

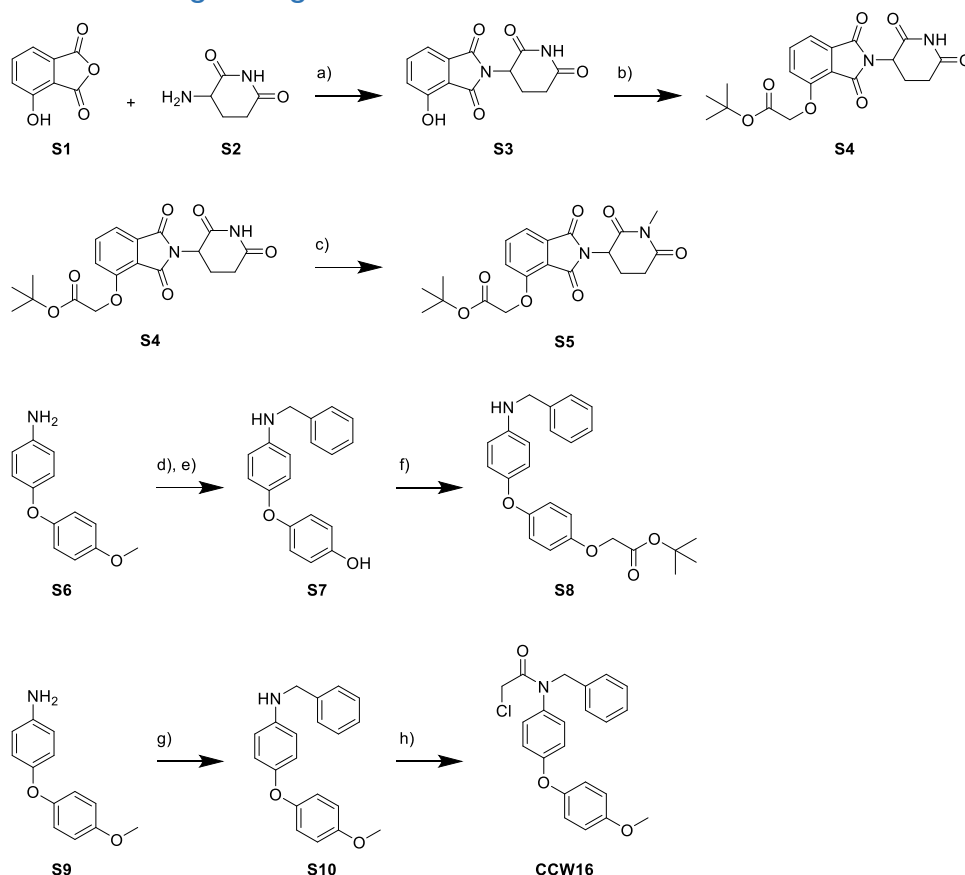
Appendix for
***Cysteine-reactive covalent chloro-N-acetamide ligands induce
ferroptosis mediated cell death***

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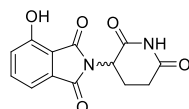
1. Synthetic procedures

1.1 Synthesis of E3 ligase ligands



Appendix Figure S1: Synthesis of CRBN and RNF4 ligands **S4**, **S7** and **CCW16**. a) KOAc, AcOH, reflux, 3 h; b) *tert*-butyl bromoacetate, K_2CO_3 , DMF, r.t., 4 h; c) K_2CO_3 , MeI; DMF, r.t., 5 h; d) BBr_3 , DCM, $-10\text{ }^\circ\text{C}$, then r.t., 2 h; e) benzaldehyde, AcOH, DCM, r.t., 30 min, then $NaBH(AcO)_3$, r.t., 21 h; f) NaH, THF, $0\text{ }^\circ\text{C}$, 15 min, then *tert*-butyl 2-bromoacetate, r.t., 3 h; g) benzaldehyde, $NaBH(AcO)_3$, AcOH, DCM, r.t., overnight; h) 2-chloroacetyl chloride, TEA, DCM, r.t., overnight.

2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione **S3**



A solution of 4-hydroxyisobenzofuran-1,3-dione **S1** (2.00 g, 12.2 mmol, 1.0eq), 3-aminopiperidine-2,6-dione hydrochloride **S2** (2.21 g, 13.4 mmol, 1.1eq) and potassium acetate (3.71 g, 37.8 mmol, 3.1eq) in acetic acid (40 mL) was refluxed for 3 h. The reaction mixture was poured on water and the precipitate was filtered. After washing with water and hexanes, the title compound was isolated as an off-white solid (2.62 g, 78%).

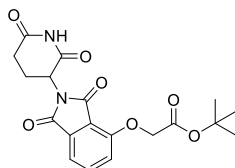
1H NMR (500 MHz, $DMSO-d_6$): δ = 11.16 (s, 1H), 11.07 (s, 1H), 7.65 (dd, 3J = 8.3 Hz, 3J = 7.3 Hz, 1H), 7.32 (d, 3J = 7.1 Hz, 1H), 7.25 (d, 3J = 8.4 Hz, 1H), 5.07 (dd, 3J = 12.8 Hz, 3J = 5.4 Hz, 1H), 2.94-2.82 (m, 1H), 2.65-2.51 (m, 2H), 2.08-1.97 (m, 1H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 172.8, 169.97, 166.99, 165.8, 155.5, 136.3, 133.1, 123.6, 114.4, 114.2, 48.6, 30.9, 22.0.

MS (ESI+):

275.0	[(M+H) ⁺	calc. 275.07]
297.0	[(M+Na) ⁺	calc. 297.05]
338.0	[(M+Na+ACN) ⁺	calc. 338.08]

tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4**



tert-Butylbromoacetate (1.1 mL, 7.7 mmol, 1.1eq) was added to a solution of 2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisindoline-1,3-dione **S3** (2.00 g, 7.29 mmol, 1.0eq) and potassiumcarbonate (2.02 g, 14.59 mmol, 2.0eq) in DMF (40 mL). The reaction mixture was stirred for 4 h. Ethylacetate and water were added and the layers were separated. The aqueous layer was extracted with ethylacetate (4x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (H/EE). The title compound was isolated as a colorless solid (1.71 g, 60%).

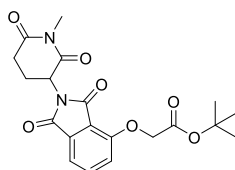
¹H NMR (500 MHz, DMSO-*d*₆): δ = 11.10 (s, 1H), 7.80 (dd, ³J = 8.5 Hz, ³J = 7.3 Hz, 1H), 7.48 (d, ³J = 7.1 Hz, 1H), 7.38 (d, ³J = 8.5 Hz, 1H), 5.10 (dd, ³J = 12.8 Hz, ³J = 5.5 Hz, 1H), 4.97 (s, 2H), 2.89 (ddd, ³J = 16.9 Hz, ³J = 13.9 Hz, ⁴J = 5.4 Hz, 1H), 2.65-2.51 (m, 2H), 2.08-2.01 (m, 1H), 1.43 (s, 9H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 172.8, 169.9, 167.1, 166.7, 165.1, 155.0, 136.8, 133.3, 119.97, 116.5, 115.9, 81.9, 65.5, 48.8, 30.9, 27.7, 21.95.

MS (ESI+):

333.0	[(M- ^t Bu+2H) ⁺	calc. 333.07]
411.0	[(M+Na) ⁺	calc. 411.19]
799.3	[(2M+Na) ⁺	calc. 799.25]

tert-butyl 2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S5**



Methyliodide (2M in MTBE, 965 μ L, 5.0eq) was added to a solution of *tert*-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4** (150 mg, 386 μ mol, 1.0eq) and K_2CO_3 (107 mg, 772 μ mol, 2.0eq) in DMF (2 mL). The reaction mixture was stirred for 5 h. Ethylacetate and water were added and the layers were separated. The aqueous layer was extracted with ethylacetate (4x) and the combined organic layers were dried with Na_2SO_4 . The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (DCM/MeOH). The title compound was isolated as a colorless solid (75 mg, 57%).

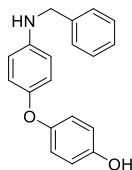
1H NMR (500 MHz, DCM): δ = 7.69 (dd, 3J = 8.5 Hz, 3J = 7.3 Hz, 1H), 7.49 (dd, 3J = 7.3, 0.5 Hz, 1H), 7.11 (d, 3J = 8.2 Hz, 1H), 4.97-4.92 (m, 1H), 4.76 (s, 2H), 3.16 (s, 3H), 2.97-2.88 (m, 1H), 2.81-2.71 (m, 2H), 2.13-2.04 (m, 1H), 1.48 (s, 9H).

^{13}C NMR (126 MHz, DCM): δ = 171.7, 169.4, 167.5, 167.4, 166.1, 156.0, 136.8, 134.6, 120.0, 118.1, 117.0, 83.4, 67, 50.5, 32.5, 28.3, 27.5, 22.4.

MS (ESI+):

347.0	$[(M-^tBu+2H)^+]$	calc. 347.08]
425.0	$[(M+Na)^+]$	calc. 425.13]
827.3	$[(2M+Na)^+]$	calc. 827.27]

4-(4-(benzylamino)phenoxy)phenol **S7** via 4-(4-aminophenoxy)phenol



BBr_3 (34.8 mL, 1 M/DCM, 3.0eq) was added to a solution of 4-(4-methoxyphenoxy)aniline **S6** (2.50 g, 11.6 mmol, 1.0eq) in DCM (40 mL) at -10 $^{\circ}C$. The reaction mixture was stirred at r.t. for 2 h. The reaction was quenched with a saturated solution of $NaHCO_3$. The layers were separated and the aqueous layer was extracted with ethylacetate (3x). The combined organic layers were dried with $MgSO_4$ and the solvent was removed under reduced pressure to yield the title compound as a brown solid (1.49 g, 64%). The crude product was used without further purification in the next step.

Acetic acid (0.950 mL, 16.65 mmol, 1.1eq) and benzaldehyde (0.5578 mL, 5.47 mmol, 1.1eq) were added to a solution of crude 4-(4-aminophenoxy)phenol (1.00 g, 4.97 mmol) in DCM (50 mL). The reaction mixture was stirred for 30 min and sodium triacetoxymethylborohydride (1.58 g, 7.45 mmol, 1.5eq) was added. The mixture was stirred for 21 h. All volatiles were removed under reduced pressure. Flash column chromatography (H/EE) yielded the title compound (0.933 g, 64%) as colorless oil.

1H NMR (500 MHz, CD_2Cl_2): δ = 7.40-7.25 (m, 5H), 6.84-6.79 (m, 4H), 6.77-6.73 (m, 2H), 6.64-6.59 (m, 2H), 4.31 (s, 2H).

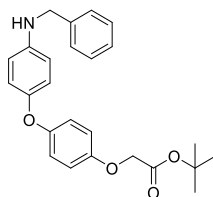
¹³C NMR (126 MHz, CD₂Cl₂): δ = 152.8, 151.6, 149.9, 144.7, 140.1, 129.1, 128.1, 127.7, 120.5, 119.6, 116.6, 114.5, 49.4.

MS (ESI+):

292.1	[(M+H) ⁺	calc. 292.14]
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293.0	[(M+2H) ²⁺	calc. 293.14]
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tert-butyl 2-(4-(4-(benzylamino)phenoxy)phenoxy)acetate **S8**



Sodium hydride (60% dispersion on mineral oil; 0.66 mg, 16.5 mmol, 3.0eq) was added to a solution of 4-(4-(benzylamino)phenoxy)phenol **S7** (1.60 mg, 5.49 mmol, 1.0eq) in THF (50 mL) at 0 °C. The reaction mixture was stirred at for 15 min. *tert*-butyl 2-bromoacetate (0.81 mL, 5.49 mmol, 1.0eq) was added and the reaction was stirred at r.t. for 3 h. All volatiles were removed under reduced pressure and the residue was dissolved with DCM and water. The layers were separated and the aqueous layer was extracted with DCM (2x). The combined organic layers were dried with MgSO₄ and the crude material was purified using flash column chromatography (CH/Ea). The title compound was isolated as yellow oil (1.32 mg, 59%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 7.41-7.25 (m, 5H), 6.89-6.78 (m, 6H), 6.64-6.59 (m, 2H), 4.46 (s, 2H), 4.31 (s, 2H), 1.48 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 168.6, 153.9, 153.6, 149.4, 145.0, 140.2, 129.1, 128.1, 127.7, 120.8, 119.2, 116.1, 114.4, 82.6, 66.9, 49.3, 28.3.

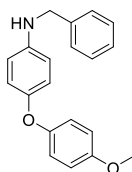
MS (ESI+):

406.1	[(M+H) ⁺	calc. 406.197]
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407.0	[(M+2H) ²⁺	calc. 407.20]
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428.1	[(M+Na) ⁺	calc. 428.19]
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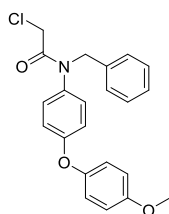
N-benzyl-4-(4-methoxyphenoxy)aniline **S9**



NaBH(OAc)₃ (2.88 g, 13.6 mmol, 1.5eq) was added to a solution of 4-(4-methoxyphenoxy)aniline **S6** (1.95 g, 9.06 mmol, 1.0eq), benzaldehyde (1.1 mL,

10.9 mmol, 1.2eq) and acetic acid (622 μ L, 10.9 mmol, 1.2eq) in DCM (80 mL). The reaction mixture was stirred overnight. The solvent removed under reduced pressure and the residue was dissolved in ethyl acetate and a sat. NaHCO_3 solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (2x). The combined organic layers were washed with water and dried using MgSO_4 . The solvent was removed under reduced pressure and the crude material was purified using flash column chromatography (CH/EA). The title compound was isolated as a yellow oil and was used directly for the next step.

N-benzyl-2-chloro-N-(4-(4-methoxyphenoxy)phenyl)acetamide **CCW16**



2-chloroacetyl chloride (238 μ L, 2.99 mmol, 4.0eq) and TEA (416 μ L, 2.99 mmol, 4.0eq) were added to a solution of N-benzyl-4-(4-methoxyphenoxy)aniline **S10** (288 mg, 0.747 mmol, 1.0eq) in DCM (20 mL). The reaction mixture was stirred overnight. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried with MgSO_4 . Reversed phase flash column chromatography (ACN/water) yielded the title compound as a yellow solid (120 mg, 42%).

$^1\text{H NMR}$ (500 MHz, CD_2Cl_2): δ = 7.32-7.19 (m, 5H), 7.01-6.94 (m, 4H), 6.93-6.89 (m, 2H), 6.89-6.85 (m, 2H), 4.86 (s, 2H), 3.90 (s, 2H), 3.80 (s, 3H).

$^{13}\text{C NMR}$ (126 MHz, CD_2Cl_2): δ = 166.7, 159.4, 157.1, 149.6, 137.5, 135.5, 130.1, 129.3, 128.98, 128.1, 121.8, 118.4, 115.5, 56.2, 54.1, 42.9.

HPLC: R_t = 5.18 min (method A): Purity: >98% (254 nm); >98% (320 nm)

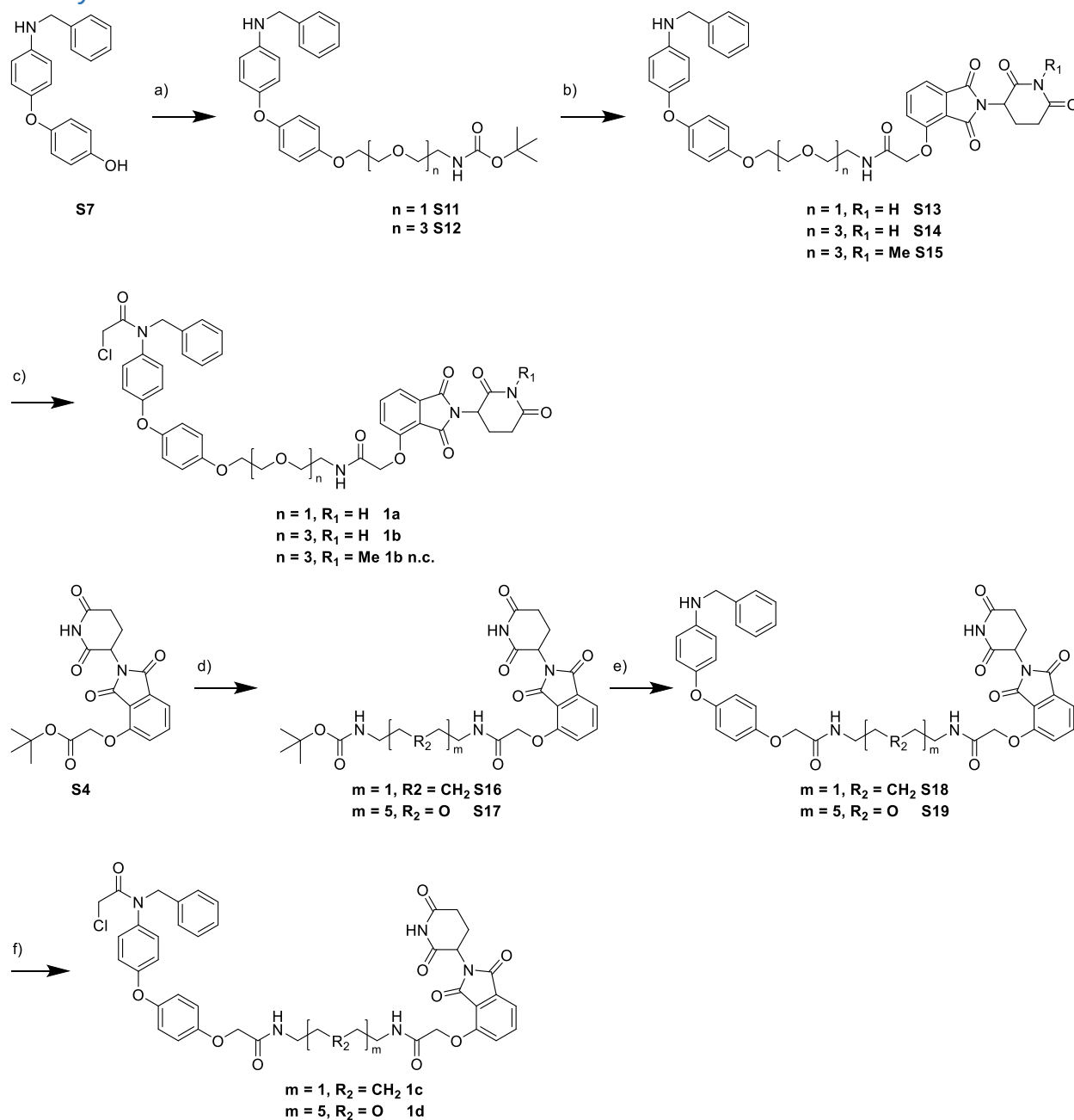
MS (ESI+):

382.0	$[(M+H)^+]$	calc. 382.12]
384.0	$[(M+3H)^{3+}]$	calc. 384.13]

HRMS (ESI+):

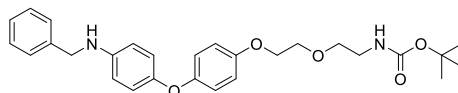
382.1199	$[(M+H)^+]$	calc. 382.1205]
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1.2 Synthesis of CRBN-based PROTACs



Appendix Figure S2: Synthesis of CRBN based PROTACs **1a-d** and negative control **1b n.c.**: a) appropriate linker bromide, K₂CO₃, Acetone, reflux, overnight; b) 1. intermediate **S4** or **S5**, TFA, DCM, r.t., 2-3 h; 2. DIPEA, HATU, DMF, r.t., 18 h; c) 2-chloroacetyl chloride, TEA, r.t., 16-18 h; d) 1. TFA, DCM, r.t., 2 h; 2. DIPEA, HATU, DMF, r.t., 18 h; e) 1. intermediate **S8**, TFA, DCM, r.t., 2-3 h; 2. DIPEA, HATU, DMF, r.t., 12-18 h; f) 2-chloroacetyl chloride, TEA, r.t., 17-20 h.

tert-butyl (2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)carbamate **S11**



A solution of 4-(4-(benzylamino)phenoxy)phenol **S7** (36 mg, 124 μmol , 1.0eq), tert-butyl (2-(2-bromoethoxy)ethyl)carbamate (50 mg, 186 μmol , 1.5eq) and potassium carbonate (52 mg, 373 μmol , 3.0eq) in Acetone (5 mL) was refluxed overnight. The solvent was removed under reduced pressure. The residue was dissolved with DCM and water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried with MgSO_4 and the solvent was removed under reduced pressure. Reversed phase column chromatography (ACN/water) yielded the title compound as a yellow oil (26 mg, 44%).

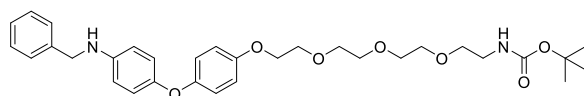
^1H NMR (500 MHz, CD_2Cl_2): δ = 7.41-7.25 (m, 5H), 6.90-6.80 (m, 6H), 6.64-6.58 (m, 2H), 5.01 (s, 1H), 4.31 (s, 2H), 4.10 (s, 1H), 4.08-4.04 (m, 2H), 3.81-3.74 (m, 2H), 3.58 (t, 3J = 5.3 Hz, 2H), 3.30 (dd, 3J = 10.7 Hz, 3J = 5.4 Hz, 2H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 156.4, 154.7, 153.1, 149.6, 145.2, 140.3, 129.1, 128.0, 127.7, 120.6, 119.4, 116.0, 114.3, 70.9, 70.1, 68.6, 55.7, 49.2, 40.96, 28.7.

MS (ESI+):

379.2	$[(\text{M-Boc}+2\text{H})^+]$	calc. 379.20]
423.2	$[(\text{M-Boc}+2\text{Na})^{3+}]$	calc. 423.17]
501.3	$[(\text{M}+\text{Na})^+]$	calc. 501.24]

tert-butyl (2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **S12**



A solution of 4-(4-(benzylamino)phenoxy)phenol **S7** (61 mg, 211 μmol , 1.0eq), tert-butyl (2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethyl)carbamate (75 mg, 211 μmol , 1.0eq) and potassium carbonate (87 mg, 632 μmol , 3.0eq) in Acetone (10 mL) was refluxed overnight. The solvent was removed under reduced pressure. The residue was dissolved with DCM and water. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were dried with MgSO_4 and the solvent was removed under reduced pressure. Reversed phase column chromatography (ACN/water) yielded the title compound as a colorless oil (88 mg, 74%).

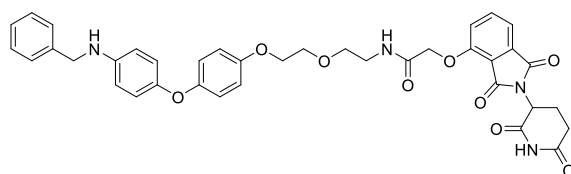
^1H NMR (500 MHz, CD_2Cl_2): δ = 7.41-7.33 (m, 4H), 7.30-7.26 (m, 1H), 6.90-6.80 (m, 6H), 6.64-6.59 (m, 2H), 5.16 (s, 1H), 4.31 (s, 2H), 4.13 (s, 1H), 4.07 (dd, 3J = 5.4 Hz, 3J = 4.0 Hz, 2H), 3.80 (dd, 3J = 5.3 Hz, 3J = 4.1 Hz, 2H), 3.69 (dd, 3J = 6.1 Hz, 3J = 3.2 Hz, 2H), 3.67-3.57 (m, 6H), 3.51 (t, 3J = 5.2 Hz, 2H), 3.27 (dd, 3J = 10.3 Hz, 3J = 5.1 Hz, 2H), 1.43 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 156.4, 154.7, 153.1, 149.6, 145.1, 140.3, 129.1, 127.99, 127.7, 120.6, 119.3, 115.99, 114.3, 79.3, 71.3, 71.1, 71.0, 70.8, 70.7, 70.3, 68.6, 49.2, 40.99, 28.7.

MS (ESI+):

467.1	[(M-Boc+2H) ⁺	calc. 467.25]
511.2	[(M-Boc+2Na) ⁺	calc. 511.23]
567.3	[(M+H) ⁺	calc. 567.31]

N-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S13**



A solution of tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4** (52 mg, 109 μmol, 1.1eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of the crude amine, DIPEA (43 μL, 247 μmol, 2.5eq), the crude acid and HATU (45 mg, 119 μmol, 1.2eq) in DMF (2 mL) was stirred for 18 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column chromatography to yield the title compound as a yellow solid (40 mg, 58%).

A solution of the crude amine, DIPEA (43 μL, 247 μmol, 2.5eq), the crude acid and HATU (45 mg, 119 μmol, 1.2eq) in DMF (2 mL) was stirred for 18 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column chromatography to yield the title compound as a yellow solid (40 mg, 58%).

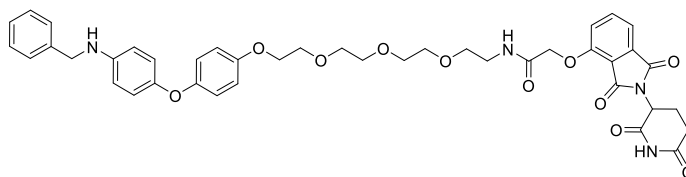
¹H NMR (500 MHz, CD₂Cl₂): δ = 8.45 (s, 1H), 7.71 (dd, ³J = 8.4 Hz, ³J = 7.4 Hz, 1H), 7.54 (t, ³J = 5.3 Hz, 1H), 7.50 (dd, ³J = 7.3 Hz, ⁴J = 0.4 Hz, 1H), 7.41-7.32 (m, 4H), 7.29-7.24 (m, 1H), 7.19 (d, ³J = 8.4 Hz, 1H), 6.82-6.77 (m, 6H), 6.62-6.58 (m, 2H), 4.90 (dd, ³J = 12.4 Hz, ³J = 5.4 Hz, 1H), 4.62 (s, 2H), 4.30 (s, 2H), 4.12 (s, 1H), 4.07 (dd, ³J = 6.0 Hz, ³J = 3.9 Hz, 2H), 3.84-3.78 (m, 2H), 3.68 (q, ³J = 5.4 Hz, 2H), 3.59-3.52 (m, 2H), 2.82-2.60 (m, 3H), 2.11-2.04 (m, 1H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 171.6, 168.9, 167.3, 167.2, 166.4, 155.0, 154.6, 153.1, 149.4, 145.1, 140.3, 137.5, 134.1, 129.1, 128.0, 127.7, 120.7, 120.1, 119.2, 118.5, 117.5, 115.95, 114.3, 70.2, 70.0, 68.6, 68.5, 49.8, 49.2, 39.5, 31.9, 23.1.

MS (ESI+):

347.1	[(M/2+H) ⁺	calc. 347.13]
693.3	[(M+H) ⁺	calc. 693.26]

N-(2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S14**



A solution of tert-butyl 2-((2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **S12** (58 mg, 102 μmol, 1.1eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4** (93 mg, 36 μmol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of the crude amine, DIPEA (41 μL, 233 μmol, 2.5eq), the crude acid and HATU (42 mg, 112 μmol, 1.2eq) in DMF (2 mL) was stirred for 18 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reverse flash column chromatography to yield the title compound as a yellow oil (21 mg, 29%).

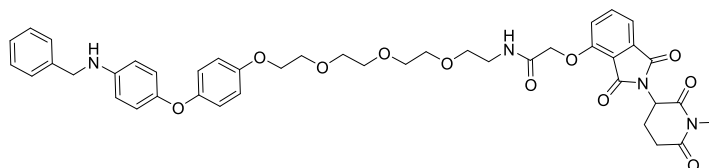
¹H NMR (500 MHz, DMSO-*d*₆): δ = 8.76 (s, 1H), 7.73 (dd, ³J = 8.4 Hz, ³J = 7.4 Hz, 1H), 7.56 (t, ³J = 4.9 Hz, 1H), 7.52 (d, ³J = 7.3 Hz, 1H), 7.41-7.24 (m, 5H), 7.21 (d, ³J = 8.4 Hz, 1H), 6.87-6.79 (m, 6H), 6.63-6.58 (m, 2H), 4.90 (dd, ³J = 12.4 Hz, ³J = 5.4 Hz, 1H), 4.63 (s, 2H), 4.30 (s, 2H), 4.08-4.04 (m, 2H), 3.81-3.77 (m, 2H), 3.69-3.59 (m, 10H), 3.58-3.46 (m, 2H), 2.86-2.60 (m, 3H), 2.14-2.06 (m, 1H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 171.7, 168.9, 167.3, 167.2, 166.5, 155.1, 154.7, 153.1, 149.6, 145.1, 140.3, 137.5, 134.2, 129.1, 128.0, 127.7, 120.6, 120.1, 119.4, 118.5, 117.5, 115.96, 114.3, 71.3, 70.96, 70.83, 70.75, 70.2, 70.0, 68.6, 68.5, 49.8, 49.2, 39.6, 31.9, 23.2.

MS (ESI+):

391.3	[(M/2+H) ⁺	calc. 391.16]
781.3	[(M+H) ⁺	calc. 781.30]

N-(2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S15**



A solution of tert-butyl 2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **S12** (22 mg, 39 μ mol, 1.1eq) in DCM/TFA (4 mL, 1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl 2-(2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S5** (14 mg, 35 μ mol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of the crude amine, DIPEA (25 μ L, 141 μ mol, 4.0eq), the crude acid and HATU (16 mg, 42 μ mol, 1.2eq) in DMF (2 mL) was stirred for 18 h. DCM, water and a sat. solution of NH₄Cl were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reverse flash column chromatography to yield the title compound as a yellow oil (21 mg, 75%).

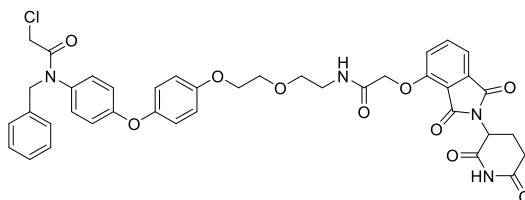
¹H NMR (500 MHz, CD₂Cl₂): δ = 7.75-7.71 (m, 1H), 7.53-7.47 (m, 2H), 7.40-7.32 (m, 4H), 7.27 (t, ³J = 7.1 Hz, 1H), 7.21 (d, ³J = 8.4 Hz, 1H), 6.88-6.78 (m, 6H), 6.66-6.61 (m, 2H), 4.99-4.93 (m, 1H), 4.64 (s, 2H), 4.31 (s, 2H), 4.07-4.02 (m, 2H), 3.80-3.74 (m, 2H), 3.66-3.58 (m, 10H), 3.52 (dd, ³J = 10.7 Hz, ³J = 5.4 Hz, 2H), 3.16 (s, 3H), 3.00-2.87 (m, 1H), 2.85-2.68 (m, 2H), 2.14-2.07 (m, 1H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 171.6, 169.4, 167.4, 167.3, 166.6, 155.1, 154.8, 152.9, 150.1, 144.3, 139.8, 137.5, 134.2, 129.1, 128.2, 127.8, 120.5, 120.2, 119.5, 118.6, 117.5, 115.99, 114.9, 71.3, 71.1, 71.0, 70.9, 70.3, 70.0, 68.7, 68.6, 50.6, 49.6, 39.6, 32.4, 27.5, 22.4.

MS (ESI+):

398.3	[(M/2+H) ⁺	calc. 398.17]
795.3	[(M+H) ⁺	calc. 795.33]

N-benzyl-2-chloro-N-(4-(4-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)ethoxy)ethoxy)phenoxy)phenyl)acetamide **1a**



2-chloroacetyl chloride (7 μ l, 92 μ mol, 1.3eq) and TEA (29 μ l, 211 μ mol, 3.0eq) were added to a solution of N-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S13** (49 mg, 70 μ mol, 1.0eq) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 20 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO_4 . Reversed phase flash column chromatography (ACN/water) yielded the title compound as a colorless oil (40 mg, 74%).

^1H NMR (500 MHz, CD_2Cl_2): δ = 8.67-8.48 (m, 1H), 7.75-7.70 (m, 1H), 7.54 (t, 3J = 5.0 Hz, 1H), 7.51 (d, 3J = 7.3 Hz, 1H), 7.31-7.17 (m, 6H), 6.98-6.94 (m, 2H), 6.94-6.87 (m, 4H), 6.87-6.83 (m, 2H), 4.92 (dd, 3J = 12.2 Hz, 3J = 5.3 Hz, 1H), 4.85 (s, 2H), 4.63 (s, 2H), 4.13-4.09 (m, 2H), 3.89 (s, 2H), 3.83 (dd, 3J = 5.5 Hz, 3J = 4.2 Hz, 2H), 3.70 (t, 3J = 5.4 Hz, 2H), 3.62-3.51 (m, 2H), 2.84-2.62 (m, 3H), 2.13-2.06 (m, 1H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 171.6, 168.9, 167.4, 167.3, 167.2, 166.7, 166.5, 159.2, 156.2, 155.1, 149.8, 137.5, 137.5, 135.6, 134.1, 130.1, 129.3, 128.96, 128.1, 121.7, 120.1, 118.5, 118.5, 117.6, 116.3, 70.3, 69.97, 68.6, 68.5, 49.8, 42.9, 39.5, 31.9, 23.1.

HPLC: R_t = 4.31 min (method A): Purity: >95% (254 nm); >96% (320 nm)

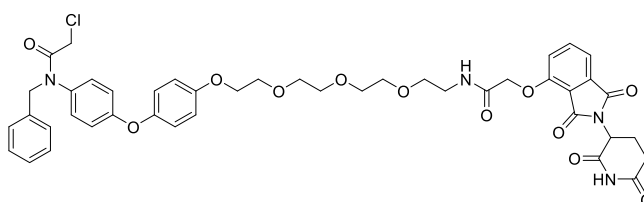
MS (ESI+):

385.1	$[(M/2+H)^+]$	calc. 385.12]
769.3	$[(M+H)^+]$	calc. 769.23]

HRMS (ESI+):

769.2264	$[(M+H)^+]$	calc. 769.2271]
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N-benzyl-2-chloro-N-(4-(4-((1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)oxy)phenoxy)phenyl)acetamide **1b**



2-chloroacetyl chloride (3 μ l, 35 μ mol, 1.3eq) and TEA (11 μ l, 81 μ mol, 3.0eq) were added to a solution of N-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S14** (21 mg, 21 μ mol, 1.0eq) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 20 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reversed phase flash column chromatography (ACN/water) yielded the title compound as a colorless oil (16 mg, 69%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 8.73 (s, 1H), 7.74 (dd, ³J = 8.3 Hz, ³J = 7.4 Hz, 1H), 7.59 (s, 1H), 7.52 (d, ³J = 7.3 Hz, 1H), 7.31-7.18 (m, 6H), 6.99-6.94 (m, 4H), 6.93-6.89 (m, 2H), 6.88-6.85 (m, 2H), 4.90 (dd, ³J = 12.3 Hz, ³J = 5.4 Hz, 1H), 4.85 (s, 2H), 4.64 (s, 2H), 4.13-4.08 (m, 2H), 3.89 (s, 2H), 3.82 (dd, ³J = 5.4 Hz, ³J = 4.0 Hz, 2H), 3.71-3.59 (m, 10H), 3.59-3.47 (m, 2H), 2.85-2.61 (m, 3H), 2.15-2.07 (m, 1H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 171.6, 168.9, 167.4, 167.2, 166.8, 166.5, 159.3, 156.2, 155.1, 149.9, 137.5, 137.5, 135.6, 134.2, 130.2, 129.3, 128.98, 128.1, 121.8, 120.1, 118.6, 118.5, 117.6, 116.3, 71.3, 70.9, 70.8, 70.7, 70.2, 70.1, 68.6, 68.5, 53.98, 49.9, 42.9, 39.6, 31.9, 23.2.

HPLC: R_t = 4.36 min (method A): Purity: >99% (254 nm); >99% (320 nm)

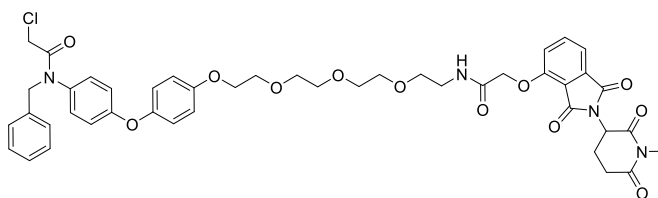
MS (ESI+):

429.2	[(M/2+H) ⁺	calc. 429.14]
857.3	[(M+H) ⁺	calc. 857.28]

HRMS (ESI+):

857.2789	[(M+H) ⁺	calc. 857.2795]
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N-benzyl-2-chloro-N-(4-(4-((1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)oxy)phenoxy)phenyl)acetamide **1b n.c.**



2-chloroacetyl chloride (3 μ l, 34 μ mol, 1.3eq) and TEA (23 μ l, 132 μ mol, 5.0eq) were added to a solution of N-(2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S15** (21 mg, 26 μ mol, 1.0eq) in DCM (3 mL) at 0 °C. The reaction mixture was stirred for 16 h at r.t. The reaction was

quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reversed phase flash column chromatography (ACN/water) yielded the title compound as colorless solid (20 mg, 87%).

¹H NMR (600 MHz, CD₂Cl₂): δ = 7.76-7.72 (m, 1H), 7.52 (d, ³J = 7.2 Hz, 1H), 7.48 (t, ³J = 5.1 Hz, 1H), 7.31-7.18 (m, 6H), 6.99-6.93 (m, 4H), 6.93-6.89 (m, 2H), 6.88-6.84 (m, 2H), 4.96 (ddd, ³J = 8.9 Hz, ³J = 5.4 Hz, ⁴J = 2.3 Hz, 1H), 4.85 (s, 2H), 4.64 (s, 2H), 4.12-4.05 (m, 2H), 3.89 (s, 2H), 3.81-3.77 (m, 2H), 3.66-3.63 (m, 2H), 3.63-3.59 (m, 8H), 3.52 (dd, ³J = 10.8 Hz, ³J = 5.3 Hz, 2H), 2.98-2.89 (m, 1H), 2.83-2.71 (m, 2H), 2.15-2.06 (m, 1H).

¹³C NMR (151 MHz, CD₂Cl₂): δ = 171.6, 169.4, 167.4, 167.3, 166.7, 166.6, 159.3, 156.3, 155.2, 149.8, 137.5, 137.5, 135.6, 134.3, 130.2, 129.3, 128.99, 128.1, 121.8, 120.2, 118.7, 118.5, 117.6, 116.3, 71.3, 71.1, 71.0, 70.9, 70.2, 70.1, 68.8, 68.6, 54.4, 54.2, 50.7, 42.9, 39.6, 32.5, 27.5, 22.4.

HPLC: R_t = 4.51 min (method A): Purity: >99% (254 nm); >97% (320 nm)

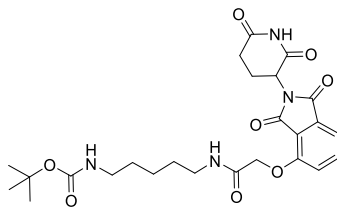
MS (ESI+):

436.2	[(M/2+H) ⁺]	calc. 436.15]
871.3	[(M+H) ⁺]	calc. 871.30]

HRMS (ESI+):

871.2943	[(M+H) ⁺]	calc. 871.2952]
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tert-butyl (5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)carbamate **S16**



A solution of tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4** (44 mg, 113 μmol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl (5-aminopentyl)carbamate (25 mg, 125 μmol, 1.1eq), DIPEA (49 μL, 283 μmol, 2.5eq), the crude acid and HATU (52 mg, 136 μmol, 1.2eq) in DMF (2 mL) was stirred for 17 h. Ethylacetate, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with ethylacetate (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column

chromatography (ACN /water) to yield the title compound as a colorless solid (48 mg, 82%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 9.53-9.09 (m, 1H), 7.75 (dd, ³J = 8.4 Hz, ³J = 7.4 Hz, 1H), 7.52 (d, ³J = 7.0 Hz, 1H), 7.49 (s, 1H), 7.24 (d, ³J = 8.3 Hz, 1H), 5.06-4.97 (m, 1H), 4.83-4.73 (m, 1H), 4.68-4.60 (m, 2H), 3.39 (dd, ³J = 12.4 Hz, ³J = 6.0 Hz, 1H), 3.28 (td, ³J = 12.5 Hz, ³J = 6.4 Hz, 1H), 3.08 (s, 2H), 2.87-2.70 (m, 3H), 2.51 (s, 1H), 2.20-2.09 (m, 1H), 1.63-1.54 (m, 2H), 1.54-1.45 (m, 2H), 1.45-1.34 (m, 11H).

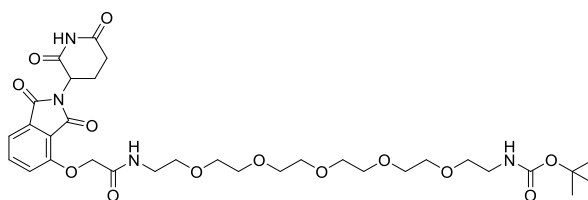
¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.0, 169.2, 167.3, 167.3, 166.8, 156.6, 155.2, 137.6, 134.1, 120.5, 118.7, 117.7, 79.4, 68.9, 49.9, 41.0, 39.5, 31.95, 30.2, 29.4, 28.7, 24.5, 23.2.

MS (ESI+):

417.1	[(M-Boc+2H) ⁺	calc. 417.16]
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418.1	[(M-Boc+3H) ²⁺	calc. 418.17]
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tert-butyl (1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)carbamate **S17**



A solution of tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4** (42 mg, 108 μmol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl (17-amino-3,6,9,12,15-pentaoxaheptadecyl)carbamate (45 mg, 119 μmol, 1.1eq), DIPEA (47 μL, 270 μmol, 2.5eq), the crude acid and HATU (49 mg, 130 μmol, 1.2eq) in DMF (2 mL) was stirred for 12 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column chromatography (ACN /water) to yield the title compound as a yellow oil (56 mg, 75%).

