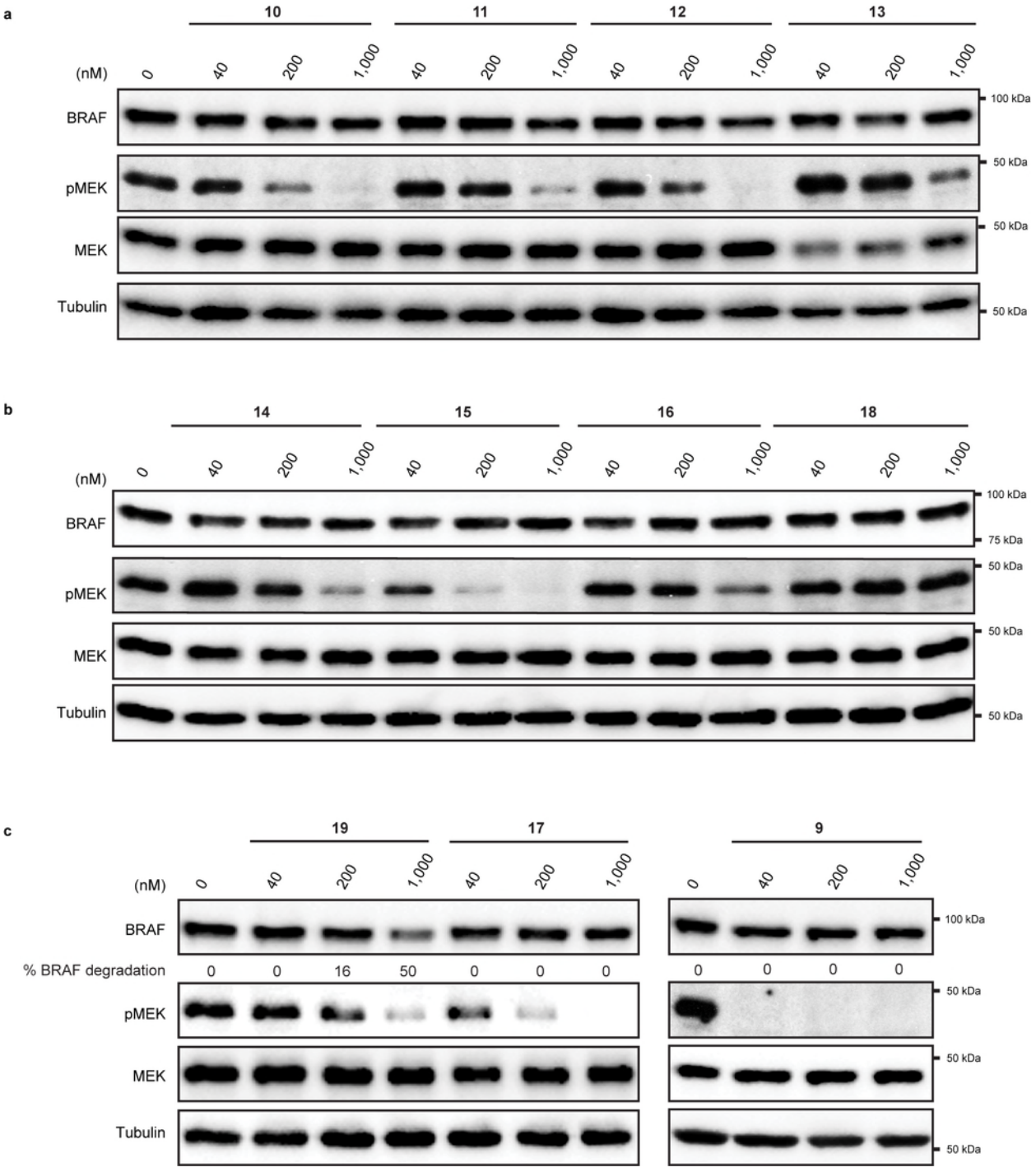
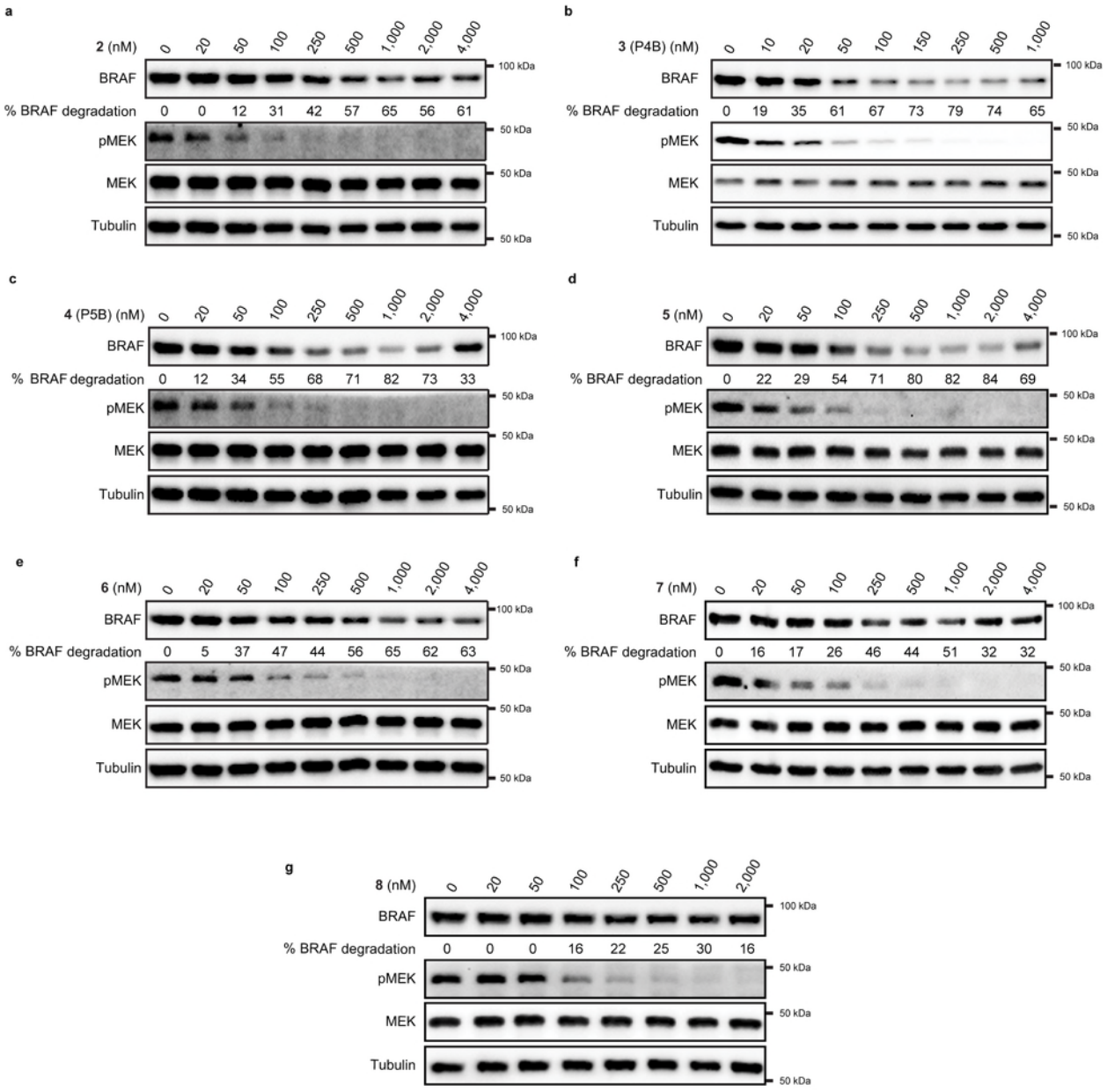
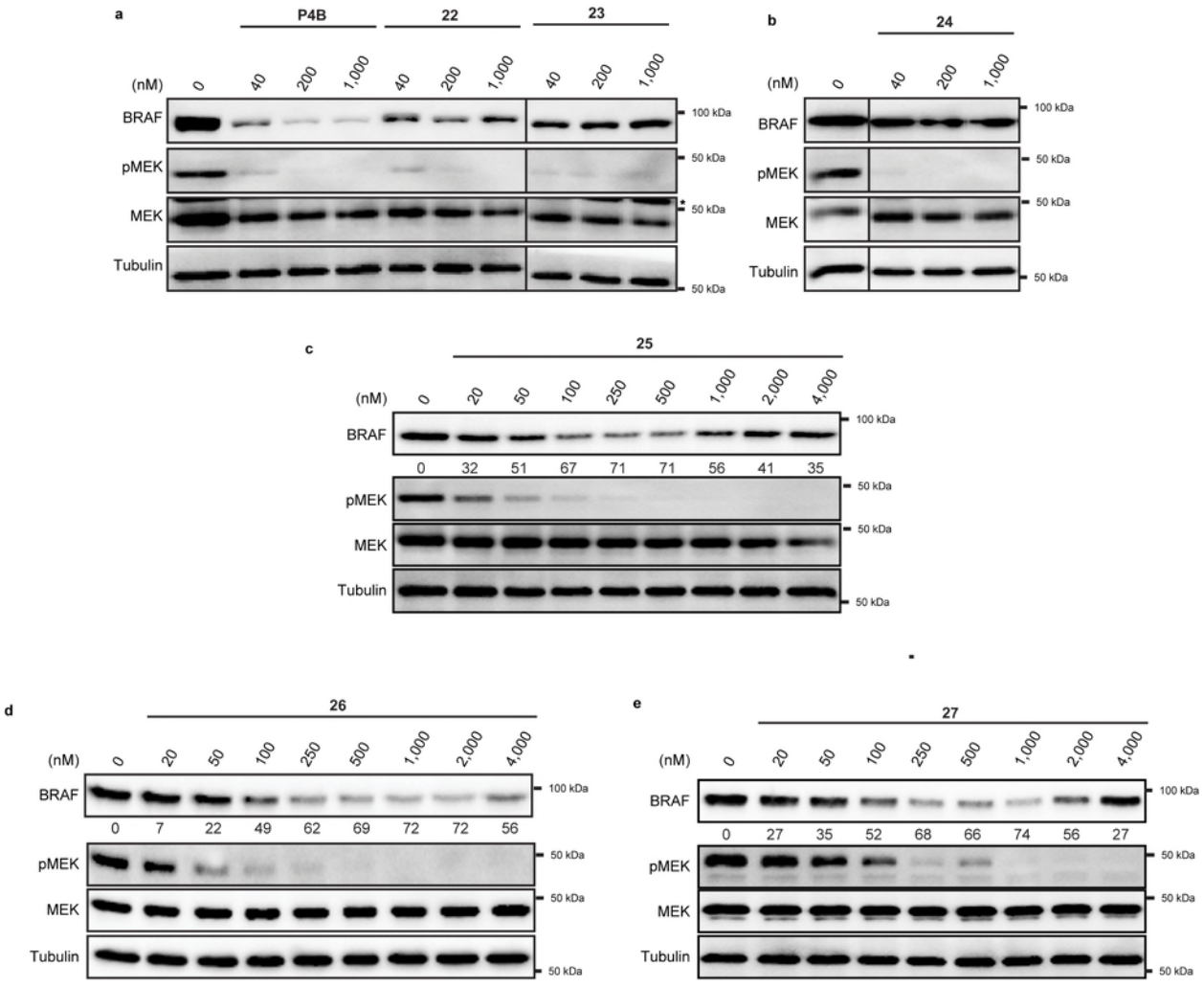


Supplementary Figure 1| Dose response analysis of dabrafenib-based PROTACs. **a-c,** A375 cells were treated for 24 h with the indicated compounds at the indicated concentrations prior to immunoblot analysis of whole cell lysates. Tubulin served as loading control. Data shown are representative of minimally two independent experiments.

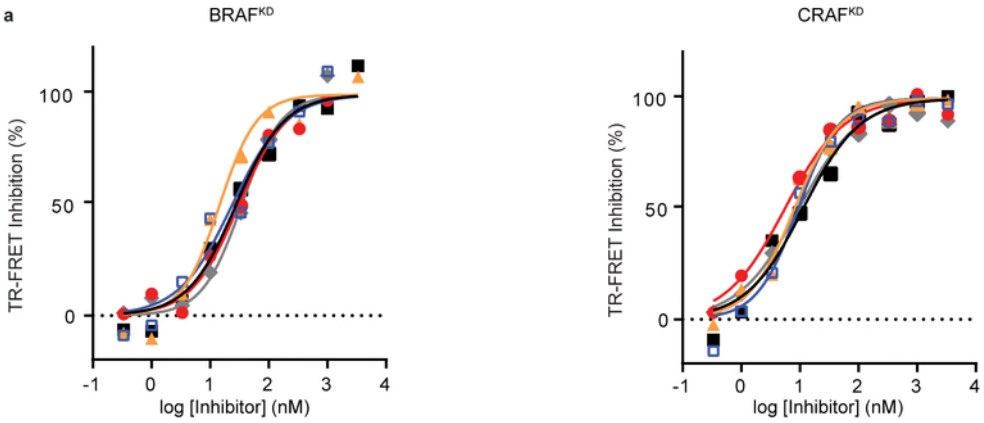


Supplementary Figure 2| Dose response analysis of BI 882370-based PROTACs. **a-g,** A375 cells were treated for 24 h with the indicated compounds at the indicated concentrations prior to immunoblot analysis of whole cell lysates. Tubulin served as loading control. Data shown are representative of minimally two independent experiments.



Supplementary Figure 3| Dose response analysis of P4B linker analogs.
a-e, A375 cells were treated for 24 h with the indicated compounds in three-point (**a-b**) or eight-point (**c-e**) concentration titrations prior to immunoblot analysis of whole cell lysates. Tubulin served as loading control. * indicates non-cropped tubulin signal. Data shown are representative of minimally two independent experiments.

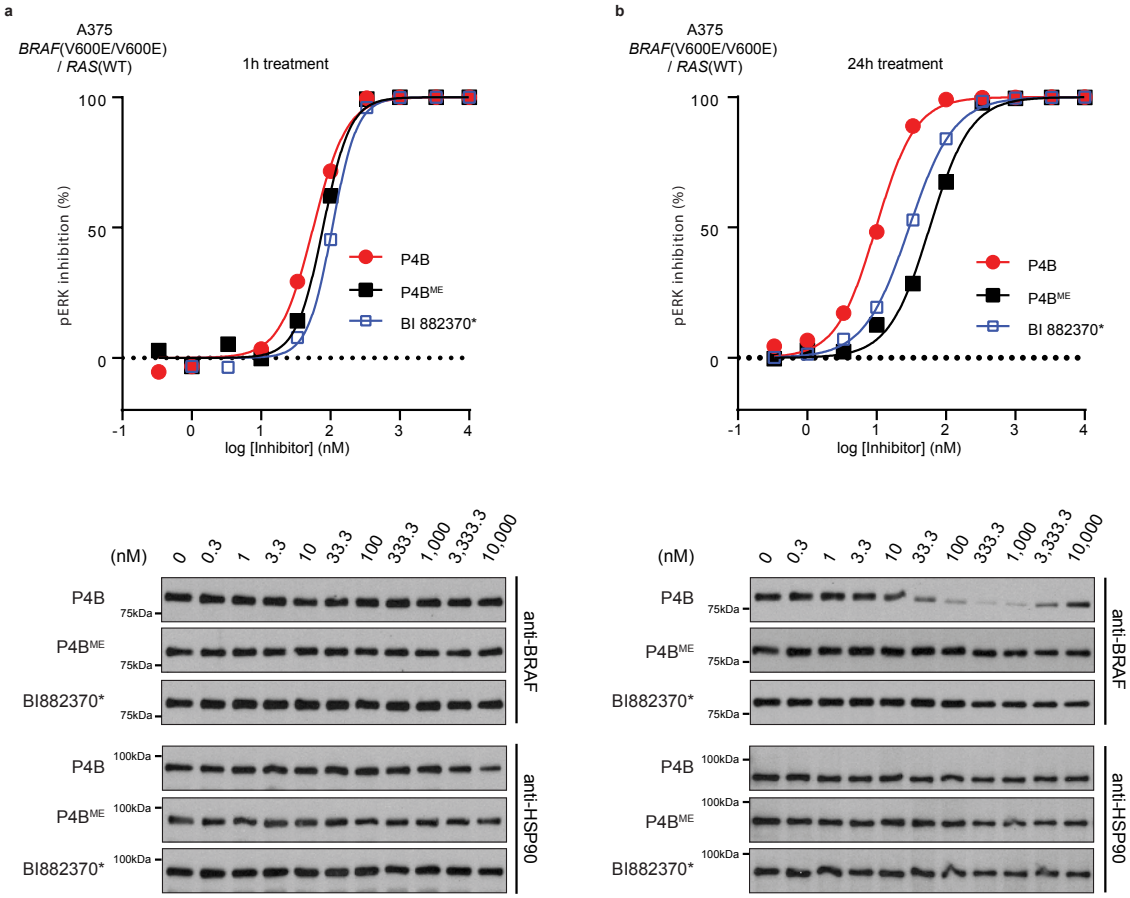
a



b

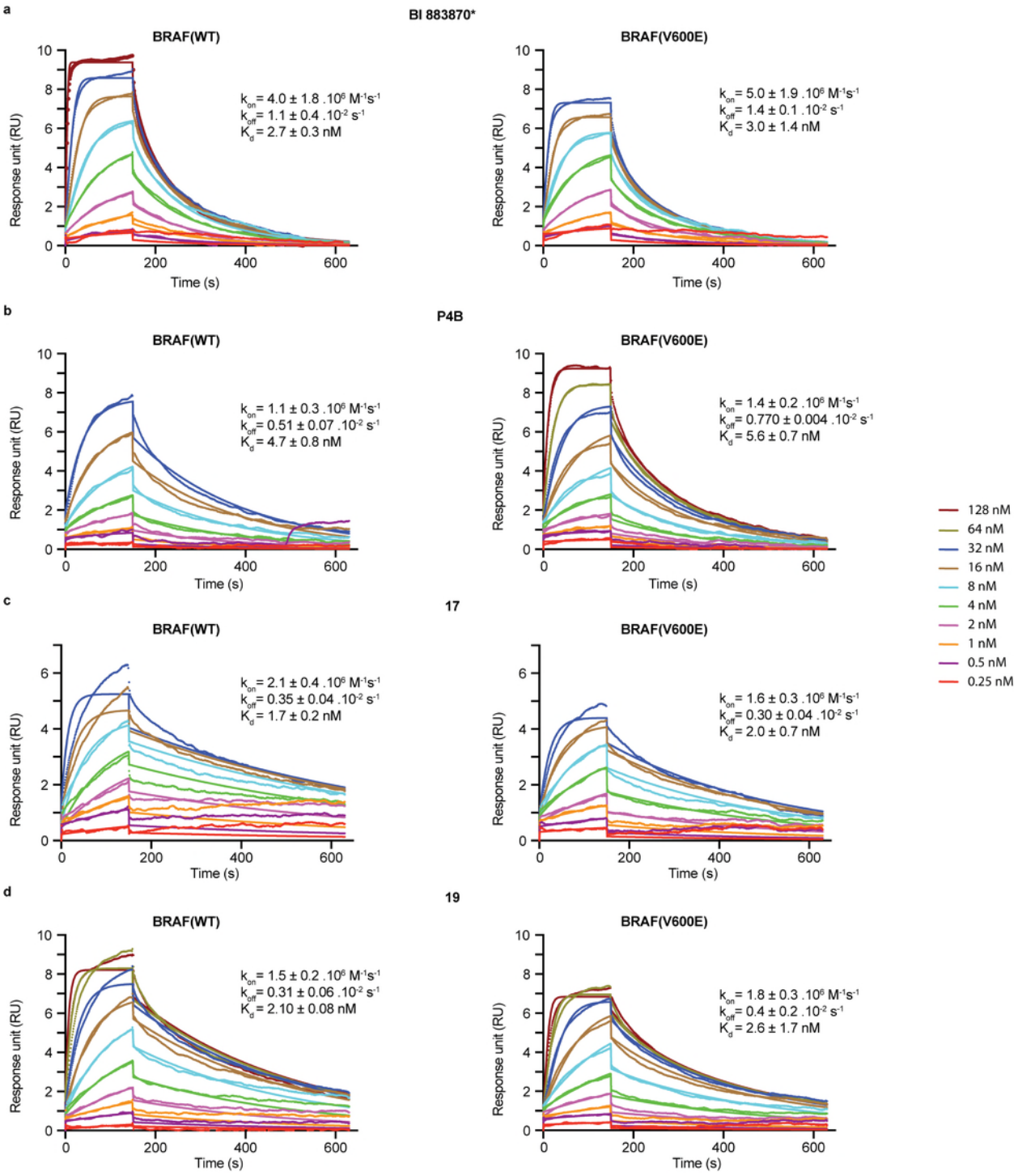
	BRAF IC_{50} (nM)	CRAF IC_{50} (nM)
P4B	33 ± 11	6 ± 3
P5B	19 ± 6	7 ± 2
$P4B^{ME}$	31 ± 7	8 ± 4
$P5B^{ME}$	36 ± 3	7 ± 3
BI 882370*	37 ± 18	12 ± 5

Supplementary Figure 4| Binding of PROTAC variants to the kinase domains of BRAF and CRAF. a, TR-FRET binding analysis of P4B, P5B, $P4B^{ME}$, $P5B^{ME}$ and BI 882370* to the kinase domain of BRAF (left panel) and CRAF (right panel). Profiles correspond to a single representative experiment. **b**, Average IC_{50} values for **a** are from four independent experiments. Data represent mean values ± s.d.



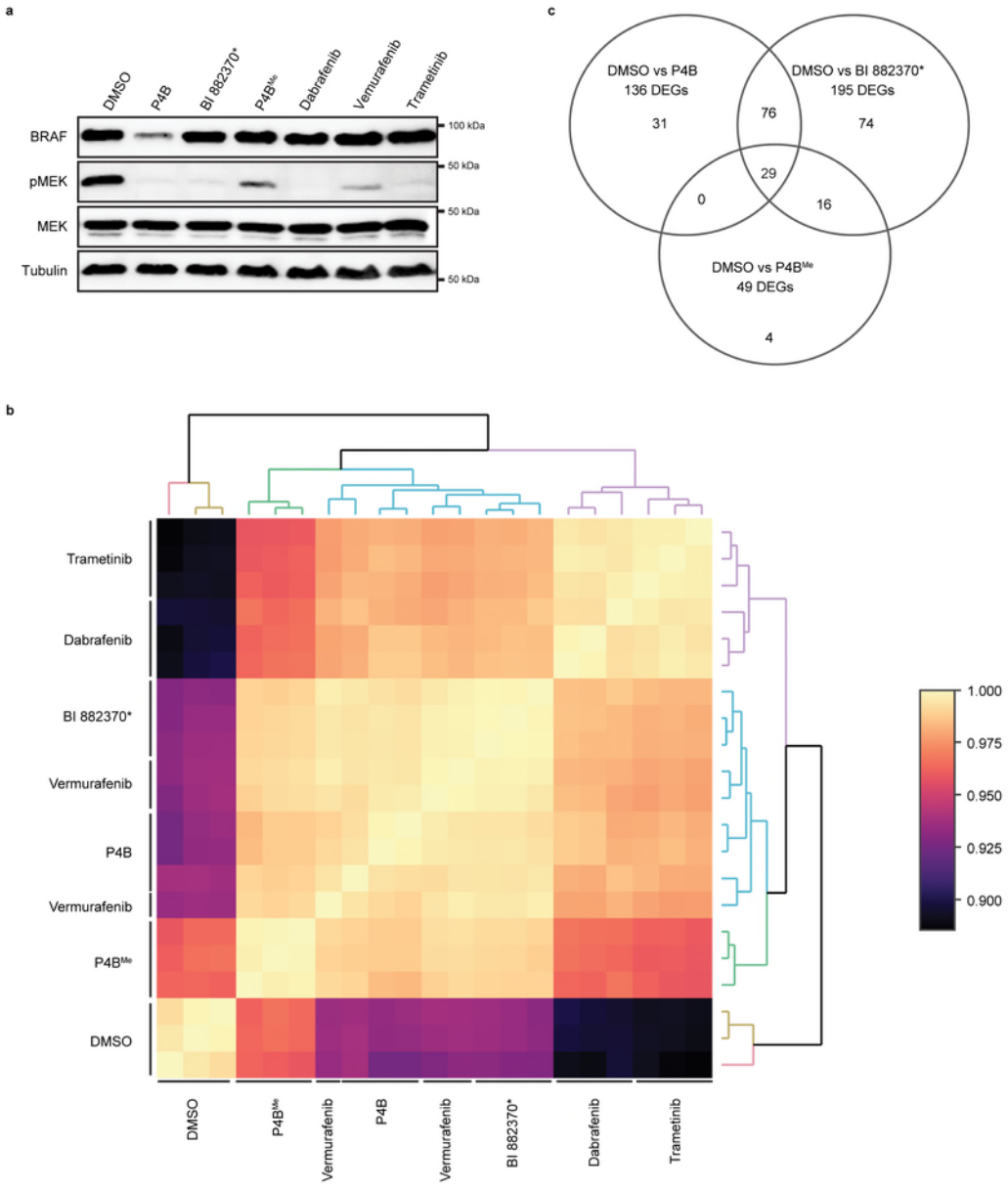
Supplementary Figure 5| Comparison of the effect of P4B, P4B^{ME} and BI 882370* on BRAF levels at 1 hour and 24 hour time points.

a-b, Dose-dependent inhibition of phospho-ERK by AlphaLISA (top panel) and immunoblot analysis of BRAF levels (bottom panels) in A375 cell line treated with an increasing concentration of P4B, P4B^{ME} and BI 882370* for 1 h (**a**) and 24 h (**b**). Data shown is representative of minimally three independent experiments. Data represent mean values ± s.d. HSP90 served as a loading control.



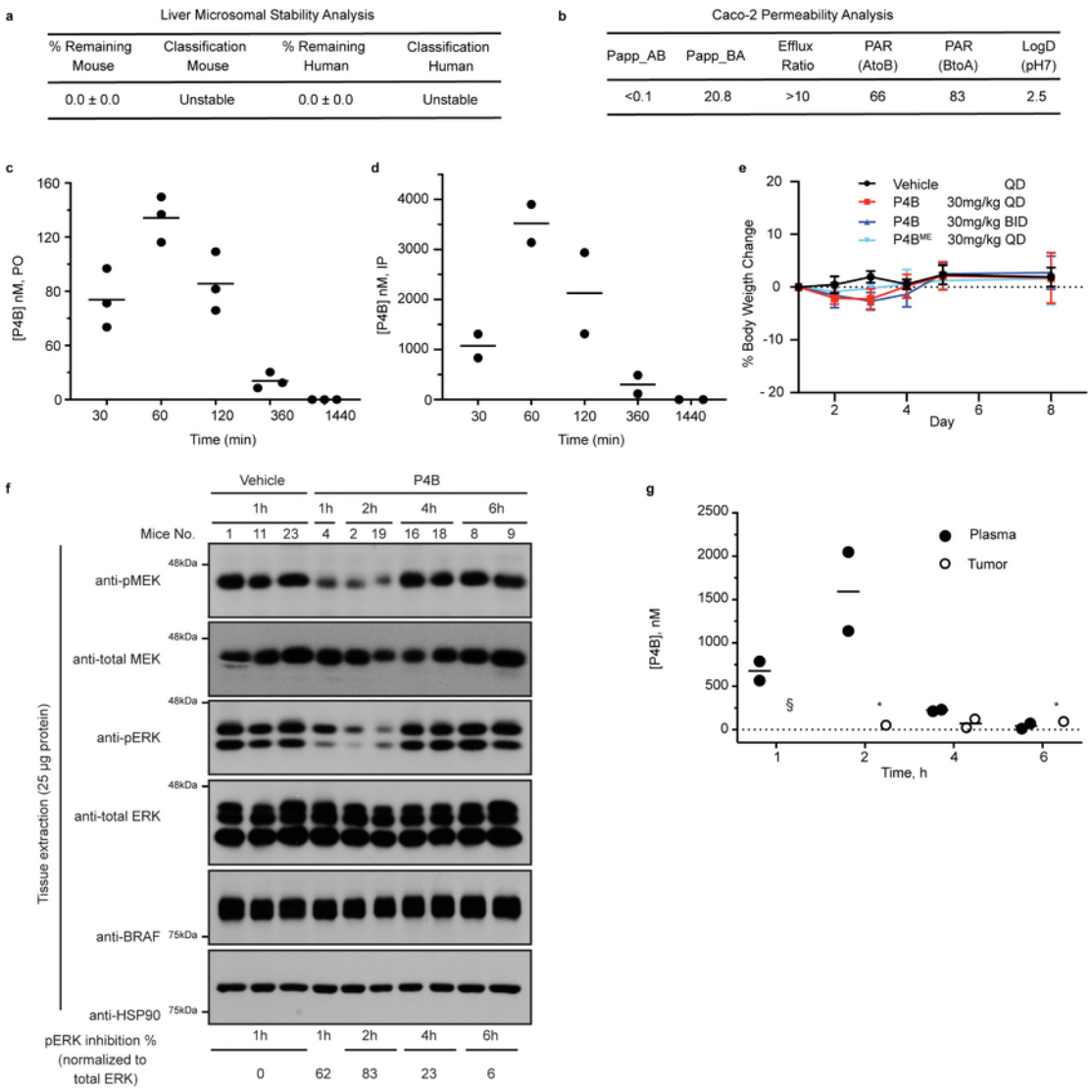
Supplementary Figure 6| Binding analysis of small molecule compounds to BRAF

a-d, SPR binding analysis of $BRAF_{16mut}$(WT) (left panel) and $BRAF_{16mut}$(V600E) (right panel) with the indicated concentrations of BI 882370 * (**a**), P4B (**b**), **17** (**c**) and **19** (**d**). K_d, k_{off}, and k_{on} values represent mean values ± s.d., Data shown are representative of two independent experiments.



Supplementary Figure 7| RNAseq analysis

A375 cells treated with 200 nM of the indicated compounds for 20 h were harvested and cell pellets divided for immunoblot analysis with the indicated antibodies (**a**), and for RNA purification and subsequent RNA-Seq. Data are representative of two independent duplicates. **b**, The whole transcriptomes as indicated were analyzed in a Spearman cross-correlation matrix and plotted in a heatmap (scale) using unsupervised hierarchical clustering. In **c,** differentially expressed genes common between DESEq2 and t-test analyses in the indicated cell treatments are plotted in a Venn diagram.



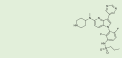
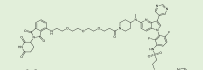
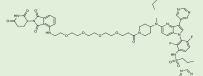
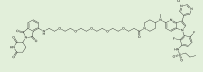
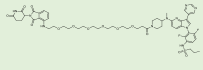
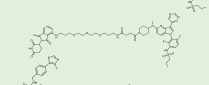
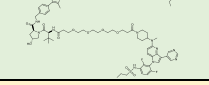
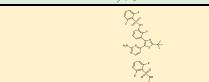
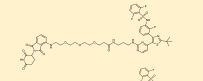
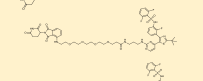
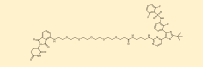
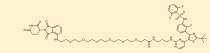
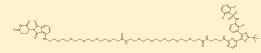
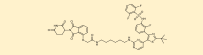
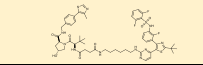
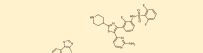
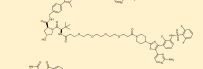
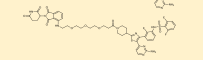
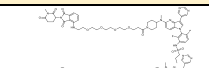
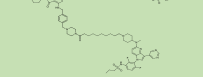
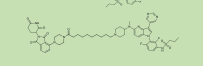
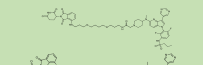
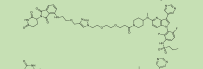
Supplementary Figure 8| MTD, Toxicity and PK-PD analysis in mouse

a, % P4B remaining after 1h incubation with mouse and human liver microsomes. **b,** Caco-2 permeability of P4B. Apparent permeability of apical to basolateral (AB) and to basolateral to apical (BA) is expressed in 10^{-6} cm/sec. Efflux is calculated from BA/AB ratio. Post assay recovery is expressed in %. LogD at pH 7 was calculated using ACDlabs PhysChem software. **c-d,** Plasma concentrations of P4B at various time points after oral (PO) (**c**) and intraperitoneal (IP) (**d**) administration in mouse. Data shown are representative of two independent experiments. **e,** Body weight change at indicated time points of mice treated by intraperitoneal injection at 30 mg/kg of P4B QD, P4B BID, $P4B^{ME}$ QD and vehicle for eight days with five mice in each group. Data represent mean values ± s.d. **f,** Xenograft mice tumors treated with vehicle or P4B were analyzed at various time points by Immunoblot analysis (top panel) and AlphaLISA to assess pERK inhibition (lower panel). **g,** Plasma and tumor concentrations of P4B at indicated time points. § Data below lower limit of quantification, * Data from one mouse.

