

Inhibition of HIV-1 Protease by a Boronic Acid with High Oxidative Stability

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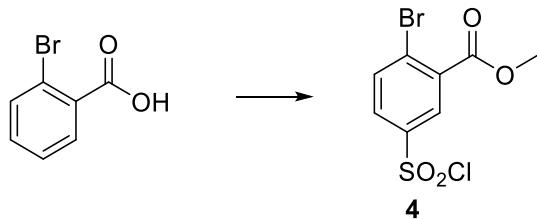
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Materials and Methods

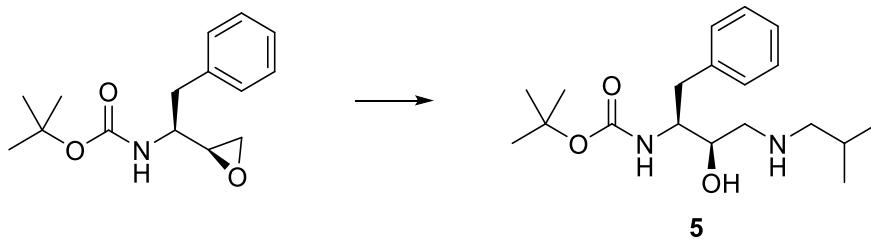
General. Commercial reagents were used without further purification. NMR spectra were obtained with an Avance-400 or Avance-600 spectrometer from Bruker (Billerica, MA). High-resolution mass spectra were obtained with an AccuTOF-DART 4G from JEOL (Peabody, MA) by helium DART ionization. The pH of buffers was determined with an Accumet XL50 pH-meter from Fischer Scientific (Hampton, NH). Column chromatography was performed on a Biotage Isolera automated purification system using prepacked SNAP KP silica gel columns or SNAP Ultra HP-Sphere C18 columns for reversed-phase purification if specified. Preparative HPLC purification was performed on an Agilent Technologies 1260 Infinity II instrument with a VP250/21 Nucleosil 100-5 C18 column from Macherey-Nagel or an XSelect Peptide CSH C18 OBD prep column (130 Å, 5 µm, 19 mm × 250 mm) from Waters. The phrase “concentrated under reduced pressure” refers to the removal of solvents and other volatile materials using a rotary evaporator at water aspirator pressure (<20 Torr) while maintaining the water-bath temperature of 40 °C. Residual solvent was removed from samples by the vacuum (<0.1 Torr) achieved by a mechanical belt-drive oil pump. All procedures were performed in air at ambient temperature (~25 °C) and pressure (1.0 atm) unless indicated otherwise.

Safety Statement. No unexpected or unusually high safety hazards were encountered in this work.

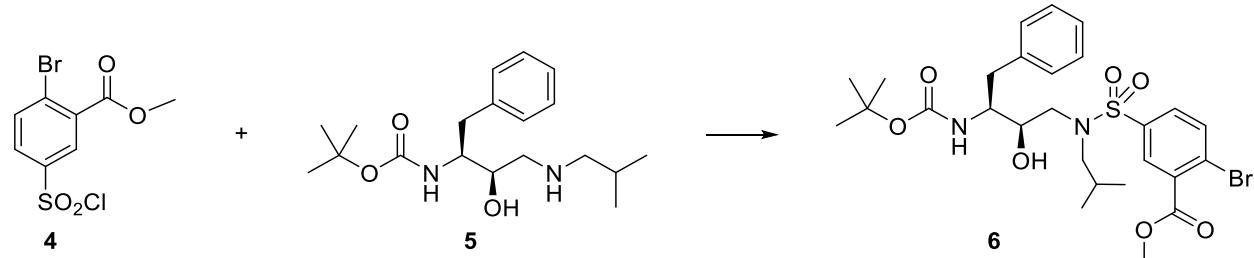
Chemical Synthesis



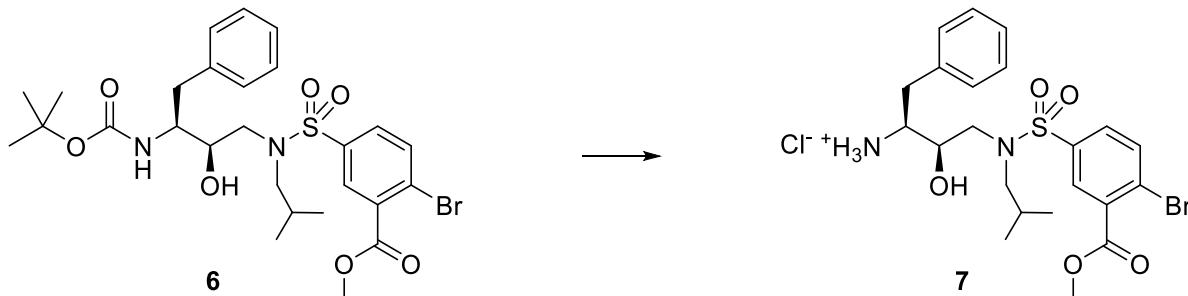
Compound 4. Chlorosulfonic acid (19.9 mL, 300 mmol, 10 equiv) was placed in a flame-dried flask under N₂(g) at 0 °C. 2-Bromobenzoic acid (6.0306 g, 30 mmol, 1 equiv) was added, and the resulting mixture was stirred at 110 °C for 4 h and then allowed to cool to room temperature. The solution was dripped onto ice, and the resulting solid was isolated by filtration and dried overnight under vacuum. The dry solid was suspended in 20 mL of toluene. Thionyl chloride (21.9 mL, 300 mmol, 10 equiv) was added, and the mixture was stirred at reflux for 1 h and then allowed to cool to room temperature. The solution was concentrated under reduced pressure, 20 mL of toluene was added, and the solution was again concentrated under reduced pressure. The residue was cooled to 0 °C, and 50 mL of ice-cold methanol was added, and the resulting solution was stirred for 10 min at 0 °C and then 15 min at room temperature. The mixture was poured into 300 mL of ice water and extracted with DCM (3 × 150 mL), and the organics were dried over MgSO₄(s), filtered, and concentrated under reduced pressure to an off-white crystalline solid, which was used without further purification (8.2160 g, 26.2 mmol, 87.3%). ¹H NMR (400 MHz, CDCl₃, δ): 8.45 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.97 (d, *J* = 1.9 Hz, 2H), 4.01 (s, 3H). ¹³C NMR (101 MHz, CDCl₃, δ): 164.22, 143.19, 136.18, 133.58, 130.17, 129.89, 129.76, 77.39, 77.07, 76.75, 53.25. HRMS (DART-TOF) (*m/z*): [M + H]⁺ calcd for C₈H₇BrClO₄S⁺, 312.8931; found, 312.8947.



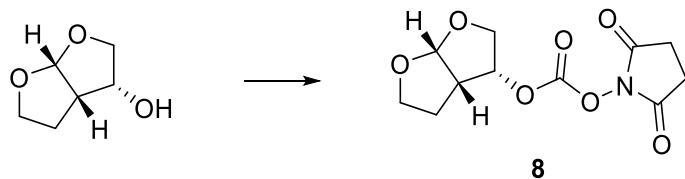
Compound 5. (2*S*,3*S*)-3-(*tert*-Butoxycarbonylamino)-1,2-epoxy-4-phenylbutane (5.0952 g, 19.3 mmol, 1 equiv) was suspended in 50 mL of 2-propanol. Isobutylamine (19.3 mL, 193 mmol, 10 equiv) was added, and the resulting mixture was stirred overnight and then concentrated under reduced pressure. The resulting white solid was dried under high vacuum and used without further purification (6.4591 g, quant). **¹H NMR** (400 MHz, CDCl₃, δ): 7.32–7.15 (m, 5H), 4.77 (d, J = 9.3 Hz, 1H), 3.80 (q, J = 7.3 Hz, 1H), 3.46 (q, J = 5.7 Hz, 1H), 2.98 (dd, J = 14.0, 4.8 Hz, 1H), 2.85 (dd, J = 14.2, 8.0 Hz, 1H), 2.68 (d, J = 5.3 Hz, 2H), 2.40 (d, J = 6.7 Hz, 2H), 1.71 (heptane, J = 6.7 Hz, 1H), 1.35 (s, 9H), 0.91 (dd, J = 6.6, 2.2 Hz, 6H). Protons directly attached to nitrogens were not observed. **¹³C NMR** (101 MHz, CDCl₃, δ): 155.88, 137.99, 129.53, 128.36, 126.27, 79.27, 77.35, 77.03, 76.72, 70.67, 57.98, 54.24, 51.47, 36.70, 28.39, 28.29, 20.55, 20.52. **HRMS** (DART–TOF) (*m/z*): [M – H][–] calcd for C₁₉H₃₁N₂O₃[–], 335.2340; found, 335.2350.



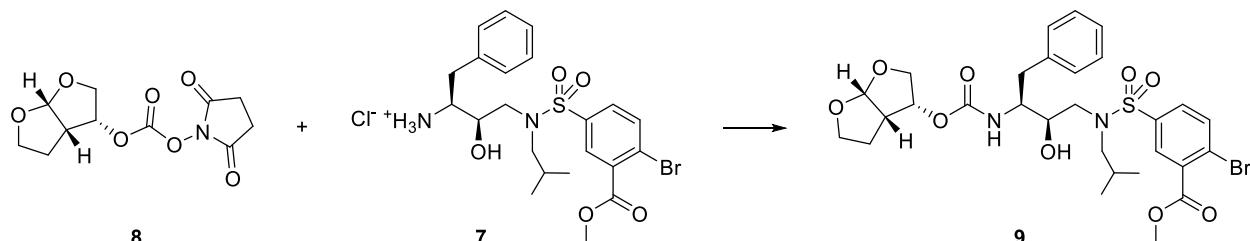
Compound 6. Sulfonyl chloride 4 (2.3516 g, 7.5 mmol, 1 equiv), amine 5 (2.5157 g, 7.5 mmol, 1 equiv) and triethylamine (2.1 mL, 15 mmol, 2 equiv) were dissolved in 20 mL of DCM, and the resulting solution was stirred overnight. The solution was then concentrated under reduced pressure. The product was isolated by chromatography on silica (30% v/v EtOAc in hexanes) as a white solid (3.5188 g, 5.7 mmol, 76%). **¹H NMR** (400 MHz, CDCl₃, δ): 8.19 (d, J = 2.3 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.69 (dd, J = 8.4, 2.3 Hz, 1H), 7.35–7.18 (m, 5H), 4.62 (d, J = 7.6 Hz, 1H), 3.97 (s, 3H), 3.88 (s, 1H), 3.83–3.70 (m, 2H), 3.19–3.13 (m, 2H), 2.95 (qd, J = 13.6, 6.1 Hz, 4H), 1.87 (heptane, J = 6.9 Hz, 1H), 1.35 (s, 9H), 0.88 (dd, J = 8.8, 6.6 Hz, 6H). **¹³C NMR** (101 MHz, CDCl₃, δ): 165.04, 138.45, 137.61, 135.38, 132.97, 130.57, 129.97, 129.45, 128.55, 126.90, 126.56, 79.98, 77.33, 77.02, 76.70, 72.47, 57.91, 55.07, 52.98, 35.44, 28.22, 27.01, 20.03, 19.84. **HRMS** (DART–TOF) (*m/z*): [M + H]⁺ calcd for C₂₇H₃₈BrN₂O₇S⁺, 613.1578, found: 613.1616.



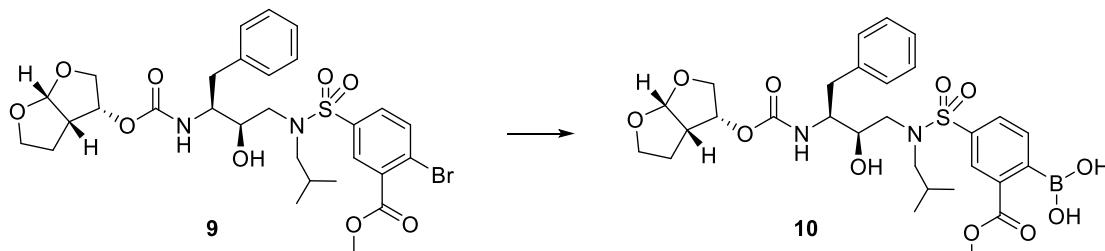
Compound 7. Sulfonamide 6 (1.1451 g, 1.87 mmol, 1 equiv) was dissolved in 8 mL of 4 M HCl in dioxane, and the resulting solution was stirred for 4 h. The solution was then concentrated to a white solid, which was used without further purification (1.0489 g, quant). **¹H NMR** (400 MHz, DMSO-*d*₆, δ): 8.21–8.03 (m, 4H), 7.97 (d, J = 8.4 Hz, 1H), 7.85 (dd, J = 8.5, 2.4 Hz, 1H), 7.42–7.20 (m, 5H), 5.62 (d, J = 5.5 Hz, 1H), 3.97 (d, J = 6.9 Hz, 1H), 3.91 (s, 3H), 3.46 (s, 1H), 3.02 (ddd, J = 20.5, 14.0, 7.4 Hz, 3H), 2.85 (ddd, J = 13.4, 7.3, 5.6 Hz, 2H), 1.96–1.81 (m, 1H), 0.78 (dd, J = 28.6, 6.5 Hz, 6H). **¹³C NMR** (101 MHz, DMSO-*d*₆, δ): 165.56, 139.28, 137.07, 135.53, 133.71, 131.43, 129.83, 129.47, 129.08, 127.31, 125.41, 68.50, 56.52, 55.57, 53.52, 50.61, 40.61, 40.41, 40.20, 39.99, 39.78, 39.57, 39.36, 33.14, 26.48, 20.29, 20.22. **HRMS** (DART–TOF) (*m/z*): calcd for C₂₂H₃₀BrN₂O₅S⁺ [M + H]: 513.1053, found: 513.1024.



