Electronic Supplementary Information

Identification of non-conventional small molecule degraders and stabilizers of squalene synthase

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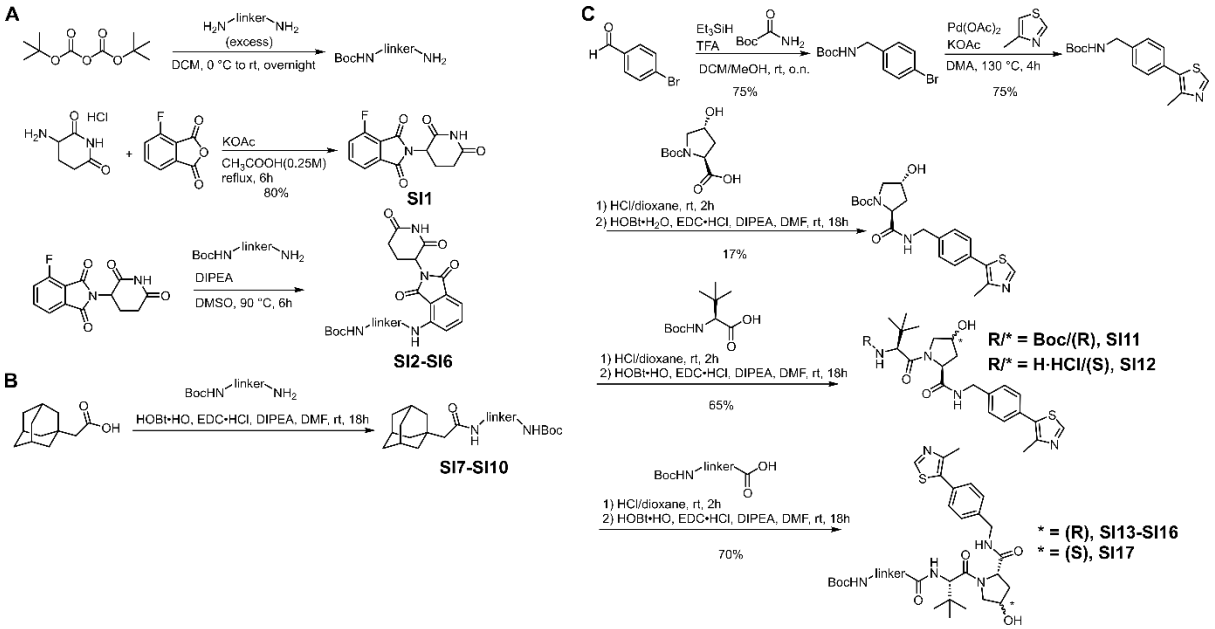
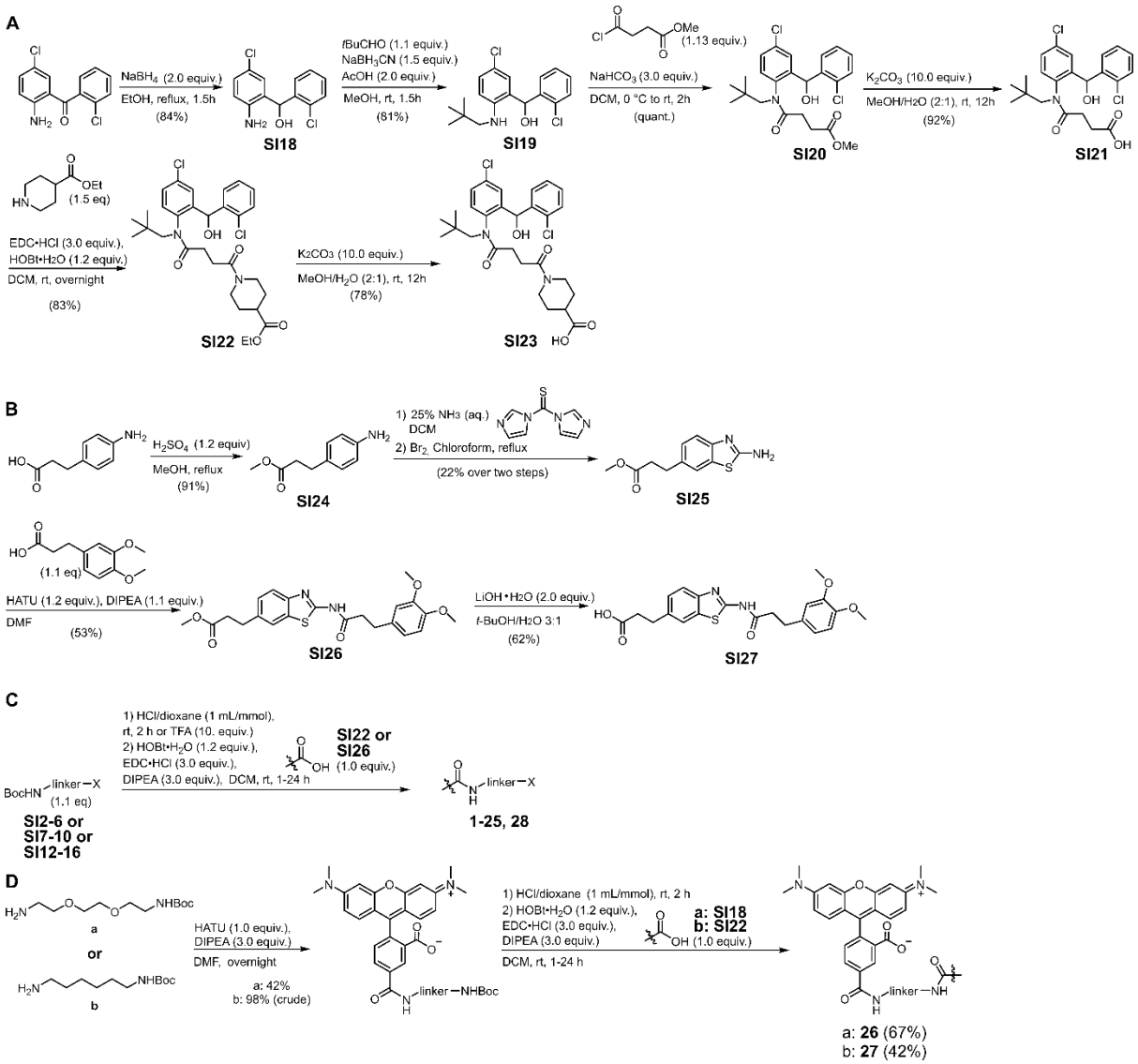
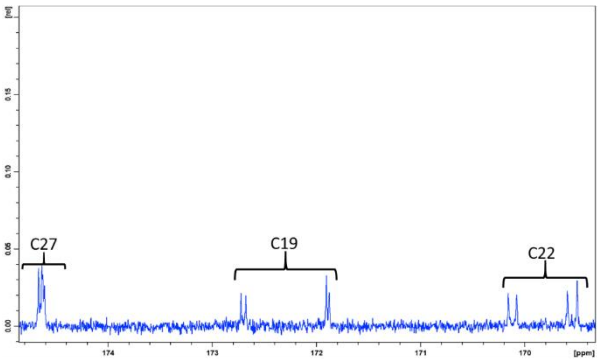


SI Figure 1: Synthesis of degrader modalities. Linker is representative for all linker-degrader sets. **A)** Linker-pomalidomide conjugates.[1] **B)** Linker-adamantane conjugates.[2] **C)** Linker-VH032 conjugates.[3]

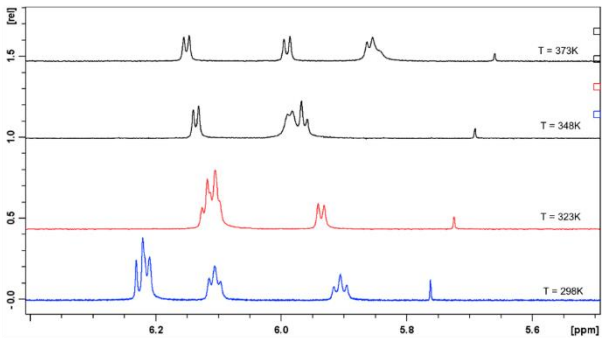


SI Figure 2: Synthesis of SQS-degrader library molecules. A) Synthesis of a SQSI-derivative, a carboxylic acid coupled to linker-degrader conjugates.[4] **B)** Synthesis of a SO2093 derivative, a carboxylic acid coupled to linker-dergrader conjugates.[5] **C)** Amide coupling procedure for the synthesis of SQS-degraders. **D)** Synthesis of FP tracers 26 and 27. 5-TAMRA was synthesized as reported before (not shown).[6]

A



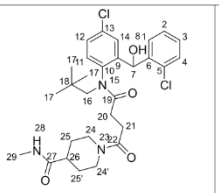
B



C

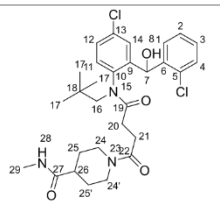
Temperature	CH ratio (H7) I2/I1	t-butyl CH3 ratio (H17) I2/I1
298K	1.1/0.8 = 1.4	9.0/6.4 = 1.4
323K	Not resolved (overlap with H8)	9.0/6.9 = 1.3
348K	Not resolved (overlap with H8)	9.0/7.6 = 1.2
373K	1.0/0.9 = 1.1	9.0/8.3 = 1.1

D



Isomer 1

Label	13C	1H	HMBC	ROESY
1	129.46	7.56	3, 5, 7	7(0.5), 8(2), 14(1)
2	127.85	7.44		
3	129.88	7.39		
4	130.02	7.48		
5	132.4	-		
6	140.06	-		
7	67.63	5.9046	5, 6, 9, 14	1, 8, 14 16a(w), 16b, 20a, 21b
8	**OH**	6.2240	5, 7, 9	1, 7, 14, 16b, 21b
9	142.75			
10	141.3			
11	134.6	7.61	**15**	21a(w)
12	128.56	7.487		
13	132.9			
14	128.91	7.04	7, 10, 12	
15	**N** 128.2			
16	57.94	4.215/2.575	A: 10, **15**, 19 B: 10, 19	A: 7, 16b, 17 B: 7, 8, 16a, 17
17	28.84	0.761		11, 16a, 16b
18	34.2	-		
19	172.7	-		
20	28.53	2.58/2.4	A: 19, 22 B: 19, 22	A: 7, 20b B: 20a, 21b
21	29.73	2.34/2.02	A: 19, 22 B: 19, 22	A: 11, 21b B: 7(w), 8 20b, 21a
22	170.11	-		
23	na			
24 24'	44.78 41.21	3.85/2.98 4.3/2.53		
25 25'	29.27 28.64	1.685/1.455 1.54/1.26		
26	42.19	2.31		
27	174.65			
28	**N** 101.2	7.72		26, 29
29	25.96	2.56		

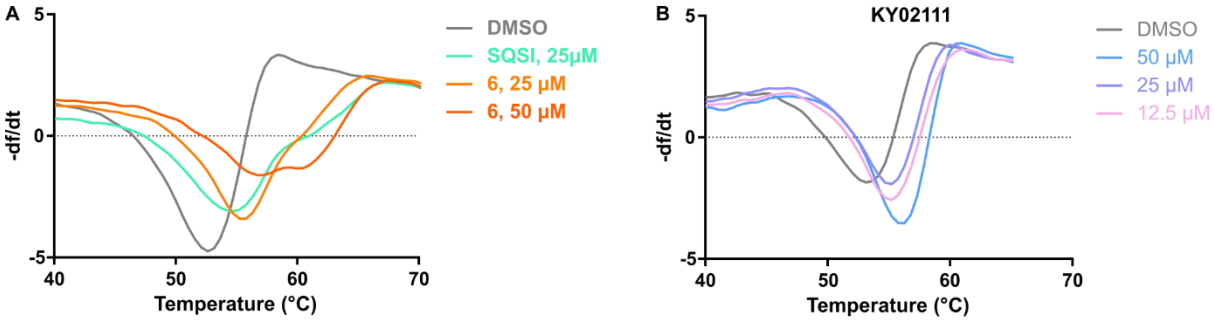


Isomer 2

Label	13C	1H	HMBC	ROESY
1	130.06	7.288	3, 5, 7	7(0.7), 8(1.4), 14(1)
2	129.85	7.40		
3	130.05	7.31		
4	129.75	7.32		
5	132.8			
6	139.95			
7	66.59	6.1064	1, 5, 6, 9, 14	1, 8, 14, 16a(w), 16b, 17
8	**OH**	6.2110	5, 7, 9	1, 7, 14, 16b, 17
9	142.94	-		
10	140.2	-		
11	134.3	7.61	**15**	21a
12	128.2	7.46		
13	132.9			
14	128.55	7.65		8
15	**N** 128.8	-		
16	58.66	4.4065/3.02	A: 10, 19 B: 10 ,19	A: 7, 16b 17 B: 7, 8, 16a 17
17	29.1	0.84		11, 16a, 16b
18	34.6	-		
19	171.9	-		
20	28.41	2.375/1.703	A: 22 B: 19, 22	A: 20b B: 20a ,21b
21	29.37	2.155/1.004	A: 19, 22 B: 19, 22	A: 11, 21b B: 20b, 21a
22	169.46	-		
23	na	-		
24 24'	44.7 41.15	3.66/2.89 4.23/2.48		
25 25'	29.2 28.6	1.64/1.396		
26	42.16	2.29		
27	174.65	-		
28	**N** 101.2	7.72		26, 29
29	25.96	2.56		

SI Figure 3: The utilized SQS-ligand is known to produce a set of atropoisomers due to hindered rotation around the C3-N bond in the presence of the *t*-butyl group. Additionally we identified a second pair of atropoisomers in DMSO-d6. **A-D)** A full spectra assignment for SQSI can be made based on 1D and 2D NMR spectra. However, it is evident that two major isomers are present in the sample, termed isomer 1 and isomer 2. The chemical shift assignment is shown in **D)**. In addition, each of the isomers then also exhibits a second type of isomerism, and thus at least four structural isomers are identified. This is most clear in the 1D 13C spectrum in-which most carbon sites show four distinct NMR signals – illustrated in **A)** for the three amide carbon atoms. Similar evidence can be seen in **B)**, the 1H spectrum, where a total of four doublets are observed for H7, and H16a and H16b for I2 are both split into two doublets. Interestingly, H16a and H16b for I1 does not show such a splitting, and both appear as single doublets. **B/C)** ^{1}H NMR spectra has been measured at 298K, 323K, 348K and 373K for the sample dissolved in DMSO-d6. It is seen that the set of "triplets" for H7 collapses into doublets already at 323K, confirming a relatively low energy barrier for the first type of isomerism (which is also suggested from the small ^{13}C chemical shift differences). In contrast, the two doublets only show minor signs of collapsing into a single doublet and stay well-separated even at 373K ($\Delta\delta$ (298K) = 0.20 ppm, $\Delta\delta$ (323K) = 0.19 ppm, $\Delta\delta$ (348K = 0.17 ppm and $\Delta\delta$ (373K

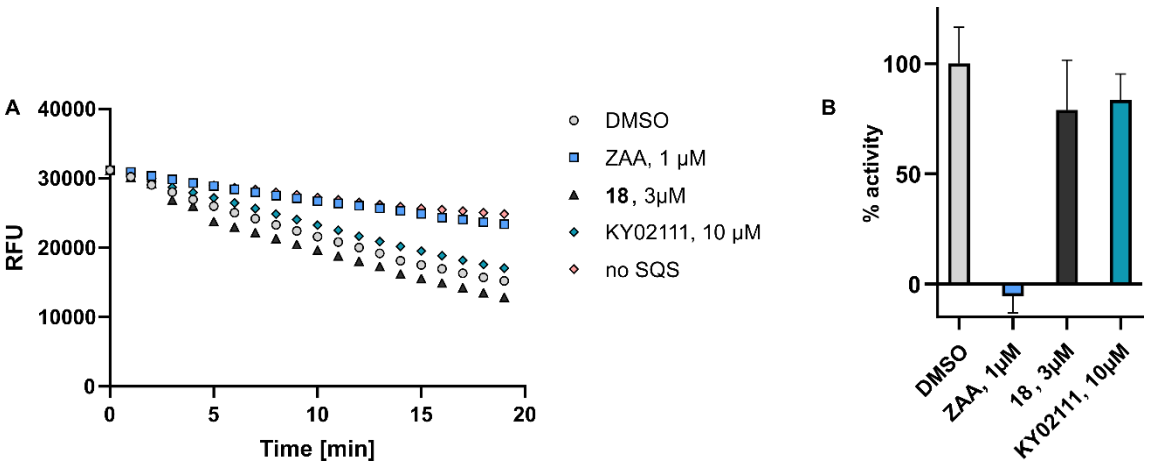
= 0.16 ppm). The relative integral area for both H7 and H17 has been determined at the four temperatures, and show that equilibrium is moving towards I1 as the temperature is increased.



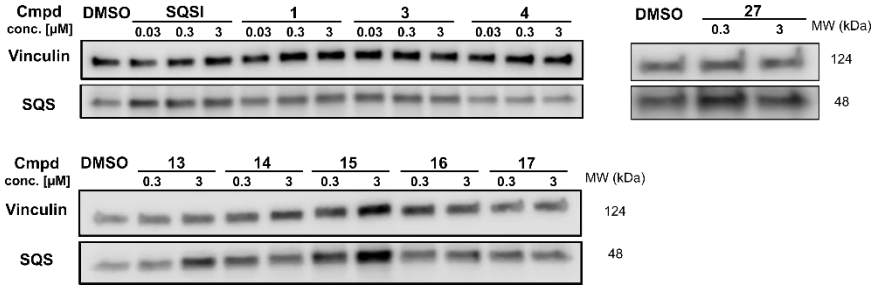
C

Compound	dTm [°C] 12.5 µM	25 µM	50 µM
SQSI	0.9 ± 0.8	1.4 ± 0.2	6.1 ± 1.0
KY02111	2.1 ± 0.4	1.8 ± 0.4	2.3 ± 0.1
SO2093	2.3 ± 0.5	2.2 ± 0.3	2.0 ± 0.5
6	0.7 ± 0.1	2.8 ± 0.3	6.3 ± 1.0
7	1.6 ± 0.1	3.0 ± 0.2	6.2 ± 1.6
8	1.5 ± 0.6	2.3 ± 0.6	5.3 ± 1.5
13	2.1 ± 0.7	2.4 ± 0.3	1.9 ± 0.1
18	2.9 ± 0.4	3.6 ± 0.3	3.3 ± 0.9
22	1.9 ± 0.6	2.6 ± 0.3	2.9 ± 0.3
23	2.0 ± 0.6	2.1 ± 0.4	1.9 ± 0.7

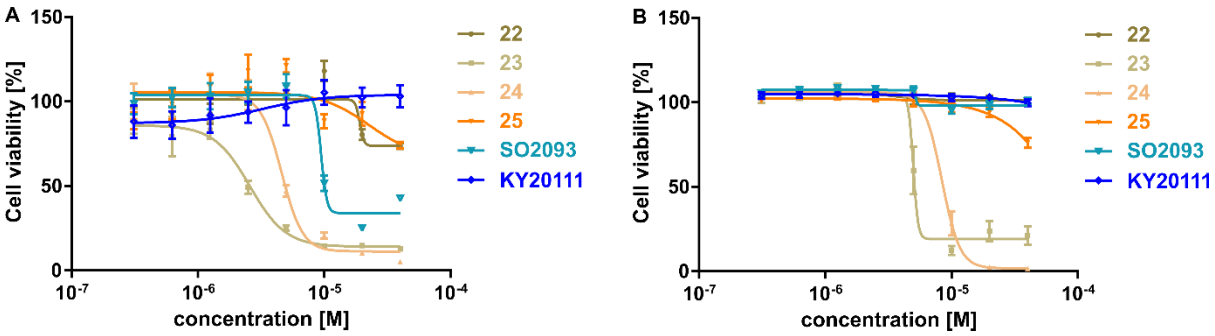
SI Figure 4: Differential scanning fluorimetry (DSF) data for selected members of the SQS degrader library. A)/B) First derivative of the melting curves for SQSI, **6** and KY02111. Recombinant SQS (His_6-31-370, 0.5 mg/mL) was incubated with sypro orange (1x) and either DMSO, 6, or KY02111 at the indicated concentrations. The fluorescence intensity was measured in a Roche LightCycler 480 II. **C)** Overview of melting temperatures ΔTm [°C] for tested members of the SQS degrader library (n = 3, mean ± SD shown).



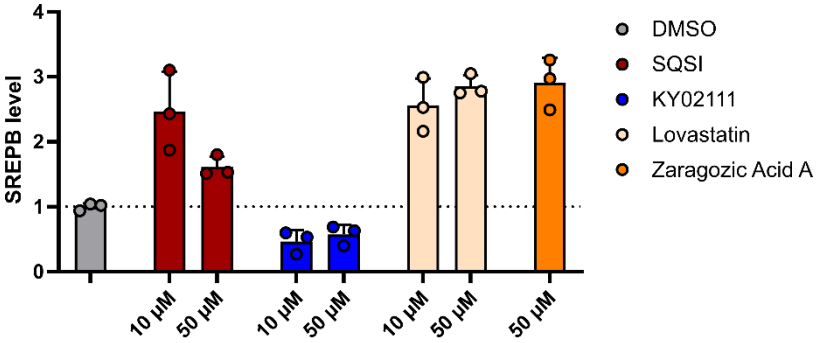
SI Figure 5: *In vitro* SQS activity assay. Recombinant SQS (31-370, 0.004 mg/mL) was incubated with the indicated compounds for 10 min at rt before addition to a 2x solution of a 1:4 NADPH/FPP mixture (final concentration 10 and 40 µM, respectively). NADPH fluorescence (excitation 340 nm, emission 465 nm) was monitored over 20 minutes in a Tecan Spark Cyto multimode microplate reader with incubation at 37 °C. **A)** NADPH fluorescence curves during incubation of the SQS catalyzed reaction. Data was normalized to the same starting point. (mean shown, n = 3 technical replicates) **B)** Normalized SQS activity for the NADPH fluorescence readout shown in **A)**. For comparison of each condition, the mean of the drop rate over 20 minutes (= curve slope) was normalized to the DMSO (100 % activity) or no SQS (0% activity) controls. (mean + SEM shown, n = 3).



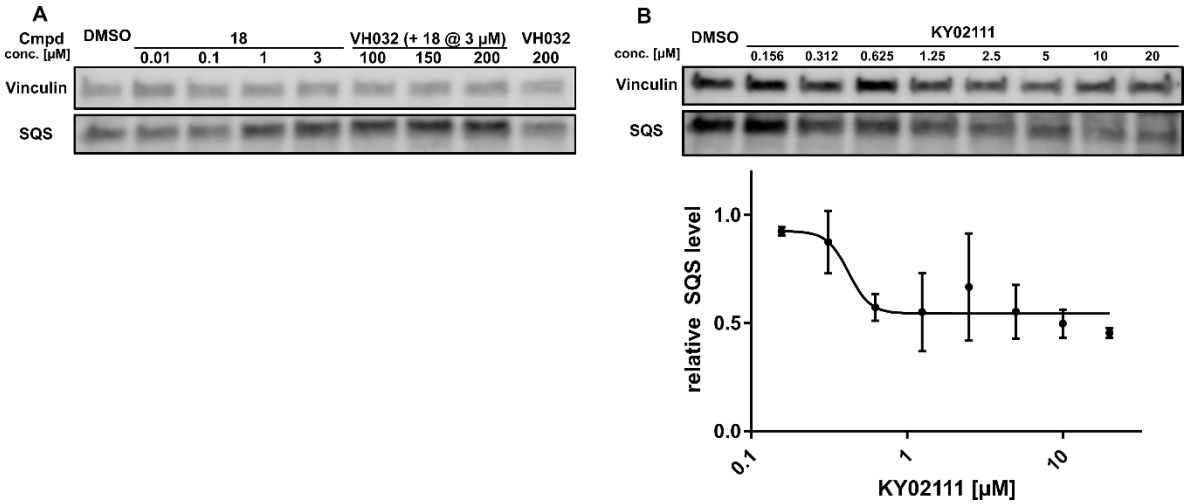
SI Figure 6: *In cellulo* SQS-degrader screen: Complimentary data for library compounds 1-5, 13-17 and 27. Western blots showing the changes in SQS protein levels after 18 h treatment of HeLa cells with compounds at indicated concentrations (n = 2 or 3).



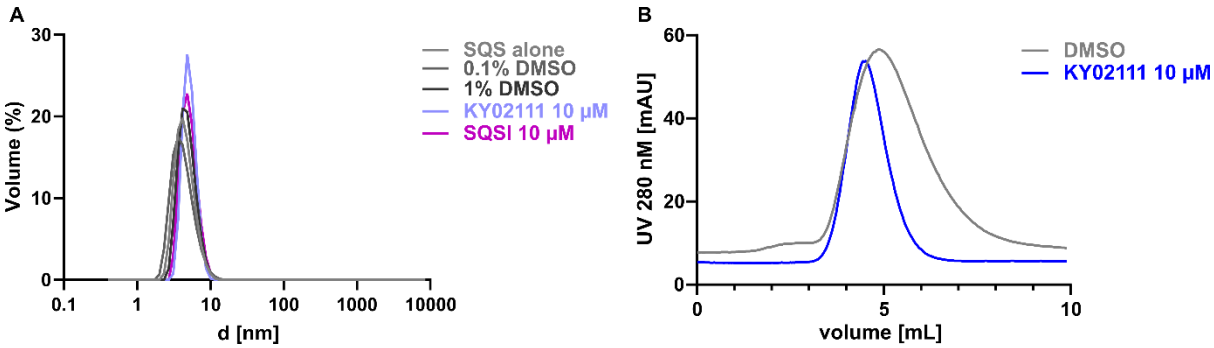
SI Figure 7: Cell viability data for selected compounds in HeLa cells. Viability was analyzed after the indicated time points utilizing the Cell-Titer Blue assay system by Promega. **A)/B)** The indicated compounds were used to incubate HeLa cells for 18 (A) and 48 (B) h. The dilution series was started at 40 µM (n = 3 (tech. and biol.), mean ± SD shown).



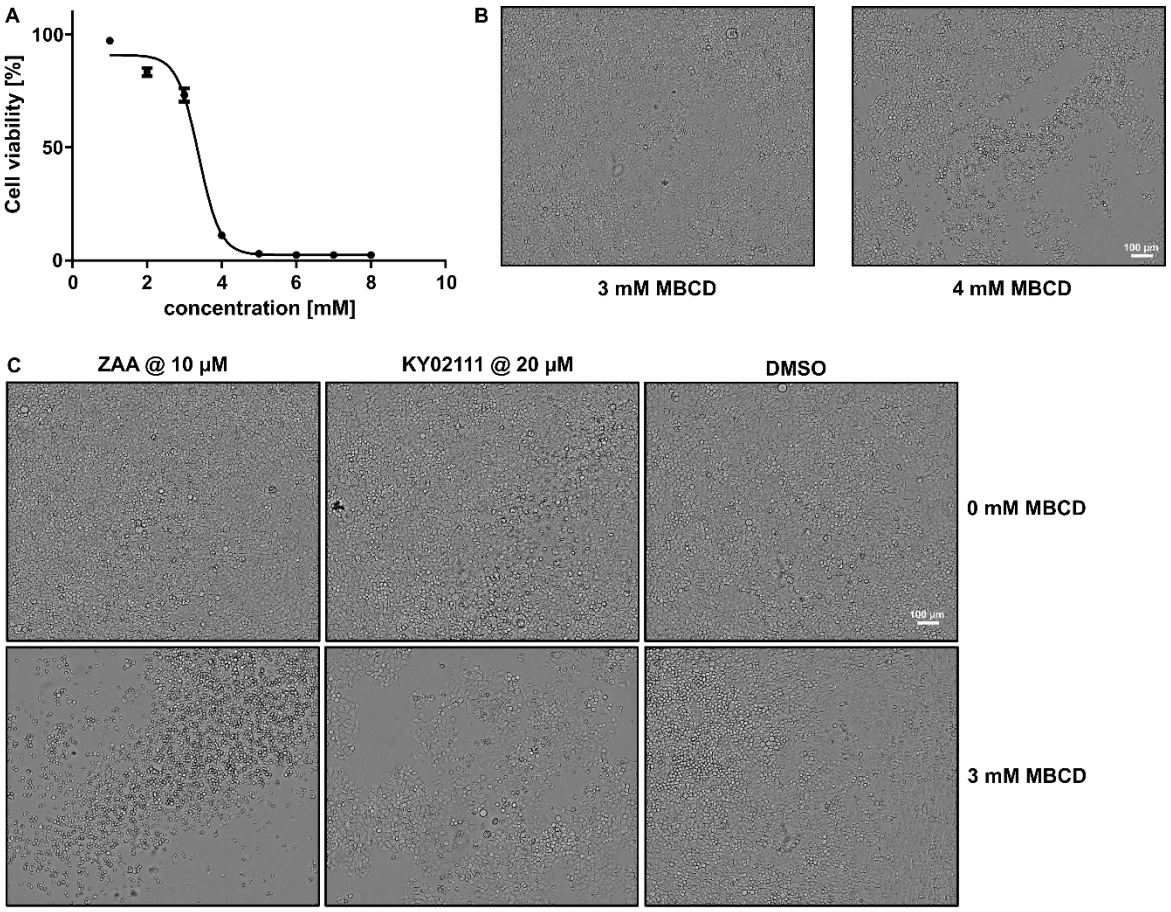
SI Figure 8: SREBP reporter gene assay to see indirect upregulation of cholesterol biosynthesis.[7] HeLa cells were transfected with a pSynSRE-T-Luc plasmid, containing the promotor for HMG-CoA synthase (HMGCS) containing the SREBP responsive region linked to a firefly luciferase and a pRL-TK (*Renilla* luciferase) vector. For transient transfection, HeLa cells were transfected by means of lipofection using Lipofectamine 2000 for 24 h. Afterwards the cells were re-plated and incubated with compounds for 18 h. The Promega Dual-Glo Luciferase assay system was used for reading out the firefly and renilla luciferase activity in the same sample (n = 2/3 (biol./tech.), mean ± SD shown).



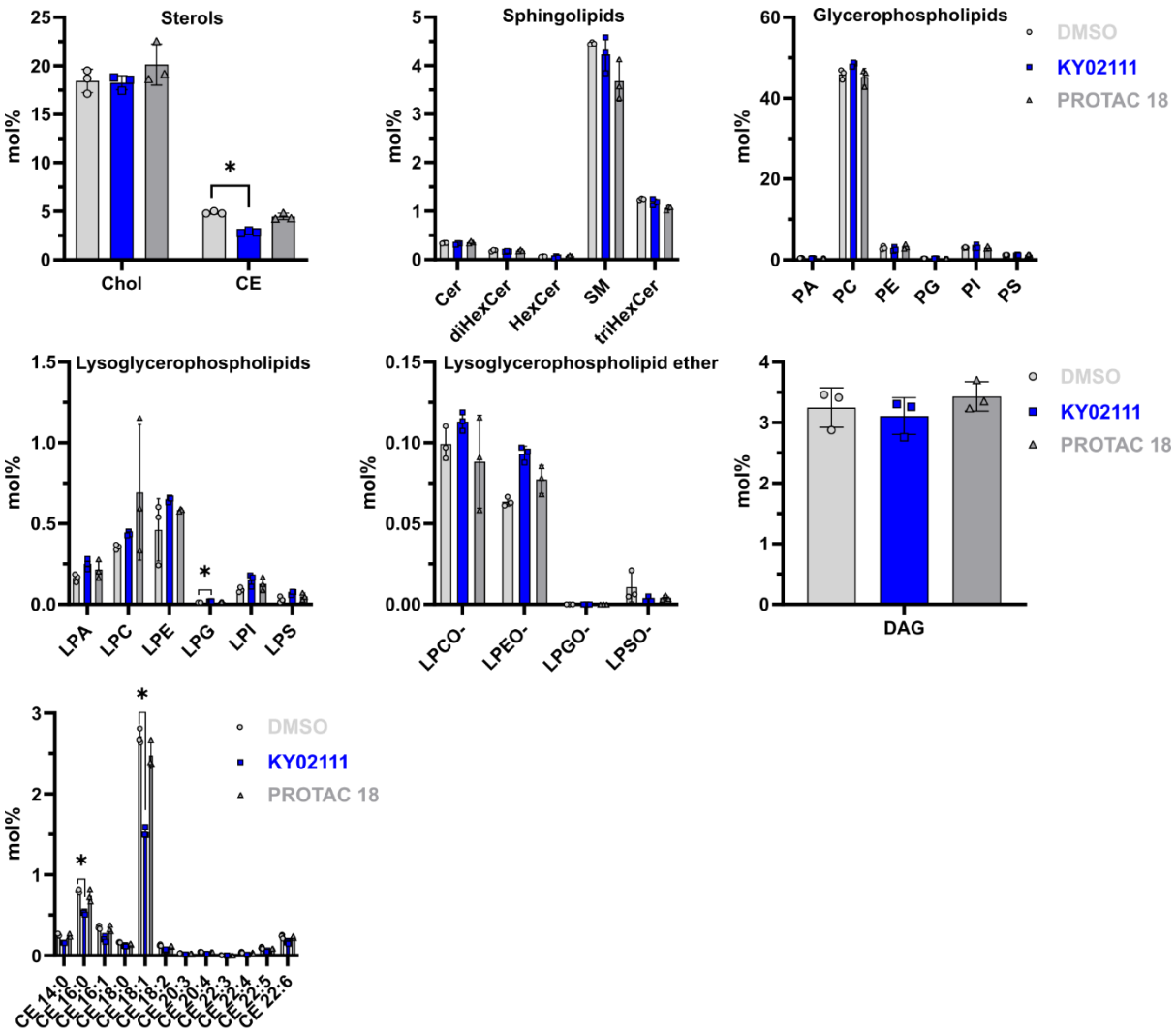
SI Figure 9: A) SQS accumulation by PROTAC **18** is independent of VHL. HeLa cells were treated with **18** and/or VH032 for 18 h at the indicated concentrations (n = 3). **B)** KY02111 dose-response in U2OS cells incubated for 18 h (n = 2, mean ± SEM shown).



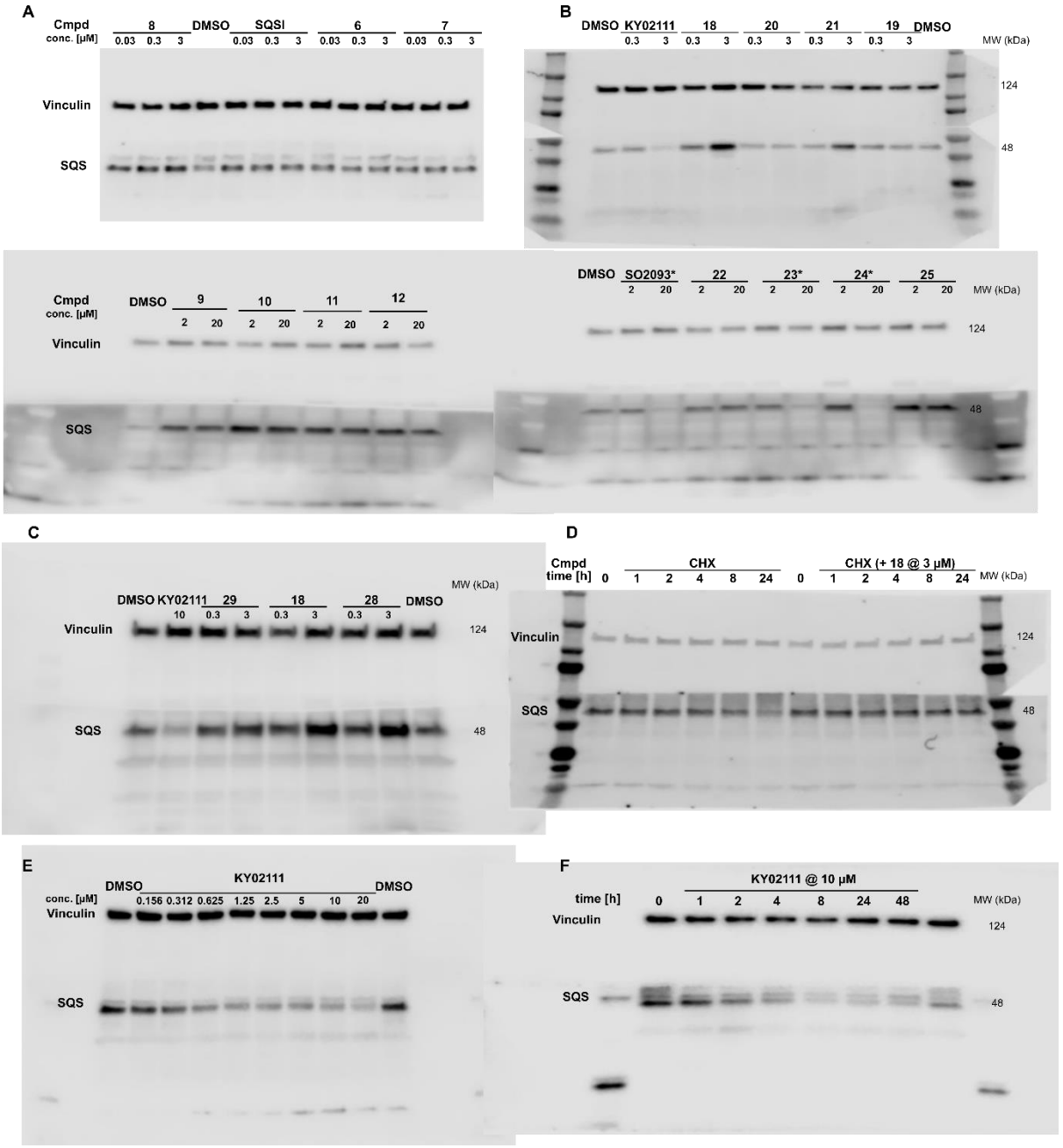
SI Figure 10: Investigation of potential SQS aggregation by KY02111. **A)** Differential light scattering (DLS) data for the indicated conditions. Recombinant SQS (31-370) was filtered by size-exclusion chromatography (SEC) and then diluted to 0.25 mg/mL). The sample was then filtered through a 0.2 µm syringe filter and added to a cuvette. After an initial measuremnt with SQS alone, compounds were added at the indicated concentrations. Each sample was prepared individually. **B)** UV peak for SEC purification of recombinant SQS (31-370, 0.25 mg/mL) pre-incubated with either DMSO or KY02111 (10 µM) for 1 h.



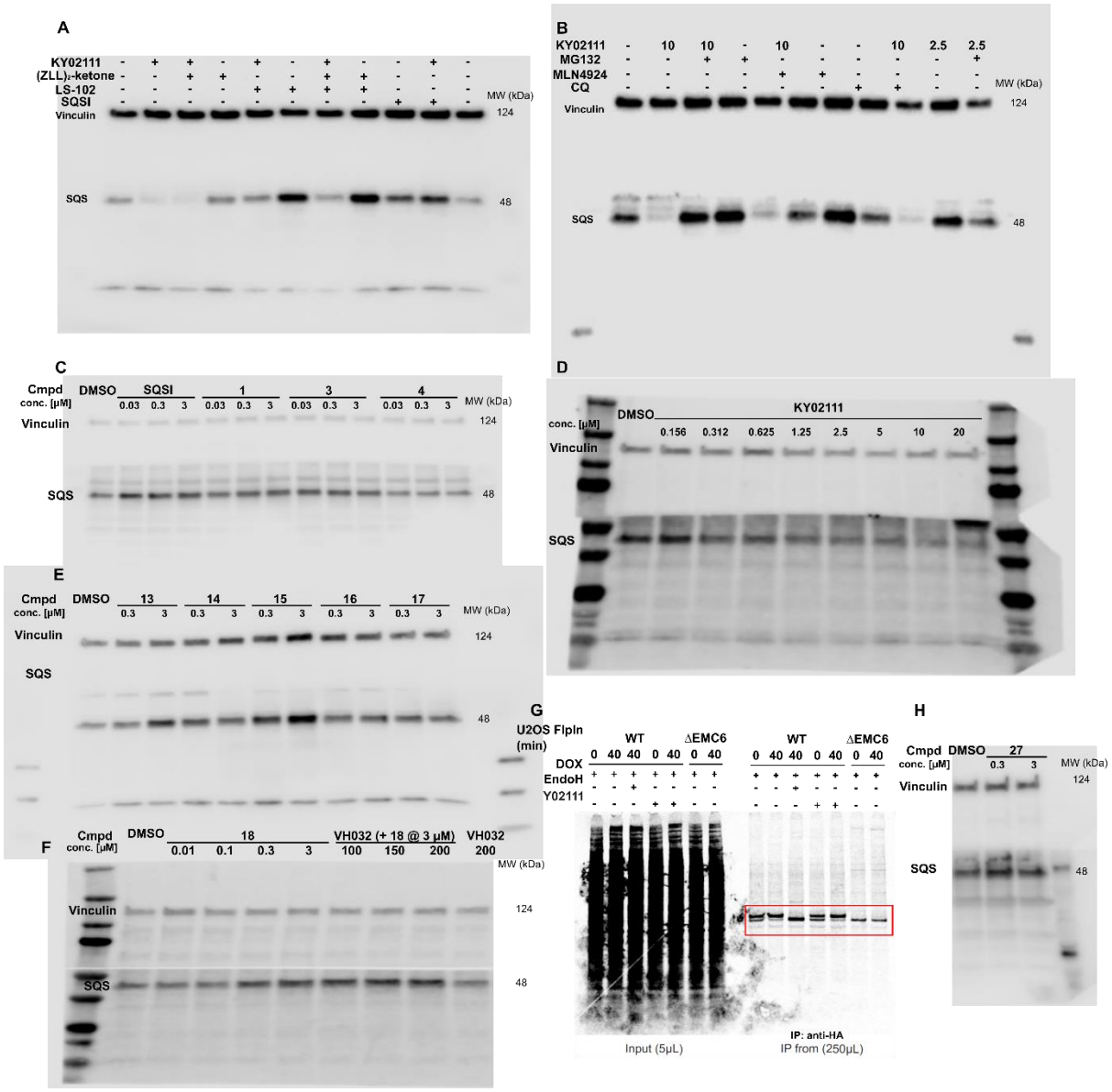
SI Figure 11: Cell viability data for selected compounds in HeLa cells. Viability was analyzed after the indicated time points utilizing the Cell-Titer Blue assay system by Promega. **A)/B)** Cells were titrated with different concentrations of MBCD for 72 h (in standard medium, 10% FBS, 1% PS). Pictures were also taken after 72 h. 3 mM MBCD was chosen as a non-toxic concentration for follow-up experiments. C) Comparison in cell viability between cells incubated with ZAA (10 µM), KY02111 (20 µM) and DMSO, grown with (3 mM) or without MBCD for 72 h.



SI Figure 12: Bar plots showing the mol% changes for respective lipid classes after treatment of HeLa cells with KY02111 (10 µM) or PROTAC 18 (5 µM) after 18 h (n = 3, Holm-Šídák correction was used to determine adjusted p-values $p < 0.005$). For changes of specific species within the lipid classes the reader is referred to the supplementary excel file containing the full data set.



SI Figure 13: Complete western blot membranes for the blots shown in Fig.3 in the main manuscript. Blots are arranged in the same order as in **Fig.3**. In cases where a minor double band was observed for SQS, the lower band was consistently showing and assigned as the SQS band.



SI Figure 14: Complete membranes for western blots and 35S radiolabeling + IP experiments shown in **Fig. 4** of the main manuscript and the ESI data, where **Fig.4B = SI Fig. 14A**, **Fig. 4C = SI Fig. 14F**, **Fig. 4D = SI Fig. 14B**, **SI Fig. 6 = SI Fig. 14C/E/H, SI Fig. 9A = SI Fig 14G** and **SI Fig. 9B = SI Fig. 14 D**.