Compound ID	Molecule Name	E3 Ligase Binder	Linker	Linker Length (Å)	RAF Binder	IC_{50}(nM)				IC50(nM)			D_{max}(%)	DC_{50}(nM)	αapp	αapp
						BRAF (V600E)	BRAF (WT)	CRAF	ARAF	SRMS	LCK	CSF1R	BRAF (V600E)	BRAF (V600E)	BRAF (WT)	BRAF (V600E)
1	BI 882370*	-	-	-	BI 882370*	31	22	64	323	-	-	-	0	-	N.T.	N.T.
2	Pmd-PEG3-BI	Pomalidomide	PEG3	15.6	BI 882370	65	27	532	>10,000	-	-	-	65	100	0.36	0.41
3	Pmd-PEG4-BI (P4B)	Pomalidomide	PEG4	19.1	BI 882370	12	58	167	2222	798	2408	6679	82	15	0.38	0.35
4	Pmd-PEG5-BI (P5B)	Pomalidomide	PEG5	22.7	BI 882370	25	66	223	3619	-	-	-	82	70	0.43	0.39
5	Pmd-PEG6-BI	Pomalidomide	PEG6	26.1	BI 882370	83	75	542	6550	-	-	-	84	90	0.38	0.39
6	Pmd-PEG8-BI	Pomalidomide	PEG8	33.2	BI 882370	85	145	592	4907	-	-	-	65	45	0.39	0.36
7	Pmd-1C-PEG3-1C-2C-BI	Pomalidomide	1C-PEG3-1C-2C	22.9	BI 882370	82	84	468	3343	-	-	-	51	100	0.43	0.41
8	VH-PEG4-BI	VH032	PEG4	19.2	BI 882370	67	27	205	402	-	-	-	40	100	N.T.	N.T.
9	Dab#1	-	-	-	Dabrafenib* #1	13	619	11	169	-	-	-	0	-	N.T.	N.T.
10	Pmd-PEG3-3C-Dab#1	Pomalidomide	PEG3-3C	20.3	Dabrafenib #1	97	227	206	2557	-	-	-	0	-	N.T.	N.T.
11	Pmd-PEG4-3C-Dab#1	Pomalidomide	PEG4-3C	24	Dabrafenib #1	122	581	175	6847	-	-	-	0	-	N.T.	N.T.
12	Pmd-PEG5-3C-Dab#1	Pomalidomide	PEG5-3C	26.6	Dabrafenib #1	99	172	128	3495	-	-	-	0	-	N.T.	N.T.
13	Pmd-PEG6-3C-Dab#1	Pomalidomide	PEG6-3C	29.4	Dabrafenib #1	199	372	212	7523	-	-	-	0	-	N.T.	N.T.
14	Pmd-PEG5-PEG5-Dab#1	Pomalidomide	PEG5-PEG5	46.1	Dabrafenib #1	243	672	510	6723	-	-	-	0	-	N.T.	N.T.
15	Thd-1C-6C-Dab#1	Thalidomide	1C-6C	10.2	Dabrafenib #1	51	111	105	5803	-	-	-	0	-	N.T.	N.T.
16	VH-2C-6C-Dab#1	VH032	2C-6C	13.4	Dabrafenib #1	73	154	123	>10,000	-	-	-	0	-	N.T.	N.T.
17	Dab#2	-	-	-	Dabrafenib* #2	15	64	36	344	-	-	-	0	-	N.T.	N.T.
18	VH-PEG4-Dab#2	VH032	PEG4	19.5	Dabrafenib #2	58	136	201	3339	-	-	-	0	-	N.T.	N.T.
19	Pmd-PEG3-Dab#2	Pomalidomide	PEG3	14.7	Dabrafenib #2	26	105	73	2341	-	-	-	50	500	N.T.	N.T.
20	Pmd^{ME}-PEG4-BI ($P4B^{ME}$)	N-methyl-Pomalidomide	PEG4	19.1	BI 882370	58	91	340	225	-	-	-	0	-	N.T.	N.T.
21	Pmd^{ME}-PEG5-BI ($P5B^{ME}$)	N-methyl-Pomalidomide	PEG5	22.7	BI 882370	121	137	552	2338	-	-	-	0	-	N.T.	N.T.
22	Pmd-PEG3-Az-C1-BI	Pomalidomide	PEG3-Az-C1	16.2	BI 882370	2	12	182	-	-	-	-	0	-	N.T.	N.T.
23	Pmd-C1-Ph-C1-PPZ-C9-BI	Pomalidomide	C1-Ph-C1-PPZ-C9	21.5	BI 882370	33	12	149	-	-	-	-	0	-	N.T.	N.T.
24	Pmd-PPZ-C9-BI	Pomalidomide	PPZ-C9	17	BI 882370	3	2	61	-	-	-	-	0	-	N.T.	N.T.
25	Pmd-DODA-C1-BI	Pomalidomide	DODA-C1	18.5	BI 882370	25	22	483	-	-	-	-	71	25	N.T.	N.T.
26	Pmd-PEG1-Trz-PEG2-BI	Pomalidomide	PEG1-Trz-PEG2	18.5	BI 882370	15	42	287	-	-	-	-	72	80	N.T.	N.T.
27	Len(C)≡PEG4-BI	Lenalidomide	(C)≡PEG4	17.1	BI 882370	90	22	187	-	-	-	-	74	50	N.T.	N.T.

Supplementary Table 1| Summary of BRAF PROTAC functional activity

IC_{50} values are from activity assays performed by Eurofins. D_{max} and DC_{50} are based on the % of BRAF degradation described in **Extended Data Fig. 2a** and Supplementary **Fig. 1-3**. α_{app} values are based on experiments described in **Supplementary Fig. 6**.

Compound ID	Structure	SMILES	Molecule Name
1		CN(C1=CC=C(N(C2=C(F)C(NS(	BI 882370*
2		O=C(N1C2C(NC(CC2)=O)=O)C:	Pmd-PEG3-BI
3		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-PEG4-BI (P4B)
4		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-PEG5-BI (P5B)
5		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-PEG6-BI
6		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-PEG8-BI
7		O=C1N(C2CCC(NC2=O)=O)C(C	Pmd-1C-PEG3-1C-2C-BI
8		O=C(N[C@H](C(N1[C@H](C(NC	VH-PEG4-BI
9		CC(C)(C1=NC(C2=CC=CC(NS(	Dab#1
10		O=C(N1C2C(NC(CC2)=O)=O)C:	Pmd-PEG3-3C-Dab#1
11		O=C(NCCCNC1=NC=CC(C(S2)	Pmd-PEG4-3C-Dab#1
12		O=C(NCCCNC1=NC=CC(C(S2)	Pmd-PEG5-3C-Dab#1
13		O=C(NCCCNC1=NC=CC(C(S2)	Pmd-PEG6-3C-Dab#1
14		O=C(NCCCNC1=NC=CC(C(S2)	Pmd-PEG5-PEG5-Dab#1
15		O=C(N1C2C(NC(CC2)=O)=O)C:	Thd-1C-6C-Dab#1
16		O=C(N[C@H](C(C)(C)C)C(N1C[	VH-2C-6C-Dab#1
17		NC1=NC=CC(C(S2)=C(C3=CC=	Dab#2
18		O=C(N1CCC(CC1)C2=NC(C3=(	VH-PEG4-Dab#2
19		O=C1N(C2CCC(NC2=O)=O)C(C	Pmd-PEG3-Dab#2
20		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd^{ME}-PEG4-BI ($P4B^{ME}$)
21		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd^{ME}-PEG5-BI ($P5B^{ME}$)
22		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-PEG3-Az-C1-BI
23		O=C(N1C2C(NC(CC2)=O)=O)C:	Pmd-C1-Ph-C1-PPZ-C9-BI
24		O=C(N1C2C(NC(CC2)=O)=O)C:	Pmd-PPZ-C9-BI
25		CN(C1=CC=C(N(C2=C(F)C(NS(	Pmd-DODA-C1-BI
26		O=C1N(C2CCC(NC2=O)=O)C(C	Pmd-PEG1-Trz-PEG2-BI
27		CN(C1=CC=C(N(C2=C(F)C(NS(	Len(C)≡PEG4-BI

Supplementary Table 2| Summary of PROTAC chemical structures

	BRAF:**P4B**
Data collection	
Space group	P 2_1 2_1 2_1
Cell dimensions	
a, *b*, *c* (Å)	52.06 104.24 109.90
α, β, γ (°)	90, 90, 90
Resolution (Å)	109.9 – 3.29 (3.55 – 3.29)
Rmeas	0.37 (2.41)
$I / \sigma I$	4.3 (0.9)
Completeness (%)	99.3 (97.0)
Redundancy	6.4 (6.4)
CC(1/2)	0.97 (0.33)
Refinement	
Resolution (Å)	54.95 – 3.29 (3.55 – 3.29)
No. reflections	61076 (11935)
R_{work} / R_{free}	26.32/28.81
No. atoms	
Protein	3618
Ligand/ion	72
Water	4
B-factors	
Protein	94.93
Ligand/ion	94.22
Water	61.62
R.m.s. deviations	
Bond lengths (Å)	0.002
Bond angles (°)	0.48

*Values in parentheses are for highest-resolution shell.

Supplementary Table 3| X-Ray data collection and refinement statistics

					pERK IC_{50} (nM)			Proliferation IC_{50} (nM)		
	Cell lines	*BRAF* Mutations	*RAS* Mutations	Recombinant	P4B	$P4B^{ME}$	BI 882370*	P4B	$P4B^{ME}$	BI 882370*
1 hour treatment	A375	V600E/V600E	WT	-	71 ± 20	96 ± 18	92 ± 18	-	-	-
24 hours treatment	A375	V600E/V600E	WT	-	8 ± 6	75 ± 26	29 ± 5	71 ± 46	726 ± 377	274 ± 170
	WM266-4	V600D/WT	WT	-	23 ± 11	192 ± 30	83 ± 30	75 ± 19	535 ± 94	203 ± 48
	RKO	V600E/WT	WT	-	70 ± 21	566 ± 186	34 ± 12	147 ± 55	1312 ± 243	145 ± 53
	COLO25	V600E/WT	WT	-	4 ± 4	43 ± 27	2 ± 0	52 ± 20	443 ± 189	27 ± 4
	HT-29	V600E/WT/WT	WT	-	11 ± 2	58 ± 21	9 ± 4	8 ± 4	25 ± 3	10 ± 2
	MeWo	WT	WT	-	induction	induction	induction	>10.000	>10.000	>10.000
	H1666	G466V/WT	WT	-	431 ± 368	4230	332 ± 45	>10.000	>10.000	>10.000
	H508	G596R/WT	WT	-	>10.000	>10.000	>10.000	>10.000	>10.000	>10.000
	NCI-H1755	G469A/WT	WT	-	8.772 ± 9.802	8912 ± 11.163	>10.000	>10.000	>10.000	>10.000
	A375-VR	V600E/ tandem V600E	WT	-	1.926 ± 318	5.158 ± 891	11.404 ± 494	1.101 ± 701	2.604 ± 482	5.143 ± 1193
	HCT116	WT	G13D	-	induction	induction	induction	>10.000	>10.000	>10.000
	SK-MEL2	WT	Q61R	-	induction	induction	induction	>10.000	>10.000	>10.000
	MDA-MB-231	G464V/WT	G13D	-	>10.000	>10.000	>10.000	>10.000	>10.000	>10.000
	NCI-H2087	L597V/WT	Q61K	-	induction	induction	induction	>10.000	>10.000	>10.000
	A375	V600E/V600E	WT	Parental	20 ± 8	128 ± 46	-	130 ± 51	719 ± 260	-
	A375	V600E/V600E	WT	Empty	27 ± 7	134 ± 19	-	172 ± 73	863 ± 244	-
	A375	V600E/V600E	WT	*KRAS*(G12V)	>10.000	>10.000	-	>10.000	>10.000	-
	A375	V600E/V600E	WT	*HRAS*(G12V)	>10.000	>10.000	-	>10.000	>10.000	-
	A375	V600E/V600E	WT	*NRAS*(G12V)	>10.000	>10.000	-	>10.000	>10.000	-
	MEF	WT	*Kras* $^{lox/lox}$	-	induction	induction	-	>10.000	>10.000	-
	MEF	WT	RASless	-	weak induction	weak induction	-	>10.000	>10.000	-
	MEF	WT	RASless	*BRAF*(V600E)	83 ± 32	714 ± 359	-	261 ± 69	2122 ± 371	-

Supplementary Table 4| Quantification of inhibitor function in select mutant cell lines

IC_{50} are obtained by fitting to the proliferation and phospho-ERK profiles shown in **Fig. 3c, 4a-c, 5a-e, Extended Data Fig. 3a-j, 6e-f,** and **Supplementary Fig. 5a.**

Supplementary Note

CHEMISTRY

General Methods

All solvents and commercially available reagents were used as obtained. Oxygen and/or moisture sensitive reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. Chromatography purification was performed using a Teledyne ISCO Combiflash system, Isolera™ One system and prepacked RediSep Rf Normal-phase Silica (60 Å mesh) Flash Cartridges or RediSep Rf C18 Reverse-phase (60 Å mesh) Flash Cartridges.

Nuclear magnetic resonance (NMR) analysis was performed on a Bruker 500 MHz NMR, 400 MHz Bruker Avance III NMR and 500 MHz Agilent DD2 NMR Spectrometers. Spectra were measured at 298K, unless indicated otherwise and were referenced relative to the solvent chemical shift. NMR chemical shifts are expressed in ppm and coupling constants (J) are expressed in Hz. Data were reported as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet, (br) broad.

Target compounds and/or intermediates were characterized by liquid chromatography/mass spectrometry (LCMS) using a Waters Acquity separation module. General conditions are as follows. Mass spectra were acquired on LC/MS systems using electrospray ionization methods from Waters ACQUITY UPLC system with a SQ (single quadrupole) MS or Waters ACQUITY UPLC H-Class system with a 3100 (single quadrupole) MS. *[M+H]* refers to the protonated molecular ion of the chemical species. The mobile phase was 0.1% formic acid in water (solvent A) and 0.1% formic acid in ACN (solvent B). The gradient that was used is presented in the table below.

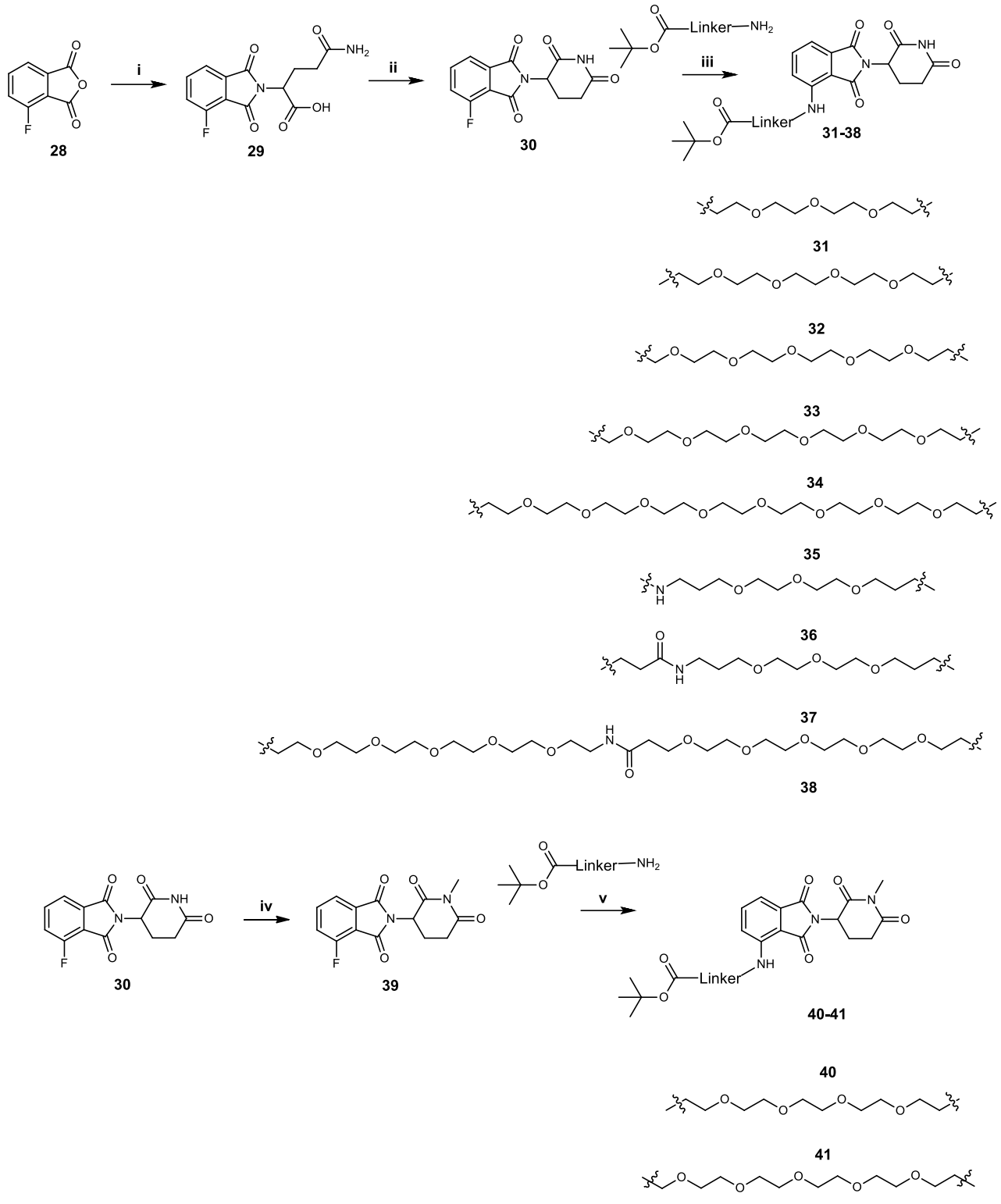
Time (min)	Flow (mL/min)	%A	%B
Initial	0.4	90	10
1.8	0.4	5	95
2.3	0.4	5	95
2.5	0.4	90	10
3	0.4	90	10
5	0	90	10

Column 1: Acquity UPLC CSH C18 (2.1 x 50 mm, 130 Å, 1.7 µm. Part No. 186005296) or Column 2: Acquity UPLC BEH C8 (2.1 x 50 mm, 130 Å, 1.7 µm. Part No. 186002877). The columns were used with column temperature maintained at 25 °C. The sample solution injection volume was 1 µL. MassLynx 4.1 was used for data analysis.

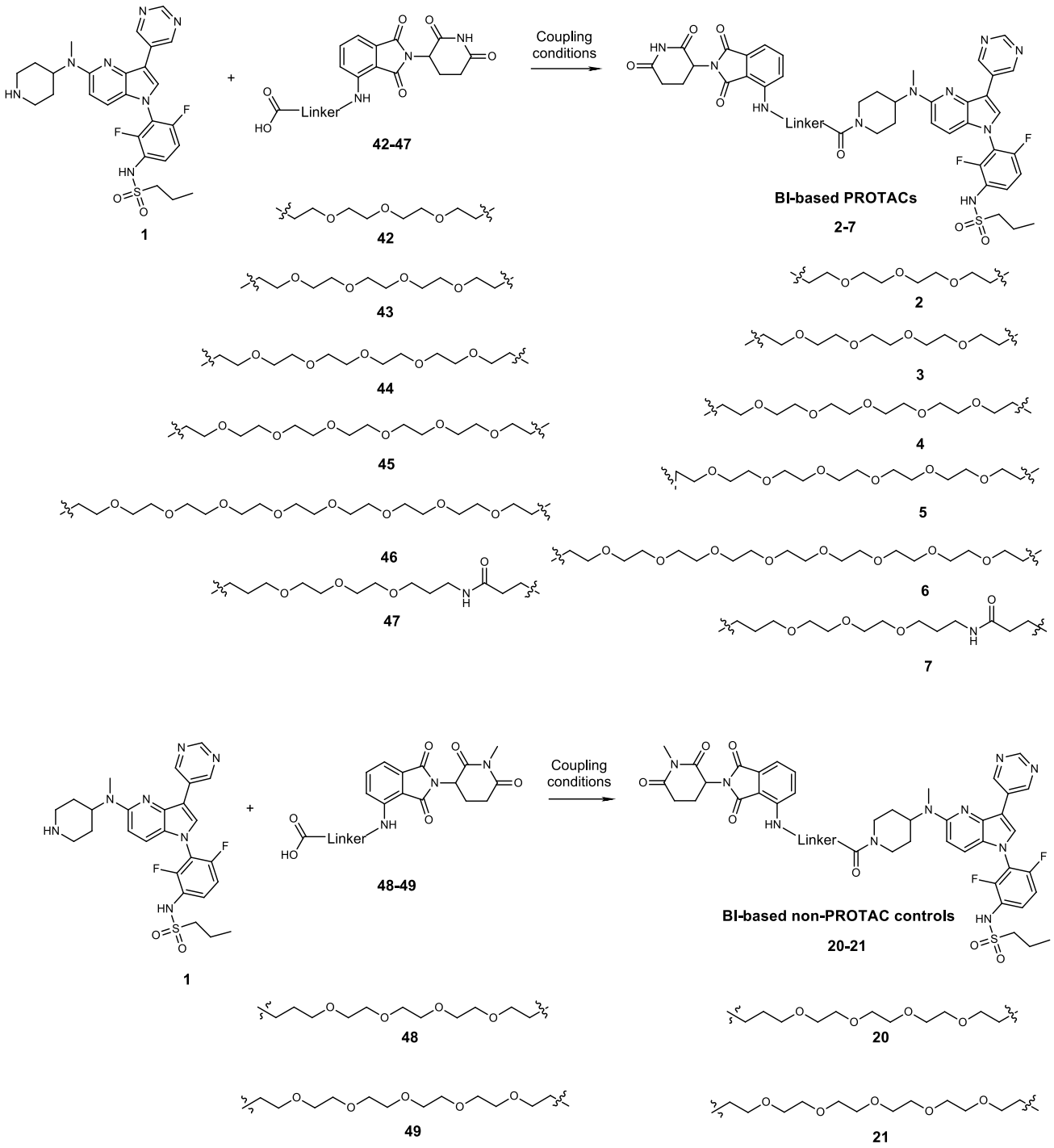
High resolution mass spectrometry (HRMS) values were measured and calculated with Agilent 6538 UHD Q-TOF MS. All of the values provided correspond to the ionic species of interest and the given ionic formula includes the charging agent.

Abbreviations used: DCM for dichloromethane, EtOAc for ethyl acetate, DMSO for dimethyl sulfoxide, DIPEA for *N,N*-diisopropylethylamine, MeOH for methanol, DMF for *N,N*-dimethylformamide, HATU for 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluoro-phosphate, TFA for trifluoroacetic acid, CDI for 1,1'-carbonyldiimidazole, DMAP for 4-dimethylaminopyridine, ACN for acetonitrile, RT for room temperature, MPLC for medium-pressure liquid chromatography.

Synthesis of BI-based compounds



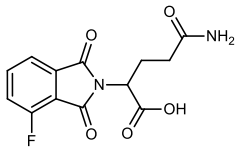
Scheme 1. Reagents and conditions: i) L-Glutamine, DMF, 90^{o}C ; ii) CDI, DMAP, ACN, RT; iii,v) dioxane, DIPEA, 100-110 ^{o}C: vi) Cs_2CO_3, CH_3I, DMF, RT.



Scheme 2. Coupling conditions: HATU, DIPEA, DMF, RT

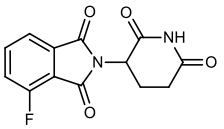
Synthetic methods for the preparation of BI-based PROTACs

5-Amino-2-(4-fluoro-1,3-dioxoisoindolin-2-yl)-5-oxopentanoic acid (29)



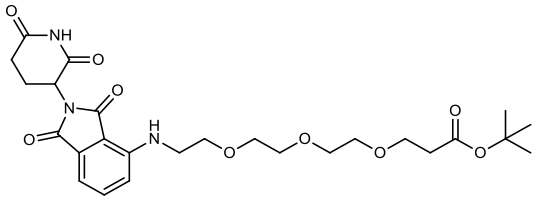
Using a literature procedure[19] starting from 3-fluorophthalic anhydride (8.81 g, 53.0 mmol) and L-glutamine (10 g, 68.4 mmol), derivative **29** (11.4 g, 70%) was obtained. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97-7.91 (m, 1H), 7.80-7.90 (m, 2H), 7.20 (br. s., 1H), 6.72 (br. s., 1H), 4.75 (dd, *J*=4.52, 10.88 Hz, 1H), 2.39-2.21 (m, 2H), 2.17-2.07 (m, 2H). ^{19}F NMR (471 MHz, DMSOd_6): δ -114.82 (s, 1F). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{12}FN_2O_5$, 295.07. Found 295.34.

2-(2,6-Dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (30)



A literature procedure[19] using **29** (5.7 g, 19.37 mmol) afforded intermediate **30** (1.1 g, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br. s., 1H), 7.81-7.71 (m, 2H), 7.44 (t, *J* = 8.4 Hz, 1H), 5.00 (dd, *J* = 12.5, 5.4 Hz, 1H), 2.96-2.73 (m, 3H), 2.21 - 2.14 (m, 1H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -111.69 (s, 1F). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{13}H_{10}FN_2O_4$, 277.06. Found 277.30.

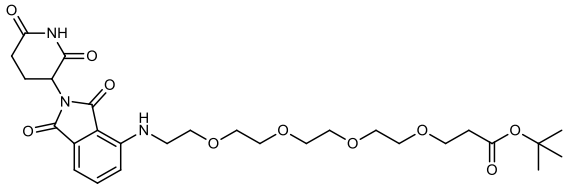
tert-Butyl 3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-ethoxy)ethoxy)propanoate (31)



A mixture of *tert*-butyl 12-amino-4,7,10-trioxadodecanoate (254 mg, 0.916 mmol) and **30** (230 mg, 0.833 mmol) in 1,4-dioxane (12 mL) was stirred at 100 °C overnight in a sealed vial. The reaction mixture was concentrated onto Celite and purified by silica gel chromatography, eluting with DCM/ACN. The relevant fractions were collected and concentrated with a rotary evaporator

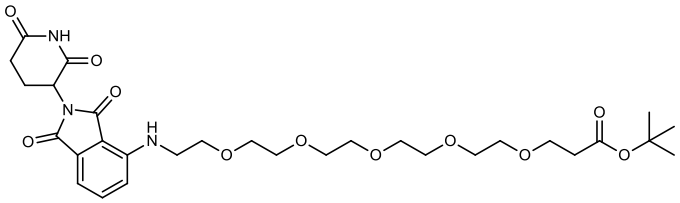
to afford intermediate **31** (410 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.15 (br s, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.51 (br s, 1H), 4.94 (dd, *J* = 5.3, 12.3 Hz, 1H), 3.77 - 3.62 (m, 12H), 3.50 (q, *J* = 5.4 Hz, 2H), 2.94 - 2.72 (m, 3H), 2.53 (t, *J* = 6.5 Hz, 2H), 2.19 - 2.12 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.36, 170.98, 169.26, 168.53, 167.63, 146.85, 135.99, 132.52, 116.79, 111.58, 110.29, 80.53, 70.72, 70.59, 70.56, 70.35, 69.51, 66.87, 48.87, 42.40 36.26, 31.42, 28.09, 22.78. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{26}H_{36}N_3O_9$, 534.24. Found 534.37.

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxa-pentadecan-15-oate (32)



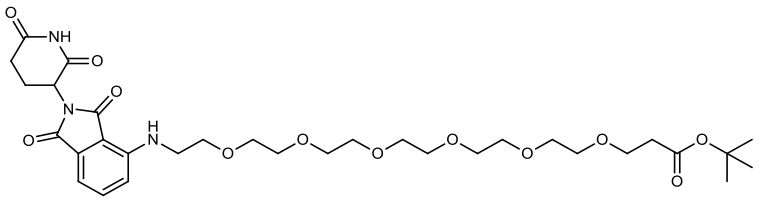
The procedure analogous to that described for intermediate **31**, with *tert*-butyl 1-amino-3,6,9,12-tetraoxapentadecan-15-oate (320 mg, 0.996 mmol), DIPEA (351 mg, 2.72 mmol) and **30** (250 mg, 0.905 mmol) in 1,4-dioxane (12 mL) afforded **32** (410 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.51 (br t, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 6.51 (br s, 1H), 4.93 (br dd, *J* = 5.0, 12.1 Hz, 1H), 3.76 - 3.62 (m, 16H), 3.52 - 3.46 (m, 2H), 2.93 - 2.71 (m, 3H), 2.52 (t, *J* = 6.5 Hz, 2H), 2.19 - 2.11(m, 1H), 1.46 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.11, 170.93, 169.26, 168.36, 167.62, 146.88, 136.02, 132.53, 116.80, 111.63, 110.33, 80.53, 70.75, 70.62, 70.60, 70.45, 70.38, 69.52, 66.90, 48.89, 42.43, 36.25, 31.42, 28.10, 22.80 LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{40}N_3O_{10}$, 578.27. Found 578.46.

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-penta-oxaoctadecan-18-oate (33)



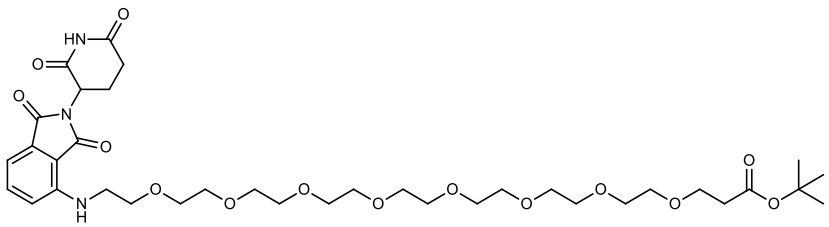
A procedure analogous to that used for intermediate **31** using *tert*-butyl 1-amino-3,6,9,12,15-pentaoxaoctadecan-18-oate (437 mg, 1.195 mmol) and **30** (300 mg, 1.086 mmol) afforded intermediate **33** (472 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.50 (br t, *J* = 5.2 Hz, 1H), 4.92 (dd, *J* = 5.3, 12.3 Hz, 1H), 3.74 - 3.60 (m, 20 H), 3.48 (q, *J* = 5.5 Hz, 2H), 2.92 - 2.70 (m, 3H), 2.50 (t, *J* = 6.6 Hz, 2H), 2.18 - 2.10 (m, 1H), 1.48 - 1.41 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.45, 170.89, 169.27, 168.59, 167.62, 146.83, 135.98, 132.50, 116.77, 111.55, 110.28, 80.46, 70.68, 70.61, 70.57, 70.49, 70.42, 70.31, 69.49, 66.85, 48.88, 42.37, 36.25, 31.42, 28.08, 22.76. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{30}H_{44}N_3O_{11}$, 622.30. Found 622.43.

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18-hexaoxaheneicosan-21-oate (34)



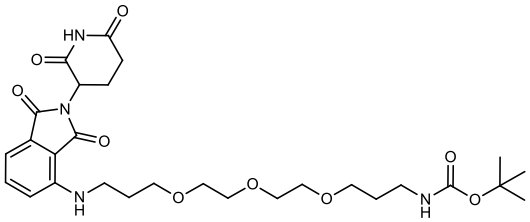
A procedure analogous to that used for intermediate **31** using amino-PEG6-*tert*-butyl ester (98 mg, 0.239 mmol) and **30** (60 mg, 0.217 mmol) afforded intermediate **34** (100 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.42 (dd, *J* = 8.4, 7.3 Hz, 1H), 7.20 (s, 1H), 7.03 (d, *J* = 7.1 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1H), 6.42 (br t, *J* = 5.3 Hz, 1H), 4.90 – 4.81 (m, 1H), 3.67 – 3.50 (m, 24H), 3.46 – 3.38 (m, 2H), 2.84 – 2.62 (m, 3H), 2.43 (t, *J* = 6.6 Hz, 2H), 2.14 – 1.91 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.20, 170.92, 169.26, 168.43, 167.63, 146.86, 136.01, 132.53, 116.78, 111.61, 110.32, 80.51, 70.74, 70.64, 70.58, 70.55, 70.51, 70.45, 70.33, 69.49, 66.88, 48.89, 42.41, 36.27, 31.43, 28.10, 22.80. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{32}H_{48}N_3O_{12}$, 666.32. Found 666.3.

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18,21,24-octaoxaheptacosan-27-oate (35)



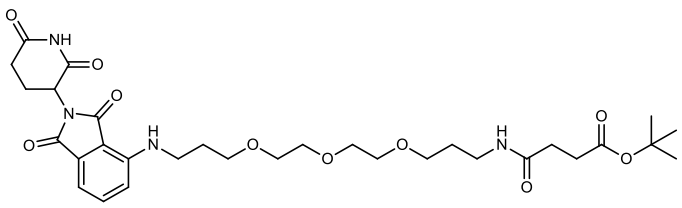
A procedure analogous to that used for intermediate **31** using amino-PEG8-t-butyl ester (41 mg, 0.082 mmol) and **30** (22.76 mg, 0.082 mmol) afforded intermediate **35** (36 mg, 58.0%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (br s, 1H), 7.51 (dd, *J* = 8.3, 7.4 Hz, 1H), 7.12 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 6.51 (br t, *J* = 5.4 Hz, 1H), 4.93 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.77 – 3.55 (m, 32H), 3.53 – 3.47 (m, 2H), 2.92 – 2.71 (m, 3H), 2.52 (t, *J* = 6.6 Hz, 2H), 2.18 – 2.11 (m, 1H), 1.53 – 1.42 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.00, 170.91, 169.25, 168.29, 167.62, 146.88, 136.03, 132.55, 116.78, 111.64, 110.36, 80.50, 70.78, 70.68, 70.61, 70.59, 70.57, 70.54, 70.50, 70.37, 69.50, 66.91, 48.90, 42.43, 36.29, 31.45, 28.11, 22.82. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{36}H_{56}N_3O_{14}$, 754.38. Found 754.52.

tert-Butyl (3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)-ethoxy)ethoxy)propyl)carbamate (36)



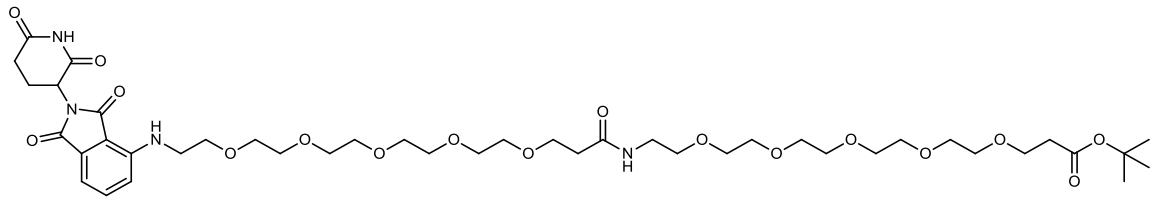
A procedure analogous to that of **31** above using *N*-Boc-4,7,10-trioxa-1,13-tridecanediamine (232 mg, 0.724 mmol) and **30** (200 mg, 0.724 mmol) afforded intermediate **36** (186 mg, 44%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (br. s., 1H), 7.42 (dd, *J* = 7.34, 8.31 Hz, 1H), 7.04 (d, *J* = 7.09 Hz, 1H), 6.86 (d, *J* = 8.56 Hz, 1H), 6.34-6.49 (m, 1H), 4.85 (s, 1H), 3.53-3.66 (m, 16H), 3.36-3.45 (m, 2H), 2.69 (s, 3H), 2.40-2.47 (m, 2H), 1.99-2.11 (m, 1H), 1.36-1.38 (m, 9H). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{28}H_{41}N_4O_9$ 577.28. Found 577.47.

