Use of a conformational switching mechanism to modulate exposed polarity: discovery of CCR2 antagonist BMS-741672

Michael G. Yang, Zili Xiao, Robert J. Cherney, Andrew J. Tebben, Douglas G. Batt, Gregory D. Brown, Jing Chen, Mary Ellen Cvijic, Marta Dabros, John V. Duncia, Michael Galella, Daniel S. Gardner, Purnima Khandelwal, Soo S. Ko, Mary F. Malley, Ruowei Mo, Jian Pang, Anne V. Rose, Joseph B. Santella, III, Hong Shi, Anurag Srivastava, Sarah Traeger, Bei Wang, Songmei Xu, Rulin Zhao, Joel C. Barrish, Sandhya Mandlekar, Qihong Zhao and Percy H. Carter*

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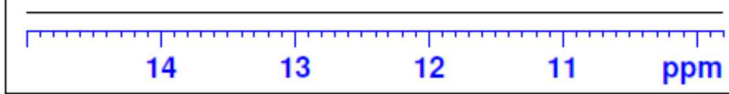
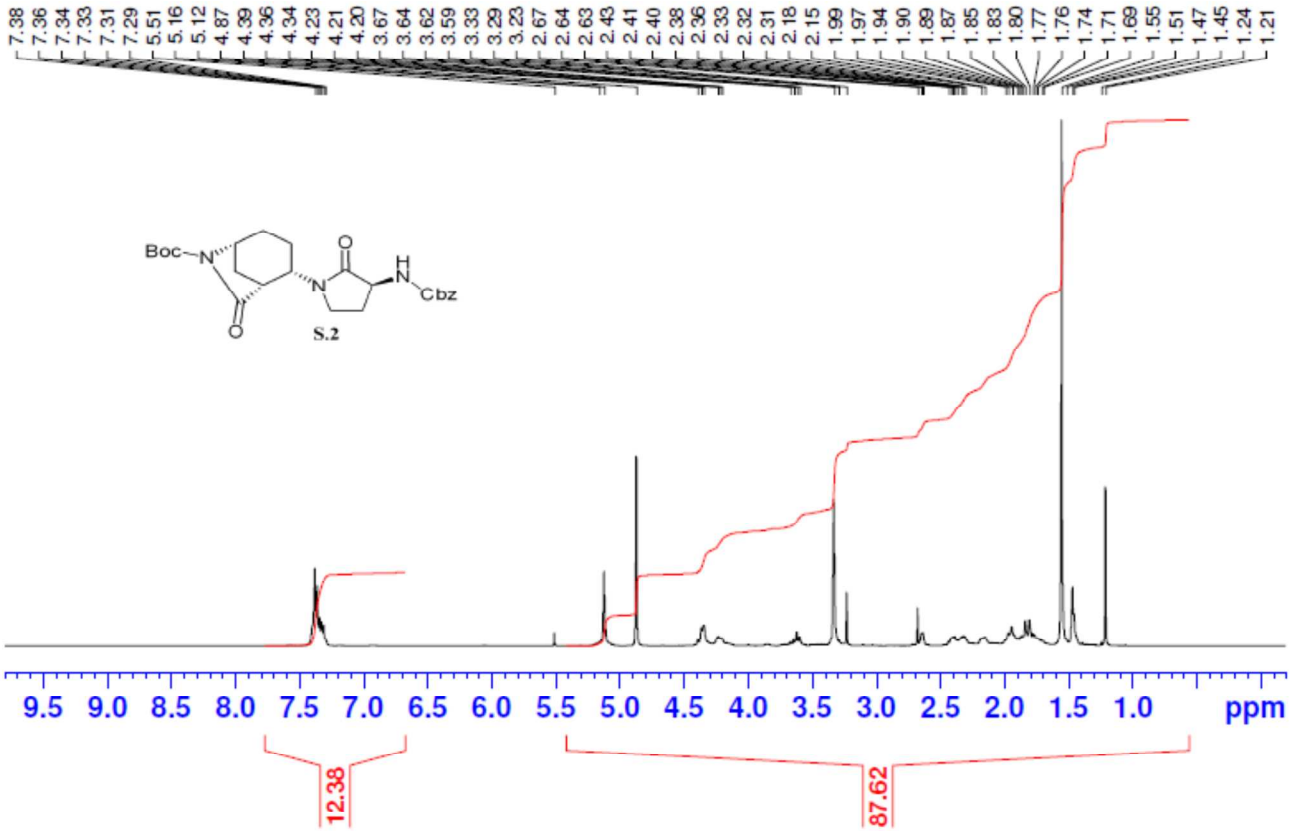
Supporting Information (2 of 2)



ROTON64 MeOD /opt/topspin3.2 yangmq

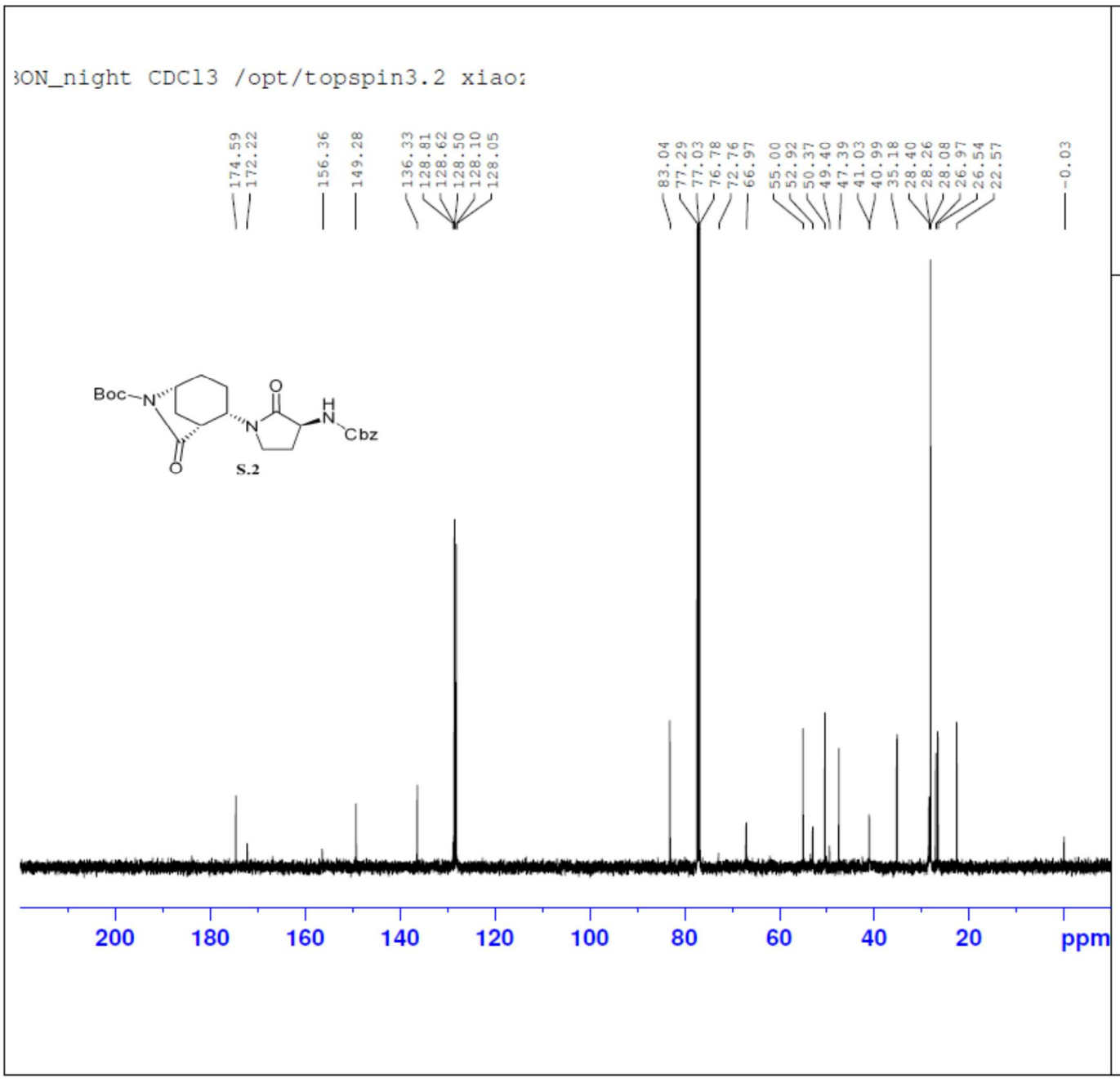


Current Data Parameters
NAME A0F8C-141-S2
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161215
Time 8.44
INSTRUM lvl_nmrl2b400b
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 32768
SOLVENT MeOD
NS 64
DS 2
SWH 8012.820 Hz
FIDRES 0.244532 Hz
AQ 2.0447233 sec
RG 192.54
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 399.8524692 MHz
NUC1 1H
P1 12.14 usec
PLW1 12.00000000 W

F2 - Processing parameters
SI 65536
SF 399.8500000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

