Supporting Information for: Desymmetrization of Pibrentasvir for Efficient Prodrug Synthesis

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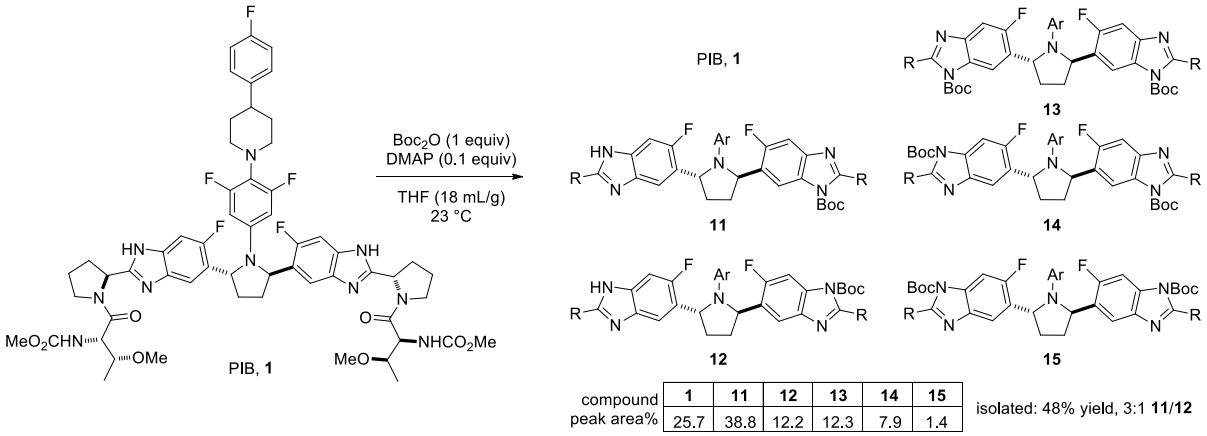
General Methods and Materials

Unless otherwise noted, commercial solvents and reagents were purchased and used without additional purification. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were measured with either a Varian 400 MHz or Varian Inova 500 MHz NMR Spectrometer. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane ($CHCl_3$ standardized at 7.26 ppm). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (central peak of $CHCl_3$ standardized at 77.16 ppm). Reactions were monitored using either LC-MS or thin-layer chromatography (TLC). Analytical LC-MS was performed on a Thermo MSQ-Plus mass spectrometer and Agilent 1100/1200 HPLC system running Xcalibur 2.0.7, Open-Access 1.4, and custom login software. The mass spectrometer was operated under positive APCI or ESI ionization conditions dependent on the system used. The HPLC system comprised an Agilent Binary pump, degasser, column compartment, autosampler and diode-array detector, with a Polymer Labs ELS-2100 evaporative light-scattering detector. The column used was a Phenomenex Kinetex C8, 2.6 µm 100 Å (2.1mm × 30mm), at a temperature of 65 °C. For LC-MS AA long method, a gradient of 3-100% acetonitrile (A) and 10 mM ammonium acetate in water (B) was used, at a flow rate of 0.5 mL/min (0-0.25 min 3% A, 0.25-5.2 min 3-100% A, 5.2-5.9 min 100% A, 5.9-6.0 min 100-3% A. 0.25 min post-run delay). Visualization of TLC was accomplished with UV light (254 or 364 nm) and/or aqueous potassium permanganate or ceric ammonium nitrate stain followed by heating. Purification of the crude reaction products, when performed, was accomplished on a Grace Reveleris X2 normal-phase chromatography system using silica gel cartridges purchased from Grace or Silicycle. Specific parameters used in the separation of individual compounds are detailed under each entry. Unless otherwise noted, reactions were carried out under an atmosphere of nitrogen. Yields refer to isolated yields of analytically pure (>95%) material unless otherwise noted.

Experimental Procedures and Characteriztion Data

I. Preliminary Experiments Toward mono-Boc Protection of PIB (1):



compound	1	11	12	13	14	15
peak area%	25.7	38.8	12.2	12.3	7.9	1.4

isolated: 48% yield, 3:1 **11/12**

Boc-Pibrentasvir isomer mixture: A solution of dimethyl ((2S,2'S,3R,3'R)-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(6-fluoro-1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate (pibrentasvir, 10.0 g, 8.98 mmol) in THF (90 mL) was stirred at ambient temperature and di-*t*-butyl dicarbonate (Boc_2O, 1.96 g, 8.98 mmol) was added. A solution of 4-dimethylaminopyridine (DMAP, 0.11 g, 0.090 mmol) in THF (90 mL) was added dropwise at 25 °C over 3 h. After the addition, the reaction mixture was stirred for 16 h at 25 °C and analyzed by HPLC:

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Method Info      : Ascentis C18 2.7 um 4.6x150nm; 35oC; 1.5  ml/min
                   30:70 to 90:10 ACN :0.1% Perchloric acid

Sample Info      : crude product mixture
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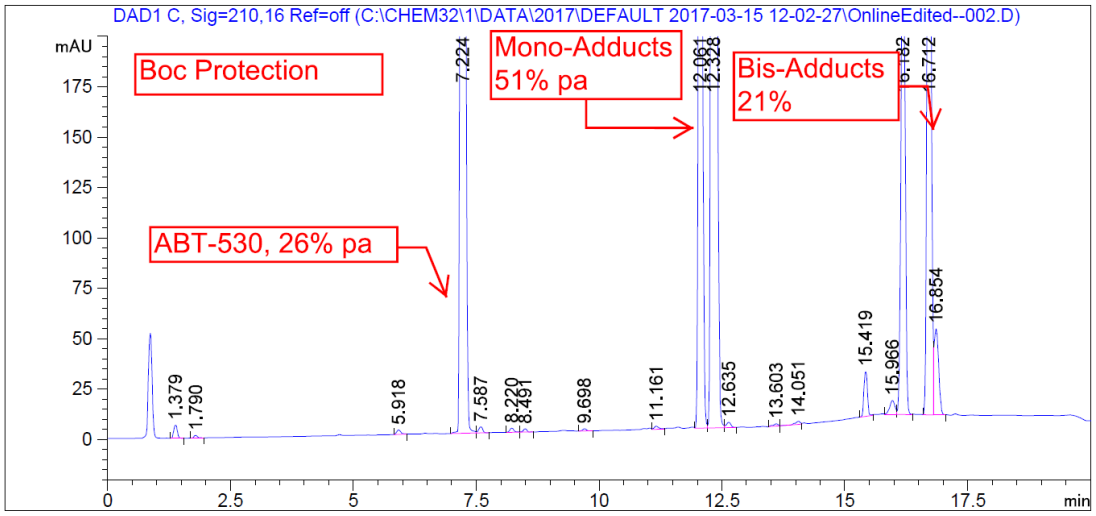


Signal 1: DAD1 C, Sig=210,16 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	1.379	BB	0.0823	32.09998	6.42706	0.1699
2	1.790	BB	0.0845	6.39620	1.23398	0.0339
3	5.918	BB	0.0957	13.57086	2.20778	0.0718
4	7.224	BV	0.0903	4856.77100	855.08600	25.7123
5	7.587	VB	0.0892	17.04044	3.04727	0.0902
6	8.220	BB	0.0933	12.09967	2.03571	0.0641
7	8.491	BB	0.0857	8.27735	1.56455	0.0438
8	9.698	BB	0.0865	5.79160	1.08092	0.0307
9	11.161	VB	0.1044	10.66400	1.54689	0.0565
10	12.061	VV	0.0864	2307.44775	431.61710	12.2159
11	12.328	VV	0.0958	7329.93799	1190.41833	38.8055
12	12.635	VB	0.0980	16.83830	2.65529	0.0891
13	13.603	BV	0.1036	8.23644	1.20789	0.0436
14	14.051	VV	0.1123	11.63996	1.47111	0.0616
15	15.419	BB	0.0828	112.41721	22.30202	0.5951
16	15.966	BV	0.1199	52.35683	6.94669	0.2772
17	16.182	VB	0.0938	1495.34912	265.02374	7.9165
18	16.712	BV	0.0873	2331.35132	429.72208	12.3424
19	16.854	VB	0.0949	260.61963	42.91091	1.3797

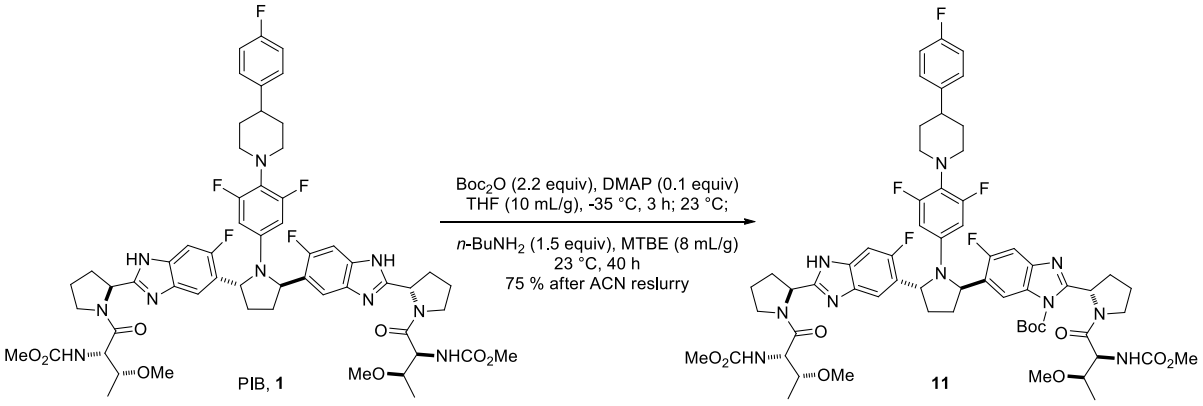
The reaction mixture was then concentrated and purified twice by silica gel column chromatography on 300 g columns using first a 0-10% methanol and ethyl acetate gradient followed by 0-2% methanol and ethyl acetate gradient. The resulting solid was slurried in ethyl ether and hexane, filtered, and dried at 45 ^{o}C under vacuum to afford a 3:1 mixture of **11/12** (5.24 g, 48% yield). A portion of this material was purified by preparative HPLC and pure fractions were concentrated, giving major isomer **tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (down-Boc-PIB 11):** ^{1}H NMR (500 MHz, $CDCl_3$, -20 °C) (tautomeric species also present; data given for major tautomeric form): δ 11.00 (s, 1H), 7.69 (br s, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 9.8 Hz, 1H), 7.31 (d, *J* = 5.0 Hz, 1H), 7.20 (m, 2H), 7.00 (apparent t, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 10.3 Hz, 1H), 6.45 (br s, 1H), 6.05 (d, *J* = 7.6 Hz, 1H), 5.89 (dd, *J* = 49.7, 14.3 Hz, 2H), 5.51 (d, *J* = 7.5 Hz, 1H), 5.40 (d, *J* = 7.5 Hz, 1H), 5.37 (d, *J* = 10 Hz, 1H), 4.70 (t, *J* = 10 Hz, 1H), 4.66 (br m, 1H), 4.23 (br m, 1H), 3.95 – 3.63 (m, 4H), 3.81 (s, 3H), 3.73 (s, 3H), 3.54 (br m, 1H), 3.35 (s, 3H), 3.31 (s, 3H), 3.21-2.89 (m, 6H), 2.59 – 2.28 (m, 6H), 2.22 – 2.08 (m, 4H), 1.90 – 1.69 (m, 5H), 1.57 (d, *J* = 19.9 Hz, 2H), 1.47 (s, 9H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.12 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, 27 °C) (tautomeric species also present): δ 170.8, 169.0, 161.2 (d, *J* = 248.0 Hz), 160.3 (d, *J* = 252.6 Hz, 2C), 158.1, 157.1, 157.0, 156.7, 154.4, 148.5, 142.2, 141.9, 141.7 (d, *J* = 13.9 Hz), 138.3, 133.3 (d, *J* = 13.9 Hz), 129.0, 128.1 (d, *J* = 7.7 Hz, 2C), 125.5 (d, *J* = 17.0 Hz), 123.2 (d, *J* = 17.0 Hz), 117.6, 117.3, 115.0 (d, *J* = 21.6 Hz, 2C), 113.6, 106.2 (d, *J* = 24.6 Hz), 98.5 (d, *J* = 27.7 Hz), 97.7 (d, *J* = 26.0 Hz, 2C), 85.6, 77.1, 76.9, 57.8, 57.7, 57.0, 56.8, 56.7, 56.2, 56.1, 54.9, 52.7, 52.6, 52.4, 52.3, 47.9, 47.5, 41.6, 34.5, 34.4, 31.2, 31.0, 30.9, 28.0 (3C),

27.6, 25.2, 24.0, 16.3, 15.2. ^{19}F NMR (376 MHz, $CDCl_3$, 27 °C) δ -117.99, -119.44, -119.99, -122.90, -123.94.

The minor mono-Boc isomer from the reaction was **tert-butyl 5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (up-Boc-PIB 12):** ^{1}H NMR (600 MHz, $CDCl_3$, 27 °C) δ 10.50 (br s, 1H), 7.68 (d, *J* = 10.7 Hz, 1H), 7.53 – 7.28 (br m, 1H), 7.19 – 7.06 (m, 4H), 6.95 (t, *J* = 8.8 Hz, 2H), 5.95 (dd, *J* = 8.2, 2.8 Hz, 1H), 5.79 (d, *J* = 12 Hz, 2H), 5.68 (br s, 1H), 5.58 (d, *J* = 8.8 Hz, 1H), 5.50 – 5.32 (m, 3H), 4.59 (dd, *J* = 8.3, 4.2 Hz, 1H), 4.40 (dd, *J* = 8.8, 2.8 Hz, 1H), 3.93 (td, *J* = 8.9, 3.8 Hz, 1H), 3.86 – 3.69 (m, 5H), 3.69 (s, 3H), 3.63 (s, 3H), 3.39 – 3.30 (m, 1H), 3.25 (s, 3H), 3.12 – 2.95 (m, 4H), 2.93 (s, 3H), 2.87 (m, 1H), 2.57 – 2.41 (m, 3H), 2.41 – 2.33 (m, 1H), 2.33 – 2.00 (m, 6H), 1.93 – 1.72 (m, 6H), 1.70 (s, 9H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$, 27 °C) δ 170.6, 168.9, 161.3 (d, *J* = 137 Hz), 160.2 (d, *J* = 140 Hz, 2C), 157.8 (d, *J* = 200 Hz), 157.3, 157.2, 157.0, 156.9, 154.8, 148.2, 142.3 (d, *J* = 3 Hz), 141.8, 138.6, 137.9, 132.6, 132.3, 128.1 (d, *J* = 7.5 Hz, 2C), 126.0, 124.0, 117.8, 117.7, 117.5, 114.9 (d, *J* = 21 Hz, 2C), 103.0 (d, *J* = 30 Hz), 98.0 (d, *J* = 27 Hz) 97.5, 97.3, 86.3, 76.9, 75.9, 57.5, 57.2, 56.8, 56.7, 56.6, 56.3, 56.1, 55.1, 52.5 (2 coincident peaks), 52.4, 52.2, 47.8, 47.0, 41.6, 34.4 (2 coincident peaks), 31.0, 30.9, 30.7, 28.0 (3 coincident Me peaks), 28.0, 25.3, 24.0, 16.6, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$, 27 °C) δ -118.19 (ddd, *J* = 14.2, 8.9, 5.4 Hz), -119.16 (br s, 2F), -121.36 (br s and tautomeric species at -121.73), -124.29 (br s and tautomeric species at -126.05).

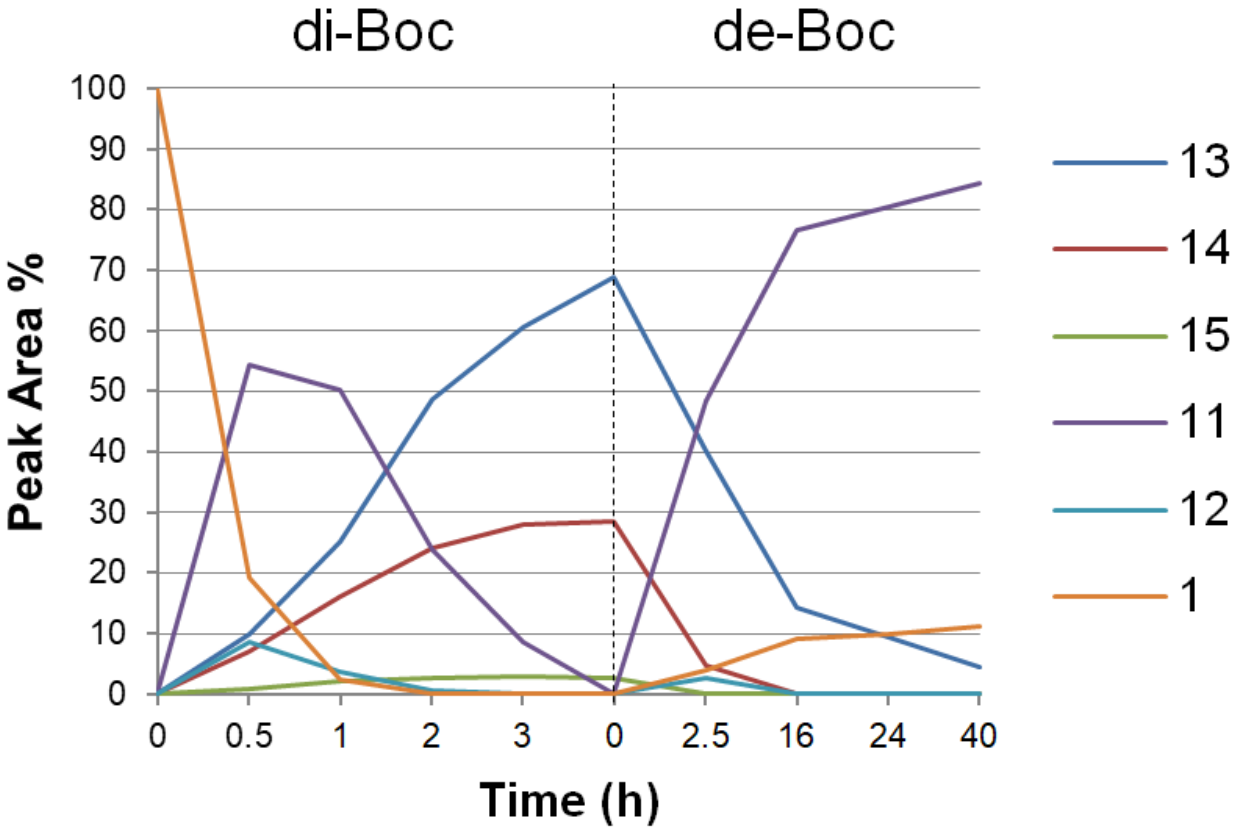
The compounds “up-Boc-PIB” **12** and “down-Boc-PIB” **11** were characterized via NMR utilizing the ^{1}H, ^{13}C {1H}, ^{1}H-^{1}H COSY, ^{1}H-^{1}H ROESY, ^{1}H-^{1}H TOCSY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC NMR techniques (see NMR Spectra section). Due to the presence of tautomer peaks resulting in broad proton signals and limited resolution, the carbon and proton atoms in up-Boc-PIB **12** and down-Boc-PIB **11** were assigned in multiple solvent systems ($(CD_3)_2SO$, $CDCl_3$ and C_5D_5N) to identify the solvent that would allow the complete assignment of the proton and carbon atoms for both samples. While all analyses were considered, data collected in $CDCl_3$ at 27 ºC and -20 ºC resulted in sufficient signals for full proton and carbon assignment for comparison of both the “up-Boc-PIB” **12** and “down-Boc-PIB” **11** samples. The compounds of interest in this study are differentiated by the substitution of the BOC group on one of the benzimidazole rings. For each compound in every solvent system, ^{1}H-^{1}H ROESY data reveals correlations between the BOC methyl protons and one or the other of the benzimidazole protons supporting these nonbonded protons are within 3.5 Å in space. There are two protons on the benzimidazole ring and for each product they are differentiated by their scalar coupling to the fluorine atom which could be used to assign the protons on the benzimidazole ring. The larger ^{1}H-^{19}F coupling is expected for the benzimidazole proton adjacent to the fluorine. In analysis of the down-Boc-PIB **11** data (temp = -20 ºC), the BOC methyl protons have the ROESY correlation to the benzimidazole peak observed at 7.54 ppm (^{1}H, d, $^4J_{H\text{-}F}$= 6.99 Hz) which has been assigned H18 due to the smaller scalar coupling between H18 and F62 as compared to proton H15 (7.40ppm, ^{1}H, d, $^3J_{H\text{-}F}$= 9.85 Hz). Proton H18 has a strong ^{1}H-^{13}C HMBC correlation to the pyrrolidine carbon assigned C1. This strong ^{1}H-^{13}C HMBC correlation is expected to be observed between proton H18 and carbon C1 as opposed to an ^{1}H-^{13}C HMBC correlation between proton H15 and carbon C1. For compound up-Boc-PIB **12** (temp = 27 ºC), the BOC methyl protons have the ROESY correlation to the benzimidazole peak at 7.68 ppm (1H, d, $^3J_{H\text{-}F}$= 10.71 Hz) which has been assigned to H15 due to its larger scalar coupling. The larger proton H18 peak is observed at 7.12ppm and its coupling to F62 is measured to be $^4J_{H\text{-}F}$ = 6.82 Hz. The expected strong ^{1}H-^{13}C HMBC correlation between benzimidazole proton H18 and the pyrrolidine carbon C1 is observed in the “up-Boc-PIB” **12** data collected at 27 ºC.

II. Development of diBoc/deBoc Protocol for Synthesis of monoBoc PIB (1)

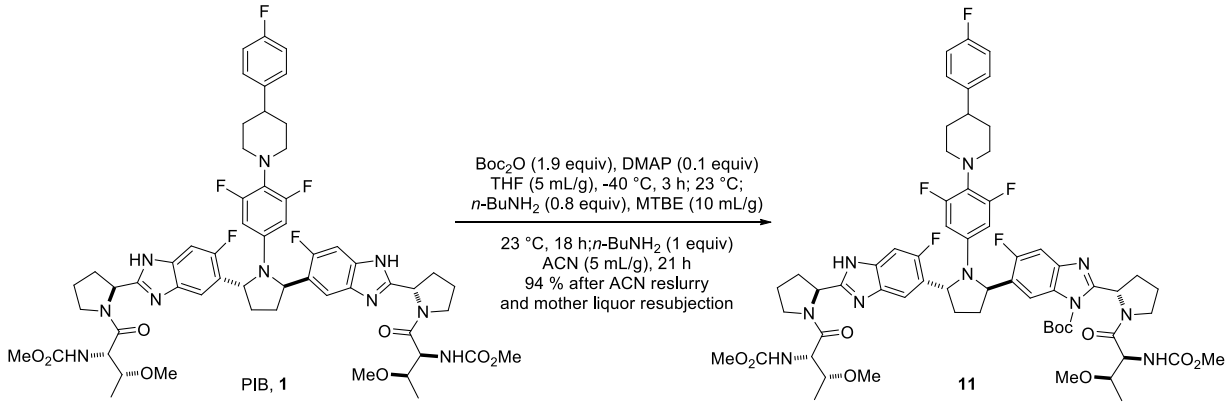


tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate: A solution of dimethyl ((2S,2'S,3R,3'R)-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(6-fluoro-1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate (pibrentasvir, 20.0 g, 18.0 mmol), THF (200 mL), and di-tert-butyl dicarbonate (Boc_2O, 8.63 g, 39.5 mmol) was cooled to < -35 °C and 4-dimethylaminopyridine (DMAP, 0.219 g, 1.80 mmol) was added. The white slurry was held between -35 and -40 °C (internal temperature) and followed by LC-MS (AA long method, see general methods for details), manually integrating signals at the indicated retention times at 220 nm detection wavelength, with identities established via comparison to previous non-selective Boc-protection procedure (compound structures/numbers shown there). After 3 h, all PIB **1** and mono-up-Boc isomer **12** consumed, so warmed to 15 °C (complete consumption of **11** to give the de-Boc t_0 profile) and concentrated on a rotovap to 33 g total mass. To remove residual THF/tBuOH, toluene (40 mL) was added and concentrated to 33 g total mass (up to 35 °C bath temp, starting to foam). Added MTBE (160 ml) and *n*-butylamine (2.67 ml, 26.9 mmol) and followed by LC-MS (AA long method).

	time (h)	13 (4.73 min)	14 (4.78 min)	15 (4.95 min)	11 (4.23 min)	12 (4.31 min)	1 (3.70 min)
di-Boc	0	0	0	0	0	0	100
	0.5	9.9	7.1	1	54.4	8.5	19.1
	1	25.2	16.2	2.2	50.2	3.7	2.5
	2	48.6	24.2	2.7	24	0.6	0
	3	60.5	27.9	2.9	8.6	0	0
de-Boc	0	68.8	28.5	2.7	0	0	0
	2.5	40.2	4.8	0	48.3	2.6	4.1
	16	14.2	0	0	76.6	0	9.2
	24	9.5	0	0	80.5	0	10
	40	4.6	0	0	84.4	0	11.1



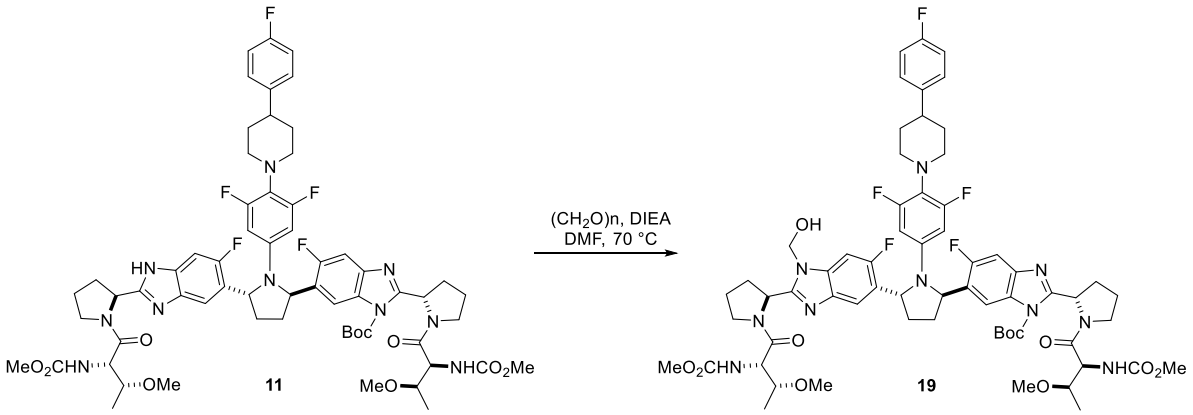
After 16 h, a white slurry was observed. After 40 h, the slurry was filtered, washing with MTBE (2 x 20 mL). Dried the white solid in a vacuum oven at 50 °C, giving product with ~95% purity. Acetonitrile (146 mL) was added, the slurry was heated to 70 °C, then cooled to ambient temperature over 1 h, stirred 1 h, and filtered, washing with ACN (2 x 18 mL). Dried the white solid in a vacuum oven at 50 °C, giving tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (16.4 g, 75%). LC-MS showed 97.9 pa% desired product **11** and 2.1 pa% PIB **1**. Characterization data were indistinguishable from that obtained from the previous non-selective Boc-PIB **11** procedure.



tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (11): A solution of DMAP (0.439 g, 3.59 mmol), dimethyl ((2S,2'S,3R,3'R)-((2S,2'S)-2,2'-(5,5'-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidine-2,5-diyl)bis(6-fluoro-1H-benzo[d]imidazole-5,2-diyl))bis(pyrrolidine-2,1-diyl))bis(3-methoxy-1-oxobutane-2,1-diyl))dicarbamate (40.0 g, 35.9 mmol), and THF (200 mL) was cooled to -40 °C and Boc_2O (14.9 g, 68.3 mmol) was added. Held between -40 and -45 °C (internal temperature) and followed by LC-MS AA long method. After 3 h, 1.5% down-mono-Boc **12** remained, so warmed to 23 °C, giving a 52.2/26.1/2.9/18.5/0.4/0 ratio of **13/14/15/11/12/1**. Concentrated to 66.3 g total mass (tan oil/foam), then added MTBE (400 mL) and *n*-butylamine (2.85 mL, 28.7 mmol) and followed by LC-MS AA long method. After 18 h, a 29.2/0/0/63.7/0/6.0 ratio of **13/14/15/11/12/1** was observed, so concentrated to minimal volume, dissolved in ACN (200 mL), heated to 75 °C, and cooled the white slurry to 23 °C over 1 h. Added *n*-butylamine (3.56 mL, 35.9 mmol) and followed by LC-MS AA long method. After 21 h, 1.7/0/0/86.4/0/11.8 ratio of **13/14/15/11/12/1** was observed. Filtered, washed with ACN (2 x 40 mL slurry washes), then added ACN (400 mL) to the wet cake, heated to 75 °C, cooled the white slurry to 23 °C over 30 min, stirred 30 min, and filtered, washing with ACN (2 x 40 mL slurry washes). Dried the white solid in a vacuum oven at 50 °C for 14 h, giving tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (36.65 g, 30.2 mmol, 84 % yield).
LC-MS:
solid 1: 3.5% PIB **1**, 95.9% **11**, 0.6% **13**; mother liquor 1: 68.2% PIB **1**, 21.7% **11**, 10.1% **13**
solid 2: 1.7% PIB **1**, 98.3% **11** ; mother liquor 2: 38.8% PIB **1**, 57.9% **11**, 3.2% **13**
The combined mother liquors were concentrated to 14.6 g total mass (including ~ 5.7 mmol mixed **1/11/13** in a 57.8/34.6/7.6 ratio + *n*-BuNHBoc and DMAP) and THF (30 mL) was added. The solution was cooled to -35 °C and Boc_2O (2.35 g, 10.8 mmol) was added. After 30 min between -35 and -40 °C LC-MS AA long method showed a 64/31/5 ratio of **13/14/15**. Concentrated to minimal volume, added MTBE (60 mL) and *n*-butylamine (0.534 mL, 5.39 mmol) and LC-MS AA long method showed 37.2/0/0/54.5/0/6.9 ratio of **13/14/15/11/12/1** after 16 h. Switched to ACN (60 mL, still solution), seeded with product **11** (~10 mg), and added *n*-butylamine (1.68 mL, 10.8 mmol). After 5 h, a 10.9/74.7/14.3 ratio of **13/11/1** was observed by LC-MS. Filtered, washing with ACN (2 x 6 mL slurry washes), then added ACN (60 mL) to the wet cake, heated to 75 °C, cooled the white slurry to 23 °C over 30 min, stirred 30 min, and filtered, washing with ACN (2 x 6 mL slurry washes). Dried the white solid in a vacuum oven at 50 °C to constant weight, giving **11** (4.25 g, 3.50 mmol). This material was 98.5% **11** by LC-MS, so combined with first cycle material, giving tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate **11** (40.9 g, 33.7 mmol, 94% yield). Characterization data were indistinguishable from that obtained from the previous non-selective Boc-PIB **11** procedure.

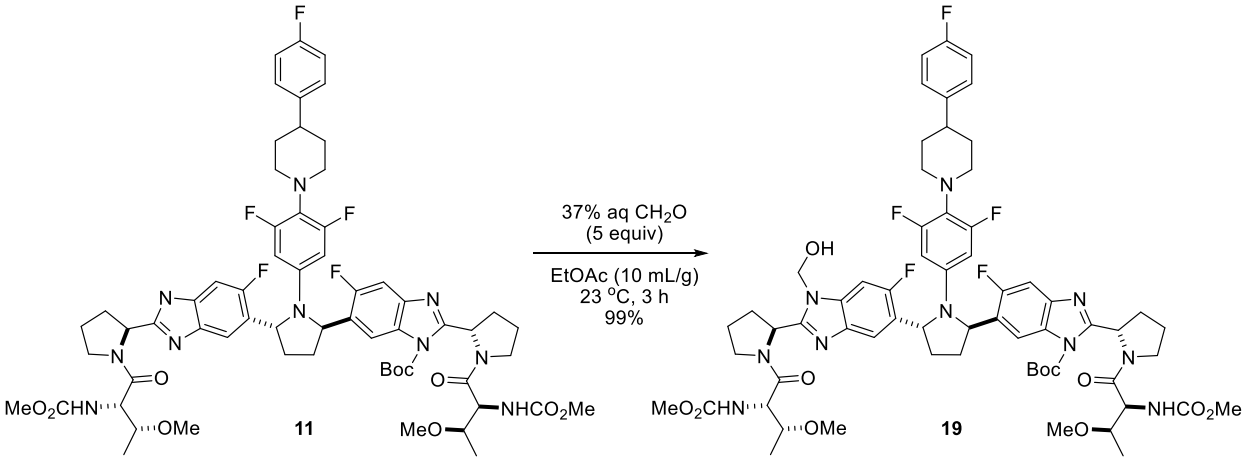
III. Preparation and Acylation Studies of Hydroxymethyl Intermediate 19

*Initial synthesis of formaldehyde adduct **19:***



Compound **11** (200 mg, 0.17 mmol), paraformaldehyde (6.7 mg), N,N-dimethyl formamide (2 ml), and N-ethyl-N-isopropylpropan-2-amine (13 µl, 0.08 mmol) were added to a 4 mL vial. The mixture was stirred for 1 h at 70 °C, then cooled to 23 °C and concentrated to a yellow oil. The crude product was suspended in a solvent mixture of MTBE (1 mL), hexane (1 mL), and EtOAc (0.3 mL), resulting in crystallization upon sonication. Filtration of the slurry and drying of the solid under high vacuum afforded **19** (119 mg, 0.10 mmol, 60% yield). Omission of the isolation of **19** resulted in an unselective acylation with **16**, giving a 1.8:1 ratio of **17** and **18** when the general acylation procedure was applied:

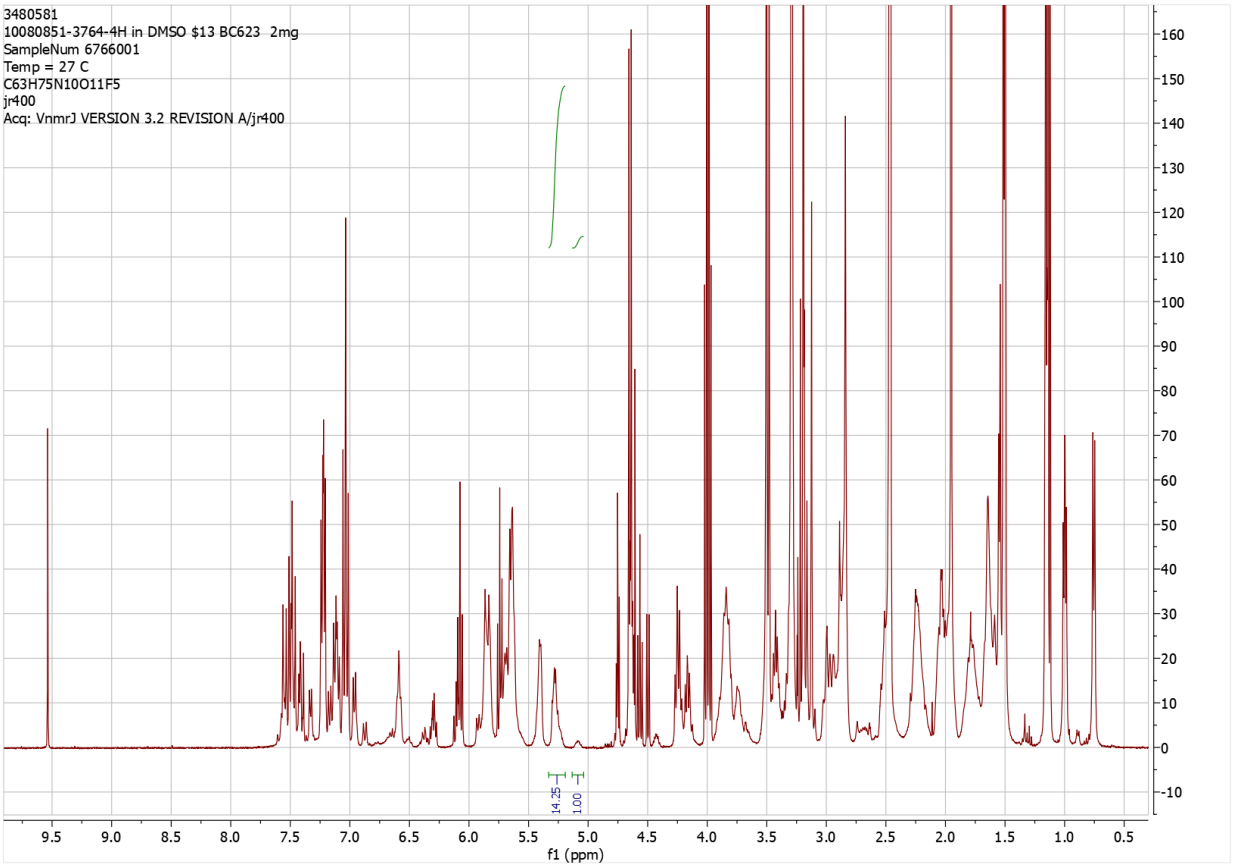
*Optimized synthesis of formaldehyde adduct **19:***

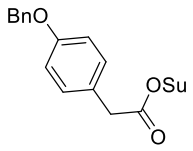


tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-1-(hydroxymethyl)-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (19): A solution of tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (18.5 g, 15.3 mmol) in EtOAc (185 ml) was stirred at 23 °C and formaldehyde (37% aqueous, 5.68 ml, 76.0 mmol) was added. After 4 h, ^{1}H NMR analysis (100 uL blown dry with air, dissolved in DMSO-d6, and immediately obtained data) showed nearly complete reaction (>7:1 pdt/sm integrating 5.3/5.1 ppm signals; partial hydrolysis always observed by ^{1}H NMR). The mixture was concentrated to 63 g total (44 g, 49 mL EtOAc) and K_f titration showed ~ 1.1 equiv water. Then, heptanes (147 mL) were added dropwise. After 60 mL had been added over 90 min, solid material had oiled out. Product seed crystals were then added (185 mg, 1%), and the slurry stirred overnight at 23 °C.