Compound 8. (*3R,3aS,6aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol (1.2411 g, 9.54 mmol, 1 equiv) and pyridine (3.1 mL, 38.2 mmol, 4 equiv) were dissolved in 25 mL of dry DCM. Disuccinimidyl dicarbonate (4.8928 g, 19.1 mmol, 2 equiv) was added. The resulting mixture was stirred at reflux overnight, then cooled to room temperature. The mixture was stirred with 20 mL of water for 5 min. The organic layer was washed with water, brine, dried over MgSO₄(s), filtered, and concentrated under reduced pressure, and the residue was crystallized from DCM/hexanes to yield the product as off-white crystals (2.0501 g, 7.6 mmol, 80%). ¹H NMR (400 MHz, CDCl₃, δ): 5.75 (d, *J* = 5.2 Hz, 1H), 5.25 (dt, *J* = 8.2, 6.0 Hz, 1H), 4.12 (dd, *J* = 10.2, 6.1 Hz, 1H), 4.03 (td, *J* = 8.4, 2.4 Hz, 1H), 3.99–3.91 (m, 2H), 3.22–3.07 (m, 1H), 2.86 (s, 4H), 2.15 (ddt, *J* = 13.4, 5.3, 2.4 Hz, 1H), 1.99 (dddd, *J* = 13.4, 10.4, 9.6, 8.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃, δ): 168.42, 151.21, 109.19, 79.64, 77.37, 77.05, 76.73, 70.03, 69.65, 45.09, 25.94, 25.46. HRMS (DART-TOF) (*m/z*): [M + H]⁺ calcd for C₁₁H₁₄NO₇⁺, 272.0765; found, 272.0784.



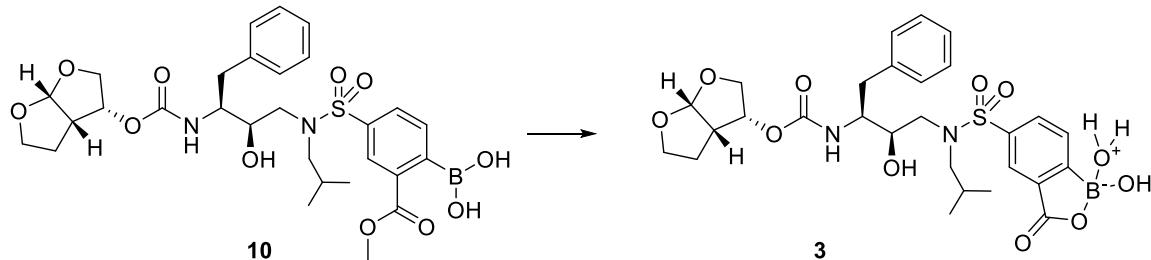
Compound 9. Amine hydrochloride 7 (0.9340 g, 1.7 mmol, 1 equiv), bis-THF carbonate 8 (0.5072 g, 1.87 mmol, 1.1 equiv) and pyridine (0.7 mL, 8.5 mmol, 5 equiv) were stirred in 12 mL of dry DCM overnight. The reaction mixture was washed with 20 mL of 1 M HCl, organics dried over MgSO₄(s), filtered, concentrated under reduced pressure, then separated on silica (65% v/v EtOAc in hexanes) to yield the product as a white solid (0.8798 g, 1.31 mmol, 77%). ¹H NMR (400 MHz, CDCl₃, δ): 8.18 (d, *J* = 2.3 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.70 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.31–7.18 (m, 5H), 5.64 (d, *J* = 5.2 Hz, 1H), 5.05 (dt, *J* = 20.3, 7.4 Hz, 2H), 3.97 (s, 3H), 3.87 (tdd, *J* = 18.8, 8.8, 2.8 Hz, 3H), 3.76–3.61 (m, 2H), 3.27–2.84 (m, 6H), 2.77 (dd, *J* = 14.1, 9.4 Hz, 1H), 1.87 (dq, *J* = 13.8, 6.8 Hz, 1H), 1.69–1.55 (m, 1H), 1.42 (dd, *J* = 13.4, 5.7 Hz, 1H), 0.90 (dd, *J* = 11.3, 6.6 Hz, 6H). ¹³C NMR (101 MHz, CDCl₃, δ): 165.11, 155.60, 138.21, 137.52, 135.45, 133.16, 130.55, 129.93, 129.29, 128.59, 126.97, 126.66, 109.32, 73.53, 72.61, 70.88, 69.59, 58.13, 55.37, 53.10, 53.04, 45.46, 35.51, 27.10, 25.85, 25.46, 20.06, 19.87, 14.19. HRMS (DART-TOF) (*m/z*): [M + H]⁺ calcd for C₂₉H₃₈BrN₂O₉S⁺, 669.1476; found, 669.1522.



Compound 10. Aryl bromide 9 (0.3999 g, 0.6 mmol, 1 equiv), B₂Pi_n (0.2285 g, 0.9 mmol, 1.5 equiv), KOAc (0.1767 g, 1.8 mmol, 3 equiv) and Pd(dppf)Cl₂ (0.4390 g, 0.6 mmol, 1 equiv) were placed in a 20-mL vial with a septum and evacuated/backfilled with N₂(g) three times. Dry 1,4-dioxane (3 mL) was added, and the solution was purged again with N₂(g), then stirred at 80 °C for 1 h. The mixture was cooled and

filtered through a pad of Celite, rinsing with DCM. The filtrate was washed with 1 M HCl, dried over MgSO₄(s), filtered, concentrated under reduced pressure, and passed through a short silica plug, eluting with 5% v/v MeOH in DCM. The resulting material was adsorbed onto 1.5 g of C18 silica gel from a solution in CH₃CN, then separated on a reversed-phase column using a gradient of CH₃CN in water and isolated by lyophilization. The major peak, which eluted at 80% v/v CH₃CN, was the desired borylation product with significant contamination from the dppf and was carried forward without further purification.

The isolated material was dissolved in 5 mL of MeOH, and 1.5 mL of 4.5 M KHF₂(aq) was added, and the resulting solution was stirred for 20 min, then concentrated under reduced pressure. The residue was stirred in 10 mL of acetone at 40 °C for 10 min, then filtered through Celite and the filtrate was concentrated under reduced pressure. The residue was dissolved in 5 mL of dry CH₃CN, chlorotrimethylsilane (0.38 mL, 3 mmol) and water (54 μL, 3 mmol) were added, and the mixture was stirred for 1 h and then concentrated under reduced pressure. The residue was taken up in MeOH, precipitated salts were removed by filtration through a small Celite plug, and the filtrate was concentrated under reduced pressure. The residue was adsorbed onto 1 g of C18 silica gel from a solution in CH₃CN and separated by reversed-phase chromatography. The major peak, which eluted at 60% v/v CH₃CN, was isolated by lyophilization and again separated by reversed-phase chromatography to yield the free boronic acid/methyl carboxy ester as a white solid (0.0473 g, 0.075 mmol, 12.5%). Due to poor signal from the free boronic acid, HRMS was performed on the potassium trifluoroborate salt formed *in situ* from a small aliquot of the boronic acid dissolved in methanol and stirred 1 h with excess aqueous KHF₂ (4.5 M). The solution was concentrated and the residue suspended in a small amount of acetone and analyzed by DART–TOF. ¹H NMR (400 MHz, CD₃CN/D₂O, δ): 8.30 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.24 (td, *J* = 12.7, 7.0 Hz, 5H), 6.01 (d, *J* = 8.9 Hz, 1H), 5.54 (d, *J* = 5.3 Hz, 1H), 4.90 (q, *J* = 5.9 Hz, 1H), 3.93 (s, 3H), 3.85 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.81–3.70 (m, 3H), 3.62 (tt, *J* = 9.9, 5.5 Hz, 2H), 3.37 (dd, *J* = 15.1, 2.5 Hz, 1H), 3.16–2.90 (m, 5H), 2.55 (dd, *J* = 14.0, 10.6 Hz, 1H), 2.03–1.91 (m, 2H), 1.57–1.45 (m, 1H), 1.36 (dd, *J* = 13.3, 5.7 Hz, 1H), 0.89 (dd, *J* = 8.3, 6.6 Hz, 6H). ¹³C NMR (101 MHz, CD₃CN, δ): 167.23, 155.79, 139.42, 138.96, 133.19, 132.49, 130.10, 129.34, 128.24, 127.00, 126.19, 109.32, 73.13, 72.29, 70.85, 69.23, 56.85, 55.93, 52.34, 51.94, 45.34, 35.30, 26.53, 25.68, 19.28. ¹¹B NMR (128 MHz, CD₃CN, δ): 29.96. HRMS (DART–TOF) (*m/z*): [M][−] calcd for C₂₉H₃₇BF₃N₂O₉S[−], 657.2270; found, 657.2270.

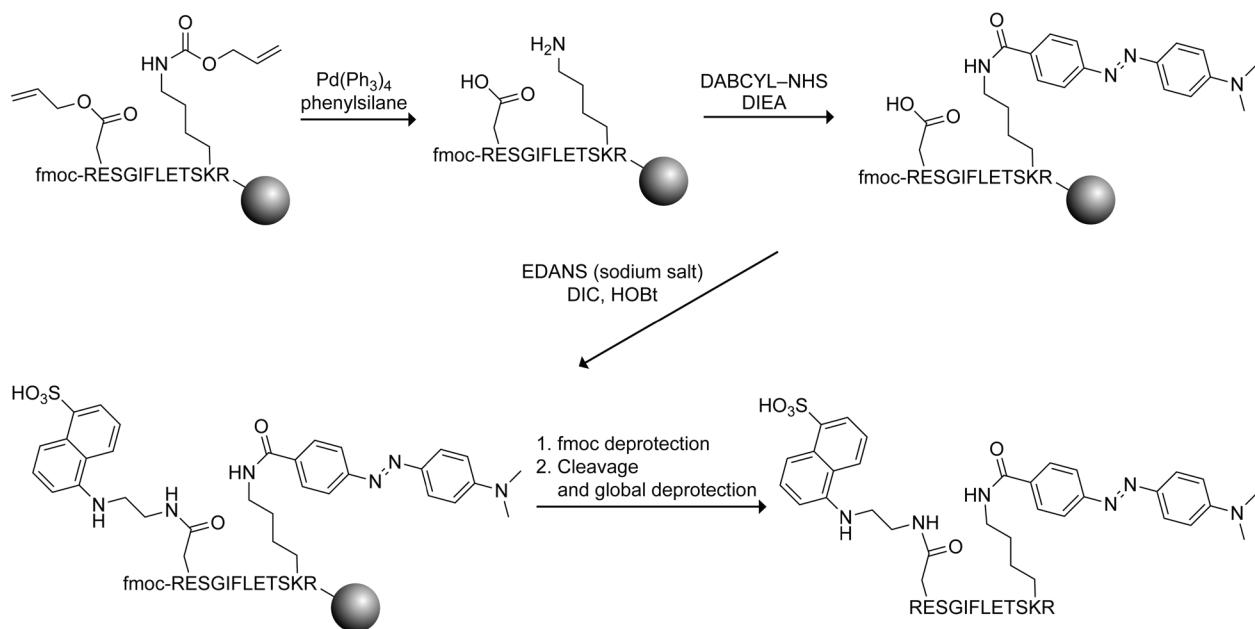


Compound 3. Compound **10** (0.0240 g, 0.04 mmol) was stirred in 1 mL CH₃CN/1 mL H₂O/0.5 mL saturated aqueous sodium bicarbonate overnight, and the resulting solution was acidified with concentrated HCl. The resulting solution separated by reversed-phase chromatography, with the major peak eluting at 40% v/v CH₃CN. NMR spectra of the resulting material in CD₃CN showed a complicated set of peaks consistent with multiple species being present. Repeating the analysis in 1:1 D₂O/CD₃CN gave clean spectra, consistent with the expected ionic nature of the benzoxaborolone. The product was a white solid (15.4 mg, 66%). Due to poor signal from the free boronic acid, HRMS was performed on the potassium difluoroborate salt formed *in situ* from a small aliquot of the boronic acid dissolved in methanol and stirred for 1 h with excess aqueous KHF₂ (4.5 M). The solution was concentrated and the residue suspended in a small amount of acetone and analyzed by DART–TOF. Due to the internal coordination of the carboxylate, benzoxaborolones form a difluoroborate salt rather than the trifluoroborate salt typical for boronic acids. The MS analysis was consistent with the corresponding protonated carboxylic acid/difluoroborane, with an additional proton for ionization. ¹H NMR (400 MHz, CD₃CN/D₂O, δ): 7.99 (s, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.18 (ddd, *J* = 18.9, 13.5, 7.2 Hz, 5H), 5.51 (d, *J* = 5.4 Hz, 1H), 4.84 (q, *J* =

5.5 Hz, 1H), 3.82 (dd, J = 10.0, 5.6 Hz, 1H), 3.79–3.66 (m, 3H), 3.67–3.50 (m, 2H), 3.31 (dd, J = 15.0, 2.7 Hz, 1H), 3.13–2.94 (m, 3H), 2.83 (dq, J = 27.6, 7.2 Hz, 2H), 2.53–2.38 (m, 1H), 2.02–1.92 (m, 1H), 1.87 (p, J = 6.9 Hz, 1H), 1.45 (td, J = 10.8, 9.9, 3.8 Hz, 1H), 1.13 (dd, J = 13.4, 5.5 Hz, 1H), 0.80 (dd, J = 9.7, 6.5 Hz, 6H). ^{13}C NMR (101 MHz, $\text{CD}_3\text{CN}/\text{D}_2\text{O}$, δ): 172.25, 155.99, 138.41, 138.25, 130.40, 129.73, 129.23, 129.03, 128.06, 126.02, 123.09, 108.98, 72.97, 71.87, 70.78, 69.33, 56.69, 55.39, 51.56, 45.10, 35.04, 26.20, 25.26, 19.01, 18.98. ^{11}B NMR (128 MHz, $\text{CD}_3\text{CN}/\text{D}_2\text{O}$, δ): 19.68, 11.50. HRMS (DART-TOF) (m/z): [M + 2H]⁺ calcd for $\text{C}_{28}\text{H}_{36}\text{BF}_2\text{N}_2\text{O}_9\text{S}^+$, 625.2197; found, 625.2243. Purity: 97% by ^1H NMR spectroscopy.

