

Supporting Information

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Experimental Section

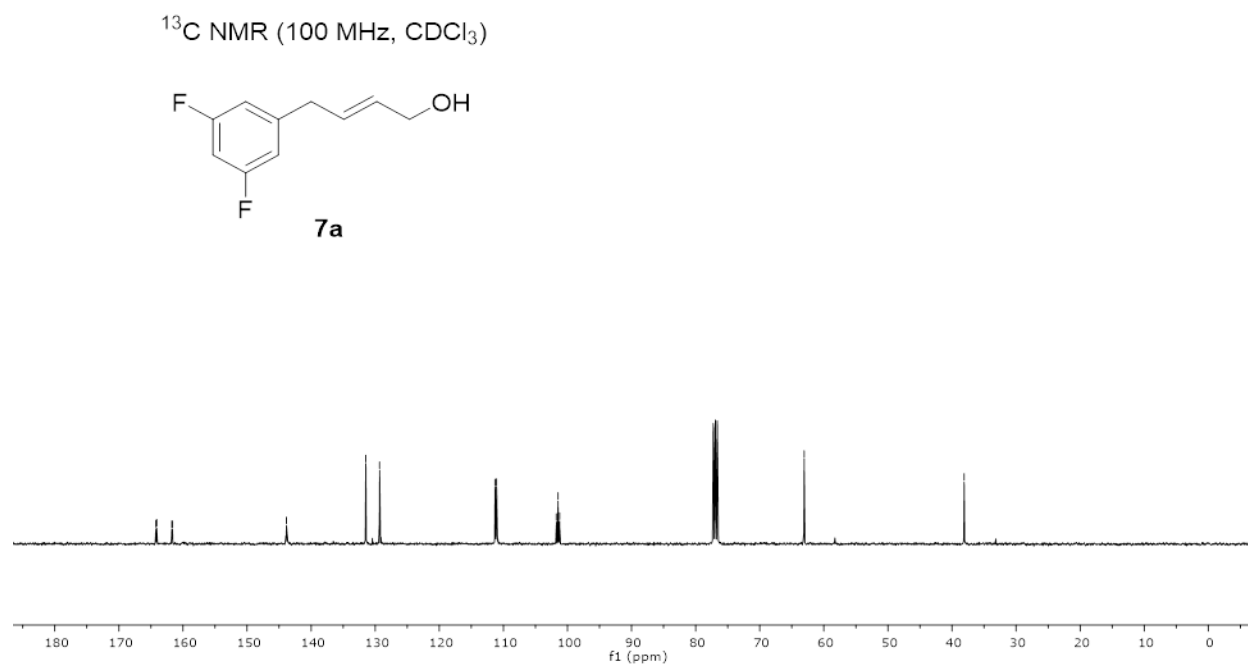
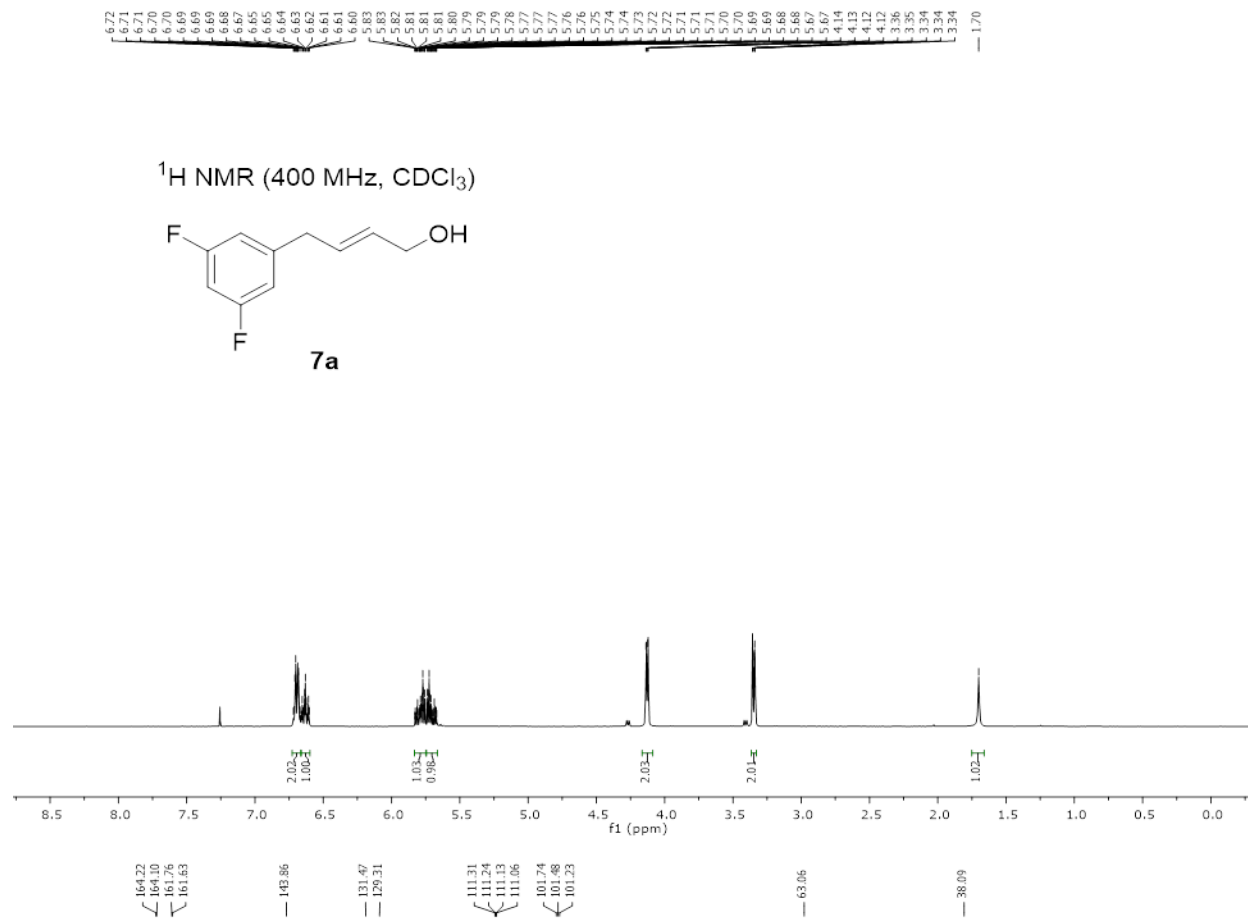
All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 °C) glassware. All reagents and chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Anhydrous solvents were obtained as follows: Dichloromethane from calcium hydride, diethyl ether and tetrahydrofuran from Na/Benzophenone, methanol and ethanol from activated magnesium under argon. All purification procedures were carried out with reagent grade solvents (purchased from VWR) in air. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 Å, 250 µm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. ¹H, ¹³C NMR spectra were recorded at room temperature on a Bruker ARX-400 and DRX-500. Chemical shifts (δ values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, *J*-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet). LRMS and HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

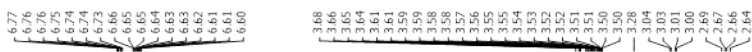
Table 1: Crystallographic Data Collection and Refinement Statistics

Space group	P2 ₁ 2 ₁ 2
Unit cell dimensions: (Å)	
a	59.04
b	86.43
c	45.93
Resolution range (Å)	50-1.67 (1.73-1.67)
Unique reflections	27,851 (2,763)
R _{merge} (%) overall (final shell)	7.1 (48.4)
I/σ(I) overall (final shell)	18.1 (4.8)
Completeness (%) overall (final shell)	99.8 (100.0)
Redundancy overall (final shell)	6.1 (6.1)
Refinement	
R (%)	19.5
R _{free} (%)	26.3
No. of solvent atoms (total occupancies)	169 (133.9)
RMS deviation from ideality	
Bonds (Å)	0.008
Angle distance (Å)	0.026
Average B-factors (Å ²)	
Wilson Plot B factor	13.0
Main-chain atoms	20.6
Side-chain atoms	28.8
Whole chain atoms	24.6
Inhibitor	16.9
Solvent	28.8

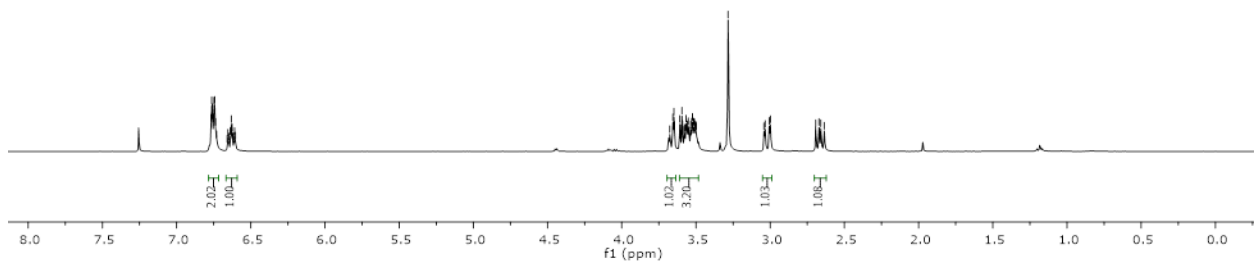
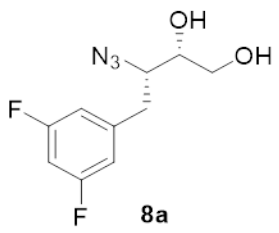
Cells, viruses, and antiviral agents. Human CD4⁺ MT-2 cells were grown in RPMI-1640-based culture medium supplemented with 10% fetal calf serum (FCS: JRH Biosciences, Lenexa, MD), 50 unit/mL penicillin, and 100 μg/mL of kanamycin. The following HIV-1 viruses were employed for the drug susceptibility assay (see below): a laboratory HIV-1 strain (HIV-1_{LAI}), a clinical HIV-1 strain isolated from drug-naive patients with AIDS (HIV-1_{ERS104pre}) (1), and six HIV-1 clinical isolates which were originally isolated from patients with AIDS, who had received 9 to 11 anti-HIV-1 drugs over the past 32 to 83 months, and were genotypically and phenotypically characterized as multi-PI-resistant HIV-1 variants (1, 2). All such primary HIV-1 strains were passaged once or twice in 3-day old phytohemagglutinin-activated peripheral blood mononuclear cells (PHA-PBM), and the culture supernatants were stored at -80 °C until use. Amprenavir (APV) was received as a gift from Glaxo-Wellcome, Research Triangle Park, NC. Darunavir (DRV) was synthesized as previously described (3).

1. Yoshimura, K., et al. *Proc. Natl. Acad. Sci. USA* **96**, 8675-8680 (1999).
2. Koh, Y., et al. *Antimicrob. Agents Chemother.* **53**, 987-996 (2009).
3. Koh Y, et al *J Mol Biol* **282**, 28709-28720 (2007).

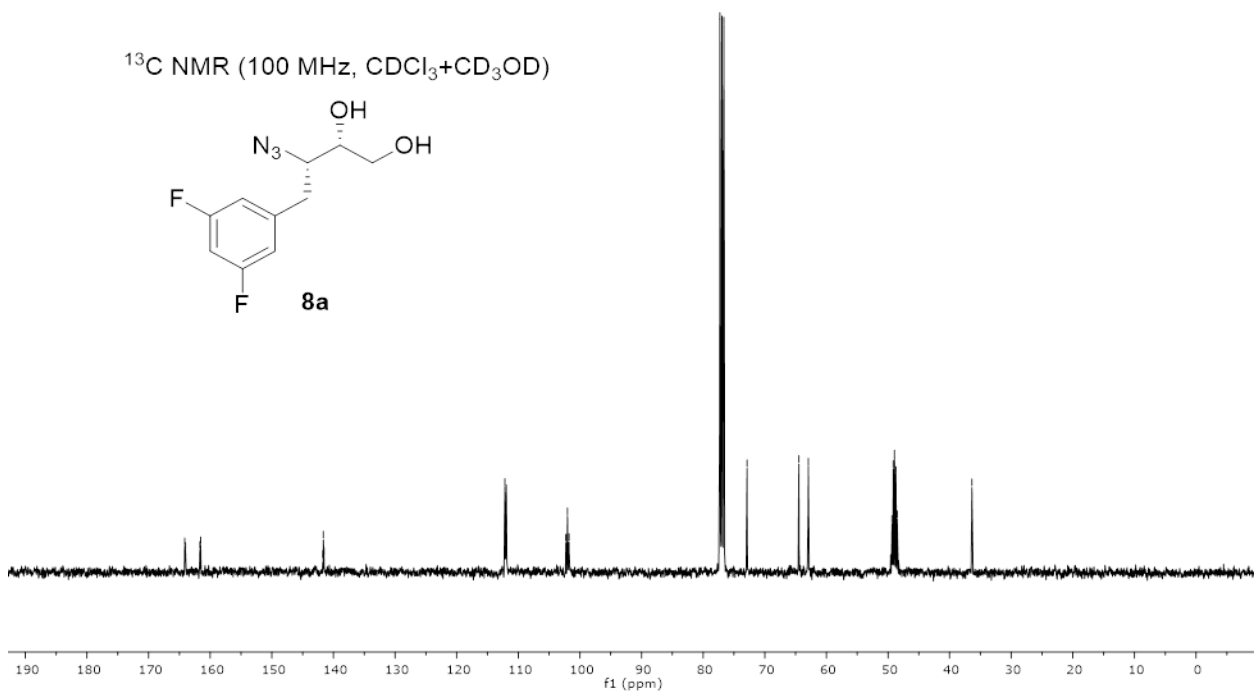
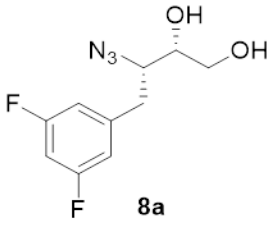




¹H NMR (400 MHz, CDCl₃+CD₃OD)



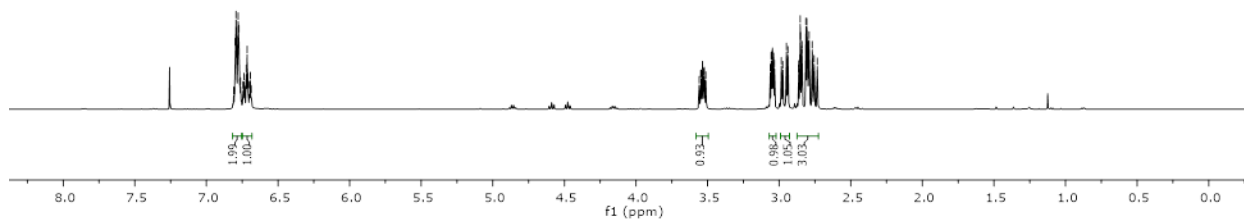
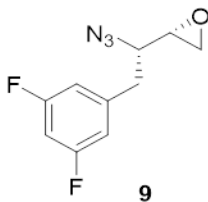
¹³C NMR (100 MHz, CDCl₃+CD₃OD)



6.81
6.80
6.79
6.78
6.78
6.77
6.76
6.74
6.74
6.73
6.72
6.71
6.70
6.69
6.69

3.56
3.55
3.54
3.54
3.53
3.52
3.51
3.16
3.06
3.05
3.05
3.04
3.04
3.03
2.96
2.95
2.94
2.86
2.86
2.85
2.85
2.84
2.84
2.81
2.81
2.80
2.79
2.77
2.76

¹H NMR (400 MHz, CDCl₃)



164.18
161.71
161.58

140.32
140.23

112.31
112.24
112.12
112.06

102.71
102.46
102.21

77.23
76.92
76.60

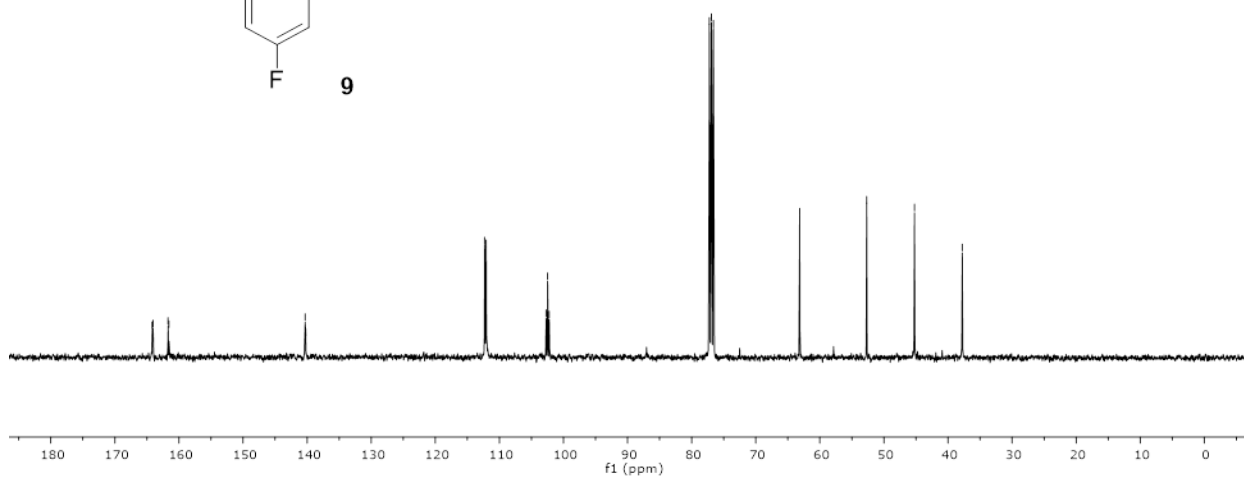
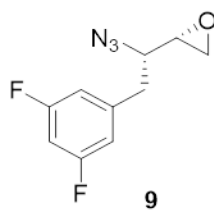
63.14

