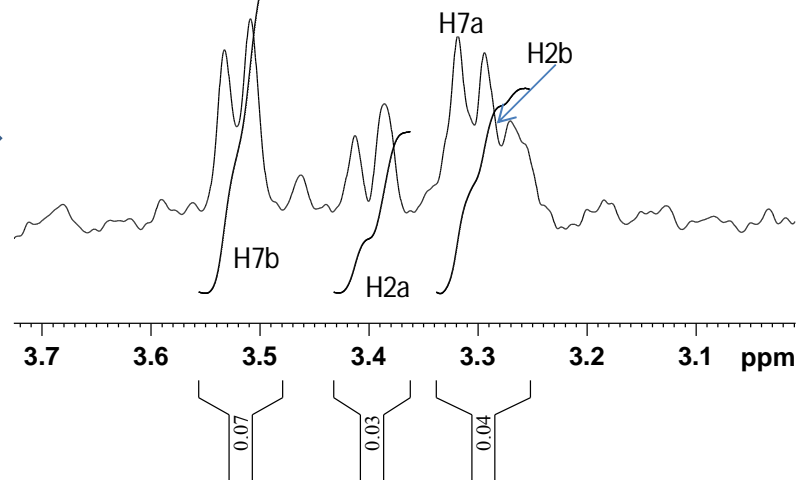
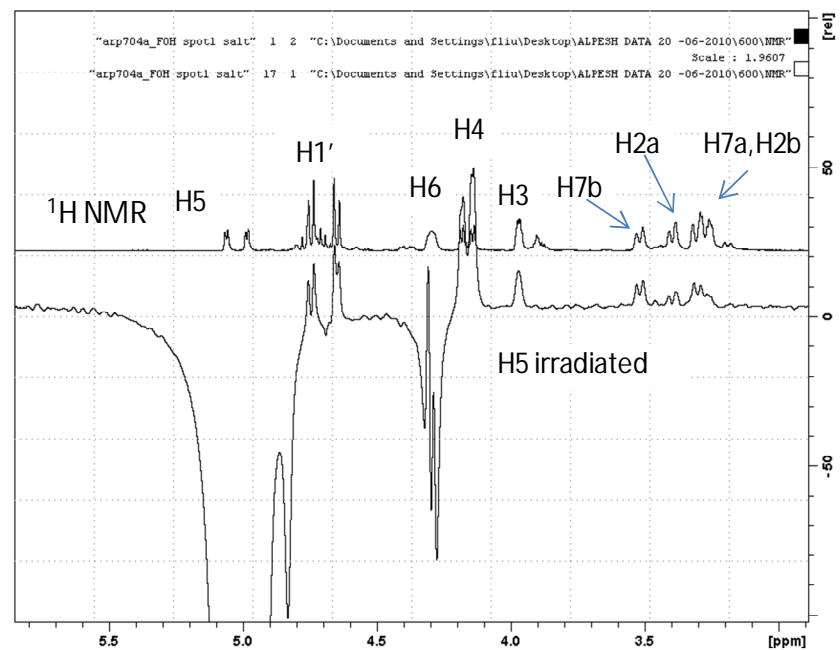
NOESY-3



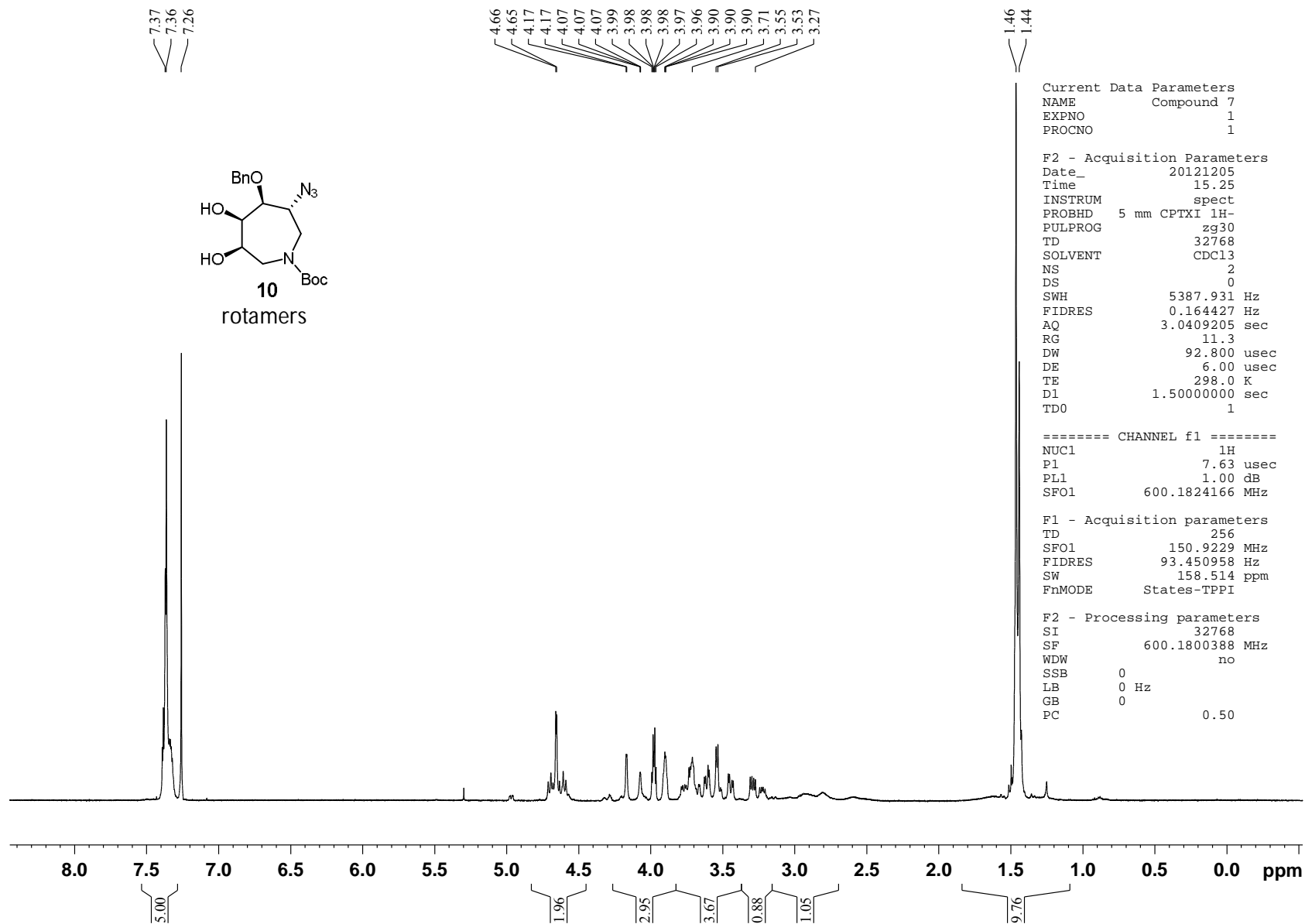
1D selective NOESY



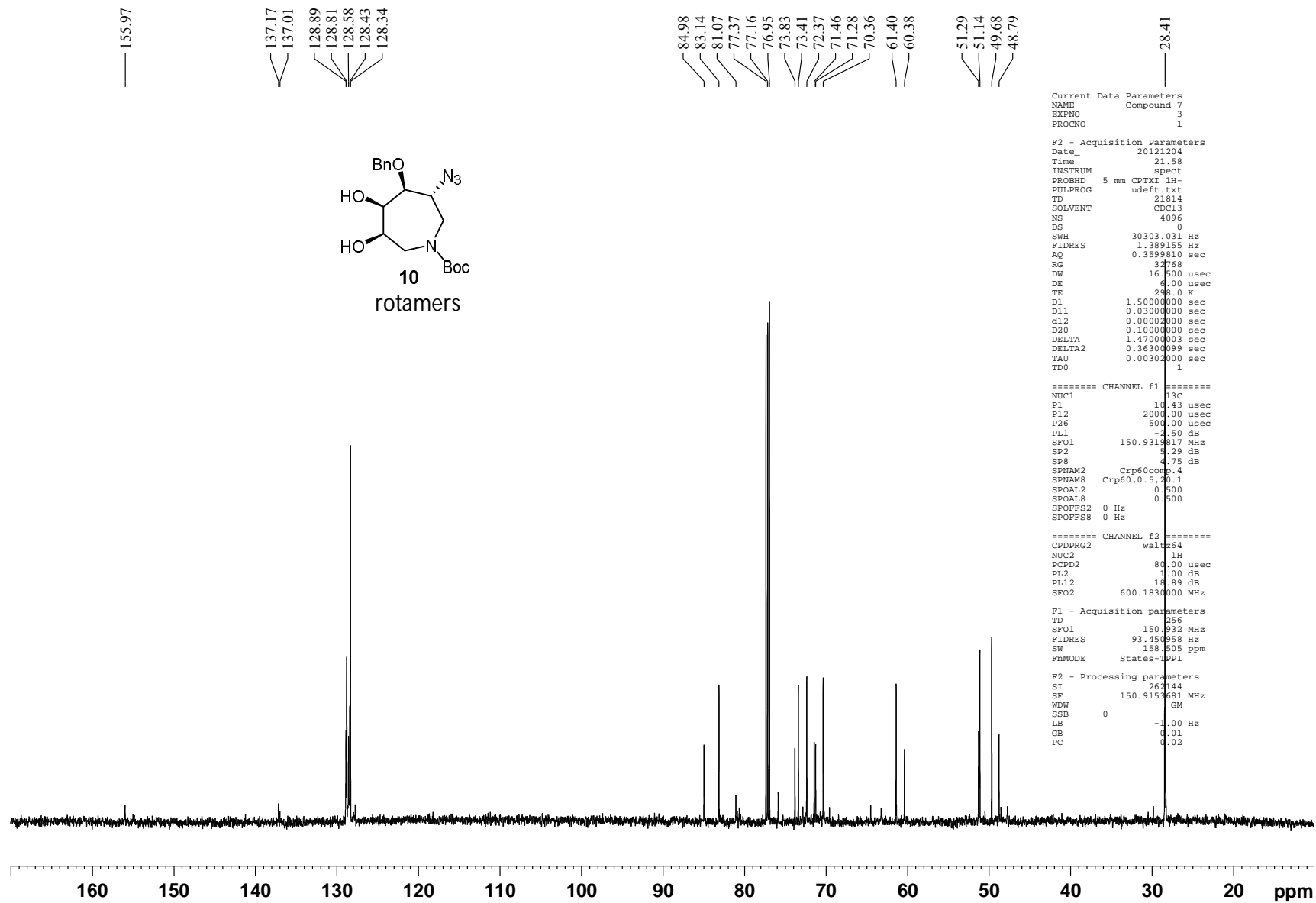
1D selective NOESY



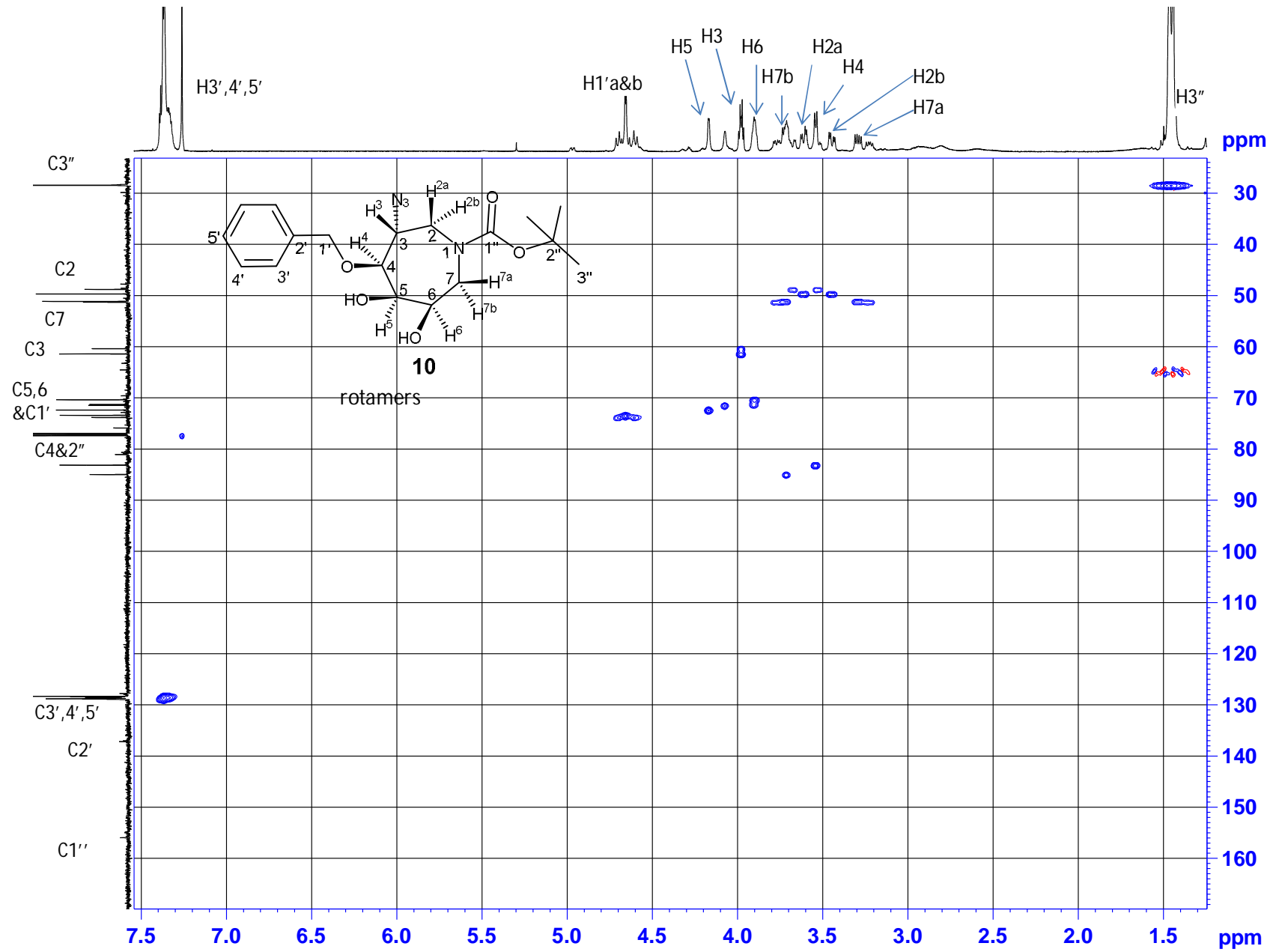
¹H NMR-10



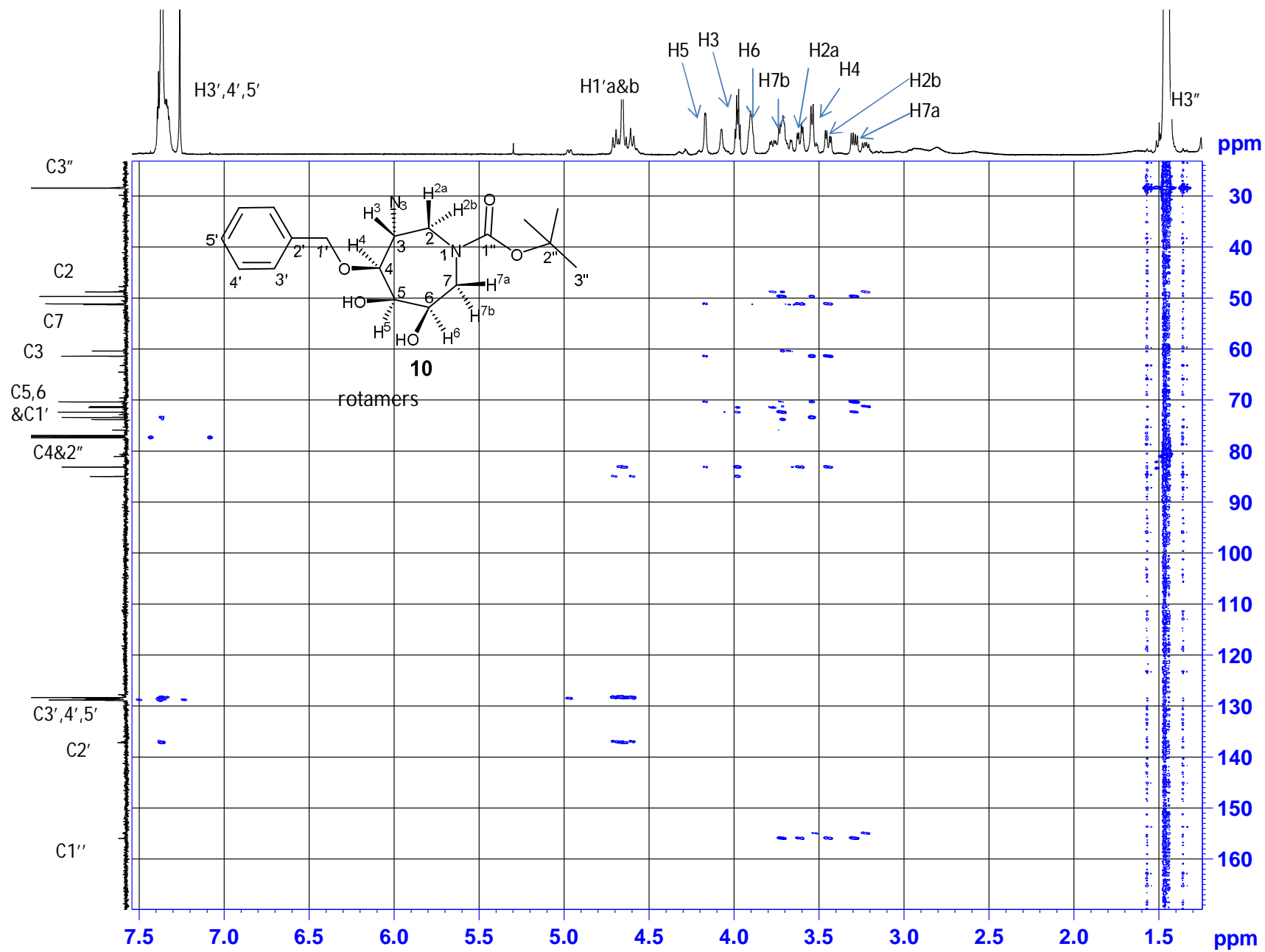
¹³C NMR-10



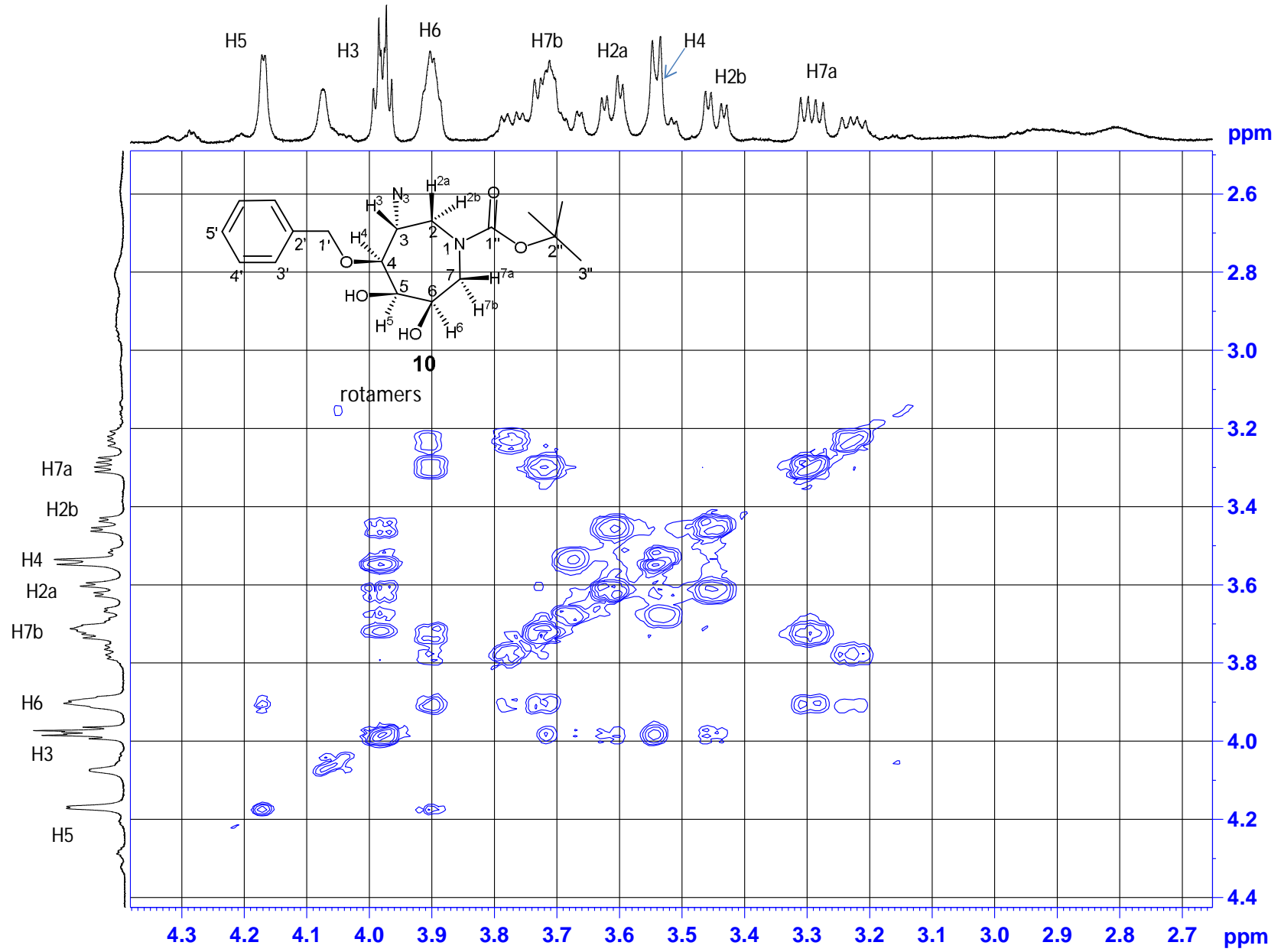
HSQC-10



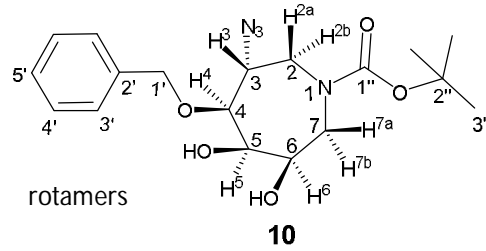
HMBC-10



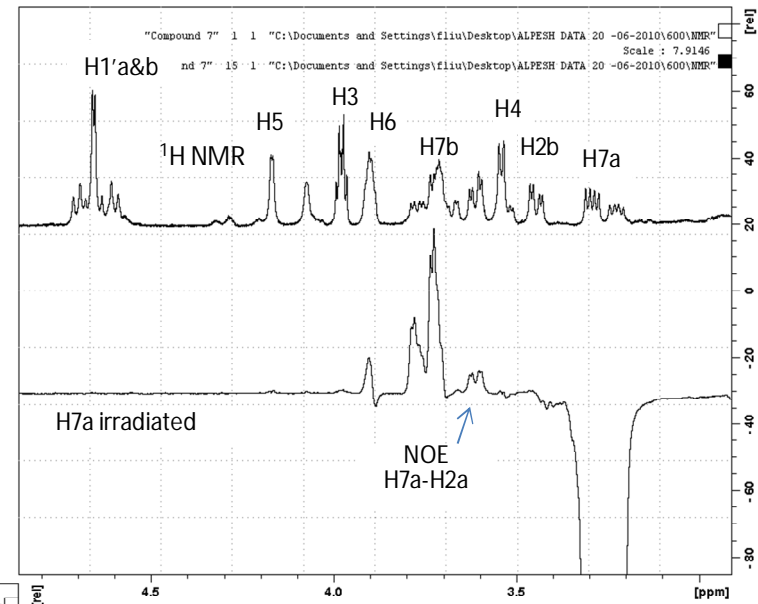
COSY-10



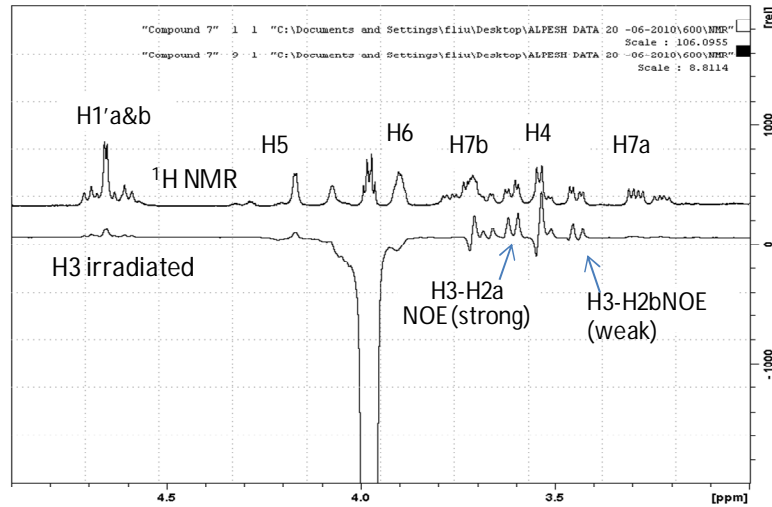
NOESY-10



1D selective NOESY

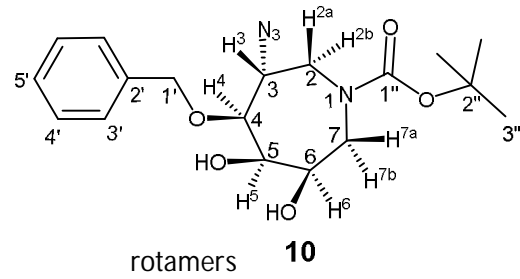


1D selective NOESY

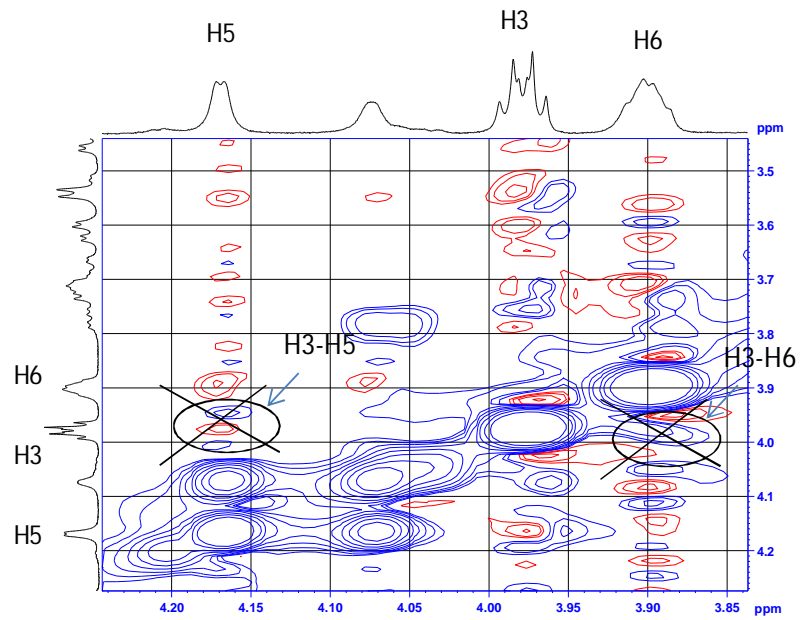
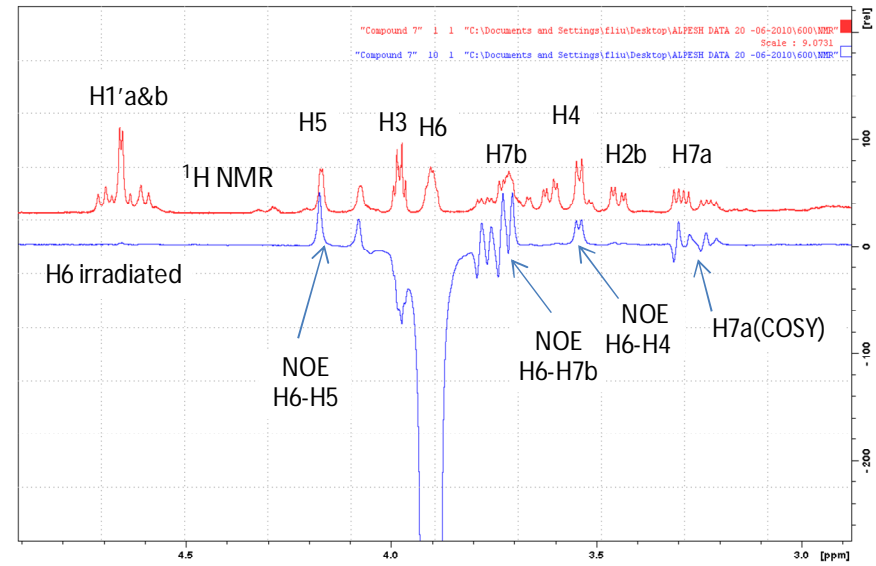


- H3 shows bigger NOE to H2a compared to H2b suggesting H2a is *cis* to H3 and H2b is *trans* to H3.
- H7a shows bigger NOE to H2a compared to H2b meaning H7a is *cis* to H3 and H2a.
- H6 shows big NOE to H7b, H4 and H5 suggesting H6 and H5 both are *cis* to H4.
- Moreover, H5 also shows NOE to H4 and H7b confirming H5 is *cis* to H4.

