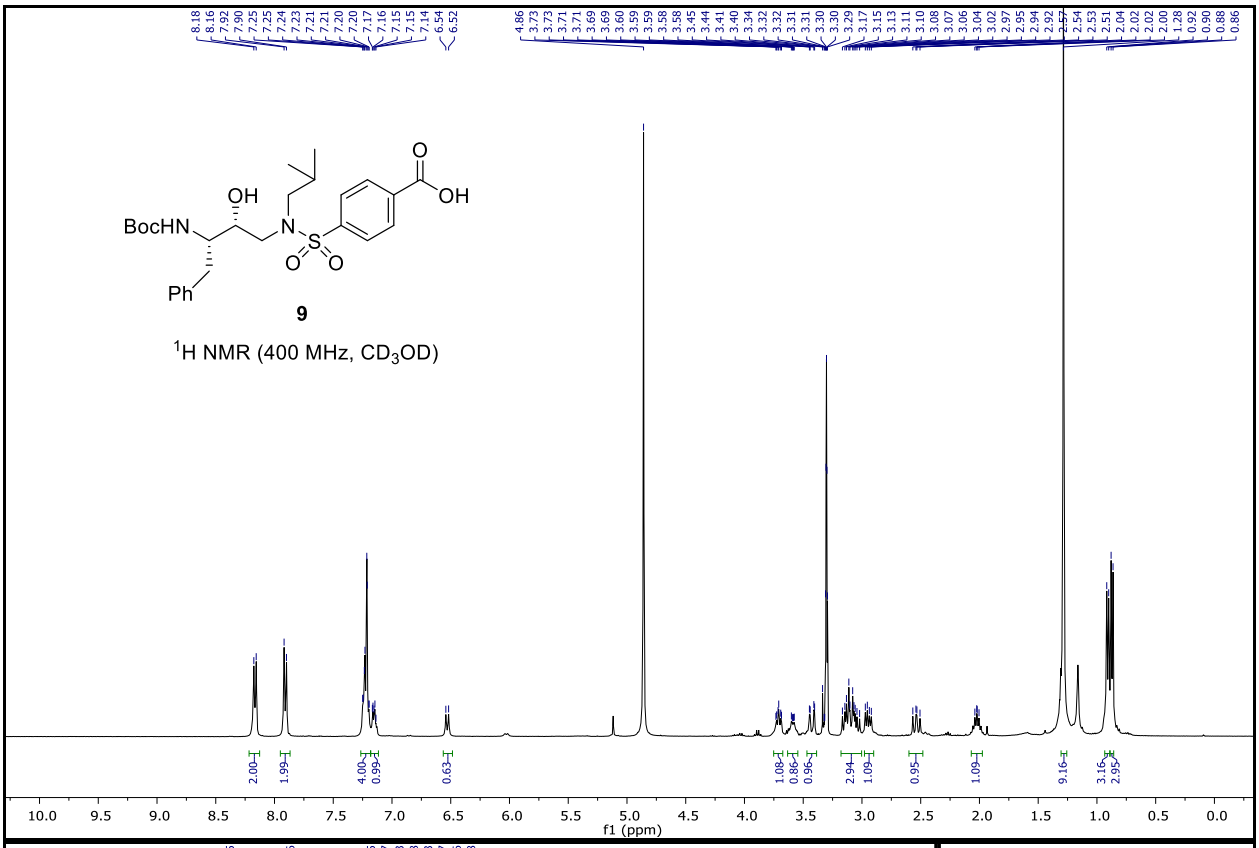
**Supporting Information**

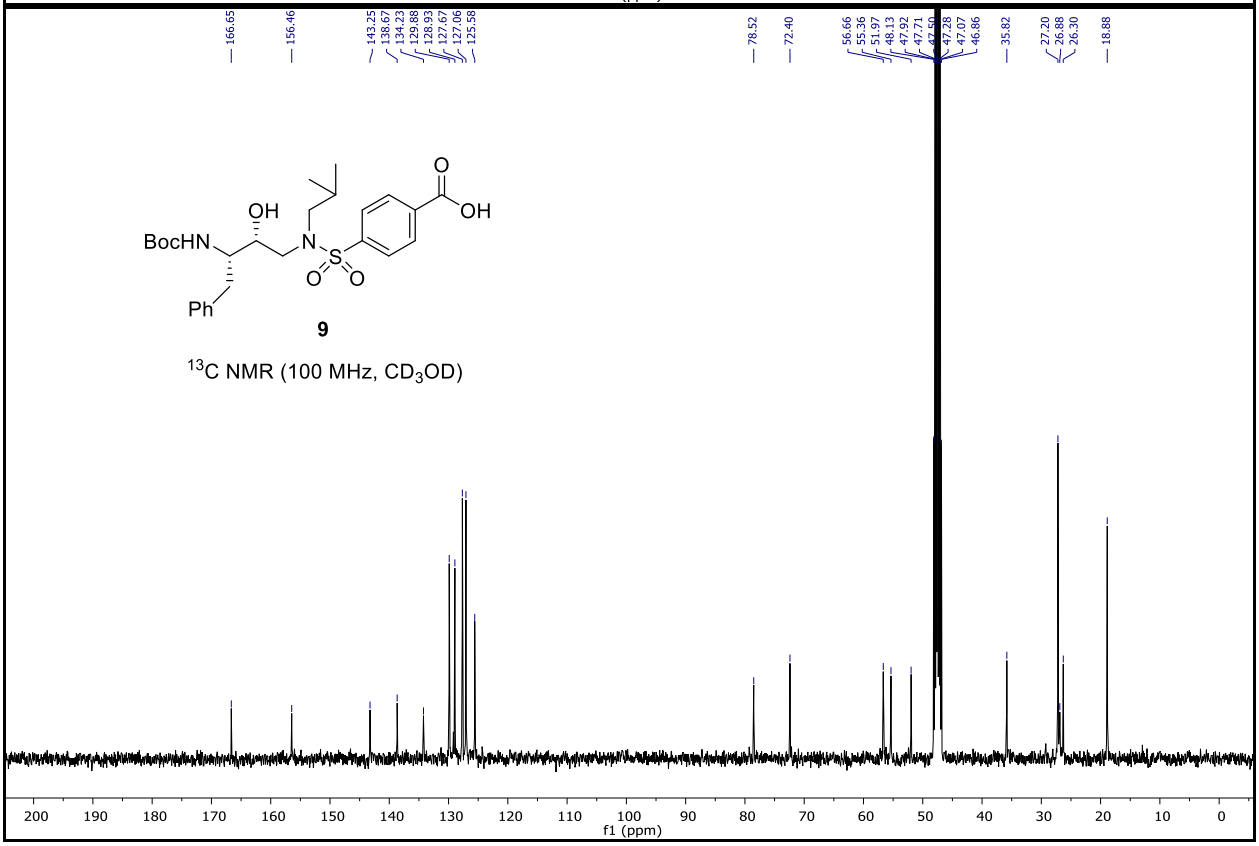
## Contents

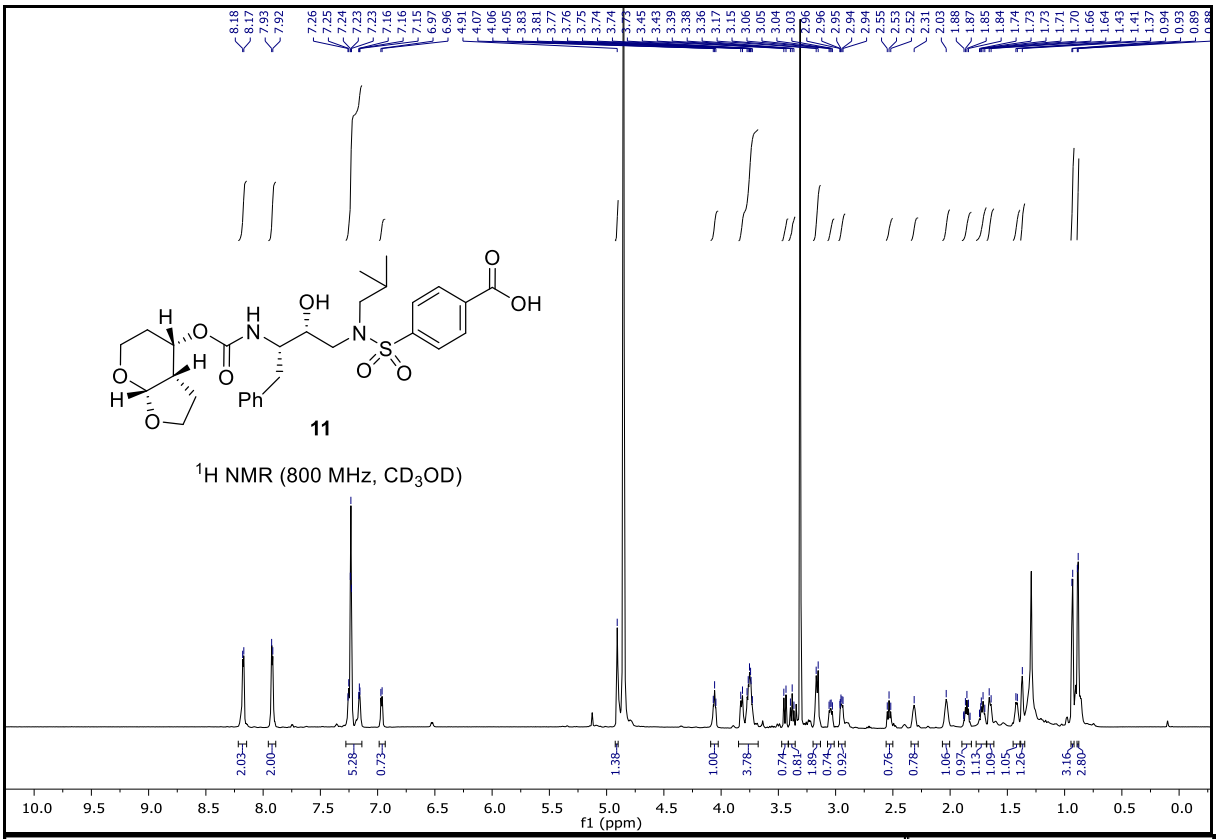


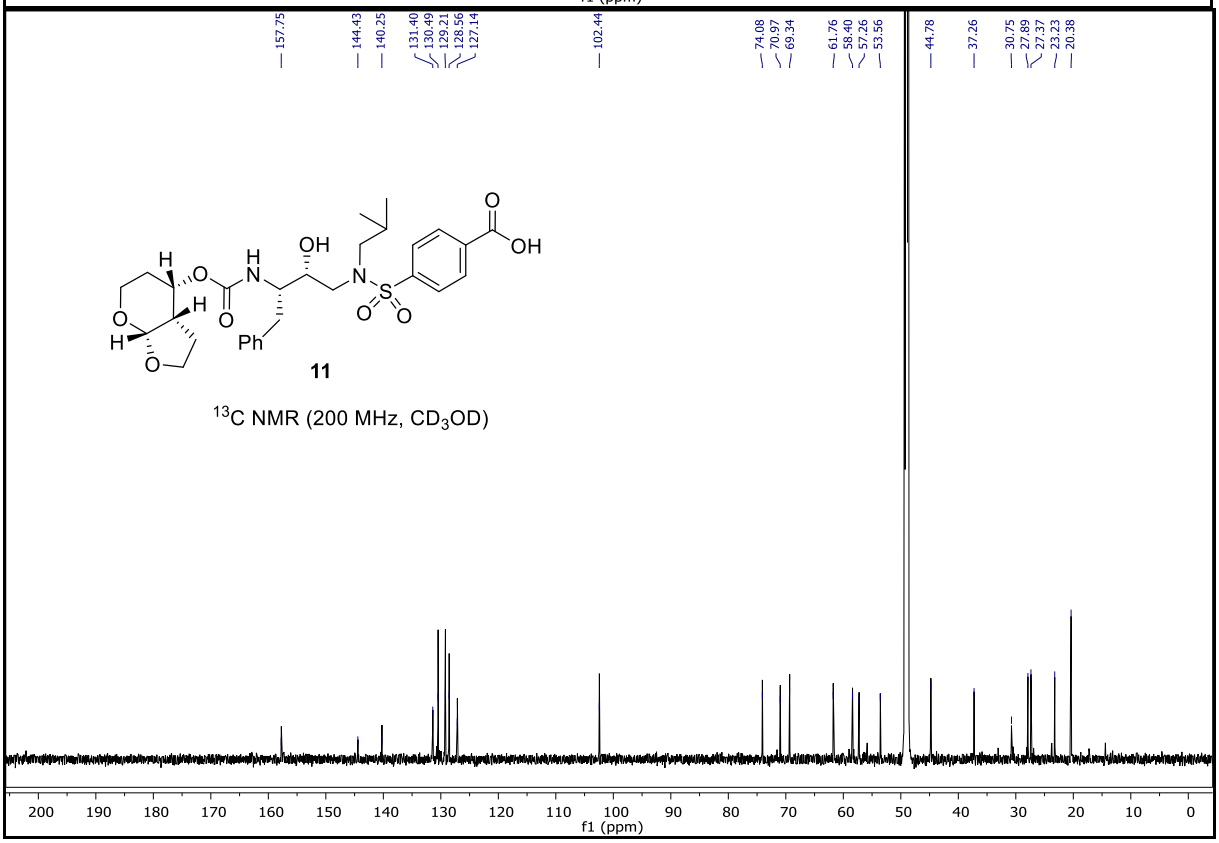
## Experimental Section

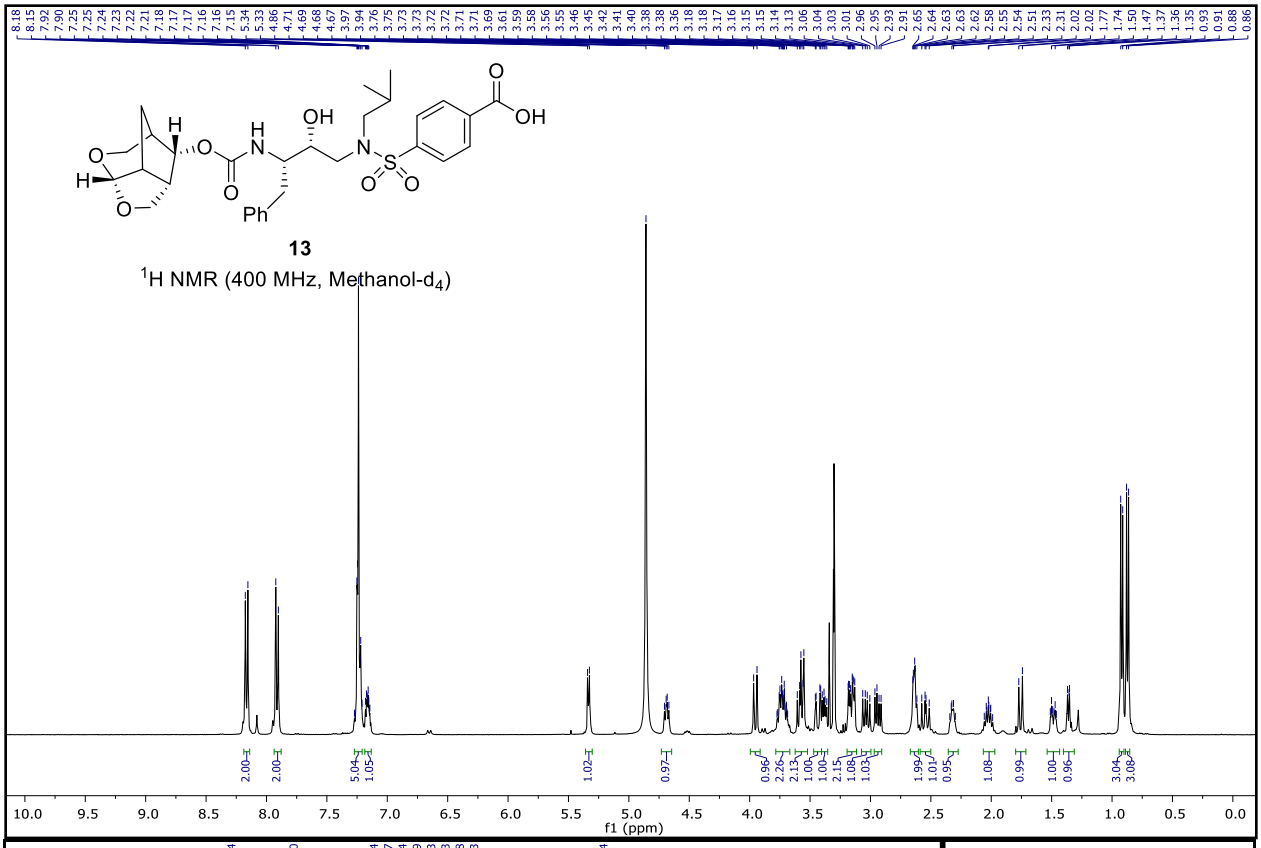
All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 $^{o}C$) glassware. All reagents and chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Anhydrous solvents were obtained as follows: Dichloromethane 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 form 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. $^{1}H$, $^{13}C$ NMR spectra were recorded at room temperature on a Bruker ARX-400 and DRX-500. Chemical shifts ($\delta$ values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as: $\delta$ 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.