52.69

46.23

37.78

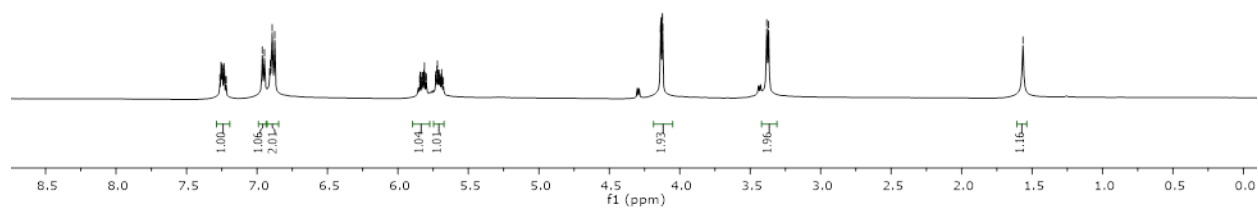
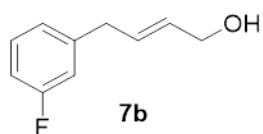
¹³C NMR (100 MHz, CDCl₃)



7.56
7.56
7.25
7.25
7.25
7.24
7.23
7.23
7.22
7.22
6.95
6.91
6.91
6.90
6.89
6.87
5.85
5.84
5.84
5.83
5.83
5.82
5.82
5.81
5.81
5.80
5.80
5.73
5.73
5.72
5.72
5.71
5.71
5.70
5.70
5.69
5.69
5.68
5.68
4.14
4.13
4.12
4.12
4.12
3.38
3.37

— 157

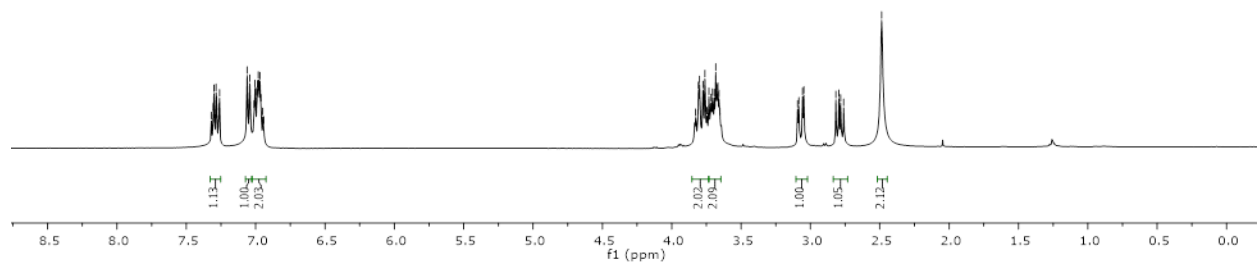
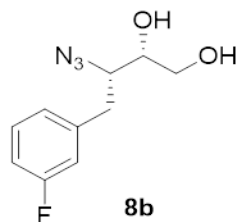
¹H NMR (500 MHz, CDCl₃)

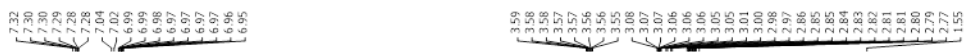


7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.06
7.04
7.01
7.00
7.00
6.99
6.99
6.98
6.98
6.97
6.96
6.95
6.94

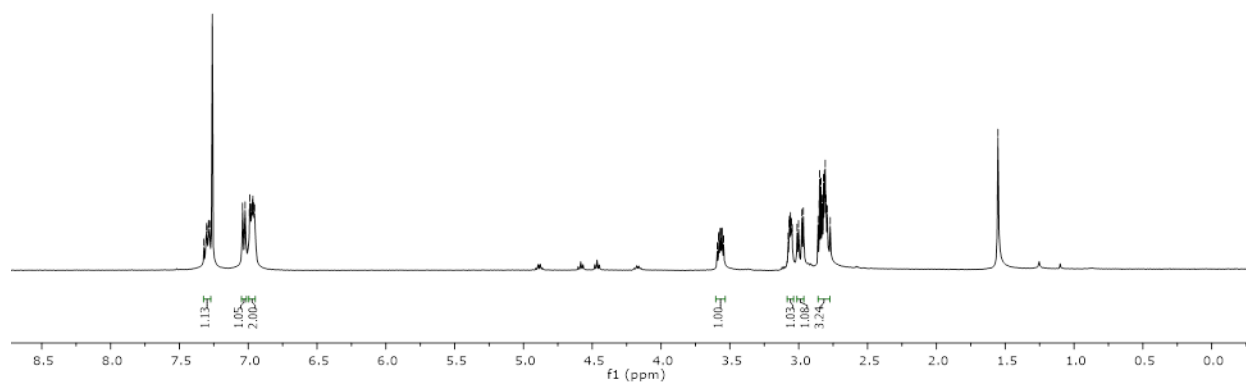
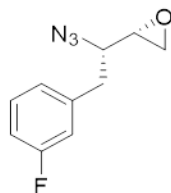
3.83
3.81
3.80
3.77
3.77
3.75
3.75
3.72
3.72
3.72
3.71
3.70
3.69
3.68
3.67
3.67
3.66
3.65
3.09
3.08
3.06
3.05
2.82
2.82
2.78
2.76
2.49

¹H NMR (400 MHz, CDCl₃)

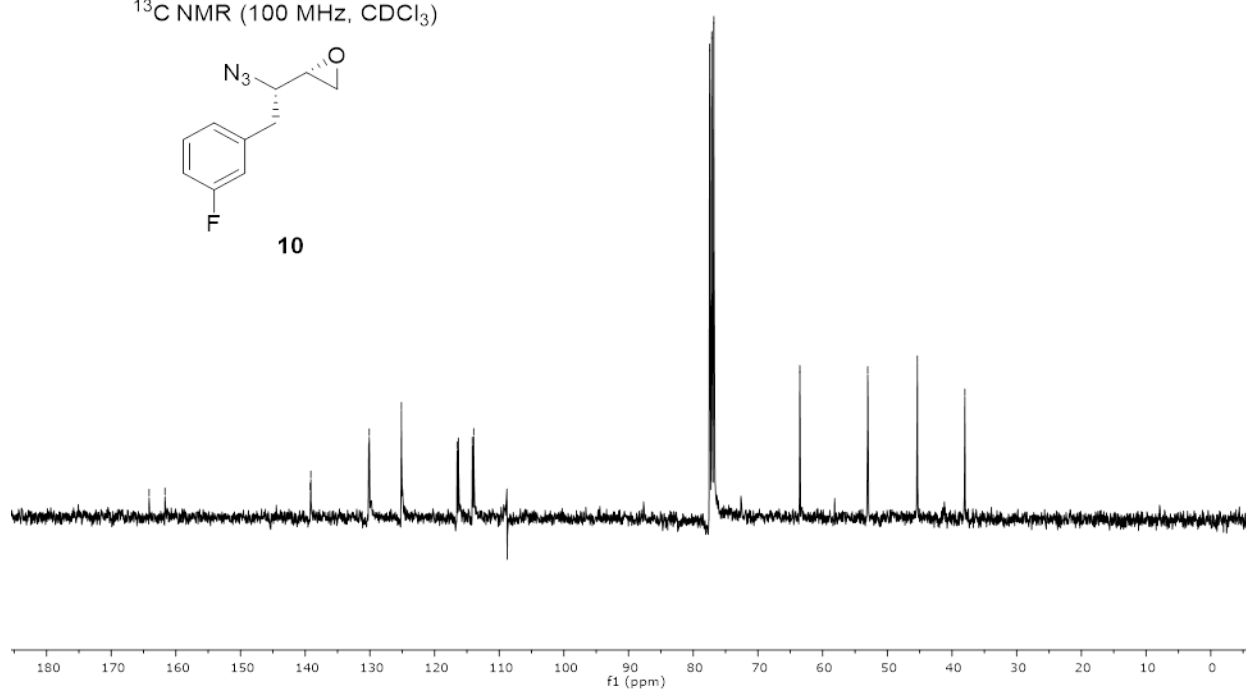
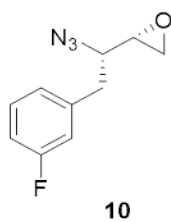


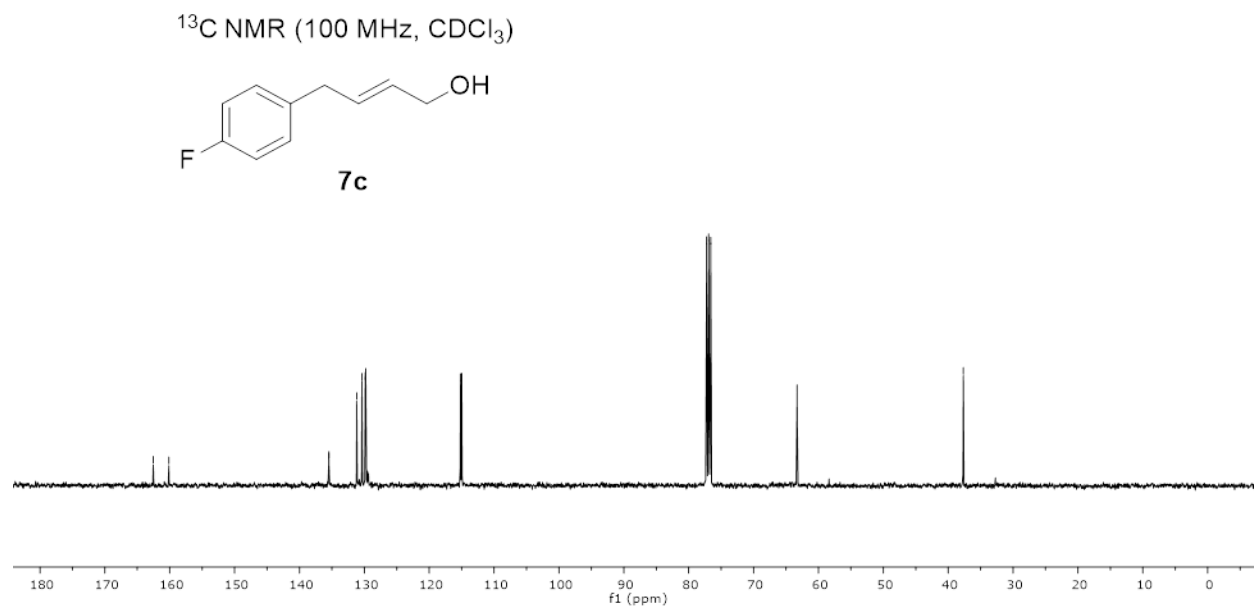
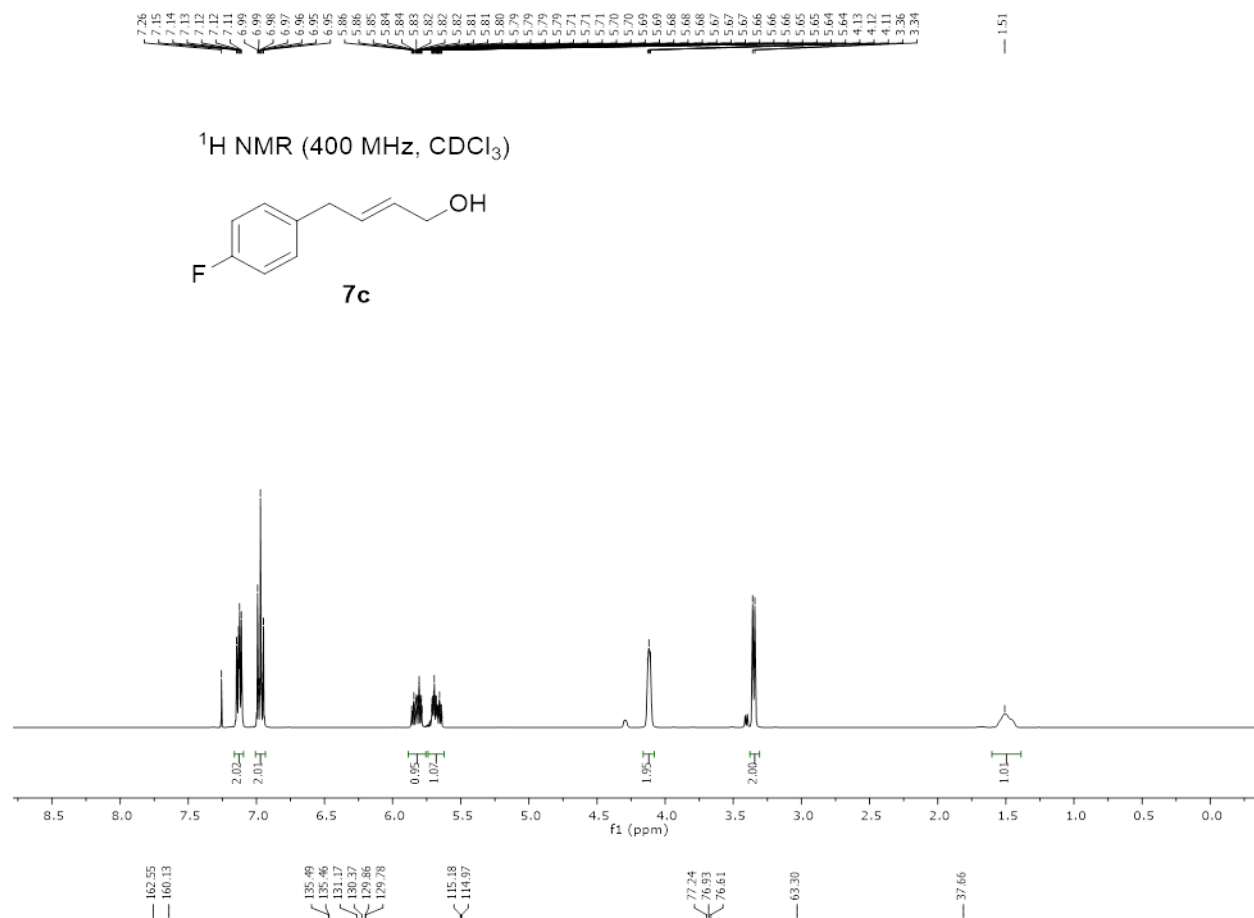


¹H NMR (400 MHz, CDCl₃)



¹³C NMR (100 MHz, CDCl₃)

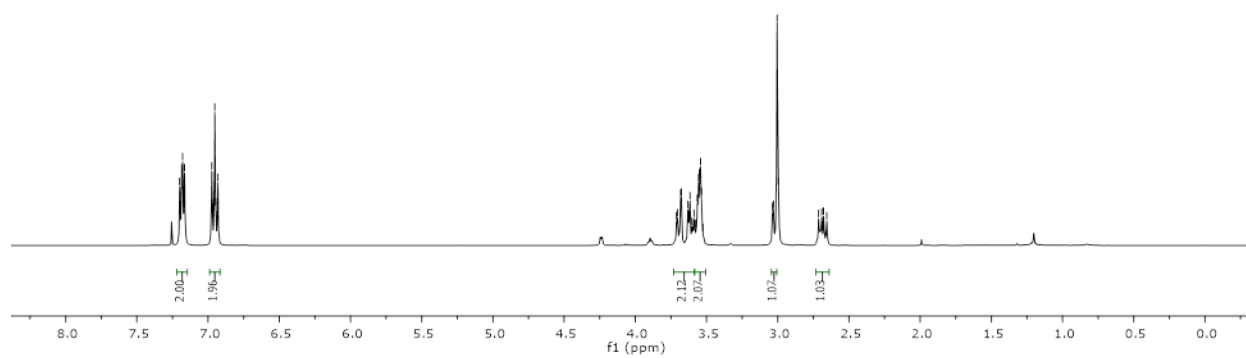
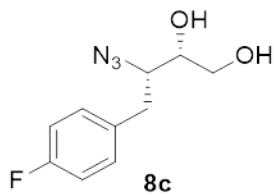




7.20
7.19
7.19
7.18
7.17
6.97
6.96
6.95
6.95
6.93

3.71
3.70
3.68
3.68
3.63
3.62
3.60
3.58
3.57
3.56
3.55
3.54
3.53
3.53
3.53
3.00
2.99
2.71
2.69
2.68
2.66

^1H NMR (400 MHz, $\text{CDCl}_3+\text{CD}_3\text{OD}$)