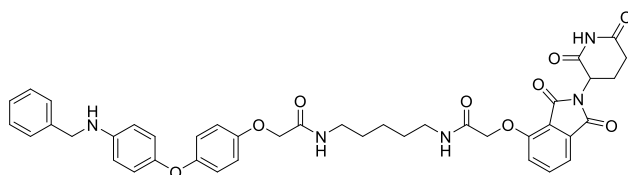
¹H NMR (600 MHz, CD₂Cl₂): δ = 8.90 (s, 1H), 7.75 (dd, ³J = 8.4 Hz, ³J = 7.4 Hz, 1H), 7.61 (t, ³J = 5.5 Hz, 1H), 7.53 (dd, ³J = 7.3 Hz, ⁴J = 0.5 Hz, 1H), 7.24 (dd, ³J = 8.5 Hz, ³J = 0.4 Hz, 1H), 5.19 (s, 1H), 4.97 (dd, ³J = 12.2 Hz, ³J = 5.6 Hz, 1H), 4.65 (s, 2H), 3.64-3.57 (m, 18H), 3.55-3.48 (m, 4H), 3.27-3.23 (m, 2H), 2.88-2.70 (m, 3H), 2.18-2.11 (m, 1H), 1.41 (s, 9H).

¹³C NMR (151 MHz, CD₂Cl₂): δ = 171.8, 168.97, 167.3, 167.3, 166.5, 156.5, 155.2, 137.5, 134.3, 120.1, 118.6, 117.6, 71.1, 70.99, 70.96, 70.95, 70.90, 70.85, 70.83, 70.76, 70.74, 70.1, 68.7, 49.9, 40.97, 39.6, 32.0, 28.7, 23.2.

MS (ESI+):

595.3	[(M-Boc+2H) ⁺	calc. 595.26]
717.3	[(M+Na) ⁺	calc. 717.299]

2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)acetamide **S18**



A solution of tert-butyl 2-(4-(4-(benzylamino)phenoxy)phenoxy)acetate **S8** (34 mg, 84 μmol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl (5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)carbamate **S16** (48 mg, 93 μmol, 1.1eq) in DCM/TFA (4 mL, 1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of the crude amine, DIPEA (37 μL, 211 μmol, 2.5eq), the crude acid and HATU (39 mg, 101 μmol, 1.2eq) in DMF (2 mL) was stirred for 18 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column chromatography (ACN /water) to yield the title compound as a colorless solid (38 mg, 60%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 9.25 (s, 1H), 7.73 (dd, ³J = 8.3 Hz, ³J = 7.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.40-7.25 (m, 5H), 7.21 (d, ³J = 8.3 Hz, 1H), 6.86 (s, 4H), 6.84-6.79 (m, 2H), 6.69 (t, ³J = 5.3 Hz, 1H), 6.63-6.59 (m, 2H), 5.00 (dd, ³J = 12.0 Hz, ³J = 5.8 Hz, 1H), 4.66-4.57 (m, 2H), 4.42 (s, 2H), 4.31 (s, 2H), 3.48-3.20 (m, 4H), 2.86-2.69 (m, 3H), 2.19-2.10 (m, 1H), 1.65-1.52 (m, 4H), 1.50-1.38 (m, 2H).

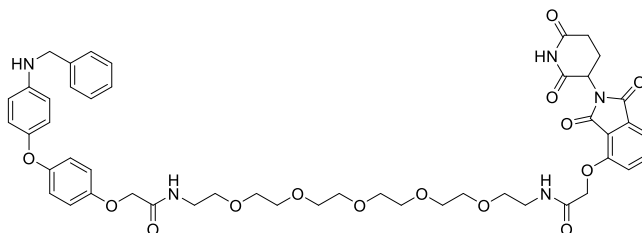
¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.0, 169.1, 168.97, 167.2, 167.1, 166.8, 155.2, 154.1, 153.2, 149.1, 145.3, 140.3, 137.6, 134.1, 129.1, 127.99, 127.7, 120.9, 120.5, 119.3,

118.8, 117.7, 116.3, 114.3, 68.95, 68.7, 49.9, 49.2, 39.6, 39.4, 31.95, 29.7, 29.4, 24.7, 23.3.

MS (ESI+):

374.7	[(M/2+H) ⁺	calc. 374.65]
748.3	[(M+H) ⁺	calc. 748.297]

2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)acetamide **S19**



A solution of tert-butyl 2-(4-(4-(benzylamino)phenoxy)phenoxy)acetate **S8** (33 mg, 81 μ mol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of tert-butyl (1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)carbamate **S17** (56 mg, 81 μ mol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

A solution of the crude amine, DIPEA (35 μ L, 202 μ mol, 2.5eq), the crude acid and HATU (37 mg, 97 μ mol, 1.2eq) in DMF (2 mL) was stirred for 12 h. DCM, water and a sat. solution of NaHCO₃ were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reversed flash column chromatography (ACN /water) to yield the title compound as a yellow oil (41 mg, 55%).

¹H NMR (400 MHz, CD₂Cl₂): δ = 9.10 (s, 1H), 7.72 (dd, ³J = 8.4 Hz, ³J = 7.4 Hz, 1H), 7.55 (t, ³J = 5.1 Hz, 1H), 7.50 (dd, ³J = 7.3 Hz, ⁴J = 0.5 Hz, 1H), 7.40-7.31 (m, 4H), 7.30-7.24 (m, 1H), 7.20 (d, ³J = 8.4 Hz, 1H), 7.07 (t, ³J = 5.4 Hz, 1H), 6.86 (s, 4H), 6.84-6.79 (m, 2H), 6.63-6.58 (m, 2H), 5.00-4.92 (m, 1H), 4.62 (s, 2H), 4.41 (s, 2H), 4.30 (s, 2H), 4.18 (s, 1H), 3.64-3.46 (m, 24H), 2.87-2.70 (m, 3H), 2.20-2.10 (m, 1H).

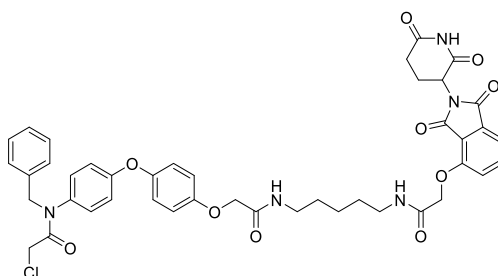
¹³C NMR (101 MHz, CD₂Cl₂): δ = 171.9, 169.1, 168.7, 167.3, 167.2, 166.4, 155.0, 153.9, 153.3, 149.1, 145.2, 140.2, 137.4, 134.2, 129.1, 127.96, 127.7, 120.8, 119.99, 119.2,

118.5, 117.4, 116.3, 114.2, 71.0, 70.96, 70.9, 70.9, 70.8, 70.2, 69.98, 68.6, 68.5, 49.9, 49.1, 39.6, 39.3, 31.98, 23.1.

MS (ESI+):

463.8	$[(M/2+H)^+]$	calc. 463.69]
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N-benzyl-2-chloro-N-(4-(4-(2-((5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)amino)-2-oxoethoxy)phenoxy)phenyl)acetamide **1c**



2-chloroacetyl chloride (5 μ l, 66 μ mol, 1.3eq) and TEA (21 μ l, 152 μ mol, 5.0eq) were added to a solution of 2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)acetamide **S18** (38 mg, 51 μ mol, 1.0eq) in DCM (3 mL) at 0 °C. The reaction mixture was stirred for 17 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reversed phase flash column chromatography (ACN/water) yielded the title compound as colorless solid (31 mg, 74%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 9.29 (s, 1H), 7.74 (dd, ³J = 8.3 Hz, ³J = 7.4 Hz, 1H), 7.55-7.48 (m, 2H), 7.32-7.18 (m, 6H), 7.01-6.92 (m, 6H), 6.89-6.85 (m, 2H), 6.70 (t, ³J = 5.5 Hz, 1H), 5.03-4.98 (m, 1H), 4.85 (s, 2H), 4.66-4.58 (m, 2H), 4.46 (s, 2H), 3.89 (s, 2H), 3.47-3.22 (m, 4H), 2.88-2.70 (m, 3H), 2.21-2.10 (m, 1H), 1.66-1.52 (m, 4H), 1.49-1.39 (m, 2H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.0, 169.2, 168.7, 167.2, 167.1, 166.8, 166.7, 158.9, 155.2, 154.7, 150.8, 137.6, 137.4, 135.8, 134.1, 130.2, 129.3, 128.97, 128.1, 121.9, 120.5, 118.8, 118.7, 117.7, 116.6, 68.97, 68.5, 54.2, 49.9, 42.9, 39.6, 39.4, 31.95, 29.7, 29.4, 24.7, 23.3.

HPLC: R_t = 4.20 min (method A): Purity: >97% (254 nm); >99% (320 nm)

MS (ESI+):

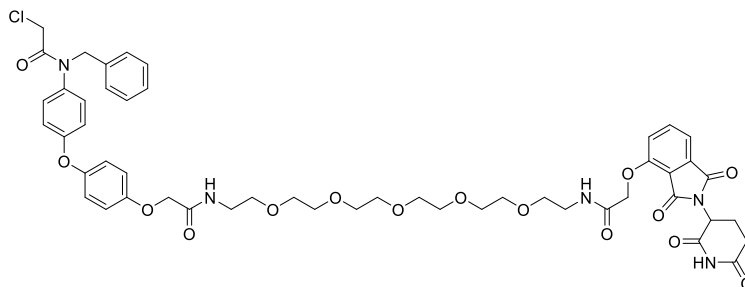
412.5	$[(M/2+H)^+]$	calc. 412.60]
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824.3	$[(M+H)^+]$	calc. 824.27]
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HRMS (ESI+):

824.2685	$[(M+H)^+]$	calc. 824.2693]
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N-benzyl-2-chloro-N-(4-(4-((23-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2,22-dioxo-6,9,12,15,18-pentaoxa-3,21-diazatricosyl)oxy)phenoxy)phenyl)acetamide **1d**



2-chloroacetyl chloride (5 μ l, 69 μ mol, 1.3eq) and TEA (22 μ l, 158 μ mol, 3.0eq) were added to a solution of 2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)acetamide **S19** (49 mg, 53 μ mol, 1.0eq) in DCM (10 mL) at 0 °C. The reaction mixture was stirred for 20 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reversed phase flash column chromatography (ACN/water) yielded the title compound as a yellow oil (31 mg, 59%).

¹H NMR (500 MHz, DMSO-*d*₆): δ = 11.11 (s, 1H), 8.06 (t, ³*J* = 5.7 Hz, 1H), 7.99 (t, ³*J* = 5.6 Hz, 1H), 7.80 (dd, ³*J* = 8.5 Hz, ³*J* = 7.3 Hz, 1H), 7.49 (d, ³*J* = 7.2 Hz, 1H), 7.40 (d, ³*J* = 8.5 Hz, 1H), 7.29 (t, ³*J* = 7.2 Hz, 2H), 7.26-7.17 (m, 5H), 7.04-6.97 (m, 4H), 6.91-6.86 (m, 2H), 5.11 (dd, ³*J* = 12.7 Hz, ³*J* = 5.5 Hz, 1H), 4.84 (s, 2H), 4.78 (s, 2H), 4.46 (s, 2H), 4.08 (s, 2H), 3.53-3.42 (m, 20H), 3.36-3.26 (m, 4H), 2.94-2.85 (m, 1H), 2.64-2.51 (m, 2H), 2.06-2.00 (m, 1H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 172.8, 169.9, 167.7, 166.9, 166.7, 165.8, 165.5, 157.6, 154.98, 154.4, 149.3, 136.9, 136.9, 135.1, 133.0, 129.7, 128.4, 127.97, 127.3, 120.98, 120.4, 117.8, 116.8, 116.2, 116.1, 69.78, 69.77, 69.7, 69.6, 69.6, 68.8, 67.5, 67.4, 52.8, 48.8, 42.5, 39.5, 38.4, 38.3, 30.95, 22.0.

HPLC: *R*_t = 4.07 min (method B): Purity: >99% (254 nm); >98% (320 nm)

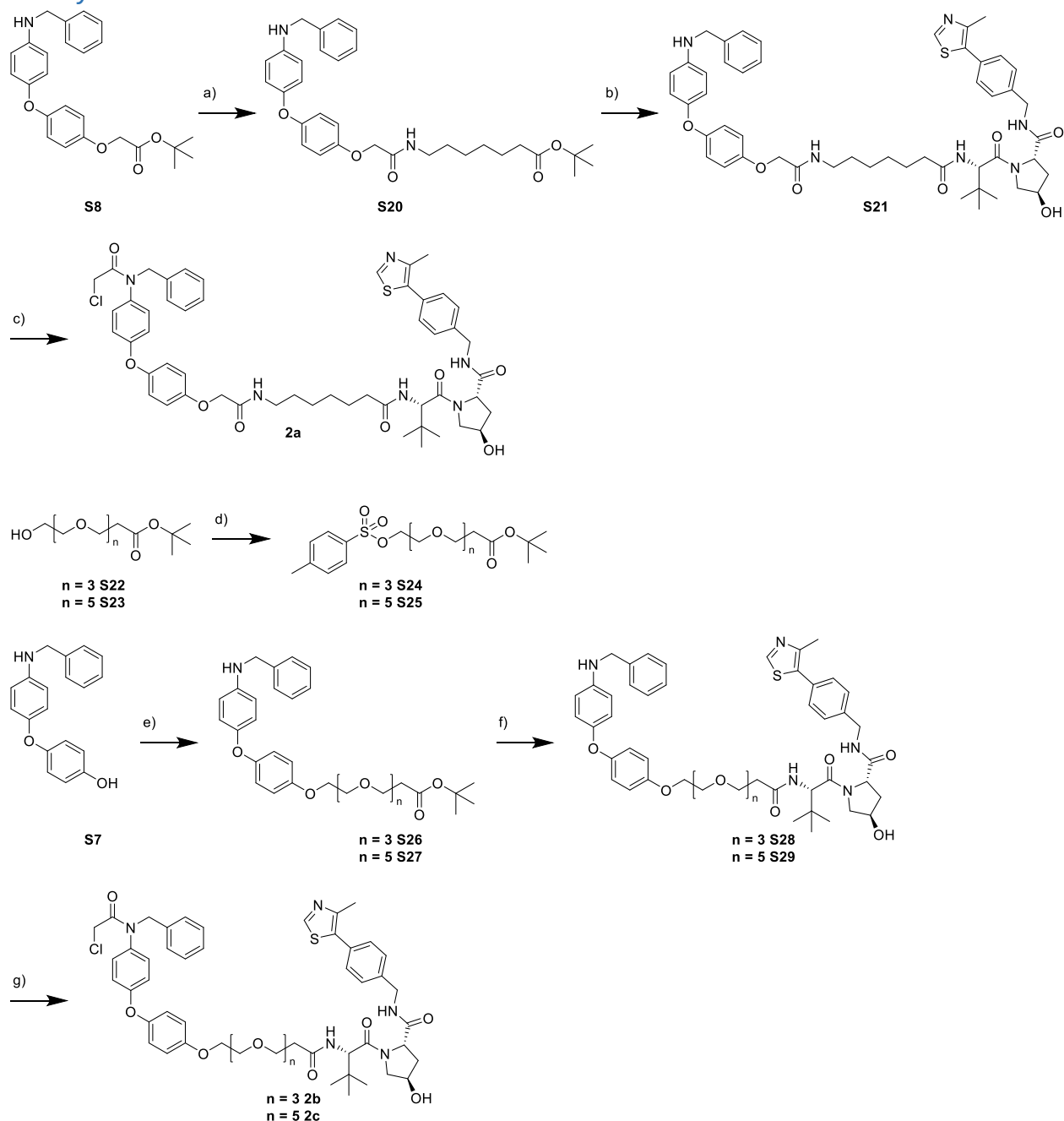
MS (ESI⁺):

501.7	[(M/2+H) ⁺	calc. 501.68]
1002.3	[(M+H) ⁺	calc. 1002.35]

HRMS (ESI⁺):

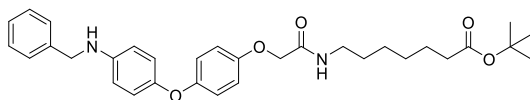
1002.3536	[(M+H) ⁺	calc. 1002.3534]
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1.3 Synthesis of VHL-based PROTACs



Appendix Figure S3: Synthesis of VHL based PROTACs **2a-c**: a) 1. TFA, DCM, r.t., 2.5 h; 2. DIPEA, linker-amine, HATU, DMF, r.t., 24.5 h; b) 1. TFA, DCM, r.t., 2.5 h; 2. DIPEA, VHL032-amine, HATU, DMF, r.t., 24.5 h; c) 2-chloroacetyl chloride, TEA, 0 °C, then r.t., 20 h; d) TsCl, 4-DMAP, TEA, DCM, -10 °C, then r.t., 24-38 h; e) intermediate **S22** or **S23**, K₂CO₃, DMF, 90 °C, overnight; f) 1. TFA, DCM, r.t., 4.5 h; 2. DIPEA, VHL032-amine, HATU, DMF, r.t., 17 h; g) 2-chloroacetyl chloride, TEA, 0 °C, then r.t., 22 h.

tert-butyl 7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanoate **S20**



A solution of tert-butyl 2-(4-(4-(benzylamino)phenoxy)phenoxy)acetate **S8** (59 mg, 146 μmol , 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2.5 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

DIPEA (51 μL , 291 μmol , 2.0eq) and HATU (66 mg, 175 μmol , 1.2eq) were added to a solution of *tert*-butyl 7-aminoheptanoate (35 mg, 175 μmol , 1.2eq) and the crude acid in DMF (1 mL). The reaction mixture was stirred for 24.5 h. Ethylacetate, water and brine were added and the layers were separated. The aqueous layer was extracted with ethylacetate (3x) and the combined organic layers were dried with MgSO_4 . The solvent was removed under reduced pressure and the residue was purified by reversed phase flash column chromatography to yield the title compound as a yellow oil (25 mg, 32%).

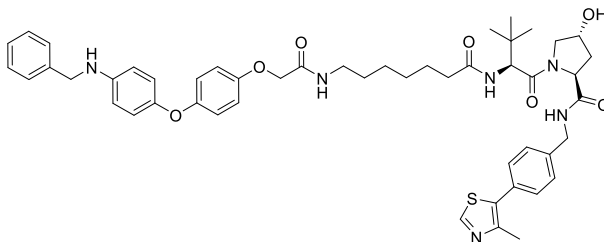
^1H NMR (500 MHz, CD_2Cl_2): δ = 7.42-7.33 (m, 4H), 7.31-7.25 (m, 1H), 6.90 – 6.85 (m, 4H), 6.84-6.81 (m, 2H), 6.63-6.59 (m, 2H), 6.59-6.56 (m, 1H), 4.40 (s, 2H), 4.31 (s, 2H), 3.29 (dd, 3J = 13.5 Hz, 3J = 6.8 Hz, 2H), 2.18 (t, 3J = 7.5 Hz, 2H), 1.60-1.49 (m, 4H), 1.42 (s, 9H), 1.36-1.29 (m, 4H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 173.4, 168.4, 154.1, 153.2, 149.1, 145.3, 140.3, 129.1, 128.0, 127.7, 120.9, 119.3, 116.2, 114.3, 80.2, 68.7, 49.2, 39.4, 35.96, 30.0, 29.3, 28.4, 27.1, 25.5.

MS (ESI+):

477.1	$[(\text{M}-t\text{Bu}+2\text{H})^+]$	calc. 477.23]
533.3	$[(\text{M}+\text{H})^+]$	calc. 533.297]

(2S,4R)-1-((S)-2-(7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S21**



A solution of tert-butyl 7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanoate **S20** (25 mg, 471 μmol , 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 2 h. All volatiles

were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated twice.

DIPEA (16 μ L, 94 μ mol, 2.0eq) and HATU (21 mg, 56 μ mol, 1.2eq) were added to a solution of the (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (24 mg, 52 μ mol, 1.1eq) and the crude acid in DMF (1.0 mL). The reaction mixture was stirred for 15 h. Ethylacetate, water and brine were added and the layers were separated. The aqueous layer was extracted with ethylacetate (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reverse flash column chromatography to yield the title compound as yellow oil (13 mg, 31%).

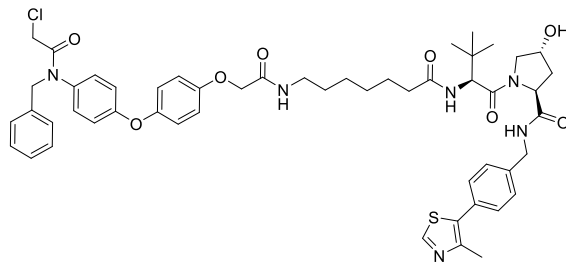
¹H NMR (500 MHz, CD₂Cl₂): δ = 8.65 (s, 1H), 7.42-7.24 (m, 10H), 6.89-6.79 (m, 6H), 6.66-6.59 (m, 3H), 6.24 (d, ³J = 8.8 Hz, 1H), 4.67 (t, ³J = 8.1 Hz, 1H), 4.57-4.50 (m, 2H), 4.48 (s, 1H), 4.37 (s, 2H), 4.33-4.27 (m, 3H), 4.04 (d, ³J = 11.4 Hz, 1H), 3.60 (dd, ³J = 11.3 Hz, ³J = 3.6 Hz, 1H), 3.27 (td, ³J = 7.4 Hz, ⁴J = 1.3 Hz, 2H), 2.48 (s, 3H), 2.39 (ddd, ²J = 13.0 Hz, ³J = 8.2 Hz, ³J = 4.5 Hz, 1H), 2.24-2.07 (m, 3H), 1.64-1.46 (m, 4H), 1.35-1.21 (m, 5H), 0.94 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 174.1, 172.3, 171.5, 168.7, 154.1, 153.2, 150.7, 149.1, 149.1, 145.3, 140.3, 139.1, 132.1, 131.5, 129.9, 129.1, 128.5, 128.0, 127.7, 120.9, 119.3, 116.2, 114.3, 70.7, 68.6, 59.1, 57.97, 57.4, 49.2, 43.5, 39.3, 36.95, 36.7, 35.4, 29.8, 28.9, 26.8, 26.7, 25.95, 16.5.

MS (ESI+):

318.0	[(fragment+2H) ⁺	calc. 318.12]
445.3	[(M/2+H) ⁺	calc. 445.22]
572.3	[(fragment) ⁺	calc. 572.31]
889.4	[(M+H) ⁺	calc. 889.43]

(2S,4R)-1-((S)-2-(7-(2-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2a**



2-chloroacetyl chloride (1 μ L, 15 μ mol, 1.3eq) and TEA (5 μ L, 34 μ mol, 3.0eq) were added to a solution of (2S,4R)-1-((S)-2-(7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S21** (10 mg, 11 μ mol, 1.0eq) in DCM (5 mL) at 0 °C. The reaction mixture was stirred for 20 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with Na₂SO₄. Reverse phase flash column chromatography yielded the title compound as beige solid (8 mg, 74%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 8.65 (s, 1H), 7.42-7.32 (m, 5H), 7.32-7.23 (m, 3H), 7.21-7.18 (m, 2H), 7.03-6.95 (m, 4H), 6.95-6.91 (m, 2H), 6.89-6.84 (m, 2H), 6.62 (t, ³J = 5.7 Hz, 1H), 6.19 (d, ³J = 8.7 Hz, 1H), 4.85 (s, 2H), 4.67 (t, ³J = 8.1 Hz, 1H), 4.58-4.50 (m, 2H), 4.49 (s, 1H), 4.42 (s, 2H), 4.31 (dd, ²J = 15.1 Hz, ³J = 5.3 Hz, 1H), 4.06 (d, ³J = 11.4 Hz, 1H), 3.90 (s, 2H), 3.59 (dd, ³J = 11.3 Hz, ³J = 3.6 Hz, 1H), 3.28 (dd, ²J = 13.3 Hz, ³J = 7.1 Hz, 2H), 2.48 (s, 3H), 2.42 (ddd, ²J = 12.9 Hz, ³J = 8.1 Hz, ⁴J = 4.5 Hz, 1H), 2.24-2.08 (m, 3H), 1.63-1.47 (m, 4H), 1.34-1.22 (m, 5H), 0.93 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 174.0, 172.4, 171.4, 168.4, 166.7, 158.99, 154.7, 150.8, 150.7, 149.2, 139.1, 137.5, 135.8, 132.1, 131.5, 130.2, 129.9, 129.3, 129.0, 128.5, 128.1, 121.9, 118.7, 116.6, 70.7, 68.5, 59.1, 57.95, 57.3, 54.02, 43.6, 42.9, 39.3, 36.8, 36.7, 35.3, 29.8, 28.9, 26.8, 26.7, 25.9, 16.5.

HPLC: R_t = 4.53 min (method B): Purity: >98% (254 nm); >96% (320 nm)

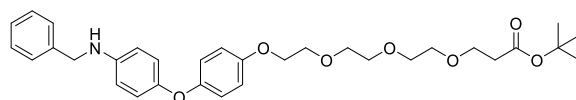
MS (ESI+):

318.1	[(fragment+2H) ⁺	calc. 318.12]
648.3	[(fragment) ⁺	calc. 648.28]
965.4	[(M+H) ⁺	calc. 965.40]

HRMS (ESI+):

965.4031	[(M+H) ⁺	calc. 965.4033]
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tert-butyl 3-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)propanoate **S26** via tert-butyl 3-(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)propanoate **S24**



TsCl (81 mg, 0.43 mmol, 1.4eq) was added portion wise (3x) to a solution of the tert-butyl 3-(2-(2-(2-(hydroxyethoxy)ethoxy)ethoxy)propanoate **S22** (84 mg, 0.30 mmol, 1.0eq), 4-DMAP (9 mg, 0.07 μ mol, 0.2eq) and Et₃N (0.055 mL, 0.40 mmol, 1.3eq) in DCM (5 mL) at -10 °C. The reaction mixture was allowed to warm to room temperature and stirred for

37.5 h. The reaction was quenched by adding 4 mL of a saturated solution of NH_4Cl in water. The organic layer was separated and the remaining aqueous layer was extracted with DCM (3x). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (DCM/MeOH 99/1) yielded the intermediate product (105 mg, 80%) as a colorless oil.

A solution of the 4-(4-(benzylamino)phenoxy)phenol **S7** (83 mg, 283 μmol , 1.0eq), the tosylate **S24** (147 mg, 340 μmol , 1.2eq) and potassium carbonate (118 mg, 850 μmol , 3.0eq) in DMF (4 mL) was stirred at 90 °C overnight. The reaction was quenched with water and extracted with ethylacetate (3x). The combined organic layers were dried with MgSO_4 and the solvent was removed under reduced pressure. Reversed phase column chromatography (ACN/water) yielded the title compound as a colorless oil (78 mg, 50%).

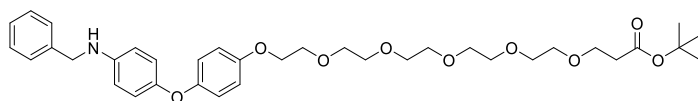
^1H NMR (500 MHz, CD_2Cl_2): δ = 7.42-7.21 (m, 5H), 6.91-6.81 (m, 6H), 6.64-6.59 (m, 2H), 4.31 (s, 2H), 4.07 (dd, 3J = 5.4 Hz, 3J = 4.1 Hz, 2H), 3.80 (dd, 3J = 5.4 Hz, 3J = 4.1 Hz, 2H), 3.70-3.65 (m, 4H), 3.64-3.57 (m, 6H), 2.47 (t, 3J = 6.5 Hz, 2H), 1.45 (s, 9H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 171.3, 154.8, 153.0, 149.6, 144.99, 140.3, 129.1, 128.0, 127.7, 120.6, 119.4, 115.98, 114.3, 80.8, 71.3, 71.1, 71.0, 70.9, 70.3, 68.6, 67.4, 49.2, 36.9, 28.4.

MS (ESI+):

496.1	$[(\text{M}-t\text{Bu}+2\text{H})^+]$	calc. 496.23]
552.2	$[(\text{M}+\text{H})^+]$	calc. 552.298]
553.3	$[(\text{M}+2\text{H})^{2+}]$	calc. 553.30]
574.33	$[(\text{M}+\text{Na})^+]$	calc. 574.279]

tert-butyl 1-(4-(4-(benzylamino)phenoxy)phenoxy)-3,6,9,12,15-pentaoxaoctadecan-18-oate **S27** via tert-butyl 1-(tosyloxy)-3,6,9,12,15-pentaoxaoctadecan-18-oate **S25**



TsCl (80 mg, 0.42 mmol, 1.4eq) was added to a solution of the tert-butyl 1-hydroxy-3,6,9,12,15-pentaoxaoctadecan-18-oate **S23** (107 mg, 0.292 mmol, 1.0eq), 4-DMAP (9 mg, 0.07 mmol, 0.2eq) and Et_3N (0.050 mL, 0.36 mmol, 1.2eq) in DCM (5 mL) at -10 °C. The reaction mixture was stirred for 30 min, allowed to warm to room temperature and stirred for another 24 h. The reaction was quenched by adding a saturated solution of NH_4Cl in water. The organic layer was separated and the remaining aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography (DCM/MeOH 99/1) yielded the intermediate product (117 mg, 77%) as a colorless oil.

A solution of the 4-(4-(benzylamino)phenoxy)phenol **S7** (54 mg, 186 μ mol, 1.0eq), the tosylate **S25** (116 mg, 223 μ mol, 1.2eq) and potassium carbonate (78 mg, 557 μ mol, 3.0eq) in DMF (3 mL) was stirred at 90 °C overnight. The reaction was quenched with water and extracted with ethylacetate (3x). The combined organic layers were dried with MgSO₄ and the solvent was removed under reduced pressure. Reversed phase column chromatography (ACN/water) yielded the title compound as a colorless oil (77 mg, 65%).

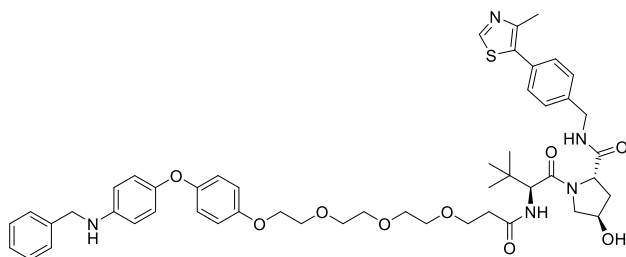
¹H NMR (500 MHz, CD₂Cl₂): δ = 7.40 – 7.25 (m, 5H), 6.89-6.79 (m, 6H), 6.63-6.58 (m, 2H), 4.31 (s, 2H), 4.10-3.99 (m, 2H), 3.80 (dd, ³J = 11.1 Hz, ³J = 6.3 Hz, 2H), 3.70-3.64 (m, 4H), 3.65-3.55 (m, 14H), 2.46 (t, ³J = 6.5 Hz, 2H), 1.44 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 171.4, 154.9, 153.1, 149.7, 145.1, 140.4, 129.2, 128.1, 127.8, 120.7, 119.4, 116.1, 114.4, 80.9, 71.4, 71.21, 71.18, 71.17, 71.1, 70.99, 70.4, 68.7, 67.5, 49.3, 36.95, 28.5.

MS (ESI+):

331.7	[(M/2+H) ⁺	calc. 331.69]
640.3	[(M+H) ⁺	calc. 640.35]
662.3	[(M+Na) ⁺	calc. 662.33]

(2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-14-(tert-butyl)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S28**



A solution of tert-butyl 3-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)propanoate **S26** (26 mg, 47 μ mol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 4.5 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated once.

DIPEA (16 μ L, 52 μ mol, 2.0eq) and HATU (22 mg, 57 μ mol, 1.2eq) were added to a solution of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (24 mg, 52 μ mol, 1.1eq) and the crude acid in DMF (1.5 mL). The reaction mixture was stirred for 17 h. Ethylacetate, water and brine were added and the layers were separated. The aqueous layer was extracted with ethylacetate (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was

purified by reverse flash column chromatography to yield the title compound as a yellow oil (26 mg, 61%).

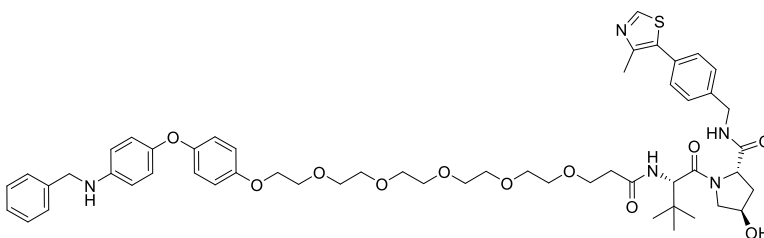
¹H NMR (500 MHz, CD₂Cl₂): δ = 8.65 (s, 1H), 7.40-7.31 (m, 9H), 7.29-7.24 (m, 1H), 6.97 (d, ³J = 8.15 Hz, 1H), 6.88-6.79 (m, 6H), 6.62-6.58 (m, 2H), 4.66 (t, ³J = 7.91 Hz, 1H), 4.53 (dd, ²J = 15.05 Hz, ³J = 6.57 Hz, 1H), 4.47-4.43 (m, 2H), 4.32-4.26 (m, 3H), 4.08-4.00 (m, 3H), 3.81-3.55 (m, 13H), 2.48 (s, 3H), 2.47-2.38 (m, 3H), 2.12-2.04 (m, 1H), 0.94 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.5, 172.3, 171.4, 154.7, 153.1, 150.7, 149.6, 149.1, 145.1, 140.3, 139.1, 132.1, 131.4, 129.9, 129.1, 128.5, 128.0, 127.7, 120.6, 119.4, 115.99, 114.3, 71.2, 71.1, 71.0, 70.96, 70.7, 70.3, 68.6, 67.7, 59.0, 58.3, 57.2, 49.2, 43.5, 37.2, 36.8, 35.3, 26.8, 16.5.

MS (ESI+):

318.1	[(fragment+2H) ⁺	calc. 318.12]
454.9	[(M/2+H) ⁺	calc. 454.72]
591.3	[(fragment) ⁺	calc. 591.31]
908.5	[(M+H) ⁺	calc. 908.43]

(2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-20-(tert-butyl)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S29**



A solution of tert-butyl 1-(4-(4-(benzylamino)phenoxy)phenoxy)-3,6,9,12,15-pentaoxaoctadecan-18-oate **S27** (31 mg, 48 μmol, 1.0eq) in DCM/TFA (4 mL, 1/1) was stirred for 4.5 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated once.

DIPEA (17 μL, 97 μmol, 2.0eq) and HATU (22 mg, 58 μmol, 1.2eq) were added to a solution of (2S,4R)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride (25 mg, 53 μmol, 1.1eq) and the crude acid in DMF (1.5 mL). The reaction mixture was stirred for 17 h. Ethylacetate, water and brine were added and the layers were separated. The aqueous layer was extracted with ethylacetate (3x) and the combined organic layers were dried with MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using reversed phase flash column chromatography. The title compound was isolated as a yellow oil (28 mg, 58%).

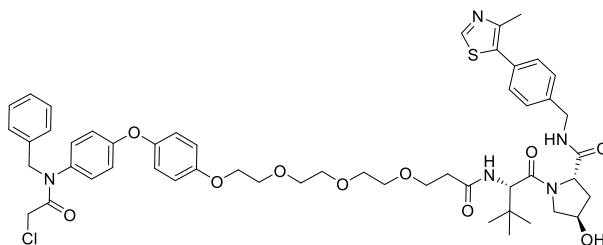
¹H NMR (500 MHz, CD₂Cl₂): δ = 8.65 (s, 1H), 7.41-7.32 (m, 8H), 7.28-7.24 (m, 1H), 6.96 (d, ³J = 8.39 Hz), 6.88-6.79 (m, 5H), 6.62-6.59 (m, 2H), 4.67 (t, ³J = 8.08 Hz, 1H), 4.54 (dd, ²J = 15.16 Hz, ³J = 6.71 Hz, 1H), 4.48-4.43 (m, 2H), 4.33-4.27 (m, 3H), 4.12 (s, 1H), 4.08-4.01 (m, 3H), 3.81-3.77 (m, 2H), 3.72-3.55 (m, 19H), 3.40 (s, 1H), 2.49 (s, 3H), 2.47-2.38 (m, 3H). 2.12-2.04 (m, 1H), 0.94 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.5, 172.3, 171.4, 154.8, 153.0, 150.7, 149.6, 149.1, 145.1, 140.3, 139.1, 132.1, 131.4, 129.9, 129.1, 128.5, 128.0, 127.7, 120.6, 119.4, 115.99, 114.3, 71.3, 71.08, 71.07, 71.05, 71.03, 71.00, 70.9, 70.7, 70.3, 68.6, 67.7, 59.0, 58.3, 57.2, 49.2, 43.5, 37.3, 36.7, 35.3, 26.8, 16.5.

MS (ESI+):

498.8	[(M/2+H) ⁺	calc. 498.74]
679.3	[(fragment) ⁺	calc. 679.36]
996.5	[(M+H) ⁺	calc. 996.50]

(2S,4R)-1-((S)-1-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)-14-(tert-butyl)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2b**



2-chloroacetyl chloride (3 μl, 37 μmol, 1.3eq) and TEA (12 μl, 86 μmol, 3.0eq) were added to a solution of (2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-14-(tert-butyl)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S28** (26 mg, 29 μmol, 1.0eq) in 2 mL DCM at 0 °C. The reaction mixture was stirred for 22 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reverse phase flash column chromatography (ACN/water) yielded the title compound (8 mg, 28%) as yellow oil.

¹H NMR (500 MHz, CD₂Cl₂): δ = 8.65 (s, 1H), 7.40-7.36 (m, 2H), 7.35-7.23 (m, 6H), 7.21-7.18 (m, 2H), 6.99-6.89 (m, 7H), 6.88-6.84 (m, 2H), 4.85 (s, 2H), 4.68 (t, ³J = 8.0 Hz, 1H), 4.54 (dd, ²J = 15.1 Hz, ³J = 6.8 Hz, 1H), 4.47 (d, ³J = 9.0 Hz, 1H), 4.42 (d, ³J = 8.2 Hz, 1H), 4.29 (dd, ²J = 15.1 Hz, 5.2 Hz, 1H), 4.11-4.03 (m, 3H), 3.89 (s, 2H), 3.81-3.77 (m, 2H), 3.72-3.59 (m, 11H), 3.56 (dd, ³J = 11.4 Hz, ³J = 3.6 Hz, 1H), 2.50-2.43 (m, 6H), 2.07 (ddt, ²J = 13.3 Hz, ³J = 8.1 Hz, ⁴J = 1.9 Hz, 1H), 0.93 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.5, 172.4, 171.2, 166.7, 159.3, 156.2, 150.6, 149.8, 149.1, 139.1, 137.5, 135.5, 132.1, 131.5, 130.2, 129.9, 129.3, 128.98, 128.5, 128.1, 121.8, 118.5, 116.3, 71.3, 71.1, 71.0, 70.97, 70.7, 70.2, 68.5, 67.7, 58.9, 58.3, 57.1, 54.0, 43.6, 42.9, 37.2, 36.5, 35.1, 26.7, 16.5.

HPLC: R_t = 4.55 min (method B): Purity: >97% (254 nm); >95% (320 nm)

MS (ESI+):

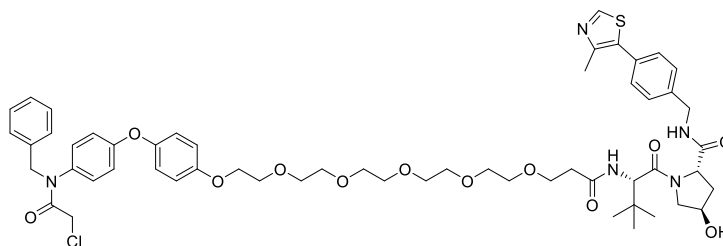
318.1	[(fragment+2H) ⁺	calc. 318.12]
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667.3	[(M/2+H) ⁺	calc. 667.28]
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HRMS (ESI+):

984.3976	[(M+H) ⁺	calc. 984.3979]
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(2S,4R)-1-((S)-1-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)-20-(tert-butyl)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2c**



2-chloroacetyl chloride (3 µl, 39 µmol, 1.3eq) and TEA (12 µl, 84 µmol, 3.0eq) were added to a solution (2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-20-(tert-butyl)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S29** (28 mg, 28 µmol, 1.0eq) in 2 mL DCM at 0 °C. The reaction mixture was stirred for 22 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. Reverse phase flash column chromatography yielded (ACN/water) the title compound as a yellow oil (14 mg, 46%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 8.66 (s, 1H), 7.40-7.31 (m, 5H), 7.31-7.23 (m, 3H), 7.23-7.17 (m, 2H), 6.99-6.90 (m, 7H), 6.88-6.84 (m, 2H), 4.85 (s, 2H), 4.68 (d, ³J = 8.0 Hz, 1H), 4.55 (dd, ²J = 15.1 Hz, ³J = 6.8 Hz, 1H), 4.46 (s, 1H), 4.44 (d, ³J = 8.2 Hz, 1H), 4.30 (dd, ²J = 15.1 Hz, ³J = 5.3 Hz, 1H), 4.10 (dd, ³J = 5.4 Hz, ³J = 4.0 Hz, 2H), 4.06 (d, ²J = 11.5 Hz, 1H), 3.89 (s, 2H), 3.82-3.79 (m, 2H), 3.71-3.66 (m, 4H), 3.64-3.55 (m, 14H), 2.50-2.48 (m, 3H), 2.47-2.41 (m, 3H), 2.08 (ddt, ²J = 13.3 Hz, ³J = 8.1 Hz, ⁴J = 1.9 Hz, 1H), 0.93 (s, 9H).

¹³C NMR (126 MHz, CD₂Cl₂): δ = 172.6, 172.4, 171.3, 166.7, 159.3, 156.3, 150.6, 149.8, 149.1, 139.1, 137.5, 135.5, 132.1, 131.5, 130.1, 129.9, 129.3, 128.97, 128.5, 128.1,

121.8, 118.5, 116.3, 71.3, 71.08, 71.06, 71.04, 71.02, 70.99, 70.91, 70.7, 70.2, 68.5, 67.7, 58.9, 58.3, 57.1, 43.5, 42.9, 37.2, 36.6, 35.2, 26.7, 16.5.

