

## Supporting Information

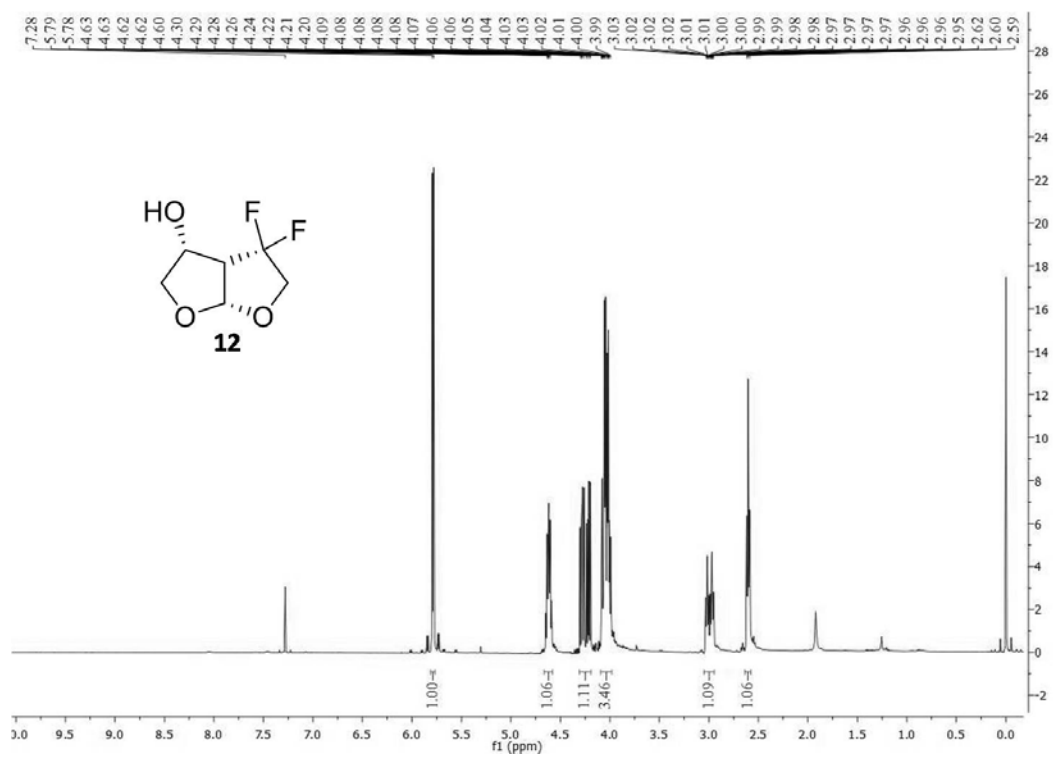
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### Experimental Section

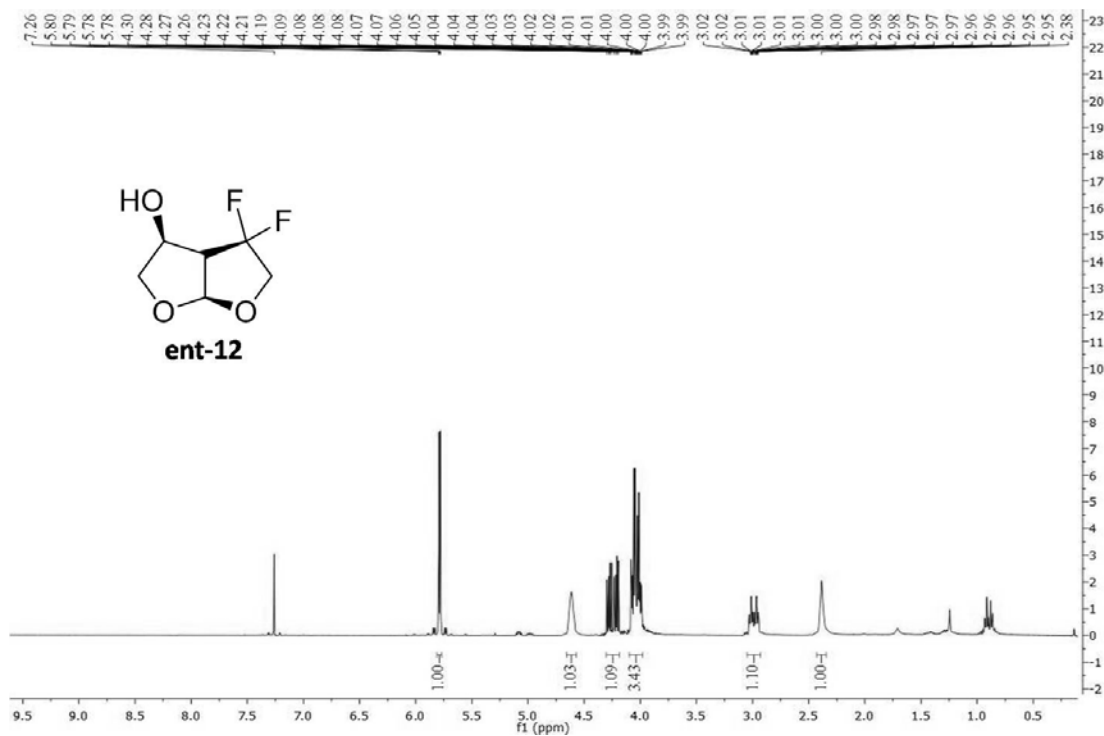
All moisture sensitive reactions were carried out in an oven dried flask under an argon atmosphere. Anhydrous solvents were obtained as follows: THF, diethyl ether and benzene, distilled from sodium and benzophenone; dichloromethane, pyridine, triethylamine, and diisopropylethylamine, distilled from  $\text{CaH}_2$ . All other solvents were HPLC grade.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded on Varian INOVA300-1 and Bruker Avance ARX-400 spectrometers. NMR data were resolved with Mestrec software. Optical rotations were recorded on a Perkin Elmer 341 polarimeter. Mass spectra were obtained at the Purdue University Campus-wide Mass Spectrometry Center. Column chromatography was performed with Whatman 240-400 mesh silica gel under a low pressure of 3-5 psi. TLC was carried out with E. Merck silica gel 60-F-254 plates. HPLC was performed on an Agilent 1100 instrument. All test inhibitors showed purity >96% by HPLC analysis.