162.91
160.98

133.71
132.58
130.71
130.64

115.31
115.10

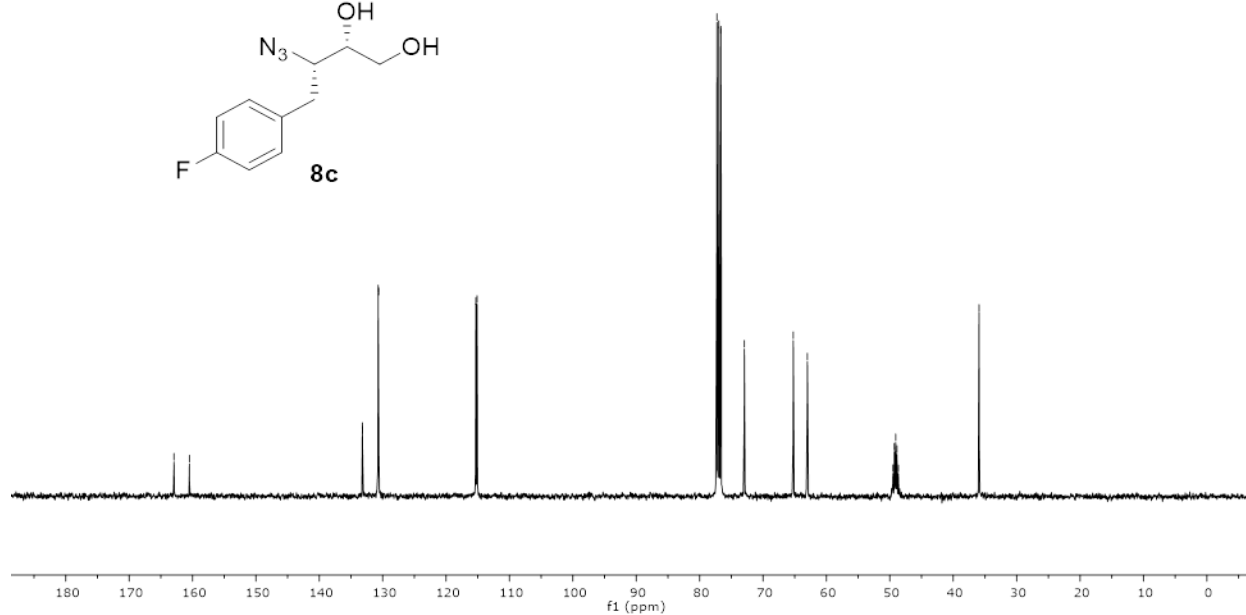
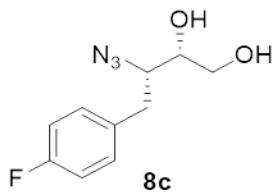
77.29
76.97
76.65
72.96

65.23
63.01

49.51
49.30
49.09
48.88
48.66

35.92

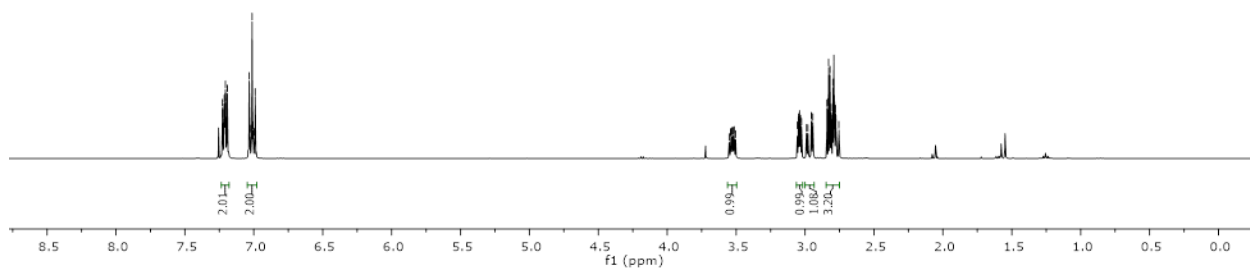
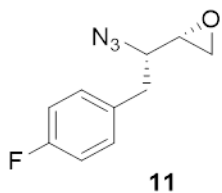
^{13}C NMR (100 MHz, $\text{CDCl}_3+\text{CD}_3\text{OD}$)



7.23
7.23
7.22
7.21
7.21
7.21
7.20
7.19
7.19
7.03
7.02
7.01
7.01
6.99

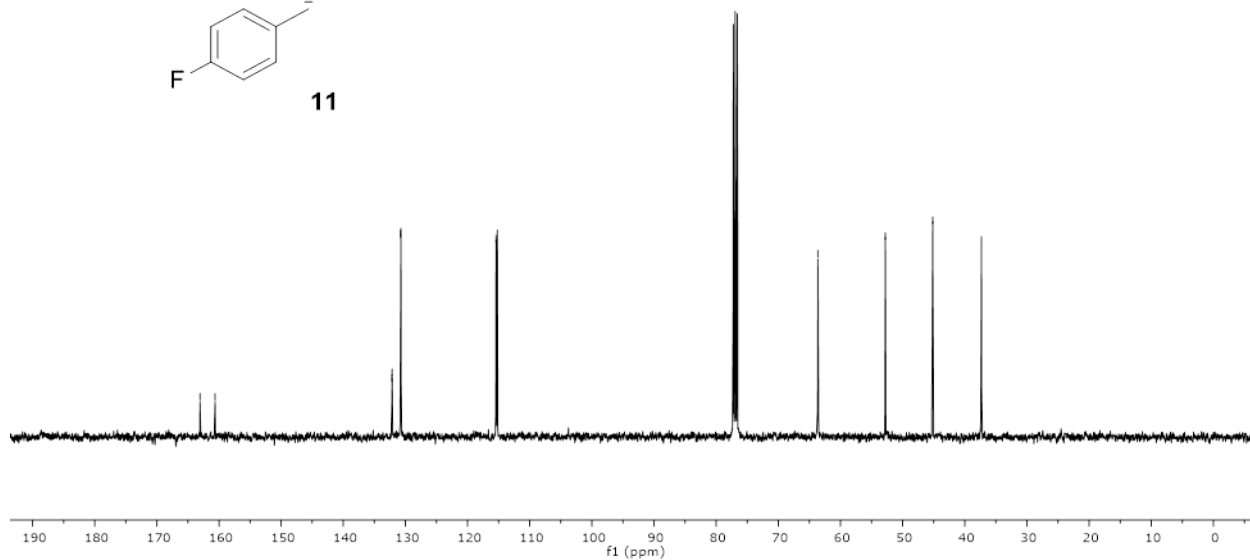
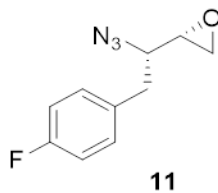
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3.54
3.53
3.52
3.52
3.50
3.06
3.05
3.05
3.04
3.04
3.03
2.99
2.98
2.95
2.84
2.84
2.83
2.82
2.81
2.79
2.79
2.78
2.78

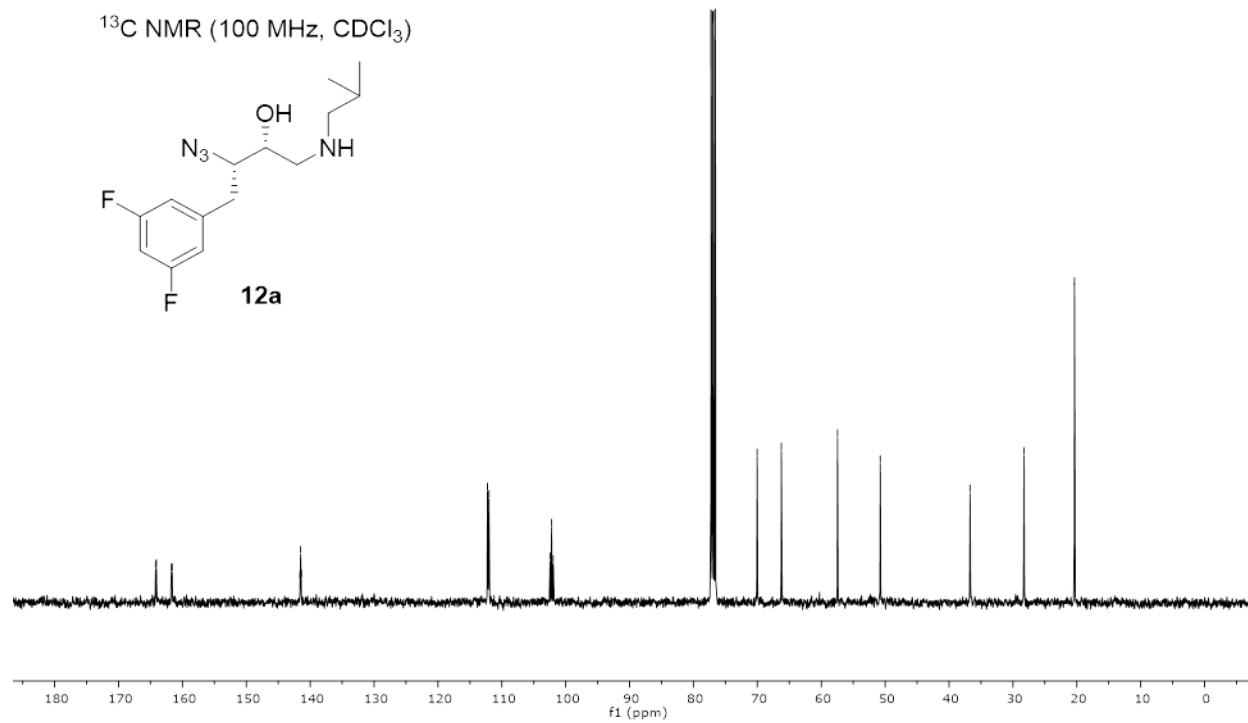
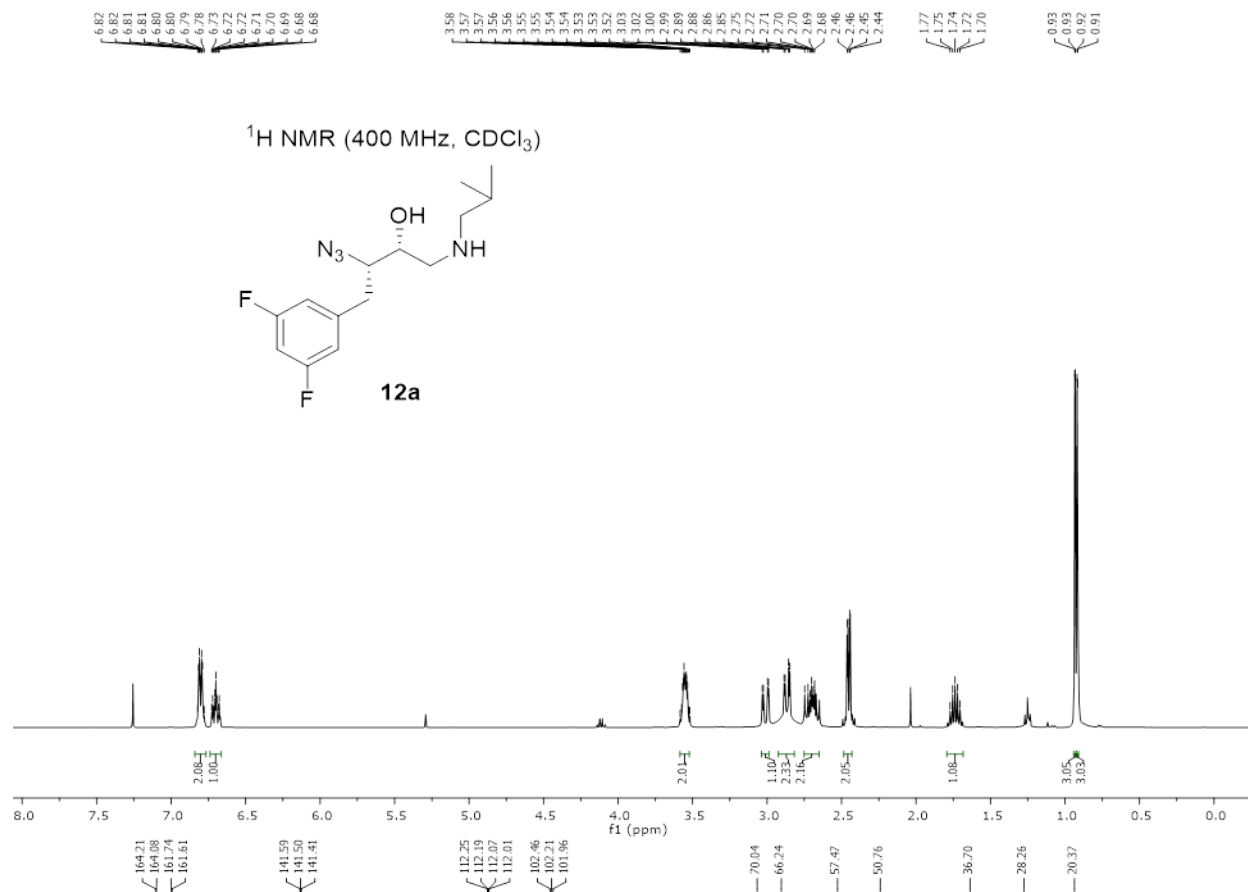
^1H NMR (400 MHz, CDCl_3)

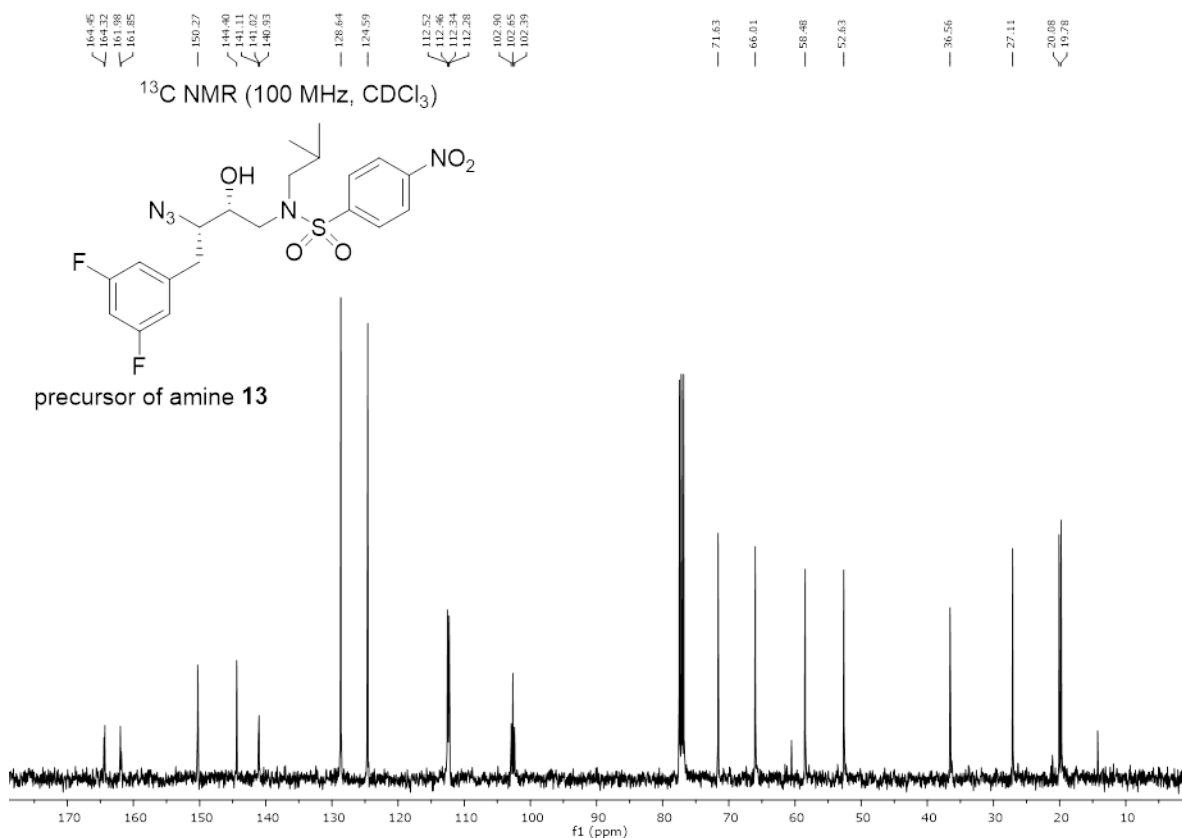
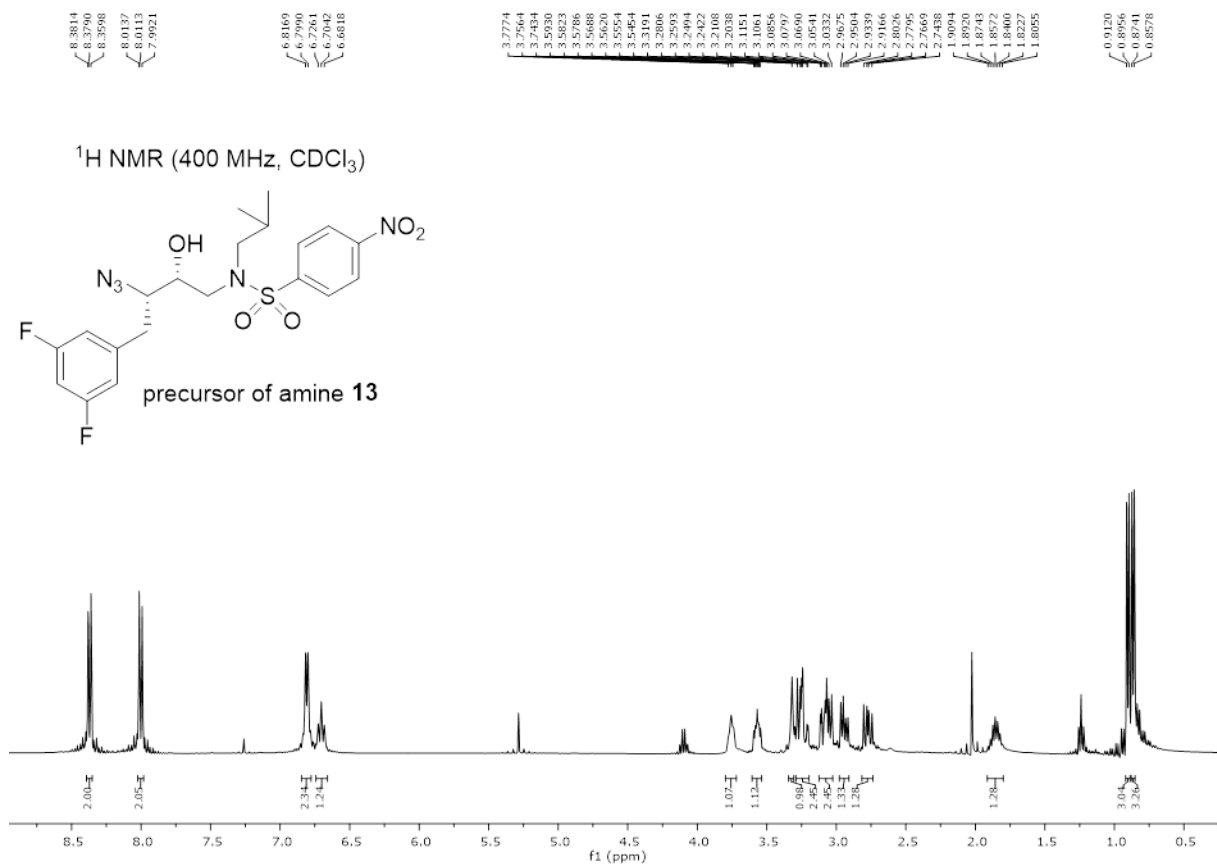