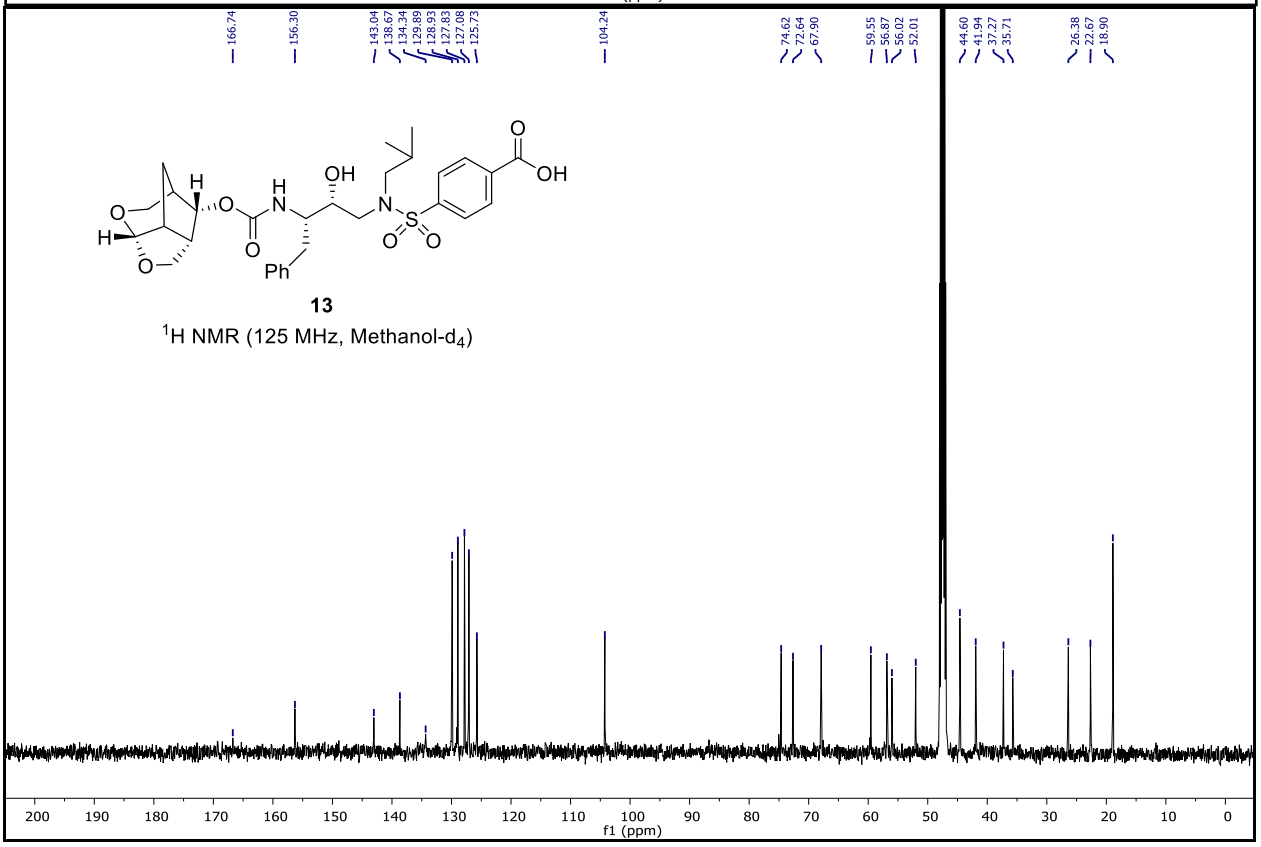

OH
BocHN
N
S
O
O
O
OH
Ph
9
1H NMR (400 MHz, CD3OD)
f1 (ppm)


OH
BocHN
N
S
O
O
O
OH
Ph
9
13C NMR (100 MHz, CD3OD)
f1 (ppm)


11
1H NMR (800 MHz, CD3OD)
f1 (ppm)


11
13C NMR (200 MHz, CD3OD)
f1 (ppm)