$^1\text{H-NMR}$  of compound **12** ( $\text{CDCl}_3$ , 400 MHz)

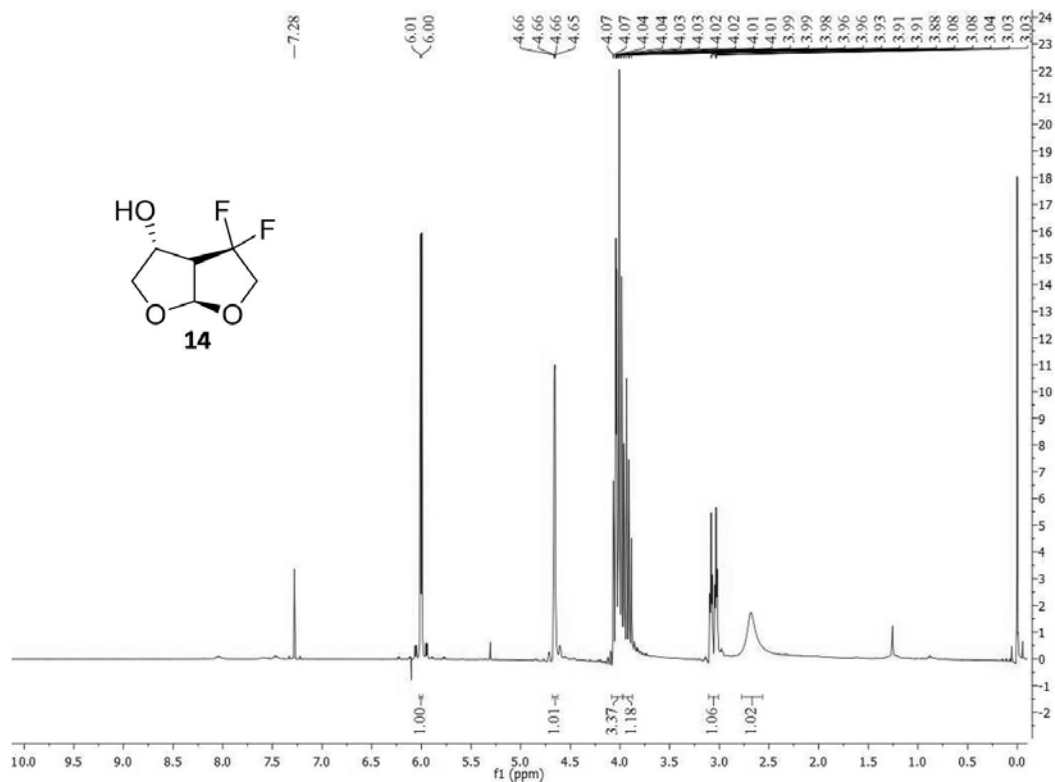




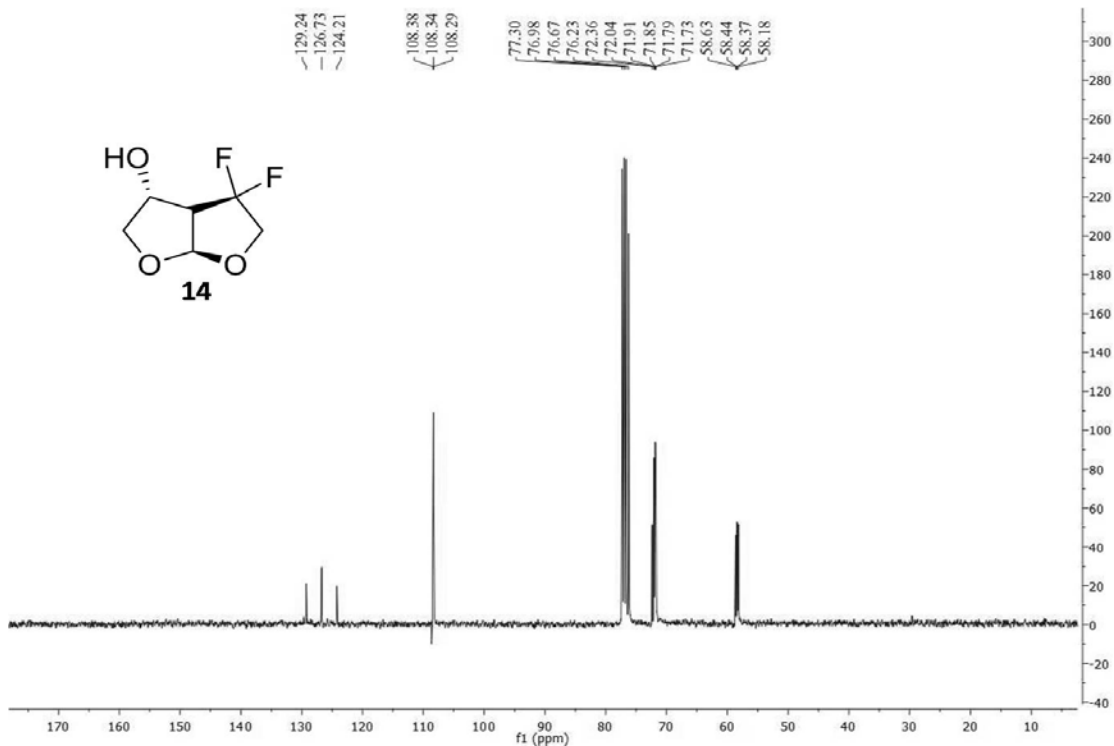
$^1\text{H-NMR}$  of compound ent-12 ( $\text{CDCl}_3$ , 400 MHz)



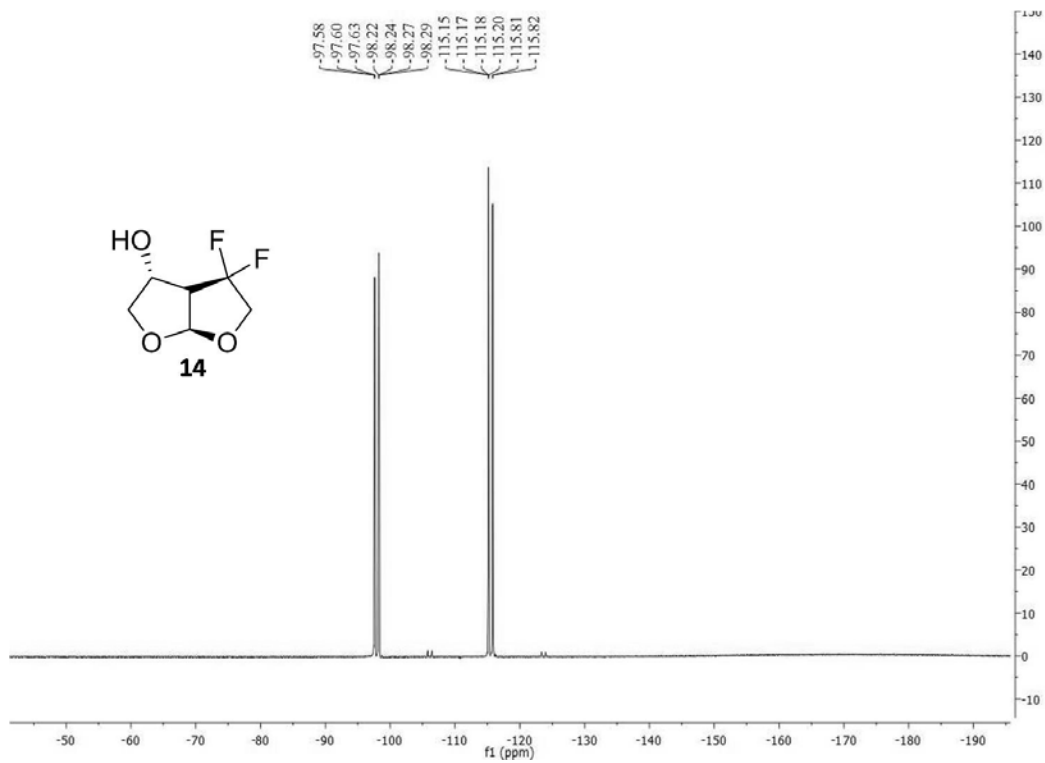
$^1\text{H-NMR}$  of compound 14 ( $\text{CDCl}_3$ , 400 MHz)



