Electronic Supplementary Material (ESI) for Digital Discovery.


# Supporting Information

# Cartridge-based automated synthesis for the efficient assembly of PROTAC-like molecules

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# 1. GENERAL REMARKS

Unless otherwise noted, all reactions were performed under $N_2$ with anhydrous conditions. All reagents and were purchased from commercial suppliers and used as received. Anhydrous solvents were purchased from Acros over 4Å MS and used as received. Reactions were monitored by thin layer chromatography (TLC) on Merck precoated aluminum-backed silica gel 60 $F_{254}$ plates with UV at 254 nm, or by subjecting to NMR analysis. TLC plates were stained using $KMnO_4$ or vanillin solutions. NMR spectra were recorded on Bruker Avance III at 400 or 500 MHz ($^1$H), at 100, 125 MHz ($^{13}$C) and 376 and 471 MHz ($^{19}$F), respectively, using $CDCl_3$ as the solvent unless indicated otherwise. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 ppm and C: δ = 77.16 ppm) as the internal standard. All $^{13}$C spectra were measured with complete proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint; quintet; sext, sextet; sept, septet; m, multiplet. LC-MS analyses were performed on a Waters Acquity UPLC H-class system with a reversed-phase Waters Acquity UPLC BEH C18 (1.7µm, 2.1 x 50 mm) column connected to a SQ Detector 2 mass spectrometer. High resolution mass spectra were measured by the Mass Spectrometry Service Facility of Molecular and Biomolecular Analysis Service MoBiAS, Laboratory of Organic Chemistry at ETH Zurich on a Bruker Daltonics maXis for ESI-Q-TOF spectrometer (ESI-MS) or on a Bruker solariX (9.4T magnet) equipped with a dual ESI/MALDI-FT-ICR source using trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) as matrix (MALDI-MS). Flash chromatography purification was performed on Silicycle Silica Flash F60 (230–400 Mesh) silica gel using a forced flow of eluent at 0.2-0.3 bar. Preparative reverse phase HPLC was carried out on a Jasco preparative instrument with dual pumps, mixer, in-line degasser, Rheodyne 7725i injector with 10 mL injection loop and a variable wavelength UV with detection at 220, 254 and 301 nm.

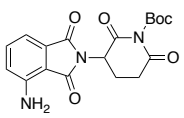
## 1.1 Reagents and solvents used for the console

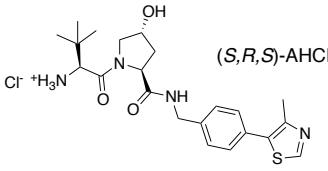
Synthesis of product compounds were performed on a Synple 2 Synthesizer console, using pre-uploaded reaction sequences and editing reaction time and purification parameters when necessary. Silica-supported cyanoborohydride, silica-supported triethylamine and silica-supported carbodiimide were purchased from SiliCycle and used as it is without further treatments. Silica-supported carbonate was purchased from SiliCycle and dried under high vacuum at 45 ˚C for at least 12 h to remove volatile impurities, then stored in a closed container. SCX-2 was purchased from Biotage and used as it is without further treatments. Partial PROTAC reagents contained in the reaction capsules were synthesized in-house with the methodologies described in this document. The purity of console-used solvents is listed as follows: $CH_2Cl_2$ (>99.8% HPLC grade), Isopropanol (99.8% GC), Acetonitrile (99.9% Extra Dry over MS), Tetrahydrofuran (99.5% Extra Dry over MS, stabilized with ca. 250 ppm BHT), DIPA (N,N-diisopropylamine, ≥99.5%), HFIP (1,1,1,3,3,3-hexafluoroisopropanol, 99.9%).

## 2. SYNTHESIS OF PROTAC BUILDING BLOCKS

E3 binders:

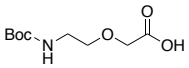
Boc-Pomalidomide (**1**)



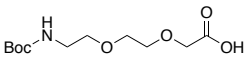


(*S,R,S*)-AHCP hydrocloride (**2**)

Reductive amination linkers:



**3a**



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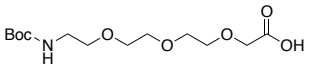
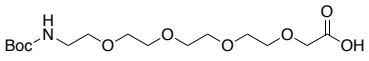


**3c**



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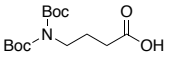

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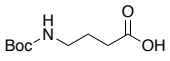
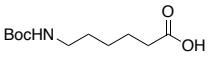


**3e'**
(commercially available)



**3f**
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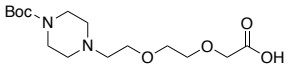
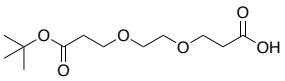
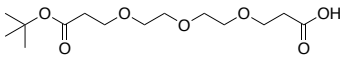


**3g**

Amide coupling linkers:



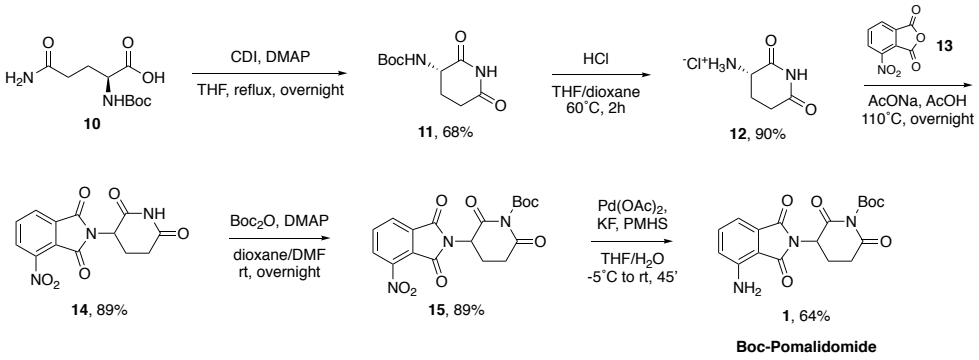
**3h**



**3i**

***Fig. S1*** *– Building blocks used for the synthesis of partial PROTAC reagents*

## 2.1 Synthesis of CRBN and VHL ligands




**10**

**11**, 68%

**12**, 90%

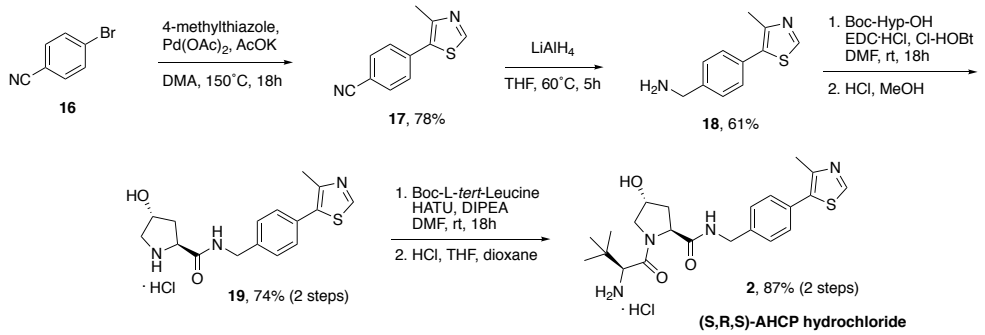
**14**, 89%

**15**, 89%

**1**, 64%

**Boc-Pomalidomide**

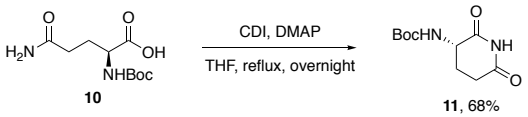
***Scheme S1*** *– synthesis of the CRBN ligand Boc-Pomalidomide **1***




***Scheme S2*** *– synthesis of the VHL ligand (S,R,S)-AHCP hydrochloride* ***2***

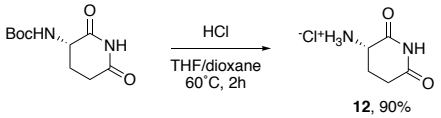
### 2.1.1 Experimental procedures

Synthesis of compound **11**:




Compound synthesized following reported procedure.[1]
Boc-OH-Gln **10** (25.00 g, 101.5 mmol, 1 equiv.) was suspended in dry THF (125 mL) and cooled to 0 ˚C. 1,1'-Carbonyldiimidazole (17.25 g, 106.58 mmol, 1.05 equiv.) was added in portions over 10 minutes (*GAS EVOLUTION!*), then DMAP (0.124 g, 1.015 mmol, 0.01 equiv.) was added and the suspension was heated to reflux and stirred overnight. The reaction was cooled to room temperature and the white precipitate was collected and washed with THF. The filtrate was concentrated to 1/3 of the volume and the formed precipitate was collected and washed with THF. The last step was repeated once more, then the collected solids were joined and dried under vacuum, affording the pure compound **11** as white solid (15.70 g, 68% yield). The compound was used directly for the next step.
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 10.75 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 4.29 – 4.18 (m, 1H), 2.72 (ddd, *J* = 18.4, 12.3, 6.5 Hz, 1H), 2.50 – 2.43 (m, 1H, overlaps with solvent), 2.01 – 1.84 (m, 2H), 1.41 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.43, 172.98, 155.87, 78.63, 50.88, 31.46, 28.66 (3C), 24.91.

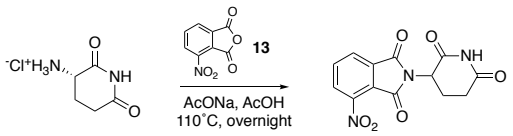
Synthesis of compound **12**:




Compound **11** (14.92 g, 65.37 mmol) was suspended in THF (40 mL), then HCl (4M solution in dioxane, 40 mL) was added. The suspension was stirred for 2 hours at 60 ˚C, and then cooled down to room temperature. $CH_2Cl_2$ (100 mL) was added to make a white solid precipitate. The solid was collected, washed with more $CH_2Cl_2$ and dried under vacuum, affording pure compound **12** as white solid (9.65 g, 90% yield).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.24 (s, 1H), 8.83 (s, 3H), 4.22 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.73 (ddd, *J* = 17.6, 13.5, 5.4 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.27 (dtd, *J* = 12.9, 5.4, 2.4 Hz, 1H), 2.06 (qd, *J* = 13.1, 4.8 Hz, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 172.84, 170.76, 49.43, 30.67, 22.53.

[1] S. M. Capitosti, T. P. Hansen, M. L. Brown; *Org. Lett.* **2003**, 5, 2865-2867

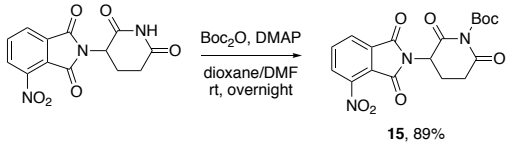
Synthesis of compound **14**:




**14**, 89%

Compound **12** (5.98 g, 36.3 mmol, 1 equiv.) and sodium acetate (3.28 g, 40 mmol, 1.1 equiv.) were suspended in acetic acid (55 mL) and stirred for 5 minutes, then 3-nitrophtalic anhydride **13** (7.01 g, 36.3 mmol, 1 equiv.) was added and the white suspension was stirred overnight at 110 ˚C. The suspension turned gradually from white to dark violet. The suspension was cooled down to room temperature and the purple solid was collected by filtration. The solid was washed with water to remove acetic acid and salts, then with acetone to remove water. Drying the solid under vacuum afforded the pure compound **14** as a purple crystalline solid (9.78 g, 89% yield).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.18 (s, 1H), 8.36 (dd, *J* = 8.1, 0.9 Hz, 1H), 8.25 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.16 – 8.09 (m, 1H), 5.21 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.90 (ddd, *J* = 17.2, 13.9, 5.4 Hz, 1H), 2.66 – 2.58 (m, 1H), 2.58 – 2.44 (m, 1H, overlaps with solvent), 2.09 (dtd, *J* = 12.7, 5.2, 2.2 Hz, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.17, 169.95, 165.63, 162.97, 144.88, 137.26, 133.46, 129.33, 127.75, 123.01, 49.90, 31.33, 22.20.

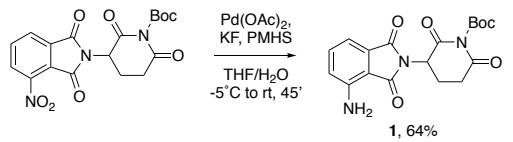
Synthesis of compound **15**:




**15**, 89%

Compound **14** (5.0 g, 16.49 mmol, 1 equiv.) was dissolved in 1,4-dioxane/DMF (150 mL, 4:1 mixture) and cooled to 0 ˚C. Boc anhydride (3.96 g, 18.14 mmol, 1.1 equiv.) was added, followed by 4-(Dimethylamino)pyridine (0.02 g, 0.165 mmol, 0.01 equiv.). Reaction was stirred at room temperature for 2 hours, then more Boc anhydride (1.08 g, 0.3 equiv.) and DMAP (0.02 g, 0.01 equiv.) were added. The addition was repeated once more after 2 more hours, then the reaction was stirred overnight. Water (150 mL) was added and the solution extracted three times with MTBE. Some unreacted starting material may be detected in the organic layer in form of an insoluble violet solid. In that case the powder was filtered off. Organics were washed with water, water/brine 1:1 and then brine, dried over sodium sulfate and evaporated, affording the crude product as a red-orange sticky oil. The crude was dissolved in $CH_2Cl_2$ and loaded onto a short silica column, washed with 100 mL of hexane, then the product was collected with hexane/EtOAc 1:2 and the solvent evaporated affording the pure compound **15** as a red-orange foam which turned into a solid by stripping multiple times with $CH_2Cl_2$ (5.9 g, 89% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.19 (ddd, *J* = 7.3, 6.5, 0.9 Hz, 2H), 8.04 – 7.93 (m, 1H), 5.15 – 5.01 (m, 1H), 3.08 – 2.78 (m, 3H), 2.28 – 2.09 (m, 1H), 1.57 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.31, 165.56, 164.73, 161.81, 147.52, 145.33, 135.89, 133.69, 129.14, 127.63, 123.53, 87.12, 50.09, 31.57, 27.43, 21.60.
**HRMS (ESI):** calcd for $C_{18}H_{17}N_3NaO_8$ $[M+Na]^+$ 426.0908, found 426.0910.

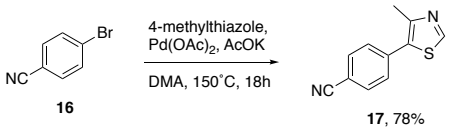
Synthesis of compound **1**:




**1**, 64%

Compound synthesized following a modified reported procedure.[2]
Compound **15** (2.75 g, 6.8 mmol, 1 equiv.) and palladium acetate (0.076 g, 0.34 mmol, 0.05 equiv.) were put in a round bottom flask and purged 3x with vacuum/$N_2$ cycles, then dissolved in dry THF (34 mL). A previously degassed aqueous solution of KF (1M, 13.6 mL, 2 equiv.) was added and the mixture was cooled to -5 °C with an ice/NaCl bath. Polymethylhydrosiloxane (PHMS, 1.63 mL, 27.2 mmol, 4 equiv.) was added dropwise **very slowly** (***CAUTION!*** *HEAT and $H_2$ EVOLUTION!*) and the dark mixture was stirred at room temperature for 45 minutes. Water (30 mL) was added and the mixture was extracted once with MTBE. Organic layer was passed through a *Celite*® plug, the filter cake was washed with $CH_2Cl_2$ and the organics were set aside. Aqueous layer was extracted twice more with MTBE, organics were joined, washed with brine and dried over sodium sulfate. Crude was purified by flash chromatography (dry loading in $CH_2Cl_2$, eluent Toluene/EtOAc 9:1 to 4:1) affording compound **1** as a yellow to yellow-orange solid (1.63 g, 64% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.45 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.19 (dd, *J* = 7.2, 0.7 Hz, 1H), 6.89 (dd, *J* = 8.3, 0.7 Hz, 1H), 5.27 (bs, 2H), 5.05 – 4.94 (m, 1H), 3.03 – 2.75 (m, 3H), 2.18 – 2.08 (m, 1H), 1.58 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.81, 167.42, 166.50, 147.88, 145.71, 135.61, 132.24, 121.47, 113.21, 110.68, 86.86, 49.05, 31.67, 27.44, 21.96.
**HRMS (ESI):** calcd for $C_{18}H_{19}N_3NaO_6$ $[M+Na]^+$ 396.1166, found 396.1167.

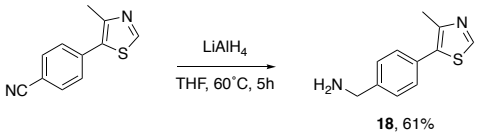
Synthesis of compound **17**:



**16** **17**, 78%

Compound synthesized following a reported procedure.[3]
4-bromobenzonitrile **16** (4.55 g, 25 mmol, 1 equiv.), palladium acetate (0.056 g, 0.25 mmol, 0.01 equiv.) and potassium acetate (4.90 g, 50 mmol, 2 equiv.) were put in a round bottom flask and purged 3 times by vacuum/$N_2$ cycles, then dissolved in dry dimethylacetamide (25 mL). 4-methylthiazole (4.55 mL, 50 mmol, 2 equiv.) was added by syringe and the mixture was stirred at 150 °C for 18 hours. The dark solution was cooled down to room temperature (the mixture solidifies) and diluted with 50 mL of EtOAc. The solution was washed 3 times with water and the first aqueous washing was back-extracted twice with EtOAc. Organics were joined and washed again 3 times with water and once with brine, then dried over sodium sulfate. Evaporation of the solvent afforded the crude product as a brown solid with a >90% purity, which can be used directly for the next step. The crude could be further purified by flash chromatography (dry loading in $CH_2Cl_2$, eluent Hexane/EtOAc 6:4), affording the pure compound **17** as a light brown solid (3.9 g, 78% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.79 (s, 1H), 7.80 – 7.69 (m, 2H), 7.64 – 7.56 (m, 2H), 2.59 (s, 3H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 151.58, 150.01, 136.84, 132.52, 130.13, 129.73, 118.46, 111.55, 16.34.

Synthesis of compound **18**:



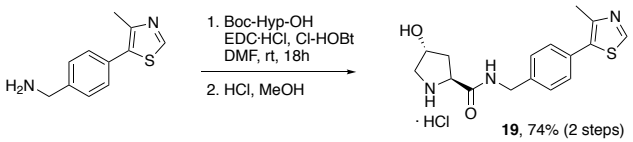
**18**, 61%

Compound synthesized following a reported procedure.[3]
Compound **17** (2.50 g, 12.48 mmol, 1 equiv.) was dissolved in dry THF (40 mL) in a Schlenk flask and cooled to 0 °C. Solid Lithium aluminium hydride (0.948 g, 24.96 mmol, 2 equiv.) was slowly added in portions, then the reaction was stirred at 60 °C for 5 hours. The brown solid mixture was cooled down to room temperature, 20 mL of THF were added and the mixture was roughly homogenized with a spatula, then 10% $NH_3$ solution in water was added **slowly dropwise** (***CAUTION!*** *STRONG GAS EVOLUTION!*) after which the mixture turned into a red/orange solution. The solution was filtered on a *Celite*® plug, the filter cake was washed with $CH_2Cl_2$/MeOH

[2] R. J. Rahaim, R. E. Maleczka; *Org. Lett.* **2005**, 7, 5087-5090
[3] A. P. Crew, K. Raina, H. Dong, Y. Qian, J. Wang, D. Vigil, Y. V. Serebrenik, B. D. Hamman, A. Morgan, C. Ferraro, K. Siu, T. K. Neklesa, J. D. Winkler, K. G. Coleman, C. G. Crews; *J. Med. Chem.* **2018**, 61, 583−598

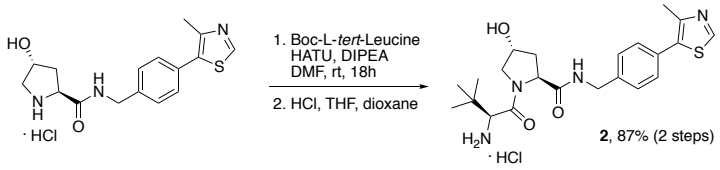
9:1 and the organics were washed with brine and dried over sodium sulfate. Evaporation of the solvent afforded compound **18** as an orange oil, pure enough to be used in the next step (1.56 g, 61% yield).
**$^1$H NMR (400 MHz, MeOD)** δ 8.89 (s, 1H), 7.47 (s, 4H), 3.87 (s, 2H), 2.50 (s, 3H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 151.36, 147.62, 142.52, 132.04, 129.96, 129.06, 127.60, 44.91, 14.43.

Synthesis of compound **19**:




Compound synthesized following a modified reported procedure.[4]
Boc-L-Hydroxyproline (2.94 g, 12.72 mmol, 1 equiv.), N-(3-Dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC, 3.17 g, 16.54 mmol, 1.3 equiv.) and 6-Chloro-1-hydroxybenzotriazole dihydrate (Cl-HOBt, 3.92 g, 19.08 mmol, 1.5 equiv.) were put in a round bottom flask and purged 3 times by vacuum/$N_2$ cycles, then dissolved in dry DMF (127 mL, 0.1 M). After stirring 5 minutes, compound **18** (2.60 g, 12.72 mmol, 1 equiv.) dissolved in 10 mL of dry DMF was added and the solution stirred overnight at room temperature. EtOAc (180 mL) was added, then the organics were washed with brine. Aqueous layer was extracted once with more EtOAc, then the combined organics were washed again with brine, twice with sat. $NaHCO_3$ and dried over sodium sulfate. Evaporation of the solvent afforded the crude product as an orange/brown foam, which was purified by flash chromatography (eluent 100% EtOAc to EtOAc/MeOH 9:1) affording the pure product as a yellow foam. LCMS: m/z 418 $[M+H]^+$, 836 $[2M+H]^+$.
The material obtained from the column was dissolved in 33 mL of HCl (1.25M MeOH solution, 6 equiv.) and stirred at room temperature for 2 h. The solvent was concentrated to ~1/4 of the volume and a solid precipitate appeared. The solid was fully precipitated by addition of acetone and collected by filtration. The liquid was concentrated again and a second crop of product was collected in the same way. The solid was dried under vacuum affording pure compound **19** as a pale-yellow solid (3.32 g, 74% yield).
**$^1$H NMR (400 MHz, MeOD)** δ 9.96 (s, 1H), 9.11 – 8.97 (m, 1H), 7.64 – 7.57 (m, 2H), 7.57 – 7.52 (m, 2H), 4.66 – 4.61 (m, 1H), 4.60 – 4.51 (m, 3H), 3.46 (dd, *J* = 12.1, 3.6 Hz, 1H), 3.39 – 3.30 (m, 1H, overlaps with solvent), 2.63 (s, 3H), 2.53 (ddt, *J* = 13.4, 7.4, 1.7 Hz, 1H), 2.11 (ddd, *J* = 13.5, 10.6, 4.0 Hz, 1H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 168.27, 155.14, 141.48, 140.44, 135.72, 129.32, 128.32, 127.21, 69.84, 58.67, 53.76, 42.55, 38.57, 11.78.

Synthesis of **2**:




Compound synthesized following a reported procedure.[3]
Compound **19** (2.00 g, 5.65 mmol, 1 equiv.), Boc-L-*tert*-Leucine (1.31 g, 5.65 mmol, 1 equiv.) and HATU (2.58 g, 6.78 mmol, 1.2 equiv.) were put in a round bottom flask and purged three times by vacuum/$N_2$ cycles, then dry DMF (28 mL, 0.2M) was added and the suspension cooled to 0 ˚C. DIPEA (4.43 mL, 25.43 mmol, 4.5 equiv.) was added and the yellow solution was stirred overnight at room temperature. The resulting orange/brown solution was cooled to 0 ˚C and water (30 mL) was added. The mixture was stirred for 5 minutes, then extracted with EtOAc. Organics were washed with water, twice with water/brine 1:1 and once with brine, then dried over sodium sulfate. Evaporation of the solvent afforded the crude coupling product as a yellow foam. LCMS: m/z = 532 $[M+H]^+$, 432 $[M-Boc]^+$.

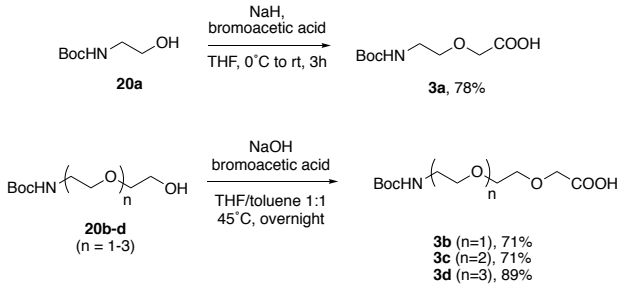
[4] D. L. Buckley, J. L. Gustafson, I. Van Molle, A. G. Roth, H. S. Tae, P. C. Gareiss, W. L. Jorgensen, A. Ciulli, C. M. Crews; *Angew. Chem. Int. Ed.* **2012**, 51, 11463 –11467

The crude product was dissolved in 14 mL of THF, then 14 mL of HCl (4M solution in 1,4-dioxane) was added. After a few minutes a yellow precipitate appeared. The suspension was stirred 2 hours at room temperature, then the solid was collected by filtration, washed with THF and dried under vacuum affording the pure compound **2** as a yellow solid (2.30 g, 87% yield).

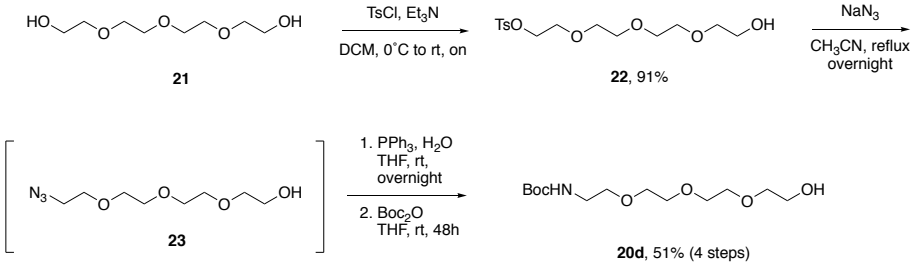
**$^1$H NMR (400 MHz, MeOD)** δ 10.00 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H), 4.71 (dd, *J* = 9.5, 7.6 Hz, 1H), 4.62 – 4.51 (m, 2H), 4.43 (d, *J* = 15.8 Hz, 1H), 4.10 (s, 1H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.73 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.37 (s, 1H), 2.63 (s, 3H), 2.34 (ddt, *J* = 13.2, 7.6, 1.7 Hz, 1H), 2.10 (ddd, *J* = 13.4, 9.6, 4.1 Hz, 1H), 1.16 (s, 9H).

**$^{13}$C NMR (101 MHz, MeOD)** δ 172.74, 167.17, 155.21, 141.10, 136.07, 129.09, 128.02, 126.63, 69.78, 59.61, 58.96, 56.71, 42.21, 37.68, 34.39, 25.29, 11.74.

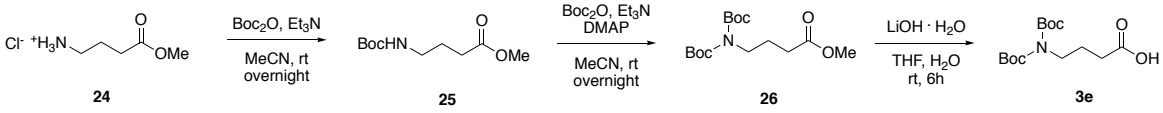
## 2.2 Synthesis of linkers



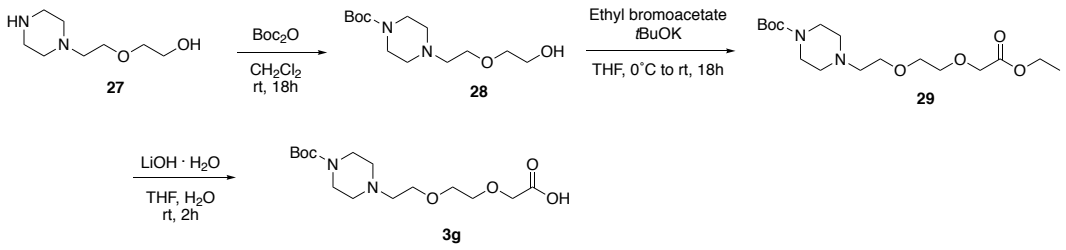

***Scheme S3*** *– synthesis of PEG-linkers* ***3a-d***



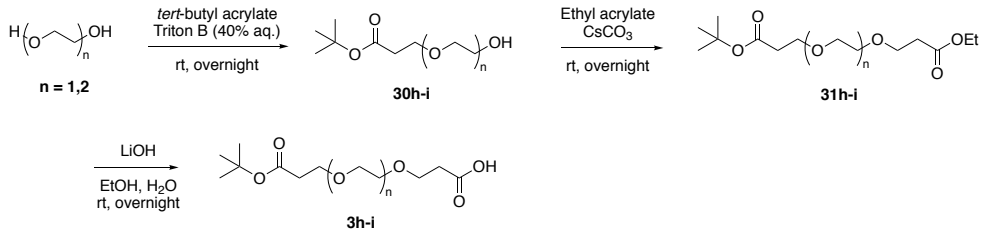

***Scheme S4*** *– synthesis of the linker precursor* ***20d***




***Scheme S5*** *– synthesis of linker* ***3e***



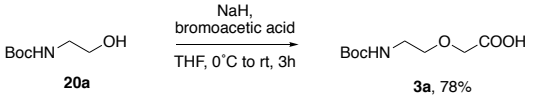

***Scheme S6*** *– synthesis of linker* ***3g***




***Scheme S7** – synthesis of linkers **3h-i***

### 2.2.1 Experimental procedures

Synthesis of linker **3a**:

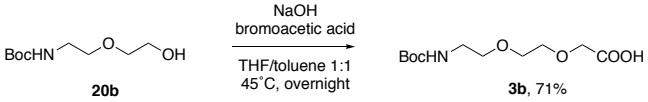



N-Boc-aminoethanol **20a** (4.00 g, 24.8 mmol, 2 equiv.) and bromoacetic acid (1.723 g, 12.4 mmol, 1 equiv.) were dissolved in dry THF (40 mL) and cooled to 0 ˚C. Sodium hydride (60% mineral oil suspension, 1.488 g, 37.2 mmol, 3 equiv.) was added in portions and then reaction was stirred at room temperature for 3 hours. Reaction was cooled down to 0 ˚C again and water (40 mL) was carefully added, then the solution was washed 3x with MTBE. Aqueous layer was acidified to pH 3 with 4M HCl and extracted three times with $CH_2Cl_2$. Evaporation of $CH_2Cl_2$ afforded pure product **3a** as yellow-orange viscous oil (2.14 g, 78% yield). Spectral data in accordance with literature.[5]

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.30 (bs, 1H), 6.56 (bs, 0.3H, NHBoc rot.), 5.20 (bs, 0.7H, NHBoc rot.), 4.15 (s, 2H), 3.64 (t, *J* = 5.1 Hz, 2H), 3.49 – 3.26 (m, 2H), 1.46 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.80, 156.38, 79.68, 70.94, 68.00, 40.37, 28.37.

Synthesis of linker **3b**:




Compound synthesized following reported procedure.[6]

2-(2-tert-butyloxycarbonylaminoethoxy)ethanol **20b** (4.00 g, 19.49 mmol, 1 equiv.) and bromoacetic acid (8.12 g, 58.46 mmol, 3 equiv.) were dissolved in a mixture of THF (30 mL) and toluene (30 mL) and the solution was heated up to 45 ˚C. NaOH (4.68 g, 116.93 mmol, 6 equiv.) was grounded to a powder and added to the solution. The suspension was stirred overnight at 45 ˚C, then cooled down to room temperature and THF was almost completely removed by rotary evaporation. Toluene residue was extracted 3 times with 5% NaOH(aq.), then aqueous layer was washed 3 times with $CH_2Cl_2$. The organics were discarded. Aqueous layer was acidified to pH 3 with 4M HCl and extracted 5 times with $CH_2Cl_2$. Organics were dried over sodium sulfate and concentrated affording pure **3b** as a pale yellow viscous oil (3.65 g, 71% yield).

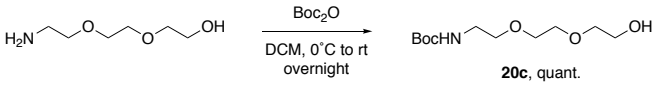
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (bs, 1H), 6.09 (bs, 0.25H, NHBoc rot.), 5.09 (bs, 0.75H, NHBoc rot.), 4.18 (s, 2H), 3.78 – 3.71 (m, 2H), 3.70 – 3.64 (m, 2H), 3.60 – 3.51 (m, 2H), 3.38 – 3.22 (m, 2H), 1.44 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.41, 156.19, 79.54, 71.03, 70.39, 70.09, 68.48, 40.27, 28.38.

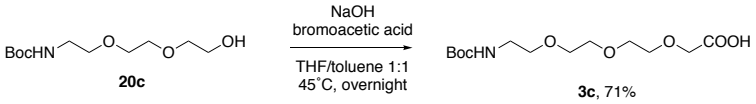
[5] N. S. Chandrakumar, A. Stapelfeld, P. M. Beardsley, O. T. Lopez, B. Drury, E. Anthony, M. A. Savage, L. N. Williamson, M. Reichman; *J. Med. Chem.* **1992**, 35, 2928-2938

[6] F. Schmidt, I. C. Rosnizeck, M. Spoerner, H. R. Kalbitzer, B. König; *Inorg. Chim. Acta* **2011**, 365, 38-48

Synthesis of linker **3c**:

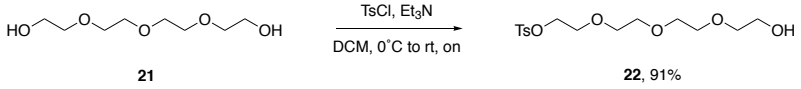



2-(2-(2-aminoethoxy)ethoxy)ethanol (2.00 g, 13.4 mmol, 1 equiv.) was dissolved in $CH_2Cl_2$ (70 mL) and cooled to 0 ˚C. Boc anhydride (3.51 g, 16.1 mmol, 1.2 equiv.) was dissolved in $CH_2Cl_2$ (20 mL) and added dropwise to the amino-alcohol solution. The solution was stirred overnight at room temperature, then washed with water, sat. $NaHCO_3$ and brine. Evaporation of the solvent afforded pure precursor **20c** as a colorless oil (3.34 g, quantitative).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 5.15 (s, 1H), 3.81 – 3.73 (m, 2H), 3.71 – 3.61 (m, 6H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.34 (t, *J* = 5.2 Hz, 2H), 2.53 (s, 1H), 1.47 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 156.04, 79.35, 72.57, 70.44, 70.30, 61.75, 40.35, 28.41.

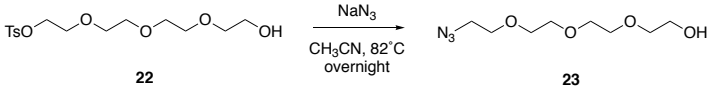



Compound synthesized following reported procedure.[6]
Compound **20c** (2.17 g, 8.7 mmol, 1 equiv.) and bromoacetic acid (3.63 g, 26.1 mmol, 3 equiv.) were dissolved in a mixture of THF (10 mL) and toluene (10 mL) and the solution was heated up to 45 ˚C. NaOH (2.88 g, 52.2 mmol, 6 equiv.) was grounded to a powder and added to the solution. The suspension was stirred overnight at 45 ˚C, then cooled down to room temperature and THF was almost completely removed by rotary evaporation. Toluene residue was extracted 3 times with 5% NaOH(aq.), then aqueous layer was washed 3 times with $CH_2Cl_2$. The organics were discarded. Aqueous layer was acidified to pH 3 with 4M HCl and extracted 5x with $CH_2Cl_2$. Organics were dried over sodium sulfate and concentrated affording pure **3c** as a colorless viscous oil (1.90 g, 71% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.02 (bs, 1H), 5.90 (bs, 0.25H, NHBoc rot.), 5.13 (bs, 0.75H, NHBoc rot.), 4.19 (s, 2H), 3.82 – 3.75 (m, 2H), 3.75 – 3.62 (m, 6H), 3.56 (t, *J* = 5.2 Hz, 2H), 3.43 – 3.25 (m, 2H), 1.46 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.22, 156.20, 79.40, 71.42, 70.53, 70.30, 70.18, 69.94, 68.84, 40.32, 28.41.

Synthesis of linker **3d**:



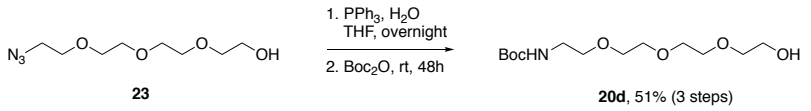

To a 0 ˚C solution of tetraethylene glycol **21** (86.3 mL, 500 mmol, 10 equiv.) in 100 mL of $CH_2Cl_2$ was added tosyl chloride (9.53 g, 50 mmol, 1 equiv.), followed by triethylamine (10.4 mL, 75 mmol, 1.5 equiv.). The solution was stirred overnight at room temperature then washed 3 times with water, dried over sodium sulfate and concentrated to afford the compound **22** as a pale-yellow oil (15.89 g, 91% yield). Spectral data in accordance with literature.[7]
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.85 – 7.74 (m, 2H), 7.39 – 7.31 (m, 2H), 4.21 – 4.13 (m, 2H), 3.74 – 3.62 (m, 8H), 3.62 – 3.57 (m, 6H), 2.56 (t, *J* = 6.2 Hz, 1H), 2.45 (s, 3H).




Tosylate **22** (3.04 g, 8.7 mmol) was dissolved in $CH_3CN$ (17.5 mL). Sodium azide (1.70 g, 26.1 mmol, 3 equiv.) was added and the suspension was stirred overnight at reflux temperature. Reaction was then cooled down to room temperature, diluted with 40 mL of THF, solids were filtered off and washed with EtOAc, then combined organics were evaporated affording the crude azide **23** as a pale-yellow oil. Compound **23** was used for the next step without further purifications. Spectral data in accordance with literature.[7]

[7] E. Chirkin, V. Muthusamy, P. Mann, T. Roemer, P. G. Nantermet, D. A. Spiegel; *Angew. Chem. Int. Ed.* **2017**, 56, 13036-13040.

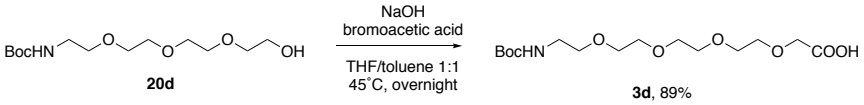
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.77 – 3.73 (m, 2H), 3.72 – 3.66 (m, 10H), 3.65 – 3.62 (m, 2H), 3.42 (t, *J* = 5.1 Hz, 2H), 2.30 (bs, 1H).




Crude azide **23** from previous step was dissolved in THF (30 mL) and triphenylphosphine (2.83 g, 10.8 mmol, 1.2 equiv.) was added. After 5 minutes water (1.5 mL) was added and reaction was stirred overnight at room temperature. TLC confirmed full conversion of azide. Boc anhydride (2.54 g, 10.8 mmol, 1.2 equiv.) was added and solution was further stirred for 48 h. Solvent was evaporated, $Et_2O$ was added and mixture left overnight in the freezer (most of triphenylphosphine oxide crystallized out). Crystals were filtered off and crude was purified by flash chromatography (eluent 100% EtOAc, product $R_f$ ~0.15), affording pure **20d** as a colorless viscous oil (1.30 g, 51% yield from **22**). Spectral data in accordance with literature.[8]

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 5.61 (bs, 1H), 3.78 – 3.70 (m, 4H), 3.70 – 3.61 (m, 8H), 3.55 (m, 2H), 3.33 (t, *J* = 5.0 Hz, 2H), 2.69 (bs, 1H), 1.46 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 156.19, 79.04, 72.65, 70.64, 70.46, 70.27, 70.09, 61.68, 40.49, 28.45.



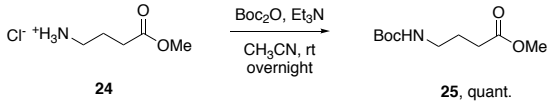

Compound synthesized following a reported procedure.[6]

Compound **20d** (0.394 g, 1.34 mmol, 1 equiv.) and bromoacetic acid (0.560 g, 4.03 mmol, 3 equiv.) were dissolved in a mixture of THF (1.7 mL) and toluene (1.7 mL) and the solution was heated up to 45 °C. NaOH (0.322 g, 8.06 mmol, 6 equiv.) was grounded to a powder and added to the solution. The suspension was stirred overnight at 45 °C, then cooled down to room temperature and THF was almost completely removed by rotary evaporation. Toluene residue was extracted 3 times with 5% NaOH(aq.), then aqueous layer was washed 3 times with $CH_2Cl_2$. The organics were discarded. Aqueous layer was acidified to pH 3 with 4M HCl and extracted 5x with $CH_2Cl_2$. Organics were dried over sodium sulfate and concentrated affording pure **3d** as a colorless viscous oil (0.422 g, 89% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.98 (bs, 1H), 6.35 (bs, 0.3H, NHBoc rot.), 5.15 (bs, 0.7H, NHBoc rot.), 4.17 (s, 2H), 3.83 – 3.60 (m, 12H), 3.56f (t, *J* = 5.2 Hz, 2H), 3.39 – 3.26 (m, 2H), 1.45 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.88, 156.14, 79.31, 71.32, 70.64, 70.40, 70.32, 69.14, 41.59 (rot.), 40.28 (rot.), 28.42.

Synthesis of linker **3e**:



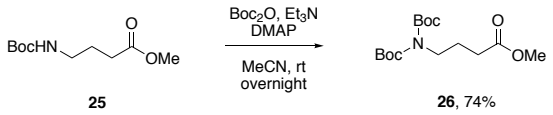

Compound synthesized following a reported procedure.[9]

Methyl 4-aminobutyrate hydrochloride **24** (1.54 g, 10.0 mmol, 1 equiv.) was suspended in 20 mL $CH_3CN$, triethylamine (1.67 mL, 12.0 mmol, 1.2 equiv.) was added followed by a solution of Boc anhydride (2.62 g, 12.0 mmol, 1.2 equiv.) in 5 mL $CH_3CN$. Mixture was stirred overnight at room temperature, then concentrated by rotary evaporation, residue taken up with 20 mL of EtOAc and washed with 20 mL of 1M HCl(aq). Aqueous layer extracted with 2x20 mL EtOAc, organics joined and washed with sat. $NaHCO_3$, water, then brine and dried over sodium sulfate. Organics concentrated to afford compound **25** as a pale-yellow oil (2.17 g, quantitative yield), which was used directly for next step. Spectral data in accordance with literature.[9]

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.63 (bs, 1H), 3.70 (s, 3H), 3.23 – 3.14 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.84 (p, *J* = 7.1 Hz, 2H), 1.46 (s, 9H).

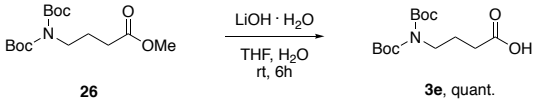
[8] A. Friese, S. Kapoor, T. Schneidewind, S. R. Vidadala, J. Sardana, A. Brause, T. Förster, M. Bischoff, J. Wagner, P. Janning, S. Ziegler, H. Waldmann; *Angew. Chem. Int. Ed.* **2019**, 58, 13009-13013.

[9] J. Y. F. Wong, J. M. Tobin, F. Vilela, G. Barker; *Chem. Eur. J.* **2019**, 25, 12439-12445




**25** **26**, 74%

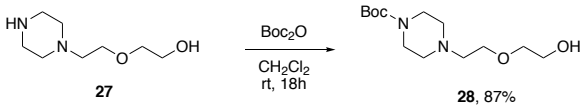
Compound synthesized following a reported procedure.[9]
Compound **25** (2.17 g, 10.0 mmol, 1 equiv.) was dissolved in 20 mL $CH_3CN$, triethylamine (1.67 mL, 12.0 mmol, 1.2 equiv.) was added followed by a solution of Boc anhydride (2.62 g, 12.0 mmol, 1.2 equiv.) in 5 mL $CH_3CN$ and DMAP (0.122 g, 1.0 mmol, 0.1 equiv.). Mixture was stirred overnight at room temperature, then concentrated by rotary evaporation and directly purified by flash chromatography (eluent Hexane/EtOAc 9:1 to 0:100) affording pure compound **26** as a yellow oil (2.35 g, 74% yield). Spectral data in accordance with literature.[9]
**$^1$H NMR (300 MHz, $CDCl_3$)** δ 3.69 (s, 3H), 3.70 – 3.59 (m, 2H), 2.36 (t, *J* = 7.5 Hz, 2H), 2.00 – 1.84 (m, 2H), 1.52 (s, 18H).




**26** **3e**, quant.

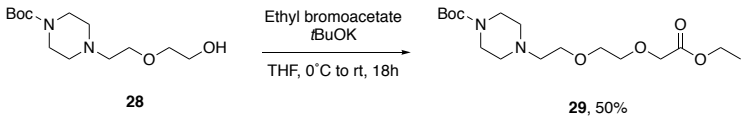
Compound **26** (2.30 g, 7.25 mmol, 1 equiv.) was dissolved in THF (24 mL), then LiOH (1M in $H_2O$, 8.0 mL) was added and mixture stirred at room temperature for 6 hours. After full consumption of starting material, volatiles were evaporated, residue was diluted with 10 mL of water, then acidified to pH 3 with 1M HCl(aq.). Aqueous layer was extracted with 3x20 mL $CH_2Cl_2$, organics dried over sodium sulfate and evaporated, affording compound **3e** as yellow oil (2.20 g, quantitative yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.71 – 3.60 (m, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.92 (p, *J* = 7.4 Hz, 2H), 1.52 (s, 18H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.72, 152.57, 82.47, 45.44, 31.21, 28.04, 23.95.

Synthesis of linker **3g**:




**27** **28**, 87%

A solution of Boc anhydride (3.09 g, 14.16 mmol, 1 equiv.) in 35 mL of $CH_2Cl_2$ was added dropwise to a solution of 1-[2-(2-Hydroxyethoxy)ethyl]piperazine **27** (2.47 g, 14.16 mmol, 1 equiv.) in 35 mL of $CH_2Cl_2$. The solution was stirred overnight at room temperature, then washed with sat. $NaHCO_3$ (35 mL) and water (35 mL), then dried over sodium sulfate. Evaporation of the solvent afforded compound **28** as yellow oil (3.38 g, 87% yield), pure enough to be directly used for next step.
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.05 (bs, 1H), 3.75 – 3.64 (m, 4H), 3.64 – 3.59 (m, 2H), 3.50 – 3.42 (m, 4H), 2.64 – 2.57 (m, 2H), 2.52 – 2.45 (m, 4H), 1.46 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 154.70, 79.70, 72.39, 67.65, 61.96, 57.97, 53.13, 44.27 – 42.42 (bm, 2C), 28.41.

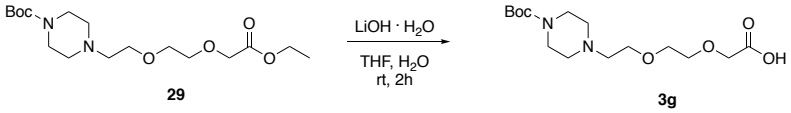



**28** **29**, 50%

Compound synthesized following a reported procedure.[10]
Compound **28** (720 mg, 2.62 mmol, 1 equiv.) was dissolved in dry THF (10.5 mL) and the solution was cooled to 0 ˚C. Potassium *tert*-butoxide (1M in THF, 2.62 mL, 1 equiv.) was added dropwise and the solution was stirred for 30 min at 0 ˚C. Ethyl bromoacetate (0.364 mL, 3.28 mmol, 1.25 equiv.) was then added dropwise and the mixture was let slowly warm up to room temperature and stirred overnight. Reaction was quenched with 5 mL of water, then concentrated by rotary evaporation. Aqueous residue was diluted with 10 mL of water and extracted

[10] M. Adamczyk, J. R. Fishpaugh, M. Thiruvazhi; *Org. Prep. Proced. Int.* **2002**, 34, 326-331

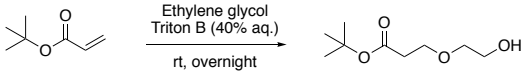
with 3x20 mL EtOAc. Organics were washed with brine and dried over sodium sulfate. Crude was purified by flash chromatography (eluent EtOAc/MeOH 9:1) affording pure compound **29** as yellow-brown oil (470 mg, 50% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.21 (q, *J* = 7.1 Hz, 2H), 4.14 (s, 2H), 3.76 – 3.69 (m, 2H), 3.67 – 3.65 (m, 2H), 3.63 (t, *J* = 5.8 Hz, 2H), 3.47 – 3.39 (m, 4H), 2.60 (t, *J* = 5.8 Hz, 2H), 2.45 (t, *J* = 5.1 Hz, 4H), 1.45 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.38, 154.71, 79.53, 70.87, 70.44, 68.90, 68.69, 60.80, 57.80, 53.36, 44.61 – 42.61 (bm, 2C), 28.41, 14.21.



**29** **3g**

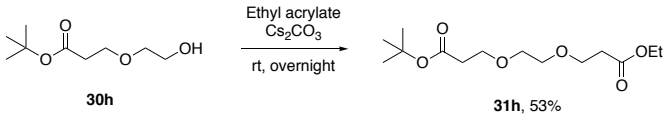
Compound **29** (350 mg, 0.97 mmol, 1 equiv.) was dissolved in THF (5 mL), LiOH (1M in $H_2O$, 1.16 mL, 1.2 equiv.) was added and the mixture was stirred at room temperature for 2 hours. Solution was concentrated to dryness and residue, containing linker **3g**, was directly used for next step.

Synthesis of linker **3h**:



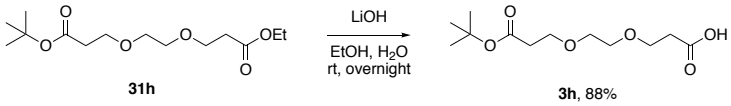
**30h**, 38%

Compound synthesized following a modified reported procedure.[11]
To a solution of tert-butyl acrylate (6.0 mL, 40.0 mmol, 1 equiv.) in ethylene glycol (11.2 mL, 200 mmol, 5 equiv.) was added Benzyltributylammonium hydroxide (Triton B, 40% aq. solution, 7.9 mL, 20.0 mmol, 0.5 equiv.) dropwise, then the mixture was vigorously stirred (RPM = 1200) overnight at room temperature. The crude mixture was directly purified by flash chromatography (eluent Hexane/EtOAc 2:1 to 1:1) to afford pure compound **30h** as a pale-yellow oil (2.92 g, 38% yield). Spectral data in accordance with literature.[11]
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.79 – 3.68 (m, 4H), 3.63 – 3.56 (m, 2H), 2.52 (t, *J* = 6.1 Hz, 2H), 2.31 (s, 1H), 1.47 (s, 9H).



**30h** **31h**, 53%

To a mixture of compound **30h** (2.92 g, 15.3 mmol, 1 equiv.) and ethyl acrylate (5.1 mL, 46.0 mmol, 3 equiv.) was added cesium carbonate (0.250 g, 0.767 mmol, 0.05 equiv.) and the suspension was stirred at room temperature overnight. Crude mixture was directly purified by flash chromatography (eluent Hexane/EtOAc 85:15 to 50:50. Product r.f. 0.4 in Hexane/EtOAc 2:1) to afford compound **31h** as a colorless oil (2.37 g, 53% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.77 (t, *J* = 6.5 Hz, 2H), 3.73 (t, *J* = 6.6 Hz, 2H), 3.62 (s, 4H), 2.60 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.6 Hz, 2H), 1.47 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H).



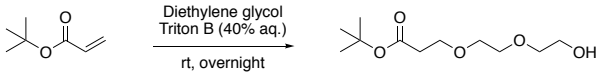
**31h** **3h**, 88%

To a solution of compound **31h** (2.36 g, 8.1 mmol, 1 equiv.) in 32.5 mL of ethanol, was added LiOH (1M in $H_2O$, 9.8 mL) in one portion, then the mixture was stirred overnight at room temperature. Volatiles were evaporated, the residue was taken up with 30 mL of water and washed with 3x30 mL of $CH_2Cl_2$ (organic layer was discarded).

[11] P. M. Cromm, K. T. G. Samarasinghe, J. Hines, C. M. Crews; *J. Am. Chem. Soc.* **2018**, 140, 17019-17026

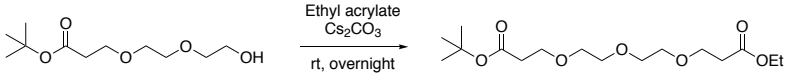
Aqueous layer was acidified to pH 2 with 1M HCl(aq.) then extracted with 4x30 mL $CH_2Cl_2$. Organics were dried over sodium sulfate and concentrated to afford linker **3h** as a pale-yellow oil (1.89 g, 88% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.79 (t, *J* = 6.2 Hz, 2H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.67 – 3.60 (m, 4H), 2.66 (t, *J* = 6.2 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 1.47 (s, 9H).

Synthesis of linker **3i**:



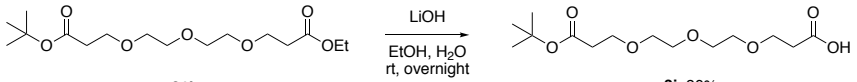

**30i**, 44%

Compound synthesized following reported procedure.[11]
To a solution of tert-butyl acrylate (24.8 mL, 0.195 mol, 1 equiv.) in ethylene glycol (92.4 mL, 0.975 mol, 5 equiv.) was added Benzyltributylammonium hydroxide (Triton B, 40% aq. solution, 38.5 mL, 0.0975 mol, 0.5 equiv.) dropwise, then the mixture was vigorously stirred (RPM = 1200) overnight at room temperature. The crude mixture was directly purified by flash chromatography (eluent Hexane/EtOAc 1:1) to afford pure compound **30i** as a pale-yellow oil (20.2 g, 44% yield). Spectral data in accordance with literature.[3]
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.78 – 3.71 (m, 4H), 3.70 – 3.66 (m, 2H), 3.66 – 3.59 (m, 4H), 2.53 (bs, 1H), 2.53 (t, *J* = 6.4 Hz, 2H), 1.47 (s, 9H).




**30i** **31i**, 64%

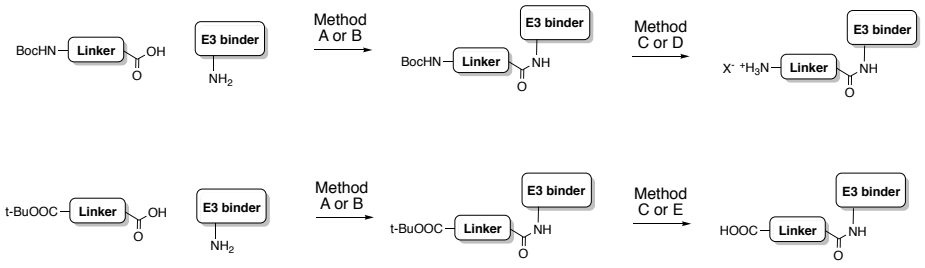
To a mixture of compound **30i** (20.2 g, 86.2 mmol, 1 equiv.) and ethyl acrylate (23.5 mL, 215 mmol, 2.5 equiv.) was added cesium carbonate (1.405 g, 4.31 mmol, 0.05 equiv.) and the suspension was stirred at room temperature overnight. Crude mixture was directly purified by flash chromatography (eluent Hexane/EtOAc 3:1) to afford compound **31i** as a colorless oil (18.52 g, 64% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 4.17 (q, *J* = 7.2 Hz, 2H), 3.77 (t, *J* = 6.6 Hz, 2H), 3.73 (t, *J* = 6.6 Hz, 2H), 3.69 – 3.57 (m, 9H), 2.61 (t, *J* = 6.5 Hz, 2H), 2.52 (t, *J* = 6.6 Hz, 2H), 1.47 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H).




**31i** **3i**, 80%

To a solution of compound **31i** (18.52 g, 55.4 mmol, 1 equiv.) in 220 mL of ethanol, was added LiOH (1M in $H_2O$, 66.5 mL), then the mixture was stirred overnight at room temperature. Volatiles were evaporated, the residue was taken up with 50 mL of water and washed with 3x50 mL of $CH_2Cl_2$ (organic layer was discarded). Aqueous layer was acidified to pH 2 with 1M HCl(aq.) then extracted with 4x50 mL $CH_2Cl_2$. Organics were dried over sodium sulfate and concentrated to afford linker **3i** as a pale-yellow oil (13.56 g, 80% yield).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 3.80 (t, *J* = 6.1 Hz, 2H), 3.74 (t, *J* = 6.5 Hz, 2H), 3.71 – 3.59 (m, 8H), 2.66 (t, *J* = 6.1 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 1.47 (s, 9H).

## 3. SYNTHESIS OF PARTIAL PROTACS




***Scheme S8*** *– general scheme for the synthesis of partial PROTAC reagents*

General procedures for Linker + E3 binder coupling:

**Method A**: Boc-Pomalidomide (1 equiv.) and the chosen linker **3a-i** (1 equiv.) were dissolved in dry EtOAc (0.2M). Triethylamine (2.2 equiv.) was added and the solution was cooled to 0 ˚C. T3P (50% in EtOAc, 2 equiv.) was added dropwise, then the solution was heated to 70 ˚C and stirred overnight. Solution was cooled down to room temperature, then saturated aq. $NaHCO_3$ (10 mL) was added, mixture was stirred 5 min, then phases were separated. Aqueous layer was extracted with EtOAc, then organics were washed with water and then brine. The desired product was purified by flash chromatography.

**Method B:** (*S,R,S*)-AHPC hydrochloride (1 equiv.), the chosen linker **3a-i** (1 equiv.) and HATU (1.2 equiv.) were dissolved in dry DMF (0.2M) and cooled to 0 ˚C. DIPEA (4.5 equiv.) was added and solution stirred overnight at room temperature. Solution was cooled down to 0 ˚C and water (20 mL) was added. Aqueous layer was extracted with EtOAc, then organics washed twice with 1:1 water/brine mixture and once with brine. The desired product was purified by flash chromatography.

General methods for Boc and *tert*-butyl ester cleavage:

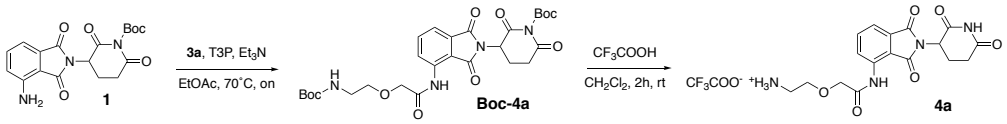
**Method C:** Boc-protected (or *tert*-butyl ester) CRBN partial PROTAC was dissolved in a 1:1 mixture of $CH_2Cl_2$ and TFA (0.1M) and stirred at room temperature for 2 hours. Volatiles were evaporated leaving a solid or a sticky oil, which were triturated with MTBE. The obtained off-white solid was collected by filtration and dried under $N_2$ stream and then under high vacuum, affording the desired partial PROTAC trifluoroacetate salt or carboxylic acid as white to yellow powder. The compounds obtained this way can be stored for months at room temperature in closed containers without particular precautions.

**Method D:** Boc-protected VHL partial PROTAC was dissolved in HCl (1.25M in MeOH, 10 equiv.) and the solution was stirred at room temperature for 2 hours. Volatiles were evaporated yielding a yellow sticky foam which was dried under vacuum and/or lyophilized ($H_2O$/ $CH_3CN$ 1:1) to afford the desired partial PROTAC HCl salt as a pale-yellow to yellow hygroscopic solid. The compounds obtained this way can be stored for months at -20 ˚C.

**Method E**: VHL partial PROTAC with tert-butyl ester chain appended was dissolved in a 1:1 mixture of $CH_2Cl_2$ and TFA (0.25M) and stirred at room temperature for 2 hours. Volatiles were evaporated and residue was triturated with $Et_2O$ to yield a sticky goo. The goo was dissolved in water and the two phases was shaken in a separation funnel. Aqueous layer was basified to pH ~8 with sat. $NaHCO_3$, then titrated back to pH 4 with 4M HCl (product started separating from aqueous layer forming a white milky suspension). The milky suspension was extracted with 3x20 mL $CH_2Cl_2$, more 4M HCl was added to bring the aqueous layer to pH 3, then extracted again with 2x20 mL $CH_2Cl_2$ and dried over sodium sulfate. Evaporation of the solvent afforded the desired PROTAC-COOH reagent as off-white foamy solid. The compounds obtained this way can be stored for months at -20 ˚C.

## 3.1 Synthesis and spectral data of partial PROTAC reagents

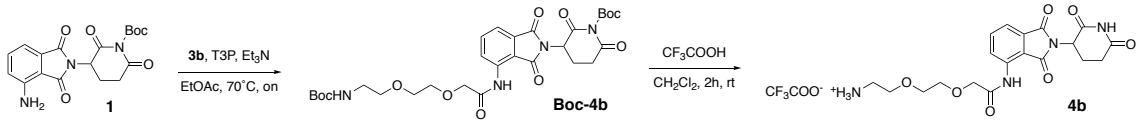
Synthesis of CRBN-PEG1-$NH_2$TFA (**4a**)




Compound **Boc-4a** was prepared following Method A, starting from Boc-Pomalidomide **1** (1.25 mmol, 466 mg) and linker **3a** (1.25 mmol, 274 mg). Flash chromatography (Hexane/EtOAc 7:3 → 5:5) afforded compound **Boc-4a** as pale-yellow foam. LCMS (ESI+) m/z = 597 $[M+Na]^+$, 475 $[M-Boc]^+$, 375 $[M-2Boc]^+$.

Compound **4a** was prepared from **Boc-4a** following Method C. Obtained as an off-white solid (477 mg, 77% yield over 2 steps).
**$^1$H NMR (400 MHz, MeOD)** δ 8.78 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.85 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.65 (dd, *J* = 7.4, 0.8 Hz, 1H), 5.17 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.30 (app. d, *J* = 0.7 Hz, 2H), 3.98 – 3.91 (m, 2H), 3.37 – 3.34 (m, 2H), 2.98 – 2.69 (m, 3H), 2.24 – 2.13 (m, 1H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 173.00, 169.87, 168.99, 168.93, 166.71, 136.07, 136.06, 131.59, 124.60, 118.38, 116.75, 69.85, 67.36, 49.26, 39.20, 30.77, 22.18.
**HRMS (MALDI):** calcd for $C_{17}H_{19}N_4O_6$ $[M-CF_3COO^-]^+$ 375.1299, found 375.1299.

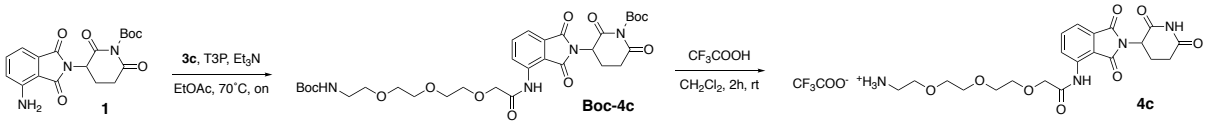
Synthesis of CRBN-PEG2-$NH_2$TFA (**4b**)




Compound **Boc-4b** was prepared following Method A, starting from Boc-Pomalidomide **1** (1.12 mmol, 418 mg) and linker **3b** (1.12 mmol, 295 mg). Flash chromatography (Hexane/EtOAc 6:4 → 3:7) afforded compound **Boc-4b** as an off-white foam. LCMS (ESI+) m/z = 641 $[M+Na]^+$, 619 $[M+H]^+$, 519 $[M-Boc]^+$, 419 $[M-2Boc]^+$.

Compound **4b** was prepared from **Boc-4b** following Method C. Obtained as a white powder (364 mg, 61% yield over 2 steps).
**$^1$H NMR (400 MHz, MeOD)** δ 8.81 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.82 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.62 (dd, *J* = 7.4, 0.8 Hz, 1H), 5.16 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.25 (d, *J* = 1.1 Hz, 2H), 3.92 – 3.82 (m, 4H), 3.82 – 3.76 (m, 2H), 3.16 (t, *J* = 5.1 Hz, 2H), 2.91 (ddd, *J* = 17.5, 13.9, 5.2 Hz, 1H), 2.84 – 2.66 (m, 2H), 2.20 (dtd, *J* = 12.8, 5.5, 2.7 Hz, 1H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 173.03, 170.01, 169.90, 168.67, 166.77, 136.16, 135.97, 131.64, 124.52, 118.24, 116.49, 71.08, 70.27, 70.05, 66.65, 49.19, 39.33, 30.72, 22.27.
**HRMS (MALDI):** calcd for $C_{19}H_{23}N_4O_7$ $[M-CF_3COO^-]^+$ 419.1561, found 419.1561.

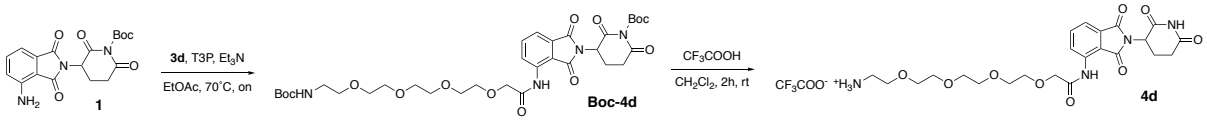
Synthesis of CRBN-PEG3-$NH_2$TFA (**4c**)




Compound **Boc-4c** was prepared following Method A, starting from Boc-Pomalidomide **1** (2.36 mmol, 0.881 g) and linker **3c** (2.36 mmol, 0.725 g). Flash chromatography (Hexane/EtOAc 4:6 → 100% EtOAc) afforded compound **Boc-4c** as a pale-yellow foam. LCMS (ESI+) m/z = 685 $[M+Na]^+$, 563 $[M-Boc]^+$, 463 $[M-2Boc]^+$.

Compound **4c** was prepared from **Boc-4c** following Method C. Obtained as an off-white solid (1.09 g, 80% yield over 2 steps).
**$^1$H NMR (400 MHz, MeOD)** δ 8.82 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.83 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.64 (dd, *J* = 7.4, 0.8 Hz, 1H), 5.17 (dd, *J* = 12.6, 5.5 Hz, 1H), 4.26 (s, 2H), 3.90 – 3.81 (m, 4H), 3.76 – 3.66 (m, 6H), 3.12 (t, *J* = 5.1 Hz, 2H), 2.97 – 2.86 (m, 1H), 2.83 – 2.69 (m, 2H), 2.25 – 2.14 (m, 1H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 173.11, 170.08, 169.96, 168.61, 166.75, 136.15, 135.96, 131.68, 124.48, 118.24, 116.52, 71.04, 70.41, 70.27, 69.88, 66.45, 49.16, 39.24, 30.72, 22.23.
**HRMS (ESI):** calcd for $C_{21}H_{27}N_4O_6$ $[M\text{-}CF_3COO^-]^+$ 463.1823, found 463.1820.

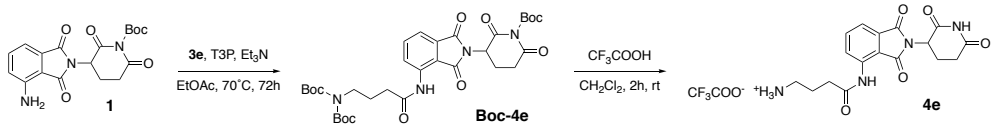
Synthesis of CRBN-PEG4-$NH_2$TFA (**4d**)




Compound **Boc-4d** was prepared following Method A, starting from Boc-Pomalidomide **1** (1.30 mmol, 485 mg) and linker **3d** (1.30 mmol, 457 mg). Flash chromatography (Hexane/EtOAc 1:2 → EtOAc/MeOH 98:2) afforded compound **Boc-4d** as an off-white foam. LCMS (ESI-) m/z = 706 $[M\text{-}H]^-$.

Compound **4d** was prepared from **Boc-4d** following Method C. Obtained as an off-white solid (556 mg, 69% yield over 2 steps).
**$^1$H NMR (400 MHz, MeOD)** δ 8.79 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.82 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.63 (dd, *J* = 7.4, 0.8 Hz, 1H), 5.17 (dd, *J* = 12.5, 5.5 Hz, 1H), 4.26 (s, 2H), 3.89 – 3.80 (m, 4H), 3.75 – 3.61 (m, 10H), 3.18 – 3.11 (m, 2H), 2.98 – 2.85 (m, 1H), 2.83 – 2.69 (m, 2H), 2.25 – 2.15 (m, 1H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 173.12, 170.12, 169.88, 168.53, 166.80, 136.14, 135.95, 131.67, 124.56, 118.25, 116.56, 71.15, 70.41, 70.18, 70.09, 70.04, 70.00, 69.70, 66.41, 49.21, 39.23, 30.75, 22.23.
**HRMS (ESI):** calcd for $C_{23}H_{31}N_4O_9$ $[M\text{-}CF_3COO^-]^+$ 507.2086, found 507.2083.

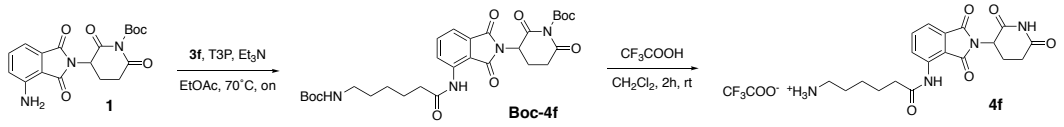
Synthesis of CRBN-C3-$NH_2$TFA (**4e**)




Compound **Boc-4e** was prepared following Method A, starting from Boc-Pomalidomide **1** (1.10 mmol, 411 mg) and linker **3e** (1.10 mmol, 334 mg). Flash chromatography (Hexane/EtOAc 3:1 → 1:1) afforded compound **Boc-4e** as a yellow foam. LCMS (ESI+) m/z = 581 $[M+Na]^+$, 459 $[M\text{-}Boc]^+$.

Compound **4e** was prepared from **Boc-4e** following Method C. Obtained as an off-white solid (286 mg, 55% yield over 2 steps).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.16 (s, 1H), 9.77 (s, 1H), 8.44 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.86 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.76 (bs, 3H), 7.65 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.15 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.98 – 2.84 (m, 3H), 2.72 – 2.52 (m, 4H), 2.16 – 2.03 (m, 1H), 1.90 (p, *J* = 7.4 Hz, 2H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.24, 171.55, 170.23, 168.03, 167.09, 136.71, 136.61, 131.98, 127.06, 119.07, 117.83, 49.39, 38.81, 33.43, 31.39, 23.07, 22.46.
**HRMS (ESI):** calcd for $C_{17}H_{19}N_4O_5$ $[M\text{-}CF_3COO^-]^+$ 359.1350, found 359.1350.

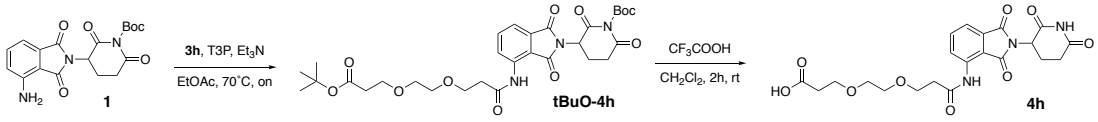
Synthesis of CRBN-C3-NH$_2$TFA (**4f**)




Compound **Boc-4f** was prepared following Method A, starting from Boc-Pomalidomide **1** (1.297 mmol, 484 mg) and linker **3f** (1.297 mmol, 300 mg). Flash chromatography (Hexane/EtOAc 3:1 → 1:1) afforded compound **Boc-4f** as a yellow foam. LCMS (ESI+) m/z = 609 $[M+Na]^+$, 487 $[M\text{-}Boc]^+$, 387 $[M\text{-}2Boc]^+$.

Compound **4f** was prepared from **Boc-4f** following Method C. Obtained as light-yellow powder (260 mg, 40% yield over 2 steps).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.17 (s, 1H), 9.73 (s, 1H), 8.47 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.84 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.71 (bs, 3H), 7.63 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.15 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.91 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.85 – 2.73 (m, 2H), 2.71 – 2.44 (m, 4H, partially overlaps with solvent peak), 2.13 – 2.02 (m, 1H), 1.70 – 1.45 (m, 4H), 1.43 – 1.31 (m, 2H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.26, 172.30, 170.28, 168.14, 167.12, 136.94, 136.60, 131.93, 126.83, 118.87, 117.51, 65.40, 49.36, 36.69, 31.40, 27.25, 25.79, 24.68, 22.45.
**HRMS (ESI):** calcd for $C_{19}H_{23}N_4O_5$ $[M\text{-}CF_3COO^-]^+$ 387.1663, found 387.1665.

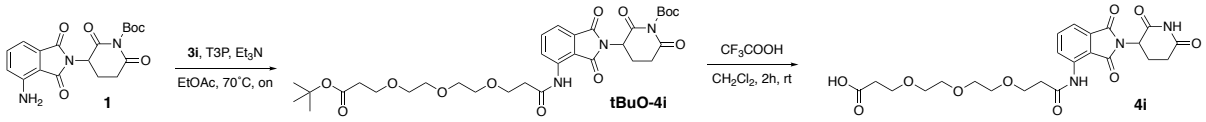
Synthesis of CRBN-P2-COOH (**4h**)




Compound ***t*BuO-4h** was prepared following Method A, starting from Boc-Pomalidomide **1** (3.62 mmol, 1.352 g) and linker **3h** (3.62 mmol, 0.950 g). Flash chromatography (Hexane/EtOAc 7:3 → 1:2) afforded compound ***t*BuO-4h** as a yellow foam. LCMS (ESI+) m/z = 641 $[M+Na]^+$.

Compound **4h** was prepared from ***t*BuO-4h** following Method C. Obtained as light-yellow powder (0.835 g, 50% yield over 2 steps).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.15 (bs, 1H), 11.17 (s, 1H), 9.90 (s, 1H), 8.55 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.84 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.62 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.15 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.63 – 3.55 (m, 4H), 3.55 – 3.49 (m, 2H), 2.91 (ddd, *J* = 16.7, 13.7, 5.3 Hz, 1H), 2.71 (t, *J* = 6.0 Hz, 2H), 2.66 – 2.52 (m, 2H), 2.40 (t, *J* = 6.3 Hz, 2H), 2.13 – 2.02 (m, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.24, 173.09, 170.90, 170.27, 168.12, 167.14, 136.91, 136.62, 131.93, 126.48, 118.75, 117.14, 70.10, 69.86, 66.66, 66.58, 49.37, 37.98, 35.15, 31.40, 22.44.
**HRMS (ESI):** calcd for $C_{21}H_{23}N_3NaO_9$ $[M+Na]^+$ 484.1327, found 484.1327.

Synthesis of CRBN-P3-COOH (**4i**)

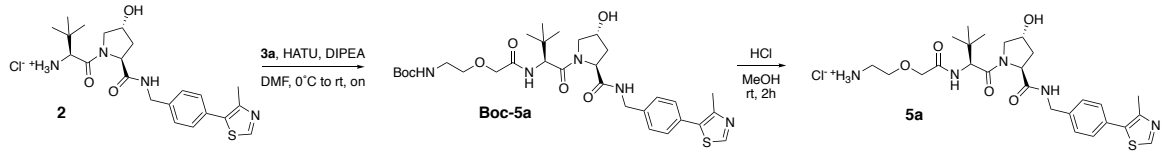



Compound ***t*BuO-4i** was prepared following Method A, starting from Boc-Pomalidomide **1** (3.26 mmol, 1.218 g) and linker **3i** (3.26 mmol, 1.00 g). Flash chromatography (Hexane/EtOAc 1:1 → 0:100) afforded compound ***t*BuO-4i** as a yellow foamy solid. LCMS (ESI+) m/z = 685 $[M+Na]^+$.

Compound **4i** was prepared from ***t*BuO-4i** following Method C. Obtained as light-yellow powder (0.627 g, 38% yield over 2 steps).

**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.19 (bs, 1H), 11.17 (s, 1H), 9.90 (s, 1H), 8.55 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.84 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.62 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.15 (dd, *J* = 12.7, 5.4 Hz, 1H), 3.74 (t, *J* = 6.0 Hz, 2H), 3.63 – 3.51 (m, 6H), 3.52 – 3.42 (m, 4H), 2.91 (ddd, *J* = 16.8, 13.7, 5.4 Hz, 1H), 2.71 (t, *J* = 6.0 Hz, 2H), 2.66 – 2.54 (m, 2H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.12 – 2.03 (m, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 173.24, 173.10, 170.91, 170.26, 168.11, 167.14, 136.92, 136.63, 131.93, 126.50, 118.76, 117.15, 70.19, 70.14, 70.04, 70.02, 66.68, 66.59, 49.36, 37.98, 35.20, 31.40, 22.44.
**HRMS (ESI):** calcd for $C_{23}H_{27}N_3NaO_{10}$ $[M+Na]^+$ 528.1589, found 528.1588.

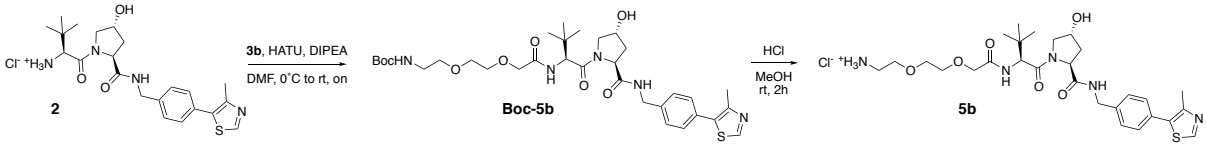
Synthesis of VHL-PEG1-$NH_3Cl$ (**5a**)




Compound **Boc-5a** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (1.59 mmol, 743 mg) and linker **3a** (1.59 mmol, 349 mg). Flash chromatography (EtOAc/MeOH 98:2 → 8:2) afforded compound **Boc-5a** as a pale-yellow sticky foam. LCMS (ESI+) m/z = 632 $[M+H]^+$, 532 $[M-Boc]^+$.

Compound **5a** was prepared from **Boc-5a** following Method D. Obtained as a pale-yellow solid (578 mg, 64% yield over 2 steps).
**$^1$H NMR (400 MHz, MeOD)** δ 10.01 (s, 1H), 7.63 – 7.51 (m, 4H), 4.74 (s, 1H), 4.64 – 4.50 (m, 3H), 4.45 (d, *J* = 15.6 Hz, 1H), 4.23 – 4.08 (app. q, 2H), 3.96 – 3.89 (m, 1H), 3.88 – 3.73 (m, 3H), 3.25 – 3.17 (m, 2H), 2.63 (s, 3H), 2.33 – 2.22 (m, 1H), 2.10 (ddd, *J* = 13.4, 9.4, 4.3 Hz, 1H), 1.08 (s, 9H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 172.97, 170.67, 170.21, 155.24, 141.25, 140.98, 136.12, 129.08, 128.06, 126.57, 69.64, 69.18, 67.07, 59.47, 57.18, 56.80, 42.21, 39.09, 37.70, 35.48, 25.53, 11.62.
**HRMS (ESI):** calcd for $C_{26}H_{37}N_5NaO_5S$ $[M+Na-HCl]^+$ 554.2408, found 554.2408.

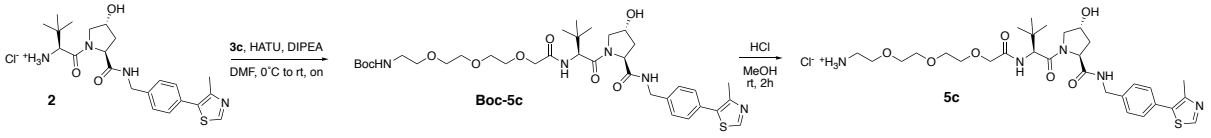
Synthesis of VHL-PEG2-$NH_3Cl$ (**5b**)




Compound **Boc-5b** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (3.15 mmol, 1.471 g) and linker **3b** (3.15 mmol, 0.829 g). Flash chromatography (EtOAc/MeOH 98:2 → 8:2) afforded compound **Boc-5b** as a yellow sticky foam. LCMS (ESI+) m/z = 677 $[M+H]^+$, 577 $[M-Boc]^+$.

Compound **5b** was prepared from **Boc-5b** following Method D. Obtained after lyophilization as a pale-yellow fluffy solid (0.925 g, 48% yield over 2 steps).
Product obtained in mixture with a small amount of bis-HCl salt.
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 9.10 (s, 1H), 8.71 (t, *J* = 6.1 Hz, 1H), 8.06 (bs, 3H), 7.50 (d, *J* = 9.5 Hz, 1H), 7.41 (s, 4H), 4.63 – 4.42 (m, 3H, overlaps with solvent peak), 4.43 – 4.33 (m, 2H), 4.29 (dd, *J* = 15.7, 5.8 Hz, 1H), 4.08 – 3.94 (m, 2H), 3.72 – 3.58 (m, 8H), 2.97 (q, *J* = 5.6 Hz, 2H), 2.46 (s, 3H), 2.09 (dd, *J* = 12.7, 7.9 Hz, 1H), 1.91 (ddd, *J* = 13.0, 8.9, 4.5 Hz, 1H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 172.18, 169.67, 169.16, 152.37, 147.56, 140.14, 131.98, 129.87, 129.19, 128.00, 70.67, 69.97, 69.31, 67.18, 59.25, 57.11, 56.23, 49.05, 42.14, 38.95, 38.39, 36.30, 26.68, 16.12.
**HRMS (ESI):** calcd for $C_{28}H_{42}N_5O_6S$ $[M-Cl^-]^+$ 576.2850, found 576.2844.

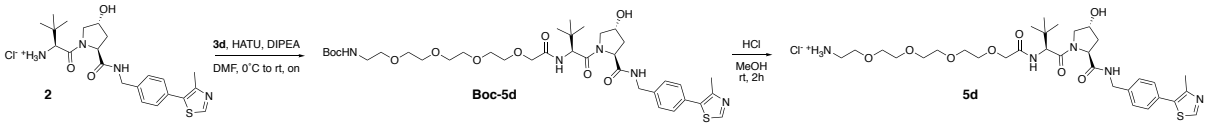
Synthesis of VHL-PEG3-$NH_3Cl$ (**5c**)




Compound **Boc-5c** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (2.78 mmol, 1.298 g) and linker **3c** (2.78 mmol, 0.855 g). Flash chromatography (EtOAc/MeOH 98:2 → 85:15) afforded compound **Boc-5c** as a yellow sticky foam. LCMS (ESI+) m/z = 720 $[M+H]^+$, 742 $[M+Na]^+$.

Compound **5c** was prepared from **Boc-5c** following Method D. Obtained after lyophilization as a pale-yellow solid (1.259 g, 69% yield over 2 steps).
Product obtained in mixture with a small amount of bis-HCl salt.
**$^1$H NMR (400 MHz, MeOD)** δ 10.09 (s, 1H), 7.65 – 7.54 (m, 4H), 4.72 (s, 1H), 4.67 – 4.51 (m, 3H), 4.47 (d, *J* = 15.7 Hz, 1H), 4.12 (d, *J* = 1.1 Hz, 2H), 3.96 – 3.88 (m, 1H), 3.83 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.79 – 3.67 (m, 10H), 3.16 (t, *J* = 5.0 Hz, 2H), 2.65 (s, 3H), 2.36 – 2.25 (m, 1H), 2.10 (ddd, *J* = 13.4, 9.4, 4.3 Hz, 1H), 1.07 (s, 9H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 173.08, 170.73, 170.46, 155.51, 141.33, 140.61, 136.34, 129.13, 128.14, 126.41, 70.56, 70.17, 70.00, 69.83, 69.68, 69.60, 66.49, 59.52, 56.96, 56.76, 42.21, 39.33, 37.76, 35.57, 25.60, 11.60.
**HRMS (ESI):** calcd for $C_{30}H_{46}N_5O_7S$ $[M-Cl^-]^+$ 620.3112, found 620.3105.

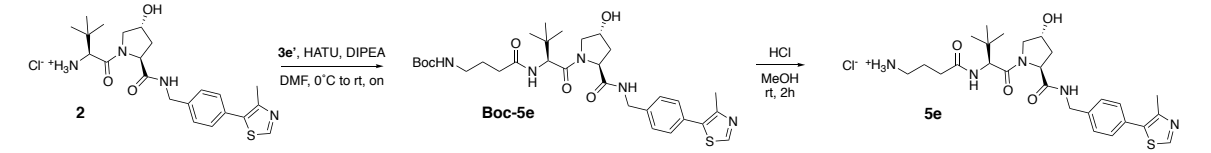
Synthesis of VHL-PEG4-$NH_3Cl$ (**5d**)




Compound **Boc-5d** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (1.14 mmol, 533 mg) and linker **3d** (1.14 mmol, 401 mg). Flash chromatography (EtOAc/MeOH 98:2 → 8:2) afforded compound **Boc-5d** as a yellow sticky foam. LCMS (ESI+) m/z = 765 $[M+H]^+$, 665 $[M-Boc]^+$.

Compound **5d** was prepared from **Boc-5d** following Method D. Obtained after lyophilization as a pale-yellow fluffy solid (551 mg, 69% yield over 2 steps).
Product obtained in mixture with a small amount of bis-HCl salt.
**$^1$H NMR (500 MHz, MeOD)** δ 9.49 (s, 1H), 7.57 – 7.48 (m, 4H), 4.67 (s, 1H), 4.61 – 4.51 (m, 3H), 4.42 (d, *J* = 15.6 Hz, 1H), 4.13 (app. d, *J* = 1.2 Hz, 2H), 3.97 – 3.89 (m, 1H), 3.83 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.78 – 3.63 (m, 16H), 3.17 – 3.12 (m, 2H), 2.57 (s, 3H), 2.27 (ddt, *J* = 13.1, 7.5, 1.9 Hz, 1H), 2.11 (ddd, *J* = 13.2, 9.4, 4.4 Hz, 1H), 1.07 (s, 9H).
**$^{13}$C NMR (126 MHz, MeOD)** δ 173.00, 170.86, 170.51, 153.48, 144.08, 140.14, 134.21, 129.04, 128.22, 127.83, 70.50, 70.04, 69.92, 69.85, 69.68, 69.45, 69.30, 66.43, 59.49, 57.30, 56.72, 42.25, 39.07, 37.76, 35.33, 25.57, 12.94.
**HRMS (ESI):** calcd for $C_{32}H_{50}N_5O_8S$ $[M-Cl^-]^+$ 664.3375, found 664.3378.

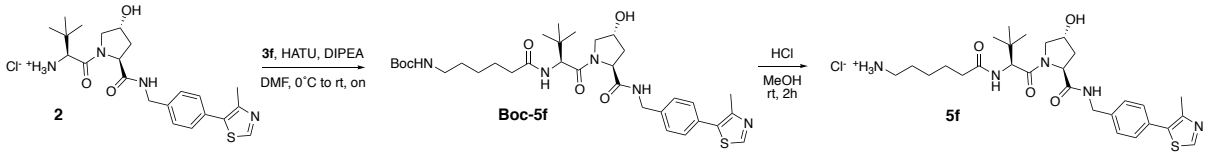
Synthesis of VHL-C3-$NH_3Cl$ (**5e**)




Compound **Boc-5e** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (0.75 mmol, 351 mg) and linker **3e'** (0.75 mmol, 153 mg). Flash chromatography (EtOAc/MeOH 100:0 → 8:2) afforded compound **Boc-5e** as a yellow foam. LCMS (ESI+) m/z = 617 $[M+H]^+$, 516 $[M-Boc]^+$.

Compound **5e** was prepared from **Boc-5e** following Method D. Obtained as a yellow foamy solid (290 mg, 70% yield over 2 steps).
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 9.27 (s, 1H), 8.65 (t, *J* = 6.0 Hz, 1H), 8.14 (bs, 3H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.53 – 7.37 (m, 4H), 4.53 (d, *J* = 9.2 Hz, 1H), 4.49 – 4.37 (m, 2H), 4.35 (s, 1H), 4.23 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.71 – 3.59 (m, 2H), 2.81 – 2.68 (m, 2H), 2.47 (s, 3H), 2.43 – 2.32 (m, 1H), 2.31 – 2.21 (m, 1H), 2.11 – 2.00 (m, 1H), 1.89 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H), 1.83 – 1.73 (m, 2H), 0.94 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 172.42, 171.71, 169.99, 152.95, 146.45, 140.47, 132.57, 129.29, 129.13, 127.95, 69.30, 59.18, 57.03, 56.84, 42.09, 38.87, 38.41, 35.69, 32.26, 26.86, 23.90, 15.66.
**HRMS (ESI):** calcd for $C_{32}H_{50}N_5O_8S$ $[M\text{-}Cl^-]^+$ 516.2639, found 516.2627.

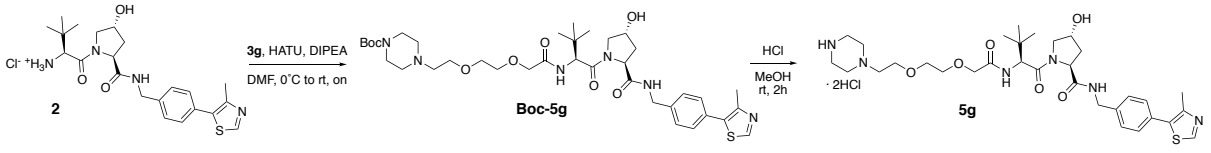
Synthesis of VHL-C5-$NH_3Cl$ (**5f**)




Compound **Boc-5f** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (1.297 mmol, 606 mg) and linker **3f** (1.297 mmol, 300 mg). Flash chromatography (EtOAc/MeOH 100:0 → 9:1) afforded compound **Boc-5f** as a yellow foam. LCMS (ESI+) m/z = 644 $[M+H]^+$, 544 $[M\text{-}Boc]^+$.

Compound **5f** was prepared from **Boc-5f** following Method D. Obtained as a yellow foamy solid (497 mg, 66% yield over 2 steps).
Product obtained in mixture with a small amount of bis-HCl salt.
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 9.32 (s, 1H), 8.67 (t, *J* = 6.1 Hz, 1H), 8.10 (bs, 3H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.48 – 7.37 (m, 4H), 4.53 (d, *J* = 9.4 Hz, 1H), 4.46 – 4.38 (m, 2H), 4.37 – 4.32 (m, 1H), 4.22 (dd, *J* = 15.9, 5.4 Hz, 1H), 3.73 – 3.60 (m, 2H), 2.78 – 2.67 (m, 2H), 2.48 (s, 3H), 2.31 – 2.21 (m, 1H), 2.19 – 2.10 (m, 1H), 2.09 – 2.00 (m, 1H), 1.89 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H), 1.61 – 1.40 (m, 4H), 1.27 (p, *J* = 7.7 Hz, 2H), 0.93 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 172.45, 170.15, 152.96, 146.47, 140.50, 132.59, 129.30, 129.14, 127.97, 69.30, 59.17, 56.82, 42.09, 39.01, 38.44, 35.67, 35.12, 27.15, 26.87, 26.04, 25.39, 15.67.
**HRMS (ESI):** calcd for $C_{32}H_{50}N_5O_8S$ $[M\text{-}Cl^-]^+$ 544.2952, found 544.2944.

Synthesis of VHL-PEG2-Pip-NHCl (**5g**)

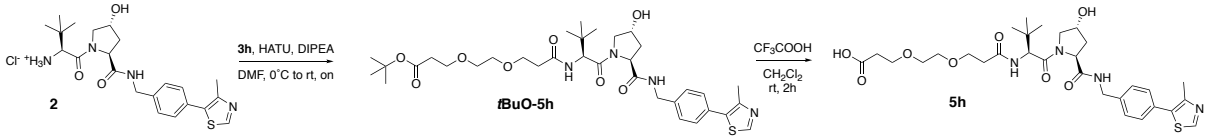



Linker **3g** (crude from previous step) and 4 A˚ MS (100 mg) were suspended in dry DMF (4.85 mL, 0.2M) and stirred for 30 minutes at room temperature. (*S,R,S*)-AHPC hydrochloride **2** (453 mg, 0.97 mmol) was added and the suspension was cooled to 0 ˚C. HATU (442 mg, 1.2 equiv.) and DIPEA (0.76 mL, 4.5 equiv.) were added and the mixture was stirred overnight at room temperature. Solution was cooled down to 0 ˚C and water (20 mL) was added. Aqueous layer was extracted with EtOAc, then organics washed twice with 1:1 water/brine mixture and once with brine. Purification by flash chromatography (EtOAc/MeOH 3:1) afforded the desired product **Boc-5g** as an off-white foam. LCMS (ESI-) m/z = 743 $[M\text{-}H]^-$, 789 $[M+HCOO]^-$.

Compound **5g** was prepared from **Boc-5g** following Method D. Obtained as a yellow solid (390 mg, 56% yield over 2 steps).
Product obtained as bis-HCl salt.
**$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.86 (bs, 1H), 9.96 (bs, 2H), 9.12 (s, 1H), 8.77 (t, *J* = 6.2 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1H), 7.42 (s, 4H), 4.59 (d, *J* = 9.5 Hz, 1H), 4.52 (t, *J* = 8.2 Hz, 1H), 4.42 – 4.27 (m, 3H), 4.07 – 3.93

(m, 2H), 3.87 (s, 2H), 3.76 – 3.59 (m, 8H), 3.42 (q, *J* = 15.2 Hz, 8H), 2.47 (s, 3H), 2.14 – 2.05 (m, 1H), 1.91 (td, *J* = 10.9, 4.5 Hz, 1H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 172.28, 169.64, 169.10, 152.38, 147.51, 140.18, 131.99, 129.84, 129.19, 127.98, 70.49, 69.97, 69.78, 69.33, 65.08, 59.23, 57.15, 56.23, 55.27, 48.71, 42.10, 38.40, 36.29, 34.61, 26.71, 16.13.

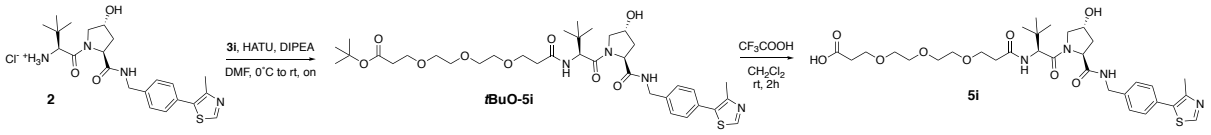
Synthesis of VHL-P2-COOH (**5h**)




Compound ***t*BuO-5h** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (3.09 mmol, 1.443 g) and linker **3h** (3.09 mmol, 0.811 g). Flash chromatography (EtOAc/MeOH 98:2 → 85:15) afforded compound ***t*BuO-5h** as light-yellow foam. LCMS (ESI+) m/z = 675 [M+H]

Compound **5h** was prepared from ***t*BuO-5h** following Method E. Obtained as an off-white foam (0.899 g, 47% yield over 2 steps).
**$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.76 (s, 1H), 7.38 (s, 4H), 7.37 – 7.30 (m, 2H), 4.73 (t, *J* = 8.2 Hz, 1H), 4.65 (dd, *J* = 15.1, 6.9 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.33 (dd, *J* = 15.1, 5.1 Hz, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 3.85 – 3.74 (m, 3H), 3.71 – 3.55 (m, 6H), 2.63 – 2.49 (m, 6H), 2.44 (ddd, *J* = 13.2, 8.6, 4.4 Hz, 1H), 2.27 – 2.17 (m, 1H), 0.99 (s, 9H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 174.34, 172.52, 172.16, 170.96, 150.46, 148.01, 138.37, 131.92, 130.56, 129.44, 128.05, 70.87, 70.21, 70.06, 67.24, 66.68, 58.97, 58.00, 57.02, 43.15, 36.94, 36.52, 35.36, 35.10, 26.47, 15.87.
**HRMS (ESI)**: calcd for $C_{30}H_{43}N_4O_8S$ $[M+H]^+$ 619.2796, found 619.2786.

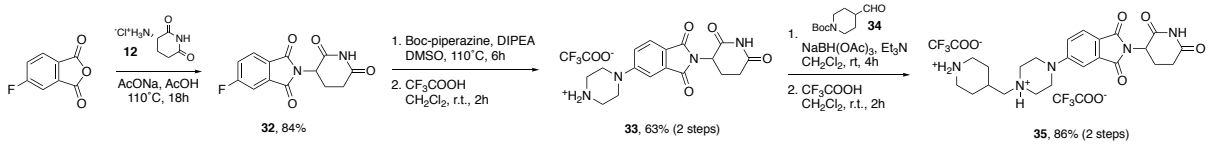
Synthesis of VHL-P3-COOH (**5i**)




Compound ***t*BuO-5i** was prepared following Method B, starting from (*S,R,S*)-AHPC hydrochloride **2** (3.26 mmol, 1.523 g) and linker **3i** (3.26 mmol, 1.00 g). Flash chromatography (EtOAc/MeOH 98:2 → 85:15) afforded compound ***t*BuO-5i** as light-yellow foam. LCMS (ESI+) m/z = 719 $[M+H]^+$, 741 $[M+Na]^+$.

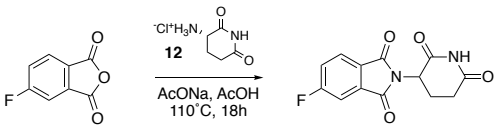
Compound **5i** was prepared from ***t*BuO-5i** following Method E. Obtained as an off-white foamy solid (1.34 g, 62% yield over 2 steps).
**$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.73 (s, 1H), 7.47 – 7.40 (m, 2H), 7.37 (s, 4H), 5.69 (bs, 2H), 4.71 (t, *J* = 8.2 Hz, 1H), 4.67 – 4.58 (m, 2H), 4.53 (bs, 1H), 4.32 (dd, *J* = 15.1, 5.2 Hz, 1H), 4.13 (d, *J* = 11.3 Hz, 1H), 3.75 (t, *J* = 5.8 Hz, 2H), 3.73 – 3.53 (m, 11H), 2.60 – 2.46 (m, 7H), 2.41 (ddd, *J* = 13.1, 8.5, 4.5 Hz, 1H), 2.21 (dd, *J* = 13.5, 7.9 Hz, 1H), 0.98 (s, 9H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 174.37, 172.62, 171.85, 171.13, 150.49, 148.16, 138.34, 131.83, 130.61, 129.43, 128.03, 70.51, 70.43, 70.40, 70.14, 67.14, 66.66, 58.97, 57.75, 57.04, 43.12, 36.68, 36.59, 35.31, 35.17, 26.39, 15.90.
**HRMS (ESI):** calcd for $C_{32}H_{47}N_4O_9S$ $[M+H]^+$ 663.3058, found 663.3053.