13
1H NMR (400 MHz, Methanol-d4)
f1 (ppm)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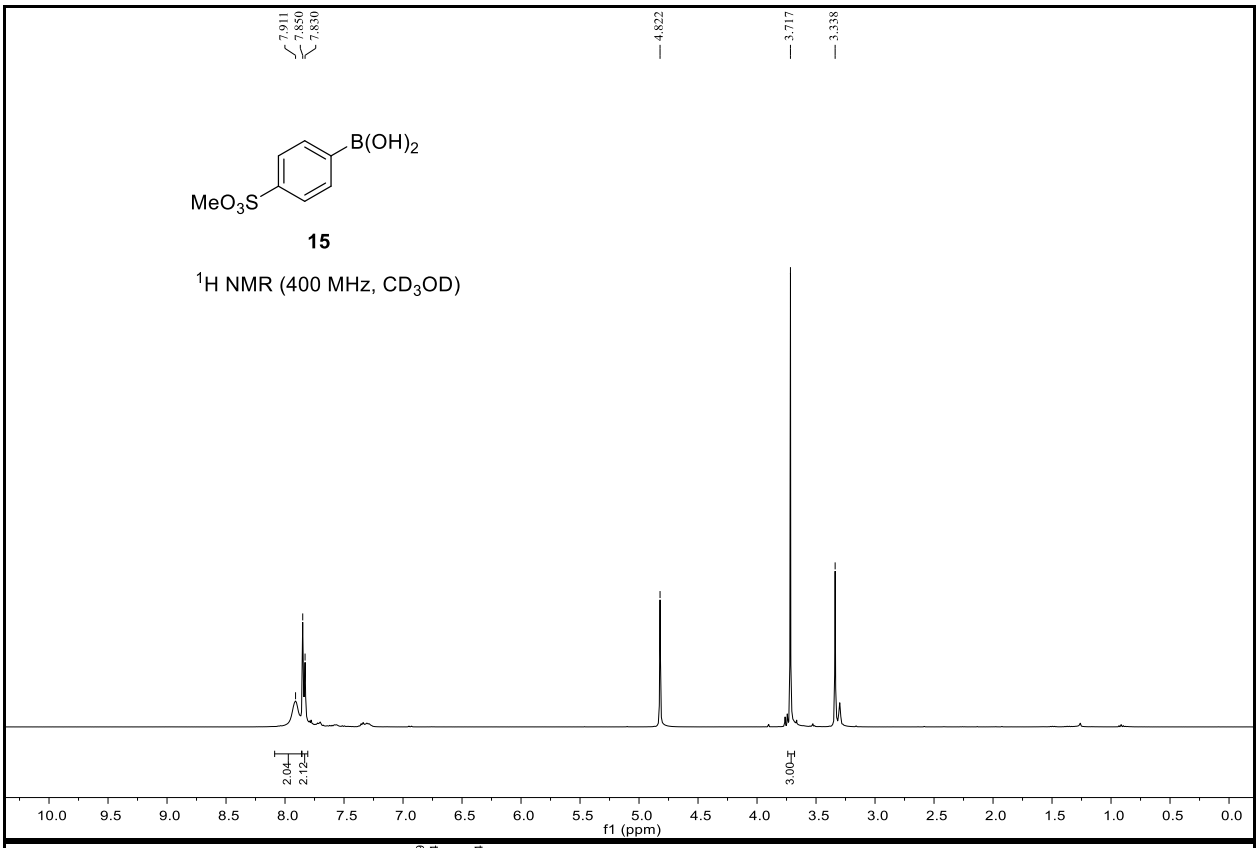
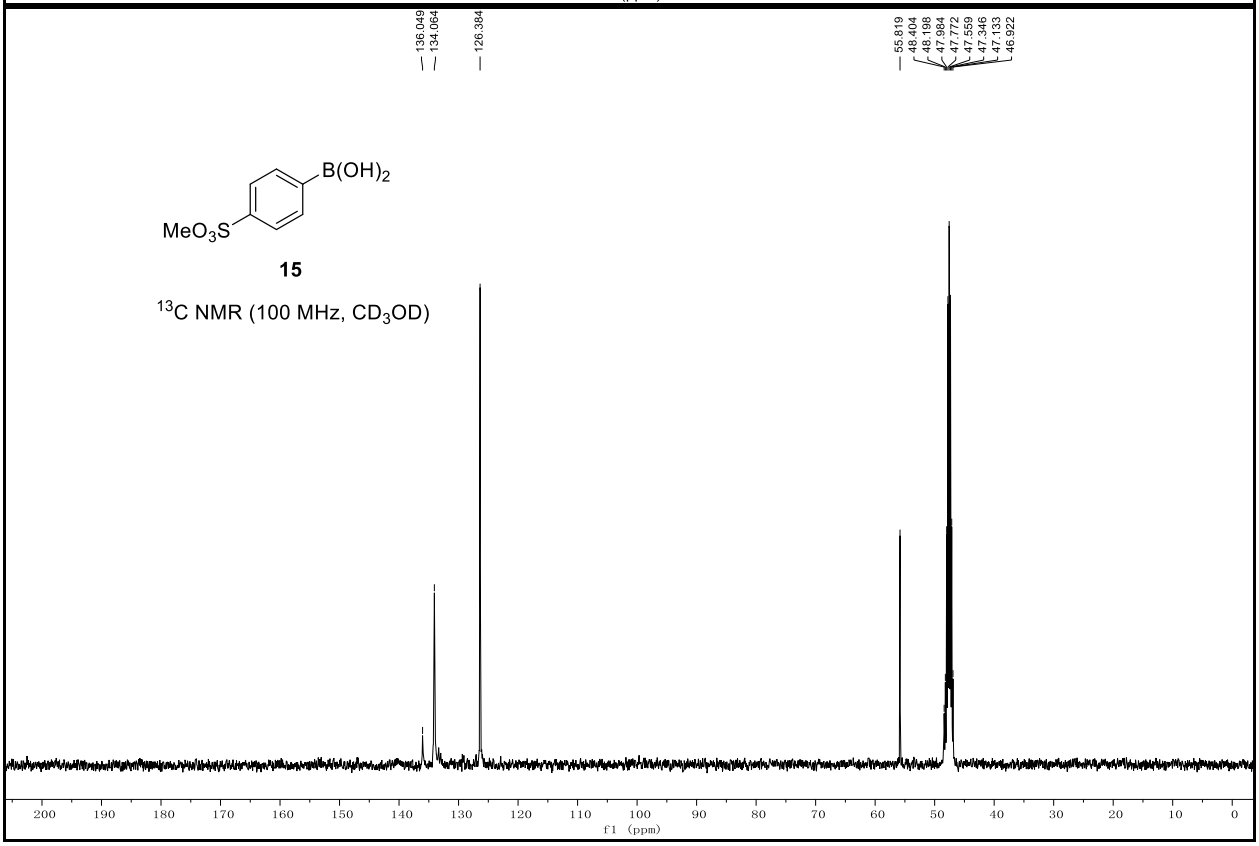
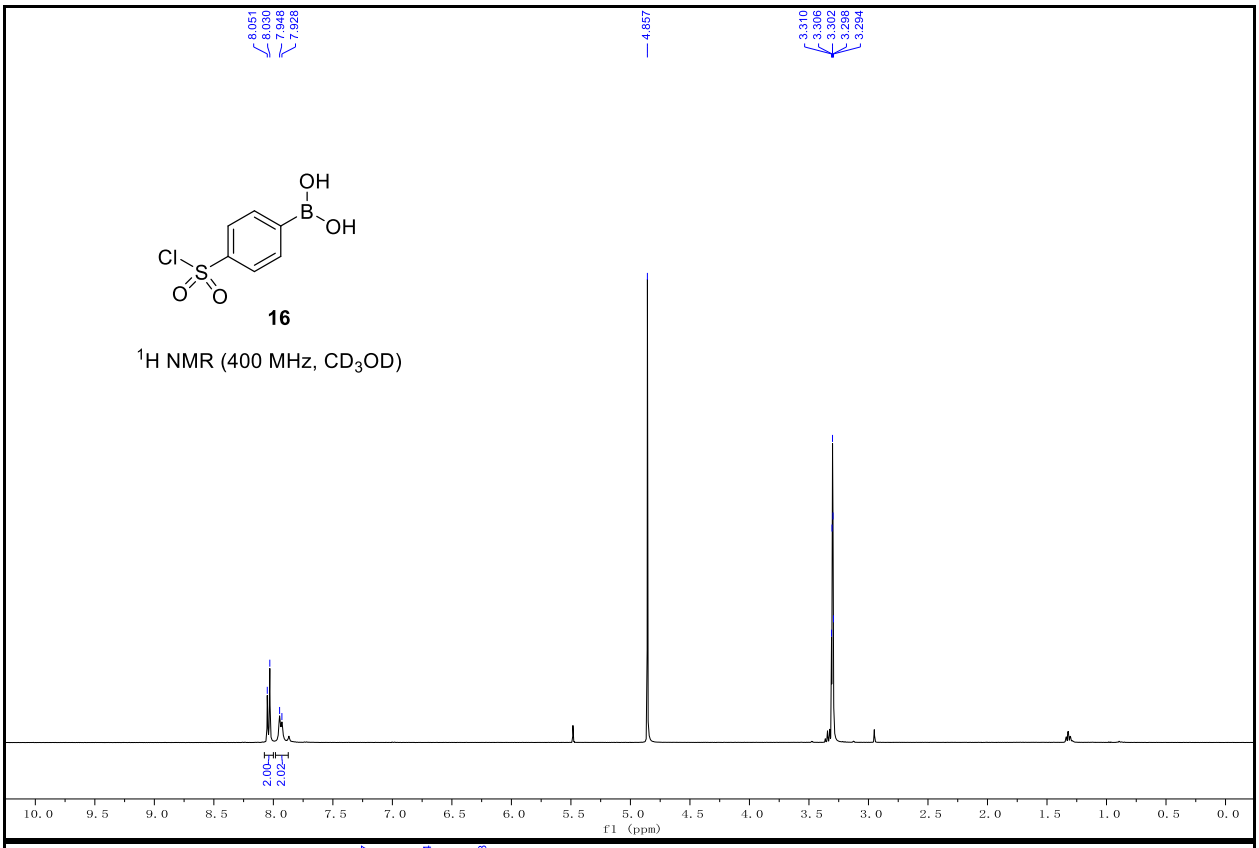
1H NMR (125 MHz, Methanol-d4)
f1 (ppm)

