Synthesis, evaluation of anti-HIV-1 and anti-HCV activity of novel 2',3'-dideoxy-2',2'-difluoro-4'-azanucleosides

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SUPPORTING INFORMATION (page 1 of 82 pages)

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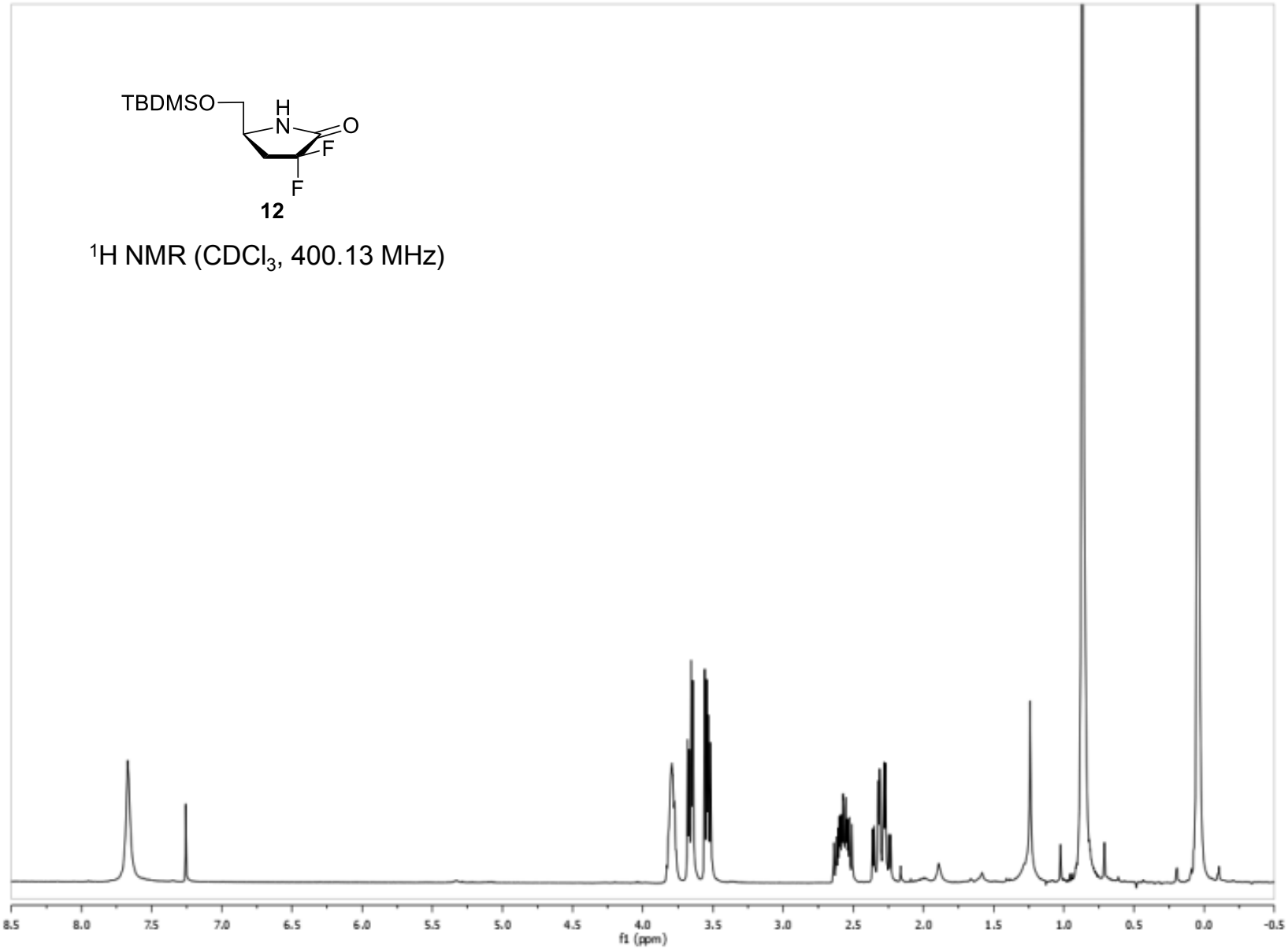
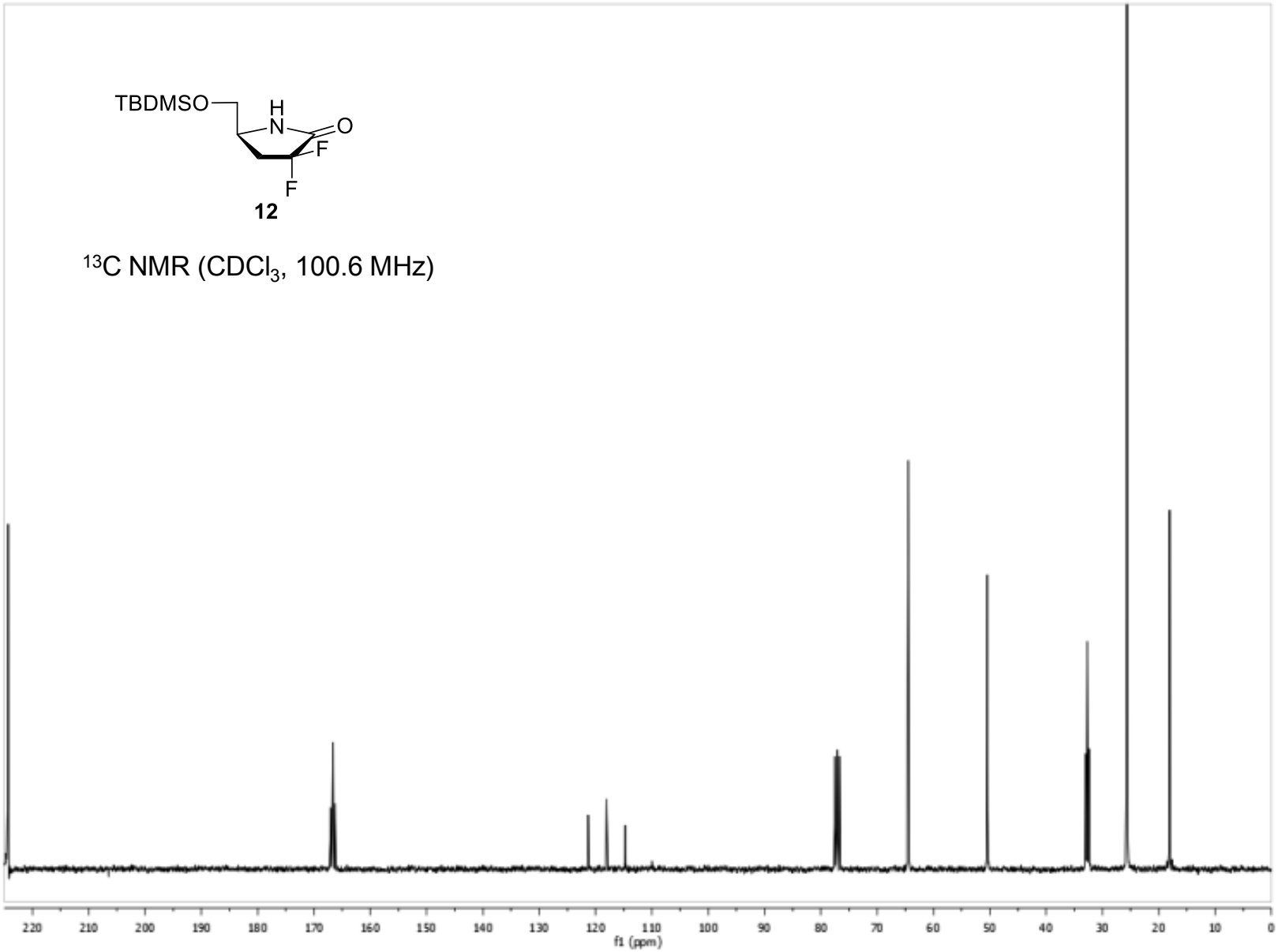
1. Copies of ^{1}H, ^{13}C, DEPT, and 2D NMR spectra of compounds **12**–**33**:


TBDMSO
H
N
O
F
F
12
^{1}H NMR ($CDCl_3$, 400.13 MHz)
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
0.0
-0.5
f1 (ppm)

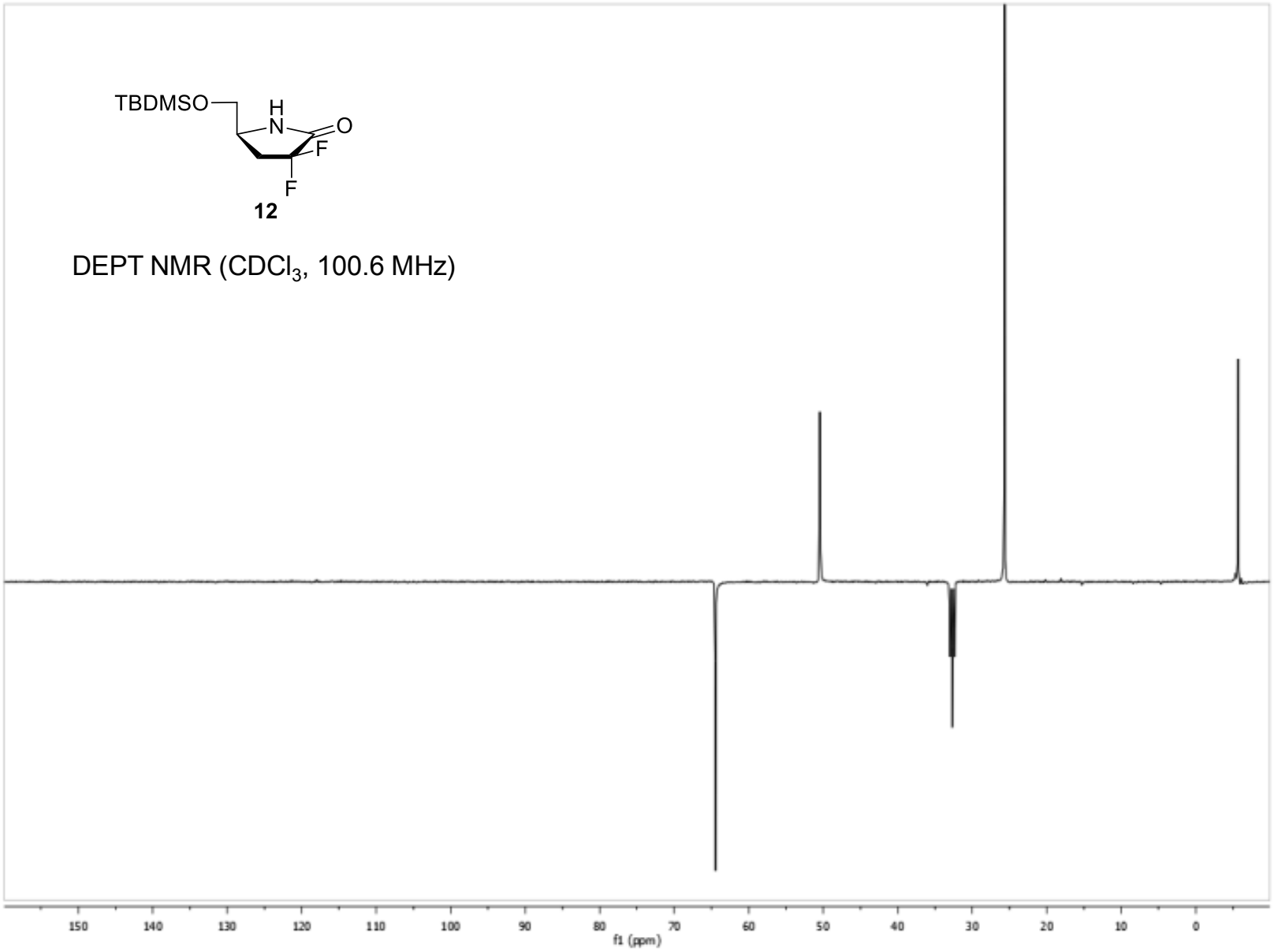
12

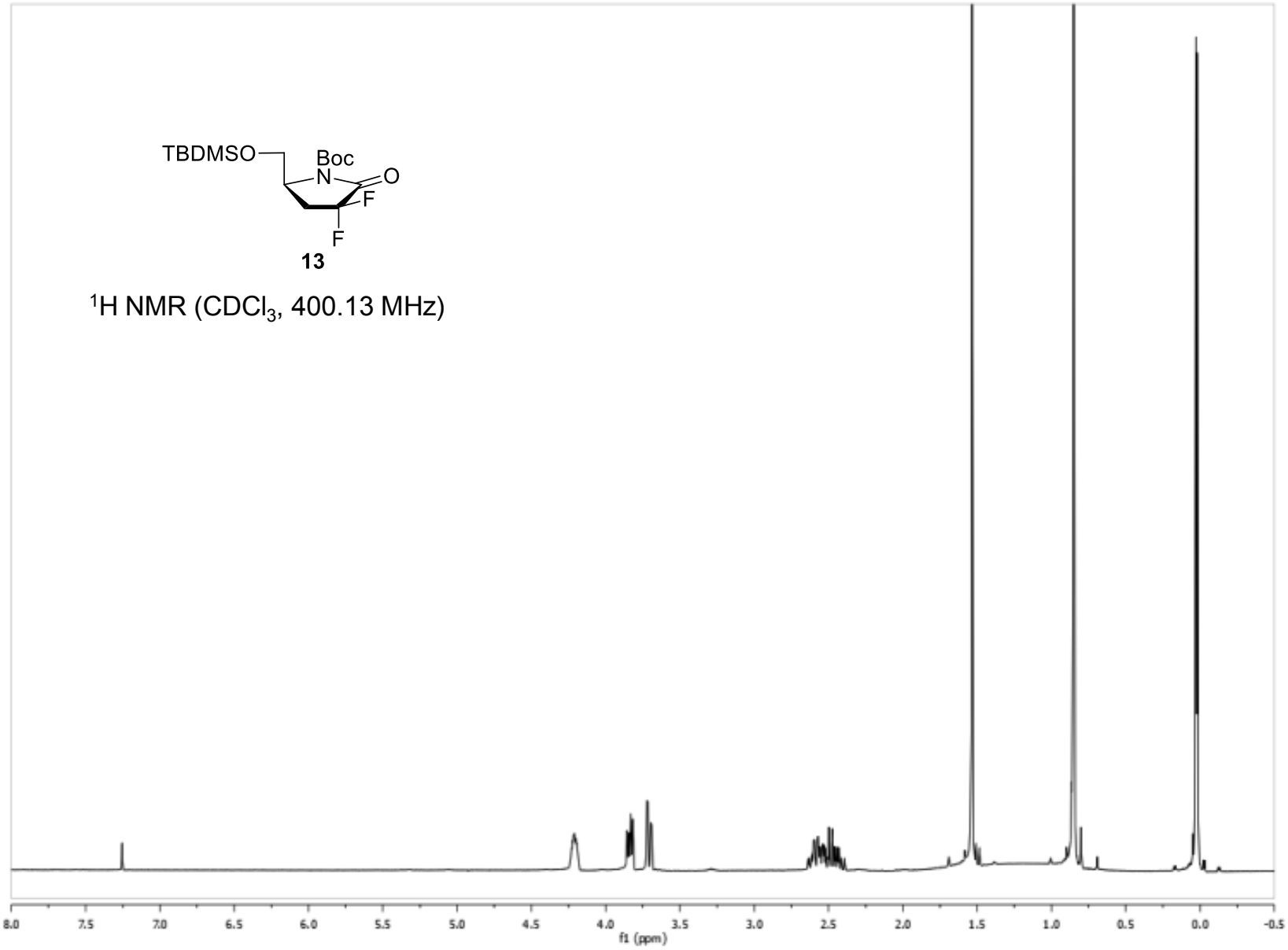
^{13}C NMR ($CDCl_3$, 100.6 MHz)

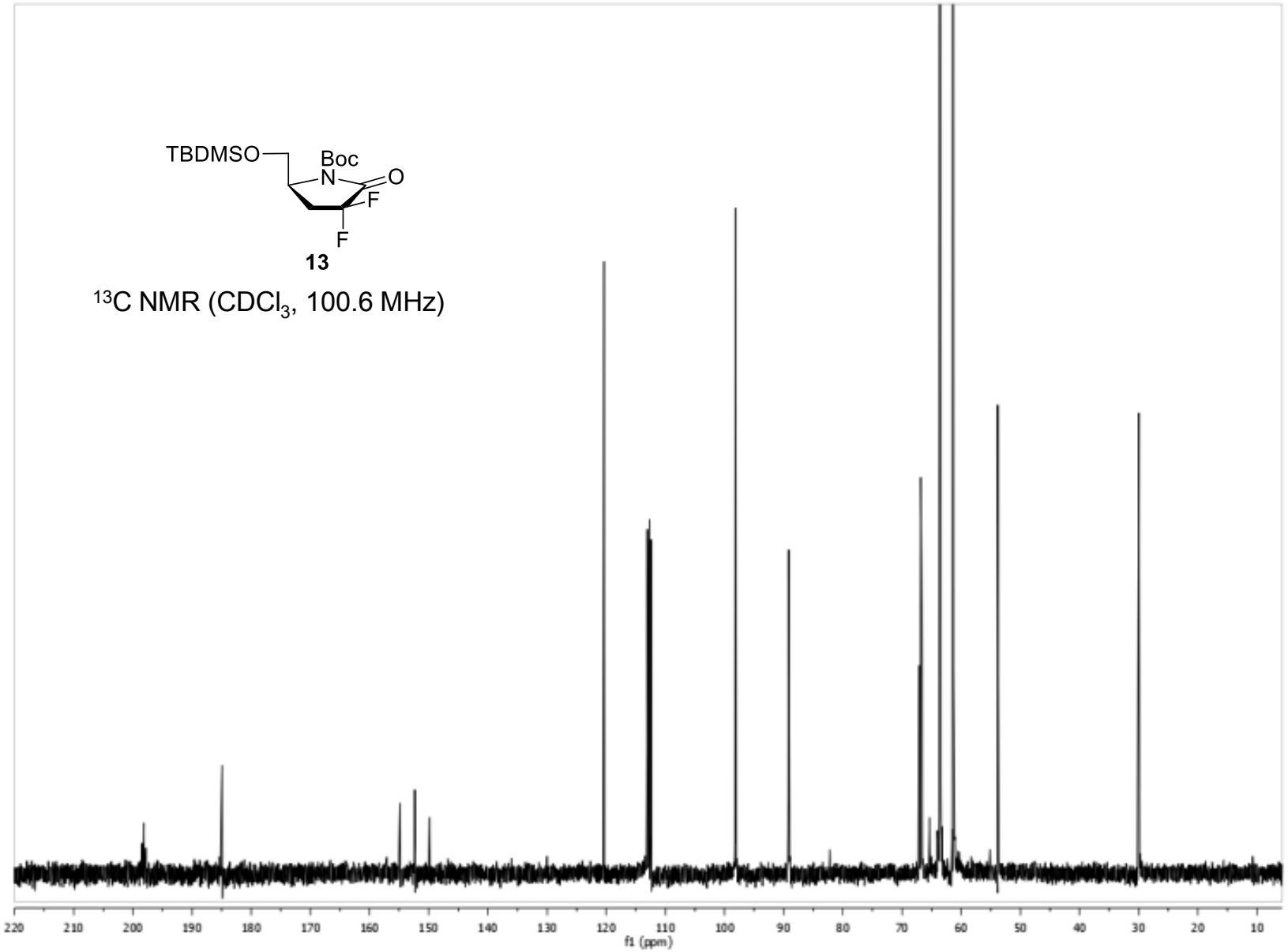


12

DEPT NMR ($CDCl_3$, 100.6 MHz)

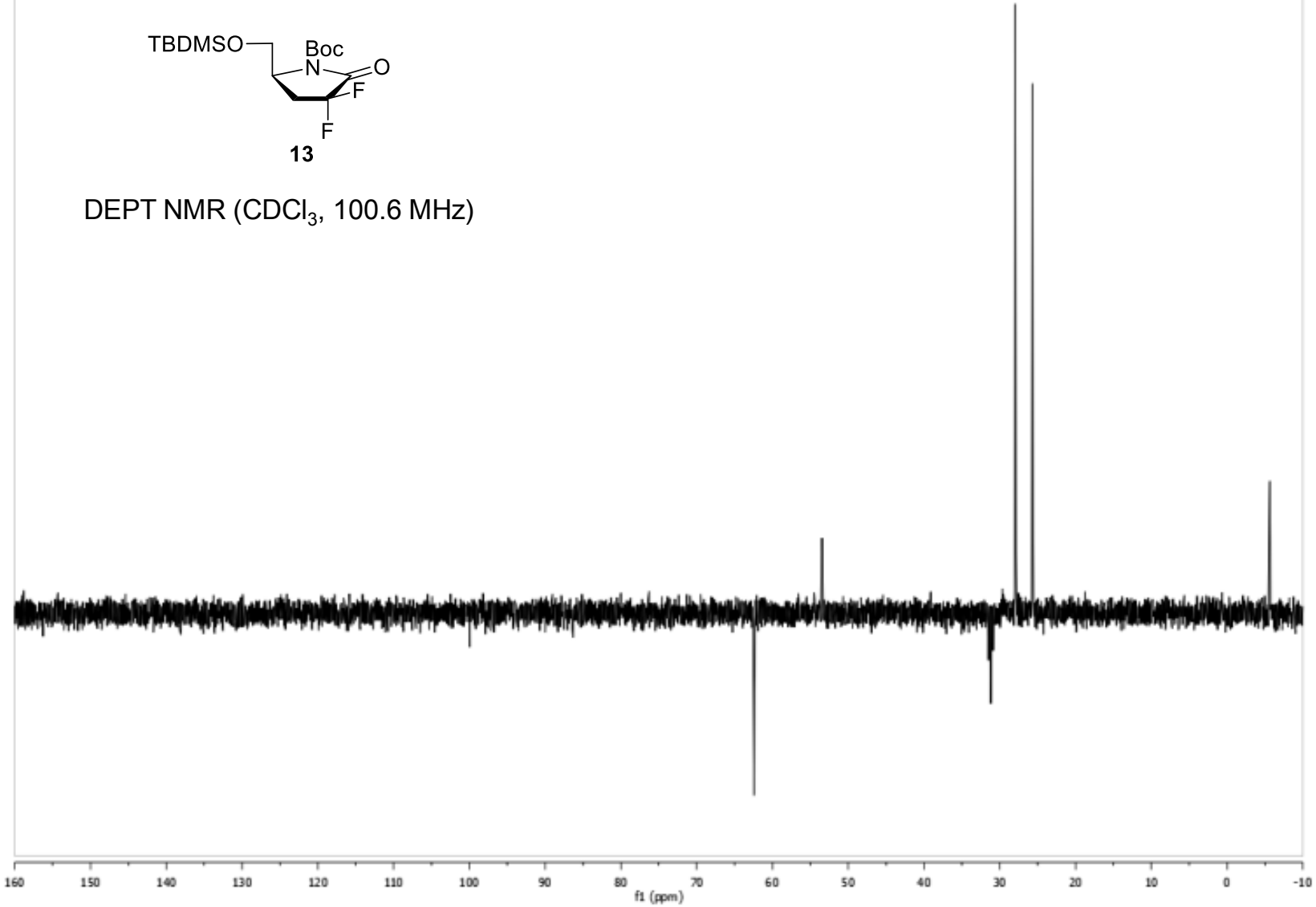



TBDMSO
Boc
N
O
F
F
13
^{1}H NMR ($CDCl_3$, 400.13 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


TBDMSO
Boc
N
O
F
F
13
^{13}C NMR ($CDCl_3$, 100.6 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

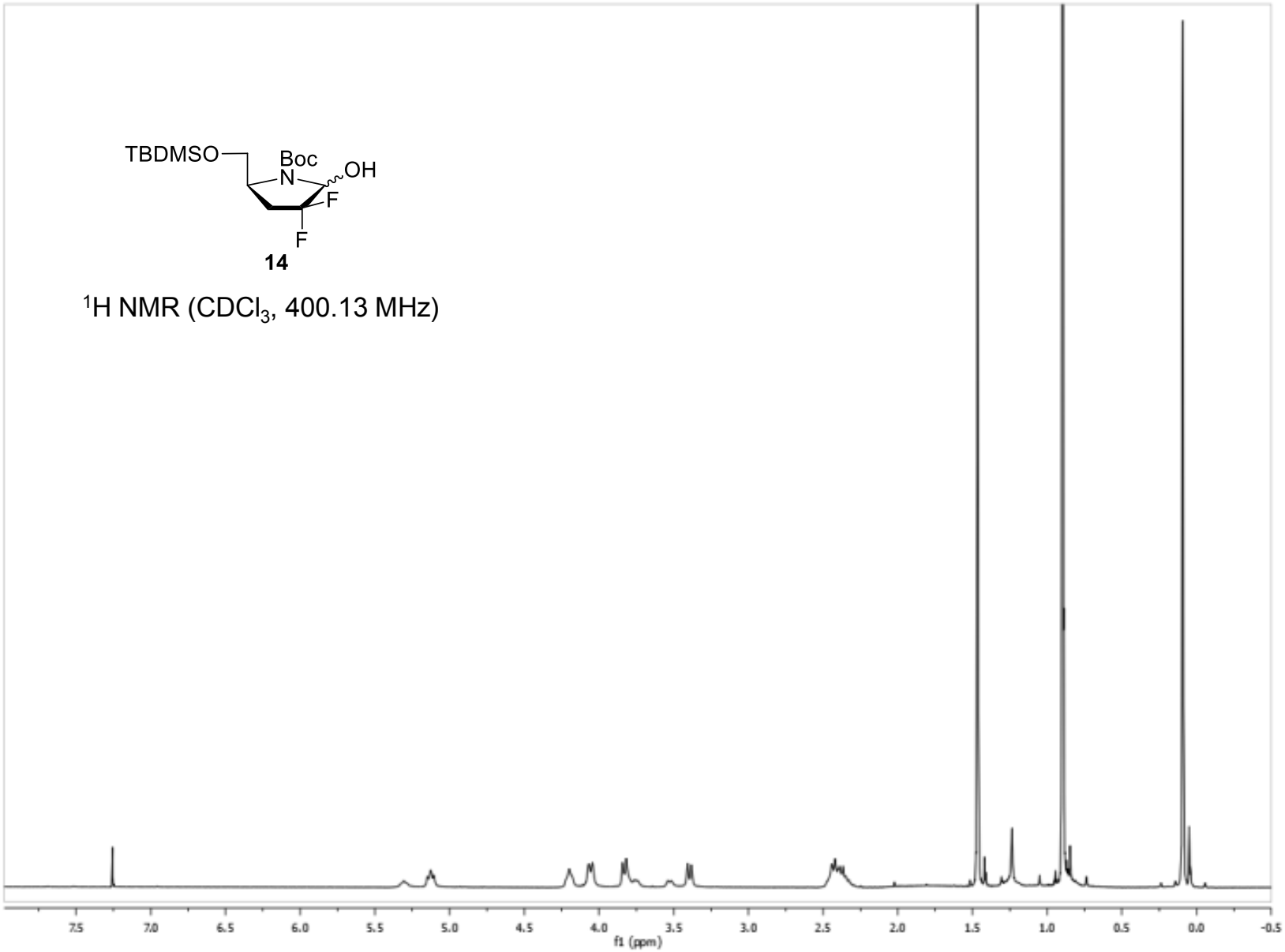
13

DEPT NMR ($CDCl_3$, 100.6 MHz)



14

^{1}H NMR ($CDCl_3$, 400.13 MHz)



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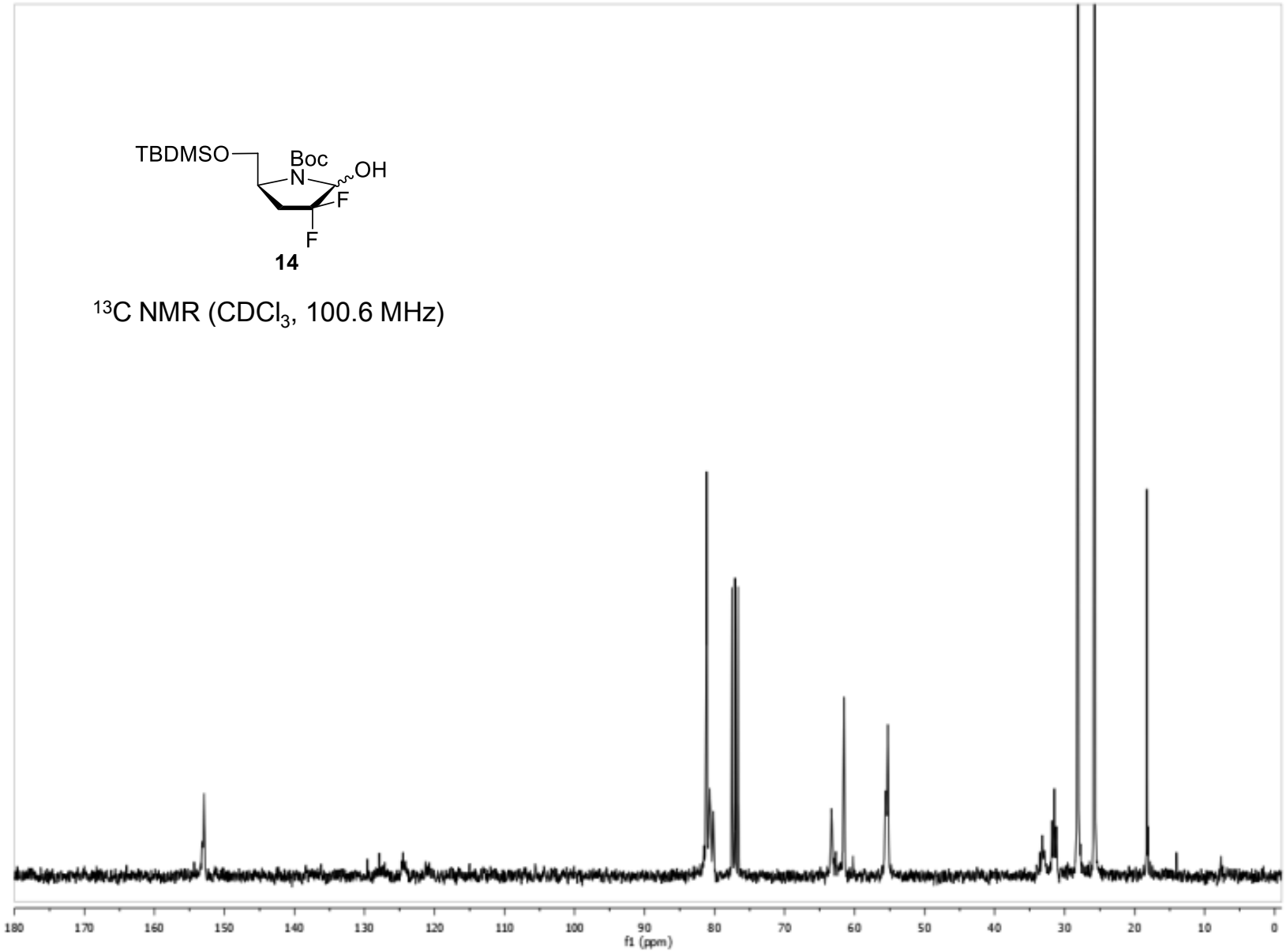
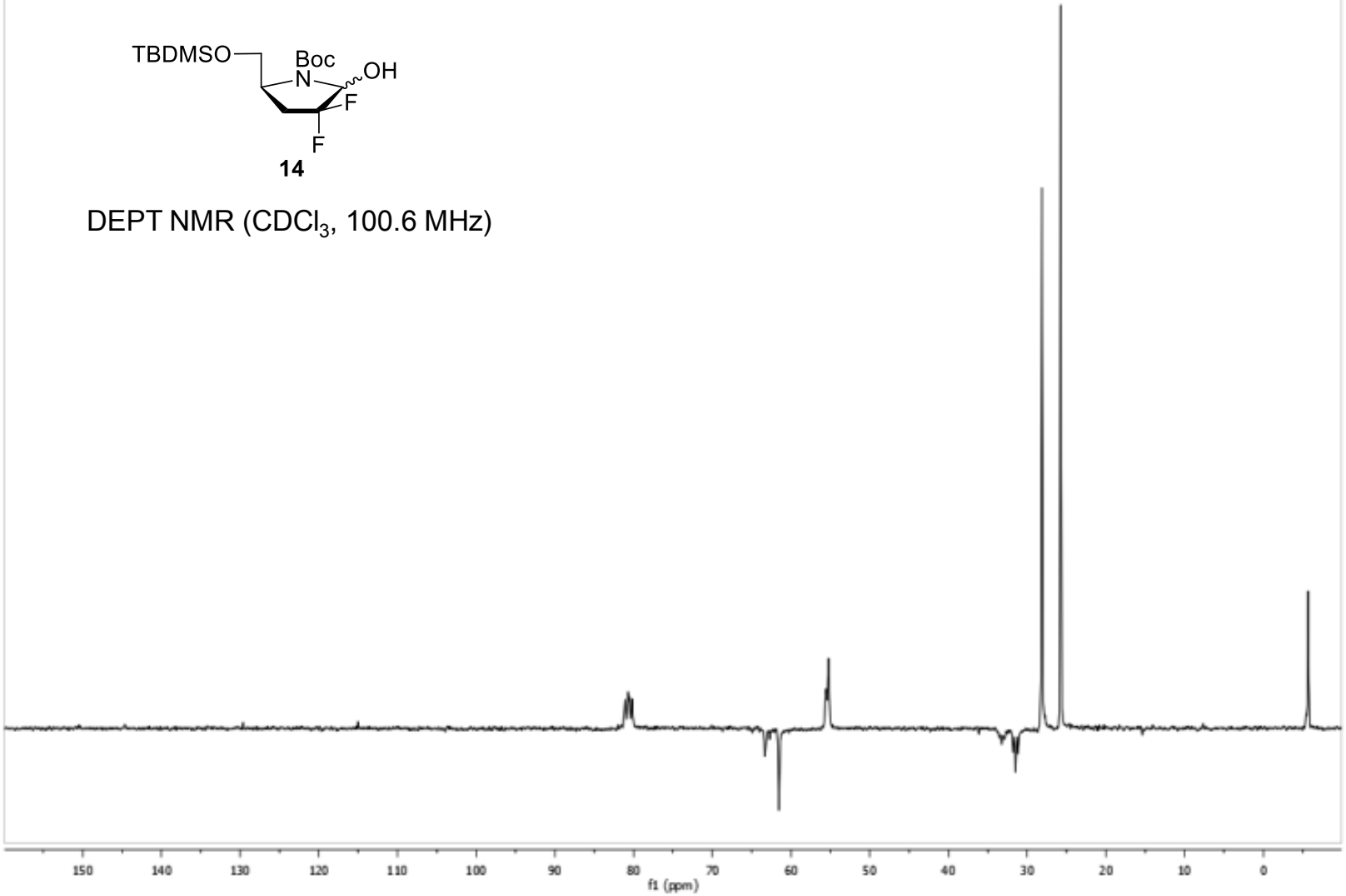
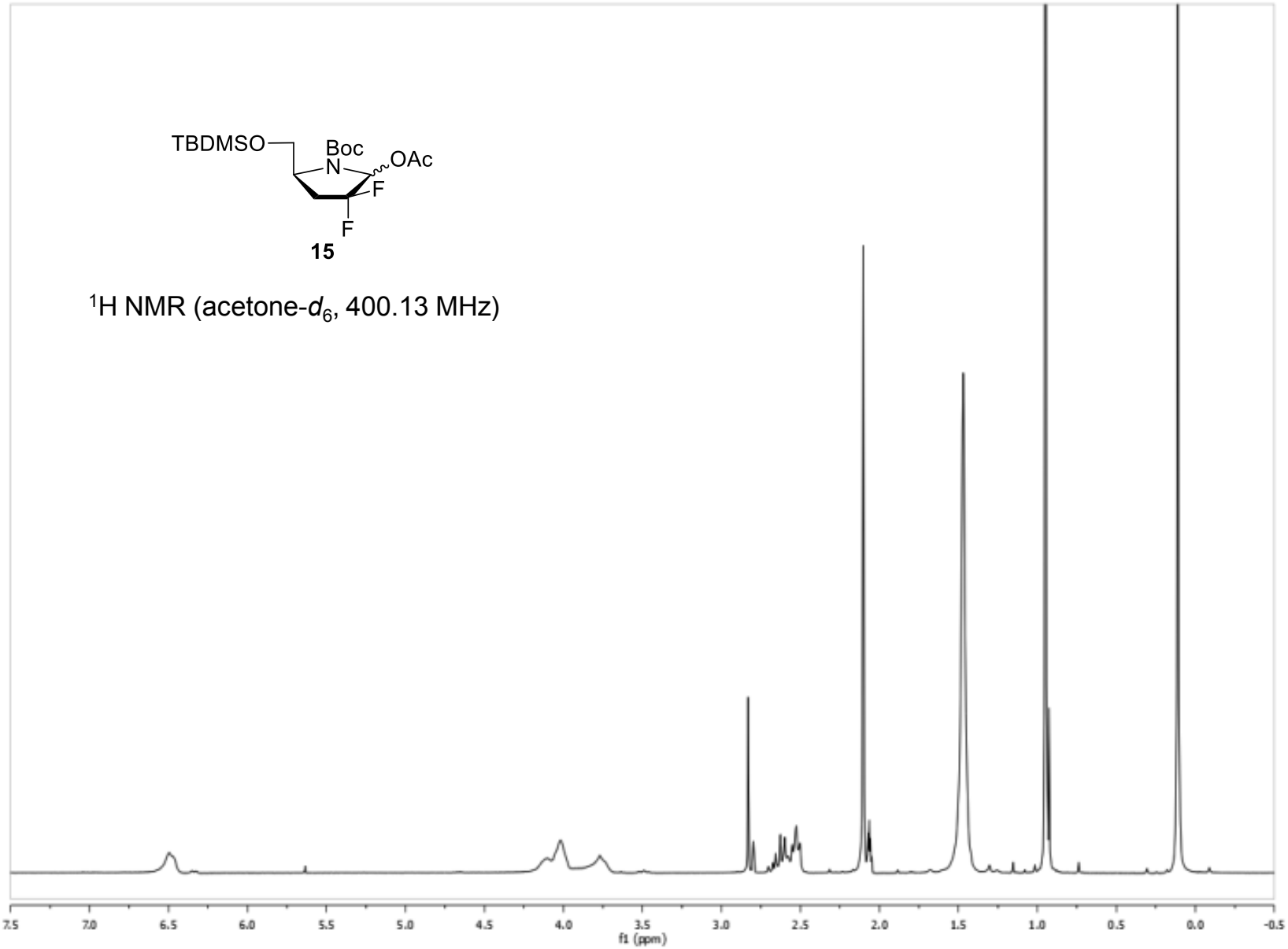
^{13}C NMR ($CDCl_3$, 100.6 MHz)