Methods

Reagent and resource table

REAGENT or RESOURCE	SOURCE	Identifier
Antibodies		
Rabbit polyclonal anti-FDFT1 antibody	Invitrogen™	PA5-97741
Rabbit polyclonal anti-vinculin antibody	Invitrogen™	PA5-32639
HRP-conjugated antibody	Invitrogen™	31460
IRDye 680RD	LI-COR	925-68071
Mouse monoclonal anti-Rap 1A antibody	Santa Cruz	sc-373968
anti-HA antibody	Volkmar *et al.*[23]	12CA5
Chemicals and plasmids		
pET-28a(+) vecor containing SQS (31-370) sequence	Genescript	N/A
E. coli BL21 (DE3)	Novagen	N/A
cOmplete protease Inhibitor Cocktail	Roche	4693132001
HiTrap cobalt-chelating TALON crude column	GE Healthcare Bio-Sciences AB	28-9574-96 AD
Thrombin immobilized on agarose	Sigma-Aldrich	RECOMT
Superdex 75 10/300 GL Column	Cytiva	N/A
SYPRO orange	ThermoFisher	
DMSO	Sigma-Aldrich	D8418
MG132	MedChemExpress	HY-13259
MLN4924	MedChemExpress	HY-70062
Chloroquine diphosphate salt	Sigma-Aldrich	C6628
ZLL2-ketone	Sigma-Aldrich	SML1442
LS-102	MedChemExpress	HY-135844
Zaragozic Acid A	Santa Cruz	sc-391058
Cycloheximide	Fisher Scientific	10286291
Methyl-β-cyclodextrin	Sigma-Aldrich	332615
Nonidet P-40	Roche	31408000
TEAB	Sigma-Aldrich	18597
TCEP	Sigma-Aldrich	C4706
Iodoacetamide	Sigma-Aldrich	I1149
TMTpro- 16plex reagents kit	ThermoFisher	A44521
hydroxylamine	ThermoFisher	90115
Acetonitrile	Pierce™	51101
Trifluoroacetic acid	Honeywell™ Fluka™)	14264
Ammonium bicarbonate	Supelco	533005
Formic acid	Pierce™	85174
pSynSRE-T-Luc plasmid	Schneidewind *et al.*[34]	N/A
pRL-TK plasmid	Schneidewind *et al.*[34]	N/A
Lipofectamine 2000	ThermoFisher	11668030
Met/Cys, EXPRE35S35S Protein Labelling Mix	PerkinElmer	NEG772002MC
Protein G resin	Roche	PROTGA-RO

NADPH, Tetrasodium salt	Sigma-Aldrich	481973-25 mg
Farnesyl pyrophosphate (FPP) ammonium salt	Santa Cruz Biotechnologies	sc-200847
Experimental models: Cell lines		
Hela	ATCC	CCL-2™
U2OS	ATCC	
U2OS Flp-In™ T-Rex™	Volkmar *et al.*[23]	N/A
Critical Assay Equipment		
LightCycler® 480 Multiwell Plate 384, white	Roche	N/A
LightCycler 480 II	Roche	N/A
black, flat bottom, non-binding 384 well plate	Corning	3577
Spark Cyto multimode microplate reader	Tecan	N/A
Sep-Pak® Plus C18 cartridges	Waters	WAT020515
SpeedVac	Eppendorf	EP022822993
Fractionation UHPLC system	Thermo Fisher	Dionex U3000
CSH C18 Acquity UPLC M-Class Peptide column	Waters	186007563
EvoTips	EvoSep	EV2003
Evosep One module	EvoSep	EV-1000
Orbitrap Eclipse™ Tribid™ mass spectrometer	ThermoFisher	N/A
EASY-Spray™ C18 column	ThermoFisher	ES804
Orbitrap Fusion™ Tribrid™ mass spectrometer	ThermoFisher	N/A
TriVersa NanoMate nanoelectrospray infusion robot	Advion Biosciences	N/A
White 96-well plate	ThermoFisher	136102
Zetasizer Nano	Malvern	N/A
Critical commercial assays		
CellTiter-Blue Cell Viability assay kit	Promega	G8080
Dual-Glo® Luciferase Assay System	Promega	E2920
Software		
TSA analysis program	Roche	N/A
Prism, Version 9.41	Graphpad Software	N/A
Proteome Discoverer 2.4	ThermoFisher	N/A
LipidXplorer version 1.2.7	Herzog *et al.*[49]	N/A
LipidQ	Nielsen *et al.*[50]	N/A
QuantityOne and Image Lab software packages	Bio-Rad	N/A

Biological experimental procedures

Protein expression, purification and thrombin cleavage:

The expression of the doubly truncated SQS protein was conducted following a reported procedure by Song *et al*.[8] with minor adjustments. In short, a bacterial expression vector pET-28a(+) containing a sequence corresponding to AA 31-370 of the SQS enzyme was bought from Genescript. The expression vector was used to transform *E. coli* BL21 (DE3)RP strain (Novagen) for overexpression. The resulting construct contained a *N*-terminal His_6-tag with a thrombin cleavage site. Bacteria expressing the constructs were cultured in LB medium supplemented with kanamycin (30 *µ*g/mL) at 37 °C, until the cells reached an OD of 0.7 at 600 nm, and were then induced at 37 °C for 4 h by incubation with 0.1 mM isopropyl-1-thio-*D*-galactopyranoside.

Cells were harvested by centrifugation (10 min, 4000 rpm) and resuspended in 40 mL of lysis/elution buffer (20 mM NaH_2PO_4, pH 7.4, 10 mM CHAPS, 2 mM $MgCl_2$, 10% glycerol, 2 mM DTT, 500 mM NaCl and a protease inhibitor cocktail (Roche), disrupted by sonication, and centrifuged at 16000 rpm for 30 min. The supernatant was then applied to a HiTrap cobalt-chelating TALON crude column (GE Healthcare Bio-Sciences AB). Enzyme purification was performed according to the manufacturer's instructions using an Äkta FPLC system. Unbound protein was washed off with 5 mM imidazole. Then the His_6-SQS was eluted with 150 mM imidazole. Purity was confirmed by SDS-PAGE electrophoresis. Fractions containing the pure enzyme were pooled and dialyzed against buffer A (25 mM sodium phosphate, pH 7.4, 20 mM NaCl, 2 mM DTT, 1 mM EDTA, 10% glycerol, 10% methanol), concentrated (2.37 mg/mL) and then stored at -80 °C for *in vitro* assays.

For cleavage of the His_6-tag, thrombin immobilized on agarose (RECOMT) was purchased from Sigma-Aldrich and used following the manufacturers instructions. Shortly, His_6-*h*SQS was transferred into a thrombin-cleavage buffer (50 mM Tris-HCl, pH 8.0, 10 mM $CaCl_2$) and the His_6-tag was cleaved after incubation at room temperature overnight. After centrifugation recovery, the cleaved protein was subjected to a second HiTrap cobalt-chelating TALON crude column to separate the cleaved His_6-tag. Successful cleavage was confirmed by SDS-PAGE analysis. The protein was concentrated using Amicon Ultra Centrifugal Filters (10.000 MWCO) and then stored at -80 °C. Before crystallization attempts, the thawed protein was subjected to a SEC column and transferred into the crystallization buffer (20 mM Tris-HCl, pH 7.3, 2 mM $MgCl_2$, 0.1 mM EDTA, 1 mM DTT, final protein concentration > 8mg/mL).

Differential scanning fluorimetry:

Differential scanning fluorimetry experiments were performed in a buffer composed of 50 mM HEPES pH 7.5 and 5 mM $MgCl_2$ in Milli-Q water. His_6-*h*SQS was diluted to a concentration of 0.5 mg/mL and 8 µL/well of the resulting solution were transferred to a 384-well plate (LightCycler® 480 Multiwell Plate 384, white). Subsequently, SYPRO orange (Thermo Fisher) was added (final concentration 1x SYPRO orange) followed by the addition of the tested compounds at the indicated concentrations (50, 25, 12.5 µM) to a total final volume of 10 µL. The fluorescence intensity was measured in a Roche LightCycler 480 II with an initial incubation at 30 °C for 1 minute followed by acquisition steps of 0.1 °C up to 95 °C with incubation for 1 second at each step. Melting temperatures were calculated with the Roche

TSA analysis program. Exemplary melting curves were plotted using Prism (Graphpad Software, Inc. Version 9.41).

Fluorescence Polarization:

Fluorescence polarization experiments were performed at room temperature in a buffer composed of 50 mM HEPES pH 7.5, 5 mM $MgCl_2$ in a final volume of 30 µl in black, flat-bottom, non-binding 384-well plates (Corning). For competition experiments 20 nM 5-TAMRA-SQSI (or 5 nM 5-TAMRA-KY02111) was mixed with 200 nM of His_6-SQS and incubated for 30 minutes. Meanwhile, a 10-point 1:1 dilution series for the tested compounds was performed from 20 µM in the assay buffer. After 30 minutes, the screening compounds were added at the indicated conentrations and the plate was incubated for 45 minutes. The fluorescence polarization signal was measured using a Spark Cyto multimode microplate reader (Tecan) with filters set at 530 ± 25 nm for excitation and at 590 ± 20 nm for emission. The data was analyzed using GraphPad Prism 9. Curves were fitted by non-linear regression to allow the determination of IC_{50} values with GraphPad Prism 9. The k_d values for the FP probes were determined by curve fitting of a 1:3 protein titration series against 20 nM/5 nM of the respective FP probes using nonlinear regression. The determined values were then used to calculate the k_i values for the respective compounds by applying equations (1) and (2):

$$\mathrm{k_D^I} = \frac{[\mathrm{D^*R}]_{50}\mathrm{IC}_{50}\mathrm{k_D^{D^*}}}{(\mathrm{D^*_T R_T}) + [\mathrm{D^*R}]_{50}(\mathrm{R_T} - \mathrm{D^*_T} + [\mathrm{D^*R}]_{50} - \mathrm{k_D^{D^*}})} \qquad (1)$$

$$[\mathrm{D^*R}]_{50} = \mathrm{D^*_T}\frac{A_S^{50} - A_{D^*}}{A_{D^*R} - A_{D^*}} \qquad (2)$$

Where R_T is the total amount of protein, D^*_T the total amount of the FP probe and $k_D^{D^*}$ the k_d value for the respective FP probe previously determined via Prism. A_{D^*R} is the anisotropy for the protein + fluorophore control well whereas A_{D^*} is the anisotropy for the fluorophore control well. A^{50}_S is the anisotropy at IC_{50} and can be calculated using the values generated by nonlinear regression (3):

$$A_S^{50} = \frac{B + (T - B)}{(1 + 10^{hs})} \qquad (3)$$

Where B is the bottom value and T is the top value. hs is the hill slope.

Cell culture and compound incubation:

HeLa or U2OS cells were purchased from ATCC and cultured in DMEM medium supplemented with 10% FBS and 1% Penicillin/Streptomycin at 37°C in 5% CO_2 atmosphere. For compound testing, cells where harvested from a T175 flask (confluence 90%, passage 3-20) by trypsination and diluted to 2*10^5 cells/mL, and finally transferred to 6-well plate with a final cell count of 4*10^5 cells per well. After attachment overnight, the medium was exchanged and compounds were added to the final indicated concentrations followed by incubation for the indicated time points. For tool compound co-incubation experiments, MG132, MLN4294 and Chloroquine were pre-incubated for 2 hours, Cycloheximide was pre-incubated for 1 hour, and $(ZLL)_2$ketone and LS-102 were simultaneously incubated with the tested compounds. Upon completed incubation, the medium was removed and the cells were washed with 2 mL of ice-cold PBS before being lysed with 150 µL SDS lysis buffer (100 mM Tris–HCl, pH 6.8, 4% (w/v) SDS, 20% (v/v) glycerol). The cell lysates were collected, sonicated

(3 x 20 cycles (1/second)) and the total protein concentration was determined using a Nanodrop (A_{280}). Finally, cell lysates were flash frozen in liquid N_2 and stored at -80 °C.

SDS-PAGE and Western Blot analysis:

Cell lysates were thawed on ice and diluted with 2x loading buffer (100 mM Tris–HCl, pH 6.8, 4% (w/v) SDS, 20% (v/v) glycerol) to a final concentration of 4 mg/mL (max, or the highest possible concentration in a lysate set). To each sample, 2x loading buffer containing bromophenol blue (0.2% (w/v)) and DTT (200 mM) was added to a final ratio of 2:1 (v/v, sample:loading buffer) and heated at 95°C for 5 min for complete protein denaturation. Samples were then loaded onto 4–15% Mini-PROTEAN TGX Protein Gels (4561086, Bio-Rad) and run at 120 V for 1 hour. Protein transfer from gels to polyvinylidene difluoride (PVDF) membranes was carried out using the Trans-Blot Turbo Transfer Kit (1704274, Bio-Rad) according to the manufacturer's instructions. Membranes were subsequently incubated with the blocking solution (5% Skim Milk Powder (10651135, Fisher Scientific) added to tris-buffered saline (TBS) solution (150 mM NaCl (S7653, Sigma-Aldrich), 50 mM Tris pH 7.6, 0.1% Triton™ X-100 (T8787, Sigma-Aldrich)) before the incubation overnight at 4 °C with the primary antibodies for SQS and vinculin. The following day membranes were incubated for 1 h with the HRP-conjugated secondary antibody at room temperature. Successively, the SuperSignal™West Femto Chemiluminescent substrate (10391544, Thermo Scientific™) was added to the membranes before imaging with a Odyssey Fc imaging system (Licor). Image acquisition was performed with Image Studio (LI-COR), quantification of the chemiluminescent intensities of the bands were performed with Empiria studio (LI-COR version 1.3).

Cycloheximide-chase assay

HeLa cells were cultured as described above. One day before compound incubation, 2 mL of a 2.0x10^5 cells/mL solution were added to single cell culture dishes (EP0030700112, Sigma-Aldrich) and incubated overnight. The next day, the medium was refreshed and cells were incubated with either Cycloheximide (100 µg/mL, 355 µM) alone or together with **18** (3 µM). After the indicated time points, cells were lysed by addition of 100 µL SDS-lysis buffer and analyzed via western blotting.

Cell viability assay ± MBCD:

HeLa cells were harvested from a T175 flask (confluence 90%) by trypsination and diluted to 3*10^4 cells/mL with medium. 100 µL/well of the diluted cell solution were transferred into a 96 well plate (Nunc™ Edge™, clear, 167425, Thermo Fisher) and cells were allowed to attach overnight (37 °C, 5% CO_2). The next day, a dilution series starting from the highest concentration was prepared for the tested compounds in DMEM medium (10 % FBS, 1 % PS), or in MBCD-containing DMEM medium (10 % FBS, 1 % PS, 4 mM MBCD). The medium was removed from the cells and 100 µL of the medium including the compounds at indicated concentrations was added (technical triplicates). Alternatively, the cells were washed with pre-warmed PBS before addition of MBCD-containing medium. The cells were incubated for the indicated time points, after which the wells were checked for potential compound precipitation. Cell viability was determined by using the Cell Titer Blue Cell Viability assay kit (G8080, Promega) according to the manufacturer's instructions. Shortly, 10 µL of equilibrated CellTiter-Blue reagent were added per well and the plates were incubated for 60 min at 37 °C. The fluorescence intensity signal was measured using a Spark Cyto multimode microplate reader

(Tecan) with filters set at 560 ± 20 nm for excitation and at 590 ± 20 nm for emission. The background (well without cells) was subtracted from the sample wells and the signals were normalized on DMSO controls. The obtained values were plotted in GraphPad Prism 9.

PROTEOMIC sample preparation:

HeLa cells were cultured and incubated as described above. Here, cells were lysed by addition of 200 µL Nonidet P-40 (NP-40) lysis buffer (0.4 % NP-40 in PBS) followed by three consecutive freeze-thaw cycles in liquid N_2 and storage at -80 °C. The next day, the lysates were thawed on ice and ultracentifuged for 25 minutes at 4 °C and 30000 rpm. The concentration of the supernatant was determined by using the DC assay kit (5000112, Bio-Rad) according to the manufacturer's instructions and the samples were diluted to a final concentration of 2 mg/mL in 75 µL NP-40 lysis buffer. For protein reduction and alkylation, 75 µL of a 100 mM TEAB (1:1, 18597, Sigma-Aldrich, prepared in pre-filtered MilliQ water) solution was added to the samples followed by the addition of 7.5 µL 200 mM TCEP (1:10, C4706, Sigma-Aldrich, prepared in solution of 140 µL TCEP 0.5 M, 140 µL MilliQ water, 70 µL 1 M TEAB). The prepared samples were incubated in a thermoblock at 55 °C for 1 hour and cooled down to room temperature before 7.5 µL of a 375 mM iodoacetamide solution (1:10, I1149, Sigma-Aldrich, prepared in 300 µL of MilliQ water and 75 µL 1 M TEAB) was added followed by incubation in the dark for 30 minutes. Finally, 900 µL of ice-cold acetone was added and each sample was left at -20 °C overnight for protein precipitation. For protein digestion, the thawed samples were centrifuged for 10 minutes at 4 °C and 8000 g. The samples were kept on ice while removing the supernatant and the pellets were dried for 4 hours. After completed drying, 150 µL of a freshly prepared 100 mM TEAB solution were added to solubilize the protein pellets, before the addition of 115 µL of a 0.03 µg/mL trypsin solution (1:80 enzyme:substrate ratio). The samples were incubated at 37 °C overnight at 500 rpm. The next day, the samples were placed in the freezer for 1 minute to stop the digestion. Half of the sample volume corresponding to 75 µg of peptides were successively labelled with TMTpro 16-plex reagents kit. TMT reaction was allowed for 2 hours and quenched with 5% hydroxylamine (90115, Thermo Fisher Scientific). All the samples were pooled and dried in a SpeedVac (EP022822993, Eppendorf) before desalting with Sep-Pak® Plus C18 cartridges (WAT020515, Waters). The peptides were eluted with 40% and 60% of acetonitrile (51101, Pierce™) in 0.1% of trifluoroacetic acid (TFA) (14264, Honeywell™ Fluka™) and dried before injection of 30 µg to the UHPLC system (Dionex U3000) for high-pH fractionation.

The separation of the peptides was carried out at a constant flowrate of 5 µl min^{-1} on a CSH C18 Acquity UPLC M-Class Peptide column, 130 Å, 1.7 µm, 300 µm x 150 mm (186007563, Waters) using a 100 min linear gradient from 5 to 35% of mobile phase B (acetonitrile) with a subsequent 15 min gradient to 70%, before 5 min re-equilibration with 95% of mobile phase A (5mM ammonium bicarbonate (533005, Supelco), pH 10). 60 time-based fractions were pooled in 30 fractions in the collection plates. Clean-up of the fractions was performed by EvoTip according to the manufacturer's instructions.

Global proteomic mass spectrometry (MS) analysis:

For MS sample analysis, the EvoTips (EV2003, EvoSep) were loaded on the Evosep One module (EV-1000, EvoSep) coupled to an Orbitrap Eclipse™ Tribid™ mass spectrometer (Thermo Fisher Scientific). The peptides were loaded onto the EASY-Spray™ C18 column, 2 µm, 100 Å, 75 µm x 15 cm (ES804, Thermo Fisher Scientific) using the standard "30 samples per day" Evosep method. The method eluted the peptides with a 44 min gradient ranging from

5% to 90% acetonitrile with 0.1% formic acid (85174, Pierce™). The MS acquisition was performed in data dependent-MS3 with real-time-search (RTS) and a FAIMS interface switching between CVs of −50 V and −70 V with cycle times of 2 s and 1.5 s, respectively. The data dependent acquisition mode was run in a MS1 scan range between 375 and 1500 *m/z* with a resolution of 120000, and a normalized gain control (AGC) *target* of 100%, with a maximum injection time of 50 ms. RF Lens set at 30%. Filtering of the precursors was performed using peptide monoisotopic peak selection (MIPS), including charge states from 2 to 7, dynamic exclusion of 120 s with ±10 ppm tolerance excluding isotopes, and a precursor fit of 70% in a window of 0.7 m/z with an intensity threshold of 5000. Selected precursors for further MS2 analysis were isolated with a window of 0.7 m/z in the quadrupole. The MS2 scan was performed over a range of 200-1400 *m/z*, collecting ions with a maximum injection time of 35 ms and normalized AGC target of 300% MS2 fragmentation was operated with normalized HCD collision energy at 30%. Fragmentation spectra were searched against the fasta files from the human Uniprot database (reviewed) in the RTS, set with tryptic digestion, TMTpro-16plex as fixed modification on Lysine (K) and N-Terminus together with cysteine (C) carbamidomethylation, and oxidation of methionine (M) as variable modification. 1 missed cleavage and 2 variable modifications were allowed with a maximum search time of 35 ms. FDR filtering was enabled with 1 as Xcorrelation and 5 ppm of precursor tolerance. Precursors identified via RTS in the MS2 scan were further isolated in the quadrupole with a 2 m/z window, maximum injection time of 86 ms and normalized AGC target of 300%. The further MS3 fragmentation was operated with a normalized HCD collision energy at 50% and fragments were scanned with a resolution of 50000 in the range of 100 to 500 m/z. The MS performances were monitored by quality control of an in-house standard of HeLa-cell lysate, both at the beginning and the end of each sample set.

Proteomic data analysis

Mass spectrometric raw files were analyzed with Proteome Discoverer 2.4 (Thermo Fisher Scientific) by using the built-in TMTpro Reporter ion standard quantification workflows. The search was run setting trypsin as enzyme (allowing maximum 2 missed cleavages), TMTpro16plex and carbamidomethylation of cysteine (C) as fixed modifications, while methionine (M) oxidation and acetylation of protein N-termini as variable modifications. Sequest search engine was used to match the MS^3 spectra in the Uniprot homo sapiens database (Swiss-Prot reviewed including isoforms) with a precursor mass tolerance of 10 ppm and fragment mass tolerance of 0.6 Da. Percolator was used to score the results and to filter at 1% FDR. Reporter ion quantification was performed on MS^3 spectra by applying isotopic error correction. Normalization and scaling were not included in the Proteome Discovery analysis and were performed successively on the protein result table. Here, proteins and proteins not identified as Master Protein or as Master Protein Candidate were removed first. Moreover, all the proteins identified with a sum of Unique + Razor peptides below 2 were removed. Loading normalization was performed summing the intensities for each TMT channel and calculating the respective correction factor on the average of the summed intensities. Hence, each protein intensity was normalized for the respective channel correction factor. Normalized intensities were further used to calculate the average among the replicates for one label, which was then used to obtain the fold changes (FC) of compound treated samples compared to DMSO control samples. The obtained values were $\log_2$ transformed. A two-sided T-test was performed on the normalized data and obtained p-values were $-\log_{10}$ transformed. Volcano plots were obtained plotting the $\log_2$ FC vs $-\log_{10}$ (p-value) in both Prism

9 (Graphpad Software, Inc. Version 9.41) and VolcanoseR. The original MS raw data are deposited to MassIVE with the accession ID MSV000092115.

Lipidomic sample preparation

HeLa cells were harvested from multiple T175 flasks (confluence 90%) by trypsination and diluted to 2*10^5 cells/mL with DMEM medium (10 % FBS, 1 % P/S). Then the cells were plated in 10 cm dishes with a final cell count of 2*10^6 cells. After attachment overnight, the medium was replaced with fresh medium followed by compound incubation at the indicated concentrations for 18 h. For sample collection, the medium was removed and the cells were washed with 1x PBS, followed by trypsination. The detached cells were collected with medium and subsequently diluted to a concentration of 3*10^6 cells/mL. Then, each sample was centrifuged and washed with cold ammonium bicarbonate buffer (1 mL, 155 mM) twice. Lastly, the cells were resuspended in ammonium bicarbonate (1 mL, 155 mM) and stored at -80 °C.

Lipidomics analysis

To Eppendorf tubes with 2*10^5 HeLa cells in 200µl 155mM ammonium bicarbonate were added 1000 µl chloroform/methanol (2:1, v/v, Rathburn Chemicals Ltd) and spiked with 12.5 µl of synthetic lipid standards (avanti polar lipids, details in table 1). Lipid extraction was executed on ice or 4°C according to our previously reported protocol.[9] Extracted lipid were subjected to FT MS and FT MS/MS analysis on an Orbitrap Fusion Tribrid mass spectrometer (Thermo Fisher Scientific) coupled to TriVersa NanoMate (Advion Biosciences, USA) a direct nanoelectrospray infusion robot. The lipid extract were mixed with positive and negative ionization mode solvents according to our previously reported protocol. Mass spectrometric settings in positive and negative mode: The FT MS analysis operated with $R_{m/z\ 200}$ = 500,000; AGC value of 1×10^5 ; maximum injection time of 50 ms; three microscan and FT MS/MS operated with $R_{m/z\ 200}$ = 15,000 ; AGC value of 2.5×10^4 ; maximum injection time of 66 ms; one microscan, while the direct infusion settings of the robot follows our according to our previously reported protocol. Lipid identification was performed with LipidXplorer version 1.2.7 and absolute quantification was performed using homemade software LipidQ.[9] Raw data was deposited to the Metabolights server with accession ID MTBLS7990.

Lipid annotation

Lipid species are annotated according to their sum composition, where glycerolipid and glycerophospholipid species denoted as: <lipid class>< total number of C in fatty acid moieties>:<total number of double bonds in fatty acid moieties>(e.g., PS 34:1). Ether glycerophospholipid species are denoted with “O-”(e.g., PS O-34:1). While sphingolipid species are denoted as <lipid class><total number of C in the long-chain base and fatty acid moiety>:<total number of double bonds in the long-chain base and fatty acid moiety>;<total number of OH groups in the long-chain base and fatty acid moiety>(e.g., Cer 34:1;2).[10–13]

SREBP reporter gene assay

The SREBP reporter gene assay was performed by applying a modified procedure.[7] Shortly, a pSynSRE-T-Luc plasmid, which contains a promotor for 3-hydroxy-3-methylglutaryl-CoenzymA (HMG-CoA) synthase containing the SREBP responsive region linked to a firefly luciferase[14], was utilized. Additionally, a pRL-TK (*Renilla* luciferase) vector was used for normalization. Both plasmids were gifts from Prof. Timothy Osborne. Shortly, for transient transfection, HeLa cells cultured in DMEM (10 % FBS) without antibiotics were transfected by means of lipofection using Lipofectamine 2000 (11668030, Thermo Fisher Scientific).

1.5*10^6 cells per T25 flask were transfected with 3 µg of pSyn-SRE-T-luc and 1 µg of pRL-TK using a DNA:LF ratio of 1:3 (total amounts). The cells were incubated for 24 h and afterwards replated in a white 96-well plate (136102, Nunclon®, Thermo Fisher Scientific) with a final cell count of 2.5*10^4 cells per well. Cell attachment was allowed for 1 h before compound addition with the indicated concentrations and incubation for 18 h. The Luciferase activities were measured using the Dual-Glo® Luciferase Assay System (E2920, Promega) according to the manufacturer's instructions. The signal for the firefly luciferase was divided by the *Renilla* luciferase signal to obtain normalized signal ratios which were then related to DMSO.

Differential Light Scattering (DLS) assay

DLS experiments were performed to detect possible *in vitro* aggregation of SQS upon treatment with KY02111. Shortly, stored recombinant SQS (without His_6-tag) was filtered using a Superdex 75 10/300 GL Column (Cytiva) to remove any aggregates formed by the freeze-thawing process. Freshly filtered protein was then diluted to 0.25 mg/mL in buffer (20 mM Tris-HCl, pH 7.3, 2 mM $MgCl_2$, 0.1 mM EDTA), slowly filtered through 0.2 µm pore size filter (6876-2502, Whatman®, GE Healthcare Life Sciences)) and added to a polystyrene cuvette (67.741, Sarstedt). The sample was allowed to equilibrate to room temperature for 2 min before Zetasizer Nano (Malvern) was used to measure and analyse the particle size. SQS alone was found to have a diameter (d) of about 6 nm. This measurement was performed for every new sample before compound addition at the indicated concentrations. The data was plotted as either intensity or volume vs size with Prism (Graphpad Software, Inc. Version 9.41).

ER membrane insertion assay

Pulse-chase assays of U2OS Flp-In™ T-Rex™ cells (WT/ΔEMC6) expressing $HA:SQS_{opsin}$ were carried out as described previously by Volkmar *et al.*[15] Briefly, cells were starved in methionine/cysteine-free DMEM (Lonza) plus 10% dialyzed FCS (10 min) and metabolically labelled by adding ^{35}S-methionine/cysteine [Met/Cys, EXPRE^{35}S^{35}S Protein Labelling Mix (PerkinElmer); 150 µCi/10 plate] for 10 min. After removal of media, cells were rinsed thrice with PBS and incubated in DMEM plus 10% FCS and methionine/cysteine (50 mM each) for the indicated times (0 and 40 min). Cells were collected and resuspended in lysis buffer (50 mM Tris-HCl pH 7.5, 150 mM NaCl, 5 mM EDTA, 2 mM NEM, 1x cOmplete™ Protease Inhibitor Cocktail (Roche)) + 1% Triton X-100 (v/v) and post-nuclear fractions pre-cleared overnight using unconjugated Sepharose beads. $HA:SQS_{opsin}$ was immunoprecipitated from the detergent-soluble fraction using 70 µl of 50% protein G resin (Roche) slurry and anti-HA antibody (12CA5). Immunoprecipitated material was resuspended in 2x Laemmli buffer plus 20 mM DTT, separated by 4-15% gradient SDS-PAGE, and the radiolabelled proteins visualised using a phosphoimager and the QuantityOne and Image Lab software packages (Bio-Rad). To deglycosylate samples, EndoHf (NEB, 500 units) was added to Laemmli eluates and incubated for 30 min at 37˚C prior to loading.

SQS activity assay

The experimental conditions for the *in vitro* activity assay were adapted from a previously published procedure.[16] Shortly, stored recombinant SQS (without His_6-tag) was thawed and ultracentrifuged at 10000g for 10 minutes at 4°C. The supernatant

was collected and the protein concentration was determined using a Nanodrop (A_{280}). A 0.0048 mg/mL SQS stock was prepared in assay buffer (50 mM Tris, pH 7.5, 10 mM $MgCl_2$, 1 mM DTT, 1mg/mL BSA). Compound stocks were pre-diluted in DMSO so that every compound stock in assay buffer contained the same DMSO concentration (final conc. 0.1 %). A 2x FPP (sc-200847, Santa-Cruz) and NADPH (481973, Sigma-Aldrich) 4:1 stock was prepared in assay buffer (80/20 µM, final conc. 40/10 µM). During the preparation process, the pre-diluted stock solutions were kept on ice. The SQS stock was mixed with the compound stocks 6:1 (final SQS conc. 0.004 mg/mL) and incubated at rt for 10 min. Meanwhile, the 2x FPP/NADPH stock was added to a black, flat-bottom, non-binding 384-well plate (Corning). After incubation, the SQS-compound solutions were added 1:1 to the plate in according triplicate wells. The fluorescence signal was measured every 60 seconds over 20 minutes using a Spark Cyto multimode microplate reader (Tecan) with filters set at 340 nm for excitation and at 465 nm for emission, while the temperature was set to 37°C. The data was analyzed using Prism (Graphpad Software, Inc. Version 9.41). For the %activity data, (SI Fig. 5B), the mean slope over 20 minutes for each condition was normalized to the DMSO (100%) or no SQS (0%) control (n = 3 biological replicates).

Chemical Synthesis

General directions

All reactions were run under a N_2 atmosphere unless otherwise specified and were monitored by thin layer chromatography (TLC) and/or reversed-phase ultra-performance liquid chromatography mass spectrometry (RP-UPLC-MS). Commercially available reagents were purified according to standard procedures or were used as received from Sigma Aldrich, Alfa Aesar, Acros Organics, Combi-Blocks, Fisher Scientific, Strem, and Merck. All solvents used were of HPLC quality and dry solvents (DCM, Et2O, THF, and Toluene) were obtained from a PureSolv system (Innovative Technology, Tronyx). Methanol was stored over activated 3 Å molecular sieves before use. Analytical TLC was conducted on Merck aluminium sheets covered with silica (C60). The plates were either visualized under UV-light or stained by dipping in a developing agent followed by heating. $KMnO_4$ [$KMnO_4$ (3 g) in water (300 mL), K_2CO_3(20 g) and 5% aqueous NaOH (5 mL)] and cerium molybdate [$Ce(NH_4)_2(NO_3)_6$ (0.5g), $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (24.0 g), and H_2SO_4 (24.0 g)] were used as developing agents. Flash column chromatography was performed using Merck Geduran® Si 60 (40-63 µm) silica gel. All new compounds were characterized by NMR, MS (ESI) and HRMS (ESI) (byproducts were not fully characterized). Structural assignments were made when possible for new compounds using COSY, HSQC, HMBC, H2BC, and NOESY spectra where appropriate. For the recording of ^{1}H NMR and ^{13}C NMR a Bruker Ascend with a Prodigy cryoprobe (operating at 400 MHz for proton and 100 MHz for carbon) was used. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) in Hz. Spectra were referenced using the residual solvent peaks of the respective solvent; DMSO (δ 2.50 ppm for ^{1}H NMR and δ 39.52 ppm for ^{13}C NMR), $CDCl_3$ (δ 7.26 ppm for 1H NMR and δ 77.16 ppm for ^{13}C NMR), CD_3OD (δ 3.31 ppm for ^{1}H NMR and δ 49.00 ppm for ^{13}C NMR). The following abbreviations were used to report peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, sept = septet, m = multiplet, bs = broad singlet. Analytical RP-UPLC-MS (ESI) analysis was performed on a S2 Waters AQUITY RP-UPLC system equipped with a diode array detector using an Thermo Accucore C18 column (d 2.6 µm, 2.1 x 50 mm; column temp: 50 °C; flow: 1.0 mL/min). Eluents A (0.1% HCO_2H in H_2O) and B (0.1% HCO_2H in MeCN) were used in a linear gradient (5% B to 100% B) in 2.4 min and then held for 0.1 min at 100% B (total run time: 2.6 min). The LC system was coupled to a SQD mass spectrometer. Preparative RP-HPLC was carried out on a Waters Alliance reversed-phase HPLC system consisting of a Waters 2545 Binary Gradient Module equipped with an xBridge BEH C18 OBD Prep Column (130 A, 5 µm, 30 x 150 mm) operating at 20 °C and a flow rate of 20 mL/min, a Waters Photodiode Array Detector (detecting at 210-600 nm), a Waters UV Fraction Manager, and a Waters 2767 Sample Manager. Eluents A1 (0.1% HCO_2H in H_2O) and B1 (0.1% HCO_2H in MeCN) were used. Analytical LC-HRMS (ESI) analysis was performed on a Waters Alliance 2695 system. Samples were injected directly and the LC system was coupled to a Waters LCT Premier XE Micromass equipped with a Lock Mass probe operating in positive electrospray mode. Eluents A (0.1%HCO_2H in H2O) and B (0.1% HCO_2H in MeCN) were used in a 1:1 ratio for a total run time of 2 min. 17 Chiral HPLC was run on a Waters 2695 Alliance Separations module with a Waters 2996 PhotoDiode Array detector, equipped with a ChiralPak AD-H column (5 µM, 250 x 4.6 mm).

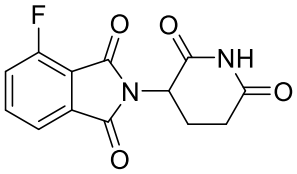
Experimental data

Note for active site binding compounds**:** The utilized SQS ligand is known to produce a set of atropoisomers due to hindered rotation around the C3-N bond in the presence of the *t*-butyl group. Additionally we identified a second pair of atropoisomers in DMSO-d_6 which we analyzed via variable temperature (VT) NMR and 2D NMR. The data is presented and discussed in SI Fig. 3. Due to the presence of 4 isomers in DMSO-d_6, we could not clearly assign all observed peaks for compounds based on SQSI. Therefore only characteristic peaks are highlighted in the data, where all 4 isomers are included, SQSI was fully assigned (SI Fig. 3D).

Pomalidomide as well as Boc-protected pomalidomide-linker conjugates were synthesized and characterized as previously described[1]. VH032 as well as Boc-protected VH032-linker conjugates were synthesized by a slightly modified reported procedure (see general procedures: amide coupling A).[3] Boc-protected adamantane-linker conjugates were synthesized via the general amide coupling A procedure and characterized by comparison with previously reported data.[17] New compounds were fully characterized.

Pomalidomide

2-(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione **SI1**[1]

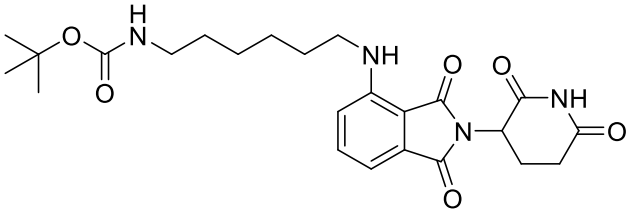


^{1}H NMR (400 MHz, DMSO-d_6): δ 11.16 (s, 1H), 8.02 – 7.90 (m, 1H), 7.82 – 7.69 (m, 2H), 5.17 (dd, *J* = 12.9, 5.4 Hz, 1H), 2.96 – 2.82 (m, 1H), 2.69 – 2.53 (m, 2H), 2.12 – 2.01 (m, 1H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{13}H_{10}FN_2O_4^+$: 278.1; found: 276.9.

S_NAr for the synthesis of pomalidomide-linker conjugates

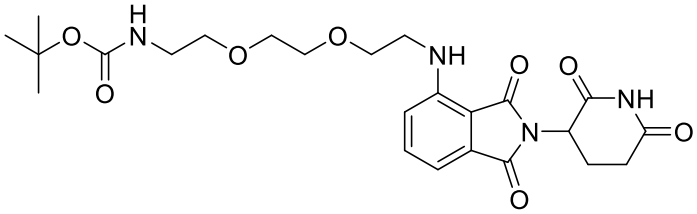
The mono-Boc protected linker (1.0 equiv.) was dissolved in dry DMSO (15 mL) and DIPEA (4.0 eq) was added. Then, 4-fluoro-thalidomide (1.0 eq) was added, and the mixture was stirred at 90 °C for 6 h. After cooling to rt, the yellow or green mixture was partitioned between half-saturated brine (100 mL) and EtOAc (3 × 50 mL). The combined organic layers were further washed with saturated NH_4Cl solution, 5% LiCl solution, and brine (each 50 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc 1:1 to 1:2) to give a yellow solid.

tert-butyl (6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)carbamate **SI2**[1]



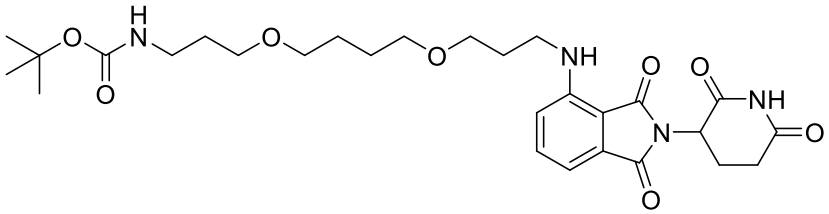
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.54 – 7.49 (m, 1H), 7.12 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 4.97 – 4.90 (m, 1H), 4.53 (s, 1H), 3.29 (t, *J* = 7.0 Hz, 2H), 3.14 (s, 2H), 2.96 – 2.71 (m, 3H), 2.08 – 1.97 (m, 1H), 1.75 – 1.57 (m, 4H), 1.53 (q, *J* = 7.3 Hz, 2H), 1.47 (s, 9H), 1.45(m, 2H) ppm. One signal for NH is missing due to H-D exchange. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{24}H_{33}N_4O_6^+$: 473.2; found: 473.0.

tert-butyl(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)carbamate **SI3**[1]



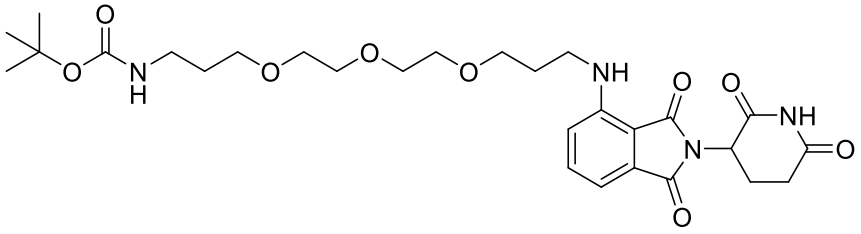
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.54 – 7.49 (m, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H), 5.09 (s, 1H), 4.97 (s, 1H), 3.74 (t, *J* = 5.3 Hz, 2H), 3.67 (hept, *J* = 2.7 Hz, 4H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.49 (t, *J* = 5.3 Hz, 2H), 3.33 (t, *J* = 5.2 Hz, 2H), 2.93 – 2.71 (m, 3H), 2.08 – 1.97 (m, 1H), 1.45 (s, 9H) ppm. One signal for NH is missing due to H-D exchange. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{24}H_{33}N_4O_8^+$: 505.2; found: 505.1.

tert-butyl(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4 yl)amino)propoxy)butoxy)propyl)carbamate **SI4**[1]



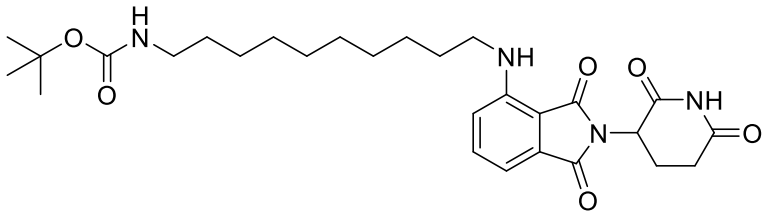
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.54 – 7.49 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.47 (s, 1H), 4.93 (dd, *J* = 12.0, 5.3 Hz, 1H), 3.56 (t, *J* = 5.7 Hz, 2H), 3.52 – 3.39 (m, 8H), 3.23 (q, *J* = 6.2 Hz, 2H), 2.96 – 2.70 (m, 3H), 2.08 – 1.97 (m, 1H), 1.94 (p, *J* = 6.2 Hz, 2H), 1.76 (p, *J* = 6.3 Hz, 2H), 1.72 – 1.61 (m, 4H), 1.46 (s, 9H) ppm. One signal for NH is missing due to H-D exchange. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{28}H_{41}N_4O_8^+$: 561.3; found: 561.2.

tert-butyl (3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)propyl)carbamate **SI5**[1]



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.54 – 7.49 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.93 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.58 – 3.41 (m, 10H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.24 (q, *J* = 5.8 Hz, 2H), 2.96 – 2.68 (m, 3H), 2.08 – 1.97 (m, 1H), 1.96 (p, *J* = 6.2 Hz, 2H), 1.77 (p, *J* = 6.2 Hz, 2H), 1.46 (s, 9H) ppm. Two signals for NH are missing due to H-D exchange. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{28}H_{41}N_4O_9^+$: 577.3; found: 577.3.

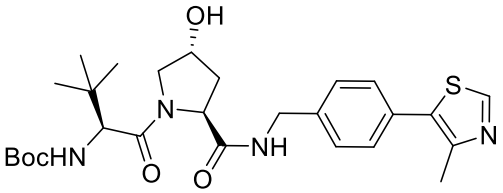
tert-butyl (10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)carbamate **SI6**[1]



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.54 – 7.49 (m, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 4.98 – 4.89 (m, 1H), 4.54 (s, 1H), 3.28 (t, *J* = 7.0 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 2.98 – 2.68 (m, 3H), 2.08 – 1.97 (m, 1H), 1.68 (p, *J* = 7.1 Hz, 4H), 1.47 (s, 9H), 1.42 (d, *J* = 8.3 Hz, 2H), 1.37 – 1.26 (m, 10H) ppm. One signal for NH is missing due to H-D exchange. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{28}H_{41}N_4O_6^+$: 529.3; found: 529.3.

VH032[3]

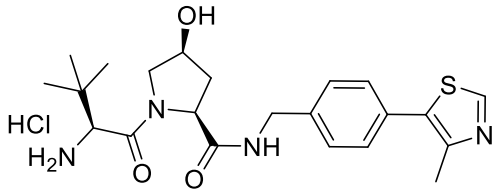
tert-butyl ((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate **SI11**



^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.58 (t, *J* = 6.1 Hz, 1H), 7.44 – 7.33 (m, 4H), 6.46 (d, *J* = 9.3 Hz, 1H), 5.15 (d, *J* = 3.5 Hz, 1H), 4.49 – 4.33 (m, 3H), 4.23 (dd, *J* = 15.8, 5.6 Hz, 1H), 4.15 (d, *J* = 9.3 Hz, 1H), 3.70 – 3.52 (m, 2H), 2.44 (s, 3H), 2.09 – 1.99 (m, 1H), 1.95 – 1.84 (m, 1H), 1.38 (s, 9H), 0.93 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{27}H_{39}N_4O_5S^+$: 531.3; found: 531.6.