Synthesis of partial PROTAC **35**



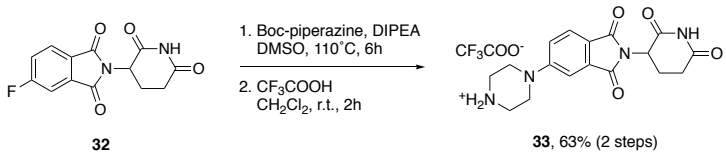

***Scheme S9*** *– synthesis of partial PROTAC **35***

Synthesis of compound **32**:



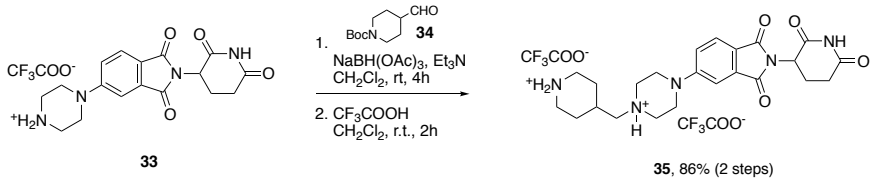

Compound **12** (438 mg, 2.66 mmol, 1 equiv.) and sodium acetate (240 mg, 2.93 mmol, 1.1 equiv.) were suspended in acetic acid (4 mL) and stirred for 5 minutes, then 4-fluorophthalic anhydride (442 mg, 2.66 mmol, 1 equiv.) was added and the white suspension was stirred for 18 hours at 110 ˚C. The suspension turned gradually from white to purple-brown. The suspension was cooled down to room temperature and the light grey-purple solid was collected by filtration. The solid was washed with water to remove acetic acid and salts. Drying the solid under vacuum afforded the pure compound **32** as a light grey-purple powder (620 mg, 84% yield).
**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 11.15 (s, 1H), 8.01 (dd, *J* = 8.3, 4.5 Hz, 1H), 7.85 (dd, *J* = 7.5, 2.3 Hz, 1H), 7.72 (ddd, *J* = 9.4, 8.3, 2.4 Hz, 1H), 5.17 (dd, *J* = 12.8, 5.4 Hz, 1H), 2.90 (ddd, *J* = 16.9, 13.8, 5.4 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.14 – 2.02 (m, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 173.22, 170.21, 166.65, 166.44 (d, $J_{C-F}$ = 254.2 Hz), 166.35 (d, $J_{C-F}$ = 2.9 Hz), 134.65 (d, $J_{C-F}$ = 9.9 Hz), 127.87 (d, $J_{C-F}$ = 2.6 Hz), 126.74 (d, $J_{C-F}$ = 9.8 Hz), 122.22 (d, $J_{C-F}$ = 23.8 Hz), 111.88 (d, $J_{C-F}$ = 25.3 Hz), 49.65, 31.37, 22.40.

Synthesis of compound **33**:




Compound **32** (552 mg, 2.0 mmol, 1 equiv.) and 1-Boc-piperazine (372 mg, 2.0 mmol, 1 equiv.) were dissolved in DMSO (10 mL). DIPEA (0.70 mL, 4.0 mmol, 2 equiv.) was added and solution was stirred at 110˚ C for 6 hours. The solution turned from purple-grey to yellow-brown. Solution was cooled down to room temperature, water (30 mL) and EtOAc (30 mL) were added shaken in a separation funnel and phases separated. Aqueous layer was extracted twice more with EtOAc, then the joined organic layers were washed three times with water/brine 1:1 (30 mL), then with brine (30 mL). Crude was purified by flash chromatography (eluent $CH_2Cl_2$/MeOH, gradient 0% → 20%) to afford the pure Boc-protected compound as a yellow foam (670 mg, 75% yield). LCMS: m/z 443 $[M+H]^+$, 343 $[M\text{-Boc}]^+$.
The material obtained from the column was dissolved in $CH_2Cl_2$ (3 mL), trifluoroacetic acid (3 mL) was added, then the solution was stirred at room temperature for 2 hours. The solvent was evaporated and the residue triturated with $Et_2O$. Solid was collected by filtration, washed several times with $Et_2O$ and dried under vacuum, affording pure compound **33** as sand-yellow solid (607 mg, 63% yield over two steps).
**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 11.10 (s, 1H), 9.04 (s, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.34 (dd, *J* = 8.6, 2.4 Hz, 1H), 5.10 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.72 – 3.65 (m, 4H), 3.32 – 3.22 (m, 4H), 2.90 (ddd, *J* = 17.4, 14.1, 5.5 Hz, 1H), 2.66 – 2.53 (m, 2H), 2.09 – 1.98 (m, 1H).
**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 173.27, 170.49, 167.87, 167.37, 154.90, 134.27, 125.46, 120.22, 119.13, 109.35, 49.32, 44.73, 42.76, 31.44, 22.61.

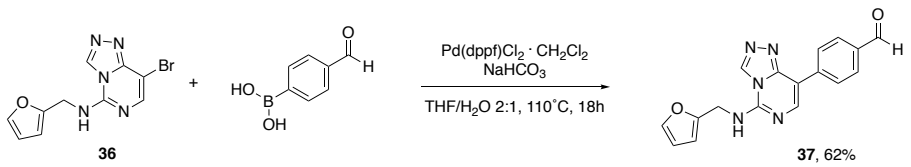
Synthesis of compound **35**:




Compound **33** (146 mg, 0.317 mmol, 1 equiv.) and aldehyde **34** (68 mg, 0.317 mmol, 1 equiv.) were dissolved in $CH_2Cl_2$ (3.2 mL). Triethylamine (0.088 mL, 0.634 mmol, 2 equiv.) was added and suspension stirred for 1 hour. Sodium triacetoxyborohydride (134 mg, 0.634 mmol, 2 equiv.) was added portionwise and suspension was stirred at room temperature until disappearance of starting materials. After 4 hours, water (5 mL) was added (*GAS EVOLUTION!*) and mixture stirred for 5 minutes. Layers were separated and aqueous layer was extracted with 3x10 mL of $CH_2Cl_2$. Crude was purified by flash chromatography (eluent $CH_2Cl_2$/MeOH, gradient 0% → 20%) to afford the pure Boc-protected compound as a yellow solid (156 mg, 91% yield). LCMS: m/z 540 $[M+H]^+$, 440 $[M\text{-}Boc]^+$.
The material obtained from the column was dissolved in 1.5 mL of $CH_2Cl_2$, 1.5 mL of trifluoroacetic acid was added, then the solution was stirred at room temperature for 2 hours. The solvent was evaporated and the residue triturated with $Et_2O$. Solid was collected by filtration, washed several times with $Et_2O$ and dried under vacuum, affording pure compound **35** as fluo-yellow solid (183 mg, 86% yield over two steps).
**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 11.10 (s, 1H), 10.12 (bs, 1H), 8.81 – 8.74 (m, 1H), 8.54 – 8.48 (m, 1H), 7.77 (d, $J$ = 8.5 Hz, 1H), 7.50 (d, $J$ = 2.3 Hz, 1H), 7.37 (dd, $J$ = 8.6, 2.4 Hz, 1H), 5.10 (dd, $J$ = 12.9, 5.4 Hz, 1H), 4.21 (bs, 2H), 3.38 – 3.25 (m, 4H), 3.18 – 3.03 (m, 3H), 2.97 – 2.83 (m, 3H), 2.66 – 2.53 (m, 2H), 2.20 – 2.11 (m, 1H), 2.07 – 1.99 (m, 1H), 1.92 (d, $J$ = 13.7 Hz, 2H), 1.45 – 1.30 (m, 2H). 3 protons overlap with solvent.
**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 173.27, 170.49, 167.89, 167.37, 158.77 (q, $J_{C\text{-}F}$ 32.0 Hz), 154.64, 134.28, 125.47, 120.32, 119.20, 109.43, 60.39, 51.22, 49.33, 44.60, 42.98, 31.44, 28.65, 26.71, 22.61.
**HRMS (ESI):** calcd for $C_{23}H_{30}N_5O_4$ $[M\text{-}2CF_3COO^-]^+$ 440.2292, found 440.2287.

## 3.2 Synthesis and spectral data of protein binders

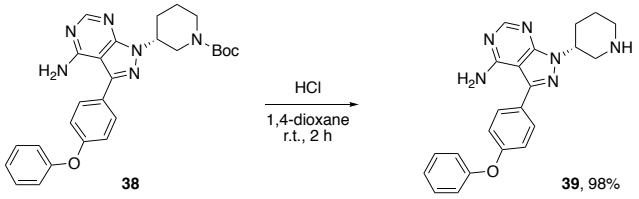
Synthesis of compound **37**:




Compound synthesized following a modified reported procedure.[12]
An oven-dried microwave vial was loaded with aryl bromide **36** (117.6 mg, 0.40 mmol, 1 equiv.), 4-formylboronic acid (90.0 mg, 0.60 mmol, 1.5 equiv.), $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (65.3 mg, 0.08 mmol, 0.2 equiv.) and sodium bicarbonate (84.0 mg, 1.0 mmol, 2.5 equiv.). The vial was sealed with a septum-cap and purged three times with vacuum/$N_2$ cycles. Previously degassed THF (2.4 mL) and $H_2O$ (1.2 mL) were added with a syringe and the mixture was stirred at 110 °C for 18 hours. The reaction was cooled down to room temperature, filtered through a Celite pad and the filter cake was washed with 3x5 mL of EtOAc. The crude product obtained this way was purified by flash chromatography ($CH_2Cl_2$/MeOH, gradient 3% → 30%) affording pure compound **37** as a yellow-brown solid (79.7 mg, 62% yield).
**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 10.04 (s, 1H), 9.50 (s, 1H), 9.08 (bs, 1H), 8.46 – 8.39 (m, 2H), 8.03 – 7.96 (m, 2H), 7.65 (dd, $J$ = 1.8, 0.9 Hz, 1H), 6.47 (dd, $J$ = 3.3, 0.9 Hz, 1H), 6.45 (dd, $J$ = 3.2, 1.8 Hz, 1H), 4.80 (s, 2H).
**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 192.98, 151.45, 148.78, 144.53, 143.08, 142.43, 140.02, 135.15, 133.54, 130.18, 127.72, 111.10, 110.26, 108.48, 38.23.

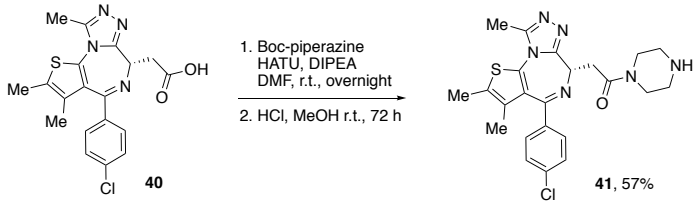
[12] F. Potjewyd, A. M. W. Turner, J. Beri, J. M. Rectenwald, J. L. Norris-Drouin, S. H. Cholensky, D. M. Margolis, K. H. Pearce, L. E. Herring, L. I. James; *Cell. Chem. Biol.* **2020**, 27, 47-56.

Synthesis of compound **39**:




Compound synthesized following reported procedure.[13]
Compound **38** (500 mg, 1.0 mmol) was stirred in 4M HCl in dioxane (1 mL) for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was suspended in EtOAc before being filtered. The residue was washed with EtOAc and dried under reduced pressure. The white solid was neutralised with a 1M NaOH aqueous solution. The water phase was extracted three times with EtOAc. The organic layers were combined and washed with $H_2O$ and brine. The organic layer was dried with $Na_2SO_4$ and concentrated *in vacuo* to provide compound **39** as a white solid (430 mg, 98% yield).
**$^1$H NMR (500 MHz, MeOD)** δ 8.22 (s, 1H), 7.66 – 7.59 (m, 2H), 7.40 – 7.32 (m, 2H), 7.16 – 7.12 (m, 1H), 7.11 – 7.07 (m, 2H), 7.06 – 7.02 (m, 2H), 4.85 – 4.79 (m, 1H), 3.26 – 3.22 (m, 2H), 3.05 (s, 1H), 2.72 (ddd, *J* = 12.8, 11.3, 3.1 Hz, 1H), 2.28 – 2.16 (m, 1H), 2.15 – 2.06 (m, 1H), 1.90 – 1.85 (m, 1H), 1.78 – 1.66 (m, 1H).
**$^{13}$C NMR (126 MHz, MeOD)** δ 159.83, 157.80, 156.59, 154.83, 145.66, 131.20, 131.04, 128.79, 125.05, 120.47, 119.90, 99.12, 54.71, 50.44, 46.05, 30.98, 25.91.

Synthesis of compound **41**:




Compound **40** (300.0 mg, 0.75 mmol) was dissolved in DMF (7.5 mL). 1-Boc-piperazine (167.3 mg, 0.90 mmol), HATU (426.8 mg, 1.12 mmol) and DIPEA (290.2 mg, 2.24 mmol) were added to the solution. The solution was stirred overnight at room temperature. Water (10 mL) was added to the solution. The compound was extracted three times with EtOAc (20 mL). The organic layers were combined and washed with $H_2O$ and brine. The organic layer was dried with $Na_2SO_4$ and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (eluent: hexane/EtOAc 100/0 to EtOAc/MeOH 9:1). The pure compound was obtained as a white solid (256 mg, 60% yield). LCMS: m/z 569 $[M+H]^+$.
The solid obtained from the column (256 mg, 0.45 mmol) was stirred in 4.0 M HCl in MeOH (3.5 mL) for 3 days. The reaction mixture was concentrated *in vacuo* and the residue was suspended in $Et_2O$ before being filtered. The residue was washed with $Et_2O$ and dried under reduced pressure. The yellow solid was neutralised with a 1M NaOH aqueous solution. The water phase was extracted three times with EtOAc. The organic layers were combined and washed with $H_2O$ and brine. The organic layer was dried with $Na_2SO_4$ and concentrated *in vacuo* to provide the compound **41** as a yellow solid (200.5 mg, 57% yield over two steps).
**$^1$H NMR (500 MHz, MeOD)** δ 7.43-7.48 (m, 2H), 7.42-7.39 (m, 2H), 4.70 (dd, *J* = 7.5, 6.3 Hz, 1H), 3.69-3.81 (m, 2H), 3.50-3.67 (m, 4H), 2.91-3.02 (m, 2H), 2.84 (t, *J* = 5.2 Hz, 2H), 2.70 (s, 3H), 2.44 (d, *J* = 0.8 Hz, 3H), 1.69 (d, *J* = 0.8 Hz, 3H).
**$^{13}$C NMR (126 MHz, MeOD)** δ 170.70, 166.11, 157.21, 152.08, 138.19, 137.91, 133.50, 133.17, 132.06, 132.01, 131.32, 129.78, 55.39, 47.48, 46.53, 46.17, 43.49, 35.89, 14.35, 12.94, 11.60.
**HRMS (ESI):** calcd for $C_{23}H_{26}ClN_6OS$ $[M+H]^+$ 469.1572, found 469.1568.

[13] N. Liu, S. Hoogendoorn, B. van de Kar, A. Kaptein, T. Barf, C. Driessen, D. V. Filippov, G. A. van der Marel, M. van der Stelt, and H. S. Overkleeft; *Org. Biomol. Chem.* **2015**, *13*, 5147-5157

# 4. AUTOMATED SYNTHESIS OF PROTACS ON THE CONSOLE

## 4.1 Synthesis of PROTACs through Reductive Amination

General procedure **A** for the automated synthesis of PROTACs via Reductive Amination:

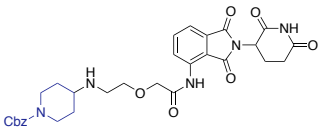
A 40 mL vial was charged with the desired carbonyl compound (0.1 mmol) and dissolved in 3 mL of $CH_2Cl_2$. 1,1,1,3,3,3-hexafluoroisopropanol (1 mL) was added and the vial was connected to the console via screw cap. The capsule, containing the partial PROTAC reagent and all the necessary reagent for reaction and purification, was inserted into the console and the capsule holder was closed. The reaction program was selected (either by manual selection or by scanning the RFID microchip on the capsule) and reaction was started. After completion of the sequence, the solution in the vial was concentrated *in vacuo* to afford the desired product.

Capsule content:

Compartment 1: Silica-supported cyanoborohydride (0.50 g)
Compartment 2: Silica-supported triethylamine (0.30 g)
Compartment 3: SCX-2 (2.0 g)
Compartment 4: partial PROTAC reagent (0.1 mmol)

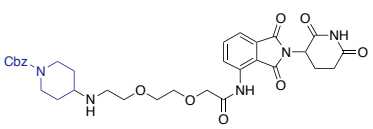
### 4.1.1. Characterization of Reaction Products

Benzyl-4-((2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethyl)amino) piperidine-1-carboxylate (**6a**)



Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **4a** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purifications as a pale-yellow solid, 40.4 mg (68%). Result is average of three runs (*see section 4.3, Reproducibility test*).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.42 (s, 1H), 8.85 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.42 – 7.27 (m, 5H), 5.21 – 5.03 (m, 2H), 5.02 – 4.88 (m, 1H), 4.31 – 3.99 (m, 4H), 3.94 – 3.60 (m, 2H), 3.13 – 2.63 (m, 8H), 2.22 – 1.88 (m, 3H), 1.43 – 1.15 (m, 3H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.37, 168.74, 168.64, 168.14, 166.73, 155.72, 136.65, 136.34, 131.30, 128.46 (2C), 127.98, 127.97 (2C), 125.18, 118.86, 116.18, 71.28, 70.51, 67.39, 54.87, 49.30, 45.78, 43.25 (2C), 32.32, 31.48, 22.81.
**HRMS (ESI):** calcd for $C_{30}H_{34}N_5O_8$ $[M+H]^+$ 592.2402, found 592.2402.

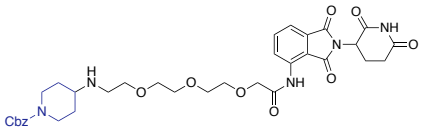
Benzyl-4-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl) amino)piperidine-1-carboxylate (**6b**)



Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **4b** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purifications as a pale-yellow solid, 45.2 mg (71%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.55 (s, 1H), 8.84 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.58 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.41 – 7.27 (m, 5H), 5.22 (bs, 1H), 5.11 (s, 2H), 5.01 – 4.92 (m, 1H), 4.27 – 4.06 (m,

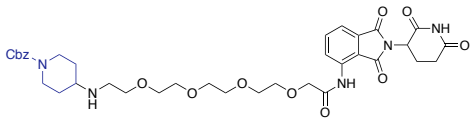
4H), 3.85 – 3.75 (m, 4H), 3.73 – 3.62 (m, 2H), 2.97 – 2.66 (m, 8H), 2.23 – 2.12 (m, 1H), 1.98 – 1.84 (m, 1H), 1.36 (qd, *J* = 11.9, 4.2 Hz, 2H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.62, 169.23, 168.76, 168.67, 166.74, 155.19, 136.75, 136.66, 136.38, 131.41, 128.48, 127.97, 127.88, 125.08, 118.85, 116.13, 71.50, 70.92, 70.36, 70.15, 67.12, 54.93, 49.27, 45.53, 42.68, 31.52, 31.27, 22.98.
**HRMS (ESI):** calcd for $C_{32}H_{37}N_5NaO_9$ $[M+Na]^+$ 658.2483, found 658.2475.

Benzyl-4-((2-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxoethoxy)ethoxy)ethyl)amino)piperidine-1-carboxylate (**6c**)



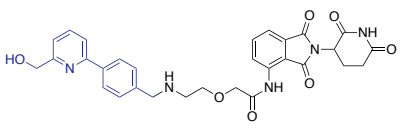
Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **4c** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a pale-yellow solid, 38.8 mg (57%).
**$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 10.48 (s, 1H), 8.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.60 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.41 – 7.30 (m, 5H), 5.12 (s, 2H), 5.03 – 4.91 (m, 1H), 4.27 – 4.11 (m, 4H), 3.89 – 3.78 (m, 5H), 3.76 – 3.63 (m, 6H), 2.98 – 2.91 (m, 2H), 2.91 – 2.71 (m, 6H), 2.23 – 2.10 (m, 1H), 2.02 – 1.92 (m, 2H), 1.51 – 1.35 (m, 2H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.69, 169.28, 168.64, 168.52, 166.77, 155.16, 136.74, 136.69, 136.30, 131.44, 128.50, 128.00, 127.90, 125.26, 118.87, 116.22, 71.75, 70.96, 70.53, 70.35, 70.29, 69.25, 67.16, 55.23, 49.30, 45.44, 42.66, 31.51, 30.95, 22.90.
**HRMS (ESI):** calcd for $C_{34}H_{42}N_5O_{10}$ $[M+H]^+$ 680.2926, found 680.2926.

Benzyl-4-((14-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-14-oxo-3,6,9,12-tetraoxatetradecyl)amino)piperidine-1-carboxylate (**6d**)



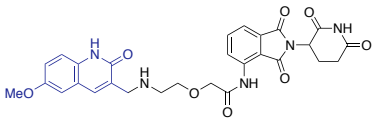
Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **4d** PROTAC reagent capsule. Reaction time 12 h. Isolated without further purification as an off-white solid, 45.6 mg (63%).
**$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 10.50 (s, 1H), 8.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 7.4 Hz, 1H), 7.59 (dd, *J* = 7.4, 0.8 Hz, 1H), 7.38 – 7.30 (m, 5H), 5.12 (s, 2H), 5.00 – 4.91 (m, 1H), 4.23 – 4.16 (m, 2H), 4.15 (s, 2H), 3.84 – 3.80 (m, 4H), 3.75 – 3.71 (m, 2H), 3.70 – 3.60 (m, 10H), 2.93 – 2.74 (m, 7H), 2.65 (tt, *J* = 10.6, 3.9 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.93 – 1.79 (m, 2H), 1.40 – 1.22 (m, 2H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.39, 169.34, 168.47, 168.31, 166.81, 155.26, 136.83, 136.70, 136.29, 131.39, 128.47, 127.94, 127.84, 125.21, 118.82, 116.17, 71.68, 70.94, 70.71, 70.49, 70.48, 70.42, 70.27, 70.24, 67.06, 54.88, 49.33, 45.84, 42.79, 32.01, 31.51, 22.72.
**HRMS (ESI):** calcd for $C_{36}H_{46}N_5O_{11}$ $[M+H]^+$ 724.3188, found 724.3178.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-2-(2-((4-(6-(hydroxymethyl)pyridin-2-yl)benzyl)amino)ethoxy)acetamide (**6e**)



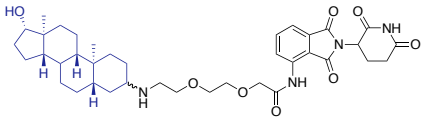
Prepared according to general procedure **A** from 2-(4-formylphenyl)-6-(hydroxymethyl)pyridine (21.3 mg, 0.1 mmol) using **4a** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a yellow foamy solid, 53.0 mg (92%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.58 (s, 1H), 8.85 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.80 – 7.66 (m, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.19 (d, *J* = 7.5 Hz, 1H), 4.82 (s, 2H), 4.64 (m, 1H), 4.27 – 4.11 (m, 2H), 3.98 (s, 2H), 3.83 (t, *J* = 4.8 Hz, 2H), 3.14 – 2.99 (m, 2H), 2.79 – 2.49 (m, 3H), 2.02 – 1.90 (m, 1H), 1.25 – 1.13 (bm, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.41, 168.82, 168.66, 167.94, 166.73, 159.06, 156.16, 141.42, 137.64, 137.35, 136.66, 136.36, 131.25, 128.03, 126.99, 125.01, 119.16, 118.77, 116.12, 70.96, 70.53, 64.38, 53.19, 49.21, 48.80, 31.37, 22.32.
**HRMS (ESI):** calcd for $C_{30}H_{30}N_5O_7$ $[M+H]^+$ 572.2140, found 572.2133.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-2-(2-(((6-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methyl)amino)ethoxy)acetamide (**6f**)



Prepared according to general procedure **A** from 2-hydroxy-6-methoxyquinoline-3-carbaldehyde (20.3 mg, 0.1 mmol) using **4a** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a yellow solid, 39.0 mg (69%).
**$^1$H NMR (400 MHz, $CD_2Cl_2$)** δ 11.66 (bs, 1H), 10.57 (bs, 1H), 8.76 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.85 (s, 1H), 7.69 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.51 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 7.04 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.96 (d, *J* = 2.7 Hz, 1H), 5.37 (s, 1H), 4.79 (dd, *J* = 11.9, 5.1 Hz, 1H), 4.26 – 4.13 (m, 2H), 3.93 – 3.82 (m, 4H), 3.80 (s, 3H), 3.17 – 2.99 (m, 2H), 2.75 (bs, 1H), 2.66 – 2.47 (m, 3H), 2.03 – 1.94 (m, 1H).
**$^{13}$C NMR (101 MHz, $CD_2Cl_2$)** δ 172.02, 168.93, 168.79, 168.56, 166.69, 162.99, 155.06, 136.64, 136.12, 136.08, 131.90, 131.80, 131.36, 124.64, 120.58, 118.97, 118.28, 116.70, 116.18, 108.62, 71.28, 70.56, 55.52, 49.19, 48.82, 48.29, 31.14, 22.60.
**HRMS (ESI):** calcd for $C_{28}H_{28}N_5O_8$ $[M+H]^+$ 562.1932, found 562.1931.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-2-(2-(2-(((5*S*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)amino)ethoxy)ethoxy)acetamide (**6g**)

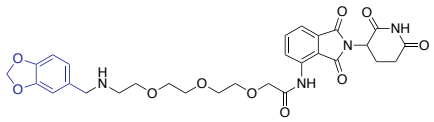


Prepared according to general procedure **A** from 5α-androstan-17β-ol-3-one (29.0 mg, 0.1 mmol) using **4b** PROTAC reagent capsule. Reaction time 3 h. Isolated as a diastereoisomeric mixture, off-white foam, 58.9 mg (85%, d.r. 72:28, determined by crude LCMS). Diastereoisomers separated by flash chromatography (eluent Acetone + 0.5% $Et_3N$). Absolute configuration not determined.

Diast. 1 (signals show extra splitting due to rotamers)
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.61 (s, 1H), 8.85 (d, *J* = 8.5 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.60 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.00 – 4.90 (m, 1H), 4.20 (q, *J* = 15.7 Hz, 2H), 3.88 – 3.75 (m, 4H), 3.73 – 3.58 (m, 3H), 3.12-3.90 (bm, 2H), 2.92 – 2.68 (m, 6H), 2.25 – 2.17 (m, 1H), 2.10 – 1.98 (m, 1H), 1.83 – 1.73 (m, 1H), 1.68 – 1.51 (m, 5H), 1.47 – 1.31 (m, 6H), 1.30 – 1.12 (m, 6H), 1.07 – 0.83 (m, 3H), 0.80 (s, 3H), 0.73 (s, 3H), 0.71 – 0.54 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.52, 169.22, 168.64 (2C), 166.75, 136.75, 136.34, 131.45, 125.04, 118.77, 116.15, 81.93, (71.52, 71.49), 70.93, 70.66, 70.31, 54.56, (52.34, 52.30), 51.09, 49.27, (46.43, 46.38), 42.98, (39.74, 39.69), 36.75, 36.24, 35.51, 32.87, (32.70, 32.64), 31.56, 31.25, 30.49, (28.57, 28.54), 25.76, 25.49, 23.35, 23.14, 20.35, 11.59, 11.15.
**HRMS (ESI):** calcd for $C_{38}H_{53}N_4O_8$ $[M+H]^+$ 693.3858, found 693.3858.

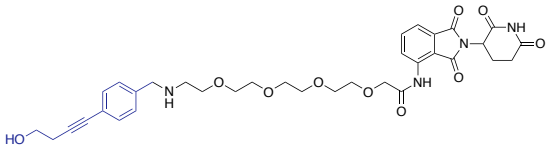
Diast. 2
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.61 (s, 1H), 8.84 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.59 (d, *J* = 7.3 Hz, 1H), 5.05 – 4.85 (m, 1H), 4.23 (d, *J* = 15.6 Hz, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 3.90 – 3.74 (m, 4H), 3.74 – 3.58 (m, 3H), 3.54 – 3.14 (bm, 2H), 2.96 – 2.80 (m, 3H), 2.80 – 2.67 (m, 2H), 2.51 (ddd, *J* = 15.5, 10.6, 4.1 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.12 – 1.99 (m, 1H), 1.84 – 1.47 (m, 7H), 1.47 – 0.87 (m, 14H), 0.78 (s, 3H), 0.74 (s, 3H), 0.68 – 0.56 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.61, 169.22, 168.79, 168.68, 166.75, 136.73, 136.34, 131.47, 125.05, 118.78, 116.19, 81.97, 71.51, 70.90, 70.75, 70.35, 57.32, 54.59, 51.05, 49.30, 45.94, 45.43, 42.99, 37.43, 36.77, 36.06, 35.54, 35.37, 35.32, 31.64, 31.25, 30.53, 28.70 (2C), 23.38, 23.16, 20.71, 12.35, 11.15.
**HRMS (ESI):** calcd for $C_{38}H_{53}N_4O_8$ $[M+H]^+$ 693.3858, found 693.3853.

1-(benzo[*d*][1,3]dioxol-5-yl)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-5,8,11-trioxa-2-azatridecan-13-amide (**6h**)



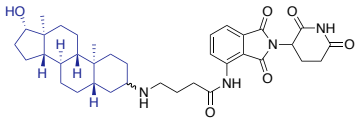
Prepared according to general procedure **A** from piperonal (15.0 mg, 0.1 mmol) using **4c** PROTAC reagent capsule. Reaction time 3 h. Isolated after filtration on silica pad as a pale-yellow solid, 43.6 mg (73%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.49 (s, 1H), 8.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.59 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.81 (dd, *J* = 1.3, 0.8 Hz, 1H), 6.77 – 6.69 (m, 2H), 5.93 (s, 2H), 5.93 (bs, 2H), 4.98 – 4.88 (m, 1H), 4.22 (d, *J* = 15.7 Hz, 1H), 4.15 (d, *J* = 15.7 Hz, 1H), 3.87 – 3.76 (m, 4H), 3.76 – 3.69 (m, 4H), 3.68 – 3.56 (m, 4H), 2.91 – 2.69 (m, 5H), 2.19 – 2.10 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.81, 169.27, 168.59, 168.43, 166.84, 147.66, 146.50, 136.69, 136.23, 133.60, 131.42, 125.19, 121.41, 118.78, 116.20, 108.75, 108.07, 100.89, 71.79, 70.90, 70.62, 70.37, 70.33, 70.21, 53.09, 49.27, 47.91, 31.51, 22.90.
**HRMS (ESI):** calcd for $C_{29}H_{32}N_4NaO_{10}$ $[M+Na]^+$ 619.2011, found 619.2003.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-1-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-5,8,11,14-tetraoxa-2-azahexadecan-16-amide (**6i**)



Prepared according to general procedure **A** from 4-(4-hydroxybut-1-yn-1-yl)benzaldehyde (17.4 mg, 0.1 mmol) using **4d** PROTAC reagent capsule. Reaction time 12 h. Isolated without further purification as a pale-yellow foamy solid, 46.5 mg (70%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.49 (bs, 1H), 8.85 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.72 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.58 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.28 – 7.19 (m, 2H), 4.95 – 4.86 (m, 1H), 4.82 (bs, 2H), 4.23 – 4.13 (m, 2H), 3.85 – 3.73 (m, 8H), 3.73 – 3.52 (m, 11H), 2.92 – 2.69 (m, 4H), 2.67 (t, *J* = 6.3 Hz, 2H), 2.20 – 2.07 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.55, 169.39, 168.44, 168.39, 166.88, 139.76, 136.67, 136.26, 131.66, 131.38, 128.14, 125.18, 121.98, 118.80, 116.16, 86.54, 82.15, 71.66, 70.91, 70.67, 70.49, 70.46, 70.39, 70.27, 70.17, 61.04, 53.15, 49.29, 48.19, 31.45, 23.85, 22.68.
**HRMS (ESI):** calcd for $C_{34}H_{41}N_4O_{10}$ $[M+H]^+$ 665.2817, found 665.2810.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-4-(((5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-17-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)amino)butanamide (**6j**)

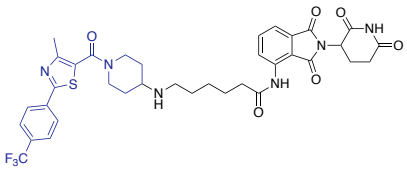


Prepared according to general procedure **A** from 5α-androstan-17β-ol-3-one (29.0 mg, 0.1 mmol) using **4e** PROTAC reagent capsule. Reaction time 3 h. Isolated as a diastereoisomeric mixture, light-yellow solid, 59.6 mg (94%, d.r. 27:73, determined by crude LCMS). Diastereoisomers separated by flash chromatography (eluent Acetone + 0.5% $Et_3N$). Absolute configuration not determined.

Diast. 1 (signals show extra splitting due to rotamers).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.60 (bs, 1H), 8.84 (dt, *J* = 8.5, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.57 (dd, *J* = 7.3, 0.8 Hz, 1H), 4.98 (dd, *J* = 11.8, 5.4 Hz, 1H), 3.61 (tt, *J* = 8.6, 4.5 Hz, 1H), 2.99 – 2.88 (m, 1H), 2.88 – 2.74 (m, 3H), 2.69 (t, *J* = 6.7 Hz, 2H), 2.57 (td, *J* = 7.1, 2.0 Hz, 2H), 2.26 – 2.10 (m, 1H), 2.10 – 2.00 (m, 1H), 1.95 (p, *J* = 6.9 Hz, 2H), 1.80 – 1.73 (m, 1H), 1.67 – 1.47 (m, 6H), 1.49 – 1.11 (m, 13H), 1.02 – 0.89 (m, 1H), 0.87 – 0.79 (m, 2H), 0.79 (s, 3H), 0.72 (s, 3H), 0.65 – 0.51 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.50, (170.76, 170.74), 169.05, 167.84, 166.69, 137.97, 136.39, 131.18, 125.62, 118.44, 115.47, (81.95, 81.93), 54.57, (52.29, 52.27), 51.10, 49.29, 46.72, 46.65, 42.95, 39.74, (36.80, 36.76), 36.27, 36.23, 35.45, 33.47, 32.67, (31.57, 31.55), (31.41, 31.40), 30.48, 28.56, 25.89, 25.55, 23.33, 22.69, 20.32, 11.58, 11.12.
**HRMS (ESI):** calcd for $C_{36}H_{49}N_4O_6$ $[M+H]^+$ 633.3647, found 663.3635.

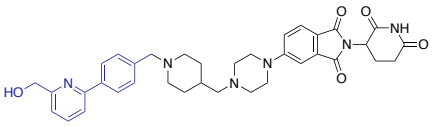
Diast. 2
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.50 (bs, 1H), 8.83 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.72 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.56 (dd, *J* = 7.3, 0.7 Hz, 1H), 5.02 – 4.93 (m, 1H), 3.63 (t, *J* = 8.5 Hz, 1H), 3.49 (bs, 2H), 2.97 – 2.87 (m, 1H), 2.86 – 2.78 (m, 2H), 2.74 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 7.4 Hz, 2H), 2.52 – 2.41 (m, 1H), 2.23 – 2.13 (m, 1H), 2.05 (dtd, *J* = 13.4, 9.3, 5.8 Hz, 1H), 1.92 (p, *J* = 7.2 Hz, 2H), 1.84 – 1.62 (m, 4H), 1.64 – 1.52 (m, 2H), 1.54 – 1.44 (m, 1H), 1.47 – 1.35 (m, 2H), 1.32 – 1.17 (m, 6H), 1.16 – 1.02 (m, 3H), 1.04 – 0.81 (m, 3H), 0.79 (s, 3H), 0.74 (s, 3H), 0.64 (ddd, *J* = 12.3, 10.4, 4.1 Hz, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.22, 170.88, 169.08, 167.97, 166.71, 137.85, 136.40, 131.14, 125.42, 118.44, 115.36, 81.96, 57.28, 54.64, 51.07, 49.28, 46.03, 45.49, 43.00, 37.55, 36.79, 36.13, 35.98, 35.86, 35.57, 31.68, 31.42, 30.54, 29.34, 28.74, 25.89, 23.40, 22.71, 20.73, 12.38, 11.15.
**HRMS (ESI):** calcd for $C_{36}H_{49}N_4O_6$ $[M+H]^+$ 633.3647, found 663.3645.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-6-((1-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbonyl)piperidin-4-yl)amino)hexanamide (**6k**)



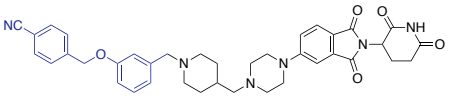
Prepared according to general procedure **A** from 1-(4-methyl-2-(4-(trifluoromethyl)phenyl)thiazole-5-carbonyl)piperidin-4-one (36.8 mg, 0.1 mmol) using **4f** PROTAC reagent capsule. Reaction time 3 h. Isolated after filtration through silica pad as a light-yellow solid, 47.0 mg (63%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.83 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.08 – 8.00 (m, 2H), 7.79 – 7.67 (m, 3H), 7.56 (dd, *J* = 7.3, 0.8 Hz, 1H), 5.01 – 4.93 (m, 1H), 4.18 (bs, 1H), 3.18 – 3.04 (m, 2H), 2.96 – 2.90 (m, 1H), 2.87 – 2.76 (m, 3H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 2.54 – 2.46 (m, 2H), 2.24 – 2.13 (m, 2H), 2.07 – 1.92 (m, 2H), 1.80 (p, *J* = 7.5 Hz, 2H), 1.60 (p, *J* = 7.4 Hz, 2H), 1.52 – 1.37 (m, 4H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.15, 170.81, 169.22, 168.00, 166.66, 165.48, 162.14, 152.92, 137.82, 136.48, 136.11, 131.99 (q, $J_{C-F}$ = 32.7 Hz), 131.12, 126.82, 126.05 (q, $J_{C-F}$ = 3.7 Hz), 125.82, 125.28, 118.51, 115.33, 54.62, 49.31, 46.41, 37.79, 32.49, 31.40, 29.73, 26.80, 24.99, 22.72, 19.77, 16.48.
**HRMS (ESI):** calcd for $C_{36}H_{38}F_3N_6O_6S$ $[M+H]^+$ 739.2520, found 739.2504.

2-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-(6-(hydroxymethyl)pyridin-2-yl)benzyl)piperidin-4-yl)methyl)piperazin-1-yl)isoindoline-1,3-dione (**6l**)



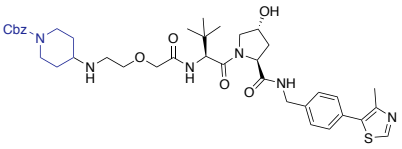
Prepared according to general procedure **A** from 4-(6-(hydroxymethyl)pyridin-2-yl)benzaldehyde (42.6 mg, 0.2 mmol, 2 equiv.) using PROTAC **35** reagent capsule. Reaction time 12 h. Isolated after flash chromatography (eluent EtOAc/MeOH + 1% $Et_3N$, gradient 0% → 40%) as a bright-yellow solid, 53.5 mg (84%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.55 (bs, 1H), 8.04 – 7.96 (m, 2H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.65 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.27 (m, 1H, overlaps with solvent peak), 7.19 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.05 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.98 – 4.90 (m, 1H), 4.83 (s, 2H), 3.69 (s, 2H), 3.48 – 3.37 (m, 4H), 3.09 – 3.00 (m, 2H), 2.92 – 2.67 (m, 3H), 2.59 – 2.52 (m, 4H), 2.26 (d, *J* = 7.0 Hz, 2H), 2.18 – 2.15 (m, 2H), 2.15 – 2.06 (m, 2H), 1.80 (d, *J* = 12.9 Hz, 2H), 1.62 – 1.52 (m, 1H), 1.48 – 1.39 (m, 2H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.22, 168.44, 167.97, 167.27, 158.63, 155.80, 155.52, 137.49, 134.25, 130.01, 126.86, 125.34, 119.34, 118.96, 118.77, 117.77, 108.56, 64.30, 63.93, 62.64, 53.37, 53.04, 49.15, 47.46, 32.98, 31.47, 30.31, 22.76.
**HRMS (ESI):** calcd for $C_{36}H_{41}N_6O_5$ $[M+H]^+$ 637.3133, found 637.3123.

4-((3-((4-((4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)methyl)phenoxy)methyl)benzonitrile (**6m**)



Prepared according to general procedure **A** from 4-((3-formylphenoxy)methyl)benzonitrile (47.5 mg, 0.2 mmol, 2 equiv.) using PROTAC **35** reagent capsule. Reaction time 12 h. Isolated after flash chromatography (eluent EtOAc/MeOH + 1% $Et_3N$, gradient 5% → 30%) as a yellow solid, 35.9 mg (54%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.35 (bs, 1H), 7.73 – 7.65 (m, 3H), 7.64 – 7.53 (m, 2H), 7.29 (d, 1H, overlaps with solvent signal), 7.26 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.00 (s, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 6.91 – 6.83 (m, 1H), 5.16 (s, 2H), 5.00 – 4.90 (m, 1H), 3.54 (s, 2H), 3.46 – 3.39 (m, 4H), 2.96 – 2.68 (m, 5H), 2.60 – 2.53 (m, 4H), 2.26 (d, *J* = 7.1 Hz, 2H), 2.21 – 2.09 (m, 1H), 2.04 – 1.96 (m, 2H), 1.81 – 1.72 (m, 2H), 1.61 – 1.50 (m, 1H), 1.36 – 1.22 (m, 2H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.08, 168.33, 167.97, 167.26, 158.24, 155.55, 142.67, 134.27, 132.38, 129.32, 127.60, 125.36, 122.41, 119.33, 118.73, 117.78, 115.50, 113.52, 111.65, 108.56, 68.84, 64.51, 63.04, 53.50, 53.06, 49.15, 47.48, 33.15, 31.47, 30.68, 22.76.
**HRMS (ESI):** calcd for $C_{38}H_{41}N_6O_5$ $[M+H]^+$ 661.3133, found 661.3113.

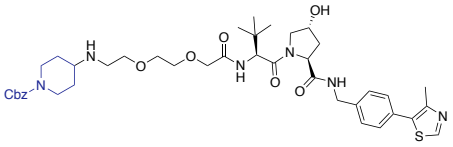
Benzyl-4-((2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethyl)amino)piperidine-1-carboxylate (**7a**)



Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **5a** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a white foam, 52.0 mg (69%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.44 (bs, 1H), 7.40 – 7.29 (m, 9H), 7.26 (d, *J* = 9.0 Hz, 1H), 5.12 (s, 2H), 4.71 (t, *J* = 7.9 Hz, 1H), 4.60 – 4.50 (m, 3H), 4.36 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.20 – 4.07 (m, 2H), 4.07 – 3.87 (m, 3H), 3.69 – 3.58 (m, 3H), 2.93 – 2.84 (m, 4H), 2.75 – 2.63 (m, 2H), 2.52 (s, 3H), 2.50 – 2.44 (m, 1H), 2.19 – 2.09 (m, 1H), 1.94 – 1.82 (m, 2H), 1.37 – 1.28 (m, 2H), 0.96 (s, 9H).

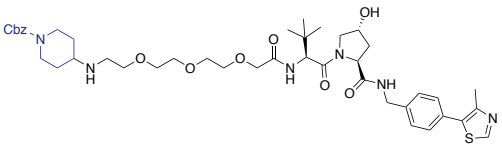
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.23, 170.83, 170.25, 155.28, 150.34, 148.46, 138.18, 136.76, 131.60, 130.94, 129.50, 128.51, 128.10, 128.03, 127.87, 71.32, 70.08, 70.05, 67.13, 58.62, 57.03, 56.81, 54.83, 45.74, 43.20, 42.67, 36.09, 35.25, 32.02, 26.43, 16.06.
**HRMS (ESI):** calcd for $C_{39}H_{53}N_6O_7S$ $[M+H]^+$ 749.3691, found 749.3688.

Benzyl-4-((2-(2-(2-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)amino)piperidine-1-carboxylate (**7b**)



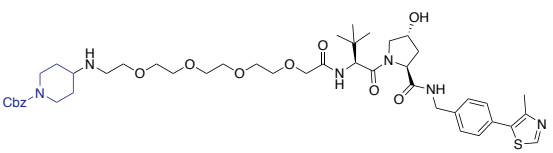
Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **5b** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a white foamy solid, 60.5 mg (93%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.43 – 7.26 (m, 11H), 5.13 (s, 2H), 4.77 – 4.64 (m, 2H), 4.62 – 4.46 (m, 2H), 4.43 (dd, *J* = 15.0, 5.7 Hz, 1H), 4.30-4.15 (m, 2H), 4.16 (d, *J* = 15.7 Hz, 1H), 4.06 (d, *J* = 11.2 Hz, 1H), 3.91 (d, *J* = 15.7 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.74 – 3.59 (m, 4H), 3.54 – 3.41 (m, 3H), 2.92 – 2.67 (m, 6H), 2.53 (s, 3H), 2.41 (ddd, *J* = 13.1, 8.9, 4.1 Hz, 1H), 2.26 – 2.13 (m, 1H), 2.03 (bs, 1H), 1.97 – 1.85 (m, 1H), 1.53 – 1.32 (m, 2H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.29, 170.95, 170.86, 155.19, 150.30, 148.48, 138.18, 136.71, 131.61, 130.94, 129.49, 128.51, 128.15, 128.04, 127.93, 71.56, 71.45, 71.36, 69.84, 69.54, 67.19, 58.85, 57.16, 56.56, 55.44, 45.86, 43.22, 42.78, 42.73, 36.62, 36.00, 31.25, 30.95, 26.36, 16.06.
**HRMS (ESI):** calcd for $C_{41}H_{57}N_6O_8S$ $[M+H]^+$ 793.3953, found 793.3941.

Benzyl-4-(((*S*)-13-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecyl)amino)piperidine-1-carboxylate (**7c**)



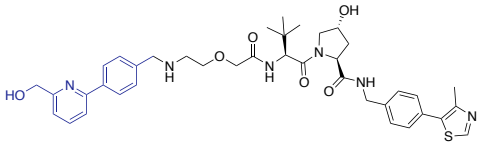
Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **5c** PROTAC reagent capsule. Reaction time 12 h. Isolated without further purification as a white foam, 56.0 mg (67%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.51 (t, *J* = 6.0 Hz, 1H), 7.42 – 7.29 (m, 9H), 5.12 (s, 2H), 4.72 (t, *J* = 7.9 Hz, 1H), 4.61 – 4.48 (m, 3H), 4.36 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.23 – 4.07 (m, 2H), 4.07 – 3.96 (m, 3H), 3.73 – 3.52 (m, 12H), 2.96 – 2.73 (m, 6H), 2.69 – 2.59 (m, 1H), 2.52 (s, 3H), 2.52 – 2.43 (m, 1H), 2.18 – 2.05 (m, 1H), 1.93 – 1.78 (m, 2H), 1.36 – 1.20 (m, 2H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.25, 170.88, 170.29, 155.26, 150.29, 148.45, 138.19, 136.82, 131.59, 130.90, 129.48, 128.48, 128.10, 127.97, 127.83, 71.07, 70.58, 70.54, 70.45, 70.41, 70.28, 69.96, 67.06, 58.57, 56.98, 56.76, 54.84, 46.05, 43.20, 42.75, 36.12, 35.18, 32.10, 26.40, 16.07.
**HRMS (ESI):** calcd for $C_{41}H_{61}N_6O_9S$ $[M+H]^+$ 837.4215, found 837.4208.

Benzyl-4-(((*S*)-16-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-17,17-dimethyl-14-oxo-3,6,9,12-tetraoxa-15-azaoctadecyl)amino)piperidine-1-carboxylate (**7d**)



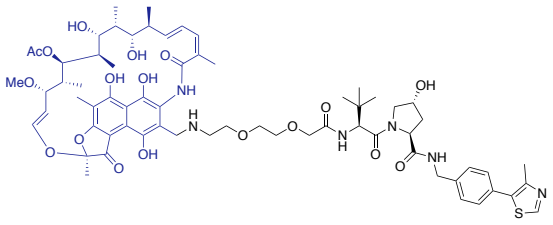
Prepared according to general procedure **A** from N-Cbz-piperidone (23.4 mg, 0.1 mmol) using **5d** PROTAC reagent capsule. Reaction time 12 h. Isolated without further purification as a white foam, 69.7 mg (79%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.49 (t, *J* = 6.0 Hz, 1H), 7.41 – 7.30 (m, 9H), 5.13 (s, 2H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.61 – 4.49 (m, 3H), 4.37 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.18 – 3.96 (m, 5H), 3.73 – 3.56 (m, 17H), 2.94 – 2.84 (m, 2H), 2.82 (t, *J* = 5.2 Hz, 2H), 2.67 (tt, *J* = 10.4, 3.8 Hz, 1H), 2.53 (s, 3H), 2.52 – 2.47 (m, 1H), 2.18 – 2.09 (m, 1H), 1.92 – 1.83 (m, 2H), 1.36 – 1.27 (m, 2H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.29, 170.85, 170.36, 155.26, 150.28, 148.47, 138.20, 136.83, 131.61, 130.91, 129.49, 129.39, 128.49, 128.12, 127.97, 127.85, 71.08, 70.63, 70.57, 70.54, 70.50, 70.43, 70.31, 70.00, 67.07, 58.56, 57.05, 56.78, 54.84, 46.02, 43.20, 42.73, 36.05, 35.10, 32.04, 26.40, 16.07.
**HRMS (ESI):** calcd for $C_{45}H_{64}N_6NaO_{10}S$ $[M+Na]^+$ 903.4297, found 903.4298.

(2*S*,4*R*)-4-hydroxy-1-((*S*)-2-(2-(2-((4-(6-(hydroxymethyl)pyridin-2-yl)benzyl)amino)ethoxy)acetamido)-3,3-dimethylbutanoyl)-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7e**)



Prepared according to general procedure **A** from 4-(6-(hydroxymethyl)pyridin-2-yl)benzaldehyde (16.0 mg, 0.075 mmol) using **5a** PROTAC reagent capsule. Reaction time 3 h. Isolated without further purification as a white solid, 37.9 mg (69%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.65 (s, 1H), 7.95 (d, *J* = 8.1 Hz, 2H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 9.4 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.36 – 7.26 (m, 4H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.79 (s, 2H), 4.69 (t, *J* = 8.0 Hz, 1H), 4.58 (d, *J* = 9.1 Hz, 1H), 4.57 – 4.45 (m, 2H), 4.31 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.06 – 3.94 (m, 2H), 3.93 – 3.82 (m, 3H), 3.71 – 3.52 (m, 4H), 2.87 – 2.76 (m, 2H), 2.53 – 2.36 (m, 1H), 2,47 (s, 3H), 2.20 – 2.06 (m, 1H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.26, 171.00, 170.35, 158.85, 155.84, 150.35, 148.34, 140.80, 138.13, 137.74, 137.48, 131.61, 130.79, 129.41, 128.50, 128.01, 127.03, 118.89, 118.84, 71.26, 70.13, 70.00, 64.06, 58.72, 57.07, 56.84, 53.20, 47.90, 43.15, 36.22, 35.34, 26.44, 15.98.
**HRMS (ESI):** calcd for $C_{39}H_{48}N_6NaO_6S$ $[M+Na]^+$ 751.3248, found 751.3241.

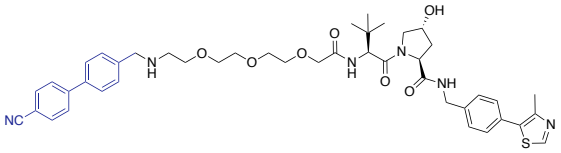
Compound **7f**



Prepared according to general procedure **A** from 3-formyl rifamycin (72.6 mg, 0.1 mmol) using **5b** protac reagent capsule. Reaction time 3 h, SCX purification skipped. Yield determined by $^1$HNMR (61%), product purified by preparative RP-HPLC ($CH_3CN/H_2O$ 20% → 95%) and isolated as orange solid.
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 10.02 (bs, 1H), 9.22 (bs, 1H), 9.00 (s, 1H), 8.34 (bs, 1H), 7.63 – 7.56 (m, 1H), 7.42 – 7.35 (m, 1H), 7.34 – 7.23 (m, 4H), 6.48-5.41 (bs, 5H), 6.37 (dd, *J* = 15.8, 10.7 Hz, 1H), 6.26 (d, *J* = 10.6 Hz, 1H), 6.17 (dd, *J* = 12.5, 1.1 Hz, 1H), 6.00 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.11 (dd, *J* = 12.6, 6.6 Hz, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.63 (d, *J* = 9.3 Hz, 1H), 4.60 – 4.55 (m, 2H), 4.49 – 4.40 (m, 2H), 4.30 (dd, *J* = 15.1, 5.6 Hz, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 4.19 – 4.12 (m, 1H), 3.99 – 3.91 (m, 2H), 3.82 – 3.60 (m, 8H), 3.46 (d, *J* = 7.0 Hz, 1H), 3.36 – 3.26 (m, 2H), 3.09 – 3.02 (m, 1H), 3.07 (s, 3H), 2.54 (s, 3H), 2.46 – 2.39 (m, 1H), 2.36 – 2.29 (m, 1H), 2.24 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 1.84 – 1.77 (m, 1H), 1.82 (s, 3H), 1.54 – 1.47 (m, 1H), 1.47 – 1.40 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.92 – 0.84 (m, 4H), 0.66 (d, *J* = 6.9 Hz, 3H), -0.29 (d, *J* = 7.0 Hz, 3H).

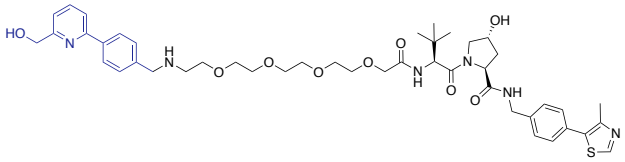
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 195.79, 174.92, 173.14, 171.96, 171.52, 170.78, 151.92, 148.49, 145.58, 142.54, 141.06, 139.44, 133.72, 133.48, 130.32, 129.30, 129.22 (2C), 128.87, 128.30 (2C), 124.37, 120.99, 118.58, 117.90, 114.85, 112.69, 108.92, 106.84, 103.88, 77.60, 73.79, 72.96, 70.86, 70.44, 70.28, 70.18, 69.58, 65.47, 59.01, 57.09, 57.05, 46.43, 42.96, 38.97, 37.92, 37.45, 37.20, 36.21, 33.06, 26.37 (multiple C), 21.20, 20.80, 19.91, 17.36, 14.54, 10.92, 8.87, 8.83, 7.46, 1.02.
**HRMS (ESI):** calcd for $C_{66}H_{89}N_6O_{18}S$ $[M+H]^+$ 1285.5949, found 1285.5920.

(2*S*,4*R*)-1-((*S*)-15-(*tert*-butyl)-1-(4'-cyano-[1,1'-biphenyl]-4-yl)-13-oxo-5,8,11-trioxa-2,14-diazahexadecan-16-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7g**)



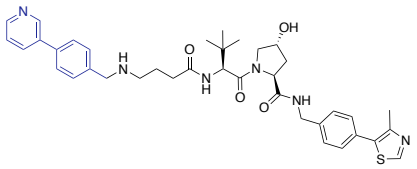
Prepared according to general procedure **A** from 4-(4-cyanophenyl)benzaldehyde (20.7 mg, 0.1 mmol) using **5c** PROTAC reagent capsule. Reaction time 3 h. Isolated after filtration on silica pad (eluent EtOAc/MeOH 3:1 + 1% $Et_3N$) as off-white foamy solid, 44.0 mg (54%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.89 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.48 (m, 4H), 7.43 – 7.31 (m, 5H), 4.87 – 4.77 (m, 1H), 4.61 (d, *J* = 9.2 Hz, 1H), 4.54 (dd, *J* = 15.0, 6.4 Hz, 1H), 4.46 (s, 1H), 4.35 (dd, *J* = 14.9, 5.5 Hz, 1H), 4.11 – 3.92 (m, 6H), 3.74 – 3.52 (m, 12H), 2.98 – 2.82 (m, 2H), 2.51 (s, 3H), 2.41 – 2.31 (m, 1H), 2.26 – 2.16 (m, 1H), 0.99 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.36, 171.06, 170.19, 150.24, 148.42, 145.05, 138.48, 132.64 (2C), 131.57, 130.80, 129.61 (2C), 129.40 (2C), 128.18 (2C), 127.60 (2C), 127.42 (2C), 118.88, 111.01, 71.05, 70.52, 70.46, 70.32, 70.23, 69.97, 69.06, 58.83, 57.21, 56.85, 52.50, 47.44, 43.07, 36.53, 35.60, 26.42 (3C), 16.09.
**HRMS (ESI):** calcd for $C_{44}H_{55}N_6O_7S$ $[M+H]^+$ 811.3847, found 811.3843.

(2*S*,4*R*)-1-((*S*)-18-(*tert*-butyl)-1-(4-(6-(hydroxymethyl)pyridin-2-yl)phenyl)-16-oxo-5,8,11,14-tetraoxa-2,17-diazanonadecan-19-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7h**)



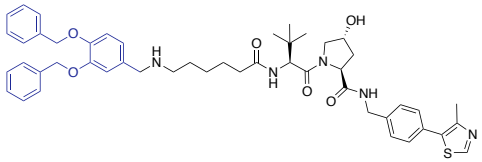
Prepared according to general procedure **A** from 4-(6-(hydroxymethyl)pyridin-2-yl)benzaldehyde (21.3 mg, 0.1 mmol) using **5d** PROTAC reagent capsule. Reaction time 12 h. Isolated after preparative RP-HPLC ($CH_3CN/H_2O$ 5% → 70%) as a white solid, 34.0 mg (39%).
**$^1$H NMR (400 MHz, MeOD)** δ 8.88 (s, 1H), 8.08 – 8.00 (m, 2H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.52 – 7.39 (m, 5H), 4.78 (s, 2H), 4.68 (s, 1H), 4.63 – 4.46 (m, 3H), 4.37 (d, *J* = 15.4 Hz, 1H), 4.04 (t, *J* = 1.8 Hz, 4H), 3.89 (d, *J* = 11.1 Hz, 1H), 3.81 (dd, *J* = 11.0, 3.8 Hz, 1H), 3.73 – 3.60 (m, 14H), 3.00 (app.t, *J* = 5.2 Hz, 2H), 2.48 (s, 3H), 2.24 (ddt, *J* = 13.2, 7.6, 1.9 Hz, 1H), 2.10 (ddd, *J* = 13.3, 9.3, 4.4 Hz, 1H), 1.05 (s, 9H).
**$^{13}$C NMR (101 MHz, MeOD)** δ 172.96, 170.71, 170.32, 161.04, 155.98, 151.44, 147.64, 139.02, 138.85, 137.74, 131.99, 130.10, 129.21, 128.97, 128.05, 127.55, 127.08, 119.00, 118.96, 70.74, 70.06, 70.00, 69.73, 69.66, 69.62, 67.68, 64.49, 59.46, 56.92, 56.72, 51.66, 42.30, 37.63, 35.57, 25.57, 14.44.
**HRMS (ESI):** calcd for $C_{45}H_{61}N_6O_9S$ $[M+H]^+$ 861.4215, found 861.4214.

(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(4-((4-(pyridin-3-yl)benzyl)amino)butanamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7i**)



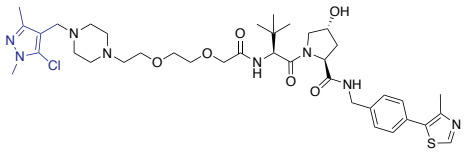
Prepared according to general procedure **A** from 4-(pyridin-3-yl)benzaldehyde (18.3 mg, 0.1 mmol) using **5e** PROTAC reagent capsule. Reaction time 3 h. Isolated after flash chromatography (eluent $CH_2Cl_2$/MeOH + 1% $Et_3N$, gradient 0% → 100%) as a white foam, 57.0 mg (83%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.85 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.68 (s, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.41 – 7.29 (m, 6H), 6.74 (d, *J* = 9.1 Hz, 1H), 4.71 (t, *J* = 8.1 Hz, 1H), 4.60 – 4.48 (m, 2H), 4.43 (bs, 1H), 4.30 (dd, *J* = 15.1, 5.2 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.86 (dd, *J* = 18.7, 13.3 Hz, 2H), 3.53 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.27 (bs, 1H), 2.71 (tt, *J* = 10.9, 5.4 Hz, 2H), 2.51 (s, 3H), 2.44 (ddd, *J* = 13.0, 8.2, 4.5 Hz, 1H), 2.31 (td, *J* = 7.3, 2.5 Hz, 2H), 2.21 – 2.09 (m, 1H), 1.83 (p, *J* = 7.3 Hz, 2H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.72, 171.91, 170.94, 150.30, 148.51, 148.22, 138.18, 136.82, 136.20, 134.22, 131.53, 130.98, 129.50, 129.12, 128.01, 127.25, 123.60, 69.93, 58.48, 57.62, 56.82, 53.20, 48.23, 43.14, 36.15, 34.93, 34.28, 26.43, 25.38, 16.07.
**HRMS (ESI):** calcd for $C_{38}H_{47}N_6O_4S$ $[M+H]^+$ 683.3374, found 683.3366.

(2*S*,4*R*)-1-((*S*)-2-(6-((3,4-bis(benzyloxy)benzyl)amino)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7j**)



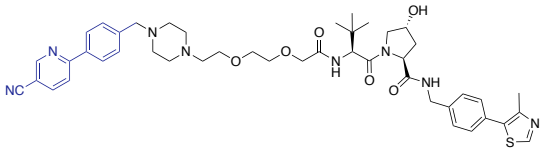
Prepared according to general procedure **A** from 3,4-bis(benzyloxy)benzaldehyde (32.8 mg, 0.1 mmol) using **5f** PROTAC reagent capsule. Reaction time 3 h. Isolated after flash chromatography (eluent $CH_2Cl_2$/MeOH + 1% $Et_3N$, gradient 0% → 30%) as a white foam, 47.4 mg (56%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.50 – 7.41 (m, 4H), 7.41 – 7.27 (m, 11H), 7.01 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.26 (d, *J* = 9.0 Hz, 1H), 5.19 (s, 2H), 5.16 (s, 2H), 4.66 (t, *J* = 8.2 Hz, 1H), 4.60 – 4.47 (m, 2H), 4.38 – 4.28 (m, 2H), 3.88 (d, *J* = 11.3 Hz, 1H), 3.66 (dd, *J* = 21.3, 12.9 Hz, 2H), 3.46 (dd, *J* = 11.3, 3.4 Hz, 1H), 2.66 – 2.54 (m, 2H), 2.52 (s, 3H), 2.41 (ddd, *J* = 13.1, 8.5, 4.4 Hz, 1H), 2.31 – 2.22 (m, 1H), 2.19 – 2.03 (m, 3H), 1.73 – 1.64 (m, 1H), 1.61 – 1.53 (m, 1H), 1.51 – 1.42 (m, 2H), 1.36 – 1.24 (m, 2H), 0.93 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.63, 172.01, 170.78, 150.29, 149.01, 148.49, 148.16, 138.13, 137.31, 137.28, 131.59, 130.96, 129.51, 128.48, 128.46, 128.10, 127.81, 127.79, 127.40, 127.30, 121.46, 115.46, 115.09, 71.37, 71.30, 69.64, 58.57, 57.40, 56.98, 53.58, 48.46, 43.21, 36.14, 36.08, 35.11, 28.71, 26.38, 26.20, 24.64, 16.07.
**HRMS (ESI):** calcd for $C_{49}H_{60}N_5O_6S$ $[M+H]^+$ 846.4259, found 846.4250.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-((5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl)piperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7k**)



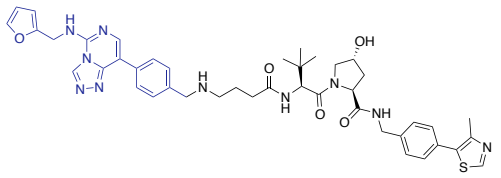
Prepared according to general procedure **A** from 5-chloro-1,3-dimethyl-1*H*-pyrazole-4-carboxaldehyde (31.7 mg, 0.2 mmol, 2 equiv.) using **5g** PROTAC reagent capsule. Reaction time 12 h. Isolated after flash chromatography (eluent EtOAc/MeOH + 1% $Et_3N$, gradient 5:1 → 2:1) as a light-yellow foam, 33.3 mg (42%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.53 – 7.47 (m, 1H), 7.40 – 7.34 (m, 4H), 7.30 – 7.26 (m, 1H), 4.74 (t, *J* = 7.9 Hz, 1H), 4.61 – 4.52 (m, 3H), 4.35 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.09 – 3.91 (m, 3H), 3.77 (s, 3H), 3.72 – 3.60 (m, 7H), 3.37 (s, 2H), 2.76 – 2.46 (m, 14H), 2.22 (s, 3H), 2.20 – 2.13 (m, 1H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.24, 170.87, 170.20, 150.28, 148.46, 148.23, 138.22, 131.59, 130.90, 129.47, 128.12, 127.49, 71.22, 70.59, 70.40, 70.00, 68.42, 58.60, 57.21, 57.00, 56.80, 53.11, 51.64, 50.58, 43.19, 36.17, 35.99, 35.37, 26.42, 16.08, 12.70.
**HRMS (ESI):** calcd for $C_{38}H_{56}ClN_8O_6S$ $[M+H]^+$ 787.3727, found 787.3720.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(4-(5-cyanopyridin-2-yl)benzyl)piperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7l**)



Prepared according to general procedure **A** from 4-(5-cyanopyridin-2-yl)benzaldehyde (41.6 mg, 0.2 mmol, 2 equiv.) using **5g** protac reagent capsule. Reaction time 12 h. Yield determined by $^1$HNMR (36%), product purified by preparative RP-HPLC ($CH_3CN/H_2O$ 5% → 70%) and isolated as white solid.
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.95 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.69 (s, 1H), 8.05 – 7.98 (m, 3H), 7.86 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.42 – 7.33 (m, 5H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.62 – 4.49 (m, 3H), 4.37 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.10 – 4.03 (m, 2H), 3.97 (d, *J* = 15.7 Hz, 1H), 3.73 – 3.56 (m, 9H), 2.75 – 2.44 (m, 10H), 2.53 (s, 3H), 2.15 (dd, *J* = 13.5, 8.1 Hz, 1H), 0.97 (s, 9H).
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.46, 170.67, 170.46, 160.30, 152.48, 150.29, 148.51, 139.87, 138.11, 136.33, 131.58, 130.99, 129.86, 129.53, 128.16, 127.35, 119.87, 117.03, 107.78, 71.20, 70.59, 70.42, 70.01, 68.73, 62.48, 58.45, 57.47, 57.12, 56.79, 53.45, 52.76, 43.27, 35.88, 35.11, 26.42, 16.08.
**HRMS (ESI):** calcd for $C_{45}H_{57}N_8O_6S$ $[M+H]^+$ 837.4116, found 837.4120.

(2*S*,4*R*)-1-((*S*)-2-(4-((4-(5-((furan-2-ylmethyl)amino)-[1,2,4]triazolo[4,3-*c*]pyrimidin-8-yl)benzyl)amino) butanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**7m**)



Prepared according to general procedure **A** from compound **37** (31.9 mg, 0.1 mmol) using **5e** PROTAC reagent capsule. Reaction time 3 h. Isolated after flash chromatography (eluent EtOAc/MeOH + 1% $Et_3N$, gradient 10% → 100%) as a brown foam, 54.6 mg (66%).
**$^1$H NMR (400 MHz, DMSO-*d6*)** δ 9.50 (s, 1H), 8.97 (s, 1H), 8.58 (t, *J* = 6.0 Hz, 1H), 8.08 – 7.96 (m, 3H), 7.90 (d, *J* = 9.3 Hz, 1H), 7.63 (dd, *J* = 1.7, 1.0 Hz, 1H), 6.48 – 6.40 (m, 2H), 4.77 (s, 2H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.40 – 4.32 (m, 1H), 4.22 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.74 (s, 2H), 3.69 – 3.64 (m, 2H), 2.44 (s, 3H), 2.38 – 2.26 (m, 1H), 2.25 – 2.14 (m, 1H), 2.10 – 1.97 (m, 1H), 1.95 – 1.89 (m, 1H), 1.88 (s, 2H), 1.77 – 1.61 (m, 2H), 0.94 (s, 9H).
**$^{13}$C NMR (101 MHz, DMSO-*d6*)** δ 172.87, 172.58, 172.44, 170.18, 151.89, 151.74, 149.12, 148.18, 143.78, 142.96, 140.41, 140.16, 139.97, 133.41, 132.15, 131.63, 130.10, 129.10, 128.61, 127.89, 127.41, 111.75, 111.07, 108.30, 69.35, 59.18, 56.83, 53.01, 48.50, 42.13, 38.42, 38.15, 35.70, 33.38, 26.86, 26.17, 22.11, 16.40.
**HRMS (ESI):** calcd for $C_{43}H_{51}N_{10}O_5S$ $[M+H]^+$ 819.3759, found 819.3748.

## 4.2 Synthesis of PROTACs via amide coupling

General procedure **B** for the automated synthesis of PROTACs via Amide coupling:

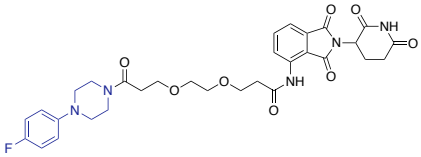
A 40 mL vial was charged with the desired amine (0.1 mmol) and dissolved in 2 mL of $CH_2Cl_2$ and 2 mL of $CH_3CN$. The vial was connected to the console via screw cap, then the capsule, containing the partial PROTAC reagent and all the necessary reagent for reaction and purification, was inserted into the console and the capsule holder was closed. The reaction program was selected (either by manual selection or by scanning the RFID microchip on the capsule) and reaction was started. After completion of the sequence, the solution in the vial was concentrated *in vacuo* to afford the desired product.

Capsule content:

Compartment 1: (top to bottom) Oxyma pure (5.9 mg), Silica-supported DCC (270 mg)
Compartment 2: Buffered SCX-2 (250 mg)
Compartment 3: Silica-supported carbonate (400 mg)
Compartment 4: partial PROTAC reagent (0.1 mmol)

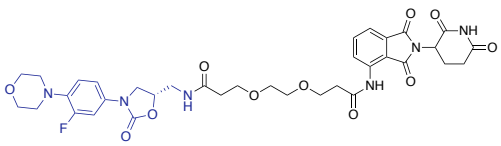
### 4.2.1 Characterization of reaction products

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(2-(3-(4-(4-fluorophenyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propenamide (**8a**)



Prepared according to general procedure **B** from 1-(4-fluorophenyl)piperazine (18.0 mg, 0.1 mmol) using **4h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a yellow foamy solid, 54.8 mg (88%).
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 9.96 (s, 1H), 9.38 (s, 1H), 8.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.71 (ddd, *J* = 8.5, 7.3, 0.5 Hz, 1H), 7.56 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.92 – 6.84 (m, 2H), 5.05 – 4.94 (m, 1H), 3.92 – 3.66 (m, 10H), 3.66 – 3.61 (m, 2H), 3.15 – 3.01 (m, 4H), 2.94 – 2.85 (m, 1H), 2.83 – 2.71 (m, 4H), 2.71 – 2.64 (m, 2H), 2.19 – 2.14 (m, 1H).
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 171.32, 170.97, 169.74, 168.52, 168.28, 166.81, 157.60 (d, $J_{C-F}$ = 240.0 Hz), 147.53 (d, $J_{C-F}$ = 2.4 Hz), 137.54, 136.16, 131.36, 125.68, 118.55 (d, $J_{C-F}$ = 7.7 Hz), 118.42, 115.76, 115.70 (d, $J_{C-F}$ = 22.2 Hz), 70.54, 69.96, 67.50, 66.62, 50.77, 50.30, 49.24, 45.67, 41.58, 38.71, 33.49, 31.40, 22.88.
**$^{19}$F NMR (471 MHz, $CDCl_3$)** δ -123.25.
**HRMS (ESI):** calcd for $C_{31}H_{35}FN_5O_8$ $[M+H]^+$ 624.2464, found 624.2467.

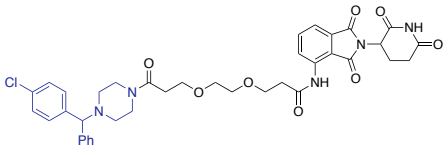
*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(2-(3-((((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)methyl)amino)-3-oxopropoxy)ethoxy)propenamide (**8b**)



Prepared according to general procedure **B** from (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (29.5 mg, 0.1 mmol) using **4h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a light-yellow solid, 61.8 mg (83%).
(Signals show extra splitting due to rotamers)

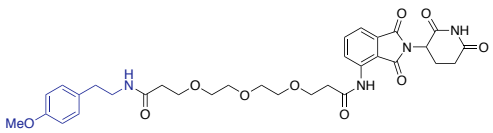
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.86 (d, *J* = 2.7 Hz, 1H), 9.22 (bs, 0.5H), 9.03 (bs, 0.5H), 8.84 (d, *J* = 9.2 Hz, 1H), 7.71 (ddd, *J* = 8.7, 7.3, 1.8 Hz, 1H), 7.55 (ddd, *J* = 7.3, 2.4, 0.8 Hz, 1H), 7.44 (ddd, *J* = 14.4, 2.6, 1.6 Hz, 1H), 7.12 – 7.02 (m, 2H), 6.90 (td, *J* = 9.1, 5.0 Hz, 1H), 5.05 – 4.94 (m, 1H), 4.81 – 4.70 (m, 1H), 3.99 (t, *J* = 9.0 Hz, 1H), 3.90 – 3.81 (m, 6H), 3.80 – 3.73 (m, 1H), 3.73 – 3.53 (m, 8H), 3.08 – 2.98 (m, 4H), 2.96 – 2.84 (m, 1H), 2.83 – 2.67 (m, 4H), 2.53 – 2.34 (m, 2H), 2.25 – 2.11 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.81, 171.25, 170.95, (168.64, 168.61), 168.52, 168.44, 166.77, 155.44 (d, $J_{C-F}$ = 246.8 Hz), (154.48, 154.38), 137.55, 136.40 (d, $J_{C-F}$ = 9.7 Hz), 136.25, 133.01 (d, $J_{C-F}$ = 10.3 Hz), 131.30, 125.68, 118.80 (m), 118.49, 115.71, (113.90, 113.87) (d, $J_{C-F}$ = 5.2 Hz), (107.46, 107.42) (d, $J_{C-F}$ = 26.4 Hz), 72.00, 71.97, 70.52, 70.47, 69.86, 69.77, 67.04, 66.94, 66.64, (50.97, 50.99) (q, $J_{C-F}$ = 3.0 Hz), 49.25, 49.23, 47.59, 47.56, 41.72, 41.61, 38.66, 38.63, 36.74, 31.37, 22.80, 22.76.
**$^{19}$F NMR (377 MHz, $CDCl_3$)** δ (-120.20, -120.22).
**HRMS (ESI):** calcd for $C_{35}H_{39}FN_6NaO_{11}$ $[M+Na]^+$ 761.2553, found 761.2543.

3-(2-(3-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-3-oxopropoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propenamide (**8c**)



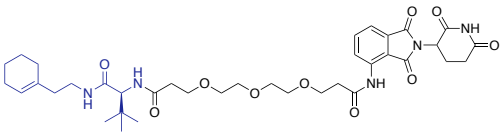
Prepared according to general procedure **B** from N-(4-chlorobenzhydryl)piperazine (28.7 mg, 0.1 mmol) using **4h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as off-white solid, 58.9 mg (80%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.97 (s, 1H), 9.46 (s, 1H), 8.85 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.69 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.55 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.36 (dq, *J* = 9.0, 2.1 Hz, 4H), 7.32 – 7.19 (m, 5H), 5.01 – 4.92 (m, 1H), 4.22 (s, 1H), 3.88 – 3.75 (m, 4H), 3.68 (ttd, *J* = 19.9, 7.2, 4.2 Hz, 6H), 3.49 – 3.42 (m, 2H), 2.86 (td, *J* = 12.9, 3.3 Hz, 1H), 2.81 – 2.67 (m, 4H), 2.60 (td, *J* = 7.1, 2.0 Hz, 2H), 2.41 – 2.31 (m, 4H), 2.20 – 2.10 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.40, 171.03, 169.49, 168.50, 168.32, 166.84, 141.56, 140.76, 137.52, 136.15, 132.80, 131.37, 129.11, 128.82, 128.76, 127.75, 127.42, 125.67, 118.42, 115.77, 75.15, 70.52, 69.93, 67.40, 66.64, 51.87, 51.44, 49.23, 45.69, 41.72, 38.72, 33.35, 31.40, 22.86.
**HRMS (ESI):** calcd for $C_{38}H_{41}ClN_5O_8$ $[M+H]^+$ 730.2638, found 730.2641.

*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-3-(2-(2-(3-((4-methoxyphenethyl)amino)-3-oxopropoxy)ethoxy)ethoxy)propenamide (**8d**)



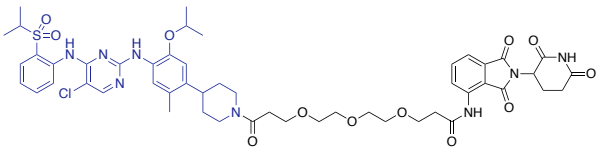
Prepared according to general procedure **B** from 4-methoxyphenethylamine (15.1 mg, 0.1 mmol) using **4i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as off-white solid, 41.0 mg (64%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.84 (s, 1H), 8.88 (bs, 1H), 8.84 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.71 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.55 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.16 – 7.06 (m, 2H), 6.89 – 6.78 (m, 2H), 6.49 – 6.41 (m, 1H), 5.02 – 4.90 (m, 1H), 3.83 (t, *J* = 6.2 Hz, 2H), 3.78 (s, 3H), 3.73 – 3.63 (m, 6H), 3.62 – 3.51 (m, 4H), 3.52 – 3.42 (m, 2H), 2.95 – 2.86 (m, 1H), 2.80 – 2.68 (m, 6H), 2.42 (t, *J* = 5.8 Hz, 2H), 2.21 – 2.13 (m, 1H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.53, 171.11, 170.77, 168.62, 168.11, 166.74, 158.13, 137.55, 136.24, 131.26, 131.09, 129.69, 125.61, 118.47, 115.66, 113.93, 70.67, 70.22, 70.18, 67.23, 66.60, 55.25, 49.23, 40.71, 38.60, 36.94, 34.69, 31.36, 22.73.
**HRMS (ESI):** calcd for $C_{32}H_{38}N_4NaO_{10}$ $[M+Na]^+$ 661.2480, found 661.2490.

(2*S*)-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-2-(3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3-oxopropoxy)ethoxy)ethoxy)propanamido)-3,3-dimethylbutanamide (**8e**)



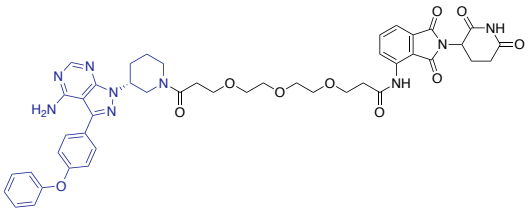
Prepared according to general procedure **B** from (*S*)-2-amino-*N*-(2-(cyclohex-1-en-1-yl)ethyl)-3,3-dimethylbutanamide (23.8 mg, 0.1 mmol) using **4i** PROTAC reagent capsule. Reaction time 4 h. Isolated after flash chromatography (eluent EtOAc/MeOH gradient 0% → 20%) as a pale-yellow solid, 56.2 mg (77%).
Signals show extra splitting due to rotamers
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.99 (d, *J* = 5.5 Hz, 1H), 9.69 (bs, 0.5H), 9.65 (bs, 0.5H), 8.87 (ddd, *J* = 8.5, 1.7, 0.8 Hz, 1H), 7.72 (ddd, *J* = 8.4, 7.3, 1.1 Hz, 1H), 7.57 (dt, *J* = 7.3, 0.8 Hz, 1H), 7.17 (d, *J* = 9.5 Hz, 0.5H), 7.07 (d, *J* = 9.5 Hz, 0.5H), 5.95 (t, *J* = 5.0 Hz, 0.5H), 5.86 (t, *J* = 5.6 Hz, 0.5H), 5.50 – 5.40 (m, 1H), 5.04 – 4.93 (m, 1H), 4.25 (dd, *J* = 15.2, 9.5 Hz, 1H), 3.90 – 3.80 (m, 2H), 3.78 – 3.62 (m, 8H), 3.62 – 3.55 (m, 2H), 3.52 – 3.37 (m, 1H), 3.26 – 3.12 (m, 1H), 2.95 – 2.85 (m, 1H), 2.84 – 2.70 (m, 4H), 2.62 – 2.42 (m, 2H), 2.23 – 2.05 (m, 3H), 2.03 – 1.94 (m, 2H), 1.93 – 1.83 (m, 2H), 1.67 – 1.48 (m, 4H), 0.98 (d, *J* = 3.9 Hz, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.77, 171.36, 171.34, 171.06, 170.40, 170.35, 168.55, 168.40, 166.86, 166.83, 137.60, 137.57, 136.19, 136.17, 134.30, 134.26, 131.37, 125.76, 125.72, 123.97, 123.88, 118.41, 115.80, 115.75, 70.82, 70.79, 70.51, 70.41, 70.36, 70.31, 70.22, 70.14, 67.41, 67.28, 66.65, 60.63, 60.55, 49.32, 49.29, 38.76, 37.32, 37.04, 37.00, 36.98, 34.70, 34.64, 31.48, 27.68, 26.57, 25.20, 22.74, 22.29.
**HRMS (ESI):** calcd for $C_{37}H_{52}N_5O_{10}$ $[M+H]^+$ 726.3709, found 726.3712.

3-(2-(2-(3-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)-5-isopropoxy-2-methylphenyl)piperidin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propenamide (**8f**)



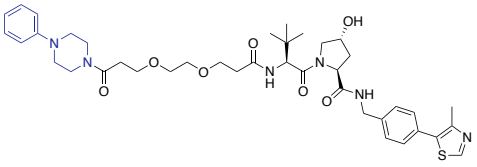
Prepared according to general procedure **B** from Ceritinib (55.8 mg, 0.1 mmol) using **4i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a light-yellow solid, 84.6 mg (81%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.90 (s, 1H), 9.57 (s, 1H), 9.18 (d, *J* = 15.6 Hz, 1H), 8.86 (dd, *J* = 8.5, 0.8 Hz, 1H), 8.58 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.17 (s, 1H), 7.98 (s, 1H), 7.94 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.76 (bs, 1H), 7.71 (dd, *J* = 8.5, 7.3 Hz, 1H), 7.62 (ddd, *J* = 8.7, 7.3, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.3, 0.8 Hz, 1H), 7.32 – 7.23 (m, 1H, ovelaps with $CHCl_3$), 6.70 (d, *J* = 2.5 Hz, 1H), 5.00 – 4.93 (m, 1H), 4.88 – 4.80 (m, 1H), 4.61 – 4.50 (m, 1H), 4.08 – 3.99 (m, 1H), 3.89 – 3.81 (m, 4H), 3.76 – 3.69 (m, 4H), 3.68 – 3.62 (m, 4H), 3.27 (hept, *J* = 6.9 Hz, 1H), 3.20 – 3.10 (m, 1H), 2.96 – 2.85 (m, 2H), 2.84 – 2.60 (m, 7H), 2.25 – 2.14 (m, 1H), 2,17 (s, 3H), 1.82 (t, *J* = 11.6 Hz, 2H), 1.66 – 1.53 (m, 2H), 1.42 – 1.30 (m, 12H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.11, 170.91, 169.30, 168.62, 168.13, 166.81, 157.23, 155.42, 154.68, 145.04, 138.37, 137.60, 136.93, 136.22, 134.63, 131.32, 131.29, 127.64, 126.82, 125.66, 124.93, 123.64, 123.23, 121.17, 118.45, 115.71, 110.87, 105.81, 71.60, 70.77, 70.40, 70.37, 70.34, 70.21, 67.33, 66.67, 55.51, 49.30, 46.53, 42.61, 38.72, 38.32, 33.57, 33.35, 32.24, 31.46, 22.75, 22.24, 22.17, 18.96, 15.37.
**HRMS (ESI):** calcd for $C_{51}H_{62}ClN_8O_{12}S$ $[M+H]^+$ 1045.3891, found 1045.3894.

3-(2-(2-(3-((*R*)-3-(4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)piperidin-1-yl)-3-oxopropoxy)ethoxy)ethoxy)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)propenamide (**8g**)



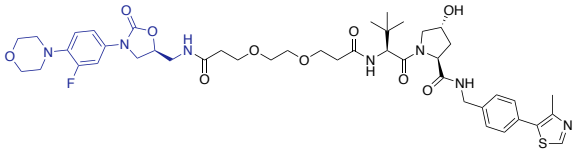
Prepared according to general procedure **B** from compound **39** (38.6 mg, 0.1 mmol) using **4i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as an off-white solid, 78.3 mg (89%).
Signals show extra splitting due to rotamers.
**$^1$H NMR (500 MHz, CDCl$_3$)** δ 9.98 – 9.94 (m, 0.5H), 9.93 – 9.89 (m, 0.5H), 9.85 (bs, 0.5H), 9.78 (bs, 0.5H), 8.89 – 8.83 (m, 1H), 8.47 (d, *J* = 7.7 Hz, 0.5H), 8.42 – 8.35 (m, 0.5H), 7.75 – 7.68 (m, 1H), 7.67 – 7.62 (m, 2H), 7.60 – 7.53 (m, 1H), 7.46 – 7.37 (m, 2H), 7.24 – 7.14 (m, 3H), 7.12 – 7.08 (m, 2H), 6.12 (bs, 2H), 5.03 – 4.93 (m, 1H), 4.93 – 4.77 (m, 1.5H), 4.59 (d, *J* = 13.1 Hz, 0.5H), 4.40 (d, *J* = 13.1 Hz, 0.5H), 4.12 (dd, *J* = 12.7, 3.7 Hz, 0.5H), 4.08 – 4.03 (m, 0.5H), 3.97 – 3.91 (m, 0.5H), 3.89 – 3.52 (m, 12H), 3.33 – 3.25 (m, 0.5H), 3.19 – 3.10 (m, 0.5H), 3.02 – 2.94 (m, 0.5H), 2.93 – 2.87 (m, 1H), 2.84 – 2.64 (m, 6H), 2.60 – 2.46 (m, 0.5H), 2.45 – 2.30 (m, 1H), 2.29 – 2.15 (m, 2H), 2.08 – 2.01 (m, 0.5H), 2.01 – 1.94 (m, 0.5H), 1.81 – 1.64 (m, 1H).
**$^{13}$C NMR (126 MHz, CDCl$_3$)** δ 173.51, 172.14, 171.50, 171.01, 170.91, 169.87, 169.66, 169.64, 169.14, 168.63, 168.60, 166.91, 166.85, 158.69, 157.80, 157.67, 156.31, 156.28, 154.98, 154.91, 154.09, 153.71, 144.39, 144.28, 137.59, 136.20, 131.36, 130.00, 129.94, 127.48, 127.41, 125.72, 124.11, 119.59, 119.58, 119.18, 118.45, 115.79, 115.74, 98.28, 70.83, 70.79, 70.69, 70.61, 70.48, 70.46, 70.39, 70.27, 70.24, 70.14, 67.70, 67.43, 67.26, 66.68, 66.63, 66.57, 53.33, 53.19, 52.66, 50.28, 50.11, 49.29, 49.24, 45.70, 41.83, 41.73, 38.72, 38.60, 34.04, 33.64, 33.62, 31.52, 31.49, 30.25, 30.21, 29.82, 29.51, 25.03, 25.00, 24.01, 23.75, 23.05, 22.80.
**HRMS (ESI):** calcd for $C_{45}H_{47}N_9NaO_{10}$ $[M+Na]^+$ 896.3338, found 896.3326.

(2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(3-(2-(3-oxo-3-(4-phenylpiperazin-1-yl)propoxy)ethoxy)propanamido)butanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9a**)



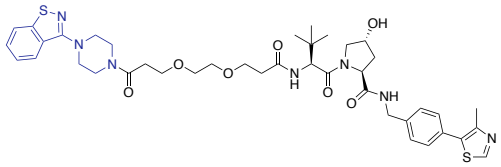
Prepared according to general procedure **B** from N-phenylpiperazine (16.2 mg, 0.1 mmol) using **5h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a light-yellow foam, 58.7 mg (77%).
**$^1$H NMR (400 MHz, CDCl$_3$)** δ 8.69 (s, 1H), 7.54 (t, *J* = 6.0 Hz, 1H), 7.40 – 7.34 (m, 4H), 7.31 – 7.25 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.96 – 6.89 (m, 3H), 4.74 (t, *J* = 8.0 Hz, 1H), 4.59 (dd, *J* = 15.0, 6.7 Hz, 1H), 4.54 – 4.48 (m, 2H), 4.35 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.08 (d, *J* = 11.5 Hz, 1H), 3.85 – 3.77 (m, 2H), 3.77 – 3.68 (m, 4H), 3.67 – 3.58 (m, 7H), 3.23 – 3.10 (m, 4H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.53 (s, 3H), 2.50 – 2.41 (m, 2H), 2.21 – 2.10 (m, 1H), 0.96 (s, 9H).
**$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.98, 171.63, 171.01, 169.59, 150.84, 150.31, 148.45, 138.30, 131.64, 130.86, 129.46, 129.28, 128.09, 120.61, 116.62, 70.50, 70.43, 70.11, 67.47, 67.18, 58.50, 57.65, 56.68, 49.77, 49.30, 45.63, 43.17, 41.50, 36.75, 36.12, 35.02, 33.53, 26.43, 16.07.
**HRMS (ESI):** calcd for $C_{40}H_{55}N_6O_7S$ $[M+H]^+$ 763.3847, found 763.3853.

(2*S*,4*R*)-1-((*S*)-14-(*tert*-butyl)-1-((*S*)-3-(3-fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl)-3,12-dioxo-6,9-dioxa-2,13-diazapentadecan-15-oyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9b**)



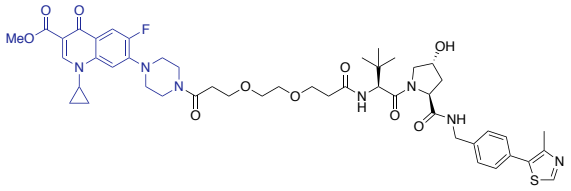
Prepared according to general procedure **B** from (*S*)-5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one (29.5 mg, 0.1 mmol) using **5h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a pale-yellow oil, 76.3 mg (85%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.81 (t, *J* = 6.1 Hz, 1H), 7.56 (t, *J* = 6.0 Hz, 1H), 7.42 (dd, *J* = 14.3, 2.6 Hz, 1H), 7.39 – 7.32 (m, 4H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.04 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.90 (t, *J* = 9.1 Hz, 1H), 4.78 – 4.65 (m, 2H), 4.64 – 4.48 (m, 3H), 4.37 (dd, *J* = 15.2, 5.4 Hz, 1H), 4.12 (d, *J* = 11.3 Hz, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.89 – 3.82 (m, 4H), 3.77 – 3.57 (m, 9H), 3.57 – 3.48 (m, 2H), 3.41 (dt, *J* = 14.4, 6.3 Hz, 1H), 3.07 – 2.99 (m, 4H), 2.68 – 2.57 (m, 1H), 2.54 – 2.47 (m, 1H), 2.51 (s, 3H), 2.45 – 2.29 (m, 3H), 2.26 – 2.18 (m, 1H), 1.00 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.96, 172.10, 171.49, 171.40, 155.43 (d, $J_{C\text{-}F}$ = 246.4 Hz), 154.72, 150.29, 148.40, 138.45, 136.59 (d, $J_{C\text{-}F}$ = 9.0 Hz), 132.82 (d, $J_{C\text{-}F}$ = 10.4 Hz), 131.64, 130.73, 129.35, 127.95, 118.81 (d, $J_{C\text{-}F}$ = 4.2 Hz), 114.03 (d, $J_{C\text{-}F}$ = 3.2 Hz), 107.61 (d, $J_{C\text{-}F}$ = 26.3 Hz), 72.32, 70.18, 70.11, 67.21, 67.16, 66.92, 58.71, 57.79, 56.95, 50.97, 50.94, 47.80, 43.03, 42.18, 36.98, 36.73, 36.33, 35.12, 26.45, 16.06.
**$^{19}$F NMR (376 MHz, $CDCl_3$)** δ -120.07.
**HRMS (ESI):** calcd for $C_{44}H_{59}FN_7O_{10}S$ $[M+H]^+$ 896.4023, found 896.4025.

(2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(4-(benzo[*d*]isothiazol-3-yl)piperazin-1-yl)-3-oxopropoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9c**)



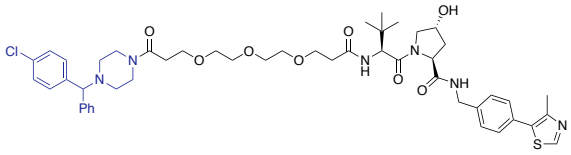
Prepared according to general procedure **B** from 3-(piperazin-1-yl)benzo[*d*]isothiazole (21.9 mg, 0.1 mmol) using **5h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a white foamy solid, 76.0 mg (92%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 6.0 Hz, 1H), 7.50 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.42 – 7.31 (m, 5H), 7.13 (d, *J* = 8.4 Hz, 1H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.59 (dd, *J* = 15.0, 6.7 Hz, 1H), 4.55 – 4.49 (m, 2H), 4.34 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.09 (d, *J* = 11.3 Hz, 1H), 3.89 – 3.77 (m, 4H), 3.76 – 3.68 (m, 4H), 3.68 – 3.59 (m, 6H), 3.57 – 3.45 (m, 5H), 2.69 (t, *J* = 6.7 Hz, 2H), 2.51 (s, 3H), 2.49 – 2.44 (m, 2H), 2.21 – 2.11 (m, 1H), 0.96 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.99, 171.54, 171.10, 169.88, 163.44, 152.77, 150.29, 148.40, 138.32, 131.63, 130.80, 129.42, 128.08, 127.83, 127.77, 124.20, 123.62, 120.70, 70.51, 70.44, 70.11, 67.54, 67.21, 58.54, 57.63, 56.67, 50.22, 49.89, 45.49, 43.15, 41.43, 36.72, 36.24, 35.06, 33.63, 26.43, 16.09.
**HRMS (ESI):** calcd for $C_{41}H_{54}N_7O_7S_2$ $[M+H]^+$ 820.3521, found 820.3516.

Methyl-1-cyclopropyl-6-fluoro-7-(4-(3-(2-(3-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl) carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-3-oxopropoxy)ethoxy)propanoyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylate (**9d**)



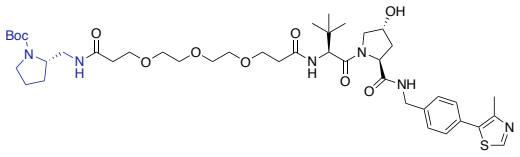
Prepared according to general procedure **B** from Ciprofloxacin methyl ester (34.5 mg, 0.1 mmol) using **5h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a white solid, 71.0 mg (75%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (s, 1H), 8.50 (s, 1H), 7.95 (d, *J* = 13.1 Hz, 1H), 7.59 (t, *J* = 6.0 Hz, 1H), 7.35 (s, 4H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.62 – 4.52 (m, 3H), 4.35 (dd, *J* = 15.1, 5.3 Hz, 1H), 4.09 – 3.94 (m, 2H), 3.89 (s, 3H), 3.84 – 3.76 (m, 4H), 3.73 – 3.57 (m, 9H), 3.49 – 3.39 (m, 1H), 3.29 – 3.23 (m, 2H), 3.19 (t, *J* = 5.2 Hz, 2H), 2.67 (t, *J* = 6.6 Hz, 2H), 2.50 (s, 3H), 2.48 – 2.38 (m, 3H), 2.22 – 2.15 (m, 1H), 1.36 – 1.28 (m, 2H), 1.17 – 1.10 (m, 2H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.00 (d, $J_{C-F}$ = 2.1 Hz), 171.57, 171.39, 171.20, 169.84, 166.06, 153.24 (d, $J_{C-F}$ = 248.5 Hz), 150.31, 148.45, 148.37, 144.02 (d, $J_{C-F}$ = 10.6 Hz), 138.35, 137.95, 131.63, 130.75, 129.40, 128.03, 123.26 (d, $J_{C-F}$ = 7.1 Hz), 113.29 (d, $J_{C-F}$ = 23.0 Hz), 109.89, 105.18 (d, $J_{C-F}$ = 2.4 Hz), 70.44, 70.06, 67.46, 67.17, 58.72, 57.48, 56.78, 52.04, 50.42 (d, $J_{C-F}$ = 5.0 Hz), 49.47, 45.64, 43.11, 41.33, 36.72, 36.44, 35.32, 34.62, 33.51, 26.42, 16.08, 8.16.
**HRMS (ESI):** calcd for $C_{48}H_{61}FN_7O_{10}S$ $[M+H]^+$ 946.4179, found 946.4178.