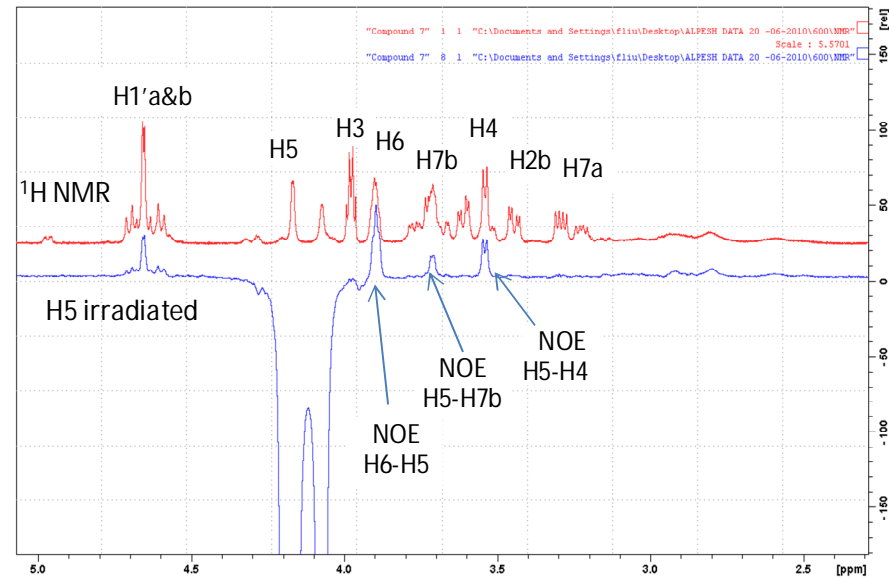
NOESY-10



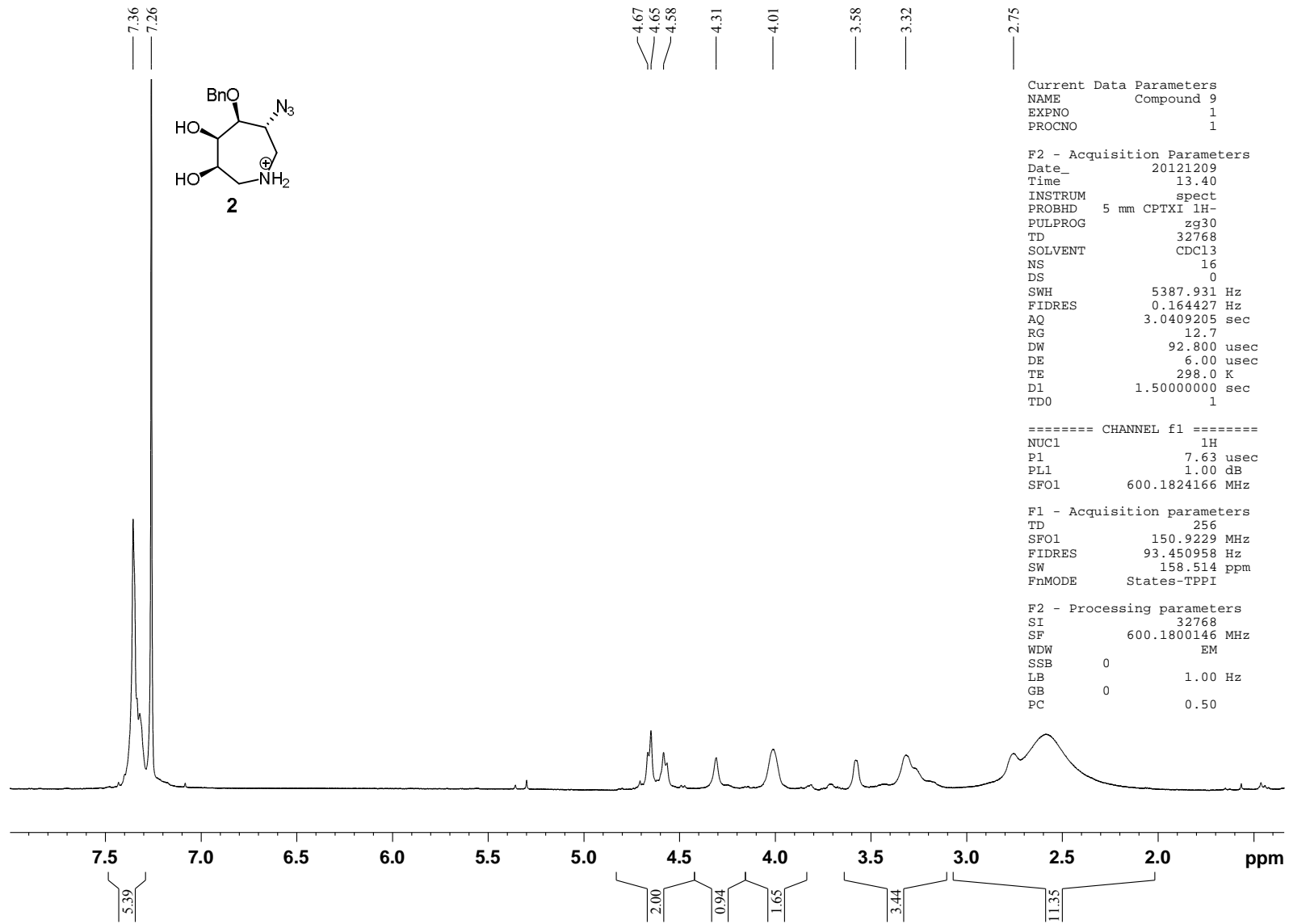
1D selective NOESY



1D selective NOESY



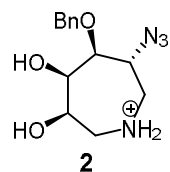
¹H NMR-2



¹³C NMR-2

Current Data Parameters
NAME Compound 9
EXPNO 3
PROCNO 1

F2 - Acquisition Parameters
Date_ 20121209
Time 17.36
INSTRUM spect
PROBHD 5 mm CPTXI 1H-
PULPROG udeflt.txt
TD 21814
SOLVENT CDCl3
NS 6144
DS 0
SWH 30303.031 Hz
FIDRES 1.389155 Hz
AQ 0.3599810 sec
RG 32768
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
DELTA2 0.36300099 sec
TAU 0.00302000 sec
TD0 1

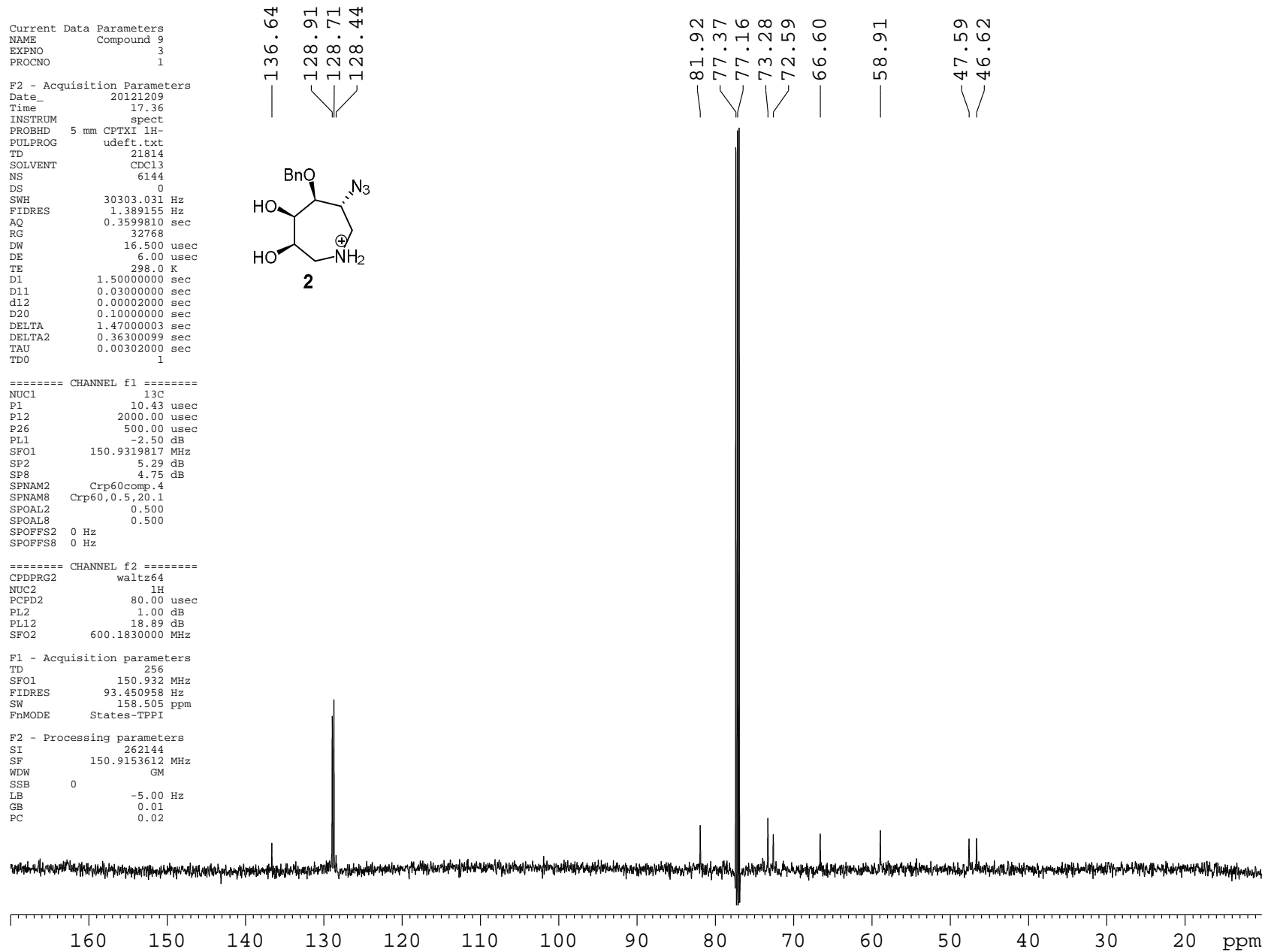


=====
CHANNEL f1
NUC1 13C
P1 10.43 usec
P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
SPNAM2 Crp60comp.4
SPNAM8 Crp60,0.5,20.1
SPOAL2 0.500
SPOAL8 0.500
SPOFFS2 0 Hz
SPOFFS8 0 Hz

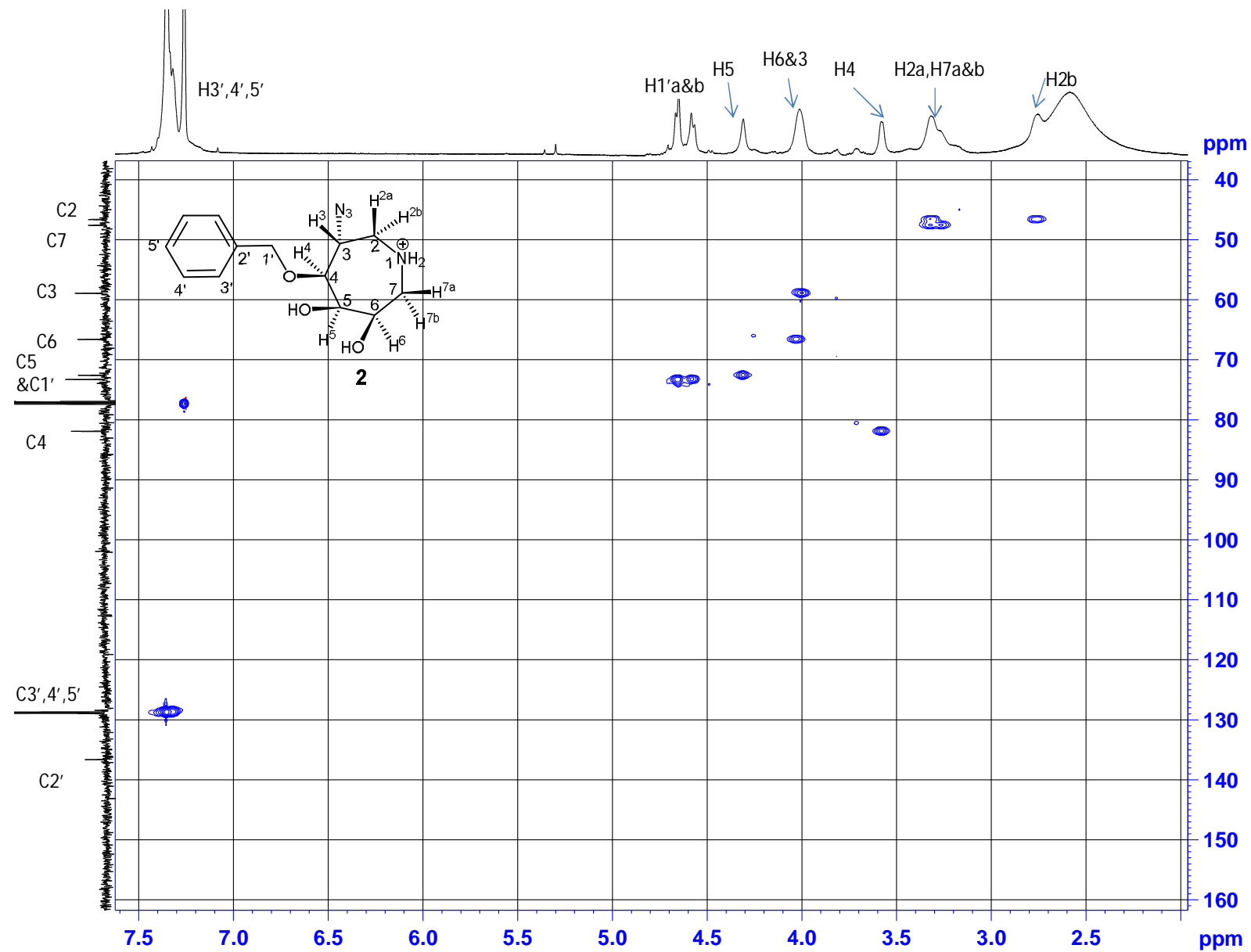
=====
CHANNEL f2
CPDPRG2 waltz64
NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
PL12 18.89 dB
SFO2 600.1830000 MHz

F1 - Acquisition parameters
TD 256
SFO1 150.932 MHz
FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI

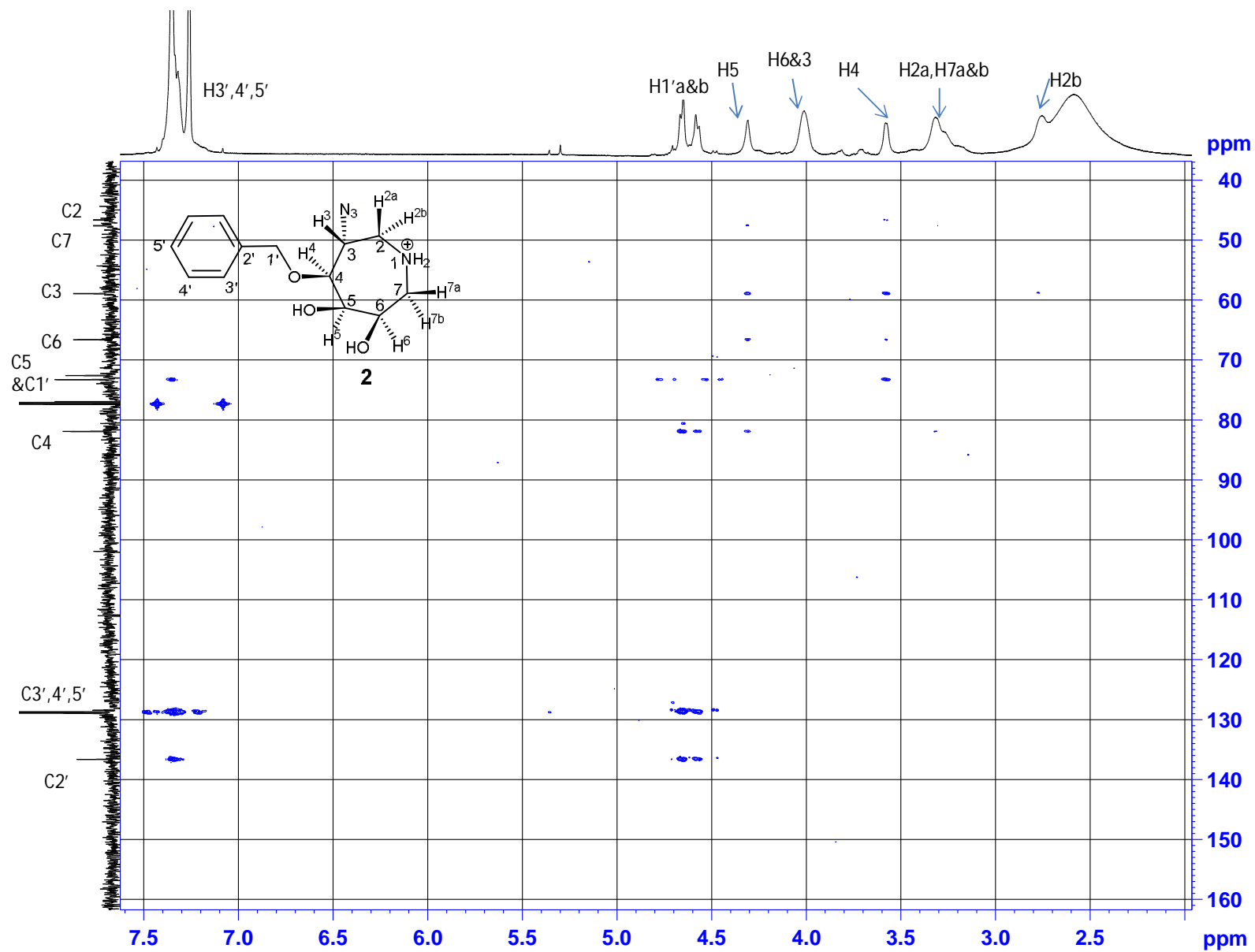
F2 - Processing parameters
SI 262144
SF 150.9153612 MHz
WDW GM
SSB 0
LB -5.00 Hz
GB 0.01
PC 0.02



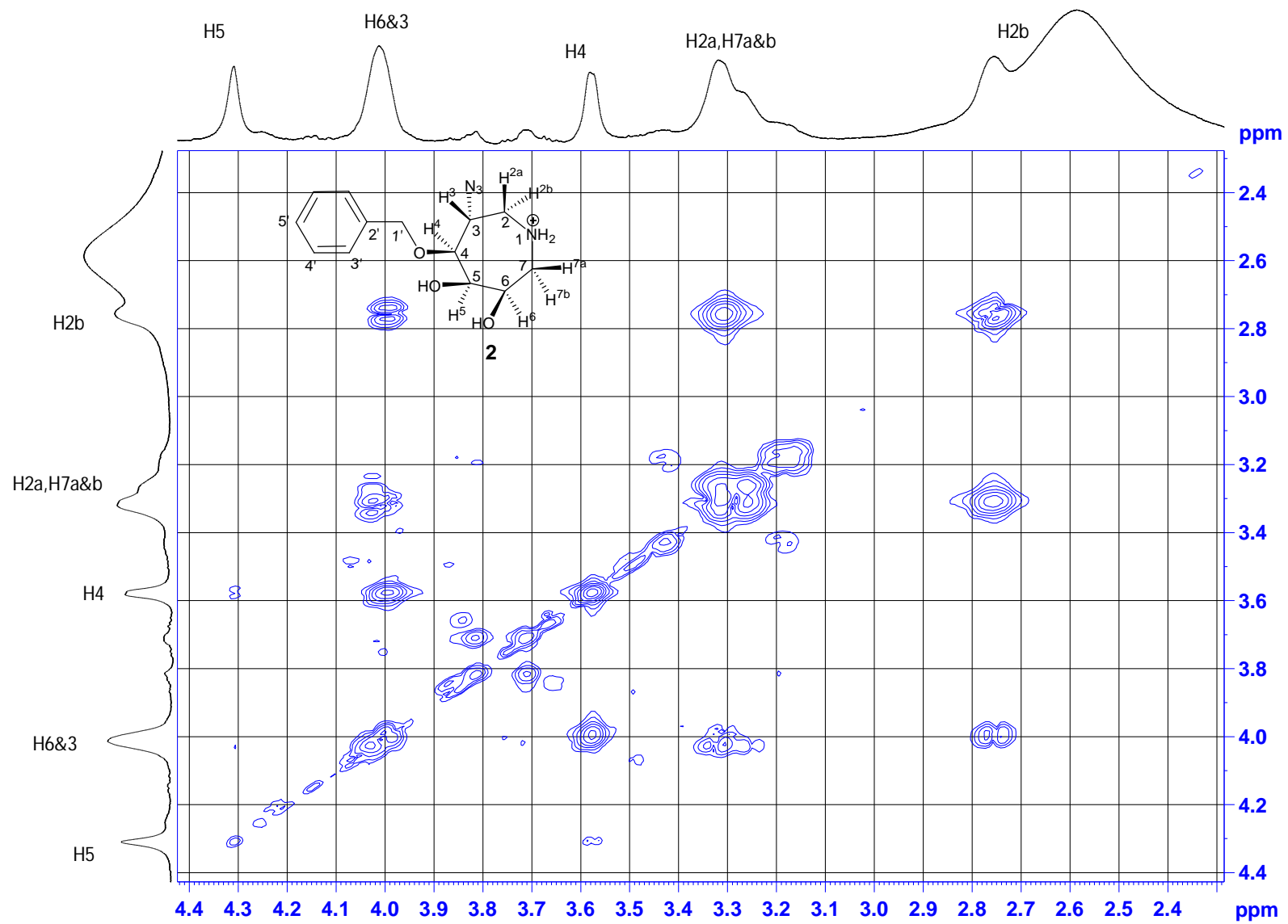
HSQC-2



HMBC-2



COSY-2



¹H NMR-11

7.39
7.37
7.26
7.26

4.81
4.70
4.60
4.52

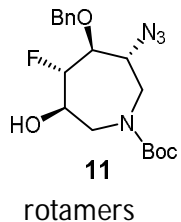
4.08
4.07

3.74

3.55
3.45

3.09
3.08

1.48



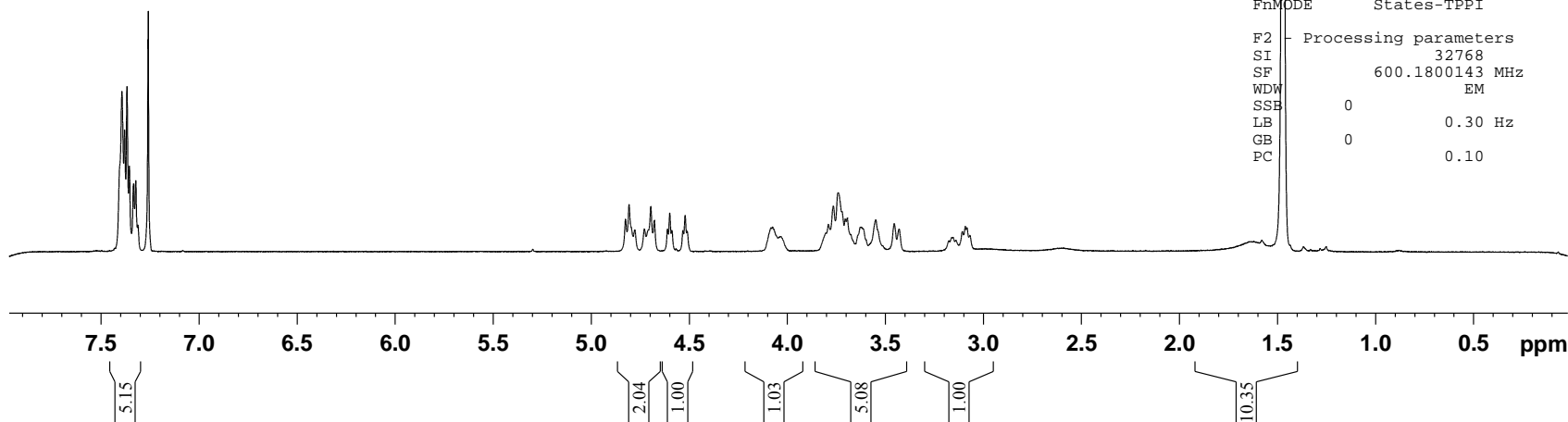
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Current Data Parameters
NAME          Compound 17
EXPNO         1
PROCNO        1