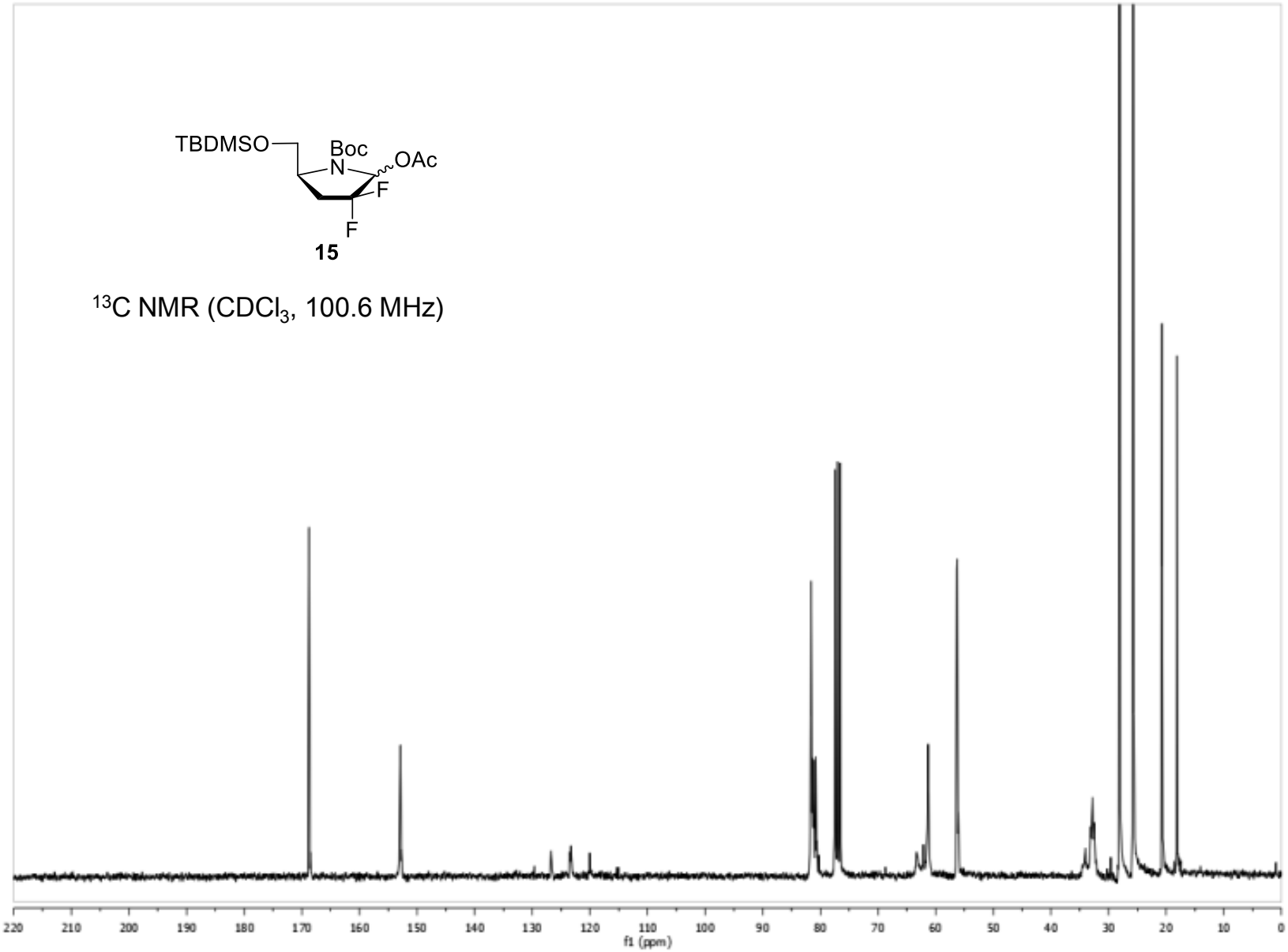


14

DEPT NMR ($CDCl_3$, 100.6 MHz)

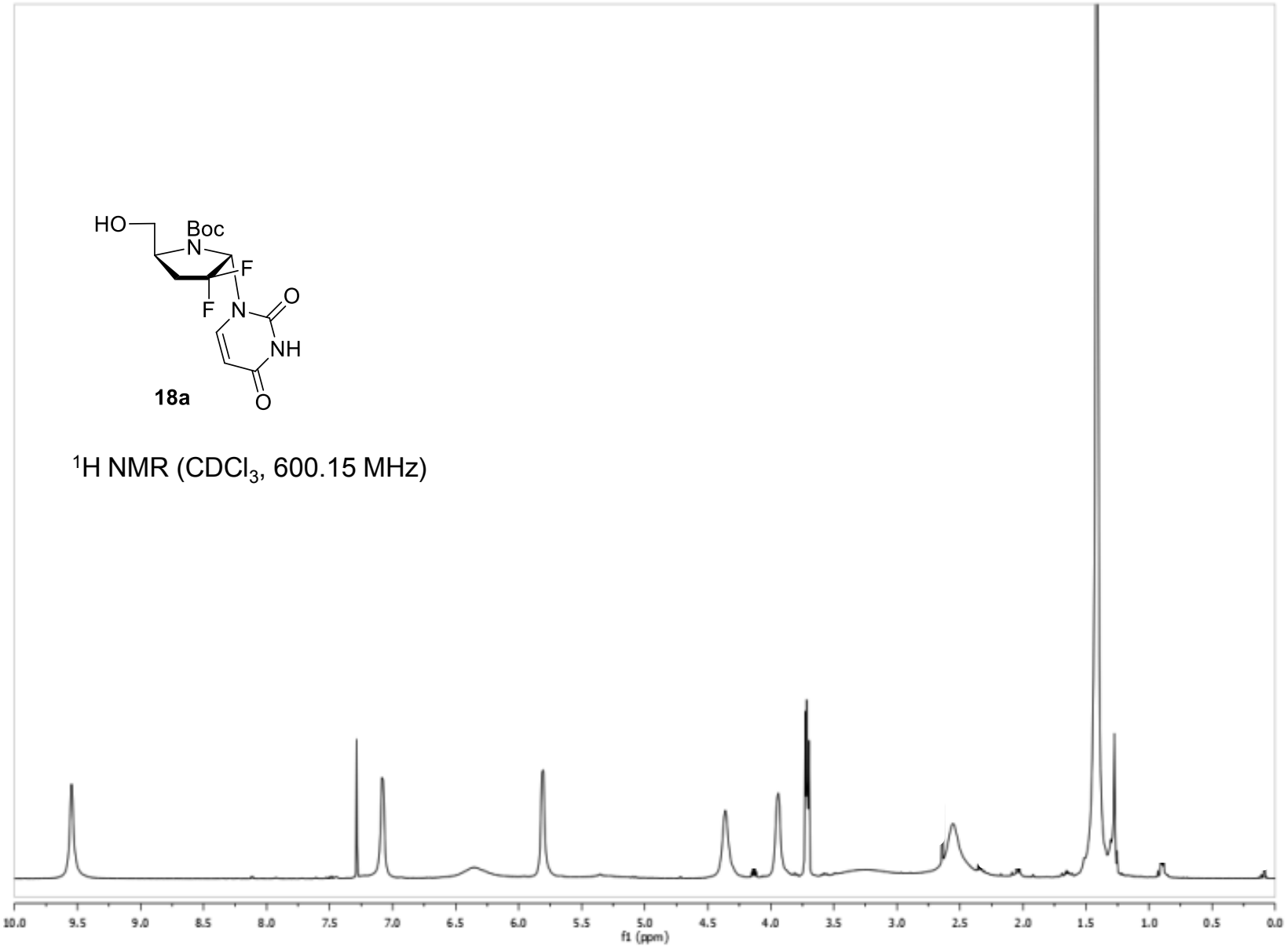



TBDMSO
Boc
N
OAc
F
F
15
^{1}H NMR (acetone-d_6, 400.13 MHz)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


TBDMSO
Boc
N
OAc
F
F
15
^{13}C NMR ($CDCl_3$, 100.6 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

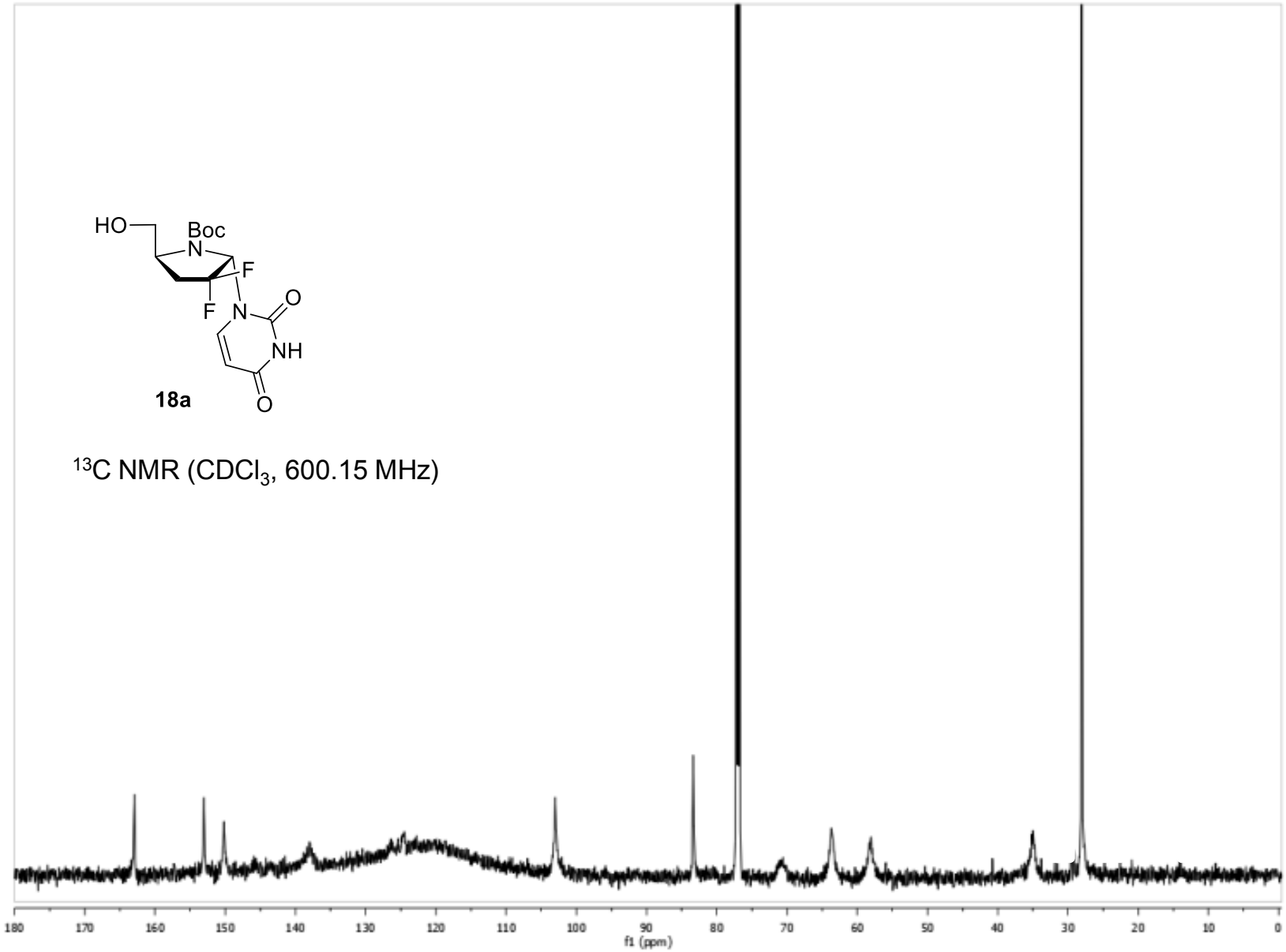
18a

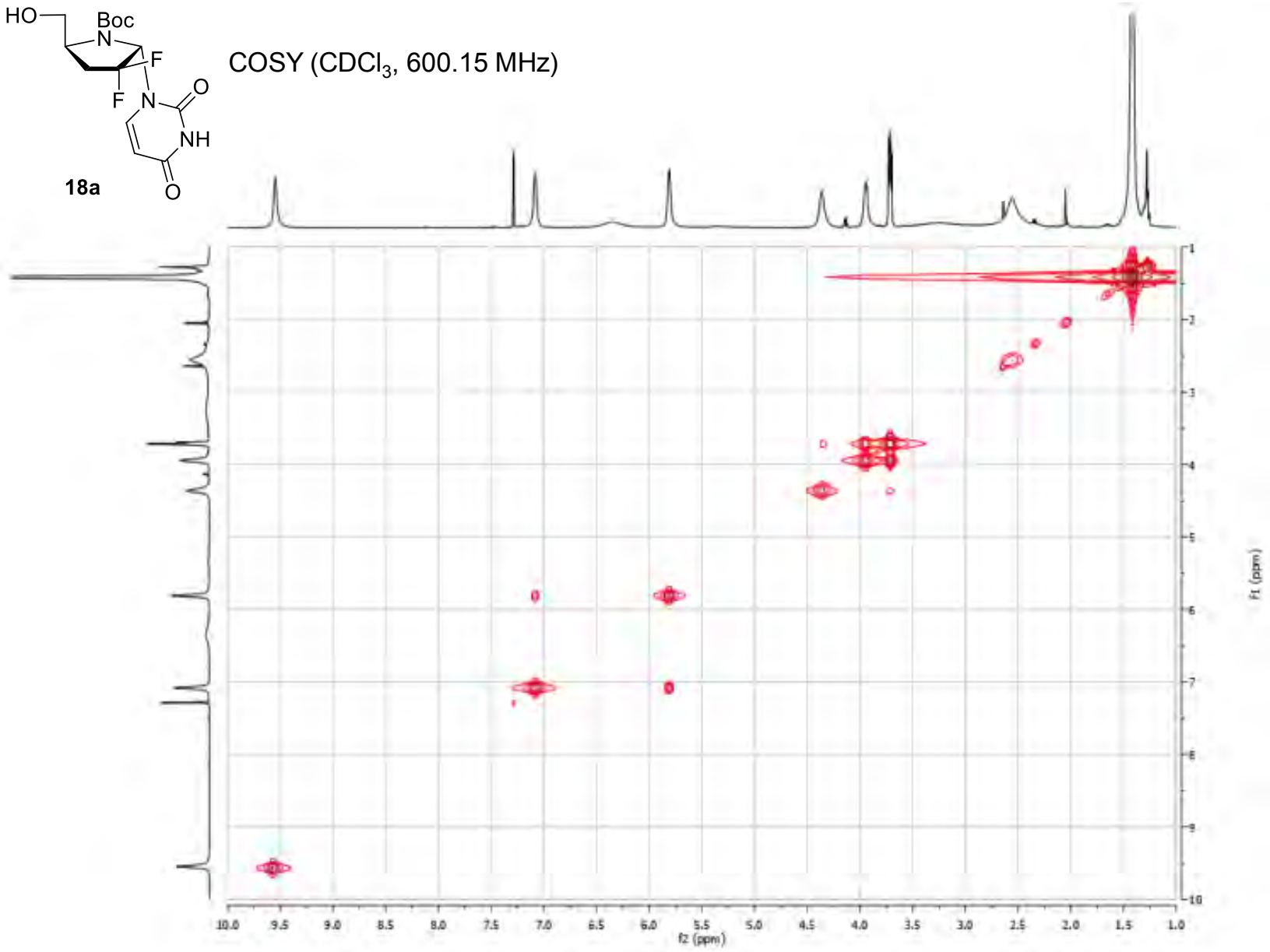
^{1}H NMR ($CDCl_3$, 600.15 MHz)

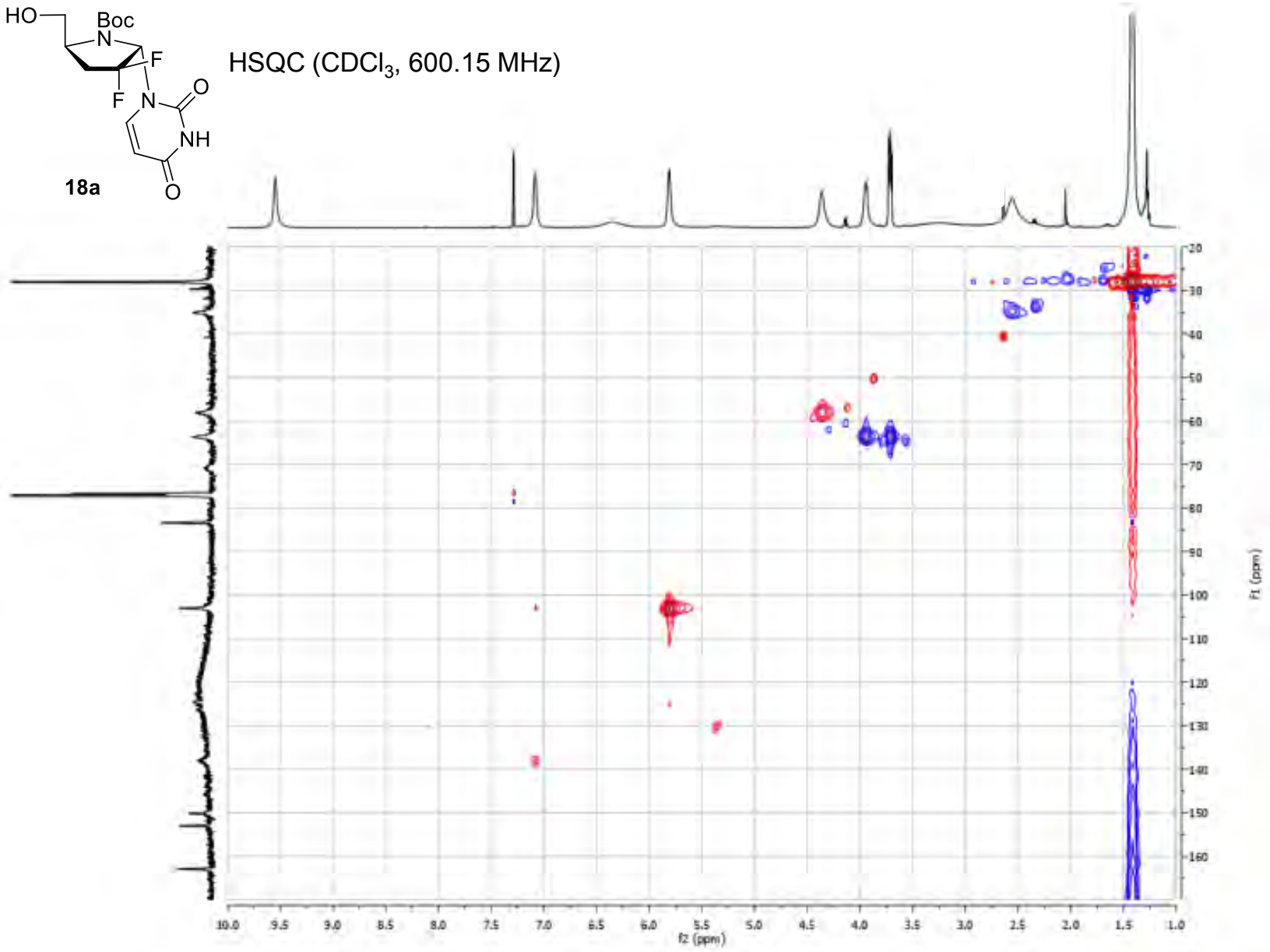


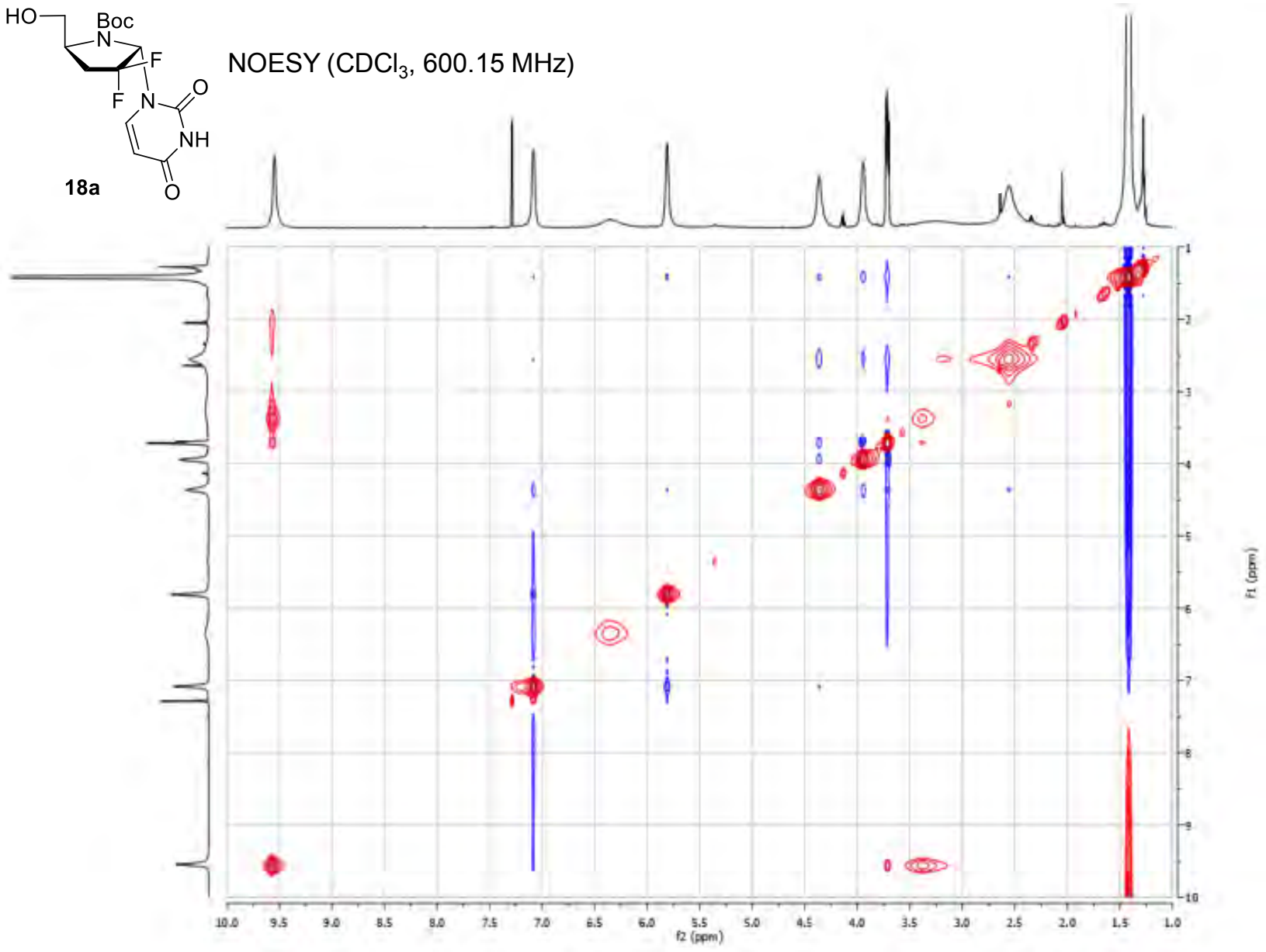
18a

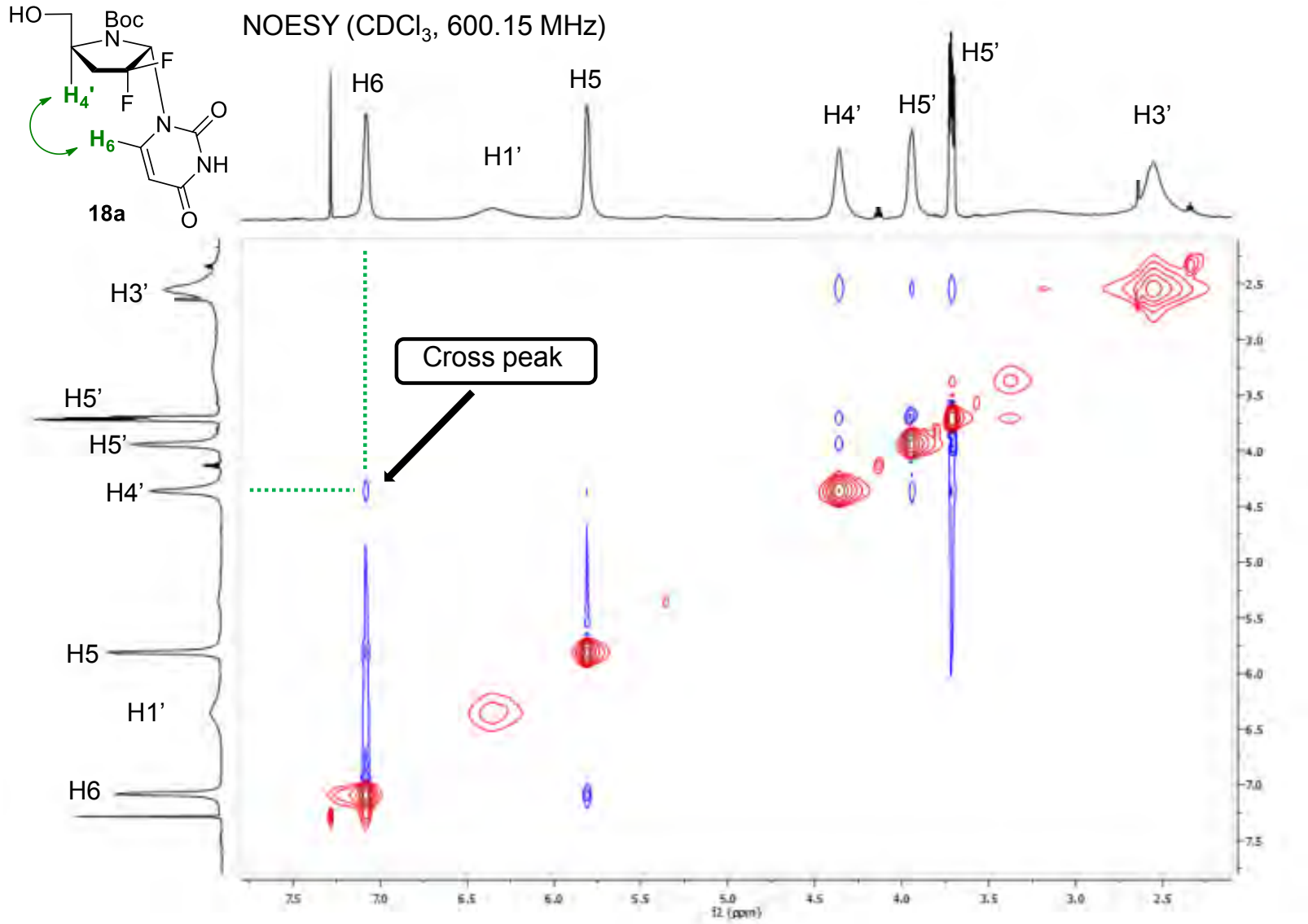
^{13}C NMR ($CDCl_3$, 600.15 MHz)




HO
Boc
N
F
F
N
O
NH
O
18a
COSY ($CDCl_3$, 600.15 MHz)
f2 (ppm)
f1 (ppm)

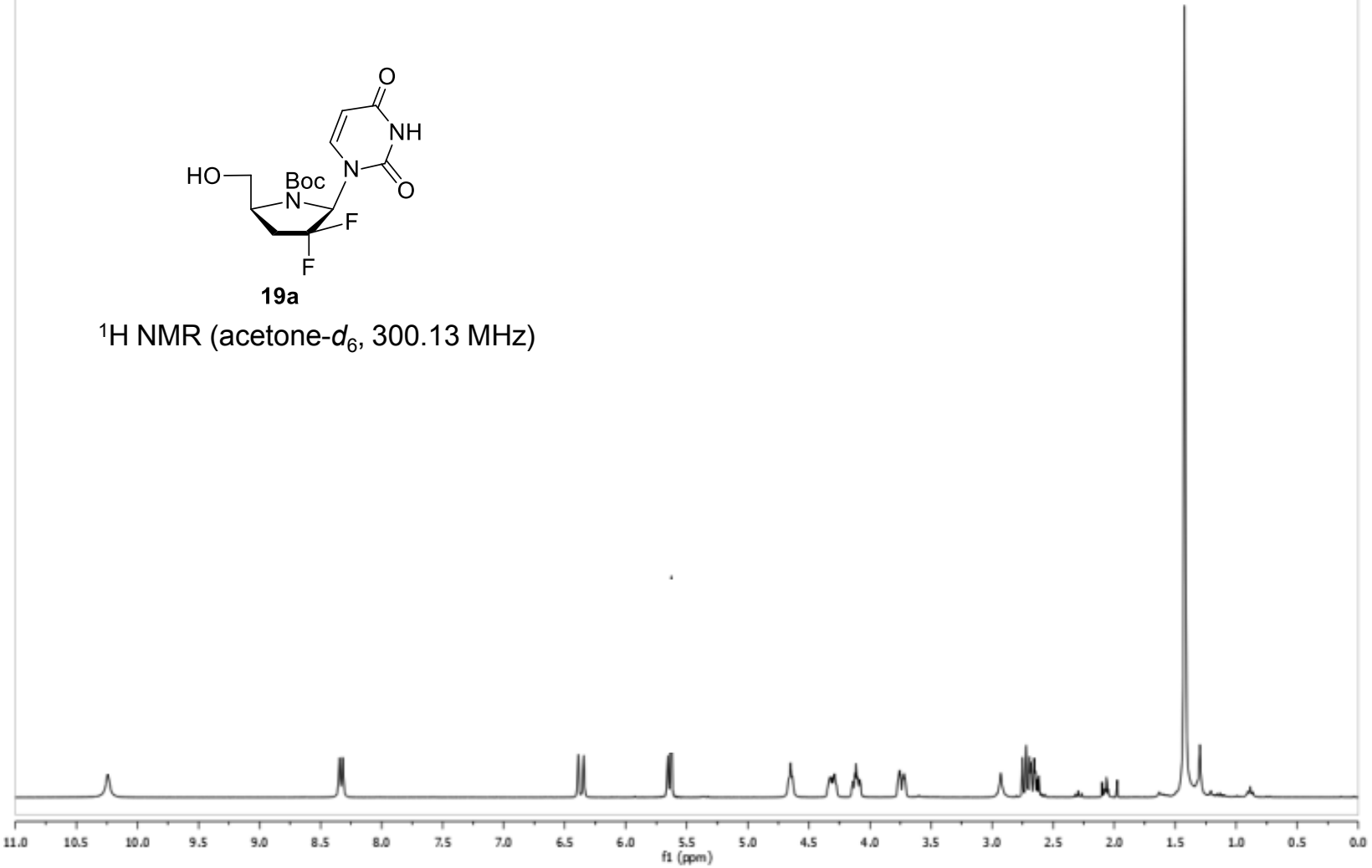

HO
Boc
N
F
F
N
O
NH
O
18a
HSQC ($CDCl_3$, 600.15 MHz)
f2 (ppm)
f1 (ppm)

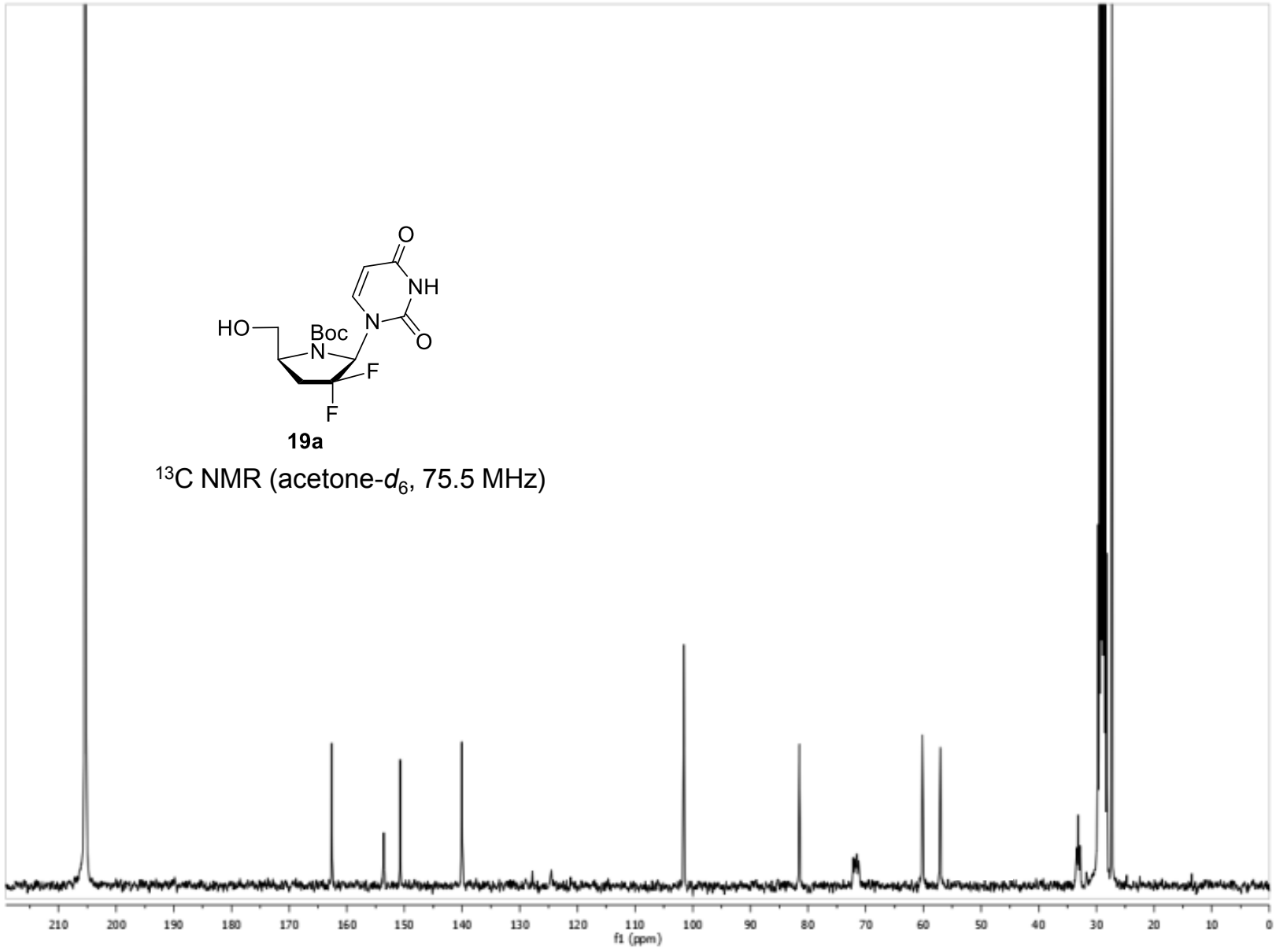

HO
Boc
N
F
F
N
O
NH
O
18a
NOESY ($CDCl_3$, 600.15 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
H_4'
N
O
H_6
NH
O
18a
NOESY ($CDCl_3$, 600.15 MHz)
H6
H5
H1'
H4'
H5'
H5'
H3'
H3'
Cross peak
H5'
H5'
H4'
H5
H1'
H6
f2 (ppm)

19a

^{1}H NMR (acetone-d_6, 300.13 MHz)