HPLC: R_t = 4.53 min (method B): Purity: >98% (254 nm); >97% (320 nm)

MS (ESI+):

318.1	$[(\text{fragment}+2\text{H})^+]$	calc. 318.12]
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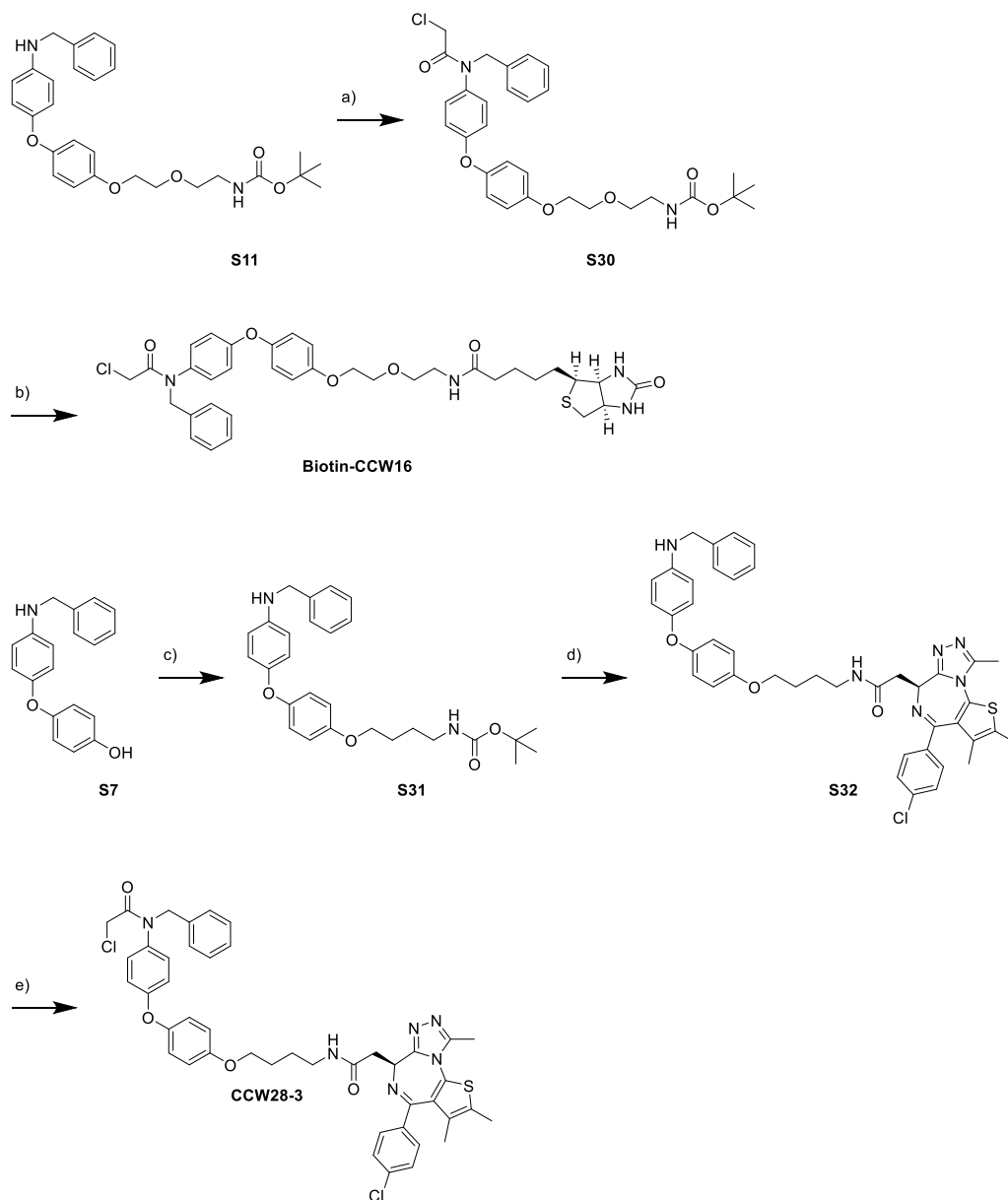
536.9	$[(M/2+H)^+]$	calc. 536.73]
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755.4	$[(\text{fragment})^+]$	calc. 755.33]
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HRMS (ESI+):

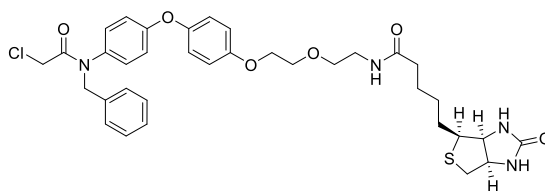
1072.4507	$[(M+H)^+]$	calc. 1072.4503]
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1.4 Synthesis of Biotin-CCW16 and CCW28-3



Appendix Figure S4: Synthesis of **Biotin-CCW16** and BRD4 PROTACs **CCW28-3**: a) 2-chloroacetyl chloride, TEA, 0 °C, then r.t., 23 h; b) 1. TFA, DCM, r.t., 2 h; 2. DIPEA, Biotin-NHS ester, DMF, r.t., 2 h; c) K₂CO₃, linker-bromide, Acetone, reflux, overnight; d) 1. TFA, DCM, r.t., 3 h; 2. DIPEA, JQ1-acid, HATU, DMF, r.t., 16 h; e) 2-chloroacetyl chloride, TEA, 0 °C, then r.t., 23 h.

N-(2-(2-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)ethoxy)ethyl)-5-
 ((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl)pentanamide **Biotin-
 CCW16** via tert-butyl (2-(2-(4-(4-(N-benzyl-2-
 chloroacetamido)phenoxy)phenoxy)ethoxy)ethyl)carbamate **S30**



2-chloroacetyl chloride (32 μ L, 401 μ mol, 4.0eq) and TEA (56 μ L, 401 μ mol, 4.0eq) were added to a solution of tert-butyl (2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)carbamate **S11** (48 mg, 100 μ mol, 1.0eq) in 2 mL DCM at 0 °C. The reaction mixture was stirred for 23 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO_4 . The solvent was removed under reduced pressure and the crude product was used without further purification for the next step (54 mg, 97%).

A solution of tert-butyl (2-(2-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)ethoxy)ethyl)carbamate **S30** (56 mg, 101 μ mol, 1.0eq) in TFA/DCM (4 mL, 1/1) was stirred for 2 h at r.t. all volatiles were removed under reduced pressure, DCM was added and the all volatiles were removed under reduced pressure. This process was repeated two additional times.

A solution of the crude amine, DIPEA (100 μ L, 575 μ mol, 5.7eq) and 2,5-dioxopyrrolidin-1-yl 5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoate (34 mg, 101 μ mol, 1.0eq) in DMF (2 mL) was stirred for 2 h at r.t. Water and DCM were added and the layers were separated. The aqueous layer was extracted with DCM (2x) and the combined organic layers were dried with MgSO_4 . The solvent was removed under reduced pressure and the crude product was purified using reversed phase column chromatography (ACN/water). The title compound was isolated as a beige solid (4 mg, 6%).

^1H NMR (500 MHz, CD_2Cl_2): δ = 7.31-7.24 (m, 3H), 7.22-7.18 (m, 2H), 7.01-6.91 (m, 6H), 6.89-6.85 (m, 2H), 6.25 (t, 3J = 4.9 Hz, 1H), 5.83 (s, 1H), 5.03 (s, 1H), 4.85 (s, 2H), 4.47-4.43 (m, 1H), 4.30-4.25 (m, 1H), 4.12-4.09 (m, 2H), 3.82-3.80 (m, 2H), 3.61 (t, 3J = 5.2 Hz, 2H), 3.45-3.40 (m, 2H), 3.13 (td, 3J = 7.4 Hz, 3J = 4.6 Hz, 1H), 2.88 (dd, 2J = 12.8 Hz, 3J = 5.0 Hz, 1H), 2.68 (d, 2J = 12.8 Hz, 1H), 2.23-2.10 (m, 2H), 1.75-1.57 (m, 4H), 1.46-1.38 (m, 2H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 173.4, 166.7, 163.9, 159.3, 156.2, 149.9, 137.5, 135.6, 130.2, 129.3, 128.99, 128.1, 121.9, 118.5, 116.3, 70.6, 70.0, 68.5, 62.2, 60.7, 55.9, 54.1, 42.9, 41.2, 39.7, 36.3, 28.6, 28.5, 26.1.

HPLC: R_t = 4.03 min (method A): Purity: >96% (254 nm); >95% (320 nm)

MS (ESI+):

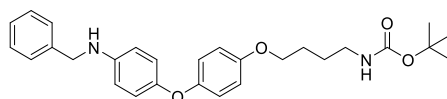
341.0	$[(M/2+H)^+]$	calc. 341.13]
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681.3	$[(M+H)^+]$	calc. 681.25]
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HRMS (ESI+):

681.2536	$[M+H]^+$	calc. 681.2508]
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tert-butyl (4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)carbamate **S31**



A solution of the 4-(4-(benzylamino)phenoxy)phenol **S7** (72 mg, 247 μ mol, 1.0eq), tert-butyl (4-bromobutyl)carbamate (93 mg, 371 μ mol, 1.5eq) and potassium carbonate (102 mg, 741 μ mol, 3.0eq) in Acetone (10 mL) was refluxed overnight. The solvent was removed under reduced pressure. Reverse phase column chromatography (ACN/water) yielded the title compound as a colorless oil (89 mg, 78%).

^1H NMR (400 MHz, CD_2Cl_2): δ = 7.42-7.24 (m, 4H), 6.90-6.78 (m, 6H), 6.63-6.57 (m, 2H), 4.31 (s, 2H), 4.08 (s, 2H), 3.93 (t, 3J = 6.3 Hz, 2H), 3.15 (q, 3J = 6.7 Hz, 2H), 1.81-1.73 (m, 2H), 1.69-1.56 (m, 2H), 1.42 (s, 9H).

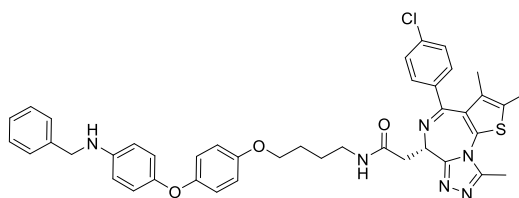
^{13}C NMR (101 MHz, CD_2Cl_2): δ = 156.4, 155.0, 152.8, 149.7, 145.0, 140.3, 129.1, 128.0, 127.7, 120.5, 119.4, 115.9, 114.3, 79.2, 68.7, 49.2, 40.8, 28.7, 27.4, 27.2.

MS (ESI+):

407.1	$[(-^t\text{Bu}+2\text{H})^+]$	calc. 407.19]
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485.3	$[(M+\text{Na})^+]$	calc. 485.24]
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(S)-N-(4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide **S32**



A solution of tert-butyl (4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)carbamate **S31** (30 mg, 65 μ mol, 1.1eq) in 4 mL DCM/TFA (1/1) was stirred for 3 h. All volatiles were removed under reduced pressure. DCM was added and the solvent was removed under reduced pressure. This procedure was repeated once.

A solution of DIPEA (21 μ L, 118 μ mol, 2.0eq), (S)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (24 mg, 59 μ mol, 1.0eq) and HATU (27 mg, 71 μ mol, 1.2eq) in DMF (1.5 mL) was stirred for 10 min. The crude

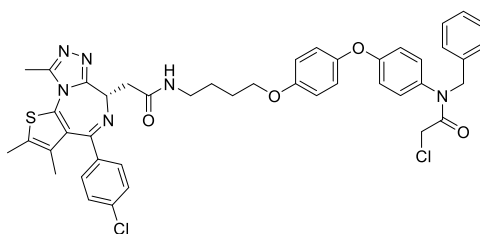
amine was added and the reaction mixture was stirred for 16 h. DCM, water and brine were added and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was evaporated under reduced pressure and the residue was purified by reverse flash column chromatography to yield the title compound as a colorless solid (34 mg, 77%).

¹H NMR (500 MHz, DMSO-*d*₆): δ = 8.22 (t, ³J = 5.6 Hz, 1H), 7.44 (d, ³J = 8.8 Hz, 2H), 7.41 (d, ³J = 8.7 Hz, 2H), 7.36 (d, ³J = 7.4 Hz, 2H), 7.32 (t, ³J = 7.6 Hz, 2H), 7.22 (t, ³J = 7.2 Hz, 1H), 6.87-6.82 (m, 2H), 6.81-6.77 (m, 2H), 6.75-6.70 (m, 2H), 6.59-6.54 (m, 2H), 6.09 (t, ³J = 6.0 Hz, 1H), 4.51 (dd, ³J = 8.3 Hz, ³J = 5.8 Hz, 1H), 4.23 (d, ³J = 5.9 Hz, 2H), 3.91 (t, ³J = 6.4 Hz, 2H), 3.29-3.09 (m, 4H), 2.59 (s, 3H), 2.40 (s, 3H), 1.77-1.69 (m, 2H), 1.63-1.55 (m, 5H).

¹³C NMR (126 MHz, DMSO-*d*₆): δ = 169.4, 162.98, 155.1, 153.8, 151.9, 149.8, 147.2, 145.1, 140.3, 136.7, 135.2, 132.2, 130.7, 130.1, 129.8, 129.6, 128.4, 128.2, 127.2, 126.6, 119.8, 118.3, 115.3, 113.1, 67.6, 53.9, 46.98, 39.5, 38.2, 37.7, 26.2, 25.9, 14.0, 12.7, 11.3.
MS (ESI+):

373.1	[(M/2+H) ⁺	calc. 373.14]
655.2	[(M-Bn+2H) ⁺	calc. 655.22]
745.3	[(M+H) ⁺	calc. 745.27]

(S)-N-benzyl-2-chloro-N-(4-(4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)phenoxy)phenyl)acetamide
CCW28-3



2-chloroacetyl chloride (4 μL, 52 μmol, 1.3eq) and TEA (28 μL, 201 μmol, 5.0eq) were added to a solution of (S)-N-(4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide **S32** (30 mg, 40 μmol, 1.0eq) in 2 mL DCM at 0 °C. The reaction mixture was stirred for 23 h at r.t. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (3x) and the combined organic layers were dried with MgSO₄. The solvent was removed under reduced pressure and the crude material was purified using reversed phase flash column chromatography (H₂O/ACN). The title compound was isolated as a colorless solid (22 mg, 67%).

¹H NMR (500 MHz, CD₂Cl₂): δ = 7.46-7.40 (m, 2H), 7.33 (d, ³J = 8.8 Hz, 2H), 7.31-7.23 (m, 3H), 7.22-7.18 (m, 2H), 6.99-6.93 (m, 4H), 6.91-6.84 (m, 4H), 6.63 (t, ³J = 5.6 Hz, 1H),

4.85 (s, 2H), 4.59 (t, $^3J = 6.9$ Hz, 1H), 3.95 (t, $^3J = 6.3$ Hz, 2H), 3.89 (s, 2H), 3.45 (dd, $^3J = 14.3$ Hz, $^3J = 7.3$ Hz, 1H), 3.38 (td, $^3J = 13.2$ Hz, $^3J = 6.9$ Hz, 1H), 3.33-3.25 (m, 2H), 2.63 (s, 3H), 2.41-2.36 (m, 3H), 1.85-1.78 (m, 2H), 1.75-1.68 (m, 3H), 1.67 (s, 3H).

^{13}C NMR (126 MHz, CD_2Cl_2): $\delta = 170.7, 166.7, 164.4, 159.4, 156.5, 156.3, 150.6, 149.6, 137.5, 137.4, 137.1, 135.5, 132.9, 131.6, 131.3, 130.9, 130.5, 130.1, 129.3, 129.1, 128.98, 128.1, 121.8, 118.4, 116.2, 68.6, 55.1, 42.9, 39.9, 39.6, 27.2, 26.9, 14.7, 13.4, 12.2$.

HPLC: $R_t = 5.36$ min (method A): Purity: >99% (254 nm); >99% (320 nm)

MS (ESI+):

411.2	$[(M/2+H)^+]$	calc. 411.13]
821.3	$[(M+H)^+]$	calc. 821.24]

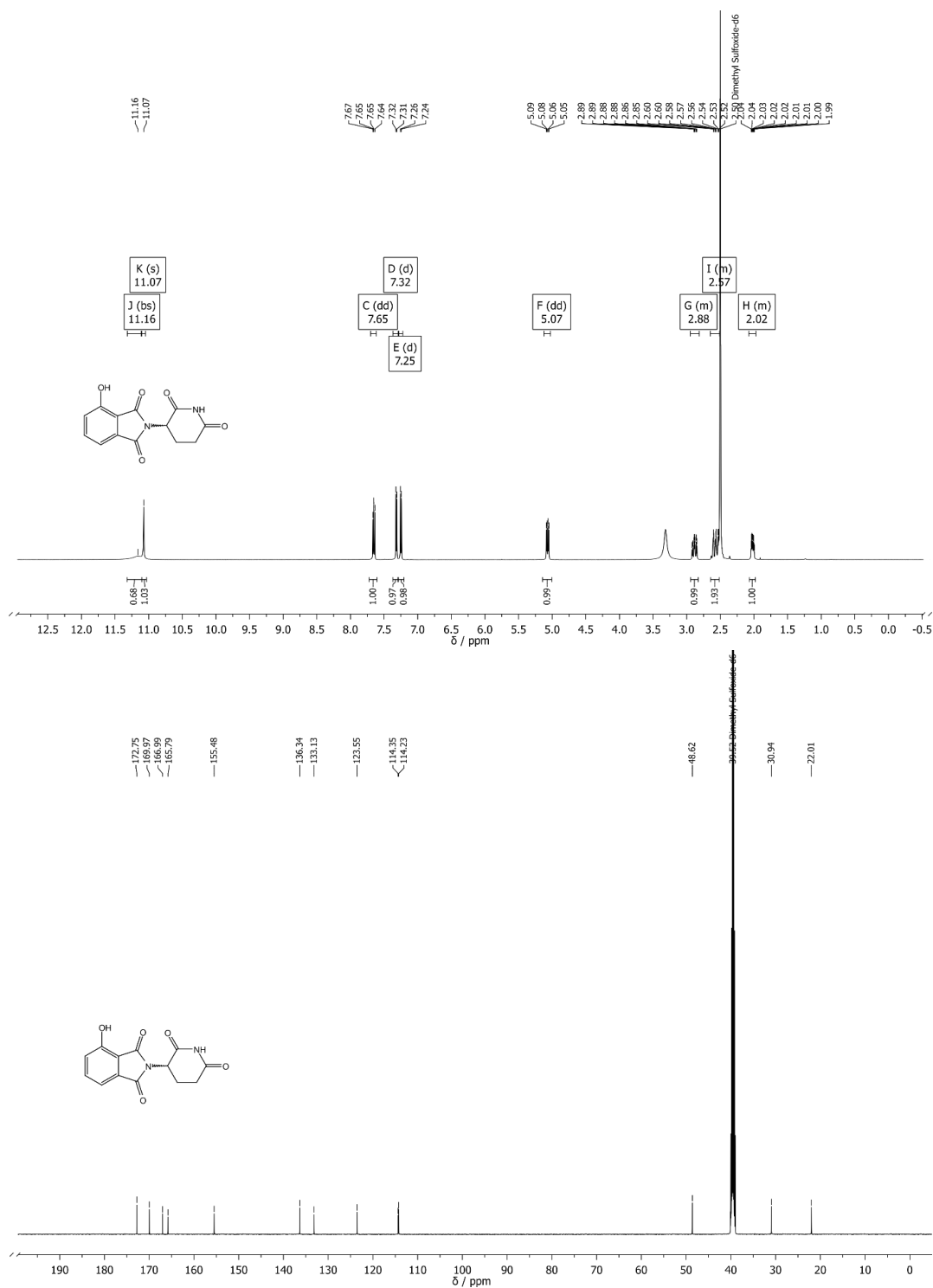
HRMS (ESI+):

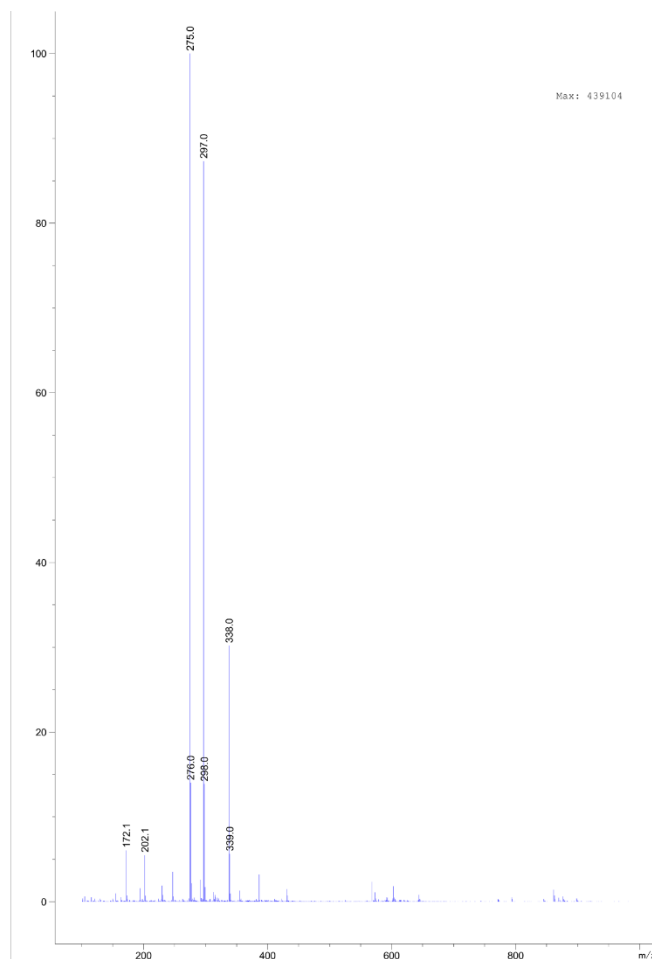
821.2434	$[(M+H)^+]$	calc. 821.2438]
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2. ^1H , ^{13}C NMR Spectra, Mass spectra and Chromatograms, HRMS

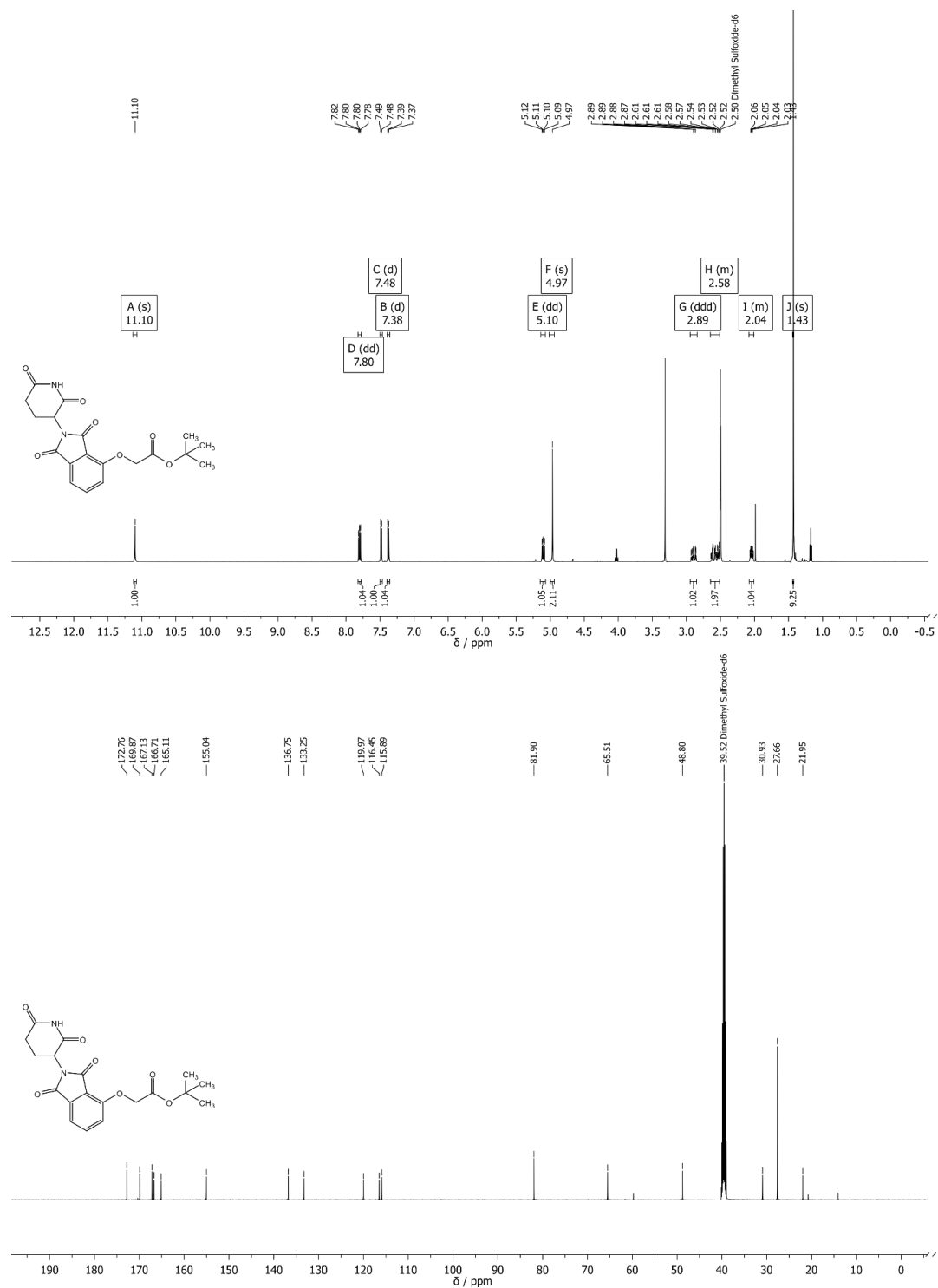
2.1 Spectra for all E3 ligase ligands and intermediates - Appendix Figure S5

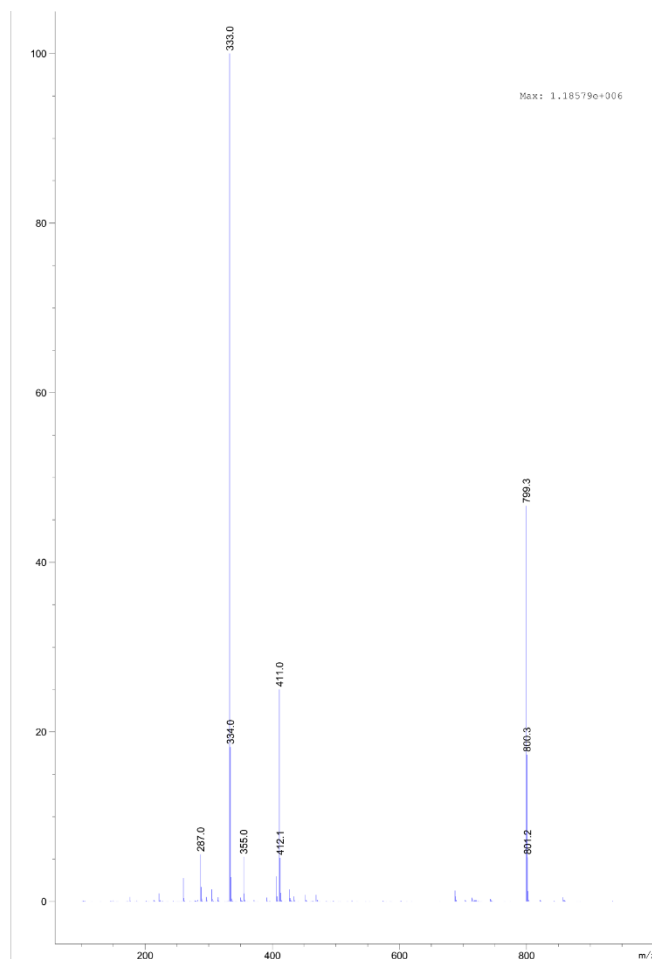
2-(2,6-dioxopiperidin-3-yl)-4-hydroxyisoindoline-1,3-dione **S3**

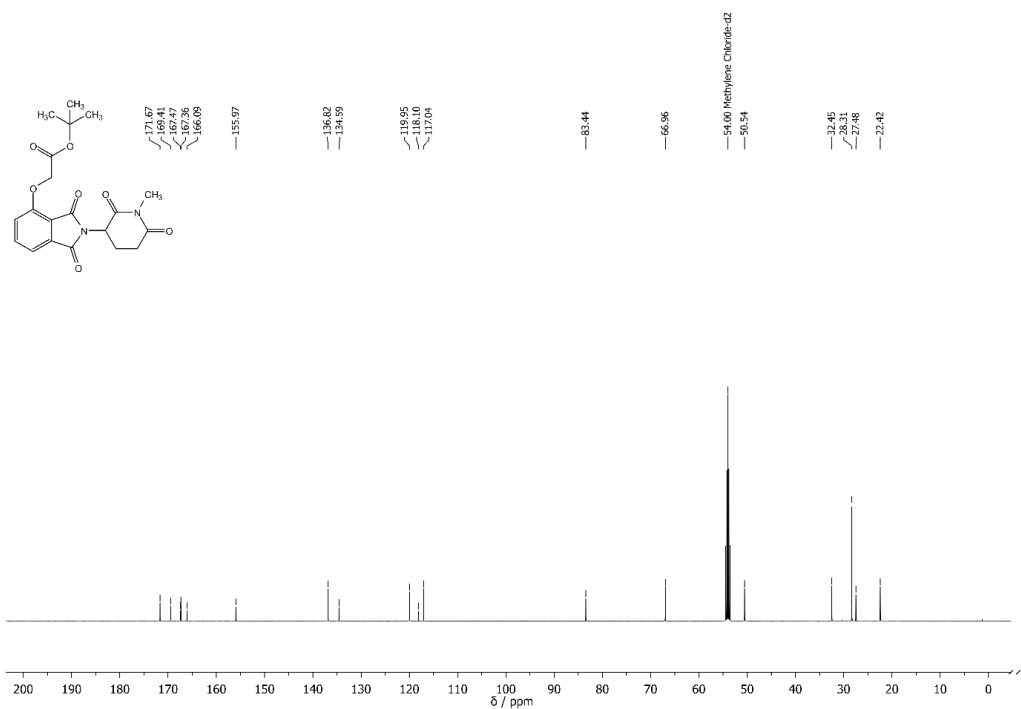
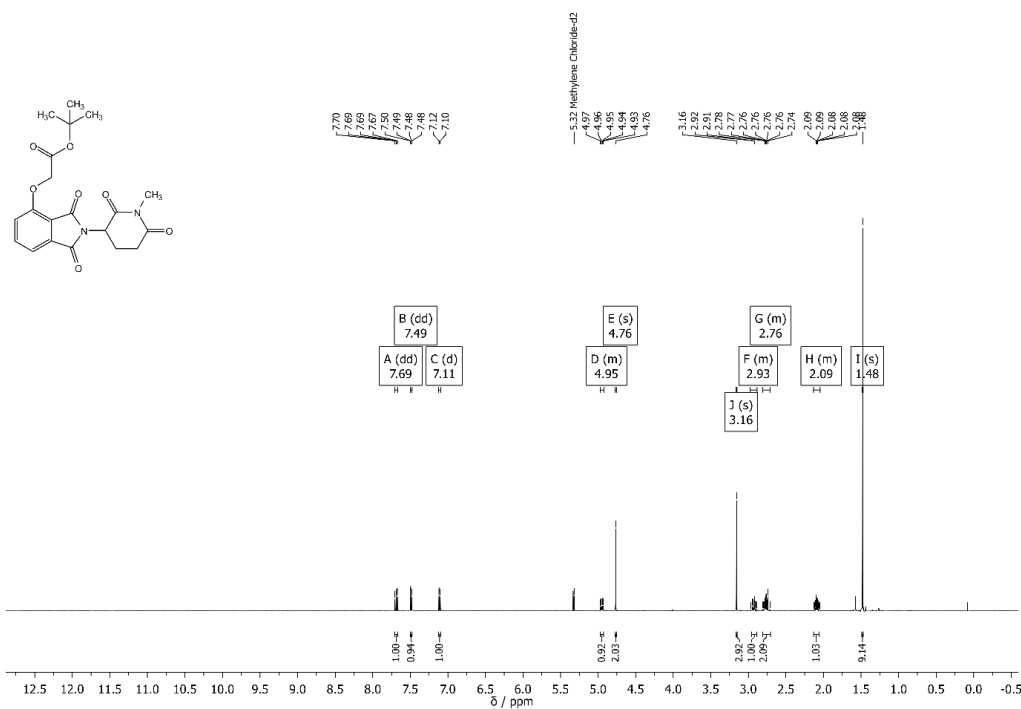


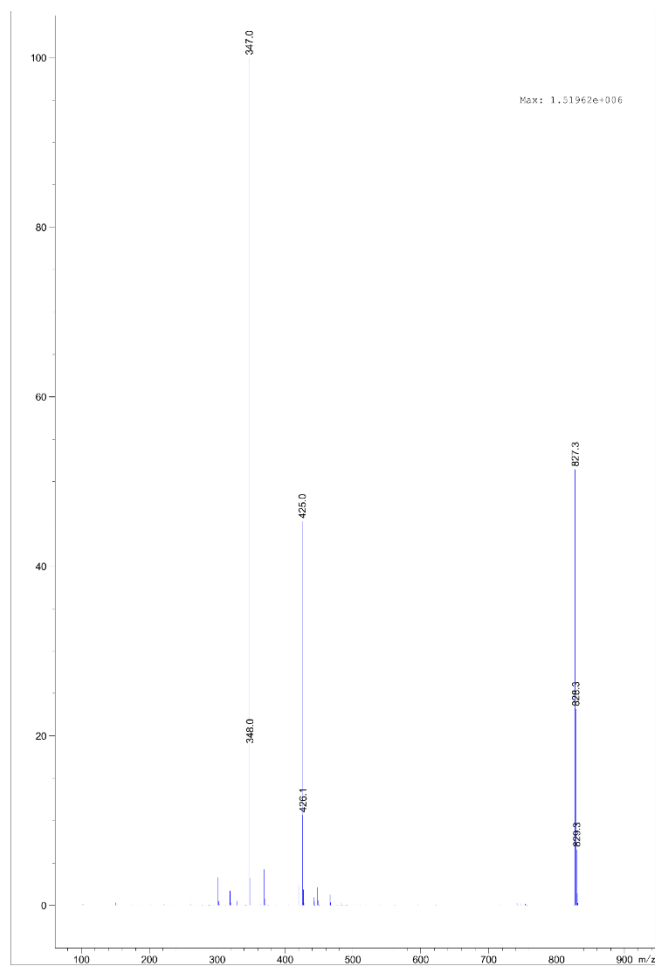


tert-butyl 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S4**

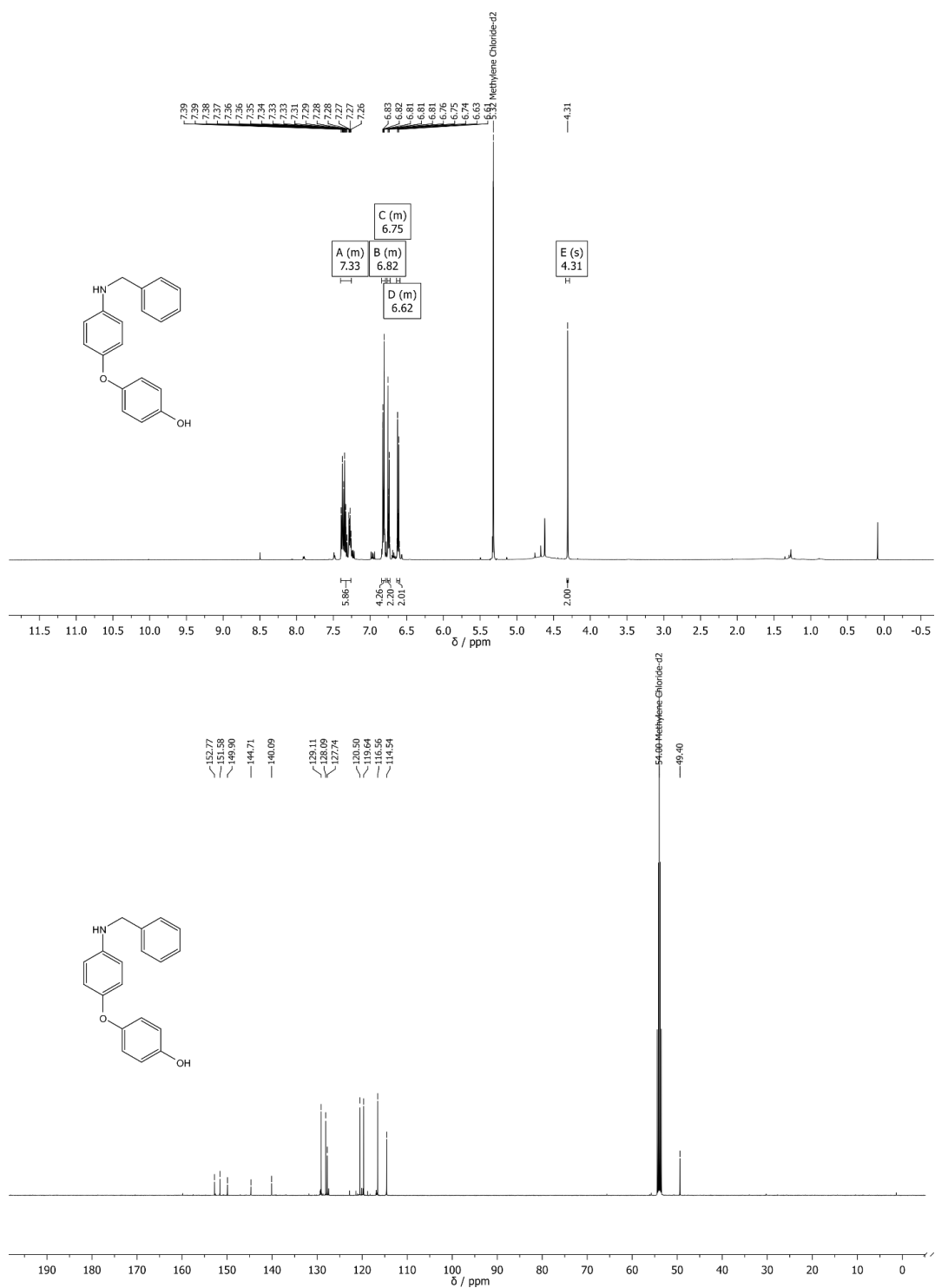


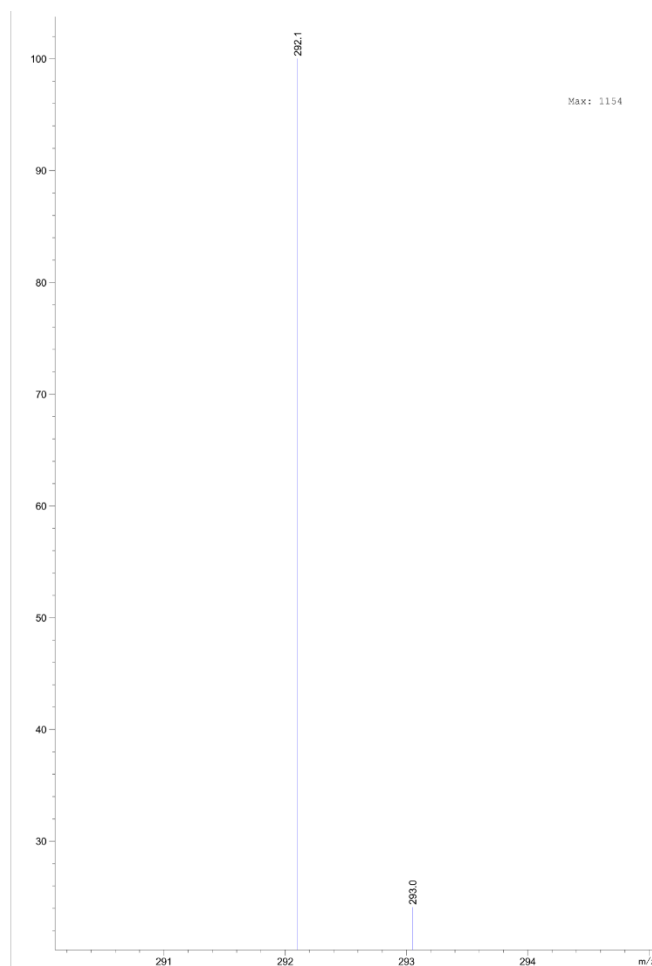


tert-butyl 2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetate **S5**

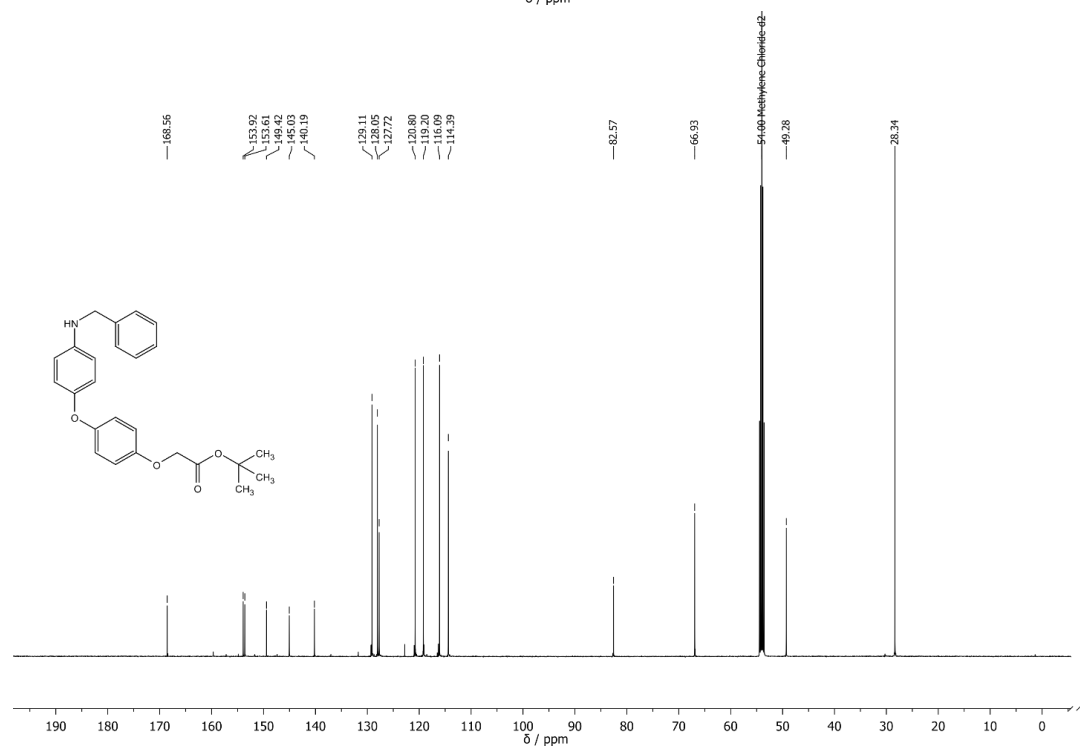
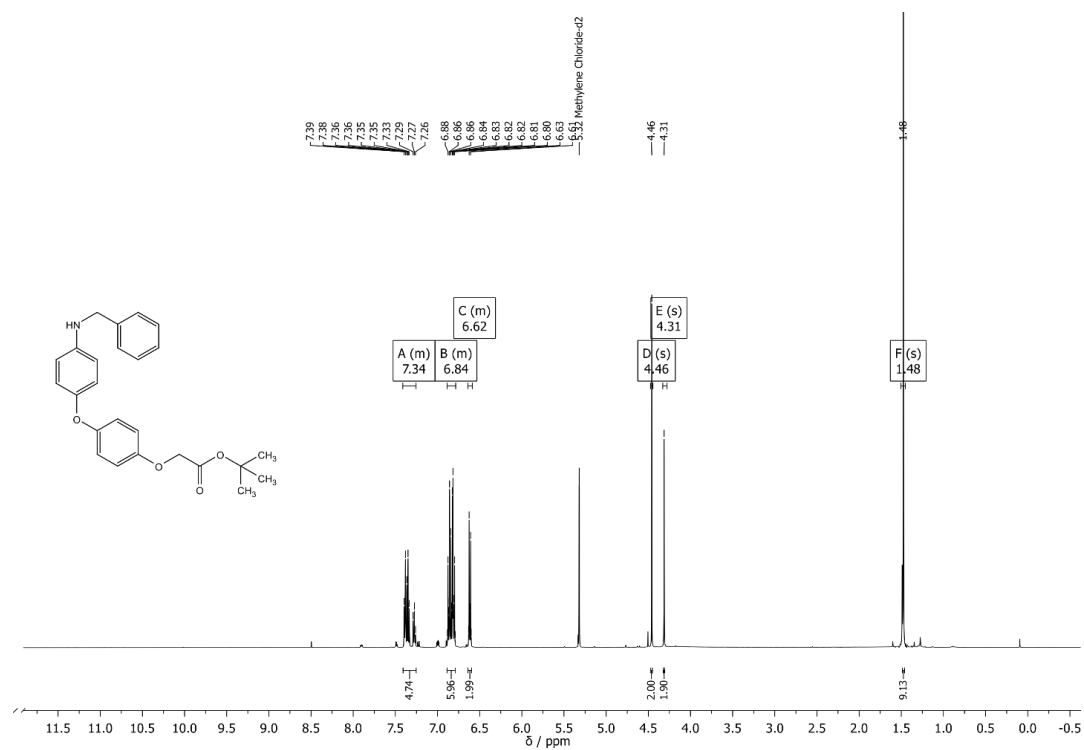