F2 - Acquisition Parameters
Date_         20121207
Time          12.32
INSTRUM       spect
PROBHD        5 mm CPTXI 1H-
PULPROG       zg30
TD            32768
SOLVENT       CDCl3
NS            2
DS            0
SWH           4770.992 Hz
FIDRES        0.145599 Hz
AQ            3.4341364 sec
RG            9
DW            104.800 usec
DE            6.00 usec
TE            298.0 K
D1            1.5000000 sec
TD0           1

===== CHANNEL f1 =====
NUC1          1H
P1            7.63 usec
PL1           1.00 dB
SF01          600.1824115 MHz

F1 - Acquisition parameters
TD            256
SF01          150.9229 MHz
FIDRES        93.450958 Hz
SW            158.514 ppm
FnmODE        States-TPPI

F2 - Processing parameters
SI            32768
SF            600.1800143 MHz
WDW           EM
SSB           0
LB            0.30 Hz
GB            0
PC            0.10
```



¹³C NMR-11

Current Data Parameters
NAME Comptind 17
EXPNO 3
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121206
Time_ 13.17
INSTRUM spect
PROBHD 5 mm CPTXI 1H-
PULPROG udeflt.txt
TD 21814
SOLVENT CDCl3
NS 5120
DS 0
SWH 30303.031 Hz
FIDRES 1.389155 Hz
AQ 0.3599810 sec
RG 32768
DW 16.500 usec
DE 6.00 usec
TE 298.0 K
D1 1.50000000 sec
D11 0.03000000 sec
d12 0.00002000 sec
D20 0.10000000 sec
DELTA 1.47000003 sec
DELTA2 0.36300099 sec
TAU 0.00302000 sec
TDO 1

==== CHANNEL f1 =====
NUC1 13C
P1 10.43 usec
P12 2000.00 usec
P26 500.00 usec
PL1 -2.50 dB
SFO1 150.9319817 MHz
SP2 5.29 dB
SP8 4.75 dB
SPNAM2 Crp60comp.4
SPNAM8 Crp60,0.5,20.1
SPOAL2 0.500
SPOAL8 0.500
SPOFFS2 0 Hz
SPOFFS8 0 Hz

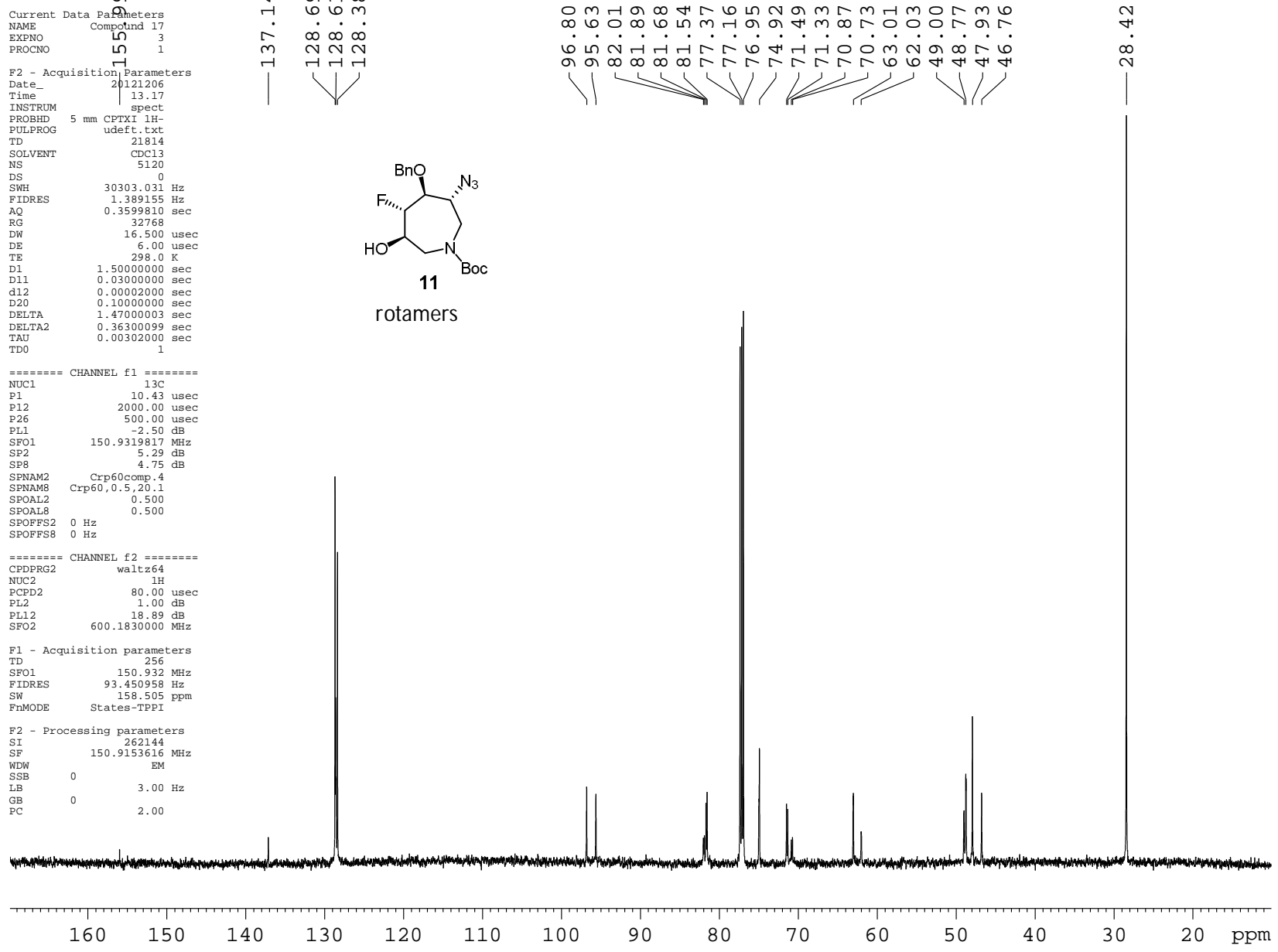
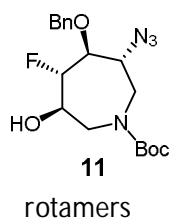
==== CHANNEL f2 =====
CPDPRG2 waltz64
NUC2 1H
PCPD2 80.00 usec
PL2 1.00 dB
PL12 18.89 dB
SFO2 600.1830000 MHz

F1 - Acquisition parameters
TD 256
SFO1 150.932 MHz
FIDRES 93.450958 Hz
SW 158.505 ppm
FnMODE States-TPPI

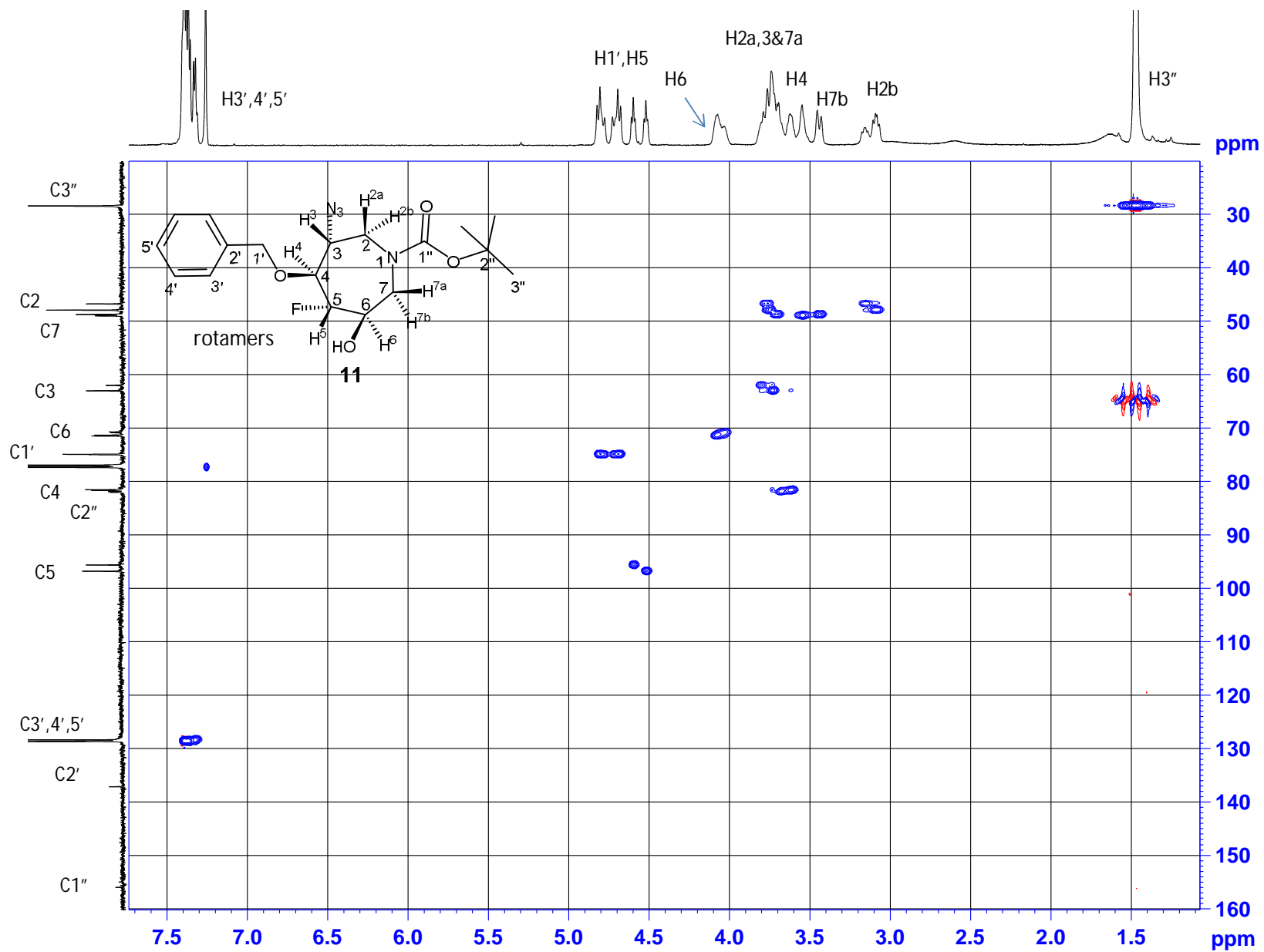
F2 - Processing parameters
SI 262144
SF 150.9153616 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 2.00

151.99
137.14
128.69
128.61
128.38

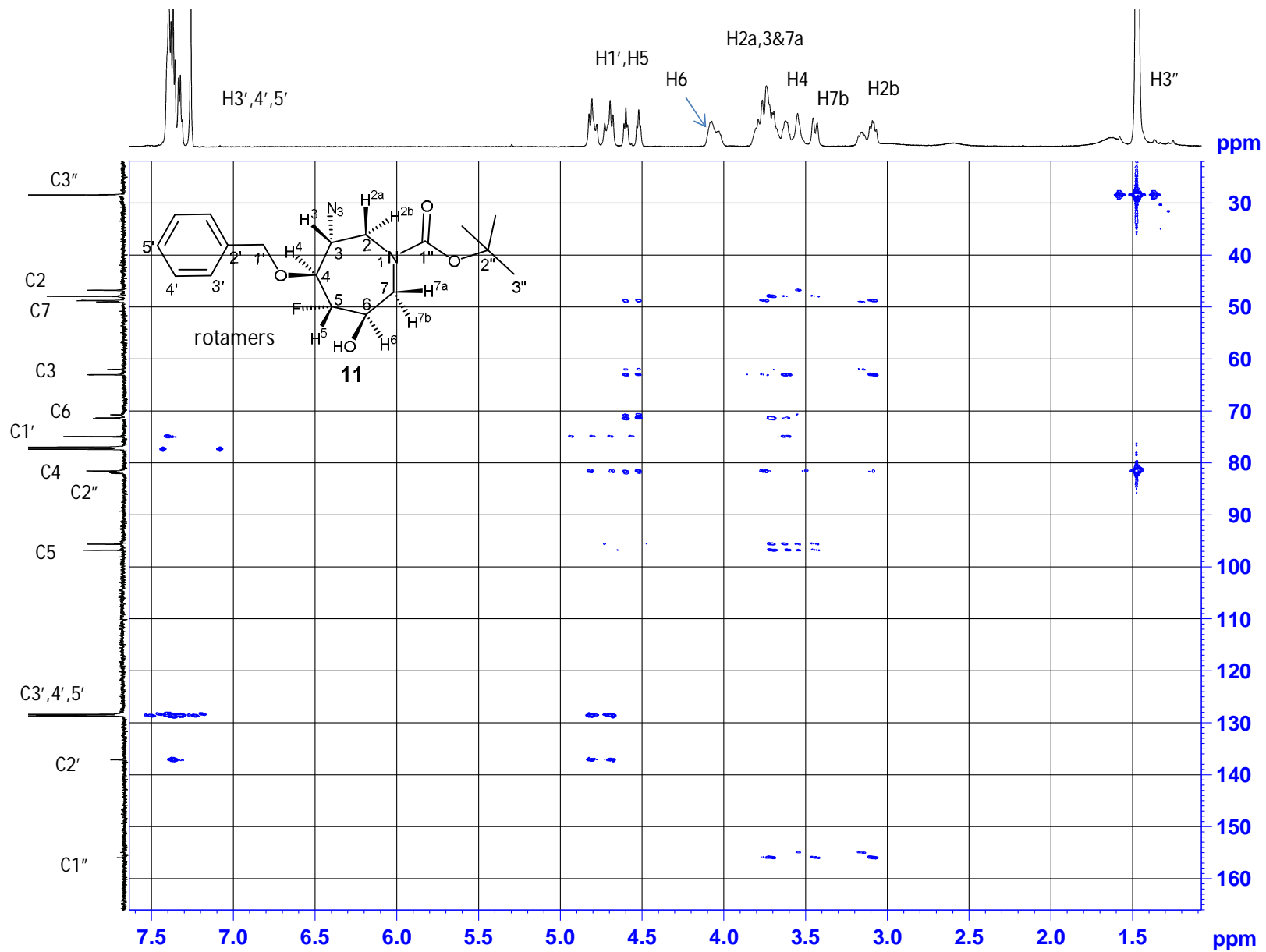
96.80
95.63
82.01
81.89
81.68
81.54
77.37
77.16
76.95
74.92
71.49
71.33
70.87
70.73
63.01
62.03
49.00
48.77
47.93
46.76



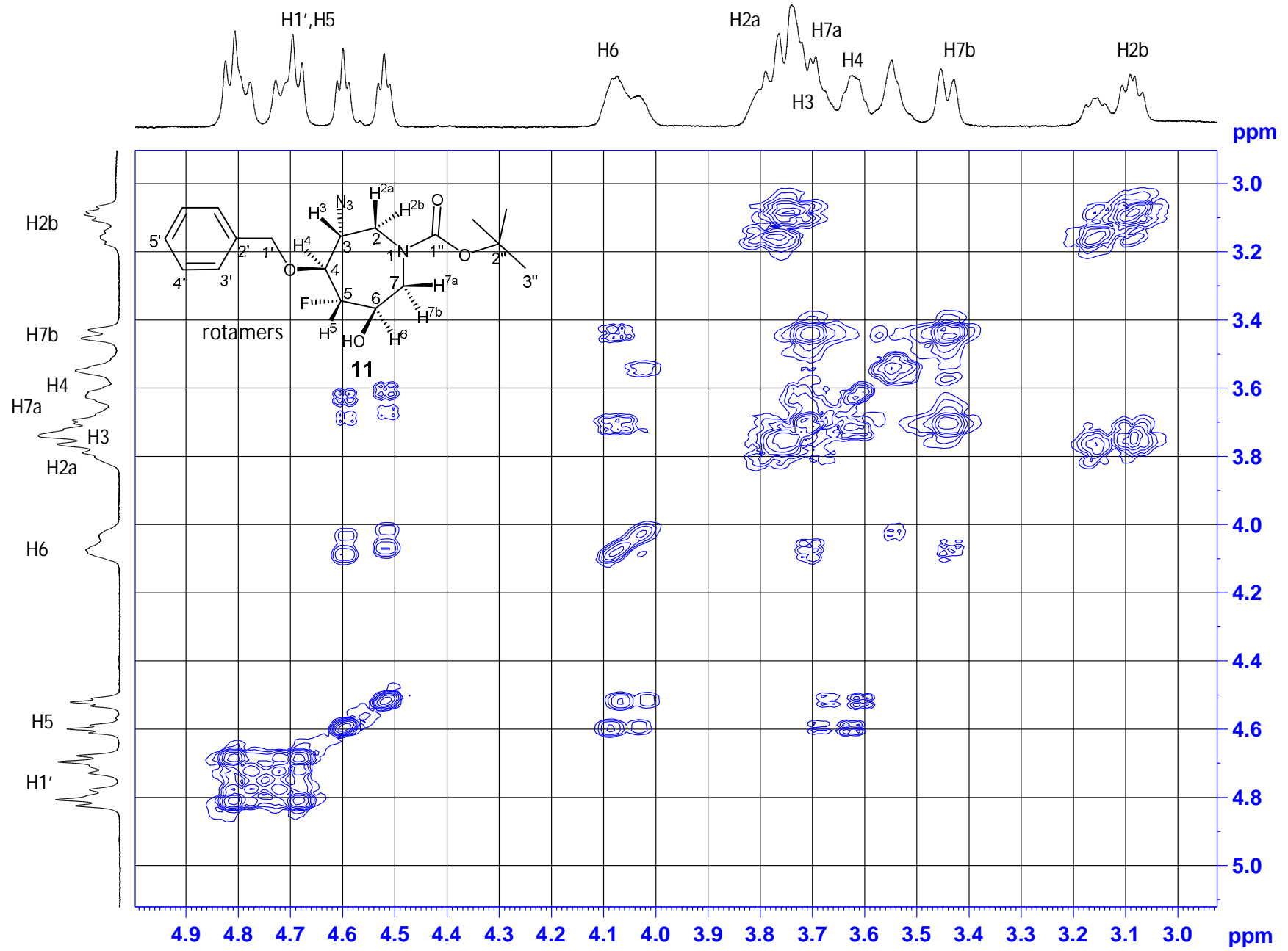
HSQC-11



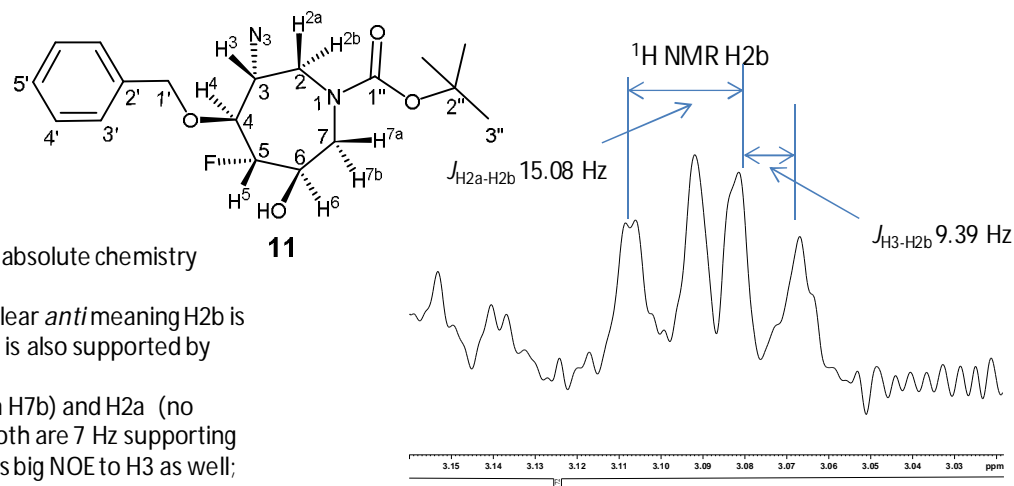
HMBC-11



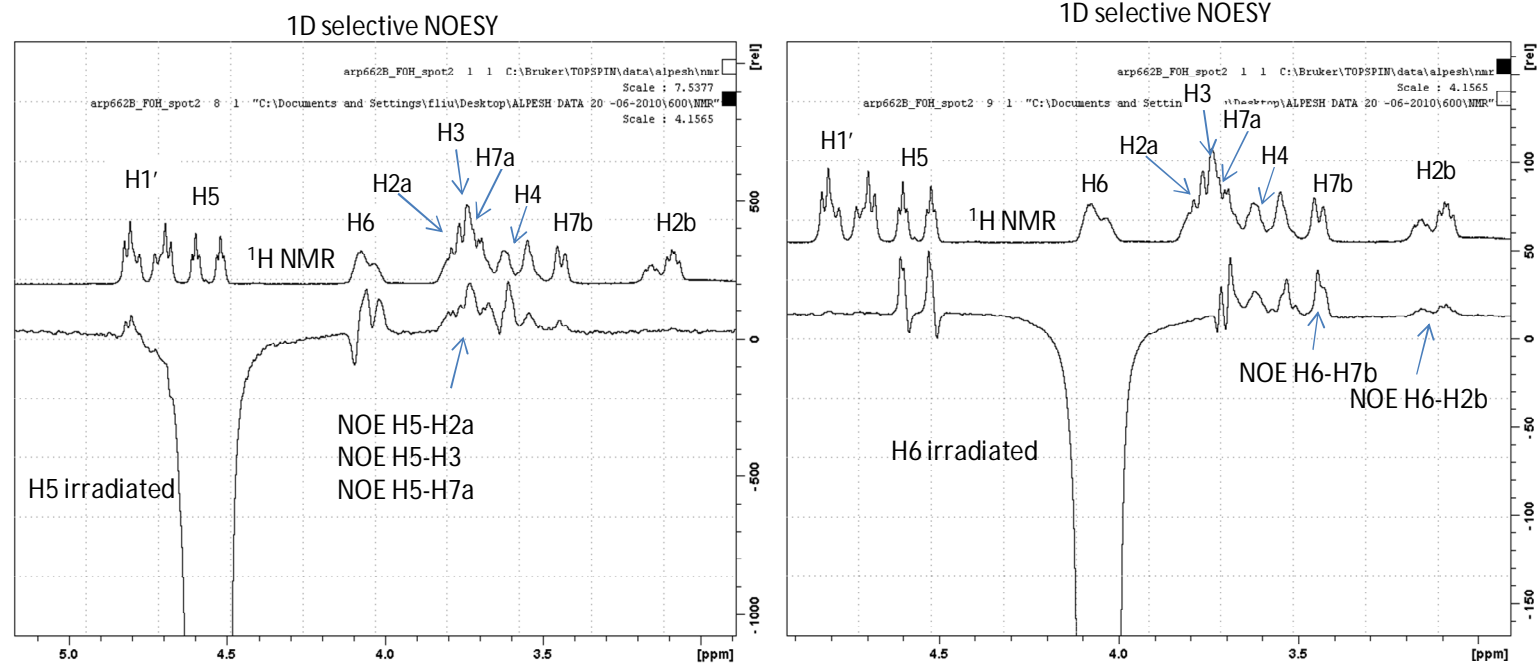
COSY-11



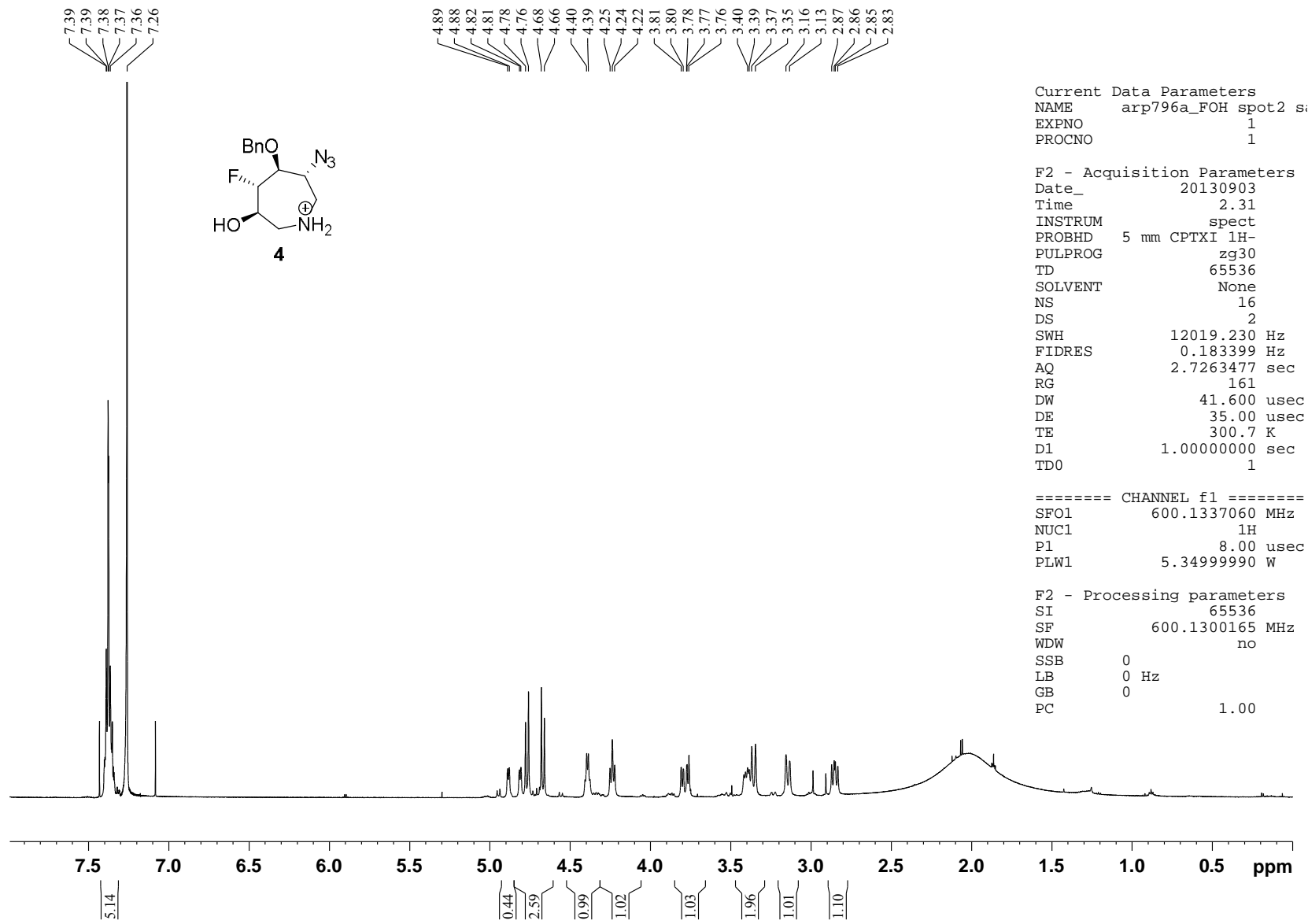
NOESY-11



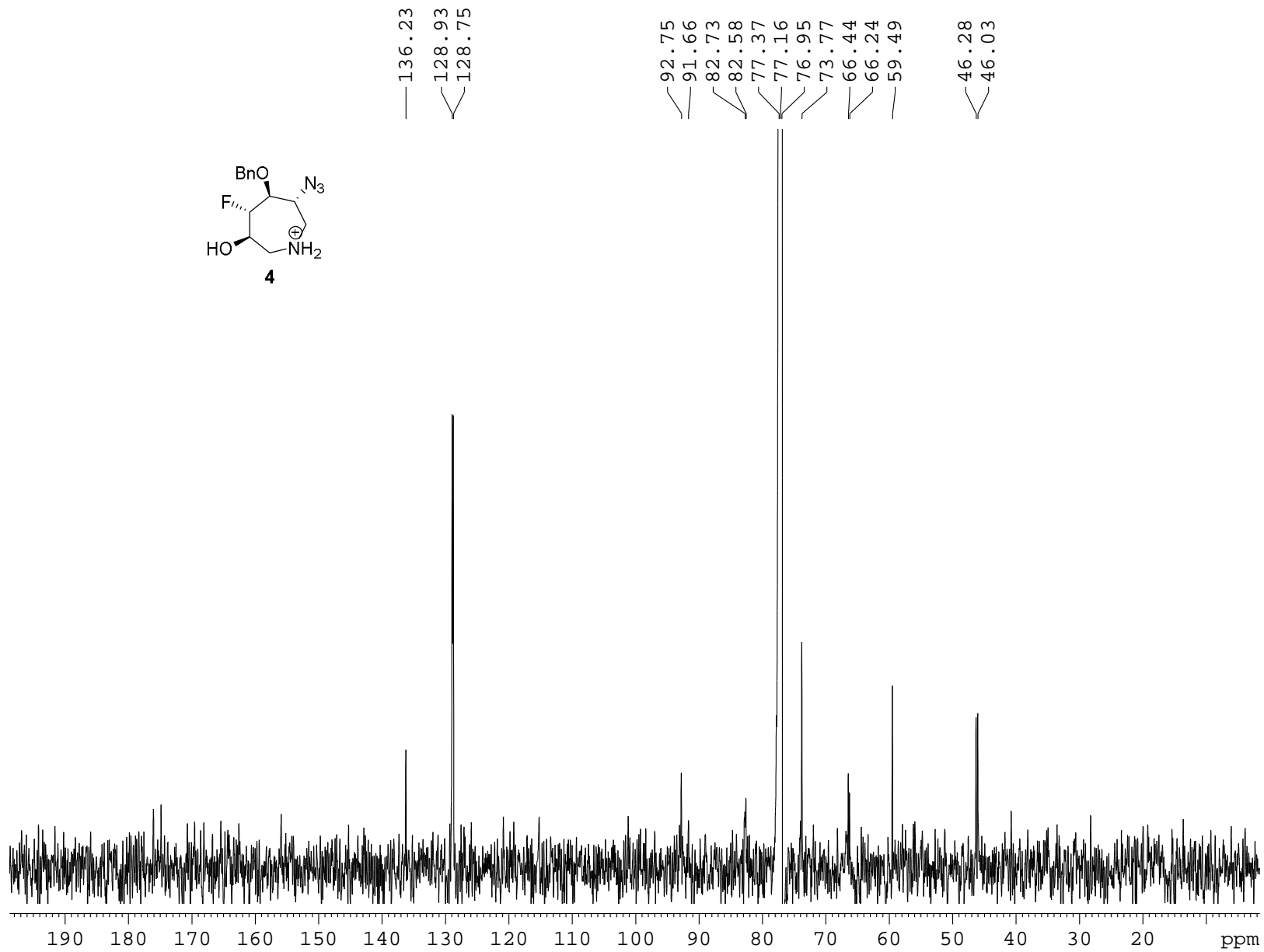
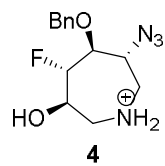
- ❑ Compound **11** has C3, C4 and C6 as known absolute chemistry stereocentres.
- ❑ **H2a and H2b** : $J_{H3-H2b} = 9.39 \text{ Hz}$ suggests a clear *anti* meaning H2b is *trans* to H3 (torsion angles 155° or 208°). It is also supported by NOE H2b-H6.
- ❑ **H5** : H5 shows NOE to H3, H7a (bigger than H7b) and H2a (no measurable NOE to H2b). J_{H5-H6} and J_{H4-H5} both are 7 Hz supporting *trans* geometry in both the cases. H5 shows big NOE to H3 as well; further confirming H5 is *cis* to H3.



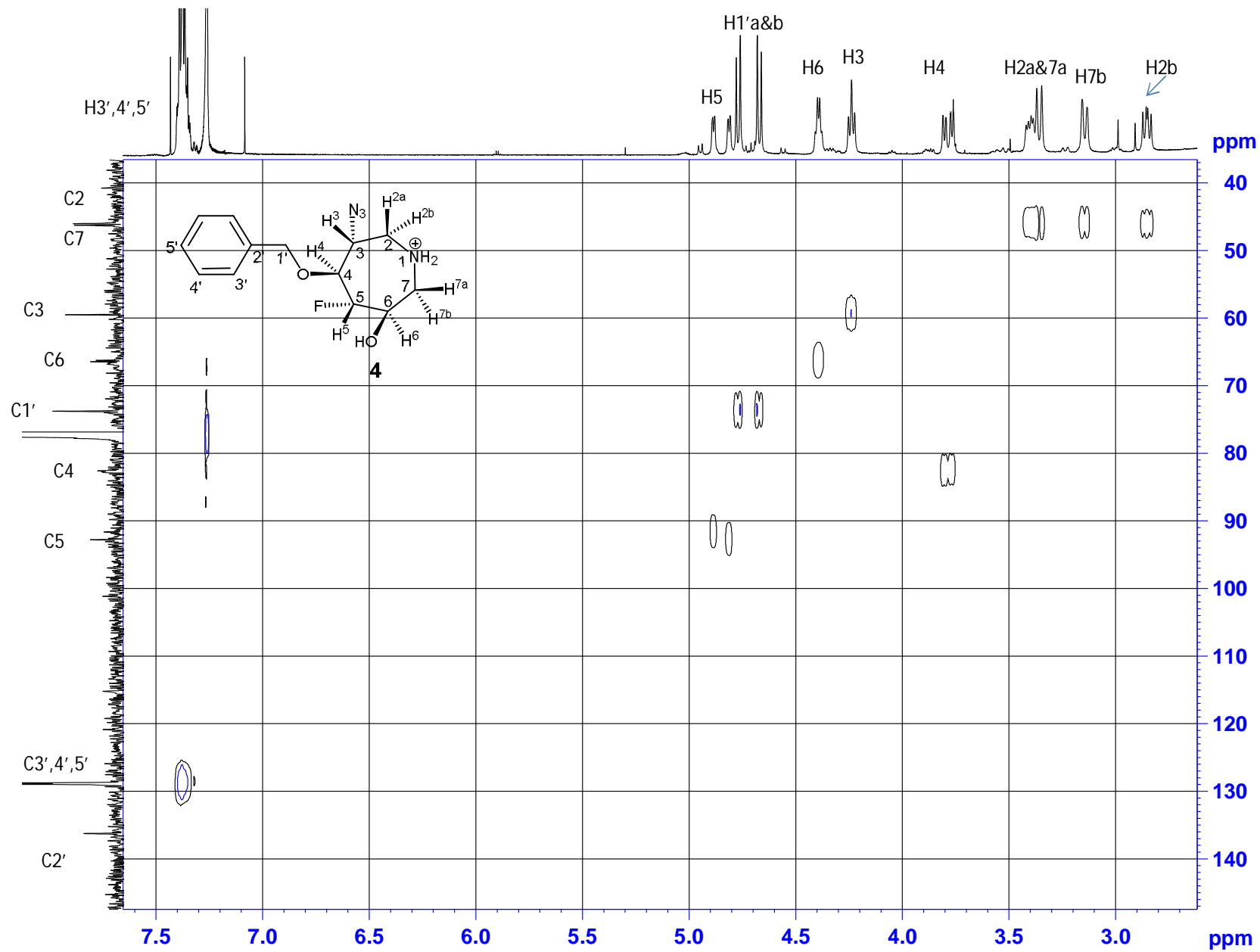
¹H NMR-4



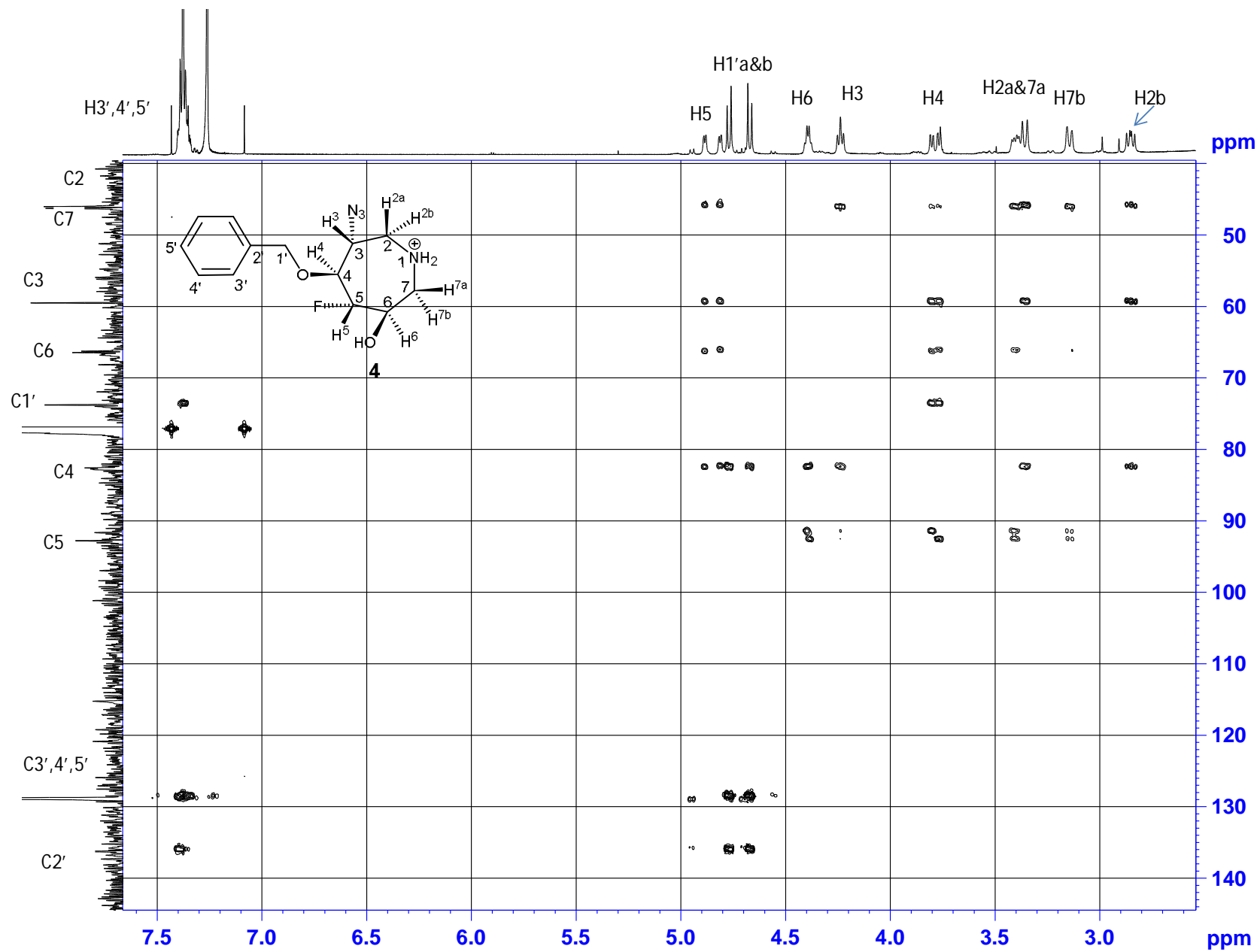
¹³C NMR-4



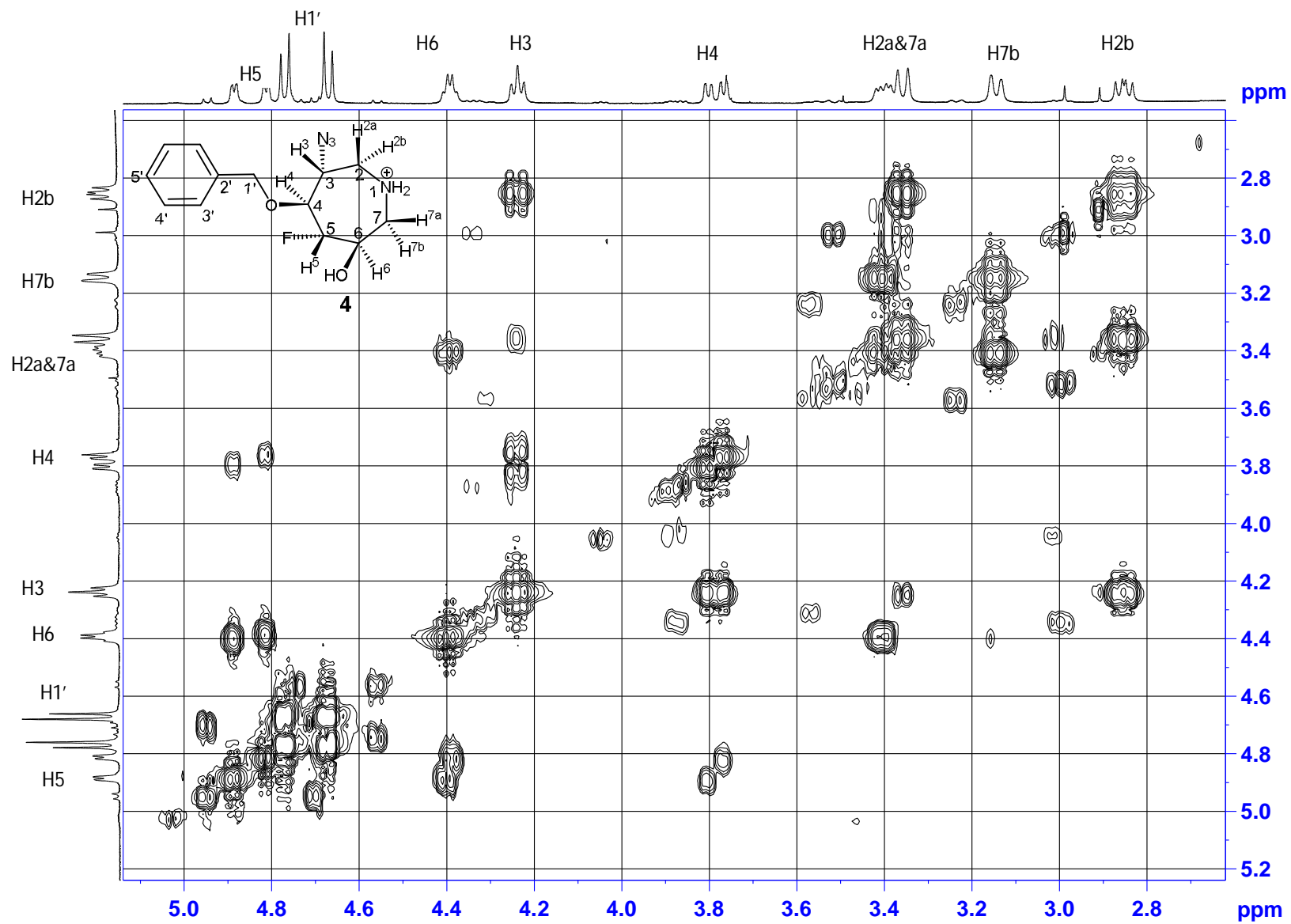
HSQC-4



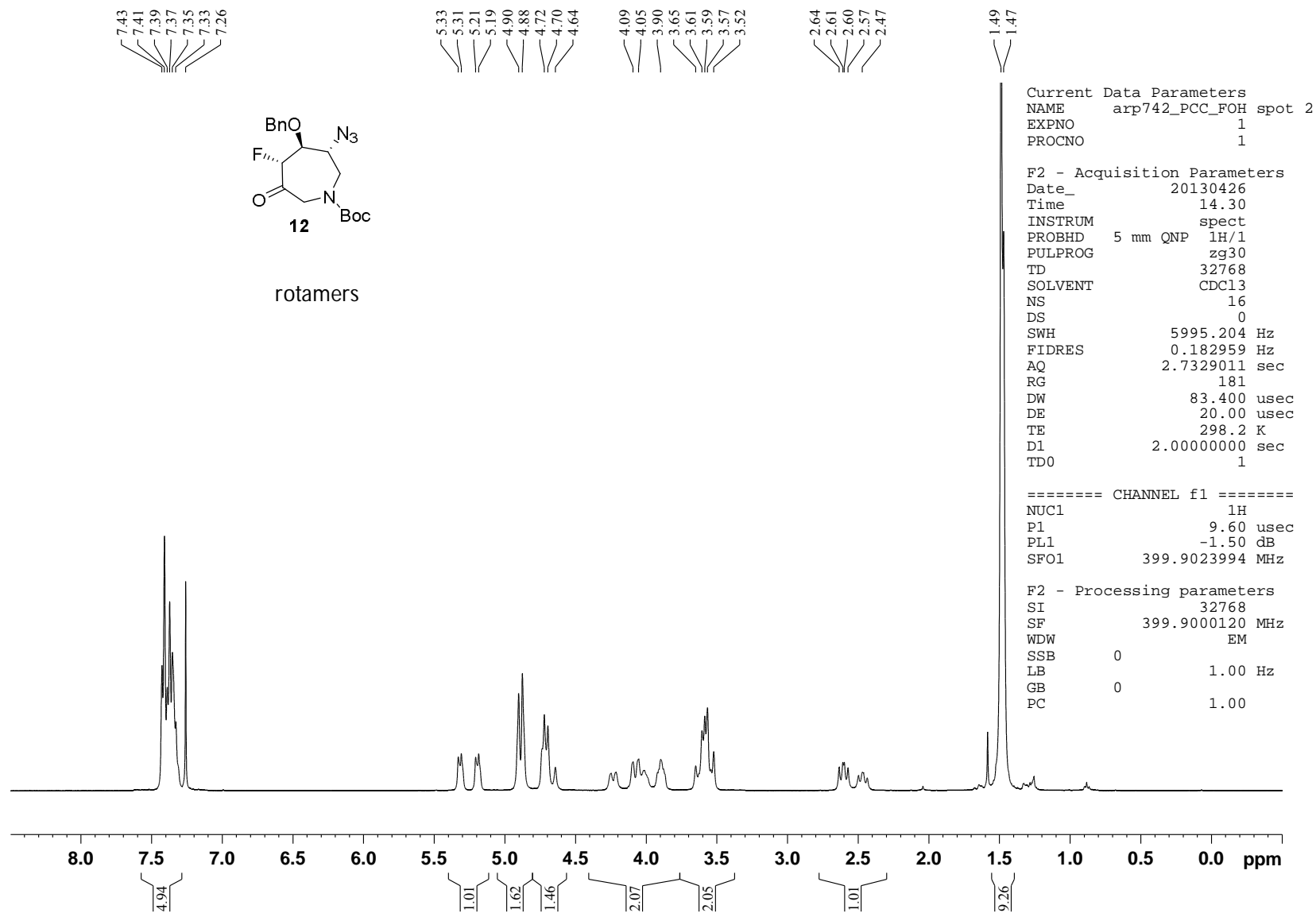
HMBC-4



NOESY-4