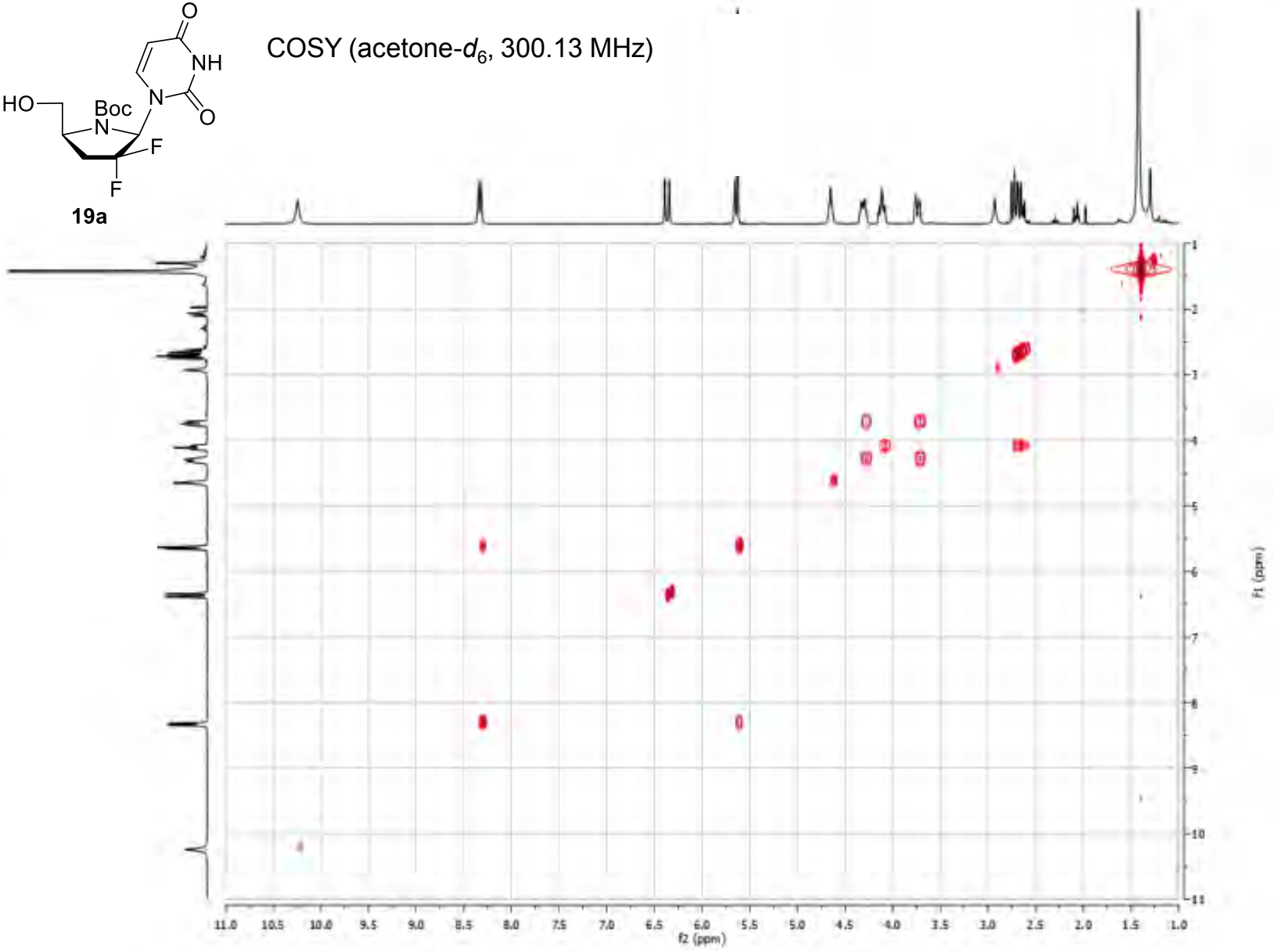


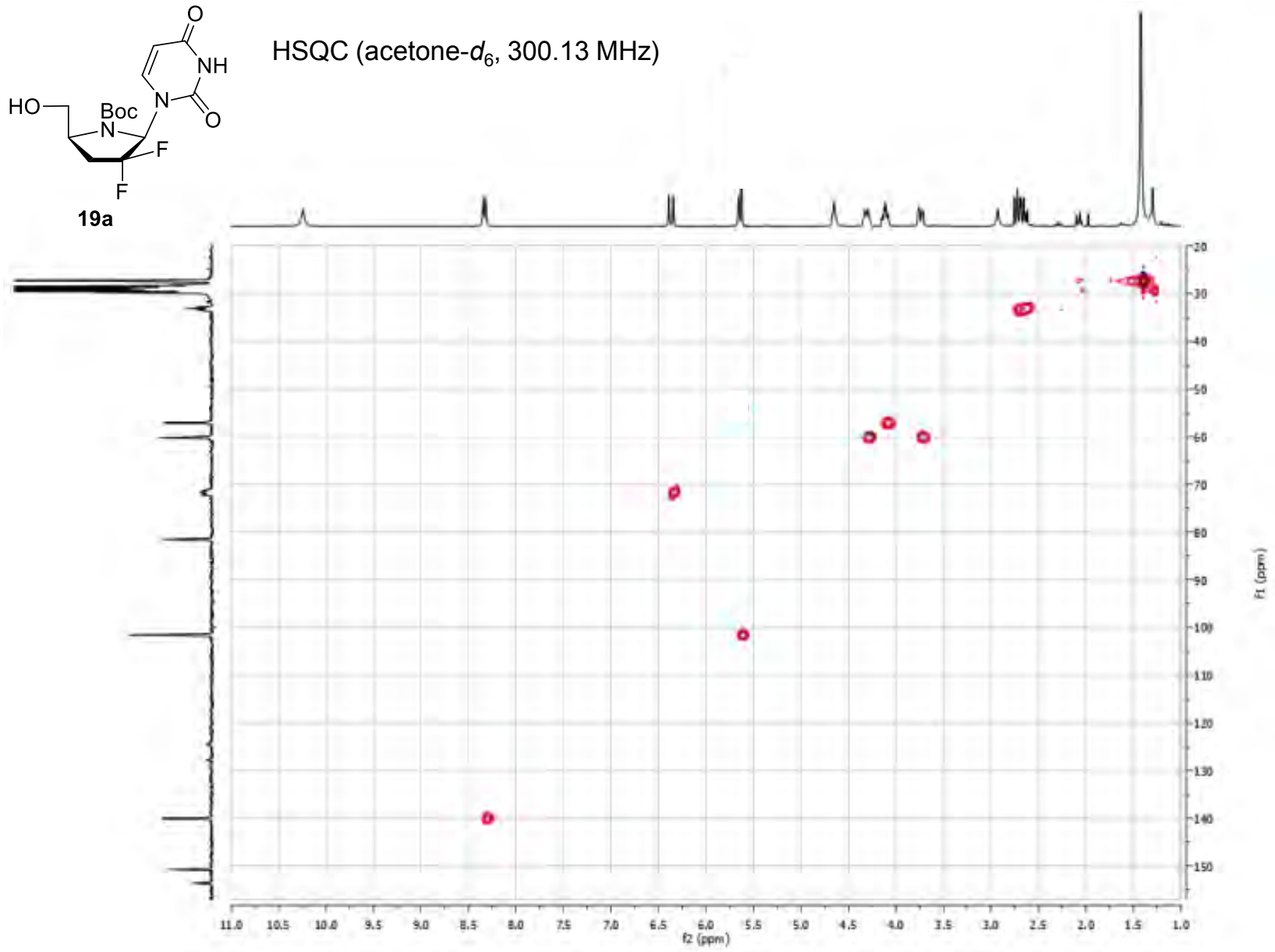
19a

^{13}C NMR (acetone-d_6, 75.5 MHz)

19a

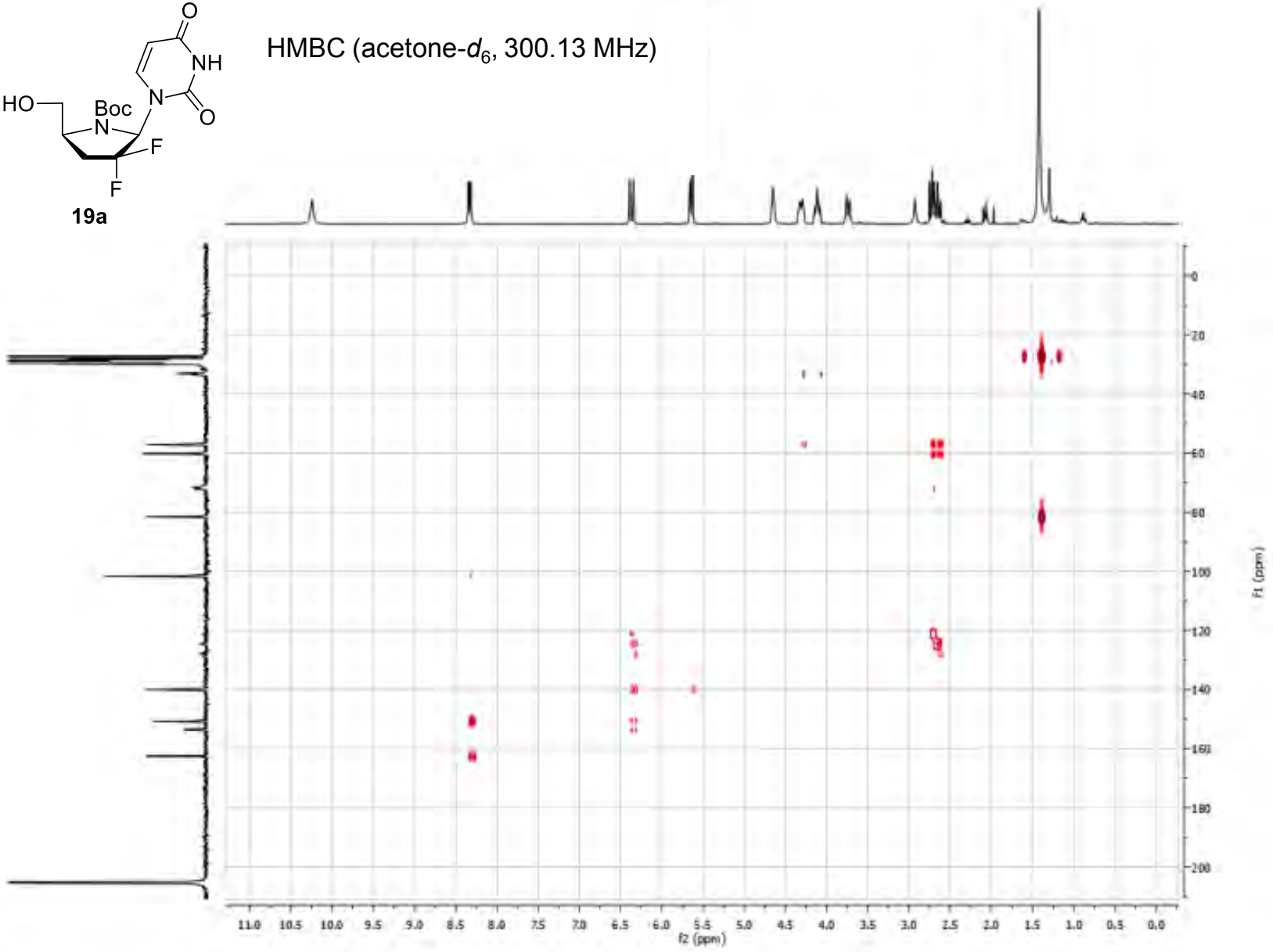
COSY (acetone-d_6, 300.13 MHz)




HO
Boc
N
N
NH
O
O
F
F
19a
HSQC (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)

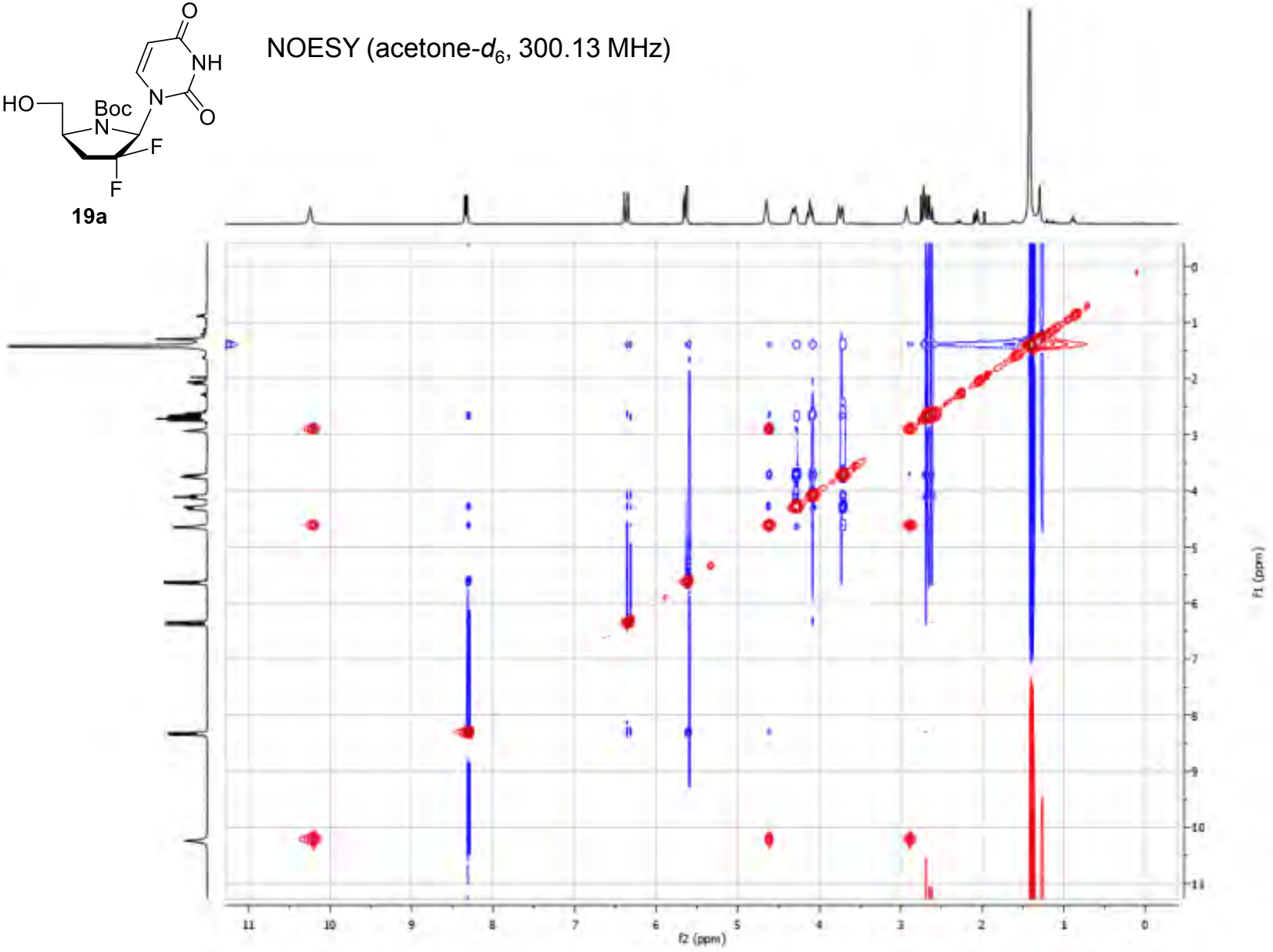
19a

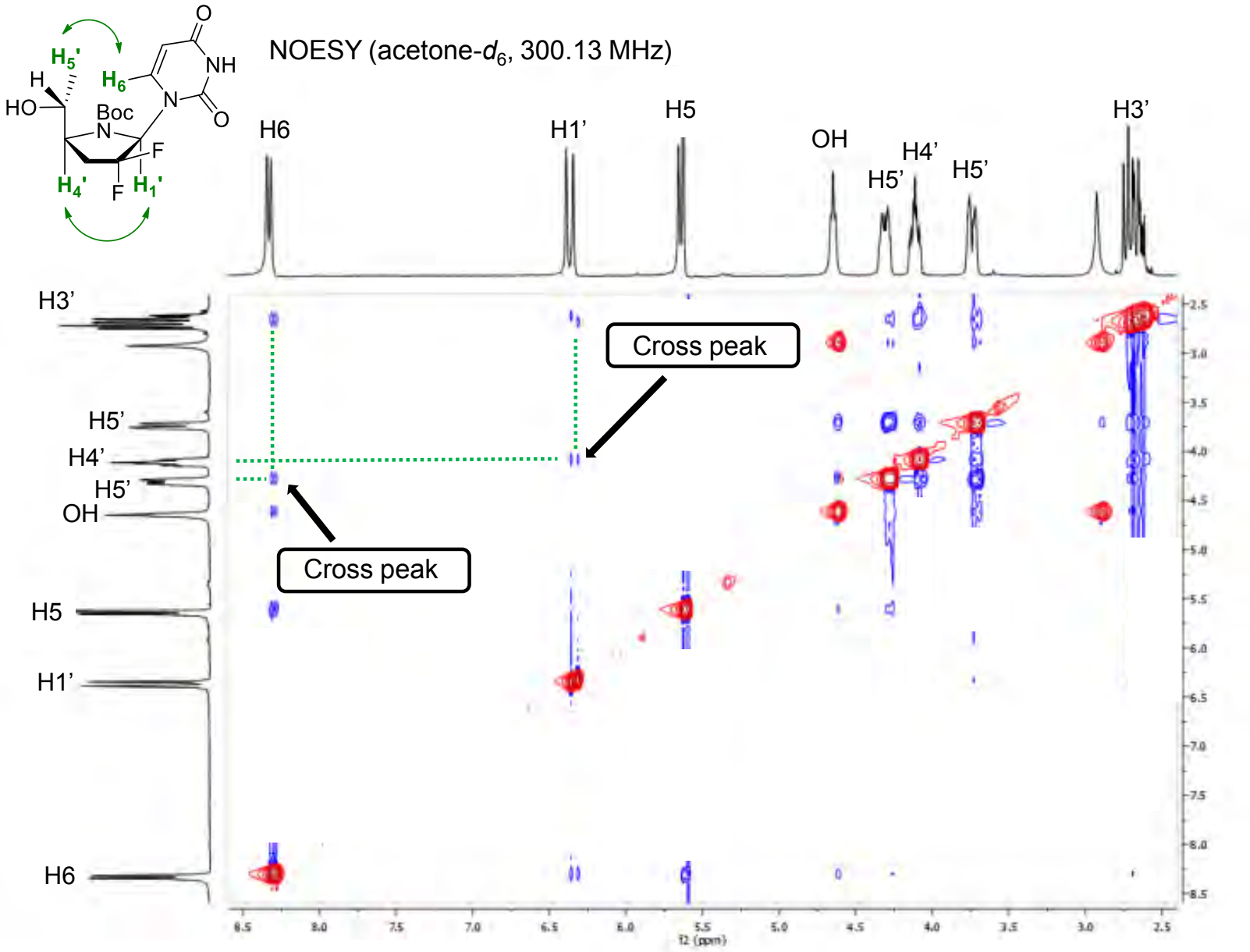
HMBC (acetone-d_6, 300.13 MHz)



19a

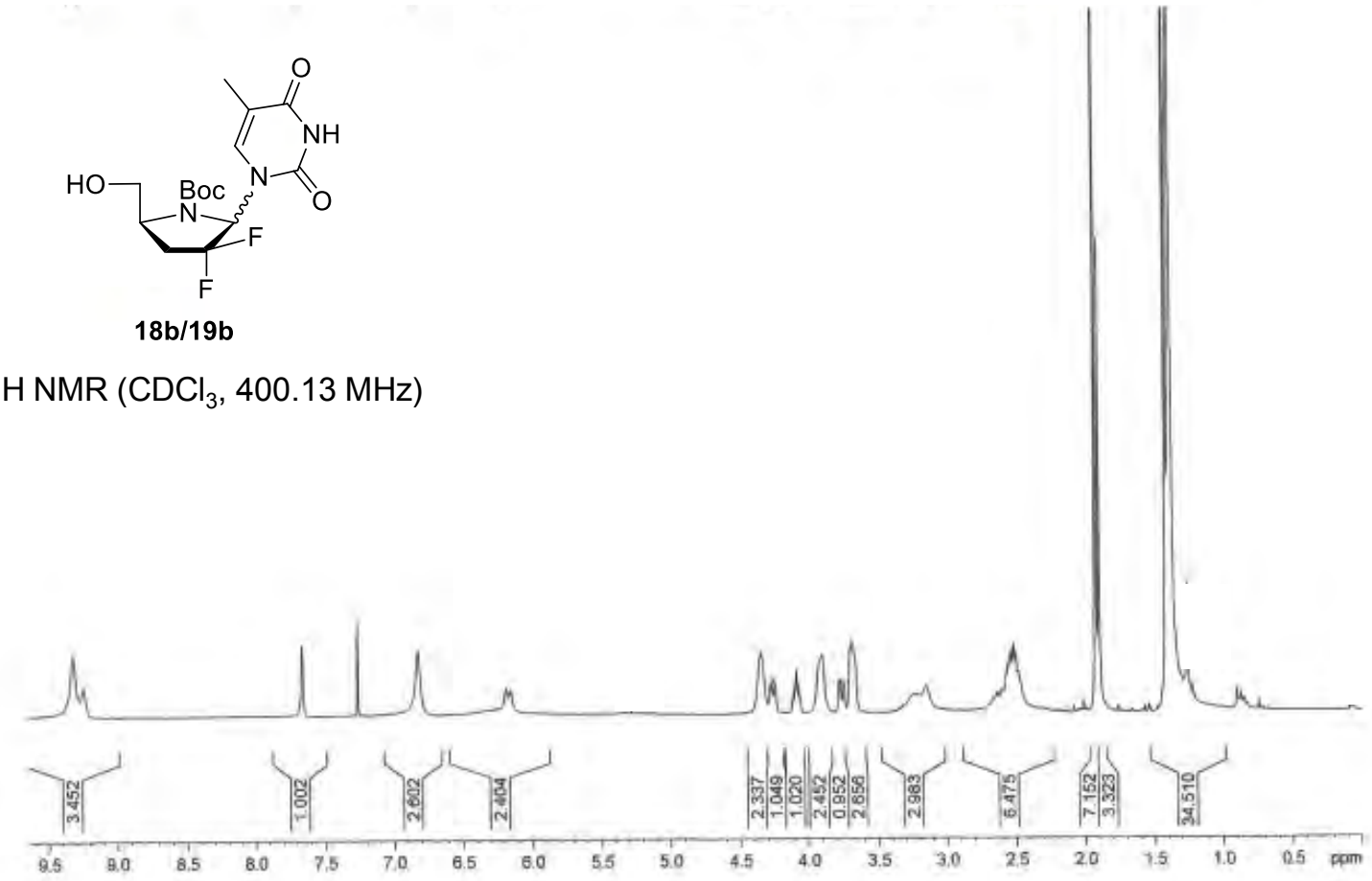
NOESY (acetone-d_6, 300.13 MHz)




NOESY (acetone-d_6, 300.13 MHz)
H5'
H6
H
HO
Boc
N
NH
O
O
F
F
H4'
H1'
H6
H1'
H5
OH
H5'
H4'
H5'
H3'
H3'
H5'
H4'
H5'
OH
H5
H1'
H6
Cross peak
Cross peak
f2 (ppm)

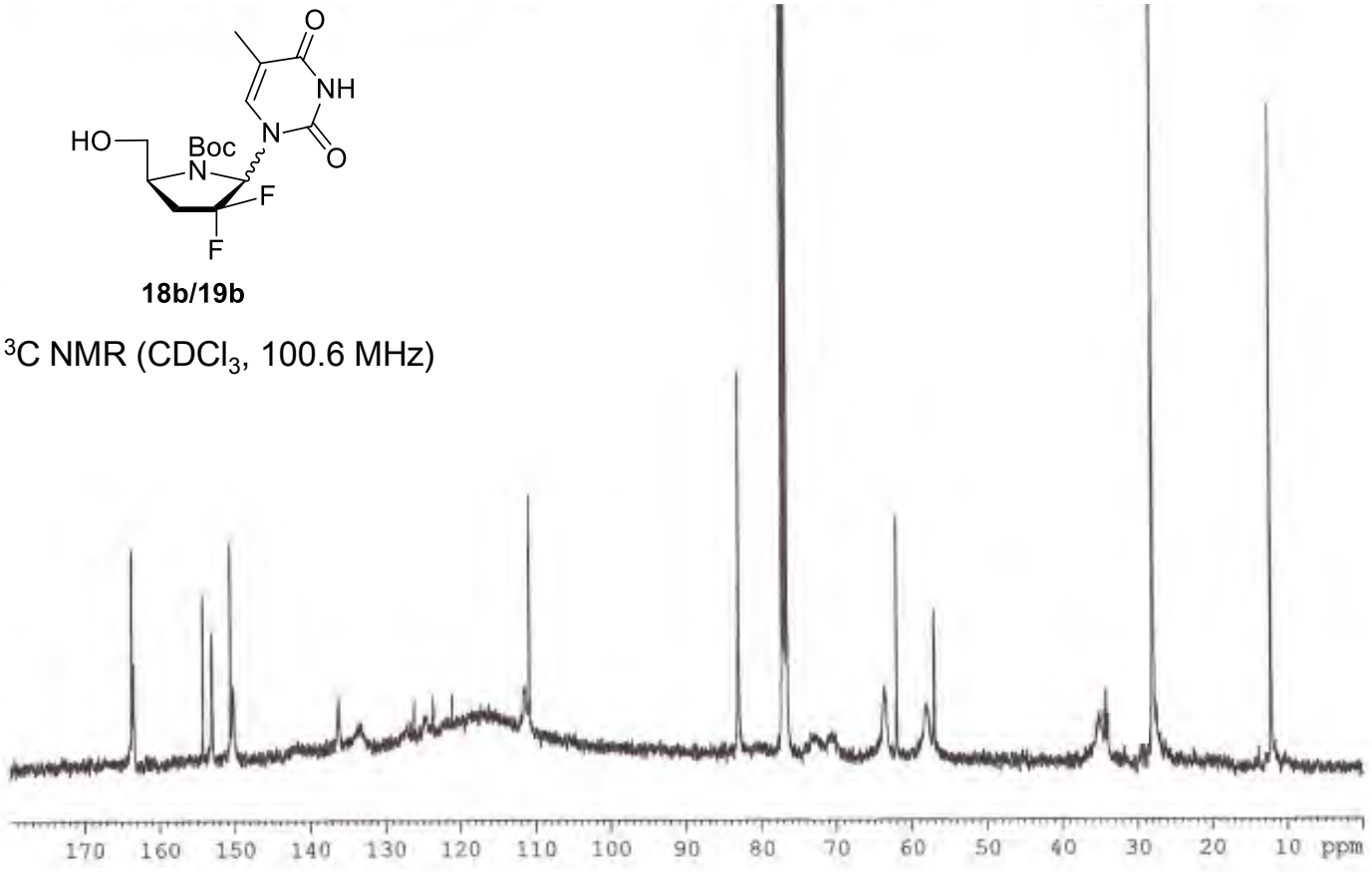
18b/19b

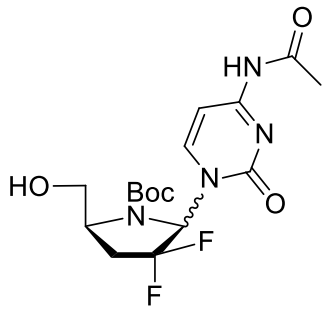
^{1}H NMR ($CDCl_3$, 400.13 MHz)



18b/19b

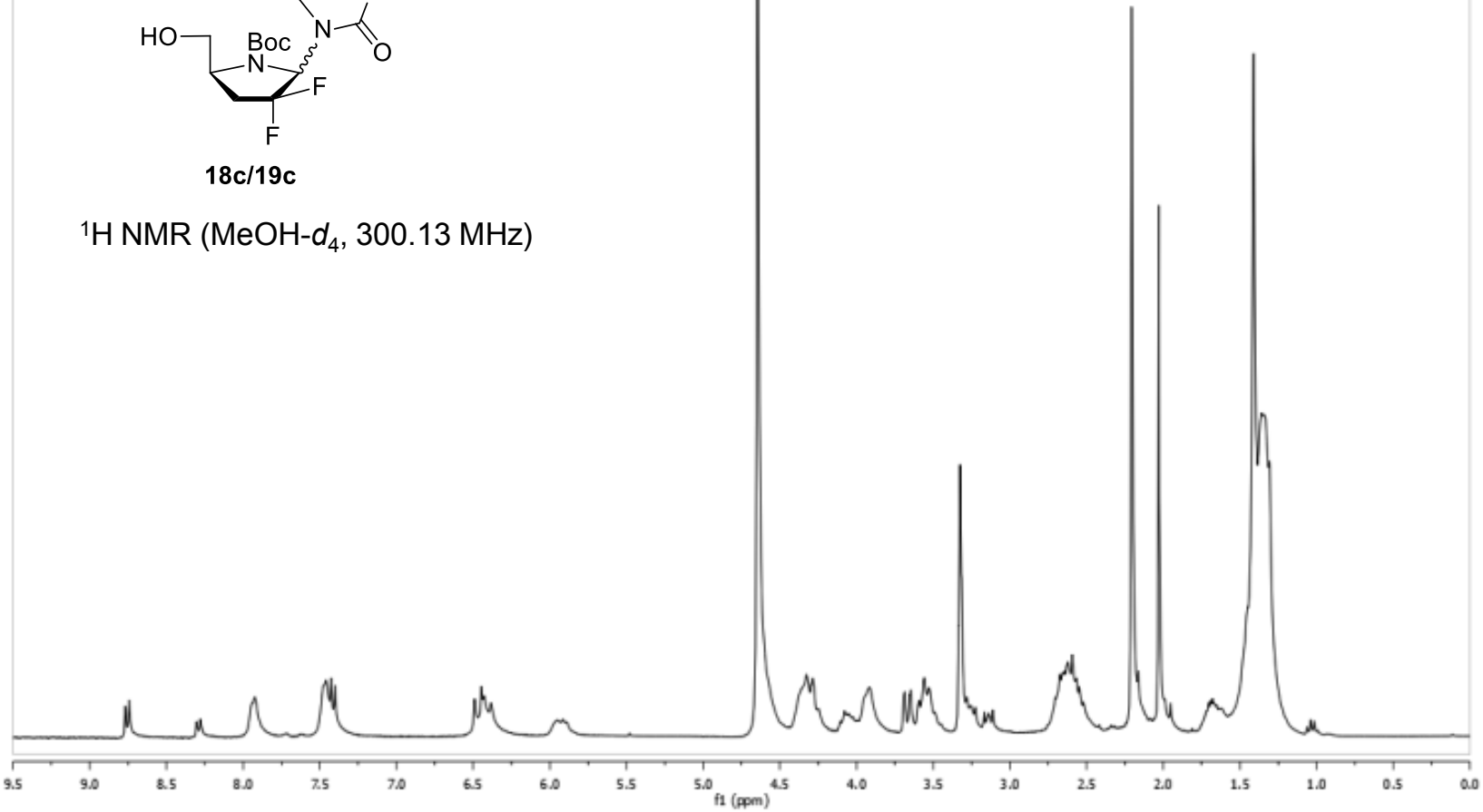
^{13}C NMR ($CDCl_3$, 100.6 MHz)





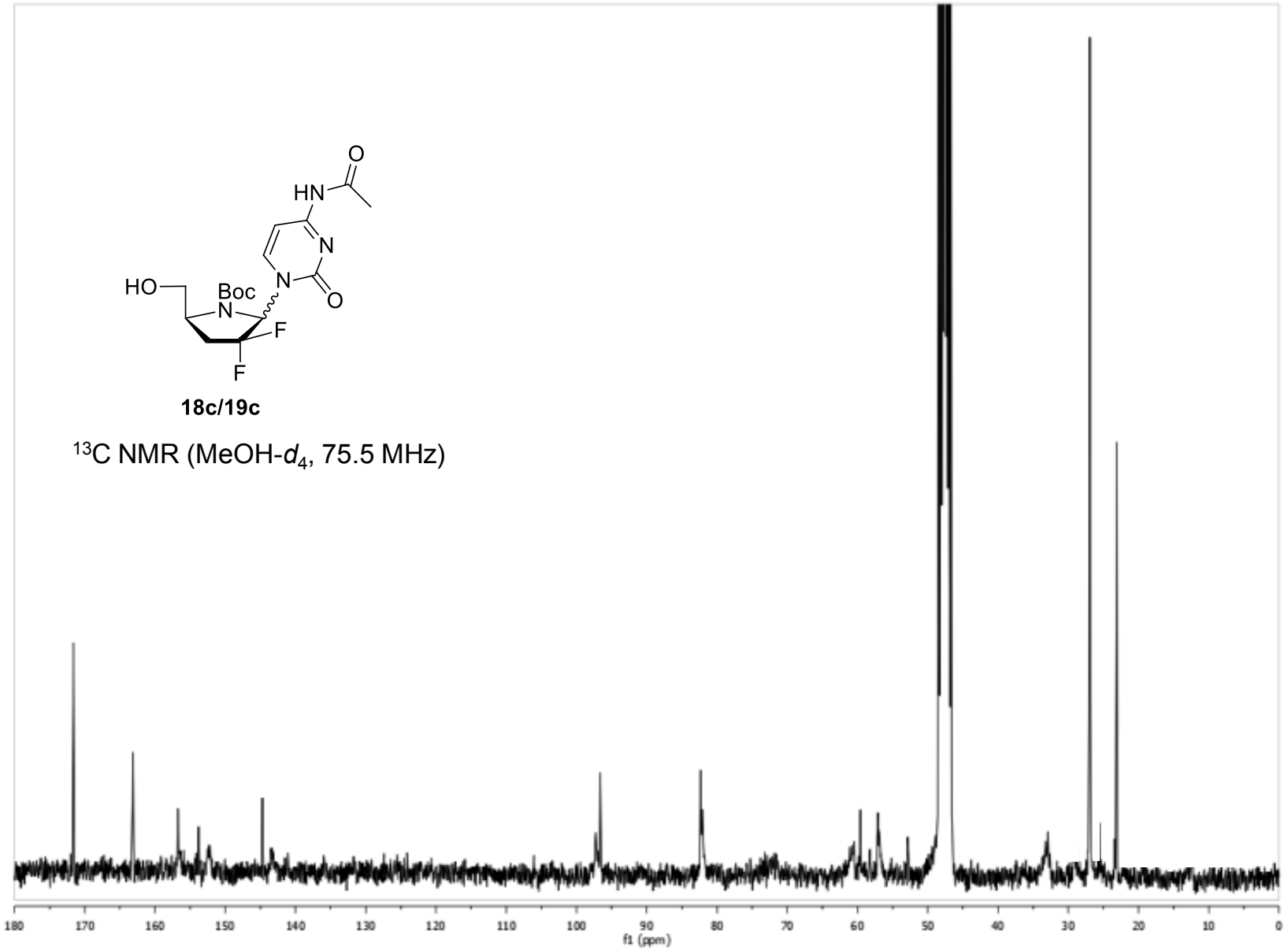
18c/19c

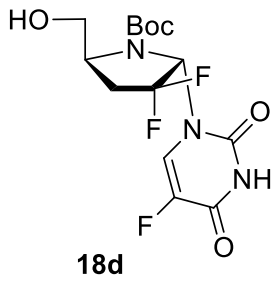
^{1}H NMR (MeOH-d_4, 300.13 MHz)



18c/19c

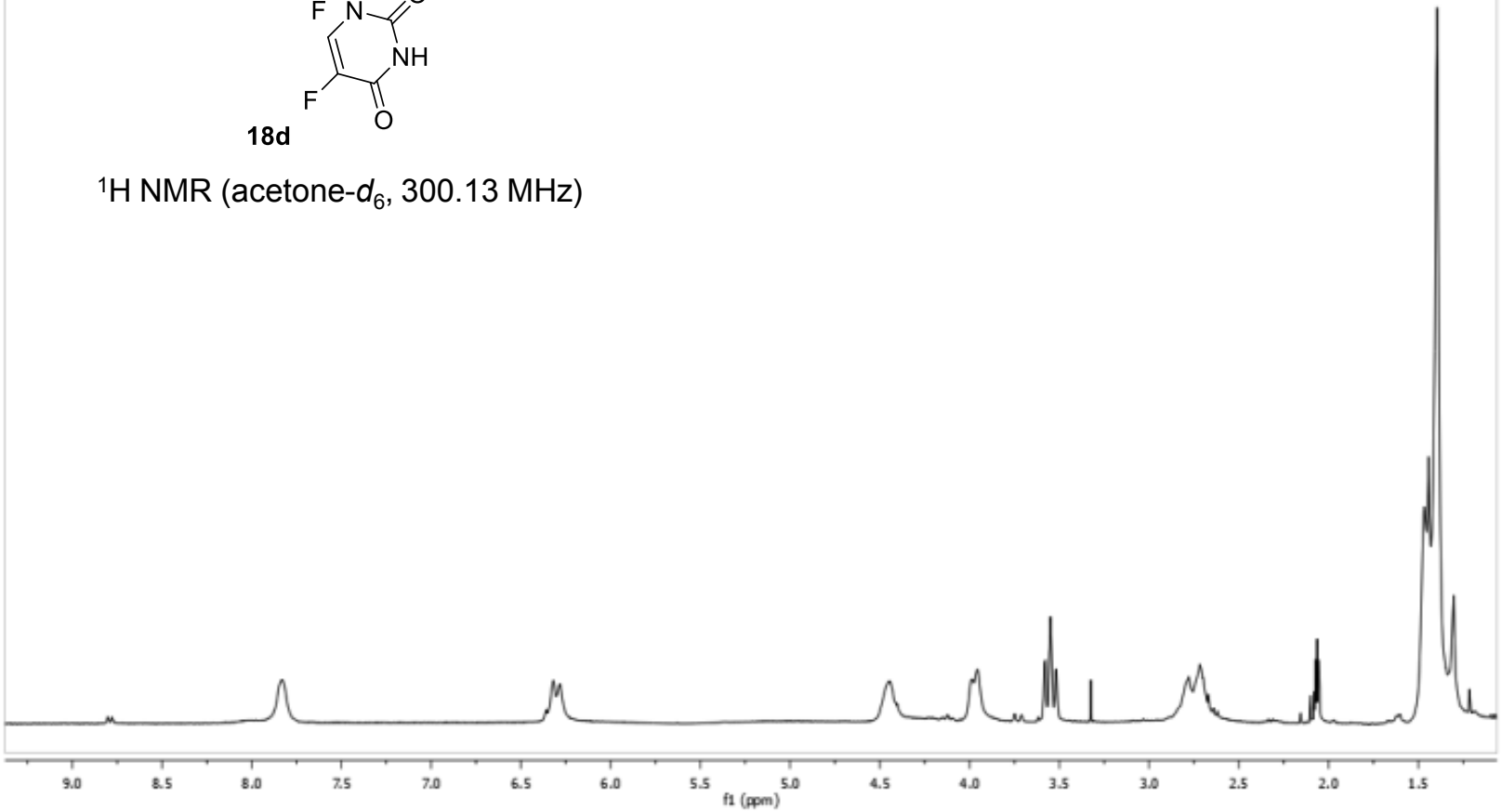
^{13}C NMR (MeOH-d_4, 75.5 MHz)