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-15-oxo-4,7,10-trioxa-14-azaocta-decan-18-oate (37)



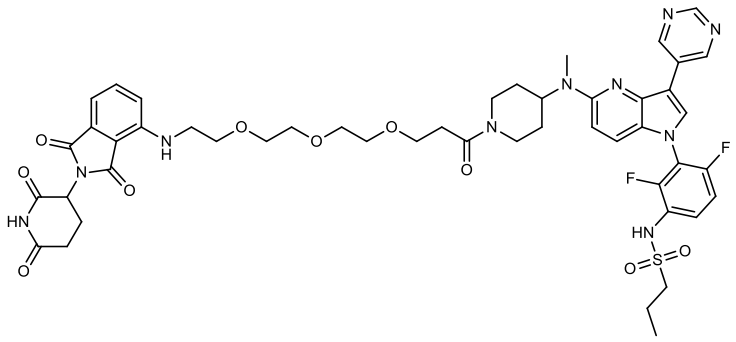
36 (66 mg, 0.114 mmol) was dissolved in a mixture of TFA (2 mL) and DCM (2 mL). The reaction mixture was stirred for 1 h at RT. The solvent was then removed with a rotary evaporator and the residue was dried under high vacuum overnight to afford the crude product 4-((3-(2-(2-(3-aminopropoxy)-ethoxy)ethoxy)propyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione trifluoroacetate (67.6 mg, 100%) which was used in the next step without any further purification. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{23}H_{34}N_4O_7$, 477.23. Found 477.49. *Tert*-butyl hydrogen succinate (21.93 mg, 0.126 mmol) was dissolved in DMF (2 mL), then HATU (52.2 mg, 0.137 mmol) was added at RT. The mixture was stirring for 5 min, DIPEA (71 mg, 0.570 mmol) was added and the mixture was stirred for another 10 min. 4-((3-(2-(2-(3-Aminopropoxy)-ethoxy)ethoxy)propyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione trifluoroacetate (67.6 mg, 0.114 mmol) was dissolved in 1 mL of DMF. After stirring overnight at RT, the reaction mixture was evaporated onto Celite and purified by silica gel chromatography, eluting with DCM/ACN. The desired fractions were collected, concentrated and dried under vacuum to afford intermediate **37** (58 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (br s, 1H), 7.50 (br t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.94 (br d, *J* = 8.6 Hz, 1H), 6.48 (br s, 1H), 6.29 (br s, 1H), 4.92 (br dd, *J* = 12.0, 5.0 Hz, 1H), 3.72 - 3.54 (m, 12H), 3.45 - 3.32 (m, 4H), 2.90 (br d, *J* = 14.4 Hz, 1H), 2.86 - 2.70 (m, 2H), 2.57 (br t, *J* = 6.8 Hz, 2H), 2.40 (br t, *J* = 6.9 Hz, 2H), 2.18 - 2.11 (m, 1H), 1.94 (br t, *J* = 6.1 Hz, 2H), 1.77 (br t, *J* = 5.9 Hz, 2H), 1.58 (s, 2H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.35, 171.61, 171.29, 169.36, 168.57, 167.66, 146.99, 136.10, 132.53, 116.65, 111.34, 109.92, 80.59, 70.50, 70.48, 70.45, 70.11, 69.84, 68.89, 48.86, 40.24, 37.78, 31.42, 31.26, 30.89, 29.28, 28.98, 28.07, 22.83. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{31}H_{45}N_4O_{10}$, 633.31. Found 633.60 .

tert-Butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-18-oxo-3,6,9,12,-15,22,25,28,31,34-decaoxa-19-azaheptatriacontan-37-oate (38)



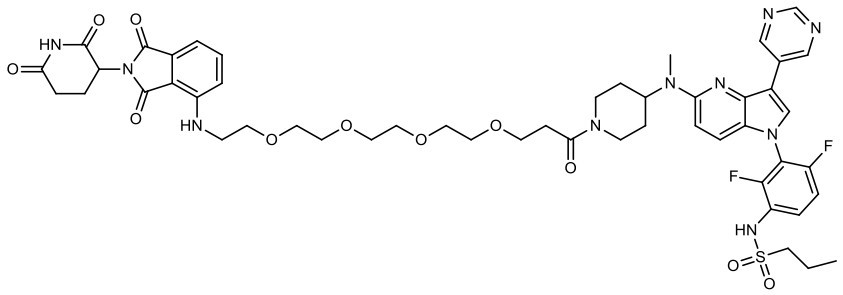
33 (100 mg, 0.160 mmol) was dissolved in a mixture of TFA (3 mL) and DCM (3 mL). The reaction mixture was stirred for 1 h at RT, the solvent was removed with a rotary evaporator and crude product was dried under high vacuum overnight to afford **44** (108.6 mg, quantitative yield). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{26}H_{37}N_3O_{11}$, 566.23. Found 566.36. To the dried crude product was added HATU (81 mg, 0.213 mmol) in DMF (1.4 mL). After 10 min DIPEA (102 mg, 0.789 mmol) was added at RT. The reaction was stirred for 10 min at RT and *tert*-butyl 1-amino-3,6,9,12,15-pentaoxanonadecan-19-oate (64 mg, 0.169 mmol) was added. The reaction was stirred at RT overnight. The reaction mixture was evaporated onto Celite under vacuum and purified using reverse phase chromatography, eluting with water:ACN. The desired fractions were collected and concentrated with a rotary evaporator to afford **38** (70 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 - 8.62 (m, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 7.0 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.65 (br s, 1H), 6.51 (br t, *J* = 5.4 Hz, 1H), 4.92 (dd, *J* = 12.1, 5.4 Hz, 1H), 3.76 - 3.59 (m, 38H), 3.56 (s, 2H), 3.46 (qd, *J* = 5.4, 16.0 Hz, 4H), 2.92 - 2.71 (m, 3H), 2.49 (td, *J* = 19.9, 6.3 Hz, 4H), 2.18 - 2.10 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.36, 171.22, 170.89, 169.26, 168.46, 167.62, 146.85, 136.02, 132.55, 116.77, 111.61, 110.35, 80.50, 70.77, 70.67, 70.59, 70.53, 70.50, 70.49, 70.38, 70.36, 70.28, 70.22, 69.85, 69.48, 67.27, 66.90, 48.91, 42.41, 39.16, 36.98, 36.27, 31.45, 28.10, 22.81. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{44}H_{71}N_4O_{17}$, 913.46. Found 913.70.

N-(3-(5-((1-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)-ethoxy)ethoxy)propanoyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (2)



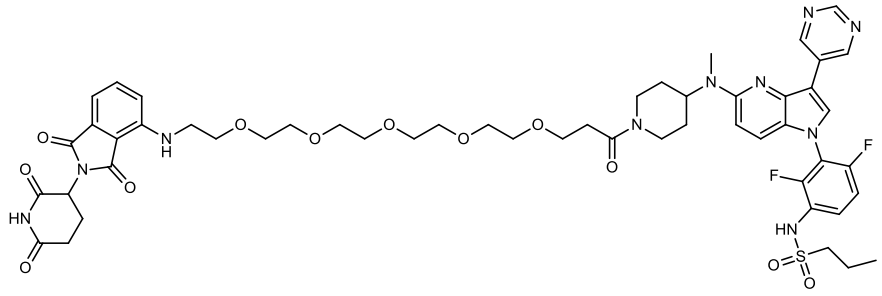
Following the procedure described for **3** using **31** (16 mg, 0.03 mmol) and **1** (18 mg, 0.027 mmol) afforded the title compound **2** (6.87 mg, 25%) as a yellow powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.53 (s, 2H), 9.09 (s, 1H), 7.69 - 7.63 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.31 (br d, J = 9.0 Hz, 1H), 7.16 (td, *J* = 9.1, 1.53 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.58 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.48 (q, *J* = 5.3 Hz, 1H), 4.86 - 4.96 (m, 1H), 4.77 - 4.86 (m, 2H), 4.04 (br d, *J* = 13.3 Hz, 1H), 3.89 - 3.75 (m, 2H), 3.74 - 3.64 (m, 12H), 3.51 - 3.40 (m, 2H), 3.23 (br t, *J* = 13.0 Hz, 1H), 3.17 - 3.12 (m, 2H), 2.90 (s, 3H), 2.87 - 2.81 (m, 1H), 2.79 - 2.65 (m, 4H), 2.15 - 2.05 (m, 1H), 1.96 - 1.84 (m, 2H), 1.83 - 1.76 (m, 1H), 1.76 - 1.58 (m, 2H), 1.06 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -130.80 (s, 1F), -121.68 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.54, 169.57, 169.25, 168.69, 167.67, 156.06, 155.77, 153.90, 153.71, 150.89, 148.91 (d, *J* = 4.54 Hz), 146.80, 142.13, 135.98, 132.54, 128.45, 126.95, 124.25, 123.59 (br d, J=9.08 Hz), 122.96 (br d, *J* = 9.99 Hz), 120.82, 116.73, 116.37 (dd, *J* = 17.26, 14.53 Hz), 112.67 (dd, *J* = 20.89, 3.63 Hz), 111.57, 111.12, 110.33, 104.03, 70.80, 70.58, 70.49, 70.44, 69.40, 67.50, 54.71, 53.53, 48.92, 45.74, 42.39, 41.81, 33.59, 31.47, 30.58, 29.50, 28.92, 28.10, 22.84, 17.30, 12.92. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{48}H_{55}F_2N_{10}O_{10}S$, 1001.38. Found 1001.32.

N-(3-(5-((1-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)-propane-1-sulfonamide (3)



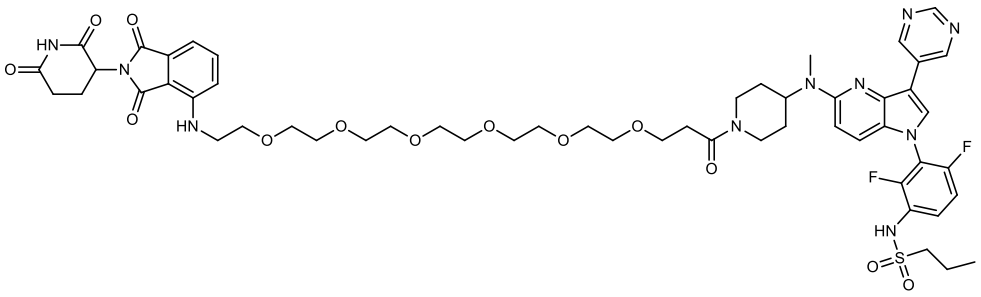
32 (58 mg, 0.101 mmol) was dissolved in a mixture of TFA (3 mL) and DCM (3 mL). The reaction mixture was stirred for 1 h at RT. After the reaction, the solvent was removed with a rotary evaporator and crude product was dried under high vacuum overnight to afford crude product **43** (64 mg, quantitative yield), which was used in the next step without further purification. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{33}N_3O_{10}$, 522.20. Found 522.21. Intermediate **43** was dissolved in DMF (0.5 mL), and HATU (46.3 mg, 0.122 mmol) was added at RT. The mixture was stirred for 10 min, then DIPEA (63.63 mg, 0.505 mmol) was added and the mixture was stirred another 10 min. Finally, **1** (67 mg, 0.101 mmol, synthesized using a known procedure[55]) in DMF (1 mL) was added to the reaction mixture at RT. The reaction mixture was stirred overnight. Water (1 mL) was added to the reaction mixture which was then extracted with EtOAc. The organic extract was separated, evaporated onto Celite and purified with reverse phase MPLC (Water/ACN). Fractions with pure compound were collected and evaporated under vacuum to obtain the title compound **3** (16 mg, 38%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 2H), 9.20 (s, 1H), 7.70 (m, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.60 (d, *J* = 9.2 Hz, 1H), 6.48 (br t, *J* = 5.1 Hz, 1H), 4.92 (dd, *J* = 12.1, 5.4 Hz, 1H), 4.9-4.8 (m, 2H), 4.1-4.0 (m, 1H), 3.9-3.8 (m, 2H), 3.8-3.6 (m, 16H), 3.45 (q, *J* = 5.4 Hz, 2H), 3.3-3.2 (m, 1H), 3.2-3.1 (m, 2H), 2.9 (s, 3H), 2.8-2.6 (m, 4H), 2.1 (m, 1H), 2.0-1.7 (m, 4H), 1.7-1.6 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -121.85 (s, 1F), -130.73 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.44, 169.46, 169.27, 168.67, 167.65, 156.05, 155.75, 153.89, 153.76, 150.93 (br d, J=5.45 Hz), 148.96, 146.83, 142.12, 136.01, 132.50, 128.48, 126.98, 124.25, 123.68 (t, *J* = 11.4 Hz), 123.15 (d, *J* = 5.45 Hz), 120.85, 116.80, 116.41 - 116.14 (m), 112.93 - 112.48 (m), 111.58, 111.08, 110.28, 104.03, 70.71, 70.62, 70.57, 70.53, 70.41, 69.48, 67.48, 54.69, 53.56, 48.91, 45.72, 42.38, 41.80, 33.56, 31.45, 30.57, 29.50, 28.93, 22.80, 17.32, 12.94. LCMS (ESI); *m/z*: $[M+H]^+$ Calcd. for $C_{50}H_{59}F_2N_{10}O_{11}S$, 1045.41. Found 1045.45

N-(3-(5-((1-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)-propane-1-sulfonamide (4).



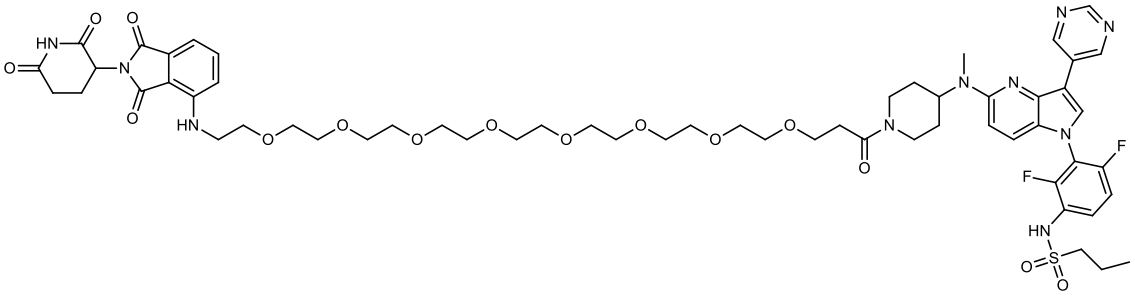
The title compound **4** (8 mg, 28%) was prepared from **33** (17 mg, 26.5 µmol) and **1** (17.4 mg, 26.5 µmol) according to the procedure described for **3.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 2H), 9.10 (s, 1H), 7.71 - 7.64 (m, 2 H), 8.95 (br s, 1H), 7.46 (t, *J* = 7.83 Hz, 1H), 7.33 (br d, *J* = 9.2 Hz, 1H), 7.21 - 7.14 (m, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 9.3 Hz, 1H), 6.48 (t, *J* = 5.5 Hz, 1H), 4.96 - 4.87 (m, 1H), 4.87 - 4.79 (m, 2H), 4.05 (br d, *J* = 13.0 Hz, 1H), 3.82 (s, *J* = 6.7 Hz, 2H), 3.71 - 3.61 (m, 20H), 3.48 - 3.42 (m, 2H), 3.24 (br t, *J* = 12.2 Hz, 1H), 3.19 - 3.13 (m, 2H), 2.93 (s, 3H), 2.89 - 2.82 (m, 1H), 2.82 - 2.65 (m, 4H), 2.17 - 2.05 (m, 1H), 1.92 (dt, *J* = 15.3, 7.6 Hz, 3H), 1.87 - 1.78 (m, 1H), 1.68 (dt, *J* = 11.9, 5.8 Hz, 2H), 1.07 (t, *J* = 7.40 Hz, 3H) ^{19}F NMR (471 MHz, $CDCl_3$): δ -130.65 (s, 1F), -121.56 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.41, 169.41, 169.27, 168.66, 167.65, 156.06, 155.76, 153.90, 153.77 (d, *J* =2.72 Hz), 150.98 (d, *J* = 3.63 Hz), 148.98 (d, *J* = 3.63 Hz), 146.83, 142.13, 136.01, 132.50, 128.46, 126.97, 124.25, 123.78 (br d, *J* = 9.1 Hz), 123.78 (br d, *J* = 9.1 Hz), 122.86 (dd, *J* = 11.8, 3.6 Hz), 120.84, 116.79, 116.37 (t, *J* = 15.4 Hz), 112.67 (dd, *J* = 20.9, 3.6 Hz), 111.57, 111.11, 110.28, 104.03, 70.72, 70.63, 70.57, 70.50, 69.48, 67.50, 54.73, 53.56, 48.91, 45.72, 42.40, 41.78, 33.58, 31.45, 30.56, 29.53, 28.94, 22.80, 17.29, 12.92. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{52}H_{63}F_2N_{10}O_{12}S$, 1089.43. Found 1089.89.

N-(3-(5-((1-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18-hexaoxa-heneicosan-21-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)-propane-1-sulfonamide (5) .



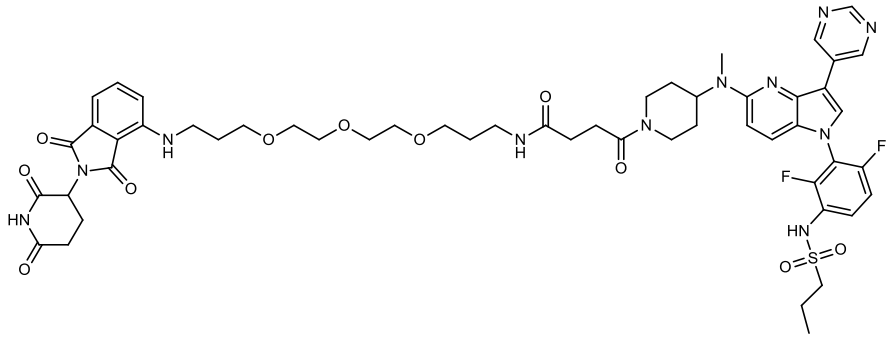
Employing the procedure similar to that described above for **3** using **34** (20 mg, 0.03 mmol*)* and **1** (16.4 mg, 0.026 mmol) afforded the title compound **5** as a yellow powder (8 mg, 28%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.56 (s, 2H), 9.12 (s, 1H), 8.66 (br s, 1H), 7.72 - 7.65 (m, 2H), 7.49 (t, *J* = 7.87 Hz, 1H), 7.34 (br d, *J* = 9.2 Hz, 1H), 7.23 - 7.17 (m, 1H), 7.10 (d, *J* = 7.09 Hz, 1H), 6.97 - 6.84 (m, 2H), 6.64 (d, *J* = 9.2 Hz, 1H), 6.51 (br s, 1H), 4.97 - 4.80 (m, 3H), 4.08 (br d, *J* = 13.5 Hz, 1H), 3.94 - 3.77 (m, 2H), 3.74 - 3.58 (m, 24H), 3.47 (q, *J* = 5.1 Hz, 2H), 3.26 (br t, *J* = 12.2 Hz, 1H), 3.21 - 3.15 (m, 2H), 2.97 (s, 3H), 2.90 - 2.67 (m, 4H), 2.20 - 2.09 (m, 1H), 2.00 - 1.89 (m, 3H), 1.86 (br d, *J* = 11.4 Hz, 1H), 1.77 - 1.67 (m, 2H), 1.10 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -131.46 (s, 1F), -121.38 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.15, 169.39, 169.27, 168.48, 167.64, 156.10, 155.91, 153.95, 153.79, 151.01, 148.65, 146.86, 142.18, 136.02, 132.53, 128.39, 126.85, 124.24, 123.76, 123.63, 120.81, 116.79, 112.89 (d, *J* = 4.54 Hz), 111.62, 111.29, 110.33, 104.06, 70.76, 70.67, 70.59, 70.51, 70.46, 70.43, 69.48, 67.53, 54.75, 53.61, 48.92, 45.72, 42.42, 41.79, 33.60, 31.45, 30.61, 29.55, 28.98, 22.82, 17.32, 12.91. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{54}H_{67}F_2N_{10}O_{13}S$, 1133.46. Found 1133.46.

N-(3-(5-((1-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,-15,18,21,24-octaoxaheptacosan-27-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (6)



A procedure similar to that employed for **3** using **35** (40.7 mg, 0.054 mmol*)* and **1** (27.7 mg, 0.042 mmol) afforded the title compound **6** as a yellow powder (10.8 mg, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.57 (s, 2 H), 9.12 (s, 1 H), 8.70 (s, 1 H), 7.74 - 7.60 (m, 2 H), 7.47 (br t, *J* = 6.5 Hz, 1 H), 7.34 (br s, 1 H), 7.23 - 7.14 (m, 1 H), 7.07 (s, 1 H), 6.91 (br d, *J* = 7.5 Hz, 1 H), 6.63 (br s, 1 H), 6.54 - 6.42 (m, 1 H), 5.00 - 4.86 (m, 1 H), 4.86 - 4.81 (m, 2 H), 4.13 - 4.01 (m, 1 H), 3.82 (m, 2 H), 3.64 (br d, *J* = 6.5 Hz, 32 H), 3.45 - 3.44 (m, 2 H), 3.25 (br s, 1 H), 3.20 - 3.08 (m, 2 H), 2.95 (s, 3 H), 2.63 - 2.89 (m, 4 H), 2.11 (m, 1 H), 1.92 (br s, 3 H), 1.86 - 1.81 (m, 1 H), 1.71 (br d, *J* = 3.4 Hz, 2 H), 1.08 (br t, *J* = 6.9 Hz, 3 H). ^{19}F NMR (471 MHs, $CDCl_3$): δ -130.90 (s, 1 F), -121.46 (s, 1 F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.22, 169.47, 169.27, 168.52, 167.63, 156.05, 155.71, 153.92, 150.83, 148.83, 146.86, 142.16, 136.07, 132.53, 128.45, 127.04, 124.30, 123.52 (br d, *J* = 9.1 Hz), 122.83 - 122.64 (m), 120.92, 116.85, 116.57 - 116.19 (m), 112.76 (br dd, *J* = 19.5, 3.2 Hz), 111.63, 111.17, 110.33, 104.22, 70.80, 70.67, 70.58, 70.52, 70.50, 70.45, 69.53, 67.55, 54.82, 53.67, 48.94, 45.85, 42.48, 41.87, 33.68, 31.49, 30.77, 29.63, 29.00, 22.84, 17.33, 12.95. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{58}H_{75}F_2N_{10}O_{15}S$, 1221.51. Found 1221.57.

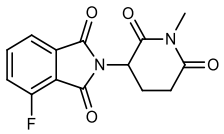
4-(4-((1-(2,6-Difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-N-(3-(2-(2-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)ethoxy)ethoxy)propyl)-4-oxobutanamide (7)



Following the procedure employed for **3** using **37** (13.92 mg, 0.022 mmol) and **1** (13.5 mg, 0.021 mmol) afforded the title compound **7** as a yellowish powder (18 mg, 22%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (s, 2H), 9.10 (s, 1H), 7.64 - 7.72 (m, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.32 (br d, *J* = 9.2 Hz, 1H), 7.18 (td, *J* = 9.1, 1.7 Hz, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.66 - 6.56 (m, 2H), 6.50 (q, *J* = 4.9 Hz, 1H), 4.92 (dd, *J* = 12.2, 5.4 Hz, 1H), 4.86 - 4.76 (m, 2H), 4.07 - 4.04 (m, 1H), 3.72 - 3.58 (m, 12H), 3.55 (t, *J* = 5.9 Hz, 2H), 3.44 - 3.32 (m, 4H), 3.25 - 3.18 (m, 1H), 3.18 -

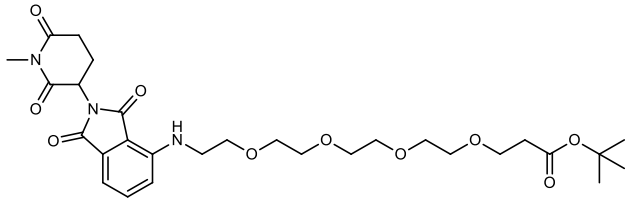
3.13 (m, 2H), 2.92 (s, 3H), 2.90 - 2.46 (m, 8H), 2.14 - 2.11 (m, 1H), 1.97 - 1.85 (m, 5H), 1.84 - 1.74 (m, 3H), 1.73 - 1.67 (m, 1H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.49, 171.39, 170.33, 169.36, 168.71, 167.70, 156.06, 155.88, 153.94, 153.79, 150.05, 148.80 (br d, *J* = 5.45 Hz), 147.00, 142.16, 136.08, 132.55, 128.40, 126.88, 124.24, 123.47 (br d, *J* = 9.1 Hz), 122.81 - 122.64 (m), 120.79, 116.66, 116.43 (d, *J* = 1.8 Hz), 112.89 - 112.60 (m), 111.29, 111.25, 109.92, 104.04, 70.51, 70.16, 69.66, 69.00, 54.73, 48.91, 45.37, 42.04, 40.37, 37.55, 31.58, 31.49, 30.61, 29.42, 29.22, 29.09, 28.93, 28.77, 22.85, 17.30, 12.92. ^{19}F NMR (471 MHz, $CDCl_3$): δ -131.09 (s, 1F), -121.40 (s, 1F). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{53}H_{64}F_2N_{11}O_{11}S$, 1100.45. Found 1100.27.

4-Fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (39)



Cesium carbonate (177 mg, 0.543 mmol) was added to a solution of **30** (100 mg, 0.362 mmol) in DMF (4 mL). After stirring the mixture for 10 min at RT, iodomethane (56.5 mg, 0.398 mmol) was added. The resulting mixture was stirred overnight at RT, glacial acetic acid (0.2 mL) was added and the solvent was removed under vacuum. The crude residue was triturated with water and was dried under high vacuum overnight to afford the final product **39** (105 mg, quantitative yield) as a light yellow powder. ^{1}H NMR (500 MHz, DMSO-d6): δ 7.96 (dt, *J* = 7.8, 4.5 Hz, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.75 (t, *J* = 8.5 Hz, 1H), 5.25 - 5.20 (m, 1H), 3.05 - 2.89 (m, 4H), 2.81 - 2.73 (m, 1H), 2.59 - 2.52 (m, 1H), 2.11 - 2.05 (m, 1H). ^{19}F NMR (471 MHz, DMSO-d_6): δ -114.67 (s, 1F). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{12}FN_2O_4$, 291.08. Found 291.24.

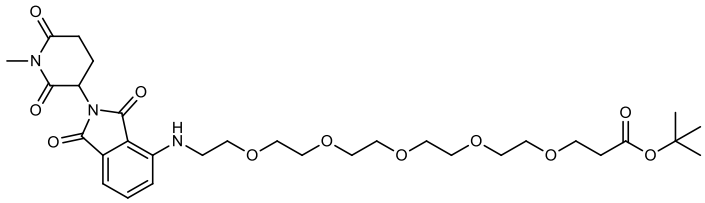
tert-Butyl 1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapenta-decan-15-oate (40).



A mixture of *tert*-butyl 3-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)propanoate (150 mg, 0.467 mmol), DIPEA (181 mg, 1.400 mmol) and **39** (135 mg, 0.467 mmol) in 1,4-dioxane (10 mL)

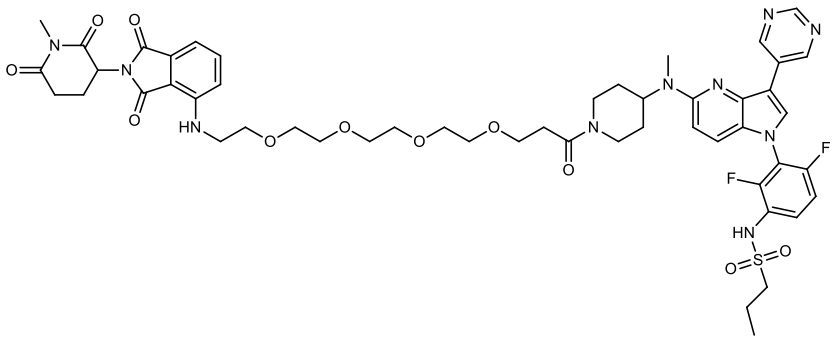
was stirred overnight at 100 °C. The reaction mixture was evaporated onto Celite and purified using silica gel chromatography, eluting with DCM/ACN. The desired fractions were collected and concentrated with a rotary evaporator to afford **40** (130 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 8.2 7.40 Hz, 1H), 7.12 (d, *J* = 7.09 Hz, 1H), 6.95 (d, *J* = 8.56 Hz, 1H), 6.49 (br t, *J* = 5.44 Hz, 1H), 4.97 - 4.89 (m, 1H), 3.81 - 3.59 (m, 18H), 3.55 - 3.47 (m, 2H), 3.23 (s, 3H), 3.05 - 2.93 (m, 1H), 2.85 - 2.73 (m, 3H), 2.51 (t, *J* = 6.5 Hz, 2H), 2.21 - 2.00 (m, 2H), 1.49 - 1.39 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.24, 170.89, 169.44, 168.99, 167.78, 146.86, 135.98, 132.58, 116.73, 111.60, 110.41, 80.51, 70.71, 70.68, 70.64, 70.62, 70.50, 70.37, 69.60, 66.91, 49.64, 42.45, 36.28, 31.94, 28.10, 27.23, 22.13. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{29}H_{42}N_3O_{10}$, 592.29. Found 592.68.

tert-Butyl 1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oate (41)



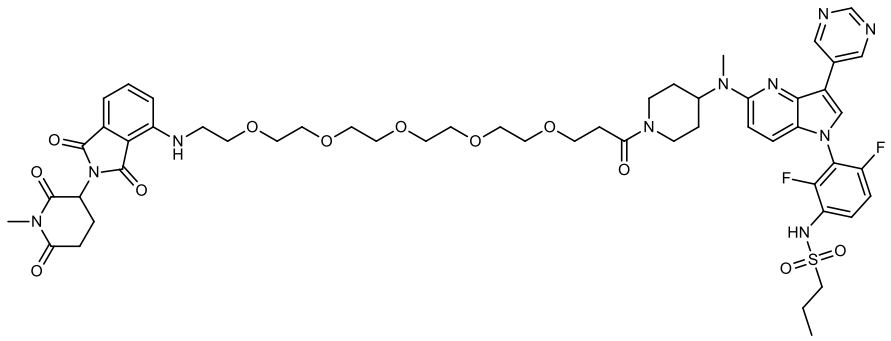
Following the procedure employed for **40** using amino-PEG5-t-butyl ester (69.3 mg, 0.189 mmol) and **39** (50 mg, 0.172 mmol) afforded the intermediate **41** (0.063 mmol, 36%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.47 (br t, *J* = 5.4 Hz, 1H), 4.96 - 4.86 (m, 1H), 3.76 - 3.53 (m, 22H), 3.47 (q, *J* = 5.5 Hz, 2 H), 3.21 (m, 3H), 3.04 - 2.88 (m, 1H), 2.84 - 2.75 (m, 2H), 2.49 (t, *J* = 6.54 Hz, 2H), 2.04 - 2.15 (m, 1 H), 1.44 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.24, 170.87, 169.42, 168.99, 167.75, 146.84, 135.96, 132.56, 116.73, 111.56, 110.39, 80.48, 70.66, 70.62, 70.59, 70.35, 69.58, 66.89, 49.62, 42.43, 36.27, 31.91, 28.09, 27.21, 22.10. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{31}H_{46}N_3O_{11}$, 636.31. Found 636.33.

N-(2,4-Difluoro-3-(5-(methyl(1-(1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oyl)piperidin-4-yl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)phenyl)propane-1-sulfonamide (20)



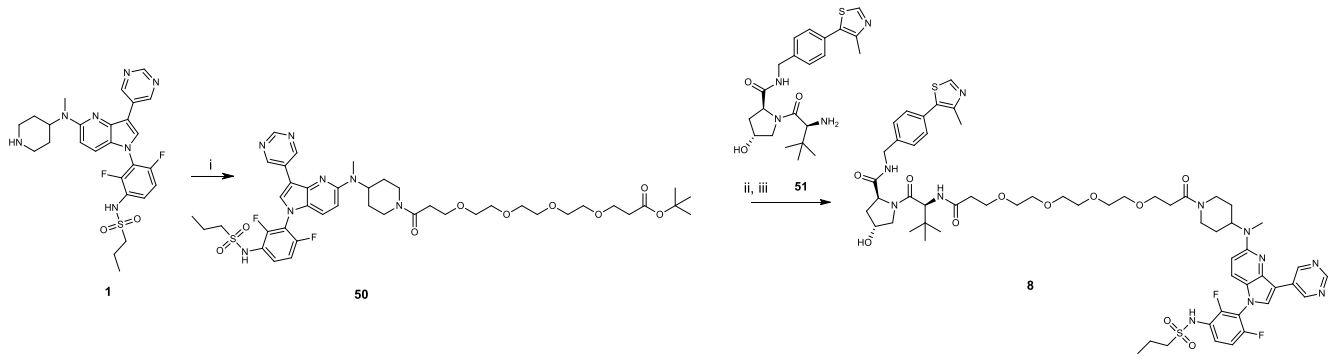
A procedure similar to that employed for **3** using **40** (44 mg, 0.075 mmol) and **1** (49 mg, 0.075 mmol) afforded the title compound **20** as a yellow powder (14 mg, 18%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 2H), 9.2 (s, 1H), 7.73 - 7.65 (m, 2H), 7.48 (dd, *J* = 8.3, 7.3 Hz, 1H), 7.33 - 7.25 (m, 1H), 7.19 (td, *J* = 9.1, 1.7 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.47 (br t, *J* = 5.6 Hz, 1H), 4.96 - 4.79 (m, 3H), 4.07 (br d, *J* = 13.3 Hz, 1H), 4.00 - 3.78 (m, 2H), 3.74 - 3.60 (m, 14H), 3.51 - 3.43 (m, 2H), 3.28 - 3.14 (m, 5H), 3.00 - 2.91 (m, 4H), 2.81 - 2.64 (m, 4H), 2.13 - 1.99 (m, 1H), 1.98 - 1.86 (m, 3H), 1.88 - 1.83 (m, 1H), 1.79 - 1.62 (m, 2H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -131.34 (s, 1F) -121.44 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.30, 169.44, 169.39, 169.05, 167.78, 156.05, 155.83, 153.92, 153.77 (d, *J* = 2.72 Hz), 150.87 (d, *J* = 3.63 Hz), 148.87 (d, *J* = 4.54 Hz), 146.83, 142.14, 135.98, 132.54, 128.43, 126.92, 124.25, 123.63 - 123.56 (m), 122.76 (dd, *J*=11.35, 4.09 Hz), 120.84, 116.77, 116.40 (t, *J* = 15.44 Hz), 112.73 (dd, *J* = 20.9, 3.6 Hz), 111.57, 111.17, 110.35, 104.05, 70.64, 70.59, 70.58, 70.51, 70.44, 70.39, 69.58, 67.48, 54.74, 53.57, 49.63, 45.72, 42.41, 41.79, 33.58, 31.91, 30.59, 29.54, 28.93, 27.22, 22.10, 17.30, 12.91. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{51}H_{61}F_2N_{10}O_{11}S$, 1059.42. Found 1059.87.