```
Current Data Parameters
NAME        A12C9-112-S2
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20161210
Time                2.14
INSTRUM   lvl_nmr13b400a
PROBHD    5 mm PABBO BB/
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                 1000
DS                    4
SWH           29761.904 Hz
FIDRES         0.454131 Hz
AQ            1.1010048 sec
RG                  456
DW               16.800 usec
DE                6.50 usec
TE               300.0 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
SFO1         125.5773561 MHz
NUC1                13C
P1                 9.23 usec
PLW1         80.52400208 W

======== CHANNEL f2 ========
SFO2         499.3619974 MHz
NUC2                1H
CPDPRG[2         waltz16
PCPD2              80.00 usec
PLW2         15.78600025 W
PLW12         0.31217000 W
PLW13         0.19979000 W

F2 - Processing parameters
SI                 32768
SF           125.5641719 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
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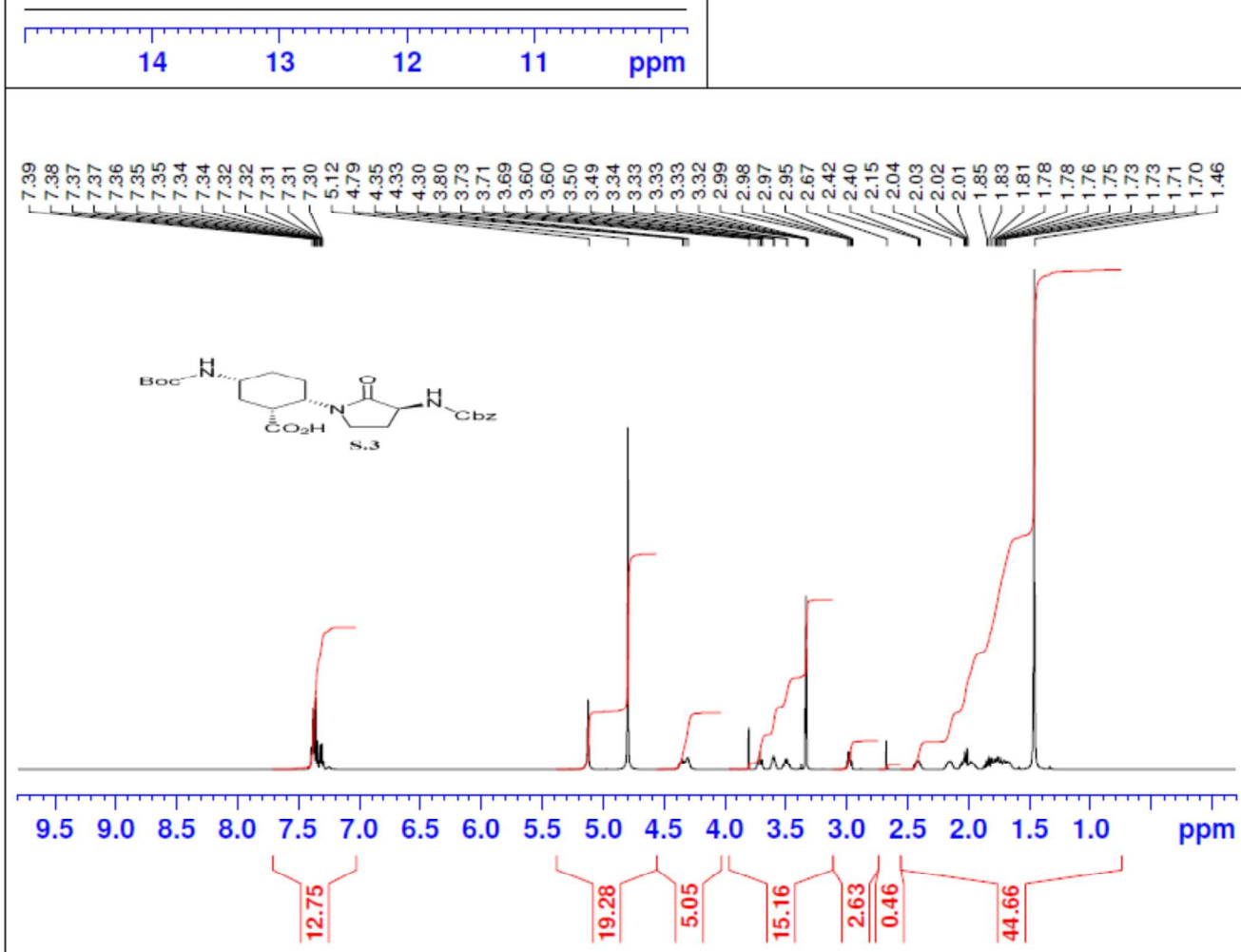
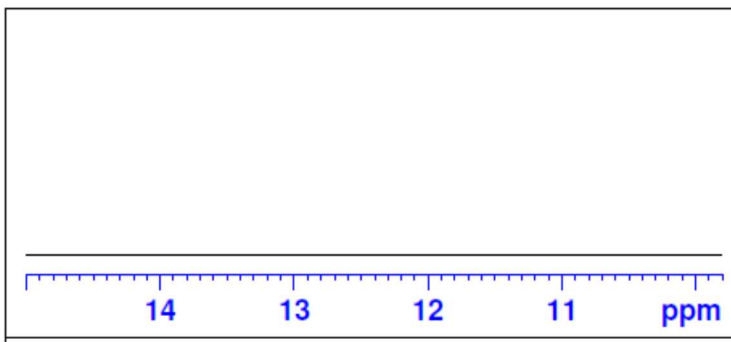




ROTON64 MeOD /opt/topspin3.2 yangmq

BRUKER

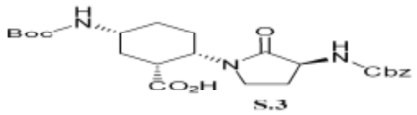
Current Data Parameters
NAME A0F8C-142-S3