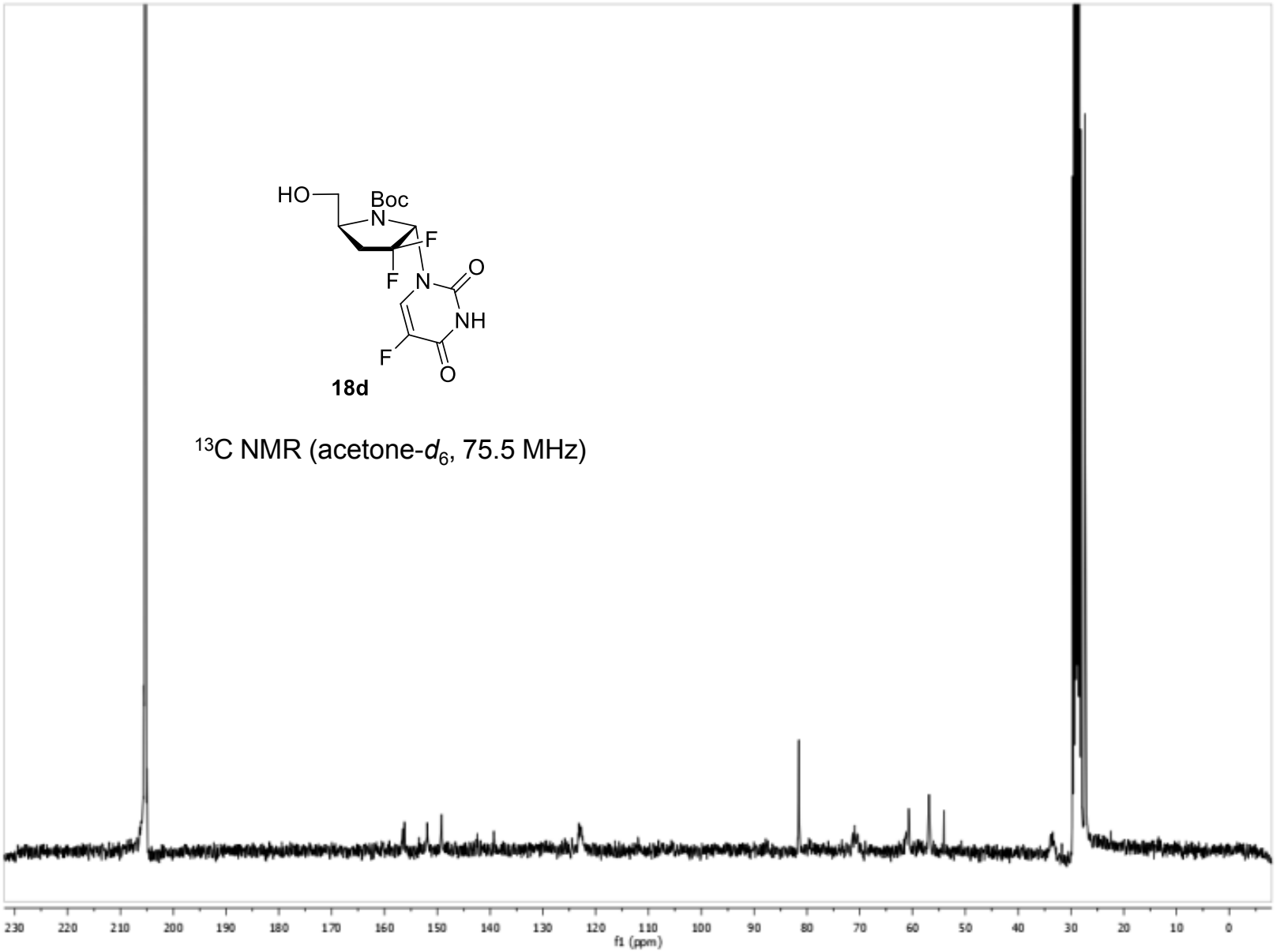


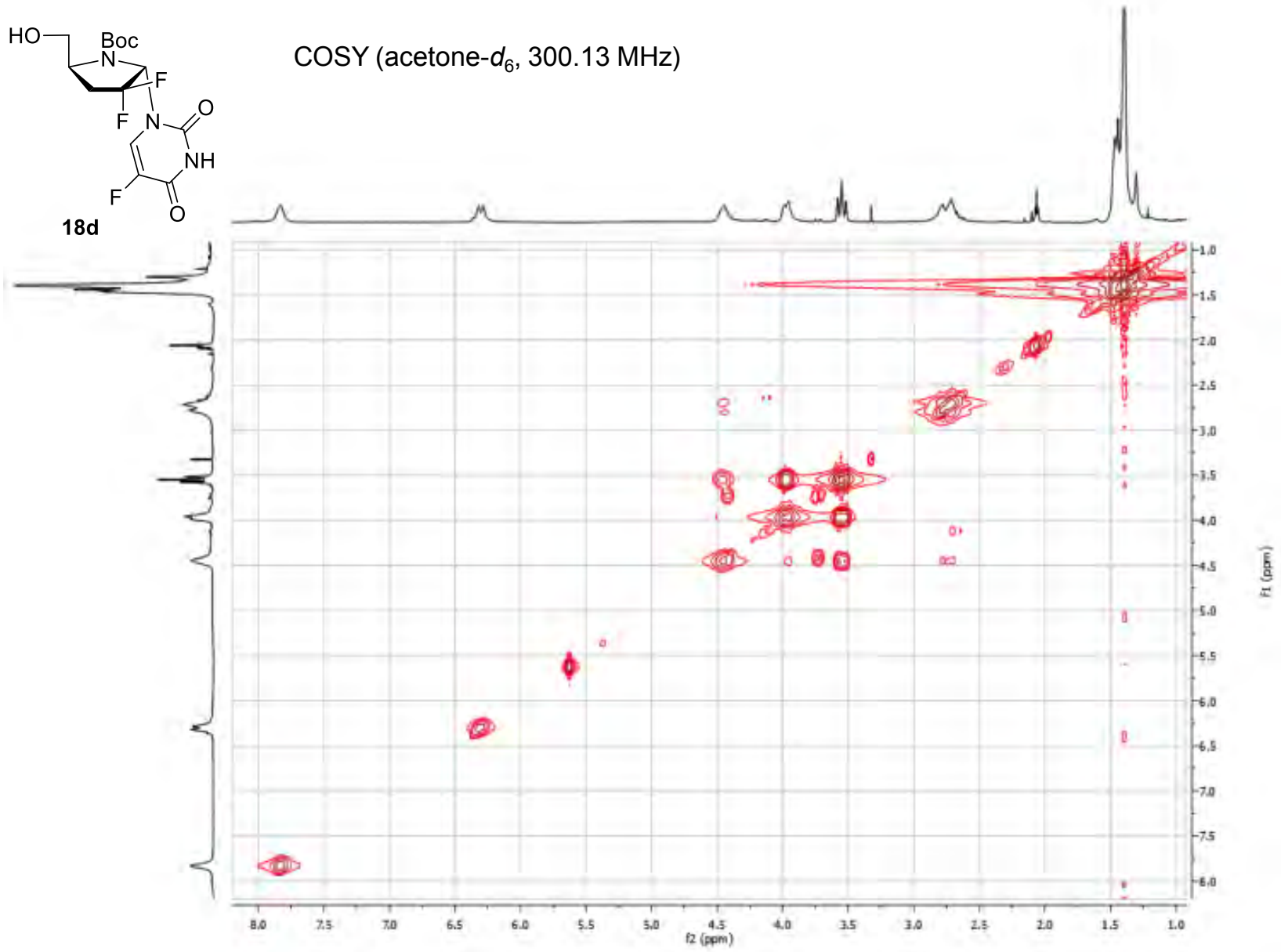


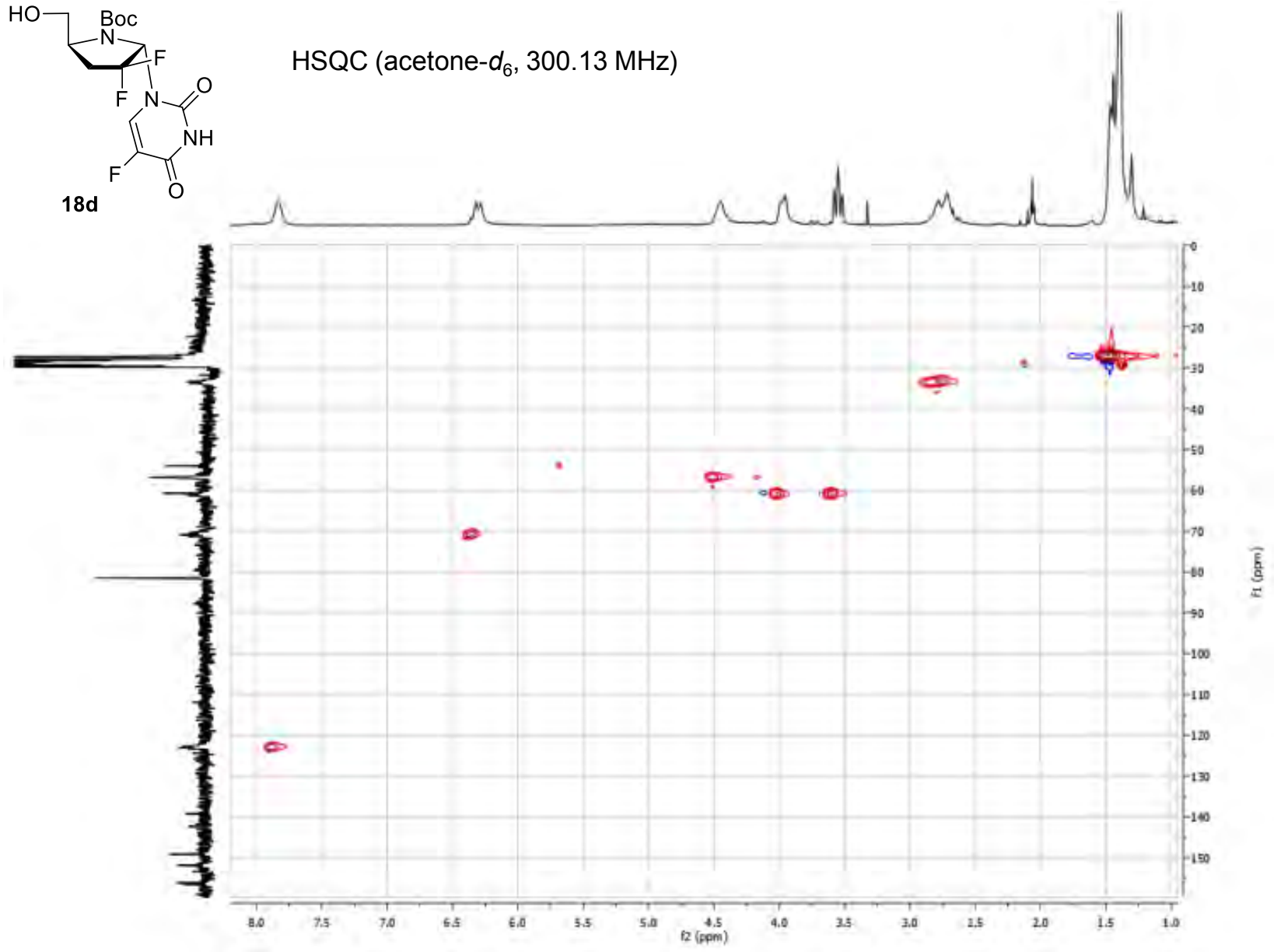
18d

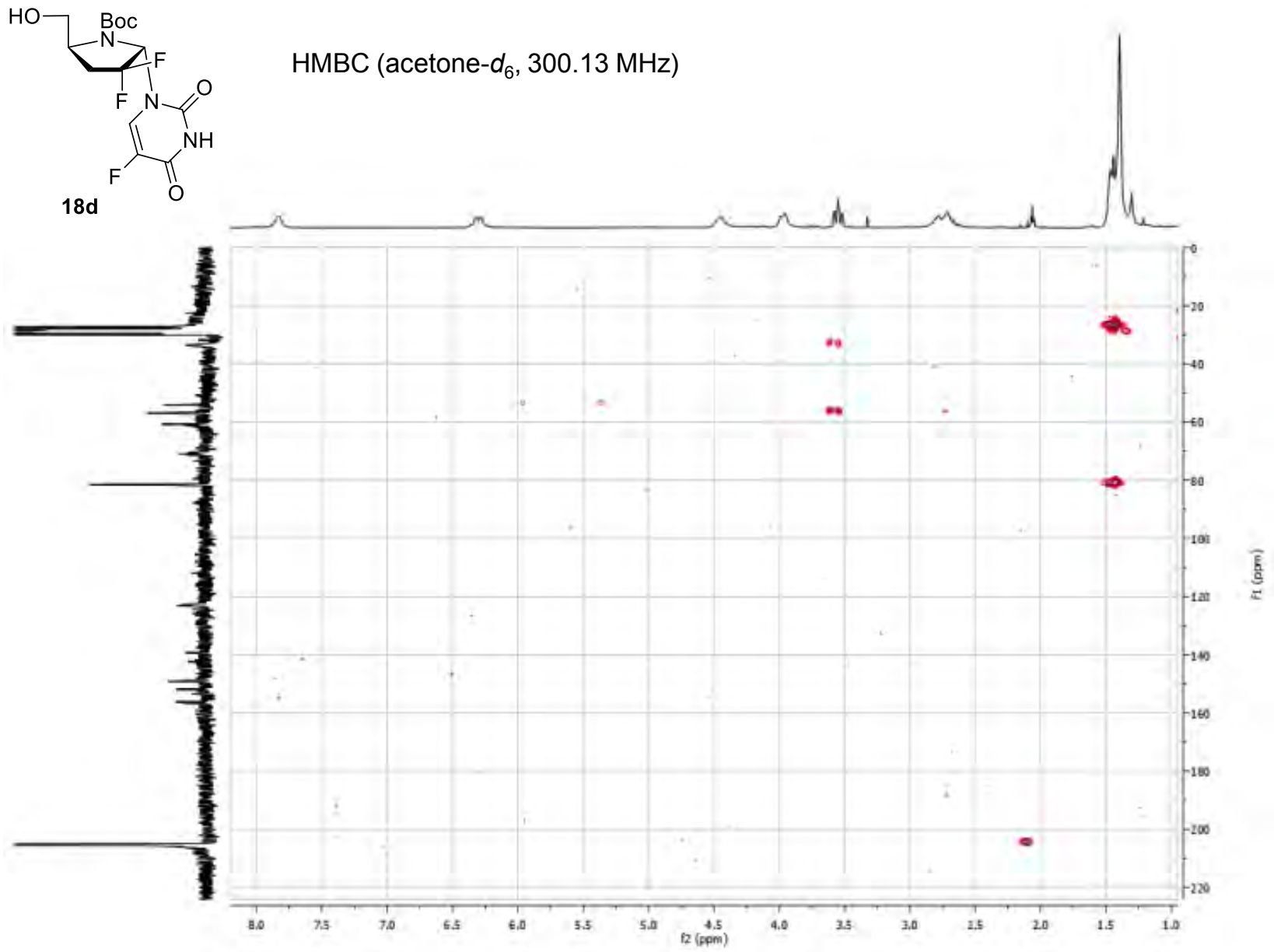
^{1}H NMR (acetone-d_6, 300.13 MHz)

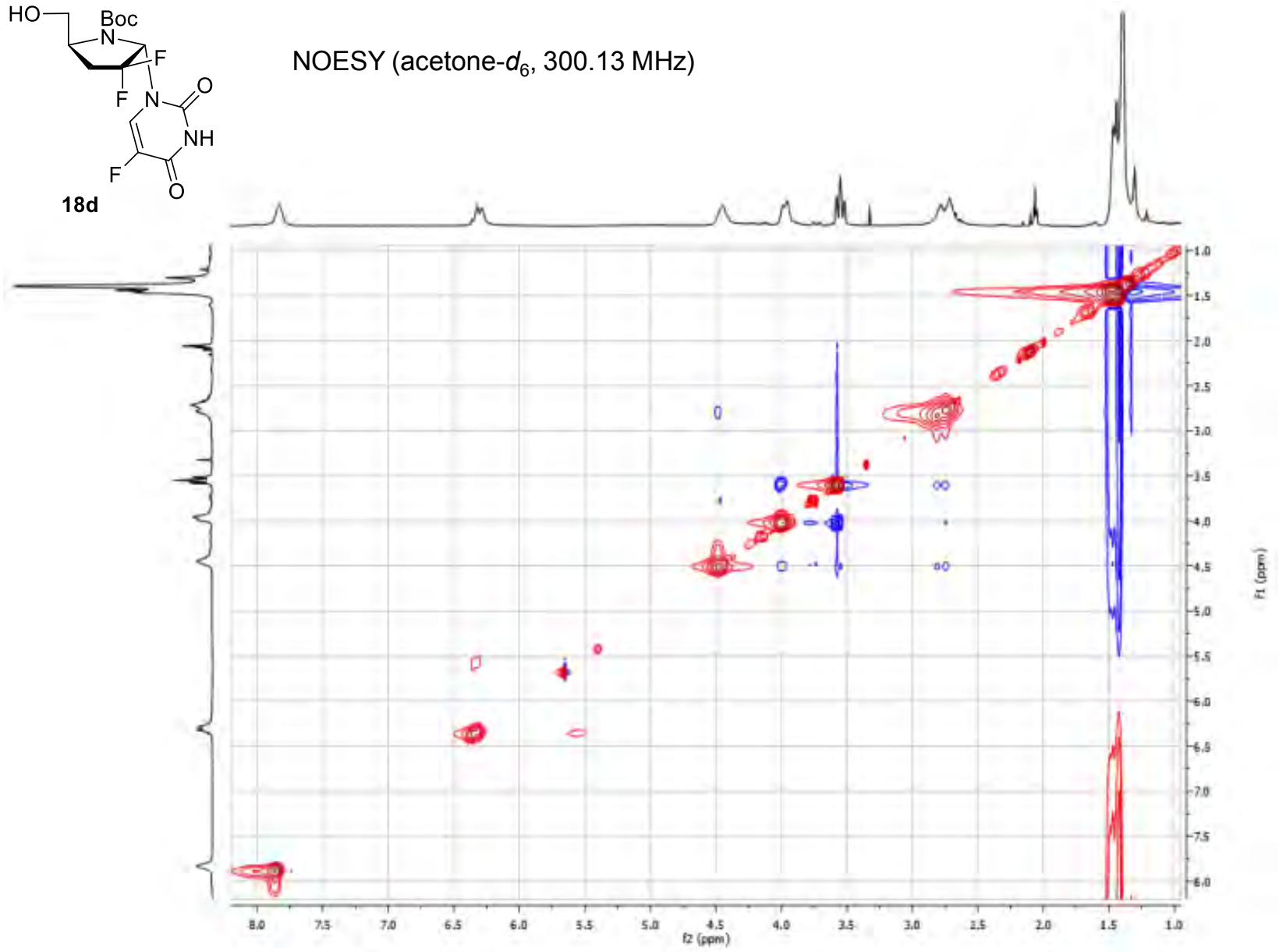



HO
Boc
N
F
F
N
O
NH
F
O
18d
^{13}C NMR (acetone-d_6, 75.5 MHz)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
Boc
N
F
F
N
O
NH
F
O
18d
COSY (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)

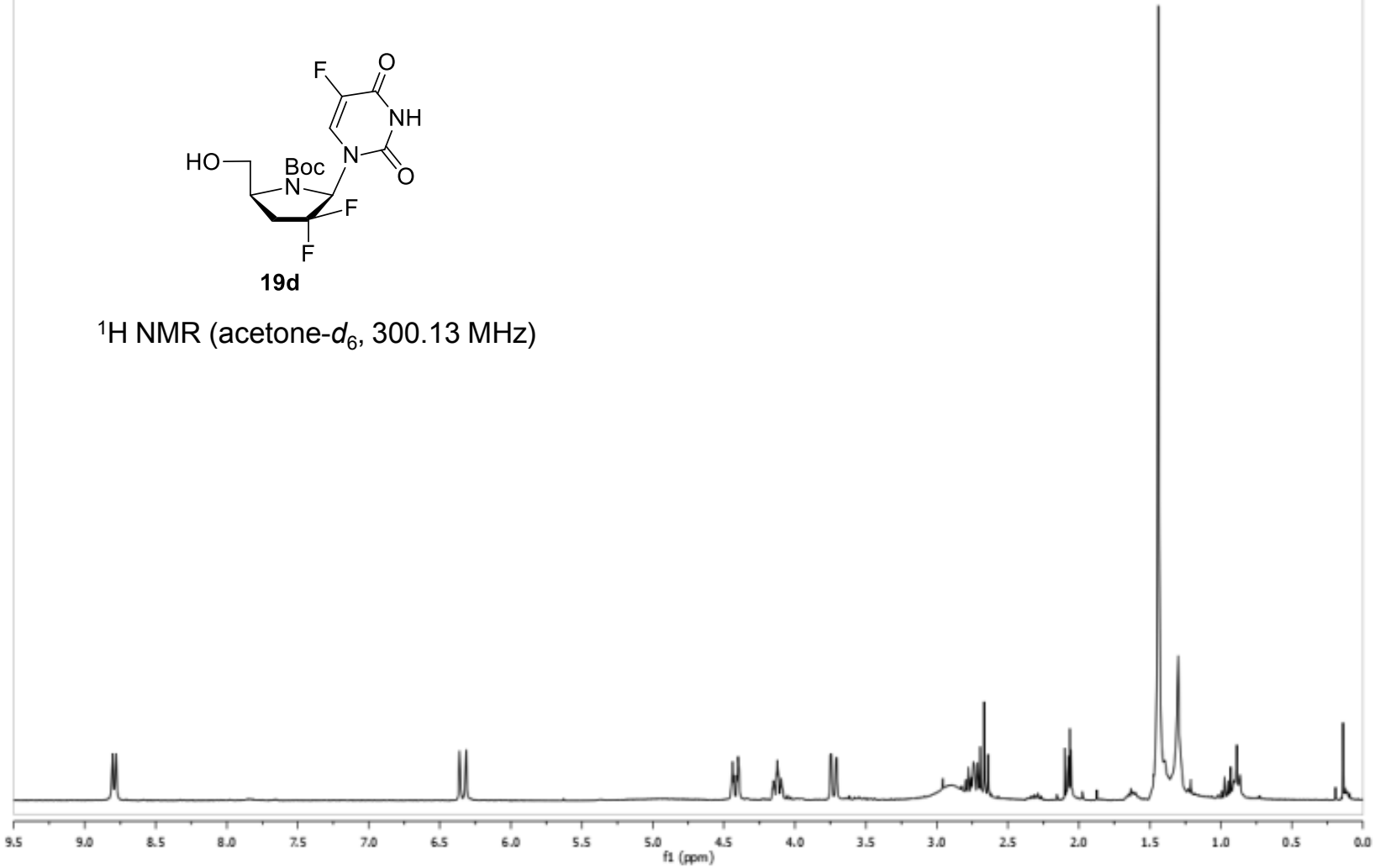

HO
Boc
N
F
F
N
O
NH
F
O
18d
HSQC (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
N
O
NH
F
O
18d
HMBC (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
N
O
NH
F
O
18d
NOESY (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)

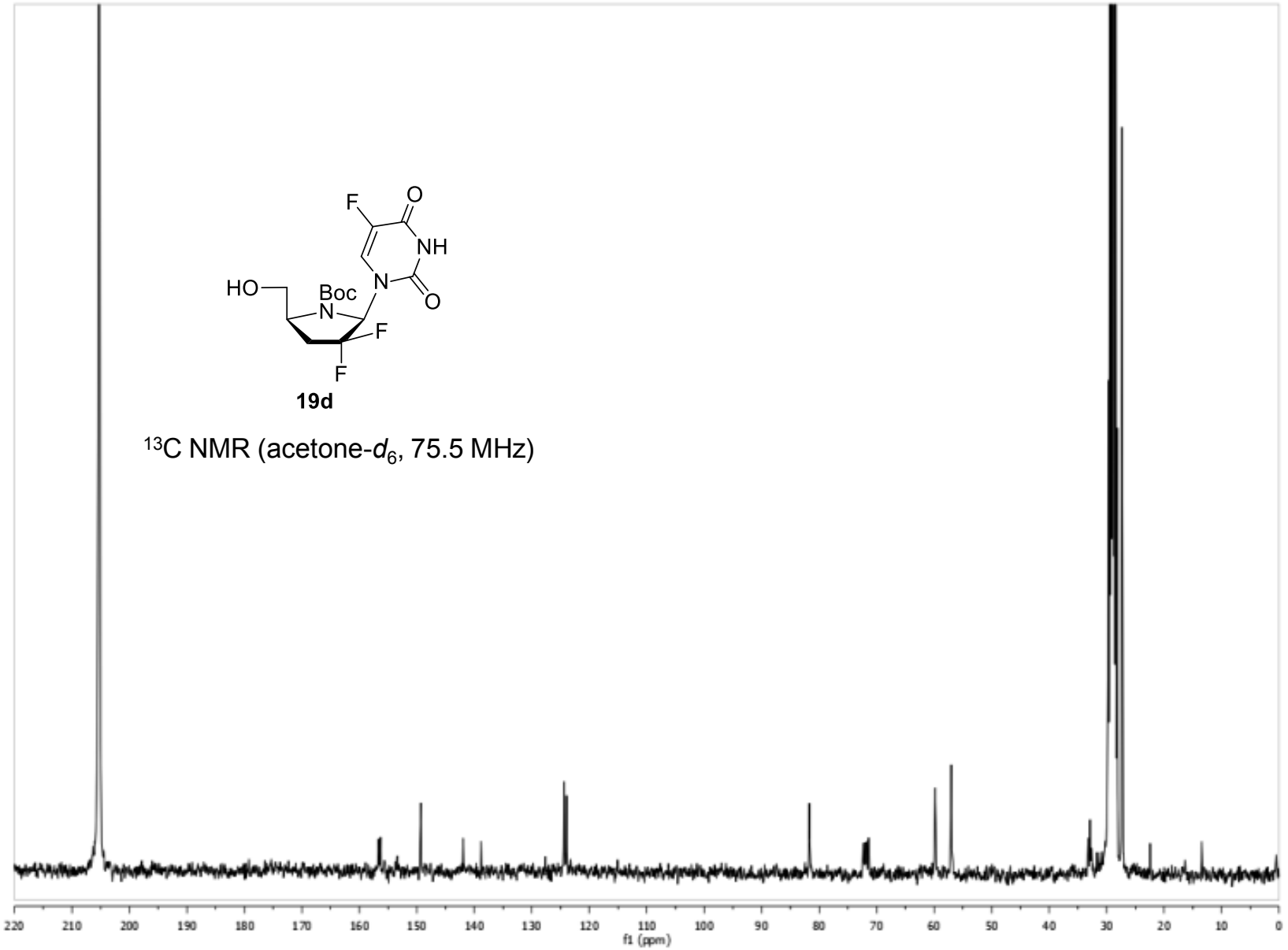
19d

^{1}H NMR (acetone-d_6, 300.13 MHz)



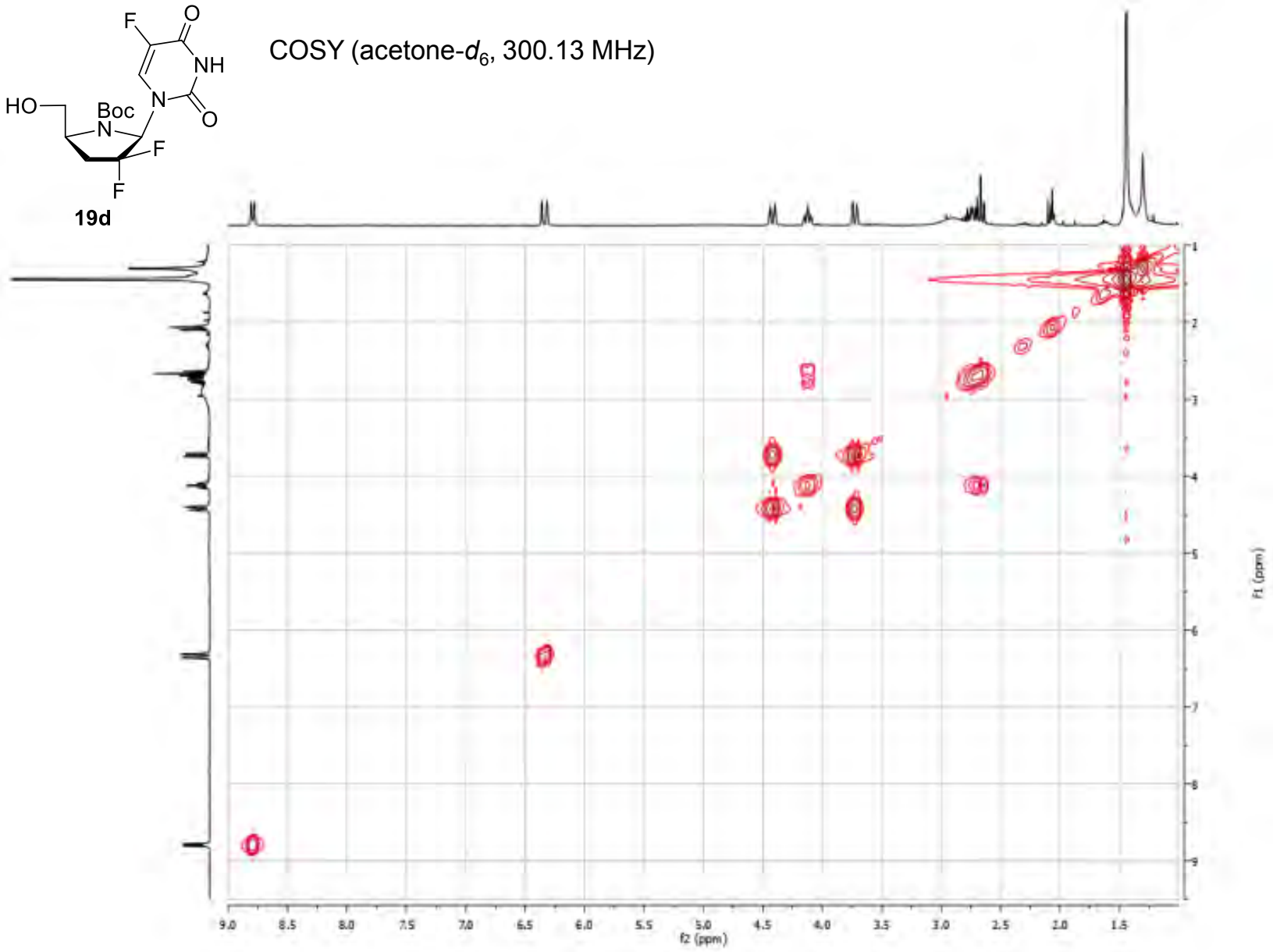
19d

^{13}C NMR (acetone-d_6, 75.5 MHz)



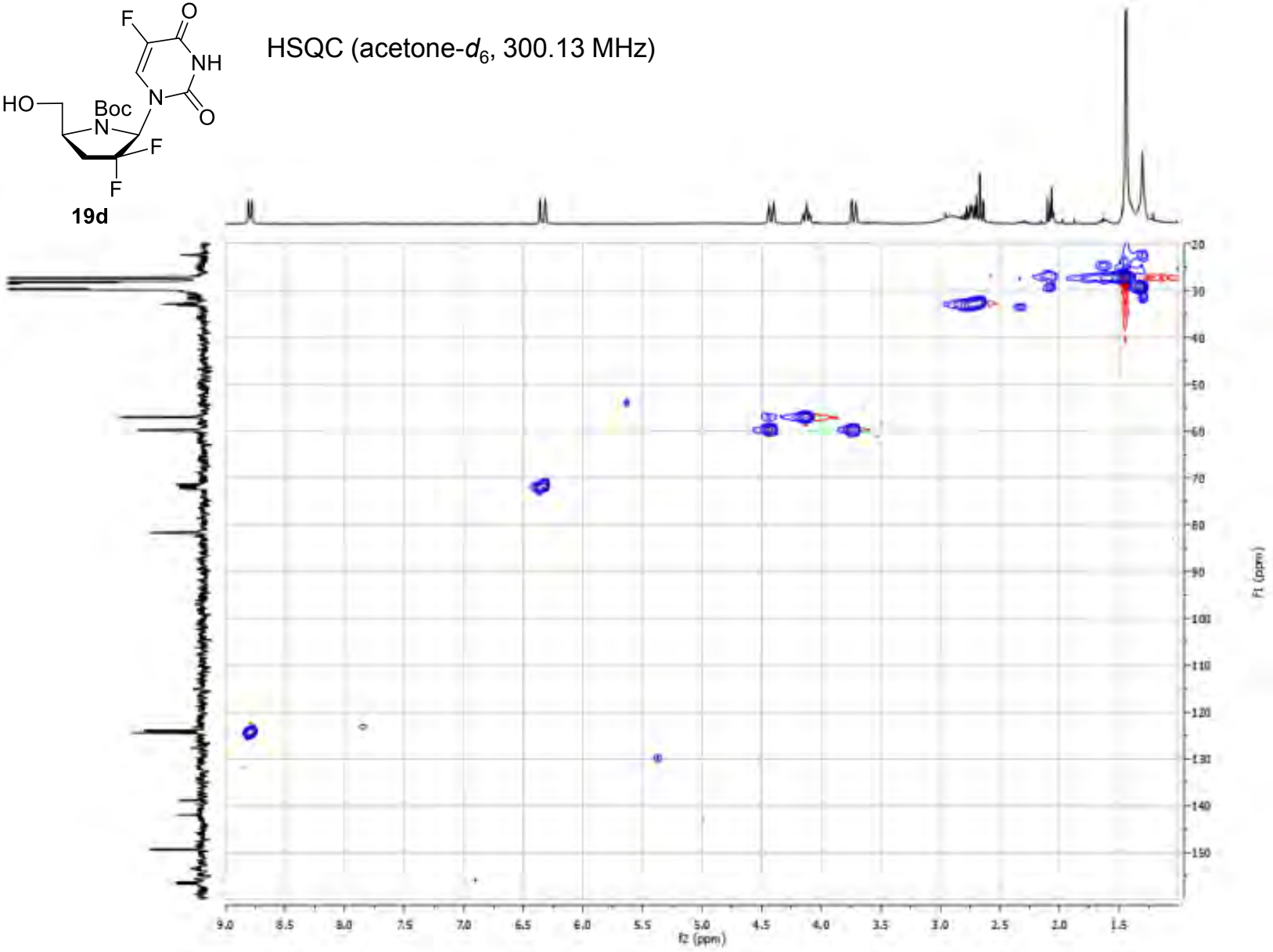
19d

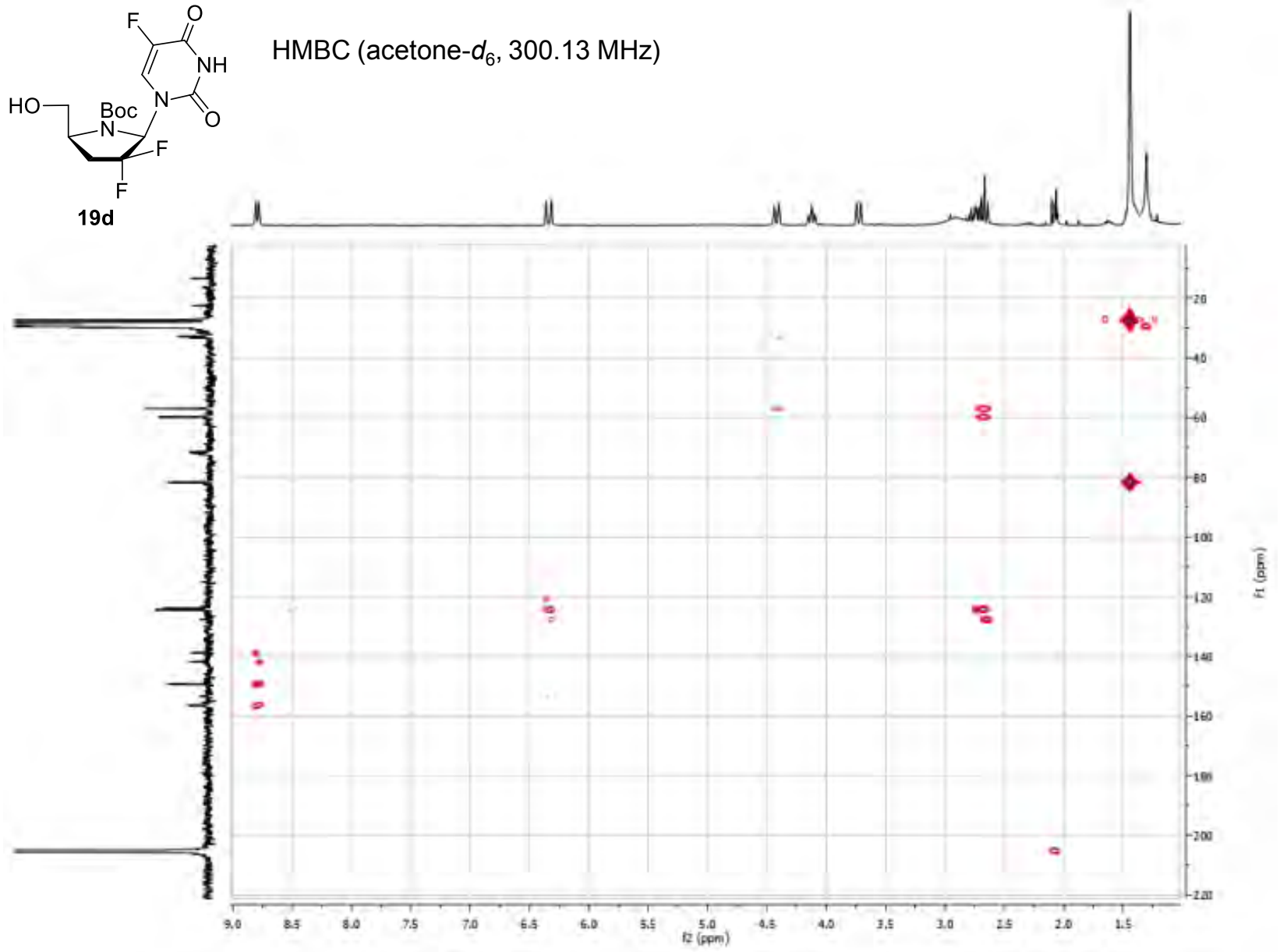
COSY (acetone-d_6, 300.13 MHz)