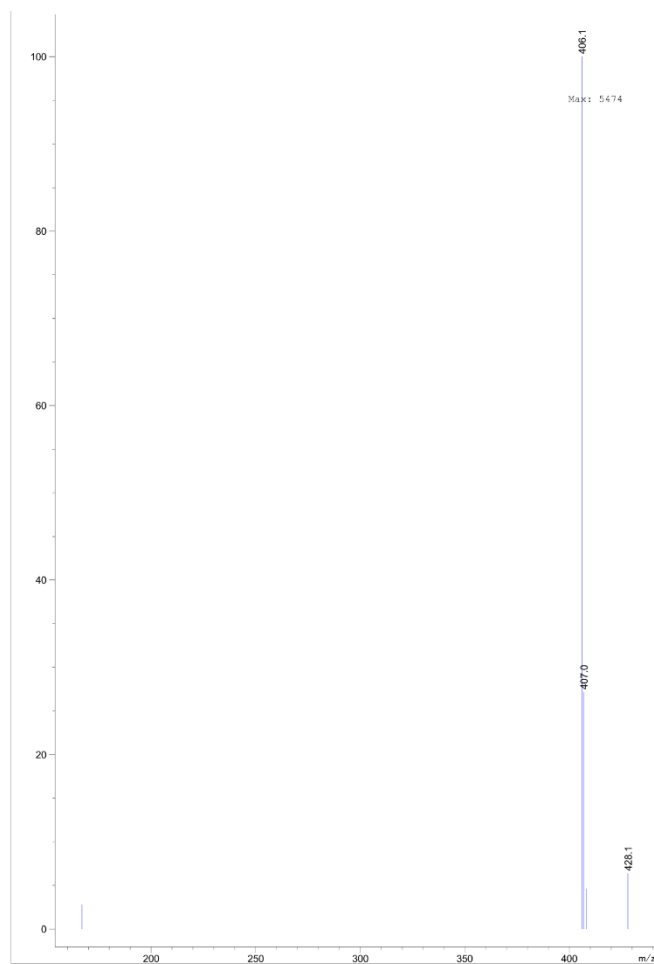
4-(4-(benzylamino)phenoxy)phenol **S7** via 4-(4-aminophenoxy)phenol



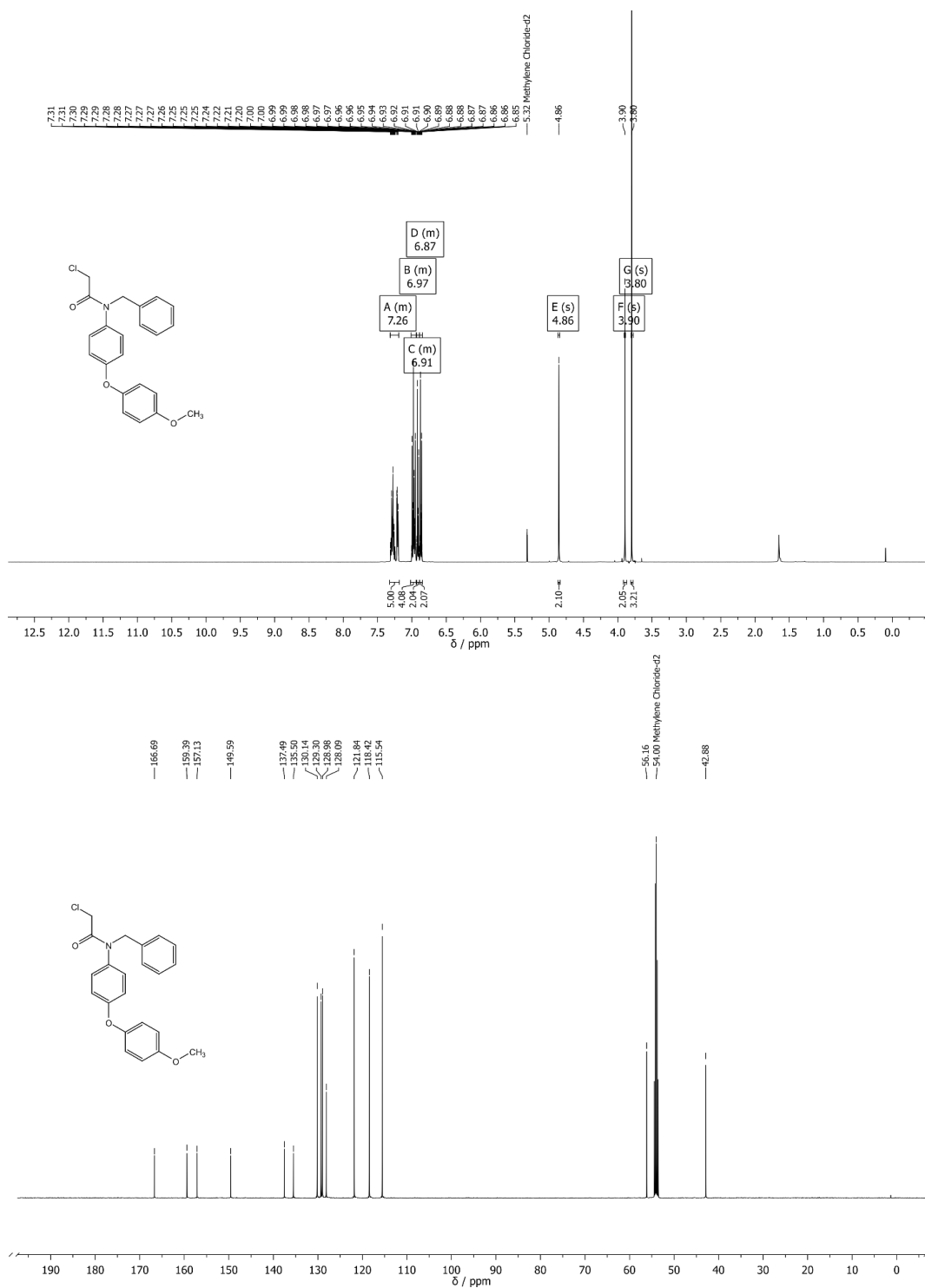


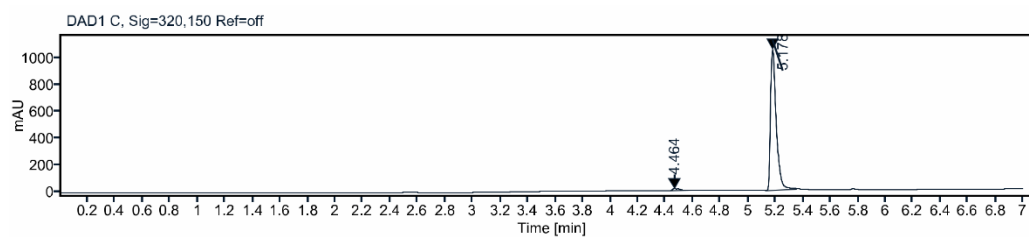
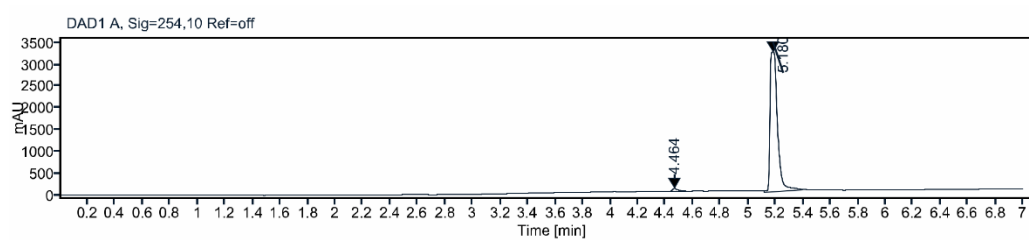
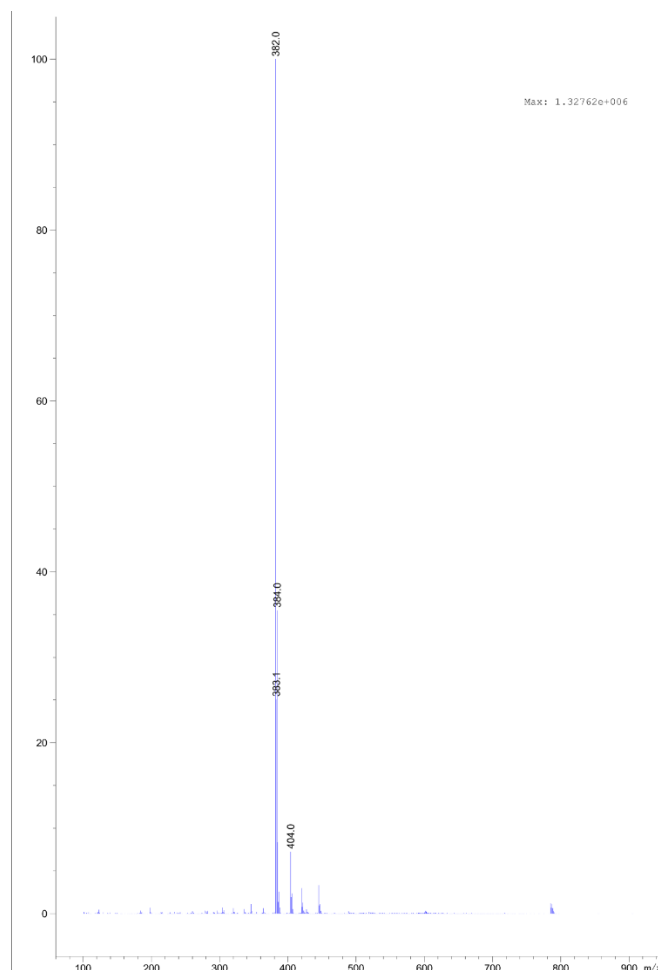
tert-butyl 2-(4-(4-(benzylamino)phenoxy)phenoxy)acetate **S8**

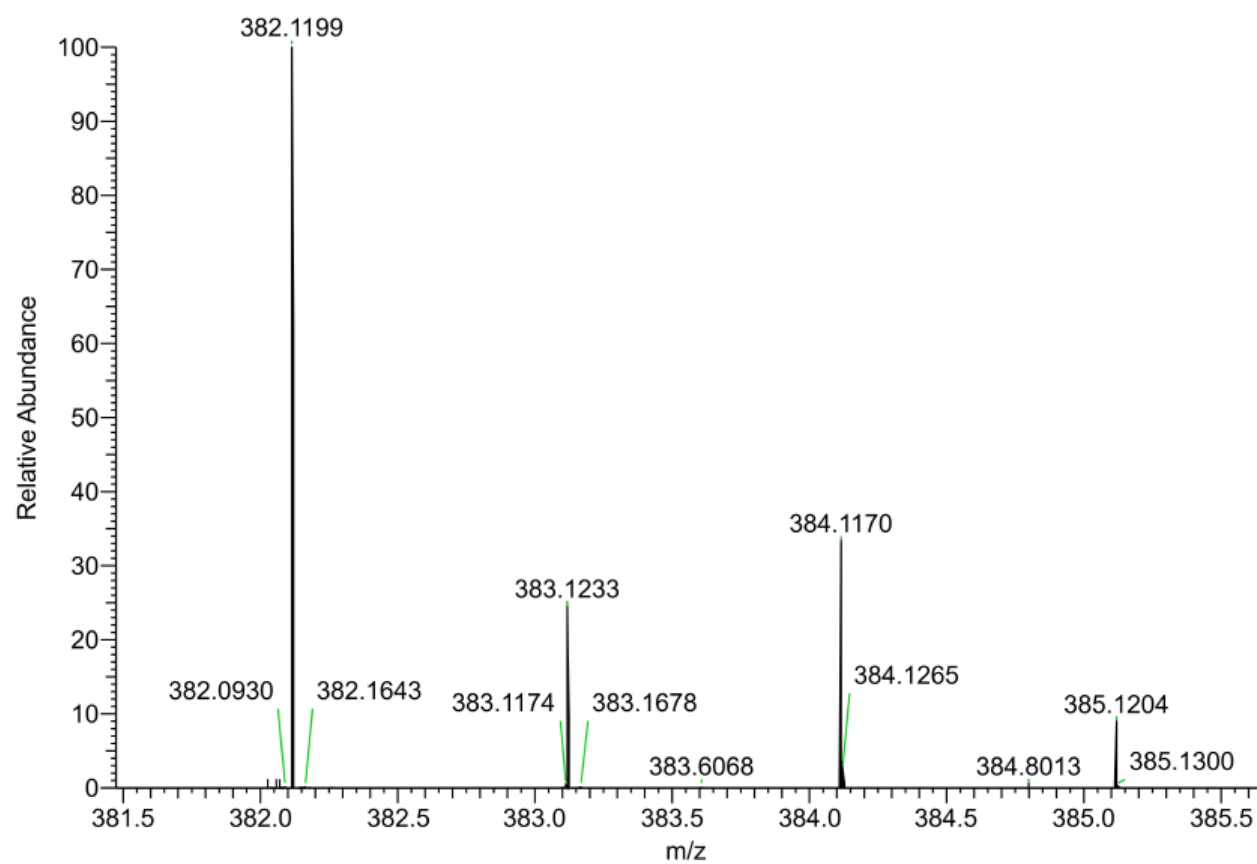




N-benzyl-2-chloro-N-(4-(4-methoxyphenoxy)phenyl)acetamide **CCW16**

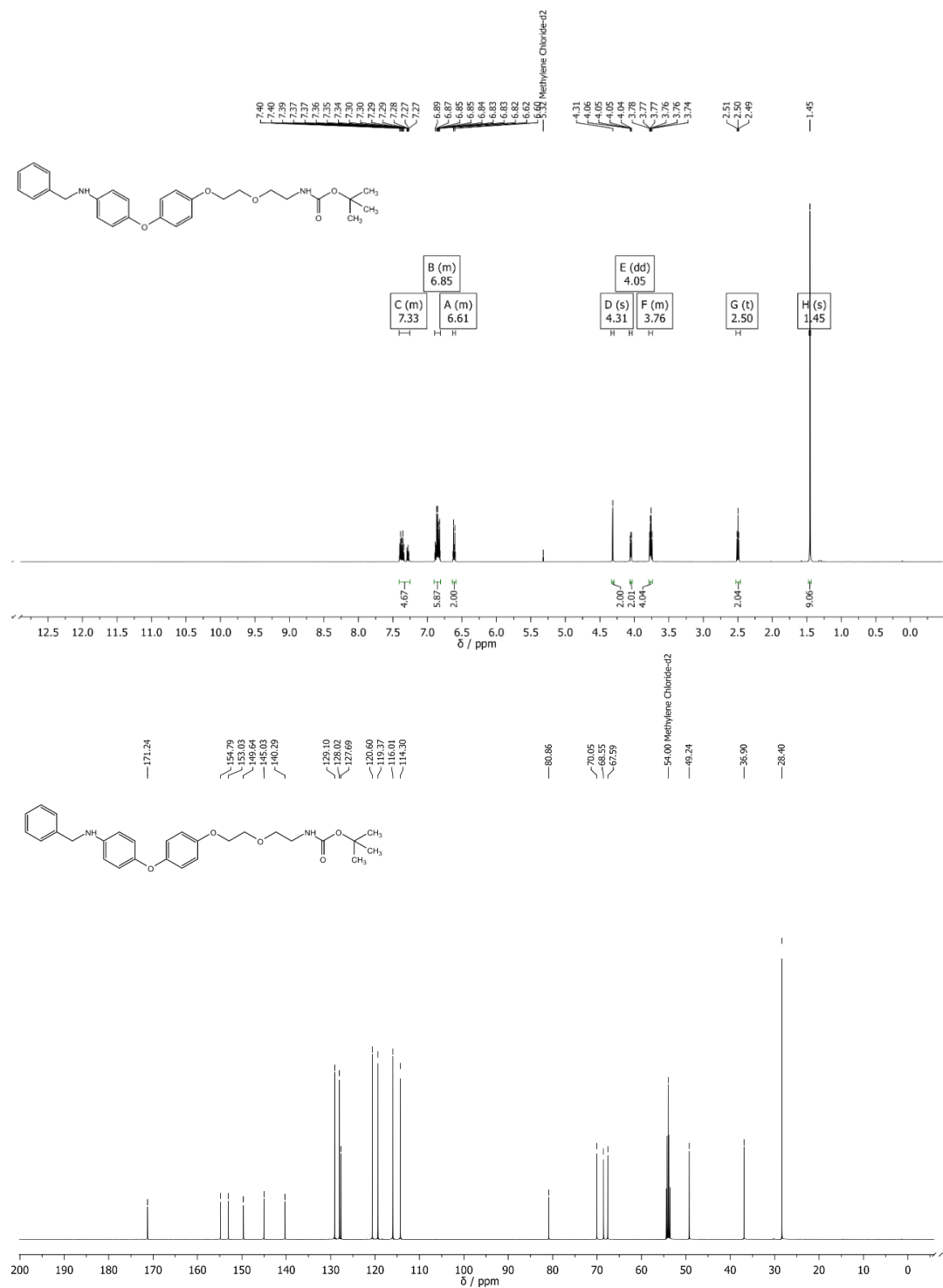


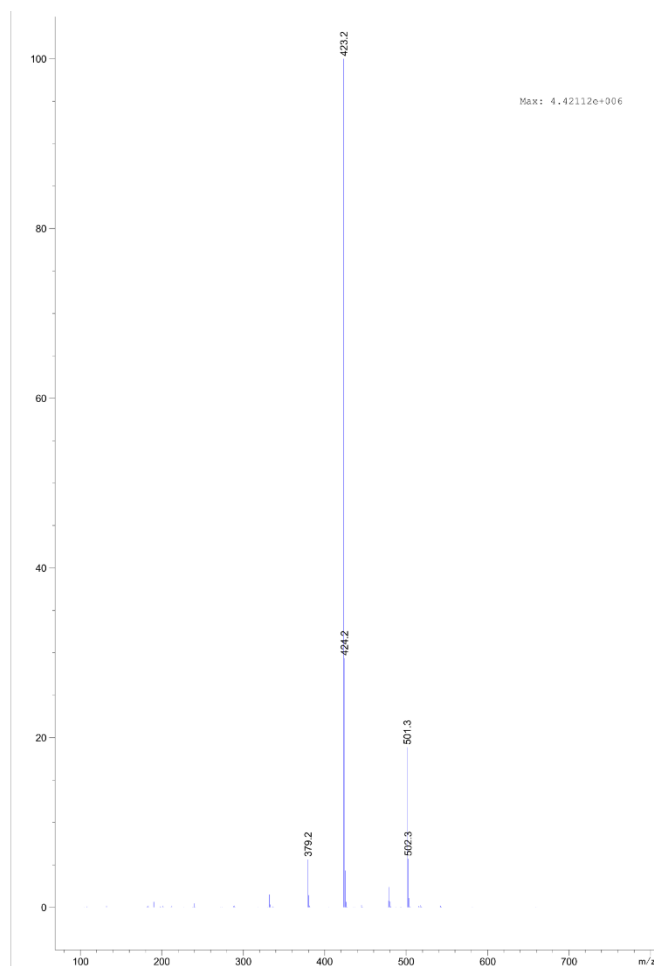




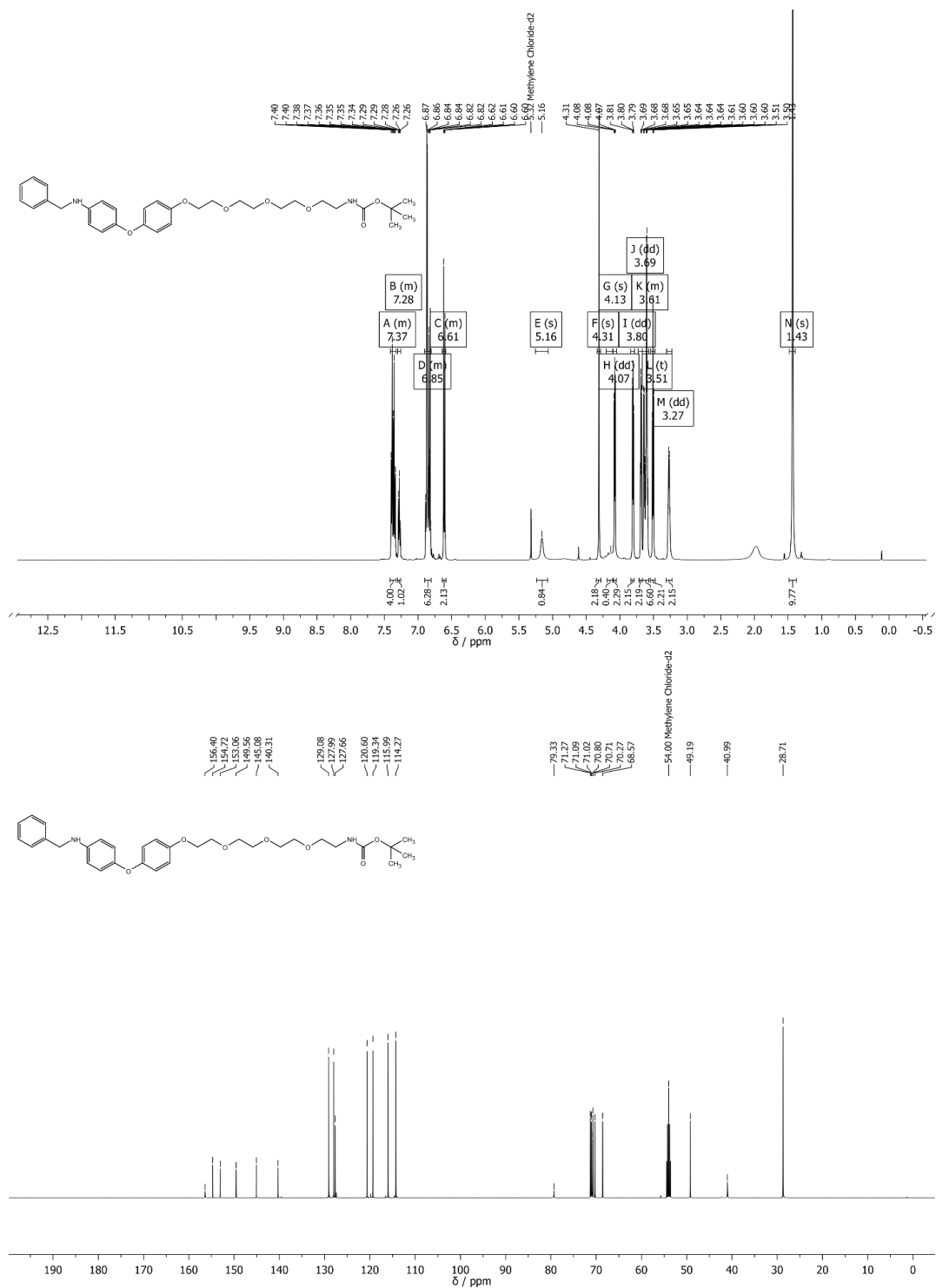
2.2 Spectra for all CRBN-based PROTACs and intermediates- Appendix Figure S6

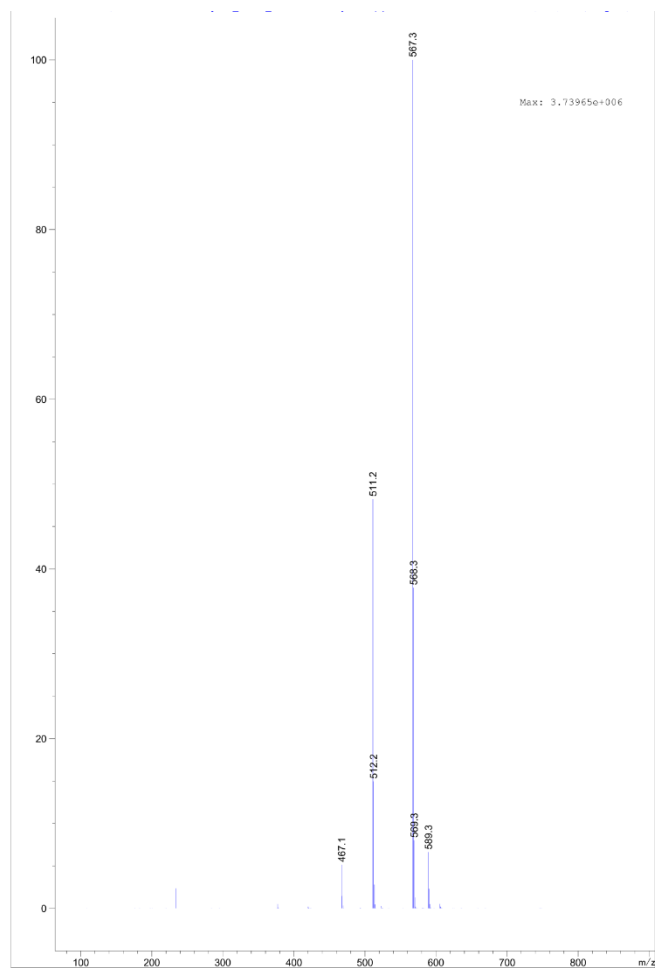
tert-butyl (2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)carbamate **S11**



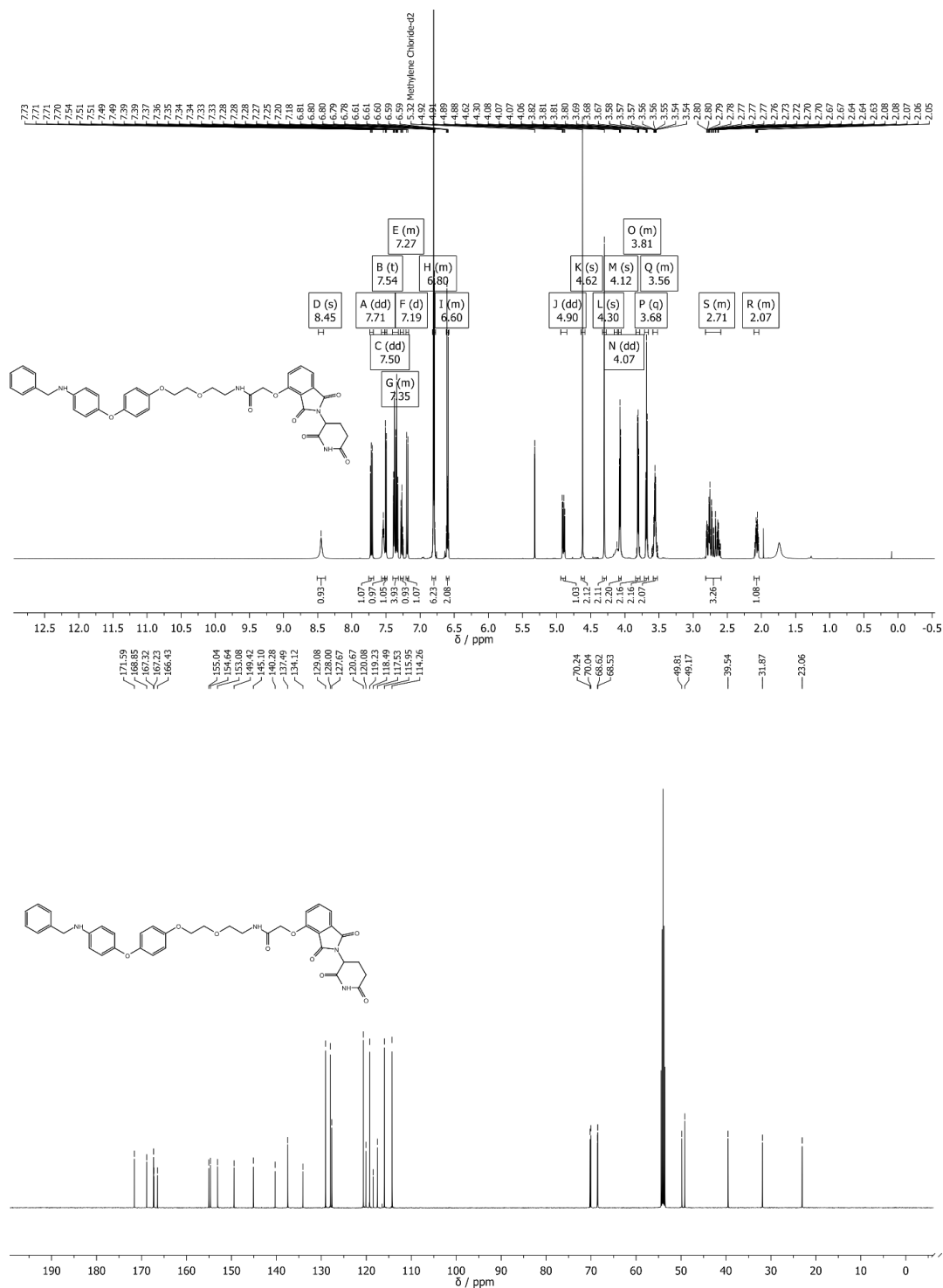


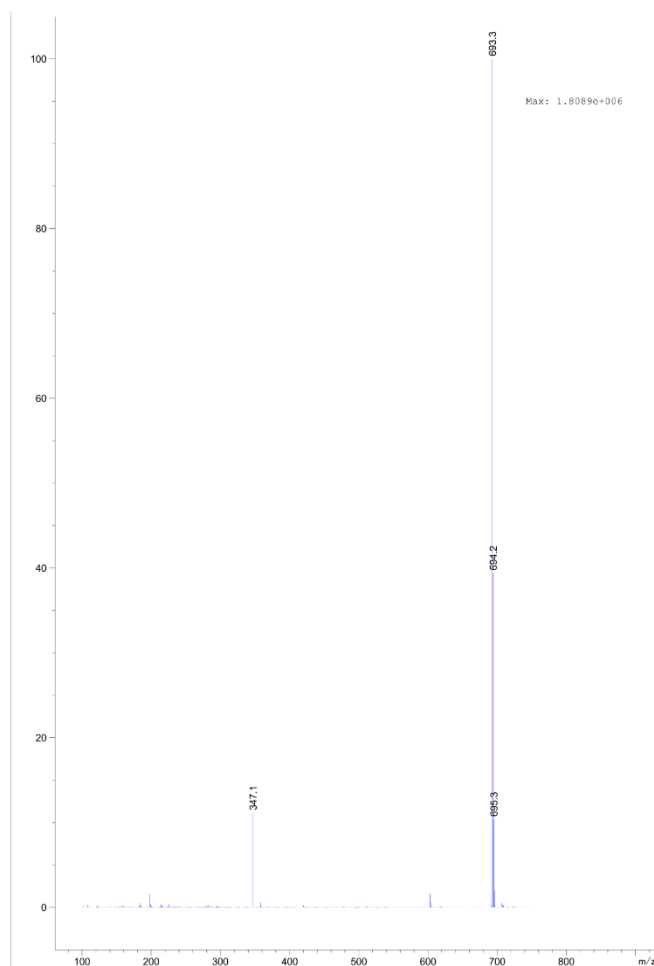
tert-butyl (2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate **S12**



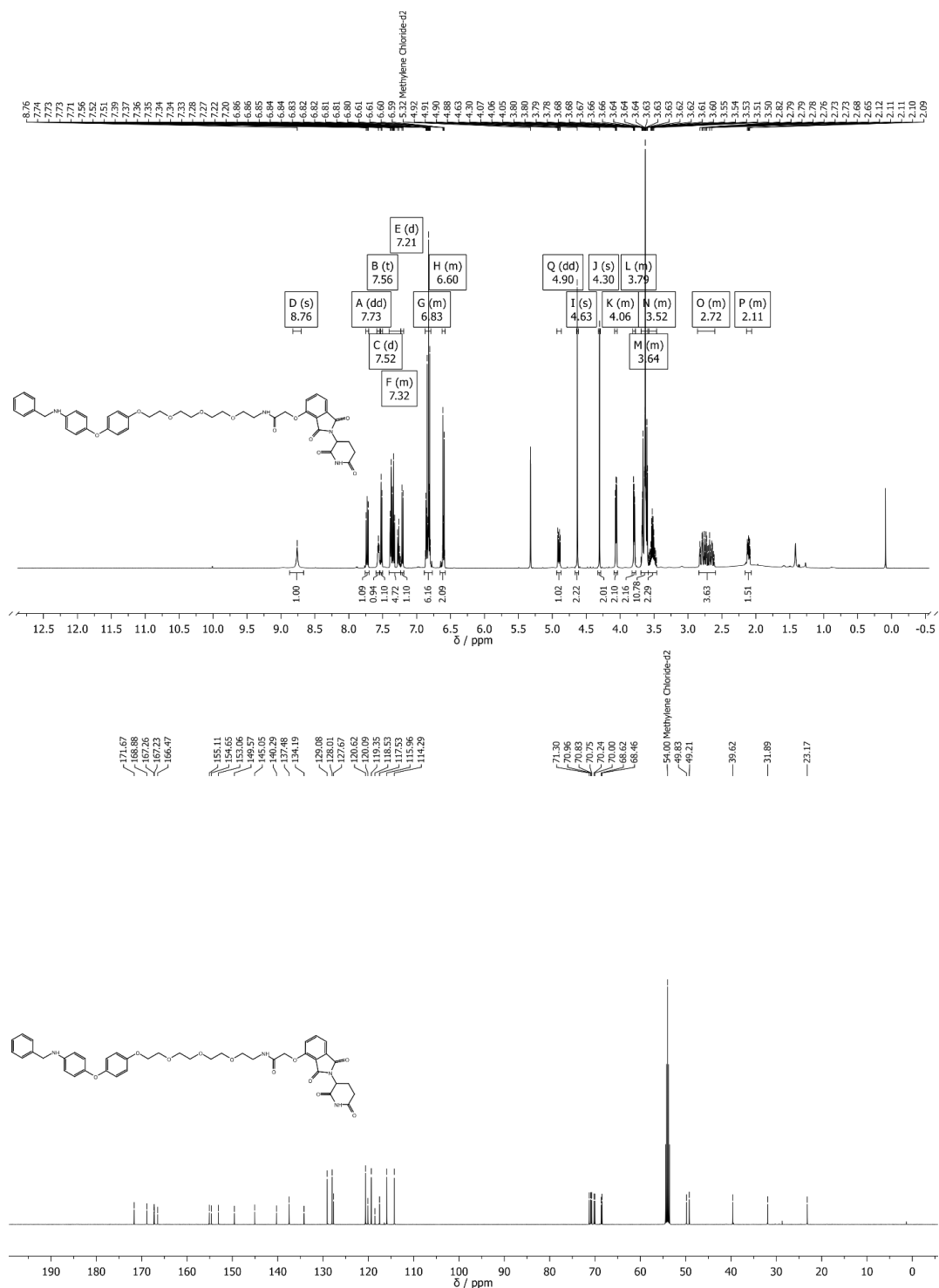


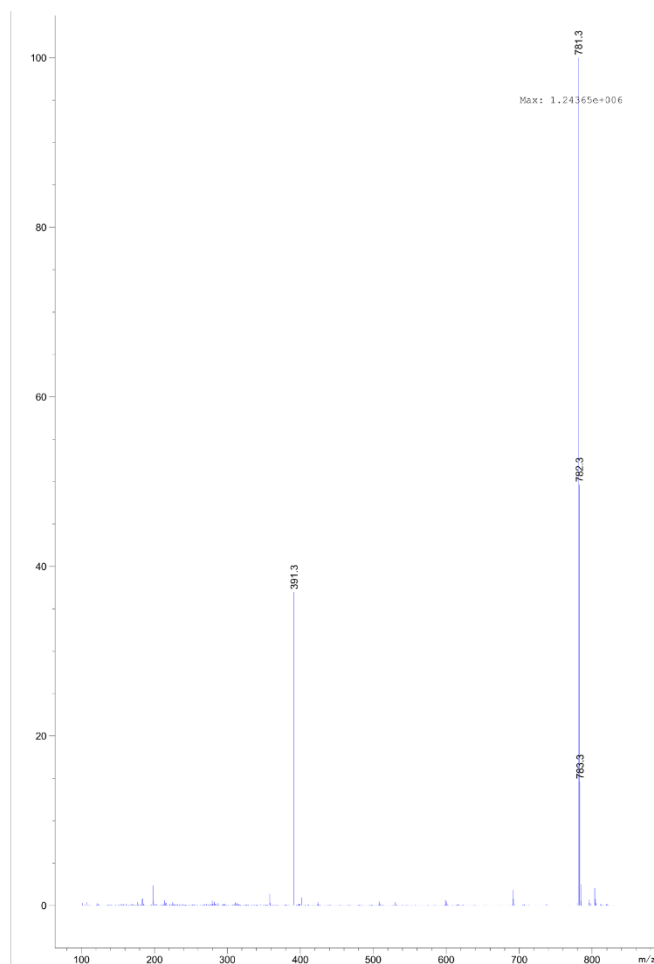
N-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S13**



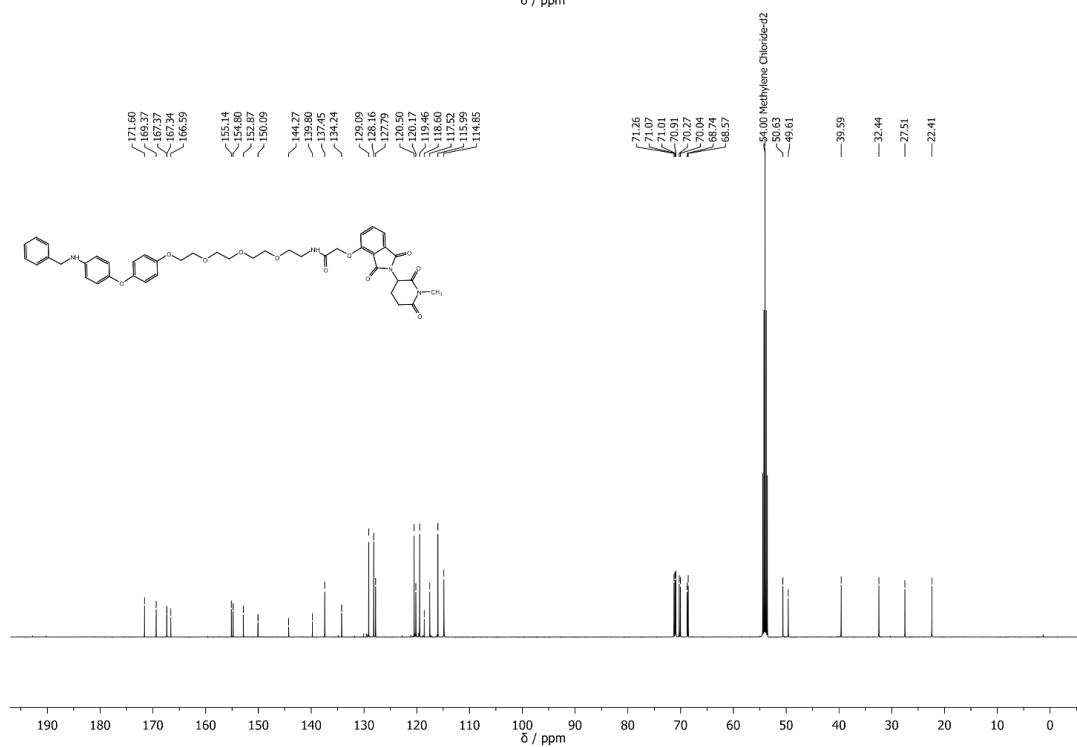
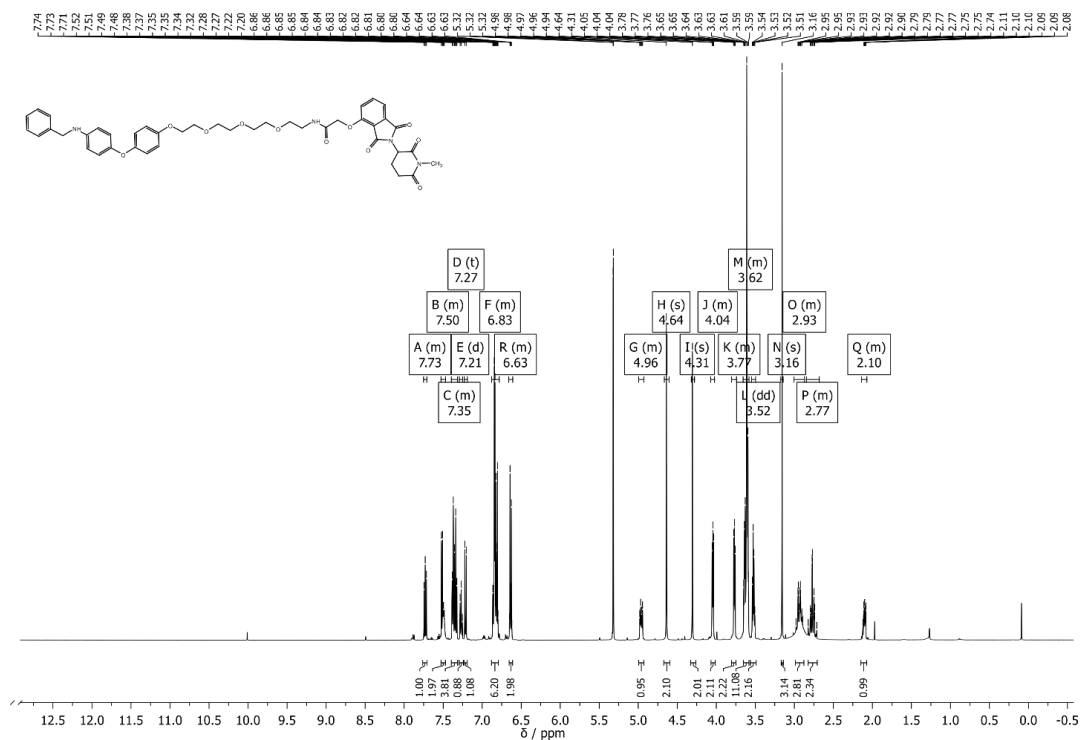