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161222
Time 9.10
INSTRUM lvl_nmrl3b400a
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 64
DS 2
SWH 9973.404 Hz
FIDRES 0.152182 Hz
AQ 3.2855382 sec
RG 203
DW 50.133 usec
DE 10.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 499.3630838 MHz
NUC1 1H
P1 11.25 usec
PLW1 15.78600025 W

F2 - Processing parameters
SI 65536
SF 499.3600000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

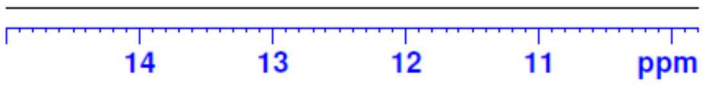
Solvent: Methanol-d4

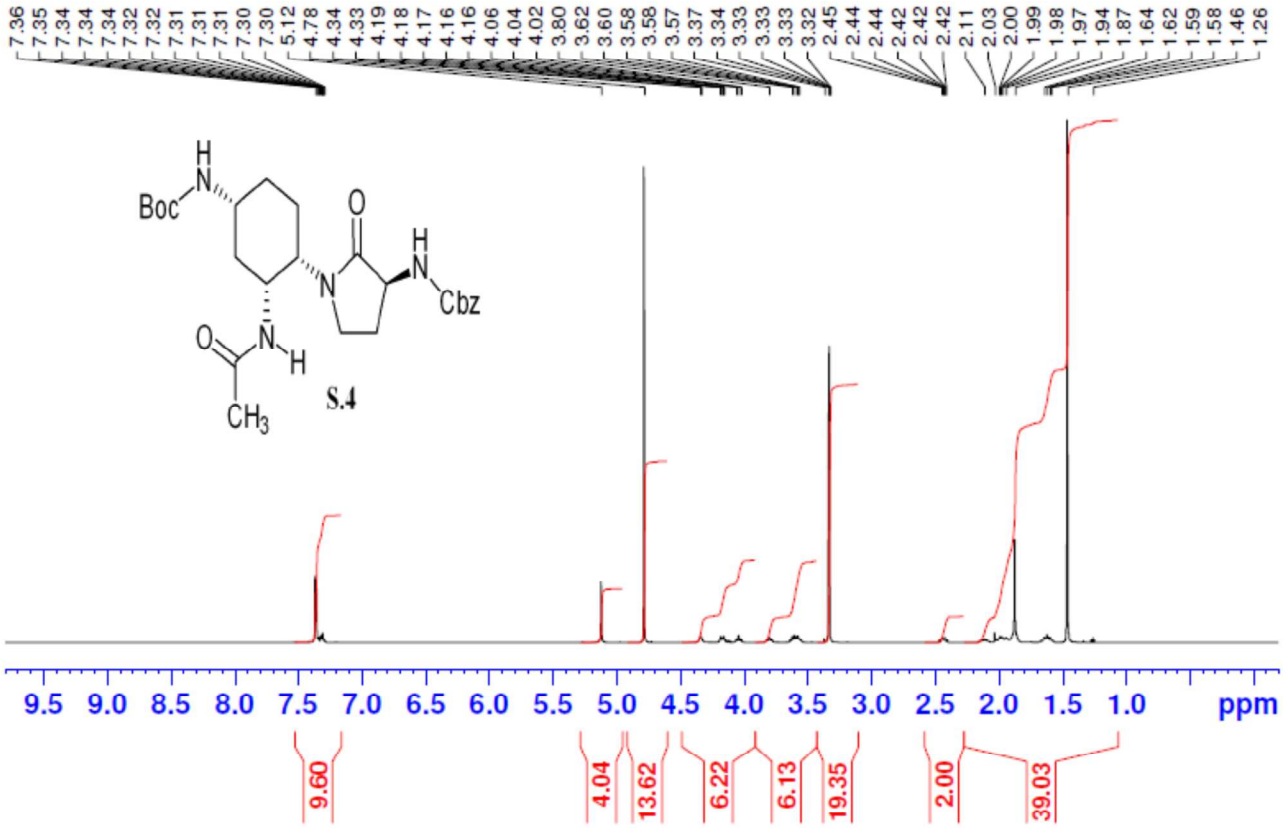


S.3

Observe Nucleus: 13C	Solvent: MeOD	Temperature: 0 °C
Observe Frequency: 125.7710 MHz	Number of Scans: 1056	Relaxation Delay: 2.00 sec
Instrumentation: Bruker NMR	Spectrometer: lvl_nmrl2b500	X Points:
BMS Site: Lawrenceville, NJ	Pulse Sequence: zgpg30	X-offset: 13207.9766 Hz

OTON16 MeOD /opt/topspin3.2 yangmg



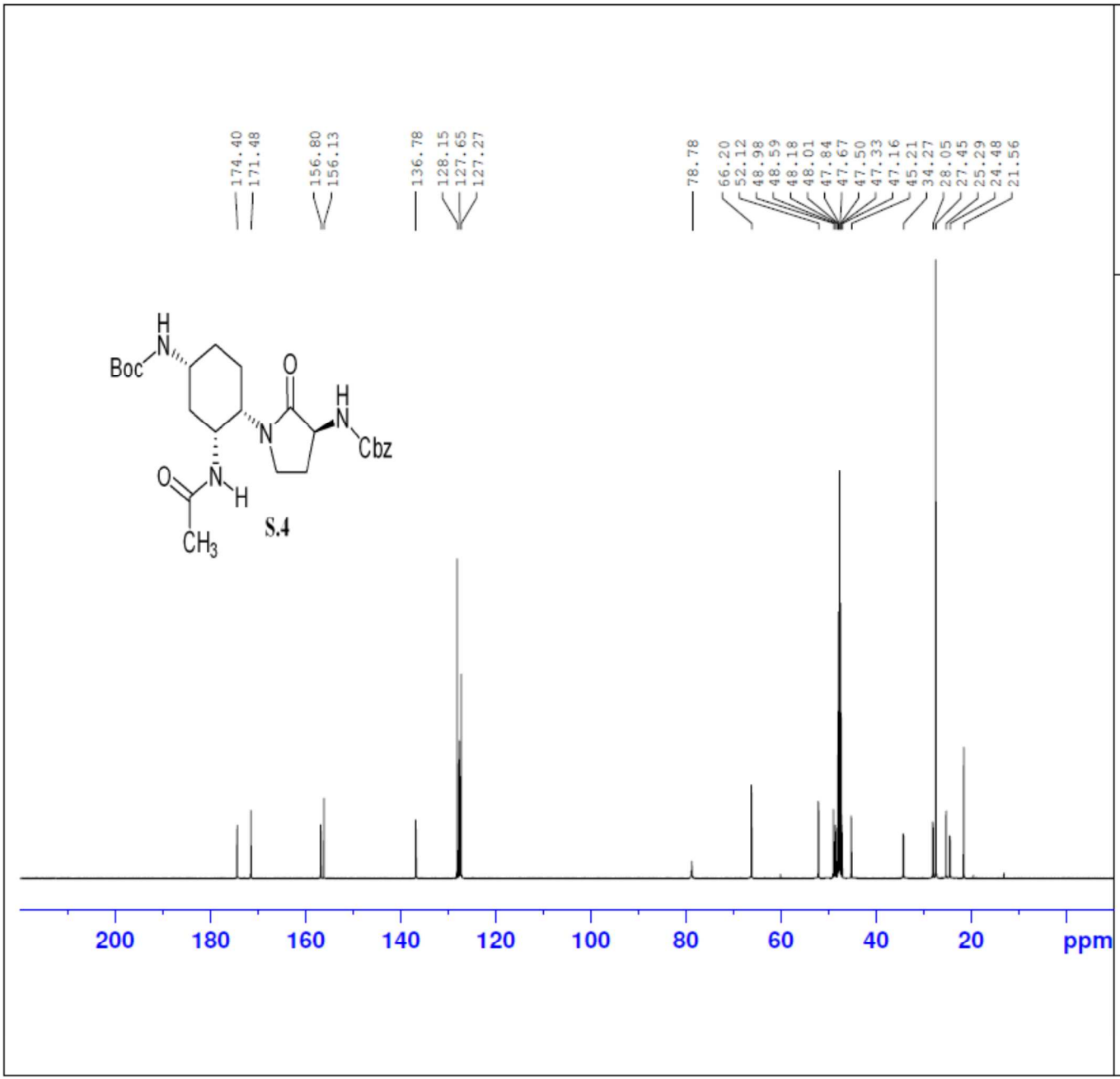


Current Data Parameters
NAME A0F8C-141-S.5
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20161213
Time 13.59
INSTRUM lvl_nmrl3b400a
PROBHD 5 mm PABBO BB/
PULPROG zg30
TD 65536
SOLVENT MeOD
NS 16
DS 2
SWH 9973.404 Hz
FIDRES 0.152182 Hz
AQ 3.2855382 sec
RG 322
DW 50.133 usec
DE 10.00 usec
TE 300.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
SFO1 499.3630838 MHz
NUC1 1H
P1 11.25 usec