The remaining heptanes were added over 1 h, the mixture stirred 1 h, and filtered, washing with 3:1 hep/EtOAc (20 mL). The white solid was dried in an ambient temperature vacuum oven for 2 days, giving tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-1-(hydroxymethyl)-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (18.8 g, 15.1 mmol, 99% yield). K_f titration showed 0.73 equiv water remaining after drying, but further drying was not attempted to avoid loss of formaldehyde.

NMR check for reaction completion after 4 h with **19** at 5.3 ppm and **11** at 5.1 ppm (ratio during reaction or when characterizing product changes based on time in DMSO-d6 solution, so only qualitative; 14:1 ratio here):

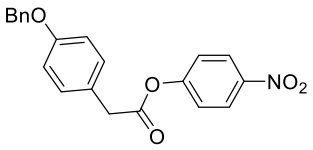




21

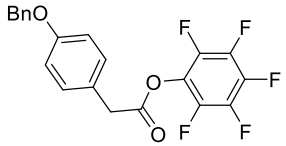
2,5-dioxopyrrolidin-1-yl 2-(4-(benzyloxy)phenyl)acetate (21): 2-(4-(benzyloxy)phenyl)acetic acid (10 mmol, 2.42 g) was dissolved in a solution of DCC (11 mmol, 2.26 g) and N-hydroxysuccinimide (11 mmol, 1.27 g) in acetone (50 ml) and ethyl acetate (150 mL). The mixture was stirred in an ice bath at 0°C for 1 h and allowed to warm to room temperature overnight, yielding a white precipitate. The solid was filtered off, and the filtrate was concentrated to afford crude product (3.86 g). The product was purified by silica

gel flash chromatography using 50% acetone in hexanes to afford **21** (2.78 g, 80%). ^{1}H NMR (400 MHz, DMSO-d6) δ 7.47 – 7.42 (m, 2H), 7.42 – 7.35 (m, 2H), 7.33 (m, 1H), 7.26 (m, 2H), 7.00 (m, 2H), 5.09 (s, 2H), 4.02 (s, 2H), 2.80 (s, 4H).
MS calculated for $C_{19}H_{19}NO_6$ $[M+H_2O]^+$: 357.4. Found 357.0.



22

4-nitrophenyl 2-(4-(benzyloxy)phenyl)acetate (22): To a 250 mL round bottom flask, 2-(4-(benzyloxy)phenyl)acetic acid (1 g, 4.1 mmol), 4-nitrophenol (0.632 g, 4.54 mmol), and methylene chloride (41 ml) were added. The flask was cooled to 0°C and N,N'-methanediylidenedicyclohexanamine (0.937 g, 4.54 mmol) and N,N-dimethylpyridin-4-amine (0.050 g, 0.413 mmol) were charged. The flask was warmed to r.t. and stirred for 18 h. At reaction completion, 5 mL 3M HCl was added and the flask chilled to -20°C in a freezer for 6 h. The slurry was filtered over a Celite pad and washed with ice-cold DCM (30 mL). The resultant filtrate was washed with saturated $NaHCO_3$ (10 mL), water (10 mL), dried over sodium sulfate, filtered, and concentrated to a solid. The crude product was purified by flash chromatography (0-30% EtOAc/Heptane) to afford **22** (1.22 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (m, 2H), 7.52 – 7.26 (m, 10H), 7.07 – 7.00 (m, 2H), 5.12 (s, 2H), 3.88 (s, 2H). No mass spectral data is available due to instability of the compound under analysis conditions.

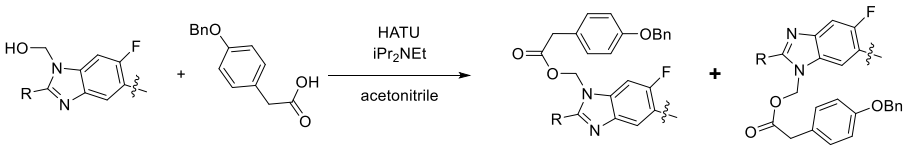


24

perfluorophenyl 2-(4-(benzyloxy)phenyl)acetate (24): To a 250 mL round bottom flask, 2-(4-(benzyloxy)phenyl)acetic acid (1 g, 4.1 mmol), 2,3,4,5,6-pentafluorophenol (0.836 g, 4.54 mmol), and methylene chloride (41 mL) were added. The flask was cooled to 0 °C and N,N'-methanediylidenedicyclohexanamine (0.937 g, 4.54 mmol) and N,N-dimethylpyridin-4-amine (0.050 g, 0.413 mmol) were charged. The flask was warmed to ambient temperature and stirred for 18 h. At reaction completion, 3M HCl (5 mL) was added and the flask chilled to -20°C in a freezer for 6 h. The slurry was filtered over a Celite pad and washed with ice-cold DCM (30 mL). The resultant filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), dried over sodium sulfate, filtered, and concentrated to a solid. The crude product was purified by silica gel flash chromatography (0-30% EtOAc/Heptane) to afford **24** (1.25 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.36 (m, 5H), 7.36 – 7.24 (m, 2H), 7.04 (m, 2H), 5.12 (s, 2H), 3.96 (s, 2H). No mass spectral data is available due to instability of the compound under analysis conditions.

*General procedure for acylation of **19** with **16**, **21**, **22**, **24**:*

Compound **19** (20 mg, 0.016 mmol) and tetrahydrofuran (250 µl) were added to a 4mL vial. The vial was cooled to -20°C and charged with N-ethyl-N-isopropylpropan-2-amine (7 µl, 0.06 mmol), **16**, **21**, **22**, or **24** (0.04 mmol) in tetrahydrofuran (250 µl), and N,N-dimethylpyridin-4-amine (0.2 mg, 1.6 µmol) in tetrahydrofuran (125 µl) . The mixture was stirred at the indicated temperature and analyzed by HPLC to determine conversion to product and isomer ratio.

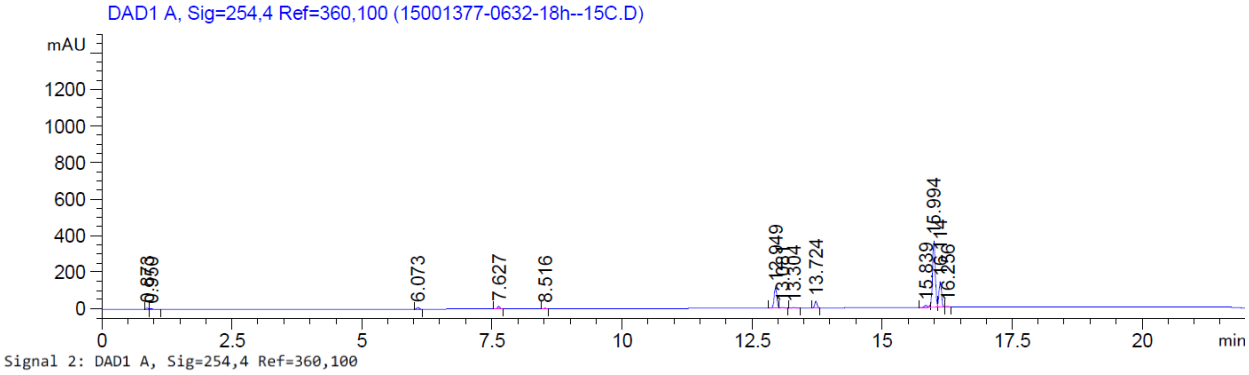


*Procedure for acylation of **19** with in situ-generated **23***:

2-(4-(benzyloxy)phenyl)acetic acid (5.9 mg, 0.024 mmol) and HATU (10.7 mg, 0.028 mmol) were added to a 4 ml vial. The contents of the vial were dissolved in acetonitrile (300 µl). Then, N-ethyl-N-isopropylpropan-2-amine (9 µl, 0.05 mmol) was added to the above vial, and the contents were stirred at 23 °C for 0.5 h. The vial was cooled to 0 °C and a solution of **12** (20 mg, 0.016 mmol) in N,N-dimethyl formamide (300 µl) was added. After 1 h at 0 °C, the reaction was analyzed by HPLC.

Representative HPLC for acylation products **17** and **1**:

Method information: Ascentis Express C18 15 cm x 4.6 mm, 2.7 micron. Column oven: 35°C. Flow rate: 1.5 mL/min. Mobile Phase A: 0.1% formic acid in water. Mobile Phase B: acetonitrile. Gradient: 0 min 30% B, gradient over 15 min to 95% B, hold until 20 min at 95% B, gradient over 2 min to 10% B, Stoptime 22 min.
Desired product **17**: 15.99 min; Undesired isomer **18**: 16.11 min.

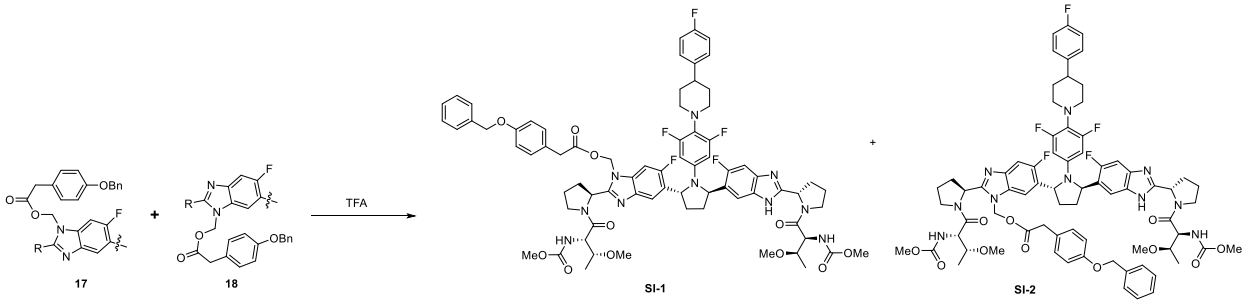


Signal 2: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	0.873	BV	0.0415	17.70080	6.99008	0.6912
2	0.950	VB	0.0625	12.28044	3.08250	0.4796
3	6.073	BB	0.0476	22.86533	7.49649	0.8929
4	7.627	BB	0.0458	38.98546	13.44819	1.5224
5	8.516	BB	0.0455	9.16830	3.19459	0.3580
6	12.949	BV R	0.0566	420.04715	114.93355	16.4030
7	13.081	VB E	0.0569	16.31980	4.43715	0.6373
8	13.304	BB	0.0578	12.60526	3.35539	0.4922
9	13.724	BB	0.0503	113.03499	36.32912	4.4141
10	15.839	BV E	0.0729	52.84001	10.46782	2.0634
11	15.994	VV R	0.0596	1365.72693	365.21188	53.3322
12	16.114	VB	0.0529	464.68671	139.40225	18.1462
13	16.256	BB	0.0511	14.53140	4.57217	0.5675

The crude product mixture was worked up by dilution with methylene chloride and sequential washing with 1M HCl (1 mL), saturated sodium bicarbonate (1 mL), and saturated brine (1 mL) solutions. The resultant product was analyzed by LCMS: calculated for $C_{73}H_{81}F_5N_{10}O_{11}$ $[M\text{-}C_5H_9O_2+3H]^{2+}$: 684. Found: 684.

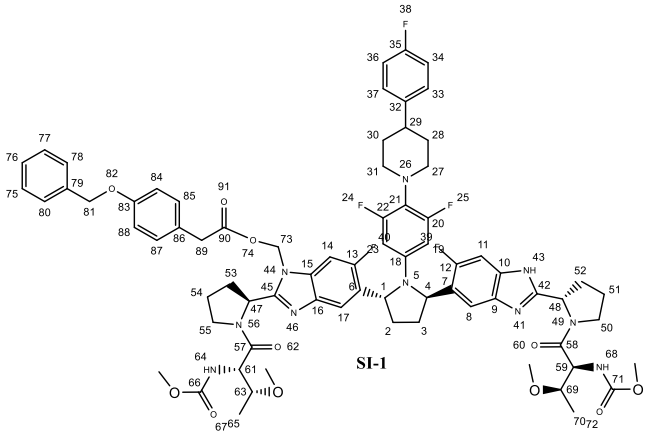
Deprotection of crude 17/18 to form SI-1/SI-2:



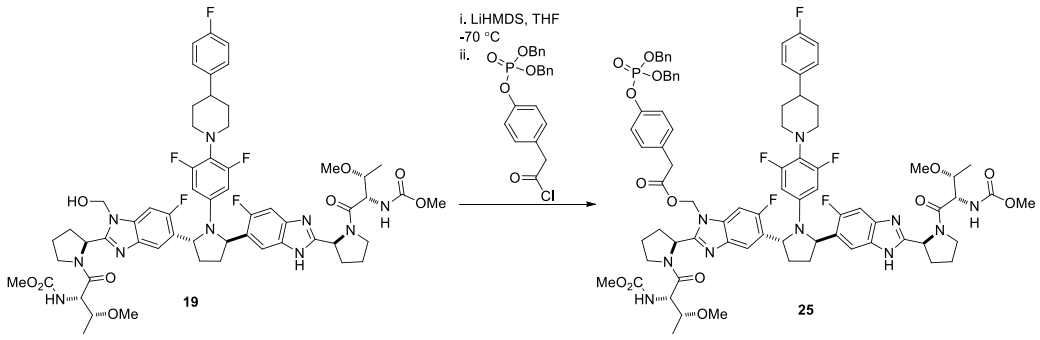
A portion of crude **17**/**18** was treated with trifluoroacetic acid (80 equiv) to generate a mixture of products **SI-1** and **SI-2**, which were isolated by successive flash chromatography (silica, 0-5% MeOH/CH_2Cl_2, then C-18 functionalized silica, 10-90% MeCN/water). A fraction containing a 4:1 mixture of **SI-1** and **SI-2** was then analyzed by NMR spectroscopy for structural assignment of the product regioisomers. The isolated material was analyzed by LCMS: calculated for $C_{73}H_{81}F_5N_{10}O_{11}$ $[M+2H]^{2+}$: 684. Found: 684.

Regioisomer Assignment:

Sample 15001377-604-ISOLATED_4-1 was analyzed by utilizing the following NMR techniques: ^{1}H-NMR, ^{1}H-^{1}H ROESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC. The major compound in 15001377-604-ISOLATED_4-1 was confirmed to be regioisomer **SI-1** due to the ^{1}H-^{1}H ROESY correlation observed between the connecting C73 methylene proton H73 having ^{1}H-^{1}H ROESY correlations to benzimidazole proton H14 (1H NMR 7.63 ppm) which shares $^3J_{H\text{-}F}$ coupling to F40 with a measured $J_{H\text{-}F}$ = 9.66 Hz. The smaller coupling for the benzimidazole proton H17 appears to be closer to $J_{H\text{-}F}$ = 7.02 Hz keeping in mind there is extensive peak overlap. The assignments of these protons were made with the consideration of compound **12** assignments generated from 2D NMR data collected in (CH3)2SO2.



IV. Preparation of PIB Prodrugs 2, 3, and 4 from Intermediate 19

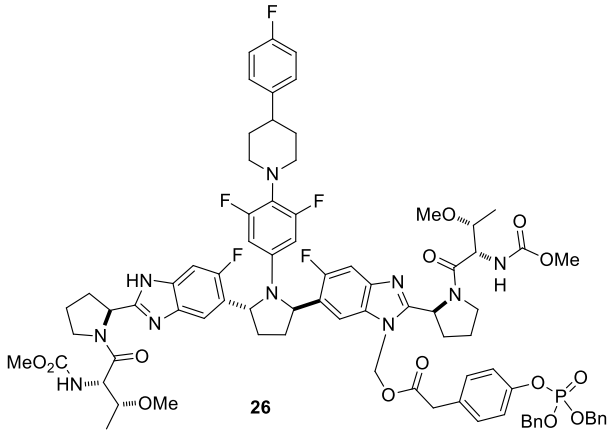


(5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 2-(4-((bis(benzyloxy)phosphoryl)oxy)phenyl)acetate (25): 2-(4-((bis(benzyloxy)phosphoryl)oxy)phenyl)acetic acid (40.0 g, 97 mmol) was dissolved in CH_2Cl_2 (400 mL) and treated with oxalyl chloride (11.0 mL, 126 mmol) and catalytic DMF (0.150 mL, 1.94 mmol). The reaction was stirred at 23 °C for 45 min, at which point full conversion was realized by LC-MS analysis, which showed production of the methyl ester when preparing samples in MeOH. The reaction was concentrated in vacuo then azeotroped with DCM (2 x 100 mL) to give the acid chloride as a light yellow oil, which was dissolved in THF (100 mL) and used directly in the acylation reaction as follows:

tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-1-(hydroxymethyl)-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (Compound **19**, 48.0 g, 38.6 mmol) was dissolved at in THF (600 mL) at -10 °C. The resulting solution was cooled to <-70 °C before addition of LiHMDS (1M in THF, 73.4 mL, 73.4 mmol) slowly via syringe over 5 minutes, maintaining the internal temperature below -65 °C during the addition. After the addition was complete, the reaction was stirred for 3 min before addition of dibenzyl (4-(2-chloro-2-oxoethyl)phenyl) phosphate (41.6 g, 97 mmol) dropwise as a solution in 75 mL of THF (120 mL) over 7 minutes. The internal temperature did not exceed -65 °C during this addition. The reaction was allowed to stir for 15 min at the same temperature then warmed to -50 °C by removing the flask from the acetone-dry ice bath. The reaction was subsequently quenched by addition of 2:1 saturated ammonium chloride:water mixture (150 mL). The mixture was diluted with ethyl acetate (300 mL) and stirred at ambient temperature for 30 min. The layers were separated, and the organic layer was washed with 1M HCl (3x50 mL) and brine (100 mL) then dried over sodium sulfate and concentrated in vacuo to give a crude solid (~63 g), which was used directly in the Boc-deprotection without additional purification as follows:

tert-butyl 6-((2R,5R)-5-(1-((2-(4-((bis(benzyloxy)phosphoryl)oxy)phenyl)acetoxy)methyl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (63.2 g, 38.6 mmol) was dissolved in 150 mL of DCM and cooled to approximately 10 °C before addition of TFA (89.0 mL, 1.15 mol) via syringe, maintaining the temperature below 25 °C. The flask was removed from the ice-water bath and stirred at RT for 90 min, at which point it was complete as indicated by LC-MS analysis. The reaction mixture was concentrated in vacuo and azeotroped with 2x200 mL of EtOAc to give a crude product that was purified via flash chromatography, eluting on a 1.5 kg silica gel column with a heptanes:acetone mobile phase (isocratic 95:5 heptanes:acetone for 5 min, 95:5 to 65:35 over 15 min, then isocratic 65:35) until complete elution of **25**. This method efficiently rejected the minor isomer **26** and unreacted starting materials/byproducts to give material of >95% HPLC purity. Note that NMR spectral data are generally complicated by the presence of rotameric and/or tautomeric forms, and spectra have been included from solvents that minimize these additional forms. Attempts at obtaining

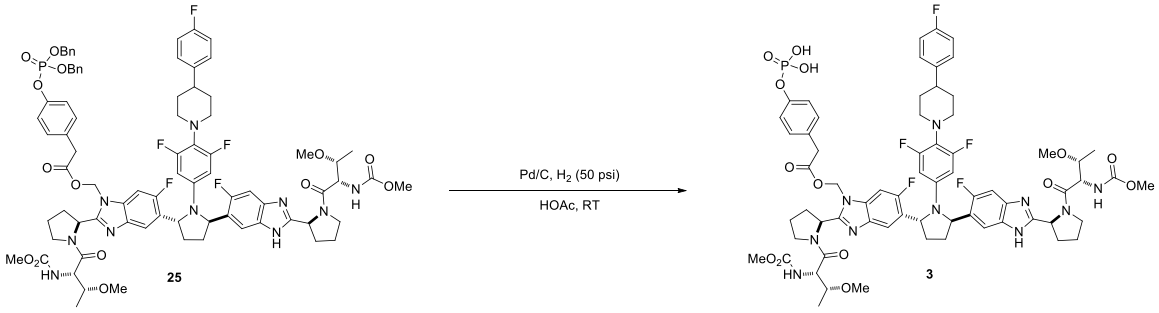
clearer NMR spectra at elevated temperatures were unsuccessful. **Major isomer** (**25**): ^{1}H NMR (400 MHz, THF-d8) δ 10.99 (t, *J* = 50.3 Hz, 1H), 7.45 (d, *J* = 10.3 Hz, 1H), 7.36 – 7.22 (m, 12H), 7.20 (dd, *J* = 8.5, 5.6 Hz, 4H), 7.16 – 7.13 (m, 1H), 7.13 – 7.09 (m, 2H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 11.7 Hz, 1H), 6.39 (d, *J* = 18.9 Hz, 1H), 6.25 (d, *J* = 11.7 Hz, 1H), 6.12 (s, 1H), 5.86 (d, *J* = 12.5 Hz, 2H), 5.51 (d, *J* = 29.4 Hz, 2H), 5.34 (dd, *J* = 8.0, 4.5 Hz, 1H), 5.27 (s, 1H), 5.10 (s, 2H), 5.09 (s, 2H), 4.44 (dd, *J* = 8.3, 5.3 Hz, 1H), 4.28 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.92 – 3.68 (m, 5H), 3.66 (d, *J* = 5.0 Hz, 2H), 3.56 (s, 3H), 3.53 (s, 3H), 3.42 – 3.30 (m, 2H), 3.16 (s, 2H), 3.12 – 2.92 (m, 6H), 2.75 (s, 3H), 2.22 – 1.93 (m, 6H), 1.93 – 1.80 (m, 3H), 1.35-1.21 (m, 4H), 1.14 – 1.04 (m, 1H), 1.12-1.05 (m, 1H), 1.01 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, THF-d8) δ 172.17, 171.74, 170.7, 164.4, 163.5, 163.4, 162.0, 161.1, 161.0, 160.2, 159.0, 158.6, 158.5, 157.9, 152.0, 144.4, 144.3, 140.5, 138.1, 138.0, 135.6, 135.4, 132.3, 132.0, 130.1, 130.0, 130.0, 129.9, 129.6, 126.8, 126.5, 121.8, 121.7, 121.6, 121.5, 119.4, 119.2, 119.0, 116.6, 116.4, 99.8, 99.5, 99.2, 98.9, 78.7, 78.1, 71.2, 71.1, 59.4, 58.7, 58.6, 57.9, 57.7, 56.5, 54.4, 54.3, 52.9, 52.8, 49.0, 48.7, 43.5, 41.3, 36.3, 33.7, 32.9, 32.7, 31.4, 31.2, 30.8, 30.6, 26.9, 26.8, 24.4, 23.9, 23.9, 21.9, 20.4, 17.4, 16.8, 15.3. ^{31}P NMR (162 MHz, THF-d8) δ -5.9; ^{19}F NMR (376 MHz, THF-d8) δ -118.8 (td, *J* = 9.1, 4.5 Hz), -120.1 (s), -124.7 (s), -126.4 (s), -128.0 (s); Specific rotation: $[\alpha]_D^{21.4}$ = +3.0 (*c* = 1.0, MeOH); ESI-LCMS: Calculated for [(M/2) + H]$^{+}$: 769.78; found: 769.80.



26

(6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 2-(4-((bis(benzyloxy)phosphoryl)oxy)phenyl)acetate (Compound 26, minor diastereomer):

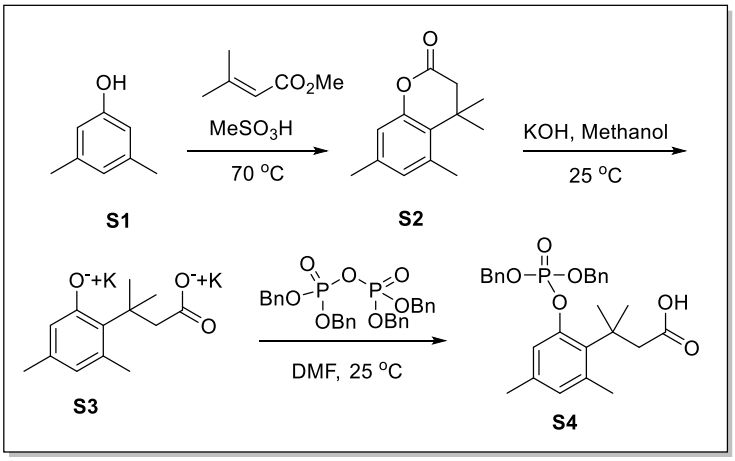
Obtained as the minor component from flash chromatographic separation on silica gel as described for compound **25**. Note that this compound exists as a mixture of tautomers and/or rotamers. Attempts to obtain sharper spectral peaks at higher temperature were unsuccessful and were generally worse in alternative solvents. ^{1}H NMR (500 MHz, DMSO-d6) δ 12.11 (s, 1H), 7.47 (d, *J* = 36.7 Hz, 2H), 7.35 (qd, *J* = 4.7, 2.4 Hz, 11H), 7.27 (d, *J* = 18.5 Hz, 12H), 6.50 – 6.25 (m, 2H), 6.01 – 5.78 (m, 2H), 5.74 – 5.43 (m, 2H), 5.31 – 5.19 (m, 1H), 5.18 (s, 1H), 5.14 (d, *J* = 1.2 Hz, 2H), 5.12 (d, *J* = 1.1 Hz, 2H), 4.36 – 4.16 (m, 2H), 3.92 (d, *J* = 4.1 Hz, 1H), 3.88 – 3.72 (m, 3H), 3.58 (s, 1H), 3.57 – 3.51 (m, 4H), 3.48 (d, *J* = 2.5 Hz, 3H), 3.27 (d, *J* = 2.9 Hz, 1H), 3.17 (s, 3H), 3.14 (s, 1H), 3.04 (s, 2H), 2.77 (s, 3H), 2.58 (s, 3H), 2.12 (s, 3H), 2.12 – 1.91 (m, 3H), 1.88 – 1.74 (m, 3H), 1.56 (br d, *J* = 110.5 Hz, 6H), 1.04 (d, *J* = 6.2 Hz, 3H, 1.01 (d, *J* = 6.2 Hz, 3H). ESI-LCMS: Calculated for [(M/2) + H]$^{+}$: 769.78; found: 769.80.



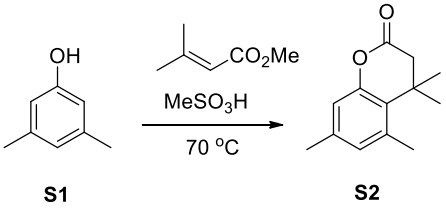
(5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 2-(4-(phosphonooxy)phenyl)acetate (compound 3): (5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 2-(4-((bis(benzyloxy)phosphoryl)oxy)phenyl)acetate (Compound **25**, 65.0 g, 41.0 mmol) and AcOH (260 mL) were added to 5% Pd/C (wet basis, 1.31 g, 5.74 mmol) in a 600 mL Hast C reactor and stirred for 2.75 h under an atmosphere of H_2 (50 psi) at RT. The reaction mixture was filtered through Celite, and the filter cake was washed with an additional 50 mL of HOAc. The filtrate was concentrated to 140 g (245 wt% of theoretical) in vacuo and iPrOH (570 mL) was added slowly while stirring with an overhead stirrer. After the addition was complete, the resulting slurry was stirred for 30 min at RT to give a faint yellow suspension. The product was isolated via filtration through a fritted funnel and washed with an additional 100 mL of iPrOH. The resulting wet cake was transferred back to a round-bottomed flask and stirred overnight with 500 mL of acetone. Solid material gummed out overnight, and the supernatant was decanted. The residual semisolid was slurried with 400 mL of iPrOH at RT for 2 h, at which point the resulting light yellow solid was isolated via filtration through a fritted funnel and dried for 1h at RT. HPLC showed a purity of 97.5%, including 3.1% of minor isomer, 0.7% unidentified impurity, and 1.3% of phenol from dephosphorylation. The solid was further dried in a vacuum oven at RT for 3 h, at which point the solid had a potency of 96% (note that in this case because 3% of the minor isomer was also present, the areas were combined for calculation of the potency) to give 48.5 g of the title compound as a 1:1 solvate with iPrOH. Spectral data was consistent with those previously reported for the title compound.[1] (*J. Med. Chem.* **2020**, *63*, 11034-11044). ^{1}H NMR (500 MHz, CD_3OD) δ 7.55 (d, *J* = 10.2 Hz, 1H), 7.38 (d, *J* = 10.4 Hz, 1H), 7.25 – 7.08 (m, 9H), 6.98 (t, *J* = 8.8 Hz, 2H), 6.46 (d, *J* = 11.7 Hz, 1H), 6.32 (d, *J* = 11.8 Hz, 1H), 5.82 (d, *J* = 12.3 Hz, 2H), 5.53 (d, *J* = 6.2 Hz, 2H), 5.35 (t, *J* = 6.6 Hz, 1H), 5.25 (dd, *J* = 8.1, 5.3 Hz, 1H), 4.43 (d, *J* = 4.5 Hz, 1H), 4.33 (d, *J* = 3.9 Hz, 1H), 4.00 – 3.79 (m, 4H), 3.74 – 3.68 (m, 1H), 3.67 (m, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 3.55 (td, *J* = 6.5, 3.9 Hz, 1H), 3.36 (s, 1H), 3.31 (d, *J* = 3.4 Hz, 1H), 3.11 (s, 3H), 3.10 – 3.00 (m, 2H), 2.99 – 2.88 (m, 2H), 2.83 (s, 3H), 2.62 – 2.48 (m, 3H), 2.48 – 2.35 (m, 2H), 2.30 (dq, *J* = 18.9, 6.3 Hz, 3H), 2.21 (dq, *J* = 12.2, 6.0 Hz, 1H), 2.14 – 2.04 (m, 3H), 1.99 – 1.92 (m, 3H), 1.81 – 1.60 (m, 4H), 1.16 (d, *J* = 6.3 Hz, 1H), 1.09 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 171.2, 170.4, 170.0, 162.5, 161.5, 161.4, 160.1, 159.0, 158.9, 158.7, 158.3, 157.9, 157.1, 156.7, 156.3, 155.9, 152.6, 152.5, 142.3, 142.2, 137.4, 133.6, 133.4, 133.2, 130.1, 129.8, 128.0, 127.9, 127.9, 124.9, 124.8, 124.6, 120.2, 120.1, 117.3, 116.8, 114.6, 114.4, 112.9, 98.4, 98.1, 97.3, 97.0, 75.9, 75.6, 65.7, 57.5, 57.4, 57.2, 55.8, 55.3, 53.2, 52.4, 51.5, 41.4, 39.4, 34.1, 34.1, 31.2, 30.7, 30.6, 25.0, 24.8, 19.5, 15.2, 15.1. ^{31}P NMR (162 MHz, CD_3OD) δ -4.2; ^{19}F NMR (376 MHz, CD_3OD) δ -119.1 – -119.4 (m), -120.3 (d, *J* = 12.1 Hz), -123.4 (d, *J* = 8.3 Hz), -125.4 (s), -125.8 (s); Specific rotation: $[\alpha]_D^{21.1}$ = +3.7 (*c* = 1.0, MeOH); ESI-LCMS: Calculated for $[(M/2) + H]^+$: 679.66; found: 679.50.

Preparation of Trimethyl Lock Acid S4

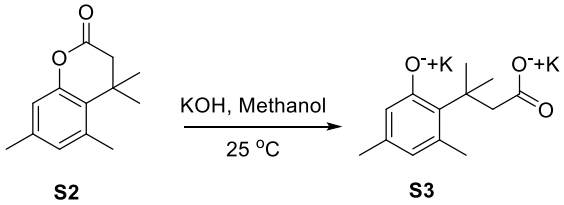
The synthesis of 3-[2'-(dibenzylphosphono)oxy-4',6'-dimethylphenyl]-3,3-dimethylpropionic acid (**S4**) was accomplished in 3 steps as shown in Scheme S1. The synthesis was first reported by Boorchardt *et al*.[2] where **S4** was prepared in 6 steps. Starting from the same commercially available 3,5 -dimethylphenol (**S1**) and methyl 3,3-dimethylacrylate, the lactone **S2** was prepared in methanesulfonic acid. At this point, several steps were eliminated from the synthesis, including a reduction, protection, and deprotection, by opening the lactone with potassium hydroxide in methanol to generate potassium 3-(2,4-dimethyl-6-oxidophenyl)-3-methylbutanoate (**S3**). The dipotassium salt **S3** was phosphorylated at the phenolic hydroxylate group using tetrabenzyl pyrophosphate to generate the trimethyl lock carboxylic acid **S4**.



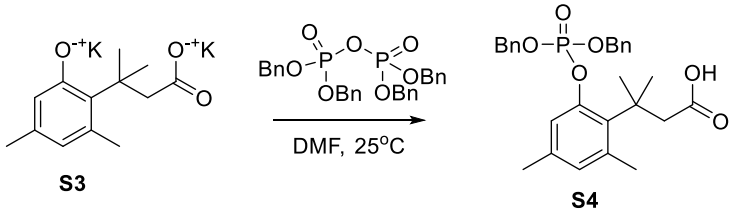
Scheme S1. New abbreviated synthesis of trimethyl lock acid S4



Compound S2. Compound **S2** was prepared according to the published procedure[2]

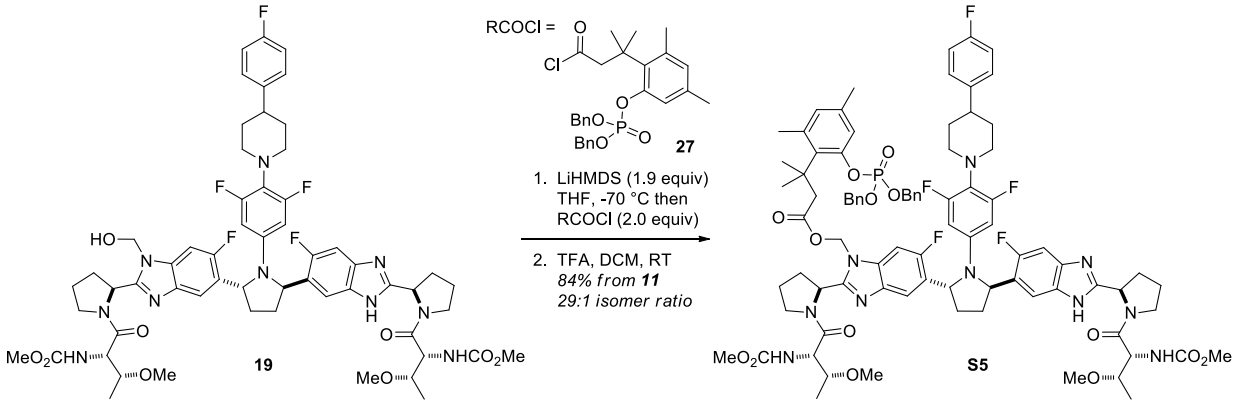


Compound S3: KOH powder (34.5 g, 5.23 mmol, 2.4 eq) was dissolved in methanol (445 mL). The solution was cooled to 25 °C and Compound **S2** (44.5 g, 218 mmol) was added. The reaction mixture was stirred at room temperature and monitored by NMR. After 3 h, the reaction mixture was clarified through a 0.45 micron filter and concentrated under reduced pressure. The resulting residue was chased with heptane to afford 3-(2,4-dimethyl-6-oxidophenyl)-3-methylbutanoate (**S3**) (78 g, 78% w/w, quant.) as a foam. The product is hygroscopic and should be stored under nitrogen. ^{1}H NMR (400 MHz, DMSO-d6) δ 5.73 (d, *J* = 2.1 Hz, 1H), 5.36 (d, *J* = 2.2 Hz, 1H), 2.60 (s, 2H), 2.23 (s, 3H), 1.89 (s, 3H), 1.46 (s, 6H).