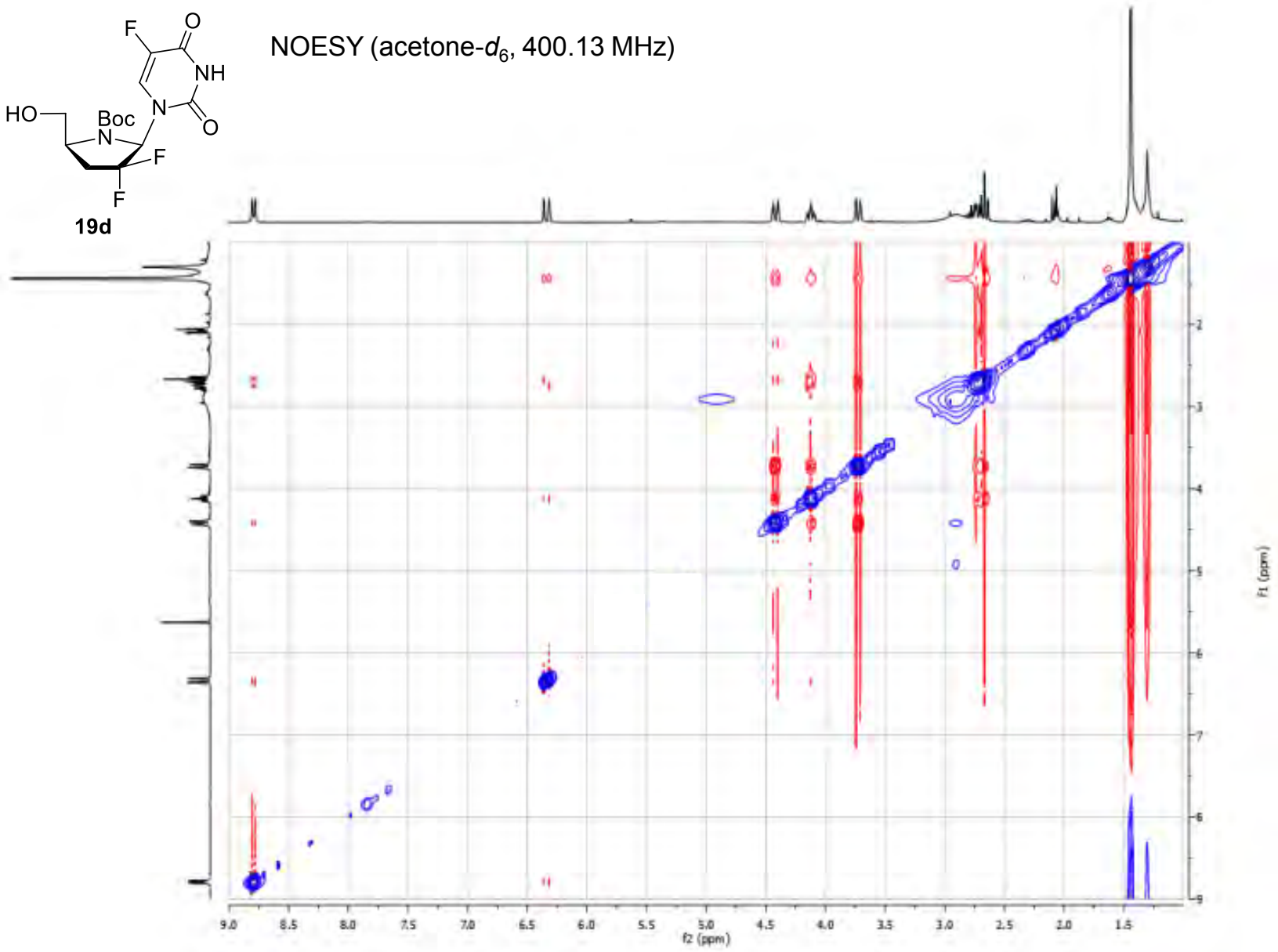


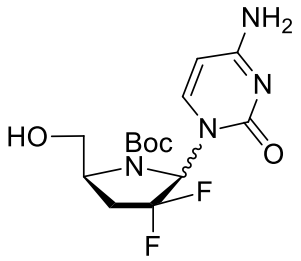
19d

HSQC (acetone-d_6, 300.13 MHz)



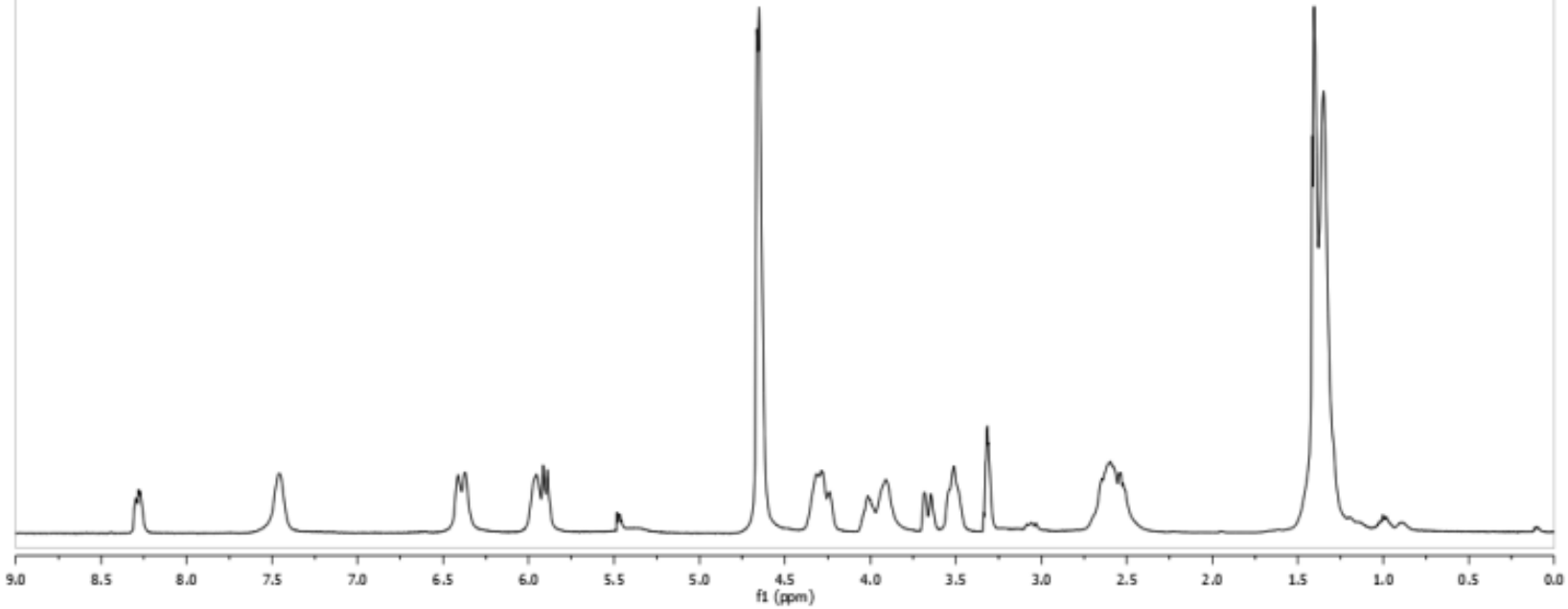

F
O
NH
N
O
HO
Boc
N
F
F
19d
HMBC (acetone-d_6, 300.13 MHz)
f2 (ppm)
f1 (ppm)


F
O
NH
N
O
HO
Boc
N
F
F
19d
NOESY (acetone-d_6, 400.13 MHz)
f2 (ppm)
f1 (ppm)



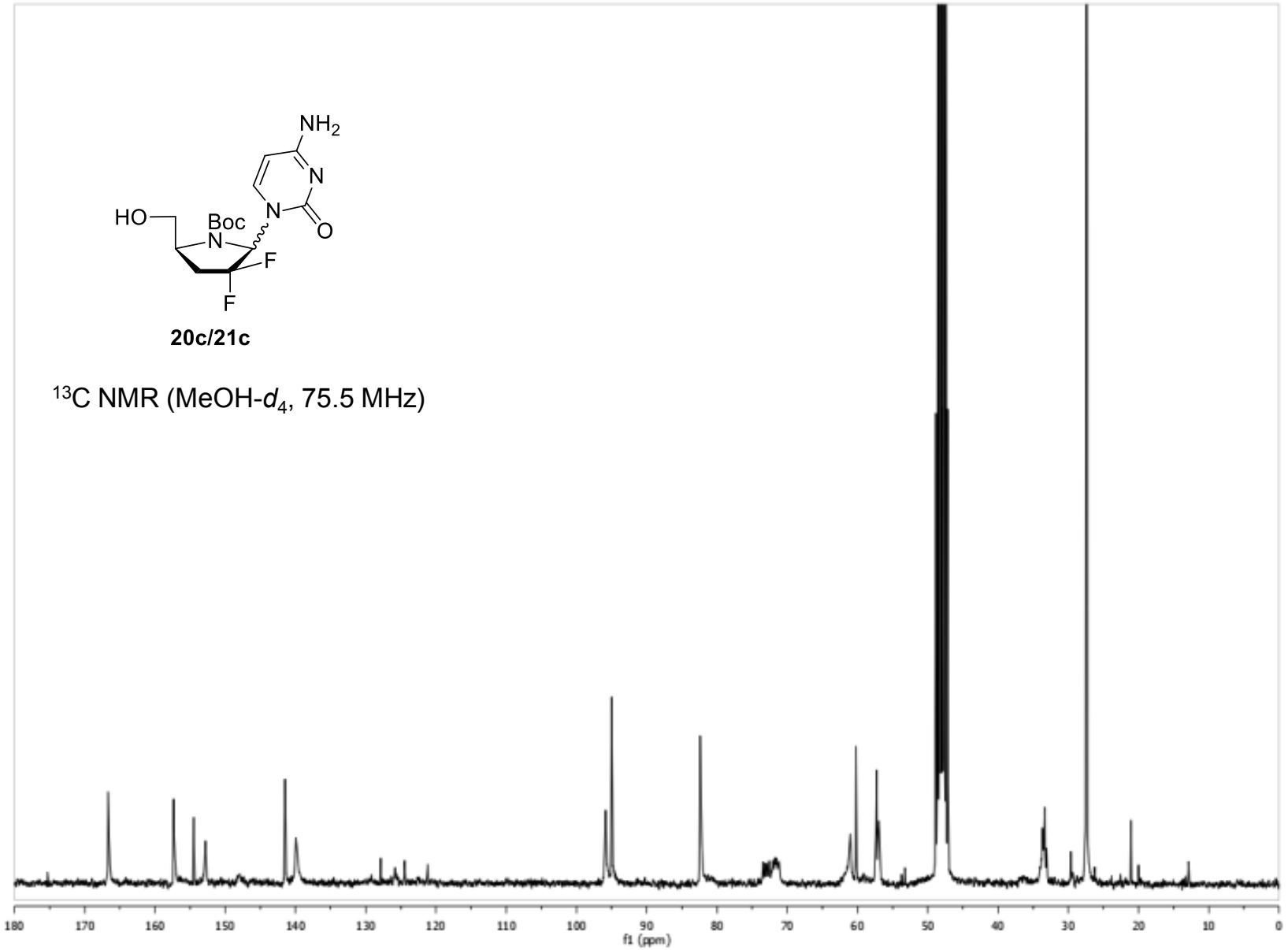
20c/21c

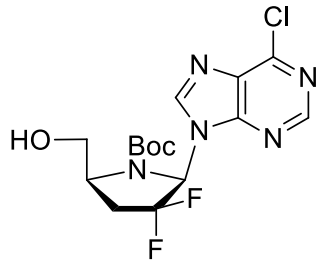
^{1}H NMR (MeOH-d_4, 300.13 MHz)



20c/21c

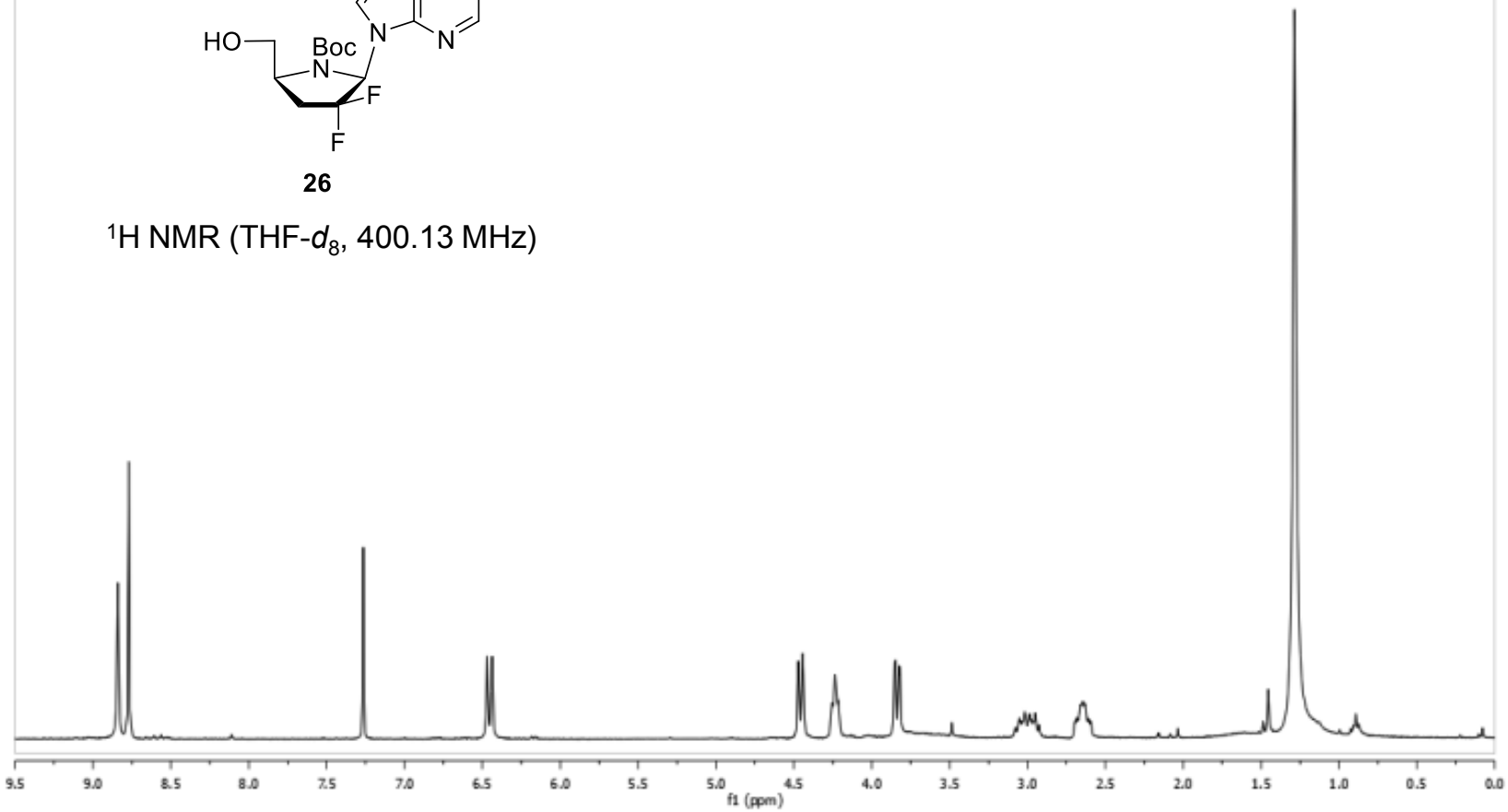
^{13}C NMR (MeOH-d_4, 75.5 MHz)

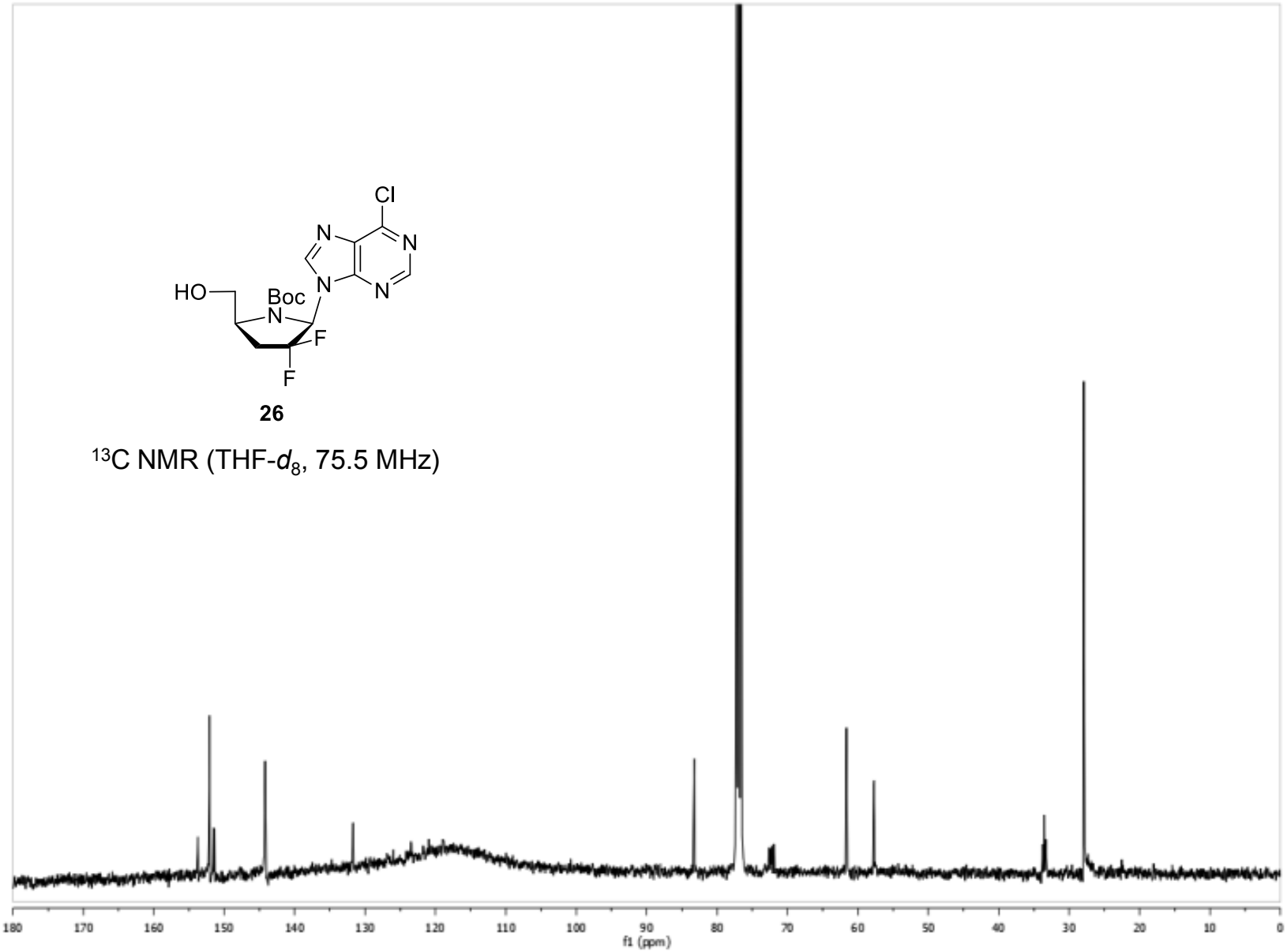




26

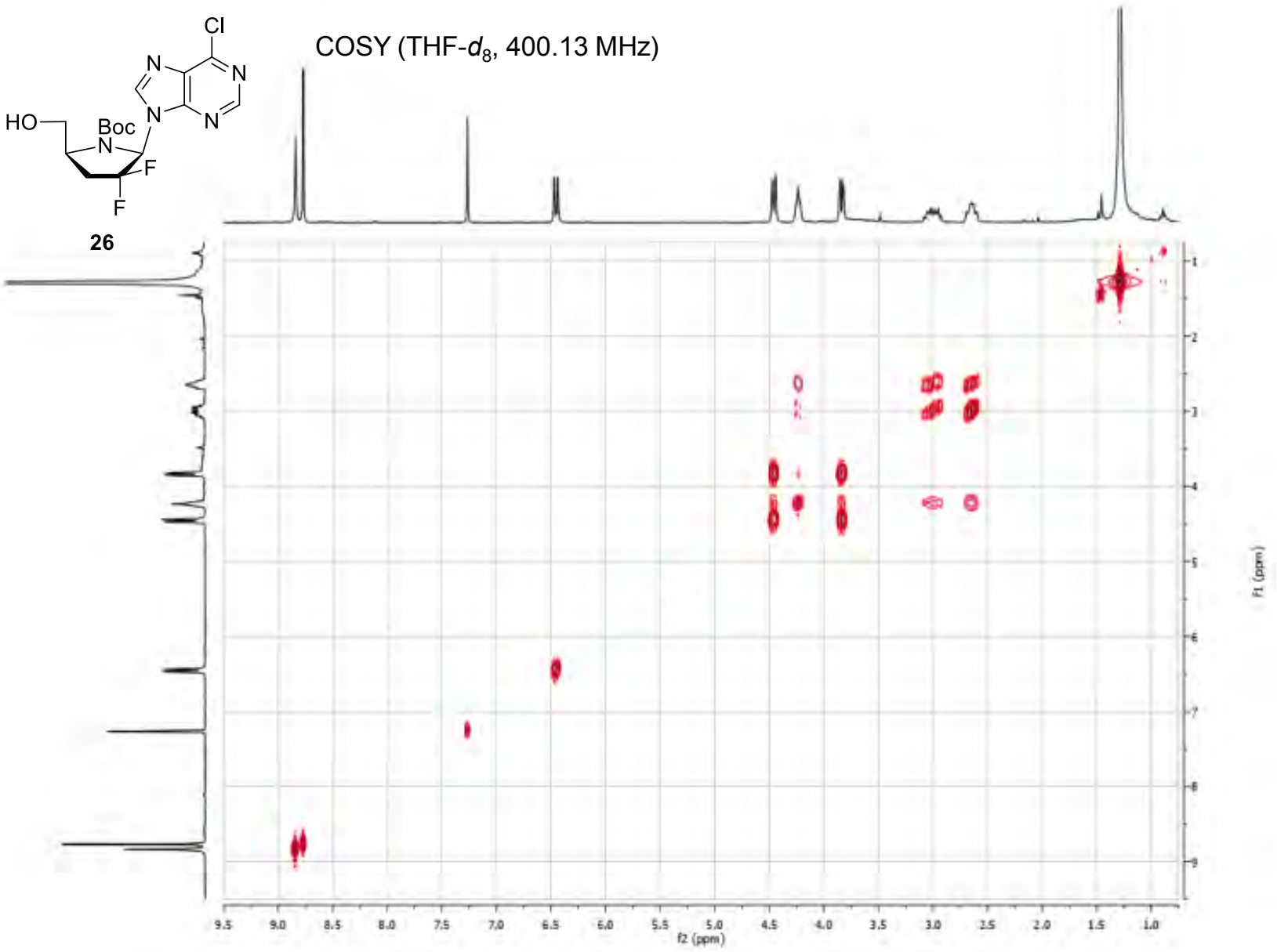
^{1}H NMR (THF-d_8, 400.13 MHz)

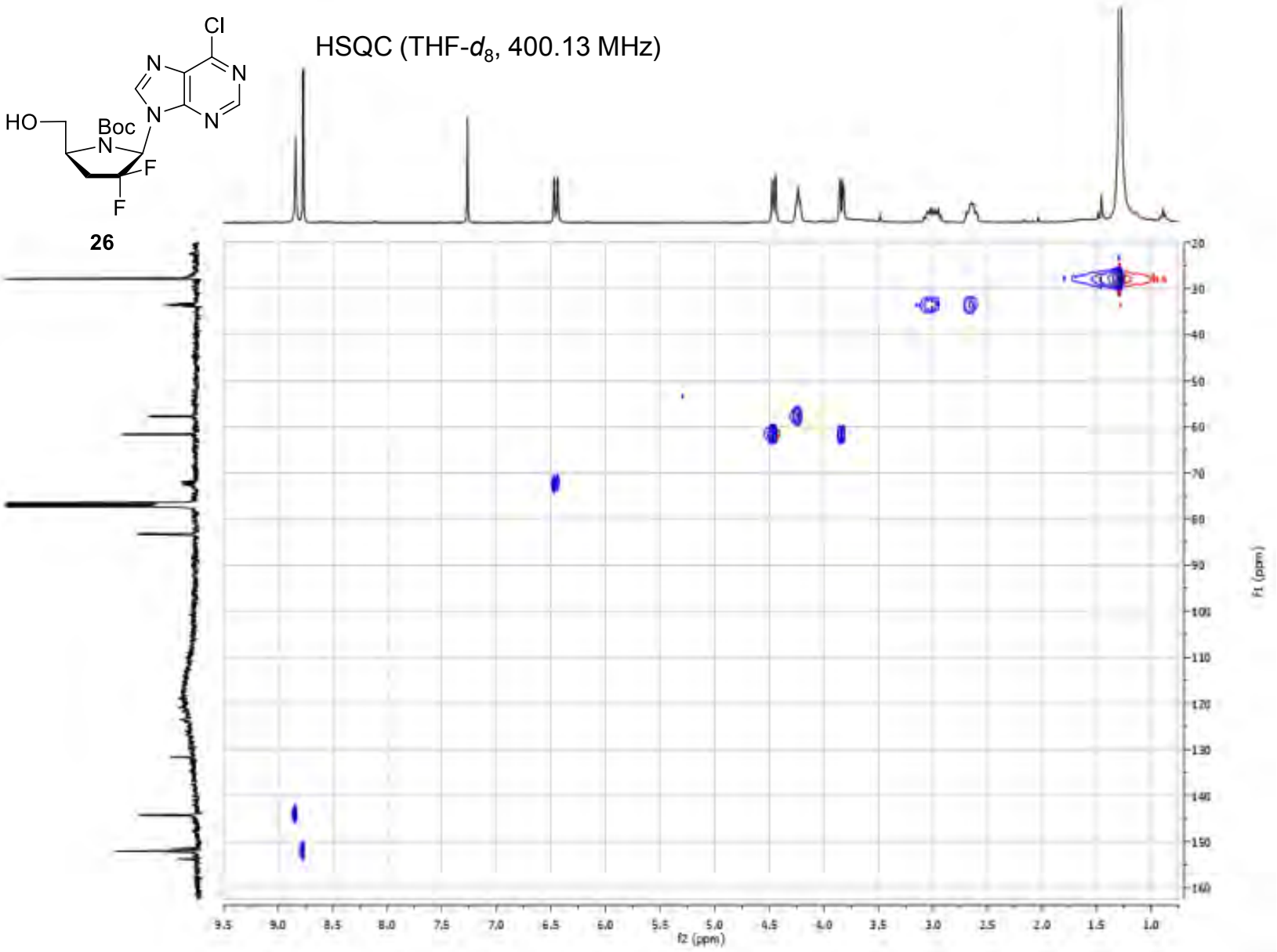




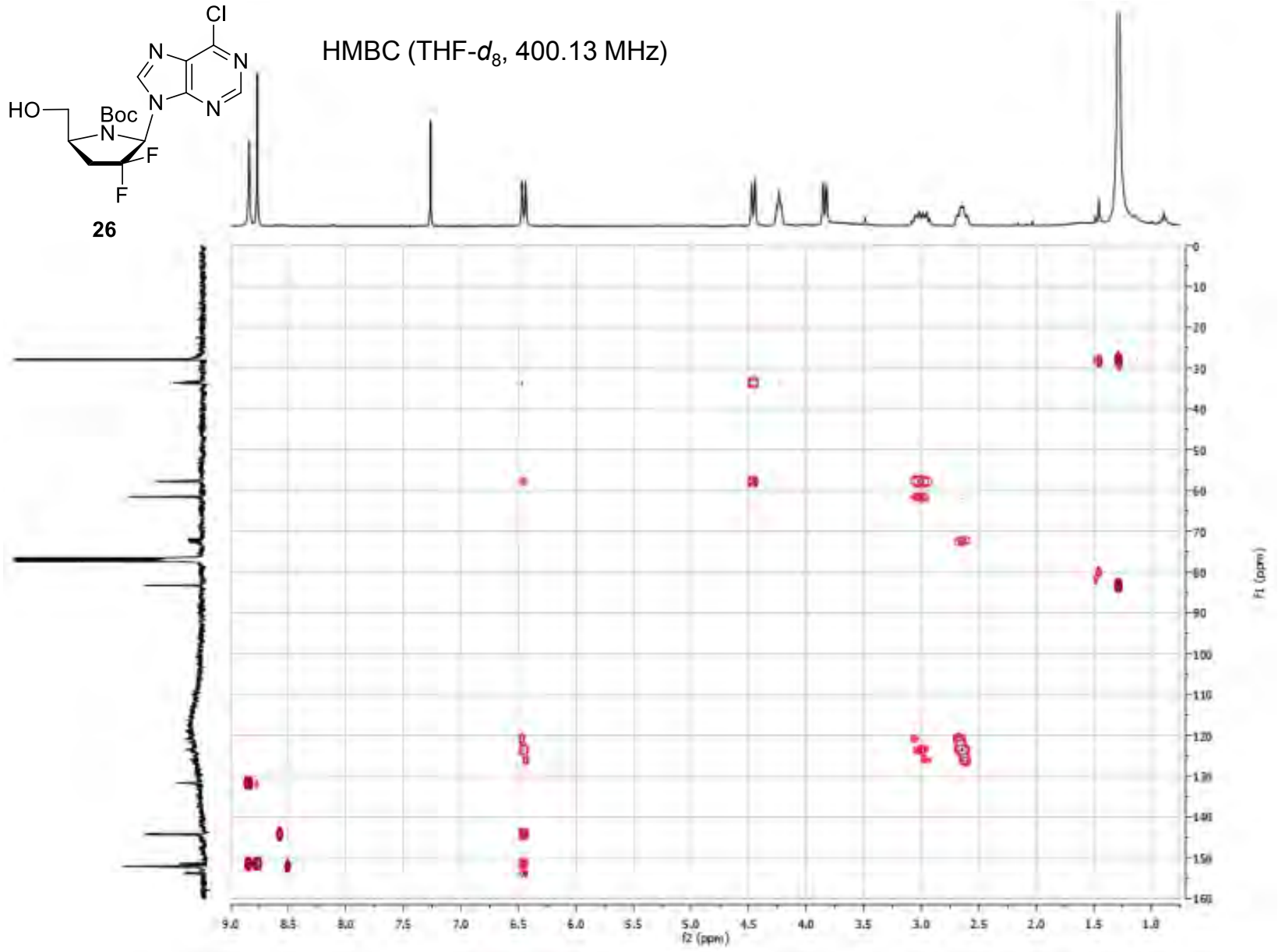
26

^{13}C NMR (THF-d_8, 75.5 MHz)

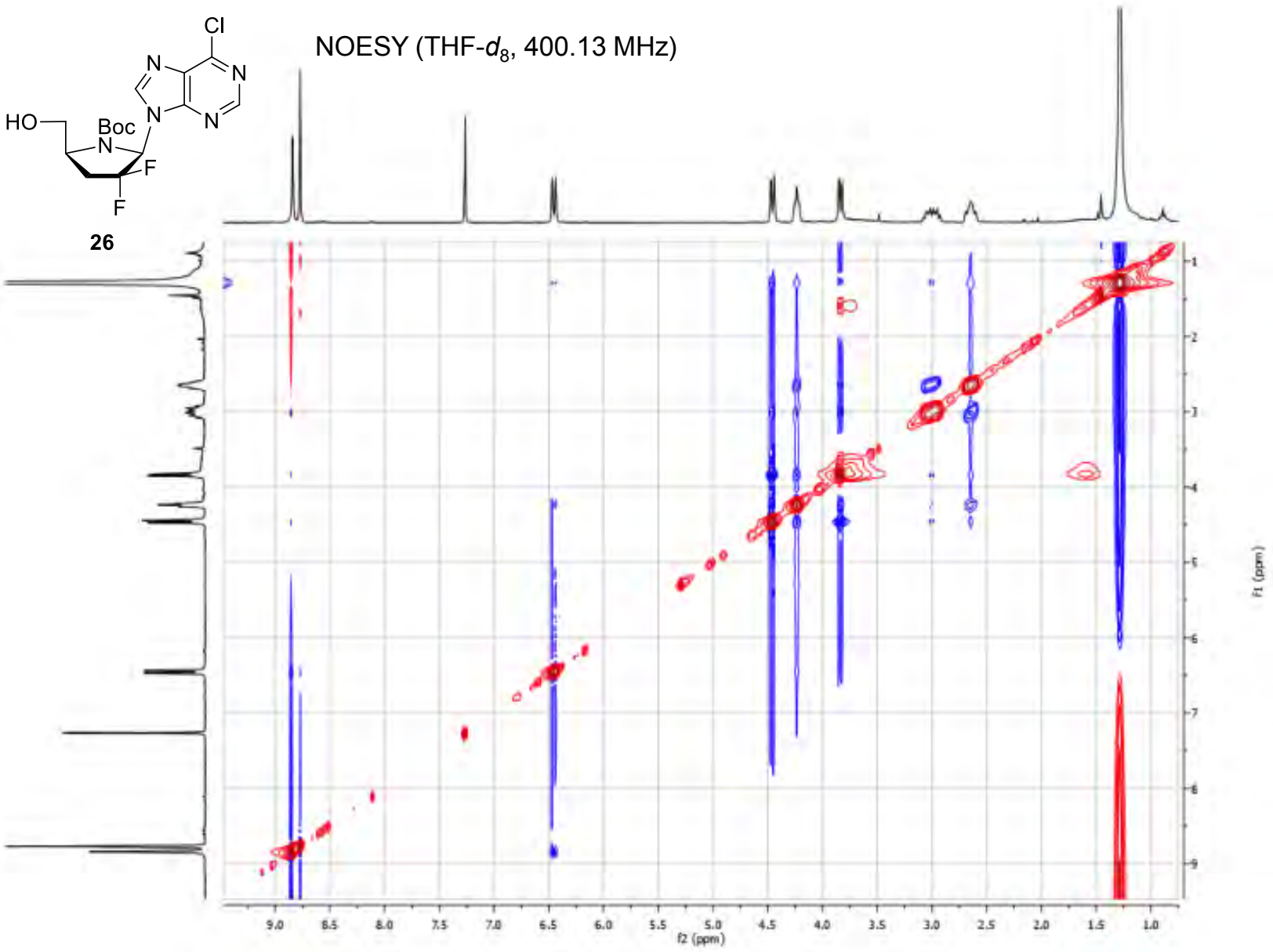

Cl
N
N
N
N
HO
Boc
N
F
F
26
COSY (THF-d_8, 400.13 MHz)
f2 (ppm)
f1 (ppm)