PLW1 15.78600025 W

F2 - Processing parameters
SI 65536
SF 499.3600000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

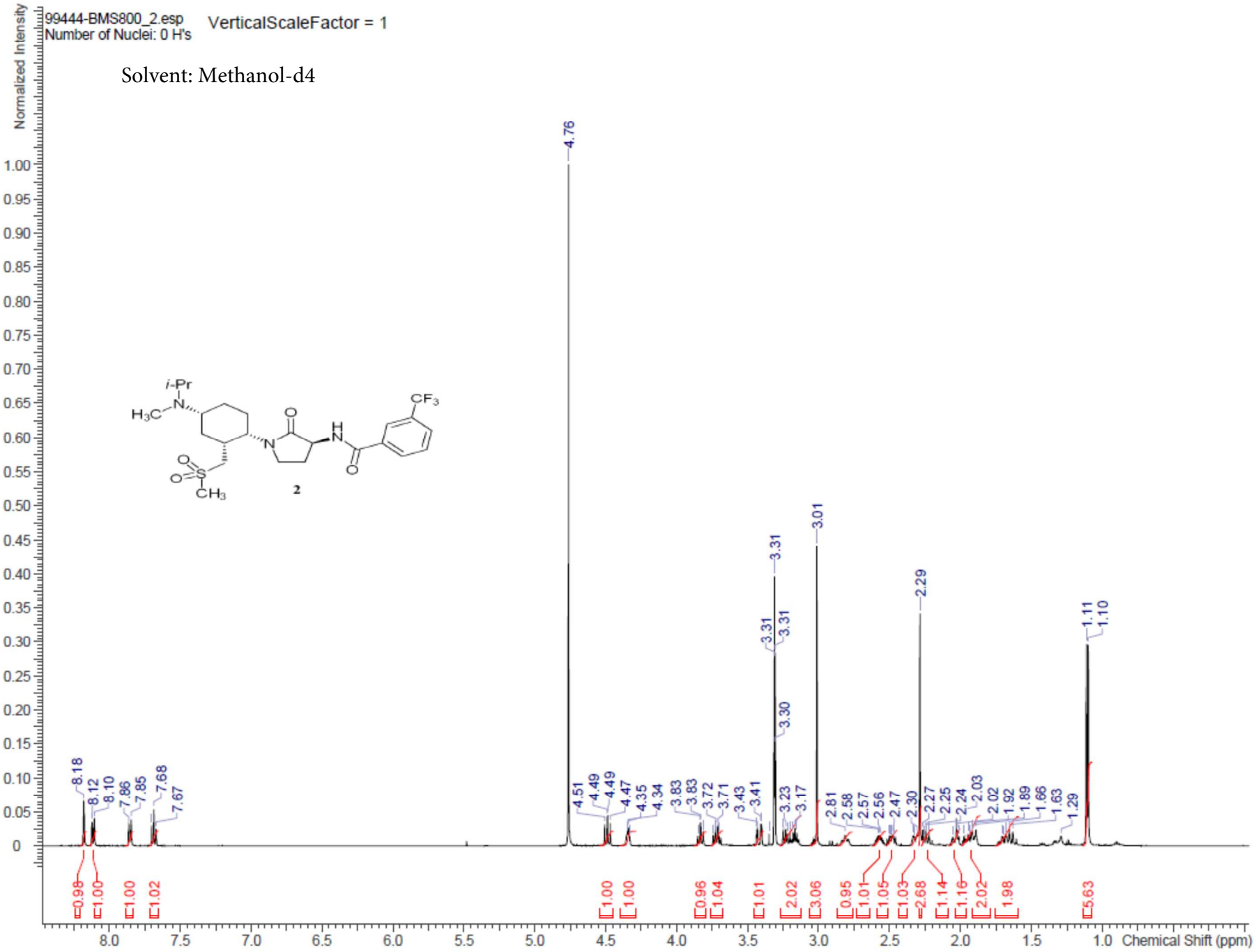


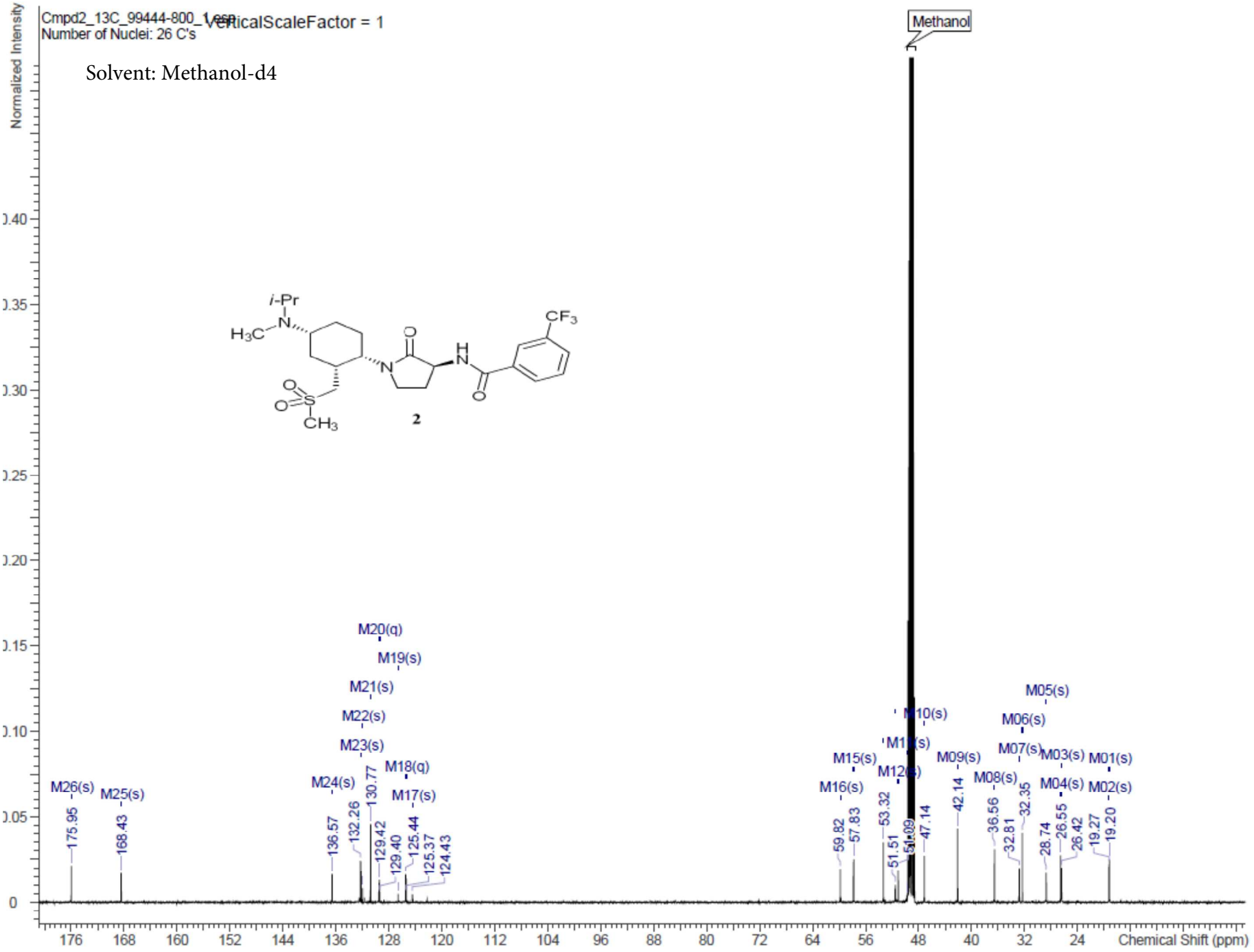
BRUKER

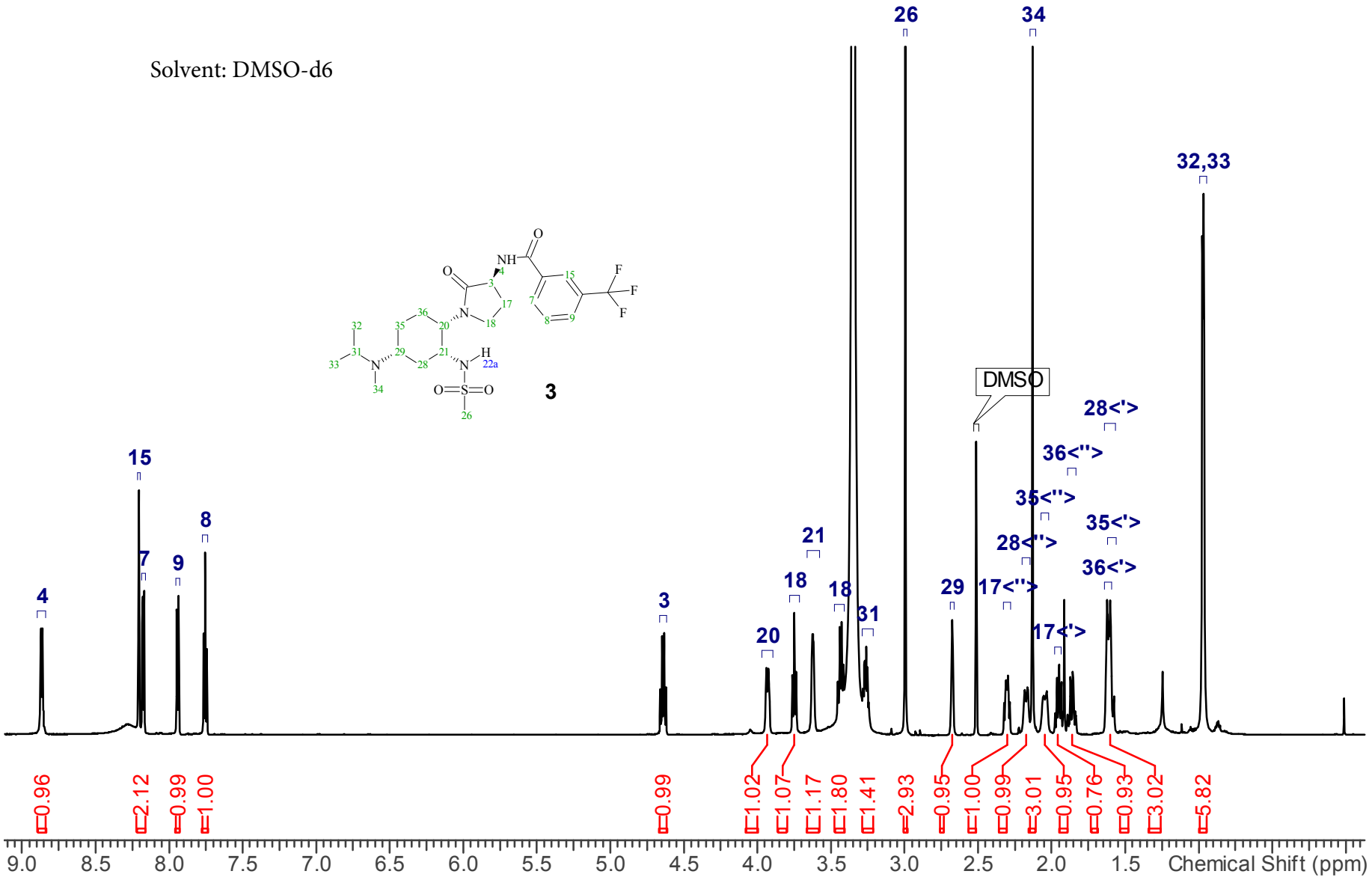
```
Current Data Parameters
NAME      A0F8C-141-S5_rerun
EXPNO                      1
PROCNO                     1

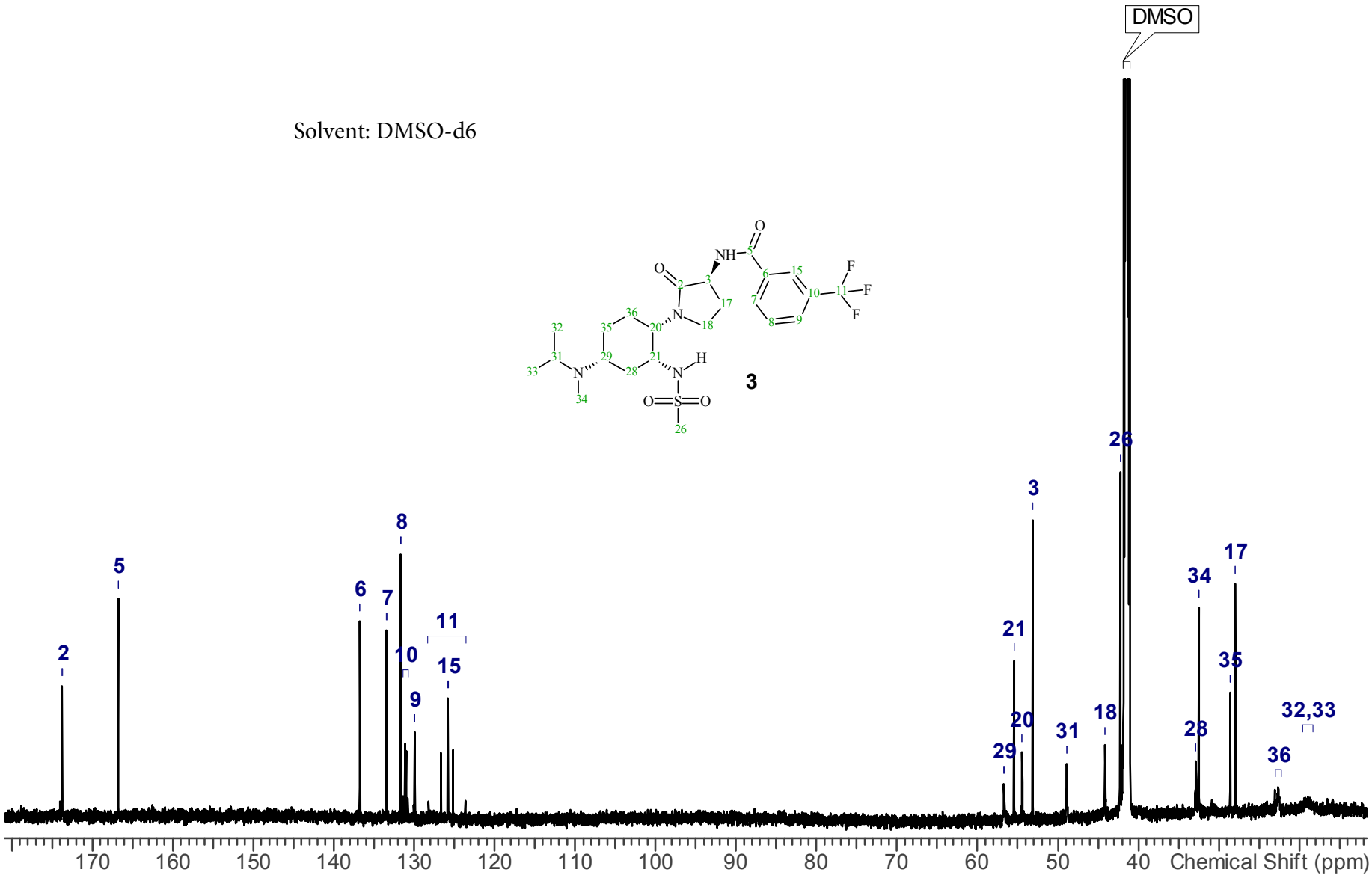
F2 - Acquisition Parameters
Date_              20161215
Time                 10.37 h
INSTRUM    lvl_nmrl2b500
PROBHD     Z130035_0013 (
PULPROG             zgpg30
TD                   65536
SOLVENT               MeOD
NS                    1056
DS                       4
SWH              29761.904 Hz
FIDRES            0.908261 Hz
AQ               1.1010048 sec
RG                   202.5
DW                  16.800 usec
DE                  28.00 usec
TE                  300.0 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                      1
SFO1           125.7709931 MHz
NUC1                   13C
P1                  10.00 usec
PLW1           59.12900162 W
SFO2           500.1320005 MHz
NUC2                   1H
CPDPRG[2            waltz16
PCPD2               90.00 usec
PLW2            9.42000008 W
PLW12           0.23615000 W
PLW13           0.19128001 W