Peptide Synthesis

Scheme S1. Route for the Synthesis of RE(EDANS)SGIFLETSK(DABCYL)R



The peptide substrate for HIV protease binding assays, RE(EDANS)SGIFLETSK(DABCYL)R,¹ was synthesized by the route in Scheme 1 using a Liberty BlueTM Automated Microwave Peptide Synthesizer from CEM (Matthews, NC) following CEM standard methods for both microwave and coupling cycles. Standard solutions of monohydrated HOBt (1 M in DMF), DIC (0.5 M in DMF), 4-methylpiperidine (20% v/v in DMF), and Fmoc-protected amino acids (0.2 M in DMF) were prepared for each synthesis. Preloaded FmocArg Wang resin was used to synthesize the peptide RE(allyl)SGIFLETSK(alloR), leaving the terminal amino group protected. The resin was removed from the synthesizer to a fritted syringe and rinsed thoroughly with DCM. The resin was suspended in 2 mL of DCM, and the slurry was stirred by bubbling $\text{N}_2(\text{g})$. $\text{Pd}(\text{PPh}_3)_4$ (10 mg) and phenylsilane (100 μL) were added, and the slurry was stirred for 30 min. The solution was removed, the resin was rinsed with DMF (3×) and DCM (3×), and the allyl/allo deprotection repeated using the same conditions. The resin was suspended in 2 mL of DMF with DABCYL-NHS ester (5 equiv) and DIPEA (10 equiv), and the resulting solution was mixed with a rotary shaker overnight at room temperature. The solution was removed, the resin was rinsed with DMF until the rinse was colorless (5×), and the resin then capped with 1 mL of DMF, 50 μL of acetic anhydride, and 100 μL of pyridine for 10 min. The resin was rinsed with DMF (5×) and suspended in 2 mL of DMF with 5 equiv of EDANS (sodium salt), 10 equiv of DIC, and 10 equiv of HOBt, and shaken for 4 h at room temperature. The resin was rinsed DMF (5×) and the EDANS coupling repeated, shaking at 37 °C overnight. The terminal amino

group was deprotected with 1 mL of 20% v/v 4-methylpiperidine in DMF for 5 min, the resin was rinsed with DMF, and the deprotection repeated for 8 min, followed by a thorough rinsing of the resin with DCM.

The peptide was cleaved from the resin by incubating in a solution of 0.1862 g of phenol, 36 μ L of water, 0.24 mL of thioanisole, and 0.12 mL of 2,2'-(ethylenedioxy)diethanethiol in 2.5 mL of TFA for 2 h. The resin was removed by filtration, and the filtrate was dripped into ice-cold diethyl ether. The peptide was isolated by centrifugation, and the pellet was dissolved in a minimum of 1:1 CH₃CN/H₂O containing TFA (0.1% v/v). The solution was frozen and lyophilized. The crude peptide mixture was then separated on a Biotage reversed-phase column, resulting in a single major peak at 36% v/v CH₃CN in H₂O containing TFA (0.1% v/v). The peptide was analyzed by MALDI-TOF MS using a microflex LRF instrument and a CHCA matrix from Bruker (Billerica, MA). The peptide was purified further by preparative HPLC (solvent A: 5% MeCN in H₂O/0.1% v/v TFA, solvent B: 5% H₂O in MeCN/0.1% v/v TFA; gradient from 25%–40% B over 20 min, then to 100% B over 10 min) The desired product eluted at 7.85 min (Figure S1).

Oxidation by Hydrogen Peroxide

Solutions (1 mM) of compounds **2** (99% purity by ¹H NMR spectroscopy) and **3** were prepared in a 1:1 mixture of 50 mM sodium phosphate buffer in D₂O (pD 7.4) and CD₃CN. A 600- μ L aliquot of the boronic acid solution was placed in an NMR tube, the spectrometer was locked to the CD₃CN signal, tuned, and shimmed. A 10- μ L aliquot of hydrogen peroxide in sodium phosphate buffer (0.305 M for **2**, 3.05 M for **3**; final [H₂O₂]: 5 mM for **2**, 50 mM for **3**) was added to the tube, which was then shaken to mix. Single-scan ¹H spectra were obtained every 10 s for at least 10 min. The reaction mixtures were allowed to sit overnight and new spectra were obtained to ensure reaction completion and the stability of the resulting phenol. All reactions were run in triplicate.

Inhibition of HIV-1 Protease

Wild-type HIV-1 protease and its D30N variant were produced in *Escherichia coli* and purified as described previously.² Inhibition kinetics for benzoxaborolone **3** with HIV-1 protease were assessed as described previously.^{1,2} Enzyme concentrations were determined by titration with darunavir, and these values were used to constrain the non-linear fit using the Morrison *K_i* subroutine in Prism 6 software. For assays with the D30N variant, the enzyme concentration determined from the Michaelis-Menten parameters of the uninhibited reaction closely matched the concentration from the active-site titration and was used to constrain the fit. For the wild-type protease, concentrations from the active-site titration were used to constrain the fit. Reactions were performed with a final substrate concentration of 9 μ M and an enzyme concentration of 50 pM for the wild-type enzyme and 500 pM for the D30N variant. All assays were performed in quadruplicate.

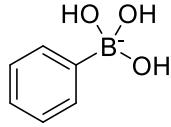
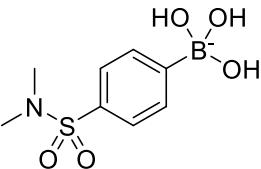
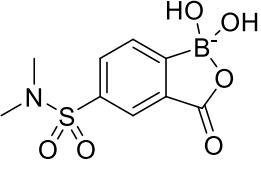
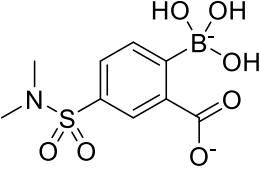
X-ray Crystallography

Structures of benzoxaborolone **3** bound to HIV-1 protease were determined by X-ray crystallography as described previously.² Crystals were grown with 2 mg/mL of wild-type protease or 10 mg/mL of D30N protease in the presence of a 50-fold molar excess of benzoxaborolone **3** by the hanging-drop method using a mother liquor composed of 100 mM Tris-HCl buffer, pH 7.5, containing NaCl (500 mM). Crystals were cryoprotected with 100 mM Tris-HCl buffer, pH 7.5, containing NaCl (750 mM) and glycerol (25% v/v). Crystals were diffracted at station 23ID-D of the NIGMS and NCI Structural Biology Facility at the Argonne National Laboratory. Data were indexed, reduced, and scaled with XDS.³ Initial phases were determined by Phaser as implemented in Phenix⁴ using PDB entry 6c8x² as a search model. Restraints were prepared for the benzoxaborolone **3** ligand using eLBOW in Phenix. Model building was performed with COOT⁵ and refinement was carried out with phenix.refine.

Computational Methods

Structure optimizations were performed with ORCA 5.0⁶⁻⁸ at the M06-2X/6-311+G(d,p) level of theory^{9,10} and employed the CPCM solvation model¹¹ for water. Frequency calculations were performed to confirm each stationary point as a minimum or first-order saddle point.

Table S1. Calculated Free Energies of Activation and Relative Rate Constants for the Oxidation of Boronic Acids with Hydrogen Peroxide^a

Boronic Acid	ΔG^\ddagger (kcal/mol)	k_{rel}
 PBA	27.0	1
 2 model	28.8	4.64×10^{-2}
 3 model	36.4	1.36×10^{-7}
 3 model dianion	27.5	4.67×10^{-1}

^aCalculations were performed at the M06-2X/6-311+G(d,p) level of theory with CPCM water.

Table S2. Crystallographic Data for the Benzoaxaborolone 3 Complexes with Wild-Type HIV-1 Protease and the D30N Variant

Parameter	Wild-Type HIV-1 Protease· Benzoaxaborolone 3 Complex	D30N HIV-1 Protease· Benzoaxaborolone 3 Complex
PDB Code	8esx	8esy
Wavelength	0.968620	0.968620
Resolution range	48.12–1.35 (1.39–1.35)	48.4–1.35 (1.39–1.35)
Space group	P 2 ₁ 2 ₁ 2	P 2 ₁ 2 ₁ 2
Unit cell, <i>a</i> , <i>b</i> , <i>c</i> (Å)	45.94, 57.97, 86.30	46.34, 58.44, 86.38
Unit cell, α , β , γ (°)	90.0, 90.0, 90.0	90.0, 90.0, 90.0
Total reflections	603,103 (35,324)	644,520 (40,394)
Unique reflections	50,842 (3,576)	52,315 (3,792)
Multiplicity	11.9 (9.9)	12.3 (10.6)
Completeness (%)	98.8 (95.6)	99.9 (99.0)
Mean $I/\sigma(I)$	18.2 (1.0)	15.7 (1.3)
Wilson <i>B</i> -factor	17.6	18.8
R_{meas}	0.076 (1.036)	0.0075 (1.537)
$CC_{1/2}$	0.999 (0.473)	99.9 (65.0)
Reflections for refinement	50793 (3295)	52256 (5125)
Reflections used for R_{free}	2000 (191)	2000 (197)
R_{work}	0.1903 (0.3300)	0.1973 (0.3280)
R_{free}	0.2084 (0.3347)	0.2219 (0.3647)
Number non-hydrogen atoms	1836	1878
Macromolecule	1566	1558
Ligand	104	175
Solvent	213	225
Protein residues	198	197
RMSD of Bond Lengths (Å)	0.007	0.052
RMSD of Bond Angles (°)	0.98	1.5
Ramachandran favored (%)	99.48	100
Ramachandran allowed (%)	0.52	0
Ramachandran outliers (%)	0	0
Rotamer outliers (%)	0.58	1.16
Clashscore	5.68	7.43
Average <i>B</i> -factor	21.86	23.07
Macromolecule	20.17	21.67
Ligand	21.54	19.63
Solvent	34.4	34.21

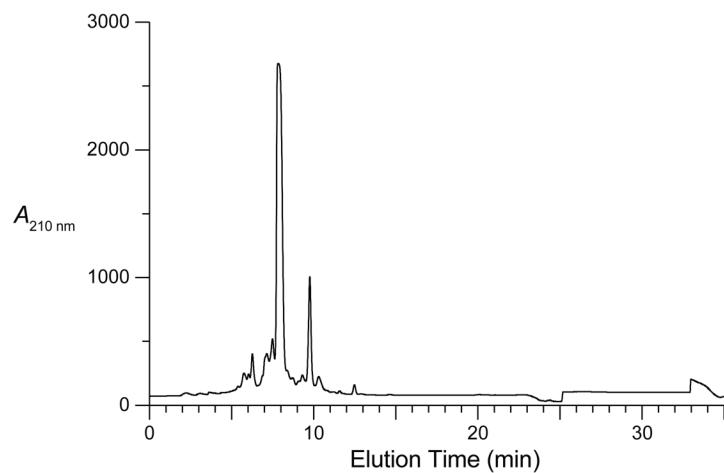


Figure S1. Preparative HPLC chromatogram of RE(EDANS)SGIFLETSK(DABCYL)R, the peptide substrate for HIV-1 protease. Fractions from the major peak (7.85 min) were combined, lyophilized, and used to assay catalysis by HIV-1 protease.