3-(2-((bis(benzyloxy)phosphoryl)oxy)-4,6-dimethylphenyl)-3-methylbutanoic acid (S4): To a solution of Compound **S3** (1.68 g, 5.63 mmol) in DMF (24 ml) was added tetrabenzyl pyrophosphate (3.18 g, 5.91 mmol) dissolved in DMF (8 mL) at 8 ^{o}C. After the addition, the reaction mixture was allowed to warm to 25 ^{o}C. After 2 h, the reaction mixture was quenched with water (100 mL) followed by extraction with MTBE (100 mL). The aq layer was acidified with 12 N HCl to pH 3 and extracted with MTBE (100 mL x 2). The organic layer was washed with brine, dried with sodium sulfate, and concentrated. The crude product was purified by reverse phase chromatography to afford **S4** (1.29 g, 53.5%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 10H), 7.04 (s, 1H), 6.80 – 6.71 (m, 1H), 5.23 – 5.03 (m, 5H), 2.89 (s, 2H), 2.54 (s, 3H), 2.17 (s, 3H), 1.64 (s, 6H). MS(ESI) $[M-H]^-$; calculated 482.5; found 481.2

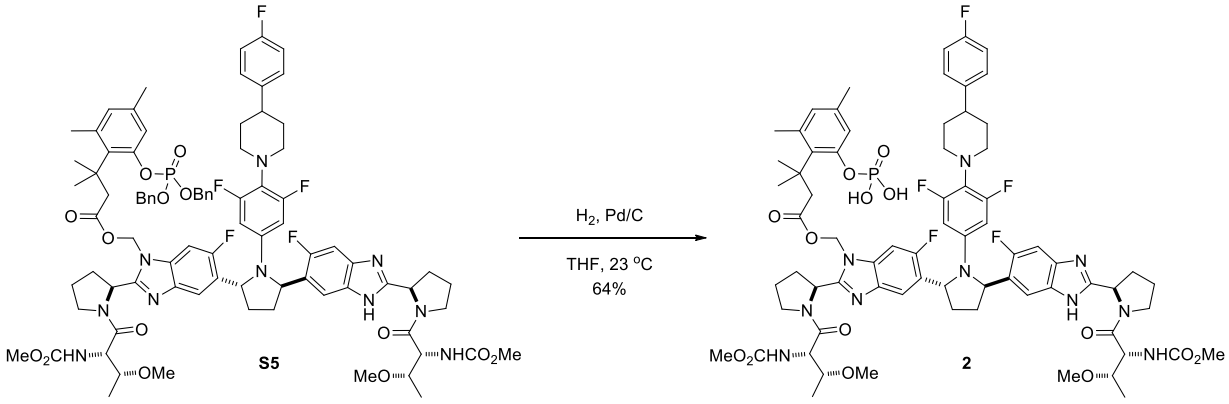
Reverse-Phase Chromatography: The gradient was 30-90% B in 4 min, 90-90% B in 2 min, 90-30% B in 0.01 min, and then hold at 30% B for 0.5 min (1 mL/min flow rate). Mobile phase A was 10 mM NH_4HCO_3, mobile phase B was HPLC grade CH_3CN. The column used for the chromatography is a 2.1 x 50 mm Xbridge C18 column (5 µm particle size).



5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 3-(2-((bis(benzyloxy)phosphoryl)oxy)-4,6-dimethylphenyl)-3-methylbutanoate (S5): A solution of 3-(2-((bis(benzyloxy)phosphoryl)oxy)-4,6-dimethylphenyl)-3-methylbutanoic acid **S4** (388 mg, 0.804 mmol) in DCM (4 mL) was stirred at 23 ^{o}C and DMF (0.1 M in DCM, 0.080 mL, 0.008 mmol) and oxalyl chloride (0.106 mL, 1.21 mmol) were added. After 1 h, LC-MS TFA method (aliquot MeOH quench) showed nearly complete acid chloride formation. The mixture was concentrated to minimal volume, THF (1 mL) was added, and the mixture was concentrated to minimal volume again. The resulting yellow oil acid chloride **27** was used without purification or characterization.

A solution of tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-1-(hydroxymethyl)-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate **19** (500 mg, 0.402 mmol) in THF (5 mL) was cooled to < -75 ^{o}C and LHMDS (1 M in THF, 0.764 mL, 0.764 mmol) was added over 2 min at < -74 ^{o}C. After 2 min, added the acid chloride prepared above in THF (0.4 + 0.3 + 0.3 mL) at < -72 ^{o}C over 2 min and LC-MS AA long method showed 97% conversion (manually integrating the peaks at 4.17 min and 4.94 min). Removed the cooling bath, added water (5 mL) and EtOAc (20 mL), separated layers, and washed the organic layer with saturated aqueous $NaHCO_3$ (5 mL) and brine (2 mL). Dried (Na_2SO_4), concentrated, and dissolved crude tert-butyl 6-((2R,5R)-5-(1-(((3-(2-((bis(benzyloxy)phosphoryl)oxy)-4,6-dimethylphenyl)-3-methylbutanoyl)oxy)methyl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-in DCM (4 mL).

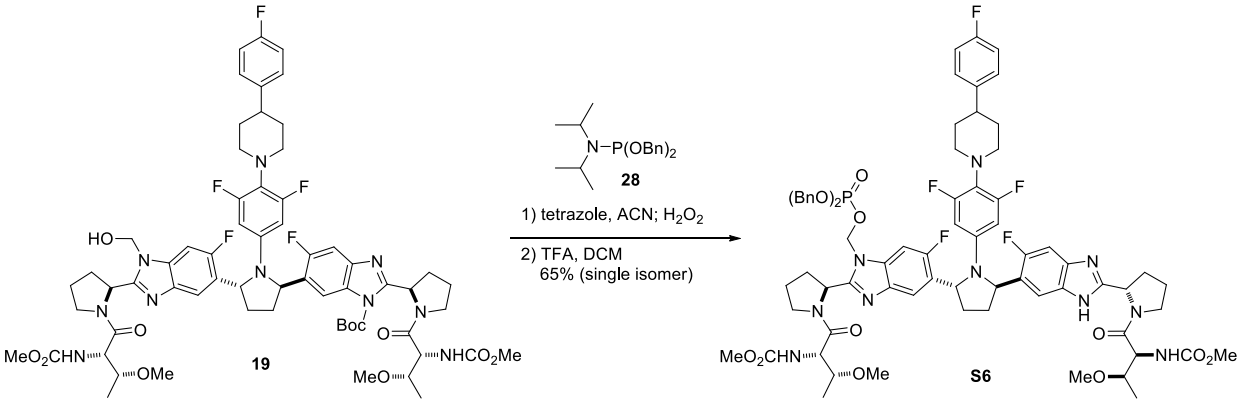
TFA (1 mL) was added and the solution was stirred at 23 °C for 1 h, when LC-MS AA long method showed a 29:1 ratio of regioisomers (integrating peaks at 4.46 min = minor and 4.52 min = major). Added EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (20 mL), separated layers, and washed with satd aq $NaHCO_3$ (2 x 10 mL) and brine (5 mL). Dried (Na_2SO_4), concentrated, and silica gel chromatography (40-75% acetone/heptanes gradient elution; good regioisomer separation at ~ 60% acetone/heptanes) gave **S5** (541 mg, 0.337 mmol, 84 % yield): ^{1}H NMR (500 MHz, THF-d8) δ 11.07 (d, *J* = 64.3 Hz, 1H), 7.44 – 7.23 (m, 12H), 7.20 (dd, *J* = 8.6, 5.6 Hz, 3H), 7.12 (d, *J* = 6.7 Hz, 1H), 7.03 (s, 1H), 6.94 (t, *J* = 8.8 Hz, 2H), 6.47 (s, 1H), 6.43 (d, *J* = 11.7 Hz, 2H), 6.11 (d, *J* = 8.5 Hz, 1H), 5.99 (d, *J* = 11.8 Hz, 1H), 5.85 (br d, *J* = 12.9 Hz, 2H), 5.60 – 5.46 (m, 2H), 5.27 (dd, *J* = 8.1, 4.7 Hz, 2H), 5.06 (s, 2H), 5.05 (s, 2H), 4.45 (dd, *J* = 8.3, 5.4 Hz, 1H), 4.26 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.91 – 3.68 (m, 4H), 3.56 (s, 3H), 3.52 (s, 3H), 3.40 – 3.33 (m, 1H), 3.20-2.87 (m, 8H), 2.71 (s, 3H), 2.64-2.46 (m, 9H), 2.43-2.36 (m, 2H), 2.33 (s, 3H), 2.22-2.18 (m, 2H), 2.09 (s, 3H), 2.00 (br s, 1H), 1.96-1.79 (m, 4H), 1.79-1.75 (m, 2H), 1.70 – 1.63 (m, 2H), 1.54 (s, 3H), 1.51 (s, 3H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.91 – 0.85 (m, 1H), 0.82 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, THF-d8) δ 170.9, 169.9, 168.9, 162.5, 161.6, 160.1, 159.2, 158.3, 157.8, 156.8, 156.0, 154.4, 150.2, 142.5, 138.6, 137.9, 136.2, 136.0, 133.6, 131.4, 130.6, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.8, 123.9, 118.8, 117.4, 114.8, 114.6, 98.0, 97.7, 97.4, 97.1, 76.8, 76.2, 69.4, 64.9, 57.6, 56.9, 56.0, 54.8, 52.5, 52.3, 51.1, 47.0, 41.6, 39.2, 34.4, 31.1, 29.6, 29.3, 19.5, 15.6, 15.1. ^{31}P NMR (162 MHz, THF-d8) δ -6.3; ^{19}F NMR (376 MHz, THF-d8) δ -117.7 – -118.9 (br s), -119.9 (s), -124.3 (s), -126.1 (s), -127.6 (s); Specific rotation: [**α**] $_D^{20.9}$ = -6.2 (*c* = 1.0, MeOH). No molecular ion was observed for this intermediate under numerous ionization conditions.



(5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 3-(2,4-dimethyl-6-(phosphonooxy)phenyl)-3-methylbutanoate (2):

A solution of (5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl 3-(2-((bis(benzyloxy)phosphoryl)oxy)-4,6-dimethylphenyl)-3-methylbutanoate **S5** (1.00 g, 0.622 mmol) in THF (7 mL) was added to 5% Pd/C (wet JM#9) (0.099 g) in a 20 mL Barnstead Hastelloy stainsless steal reactor and stirred for 24 h at 50 psi hydrogen pressure at 25 °C. The mixture was filtered, washing the catalyst bed with THF (2 x 5 mL). The solution was concentrated, IPA (25 mL) was added, the slurry was heated to 70 °C, and a dark solution was observed. This was cooled to ambient temperature, filtered, and the gray solid was dried in an ambient temperature vacuum oven, giving crude product (644 mg, 73%). This material was slurried in acetone (20 mL) for 10 min, filtered, and washed with acetone (2 x 5 mL). The white solid was dried in an ambient temperature vacuum oven to constant weight, giving **2** (565 mg, 0.396 mmol, 64%): ^{1}H NMR (500 MHz, CD_3OD) δ 7.34 (d, *J* = 10.3 Hz, 2H), 7.26 – 7.18 (m, 3H), 7.15 (dd, *J* = 10.5, 6.5 Hz, 2H), 6.96 (t, *J* = 8.8 Hz, 2H),

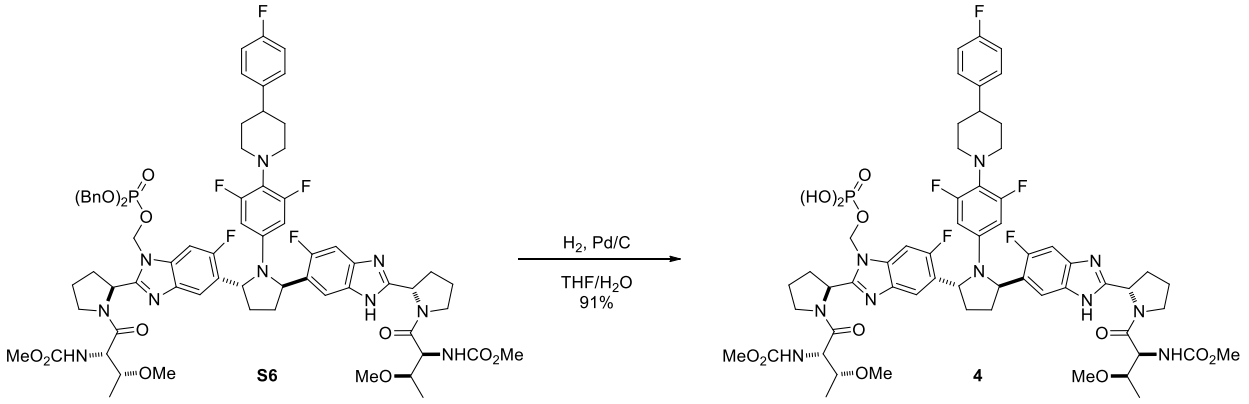
6.35 (d, *J* = 11.8 Hz, 1H), 6.13 (d, *J* = 2.0 Hz, 1H), 6.08 (d, *J* = 11.9 Hz, 1H), 5.81 (d, *J* = 12.4 Hz, 2H), 5.54 (d, *J* = 6.6 Hz, 2H), 5.30 (t, *J* = 7.0 Hz, 1H), 5.23 (dd, *J* = 8.1, 5.1 Hz, 1H), 4.41 (d, *J* = 4.7 Hz, 1H), 4.29 (d, *J* = 4.0 Hz, 1H), 3.97 – 3.76 (m, 4H), 3.65 (m, 1H), 3.64 (s, 3H), 3.61 (s, 3H), 3.50 (dd, *J* = 6.5, 4.0 Hz, 1H), 3.21 (d, *J* = 14.7 Hz, 1H), 3.09 (s, 3H), 3.08 – 2.97 (m, 3H), 2.92 (dd, *J* = 8.8, 5.4 Hz, 2H), 2.78 (s, 3H), 2.63 (br s, 3H), 2.55 – 2.45 (m, 1H), 2.45 – 2.35 (m, 2H), 2.34-2.17 (m, 4H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08 – 2.00 (m, 4H), 1.78 – 1.66 (m, 4H), 1.58 (s, 3H), 1.54 (s, 3H), 1.14 (d, *J* = 6.3 Hz, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.93 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 174.1, 172.4, 170.4, 170.0, 162.5, 161.5, 161.4, 160.1, 159.0, 158.9, 158.6, 158.2, 157.9, 156.9, 156.89, 156.8, 156.2, 155.8, 152.5, 152.5, 142.4, 142.3, 142.2, 142.1, 137.3, 136.4, 135.2, 133.4, 133.2, 130.5, 130.4, 128.2, 128.0, 127.9, 124.6, 124.5, 118.7, 117.4, 117.3, 117.1, 116.6, 114.6, 114.4, 112.9, 98.4, 98.2, 97.4, 97.1, 76.0, 75.7, 64.5, 57.5, 57.1, 56.1, 55.9, 55.4, 53.0, 52.5, 52.4, 51.5, 51.5, 51.2, 41.4, 39.5, 39.0, 34.1, 34.0, 31.3, 31.1, 30.8, 25.2, 24.8, 24.5, 19.5, 19.3, 15.3, 15.1.^{31}P NMR (162 MHz, CD_3OD) δ -5.5; ^{19}F NMR (376 MHz, CD_3OD) δ -119.3 (tt, *J* = 8.8, 5.4 Hz), -120.3 (s), -120.4 (s) -123.4 – -123.7 (m), -125.75; Specific rotation: $[\alpha]_D^{21.2}$ = -2.5 (*c* = 1.0, MeOH); ESI-LCMS: Calculated for $[(M/2) + H]^+$: 714.73; found: 714.73.



Dibenzyl (5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((R)-1-((2R,3S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl phosphate (S6): A solution of 1H-tetrazole (0.45 M in acetonitrile) (8.94 ml, 4.02 mmol) was cooled in a dry ice/acetonitrile bath, and tert-butyl 6-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(6-fluoro-1-(hydroxymethyl)-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-5-yl)pyrrolidin-2-yl)-5-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazole-1-carboxylate (1.00 g, 0.804 mmol) was added. The cooled mixture was vigorously stirred while dibenzyl diisopropylphosphoramidite (1.55 mL, 4.02 mmol) was added dropwise over 10 min. The mixture was allowed to slowly warm to -10 °C over 2h. The mixture was slowly warmed to 0 °C, then hydrogen peroxide (50% aq) (0.493 ml, 8.04 mmol) was added, and the resulting solution was allowed to warm to ambient temperature. Diluted with EtOAc, washed with aq NaS_2O_3 and aq $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude product was dissolved in DCM (8 mL) and TFA (trifluoroacetic acid) (4 mL, 51.9 mmol) was added. After stirrin for 30 min, concentrated to give an oil. The oil was dissolved in DCM (20 mL), washed with satd aq $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel using a solvent gradient of 30-80% acetone in heptanes, giving **S6** (725 mg, 65%). A minor byprod eluted just before the desired prod, which is a bis-phosphomethyl byprod (98 mg, MW = 1694).

S6: ^{1}H NMR (500 MHz, CD_3OD) δ 7.46 (d, *J* = 10.0 Hz, 1H), 7.39-7.26 (m, 7H), 7.27-7.06 (s, 7H), 6.98 (t, *J* = 8.8 Hz, 2H), 6.42 (t, *J* = 11.9 Hz, 1H), 6.16 (t, *J* = 12.1 Hz, 1H), 5.82 (d, *J* = 12.9 Hz, 2H), 5.64 – 5.51 (m, 2H), 5.29 – 5.18 (m, 2H), 5.02 (dd, *J* = 9.0, 6.8 Hz, 4H), 4.58 (br s, 2H), 4.43 (br s, 1H), 4.33 (d, *J* = 4.0 Hz, 1H), 3.93 (m, 3H), 3.81 (dt, *J* = 9.5, 6.9 Hz, 1H), 3.66 (br s, 3H), 3.65 (s, 3H), 3.56 – 3.49 (m, 1H), 3.12-3.00 (m, 3H), 2.97-2.89 (br m, 2H), 2.81 (s, 3H), 2.62-2.49 (m, 3H), 2.44-2.34 (m, 1H), 2.35-2.18 (m, 4H), 2.15-2.06 (m, 2H), 2.09-1.86 (m, 4H), 1.86-1.73 (m, 5H), 1.09 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.3 Hz,

3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.4, 170.0, 162.4, 161.5, 161.4, 160.0, 159.1, 159.0, 158.8, 158.4, 157.9, 156.8, 156.7, 156.4, 156.0, 142.3, 137.6, 135.3, 135.19, 135.2, 135.21, 133.1, 133.0, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 125.0, 124.9, 117.4, 117.2, 115.0, 114.5, 113.0, 101.2, 100.9, 98.2, 97.9, 97.4, 97.1, 76.1, 75.7, 69.9, 69.9, 69.8, 69.8, 69.2, 67.1, 57.5, 57.2, 56.1, 55.9, 55.2, 52.8, 52.4, 51.6, 41.3, 34.1, 31.2, 30.7, 25.0, 24.9, 15.3, 15.1, 14.3; ^{31}P NMR (162 MHz, CD_3OD) δ -2.3; ^{19}F NMR (376 MHz, CD_3OD) δ -118.8 (tt, *J* = 8.4, 4.8 Hz), -119.5 (br s), -119.6 – -120.0 (m), -122.6 (s), -123.4 (s); Specific rotation: [**α**]$_D^{21.3}$ = +8.8 (*c* = 1.0, MeOH); ESI-LCMS: Calculated for [(M/2) + H]$^+$: 702.72; found: 702.58.



(5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((R)-1-((2R,3S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl dihydrogen phosphate 4: A solution of dibenzyl (5-((2R,5R)-1-(3,5-difluoro-4-(4-(4-fluorophenyl)piperidin-1-yl)phenyl)-5-(5-fluoro-2-((R)-1-((2R,3S)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-6-yl)pyrrolidin-2-yl)-6-fluoro-2-((S)-1-((2S,3R)-3-methoxy-2-((methoxycarbonyl)amino)butanoyl)pyrrolidin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl phosphate **S6** (11.3 g, 8.05 mmol) in THF (110 mL) and water (110 mL) was added to 5% Pd/C (wet JM#9) (2.26 g, 9.90 mmol) in a 600 mL 316SS reactor and stirred for 1.7 h at 50 psi hydrogen pressure without external heating. The reaction mixture was filtered and concentrated until THF distillation was complete, giving a white slurry. Sonicated the slurry, stirred 30 min, and filtered, washing with water (2 x 50 mL). The wet cake was stirred with ACN (110 mL) overnight and the white solid was filtered, washing with ACN (2 x 22 mL). After drying in a vacuum oven at 50 °C to constant weight, **4** (8.92 g, 91%) was obtained as a white solid: ^{1}H NMR (600 MHz, CD_3OD) δ 7.60 (d, *J* = 10.3 Hz, 1H), 7.33 (d, *J* = 10.0 Hz, 1H), 7.25 – 7.17 (m, 3H), 7.14 (d, *J* = 6.6 Hz, 2H), 6.96 (t, *J* = 8.8 Hz, 2H), 6.28 – 6.15 (m, 1H), 5.97 (dd, *J* = 11.1, 9.2 Hz, 1H), 5.81 (d, *J* = 12.6 Hz, 2H), 5.52 (t, *J* = 7.6 Hz, 3H), 5.44 (t, *J* = 7.1 Hz, 1H), 5.23 (dd, *J* = 8.1, 5.2 Hz, 1H), 4.41 (d, *J* = 4.5 Hz, 1H), 4.34 (d, *J* = 4.0 Hz, 1H), 4.01 – 3.78 (m, 4H), 3.64 (s, 3H), 3.62 (s, 3H), 3.56 (qd, *J* = 6.3, 3.8 Hz, 2H), 3.34 (s, 1H), 3.16 – 2.97 (m, 5H), 2.92 (dt, *J* = 11.7, 3.5 Hz, 2H), 2.85 (s, 3H), 2.60 – 2.47 (m, 5H), 2.38 (dq, *J* = 12.6, 7.4 Hz, 1H), 2.35 – 2.22 (m, 3H), 2.19 (dq, *J* = 12.2, 6.0 Hz, 1H), 2.09 (tt, *J* = 8.3, 5.2 Hz, 1H), 1.95 (dt, *J* = 10.6, 5.3 Hz, 3H), 1.72 (tdd, *J* = 17.3, 8.2, 3.2 Hz, 4H), 1.14 (d, *J* = 6.3 Hz, 1H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, CD_3OD) δ 170.3, 169.9, 162.5, 161.5, 161.4, 160.1, 159.1, 159.0, 158.6, 157.9, 157.8, 157.1, 157.0, 156.9, 156.2, 142.4, 142.3, 142.3, 137.5, 133.7, 133.6, 128.0, 127.9, 124.3, 124.1, 117.2, 116.5, 116.5, 114.6, 114.4, 98.3, 98.0, 97.3, 97.0, 77.4, 76.1, 75.7, 67.9, 57.6, 57.5, 57.1, 56.1, 55.9, 55.8, 55.5, 53.4, 52.5, 52.4, 51.5, 51.4, 51.2, 41.4, 34.1, 34.1, 31.3, 31.2, 30.7, 30.6, 24.9, 24.8, 15.3, 15.0, 14.3, 14.2. ^{31}P NMR (162 MHz, CD_3OD) δ -2.3. ^{19}F NMR (376 MHz, CD_3OD) δ -119.4 (ddd, *J* = 14.0, 8.8, 5.3 Hz), -120.2 (s) -120.5 (s), -124.1 – -124.7 (m), -126.3 (s). Specific rotation: [**α**]$_D^{21.6}$ = +16.6 (*c* = 1.0, MeOH); ESI-LCMS: Calculated for [(M/2) + H]$^+$: 612.60; found: 612.34.

References

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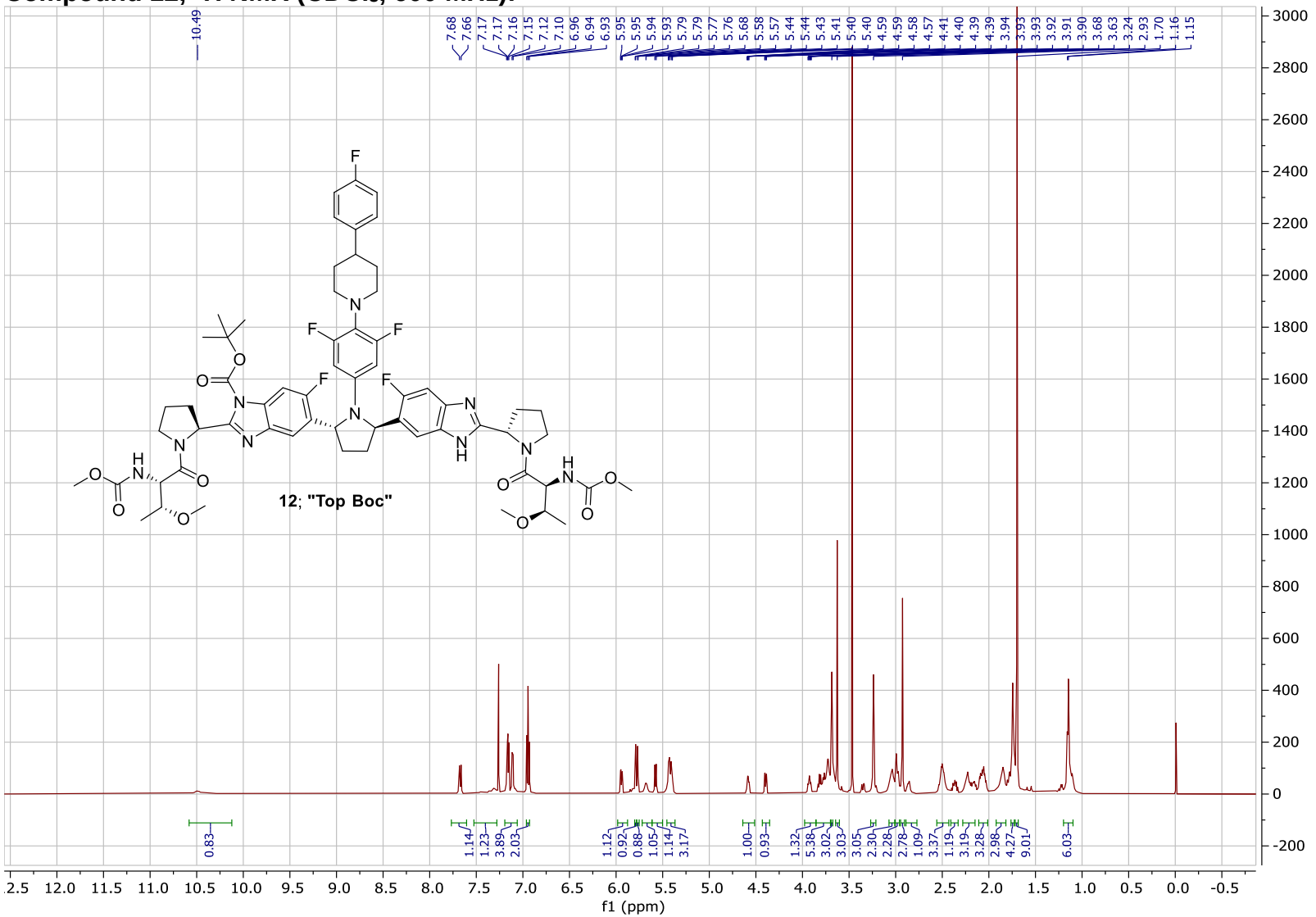
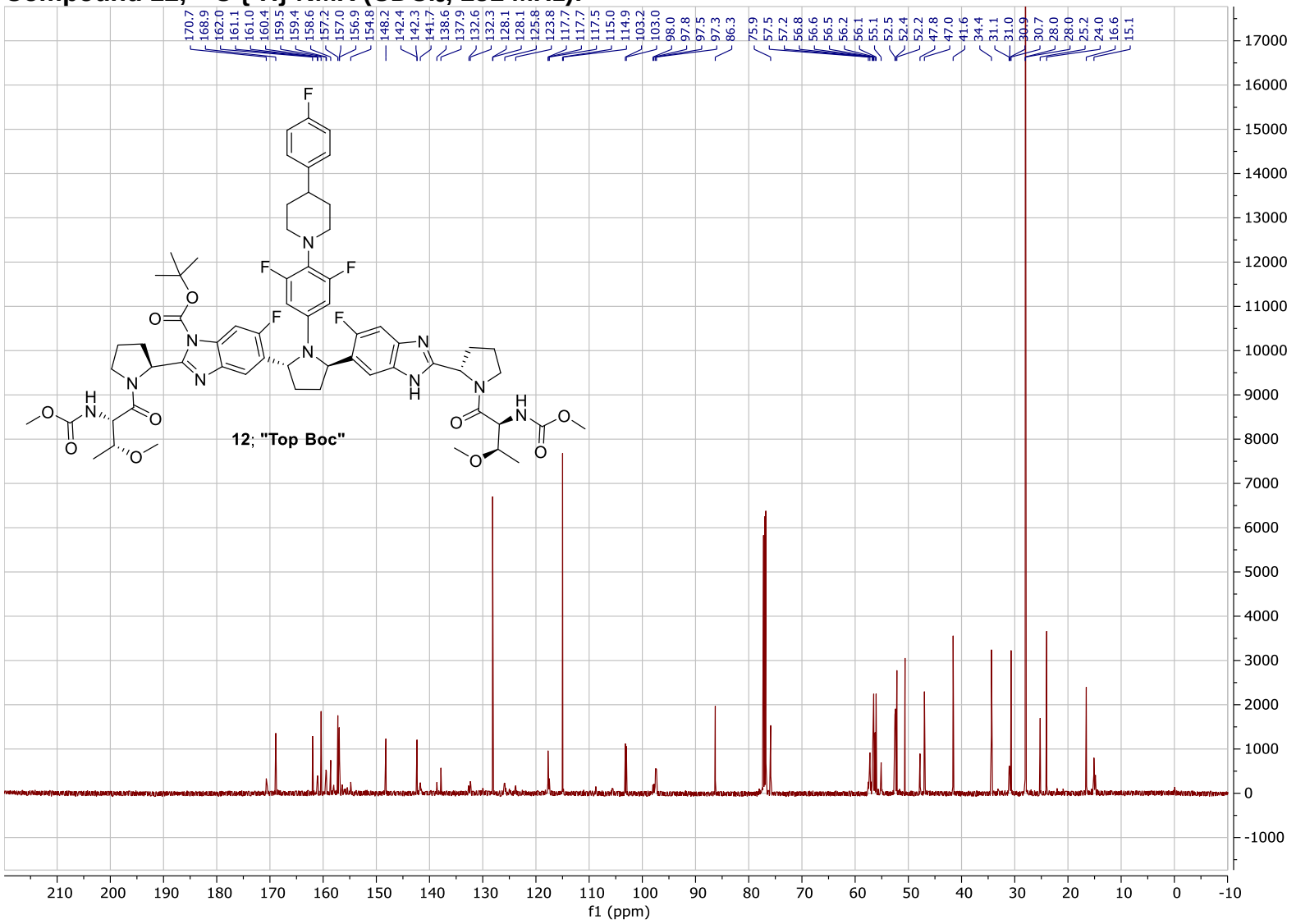
2. a). Amsberry, K.L.; Borchardt, R.T. “The Lactonization of 2’-Hydroxyhydrocinnamic Acid Amides: A Potential Prodrug for Amines.” *J. Org. Chem.* 1990, 55, 5867. b). Nicolaou, M. G.; Yuan, C.-S.; Borchardt, R. T.; “Phosphate Prodrugs for Amines Utilizing a Fast Intramolecular Hydroxy Amide Lactonization” *J. Org. Chem.* **1996**, *61*, 8636-8641**.**

Spectral Data for New Compounds

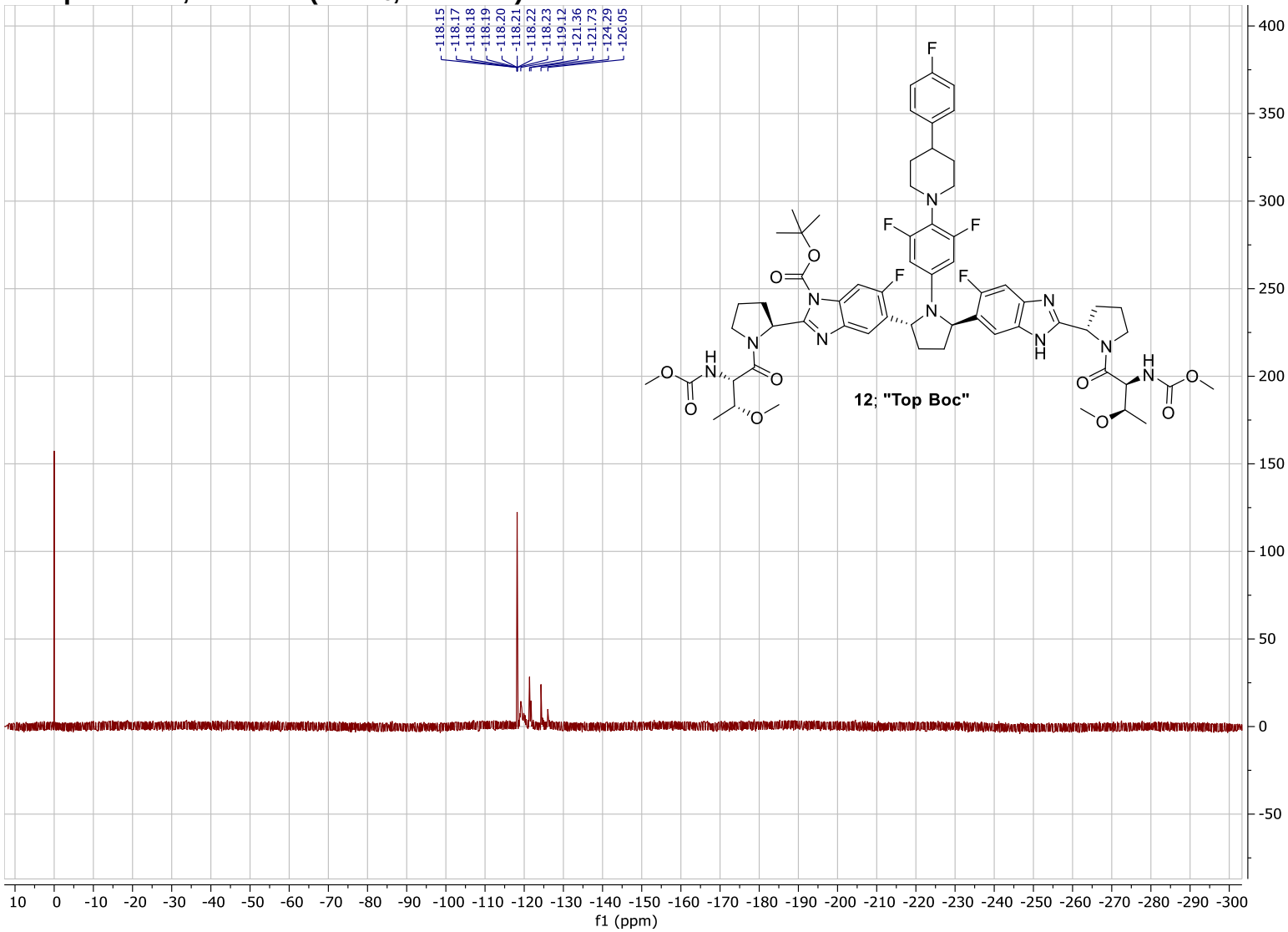
Compound 12, ^{1}H NMR ($CDCl_3$, 600 MHz):