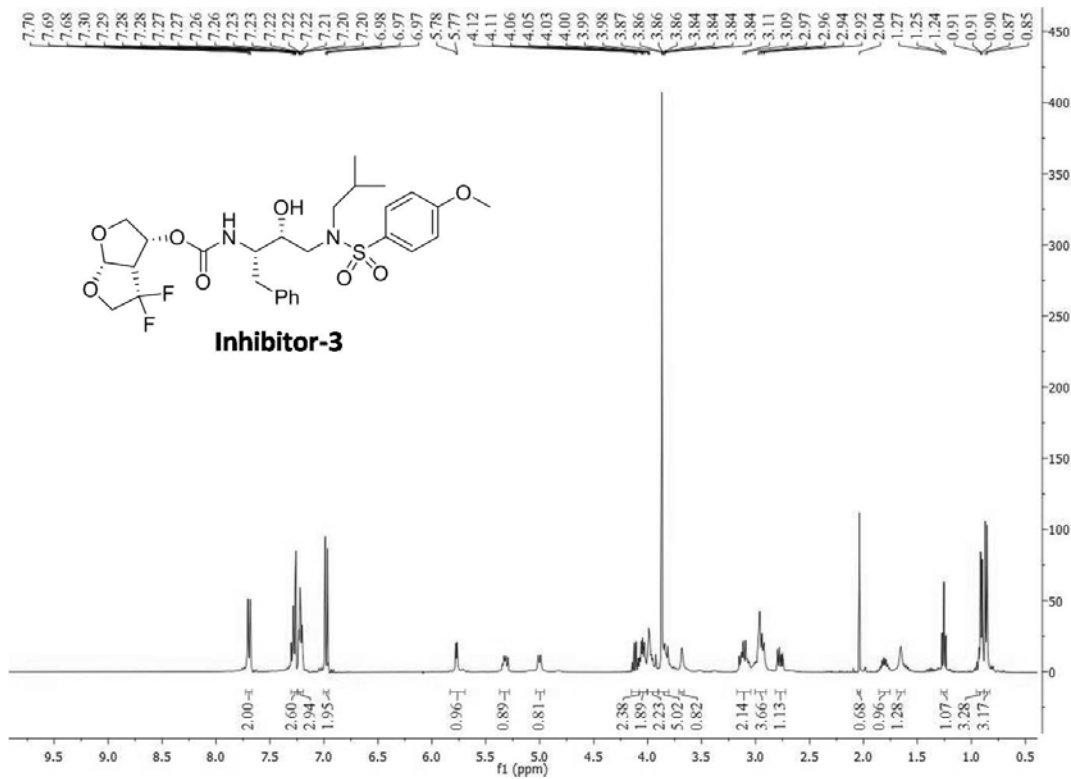
<sup>13</sup>C-NMR of compound 14 (CDCl<sub>3</sub>, 400 MHz)



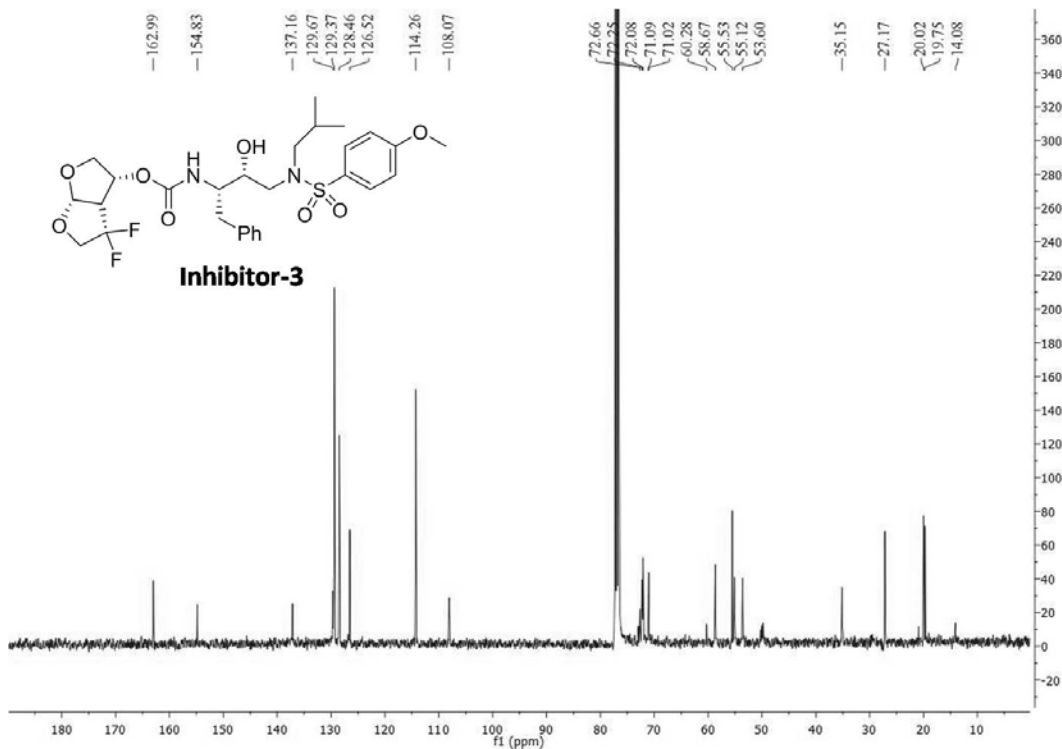
<sup>19</sup>F-NMR of compound 14 (CDCl<sub>3</sub>, 400 MHz)