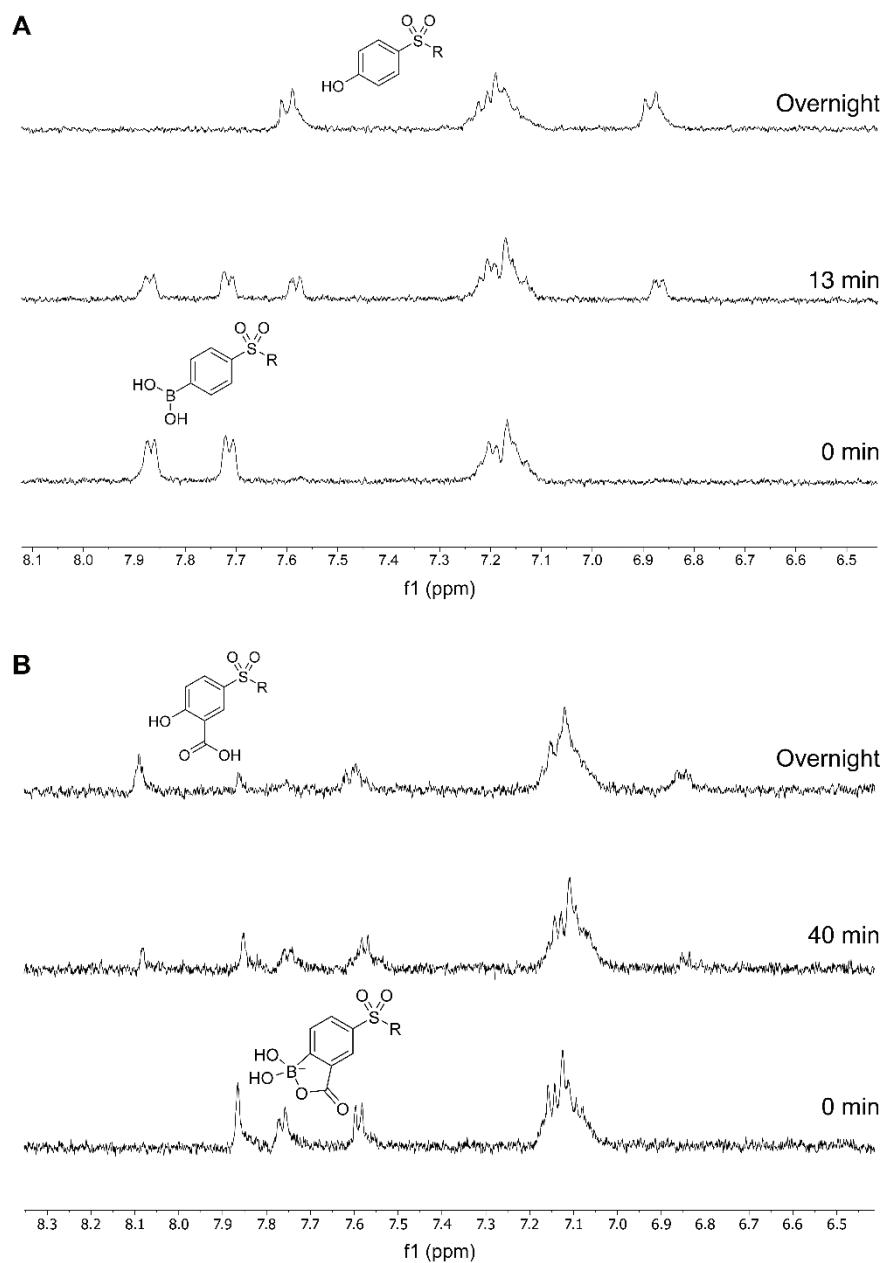


Figure S2. Representative ^1H NMR spectra for the oxidation of compounds **2** and **3** by hydrogen peroxide. Only the aromatic region is shown for clarity. (A) Compound **2**, which shows a clean transition from the boronic acid peaks to the expected phenol peaks after sitting overnight. (B) Compound **3**, showing clean transition from the benzoxaborolone peaks to the corresponding salicylic acid peaks, with some starting material remaining after sitting overnight. In both cases, incubation overnight in excess hydrogen peroxide did not result in detectable degradation of the phenolic product.

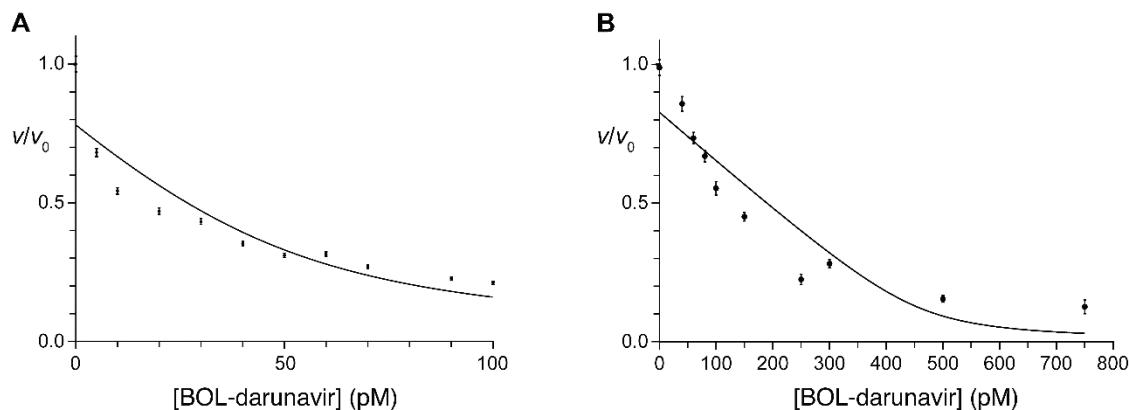
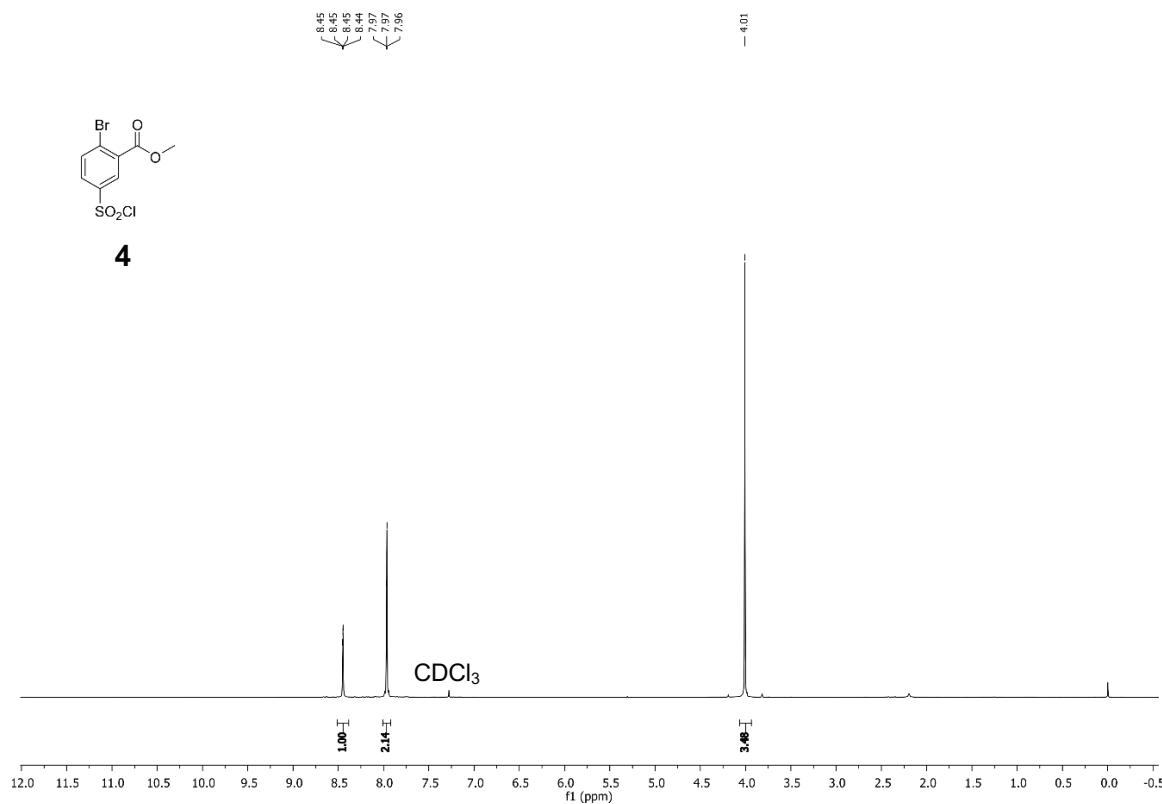
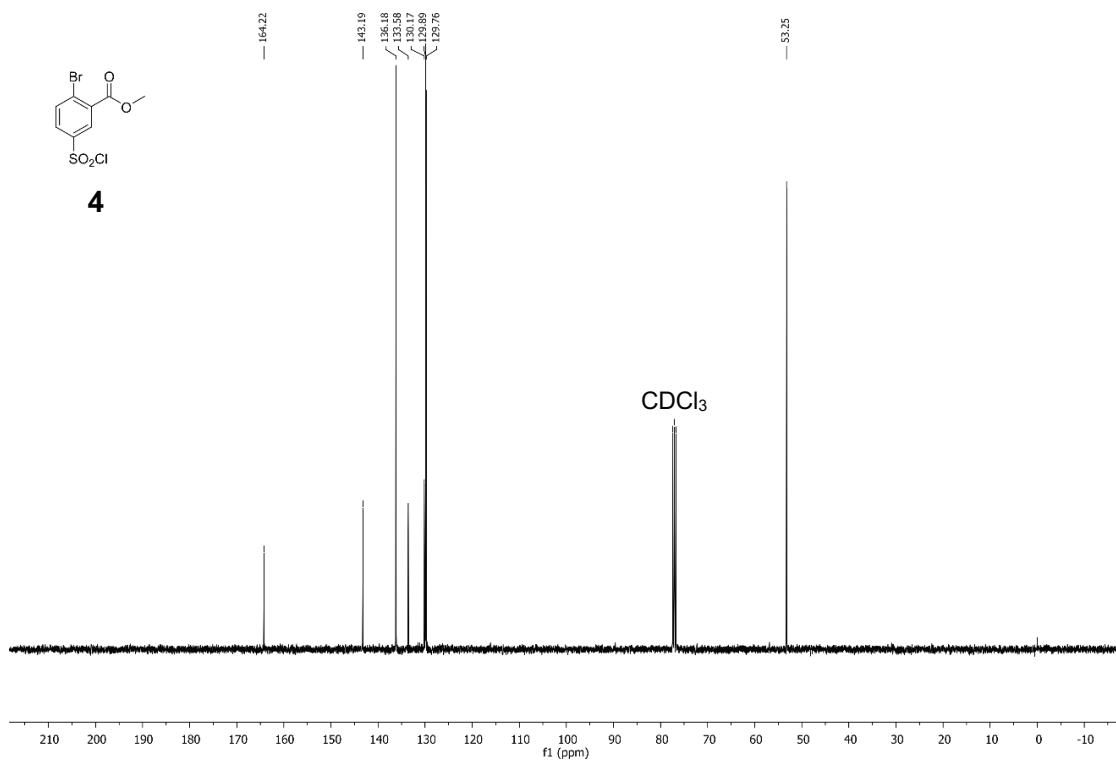
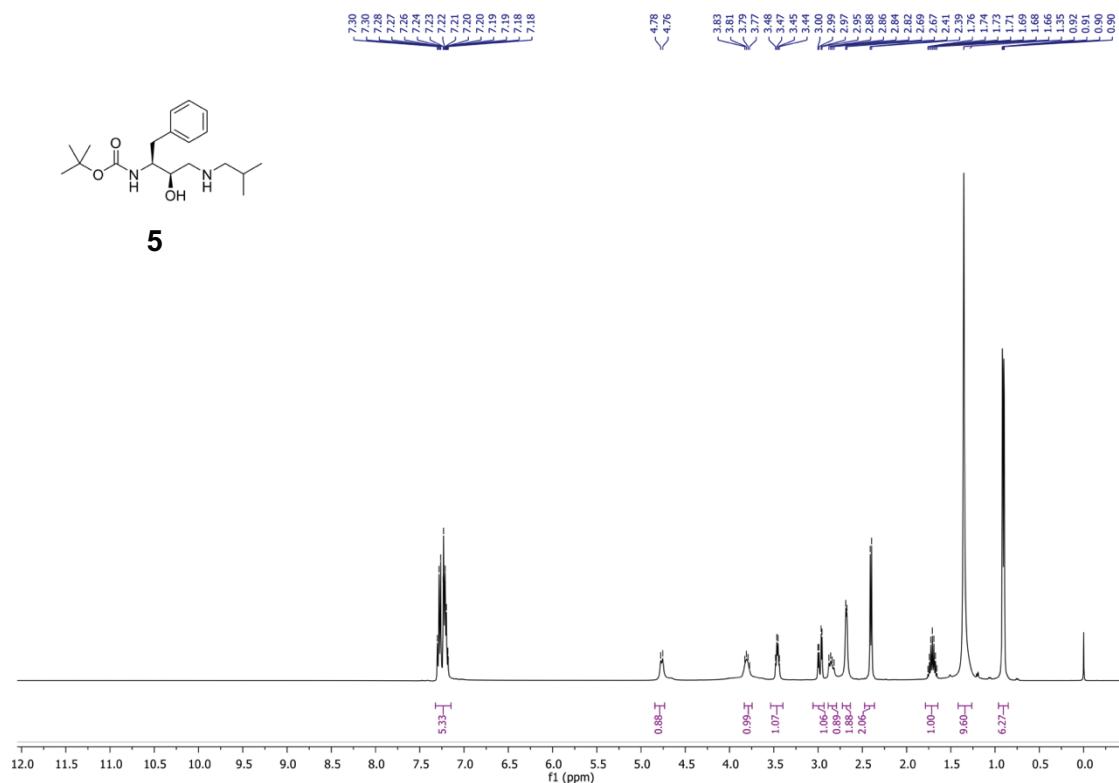
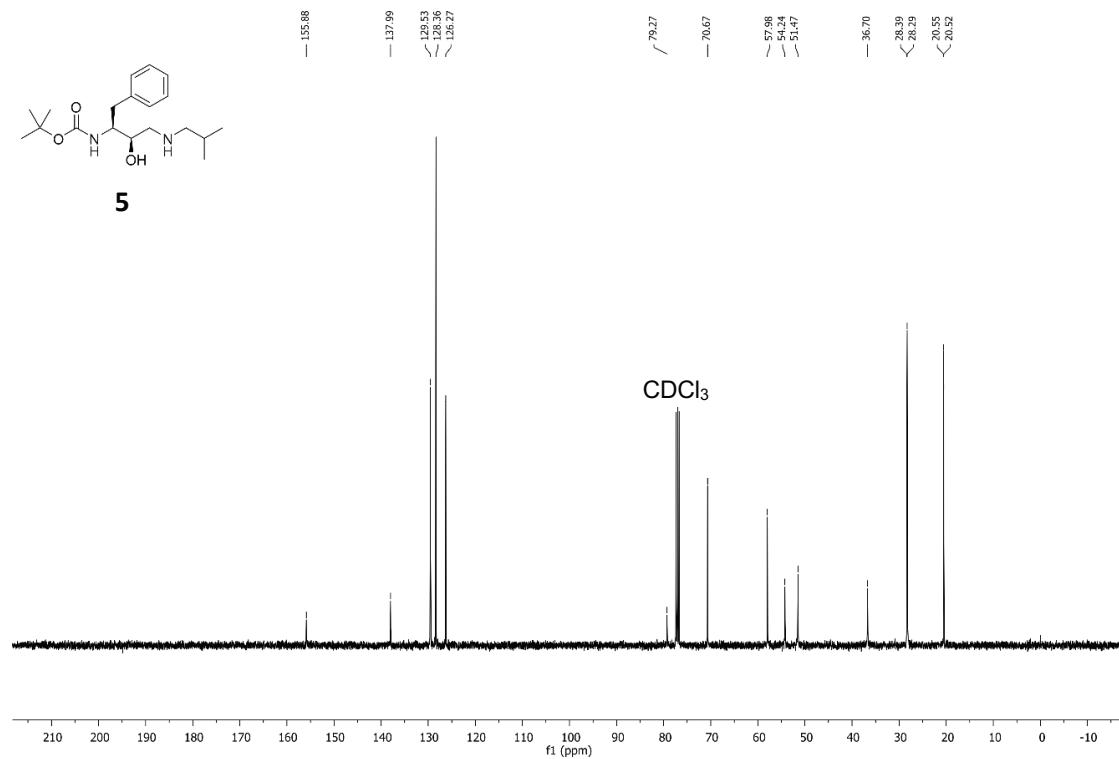
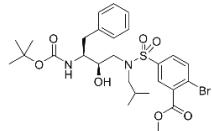