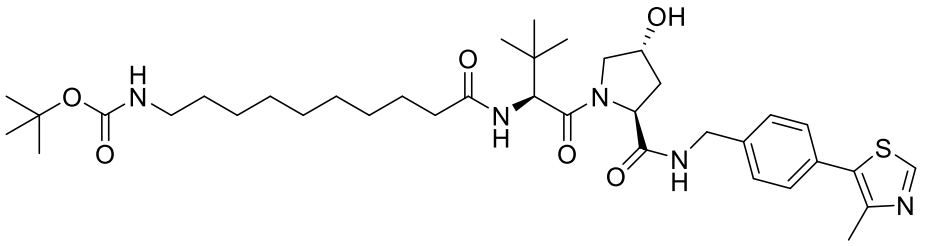
***cis*-VH032 amine hydrochloride**[18]

(2*S*,4*S*)-1-((*S*)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide hydrochloride **SI12**



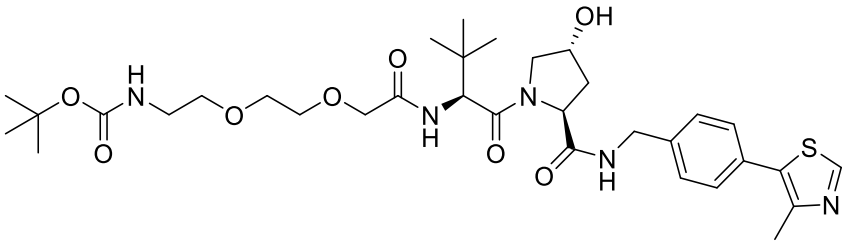
^{1}H NMR (400 MHz, MeOD): δ 9.96 (s, 1H), 7.60 – 7.50 (m, 5H), 4.65 – 4.52 (m, 2H), 4.48 – 4.36 (m, 2H), 4.04 (s, 1H), 3.95 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.62 (dd, *J* = 10.5, 4.8 Hz, 1H), 2.60 (s, 3H), 2.59 – 2.46 (m, 1H), 2.05 – 1.92 (m, 1H), 1.13 (s, 9H) ppm. **^{13}C NMR** (101 MHz, MeOD): δ 174.4, 168.7, 156.6, 142.5, 142.4, 137.4, 130.5, 129.5, 128.1, 71.2, 61.0, 60.2, 57.2, 43.7, 38.0, 35.6, 26.7, 13.1 ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{22}H_{31}N_4O_3S^+$: 431.2; found: 431.5.

tert-butyl (10-(((*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)-10-oxodecyl)carbamate **SI13**[3]



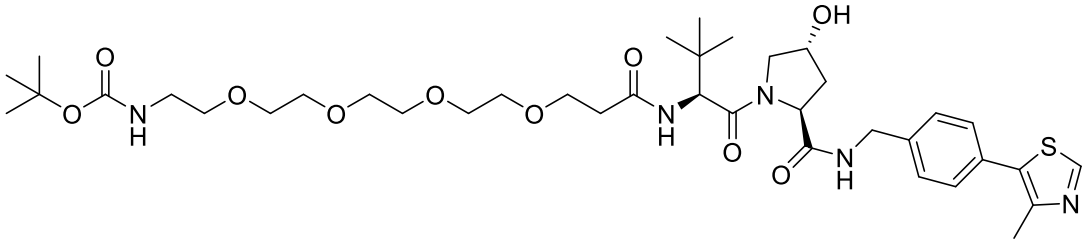
^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.40 (q, *J* = 8.2 Hz, 4H), 6.74 (t, *J* = 5.8 Hz, 1H), 5.12 (d, *J* = 3.4 Hz, 1H), 4.54 (d, *J* = 9.3 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.37 – 4.33 (m, 1H), 4.21 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.71 – 3.60 (m, 2H), 2.87 (q, *J* = 6.6 Hz, 2H), 2.44 (s, 3H), 2.31 – 2.18 (m, 1H), 2.15 – 1.98 (m, 2H), 1.95 – 1.84 (m, 1H), 1.56 – 1.39 (m, 2H), 1.36 (s, 9H), 1.22 (s, 12H), 0.93 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{37}H_{58}N_4O_5S^+$: 700.4; found: 700.8.

tert-butyl (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)carbamate **SI14**



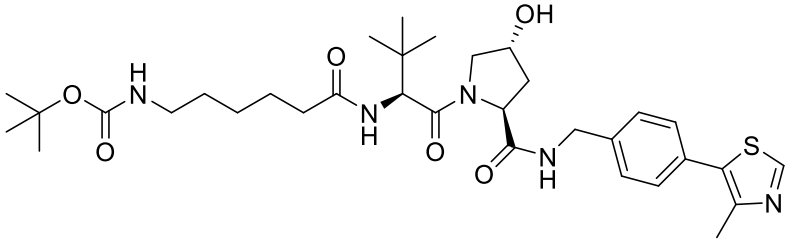
^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.57 (t, *J* = 6.0 Hz, 1H), 7.48 – 7.37 (m, 4H), 6.76 (t, *J* = 5.8 Hz, 1H), 5.15 (d, *J* = 3.4 Hz, 1H), 4.57 (d, *J* = 9.5 Hz, 1H), 4.46 – 4.33 (m, 3H), 4.26 (dd, *J* = 15.8, 5.7 Hz, 1H), 3.96 (s, 2H), 3.69 – 3.50 (m, 7H), 3.40 (dt, *J* = 6.9, 3.8 Hz, 2H), 3.08 (q, *J* = 6.0 Hz, 2H), 2.44 (s, 3H), 2.11 – 2.01 (m, 1H), 1.96 – 1.85 (m, 1H), 1.35 (s, 9H), 0.94 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{33}H_{50}N_4O_8S^+$: 676.3; found: 676.8.

tert-butyl ((*S*)-17-((2*S*,4*R*)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidine-1-carbonyl)-18,18-dimethyl-15-oxo-3,6,9,12-tetraoxa-16-azanonadecyl)carbamate **SI15**[3]



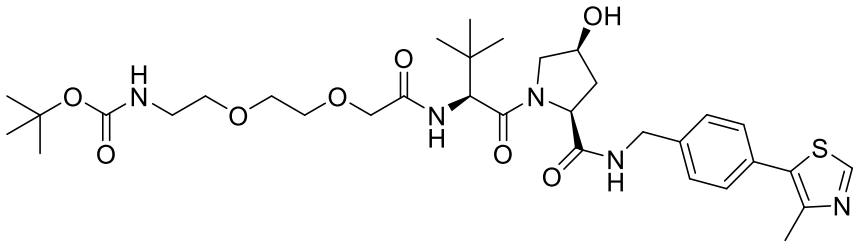
^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.92 (d, *J* = 9.4 Hz, 1H), 7.40 (q, *J* = 8.4 Hz, 4H), 6.74 (t, *J* = 5.8 Hz, 1H), 5.13 (d, *J* = 3.5 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.38 – 4.31 (m, 1H), 4.21 (dd, *J* = 15.9, 5.5 Hz, 1H), 3.72 – 3.54 (m, 4H), 3.49 (d, *J* = 3.1 Hz, 12H), 3.36 (t, *J* = 6.1 Hz, 2H), 3.05 (q, *J* = 6.0 Hz, 2H), 2.60 – 2.50 (m, 1H), 2.44 (s, 3H), 2.41 – 2.29 (m, 1H), 2.09 – 1.96 (m, 1H), 1.95 – 1.84 (m, 1H), 1.36 (s, 9H), 0.93 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{38}H_{60}N_5O_{10}S^+$: 778.4; found: 777.8.

tert-butyl (7-(((*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)-7-oxoheptyl)carbamate **SI16**[3]



^{1}H NMR (400 MHz, DMSO): δ 8.98 (s, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.84 (d, *J* = 9.3 Hz, 1H), 7.40 (q, *J* = 8.3 Hz, 4H), 6.74 (t, *J* = 5.7 Hz, 1H), 5.12 (d, *J* = 3.5 Hz, 1H), 4.54 (d, *J* = 9.3 Hz, 1H), 4.50 – 4.39 (m, 2H), 4.39 – 4.30 (m, 1H), 4.21 (dd, *J* = 15.9, 5.4 Hz, 1H), 3.71 – 3.60 (m, 2H), 2.87 (q, *J* = 6.6 Hz, 2H), 2.44 (s, 3H), 2.30 – 2.18 (m, 1H), 2.16 – 1.96 (m, 2H), 1.95 – 1.84 (m, 1H), 1.55 – 1.39 (m, 2H), 1.36 (s, 12H), 1.26 – 1.12 (m, 3H), 0.93 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{34}H_{52}N_5O_6S^+$: 657.4; found: 657.4.

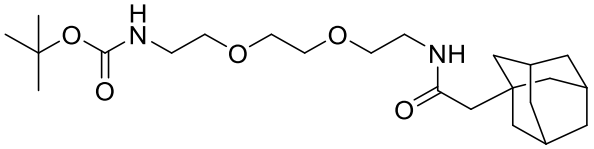
tert-butyl (2-(2-(2-(((S)-1-((2S,4S)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)carbamate **SI17**



2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-oic acid (1.0 equiv., 0.44 mmol) was dissolved in DCM (2 mL) and EDC x HCl (3.0 equiv.) and HOBt x H_2O (1.5 equiv.) were added. After stirring for 30 min, the solution was cooled to 0°C and *cis*-VH032 amine hydrochloride **SI12** (1.0 equiv., 0.44 mmol) and DIPEA (3.0 equiv.), dissolved in DCM (2 mL), were added to the ligand. The combined mixture was stirred at rt for 2h. After the reaction was finished as indicated by TLC (DCM/MeOH 95:5), the mixture was diluted with water (10 ml) and the organics were extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash silica gel column chromatography (DCM/MeOH 98:2 to 95:5) to give the title compound as a white solid (112.00 mg, 38%); **Rf** = 0.51 (DCM/MeOH 95:5); (**^{1}H NMR** (400 MHz, DMSO): δ 8.98 (s, 1H), 8.69 – 8.61 (m, 1H), 7.43 – 7.35 (m, 4H), 6.79 – 6.71 (m, 1H), 5.45 (d, *J* = 7.2 Hz, 1H), 4.52 (d, *J* = 9.2 Hz, 1H), 4.47 – 4.34 (m, 2H), 4.33 – 4.19 (m, 2H), 3.97 – 3.84 (m, 3H), 3.63 – 3.51 (m, 4H), 3.49 – 3.36 (m, 3H), 3.07 (q, *J* = 6.0 Hz, 2H), 2.44 (s, 3H), 2.40 – 2.29 (m, 1H), 1.75 (dt, *J* = 12.3, 6.0 Hz, 1H), 1.35 (s, 9H), 1.29 – 1.20 (m, 1H), 0.95 (s, 9H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.2, 169.4, 168.9, 155.6, 151.5, 147.8, 139.1, 131.1, 129.8, 128.7, 127.5, 77.6, 70.4, 69.5, 69.3, 69.0, 58.6, 55.8, 55.6, 41.8, 36.9, 35.2, 28.2, 26.2, 15.9 ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{33}H_{49}N_5O_8S^+$: 676.3; found: 577.0 (Boc group removed in acidic run). **Optical Rotation:** $[\alpha]_D^{20}$ = -12.98 (c = 0.91, EtOH).

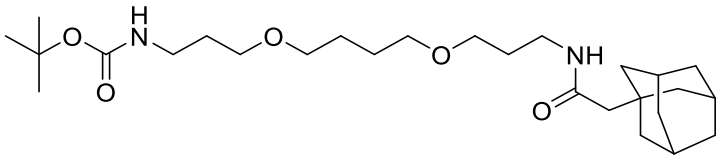
Hydrophobic tags

tert-butyl (2-(2-(2-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)ethoxy)ethoxy)ethyl)carbamate **SI7**[17]



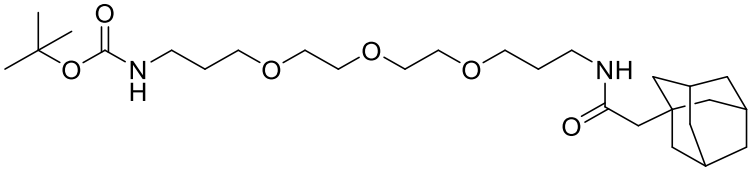
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (s, 1H), 5.02 (s, 1H), 3.69 – 3.54 (m, 8H), 3.48 (q, *J* = 5.1 Hz, 2H), 3.34 (s, 2H), 2.02 – 1.95 (m, 5H), 1.76 – 1.61 (m, 12H), 1.48 (s, 9H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{23}H_{41}N_2O_5^+$: 425.3; found: 425.3.

tert-butyl (3-(4-(3-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)propoxy)butoxy)propyl)carbamate **SI8**



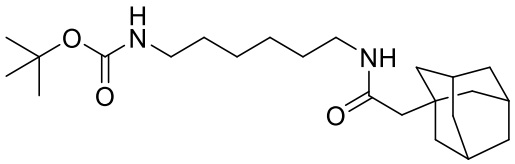
The adamantane-carbaxylic acid (1.0 equiv., 1.0 mmol) was dissolved in DCM (2 mL) and EDC x HCl (3.0 equiv.) and HOBt x H_2O (1.2 equiv.) were added. After stirring for 5 min, the respective mono-Boc protected linker (1.0 equiv., 1.0 mmol) and DIPEA (3.0 equiv.) were dissolved in DCM (4 mL) and added to the ligand. The combined mixture was stirred at rt overnight. After the reaction was finished as indicated by TLC (DCM/MeOH 9:1), the mixture was diluted with water (10 ml) and the organics were extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash silica gel column chromatography (DCM/MeOH 98:2 to 95:5) to give the title compound as a colorless oil (344 mg, 70%). **Rf** = 0.57 (DCM/MeOH 9:1). **^{1}H NMR** (400 MHz, DMSO): δ 7.63 (t, *J* = 5.6 Hz, 1H), 6.75 (t, *J* = 5.7 Hz, 1H), 3.53 – 3.43 (m, 1H), 3.41 – 3.31 (m, 7H), 3.05 (q, *J* = 6.6 Hz, 2H), 2.95 (q, *J* = 6.6 Hz, 2H), 1.90 (s, 3H), 1.79 (s, 2H), 1.68 – 1.46 (m, 20H), 1.37 (s, 9H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 170.2, 155.4, 132.7, 70.3, 68.2, 50.6, 42.6, 37.7, 36.9, 36.1, 32.6, 30.2, 30.0, 28.7, 28.5, 26.5 ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{27}H_{49}N_2O_5^+$: 481.4; found: 481.3.

tert-butyl (1-((3r,5r,7r)-adamantan-1-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)carbamate **SI9**



The adamantane-carbaxylic acid (1.0 equiv., 1.0 mmol) was dissolved in DCM (2 mL) and EDC x HCl (3.0 equiv.) and HOBt x H_2O (1.2 equiv.) were added. After stirring for 5 min, the respective mono-Boc protected linker (1.0 equiv., 1.0 mmol) and DIPEA (3.0 equiv.) were dissolved in DCM (4 mL) and added to the ligand. The combined mixture was stirred at rt overnight. After the reaction was finished as indicated by TLC (DCM/MeOH 9:1), the mixture was diluted with water (10 ml) and the organics were extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash silica gel column chromatography (DCM/MeOH 98:2 to 95:5) to give the title compound as a colorless oil (432 mg, 85%). **Rf** = 0.57 (DCM/MeOH 9:1). **^{1}H NMR** (400 MHz, DMSO): δ 7.63 (t, *J* = 5.7 Hz, 1H), 6.75 (t, *J* = 5.7 Hz, 1H), 3.54 – 3.42 (m, 7H), 3.38 (q, *J* = 6.6 Hz, 4H), 3.05 (q, *J* = 6.5 Hz, 2H), 2.95 (q, *J* = 6.6 Hz, 2H), 1.93 – 1.87 (m, 3H), 1.80 (s, 2H), 1.69 – 1.51 (m, 17H), 1.37 (s, 9H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 170.2, 156.0, 77.8, 70.2, 70.0, 70.0, 68.6, 68.6, 50.5, 42.6, 37.7, 36.9, 36.1, 32.6, 30.2, 30.0, 28.7, 28.5 ppm. **HRMS** (ESI) *m/z* [M + Na] calcd for $C_{27}H_{49}N_2O_7Na^+$: 519.3405; found: 519.3408.

tert-butyl (6-(2-((3r,5r,7r)-adamantan-1-yl)acetamido)hexyl)carbamate **SI10**[17]

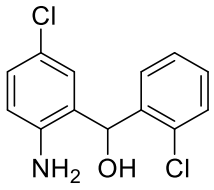


^{1}H NMR (400 MHz, DMSO): δ 7.61 (t, *J* = 5.6 Hz, 1H), 6.75 (t, *J* = 5.7 Hz, 1H), 2.99 (q, *J* = 6.7 Hz, 2H), 2.88 (q, *J* = 6.6 Hz, 2H), 1.93 – 1.87 (m, 3H), 1.79 (s, 2H), 1.68 – 1.61 (m, 3H), 1.61 – 1.51 (m, 9H), 1.36 (s, 9H), 1.37 – 1.30 (m, 4H), 1.29 – 1.15 (m, 4H) ppm. **LCMS** (ESI) *m/z* [M + H] calcd for $C_{23}H_{41}N_2O_3^+$: 393.3; found: 393.3.

SQSI Ligands

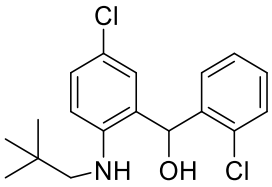
SQSI was synthesized following a previously reported procedure (SI Fig.1).[4]

(2-amino-5-chlorophenyl)(2-chlorophenyl)methanol **SI18**[4]



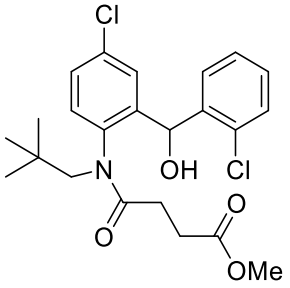
Rf = 0.51 (hexane/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.47 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.41 (dd, *J* = 7.0, 2.2 Hz, 1H), 7.37 – 7.23 (m, 2H), 7.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.15 (s, 1H) ppm. OH and NH2 peaks missing due to proton-deuterium exchange.; **^{13}C NMR** (101 MHz, $CDCl_3$): δ 143.4, 138.4, 133.0, 129.8, 129.5, 128.8, 128.6, 127.6, 127.4, 127.3, 123.2, 117.8, 70.4 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{12}Cl_2O^+$: 268.0; found: 268.4.

(5-chloro-2-(neopentylamino)phenyl)(2-chlorophenyl)methanol **SI19**[4]



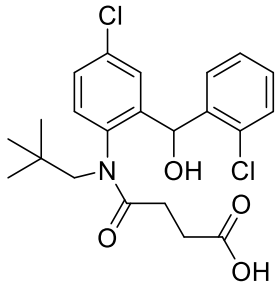
Rf = 0.54 (hexane/EtOAc 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (dt, *J* = 5.7, 3.9 Hz, 2H), 7.37 – 7.27 (m, 2H), 7.18 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 2.87 (s, 2H), 0.96 (s, 9H) ppm. OH and NH peaks missing due to proton-deuterium exchange.; **^{13}C NMR** (101 MHz, $CDCl_3$): δ 145.3, 138.5, 133.4, 130.0, 129.8, 129.0, 128.9, 127.5, 127.5, 126.9, 121.6, 112.5, 70.8, 56.1, 31.7, 27.8 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{12}Cl_2O^+$: 338.1; found: 338.2.

Methyl 4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoate **SI20**[4]



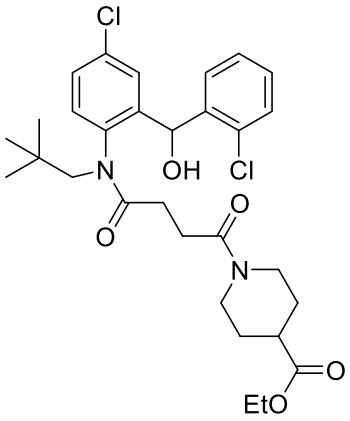
Rf = 0.51 (hexane/EtOAc 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.81 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 2H), 7.39 – 7.17 (m, 3H), 7.03 (d, *J* = 1.9 Hz, 1H), 6.15 (6.34) (s, 1H), 4.47 (4.53) (d, *J* = 13.6 Hz, 1H), 3.68 (3.58) (s, 3H), 3.06 (3.02) (d, *J* = 13.7 Hz, 1H), 2.94 – 2.79 (m, 2H), 2.47 – 2.37 (m, 2H), 2.31 – 2.17 (1.83) (m, 1H), 0.89 (0.91) (s, 9H) ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{23}H_{28}Cl_2NO_4^+$: 452.1; found: 452.6.

4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoic acid **SI21**[4]



^{1}H NMR (400 MHz, DMSO): δ 11.99 (s, 1H), 7.61 – 7.24 (m, 6H), 7.06 (d, *J* = 2.5 Hz, 1H), 6.08 (6.23) (d, *J* = 4.7 Hz, 1H), 5.88 (6.18) (s, 1H), 4.40 (4.20) (d, *J* = 13.6 Hz, 1H), 3.03 (2.52) (d, *J* = 13.7 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.39 – 2.09 (m, 3H), 2.08 – 2.00 (m, 1H), 1.76 – 1.63 (m, 1H), 0.76 (0.83) (s, 9H) ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}Cl_2NO_4^+$: 438.1; found: 438.6.

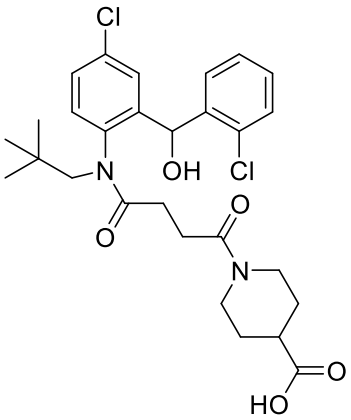
Ethyl 1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxylate **SI22**[4]



R_f = 0.33 (DCM/MeOH 99:1); **^{1}H NMR** (400 MHz, DMSO): δ 7.65 – 7.52 (m, 2H), 7.51 – 7.32 (m, 3H), 7.31 – 7.24 (m, 1H), 7.03 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.21 (d, *J* = 5.7 Hz, 1H), 5.90 (6.09) (d, *J* = 5.8 Hz, 1H), 4.40 (4.21) (d, *J* = 13.6 Hz, 1H), 4.18 – 4.12 (m, 1H), 4.07 (q, *J* =

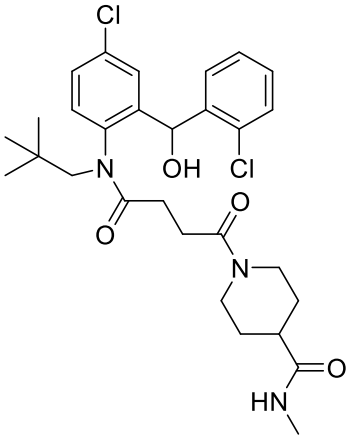
7.1 Hz, 2H), 3.79 (3.61) (dd, *J* = 13.8, 3.9 Hz, 1H), 3.17 (d, *J* = 5.2, 1H), 3.12 – 2.96 (m, 1H), 2.74 – 2.53 (m, 3H), 2.46 – 2.28 (m, 2H), 2.07 – 1.95 (m, 1H), 1.88 – 1.67 (m, 2H), 1.54 – 1.22 (1.00) (m, 2H), 1.18 (1.05) (t, *J* = 7.1 Hz, 3H), 0.76 (0.83) (s, 9H) ppm. **LCMS** (ESI): *m/z* [M + H]$^+$ calcd for $C_{30}H_{39}Cl_2N_2O_5^+$: 577.2; found: 577.7.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxylic acid **SI23**[4]



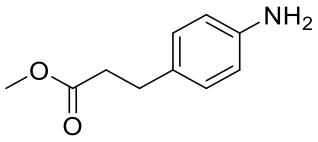
R_f = 0.01 (DCM/MeOH 99:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.25 (s, 1H), 7.65 – 7.52 (m, 2H), 7.51 – 7.34 (m, 4H), 7.28 (q, *J* = 4.2 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.22 (d, *J* = 5.8 Hz, 1H), 6.10 (s, 1H), 5.93 – 5.87 (m, 1H), 4.40 (d, *J* = 13.6 Hz, 1H), 4.21 (d, *J* = 13.7 Hz, 1H), 4.16 (d, *J* = 13.4 Hz, 1H), 4.12 – 4.04 (m, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.12 – 2.91 (m, 1H), 2.76 – 2.52 (m, 3H), 2.49 – 2.28 (m, 2H), 2.17 (dt, *J* = 15.8, 7.6 Hz, 1H), 2.08 – 1.94 (m, 1H), 1.87 – 1.67 (m, 3H), 1.55 – 1.20 (m, 2H), 1.04 – 0.93 (m, 1H), 0.83 (s, 3H), 0.76 (s, 6H) ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{28}H_{35}Cl_2N_2O_5^+$: 549.2; found: 549.1.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-methylpiperidine-4-carboxamide **(SQSI)**[4]



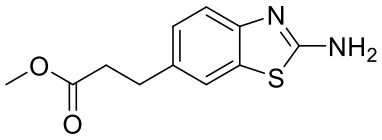
R_f = 0.59 (DCM/MeOH 95:5); NMR assignment can be found in SI Fig. 3. **HRMS** (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{37}Cl_2N_3NaO_4^+$: 584.2054; found: 584.2056.

Methyl 3-(4-aminophenyl)propanoate **SI24**[5]



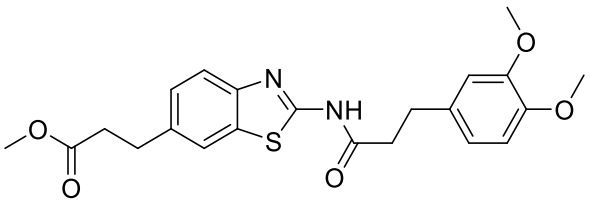
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 – 6.95 (m, 2H), 6.66 – 6.59 (m, 2H), 3.66 (s, 3H), 3.51 (br s, 2H), 2.84 (t, *J* = 7.8 Hz, 2H), 2.60 – 2.55 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.7, 144.6, 130.7, 129.2, 115.5, 51.7, 36.3, 30.3 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{10}H_{14}NO_2^+$: 180.1; found: 179.9.

Methyl 3-(2-aminobenzo[*d*]thiazol-6-yl)propanoate **SI25**[5]



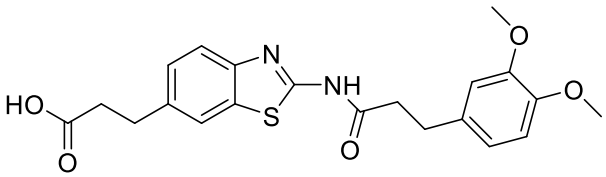
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.67 (s, 3H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.65 (t, *J* = 7.7 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ 173.5, 166.6, 159.3, 147.0, 136.0, 127.2, 121.1, 118.4, 51.9, 36.0, 30.8 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{16}N_2O_2S^+$: 237.1; found: 236.9.

Methyl 3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanoate **SI26**[5]



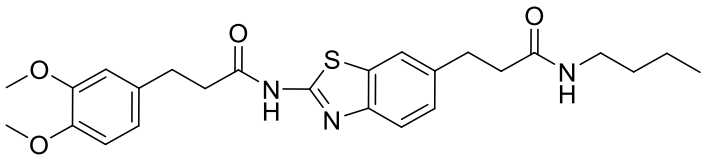
^{1}H NMR (400 MHz, DMSO): δ 12.28 (s, 1H), 7.80 (d, *J* = 1.7 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.74 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.58 (s, 3H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.88 (t, *J* = 7.2 Hz, 2H), 2.80 – 2.74 (m, 2H), 2.68 (t, *J* = 7.6 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.6, 171.5, 157.3, 148.6, 147.2, 147.0, 136.1, 133.1, 131.6, 126.7, 120.8, 120.2, 119.9, 112.2, 111.9, 55.5, 55.4, 51.3, 37.1, 35.2, 30.2, 30.0 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_5S^+$: 429.2; found: 429.0.

3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanoic acid **SI27**[5]



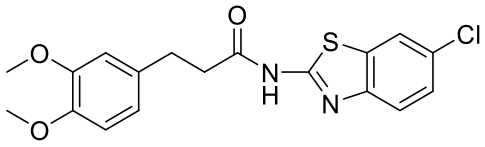
^{1}H NMR (400 MHz, DMSO): δ 12.27 (s, 1H), 12.13 (s, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.29 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.90 (dt, *J* = 15.6, 7.5 Hz, 4H), 2.81 – 2.73 (m, 2H), 2.58 (t, *J* = 7.6 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 173.7, 171.5, 157.3, 148.6, 147.2, 146.9, 136.5, 133.1, 131.5, 126.7, 120.8, 120.2, 120.0, 112.2, 111.9, 55.5, 55.4, 37.2, 35.5, 30.3, 30.0 ppm. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_5S^+$: 415.1; found: 415.0.

N-butyl-3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[d]thiazol-6-yl)propanamide **SO2093**[5]



R_f = 0.63 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H), 7.78 – 7.71 (m, 2H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.71 (s, 3H), 3.69 (s, 3H), 3.00 (td, *J* = 6.9, 5.6 Hz, 2H), 2.89 (dt, *J* = 9.9, 7.6 Hz, 4H), 2.83 – 2.72 (m, 2H), 2.39 (dd, *J* = 8.3, 6.9 Hz, 2H), 1.35 – 1.24 (m, 2H), 1.22 – 1.12 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.5, 171.0, 157.2, 148.6, 147.2, 146.8, 136.9, 133.1, 131.5, 126.7, 120.7, 120.1, 120.0, 112.2, 111.9, 55.5, 55.4, 38.0, 37.3, 37.2, 31.2, 31.1, 30.0, 19.5, 13.6 ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{25}H_{31}N_3O_4S^+$ 470.2113; found 470.2114.

N-(6-chlorobenzo[d]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **KY02111**[5]



Rf = 0.50 (Hex/EtOAc 1:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.43 (s, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.88 – 6.81 (m, 2H), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 2.92 – 2.84 (m, 2H), 2.82 – 2.76 (m, 2H) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.8, 158.7, 148.6, 147.4, 147.2, 133.1, 133.0, 127.5, 126.4, 121.7, 121.4, 120.0, 112.2, 111.9, 55.5, 55.4, 37.1, 29.9 ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{18}H_{18}ClN_2O_3S^+$ 377.0721; found 377.0718.

SQS degrader library

General Procedure A for the amide coupling of linker-pomalidomide conjugate to the SQS-ligands:

The Boc-protected linker-pomalidomide conjugate (1.1 equiv.) was dissolved in DCM (2 mL/0.1mmol) and treated with trifluoroacetic acid (0.75 mL). The reaction mixture was stirred for 30min to 2h at rt. After the reaction was completed as confirmed by TLC (Et_2O/EtOAc 1:1), the reaction was slowly quenched by the addition of sat. $NaHCO_3$ (15 ml). The aqueous solution was extracted with DCM until the organic phase was not fluorescent anymore (ca. 6 × 20 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The oily residue was further dried in high vacuum. In a separate flask, the respective SQS ligand (1.0 equiv.) was dissolved in DCM (2 mL) and EDC x HCl (3.0 equiv.) and HOBt x H_2O (1.2 equiv.) were added. After stirring for 5 min, the deprotected amine derivative and DIPEA (3.0 equiv.) were dissolved in DCM (4 mL) and added to the ligand. The combined mixture was stirred at rt for 1-18 h. After the reaction was finished as indicated by TLC (DCM/MeOH 9:1), the mixture was diluted with water (10 ml) and the organics were extracted with DCM (3 × 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude

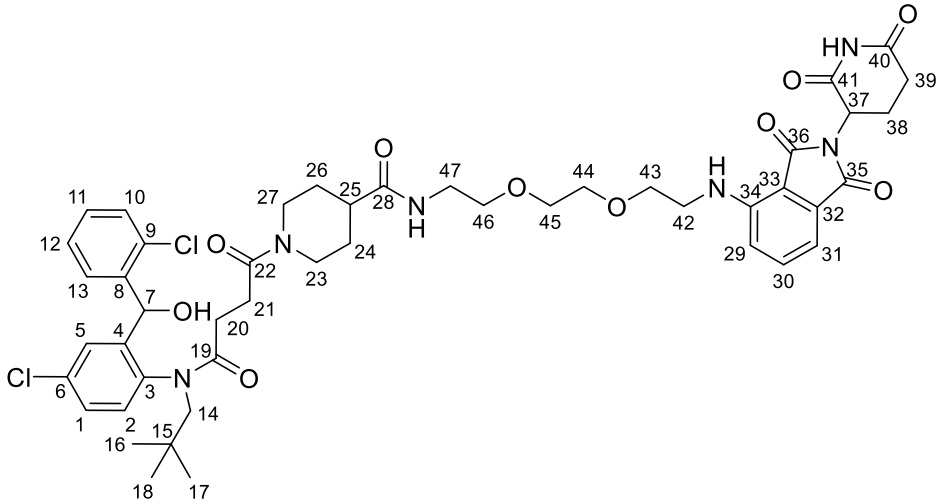
was purified by flash silica gel column chromatography (DCM/MeOH 98:2 to 95:5) to give the title compound as a yellow amorph solid.

General Procedure B for the amide coupling of linker-VH032 and linker-adamantane conjugates to the SQS-ligands:

The Boc-protected linker-VHL or linker-adamantane conjugate (1.2 equiv.) was dissolved in DCM (2 mL/0.1mmol) and treated with 4M HCL in dioxane (1 ml/mmol). The reaction mixture was stirred for 30min to 2h at rt. After the reaction was completed as confirmed by TLC (DCM/MeOH 9:1), the solvent was evaporated in reduced pressure and co-evaporated with Et_2O (3 × 20 mL). The precipitate was further dried in high vacuum. In a separate flask, the respective SQS ligand (1.0 equiv.) was dissolved in DCM (2 mL) and EDC x HCl (3.0 equiv.) and HOBt x H_2O (1.2 equiv.) were added. After stirring for 5 min, the deprotected amine derivative and DIPEA (3.0 equiv.) were dissolved in DCM (4 mL) and added to the ligand. The combined mixture was stirred at rt for 1-18 h. After the reaction was finished as indicated by TLC (DCM/MeOH 9:1), the mixture was diluted with water (10 ml) and the organics were extracted with DCM (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by flash silica gel column chromatography (DCM/MeOH 98:2 to 95:5) to give the title compound as a white amorph solid.

Active-site binding compounds

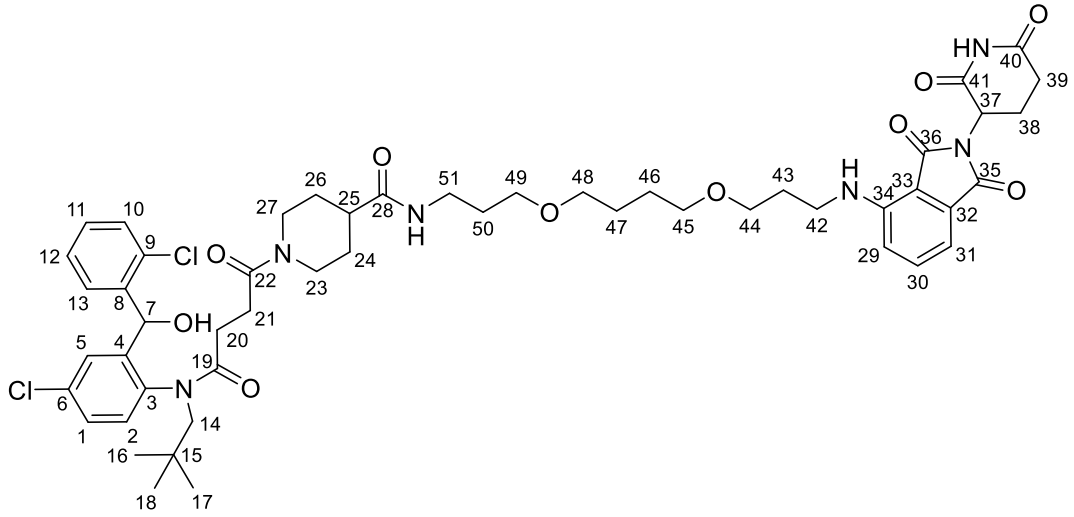
1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)piperidine-4-carboxamide **1**



According to general procedure A, SI23 (0.091 mmol) and SI3 (0.14 mmol) provided the title compound as a yellow solid (77.00 mg, 90%). $\mathbf{R_f}$ = 0.48 (DCM/MeOH 95:5); **^{1}H NMR** (400 MHz, DMSO): δ 11.09 (s, 1H, **C40-NH-C41**), 7.82 (t, *J* = 5.9 Hz, 1H), 7.67 – 7.53 (m, 3H), 7.52 – 7.34 (m, 3H), 7.34 – 7.23 (m, 2H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.61 (t, *J* = 5.8 Hz, 1H), 6.22 (d, *J* = 5.6 Hz, 1H, **OH-8**), 6.10 (t, *J* = 4.3 Hz, 1H, **H7**), 5.90 (t, *J* = 4.9 Hz, 1H, **H7**), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H, **H37**), 4.40 (d, *J* = 13.6 Hz, 1H), 4.28 (d, *J* = 13.0 Hz, 1H), 4.21 (d, *J* = 13.6 Hz, 1H), 3.83 (d, *J* = 13.6 Hz, 1H), 3.66 – 3.37 (m, 10H), 3.18 (q, *J*

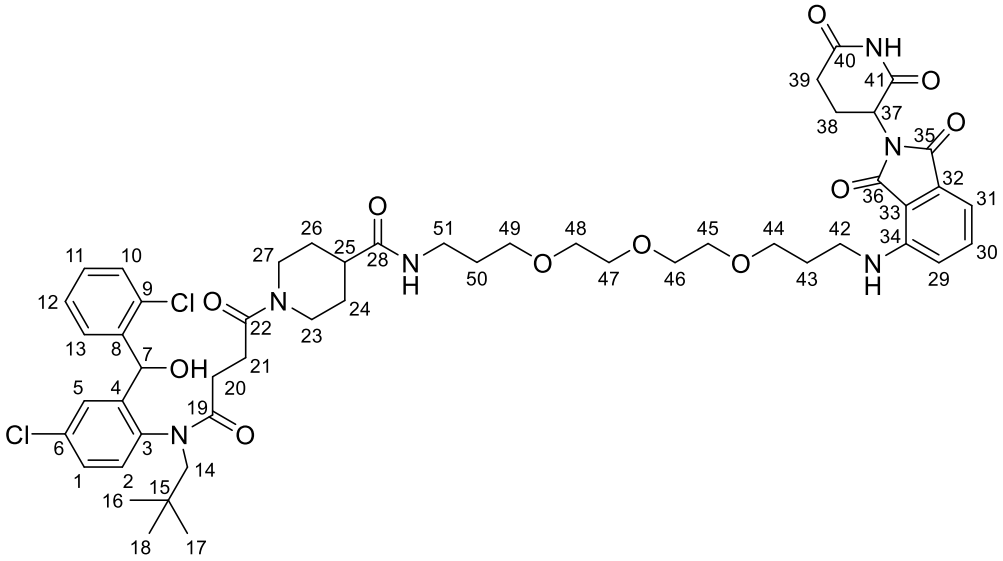
= 5.8 Hz, 2H), 3.05 – 2.80 (m, 2H), 2.64 – 2.51 (m, 4H), 2.50 – 2.28 (m, 3H), 2.23 – 1.99 (m, 2H), 1.62 (q, *J* = 15.1, 14.4 Hz, 2H), 1.50 – 1.21 (m, 2H), 0.83 (s, 4H, **H16-18**), 0.76 (s, 5H, **H16-18**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 173.9, 172.8, 172.3, 171.1, 170.3, 170.1, 169.6 (d, *J* = 7.5 Hz), 169.0 (d, *J* = 7.7 Hz), 167.3, 146.4, 142.5, 142.3, 140.9, 139.8, 139.6, 136.2, 134.1, 133.8, 132.5, 132.3, 132.1, 131.9, 129.6, 129.4 (d, *J* = 7.6 Hz), 129.3, 129.0, 128.4, 128.1, 127.7, 127.4, 117.4, 110.7, 109.3, 69.7, 69.6, 69.1, 68.9, 67.2, 66.1, 58.2, 57.5, 48.6, 44.3, 41.7, 41.6, 40.7, 38.4, 34.2, 33.7, 31.0, 28.8 (**C16-18**), 28.6 (**C16-18**), 28.4, 28.1, 27.9, 22.1 ppm.; **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{47}H_{57}Cl_2N_6O_{10}^+$ 935.3508; found 935.3513.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)piperidine-4-carboxamide **2**



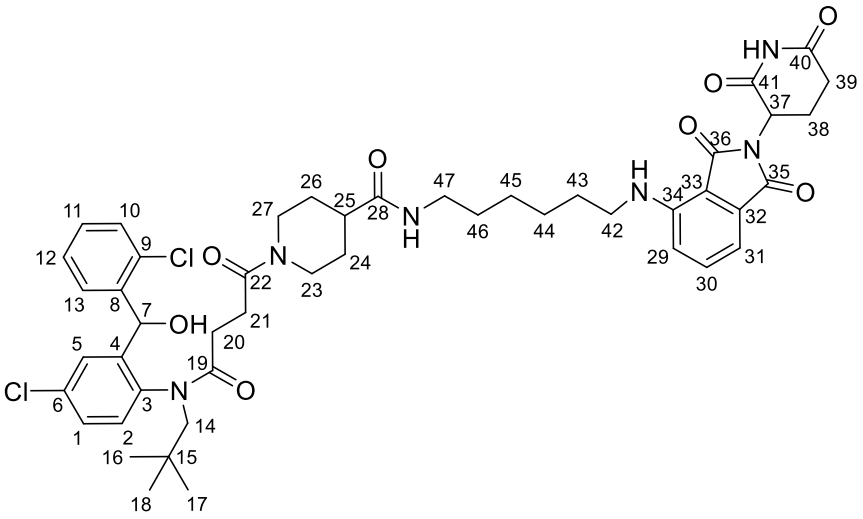
According to general procedure A, SI23 (0.091 mmol) and SI4 (0.14 mmol) provided the title compound as a yellow solid (55.90 mg, 62%). $\mathbf{R_f}$ = 0.63 (DCM/MeOH 95:5); **^{1}H NMR** (400 MHz, DMSO): δ 11.10 (s, 1H, **C40-NH-C41**), 7.75 (d, *J* = 6.2 Hz, 1H), 7.69 – 7.52 (m, 3H), 7.51 – 7.35 (m, 3H), 7.35 – 7.24 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.67 (t, *J* = 5.9 Hz, 1H), 6.22 (t, *J* = 5.1 Hz, 1H, **OH-8**), 6.10 (t, *J* = 4.1 Hz, 1H, **H7**), 5.90 (t, *J* = 4.9 Hz, 1H, **H7**), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H, **H37**), 4.44 – 4.37 (m, 1H), 4.30 (d, *J* = 13.1 Hz, 1H), 4.26 – 4.18 (m, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.66 (d, *J* = 13.8 Hz, 1H), 3.46 (t, *J* = 5.9 Hz, 2H), 3.37 (q, *J* = 5.2 Hz, 8H), 3.06 (p, *J* = 6.1, 5.5 Hz, 2H), 3.03 – 2.95 (m, 1H), 2.89 (ddd, *J* = 17.4, 14.1, 5.4 Hz, 1H), 2.57 (tdd, *J* = 14.4, 5.4, 2.7 Hz, 2H), 2.48 – 2.23 (m, 4H), 2.16 (dt, *J* = 15.9, 7.7 Hz, 1H), 2.03 (dtt, *J* = 7.9, 5.7, 3.5 Hz, 1H), 1.81 (p, *J* = 6.3 Hz, 2H), 1.73 – 1.49 (m, 8H), 1.49 – 1.22 (m, 2H), 0.84 (s, 4H, **H16-18**), 0.76 (s, 5H **H16-18**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 174.1, 173.2, 172.7, 171.9, 170.5, 170.1 (d, *J* = 8.0 Hz), 169.5 (d, *J* = 9.4 Hz), 169.3, 167.8, 146.9, 142.9, 141.4, 140.2, 140.1, 140.0, 136.7, 134.6, 134.2, 132.9, 132.7, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.5, 128.2, 127.8, 117.5, 110.8, 109.5, 70.5, 70.3, 68.3, 68.1, 67.6, 66.5, 58.6, 57.9, 49.0, 44.7, 42.2, 41.2, 36.2, 34.6, 34.2, 31.4, 29.9, 29.3, 29.3, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.6, 28.4, 26.5, 26.4, 22.6 ppm one linker-CH_2 group missing due to superimposition with DMSO-d6). **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{51}H_{65}Cl_2N_6O_{10}^+$ 991.4134; found 991.4140.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(3(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)propyl)piperidine-4-carboxamide **3**



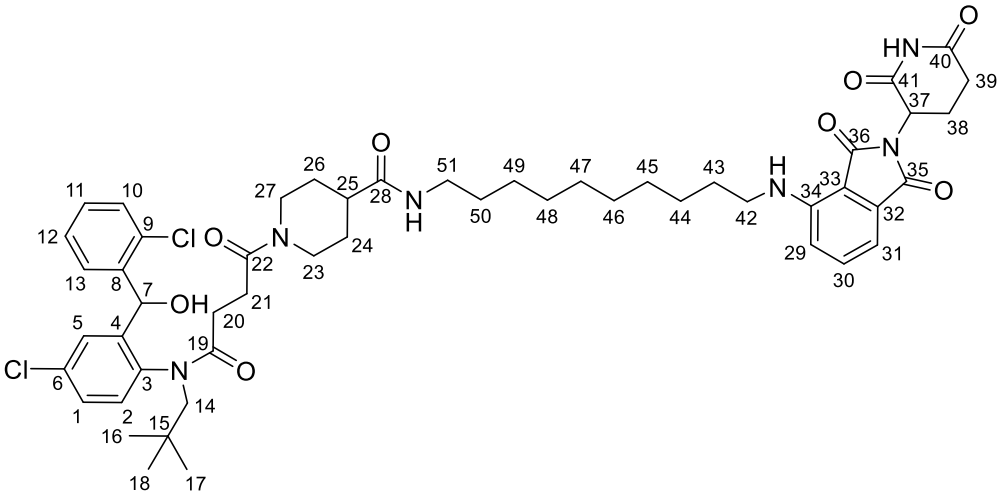
According to general procedure A, SI23 (0.091 mmol) and SI5 (0.14 mmol) provided the title compound as a yellow solid (45.00 mg, 49%). $\mathbf{R_f}$ = 0.55 (DCM/MeOH 95:5); **^{1}H NMR** (400 MHz, DMSO) δ 11.09 (s, 1H), 7.79 – 7.70 (m, 1H), 7.67 – 7.54 (m, 3H), 7.52 – 7.35 (m, 2H), 7.30 (d, *J* = 5.4 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.71 – 6.64 (m, 1H), 6.26 – 6.19 (m, 1H, **OH-8**), 6.14 – 6.07 (m, 1H, **H7**), 5.91 (d, *J* = 4.9 Hz, 1H, **H7**), 5.11 – 5.01 (m, 1H, **H37**), 4.41 (d, *J* = 14.3 Hz, 1H), 4.30 (d, *J* = 13.0 Hz, 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 3.86 (s, 1H), 3.66 (d, *J* = 12.9 Hz, 1H), 3.60 – 3.44 (m, 10H), 3.37 (tt, *J* = 6.7, 3.4 Hz, 4H), 3.12 – 2.82 (m, 4H), 2.58 (dd, *J* = 13.6, 3.8 Hz, 4H), 2.49 – 2.23 (m, 3H), 2.22 – 2.12 (m, 1H), 2.09 – 1.96 (m, 2H), 1.82 (q, *J* = 6.4 Hz, 2H), 1.77 – 1.55 (m, 5H), 1.52 – 1.21 (m, 2H), 0.84 (s, 4H, **H16-18**), 0.76 (s, 5H, **H16-18**). **^{13}C NMR** (101 MHz, DMSO): δ 174.1, 173.3, 172.7, 171.9, 170.5, 169.7, 169.5, 169.3, 167.8, 146.9, 142.9, 141.5, 140.2, 140.1, 136.7, 134.6, 134.2, 132.9, 132.6, 132.4, 130.0, 129.9, 129.8, 129.7, 128.9, 128.5, 128.2, 127.8, 117.5, 110.8, 109.5, 70.2, 70.2, 70.1, 70.0, 68.7, 68.5, 67.6, 66.5, 58.6, 57.9, 49.0, 44.7, 42.2, 41.2, 36.2, 34.6, 34.2, 31.4, 29.8, 29.3, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.6, 28.4, 22.6 ppm (one linker CH2 group missing due to superimposition with DMSO-d6). **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{51}H_{65}Cl_2N_6O_{11}^+$ 1007.4083; found 1007.4091.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)piperidine-4-carboxamide **4**