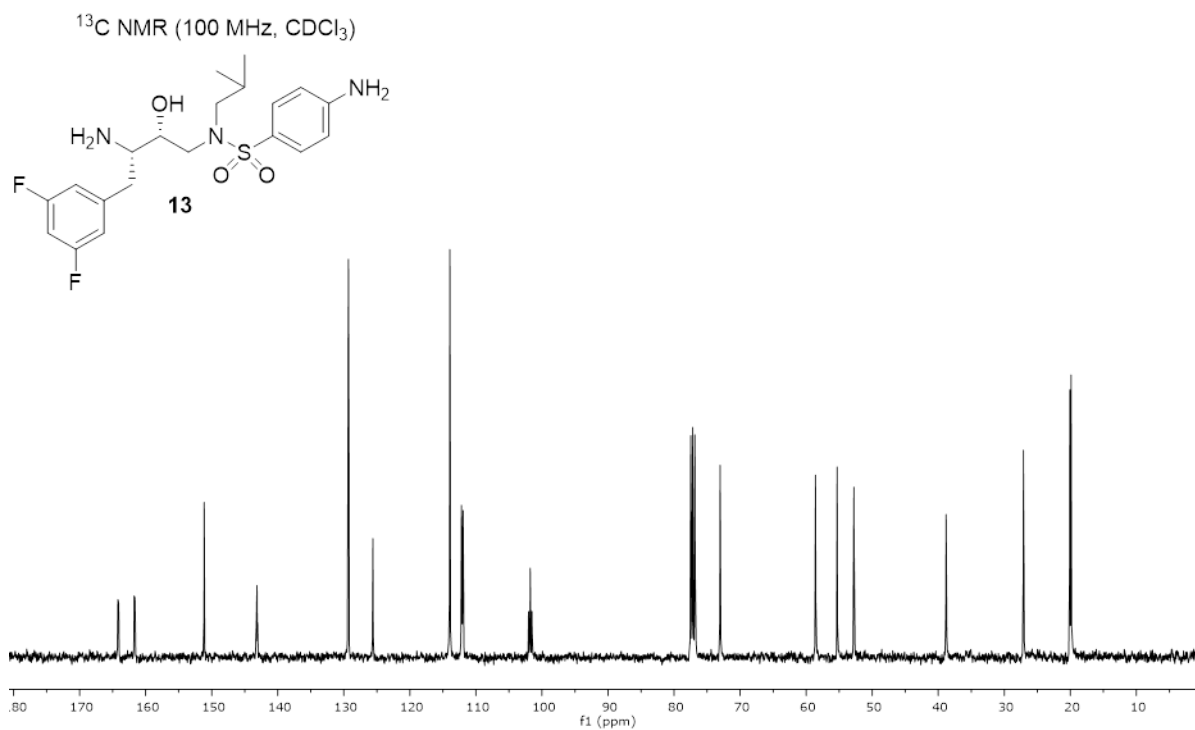
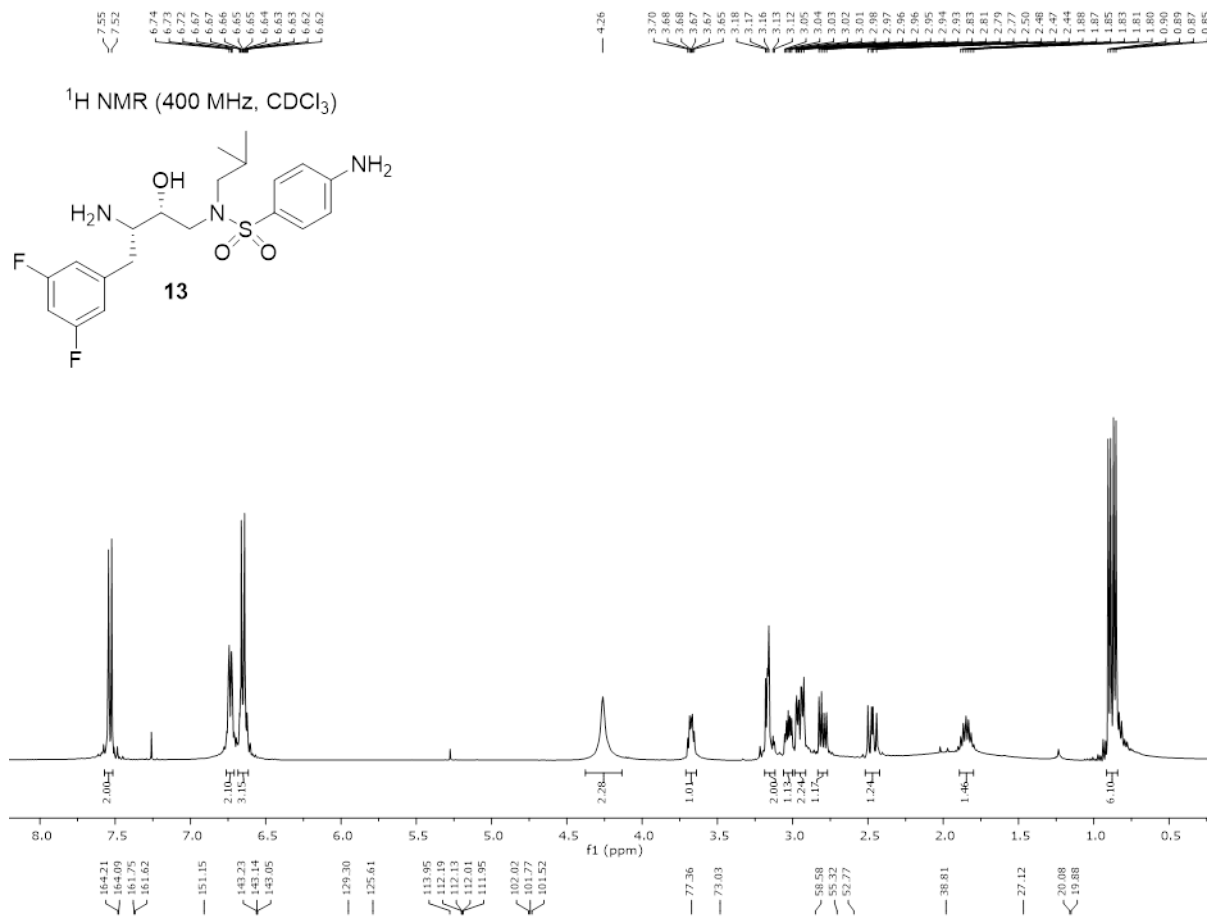
163.06
160.82
132.17
132.14
130.81
130.73
115.49
115.21
63.63
52.78
46.16
37.31

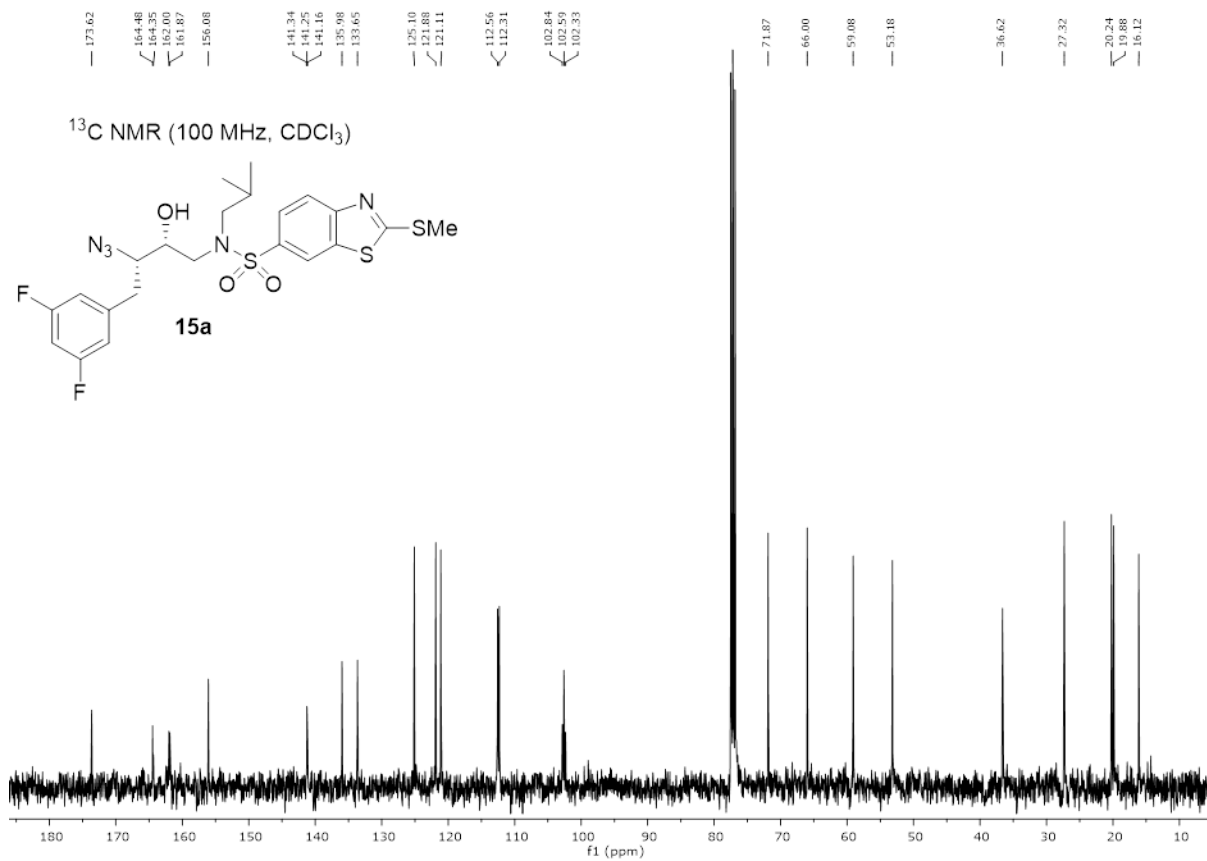
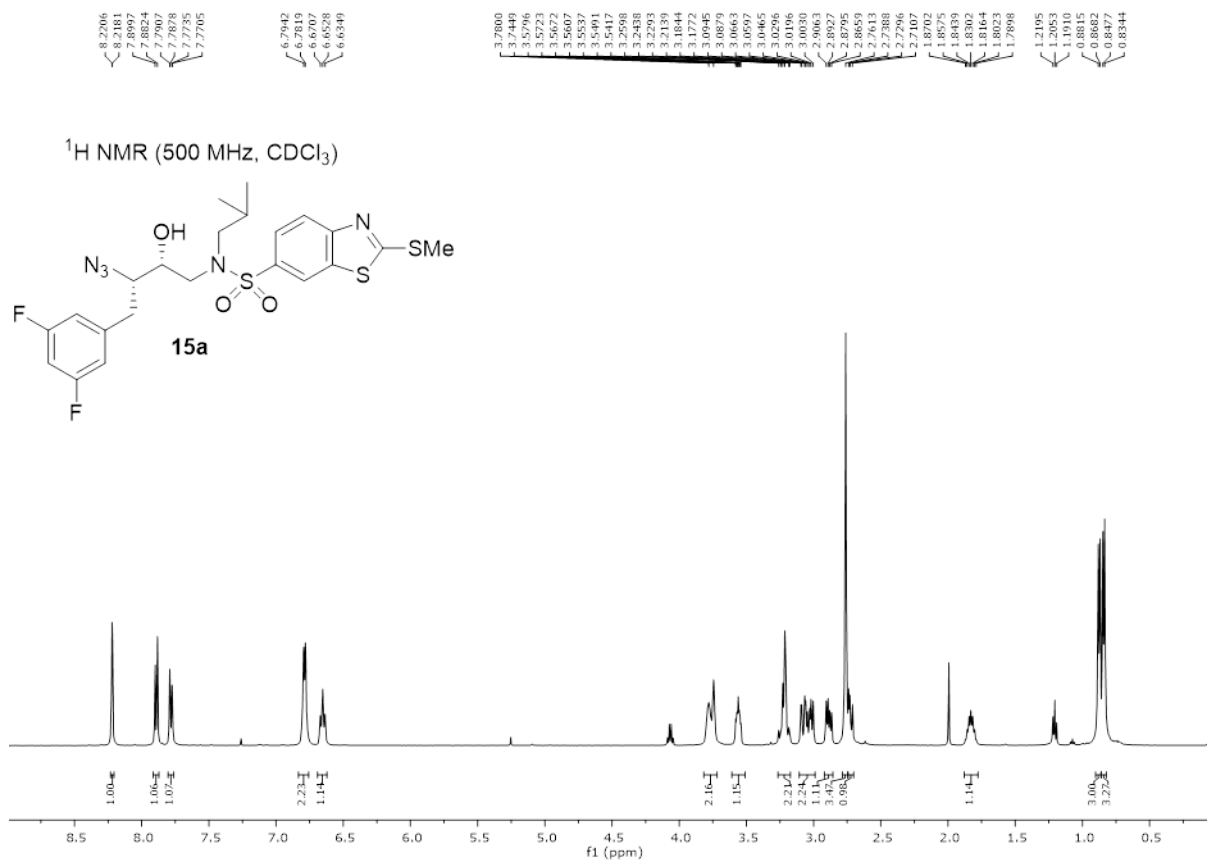
^{13}C NMR (100 MHz, CDCl_3)