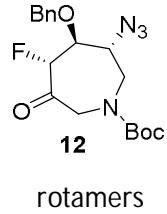
¹H NMR-12



NOESY-12

Current Data Parameters
 NAME arp742201_FOH spot 2
 EXPNO 2
 PROCNO 1

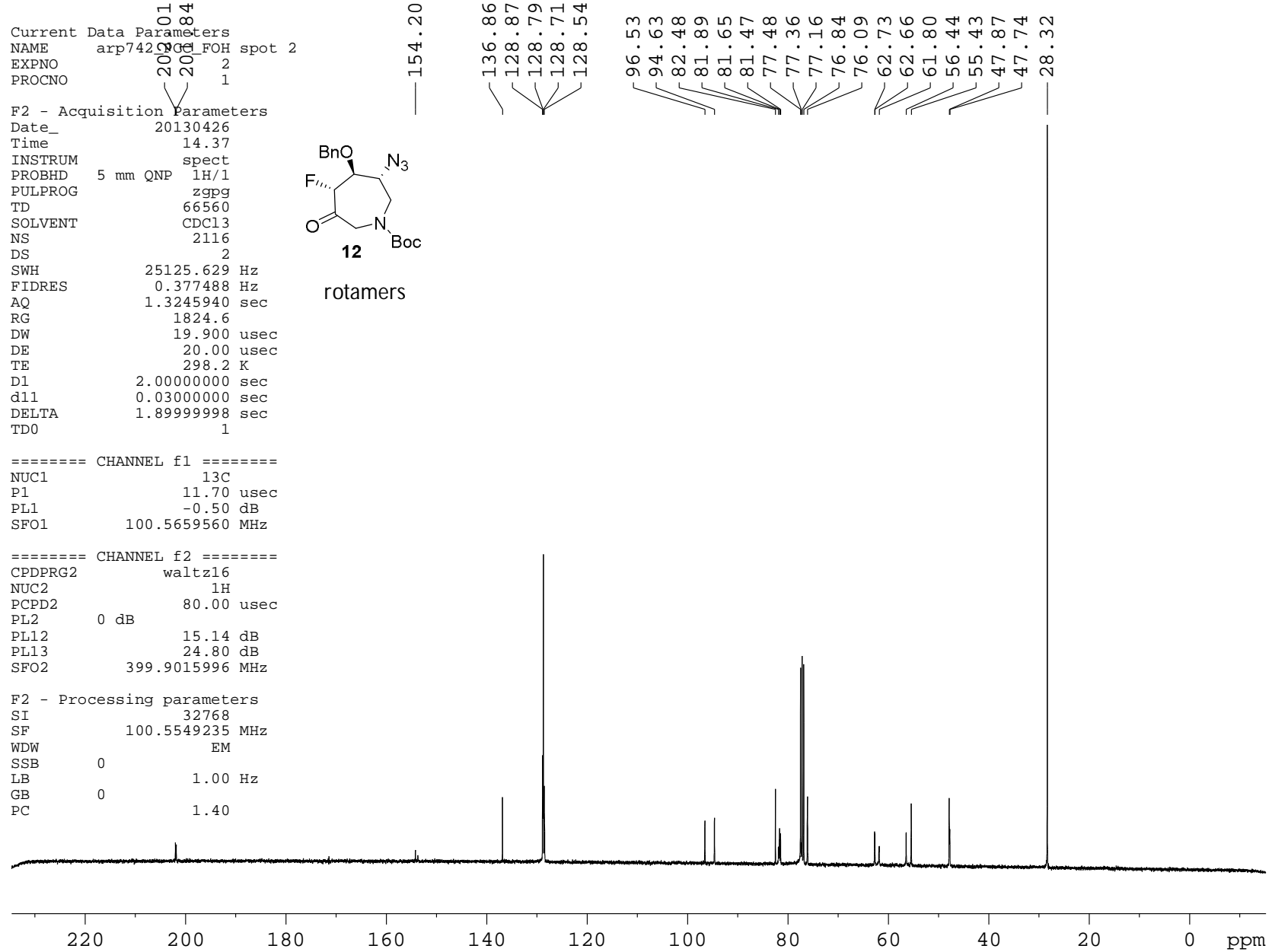
F2 - Acquisition Parameters
 Date_ 20130426
 Time 14.37
 INSTRUM spect
 PROBHD 5 mm QNP 1H/1
 PULPROG zgpg
 TD 66560
 SOLVENT CDCl3
 NS 2116
 DS 2
 SWH 25125.629 Hz
 FIDRES 0.377488 Hz
 AQ 1.3245940 sec
 RG 1824.6
 DW 19.900 usec
 DE 20.00 usec
 TE 298.2 K
 D1 2.00000000 sec
 d11 0.03000000 sec
 DELTA 1.89999998 sec
 TD0 1



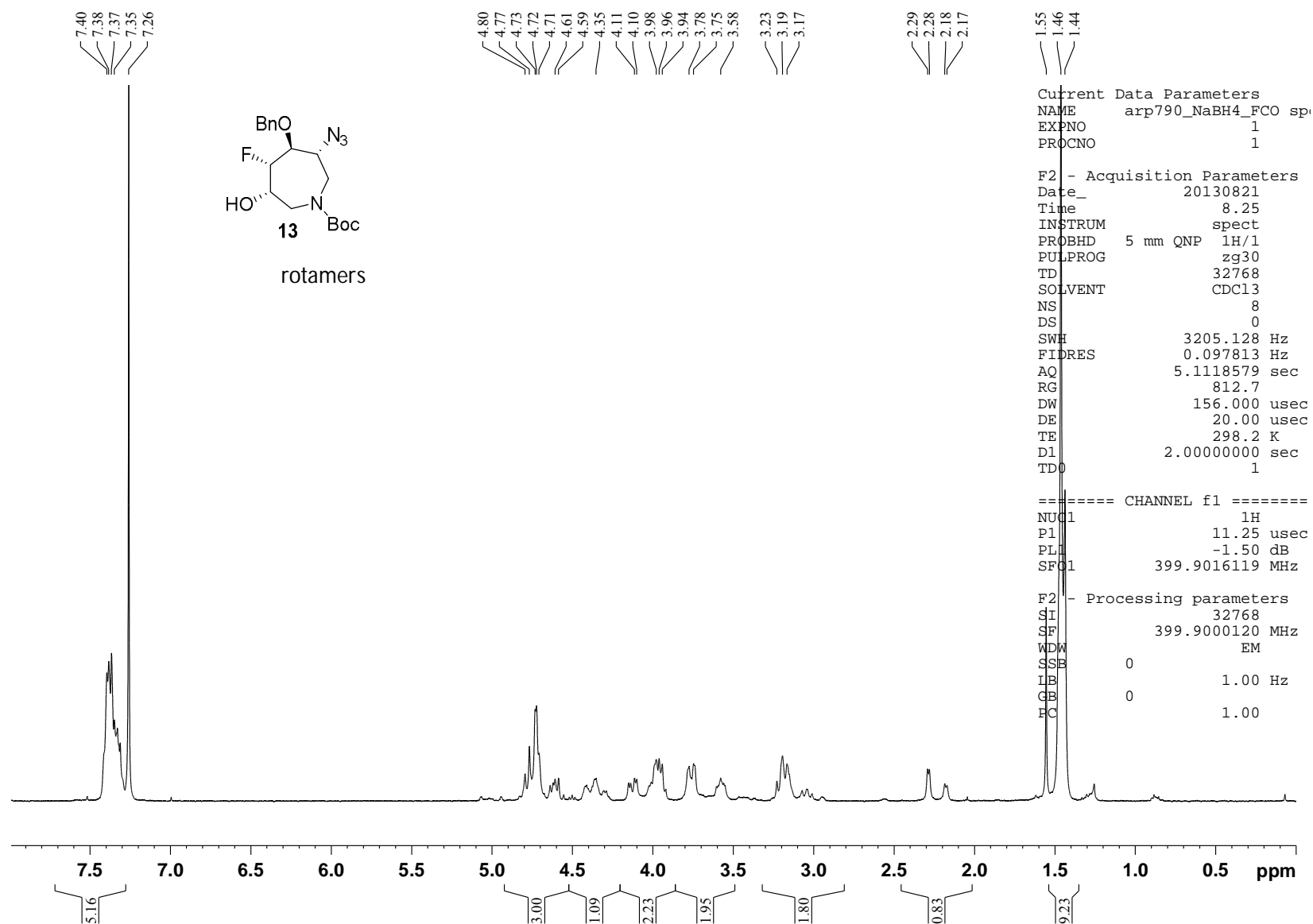
==== CHANNEL f1 =====
 NUC1 13C
 P1 11.70 usec
 PL1 -0.50 dB
 SFO1 100.5659560 MHz

==== CHANNEL f2 =====
 CPDPRG2 waltz16
 NUC2 1H
 PCPD2 80.00 usec
 PL2 0 dB
 PL12 15.14 dB
 PL13 24.80 dB
 SFO2 399.9015996 MHz

F2 - Processing parameters
 SI 32768
 SF 100.5549235 MHz
 WDW EM
 SSB 0
 LB 1.00 Hz
 GB 0
 PC 1.40



¹H NMR-13



Current Data Parameters
NAME arp790_NaBH4_FCO sp
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20130821
Time 8.25
INSTRUM spect
PROBHD 5 mm QNP 1H/1
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 0
SWH 3205.128 Hz
FIDRES 0.097813 Hz
AQ 5.1118579 sec
RG 812.7
DW 156.000 usec
DE 20.00 usec
TE 298.2 K
D1 2.00000000 sec
TD0 1

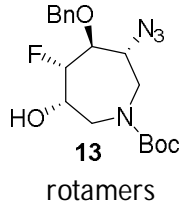
==== CHANNEL f1 =====
NUC1 1H
P1 11.25 usec
PL1 -1.50 dB
SFO1 399.9016119 MHz

F2 - Processing parameters
SI 32768
SF 399.9000120 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
EC 1.00

NOESY-13

Current Data Parameters
 NAME arp790_NaBH4_FCO spot 2 after column
 EXPNO 3
 PROCNO 1

F2 - Acquisition Parameters
 Date_ 20130820
 Time 18.10
 INSTRUM spect
 PROBHD 5 mm QNP 1H/1
 PULPROG zgpg
 TD 66560
 SOLVENT CDCl3
 NS 4414
 DS 2
 SWH 25125.629 Hz
 FIDRES 0.377488 Hz
 AQ 1.3245940 sec
 RG 4597.6
 DW 19.900 usec
 DE 20.00 usec
 TE 298.2 K
 D1 2.00000000 sec
 d11 0.03000000 sec
 DELTA 1.89999998 sec
 TD0 1



154.83

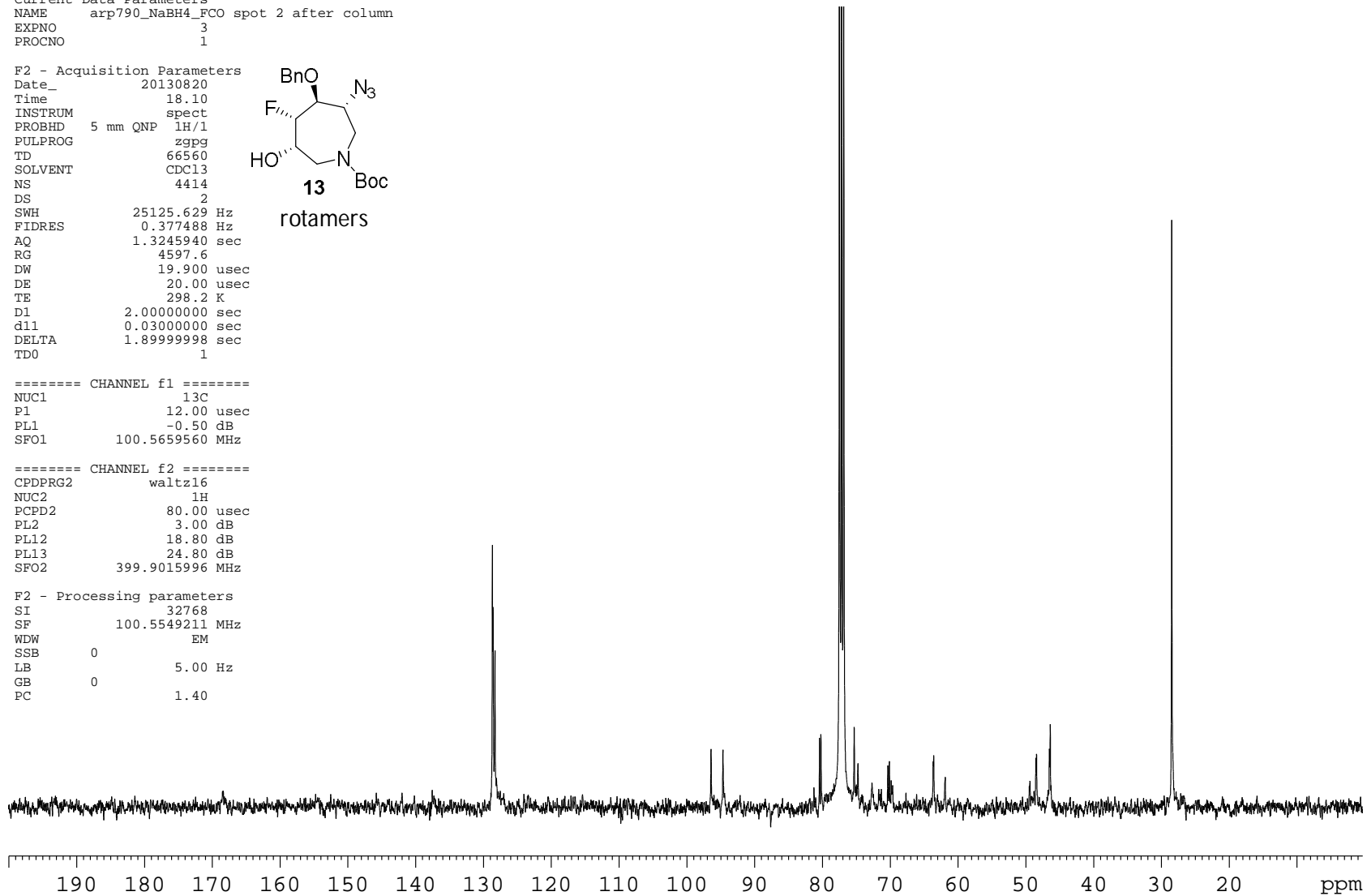
137.52

128.66

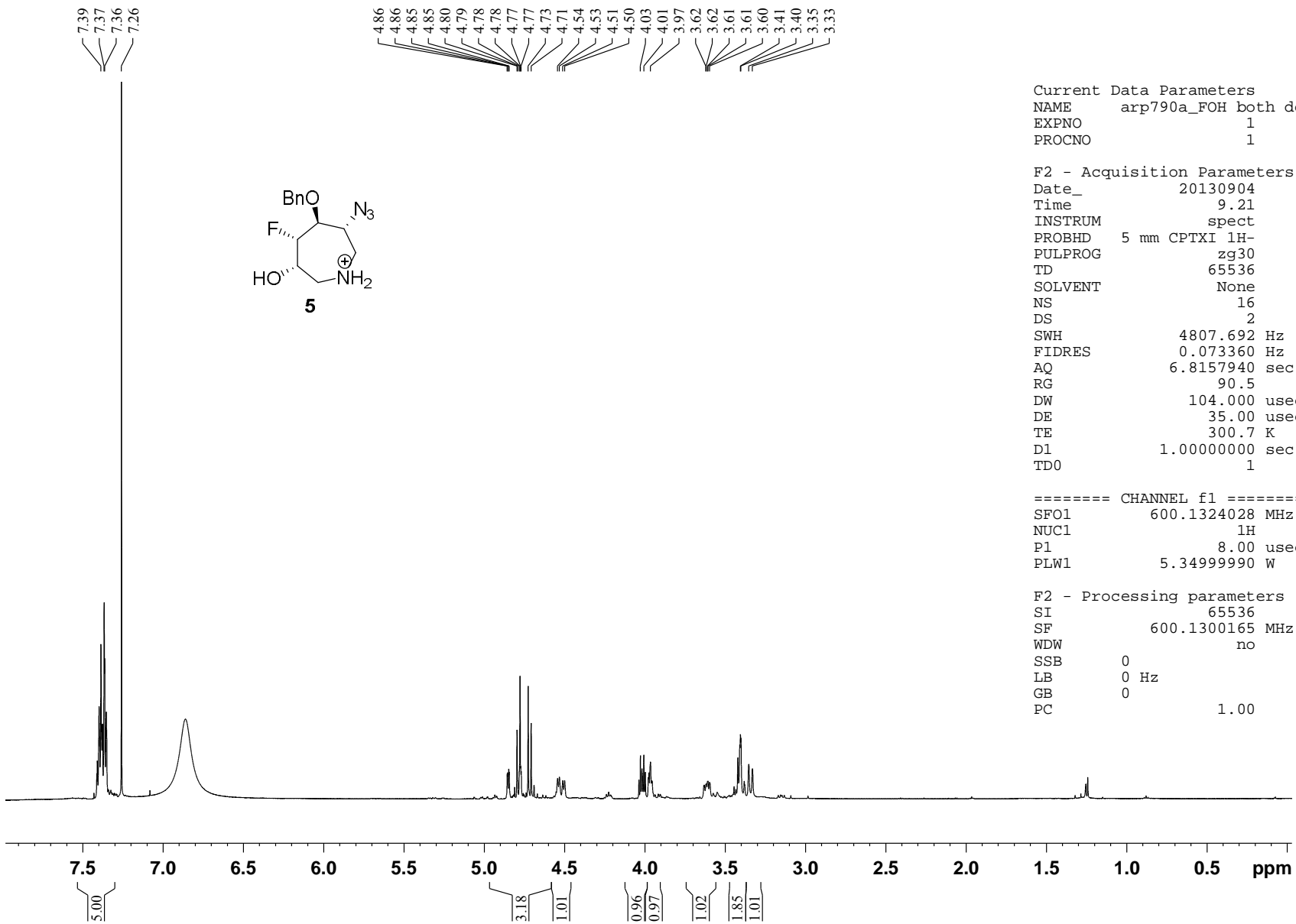
128.57

128.28

96.41
 94.66
 81.23
 80.95
 80.41
 80.20
 77.48
 77.16
 76.84
 75.29
 74.73
 70.33
 70.10
 69.82
 69.64
 63.57
 61.86
 49.48
 49.37
 48.50
 48.40
 46.51
 46.37
 28.45



¹H NMR-5



¹³C NMR-5

160.96
160.68
160.41
160.14

136.09
128.99
128.59

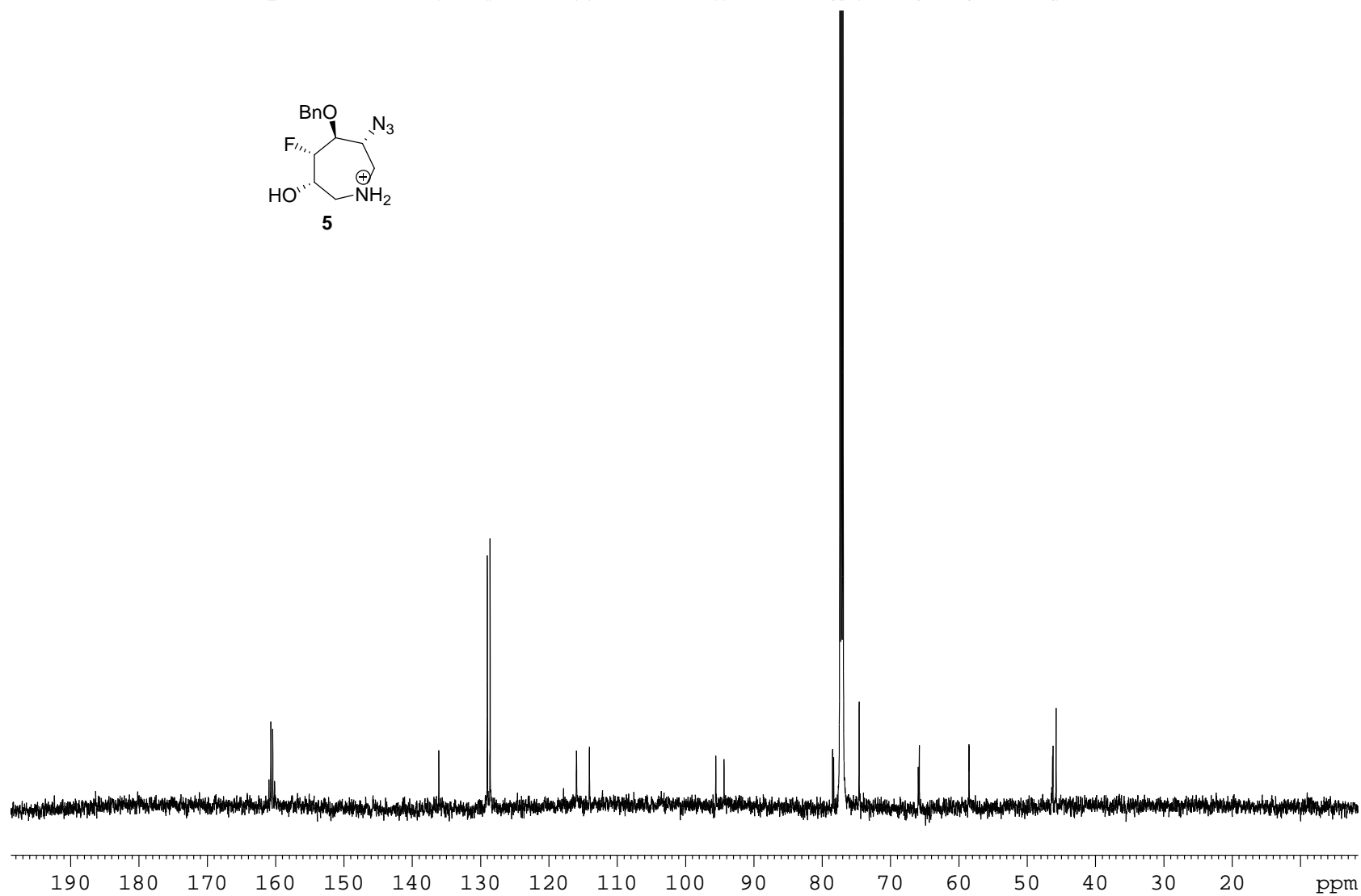
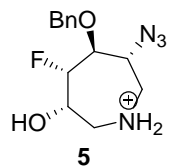
115.95
114.05

95.56
94.35

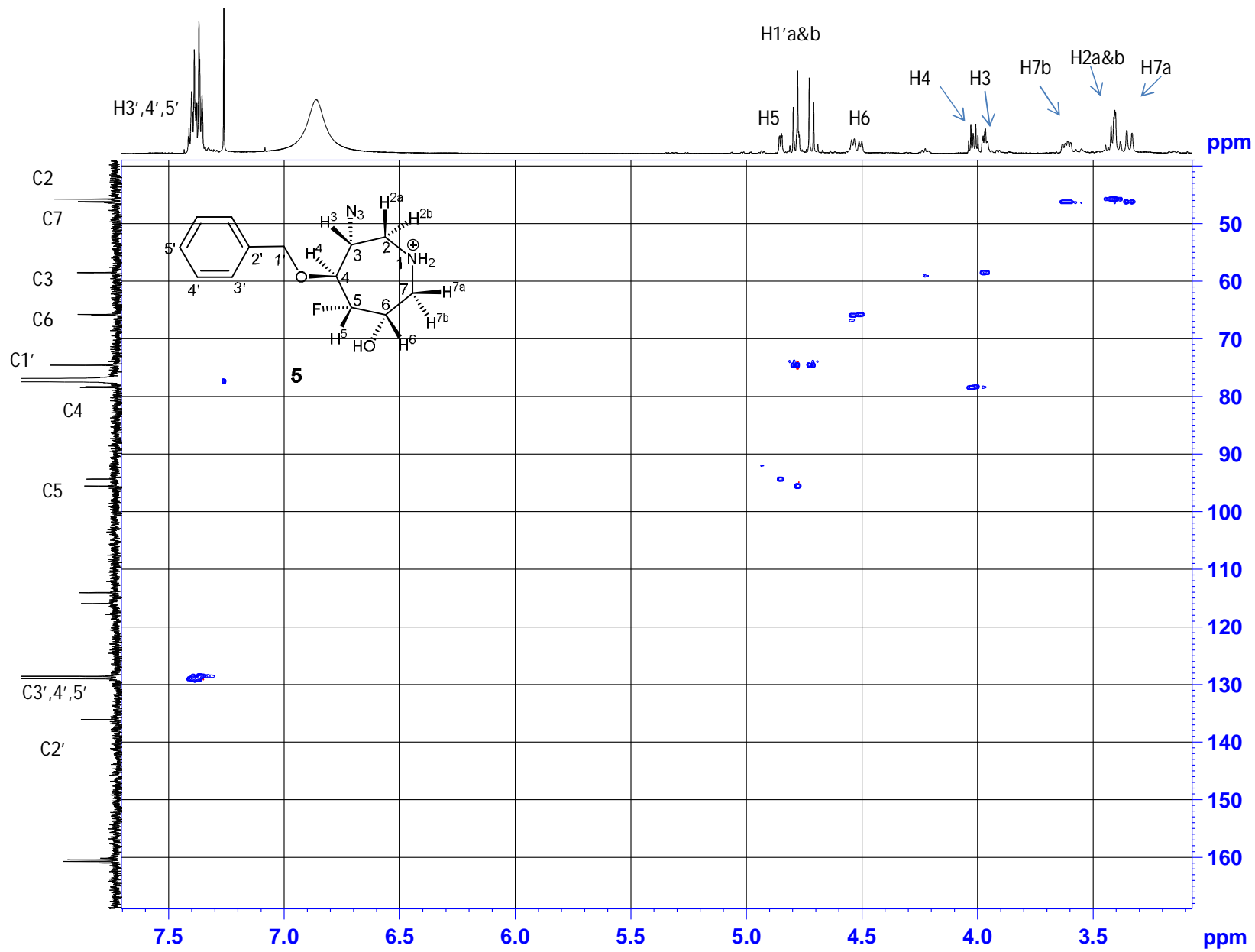
78.46
78.30
77.37
77.16
76.95
74.57

65.91
65.77
58.50
58.47

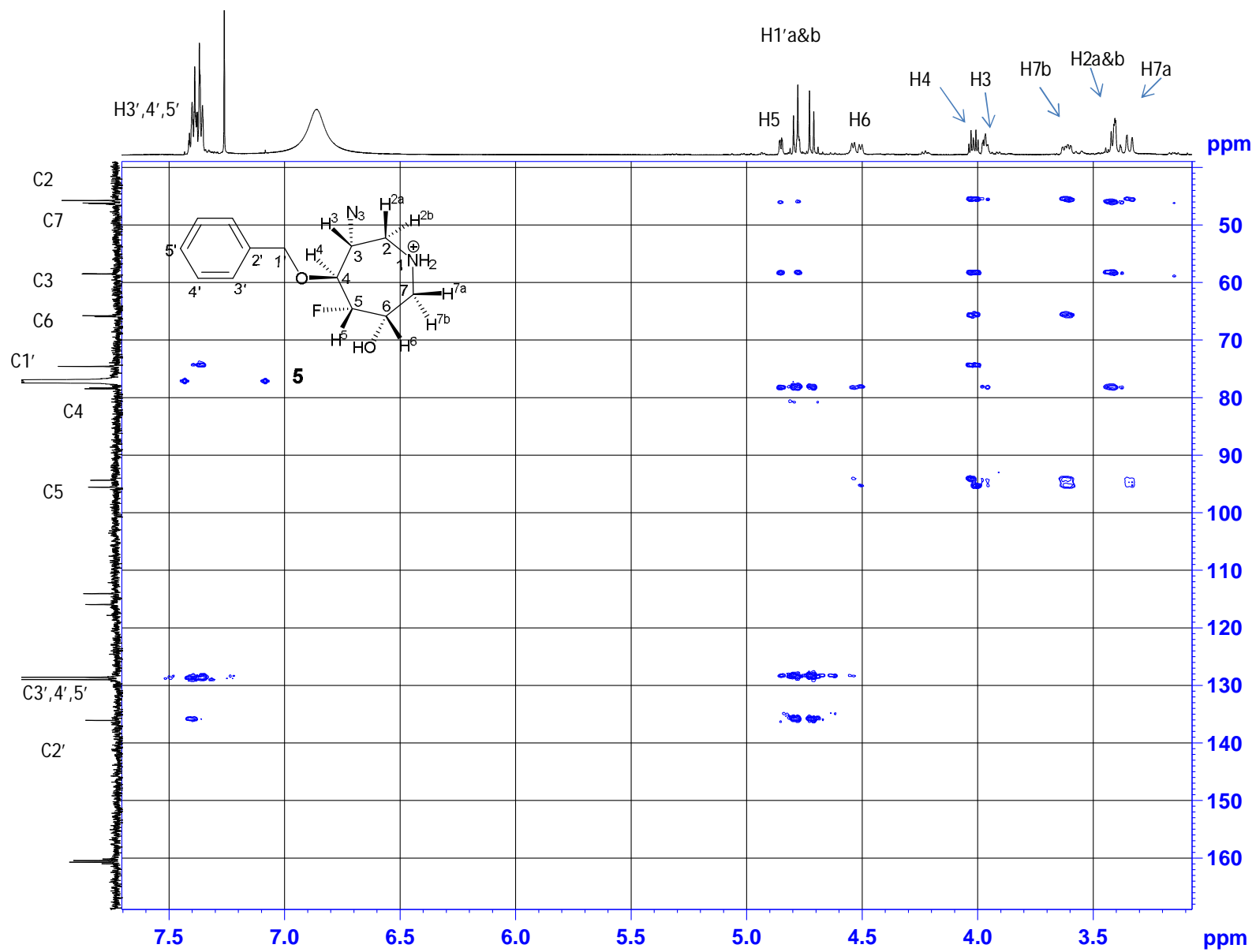
46.26
46.19
45.74

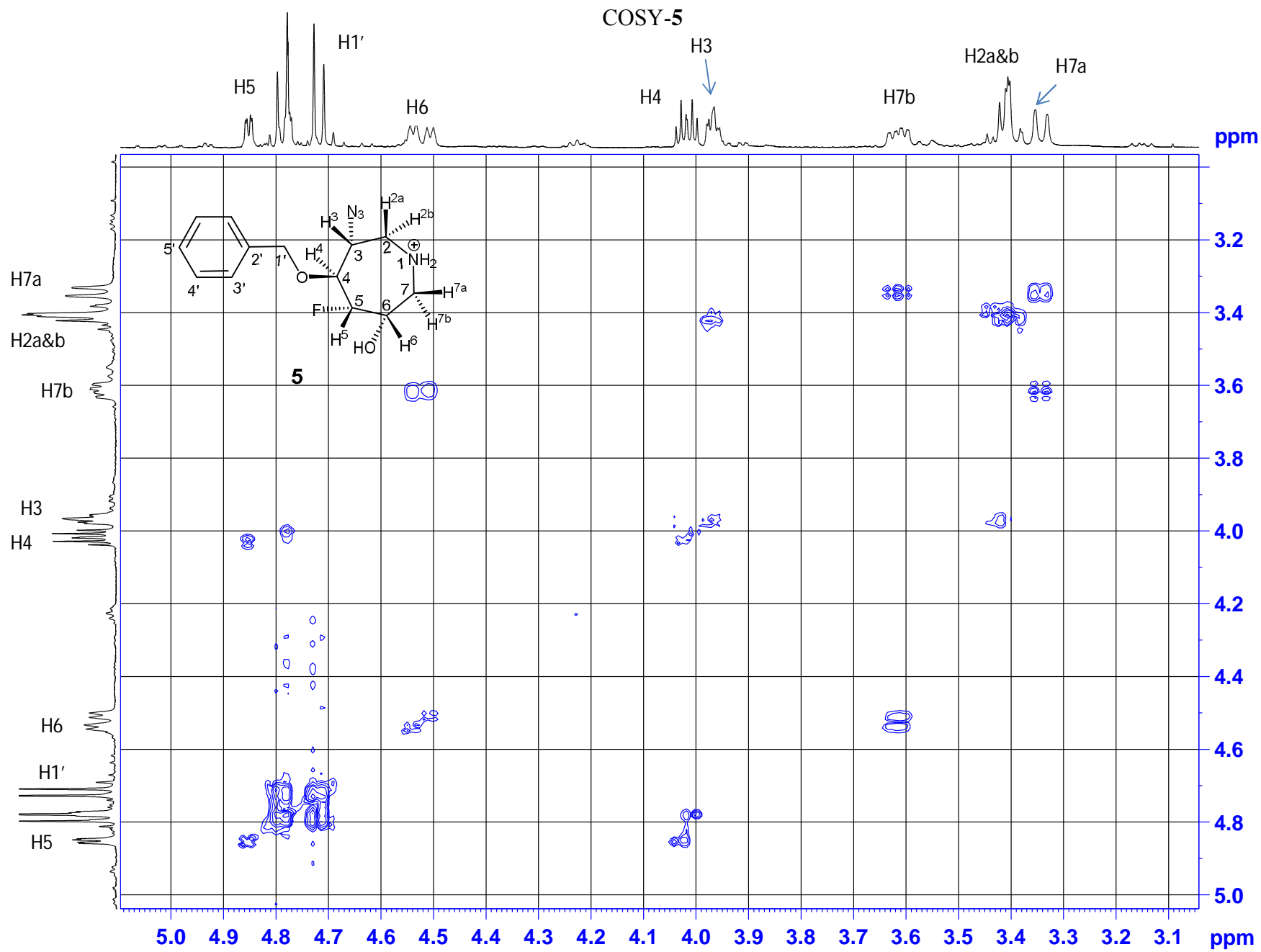


HSQC-5

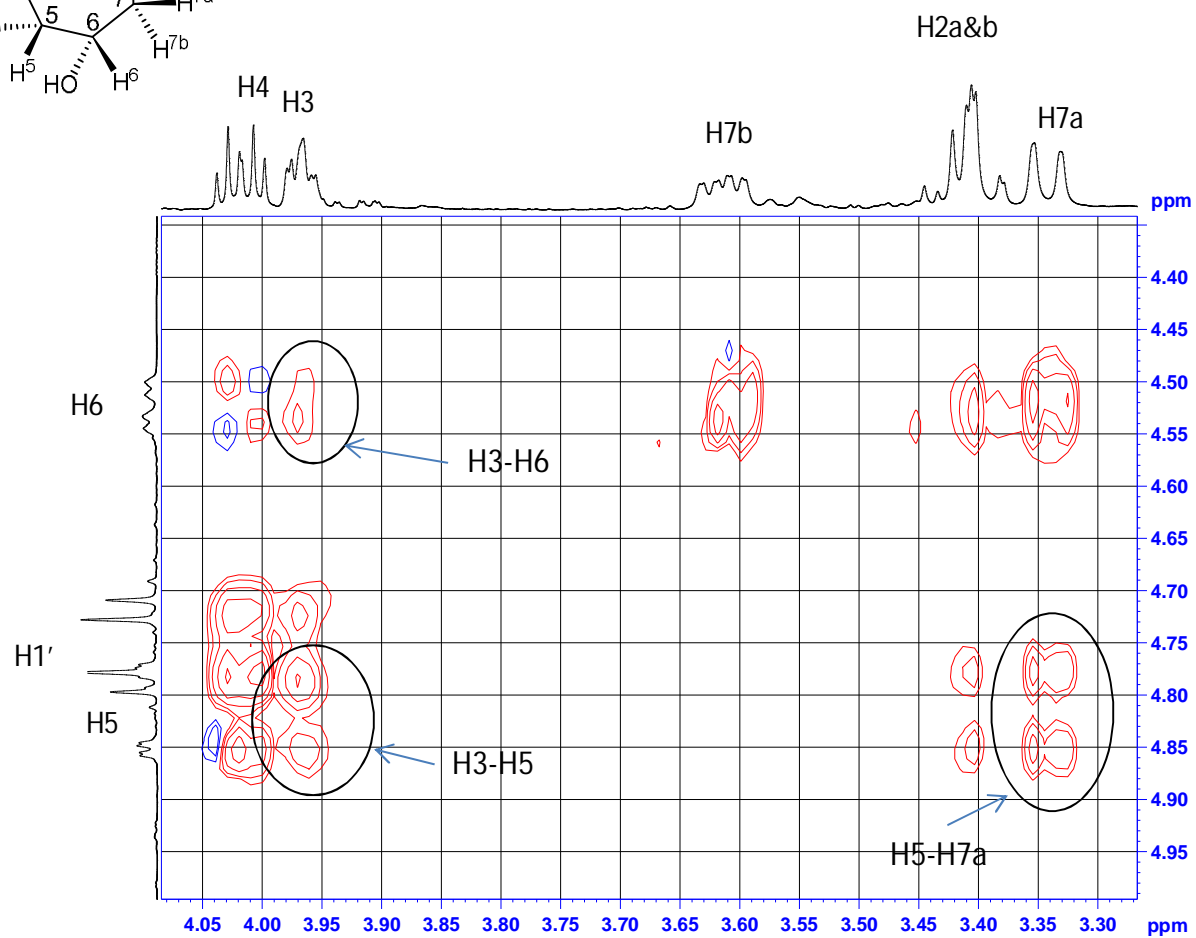
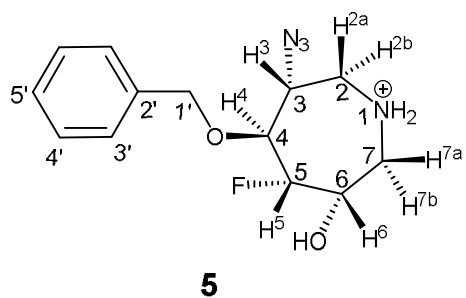


HMBC-5

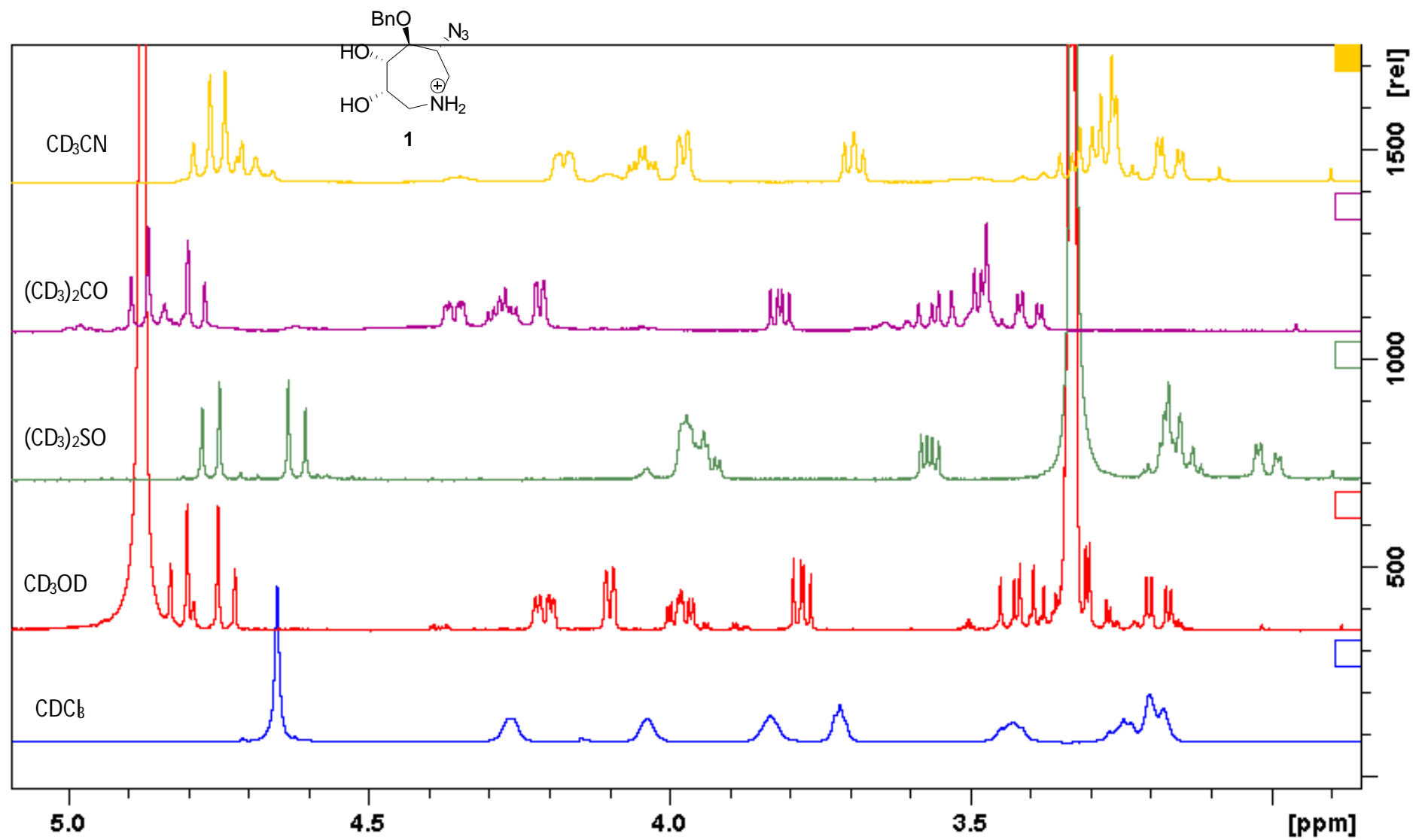




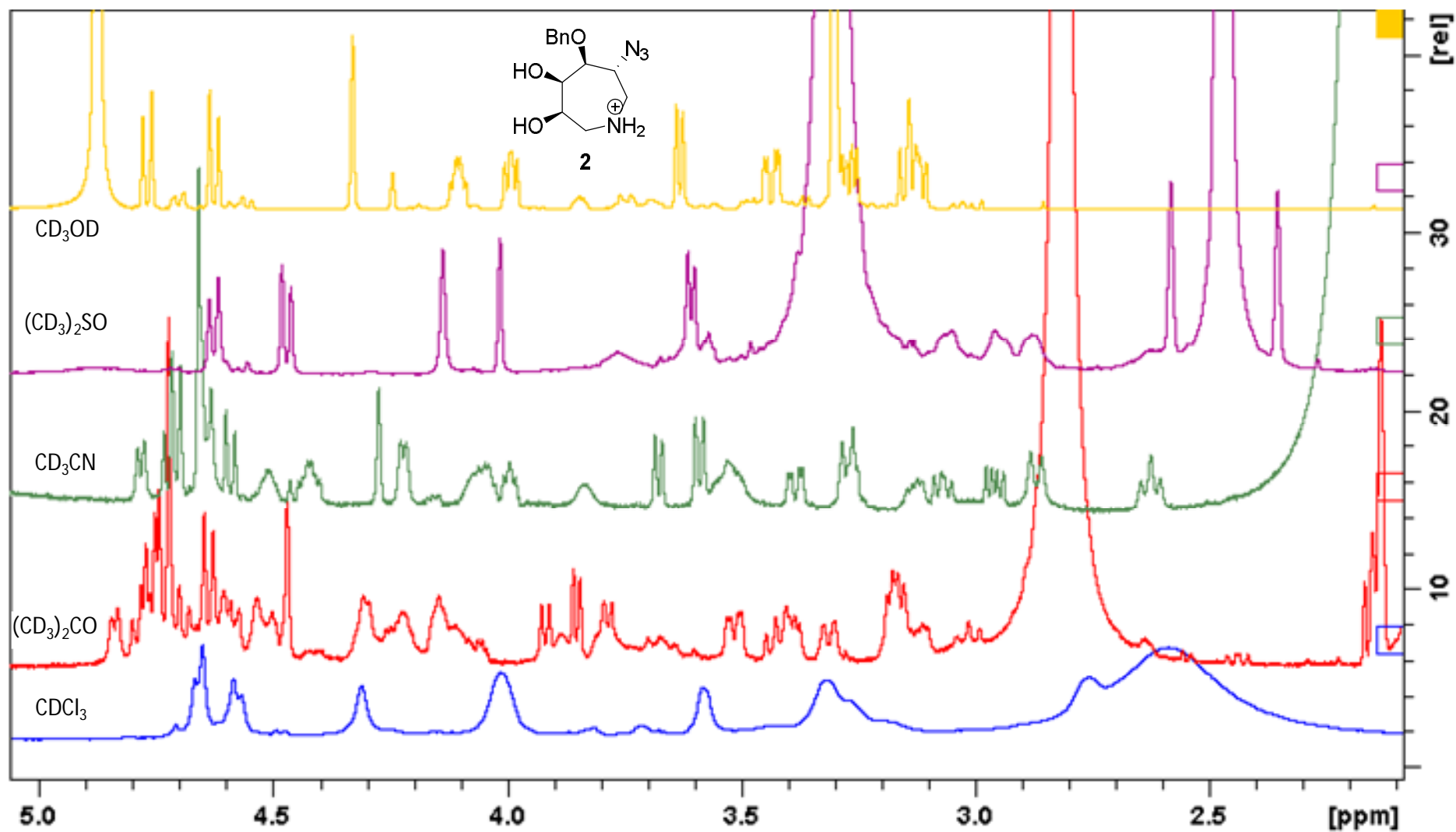
NOESY-5



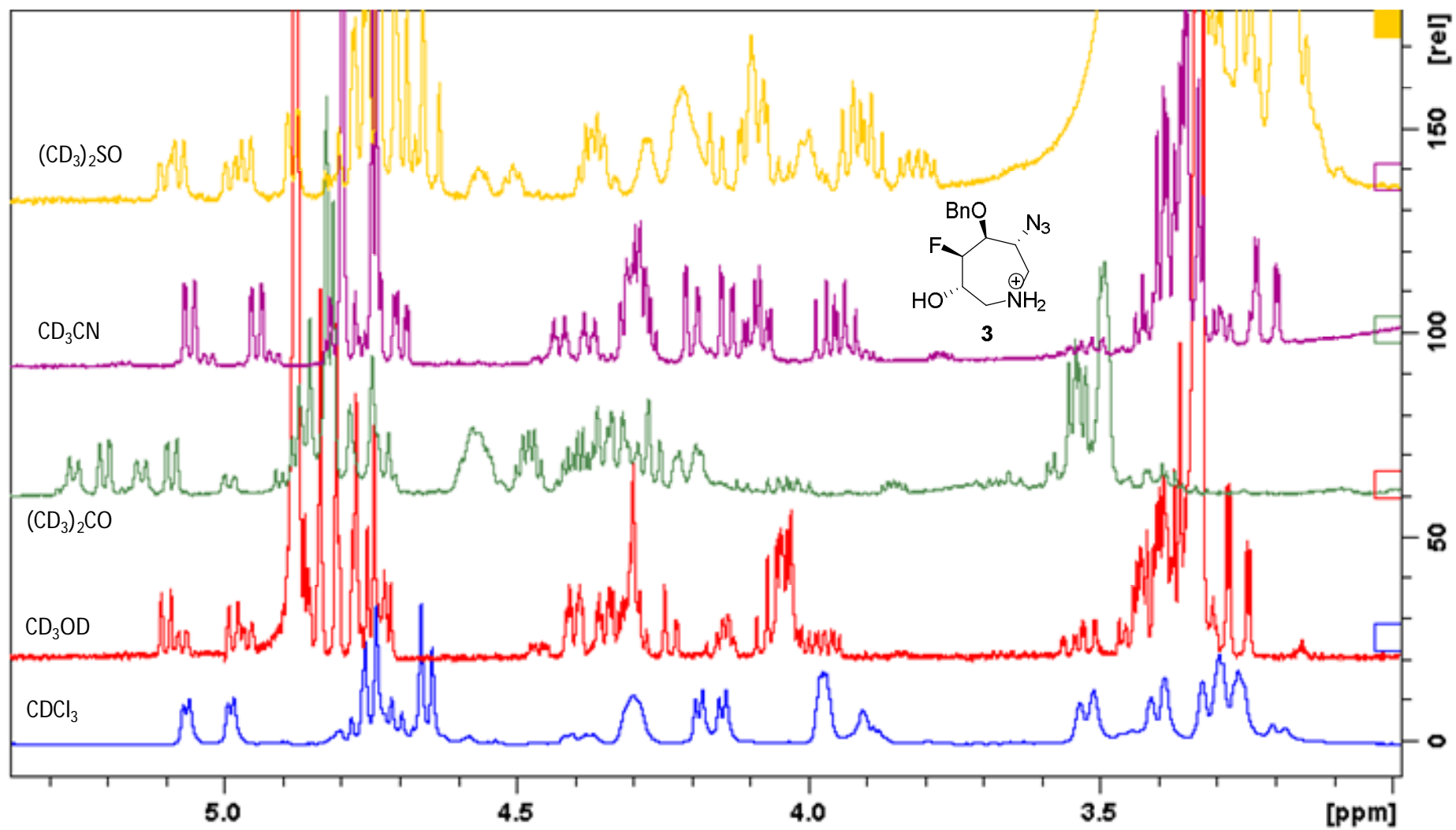
2. Solventstudies:



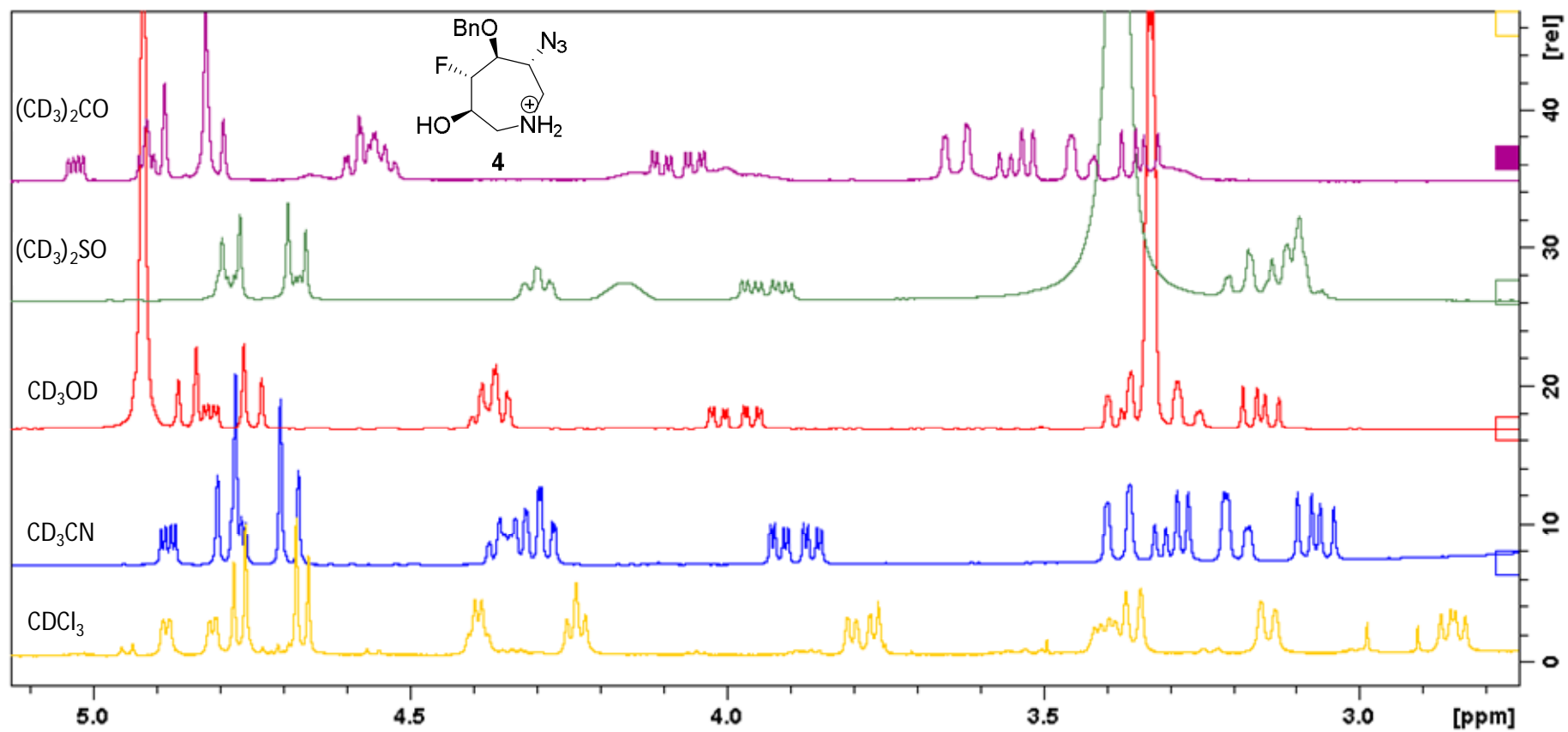
Solvent studies



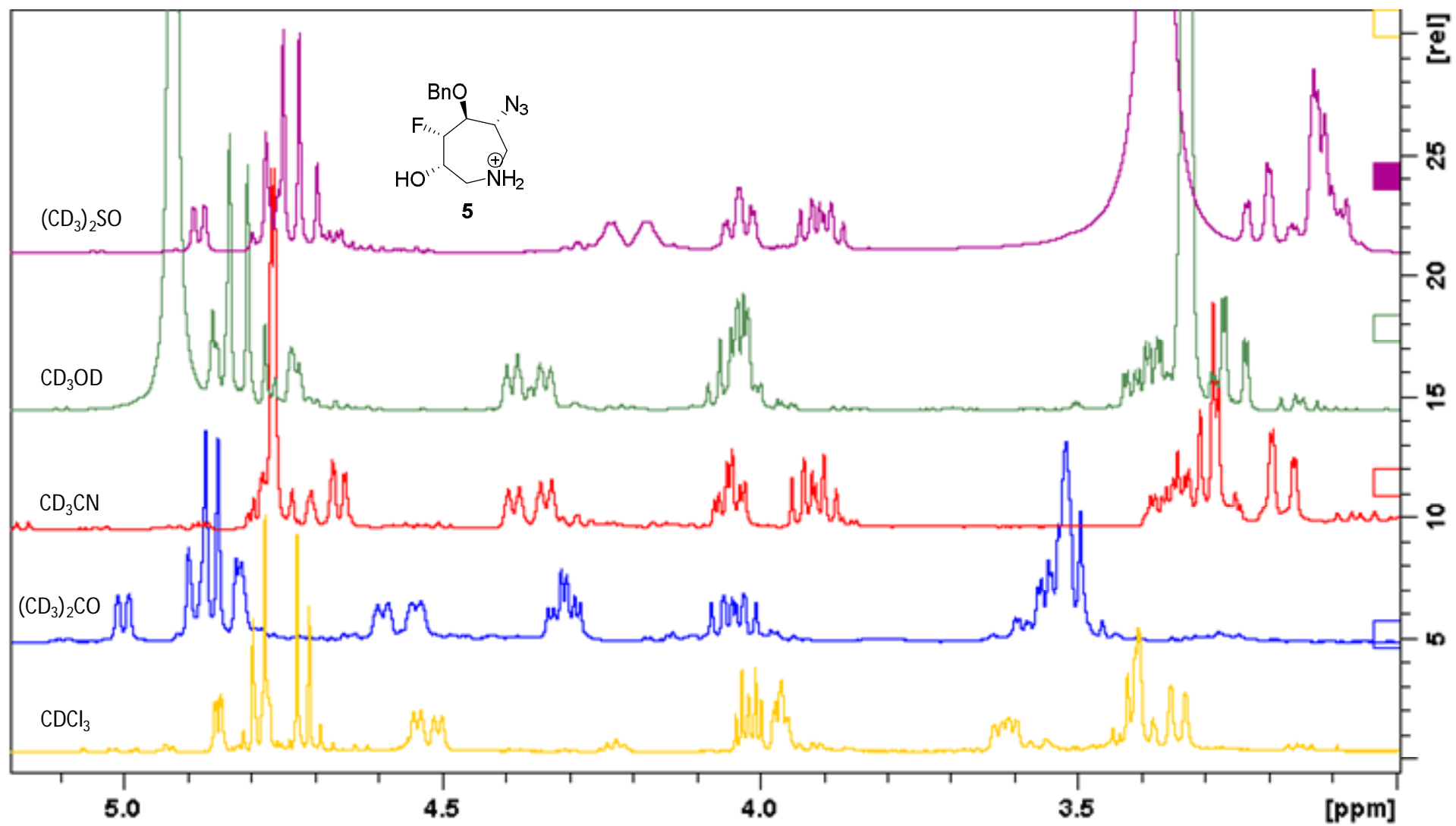
Solvent studies



Solvent studies

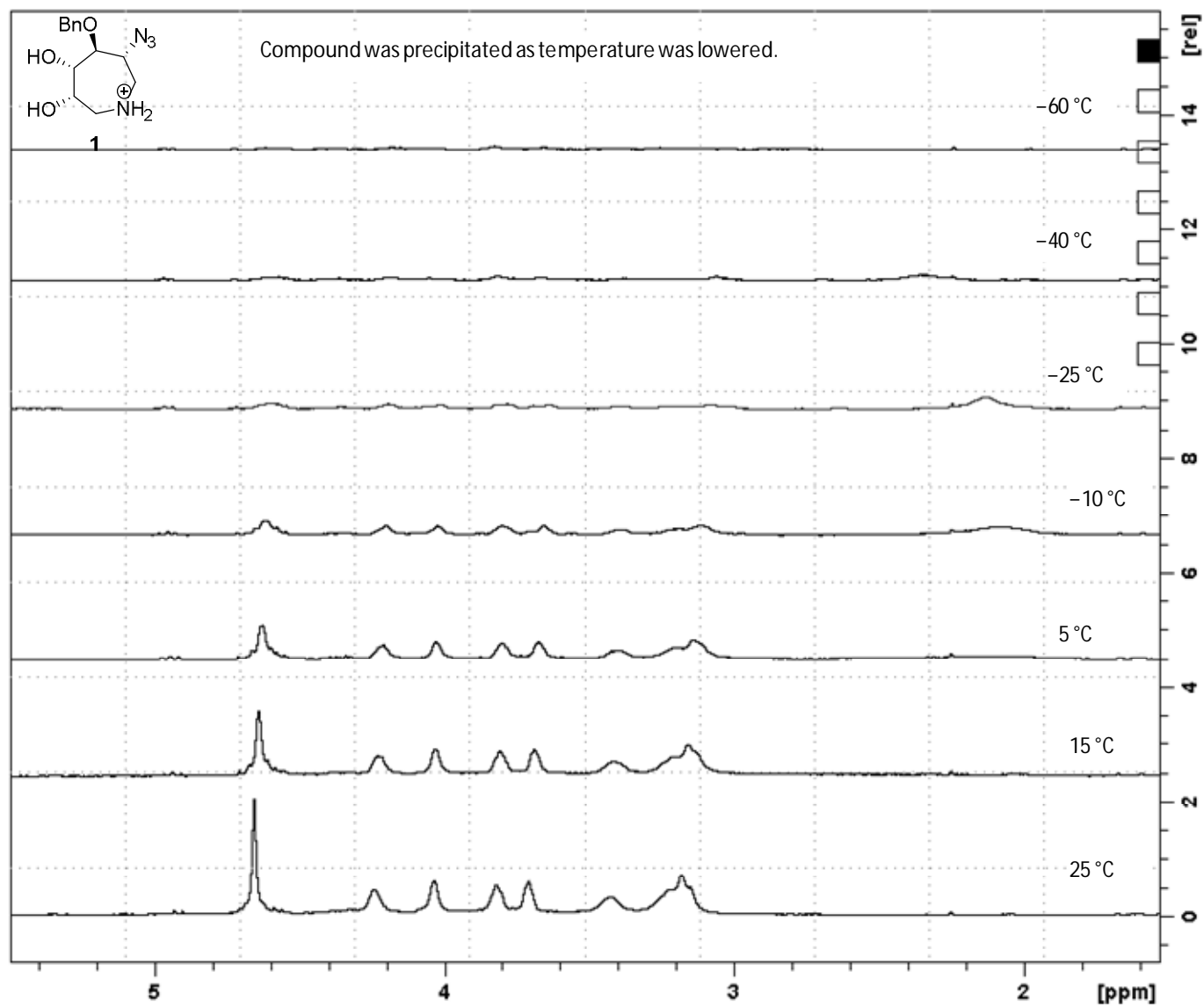


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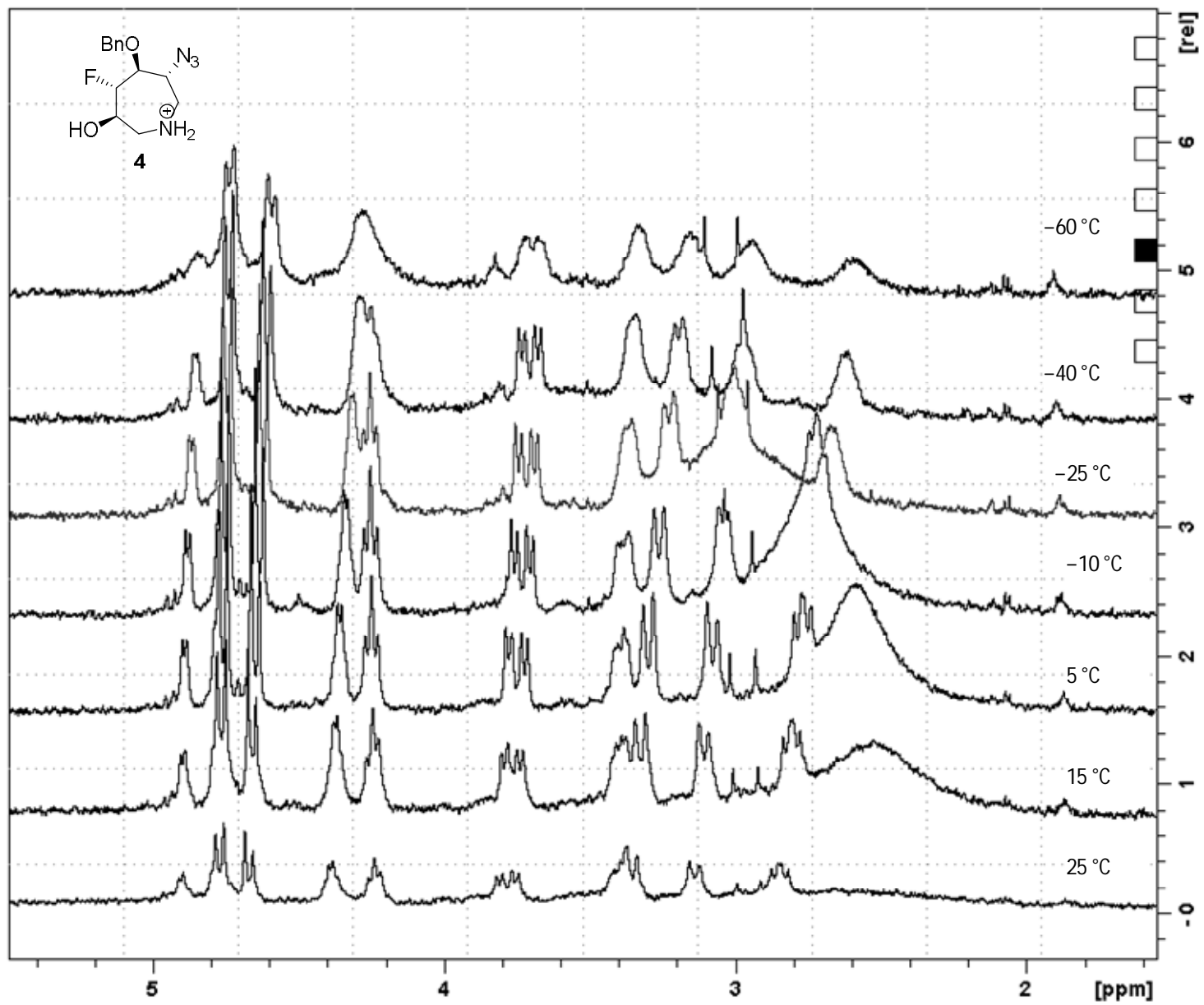


Temperature studies

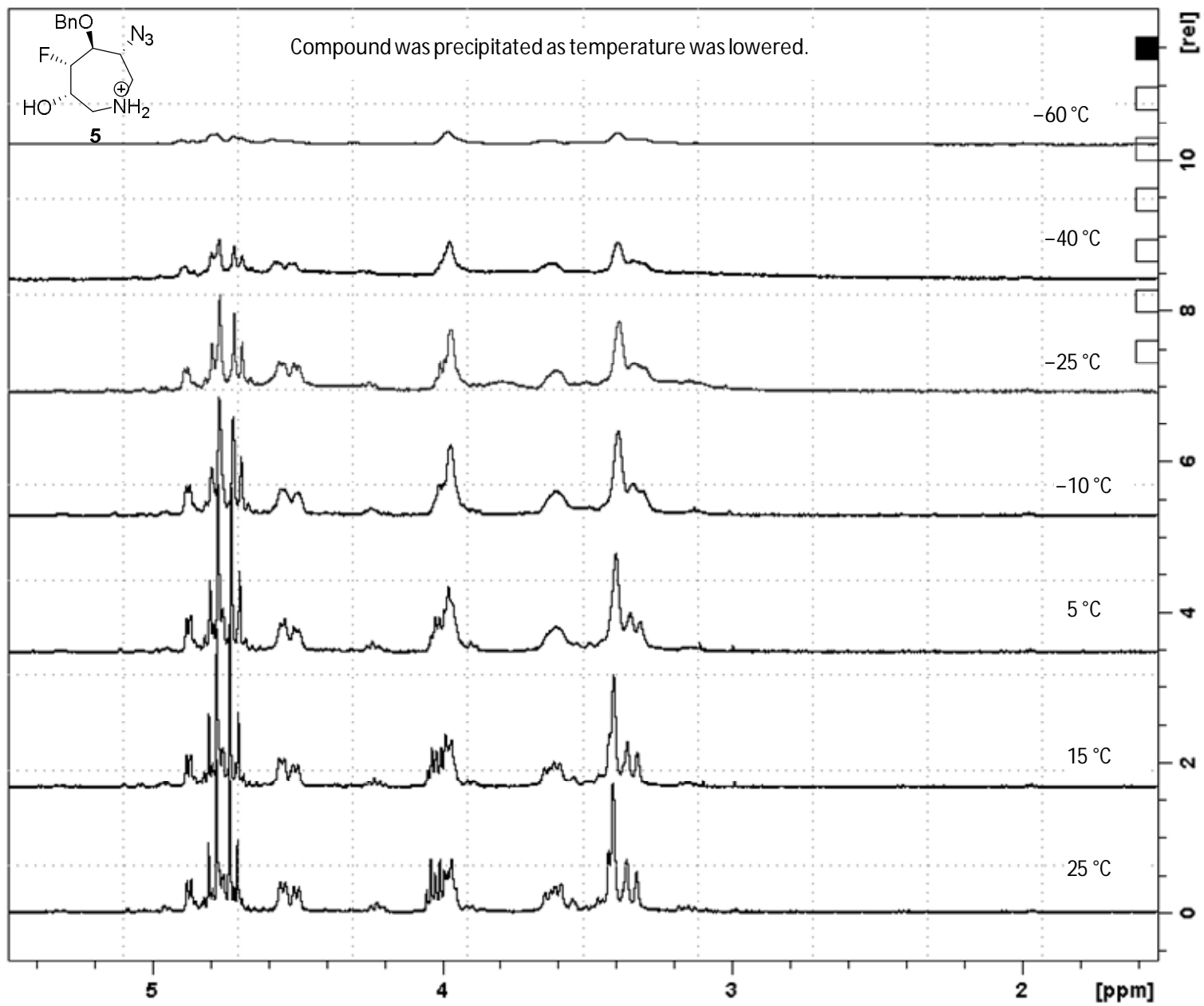
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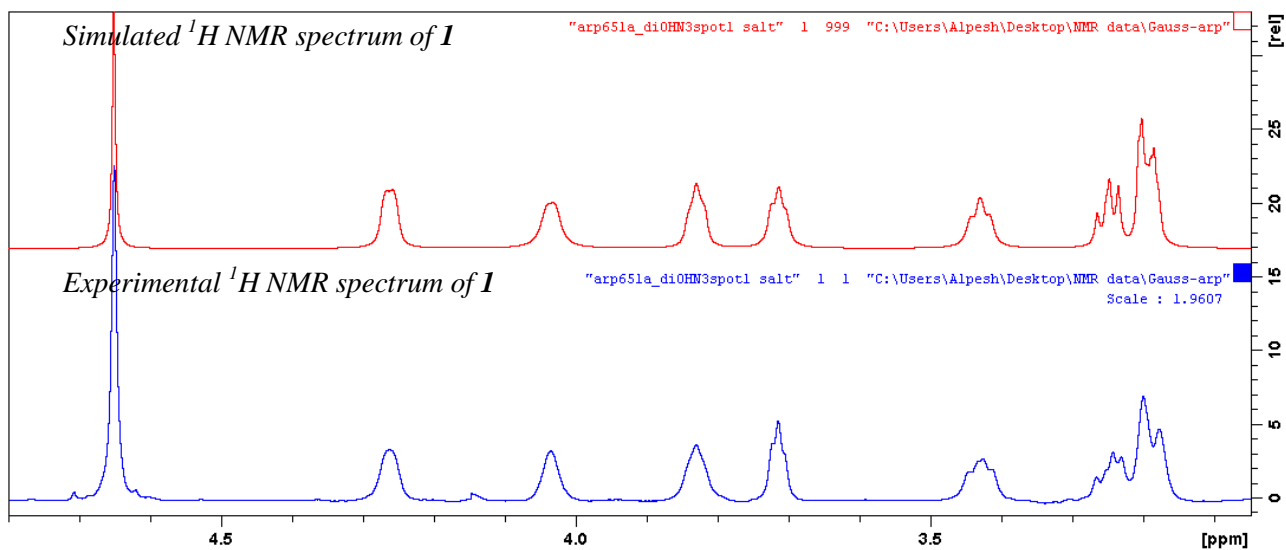
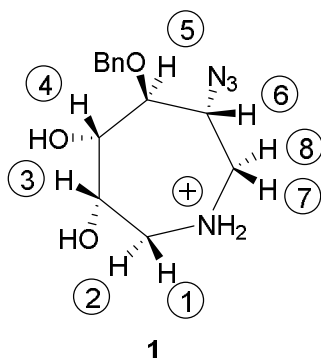