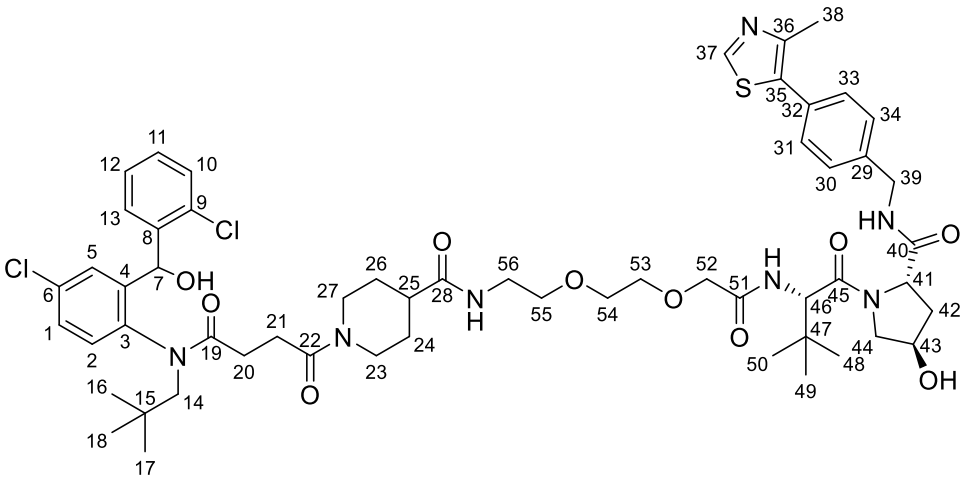
According to general procedure A, SI23 (0.091 mmol) and SI1 (0.14 mmol) provided the title compound as a yellow solid (88.00 mg, 54%). $\mathbf{R_f}$ = 0.61 (DCM/MeOH 95:5); **^{1}H NMR** (400 MHz, DMSO): δ 11.10 (s, 1H, **C40-NH-C41**), 7.75 (q, *J* = 7.1, 6.4 Hz, 1H), 7.66 – 7.54 (m, 3H), 7.47 (ddd, *J* = 11.4, 7.5, 1.6 Hz, 2H), 7.43 (s, 1H), 7.35 – 7.25 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.05 – 7.00 (m, 2H), 6.54 (t, *J* = 6.0 Hz, 1H), 6.23 (d, *J* = 5.6 Hz, 1H, **OH-8**), 6.11 (d, *J* = 4.1 Hz, 1H, **H7**), 5.91 (t, *J* = 4.7 Hz, 1H, **H7**), 5.06 (dd, *J* = 12.9, 5.4 Hz, 1H, **H37**), 4.41 (d, *J* = 13.6 Hz, 1H), 4.30 (d, *J* = 13.1 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.66 (d, *J* = 13.4 Hz, 1H), 3.29 (q, *J* = 6.7 Hz, 2H), 3.08 – 2.81 (m, 5H), 2.64 – 2.52 (m, 3H), 2.49 – 2.24 (m, 3H), 2.16 (dt, *J* = 15.8, 7.6 Hz, 1H), 2.03 (dtd, *J* = 11.6, 5.4, 4.3, 2.5 Hz, 1H), 1.78 – 1.49 (m, 5H), 1.46 – 1.21 (m, 9H), 0.84 (s, 4H, **H16-18**), 0.76 (s, 5H, **H16-18**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 174.0, 173.3, 172.7, 171.9, 170.6, 170.1, 169.5, 169.4, 167.7, 146.9, 142.9, 141.3, 140.2, 140.1, 136.7, 134.6, 134.2, 132.9, 132.7, 132.6, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.6, 128.2, 127.8, 117.6, 110.8, 109.5, 67.6, 66.5, 58.6, 57.9, 49.0, 44.7, 42.2, 41.2, 38.7, 34.6, 34.2, 31.4, 31.1, 29.5, 29.3, 29.1, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.4, 26.5, 26.5, 22.6 ppm. **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{47}H_{58}Cl_2N_6O_8^+$ 903.3609; found 903.3614.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)piperidine-4-carboxamide **5**



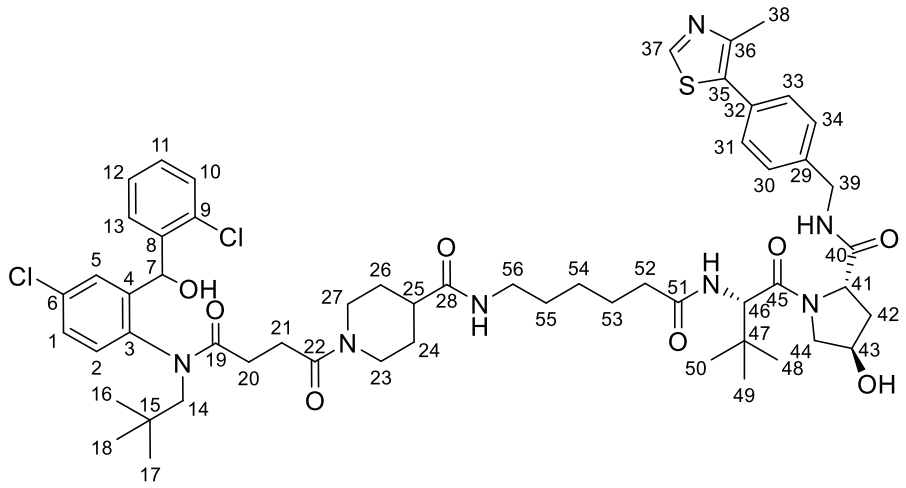
According to general procedure A, SI23 (0.091 mmol) and SI6 (0.14 mmol) provided the title compound as a yellow solid (96.70 mg, 74%). $\mathbf{R_f}$ = 0.60 (DCM/MeOH 95:5); **^{1}H NMR** (800 MHz, DMSO): δ 11.09 (s, 1H, **C40-NH-H41**), 7.76 – 7.70 (m, 1H), 7.66 – 7.54 (m, 3H), 7.51 – 7.37 (m, 3H), 7.33 – 7.25 (m, 2H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.52 (t, *J* = 5.9 Hz, 1H), 6.24 – 6.19 (m, 1H, **OH-8**), 6.10 (dd, *J* = 8.0, 5.1 Hz, 1H, **H7**), 5.90 (dd, *J* = 8.2, 5.8 Hz, 1H, **H7**), 5.05 (dd, *J* = 12.9, 5.5 Hz, 1H), 4.41 (dd, *J* = 13.7, 4.3 Hz, 1H), 4.33 – 4.27 (m, 1H), 4.22 (ddd, *J* = 13.6, 10.0, 3.1 Hz, 1H), 3.85 (d, *J* = 13.6 Hz, 1H), 3.66 (d, *J* = 12.9 Hz, 1H), 3.29 (q, *J* = 6.7 Hz, 2H), 3.04 – 2.94 (m, 3H), 2.92 – 2.85 (m, 2H), 2.63 – 2.51 (m, 2H), 2.49 – 2.44 (m, 1H), 2.44 – 2.25 (m, 2H), 2.19 – 2.13 (m, 1H), 2.03 (dtd, *J* = 13.1, 5.4, 2.4 Hz, 1H), 1.74 – 1.54 (m, 5H), 1.50 – 1.19 (m, 16H), 0.84 (s, 5H), 0.76 (s, 4H) ppm. **^{13}C NMR** (201 MHz, DMSO) δ 174.1, 173.2, 172.7, 171.9, 170.5, 170.1, 170.1, 169.6, 169.5, 169.4, 167.8, 146.9, 142.9, 142.8, 141.4, 141.3, 140.3, 140.2, 140.1 (d, *J* = 3.4 Hz), 140.0, 136.7, 134.6, 134.2, 132.9 (d, *J* = 3.9 Hz), 132.8, 132.7, 132.6, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.5, 128.2, 127.8, 117.6, 110.8, 109.5, 67.6 (d, *J* = 7.8 Hz), 66.6, 58.6, 57.9, 49.0, 44.8 – 44.6 (m), 42.3, 42.2, 41.3 – 41.0 (m), 38.8, 34.6, 34.2, 31.4, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.1, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.5, 28.4, 26.8, 22.6. **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{51}H_{65}Cl_2N_6O_8^+$ 959.4235; found 959.4241.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(2-(2-(2-(((S)-1-((2S,4R)-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)piperidine-4-carboxamide **6**



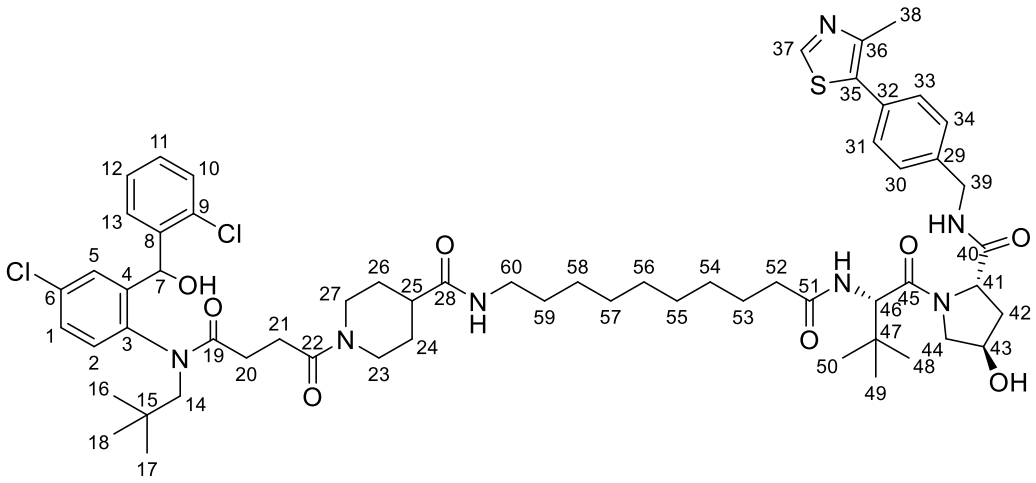
According to general procedure B, SI23 (0.091 mmol) and SI13 (0.14 mmol) provided the title compound as a white solid (114.40 mg, 81%). **Rf** = 0.43 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 8.98 (s, 1H), 8.58 (t, *J* = 6.0 Hz, 1H), 7.89 – 7.80 (m, 1H), 7.67 – 7.52 (m, 2H), 7.51 – 7.41 (m, 3H), 7.39 (s, 5H), 7.32 – 7.24 (m, 2H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.22 (d, *J* = 5.9 Hz, 1H, **OH-8**), 6.10 (s, 1H, **H7**), 5.90 (s, 1H, **H7**), 5.16 (d, *J* = 3.4 Hz, 1H), 4.58 (d, *J* = 9.6 Hz, 1H), 4.50 – 4.33 (m, 4H), 4.31 – 4.17 (m, 2H), 3.97 (s, 2H), 3.70 – 3.50 (m, 7H), 3.43 (t, *J* = 5.8 Hz, 2H), 3.30 – 3.13 (m, 2H), 3.05 – 2.82 (m, 2H), 2.61 – 2.53 (m, 1H), 2.44 (s, 3H), 2.40 – 2.26 (m, 1H), 2.22 – 1.84 (m, 2H), 1.61 (d, *J* = 16.6 Hz, 2H), 1.43 – 1.21 (m, 2H), 0.95 (s, 9H, **H48-H50**), 0.83 (s, 5H, **H16-H18**), 0.75 (s, 4H, **H16-H18**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 173.9, 171.6, 171.4, 169.1, 168.6, 151.4, 147.7, 142.5, 139.7, 139.5, 139.3, 134.0, 132.4, 131.8, 131.1, 129.6, 129.5, 129.4, 129.3, 128.6, 128.1, 127.7, 127.4, 127.3, 70.3, 69.5, 69.3, 69.1, 68.8, 66.0, 58.7, 58.2, 56.6, 55.6, 41.6, 41.5, 40.4, 38.3, 37.9, 35.7, 34.1, 33.7, 29.2 (**C16-18**), 28.8 (**C16-18**), 28.5, 28.3, 28.0, 27.9, 26.1 (**C-48-50**), 15.9 ppm. **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{56}H_{74}Cl_2N_7O_{10}S^+$ 1106.4595; found 1106.4605.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperidine-4-carboxamide **7**



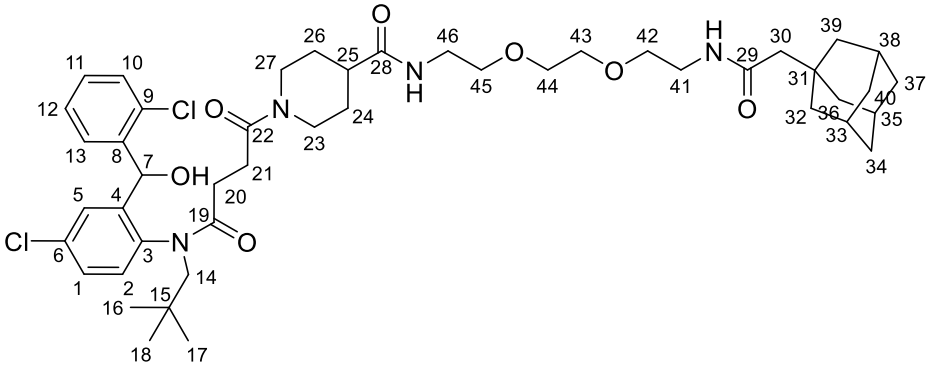
According to general procedure B, SI23 (0.091 mmol) and SI14 (0.14 mmol) provided the title compound as a white solid (98.00 mg, 86%). **Rf** = 0.50 (DCM/MeOH 9:1); **^{1}H NMR** (800 MHz, DMSO): δ 8.99 (s, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.84 (d, *J* = 9.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.67 – 7.54 (m, 2H), 7.49 – 7.37 (m, 7H), 7.33 – 7.26 (m, 2H), 7.04 (t, *J* = 3.0 Hz, 1H), 6.24 – 6.20 (m, 1H, **OH-8**), 6.10 (dd, *J* = 8.6, 5.1 Hz, 1H, **H7**), 5.91 (dd, *J* = 8.7, 5.9 Hz, 1H, **H7**), 5.12 (d, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.46 – 4.39 (m, 3H), 4.36 (h, *J* = 3.7 Hz, 1H), 4.32 – 4.28 (m, 1H), 4.26 – 4.20 (m, 2H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.70 – 3.63 (m, 3H), 3.01 (td, *J* = 13.4, 12.9, 9.1 Hz, 3H), 2.89 (q, *J* = 13.6 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.45 (s, 3H), 2.43 – 2.22 (m, 4H), 2.14 (dddd, *J* = 34.6, 14.4, 8.4, 6.0 Hz, 1H), 2.06 – 2.01 (m, 1H), 1.94 – 1.88 (m, 1H), 1.75 – 1.57 (m, 2H), 1.53 – 1.41 (m, 2H), 1.38 (p, *J* = 7.3 Hz, 2H), 1.34 – 1.18 (m, 3H), 1.05 – 0.97 (m, 1H), 0.94 (s, 9H, **H48-50**), 0.84 (s, 5H **H16-18**), 0.76 (s, 4H, **H16-18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.0, 172.7, 172.5, 172.4, 171.9, 170.2, 170.1, 169.5, 151.9, 148.2, 142.9, 142.8, 141.4, 140.2, 140.1, 140.0, 134.6, 134.2, 132.9, 132.7, 132.4, 131.6, 130.1, 130.0, 129.9, 129.8, 129.7, 129.4, 129.1, 128.9, 128.6, 128.2, 127.9, 127.8, 69.3, 67.6, 66.6, 59.1, 58.6, 57.9, 56.8, 56.7, 55.4, 45.1, 42.2, 42.1, 41.2, 38.7, 38.4, 35.7, 35.3, 34.6, 34.2, 29.8, 29.6, 29.3, 29.3, 29.2, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.5, 28.4, 26.8 (**C48-50**), 26.5, 25.6, 16.4 ppm. **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{56}H_{74}Cl_2N_7O_8S^+$ 1074.4696; found 1074.4699.

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(10-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecyl)piperidine-4-carboxamide **8**



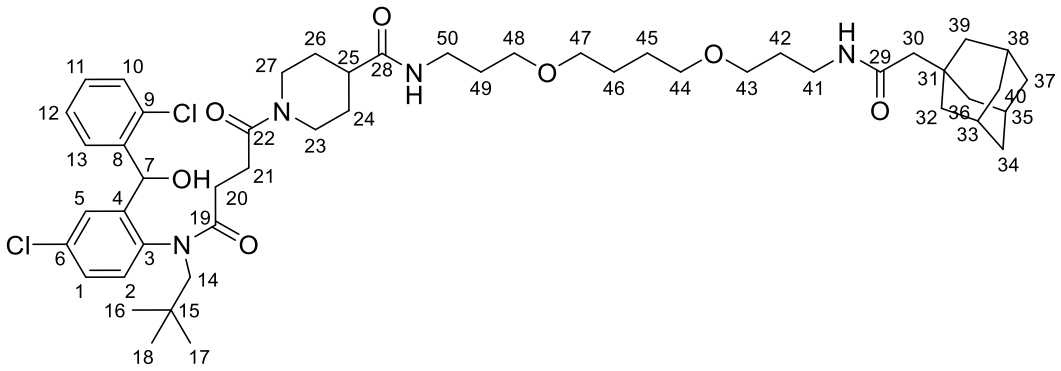
According to general procedure B, SI23 (0.091 mmol) and SI12 (0.14 mmol) provided the title compound as a white solid (94.00 mg, 65%). **Rf** = 0.56 (DCM/MeOH 9:1); **^{1}H NMR** (800 MHz, DMSO): δ 8.99 (s, 1H), 8.56 (t, *J* = 6.1 Hz, 1H), 7.83 (d, *J* = 9.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.67 – 7.55 (m, 2H), 7.51 – 7.36 (m, 7H), 7.33 – 7.25 (m, 2H), 7.04 (dd, *J* = 4.6, 2.6 Hz, 1H), 6.24 – 6.20 (m, 1H, **OH-8**), 6.11 (dd, *J* = 8.2, 5.1 Hz, 1H, **H7**), 5.91 (dd, *J* = 8.6, 5.9 Hz, 1H, **H7**), 5.12 (d, *J* = 3.6 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.47 – 4.38 (m, 2H), 4.36 (dtd, *J* = 6.9, 4.3, 2.7 Hz, 1H), 4.32 – 4.28 (m, 1H), 4.26 – 4.19 (m, 2H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.71 – 3.60 (m, 3H), 3.31 (d, *J* = 12.7 Hz, 1H), 3.05 – 2.95 (m, 3H), 2.89 (q, *J* = 13.2, 12.3 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.45 (s, 3H), 2.43 – 2.23 (m, 2H), 2.16 (dtd, *J* = 16.0, 7.8, 3.1 Hz, 1H), 2.11 (ddd, *J* = 14.1, 8.0, 6.1 Hz, 1H), 2.06 – 1.98 (m, 1H), 1.91 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H), 1.74 – 1.56 (m, 2H), 1.48 (ddd, *J* = 47.1, 13.3, 6.5 Hz, 1H), 1.42 – 1.27 (m, 2H), 1.26 – 1.21 (m, 13H), 1.04 – 0.97 (m, 2H), 0.94 (s, 9H, **H48-H50**), 0.84 (d, *J* = 1.6 Hz, 5H, **H16-18**), 0.76 (s, 4H, **H16-H18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.1, 172.7, 172.5, 172.4, 172.0, 170.2, 170.1, 169.5, 151.9, 148.2, 142.9, 142.8, 141.4, 140.2, 140.1, 140.0, 134.6, 134.2, 132.9, 132.8, 132.4, 131.6, 130.1, 130.0, 129.9, 129.8, 129.7, 129.4, 129.3, 129.1, 128.9, 128.6, 128.5, 128.2, 127.9, 127.8, 69.3, 67.6, 66.6, 59.1, 58.6, 57.9, 56.8, 56.7, 55.4, 44.5, 42.2, 42.1, 41.3, 38.8, 38.4, 35.7, 35.3, 34.6, 34.2, 29.8, 29.5, 29.3, 29.2, 29.1, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.4, 26.8, 26.8 (**C-48-50**), 25.9, 16.4 ppm. **HRMS (ESI):** m/z $[M+H]^+$ calcd for $C_{60}H_{82}Cl_2N_7O_8S^+$ 1130.5322; found 1130.5329.

N-(2-(2-(2-(2-((1s,3s)-adamantan-1-yl)acetamido)ethoxy)ethoxy)ethyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **9**



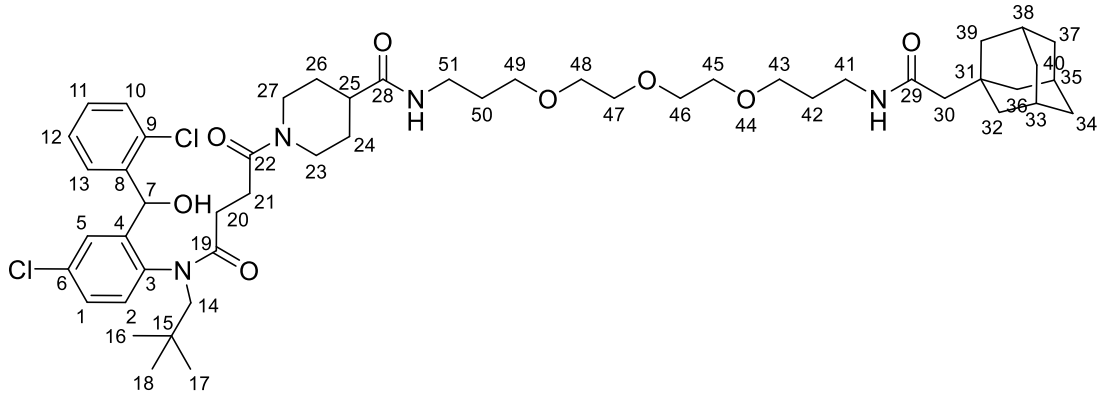
According to general procedure B, SI23 (0.091 mmol) and SI7 (0.14 mmol) provided the title compound as a white solid (61.40 mg, 79%). **Rf** = 0.65 (DCM/MeOH 9:1); **^{1}H NMR** (800 MHz, DMSO): δ 7.87 – 7.82 (m, 1H), 7.73 – 7.54 (m, 3H), 7.51 – 7.36 (m, 3H), 7.29 (dtd, *J* = 12.6, 9.0, 8.5, 4.7 Hz, 2H), 7.04 (dd, *J* = 4.4, 2.5 Hz, 1H), 6.24 – 6.20 (m, 1H, **OH-8**), 6.10 (dd, *J* = 8.3, 5.1 Hz, 1H, **H7**), 5.91 (dd, *J* = 8.7, 5.9 Hz, 1H, **H7**), 4.41 (dd, *J* = 13.7, 4.8 Hz, 1H), 4.33 – 4.28 (m, 1H), 4.22 (d, *J* = 13.5 Hz, 1H), 3.85 (d, *J* = 13.6 Hz, 1H), 3.67 (dd, *J* = 14.2, 4.5 Hz, 1H), 3.50 (s, 4H), 3.39 (td, *J* = 5.9, 2.6 Hz, 4H), 3.30 (s, 1H), 3.18 (dq, *J* = 11.9, 5.9 Hz, 4H), 3.05 – 2.94 (m, 1H), 2.89 (q, *J* = 13.7, 13.0 Hz, 1H), 2.60 – 2.56 (m, 2H), 2.49 – 2.45 (m, 1H), 2.43 – 2.30 (m, 2H), 2.16 (dtd, *J* = 15.8, 7.6, 4.3 Hz, 1H), 2.02 (ddt, *J* = 22.6, 16.2, 6.6 Hz, 1H), 1.90 (q, *J* = 3.2 Hz, 3H), 1.82 (s, 2H), 1.65 (d, *J* = 12.3 Hz, 4H), 1.59 – 1.52 (m, 10H), 1.51 – 1.21 (m, 2H), 1.00 (dddd, *J* = 24.7, 16.4, 8.0, 5.0 Hz, 1H), 0.84 (d, *J* = 2.4 Hz, 5H, **H16-18**), 0.77 (s, 4H, **H18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.4, 172.7, 171.9, 170.4, 170.1, 169.6, 142.9, 142.8, 141.3, 140.2, 140.0, 134.6, 134.2, 132.9, 132.8, 132.7, 132.4, 130.0, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.6, 128.5, 128.2, 127.8, 127.8, 70.0, 70.0, 69.6, 69.5, 67.6, 66.6, 58.6, 57.9, 50.4, 44.8, 42.5, 42.0, 41.3, 40.4, 38.9, 38.8, 36.9, 34.6, 34.2, 32.6, 29.8, 29.6, 29.3, 29.3, 29.1, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.6, 28.6, 28.5, 28.5, 28.4, 28.4 ppm. **HRMS (ESI):** m/z [M + Na]$^{+}$ calcd for $C_{46}H_{64}Cl_2N_4O_7Na^{+}$ 877.4044; found 877.4049.

N-(3-(4-(3-(2-((1s,3s)-adamantan-1-yl)acetamido)propoxy)butoxy)propyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **10**



According to general procedure B, SI23 (0.091 mmol) and SI8 (0.14 mmol) provided the title compound as a light brown solid (56.40 mg, 68%). **Rf** = 0.65 (DCM/MeOH 9:1); **^{1}H NMR** (800 MHz, DMSO): δ 7.76 (dt, *J* = 13.2, 6.4 Hz, 1H), 7.68 – 7.56 (m, 3H), 7.52 – 7.37 (m, 3H), 7.34 – 7.25 (m, 2H), 7.04 (dd, *J* = 4.3, 2.5 Hz, 1H), 6.24 – 6.20 (m, 1H, **OH-8**), 6.11 (dd, *J* = 8.2, 5.1 Hz, 1H, **H7**), 5.91 (dd, *J* = 8.5, 5.9 Hz, 1H, **H7**) 4.41 (dd, *J* = 13.7, 5.0 Hz, 1H), 4.30 (dd, *J* = 12.9, 4.1 Hz, 1H), 4.23 (t, *J* = 13.4 Hz, 1H), 3.85 (d, *J* = 13.7 Hz, 1H), 3.67 (d, *J* = 13.1 Hz, 1H), 3.37 – 3.32 (m, 8H), 3.09 – 3.04 (m, 5H), 3.00 (ddd, *J* = 41.4, 13.5, 9.0 Hz, 1H), 2.89 (q, *J* = 13.8, 13.1 Hz, 1H), 2.60 – 2.56 (m, 1H), 2.60 – 2.53 (m, 1H), 2.49 – 2.44 (m, 1H), 2.43 – 2.26 (m, 2H), 2.16 (dtd, *J* = 15.9, 8.0, 2.8 Hz, 1H), 2.02 (tt, *J* = 16.3, 7.0 Hz, 1H), 1.92 – 1.89 (m, 3H), 1.80 (d, *J* = 1.3 Hz, 3H), 1.65 (d, *J* = 11.6 Hz, 5H), 1.63 – 1.53 (m, 19H), 1.51 (q, *J* = 3.0, 2.5 Hz, 5H), 1.43 (dddd, *J* = 48.8, 24.2, 12.0, 3.8 Hz, 1H), 1.34 – 1.21 (m, 2H), 0.84 (d, *J* = 2.1 Hz, 5H, **H16-18**), 0.77 (s, 4H, **H16-18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.2, 172.6, 171.8, 170.2, 170.1, 169.6, 142.9, 142.8, 141.3, 140.3, 140.0, 134.6, 134.2, 132.9, 132.8, 132.4, 130.0, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.6, 128.5, 128.2, 127.8, 70.3, 70.3, 68.6, 68.2, 68.1, 67.6, 66.6, 58.6, 57.9, 50.5, 44.9, 42.6, 42.2, 41.2, 40.4, 36.9, 36.2, 36.1, 34.6, 34.2, 32.6, 30.0, 29.8, 29.3, 29.2, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.6, 28.6, 28.5, 28.4, 26.5 ppm. **HRMS (ESI):** m/z [M + H]$^{+}$ calcd for $C_{50}H_{73}Cl_2N_4O_7^{+}$ 911.4851; found 911.4851.

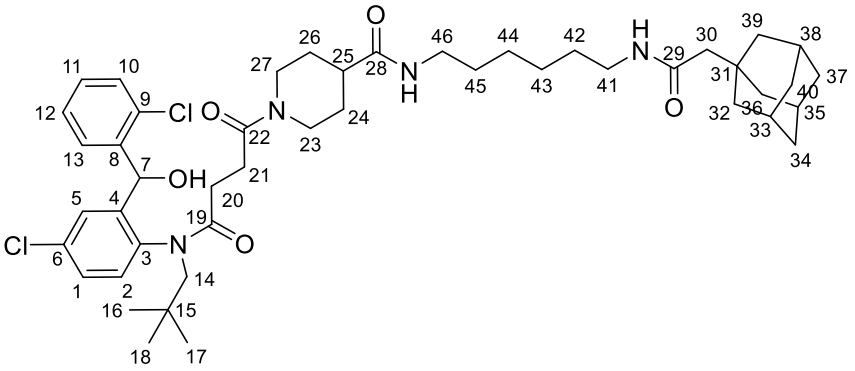
N-(1-((3r,5r,7r)-adamantan-1-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **11**



According to general procedure B, SI23 (0.091 mmol) and SI9 (0.14 mmol) provided the title compound as a white solid (59.60 mg, 71%). **Rf** = 0.65 (DCM/MeOH 9:1); **^{1}H NMR** (800 MHz, DMSO): δ 7.79 – 7.73 (m, 1H), 7.67 – 7.54 (m, 3H), 7.50 – 7.39 (m, 3H), 7.33 – 7.25 (m, 2H), 7.04 (dd, *J* = 4.1, 2.5 Hz, 1H), 6.22 (dd, *J* = 9.9, 5.6 Hz, 1H, **OH-8**), 6.10 (dd, *J* = 8.3, 5.0 Hz, 1H, **H7**), 5.91 (dd, *J* = 8.8, 5.9 Hz, 1H, **H7**), 4.41 (dd, *J* = 13.7, 5.0 Hz, 1H), 4.30 (dd, *J* = 13.5, 4.2 Hz, 1H), 4.26 – 4.19 (m, 1H), 3.85 (d, *J* = 13.5 Hz, 1H), 3.67 (d, *J* = 13.4 Hz, 1H), 3.53 – 3.50 (m, 3H), 3.49 – 3.45 (m, 7H), 3.39 (dt, *J* = 8.0, 6.3 Hz, 5H), 3.30 (d, *J* = 2.8 Hz, 1H), 3.06 (dp, *J* = 12.7, 6.5 Hz, 5H), 3.04 – 2.95 (m, 1H), 2.93 – 2.86 (m, 1H), 2.61 – 2.53 (m, 1H), 2.50 – 2.44 (m, 1H), 2.43 – 2.27 (m, 2H), 2.16 (dtd, *J* = 16.1, 7.8, 2.7 Hz, 1H), 2.02 (tt, *J* = 16.6, 6.8 Hz, 1H), 1.90 (q, *J* = 3.1 Hz, 4H), 1.80 (s, 2H), 1.74 – 1.51 (m, 17H), 1.51 – 1.36 (m, 1H), 1.35 – 1.22 (m, 1H), 1.05 – 0.96 (m, 1H), 0.84 (d, *J* = 2.4 Hz, 5H, **H16-18**), 0.77 (s, 4H, **H16-18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.2, 172.7, 171.9, 170.2, 170.1, 169.5, 142.9, 142.8, 141.3, 140.3, 140.0, 134.6, 134.2, 132.9, 132.8, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.6, 128.5, 128.2, 127.8, 127.8, 70.2, 70.2, 70.0, 70.0, 68.6, 68.5, 67.6, 66.6, 58.6, 57.9, 50.5, 44.8, 42.6, 42.2, 41.2, 40.4, 36.9, 36.2, 36.0, 34.6, 34.2, 32.6, 31.4, 29.9, 29.8,

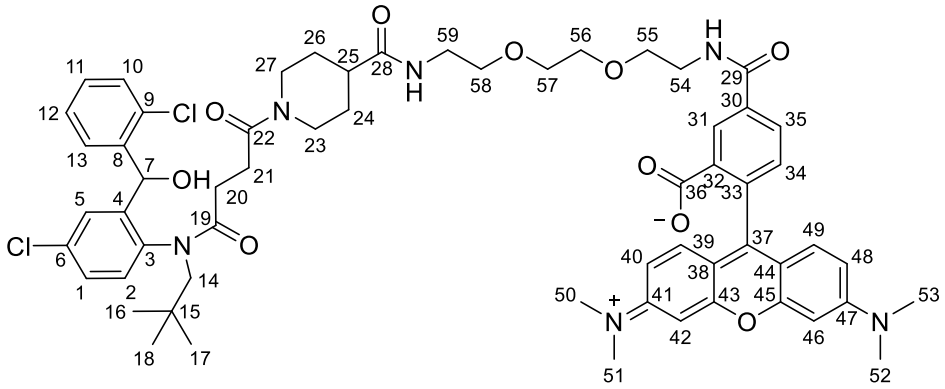
29.3, 29.3, 29.2, 29.0 (**C16-18**), 28.9 (**C16-18**), 28.7, 28.6, 28.6, 28.5, 28.5, 28.4, 22.5 ppm. **HRMS (ESI):** m/z [M + Na]$^+$ calcd for $C_{50}H_{73}Cl_2N_8O_7Na^+$ 949.4619; found 949.4625.

N-(6-(2-((1s,3s)-adamantan-1-yl)acetamido)hexyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **12**



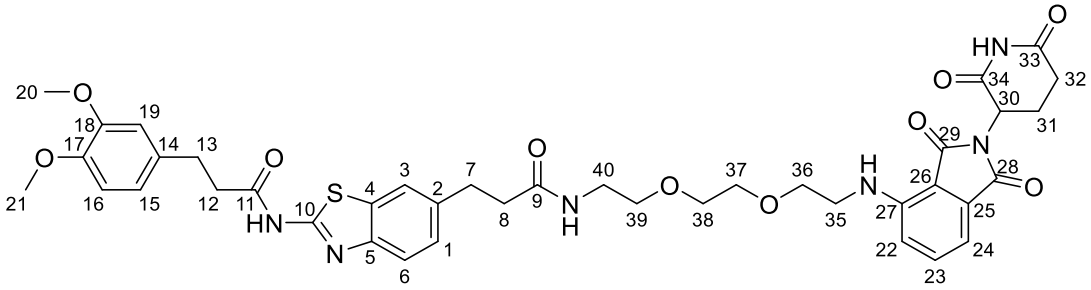
According to general procedure B, SI23 (0.091 mmol) and SI10 (0.14 mmol) provided the title compound as a white solid (65.00 mg, 86%). **Rf** = 0.65 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 7.75 (q, *J* = 6.2 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.52 – 7.36 (m, 3H), 7.30 (ddt, *J* = 6.5, 5.1, 3.2 Hz, 2H), 7.04 (t, *J* = 2.2 Hz, 1H), 6.22 (t, *J* = 5.0 Hz, 1H, **OH-8**), 6.11 (t, *J* = 4.5 Hz, 1H, **H7**), 5.91 (t, *J* = 4.9 Hz, 1H, **H7**), 4.45 – 4.37 (m, 1H), 4.30 (d, *J* = 13.1 Hz, 1H), 4.26 – 4.18 (m, 1H), 3.85 (d, *J* = 13.6 Hz, 1H), 3.67 (d, *J* = 13.5 Hz, 1H), 3.00 (p, *J* = 6.6 Hz, 5H), 2.89 (q, *J* = 11.8, 9.0 Hz, 1H), 2.58 (d, *J* = 13.5 Hz, 1H), 2.48 – 2.25 (m, 1H), 2.16 (dt, *J* = 15.8, 7.6 Hz, 1H), 2.09 – 1.97 (m, 1H), 1.90 (s, 3H), 1.80 (s, 2H), 1.65 (d, *J* = 12.2 Hz, 5H), 1.58 (s, 3H), 1.56 – 1.50 (m, 7H), 1.36 (p, *J* = 6.8 Hz, 4H), 1.28 – 1.21 (m, 5H), 1.07 – 0.94 (m, 1H), 0.84 (s, 5H, **H16-18**), 0.77 (s, 4H, **H16-18**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 174.0, 172.7, 171.9, 170.1, 169.5, 142.9, 142.5, 141.4, 140.2, 140.0, 134.6, 134.2, 132.9, 132.8, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.5, 128.2, 127.8, 67.6, 66.5, 58.6, 57.9, 50.5, 44.8, 42.6, 42.2, 41.2, 38.7, 38.6, 36.9, 34.6, 34.2, 32.6, 29.6, 29.5, 29.2, 29.0 (**C16-C18**), 28.9 (**C16-C18**), 28.6, 28.5, 26.6, 26.5 ppm. **HRMS (ESI):** m/z [M + Na]$^+$ calcd for $C_{46}H_{65}Cl_2N_4O_5Na^+$ 845.4146; found 845.3151.

5-((2-(2-(2-(1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamido)ethoxy)ethoxy)ethyl)carbamoyl)-2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)benzoate **26**



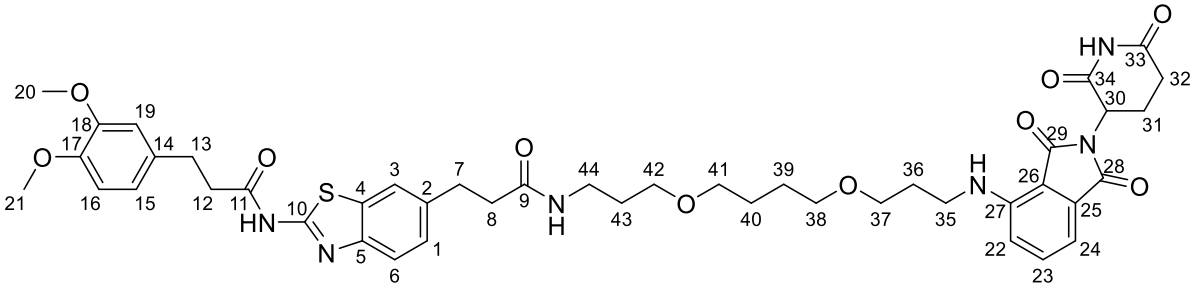
Dark violet solid (80.00 mg, 67%); **Rf** = 0.48 (DCM/MeOH 7:3); **^{1}H NMR** (800 MHz, DMSO): δ 8.89 (t, *J* = 5.6 Hz, 1H), 8.47 – 8.44 (m, 1H), 8.24 (dt, *J* = 7.9, 1.6 Hz, 1H), 7.84 (d, *J* = 16.0 Hz, 1H), 7.67 – 7.53 (m, 2H), 7.49 – 7.42 (m, 2H), 7.39 (ddt, *J* = 9.3, 4.7, 2.5 Hz, 1H), 7.35 – 7.24 (m, 2H), 7.04 (t, *J* = 3.1 Hz, 1H), 6.55 – 6.46 (m, 7H), 6.24 – 6.19 (m, 1H, **OH-8**), 6.10 (dd, *J* = 8.0, 5.0 Hz, 1H, **H7**), 5.92 – 5.88 (m, 1H, **H7**), 4.40 (dd, *J* = 13.7, 4.0 Hz, 1H), 4.28 (d, *J* = 13.0 Hz, 1H), 4.21 (d, *J* = 13.5 Hz, 1H), 3.84 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.4 Hz, 1H), 3.60 – 3.55 (m, 5H), 3.53 (dd, *J* = 5.7, 3.4 Hz, 2H), 3.48 (q, *J* = 5.8 Hz, 2H), 3.41 (t, *J* = 6.0 Hz, 2H), 3.18 (d, *J* = 6.0 Hz, 2H), 3.04 – 3.00 (m, 1H), 2.95 (s, 12H, **H50-53**), 2.91 – 2.84 (m, 1H), 2.62 – 2.52 (m, 2H), 2.49 – 2.29 (m, 3H), 2.16 (dq, *J* = 14.7, 7.0 Hz, 1H), 2.01 (td, *J* = 17.5, 17.0, 7.2 Hz, 1H), 1.71 – 1.57 (m, 3H), 1.51 – 1.38 (m, 1H), 1.33 – 1.20 (m, 2H), 0.84 (s, 5H, **H16-18**), 0.76 (s, 4H, **H16-18**) ppm. **^{13}C NMR** (201 MHz, DMSO): δ 174.4, 172.4, 171.8, 170.5, 169.5, 168.8, 165.3, 155.3, 142.9, 140.1, 136.4, 134.9, 134.5, 134.2, 132.9, 132.4, 130.0, 129.9, 129.8, 129.7, 129.4, 128.9, 128.6, 128.2, 127.8, 127.3, 124.6, 123.6, 109.4, 106.0, 98.4, 85.2, 70.0, 69.5, 69.2, 67.6, 66.5, 58.6, 57.9, 55.4, 44.7, 42.0, 41.3, 38.9, 34.6, 34.2, 29.3, 29.1, 29.0 (**C-16-18**), 28.9 (**C16-18**), 28.7, 28.6, 28.4 ppm. One CH_2 group as well as $N(CH_3)_2$ groups are superimposing with the solvent peak. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{59}H_{69}Cl_2N_6O_{10}^+$ 845.4146; found 845.3151.

3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **13**



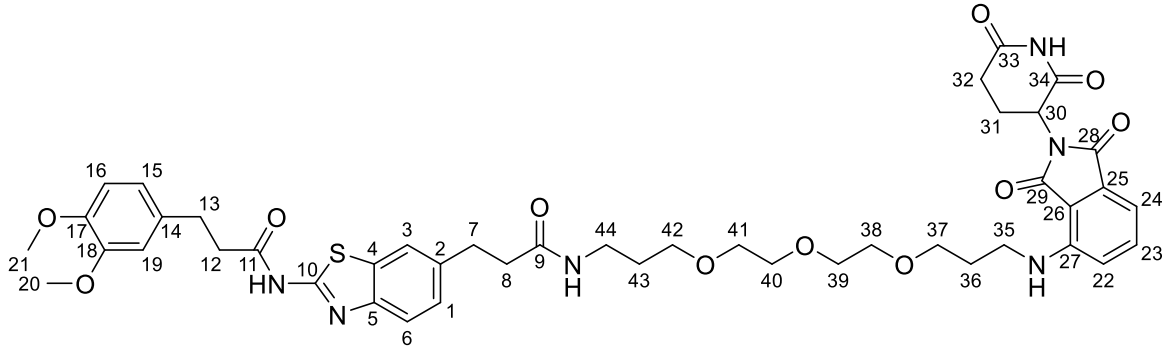
According to general procedure A, SI27 (0.12 mmol) and SI3 (0.13 mmol) provided the title compound as a yellow solid (46.00 mg, 66%). **Rf** = 0.50 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 11.09 (s, 1H, C33-**NH**-C34), 7.86 (t, *J* = 5.7 Hz, 1H, C9-**NH**-C40), 7.75 (d, *J* = 1.7 Hz, 1H, **H3**), 7.64 – 7.52 (m, 2H, **H6, H23**), 7.24 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 7.12 (d, *J* = 8.6 Hz, 1H, **H22**), 7.03 (d, *J* = 7.0 Hz, 1H, **H24**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 6.59 (t, *J* = 5.8 Hz, 1H, C27-**NH**-C35), 5.05 (dd, *J* = 12.9, 5.3 Hz, 1H, **H30**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.60 (t, *J* = 5.4 Hz, 2H, **H36**), 3.53 (dd, *J* = 6.3, 3.7 Hz, 2H, **H38**), 3.50 – 3.41 (m, 4H, **H35, H37**), 3.36 (t, *J* = 5.8 Hz, 2H, **H39**), 3.17 (q, *J* = 5.8 Hz, 2H, **H40**), 2.88 (hept, *J* = 5.6, 4.9 Hz, 5H, **H7, H13, H32**), 2.80 – 2.72 (m, 2H, **H12**), 2.63 – 2.51 (m, 2H, **H31, H32**), 2.41 (t, *J* = 7.7 Hz, 2H, **H8**), 2.07 – 1.96 (m, 1H, **H31**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.8 (**C33**), 171.5 (**C11**), 171.3 (**C9**), 170.1 (**C34**), 168.9 (**C29**), 167.3 (**C28**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 146.4 (**C27**), 136.9 (**C2**), 136.2 (**C23**), 133.1 (**C14**), 132.1 (**C25**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 117.4 (**C22**), 112.2 (**C19**), 111.9 (**C16**), 110.7 (**C24**), 109.3 (**C26**), 69.7 (**C37**), 69.6 (**C38**), 69.2 (**C39**), 68.9 (**C36**), 55.5 (**C20**), 55.4 (**C21**), 48.6 (**C30**), 41.7 (**C35**), 38.5 (**C40**), 37.2 (**C8**), 37.1 (**C12**), 31.1 (**C32**), 31.0 (**C7**), 30.0 (**C13**), 22.1 (**C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{40}H_{45}N_6O_{10}S^+$ 801.2912; found 801.2918.