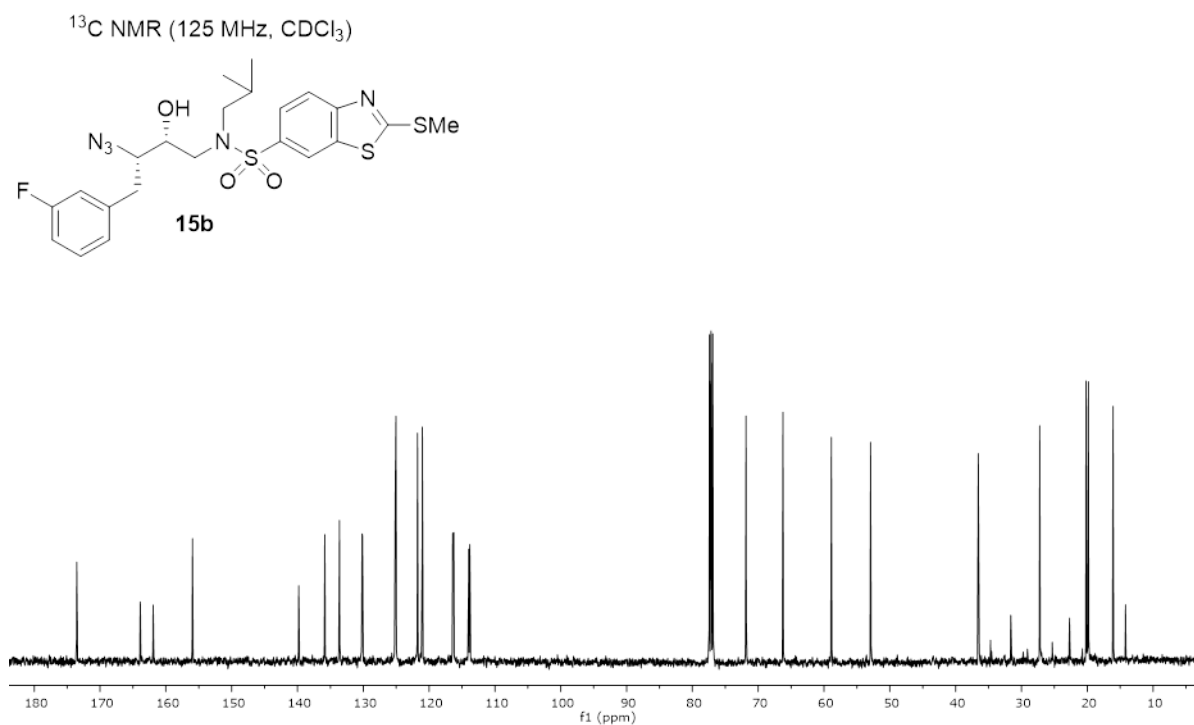
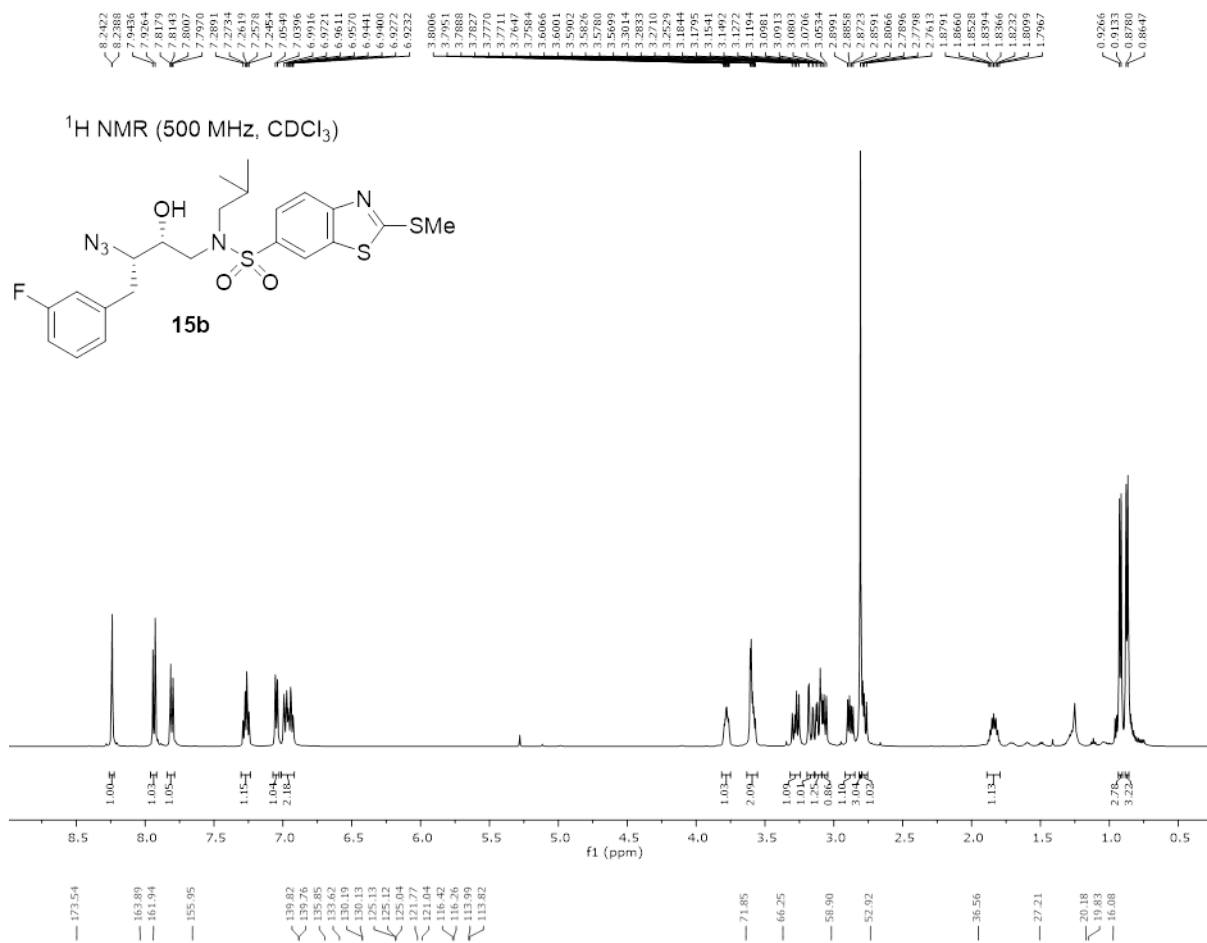


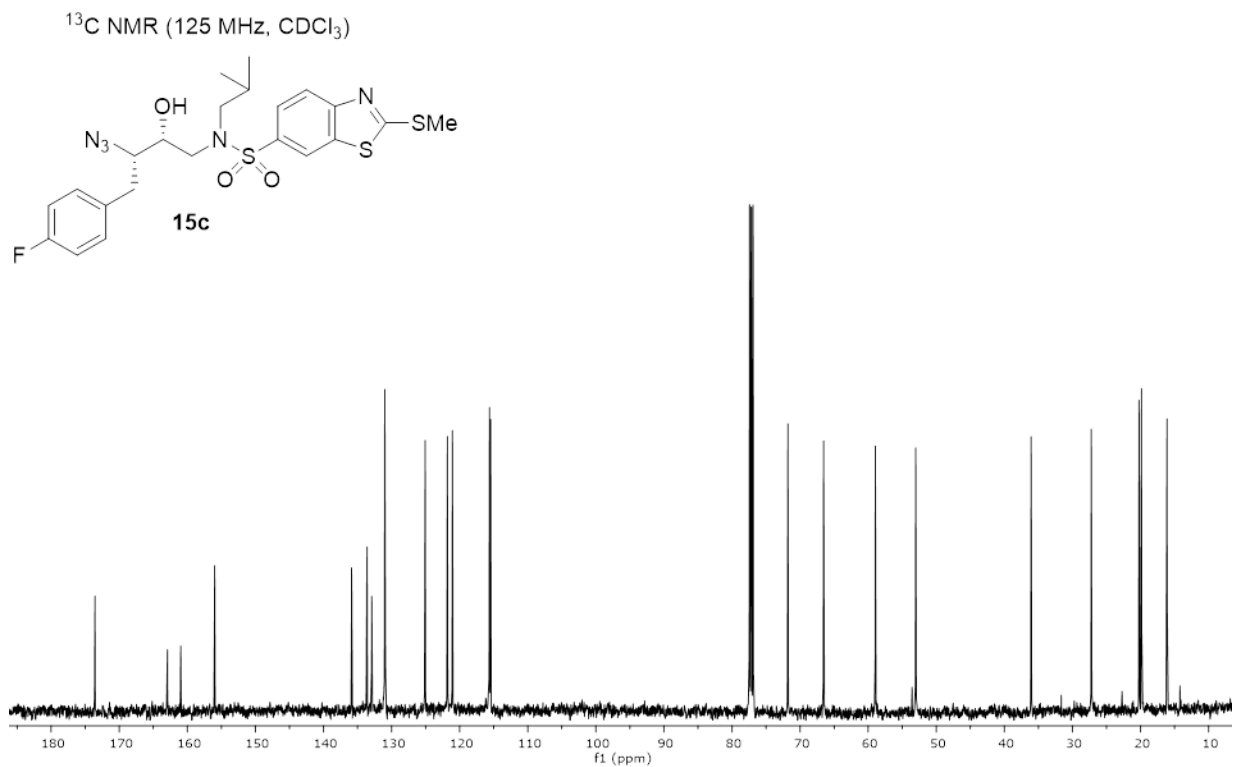
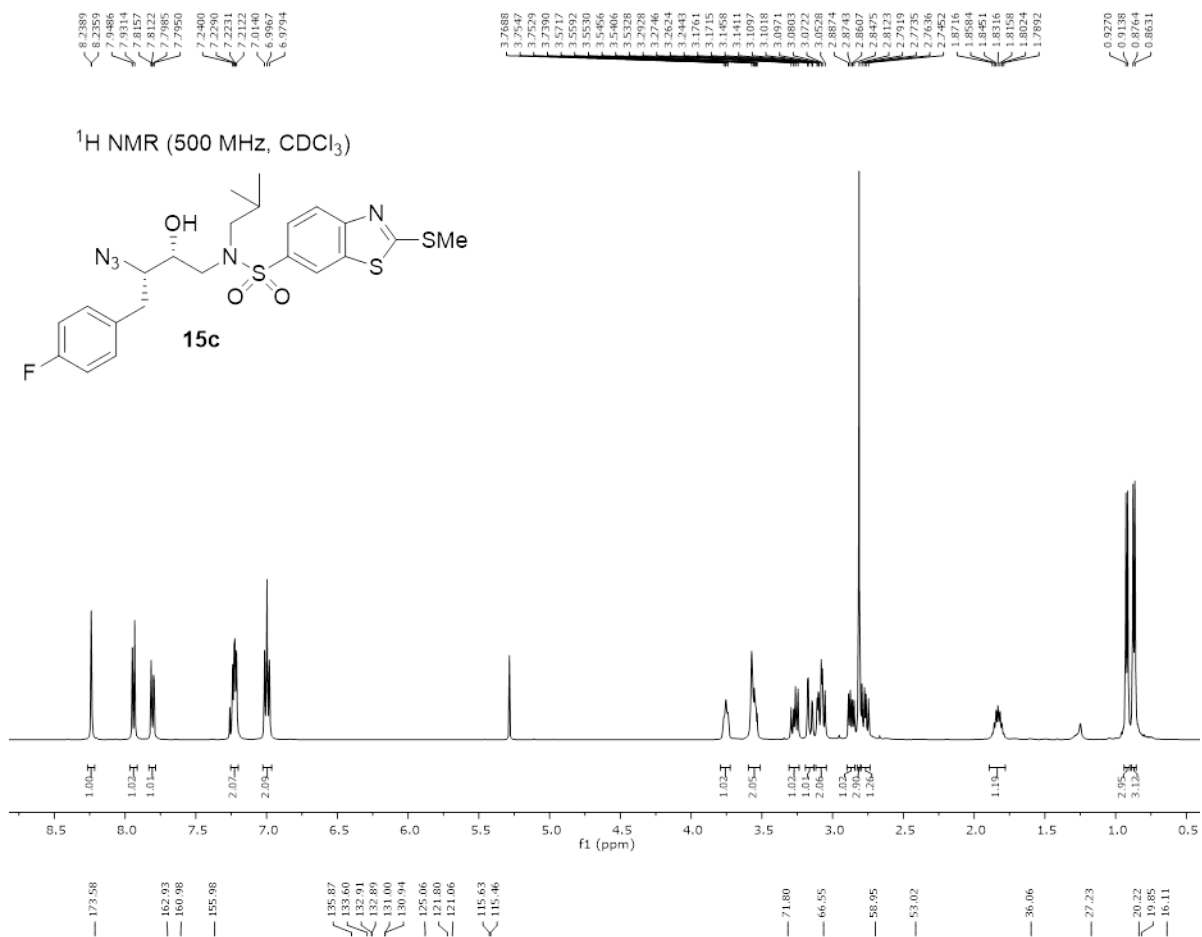


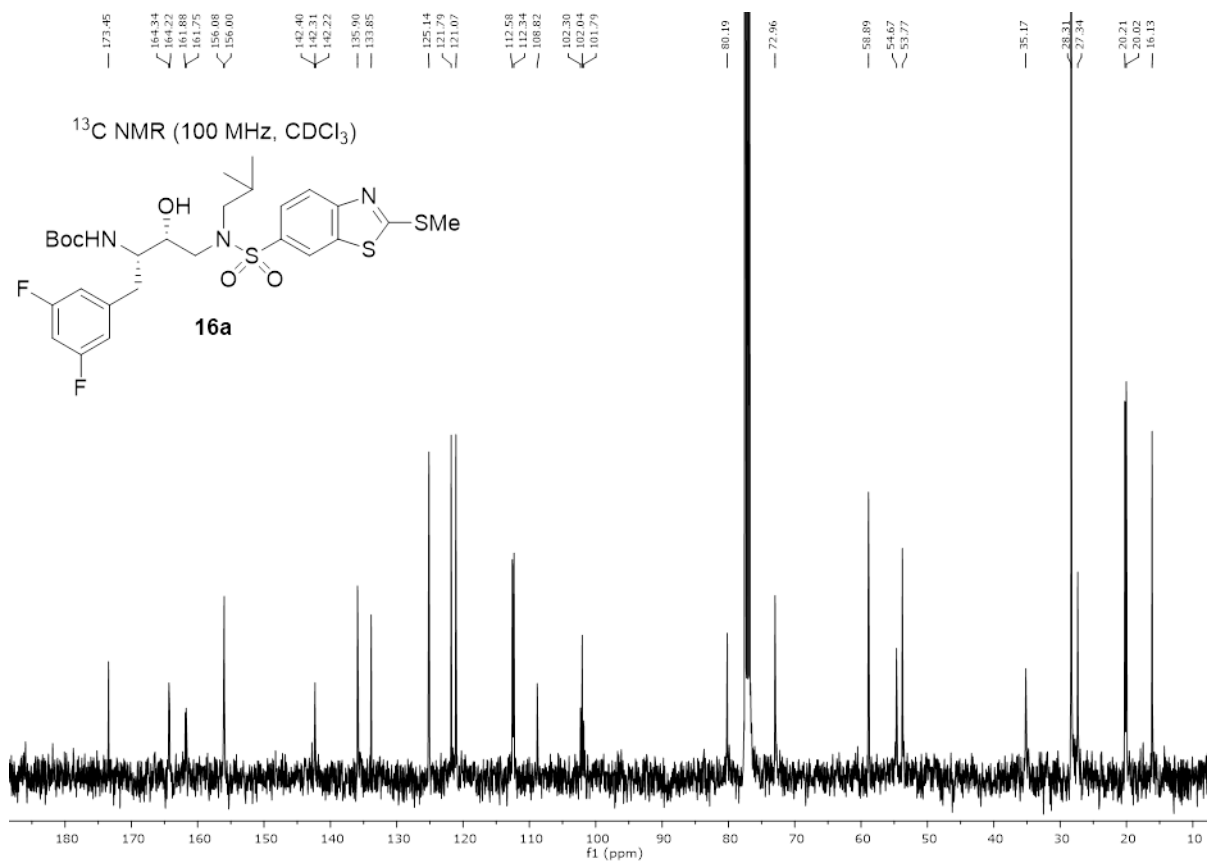
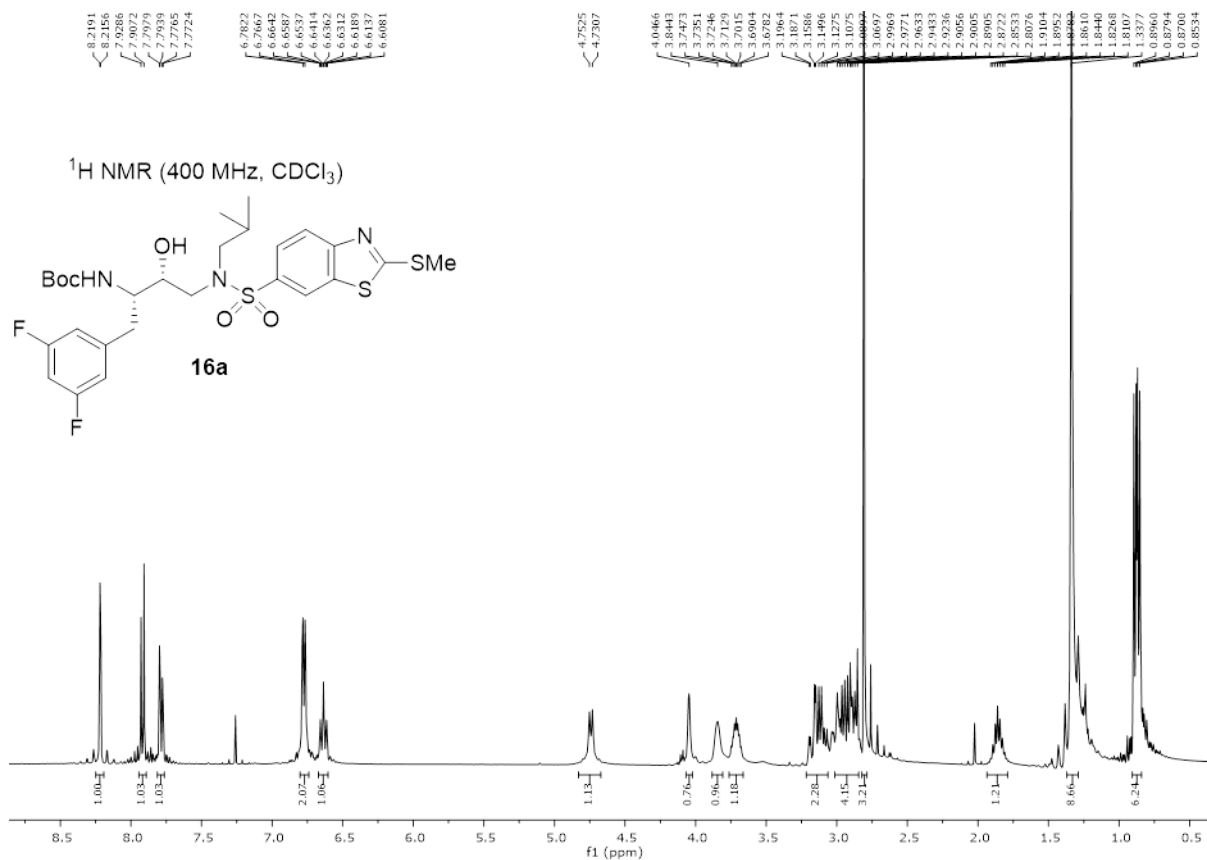