Temperature studies



Temperature studies

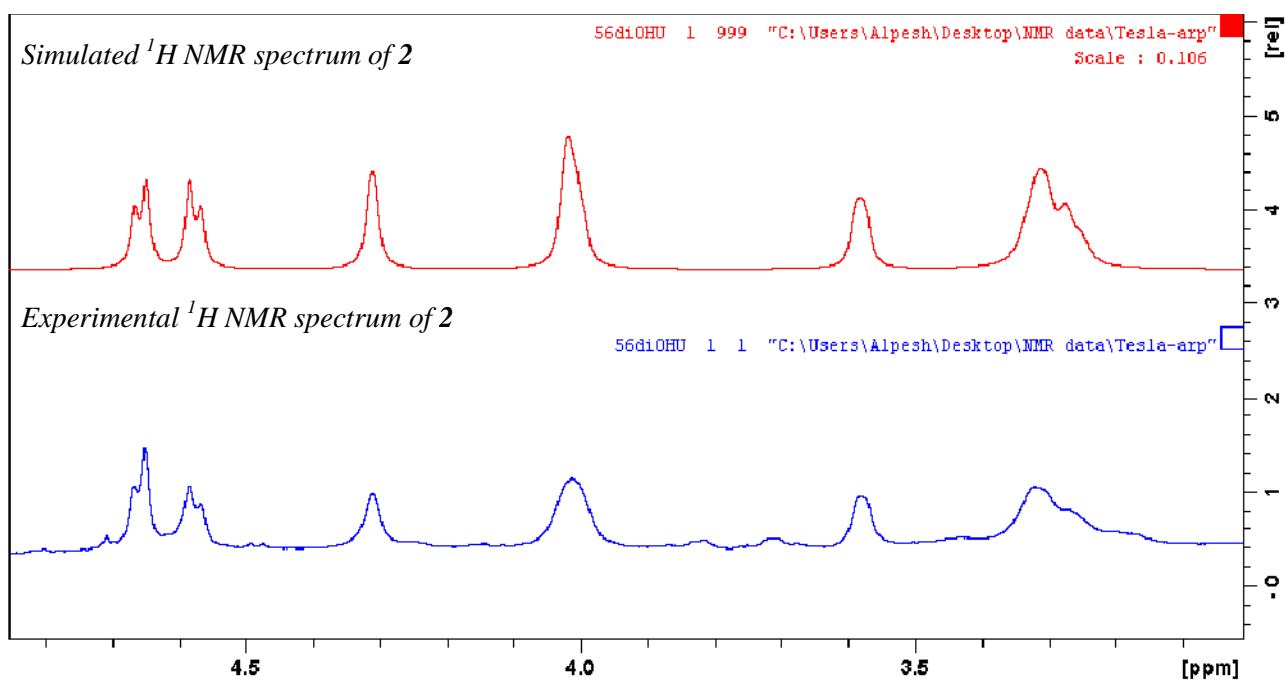
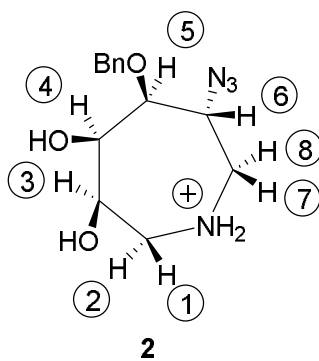


4. Simulated NMR spectra



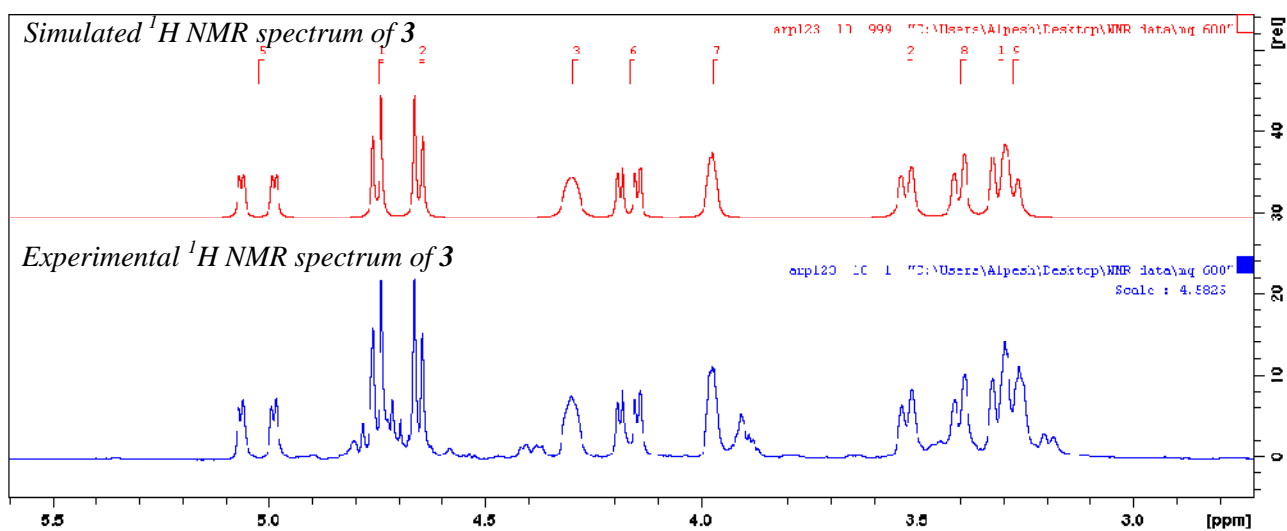
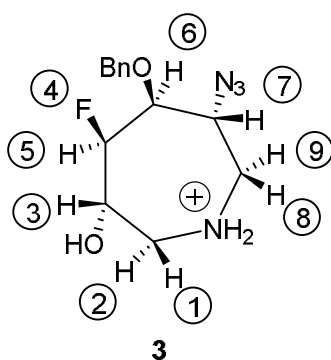
Nuclei	②	③	④	⑤	⑥	⑦	⑧
①	9.3 Hz	3.4 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
②		7.5 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
③			1.8 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
④				7.5 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑤					5.5 Hz	0.0 Hz	0.0 Hz
⑥						2.5 Hz	7.5 Hz
⑦							10.5 Hz

FigureS1:Expansion from the ¹H NMR spectrum of azepane **1**. The good match between the simulated and experimental spectra confirms that the *J* value assignments (see grid) are accurate.



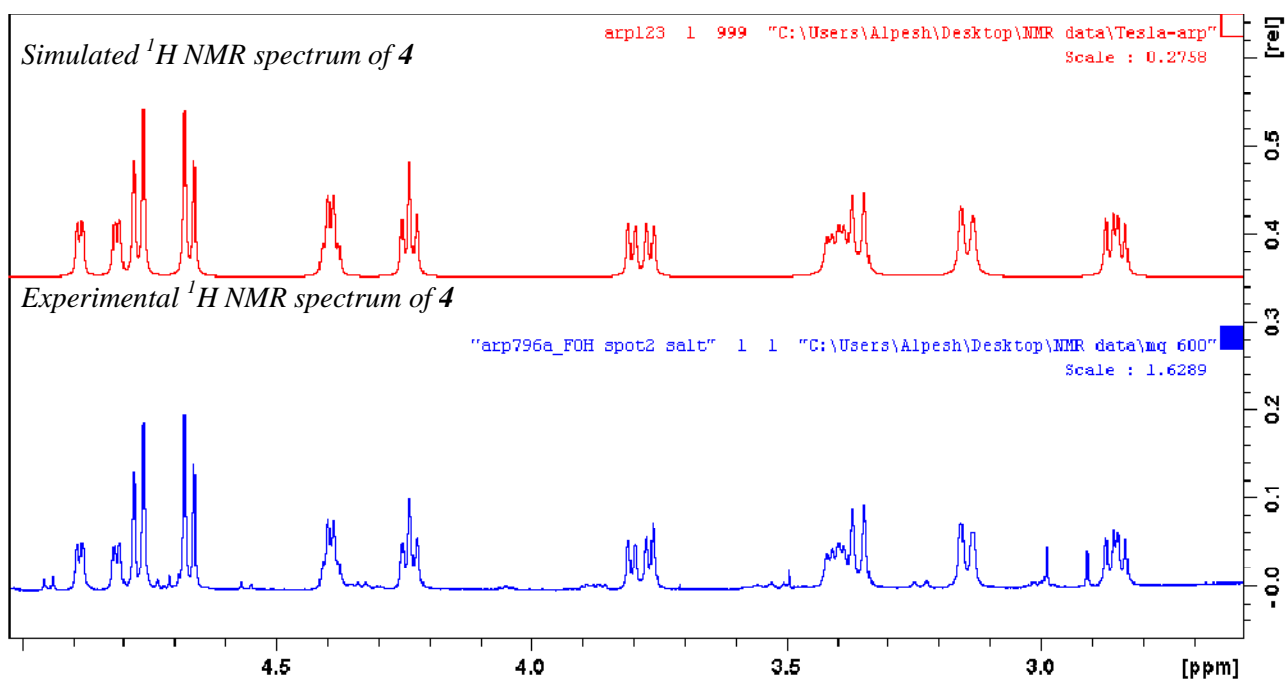
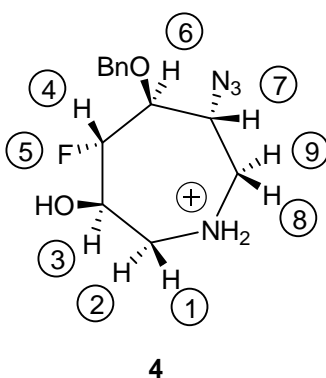
Nuclei	②	③	④	⑤	⑥	⑦	⑧
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②		4.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
③			2.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
④				4.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑤					8.0 Hz	0.0 Hz	0.0 Hz
⑥						2.0 Hz	6.0 Hz
⑦							12.0 Hz

FigureS2:Expansion from the ^1H NMR spectrum of azepane **2**. The good match between the simulated and experimental spectra confirms that the J value assignments (see grid) are accurate.



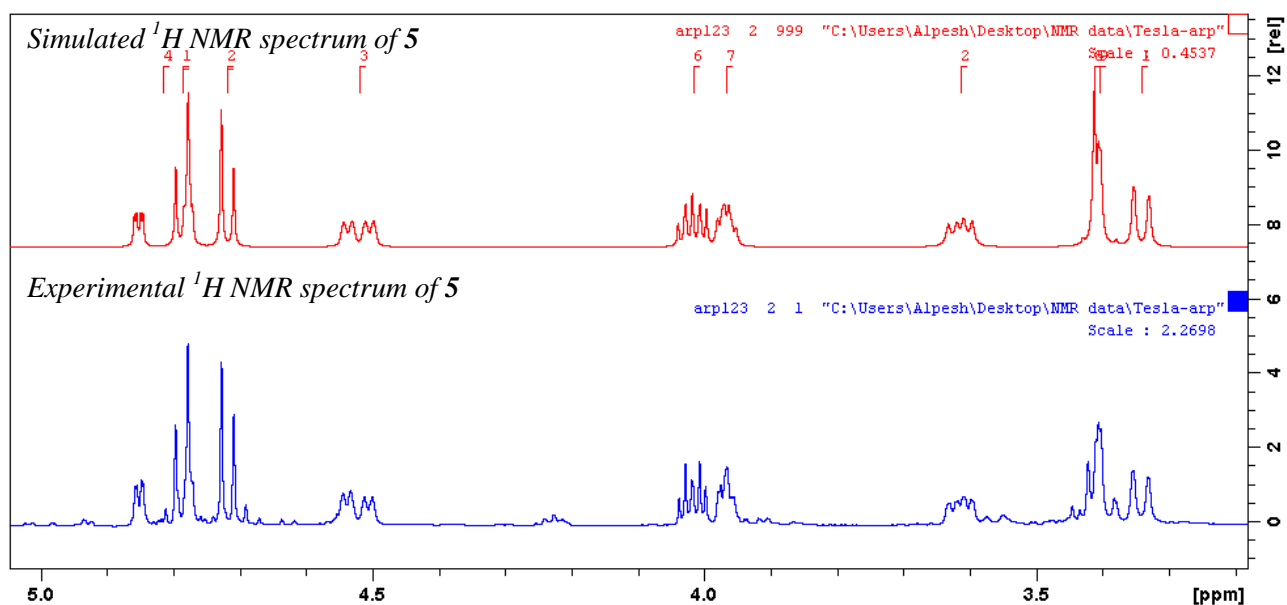
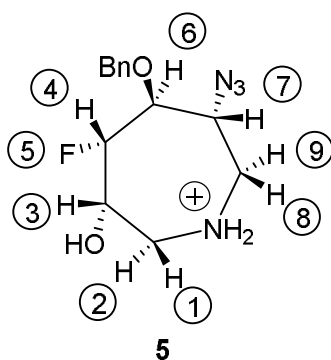
Nuclei	②	③	④	⑤	⑥	⑦	⑧	⑨
①	14.7 Hz	3.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
②		3.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
③			11.0 Hz	6.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
④				45.8 Hz	24.2 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑤					1.7 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑥						7.1 Hz	0.0 Hz	0.0 Hz
⑦							3.0 Hz	4.0 Hz
⑧								14.6 Hz

FigureS3:Expansion from the ^1H NMR spectrum of azepane **3**. The good match between the simulated and experimental spectra confirms that the J value assignments (see grid) are accurate.



Nuclei	②	③	④	⑤	⑥	⑦	⑧	⑨
①	14.1 Hz	6.2 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
②		1.4 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
③			5.9 Hz	7.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
④				44.1 Hz	2.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑤					21.4 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑥						8.7 Hz	0.0 Hz	0.0 Hz
⑦							2.0 Hz	8.9 Hz
⑧								14.1 Hz

FigureS4:Expansion from the ¹H NMR spectrum of azepane **4**. The good match between the simulated and experimental spectra confirms that the *J* value assignments (see grid) are accurate.



Nuclei	②	③	④	⑤	⑥	⑦	⑧	⑨
①	13.9 Hz	1.7 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
②		7.5 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
③			2.2 Hz	19.4 Hz	0.0 Hz	0.0 Hz	0.0 Hz	0.0 Hz
④				44.8 Hz	5.8 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑤					13.1 Hz	0.0 Hz	0.0 Hz	0.0 Hz
⑥						7.0 Hz	0.0 Hz	0.0 Hz
⑦							1.9 Hz	8.2 Hz
⑧								14.0 Hz

FigureS5:Expansion from the ¹H NMR spectrum of azepane **5**. The good match between the simulated and experimental spectra confirms that the *J* value assignments (see grid) are accurate.

4. Conformational analysis