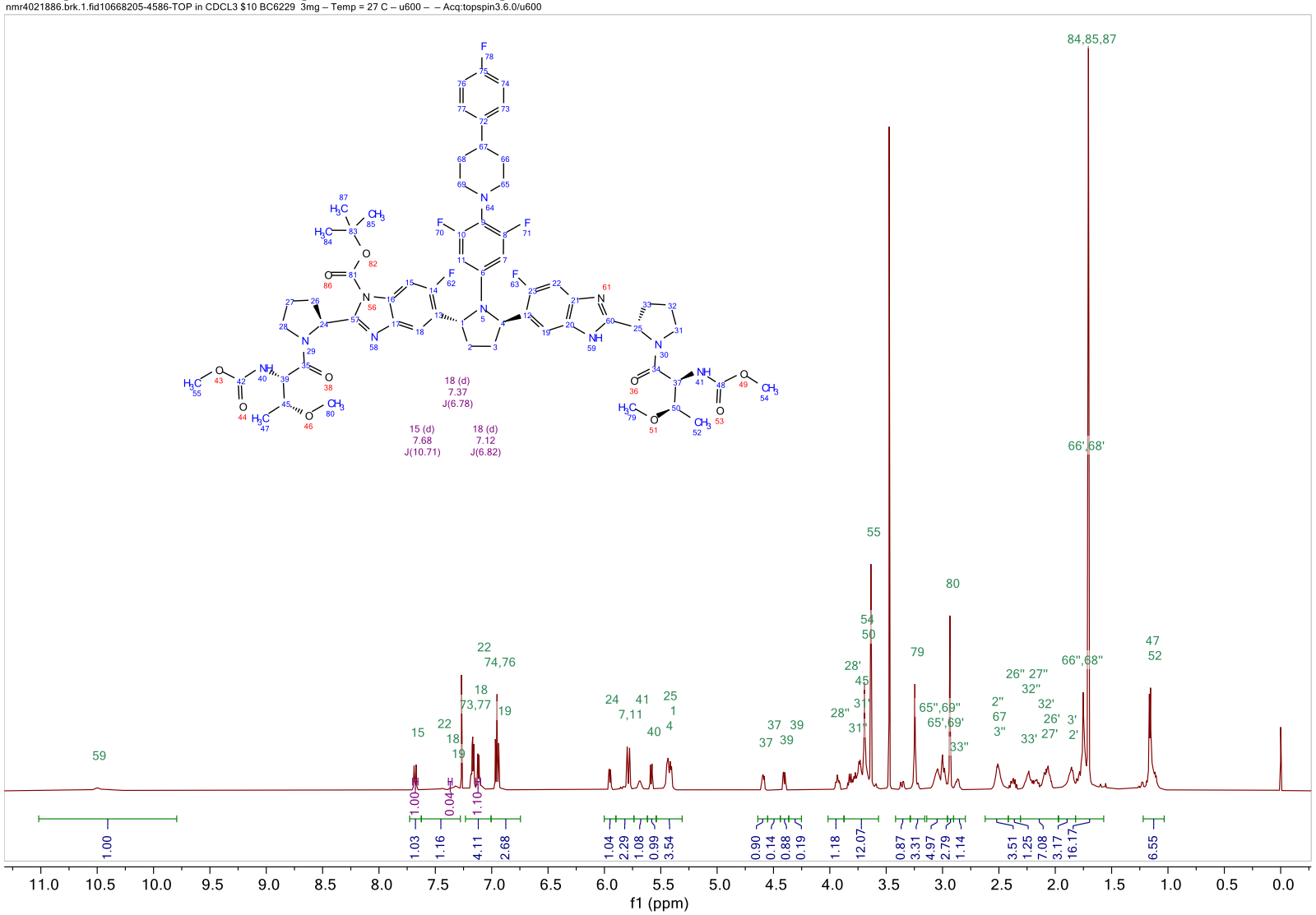
Compound 12, ^{13}C {^{1}H} NMR ($CDCl_3$, 151 MHz):



Compound 12, ^{19}F NMR ($CDCl_3$, 376 MHz):

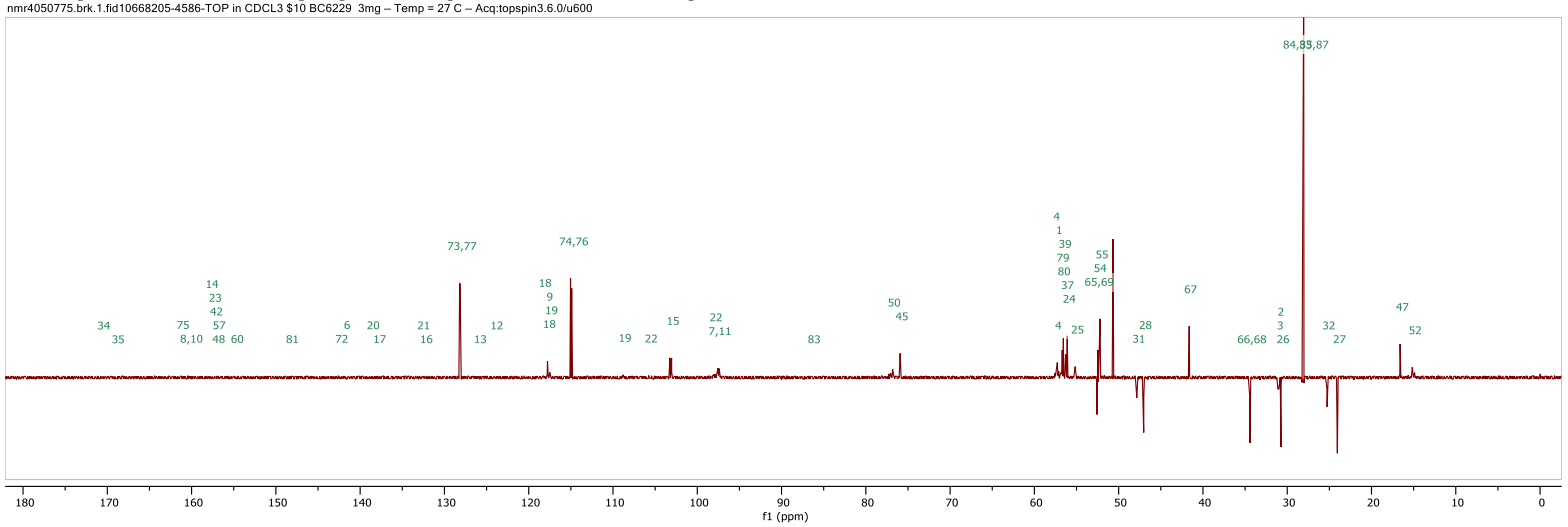


Compound 12, ^{1}H NMR ($CDCl_3$, 600 MHz):

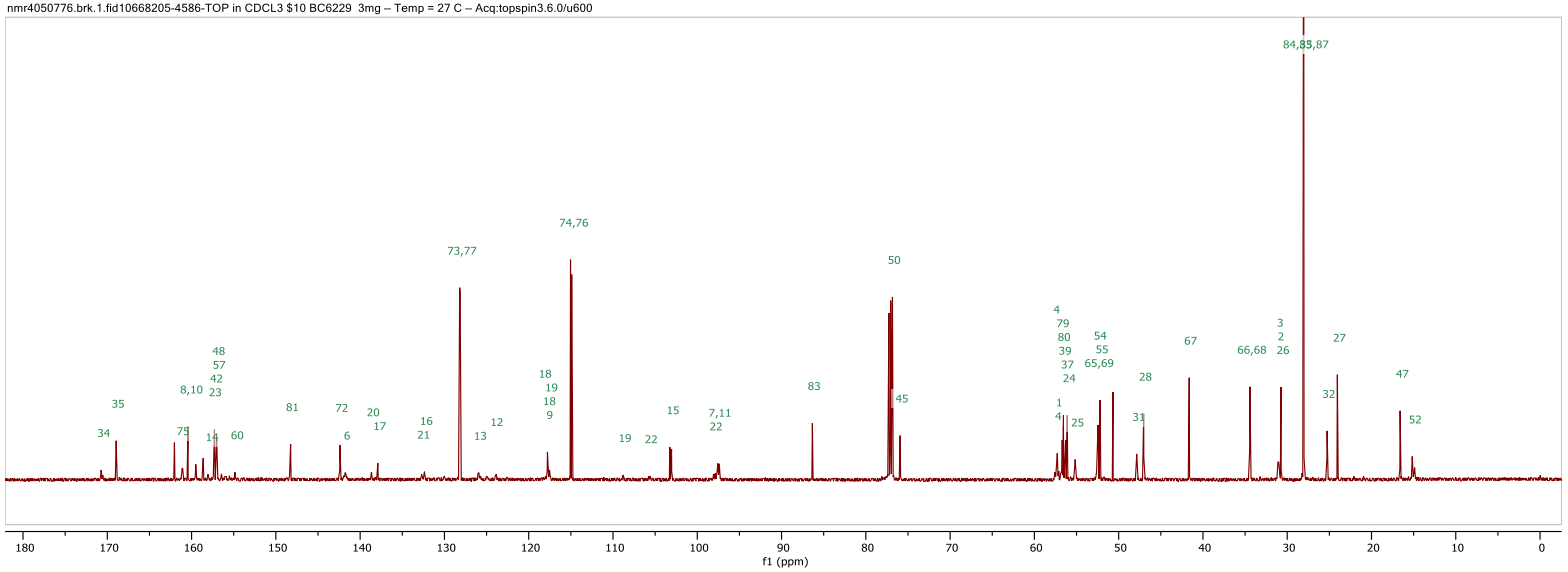


Compound 12, ^{13}C {^{1}H} NMR ($CDCl_3$, 151 MHz):

nmr4050775.brk.1.fid10668205-4586-TOP in CDCL3 $10 BC6229 3mg – Temp = 27 C – Acq:topspin3.6.0/u600

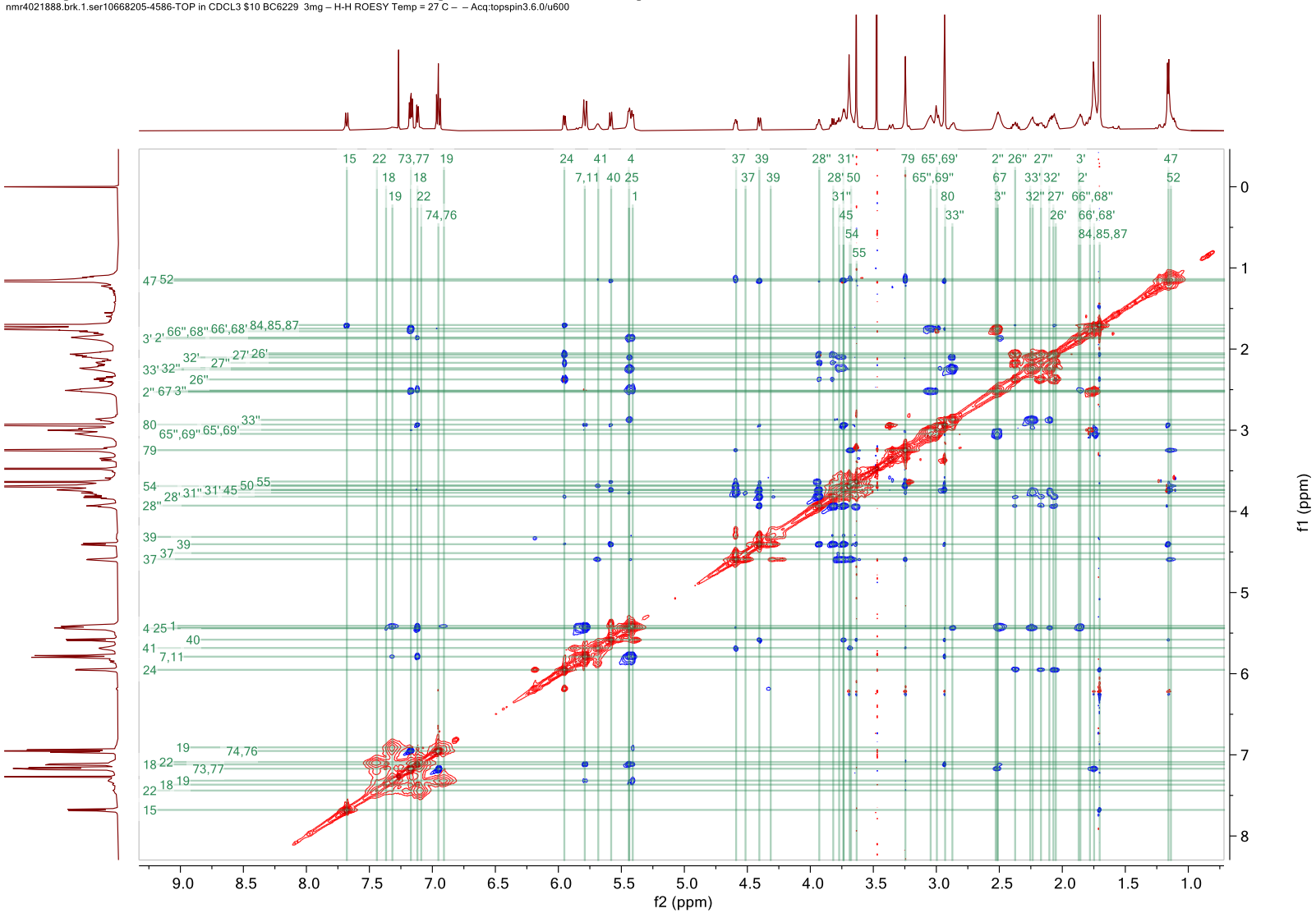


nmr4050776.brk.1.fid10668205-4586-TOP in CDCL3 $10 BC6229 3mg – Temp = 27 C – Acq:topspin3.6.0/u600

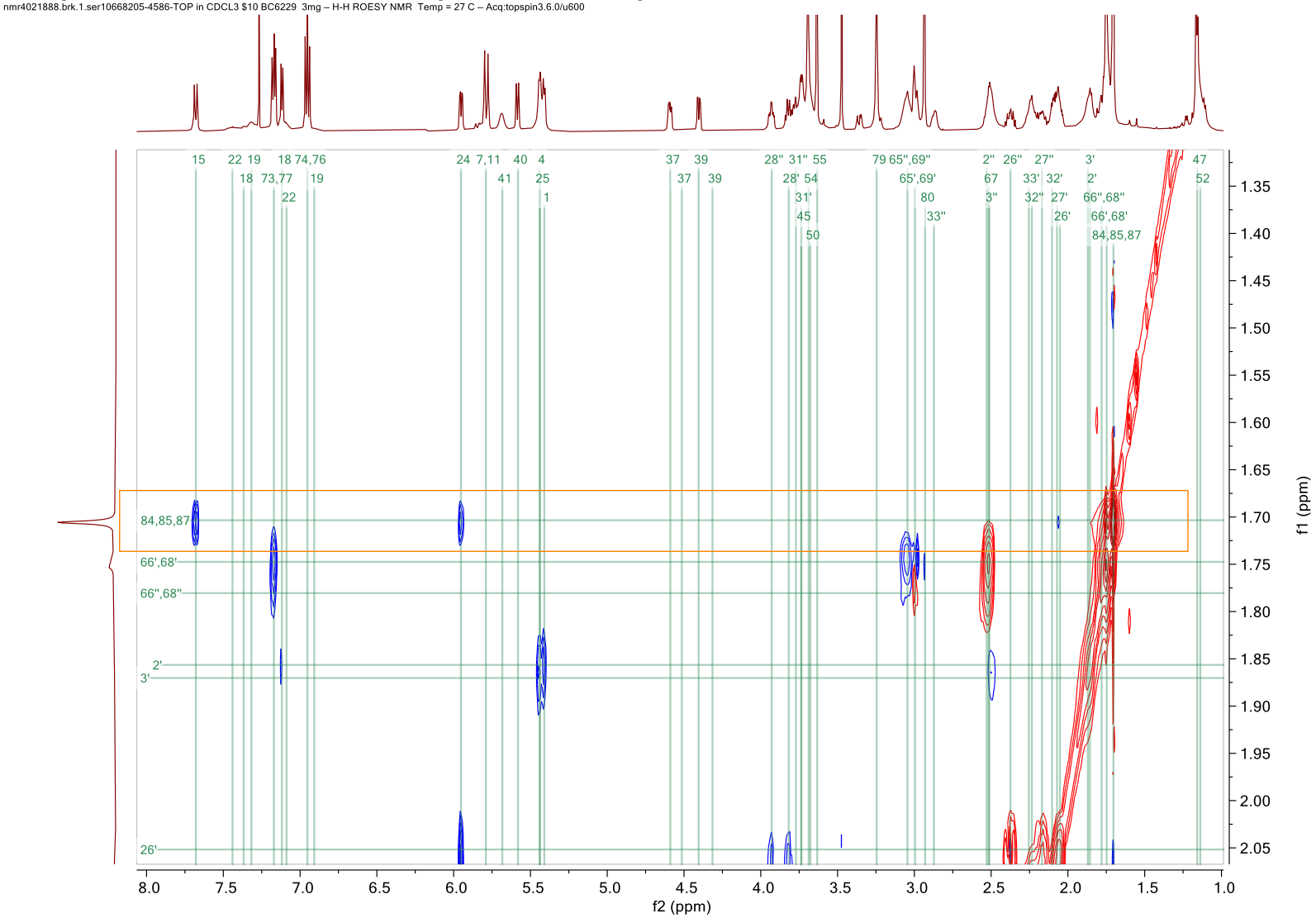


Compound 12, ^{1}H-^{1}H ROESY NMR ($CDCl_3$, 600 MHz):

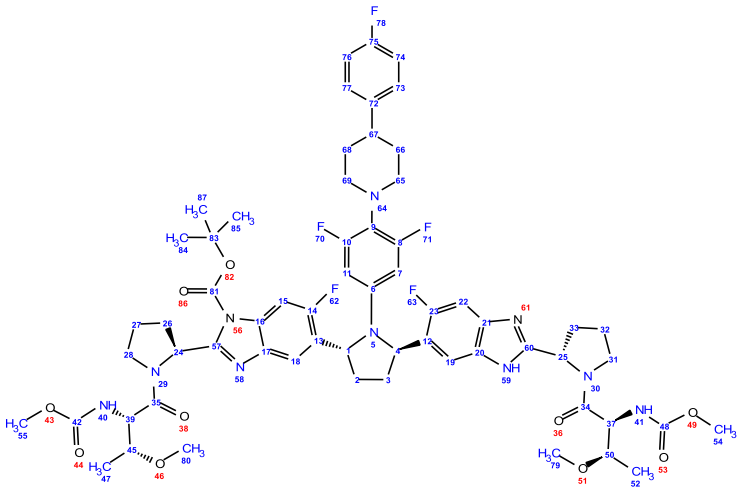
nmr4021888.brk.1.ser10668205-4586-TOP in CDCL3 $10 BC6229 3mg – H-H ROESY Temp = 27 C – – Acq:topspin3.6.0/u600



Compound 12, ^{1}H-^{1}H ROESY NMR ($CDCl_3$, 600 MHz):



Compound 12, ^{1}H NMR ($CDCl_3$, 600 MHz)



Temperature = 27 C assignments

Atom	Chemical Shift
1 C	57.27
H	5.41
2 C	30.96
H'	1.86
H''	2.53
3 C	31.04
H'	1.87
H''	2.51
4 C	57.37, 57.57
H	5.44
5 N	80.90
6 C	141.76
7 C	97.52
H	5.79
8 C	160.22
9 C	117.72
10 C	160.22
11 C	97.52
H	5.79
12 C	124.00
13 C	125.95
14 C	157.79
15 C	103.09
H	7.68
16 C	132.36
17 C	137.90
18 C	117.76, 118.26
H	7.12, 7.37
19 C	108.79, 117.51
H	6.91, 7.32

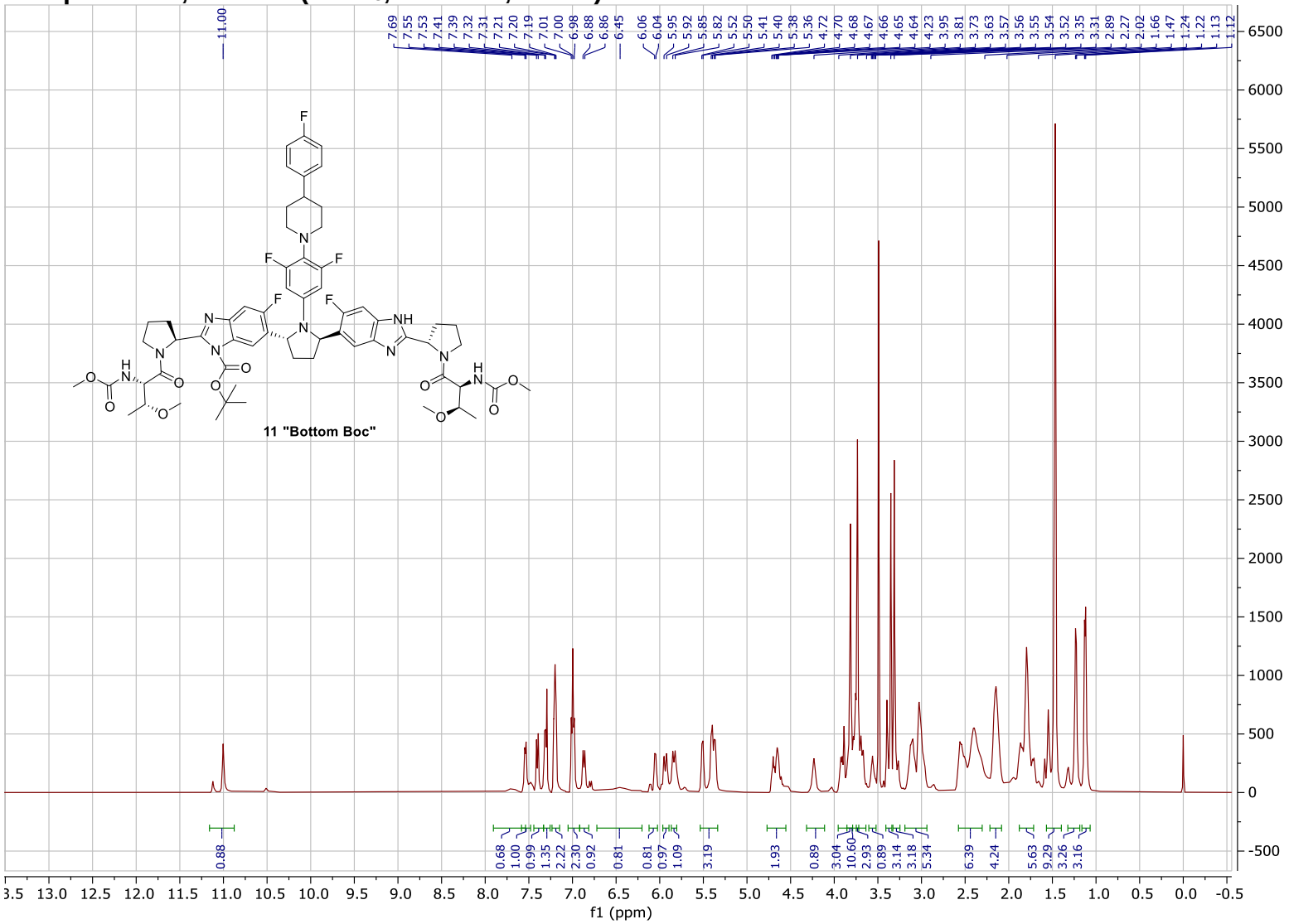
Atom	Chemical Shift
20 C	138.66
21 C	132.68
22 C	97.99, 105.68
H	7.09, 7.44
23 C	157.40
24 C	56.08
H	5.95
25 C	55.09
H	5.44
26 C	30.71
H'	2.05
H''	2.37
27 C	24.02
H'	2.07
H''	2.17
28 C	47.03
H'	3.82
H''	3.93
29 N	132.81
30 N	137.53
31 C	47.82
H'	3.74
H''	3.77
32 C	25.28
H'	2.10
H''	2.23
33 C	28.02
H'	2.25
H''	2.87

Atom	Chemical Shift
34 C	170.64
35 C	168.93
36 O	
37 C	56.29
H	4.51, 4.59
38 O	
39 C	56.57
H	4.31, 4.40
40 N	78.25
H	5.58
41 N	79.22
H	5.68
42 C	157.27
43 O	
44 O	
45 C	75.93
H	3.74
46 O	
47 C	16.56
H3	1.16
48 C	156.99
49 O	
50 C	76.85
H	3.68
51 O	
52 C	15.03
H3	1.14
53 O	
54 C	52.41
H3	3.69

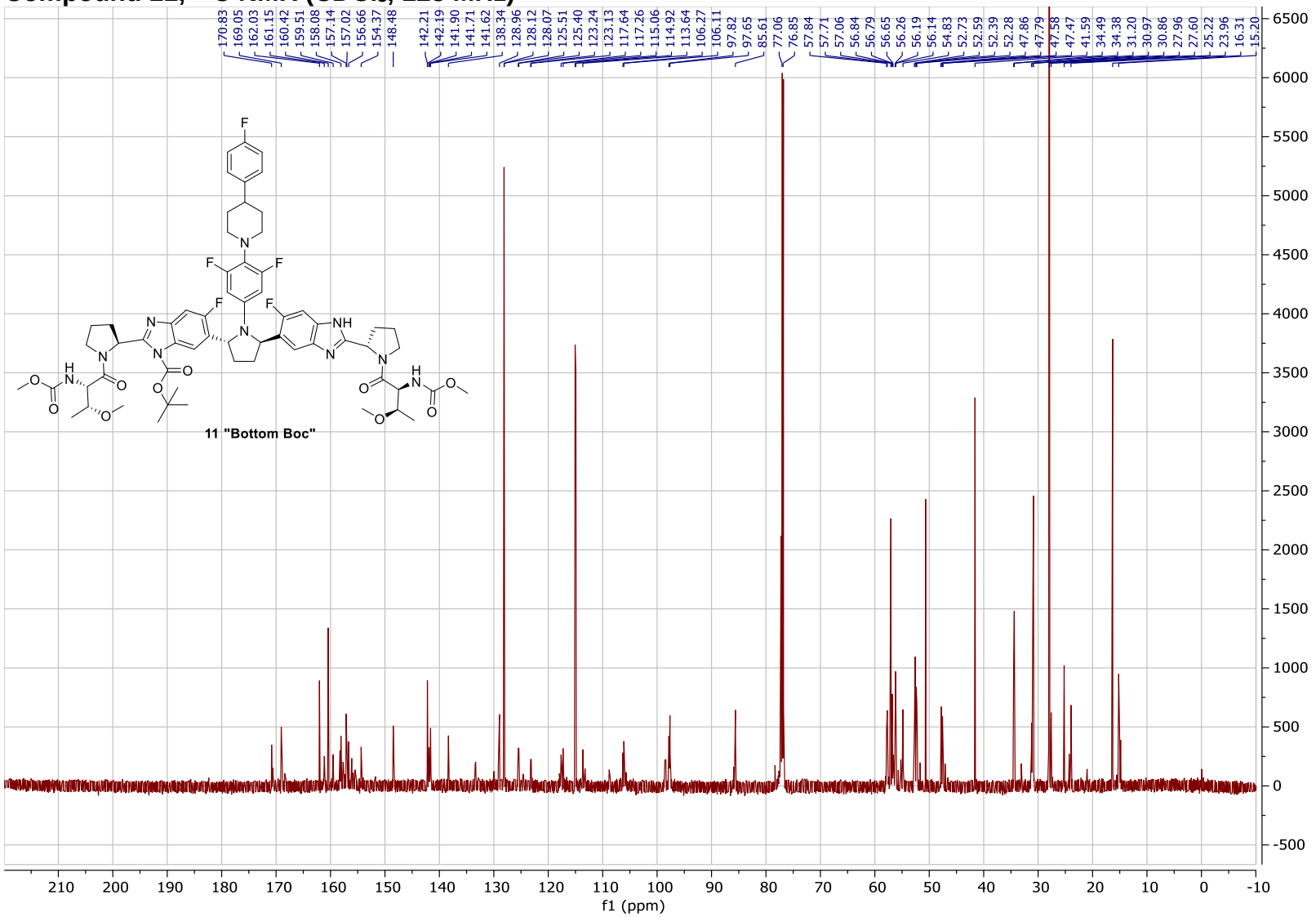
Atom	Chemical Shift
55 C	52.19
H3	3.63
56 N	
57 C	156.95
58 N	251.44
59 N	
H	10.50
60 C	154.79
61 N	
62 F	-121.74, -121.36
63 F	-126.03, -124.25
64 N	39.15
65 C	52.52
H'	3.00
H''	3.05
66 C	34.40
H'	1.75
H''	1.78
67 C	41.68
H	2.52
68 C	34.40
H'	1.75
H''	1.78
69 C	52.52
H'	3.00
H''	3.05
70 F	-119.23
71 F	-119.23
72 C	142.40

Atom	Chemical Shift
73 C	128.13
H	7.17
74 C	114.86
H	6.95
75 C	161.23
76 C	114.86
H	6.95
77 C	128.13
H	7.17
78 F	-118.16
79 C	56.83
H3	3.25
80 C	56.69
H3	2.93
81 C	148.25
82 O	
83 C	86.34
84 C	28.00
H3	1.70
85 C	28.00
H3	1.70
86 O	
87 C	28.00
H3	1.70

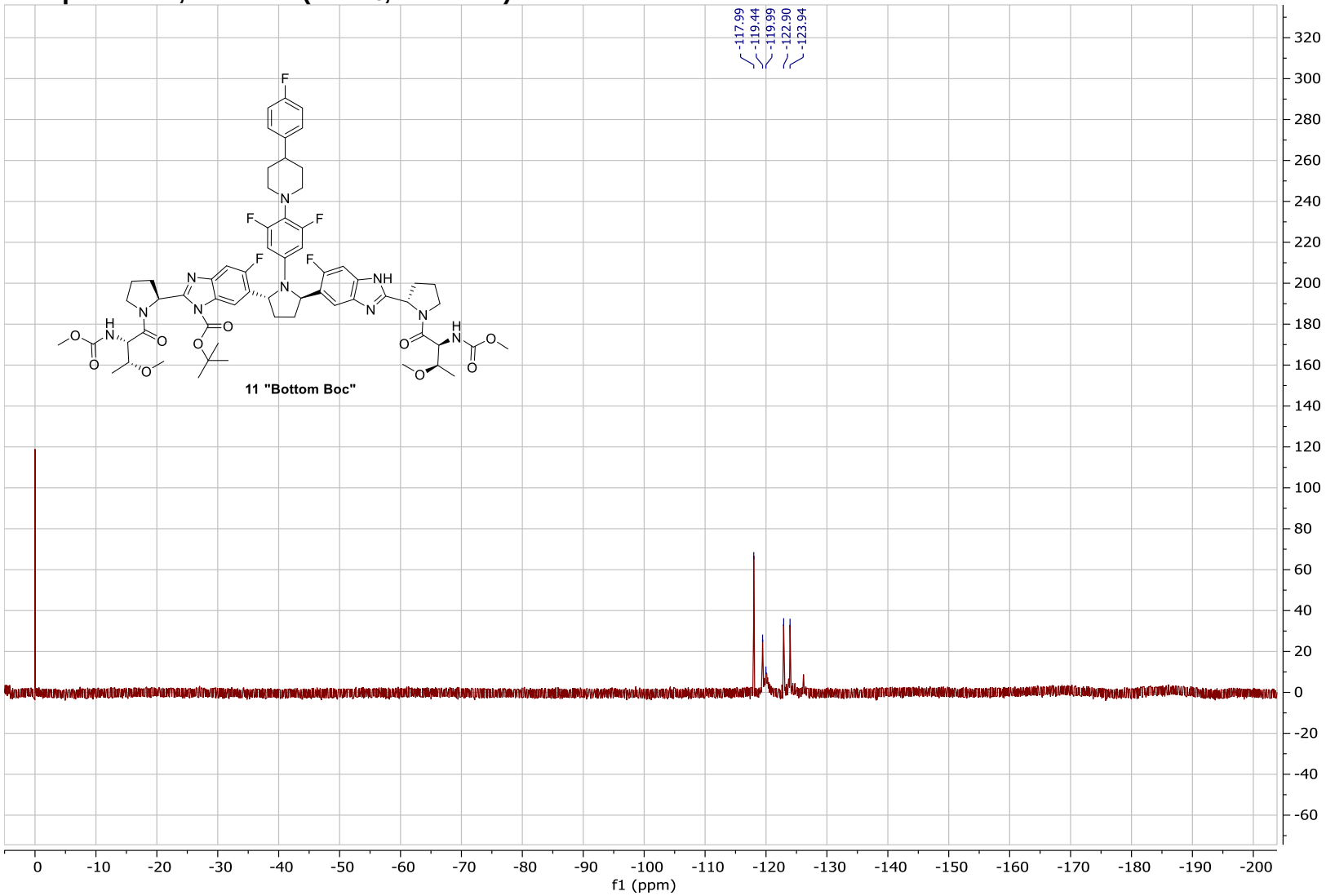
Compound 11, ^{1}H NMR ($CDCl_3$, 500 MHz, -20 ºC)



Compound 11, ^{13}C NMR ($CDCl_3$, 125 MHz)

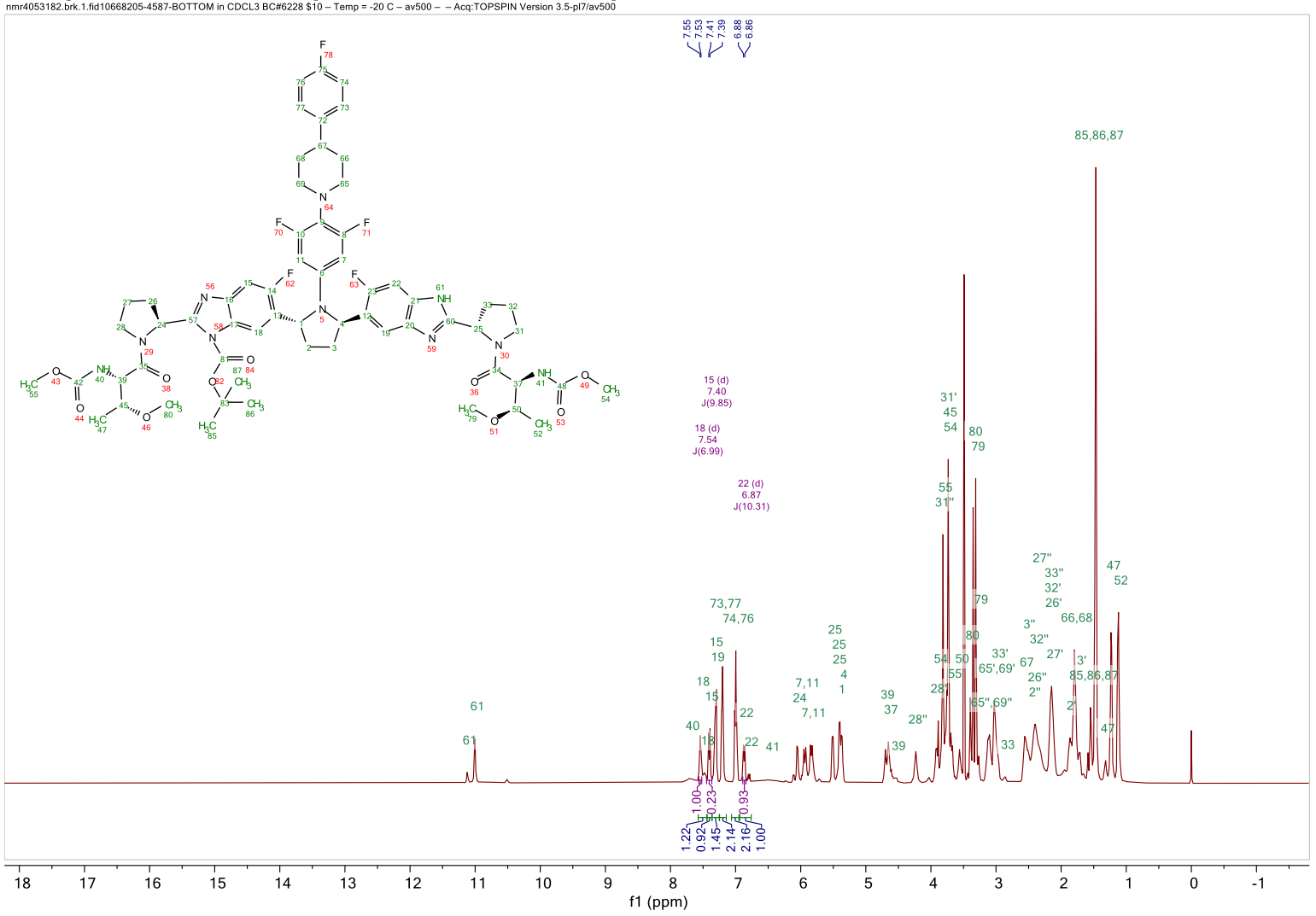


Compound 11, ^{19}F NMR ($CDCl_3$, 376 MHz)