(2*S*,4*R*)-1-((2*S*)-2-(*tert*-butyl)-16-(4-((4-chlorophenyl)(phenyl)methyl)piperazin-1-yl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9e**)



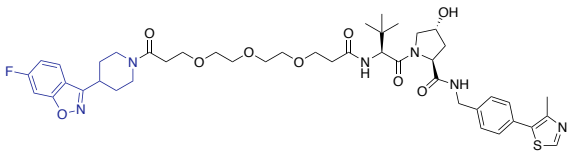
Prepared according to general procedure **B** from N-(4-chlorobenzhydryl)piperazine (28.7 mg, 0.1 mmol) using **5i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a white foamy solid, 72.0 mg (77%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.50 (t, *J* = 6.0 Hz, 1H), 7.41 – 7.32 (m, 8H), 7.32 – 7.24 (m, 7H), 7.26 – 7.17 (m, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 4.73 (t, *J* = 8.0 Hz, 1H), 4.57 (dd, *J* = 15.0, 6.6 Hz, 1H), 4.52 (s, 1H), 4.49 (d, *J* = 8.3 Hz, 1H), 4.34 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.22 (bs, 1H), 4.09 (dt, *J* = 11.6, 1.8 Hz, 1H), 3.76 (td, *J* = 6.9, 1.4 Hz, 2H), 3.71 (t, *J* = 5.7 Hz, 2H), 3.67 – 3.54 (m, 11H), 3.50 – 3.43 (m, 2H), 2.59 (td, *J* = 6.9, 1.2 Hz, 2H), 2.53 (s, 3H), 2.51 – 2.44 (m, 3H), 2.40 – 2.31 (m, 4H), 2.17 – 2.09 (m, 1H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.01, 171.70, 170.88, 169.28, 150.28, 148.43, 141.51, 140.71, 138.24, 132.83, 131.61, 130.86, 129.46, 129.09, 128.81, 128.74, 128.08, 127.75, 127.42, 75.18, 70.52, 70.44, 70.34, 70.26, 70.07, 67.23, 67.16, 58.39, 57.71, 56.61, 51.90, 51.45, 45.67, 43.17, 41.65, 36.71, 35.99, 34.89, 33.44, 26.42, 16.07.
**HRMS (ESI):** calcd for $C_{49}H_{64}ClN_6O_8S$ $[M+H]^+$ 931.4189, found 931.4187.

*tert*-butyl-(*S*)-2-((*S*)-17-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-18,18-dimethyl-3,15-dioxo-6,9,12-trioxa-2,16-diazanonadecyl)pyrrolidine-1-carboxylate (**9e**)



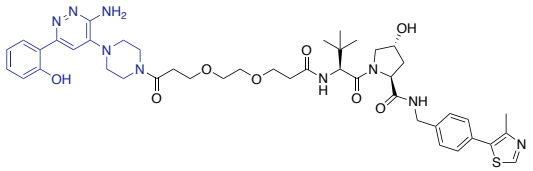
Prepared according to general procedure **B** from *tert*-butyl (*S*)-2-(aminomethyl)pyrrolidine-1-carboxylate (20.0 mg, 0.1 mmol) using **5i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a off-white foam, 60.0 mg (71%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.66 – 7.59 (m, 1H), 7.51 – 7.43 (m, 1H), 7.36 (s, 4H), 7.18 – 7.06 (m, 1H), 4.75 (t, *J* = 7.9 Hz, 1H), 4.61 – 4.46 (m, 3H), 4.35 (dd, *J* = 15.1, 5.4 Hz, 1H), 4.13 – 4.03 (m, 1H), 3.99 – 3.92 (m, 1H), 3.81 – 3.67 (m, 5H), 3.67 – 3.57 (m, 9H), 3.40 – 3.29 (m, 2H), 3.25 – 3.14 (m, 1H), 2.52 (s, 3H), 2.50 – 2.40 (m, 5H), 2.21 – 2.11 (m, 1H), 2.00 – 1.75 (m, 3H), 1.69 (s, 1H), 1.45 (s, 9H), 0.97 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.02, 171.63, 171.36, 171.12, 156.17, 150.28, 148.43, 138.32, 131.64, 130.83, 129.44, 128.04, 79.84, 70.57, 70.45, 70.41, 70.23, 70.07, 67.28, 58.49, 57.73, 56.67, 56.59, 47.00, 44.53, 43.12, 37.06, 36.74, 36.30, 34.96, 29.14, 28.46, 26.44, 23.74, 16.05.
**HRMS (ESI):** calcd for $C_{42}H_{65}N_6O_{10}S$ $[M+H]^+$ 845.4477, found 845.4474.

(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-16-(4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9f**)



Prepared according to general procedure **B**, using dry THF (4 mL) as solvent in place of $CH_2Cl_2$ and $CH_3CN$, from 6-fluoro-3-(piperidin-4-yl)benzo[*d*]isoxazole (22.0 mg, 0.1 mmol) using **5i** PROTAC reagent capsule. Reaction time 12 h. Isolated after filtration through a silica pad as off-white solid, 49.9 mg (57%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (s, 1H), 7.64 (ddd, *J* = 8.7, 5.1, 2.0 Hz, 1H), 7.52 (t, *J* = 6.0 Hz, 1H), 7.39 – 7.33 (m, 4H), 7.27 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.13 – 7.03 (m, 2H), 4.74 (t, *J* = 7.9 Hz, 1H), 4.67 – 4.46 (m, 4H), 4.35 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.13 – 4.01 (m, 2H), 3.81 (td, *J* = 6.8, 1.3 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 3.67 – 3.60 (m, 9H), 3.38 – 3.20 (m, 2H), 2.96 – 2.83 (m, 1H), 2.78 – 2.61 (m, 2H), 2.58 – 2.44 (m, 2H), 2.52 (s, 3H), 2.25 (bs, 1H), 2.20 – 2.08 (m, 3H), 2.07 – 1.96 (m, 1H), 1.96 – 1.81 (m, 1H), 0.95 (s, 9H).
**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.02, 171.71, 170.94, 169.46 (d, *J* = 2.3 Hz), 164.21 (d, *J* = 251.2 Hz), 163.97, 163.83, 160.21, 150.29, 148.45, 138.27, 131.62, 130.87, 129.47, 128.09, 122.19 (d, *J* = 11.1 Hz), 117.08, 112.67 (d, *J* = 25.4 Hz97.60 (d, *J* = 26.7 Hz), 70.53, 70.47, 70.37, 70.33, 70.08, 67.40, 67.17, 58.43, 57.71, 56.63, 45.50, 43.18, 41.41, 36.72, 36.05, 34.92, 34.22, 33.61, 30.49, 30.15, 26.42, 16.07.
**$^{19}$F NMR (377 MHz, $CDCl_3$)** δ -108.99, -109.00 (F signal split due to rotamers).
**HRMS (ESI):** calcd for $C_{44}H_{58}FN_6O_9S$ $[M+H]^+$ 865.3965, found 865.3962.

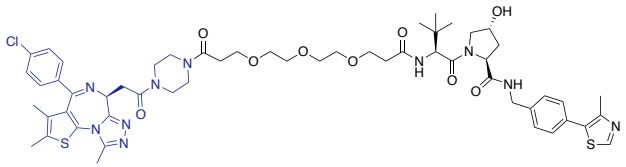
(2*S*,4*R*)-1-((*S*)-2-(3-(2-(3-(4-(3-amino-6-(2-hydroxyphenyl)pyridazin-4-yl)piperazin-1-yl)-3-oxopropoxy) ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9h**)



Prepared according to general procedure **B** from 2-(6-amino-5-(piperazin-1-yl)pyridazine-3-yl)phenol (27.1 mg, 0.1 mmol) using **5h** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as a light-yellow foam, 75.9 mg (87%).
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.59 – 7.49 (m, 2H), 7.36 (s, 4H), 7.31 – 7.24 (m, 1H), 7.06 (d, *J* = 8.6 Hz, 1H), 7.02 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.90 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 5.28 (bs, 2H), 4.73 (t, *J* = 8.1 Hz, 1H), 4.62 – 4.51 (m, 3H), 4.36 (dd, *J* = 15.0, 5.3 Hz, 1H), 4.08 (d, *J* = 11.3 Hz, 1H), 3.87 – 3.75 (m, 4H), 3.75 – 3.68 (m, 4H), 3.67 – 3.57 (m, 6H), 3.17 – 3.05 (m, 4H), 2.68 (t, *J* = 6.3 Hz, 2H), 2.51 (s, 3H), 2.50 – 2.41 (m, 3H), 2.24 – 2.16 (m, 1H), 0.98 (s, 9H).

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.70, 171.55, 171.14, 170.31, 159.02, 154.86, 154.05, 150.32, 148.43, 140.74, 138.29, 131.61, 131.04, 130.84, 129.43, 128.06, 125.28, 118.88, 118.44, 117.38, 111.23, 70.50, 70.48, 70.11, 67.68, 67.15, 58.76, 57.62, 56.89, 49.41, 48.99, 45.70, 43.16, 41.33, 36.78, 36.54, 35.22, 33.66, 26.45, 16.08.
**HRMS (ESI):** calcd for $C_{44}H_{58}N_9O_8S$ $[M+H]^+$ 872.4124, found 872.4112.

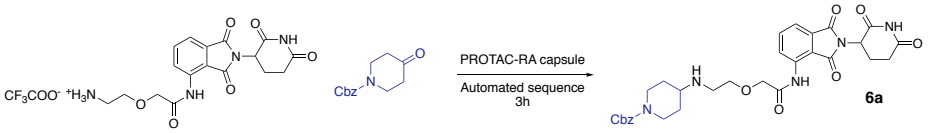
(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-16-(4-(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)-4,16-dioxo-7,10,13-trioxa-3-azahexadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (**9i**)



Prepared according to general procedure **B** from compound **41** (46.9 mg, 0.1 mmol) using **5i** PROTAC reagent capsule. Reaction time 4 h. Isolated without further purification as off-white foam, 90.2 mg (81%).
Signals show extra splitting due to rotamers.
**$^1$H NMR (500 MHz, $CDCl_3$)** δ 8.68 (s, 1H), 7.65 (t, *J* = 6.1 Hz, 0.5H), 7.57 (t, *J* = 5.9 Hz, 0.5H), 7.42 – 7.38 (m, 2H), 7.37 – 7.31 (m, 6H), 7.11 (t, *J* = 8.2 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.69 (dt, *J* = 15.7, 7.9 Hz, 1H), 4.63 – 4.50 (m, 3H), 4.34 (dd, *J* = 15.0, 5.4 Hz, 1H), 4.09 – 4.03 (m, 1H), 3.94 – 3.47 (m, 24H), 2.69 – 2.64 (m, 1H), 2.65 (s, 3H), 2.51 (s, 3H), 2.50 – 2.43 (m, 3H), 2.40 (s, 3H), 2.17 – 2.12 (m, 1H), 1.68 (s, 3H), 0.95 (s, 9H).
**$^{13}$C NMR (126 MHz, $CDCl_3$)** δ 174.13, 172.36, 171.88, 171.79, 171.59, 171.42, 171.28, 171.15, 170.17, 170.01, 169.35, 169.13, 163.89, 163.81, 155.74, 150.31, 149.92, 148.40, 138.46, 138.35, 136.74, 136.69, 132.13, 132.10, 131.69, 131.66, 130.96, 130.89, 130.84, 130.80, 130.73, 130.55, 130.50, 129.81, 129.42, 128.72, 128.07, 70.51, 70.46, 70.41, 70.33, 69.98, 67.42, 67.39, 67.22, 58.66, 58.61, 57.64, 57.55, 56.75, 54.44, 54.39, 45.98, 45.93, 45.76, 45.58, 45.51, 43.11, 41.86, 41.62, 41.41, 36.69, 36.50, 36.32, 35.35, 35.24, 35.10, 33.70, 26.43, 16.07, 14.39, 13.10, 11.82.
**HRMS (ESI):** calcd for $C_{55}H_{69}ClN_{10}NaO_9S_2$ $[M+Na]^+$ 1135.4271, found 1135.4276.

## 4.3 Reproducibility test

Same reaction run on the same Synple console to test reproducibility of the methodology. Product prepared following general procedure A for the automated synthesis of PROTACs via Reductive Amination.




1st run —> 41.0 mg, 69.3% yield

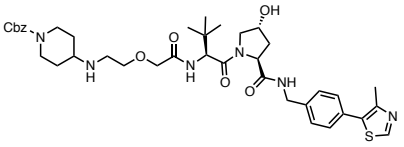
2nd run —> 40.1 mg, 67.8% yield

3rd run —> 40.2 mg, 68.0% yield

## 4.4 Cartridge stability test

Two full PROTAC **5a** and PROTAC **5h** capsules were prepared and stored in a close container at room temperature for 9+ months. A reaction was then performed on Synple console using those old capsules and the results were compared with the results obtained with a freshly prepared capsule.

PROTAC-RA:
Product prepared using general procedure A for the automated synthesis of PROTACs via reductive amination.



Fresh capsule: 69% yield

>9 months old: 64% yield

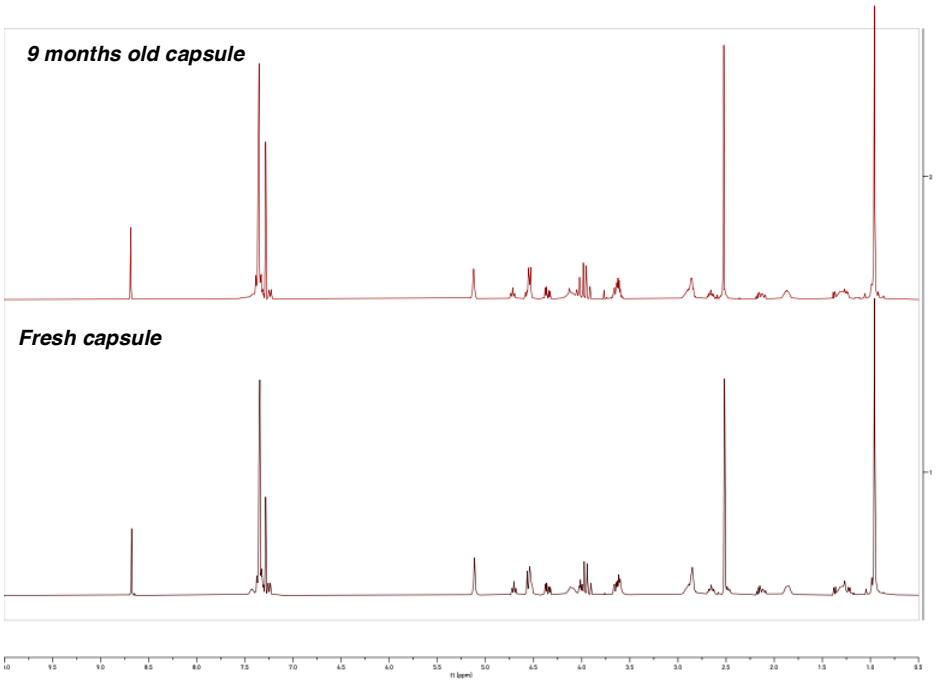
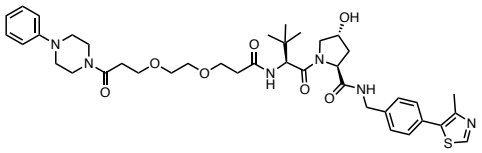



***Fig. S2*** Comparison between $^{1}$H NMR of crude product obtained from >9 months old capsule vs product obtained from freshly prepared capsule

PROTAC-Amide:
Product prepared using general procedure B for the automated synthesis of PROTACs via amide coupling.



Fresh cartridge: 81% yield

>9 months old: 75% yield

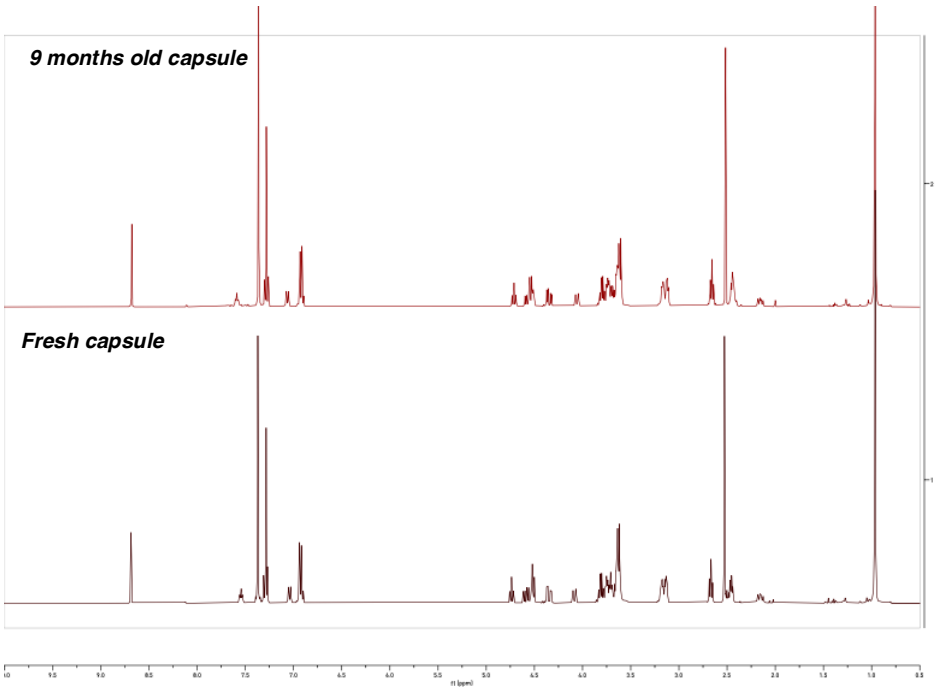
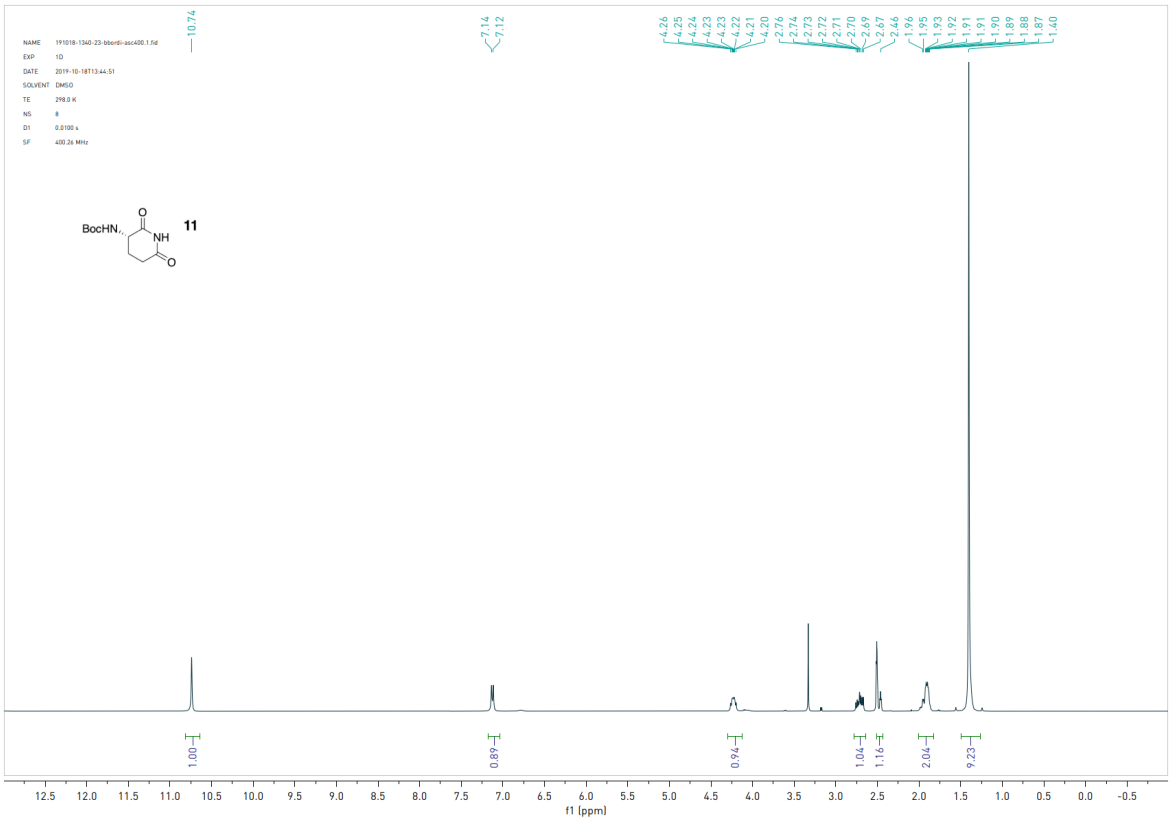


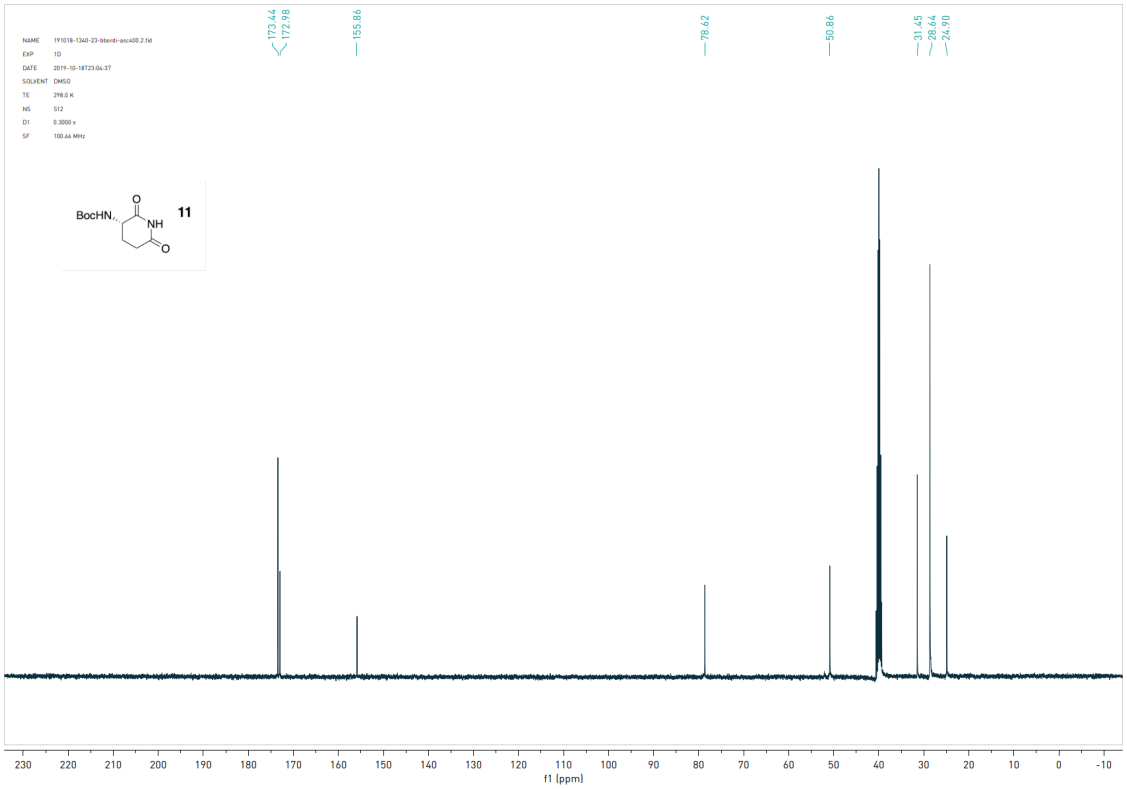

***Fig. S3*** Comparison between $^{1}$H NMR of crude product obtained from >9 months old capsule vs product obtained from freshly prepared capsule

## 5. NMR SPECTRA

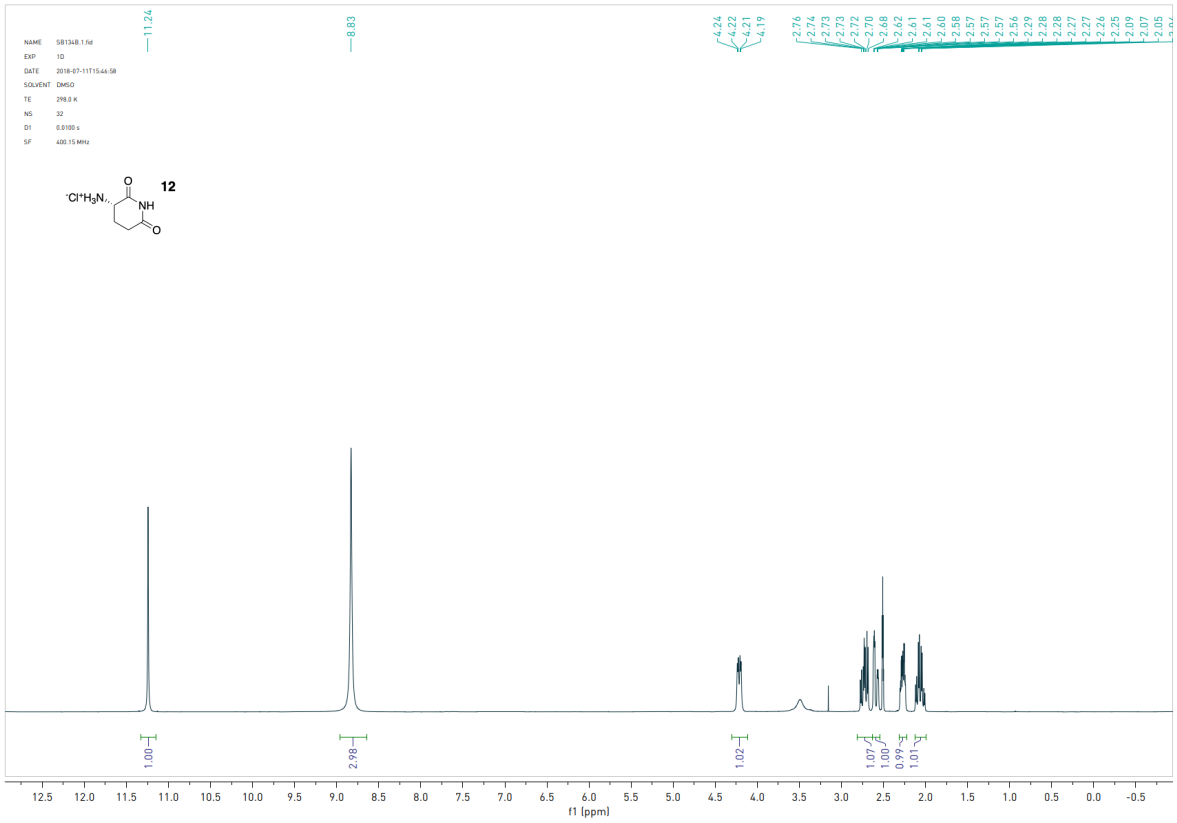
## 5.1 NMR Spectra of starting materials

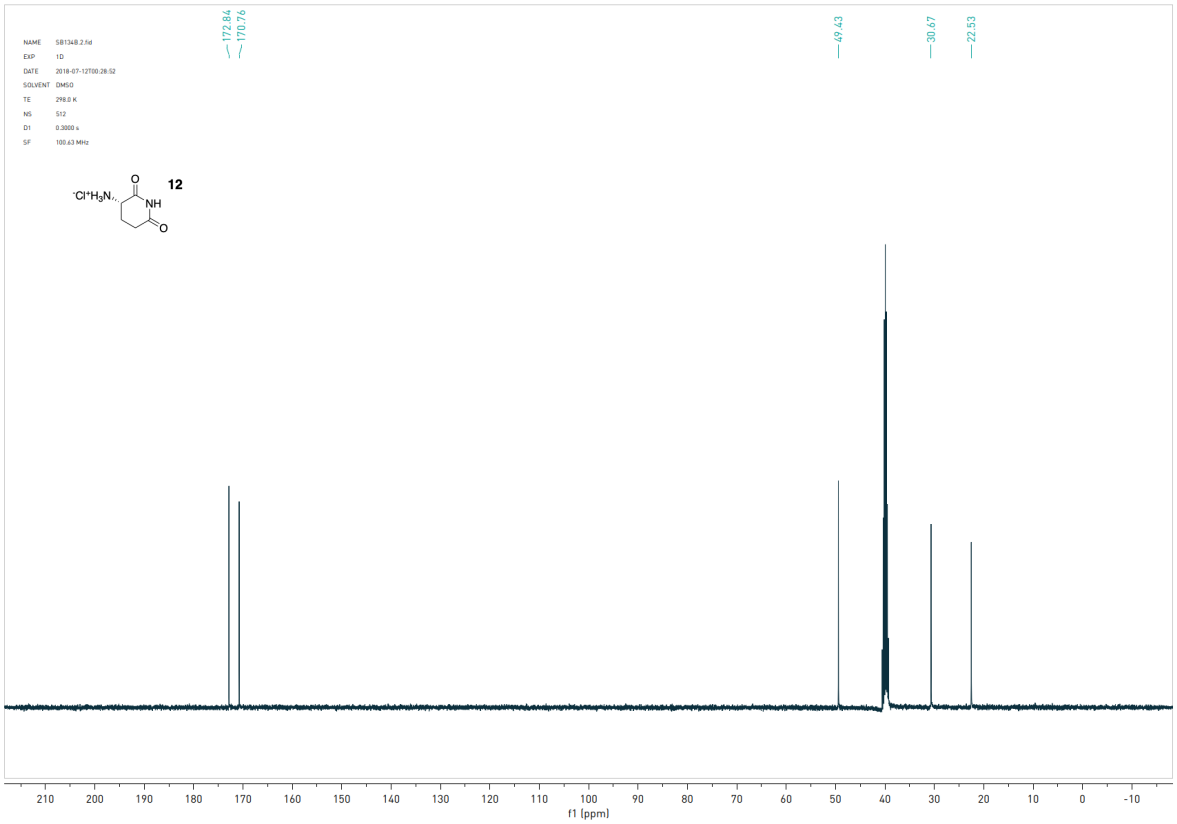
NMR of compound **11**:



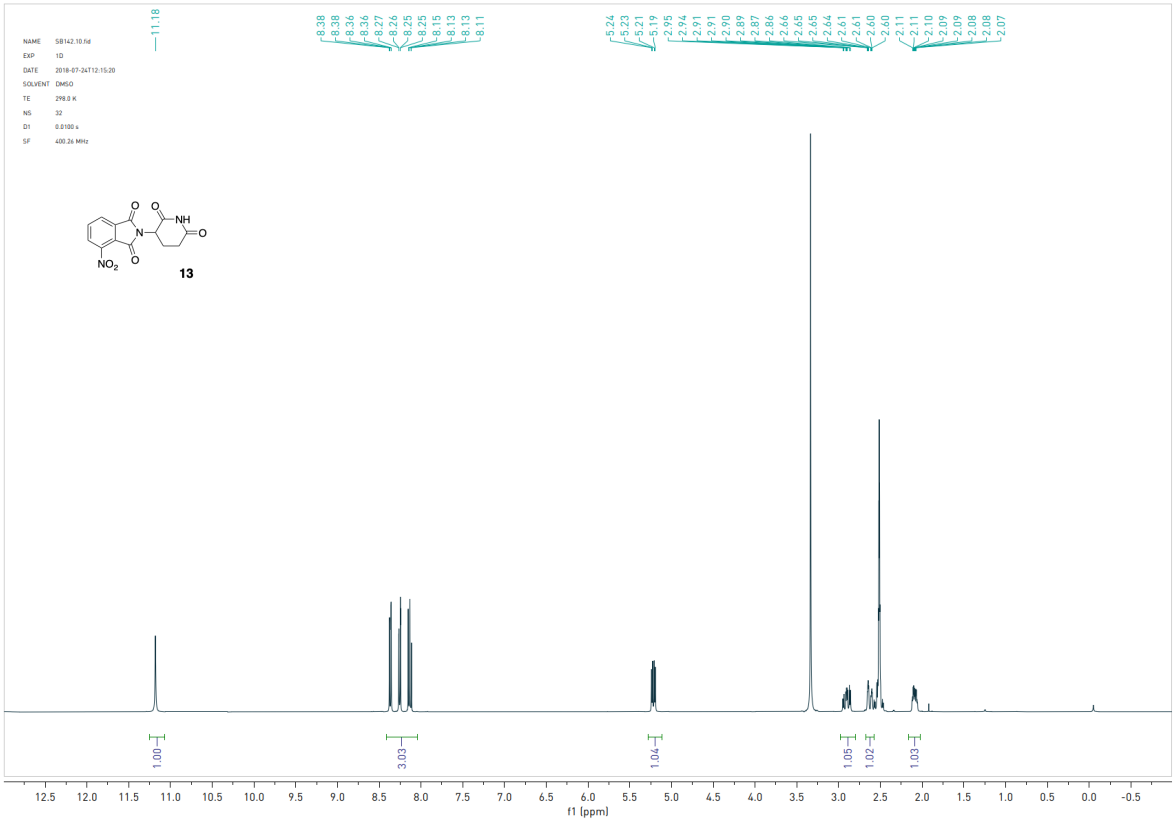



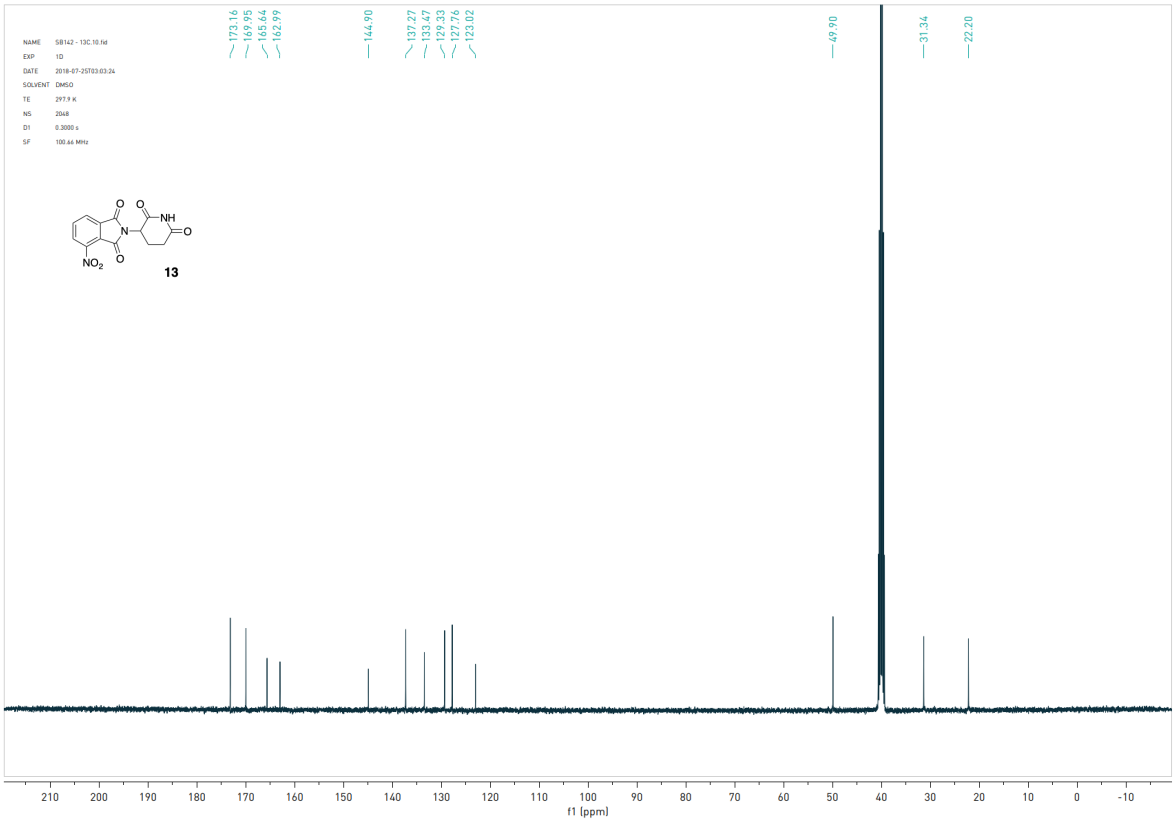
NMR of compound **12**:



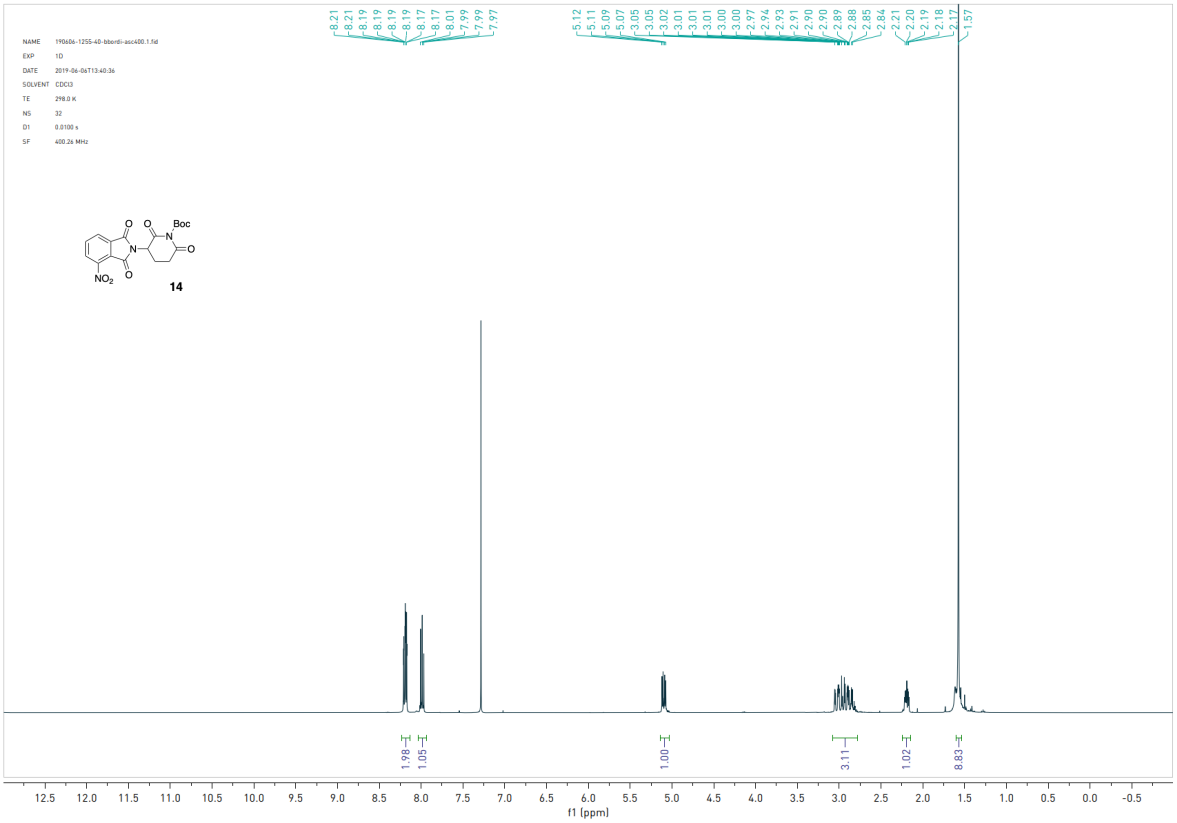



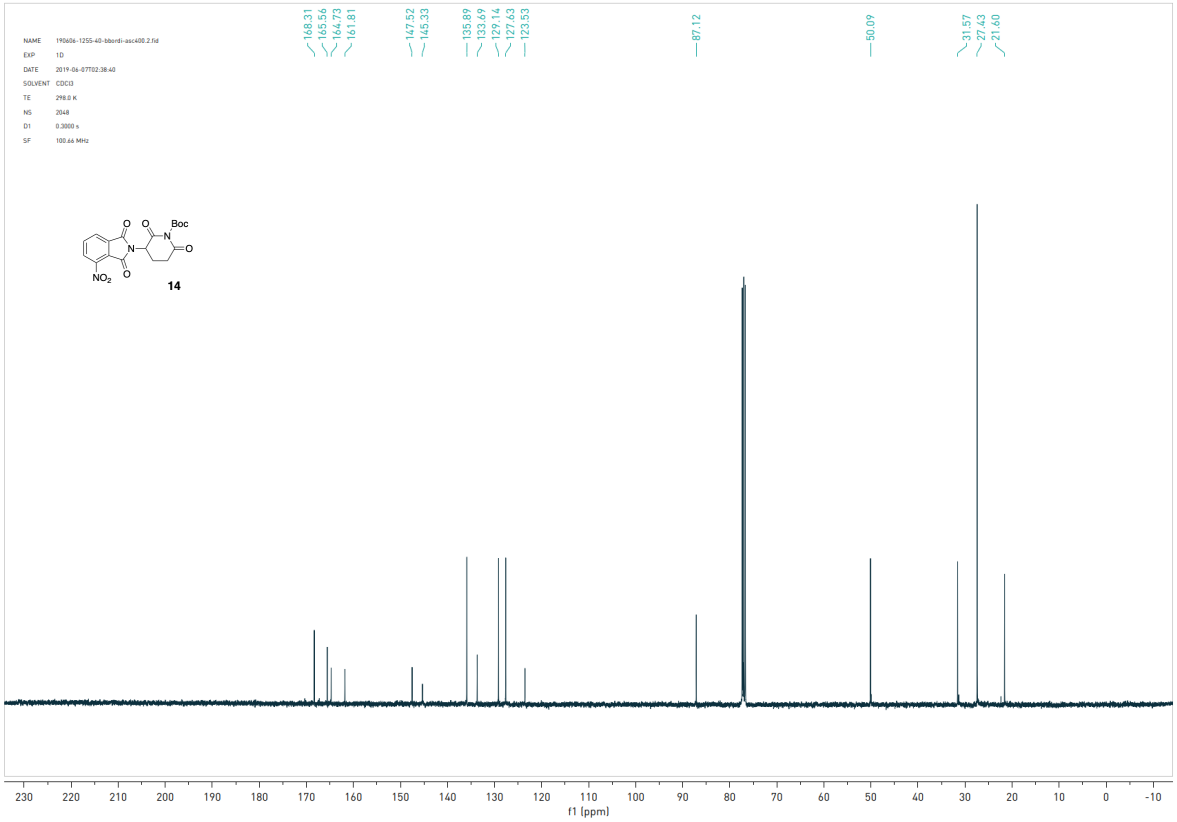
NMR of compound **13**:



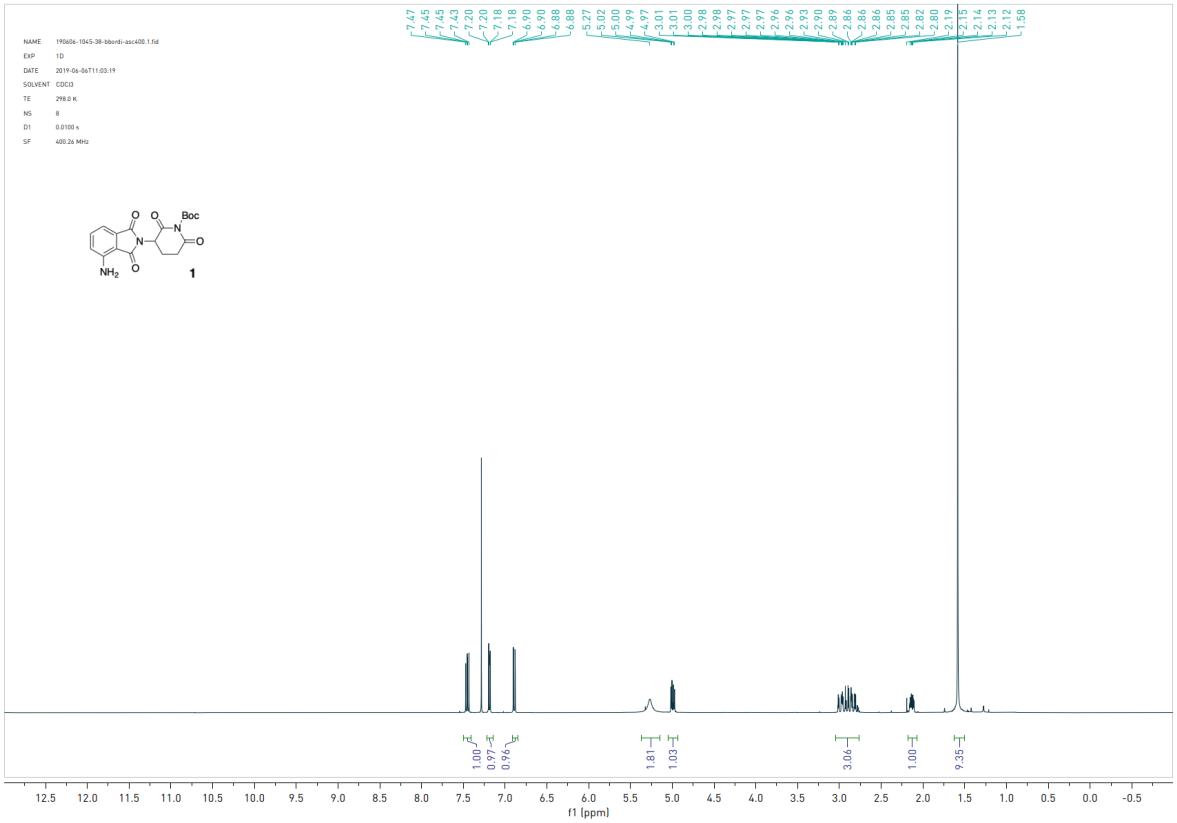



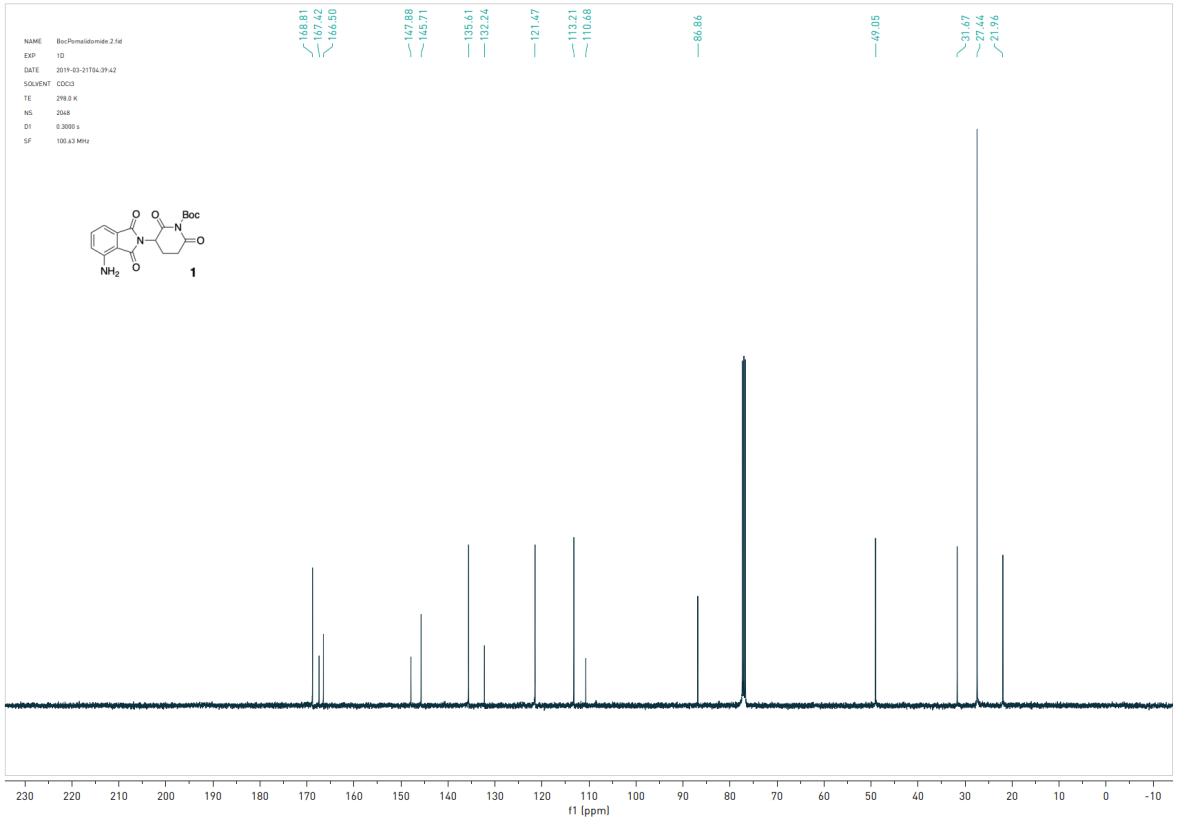
NMR of compound **14**:



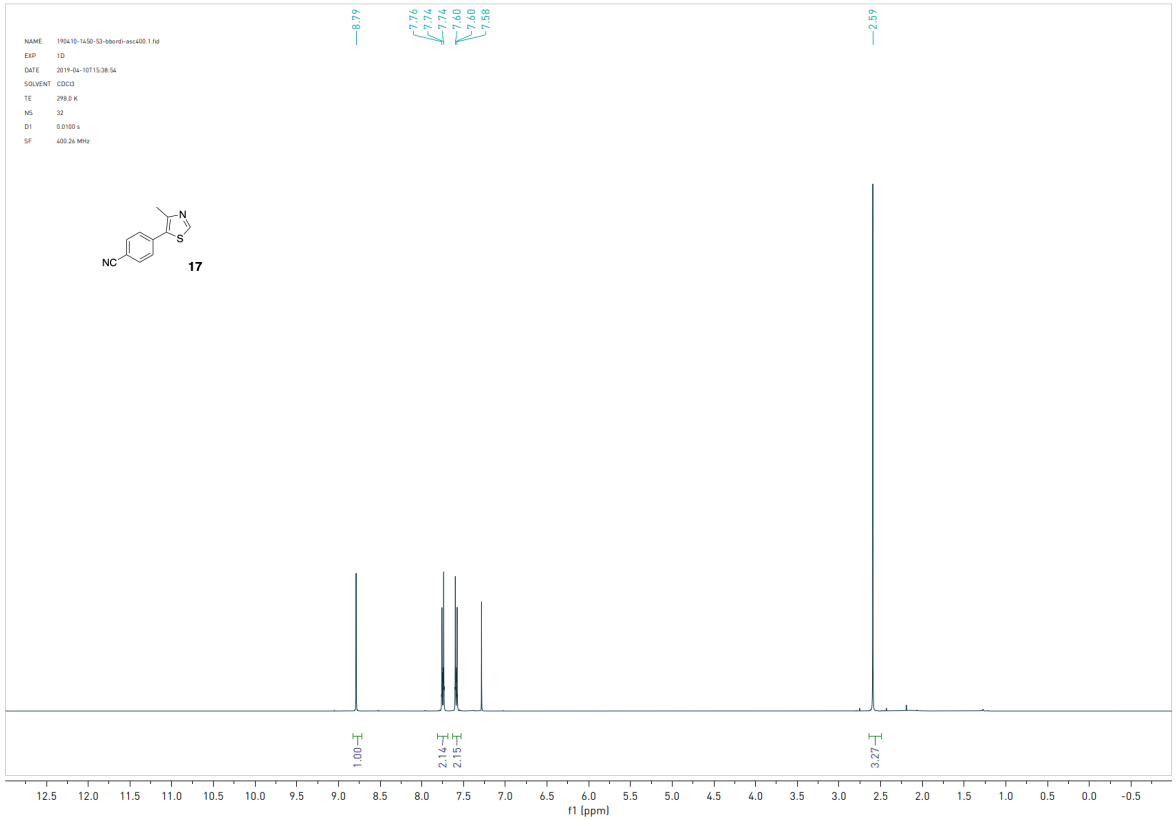



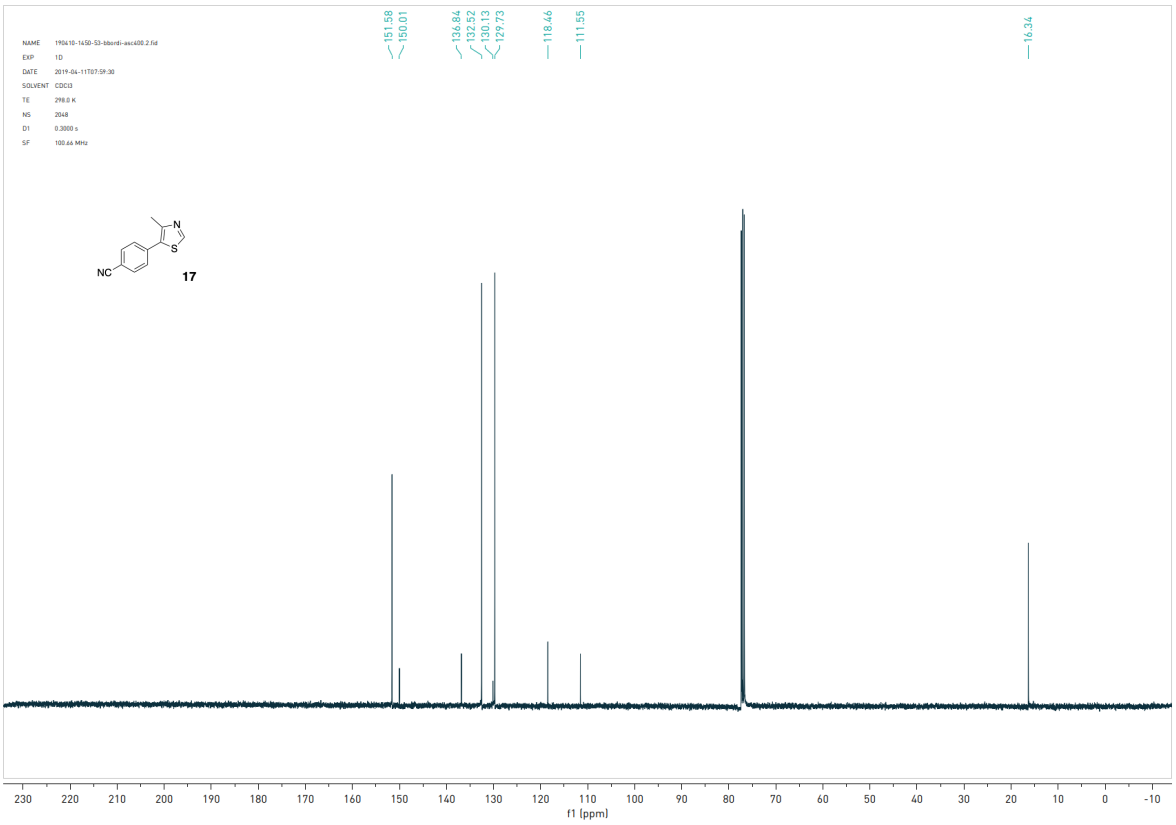
NMR of compound **1**:



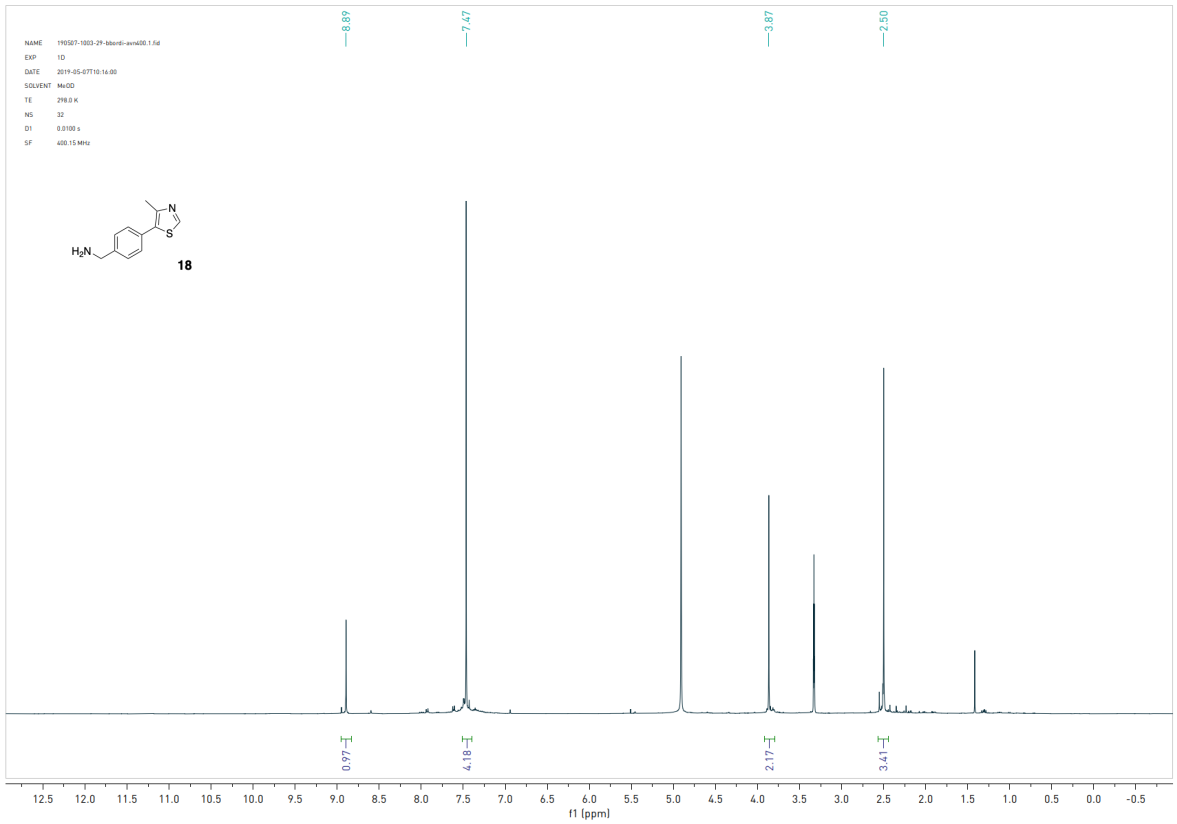



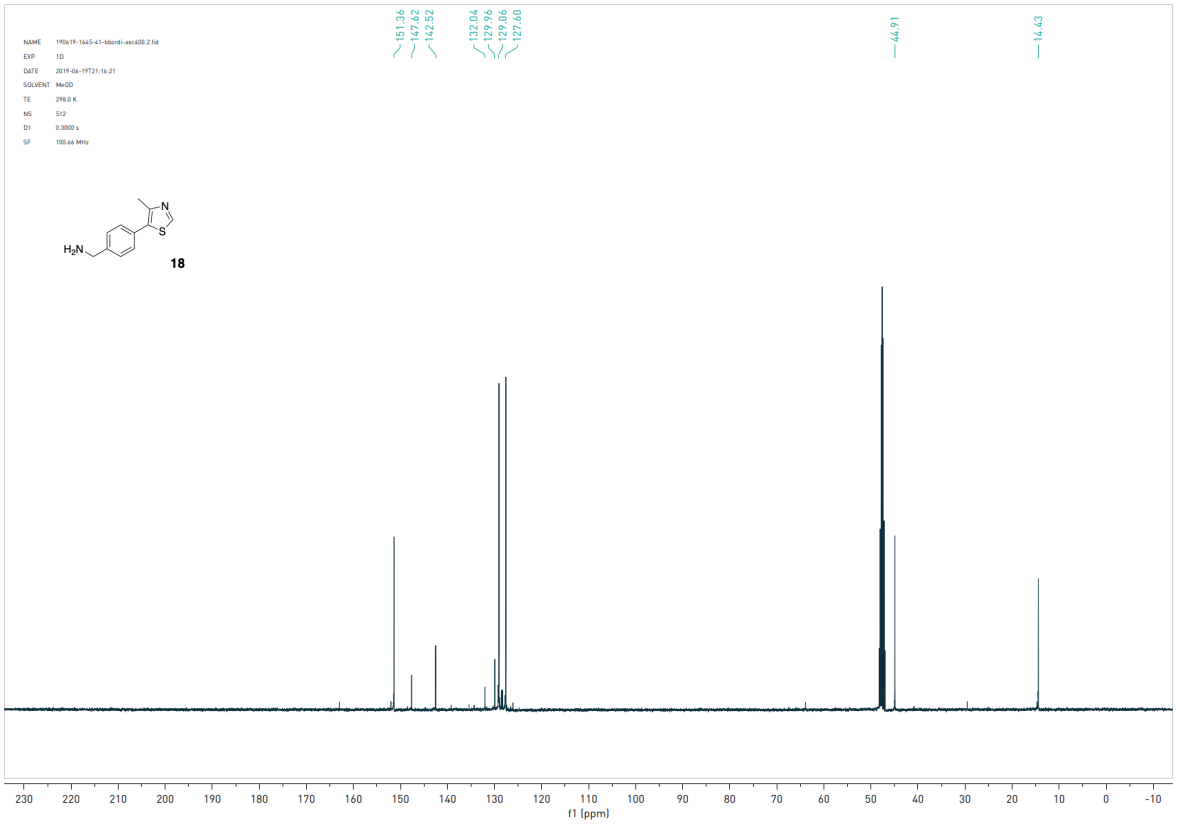
NMR of compound **17**:



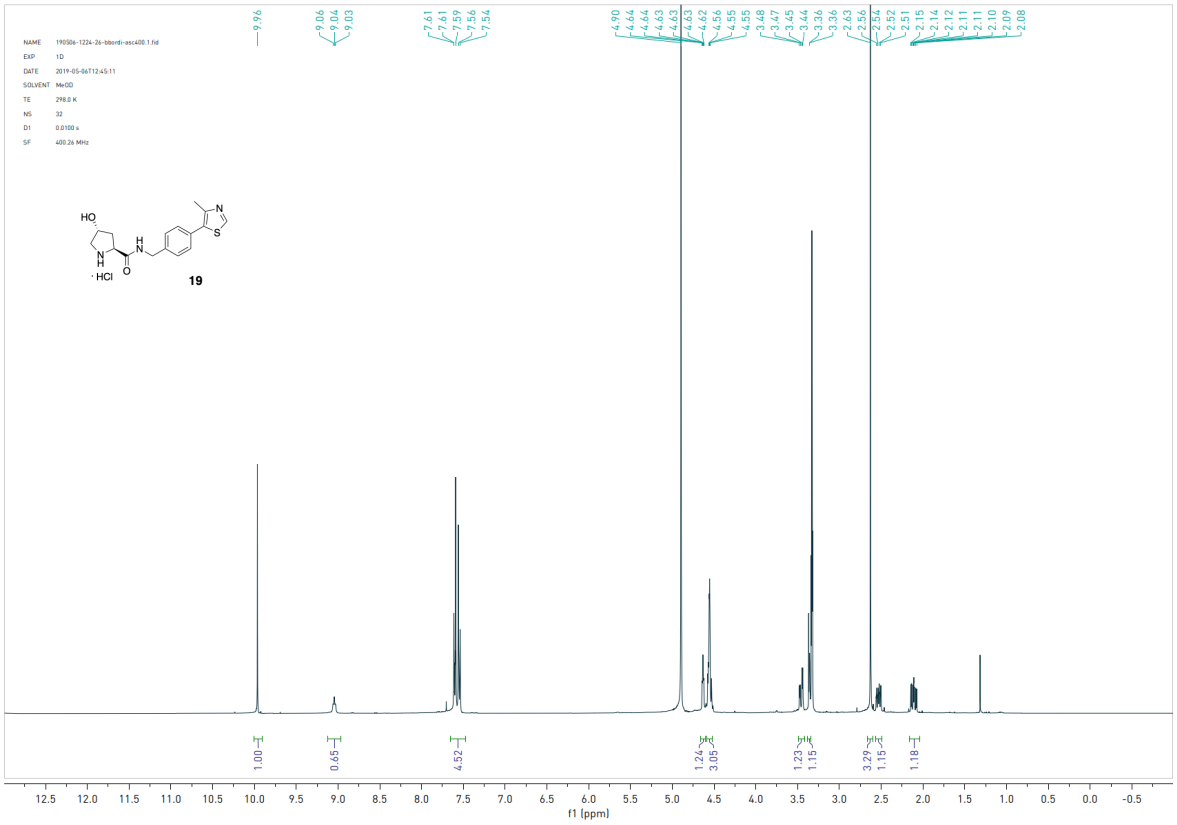



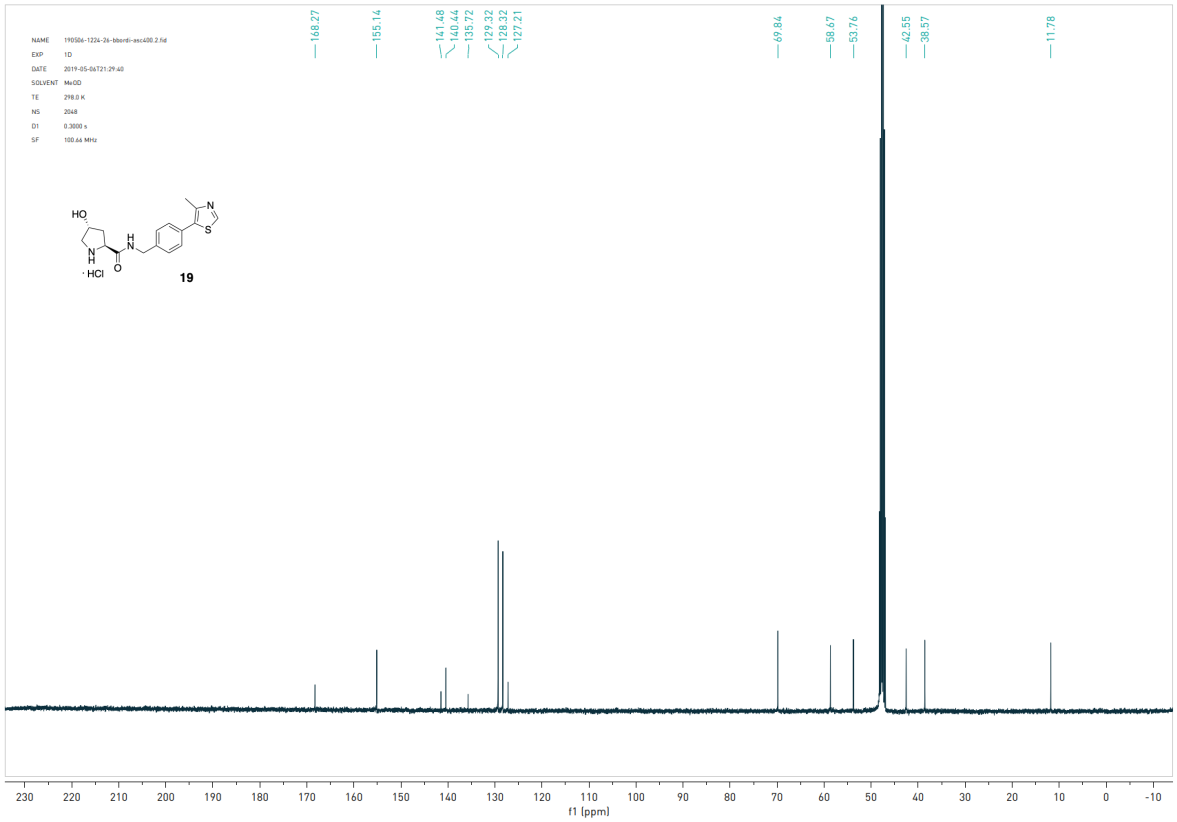
NMR of compound **18**:



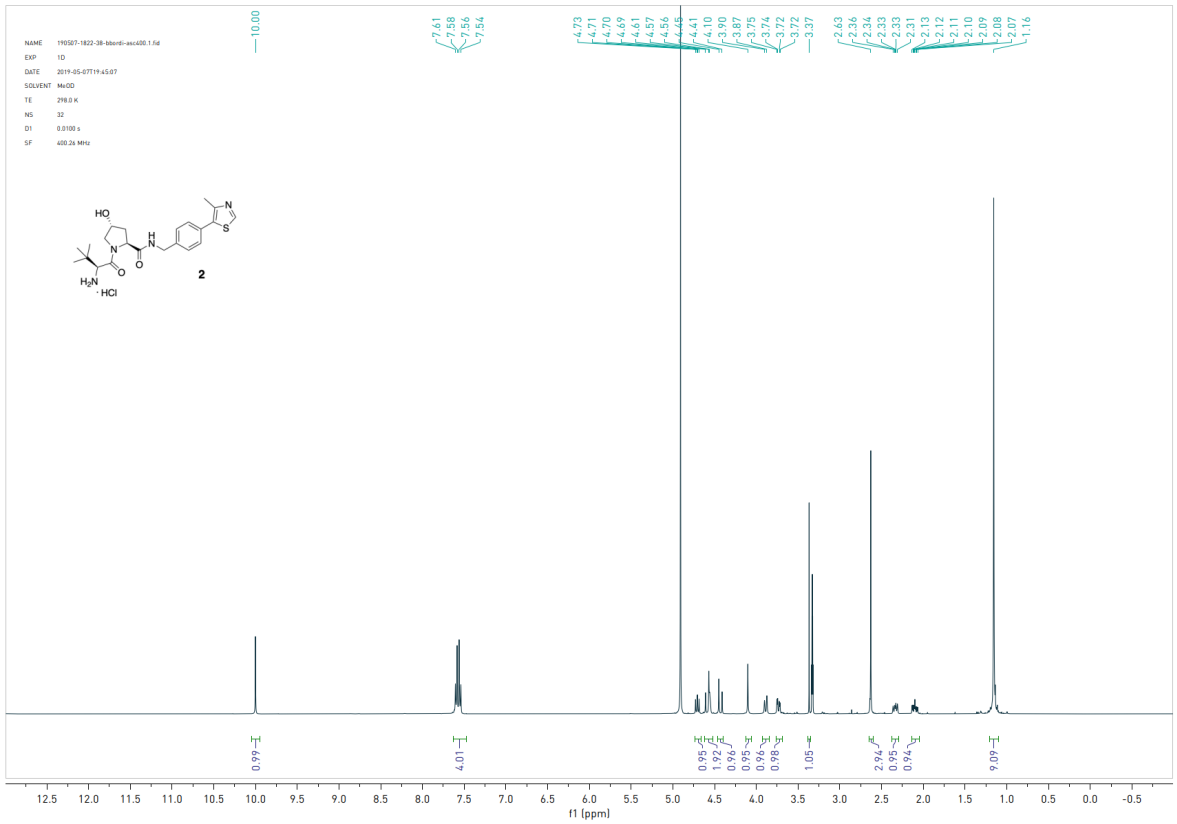



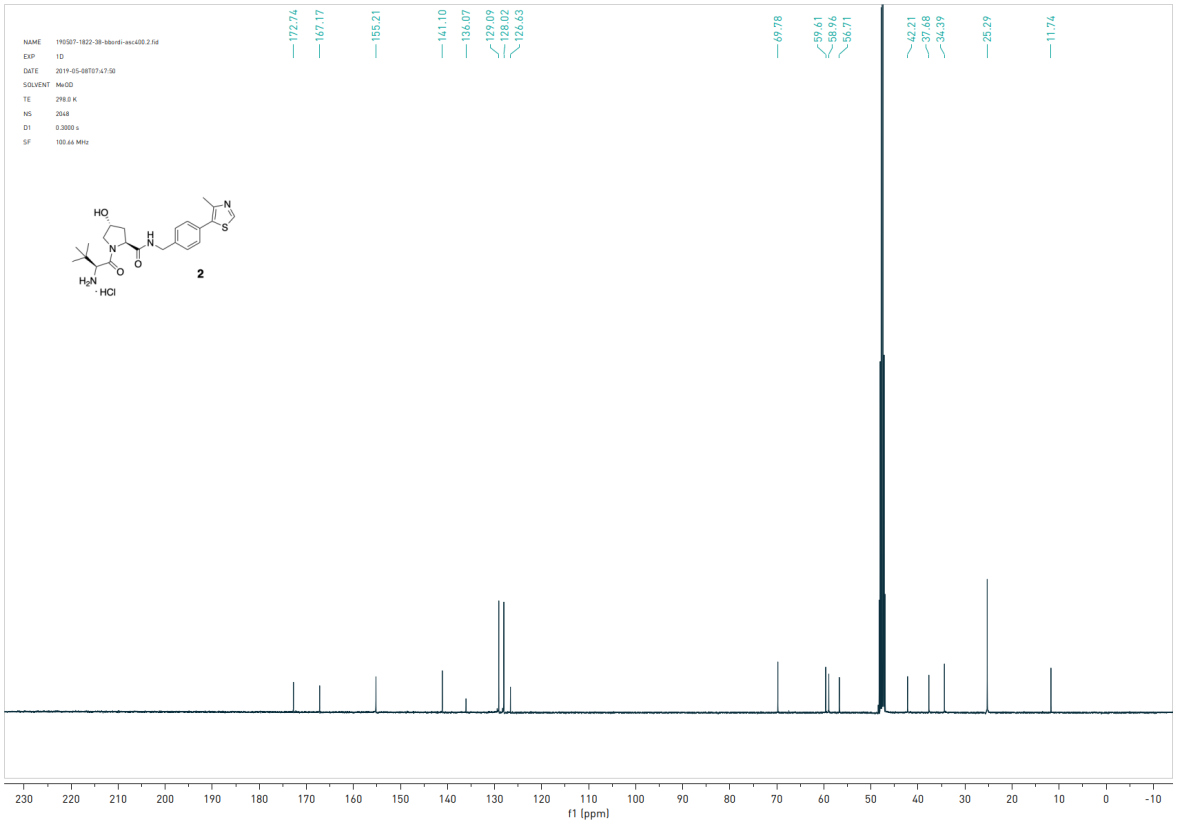
NMR of compound **19**:



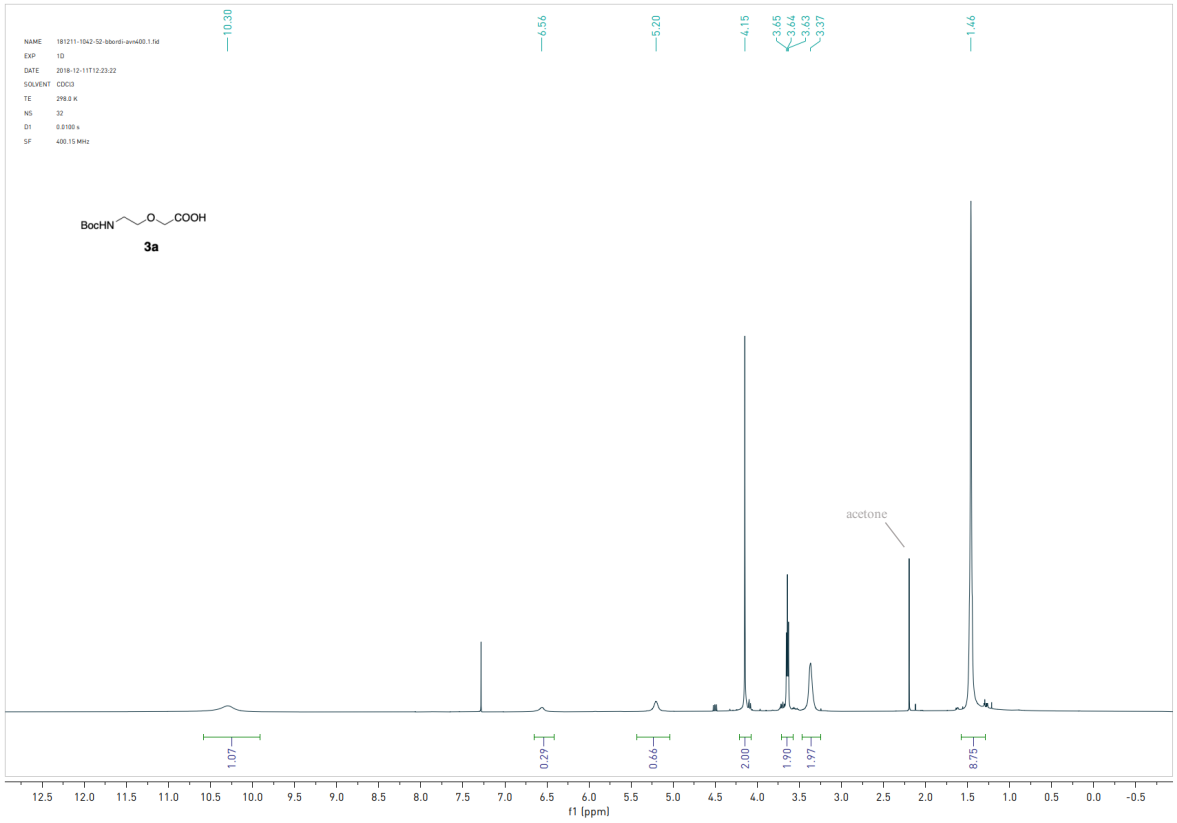



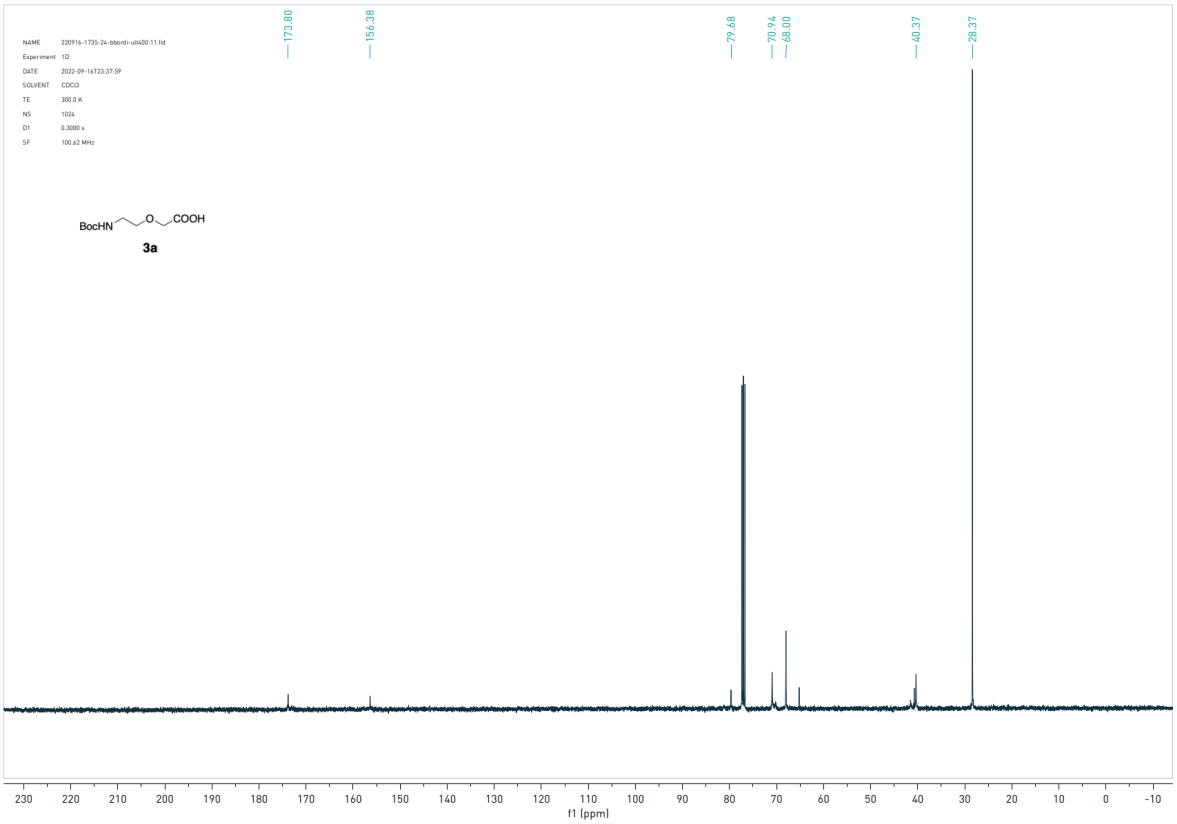
NMR of compound **2**:



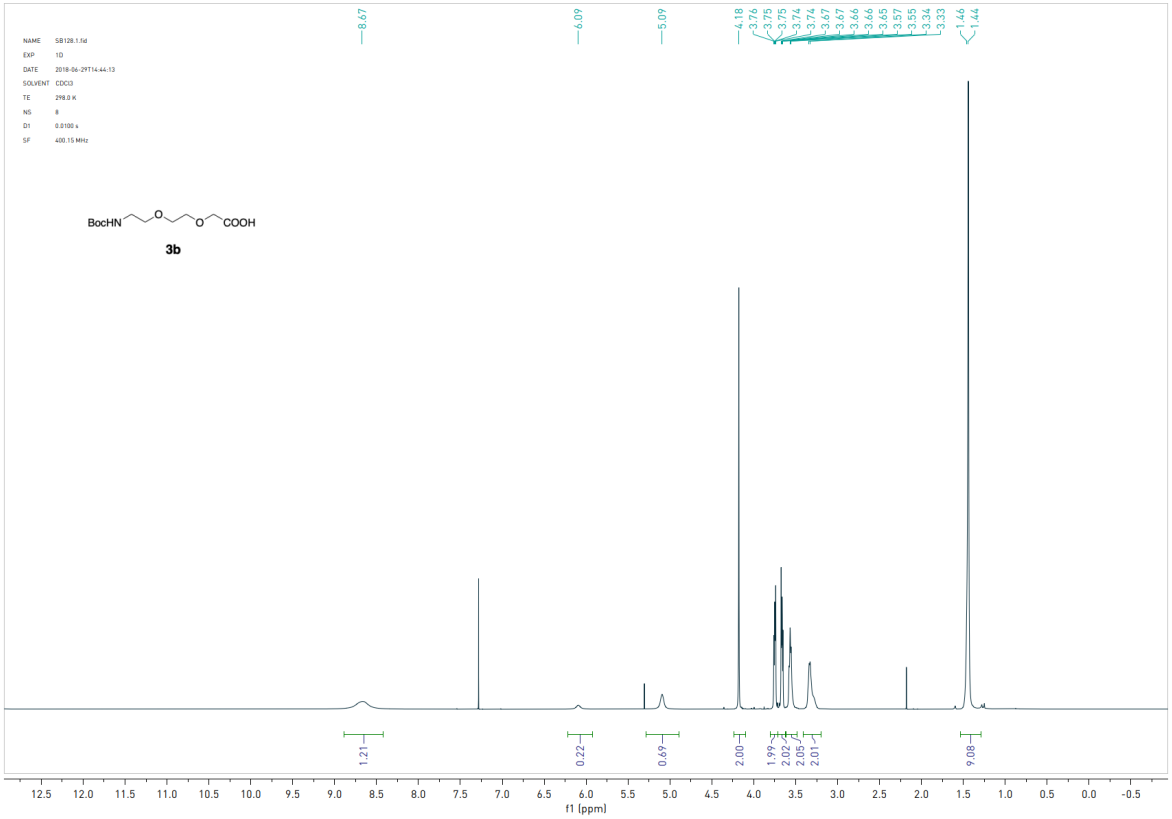



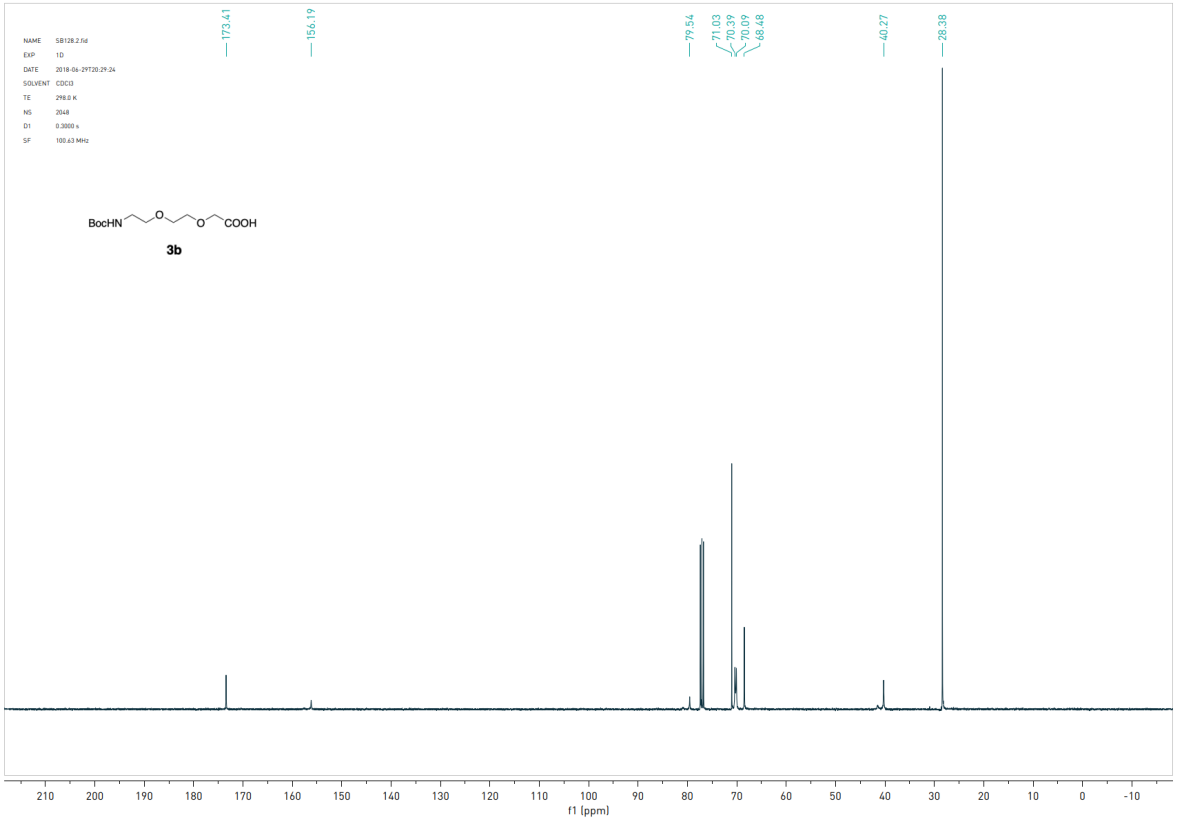
NMR of compound **3a**:



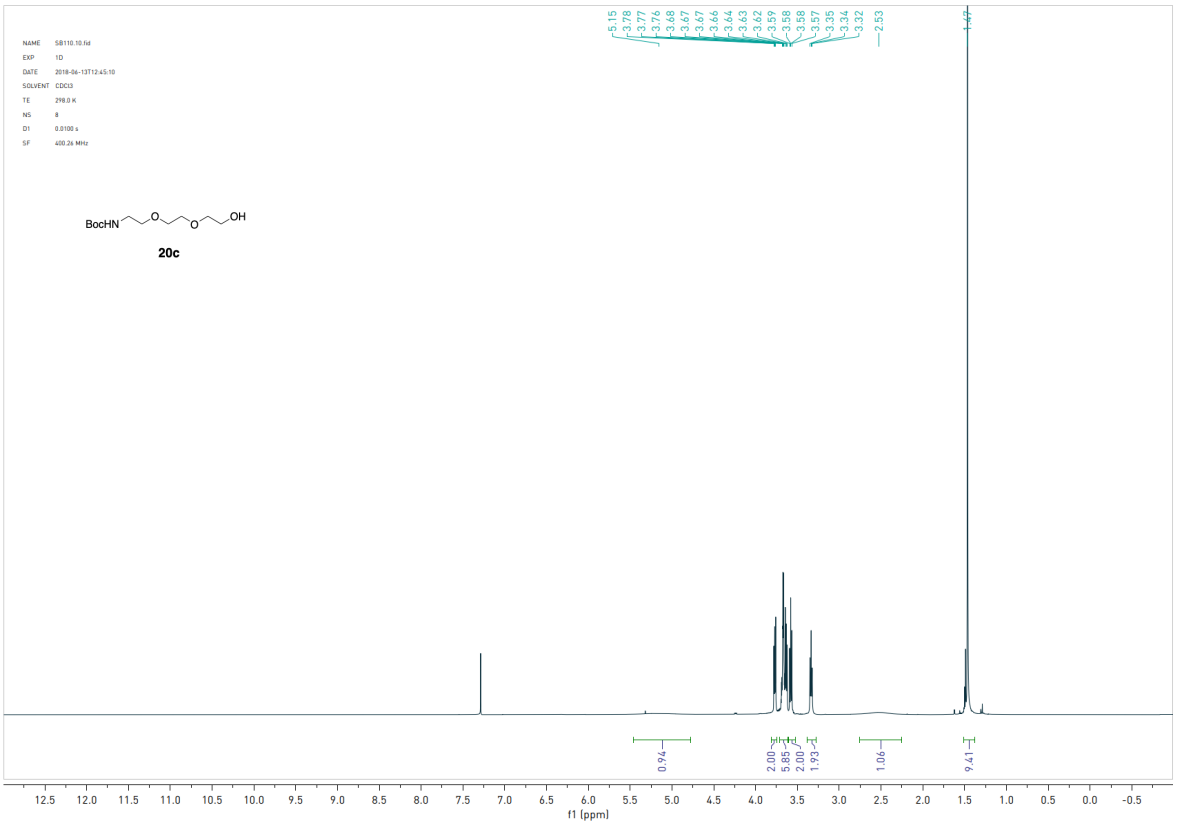



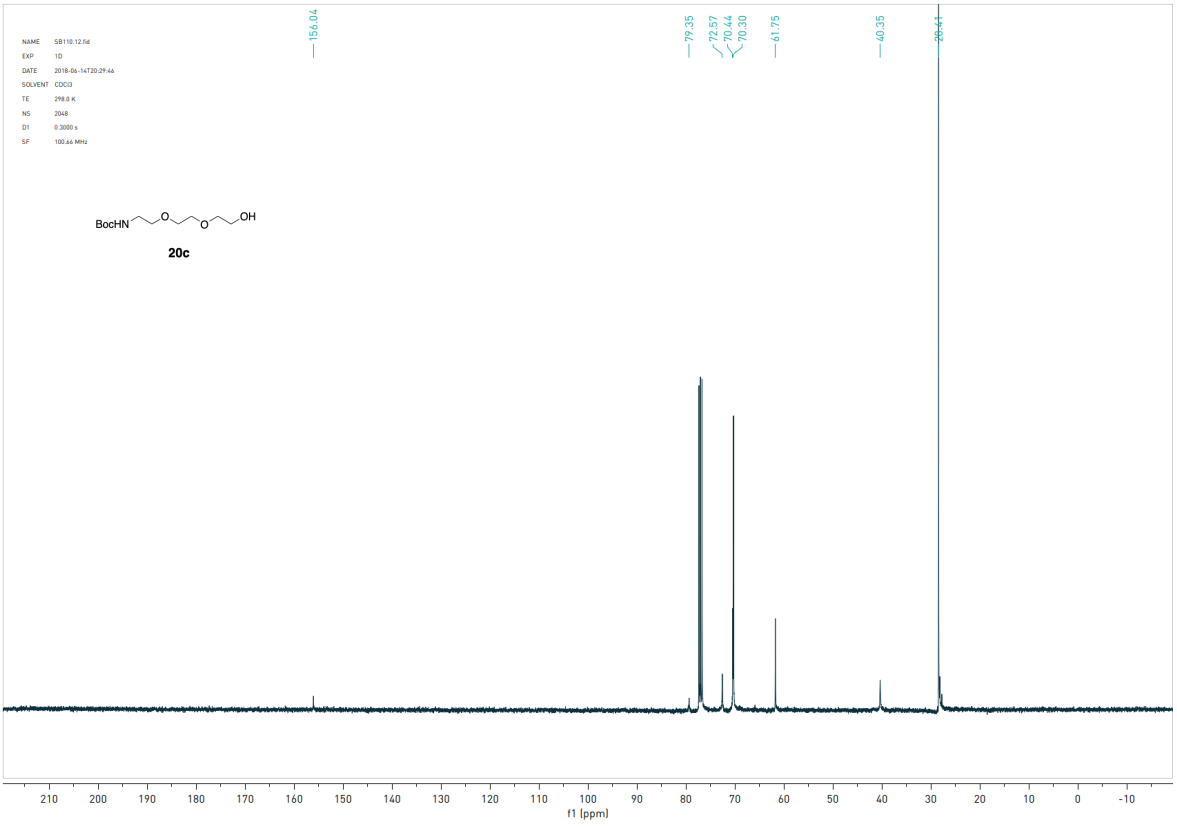
NMR of compound **3b**:



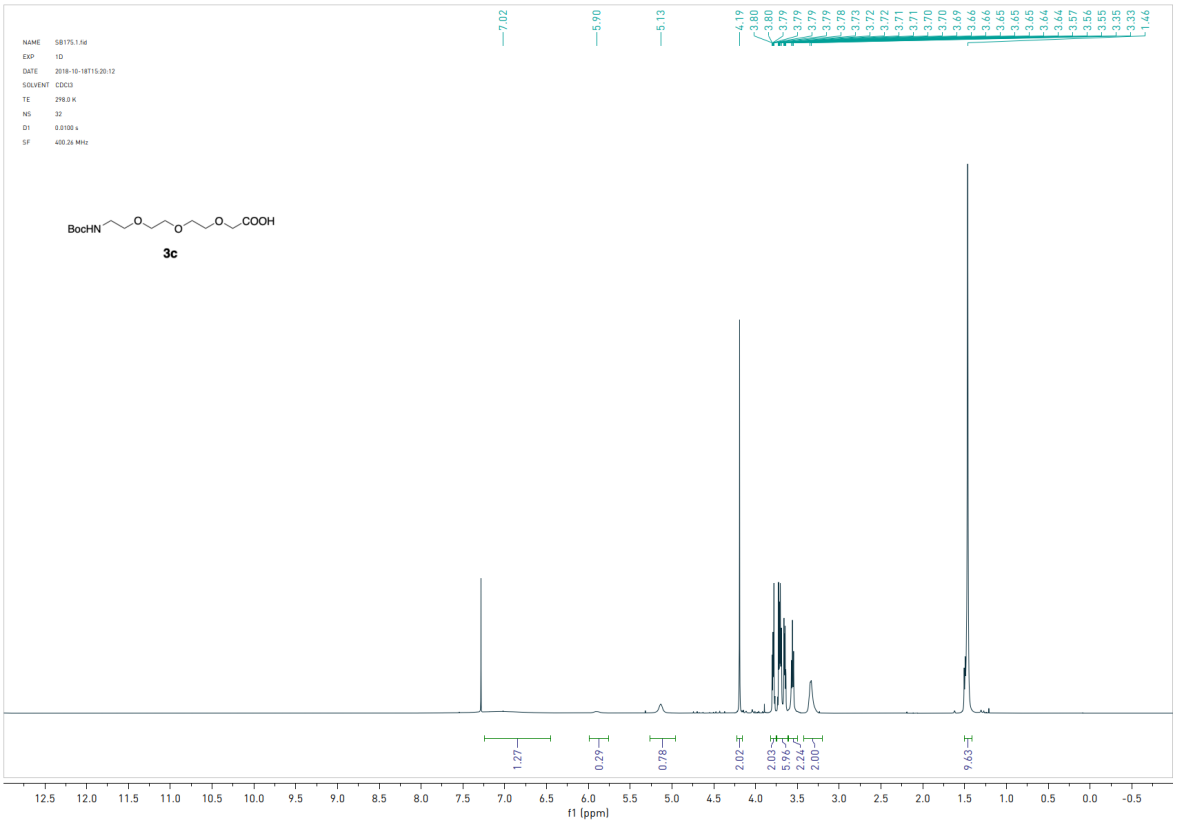



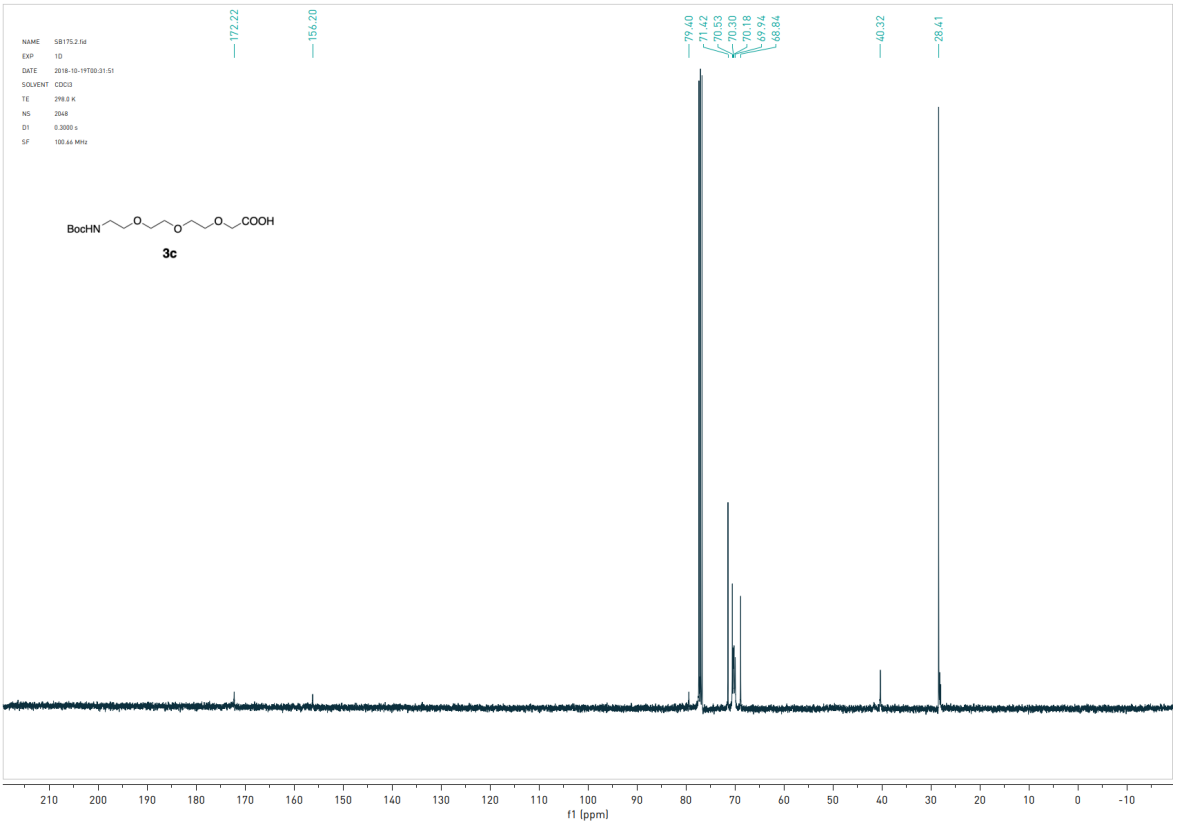
NMR of compound **20c**:



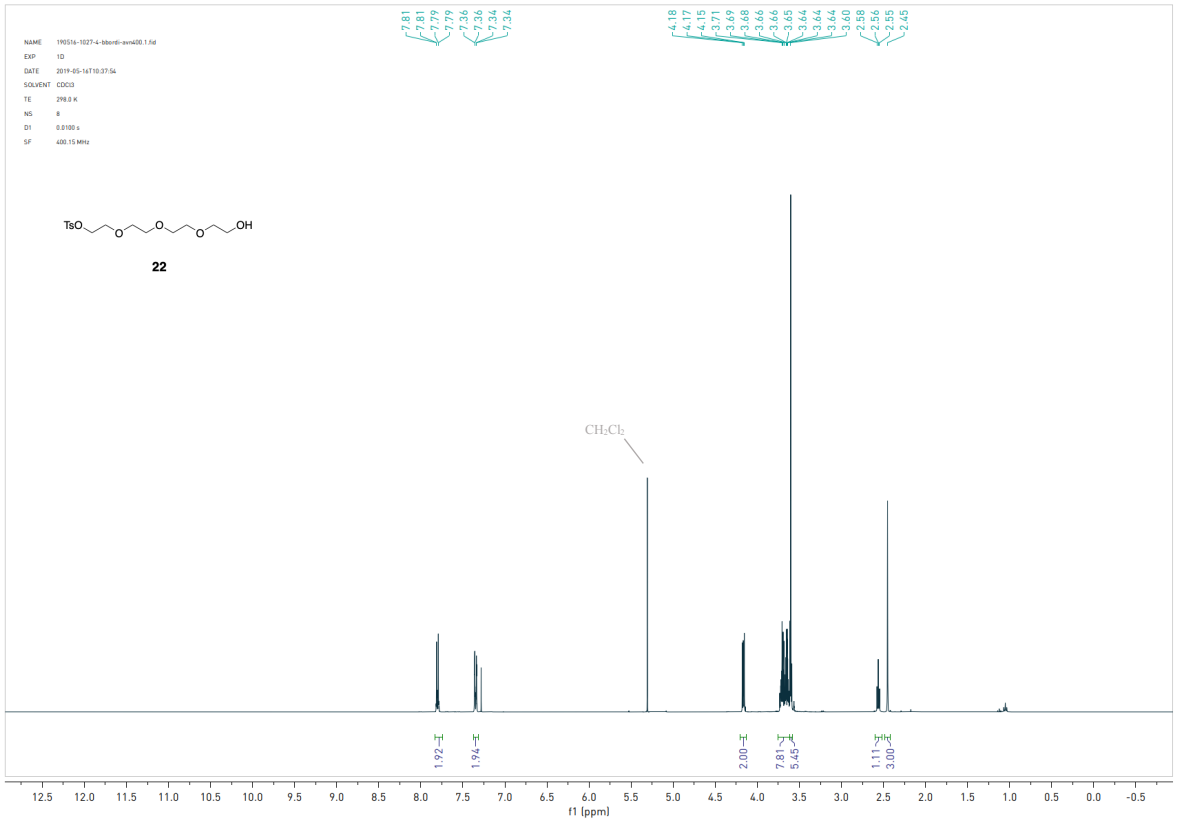



NMR of compound **3c**:

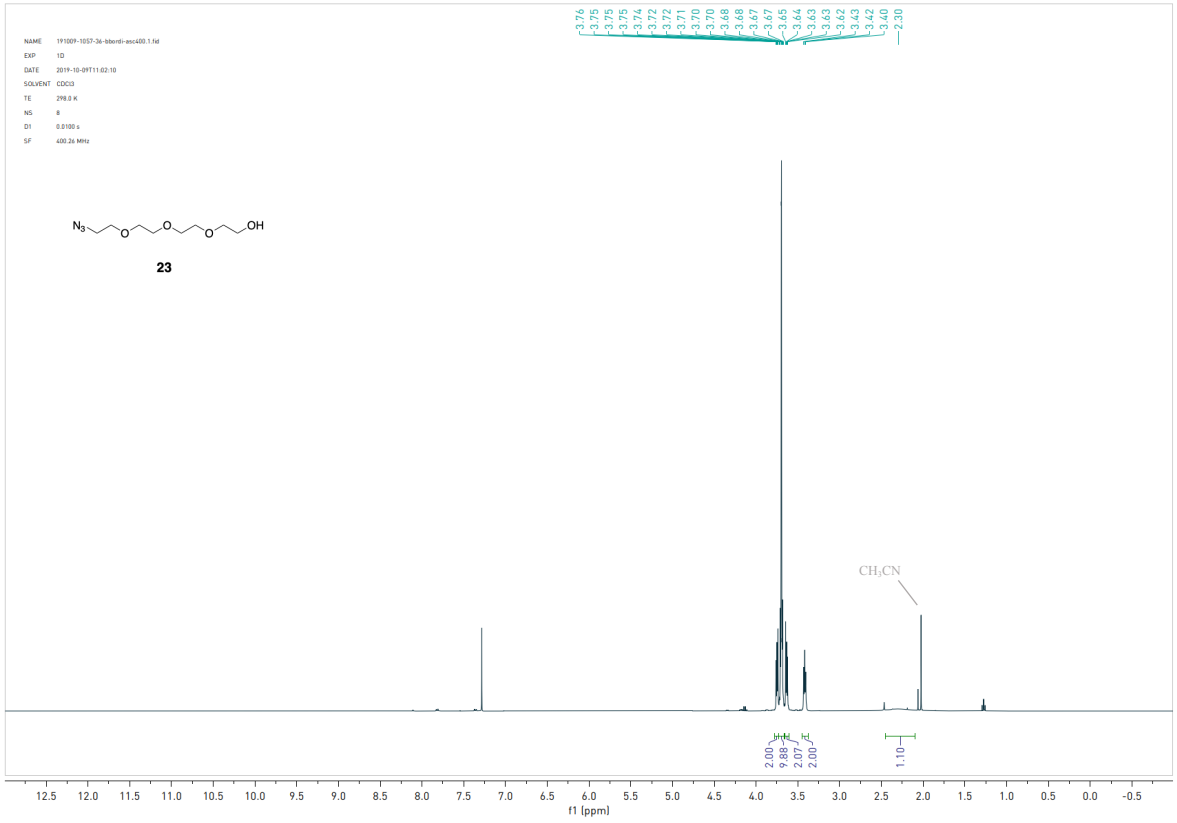


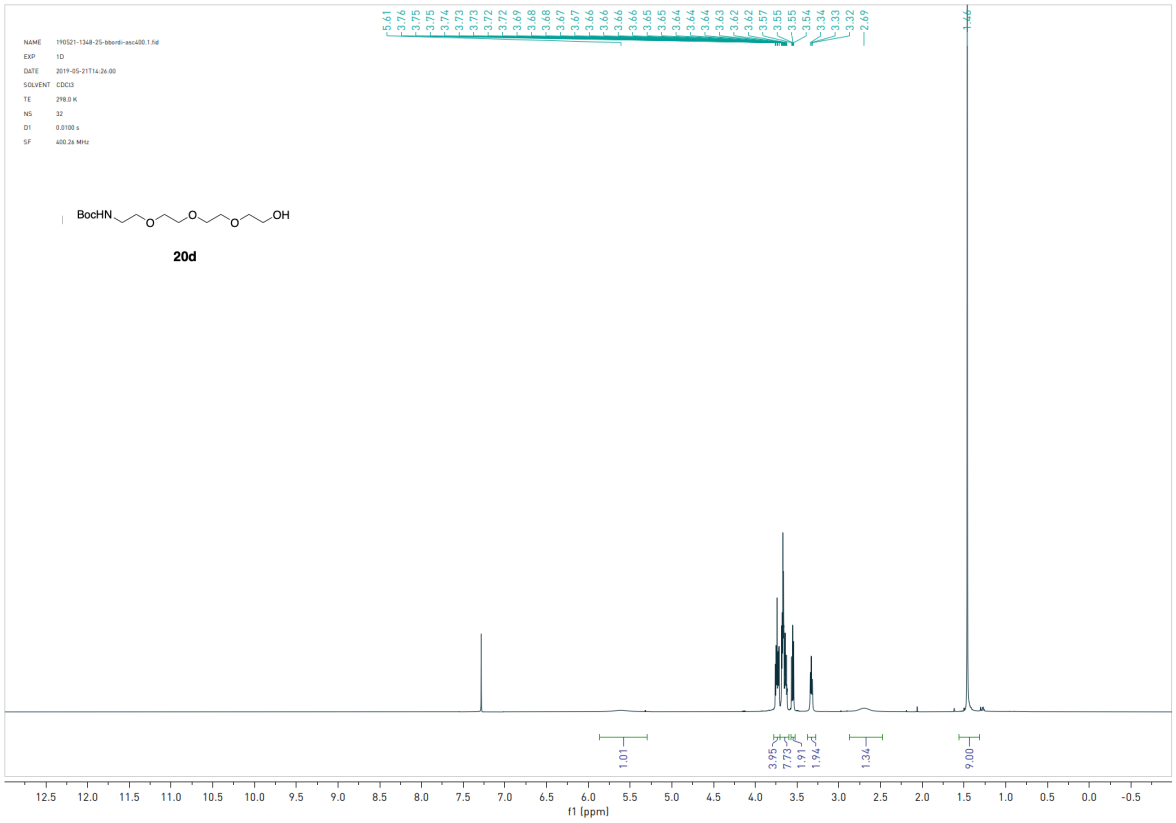
NMR of compound **22**:

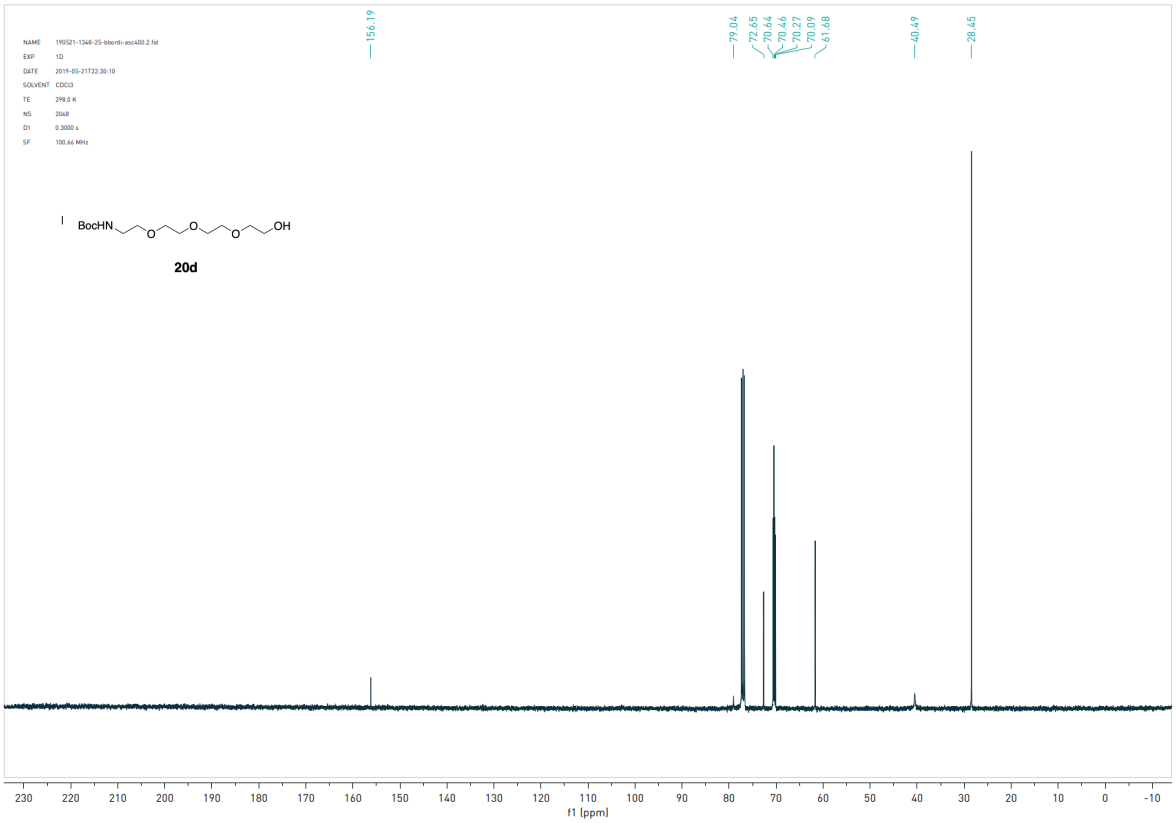



NMR of compound **23**:

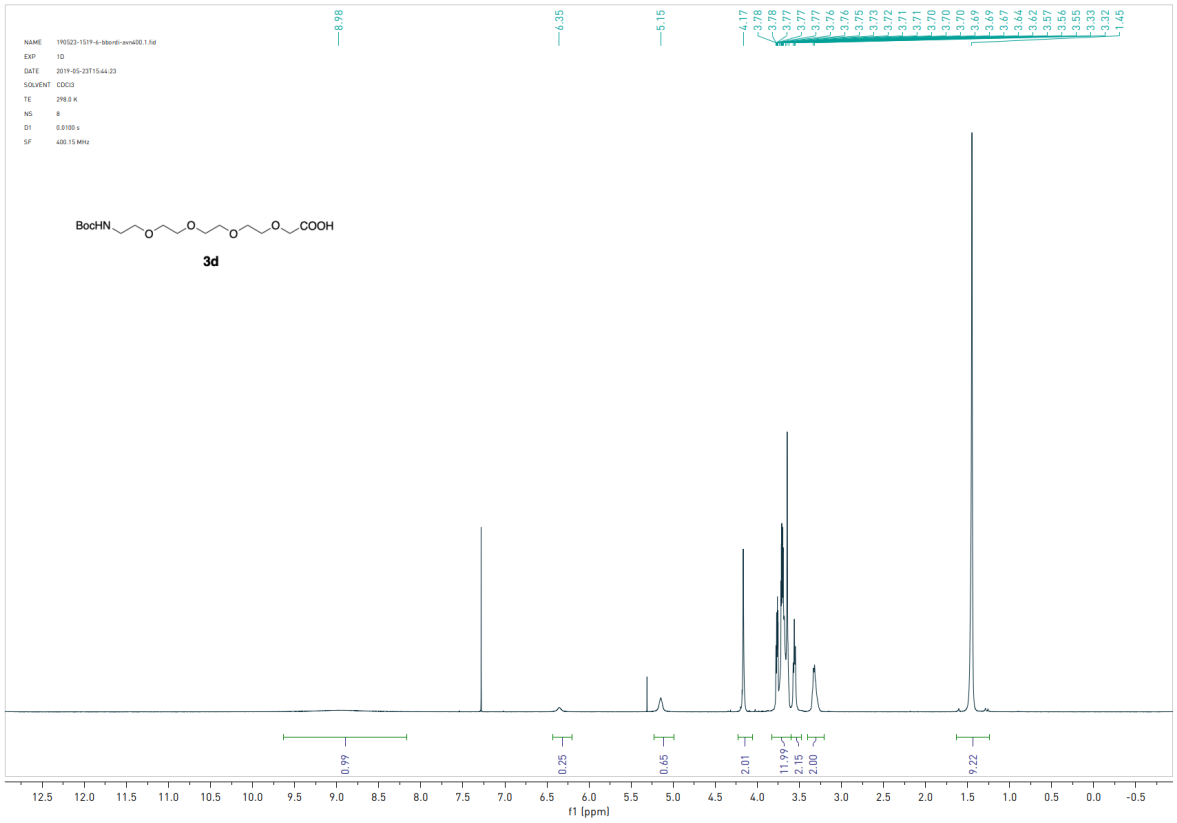


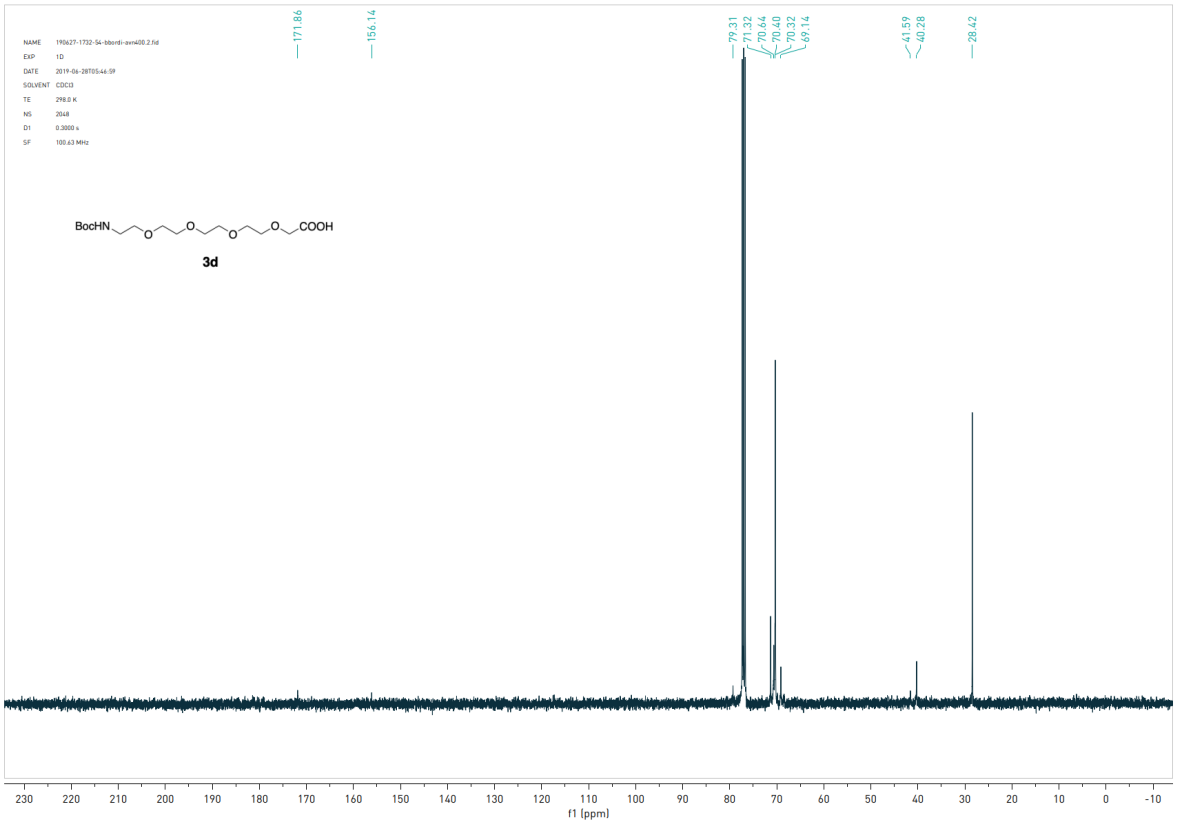
NMR of compound **20d**:



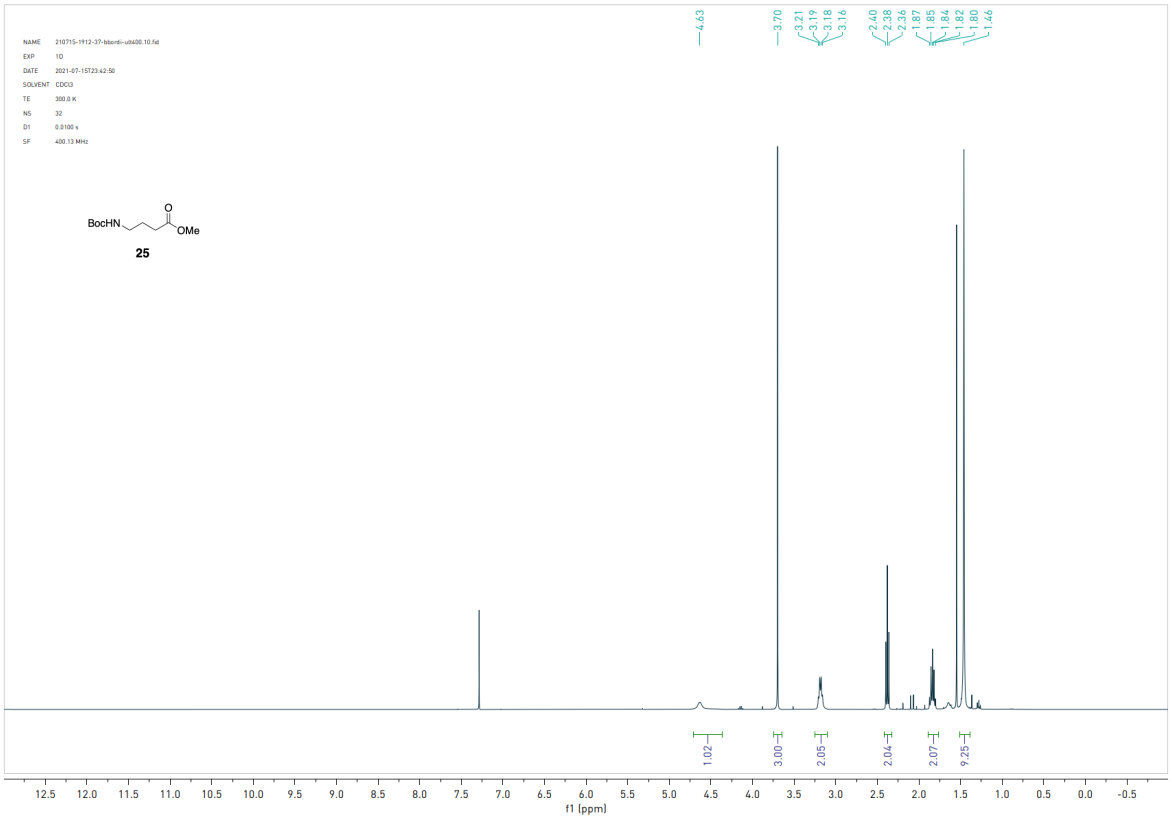



NMR of compound **3d**:

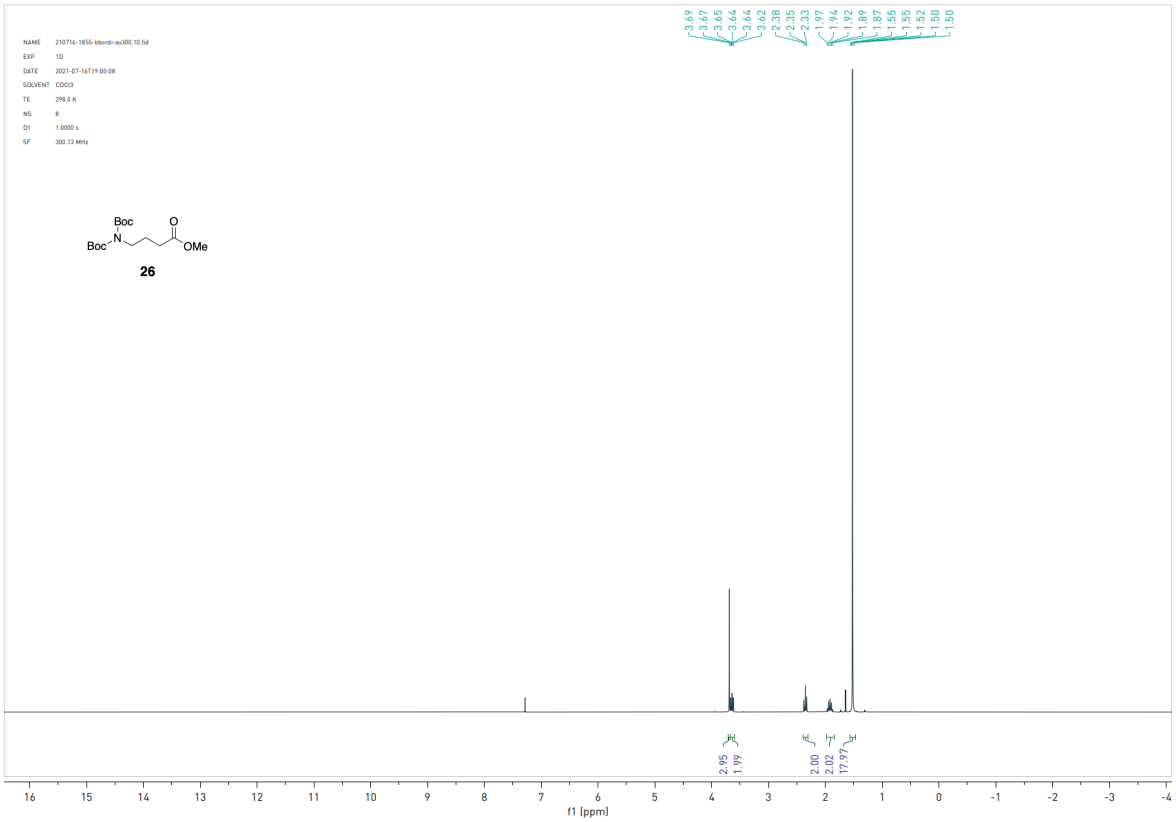


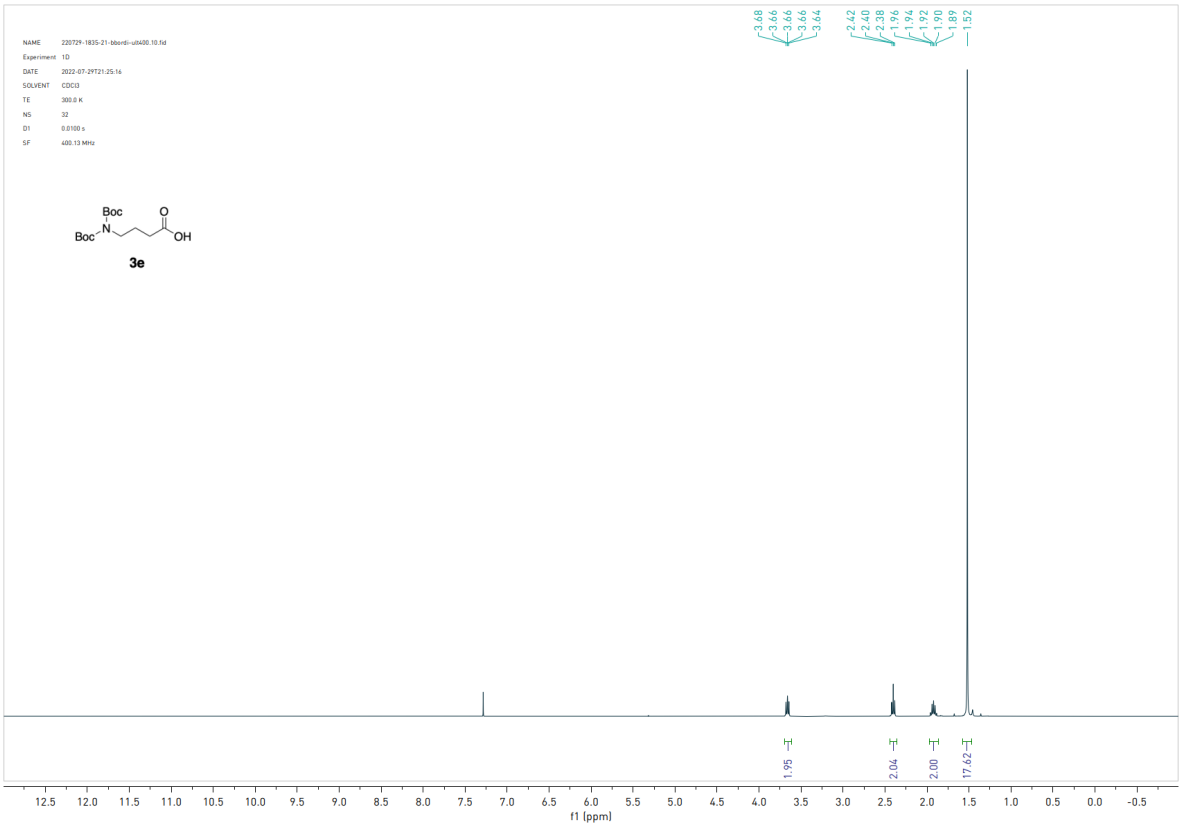
NMR of compound **25**:

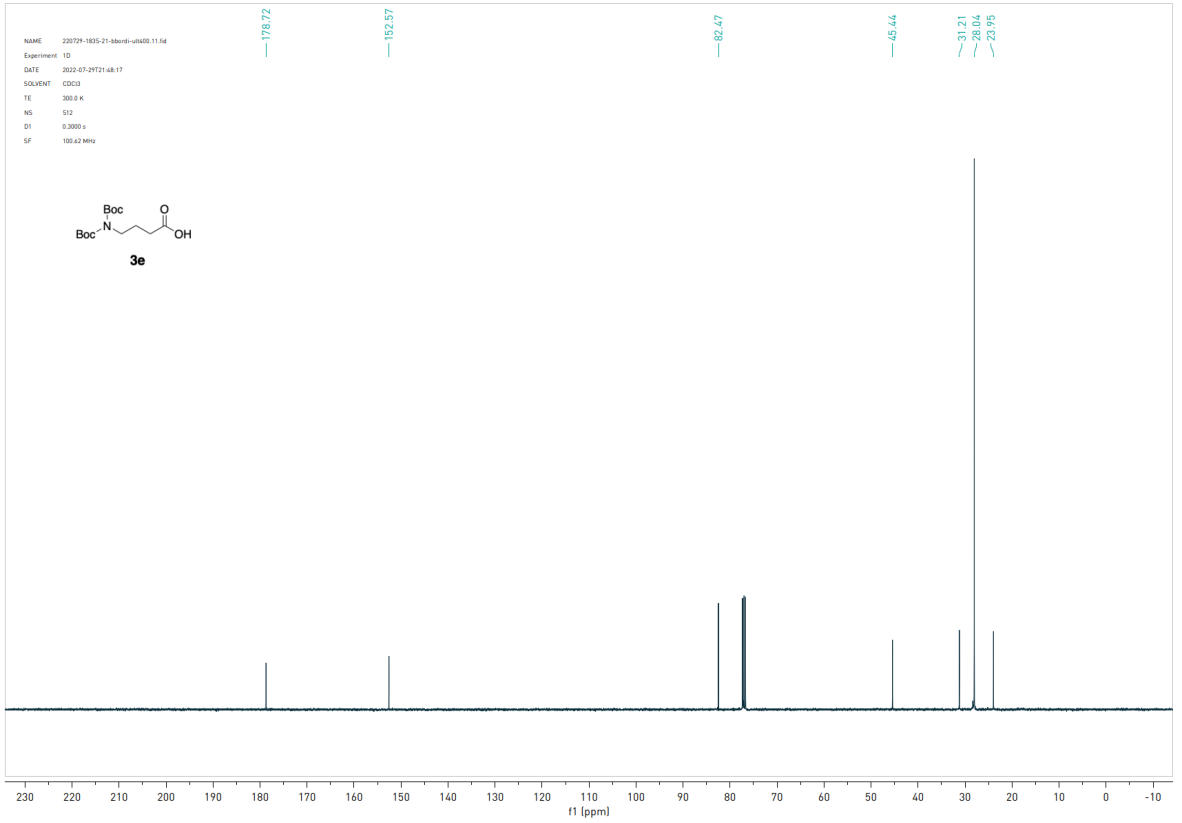



NMR of compound **26**:

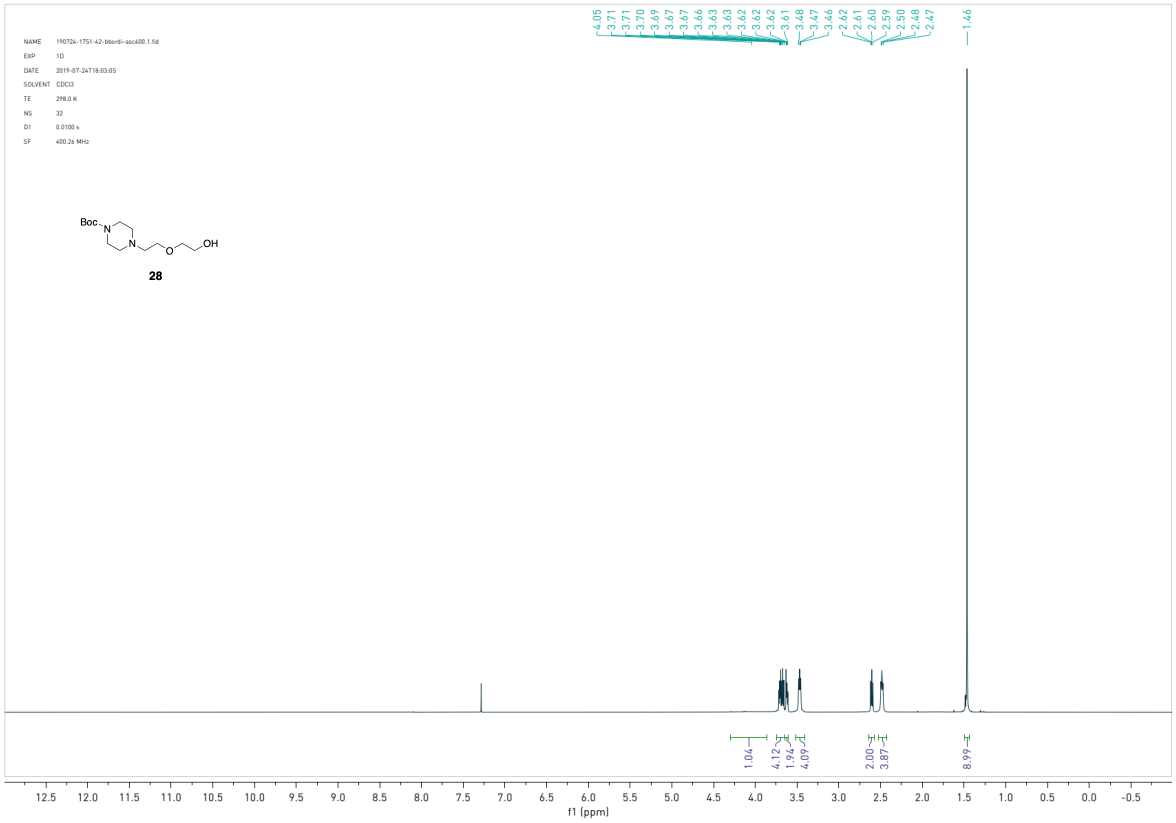


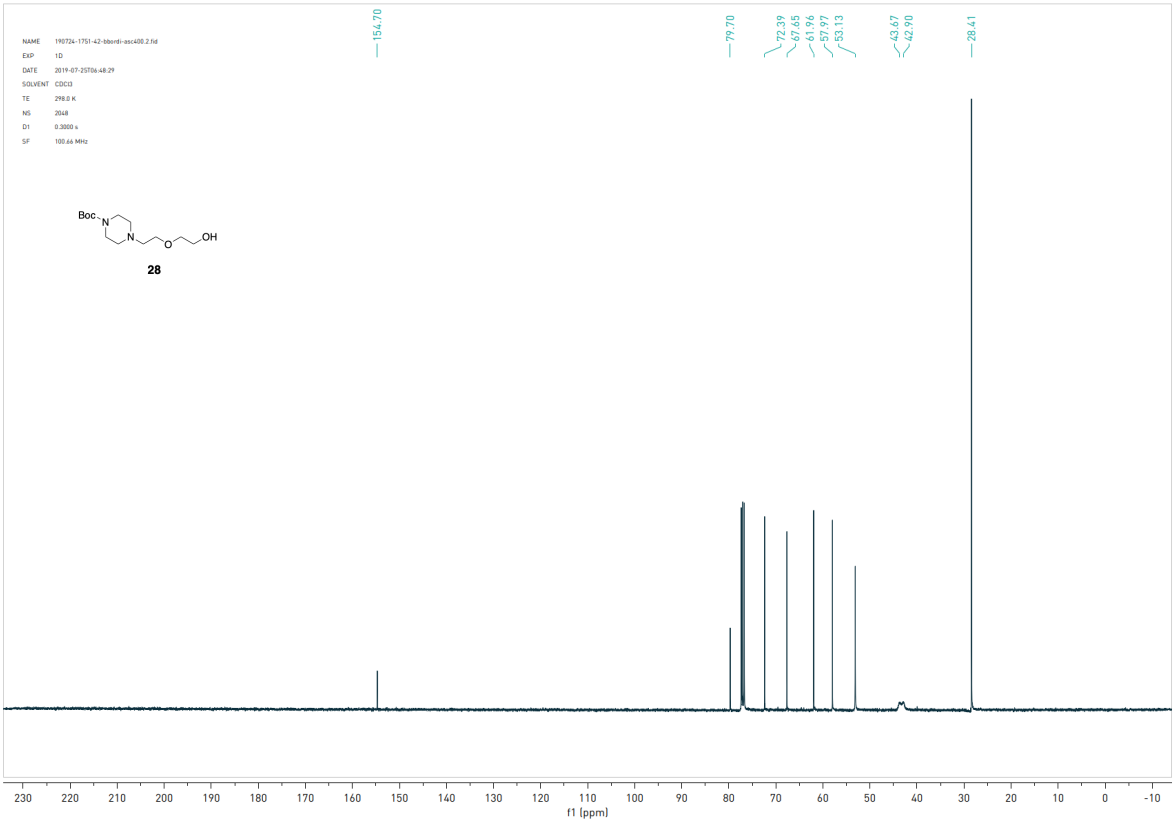
NMR of compound **3e**:



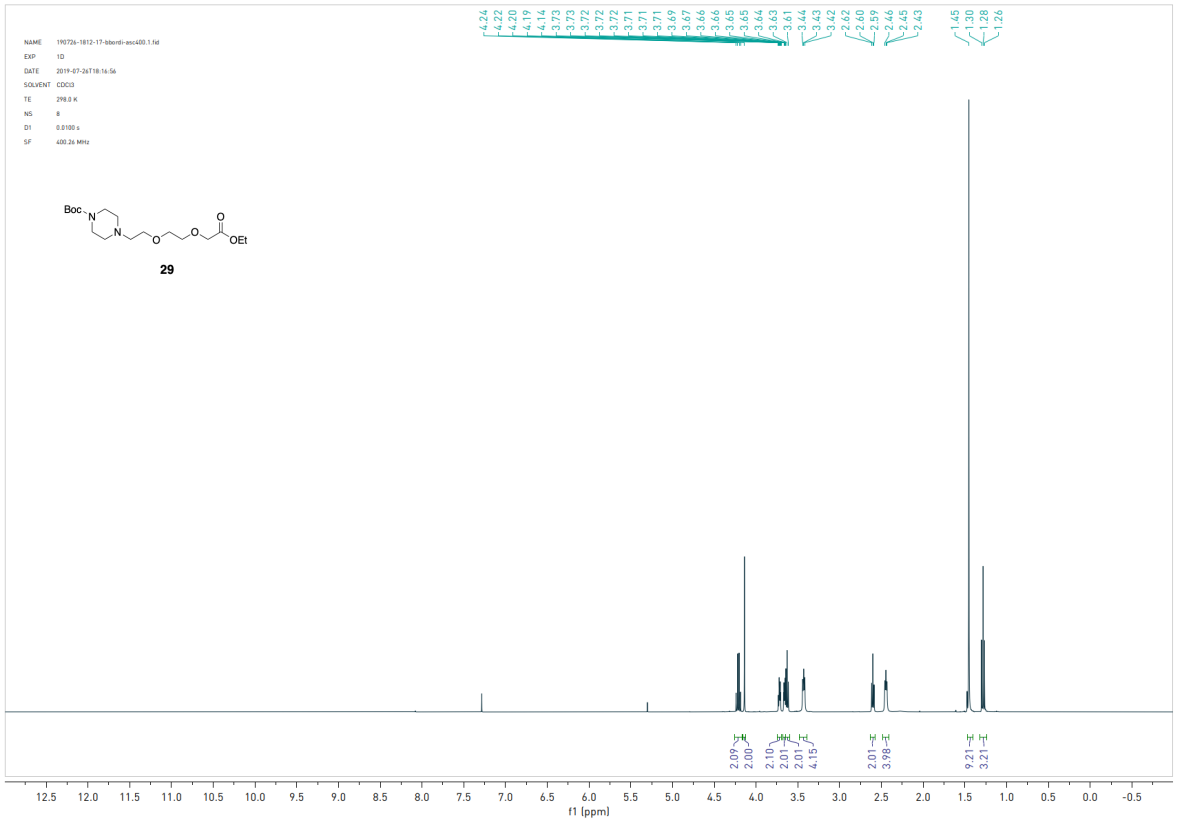



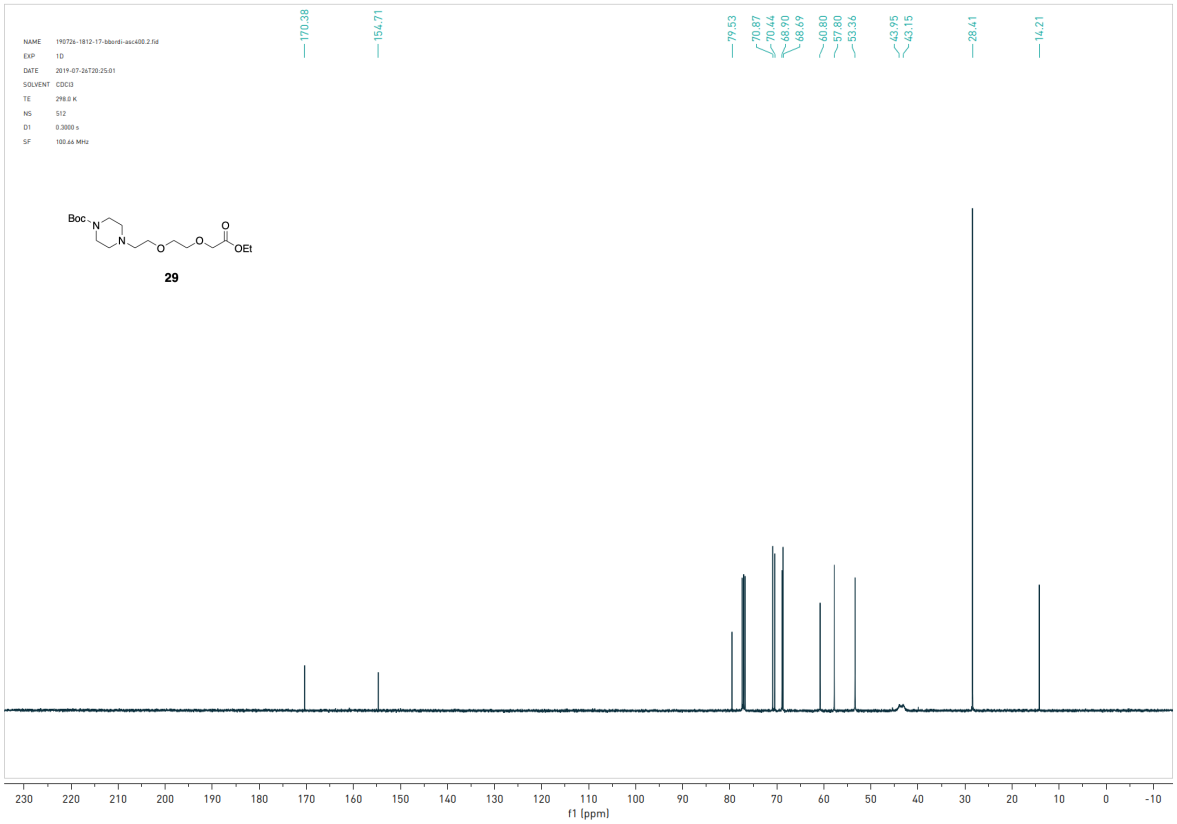
NMR of compound **28**:



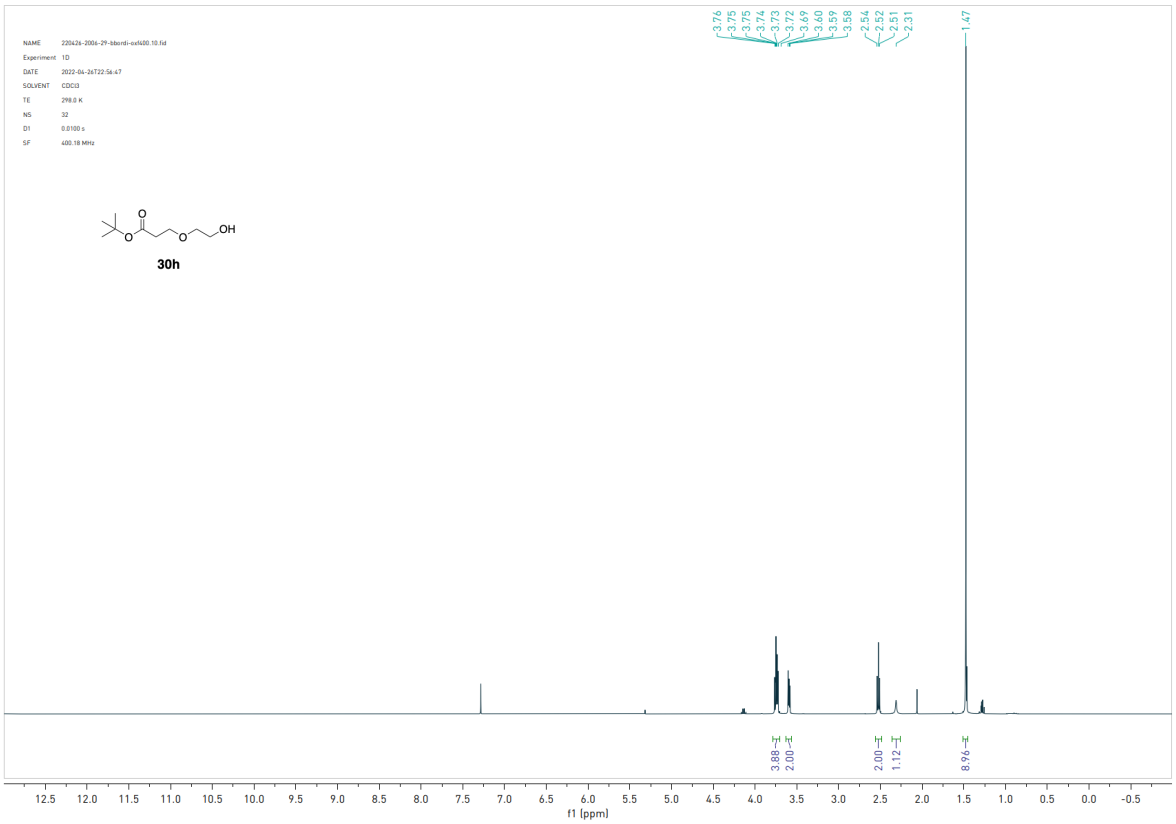



NMR of compound **29**:

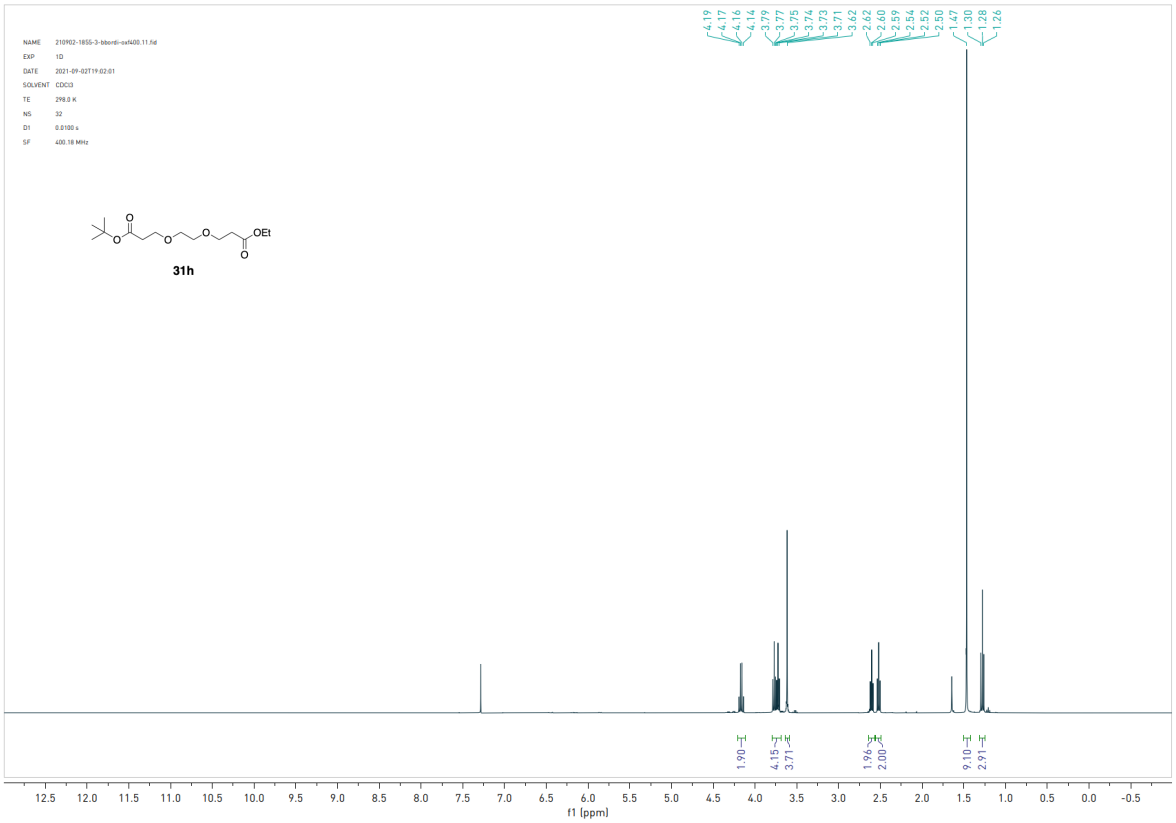


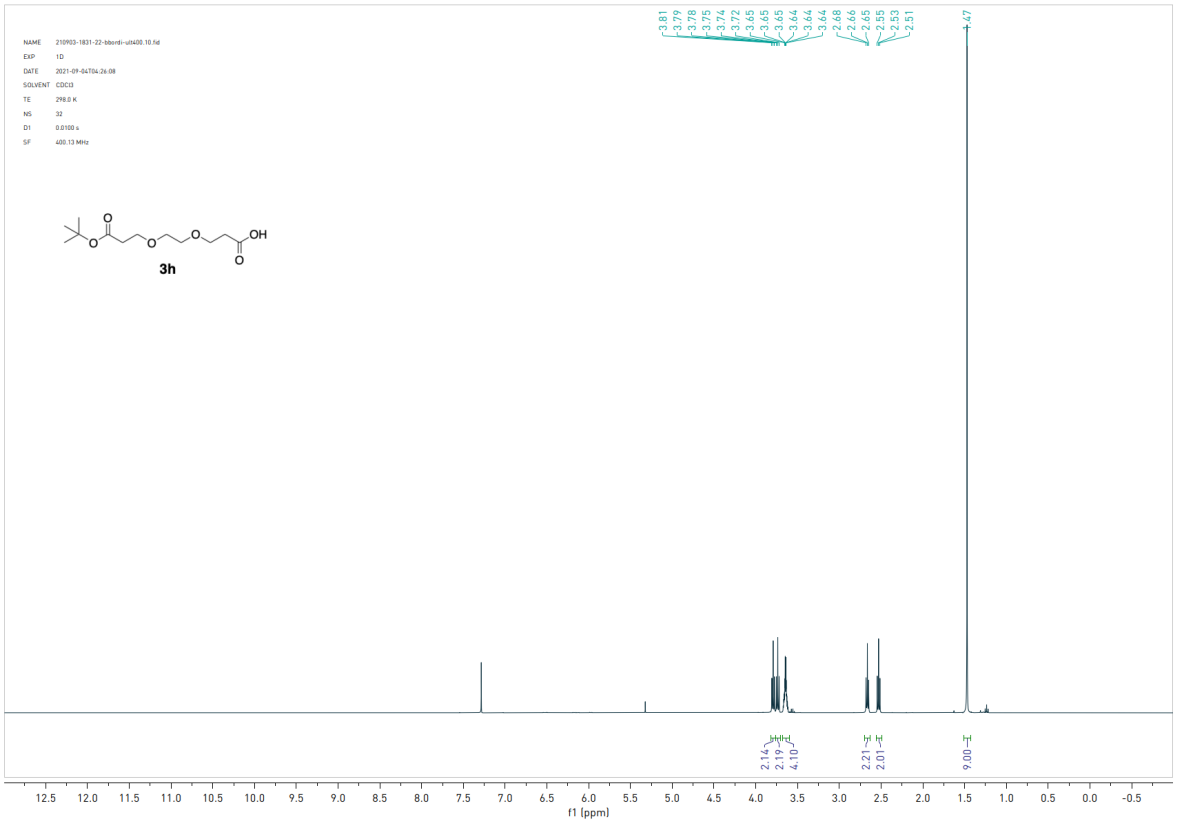
NMR of compound **30h**:



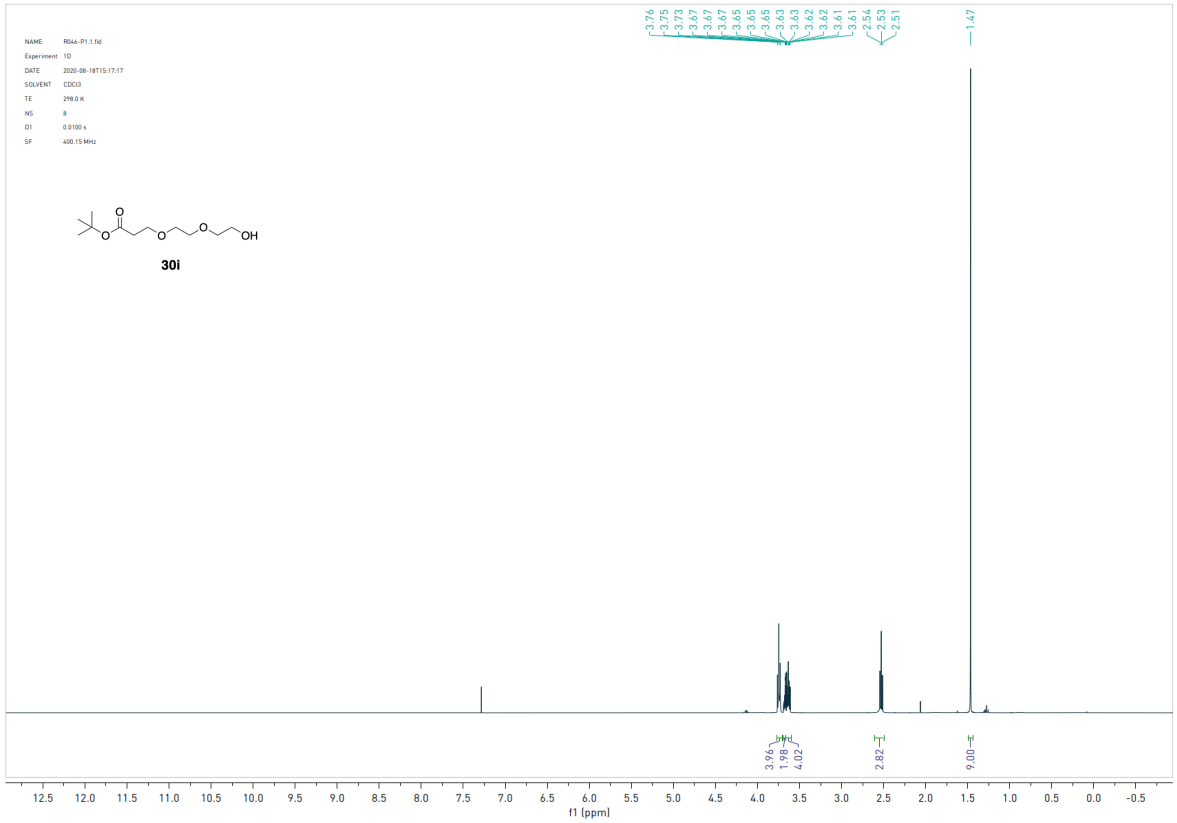

NMR of compound **31h**:



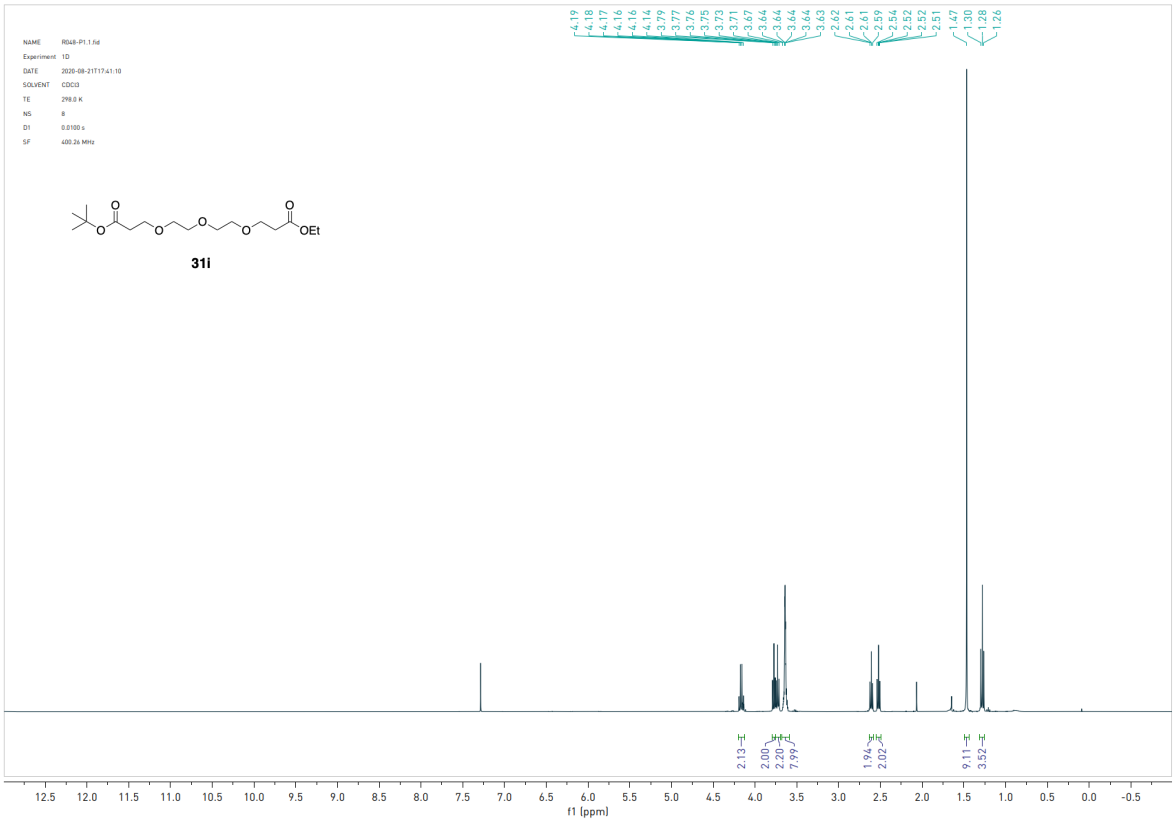
NMR of compound **3h**:



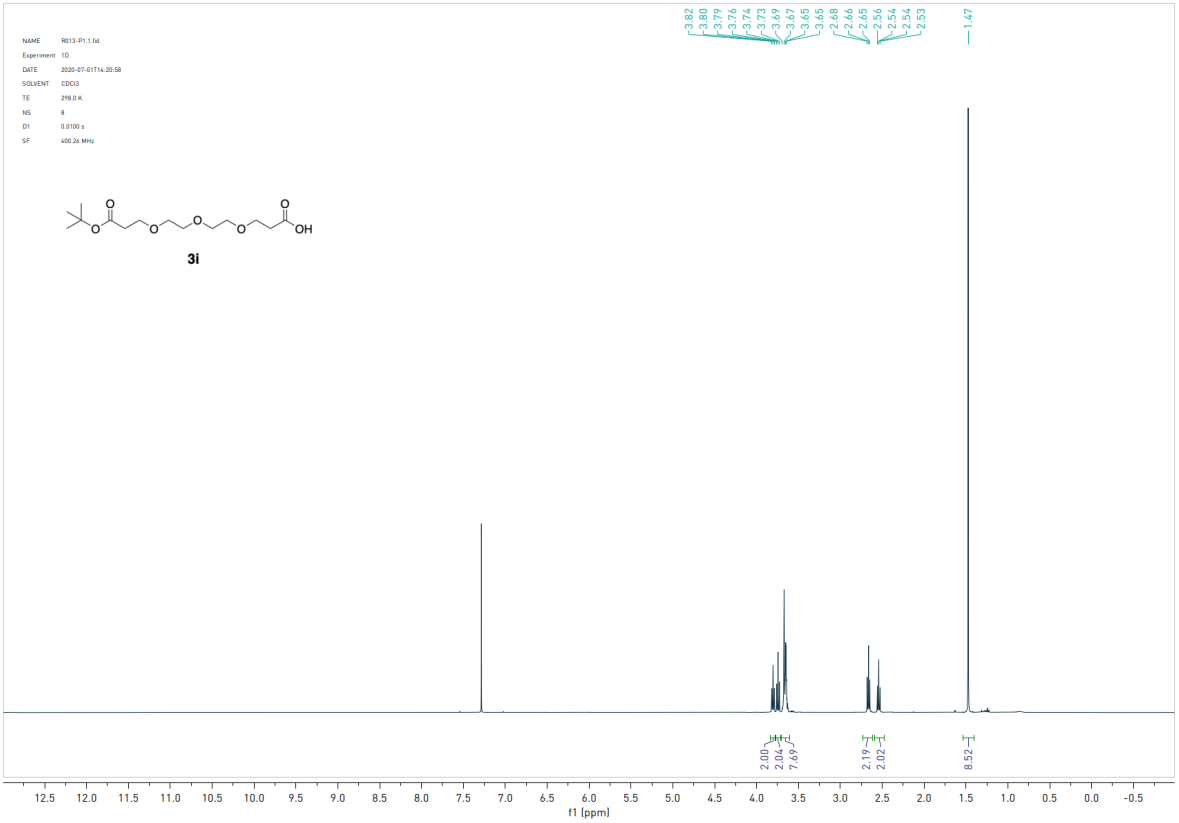

NMR of compound **30i**:



NMR of compound **31i**:

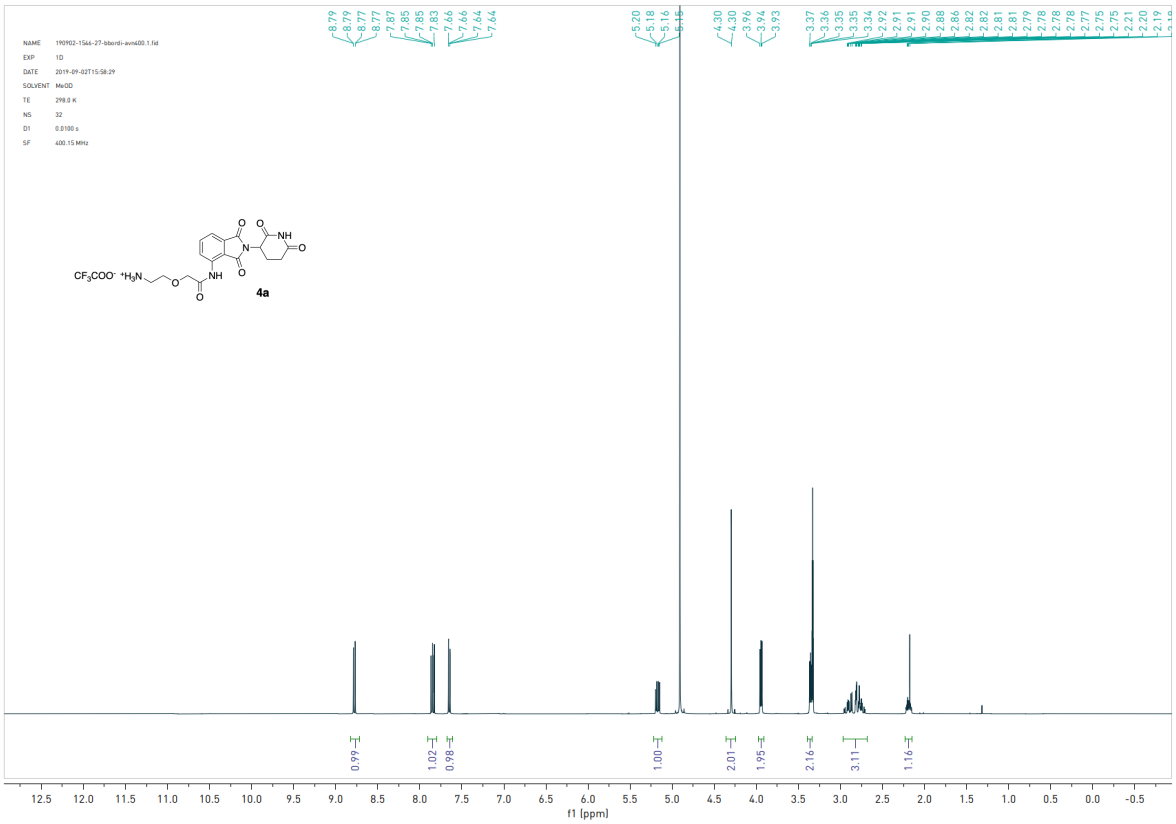


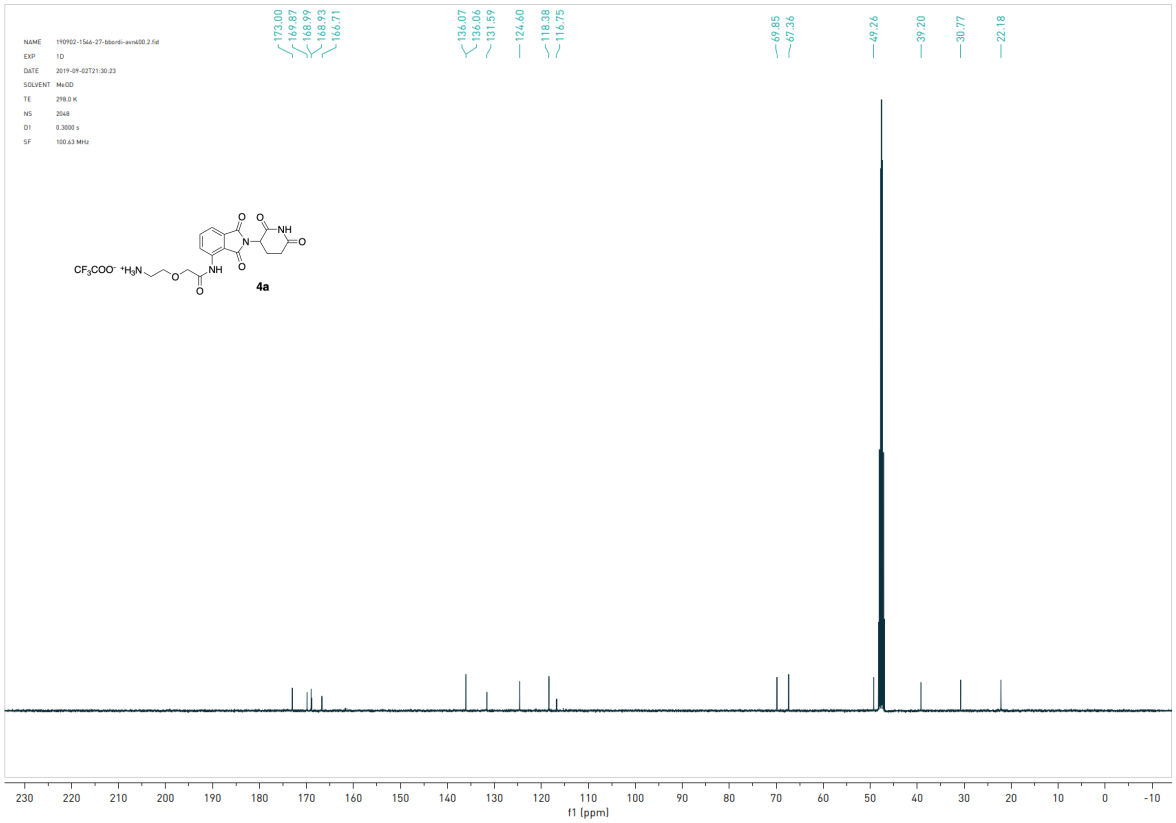

NMR of compound **3i**:



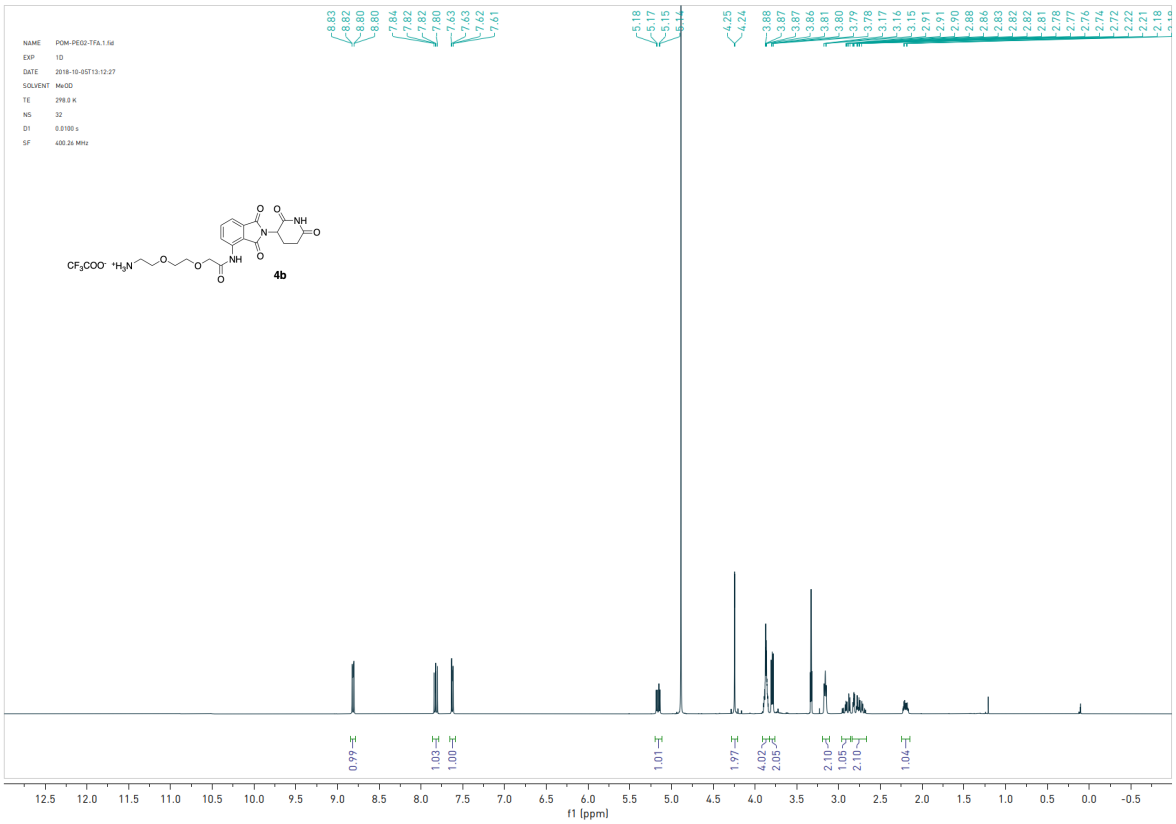
## 5.2 NMR spectra of PROTAC reagents

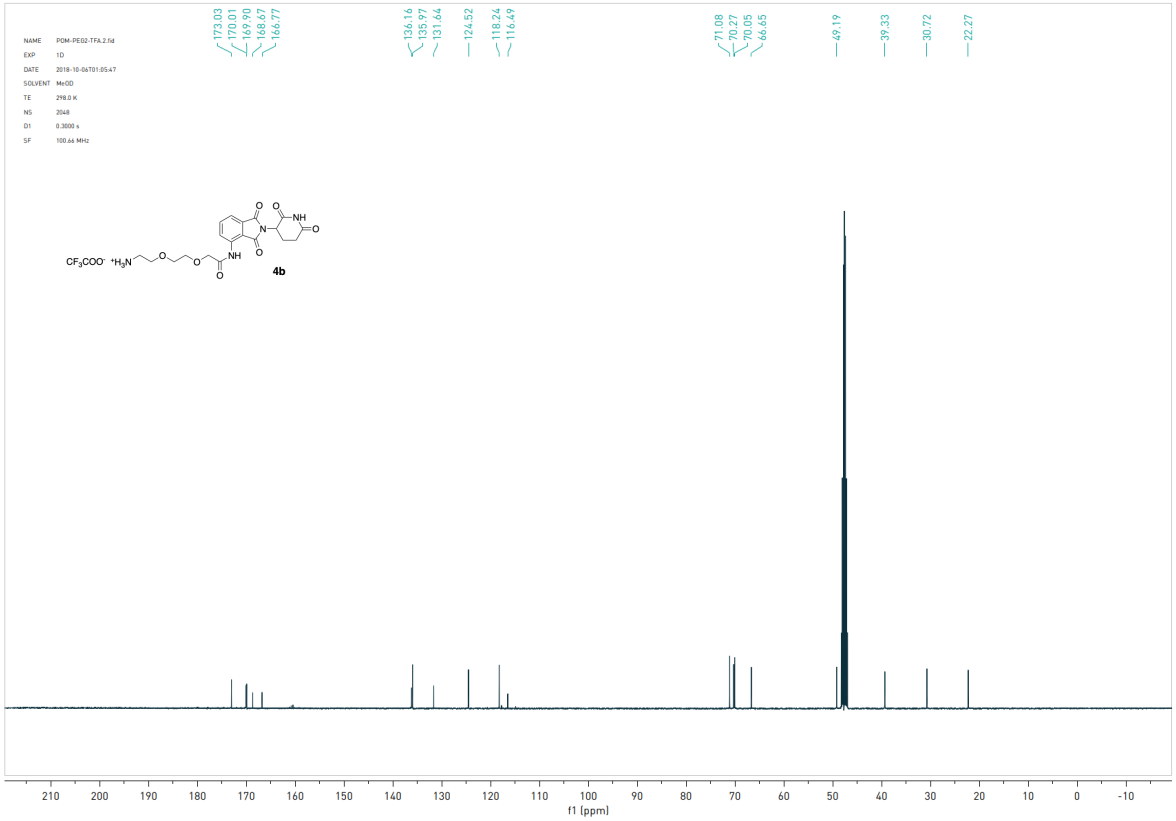
NMR of compound **4a**:



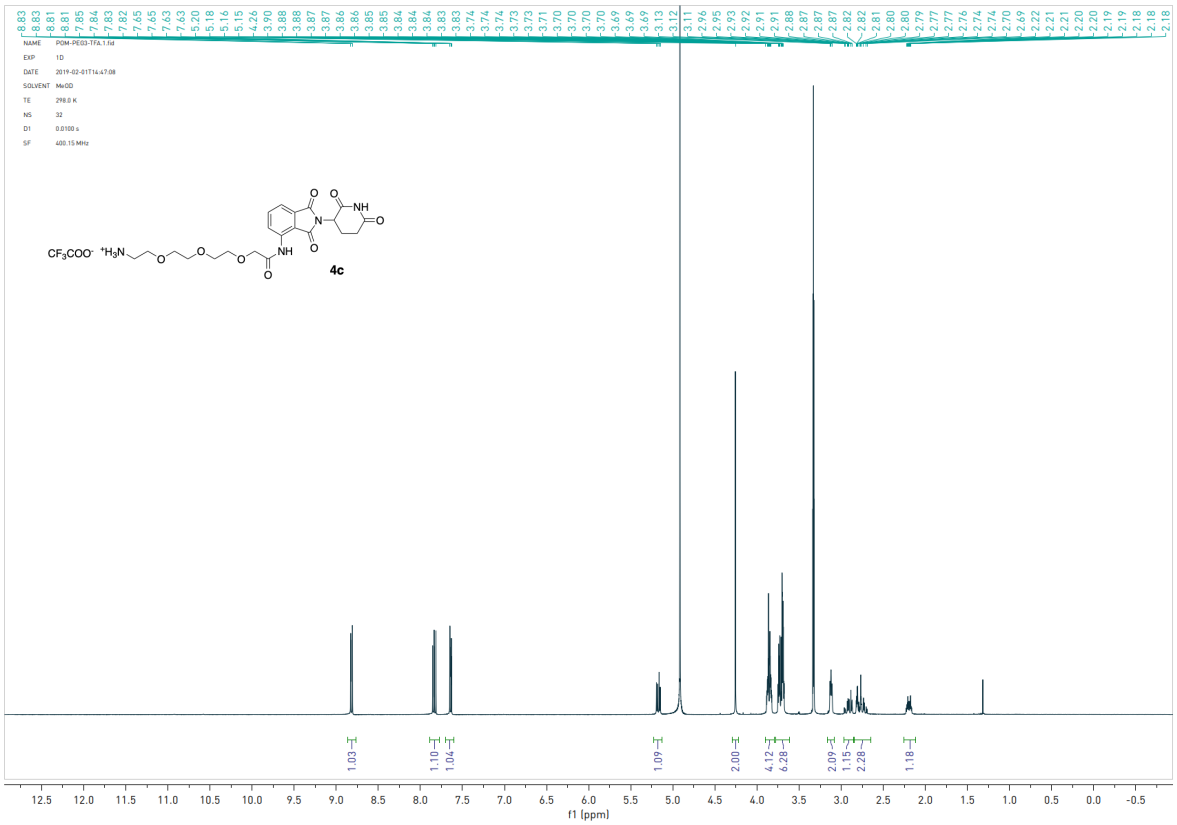



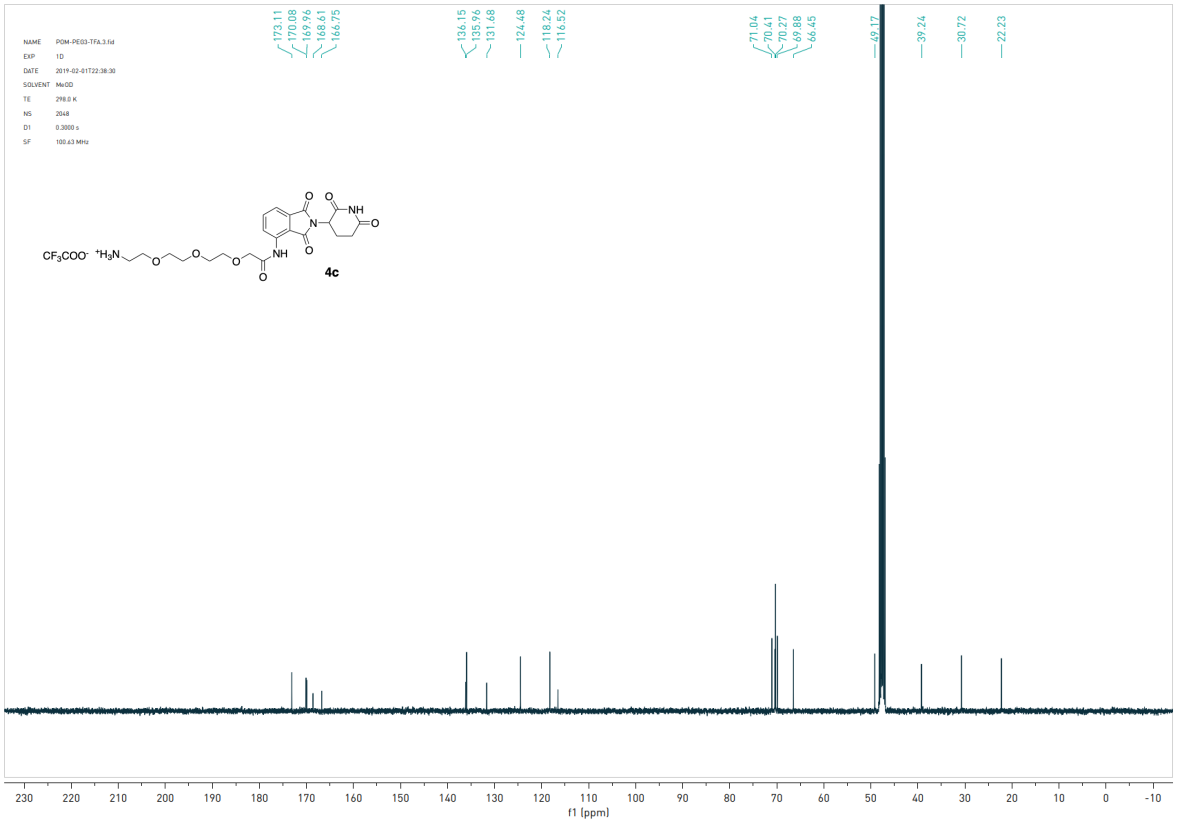
NMR of compound **4b**:



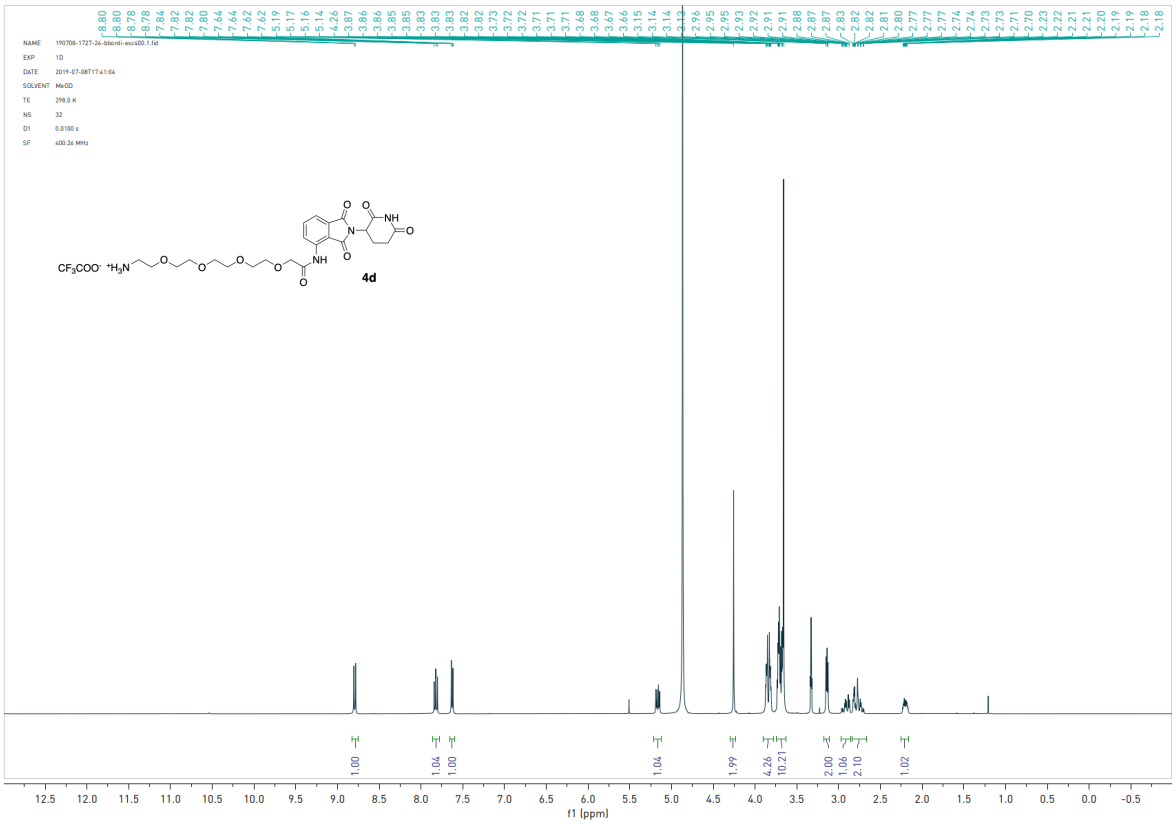



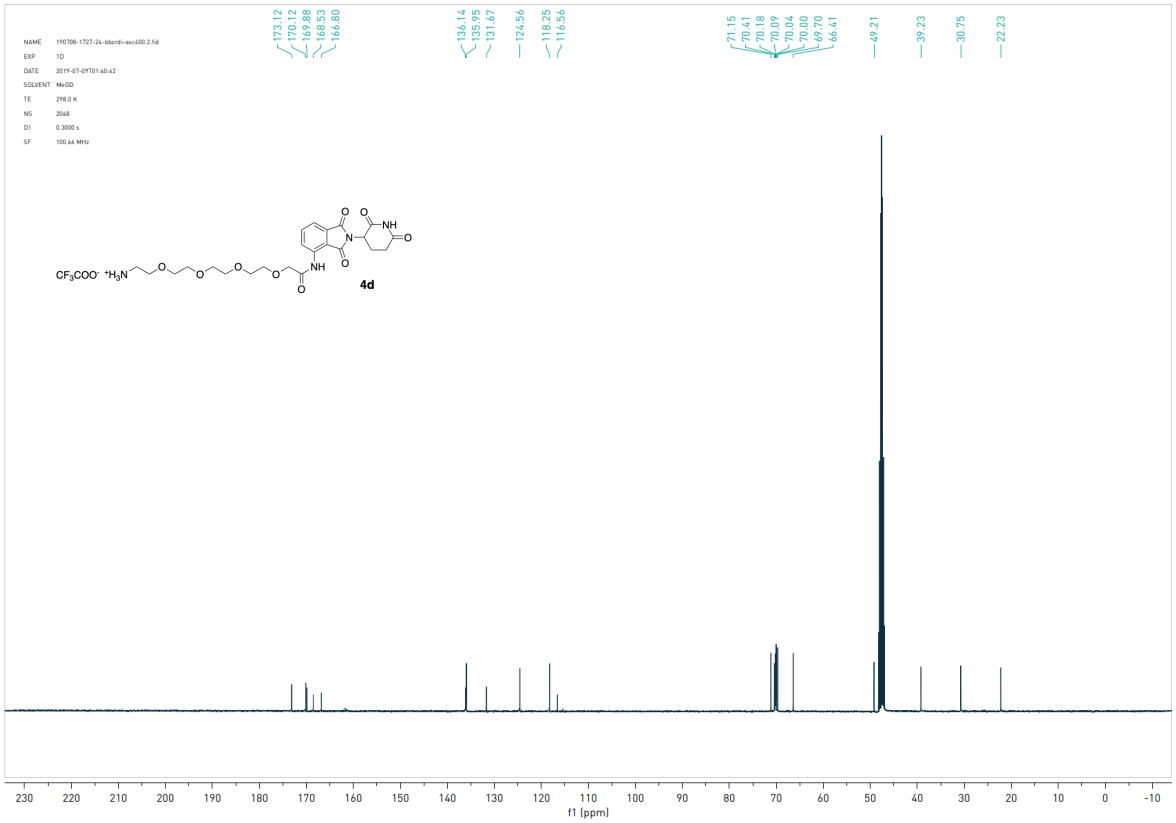
NMR of compound **4c**:



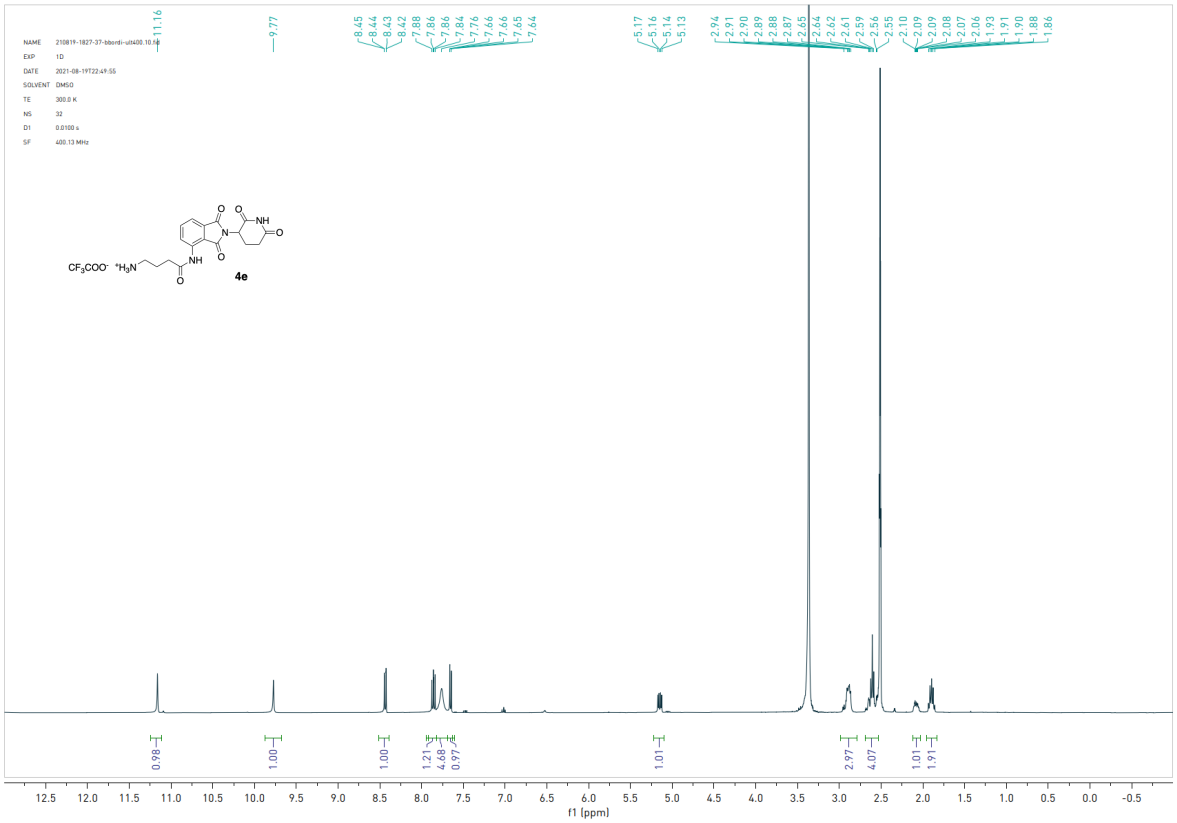



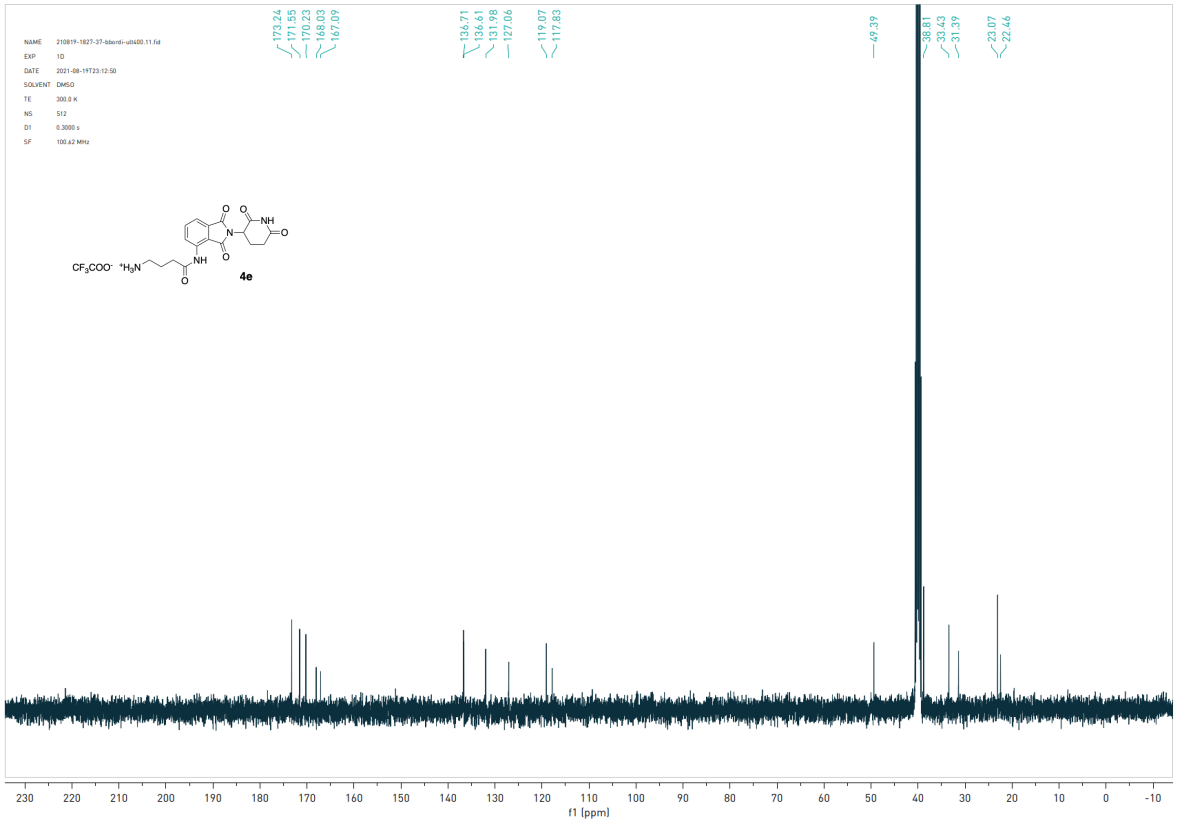
NMR of compound **4d**:



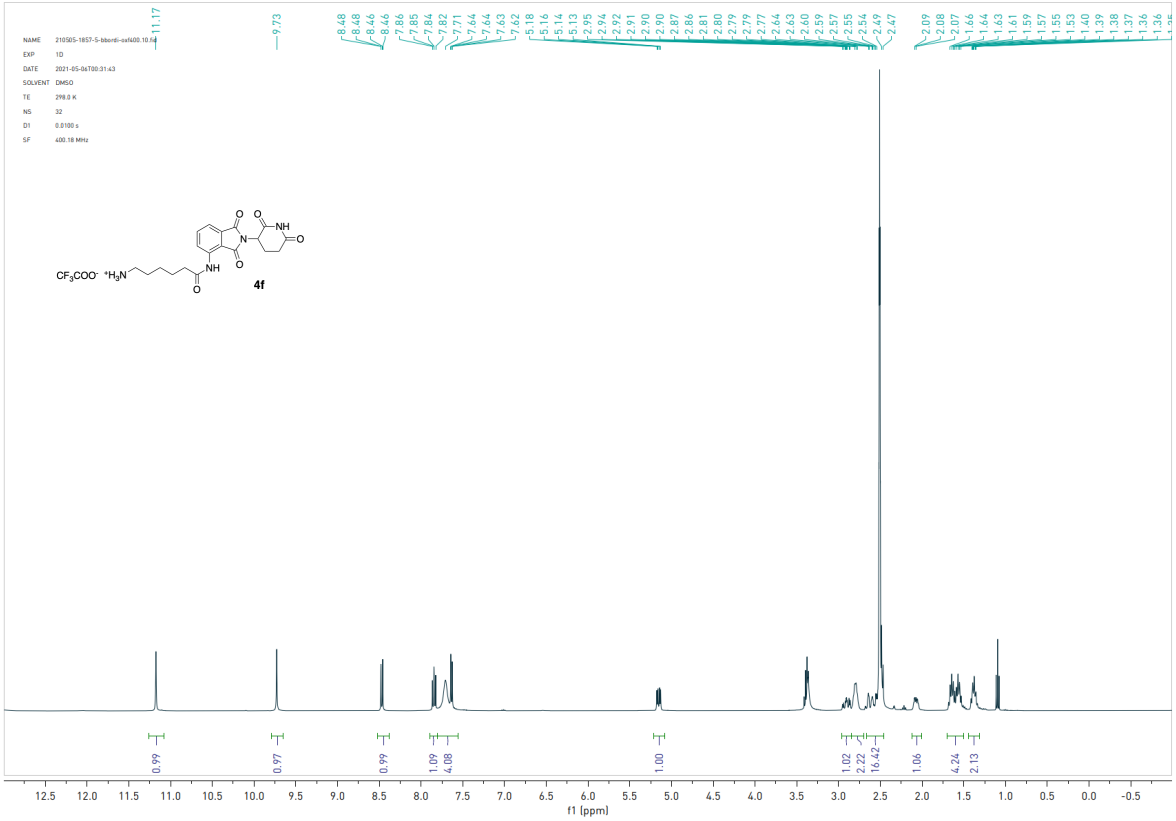



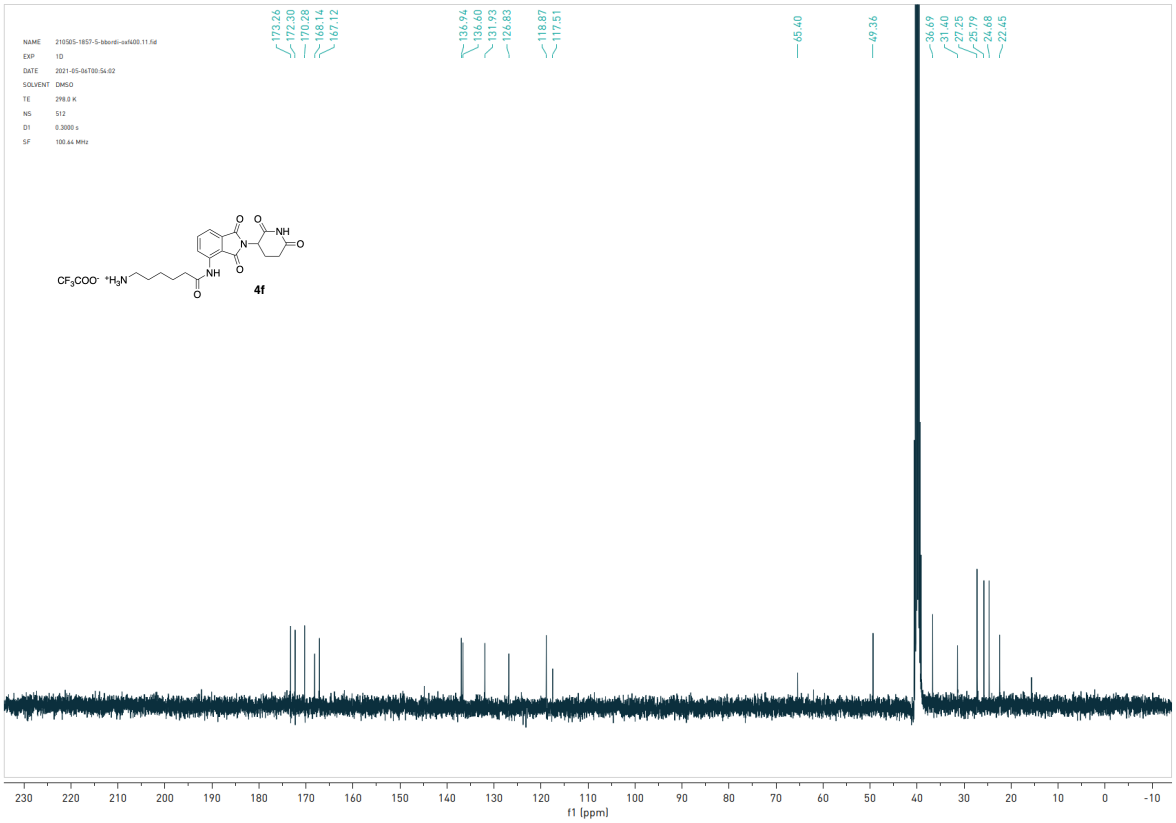
NMR of compound **4e**:



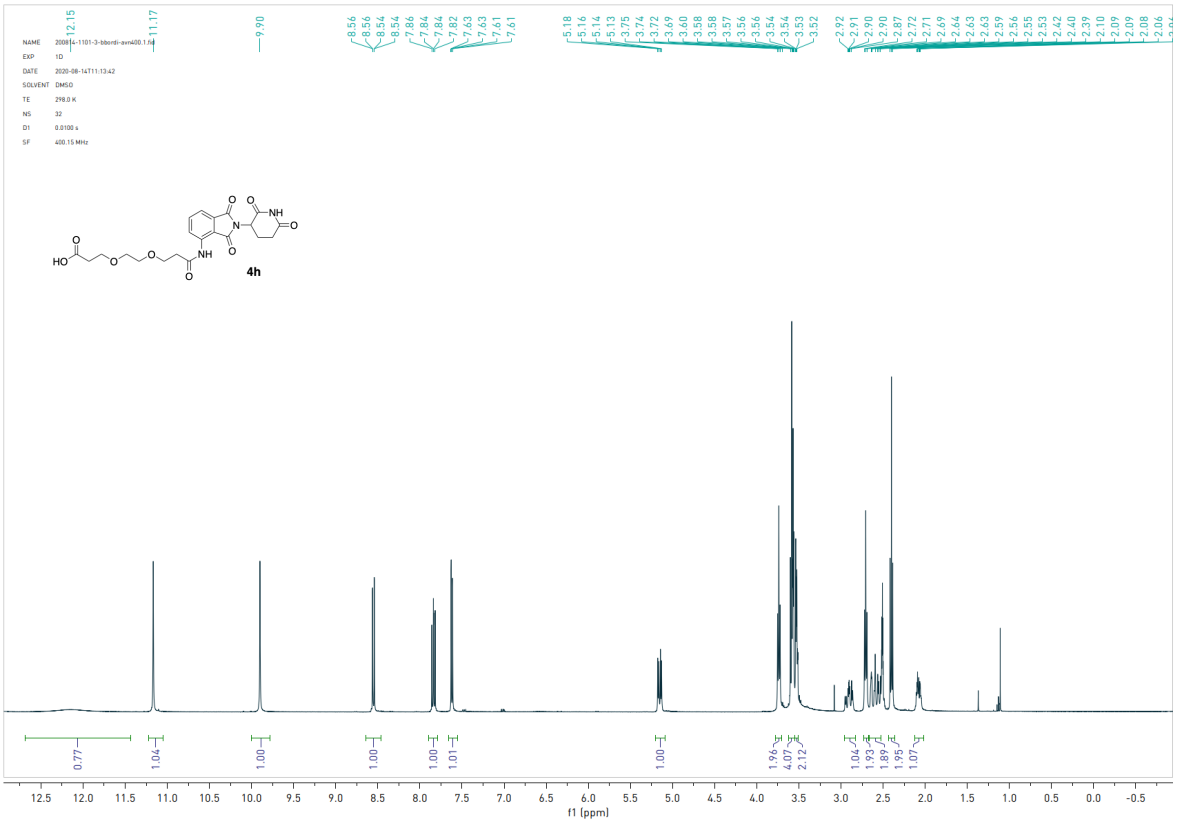



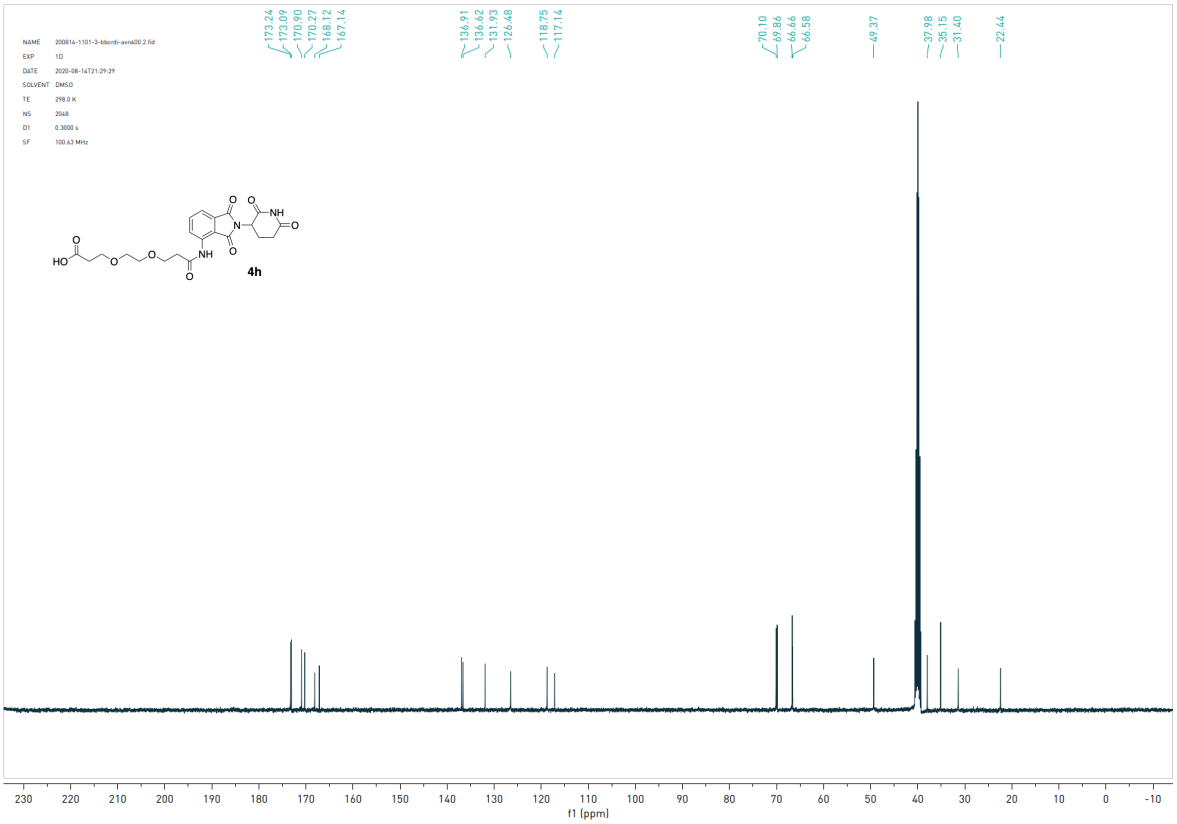
NMR of compound **4f**:



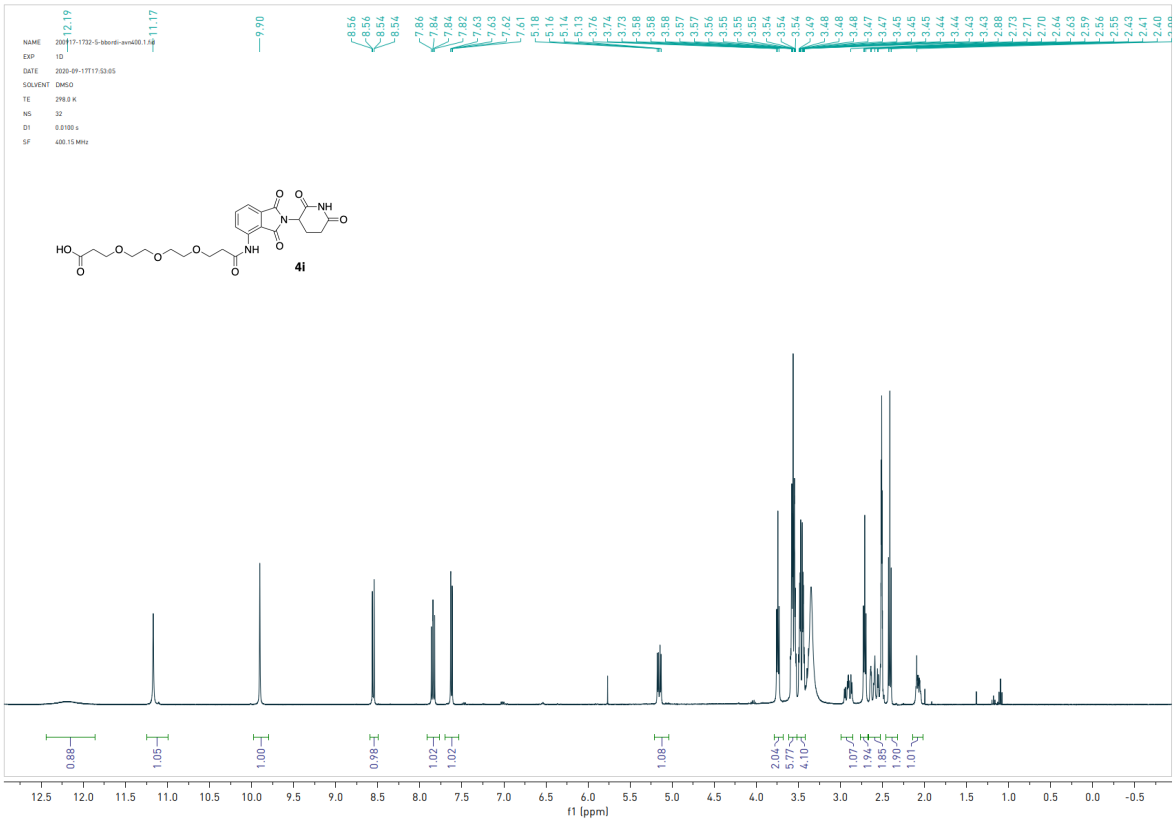



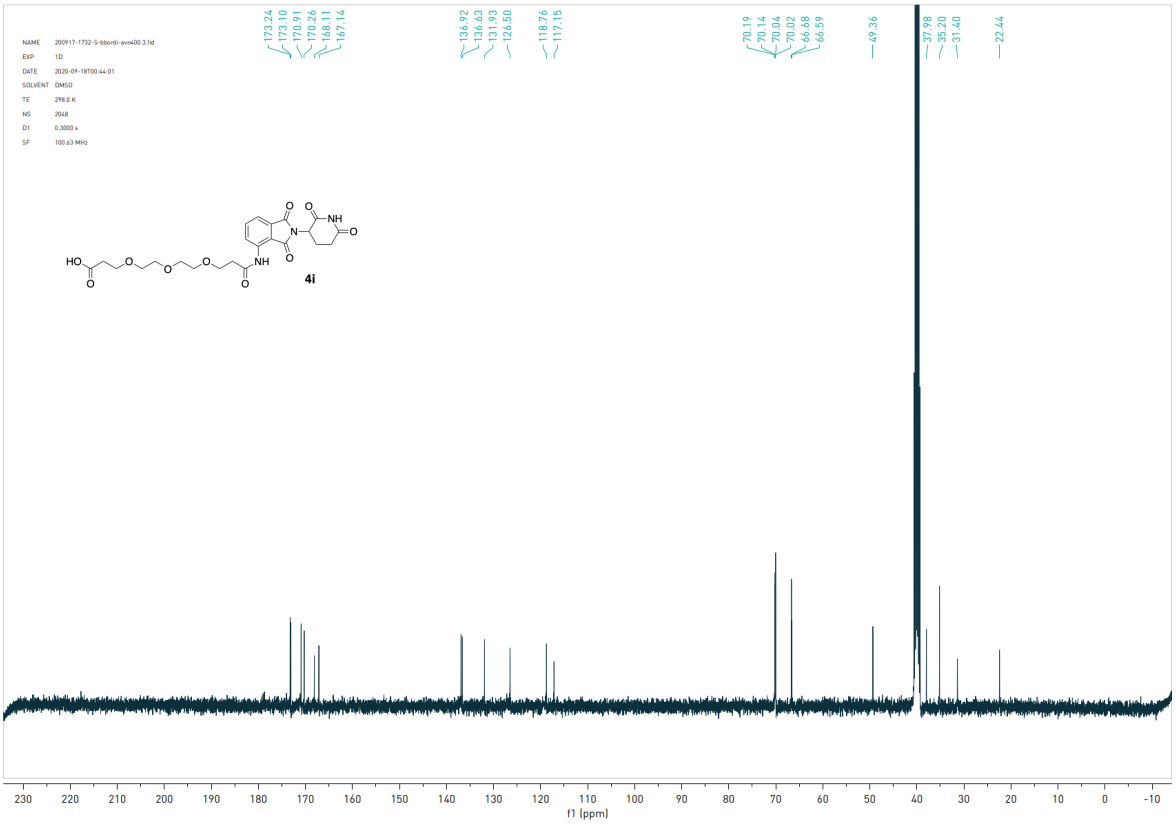
NMR of compound **4h**:



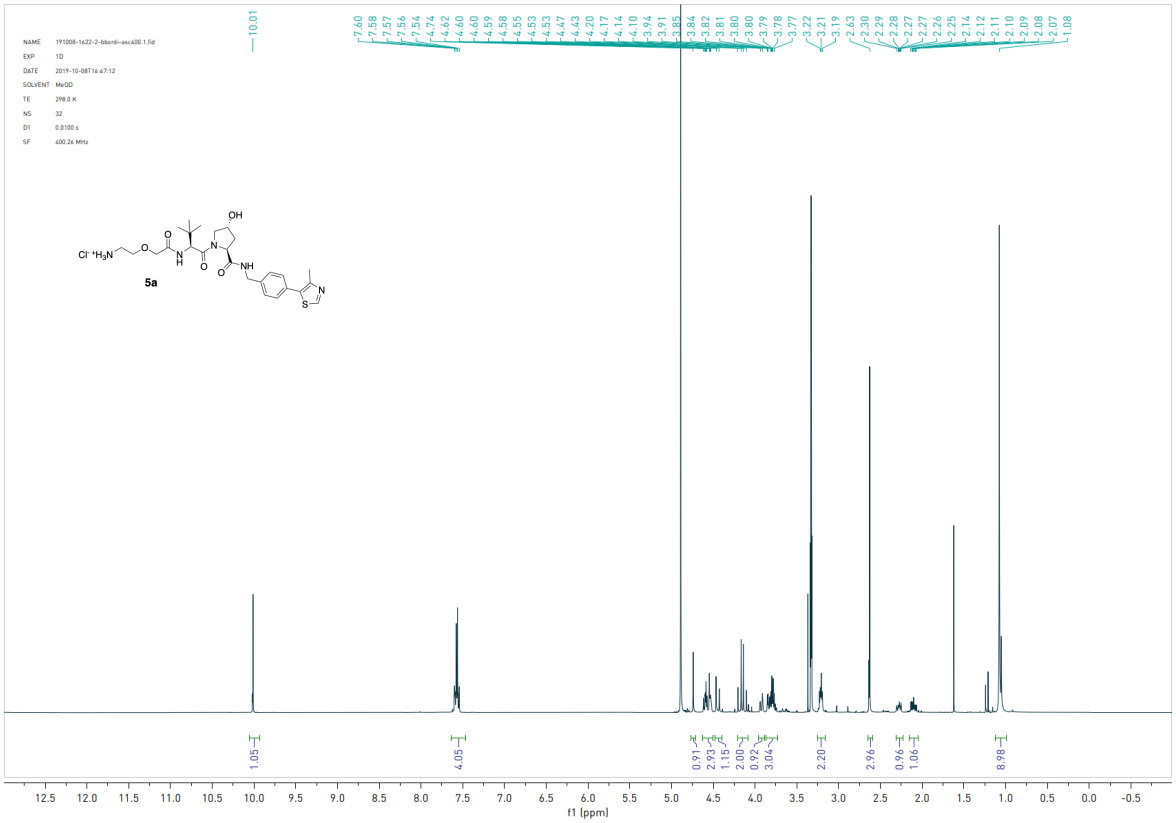



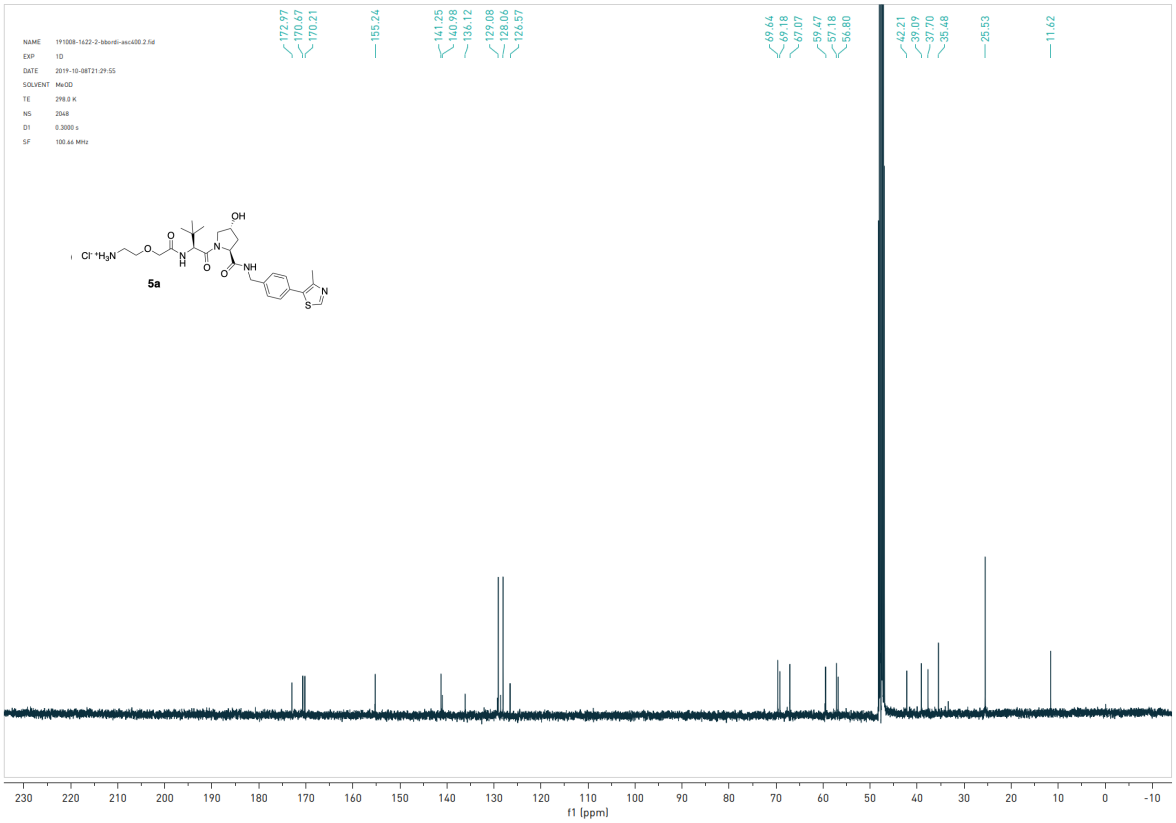
NMR of compound **4i**:



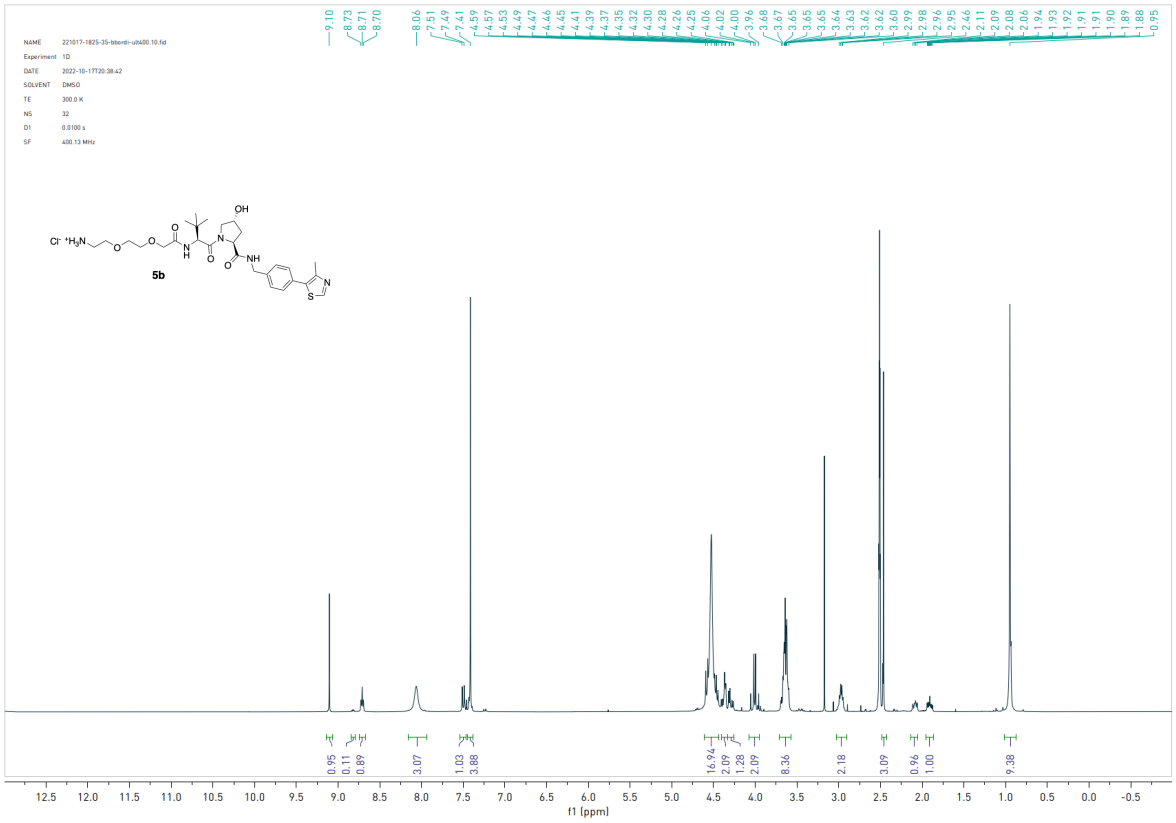



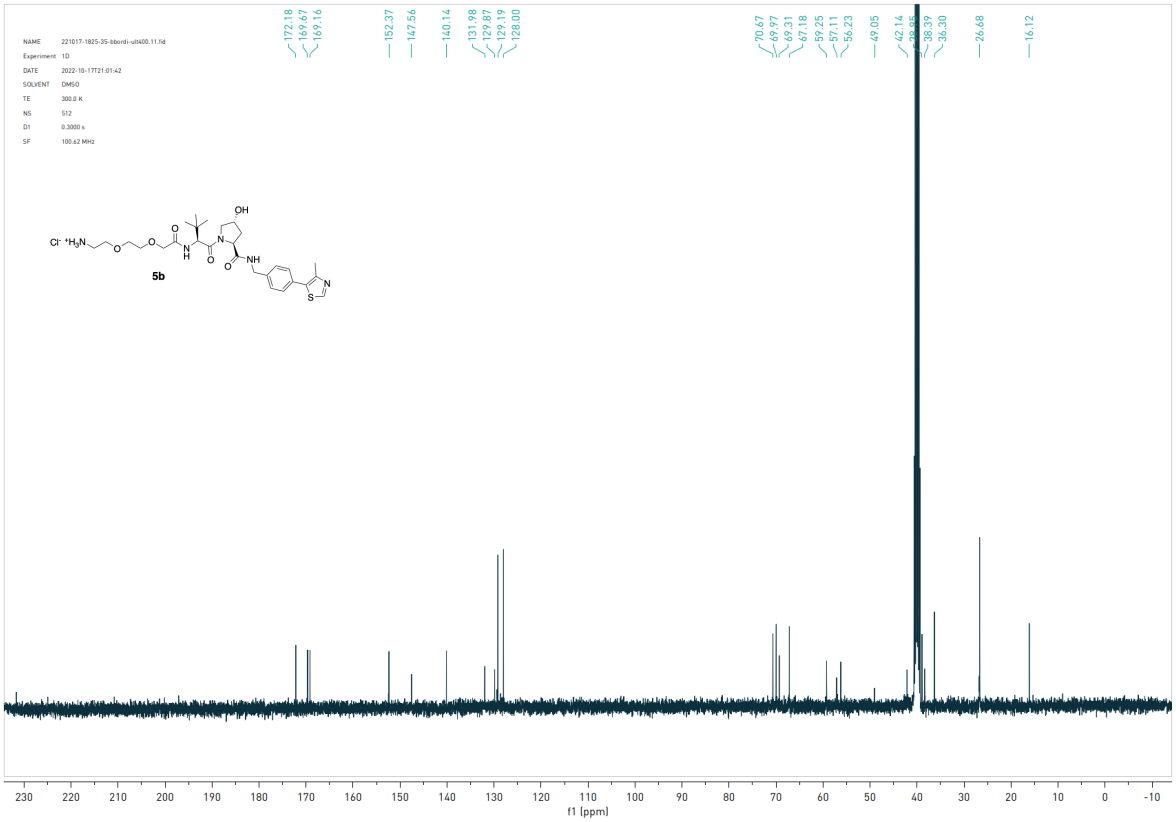
NMR of compound **5a**:



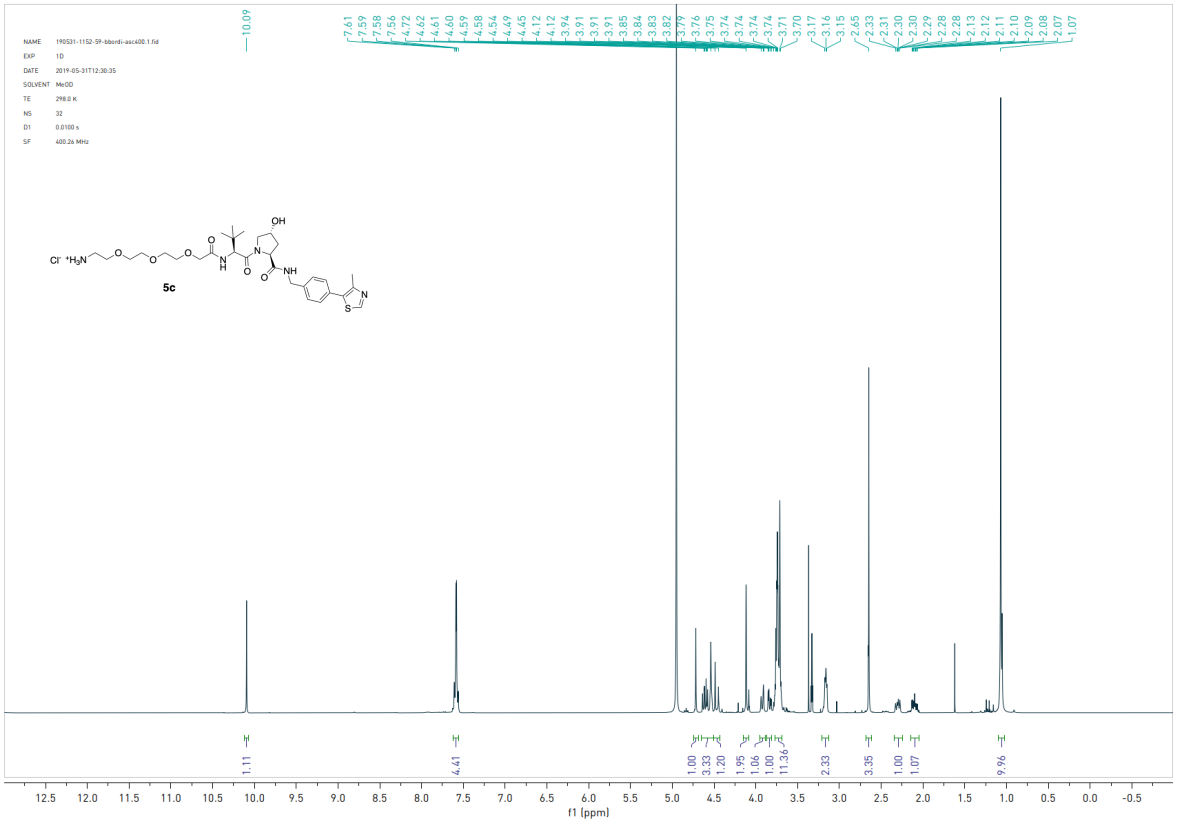



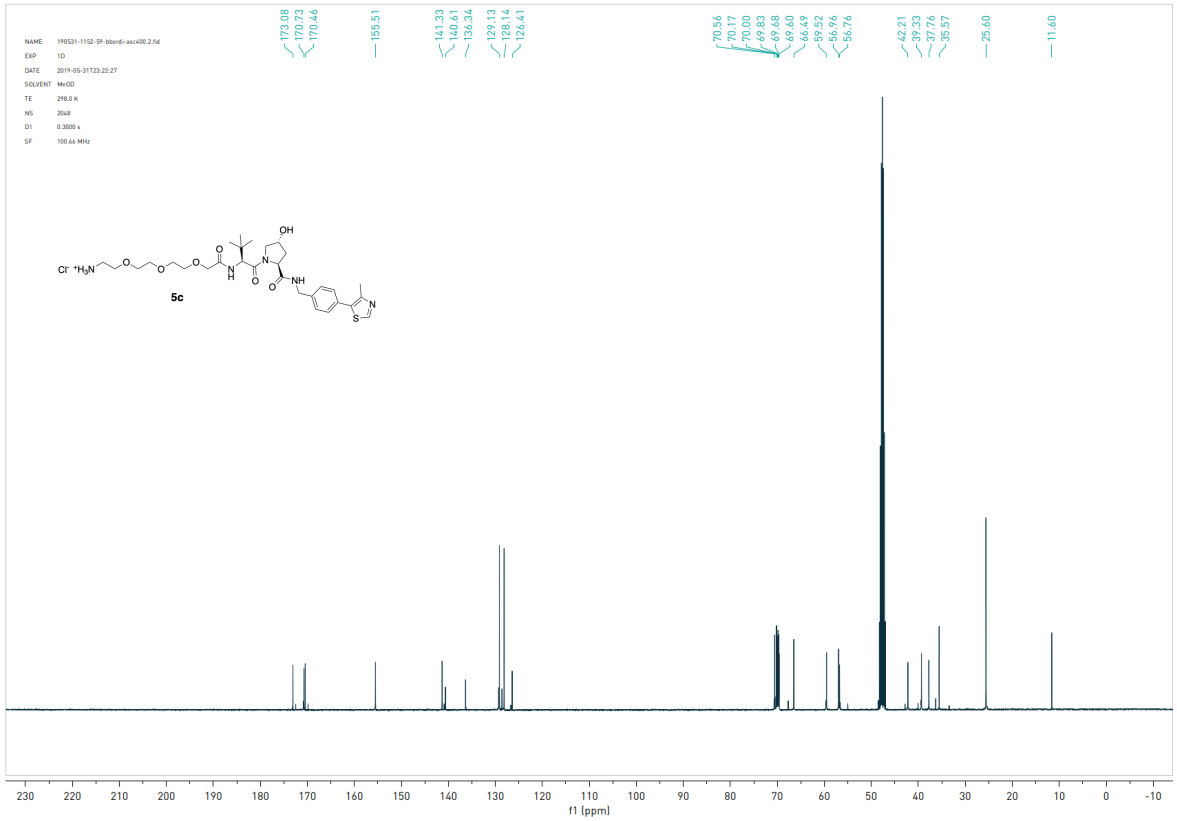
NMR of compound **5b**:



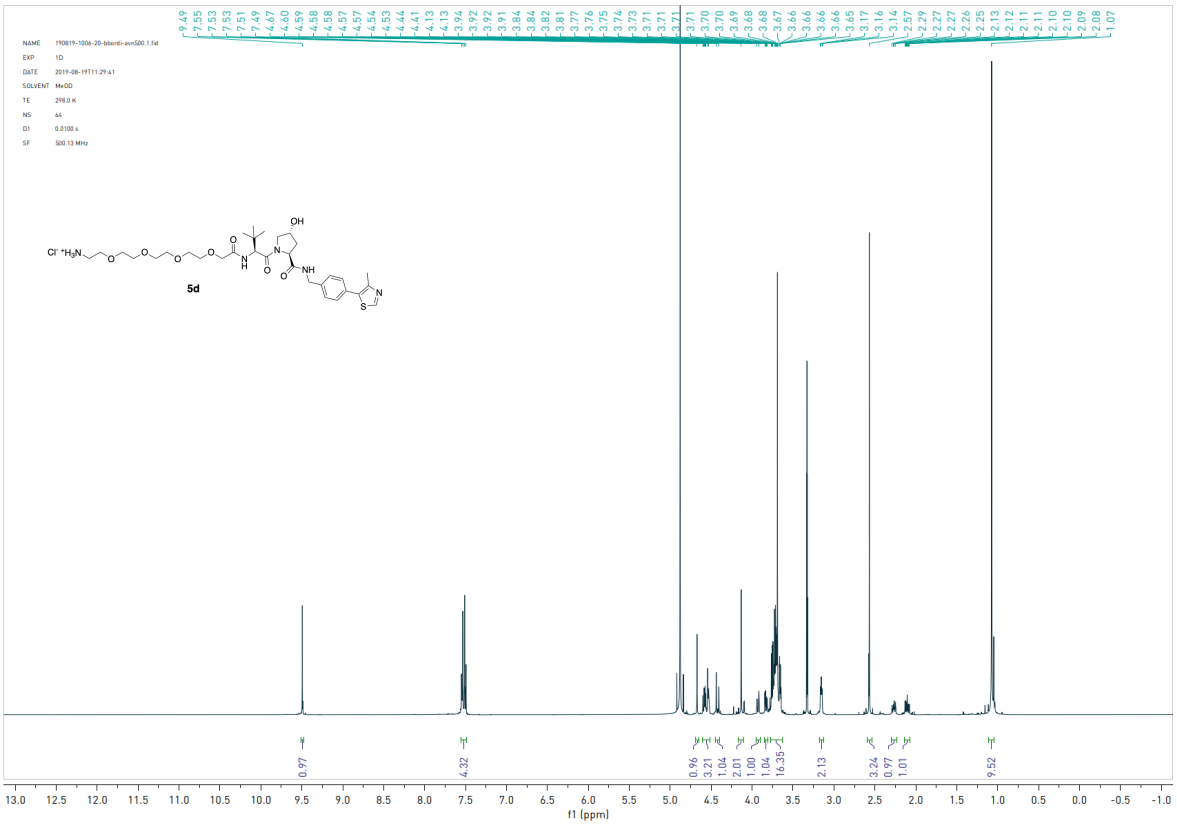



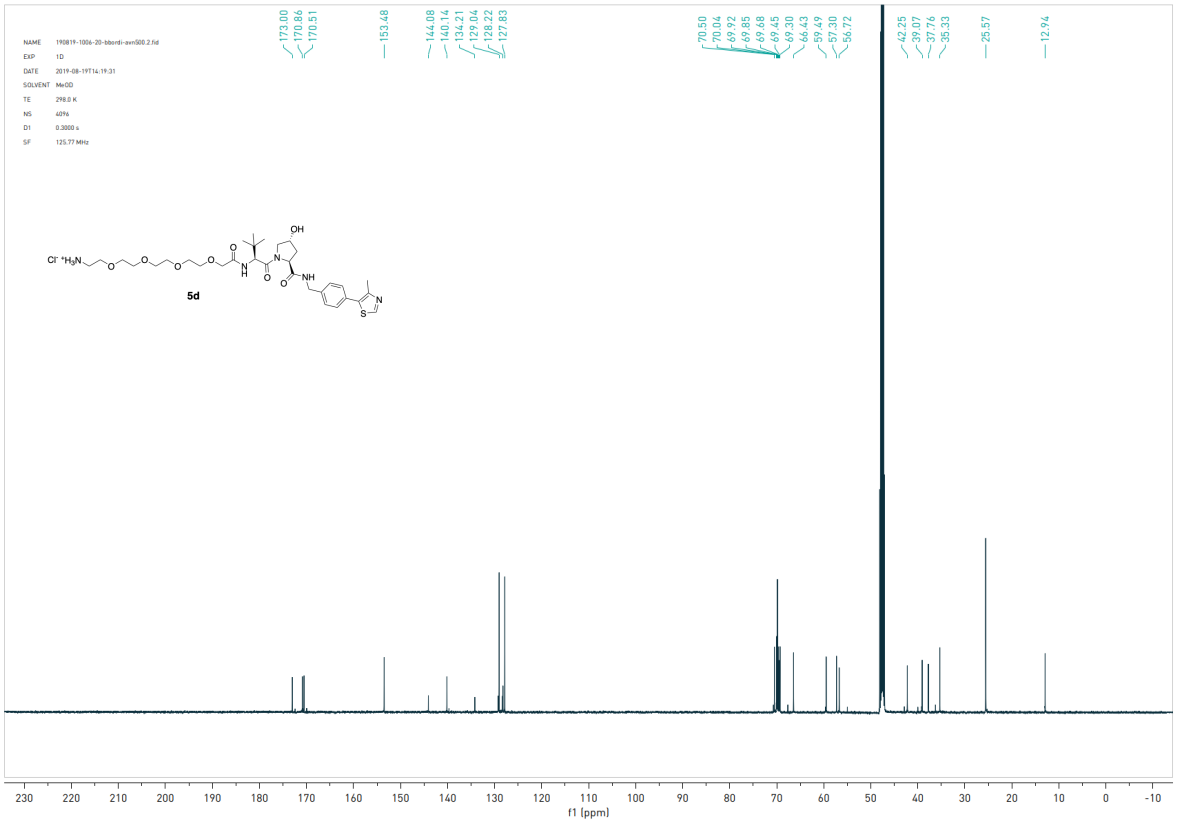
NMR of compound **5c**:



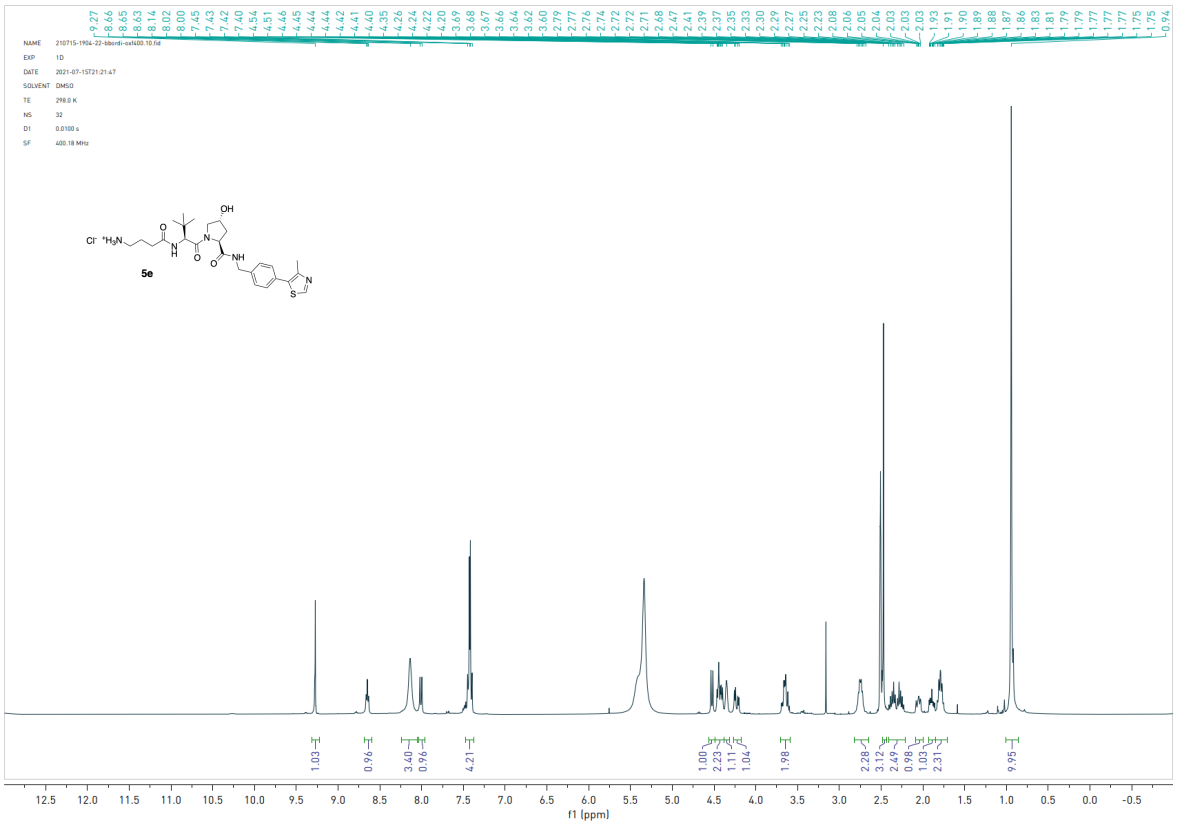



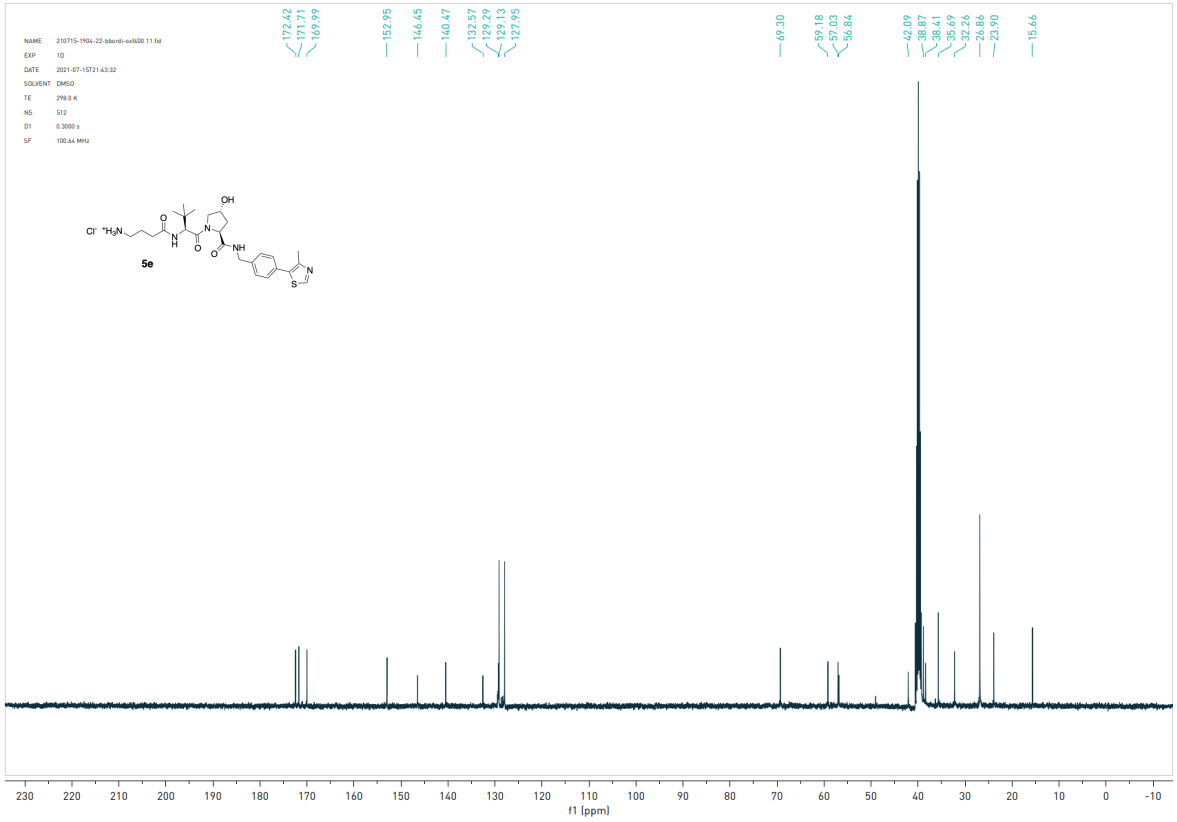
NMR of compound **5d**:



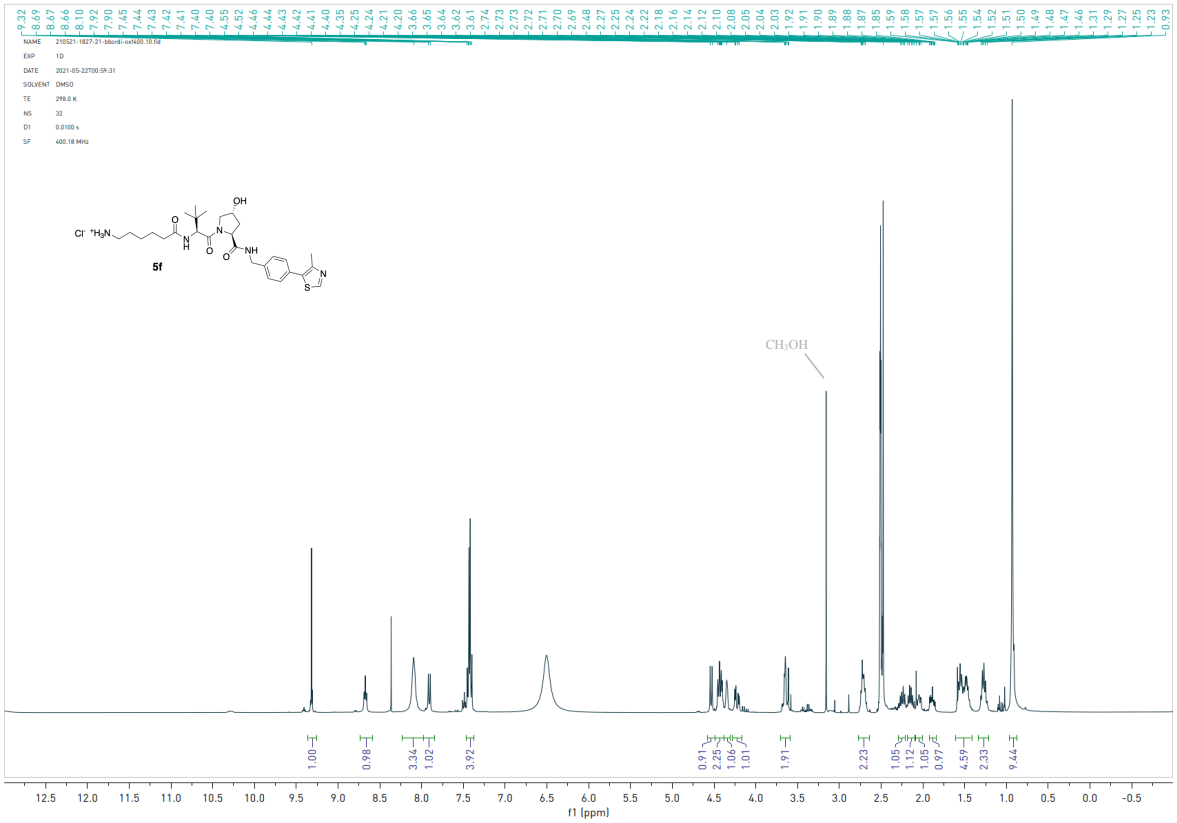



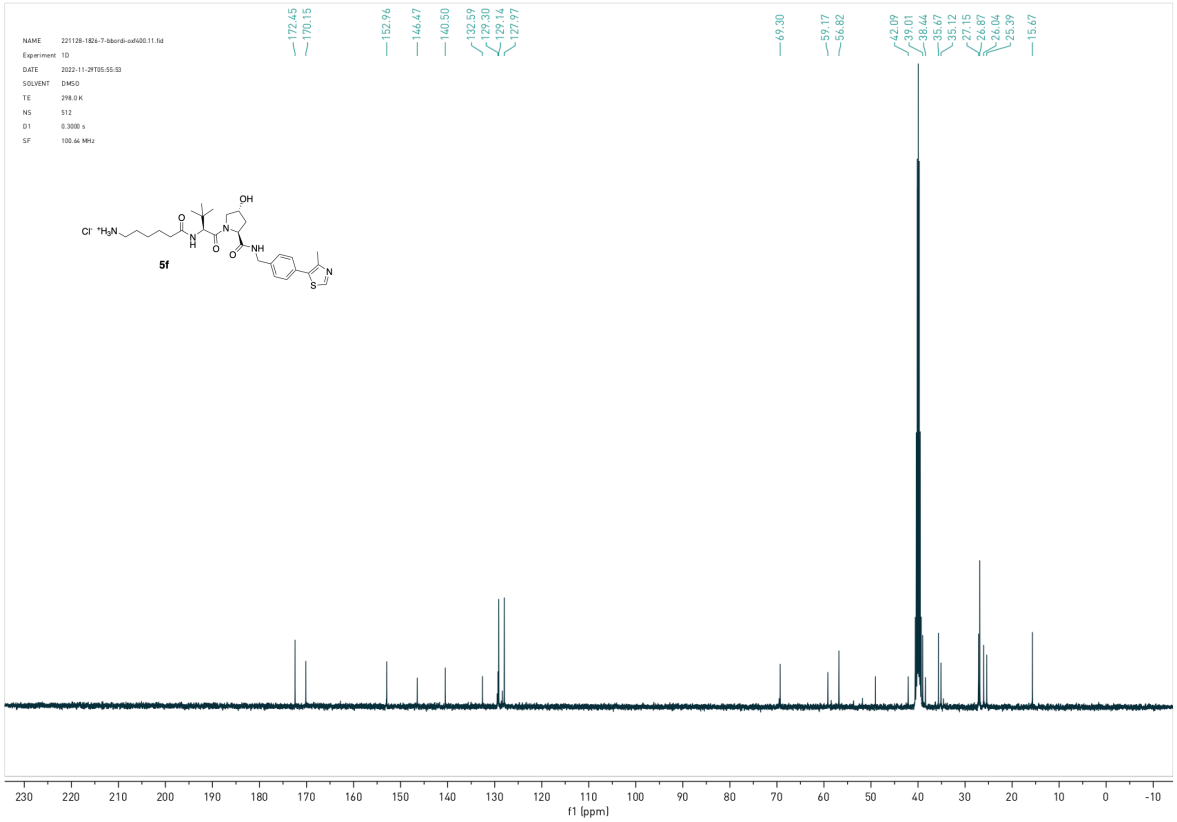
NMR of compound **5e**:



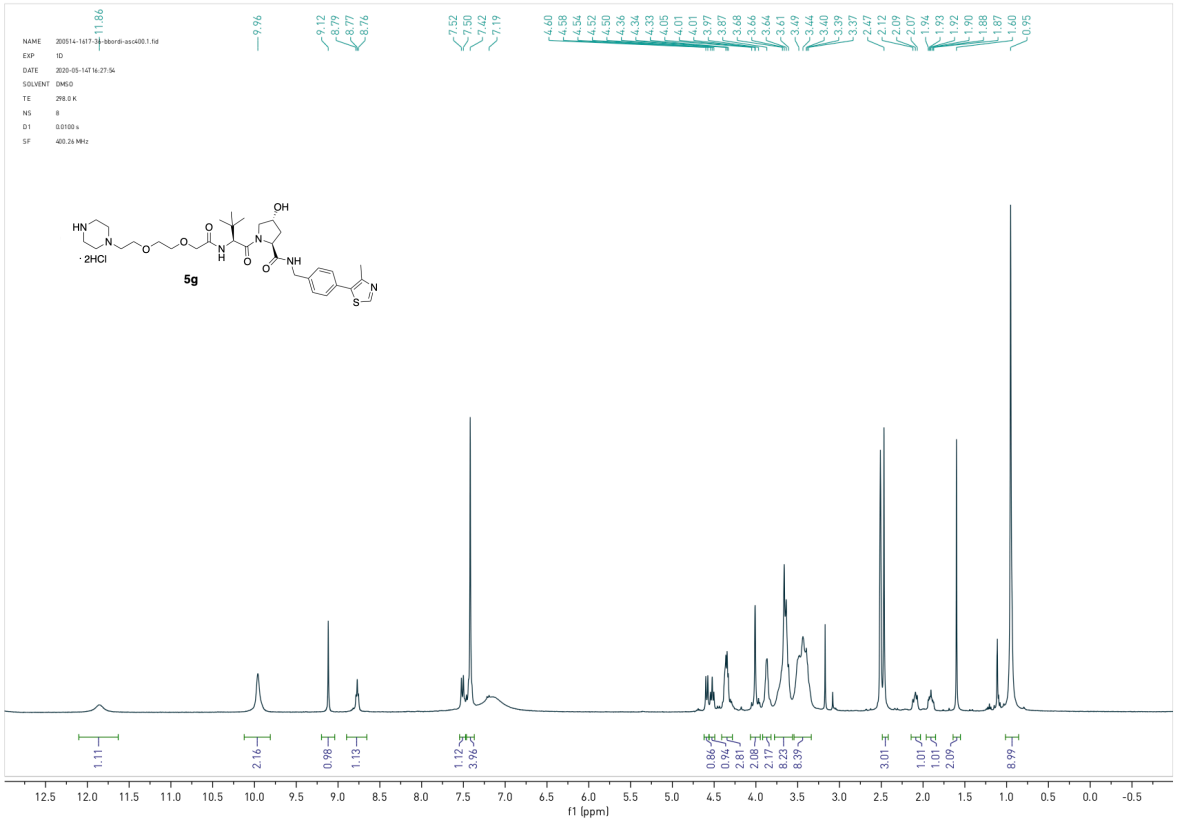



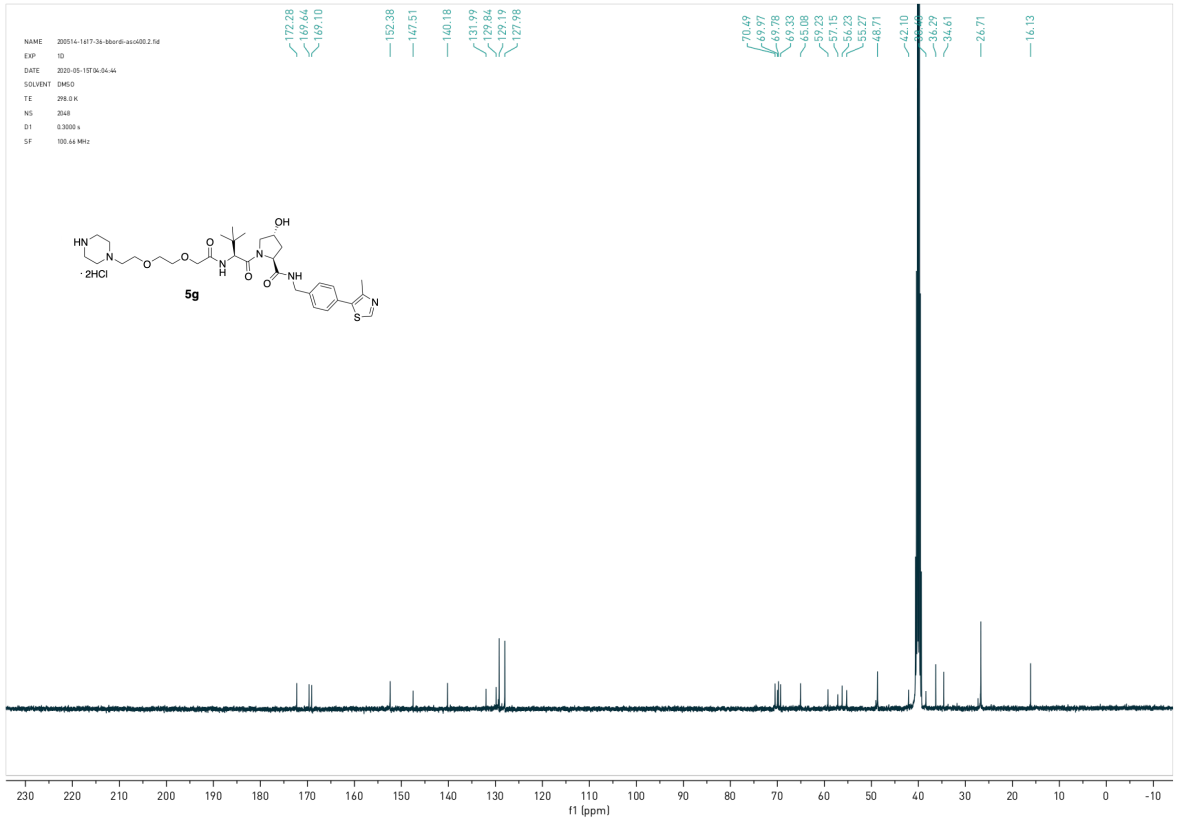
NMR of compound **5f**:



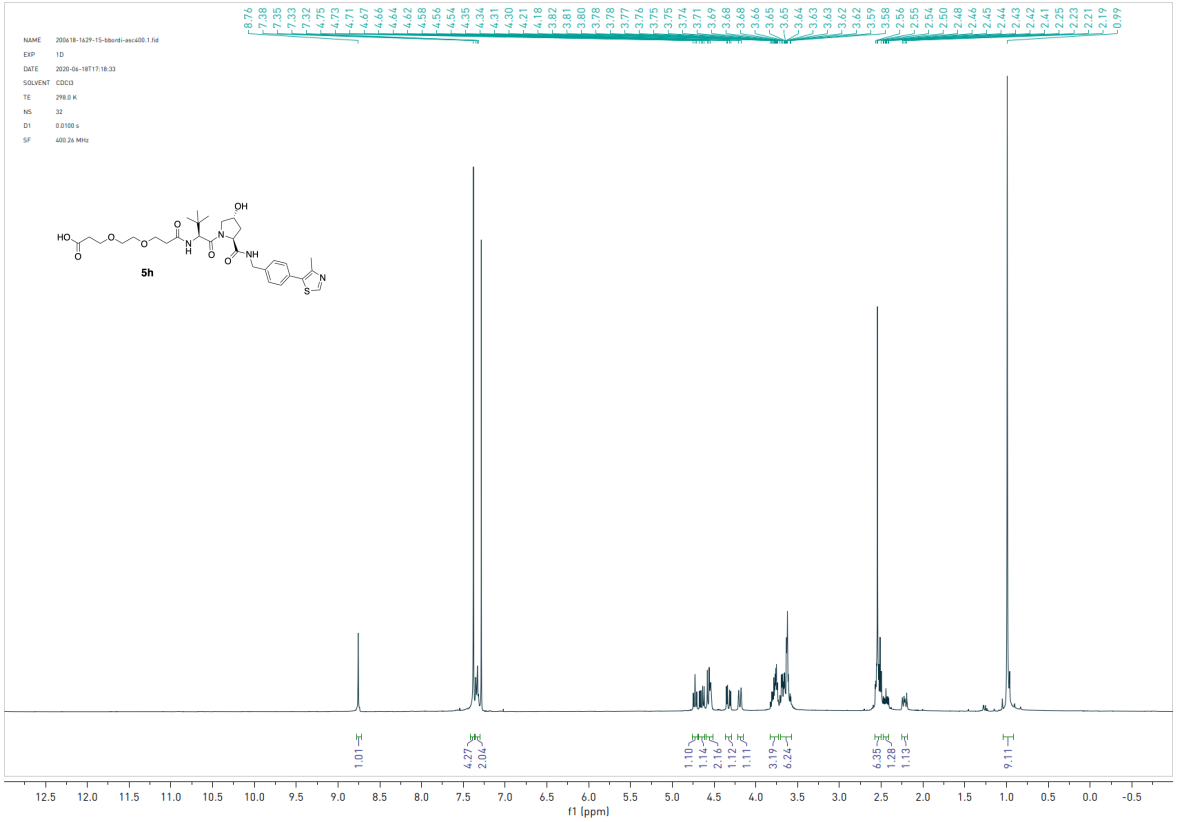



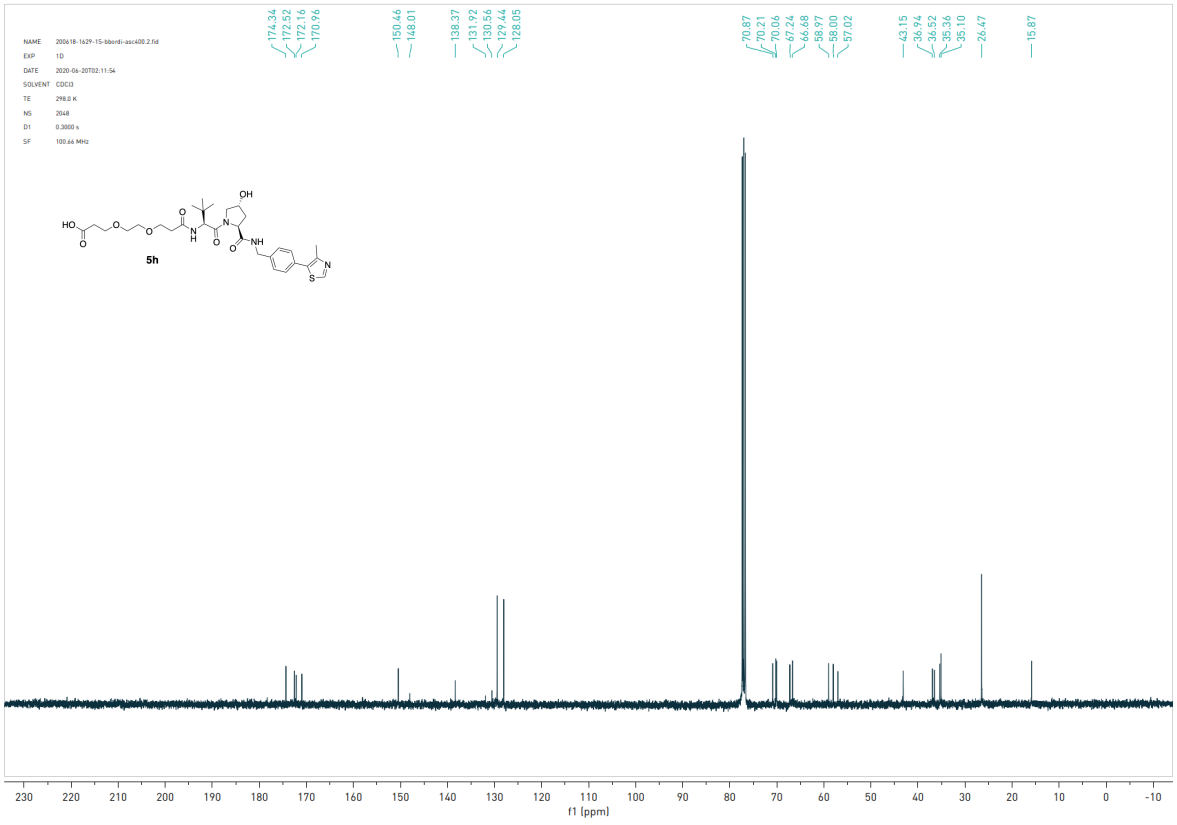
NMR of compound **5g**:



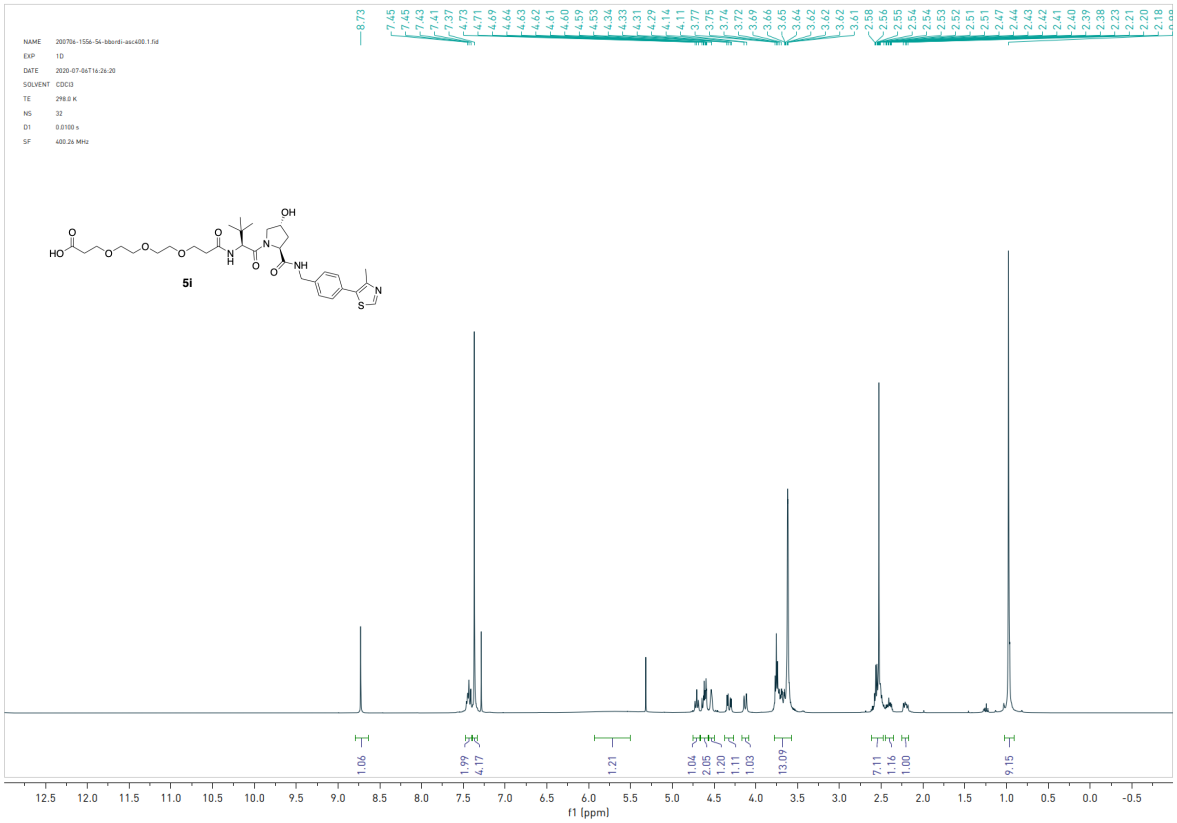



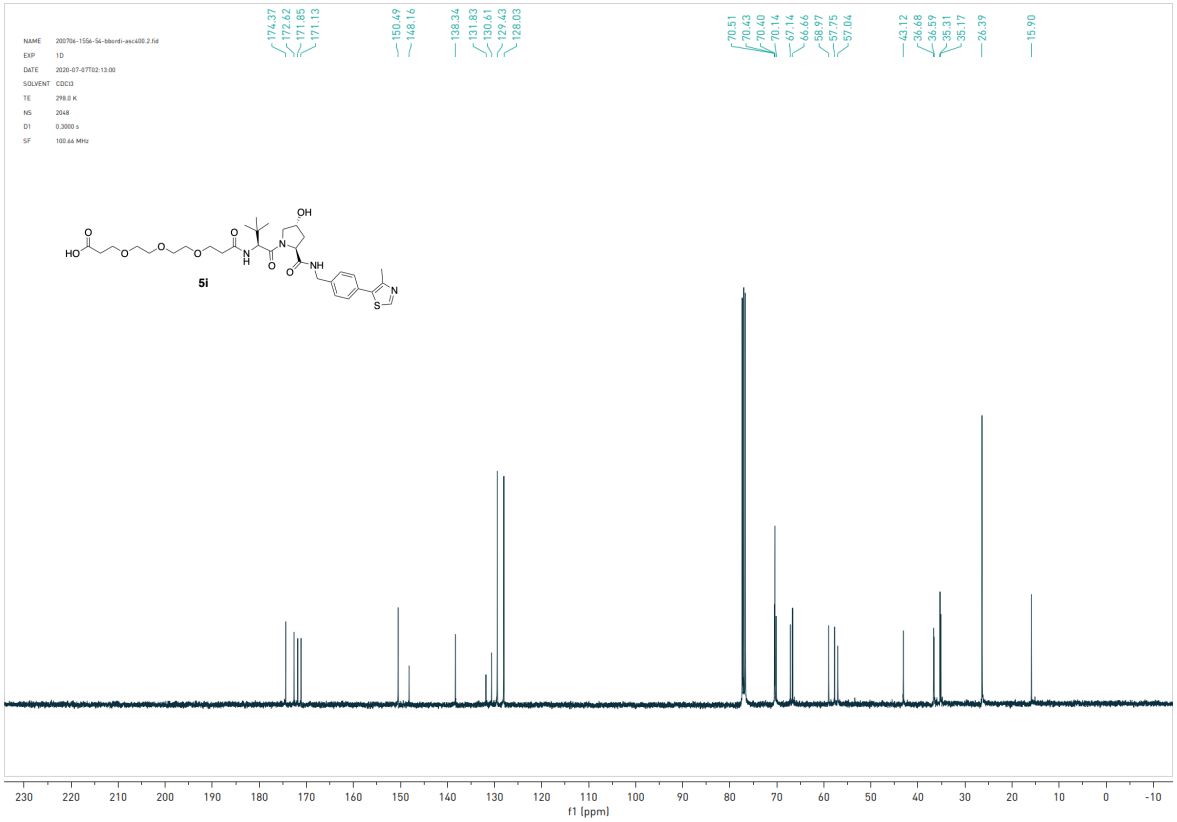
NMR of compound **5h**:



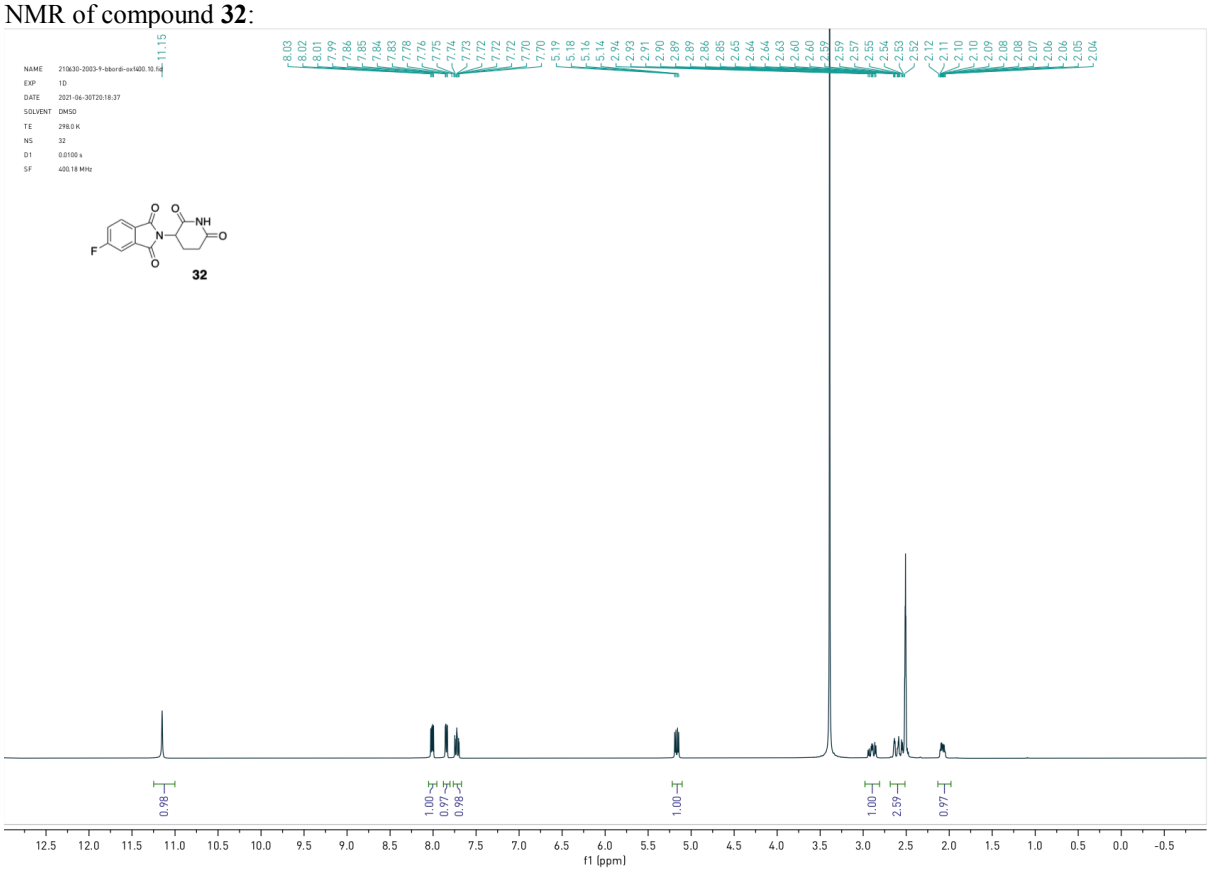



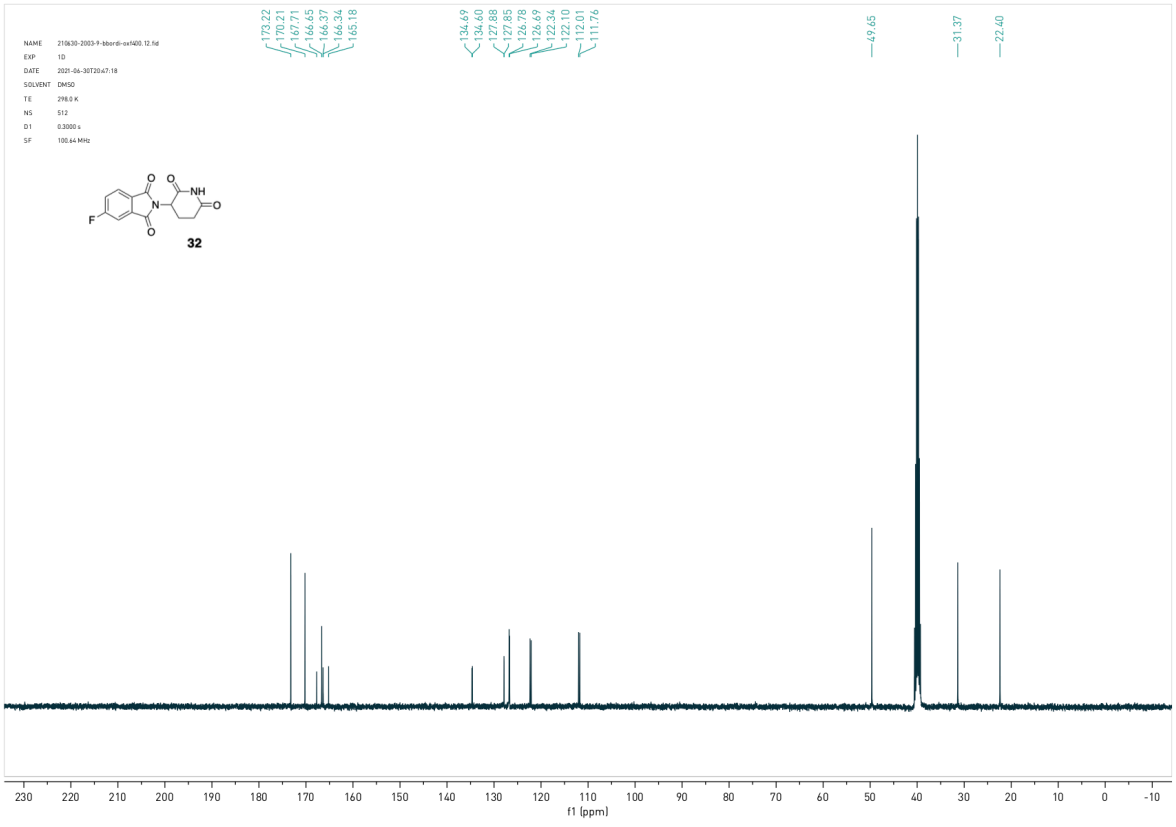
NMR of compound **5i**:



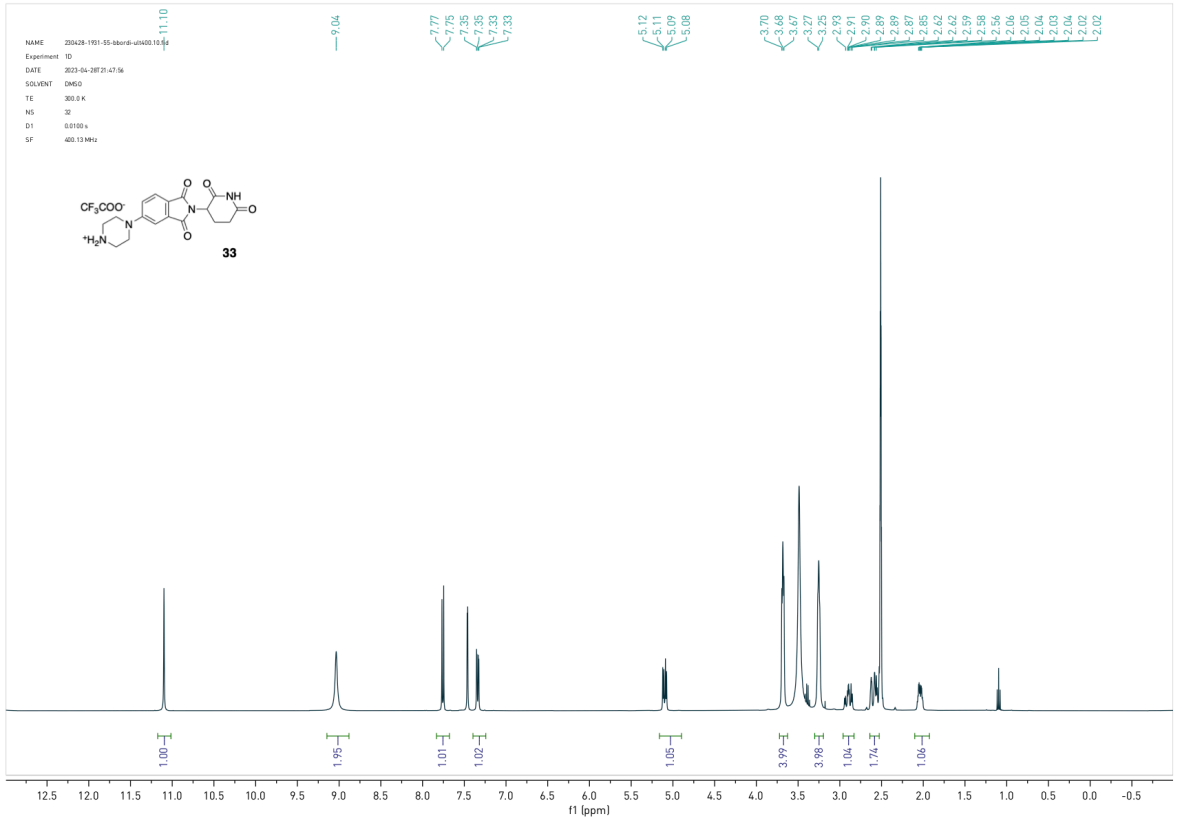



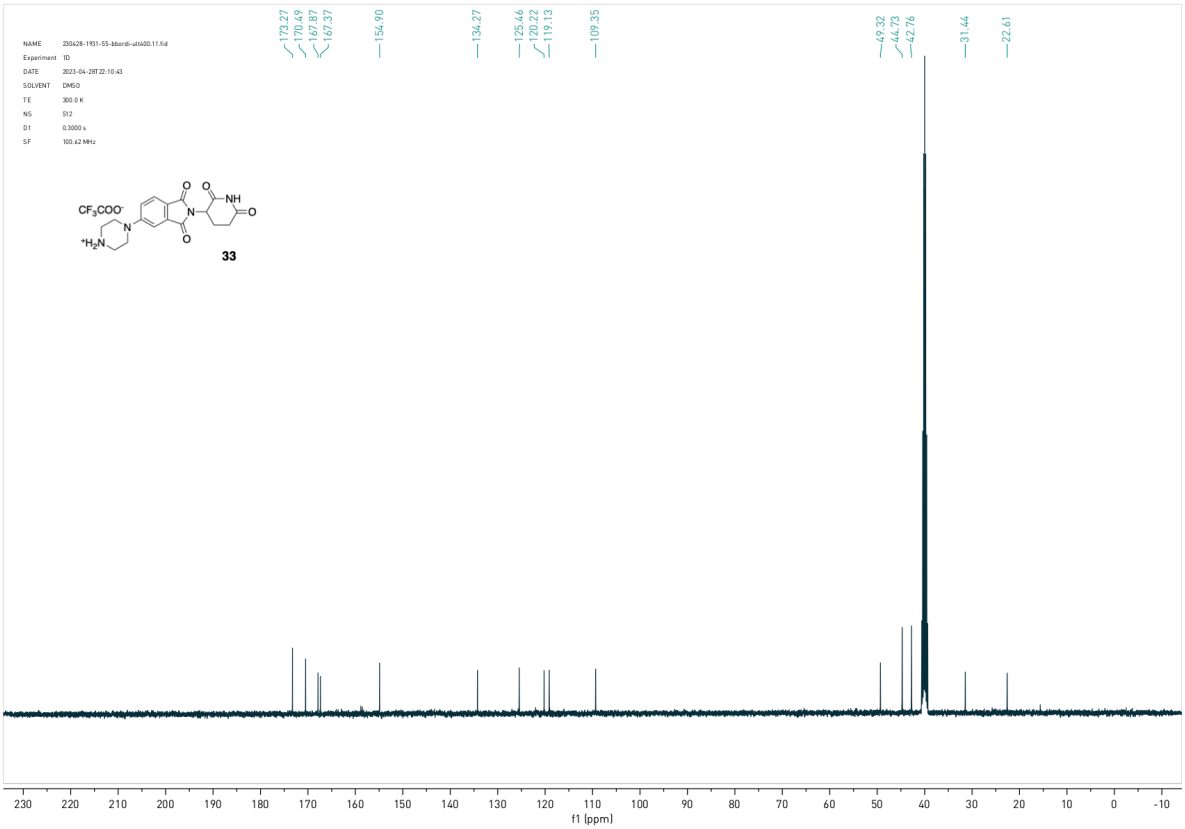
NMR of compound **32**:



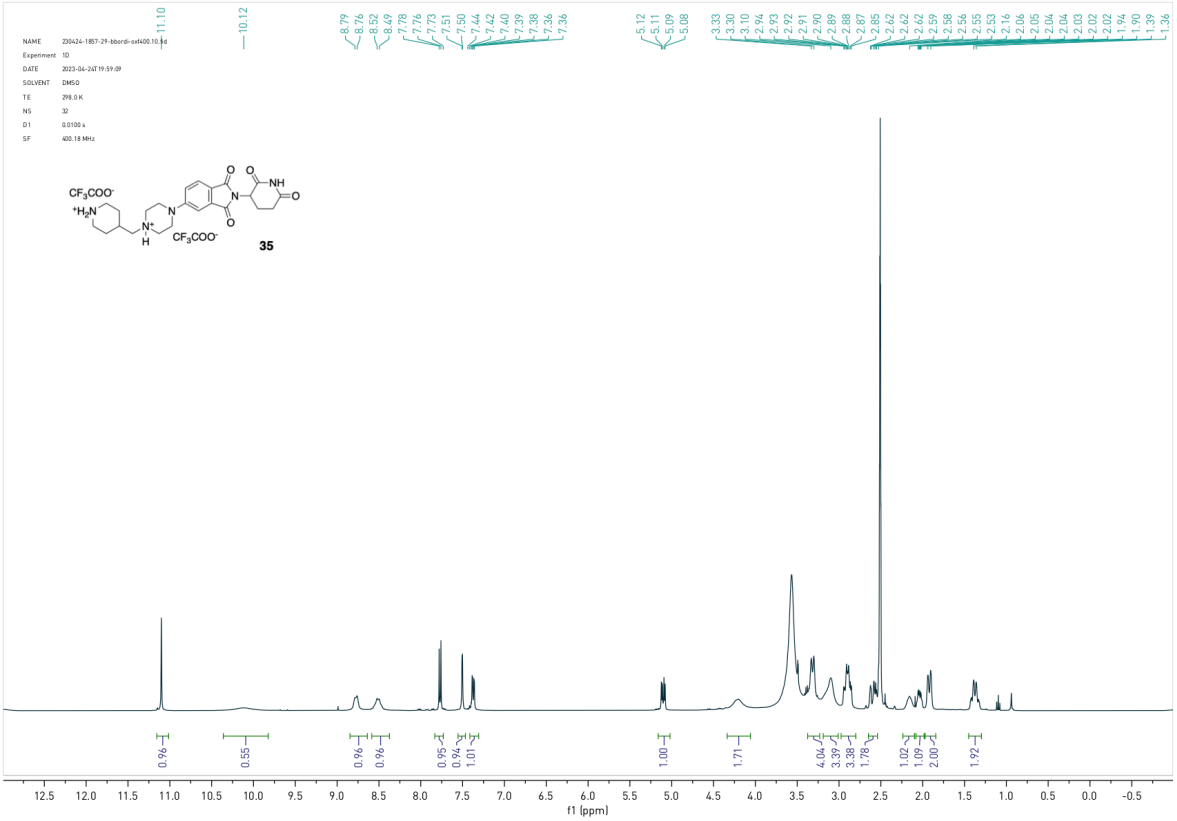



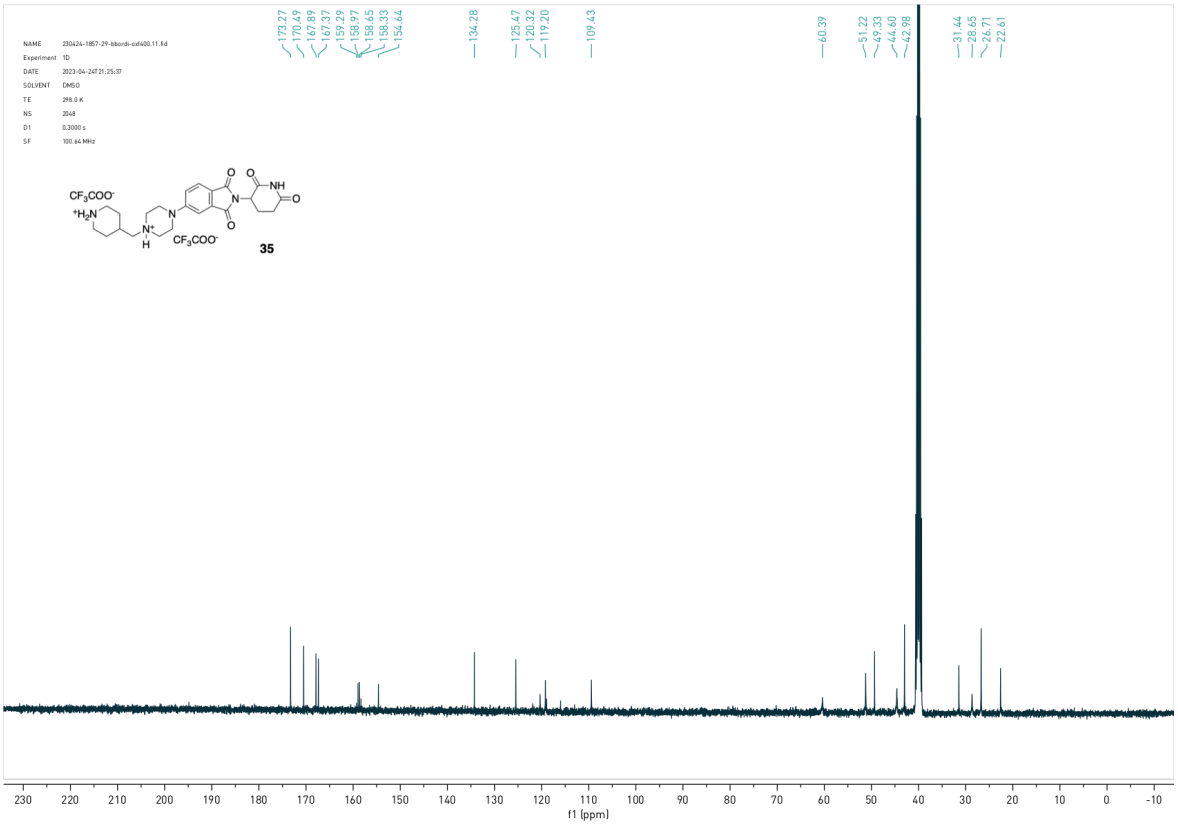
NMR of compound **33**:



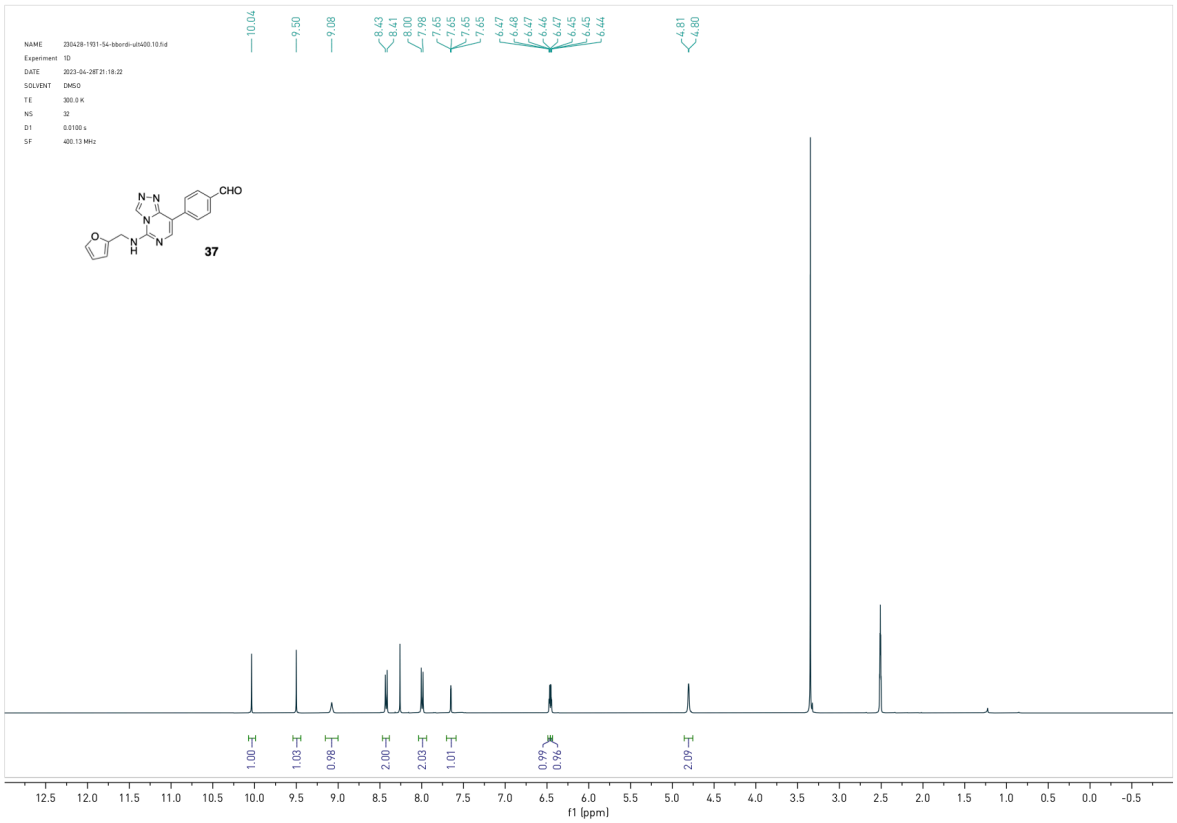
NMR of compound **35**:

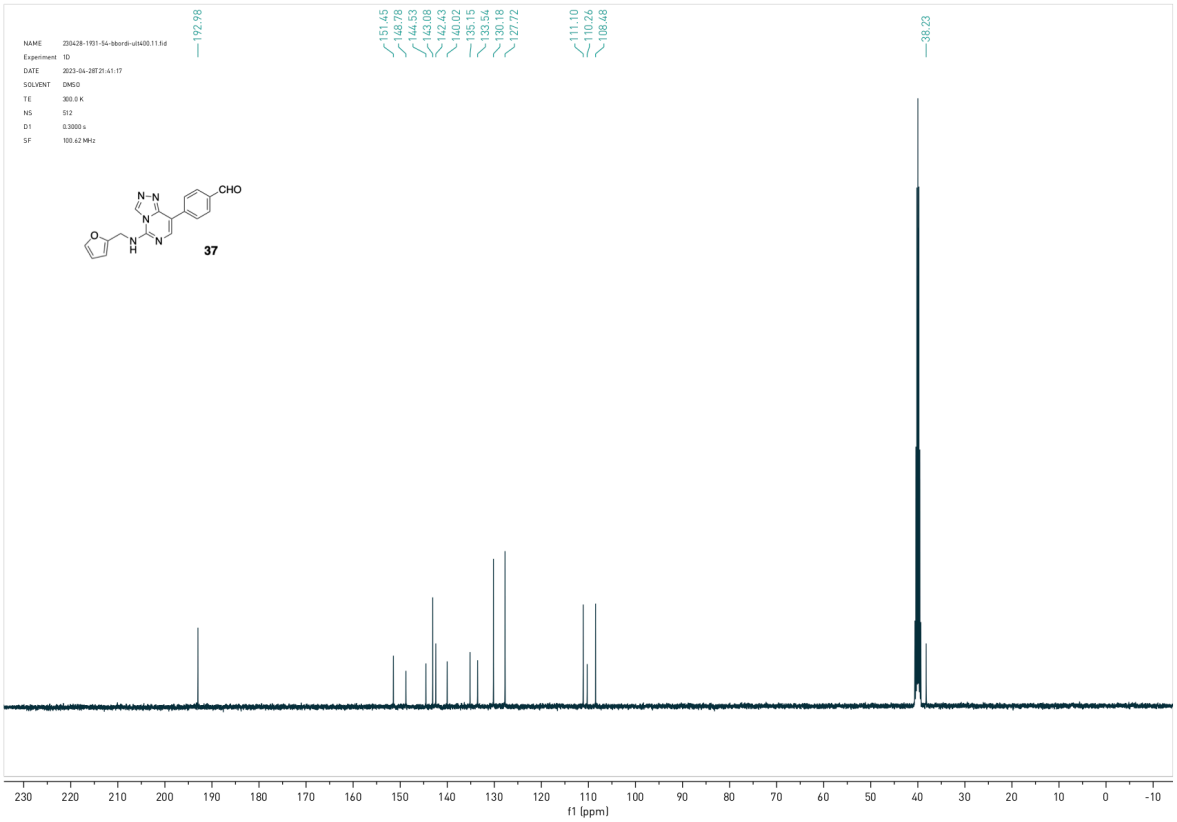


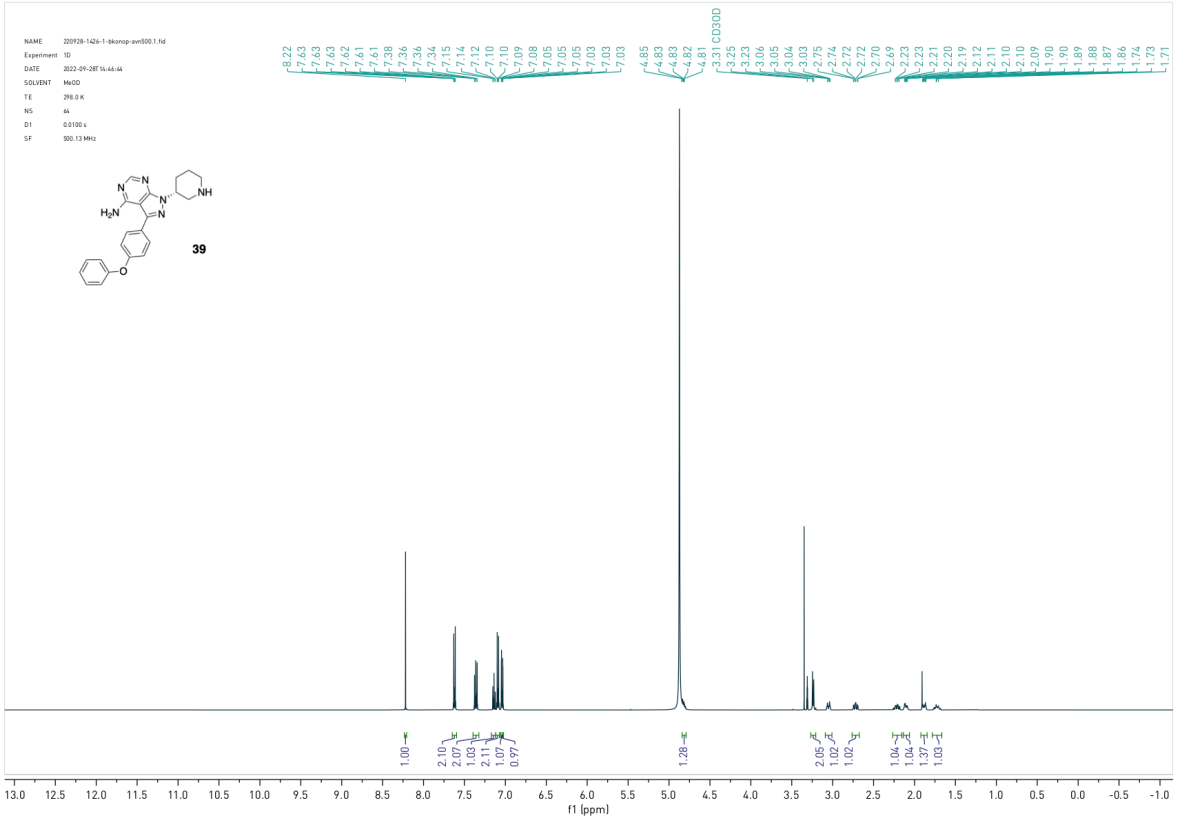
## 5.3 NMR of protein binders

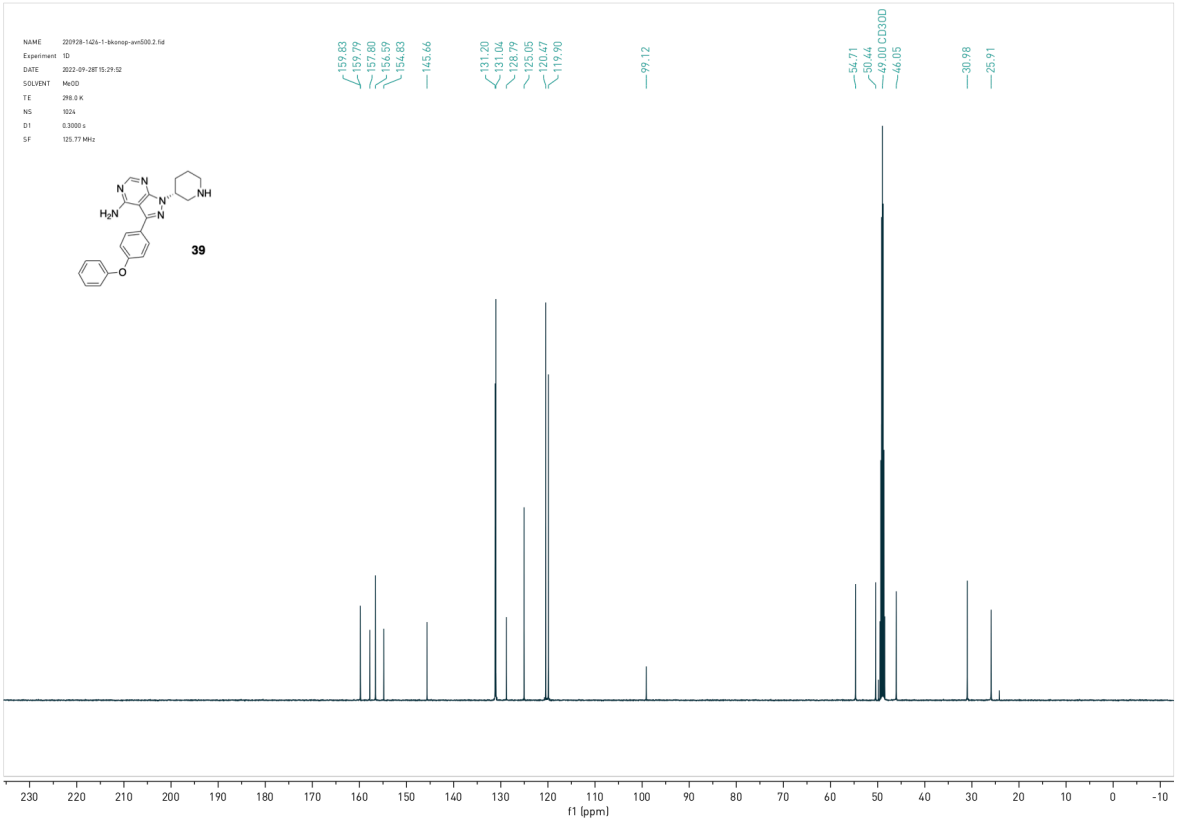
NMR of compound **37**:



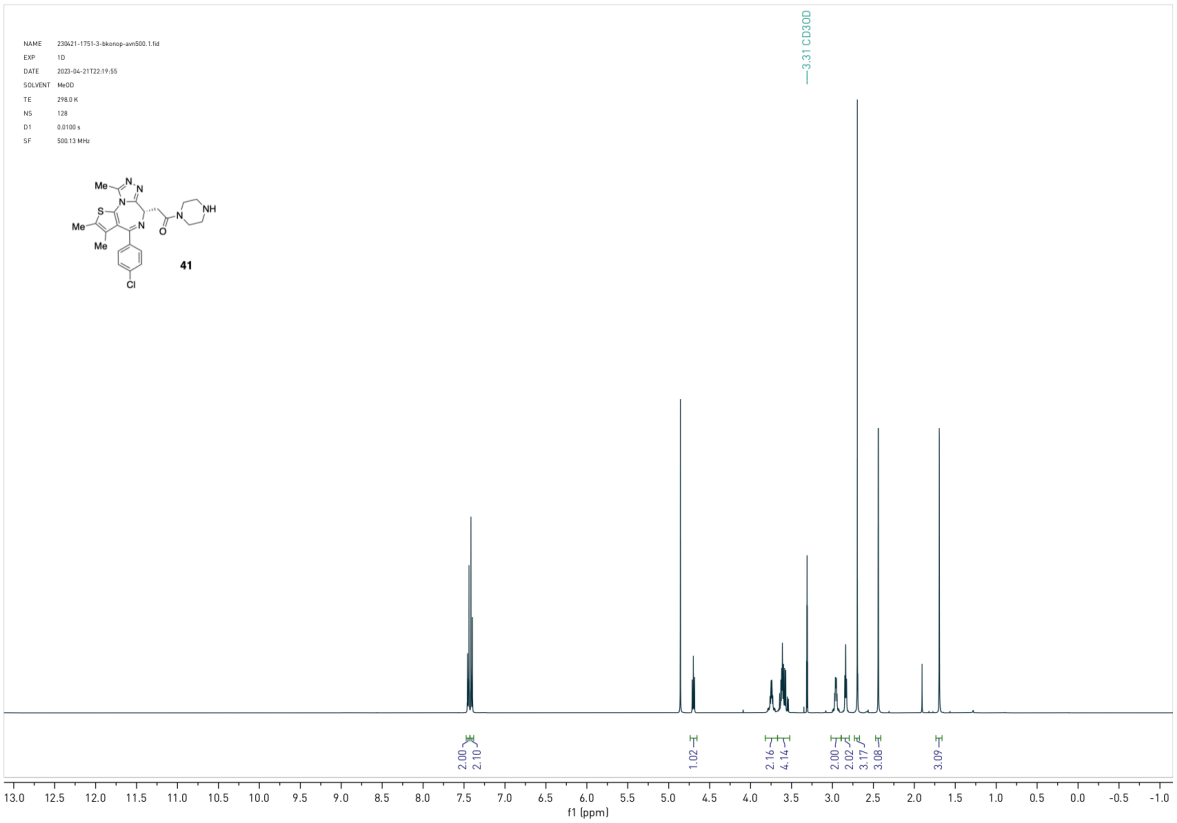



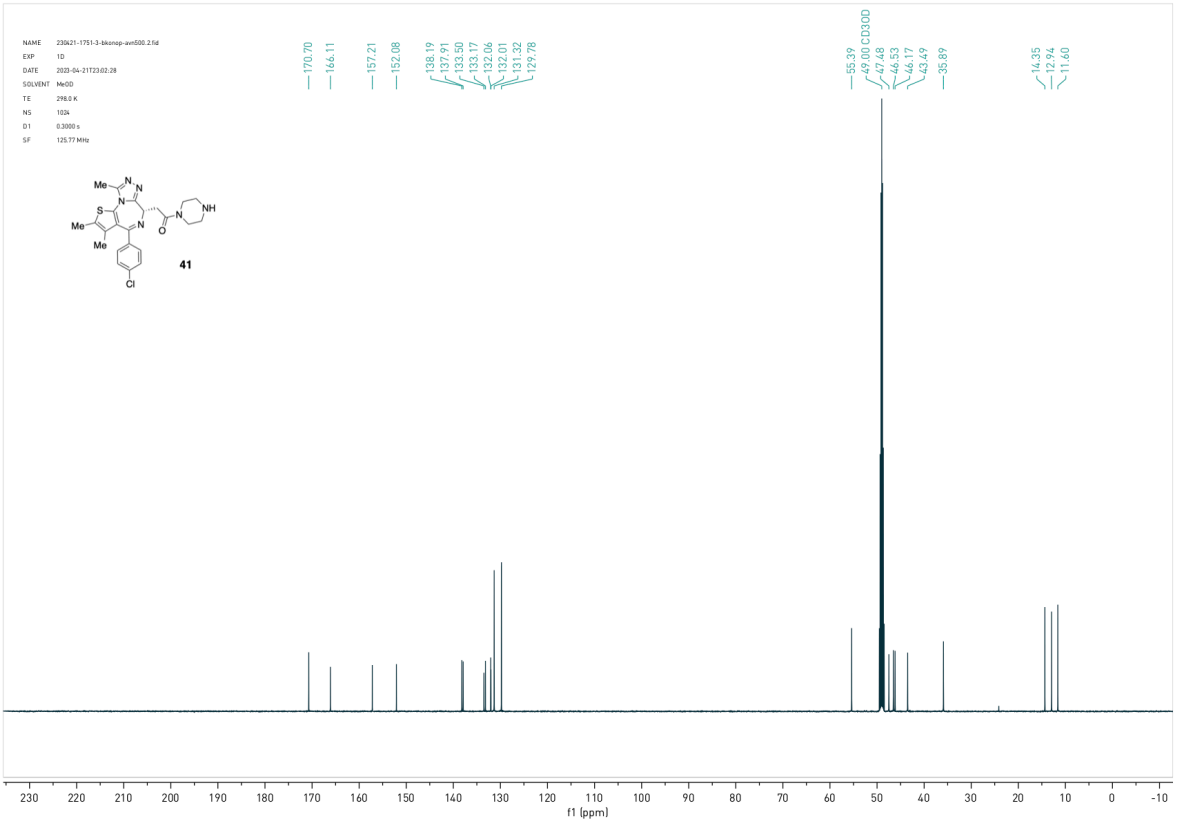
NMR of compound **39**:



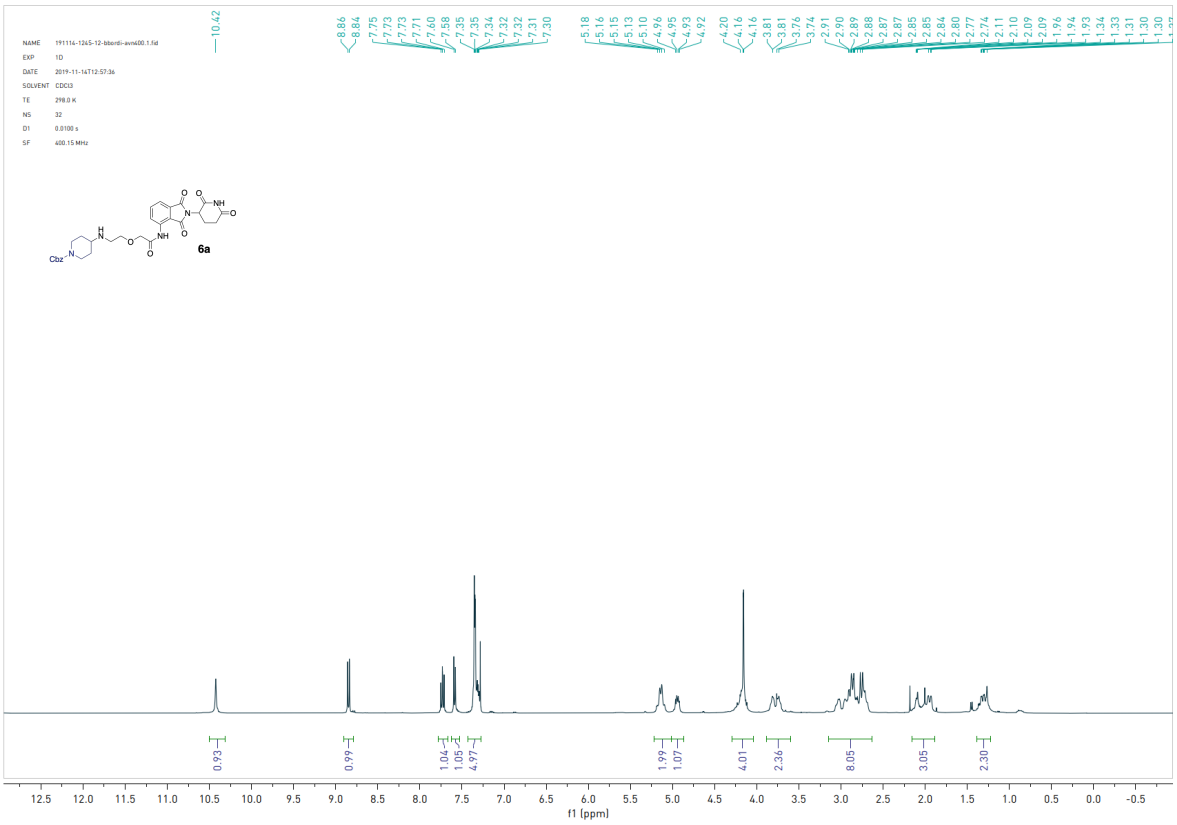
NMR of compound **41**:

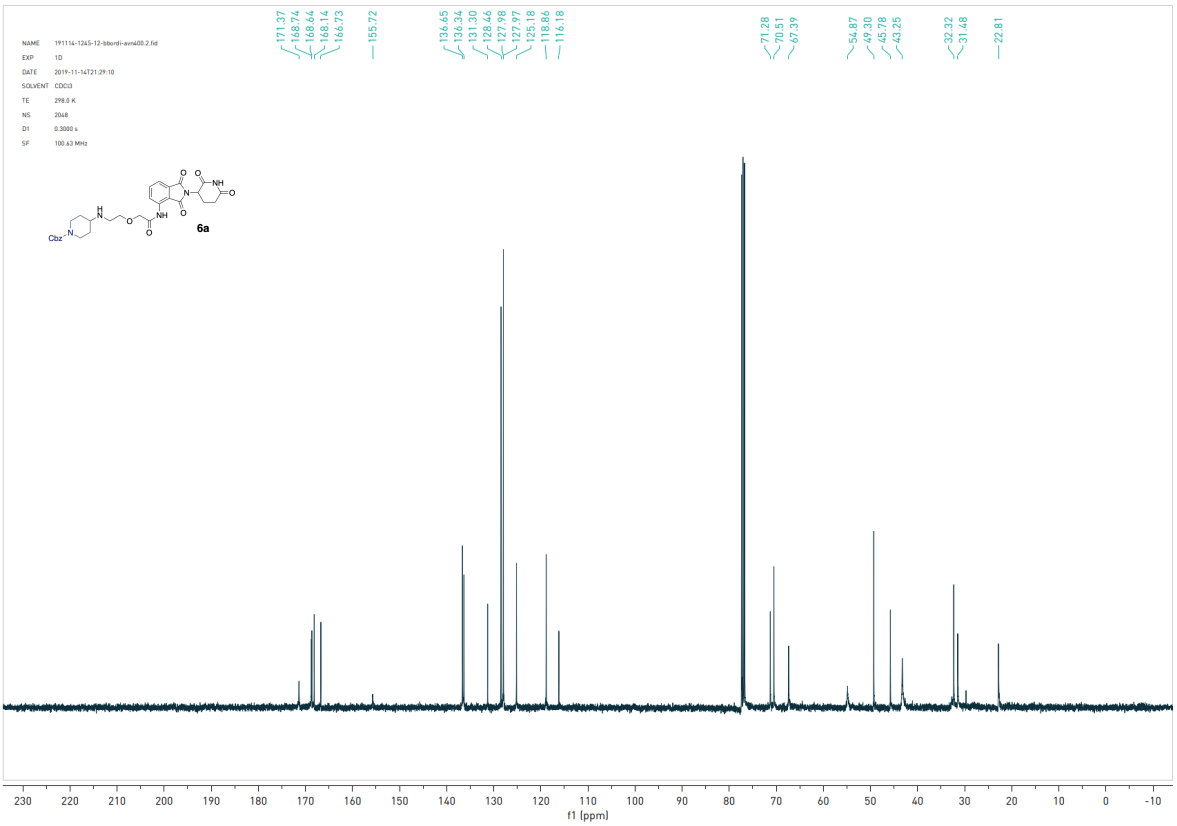


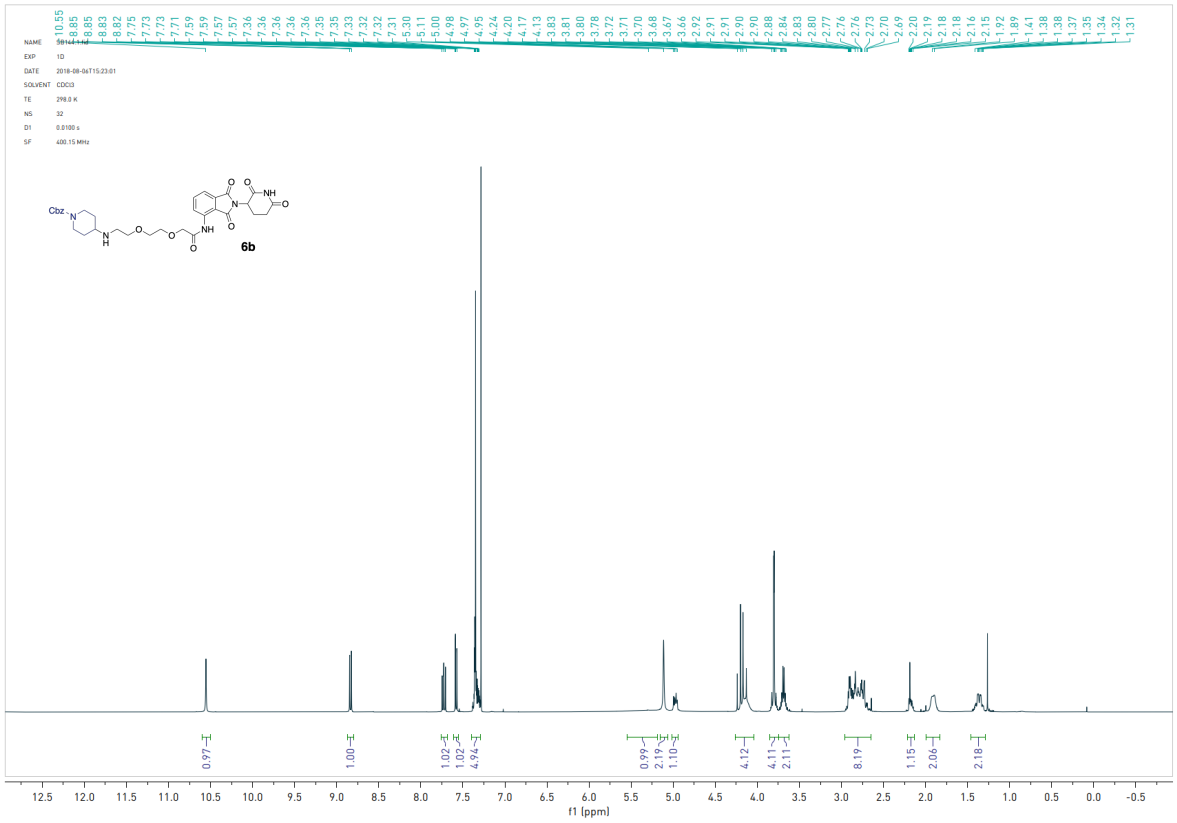
## 5.4 NMR of PROTAC products

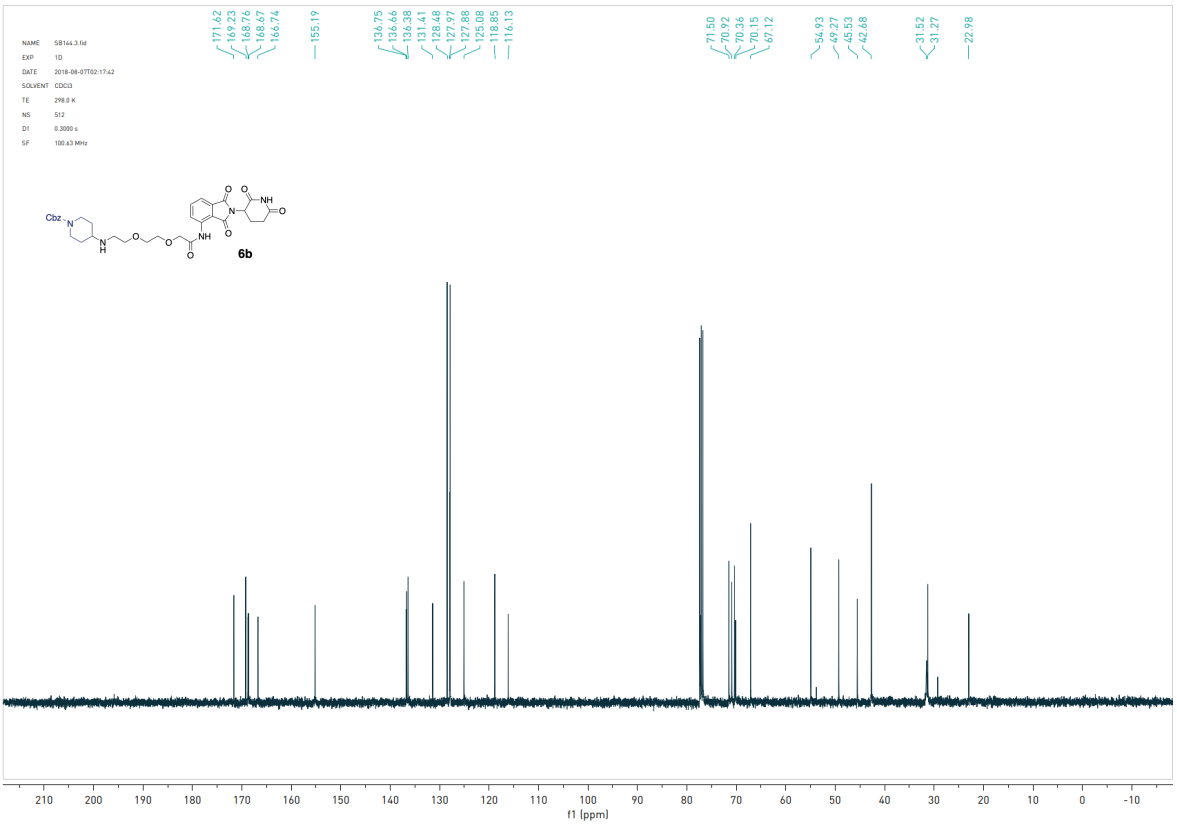
NMR of compound **6a**:



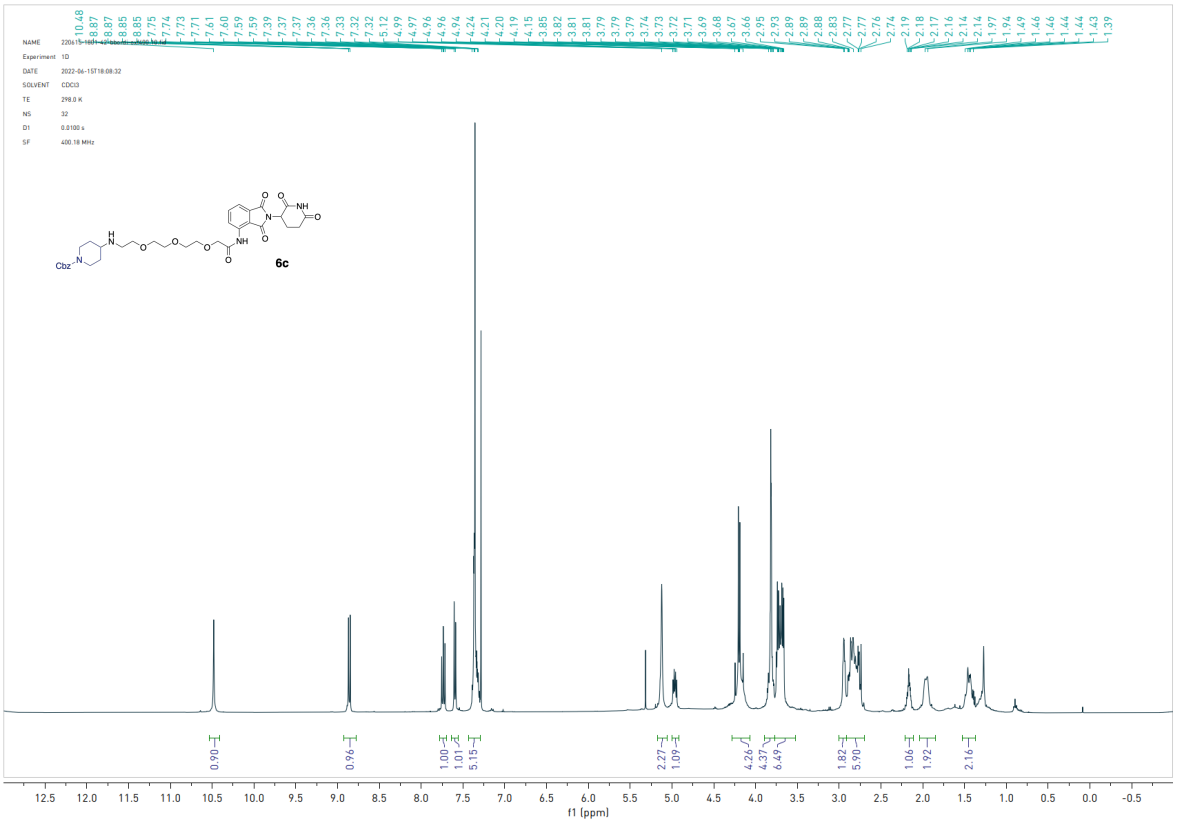



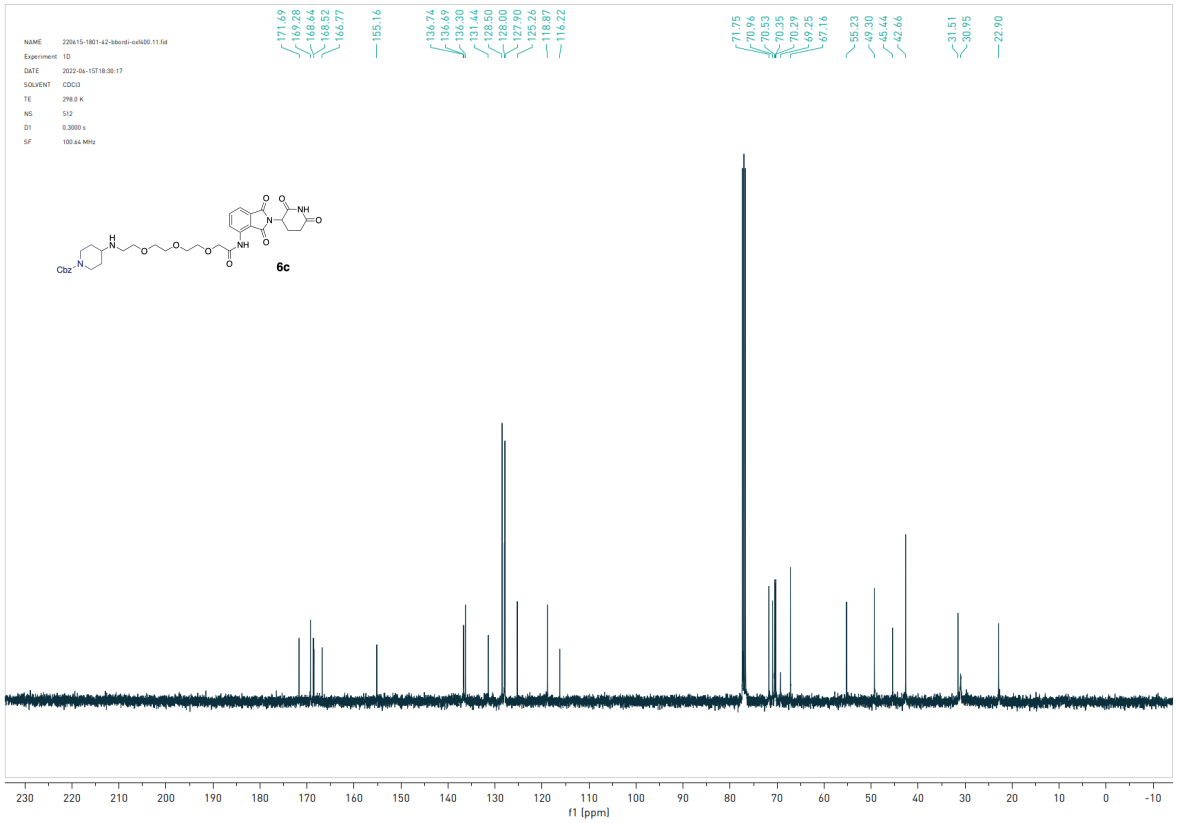
NMR of compound **6b**:



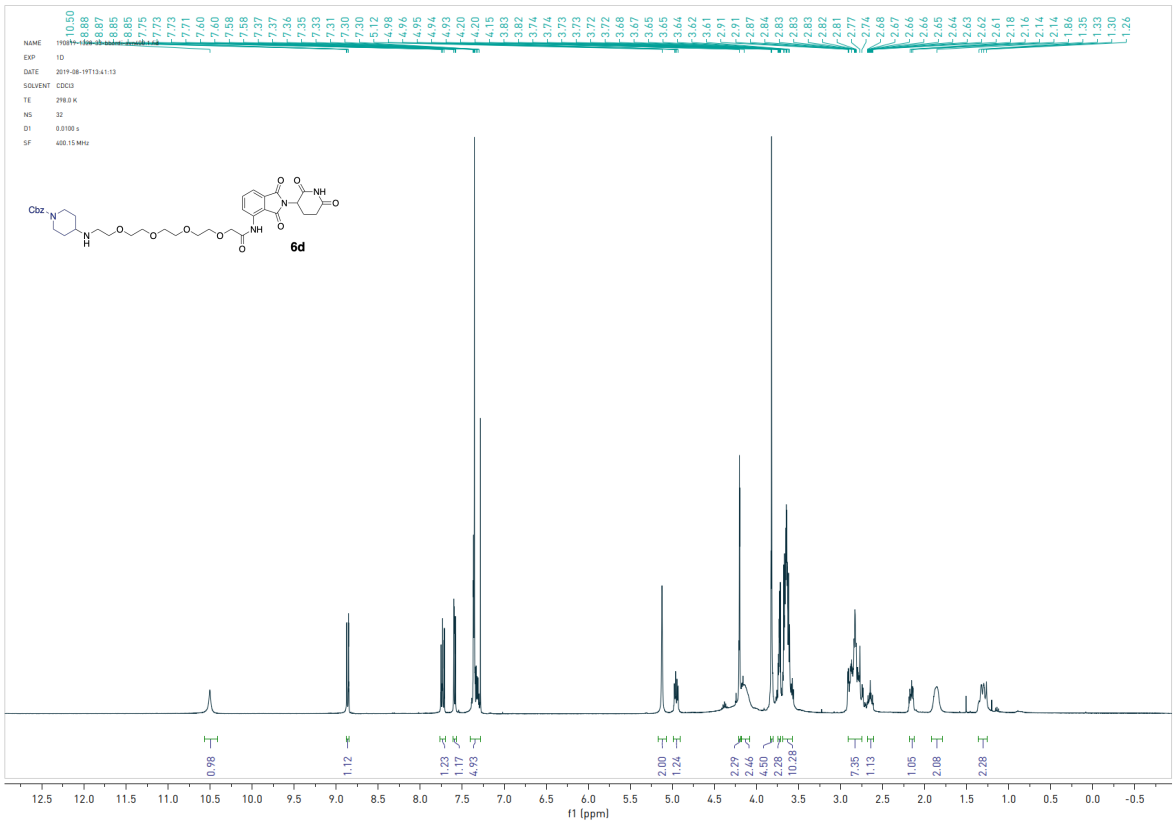



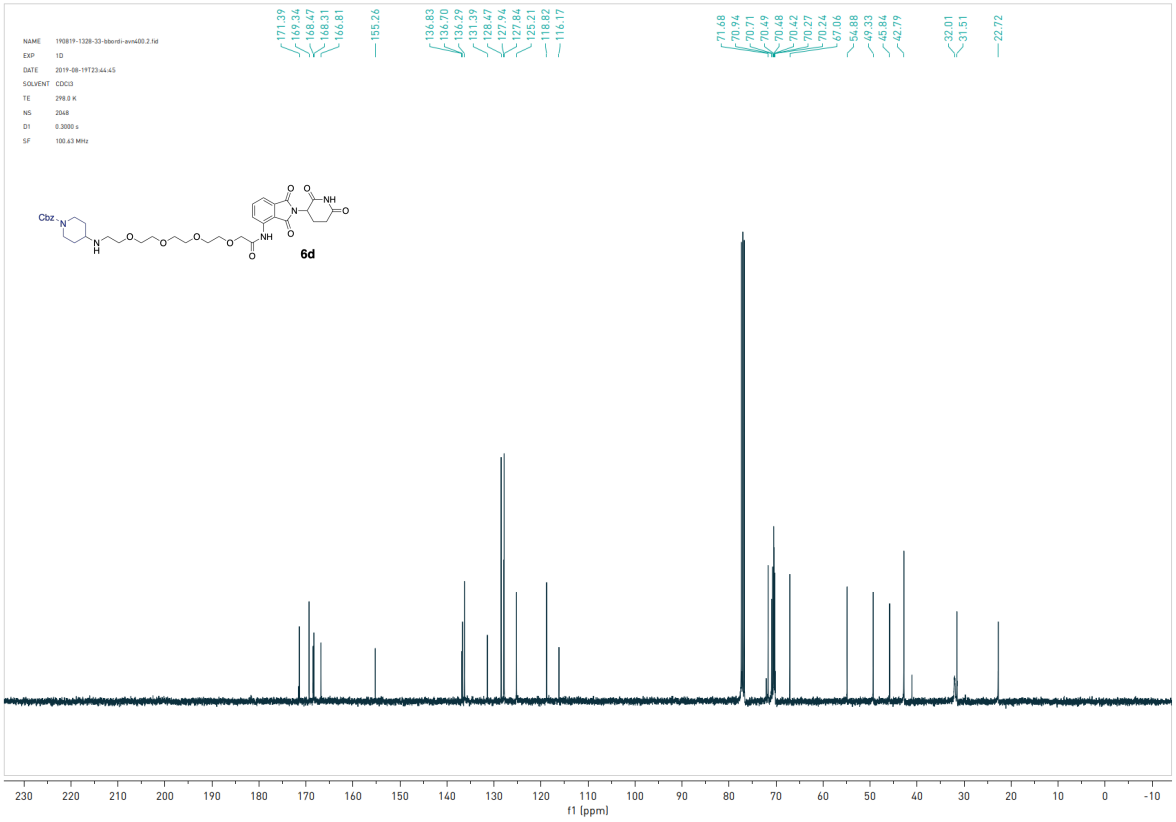
NMR of compound **6c**:



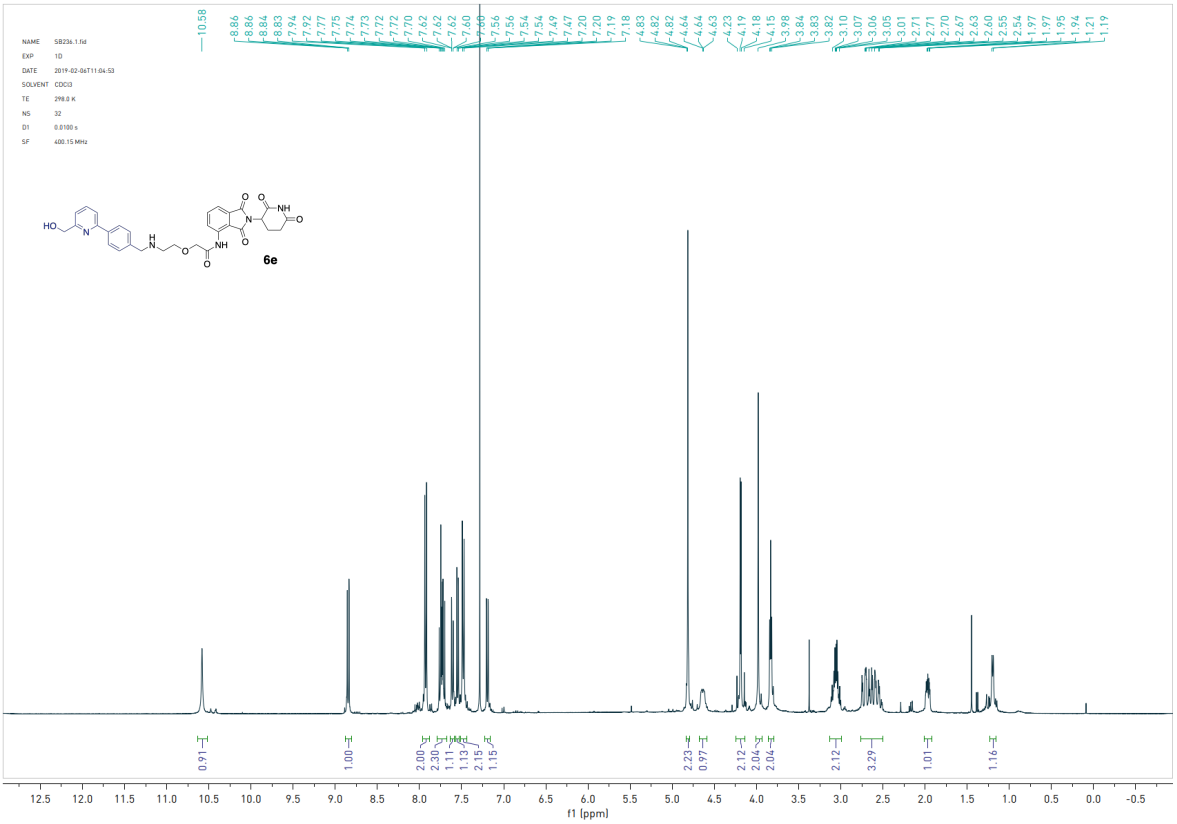



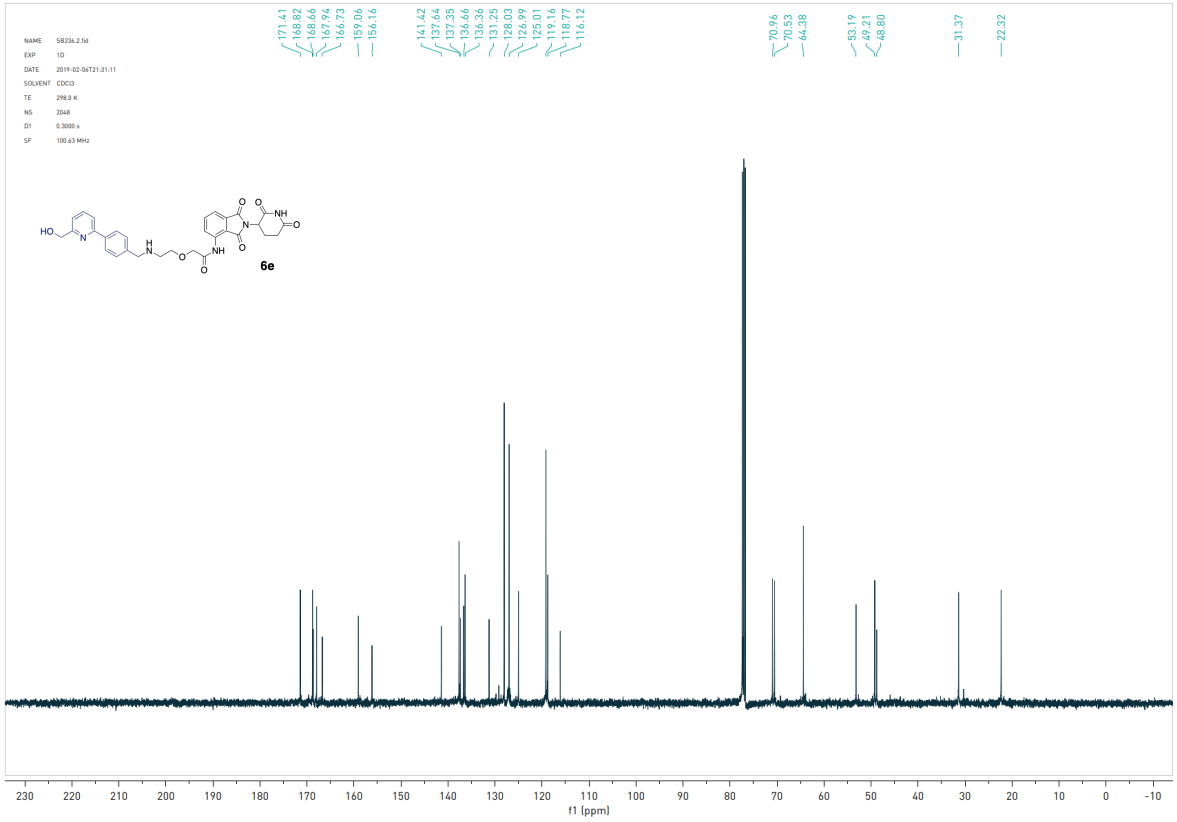
NMR of compound **6d**:



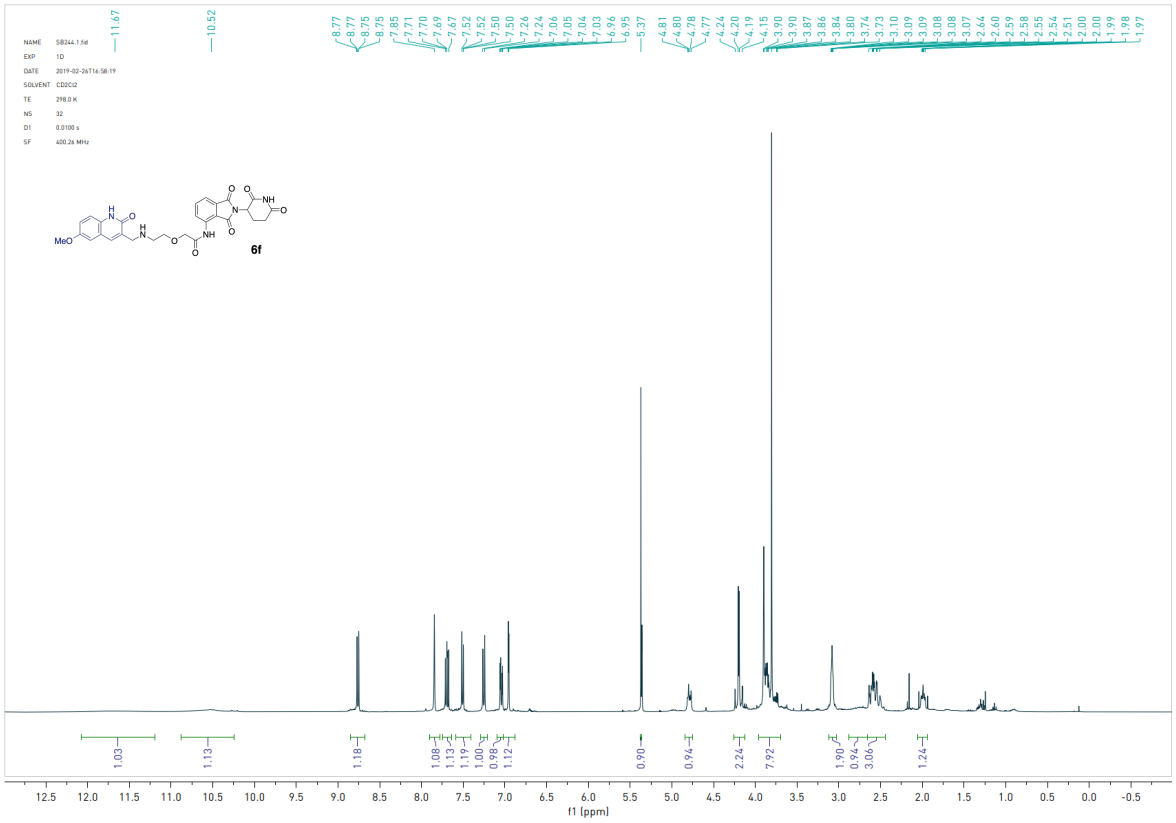



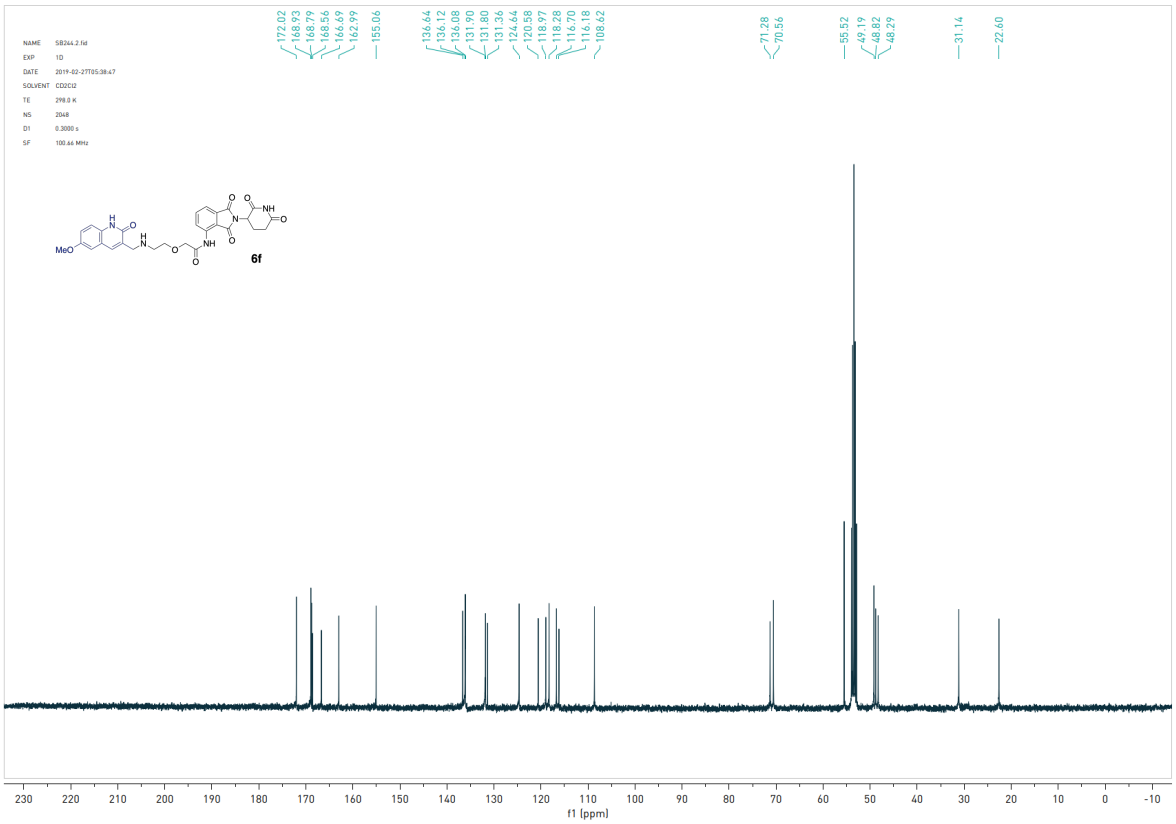
NMR of compound **6e**:



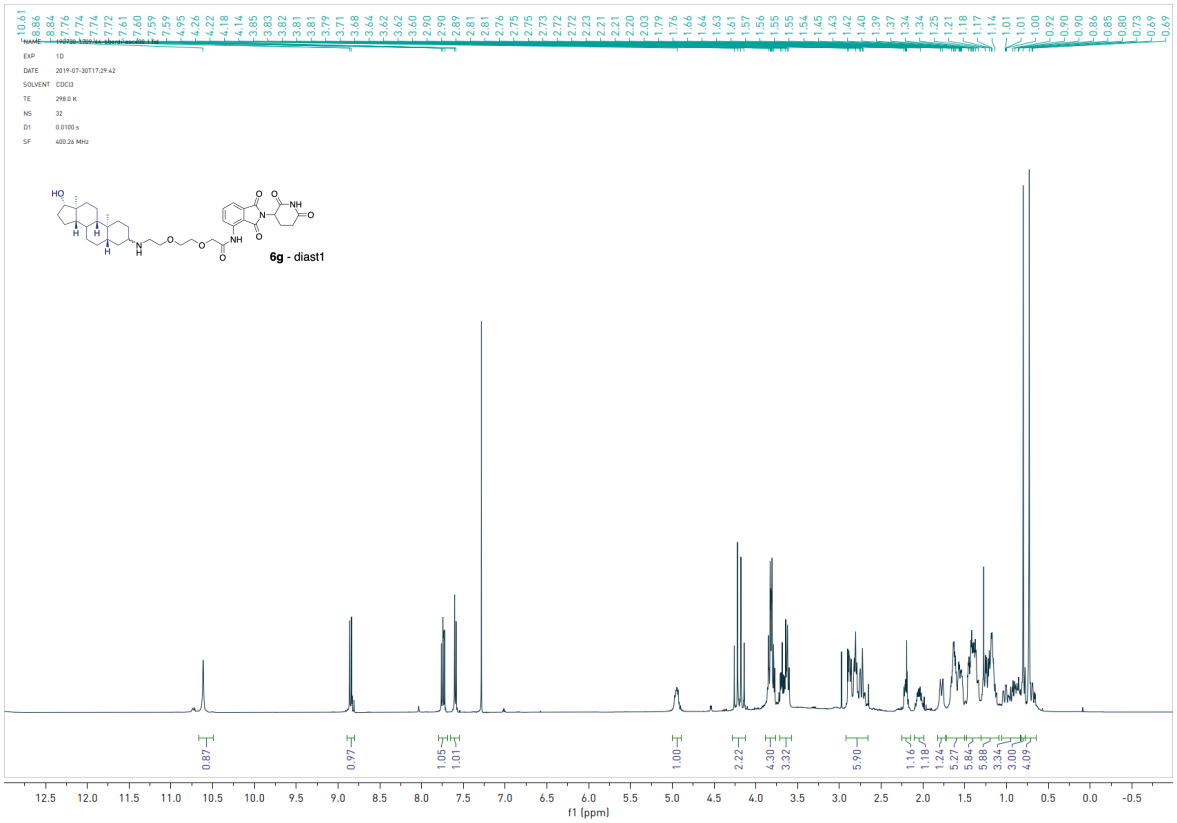



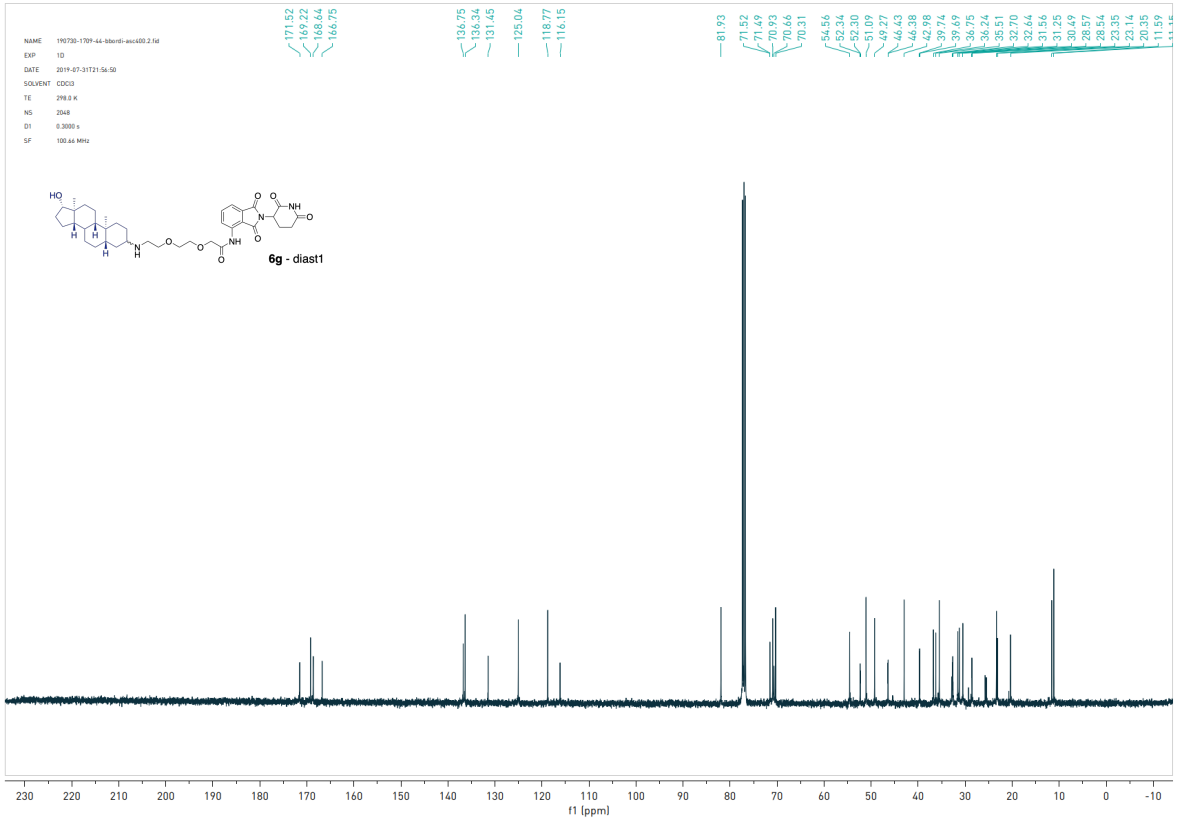
NMR of compound **6f**:

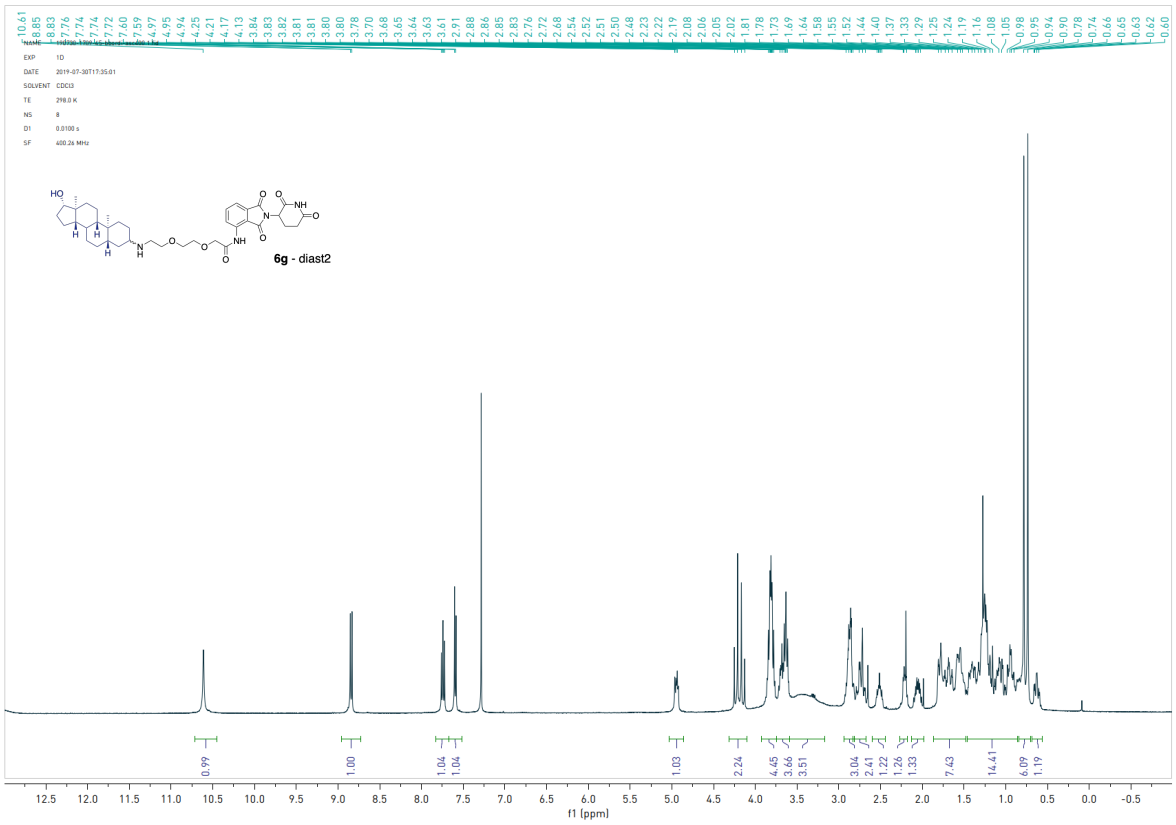


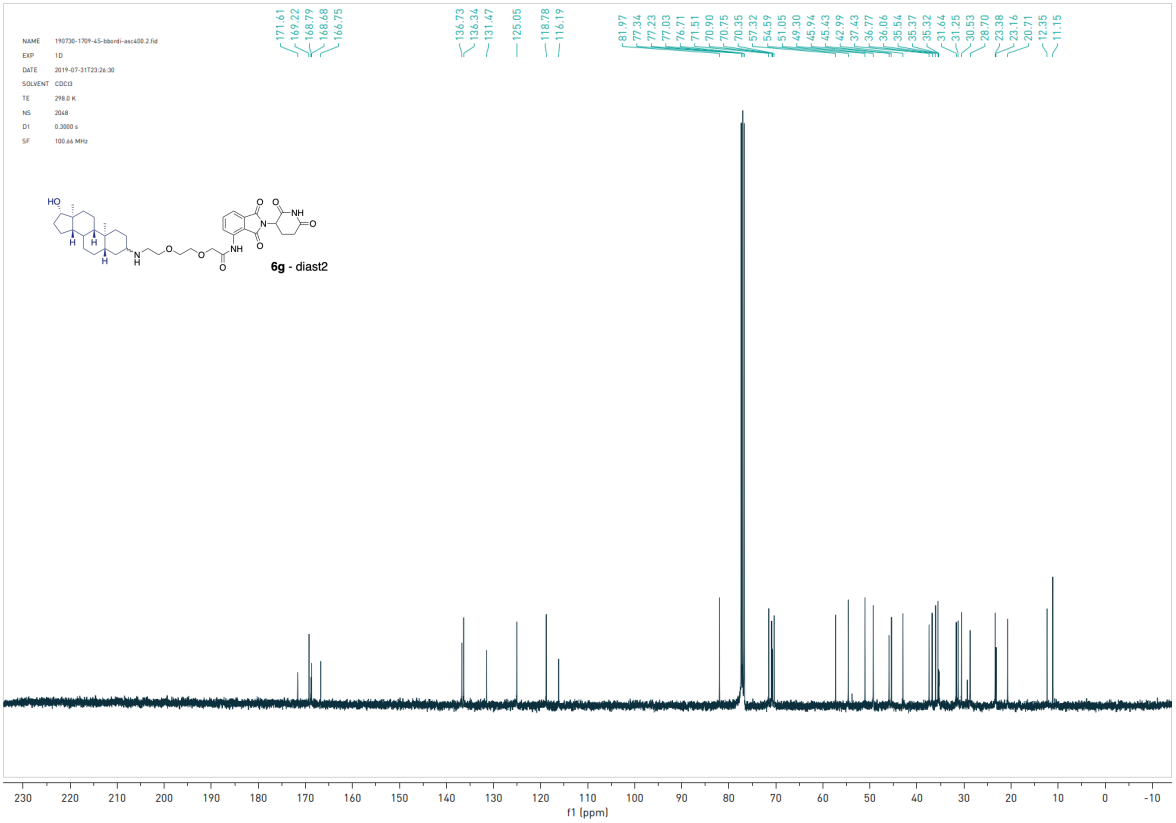



NMR of compound **6g** (2 diastereoisomers):

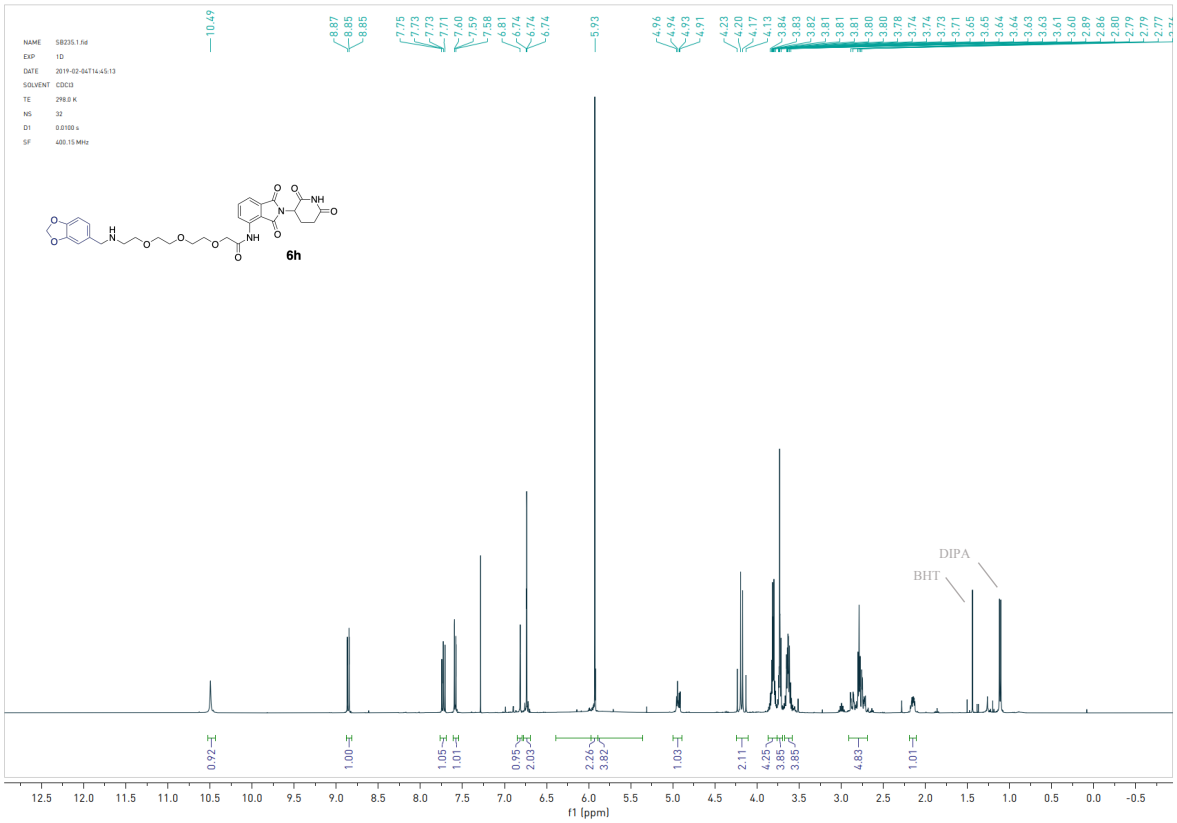


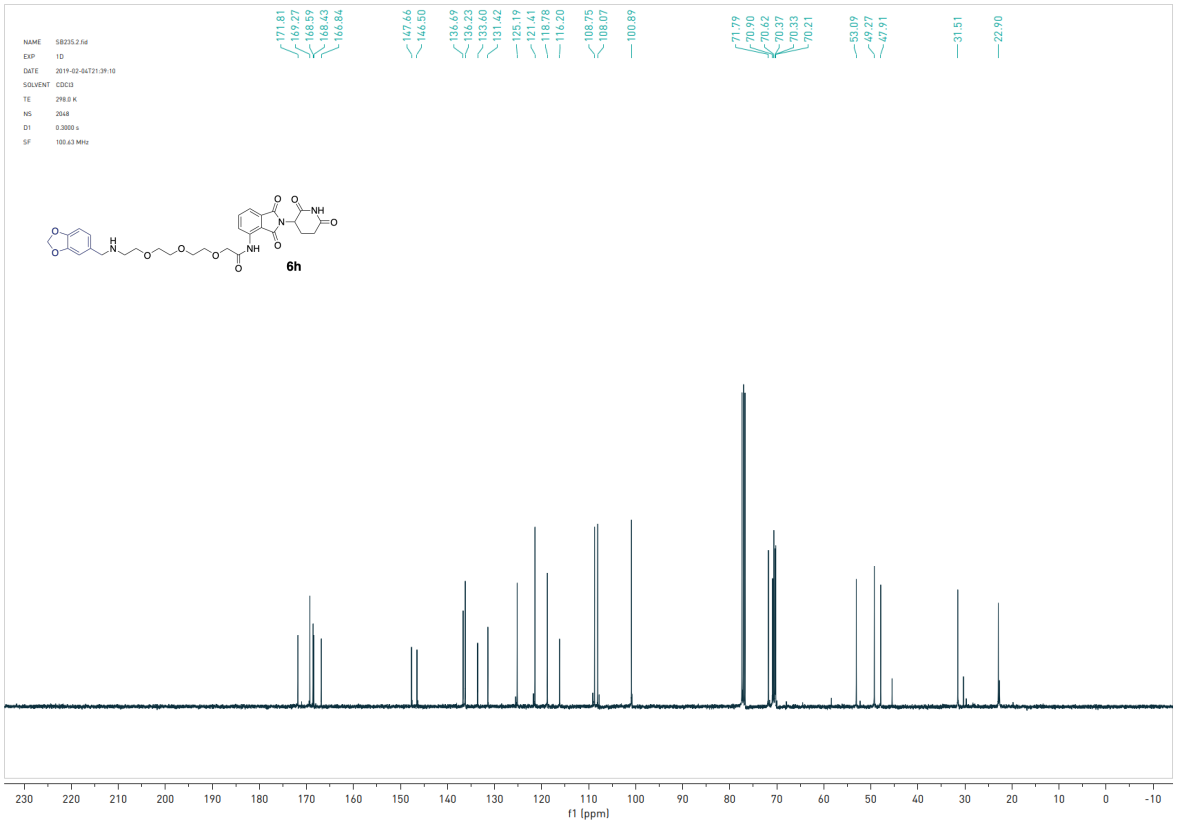




EXP 1D
DATE 2019-07-30T17:35:01
SOLVENT CDCl3
TE 298.0 K
NS 8
D1 0.0100 s
SF 400.26 MHz
6g - diast2
f1 (ppm)

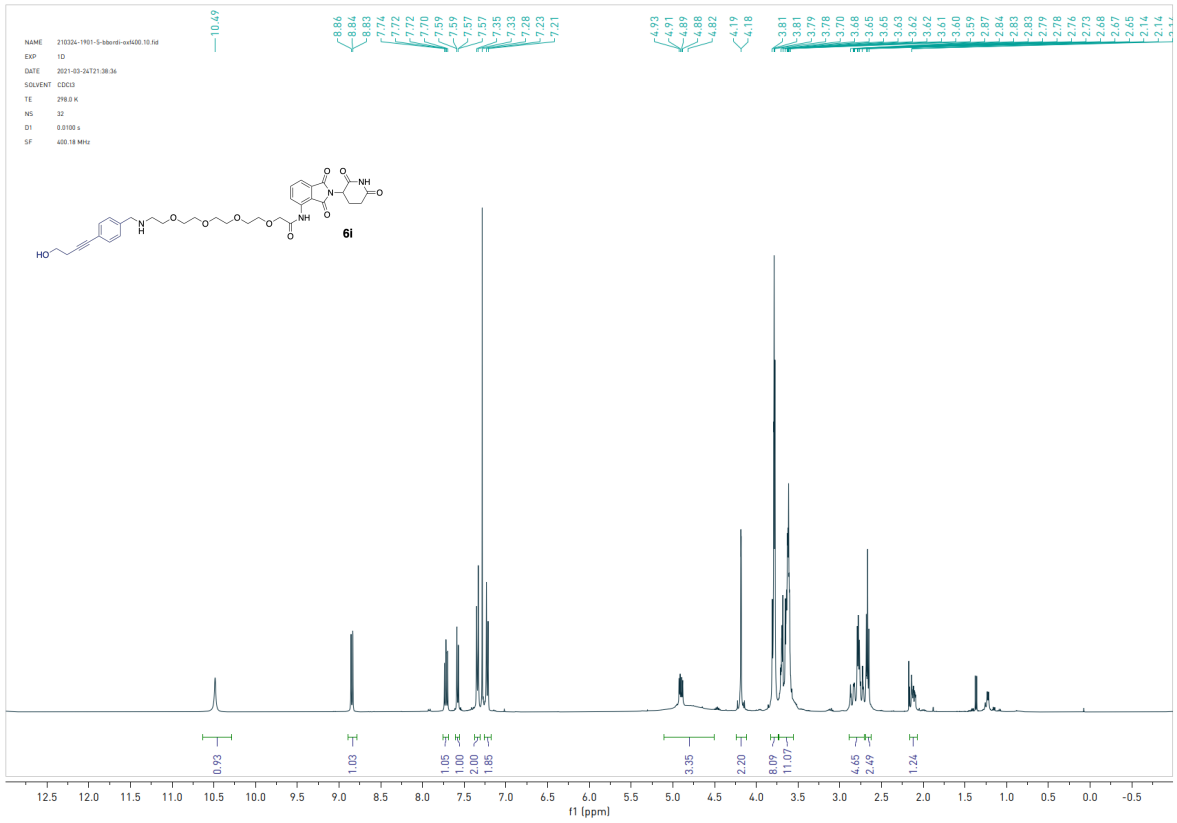

NAME 190730-1709-45-bbordi-asc400.2.fid
EXP 1D
DATE 2019-07-31T23:24:30
SOLVENT CDCl3
TE 298.0 K
NS 2048
D1 0.3000 s
SF 100.66 MHz
6g - diast2
f1 (ppm)

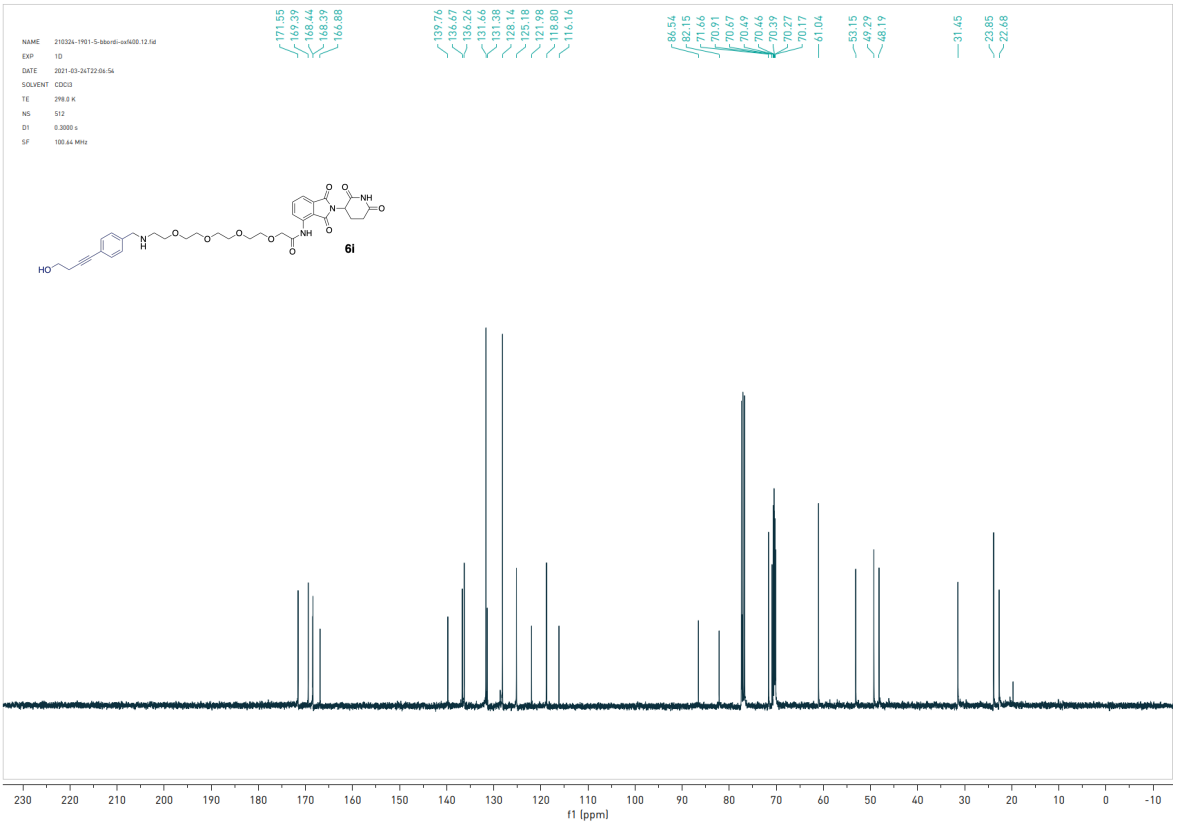
NMR of compound **6h**:



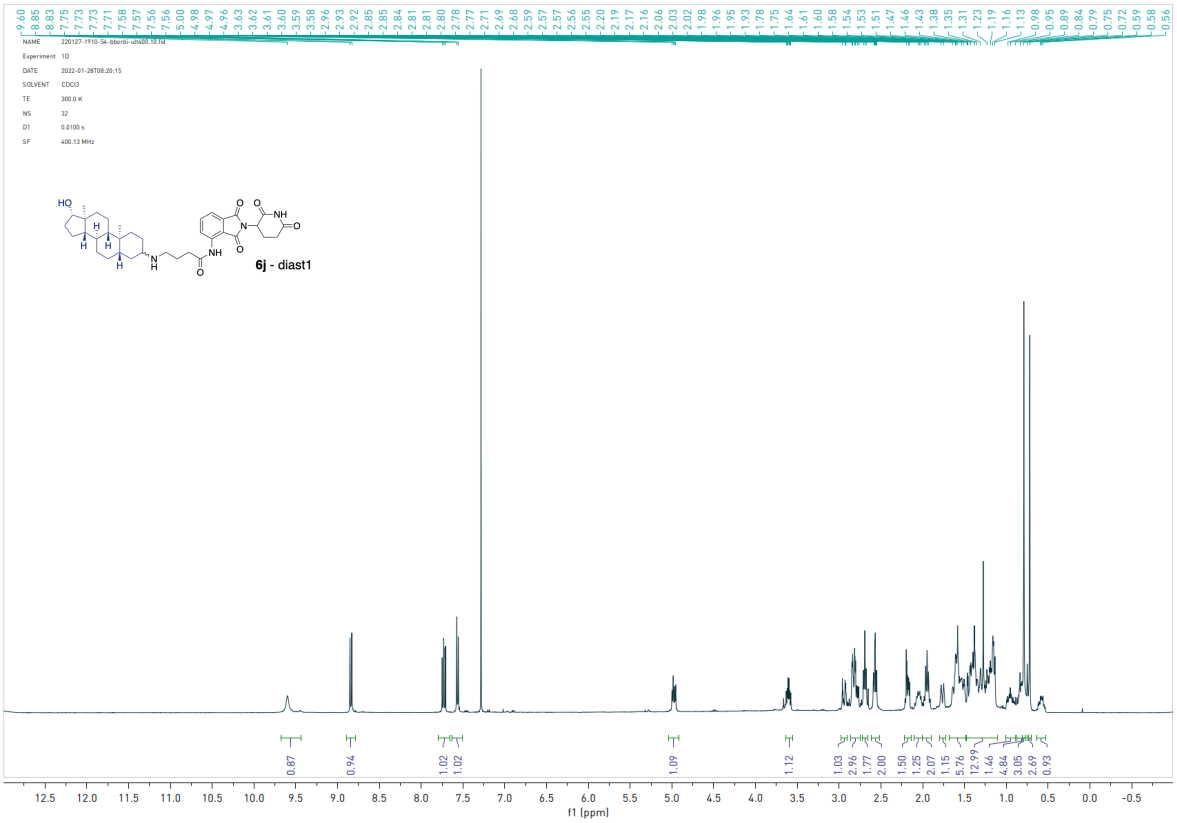



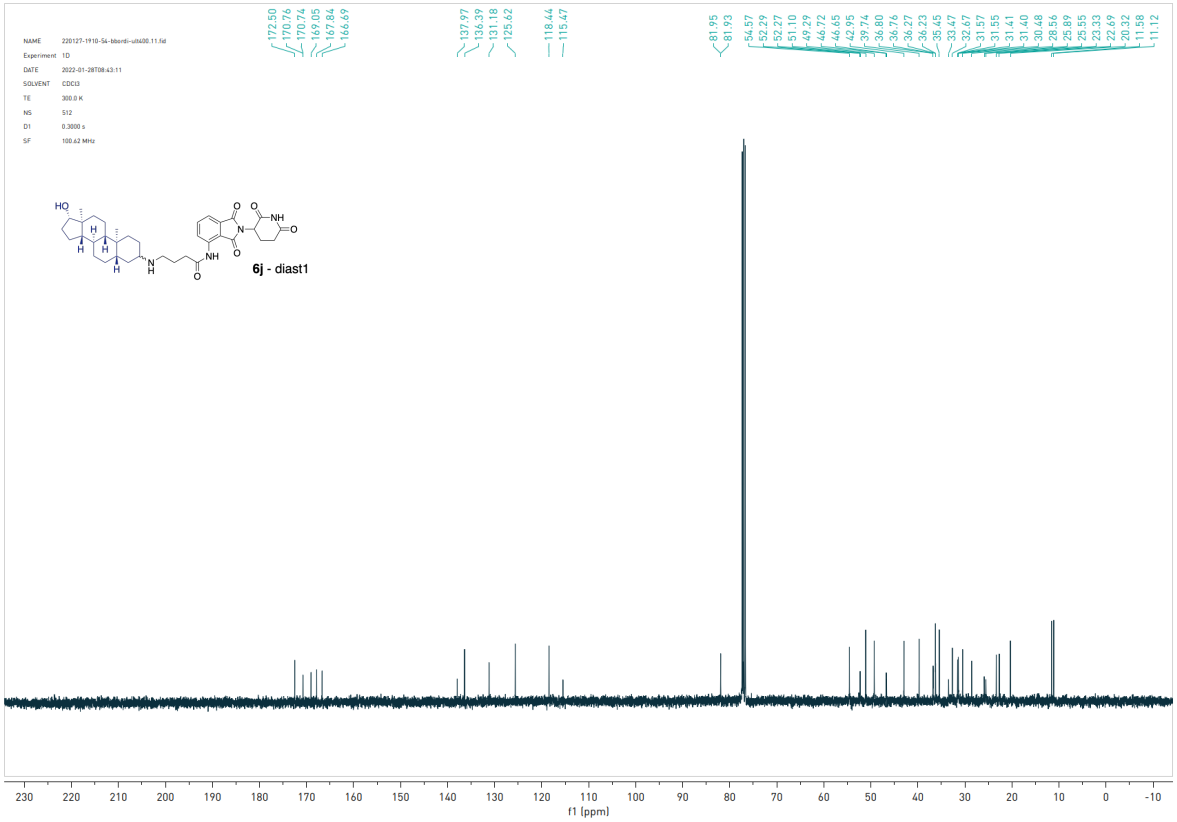
NMR of compound **6i**:

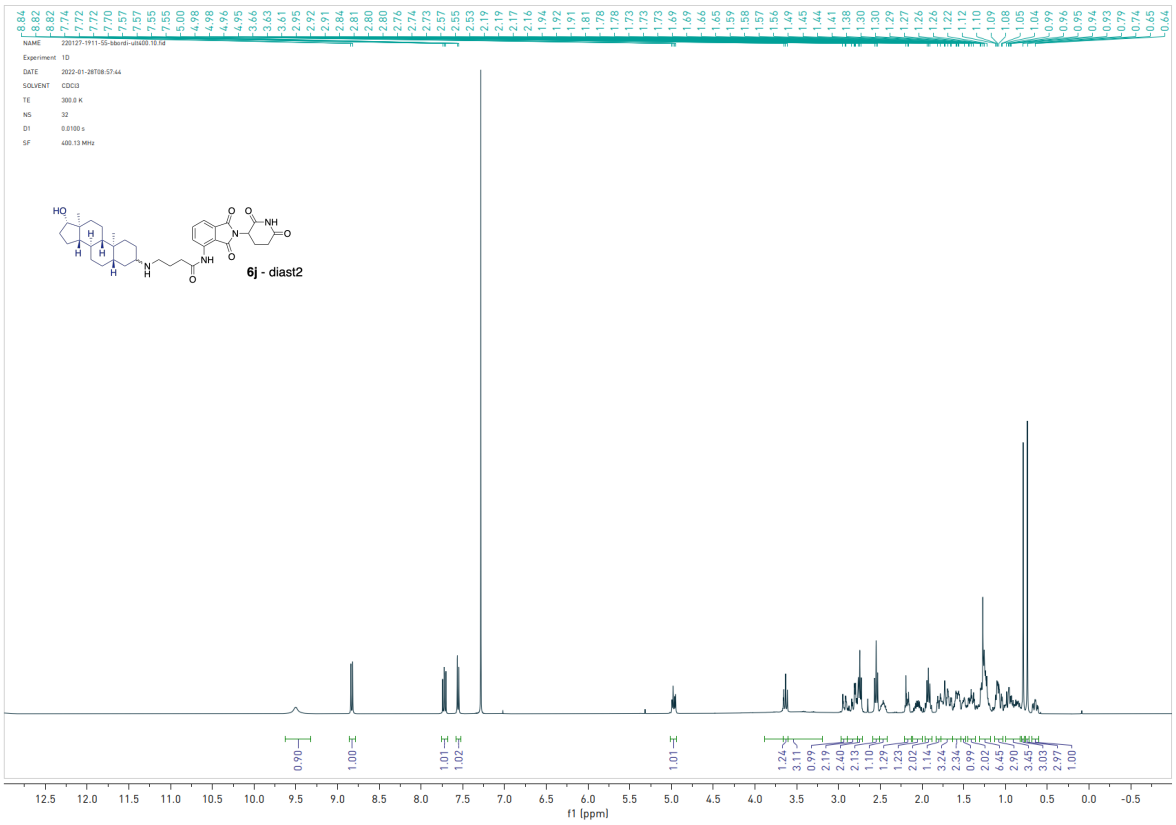


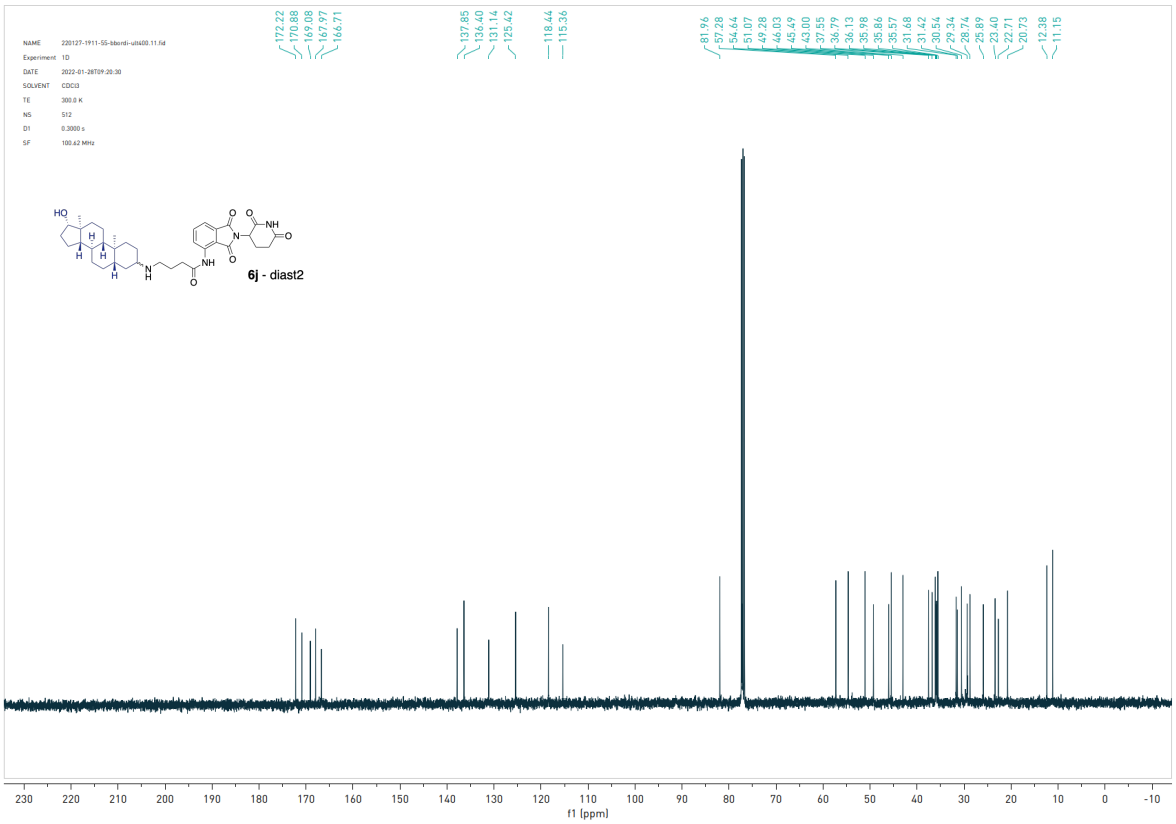



NMR of compound **6j** (2 diastereoisomers):

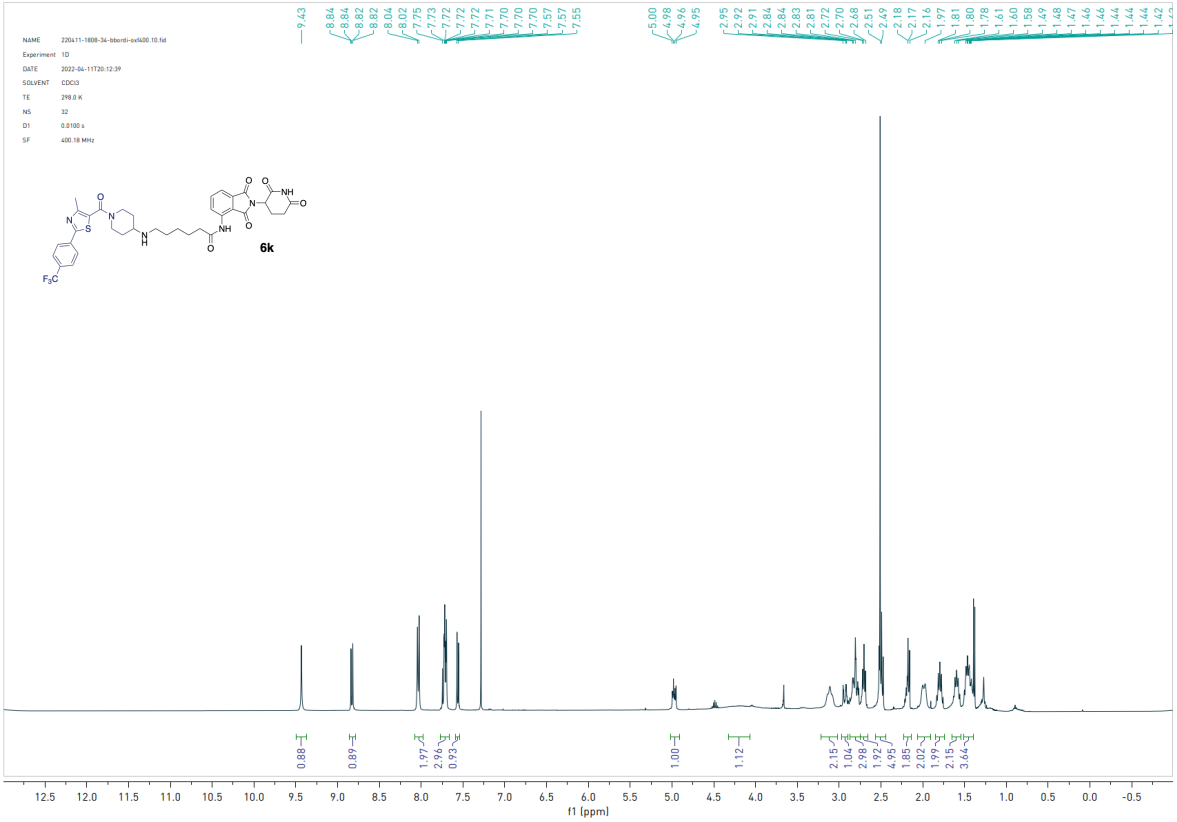


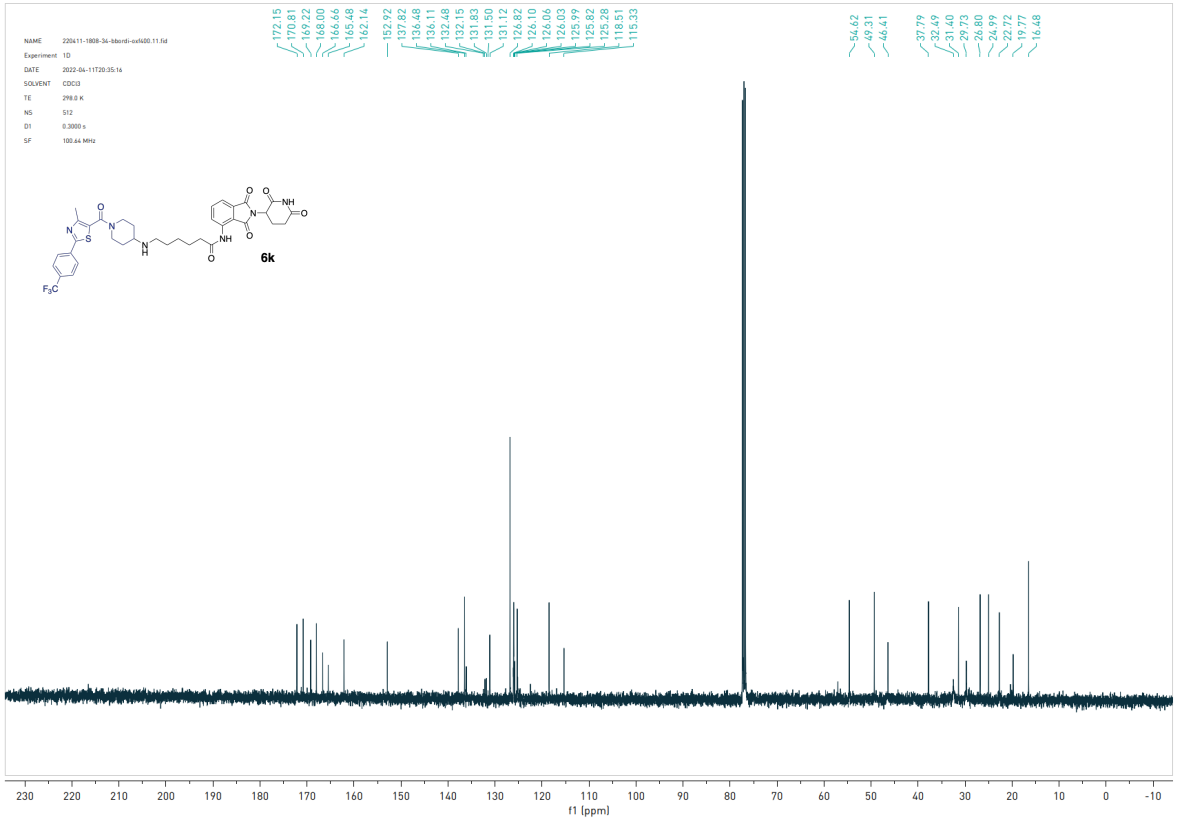




NAME 220127-1911-5S-bbordi-ult400.10.fid
Experiment 1D
DATE 2022-01-28T08:57:44
SOLVENT CDCl3
TE 300.0 K
NS 32
D1 0.0100 s
SF 400.13 MHz
6j - diast2
f1 (ppm)

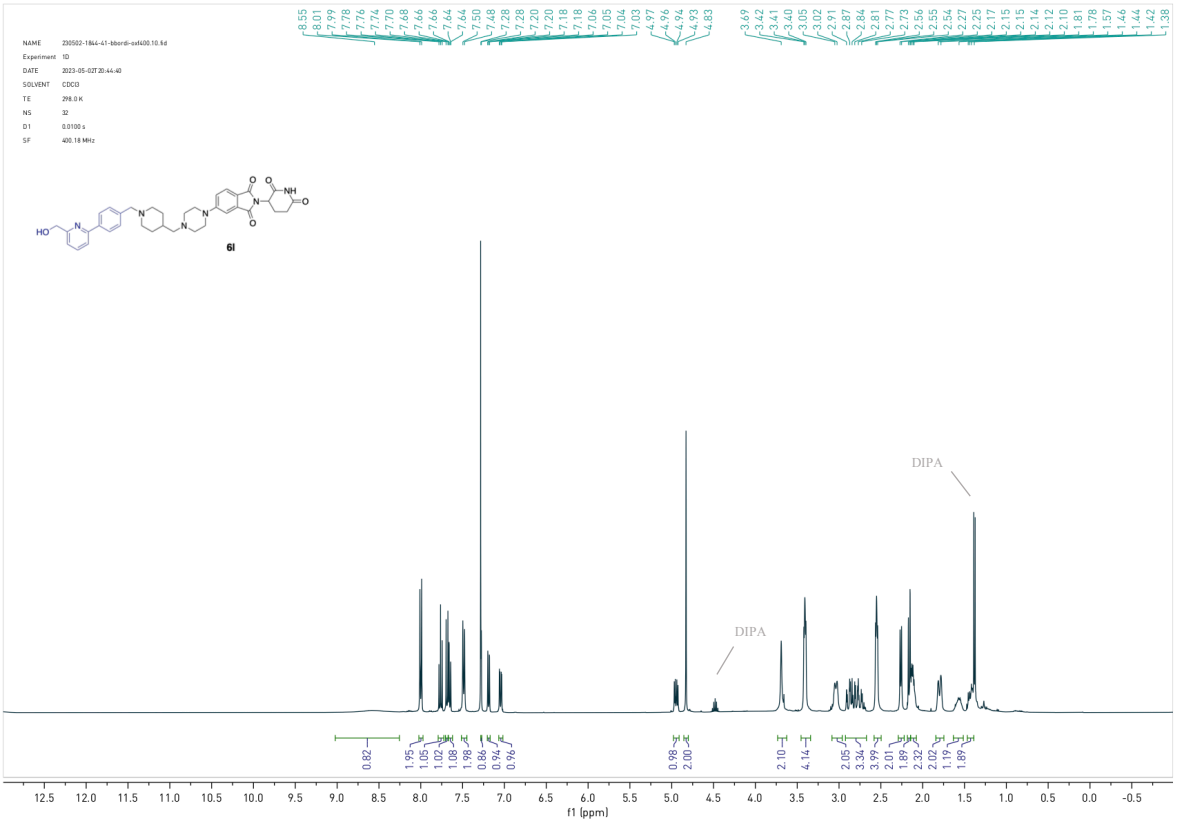

NAME 220127-1911-5S-bbordi-ult400.11.fid
Experiment 1D
DATE 2022-01-28T09:20:30
SOLVENT CDCl3
TE 300.0 K
NS 512
D1 0.3000 s
SF 100.62 MHz
6j - diast2
f1 (ppm)