Figure S3. Inhibition of HIV protease by benzoxaborolone **3**. (A) Inhibition of wild-type HIV protease at 50 pM enzyme ($R^2 = 0.84$). (B) Inhibition of D30N HIV protease at 500 pM enzyme ($R^2 = 0.87$). Data were fitted by non-linear regression to Morrison's equation (fit lines are shown) to derive values of K_i .

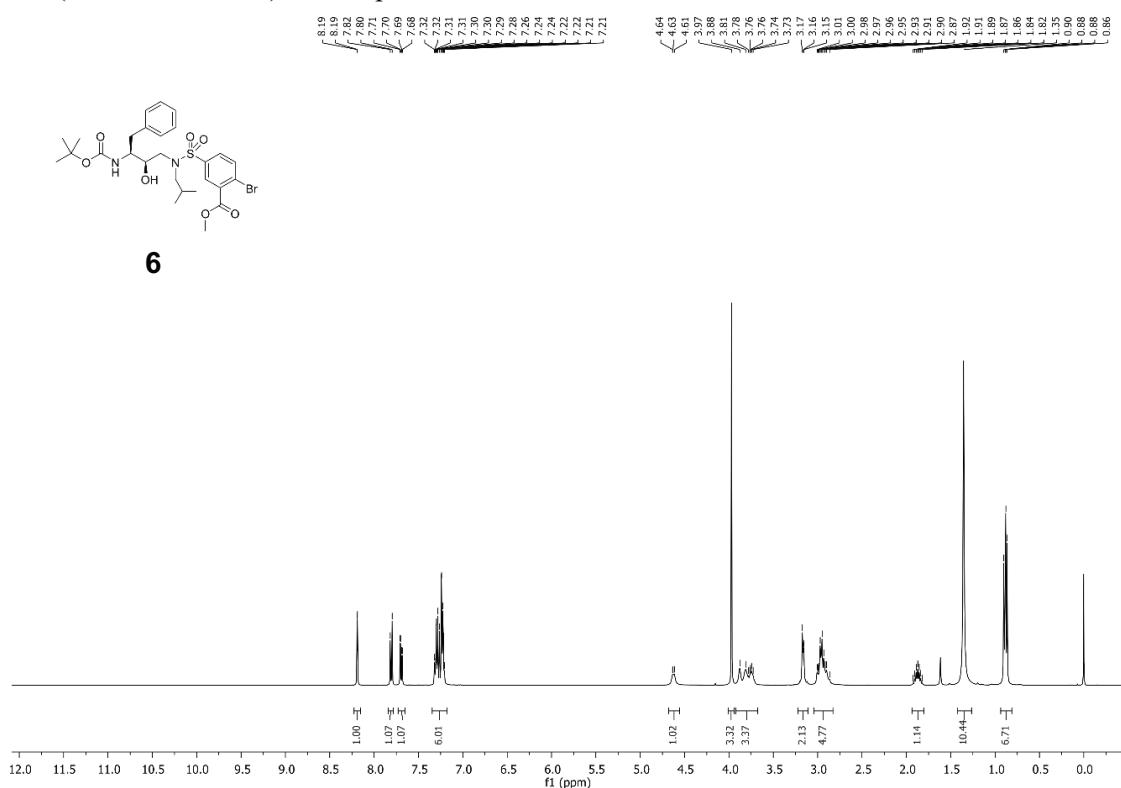
NMR Spectra¹H NMR (400 MHz, CDCl₃) of Compound 4¹³C NMR (101 MHz, CDCl₃) of Compound 4