F2 - Processing parameters
SI                   32768
SF             125.7577885 MHz
WDW                     EM
SSB          0
LB                   1.00 Hz
GB           0
PC                   1.40
```

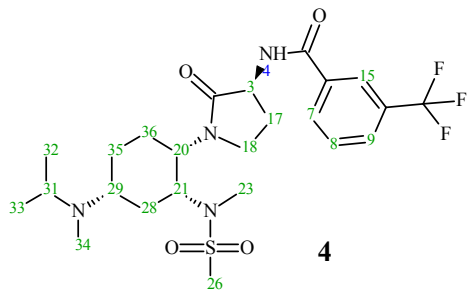

99444-BMS800_2.esp
Number of Nuclei: 0 H's
VerticalScaleFactor = 1
Solvent: Methanol-d4
Normalized Intensity
Chemical Shift (ppm)
2


Cmpd2_13C_99444-800_1.esp
Number of Nuclei: 26 C's
VerticalScaleFactor = 1
Solvent: Methanol-d4
Normalized Intensity
Methanol
i-Pr
H3C
CF3
CH3
2
M20(q)
M19(s)
M21(s)
M22(s)
M23(s)
M18(q)
M24(s)
M17(s)
M26(s)
M25(s)
M15(s)
M16(s)
M09(s)
M05(s)
M06(s)
M07(s)
M03(s)
M01(s)
M08(s)
M04(s)
M02(s)
175.95
168.43
136.57
132.26
130.77
129.42
129.40
125.44
125.37
124.43
59.82
57.83
53.32
51.51
47.14
42.14
36.56
32.81
32.35
28.74
26.55
26.42
19.27
19.20
Chemical Shift (ppm)

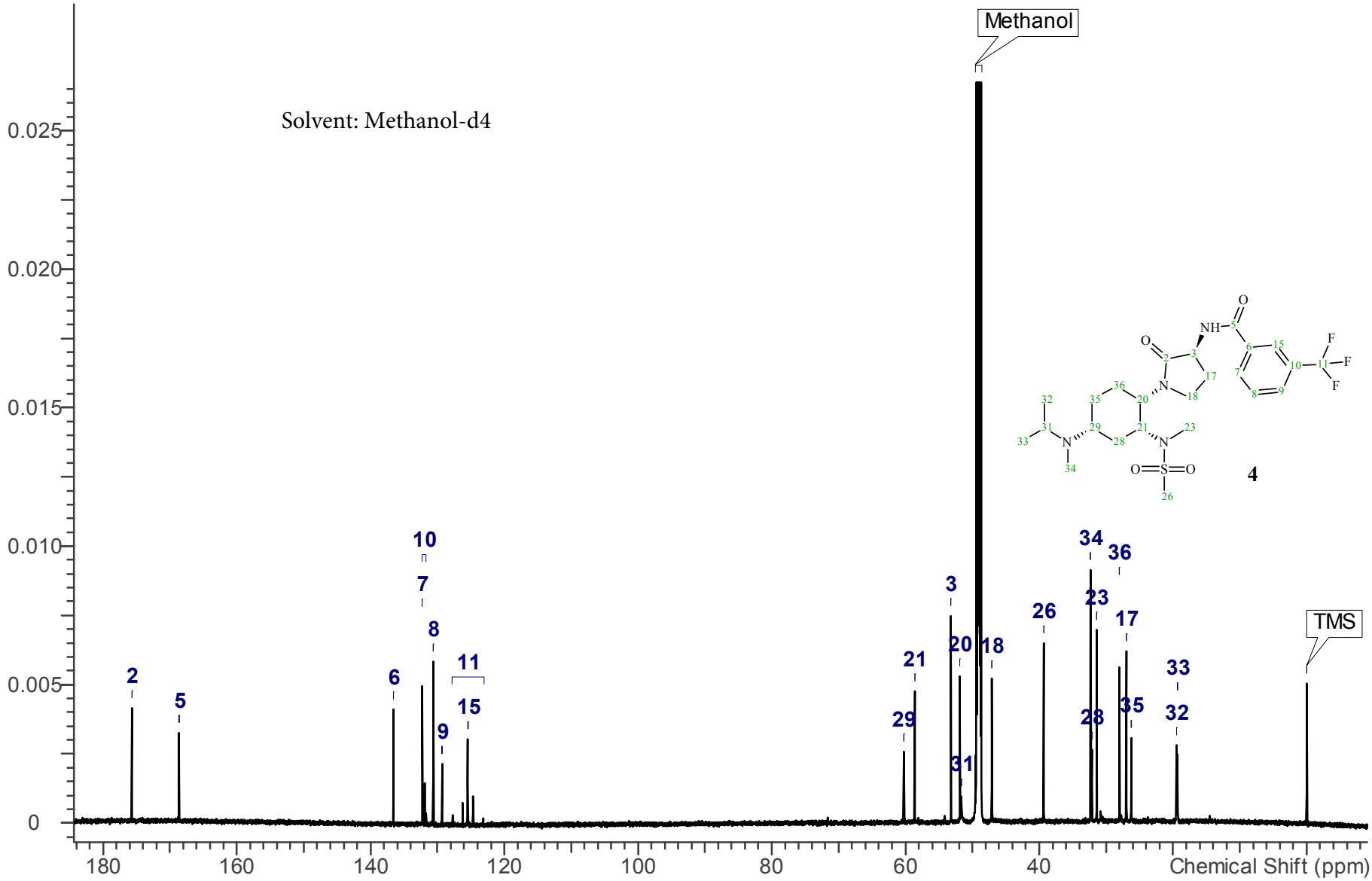

Solvent: DMSO-d6
3
DMSO
Chemical Shift (ppm)

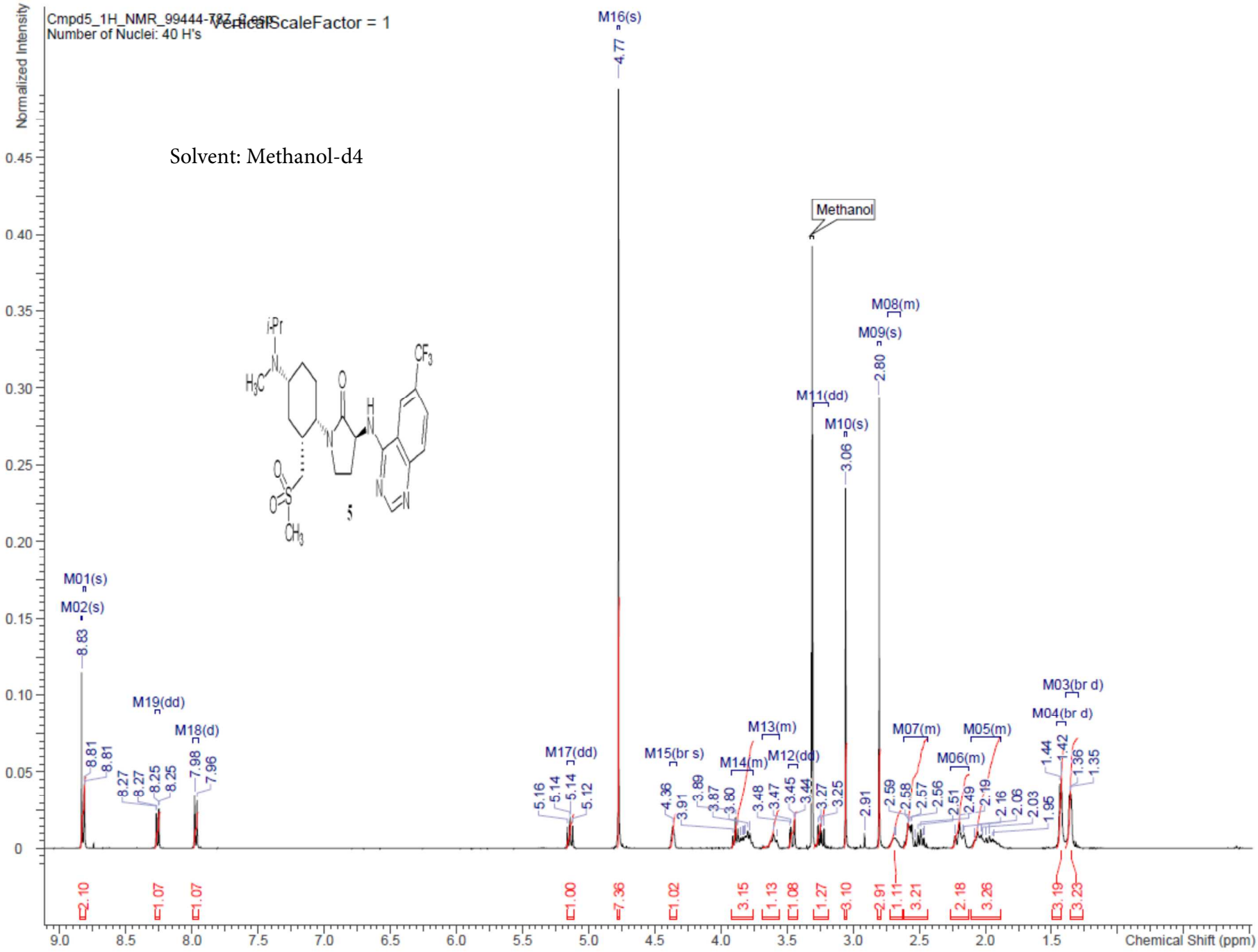

DMSO
Solvent: DMSO-d6
3
2
5
6
7
8
10
11
15
9
26
3
21
20
29
31
18
28
34
17
35
36
32,33
170
160
150
140
130
120
110
100
90
80
70
60
50
40
Chemical Shift (ppm)

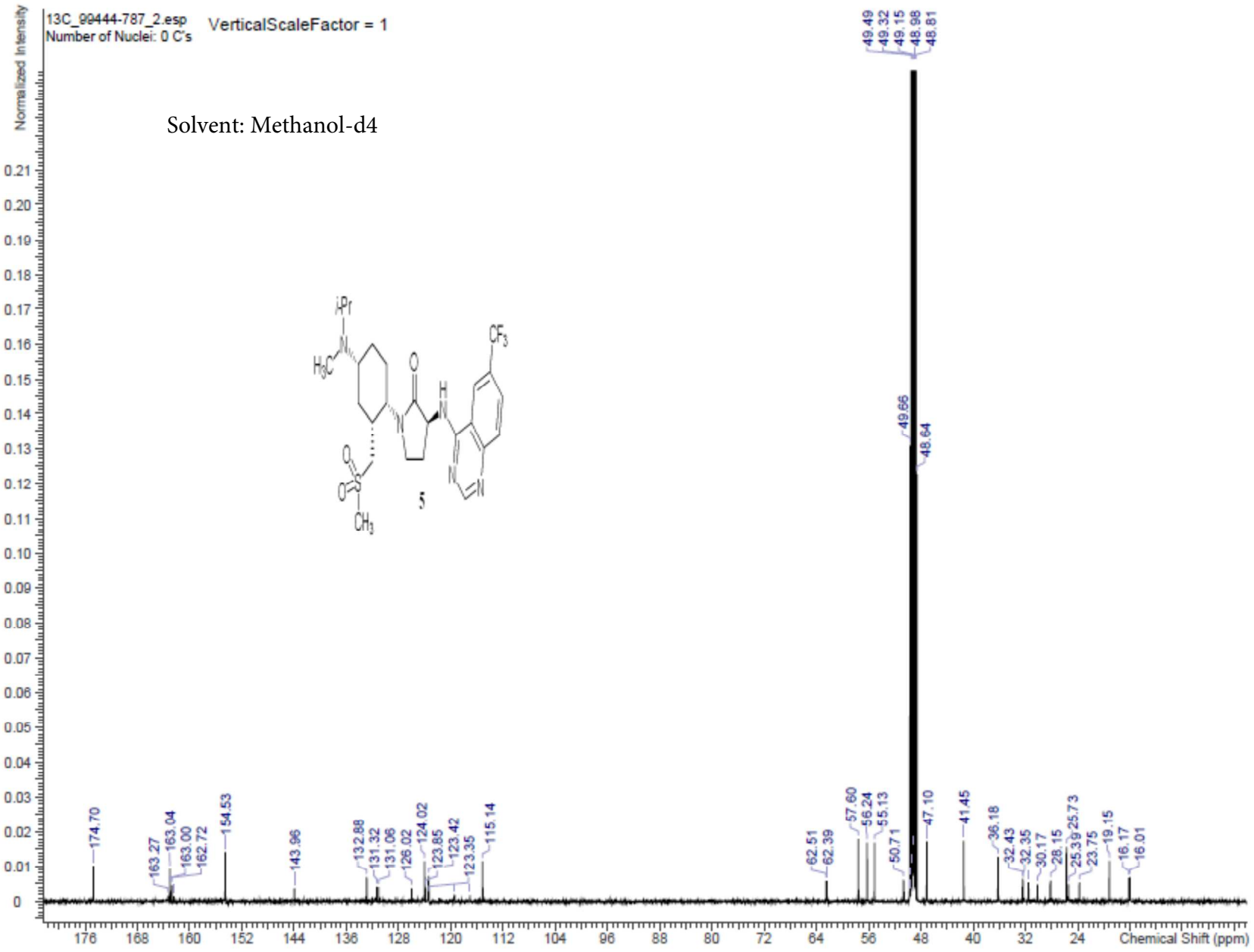
Solvent: Methanol-d4



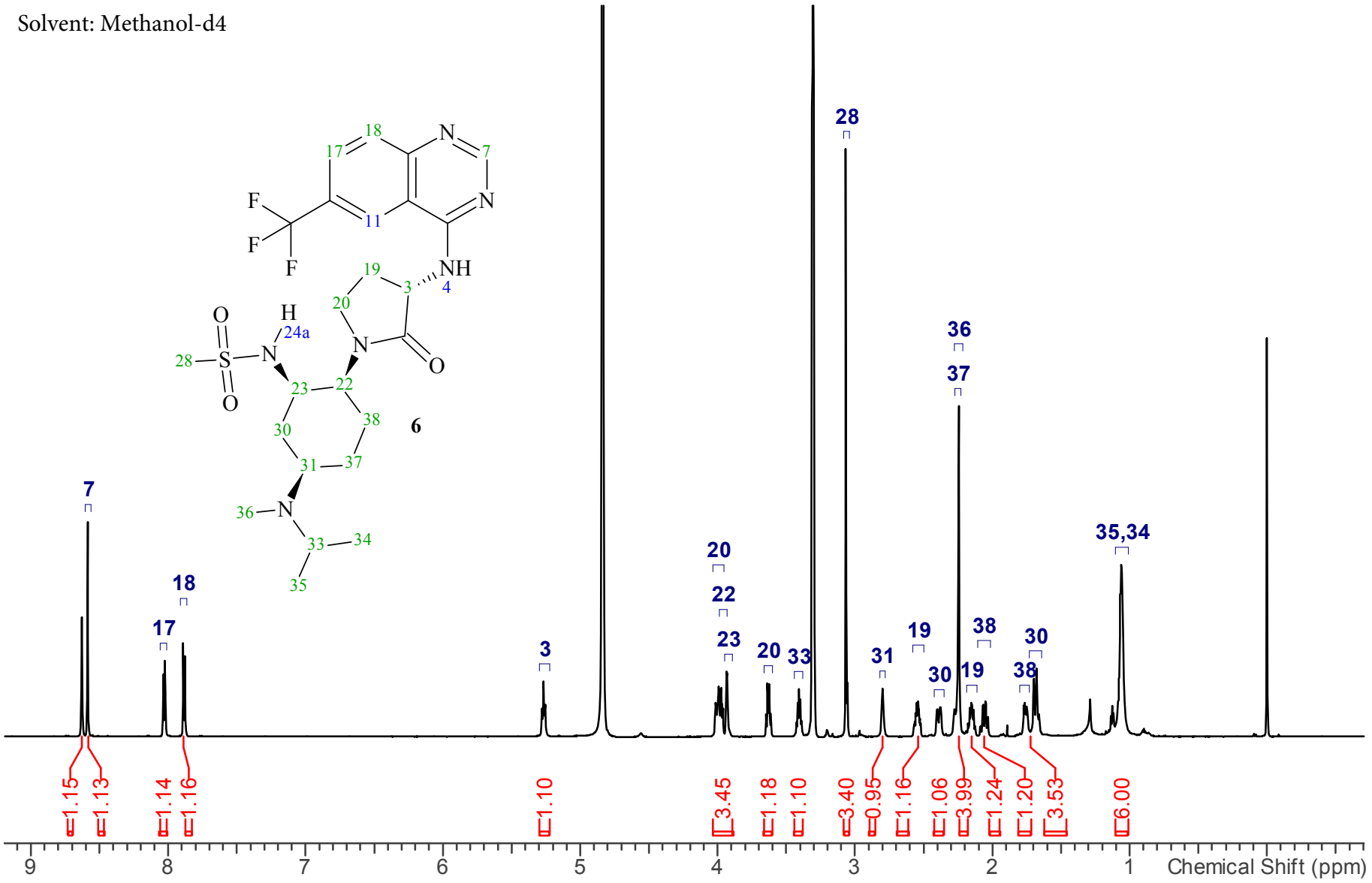
4


Methanol
Solvent: Methanol-d4
TMS
4
2
5
6
10
7
8
11
15
9
29