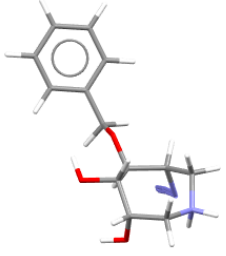
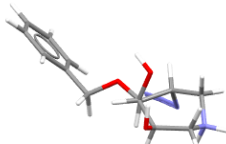

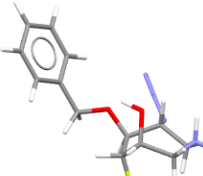
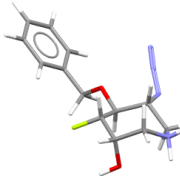

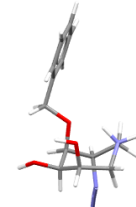
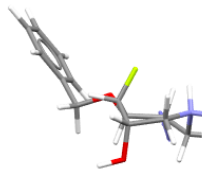
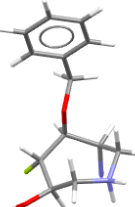
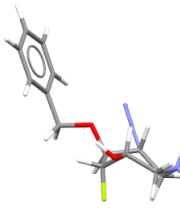
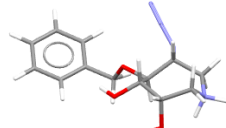
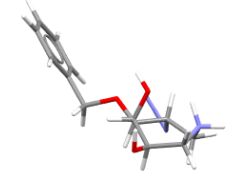
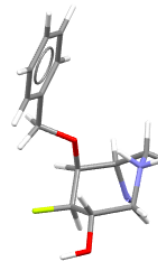
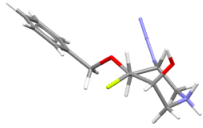
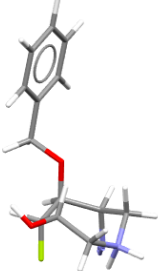
4.1. General

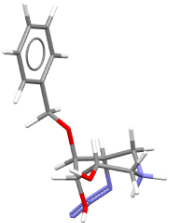
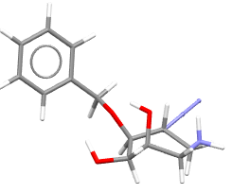
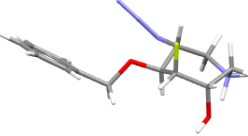
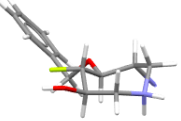
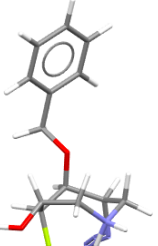
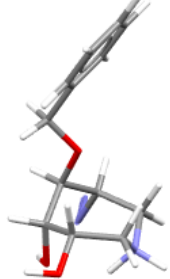
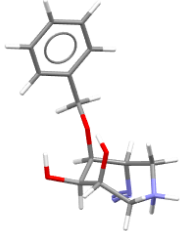
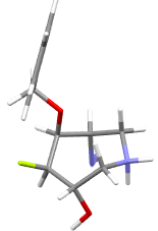
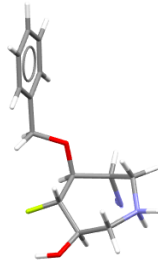
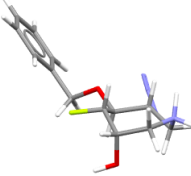
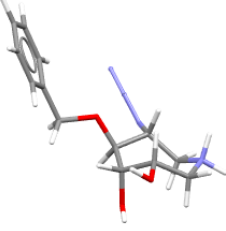
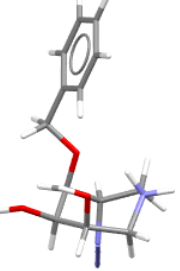
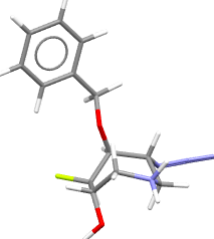
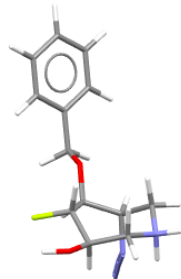
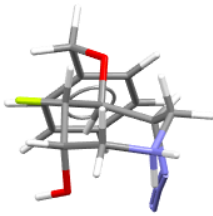
The conformational search for azepanes **1–5** was performed as implemented in the program MOE. Conformers were generated by the stochastic method and minimized in the MMFF94X forcefield with chloroform as the solvent. Conformers within 5 kcal/mol in energy were clustered to identify unique members with different azepane ring conformations. Each unique ring conformer was subjected to DFT geometry optimisation as implemented in the program Turbomole (with the SV(P) basis set at the B3LYP level in the specified COSMO solvent CHCl₃, MeOD or CD₃CN). As observed earlier (see ESI of ref 14b), the side chain OBn and azido substituents contribute 2 to 3 kcal/mol in energy variation. Thus the calculated energies of the conformers cannot be reliably used to rank conformational preferences but only to provide conformational candidates of the ring geometry. The filtering of the conformers was performed with the use of *J* values from NMR experiments.

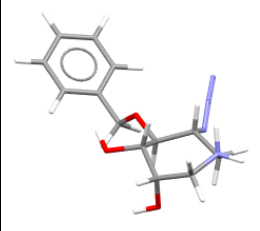
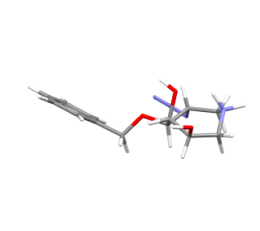
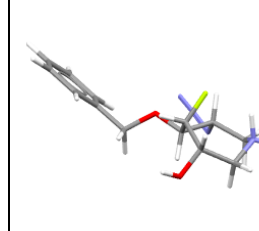
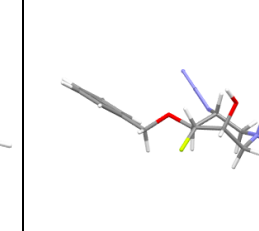
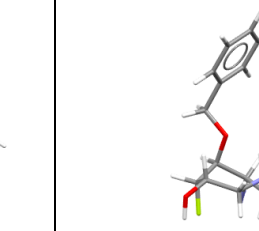
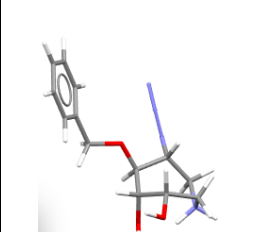

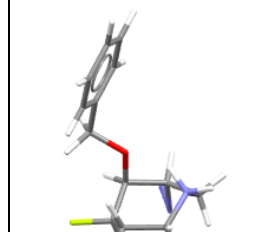
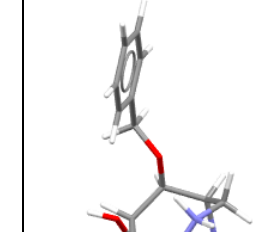
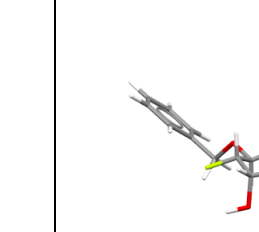
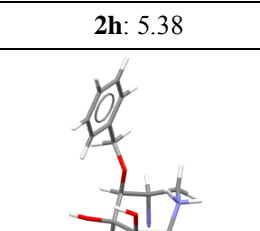
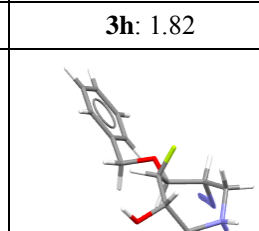
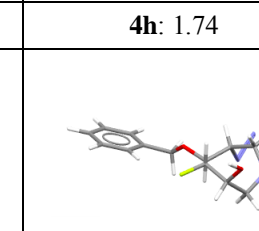
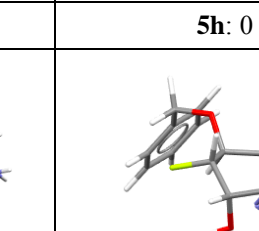
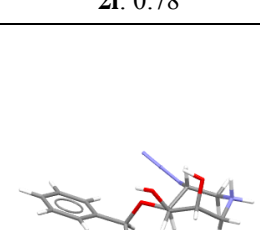
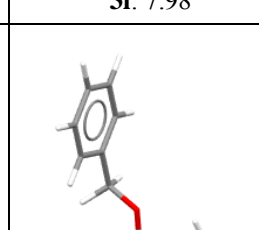
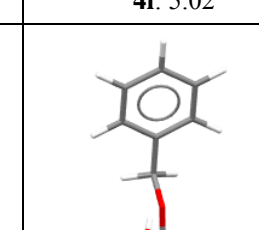
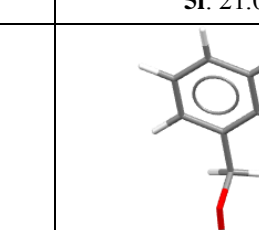
4.2. Conformations of azepanes **1–5** within 5 kcal/mol.

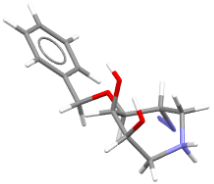
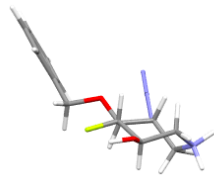
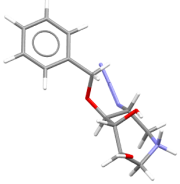
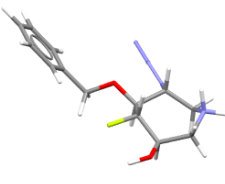
For azepanes **1–5**, clusters of distinct azepane ring conformations were found in the conformation search in MOE. A representative member of each cluster with distinct azepane ring conformation was geometry optimized and shown in the following table (Table S1). The conformers are visualized using the program Mercury 3.3.1 or Chimera (UCSF Chimera, version 1.7).