3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **14**



According to general procedure A, SI27 (0.12 mmol) and SI4 (0.13 mmol) provided the title compound as a yellow solid (87.00 mg, 84%). **Rf** = 0.50 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 11.09 (s, 1H, C33-**NH**-C34), 7.80 – 7.72 (m, 2H, C9-**NH**-C44, **H3**), 7.64 – 7.51 (m, 2H, **H6, H23**), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 7.07 (d, *J* = 8.6 Hz, 1H, **H22**), 7.01 (d, *J* = 7.0 Hz, 1H, **H24**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 6.65 (t, *J* = 5.9 Hz, 1H, C27-**NH**-C35), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H, **H30**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.44 (t, *J* = 5.9 Hz, 2H, **H37**), 3.38 – 3.33 (m, 4H, **H35/H38**), 3.30 – 3.20 (m, 4H, **H41/H42**), 3.05 (q, *J* = 6.6 Hz, 2H, **H44**), 2.95 – 2.81 (m, 5H, **H7, H13, H32**), 2.80 – 2.72 (m, 2H, **H12**), 2.64 – 2.51 (m, 2H, **H31, H32**), 2.39 (t, *J* = 7.6 Hz, 1H, **H8**), 2.07 – 1.96 (m, 1H, **H31**), 1.80 (p, *J* = 6.3 Hz, 2H, **H36**), 1.60 – 1.43 (m, 6H **H39, H40, H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.8 (**C33**), 171.5 (**C11**), 171.1 (**C9**), 170.1 (**C43**), 168.8 (**C29**), 167.3 (**C28**), 157.1 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 146.4 (**C27**), 136.9 (**C2**), 136.2 (**C23**), 133.1 (**C14**), 132.2 (**C25**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 117.0 (**C22**), 112.2 (**C19**), 111.9 (**C16**), 110.4 (**C24**), 109.1 (**C26**), 70.0 (**C38**), 69.8 (**C41**), 67.9 (**C42**), 67.6 (**C37**), 55.5 (**C20**), 55.3 (**C21**), 48.5 (**C30**), 37.3 (**C8**), 37.1 (**C12**), 35.7 (**C44**), 31.1 (**C32**), 31.0 (**C7**), 30.0 (**C13**), 29.4 (**C39/C40/C43**), 28.9 (**C36**), 26.0 (**C39/C40/C43**), 26.0 (**C39/C40/C43**), 22.2 (**C31**) ppm. (One CH2 group missing due to superimposition with DMSO-d6 (**C35**)).; **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{44}H_{53}N_6O_{10}S^+$ 857.3544; found 857.3541.

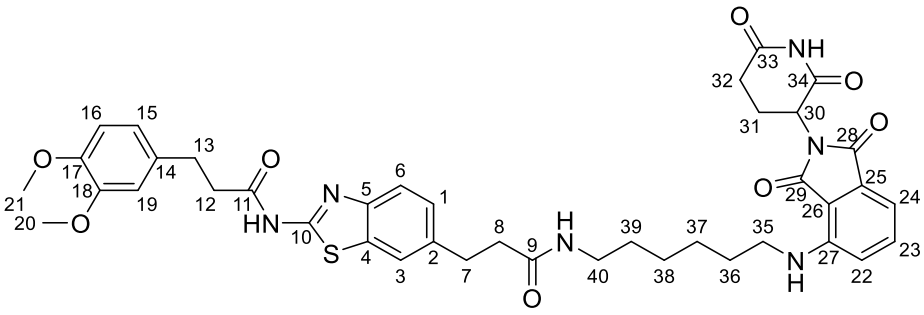
3-(3,4-dimethoxyphenyl)-*N*-(6-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-15-oxo-4,7,10-trioxa-14-azaheptadecan-17-yl)benzo[d]thiazol-2-yl)propanamide **15**



According to general procedure A, SI27 (0.12 mmol) and SI5 (0.13 mmol) provided the title compound as a yellow solid (76.00 mg, 72%). **Rf** = 0.56 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 11.09 (s, 1H, C33-**NH**-C34), 7.80 – 7.72 (m, 2H, C9-

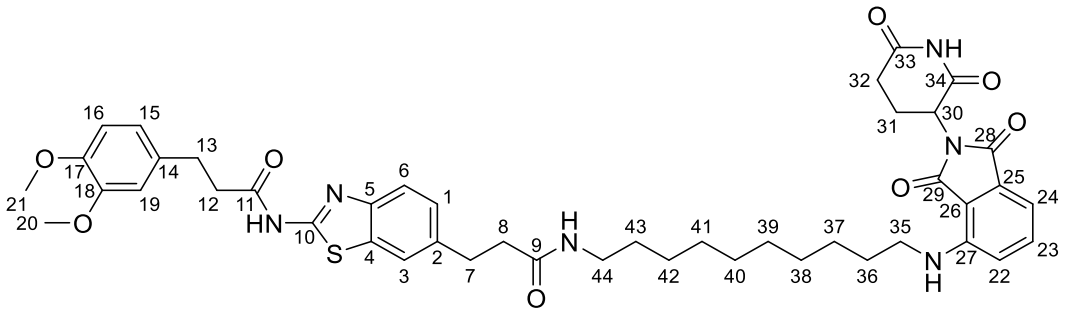
NH-C44, **H3**), 7.64 – 7.52 (m, 2H, **H6, H23**), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 7.09 (d, *J* = 8.6 Hz, 1H, **H22**), 7.01 (d, *J* = 7.0 Hz, 1H, **H24**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 6.66 (t, *J* = 5.9 Hz, 1H, C27-**NH**-C35), 5.04 (dd, *J* = 12.9, 5.4 Hz, 1H, **H30**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.53 (dd, *J* = 6.3, 3.8 Hz, 2H, **H40**), 3.52 – 3.44 (m, 6H **H38, H39, H42**), 3.42 – 3.33 (m, 4H, **H35, H41**), 3.28 (t, *J* = 6.4 Hz, 2H, **H37**), 3.05 (q, *J* = 6.6 Hz, 2H, **H44**), 2.95 – 2.81 (m, 5H, **H7, H13, H32**), 2.81 – 2.72 (m, 2H, **H12**), 2.63 – 2.51 (m, 2H, **H31, H32**), 2.39 (t, *J* = 7.6 Hz, 1H, **H8**), 2.07 – 1.96 (m, 1H, **H31**), 1.80 (p, *J* = 6.4 Hz, 2H, **H36**), 1.55 (p, *J* = 6.7 Hz, 2H, **H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.8 (**C33**), 171.5 (**C11**), 171.1 (**C9**), 170.1 (**C34**), 168.8 (**C29**), 167.3 (**C28**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 146.4 (**C27**), 136.9 (**C2**), 136.3 (**C23**), 133.1 (**C14**), 132.2 (**C25**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 117.1 (**C22**), 112.2 (**C19**), 111.9 (**C16**), 110.4 (**C24**), 109.0 (**C26**), 69.8 (**C38/C39/C40**), 69.7 (**C38/C39/C40**), 69.7 (**C38/C39/C40**), 69.5 (**C41**), 68.2 (**C42**), 68.0 (**C37**), 55.5 (**C20**), 55.4 (**C21**), 48.5 (**C30**), 37.3 (**C8**), 37.1 (**C12**), 35.7 (**C44**), 31.1 (**C32**), 31.0 (**C7**), 30.0 (**C13**), 29.3 (**C43**), 28.9 (**H36**), 22.2 (**C31**) ppm. (one CH2 group missing due to superimposition with DMSO-d6 (**C35**)). **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{44}H_{53}N_6O_{11}S^+$ 873.3493; found 873.3491.

3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **16**



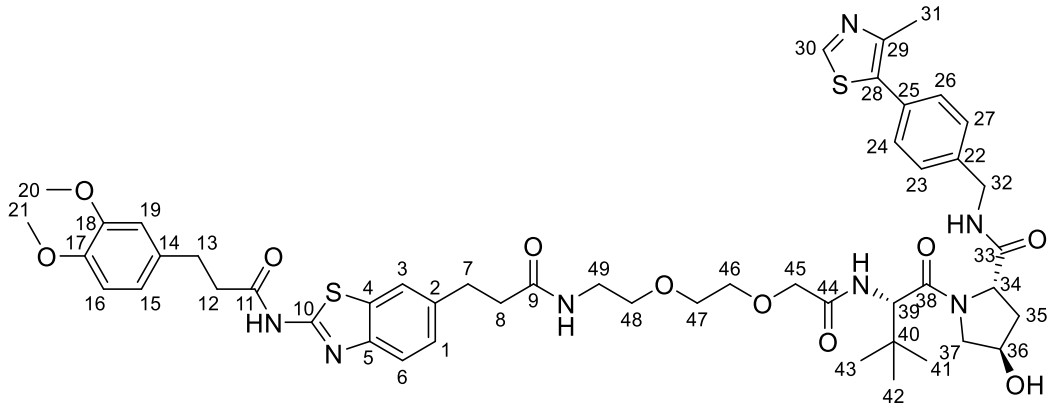
According to general procedure A, SI27 (0.07 mmol) and SI1 (0.08 mmol) provided the title compound as a yellow solid (25.00 mg, 45%). **Rf** = 0.55 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 11.09 (s, 1H, C33-**NH**-C34), 7.79 – 7.72 (m, 2H, C9-**NH**-C44, **H3**), 7.64 – 7.54 (m, 2H, **H6, H23**), 7.25 (dt, *J* = 8.3, 2.2 Hz, 1H, **H1**), 7.06 (d, *J* = 8.6 Hz, 1H, **H22**), 7.01 (d, *J* = 6.9 Hz, 1H , **H24**), 6.88 – 6.80 (m, 2H, **H16, H19**), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 6.50 (t, *J* = 5.9 Hz, 1H, C27-**NH**-C35), 5.05 (dd, *J* = 12.9, 5.4 Hz, 1H, **H30**), 3.71 (s, 3H, **H20**), 3.69 (d, *J* = 1.0 Hz, 3H, **H21**), 3.31 – 3.16 (m, 2H, **H35**), 3.00 (q, *J* = 6.5 Hz, 2H, **H40**), 2.94 – 2.81 (m, 5H, **H7, H13, H32**), 2.80 – 2.71 (m, 2H, **H12**), 2.63 – 2.51 (m, 2H, **H31, H32**), 2.39 (t, *J* = 7.6 Hz, 2H, **H8**), 2.07 – 1.96 (m, 1H, **H31**), 1.50 (p, *J* = 7.2 Hz, 2H, **H36**), 1.38 – 1.14 (m, 6H, **H37, H38, H39**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.8 (**C33**), 171.5 (**C11**), 171.0 (**C9**), 170.1 (**C34**), 168.9 (**C29**), 167.3 (**C28**), 157.1 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 146.4 (**C27**), 136.9 (**C2**), 136.3 (**C23**), 133.1 (**C14**), 132.2 (**C25**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 117.1 (**C22**), 112.2 (**C19**), 111.9 (**C16**), 110.4 (**C24**), 109.0 (**C26**), 55.5 (**C20**), 55.3 (**C21**), 48.5 (**C30**), 41.8 (**C35**), 38.3 (**C40**), 37.3 (**C8**), 37.1 (**C12**), 31.1 (**C32**), 31.0 (**C7**), 30.0 (**C13**), 29.1 (**C39**), 28.6 (**C36**), 26.1 (**C37/C38**), 26.1 (**C37/C38**), 22.1 (**C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{40}H_{45}N_6O_8S^+$ 769.3019; found 769.3020.

3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **17**



According to general procedure A, SI27 (0.07 mmol) and SI6 (0.08 mmol) provided the title compound as a yellow solid (45.00 mg, 74%). **Rf** = 0.63 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 11.09 (s, 1H, C33-**NH**-C34), 7.76 – 7.71 (m, 2H, C9-**NH**-C44, **H3**), 7.62 – 7.53 (m, 2H, **H6, H23**), 7.25 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 7.07 (d, *J* = 8.6 Hz, 1H, **H22**), 7.01 (dd, *J* = 6.9, 2.0 Hz, 1H, **H24**), 6.88 – 6.78 (m, 2H, **H16, H19**), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 6.51 (t, *J* = 5.8 Hz, 1H, C27-**NH**-C35), 5.05 (dd, *J* = 12.9, 5.3 Hz, 1H, **H30**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.27 (q, *J* = 6.6 Hz, 2H, **H35**), 2.98 (q, *J* = 6.6 Hz, 2H, **H44**), 2.93 – 2.81 (m, 5H, **H7, H13, H32**), 2.80 – 2.72 (m, 2H, **H12**), 2.63 – 2.51 (m, 2H, **H31, H32**), 2.39 (t, *J* = 7.5 Hz, 2H, **H8**), 2.06 – 1.97 (m, 1H, **H31**), 1.60 – 1.50 (m, 2H, **H36**), 1.35 – 1.05 (m, 14H, **H37-H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.8 (**C33**), 171.4 (**C11**), 170.9 (**C9**), 170.1 (**C34**), 169.0 (**C29**), 167.3 (**C28**), 157.1 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 146.4 (**C27**), 136.9 (**C2**), 136.3 (**C23**), 133.1 (**C14**), 132.2 (**C25**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 117.2 (**C22**), 112.2 (**C19**), 111.9 (**C16**), 110.4 (**C24**), 109.0 (**C26**), 55.5 (**C20**), 55.3 (**C21**), 48.5 (**C30**), 41.8 (**C35**), 38.4 (**C44**), 37.3 (**C8**), 37.1 (**C12**), 31.1 (**C32**), 31.0 (**C7**), 30.0 (**C13**), 29.1 (**C37-C43**), 29.0 (**C37-C43**), 28.9 (**C37-C43**), 28.8 (**C37-C43**), 28.7 (**C37-C43**), 26.3 (**C37-C43**), 22.2 (**C31**) ppm. LCMS: **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{44}H_{53}N_6O_8S^+$ 825.3645; found 825.3646.

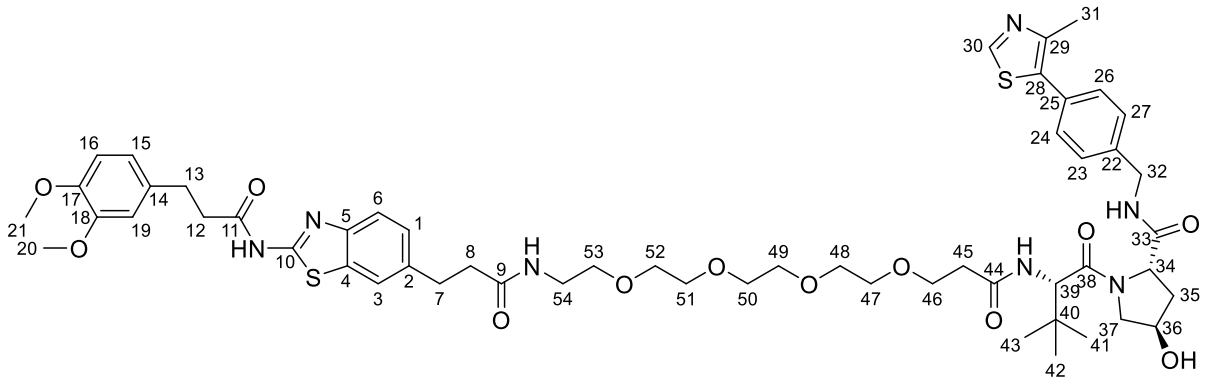
(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-15-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)-4,13-dioxo-6,9-dioxa-3,12-diazapentadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **18**



According to general procedure B, SI27 (0.07 mmol) and SI13 (0.08 mmol) provided the title compound as a white solid (59.00 mg, 84%). **Rf** = 0.47 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.25 (s, 1H, C10-**NH**-C11), 8.97 (s, 1H, **H30**), 8.58 (t, *J* = 6.0 Hz, 1H, C32-**NH**-

C33), 7.89 (t, *J* = 5.7 Hz, 1H, C9-**NH**-C49), 7.75 (d, *J* = 1.7 Hz, 1H, **H3**), 7.60 (d, *J* = 8.3 Hz, 1H, **H6**), 7.44 (d, *J* = 6.4 Hz, 1H, C39-**NH**-C44), 7.38 (s, 4H, **H23, H24, H26, H27**), 7.28 – 7.20 (m, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 5.16 (d, *J* = 3.5 Hz, 1H, C36-**OH**), 4.58 (d, *J* = 9.6 Hz, 1H, **H39**), 4.45 (t, *J* = 8.2 Hz, 1H, **H34**), 4.41 – 4.31 (m, 2H, **H32, H36**), 4.26 (dd, *J* = 15.7, 5.8 Hz, 1H, **H32**), 3.96 (s, 2H, **H45**), 3.71 (s, 3H **H20**), 3.69 (s, 3H, **H21**), 3.68 – 3.54 (m, 4H, **H37, H46**), 3.50 (q, *J* = 4.8, 4.2 Hz, 2H, **H47**), 3.39 (t, *J* = 5.8 Hz, 2H, **H48**), 3.25 – 3.15 (m, 2H, **H49**), 2.95 – 2.81 (m, 4H, **H7, H13**), 2.80 – 2.72 (m, 2H, **H12**), 2.47 – 2.37 (m, 5H, **H8, H31**), 2.06 (dd, *J* = 13.0, 7.7 Hz, 1H, **H35**), 1.90 (ddd, *J* = 13.0, 8.8, 4.5 Hz, 1H, **H35**), 0.94 (s, 9H, **H41-H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.7 (**C33**), 171.5 (**C11**), 171.4 (**C9**), 169.2 (**C38**), 168.6 (**C44**), 157.2 (**C10**), 151.4 (**C30**), 148.6 (**C17**), 147.8 (**C29**), 147.2 (**C18**), 146.8 (**C5**), 139.4 (**C22**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 131.1 (**C28**), 129.7 (**C25**), 128.7 (**C23/24/26/27**), 127.4 (**C23/24/26/27**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 70.4 (**C46**), 69.5 (**C45**), 69.4 (**C47**), 69.3 (**C48**), 68.9 (**C36**), 58.7 (**C34**), 56.6 (**C37**), 55.7 (**C39**), 55.5 (**C20**), 55.4 (**C21**), 41.7 (**C32**), 38.5 (**C49**), 38.0 (**C35**), 37.2 (**C8**), 37.2 (**C12**), 35.7 (**C40**), 31.1 (**C7**), 30.0 (**C13**), 26.2 (**C41-C43**), 15.9 (**C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{49}H_{62}N_7O_{10}S_2^+$ 972.3999; found 972.3996. **Optical Rotation:** $[\alpha]_D^{20}$ = -26.61 (c = 0.68, EtOH).

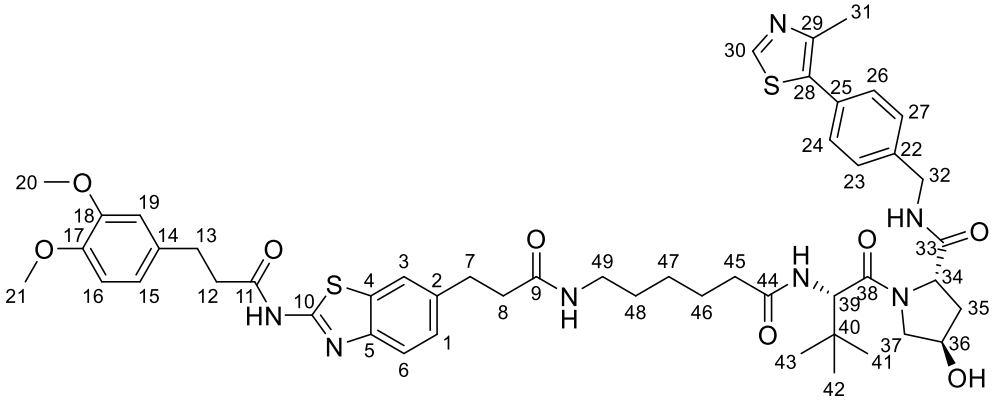
(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-22-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)-4,20-dioxo-7,10,13,16-tetraoxa-3,19-diazadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **19**



According to general procedure B, SI27 (0.07 mmol) and SI14 (0.08 mmol) provided the title compound as a white solid (71.50 mg, 92%). **Rf** = 0.41 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 8.98 (s, 1H, **H30**), 8.57 (t, *J* = 6.1 Hz, 1H, C32-**NH**-C33), 7.97 – 7.85 (m, 2H, C9-**NH**-C54, C39-**NH**-C44), 7.75 (d, *J* = 1.7 Hz, 1H, **H3**), 7.61 (d, *J* = 8.3 Hz, 1H, **H6**), 7.40 (q, *J* = 8.4 Hz, 4H, **H23, H24, H26, H27**), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 5.13 (d, *J* = 3.5 Hz, 1H, C36-**OH**), 4.55 (d, *J* = 9.4 Hz, 1H, **H39**), 4.50 – 4.38 (m, 2H, **H32, H34**), 4.35 (s, 1H, **H36**), 4.21 (dd, *J* = 15.9, 5.4 Hz, 1H, **H32**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.68 – 3.53 (m, 4H, **H37, H46**), 3.50 – 3.42 (m, 12H, **H47-H52**), 3.35 – 3.31 (m, 2H **H53**), 3.17 (q, *J* = 5.8 Hz, 2H, **H54**), 2.94 – 2.83 (m, 4H, **H7, H13**), 2.80 – 2.72 (m, 2H, **H12**), 2.59 – 2.52 (m, 1H, **H45**), 2.47 – 2.29 (m, 6H, **H8, H31, H45**), 2.03 (ddd, *J* = 11.0, 7.6, 2.5 Hz, 1H, **H35**), 1.90 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H, **H35**), 0.93 (s, 9H, **H41-H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.9 (**C33**), 171.5 (**C11**), 171.3 (**C44**), 169.9 (**C38**), 169.5 (**C9**), 157.2 (**C10**), 151.5 (**C30**), 148.6 (**C17**), 147.7 (**C29**), 147.2 (**C18**), 146.9 (**C5**), 139.5 (**C22**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 131.2 (**C28**), 129.6 (**C25**), 128.6 (**C23/24/26/27**), 127.4 (**C23/24/26/27**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 69.8 (**C47-C52**), 69.7 (**C47-C52**), 69.6

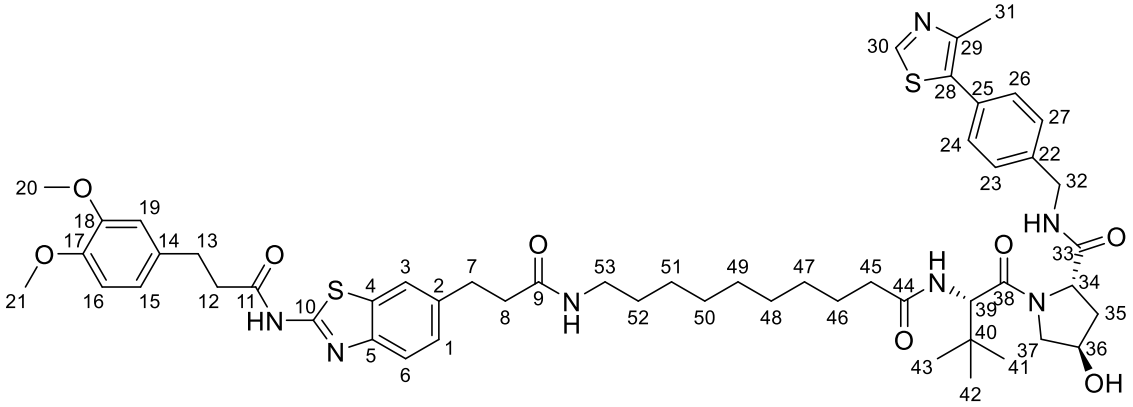
(**C47-C52**), 69.5 (**C47-C52**), 69.2 (**C53**), 68.9 (**C36**), 66.9 (**C46**), 58.7 (**C34**), 56.4 (**C37**), 56.3 (**C39**), 55.5 (**C20**), 55.4 (**C21**), 41.6 (**C32**), 38.5 (**C54**), 37.9 (**C35**), 37.3 (**C8**), 37.2 (**C12**), 35.6 (**C45**), 35.4 (**C40**), 31.1 (**C7**), 30.0 (**C13**), 26.3 (**C41-C43**), 15.9 (**C31**) ppm. LCMS: **HRMS (ESI):** m/z $[M + Na]^+$ calcd for $C_{54}H_{72}N_7O_{12}S_2Na^+$ 1096.4494; found 1096.4501. **Optical Rotation:** $[\alpha]_D^{20}$ = -11.04 (c = 1.03, EtOH).

(2*S*,4*R*)-1-((*S*)-2-(6-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20**



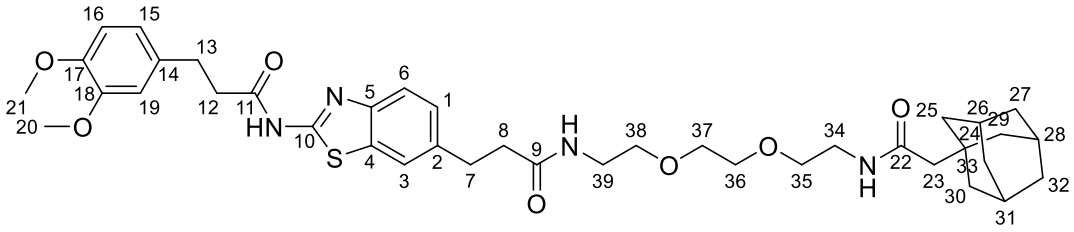
According to general procedure B, SI27 (0.06 mmol) and SI15 (0.07 mmol) provided the title compound as a white solid (49.00 mg, 72%). **Rf** = 0.40 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.25 (s, 1H, C10-**NH**-C11), 8.98 (s, 1H, **H30**), 8.56 (t, *J* = 6.1 Hz, 1H C32-**NH**-C33), 7.85 (d, *J* = 9.4 Hz, 1H, C9-**NH**-C49), 7.80 – 7.73 (m, 2H, **H3**, C39-**NH**-C44), 7.61 (d, *J* = 8.3 Hz, 1H, **H6**), 7.40 (q, *J* = 8.5 Hz, 4H, **H23, H24, H26, H27**), 7.25 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 6.88 – 6.79 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 5.13 (d, *J* = 3.5 Hz, 1H, C36-**OH**), 4.54 (d, *J* = 9.4 Hz, 1H, **H39**), 4.48 – 4.38 (m, 2H, **H32, H34**), 4.35 (br s, 1H, **H36**), 4.21 (dd, *J* = 15.9, 5.5 Hz, 1H, **H32**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.70 – 3.60 (m, 2H, **H37**), 2.99 (q, *J* = 6.6 Hz, 2H, **H49**), 2.94 – 2.83 (m, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.44 (s, 3H, **H31**), 2.39 (t, *J* = 7.8 Hz, 2H, **H8**), 2.25 – 2.16 (m, **H45**), 2.14 – 1.98 (m, 2H, **H35, H45**), 1.90 (ddd, *J* = 12.9, 8.7, 4.6 Hz, 1H, **H35**), 1.47 (dq, *J* = 14.6, 7.0 Hz, 2H, **H46**), 1.40 – 1.28 (m, 2H, **H48**), 1.25 – 1.12 (m, 2H, **H47**), 0.93 (s, 9H, **H41-43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.0 (**C33**), 171.9 (**C44**), 171.5 (**C11**), 171.0 (**C9**), 169.8 (**C38**), 157.2 (**C10**), 151.5 (**C30**), 148.6 (**C17**), 147.7 (**C29**), 147.2 (**C18**), 146.8 (**C5**), 139.5 (**C22**), 137.0 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 131.2 (**C28**), 129.6 (**C25**), 128.6 (**C23/24/26/27**), 127.4 (**C23/24/26/27**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 68.9 (**C36**), 58.7 (**C34**), 56.4 (**C37**), 56.3 (**C39**), 55.5 (**C20**), 55.4 (**C21**), 41.6 (**C32**), 38.4 (**C49**), 38.0 (**C35**), 37.4 (**C8**) , 37.1 (**C12**), 35.2 (**C40**), 34.8 (**C45**), 31.2 (**C7**), 30.0 (**C13**), 28.9 (**C48**), 26.4 (**C41-43**), 26.1 (**C47**), 25.2 (**C46**), 15.9 (**C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{49}H_{62}N_7O_8S_2^+$ 940.4101; found 940.4096. **Optical Rotation:** $[\alpha]_D^{20}$ = -91.90 (c = 0.65, EtOH).

(2*S*,4*R*)-1-((*S*)-2-(10-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **21**



According to general procedure B, SI27 (0.07 mmol) and SI12 (0.08 mmol) provided the title compound as a white solid (70.00 mg, 97%). **Rf** = 0.48 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.26 (s, 1H, C10-**NH**-C11), 8.98 (s, 1H, **H30**), 8.56 (t, *J* = 6.0 Hz, 1H, C32-**NH**-C33), 7.83 (d, *J* = 9.3 Hz, 1H, C9-**NH**-C53), 7.78 – 7.71 (m, 2H, **H3**, C39-**NH**-C44), 7.60 (d, *J* = 8.3 Hz, 1H, **H6**), 7.40 (q, *J* = 8.4 Hz, 4H, **H23, H24, H26, H27**), 7.25 (dd, *J* = 8.4, 1.8 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 5.12 (d, *J* = 3.5 Hz, 1H, C36-**OH**), 4.54 (d, *J* = 9.4 Hz, 1H, **H39**), 4.48 – 4.39 (m, 2H, **H32, H34**), 4.39 – 4.31 (m, 1H, **H36**), 4.21 (dd, *J* = 15.9, 5.4 Hz, 1H, **H32**), 3.71 (s, 3H, **H20**), 3.69 (s, 3H, **H21**), 3.70 – 3.60 (m, 2H, **H37**), 2.99 (q, *J* = 6.6 Hz, 2H, **H53**), 2.89 (q, *J* = 8.1 Hz, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.44 (s, 3H, **H31**), 2.39 (t, *J* = 7.6 Hz, 2H, **H8**), 2.31 – 2.19 (m, 1H, **H45**), 2.16 – 1.98 (m, 2H, **H35, H45**), 1.90 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H, **H35**), 1.45 – 1.37 (m, 2H, **H46**), 1.33 – 1.07 (m, 12H, **H47-H52**), 0.93 (s, 9H, **H41-H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.1 (**C33**), 171.9 (**C44**), 171.5 (**C11**), 171.0 (**C9**), 169.7 (**C38**), 157.2 (**C10**), 151.5 (**C30**), 148.6 (**C17**), 147.7 (**C29**), 147.2 (**C18**), 146.8 (**C5**), 139.5 (**C22**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 131.2 (**C28**), 129.6 (**C25**), 128.6 (**C23/24/26/27**), 127.4 (**C23/24/26/27**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 68.9 (**C36**), 58.7 (**C34**), 56.3 (**C37**), 56.3 (**C39**), 55.5 (**C20**), 55.3 (**C21**), 41.6 (**C32**), 38.4 (**C53**), 38.0 (**C35**), 37.3 (**C8**), 37.2 (**C12**), 35.2 (**C40**), 34.9 (**C45**), 31.1 (**C7**), 30.0 (**C13**), 29.1 (**C52**), 28.9 (**C47-C52**), 28.7 (**C47-C52**), 28.7 (**C47-C52**), 26.4 (**C41-C43**), 25.5 (**C46**), 15.9 (**C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{53}H_{70}N_7O_8S_2^+$ 996.4727; found 996.4720. **Optical Rotation:** $[\alpha]_D^{20}$ = -18.41 (c = 1.03, EtOH).

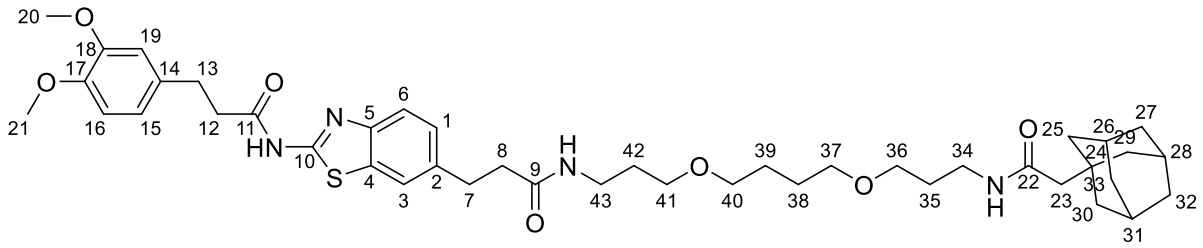
N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,13-dioxo-6,9-dioxa-3,12-diazapentadecan-15-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **22**



According to general procedure B, SI27 (0.07 mmol) and SI7 (0.08 mmol) provided the title compound as a white solid (41.00 mg, 79%). **Rf** = 0.48 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz,

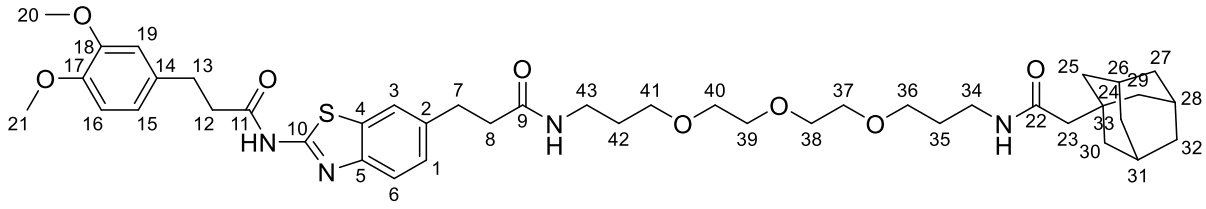
DMSO): δ 12.27 (s, 1H, C10-**NH**-C11), 7.89 (t, *J* = 5.7 Hz, 1H C9-**NH**-C39), 7.76 (d, *J* = 1.7 Hz, 1H, **H3**), 7.69 (t, *J* = 5.7 Hz, 1H, C22-**NH**-C34), 7.61 (d, *J* = 8.3 Hz, 1H, **H6**), 7.26 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 3.72 (s, 3H, **H20**), 3.70 (s, 3H, **H21**), 3.45 (s, 4H, **H35, H38**), 3.40 – 3.34 (m, 4H, **H36, H37**), 3.17 (p, *J* = 5.7 Hz, 4H, **H34, H39**), 2.94 – 2.84 (m, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.42 (dd, *J* = 8.5, 6.9 Hz, 2H, **H8**), 1.91 – 1.84 (m, 3H, **H26, H28, H31**), 1.80 (s, 2H, **H23**), 1.67 – 1.50 (m, 12H, **H25, H27, H29, H30, H32, H33**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.5 (**C11**), 171.3 (**C9**) , 170.0 (**C22**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.9 (**C5**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.2 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 69.5, 69.5, 69.2, 69.2, 55.5 (**C20**), 55.4 (**C21**), 50.0 (**C23**), 42.1 (**C25, C27, C29, C30, C32, C33**), 38.5 (**C39**), 38.3 (**C34**), 37.3 (**C8**), 37.2 (**C12**), 36.5 (**C25, C27, C29, C30, C32, C33**), 32.1 (**C24**), 31.1 (**C7**), 30.0 (**C13**), 28.0 (**C26, C28, C31**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{39}H_{53}N_4O_7S^+$ 721.3635; found 721.3638.

N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,17-dioxo-7,12-dioxa-3,16-diazanonadecan-19-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **23**



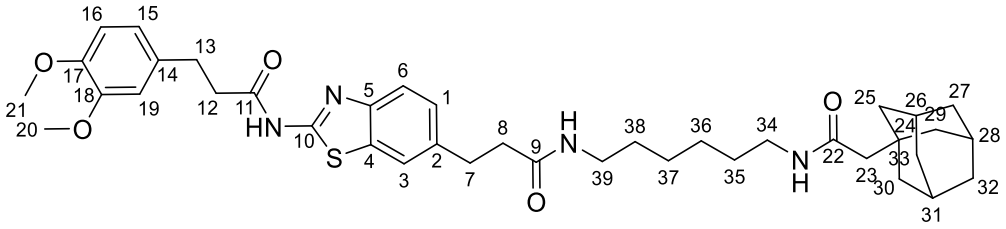
According to general procedure B, SI27 (0.07 mmol) and SI8 (0.08 mmol) provided the title compound as a white solid (40.00 mg, 71%). **Rf** = 0.41 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.27 (s, 1H, C10-**NH**-C11), 7.81 – 7.73 (m, 2H, C9-**NH**-C43, **H3**), 7.72 – 7.56 (m, 2H, C22-**NH**-C34, **H6**), 7.25 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 3.71 (s, 3H, **H20**), 3.70 (s, 3H, **H21**), 3.38 – 3.28 (m, 4H, **H40, H41**), 3.29 – 3.19 (m, 4H, **H36, H37**), 3.05 (q, *J* = 6.5 Hz, 4H, **H34, H43**), 2.89 (dt, *J* = 10.6, 7.5 Hz, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.40 (dd, *J* = 8.3, 6.9 Hz, 2H, **H8**), 1.89 (q, *J* = 3.2 Hz, 3H, **H26, H28, H31**), 1.79 (s, 2H, **H23**), 1.67 – 1.44 (m, 20H, **H25, H27, H29, H30, H32, H33, H35, H38, H39, H42**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.5 (**C11**), 171.1 (**C9**), 169.8 (**C22**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.9 (**C5**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 69.9 (**C40**), 69.8 (**C37**), 67.7 (**C41**), 67.5 (**C36**), 55.5 (**C20**), 55.4 (**C21**), 50.1 (**C23**), 42.1 (**C25, C27, C29, C30, C32, C33**), 37.3 (**C8**), 37.1 (**C12**), 36.5 (**C25, C27, C29, C30, C32, C33**), 35.7 (**C43**), 35.6 (**C34**), 32.1 (**C24**), 31.1 (**C7**), 30.0 (**C13**), 29.5 (**C35/C38/C39/C42**), 29.4 (**C35/C38/C39/C42**), 28.0 (**C26, C28, C31)**, 26.0 (**C35/C38/C39/C42**), 26.0 (**C35/C38/C39/C42**) ppm. LCMS: **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{43}H_{61}N_4O_7S^+$ 777.4261; found 777.4265.

N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,18-dioxo-7,10,13-trioxa-3,17-diazaicosan-20-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **24**



According to general procedure B, SI27 (0.07 mmol) and SI9 (0.08 mmol) provided the title compound as a white solid (44.00 mg, 77%). **Rf** = 0.37 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.27 (s, 1H, C10-**NH**-C11), 7.82 – 7.73 (m, 2H, C9-**NH**-C43, **H3**), 7.70 – 7.58 (m, 2H, C22-**NH**-C34, **H6**), 7.25 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 3.71 (s, 3H, **H20**), 3.70 (s, 3H, **H21**), 3.52 – 3.43 (m, 6H, **H38-H40**), 3.43 – 3.36 (m, 4H, **H37, H41**), 3.29 (t, *J* = 6.4 Hz, 2H, **H36**), 3.05 (qd, *J* = 6.7, 2.5 Hz, 4H, **H34, H43**), 2.89 (dt, *J* = 10.5, 7.4 Hz, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.40 (dd, *J* = 8.4, 6.9 Hz, 2H, **H8**), 1.89 (dd, *J* = 5.8, 3.0 Hz, 3H, **H26, H28, H31**), 1.79 (s, 2H, **H23**), 1.67 – 1.51 (m, 16H, **H25, H27, H29, H30, H32, H33, H35, H42**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.5 (**C11**), 171.1 (**C9**), 169.8 (**C22**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.9 (**C5**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 69.7 (**C37-C40**), 69.5 (**C37-C40**), 69.5 (**C37-C40**), 68.1 (**C41**), 68.0 (**C36**), 55.5 (**C20**), 55.4 (**C21**), 50.1 (**C23**), 42.1 (**C25, C27, C29, C30, C32, C33**), 37.3 (**C8**), 37.2 (**C12**), 36.5 (**C25, C27, C29, C30, C32, C33**), 35.7 (**C43**), 35.6 (**C34**), 32.2 (**C24**), 31.1 (**C7**), 30.0 (**C13**), 29.5 (**C35/C42**), 29.3(**C35/C42**), 28.0 (**C26, C28, C31)** ppm. **HRMS (ESI):** m/z [M + H]$^{+}$ calcd for $C_{43}H_{61}N_4O_8S^{+}$ 793.4210; found 793.4211.

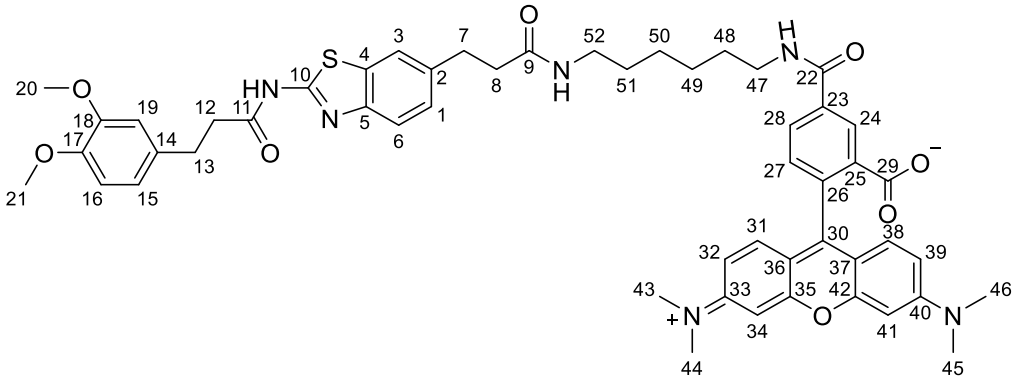
N-(6-(2-((3*r*,5*r*,7*r*)-adamantan-1-yl)acetamido)hexyl)-3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamide **25**



According to general procedure B, SI27 (0.07 mmol) and SI10 (0.08 mmol) provided the title compound as a white solid (40.00 mg, 80%). **Rf** = 0.67 (DCM/MeOH 9:1); **^{1}H NMR** (400 MHz, DMSO): δ 12.27 (s, 1H, C10-**NH**-C11), 7.80 – 7.72 (m, 2H, C9-**NH**-C43, **H3**), 7.64 – 7.57 (m, 2H, C22-**NH**-C34, **H6**), 7.25 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**), 6.74 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 3.71 (s, 3H, **H20**), 3.70 (s, 3H, **H21**), 2.98 (p, *J* = 6.6 Hz, 4H, **H34, H39**), 2.89 (td, *J* = 8.8, 6.7 Hz, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.39 (dd, *J* = 8.4, 6.9 Hz, 2H, **H8**), 1.92 – 1.85 (m, 3H, **H26, H28, H31**), 1.79 (s, 2H, **H23**), 1.67 – 1.51 (m, 12H, **H25, H27, H29, H30, H32, H33**), 1.37 – 1.25 (m, 4H, **H35, H38**), 1.25 – 1.11 (m, 4H, **H36, H37**) ppm.**^{13}C NMR** (101 MHz, DMSO): δ 171.5 (**C11**), 171.1 (**C9**), 169.7 (**C22**), 157.2 (**C10**), 148.6 (**C17**), 147.2 (**C18**), 146.9 (**C5**), 137.0 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 55.5 (**C20**), 55.4 (**C21**), 50.1 (**C23**), 42.1 (**C25, C27, C29, C30, C32, C33**), 38.3 (**C34/C39**), 38.2 (**C34/C39**), 37.4 (**C8**), 37.2 (**C12**), 36.5 (**C25, C27, C29, C30, C32, C33**), 32.1 (**C24**), 31.1 (**C7**), 30.0 (**C13**), 29.1 (**C37, C38**),

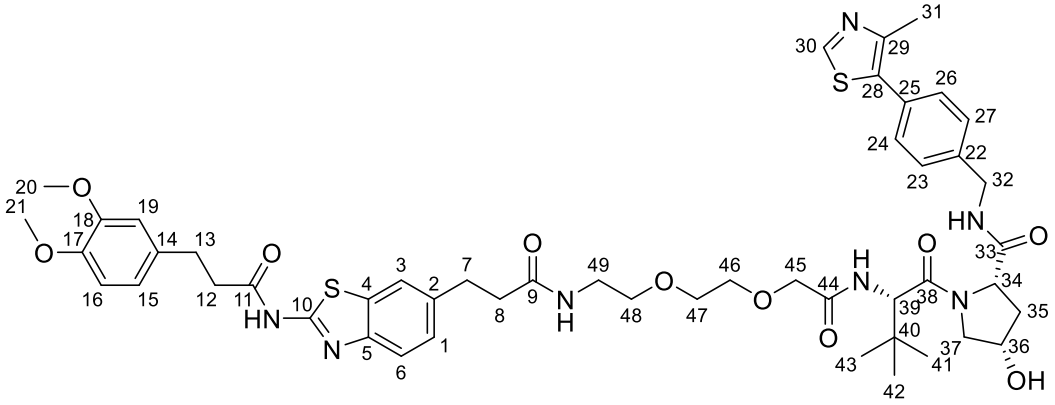
28.0 (**C26, C28, C31**), 26.1 (**C36/C37**), 26.0 (**C36/C37**) ppm. **HRMS (ESI):** m/z $[M + H]^+$ calcd for $C_{39}H_{53}N_4O_5S^+$ 689.3736; found 689.3742.