21
3
20
18
31
26
34
36
23
17
28
35
33
32
0.025
0.020
0.015
0.010
0.005
0
180
160
140
120
100
80
60
40
Chemical Shift (ppm)

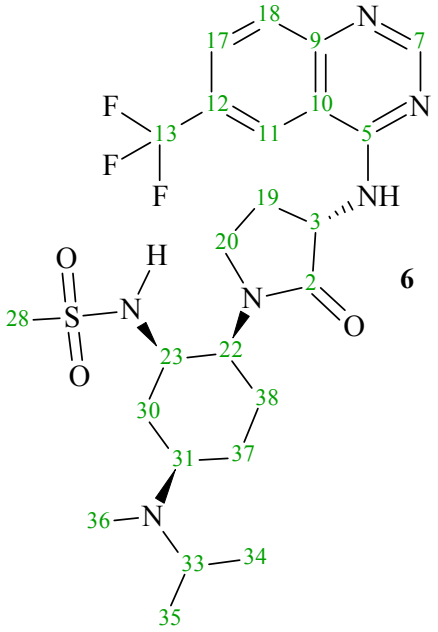

Cmpd5_1H_NMR_99444-787-2.esp
Number of Nuclei: 40 H's
VerticalScaleFactor = 1
Normalized Intensity
Solvent: Methanol-d4
i-Pr
CF3
5
Methanol
M16(s)
4.77
M08(m)
M09(s)
2.80
M11(dd)
M10(s)
3.06
M01(s)
M02(s)
8.83
M19(dd)
M18(d)
M17(dd)
M15(br s)
M14(m)
M13(m)
M12(dd)
M07(m)
M06(m)
M05(m)
M04(br d)
M03(br d)
Chemical Shift (ppm)


13C_99444-787_2.esp
Number of Nuclei: 0 C's
VerticalScaleFactor = 1
Normalized Intensity
Solvent: Methanol-d4
5
Chemical Shift (ppm)

Solvent: Methanol-d4



Solvent: Methabol-d4



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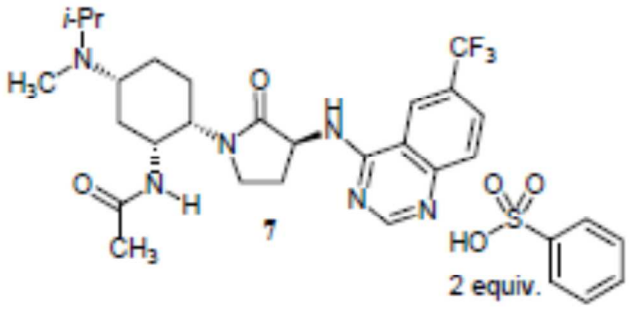
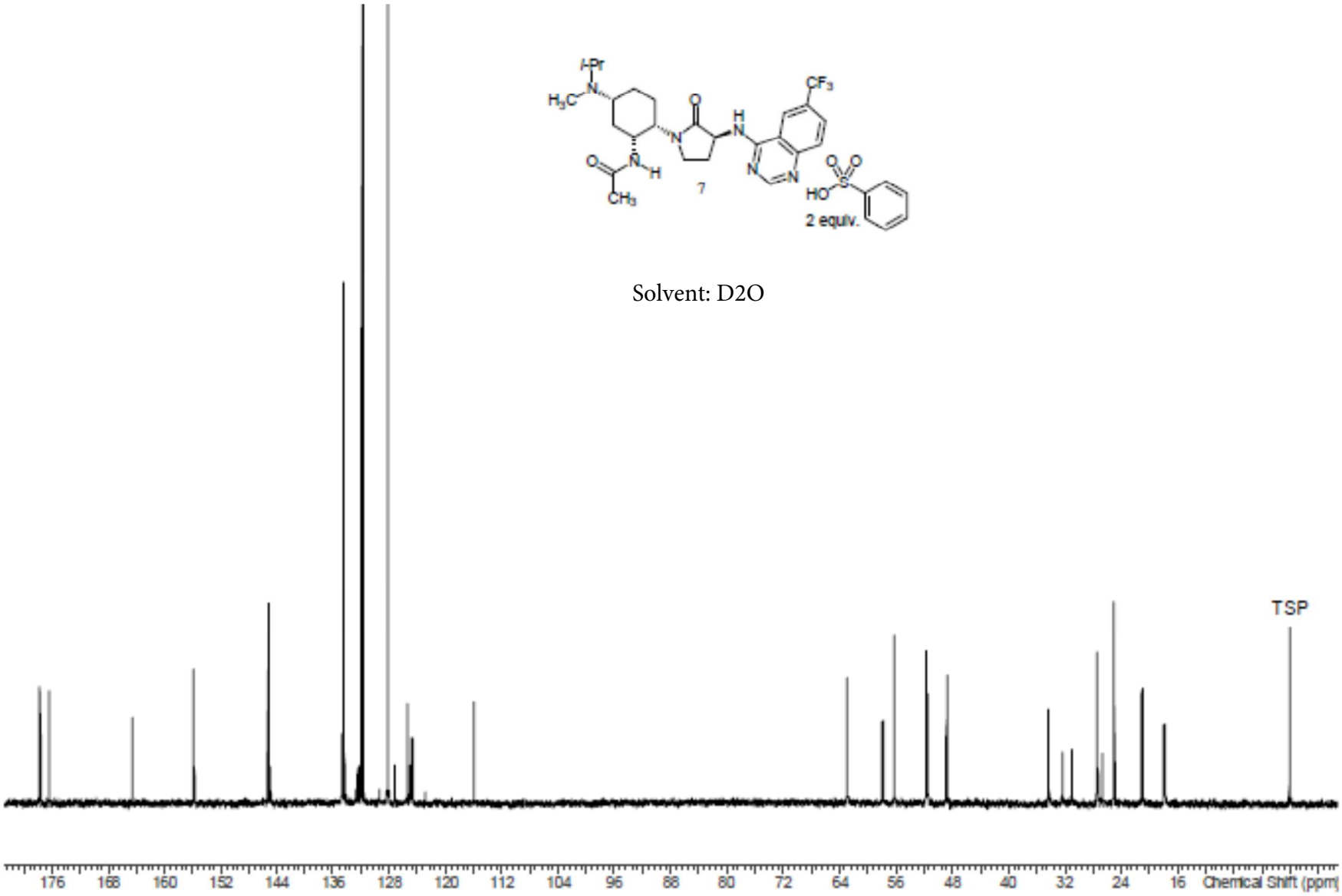


7

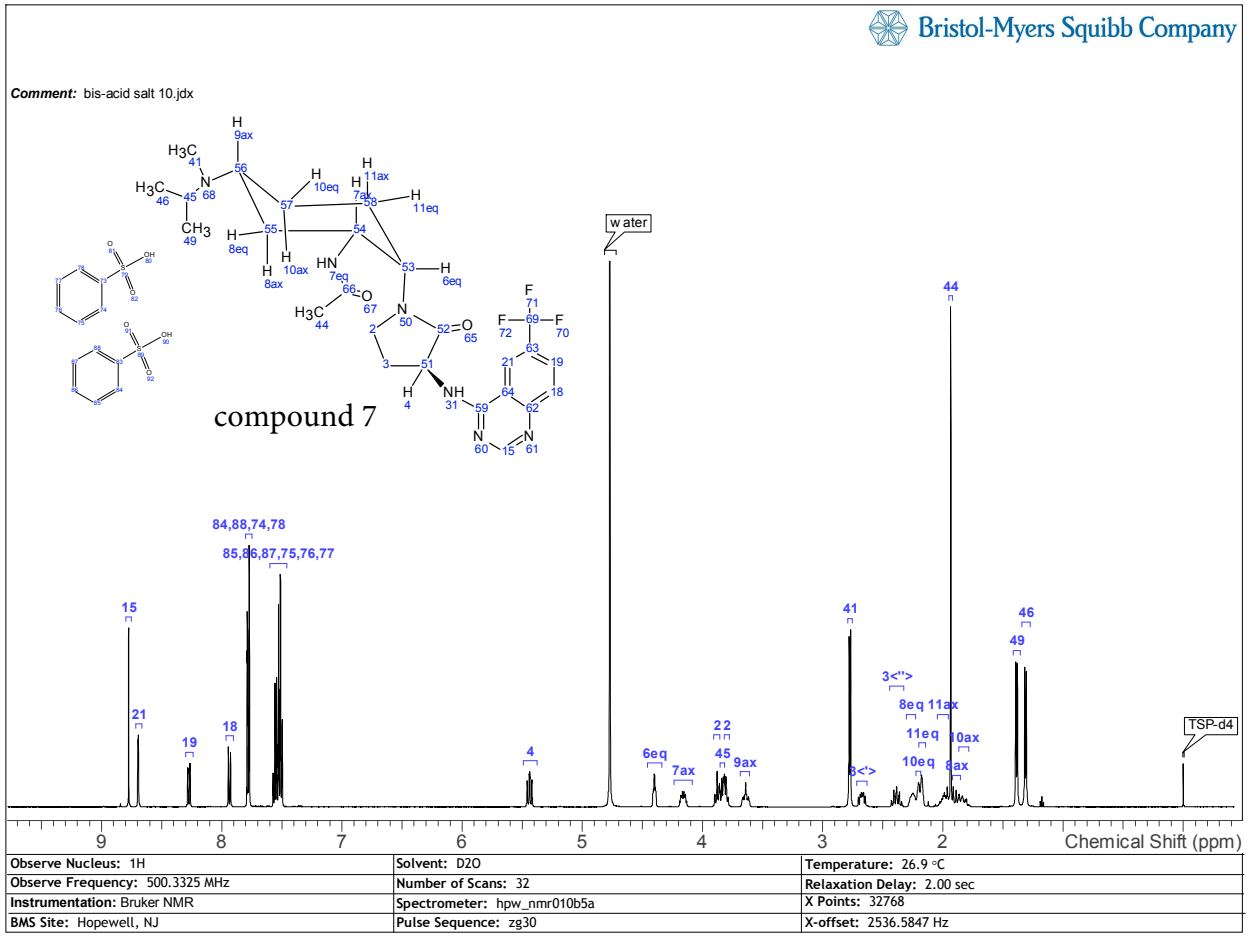
Solvent: D2O


i-Pr
H3C
N
O
H
N
CF3
N
N
O
N
H
CH3
7
N
HO
S
O
O
2 equiv.
TSP
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

Solvent: D2O

1D-NMR Plots for Compound 7: COSY, NOESY, ^{1}H-^{13}C-dept-HSQC

Compound 7-Chair 1 (Bis-benzene sulfonic acid salt): D_2O with TSP-d4, 500 MHz



Observe Nucleus: 1H	**Solvent:** D2O	**Temperature:** 26.9 °C
Observe Frequency: 500.3325 MHz	**Number of Scans:** 32	**Relaxation Delay:** 2.00 sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2536.5847 Hz