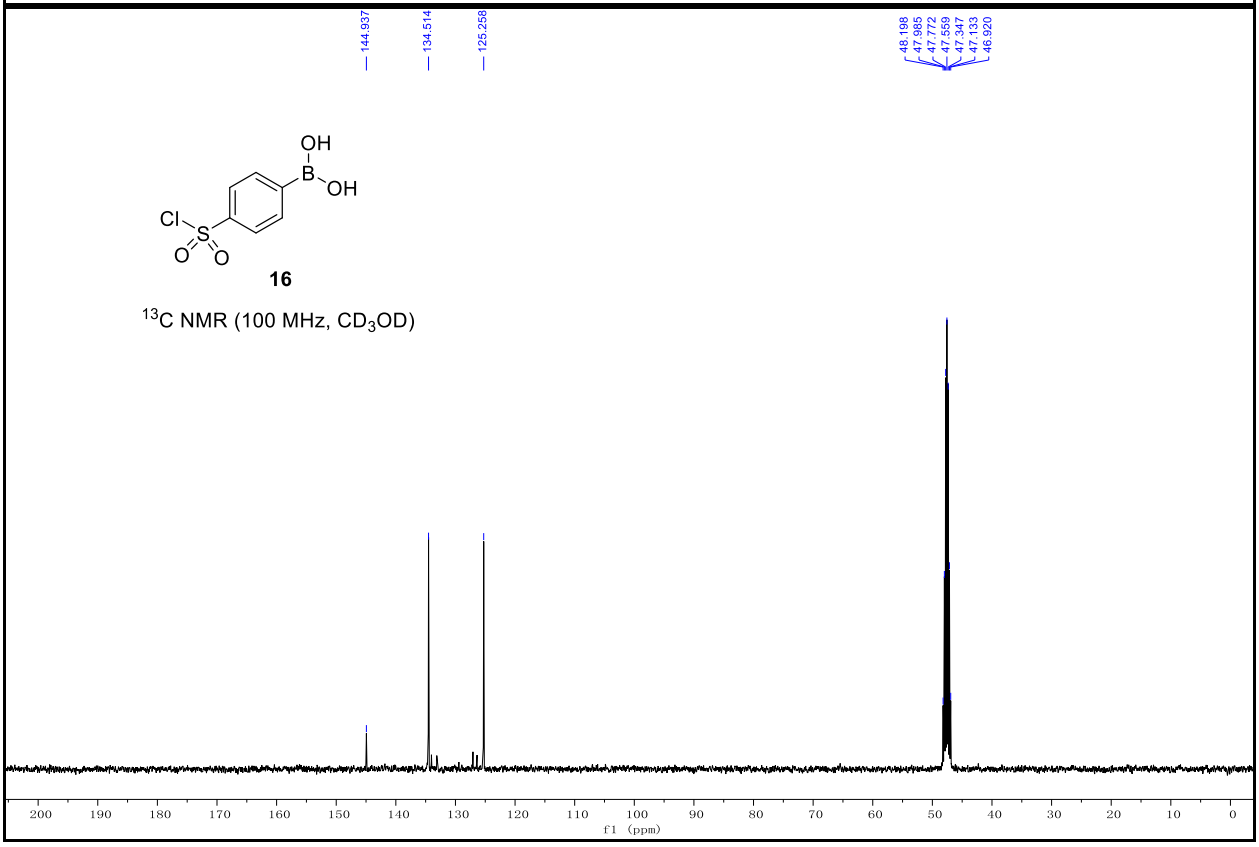

7.911
7.850
7.830
4.822
3.717
3.338
B(OH)2
MeO3S
15
1H NMR (400 MHz, CD3OD)
2.04
2.12
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


136.049
134.064
126.384
55.819
48.404
48.198
47.984
47.772
47.559
47.346
47.133
46.922
B(OH)2
MeO3S
15
13C NMR (100 MHz, CD3OD)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



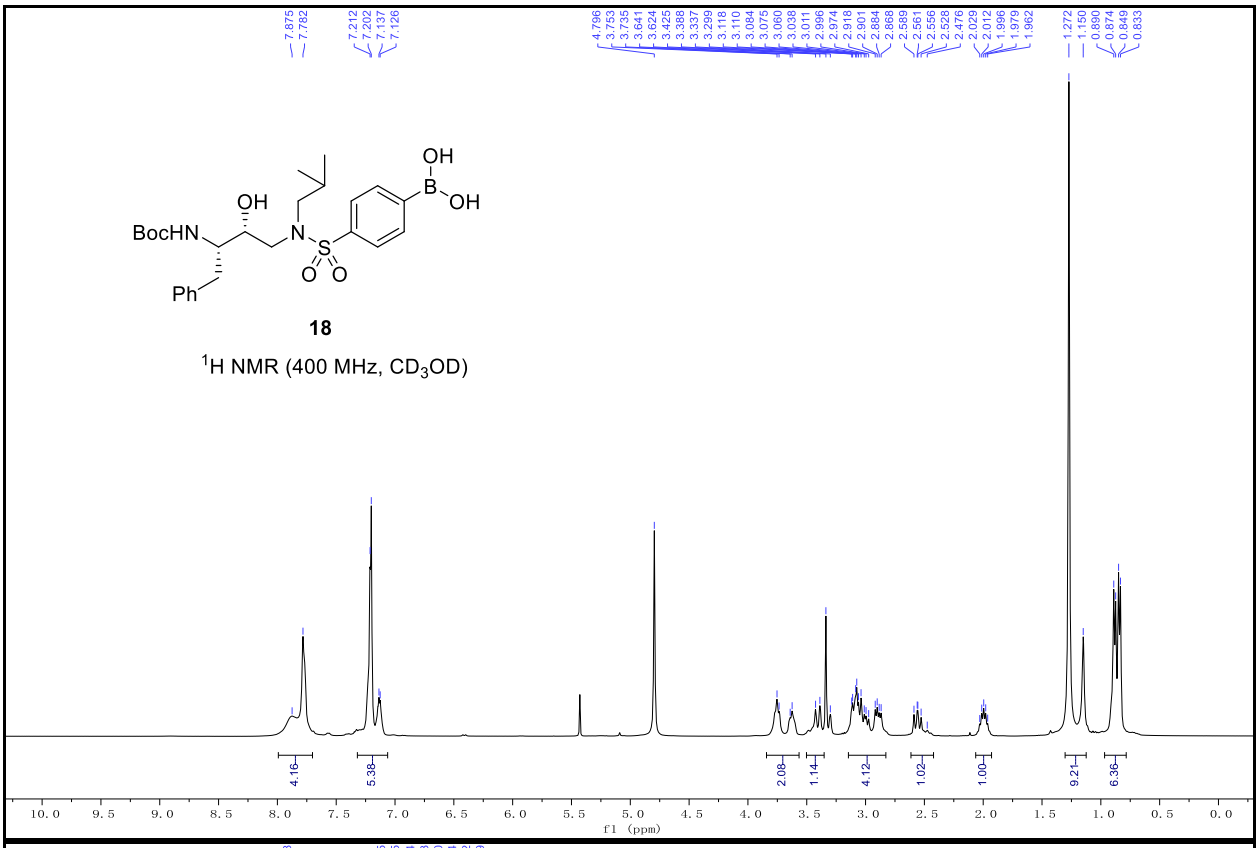

**16**

$^{1}$H NMR (400 MHz, $CD_3OD$)