5-((6-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[d]thiazol-6-yl)propanamido)hexyl)carbamoyl)-2-(6-(dimethylamino)-3-(dimethyliminio)-3*H*-xanthen-9-yl)benzoate **27**



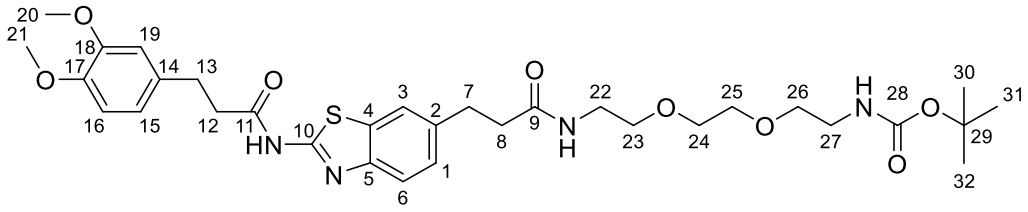
Purple solid (50.00 mg, 42%); **Rf** = 0.45 (DCM/MeOH/Et_3N 90/8/2); **^{1}H NMR** (400 MHz, MeOD): δ 8.69 (t, *J* = 5.7 Hz, 1H, NH, C22-**NH**-C47), 8.65 (d, *J* = 1.8 Hz, 1H, **H24**), 8.14 (dd, *J* = 7.9, 1.9 Hz, 1H, **H28**), 7.88 (t, *J* = 5.8 Hz, 1H, NH, C9-**NH**-C52), 7.65 (d, *J* = 1.7 Hz, 1H, **H3**), 7.59 (d, *J* = 8.3 Hz, 1H, **H6**), 7.39 (d, *J* = 7.9 Hz, 1H, **H27**), 7.26 (dd, *J* = 8.3, 1.8 Hz, 1H, **H1**), 7.14 (d, *J* = 9.5 Hz, 2H, **H31, H38**), 6.92 (dd, *J* = 9.5, 2.5 Hz, 2H, **H32, H39**), 6.86 (d, *J* = 2.4 Hz, 2H, **H34, H41**), 6.82 – 6.78 (m, 2H, **H16, H19**), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 3.74 (s, 3H, **H20**), 3.73 (s, 3H, **H21**), 3.36 (t, *J* = 7.1 Hz, 2H, **H47**), 3.24 (s, 12H, **H43-H46**), 3.15 – 3.04 (m, 2H, **H52**), 3.01 (t, *J* = 7.2 Hz, 2H, **H7**), 2.92 (dd, *J* = 14.4, 6.8 Hz, 2H, **H13**), 2.79 – 2.71 (m, 2H, **H12**), 2.51 (t, *J* = 7.2 Hz, 2H, **H8**), 1.53 (p, *J* = 7.2 Hz, 2H, **H48**), 1.39 – 1.32 (m, 2H, **H51**), 1.29 – 1.23 (m, 2H), 1.20 – 1.10 (m, 2H) ppm. One NH missing due to deuterium exchange (C10-**NH**-C11). **^{13}C NMR** (101 MHz, MeOD): δ 174.9 (**C9**), 173.6 (**C11**), 170.4 (**C29**), 168.6 (**C22**), 161.5 (**C30**), 159.2 (**C33/C40**), 158.9 (**C33/C40**), 158.7, 150.4 (**C17/C18**), 148.4 (**C17/C18**), 148.1 (**C5**), 138.1 (**C2**), 137.5, 137.3, 134.7 (**C14**), 133.4 (**C4**), 132.3 (**C31 + C38**), 131.3 (**C27**), 130.6 (**C28**), 130.3 (**C24**), 128.2 (**C1**), 121.8 (**C3**), 121.6 (**C15**), 121.6 (**C6**), 115.2 (**C32/C39**), 114.7 (**C32/C39**), 113.4 (**C16/C19**), 113.1(**C16/C19**), 97.4 (**C34 + C41**), 56.5 (**C20**), 56.4 (**C21**), 41.1 (**C47**), 40.9 (**C43-C46**), 40.2 (**C52**), 39.0 (**C8**), 38.8 (**C12**), 32.8 (**C7**), 31.7 (**C13**), 30.4 (**C51**), 30.3 (**C48**), 27.7 (**C49/C50**), 27.5 (**C49/C50**) ppm. **HRMS (ESI):** m/z $[M + 2H]^+$ calcd for $C_{52}H_{58}N_6O_8S^+$ 463.2013; found 463.2015.

(2*S*,4*S*)-1-((*S*)-2-(*tert*-butyl)-15-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)-4,13-dioxo-6,9-dioxa-3,12-diazapentadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **28**



According to general procedure B, SI27 (0.1 mmol) and SI17 (0.1 mmol) provided the title compound as a white solid (50.00 mg, 50%). **Rf** = 0.29 (DCM/MeOH 95:5); **^{1}H NMR** (400 MHz, DMSO): δ 12.28 (s, 1H, C10-**NH**-C11), 8.99 (s, 1H, **H30**), 8.65 (t, *J* = 6.0 Hz, 1H, C32-**NH**-C33), 7.89 (t, *J* = 5.7 Hz, 1H, C9-**NH**-C49), 7.76 (d, *J* = 1.7 Hz, 1H, **H3**), 7.62 (d, *J* = 8.3 Hz, 1H, **H6**), 7.47 – 7.37 (m, 5H, C39-**NH**-C44, **H23, H24, H26, H27**), 7.26 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 6.89 – 6.82 (m, 2H, **H16, H19**), 6.75 (dd, *J* = 8.2, 2.0 Hz, 1H, **H15**), 5.45 (d, *J* = 7.2 Hz, 1H, C36-**OH**), 4.54 (d, *J* = 9.3 Hz, 1H, **H39**), 4.45 – 4.35 (m, 2H, **H34, H32**), 4.35 – 4.17 (m, 2H, **H32, H36**), 4.02 – 3.85 (m, 3H, **H37, H45**), 3.73 (s, 3H, **H20**), 3.71 (s, 3H, **H21**), 3.63 – 3.53 (m, 2H, **H46**), 3.57 – 3.43 (m, 3H, **H37, H47**), 3.40 (t, *J* = 5.9 Hz, 2H, **H48**), 3.28 – 3.14 (m, 2H, **H49**), 2.96 – 2.85 (m, 4H, **H7, H13**), 2.82 – 2.74 (m, 2H, **H12**), 2.47 – 2.40 (m, 5H, **H8, H31**), 2.41 – 2.29 (m, 1H, **H35**), 1.75 (dt, *J* = 12.4, 6.1 Hz, 1H, **H35**), 0.96 (s, 9H, **H41-H43**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 172.1 (**C33**), 171.4 (**C11**), 171.3 (**C9**), 169.4 (**C38**), 168.9 (**C44**), 157.1 (**C10**), 151.4 (**C30**), 148.5 (**C17**), 147.7 (**C29**), 147.1 (**C18**), 146.8 (**C5**), 139.1 (**C22**), 136.9 (**C2**), 133.0 (**C14**), 131.4 (**C4**), 131.0 (**C28**), 129.7 (**C25**), 128.7 (**C23/24/26/27**), 127.4 (**C23/24/26/27**), 126.6 (**C1**), 120.7 (**C3**), 120.1 (**C6**), 119.9 (**C15**), 112.2 (**C19**), 111.8 (**C16**), 70.3 (**C46**), 69.4 (**C45**), 69.3 (**C47**), 69.2 (**C48**), 68.9 (**C36**), 58.5 (**C34**), 55.8 (**C39**), 55.6 (**C37**), 55.4 (**C20**), 55.3 (**C21**), 41.7 (**C32**), 38.4 (**C49**), 37.2 (**C8**), 37.1 (**C12**), 36.9 (**C35**), 35.1 (**C40**), 31.0 (**C7**), 29.9 (**C13**), 26.1 (**C41-C43**), 15.9 (**C31**) ppm. **LCMS** (ESI): *m/z* [M + H]$^+$ calcd for $C_{49}H_{61}N_7O_{10}S_2^+$: 972.40; found: 973.11. **Optical Rotation:** $[\alpha]_D^{20}$ = -14.68 (c = 0.95, EtOH).

tert-butyl (2-(2-(2-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamido)ethoxy)ethoxy)ethyl)carbamate **29**



An amide coupling procedure as in general procedure B provided the title compound from SI27 (0.2 mmol) and tert-butyl (2-(2-(2-aminoethoxy)ethoxy)ethyl)carbamate (0.22 mmol) as a white solid (59.00 mg, 50%); **Rf** = 0.51 (DCM/MeOH 95:5). **^{1}H NMR** (400 MHz, DMSO): δ 12.27 (s, 1H, C10-**NH**-C11), 7.88 (t, *J* = 5.6 Hz, 1H C9-**NH**-C22), 7.76 (d, *J* = 1.7 Hz, 1H, **H3**), 7.61 (d, *J* = 8.3 Hz, 1H, **H6**), 7.26 (dd, *J* = 8.3, 1.7 Hz, 1H, **H1**), 6.88 – 6.81 (m, 2H, **H16, H19**),

6.81 – 6.71 (m, 2H, **H15**, C27-**NH**-C28), 3.72 (s, 3H, **H20**), 3.70 (s, 3H, **H21**), 3.45 (s, 4H, **H24, H25**), 3.39 – 3.31 (m, 4H, **H23, H26**), 3.18 (q, *J* = 5.8 Hz, 2H, **H22**), 3.05 (q, *J* = 6.0 Hz, 2H, **H27**), 2.94 – 2.84 (m, 4H, **H7, H13**), 2.81 – 2.72 (m, 2H, **H12**), 2.42 (dd, *J* = 8.5, 6.9 Hz, 2H, **H8**), 1.36 (s, 9H, **H30-H32**) ppm. **^{13}C NMR** (101 MHz, DMSO): δ 171.6, 171.5 (**C11**), 171.3 (**C9**), 157.2 (**C10**), 155.6 (**C28**), 148.6 (**C17**), 147.2 (**C18**), 146.8 (**C5**), 136.9 (**C2**), 133.1 (**C14**), 131.5 (**C4**), 126.7 (**C1**), 120.7 (**C3**), 120.2 (**C6**), 120.0 (**C15**), 112.2 (**C19**), 111.9 (**C16**), 77.6 (**C29**), 69.5 (**C24**), 69.4 (**C25**), 69.2 (**C23, C26**), 55.5 (**C20**), 55.4 (**C21**), 38.5 (**C22**), 37.2 (**C8**), 37.1 (**C12**), 31.1 (**C7**), 30.0 (**C13**), 28.2 (**C30-C32**) ppm. **C27** missing due to superimposition with DMSO-d6. **LCMS** (ESI): *m/z* $[M + H]^+$ calcd for $C_{32}H_{45}N_4O_8S^+$: 645.4; found: 645.3.

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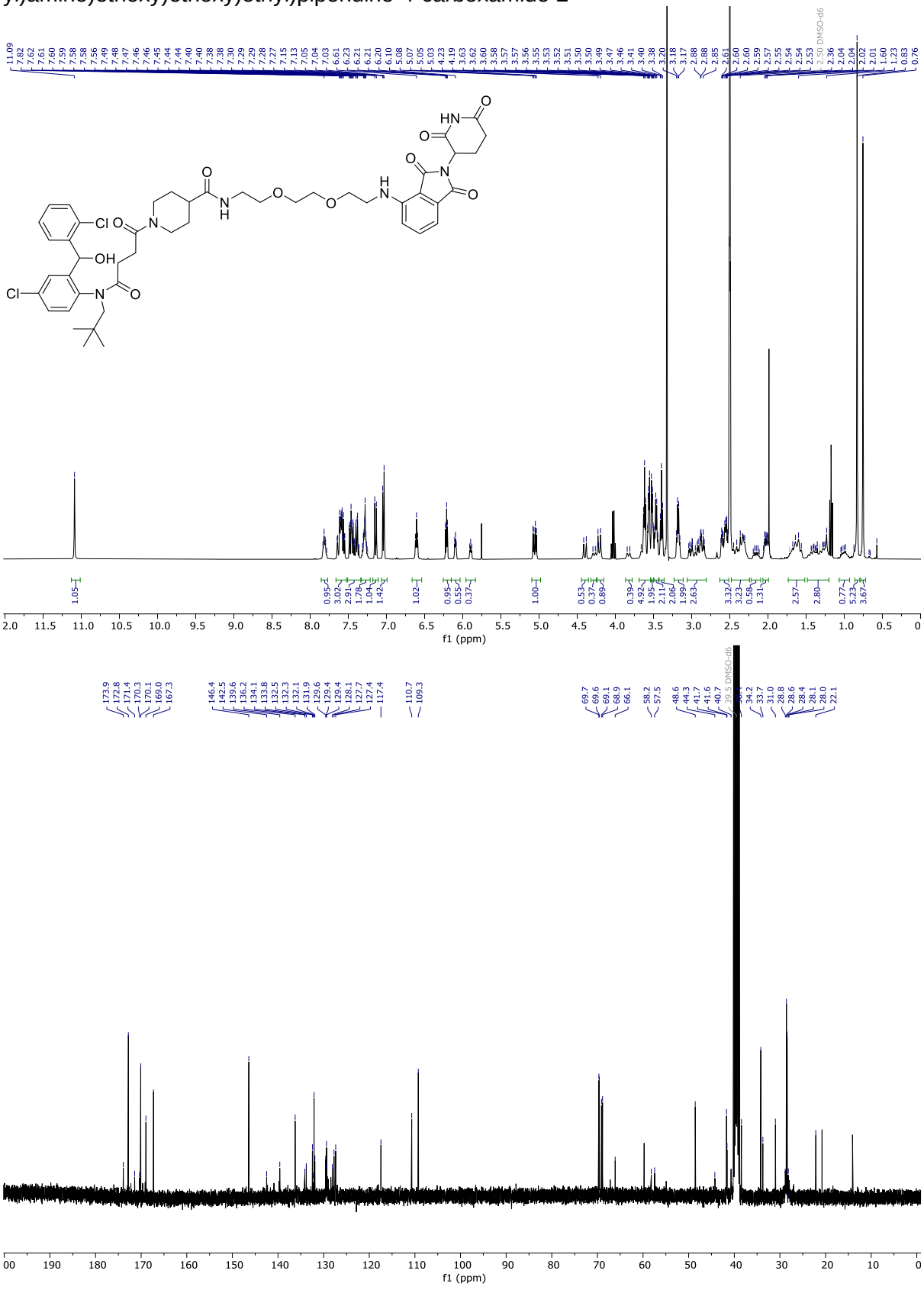
NMR data

1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)piperidine-4-carboxamide **1**



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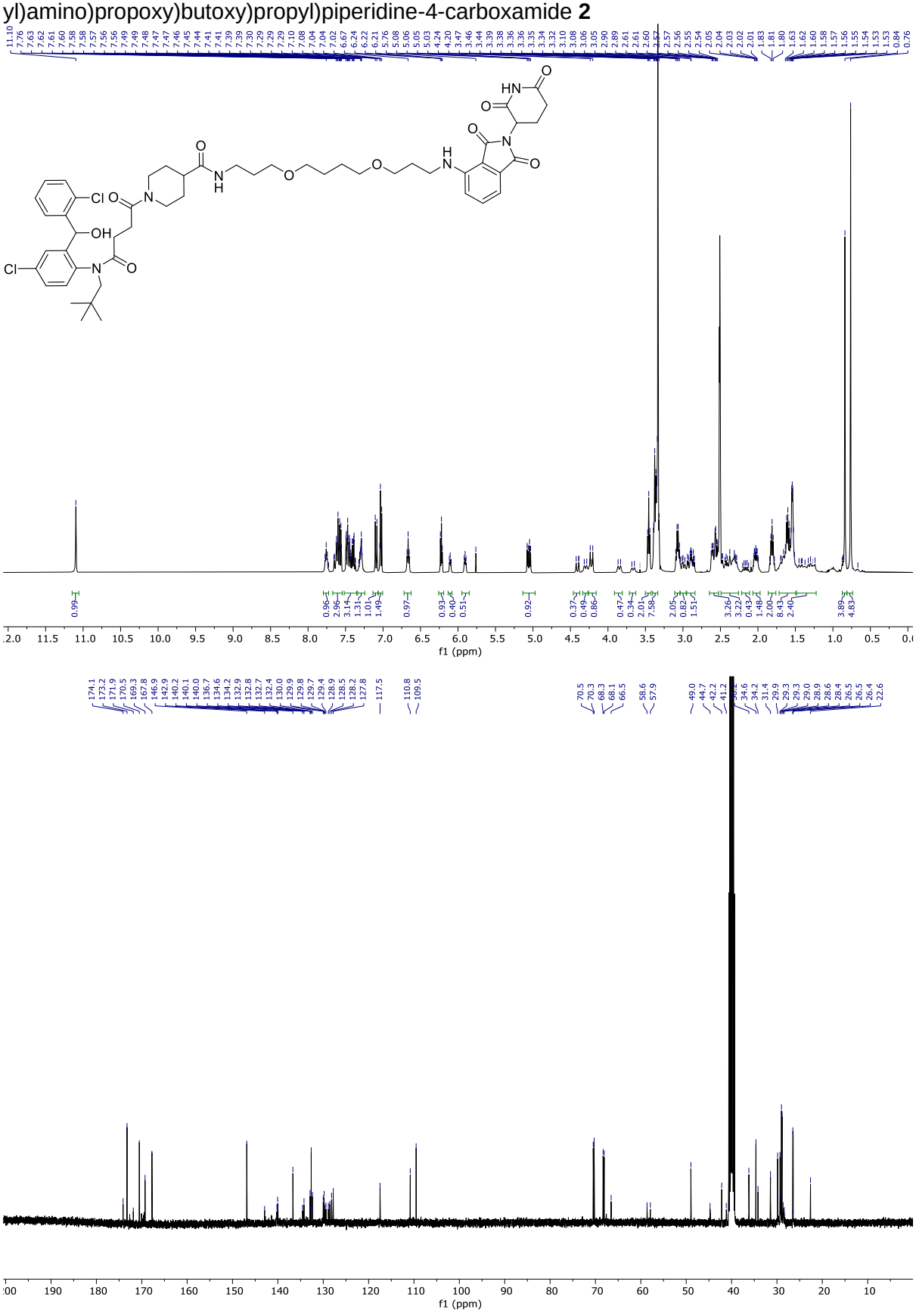

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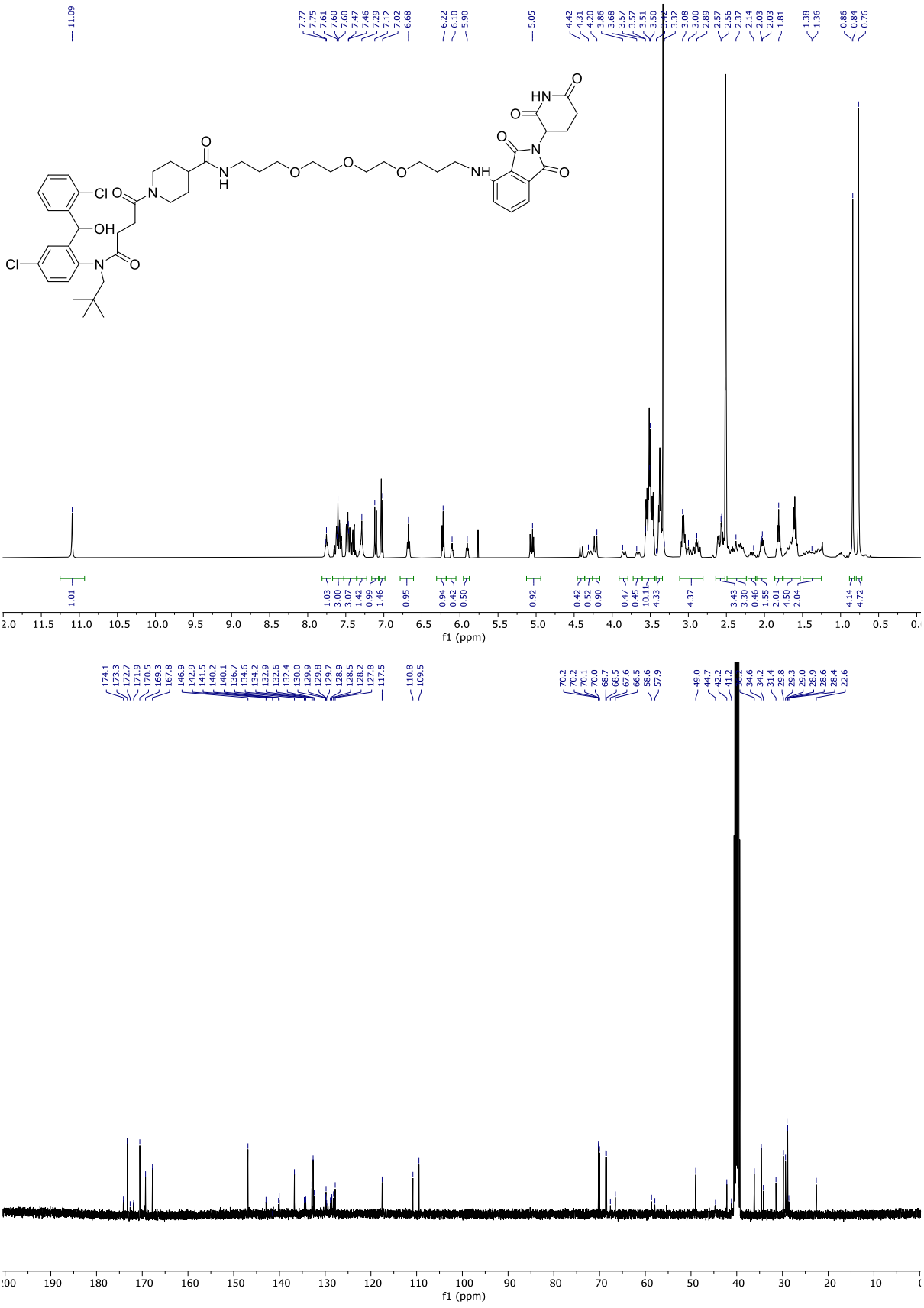

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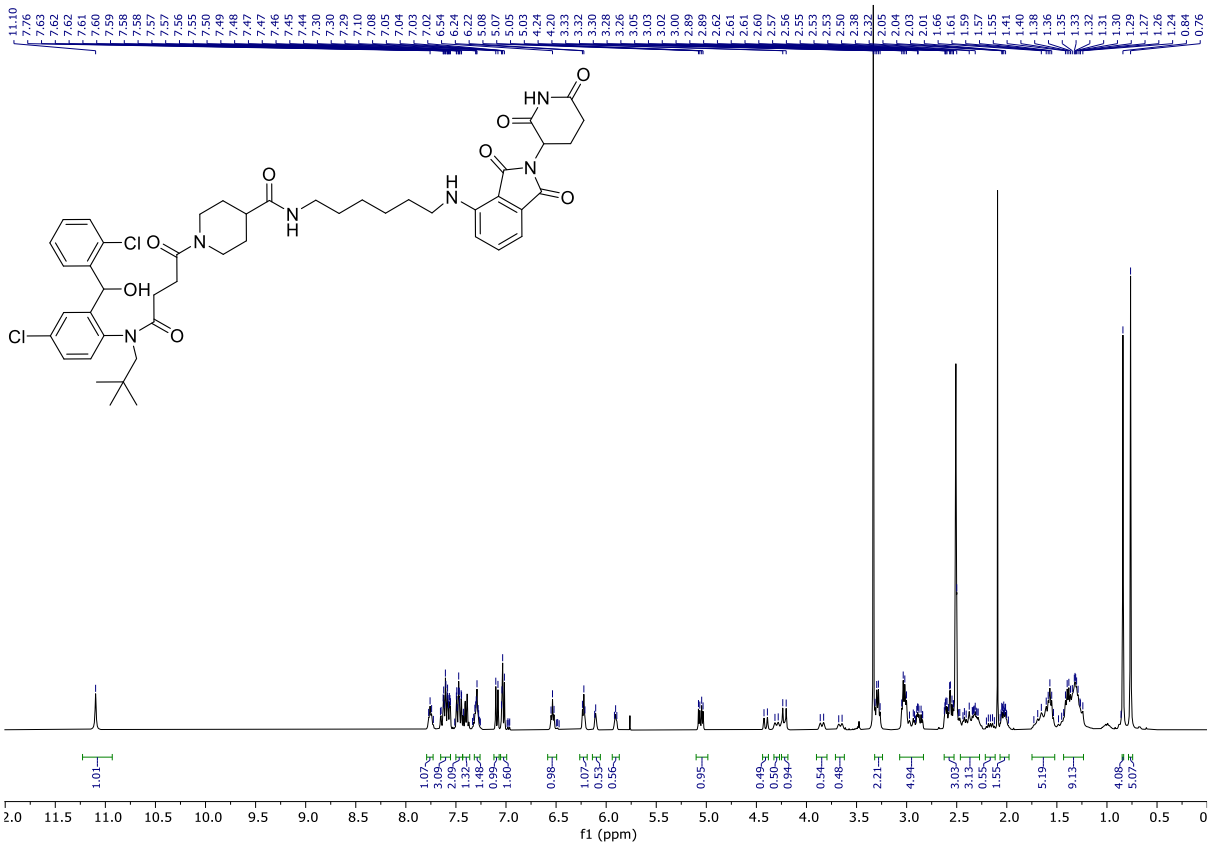
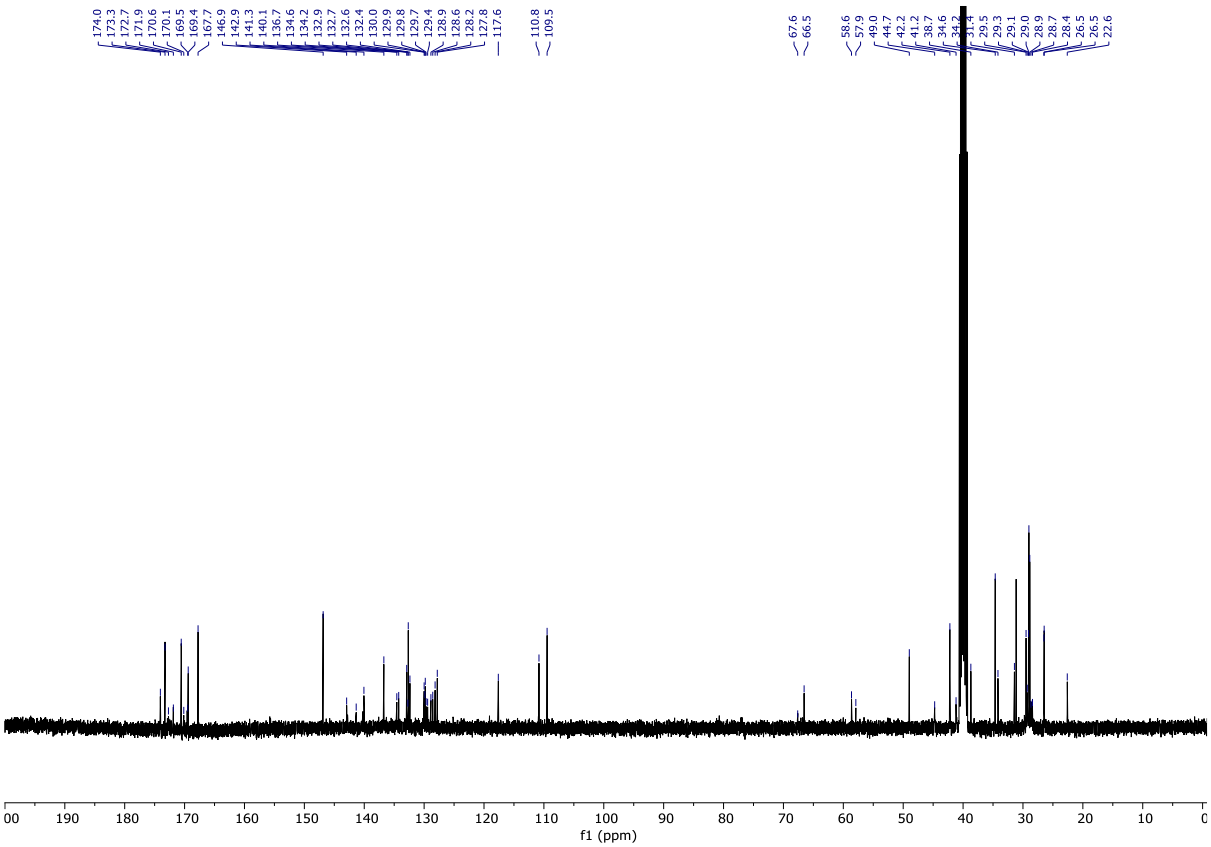
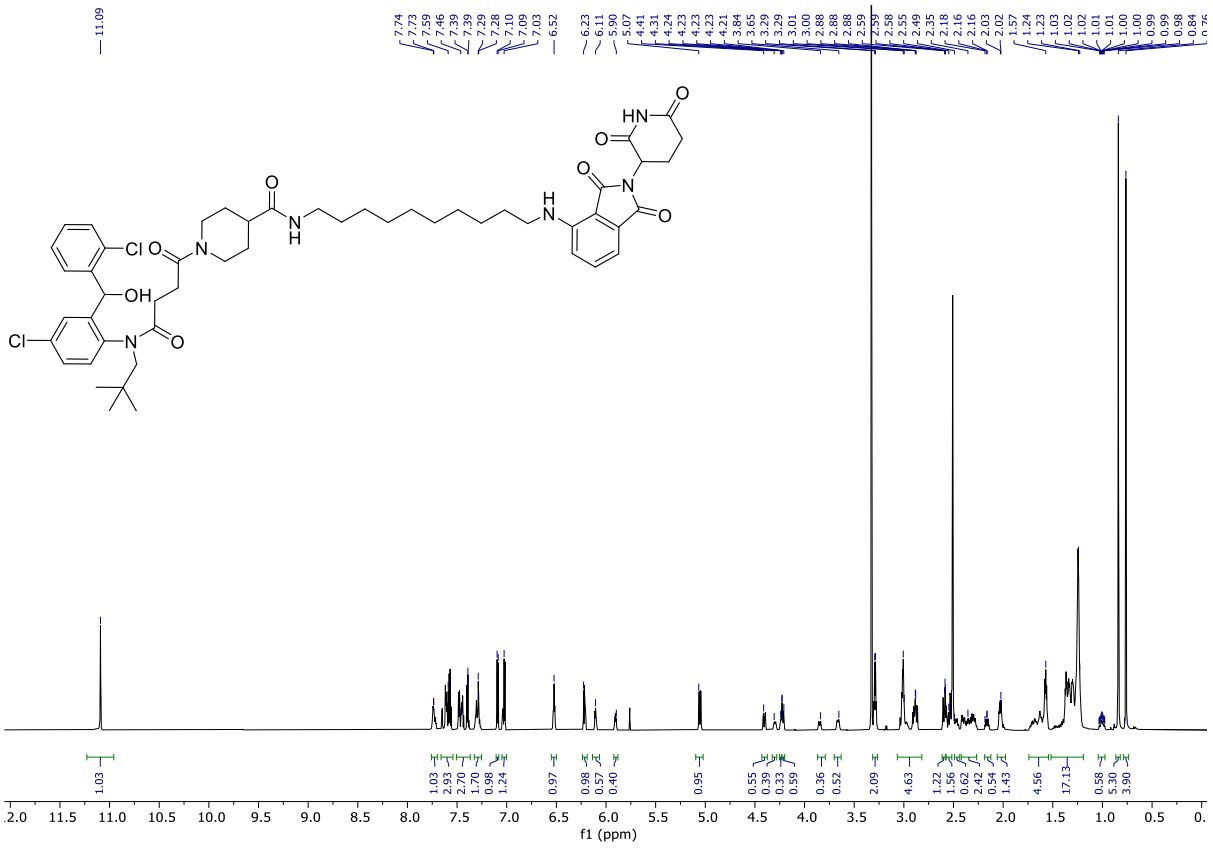
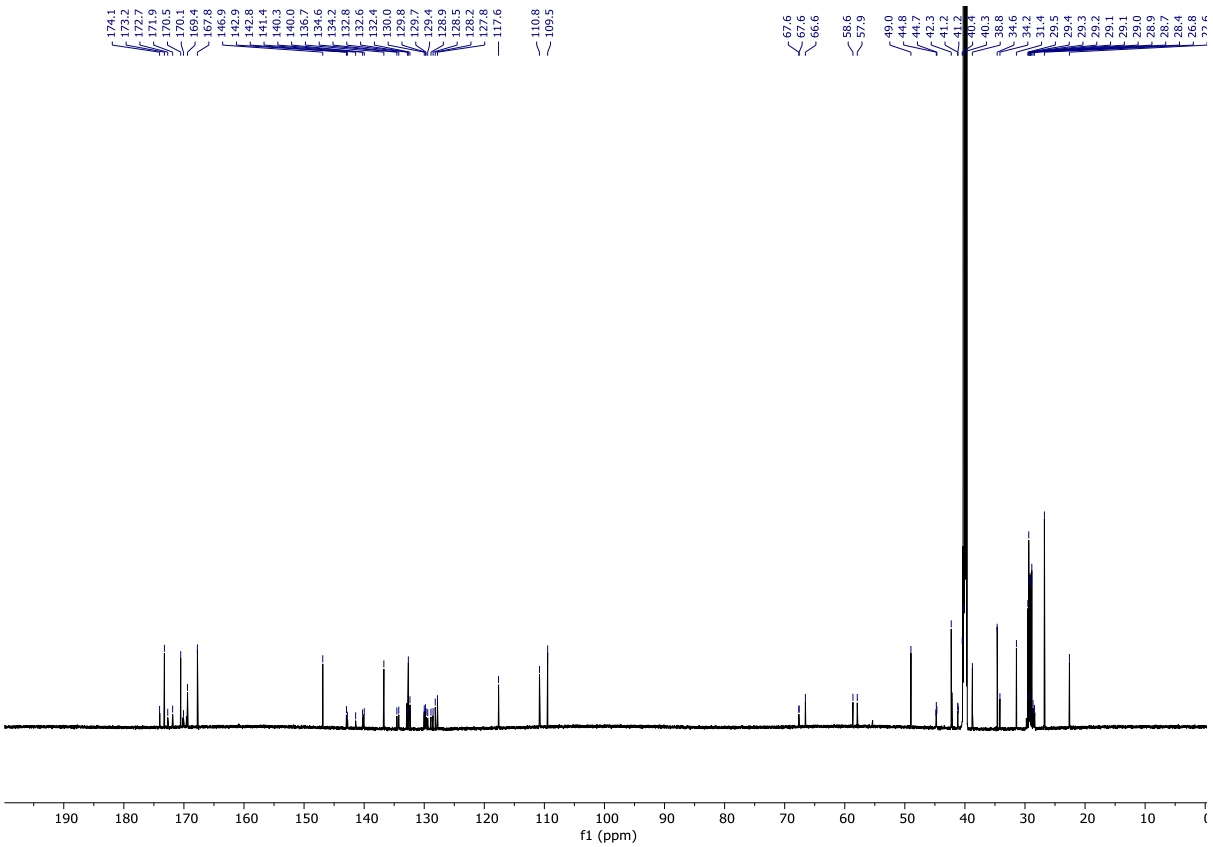


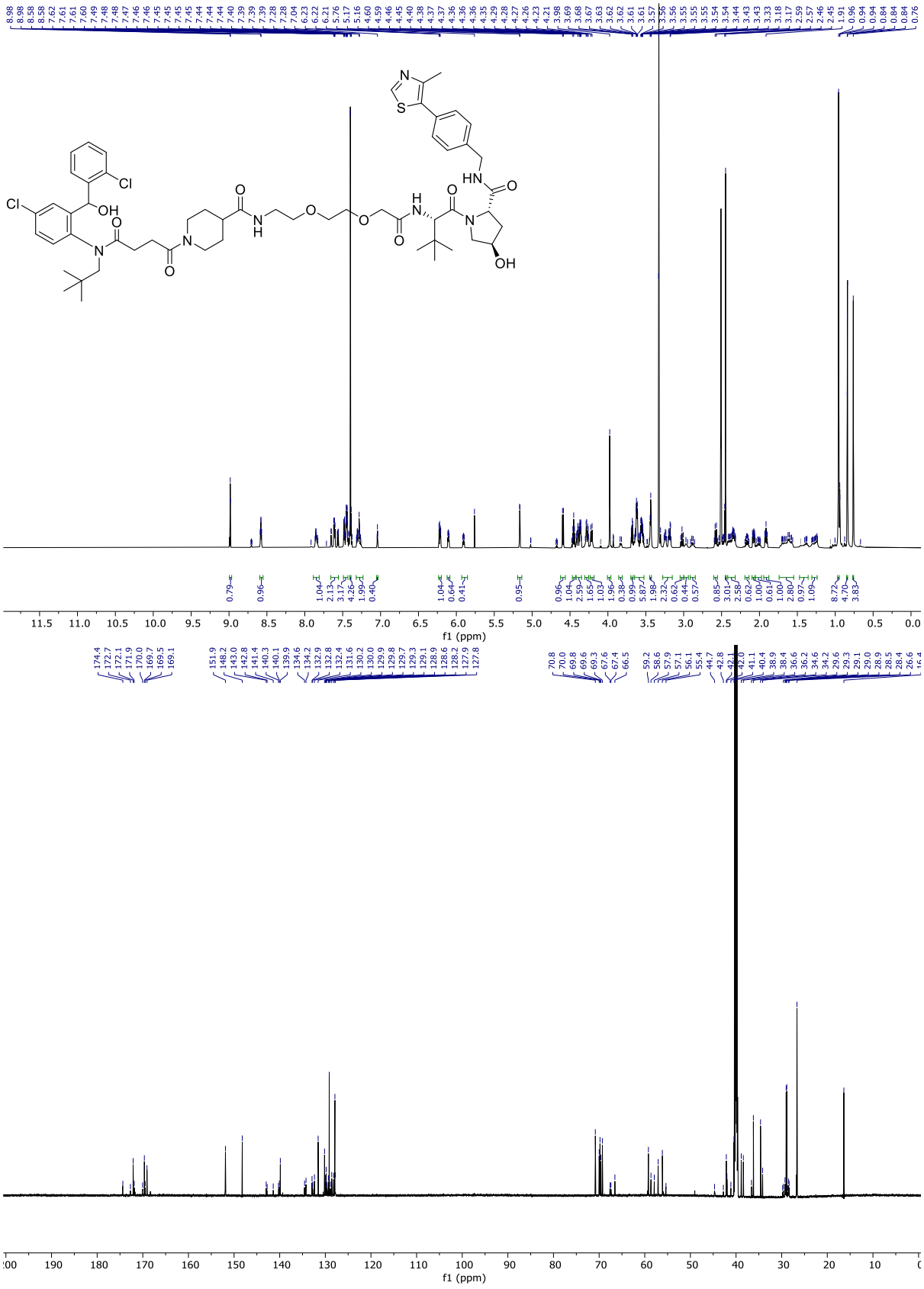


1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)piperidine-4-carboxamide **5**

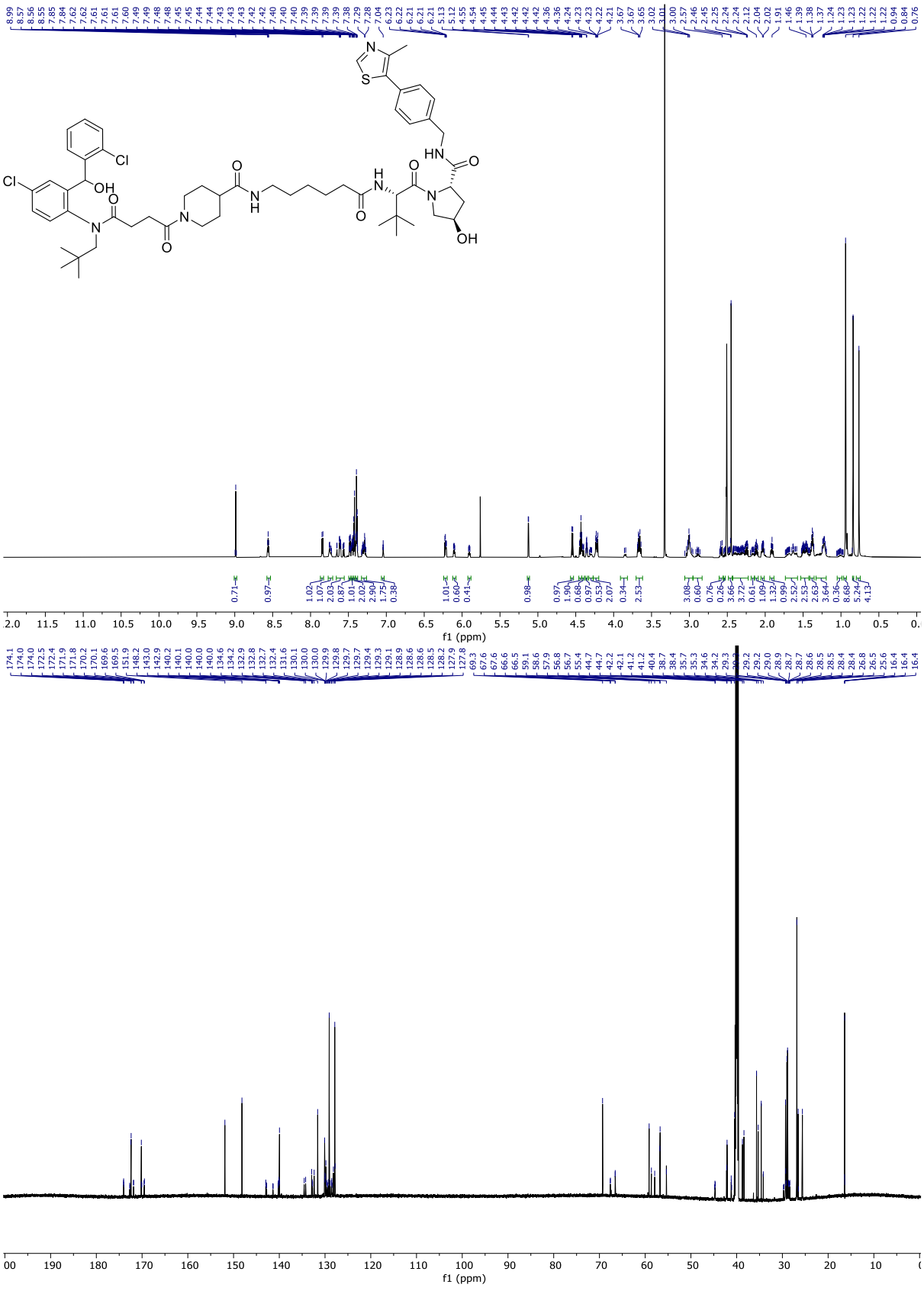




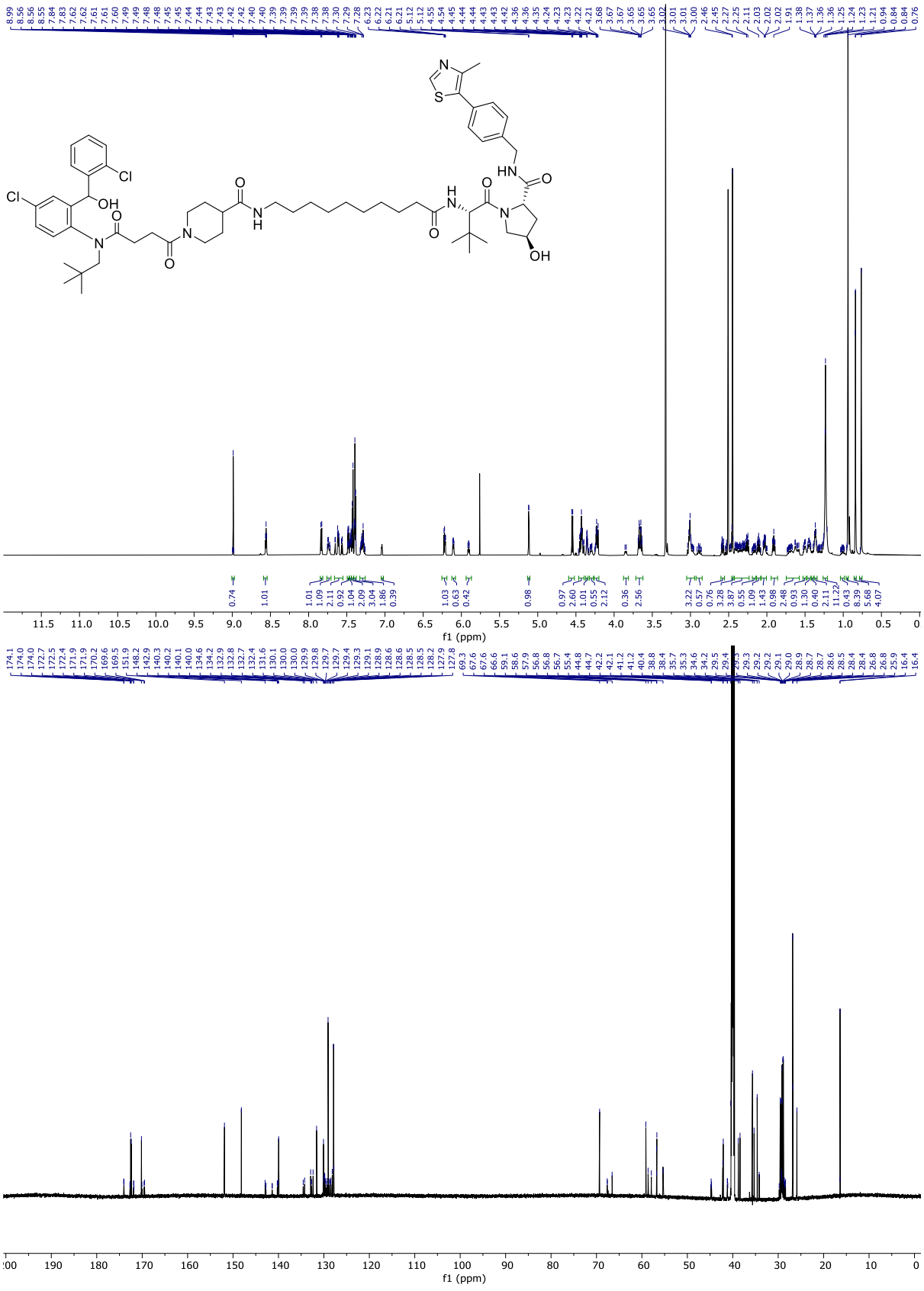
1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(2-(2-(2-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-2-oxoethoxy)ethoxy)ethyl)piperidine-4-carboxamide **6**