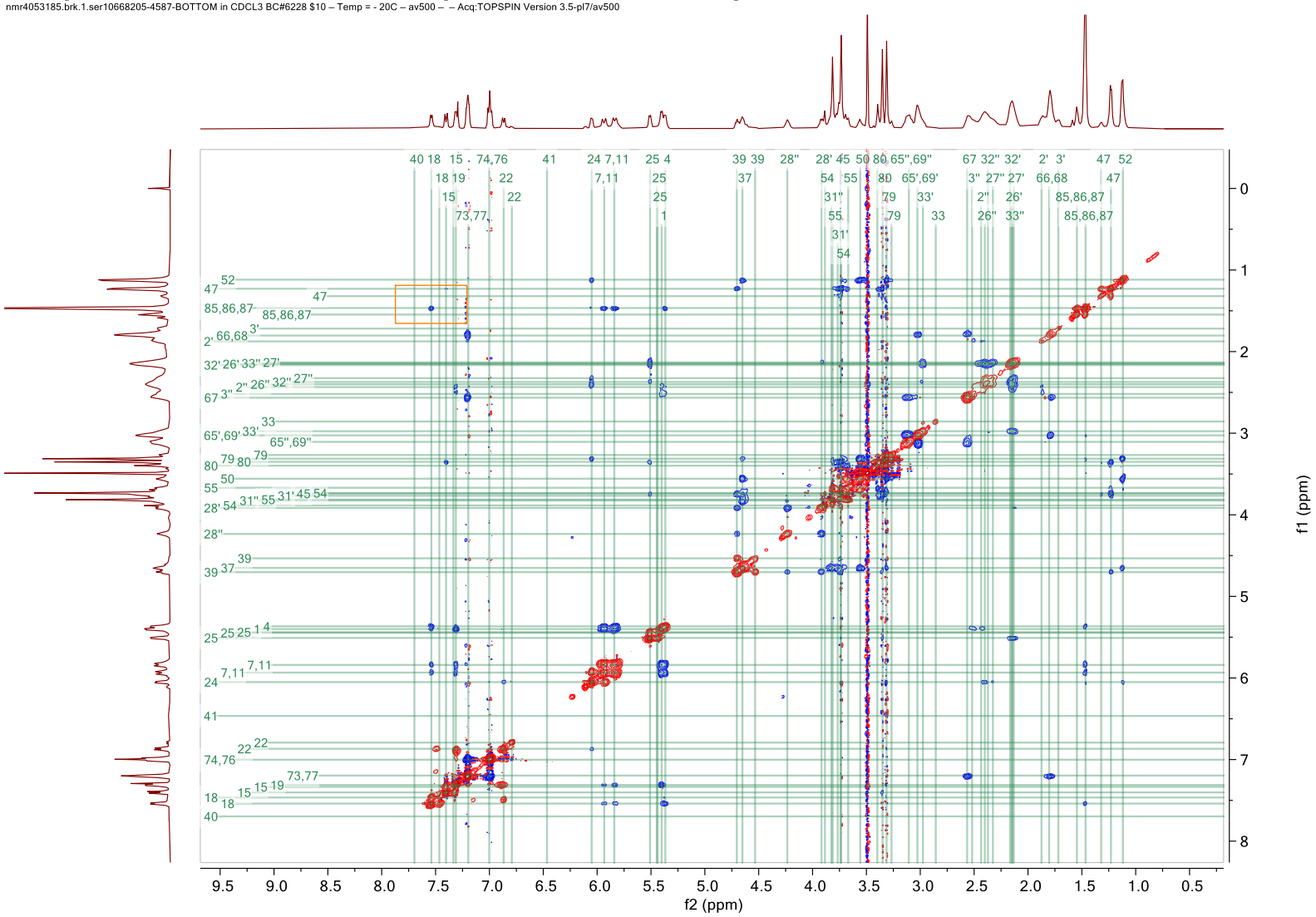
Compound 11, ^{1}H NMR ($CDCl_3$, 500 MHz, -20 ºC)

nmr4053182.brk.1.fid10668205-4587-BOTTOM in CDCL3 BC#6228 $10 – Temp = -20 C – av500 – – Acq:TOPSPIN Version 3.5-pl7/av500

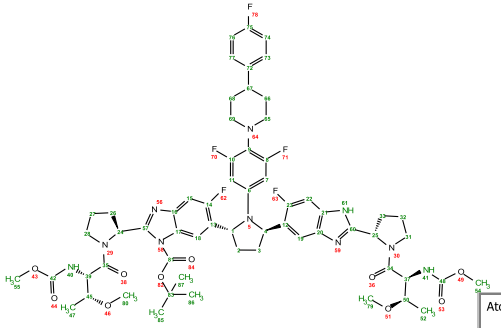


Compound 11, ^{1}H-^{1}H ROESY NMR ($CDCl_3$, 500 MHz, -20 ºC)

nmr4053185.brk.1.ser10668205-4587-BOTTOM in CDCL3 BC#6228 $10 – Temp = - 20C – av500 – – Acq:TOPSPIN Version 3.5-pl7/av500



Compound 11, - 20 ºC assignments NMR ($CDCl_3$, 500 MHz)

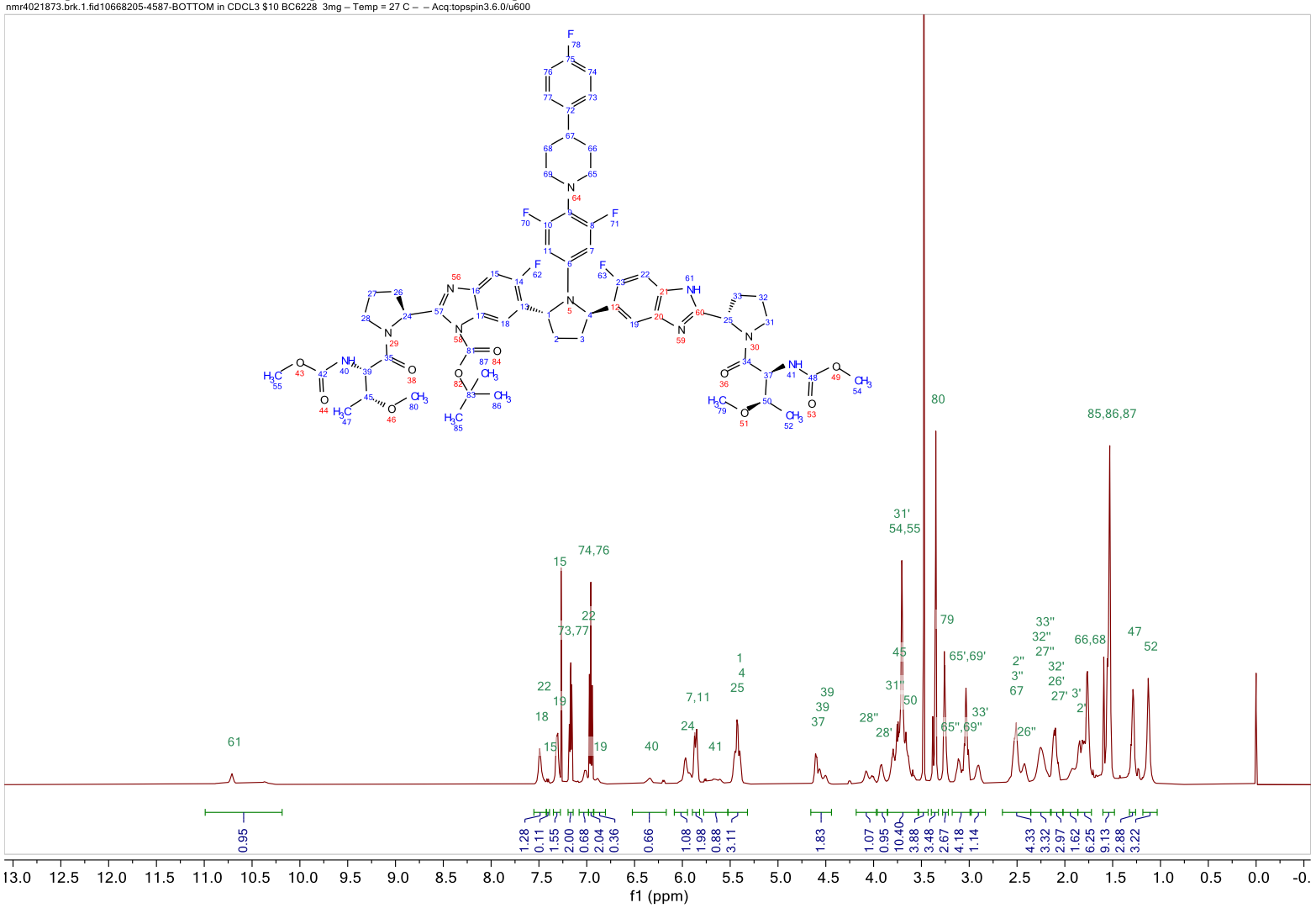


Temperature = -20C assignments

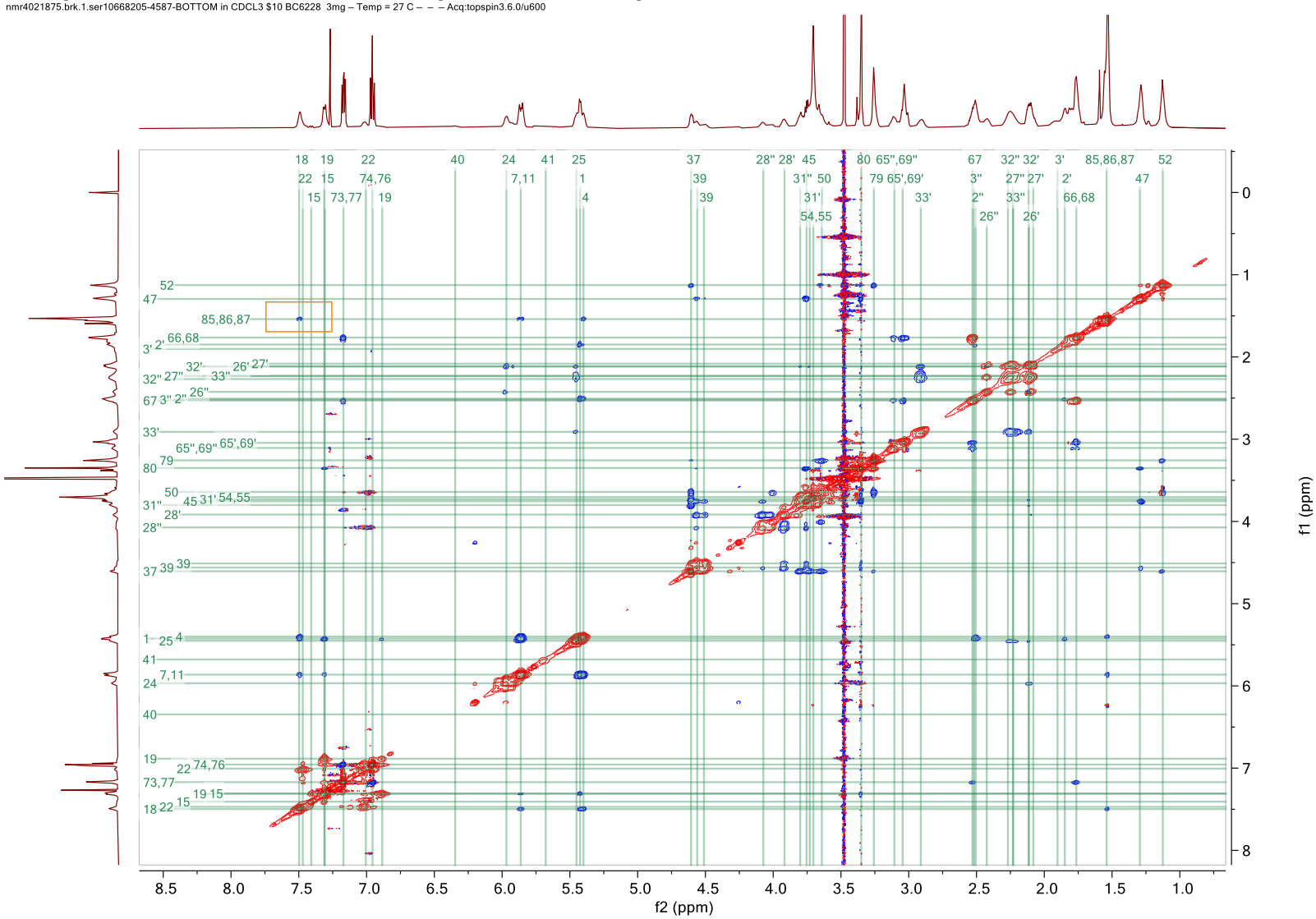
Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift	Atom	Chemical Shift
1 C	58.04	19 C	117.06	33 C	27.25	52 C	15.33	70 F	
H	5.40	H	7.31	H'	2.86, 2.98	H3	1.12	71 F	
2 C	30.92	20 C	137.69	H''	2.14, 2.86	53 O		72 C	142.24
H'	1.87	21 C	134.06, 134.61	34 C	171.09	54 C	52.70, 53.33..53.35	73 C	128.18
H''	2.43	22 C	99.24, 99.36	35 C	169.11	H3	3.73, 3.88..3.89	H	7.20
3 C	31.53	H	6.79, 6.87	36 O		55 C	52.82	74 C	115.07
H'	1.72	23 C	156.59	37 C	55.86	H3	3.67, 3.81	H	7.00
H''	2.52	24 C	56.08	H	4.65	56 N		75 C	161.24
4 C	57.84	H	6.05	38 O		57 C	157.99	76 C	115.07
H	5.37	25 C	54.55, 55.05	39 C	56.82	58 N		H	7.00
5 N		H	5.44, 5.45, 5.51	H	4.53, 4.70	59 N		77 C	128.18
6 C	141.81	26 C	30.98	40 N		60 C	153.82	H	7.20
7 C	97.86	H'	2.15	H	7.70	61 N		78 F	
H	5.84, 5.93	H''	2.40	41 N		H	11.00, 11.12	79 C	57.07
8 C	160.33	27 C	23.88	H	6.47	62 F		H3	3.27, 3.31
9 C	117.45	H'	2.13	42 C	157.33	63 F		80 C	57.20
10 C	160.33	H''	2.33	43 O		64 N		H3	3.35, 3.40
11 C	97.86	28 C	47.80	44 O		65 C	52.80	81 C	148.51
H	5.84, 5.93	H'	3.92	45 C	76.97	H'	3.03	82 O	
12 C	122.41, 122.59	H''	4.23	H	3.74	H''	3.11	83 C	85.50, 85.69
13 C	125.07	29 N		46 O		66 C	34.49	84 O	
14 C	157.52	30 N		47 C	16.15	H2	1.80	85 C	28.03
15 C	106.48	31 C	47.95	H3	1.23, 1.32	67 C	41.62	H3	1.47, 1.55
H	7.33, 7.40	H'	3.77	48 C	157.20	H	2.56	86 C	28.03
16 C	141.46	H''	3.83	49 O		68 C	34.49	H3	1.47, 1.55
17 C	128.66	32 C	25.34	50 C	77.32	H2	1.80	87 C	28.03
18 C	113.51, 114.23	H'	2.16	H	3.56	69 C	52.80	H3	1.47, 1.55
H	7.47, 7.54	H''	2.37	51 O		H'	3.03		
						H''	3.11		

Compound 11, ^{1}H-NMR ($CDCl_3$, 600 MHz):

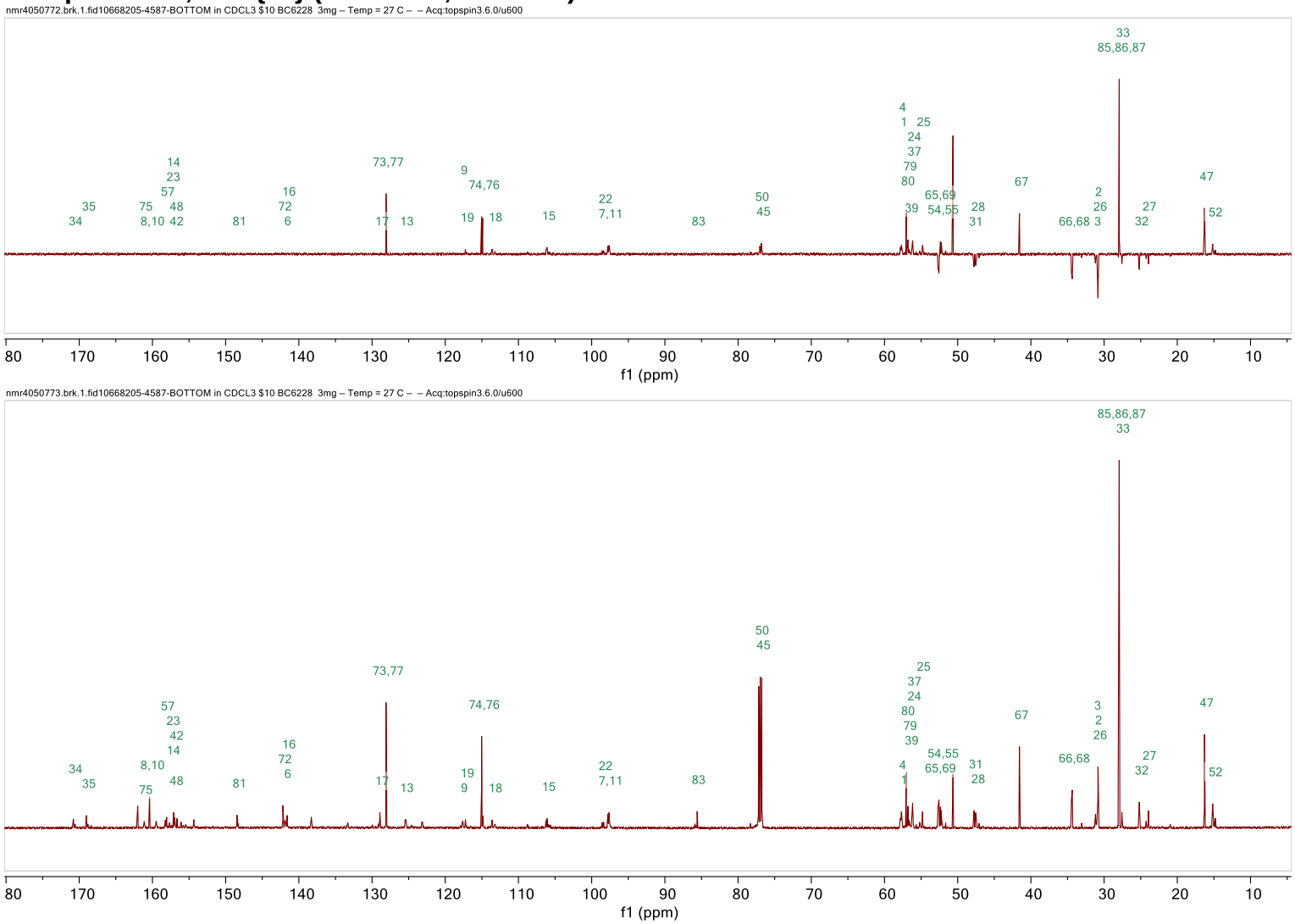
nmr4021873.brk.1.fid10668205-4587-BOTTOM in CDCL3 $10 BC6228 3mg – Temp = 27 C – – Acq:topspin3.6.0/u600



Compound 11, ^{1}H-^{1}H ROESY NMR ($CDCl_3$, 600 MHz):

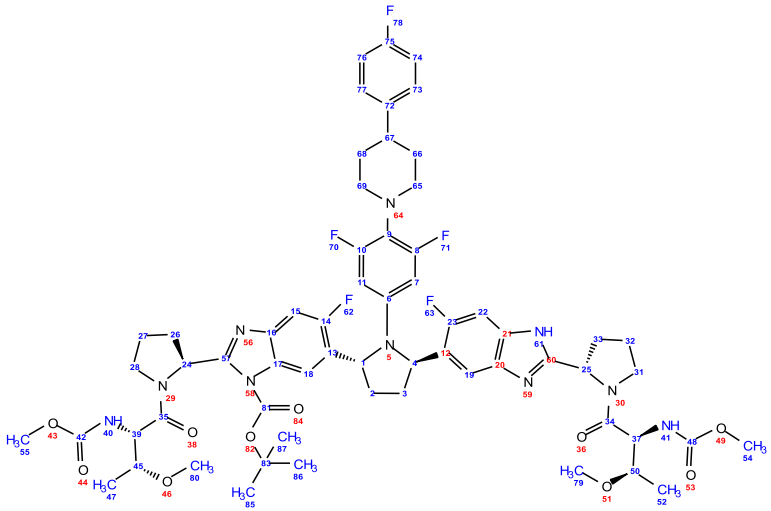


Compound 11, ^{13}C {^{1}H} (DMSO-d6, 151 MHz):



Compound 11, 27 ºC assignments NMR ($CDCl_3$, 600 MHz)

BOTTOM Temperature = 27 C



Mol Formula: $C_{62}H_{73}F_5N_{10}O_{10}$
Mono Mass: 1212.54
Molecule Name: 27C
Molecule Label: 27C

Atom	Chemical Shift
1 C	57.65
H	5.42
2 C	31.05
H'	1.85
H''	2.51
3 C	31.18
H'	1.90
H''	2.52
4 C	57.79
H	5.40
5 N	
6 C	141.81
7 C	97.76
H	5.86
8 C	160.33
9 C	117.70
10 C	160.33
11 C	97.76
H	5.86
12 C	
13 C	125.58
14 C	157.46
15 C	106.20
H	7.31, 7.41
16 C	141.69
17 C	128.98
18 C	113.47
H	7.50

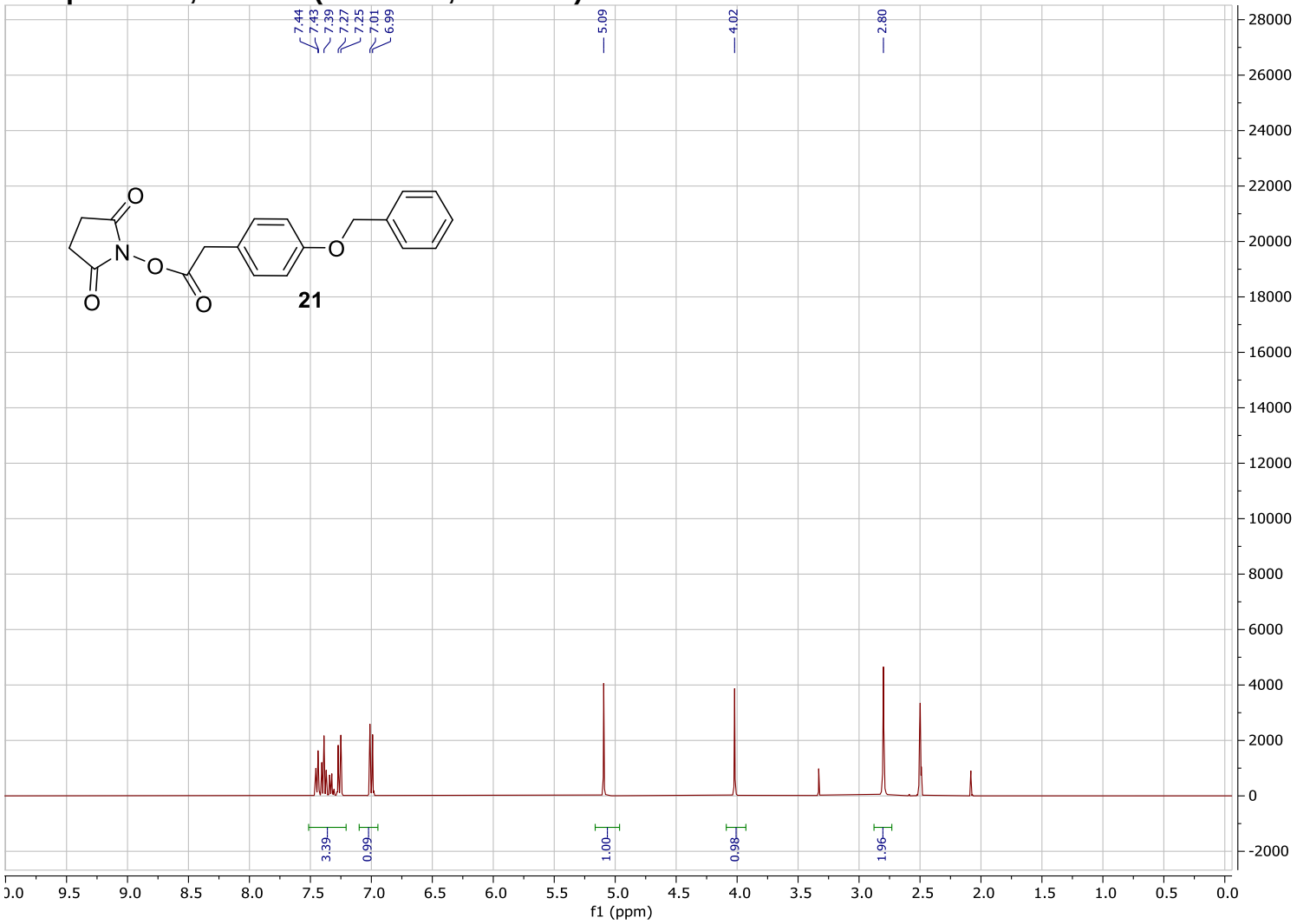
Atom	Chemical Shift
19 C	117.32
H	6.88, 7.31
20 C	
21 C	
22 C	98.43
H	7.01, 7.47
23 C	157.48
24 C	56.24
H	5.97
25 C	54.98
H	5.45
26 C	30.86
H'	2.11
H''	2.42
27 C	24.14
H'	2.08
H''	2.23
28 C	47.52
H'	3.92
H''	4.07
29 N	
30 N	
31 C	47.85
H'	3.73
H''	3.80
32 C	25.20
H'	2.12
H''	2.27

Atom	Chemical Shift
33 C	27.75
H'	2.91
H''	2.23
34 C	170.82
35 C	169.01
36 O	
37 C	56.24
H	4.61
38 O	
39 C	56.62
H	4.51, 4.56
40 N	
H	6.35
41 N	
H	5.68
42 C	157.02
43 O	
44 O	
45 C	76.85
H	3.75
46 O	
47 C	16.32
H3	1.29
48 C	157.02
49 O	
50 C	77.04
H	3.64
51 O	

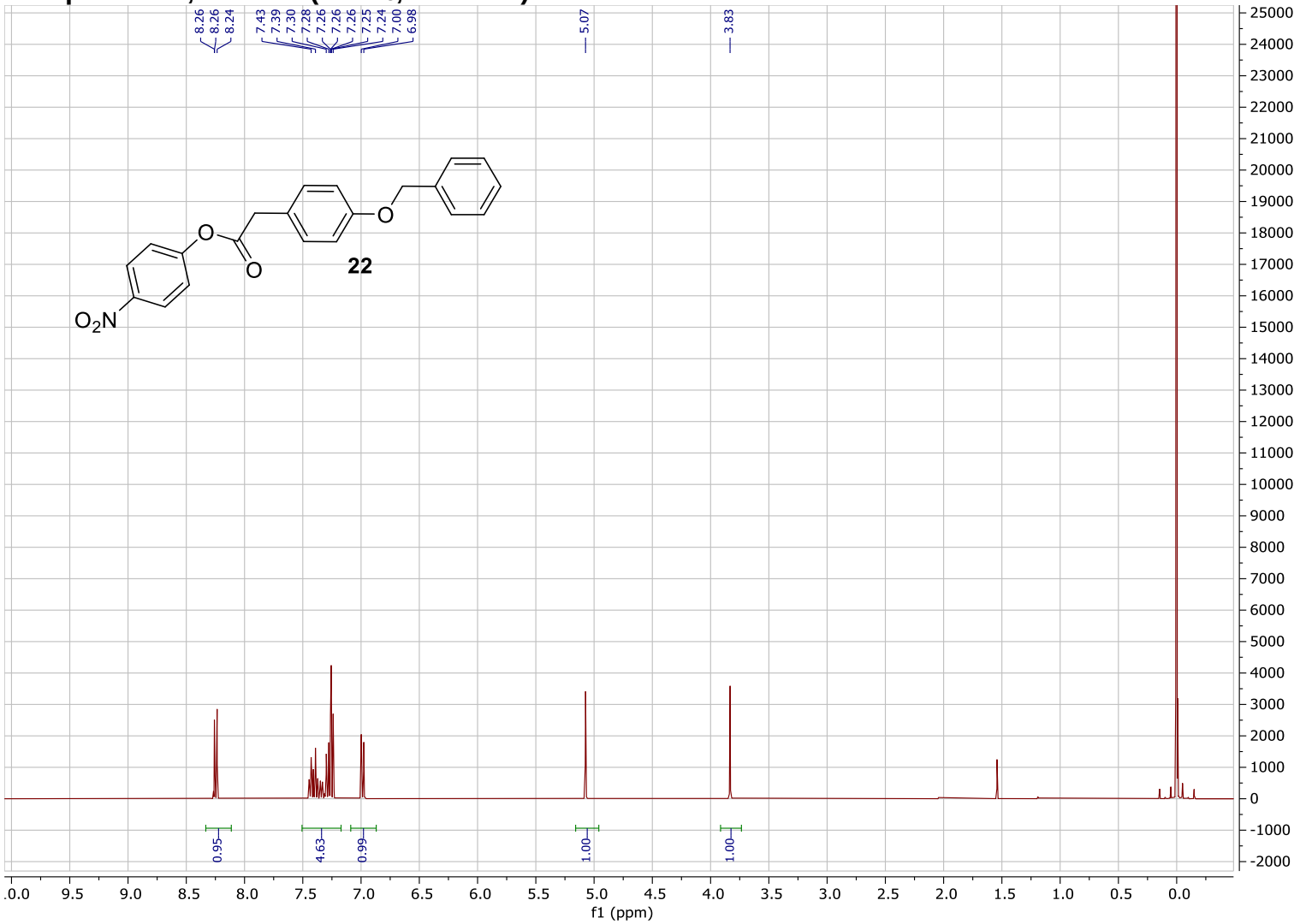
Atom	Chemical Shift
52 C	15.10
H3	1.13
53 O	
54 C	52.37
H3	3.70
55 C	52.37
H3	3.70
56 N	
57 C	158.23
58 N	
59 N	
60 C	
61 N	
H	10.71
62 F	-122.89
63 F	-123.93
64 N	
65 C	52.74
H'	3.04
H''	3.11
66 C	34.44
H2	1.76
67 C	41.62
H	2.53
68 C	34.44
H2	1.76
69 C	52.74
H'	3.04
H''	3.11

Atom	Chemical Shift
70 F	-119.47
71 F	-119.47
72 C	142.24
73 C	128.18
H	7.17
74 C	115.07
H	6.96
75 C	161.24
76 C	115.07
H	6.96
77 C	128.18
H	7.17
78 F	-117.98
79 C	56.84
H3	3.26
80 C	57.12
H3	3.35
81 C	148.45
82 O	
83 C	85.73
84 O	
85 C	28.03
H3	1.54
86 C	28.03
H3	1.54
87 C	28.03
H3	1.54

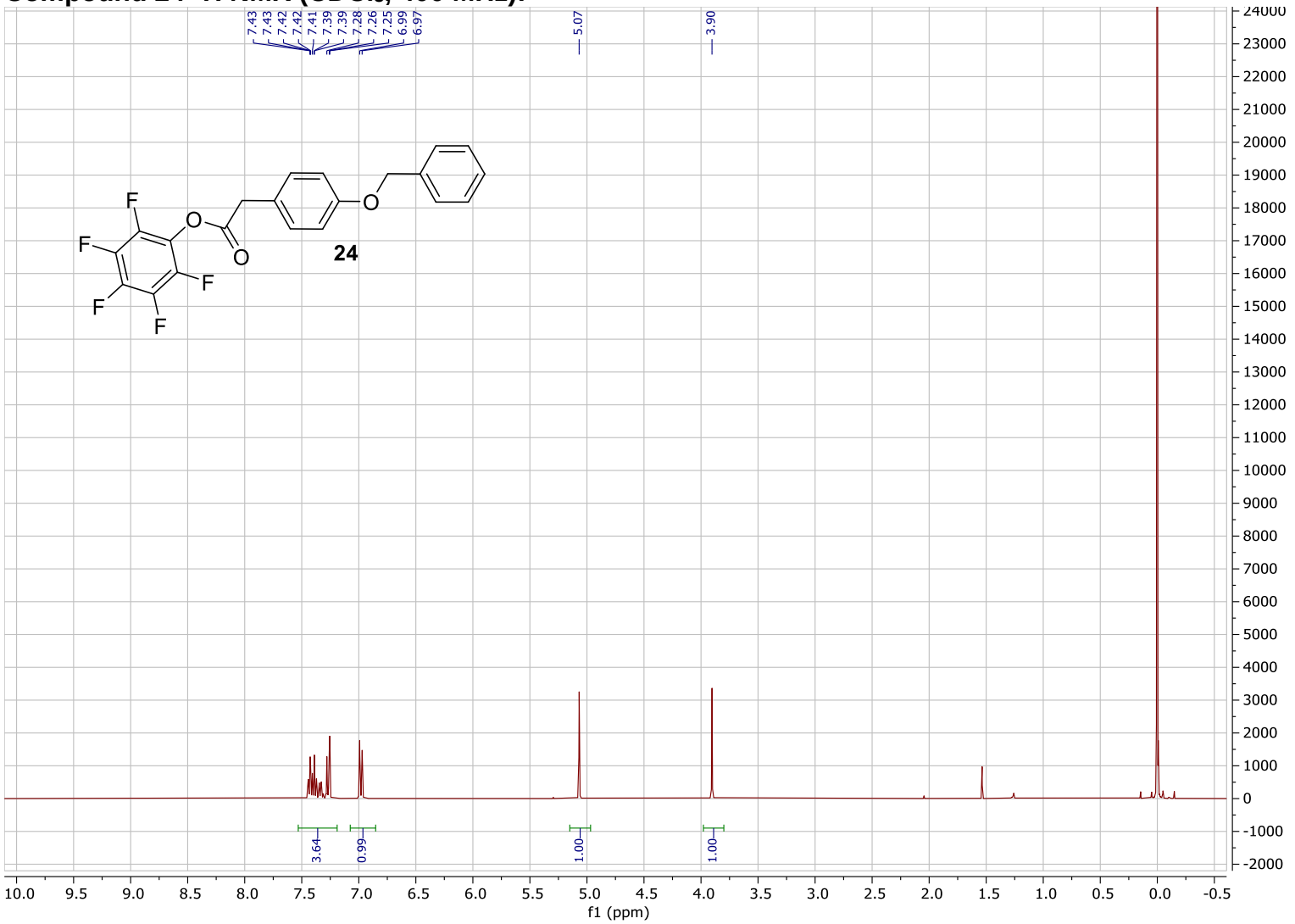
Compound 21, ^{1}H NMR (DMSO-d6, 400 MHz)