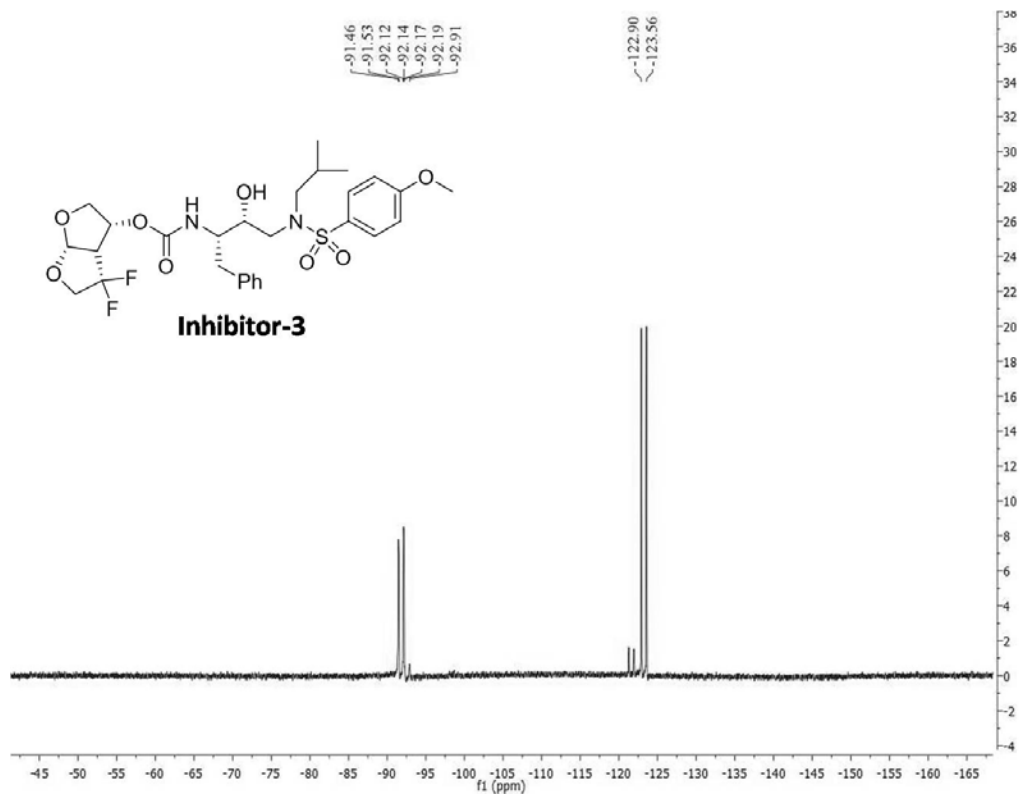
<sup>1</sup>H-NMR of Inhibitor 3 (CDCl<sub>3</sub>, 400 MHz)



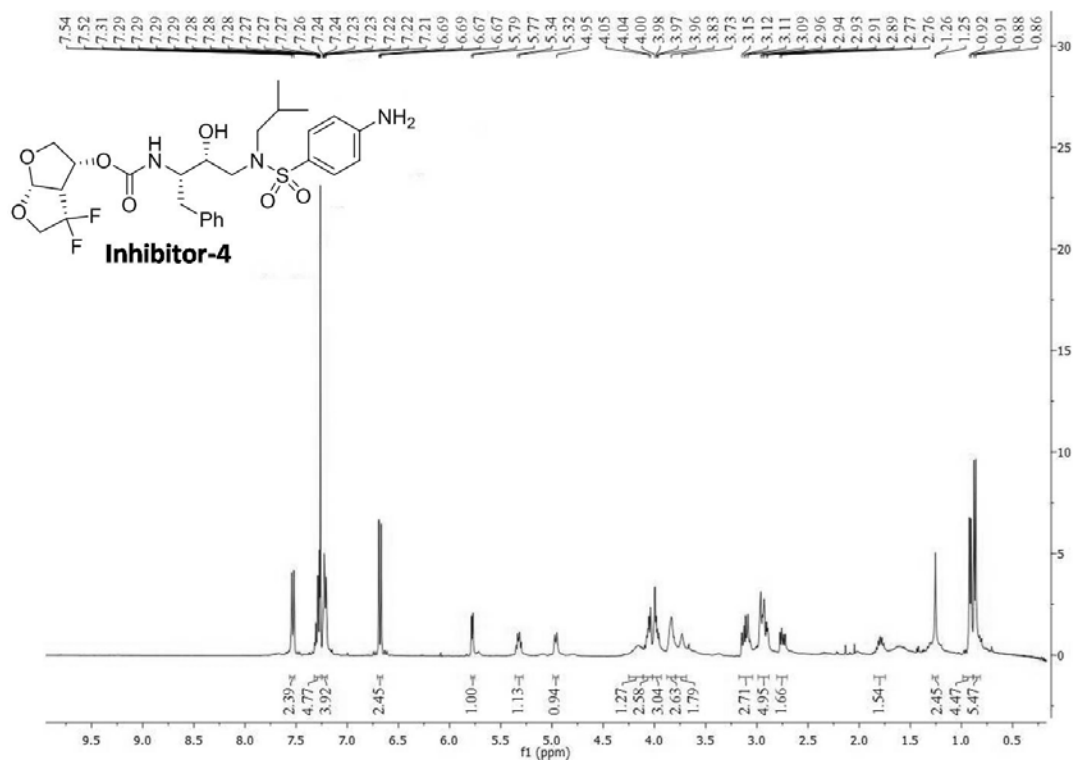
<sup>13</sup>C-NMR of Inhibitor 3 (CDCl<sub>3</sub>, 400 MHz)