Table S1: Geometries of azepanes 1–5 in chloroform.

No	Azepane Geometries (relative energies (kcal/mol) are from chloroform)				
	1	2	3	4	5
1					
	1a: 1.96	2a: 4.72	3a: 3.40	4a: 0.12	5a: 1.02
2					
	1b: 3.54	2b: 0.10	3b: 3.61	4b: 2.44	5b: 2.88
3					
	1c: 0	2c: 2.87	3c: 1.40	4c: 0	5c: 3.50

4					
	1d: 3.12	2d: 4.11	3d: 3.30	4d: 3.41	5d: 5.87
5					
	1e: 5.28	2e: 2.92	3e: 0	4e: 1.25	5e: 1.73
6					
	1f: 3.83	2f: 0.11	3f: 7.91	4f: 2.07	5f: 2.24

7					
	1g: 3.47	2g: 4.34	3g: 4.15	4g: 0.10	5g: 3.55
8					
	1h: 2.48	2h: 5.38	3h: 1.82	4h: 1.74	5h: 0
9					
		2i: 0.78	3i: 7.98	4i: 5.02	5i: 21.0
10					

		2j: 0	3j: 2.97	4j: 1.73	5j: 0.67
11					
		2k: 4.82		4k: 3.38	
12					
		2l: 5.31		4l: 3.82	

4.3. Weighted contribution calculations for azepanes 1–5 in CDCl₃

Azepane 1:

In azepane **1**, out of eight ring conformations found from a conformational search only three (**1a**, **1b** and **1c**; Table S1) could match reasonably well to the characteristic $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum. The following graph (Fig. S6) illustrates that it was possible to obtain a good match between experimental and calculated $^3J_{\text{HH}}$ values by creating a weighted average of these three geometries.

A series of weighted averages of these conformers were investigated, in order to determine the best ratio of **1a** : **1b** : **1c** for matching the experimental J values. It was found that a ratio of 50 : 40 : 10 gave a weighted average set of $^3J_{\text{HH}}$ values that matched the experimental values reasonably well (Fig. S6).

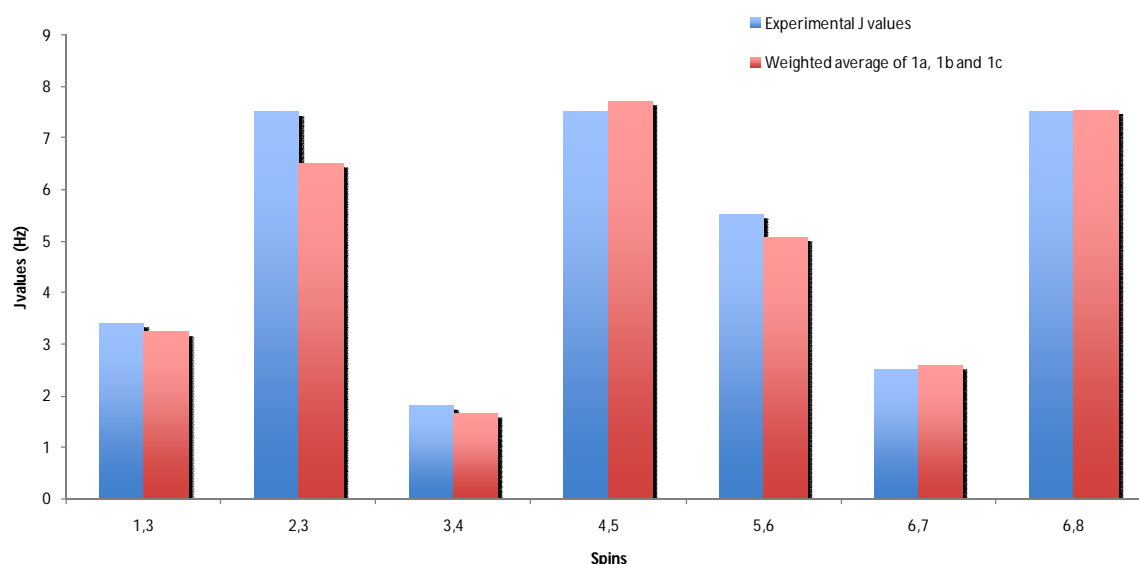


Figure S6: J values of azepane **1**, calculated for a 50:40 : 10 distribution of conformers **1a**, **1b** and **1c**.

Azepane 3:

In azepane **3**, out of ten ring conformations found from a conformational search only two (**3a** and **3b**, Table S1) could match the $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum closely. The following graph (Fig. S7) illustrates that it was possible to obtain a good match between experimental and calculated $^3J_{\text{HH}}$ values by creating a weighted average of these two geometries. A series of weighted averages of these conformers were investigated, in order to determine the ratio of **3a** : **3b** that gave the best match with the experimental $^3J_{\text{HH}}$ values. It was found that a ratio of 70

:30 gave a weighted average set of J values that matched the experimental values reasonably well (Fig. S7).

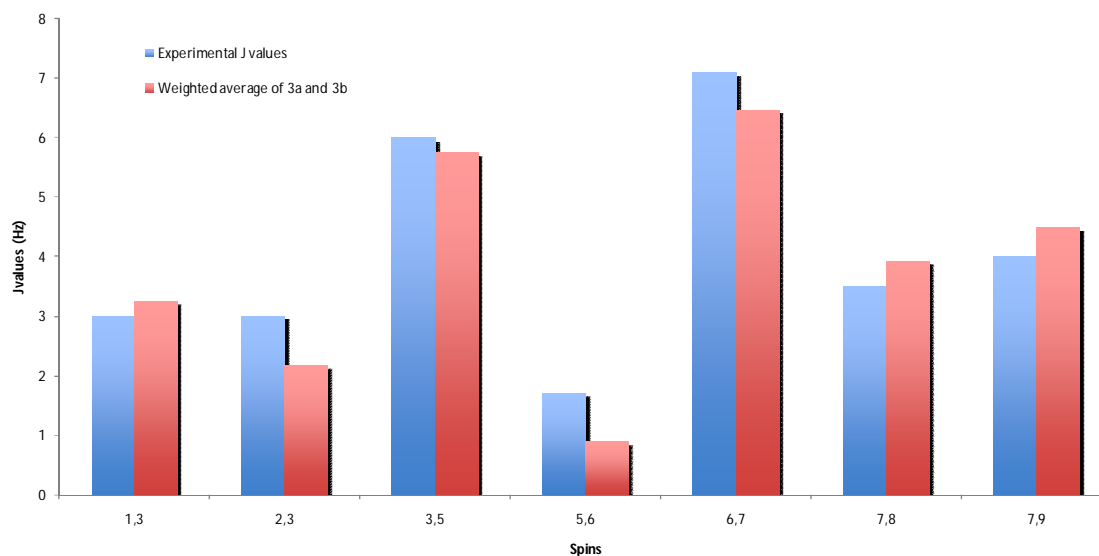


Figure S7: J values of azepane **3**, calculated for a 70: 30 distribution of conformers **3a** and **3b**.

Azepane **4**:

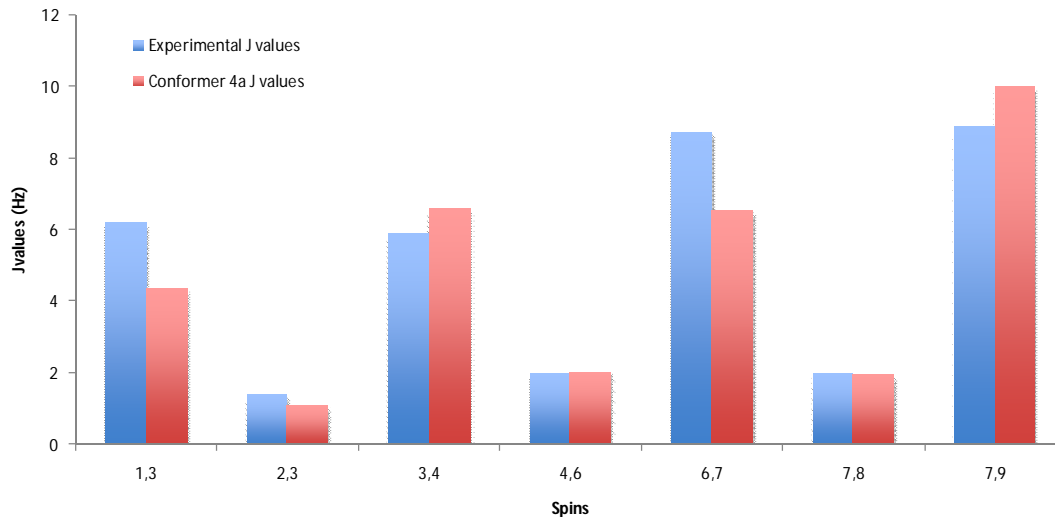


Figure S8: J values of azepane **4**, calculated for a conformer **4a** is the closest match.

In azepane **4**, out of twelve ring conformations found from a conformational search only one conformer (**4a**, Table S1) could match all three characteristic $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum. The weighted average of **4a** was calculated with various other conformers to improve the match with experimental $^3J_{\text{HH}}$ values. However, none of the weighted average gave the