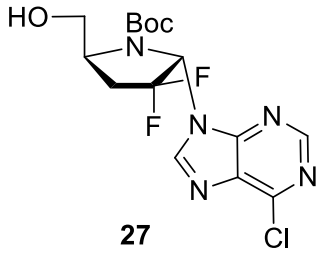
26



26

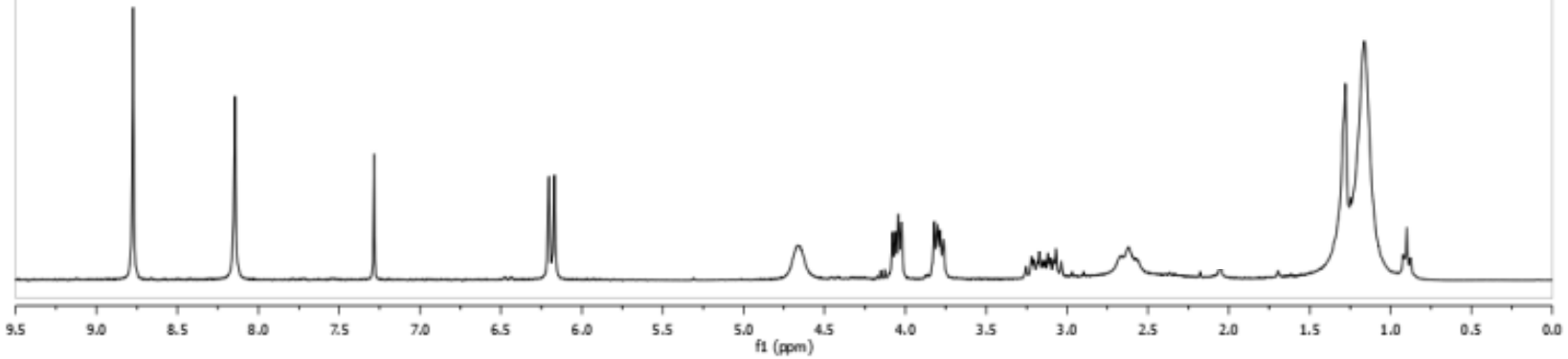


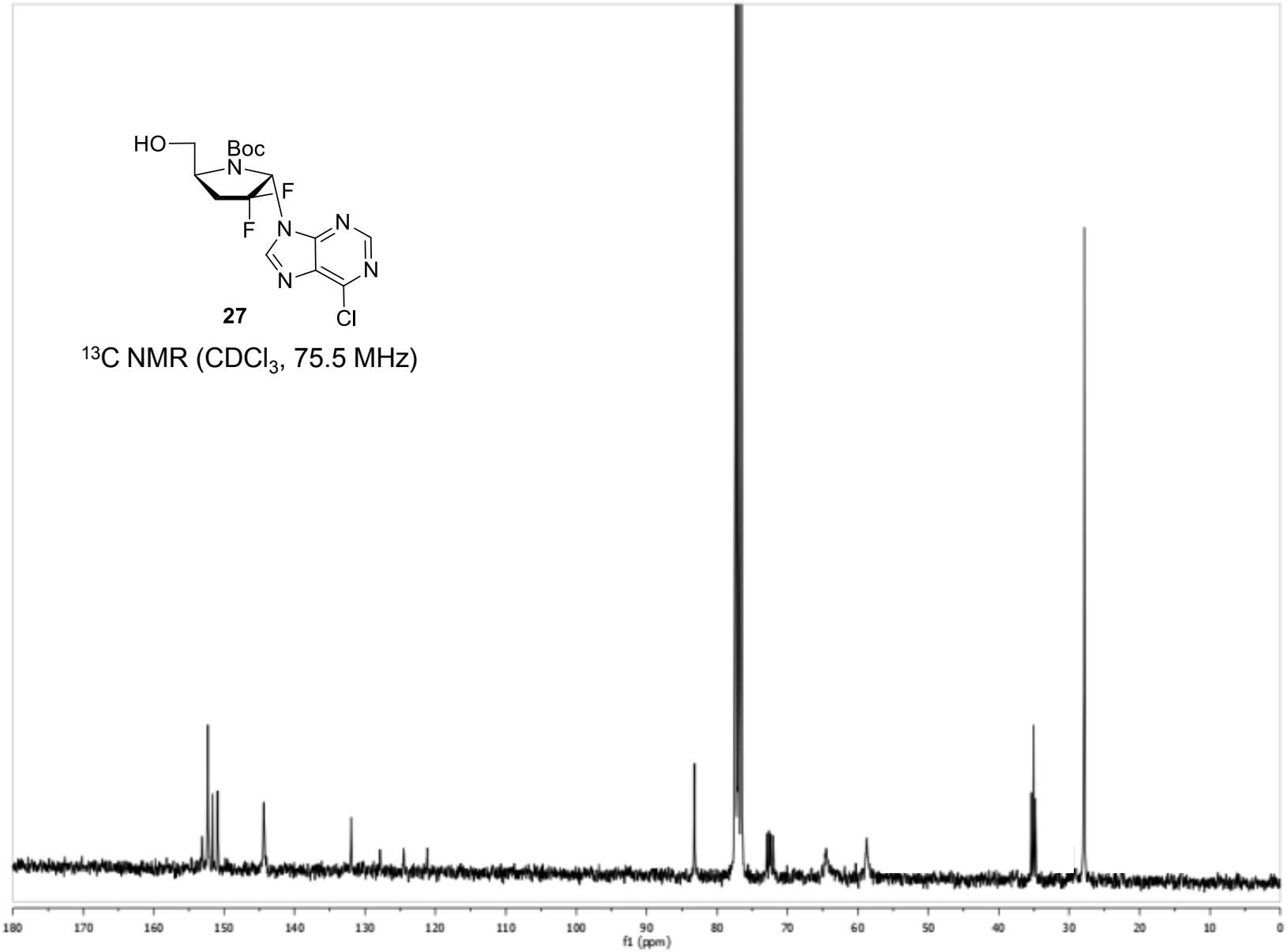
26

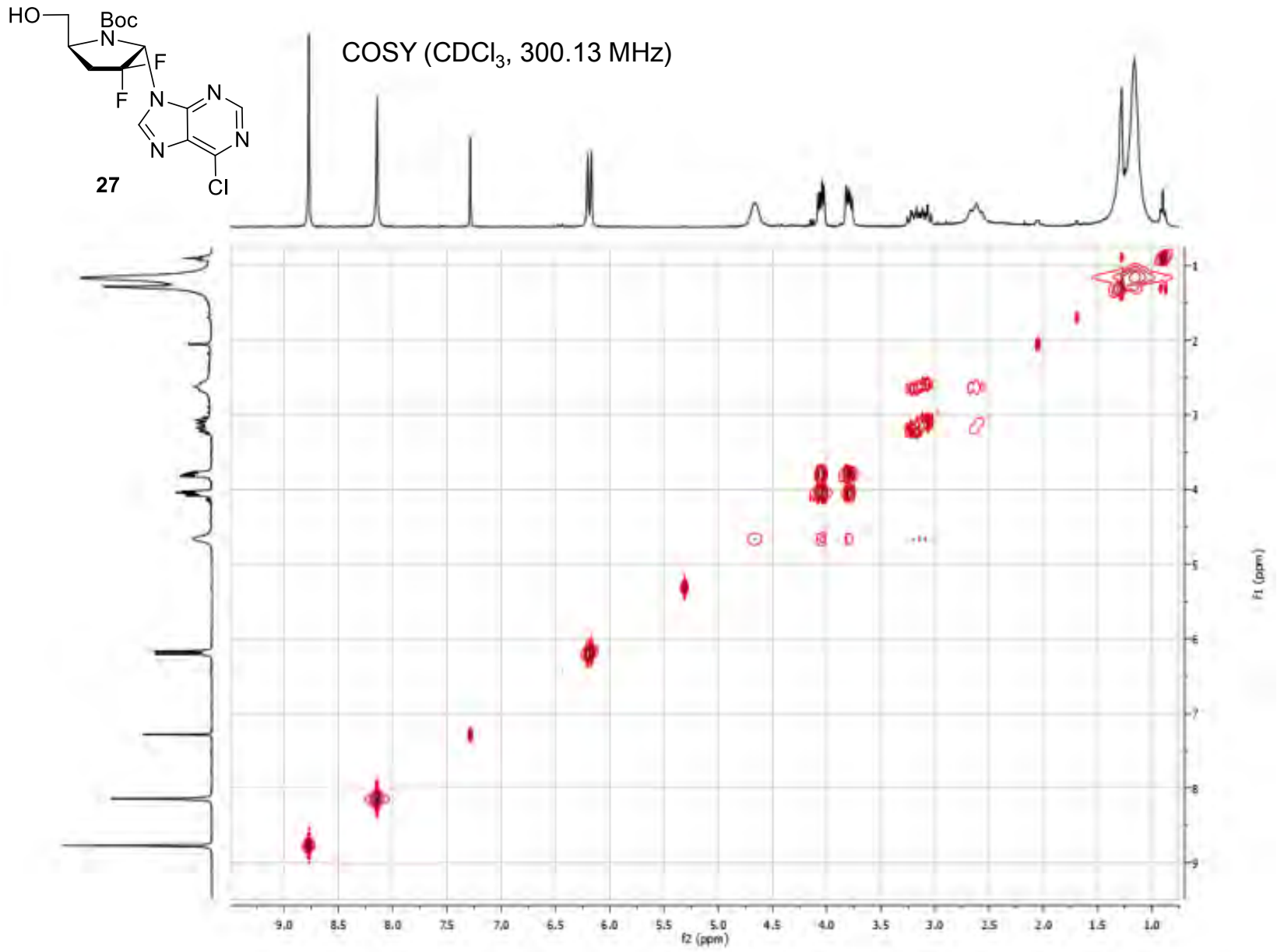


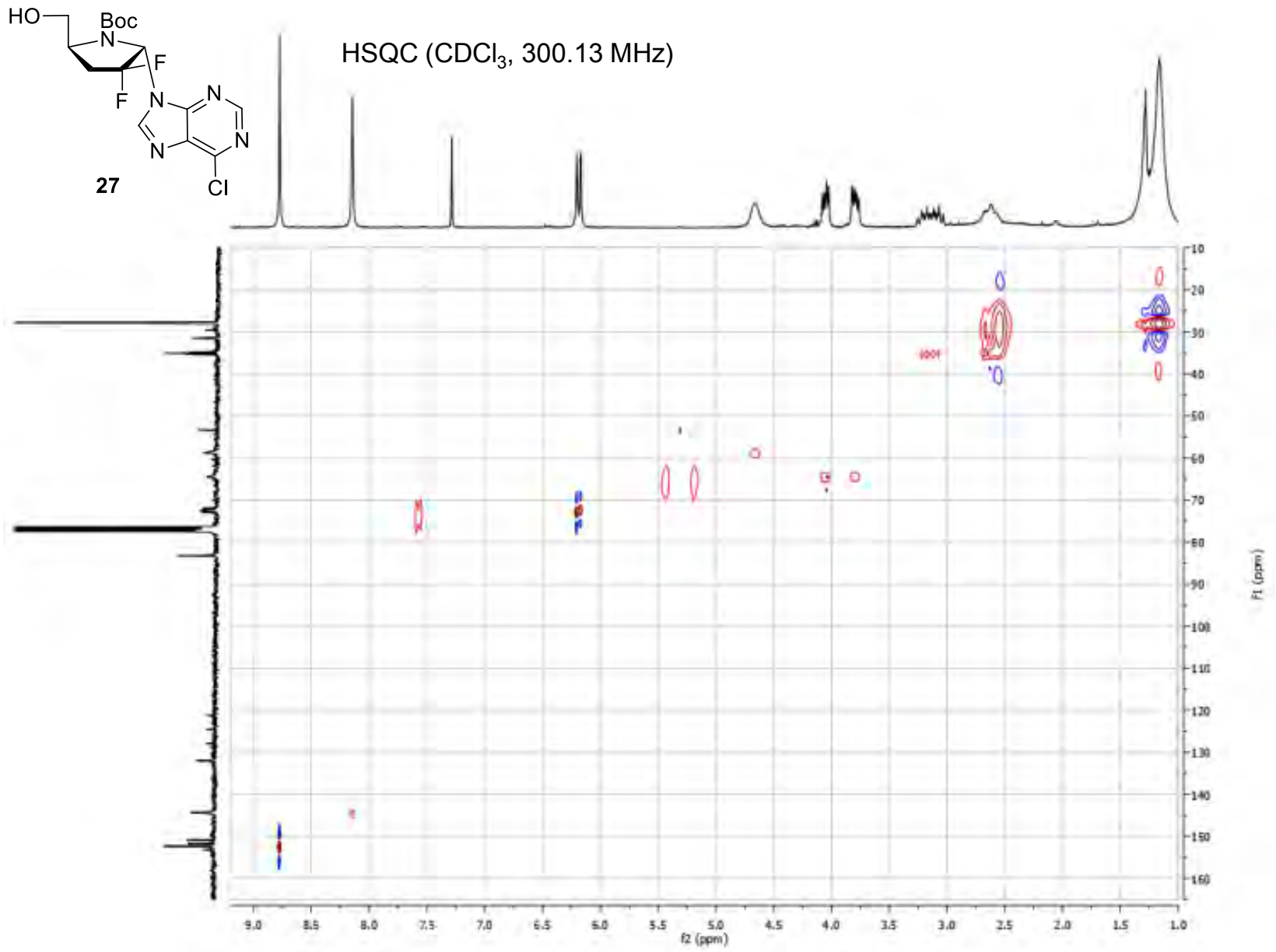
27

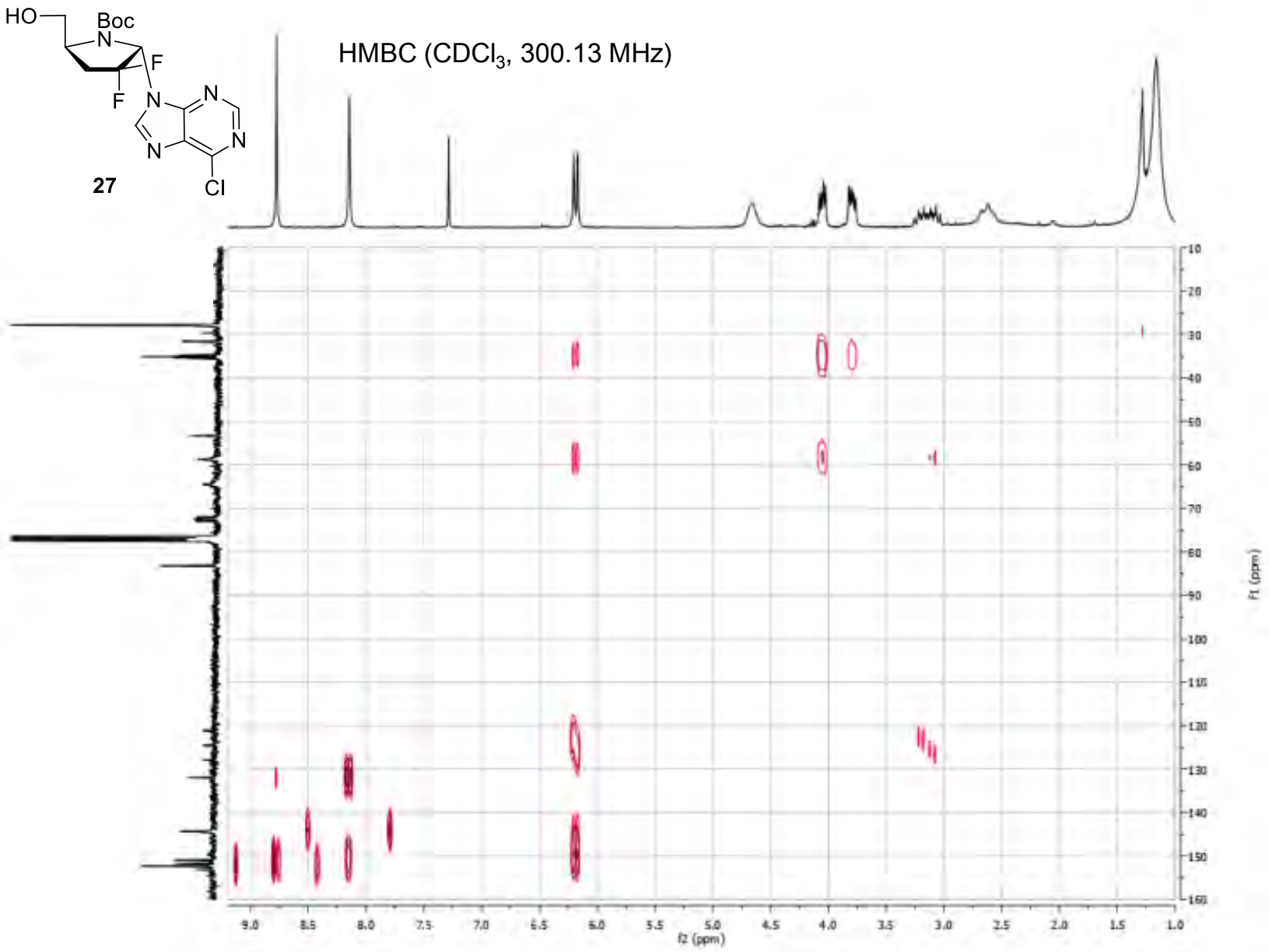
^{1}H NMR ($CDCl_3$, 300.13 MHz)

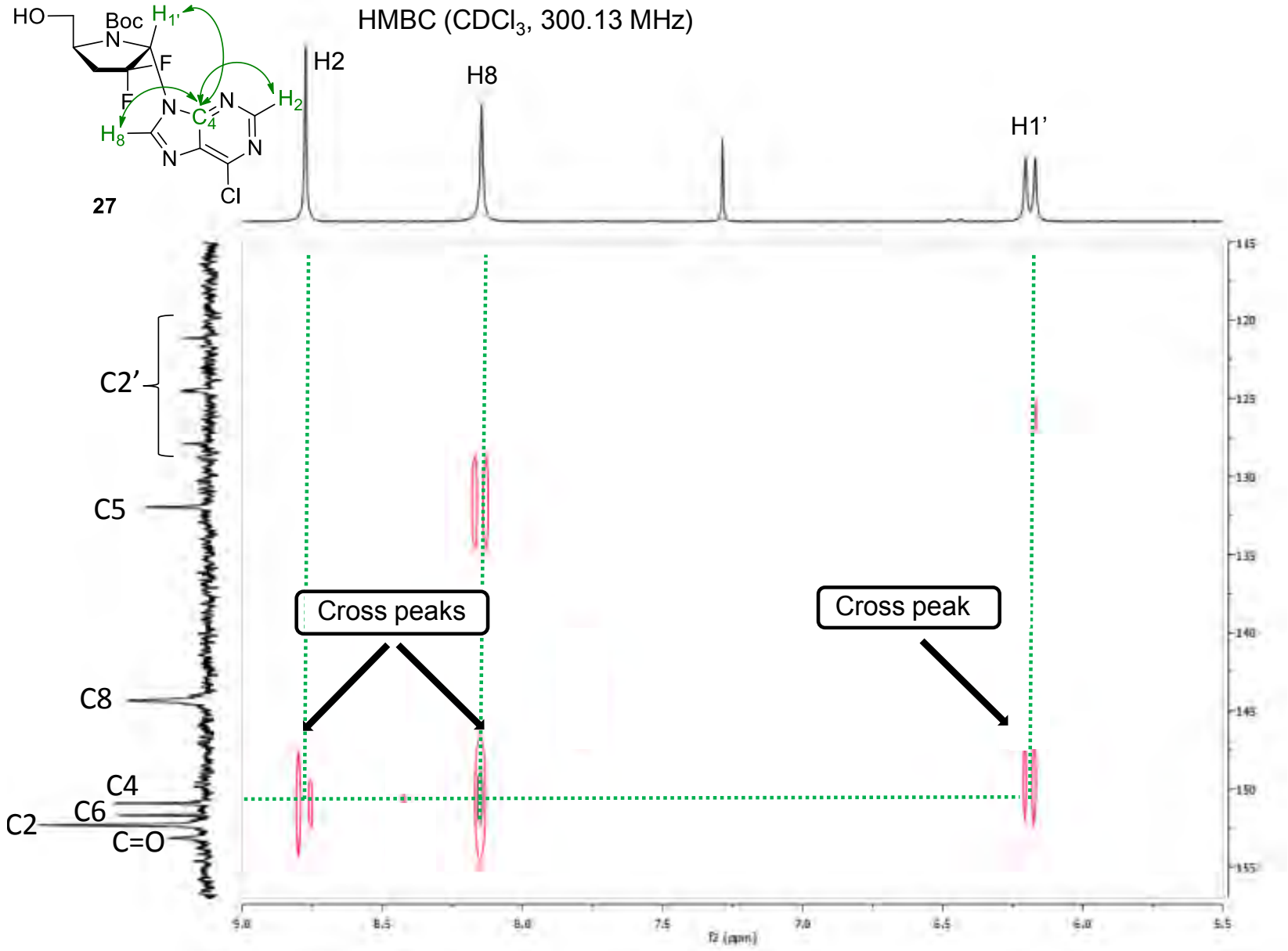


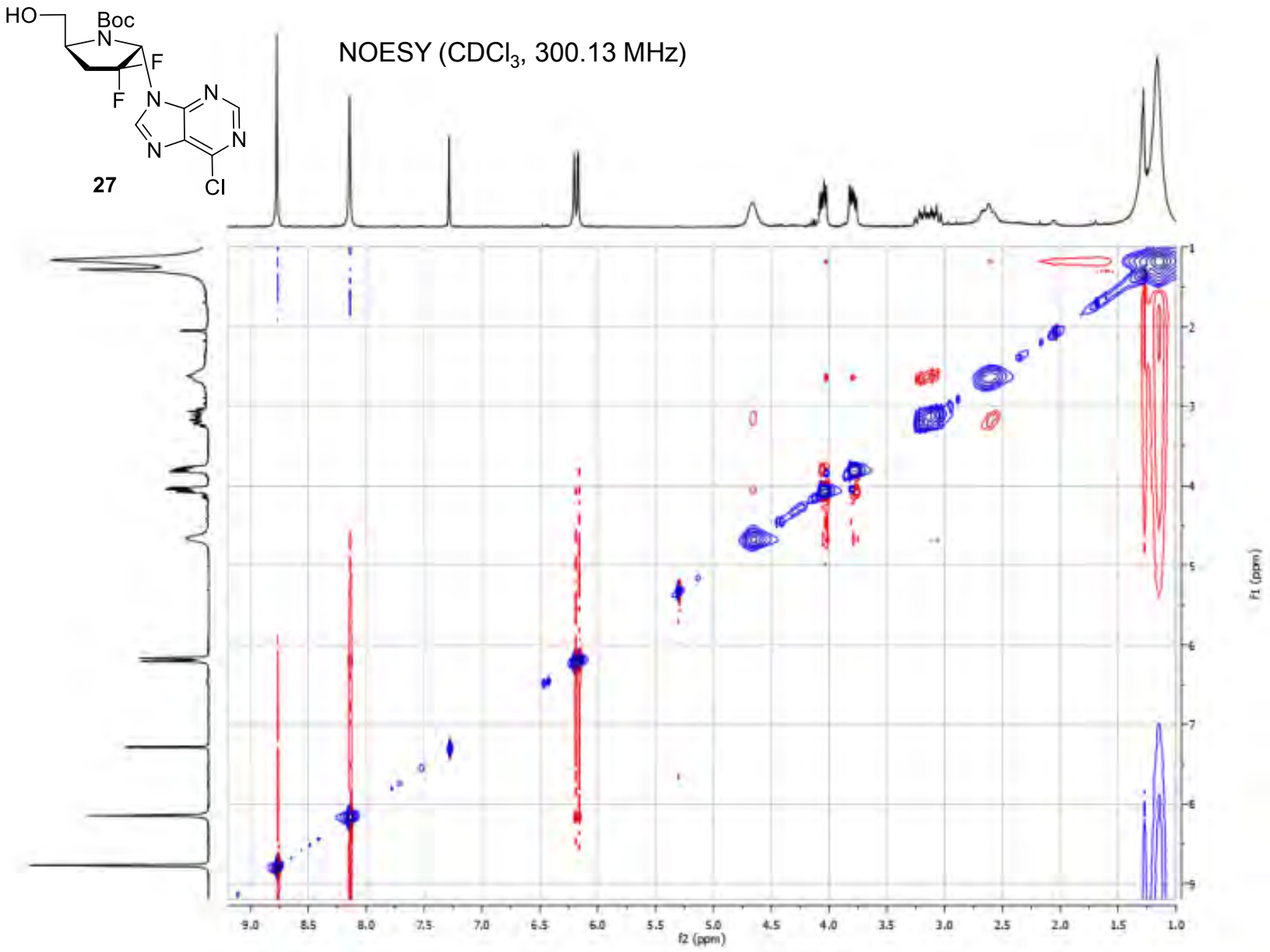

HO
Boc
N
F
F
N
N
N
N
Cl
27
^{13}C NMR ($CDCl_3$, 75.5 MHz)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

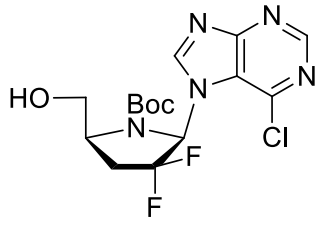

HO
Boc
N
F
F
N
N
N
N
Cl
27
COSY ($CDCl_3$, 300.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
N
N
N
N
Cl
27
HSQC ($CDCl_3$, 300.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
N
N
N
N
Cl
27
HMBC ($CDCl_3$, 300.13 MHz)
f2 (ppm)
f1 (ppm)

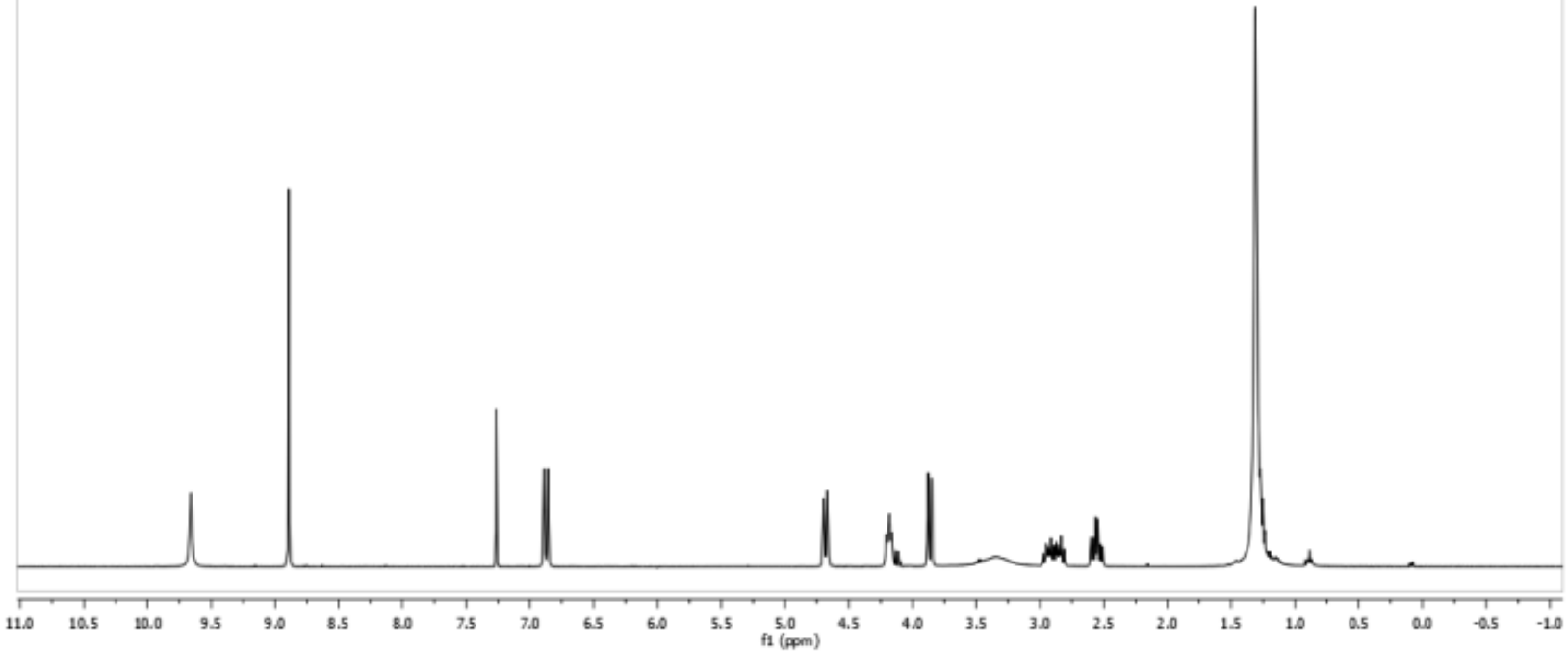

HO
Boc
N
F
F
$H_{1'}$
H_2
H_8
N
C_4
N
N
N
Cl
27
HMBC ($CDCl_3$, 300.13 MHz)
H2
H8
H1'
C2'
C5
C8
C4
C6
C2
C=O
Cross peaks
Cross peak
f2 (ppm)

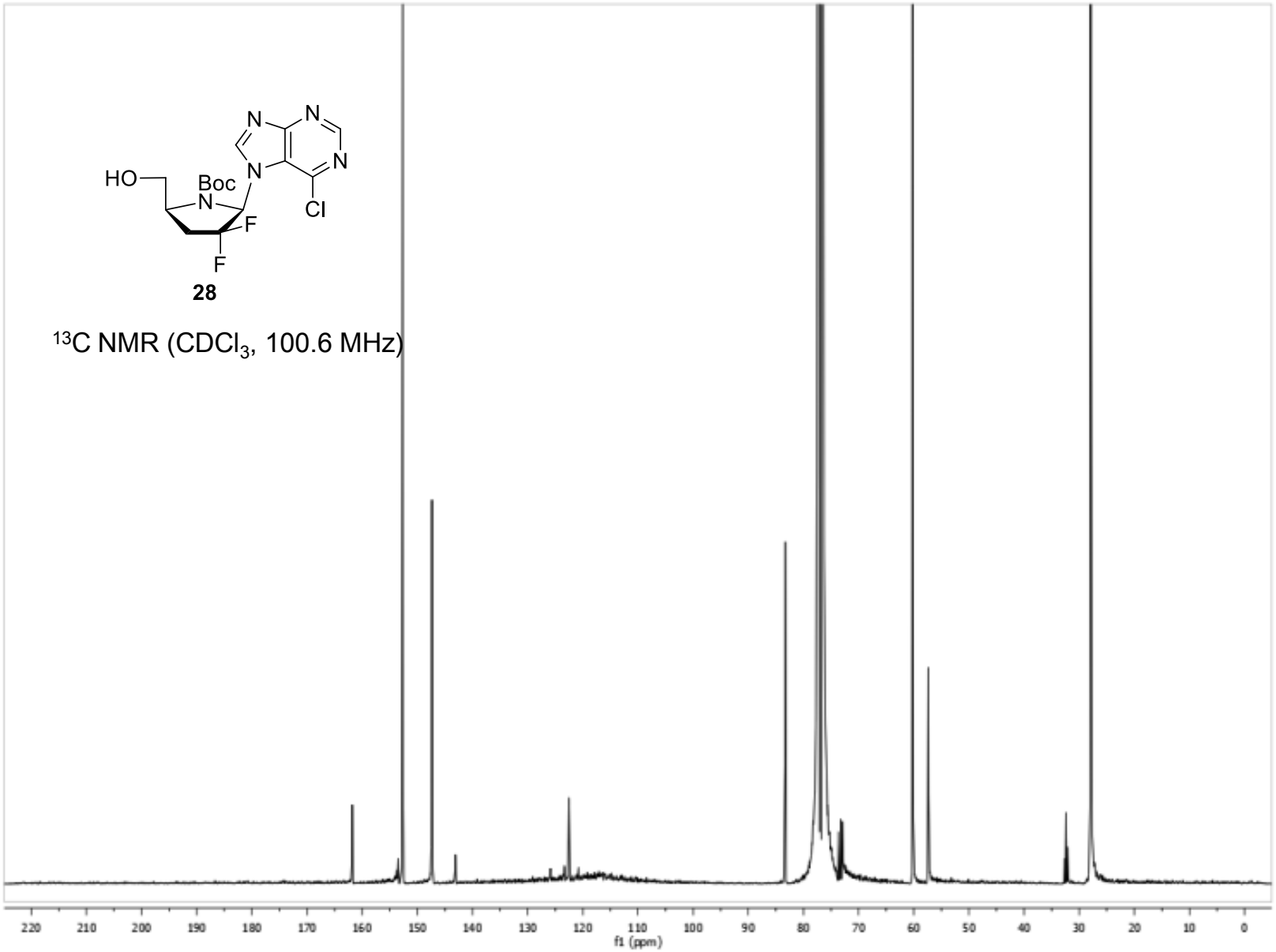

HO
Boc
N
F
F
N
N
N
N
Cl
27
NOESY (CDCl3, 300.13 MHz)
f2 (ppm)
f1 (ppm)

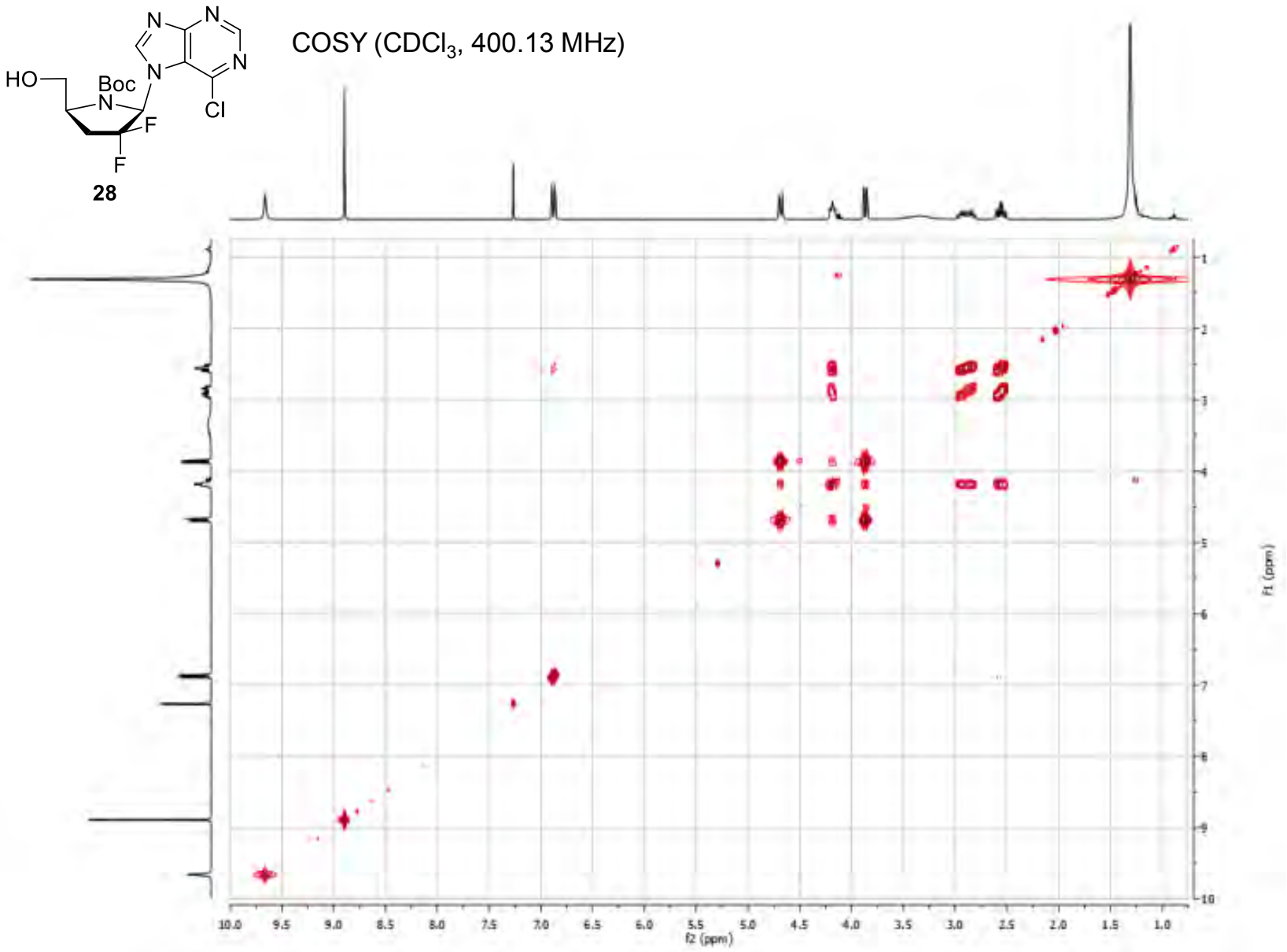


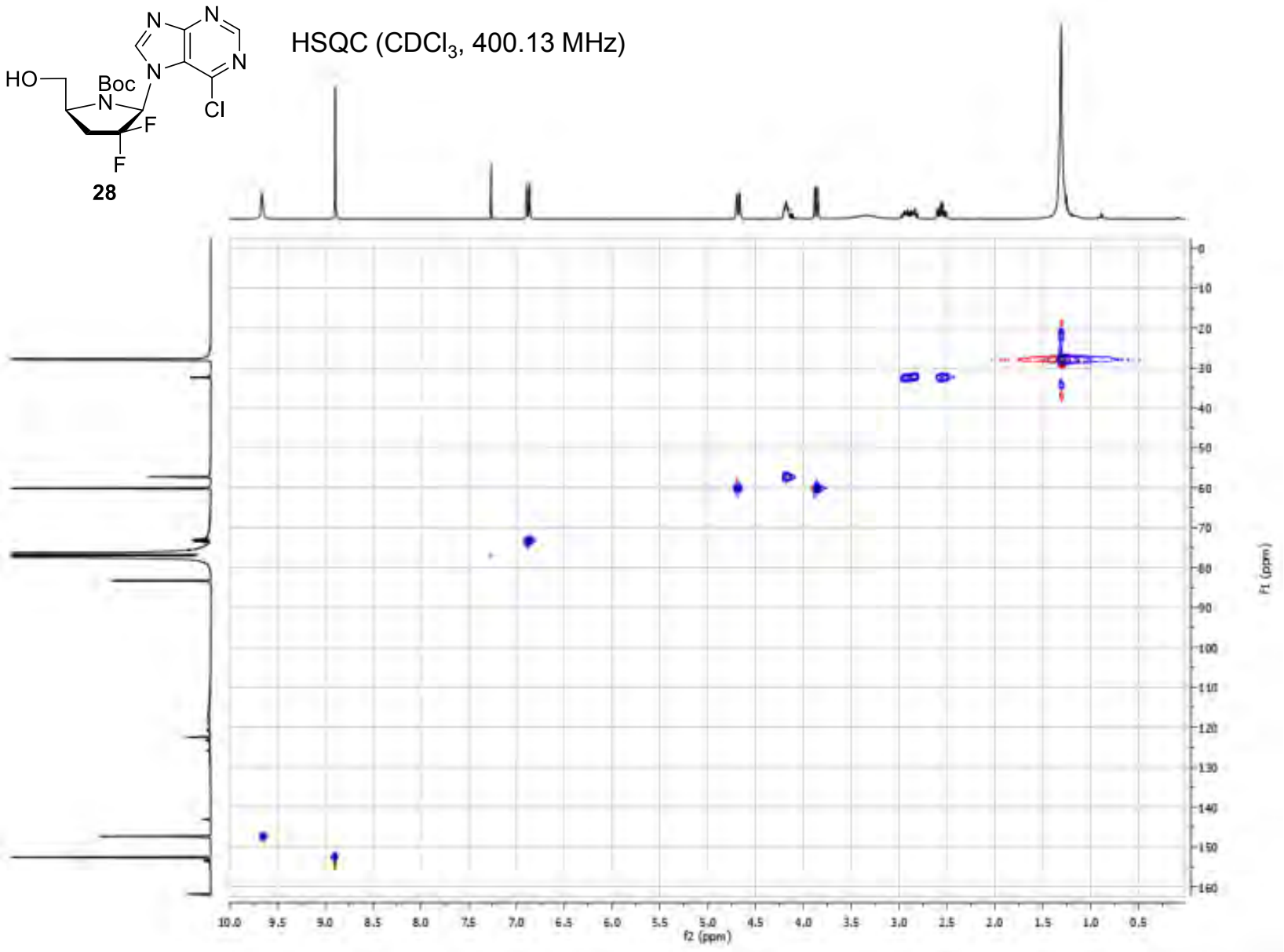
28

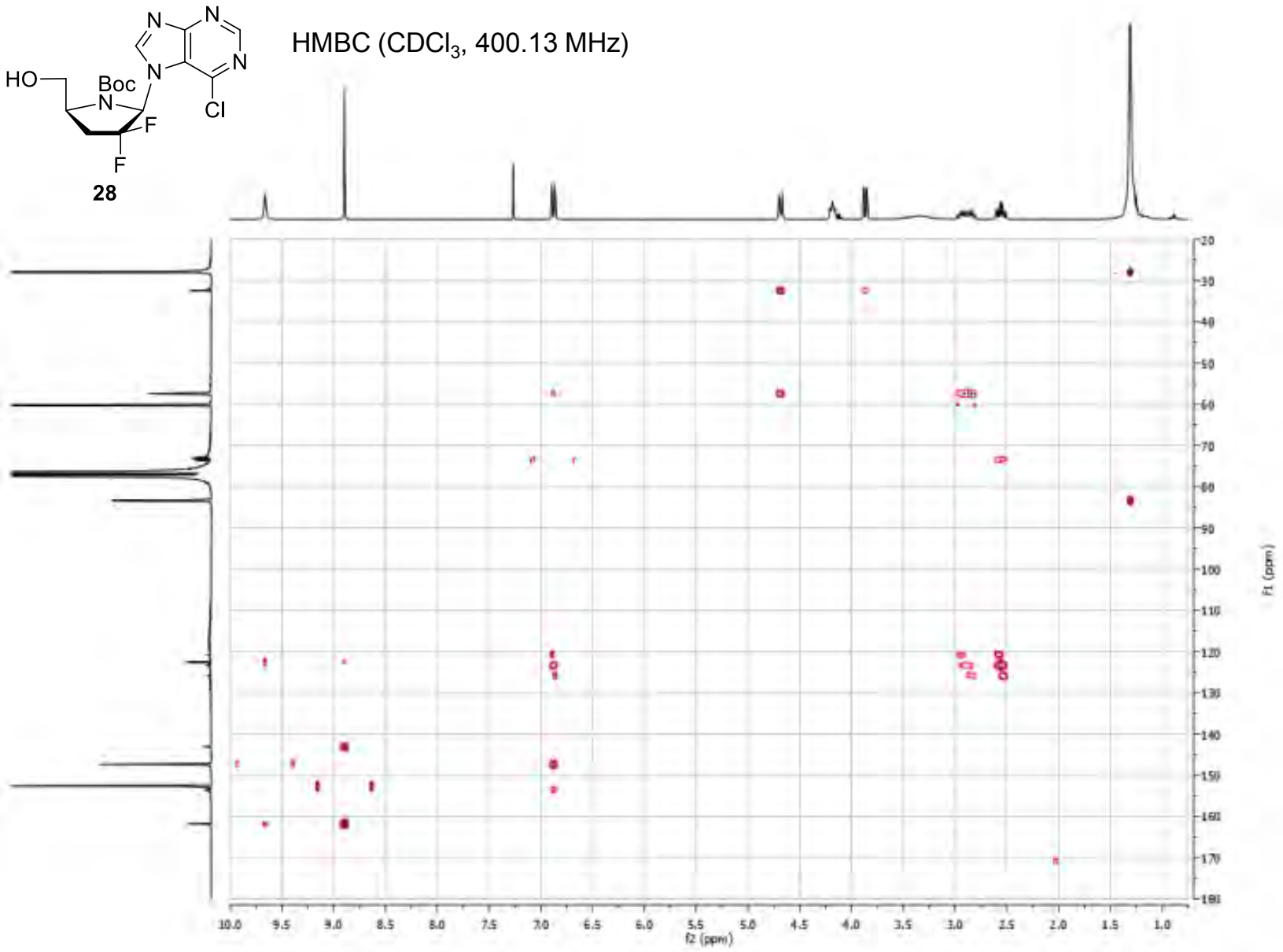
^{1}H NMR ($CDCl_3$, 400.13 MHz)