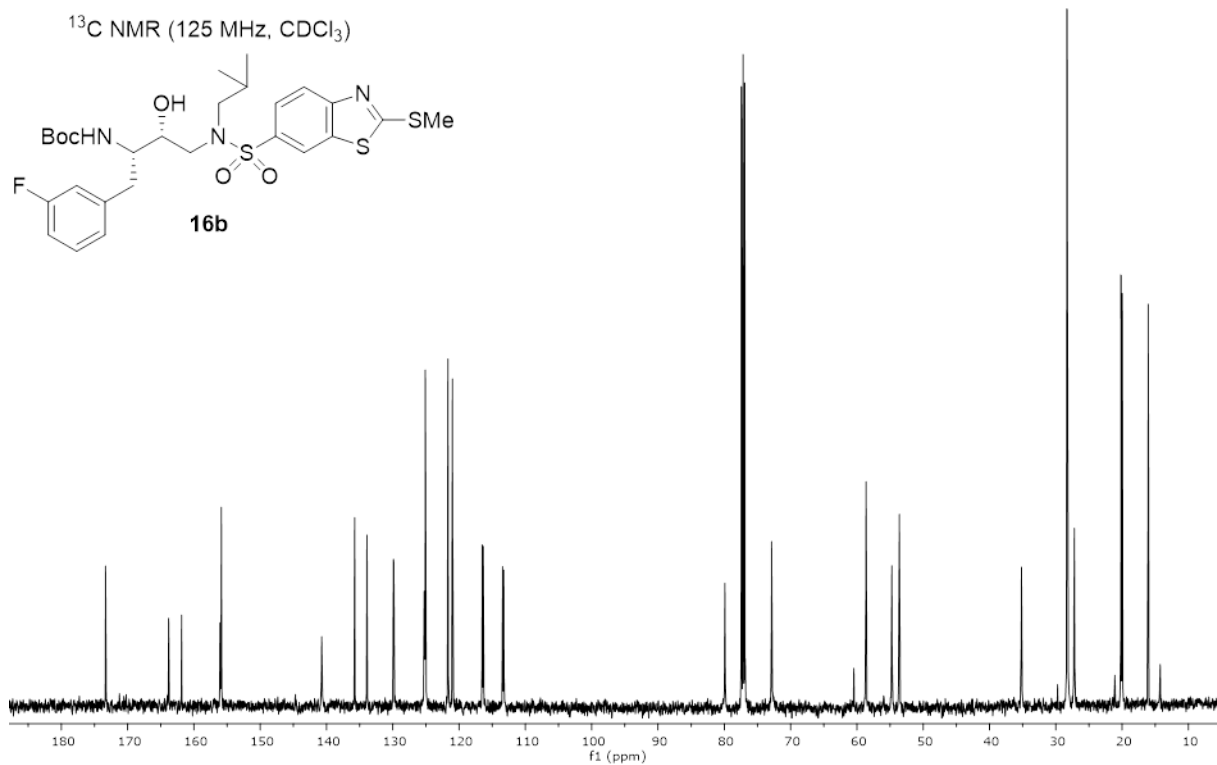
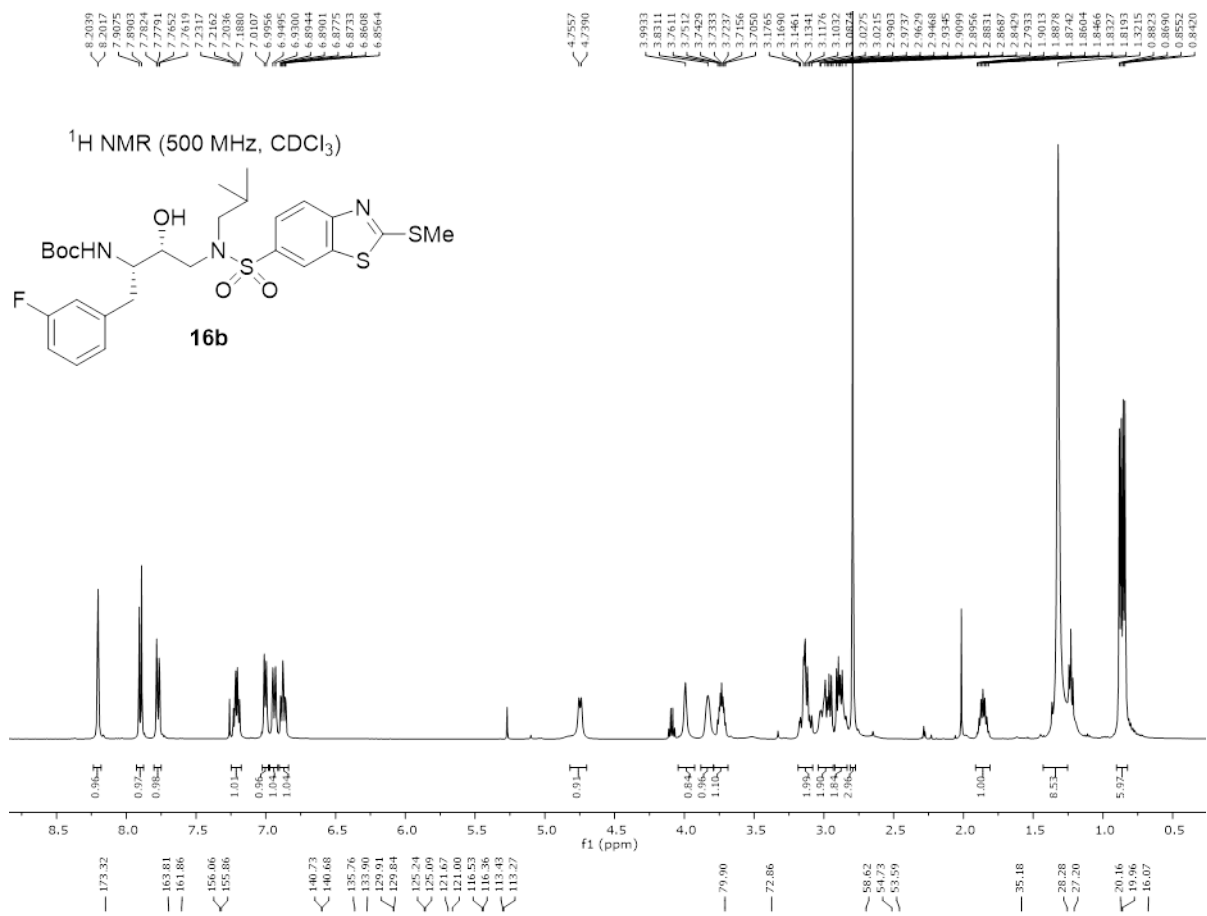


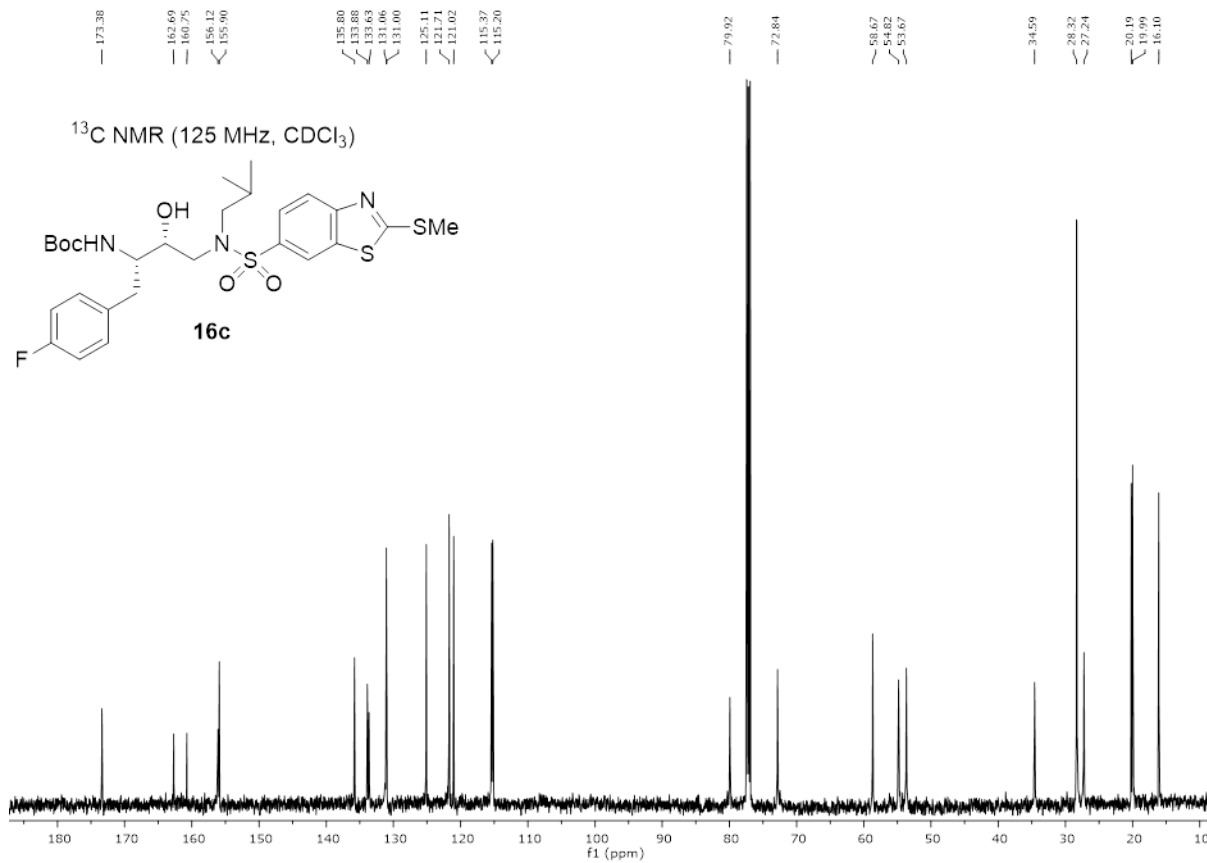
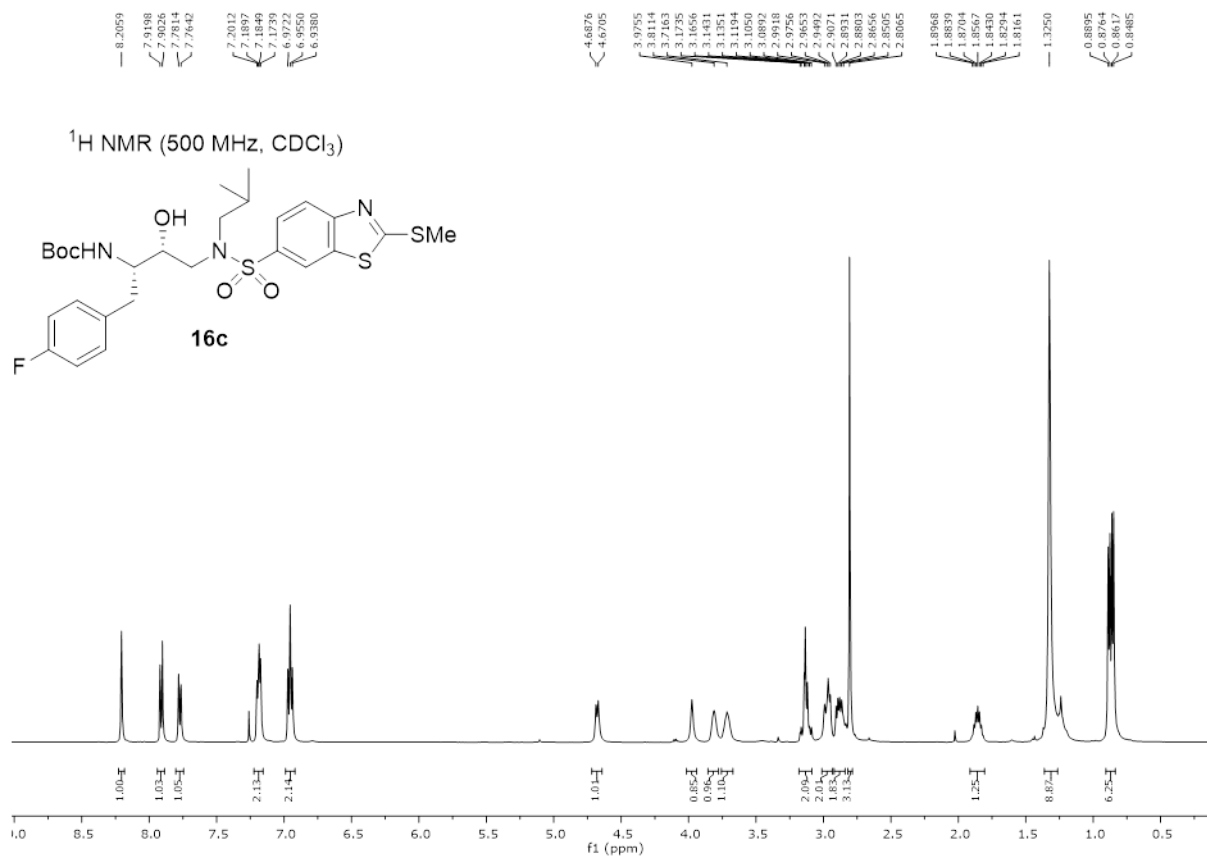


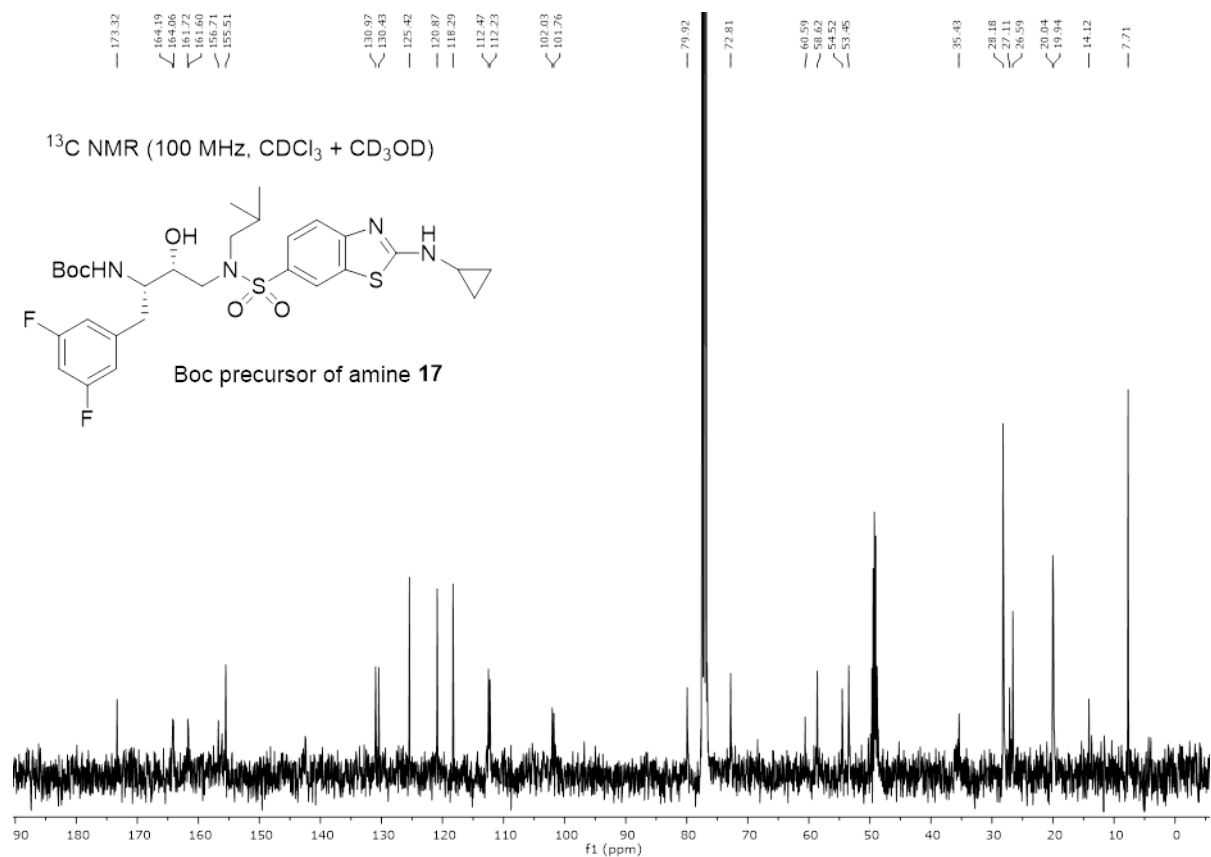
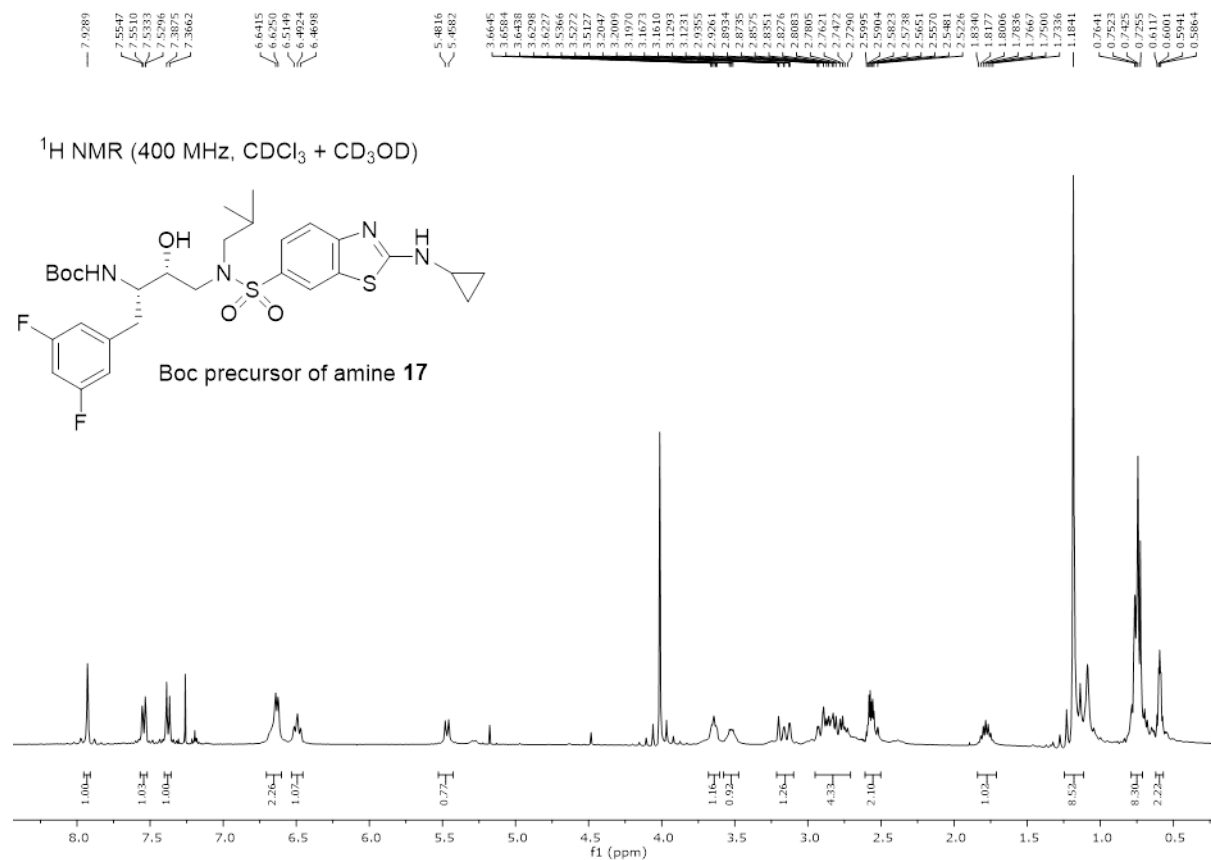