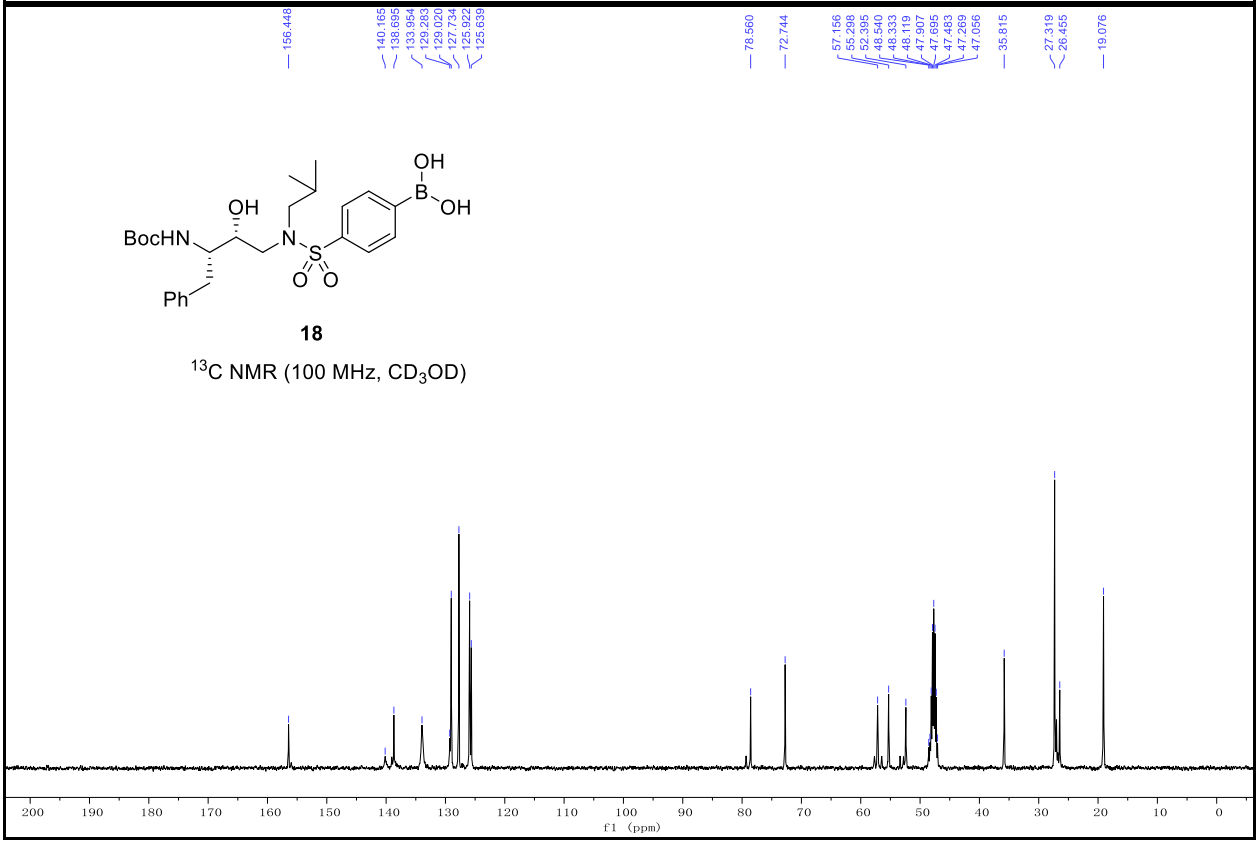

**16**

$^{13}$C NMR (100 MHz, $CD_3OD$)



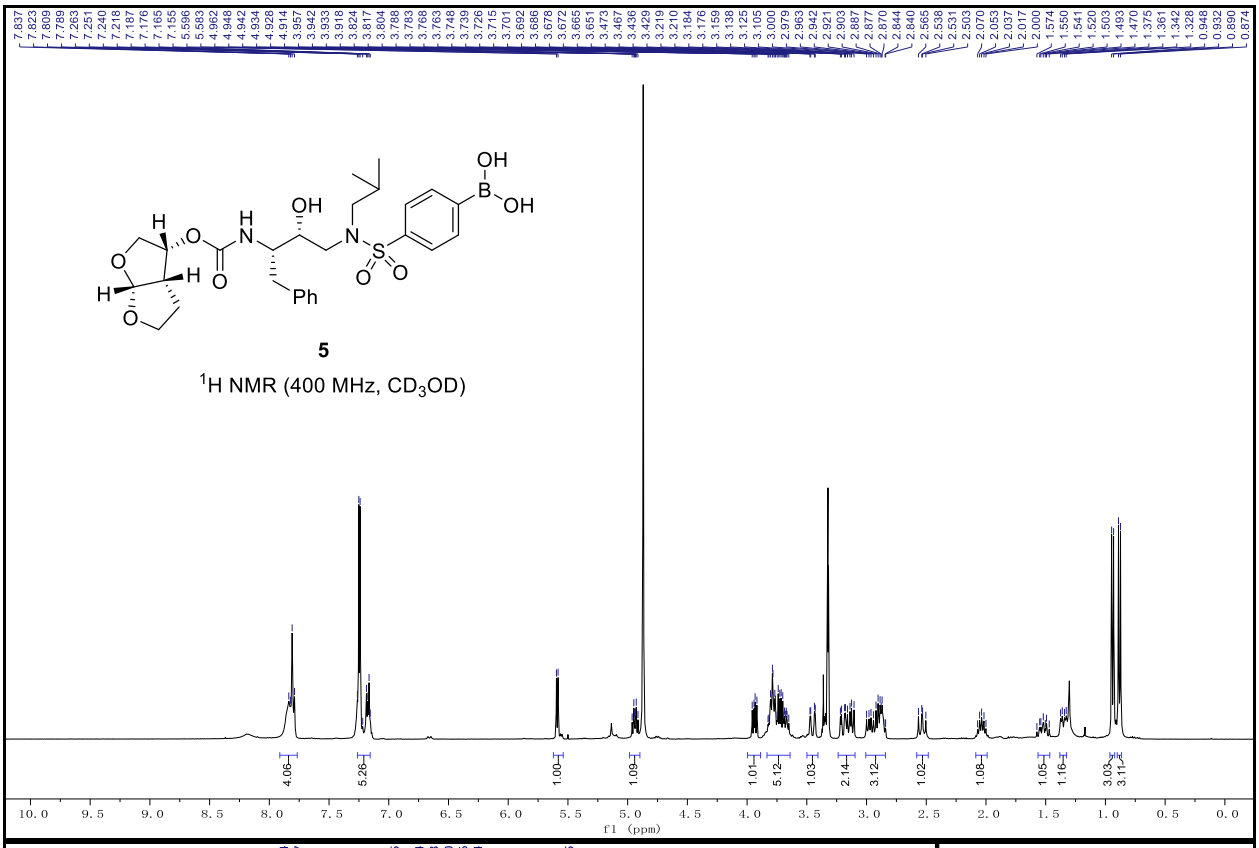

**18**

$^{1}$H NMR (400 MHz, $CD_3OD$)



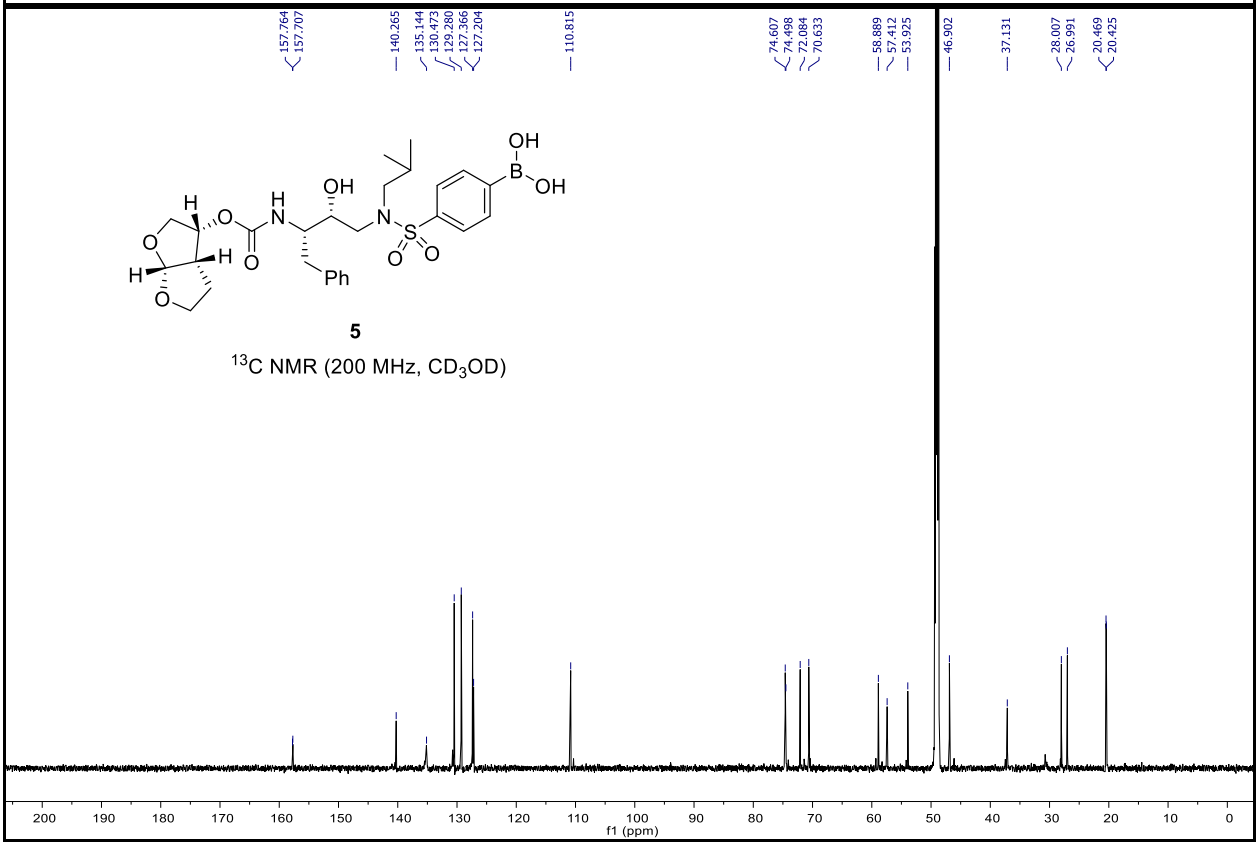

**18**

$^{13}$C NMR (100 MHz, $CD_3OD$)