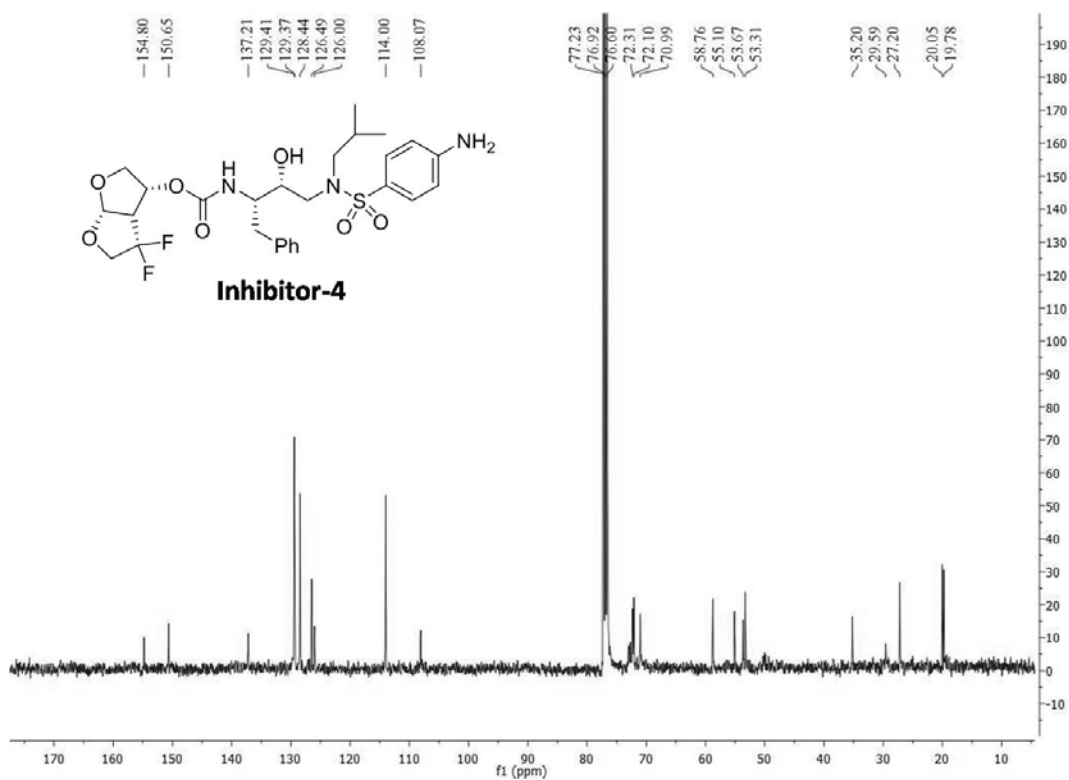
$^{19}\text{F}$ -NMR of Inhibitor 3 ( $\text{CDCl}_3$ , 400 MHz)



$^1\text{H}$ -NMR of Inhibitor 4 ( $\text{CDCl}_3$ , 400 MHz)

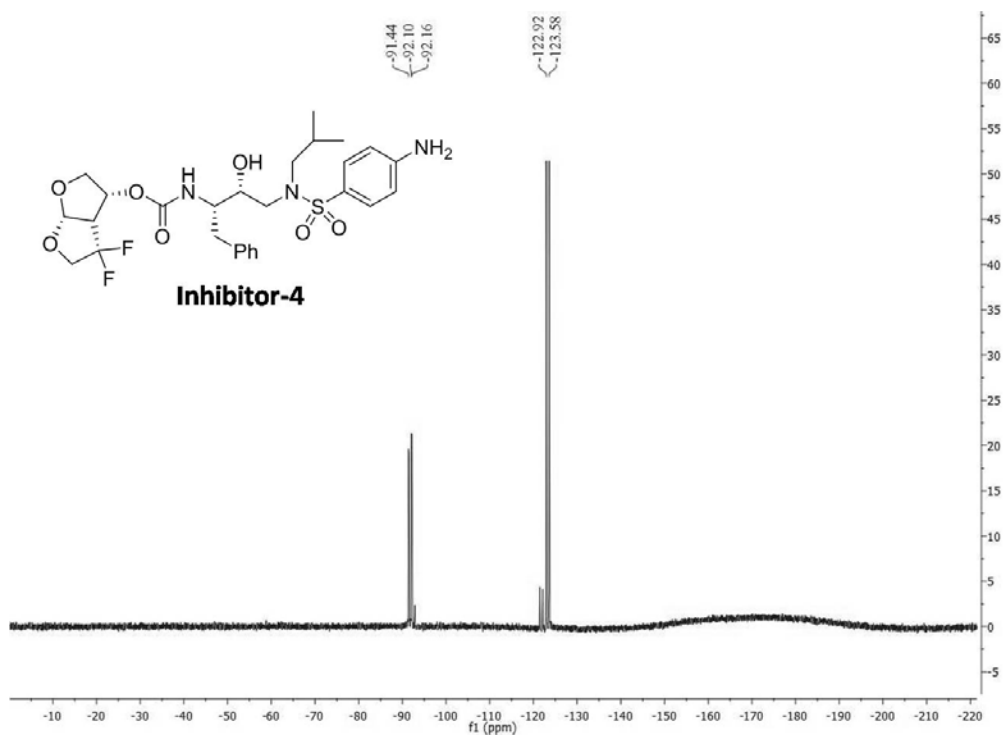


<sup>13</sup>C-NMR of Inhibitor 4 (CDCl<sub>3</sub>, 400 MHz)

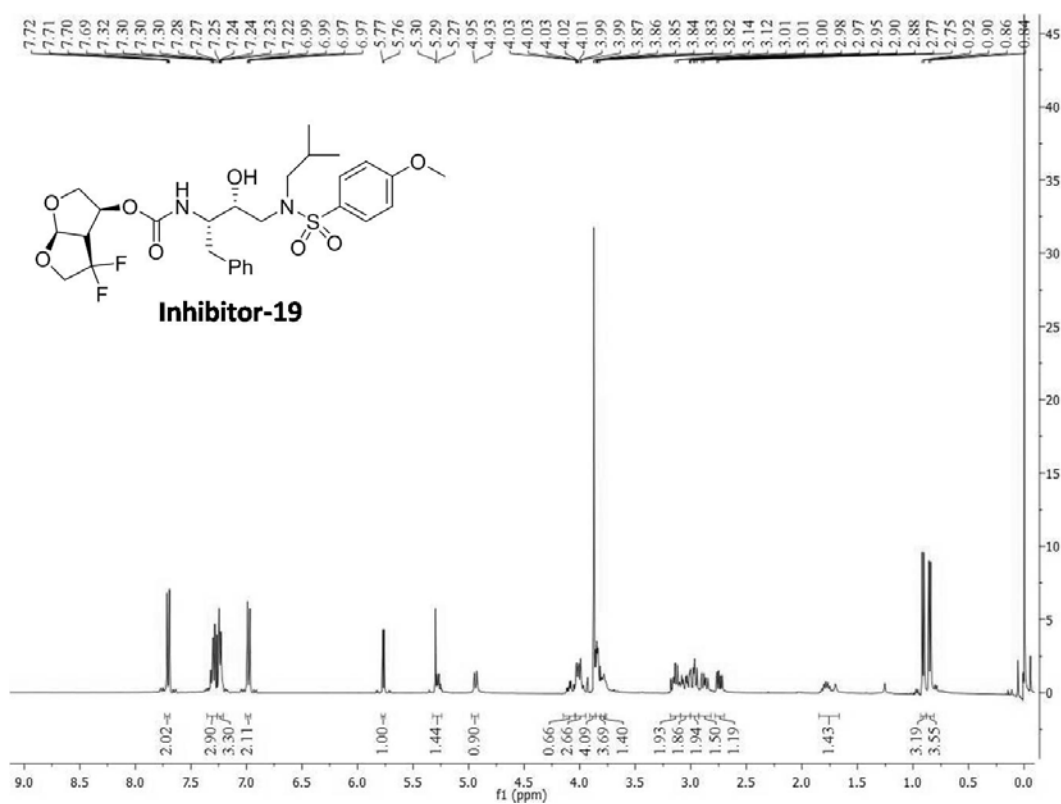


<sup>19</sup>F-NMR of Inhibitor 4 (CDCl<sub>3</sub>, 400 MHz)