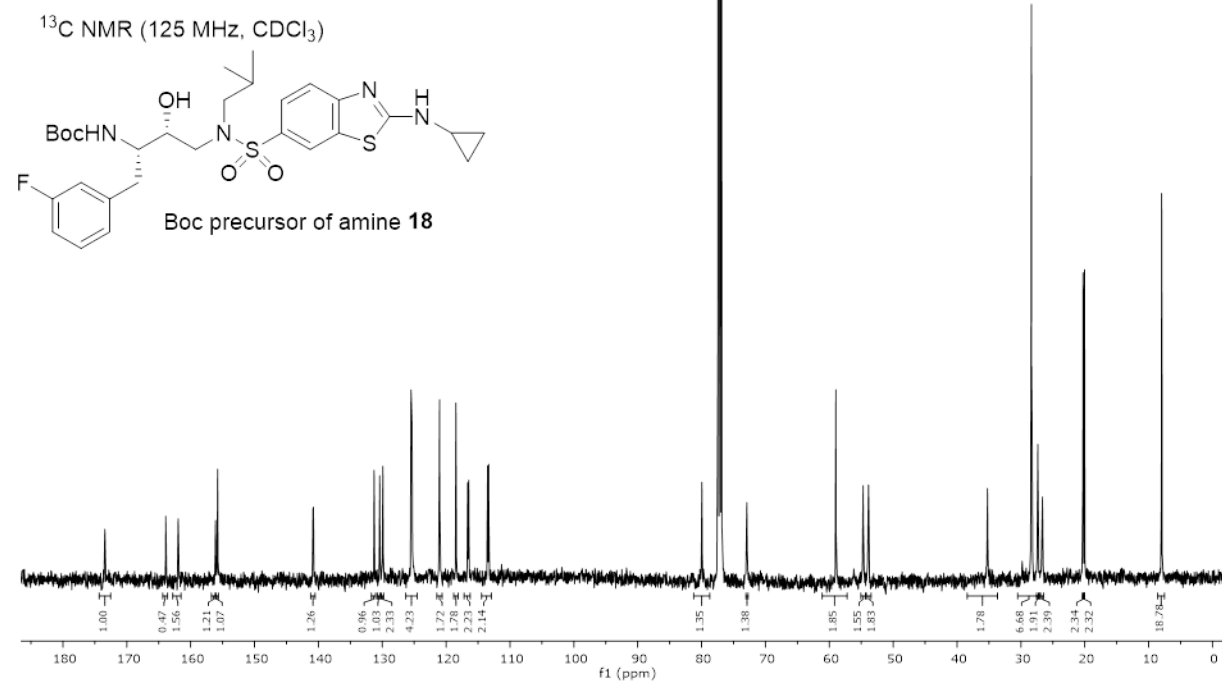
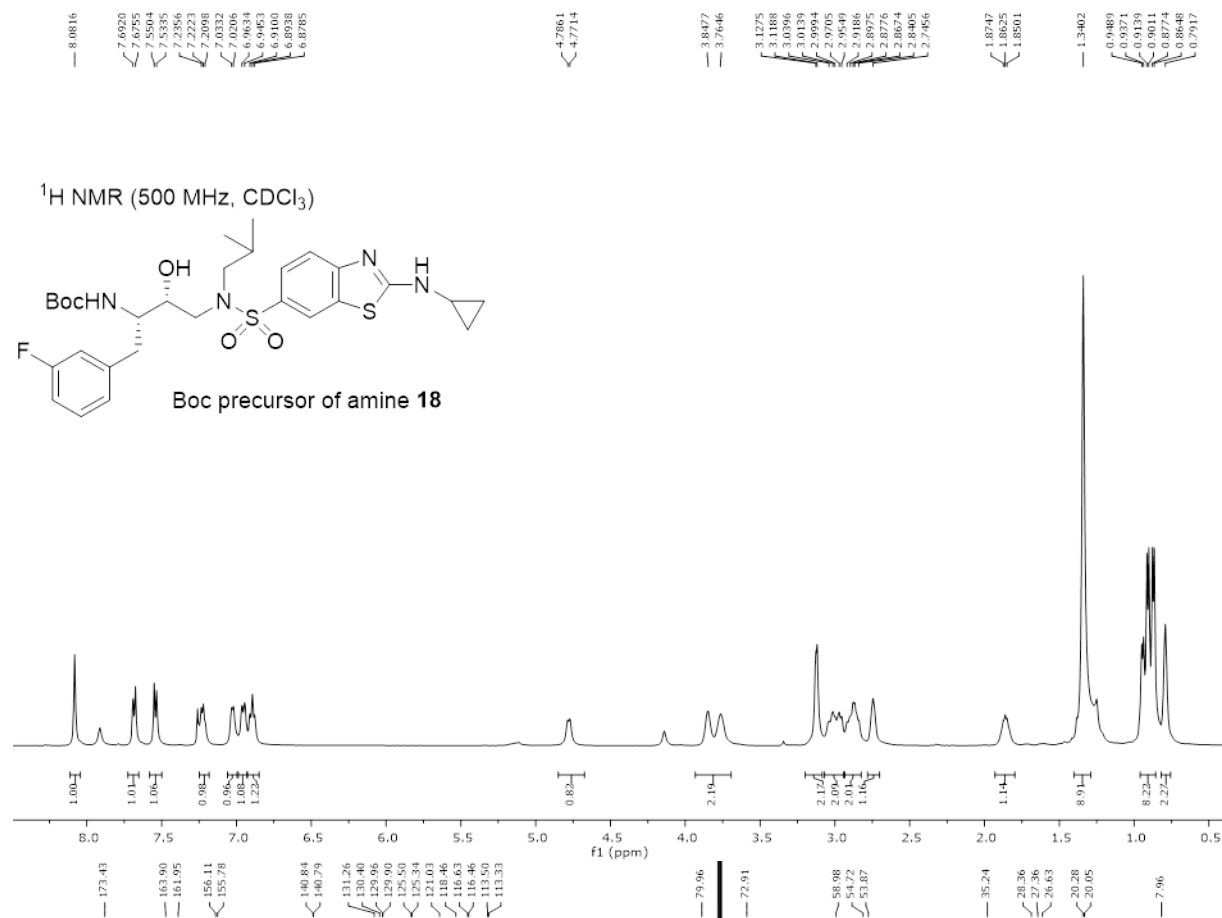


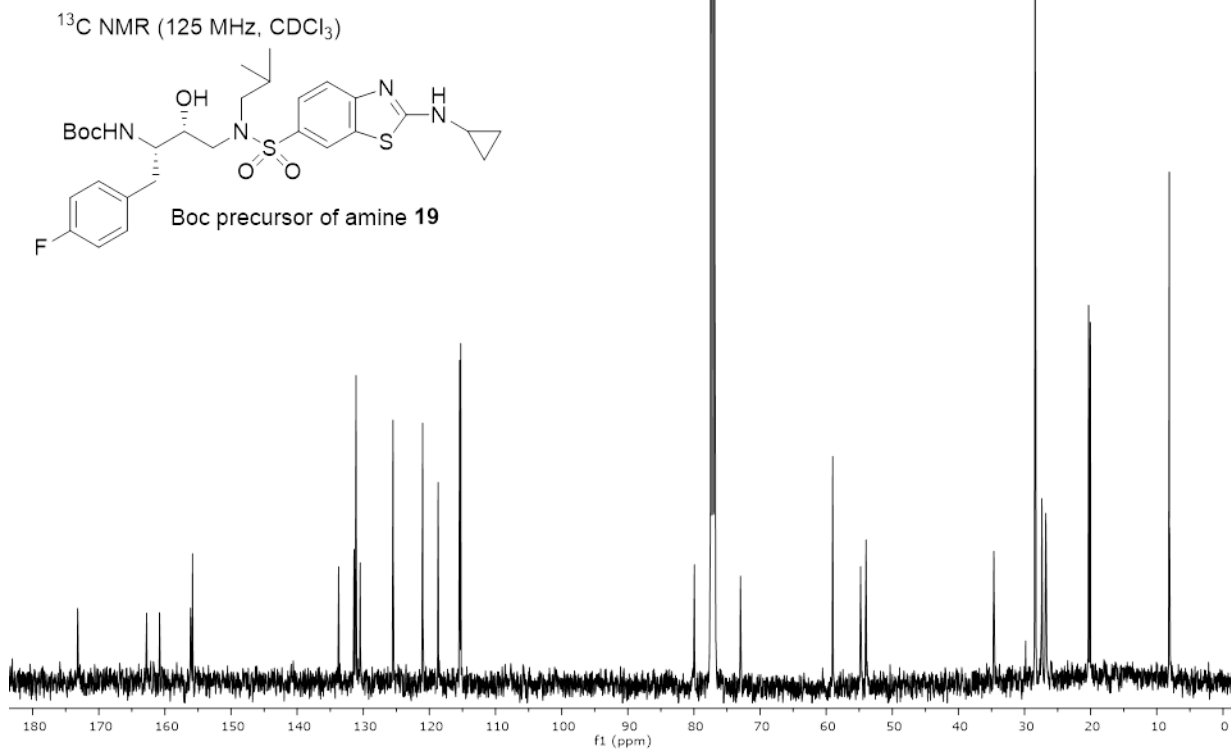
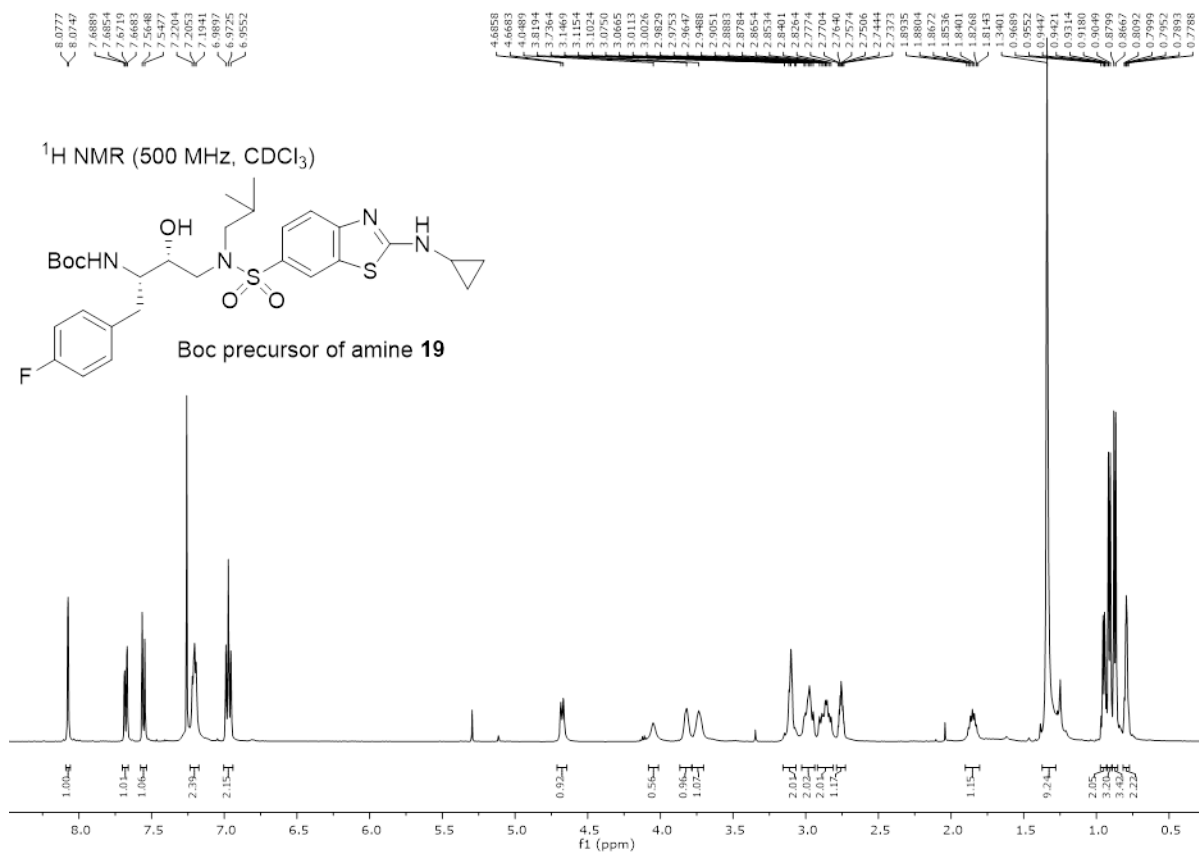