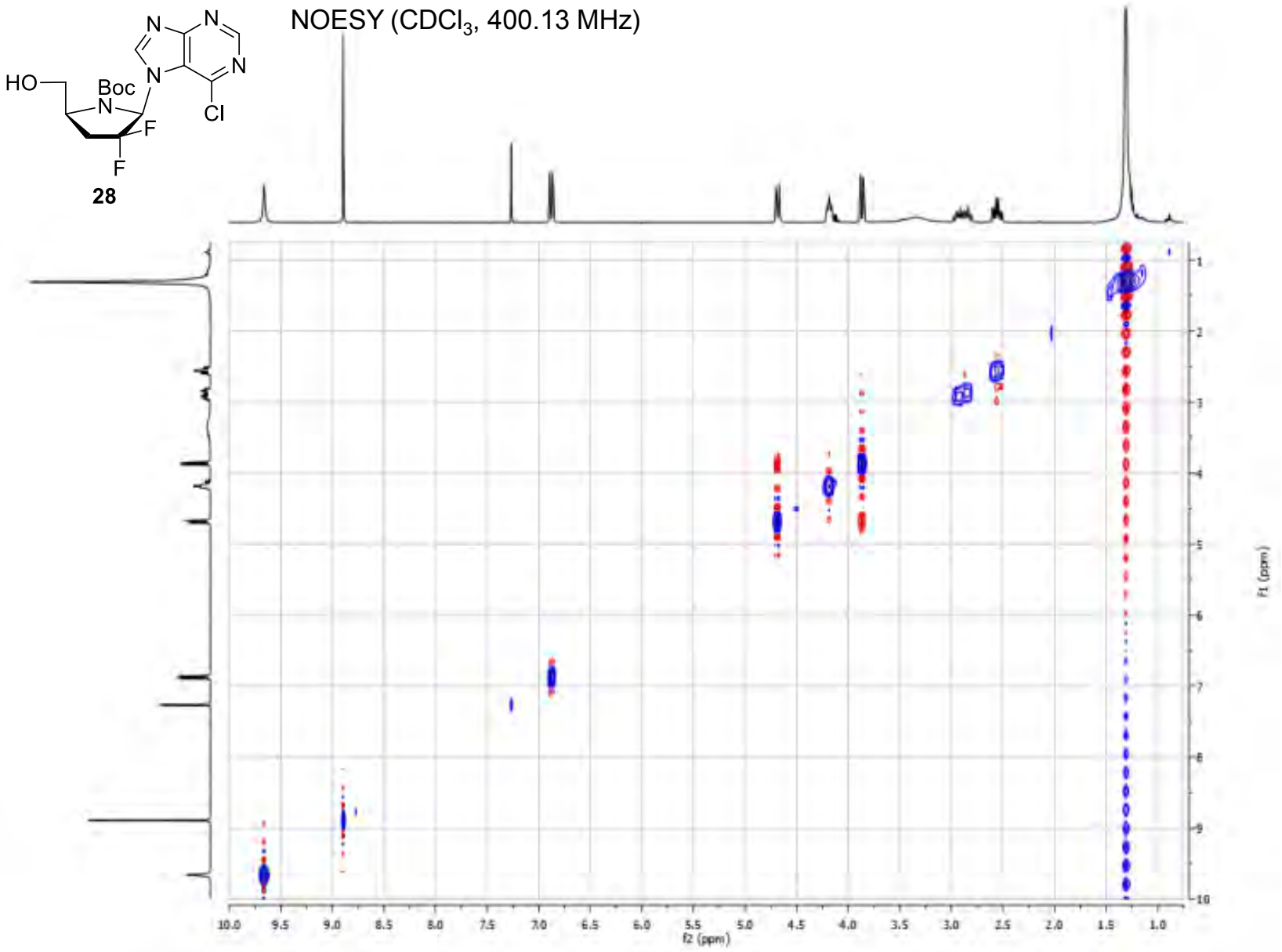


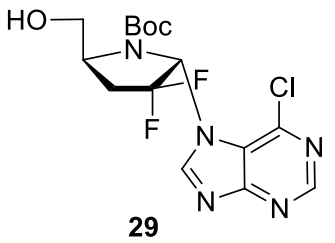

HO
Boc
N
F
F
N
N
N
N
Cl
28
^{13}C NMR ($CDCl_3$, 100.6 MHz)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HO
Boc
N
N
N
N
N
Cl
F
F
28
COSY ($CDCl_3$, 400.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
N
N
N
N
Cl
F
F
28
HSQC ($CDCl_3$, 400.13 MHz)
f2 (ppm)
f1 (ppm)

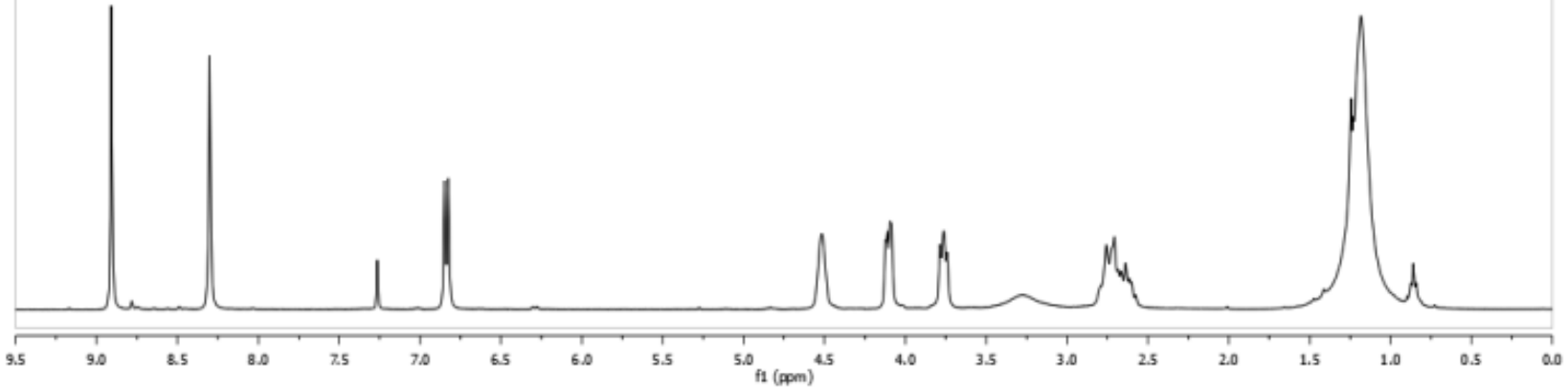

HO
Boc
N
N
N
N
N
Cl
F
F
28
HMBC ($CDCl_3$, 400.13 MHz)
f2 (ppm)
f1 (ppm)


NOESY (CDCl3, 400.13 MHz)
HO
Boc
N
N
N
N
N
Cl
F
F
28
f2 (ppm)
f1 (ppm)



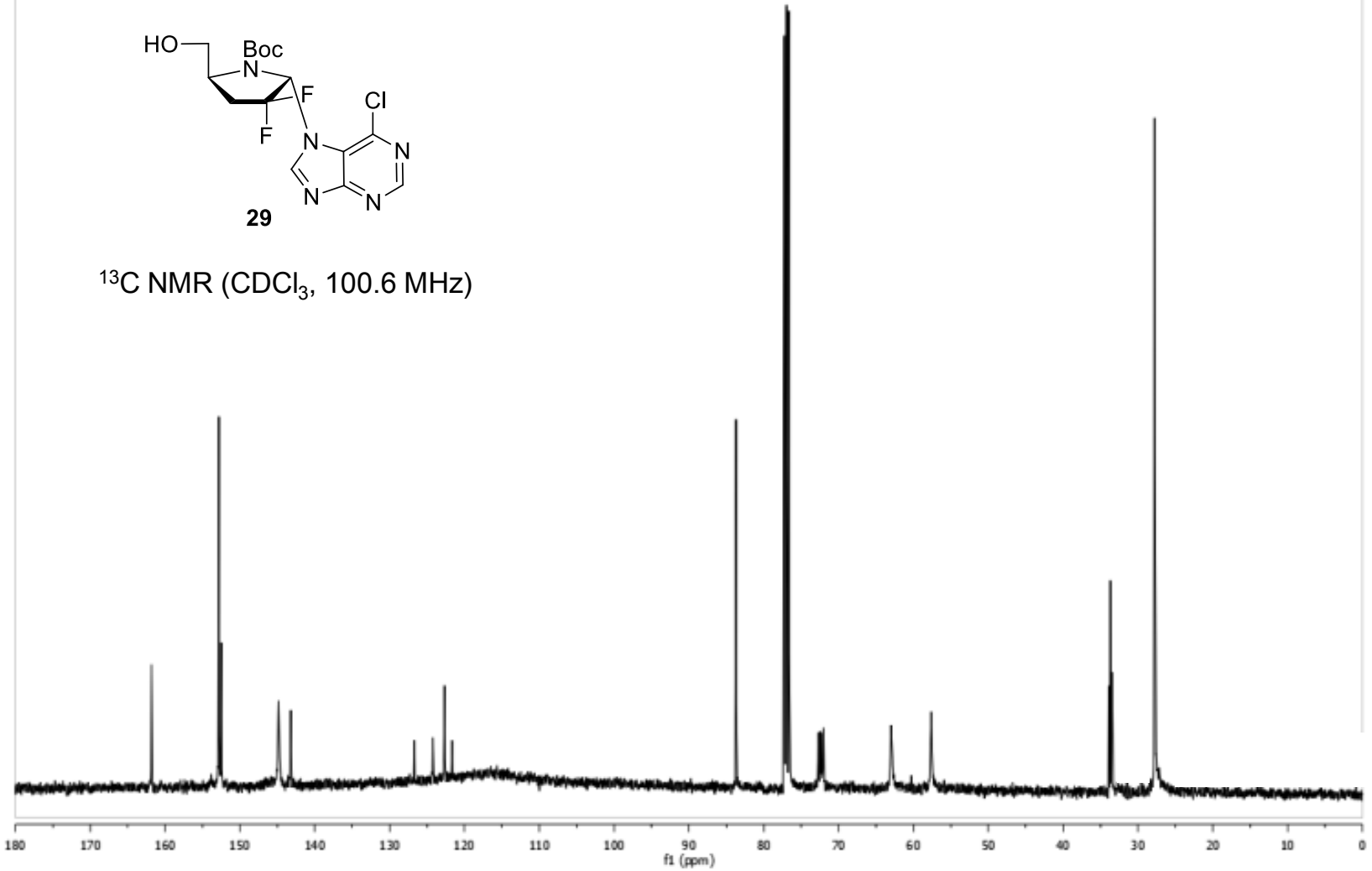
29

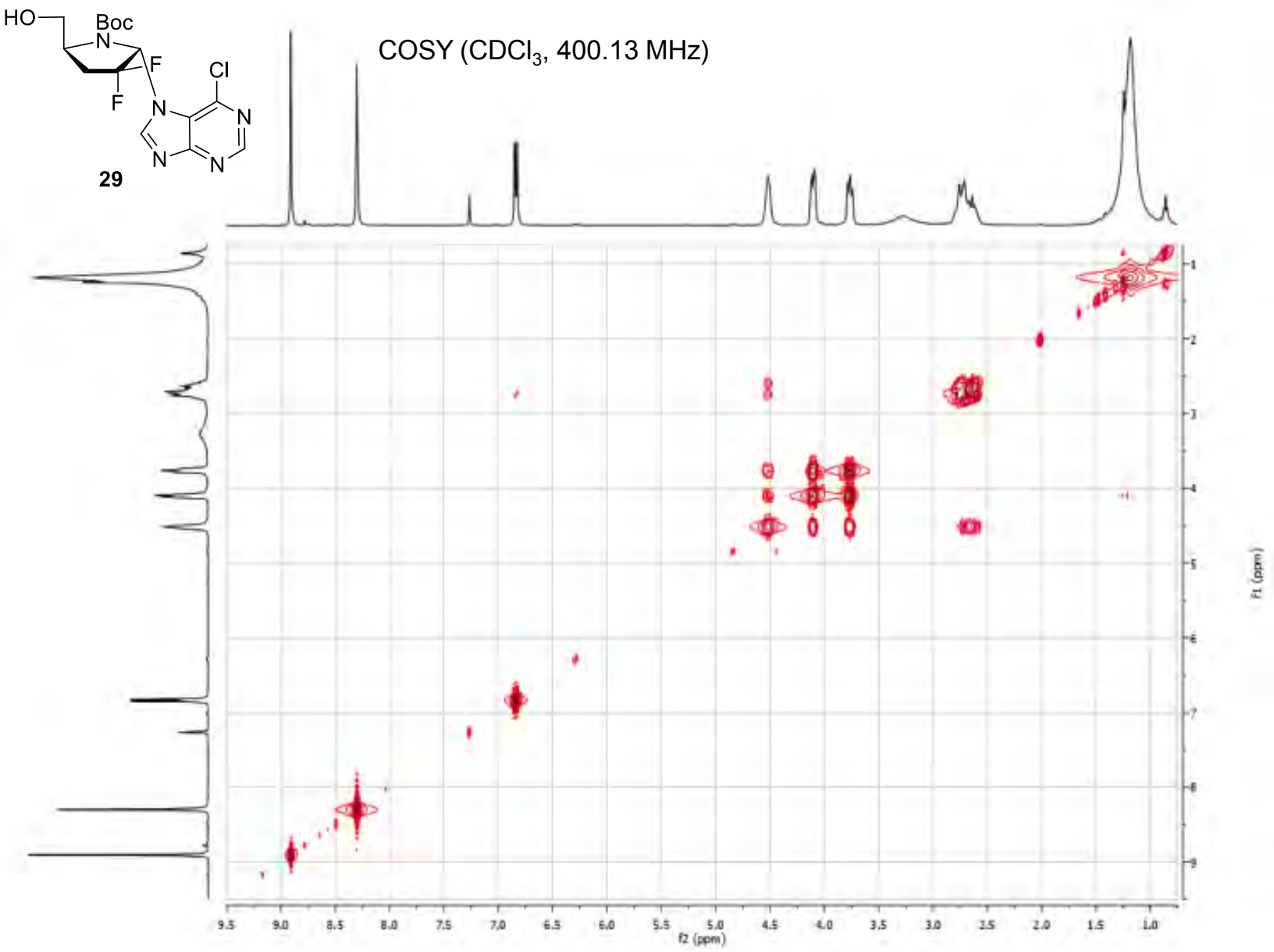
^{1}H NMR ($CDCl_3$, 400.13 MHz)

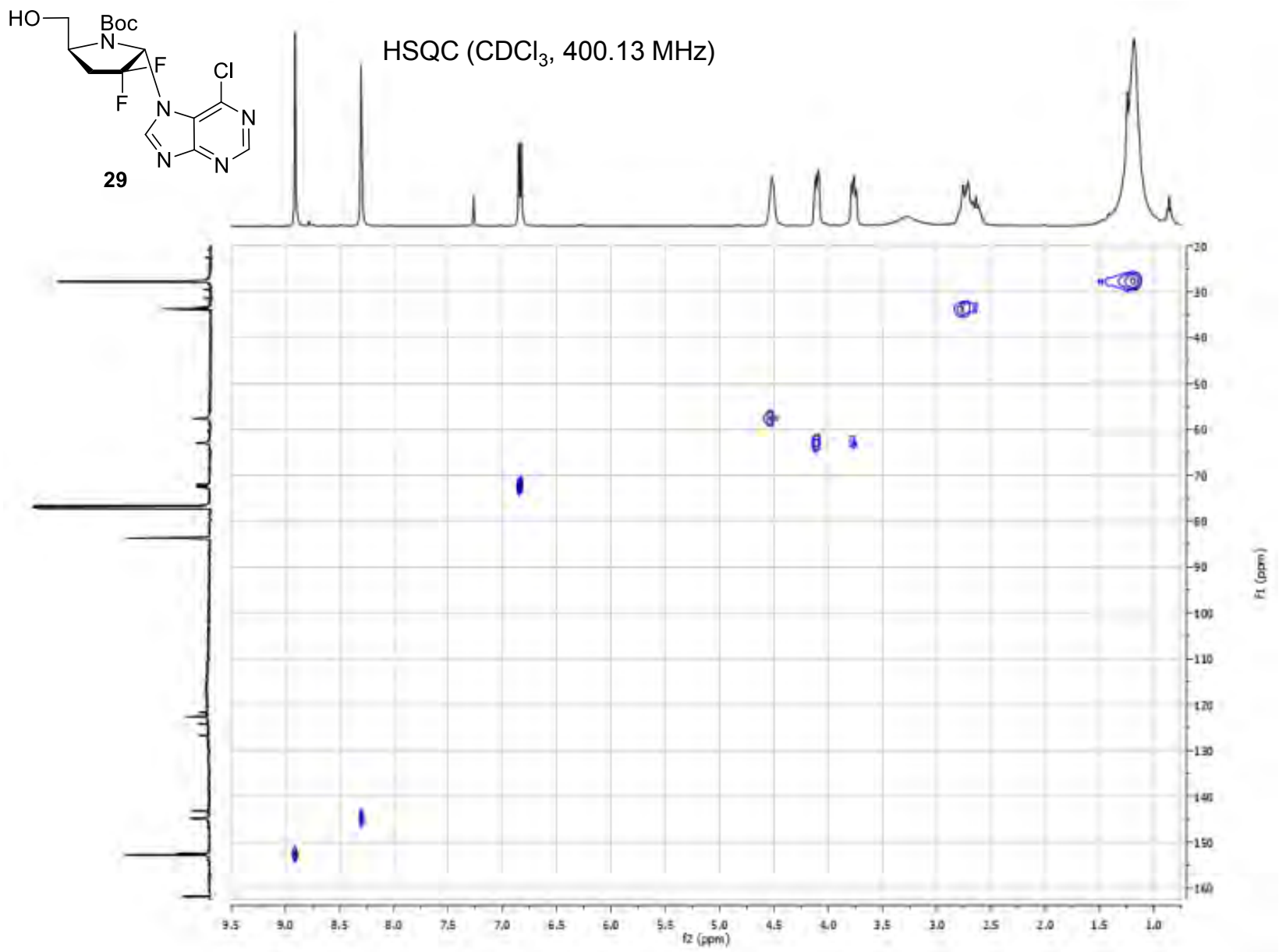


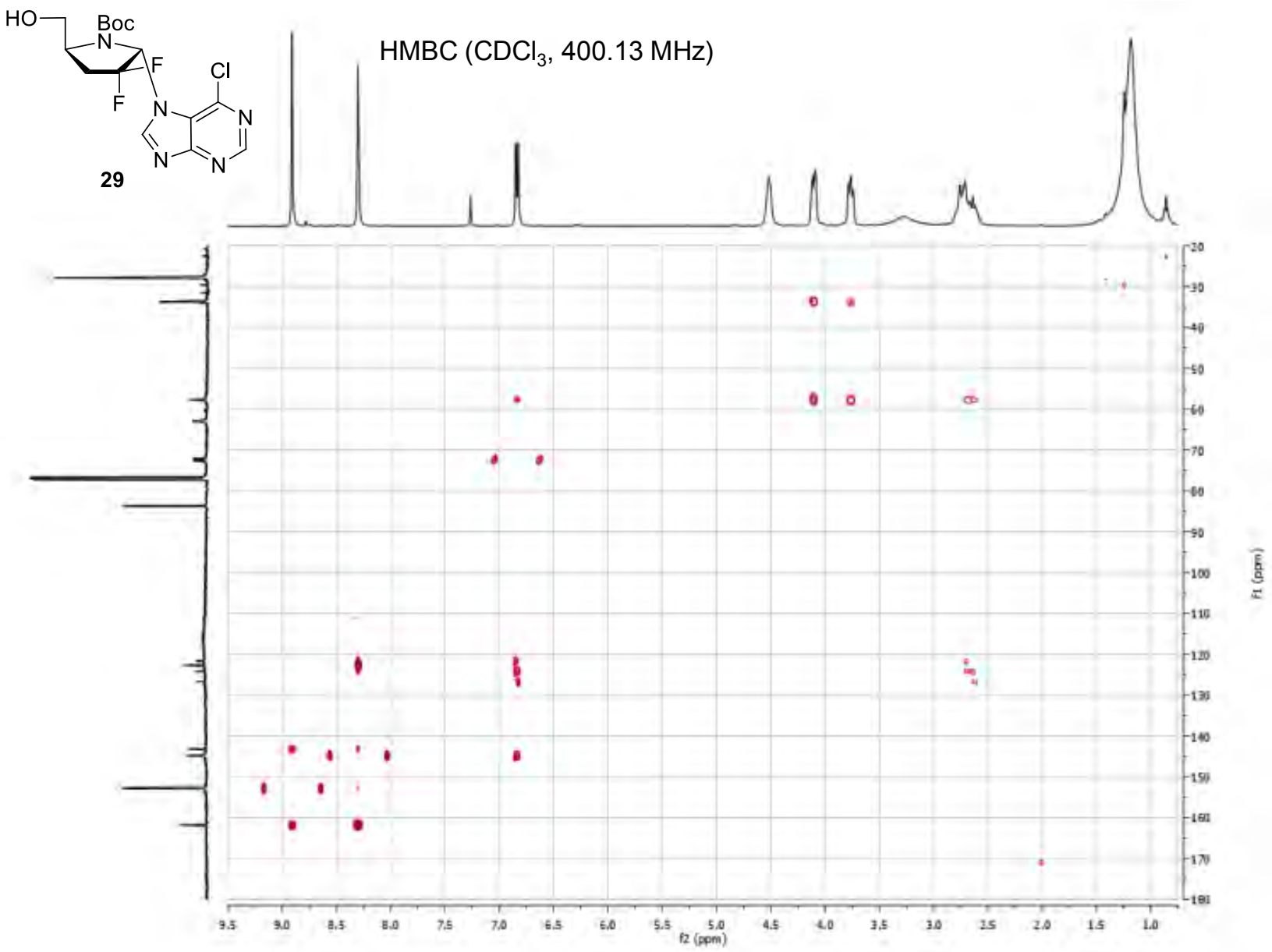
29

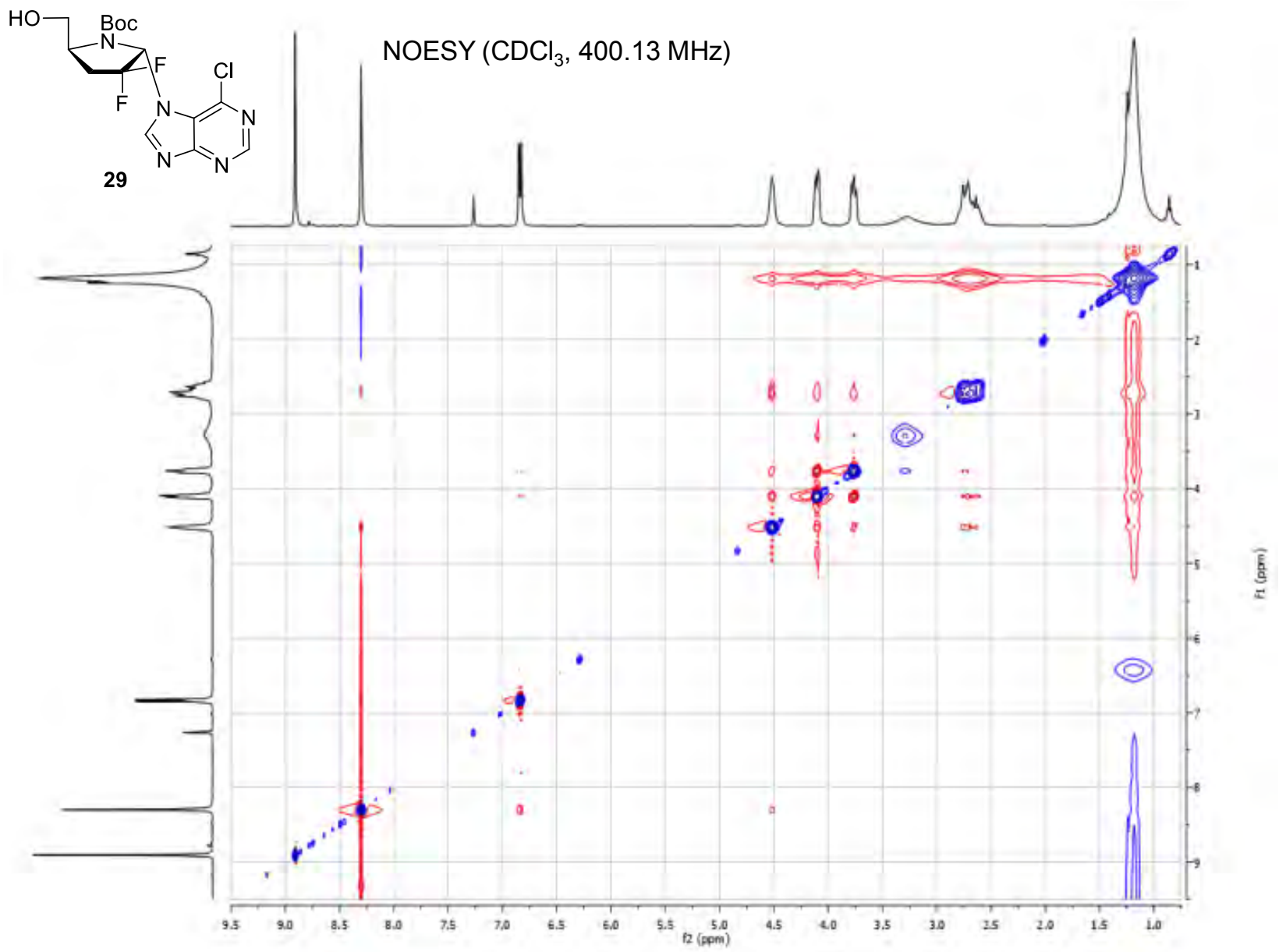
^{13}C NMR ($CDCl_3$, 100.6 MHz)

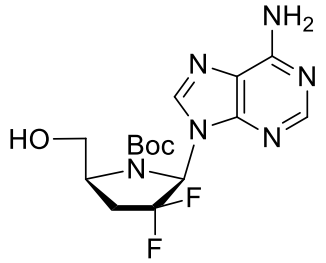



HO
Boc
N
F
F
Cl
N
N
N
N
29
COSY (CDCl3, 400.13 MHz)
f2 (ppm)
f1 (ppm)


HO
Boc
N
F
F
Cl
N
N
N
N
29
HSQC (CDCl3, 400.13 MHz)
f2 (ppm)
f1 (ppm)

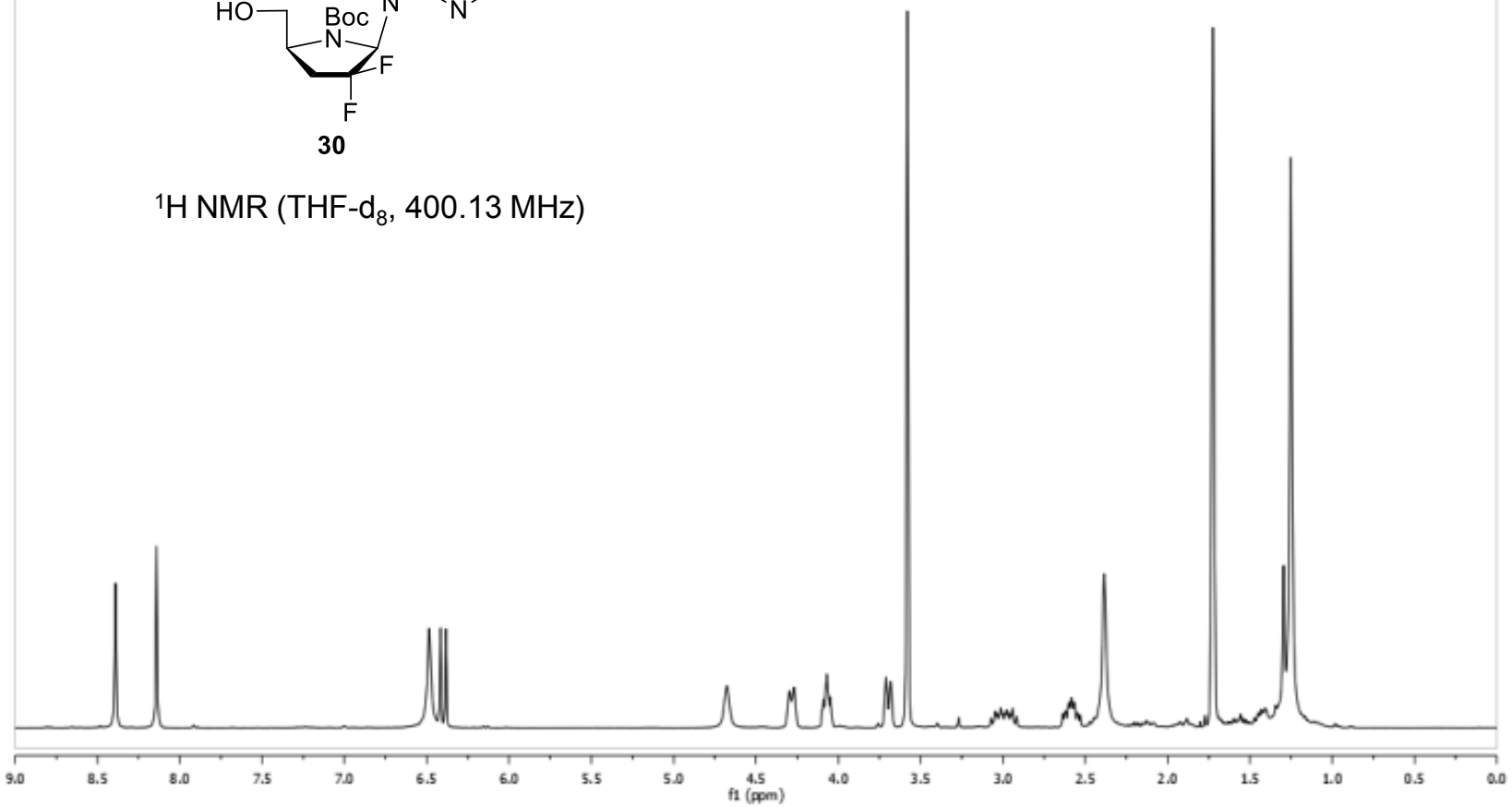

HO
Boc
N
F
F
Cl
N
N
N
N
29
HMBC (CDCl3, 400.13 MHz)
f2 (ppm)
f1 (ppm)

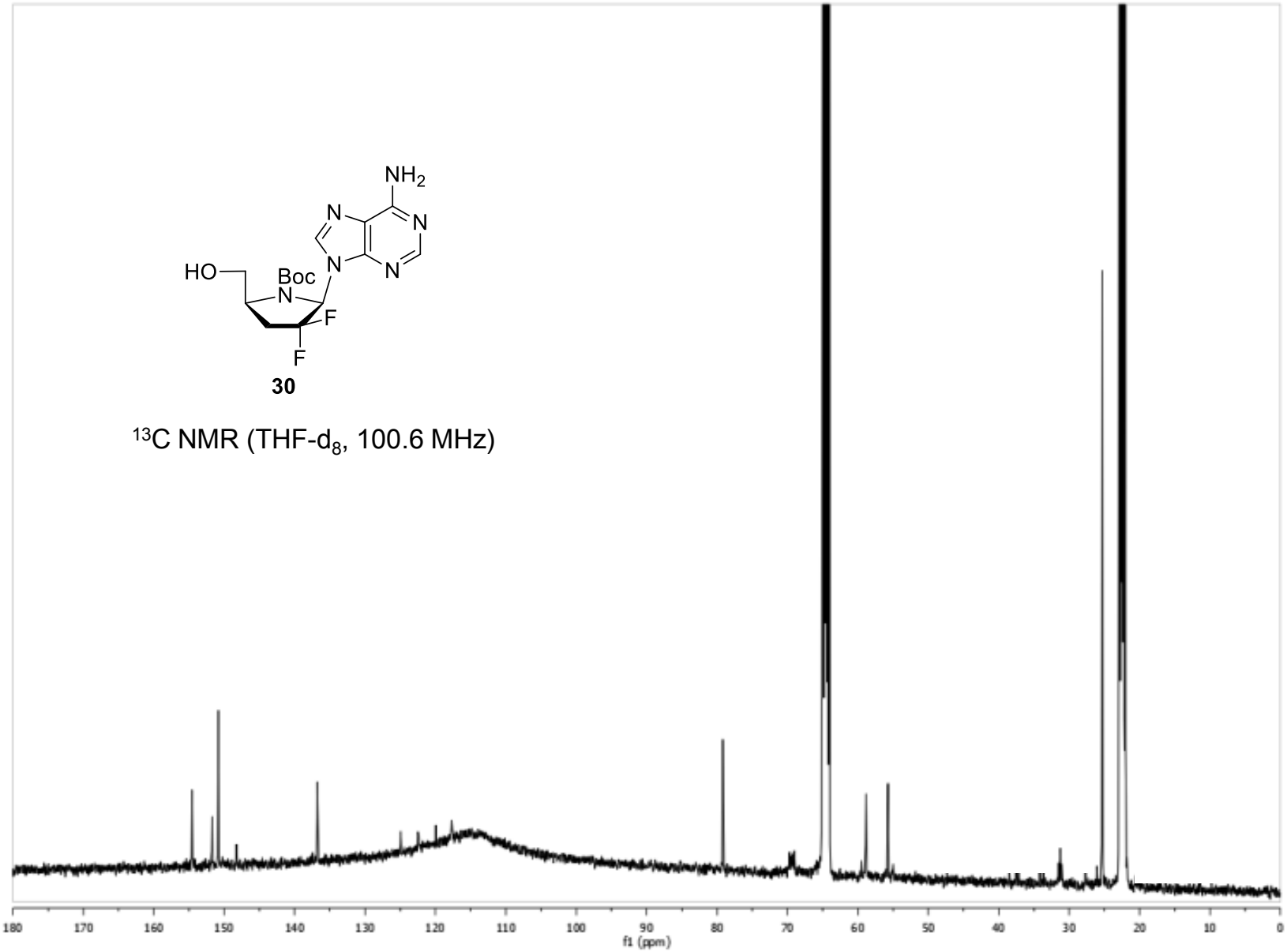

HO
Boc
N
F
F
Cl
N
N
N
N
29
NOESY (CDCl3, 400.13 MHz)
f2 (ppm)
f1 (ppm)



30

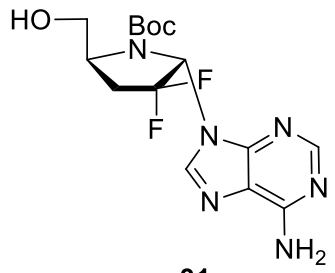
^{1}H NMR (THF-d_8, 400.13 MHz)





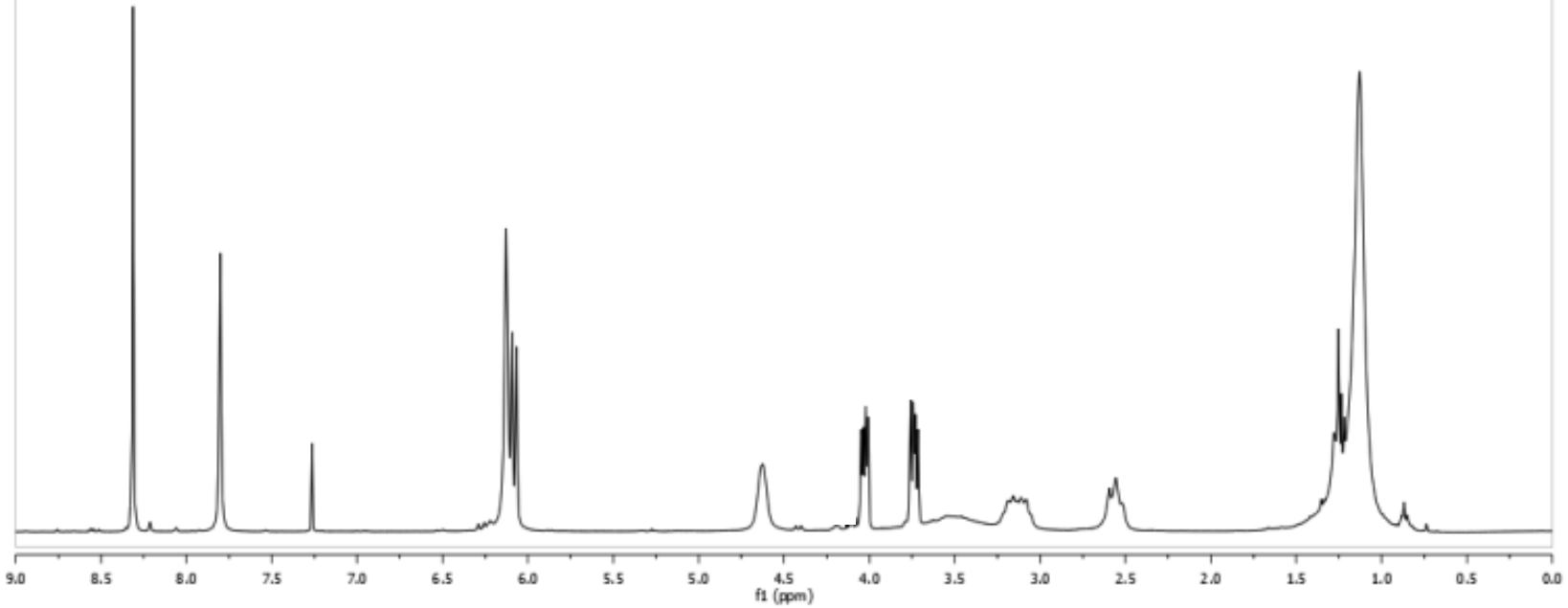
30

^{13}C NMR (THF-d_8, 100.6 MHz)