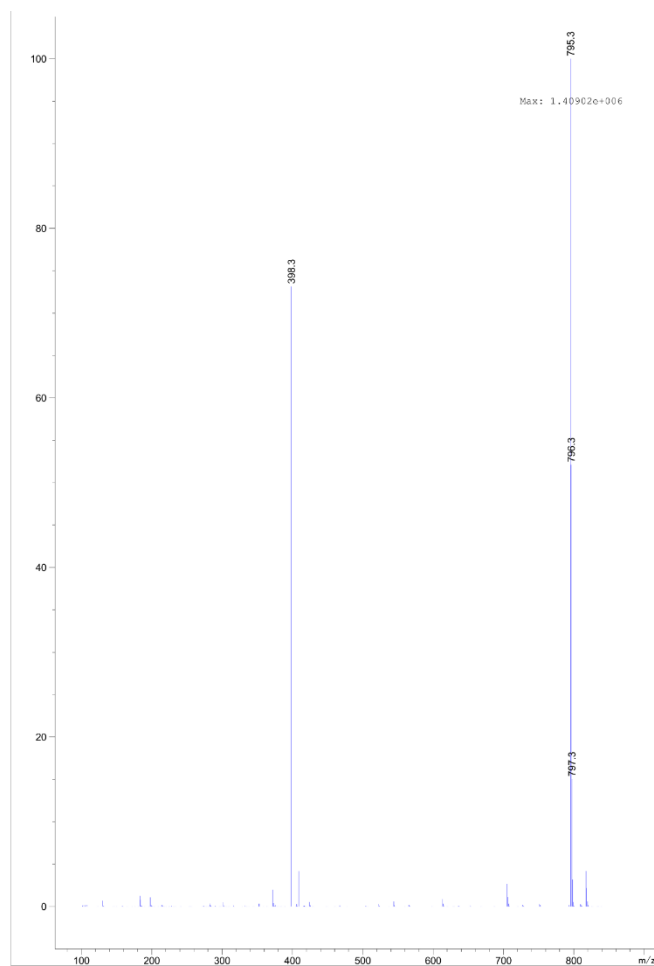
N-(2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S14**



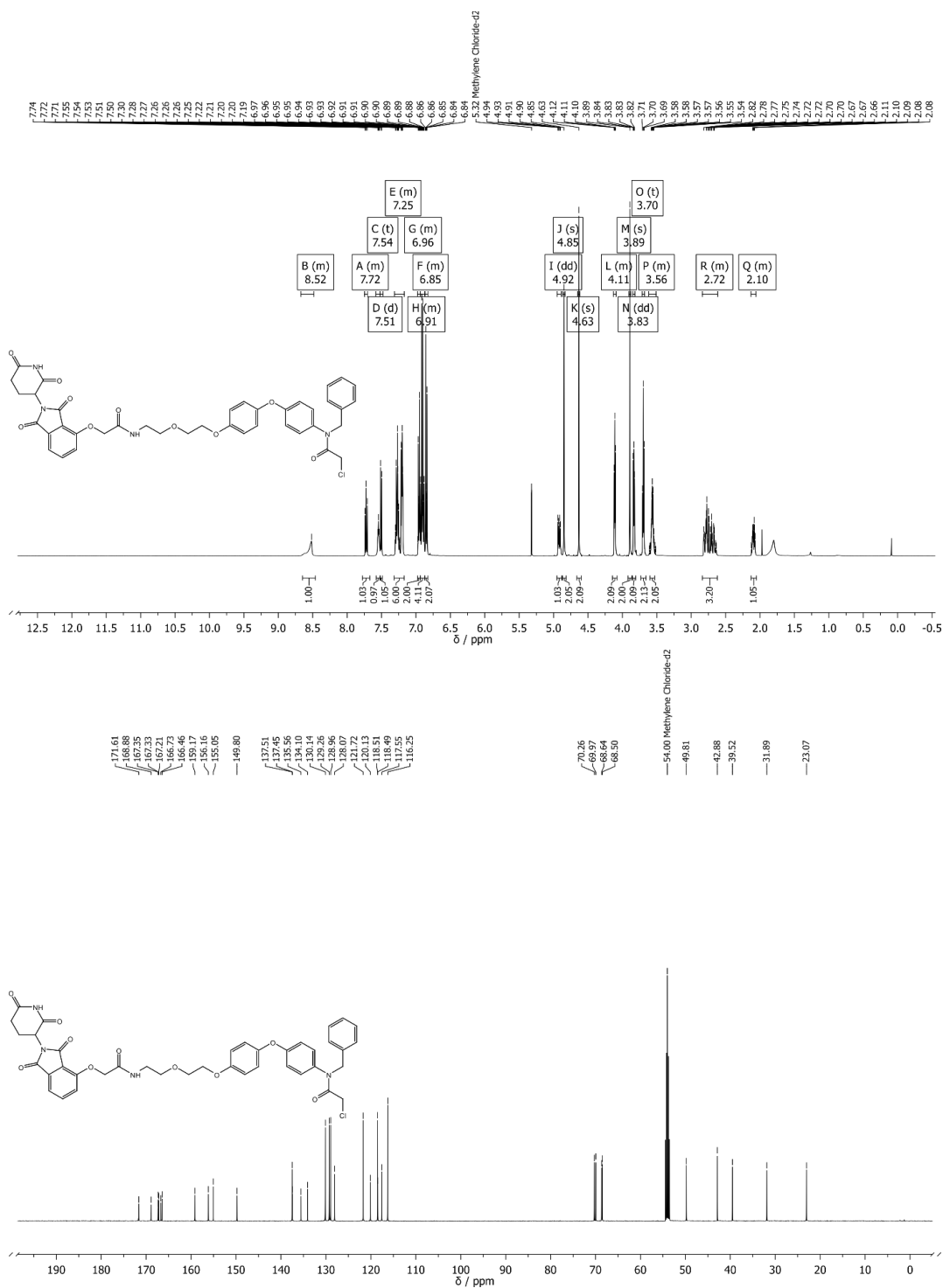


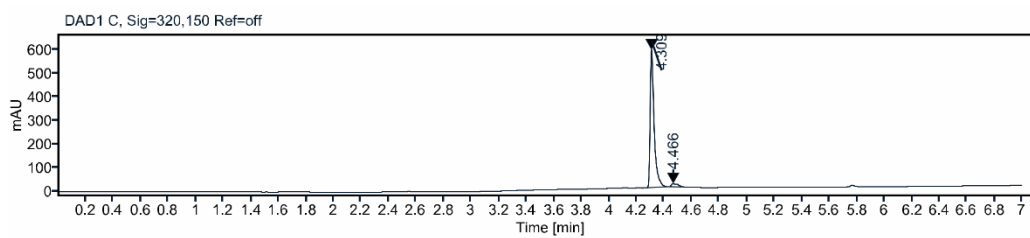
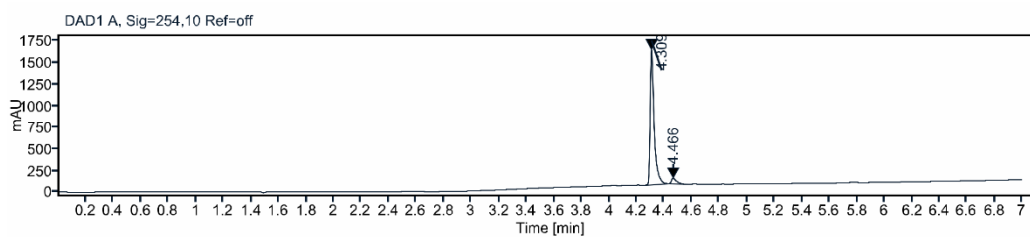
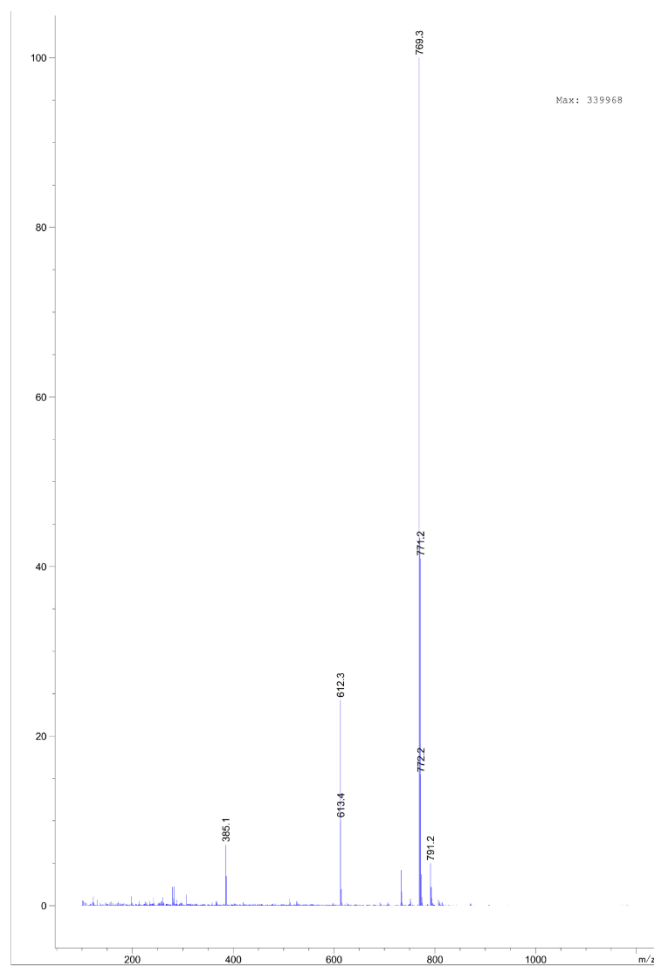
N-(2-(2-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamide **S15**

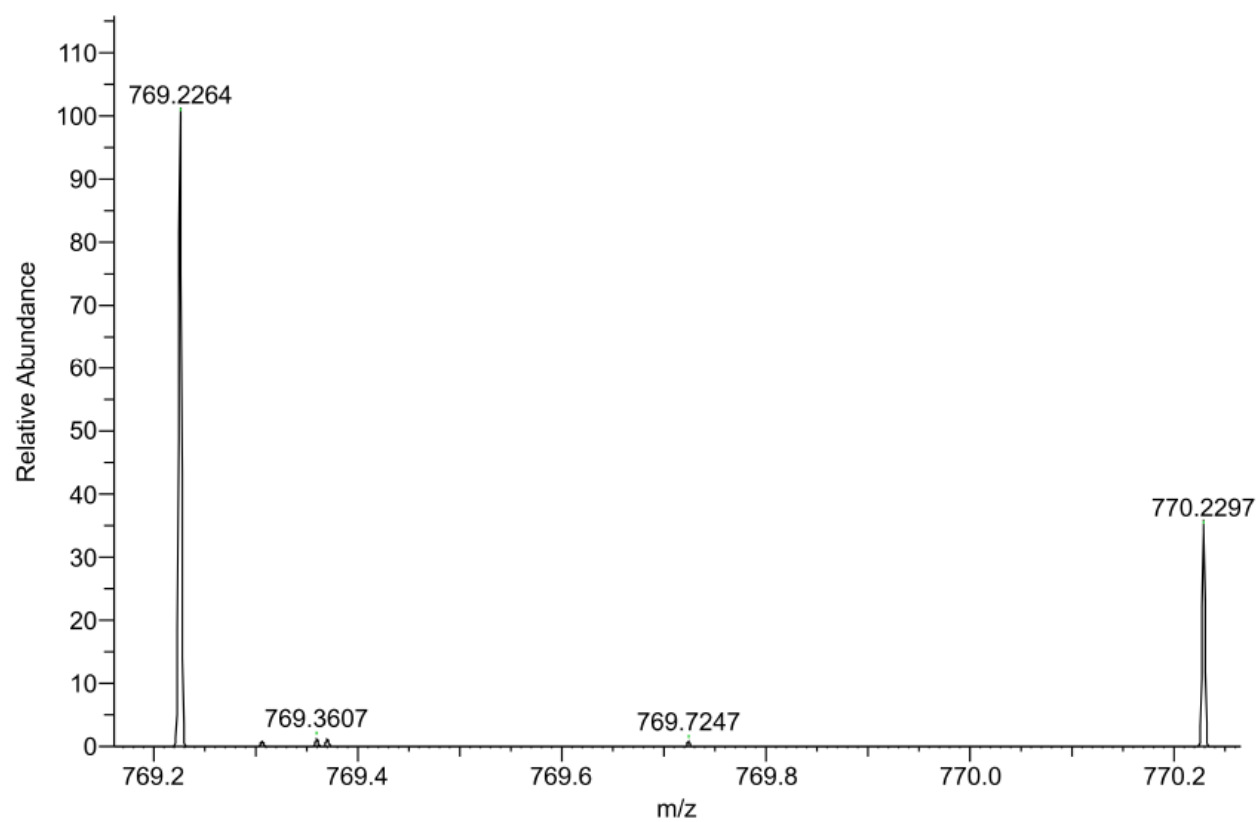




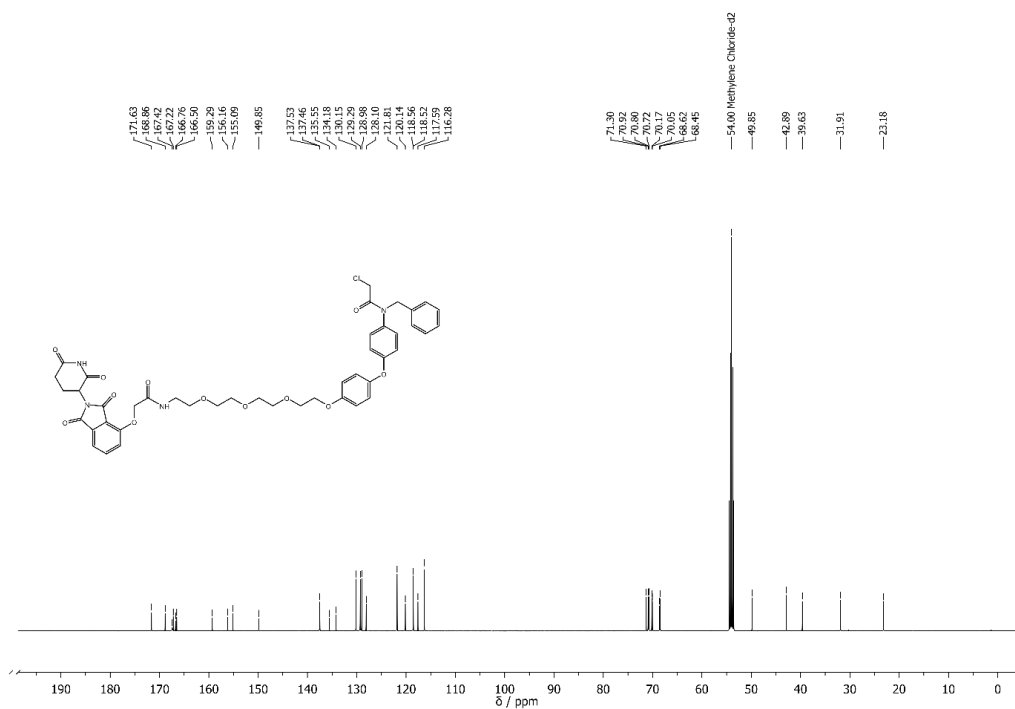
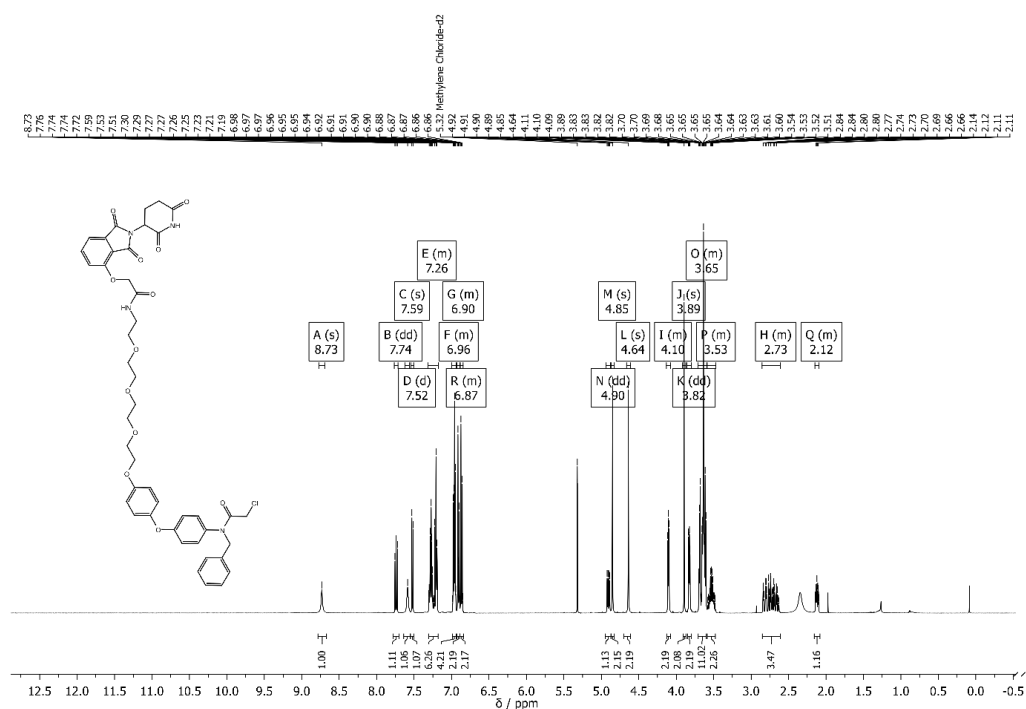
N-benzyl-2-chloro-N-(4-(4-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)ethoxy)ethoxy)phenoxy)phenyl)acetamide **1a**

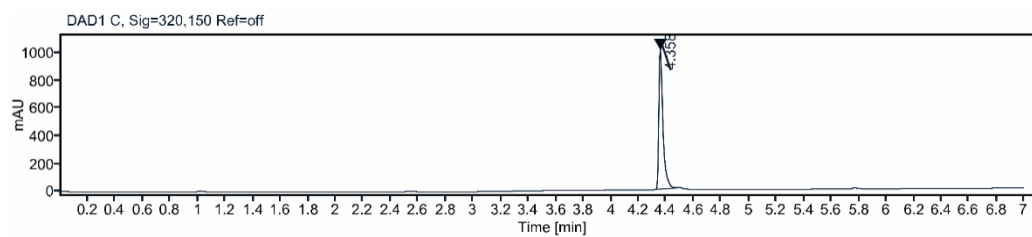
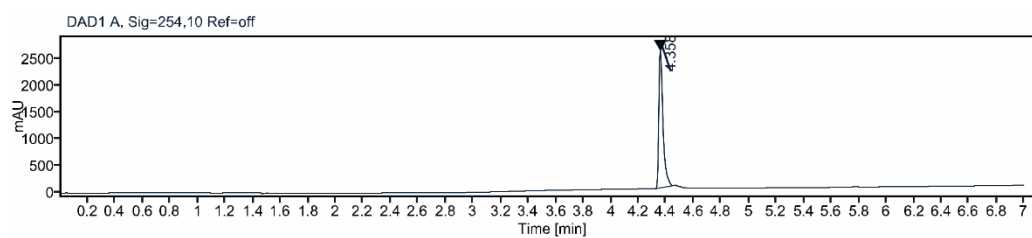
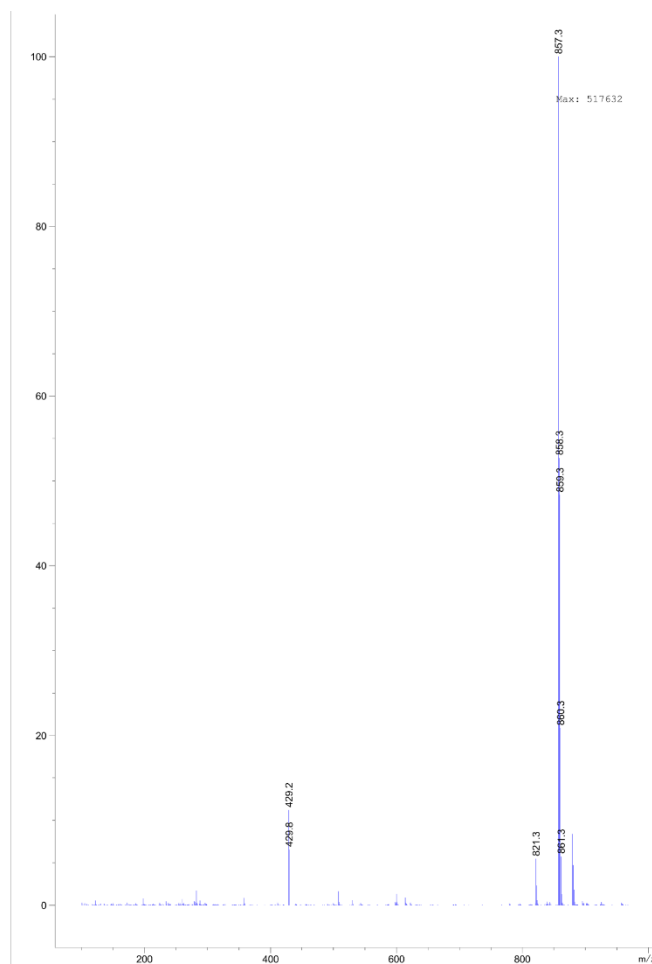


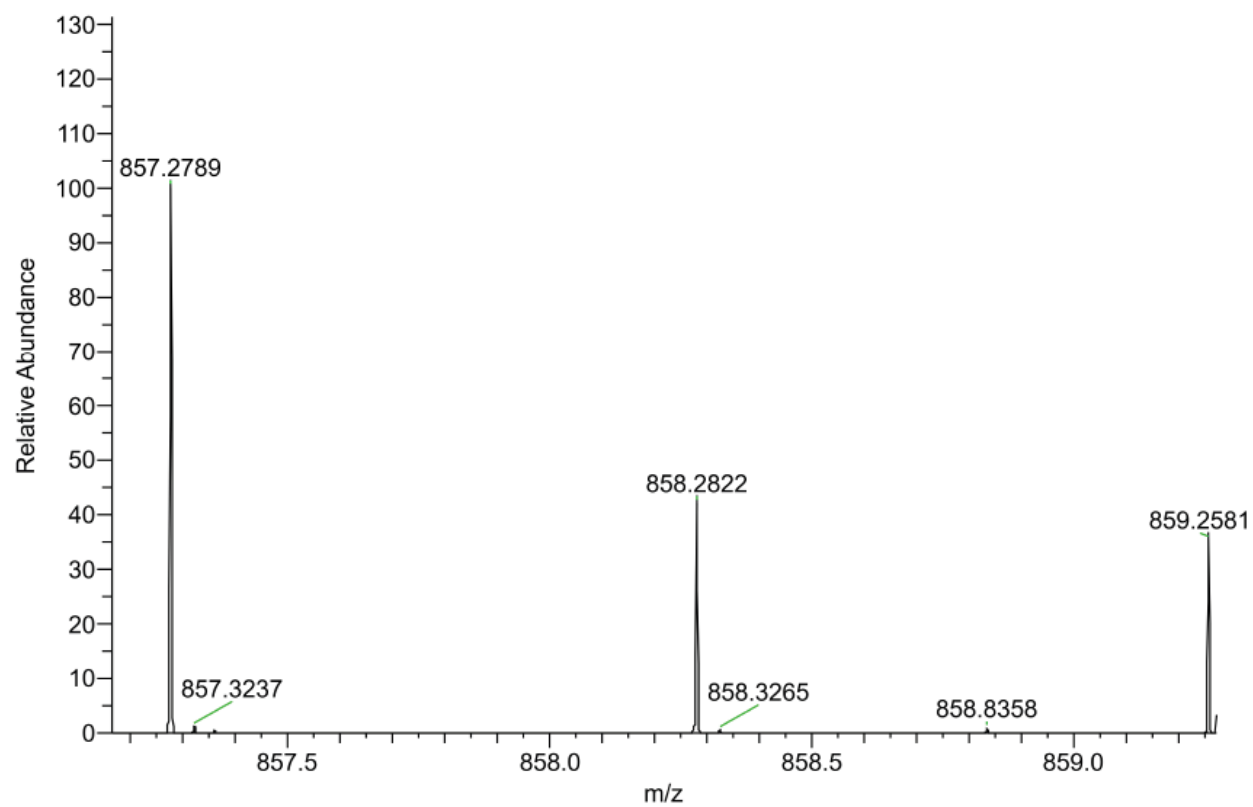




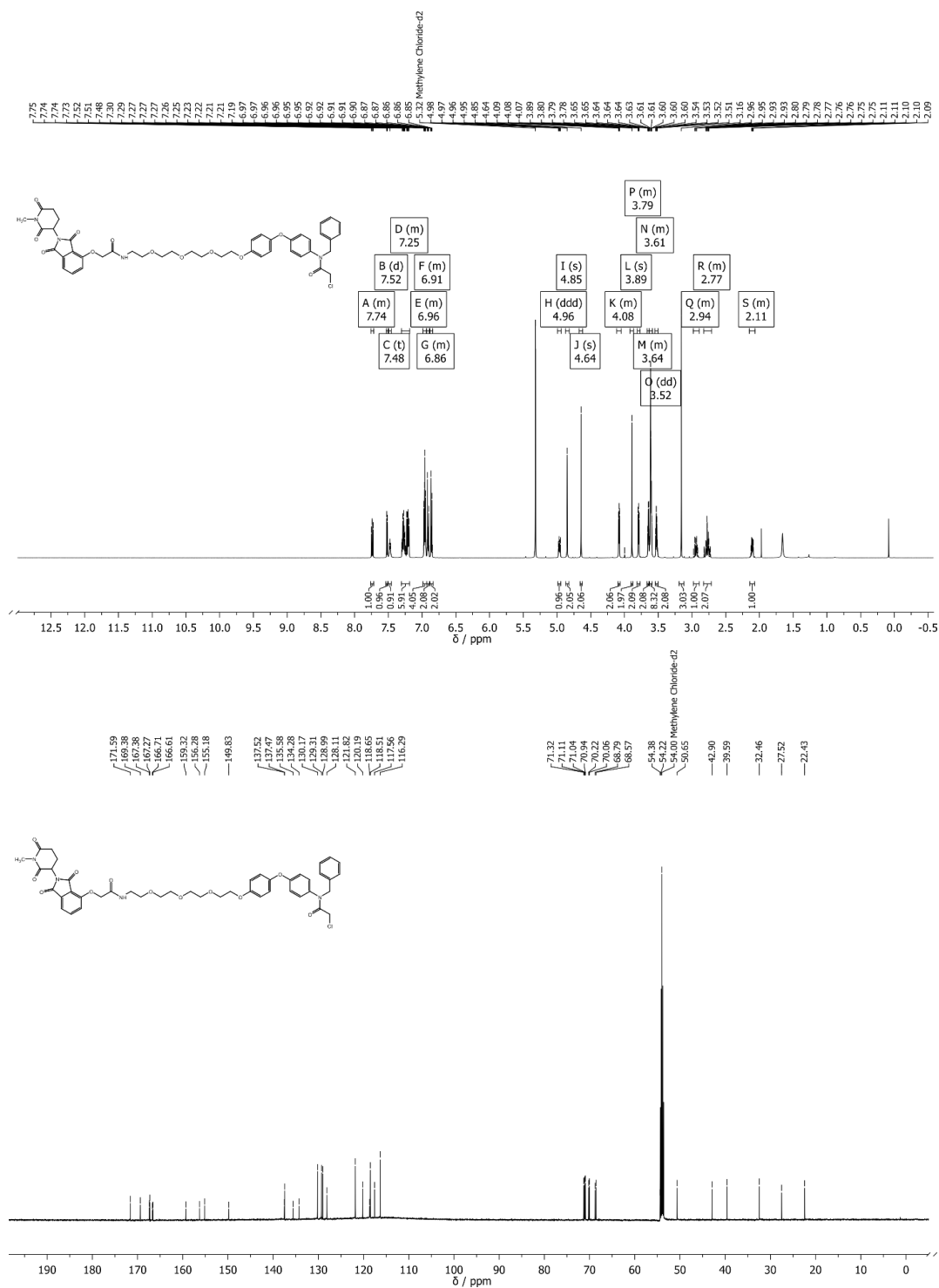
N-benzyl-2-chloro-N-(4-(4-((1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)oxy)phenoxy)phenyl)acetamide **1b**

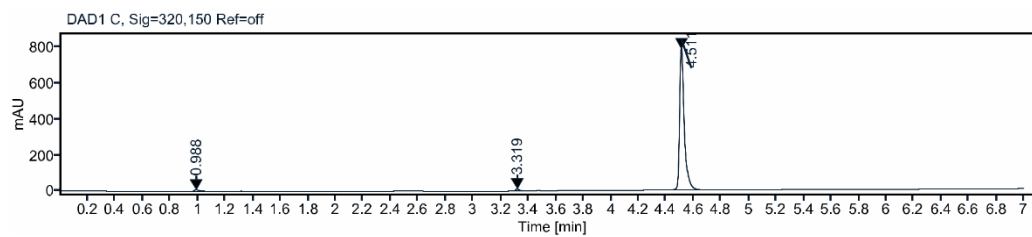
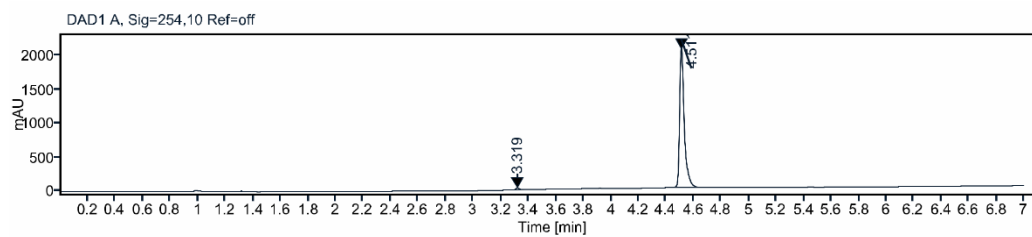
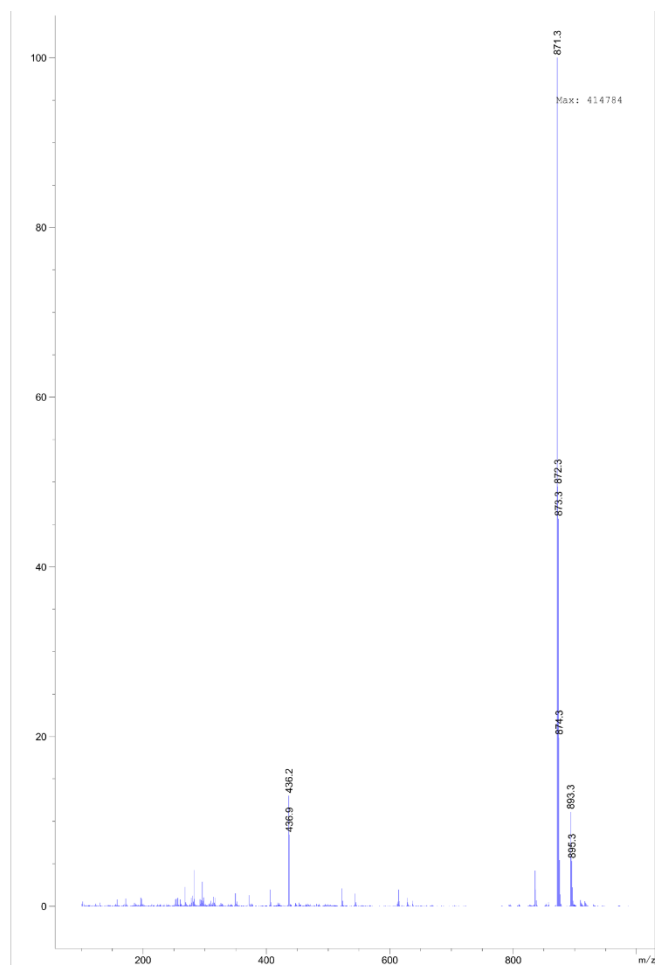


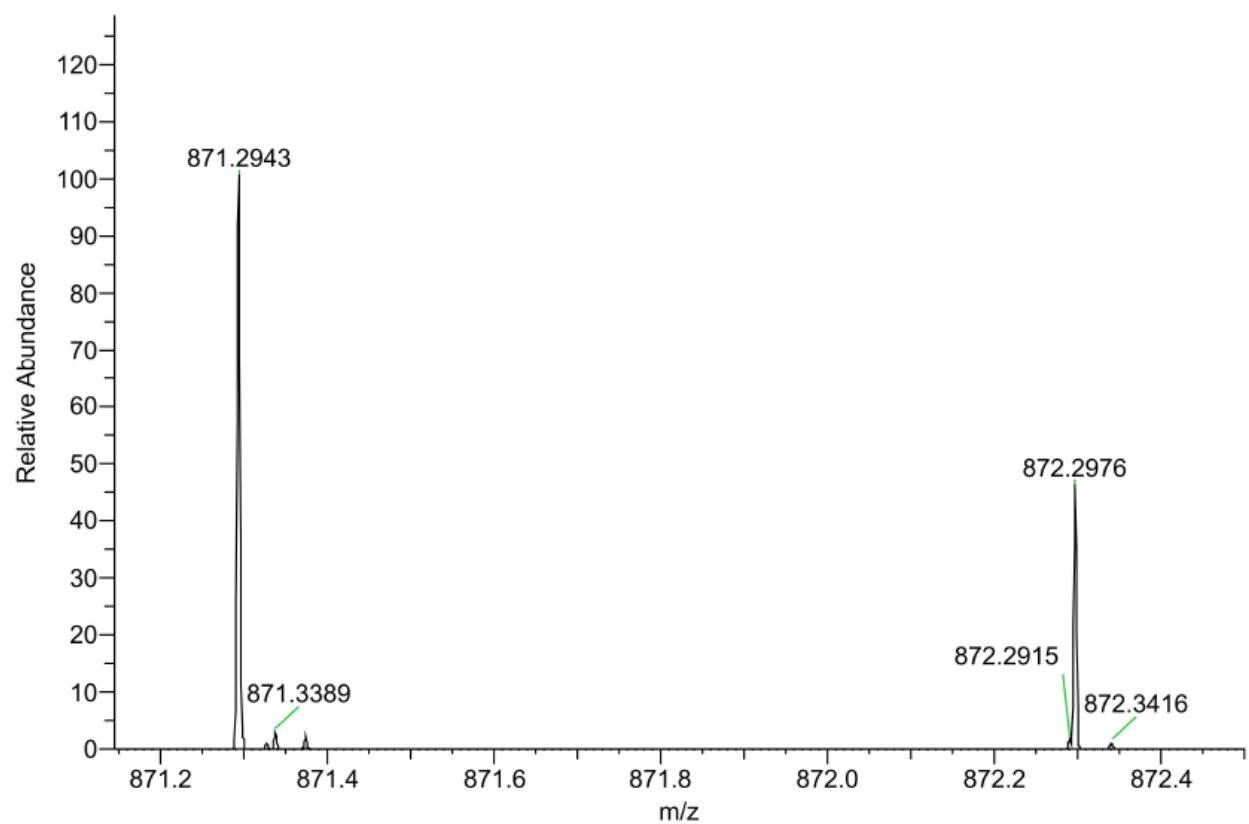




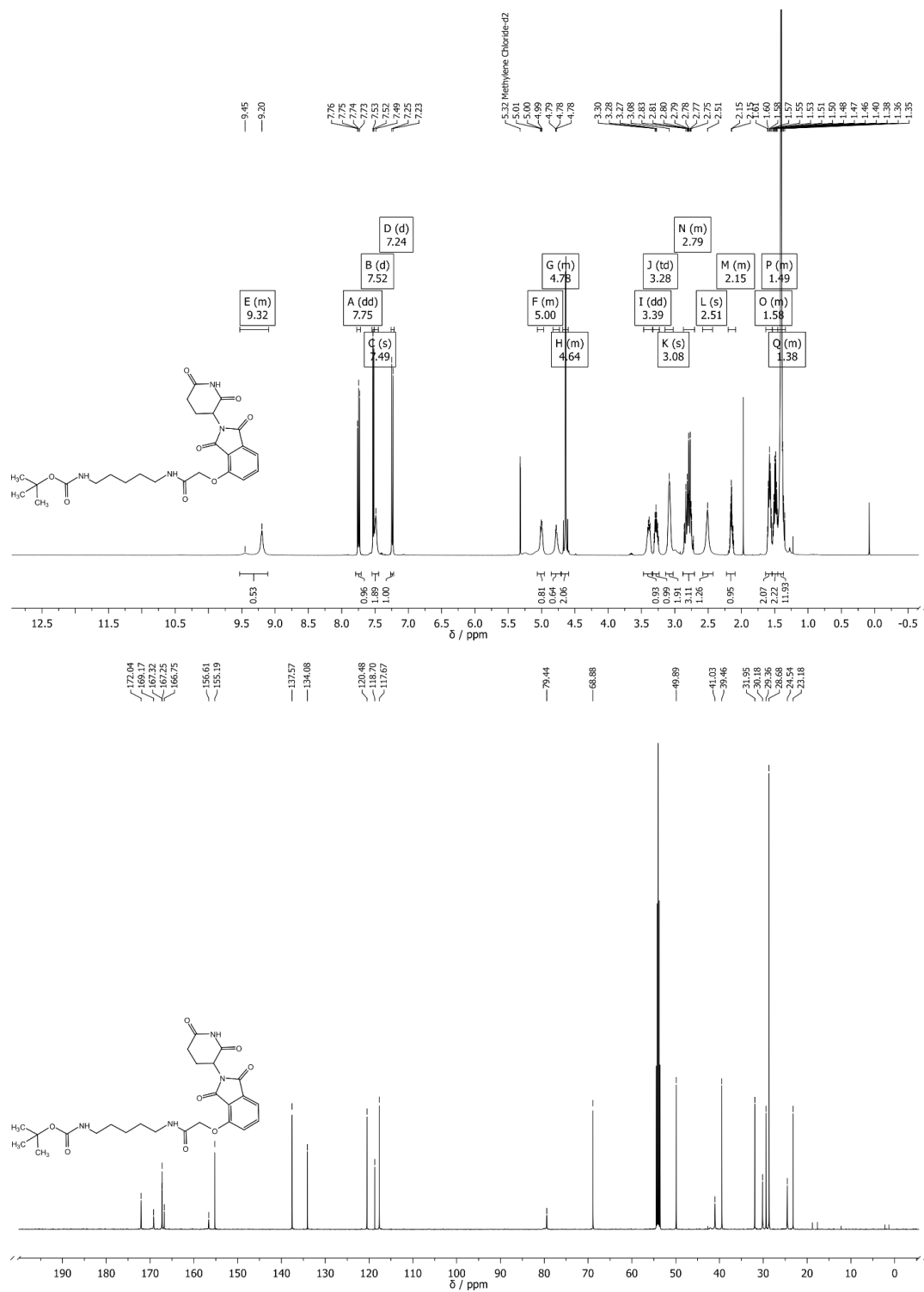
N-benzyl-2-chloro-N-(4-(4-((1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12-trioxa-3-azatetradecan-14-yl)oxy)phenoxy)phenyl)acetamide **1b**
n.c.