¹H NMR (400 MHz, CDCl₃) of Compound 5¹³C NMR (101 MHz, CDCl₃) of Compound 5

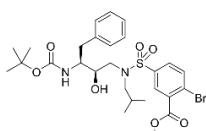
¹H NMR (400 MHz, CDCl₃) of Compound 6



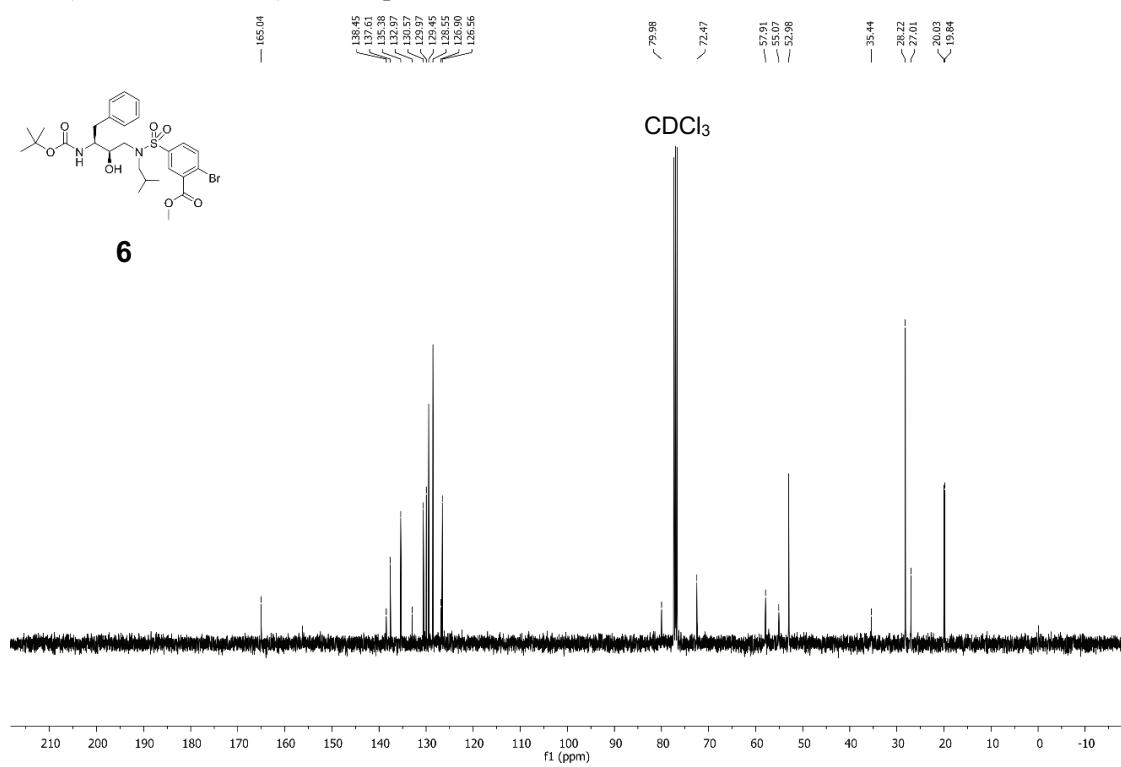
6

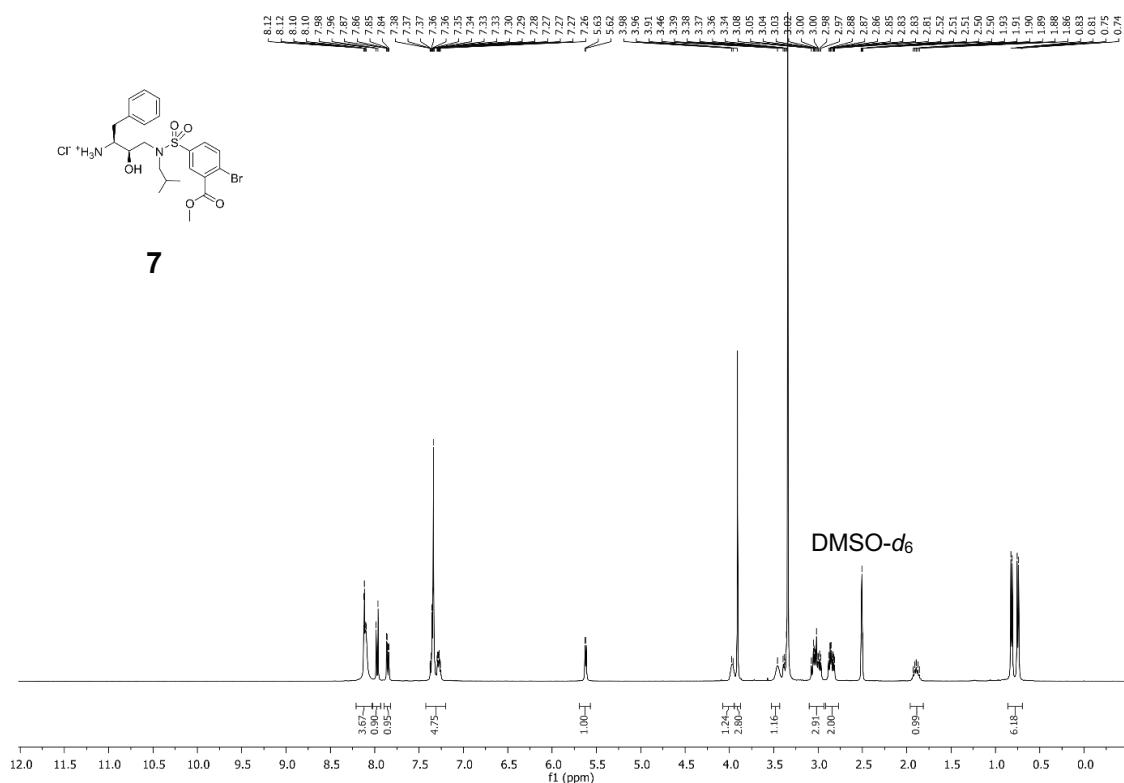


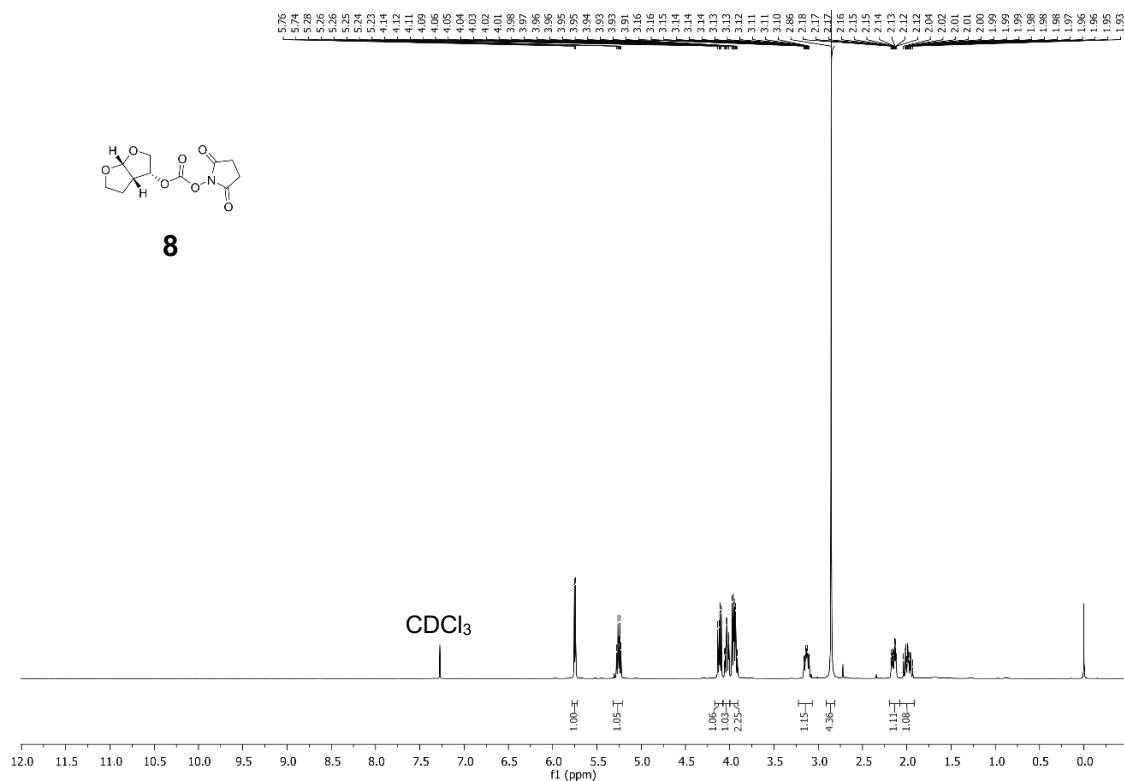
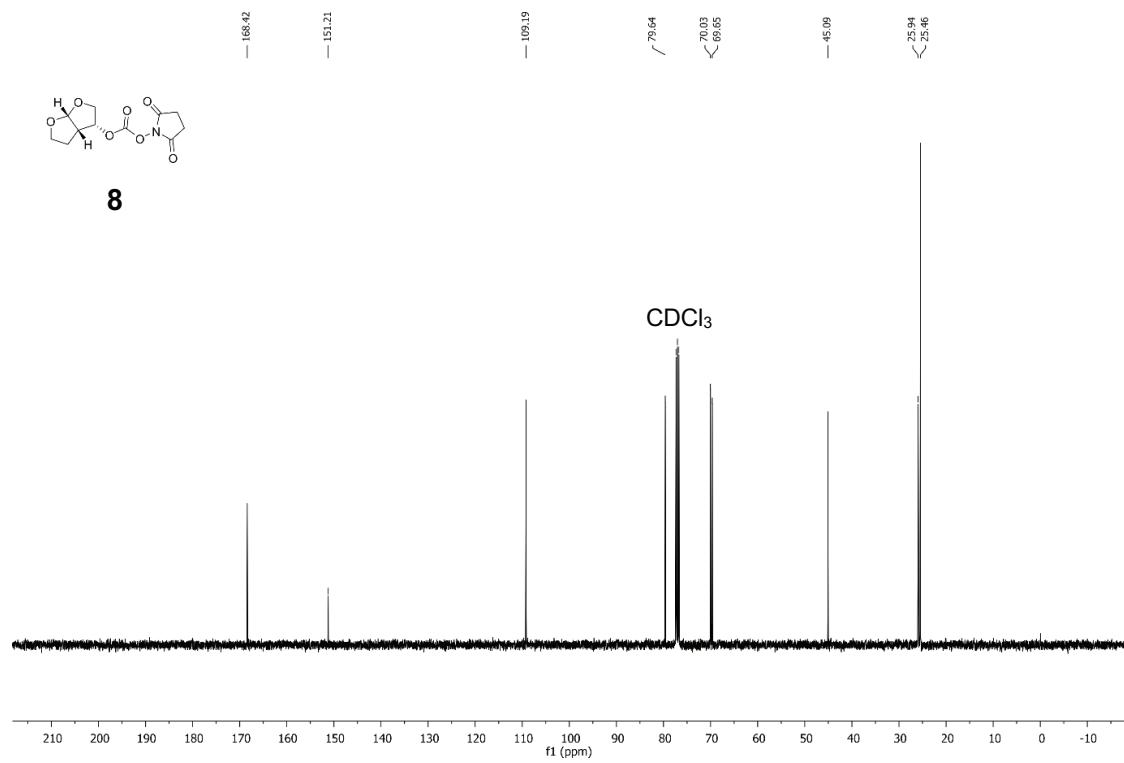
¹³C NMR (101 MHz, CDCl₃) of Compound 6



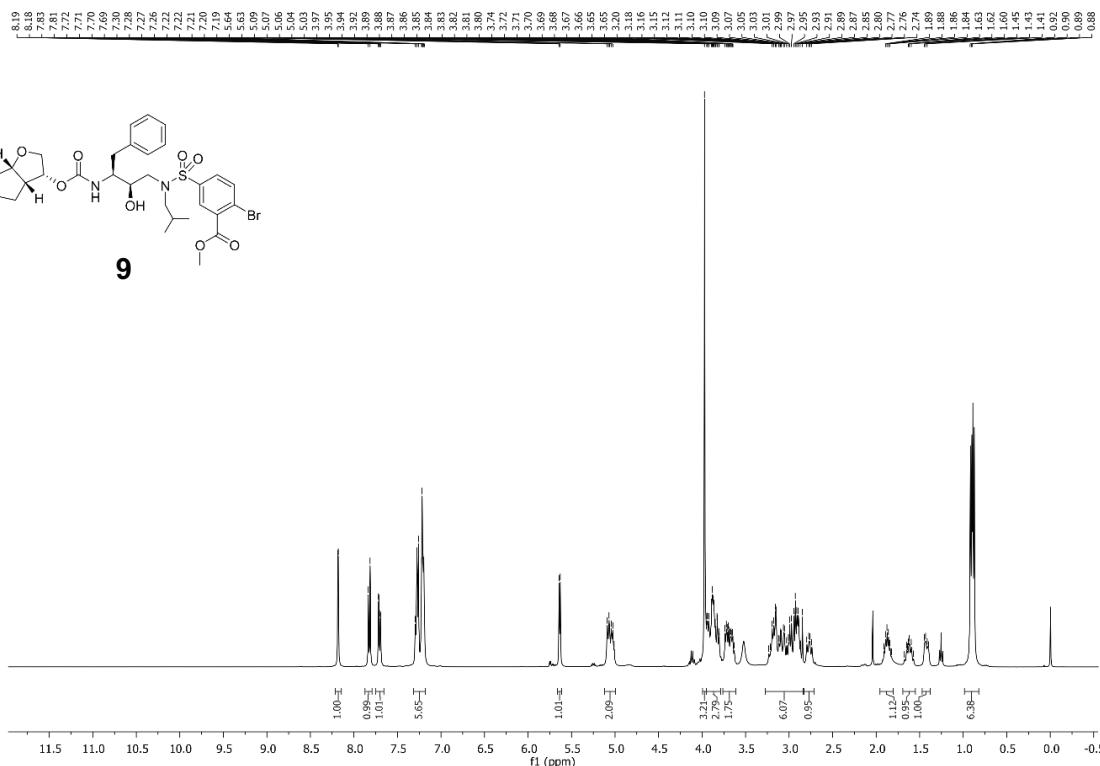
6



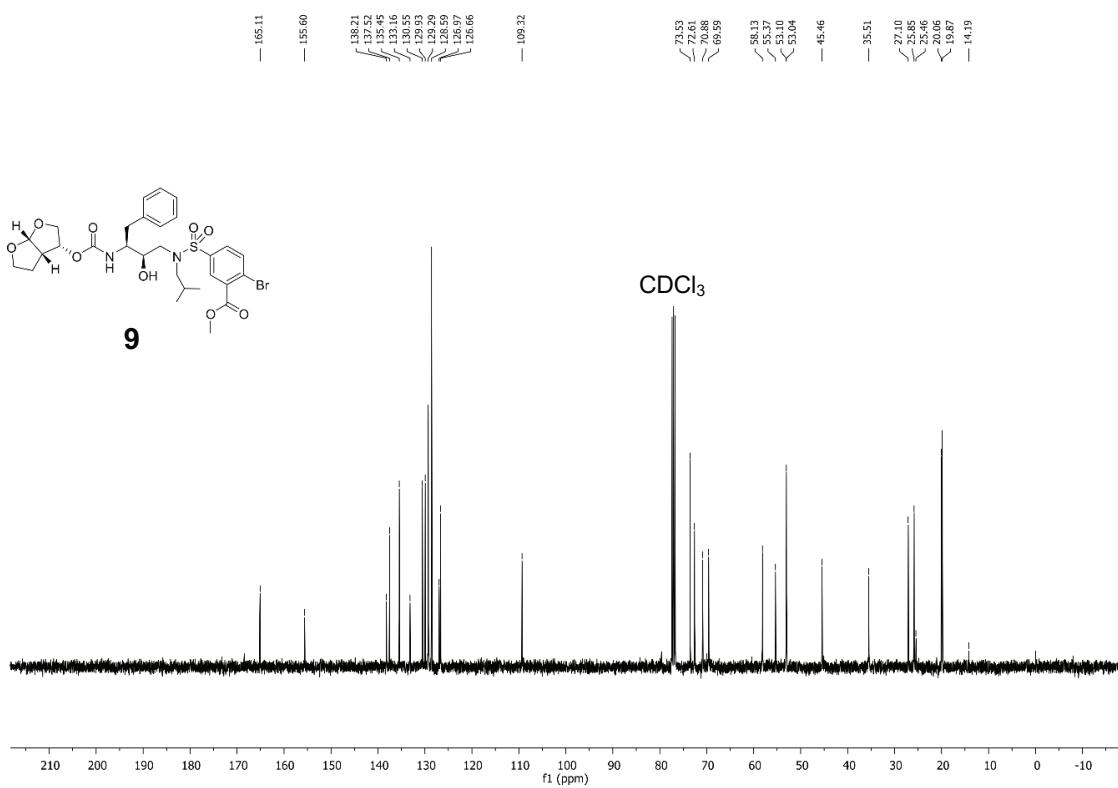
¹H NMR (400 MHz, DMSO-*d*₆) of Compound 7

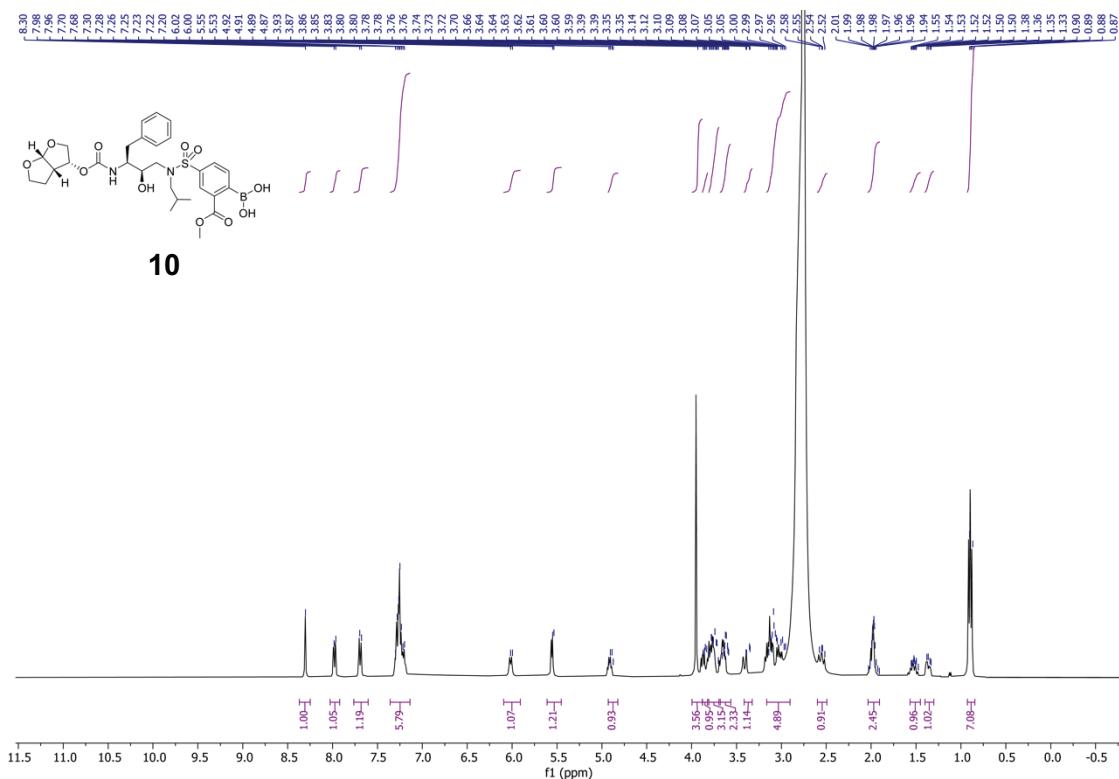
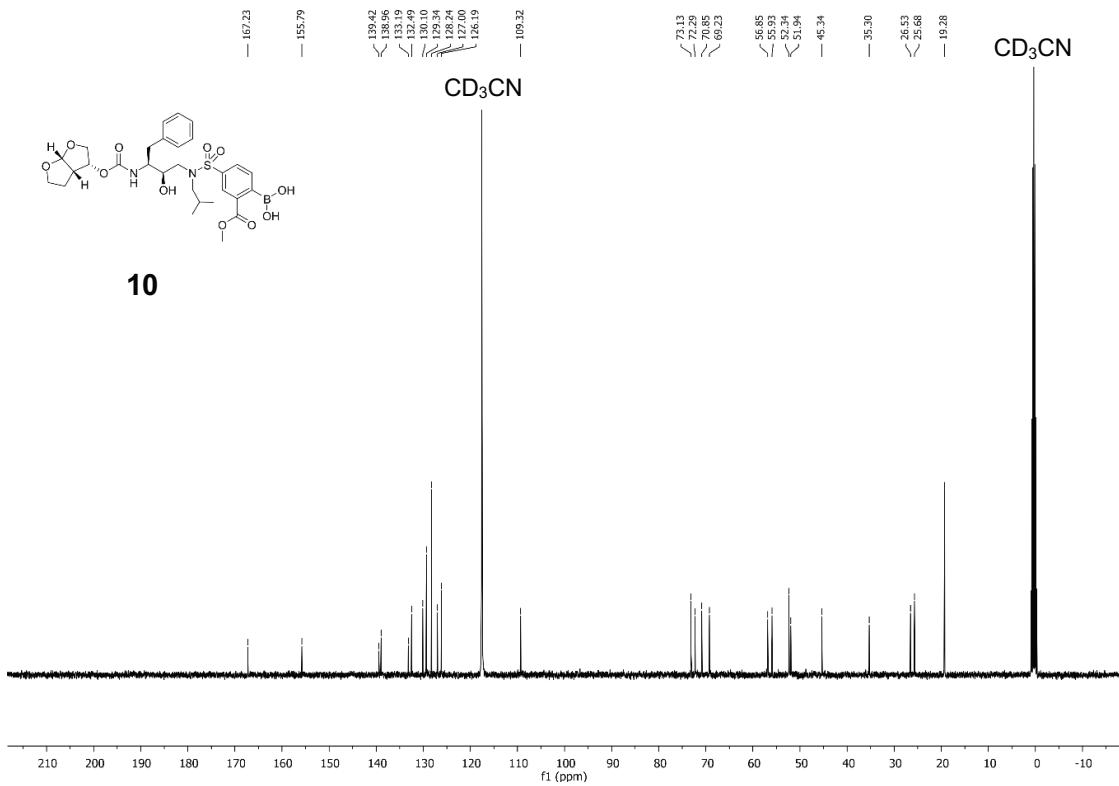
¹H NMR (400 MHz, CDCl₃) of Compound 8¹³C NMR (101 MHz, CDCl₃) of Compound 8