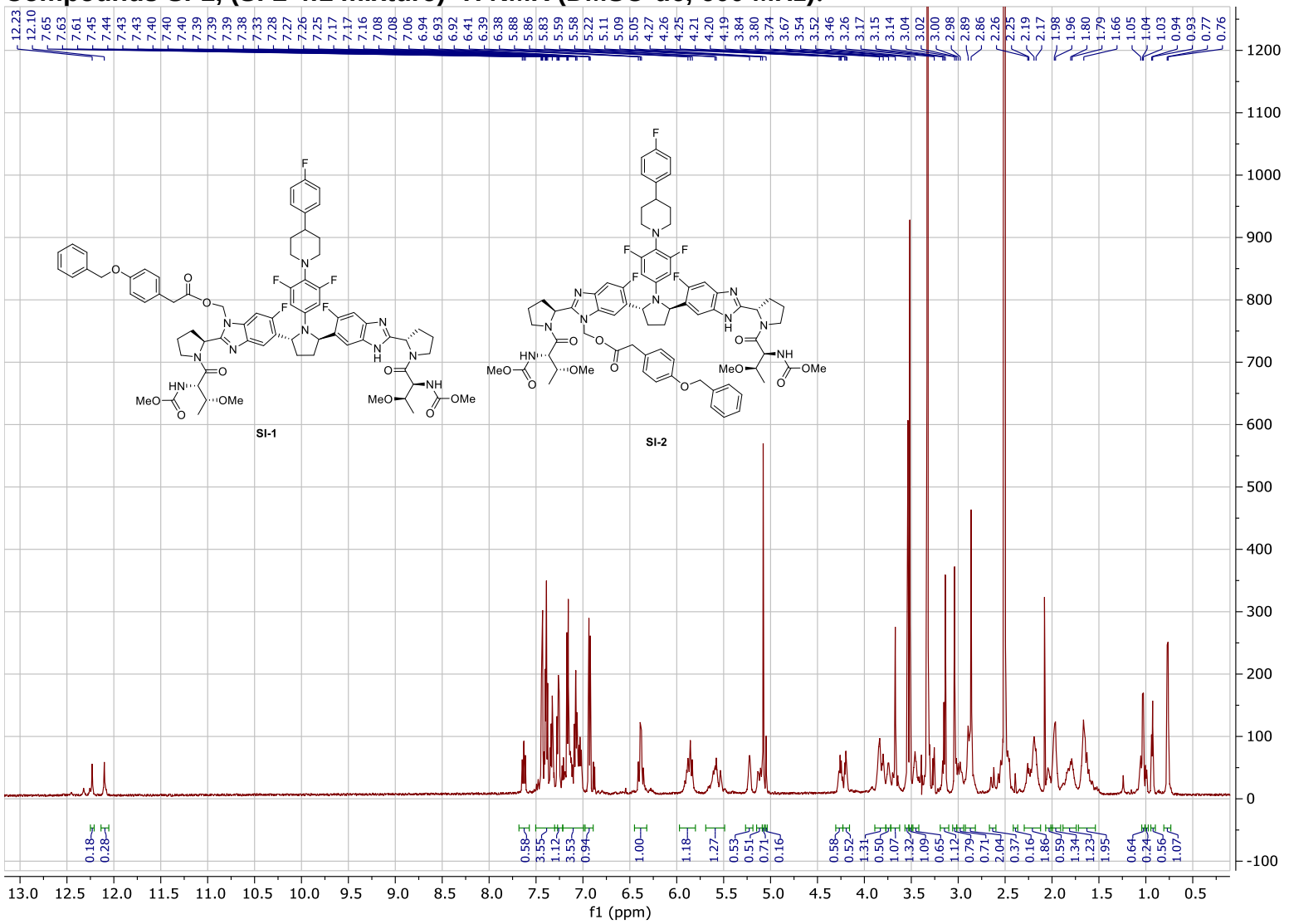
Compound 22, ^{1}H NMR ($CDCl_3$, 400 MHz):



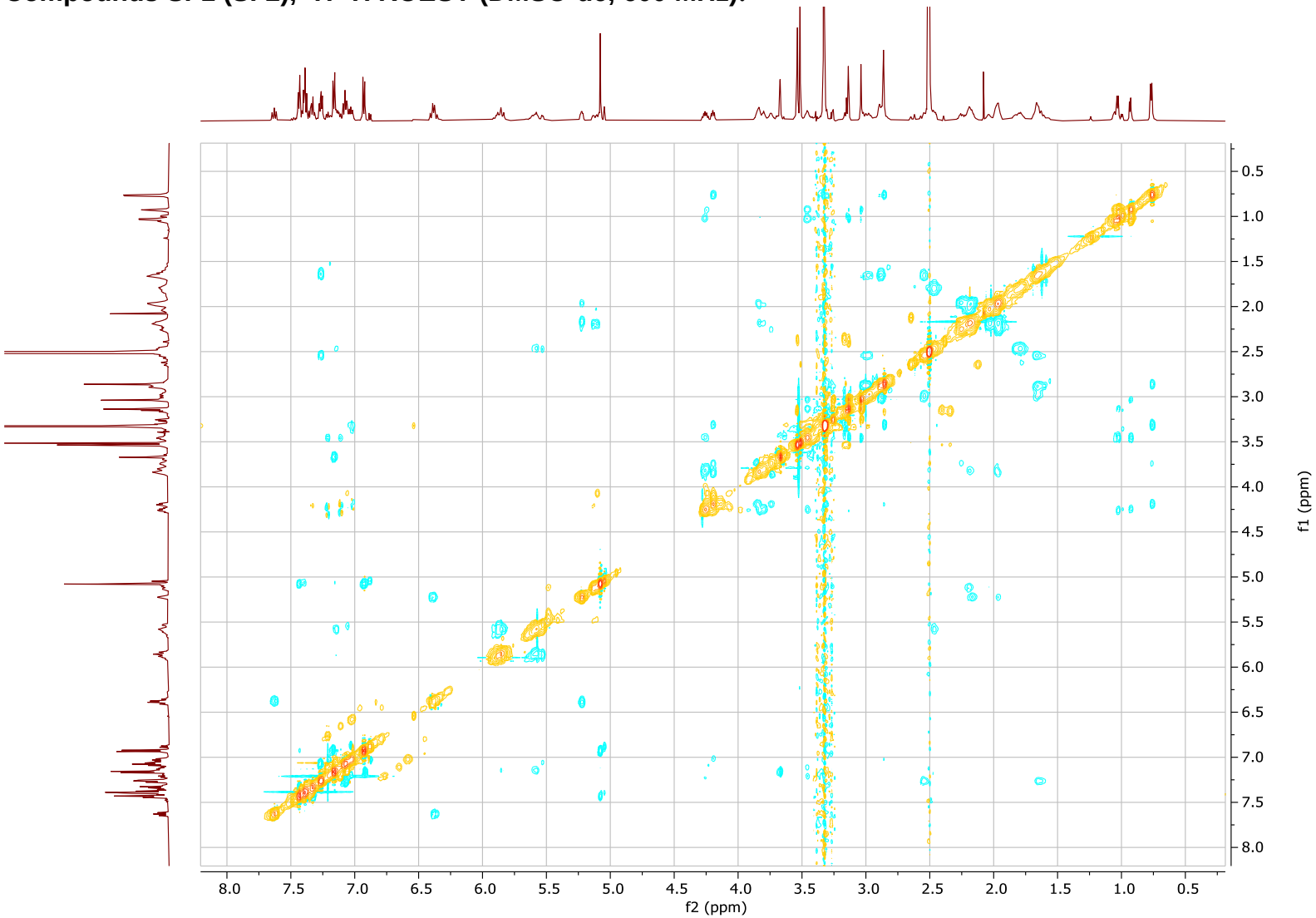
Compound 24 ^{1}H NMR ($CDCl_3$, 400 MHz):



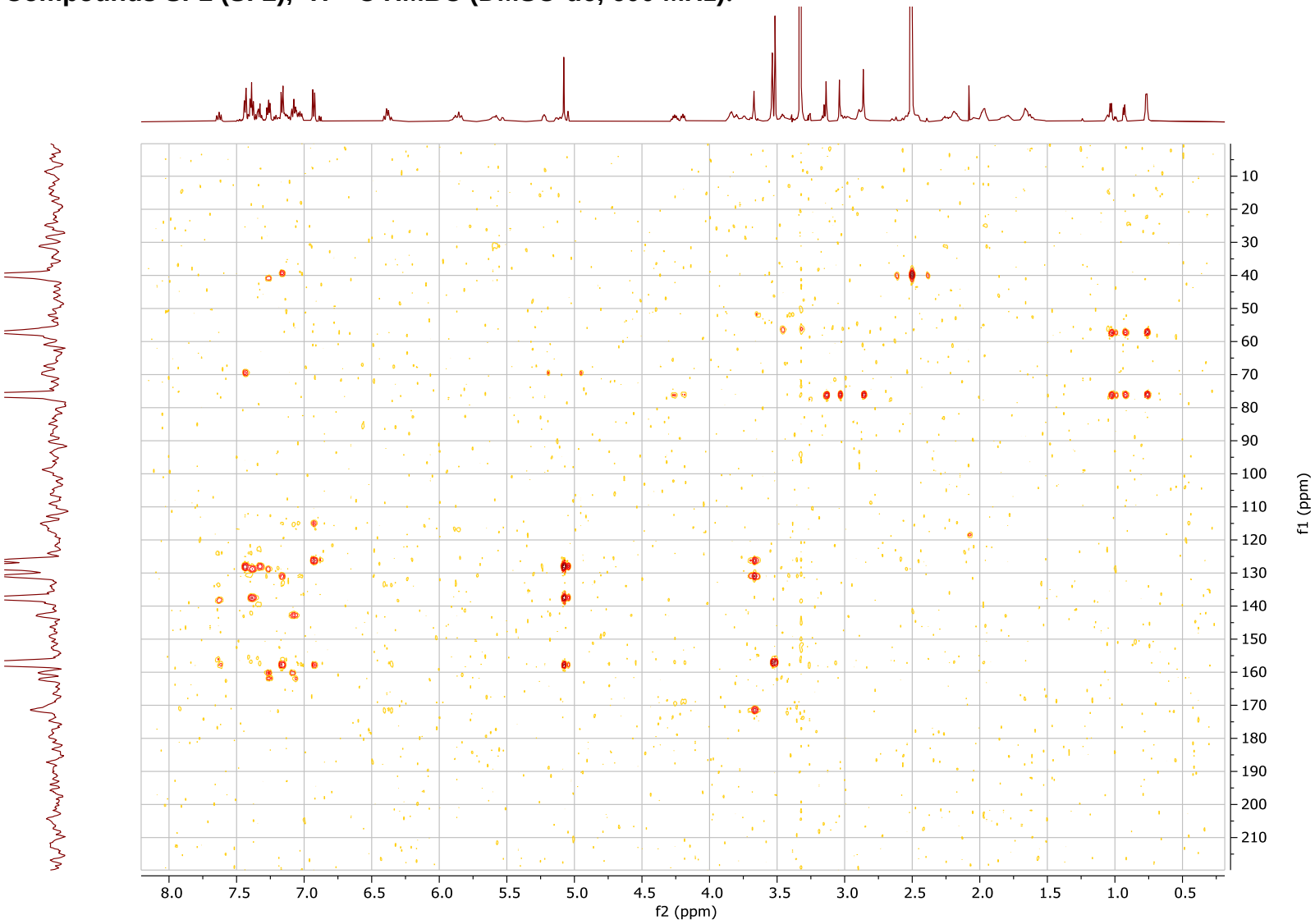
Compounds SI-1, (SI-2 4:1 mixture) ^{1}H NMR (DMSO-d6, 600 MHz):



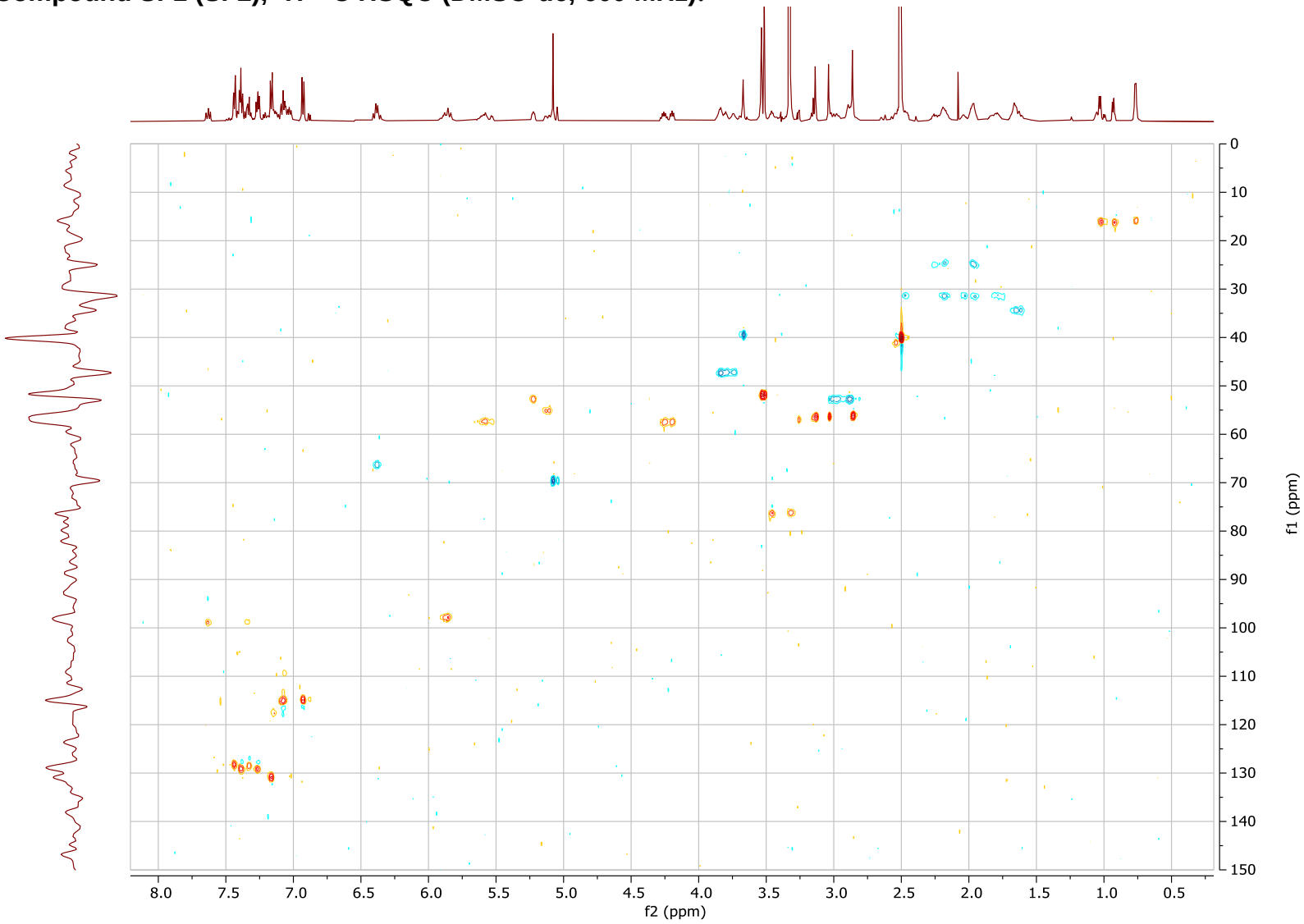
Compounds SI-1 (SI-2), ^{1}H-^{1}H ROESY (DMSO-d6, 600 MHz):



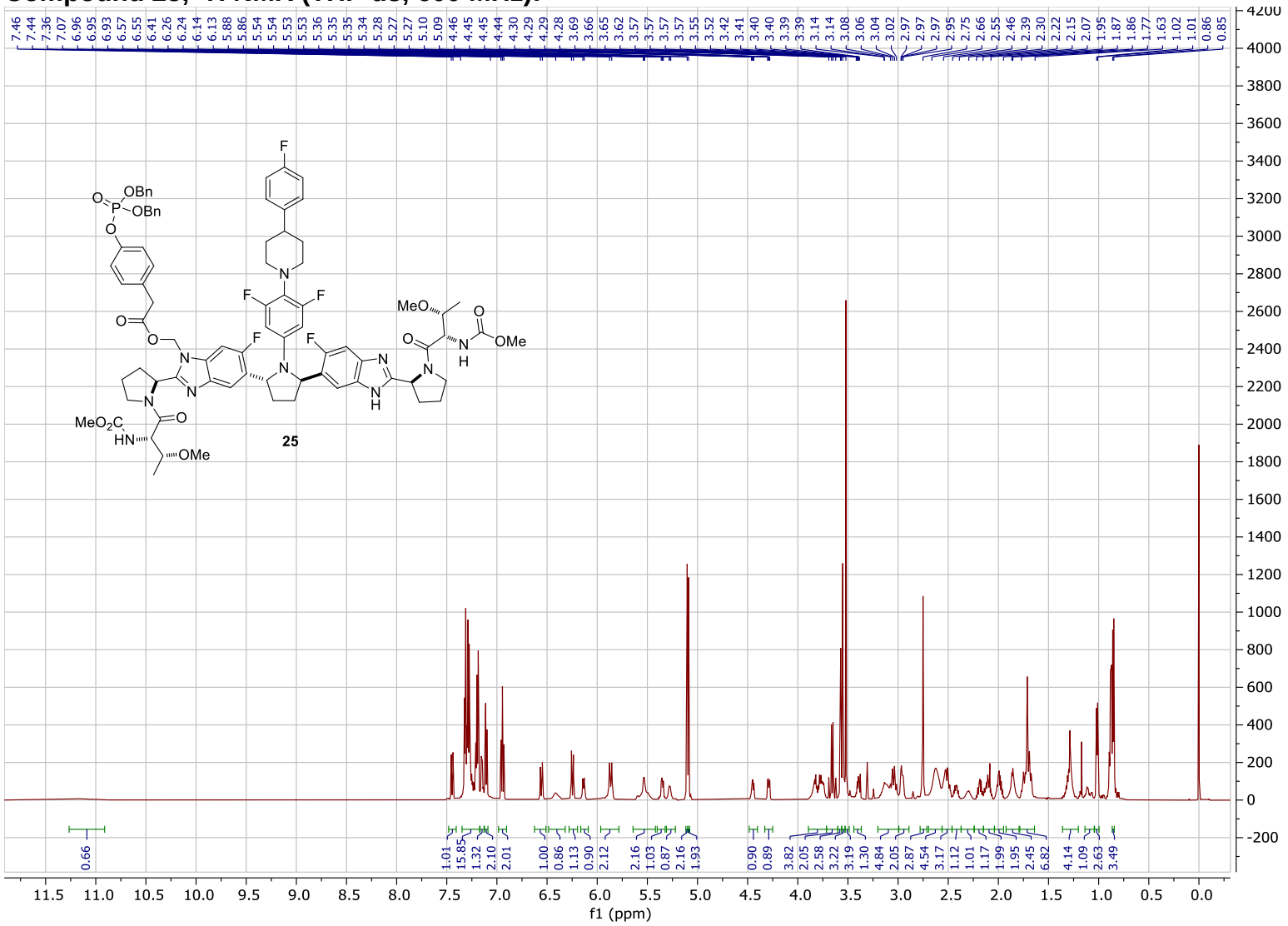
Compounds SI-1 (SI-2), ^{1}H-^{13}C HMBC (DMSO-d6, 600 MHz):



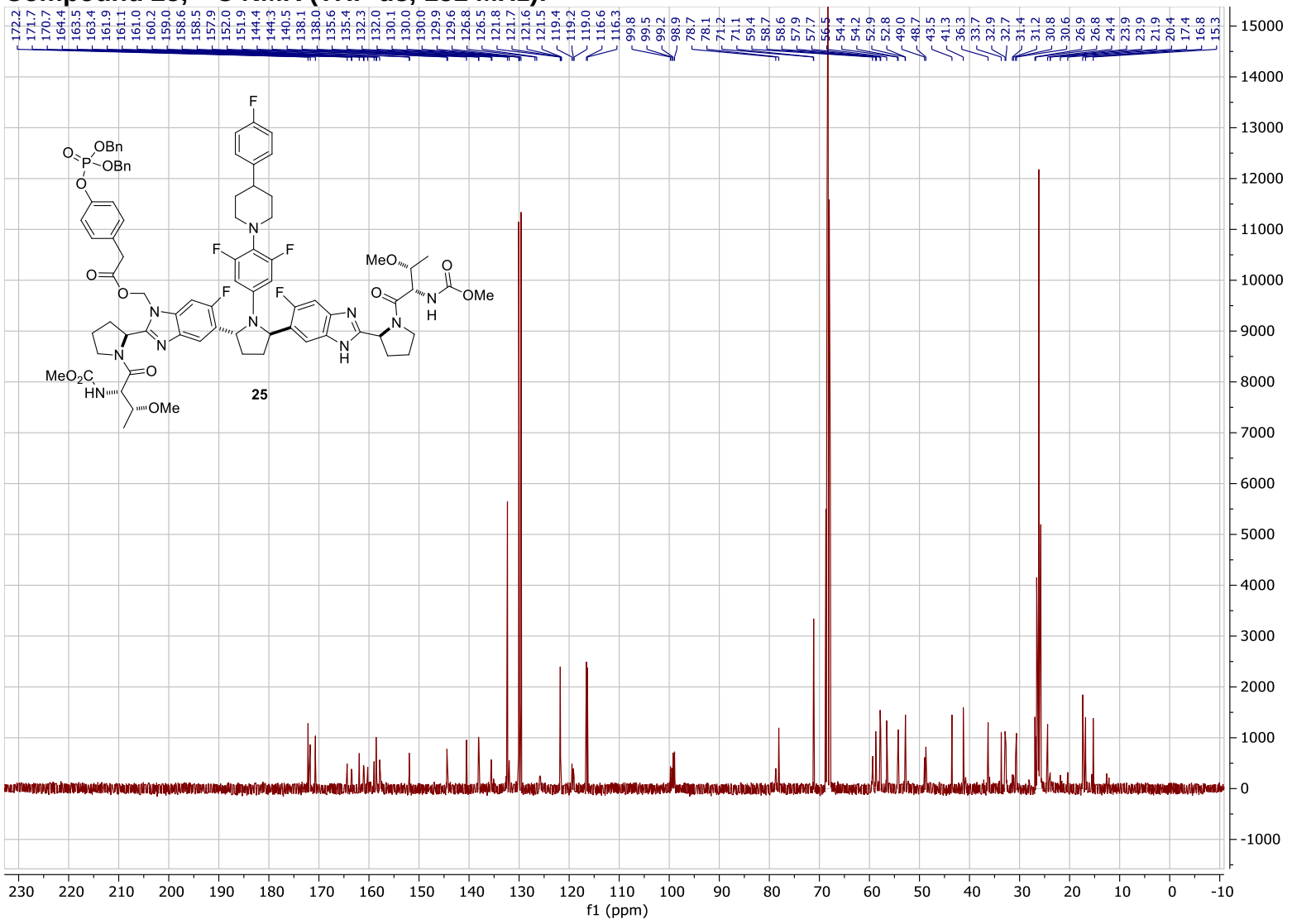
Compound SI-1 (SI-2), ^{1}H-^{13}C HSQC (DMSO-d6, 600 MHz):



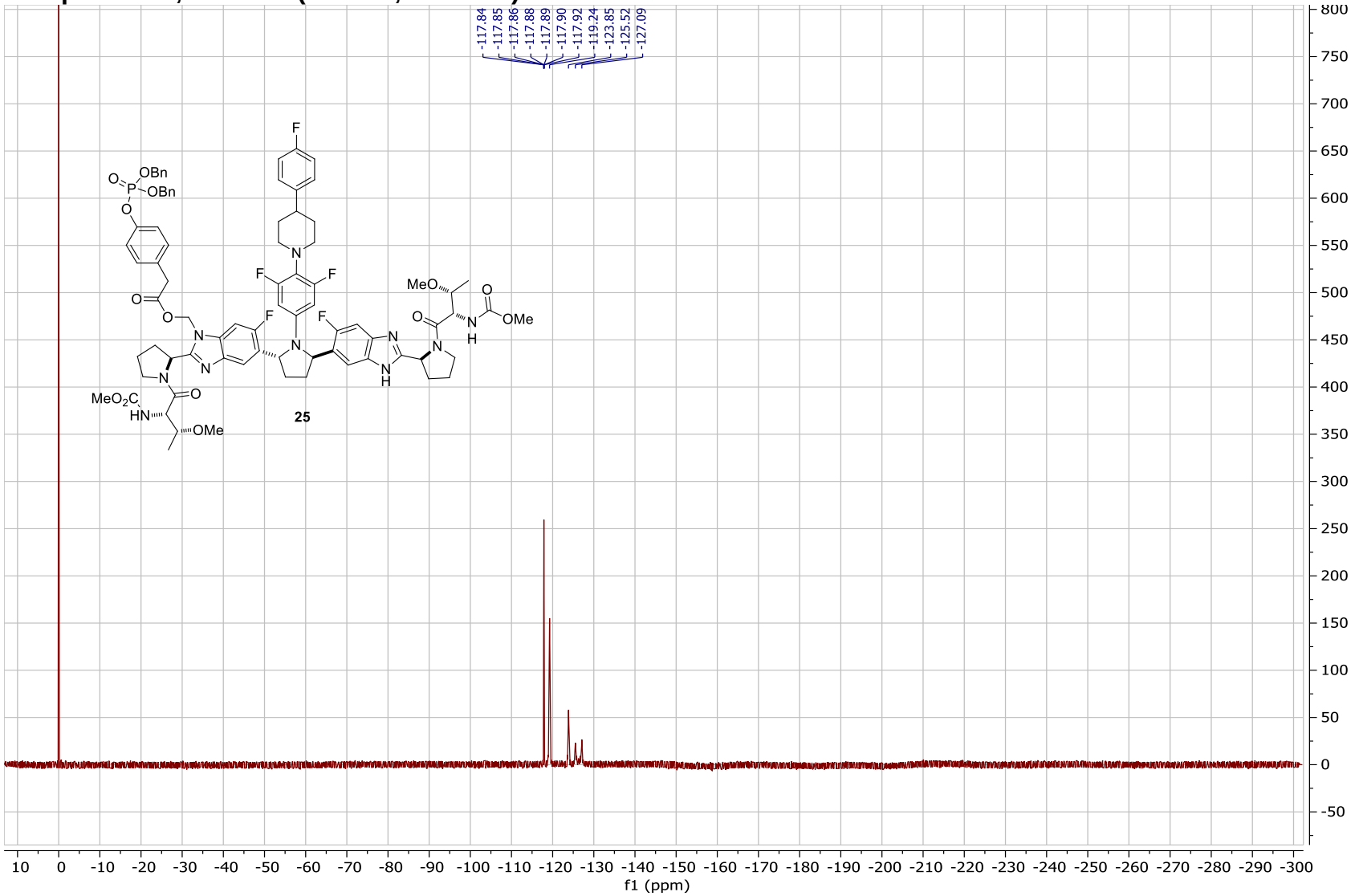
Compound 25, ^{1}H NMR (THF-d8, 600 MHz):



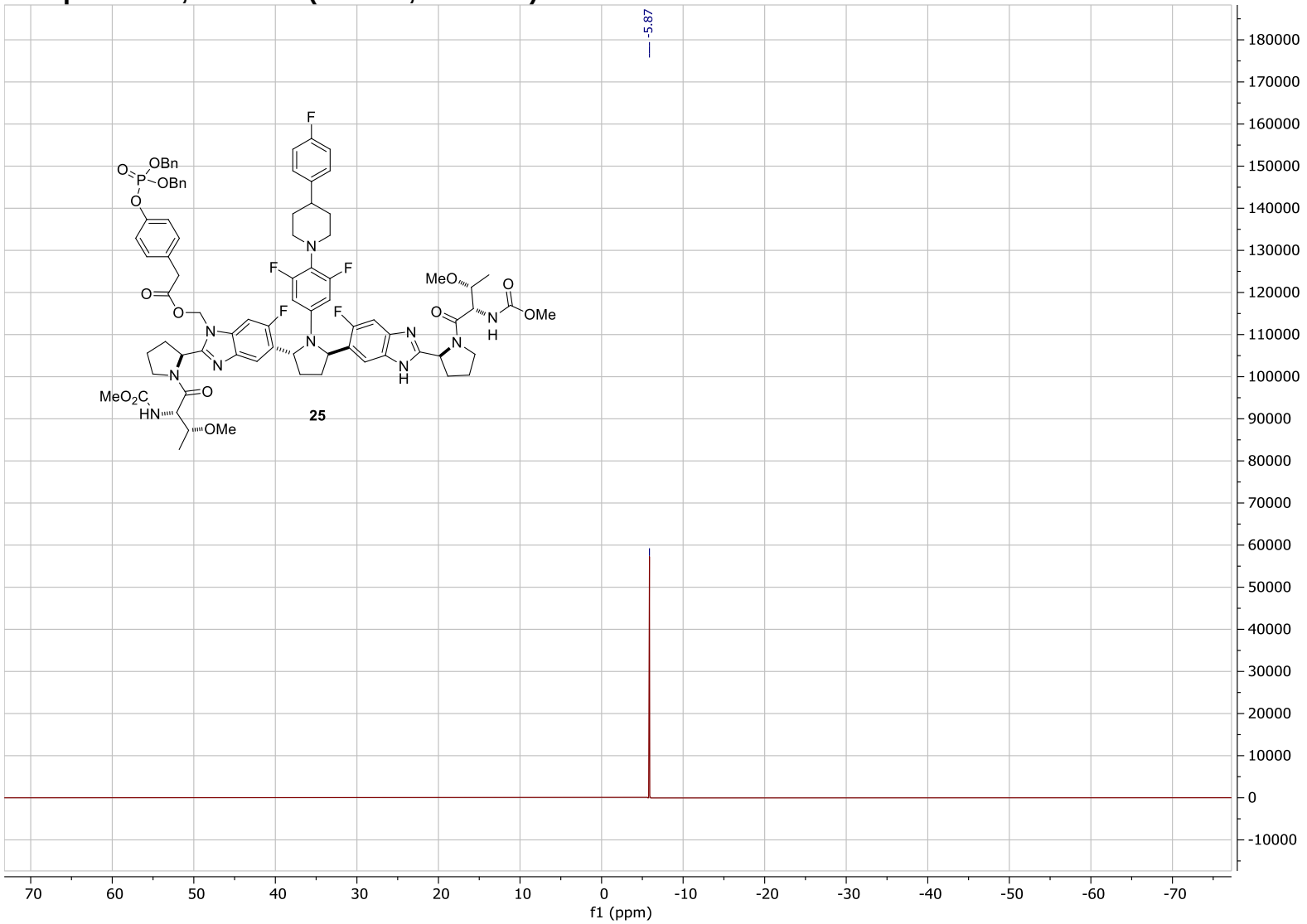
Compound 25, ^{13}C NMR (THF-d8, 151 MHz):



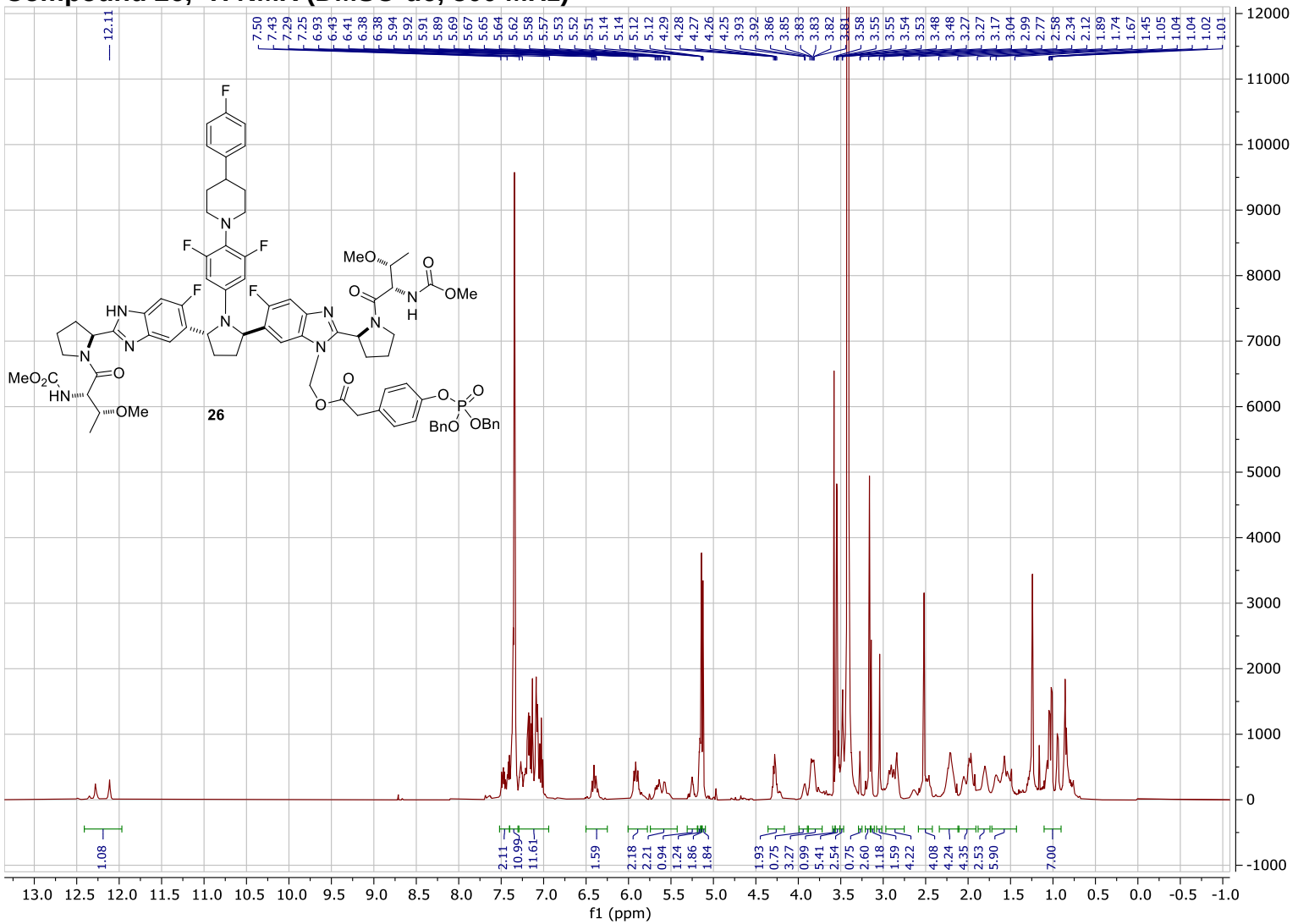
Compound 25, ^{19}F NMR (THF-d8, 376 MHz)