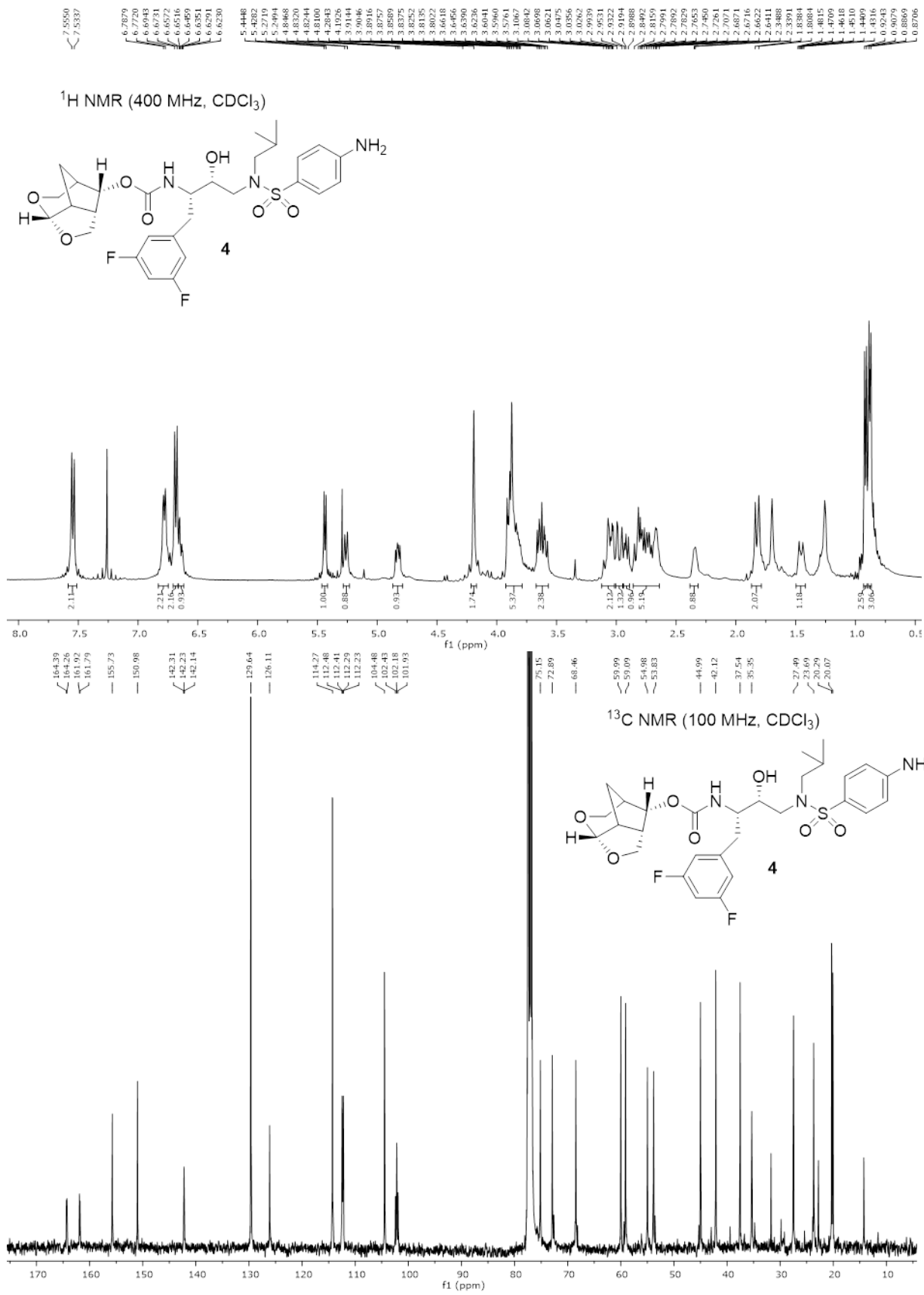






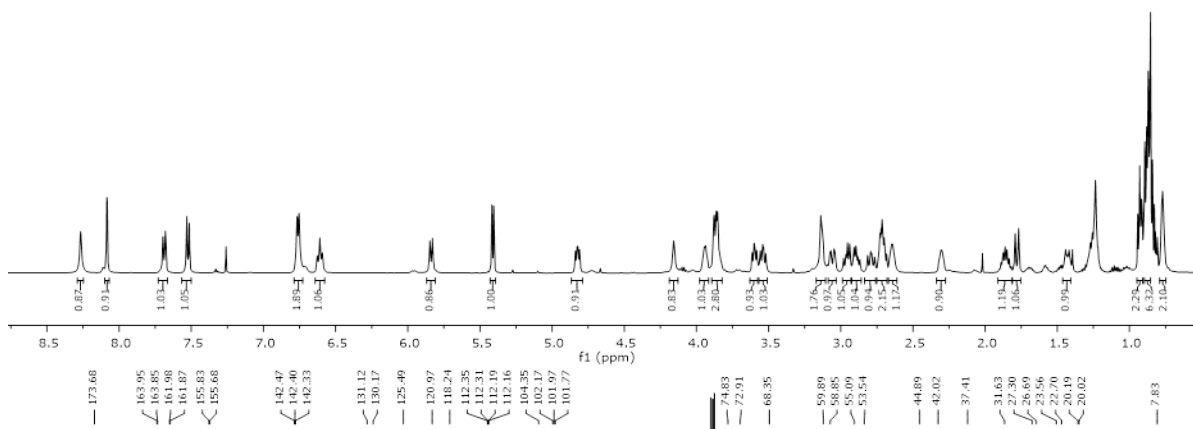
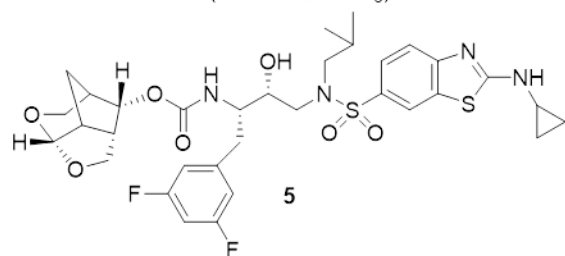




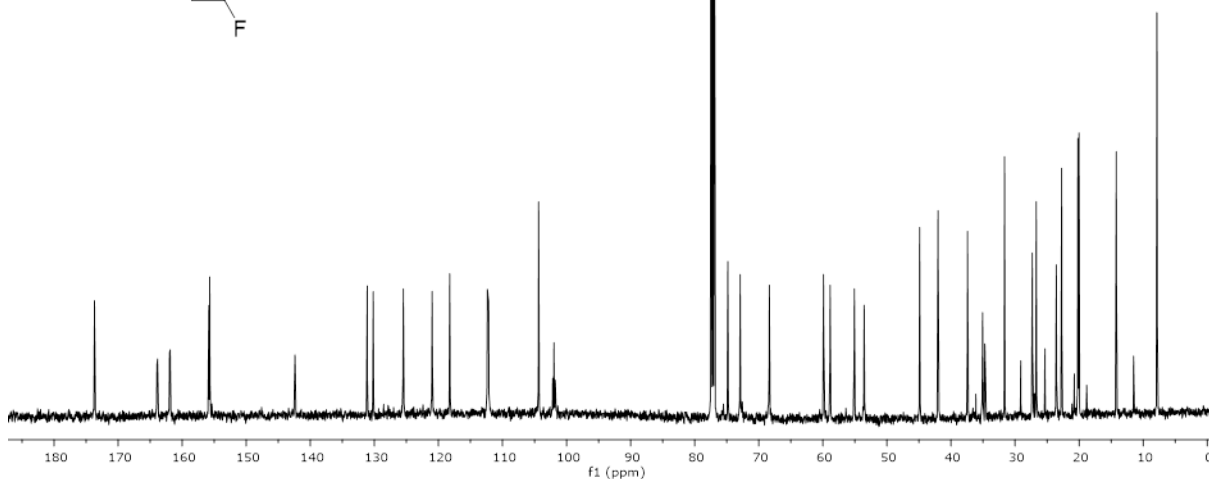
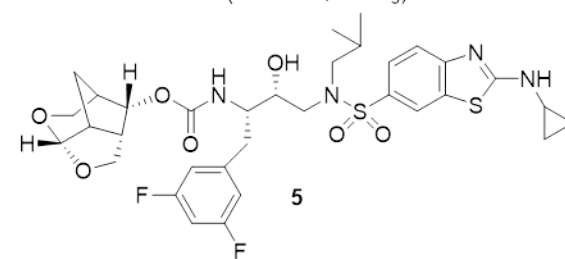


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1.4262
1.4183
1.4183
0.9425
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0.8697
0.8545
0.7710

¹H NMR (500 MHz, CDCl₃)

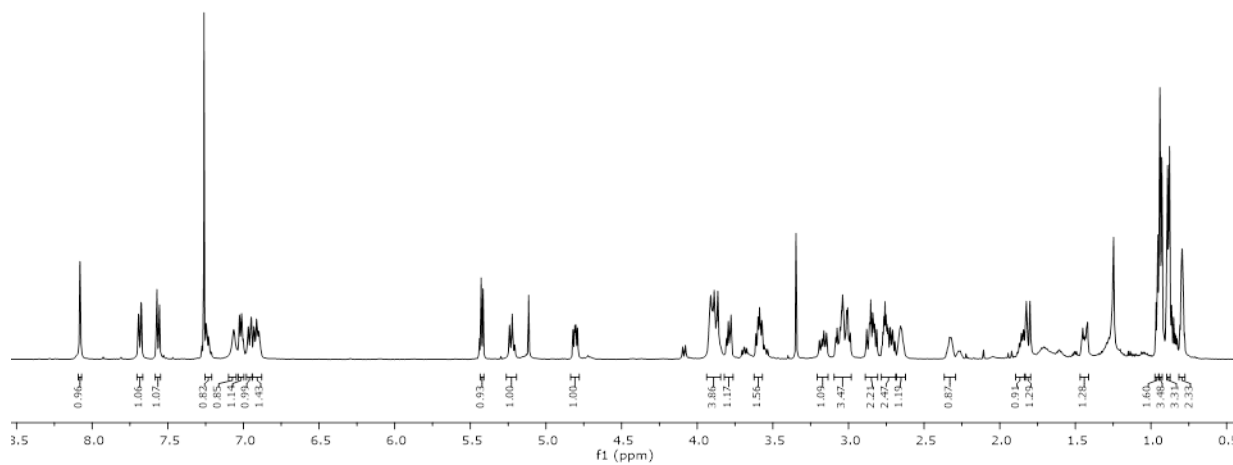
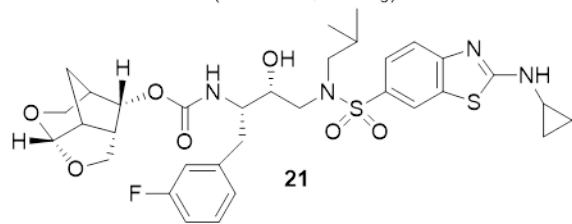


¹³C NMR (125 MHz, CDCl₃)

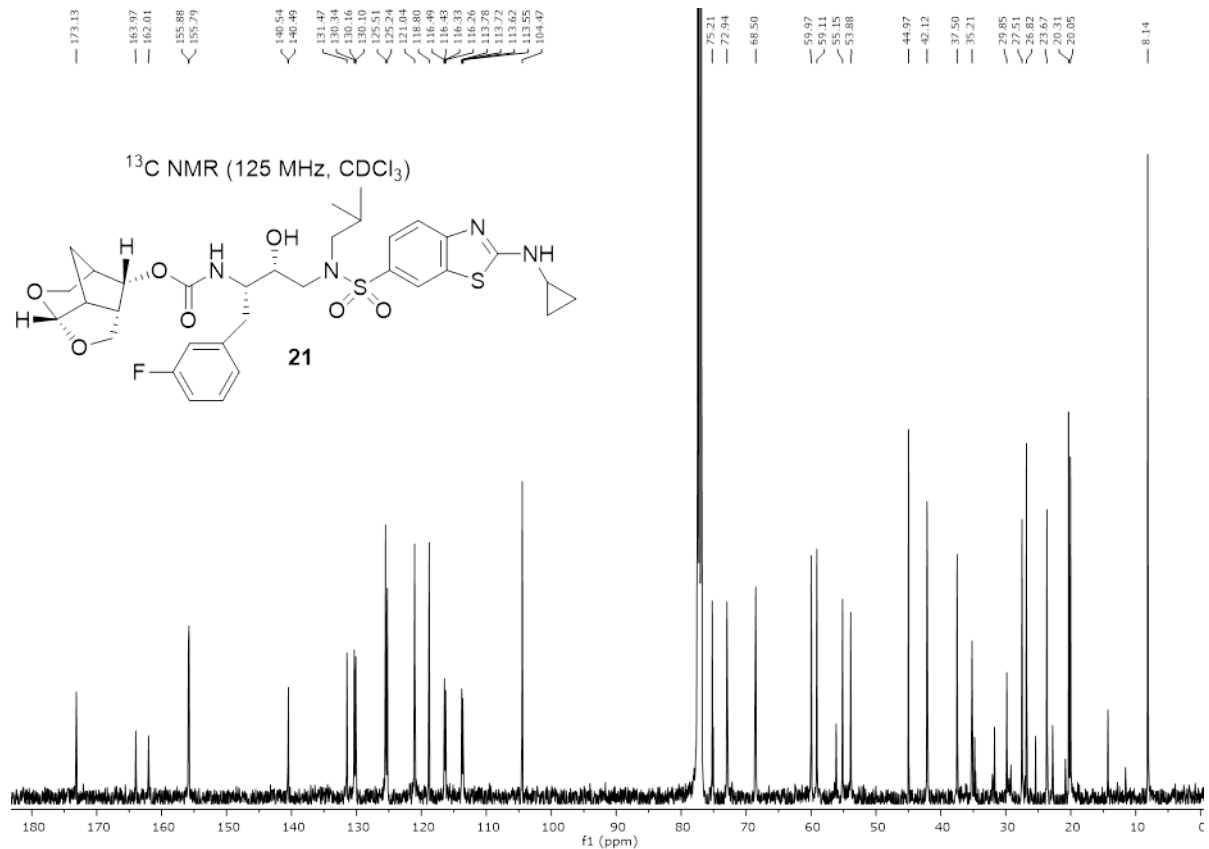


8.08804
7.6948
7.6918
7.6773
7.6747
7.5540
7.22466
7.2309
7.0642
7.0265
7.0127
6.9881
6.9844
6.9311
6.9140
6.8979
5.4287
5.4155
5.2408
5.2233
4.9666
4.8093
4.8027
4.7912
3.9100
3.9001
3.8876
3.8720
3.8642
3.7946
3.7881
3.7766
3.6117
3.5983
3.5877
3.5815
3.5769
3.5694
3.5604
3.1624
3.1463
3.0753
3.0559
3.0459
3.0383
3.0254
3.0120
3.0052
2.9879
2.88804
2.8613
2.8528
2.8396
2.8341
2.8245
2.8116
2.7717
2.7653
2.7586
2.7519
2.7463
2.7384
2.7294
2.7204
2.6560
2.6500
2.3321
2.3215
1.8576
1.8446
1.8402
1.8000
1.9514
1.4433
1.4345
1.4270
1.4194
0.6669
0.6599
0.6499
0.6413
-0.0280
-0.8902
-0.8773
-0.8087
-0.7993
-0.7946
-0.7785

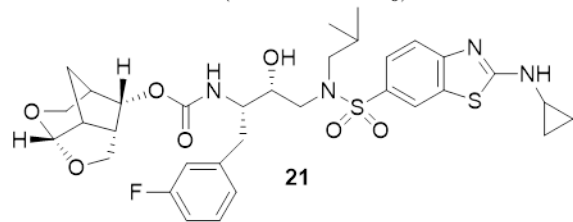
¹H NMR (500 MHz, CDCl₃)



173.13
163.97
162.01
155.88
155.79
140.54
140.49
131.47
130.34
130.16
129.51
125.51
125.24
121.04
118.80
116.49
116.43
116.26
113.78
113.72
113.62
113.55
104.47

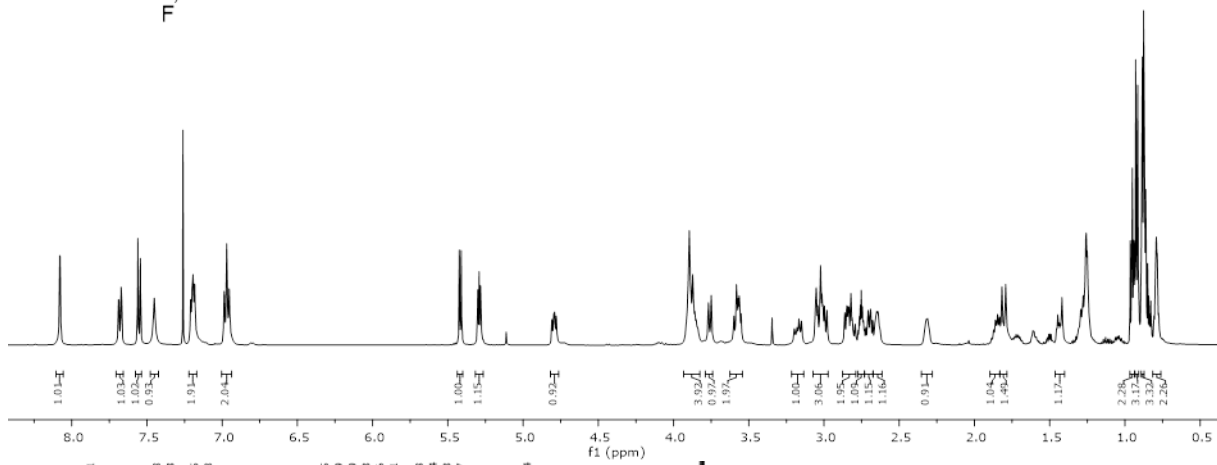
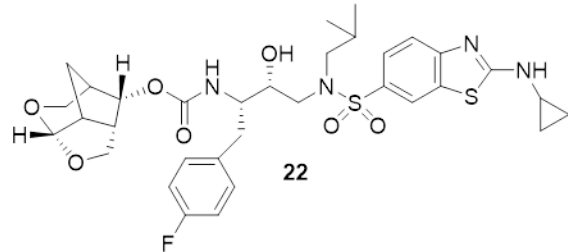


¹³C NMR (125 MHz, CDCl₃)



8.0793
6.0765
7.6890
7.6856
7.6785
7.6750
7.5603
7.5432
7.4514
7.2098
7.1985
7.1933
7.1898
6.4870
6.0608
6.9526
5.4245
5.4112
5.3010
5.2921
5.2854
4.8085
4.7970
4.7908
4.7792
3.8952
3.8722
3.8644
3.8598
3.7679
3.7494
3.5990
3.5826
3.5769
3.5695
3.5638
3.5512
3.1668
3.1499
3.1499
3.0417
3.0226
3.0134
3.0067
2.9962
2.9801
2.8620
2.8484
2.8398
2.8358
2.8246
2.8152
2.7933
2.7657
2.7592
2.7525
2.7456
2.7392
2.7392
2.7351
2.7072
2.6907
2.6766
2.6766
2.6498
2.6419
2.3204
2.3116
1.8442
1.8445
1.8327
1.8175
1.7929
1.4458
1.4378
1.3936
1.1484
0.9515
0.9415
0.9383
0.9281
0.9149
0.9022
0.8767
0.7962
0.7917
0.7891
0.7859

¹H NMR (500 MHz, CDCl₃)



¹³C NMR (125 MHz, CDCl₃)