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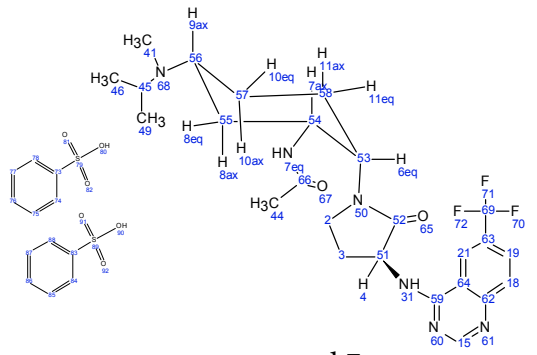
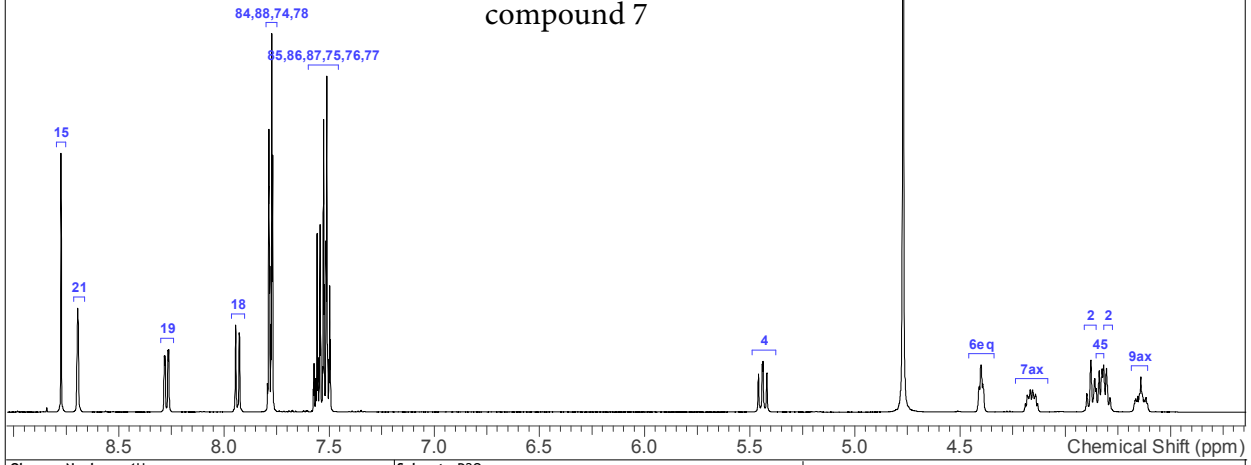


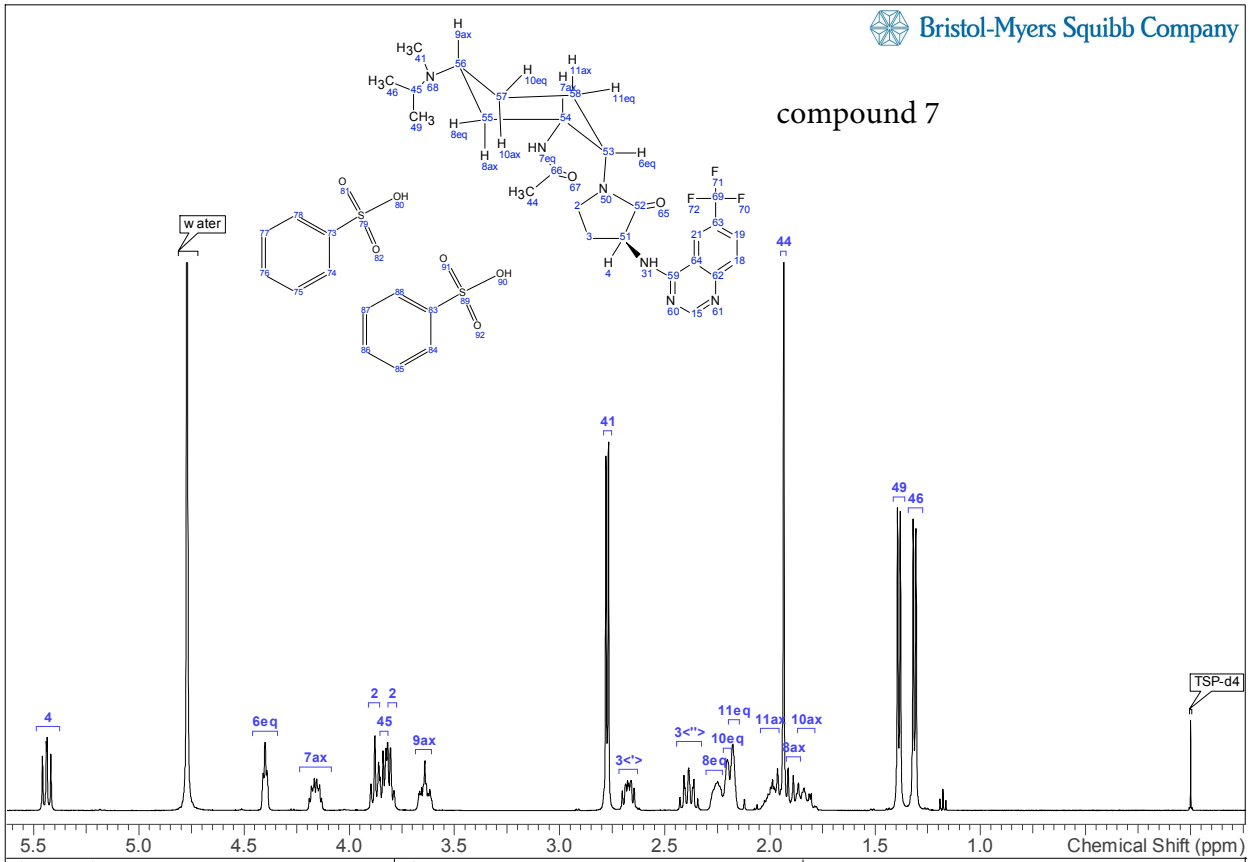
compound 7



Observe Nucleus: 1H	**Solvent:** D2O	**Temperature:** 26.9 °C
Observe Frequency: 500.3325 MHz	**Number of Scans:** 32	**Relaxation Delay:** 2.00 sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2536.5847 Hz

Bristol-Myers Squibb Company

compound 7



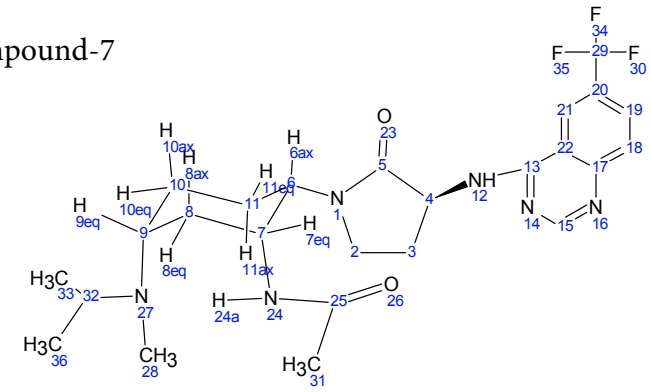
Observe Nucleus: 1H	**Solvent:** D2O	**Temperature:** 26.9 °C
Observe Frequency: 500.3325 MHz	**Number of Scans:** 32	**Relaxation Delay:** 2.00 sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2536.5847 Hz

Compound 7-Chair 2 (Free Base): Acetonitrile-d_3, 500 MHz

Bristol-Myers Squibb Company

Comment: se_PROTON CD3CN /opt/topspin3.5pl6 traegers 21

compound-7

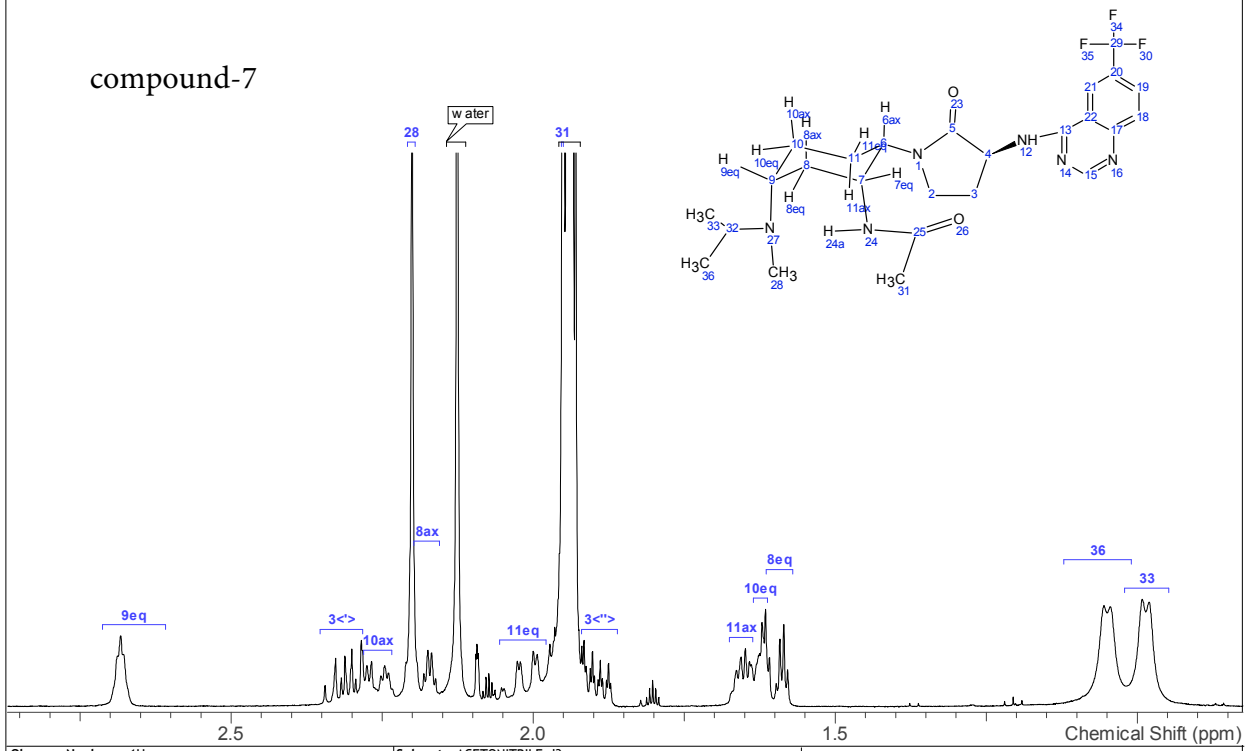


Observe Nucleus: 1H	**Solvent:** ACETONITRILE-d3	**Temperature:** 26.9995 °C
Observe Frequency: 500.3300 MHz	**Number of Scans:** 16	**Relaxation Delay:** sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2487.4919 Hz

Bristol-Myers Squibb Company

Comment: se_PROTON CD3CN /opt/topspin3.5pl6 traegers 21

compound-7