better match than **4a** alone. The following graph (Fig. S8) illustrates that it was possible to obtain a good match between experimental and calculated $^3J_{\text{HH}}$ values geometry **4a**. (Fig. S8).

Azepane **5**:

In azepane **5**, out of ten ring conformations found from a conformational search only two (**5a** and **5b**, Table S1) could closely match $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum. The following graph (Fig. S9) illustrates that it was possible to obtain a good match between experimental and calculated J values by creating a weighted average of these **two** geometries. A series of weighted averages of these conformers were investigated, in order to determine the ratio of **5a** :**5b** that gave the best match with the experimental J values. It was found that a ratio of 80 :20 gave a weighted average set of J values that matched the experimental values reasonably well (Fig. S9).

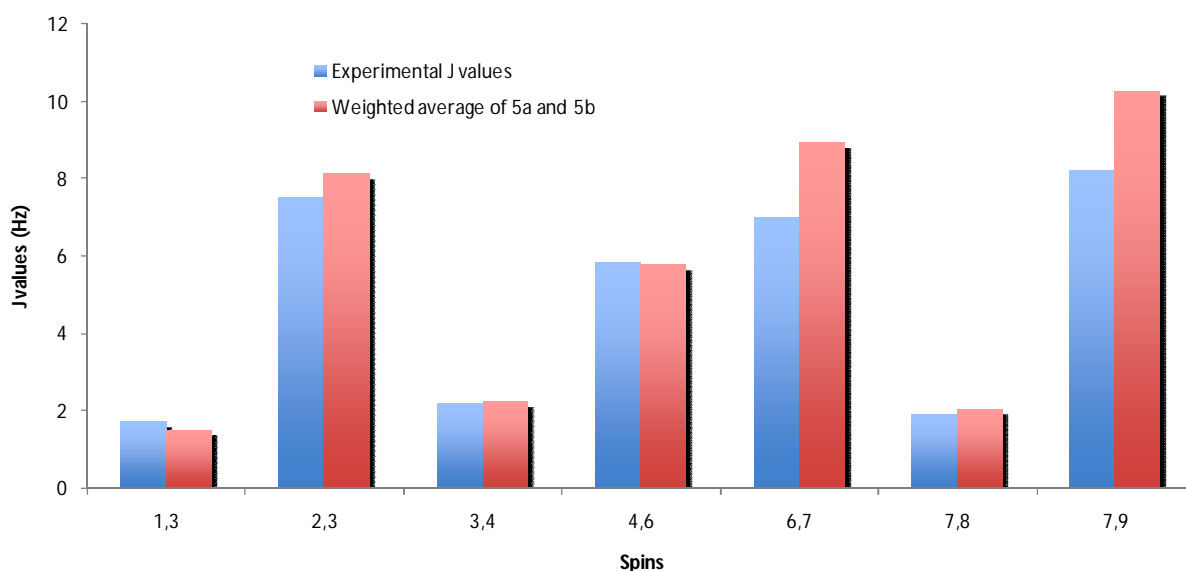


Figure S9: J values of azepane **5**, calculated for a 80:20 distribution of conformers **5a** and **5b**.

4.4. Weighted contribution calculations for azepane **2** in CD_3OD

In azepane **2**, out of twelve ring conformations found from a conformational search only two (**2a** and **2l**; Table S1) could match reasonably well to the characteristic $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum in CD_3OD . The following graph (Fig. S10) illustrates that it was possible to obtain a good match between experimental and calculated $^3J_{\text{HH}}$ values by creating a weighted average of these **two** geometries.

A series of weighted averages of these conformers were investigated, in order to determine the best ratio of **2a** :**2l** for matching the experimental J values. It was found that a ratio of 40 :60 gave a

weighted average set of $^3J_{\text{HH}}$ values that matched the experimental values reasonably well (Fig. S10).

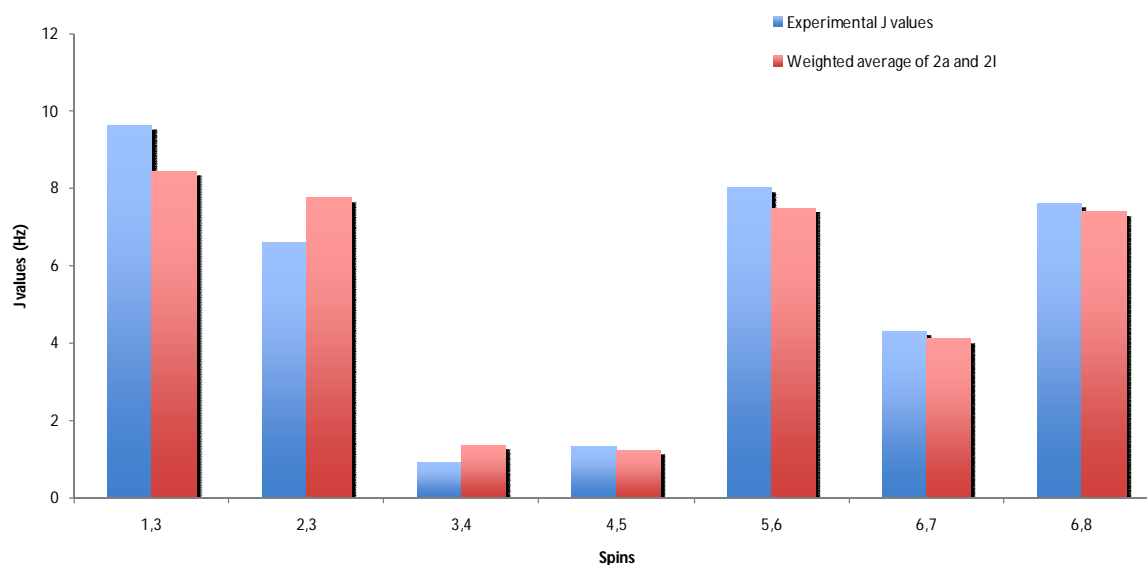


Figure S10: J values of azepane **2** in CD_3OD , calculated for a 40 :60 distribution of conformers **2a** and **2l**.

4.5. Weighted contribution calculations for azepane **3** in CD_3CN

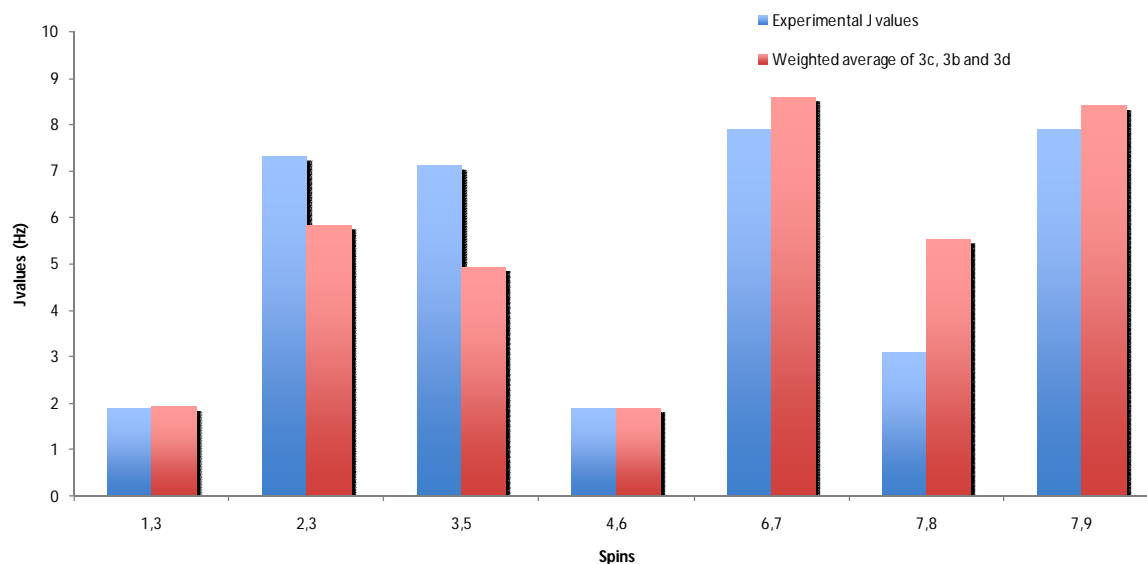


Figure S11: J values of azepane **3** in CD_3CN , calculated for a 60 :10 : 30 distribution of conformers **3c**, **3b** and **3d**.

In azepane **3**, out of ten ring conformations found from a conformational search only three (**3c**, **3b** and **3d**; Table S1) could match reasonably well to the characteristic $^3J_{\text{HH}}$ values extracted from its ^1H NMR spectrum in CD_3CN . The following graph (Fig. S11) illustrates that it was possible to

obtain a good match between experimental and calculated ${}^3J_{\text{HH}}$ values by creating a weighted average of these **three** geometries.

A series of weighted averages of these conformers were investigated, in order to determine the best ratio of **3c** : **3b** : **3d** for matching the experimental J values. It was found that a ratio of 60 : 10 : 30 gave a weighted average set of ${}^3J_{\text{HH}}$ values that matched the experimental values reasonably well (Fig. S11).