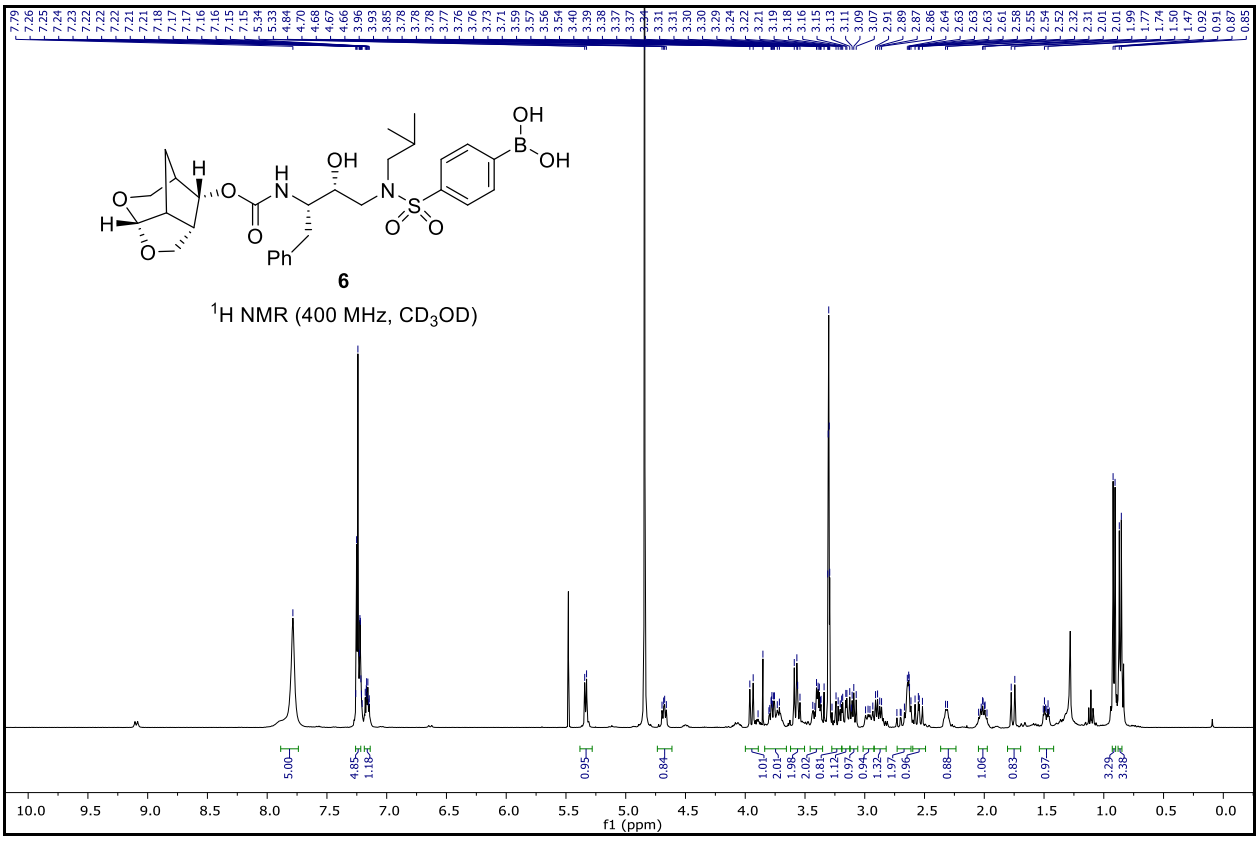

**5**

$^{1}$H NMR (400 MHz, $CD_3OD$)



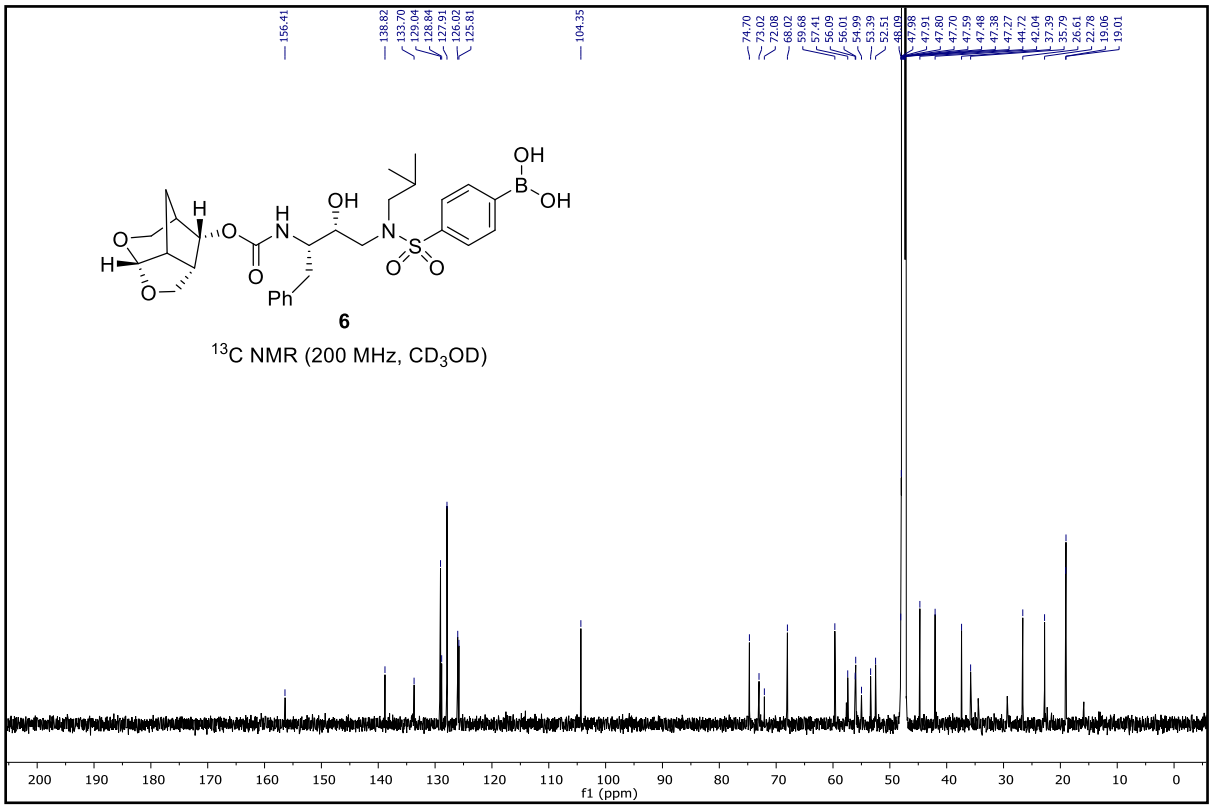

**5**

$^{13}$C NMR (200 MHz, $CD_3OD$)