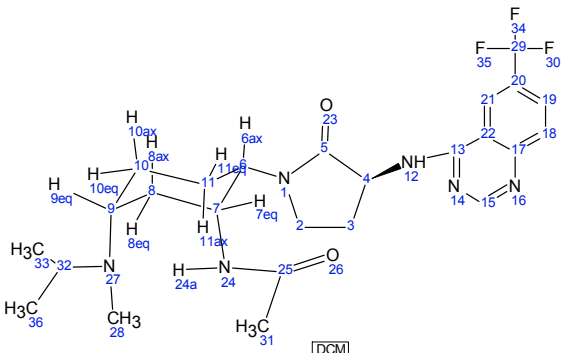


Observe Nucleus: 1H	**Solvent:** ACETONITRILE-d3	**Temperature:** 26.9995 °C
Observe Frequency: 500.3300 MHz	**Number of Scans:** 16	**Relaxation Delay:** sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2487.4919 Hz

Bristol-Myers Squibb Company

Comment: se_PROTON CD3CN /opt/topspin3.5pl6 traegers 21

compound-7

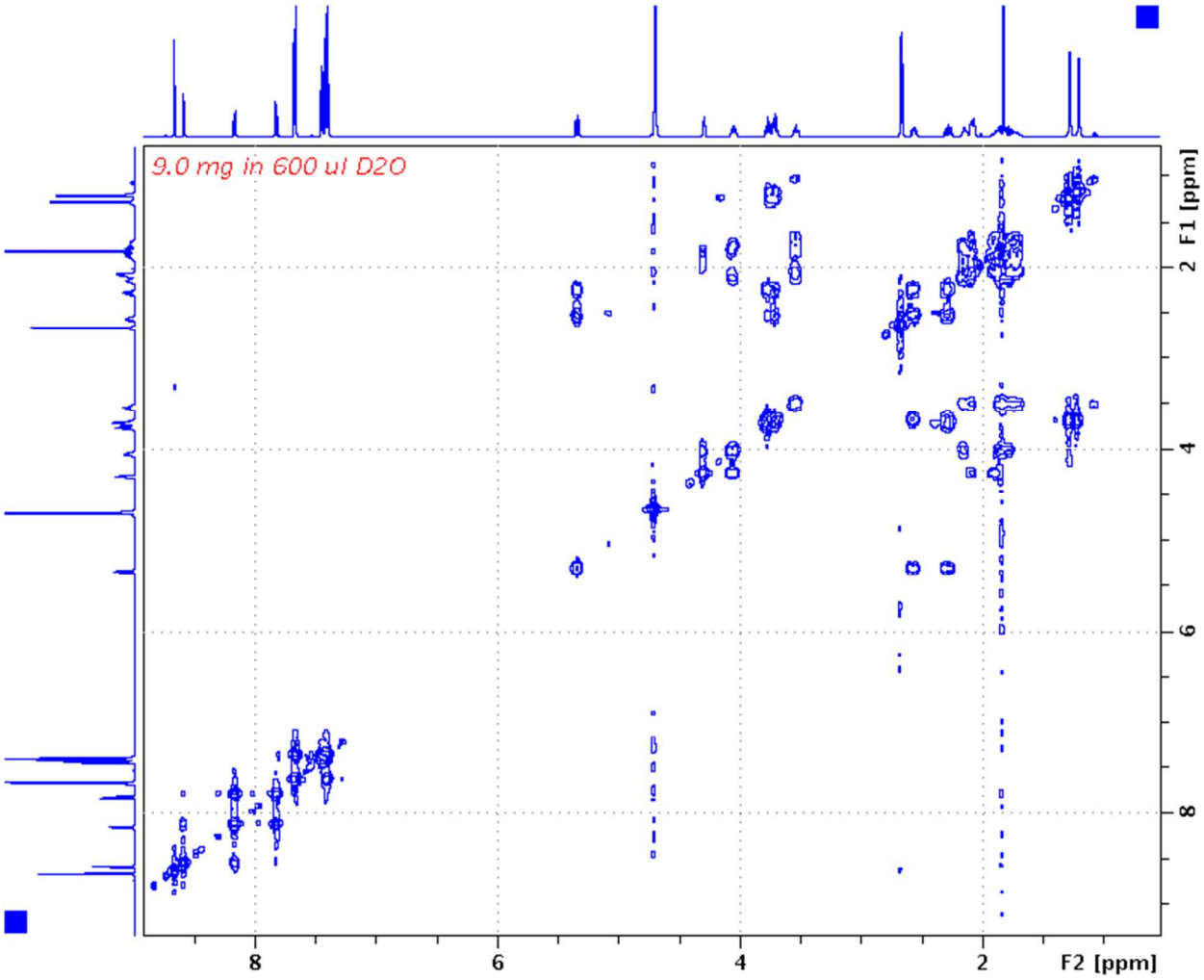


Observe Nucleus: 1H	**Solvent:** ACETONITRILE-d3	**Temperature:** 26.9995 °C
Observe Frequency: 500.3300 MHz	**Number of Scans:** 16	**Relaxation Delay:** sec
Instrumentation: Bruker NMR	**Spectrometer:** hpw_nmr010b5a	**X Points:** 32768
BMS Site: Hopewell, NJ	**Pulse Sequence:** zg30	**X-offset:** 2487.4919 Hz

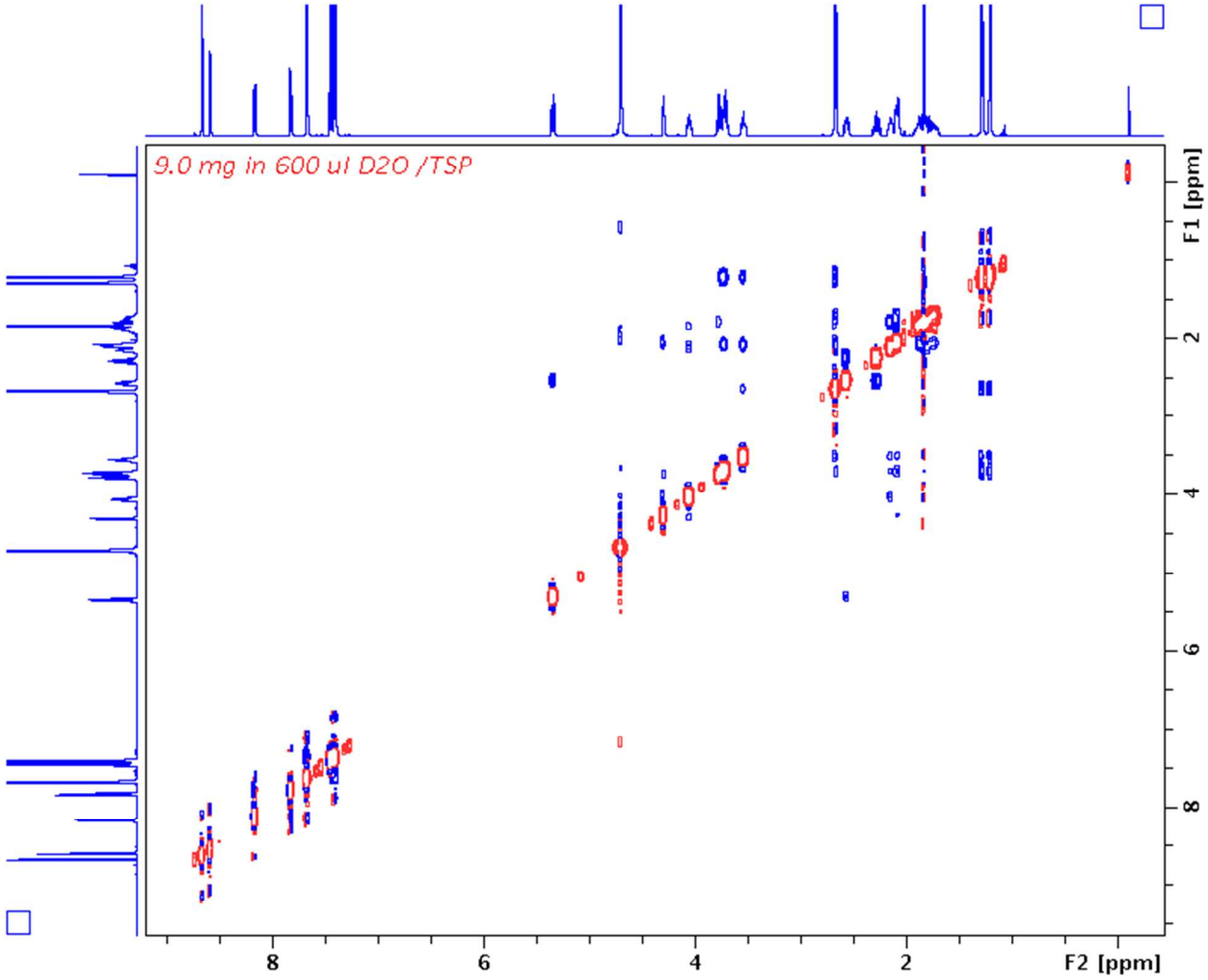
2D-NMR Plots for Compound 7: COSY, NOESY, ^{1}H-^{13}C-dept-HSQC

Compound 7-Chair 1 (Bis-benzene sulfonic acid salt): D_2O with TSP-d4, 600 MHz

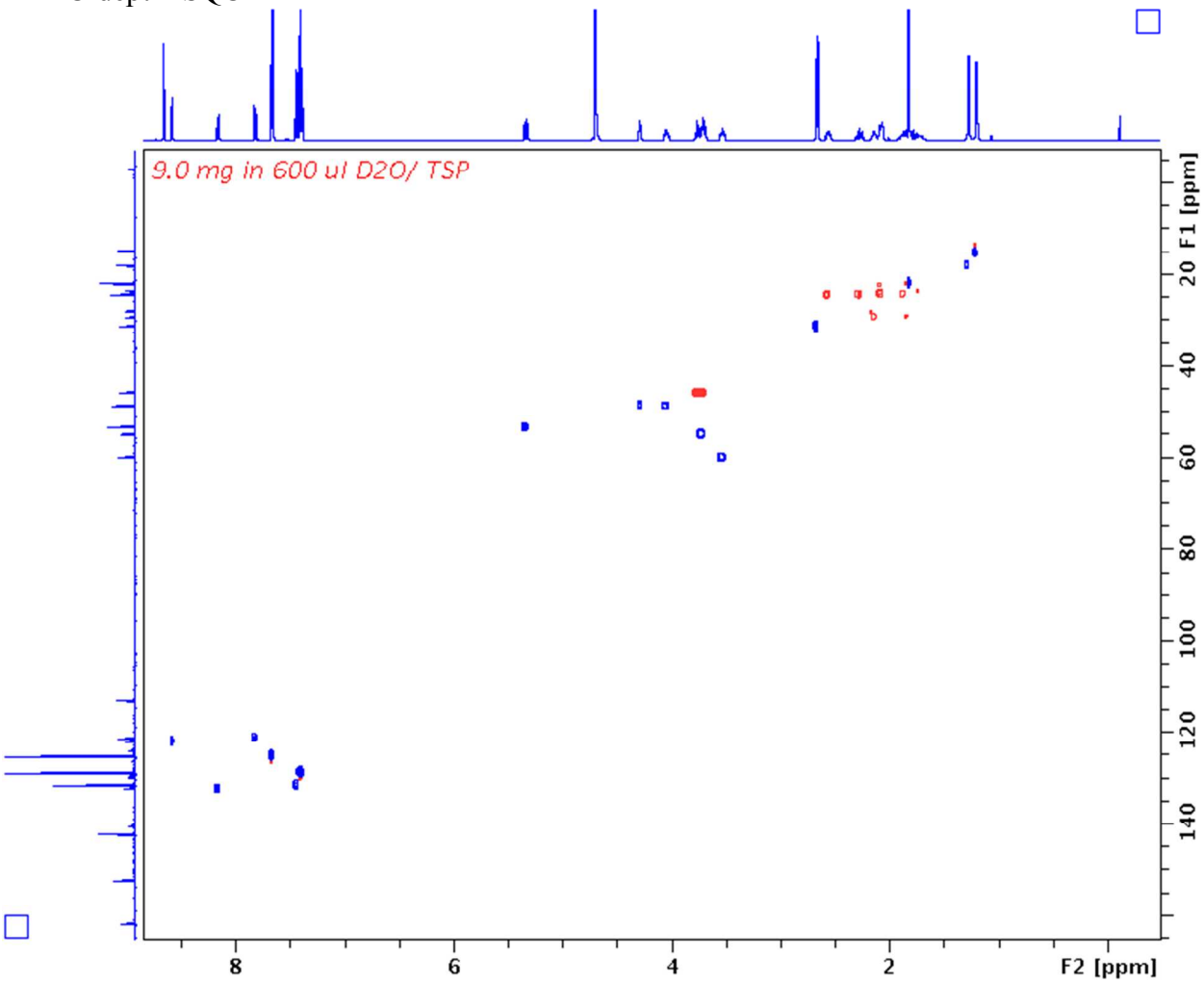
COSY



NOESY



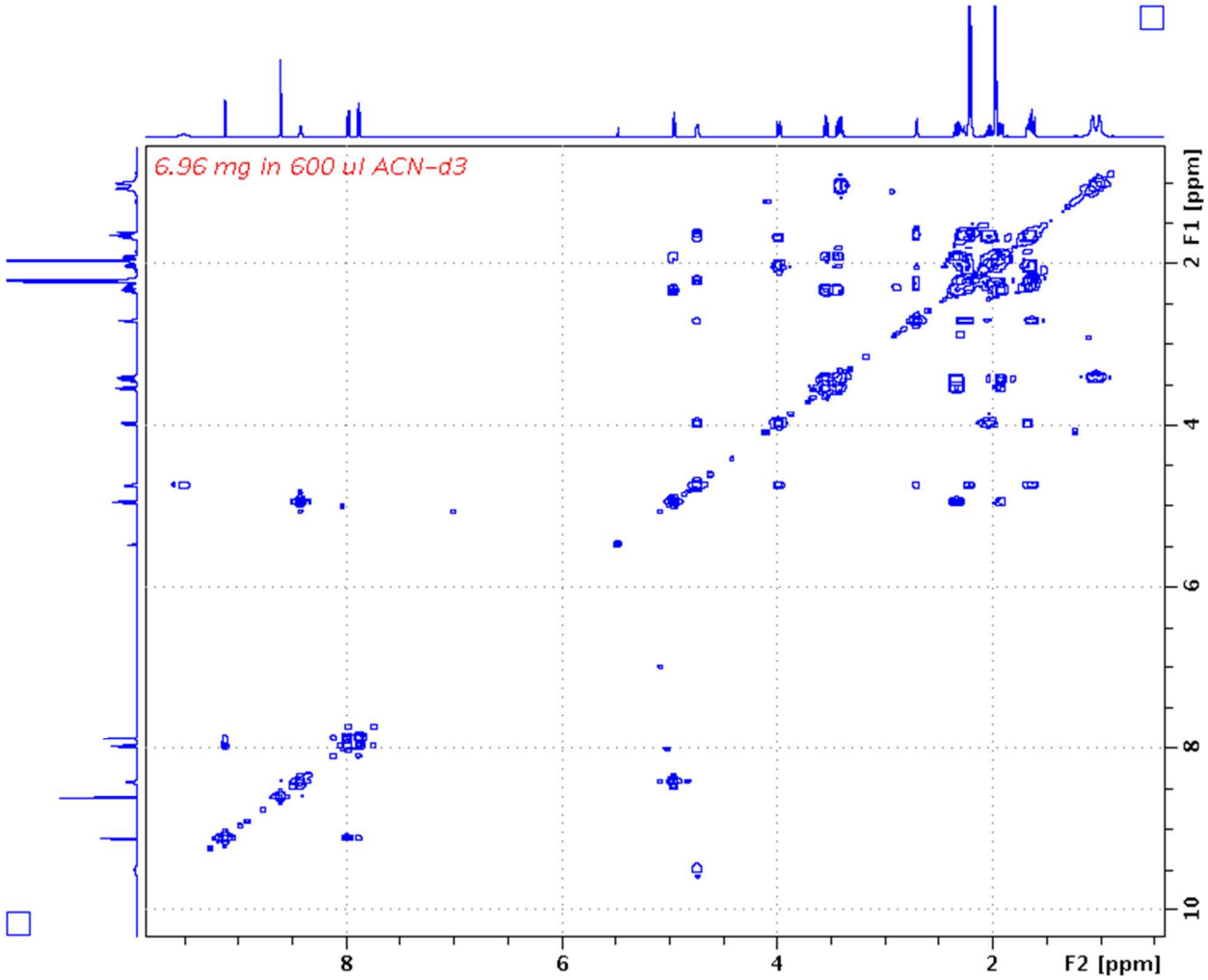
^{1}H-^{13}C-dept-HSQC



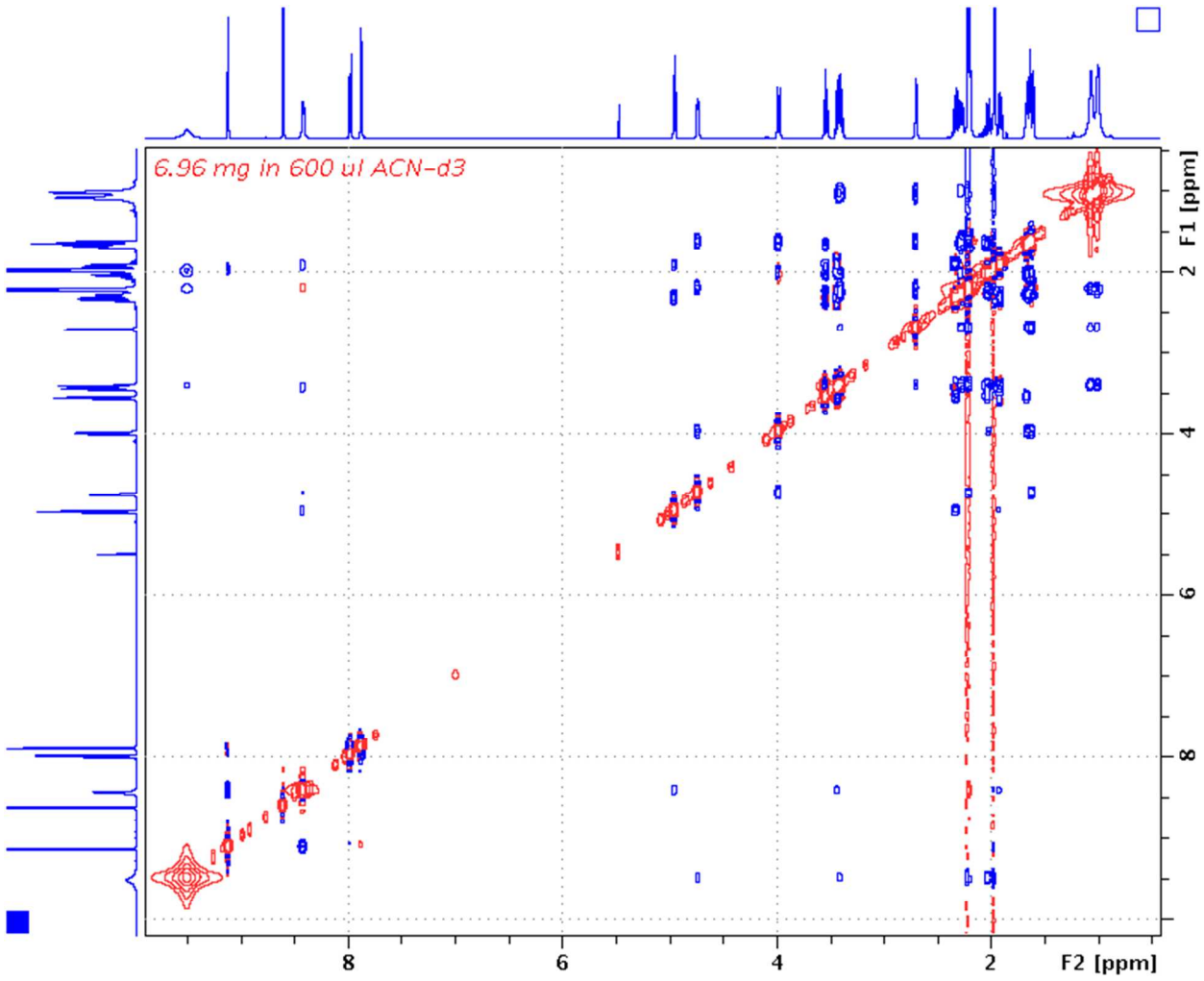
2D-NMR Plots for Compound 7: COSY, NOESY, ^{1}H-^{13}C-dept-HSQC

Compound 7-Chair 2 (Free Base): Acetonitrile-d_3, 600 MHz

COSY



NOESY


6.96 mg in 600 ul ACN-d3
F1 [ppm]
F2 [ppm]
2
4
6
8
8
6
4
2

^{1}H-^{13}C-dept-HSQC