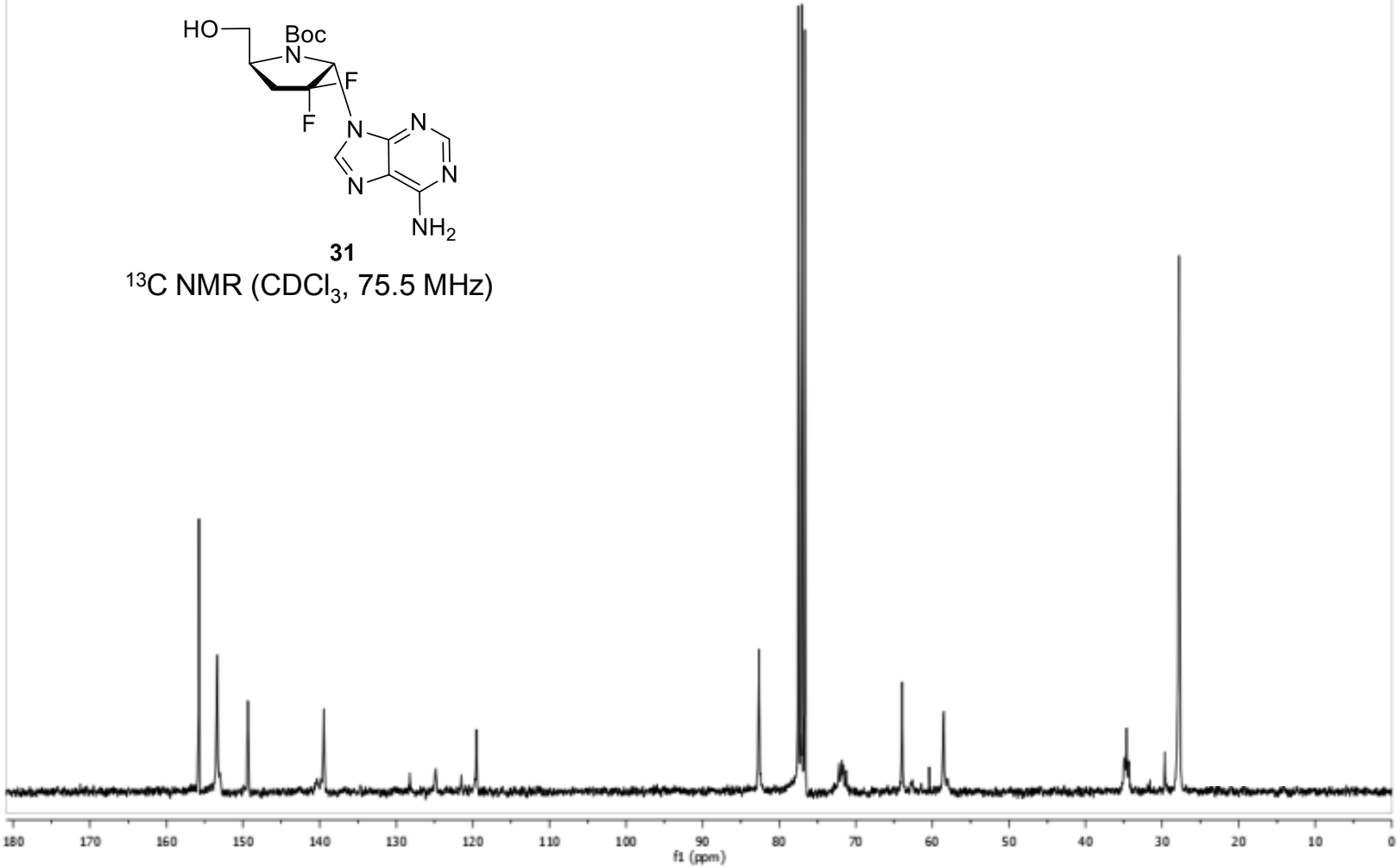
31

^{1}H NMR ($CDCl_3$, 400.13 MHz)



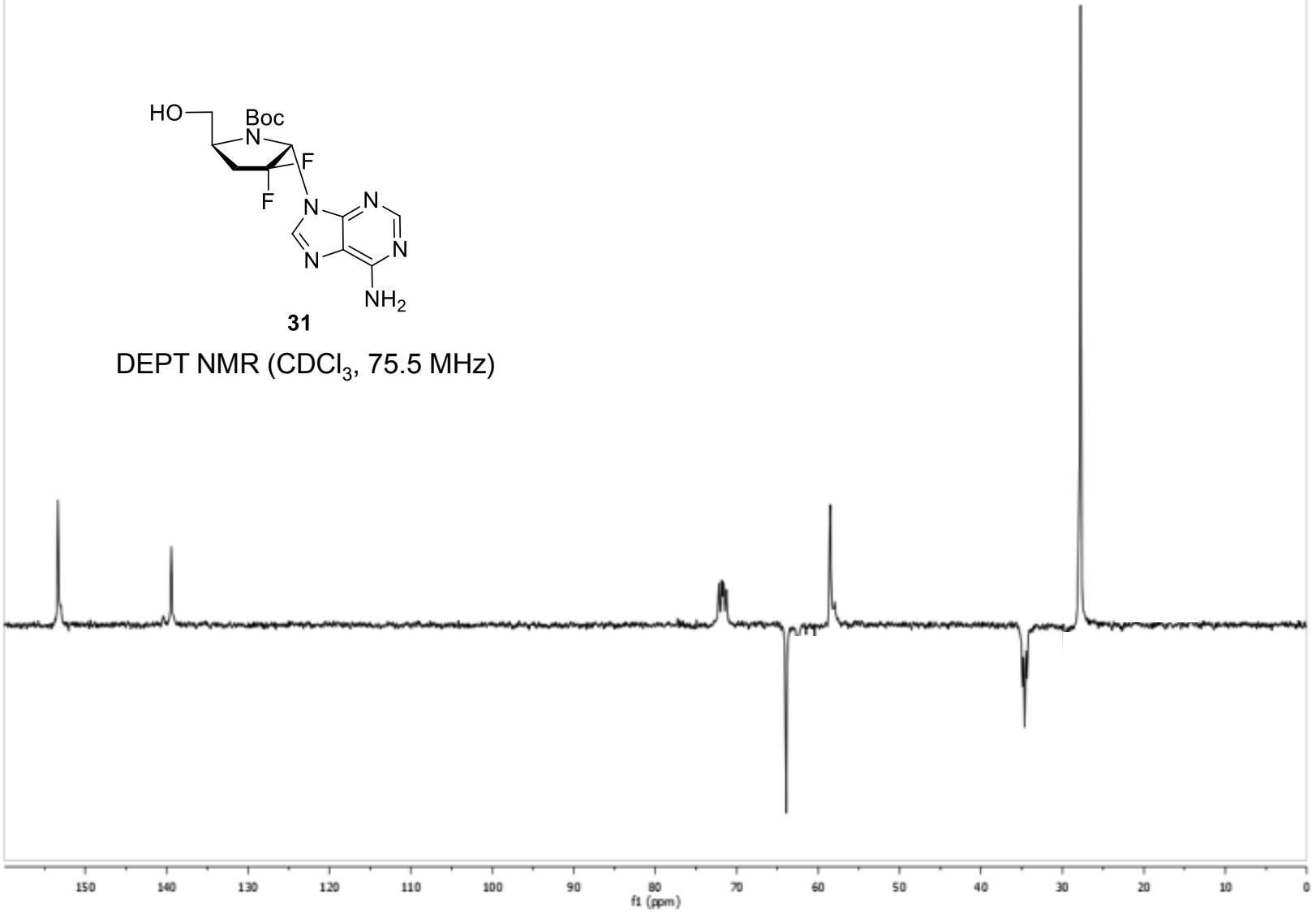
31

^{13}C NMR ($CDCl_3$, 75.5 MHz)



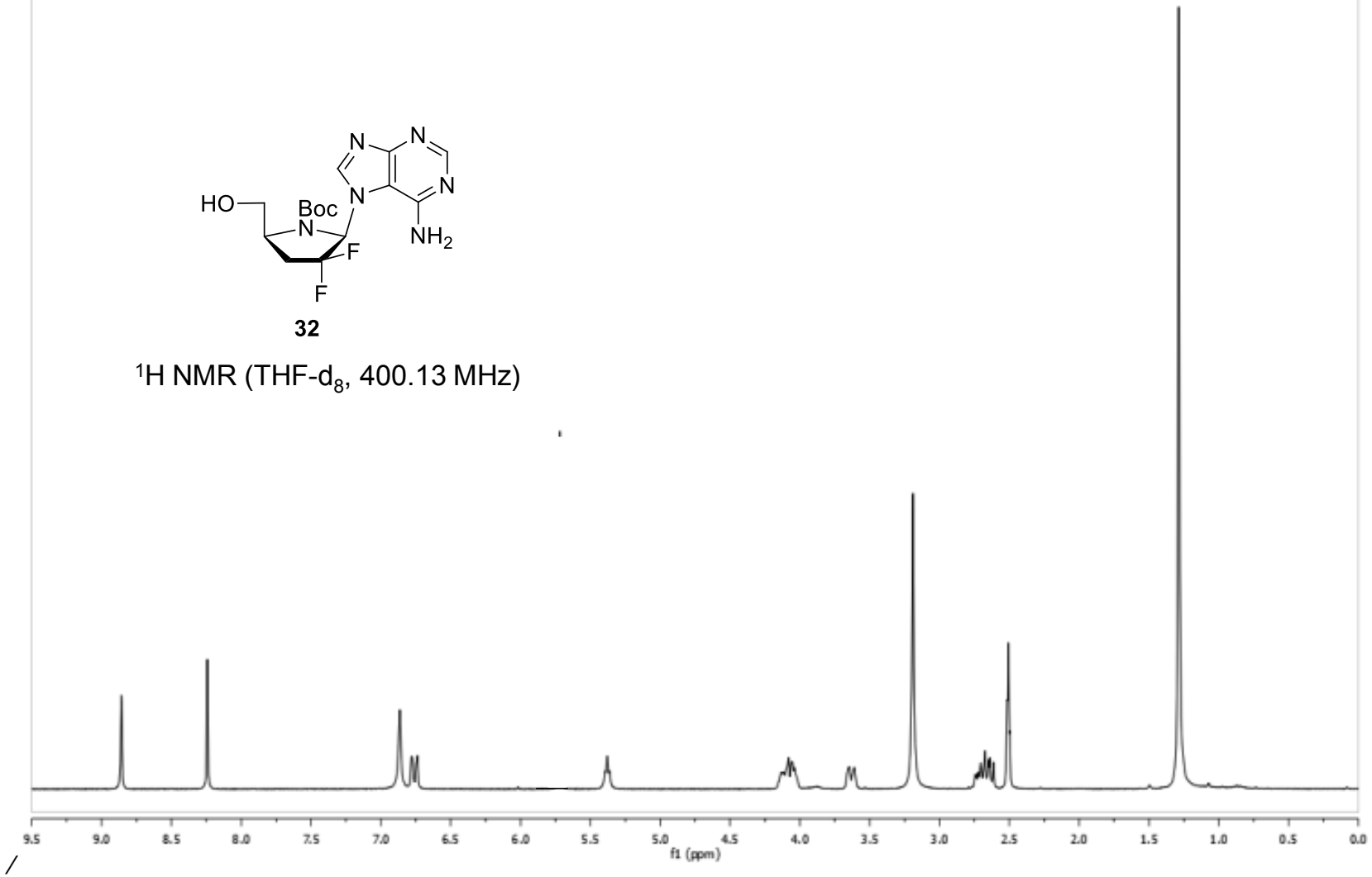
31

DEPT NMR ($CDCl_3$, 75.5 MHz)



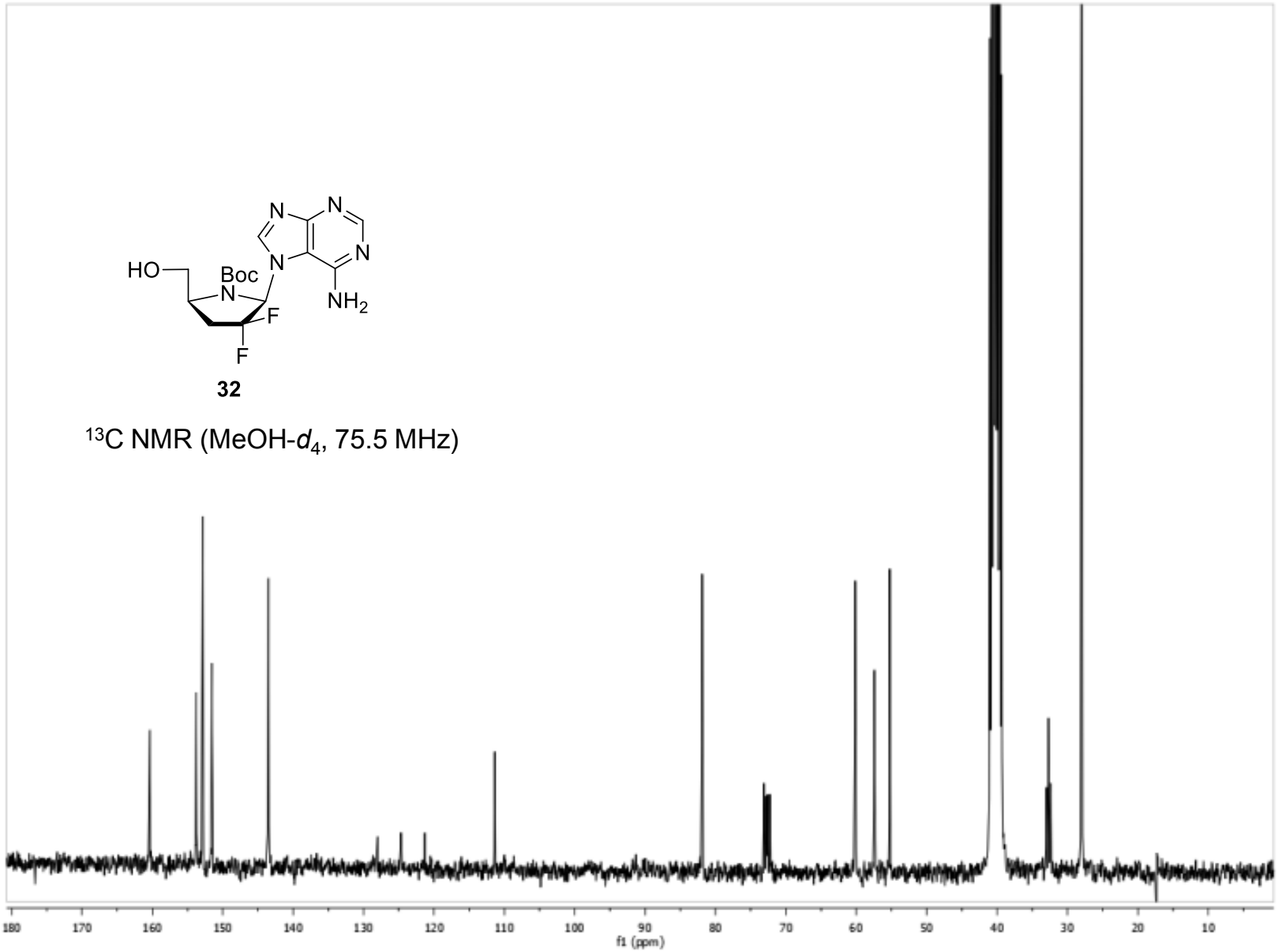
32

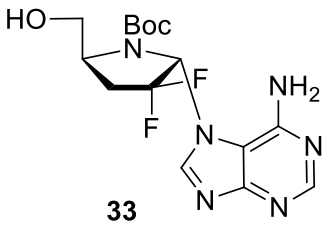
^{1}H NMR (THF-d_8, 400.13 MHz)



32

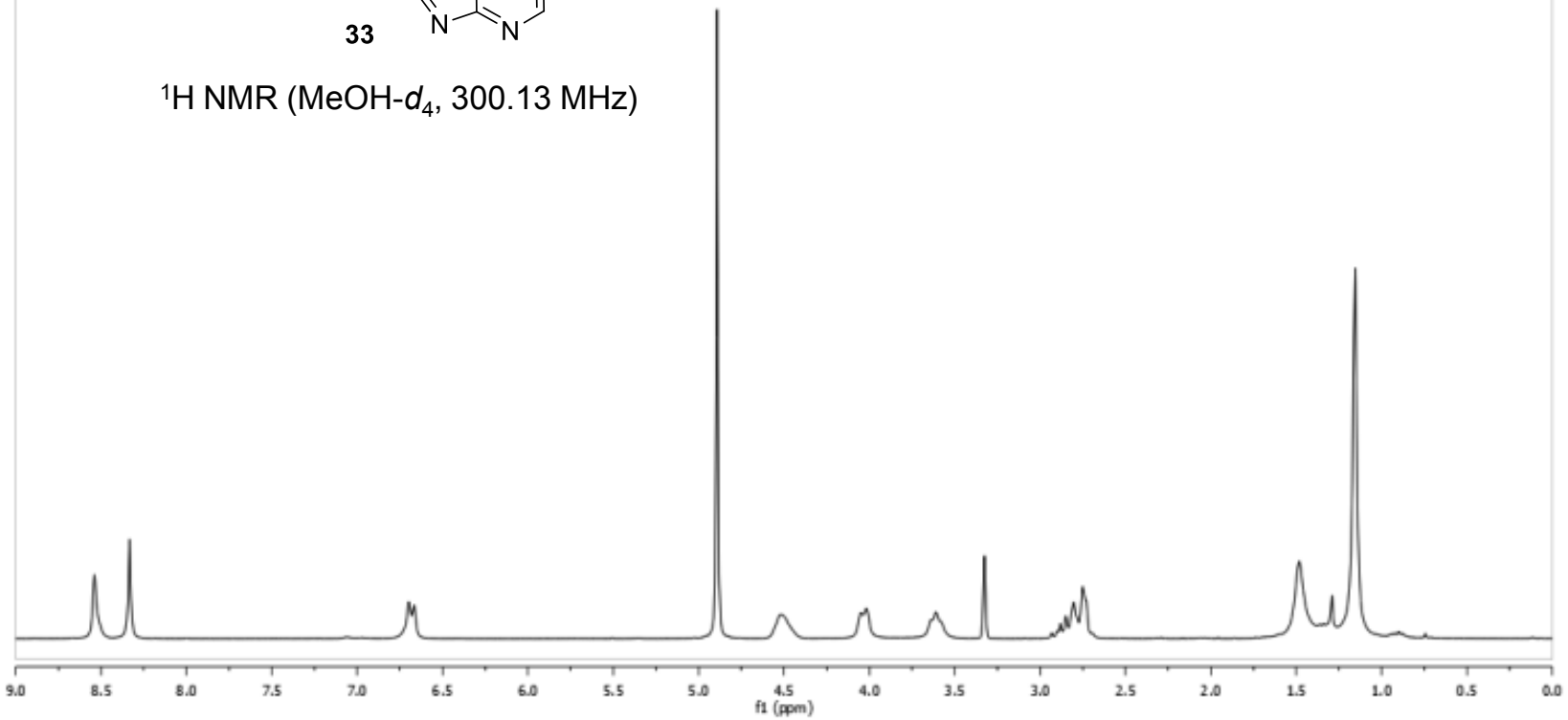
^{13}C NMR (MeOH-d_4, 75.5 MHz)





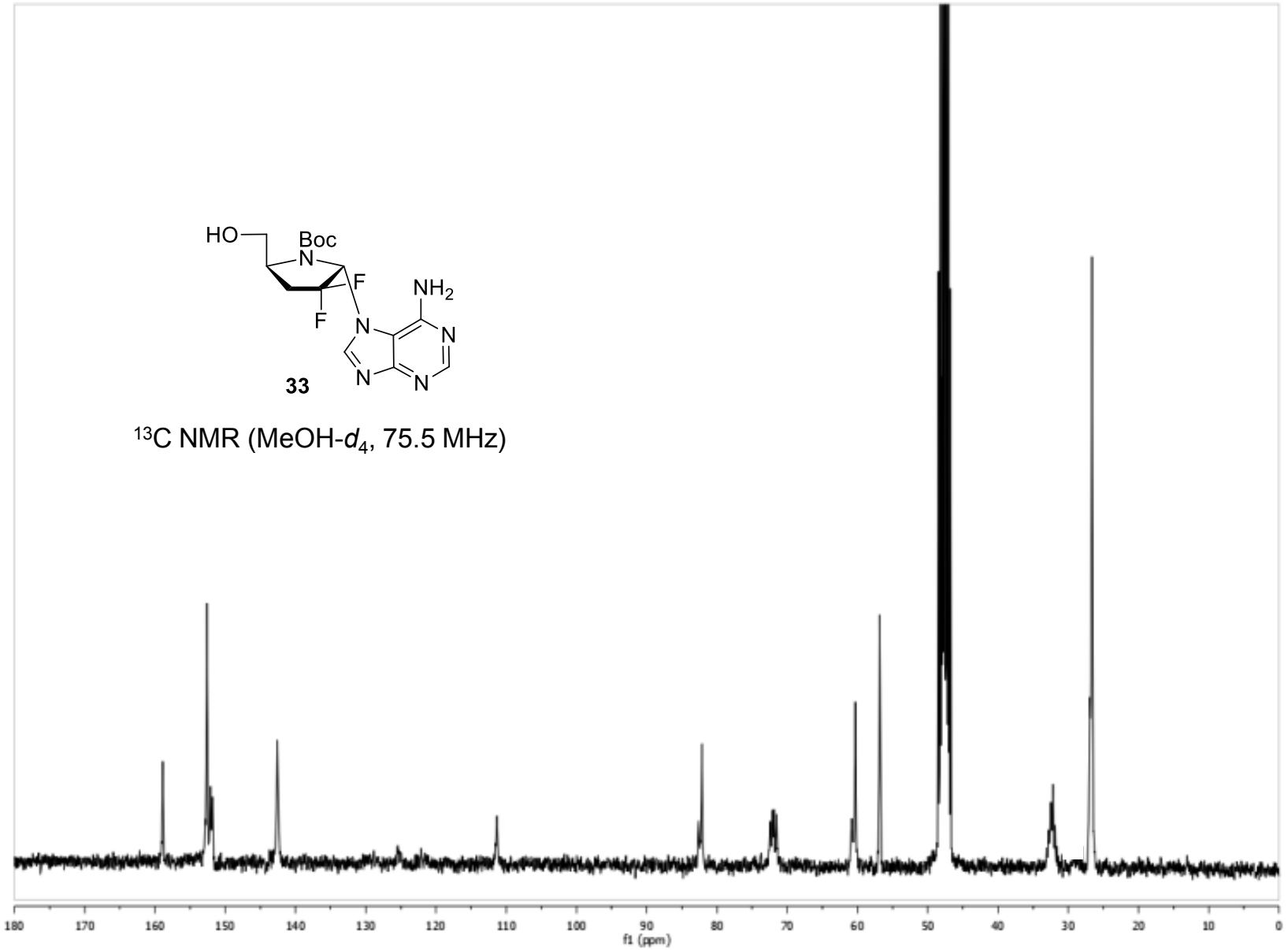
33

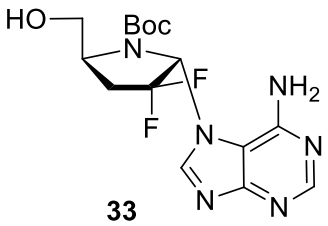
^{1}H NMR (MeOH-d_4, 300.13 MHz)



33

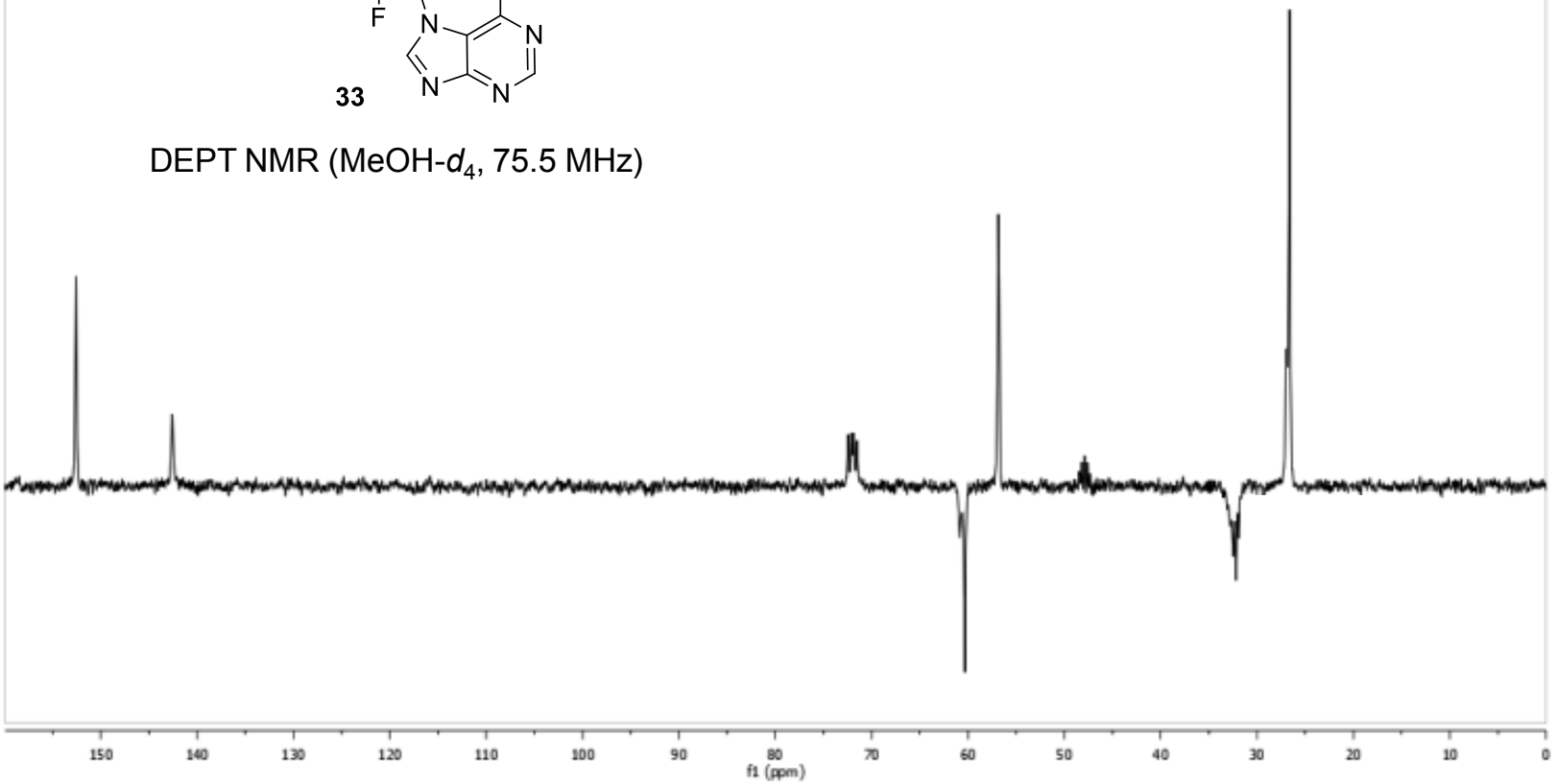
^{13}C NMR (MeOH-d_4, 75.5 MHz)





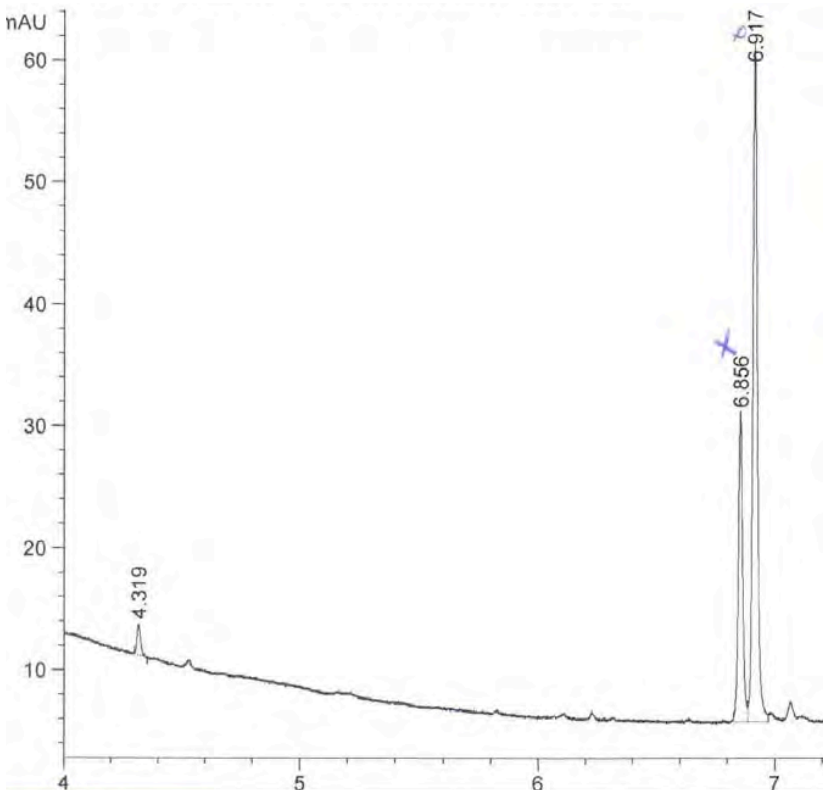
33

DEPT NMR (MeOH-d_4, 75.5 MHz)

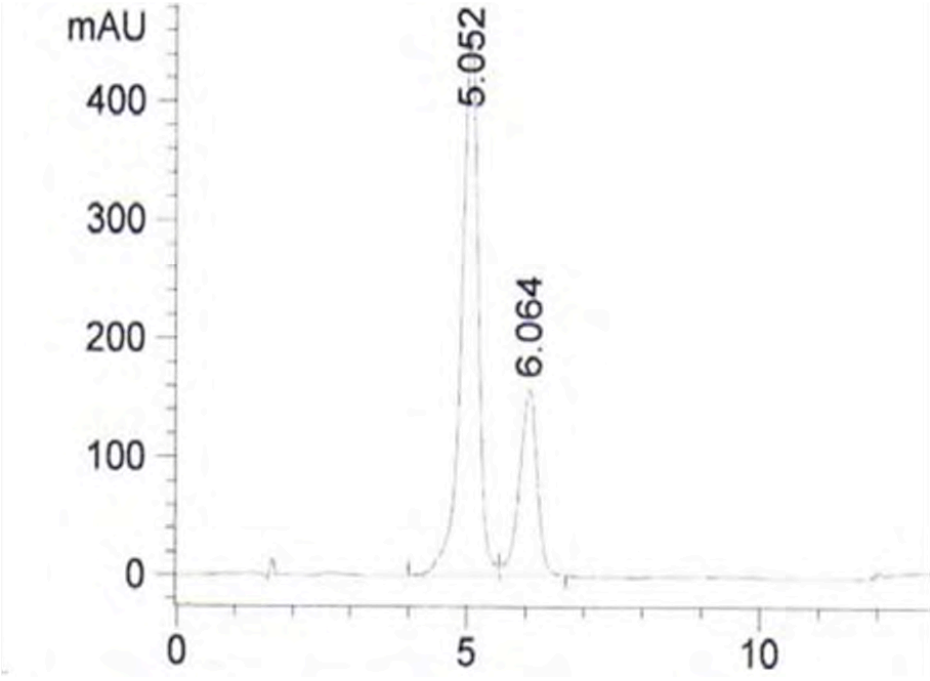


-> HPLC separation for both uracil anomers **16a/17a** after the glycosylation reaction

Conditions: Agilent Poroshel 120 SB, C18; mixture (A: MeCN y B: H_2O) gradient starting at 2.5% of B to reach 95% of B in 5 min; 1 mL/min, 30 ºC.

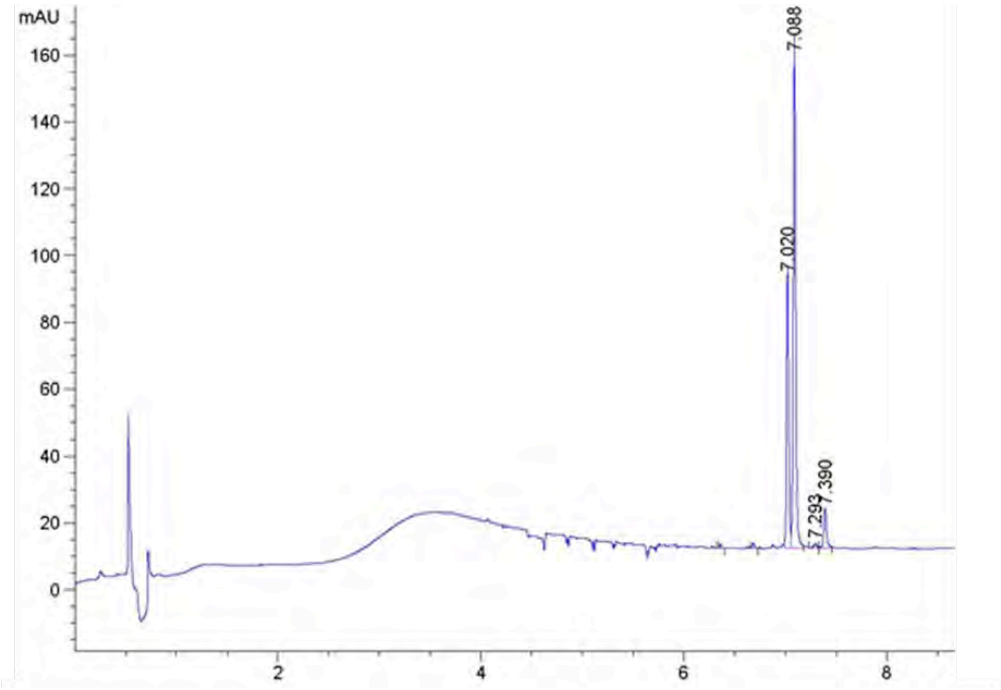


-> HPLC separation for both thymine anomers **18b/19b** (no conditions were found to separate the TBDMS protected nucleosides **16b/17b**). ***Conditions***: Mediterranea column C18 (250 x 45), mixture (A: 35% MeCN; B: 65% H_2O), 1 mL/min, 30 ºC.

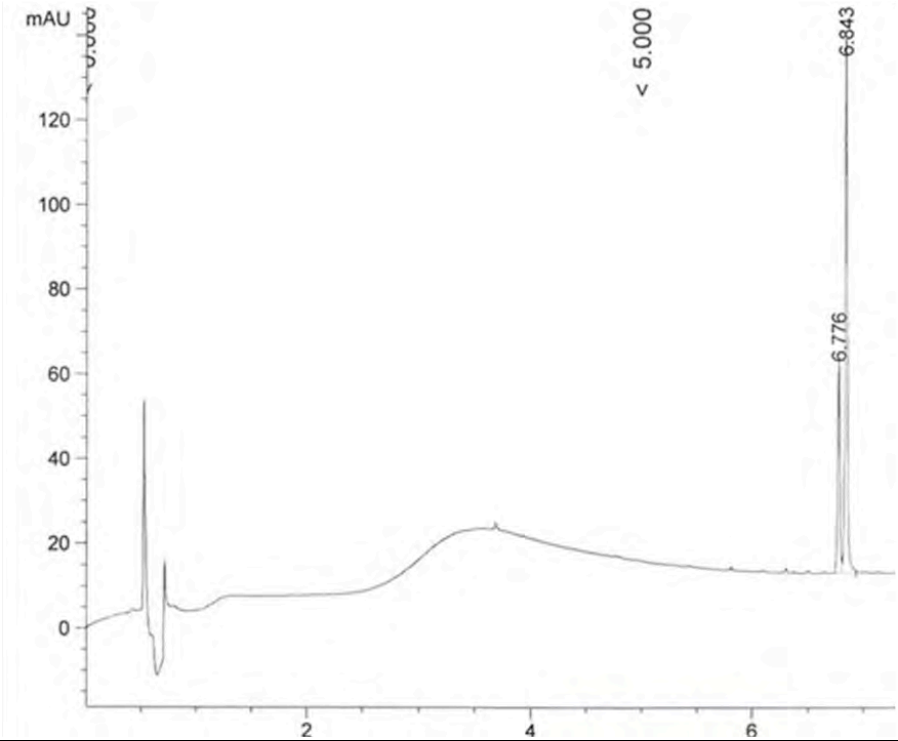


-> HPLC separation for both cytidine anomers **16c/17c** after the glycosylation reaction.

Conditions: Agilent Poroshel 120 SB, C18; mixture (A: MeCN y B: H_2O) gradient starting at 2.5% of B to reach 95% of B in 5 min; 1 mL/min, 30 ºC.



-> HPLC separation for both 5-fluorouracil anomers **16d/17d** after the glycosylation reaction. ***Conditions***: Agilent Poroshel 120 SB, C18; mixture (A: MeCN y B: H_2O) gradient starting at 2.5% of B to reach 95% of B in 5 min; 1 mL/min, 30 ºC.



-> HPLC separation for the four anomers **22-25** after glyosilation with 6-chloropurine.

Conditions: Mediterranea column C18 (250 x 45), mixture (A: MeCN y B: H_2O) gradient starting at 40% of B to reach 100% of B in 35 min; 1 mL/min, 30 ºC.