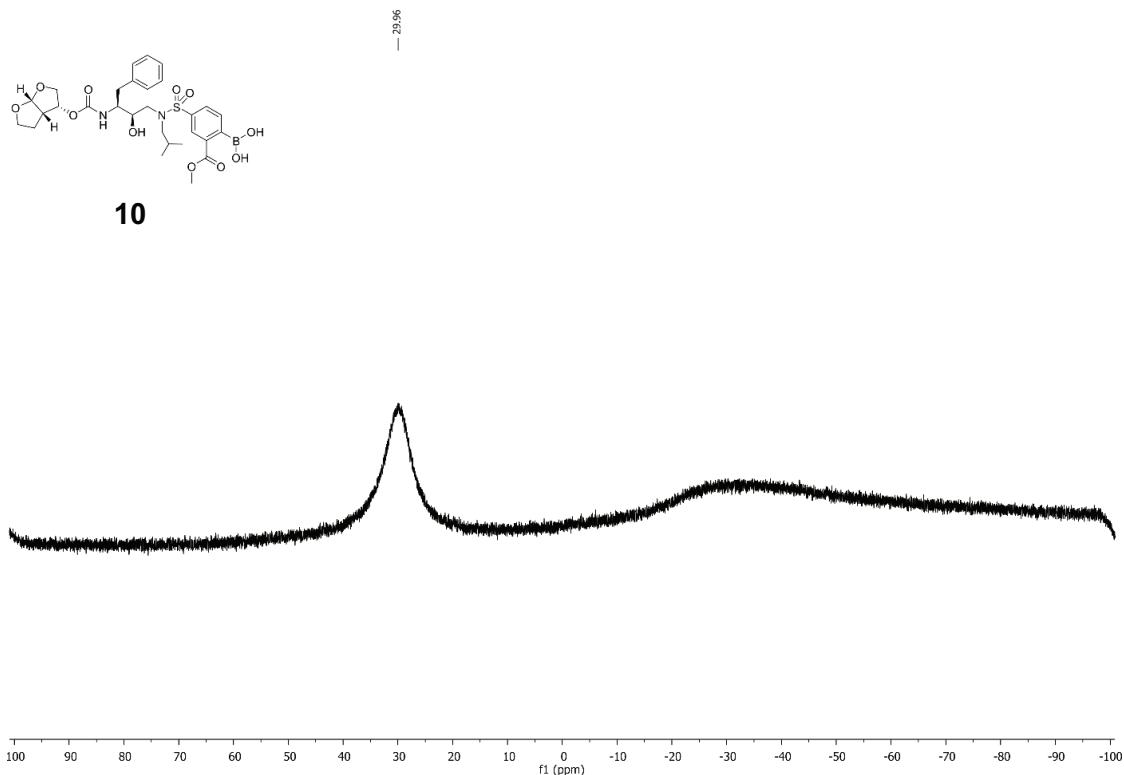
¹H NMR (400 MHz, CDCl₃) of Compound 9



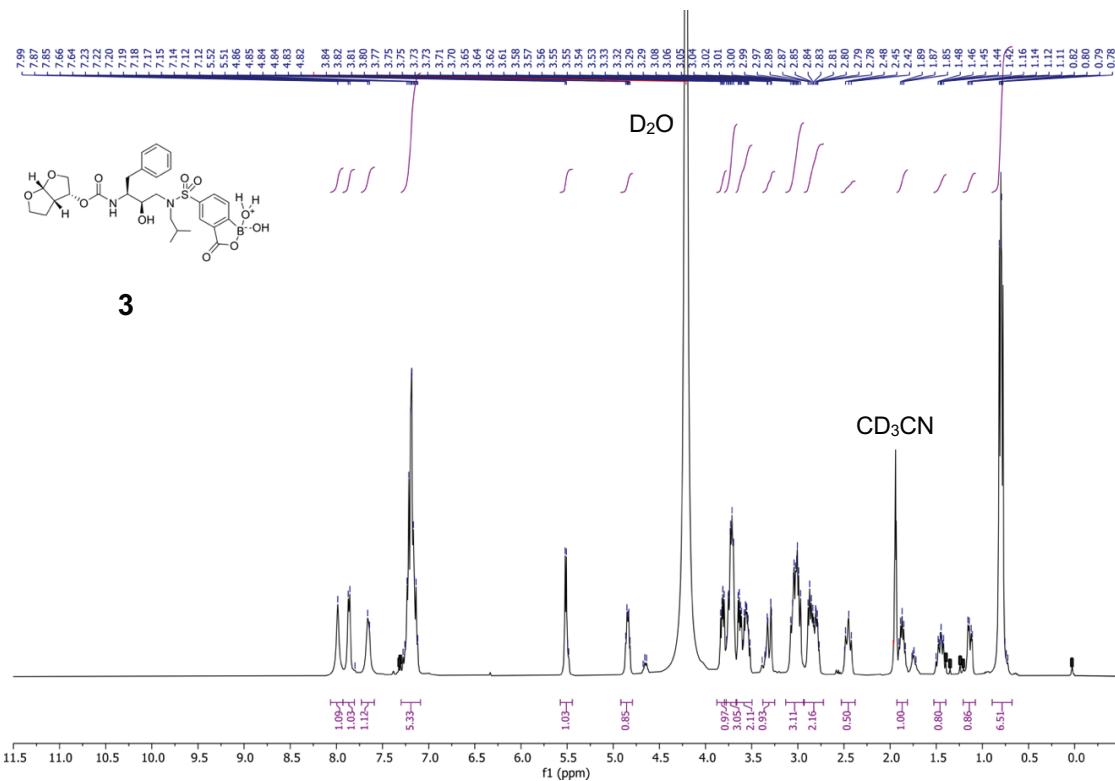
¹³C NMR (101 MHz, CDCl₃) of Compound 9



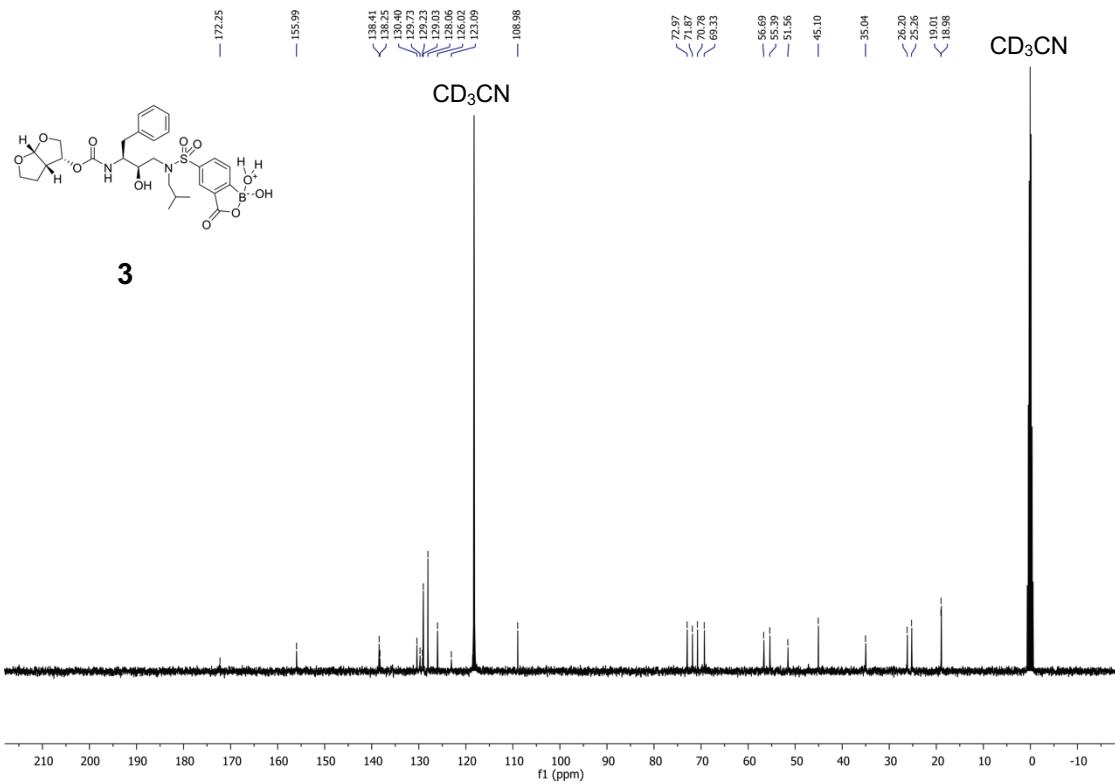
¹H NMR (400 MHz, CDCl₃) of Compound 10¹³C NMR (101 MHz, CDCl₃) of Compound 10

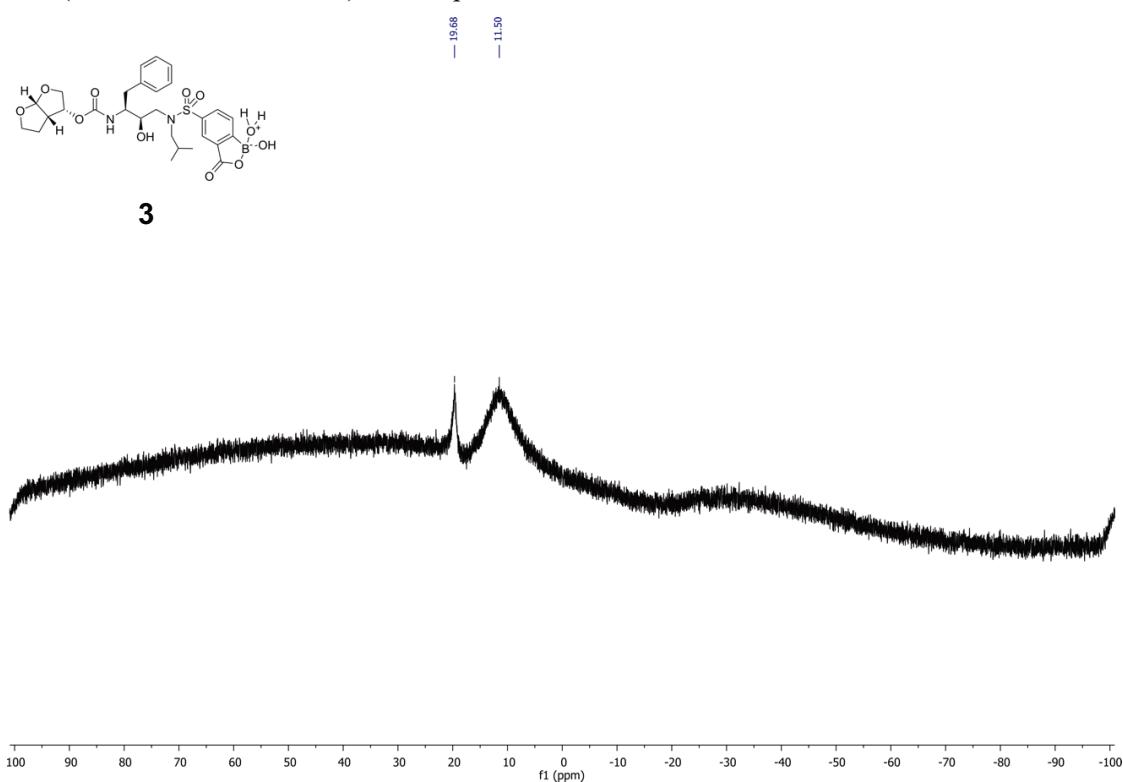
¹¹B NMR (128 MHz, CD₃CN/D₂O) of Compound **10**

¹H NMR (400 MHz, CD₃CN/D₂O) of Compound 3



¹³C NMR (101 MHz, CD₃CN/D₂O) of Compound 3



¹¹B NMR (128 MHz, CD₃CN/D₂O) of Compound 3

Computational Coordinates

PBA_SM

Energy (G): -559.23483981

C	2.6043170000	1.1733930000	-0.0059670000
C	1.2165160000	1.2092180000	0.1385890000
C	0.4402840000	0.0435210000	0.1072610000
C	1.1215160000	-1.1666080000	-0.0849010000
C	2.5063720000	-1.2191160000	-0.2370020000
C	3.2550560000	-0.0434310000	-0.1959010000
H	3.1794340000	2.0931670000	0.0293430000
H	0.7243300000	2.1652140000	0.2890650000
H	0.5497340000	-2.0904790000	-0.1071660000
H	3.0028660000	-2.1727130000	-0.3844740000
H	4.3332330000	-0.0766170000	-0.3087090000
O	-1.7127410000	-1.1047420000	1.0121490000
H	-1.7662680000	-0.8969050000	1.9475540000
O	-1.6155880000	1.3279100000	0.8546710000
H	-2.5757250000	1.3715020000	0.8147140000
O	-1.7068950000	-0.1249400000	-1.1320980000
O	-3.1394120000	-0.2429370000	-1.0444420000
H	-3.2317010000	-0.8979920000	-0.3321300000
B	-1.1753090000	0.0620060000	0.2626730000

Compound 2 Model_SM

Energy (G): -1241.68737039

C	-0.4247640000	-0.9805170000	-0.9467520000
C	0.9621840000	-0.8815280000	-0.9638830000
C	1.6866150000	-0.4097410000	0.1395080000
C	0.9628630000	-0.0586020000	1.2863620000
C	-0.4265690000	-0.1486620000	1.3371450000

C	-1.1065510000	-0.5997780000	0.2071130000
H	-0.9736210000	-1.3442300000	-1.8081620000
H	1.4978770000	-1.1797220000	-1.8593510000
H	1.4996230000	0.2993000000	2.1589720000
H	-0.9751990000	0.1321610000	2.2294620000
O	3.9505160000	0.0987970000	1.3299710000
H	4.3053280000	-0.7006740000	1.7251660000
O	3.9042830000	-1.3796290000	-0.6059290000
H	4.8168370000	-1.1717940000	-0.8292910000
O	3.4530370000	1.0283250000	-0.7859080000
O	4.8607720000	1.3036970000	-0.8950190000
H	5.1341280000	1.2873910000	0.0368200000
B	3.2999460000	-0.2149800000	0.0407160000
S	-2.8791700000	-0.5563940000	0.1821630000
O	-3.3680050000	-1.5253200000	-0.7927610000
O	-3.3734900000	-0.6342660000	1.5509160000
N	-3.3016670000	0.9519990000	-0.3936200000
C	-2.9172570000	2.0706330000	0.4802430000
H	-1.8377660000	2.2611860000	0.4358890000
H	-3.4460100000	2.9547710000	0.1241200000
H	-3.2171050000	1.8672260000	1.5060670000
C	-2.9227060000	1.1958600000	-1.7932950000
H	-3.4632050000	2.0824240000	-2.1244970000
H	-1.8454580000	1.3780330000	-1.8907620000
H	-3.2147560000	0.3502730000	-2.4121930000

Compound 3 Model_SM

Energy (G): -1353.85183531

C	-1.5556552521	-0.6139135092	0.0366852997
C	-0.9489023583	0.6372556037	-0.0464425265

C	0.4049853032	0.8129996901	-0.2894213682
C	1.1648914090	-0.3438790954	-0.4458912399
C	0.6022708620	-1.6196525421	-0.3498341202
C	-0.7648438220	-1.7527696839	-0.1121468273
H	0.8464471592	1.8000386989	-0.3784219440
H	1.2328785666	-2.4929149449	-0.4707986197
H	-1.1965856981	-2.7460003227	-0.0484600714
B	-3.1386518175	-0.3629930861	0.2893482907
O	-3.1522418637	1.1885482850	0.3538609548
O	-3.8612228086	-0.8390916752	-0.8862120856
O	-3.7762181825	-0.8950118312	1.4649098311
H	-3.5252904850	-0.4297767894	2.2666279966
O	-5.2703340050	-0.6451242407	-0.6978491895
H	-5.4034838795	-0.9566106224	0.2127402873
C	-1.9671653898	1.7176793079	0.1470915273
O	-1.7421222835	2.9125100829	0.1269215608
S	2.9183286188	-0.1783272337	-0.7016899668
O	3.4315285475	-1.4529065604	-1.1856791940
O	3.1574028540	1.0228413729	-1.4914926051
N	3.6050069221	0.0864080237	0.7882475754
C	3.4880820537	-1.0416523013	1.7237829810
H	4.1653156396	-0.8424428630	2.5542838093
H	2.4667196454	-1.1350030943	2.1124971362
H	3.7896505318	-1.9654980936	1.2351908429
C	3.2542835226	1.3690573951	1.4176137459
H	2.2475990682	1.3400734885	1.8512877889
H	3.9777878145	1.5449688909	2.2136956450
H	3.3265793274	2.1748276498	0.6903944851

Compound 3 Model Dianion_SM

Energy (G): -1429.79985969

C	-1.6183200000	-0.7293390000	0.0774950000
C	-1.0716420000	0.5522380000	-0.1425300000
C	0.2902560000	0.7090350000	-0.4100030000
C	1.1304220000	-0.3992730000	-0.4086220000
C	0.6345790000	-1.6770590000	-0.1707720000
C	-0.7302960000	-1.8175840000	0.0541510000
H	0.6950140000	1.6936590000	-0.6226830000
H	1.2944780000	-2.5368180000	-0.1794890000
H	-1.1322010000	-2.8129720000	0.2064000000
B	-3.1978900000	-1.0507310000	0.3654930000
O	-2.2703670000	2.2629600000	0.9924800000
O	-3.9809550000	-0.1247380000	-0.5025780000
O	-3.6299160000	-0.7619890000	1.7563860000
H	-3.5517920000	-1.5580460000	2.2867070000
O	-5.3727430000	-0.2895770000	-0.1813440000
H	-5.3507480000	-0.2456970000	0.7895700000
C	-1.8819940000	1.8484710000	-0.1227780000
O	-2.0235680000	2.4290810000	-1.2253550000
S	2.8720220000	-0.1779250000	-0.6492900000
O	3.4333360000	-1.4507150000	-1.0897570000
O	3.0929980000	1.0107560000	-1.4661080000
N	3.5484960000	0.1510830000	0.8375960000
C	3.4171100000	-0.9339150000	1.8195680000
H	4.0874930000	-0.7042490000	2.6478510000
H	2.3915660000	-1.0069880000	2.2011480000
H	3.7180370000	-1.8800960000	1.3745340000
C	3.1852060000	1.4591080000	1.4028090000
H	2.1561660000	1.4624300000	1.7814830000

H	3.8685430000	1.6521980000	2.2297950000
H	3.3102200000	2.2362560000	0.6523150000
O	-3.4556670000	-2.4598450000	0.0405490000
H	-4.4026040000	-2.6164710000	0.1034600000

PBA_TS

Energy (G): -559.19177457

Negative vibration: -763.83

C	2.4887000000	-1.2132490000	0.1486080000
C	1.0959350000	-1.2150660000	0.1157370000
C	0.3888930000	-0.0145290000	0.0420530000
C	1.0871100000	1.1930670000	0.0490350000
C	2.4809150000	1.1991780000	0.0716430000
C	3.1833220000	-0.0040270000	0.1217080000
H	3.0328740000	-2.1502540000	0.1996950000
H	0.5597910000	-2.1594800000	0.1476810000
H	0.5368490000	2.1270890000	0.0055840000
H	3.0199040000	2.1403850000	0.0524020000
H	4.2673840000	0.0002040000	0.1457870000
O	-1.7334860000	1.3097680000	-0.9493300000
H	-2.0082850000	1.2288930000	-1.8663840000
O	-1.7195130000	-1.0210670000	-1.3141270000
H	-1.5586920000	-1.8775640000	-0.9091110000
O	-1.3013060000	-0.1166260000	0.9431870000
O	-3.0347420000	-0.1773570000	1.5885700000
H	-3.2317400000	0.7454170000	1.3999000000
B	-1.3375640000	0.0403990000	-0.4422070000

Compound 2 Model_TS

Energy (G): -1241.64140607

Negative vibration: -777.94

C	0.3259280000	-0.3952800000	1.2635420000
C	-1.0565010000	-0.2398310000	1.2460430000
C	-1.7487360000	-0.1793850000	0.0366450000
C	-1.0470740000	-0.2388900000	-1.1675890000
C	0.3323720000	-0.4068720000	-1.1718690000
C	1.0021840000	-0.4817100000	0.0486590000
H	0.8703200000	-0.4585970000	2.1989710000
H	-1.5938540000	-0.1716320000	2.1864180000
H	-1.5872800000	-0.1805860000	-2.1059230000
H	0.8816420000	-0.4860180000	-2.1031930000
O	-3.9787890000	-0.9020360000	-1.2699420000
H	-4.4417280000	-1.7354740000	-1.1502710000
O	-4.0922200000	-1.0829750000	1.0903500000
H	-3.9691830000	-0.5858670000	1.9034240000
O	-3.2466360000	0.9757560000	0.0578140000
O	-4.8223910000	1.9514290000	0.0467910000
H	-4.9204440000	1.9463970000	-0.9104250000
B	-3.5541660000	-0.3822070000	-0.0215080000
S	2.7737480000	-0.6225660000	0.0409130000
O	3.1979720000	-1.1658840000	1.3255150000
O	3.1660860000	-1.3039060000	-1.1870860000
N	3.3994440000	0.9149020000	-0.0517790000
C	3.1058820000	1.6214880000	-1.3066330000
H	2.0618420000	1.9543710000	-1.3448190000
H	3.7569240000	2.4946480000	-1.3441840000
H	3.3256490000	0.9785400000	-2.1561280000
C	3.1491920000	1.7489310000	1.1335180000

H	3.8020710000	2.6184080000	1.0605140000
H	2.1071040000	2.0883320000	1.1727440000
H	3.3967420000	1.1953450000	2.0365510000

Compound 3 Model_TS

Energy (G): -1353.79384479

Negative vibration: -775.04

C	-1.5427970000	-0.6492570000	0.0218720000
C	-1.0132520000	0.6105280000	-0.2443420000
C	0.3365570000	0.7836800000	-0.5187830000
C	1.1412800000	-0.3511560000	-0.4934520000
C	0.6272710000	-1.6225860000	-0.2236220000
C	-0.7340390000	-1.7775980000	0.0223540000
H	0.7481100000	1.7669370000	-0.7221060000
H	1.2878020000	-2.4821710000	-0.2182750000
H	-1.1501190000	-2.7620370000	0.2020350000
B	-3.1998520000	-0.2167040000	0.6133270000
O	-3.1422040000	1.2498240000	0.4275390000
O	-3.2782430000	-1.0067190000	-0.5039930000
O	-3.6927740000	-0.6215500000	1.8429700000
H	-3.6943220000	0.0898350000	2.4904120000
O	-5.1128730000	-1.0945940000	-0.9513580000
H	-5.0075830000	-0.6473710000	-1.7967010000
C	-2.0131100000	1.7101410000	-0.0982240000
O	-1.8351640000	2.8697770000	-0.3837590000
S	2.9001200000	-0.1594630000	-0.6941990000
O	3.4417920000	-1.4436850000	-1.1153430000
O	3.1445630000	1.0235710000	-1.5069160000
N	3.5148560000	0.1632140000	0.8134620000
C	3.3545390000	-0.9240430000	1.7896880000

H	3.9976800000	-0.6920010000	2.6383720000
H	2.3176310000	-0.9968900000	2.1393790000
H	3.6714410000	-1.8689890000	1.3535920000
C	3.1374110000	1.4733880000	1.3674890000
H	2.0996400000	1.4742220000	1.7219250000
H	3.7996850000	1.6684440000	2.2106540000
H	3.2787640000	2.2501630000	0.6194420000

Compound 3 Model Dianion_TS

Energy (G): -1429.75607475

Negative vibration: -764.52

C	-1.6288220000	-0.8403820000	0.1837260000
C	-1.1723610000	0.4807990000	0.0709100000
C	0.1665250000	0.7079250000	-0.2600860000
C	1.0240290000	-0.3648850000	-0.4808470000
C	0.5842150000	-1.6827780000	-0.3804680000
C	-0.7499510000	-1.9005890000	-0.0584570000
H	0.5367020000	1.7246930000	-0.3355350000
H	1.2653000000	-2.5087710000	-0.5512430000
H	-1.1099170000	-2.9213560000	0.0201240000
B	-3.1735760000	-1.2249520000	1.0685630000
O	-1.6225020000	2.5259590000	1.1533360000
O	-3.4219230000	-1.2963050000	-0.3015450000
O	-3.6352160000	-0.1102300000	1.8125440000
H	-3.6913170000	-0.3379350000	2.7442420000
O	-5.1792820000	-1.7951550000	-0.5532890000
H	-5.4987660000	-0.9006920000	-0.7060650000
C	-2.0306460000	1.7331270000	0.2721680000
O	-2.9980480000	1.8962790000	-0.4986580000
S	2.7457110000	-0.0132390000	-0.7318800000

O	3.3898090000	-1.1645330000	-1.3510080000
O	2.8631740000	1.2841190000	-1.3845310000
N	3.4121040000	0.1552890000	0.7858110000
C	3.3742420000	-1.0631630000	1.6080450000
H	4.0448200000	-0.9040180000	2.4526840000
H	2.3636800000	-1.2559280000	1.9887940000
H	3.7259620000	-1.9173590000	1.0331910000
C	2.9527160000	1.3361710000	1.5330650000
H	1.9407210000	1.1914370000	1.9309230000
H	3.6431150000	1.4786950000	2.3645590000
H	2.9792670000	2.2171180000	0.8955380000
O	-3.1126560000	-2.4124130000	1.8527800000
H	-3.0293500000	-3.1898670000	1.2947770000

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