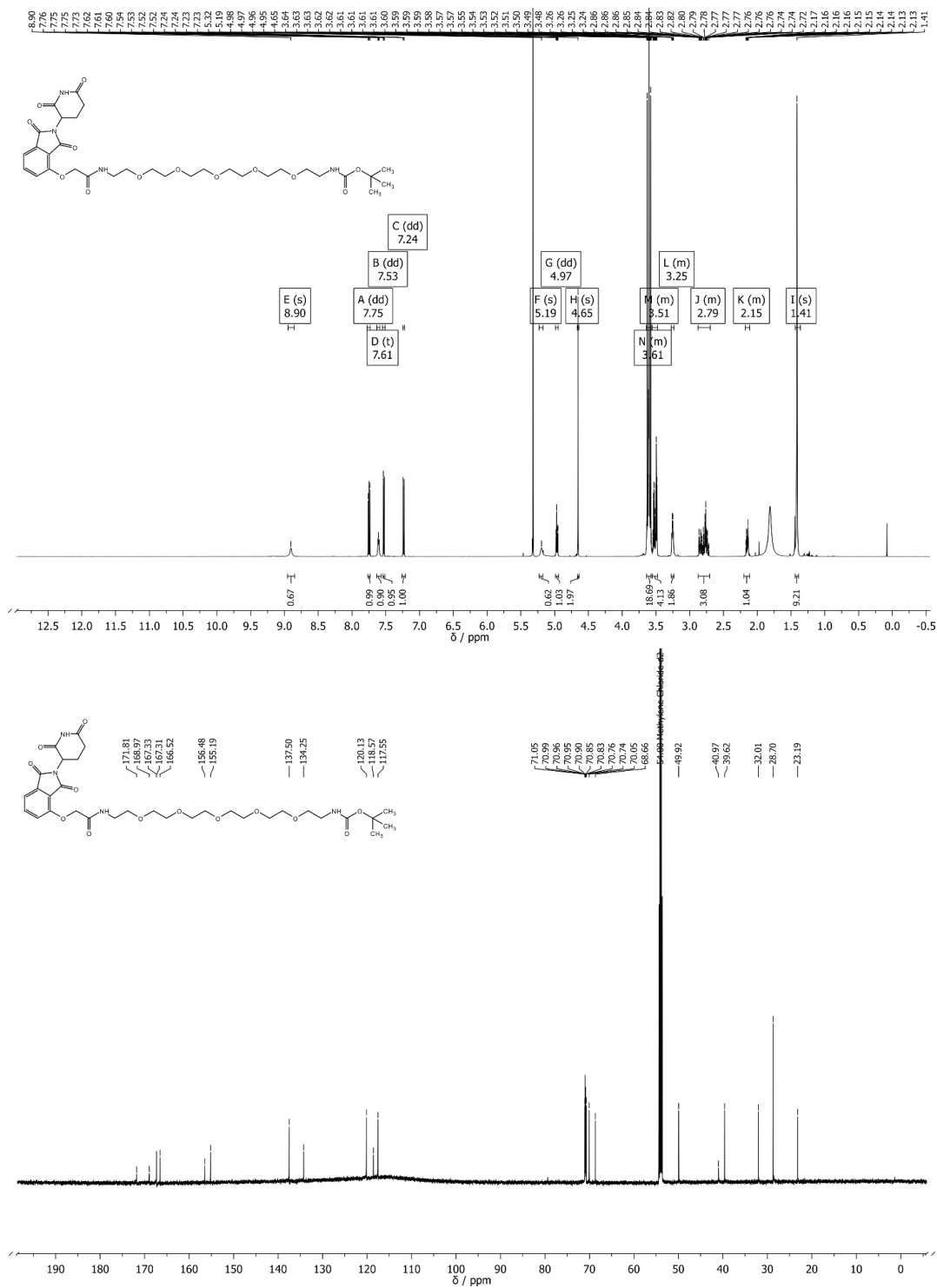


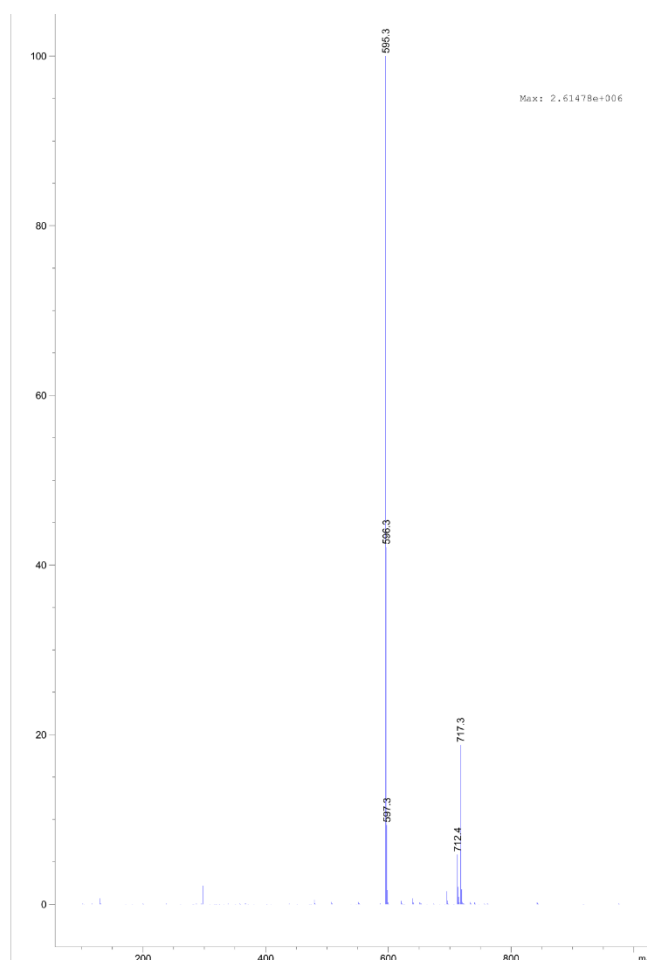
tert-butyl (5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)carbamate **S16**



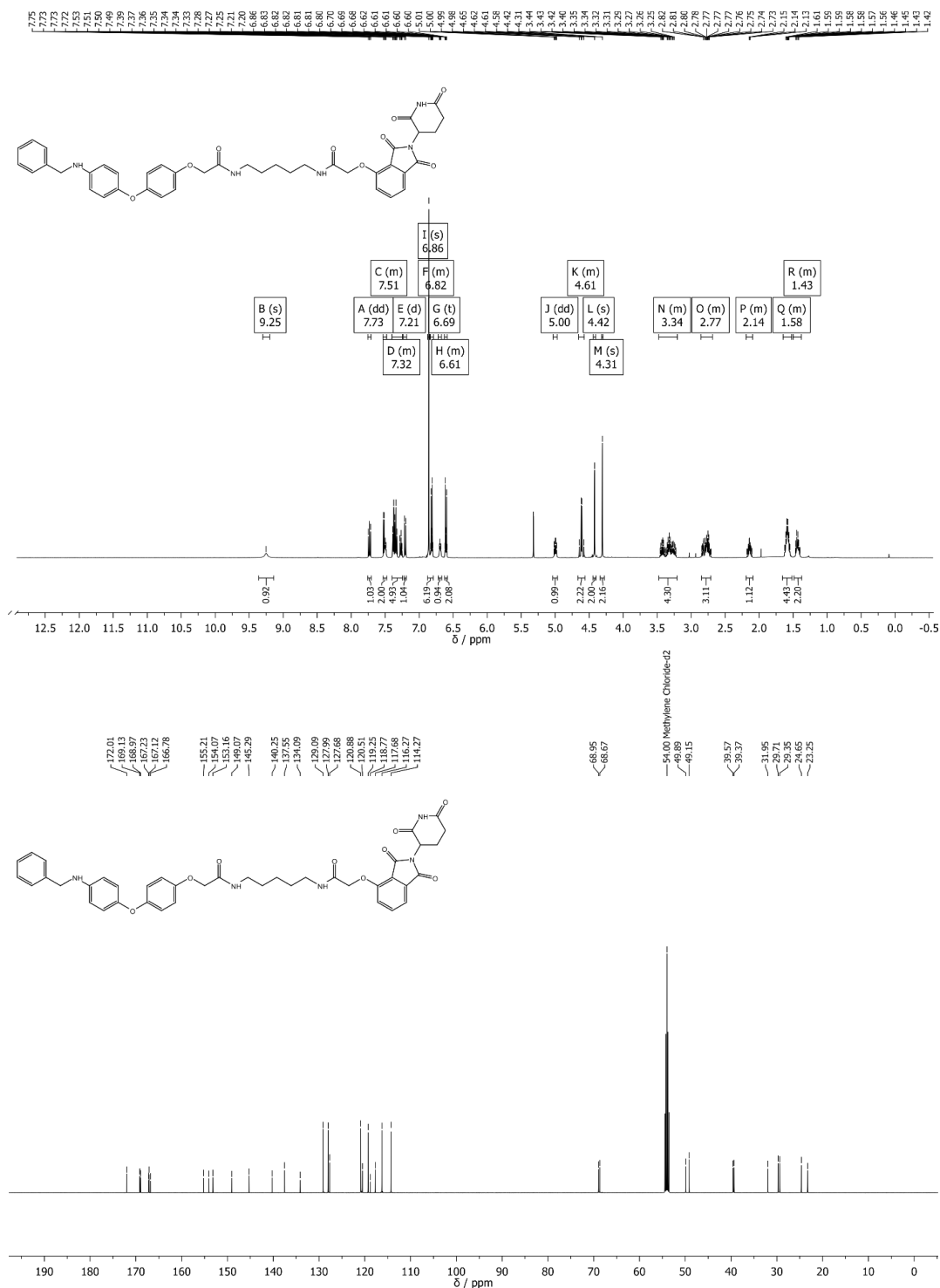


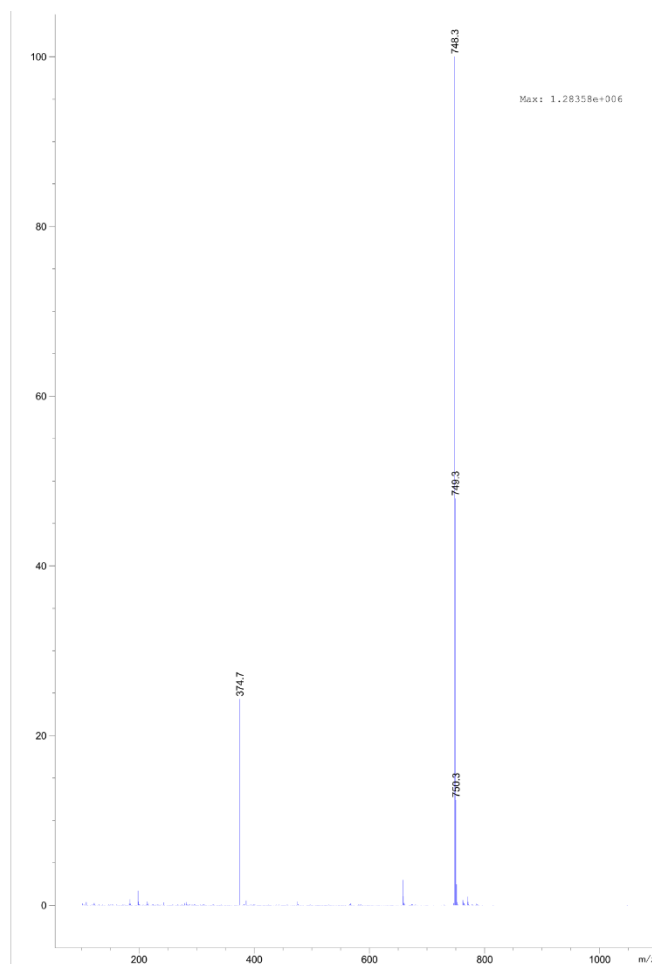
tert-butyl (1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)carbamate **S17**



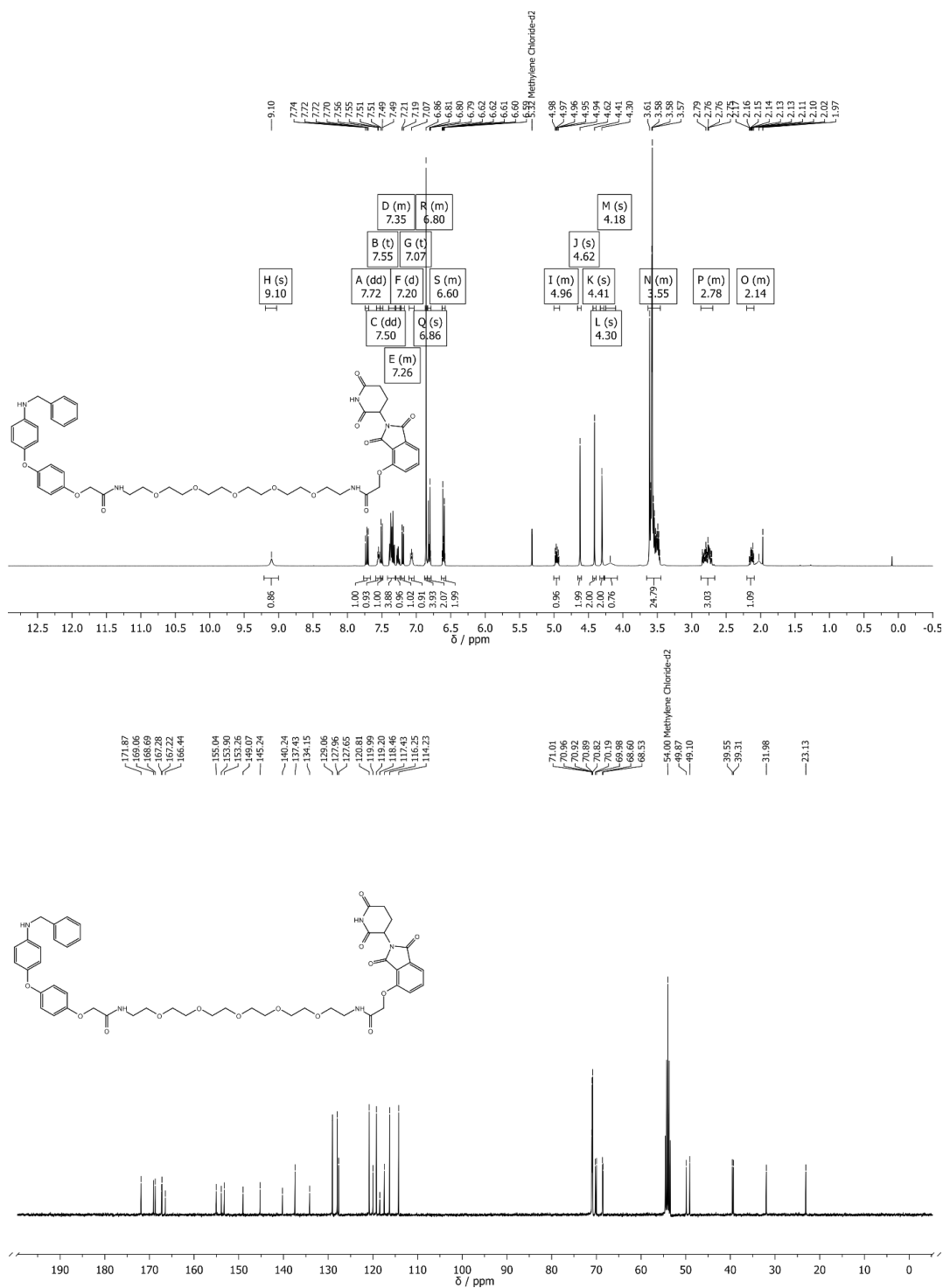


2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)acetamide **S18**



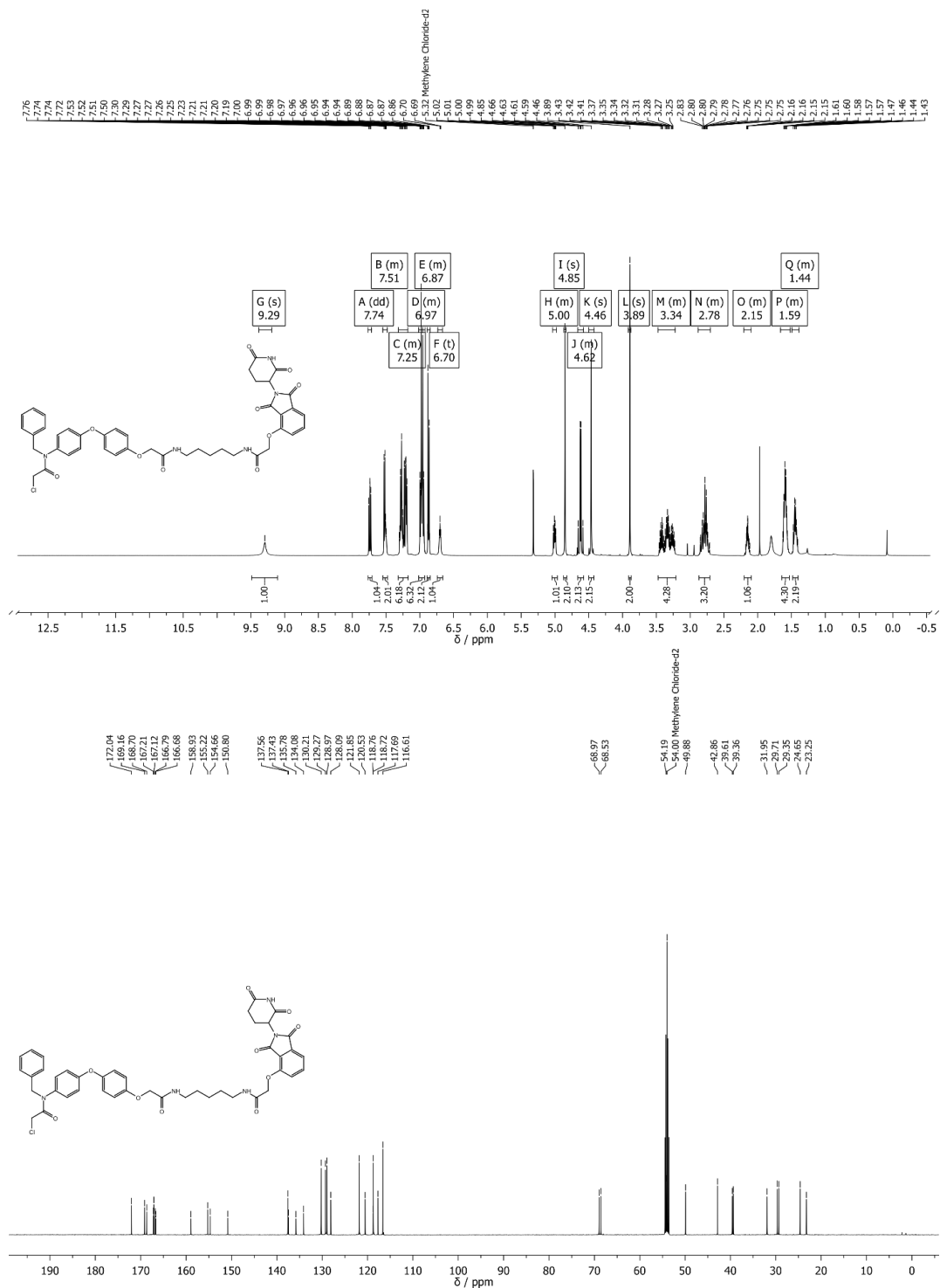


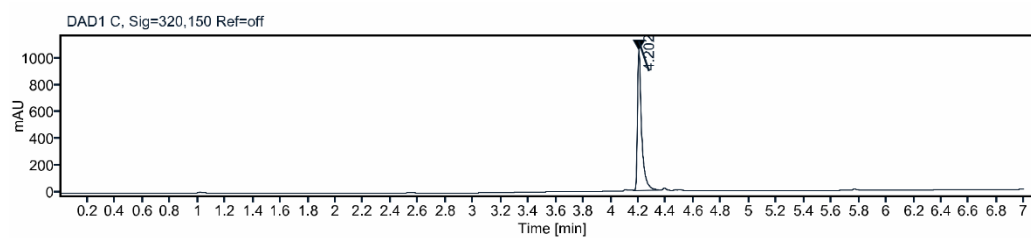
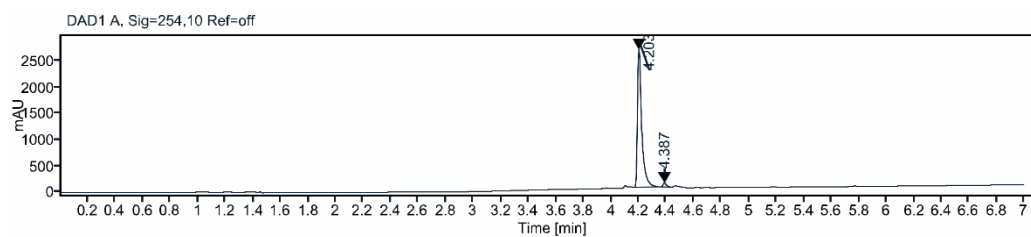
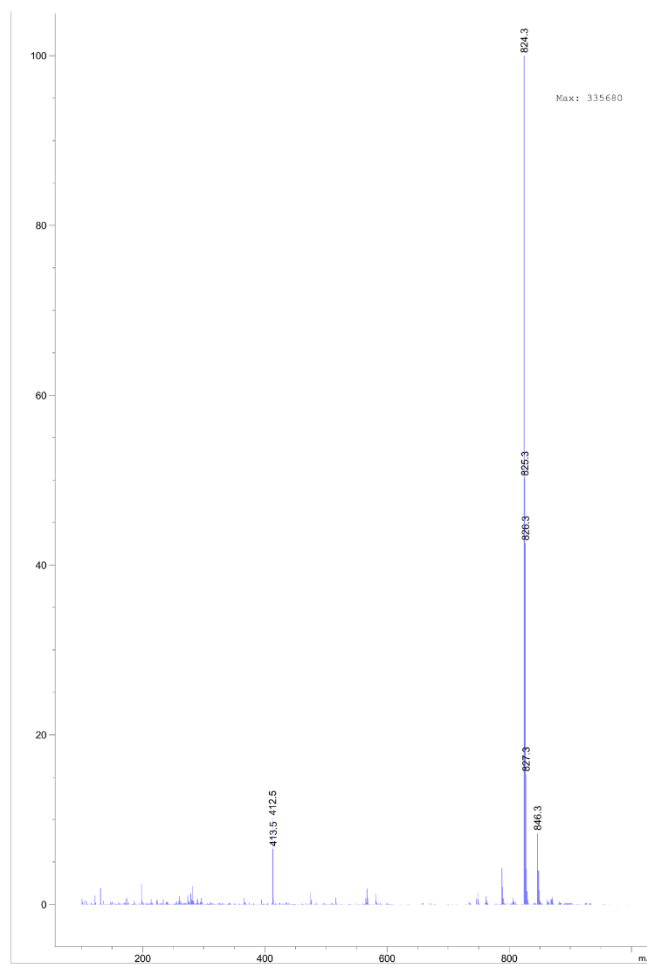
2-(4-(4-(benzylamino)phenoxy)phenoxy)-N-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)acetamide **S19**

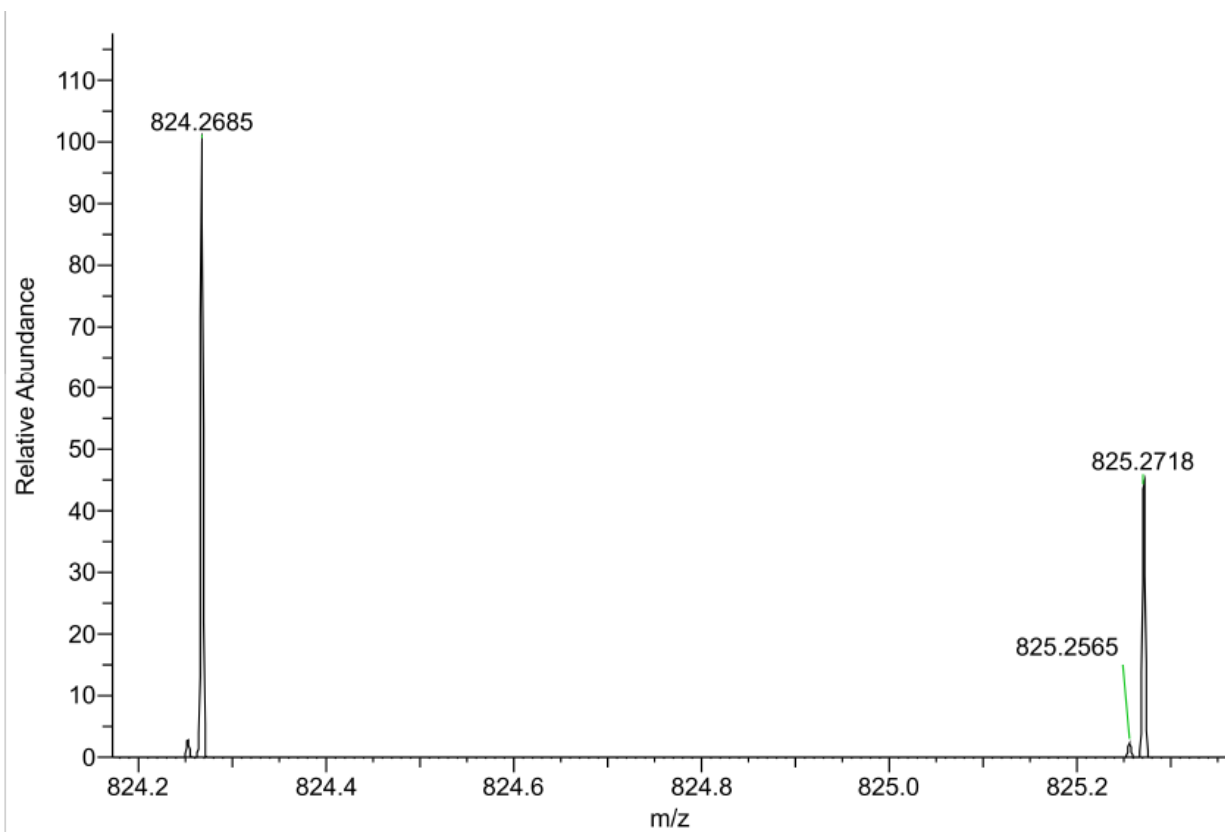




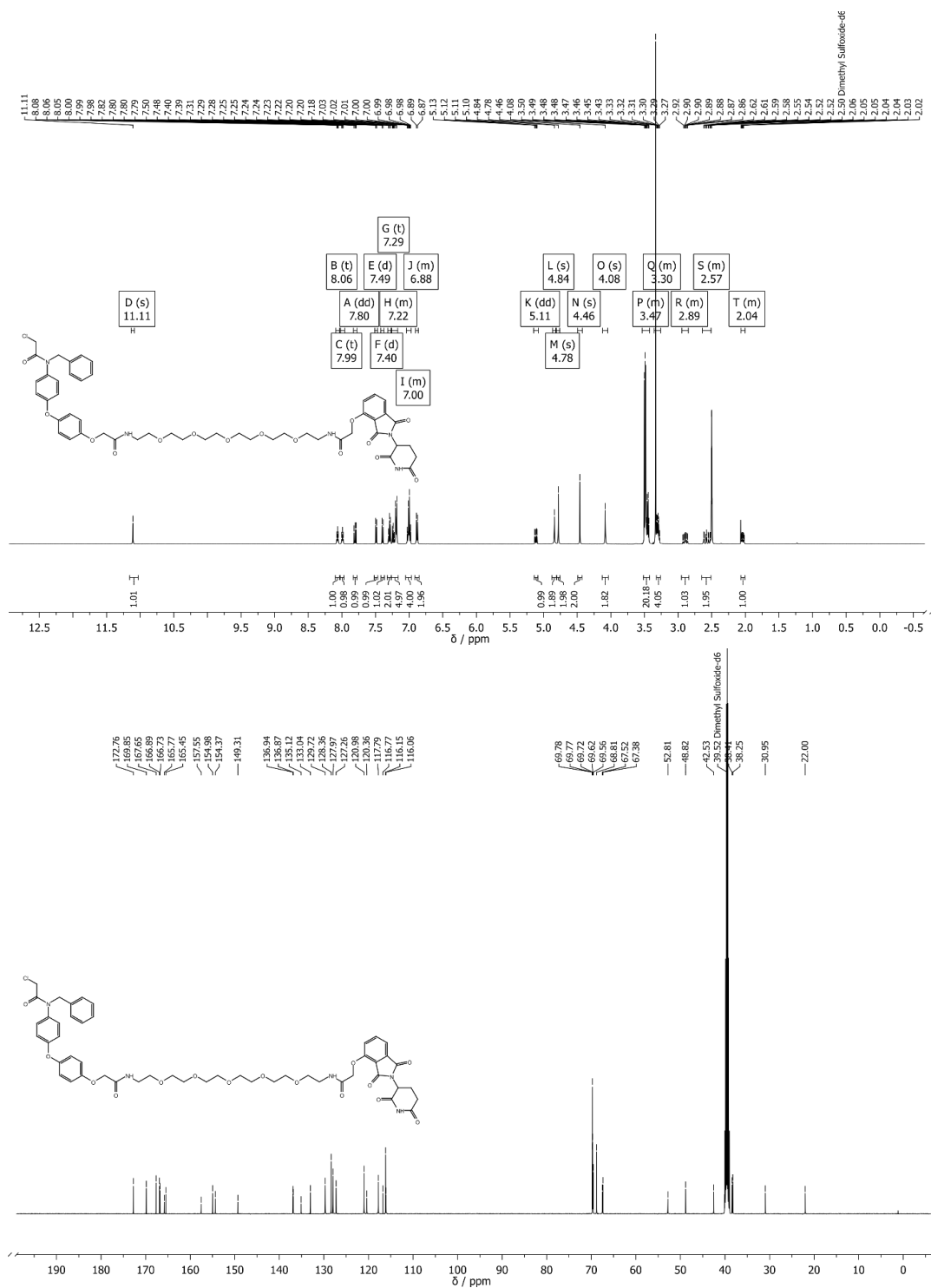
N-benzyl-2-chloro-N-(4-(4-(2-((5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)acetamido)pentyl)amino)-2-oxoethoxy)phenoxy)phenyl)acetamide **1c**

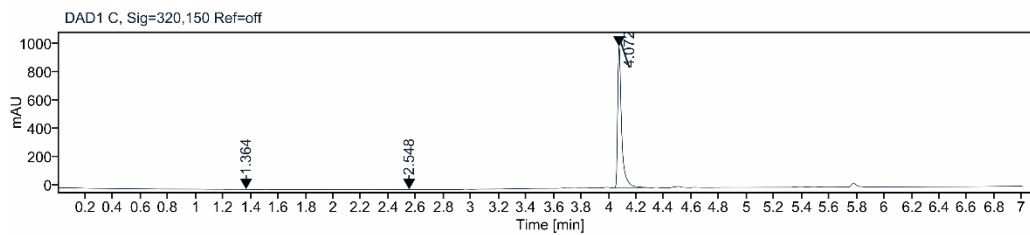
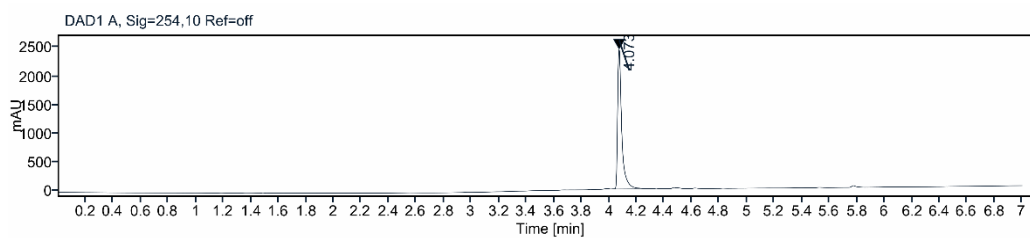
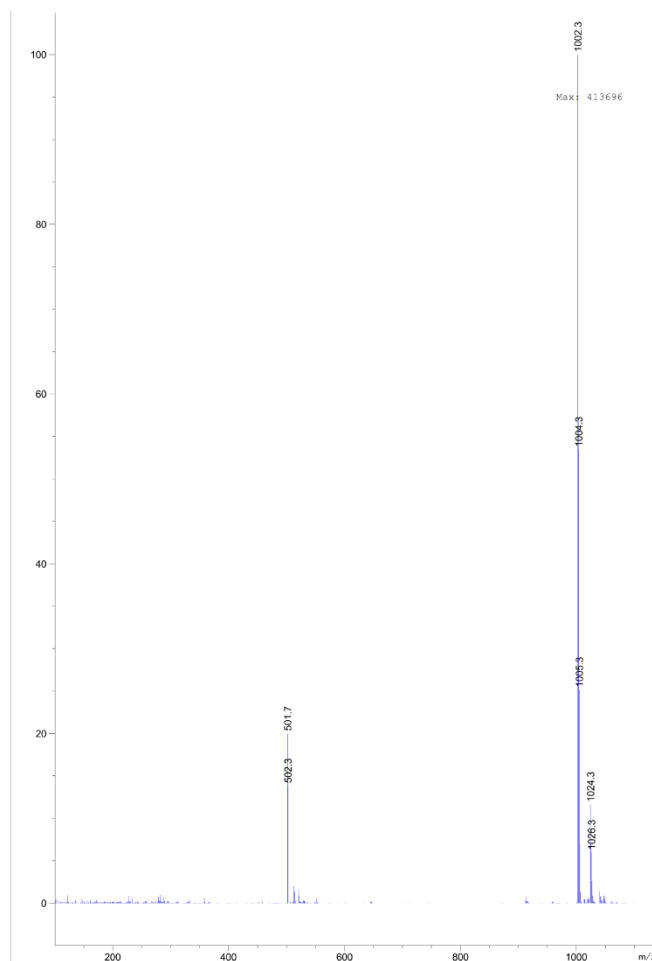


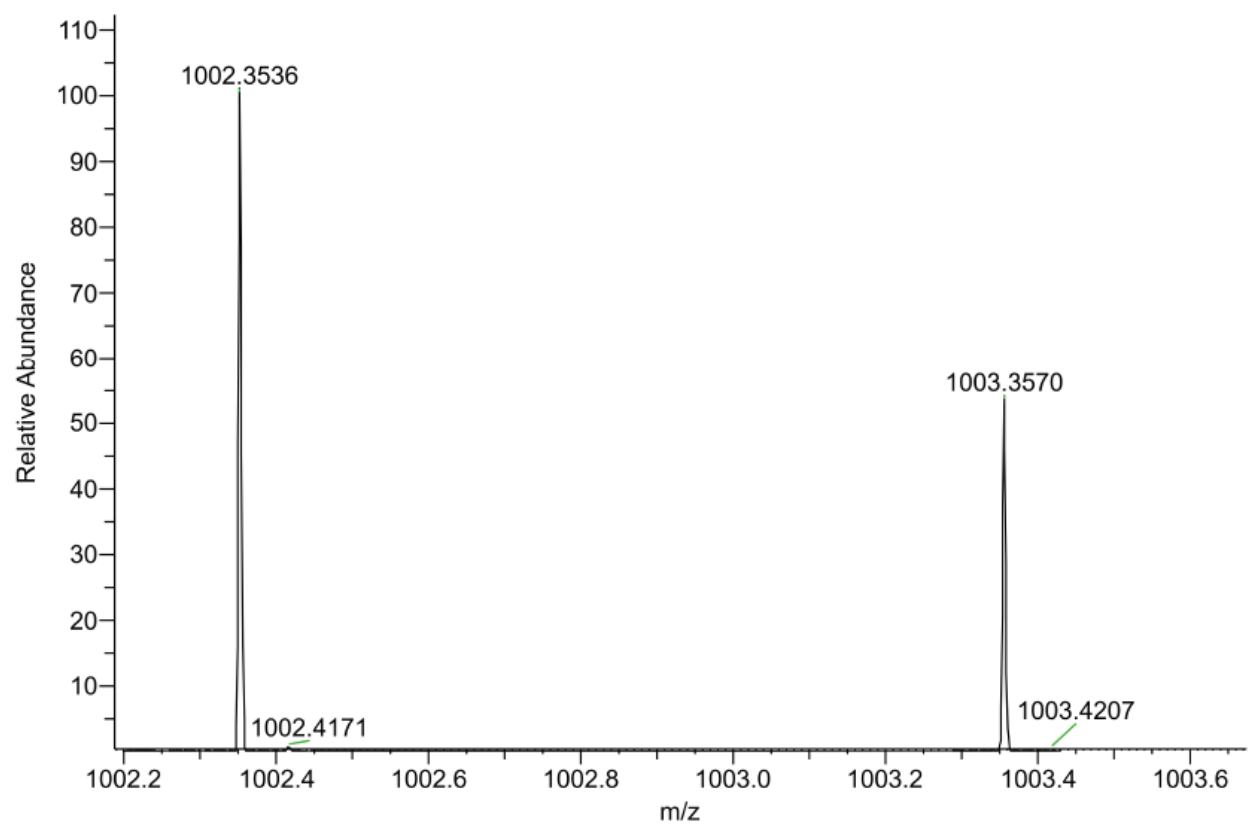




N-benzyl-2-chloro-N-(4-(4-((23-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)oxy)-2,22-dioxo-6,9,12,15,18-pentaoxa-3,21-diazatricosyl)oxy)phenoxy)phenyl)acetamide **1d**

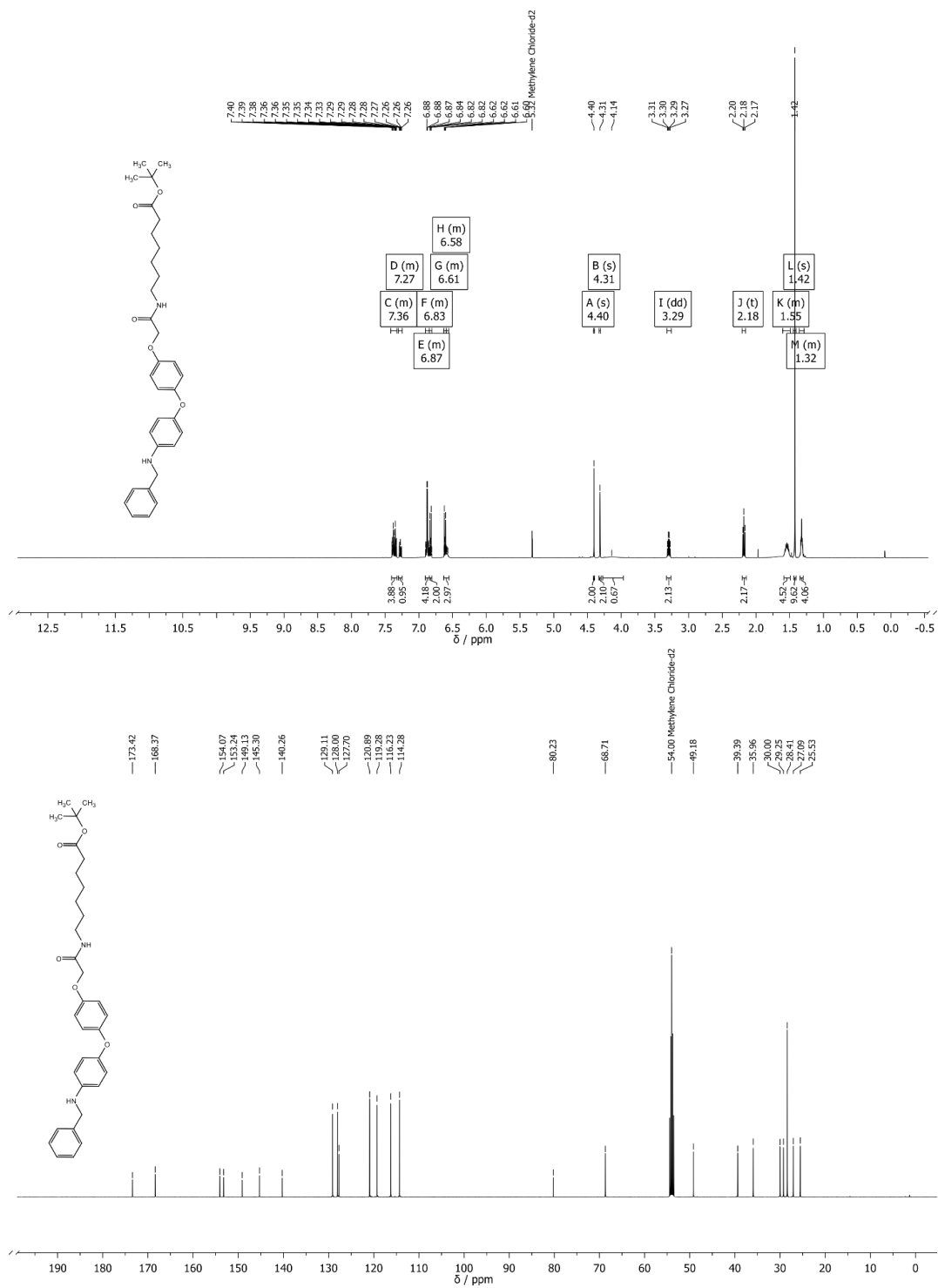


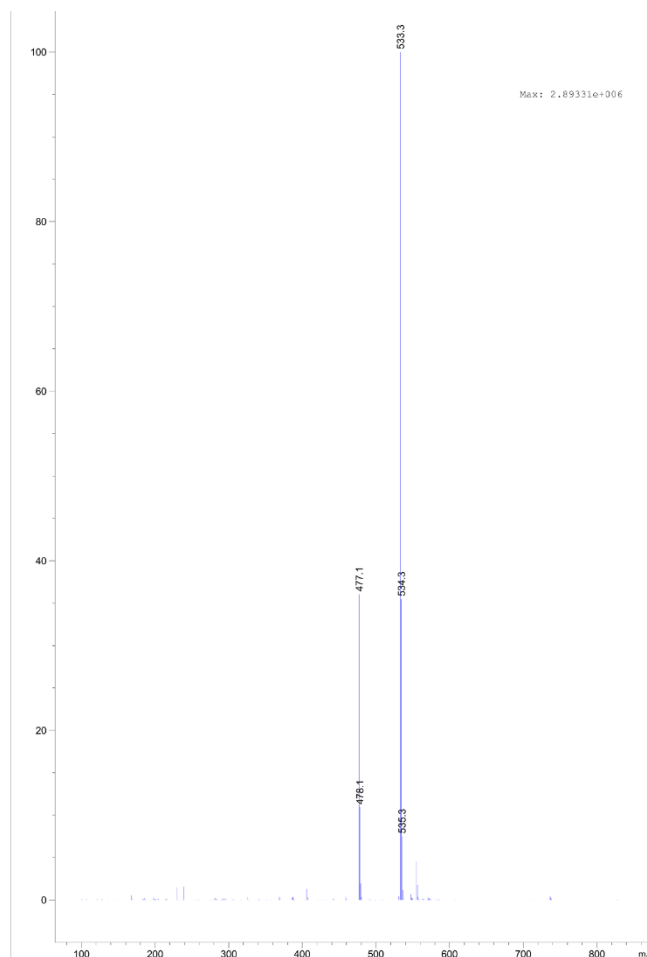




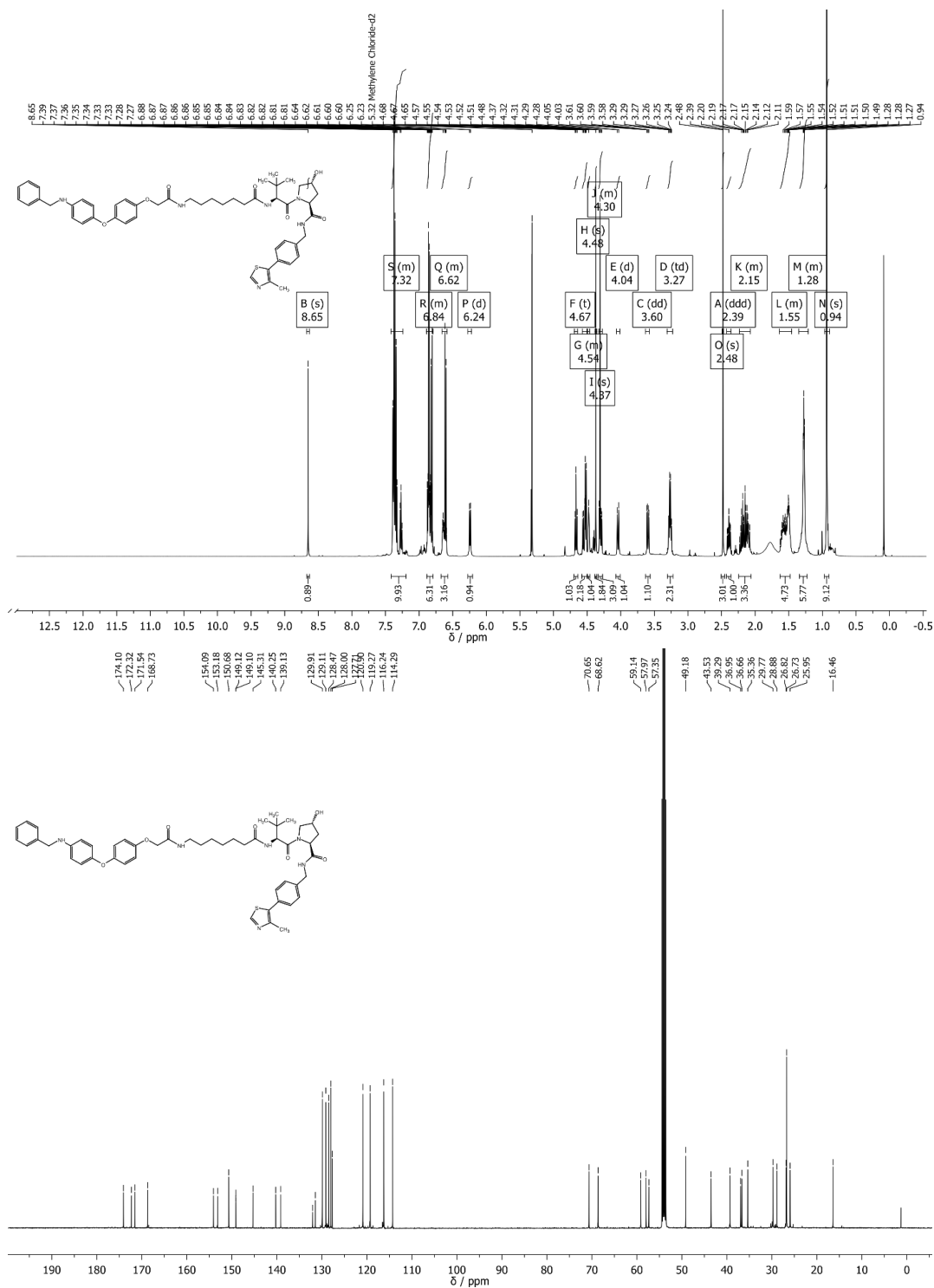
2.3 Spectra for all VHL-based PROTACs and intermediates- Appendix Figure S7