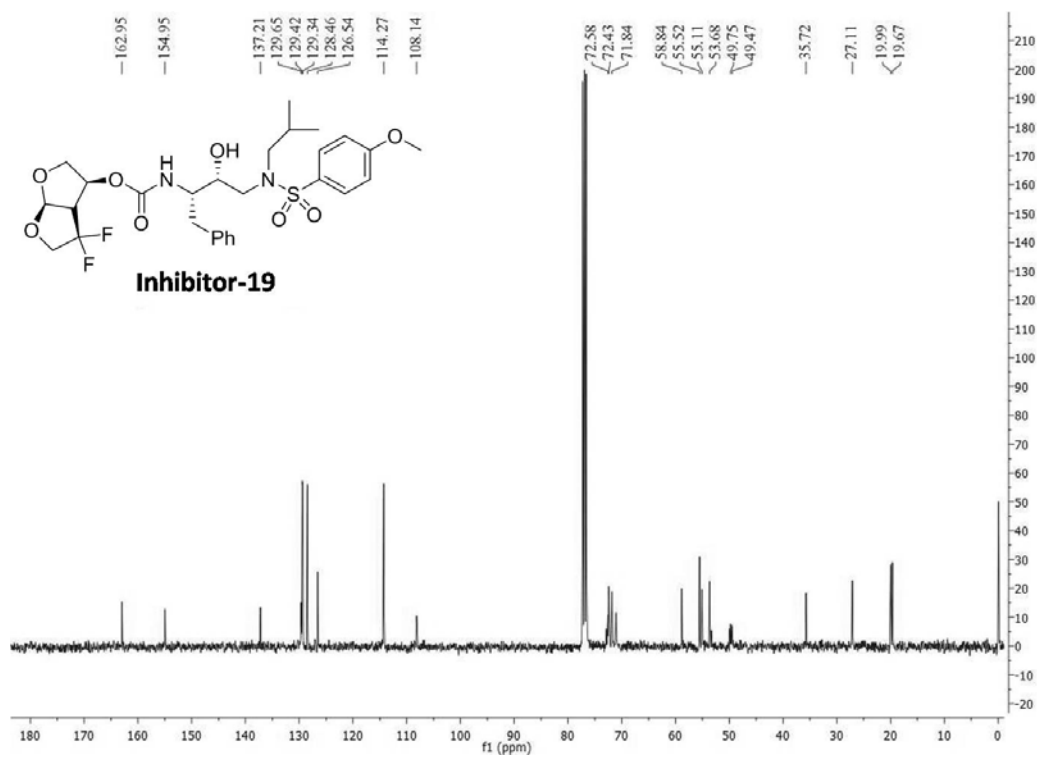




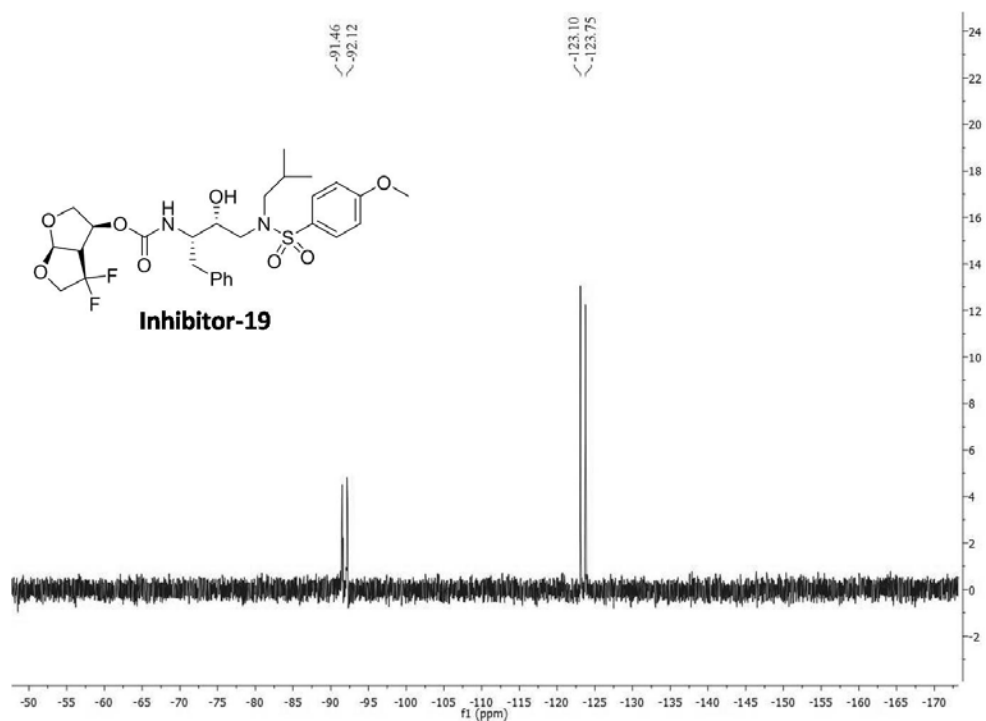
$^1\text{H}$ -NMR of Inhibitor 19 ( $\text{CDCl}_3$ , 400 MHz)



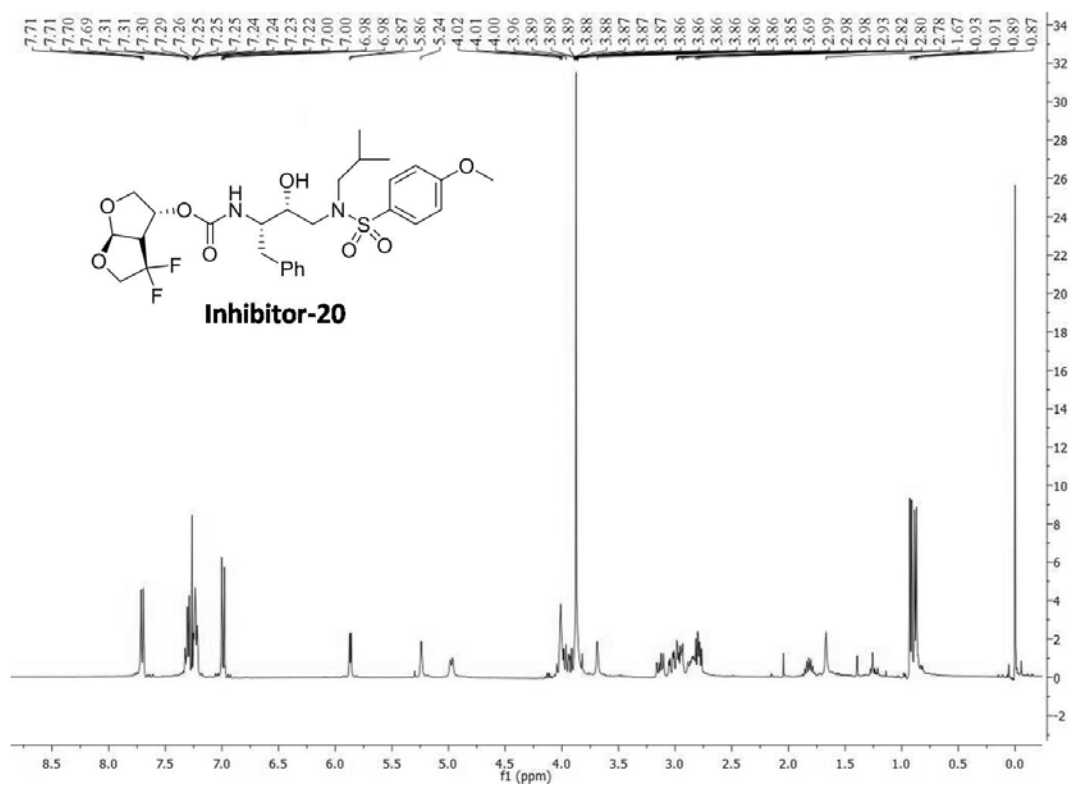
<sup>13</sup>C-NMR of Inhibitor 19 (CDCl<sub>3</sub>, 400 MHz)