N-(2,4-difluoro-3-(5-(methyl(1-(1-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-oyl)piperidin-4-yl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)phenyl)propane-1-sulfonamide (21)



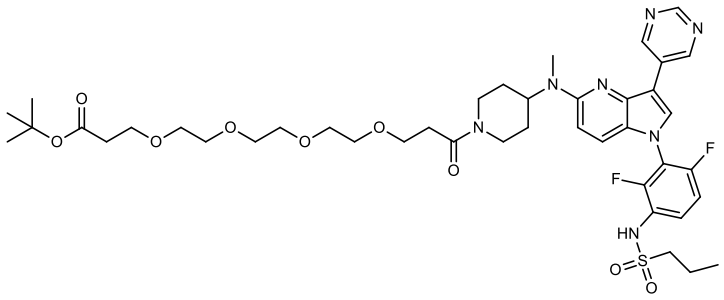
A procedure similar to that employed for **3** using **41** (45.8 mg, 0.066 mmol) and **1** (40.9 mg, 0.062 mmol) afforded the title compound **21** as a yellow powder (20 mg, 28%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 - 9.83 (m, 1H), 9.65 (s, 2H), 9.03 (s, 1H), 8.41 (s, 1H), 7.63 - 7.54 (m, 2H), 7.50 - 7.41 (m, 2H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 6.62 - 6.56 (m, 1H), 5.15 - 5.09 (m, 1H), 4.66 - 4.55 (m, 2H), 4.11 - 4.02 (m, 1H), 3.67 - 3.58 (m, 4H), 3.55 - 3.41 (m, 18H), 3.19 - 3.11 (m, 3H), 3.01 (s, 3H), 2.93 (s, 3H), 2.80 - 2.71 (m, 1H), 2.69 - 2.53 (m, 4H), 2.08 - 2.00 (m, 1H), 1.82 - 1.68 (m, 5H), 1.64 - 1.53 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -127.49 (s, 1F) -123.00 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.28, 169.45, 169.31, 169.03, 167.78, 156.07, 155.93, 153.95, 153.76, 150.69 (d, J = 4.5 Hz), 148.70 (br d, *J* = 5.4 Hz), 146.85, 142.17, 135.98, 132.55, 128.38, 126.87, 124.25, 123.29 (br d, J = 10.0 Hz), 122.92 – 122.57 (m), 120.82, 116.75, 116.47 – 116.21 (m), 112.78 (dd, *J* = 20.4, 4.1 Hz), 111.59, 111.27, 110.37, 104.04, 70.69, 70.66, 70.62, 70.59, 70.57, 70.51, 70.46, 69.58, 67.55, 54.74, 53.59, 49.64, 45.72, 42.44, 41.78, 33.61, 31.92, 30.59, 29.58, 28.97, 27.24, 22.12, 17.31, 12.91. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{53}H_{65}F_2N_{10}O_{12}S$, 1103.45. Found 1104.19.

Synthesis of (2S,4R)-1-((2S)-2-(tert-butyl)-19-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (8) .



Scheme 3. Reagents and conditions: i) acid-PEG4-t-butyl ester, HATU, DIPEA, DMF, RT; ii) TFA, DCM, RT; iii) **51**, HATU, DIPEA, DMF, RT

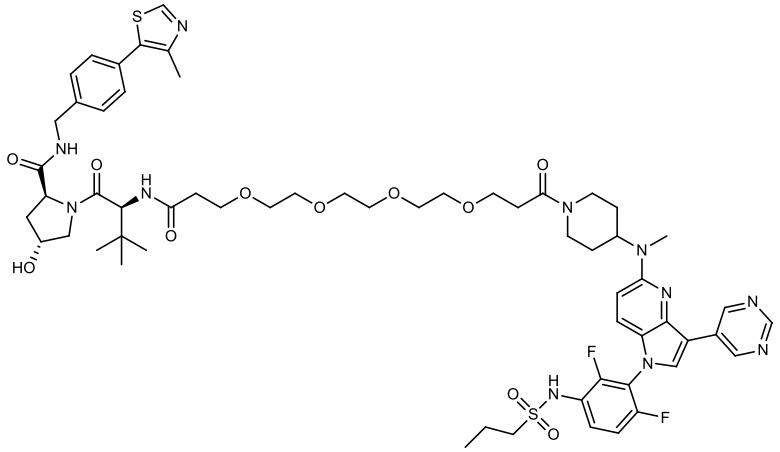
Step 1. tert-Butyl 16-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-16-oxo-4,7,10,13-tetraoxahexadecanoate (50)



1 (35 mg, 0.053 mmol), 2,2-dimethyl-4-oxo-3,7,10,13,16-pentaoxanonadecan-19-oic acid (20.58 mg, 0.059 mmol), HATU (22.33 mg, 0.059 mmol) and DIPEA (20.70 mg, 0.160 mmol) in DMF (10 mL) was stirred at RT overnight. The reaction mixture was evaporated onto Celite and purified using silica gel chromatography, eluting with DCM/ACN. The desired fractions were collected and concentrated with a rotary evaporator to afford **50** (6 mg, 12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.54 (s, 2H), 9.09 (s, 1H), 7.71 - 7.64 (m, 2H), 7.36 - 7.30 (m, *J* = 9.2 Hz, 1H), 7.21 - 7.14 (m, 1H), 6.65 - 6.58 (m, *J* = 9.2 Hz, 1H), 4.84 (br. s., 2H), 4.04 (m, 1H), 3.82 (d, *J* = 6.7 Hz, 2H), 3.72 - 3.59 (m, 14H), 3.27 - 3.12 (m, 3H), 2.93 (s, 3H), 2.77 - 2.64 (m, 3H), 2.49 (t, *J* = 6.5 Hz, 2H), 1.92 (dt, *J* = 15.3, 7.6 Hz, 4H), 1.70 (br. s., 2H), 1.44 (s, 9H), 1.07 (t, *J* = 7.4 Hz, 3 H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -130.94

(s, 1F) -121.56 (s, 1F). ^{13}C NMR (126MHz, $CDCl_3$): δ 170.95, 169.36, 156.07, 155.86, 153.94, 153.75, 150.88, 148.91, 146.91, 142.15, 128.43, 126.89, 124.27, 123.63 - 123.55 (m), 122.94 – 122.85 (m), 120.82, 116.54 - 116.28 (m), 112.94 - 112.61 (m), 111.20, 104.03, 80.52, 70.54, 70.52, 70.47, 70.42, 70.32, 67.50, 66.89, 54.73, 53.57, 45.72, 41.78, 36.27, 33.60, 30.57, 29.55, 28.94, 28.10, 17.31, 12.92 . LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{42}H_{58}F_2N_7O_9S$, 874.40. Found 874.44.

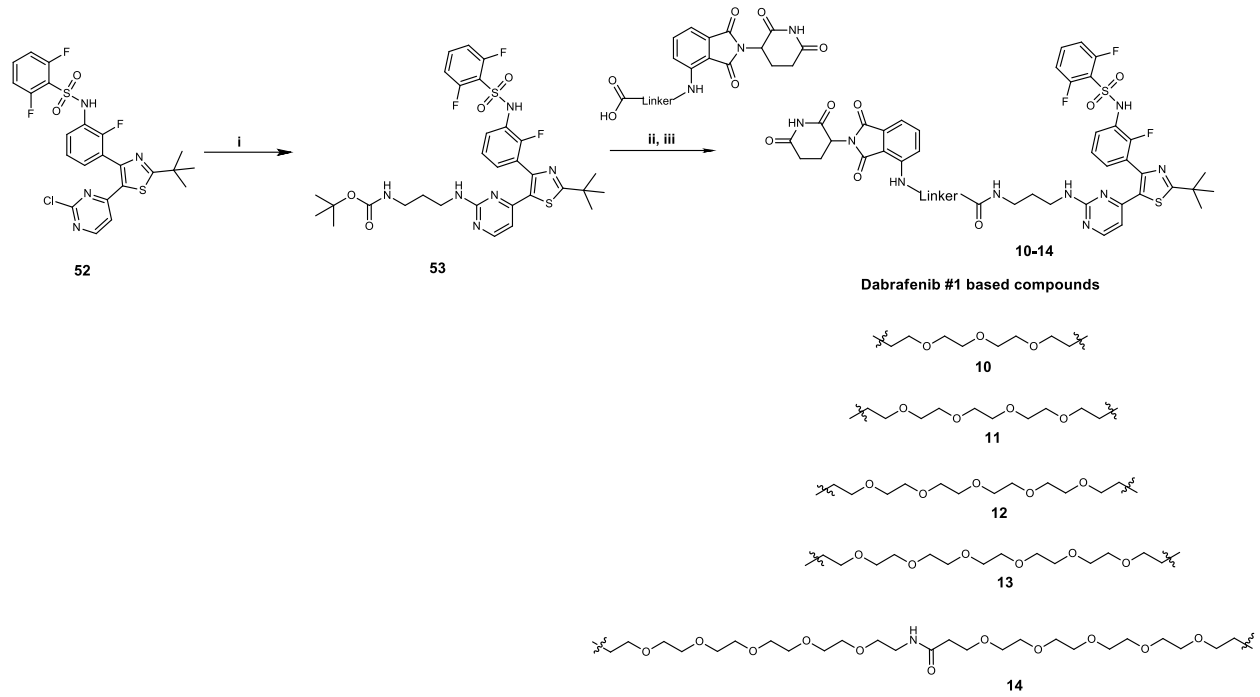
Step 2. (2S,4R)-1-((2S)-2-(tert-butyl)-19-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (8)



50 (41 mg, 0.047 mmol) was dissolved in a mixture of TFA (5 mL) and DCM (5 mL). The reaction mixture was stirred for 3 h at RT, the solvent was removed with a rotary evaporator and crude product was placed under high vacuum overnight. To a solution of resulting crude product in DMF (2 mL), HATU (19.5 mg, 0.051 mmol) was added, followed by DIPEA (24.1 mg, 0.187 mmol). The mixture was stirred for 5 min at RT and (*2S,4R*)-1-((S)-2-amino-3,3-dimethylbutanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide **(51)** (25.6 mg, 0.047 mmol, synthesized using the synthetic procedures described previously[56]) was added. After stirring the mixture overnight at RT, water was added, and the mixture was then extracted with DCM (2 x). The combined organic phases were washed with brine, dried over $MgSO_4$, and evaporated under vacuum to give the corresponding crude material, which was purified by silica gel chromatography (eluting with DCM/ACN) to yield the product **8** (12.3 mg, 21%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 2H), 9.02 (s, 1H), 8.60 (s, 1H), 7.64 – 7.57 (m, 2H), 7.46 – 7.30 (m, 2H), 7.32 – 7.21 (m, 4H), 7.11 (t,

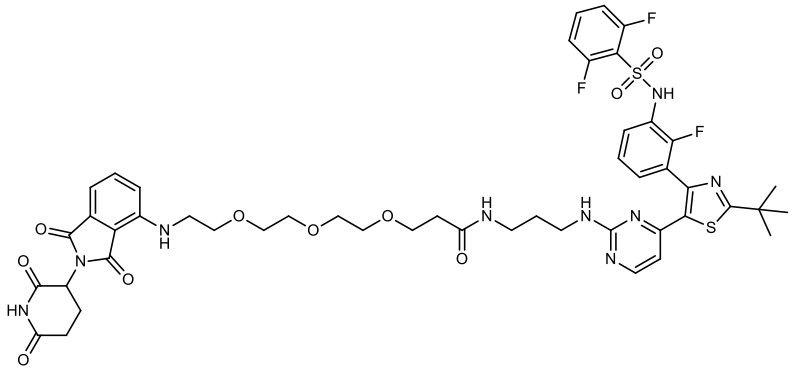
J = 8.8 Hz, 1H), 7.05 – 6.91 (m, 1H), 6.54 (d, *J* = 7.9 Hz, 1H), 4.75 (br d, J = 12.6 Hz, 2H), 4.71 – 4.61 (m, 1H), 4.53 – 4.43 (m, 2H), 4.38 (dd, *J* = 14.4, 8.2 Hz, 1H), 4.27 (dd, *J* = 15.0, 5.2 Hz, 1H), 4.09 – 3.96 (m, 2H), 3.78 – 3.66 (m, 2H), 3.62 – 3.48 (m, 16H), 3.17 (br t, *J* = 12.3 Hz, 1H), 3.12 – 3.04 (m, 2H), 2.88 (s, 3H), 2.73 – 2.54 (m, 3H), 2.51 – 2.33 (m, 5H), 2.07 (br dd, *J* = 12.3, 8.6 Hz, 1H), 1.90 – 1.80 (m, 3H), 1.76 (br d, *J* = 11.9 Hz, 2H), 1.06 – 0.95 (t, *J* = 7.5 Hz, 3H), 0.86 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -121.49 (s, 1F), -131.15 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.08, 171.74, 171.04, 169.62, 156.04, 155.82, 153.89, 153.79, 150.99, 150.31, 148.98, 148.41, 142.14, 138.30, 131.66, 130.85, 129.45, 128.45, 128.10, 126.94, 124.26, 123.94 - 123.86 (m), 122.90 - 122.78 (m), 120.84, 116.49 - 116.37 (m), 112.80 - 112.61 (m), 111.14, 104.05, 70.50, 70.47, 70.43, 70.38, 70.34, 70.07, 67.55, 67.16, 58.49, 57.80, 56.76, 54.74, 53.59, 45.78, 43.18, 41.82, 36.66, 36.18, 34.96, 33.58, 30.61, 29.51, 28.98, 28.10, 26.40, 17.30, 16.03, 12.93. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{60}H_{78}F_2N_{11}O_{11}S_2$, 1230.52. Found 1230.76.

Synthesis of Dabrafenib #1 -based compounds

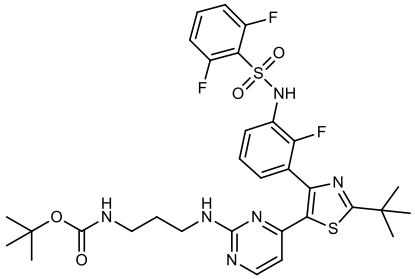


Scheme 4. Reagents and conditions: i) *tert*-butyl (3-aminopropyl)carbamate, 2-Propanol, 90 ^{o}C , 2 days ii) TFA, DCM, RT; iii) HATU, DIPEA, DMF, RT

Synthesis of N-(3-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanamide (10)



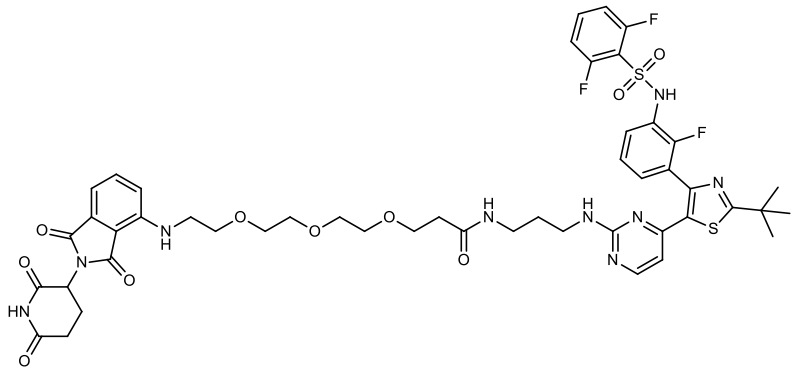
Step 1. tert-Butyl (3-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)carbamate (53)



N-Boc-1,3-diaminopropane (100 mg, 0.574 mmol) and **52** (300 mg, 0.557 mmol, synthesized according to known procedures[57]) were dissolved in 2-propanol (1 mL) and the reaction mixture was heated in a sealed vial at 90 °C during 2 days. The reaction mixture was evaporated onto Celite and purified by silica gel chromatography, eluting with DCM/MeOH. The desired fractions were collected, concentrated and dried under vacuum to obtain 100 mg of **53** (95 mg, 25%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br d, *J* = 4.8 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.53 – 7.38 (m, 1H), 7.23 – 7.14 (m, 1H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.14 – 6.03 (m, 1H), 5.53 (br s, 1H), 4.86 (br s, 1H), 3.35 (br s, 2H), 3.19 (br d, *J* = 5.6 Hz, 2H), 1.76 – 1.66 (m, 2H), 1.53 – 1.31 (m, 18H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.83 (s, 1F), -130.13 (s, 2F). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.59, 162.15, 160.81 (d, *J* = 3.6 Hz), 158.74 (d, *J* = 2.7 Hz), 158.62, 158.21, 156.21, 152.04, 150.06, 145.65, 135.18 (t, J = 10.9 Hz), 134.12, 128.17, 125.04 (d, *J* = 4.5 Hz), 124.59 - 124.49 (m), 123.04, 117.00 (t, *J* = 15.4 Hz),

113.25 (d, *J* = 3.6 Hz), 113.07 (d, *J* = 3.6 Hz), 106.44, 79.24, 38.26, 38.02, 37.74, 30.73, 30.17, 28.44. LCMS (ESI); *m/z*: $[M+H]^+$ Calcd. for $C_{31}H_{36}F_3N_6O_4S_2$, 677.22. Found 677.16.

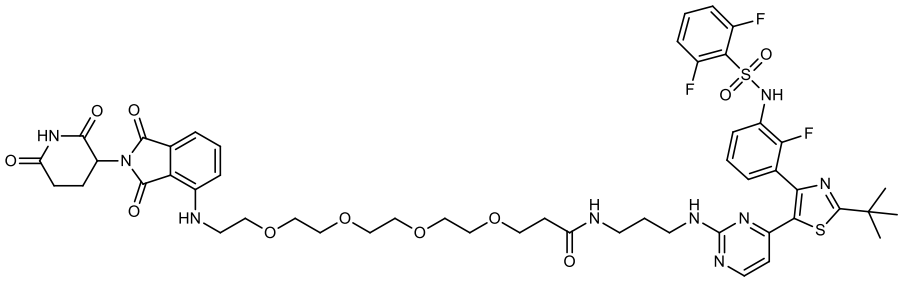
Step 2. N-(3-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)-ethoxy)propanamide (10)



53 (9.79 mg, 0.014 mmol) was dissolved in a mixture of TFA (1 mL) and DCM (1 mL). The reaction mixture was stirred for 1 h at RT. After the reaction was complete, the solvent was removed with a rotary evaporator and crude product was dried under high vacuum overnight to give the crude product *N*-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate which was obtained in a quantitative yield (10 mg, 0.014 mmol) and used in the next step without any further purification. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{33}N_3O_{10}$, 577.17. Found 577.38. HATU (6.06 mg, 0.016 mmol) was added to a solution of acid **42** (9.47 mg, 0.016 mmol) in DCM (2 mL). After 5 min DIPEA (5.61 mg, 0.043 mmol) was added. The mixture was stirred 0.5 h and *N*-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (10 mg, 0.014 mmol) was added and stirred overnight. The reaction mixture was evaporated onto Celite and purified by silica gel chromatography, eluting with DCM/ACN. The desired fractions were collected, and concentrated with a rotary evaporator to afford **10** (10 mg, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 5.3 Hz, 1H), 7.63 (m, 1H), 7.46-7.39 (m, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.12 (m, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.91 (t, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.46 (br. s., 1H), 6.00 (d, *J* = 5.3 Hz, 1H), 4.86 (dd, *J* = 12.10, 5.4 Hz, 1H), 3.68 - 3.51 (m, 14H), 3.38 (d, *J* = 5.1 Hz, 2H), 3.23 (d, *J* = 5.9 Hz, 2H), 2.68 (s, 3H), 2.41 - 2.27 (m,

2H), 2.13 - 1.99 (m, 1H), 1.64 (br. s., 2H), 1.39 (s, 9H). ^{19}F NMR (471MHz, DMSO-d_6): δ -107.36 (s, 2F), -124.44 (s, 1F). ^{13}C NMR (176 MHz, $CDCl_3$) δ 182.85, 171.92, 169.70, 169.34, 167.66, 160.47 (d, *J* = 3.2 Hz), 159.00 (d, *J* = 4.2 Hz), 151.96, 150.47, 146.81, 146.07, 136.06, 135.29, 133.84, 132.53, 128.14, 125.02, 124.56 - 124.49 (m), 123.28, 116.80, 113.27(d, *J* = 3.2 Hz), 113.12 (d, *J* = 4.2 Hz), 111.65, 110.30, 106.18, 70.83, 70.50, 70.23, 69.37, 67.25, 48.88, 42.36, 42.06, 38.37, 38.06, 36.95, 36.83, 31.46, 30.73, 29.70, 29.07. 22.89. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{48}H_{53}F_3N_9O_{10}S_2$, 1036.33. Found 1036.7.

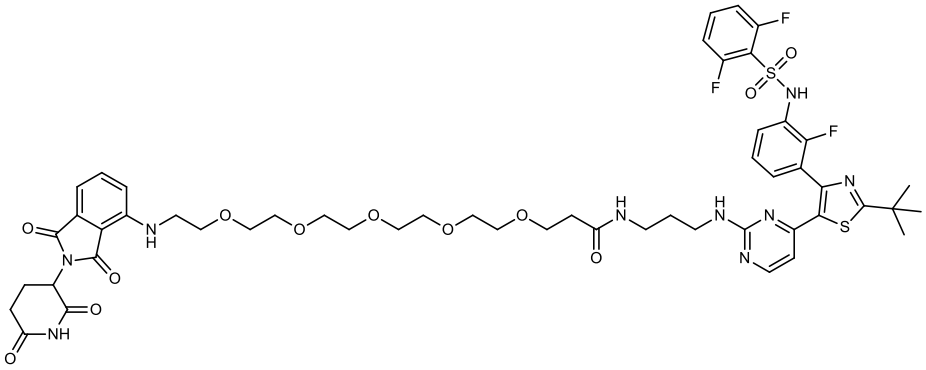
N-(3-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12-tetraoxa-pentadecan-15-amide (11)



A procedure similar to that employed above for **10** using *N*-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluoro-benzenesulfonamide trifluoroacetate (40.1 mg, 0.058 mmol) and acid **43** (34 mg, 0.058 mmol) afforded the title compound **11** as a yellowish powder (15.1 mg 25%).^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 5.3 Hz, 1H), 7.63 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.04 (d, *J* = 7.0 Hz, 1H), 6.91 (t, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.71 - 6.59 (br s, 1H), 6.51 - 6.43 (br s, 1H), 5.99 (d, *J* = 5.3 Hz, 1H), 4.86 (s, 1H), 3.67 - 3.49 (m, 18H), 3.43 - 3.30 (m, 2H), 3.23 (d, *J* = 5.8 Hz, 2H), 2.68 (d, *J* = 2.9 Hz, 3H), 2.36 (br. s., 2H), 2.10 - 2.02 (m, 1H), 1.72 - 1.59 (m, 2H), 1.39 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.72 (br. s., 2F), -130.70--129.57 (br s, 1F). ^{13}C NMR (176 MHz, $CDCl_3$): δ 182.68, 172.12, 171.97, 169.32, 167.67, 161.86, 160.48 (d, *J* = 3.2 Hz), 159.00 (d, *J* = 3.2 Hz), 158.97, 157.63, 151.89, 150.47, 146.83, 145.89, 136.08, 135.31, 133.96, 132.54, 128.14, 125.01, 124.34 (d, *J*=12.7 Hz), 123.16, 116.81, 113.25 (d, *J* = 4.2 Hz), 113.12 (d, *J* = 3.2 Hz), 111.64, 110.29, 106.12, 70.77, 70.56, 70.51, 70.24, 69.37, 67.30, 48.88, 42.36, 38.28,

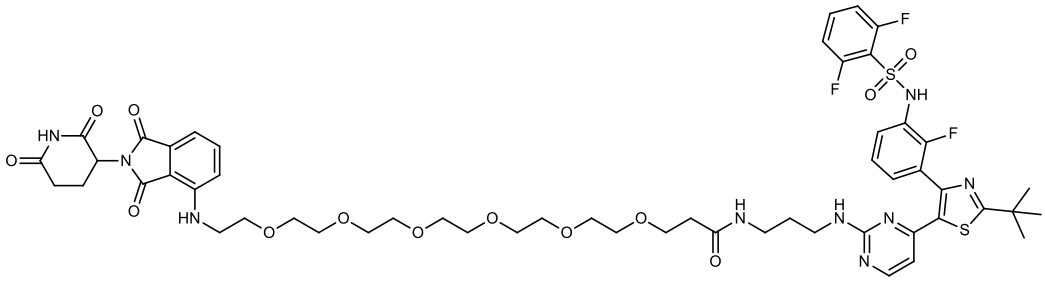
38.04, 36.97, 36.71, 31.46, 30.74, 29.70, 29.04, 22.91. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{50}H_{57}F_3N_9O_{11}S_2$, 1080.36. Found 1080.48.

N-(3-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide (12)



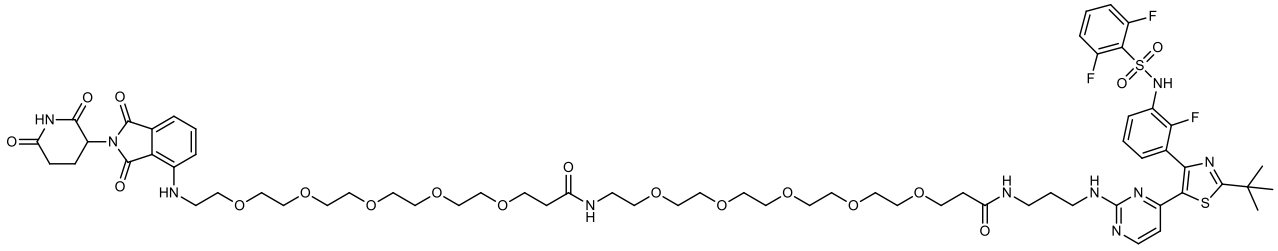
Following the procedure employed for **10** using *N*-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (50 mg, 0.072 mmol) and acid **44** (50 mg, 0.081 mmol) afforded the title compound **12** as a yellowish powder (9.5 mg, 12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 5.3 Hz, 1H), 7.63 (br t, *J* = 7.0 Hz, 1H), 7.45 - 7.39 (m, 2H), 7.25 - 7.19 (m, 1H), 7.16 - 7.08 (m, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.90 (t, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 1H), 6.75 - 6.64 (br s, 1H), 6.52 - 6.39 (br s, 1H), 6.04 - 5.90 (m, 1H), 4.85 (dd, *J* = 5.3, 12.3 Hz, 1H), 3.66 - 3.50 (m, 22H), 3.37 (q, *J* = 5.3 Hz, 2H), 3.24 (br d, *J* = 6.1 Hz, 2H), 2.83 - 2.62 (m, 3H), 2.38 (br s, 2H), 2.10 - 2.03 (m, 1H), 1.67 (quin, *J* = 6.6 Hz, 2H), 1.42 - 1.37 (m, 9H). ^{19}F NMR (471MHz, DMSO-d6): δ -107.35 (s, 1F), -124.43 (s, 1F). ^{13}C NMR (176MHz): δ 182.69, 172.25, 171.98, 169.30, 167.70, 161.69, 160.46 (d, *J* = 3.2 Hz), 158.98 (d, *J* = 3.2 Hz), 157.50, 151.95, 150.54, 146.81, 145.90, 136.05, 135.30, 133.99, 132.52, 128.18, 124.99, 124.51 (d, *J* = 12.7), 123.40, 116.98, 116.82, 113.24 (d, *J* = 3.2 Hz), 113.11 (d, J = 3.2 Hz), 111.61, 110.27, 106.07, 70.77, 70.65, 70.57, 70.52, 70.47, 70.26, 70.18, 69.35, 67.27, 48.89, 42.36, 38.30, 38.03, 36.95, 36.72, 31.47, 30.74, 29.69, 29.17, 22.88. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{52}H_{61}F_3N_9O_{12}S_2$, 1124.38. Found 1124.50.

N-(3-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15,18-hexaoxahenicosan-21-amide (13)



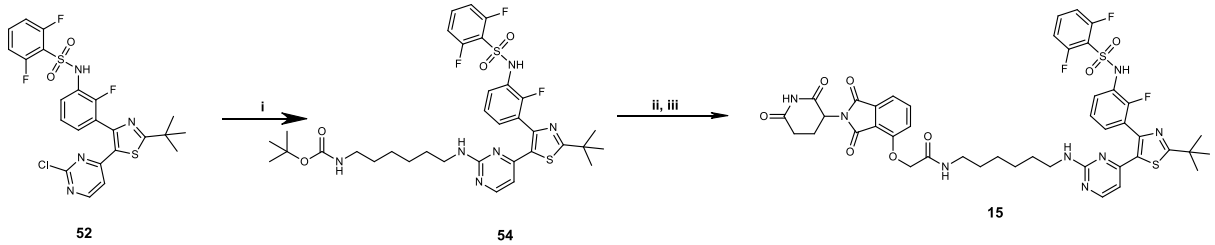
Following the procedure employed for **10** using N-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(tert-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (25 mg, 0.036 mmol) and acid **45** (52 mg, 0.072 mmol) afforded the title compound **13** as a yellow powder (4.2 mg, 10%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 5.3 Hz, 1H), 7.66 - 7.53 (m, 1H), 7.45 - 7.32 (m, 2H), 7.11 - 7.00 (m, 2H), 6.91 - 6.80 (m, 3H), 6.44 (br t, *J* = 5.3 Hz, 1H), 6.02 (br s, 1H), 4.84 (dd, *J* = 12.2, 5.4 Hz, 1H), 3.63 (br t, *J* = 5.1 Hz, 4H), 3.49 - 3.60 (m, 22H), 3.37 (q, *J* = 5.3 Hz, 2H), 3.22 (br d, *J* = 5.9 Hz, 2H), 2.82 - 2.61 (m, 3H), 2.47 - 2.32 (m, 2H), 2.11 - 1.96 (m, 1H), 1.76 - 1.65 (m, 2H), 1.38 (s, 9H). ^{19}F NMR (471MHz, $CDCl_3$): δ -106.92 (s, 1F), -130.18 (s, 1F). ^{13}C NMR (176 MHz, $CDCl_3$): δ 182.49, 172.21, 171.99, 169.30, 167.71, 162.00, 160.49, 159.02, 158.77, 157.90, 152.07, 150.57, 146.82, 145.84, 136.06, 135.15, 134.00, 132.54, 127.92, 124.95, 124.51, (d, *J* = 13.8), 123.21, 117.09, 116.81, 113.22, 113.09, 111.62, 110.30, 106.27, 70.74, 70.58, 70.49, 70.43, 70.35, 70.20, 70.14, 69.35, 67.34, 48.91, 42.36, 38.28, 38.01, 36.95, 36.69, 31.49, 30.74, 29.65, 29.26, 22.86. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{54}H_{65}F_3N_9O_{13}S_2$, 1168.52. Found 1168.41.

N-(22-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)-18-oxo-3,6,9,12,15-pentaoxa-19-azadocosyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide (14)



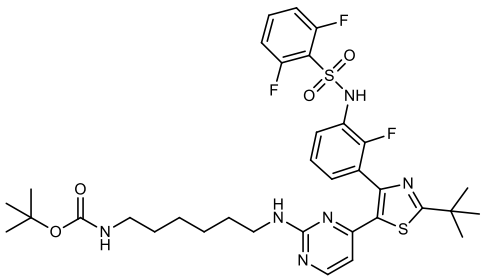
A procedure similar to that employed for **10** using *N*-(3-(5-(2-((3-aminopropyl)amino)pyrimidin-4-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (54.6 mg, 0.079 mmol) and acid (76.6 mg, 0.079 mmol), obtained from **38** by common deprotection procedure with TFA/DCM described above, afforded the title compound **14** as a yellow powder (1.25 mg, 1%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 5.1 Hz, 1H), 7.60 – 7.52 (m, 1H), 7.43 – 7.30 (m, 2H), 7.17 – 7.12 (m, 1H), 7.09 – 6.98 (m, 2H), 6.91 – 6.78 (m, 4H), 6.48 – 6.37 (m, 1H), 6.05 (br s, 1H), 4.89 – 4.78 (m, 1H), 3.67 – 3.61 (m, 2H), 3.60 – 3.49 (m, 36H), 3.45 (t, *J* = 5.2 Hz, 2H), 3.40 – 3.29 (m, 4H), 3.28 – 3.19 (m, 2H), 2.82 – 2.60 (m, 3H), 2.43 – 2.31 (m, 4H), 2.09 – 2.01 (m, 1H), 1.69 – 1.60 (m, 2H), 1.38 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.90 (s, 2F), -129.90 (s, 1F). ^{13}C NMR (176MHz, $CDCl_3$): δ = 182.37, 172.03, 171.70, 169.29, 167.69, 162.04, 160.48, 159.00 (d, *J* = 3.2 Hz), 158.71, 158.02, 150.85, 150.32, 146.81, 145.96, 136.05, 134.85, 133.89, 132.51, 129.33, 128.09, 124.85 (d, *J* = 4.2), 124.48, 123.34, 116.83, 113.15 (d, *J* = 3.2 Hz), 113.02 (d, *J* = 3.2 Hz), 111.58, 110.26, 106.28, 70.69, 70.55, 70.49, 70.48, 70.41, 70.39, 70.33, 70.27, 70.26, 70.23, 70.14, 70.12, 70.04, 70.02, 69.92, 69.42, 67.31, 67.26, 48.90, 42.36, 39.10, 38.25, 37.99, 36.84, 36.77, 31.48, 30.74, 30.65, 29.68, 29.24, 22.82. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{65}H_{86}F_3N_{10}O_{18}S_2$, 1415.55. Found 1415.49.

Synthesis of N-(6-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)-thiazol-5-yl)pyrimidin-2-yl)amino)hexyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide (15)



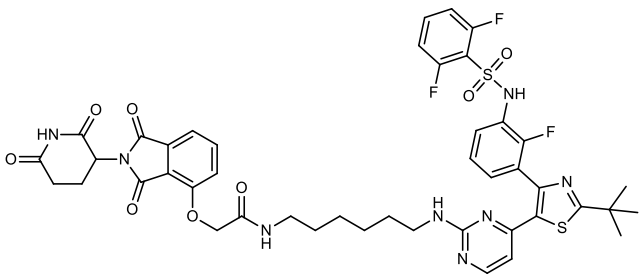
Scheme 5. Reagents and conditions: i) tert-butyl (6-aminohexyl)carbamate**,** ACN, 90-100 ^{o}C, overnight ii) 4-(tert-butoxy)-4-oxobutanoic acid, TFA, DCM, RT; iii) HATU, DIPEA, DMF, RT, iv) TFA, DCM, RT, v) 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid , HATU, DIPEA, DMF, RT.