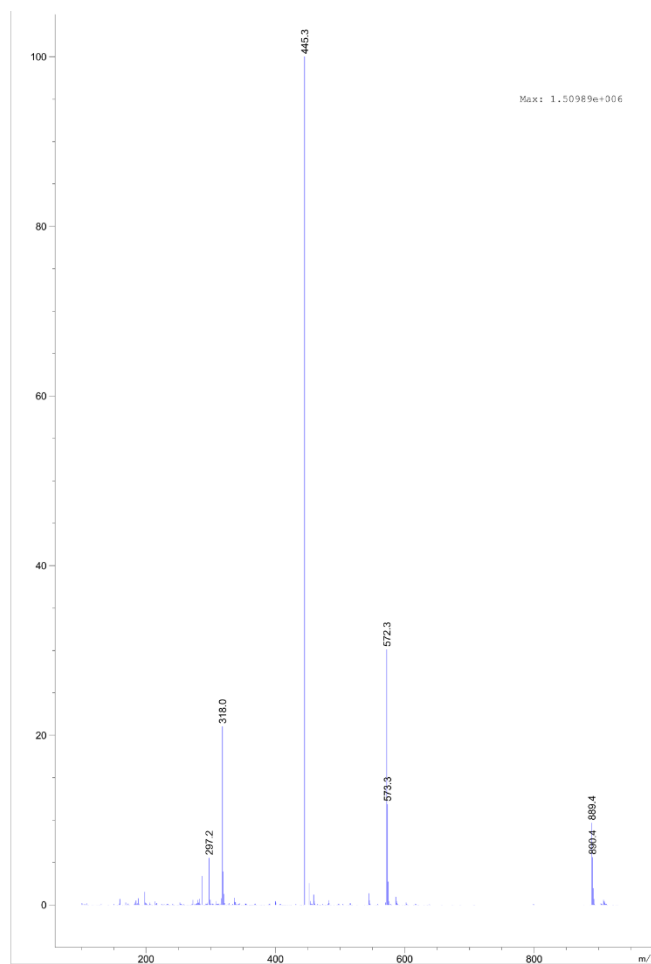
tert-butyl 7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanoate **S20**



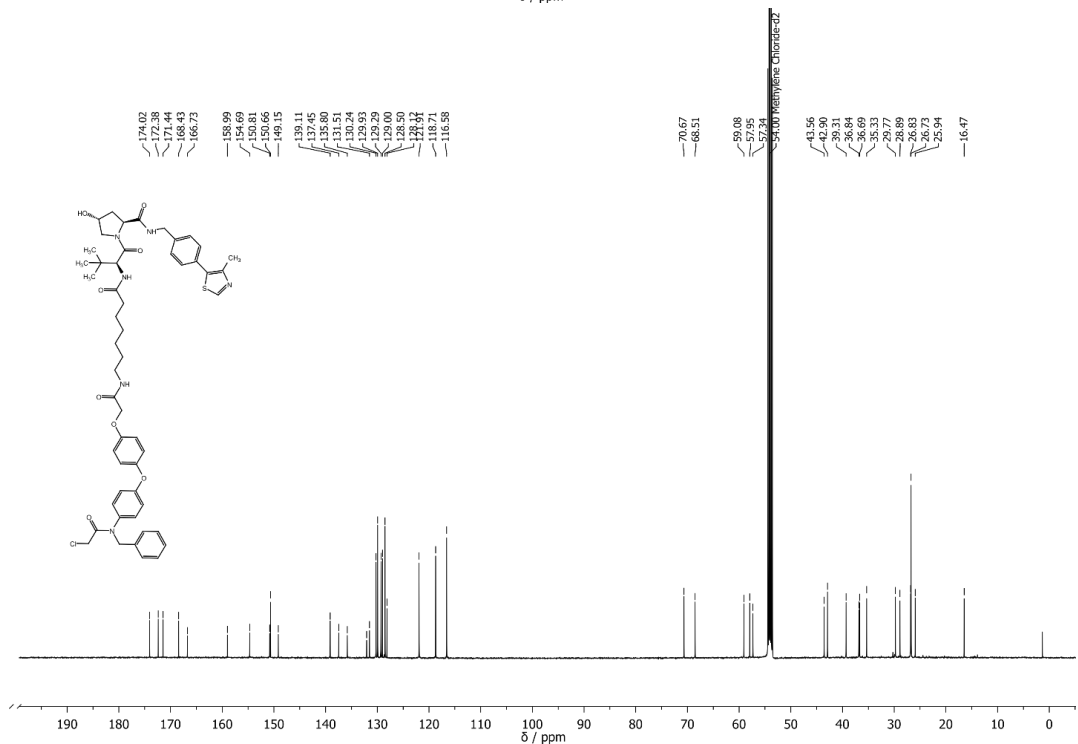
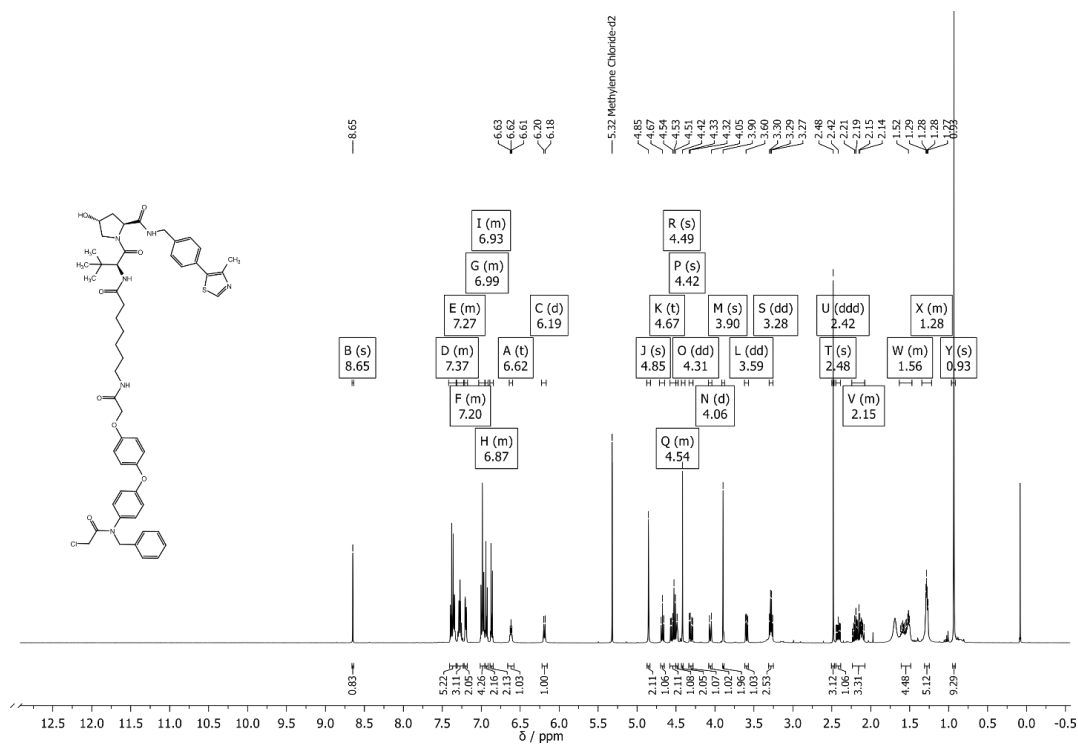


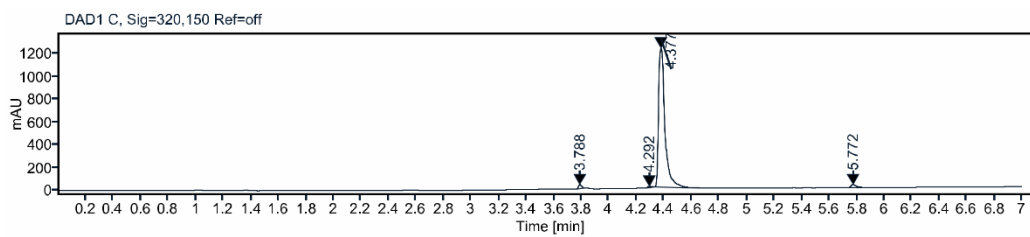
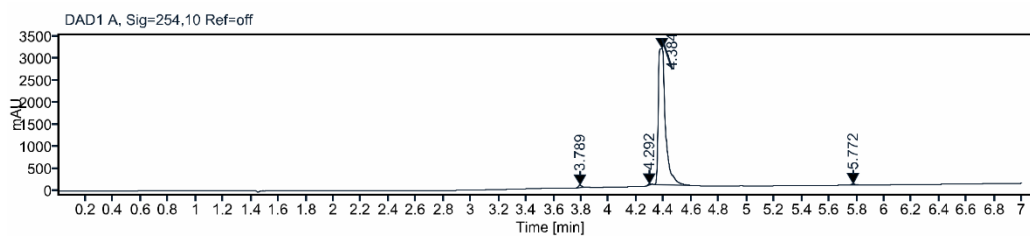
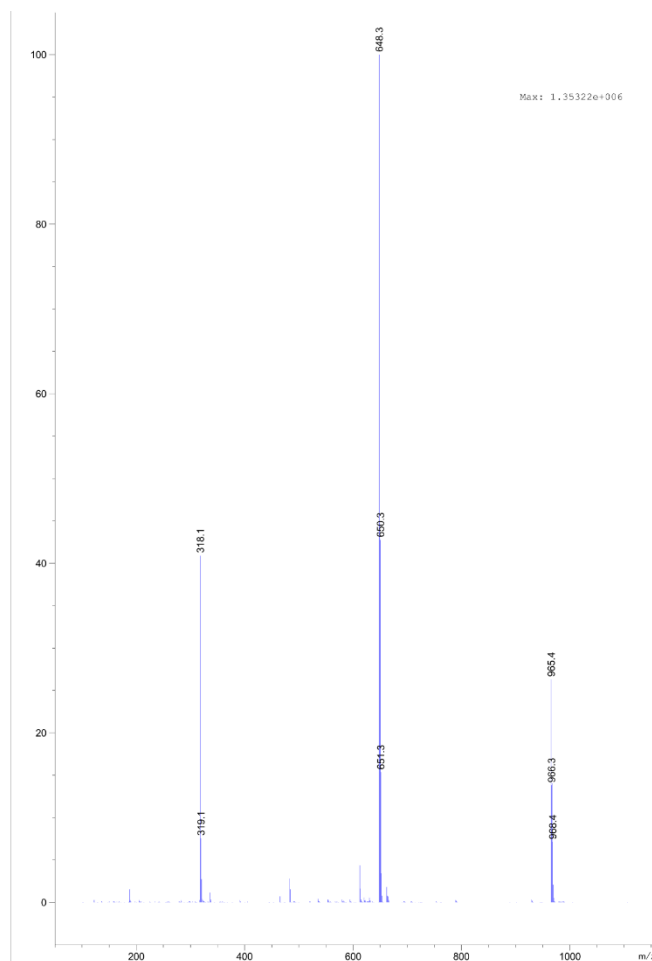
(2S,4R)-1-((S)-2-(7-(2-(4-(4-(benzylamino)phenoxy)phenoxy)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S21**

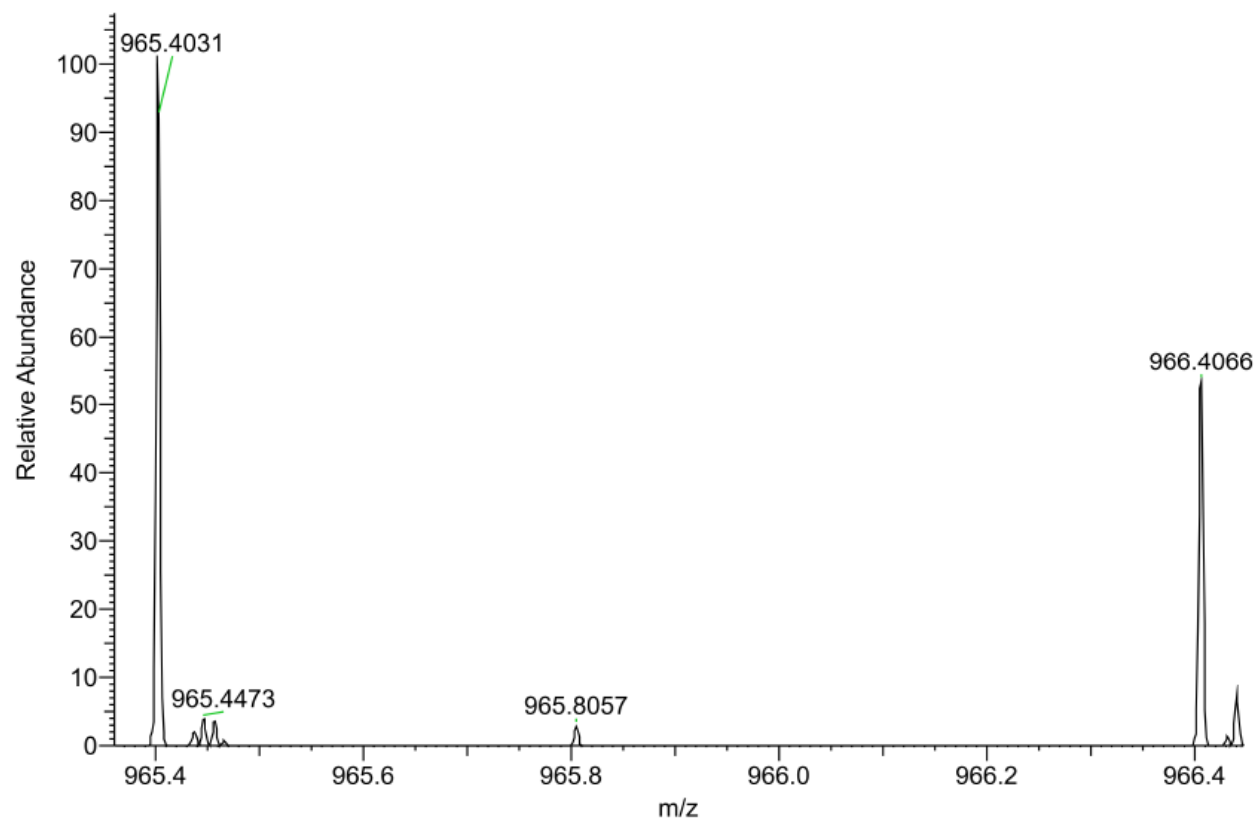




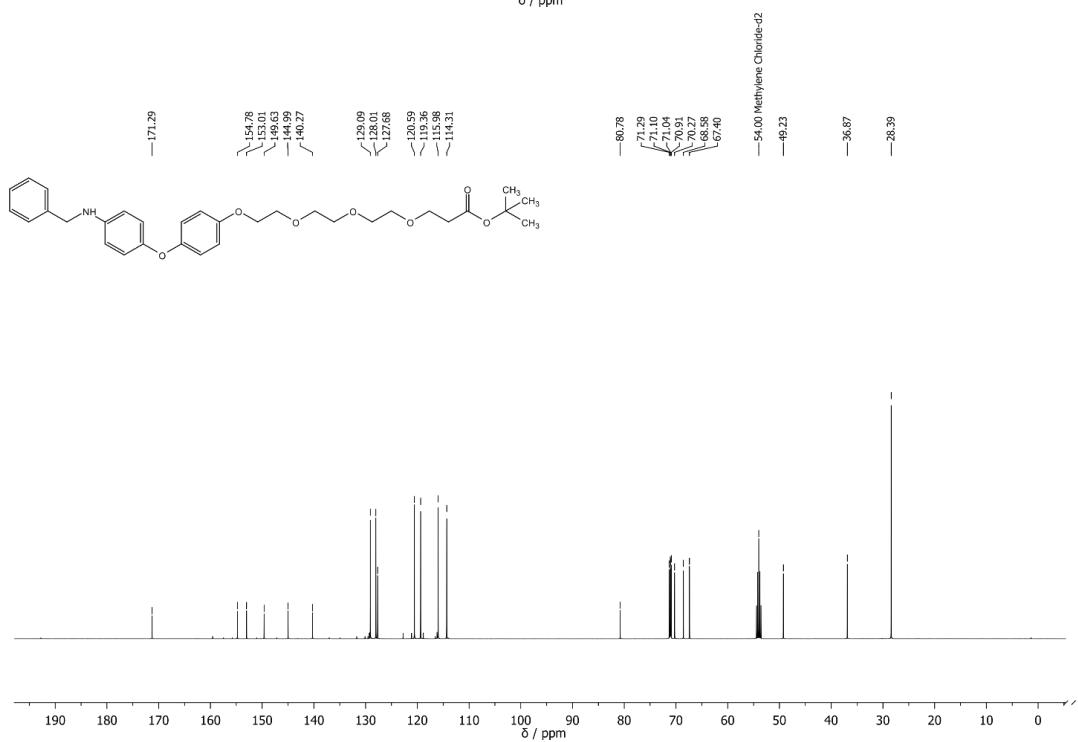
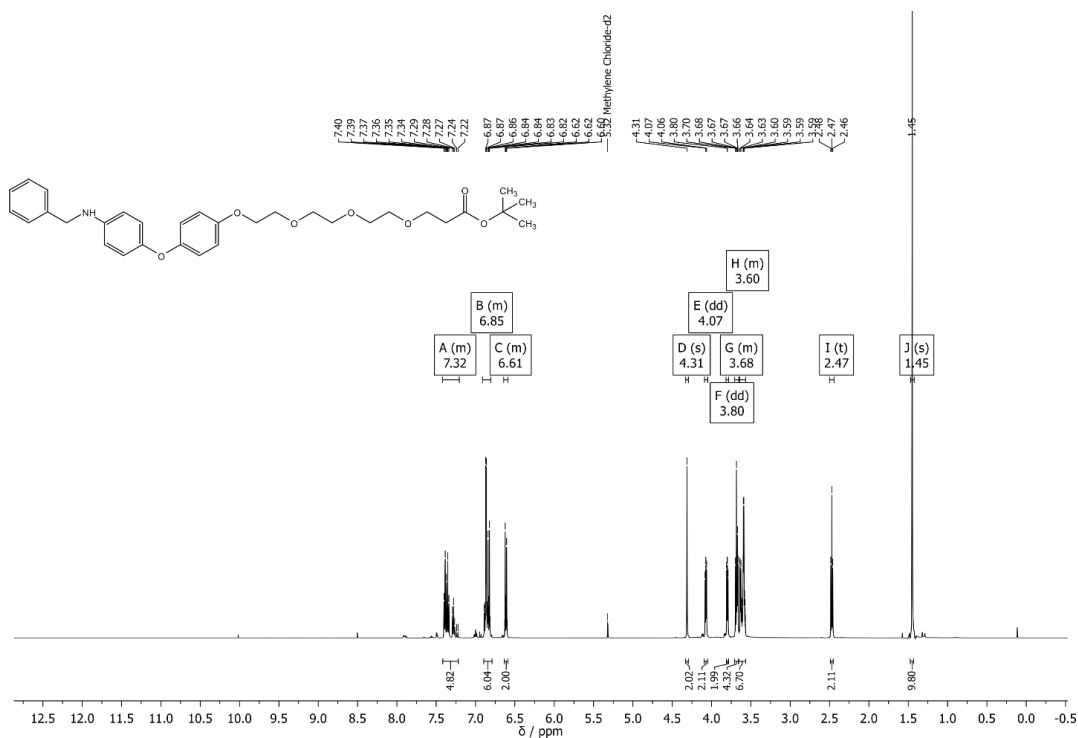
(2S,4R)-1-((S)-2-(7-(2-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)acetamido)heptanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2a**

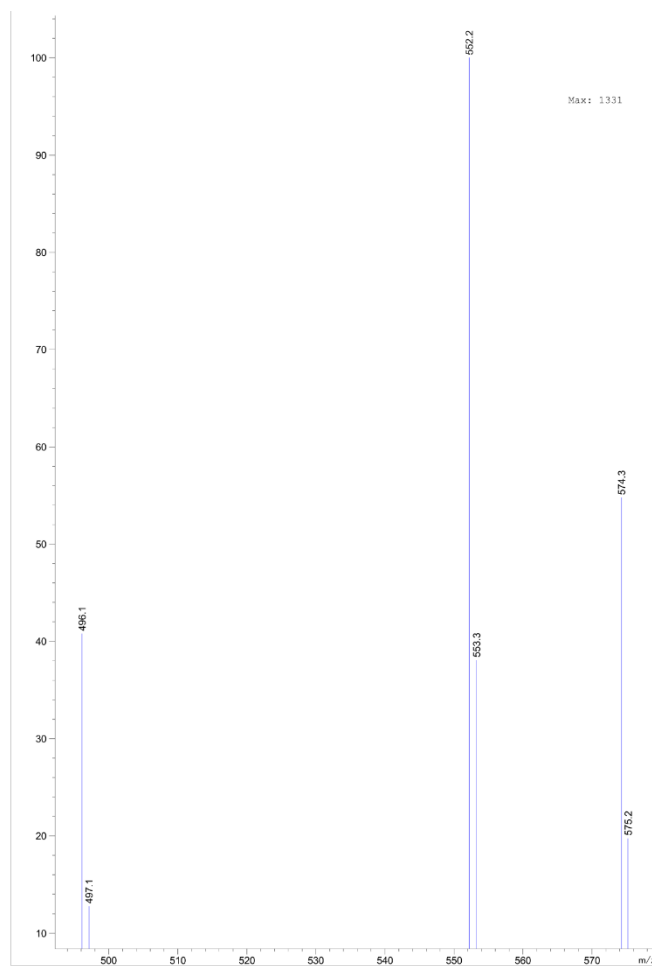


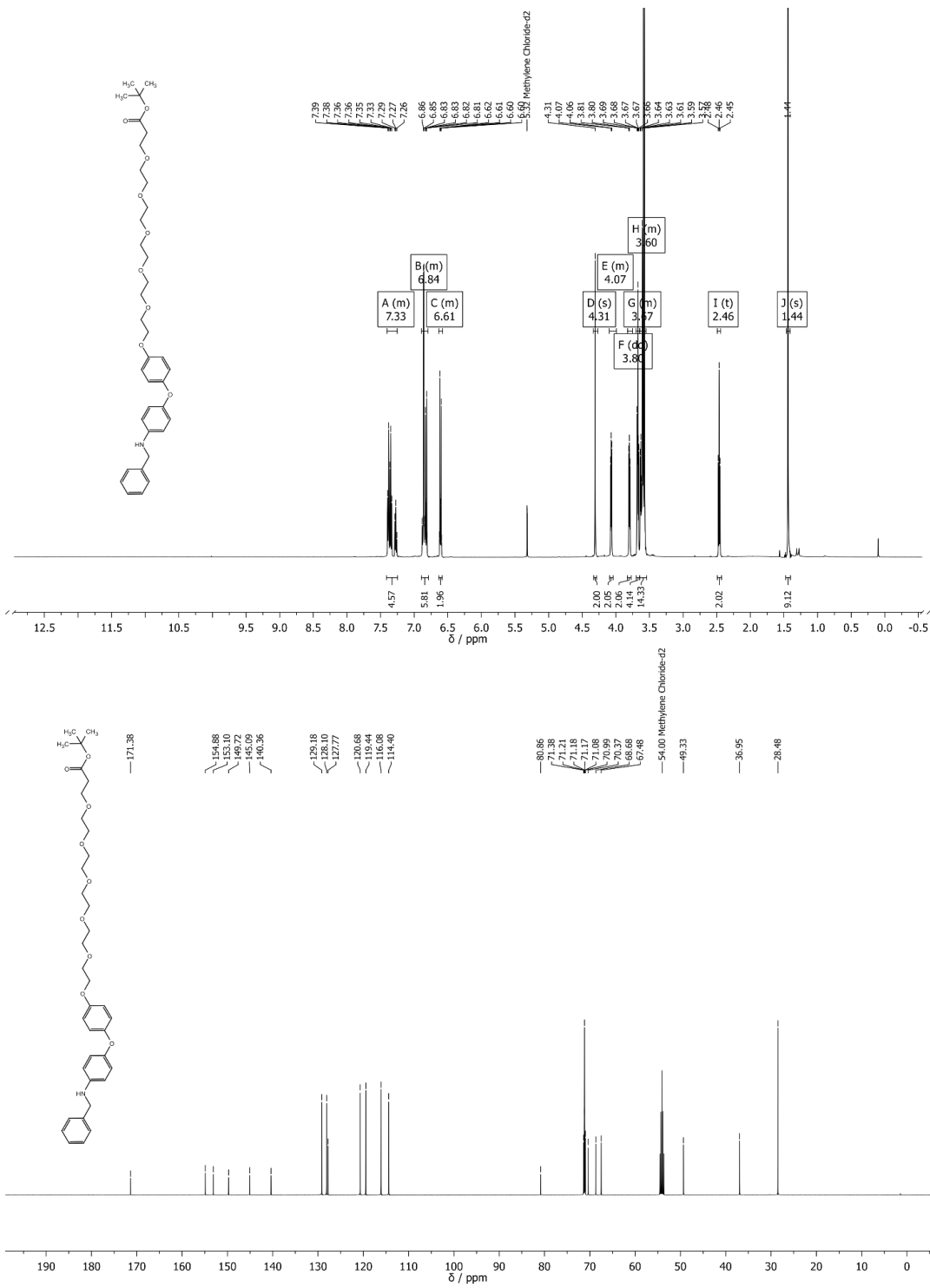


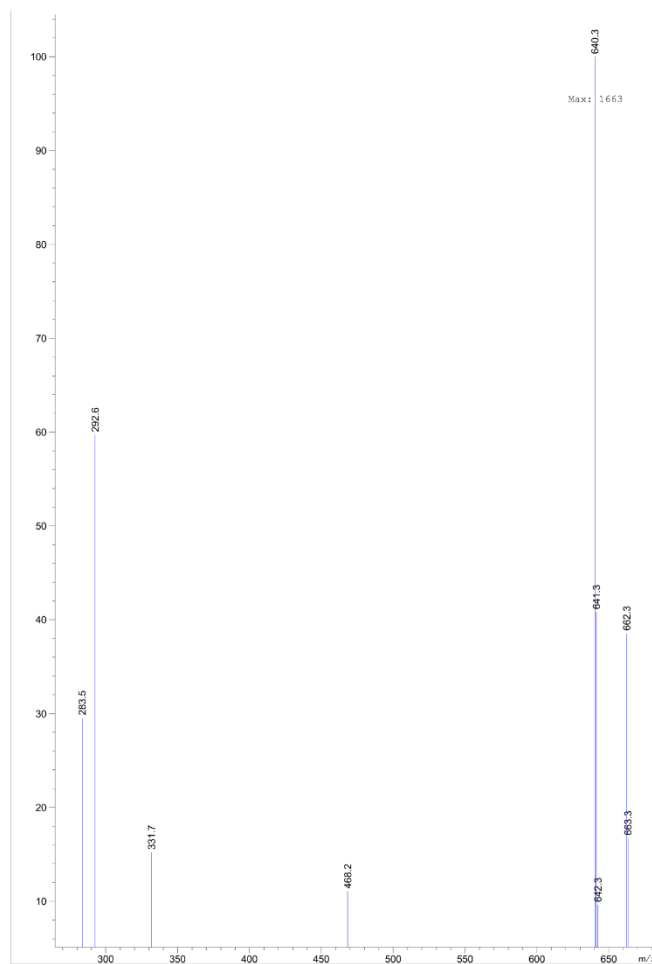


tert-butyl 3-(2-(2-(4-(4-(benzylamino)phenoxy)phenoxy)ethoxy)ethoxy)ethoxy)propanoate **S26**

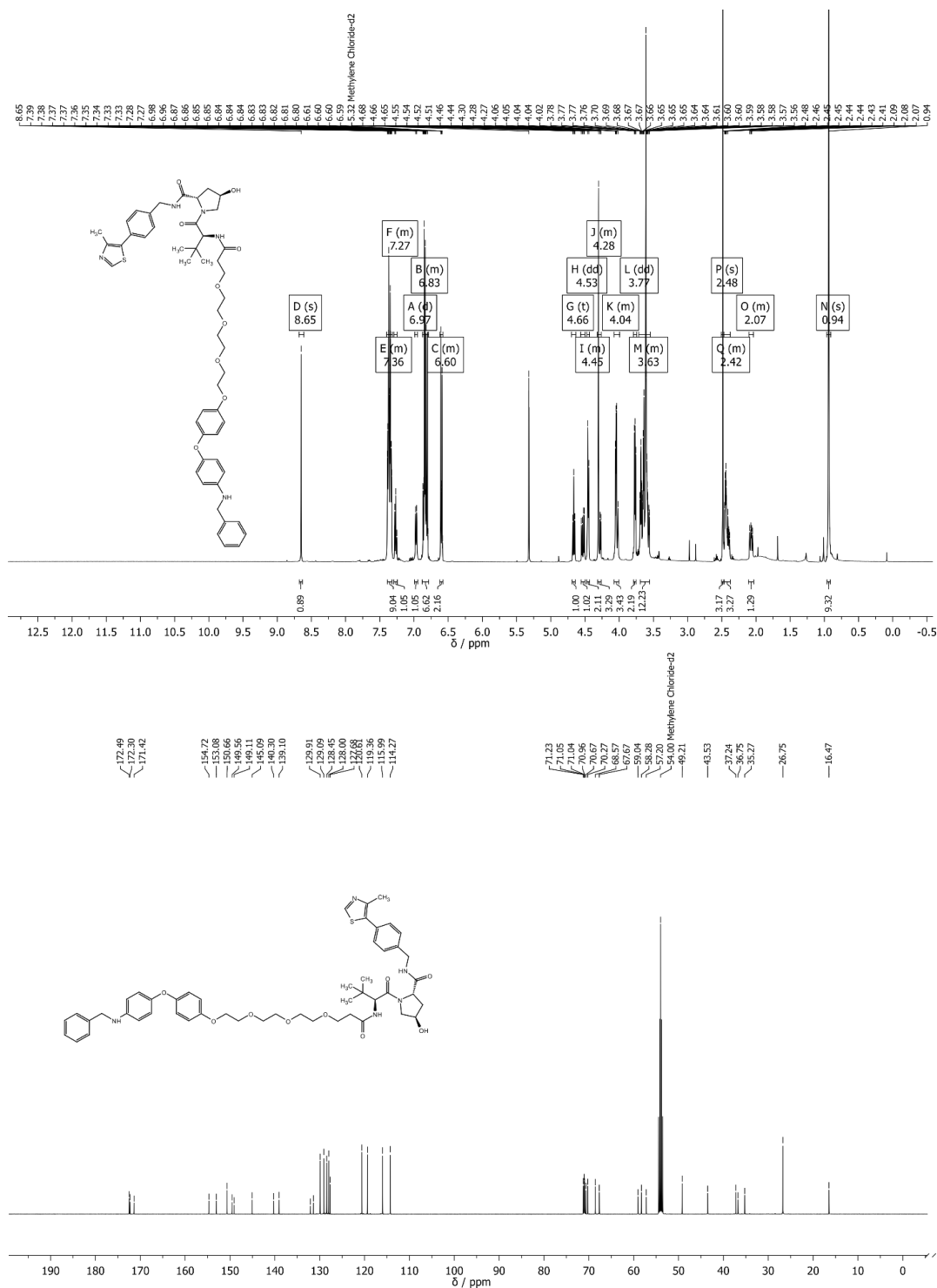


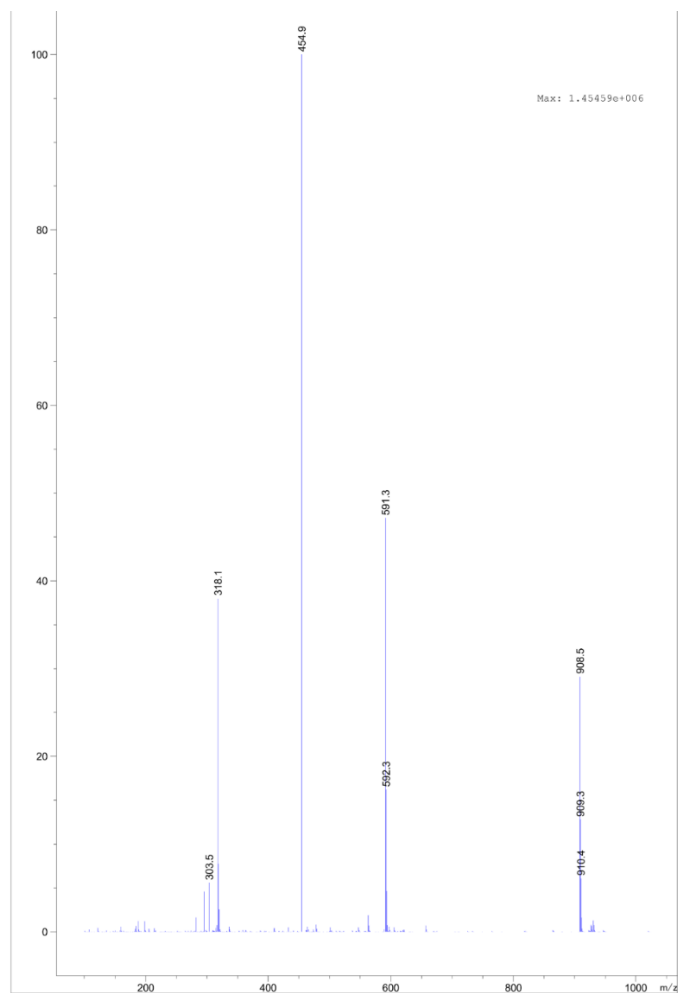


tert-butyl
oate **S27**

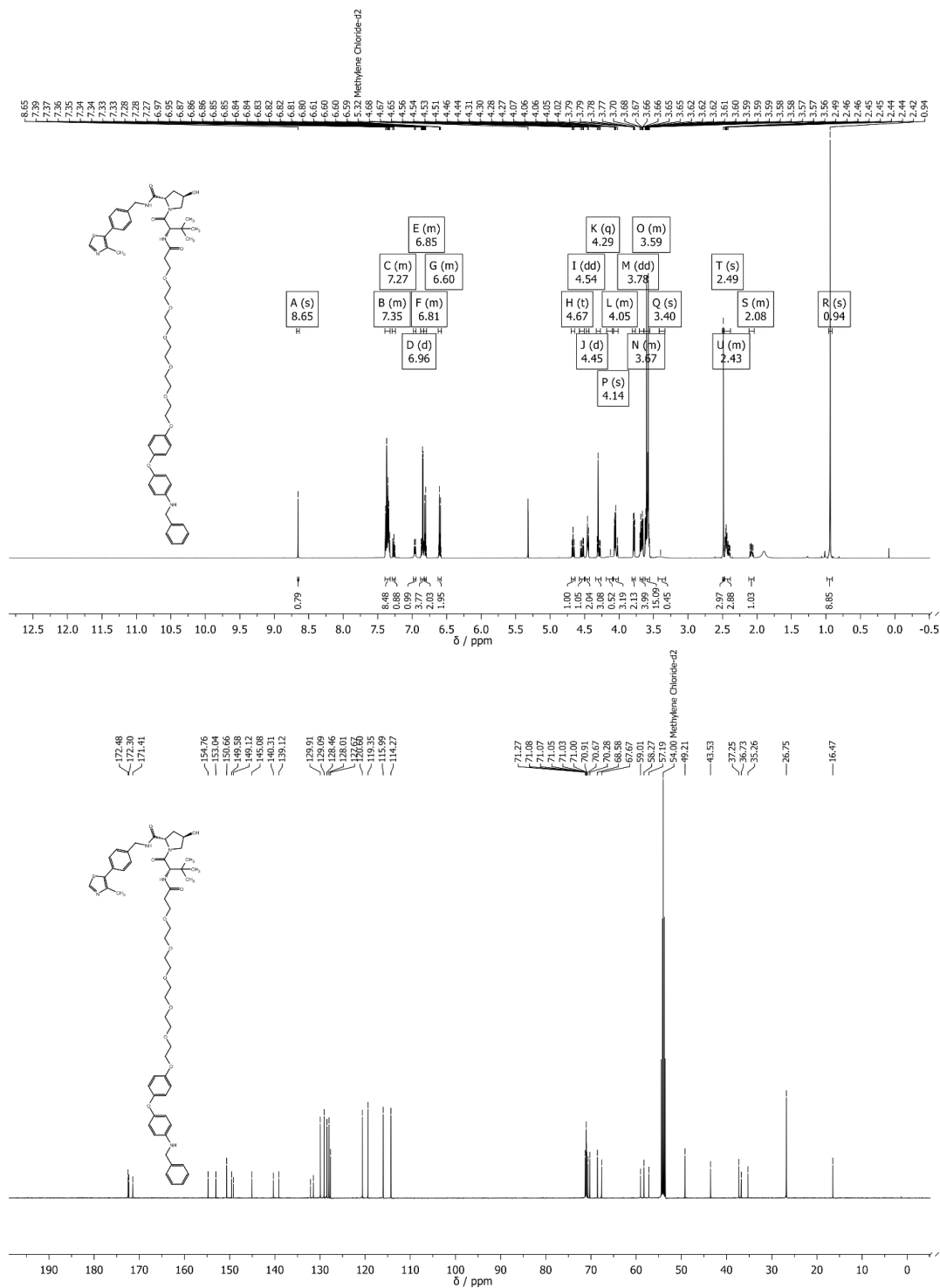


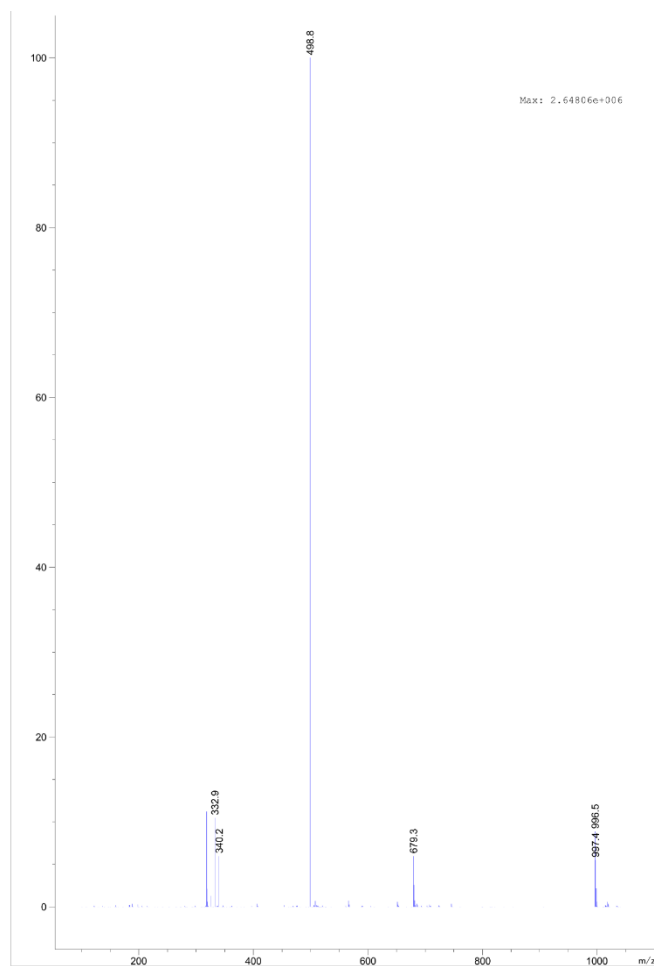
(2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-14-(tert-butyl)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S28**