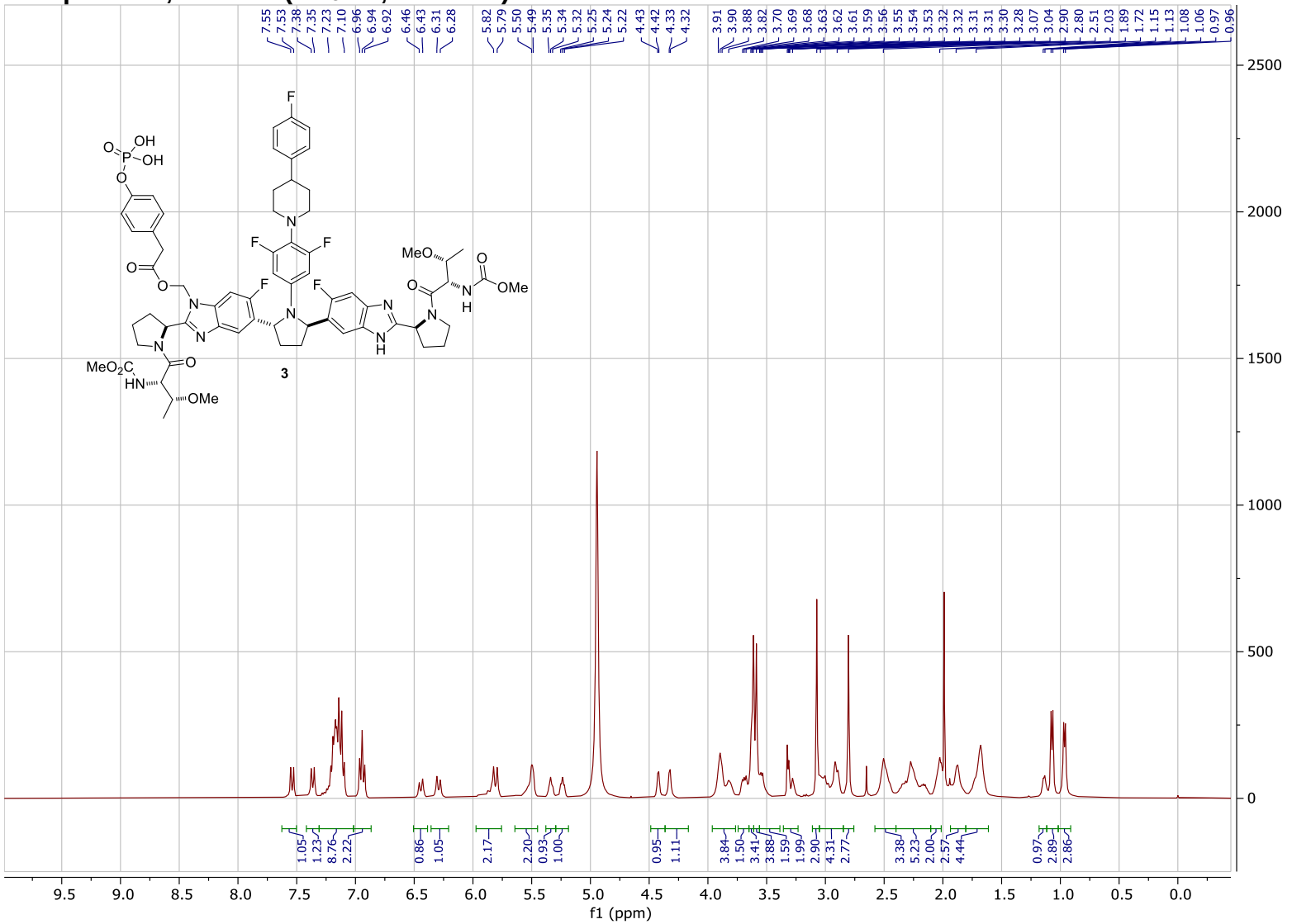
Compound 25, ^{31}P NMR (THF-d8, 162 MHz):



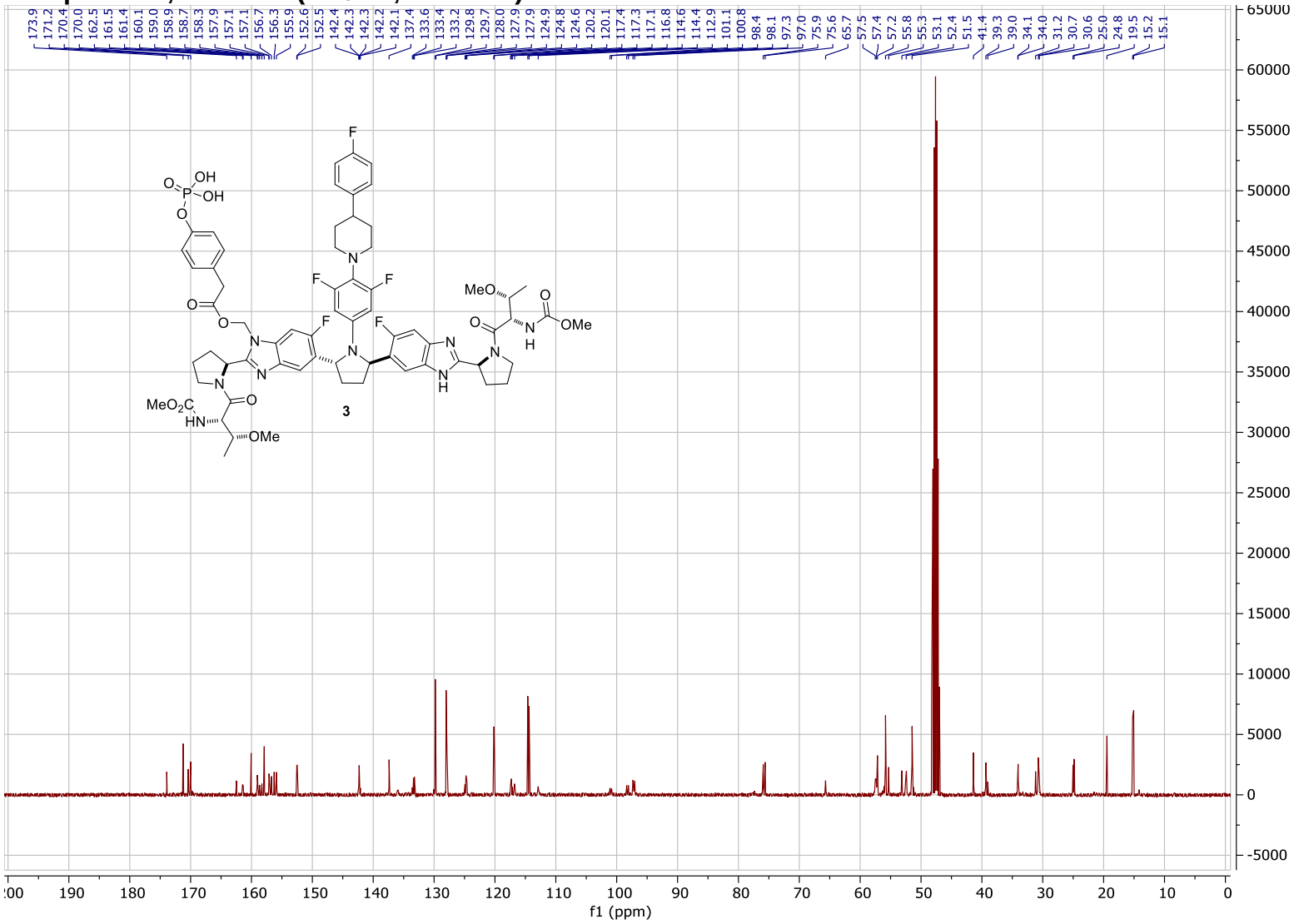
Compound 26, ^{1}H NMR (DMSO-d6, 500 MHz)



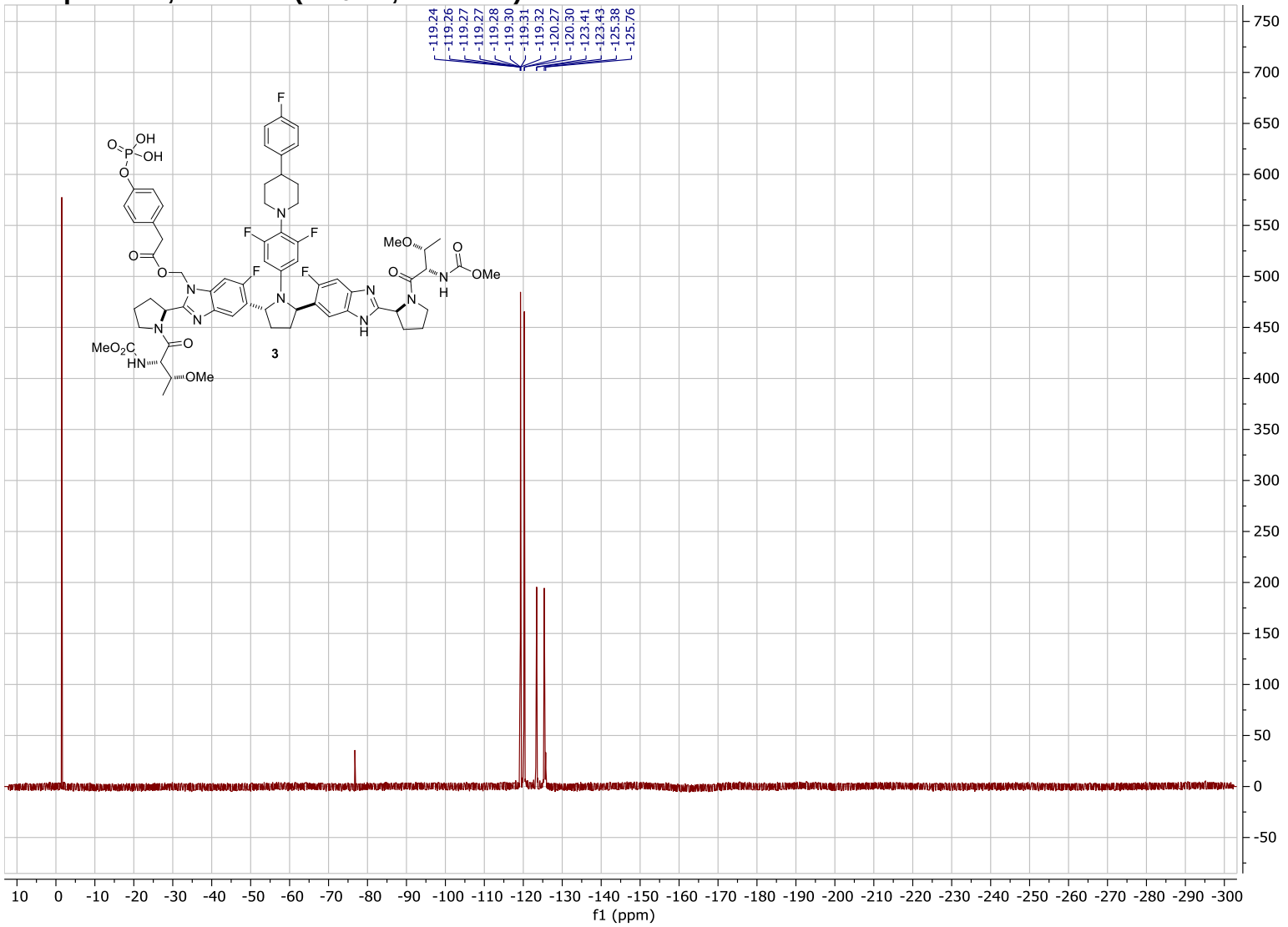
Compound 3, ^{1}H NMR (CD_3OD, 400 MHz):



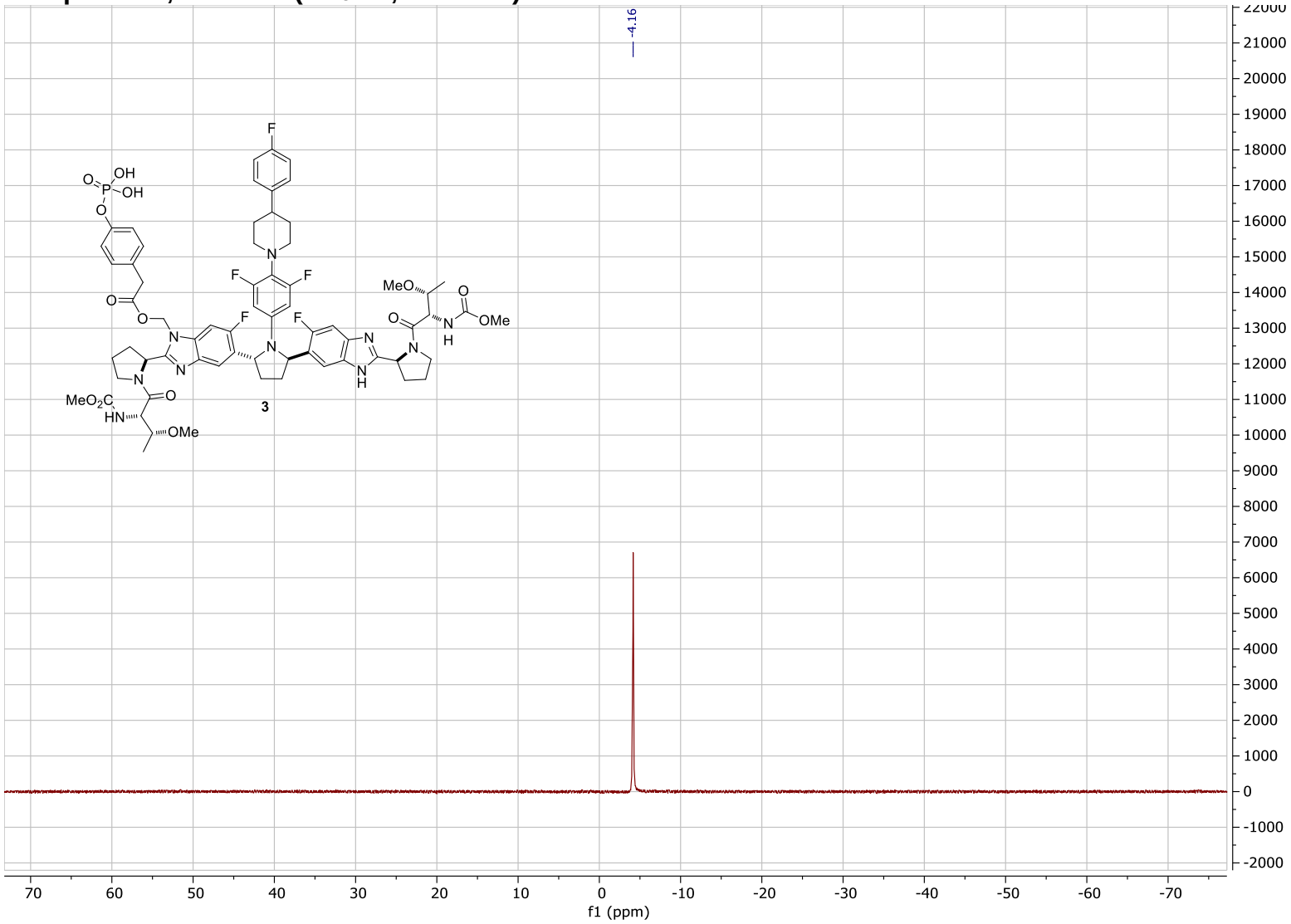
Compound 3, ^{13}C NMR (CD_3OD, 101 MHz):



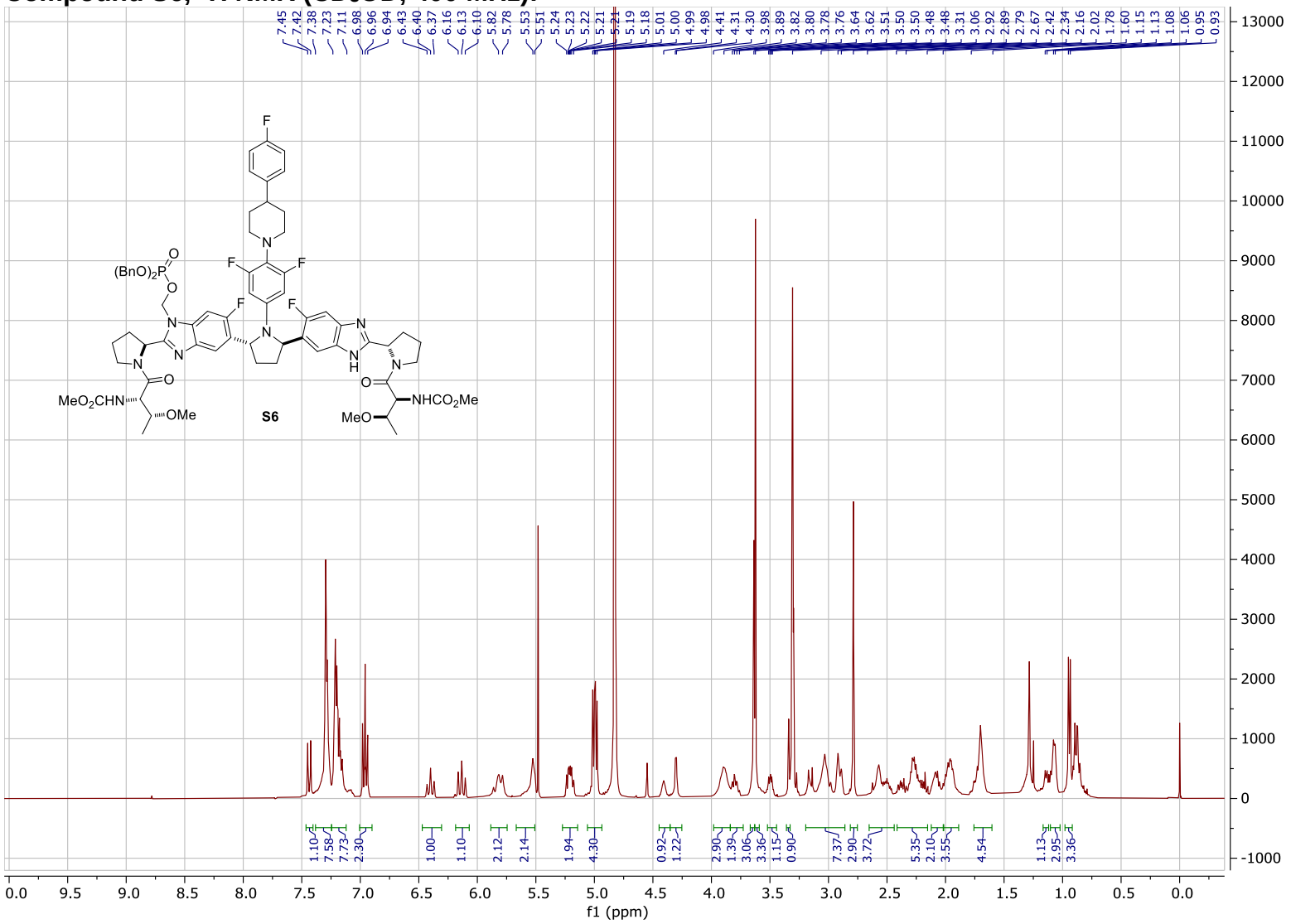
Compound 3, ^{19}F NMR (CD_3OD, 376 MHz):



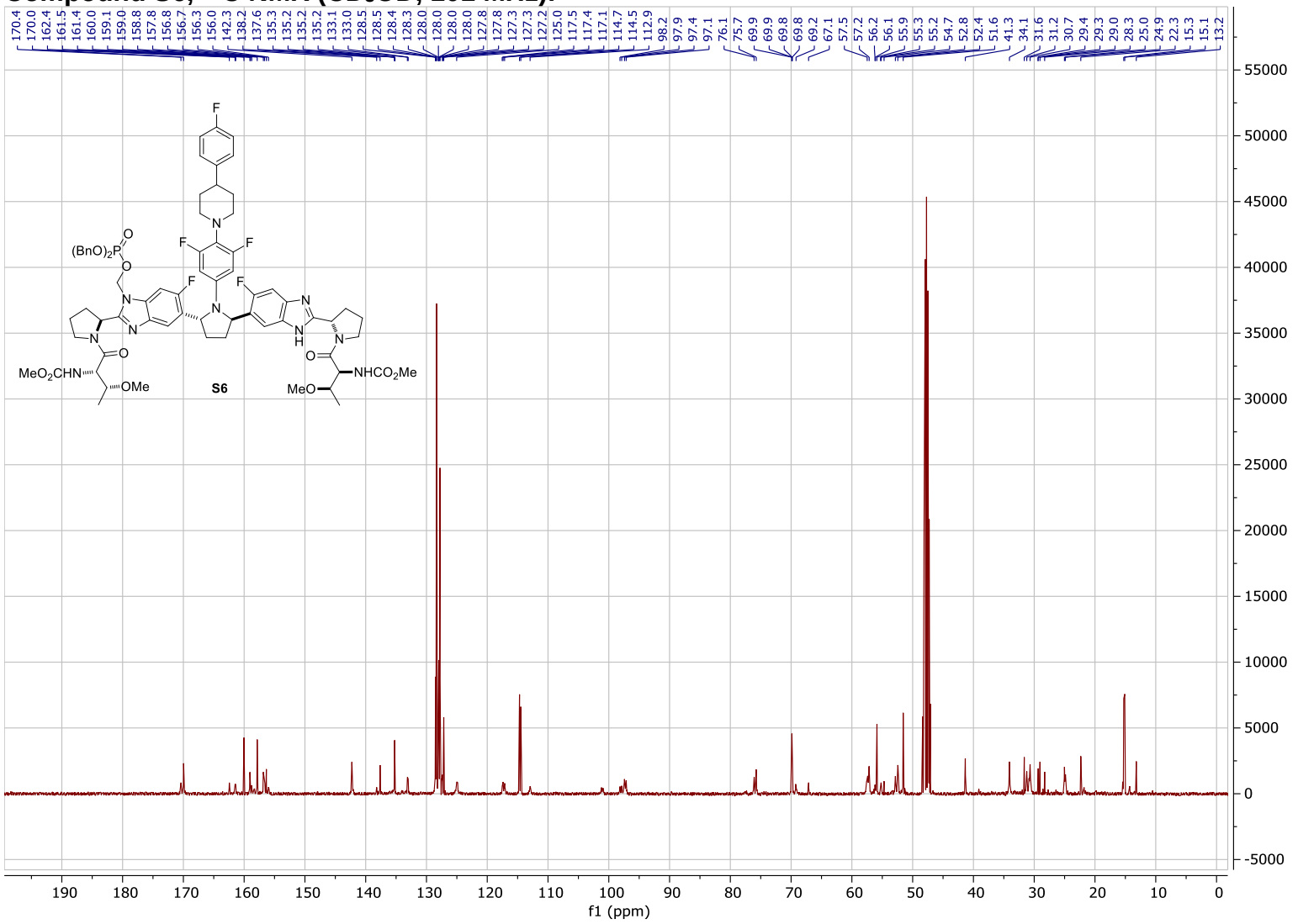
Compound 3, ^{31}P NMR (CD_3OD, 162 MHz):



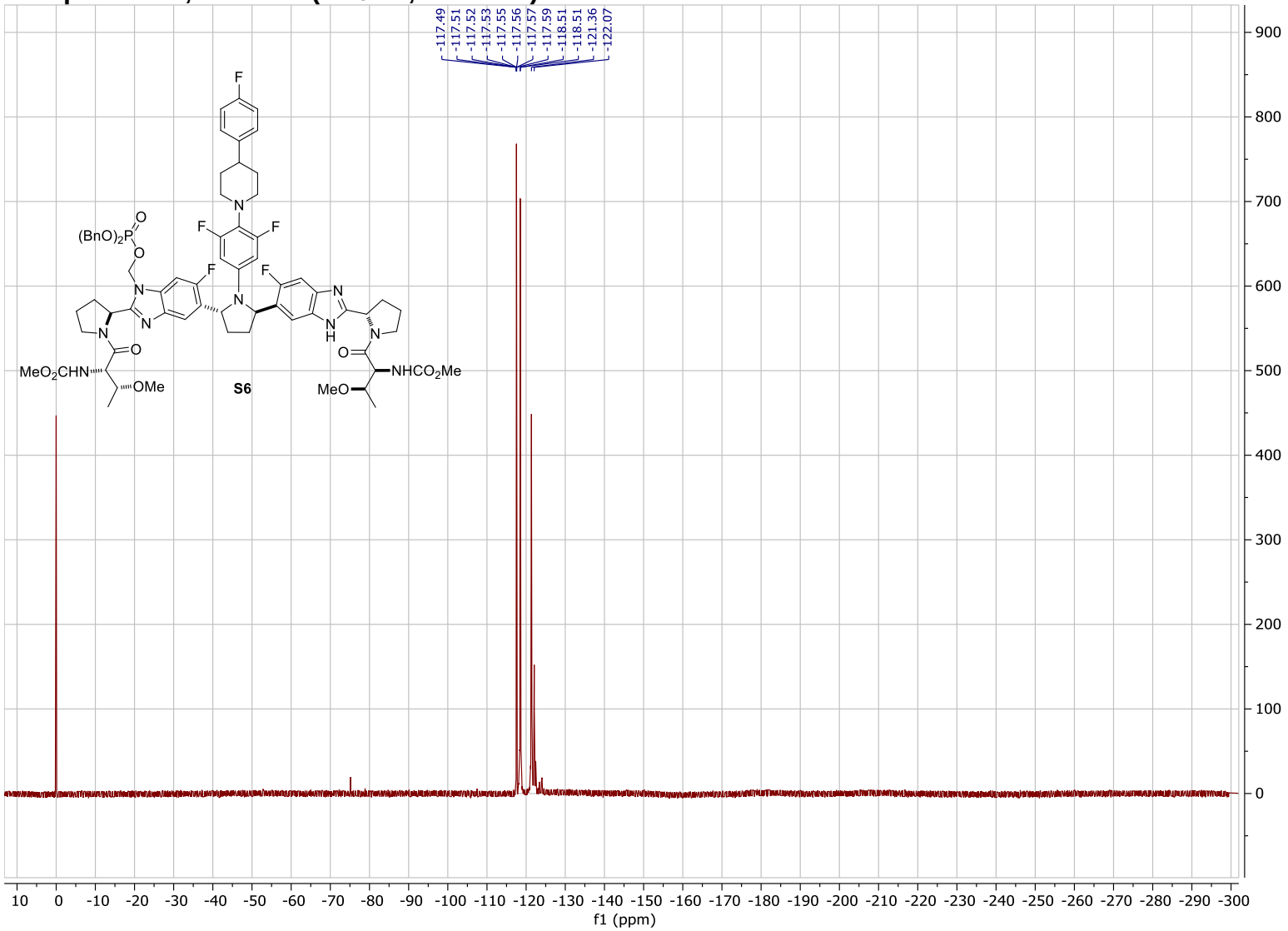
Compound S6, ^{1}H NMR (CD_3OD, 400 MHz):



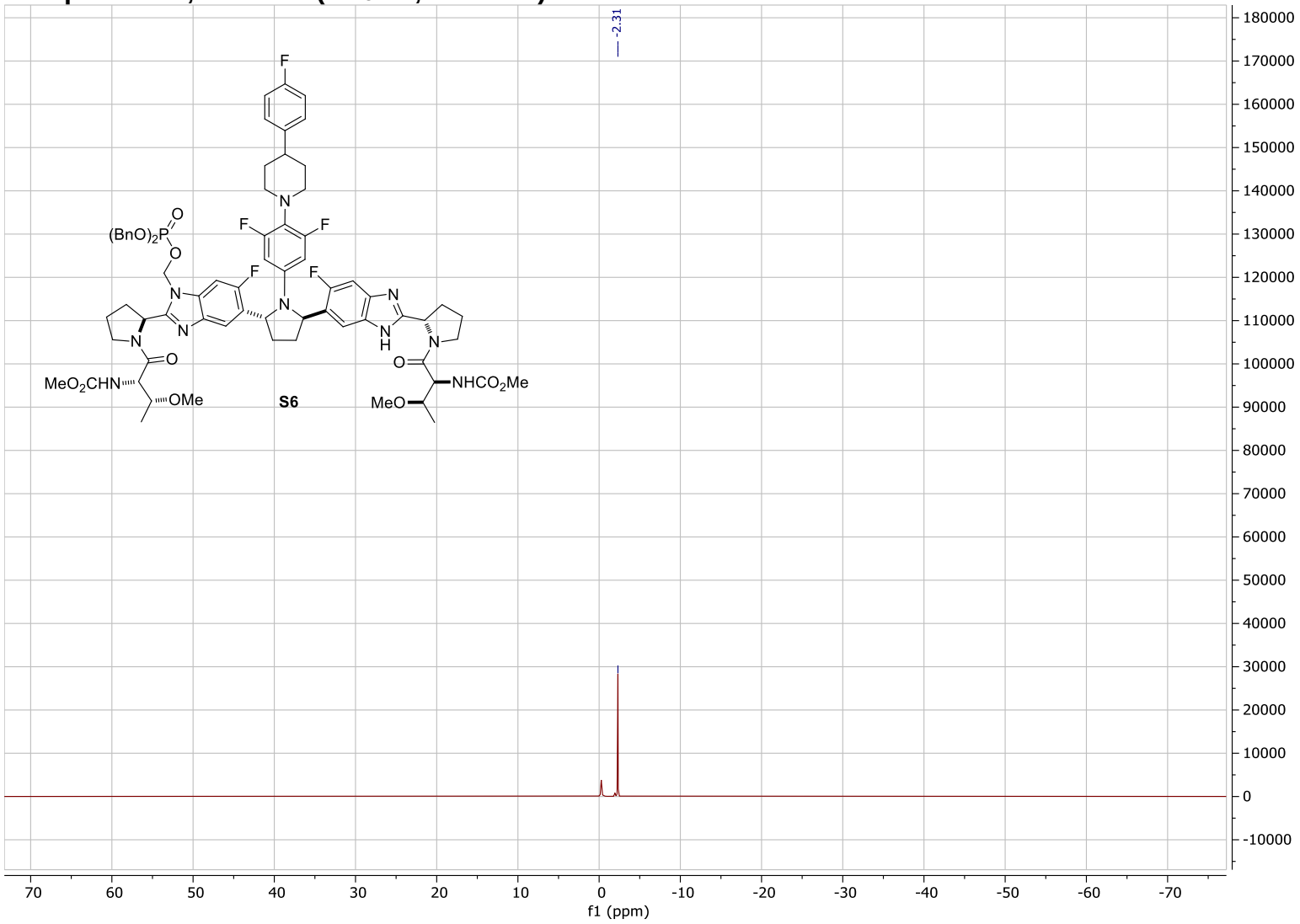
Compound S6, ^{13}C NMR (CD_3OD, 101 MHz):



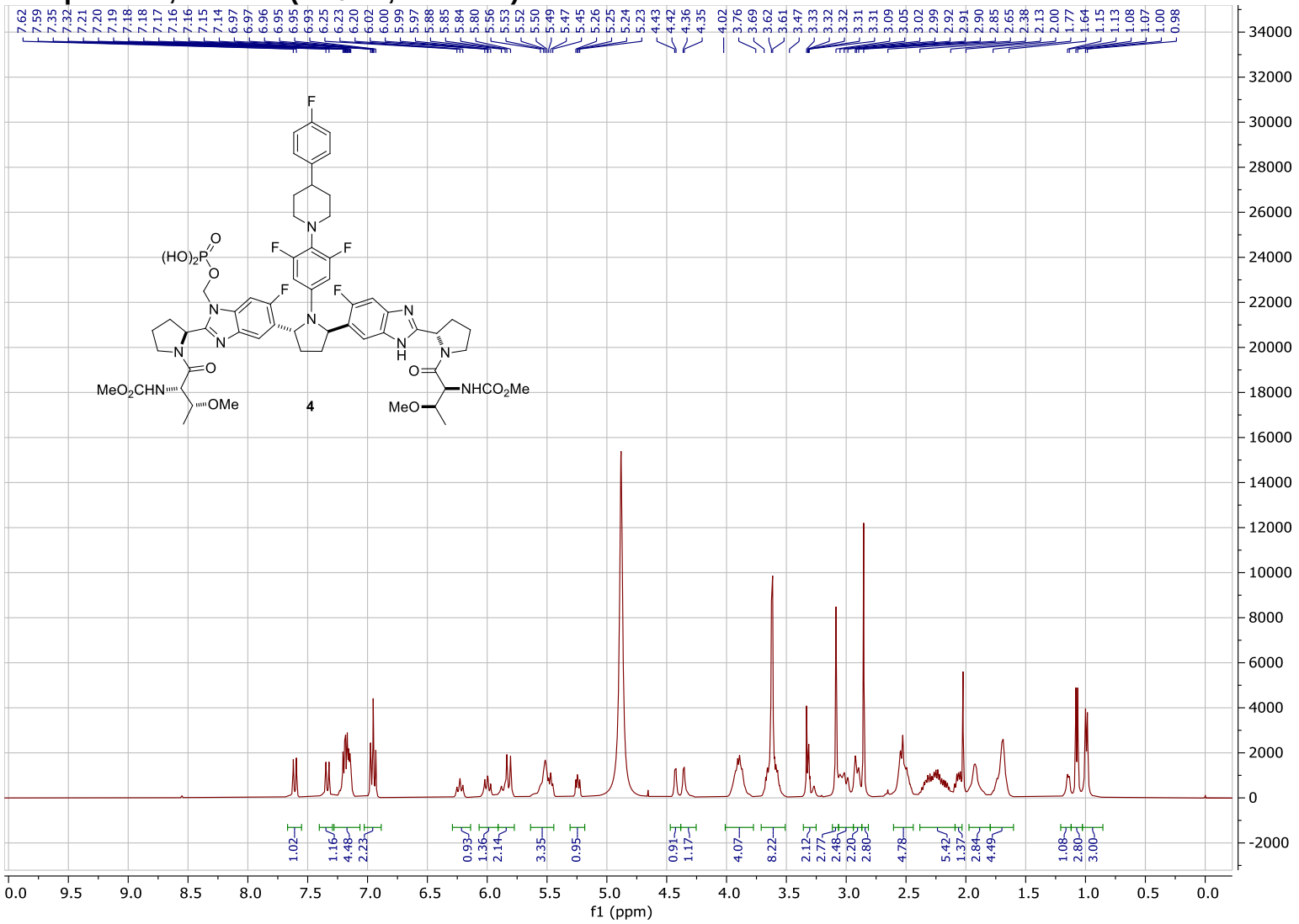
Compound S6, ^{19}F NMR (CD_3OD, 376 MHz):



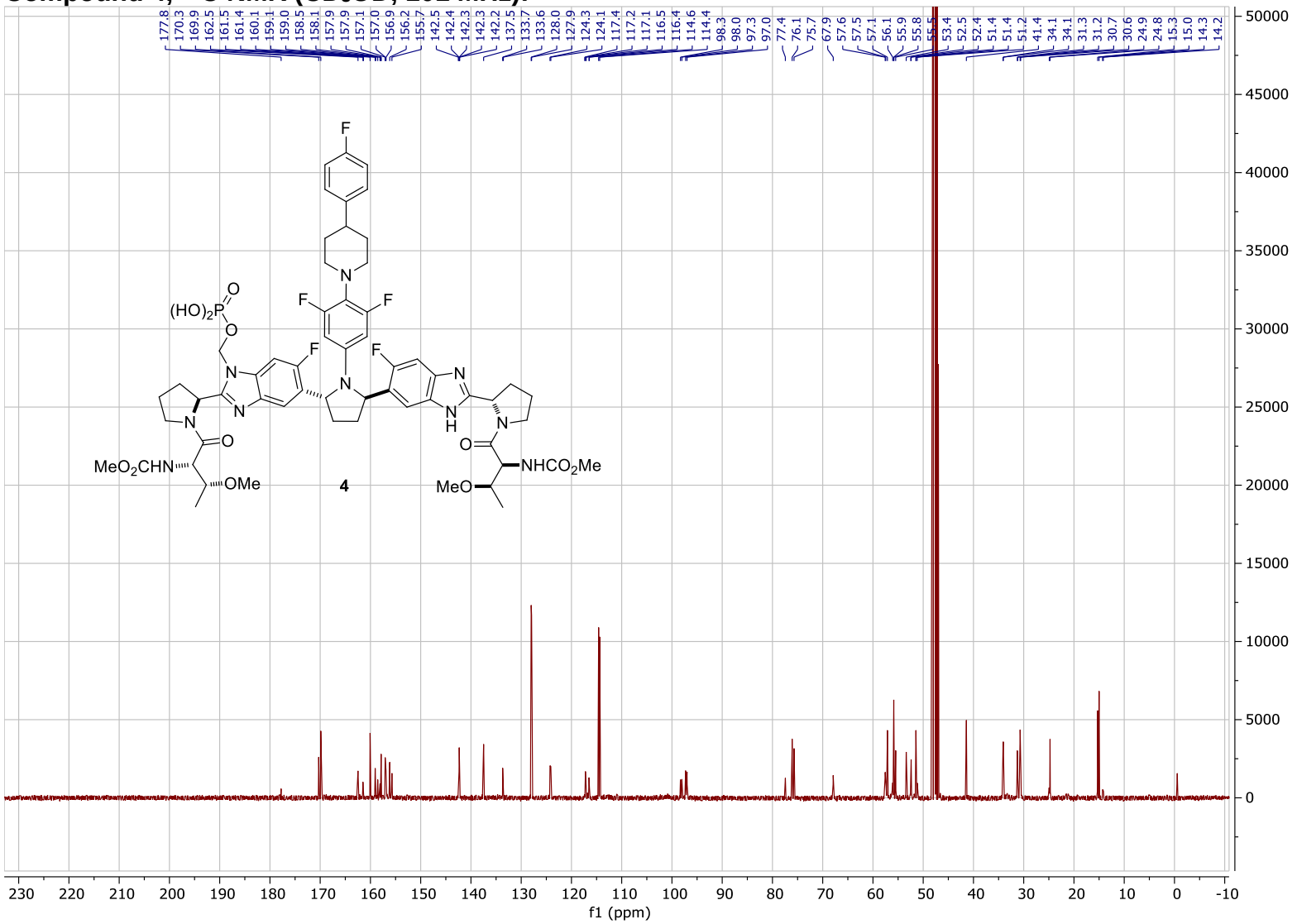
Compound S6, ^{31}P NMR (CD_3OD, 162 MHz):