Step 1: tert-Butyl (6-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyramid-in-2-yl)amino)hexyl)carbamate (54)



52 (130 mg, 0.241 mmol) was heated in a sealed vial with *N*-(6-aminohexyl)carbamic acid tert-butyl ester (52.2 mg, 0.241 mmol)overnight at 90-100 °C in ACN (5 mL). The reaction mixture was evaporated onto Celite and purified using reverse phase chromatography, eluting with water/ACN. Fractions with pure compound were concentrated to obtain **54** (55 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (br d, *J* = 4.4 Hz, 1H), 7.71 (t, *J* = 7.4 Hz, 1H), 7.52 – 7.45 (m, 1H), 7.38 – 7.33 (m, 1H), 7.20 (m, 1H), 6.97 (t, *J* = 8.8 Hz, 2H), 6.10 – 6.01 (m, 1H), 5.26 – 5.09 (m, 1H), 4.54 (br s, 1H), 3.31 (br s, 2H), 3.12 (br d, *J* = 6.2 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.53 – 1.48 (m, 2H), 1.47 (s, 9H), 1.45 (s, 9H), 1.41 – 1.31 (m, 4H). 19F NMR (471 MHz, $CDCl_3$): δ -106.82 (s, 1F), -130.25 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.55, 162.09, 160.82 (d, *J* = 3.6 Hz), 158.75 (d, *J* = 3.6 Hz), 158.55, 158.18, 156.00, 152.02, 150.05, 145.62, 135.05 (t, *J* = 10.9 Hz), 134.28, 127.93, 125.03 (d, *J* = 4.5 Hz), 124.46 (br d, *J* = 13.6 Hz), 122.93, 117.00, 113.23 (d, *J* = 3.6 Hz), 113.04 (d, *J* = 3.6 Hz), 106.20, 79.05, 41.24, 40.50, 38.00, 30.73, 30.06, 29.44, 28.45, 26.60, 26.53. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{34}H_{42}F_3N_6O_4S_2$, 719.27. Found 719.31

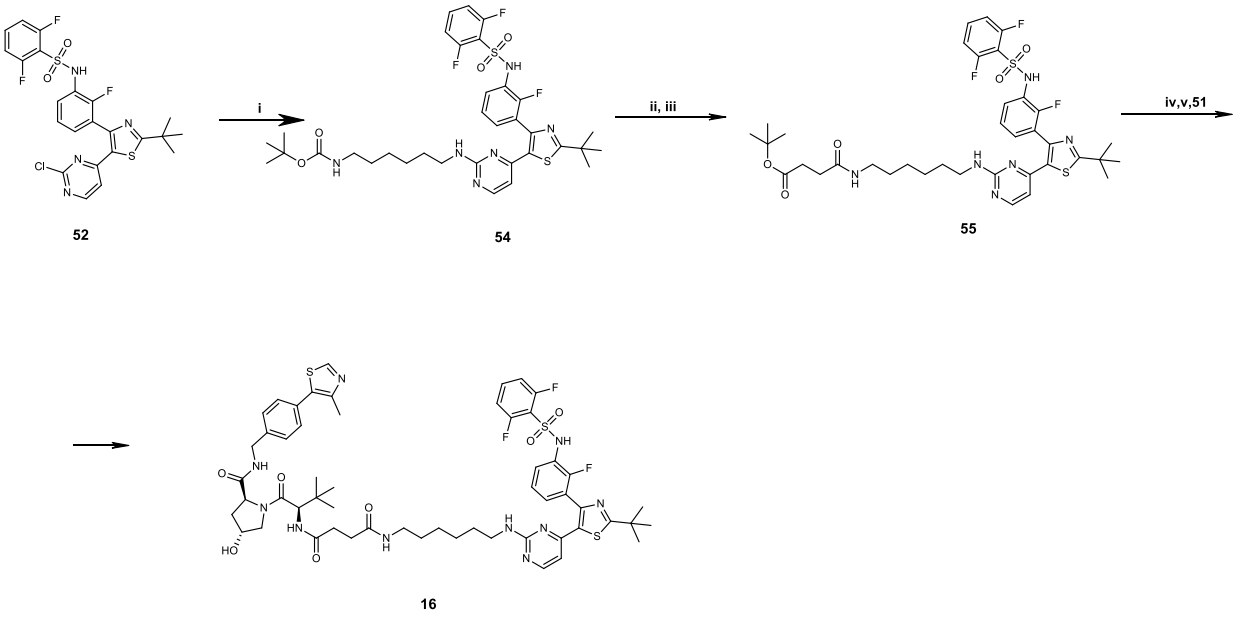
Step 2. N-(6-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)-thiazol-5-yl)pyrimidin-2-yl)amino)hexyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide (15)



54 (65.5 mg, 0.091 mmol) was dissolved in a mixture of TFA (2 mL) and DCM (2 mL). The reaction mixture was stirred for 1 h at RT, the solvent was removed with a rotary evaporator and residue

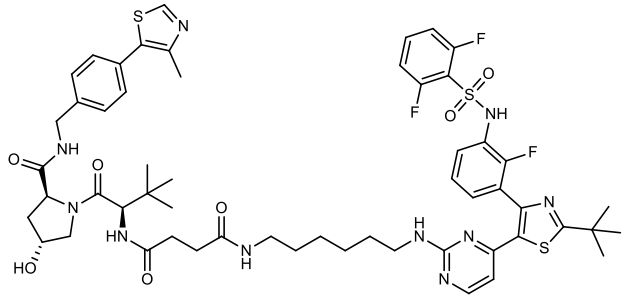
was placed under high vacuum overnight to yield the crude product *N*-(3-(5-(2-((6-aminohexyl)amino)pyrimidin-4-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzene-sulfonamide trifluoroacetate was obtained (67 mg, quantititative yield), which was used in the next step without further purification. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{29}H_{35}F_3N_6O_2S_2$ 619.21. Found 619.31. To 2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetic acid (30.4 mg, 0.091 mmol, synthesized using procedures described previously[58]) was added HATU (38.2 mg, 0.101 mmol) in DMF (1 mL) and after 10 min DIPEA (35.5 mg, 0.274 mmol) was added at RT. The reaction was stirred for 10 min and *N*-(3-(5-(2-((6-aminohexyl)amino)pyrimidin-4-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (67 mg, 0.091 mmol) was added. The reaction was stirred at RT overnight. The reaction mixture was evaporated onto Celite and purified using reverse phase chromatography, eluting with water/ACN. Fractions with pure compound were concentrated to obtain **15** (4.28 mg, 5%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 5.3 Hz, 1H), 7.73 - 7.58 (m, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.45 - 7.37 (m, 2H), 7.23 (br t, *J* = 6.5 Hz, 1H), 7.16 - 7.07 (m, 2H), 6.90 (t, *J* = 8.9 Hz, 2H), 5.96 (d, *J* = 5.1 Hz, 1H), 4.91 (br dd, *J* = 12.6, 5.3 Hz, 1H), 4.60 (s, 2H), 3.63 - 3.47 (m, 1H), 3.39 - 3.20 (m, 3H), 3.14 (br s, 1H), 2.85 - 2.71 (m, 2H), 2.70 - 2.56 (m, 1H), 2.10 - 2.01 (m, 1H), 1.49 - 1.43 (m, 2H), 1.40 - 1.29 (m, 14H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.83 (s, 1F), -130.22 (br s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.71, 172.10, 166.82, 166.74, 166.14, 161.83, 160.49 (d, *J* = 3.2 Hz), 159.04, 159.01 (d, *J* = 3.2 Hz), 157.59, 154.68, 151.68, 150.27, 145.78, 137.05, 135.29 (t, *J* = 10.6 Hz), 134.16, 133.56, 127.94, 125.03 (d, *J* = 4.2 Hz), 124.70 (br d, *J* = 11.7 Hz), 124.43 (br d, *J* = 13.8 Hz) 122.97, 119.94, 118.24, 117.45, 116.90, 113.25 (d, *J* = 3.2 Hz), 113.12 (d, *J* = 3.2 Hz), 105.95, 68.35, 49.38, 40.94, 39.08, 38.02, 31.48, 30.74, 28.97, 28.86, 26.57, 26.53, 22.64. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{44}H_{44}F_3N_8O_8S_2$, 933.27. Found 933.30.

Synthesis of N1-(6-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)-thiazol-5-yl)pyrimidin-2-yl)amino)hexyl)-N4-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)-pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide (16).



Scheme 6. Reagents and conditions: i) tert-butyl (6-aminohexyl)carbamate**,** ACN, 90-100 ^{o}C, overnight ii) 4-(tert-butoxy)-4-oxobutanoic acid, TFA, DCM, RT; iii) HATU, DIPEA, DMF, RT, iv) TFA, DCM, RT, v) HATU, DIPEA, DMF, RT.

N1-(6-((4-(2-(tert-Butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)hexyl)-N4-((R)-1-((2S,4R)-4-hydroxy-2-((4-(4-methylthiazol-5-yl)benzyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide (16) .

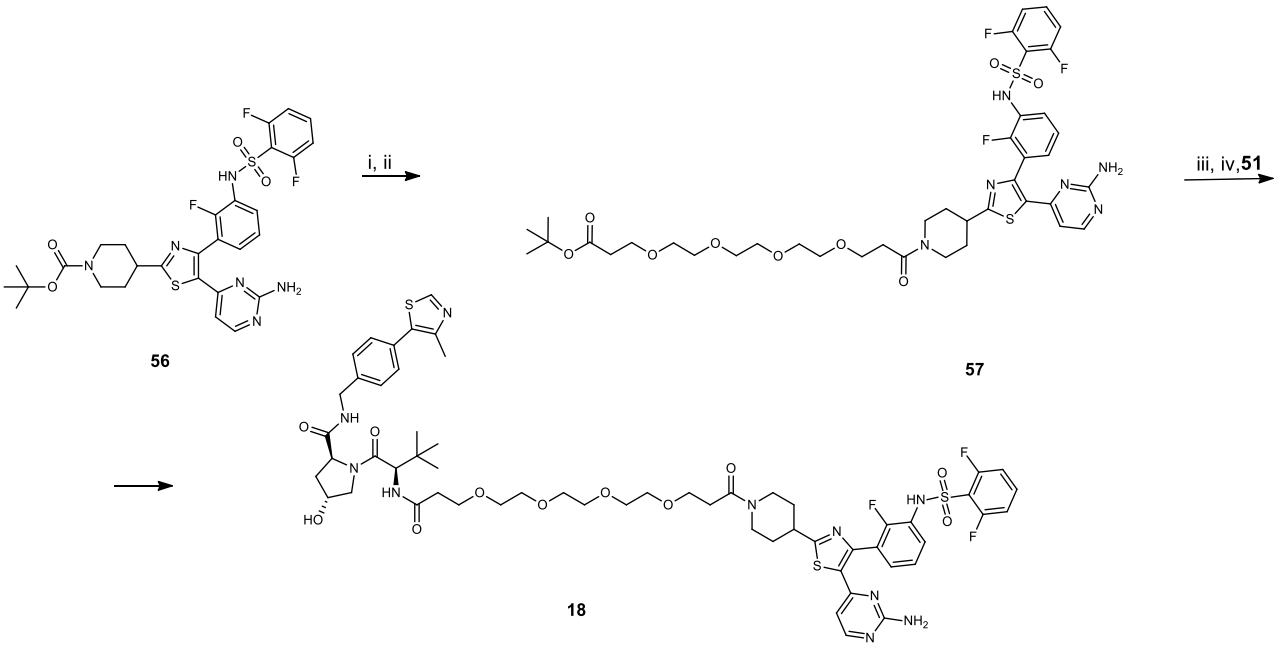


To a solution of *N*-(3-(5-(2-((6-aminohexyl)amino)pyrimidin-4-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide trifluoroacetate (48 mg, 0.078 mmol) in DMF (5 mL) was added the *tert*-butyl hydrogen succinate (13.5 mg, 0.078 mmol), and the solution was stirred at RT. DIPEA (40.1 mg, 0.310 mmol) was added dropwise, and the mixture was stirred for 5 min at RT. HATU (32.6 mg, 0.086 mmol) was added, and the mixture was stirred at RT for another 30 min. Water was added, and the mixture was extracted with EtOAc. The combined organic

phases were washed with brine, dried over $MgSO_4$, and evaporated under vacuum to give the corresponding crude product, which was purified by flash column chromatography to yield 35 mg of **55,** which was stirred for 1 hour at DCM/TFA, evaporated to obtain 4-((6-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)hexyl)amino)-4-oxobutanoic acid (30 mg, 48%). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{33}H_{38}F_3N_6O_5S_2$, 719.27. Found 719.31. This material and **51** (20.7 mg, 0.038 mmol) was dissolved in DMF (2 mL). DIPEA (39.6 mg, 0.306 mmol) was added dropwise, and the mixture was stirred for 5 min at RT. HATU (32.0 mg, 0.084 mmol) was added, and the mixture was stirred at RT overnight. Brine (2 mL) was added, and the mixture was extracted with DCM. The combined organic phases were washed with brine, dried over MgSO4, and evaporated under vacuum to give the crude product, which was purified by reverse phase column chromatography (water/ACN) to yield **16** (9.8 mg, 11%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.88 (br d, *J* = 4.9 Hz, 1H), 7.54 (br s, 1H), 7.32 (br s, 1H), 7.29 - 7.21 (m, 4H), 7.15 (br s, 1H), 7.05 (br s, 1H), 6.98 (br s, 1H), 6.84 (br t, *J* = 8.4 Hz, 2H), 6.10 (br s, 1H), 5.29 (br s, 1H), 4.63 (br t, *J* = 7.8 Hz, 1H), 4.43 (br dd, *J* = 6.1, 14.7 Hz, 1H), 4.36 (br s, 1H), 4.34 - 4.19 (m, 2H), 3.93 (br d, *J* = 11.0 Hz, 1H), 3.45 (br d, *J* = 8.9 Hz, 1H), 3.17 (br s, 1H), 3.09 (br s, 2H), 2.47 - 2.38 (m, 5H), 2.37 - 2.27 (m, 2H), 2.16 - 1.95 (m, 1H), 1.60 (br s, 2H), 1.56 - 1.46 (m, 1H), 1.43 (br s, 2H), 1.38 (s, 9H), 1.35 - 1.11 (m, 6H), 0.85 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -129.38 (s, 1 F), -107.06 (s, 1 F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 182.37, 173.15, 172.36, 171.70, 171.15, 162.09, 160.83 (d, *J* = 4.2 Hz), 158.78 (d, *J* = 4.2 Hz), 158.15, 150.28, 148.44, 138.26, 133.75, 131.62, 130.82, 129.44, 128.01, 125.12, 124.81, 122.62 (d, *J* = 3.63 Hz), 116.28, 113.11, 112.93 (d, *J* = 3.2 Hz), 106.54, 70.05, 58.63, 58.26, 56.76, 43.13, 40.92, 39.43, 38.01, 36.47, 34.90, 31.32, 30.75, 29.70, 29.16, 26.46, 26.31, 16.02. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{55}H_{66}F_3N_{10}O_7S_3$, 1131.42. Found 1131.43.

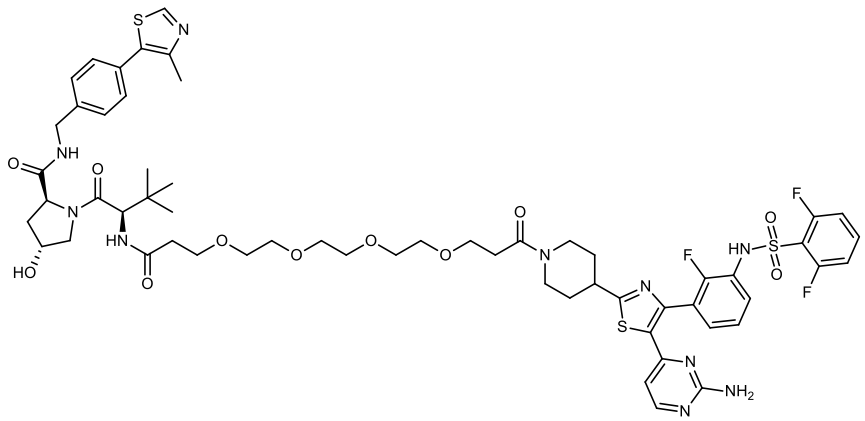
Synthesis of Dabrafenib #2 -based compounds

Synthesis of (2S,4R)-1-((S)-19-(4-(5-(2-aminopyrimidin-4-yl)-4-(3-((2,6-difluorophenyl)-sulfonamido)-2-fluorophenyl)thiazol-2-yl)piperidin-1-yl)-2-(tert-butyl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (18).



Scheme 7. Reagents and conditions: i) TFA, DCM, RT; ii) Acid-PEG4-t-butyl ester, HATU, DIPEA, DMF, RT, iii) TFA, DCM, RT; iv) HATU, DIPEA, DMF, RT.

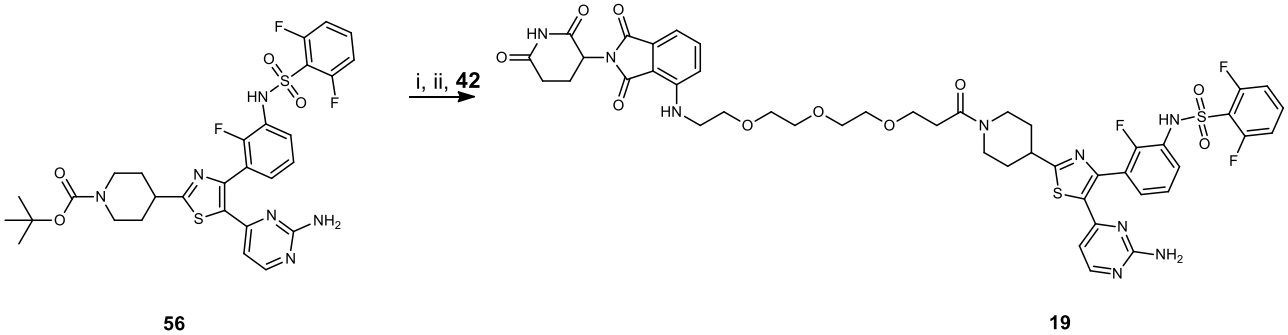
(2S,4R)-1-((S)-19-(4-(5-(2-Aminopyrimidin-4-yl)-4-(3-((2,6-difluorophenyl)-sulfonamido)-2-fluorophenyl)thiazol-2-yl)piperidin-1-yl)-2-(tert-butyl)-4,19-dioxo-7,10,13,16-tetraoxa-3-azanonadecanoyl)-4-hydroxy-N-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (18).



A portion of **56** (65.4 mg, 0.101 mmol) (synthesized using the synthetic procedures described previously[59]) was dissolved in a mixture of TFA (2.5 mL) and DCM (2.5 mL). The reaction mixture was stirred for 1 h at RT and the solvent was removed with a rotary evaporator and crude product and placed under high vacuum overnight to afford *N*-(3-(5-(2-aminopyrimidin-4-yl)-2-(piperidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzene-sulfonamide trifluoroacetate in quantitative yield (67 mg, 0.101 mmol), which was used in the next step without any further purification. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{24}H_{23}F_3N_6O_2S_2$ 547.12. Found 547.31. 2,2-Dimethyl-4-oxo-3,7,10,13,16-pentaoxanonadecan-19-oic acid (35.5 mg, 0.101 mmol) was dissolved in DMF (0.5 mL), then HATU (46.3 mg, 0.122 mmol) was added at RT, the mixture was stirred for 10 min, then DIPEA (39.3 mg, 0.304 mmol) was added and the mixture was stirred for an additional 10 min. *N*-(3-(5-(2-Aminopyrimidin-4-yl)-2-(piperidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzene-sulfonamide trifluoroacetate (67 mg, 0.101 mmol) was dissolved in DMF (1 mL). The reaction mixture was stirred overnight at RT. Water (1 mL) was added to the reaction mixture and extracted with EtOAc. The organic extract was evaporated onto Celite and purified with reverse phase MPLC (Water/ACN). Fractions with pure compound were collected and evaporated under vacuum to obtain **57** (35 mg, 37%). LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{40}H_{51}F_3N_6O_9S_2$, 879.30. Found 879.65. TFA:DCM (1:1, 2 mL) was added to the **57** obtained above and the reaction mixture was stirred for 1 h. The solvents were then evaporated to give 16-(4-(5-(2-aminopyrimidin-4-yl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-2-yl)piperidin-1-yl)-16-oxo-4,7,10,13-tetraoxahexadecanoic acid (33 mg, quantitative yield), which was added to a solution of **51** (17 mg, 0.037 mmol) in DMF (1 mL). DIPEA (20.73 mg, 0.160 mmol) and HATU (16.8 mg, 0.044 mmol) were added, and the mixture was stirred at RT overnight. Water was then added, and the mixture was extracted with EtOAc. The combined organic phases were washed with brine, dried over

$MgSO_4$, and evaporated under reduced pressure to give the corresponding crude material, which was purified by reverse phase chromatography (water/ACN) to yield the target compound **18** (10 mg, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H), 7.95 (br d, *J* = 5.1 Hz, 1H), 7.69 (br t, *J* = 7.3 Hz, 1H), 7.58 (br d, *J* = 5.7 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.34 (s, 4H), 7.19 (br d, *J* = 7.9 Hz, 1H), 7.08 (br dd, *J* = 7.9, 3.8 Hz, 1H), 6.95 (t, *J* = 8.8 Hz, 2H), 6.10 (d, *J* = 5.1 Hz, 1H), 5.29 (br d, *J* = 13.0 Hz, 2H), 4.76 – 4.65 (m, 2H), 4.58 – 4.45 (m, 3H), 4.33 (dd, *J* = 14.9, 5.3 Hz, 1H), 4.10 (br d, *J* = 11.4 Hz, 1H), 4.03 (br d, *J* = 11.7 Hz, 1H), 3.85 – 3.73 (m, 2H), 3.69 (br t, *J* = 5.7 Hz, 2H), 3.62 (br s, 14H), 3.28 – 3.12 (m, 2H), 2.80 – 2.67 (m, 2H), 2.65 – 2.54 (m, 1H), 2.49 (s, 3H), 2.48 – 2.43 (m, 2H), 2.21 – 2.07 (m, 3H), 1.85 – 1.75 (m, 1H), 1.75 – 1.67 (m, 1H), 0.94 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$): δ -106.76 (s, 1F), -128.96 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.83, 171.99, 171.60, 171.17, 169.71, 162.79, 160.44 (d, *J* = 3.2 Hz), 158.96 (d, *J* = 3.2 Hz), 158.54, 158.41, 152.31, 150.89, 150.37, 148.44, 146.11, 138.32, 134.99-134.88 (m), 134.64 (d, *J* = 4.2 Hz), 131.65, 130.74, 129.40, 128.06, 125.09 (d, *J* = 4.2 Hz), 124.58, 123.70 (d, *J* = 13.8 Hz), 113.13 (d, *J* = 3.2 Hz), 113.02 (d, *J* = 4.2 Hz), 107.03, 70.39, 70.33, 70.29, 70.03, 67.70, 67.15, 58.66, 57.67, 56.74, 45.60, 43.12, 41.47, 40.85, 36.53, 36.33, 35.09, 33.53, 32.75, 32.13, 29.69, 26.43, 16.01. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{58}H_{70}F_3N_{10}O_{11}S_3$, 1235.43. Found 1235.72.

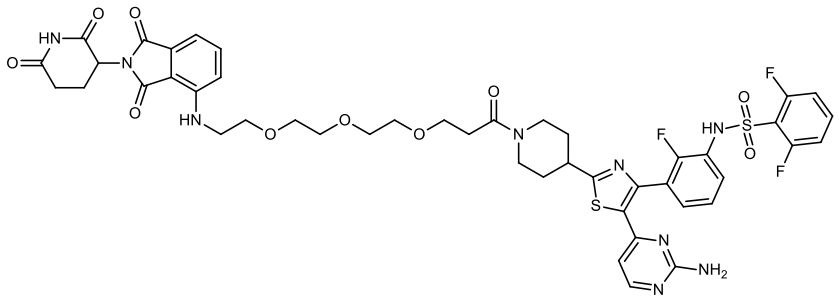
Synthesis of N-(3-(5-(2-aminopyrimidin-4-yl)-2-(1-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoyl)piperidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide (19) .



56 19

Scheme 8. Reagents and conditions: i) TFA, DCM, RT; ii) HATU, DIPEA, DMF, RT.

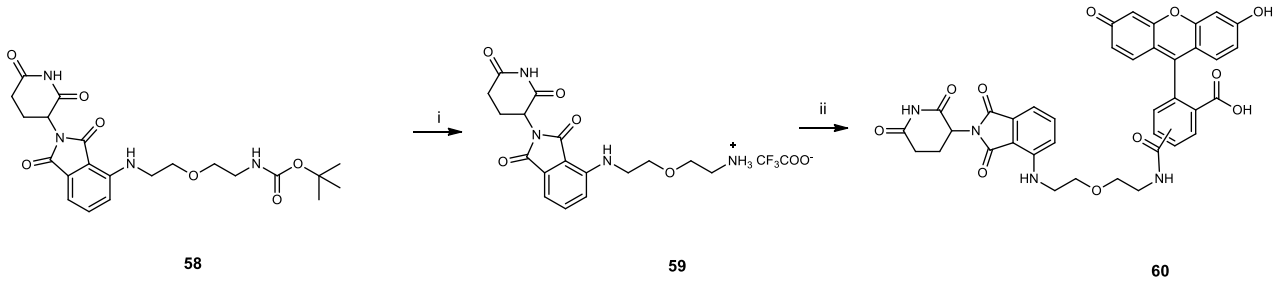
N-(3-(5-(2-Aminopyrimidin-4-yl)-2-(1-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoyl)piperidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzene-sulfonamide (19).



56 (55.3 mg, 0.084 mmol), (synthesized using the synthetic procedures described previously[59]) was dissolved in a mixture of TFA (2 mL) and DCM (2 mL). The reaction mixture was stirred for 1 h at RT, the solvent was removed with a rotary evaporator and residue was placed under high vacuum overnight to yield the crude product *tert*-butyl 4-(5-(2-aminopyrimidin-4-yl)-4-(3-(2,6-difluorophenylsulfonamido)-2-fluorophenyl)thiazol-2-yl)piperidine-1-carboxylate trifluoroacetate was obtained with a quantitative yield and used in the next step without further purification. To a solution of acid **42** (49.6 mg, 0.084 mmol) in DMF (1 mL) was added HATU (35.0 mg, 0.092 mmol) and the solution was stirred at RT for 5 min. DIPEA (54 mg, 0.42 mmol) was added dropwise, and the mixture was stirred for another 5 min at RT. *tert*-butyl 4-(5-(2-aminopyrimidin-4-yl)-4-(3-(2,6-difluorophenylsulfonamido)-2-fluorophenyl)thiazol-2-yl)piperidine-1-carboxylate trifluoroacetate (56 mg, 0.084 mmol) in DMF (1 mL) was added, and the mixture was stirred overnight at RT. Water was added to the reaction, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the corresponding crude material, which was purified by reverse phase chromatography (water/ACN) to yield the final compound **19** (10 mg, 11%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 – 9.49 (m, 1H), 7.97 (br d, *J* = 5.3 Hz, 1H), 7.69 (br t, *J* = 7.5 Hz, 1H), 7.48 (br t, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.10 (br d, *J* = 7.0 Hz, 1H), 7.00 – 6.88 (m, 3H), 6.49 (br s, 1H), 6.08 (br d, *J* = 5.0 Hz, 1H), 5.38 – 5.28 (m, 2H), 4.97 – 4.90 (m, 1H), 4.68 (br d, *J* = 12.8 Hz, 1H), 4.00 (br d, *J* = 13.7 Hz, 1H), 3.80 (br t, *J* = 6.3 Hz, 2H), 3.74 – 3.62 (m, 10H), 3.45 (br d, *J* = 4.8 Hz, 2H), 3.28 – 3.12 (m, 2H), 2.89 – 2.82 (m, 1H), 2.81 – 2.63 (m, 5H), 2.22 – 2.07 (m, 3H), 1.84 – 1.65 (m, 2H). ^{19}F

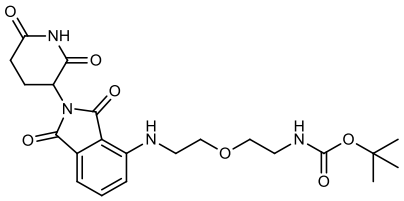
NMR (471 MHz, $CDCl_3$): δ -129.45 (s, 1F), -106.83 (s, 1F). ^{13}C NMR (126 MHz, $CDCl_3$): δ 175.95, 172.28, 169.60 (d, *J* = 3.2 Hz), 169.32, 169.28, 167.72, 162.66, 160.40 (d, *J* = 4.2 Hz), 158.91 (d, *J* = 4.2 Hz), 158.75, 158.05, 152.01, 150.60, 146.78, 146.02, 136.02, 135.29 (m), 134.51 (d, *J* = 3.2 Hz), 132.52, 128.02, 125.07 (d, *J* =3.2 Hz), 124.34, 123.61 (dd, *J* = 13.8, 4.2 Hz), 117.12 (br t, *J* = 14.8 Hz), 116.78, 113.21 (d, *J* = 3.2 Hz), 113.15 (d, *J*= 3.2 Hz), 111.60, 110.27, 106.83, 70.75, 70.55, 70.46, 69.38, 67.48, 48.91, 45.46, 42.35, 41.40, 40.79, 35.59, 32.72, 31.99, 31.48, 29.69, 22.86. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{46}H_{47}F_3N_9O_{10}S_2$, 1006.28. Found 1006.67.

Synthesis of Pomalidomide-PEG1-Fluorescein (fluorescein labeled pomalidomide) (60).



Scheme 9. Reagents and conditions: i) dioxane, DIPEA, 100-110 ^oC: ii) 6-[fluorescein-5(6)-carboxamido]hexanoic acid-N-hydroxysuccinimide ester, Et_3N, DCM, RT.

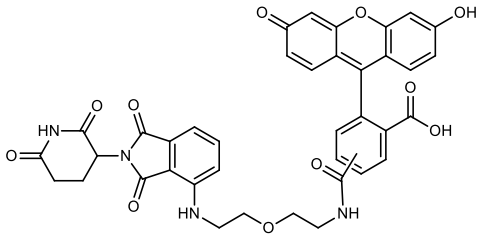
tert-Butyl (2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-carbamate (58)



A procedure similar to that employed for **31** using *tert*-butyl (2-(2-aminoethoxy)ethyl)carbamate (103 mg, 0.504 mmol) and **30** (100 mg, 0.362 mmol) afforded the intermediate **58** (204 mg, 88%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.20 (br s, 1H), 7.42 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.46 (br s, 1H), 4.92 (br s, 1H), 4.85 (dd, *J* = 12.2, 5.3 Hz, 1H), 3.61 (t, *J* = 5.3 Hz, 2H), 3.48 (t, *J* = 5.1 Hz, 2H), 3.40 - 3.36 (m, 2H), 3.27 - 3.23 (m, 2H), 2.83 - 2.59 (m, 3H), 2.06 - 2.03 (m, 1H), 1.35 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.24, 169.37, 168.47, 167.57, 155.98,

146.81, 136.06, 132.45, 116.76, 111.74, 110.33, 79.24, 70.24, 48.88, 42.21, 40.36, 31.40, 28.37, 22.72. LCMS (ESI); *m/z*: $[M+Na]^+$ calcd. for $C_{22}H_{28}N_4NaO_7$ 483.18. Found 483.19.

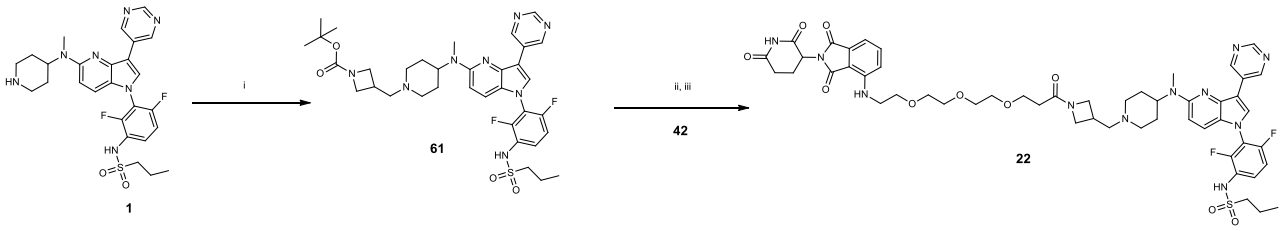
Pomalidomide-PEG1-Fluorescein (60)



tert-Butyl (2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)-carbamate **58** was dissolved in a mixture of TFA (2 mL) and DCM (2 mL). The reaction mixture was stirred for 1 h at RT, the solvent was removed and the residue was placed under high vacuum overnight to afford the crude product in a quantitative yield (50 mg), used in the next step without further purification. The TFA salt **59** (50 mg, 10.5 mmol) in DMF (5 mL) was added to 6-[fluorescein-5(6)-carboxamido]hexanoic acid-N-hydroxysuccinimide ester (44 mg, 10.5 mmol; Thermo Scientific™). This was followed by addition of DIPEA (26 mg, 21 mmol). After stirring for 30 min at RT, the reaction mixture was quenched with $NaHCO_3$ and extracted with DCM. The organic phase was concentrated and purified by reverse phase chromatography (Water/ACN). The pure product was dried under vacuum to yield the product **60** (5 mg, 10%) as a dark yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.07 (s, 1H), 10.40 (s, 1H), 8.86 (t, *J* = 5.5 Hz, 1H), 8.72 (t, *J* = 5.6 Hz, 1H), 8.46 – 8.36 (m, 1H), 8.19 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.12 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.04 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.65 (s, 1H), 7.52 (ddd, *J* = 23.3, 8.4, 7.2 Hz, 1H), 7.32 (s, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 7.1 Hz, 1H), 6.63 (d, *J* = 7.4 Hz, 3H), 6.57 (dd, *J* = 8.7, 5.4 Hz, 2H), 6.51 (dd, *J* = 8.8, 2.3 Hz, 2H), 5.02 (dt, *J* = 12.8, 5.3 Hz, 1H), 3.68 – 3.60 (m, 2H), 3.63 – 3.56 (m, 1H), 3.57 (d, *J* = 5.4 Hz, 1H), 3.49 (dt, *J* = 9.5, 5.8 Hz, 4H), 3.41 (d, *J* = 5.7 Hz, 1H), 3.36 (d, *J* = 5.8 Hz, 2H), 2.91 – 2.76 (m, 1H), 2.52 (s, 1H), 2.03 – 1.94 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 173.20, 170.50, 169.37, 169.33, 168.54, 168.40, 167.70, 165.93, 165.92, 165.59, 165.27, 165.09, 146.87, 146.79, 136.61, 136.41, 132.51, 129.78, 129.62, 117.95, 117.86, 111.07, 109.67, 109.63, 102.73, 69.24, 69.12, 68.98, 48.99, 42.17, 42.04, 31.39, 22.58. NB spectral analysis subject to presence of isomeric forms. LCMS (ESI); *m/z*: $[M+H]^+$ calcd. for $C_{38}H_{31}N_4O_{11}$, 719.19. Found 719.20.

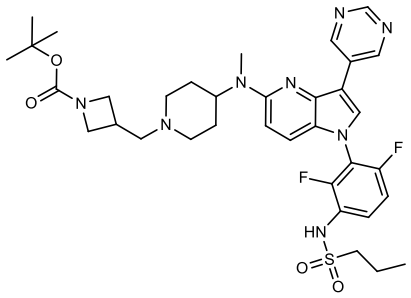
Synthetic methods for the preparation of BI-based PROTACs with modified linkers

Synthesis of N-(3-(5-((1-((1-(3-(2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoyl)azetidin-3-yl)methyl)piperidin-4-yl)(methyl)-amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (22)



Scheme 10. Reagents and conditions: i) tert-butyl 3-(bromomethyl)azetidine-1-carboxylate, ACN, K_2CO_3, 50 ^{o}C; ii) DCM, TFA, RT; iii) HATU, DIPEA, DMF, RT.

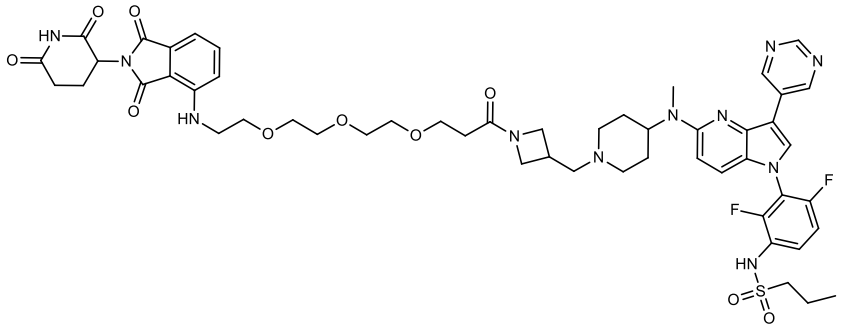
Step 1: tert-Butyl 3-((4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)methyl)azetidine-1-carboxylate (61)



Potassium carbonate (150 mg, 1.08 mmol) was added to the mixture of **1** (102 mg, 0.15 mmol) and *tert*-butyl 3-(bromomethyl)azetidine-1-carboxylate (80 mg, 0.32 mmol) in 0.5 mL ACN. The reaction mixture was stirred at 50 °C for 2 d. The reaction was diluted with $NaHCO_3$ solution and extracted with DCM. The organic layer was concentrated and purified by reverse phase

chromatography (Water/ACN) to give the title compound **61** (53 mg, 50%) as an off-white semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (s, 2H), 9.01 (s, 1H), 7.59 (m, 2H), 7.22 (dt, *J* = 10.0, 2.2 Hz, 1H), 7.10 (dd, *J* = 9.2, 1.9 Hz, 1H), 6.49 (d, *J* = 9.2 Hz, 1H), 4.61 – 4.51 (m, 1H), 3.98 (t, *J* = 8.2 Hz, 2H), 3.57 (dd, *J* = 8.6, 5.3 Hz, 2H), 3.13 (s, 2H), 3.05 (d, *J* = 7.9 Hz, 2H), 2.86 (s, 3H), 2.81 – 2.70 (m, 3H), 2.33 (td, *J* = 12.0, 11.5, 2.6 Hz, 2H), 1.96 – 1.66 (m, 6H), 1.36 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -121.50 (s, *1F*), -130.04 (s, *1F*). ^{13}C NMR (101 MHz, CDCl3): δ 156.28, 156.21, 156.08, 155.59, 154.85, 153.89, 153.60, 151.54, 149.08, 142.10, 128.61, 126.91, 124.29, 124.20, 122.90 (d, *J* = 5.45 Hz), 120.78, 116.54, 112.53, 111.00, 104.94, 79.48, 61.73, 54.71, 53.33, 52.66, 49.41, 31.23, 30.52, 28.40, 26.35, 17.96, 12.53. LCMS (ES^+): *m/z* 711.3 $[M+1]^+$.

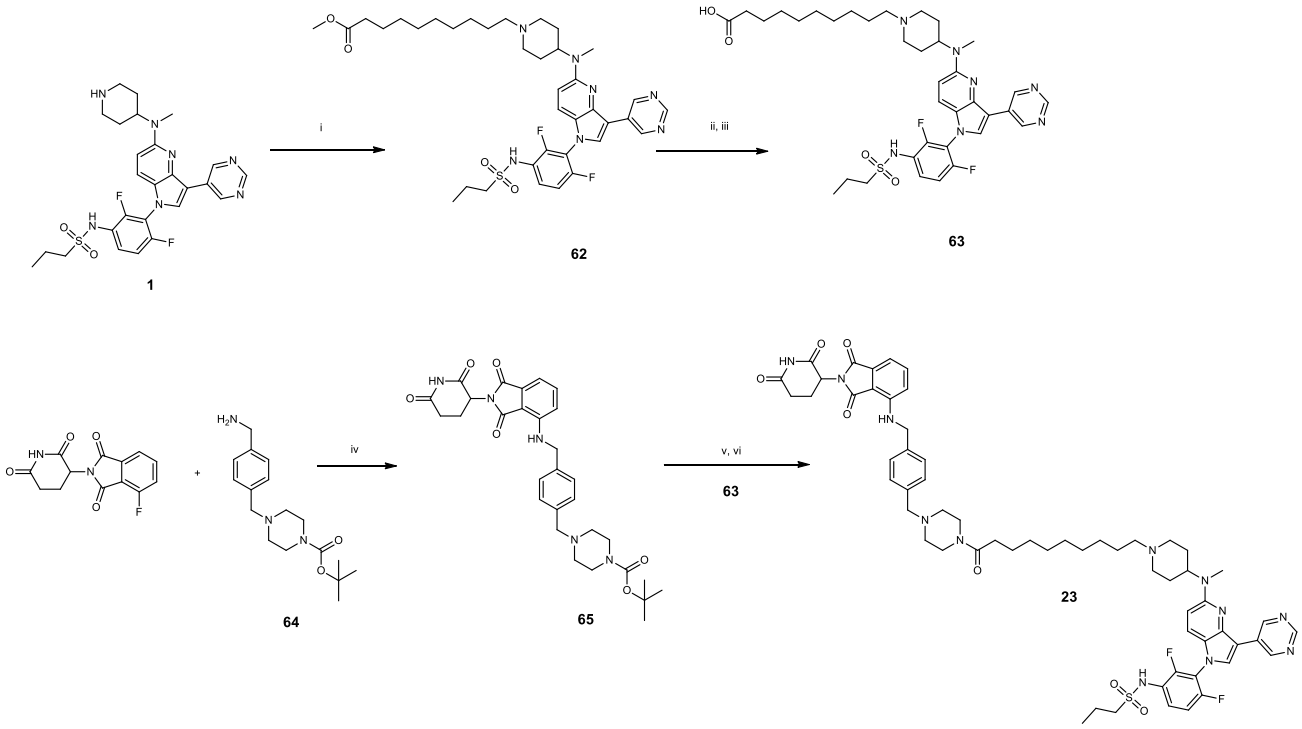
Step 2: N-(3-(5-((1-((1-(3-(2-(2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoyl)azetidin-3-yl)methyl)piperidin-4-yl)(methyl)-amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (22)



42 (66 mg, 0.138 mmol) was dissolved in DMF (4 mL), then HATU (50 mg, 0.131 mmol) was added at RT. The mixture was stirring during 10 min before DIPEA (85 mg, 0.66 mmol) was added, and the mixture was stirred for another 5 min. **61** (80 mg, 0.112 mmol) was dissolved in 2 mL DCM/TFA (1:1) and the reaction mixture was stirred for 1 h at RT. After the reaction the solvent was evaporated and crude product was dried under high vacuum overnight. N-(3-(5-((1-(azetidin-3-ylmethyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide trifluoroacetate was obtained in a quantitative yield (94 mg, 0.112 mmol) and used in the next step without any further purification. Obtained TFA salt was dissolved in 1 mL of DMF and added to the reaction mixture. After stirring overnight at RT, the reaction mixture was evaporated onto Celite and purified by reverse phase chromatography,

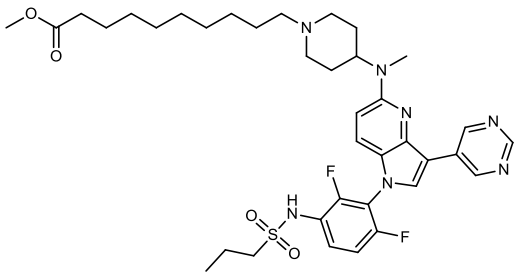
eluting with Water/ACN. The desired fractions were collected, concentrated and dried under vacuum to afford the residue, which was repurified by reverse phase chromatography, eluting with Water/MeOH to obtain desired compound **22** as a yellow powder (11 mg, 10 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 9.47 (s, 2H), 9.05 (d, *J* = 7.3 Hz, 1H), 7.65 – 7.56 (m, 2H), 7.41 (ddd, *J* = 8.5, 7.1, 5.5 Hz, 1H), 7.26 (dt, *J* = 9.2, 1.9 Hz, 1H), 7.12 (td, *J* = 9.2, 1.9 Hz, 1H), 7.01 (dd, *J* = 7.1, 5.6 Hz, 1H), 6.86 (dd, *J* = 8.6, 4.4 Hz, 1H), 6.52 (d, *J* = 9.2 Hz, 1H), 6.47 (s, 1H), 5.02 – 4.79 (m, 2H), 4.30 (s, 1H), 4.17 – 4.08 (m, 1H), 3.94 (t, *J* = 12.5 Hz, 1H), 3.72 – 3.53 (m, 16H), 3.41 (d, *J* = 5.6 Hz, 5H), 3.16 – 3.05 (m, 4H), 2.95 – 2.66 (m, 6H), 2.28 (h, *J* = 6.8 Hz, 4H), 2.06 – 2.02 (m, 1H), 1.86 (m, 3H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -121.45 (q, *J* = 7.4 Hz), -131.04 (d, *J* = 8.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.84, 169.33, 167.70, 155.92, 153.87, 148.76, 146.51, 141.55, 136.09, 132.46, 128.62, 124.15, 123.04, 121.00, 116.62, 111.59, 110.15, 104.26, 70.82, 70.54, 70.43, 69.35, 66.91, 54.76, 51.85, 48.97, 42.39, 35.08, 31.55, 30.80, 27.24, 22.68, 17.30, 12.90. HRMS (*m/z*): $[M]^+$ calcd. for $C_{52}H_{62}F_2N_{11}O_{10}S$, 1070.4364; found, 1070.4365.

Synthesis of N-(3-(5-((1-(10-(4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-amino)methyl)benzyl)piperazin-1-yl)-10-oxodecyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (23)



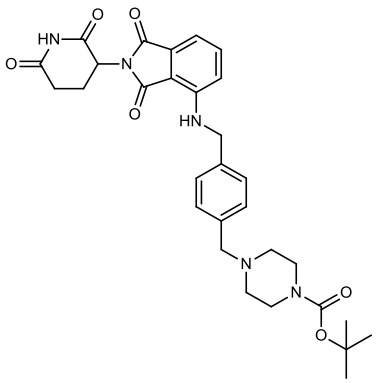
Scheme 11. Reagents and conditions: i) methyl 10-bromodecanoate, ACN, K_2CO_3, 50 ^oC; ii) THF/Water, LiOH, RT; iii) 1M HCl; iv)) dioxane, DIPEA, 100 ^oC; v) DCM, TFA, RT; vi) **63**, HATU, DIPEA, DMF, RT.

Step 1: Methyl 10-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)decanoate (62)



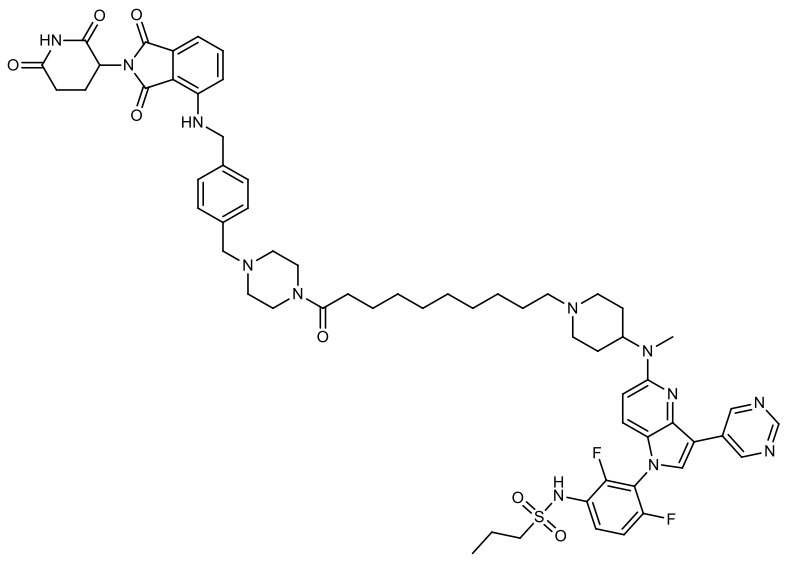
Potassium carbonate (41 mg, 0.3 mmol) was added to the mixture of **1** (100 mg, 0.15 mmol) and methyl 10-bromodecanoate (80 mg, 0.3 mmol) in ACN. The reaction mixture was stirred at 50 °C for 8 h. The reaction was diluted with semi-concentrated $NaHCO_3$ solution and extracted with DCM. Organic layer was concentrated and purified by reverse phase chromatography (Water/ACN) to give the title compound **62** (54 mg, 50%) as an off-white semi-solid. ^1H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 2H), 9.12 (s, 1H), 8.54 (s, 2H), 7.76 – 7.59 (m, 2H), 7.35 (dt, *J* = 9.2, 1.9 Hz, 1H), 7.20 (td, *J* = 9.2, 1.9 Hz, 1H), 6.58 (d, *J* = 9.2 Hz, 1H), 5.05 (t, *J* = 12.3 Hz, 1H), 3.73, (s, 1H), 3.70 (s, 3H), 3.26 – 3.12 (m, 2H), 3.00 – 2.91 (m, 6H), 2.83 (t, *J* = 12.1 Hz, 2H), 2.42 (d, *J* = 12.5 Hz, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.02 – 1.91 (m, 4H), 1.64 (q, *J* = 7.3 Hz, 3H), 1.33 (t, *J* = 5.8 Hz, 12H), 1.10 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -121.94, -129.78. ^{13}C NMR (101 MHz, CDCl3): δ 174.31, 156.04, 155.67, 153.92, 141.94, 128.60, 127.12, 124.47, 123.65, 122.68, 121.01, 116.19, 113.22, 110.90, 104.15, 77.37, 77.06, 76.74, 54.78, 52.69, 51.46, 43.12, 34.08, 32.81, 30.68, 29.37, 29.34, 29.20, 29.10, 29.06, 27.00, 26.51, 25.73, 24.91, 24.63, 17.32, 12.96. LCMS (ES^+): *m/z* 726.4 $[M+1]^+$.

Step 2: tert-Butyl 4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-benzyl)piperazine-1-carboxylate (65)



A procedure analogous to that used for intermediate **31** using **64** (110 mg, 0.360 mmol) and **30** (100 mg, 0.361 mmol) afforded the crude product, which was purified by normal phase chromatography eluting with the mixture MeOH/ACN in DCM. Fractions with pure compound were collected, concentrated with a rotary evaporator to afford intermediate **65** as a bright yellow powder (240 mg, 43%). ^{1}H NMR (400 MHz, CDCl3): δ 8.17 (s, 1H), 7.38 (dd, *J* = 8.5, 7.2 Hz, 1H), 7.24 (d, *J* = 1.9 Hz, 4H), 7.05 (dd, *J* = 7.2, 0.6 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.61 (t, *J* = 5.9 Hz, 1H), 4.85 (dd, *J* = 12.1, 5.3 Hz, 1H), 4.42 (d, *J* = 5.8 Hz, 2H), 3.46 (s, 2H), 3.37 (d, *J* = 5.3 Hz, 4H), 2.88 – 2.62 (m, 3H), 2.35 (t, *J* = 4.9 Hz, 4H), 2.11 – 2.04 (m, 1H), 1.38 (s, 9H). 13C NMR (126 MHz, CDCl3): δ 171.13, 169.46, 168.42, 167.54, 153.56, 146.63, 136.15, 132.43,129.82, 127.05, 117.07, 111.99, 110.44, 79.71, 62.36, 52.74, 48.90, 46.50, 43.33, 42.81, 31.40, 28.40, 22.78. LCMS (ES^{+}): *m/z* 562.2 $[M+1]^{+}$.

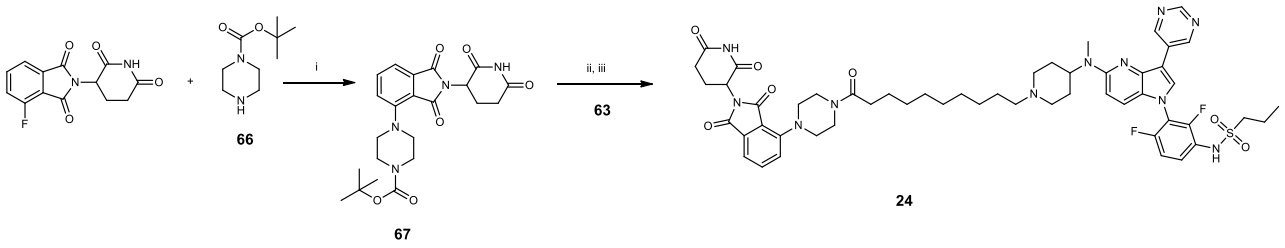
Step 3: N-(3-(5-((1-(10-(4-(4-(((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-amino)methyl)benzyl)piperazin-1-yl)-10-oxodecyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (23)



tert-Butyl 4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)benzyl)-piperazine-1-carboxylate **65** (30 mg, 0.053 mmol) was dissolved in a mixture of TFA (1 mL) and DCM (1 mL). The reaction mixture was stirred for 3 h at RT. After the reaction, the solvent was evaporated and crude product was dried under high vacuum overnight. TFA salt was obtained in a quantitative yield (30.5 mg, 0.053 mmol) and used in the next step without any further purification. A solution of **62** (60 mg, 0.08 mmol) and LiOH (4 mg, 0.04 mmol) in 4 mL THF/water (1:1) was stirred at RT overnight, then the reaction was acidified until it reached pH 2 with 1M HCl, extracted with EtOAc and the organic layer was separated and dried to afford **63** (40 mg, 100%). A portion of **63** (40 mg, 0.055 mmol) was dissolved in DMF (3 mL), then HATU (36 mg, 0.1 mmol) was added at RT. The mixture was stirring during 10 min before N,N-DIPEA (52 mg, 0.4 mmol) was added and the mixture was stirred for another 5 min. 2-(2,6-dioxopiperidin-3-yl)-4-((4-(piperazin-1-ylmethyl)benzyl)amino)-isoindoline-1,3-dione trifluoroacetate (30.5 mg, 0.053 mmol) was dissolved in 1 mL of DMF and added to the reaction mixture. After stirring for 6 hours at RT, the reaction mixture was evaporated onto Celite and purified by reverse phase chromatography, eluting with Water/ACN (0% to 100% of ACN). The desired fractions were collected, concentrated and dried under vacuum to afford the residue, which was repurified by normal phase chromatography (DCM/MeOH) to obtain the desired compound **23** as a yellow semi-solid (7 mg, 12%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.51 (s, 2H), 9.10 (s, 1H), 7.67 (m, 2H), 7.45 (ddd, *J* = 8.5, 7.1, 0.7 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.30 (s, 4H), 7.18 (td, *J* = 9.2, 2.0 Hz, 1H), 7.11 (dd, *J* = 7.1, 0.6 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.67 – 6.60 (m, 2H), 4.98 – 4.86 (m, 2H), 4.48 (d, *J* = 5.8 Hz, 2H), 3.64 –

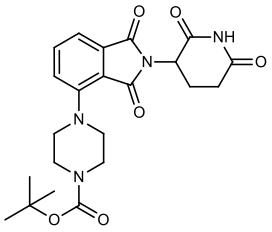
3.55 (m, 4H), 3.51 (s, 2H), 3.46 (t, *J* = 5.0 Hz, 2H), 3.18 – 3.12 (m, 2H), 2.98 – 2.94 (m, 4H), 2.91 – 2.84 (m, 1H), 2.82 – 2.70 (m, 2H), 2.41 (t, *J* = 5.1 Hz, 4H), 2.30 (t, *J* = 7.7 Hz, 3H), 2.16 – 2.10 (m, 1H), 1.98 – 1.88 (m, 4H), 1.74 (m, 3H), 1.60 (m, 3H), 1.36 – 1.20 (m, 12H), 1.08 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d6): δ 173.31, 171.06, 170.56, 169.40, 167.74, 156.18, 155.01,153.45, 146.53, 141.78, 138.12, 136.86, 132.62, 129.57, 127.32, 124.39, 122.92, 122.39, 121.34, 117.89, 111.19, 109.93, 62.01, 54.00, 53.90, 53.75, 53.35, 53.03, 49.07, 45.92, 45.49, 43.83, 40.48, 40.39, 40.31, 40.22, 40.15, 40.06, 39.98, 39.89, 39.81, 39.72, 39.55, 39.39, 34.97, 32.67, 31.41, 30.62, 29.36, 29.24, 29.15, 28.98, 27.43, 27.09, 25.28, 22.59, 17.98, 13.49. HRMS (*m/z*): $[M]^+$ calcd. for $C_{61}H_{73}F_2N_{12}O_7S$,1155.5408; found, 1155.5402.

Synthesis of N-(3-(5-((1-(11-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazin-1-yl)-11-oxoundecyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (24)



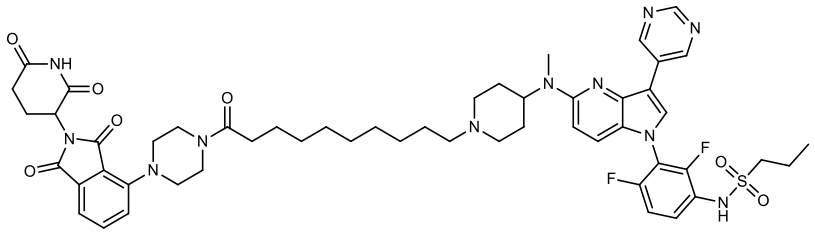
Scheme 12. Reagents and conditions: i) dioxane, DIPEA, 100-110 ^{o}C; ii) DCM, TFA, RT; iii) **22**, HATU, DIPEA, DMF, RT.

Step 1: tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazine-1-carboxylate (67)



A procedure similar to that used for intermediate **31** using *tert*-butyl piperazine-1-carboxylate (75 mg, 0.401 mmol) and **30** (101 mg, 0.365 mmol) afforded crude product, which was purified by normal phase chromatography eluting with MeOH in DCM. Fractions with pure compound were collected and concentrated with a rotary evaporator to afford intermediate **67** (472 mg, 70%) as a bright yellow powder (110 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.64 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.46 (dd, *J* = 7.2, 0.8 Hz, 1H), 7.19 (dd, *J* = 8.4, 0.8 Hz, 1H), 4.99 (dd, *J* = 12.3, 5.3 Hz, 1H), 3.68 (m, 4H), 3.31 (m, 4H), 2.96 – 2.68 (m, 3H), 2.15 (m, 1H), 1.51 (s, 9H). LCMS (ES^+): *m/z* 443.1 $[M+1]^+$.

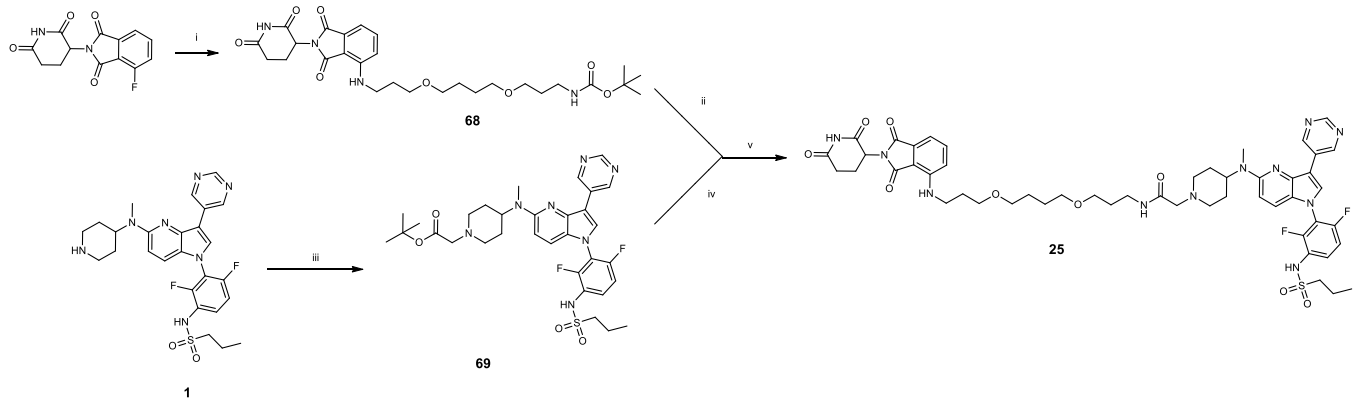
Step 2: N-(3-(5-((1-(11-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)piperazin-1-yl)-11-oxoundecyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (24)



67 (25 mg, 0.05 mmol) was dissolved in a mixture of TFA (1 mL) and DCM (1 mL). The reaction mixture was stirred for 1 h at RT. After the reaction, the solvent was evaporated and crude product was dried under high vacuum overnight. TFA salt was obtained in a quantitative yield (19 mg, 100%) and used in the next step without any further purification. A portion of **63** (22 mg, 0.05 mmol) was dissolved in DMF (2 mL), then HATU (18 mg, 0.04 mmol) was added at RT. The mixture was stirring during 15 min before DIPEA (16 mg, 0.12 mmol) was added and the mixture was stirred for another 10 min. 2-(2,6-dioxopiperidin-3-yl)-4-(piperazin-1-yl)isoindoline-1,3-dione trifluoroacetate (19 mg, 0.04 mmol) was dissolved in 1 mL of DMF and added to the reaction mixture. After stirring overnight at RT, the reaction mixture was evaporated onto Celite and purified by normal phase silica gel, eluting with EtOAc-MeOH (0% to 100% of EtOAc). The desired fractions were collected, concentrated and dried to afford the desired compound **24** as a yellow solid (7 mg, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 2H), 9.14 (s, 1H), 8.65 (s, 1H), 7.74 – 7.61

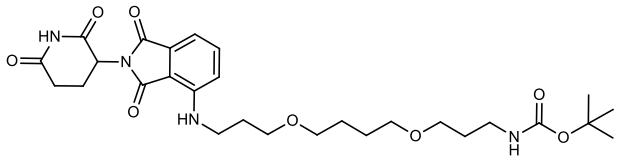
(m, 3H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 1.9 Hz, 1H), 7.22 – 7.15 (m, 2H), 6.60 (d, *J* = 9.2 Hz, 1H), 5.04 – 4.82 (m, 2H), 4.01 – 3.71 (m, 5H), 3.50 (m, 3H), 3.33 (m, 4H), 3.22 – 3.14 (m, 2H), 2.99 (s, 1H), 2.97 (s, 3H), 2.92 – 2.70 (m, 3H), 2.65 (s, 1H), 2.47 – 2.38 (m, 2H), 2.29 (m, 1H), 2.18 – 2.11 (m, 1H), 1.95 (m, 4H), 1.70 (m, 1H), 1.35 (s, 14H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.76, 171.99, 171.15, 168.31, 166.67, 164.79, 156.09, 155.69, 153.94, 150.11, 141.48, 135.83, 133.49, 132.96, 123.38, 122.78, 118.01, 116.36, 112.93, 112.79, 104.22, 77.34, 77.02, 76.70, 54.83, 52.73, 49.28, 45.79, 35.17, 33.31, 31.48, 30.84, 29.98, 29.70, 29.29, 29.13, 29.02, 27.00, 25.32, 24.52, 22.71, 17.33, 12.93. HRMS (*m/z*): $[M]^+$ calcd. for $C_{53}H_{64}F_2N_{11}O_7S$, 1036.4673; found, 1036.4665.

Synthesis of 2-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-N-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)acetamide (25)



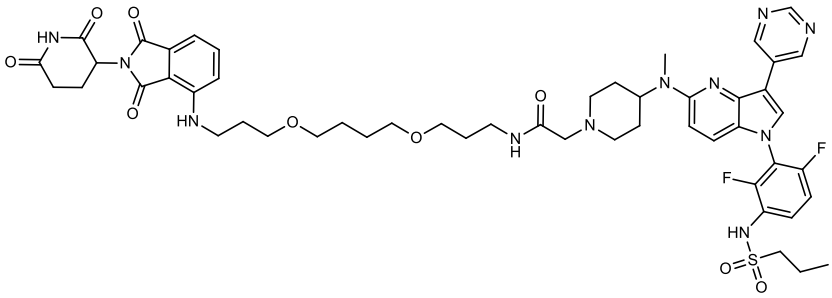
Scheme 13. Reagents and conditions: i) *tert*-butyl (3-(4-(3-aminopropoxy)-butoxy)propyl)carbamate, DMF, DIPEA, 100 ^{o}C; ii) DCM, TFA, RT; iii) THF, *tert*-butyl bromoacetate, DIPEA, reflux, iv) DCM, TFA, RT, v) DMF, HATU, DIPEA, RT.

Step 1: tert-Butyl (3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-propoxy)butoxy)propyl)carbamate (68)



A mixture of *tert*-butyl (3-(4-(3-aminopropoxy)butoxy)propyl)carbamate (60.6 mg, 0.199 mmol), DIPEA (70.2 mg, 0.543 mmol) and **30** (50 mg, 0.181 mmol) in DMF (4 mL) was stirred at 90 °C overnight. The reaction mixture was evaporated onto Celite and purified with normal phase, eluting with hexane/isopropanol. The desired fractions were collected, concentrated and dried on the rotavap to afford **68** (90 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): 7.42 (t, *J* = 7.8 Hz, 1H), 7.19 (s, 1H), 7.02 (d, *J* = 7.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.38 (br s, 1H),4.84 (br dd, *J* = 5.1, 11.4 Hz, 2H), 3.49 - 3.31 (m, 11H), 3.22 - 3.07 (m, 2H), 2.85 - 2.62 (m, 3H), 2.14 - 1.95 (m, 1H), 1.85 (br t, *J* = 6.0 Hz, 3H), 1.74- 1.63 (m, 3H), 1.58 (br s, 5H), 1.49 (br s, 1H), 1.37 (br s, 9H). LCMS (ES$^+$): *m/z* 561.3 $[M+1]^+$.

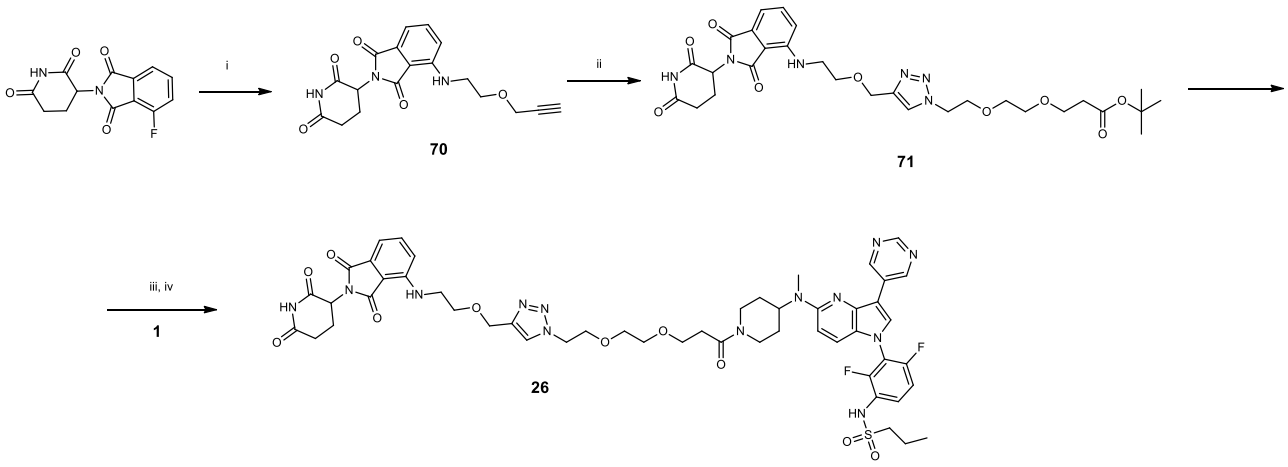
Step 2. 2-(4-((1-(2,6-Difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)piperidin-1-yl)-N-(3-(4-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propoxy)butoxy)propyl)acetamide (25)



tert-Butyl bromoacetate (11.88 mg, 0.061 mmol) was dissolved in THF (7 mL) and the solution treated by dropwise addition with an equimolar mixture of **1** (30 mg, 0.055 mmol) and DIPEA (10.74 mg, 0.083 mmol) at such a rate as to maintain a gentle reflux of the solvent. At the end of the addition of the amine, the reaction mixture was refluxed for 2 h. After this time the mixture was cooled to room temperature and then to 0 °C. The suspension was then isolated by suction filtration and the filtrate evaporated down to dryness. The semisolid residue was then taken up in EtOAc (10 mL) and the extract washed with water (10 mL) and then dried over Na_2SO_4. Removal of the solvent under reduced pressure gave the product **69** (20 mg, 55%). LCMS (ES$^+$): *m/z* 656.3 $[M+1]^+$, which was used in the next step without any further purification. Solution of **69** (20 mg, 0.03 mmol) in 1 mL TFA/DCM (1:1) was stirred for 1 h at RT. After the reaction, the solvent was

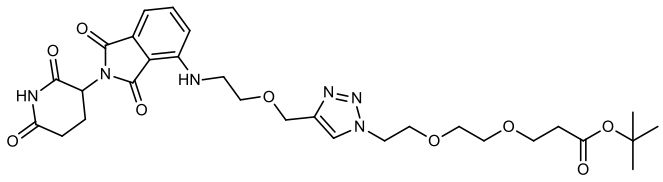
evaporated and crude product was dried under high vacuum overnight. 2-(4-((1-(2,6-difluoro-3-(propylsulfonamido)phenyl)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-5-yl)(methyl)amino)-piperidin-1-yl)acetic acid was obtained in a quantitative yield (19 mg, 0.03 mmol) and used in the next step without any further purification. Obtained acid was dissolved in DMF (1 mL), then HATU (18 mg, 0.046 mmol) was added at RT. The mixture was stirring during 5 min before DIPEA (28 mg, 0.2 mmol) was added and the mixture was stirred for another 10 min. 4-((3-(4-(3-aminopropoxy)butoxy)propyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione trifluoroacetate (21 mg, 0.04 mmol) was dissolved in 1 mL of DMF and added to the reaction mixture. After stirring overnight at RT, the reaction mixture was evaporated onto Celite and purified by normal phase silica gel, eluting with DCM-MeOH. The desired fractions were collected, concentrated and dried to afford the desired compound **25** as a dark yellow solid (10 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.59 (s, 2H), 9.15 (s, 1H), 8.70 (s, 1H), 7.74 – 7.66 (m, 2H), 7.58 (s, 1H), 7.46 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.20 (td, *J* = 9.2, 2.1 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 1H), 6.62 (d, *J* = 9.2 Hz, 1H), 6.46 (s, 1H), 4.94 (dd, *J* = 11.9, 5.3 Hz, 1H), 4.46 (s, 1H), 3.59 – 3.42 (m, 12H), 3.38 (q, *J* = 6.5 Hz, 2H), 3.23 – 3.13 (m, 4H), 3.05 (s, 3H), 2.94 – 2.71 (m, 3H), 2.52 (s, 1H), 2.21 – 1.80 (m, 12H), 1.70 (p, *J* = 3.2 Hz, 4H), 1.11 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3): δ 172.92, 171.19, 169.50, 168.23, 156.16, 155.87, 155.28, 153.93, 141.63, 128.50, 126.91, 123.54, 123.01, 122.75, 120.73, 116.56, 112.96, 111.55, 105.57, 71.03, 70.94, 68.86, 68.47, 54.63, 54.11, 48.94, 43.04, 40.51, 40.06, 39.00, 31.53, 31.44, 31.34, 29.47, 26.49, 26.47, 23.03, 22.85, 17.31, 12.91. HRMS (*m/z*): $[M]^+$ calcd. for $C_{51}H_{62}F_2N_{11}O_9S$, 1042.4415; found, 1042.4419.

Synthesis of N-(3-(5-((1-(3-(2-(2-(4-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)propanoyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (26)



Scheme 14. Reagents and conditions: i) 2-(prop-2-yn-1-yloxy)ethanamine**,** dioxane, DIPEA, 100 ^{o}C; ii) DCM, TFA, RT; iii) DMF, DIPEA, HATU, RT.

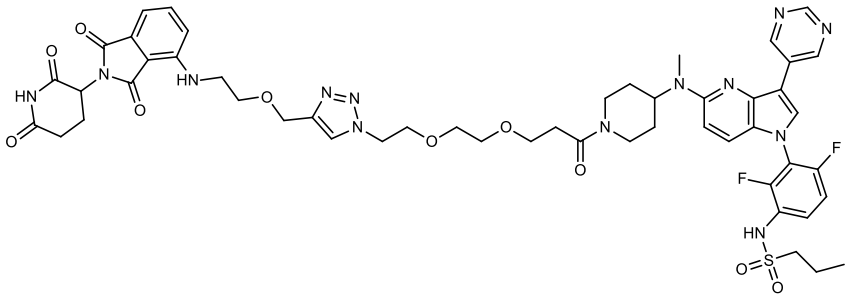
Step 1: tert-butyl 3-(2-(2-(4-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)propanoate (71)



Into a 3 mL vial was weighed **70,** (synthesized using the synthetic procedures described previously[60]) (30 mg, 0.084 mmol), (+)-sodium L-ascorbate (6.69 mg, 0.034 mmol), $CuSO_4$ (6.00 mg, 0.034 mmol) and azido-PEG2-t-butyl ester (21.89 mg, 0.084 mmol). The reaction mixture was treated with THF (1 mL) and 3−4 drops of water, and then the headspace of the vial was purged briefly with argon and stirred at RT for 16 h. LCMS analysis of the crude reaction mixture indicated clean conversion to the desired product. The reaction mixture was transferred to a 5 g silica gel

sample loader using a pipette and purified by silica gel chromatography, using a gradient of 0−100% (20% MeOH in DCM) in DCM, affording the 52 mg of desired **71** (0.080 mmol, 95%) after drying overnight in a vacuum oven at 45 °C. The resulting material was slurried with DCM/TFA and stirred for 1 h. The solvents were evaporated to afford pure 3-(2-(2-(4-((2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)-propanoic acid (52 mg, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (s, 1H), 7.92 (s, 1H), 7.51 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.13 (d, *J* = 7.1 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.49 (s, 1H), 4.95 (q, *J* = 5.8, 5.2 Hz, 1H), 4.74 (s, 1H), 4.65 – 4.43 (m, 1H), 4.04 – 3.25 (m, 10H), 3.01 – 2.71 (m, 4H), 2.51 (t, *J* = 6.4 Hz, 2H), 2.17 (s, 4H), 1.46 (d, *J* = 3.8 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.22, 170.83, 169.43, 168.54, 167.56, 146.80, 136.11, 132.49, 117.63, 111.78, 110.34, 80.38, 70.39, 70.16, 69.37, 68.05, 66.85, 64.72, 58.47, 50.15, 48.88, 42.29, 36.13, 30.88, 29.68, 28.08, 22.96. LCMS (ES^+): *m/z* 483.19 $[M + Na]^+$.

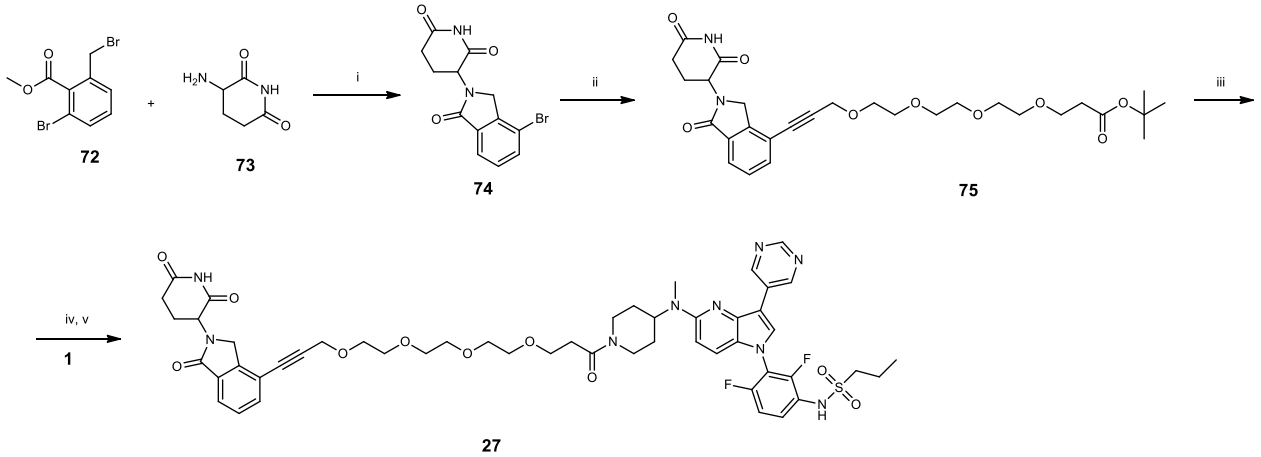
Step 2: N-(3-(5-((1-(3-(2-(2-(4-((2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)propanoyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (26)



3-(2-(2-(4-((2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)propanoic acid (37 mg, 0.066 mmol) was dissolved in 0.5 mL DMF, and HATU (26.4 mg, 0.070 mmol) was added at RT. The mixture was stirring during 10 min, DIPEA (25.7 mg, 0.199 mmol) was added and the mixture was stirred another 10 min. **1** (43.4 mg, 0.066 mmol) was dissolved in 1 mL of DMF. The reaction mixture was stirred overnight at RT. Water (1 mL) was added to the reaction mixture and extracted with EtOAc. The organic extract was evaporated with Celite and purified with RP-MPLC, eluting with Water/ACN. Fractions with pure

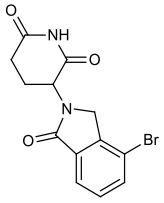
compound were collected and evaporated to obtain 10 mg of the product **26** (10 mg, 13.25 %). ^{1}H NMR (500 MHz, DMSO-d6): δ 11.09 (s, 1H), 9.66 (s, 2H), 8.99 (s, 1H), 8.36 (s, 1H), 8.06 (s,1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.43 (dt, *J* = 9.6, 4.7 Hz, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 7.15 – 6.98 (m, 2H), 6.79 (d, *J* = 9.2 Hz, 1H), 6.58 (t, *J* = 5.9 Hz, 1H), 6.28 (s, 1H), 5.04 (dd, *J* = 12.8, 5.4 Hz, 1H), 4.49 (m, 4H), 4.51 (t, *J* = 5.2 Hz, 2H), 4.04 (d, *J* = 13.4 Hz, 1H), 3.81 (m, 2H), 3.62 (dd, *J* = 14.0, 6.4 Hz, 4H), 3.34 (m, 10H), 2.82 (m, 6H), 2.60 (s, 2H), 2.02 (m, 1H), 1.78 – 1.62 (m, 5H), 1.56 (m, 1H), 0.93 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.60, 169.93, 169.64, 167.87, 156.07, 155.63, 153.87, 153.48, 148.89, 142.34, 142.10, 132.77, 131.49, 131.06, 128.57, 127.11, 124.26, 122.93, 122.80, 120.89, 119.83, 116.25, 116.18, 112.66, 112.46, 110.97, 104.09, 91.84, 82.44, 77.40, 77.28, 77.08, 76.76, 70.39, 70.35, 70.33, 69.10, 67.50, 59.20, 54.74, 53.56, 51.92, 46.65, 45.75, 41.80, 33.57, 31.58, 30.56, 29.47, 28.94, 23.31, 17.25, 12.92. HRMS (*m/z*): $[M]^+$ calcd. for $C_{51}H_{58}F_2N_{13}O_{10}S$, 1082.4113; found, 1082.4107.

Synthesis of N-(3-(5-((1-(16-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4,7,10,13-tetraoxahexadec-15-yn-1-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (27)



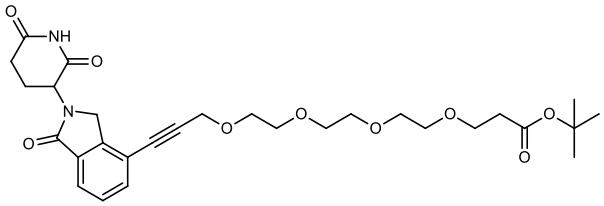
Scheme 15. Reagents and conditions: i) ACN, TEA, reflux; ii) DMF, CuI, $Pd(Ph_3P)Cl_2$, TEA, propargyl-PEG4-t-butyl ester; iii) DCM, TFA, RT; iv) DMF, DIPEA, HATU, RT.

Step 1. 3-(4-Bromo-1-oxoisoindolin-2-yl)piperidine-2,6-dione (74)



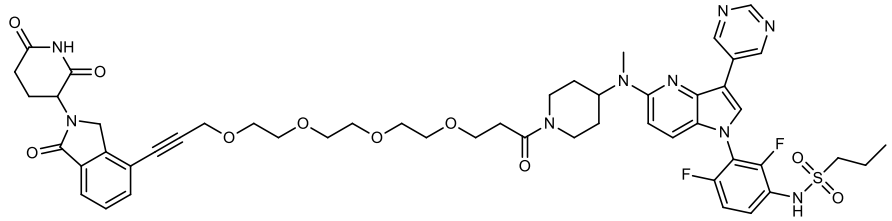
A solution of **72** (970 mg, 3.16 mmol), **73** (667 mg, 4.06 mmol) and TEA (0.62 mL, 4.4 mmol) in 10 mL of ACN was heated at reflux overnight. The mixture was cooled to RT and concentrated under vacuum. EtOAc (10 mL) and water (10 mL) were added to the concentrated residue. After the filtration the solid was collected and purified by normal phase chromatography (DCM/ACN) to yield the title compound **74** (510 mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.02 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.51 – 4.23 (m, 2H), 2.93 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.63 (ddd, *J* = 17.3, 4.5, 2.3 Hz, 1H), 2.52 – 2.33 (m, 1H), 2.04 (dtd, *J* = 12.6, 5.2, 2.3 Hz, 1H).

Step 2. tert-Butyl 16-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4,7,10,13-tetraoxahexadec-15-yn-1-oate (75)



74 (140 mg, 0.434 mmol) in 3 mL DMF was purged with N_2 for 5 min. CuI (17mg, 0.089 mmol), $Pd(Ph_3P)Cl_2$ (30 mg, 0.042 mmol) and *tert*-butyl 4,7,10,13-tetraoxahexadec-15-yn-1-oate (150 mg, 0.474 mmol) in 0.6 mL of TEA were added to the reaction vial and purged with N_2 again. The vial was sealed and the reaction was stirred at 80 °C overnight. Then the reaction mixture was evaporated onto Celite and purified by reverse phase chromatography, eluting with water/ACN. The desired fractions were collected, concentrated and dried under vacuum and repurified by normal phase chromatography (DCM/ACN) to afford the desired compound **75** as a yellowish powder (150 mg, 58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.57 – 7.50 (m, 2H), 7.45 – 7.38 (m, 1H), 5.22 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.55 (s, 2H), 4.51 – 4.25 (m, 2H), 3.93 – 3.83 (m, 2H), 3.76 – 3.57 (m, 10H), 2.92 – 2.79 (m, 2H), 2.52 (t, *J* = 6.6 Hz, 2H), 2.38 (qd, *J* = 13.0, 5.3 Hz, 1H), 2.26 – 2.16 (m, 1H), 1.46 (s, 9H). LCMS (ES^+): *m/z* 557.2 $[M+1]^+$.

Step 3. N-(3-(5-((1-(16-(2-(2,6-Dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4,7,10,13-tetraoxahexadec-15-yn-1-oyl)piperidin-4-yl)(methyl)amino)-3-(pyrimidin-5-yl)-1H-pyrrolo[3,2-b]pyridin-1-yl)-2,4-difluorophenyl)propane-1-sulfonamide (27)



75 (45 mg, 0.08 mmol) was dissolved in a mixture of TFA (1.5 mL) and DCM (1.5 mL). The reaction mixture was stirred for 3 h at RT. After the reaction, the solvent was evaporated and crude product was dried under high vacuum overnight. 16-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4,7,10,13-tetraoxahexadec-15-yn-1-oic acid was obtained in a quantitative yield (40 mg, 100%) and used in the next step without any further purification. This material was then dissolved in DMF (4 mL), then HATU (33 mg, 0.091 mmol) was added at RT. The mixture was stirred for 10 min before DIPEA (30 mg, 0.23 mmol) was added and the mixture was stirred for another 10 min. **1** (43 mg, 0.065 mmol) was dissolved in 1 mL of DMF and added to the reaction mixture. After stirring overnight at RT, the reaction mixture was evaporated onto Celite and purified by reverse phase chromatography, eluting with Water/ACN with 0.1% formic acid. The title compound was obtained in a partially pure form as brown oil, which was repurified by normal phase chromatography eluting with MTBE/MeOH. The desired fractions were collected, concentrated and dried to afford the desired compound **27** as a yellowish powder (18 mg, 27%). ^{1}NMR (400 MHz, CDCl3): δ 9.56 (d, *J* = 1.3 Hz, 2H), 9.10 (s, 1H), 8.04 (s, 1H), 7.71 (s, 1H), 7.65 (td, *J* = 8.7, 5.1 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.39 (dd, *J* = 6.6, 1.9 Hz, 1H), 7.33 (dt, *J* = 9.1, 1.9 Hz, 1H), 7.15 (td, *J* = 9.2, 1.9 Hz, 1H), 6.60 (d, *J* = 9.3 Hz, 1H), 5.24 – 5.14 (m, 1H), 4.87 – 4.70 (m, 2H), 4.47 (s, 2H), 4.44 – 4.26 (m, 2H), 4.04 (d, *J* = 13.3 Hz, 1H), 3.81 (dd, *J* = 6.4, 3.9 Hz, 4H), 3.72 – 3.62 (m, 12H), 3.28 – 3.08 (m, 3H), 2.94 – 2.64 (m, 6H), 2.36 (qd, *J* = 12.3, 5.7 Hz, 1H), 2.19 (s, 1H), 1.96 – 1.61 (m, 5H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{19}F NMR (377 MHz, $CDCl_3$): δ -121.36 (s, 1F), -131.10 (s, 1F). ^{13}C NMR (101

MHz, $CDCl_3$): δ 171.60, 169.93, 169.64, 167.87, 156.07, 155.63, 153.87, 153.48, 148.89, 142.34, 142.10, 132.77, 131.49, 131.06, 128.57, 127.11, 124.26, 122.93-122.80 (d, *J* = 5.45 Hz), 120.89, 119.83, 116.25 - 116.18 (m), 112.66 - 112.46 (m), 110.97, 104.09, 91.84, 82.44, 77.40,77.28, 77.08, 76.76, 70.39, 70.35, 70.33, 69.10, 67.50, 59.20, 54.74, 53.56, 51.92, 46.65, 45.75, 41.80, 33.57, 31.58, 30.56, 29.47, 28.94, 23.31, 17.25, 12.92. HRMS (*m/z*): $[M]^+$ calcd. for $C_{51}H_{58}F_2N_9O_{10}S$, 1026.3990; found, 1026.3993.

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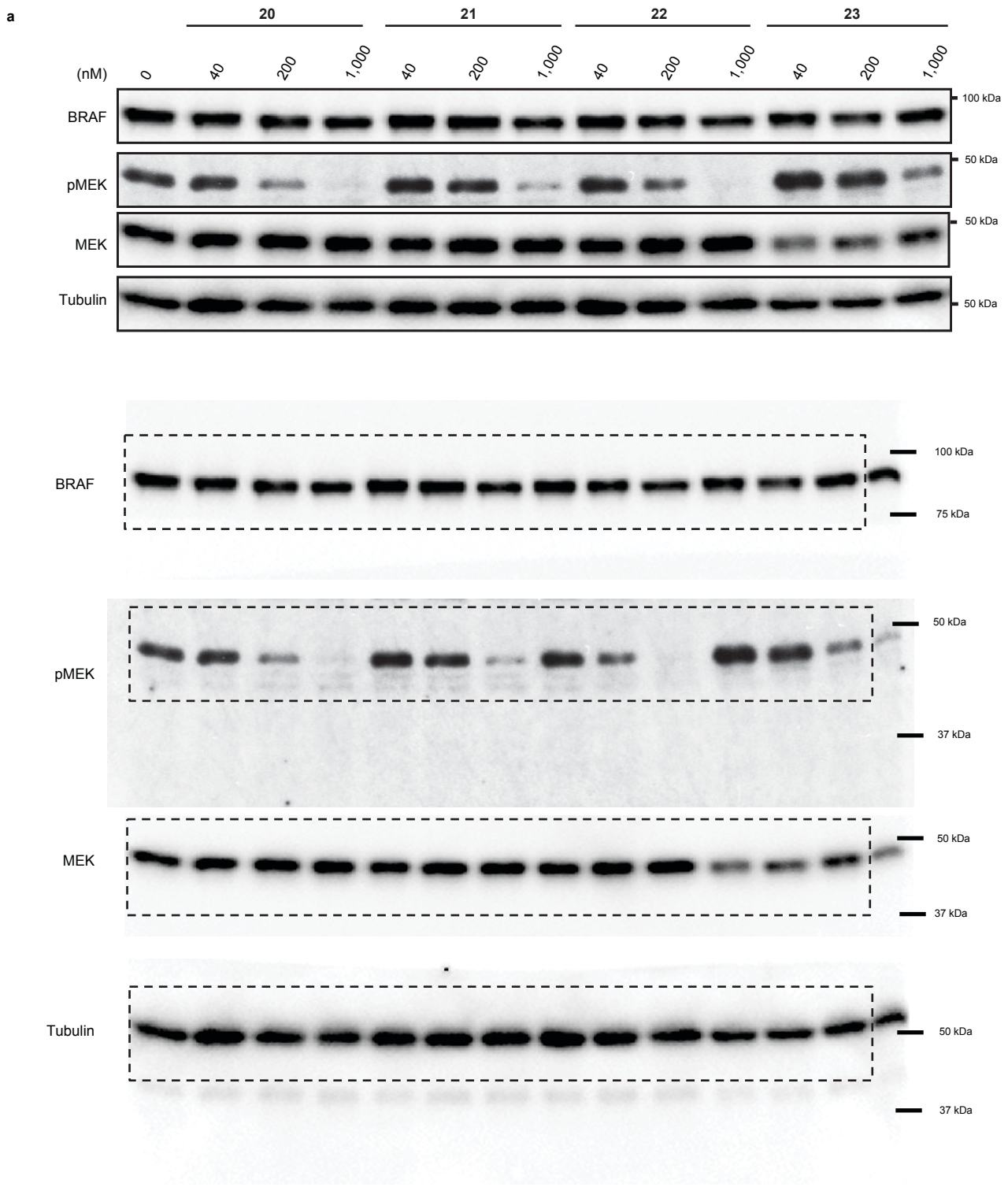

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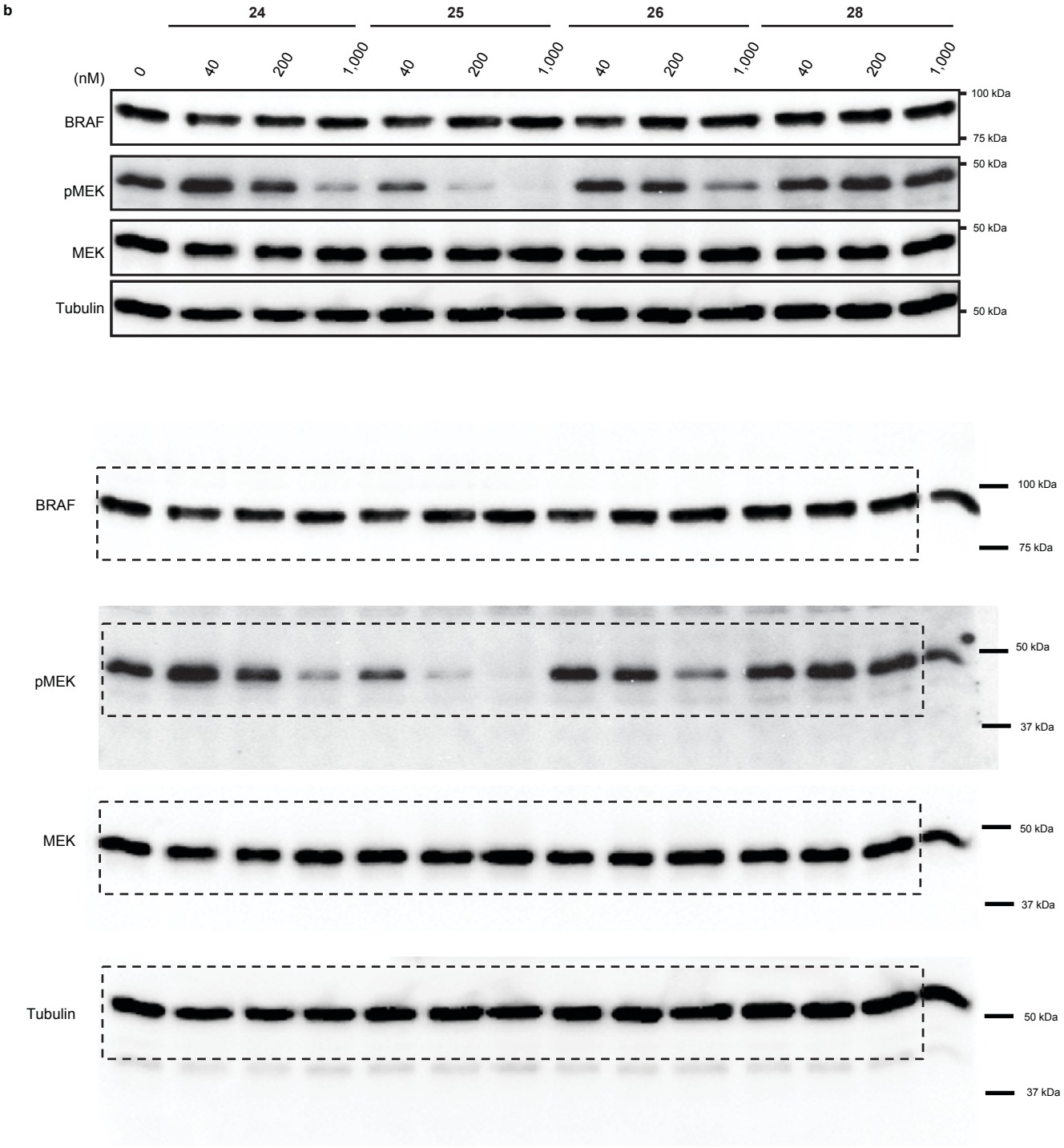

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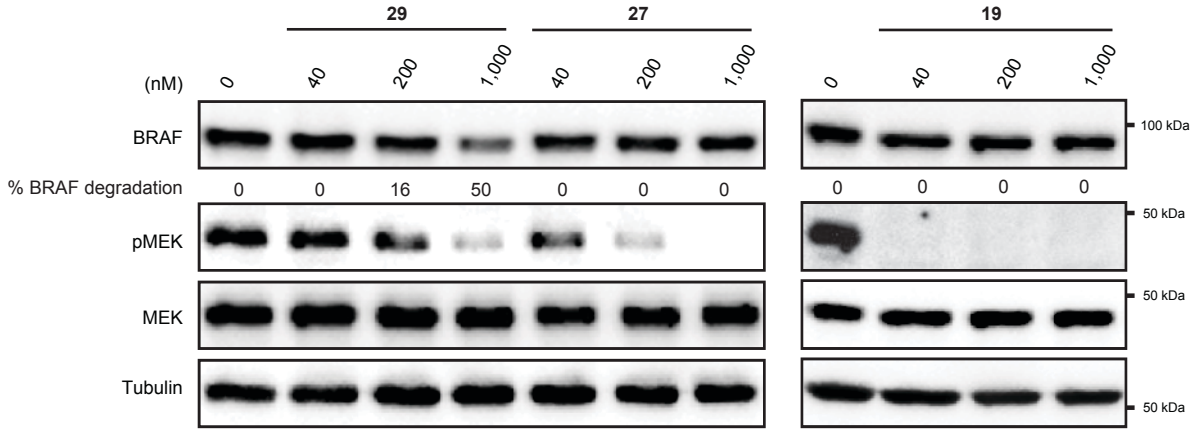

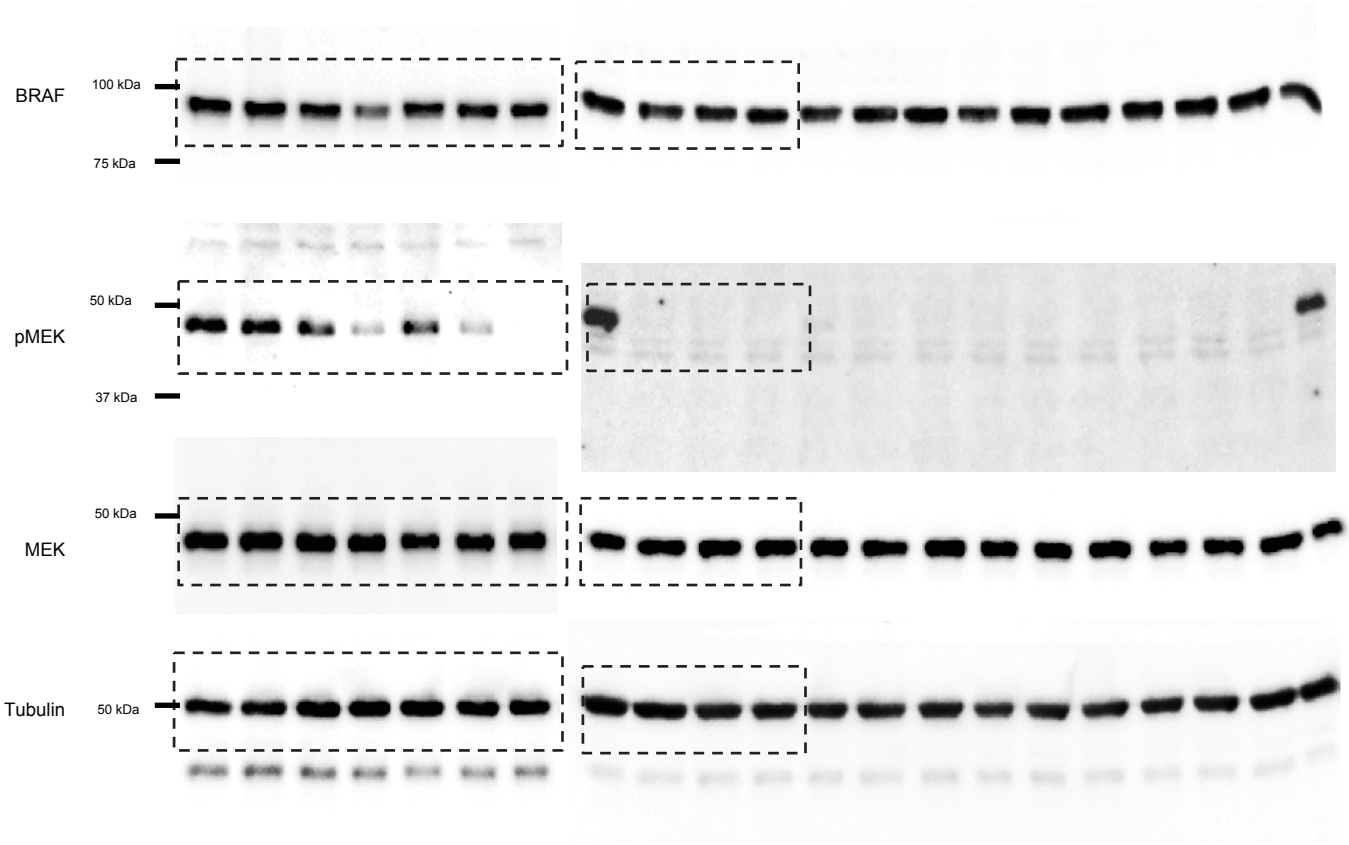

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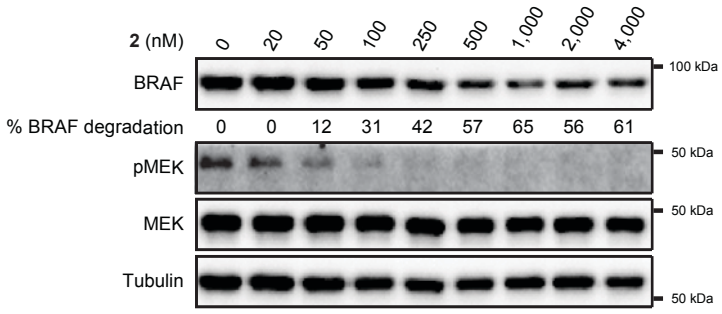

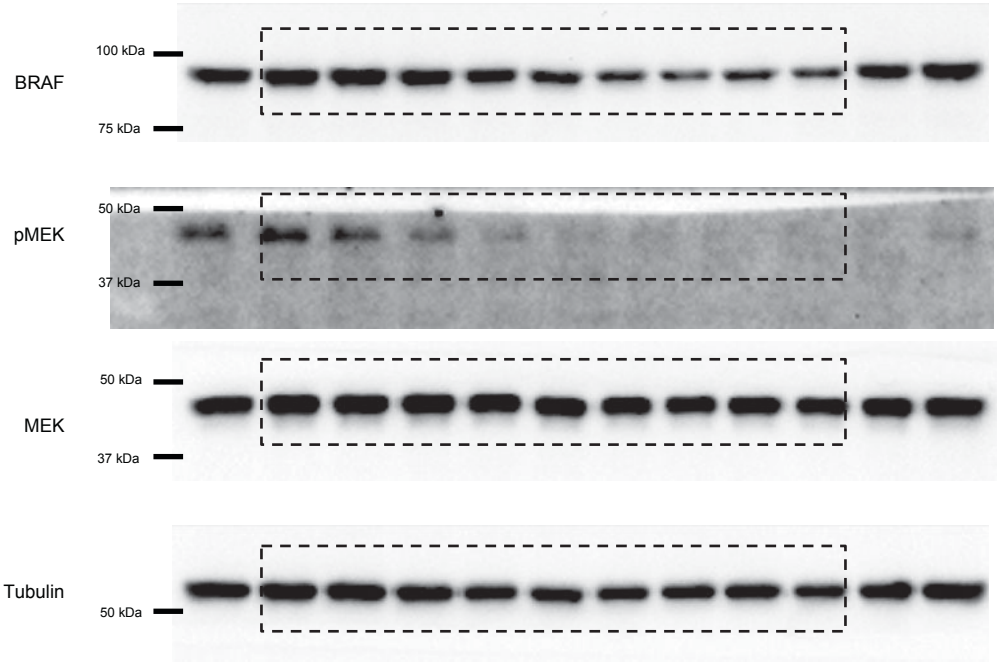

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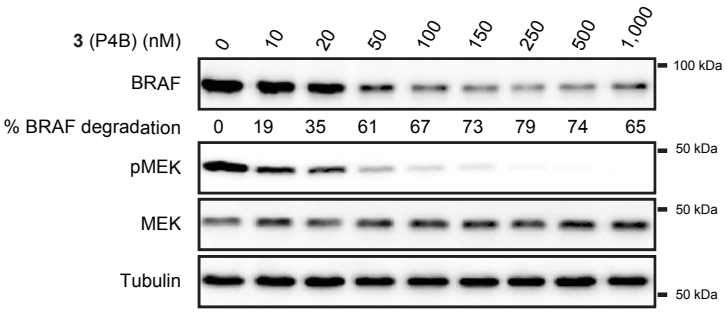

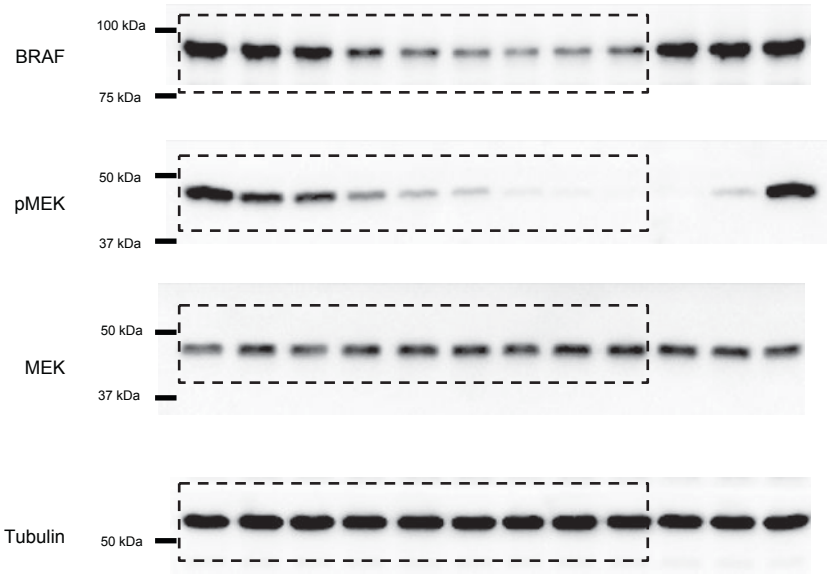

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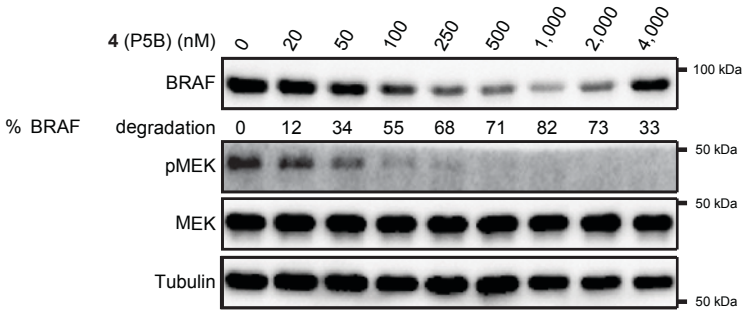

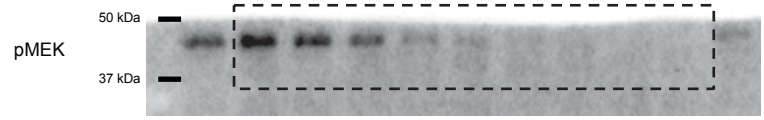

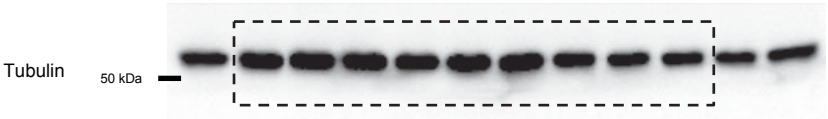

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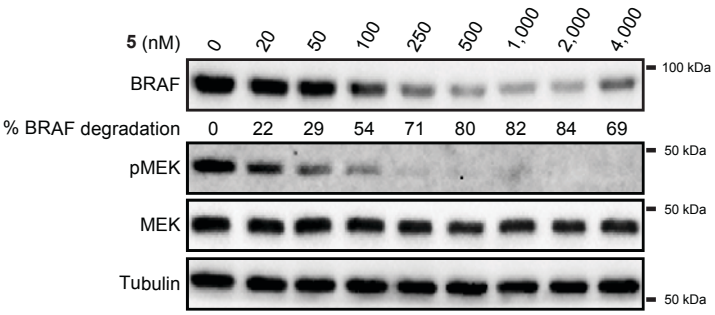

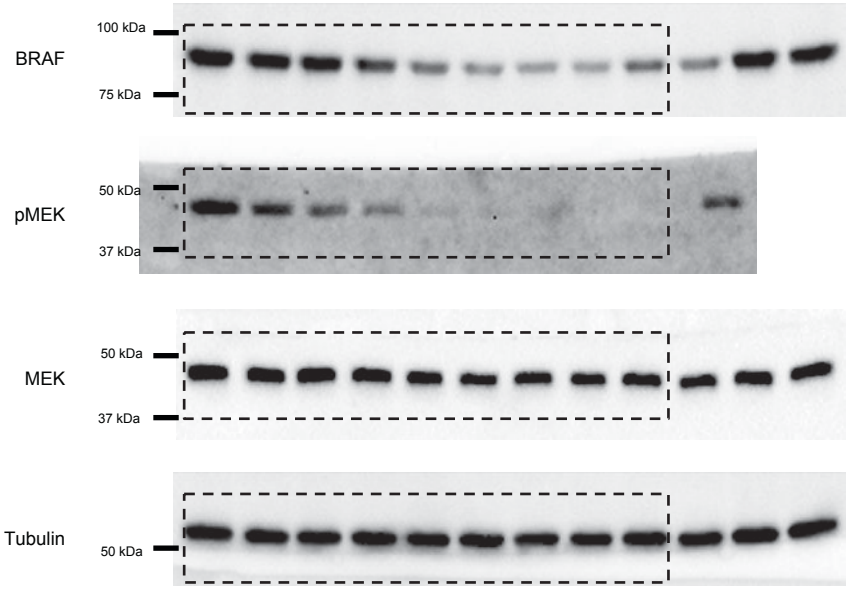

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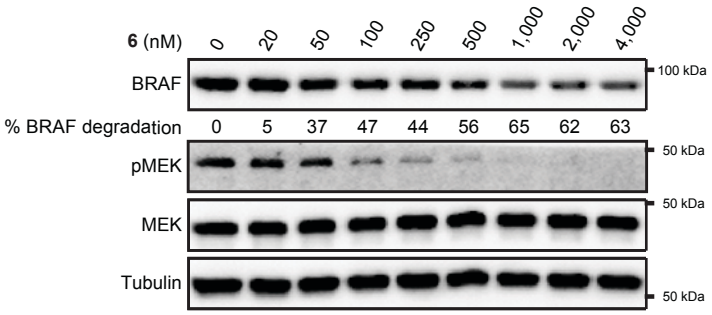

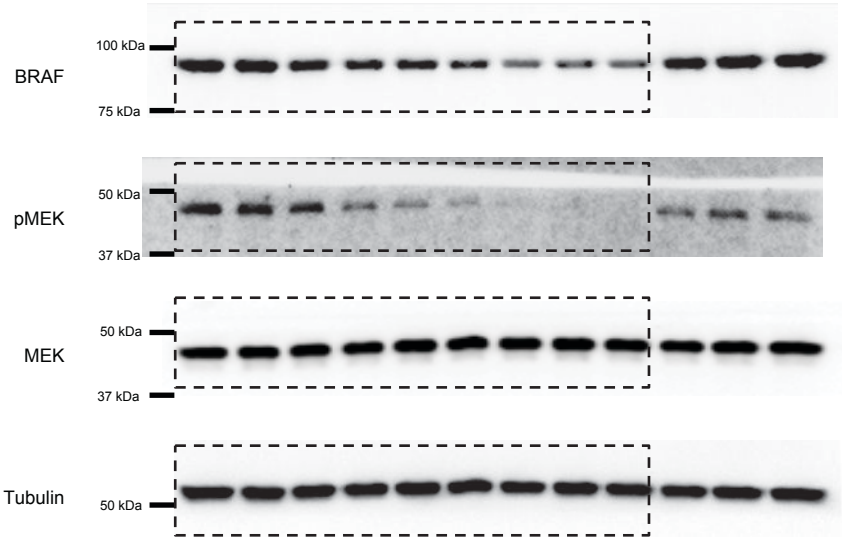

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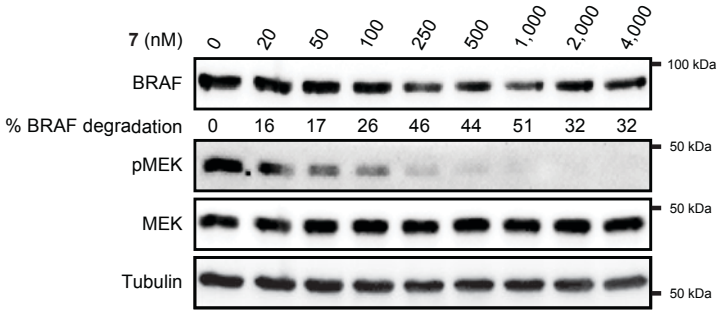

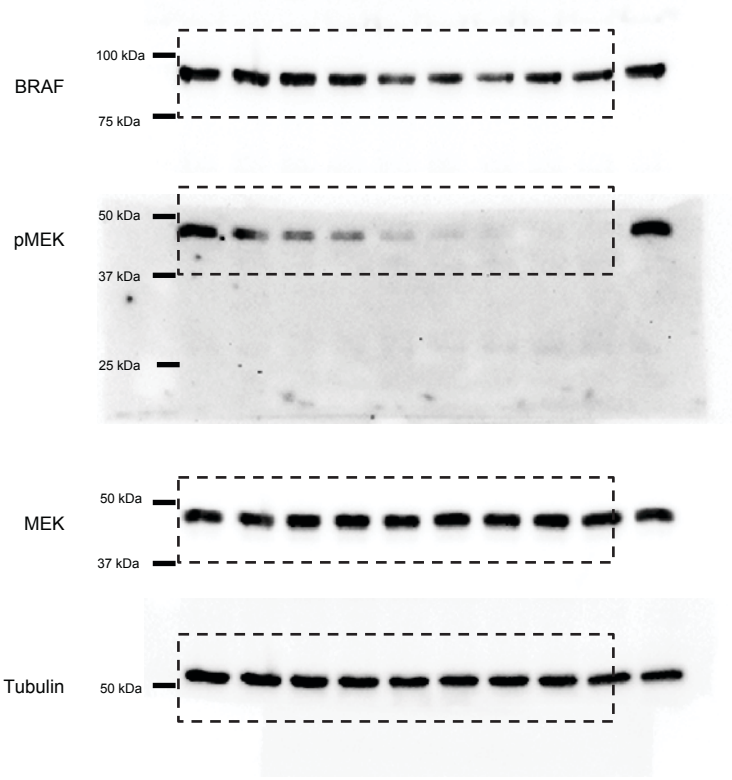

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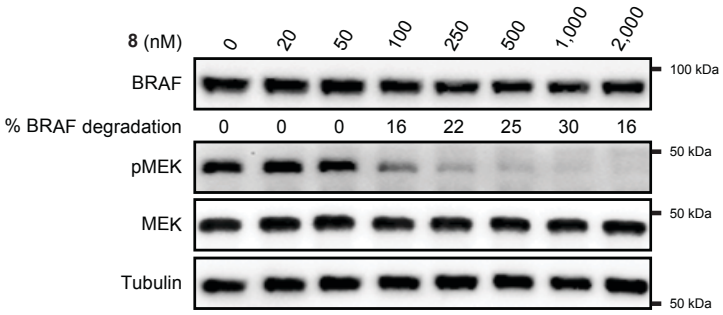

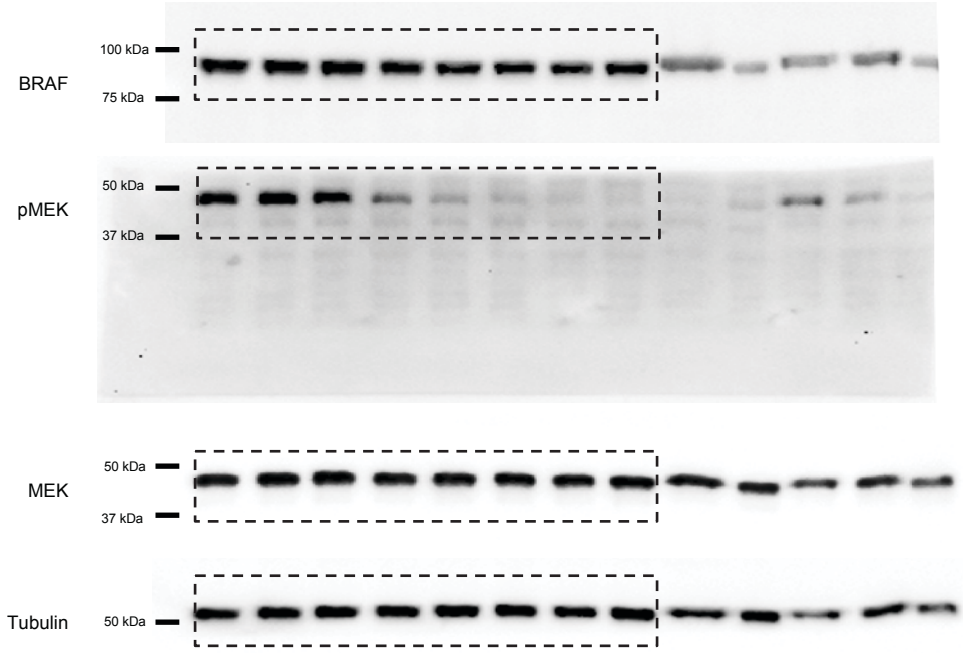

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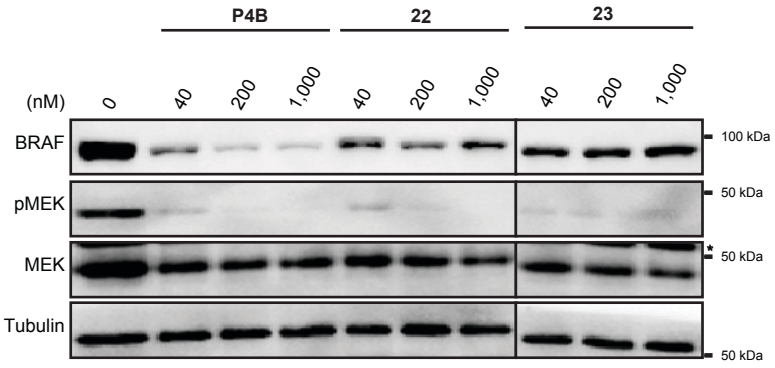

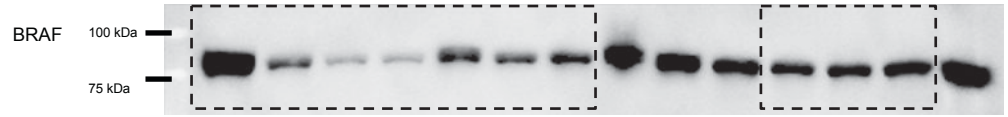

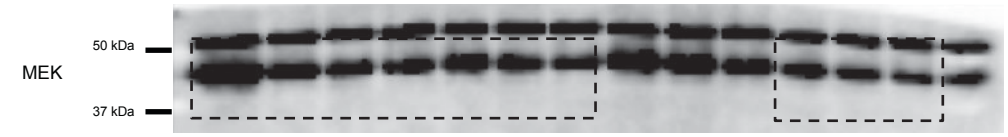

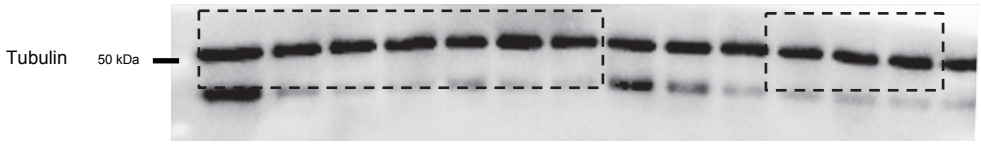

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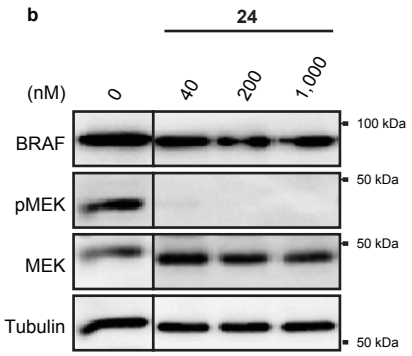

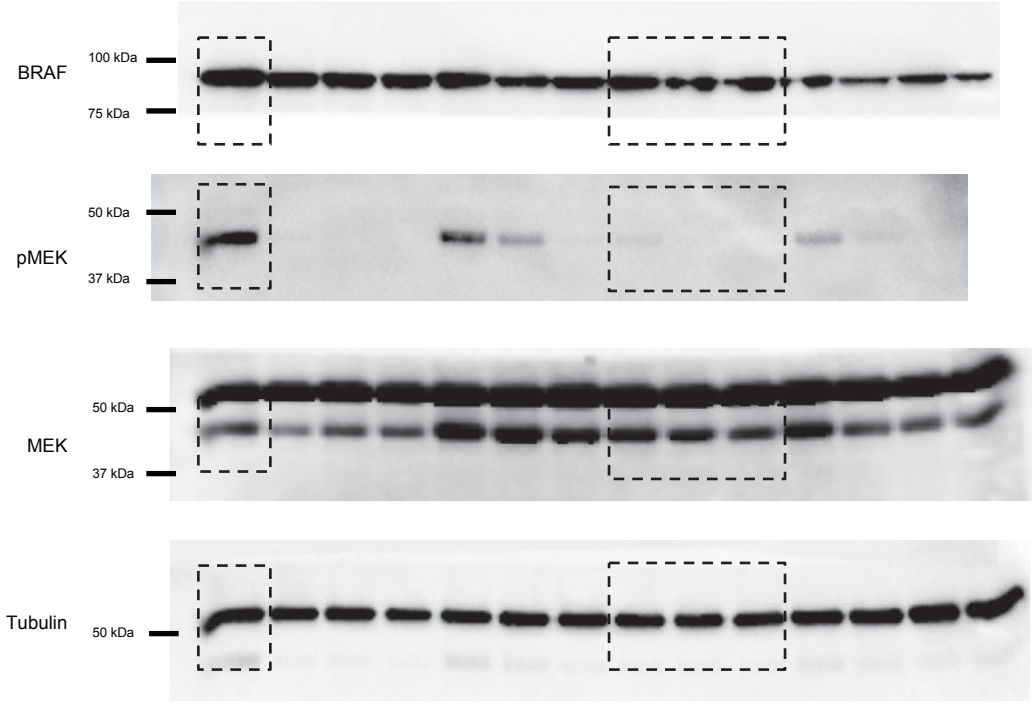

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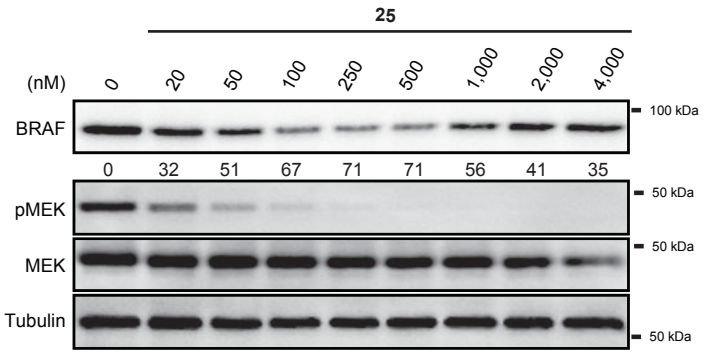

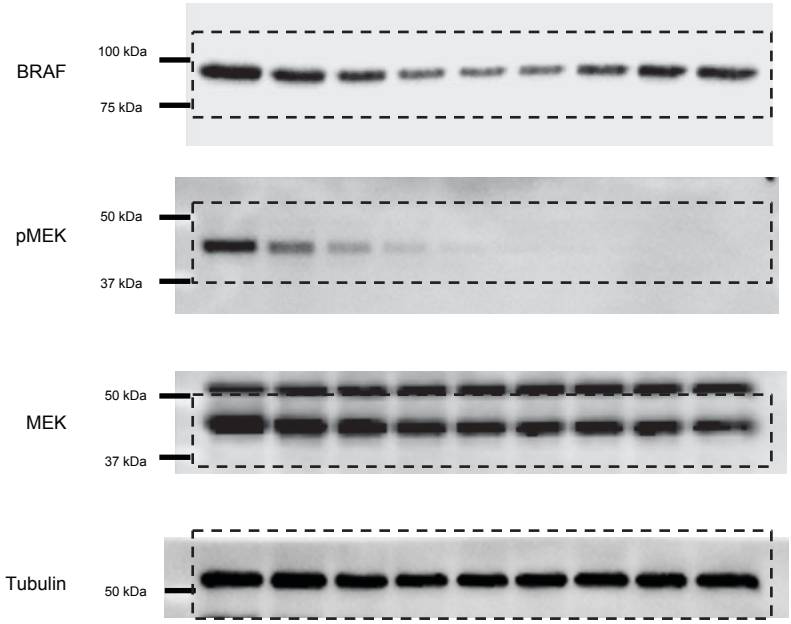

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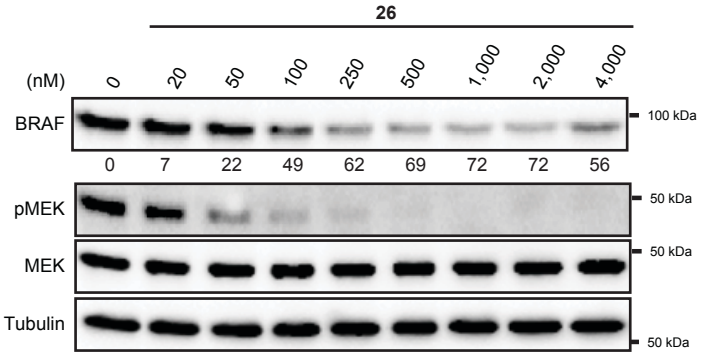

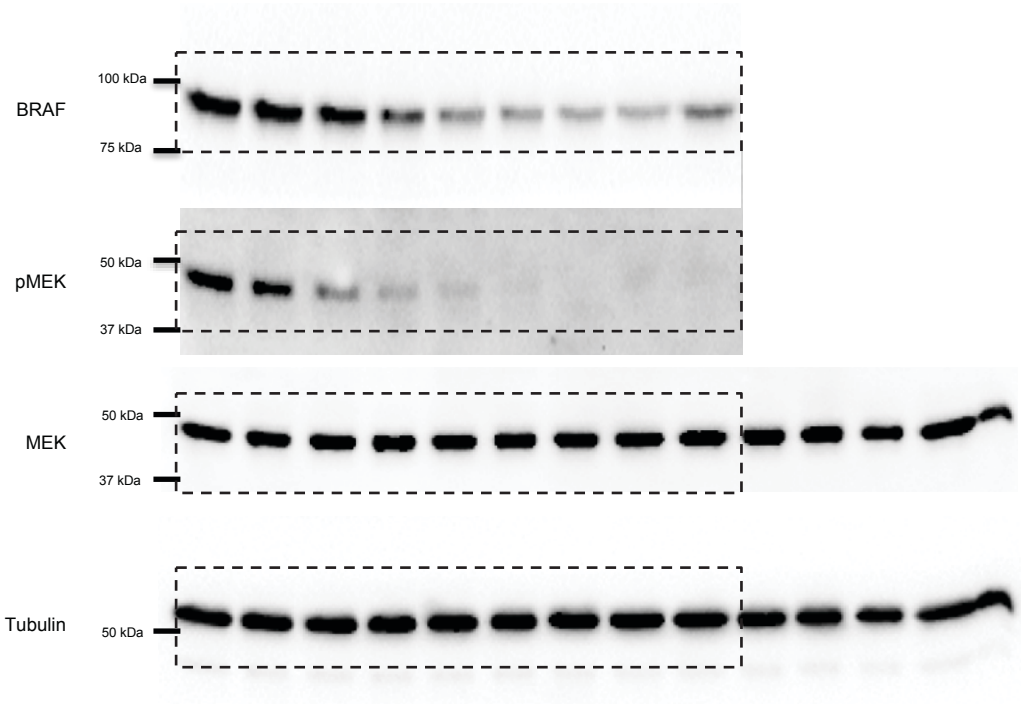

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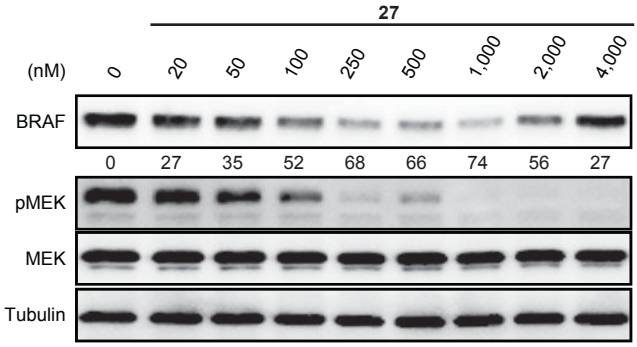

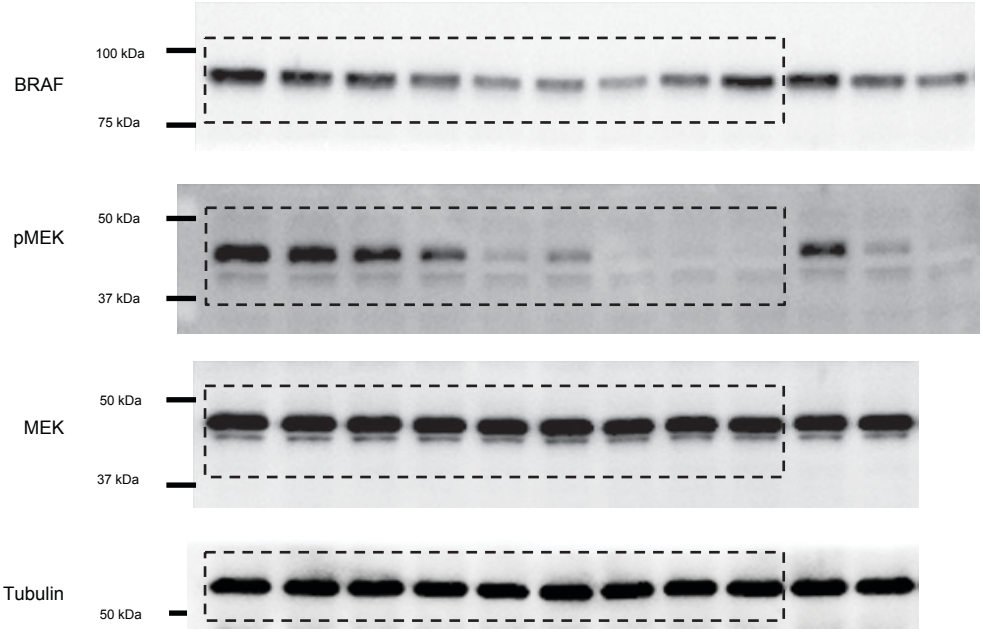

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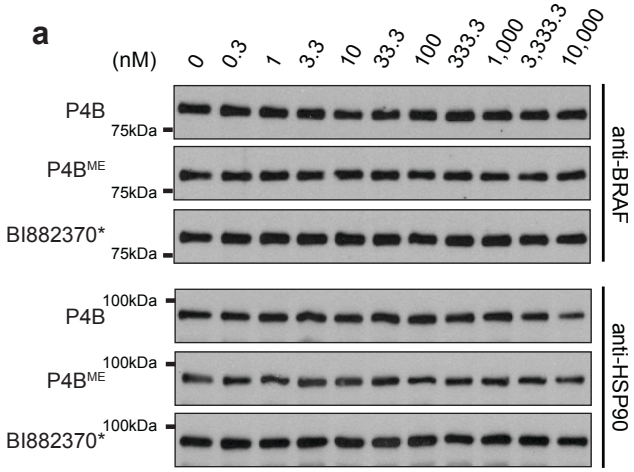

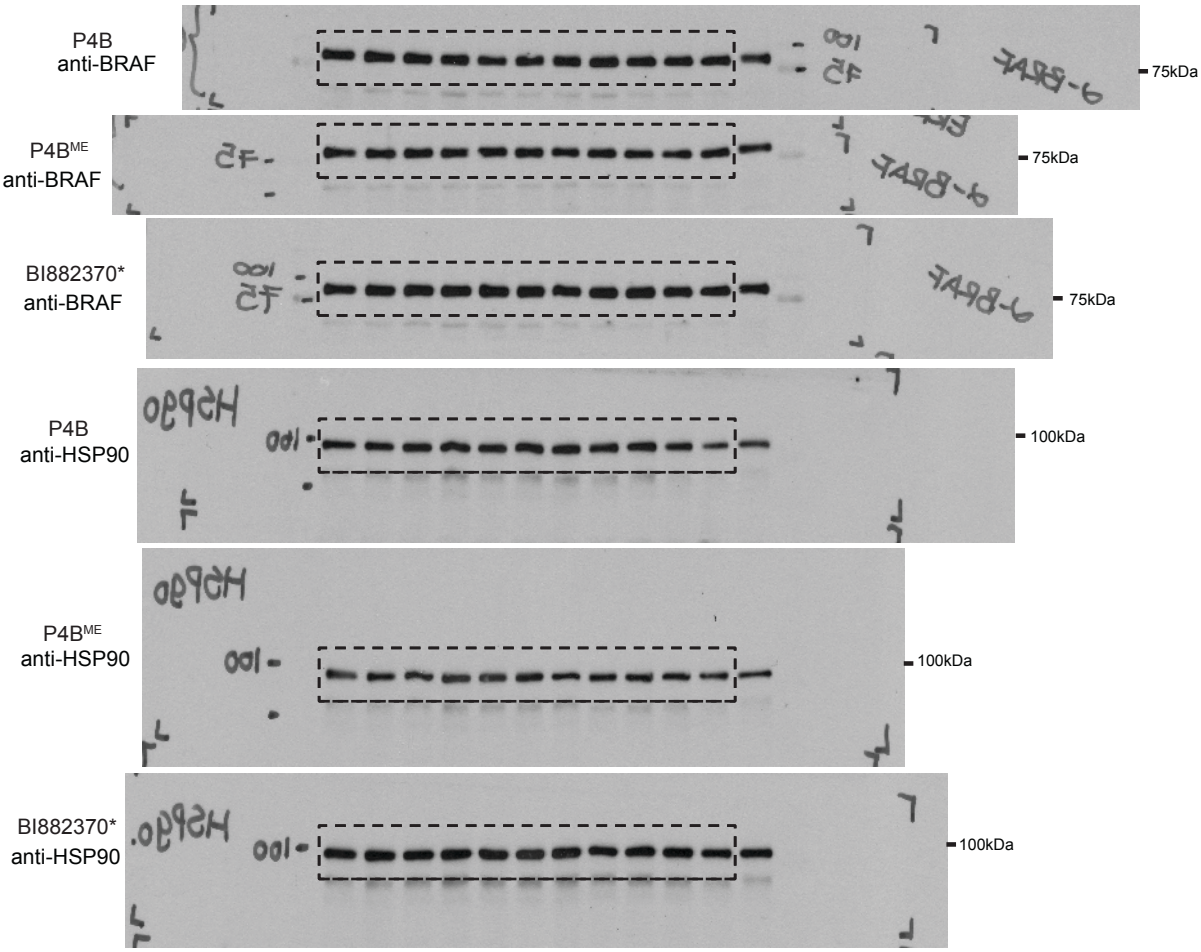

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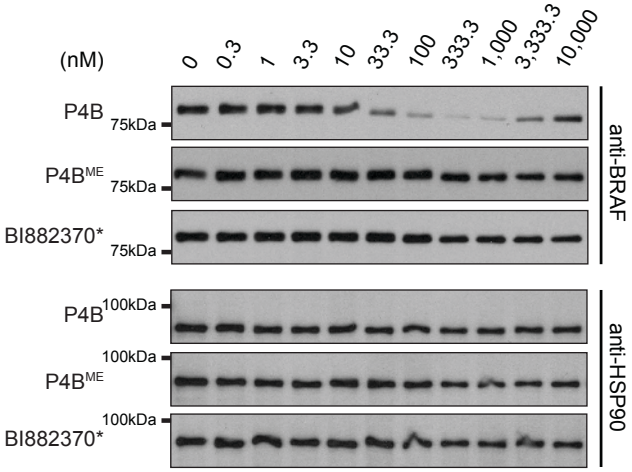

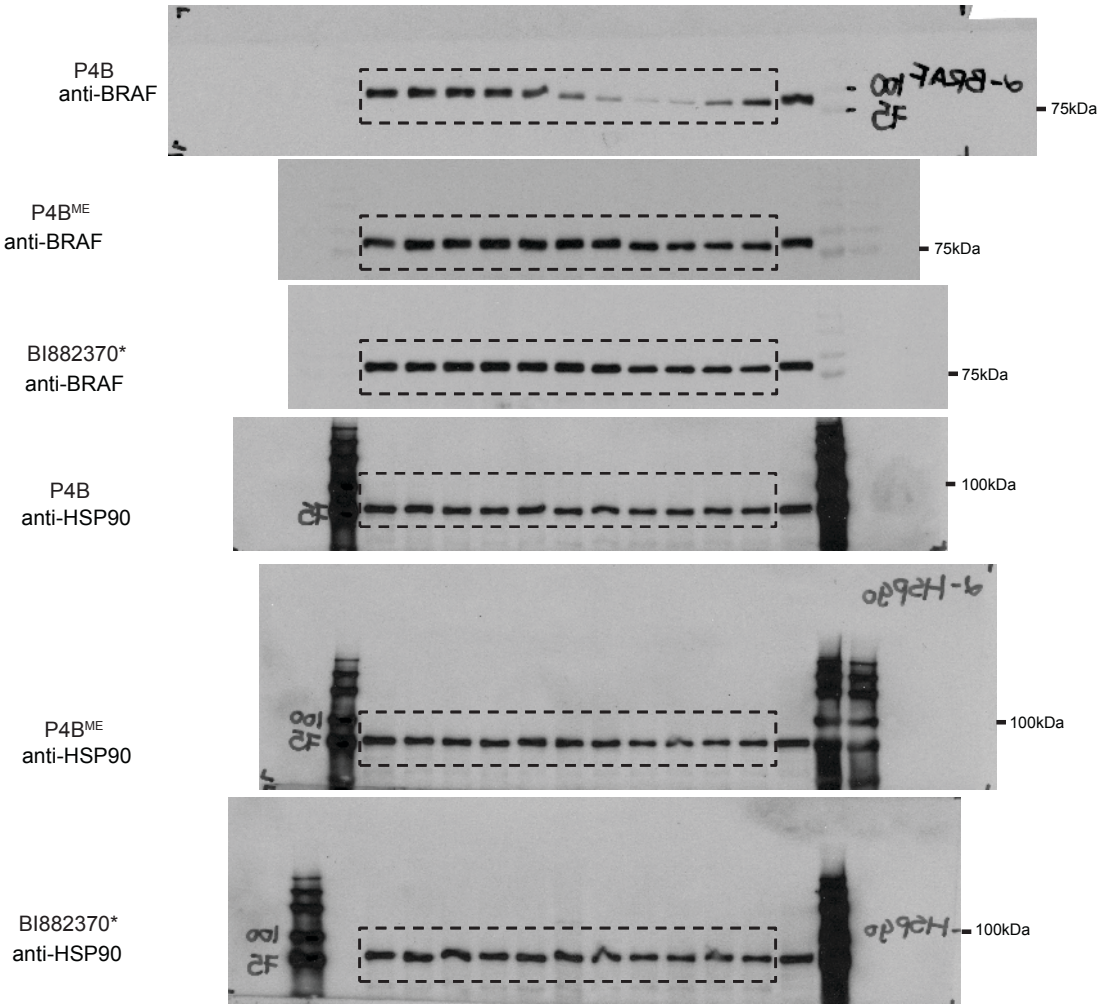

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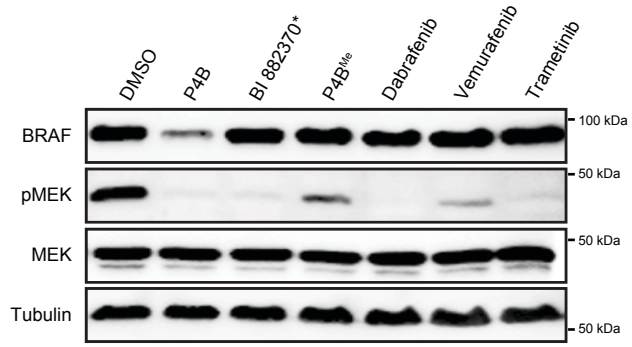

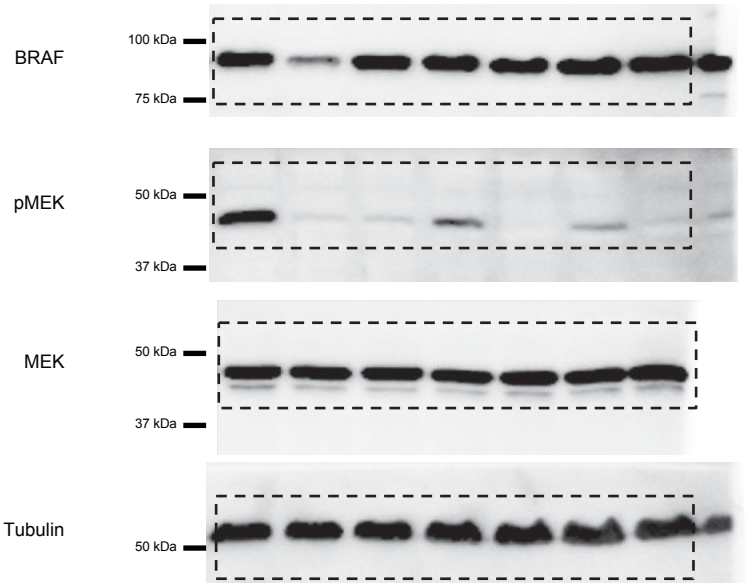

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