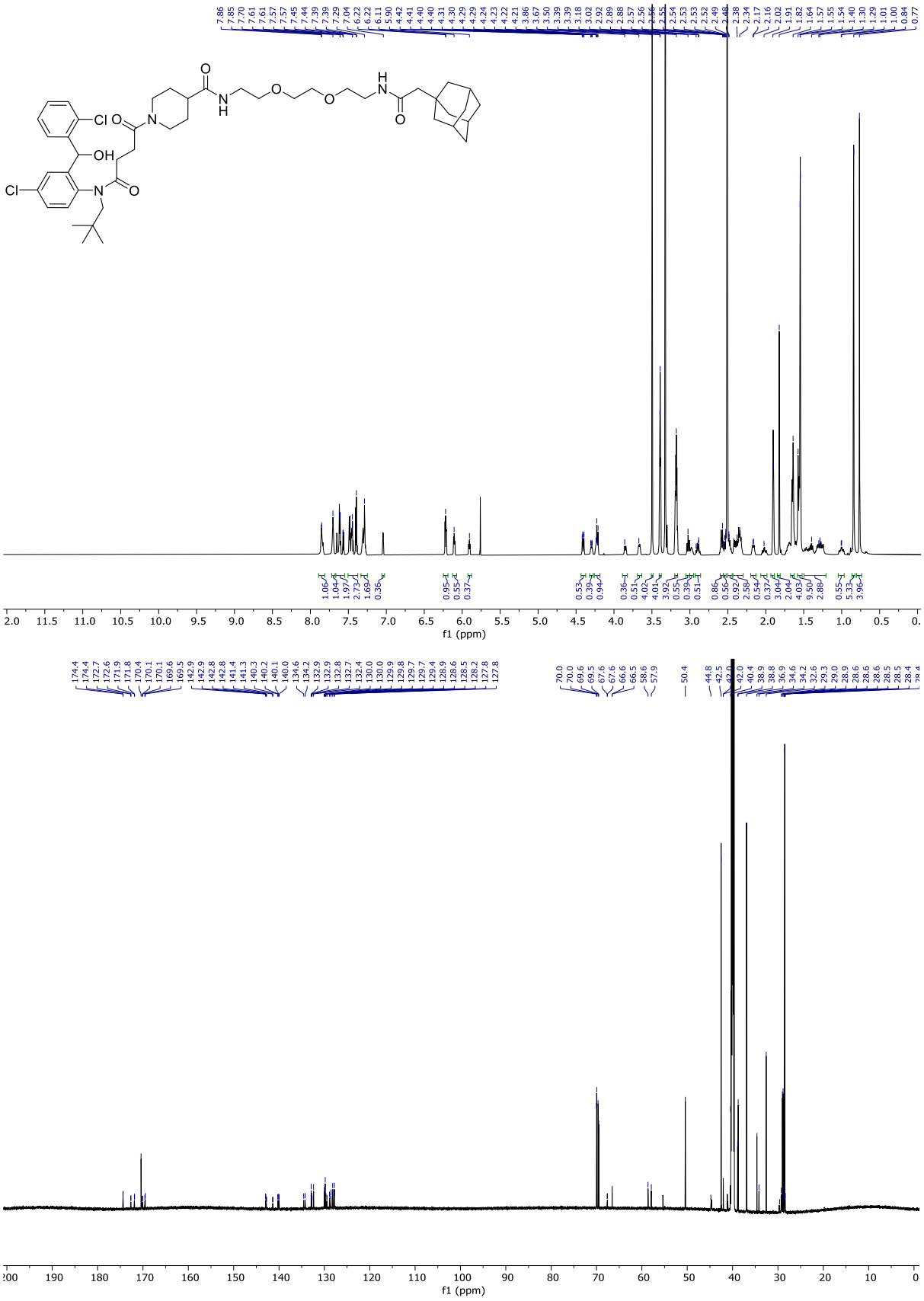
1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(6-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-6-oxohexyl)piperidine-4-carboxamide **7**



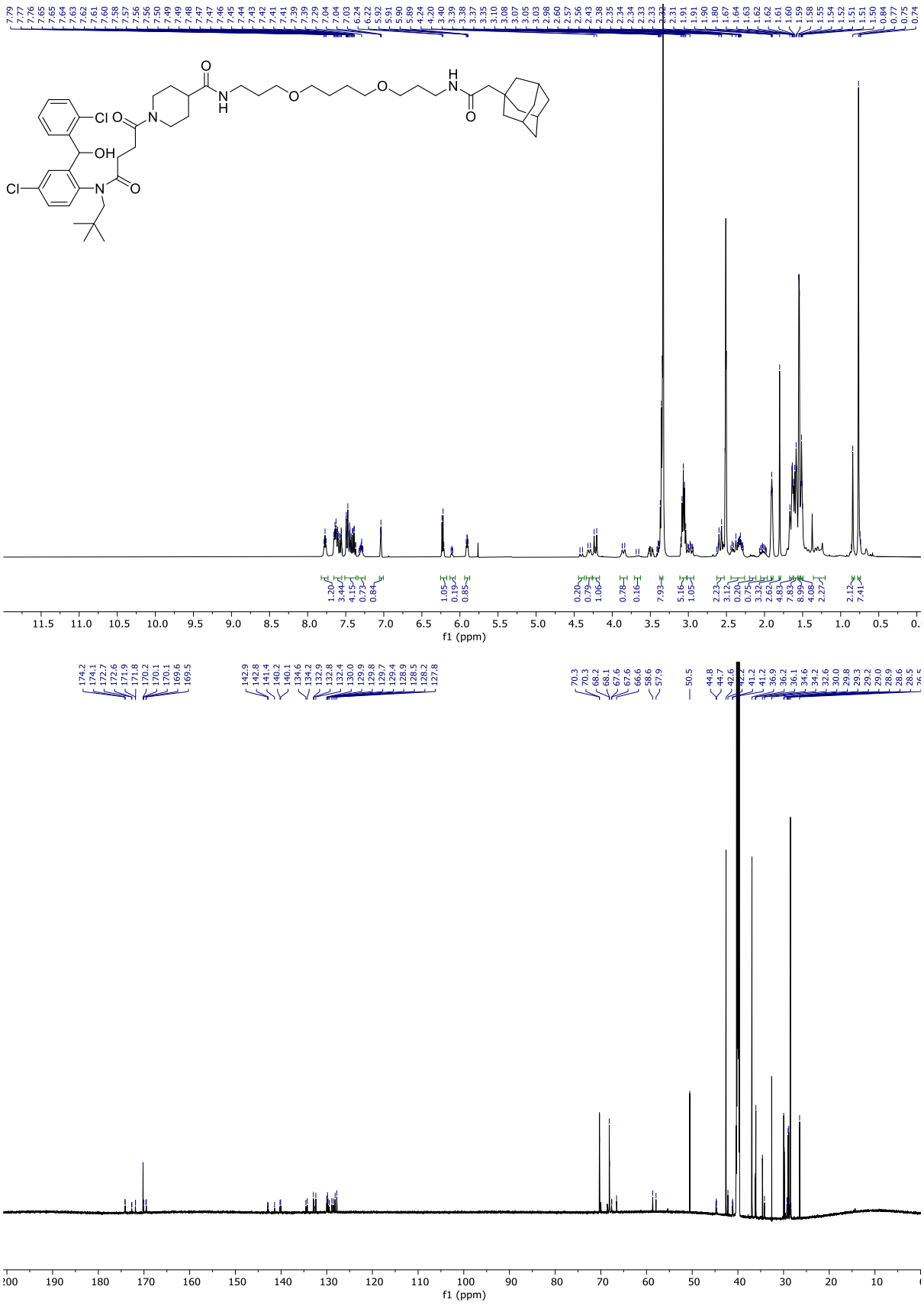
1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)-N-(10-(((S)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-10-oxodecyl)piperidine-4-carboxamide **8**



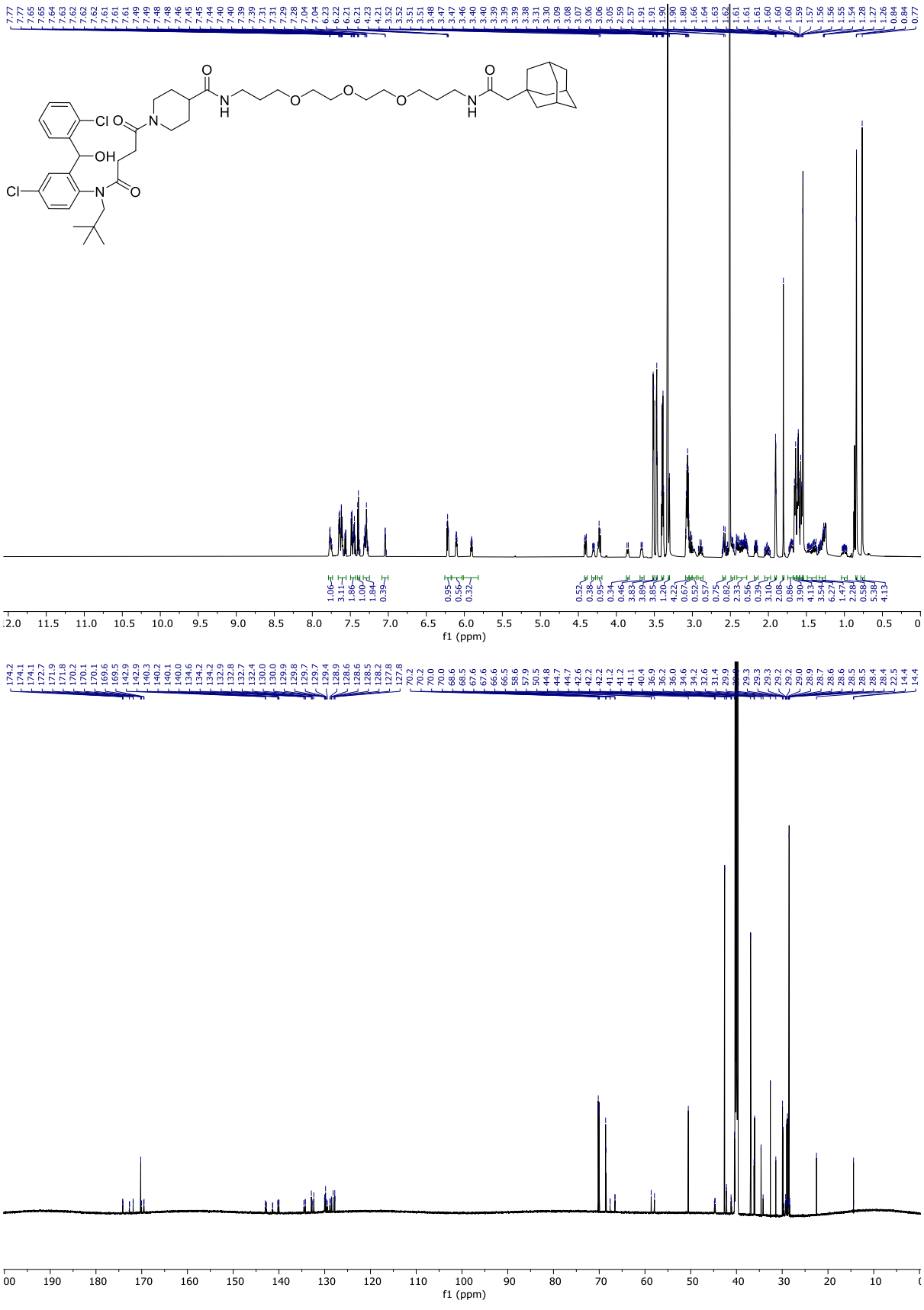
N-(2-(2-(2-(2-((1s,3s)-adamantan-1-yl)acetamido)ethoxy)ethoxy)ethyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **9**



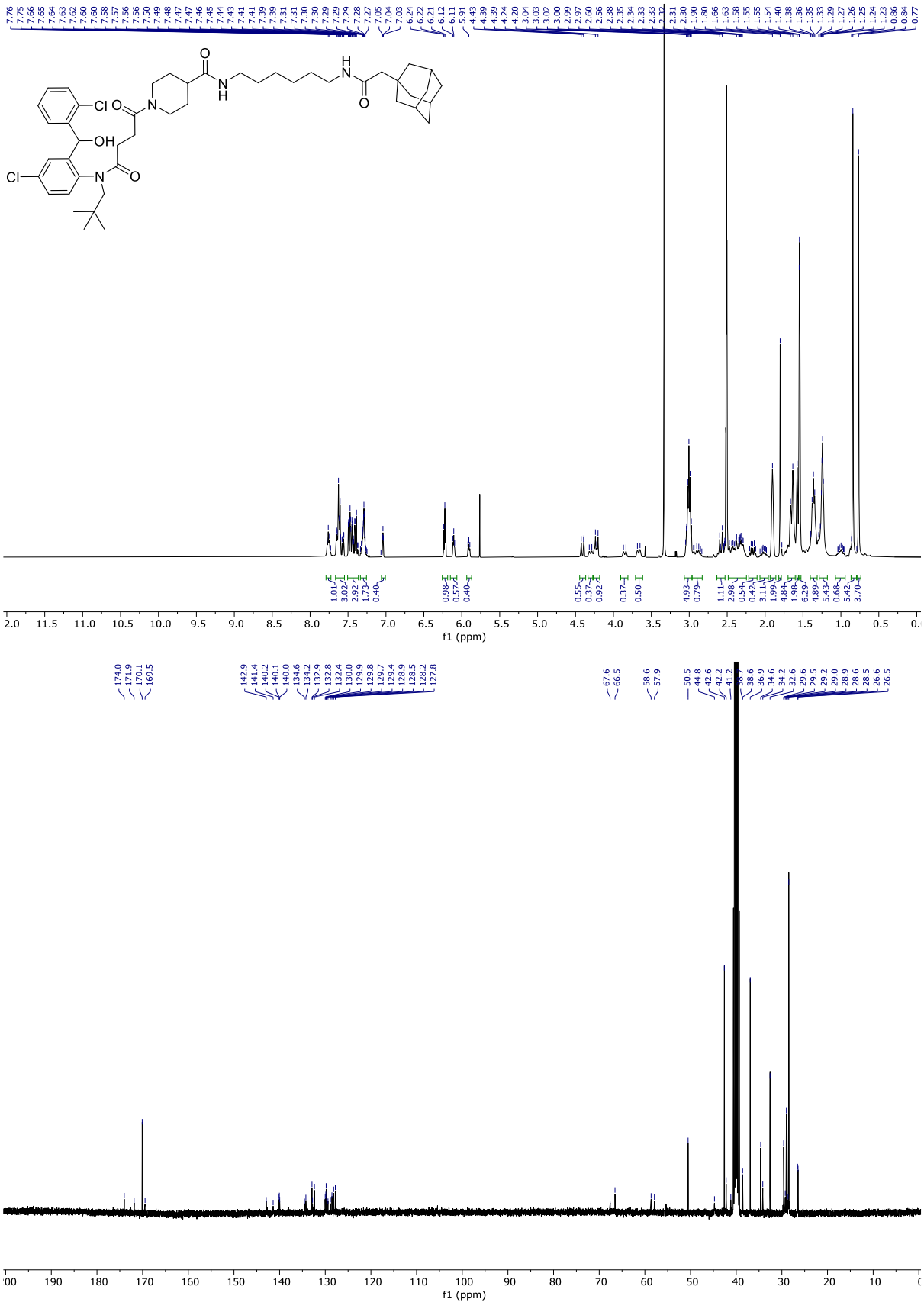
N-(3-(4-(3-(2-((1s,3s)-adamantan-1-yl)acetamido)propoxy)butoxy)propyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **10**



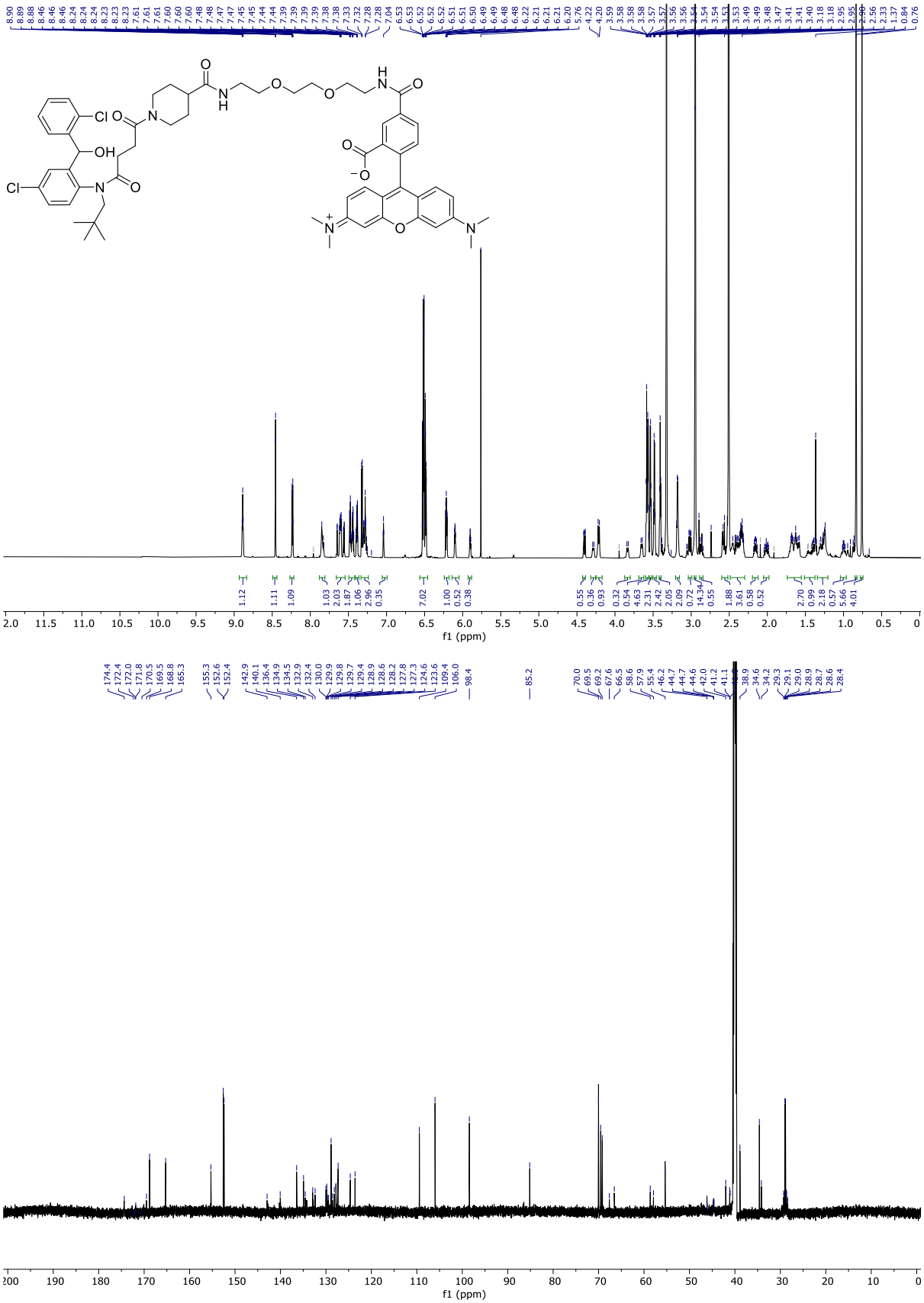
N-(1-((3r,5r,7r)-adamantan-1-yl)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **11**



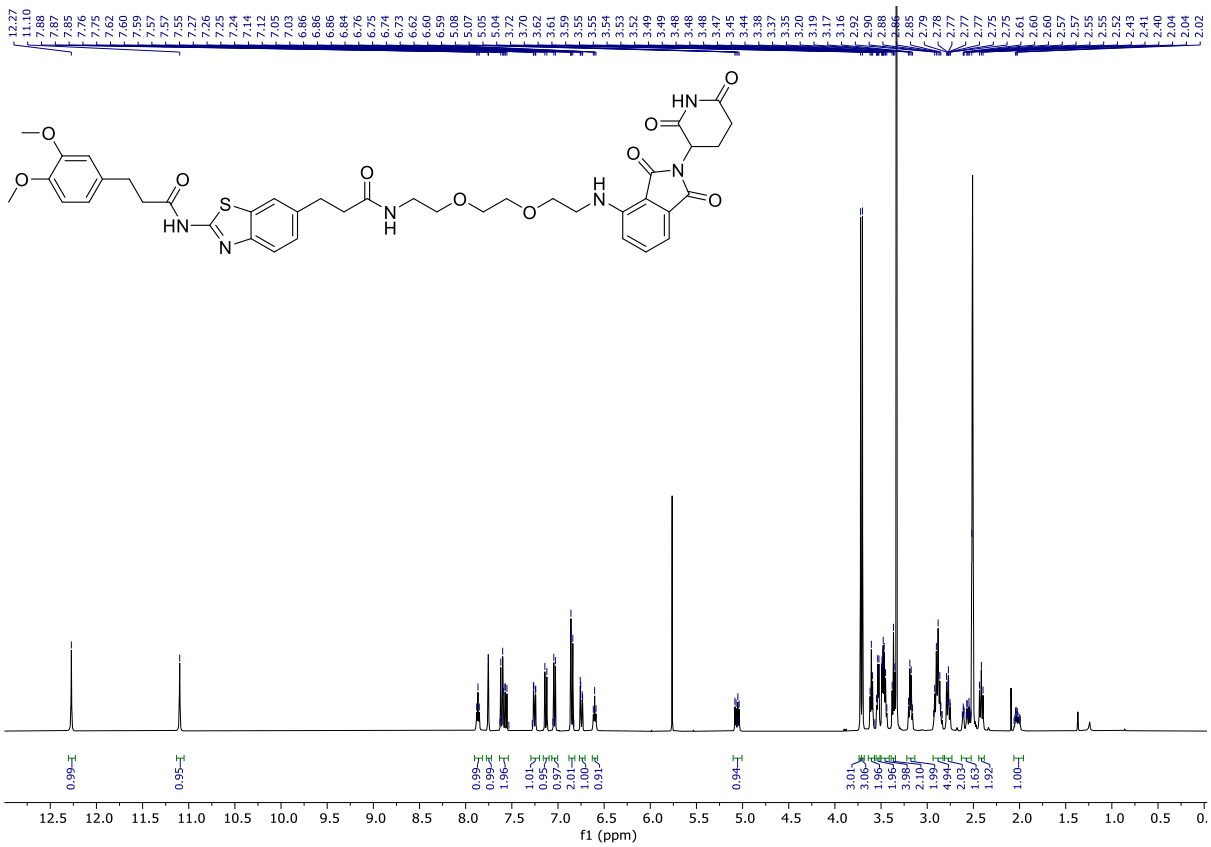
N-(6-(2-((1s,3s)-adamantan-1-yl)acetamido)hexyl)-1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamide **12**

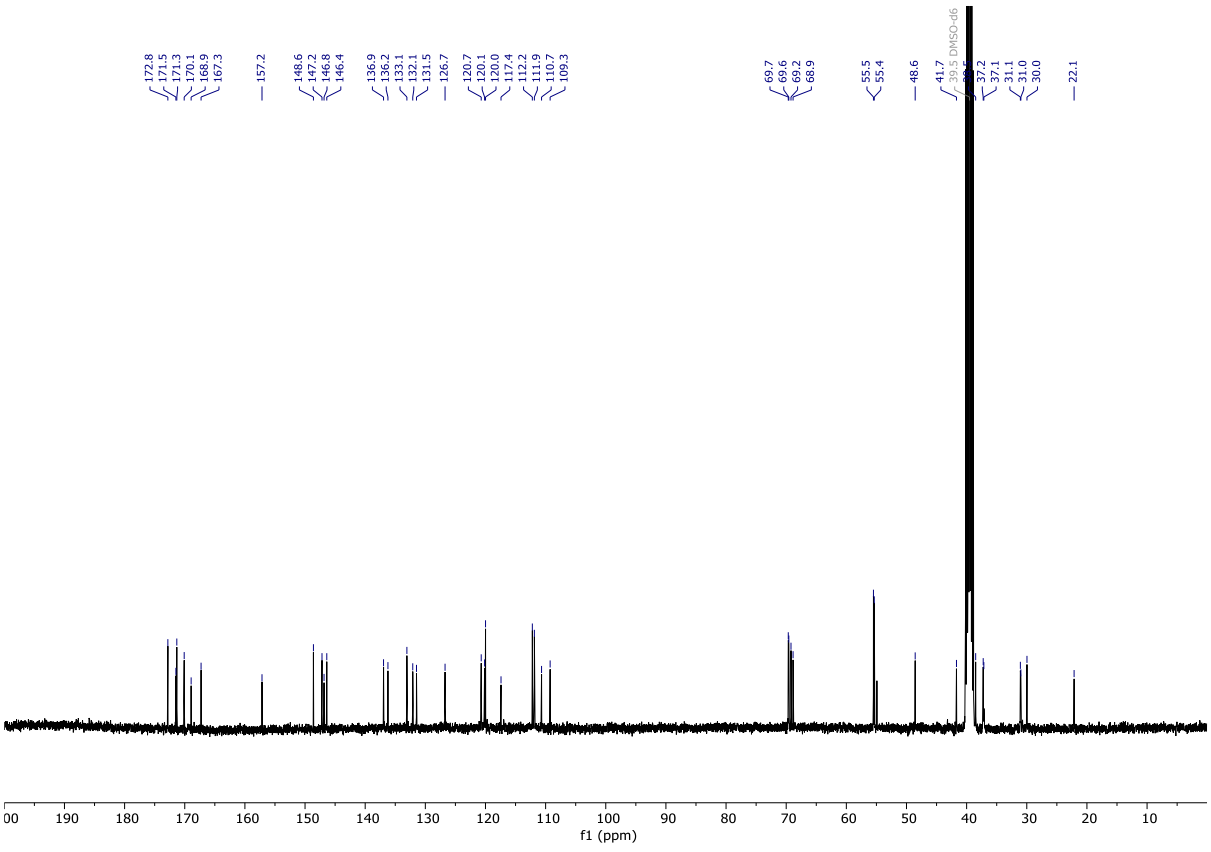


5-((2-(2-(2-(1-(4-((4-chloro-2-((2-chlorophenyl)(hydroxy)methyl)phenyl)(neopentyl)amino)-4-oxobutanoyl)piperidine-4-carboxamido)ethoxy)ethoxy)ethyl)carbamoyl-2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)benzoate **26**

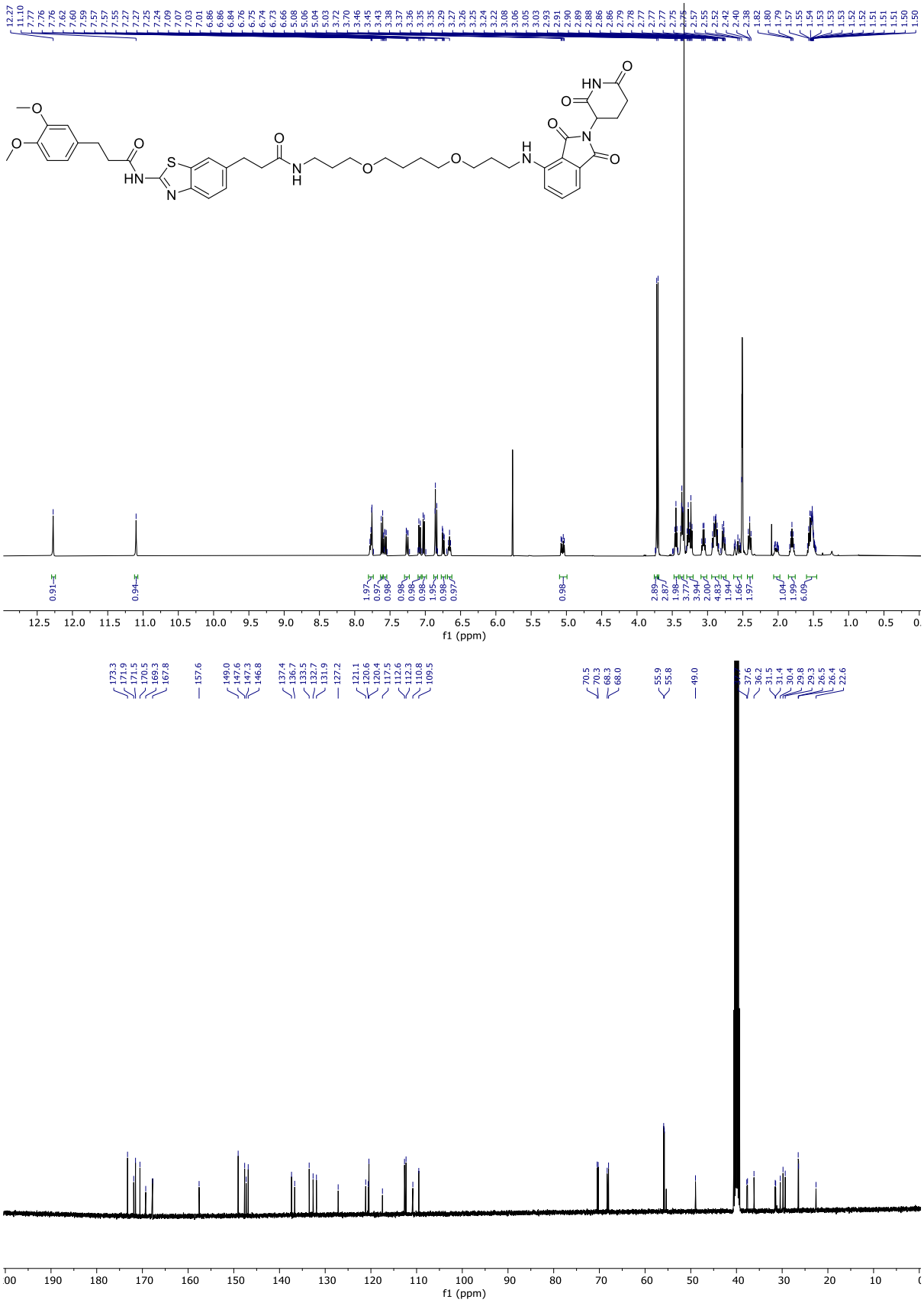


3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **13**

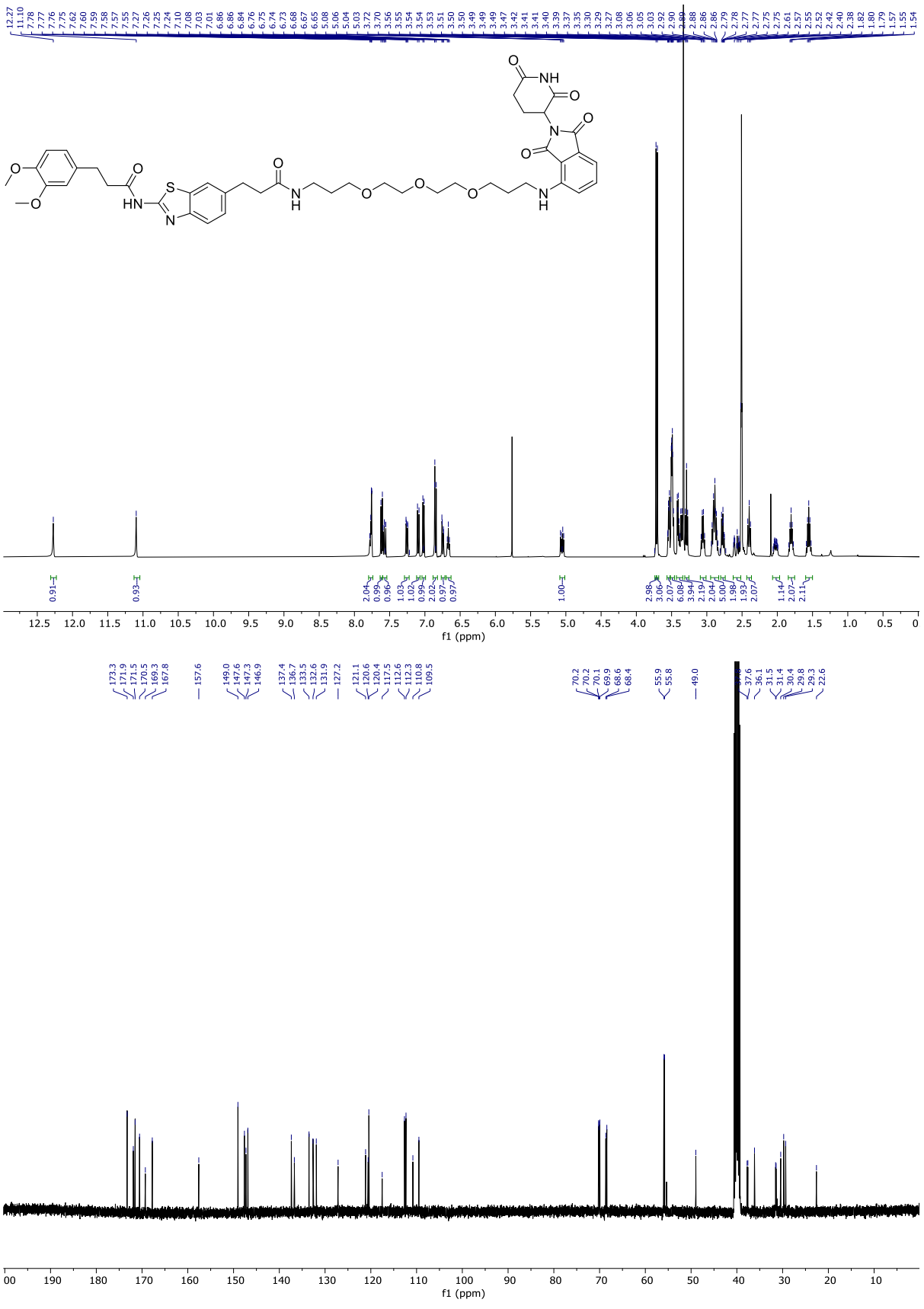




3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **14**

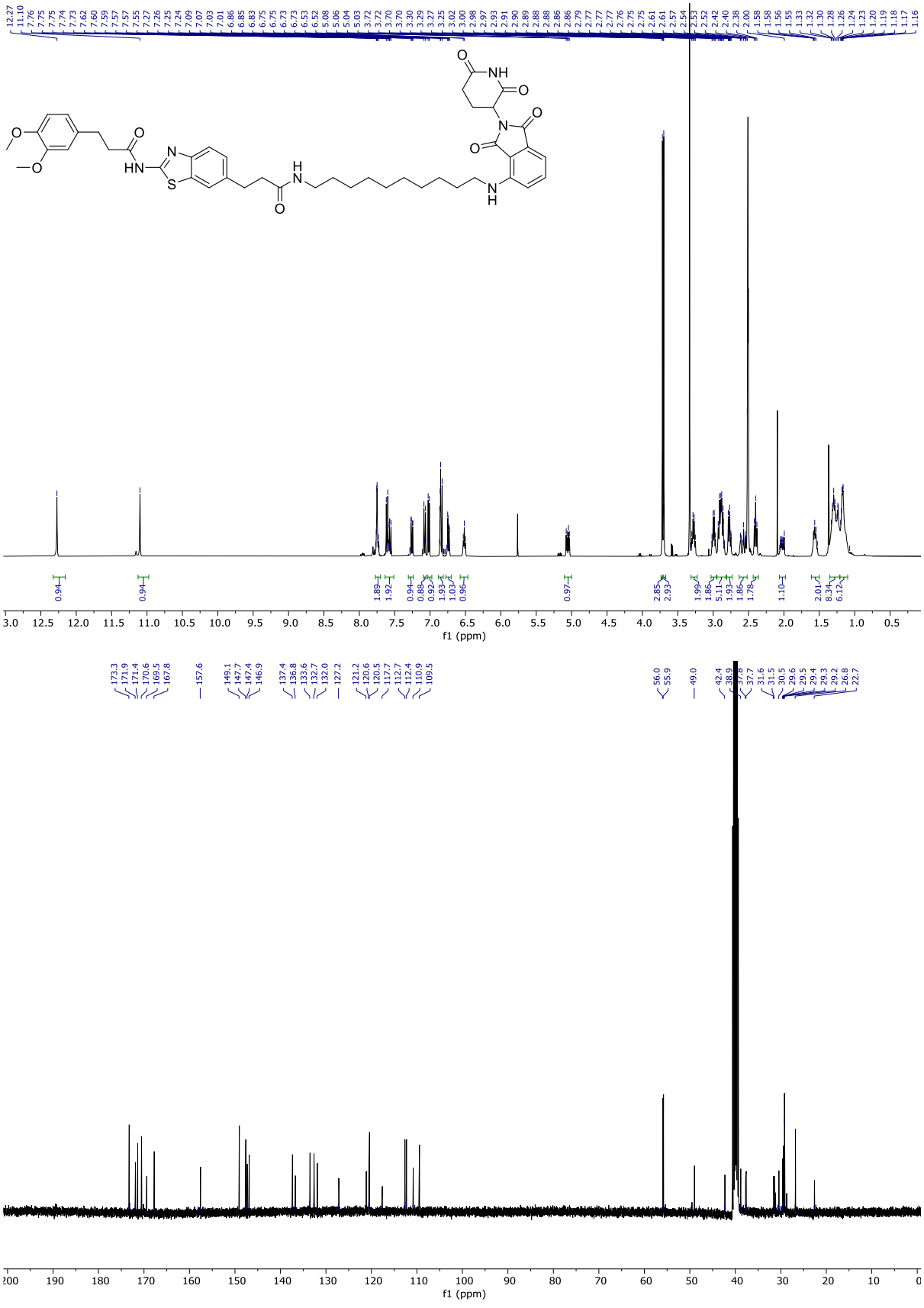


3-(3,4-dimethoxyphenyl)-*N*-(6-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-15-oxo-4,7,10-trioxa-14-azaheptadecan-17-yl)benzo[d]thiazol-2-yl)propanamide **15**

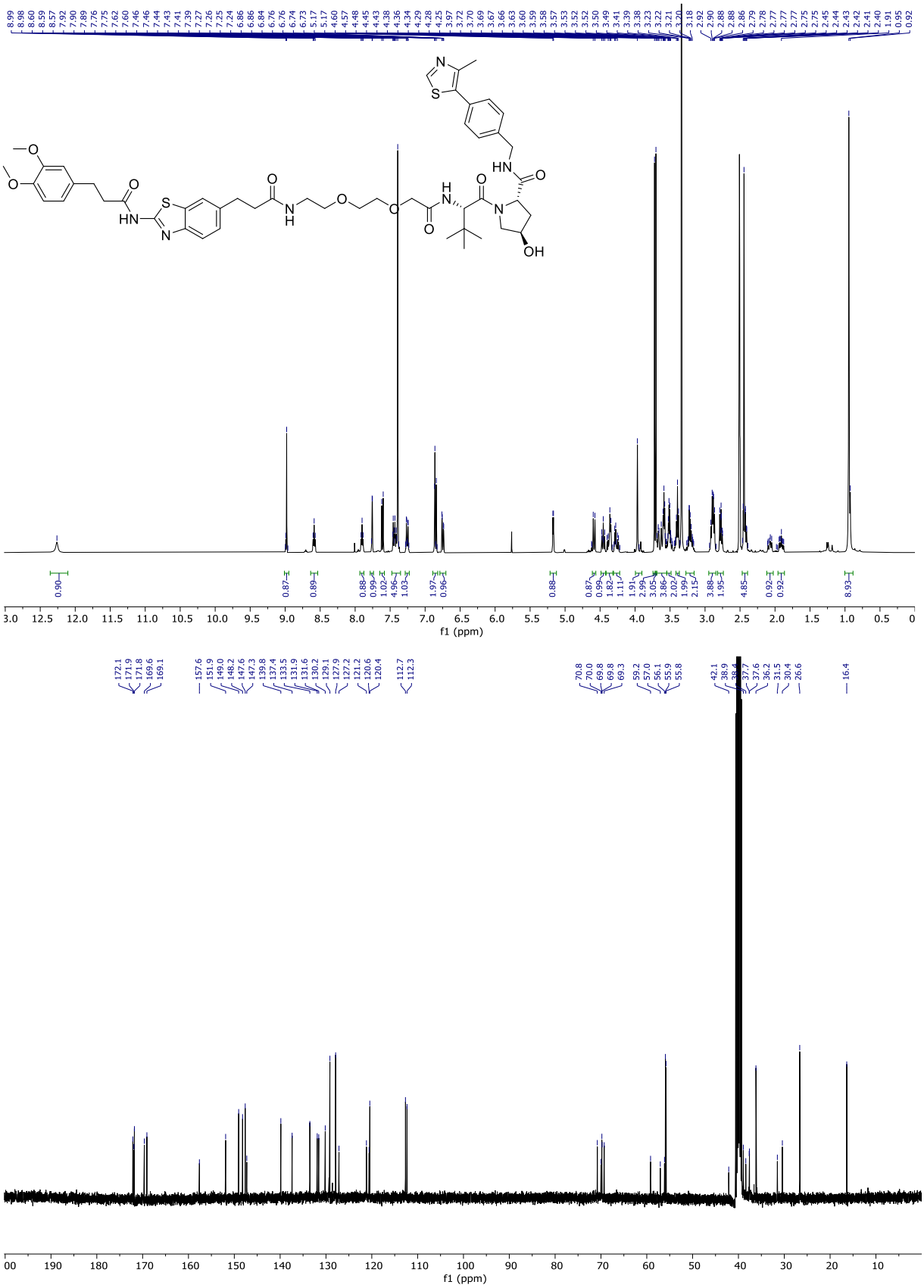


3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)hexyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **16**

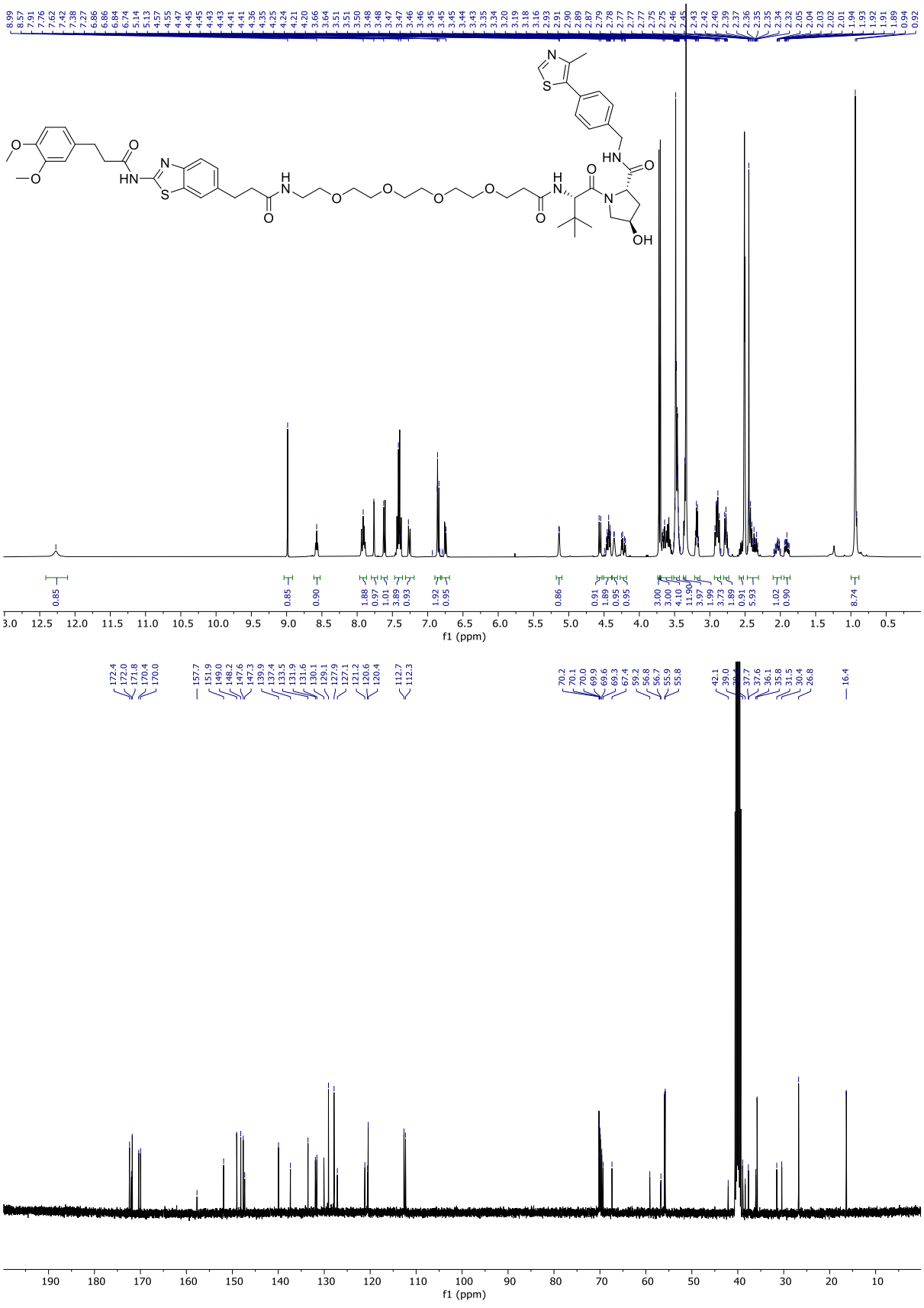
3-(3,4-dimethoxyphenyl)-*N*-(6-(3-((10-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)decyl)amino)-3-oxopropyl)benzo[d]thiazol-2-yl)propanamide **17**