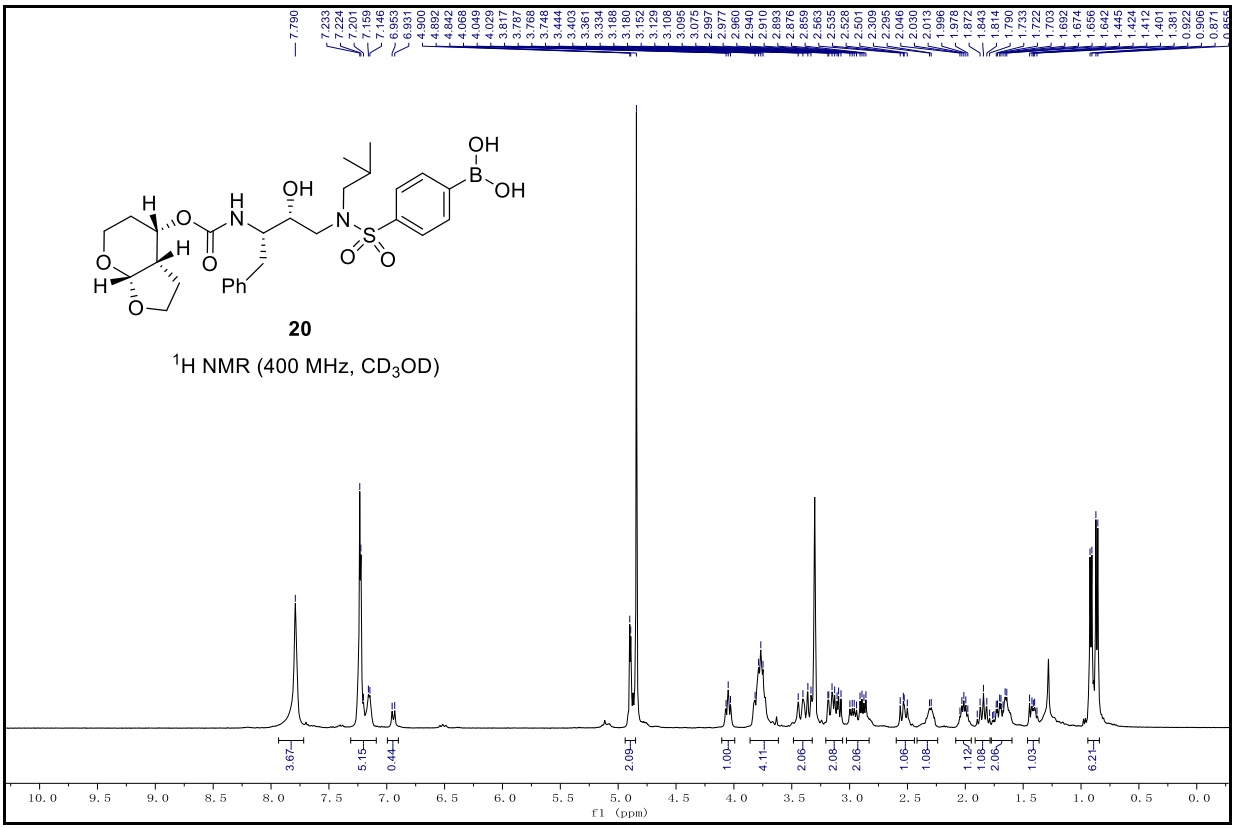

**6**

$^{1}$H NMR (400 MHz, $CD_3OD$)



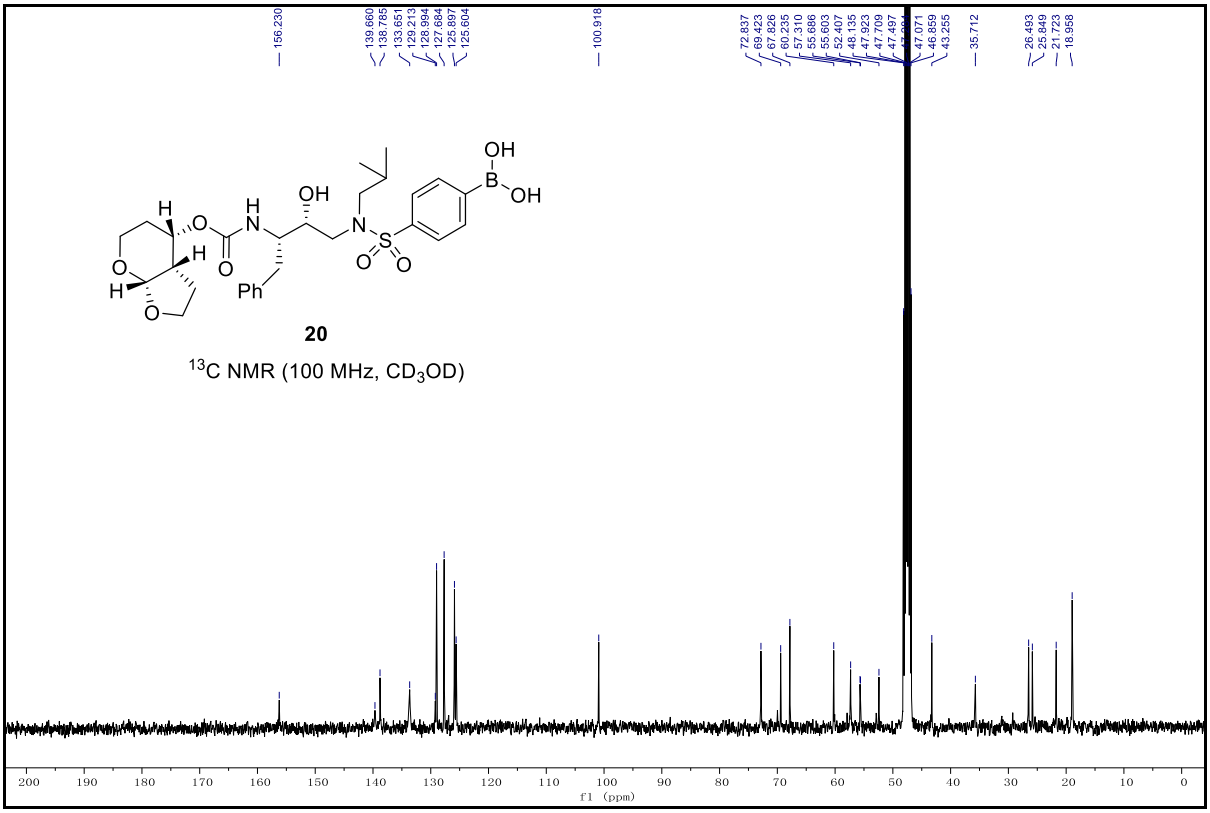

**6**

$^{13}$C NMR (200 MHz, $CD_3OD$)




**20**

$^{1}$H NMR (400 MHz, $CD_3OD$)




**20**

$^{13}$C NMR (100 MHz, $CD_3OD$)

Table 1: Crystallographic Data Collection and Refinement Statistics

| Complex Name | **6** (GRL-008-19A) | **20** (GRL-031-19A) |
|---|---|---|
| Space group | $P2_12_12$ | $P2_12_12$ |
| Unit cell dimensions: (Å) | | |
| a | 58.92 | 58.49 |
| b | 86.48 | 86.10 |
| c | 45.88 | 46.09 |
| Resolution range (Å) | 50-1.33 (1.38-1.33) | 50-1.13 (1.17-1.13) |
| Redundancy (final shell) | 6.0 (4.3) | 5.7 (2.0) |
| Unique reflections | 53993 (5048) | 79649 (4384) |
| Completeness (%) overall (final shell) | 98.9 (94.1) | 90.8 (50.7) |
| $R_{merge}$ (%) overall (final shell) | 6.1 (74.9) | 6.1 (44.5) |
| I/σ(I) overall (final shell) | 22.6 (2.0) | 23.5 (2.0) |
| R (%) | 13.7 | 12.5 |
| $R_{free}$ (%) | 17.7 | 14.1 |
| RMS deviation from ideality | | |
| Bonds (Å) | 0.020 | 0.025 |
| Angle distance (Å) | 2.3 | 2.5 |
| Average B-factors ($Å^2$) | | |
| Wilson Plot B factor | 16.5 | 11.2 |
| Main-chain atoms | 16.1 | 13.6 |
| Side-chain atoms | 21.8 | 19.3 |
| Inhibitor | 11.9 | 11.9 |
| Solvent | 26.7 | 25.0 |

**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-1strain ($HIV\text{-}1_{LAI}$), a clinical HIV-1 strain isolated from drug-naive patients with AIDS ($HIV\text{-}1_{ERS104pre}$) (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)