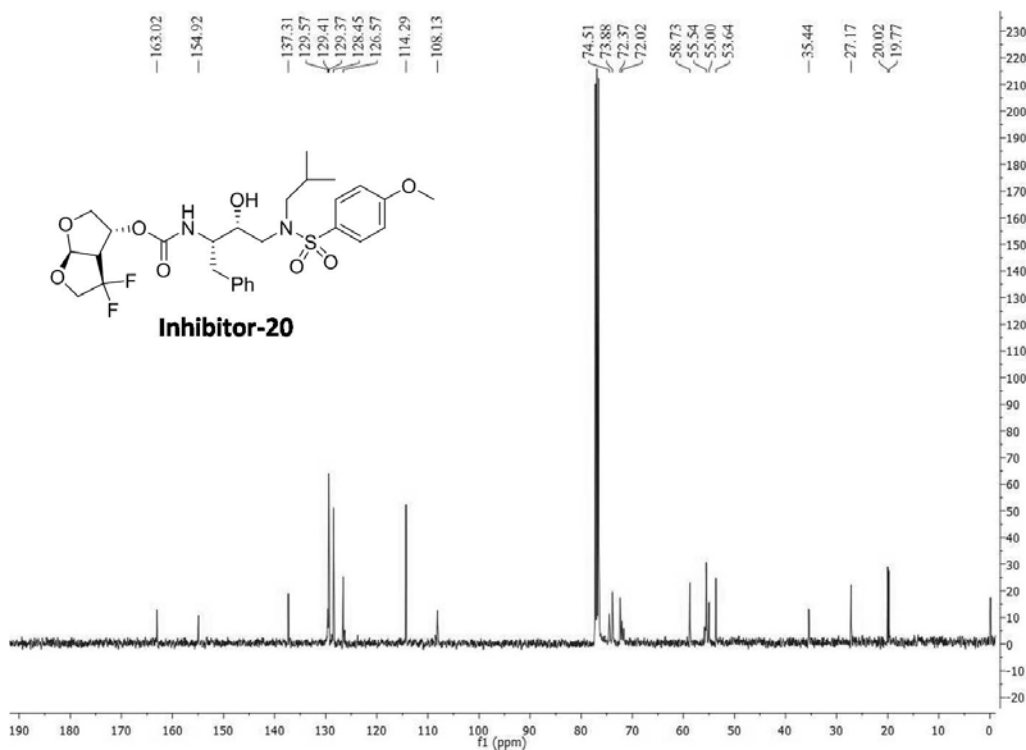
<sup>19</sup>F-NMR of Inhibitor 19 (CDCl<sub>3</sub>, 400 MHz)



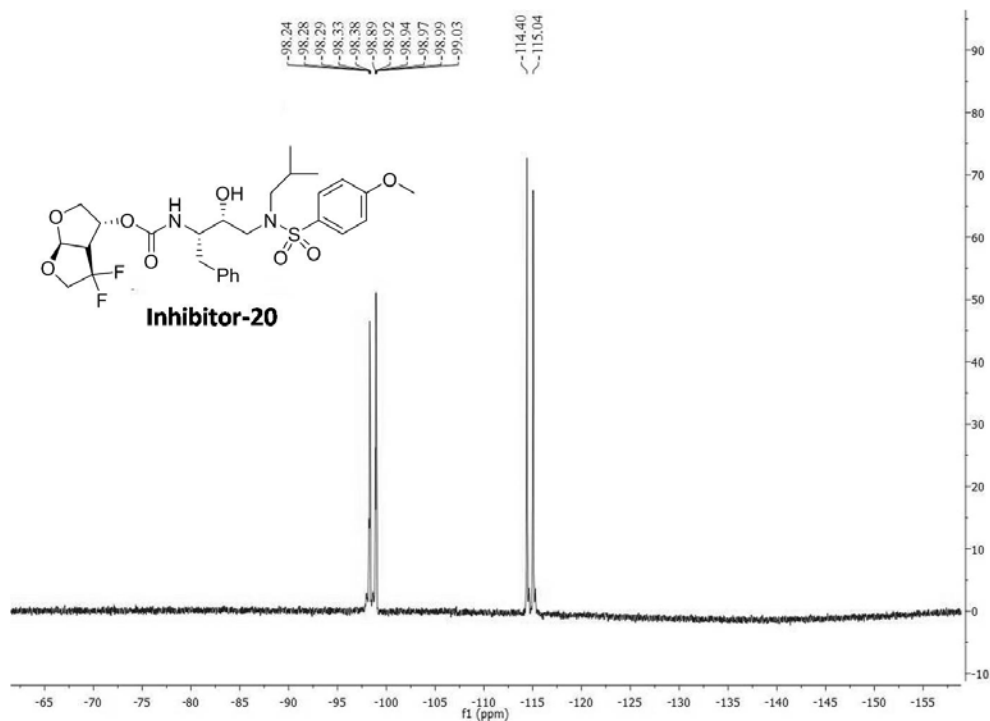
<sup>1</sup>H-NMR of Inhibitor 20 (CDCl<sub>3</sub>, 400 MHz)