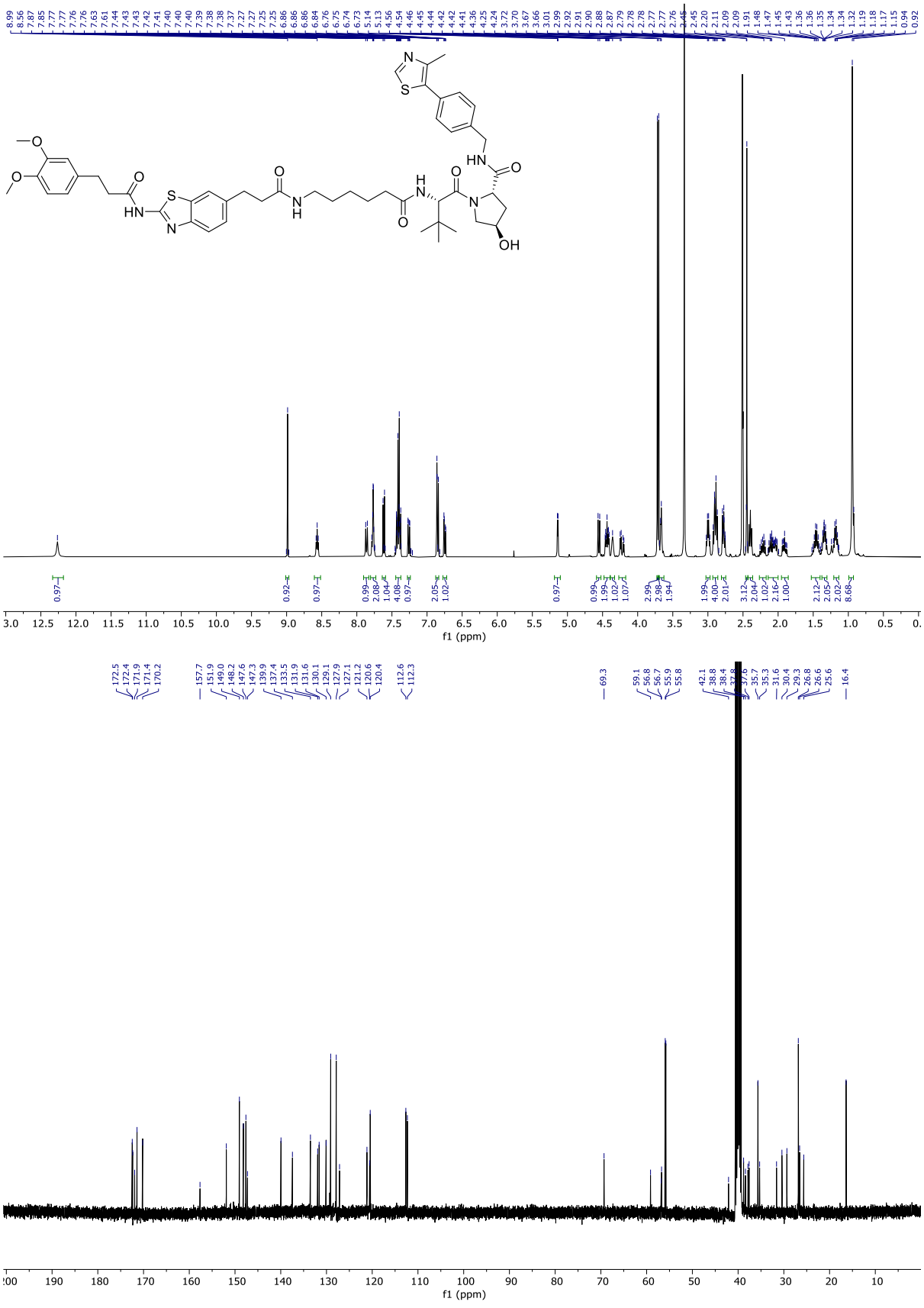
(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-15-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)-4,13-dioxo-6,9-dioxa-3,12-diazapentadecanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl) pyrrolidine-2-carboxamide **18**



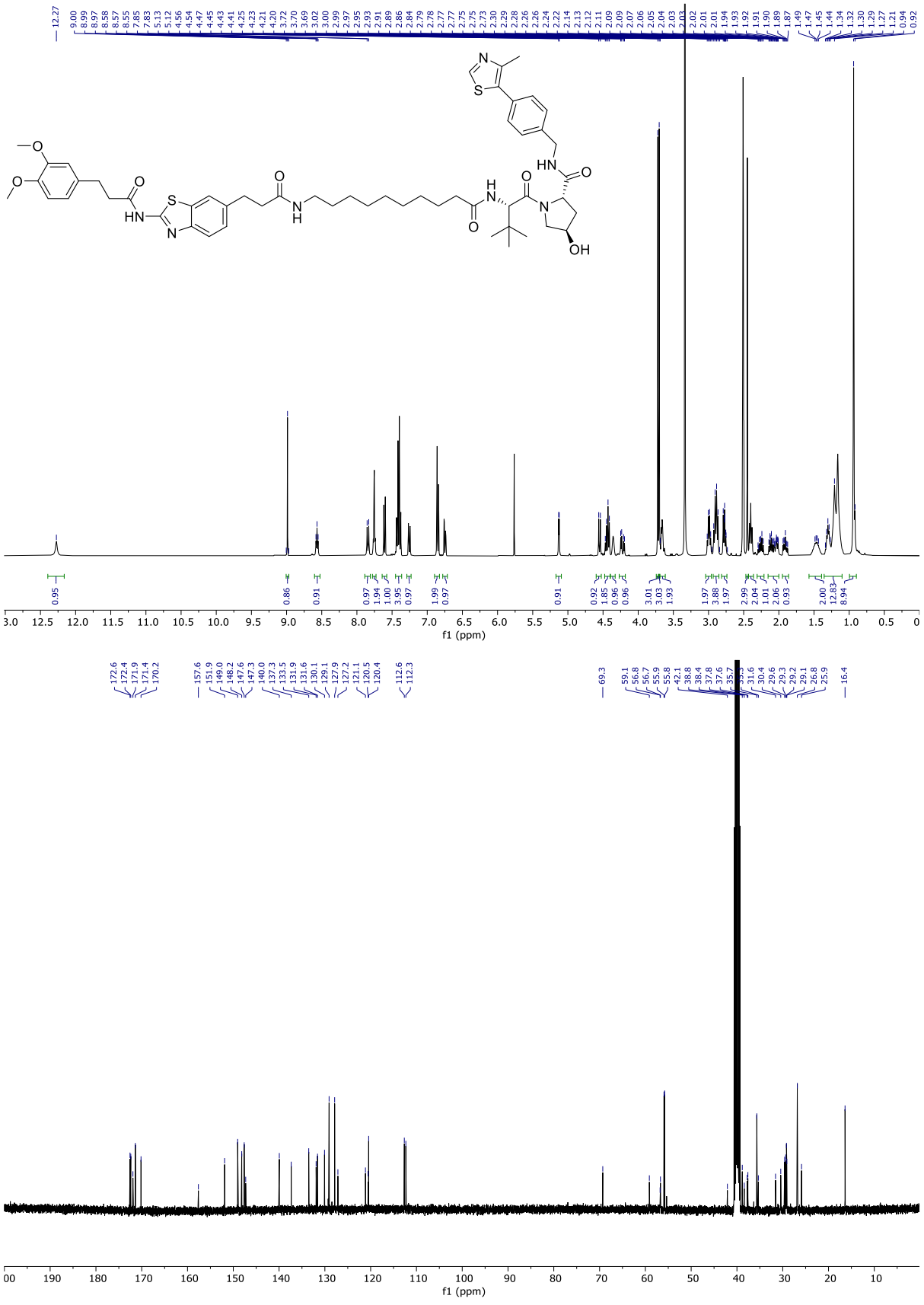
(2*S*,4*R*)-1-((*S*)-2-(*tert*-butyl)-22-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)-4,20-dioxo-7,10,13,16-tetraoxa-3,19-diazadocosanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **19**



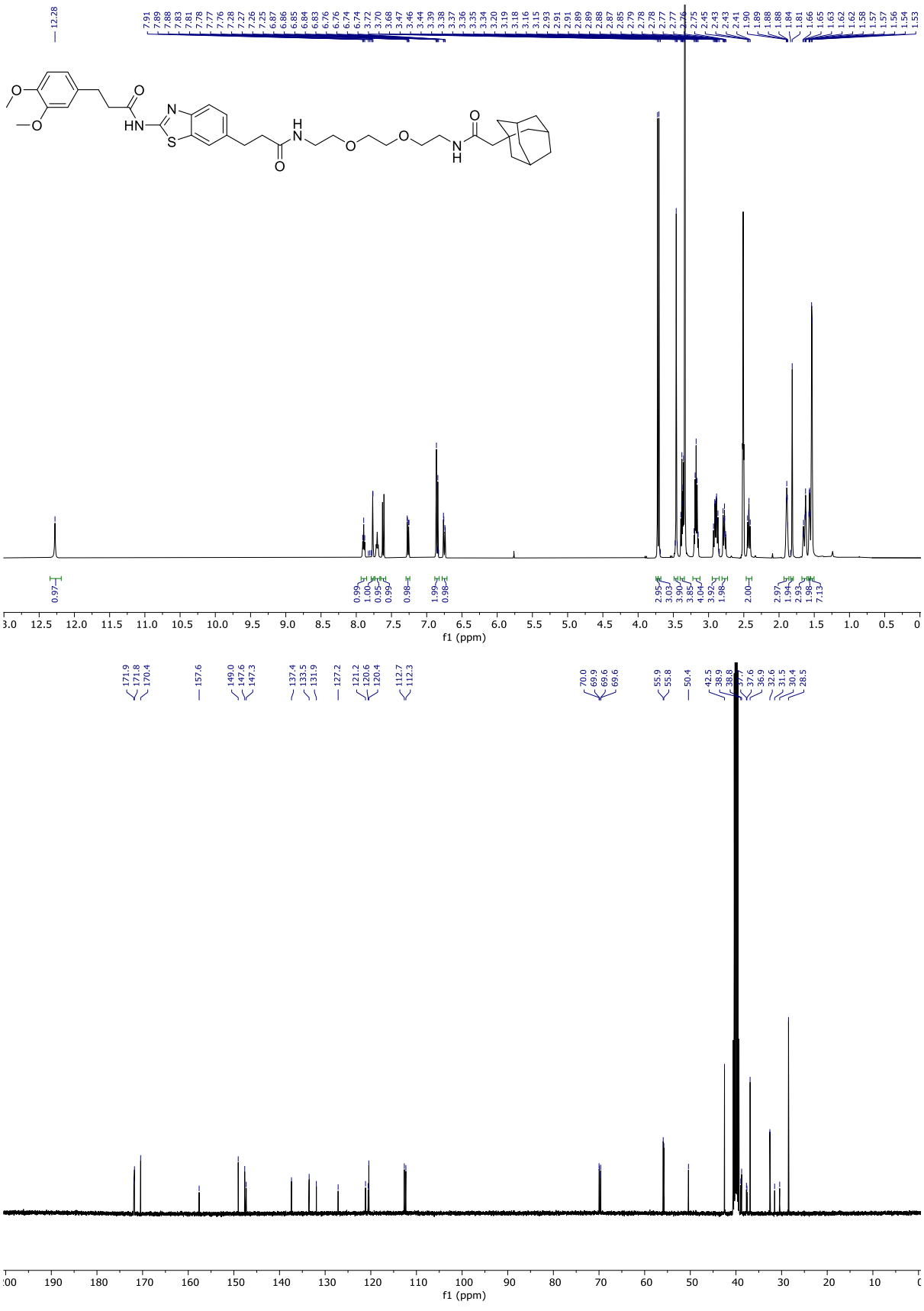
(2*S*,4*R*)-1-((*S*)-2-(6-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamido)hexanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **20**



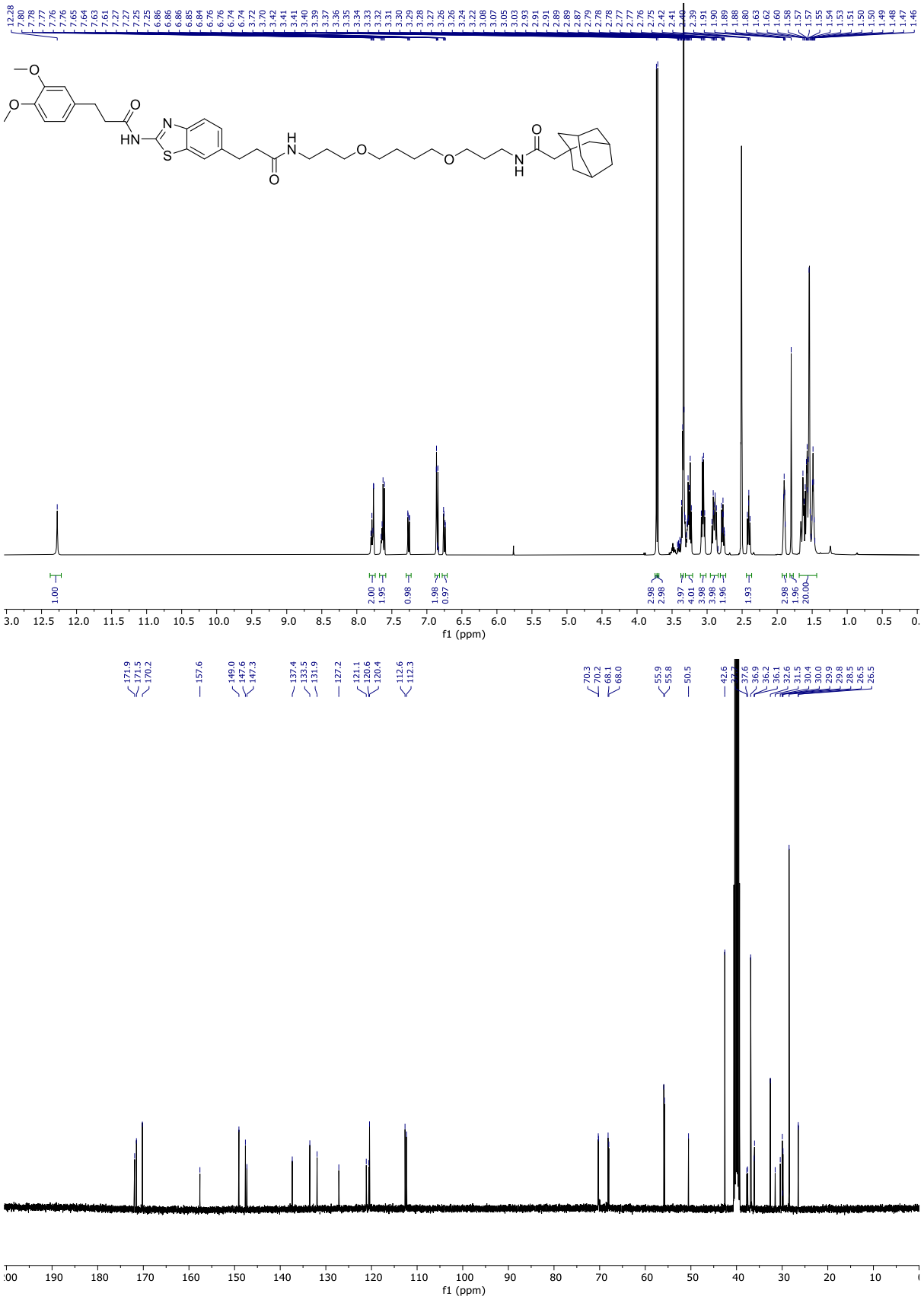
(2*S*,4*R*)-1-((*S*)-2-(10-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamido)decanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **21**



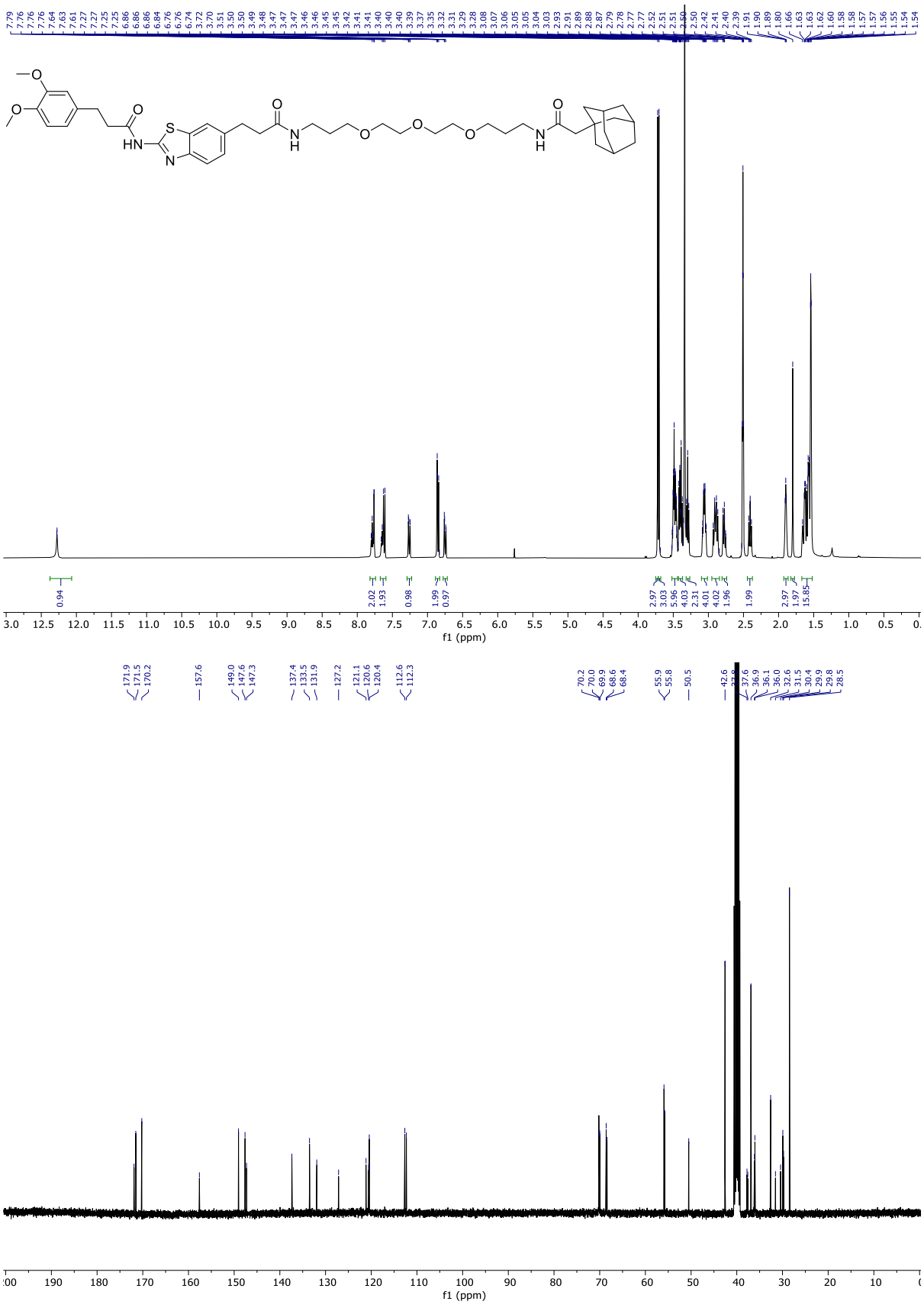
N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,13-dioxo-6,9-dioxa-3,12-diazapentadecan-15-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **22**



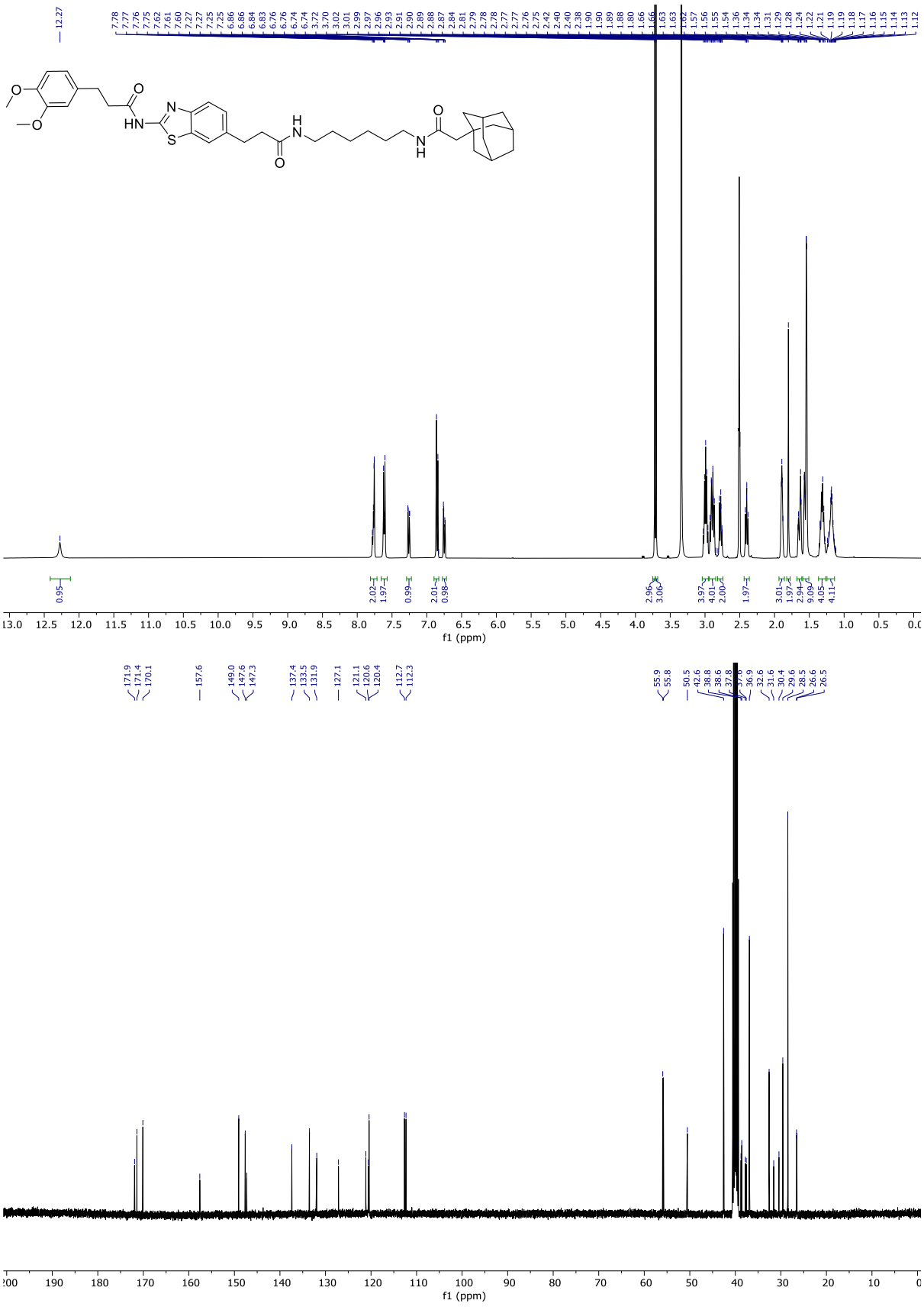
N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,17-dioxo-7,12-dioxa-3,16-diazanonadecan-19-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **23**



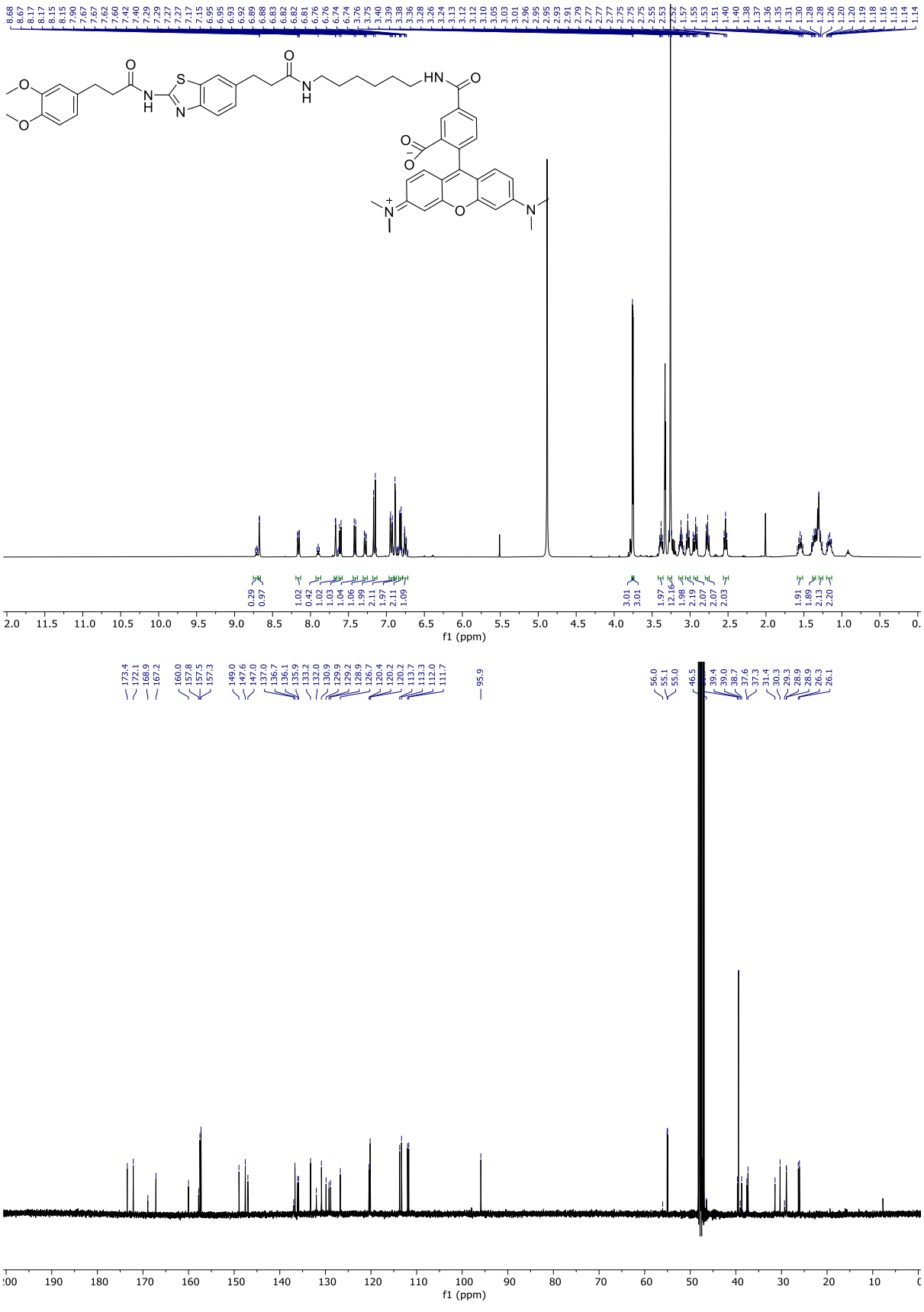
N-(6-(1-((3*r*,5*r*,7*r*)-adamantan-1-yl)-2,18-dioxo-7,10,13-trioxa-3,17-diazaicosan-20-yl)benzo[*d*]thiazol-2-yl)-3-(3,4-dimethoxyphenyl)propanamide **24**



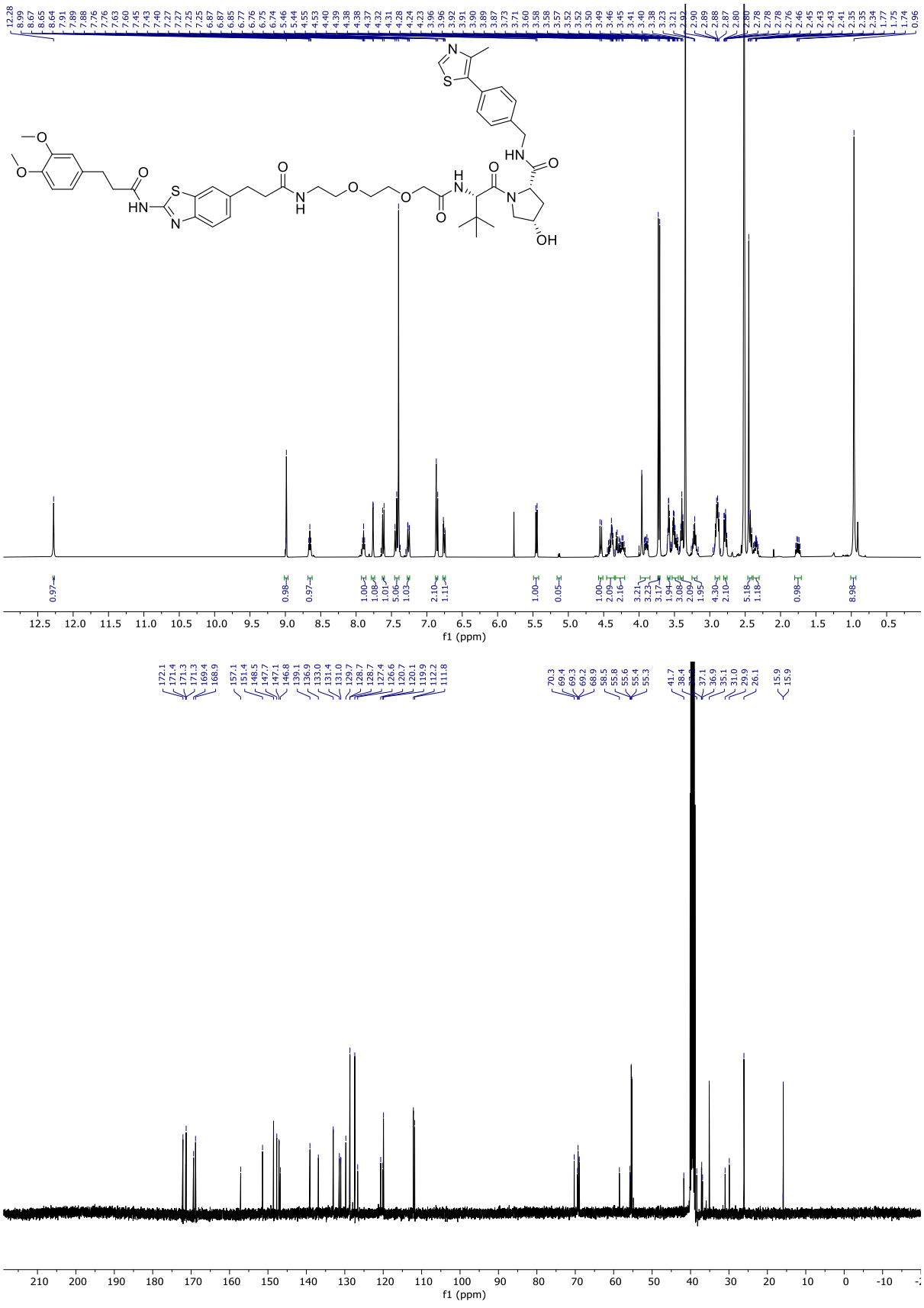
N-(6-(2-((3*r*,5*r*,7*r*)-adamantan-1-yl)acetamido)hexyl)-3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[*d*]thiazol-6-yl)propanamide **25**



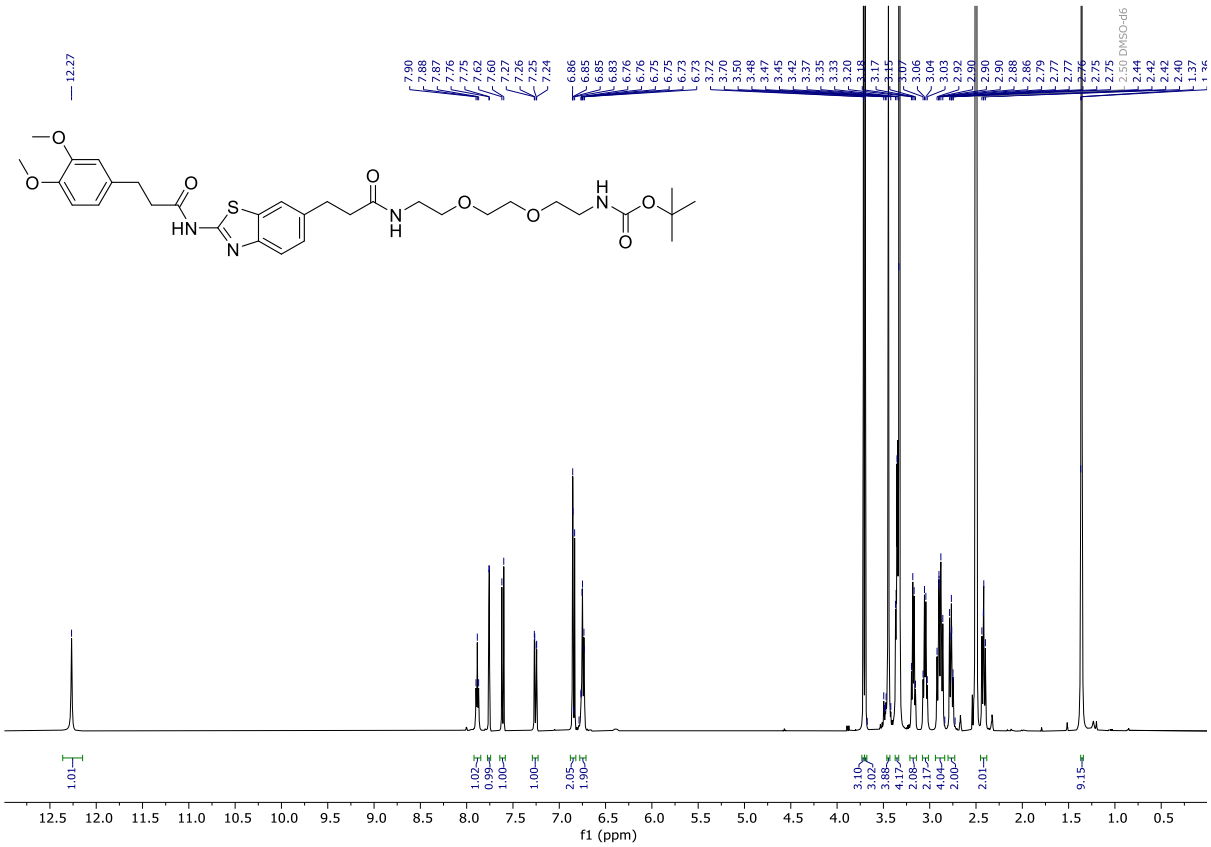
5-((6-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[d]thiazol-6-yl)propanamido)hexyl)carbamoyl)-2-(6-(dimethylamino)-3-(dimethyliminio)-3H-xanthen-9-yl)benzoate **27**

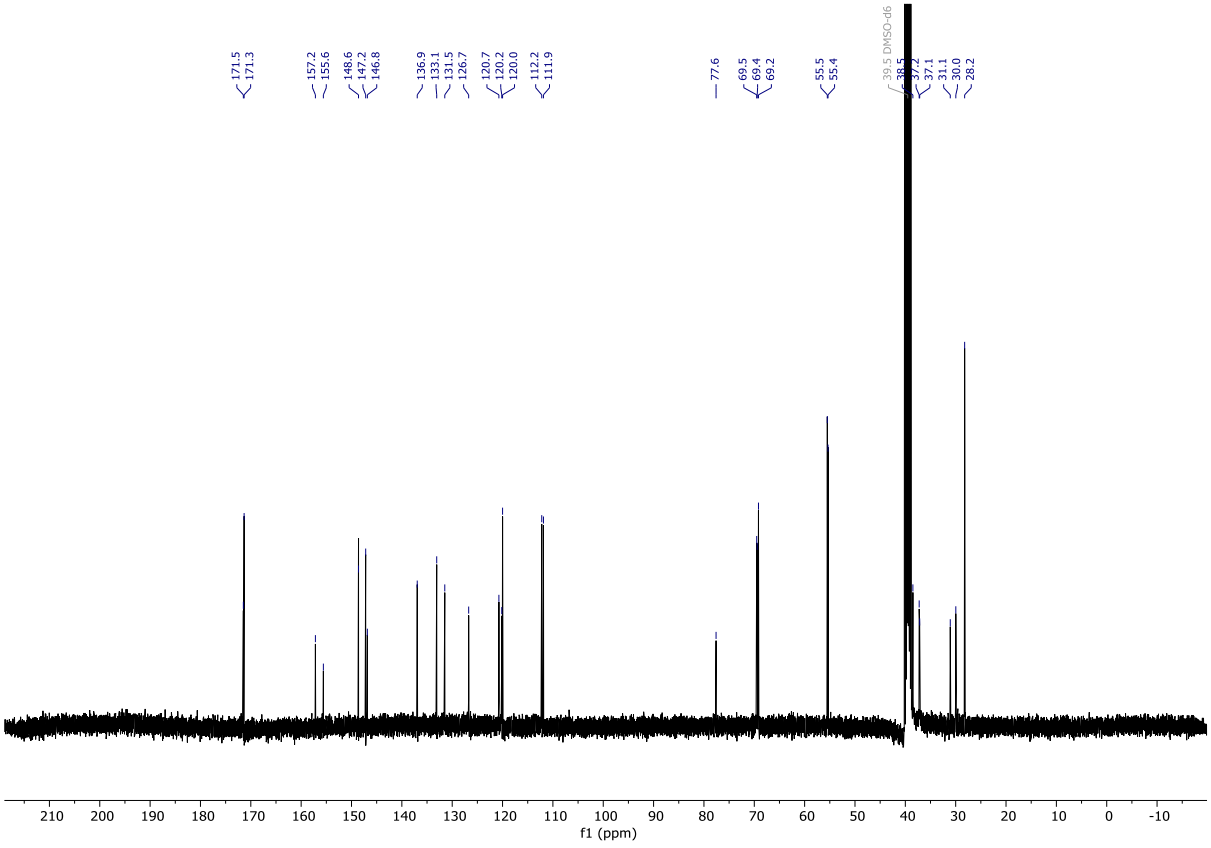


(2S,4S)-1-((S)-2-(tert-butyl)-15-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[d]thiazol-6-yl)-4,13-dioxo-6,9-dioxa-3,12-diazapentadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **28**

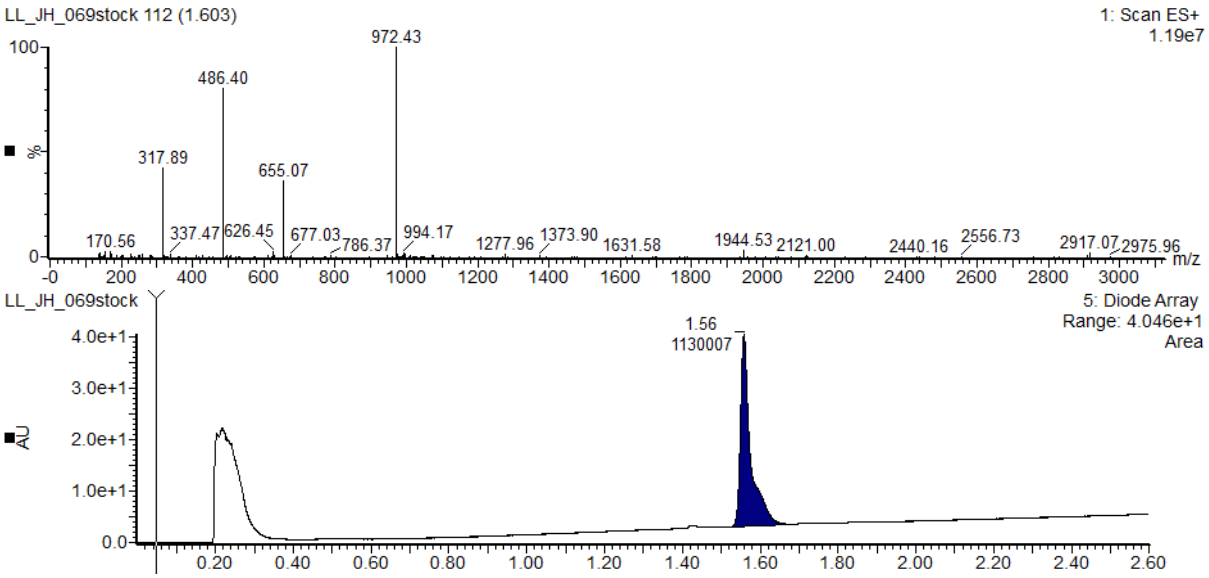


tert-butyl (2-(2-(2-(3-(2-(3-(3,4-dimethoxyphenyl)propanamido)benzo[d]thiazol-6-yl)propanamido)ethoxy)ethoxy)ethyl)carbamate **29**

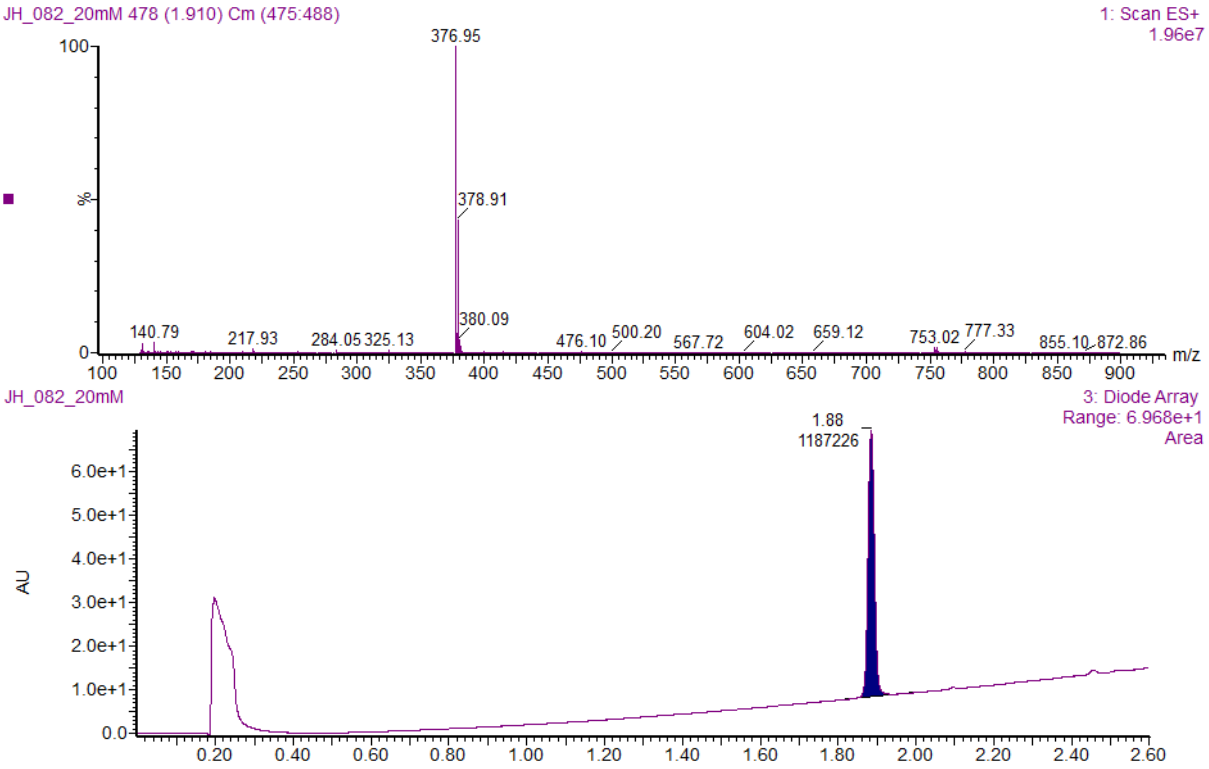




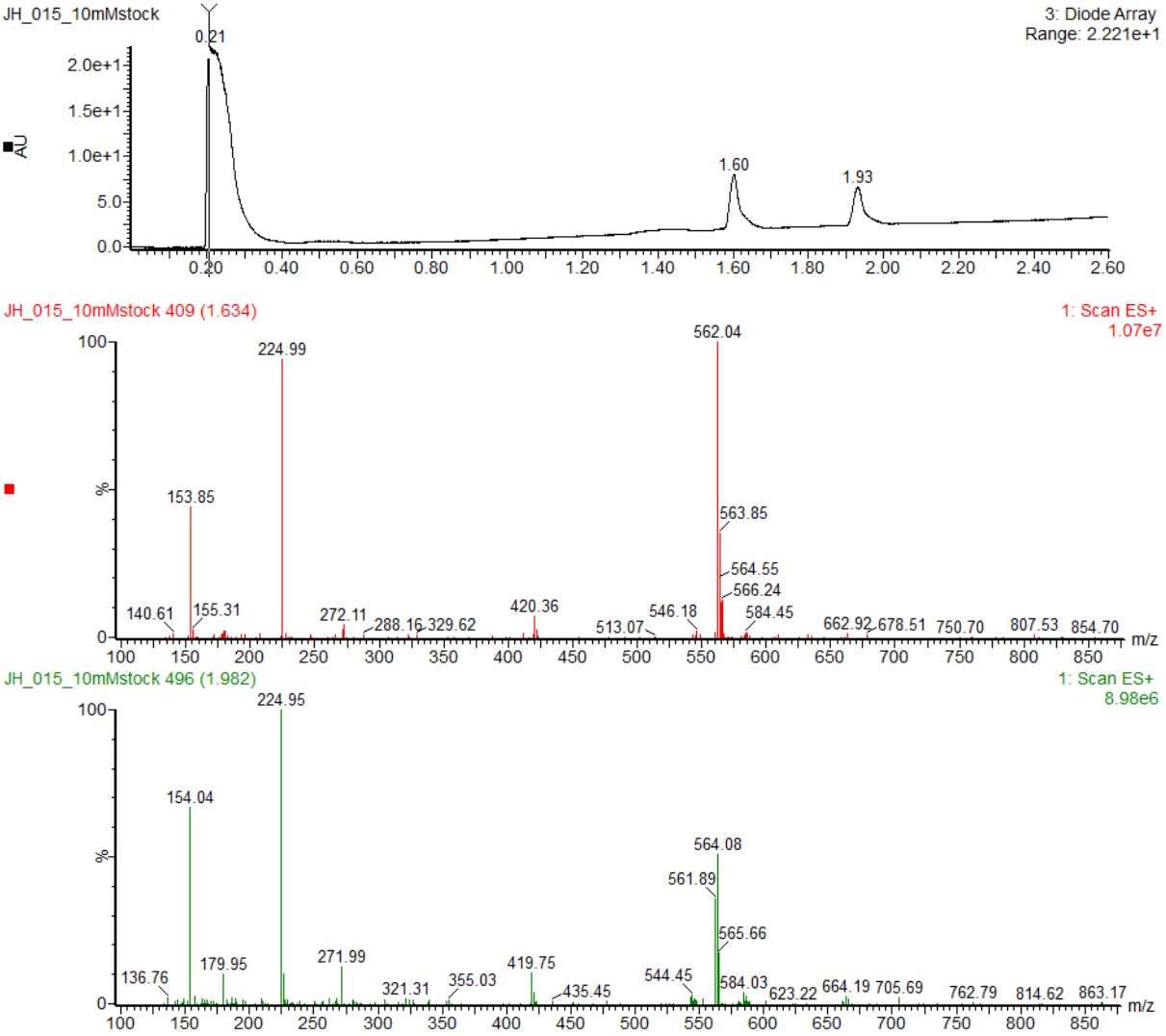
LCMS purity



LCMS data for a sample taken from a DMSO stock for PROTAC **18**.



LCMS data for a sample taken from a DMSO stock for KY02111.



LCMS Data for a sample from a SQSI stock in DMSO. Two atropisomers are visible.