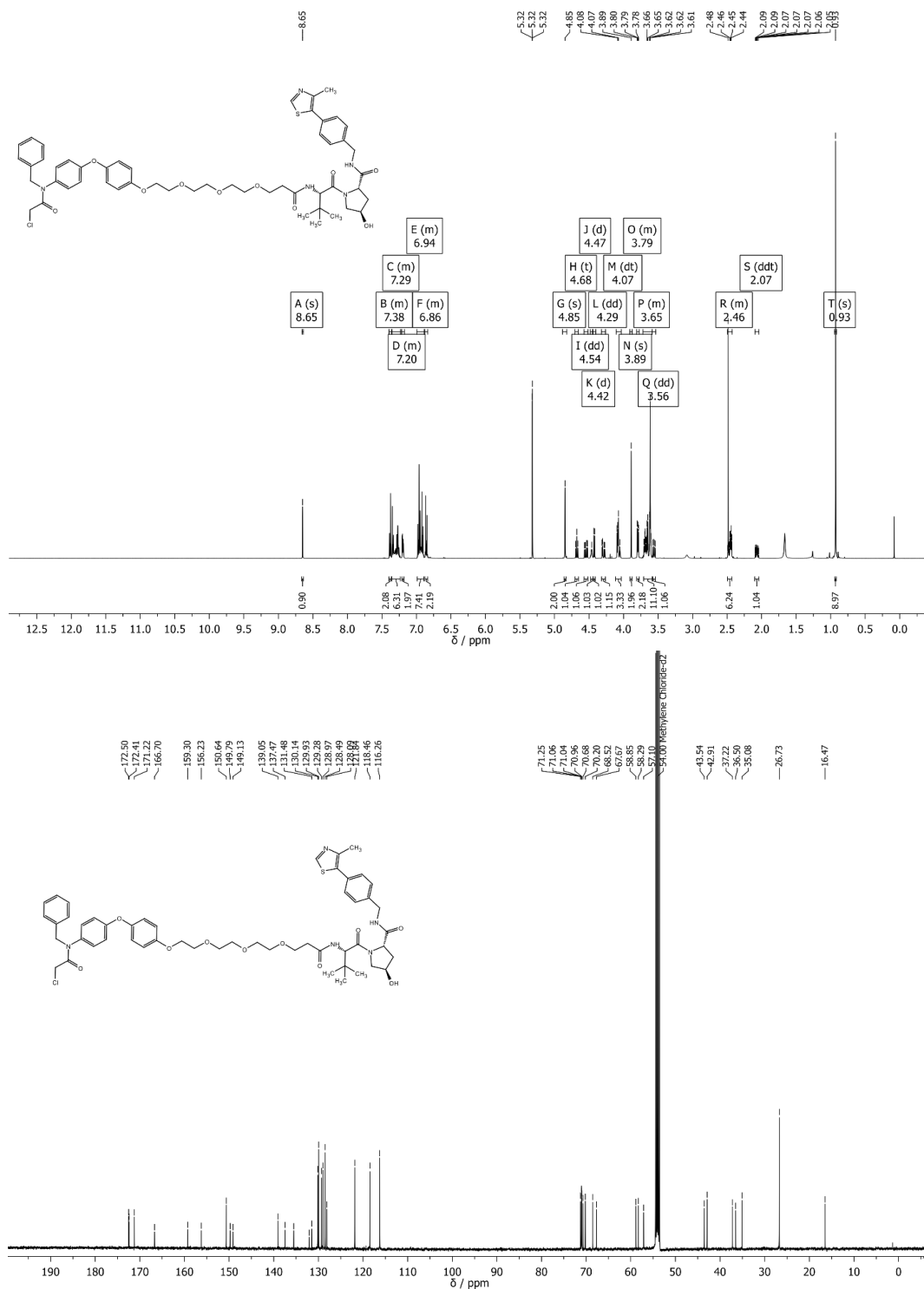


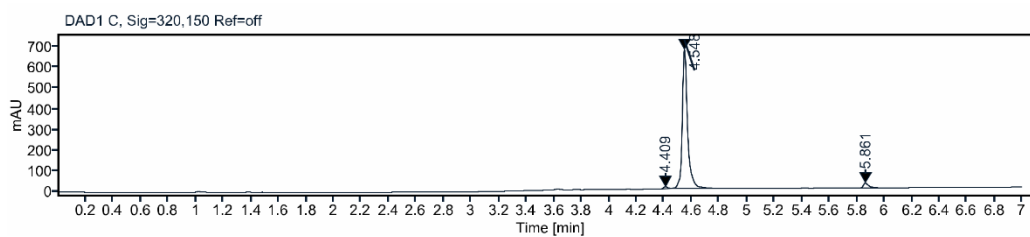
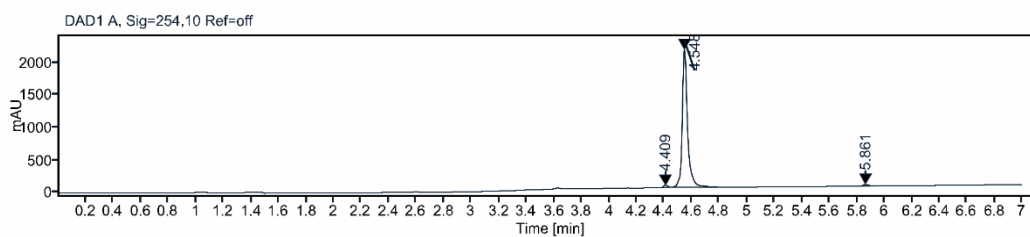
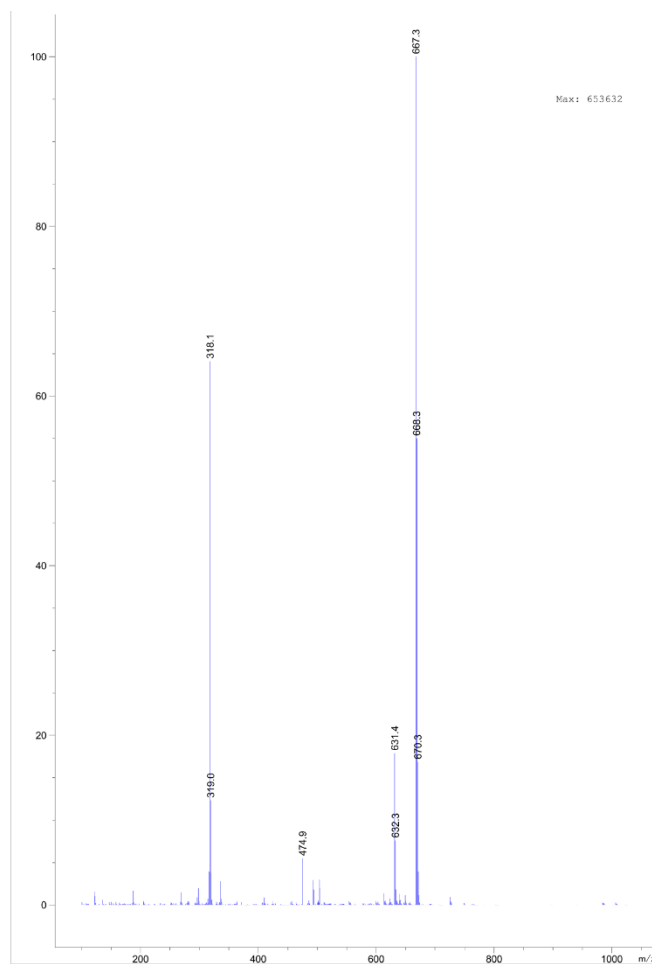
(2S,4R)-1-((S)-1-(4-(4-(benzylamino)phenoxy)phenoxy)-20-(tert-butyl)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **S29**

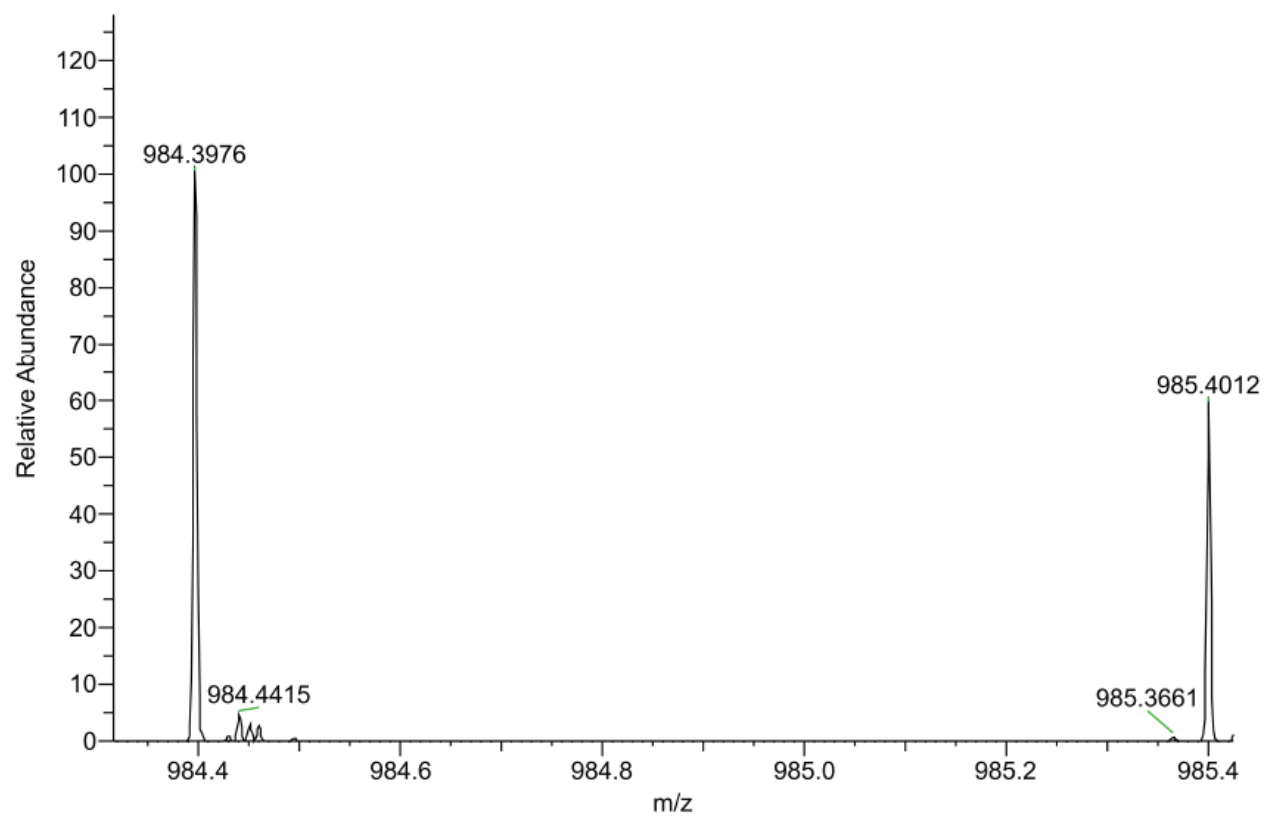




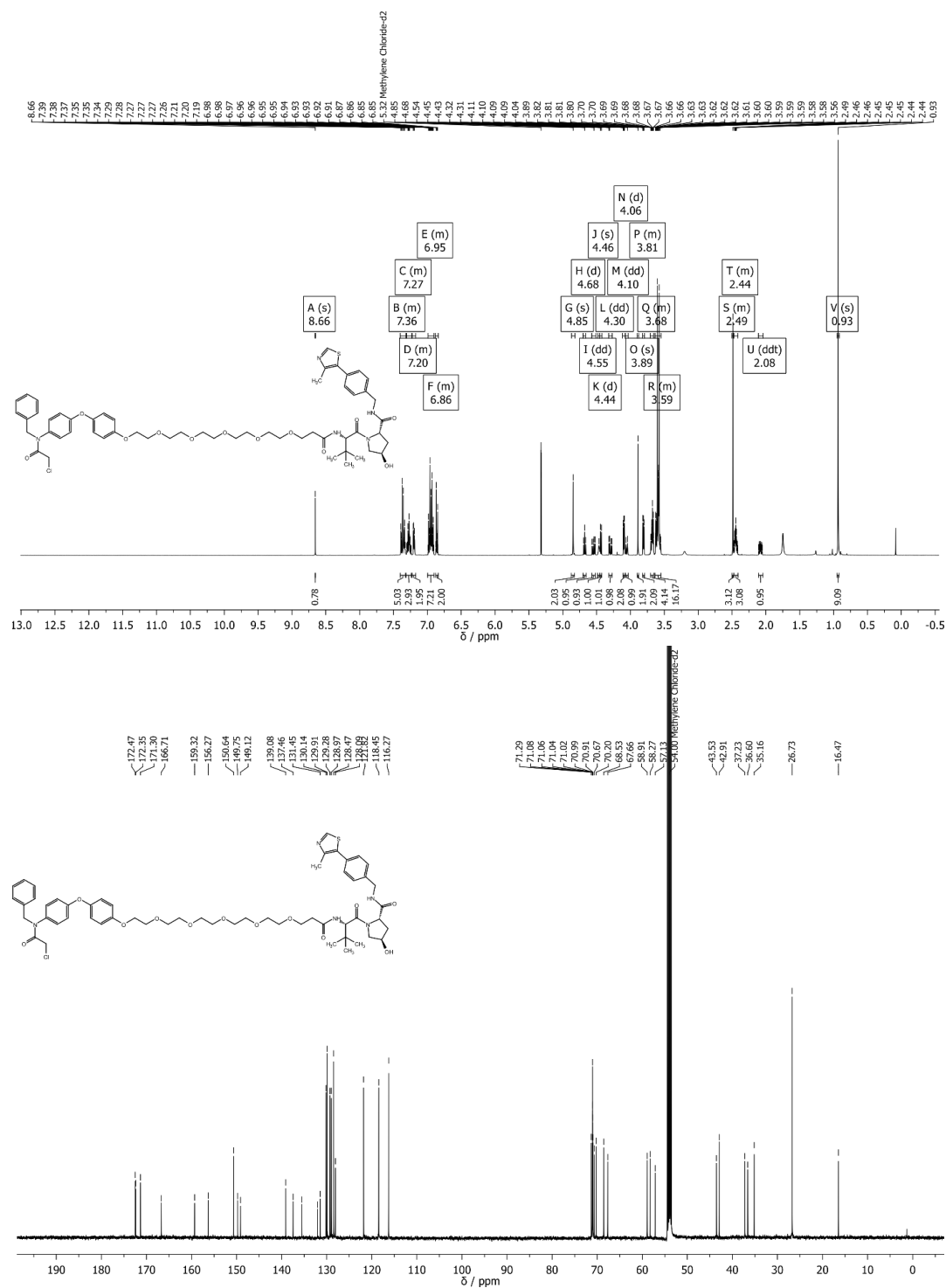
(2S,4R)-1-((S)-1-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)-14-(tert-butyl)-12-oxo-3,6,9-trioxa-13-azapentadecan-15-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2b**

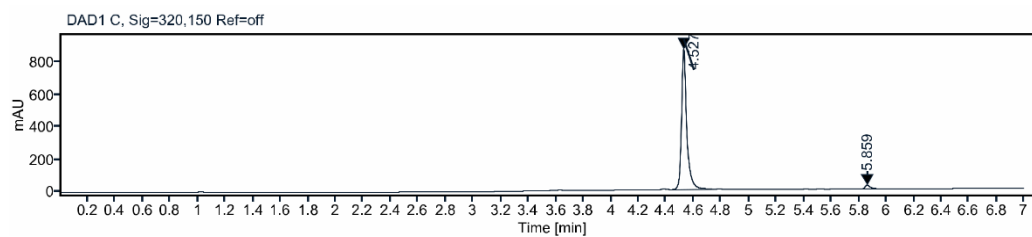
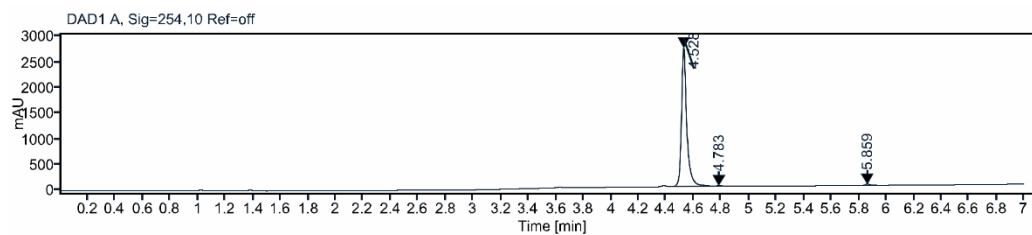
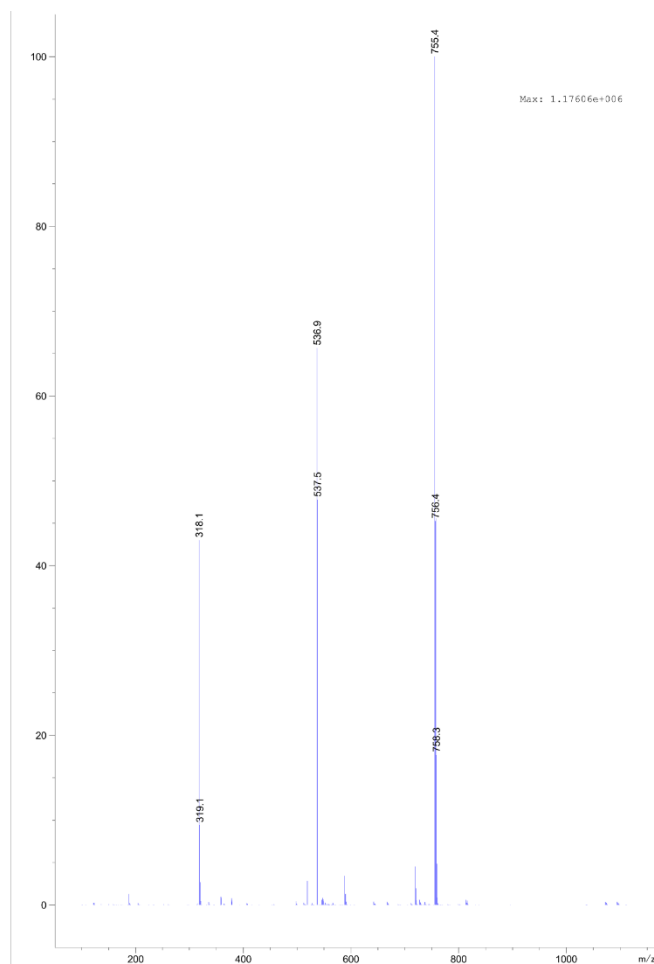


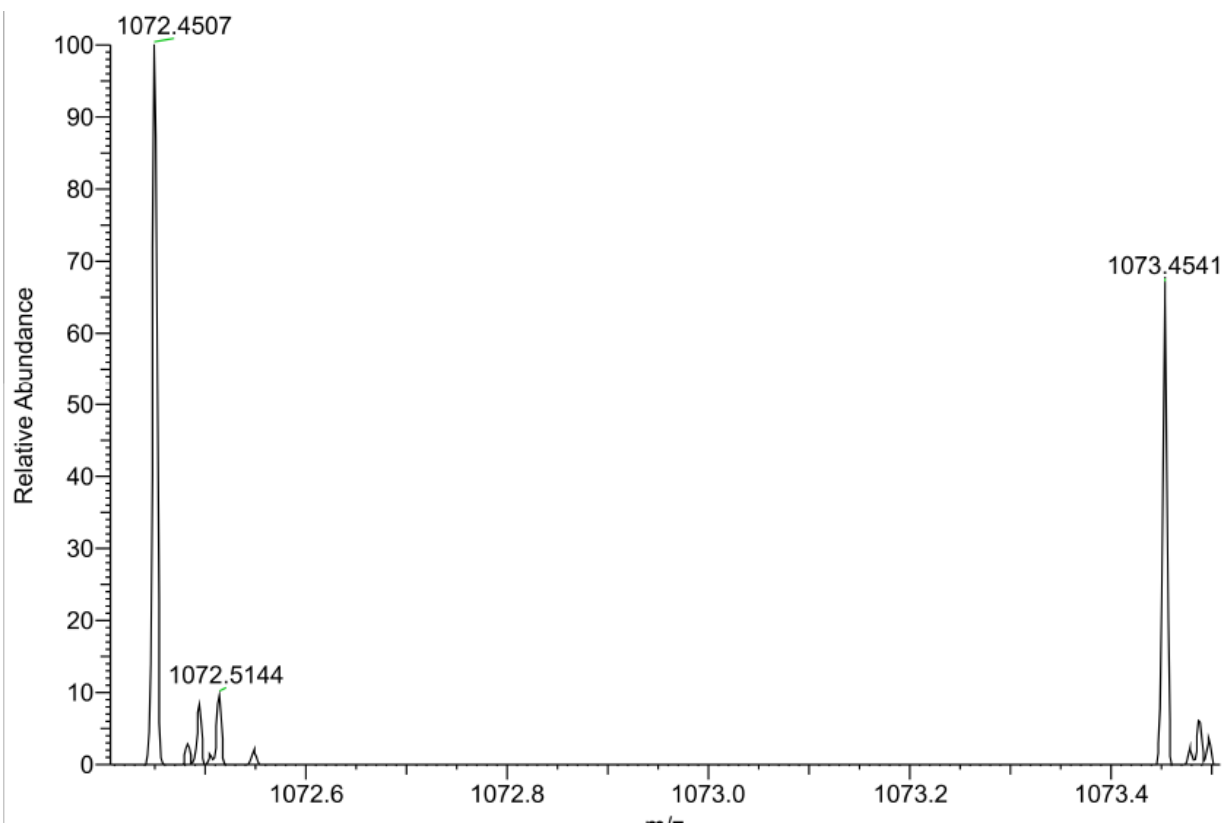




(2S,4R)-1-((S)-1-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)-20-(tert-butyl)-18-oxo-3,6,9,12,15-pentaoxa-19-azahenicosan-21-oyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **2c**

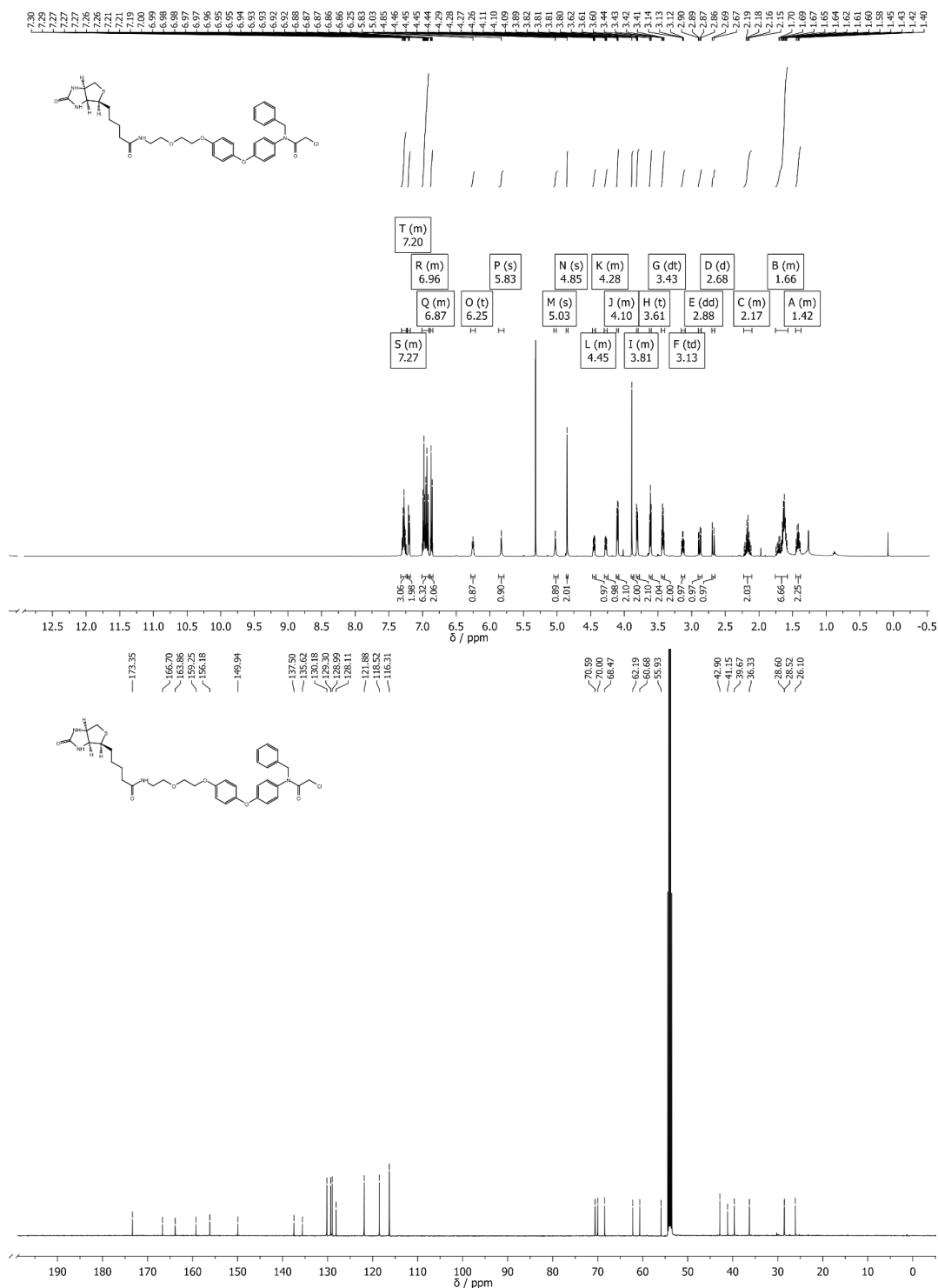


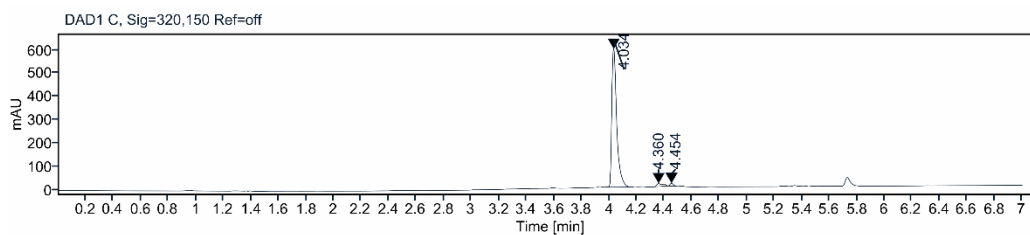
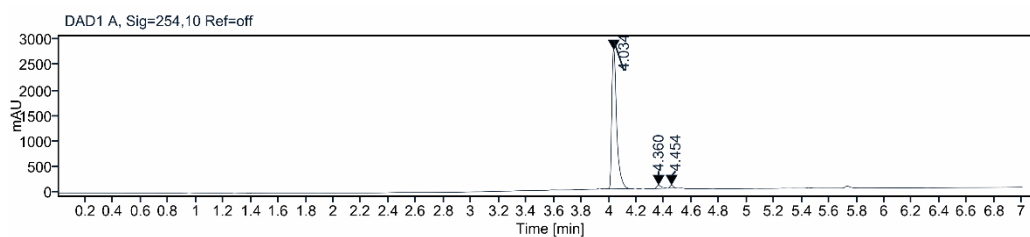


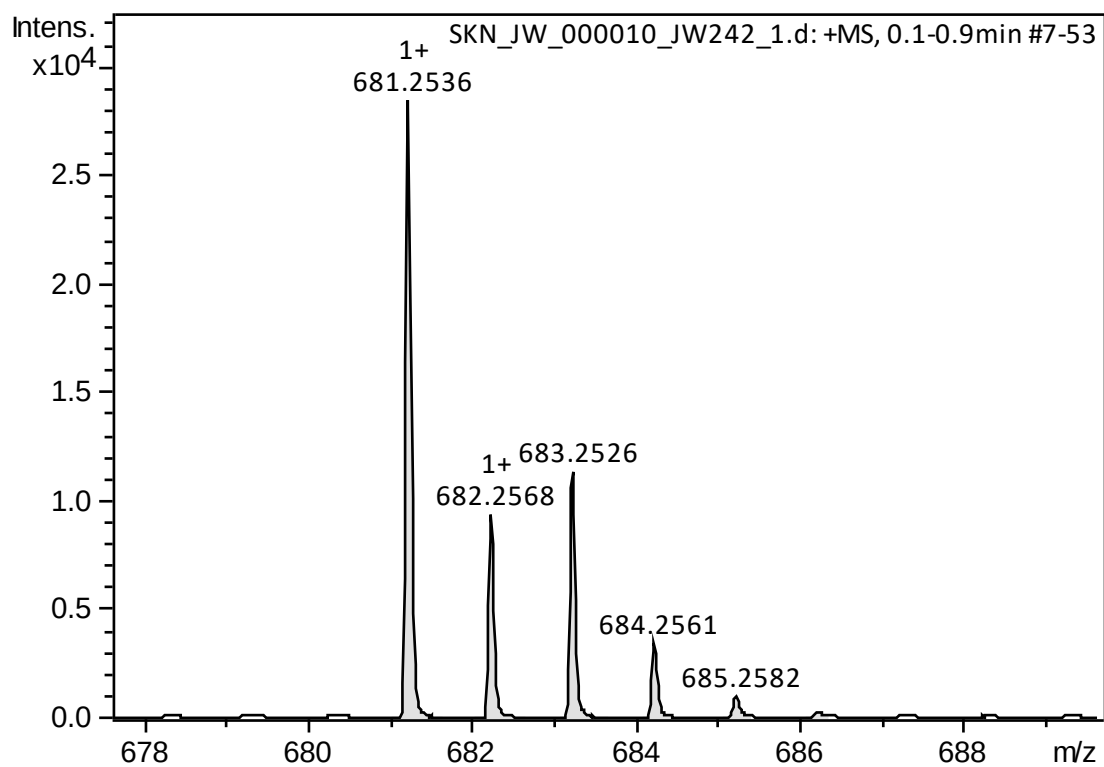


2.4 Spectra for Biotin-CCW16, CCW28-3 and intermediates- Appendix Figure S8

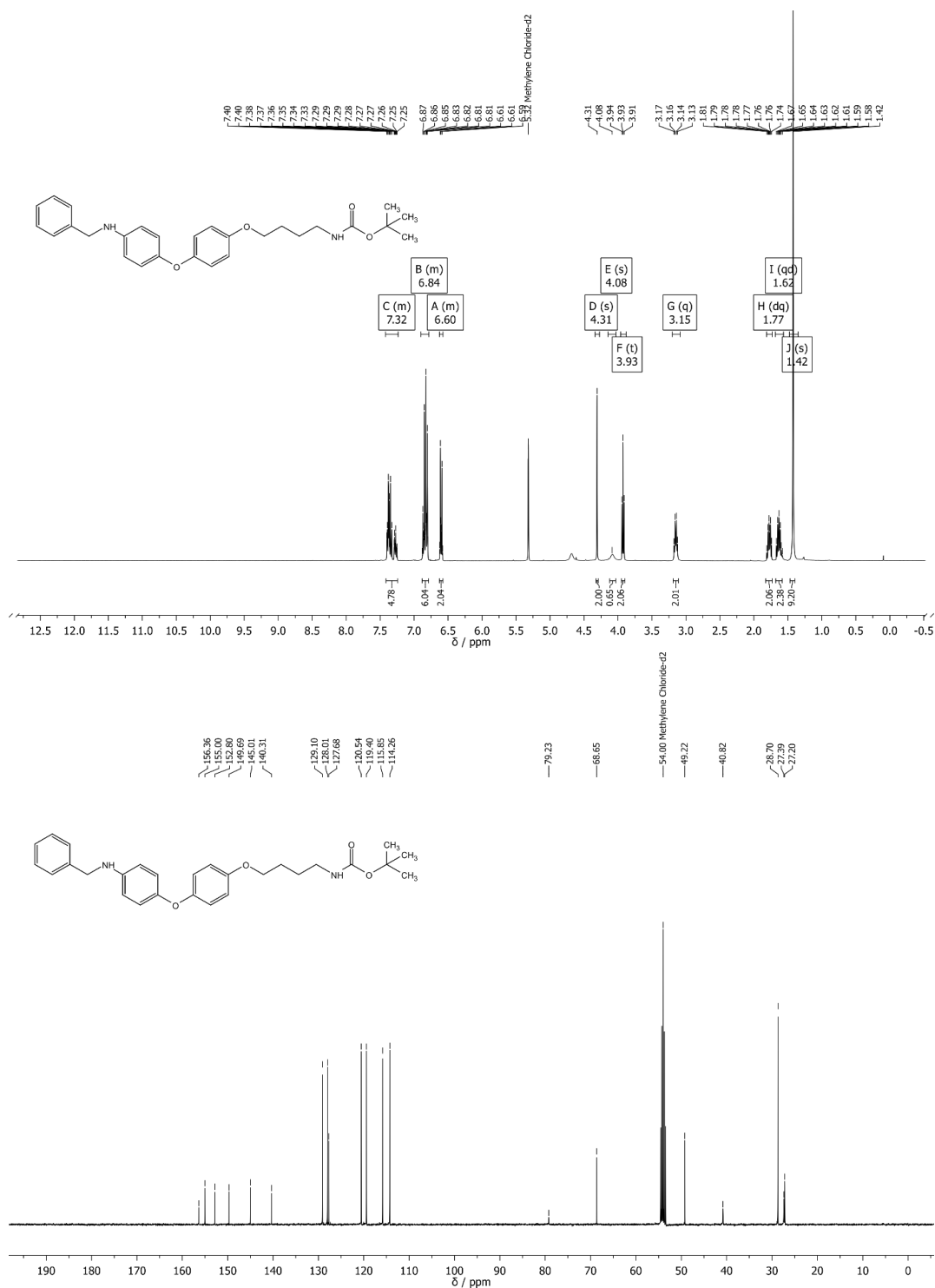
N-(2-(2-(4-(4-(N-benzyl-2-chloroacetamido)phenoxy)phenoxy)ethoxy)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide **Biotin-CCW16**

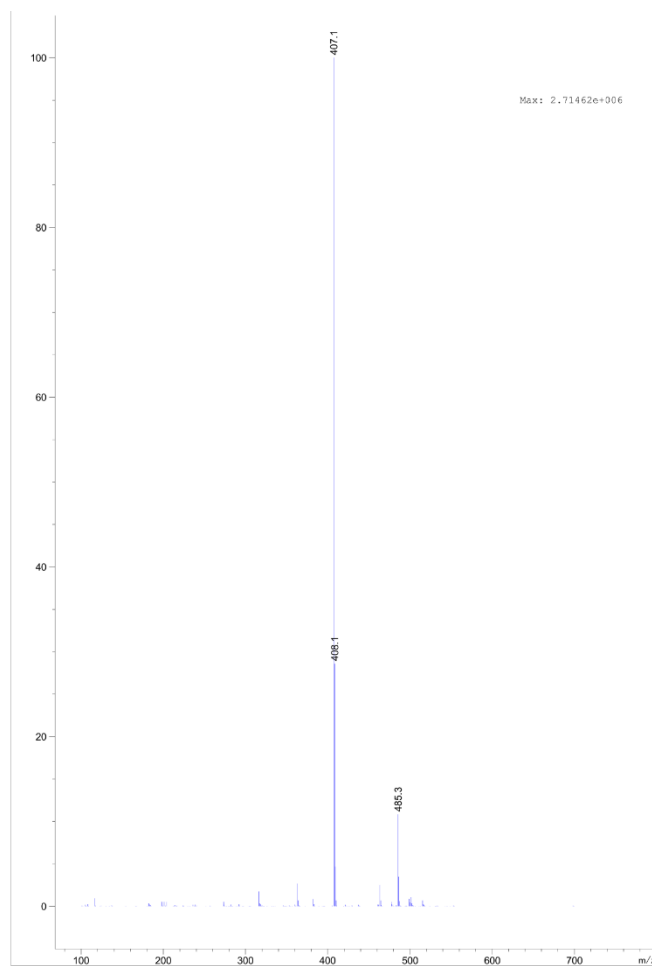




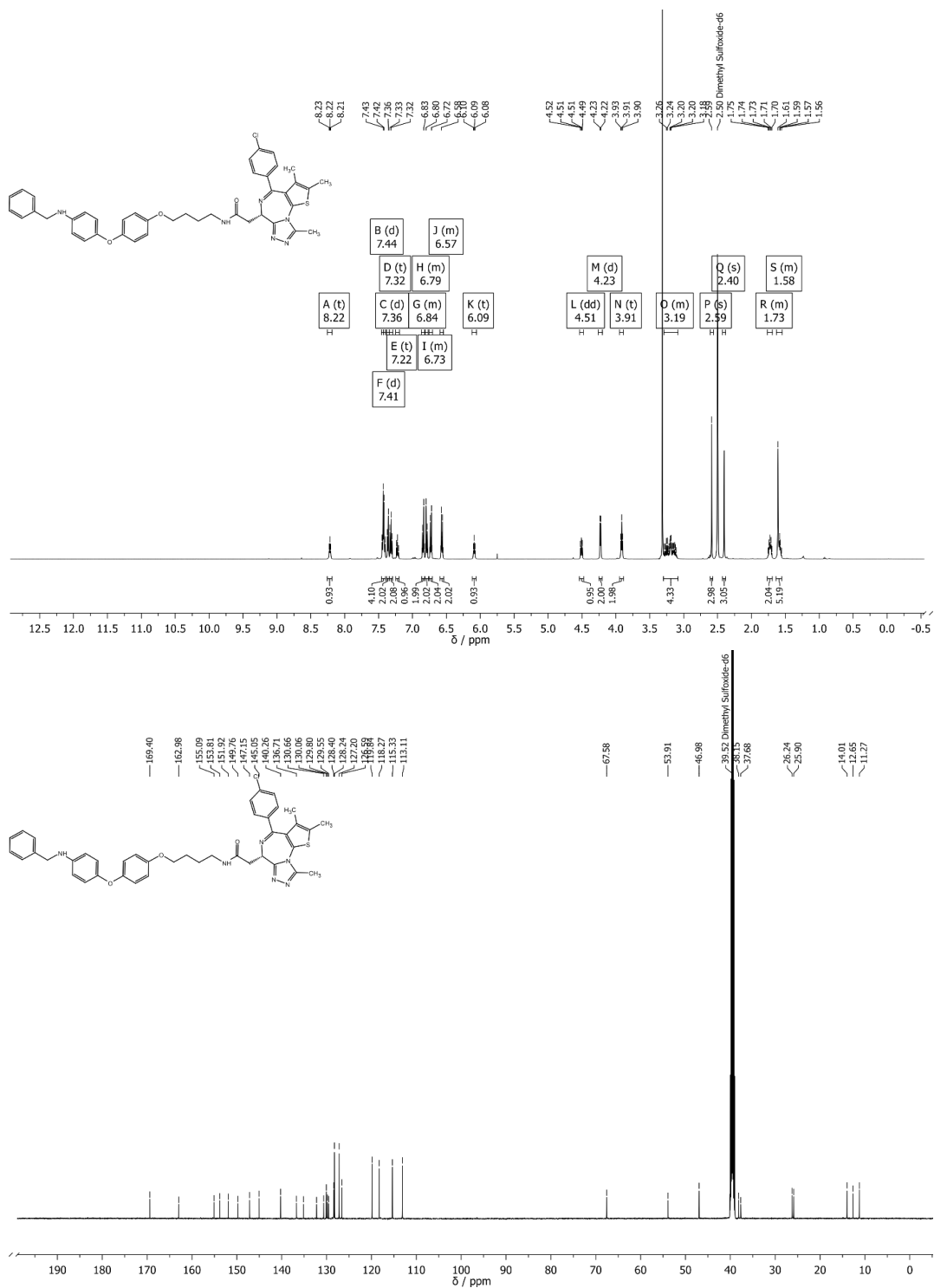


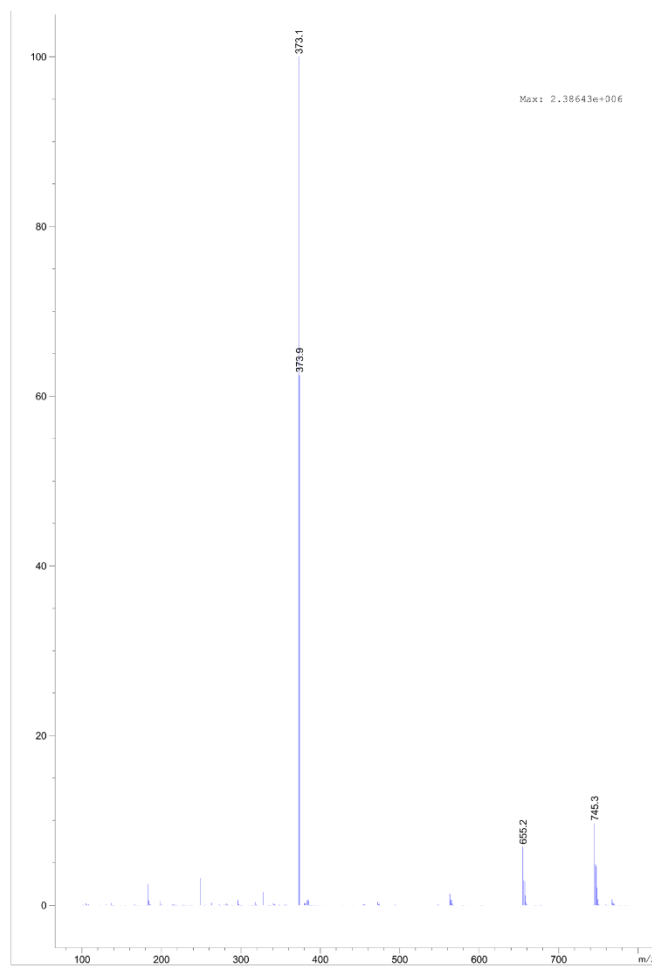
tert-butyl (4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)carbamate **S31**





(S)-N-(4-(4-(4-(benzylamino)phenoxy)phenoxy)butyl)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamide **S32**





(S)-N-benzyl-2-chloro-N-(4-(4-(4-(2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetamido)butoxy)phenoxy)phenyl)acetamide
CCW28-3