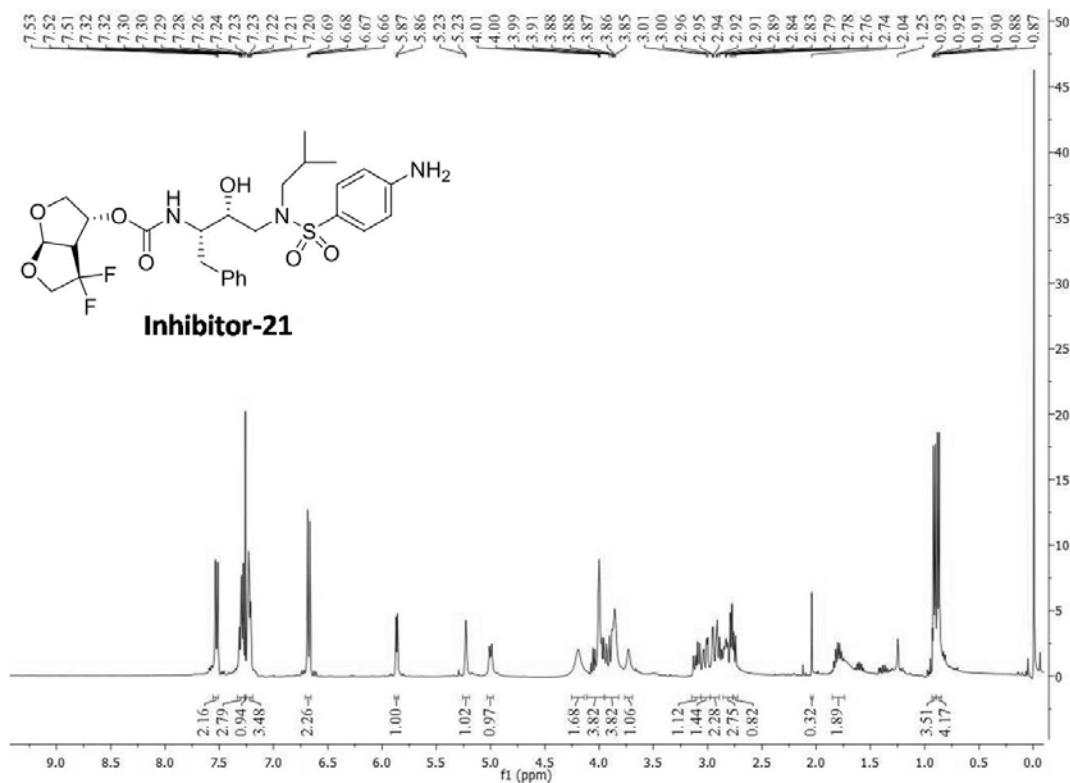
$^{13}\text{C-NMR}$  of Inhibitor 20 ( $\text{CDCl}_3$ , 400 MHz)



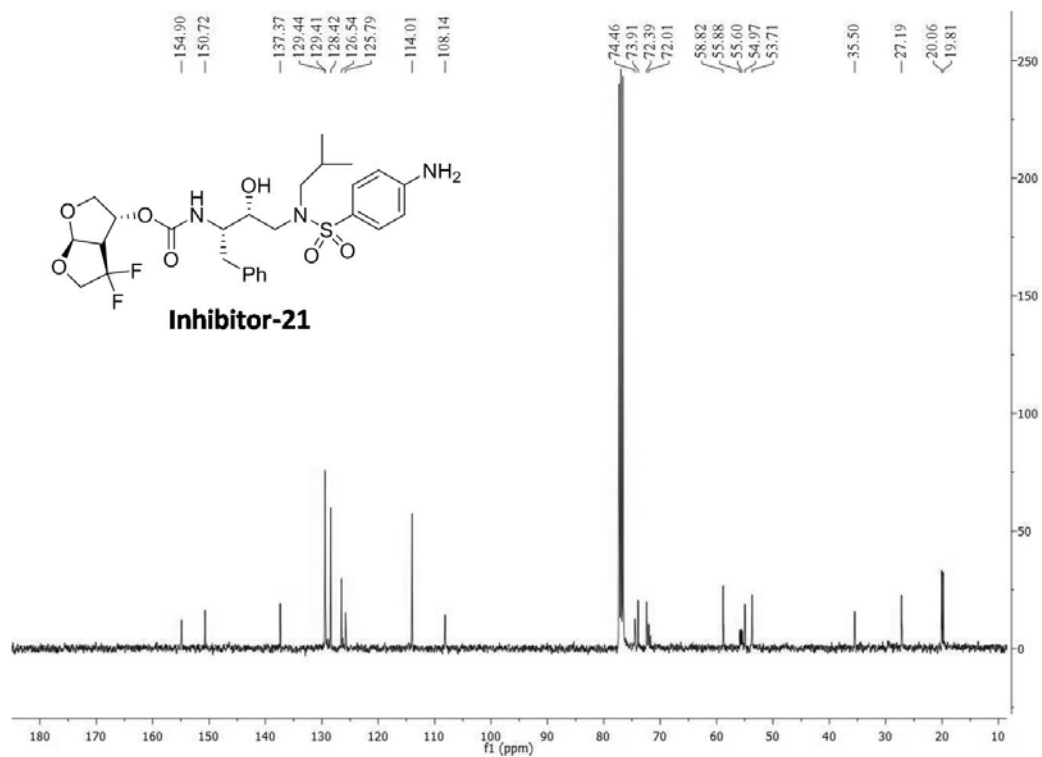
$^{19}\text{F-NMR}$  of Inhibitor 20 ( $\text{CDCl}_3$ , 400 MHz)



<sup>1</sup>H-NMR of Inhibitor 21 (CDCl<sub>3</sub>, 400 MHz)



<sup>13</sup>C-NMR of Inhibitor 21 (CDCl<sub>3</sub>, 400 MHz)



<sup>19</sup>F-NMR of Inhibitor 21 (CDCl<sub>3</sub>, 400 MHz)

**Table 1:** Crystallographic Data Collection and Refinement Statistics

	PR-GRL-050-10A
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2
Unit cell dimensions: (Å)	
A	58.54
B	85.99
C	46.21
Resolution range (Å)	50-1.30
Unique reflections	56,059
R <sub>merge</sub> (%) overall (final shell)	6.2 (40.5)
I/σ(I) overall (final shell)	19.0 (2.0)
Completeness (%) overall (final shell)	96.4 (75.9)
Data range for refinement (Å)	10-1.30
R (%)	15.4
R <sub>free</sub> (%)	18.6
No. of solvent atoms (total occupancies)	141 (123.5)
RMS deviation from ideality	
Bonds (Å)	0.012
Angle distance (Å)	0.033
Average B-factors (Å <sup>2</sup> )	
Main-chain atoms	14.6
Side-chain atoms	19.7
Inhibitor	11.0
Solvent	26.1

**Cells, viruses, and antiviral agents.** Human CD4<sup>+</sup> 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<sub>LAI</sub>), a clinical HIV-1 strain isolated from drug-naïve patients with AIDS (HIV-1<sub>ERS104pre</sub>) (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)