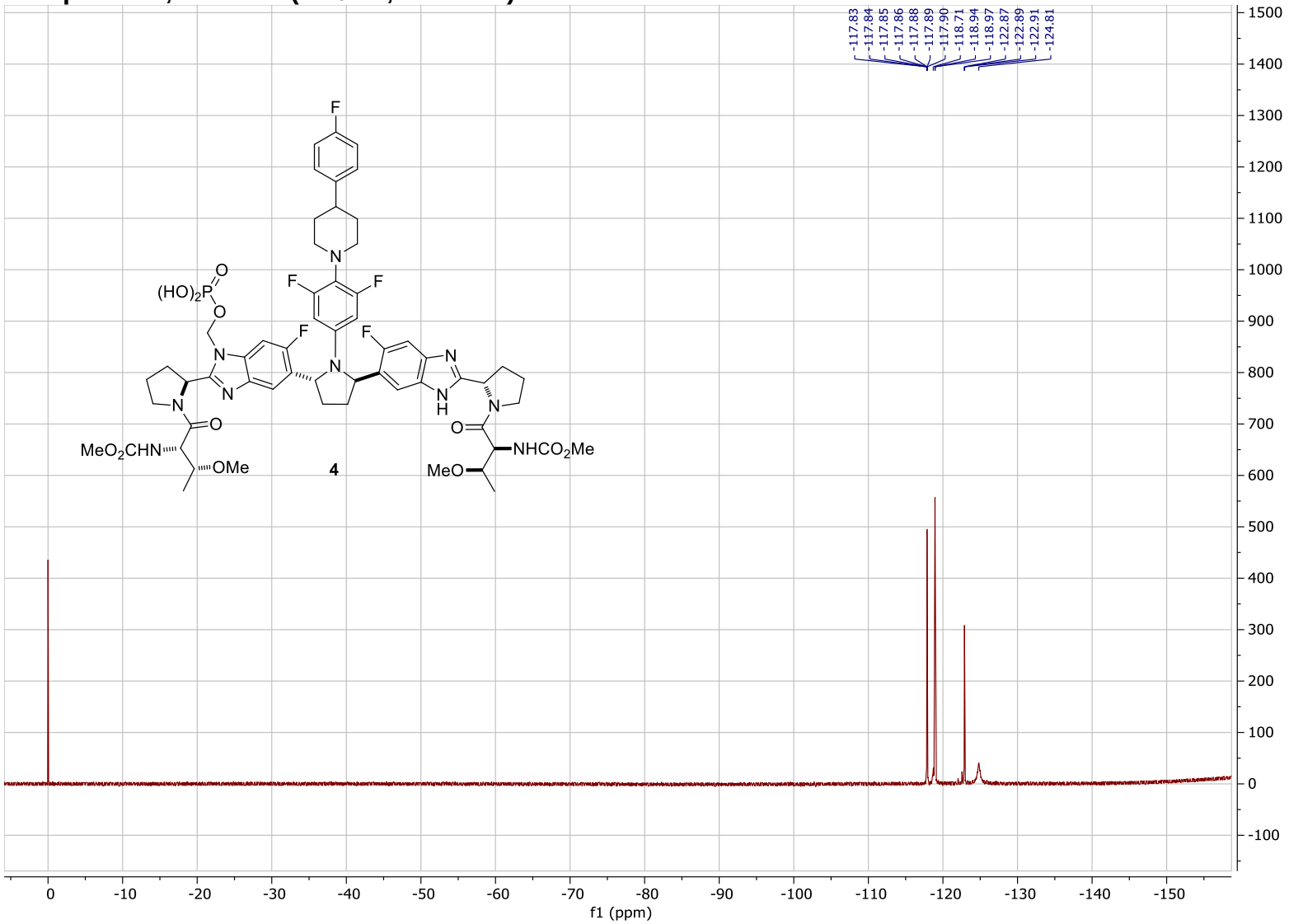
Compound 4, ^{1}H NMR (CD_3OD, 400 MHz):



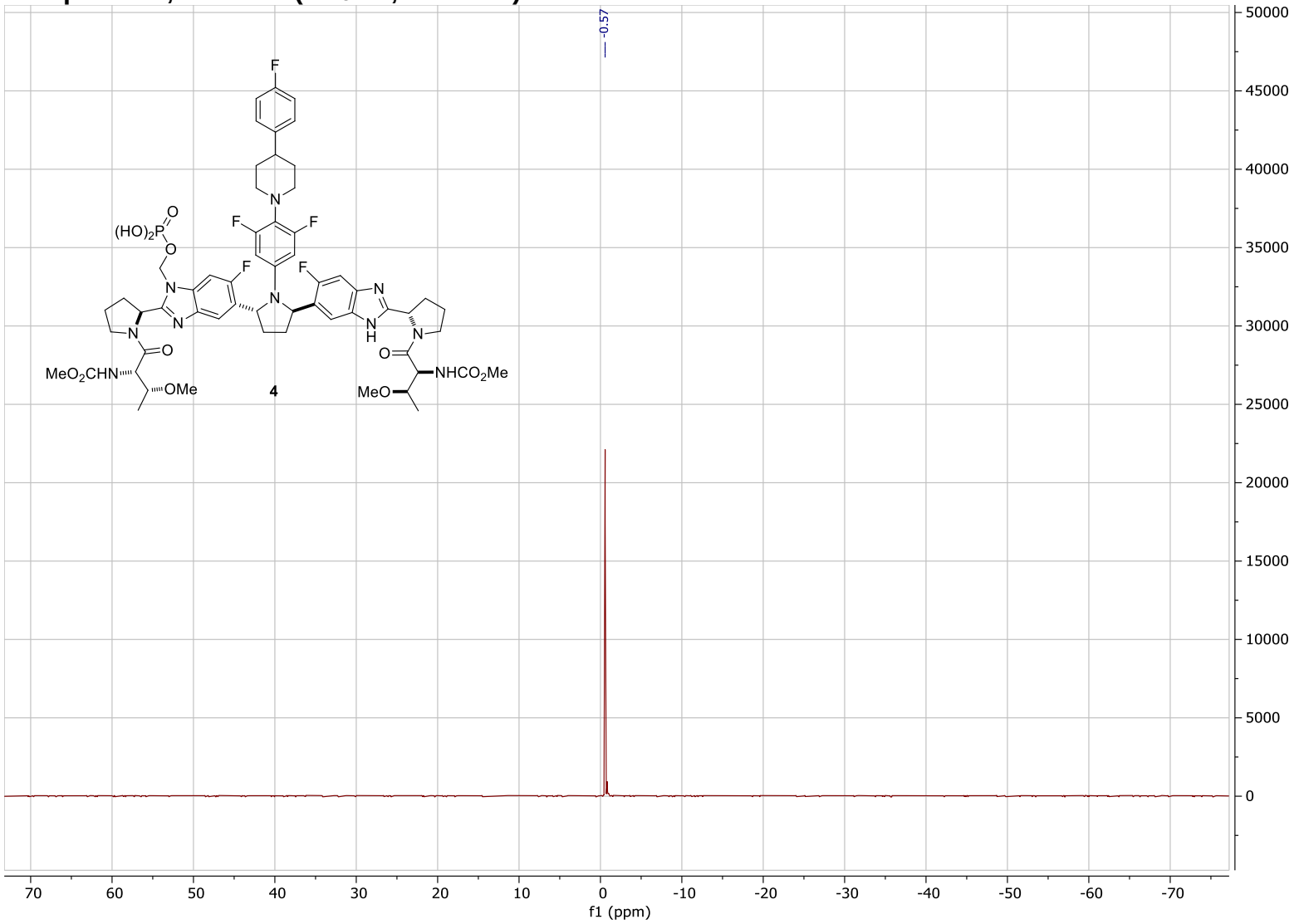
Compound 4, ^{13}C NMR (CD_3OD, 101 MHz):



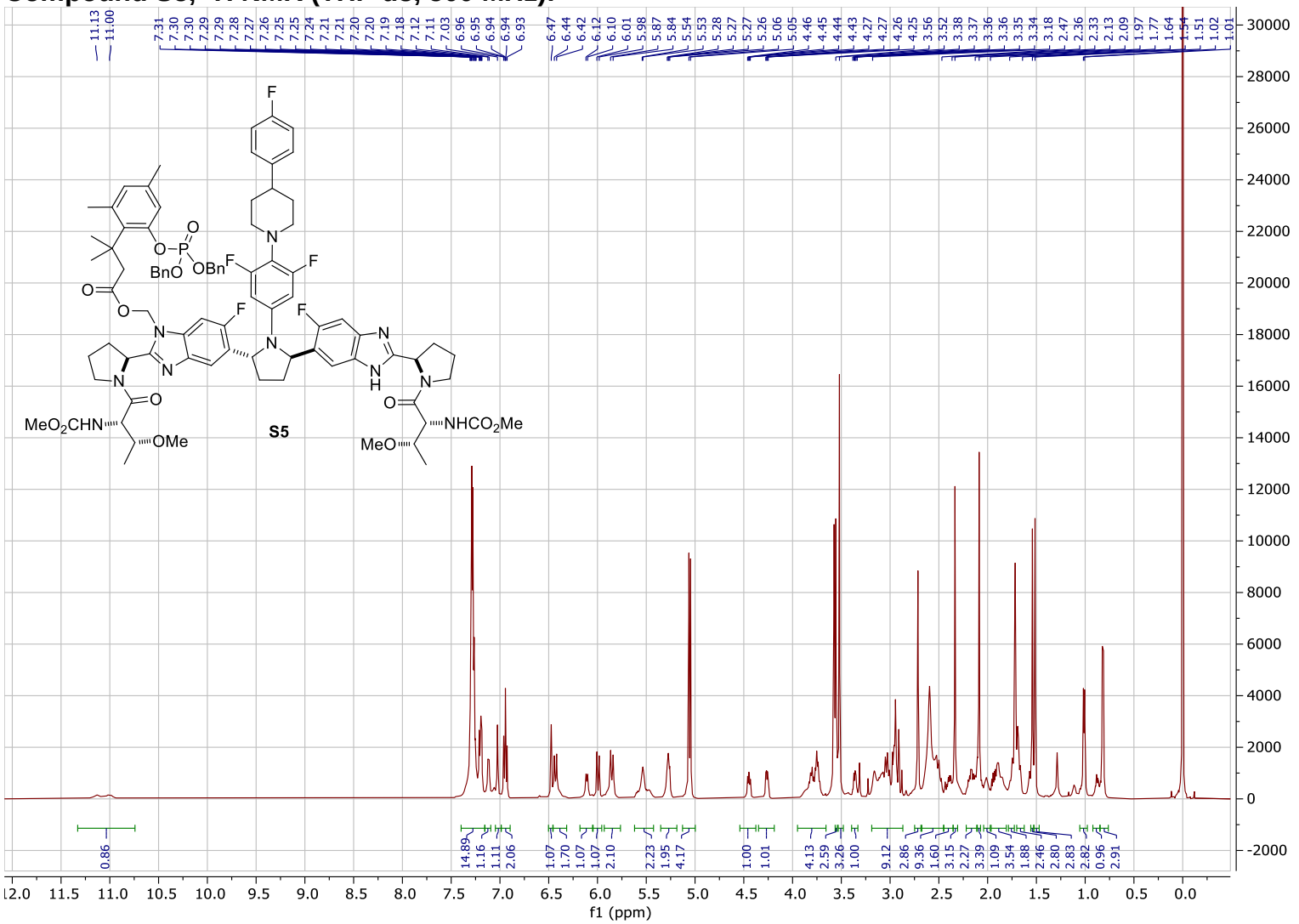
Compound 4, ^{19}F NMR (CD_3OD, 376 MHz):



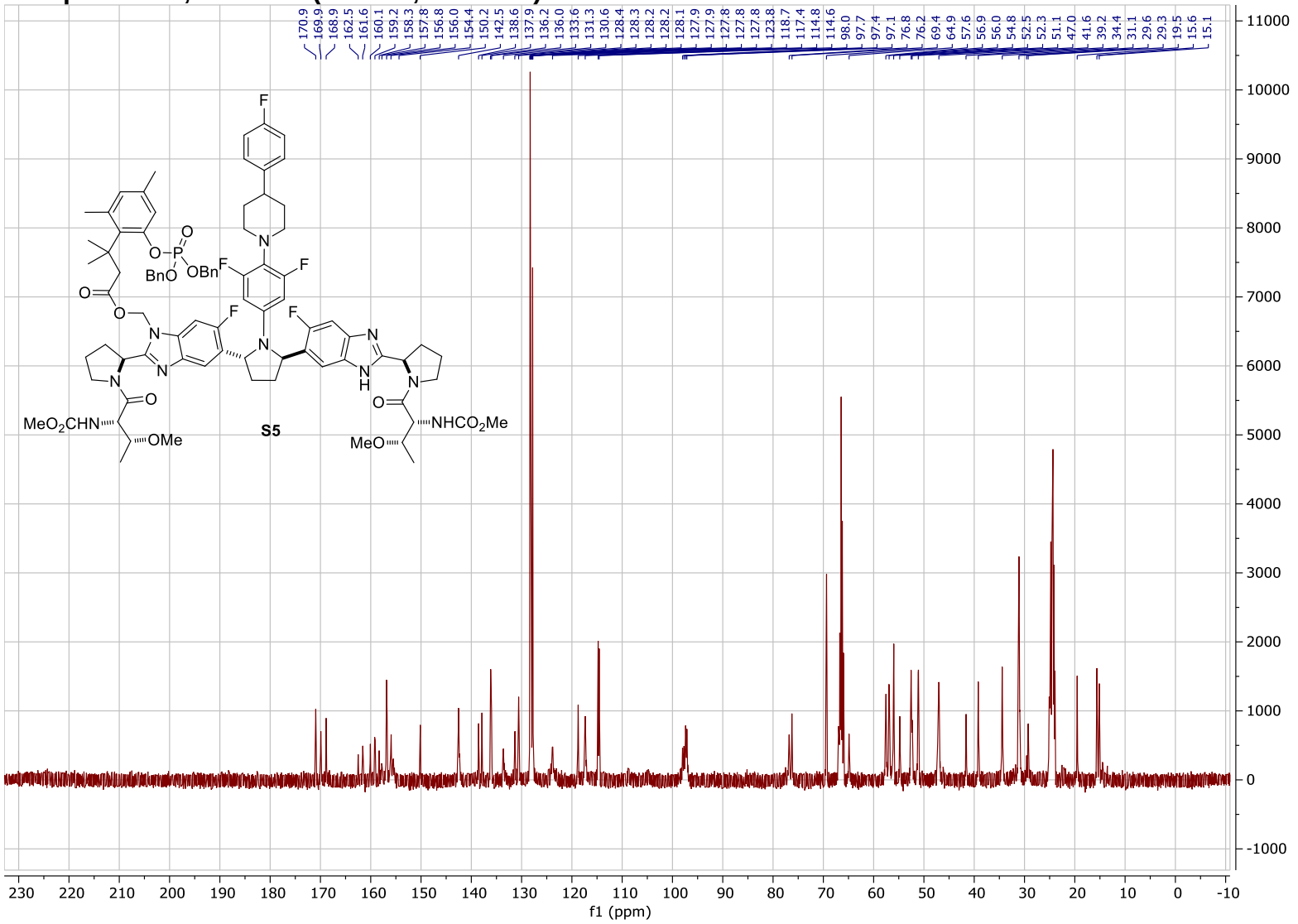
Compound 4, ^{31}P NMR (CD_3OD, 162 MHz):



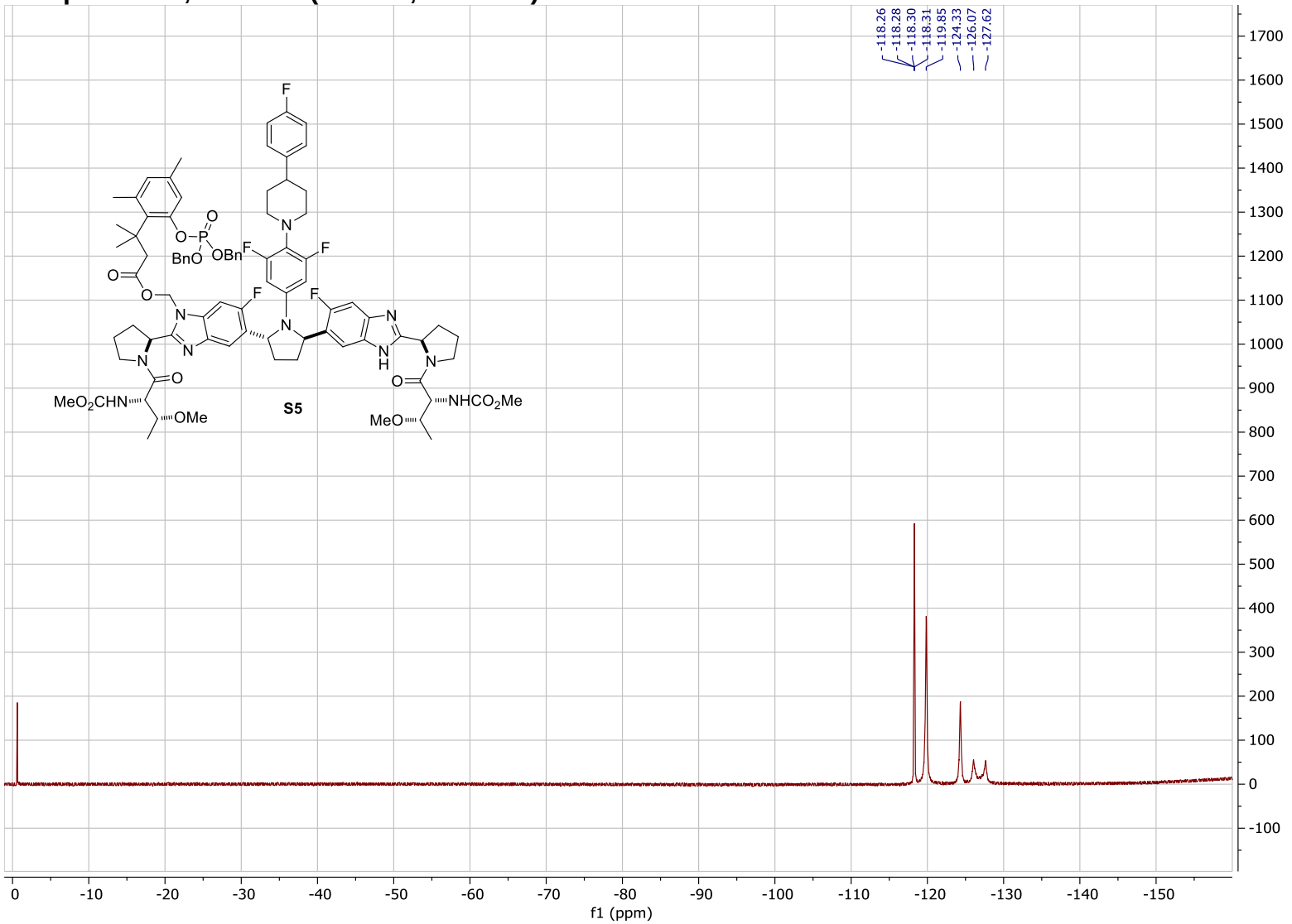
Compound S5, ^{1}H NMR (THF-d8, 500 MHz):



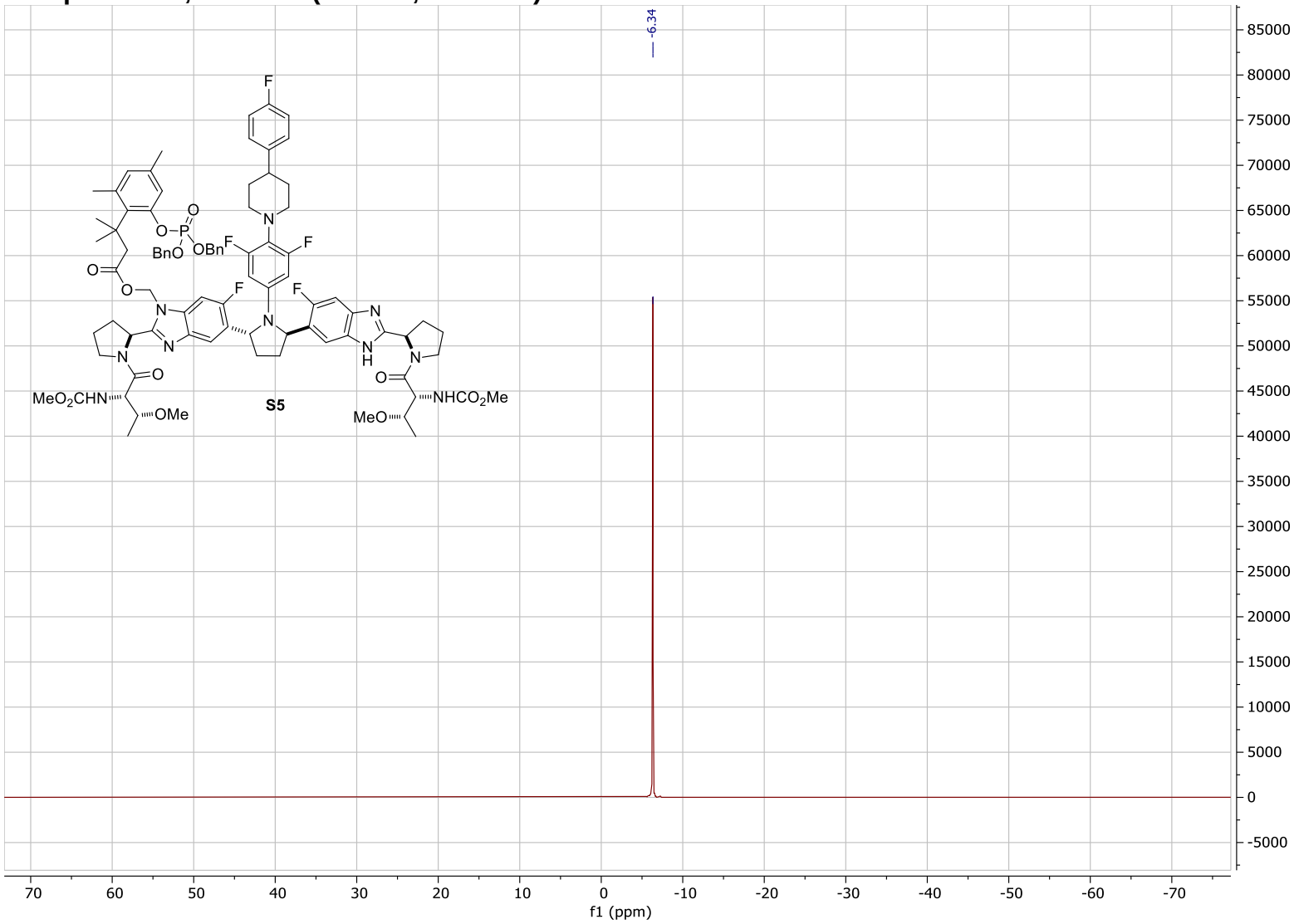
Compound S5, ^{13}C NMR (THF-d8, 125 MHz):



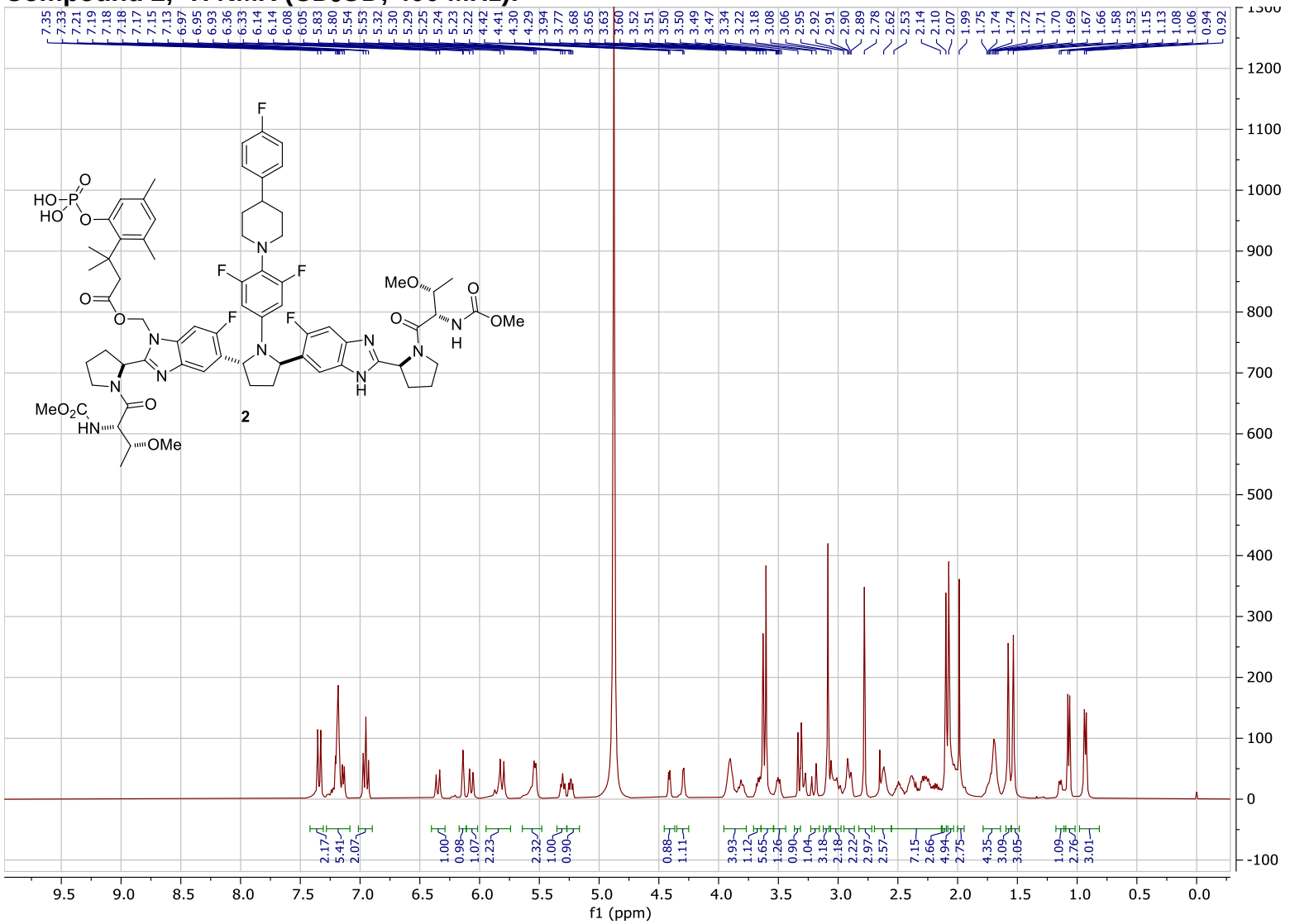
Compound S5, ^{19}F NMR (THF-d8, 376 MHz):



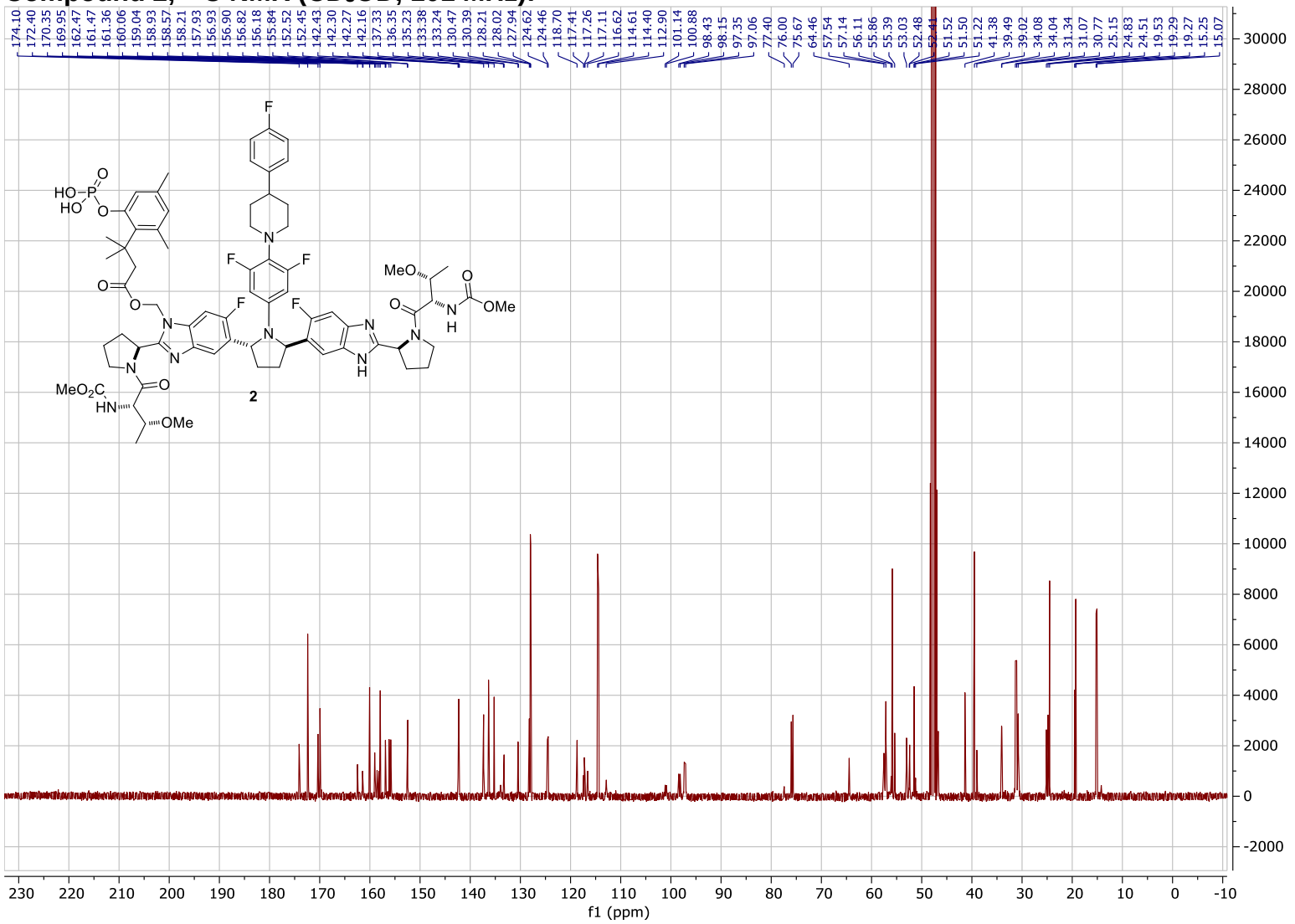
Compound S5, ^{31}P NMR (THF-d8, 162 MHz):



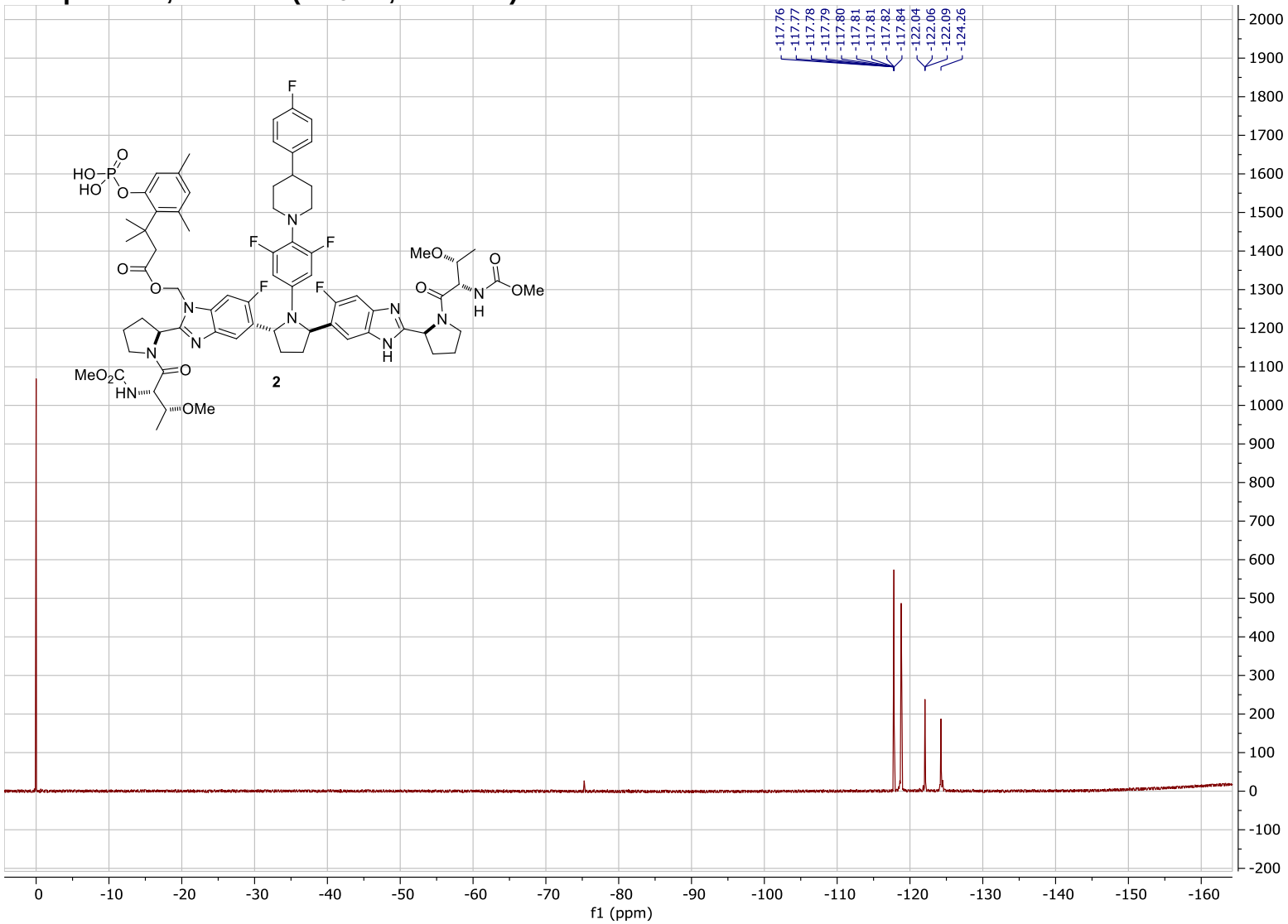
Compound 2, ^{1}H NMR (CD_3OD, 400 MHz):



Compound 2, ^{13}C NMR (CD_3OD, 101 MHz):



Compound 2, ^{19}F NMR (CD_3OD, 376 MHz):



Compound 2, ^{13}P NMR (CD_3OD, 162 MHz):