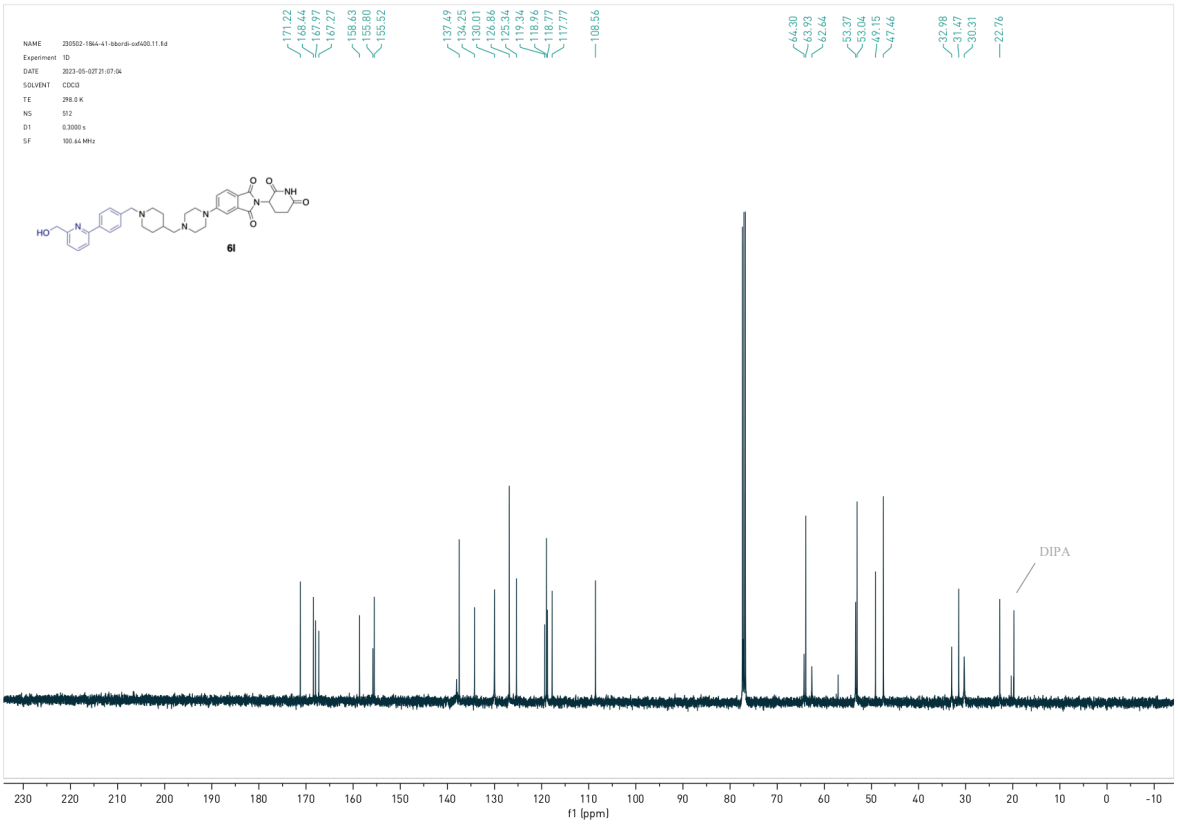
NMR of compound **6k**:



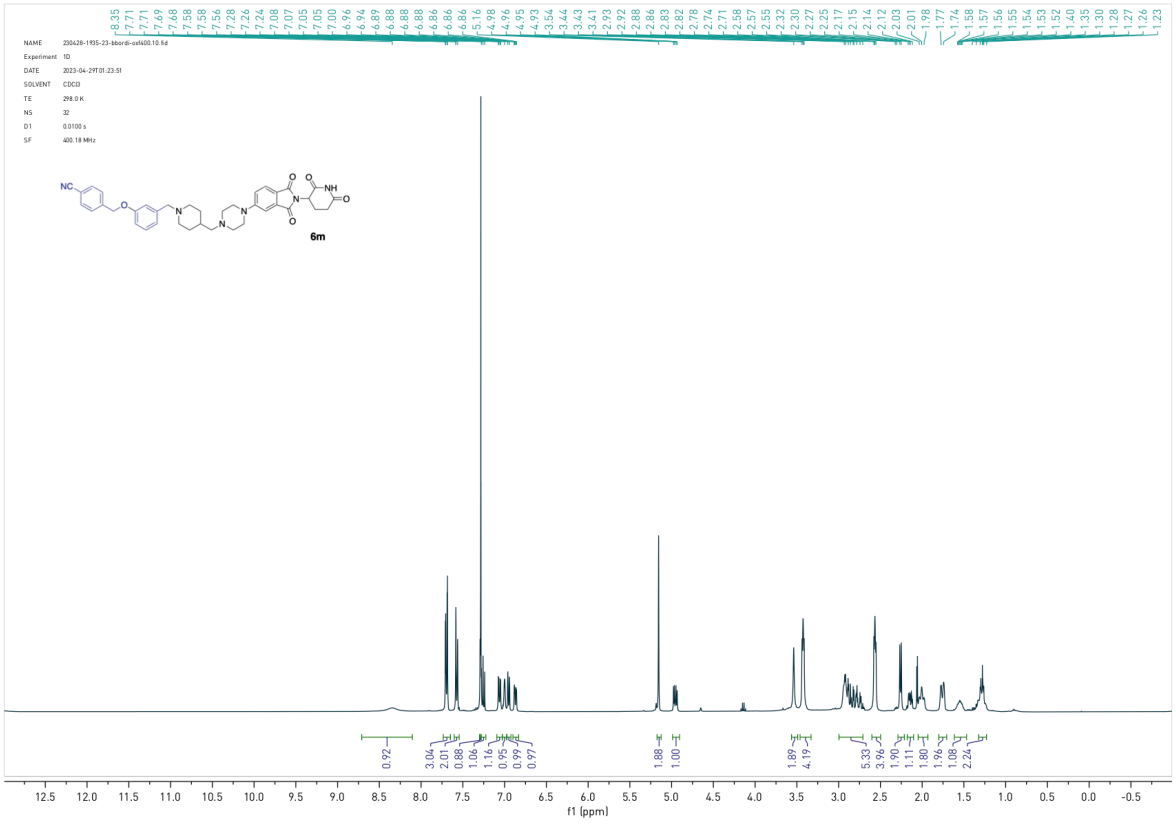



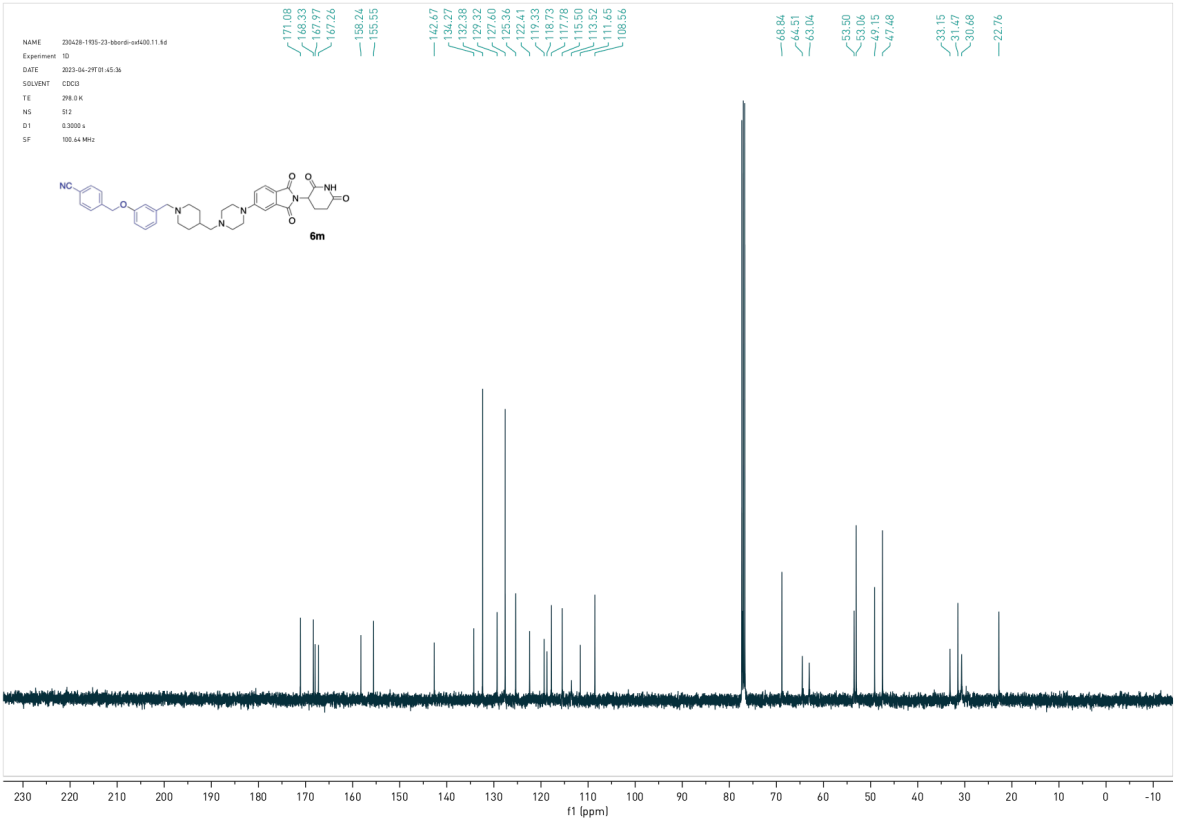
NMR of compound **6l**:



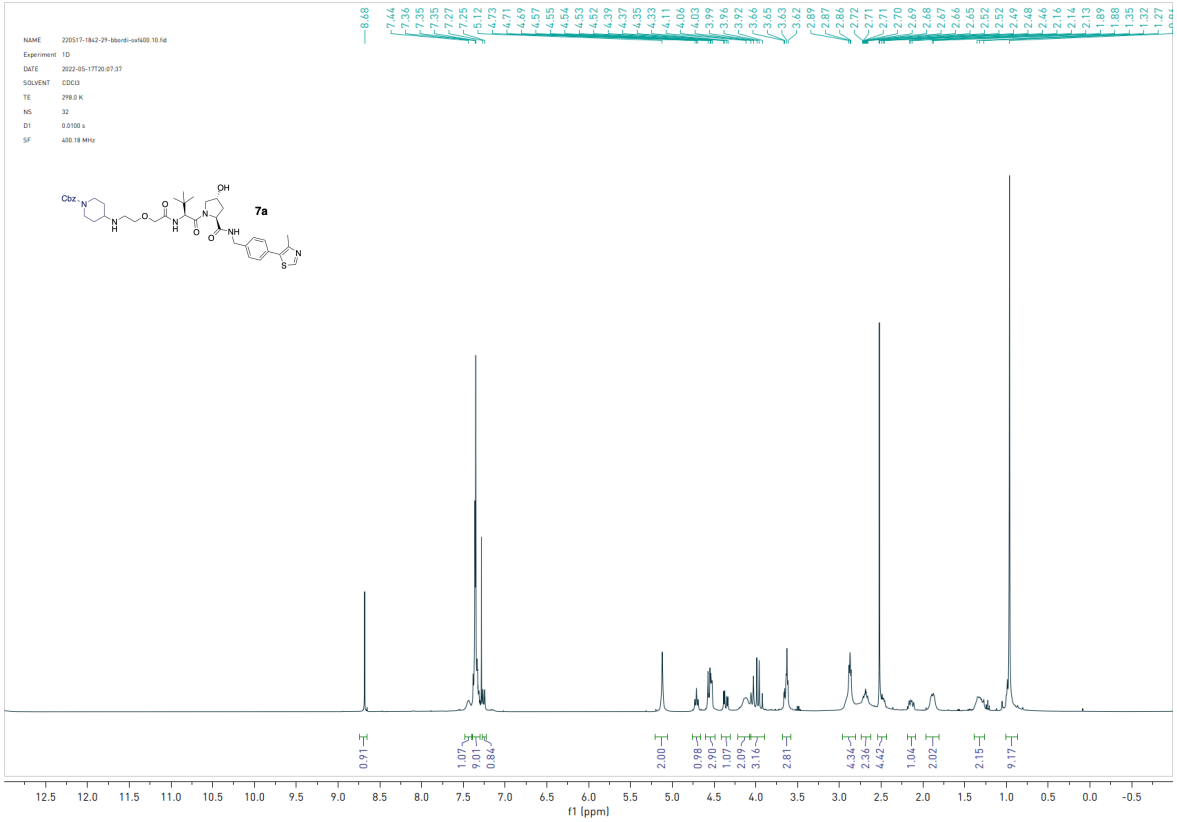



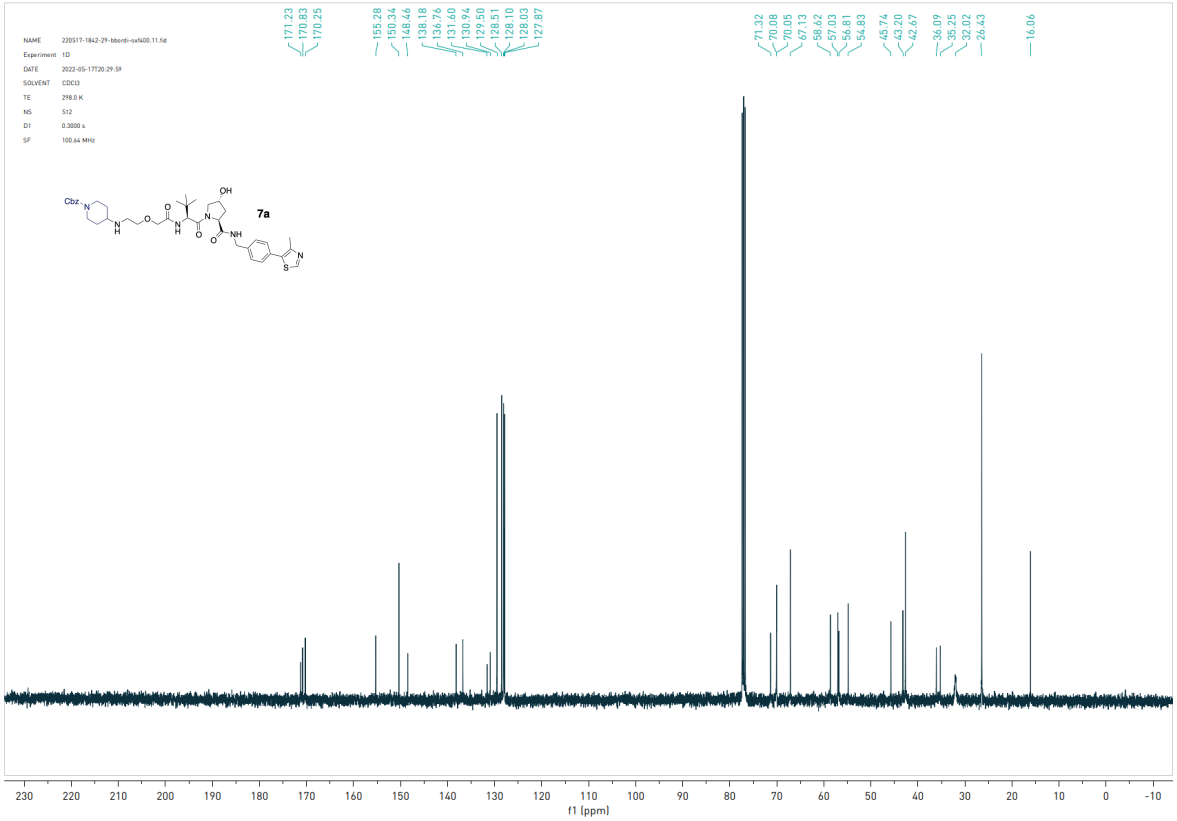
NMR of compound **6m**:



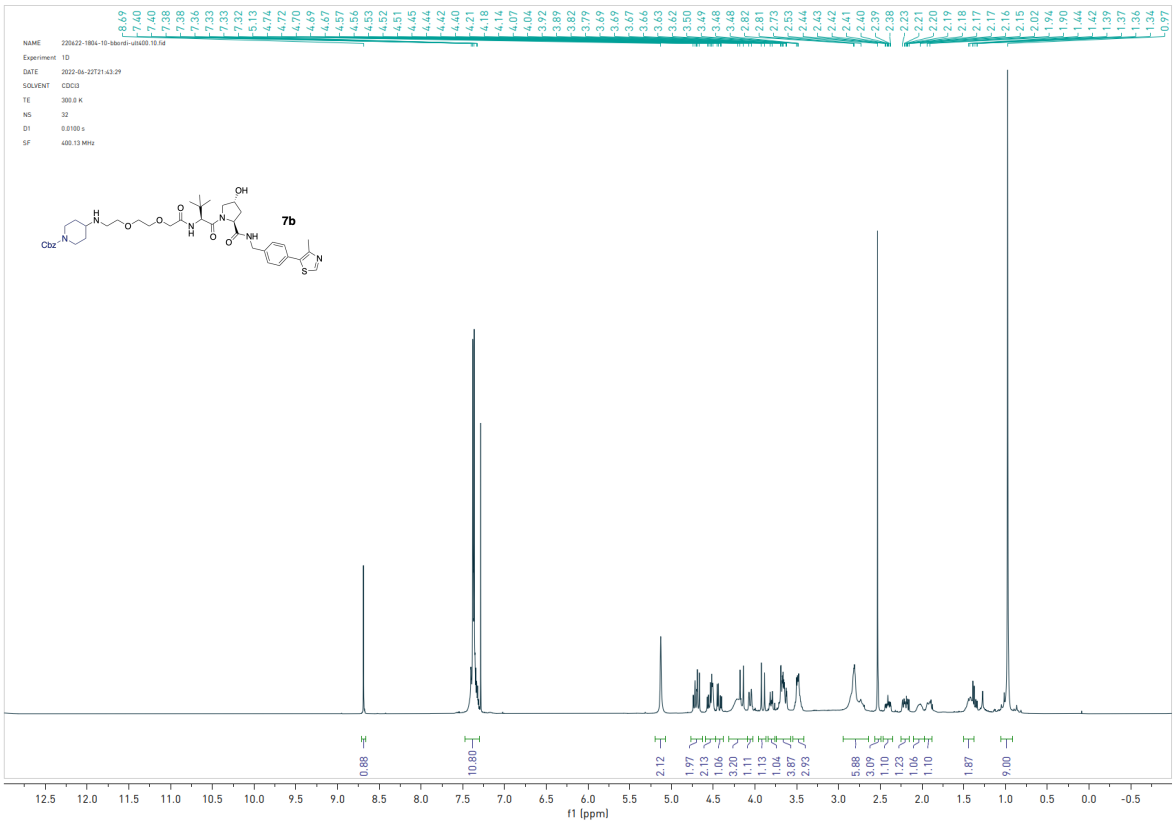



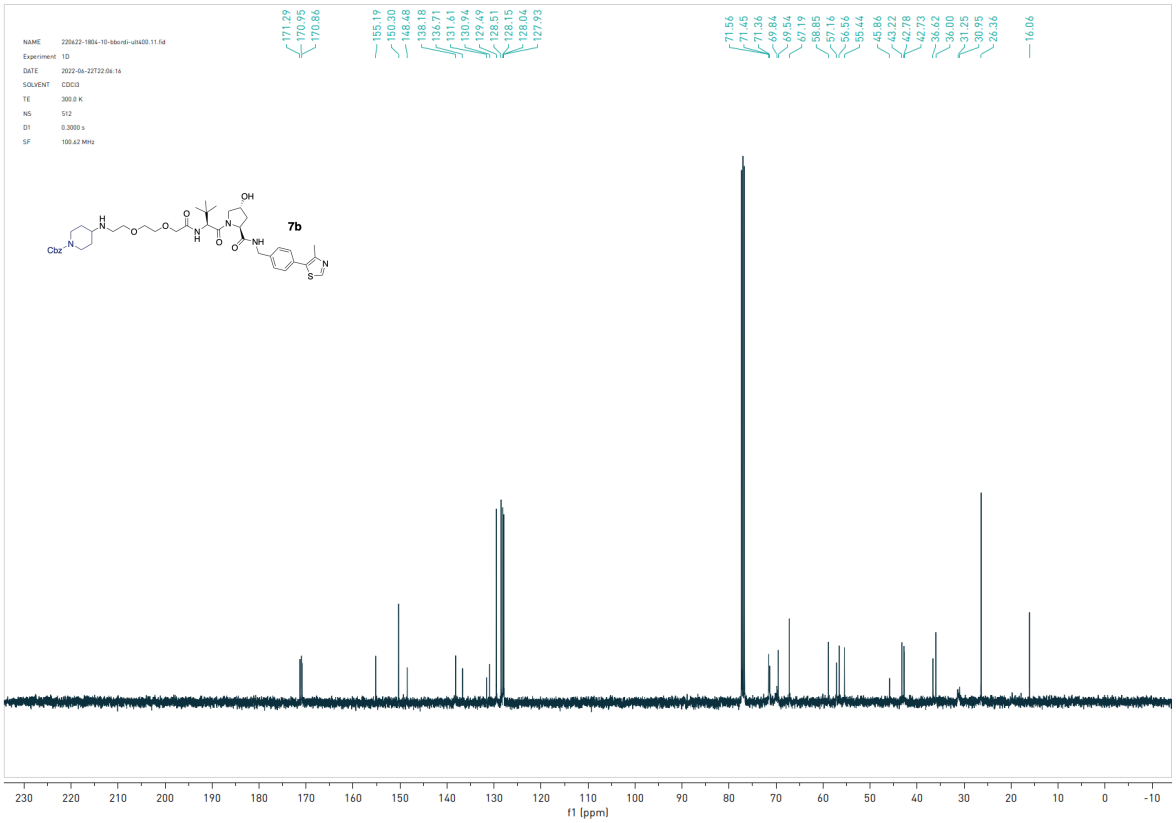
NMR of compound **7a**:



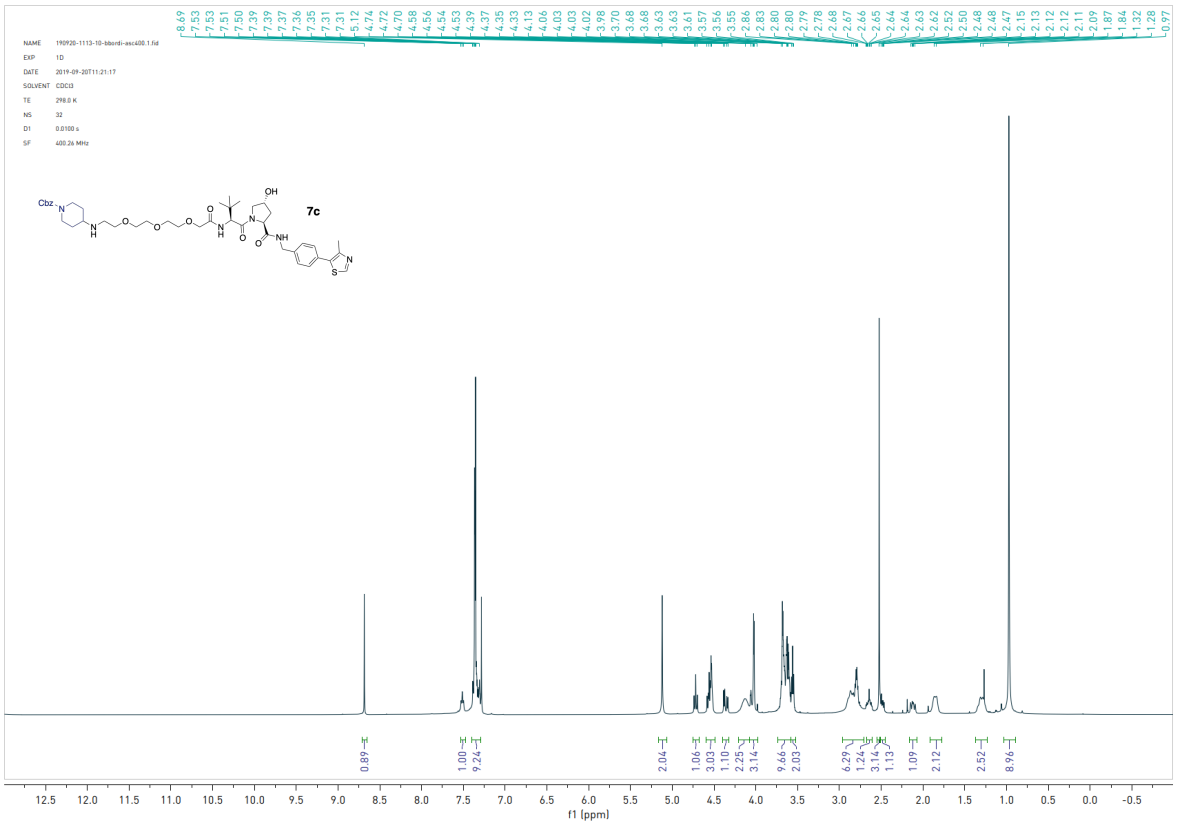



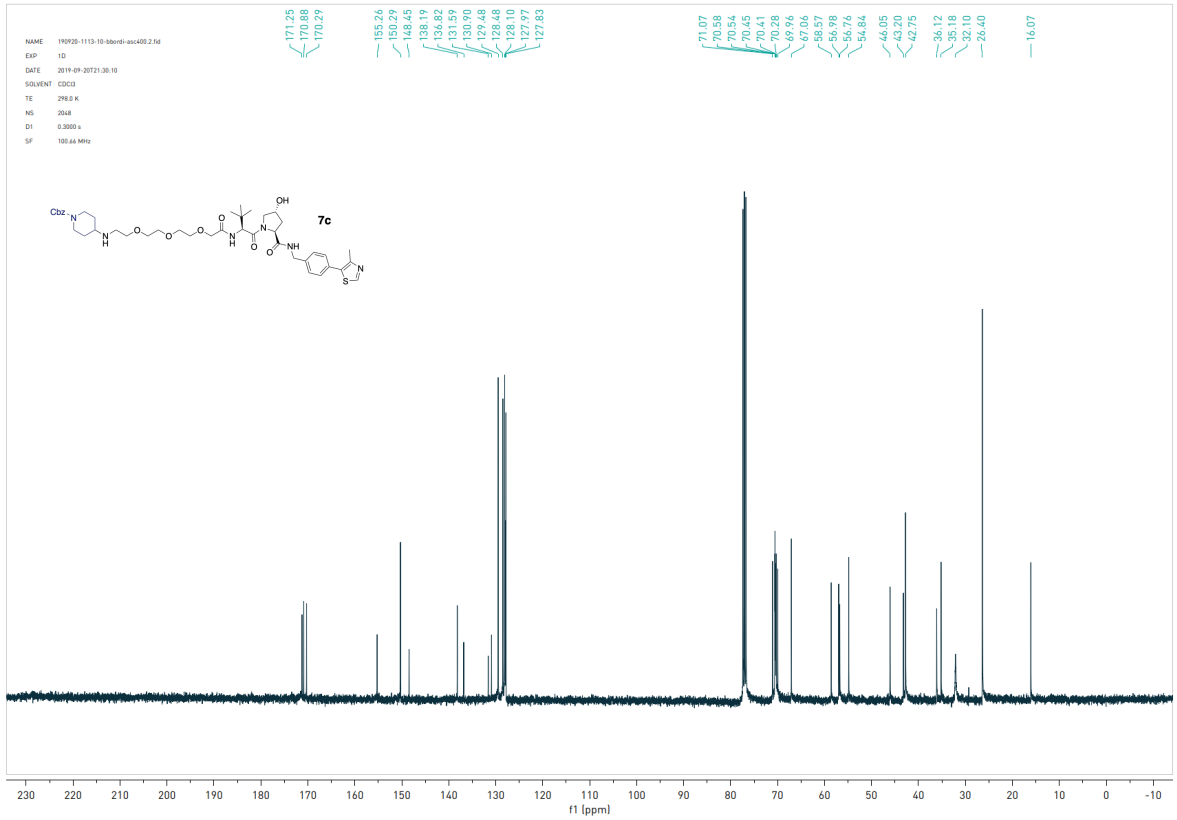
NMR of compound **7b**:



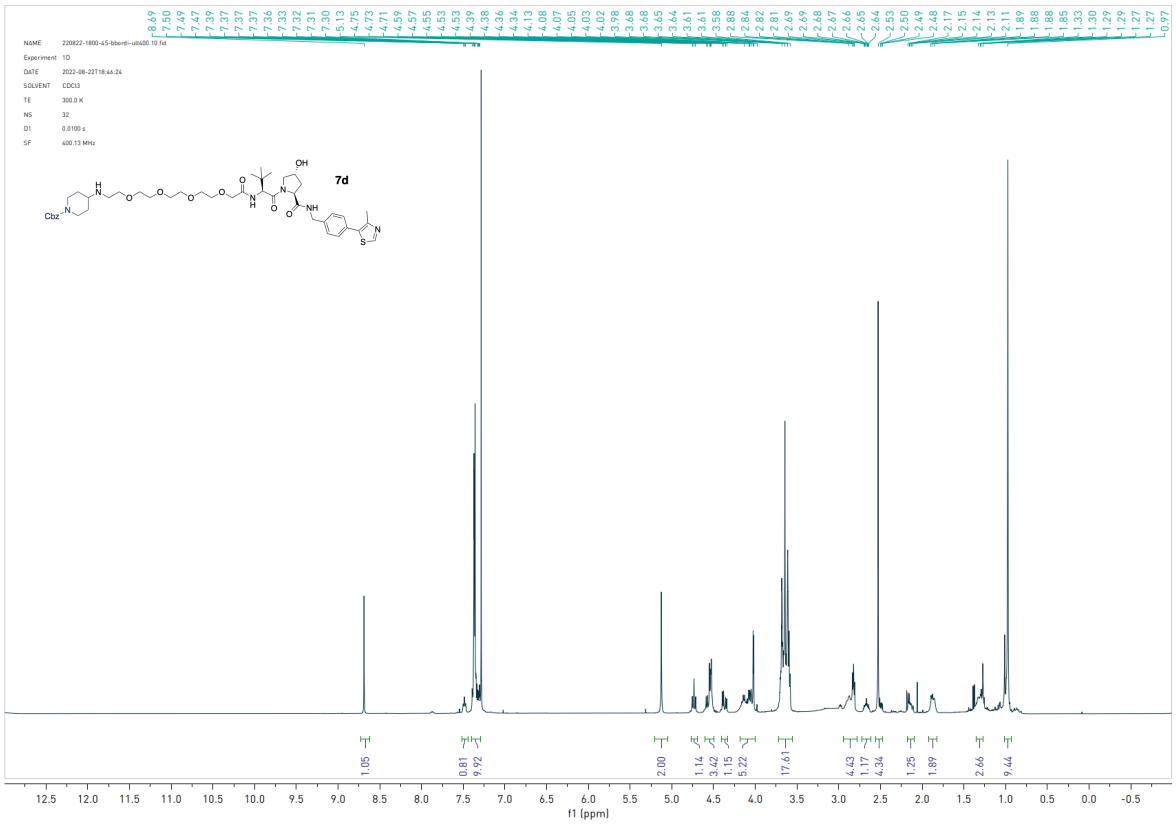



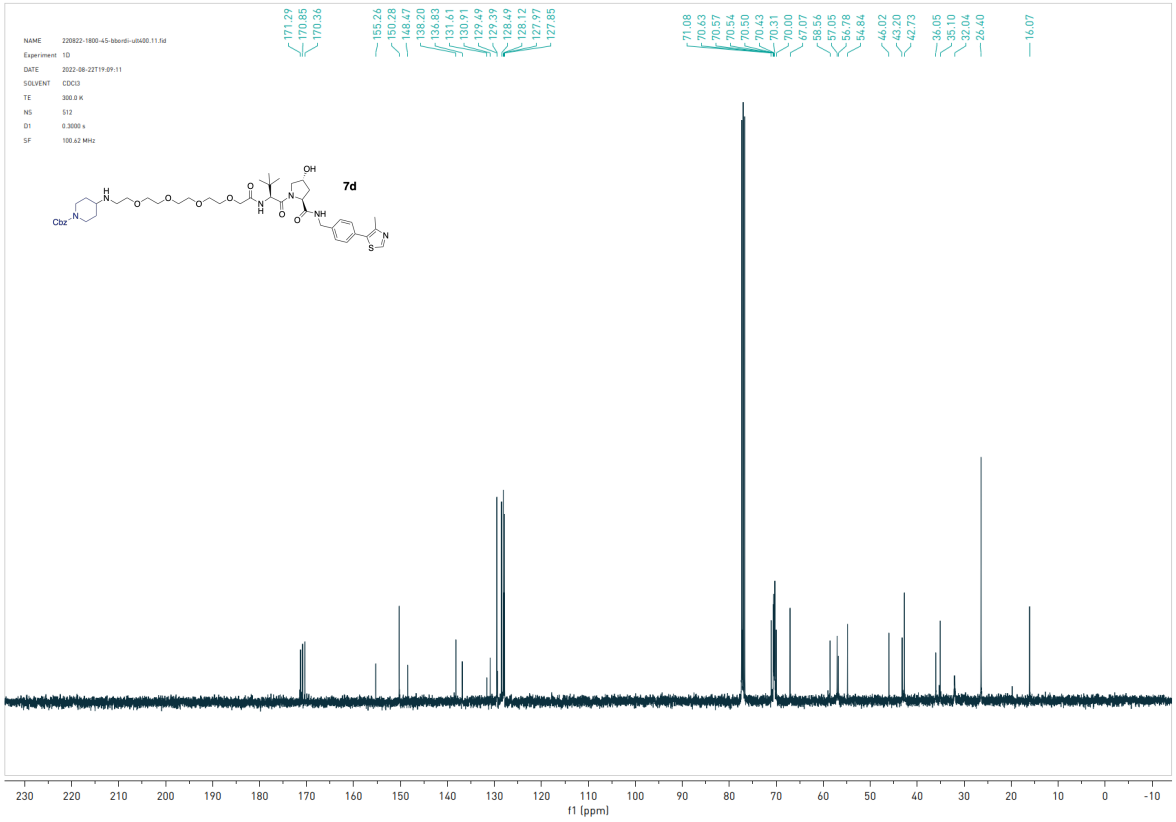
NMR of compound **7c**:



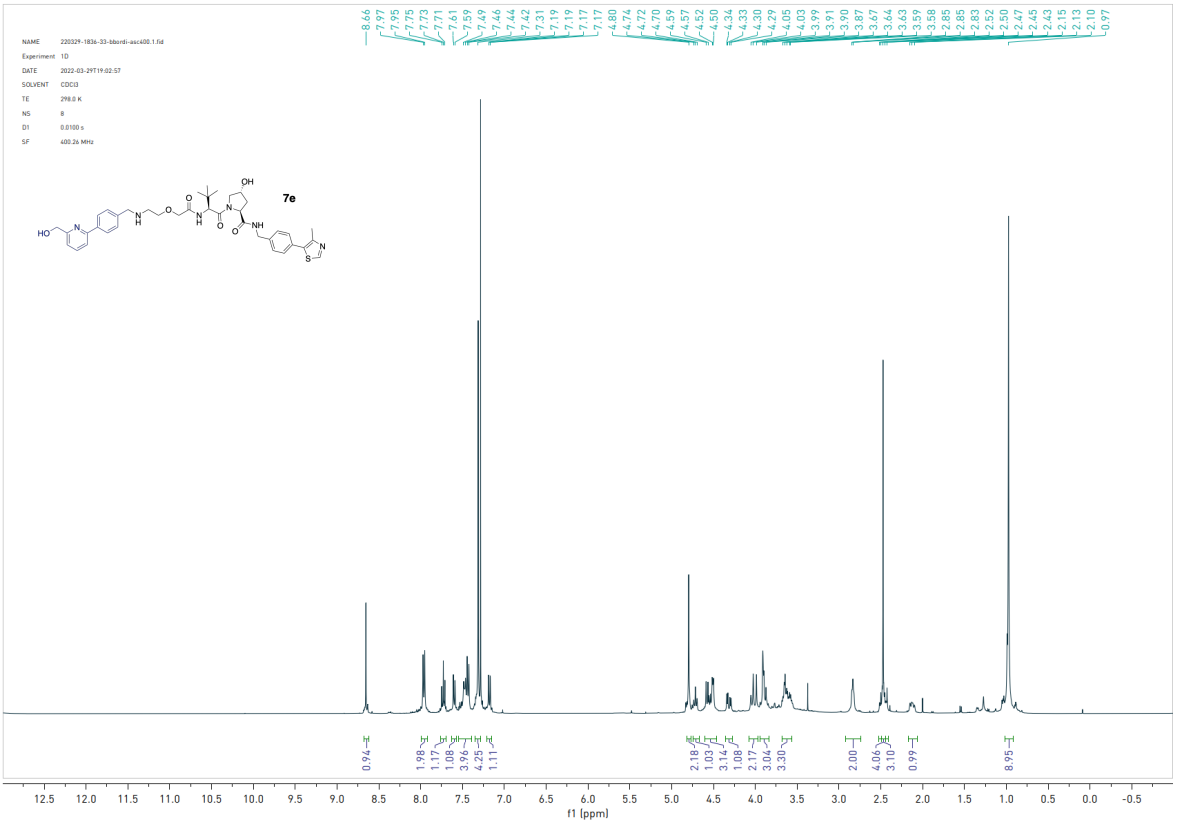



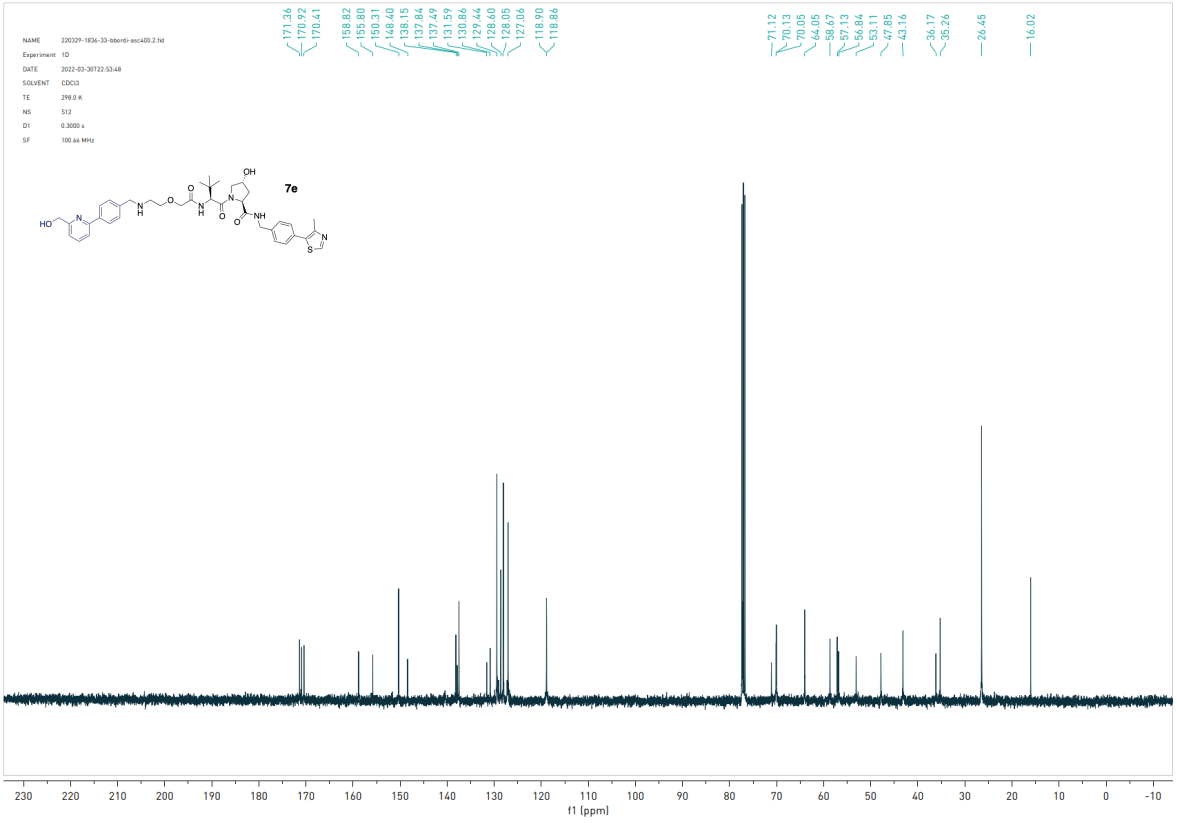
NMR of compound **7d**:



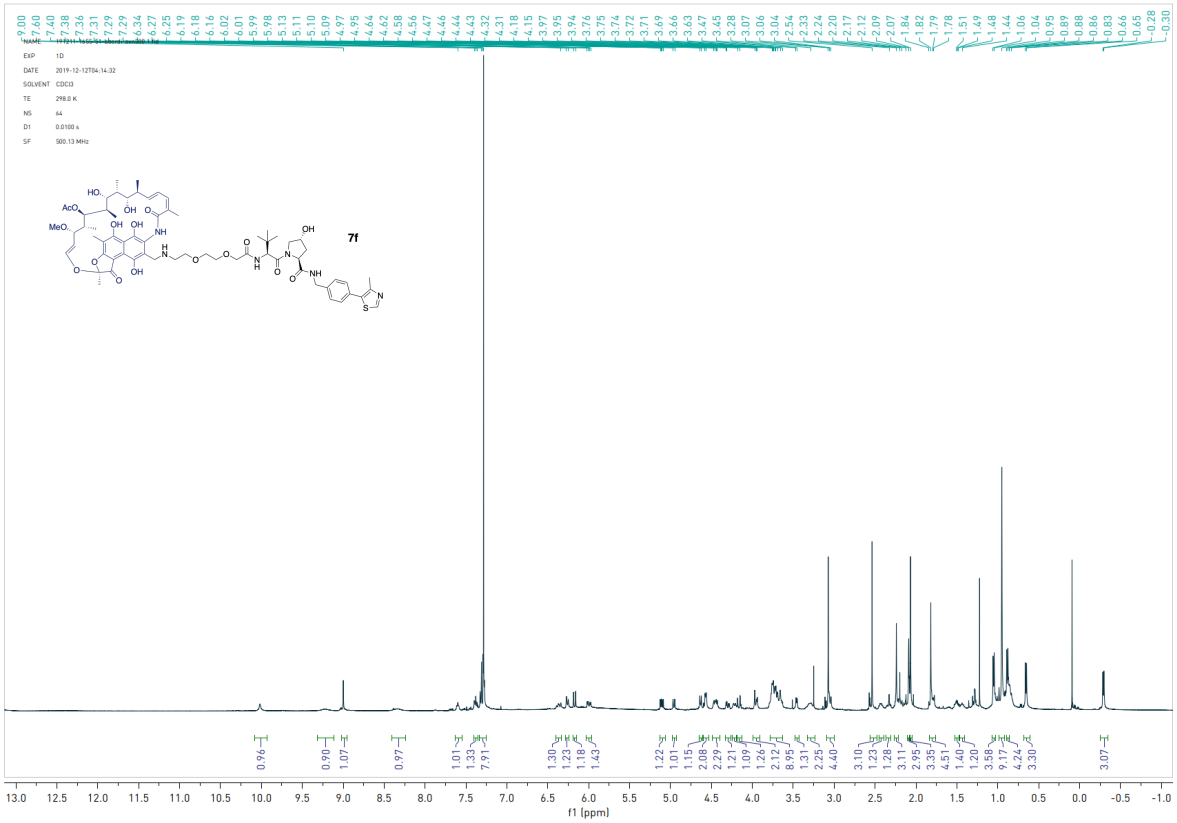



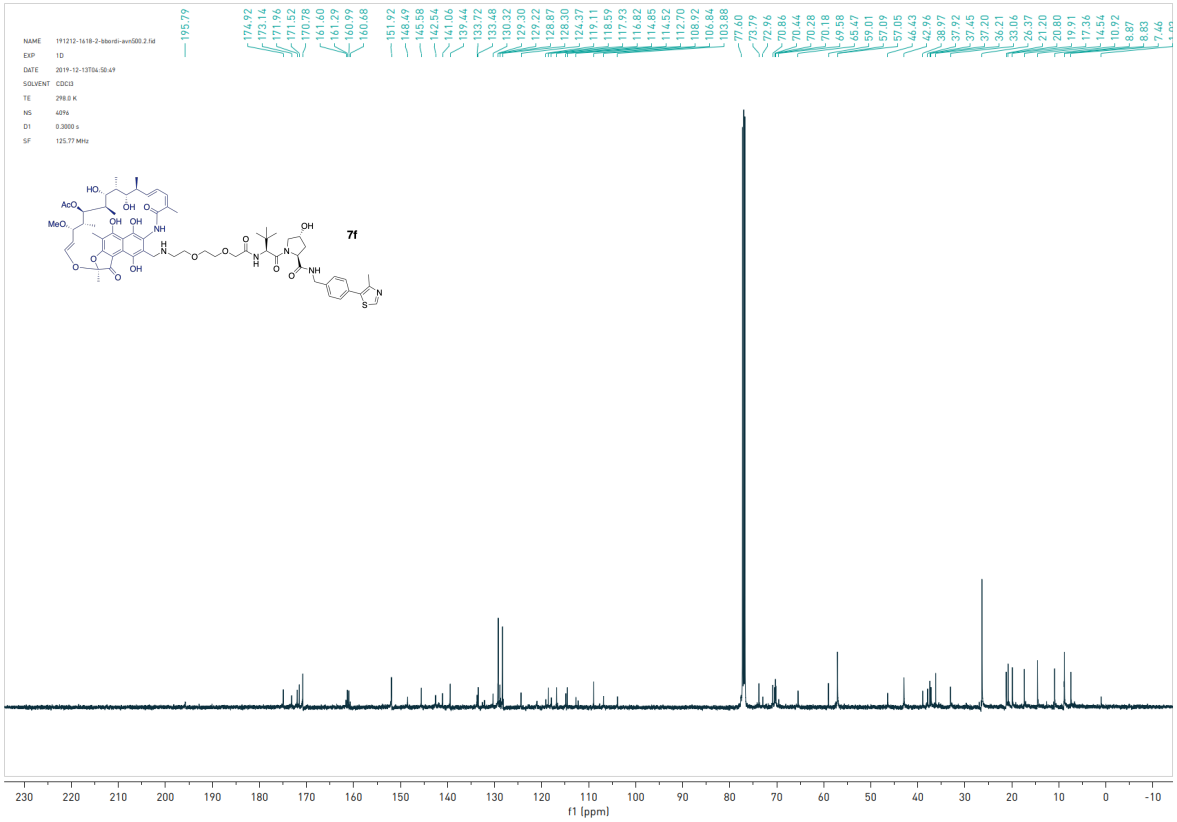
NMR of compound **7e**:



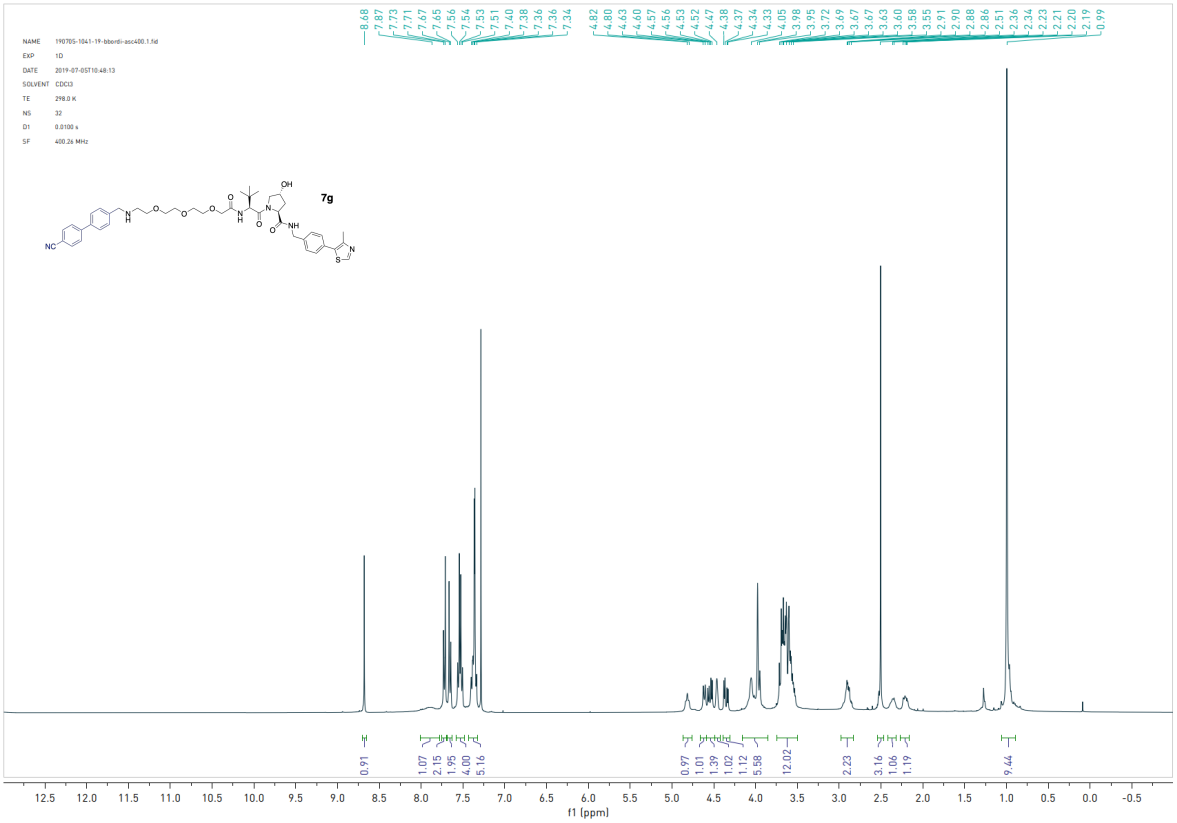



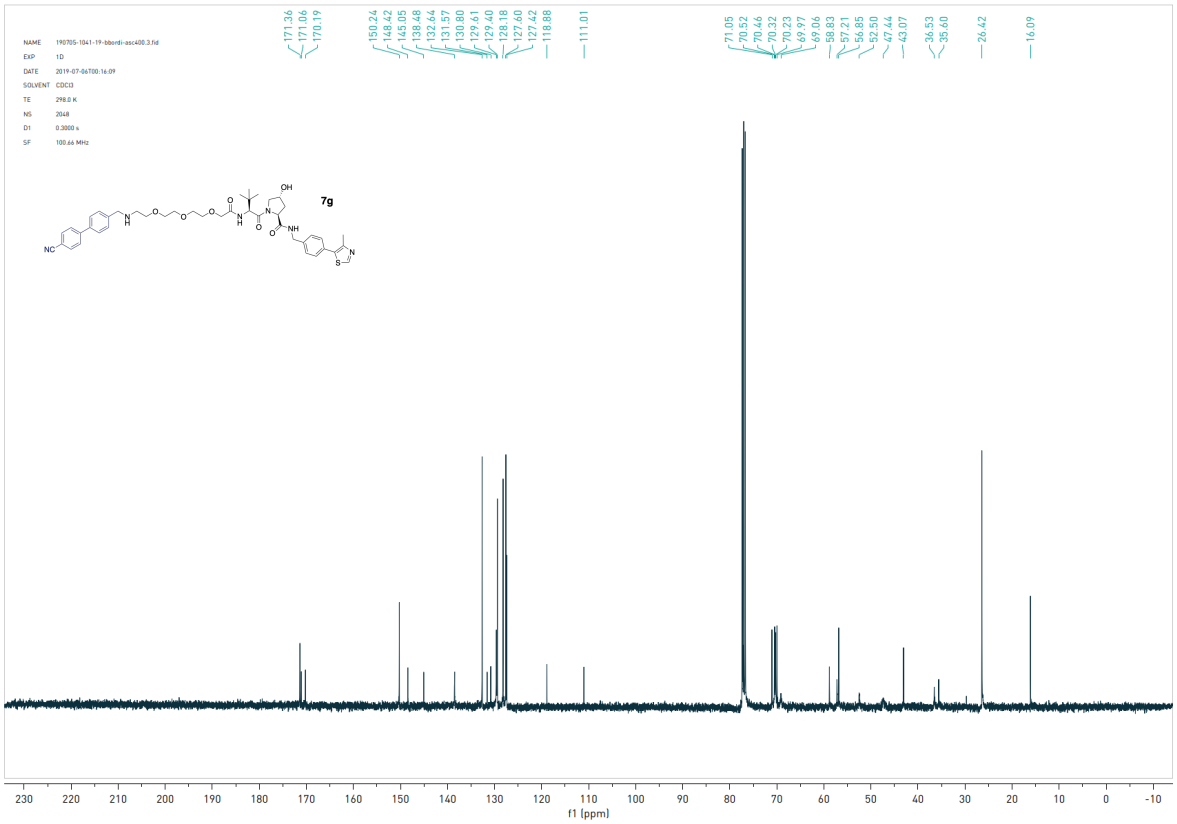
NMR of compound **7f**:



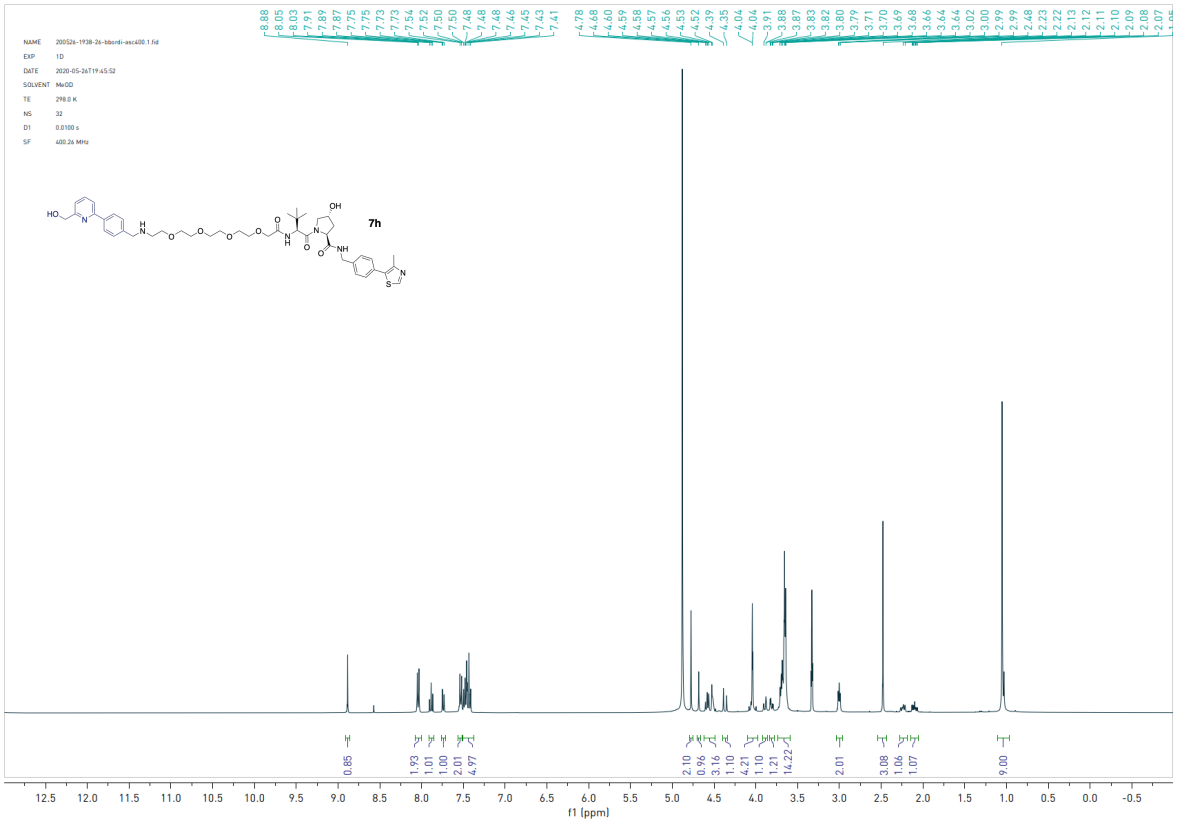



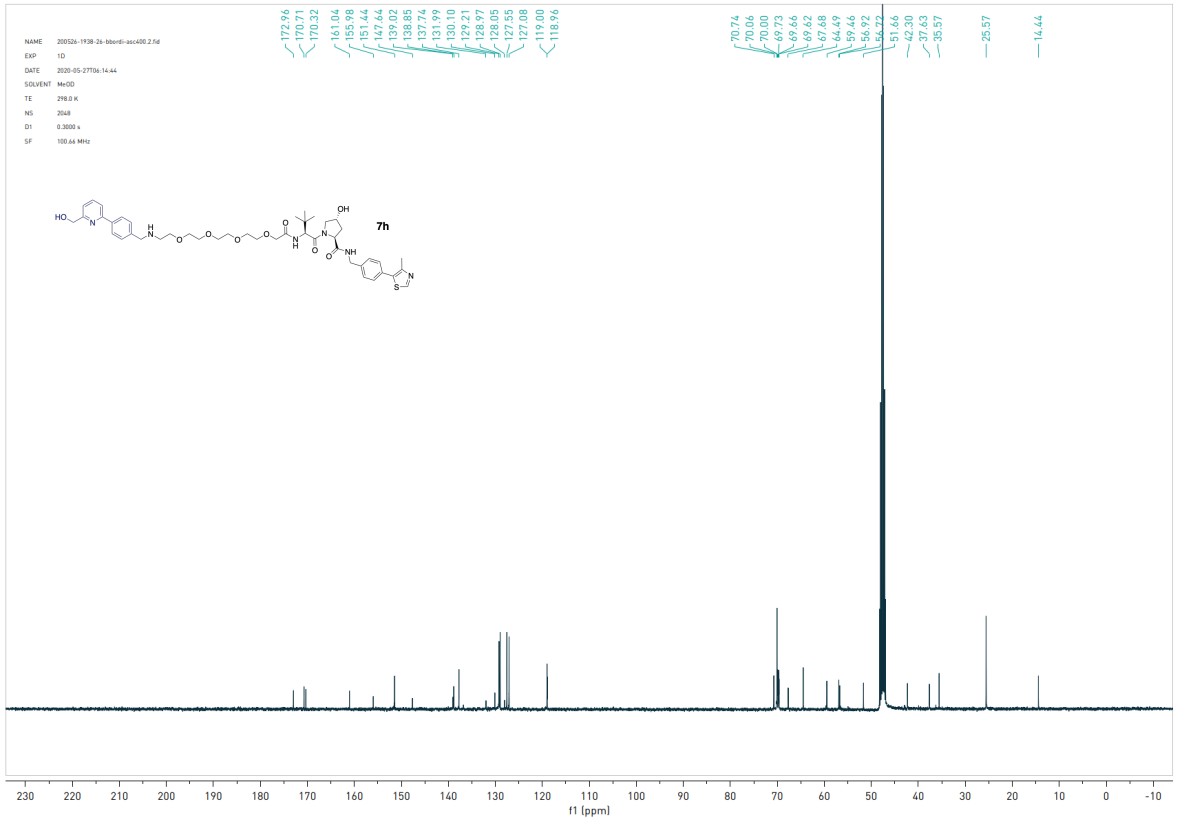
NMR of compound **7g**:



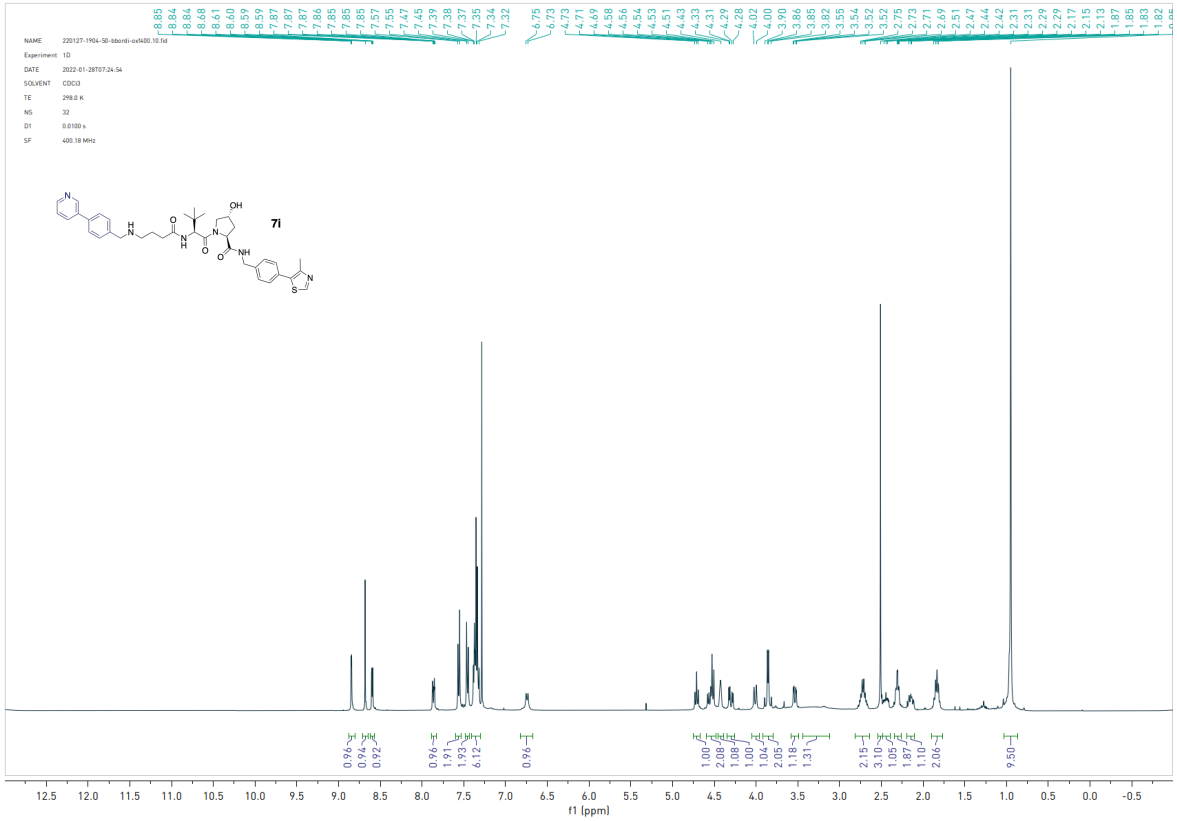



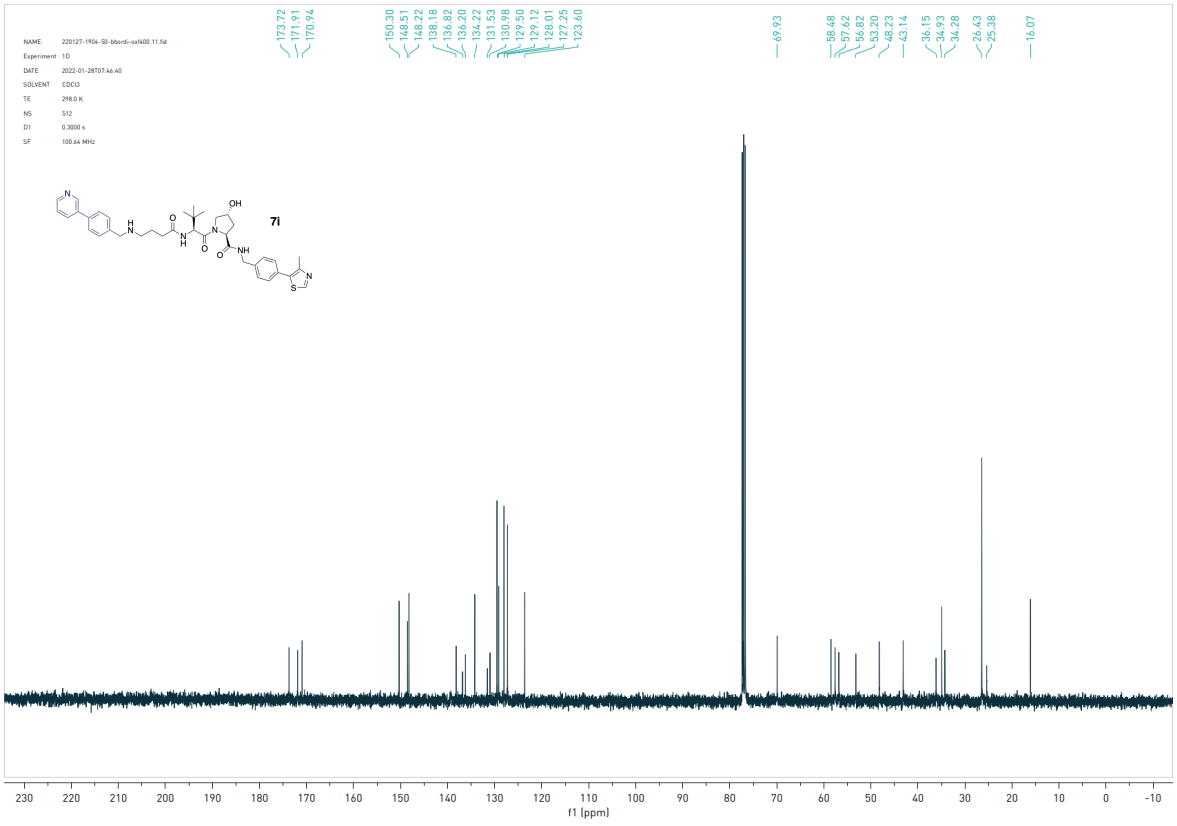
NMR of compound **7h**:



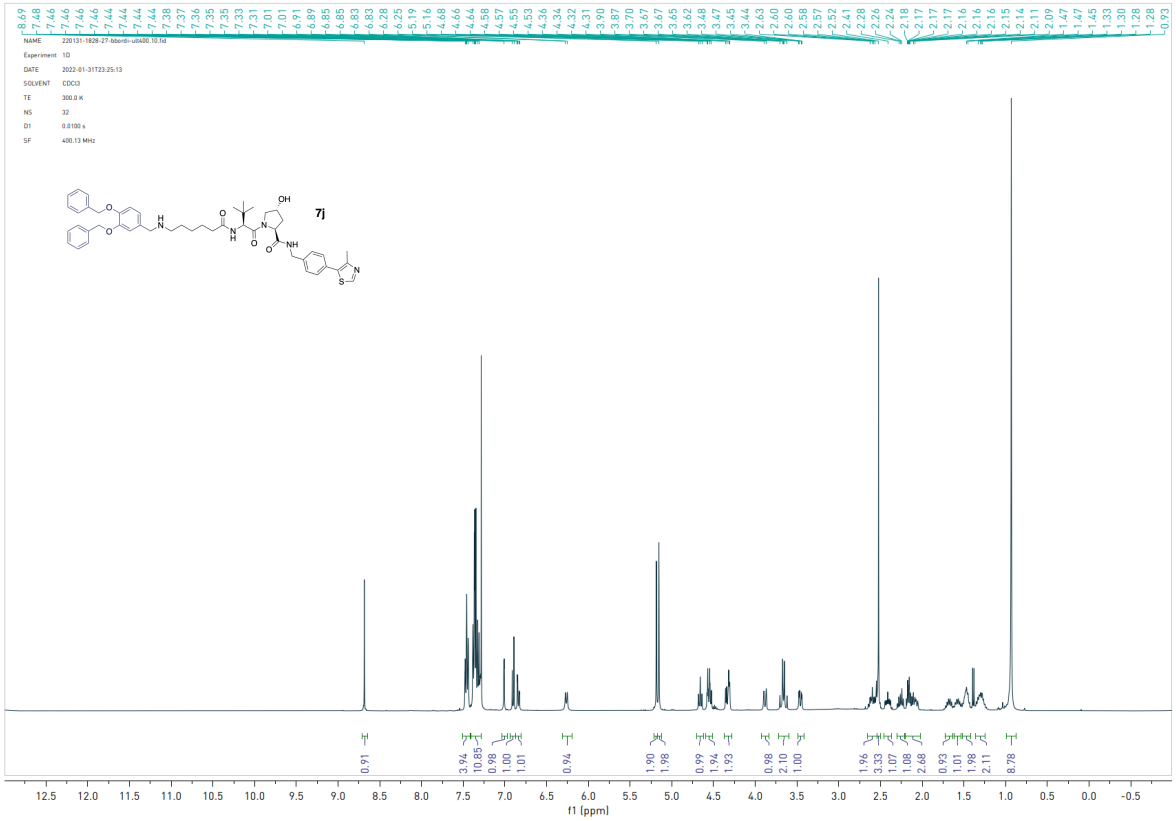



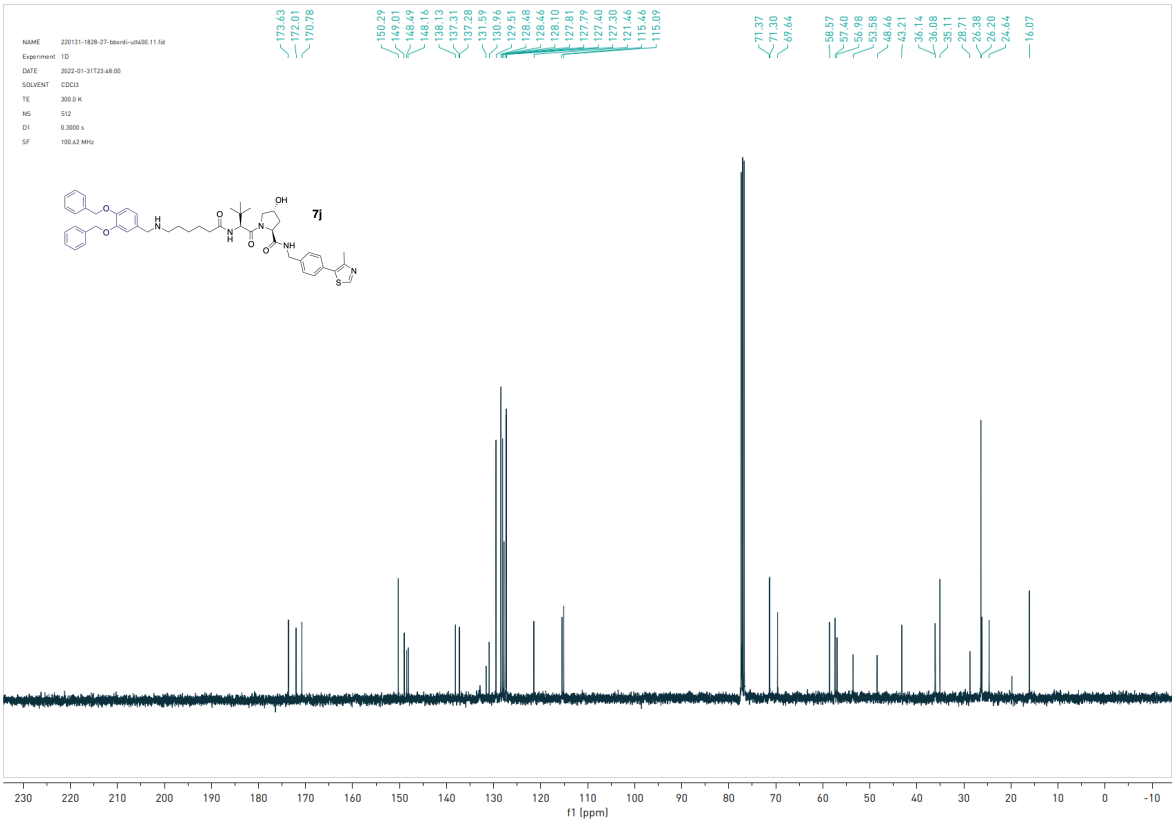
NMR of compound **7i**:



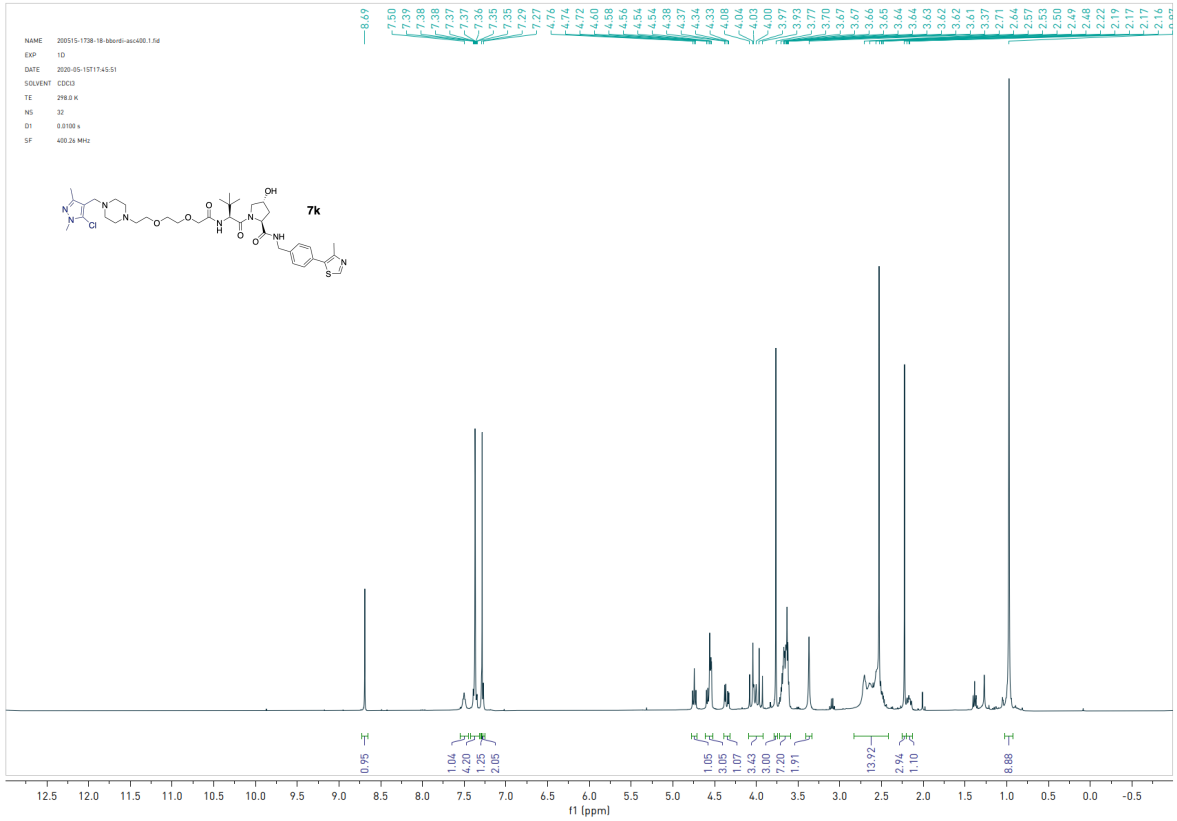



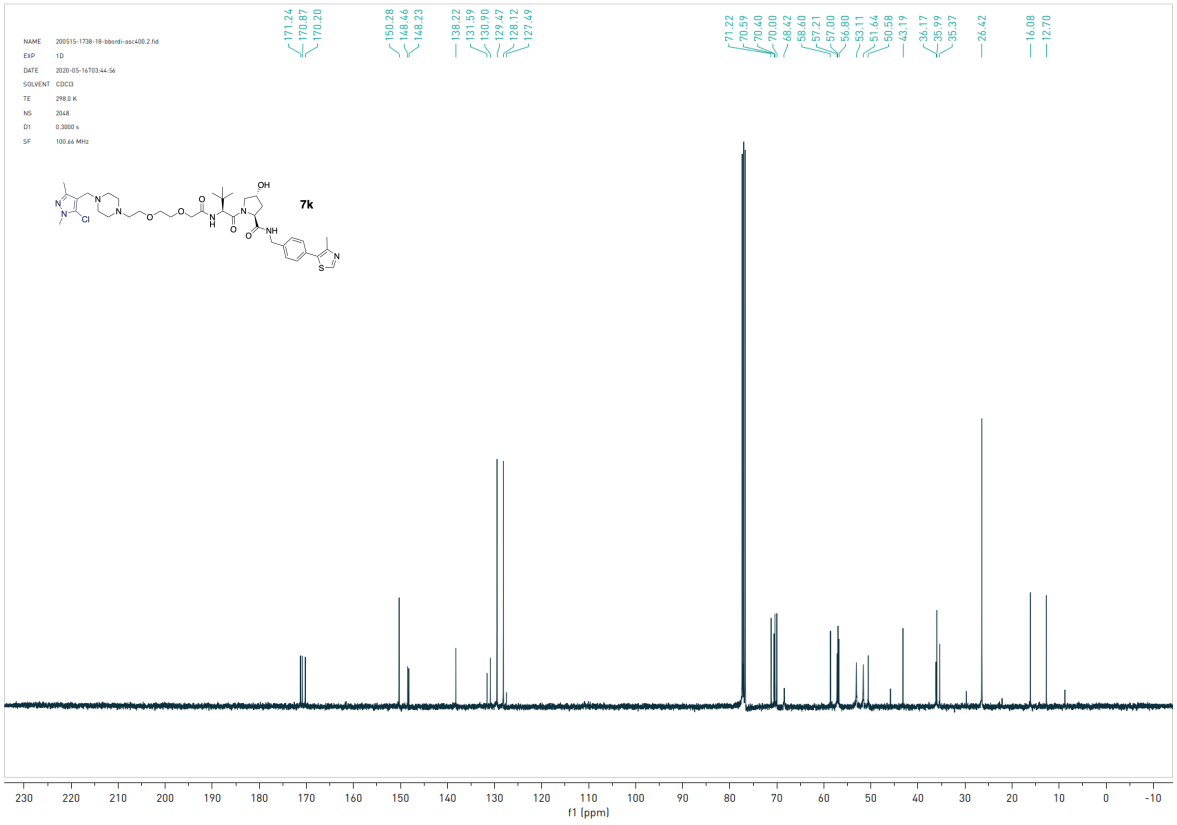
NMR of compound **7j**:



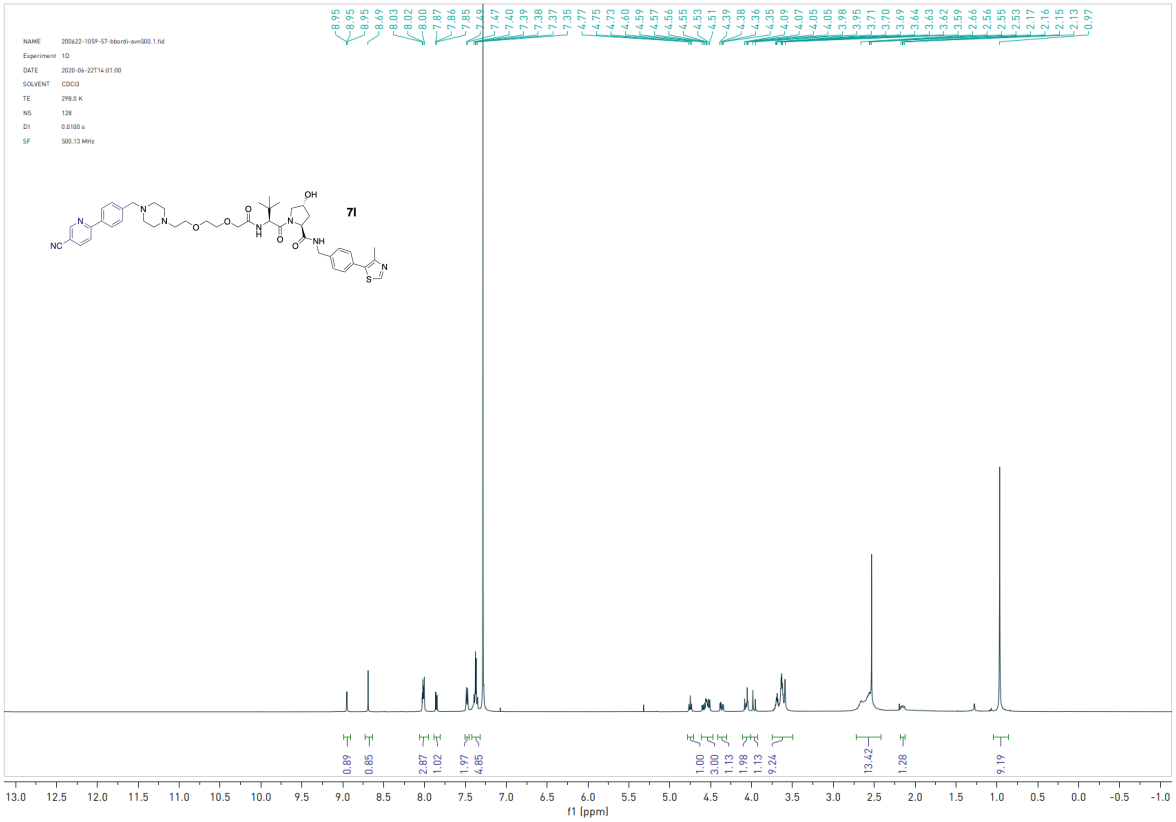



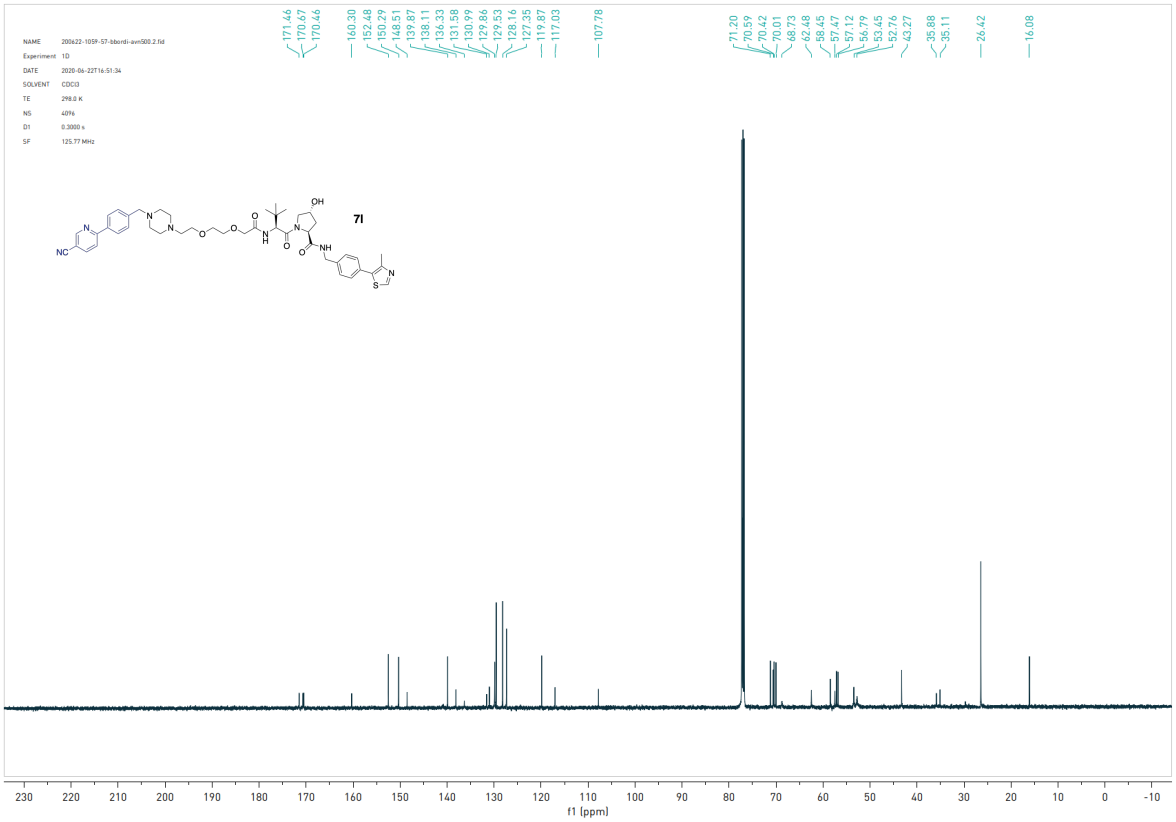
NMR of compound **7k**:



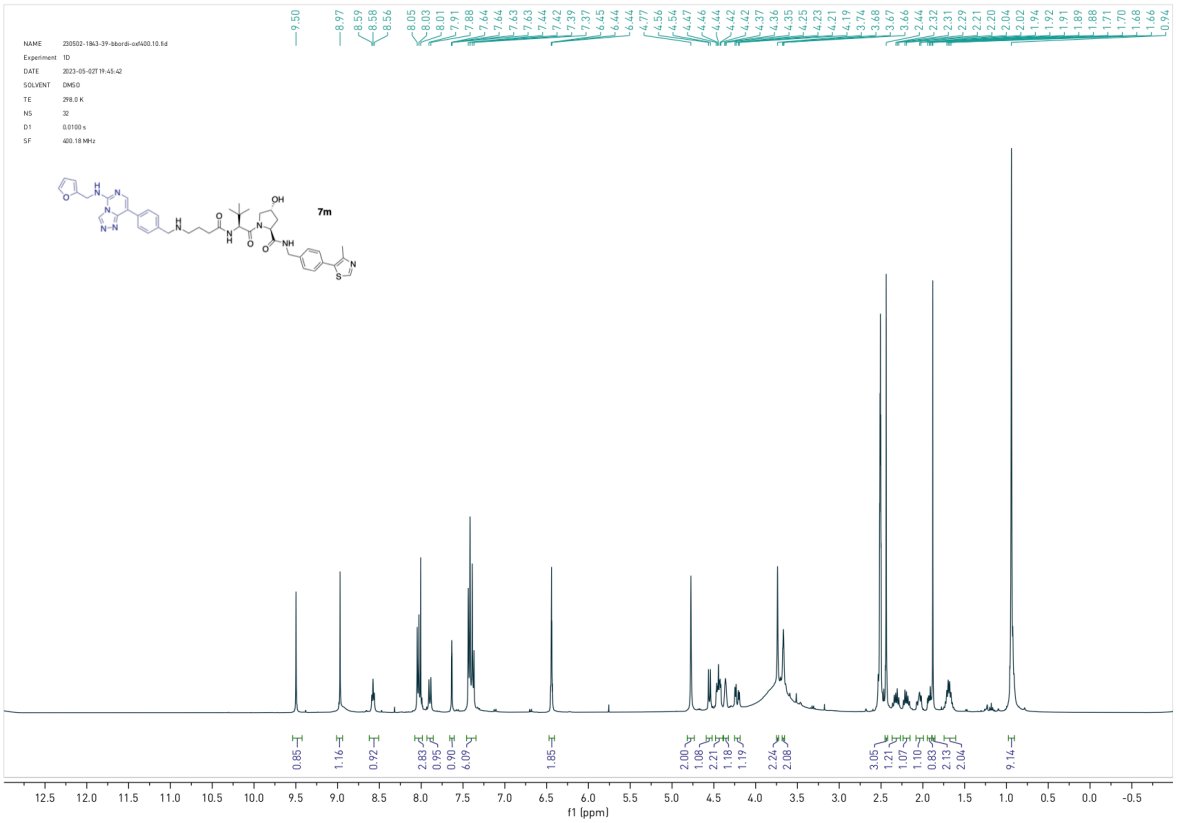



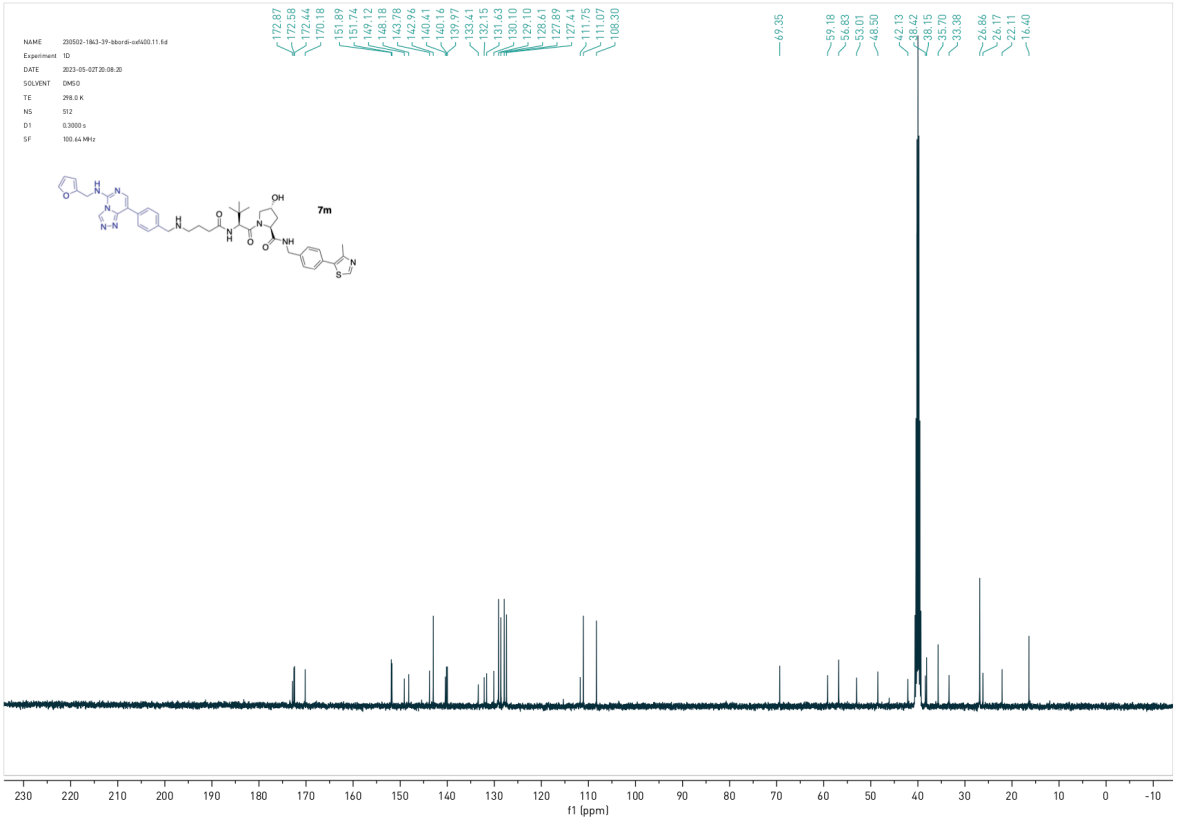
NMR of compound **7l**:



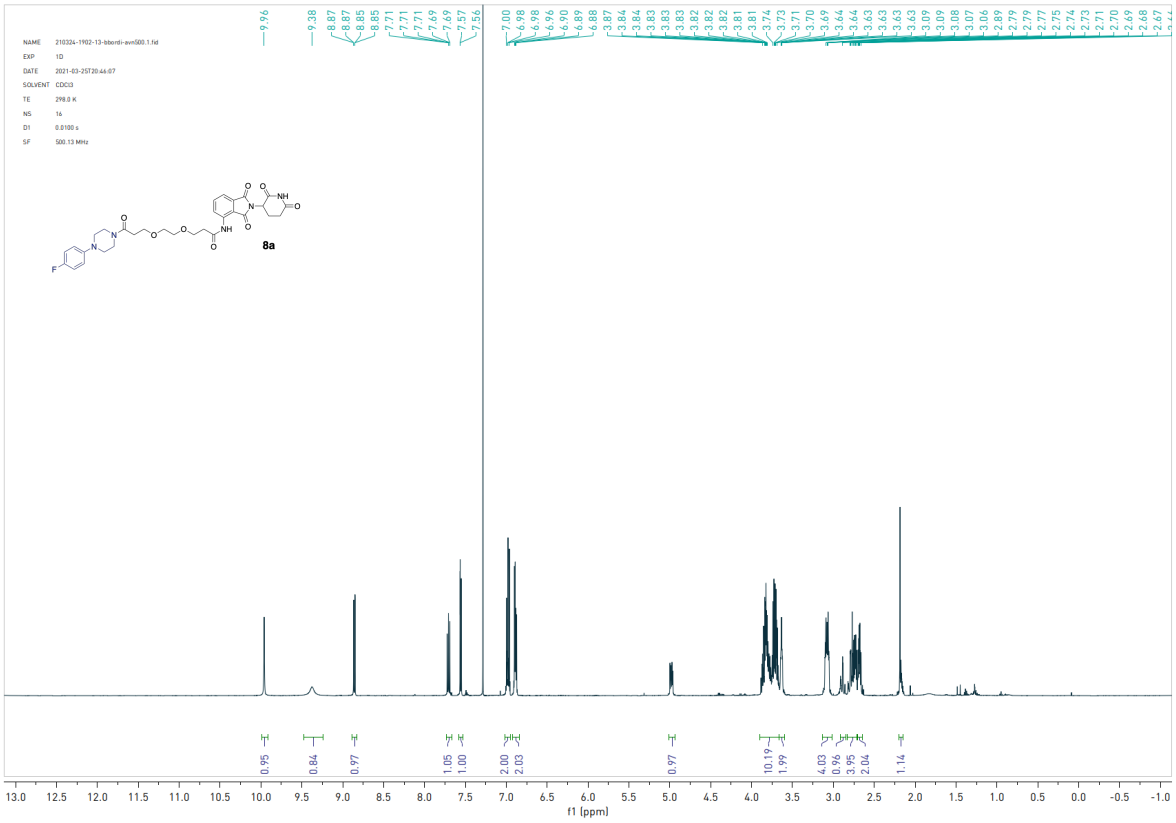



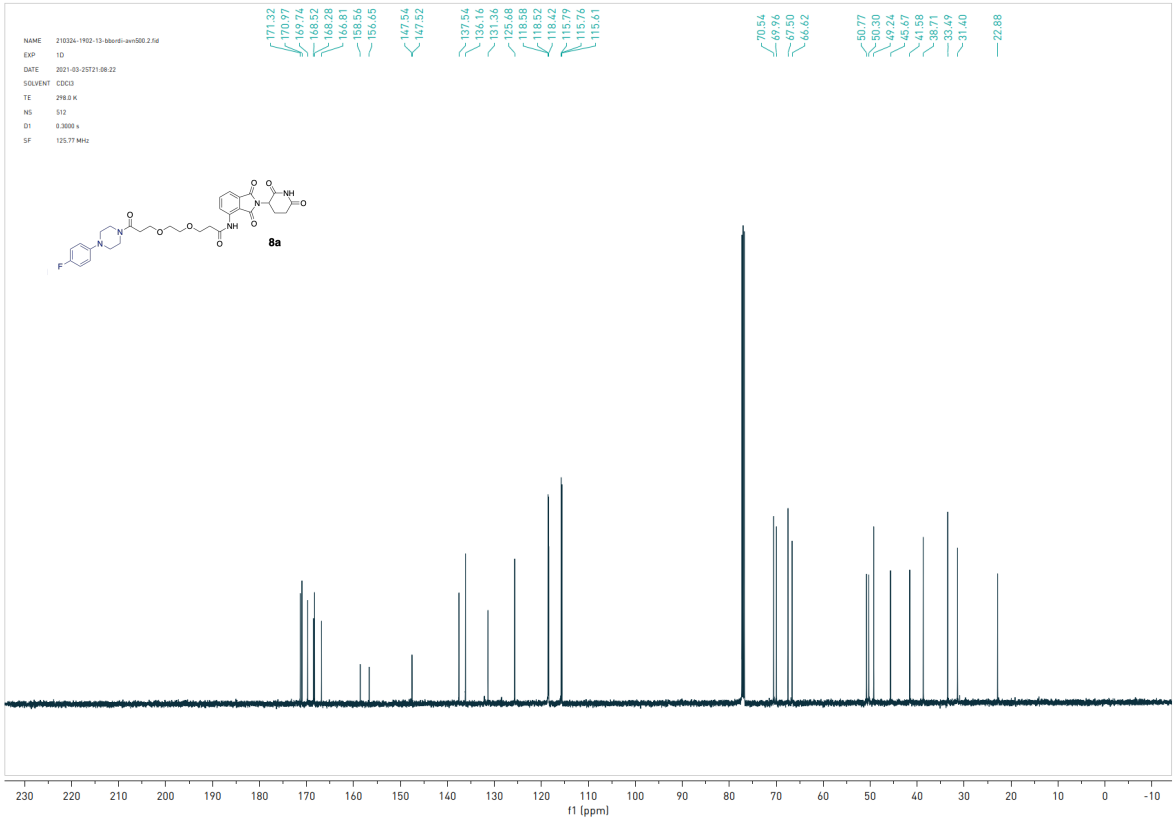
NMR of compound **7m**:

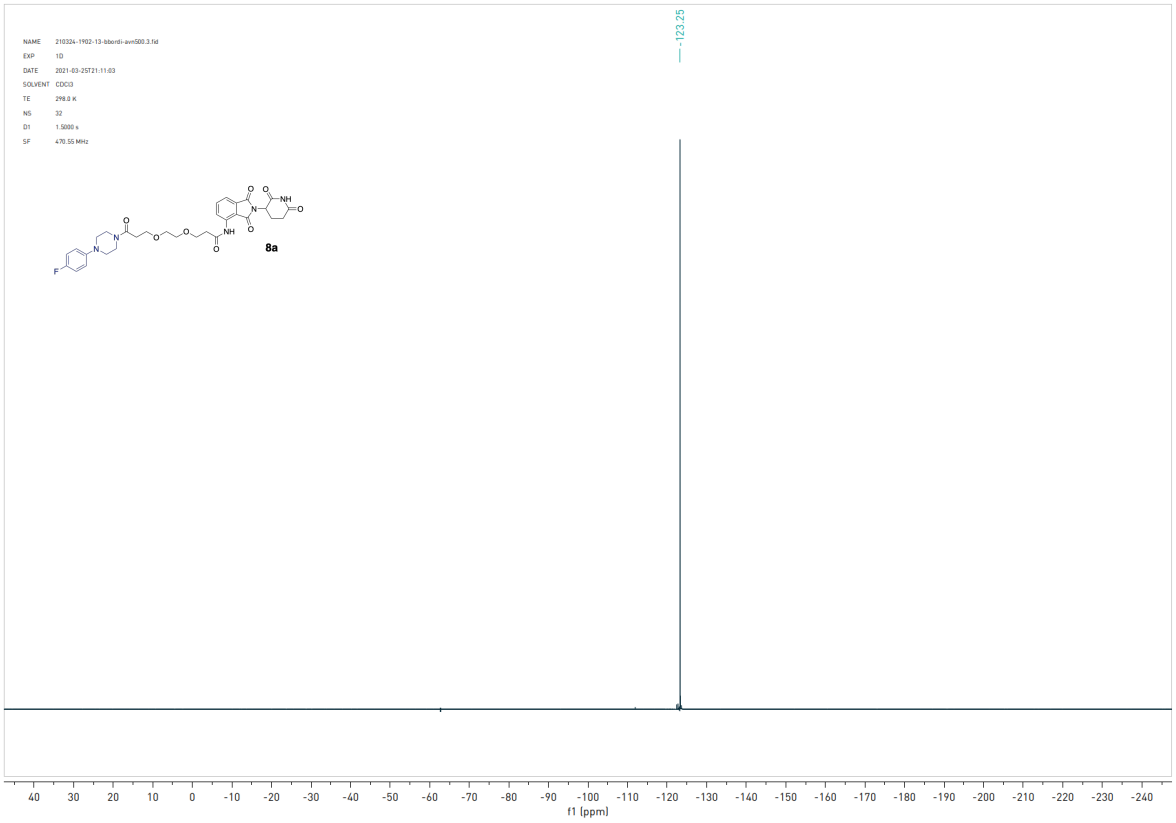


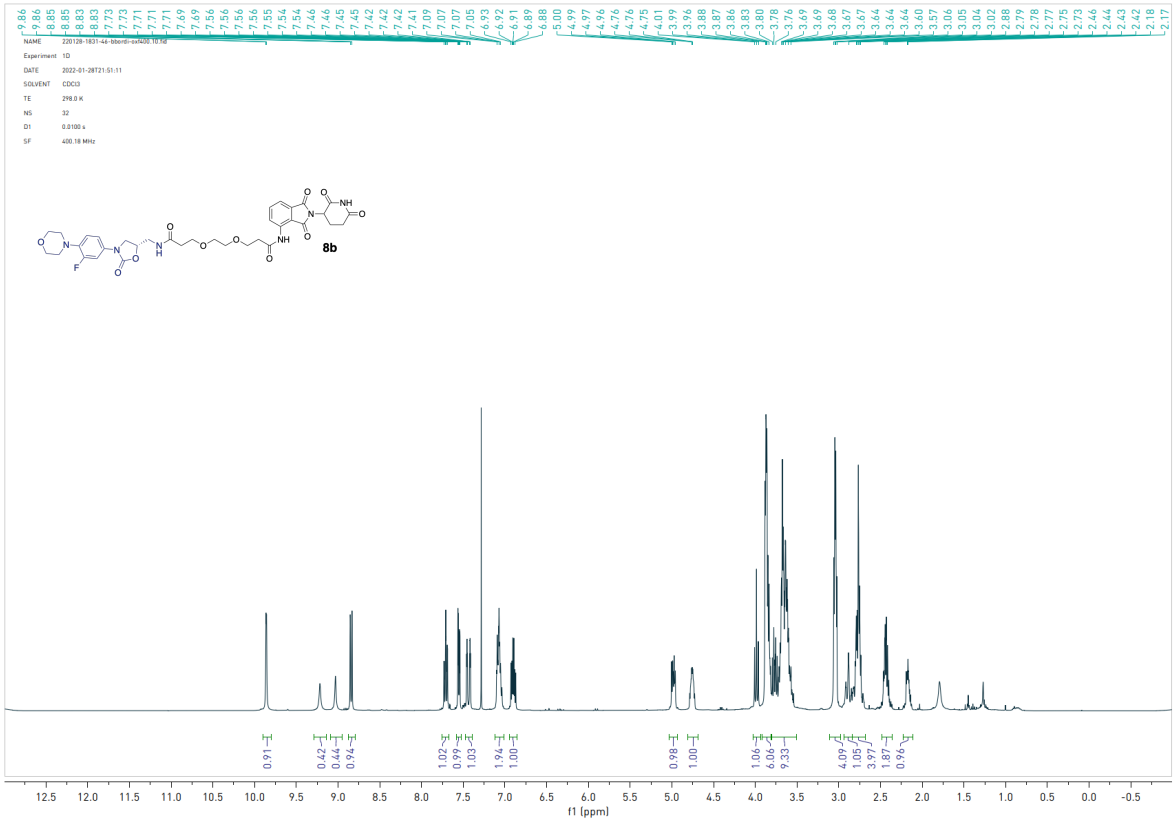
NMR of compound **8a**:

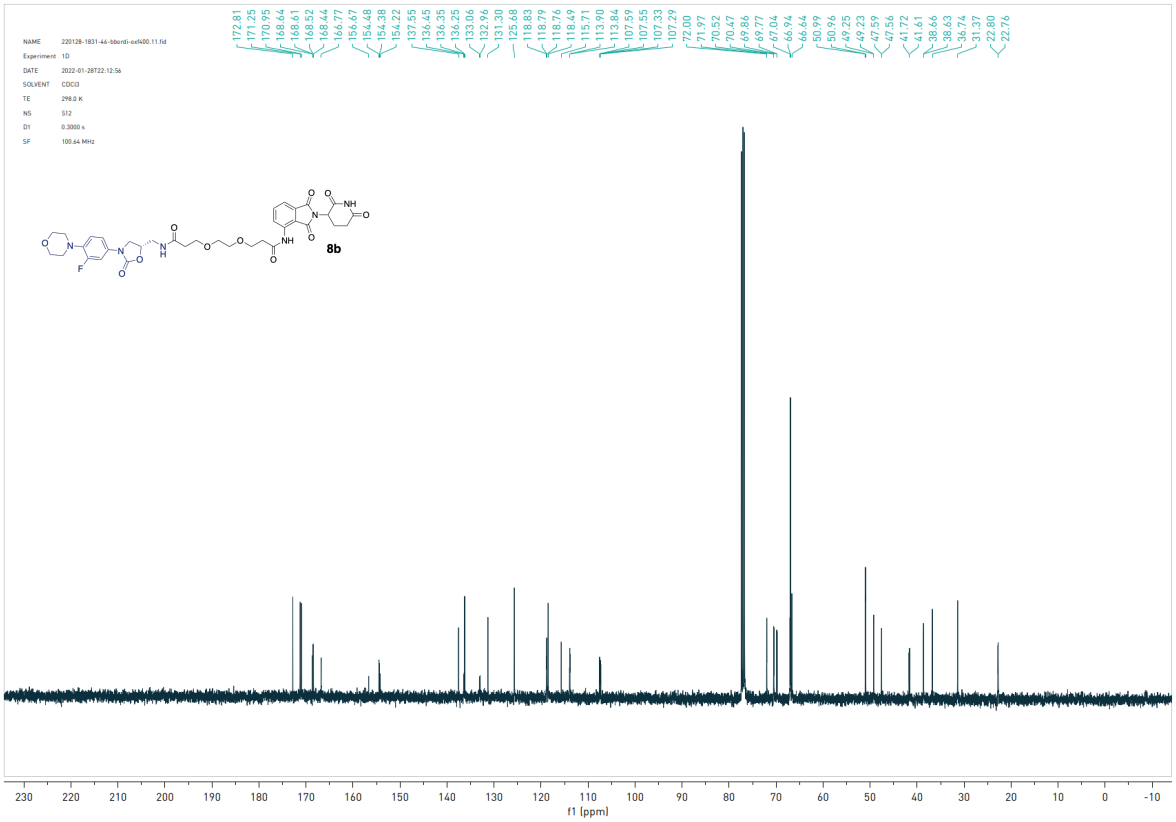


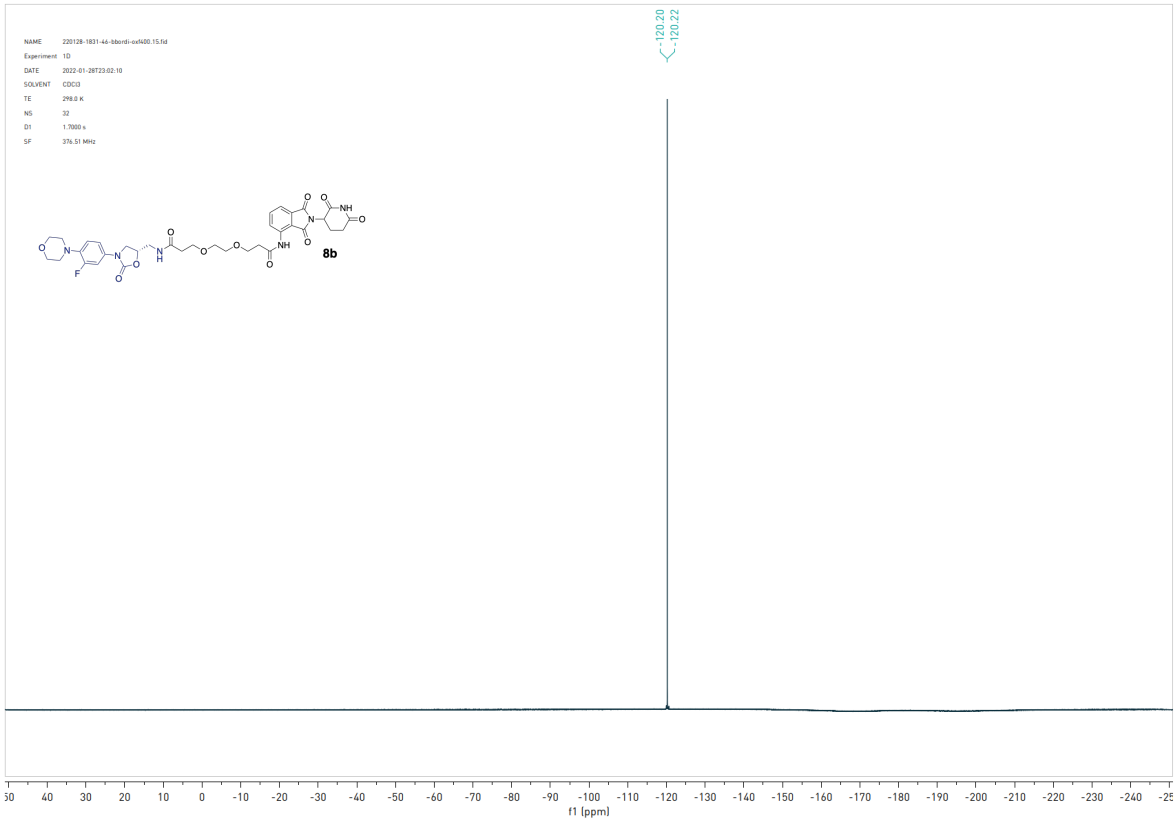




NAME 210324-1902-13-bbordi-avn500.3.fid
EXP 1D
DATE 2021-03-25T21:11:03
SOLVENT CDCl3
TE 298.0 K
NS 32
D1 1.5000 s
SF 470.55 MHz
8a
-123.25
40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220 -230 -240
f1 (ppm)

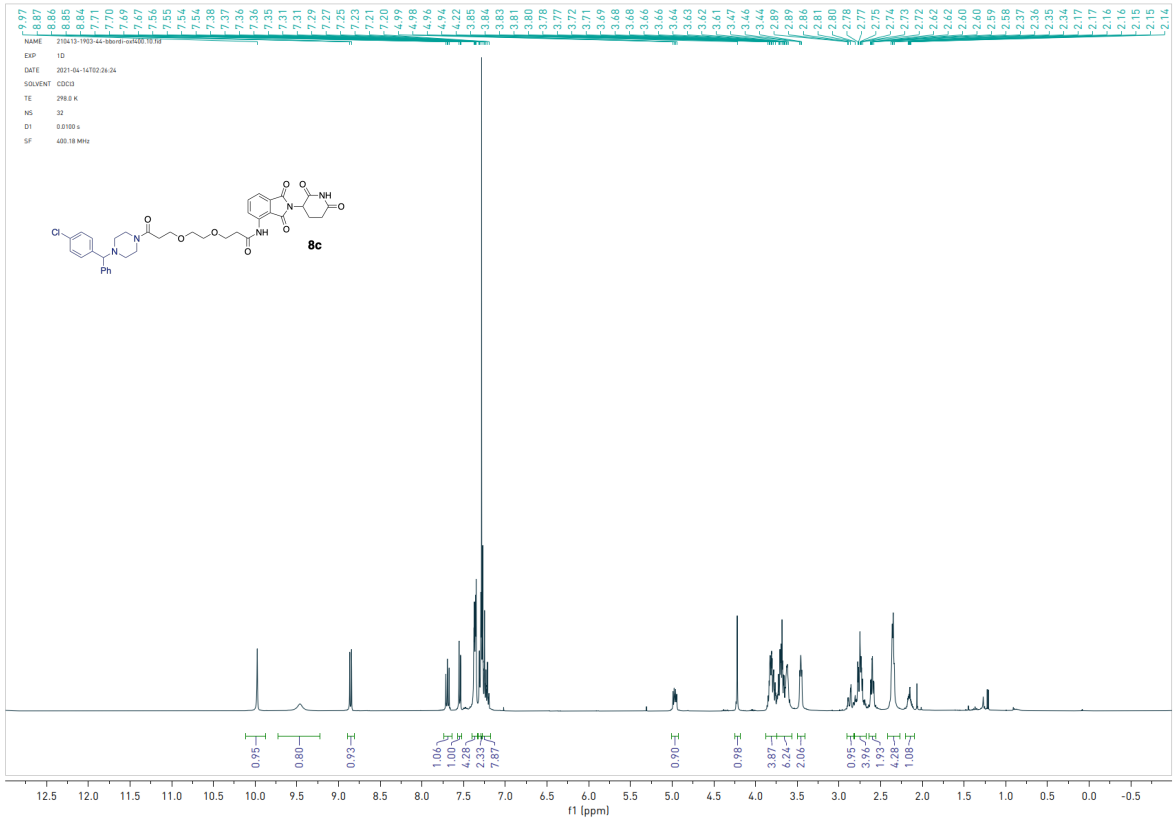
NMR of compound **8b**:

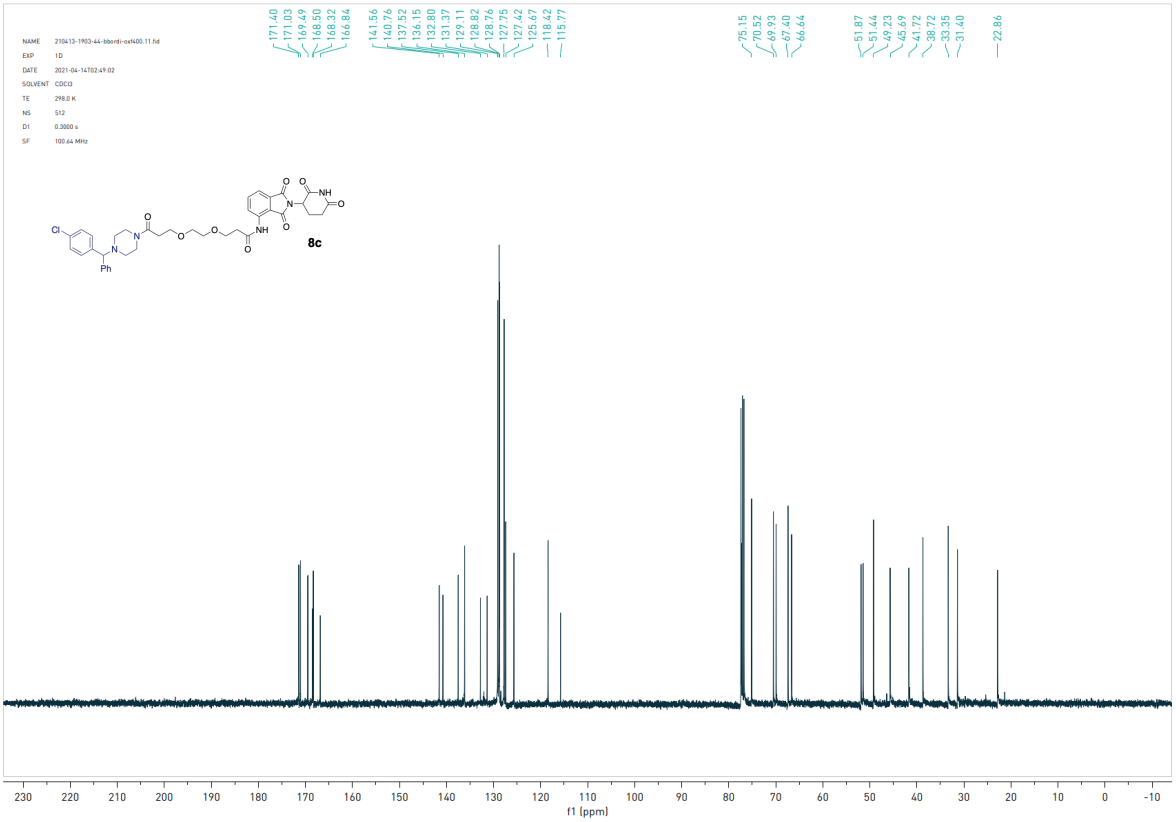


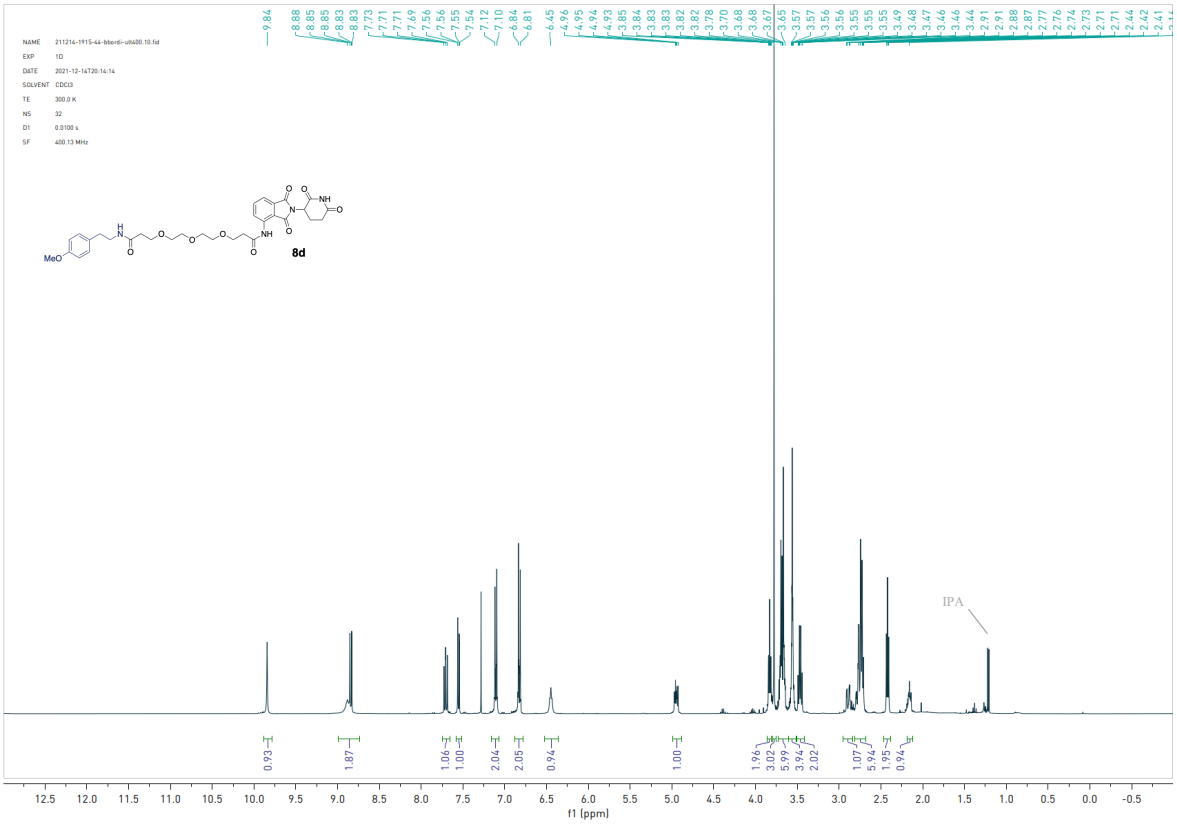

NAME 220128-1831-44-bbordi-ox400.15.fid
Experiment 1D
DATE 2022-01-28T23:02:10
SOLVENT CDCl3
TE 298.0 K
NS 32
D1 1.7000 s
SF 376.51 MHz
8b
120.20
120.22
f1 (ppm)

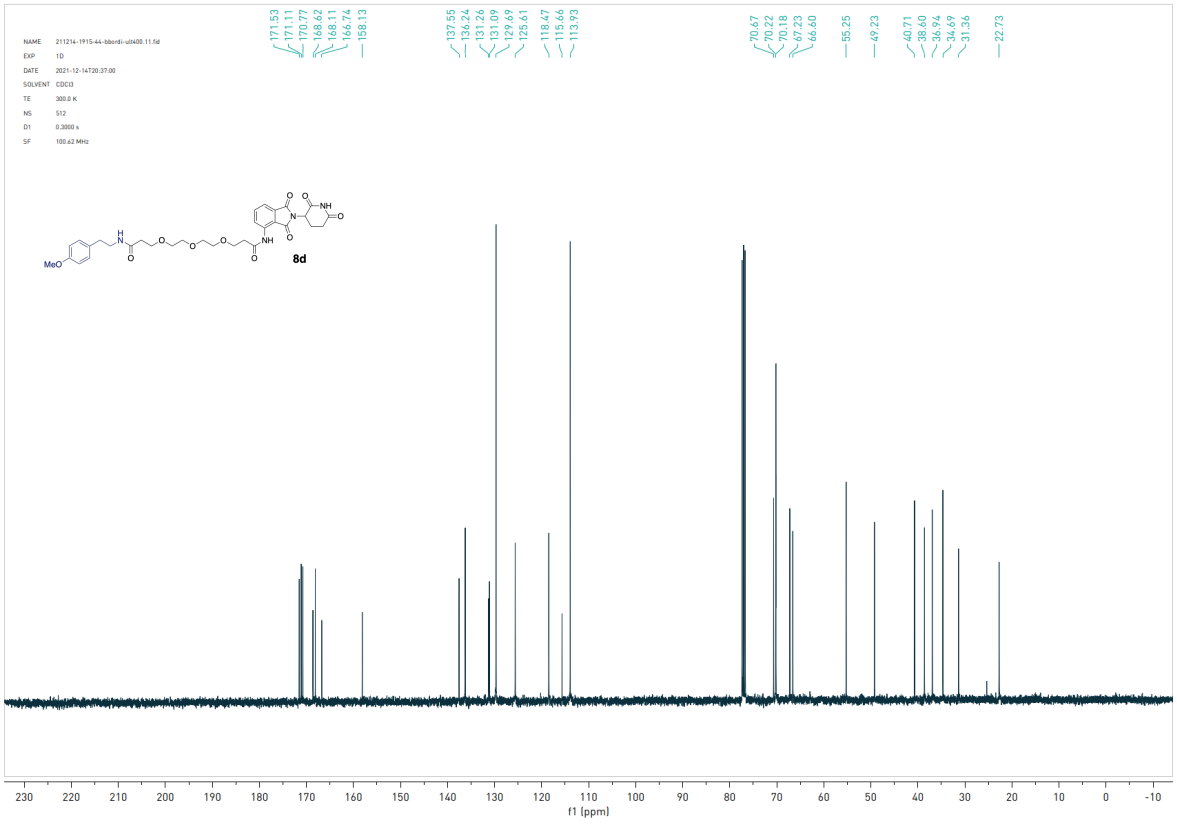
NMR of compound **8c**:



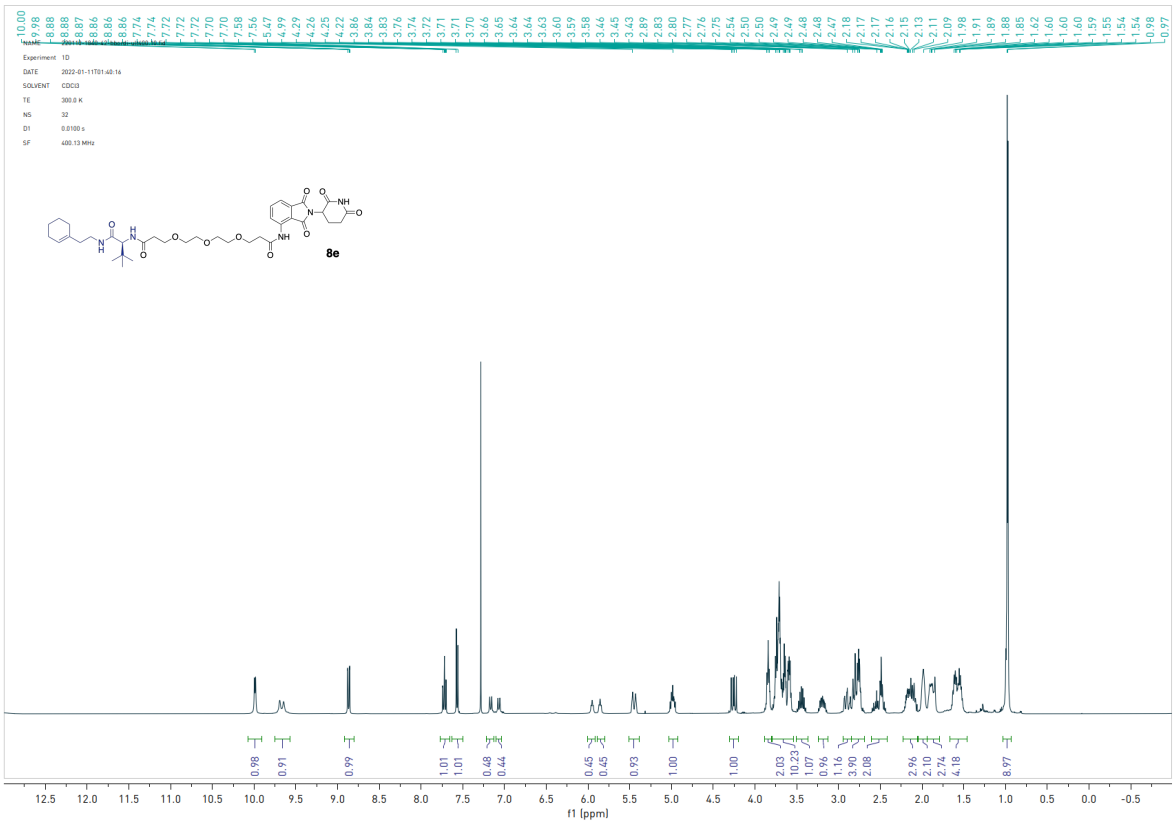



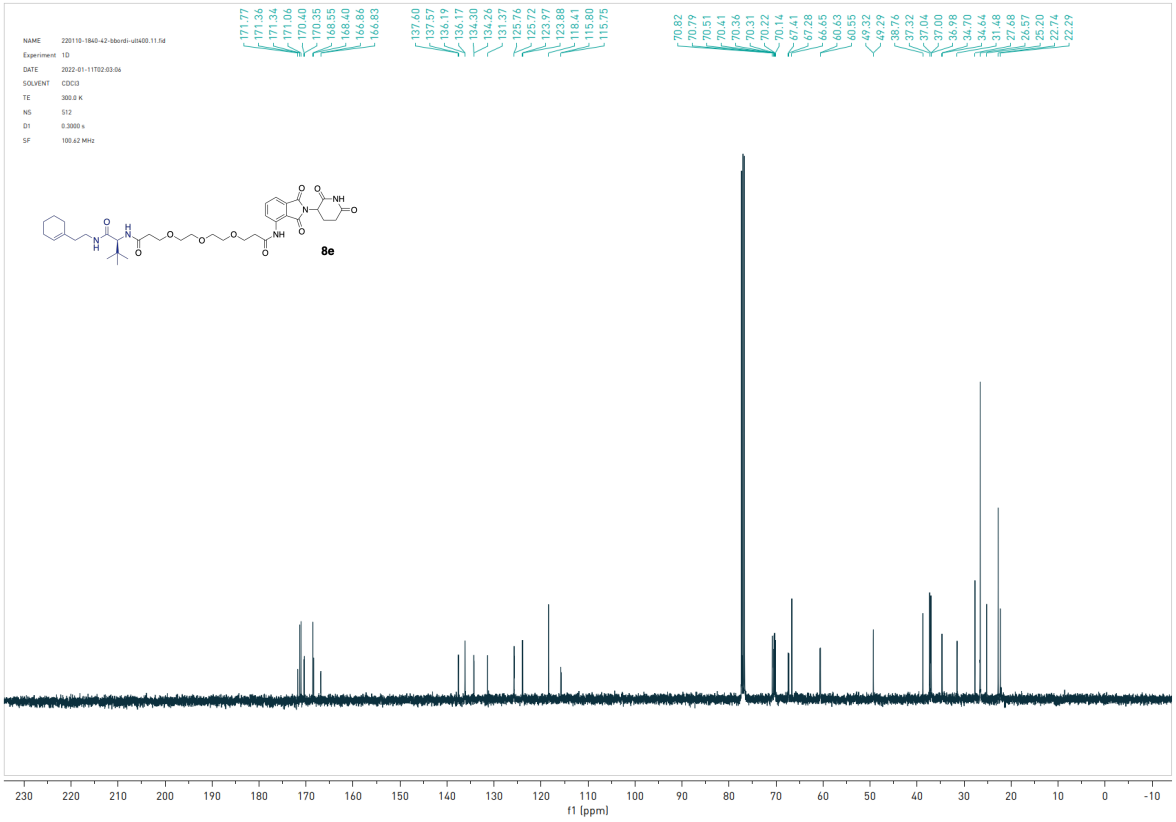
NMR of compound **8d**:



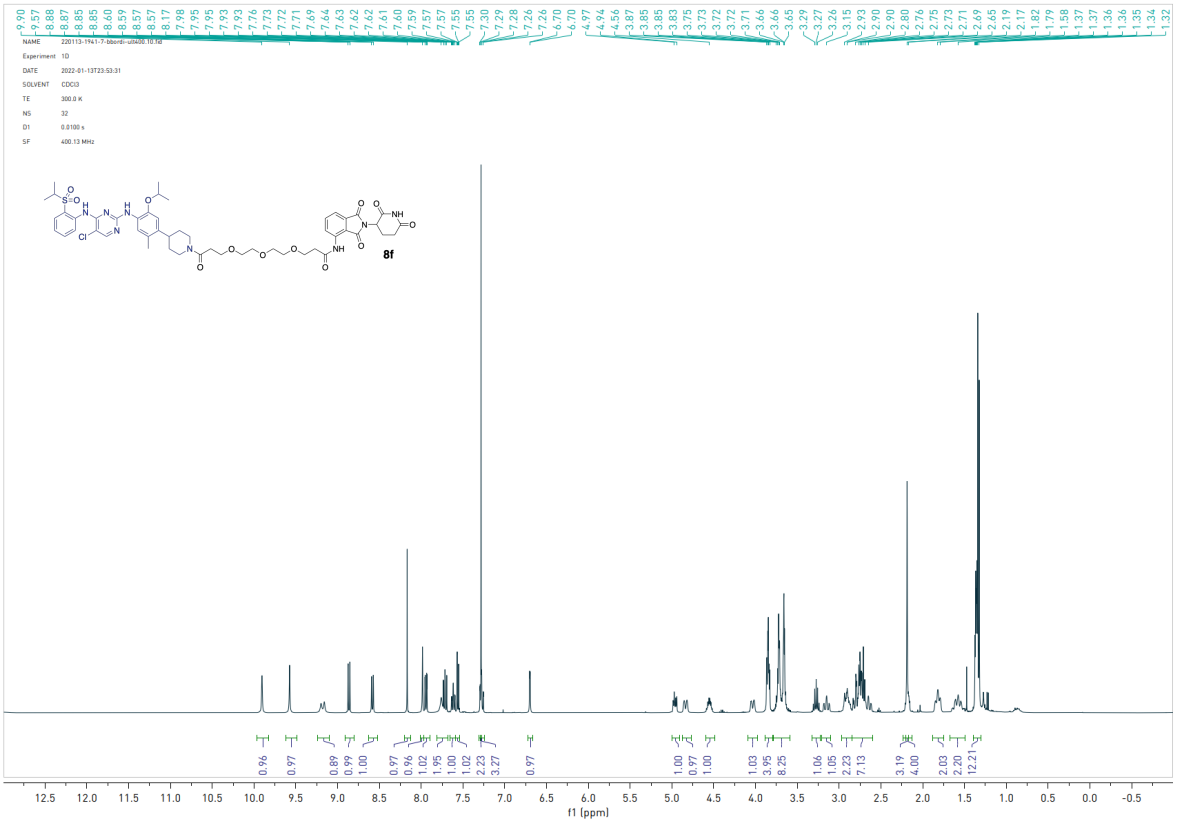



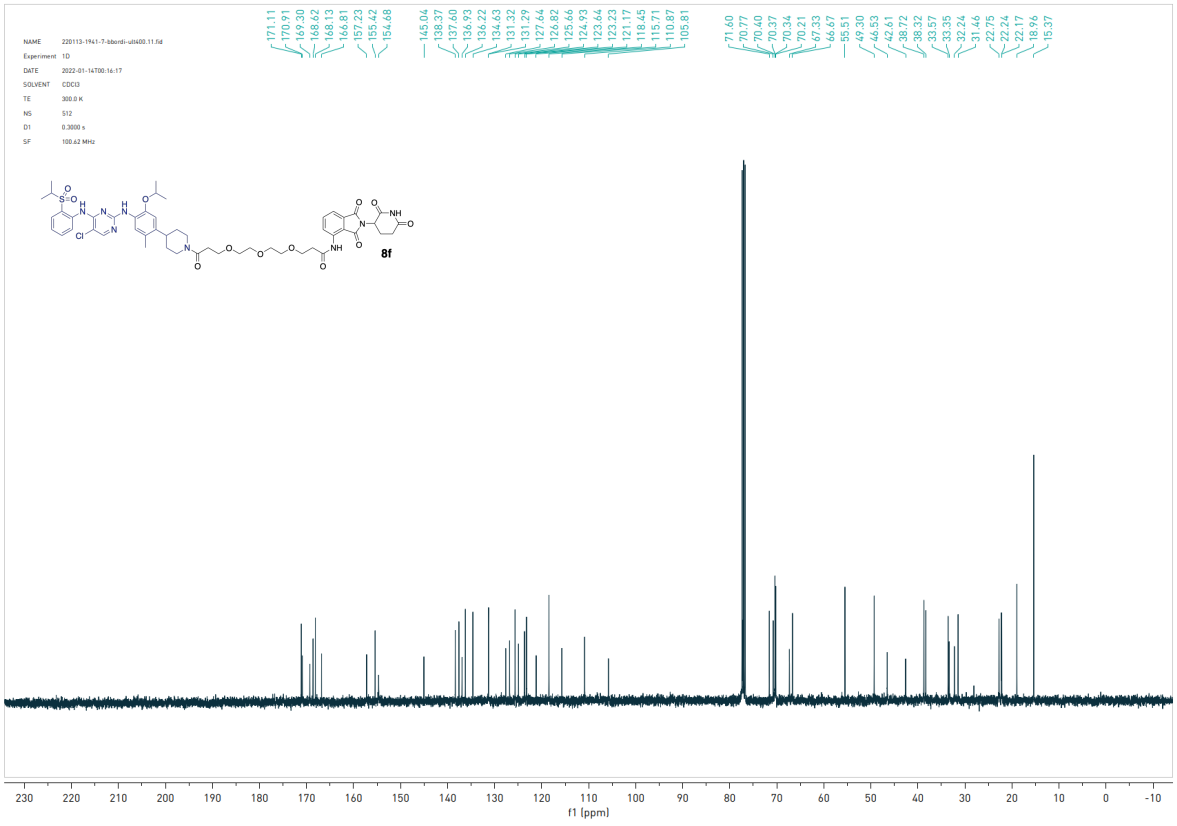
NMR of compound **8e**:



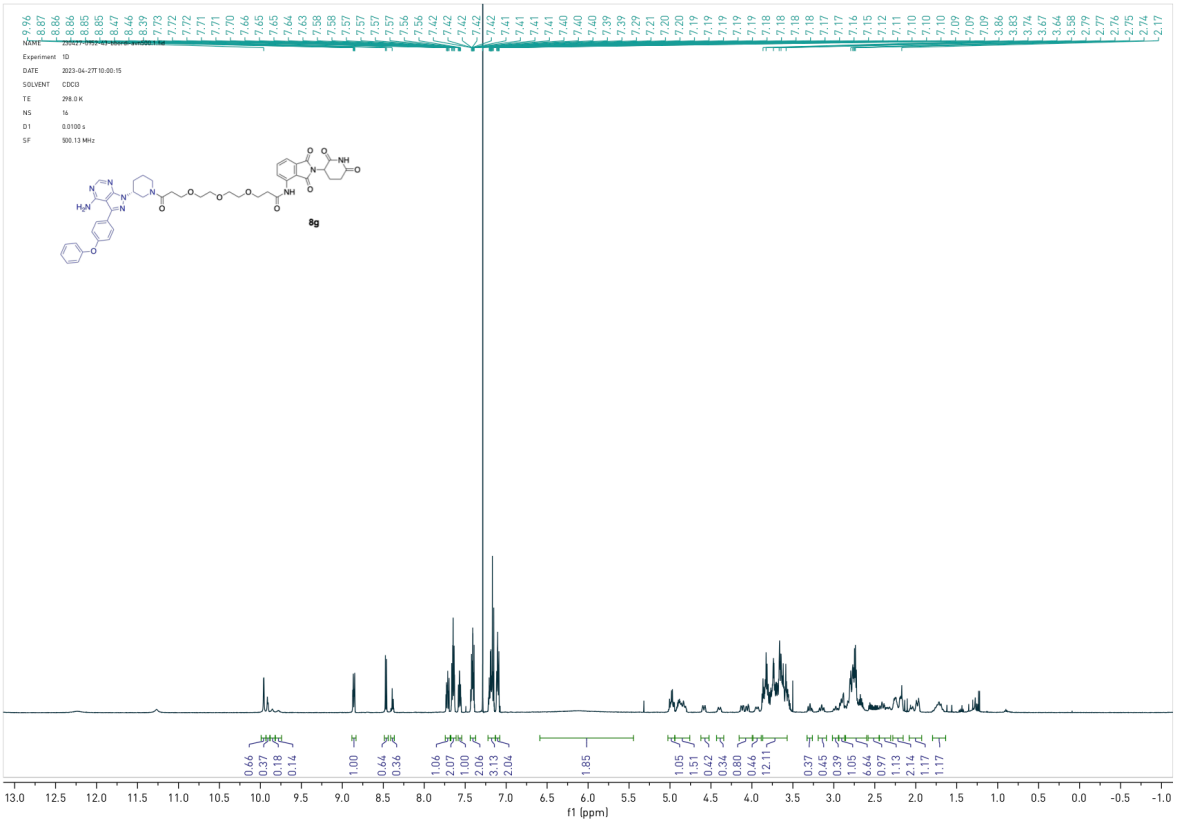



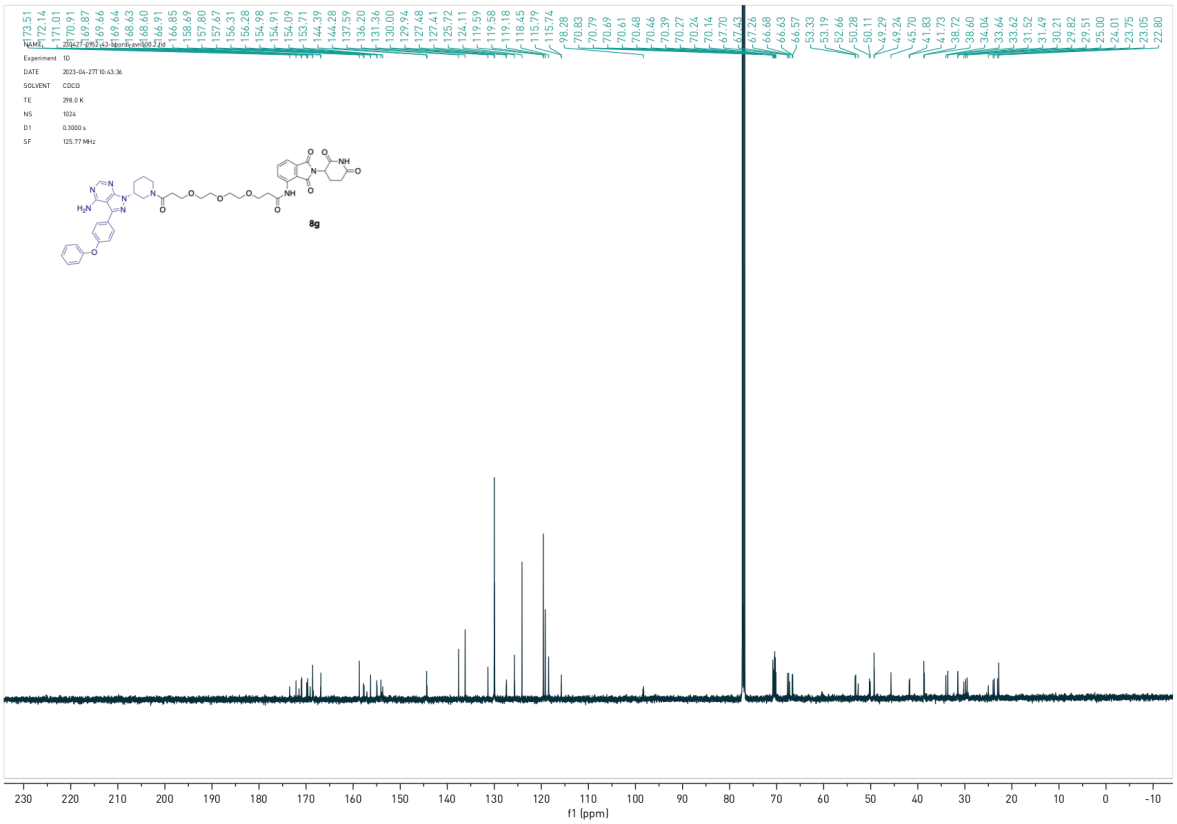
NMR of compound **8f**:



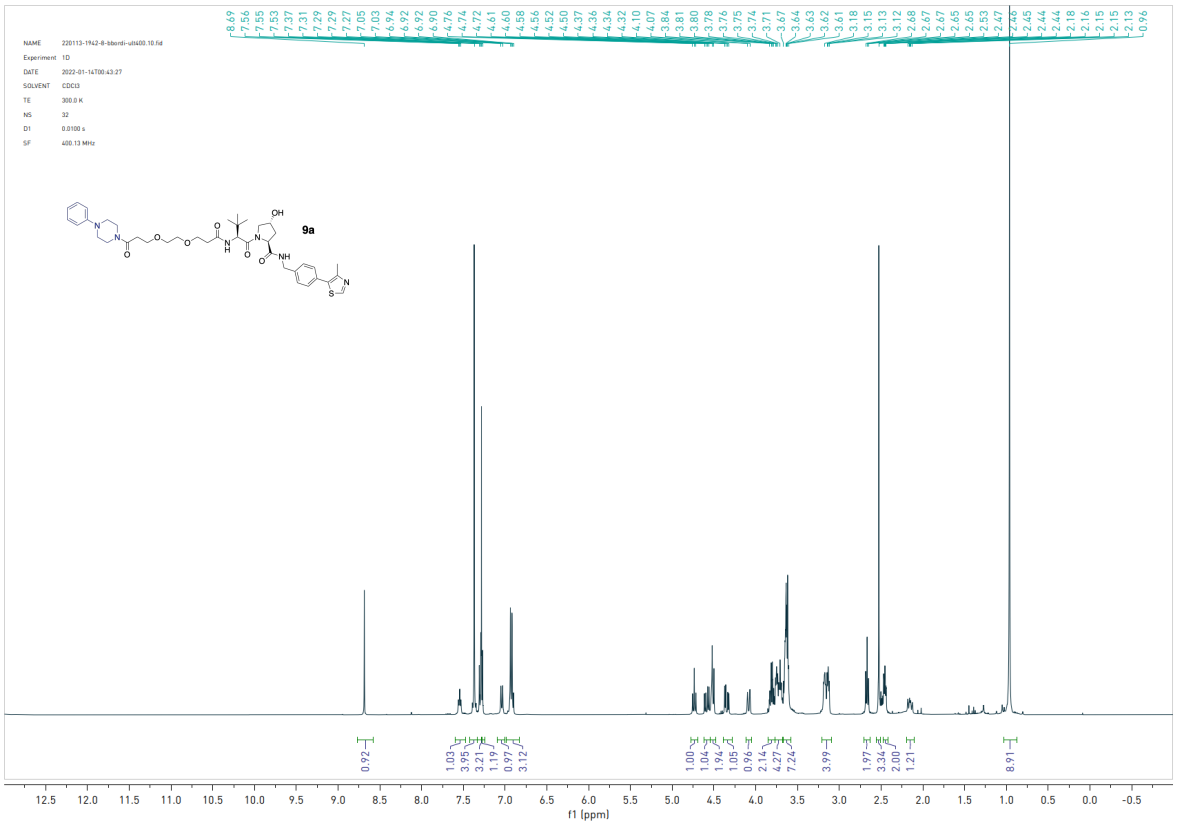



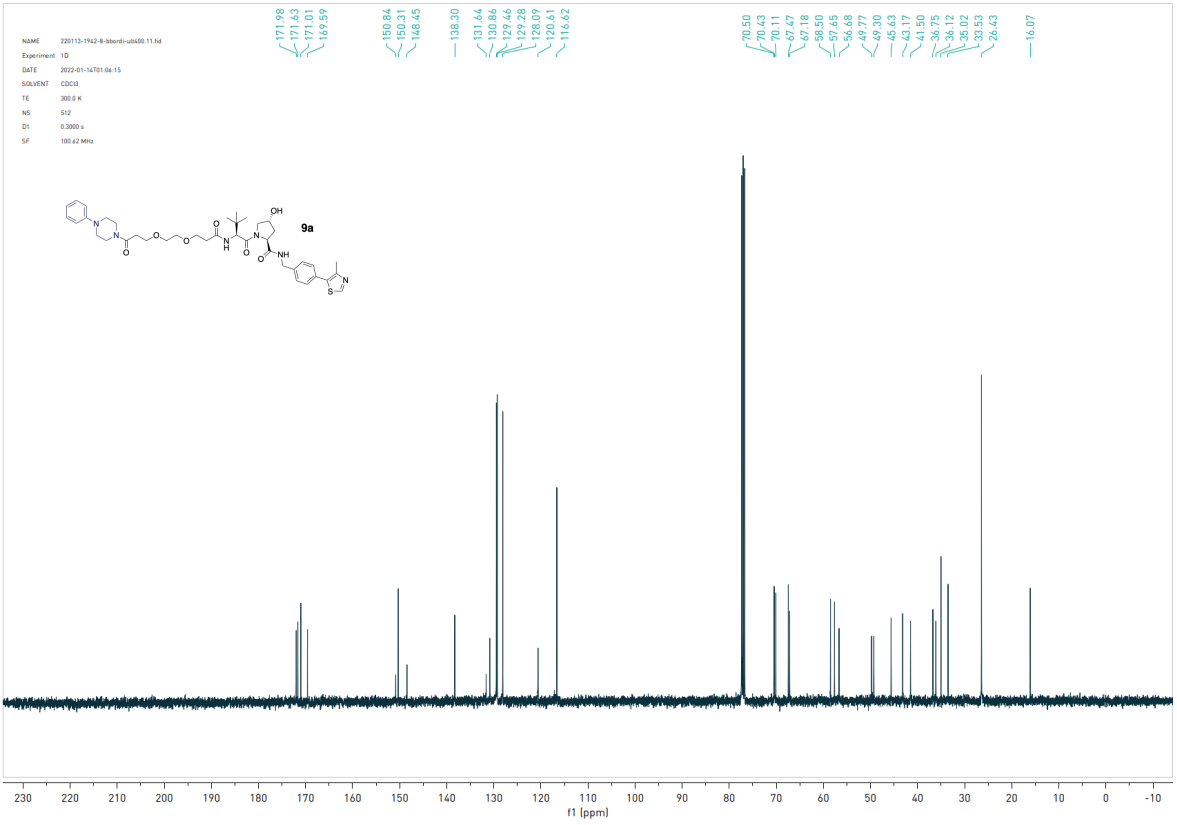
NMR of compound **8g**:



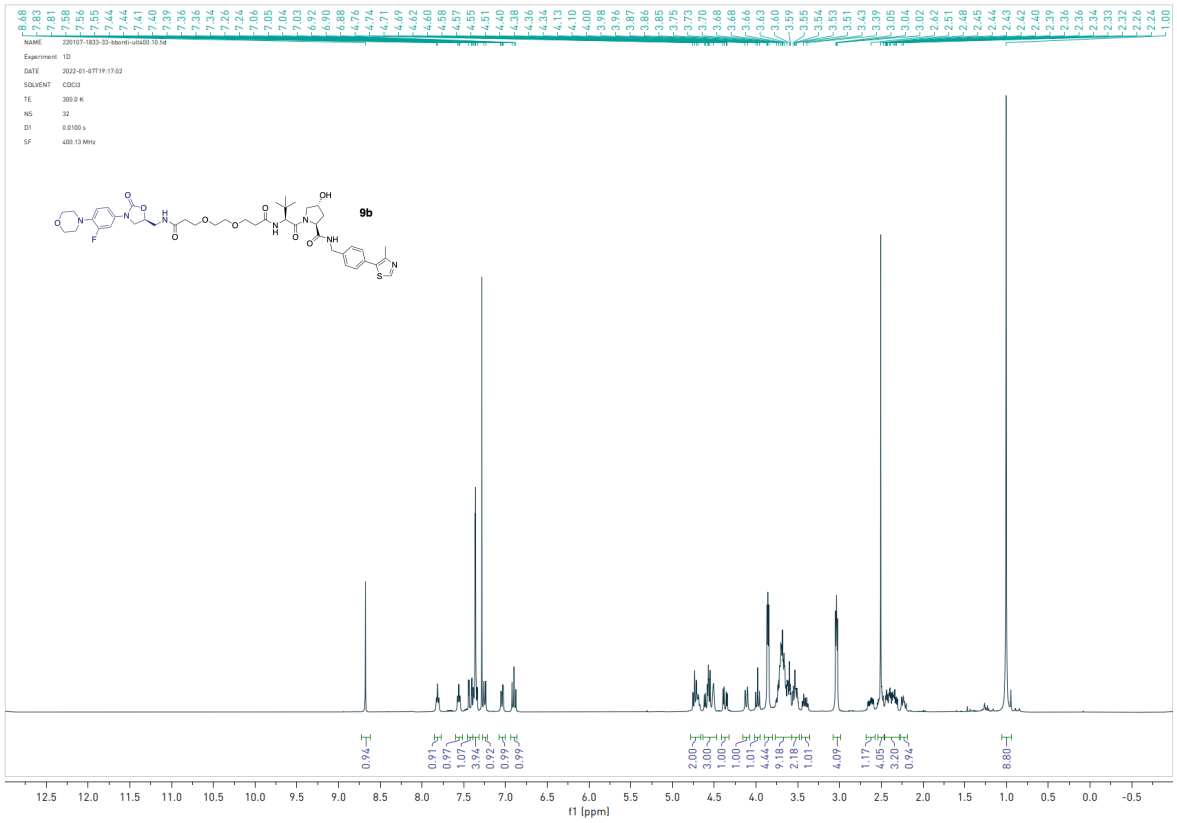



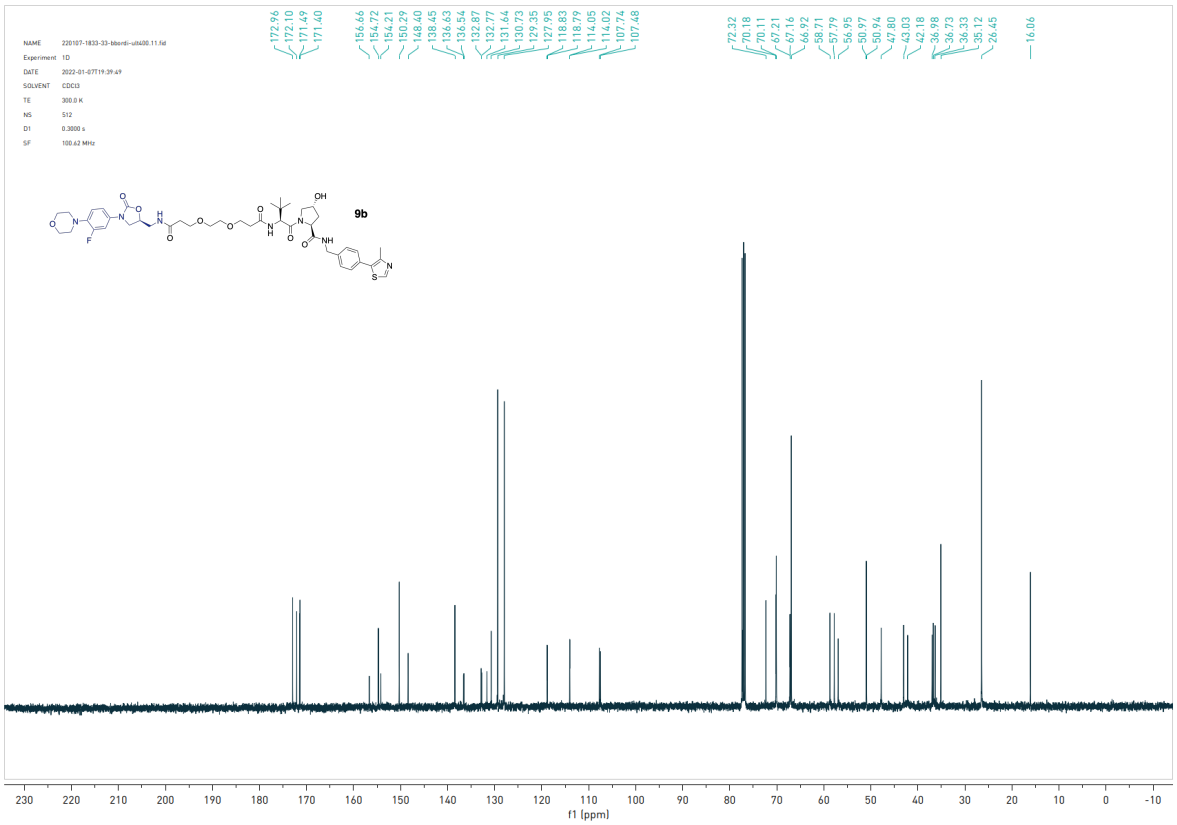
NMR of compound **9a**:

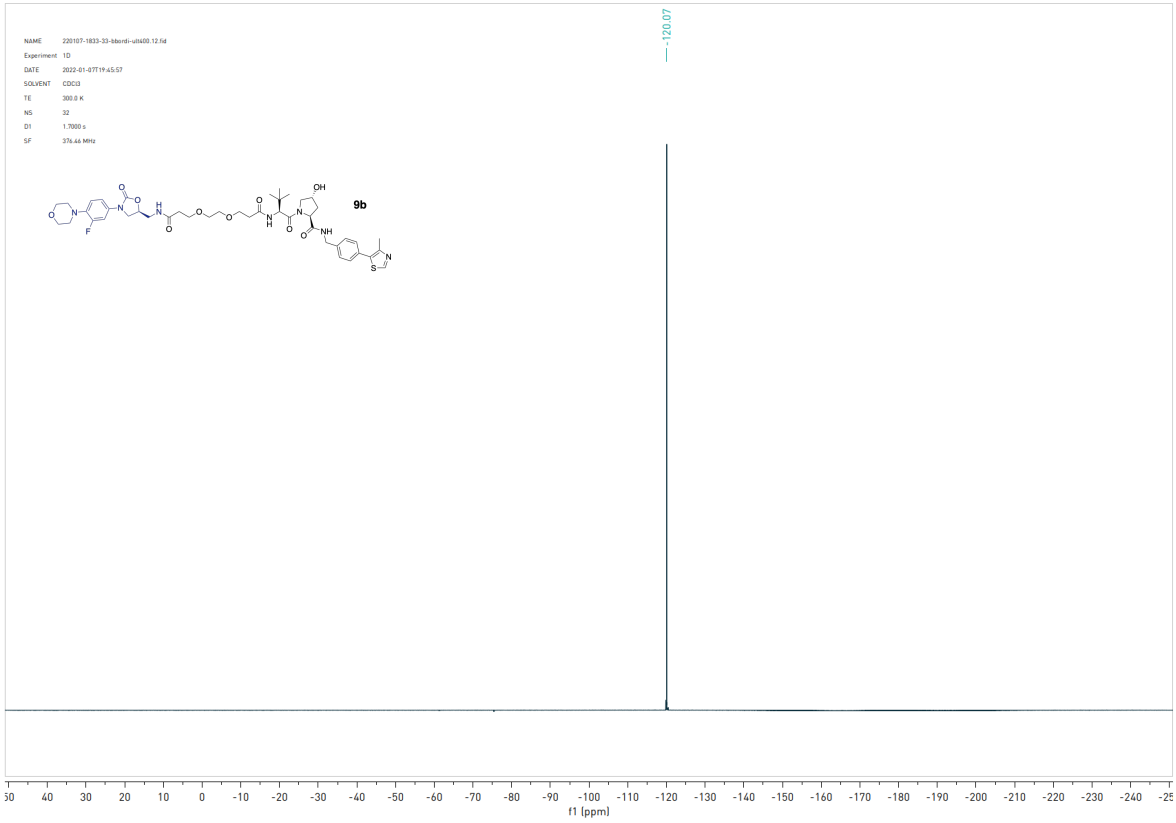


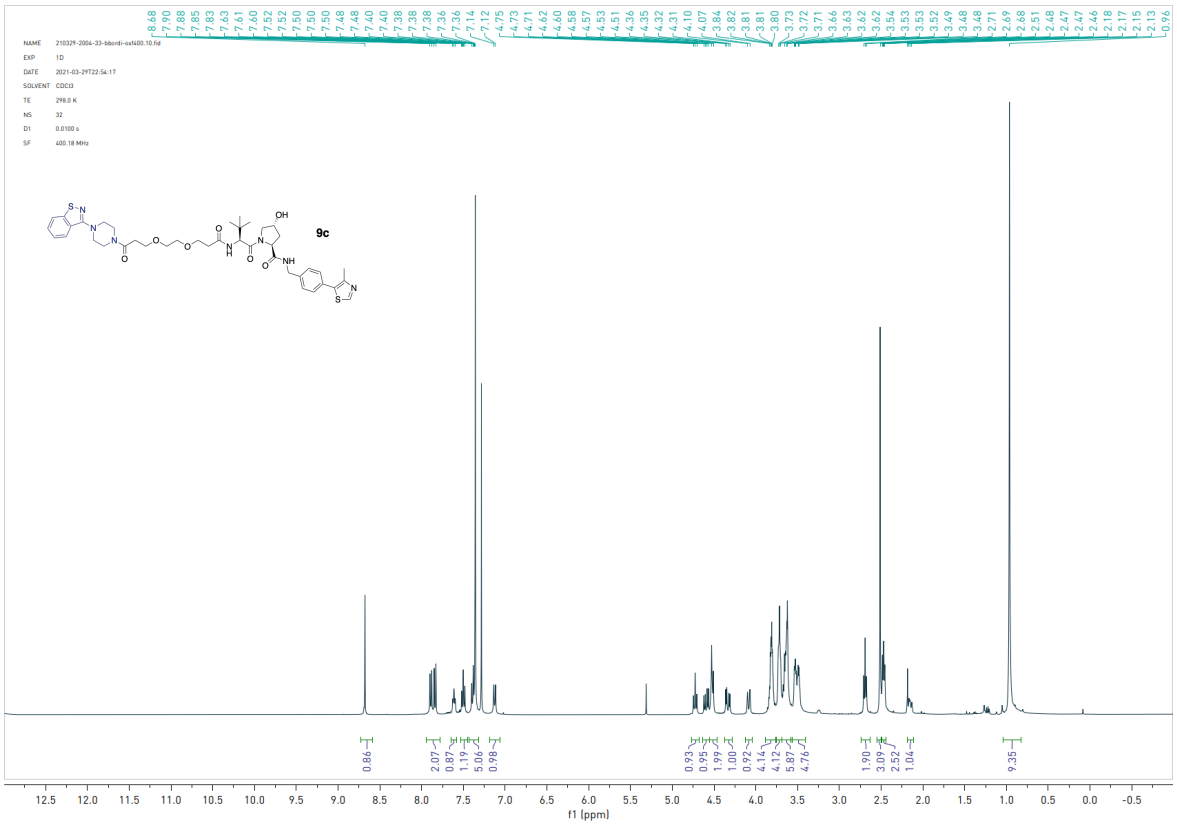
NMR of compound **9b**:

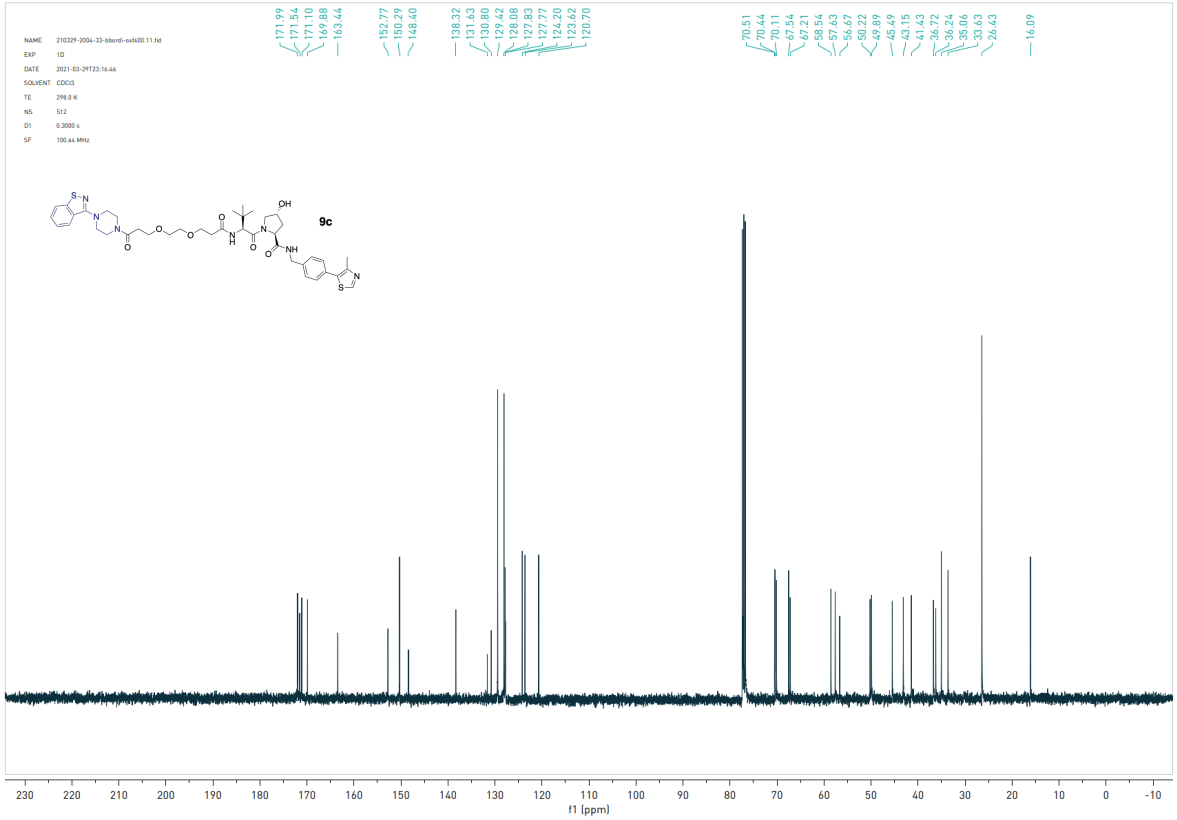


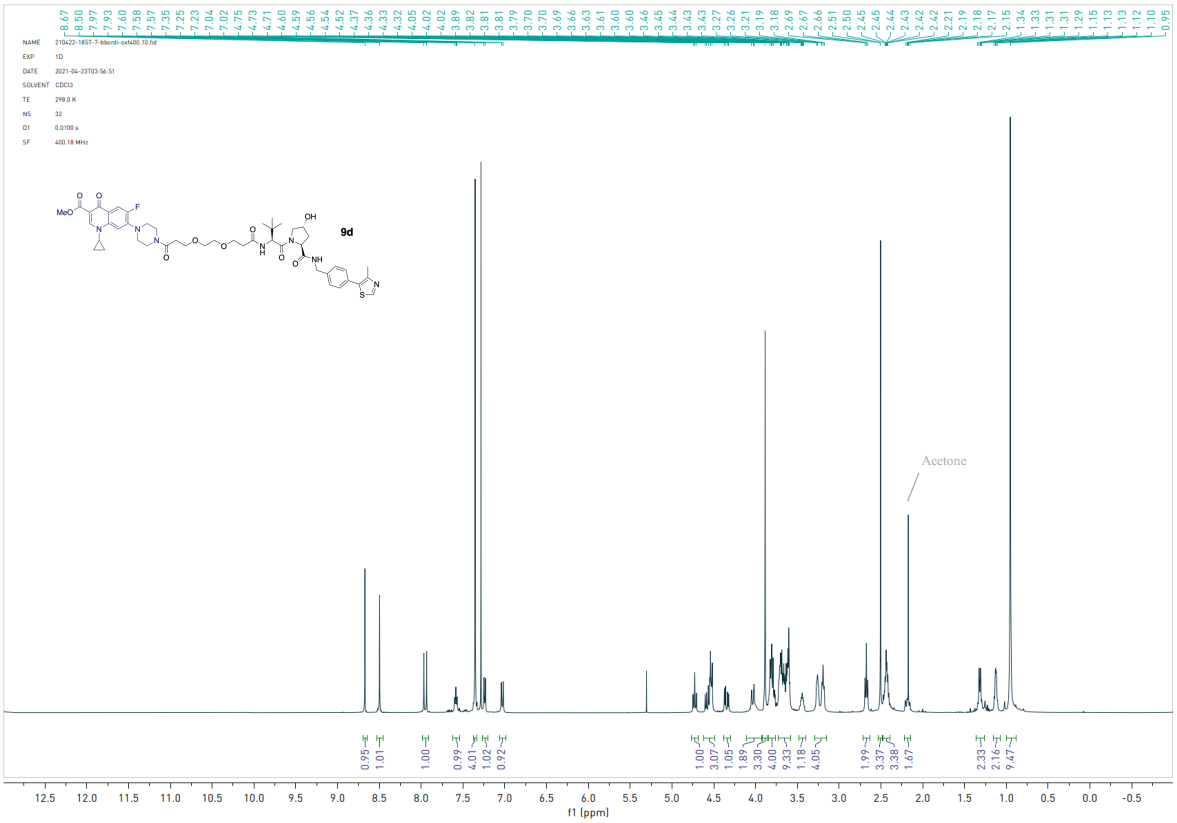

NAME 220107-1833-33-bbordi-ut400.12.fid
Experiment 1D
DATE 2022-01-07T19:45:57
SOLVENT CDCl3
TE 300.0 K
NS 32
D1 1.7000 s
SF 376.46 MHz
9b
-120.07
f1 (ppm)

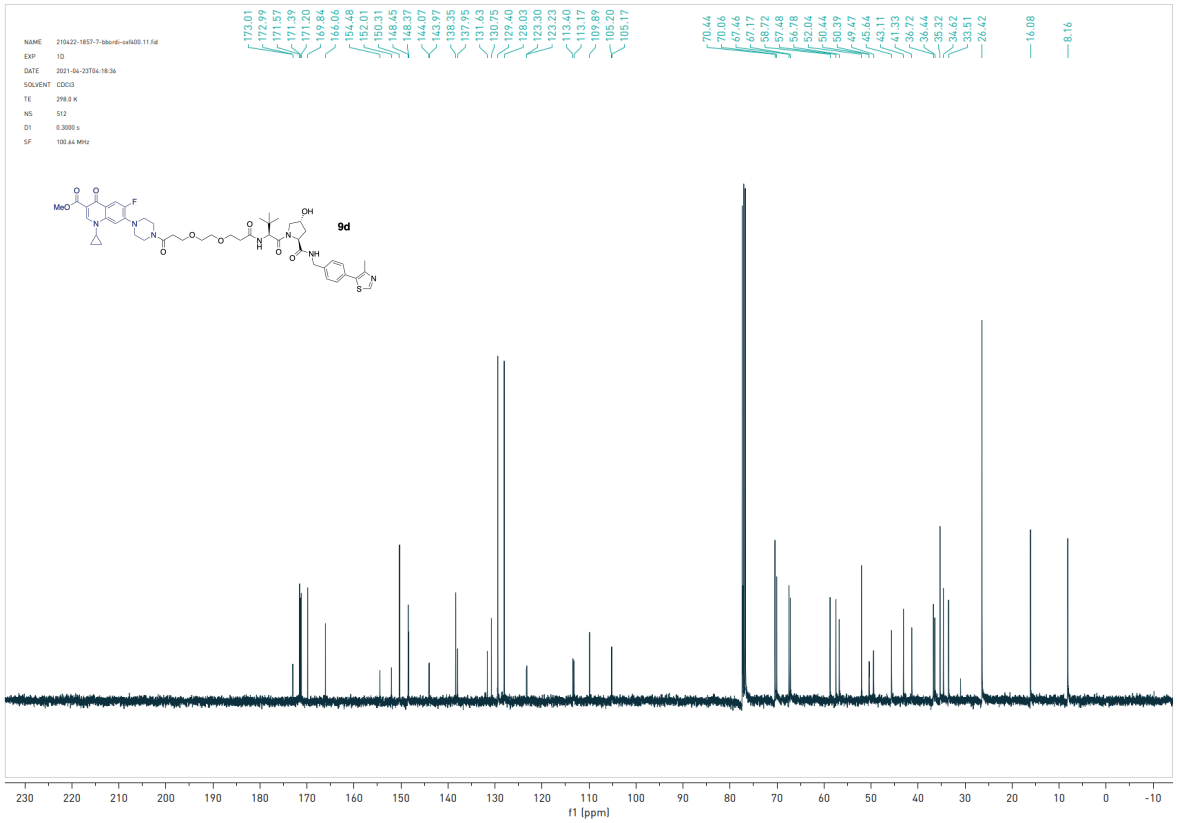
NMR of compound **9c**:



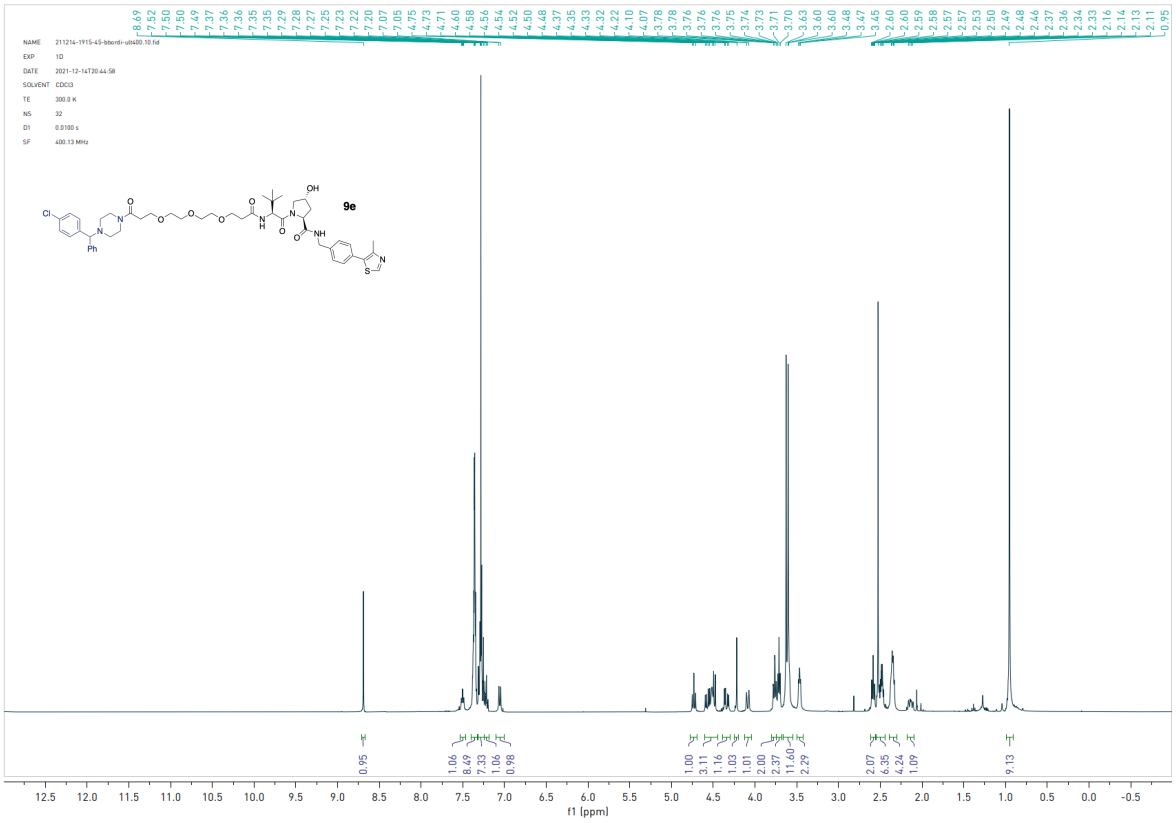



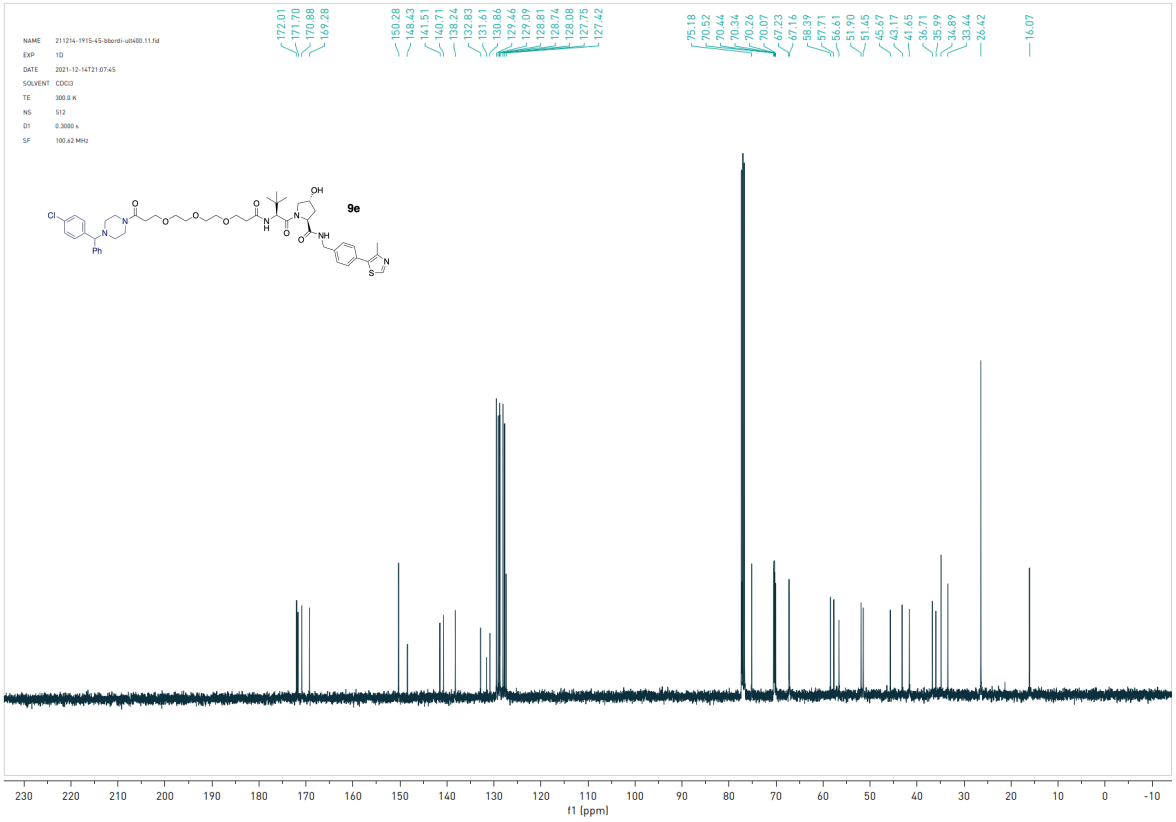
NMR of compound **9d**:



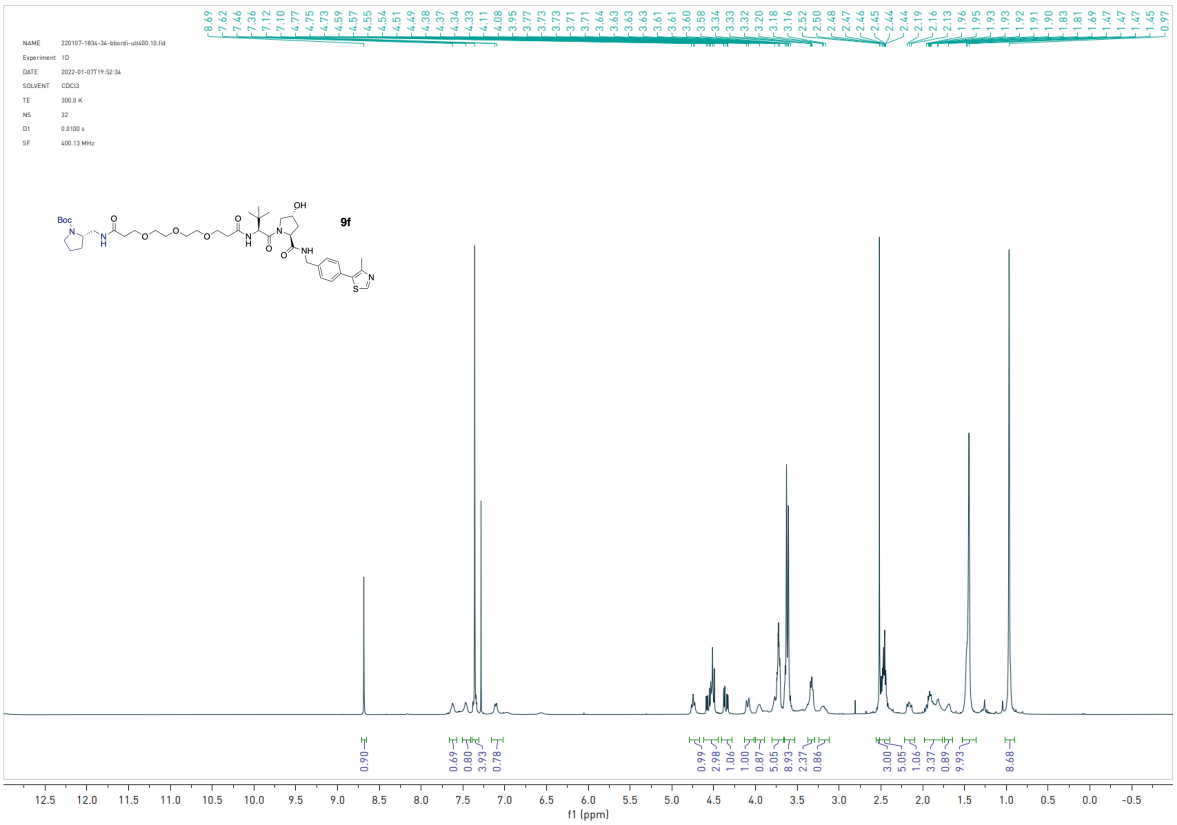



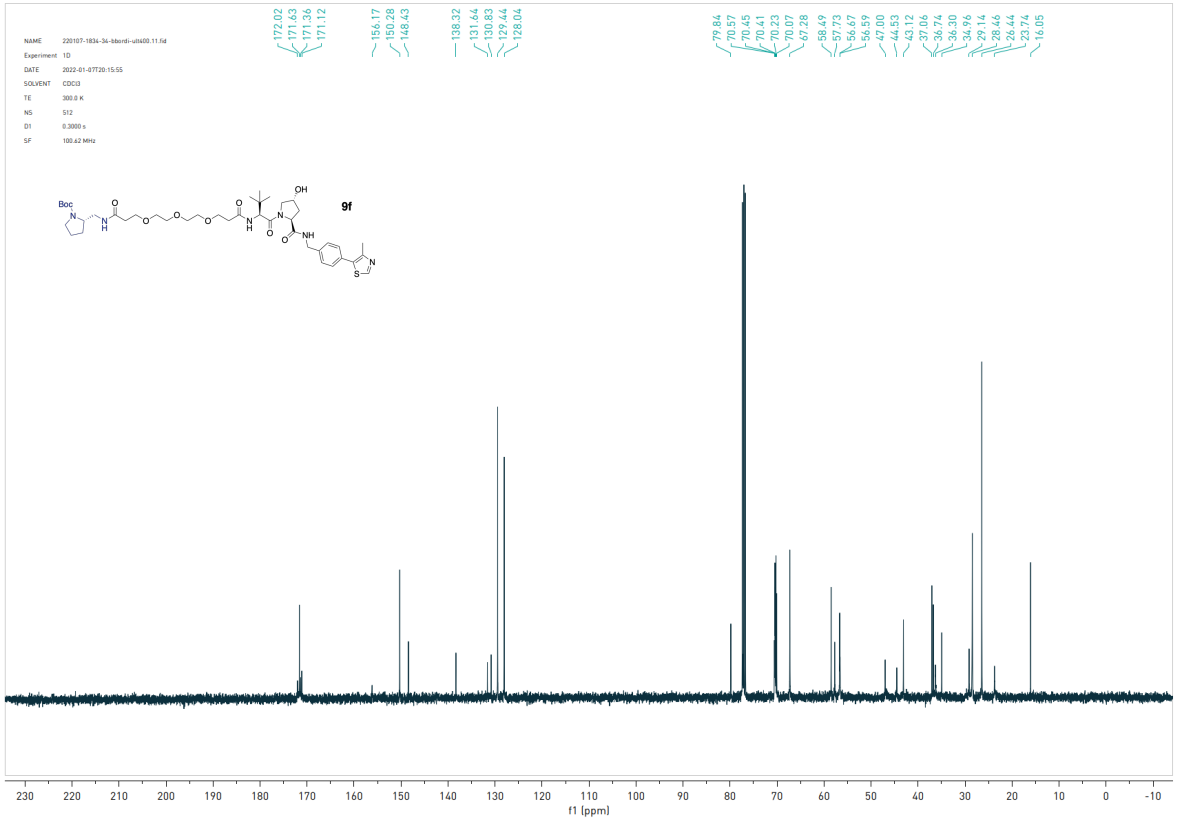
NMR of compound **9e**:



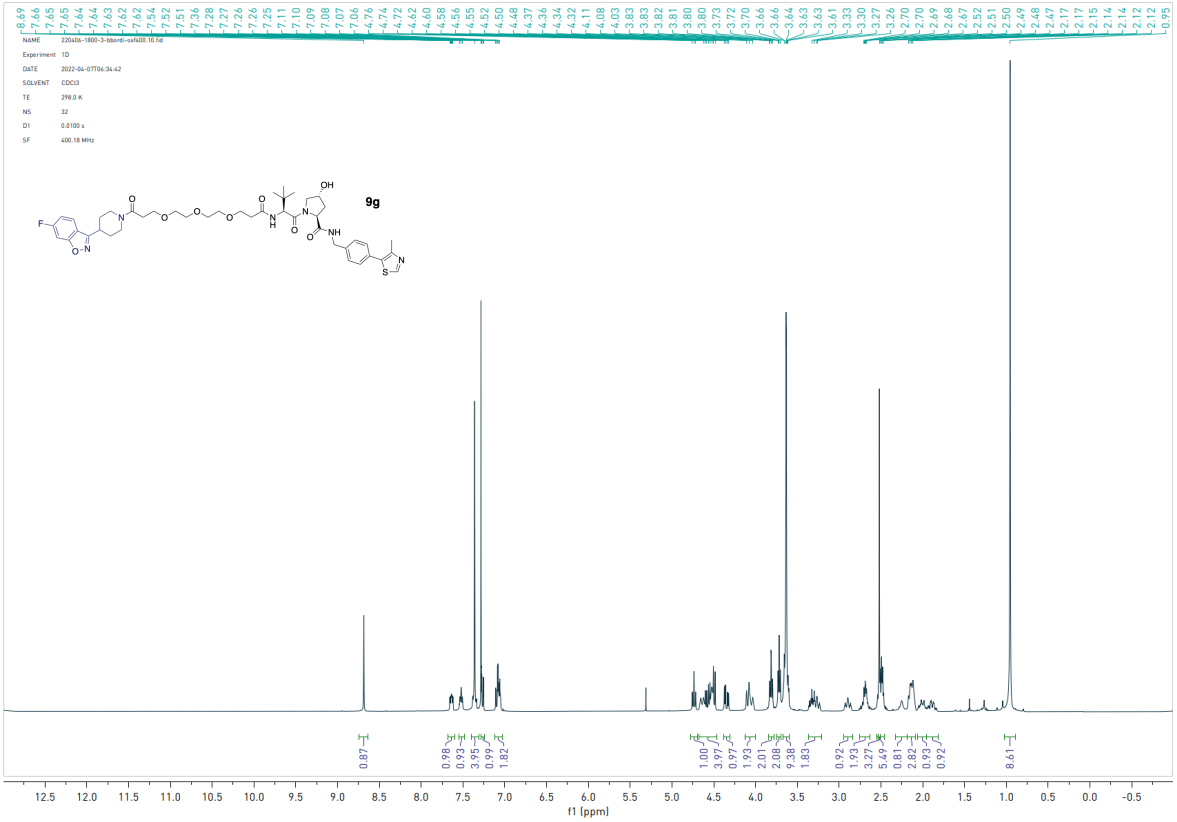



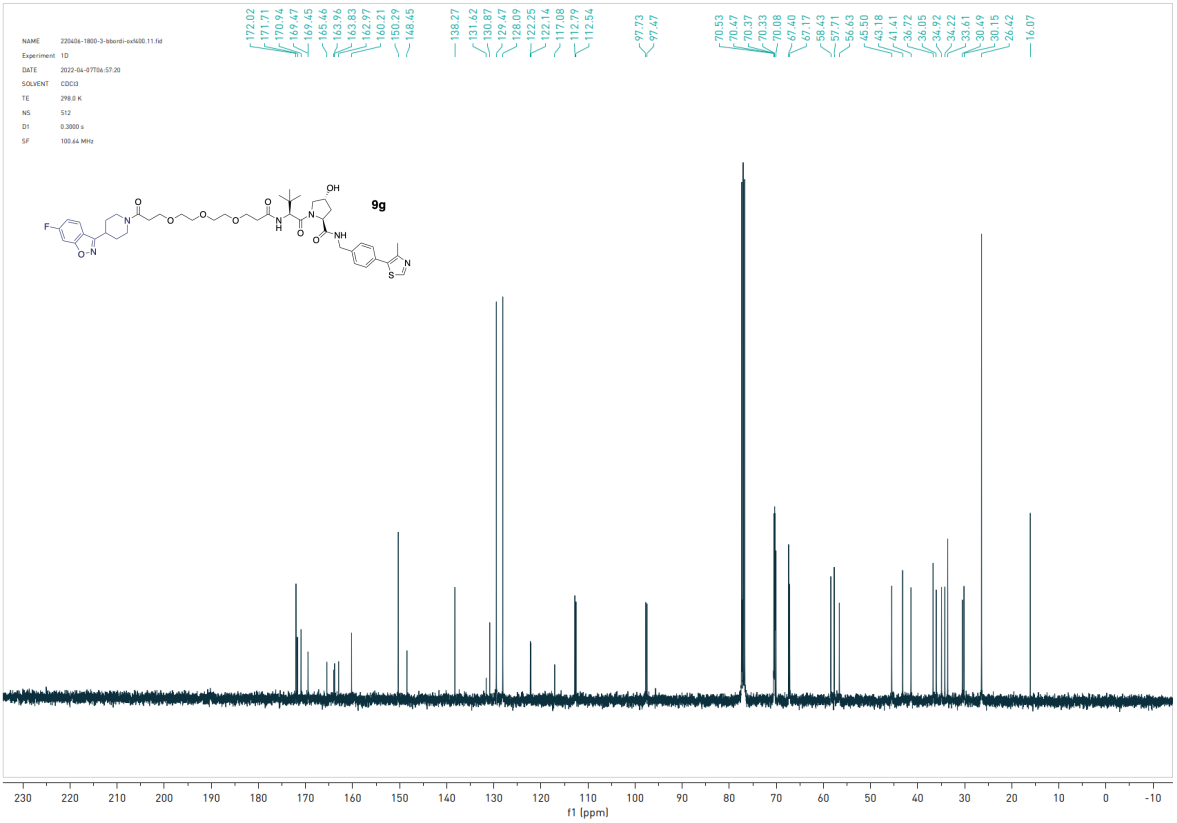
NMR of compound **9f**:

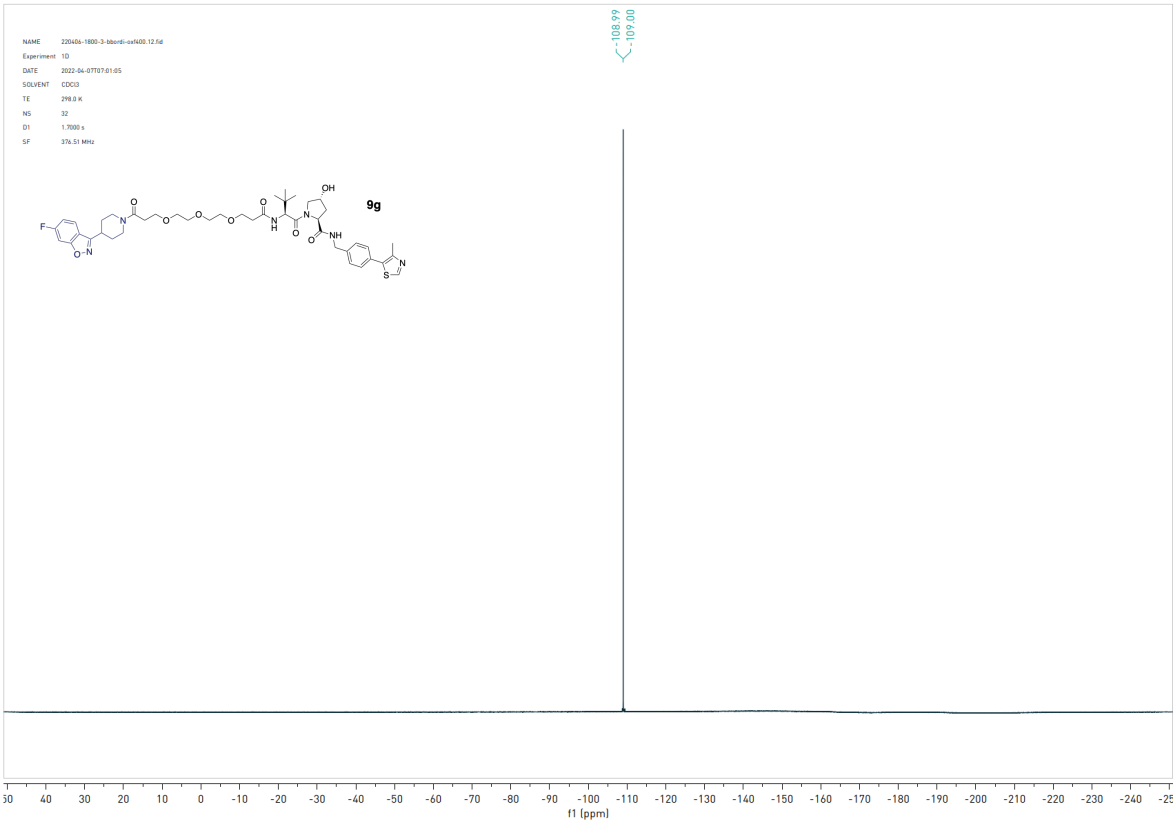


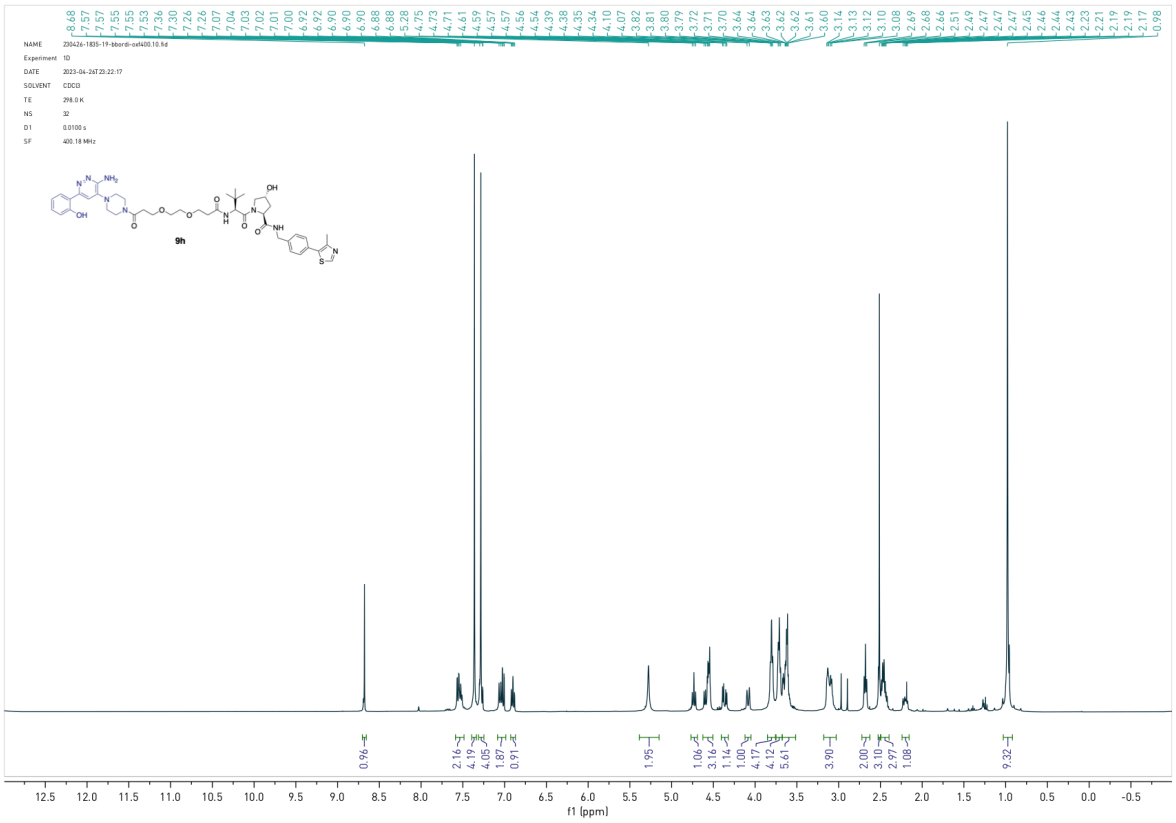
NMR of compound **9g**:

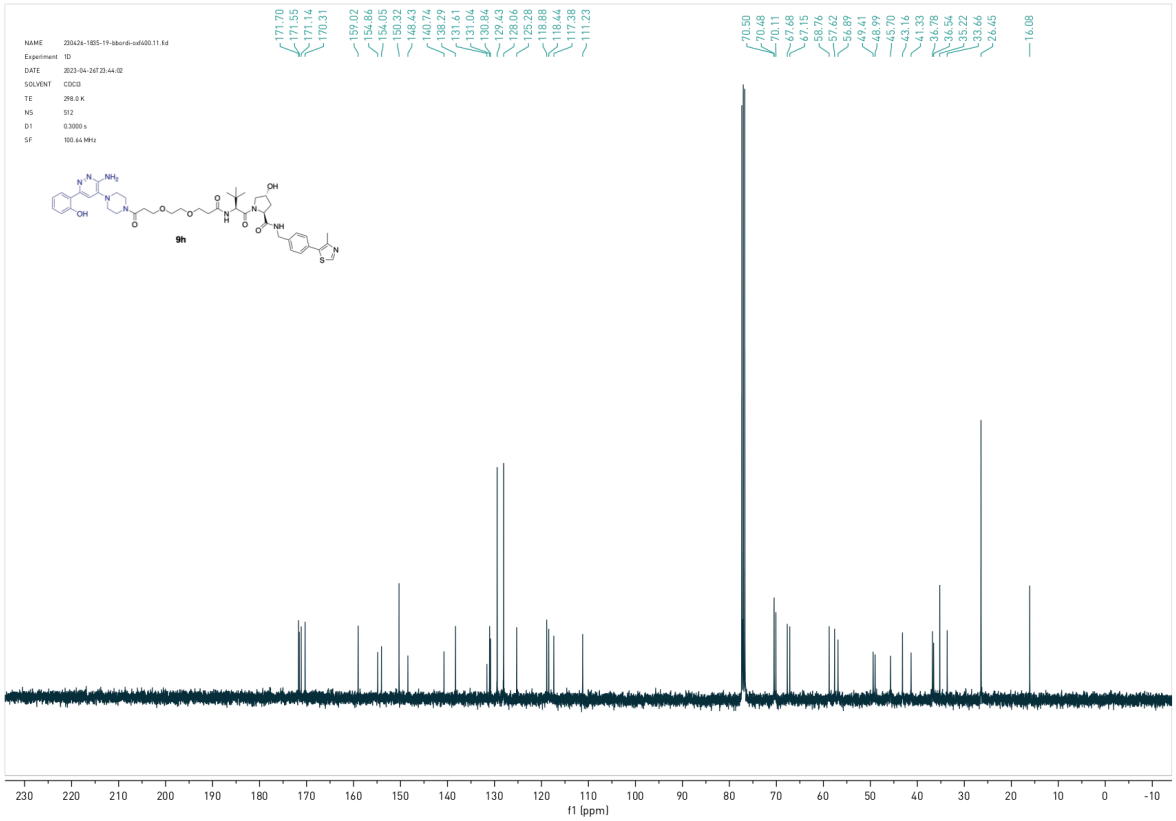



NAME 220406-1800-3-bbordi-ox400.12.fid
Experiment 1D
DATE 2022-04-07T07:01:05
SOLVENT CDCl3
TE 298.0 K
NS 32
D1 1.7000 s
SF 376.51 MHz
9g
-108.99
-109.00
f1 (ppm)

NMR of compound **9h**:



NMR of compound **9h**: