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Supplementary Materials for

PHOTACs enable optical control of protein degradation

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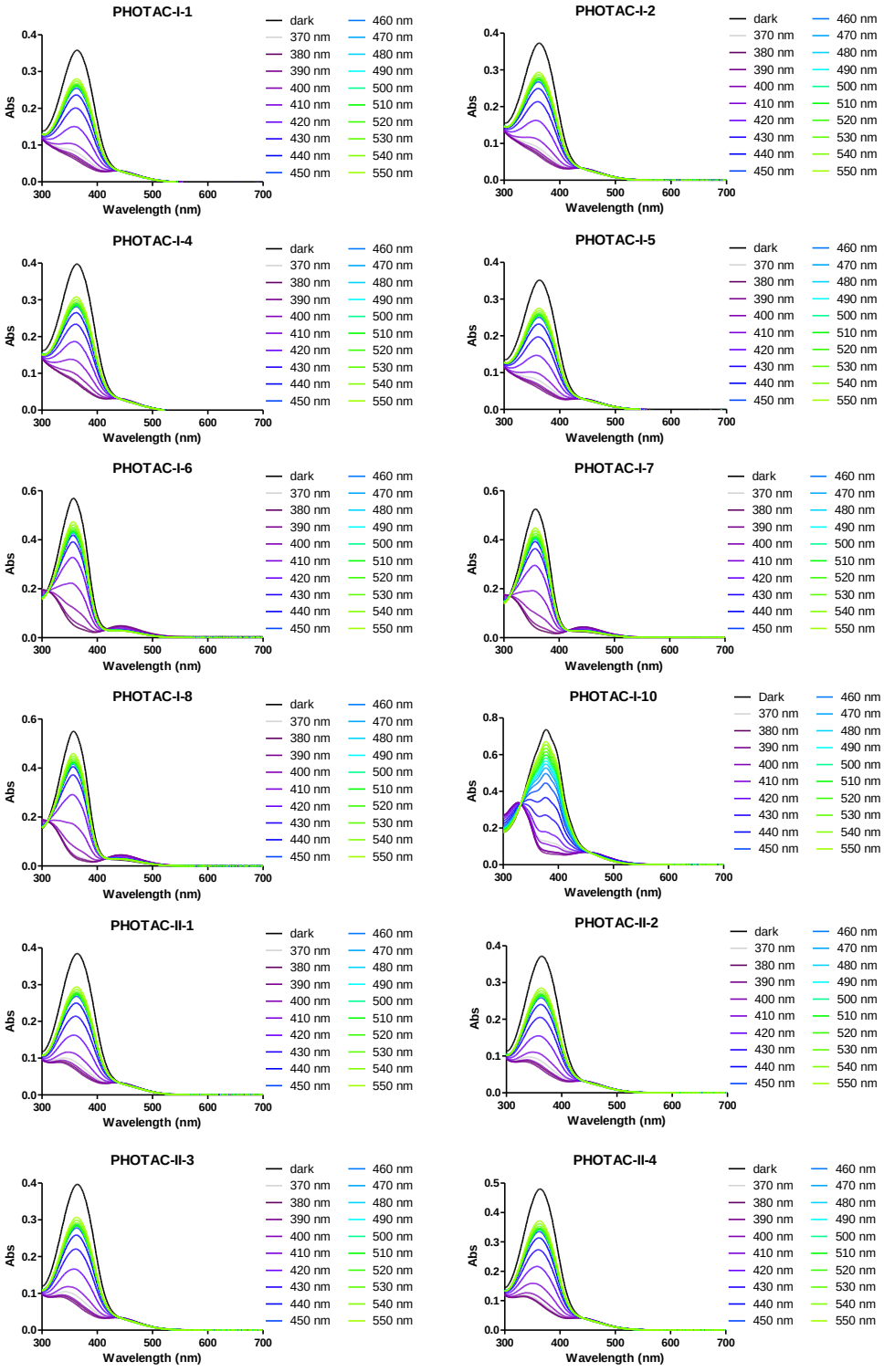
This PDF file includes:

Supplementary Figures

A



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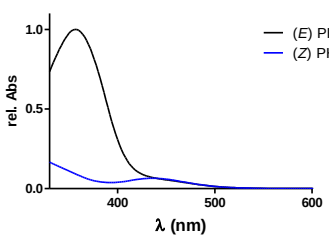


Fig. S1. UV-Vis characterization. A) UV-VIS spectra of **PHOTACs-I** and **PHOTACs-II** following irradiation with the indicated wavelengths for 5 min. B) Separated UV-VIS spectra of **(*E*)-** and **(*Z*)-PHOTAC-I-3** as obtained from the LCMS and normalized at the isosbestic point.

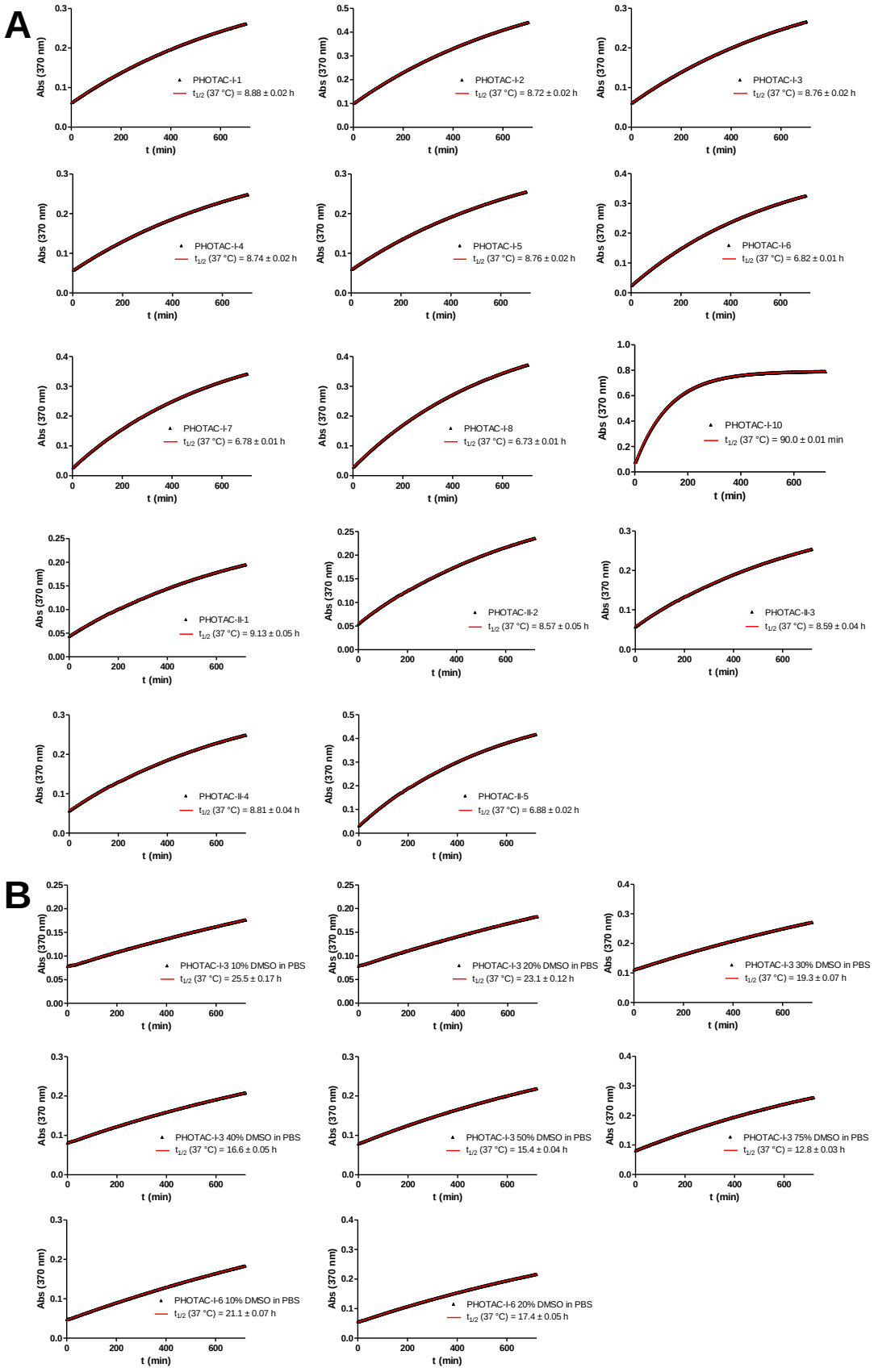
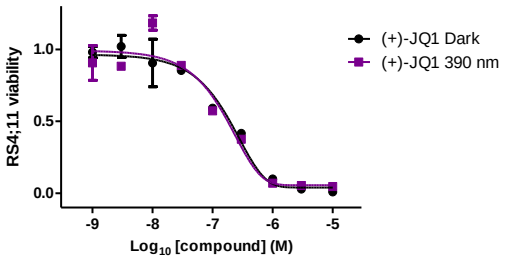
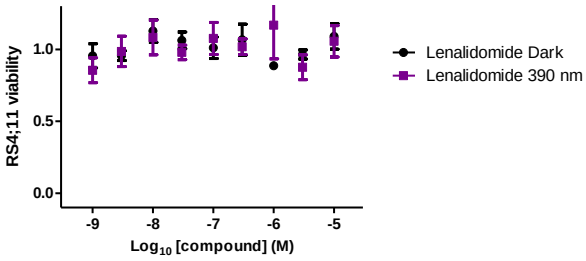
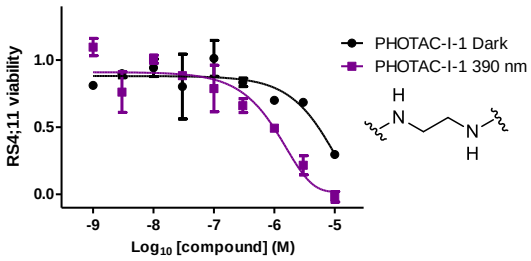
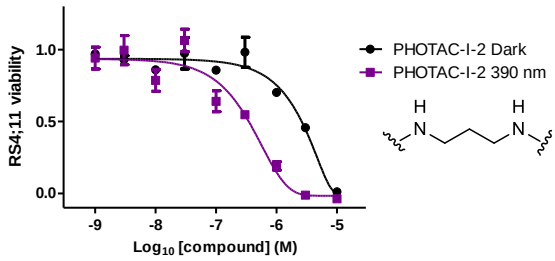


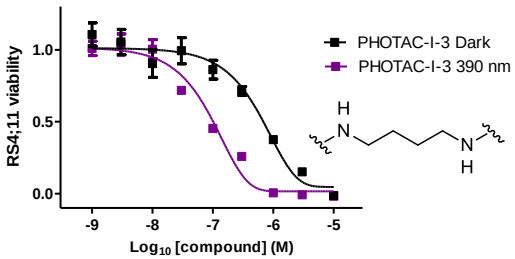
Fig. S2. Thermal relaxation. A) Thermal relaxation of **(*Z*)-PHOTACs** in DMSO. B) Thermal relaxation of **(*Z*)-PHOTACs** in DMSO-PBS mixtures.

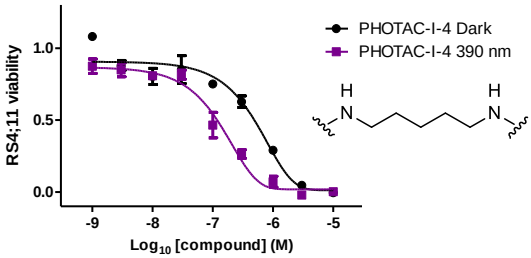

(+)-JQ1 Dark
(+)-JQ1 390 nm
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)

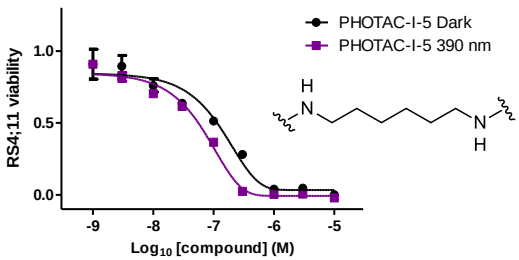

Lenalidomide Dark
Lenalidomide 390 nm
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)

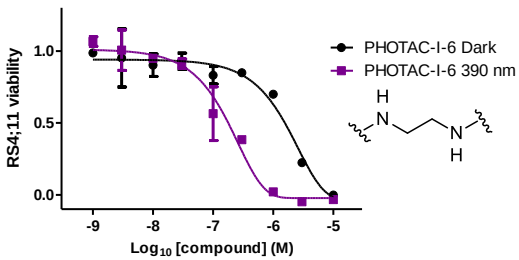

PHOTAC-I-1 Dark
PHOTAC-I-1 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)

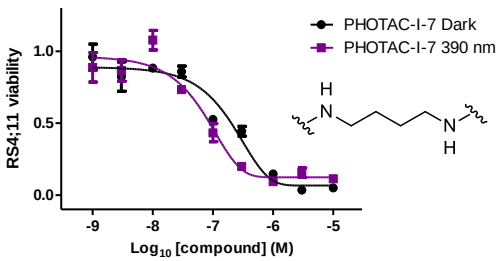

PHOTAC-I-2 Dark
PHOTAC-I-2 390 nm
H
N
H
N
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)

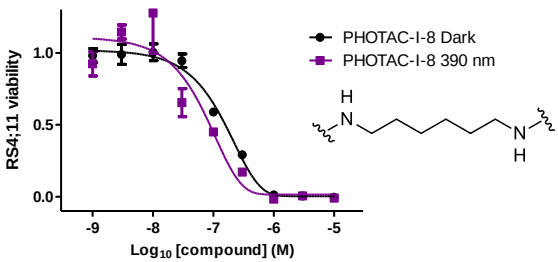

PHOTAC-I-3 Dark
PHOTAC-I-3 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)


PHOTAC-I-4 Dark
PHOTAC-I-4 390 nm
H
N
H
N
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)


PHOTAC-I-5 Dark
PHOTAC-I-5 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)


PHOTAC-I-6 Dark
PHOTAC-I-6 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)


PHOTAC-I-7 Dark
PHOTAC-I-7 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)


PHOTAC-I-8 Dark
PHOTAC-I-8 390 nm
H
N
N
H
RS4;11 viability
1.0
0.5
0.0
-9
-8
-7
-6
-5
Log10 [compound] (M)

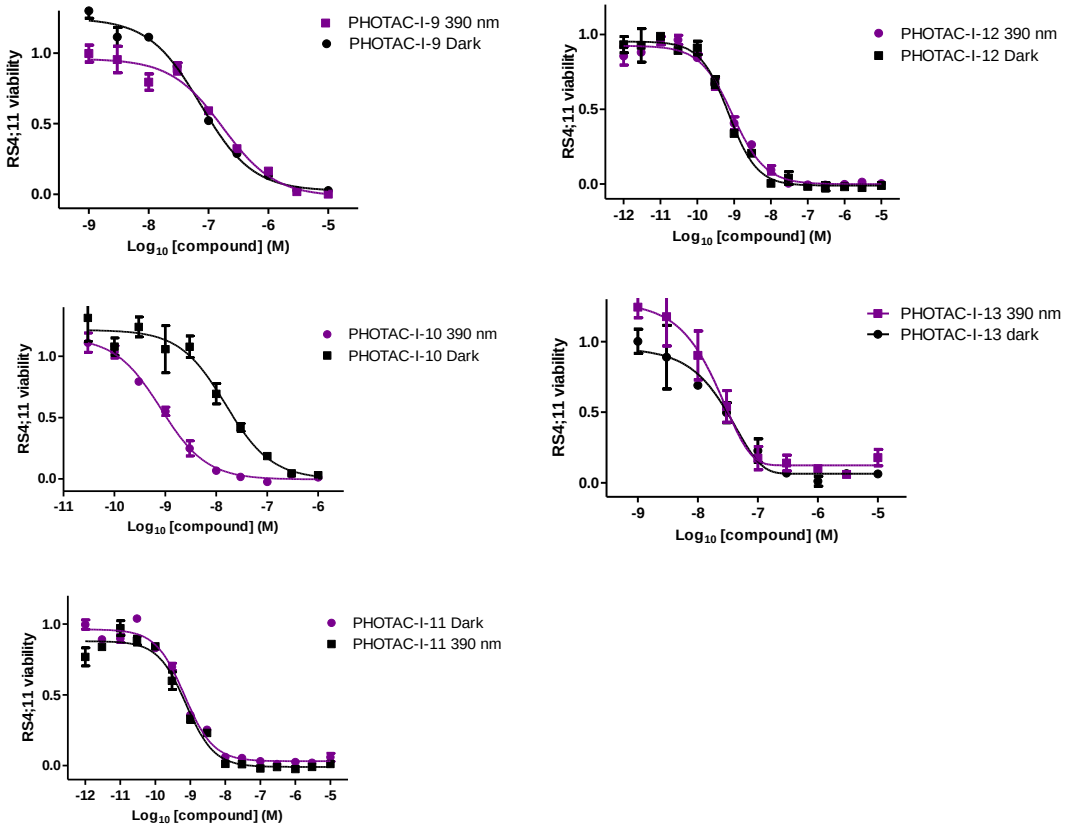


Fig. S3. Viability of RS4;11 acute lymphoblastic leukemia cells after treatment with PHOTACs-I for 72 hours in the dark or under pulsed (100 ms every 10 s) 390-nm irradiation.

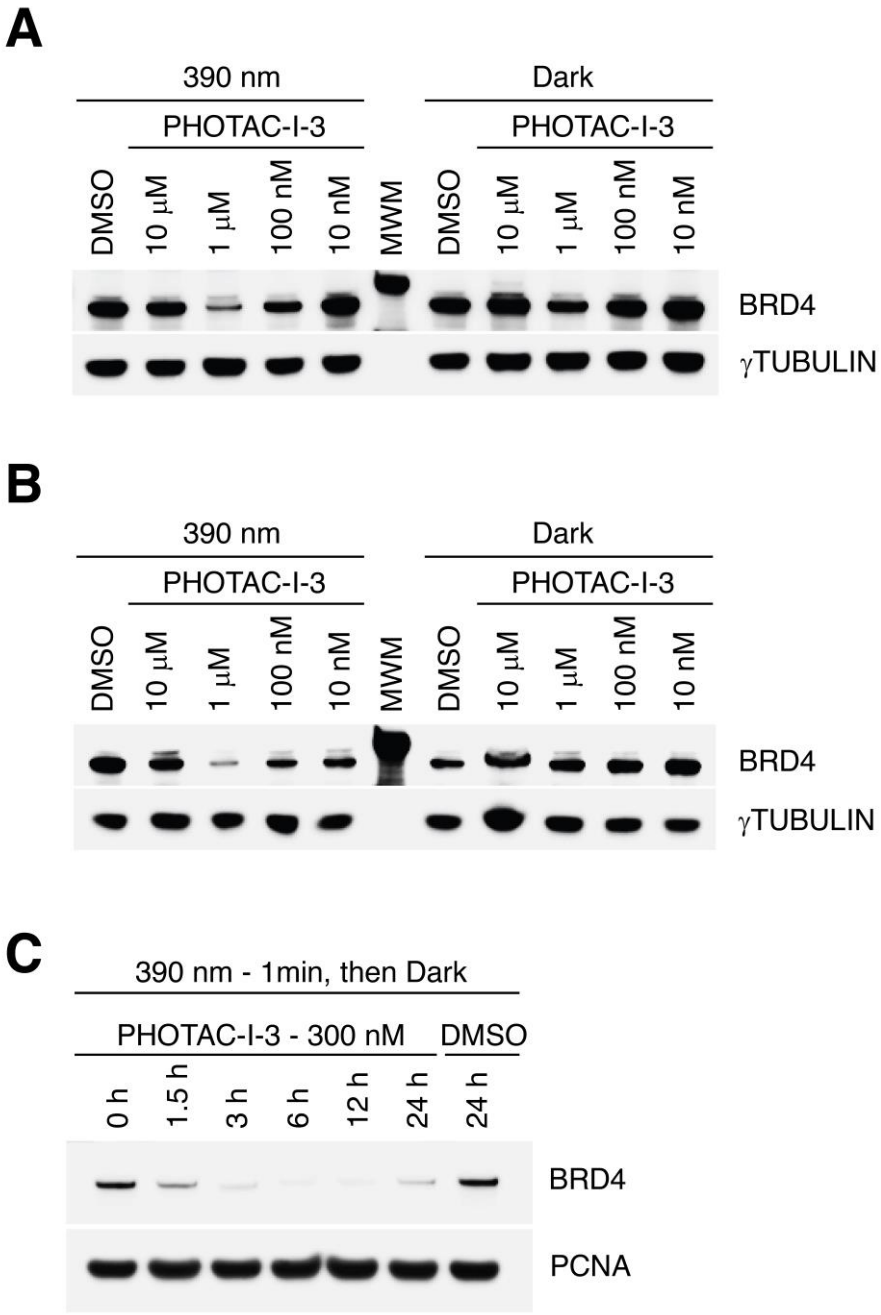


Fig. S4. Immunoblot analysis of PHOTAC-I-3. A) Immunoblot analysis after treatment of MB-MDA-231 cells with **PHOTAC-I-3** for 18 h at different concentrations. Cells were either irradiated with 100 ms pulses of 390 nm light every 10 s (left) or kept the dark (right). B) Immunoblot analysis after treatment of MB-MDA-468 cells with **PHOTAC-I-3** for 18 h at different concentrations. Cells were either irradiated with 100 ms pulses of 390 nm light every 10 s (left) or kept the dark (right). (MWM, molecular weight marker). C) Immunoblot of BRD4 degradation in RS4;11 cells, promoted by **PHOTAC-I-3** (300 nM) after 1 minute of irradiation (100 ms every 10 s), highlighting sustained degradation at the applied dosage.

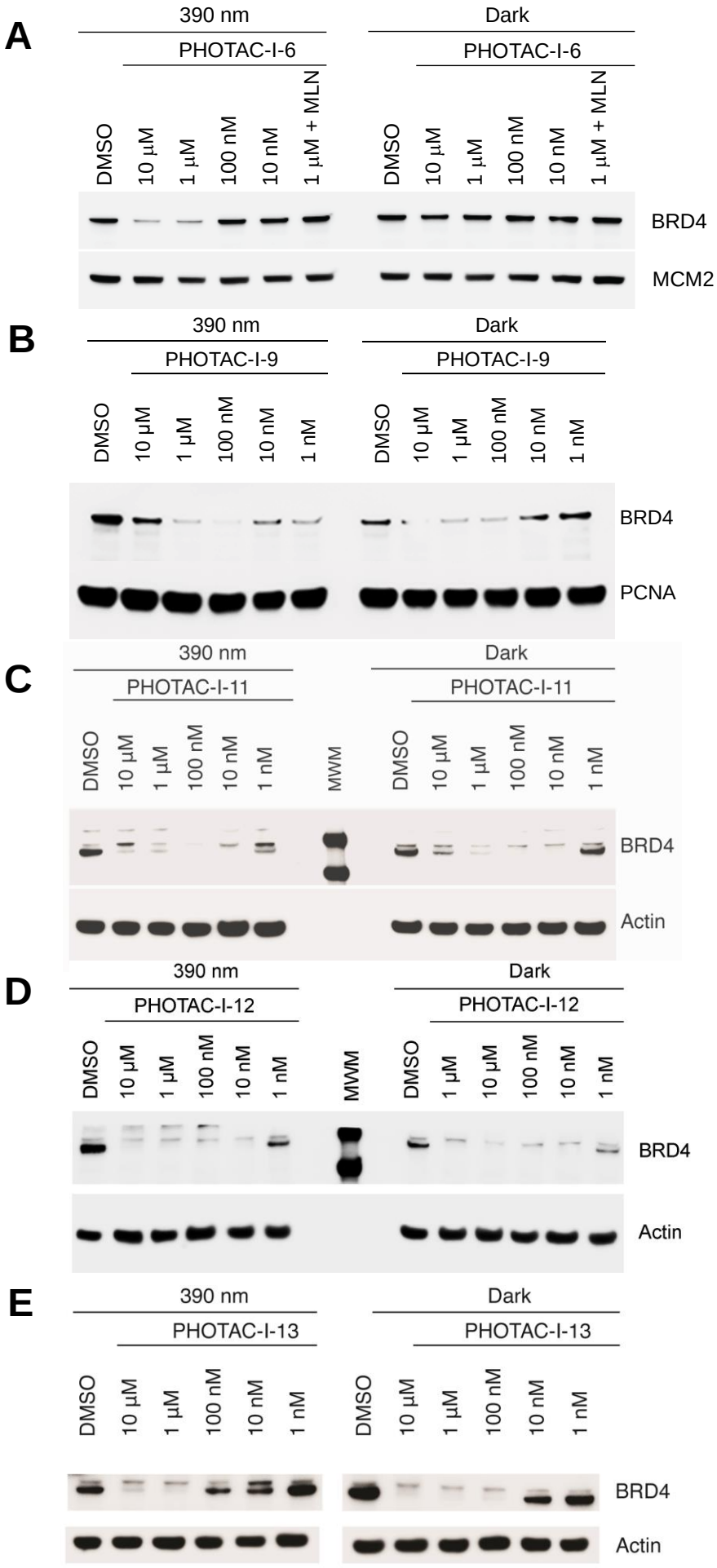

A
390 nm
Dark
PHOTAC-I-6
PHOTAC-I-6
DMSO
10 µM
1 µM
100 nM
10 nM
1 µM + MLN
DMSO
10 µM
1 µM
100 nM
10 nM
1 µM + MLN
BRD4
MCM2
B
390 nm
Dark
PHOTAC-I-9
PHOTAC-I-9
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
BRD4
PCNA
C
390 nm
Dark
PHOTAC-I-11
PHOTAC-I-11
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
MWM
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
BRD4
Actin
D
390 nm
Dark
PHOTAC-I-12
PHOTAC-I-12
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
MWM
DMSO
1 µM
10 µM
100 nM
10 nM
1 nM
BRD4
Actin
E
390 nm
Dark
PHOTAC-I-13
PHOTAC-I-13
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
DMSO
10 µM
1 µM
100 nM
10 nM
1 nM
BRD4
Actin

Fig. S5. **Immunoblot analysis of BRD4 after treatment of RS4;11 cells with PHOTACs.** A) **PHOTAC-I-6**, B) **PHOTAC-I-9**, C) **PHOTAC-I-11**, D) **PHOTAC-I-12** or E) **PHOTAC-I-13** for 4 h at different concentrations. Cells were either irradiated with 100 ms pulses of 390 nm light every 10 s (left) or kept the dark (right). (MWM, molecular weight marker).

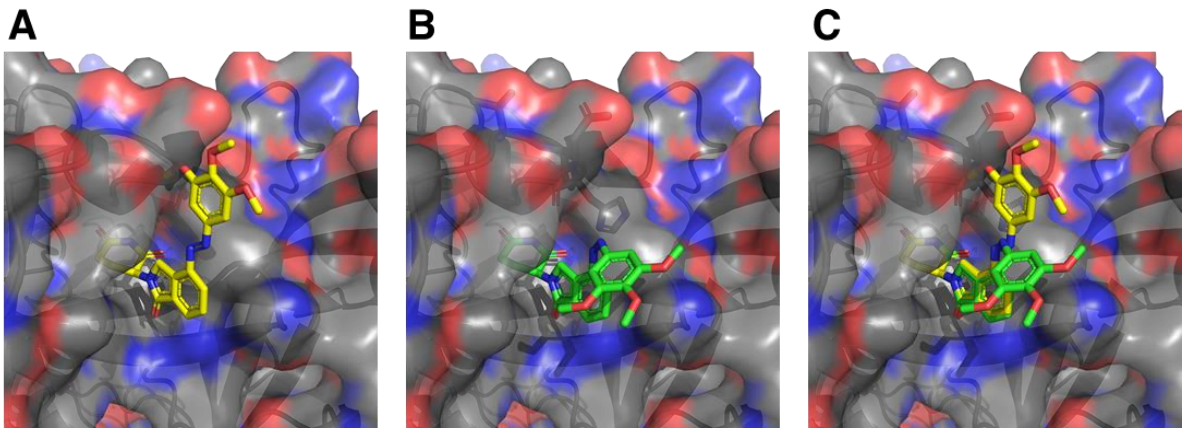


Fig. S6. Model of the photoswitch-cereblon interaction. Structure model of an (*E*)- (**A**) or (*Z*)- (**B**) azobenzene bound to cereblon. Model derived from the crystal structure of lenalidomide bound to cereblon (PDB: 4CI2)(*60*), showing the clash between the (*E*)-azobenzene and cereblon, whereas the (*Z*)-isomer is accommodated by the binding pocket. Models were created using Schrödinger Maestro 11.9. (**C**) Overlay of both structures.

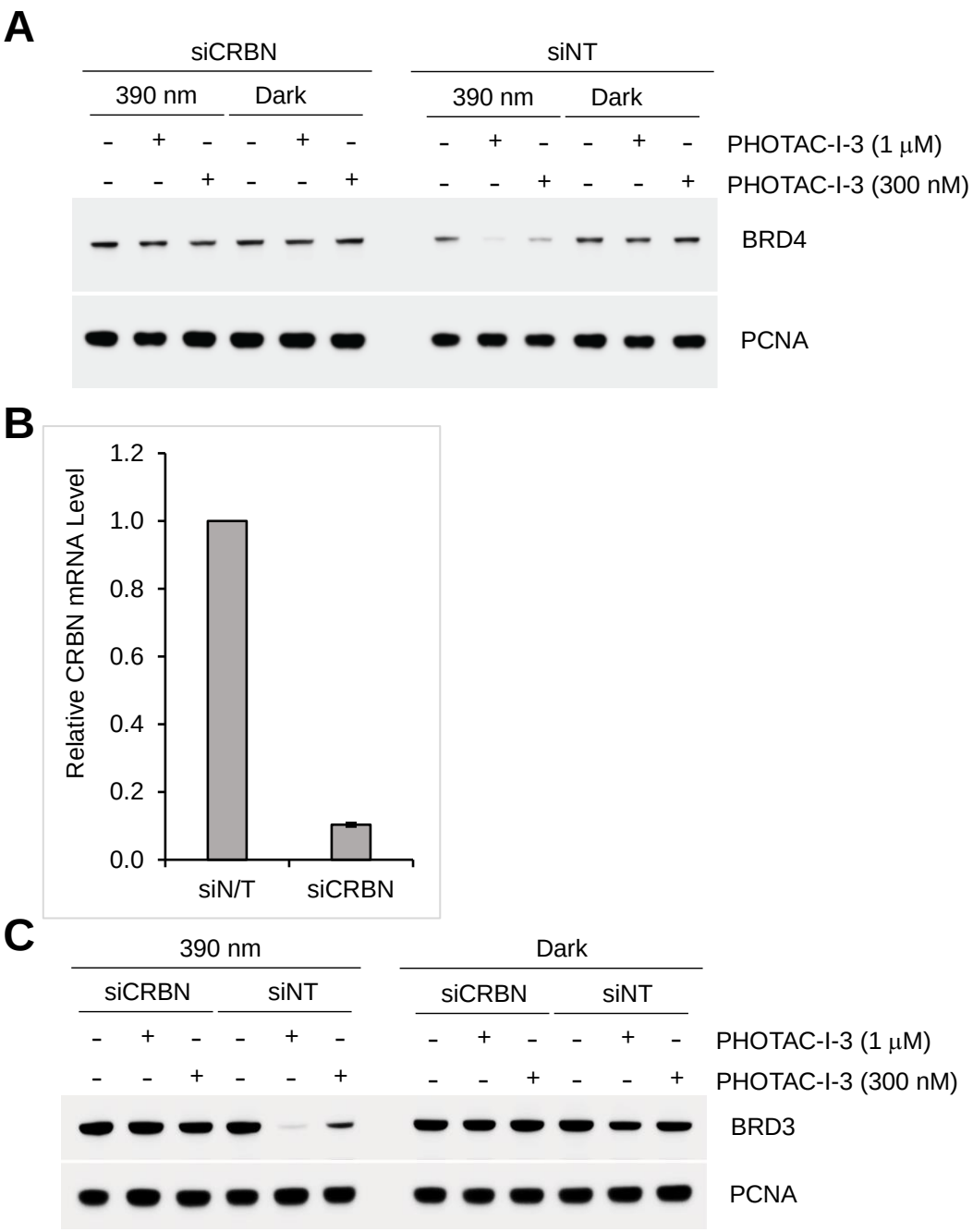


Fig. S7. CRBN knockdown control. A) Immunoblot of BRD4 degradation after 18 h of **PHOTAC-I-3** treatment in the dark or with 390 nm pulsed irradiation (100 ms every 10 s) in MB-MDA-231 cells, pre-treated with CRBN siRNA or non-targeting (NT) siRNA. B) mRNA expression levels of CRBN in MB-MDA-231 cells, treated with CRBN siRNA or non-targeting (NT) siRNA. C) Immunoblot of BRD3 degradation after 18h of **PHOTAC-I-3** treatment in the dark or with 390 nm pulsed irradiation (100 ms every 10 s) in MB-MDA-231 cells, pre-treated with CRBN siRNA or non-targeting (NT) siRNA.

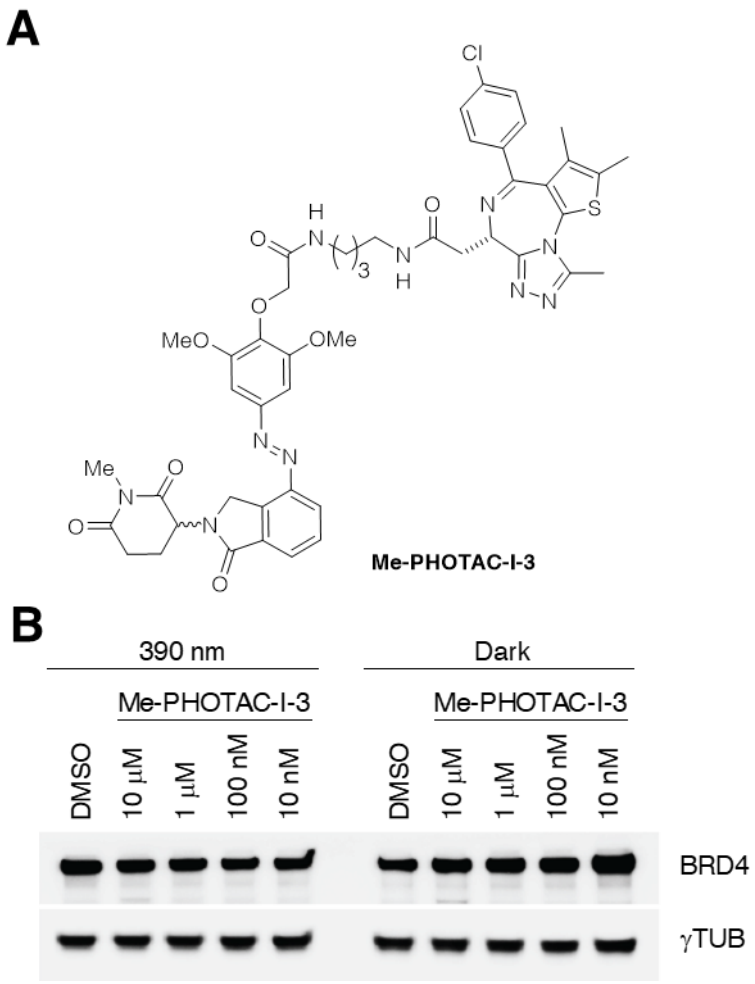


Fig. S8. **Me-PHOTAC-I-3 control.** A) Structure of inactive control **Me-PHOTAC-I-3** B) Immunoblot of BRD4 levels after 4 h of **Me-PHOTAC-I-3** treatment in RS4;11 cells in the dark or with 390 nm pulsed irradiation (100 ms every 10 s).

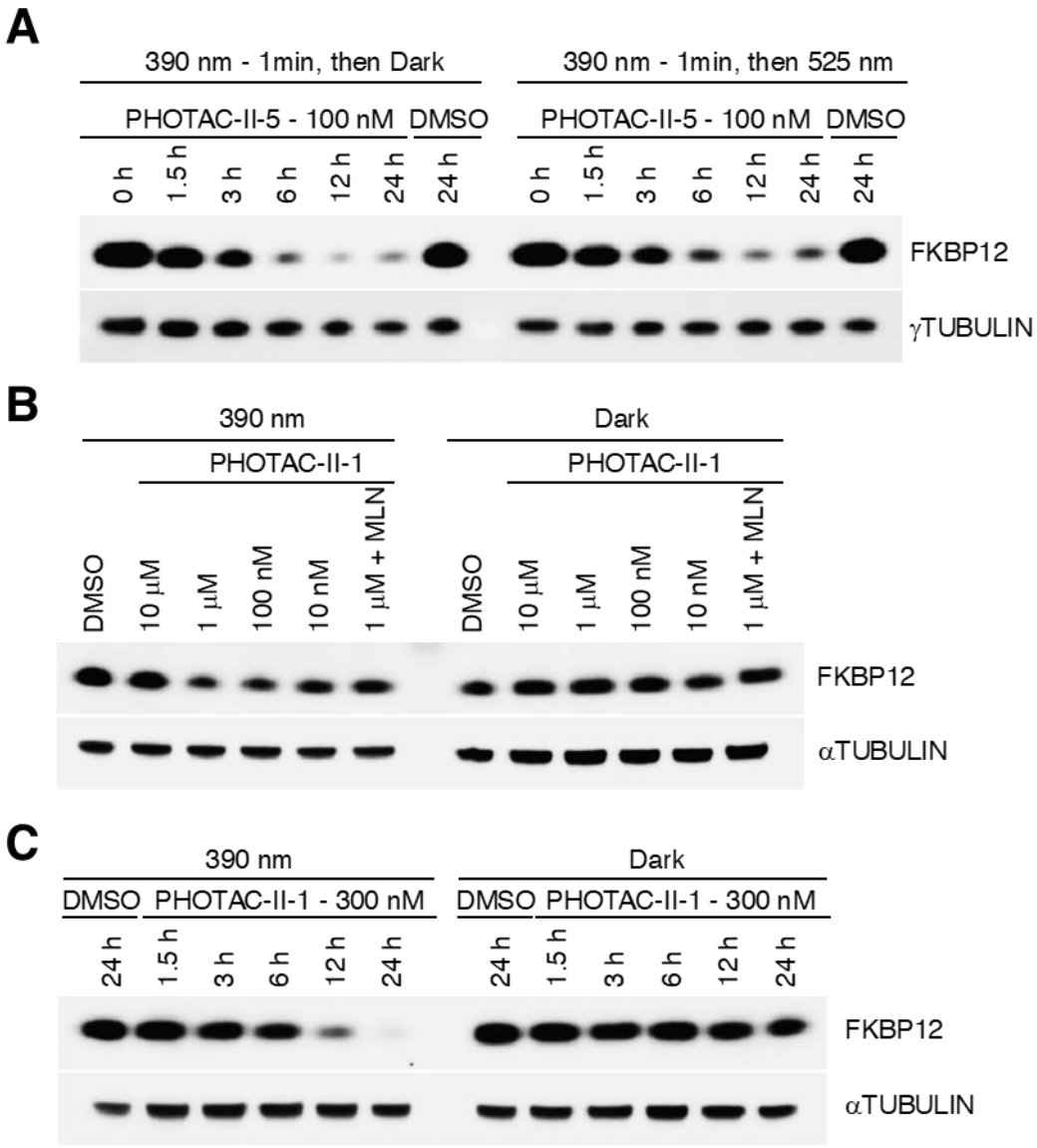


Fig. S9. FKBP12 Immunoblots in RS4;11 cells. A) Immunoblot of a rescue experiment demonstrating the reversibility of FKBP12 degradation promoted by **PHOTAC-II-5** through thermal relaxation (left) or optical inactivation by 525 nm pulsed irradiation (right, 100 ms every 10 s). B) Degradation of FKBP12. Immunoblot analysis of FKBP12 after treatment of RS4;11 cells with **PHOTAC-II-1** for 4 h at different concentrations. Cells were either irradiated with 100 ms pulses of 390 nm light every 10 s (left) or kept the dark (right). C) Time course of FKBP12 degradation visualized by immunoblotting. RS4;11 cells were treated with **PHOTAC-II-1** (300 nM) and collected at the indicated time points, showing slow, but sustained FKBP12 degradation over time when irradiated with 390 nm light (left, 100 ms every 10 s), but not when kept in the dark (right).

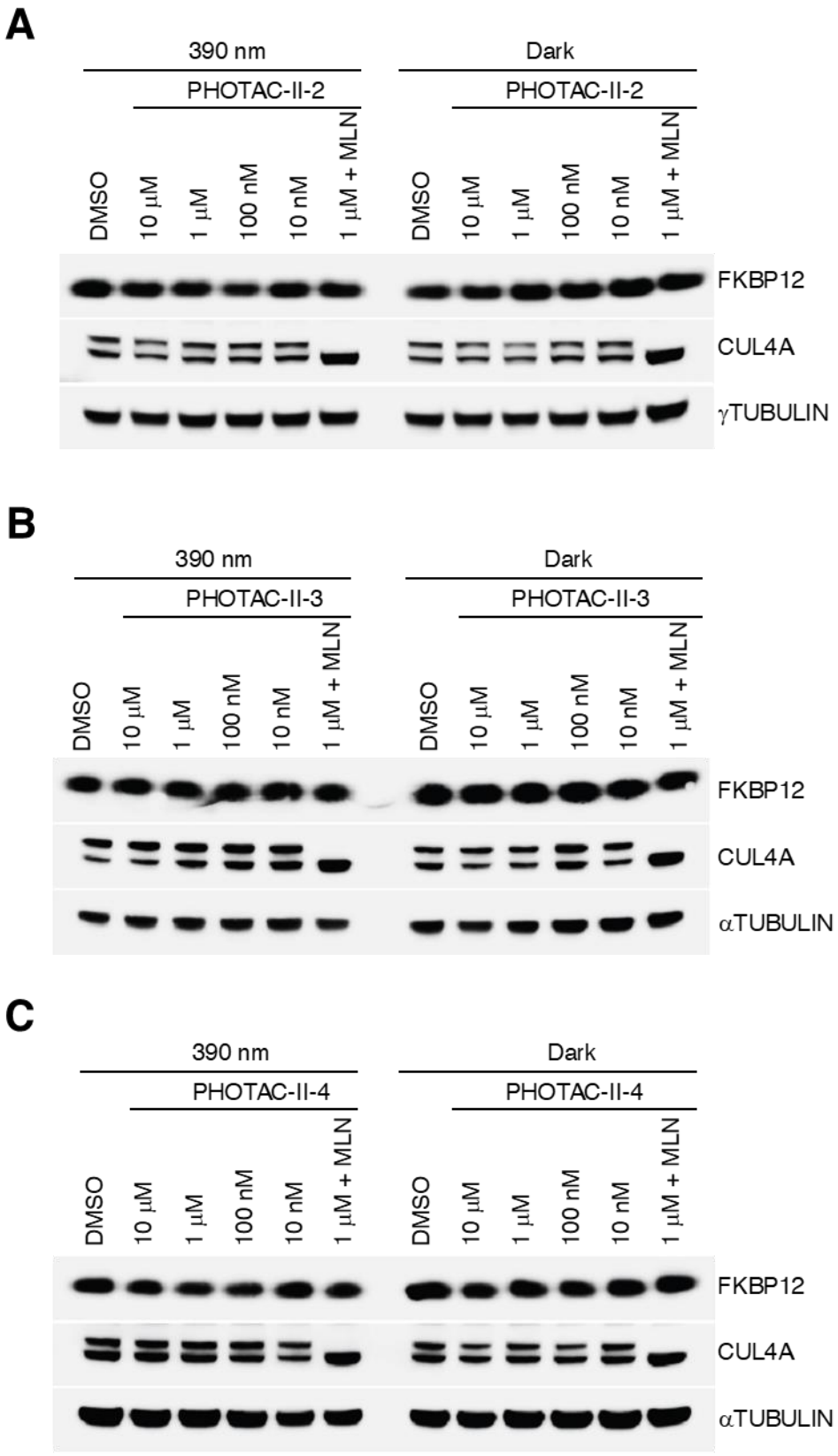


Fig. S10. Immunoblot analysis of FKBP12 after treatment of RS4;11 cells. A) **PHOTAC-II-2**, B) **PHOTAC-II-3** or C) **PHOTAC-II-4** for 4 h at different concentrations. Cells were either irradiated with pulses of 390 nm light (right, 100 ms every 10 s) or kept the dark (left).

General information

The reagents and solvents used in this study were bought from the following chemical suppliers: ABCR, Acros Organics, Alfa Aesar, Ark Pharm, Combi-Blocks, Oakwood, OxChem, Sigma-Aldrich, Strem, Toronto Research Chemicals and were used as purchased.

Dry solvents used in reactions performed under inert atmosphere were obtained by passing the degassed solvents through activated alumina columns.

Column chromatography was carried out on silica gel (60 Å pore size, 40–63 µm, Merck KGaA) using a Teledyne Isco Combiflash EZprep flash purification system.

Thin-layer chromatography (TLC) was performed on glass plates precoated with silica gel (0.25 mm,60-Å pore size, Merck). TLC plates were visualized by exposure to UV light (254 and 366 nm).

NMR spectra were obtained on a Bruker Avance III HD 400 MHz spectrometer equipped with a CryoProbe^{TM} operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C spectra or on a Bruker AVIII-600 High Performance Digital NMR Spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C spectra) with CPTCI-cryoprobehead.

Integration results and multiplets are reported as observed and denoted as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), and m (multiplet) and as combinations thereof.

High-resolution mass spectra (HRMS) were recorded on an Agilent Technologies 6224 Accurate-Mass time-of-flight spectrometer with either atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) ionization sources.

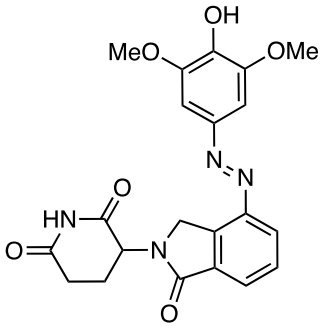
LCMS were measured on an Agilent Technologies 1260 II Infinity connected to an Agilent Technologies 6120 Quadrupole mass spectrometer with ESI ionization source. Elution was performed using a gradient from 5:95% to 100:0% MeCN:H_2O with 0.1% formic acid over 5 min, if not indicated otherwise. Separated isomer spectra of azobenzenes were obtained by irradiation of the LCMS sample prior to injection.

UVVis spectrometry was performed on a Varian Cary 60 UV-Visible Spectrophotometer using disposable BRAND UV-Cuvette Disposable Spectrophotometer/Photometer Ultra-Micro Cuvettes, BrandTech (10 mm light path), an Agilent Technologies PCB 1500 Water Peltier system for temperature control and samples were irradiated with a Cairn Research Optoscan Monochromator with

Optosource High Intensity Arc Lamp equipped with a 75 W UXL-S50A lamp from USHIO Inc. Japan and set to 15 nm full width at half maximum.

Synthetic Procedures and Characterization

(*E*)-3-(4-((4-hydroxy-3,5-dimethoxyphenyl)diazenyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (2)



Lenalidomide (500 mg, 1.93 mmol, 1.0 eq.) was dissolved in 1 M HCl (50 mL). Concentrated aqueous HBF_4 (2 mL, 48 wt.%) was added to the mixture. After completely dissolving of the starting material, 2 M $NaNO_2$ (1.06 mL) was added to the solution at 0 °C. After stirring for 1 h the solution was added dropwise into a mixture of 2,6-Dimethoxyphenol (357 mg, 2.32 mmol, 1.2 eq.) in H_2O (50 mL), MeOH (20 mL), $NaHCO_3$ (4.000 g, 47.62 mmol, 24.7 eq.) and Na_2CO_3 (5.000 g, 47.18 mmol, 24.5 eq.). Upon addition the solution turned from violet to strong red and was stirred for 1 additional hour at 0 °C. The reaction was extracted with EtOAc (7x 100 mL) and washed once with brine (1x 100 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0 → 10% MeOH) gave **2** (562.0 mg, 1.324 mmol, 69%) as a yellow solid.

R_f = 0.33 (CH_2Cl_2:MeOH, 19:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (s, 1H), 9.48 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.77 (t, *J* = 7.6 Hz, 1H), 7.34 (s, 2H), 5.16 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.82 (d, *J* = 19.0 Hz, 1H), 4.69 (d, *J* = 19.0 Hz, 1H), 3.90 (s, 6H), 2.95 (ddd, *J* = 17.5, 13.4, 5.2 Hz, 1H), 2.63 (d, *J* = 18.8 Hz, 1H), 2.55 (dd, *J* = 13.1, 4.5 Hz, 1H), 2.11 – 2.03 (m, 1H) ppm.

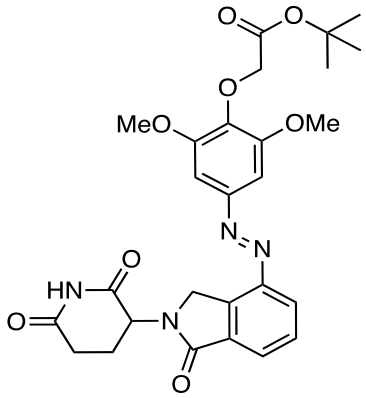
^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.39, 171.52, 167.76, 148.68, 147.05, 144.80, 140.86, 134.77, 134.21, 129.98, 128.37, 125.04, 101.69, 56.68, 52.30, 48.76, 31.76, 22.7 ppm.

HRMS (ESI):calcd. for $C_{21}H_{21}N_4O_6^+$: 425.1456 m/z $[M+H]^+$

found: 425.1458 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 2.90 min. 425 m/z $[M+H]^+$.

***Tert*-butyl (*E*)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetate (S1)**



To tert-butyl bromoacetate (234 mg, 1.20 mmol, 1 eq.) was added dry DMF (10 mL), **2** (509 mg, 1.20 mmol, 1 eq.) and K_2CO_3 (215 mg, 1.56 mmol, 1.3 eq.) at room temperature. After stirring for 2.5 hours, the mixture was diluted with EtOAc (100 mL), separated against $NaHCO_3$ (50 mL), extracted with EtOAc (3x 50 mL) and washed with 10% LiCl (3x 50 mL) and brine (2x 50 mL). The reaction was concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/Ea gradient, 20 → 100% Ea, the product was eluted at 75%.) gave **S1** (501 mg, 0.93 mmol, 78%) as a yellow solid.

R$_f$ = 0.64 [EtOAc].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (s, 1H), 8.22 (d, *J* = 7.7 Hz, 1H), 7.92 (d, *J* = 7.4 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.34 (s, 2H), 5.16 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.83 (d, *J* = 19.1 Hz, 1H), 4.70 (d, *J* = 19.1 Hz, 1H), 4.60 (s, 2H), 3.90 (s, 6H), 2.93 (d, *J* = 12.7 Hz, 1H), 2.63 (d, *J* = 19.6 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.11 – 2.03 (m, 1H), 1.43 (s, 9H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ = 173.38, 171.48, 168.16, 167.64, 152.82, 148.14, 146.86, 139.71, 134.96, 134.28, 130.08, 128.97, 125.78, 101.26, 81.47, 69.69, 56.77, 52.31, 48.78 31.75, 28.20, 22.77 ppm.

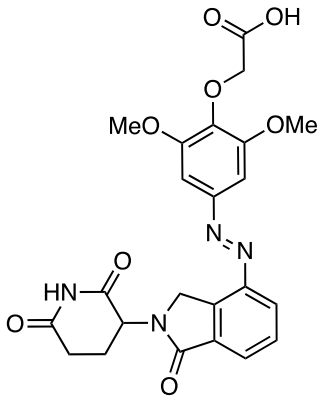
HRMS (ESI): calcd. for $C_{27}H_{31}N_4O_8^+$: 539.2137 m/z $[M+H]^+$

found: 539.2172 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 3.42 (*Z*). 539 m/z $[M+H]^+$.

t_{ret} = 3.93 (*E*) min. 539 m/z $[M+H]^+$.

(*E*)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetic acid (3)



S2 (475 mg, 0.88 mmol, 1 eq.) was dissolved in CH_2Cl_2:TFA (1:1; 5 mL each). Upon TFA addition (5 mL) the solution turned from yellow to dark red. After 2 hours the reaction was concentrated under reduced pressure, turning from red to an orange solid. The reaction was dried under high vacuum for 48 h. **3** (557 mg, 0.878 mmol, 99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

R$_f$ = 0.5 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.34 (s, 2H), 5.16 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.83 (d, *J* = 19.1 Hz, 1H), 4.70 (d, *J* = 19.1 Hz, 2H), 4.60 (s, 2H), 3.90 (s, 6H), 2.95 (ddd, *J* = 17.7, 13.6, 5.3 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.11 – 2.03 (m, 1H). ppm.

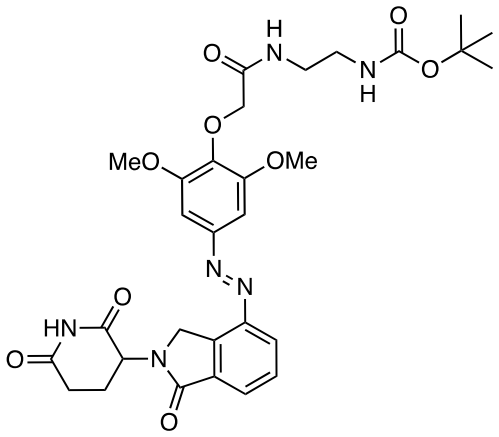
^{13}C NMR (100 MHz, DMSO) δ = 172.91, 171.01, 169.95, 167.17, 152.58, 147.80, 146.41, 139.24, 134.50, 133.82, 129.63, 128.52, 125.35, 100.87, 68.67, 56.33, 51.85, 48.30, 31.28, 22.30 ppm.

HRMS (ESI): calcd. for $C_{23}H_{23}N_4O_8^+$: 483.1510 m/z $[M+H]^+$

found: 483.1549 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 2.93 min. 483.1 m/z $[M+H]^+$.

***tert*-butyl (*E*)-(2-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)ethyl)carbamate (S4)**



3 (19.0 mg, 0.039 mmol, 1.0 eq.) and HATU (26.9 mg, 0.083 mmol, 2.1 eq.) were dissolved in dry DMF (1 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,2-ethylendiamine (33.2 mg, 0.207 mmol, 5.3 eq.) and *i*-Pr_2NEt (26.8 mg, 0.207 mmol, 5.3 eq., 36 μL) were added to the mixture and stirred for additional 12 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against H_2O (20 mL), extracted with EtOAc (3x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (3x 30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S4** (15.3 mg, 0.024 mmol, 62%) as a yellow solid.

R_f = 0.32 [Hx:EA, 2:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.21 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.99 (s, 1H), 7.89 (t, *J* = 5.6 Hz, 1H, br), 7.72 (t, *J* = 7.7 Hz, 1H), 7.22 (s, 2H), 5.27 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.75 (s, 1H), 4.62 (s, 2H), 4.01 (s, 6H), 3.49 (q, *J* = 6.0 Hz, 2H), 3.32 (d, *J* = 5.7 Hz, 2H), 3.00 – 2.81 (m, 2H), 2.47 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.27 (ddd, *J* = 10.3, 5.1, 2.6 Hz, 1H), 1.44 (d, *J* = 4.7 Hz, 9H) ppm.

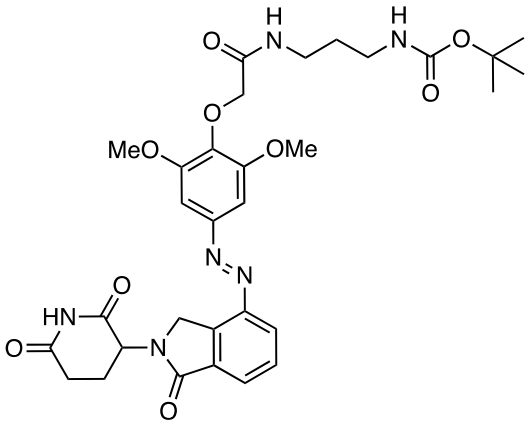
^{13}C NMR (100 MHz, $CDCl_3$) δ =170.98, 170.37, 169.51, 168.57, 156.18, 152.79, 149.09, 146.93, 139.86, 134.12, 133.45, 130.05, 129.66, 126.44, 100.65, 79.66, 72.84, 56.60, 52.15, 48.29, 39.17, 31.76, 28.54, 23.62, 19.18 ppm.

HRMS (ESI): calcd. for $C_{30}H_{37}N_6O_9^+$: 265.2617 m/z $[M+H]^+$

found: 265.2629 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 3.11 (*Z*) min. 623 m/z $[M–H]^-$.
t_{ret} = 3.44 (*E*) min. 623 m/z $[M–H]^-$.

***tert*-butyl (*E*)-(3-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)propyl)carbamate (S5)**



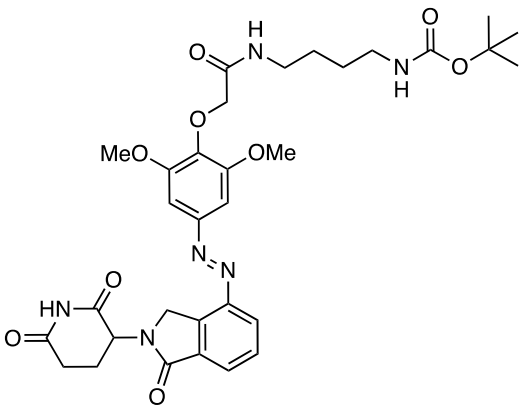
3 (60.0 mg, 0.095 mmol, 1.0 eq.) and HATU (46.0 mg, 0.142 mmol, 1.5 eq.) were dissolved in dry DMF (5 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,3-diaminopropane (65.9 mg, 0.378 mmol, 4.0 eq. 70 μL) and *i*-Pr_2NEt (48.9 mg, 0.378 mmol, 4.0 eq., 66 μL) were added to the mixture and stirred for additional 12 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against H_2O/10% LiCl (1:1, 10 mL:10 mL), extracted with EtOAc (2x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S5** (51.5 mg, 0.081 mmol, 86%) as a yellow solid.

R_f = 0.19 [CH_2Cl_2:MeOH, 9:1].
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.21 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.99 (s, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.70 (s, 1H), 7.22 (s, 2H), 5.27 (dd, *J* = 13.3, 5.1 Hz, 1H), 5.01 (s, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.72 (d, *J* = 17.9 Hz, 1H), 4.60 (s, 2H), 4.00 (s, 6H), 3.43 (q, *J* = 6.5 Hz, 2H), 3.18 (d, *J* = 6.3 Hz, 2H), 2.99 – 2.81 (m, 2H), 2.47 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.27 (dtd, *J* = 12.8, 5.1, 2.5 Hz, 1H), 1.74 (p, *J* = 6.6 Hz, 1H), 1.43 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.99, 170.05, 169.51, 168.57, 156.22, 152.82, 149.07, 146.93, 139.88, 134.11, 133.45, 130.06, 129.66, 126.42, 100.61, 79.22, 72.83, 56.54, 52.15, 48.29, 37.68, 36.24, 31.76, 30.30, 28.57, 23.63 ppm.

HRMS (ESI):	calcd. for $C_{31}H_{39}N_6O_9^+$:	639.2773 m/z $[M+H]^+$
	found:	639.2785 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.23 min (*Z*).	639.2 m/z $[M+H]^+$.

***tert*-butyl (*E*)-(4-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)butyl)carbamate (S3)**



3 (70.0 mg, 0.11 mmol, 1.0 eq.) and HATU (62.9 mg, 0.165 mmol, 1.5 eq.) were dissolved in dry DMF (1 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,4-diaminobutane (83.1 mg, 0.441 mmol, 4 eq.) and *i*-Pr_2NEt (57 mg, 0.44 mmol, 4 eq., 74 μL) were added to the mixture and stirred for additional 14 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (3x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S3** (53.7 mg, 0.082 mmol, 75%) as a yellow solid.

R_f = 0.42 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.21 (d, *J* = 7.7 Hz, 1H), 8.10 (s, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.69 (s, 1H), 7.22 (s, 2H), 5.26 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.72 (d, *J* = 17.9 Hz, 1H), 4.60 (s, 2H), 3.99 (s, 6H), 3.37 (q, *J* = 6.5 Hz, 2H), 3.17 (d, *J* = 5.9 Hz, 2H), 2.99 – 2.81 (m, 2H), 2.47 (dd,

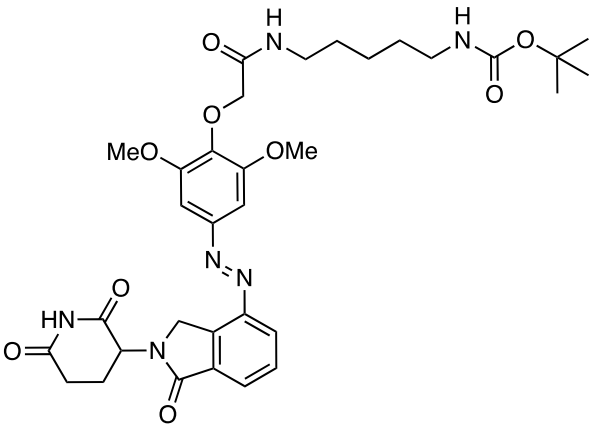
J = 13.1, 5.1 Hz, 1H), 2.27 (dtd, *J* = 12.8, 7.6, 6.3, 3.7 Hz, 1H), 1.66-1.53 (m, 4H), 1.43 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.04, 169.58, 169.55, 168.57, 156.14, 152.76, 149.02, 146.92, 139.91, 134.12, 133.45, 130.03, 129.64, 126.41, 100.60, 79.36, 72.89, 56.52, 52.15, 48.30, 40.39, 38.80, 31.76, 28.56, 27.73, 27.13, 23.62 ppm.

HRMS (APCI): calcd. for $C_{31}H_{41}N_6O_9^+$: 653.2929 m/z $[M+H]^+$
found: 653.2928.9606 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 3.31 min (*Z*) 675 m/z $[M+Na]^+$.
t_{ret} = 3.63 min (*E*) 675 m/z $[M+Na]^+$.

***Tert*-butyl (*E*)-(5-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)pentyl)carbamate (S6)**



3 (60.0 mg, 0.095 mmol, 1.0 eq.) and HATU (46.0 mg, 0.142 mmol, 1.5 eq.) were dissolved in dry DMF (5 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,4-diaminopentane (76.9 mg, 0.380 mmol, 4 eq.) and *i*-Pr_2NEt (49.1 mg, 0.380 mmol, 4 eq., 66 μL) were added to the mixture and stirred for additional 12 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (3x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) yielded **S6** (54.2 mg, 0.081 mmol, 85%) as a yellow solid.

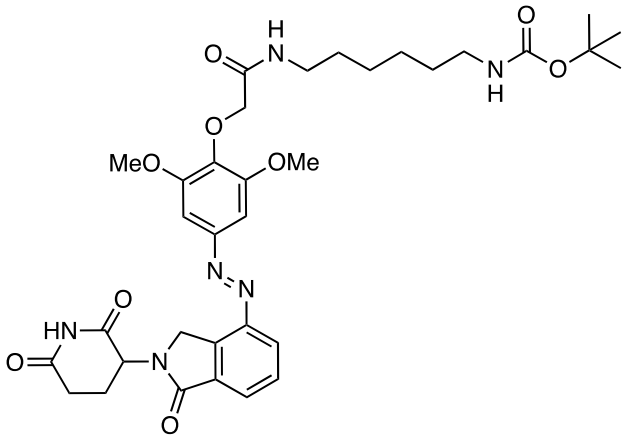
R_f = 0.42 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.21 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 13.9 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.66 (s, 1H), 7.22 (s, 2H), 5.26 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.73 (d, *J* = 17.9 Hz, 1H), 4.61 (s, 2H), 3.99 (s, 6H), 3.35 (q, *J* = 6.8 Hz, 2H), 3.12 (d, *J* = 5.7 Hz, 3H), 3.00 – 2.81 (m, 2H), 2.47 (qd, *J* = 13.1, 5.0 Hz, 1H), 2.30 – 2.21 (m, 1H), 1.67-1.48 (m, 6H), 1.43 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.11, 171.04, 169.54, 168.57, 156.14, 152.77, 149.02, 146.93, 139.93, 134.10, 133.44, 130.07, 129.64, 126.39, 100.60, 79.29, 72.90, 56.51, 52.15, 48.31, 40.52, 38.96, 31.76, 29.92, 29.45, 28.56, 24.23, 23.62 ppm.

HRMS (ESI):	calcd. for $C_{33}H_{42}N_6NaO_9^+$:	689.2905 m/z $[M+Na]^+$
	found:	689.2935 m/z $[M+Na]^+$
LCMS (ESI):	t_{ret} = 3.43 min (*Z*)	665 m/z $[M–H]^–$.

***tert*-butyl (*E*)-(6-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)hexyl)carbamate (S7)**



3 (60.0 mg, 0.095 mmol, 1.0 eq.) and HATU (46.0 mg, 0.142 mmol, 1.5 eq.) were dissolved in dry DMF (5 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,4-diaminohexane (81.8 mg, 0.378 mmol, 4 eq., 0.09 mL) and *i*-Pr_2NEt (48.9 mg, 0.378 mmol, 4 eq., 66 μL) were added to the mixture and stirred for additional 13 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against 5 % LiCl (20 mL), extracted with EtOAc (3x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over

Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S7** (56.7 mg, 0.083 mmol, 88%) as a yellow solid.

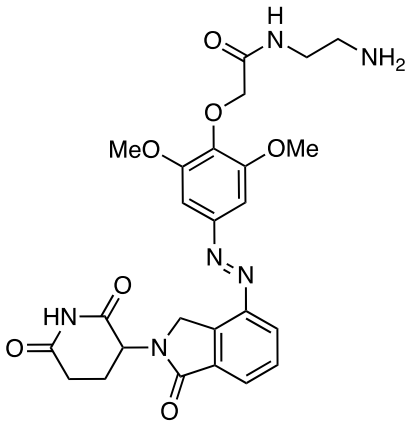
R_f = 0.25 [CH_2Cl_2: MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.20 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 5.3 Hz, 1H), 7.21 (s, 2H), 5.26 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.72 (d, *J* = 17.9 Hz, 1H), 4.61 (s, 2H), 3.99 (s, 6H), 3.34 (q, *J* = 6.6 Hz, 2H), 3.10 (d, *J* = 6.1 Hz, 2H), 2.99 – 2.80 (m, 2H), 2.46 (qd, *J* = 13.1, 5.0 Hz, 1H), 2.26 (dtd, *J* = 12.8, 5.1, 2.6 Hz, 1H), 1.58 (p, *J* = 7.1 Hz, 2H), 1.52 – 1.46 (m, 2H), 1.43 (s, 9H), 1.40 – 1.34 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.16, 169.64, 169.48, 168.56, 156.14, 152.76, 148.99, 146.92, 139.93, 134.08, 133.44, 130.08, 129.63, 126.38, 100.59, 79.25, 72.89, 56.50, 52.13, 48.29, 40.64, 39.02, 31.76, 30.17, 29.67, 28.57, 26.74, 26.63, 23.63 ppm.

HRMS (APCI): calcd. for $C_{34}H_{45}N_6O_9^+$: 681.3243 m/z $[M+H]^+$
found: 681.3236 m/z $[M+H]^+$.

(*E*)-(2-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)ethyl)carbamic acid (S8)



S4 (15.3 mg, 0.024 mmol, 1 eq.) was dissolved in TFA:CH_2Cl_2 (1 mL:0.5 mL) and stirred at room temperature. After 2 h, the mixture was diluted with CH_2Cl_2, concentrated under reduced pressure and dried on high vacuum overnight. **S8** (15.6

mg, 0.024 mmol, >99%.) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

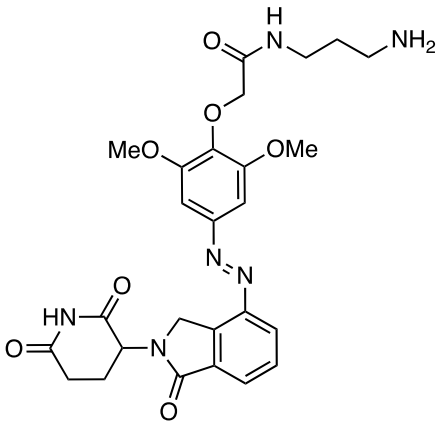
R_f = 0.18 [CH_2Cl_2:MeOH, 7:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.04 (s, 1H), 8.23 (dd, *J* = 9.3, 7.1 Hz, 2H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 3H), 7.37 (s, 2H), 5.17 (dd, *J* = 13.3, 5.0 Hz, 1H), 4.82 (d, *J* = 19.1 Hz, 1H), 4.69 (d, *J* = 19.1 Hz, 1H), 4.44 (s, 2H), 3.94 (s, 6H), 3.45 (q, *J* = 6.3 Hz, 2H), 3.02 – 2.88 (m, 4H), 2.69 – 2.54 (m, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ = 172.92, 171.02, 169.13, 167.14, 152.77, 148.38, 146.35, 139.08, 134.49, 133.84, 129.68, 128.67, 125.54, 100.57, 71.67, 56.36, 51.83, 48.26, 38.80, 36.23, 31.28, 30.70 ppm.

HRMS (ESI):	calcd. for $C_{25}H_{29}N_6O_7^+$:	525.2092 m/z $[M+H]^+$
	found:	525.2096 m/z $[M+H]^+$
LCMS (ESI):	t_{ret} = 2.39 min.	525 m/z $[M+H]^+$.

(*E*)-*N*-(3-aminopropyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamide (S9)



S5 (41.5 mg, 0.061 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1, 1 mL:1 mL) and stirred for 2 h at room temperature. The reaction was diluted with MeOH and concentrated under reduced pressure. The mixture was triturated with CH_2Cl_2 and dried on high vacuum overnight. **S9** (40 mg, 0.061 mmol, >99%) was obtained as a yellow solid with traces of residual TFA.

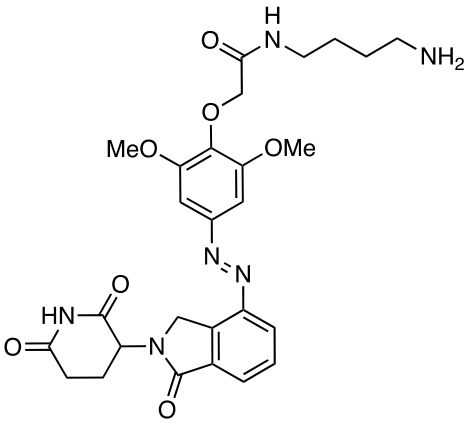
R_f = 0.19 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.04 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.16 (t, *J* = 5.9 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.73 (s, 2H), 7.36 (s, 2H), 5.17 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.82 (d, *J* = 19.1 Hz, 1H), 4.69 (d, *J* = 19.1 Hz, 1H), 4.43 (s, 2H), 3.94 (s, 6H), 3.27 (q, *J* = 6.5 Hz, 2H), 2.95 (ddd, *J* = 17.9, 13.8, 5.2 Hz, 1H), 2.82 (dt, *J* = 12.9, 6.2 Hz, 2H), 2.69 – 2.53 (m, 2H), 2.11 – 2.03 (m, 1H), 1.77 (p, *J* = 6.9 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.92, 171.02, 168.55, 167.15, 152.72, 148.34, 146.35, 139.15, 134.48, 133.84, 129.68, 128.70, 125.54, 100.60, 71.72, 56.39, 51.83, 48.27, 36.75, 35.36, 31.28, 27.39, 22.34 ppm.

HRMS (ESI):	calcd. for $C_{26}H_{31}N_6O_7^+$:	539.2249 m/z $[M+H]^+$
	found:	539.2312 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.34 min (*Z*)	539 m/z $[M+H]^+$.
	t_{ret} = 2.45 min (*E*)	539 m/z $[M+H]^+$.

(*E*)-*N*-(4-aminobutyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamide (4)



S3 (39.5 mg, 0.057 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 1mL:1mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and dried on high vacuum overnight. **4** (38 mg, 0.057 mmol, >99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

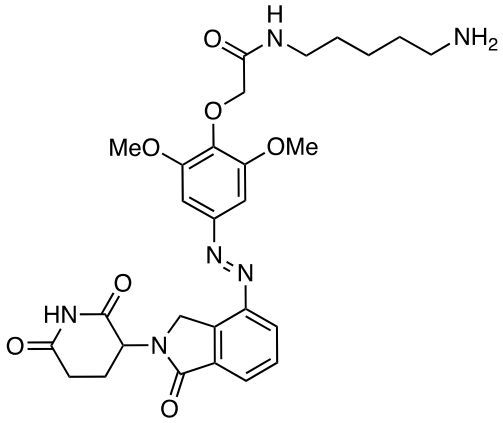
R_f = 0.4 [CH_2Cl_2:MeOH, 8:2].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.04 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 8.02 (t, *J* = 5.8 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.70 (s, 2H), 7.37 (s, 2H), 5.17 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.82 (d, *J* = 19.1 Hz, 1H), 4.69 (d, *J* = 19.1 Hz, 1H), 4.42 (s, 2H), 3.95 (s, 6H), 3.25 – 3.19 (m, 2H), 2.95 (ddd, *J* = 17.9, 13.7, 5.3 Hz, 1H), 2.86 – 2.79 (m, 2H), 2.67 – 2.53 (m, 2H), 2.11 – 2.03 (m, 1H), 1.58 – 1.51 (m, 4H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.92, 171.02, 168.11, 167.15, 152.66, 148.34, 146.35, 139.20, 134.48, 133.84, 129.68, 128.70, 125.54, 100.59, 71.83, 56.39, 51.83, 48.28, 38.58, 37.58, 31.28, 26.13, 24.46, 22.33 ppm.

HRMS (APCI):	calcd. for $C_{27}H_{33}N_6O_9^+$:	553.2405 m/z $[M+H]^+$
	found:	553.2384 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} =2.23 min (*Z*).	553 m/z $[M+H]^+$.
	t_{ret} =2.49 min (*E*).	553 m/z $[M+H]^+$.

(*E*)-*N*-(5-aminopentyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamide (S10)



S6 (40.5 mg, 0.057 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 1mL:1mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and dried on high vacuum overnight. **S10** (38.8 mg, 0.057 mmol, >99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

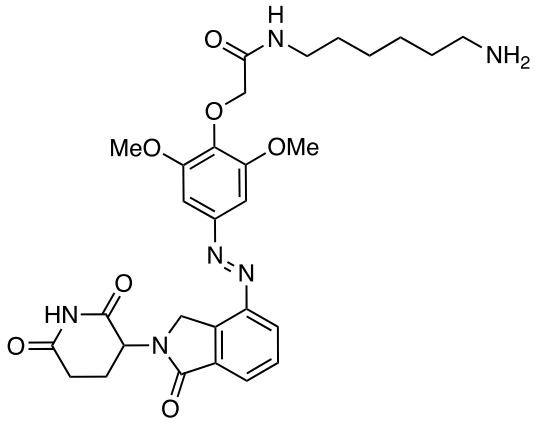
R_f = 0.03 [CH_2Cl_2:MeOH, 8:2].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 5.7 Hz, 1H), 7.93 (d, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.68 (s, 2H), 7.36 (s, 2H), 5.17 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.82 (d, *J* = 19.1 Hz, 1H), 4.69 (d, *J* = 19.1 Hz, 1H), 4.42 (s, 2H), 3.95 (s, 6H), 3.19 (q, *J* = 6.7 Hz, 2H), 2.95 (ddd, *J* = 17.9, 13.7, 5.3 Hz, 1H), 2.79 (h, *J* = 5.8 Hz, 2H), 2.68 – 2.53 (m, 2H), 2.11 – 2.03 (m, 1H), 1.53 (dp, *J* = 22.1, 7.5 Hz, 4H), 1.33 (p, *J* = 7.5, 6.9 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.92, 171.02, 168.00, 167.15, 152.64, 148.31, 146.35, 139.24, 134.49, 133.84, 129.67, 128.68, 125.53, 100.61, 71.85, 56.38, 51.83, 48.28, 38.76, 37.92, 31.29, 28.59, 26.67, 23.12, 22.33 ppm.

HRMS (ESI):	calcd. for $C_{28}H_{35}N_6O_7^+$:	567.2562 m/z $[M+H]^+$
	found:	567.2656 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.27 min (*Z*)	567 m/z $[M+H]^+$.
	t_{ret} = 2.53 min (*E*)	567 m/z $[M+H]^+$.

(*E*)-*N*-(6-aminohexyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamide (S11)



S7 (51.3 mg, 0.071 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 1mL:1mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and dried on high vacuum overnight. **S11** (49.3 mg, 0.071 mmol, >99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

R_f = 0.19 [CH_2Cl_2: MeOH, 9:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.03 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.94 (dd, *J* = 11.5, 6.5 Hz, 2H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.66 (s, 2H), 7.36 (s, 2H), 5.16 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.82 (d, *J* = 19.1 Hz, 1H), 4.69 (d, *J* = 19.1 Hz, 1H), 4.42 (s, 2H), 3.94 (s, 6H), 3.19 (q, *J* = 6.6 Hz, 2H), 2.95 (ddd, *J* = 17.9, 13.8, 5.3 Hz, 1H), 2.78 (h, *J* = 5.8 Hz, 2H), 2.63 (d, *J* = 18.1 Hz, 1H), 2.56 (dd, *J* = 13.1, 4.4 Hz, 1H), 2.06 (d, *J* = 5.4 Hz, 1H), 1.51 (dp, *J* = 13.7, 6.9 Hz, 4H), 1.37 – 1.25 (m, 4H) ppm.

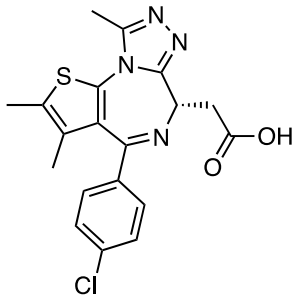
^{13}C NMR (100 MHz, DMSO) δ = 172.95, 171.04, 167.99, 167.18, 152.64, 148.32, 146.37, 139.28, 134.51, 133.85, 129.70, 128.71, 125.56, 100.63, 71.89, 56.40, 51.86, 48.31, 38.82, 38.09, 31.30, 28.95, 26.98, 25.84, 25.48, 22.35 ppm.

HRMS (APCI): calcd. for $C_{29}H_{37}N_6O_7^+$: 581.2718 m/z $[M+H]^+$

found: 581.2717 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 2.66 min. 581 m/z $[M+H]^+$.

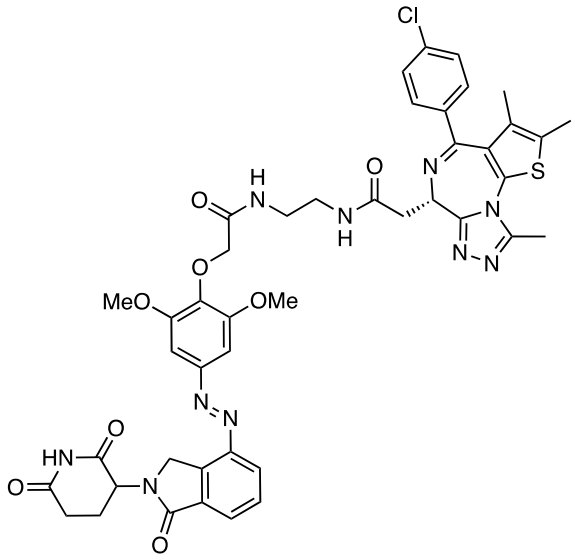
(*S*)-2-(4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetic acid ((+)-JQ1 free acid, 5)



As previously described,(*7*) (+)-JQ1 (9 mg, 0.02 mmol, 1 eq.) was dissolved in formic acid (0.5 mL) and stirred for 3 days at room temperature. The reaction was concentrated under reduced pressure and was dried on high vacuum overnight. **(+)-JQ1 free acid**, **5** (8.0 mg, 0.02 mmol, >99%) was obtained as yellow solid and used without further purification.

LCMS (ESI): t_{ret} = 3.35 min. 401, 402 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(2-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)ethyl)acetamide (PHOTAC-I-1)



S8 (15.3 mg, 0.024 mmol, 1 eq.) and HATU (11.7 mg, 0.036 mmol, 1.5 eq.) were added to a round bottom flask under nitrogen. **(+)-JQ1 free acid** was taken up in dry DMF (1 mL) and added to the mixture. After addition of *i*-Pr_2NEt (0.025 mL, 0.144 mmol, 6 eq.) the reaction was stirred for 15 h at room temperature. Then the mixture was diluted with EtOAc (20 mL), separated against H_2O (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-1** (8.6 mg, 0.009 mmol, 38%) as a yellow solid.

R_f = 0.19 [CH_2Cl_2:MeOH, 19:1].

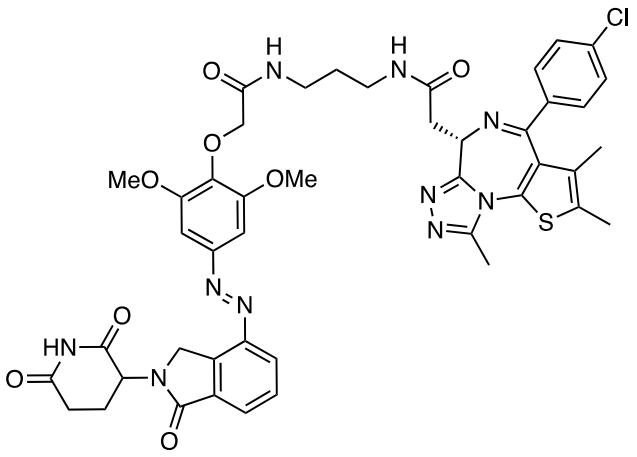
^{1}H NMR (400 MHz, Methanol-d_4) δ = 8.20 (d, *J* = 7.8 Hz, 1H), 7.90 (dd, *J* = 7.5, 4.1 Hz, 1H), 7.74 (td, *J* = 7.7, 2.8 Hz, 1H), 7.40 (dd, *J* = 8.7, 3.0 Hz, 2H), 7.36 – 7.28 (m, 4H), 5.23 – 5.09 (m, 1H), 4.83 (s, 2H), 4.60 – 4.47 (m, 3H), 3.96 (d, *J* = 2.8 Hz, 6H), 3.58 – 3.33 (m, 5H), 3.30 – 3.19 (m, 1H), 2.92 (ddt, *J* = 17.9, 13.4, 4.8 Hz, 1H), 2.79 (ddt, *J* = 17.8, 5.1, 2.8 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.58 (d, *J* = 19.6 Hz, 3H), 2.40 (d, *J* = 2.2 Hz, 3H), 2.25 – 2.14 (m, 1H), 1.66 (s, 3H).

^{13}C NMR (100 MHz, MeOD) δ = 174.68, 173.16, 172.58, 172.18, 170.35, 166.19, 156.89, 154.11, 152.07, 150.18, 148.12, 141.02, 138.01, 137.92, 135.56, 134.82, 133.42, 133.14, 132.07, 131.92, 131.57, 131.30, 130.69, 129.74, 126.55, 101.71,

73.23, 56.97, 54.99, 53.91, 50.68, 40.04, 39.91, 38.72, 32.42, 24.03, 14.39, 12.93, 11.58 ppm.

HRMS (ESI):	calcd. for $C_{44}H_{44}ClN_{10}O_8S^+$:	907.2747 m/z $[M+H]^+$
	found:	907.2790 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.51 min (*Z*).	907 m/z $[M+H]^+$.
	t_{ret} = 3.67 min (*E*).	907 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(3-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)propyl)acetamide (PHOTAC-I-2)



Into a round bottom flask with dry **(+)-JQ1 free acid** (7.2 mg, 0.018 mmol, 1 eq.) were added **S9** (23.5 mg, 0.036 mmol, 2 eq.) and HATU (11.7 mg, 0.036 mmol, 1.5 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (17 mg, 0.13 mmol, 7.2 eq., 0.023 mL) the reaction was stirred for 14 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-2** (15.1 mg, 0.016 mmol, 91%) as a yellow solid.

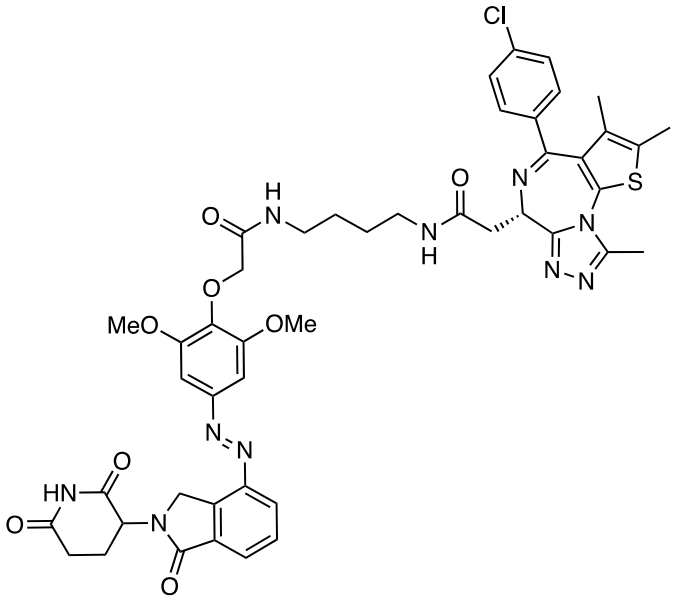
$\mathbf{R}_f$ = 0.31 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.52 (s, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.80 (t, *J* = 5.8 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 2.9 Hz, 2H), 7.07 (s, 1H), 5.28 – 5.19 (m, 1H), 4.85 (d, *J* = 18.0 Hz, 1H), 4.71 (dd, *J* = 18.1, 3.2 Hz, 1H), 4.63 (d, *J* = 6.8 Hz, 1H), 4.60 (s, 2H), 3.97 (s, 6H), 3.55 (dd, *J* = 14.4, 7.6 Hz, 1H), 3.42 (q, *J* = 6.4 Hz, 2H), 3.35 (q, *J* = 7.6, 6.9 Hz, 3H), 2.95 – 2.77 (m, 2H), 2.64 (s, 3H), 2.46 (dt, *J* = 12.9, 4.5 Hz, 1H), 2.38 (s, 3H), 2.28 – 2.18 (m, 1H), 1.79 (p, *J* = 6.4 Hz, 2H), 1.66 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.37, 170.84, 169.95, 169.72, 168.57, 164.10, 155.77, 152.78, 150.07, 148.99, 146.90, 139.86, 136.92, 136.69, 134.15, 133.46, 132.26, 131.02, 130.98, 130.58, 130.02, 129.96, 129.57, 128.83, 126.29, 100.64, 72.79, 56.55, 54.55, 52.12, 48.37, 39.39, 36.91, 36.45, 31.73, 29.76, 23.56, 14.52, 13.22, 11.94 ppm.

HRMS (ESI):	calcd. for $C_{45}H_{45}ClN_{10}NaO_8S^+$:	943.2723 m/z $[M+Na]^+$
	found:	943.2738 m/z $[M+Na]^+$.
LCMS (ESI):	t_{ret} = 3.71 min.	920 m/z $[M–H]^–$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(4-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)butyl)acetamide (PHOTAC-I-3)



Into a round bottom flask with dry **(+)-JQ1 free acid** (7.2 mg, 0.018 mmol, 1 eq.) were added **4** (26.6 mg, 0.04 mmol, 2 eq.) and HATU (11.7 mg, 0.036 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (18.6 mg, 0.144 mmol, 7.2 eq., 0.025 mL) the reaction was stirred for 16 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-3** (15.6 mg, 0.017 mmol, 85%) as a yellow solid.

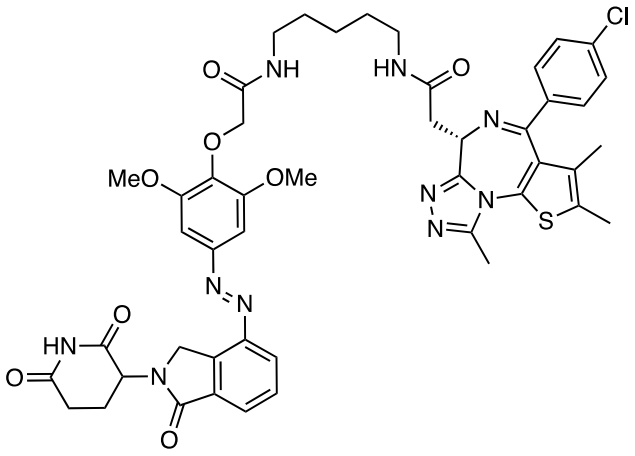
R_f = 0.30 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.80 (d, *J* = 67.2 Hz, 1H), 8.15 (t, *J* = 8.7 Hz, 1H), 8.00 – 7.92 (m, 1H), 7.75 (d, *J* = 4.9 Hz, 1H), 7.67 (q, *J* = 7.2 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.85 (dt, *J* = 10.4, 5.2 Hz, 1H), 5.21 (dd, *J* = 9.2, 3.9 Hz, 1H), 4.84 (d, *J* = 18.0 Hz, 1H), 4.69 (d, *J* = 18.0 Hz, 1H), 4.62 (d, *J* = 6.8 Hz, 3H), 3.97 (d, *J* = 2.5 Hz, 6H), 3.53 (dd, *J* = 12.5, 7.5 Hz, 1H), 3.42 – 3.23 (m, 5H), 2.90 – 2.72 (m, 2H), 2.64 (d, *J* = 5.4 Hz, 3H), 2.50 – 2.41 (m, 1H), 2.38 (s, 3H), 2.24 – 2.13 (m, 1H), 1.65 (s, 4H), 1.61 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.44, 170.62, 169.90, 169.64, 168.53, 164.21, 155.74, 152.69, 150.12, 148.91, 146.83, 139.88, 136.96, 136.68, 134.18, 133.45, 132.24, 131.04, 131.01, 130.58, 130.01, 129.94, 129.52, 128.85, 126.20, 100.64, 72.85, 56.54, 54.59, 52.10, 48.35, 39.46, 39.37, 38.78, 31.71, 27.17, 27.04, 23.54, 14.51, 13.21, 11.91 ppm.

HRMS (ESI):	calcd. for $C_{46}H_{48}ClN_{10}O_8S^+$:	935.3060 m/z $[M+H]^+$
	found:	973.2597 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.55 min (*Z*).	935 m/z $[M+H]^+$.
	t_{ret} = 3.74 min (*E*).	935 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(5-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)pentyl)acetamide (PHOTAC-I-4)



Into a round bottom flask with dry **(+)-JQ1 free acid** (7.2 mg, 0.018 mmol, 1 eq.) were added **S10** (24.4 mg, 0.036 mmol, 2 eq.) and HATU (10.5 mg, 0.032 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (16.7 mg, 0.129 mmol, 7.2 eq., 0.023 mL) the reaction was stirred for 15 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography

(CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-4** (15.4 mg, 0.016 mmol, 89%) as a yellow solid.

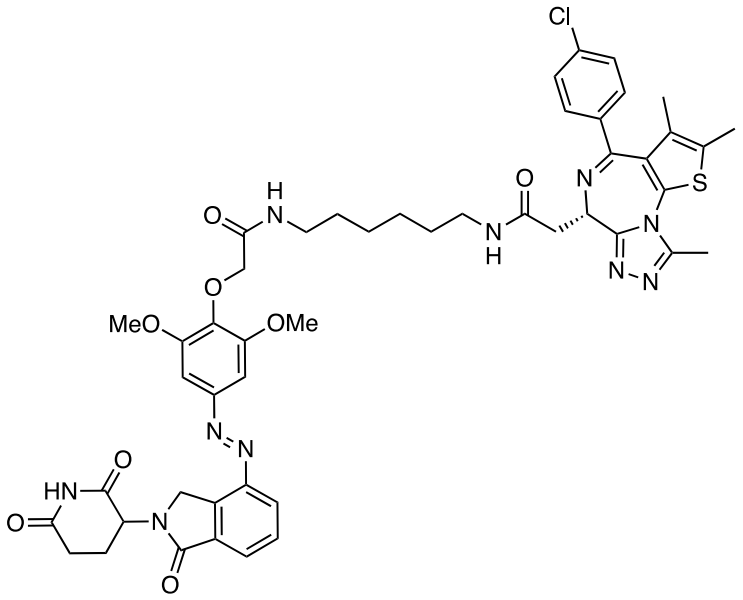
R_f = 0.31 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.66 (d, *J* = 14.5 Hz, 1H), 8.18 (dd, *J* = 7.6, 3.5 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 7.2 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.22 (d, *J* = 5.8 Hz, 2H), 6.79 – 6.68 (m, 1H), 5.23 (dt, *J* = 12.2, 5.2 Hz, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 4.60 (d, *J* = 11.6 Hz, 3H), 3.98 (s, 6H), 3.55 (dt, *J* = 10.9, 5.4 Hz, 1H), 3.31 (dt, *J* = 14.7, 5.9 Hz, 5H), 2.95 – 2.77 (m, 2H), 2.65 (s, 3H), 2.46 (d, *J* = 12.7 Hz, 1H), 2.39 (s, 3H), 2.31 – 2.14 (m, 1H), 1.66 (s, 3H), 1.57 (q, *J* = 6.9 Hz, 4H), 1.48 – 1.34 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.39, 170.62, 169.82, 169.59, 168.57, 164.15, 155.73, 152.71, 150.09, 148.96, 146.90, 139.89, 136.97, 136.67, 134.17, 133.45, 132.23, 131.05, 131.04, 130.59, 130.09, 129.94, 129.56, 128.86, 126.29, 100.65, 72.86, 56.53, 54.65, 52.11, 48.35, 39.58, 39.51, 38.92, 31.73, 29.37, 29.26, 24.30, 23.57, 14.51, 13.23, 11.92 ppm.

HRMS (ESI):	calcd. for $C_{47}H_{49}ClIKN_{10}O_8S^+$:	987.2776 m/z $[M+K]^+$
	found:	987.2755 m/z $[M+K]^+$.
LCMS (ESI):	t_{ret} = 3.83 min	949 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(6-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)hexyl)acetamide (PHOTAC-I-5)



Into a round bottom flask with dry **(+)-JQ1 free acid** (7.6 mg, 0.019 mmol, 1 eq.) were added **S11** (26.3 mg, 0.038 mmol, 2 eq.) and HATU (11.1 mg, 0.034 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (17.6 mg, 0.137 mmol, 7.2 eq., 0.024 mL) the reaction was stirred for 16 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-5** (16.4 mg, 0.017 mmol, 90%) as a yellow solid.

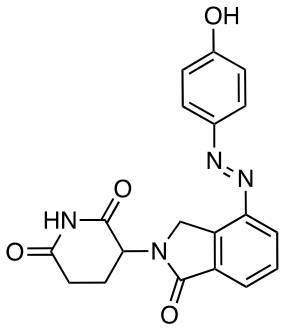
R_f = 0.31 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.78 (d, *J* = 29.2 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.26 (s, 1H), 7.22 (s, 1H), 6.72 – 6.60 (m, 1H), 5.22 (td, *J* = 13.8, 4.9 Hz, 1H), 4.93 – 4.79 (m, 1H), 4.70 (dd, *J* = 18.0, 5.8 Hz, 1H), 4.62 (s, 3H), 3.98 (d, *J* = 3.6 Hz, 6H), 3.54 (td, *J* = 7.7, 3.8 Hz, 1H), 3.38 – 3.21 (m, 5H), 2.96 – 2.74 (m, 2H), 2.64 (d, *J* = 10.7 Hz, 3H), 2.52 – 2.42 (m, 1H), 2.38 (s, 3H), 2.22 (s, 1H), 1.65 (s, 3H), 1.60 – 1.48 (m, 4H), 1.44 – 1.31 (m, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.42, 170.53, 169.87, 169.53, 168.56, 164.29, 155.70, 152.71, 150.10, 148.94, 146.88, 139.91, 136.98, 136.67, 134.29, 133.46, 132.27, 131.04, 131.02, 130.58, 129.96, 129.75, 129.56, 128.85, 126.29, 100.68, 72.91, 56.51, 54.65, 52.03, 48.24, 39.64, 39.51, 38.98, 31.74, 29.57, 29.55, 26.74, 26.70, 23.58, 14.50, 13.22, 11.88 ppm.

HRMS (ESI):	calcd. for $C_{48}H_{51}ClN_{10}NaO_8S^+$:	985.3193 m/z $[M+Na]^+$
	found:	985.3234 m/z $[M+Na]^+$.
LCMS (ESI):	t_{ret} = 3.93 min.	963 m/z $[M+H]^+$.

(*E*)-3-(4-((4-hydroxyphenyl)diazenyl)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (S12)



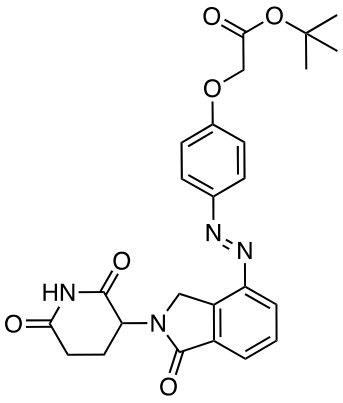
Lenalidomide (500 mg, 1.93 mmol, 1.0 eq.) was dissolved in 1 M HCl (50 mL). Concentrated aqueous HBF_4 (1 mL) was added to the mixture. After complete dissolving of the starting material, 2 M $NaNO_2$ (1.06 mL) was added to the solution at 0 °C. After stirring for 1 h the solution was added dropwise into a mixture of Phenol (217.9 mg, 2.315 mmol, 1.2 eq., 0.204 mL) in H_2O (50 mL), MeOH (20 mL), $NaHCO_3$ (4.000 g, 47.62 mmol, 24.7 eq.) and Na_2CO_3 (5.000 g, 47.18 mmol, 24.5 eq.) at 0°C. Upon addition the solution turned from white to orange and stirred for additional 1 h at 0°C. The reaction was extracted with EtOAc (7x 100 mL) and washed once with brine (1x 100 mL). The organic phase was dried over Na_2SO_4 and then concentrated under reduced pressure. **S12** (605.2 mg, 1.661 mmol, 86%) was obtained as a yellow solid.

R_f = 0.26 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (s, 1H), 10.42 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.97 – 7.68 (m, 4H), 6.96 (d, *J* = 8.1 Hz, 2H), 5.23 – 5.07 (m, 1H), 4.84 – 4.57 (m, 2H), 2.94 (t, *J* = 12.9 Hz, 1H), 2.67 – 2.54 (m, 2H), 2.10 – 1.95 (m, 1H) ppm.
^{13}C NMR (100 MHz, DMSO) δ = 172.92, 171.02, 167.28, 161.61, 146.70, 145.40, 134.16, 133.69, 129.50, 128.11, 125.16, 124.52, 115.97, 51.65, 48.21, 31.25, 22.34 ppm.

HRMS (ESI):	calcd. for $C_{19}H_{17}N_4O_4^+$:	365.1244 m/z $[M+H]^+$
	found:	365.1257 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.94 min.	365 m/z $[M+H]^+$.

(*E*)-3-(4-((4-(2-(*tert*-butoxy)-2-oxoethoxy)phenyl)diazenyl)-1-oxoisoindolin-2-yl)-2,6-dioxopiperidin-1-ium (S13)



To a solution of tert-butyl bromoacetate (267.6 mg, 1.372 mmol, 1 eq., 0.20 mL) was added **S12** (500 mg, 1.372 mmol, 1 eq.) dissolved in dry DMF (13 mL). After addition of K_2CO_3 (246.6 mg, 1.784 mmol, 1.3 eq.) the reaction was stirred for 6.5 h at room temperature. Upon addition the solution turned from orange to dark red. After 6.5 hours of stirring, the mixture was diluted with EtOAc (100 mL), separated against $NaHCO_3$ (50 mL), extracted with EtOAc (3x 50 mL) and washed with brine (4x 50 mL). The reaction was concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (Hx/Ea gradient, 20 → 100% Ea) gave **S13** (397.7 mg, 0831 mmol, 61%) as a yellow solid.

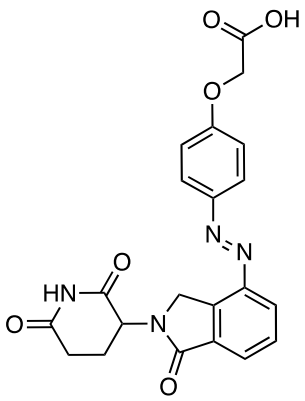
R_f = 0.44 [Hx:EA,1:4].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 8.03 – 7.94 (m, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.17 – 7.08 (m, 2H), 5.17 (dd, *J* = 13.5, 5.0 Hz, 1H), 4.79 (m, 3H), 4.67 (d, *J* = 18.9 Hz, 1H), 2.92 (d, *J* = 12.7 Hz, 1H), 2.58 (dd, *J* = 23.6, 14.7 Hz, 2H), 2.02 (dd, *J* = 16.0, 9.6 Hz, 1H), 1.44 (s, 9H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.92, 171.01, 167.42, 167.22, 160.89, 146.64, 146.60, 134.26, 133.75, 129.58, 128.58, 124.99, 124.73, 115.18, 81.70, 65.20, 51.66, 48.26, 31.25, 27.70, 22.32 ppm.

HRMS (APCI):	calcd. for $C_{25}H_{27}N_4O_6^+$:	479.1925 m/z $[M+H]^+$
	found:	479.1928 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.45 min.	479 m/z $[M+H]^+$.

(*E*)-3-(4-((4-(carboxymethoxy)phenyl)diazenyl)-1-oxoisoindolin-2-yl)-2,6-dioxopiperidin-1-ium (S14)



S13 (331.1 mg, 0.692 mmol, 1 eq.) was dissolved in CH_2Cl_2:TFA (1:1; 4 mL each). Upon TFA addition (4 mL) the solution turned from yellow to dark red. After 4 hours the reaction was concentrated under reduced pressure, turning from red to an orange solid. The reaction was triturated with Et_2O and dried under high vacuum for 24 h. **S14** (340.5 mg, 0.635 mmol, 92%) was obtained in form of a yellow solid.

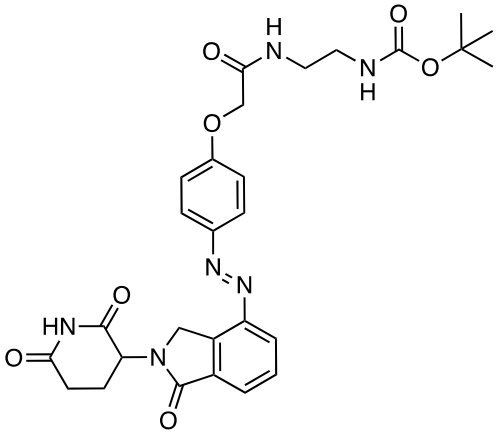
R_f = 0.10 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.01 (s, 1H), 8.22 – 8.13 (m, 1H), 8.02 – 7.94 (m, 2H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.20 – 7.09 (m, 2H), 5.16 (dd, *J* = 13.4, 5.0 Hz, 1H), 4.80 (m, 3H), 4.67 (d, *J* = 19.2 Hz, 1H), 2.94 (ddd, *J* = 18.4, 13.9, 5.3 Hz, 1H), 2.69 – 2.54 (m, 2H), 2.08 – 1.98 (m, 1H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.93, 171.01, 169.76, 167.23, 161.01, 146.62, 146.62, 134.32, 133.75, 129.58, 128.43, 124.97, 124.74, 115.19, 64.76, 51.68, 48.24, 31.25, 22.32 ppm.

HRMS (APCI):	calcd. for $C_{21}H_{19}N_4O_6^+$:	423.1299 m/z $[M+H]^+$
	found:	423.1284 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.01 min.	423 m/z $[M+H]^+$.

***tert*-butyl (*E*)-(2-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)ethyl)carbamate (S15)**



S14 (50.0 mg, 0.093 mmol, 1.0 eq.) and HATU (45.3 mg, 0.140 mmol, 1.5 eq.) were dissolved in dry DMF (4.5 mL) at room temperature under nitrogen atmosphere. After 5 minutes of stirring *N*-Boc-1,4-diaminoethane (80.7 mg, 0.373 mmol, 4 eq.) and *i*-Pr_2NEt (48.2 mg, 0.373 mmol, 4 eq., 66 μL) were added to the mixture and stirred for further 12 hours. The reaction was diluted with EtOAc (20 mL), separated against H_2O: sat. NaCl (20 mL), extracted with EtOAc (3x 20 mL) and washed with brine (4x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. **S15** (57.2 mg, 0.092 mmol, 99%) was obtained as an orange solid.

R_f = 0.38 [CH_2Cl_2:MeOH, 19:1].

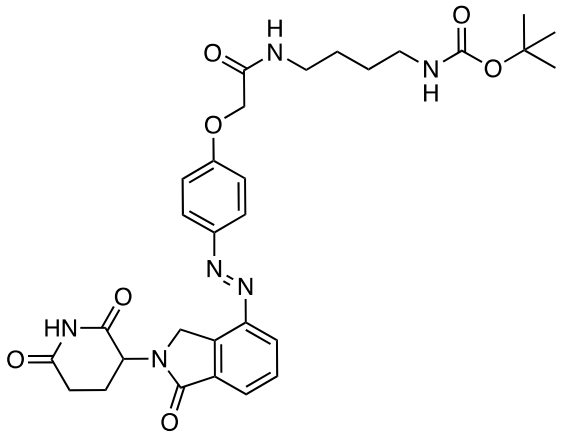
^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.99 (s, 1H), 8.20 (dd, *J* = 16.2, 6.6 Hz, 2H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.87 (q, *J* = 5.7, 4.7 Hz, 1H), 5.17 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.80 (d, *J* = 19.1 Hz, 1H), 4.67 (d, *J* = 19.3 Hz, 1H), 4.61 (s, 2H), 3.18 (q, *J* = 6.3 Hz, 2H), 3.04 (q,

J = 6.3 Hz, 2H), 2.96 – 2.88 (m, 1H), 2.60 (dd, *J* = 16.2, 12.6 Hz, 2H), 2.09 – 1.98 (m, 1H), 1.37 (s, 9H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.91, 171.00, 167.26, 167.21, 160.88, 155.74, 146.68, 146.59, 134.27, 133.74, 129.59, 128.52, 124.99, 124.75, 115.40, 77.73, 67.11, 51.66, 48.24, 38.72, 31.25, 28.22, 22.34, 22.30 ppm.

HRMS (APCI):	calcd. for $C_{28}H_{33}N_6O_7^+$:	565.2405 m/z $[M+H]^+$
	found:	565.2381 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.96 min (*Z*).	563 m/z $[M–H]^–$.
	t_{ret} = 3.38 min (*E*).	563 m/z $[M–H]^–$.

***tert*-butyl (*E*)-(4-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)butyl)carbamate (S16)**



S14 (50.0 mg, 0.093 mmol, 1.0 eq.) and HATU (46.0 mg, 0.142 mmol, 1.5 eq.) were dissolved in dry DMF (4.5 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,4-diaminobutane (70.2 mg, 0.373 mmol, 4 eq.) and *i*-Pr_2NEt (48.2 mg, 0.373 mmol, 4 eq., 66 μL) were added to the mixture and stirred for additional 12 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (3x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S16** (50.9 mg, 0.086 mmol, 92%) as an orange solid.

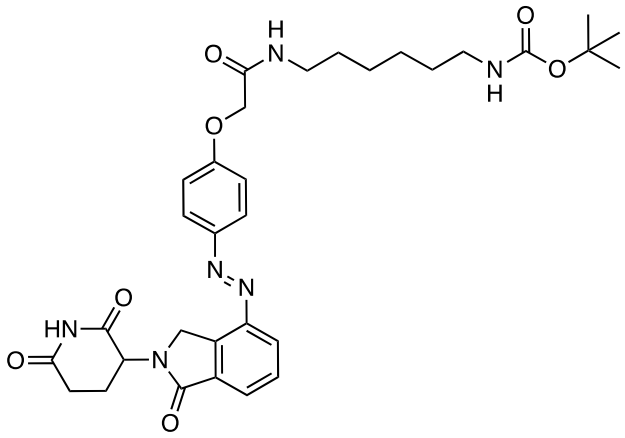
R_f = 0.38 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.18 (d, *J* = 7.9 Hz, 1H), 8.12 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.95 – 7.90 (m, 2H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.66 (s, 1H), 5.26 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.85 (d, *J* = 17.9 Hz, 1H), 4.74 (d, *J* = 18.0 Hz, 1H), 4.57 (s, 2H), 3.39 (q, *J* = 6.6 Hz, 2H), 3.14 (q, *J* = 6.5 Hz, 2H), 3.01 – 2.79 (m, 2H), 2.46 (qd, *J* = 13.1, 5.0 Hz, 1H), 2.26 (dtd, *J* = 12.9, 5.0, 2.5 Hz, 1H), 1.62 – 1.48 (m, 4H), 1.43 (s, 9H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.08, 169.55, 168.67, 167.59, 160.02, 156.19, 147.95, 147.09, 134.17, 133.37, 129.70, 129.57, 126.02, 125.12, 115.24, 79.43, 67.62, 52.11, 48.35, 40.26, 38.94, 31.74, 28.56, 27.69, 26.93, 23.61 ppm.

HRMS (APCI):	calcd. for $C_{30}H_{37}N_6O_7^+$:	593.2718 m/z $[M+H]^+$
	found:	593.2700 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.17 min (*Z*).	591 m/z $[M–H]^–$.
	t_{ret} = 3.53 min (*E*).	591 m/z $[M–H]^–$.

***tert*-butyl (*E*)-(6-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)hexyl)carbamate (S17)**



S14 (50.0 mg, 0.093 mmol, 1.0 eq.) and HATU (45.3 mg, 0.140 mmol, 1.5 eq.) were dissolved in dry DMF (4.5 mL) at room temperature. After 5 minutes of stirring *N*-Boc-1,4-diaminohexane (80.7 mg, 0.373 mmol, 4 eq.) and *i*-Pr_2NEt (48.2 mg, 0.373 mmol, 4 eq., 66 μL) were added to the mixture and stirred for additional 12 h at room temperature. The reaction was diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (3x 20 mL) and washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude

product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0-20% MeOH) gave **S17** (57.2 mg, 0.092 mmol, 99%) as an orange solid.

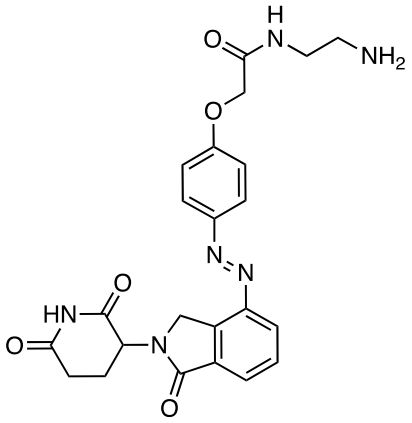
R_f = 0.34 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.19 (d, *J* = 7.8 Hz, 1H), 8.04 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 8.9 Hz, 2H), 6.59 (s, 1H), 5.26 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.86 (d, *J* = 17.9 Hz, 1H), 4.74 (d, *J* = 18.0 Hz, 1H), 4.59 (s, 2H), 3.36 (q, *J* = 6.8 Hz, 2H), 3.09 (s, 2H), 3.00 – 2.79 (m, 2H), 2.46 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.27 (ddd, *J* = 13.9, 7.0, 3.6 Hz, 1H), 1.55 (d, *J* = 7.0 Hz, 2H), 1.50 – 1.43 (m, 2H), 1.44 (s, 9H), 1.34 (d, *J* = 6.0 Hz, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.90, 169.91, 169.40, 168.53, 167.38, 159.95, 147.82, 146.98, 134.03, 133.25, 129.63, 129.45, 125.90, 125.00, 115.11, 79.16, 67.54, 51.96, 48.19, 40.29, 38.93, 31.61, 30.00, 29.47, 28.44, 26.34, 26.23, 23.50 ppm.

HRMS (ESI):	calcd. for $C_{32}H_{41}N_6O_7^+$:	621.3031 m/z $[M+H]^+$
	found:	621.3017 m/z $[M+H]^+$.
LCMS (APCI):	t_{ret} = 3.44 min. (*Z*)	619 m/z $[M–H]^–$.
	t_{ret} = 3.80 min. (*E*)	619 m/z $[M–H]^–$.

(*E*)-*N*-(2-aminoethyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamide (S18)



S15 (35.0 mg, 0.062 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 1mL:1mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and

dried on high vacuum overnight. **S18** (34.5 mg, 0.06 mmol, 96%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

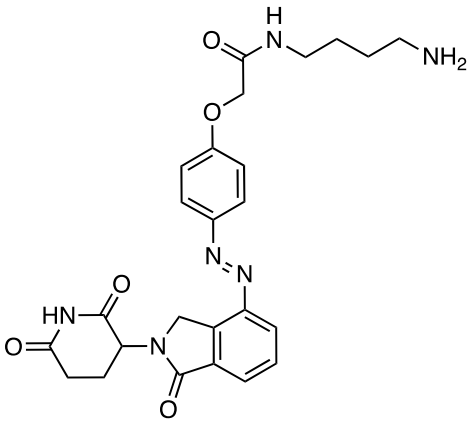
R$_f$ = 0.13 [CH_2Cl_2+1%TEA:MeOH, 5:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.02 (s, 1H), 8.36 (t, *J* = 6.0 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 7.4 Hz, 1H), 7.83 – 7.71 (m, 4H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.19 (d, *J* = 13.4 Hz, 1H), 4.80 (d, *J* = 19.1 Hz, 1H), 4.67 (d, *J* = 16.9 Hz, 3H), 2.99 – 2.87 (m, 3H), 2.69 – 2.51 (m, 1H), 2.11 – 1.98 (m, 1H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.93, 171.02, 168.11, 167.21, 160.73, 146.76, 146.58, 134.27, 133.76, 129.62, 128.57, 125.07, 124.80, 115.44, 67.14, 51.65, 48.22, 38.72, 36.20, 31.25, 22.35 ppm.

HRMS (APCI):	calcd. for $C_{23}H_{25}N_6O_5^+$:	465.1881 m/z $[M+H]^+$
	found:	465.1887 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.00 min (*Z*).	465 m/z $[M+H]^+$.
	t_{ret} = 2.32 min (*E*).	465 m/z $[M+H]^+$.

***N*-(4-aminobutyl)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamide (S19)**



S16 (40.0 mg, 0.067 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 1mL:1mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and dried on high vacuum overnight. **S19** (40.5 mg, 0.067 mmol, 99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

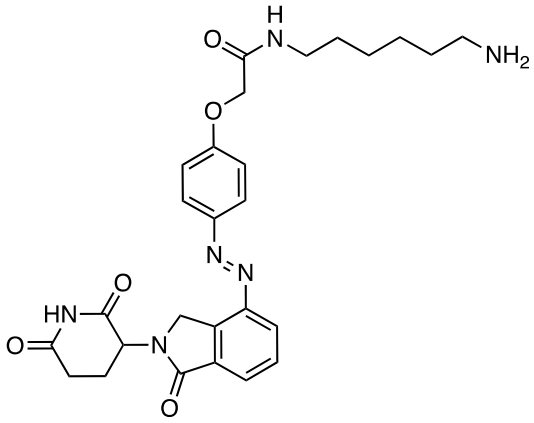
R_f = 0.13 [CH_2Cl_2+1%TEA:MeOH, 5:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.02 (s, 1H), 8.26 (t, *J* = 5.9 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.03 – 7.97 (m, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.67 (s, 2H), 7.22 – 7.14 (m, 2H), 5.18 (dd, *J* = 13.1, 5.0 Hz, 1H), 4.80 (d, *J* = 19.1 Hz, 1H), 4.67 (d, *J* = 19.3 Hz, 1H), 4.62 (s, 2H), 3.17 (q, *J* = 6.2 Hz, 2H), 2.94 (dd, *J* = 10.9, 6.4 Hz, 1H), 2.80 (q, *J* = 6.4 Hz, 2H), 2.65 – 2.54 (m, 2H), 2.05 (d, *J* = 6.1 Hz, 1H), 1.51 (hept, *J* = 6.0, 5.4 Hz, 4H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.94, 171.03, 167.22, 167.09, 160.89, 146.71, 146.59, 134.28, 133.76, 129.62, 128.53, 125.04, 124.78, 115.41, 67.18, 51.65, 48.22, 38.60, 37.67, 31.25, 26.18, 24.48, 22.34 ppm.

HRMS (APCI):	calcd. for $C_{25}H_{29}N_6O_5^+$:	493.2194 m/z $[M+H]^+$
	found:	493.2177 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.21 min (*Z*)	493 m/z $[M+H]^+$.
	t_{ret} = 2.44 min (*E*)	493 m/z $[M+H]^+$.

***Tert*-butyl-(6-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)-acetamido)hexyl)carbamate (S20)**



S17 (44.5 mg, 0.072 mmol, 1 eq.) was dissolved in TFA/CH_2Cl_2 (1:1; 2mL:2mL) and stirred for 2 h at room temperature. The reaction was diluted with CH_2Cl_2 and concentrated under reduced pressure. The reaction was triturated with Et_2O and dried on high vacuum overnight. **S20** (45.6 mg, 0.072 mmol, >99%) was obtained as trifluoroacetate in form of a yellow solid with traces of residual TFA.

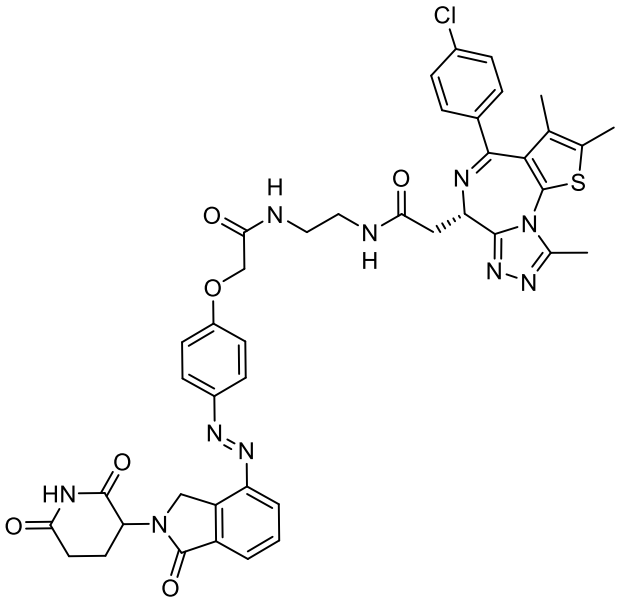
R_f = 0.16 [CH_2Cl_2+1%TEA:MeOH, 5:1].

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.02 (s, 1H), 8.24 – 8.14 (m, 2H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.66 (s, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 5.18 (dd, *J* = 13.2, 5.0 Hz, 1H), 4.80 (d, *J* = 19.1 Hz, 1H), 4.67 (d, *J* = 19.4 Hz, 1H), 4.61 (s, 2H), 3.14 (q, *J* = 6.7 Hz, 2H), 2.94 (ddd, *J* = 21.8, 11.5, 4.6 Hz, 1H), 2.76 (h, *J* = 6.2 Hz, 2H), 2.67 – 2.53 (m, 2H), 2.04 (dt, *J* = 11.8, 4.5 Hz, 1H), 1.57 – 1.39 (m, 4H), 1.29 (tq, *J* = 11.9, 7.0 Hz, 4H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.94, 171.03, 167.22, 166.92, 160.95, 146.69, 146.59, 134.29, 133.76, 129.61, 128.51, 125.03, 124.75, 115.40, 67.19, 51.66, 48.23, 38.78, 38.19, 31.25, 28.93, 26.95, 25.84, 25.46, 22.34 ppm.

HRMS (APCI):	calcd. for $C_{27}H_{33}N_6O_5^+$:	521.2507 m/z $[M+H]^+$
	found:	521.2498 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 2.37 min (cis)	521 m/z $[M+H]^+$.
	t_{ret} = 2.80 min (trans)	521 m/z $[M+H]^+$.

2-((*R*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(2-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)ethyl)acetamide (PHOTAC-I-6)



Into a round bottom flask with dry (+)-JQ1 free acid (6.0 mg, 0.015 mmol, 1 eq.) were added **S18** (17.3 mg, 0.030 mmol, 2 eq.) and HATU (8.7 mg, 0.027 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (17.6 mg, 0.137 mmol, 7.2 eq., 0.024 mL) the reaction was stirred

for 15 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5%LiCl (30 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-6** (12.4 mg, 0.015 mmol, 98%) as a yellow solid.

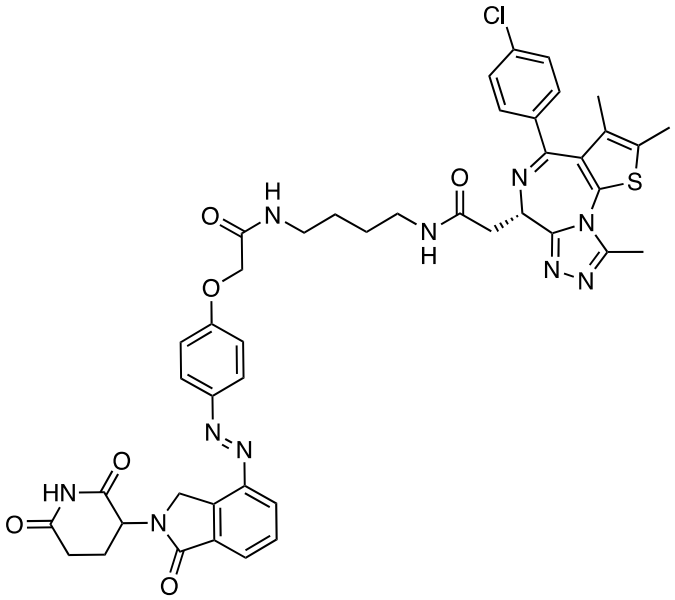
R_f = 0.10 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.71 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.55 (s, 1H), 7.37 (d, *J* = 8.2 Hz, 3H), 7.29 (d, J = 8.3 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.19 (dt, *J* = 13.5, 4.6 Hz, 1H), 4.74 (d, *J* = 18.9 Hz, 1H), 4.64 (dt, *J* = 11.4, 5.9 Hz, 2H), 4.43 (s, 2H), 3.48 (dddd, *J* = 51.8, 22.1, 11.6, 5.5 Hz, 6H), 2.93 – 2.74 (m, 2H), 2.61 (s, 3H), 2.45 (s, 1H), 2.35 (s, 3H), 2.24 – 2.14 (m, 1H), 1.62 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.67, 171.50, 169.95, 168.67, 168.28, 164.30, 160.24, 155.76, 150.14, 147.54, 147.01, 137.04, 136.62, 134.10, 133.41, 132.22, 131.10, 130.50, 130.00, 129.73, 129.69, 129.47, 128.88, 125.67, 124.97, 115.18, 67.39, 54.46, 52.25, 48.67, 39.80, 39.33, 39.11, 31.65, 23.44, 14.49, 13.22, 11.91 ppm.

HRMS (ESI):	calcd. for $C_{42}H_{39}ClN_{10}NaO_6S^+$:	869.2355 m/z $[M+Na]^+$
	found:	869.2362 m/z $[M+Na]^+$.
LCMS (ESI):	t_{ret} = 3.44 min (*Z*).	847 m/z $[M+H]^+$.
	t_{ret} = 3.74 min (*E*).	847 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(4-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)butyl)acetamide (PHOTAC-I-7)



Into a round bottom flask with dry (+)-JQ1 free acid (6.0 mg, 0.015 mmol, 1 eq.) were added **S19** (18.2 mg, 0.030 mmol, 2 eq.) and HATU (8.7 mg, 0.027 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (13.9 mg, 0.108 mmol, 7.2 eq., 0.020 mL) the reaction was stirred for 16 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (30 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-7** (12.7 mg, 0.015 mmol, 97%) as a yellow solid.

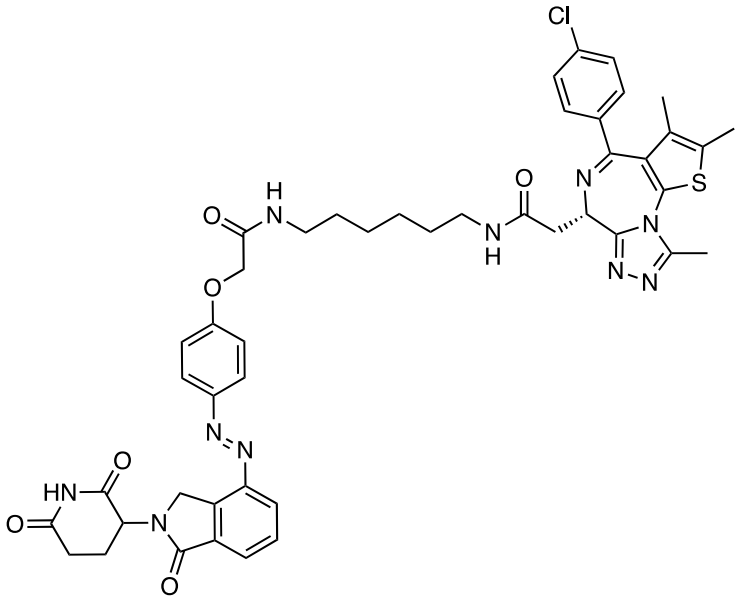
R$_f$ = 0.09 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.57 (s, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.92 (t, *J* = 7.1 Hz, 1H), 6.82 (s, 1H), 5.23 (dt, *J* = 13.4, 4.3 Hz, 1H), 4.80 (dd, *J* = 18.1, 3.2 Hz, 1H), 4.71 (dd, *J* = 18.1, 4.5 Hz, 1H), 4.62 (t, *J* = 7.1 Hz, 1H), 4.51 (s, 2H), 3.56 (dd, *J* = 14.3, 8.2 Hz, 1H), 3.34 (qd, *J* = 17.8, 15.6, 6.3 Hz, 5H), 2.94 – 2.75 (m, 2H), 2.64 (s, 3H), 2.51 – 2.43 (m, 1H), 2.37 (s, 3H), 2.27 – 2.18 (m, 1H), 1.65 (s, 3H), 1.57 (s, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.33, 170.67, 169.81, 168.65, 167.67, 164.26, 160.15, 155.72, 150.14, 147.78, 147.05, 137.03, 136.63, 134.15, 133.40, 132.22, 131.11, 130.58, 129.99, 129.75, 129.69, 129.52, 128.88, 125.86, 125.09, 115.25, 67.60, 54.63, 52.09, 48.45, 39.52, 39.12, 38.85, 31.70, 26.89, 26.79, 23.53, 14.51, 13.22, 11.93 ppm.

HRMS (ESI):	calcd. for $C_{44}H_{43}ClIKN_{10}O_6S^+$:	913.2408 m/z $[M+K]^+$
	found:	913.2419 m/z $[M+K]^+$.
LCMS (ESI):	t_{ret} = 3.48 min (*Z*).	875 m/z $[M+H]^+$.
	t_{ret} = 3.71 min (*E*).	875 m/z $[M+H]^+$.

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-*N*-(6-(2-(4-((*E*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)hexyl)acetamide (PHOTAC-I-8)



Into a round bottom flask with dry (+)-JQ1 free acid (6.0 mg, 0.015 mmol, 1 eq.) were added **S20** (19.0 mg, 0.030 mmol, 2 eq.) and HATU (8.7 mg, 0.027 mmol, 1.8 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (13.9 mg, 0.108 mmol, 7.2 eq., 0.020 mL) the reaction was stirred for 18 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (30 mL), extracted with EtOAc (2x 20 mL), washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the

resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-I-8** (12.8 mg, 0.014 mmol, 95%) as a yellow solid.

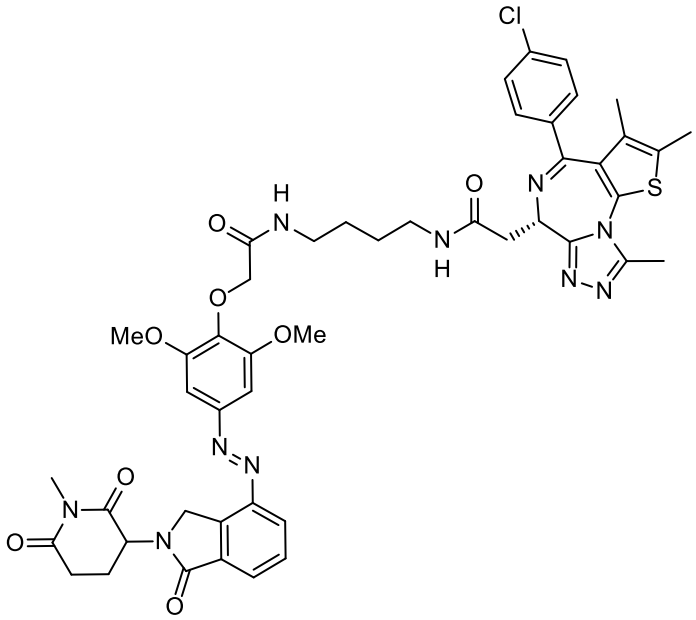
R_f = 0.16 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.51 (d, *J* = 28.6 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.76 – 6.66 (m, 1H), 6.61 (d, *J* = 4.7 Hz, 1H), 5.24 (d, *J* = 13.1 Hz, 1H), 4.84 (d, *J* = 18.0 Hz, 1H), 4.73 (d, *J* = 18.1 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 3H), 3.55 (dd, *J* = 14.0, 8.0 Hz, 1H), 3.29 (dd, *J* = 28.3, 5.6 Hz, 5H), 2.96 – 2.77 (m, 2H), 2.64 (s, 3H), 2.46 (dt, *J* = 13.0, 6.7 Hz, 1H), 2.38 (s, 3H), 2.30 – 2.18 (m, 1H), 1.65 (s, 3H), 1.51 (s, 4H), 1.31 (s, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.27, 170.59, 169.77, 168.65, 167.62, 164.16, 160.14, 155.76, 150.07, 147.88, 147.09, 136.98, 136.69, 134.19, 133.41, 132.26, 131.05, 130.57, 129.97, 129.73, 129.67, 129.53, 128.86, 125.94, 125.11, 115.25, 67.69, 54.66, 52.07, 48.36, 39.58, 39.43, 38.92, 31.74, 29.47, 29.45, 26.34, 26.27, 23.58, 14.51, 13.23, 11.93 ppm.

HRMS (ESI):	calcd. for $C_{46}H_{47}ClN_{10}NaO_6S^+$:	925.2981 m/z $[M+Na]^+$
	found:	925.2975 m/z $[M+Na]^+$.
LCMS (ESI):	t_{ret} = 3.57 min (*Z*)	903 m/z $[M+H]^+$.
	t_{ret} = 3.85 min (*E*)	903 m/z $[M+H]^+$.

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-(2-(2,6-dimethoxy-4-((E)-(2-(1-methyl-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)butyl)acetamide (Me-PHOTAC-I-3)



Into a round bottom flask with dry **PHOTAC-I-3** (10.0 mg, 0.011 mmol, 1 eq.) was added K_2CO_3 (3.0 mg, 0.021 mmol, 2 eq.) under nitrogen atmosphere. The solids were dissolved in dry DMF (1 mL) and methyl iodide (1.8 mg, 0.013 mmol, 1.2 eq.) was added. The reaction was stirred for 16 h at room temperature. The mixture was then diluted with EtOAc (20 mL) and separated against 5% LiCl (20 mL). The aqueous phase was extracted with EtOAc (2x 10 mL), and the combined organic phases were washed with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **Me-PHOTAC-I-3** (5.2 mg, 0.005 mmol, 51%) as a yellow solid.

R_f = 0.37 [CH_2Cl_2:MeOH, 19:1].

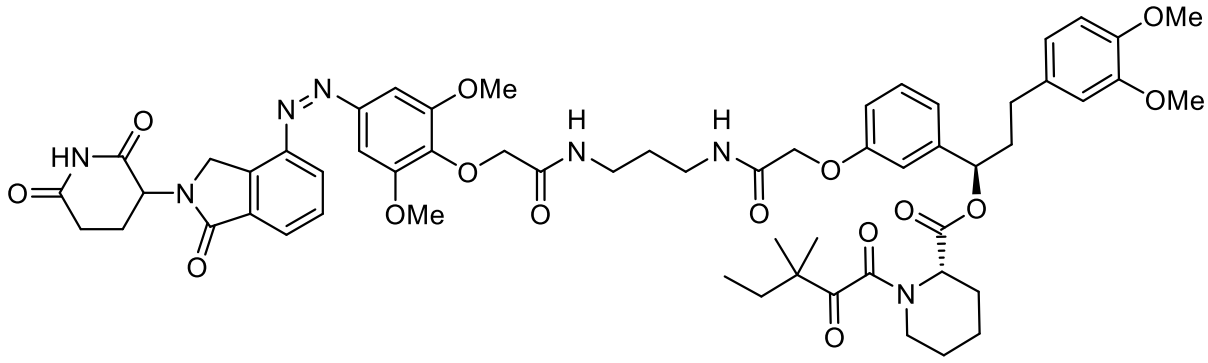
^{1}H NMR (400 MHz, DMSO-d_6) δ = δ 8.26 – 8.18 (m, 2H), 7.98 – 7.91 (m, 2H), 7.80 (t, J = 7.7 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.35 (s, 2H), 5.23 (dd, J = 13.5, 5.0 Hz, 1H), 4.83 (d, J = 19.1 Hz, 1H), 4.69 (d, J = 19.0 Hz, 1H), 4.51 (ddd, J = 7.9, 6.1, 1.3 Hz, 1H), 4.44 (s, 2H), 3.94 (s, 6H), 3.29 – 3.10 (m, 6H), 3.02 (s,

3H), 3.08 – 2.98 (m, 1H), 2.79 (ddd, J = 17.3, 4.5, 2.4 Hz, 1H), 2.59 (s, 3H), 2.63 – 2.55 (m, 1H), 2.40 (s, 3H), 2.12 – 2.04 (m, 1H), 1.61 (s, 3H), 1.58 – 1.44 (m, 4H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6) δ = 171.92, 170.64, 169.33, 167.98, 167.19, 163.05, 155.06, 152.58, 149.85, 148.28, 146.38, 139.31, 136.68, 135.23, 134.66, 133.81, 132.22, 130.74, 130.10, 129.83, 129.65, 129.56, 128.45, 128.41, 125.52, 100.61, 71.92, 56.37, 53.84, 52.36, 48.24, 38.20, 37.96, 37.60, 31.42, 26.69, 26.63, 26.62, 21.59, 14.04, 12.67, 11.28 ppm.

HRMS (ESI):	calcd. for $C_{47}H_{50}ClN_{10}O_8S^+$:	949.3217 m/z $[M+H]^+$
	found:	949.3235 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 3.94 min (*Z*).	949 m/z $[M+H]^+$.
	t_{ret} = 4.19 min (*E*).	949 m/z $[M+H]^+$.

(1R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((3-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)propyl)-amino)-2-oxoethoxy)phenyl)propyl-(2S)-1-(3,3-dimethyl-2-oxopentanoyl)-piperidine-2-carboxylate (PHOTAC-II-1)



Into a round bottom flask with dry **2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid** (10.2 mg, 0.017 mmol, 1 eq.) were added **S9** (22.8 mg, 0.035 mmol, 2 eq.) and HATU (12 mg, 0.031 mmol, 1.8 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (17 mg, 0.13 mmol, 7.5 eq., 0.023 mL) the reaction was stirred for 14 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure.

Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-II-1** (17.8 mg, 0.016 mmol, 92%) as a yellow solid.

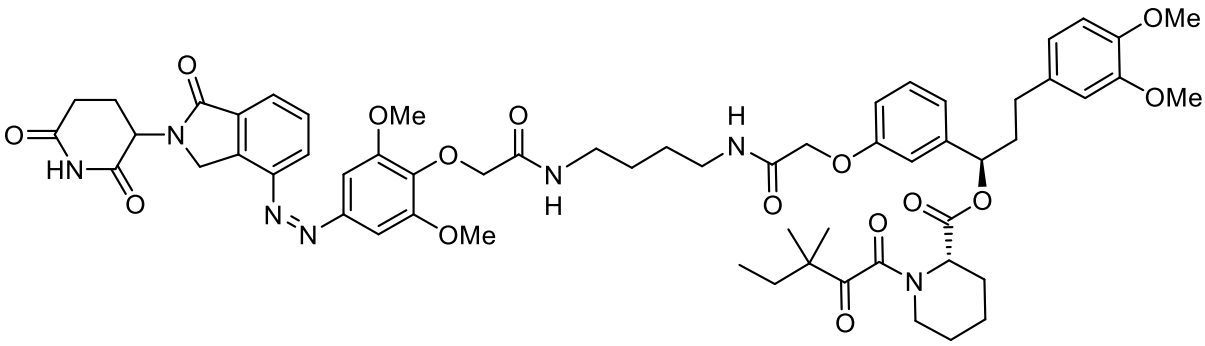
R_f = 0.59 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.33 (s, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 6.3 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 6.3 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.21 (s, 2H), 7.00 – 6.92 (m, 2H), 6.87 (dd, J = 8.2, 2.8 Hz, 1H), 6.80 – 6.73 (m, 1H), 6.69 – 6.65 (m, 2H), 5.77 (dd, J = 8.0, 5.6 Hz, 1H), 5.30 (d, J = 4.9 Hz, 1H), 5.25 (dd, J = 13.4, 5.1 Hz, 1H), 4.85 (d, J = 17.8 Hz, 1H), 4.72 (d, J = 17.8 Hz, 1H), 4.60 (d, 2H), 4.46 (s, 2H), 3.96 (s, 6H), 3.86 – 3.81 (m, 6H), 3.47 – 3.33 (m, 5H), 3.16 (td, J = 13.2, 3.2 Hz, 1H), 2.95 – 2.81 (m, 2H), 2.64 – 2.42 (m, 3H), 2.36 (d, J = 13.9 Hz, 1H), 2.28 – 2.18 (m, 2H), 2.04 (dtd, J = 11.6, 9.7, 4.8 Hz, 1H), 1.83 – 1.57 (m, 7H), 1.47 (qt, J = 13.0, 4.0 Hz, 1H), 1.35 (tt, J = 13.6, 3.6 Hz, 1H), 1.20 (d, J = 11.9 Hz, 6H), 0.87 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.01, 171.22, 170.36, 169.77, 169.65, 168.55, 168.42, 167.38, 157.54, 152.75, 149.04, 148.99, 147.46, 146.88, 141.90, 139.76, 134.09, 133.49, 133.44, 130.08, 130.07, 129.61, 126.37, 120.25, 120.17, 114.23, 113.49, 111.81, 111.41, 100.56, 76.64, 72.73, 67.36, 56.50, 56.04, 55.96, 52.12, 51.39, 48.33, 46.82, 44.28, 38.28, 36.21, 36.08, 32.59, 31.73, 31.35, 29.84, 26.53, 25.06, 23.59, 23.57, 23.25, 21.32, 8.88 ppm.

HRMS (ESI):	calcd. for $C_{58}H_{73}N_8O_{15}^+$:	1121.5189 m/z $[M+NH_4]^+$
	found:	1121.5246 m/z $[M+NH_4]^+$.
LCMS (ESI):	t_{ret} = 4.56 min.	1104 m/z $[M+H]^+$.

(1R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((4-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)butyl)-amino)-2-oxoethoxy)phenyl)propyl(2S)-1-(3,3-dimethyl-2-oxopentanoyl)-piperidine-2-carboxylate (PHOTAC-II-2)



Into a round bottom flask with dry **2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid** (10.2 mg, 0.018 mmol, 1 eq.) were added **3** (23.3 mg, 0.035 mmol, 2 eq.) and HATU (12 mg, 0.031 mmol, 1.8 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (17 mg, 0.13 mmol, 7.5 eq., 0.023 mL) the reaction was stirred for 14 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-II-2** (17.7 mg, 0.016 mmol, 91%) as a yellow solid.

R_f = 0.59 [CH_2Cl_2:MeOH, 9:1].

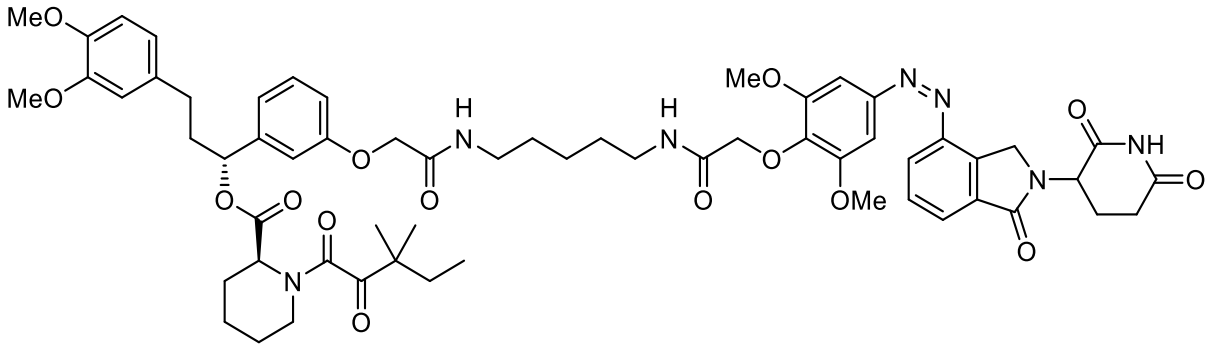
^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.35 (s, 1H), 8.19 (dd, J = 7.8, 1.0 Hz, 1H), 7.99 (dd, J = 7.5, 1.0 Hz, 1H), 7.74 – 7.67 (m, 2H), 7.28 (t, J = 7.9 Hz, 1H), 7.22 (s, 2H), 6.99 – 6.93 (m, 2H), 6.84 – 6.75 (m, 3H), 6.70 – 6.64 (m, 2H), 5.79 – 5.73 (m, 1H), 5.33 – 5.27 (m, 1H), 5.24 (dd, J = 13.4, 5.1 Hz, 1H), 4.85 (d, J = 17.9 Hz, 1H), 4.72 (d, J = 17.8 Hz, 1H), 4.60 (s, 2H), 4.48 (s, 2H), 3.98 (s, 6H), 3.86 – 3.82 (m, 6H), 3.44 – 3.32 (m, 5H), 3.16 (td, J = 13.2, 3.2 Hz, 1H), 2.92 – 2.80 (m, 2H), 2.65 – 2.43 (m, 3H), 2.36 (d, J = 14.0 Hz, 1H), 2.28 – 2.18 (m, 2H), 2.04 (ddt, J = 13.9, 10.1, 5.9

Hz, 1H), 1.78 – 1.59 (m, 9H), 1.48 (qt, J = 13.2, 4.4 Hz, 1H), 1.35 (tt, J = 13.3, 3.4 Hz, 1H), 1.20 (d, J = 8.2 Hz, 6H), 0.87 (t, J = 7.5 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.03, 171.25, 169.78, 169.69, 169.68, 168.55, 168.20, 167.37, 157.43, 152.73, 149.00, 148.99, 147.47, 146.87, 142.04, 139.81, 134.13, 133.46, 133.44, 130.13, 130.01, 129.59, 126.33, 120.26, 120.24, 113.88, 113.63, 111.82, 111.41, 100.58, 76.54, 72.82, 67.37, 56.50, 56.04, 55.96, 52.15, 51.37, 48.38, 46.82, 44.27, 38.82, 38.69, 38.29, 32.59, 31.72, 31.34, 27.22, 27.20, 26.52, 25.06, 23.56, 23.53, 23.31, 21.29, 8.89 ppm.

HRMS (ESI):	calcd. for $C_{59}H_{72}N_7O_{15}^+$:	1118.5081 m/z $[M+H]^+$
	found:	1118.5081 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.56 min.	1118 m/z $[M+H]^+$.

(1*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((5-(2-(4-((*Z*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)pentyl)amino)-2-oxoethoxy)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylate (PHOTAC-II-3)



Into a round bottom flask with dry **2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid** (10.0 mg, 0.018 mmol, 1 eq.) were added **S10** (25.1 mg, 0.034 mmol, 2 eq.) and HATU (11.7 mg, 0.031 mmol, 1.8 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (15.5 mg, 0.12 mmol, 7 eq., 0.021 mL) the reaction was stirred for 14 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined

organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-II-3** (14.4 mg, 0.013 mmol, 74%) as a yellow solid.

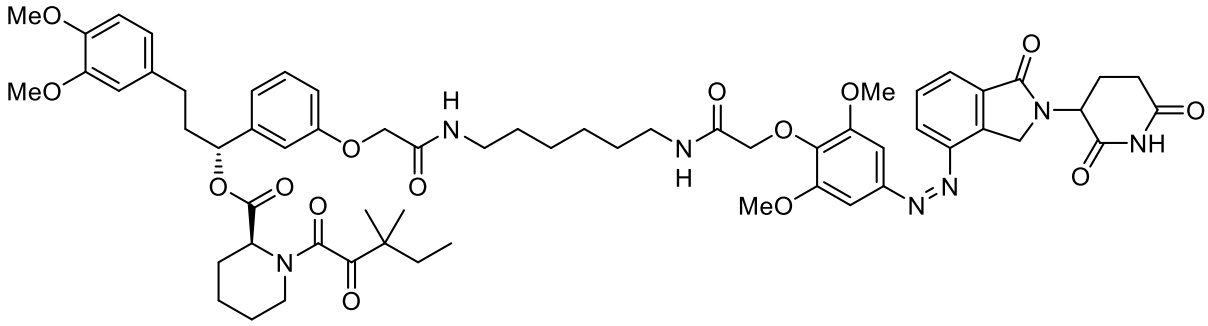
R_f = 0.28 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.36 (d, *J* = 3.6 Hz, 1H), 8.20 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.22 (s, 2H), 7.00 – 6.92 (m, 2H), 6.82 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.71 – 6.63 (m, 2H), 5.77 (dd, *J* = 8.2, 5.5 Hz, 1H), 5.31 (d, *J* = 6.1 Hz, 1H), 5.25 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.86 (d, *J* = 17.8 Hz, 1H), 4.72 (d, *J* = 17.8 Hz, 1H), 4.61 (s, 2H), 4.47 (s, 2H), 3.98 (s, 6H), 3.87 – 3.81 (m, 6H), 3.35 (q, *J* = 6.7 Hz, 5H), 3.21 – 3.12 (m, 1H), 3.04 – 2.90 (m, 1H), 2.85 (ddd, *J* = 18.1, 13.3, 5.2 Hz, 1H), 2.59 – 2.41 (m, 3H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.24 (m, 2H), 2.04 (m, 1H), 1.81 – 1.57 (m, 9H), 1.48 (m, 1H), 1.44 – 1.30 (m, 3H), 1.20 (d, *J* = 8.0 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.03, 171.19, 169.79, 169.68, 169.64, 168.55, 168.17, 167.38, 157.45, 152.72, 149.03, 149.00, 147.49, 146.89, 142.04, 139.85, 134.11, 133.45, 133.42, 130.14, 130.06, 129.60, 126.36, 120.27, 120.24, 113.85, 113.70, 111.83, 111.42, 100.59, 76.54, 72.81, 67.38, 56.51, 56.05, 55.97, 52.13, 51.37, 48.33, 46.83, 44.28, 39.04, 38.91, 38.30, 32.60, 31.75, 31.35, 29.44, 29.35, 26.53, 25.07, 24.24, 23.59, 23.57, 23.32, 21.30, 8.90 ppm.

HRMS (APCI):	calcd. for $C_{60}H_{74}N_7O_{15}^+$:	1132.5273 m/z $[M+H]^+$
	found:	1132.5217 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.67 (*Z*) min.	566.7 m/z $[M+2H]^{2+}$.
	t_{ret} = 4.83 (E) min.	566.7 m/z $[M+2H]^{2+}$.

(1*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((6-(2-(4-((*Z*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)hexyl)amino)-2-oxoethoxy)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylate (PHOTAC-II-4)



Into a round bottom flask with dry **2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid** (10.0 mg, 0.018 mmol, 1 eq.) were added **S11** (23.8 mg, 0.034 mmol, 2 eq.) and HATU (11.7 mg, 0.031 mmol, 1.8 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (15.5 mg, 0.12 mmol, 7 eq., 0.021 mL) the reaction was stirred for 14 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-II-4** (16.9 mg, 0.015 mmol, 86%) as a yellow solid.

R_f = 0.33 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (600 MHz, Chloroform-*d*) δ = 8.30 (s, 1H), 8.20 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.00 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.65 (t, *J* = 5.9 Hz, 1H), 7.29 (td, *J* = 7.9, 3.6 Hz, 1H), 7.22 (s, 2H), 7.00 – 6.88 (m, 2H), 6.85 – 6.75 (m, 2H), 6.72 (t, *J* = 6.0 Hz, 1H), 6.70 – 6.64 (m, 2H), 5.82 – 5.69 (m, 1H), 5.31 (d, *J* = 5.9 Hz, 1H), 5.26 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.85 (d, *J* = 17.8 Hz, 1H), 4.72 (d, *J* = 17.8 Hz, 1H), 4.60 (s, 2H), 4.48 (d, *J* = 2.5 Hz, 2H), 3.98 (s, 6H), 3.85 (dd, *J* = 4.8, 2.5 Hz, 6H),

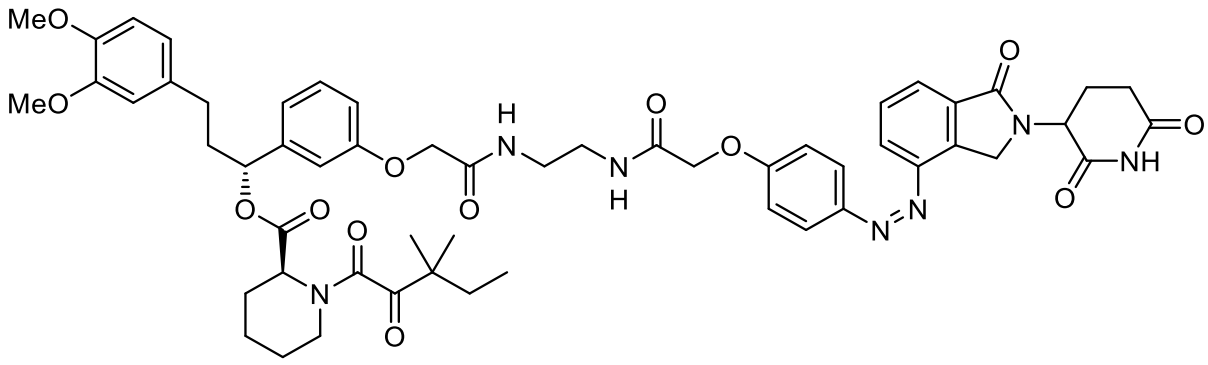
3.40 – 3.30 (m, 5H), 3.16 (td, *J* = 13.2, 3.1 Hz, 1H), 3.01 – 2.78 (m, 2H), 2.61 – 2.42 (m, 3H), 2.36 (d, *J* = 14.0 Hz, 1H), 2.24 (dddd, *J* = 17.8, 15.2, 7.8, 5.4 Hz, 2H), 2.10 – 1.99 (m, 1H), 1.80 – 1.52 (m, 9H), 1.48 (dt, *J* = 13.1, 4.0 Hz, 1H), 1.38 (tt, *J* = 10.4, 4.7 Hz, 5H), 1.21 (d, *J* = 8.3 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, $CDCl_3$) δ = 208.01, 171.17, 169.79, 169.63, 169.50, 168.54, 168.08, 167.37, 157.49, 152.74, 149.01, 148.99, 147.50, 146.91, 142.03, 139.91, 134.10, 133.45, 133.45, 130.14, 130.04, 129.61, 126.36, 120.27, 120.23, 113.89, 113.70, 111.84, 111.43, 100.59, 76.54, 72.88, 67.44, 56.50, 56.06, 55.97, 52.12, 51.37, 48.29, 46.83, 44.28, 39.12, 38.98, 38.30, 32.61, 31.74, 31.35, 29.74, 29.64, 26.69, 26.67, 26.52, 25.08, 23.61, 23.58, 23.32, 21.30, 8.90 ppm.

HRMS (APCI): calcd. for $C_{61}H_{76}N_7O_{15}^+$: 1146.5394 m/z $[M+H]^+$
found: 1146.5392 m/z $[M+H]^+$.

LCMS (ESI): t_{ret} = 4.89 min. 573 m/z $[M+2H]^{2+}$.

(1*R*)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((2-(2-(4-((*Z*)-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)diazenyl)phenoxy)acetamido)ethyl)amino)-2-oxoethoxy)phenyl)propyl (2*S*)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylate (PHOTAC-II-5)



Into a round bottom flask with dry **2-(3-((R)-3-(3,4-dimethoxyphenyl)-1-(((S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carbonyl)oxy)propyl)phenoxy)acetic acid** (8.0 mg, 0.014 mmol, 1 eq.) were added **S18** (15.9 mg, 0.027 mmol, 2 eq.) and HATU (9.4 mg, 0.025 mmol, 1.8 eq.) under nitrogen. The reaction was dissolved in dry DMF (1 mL). After addition of *i*-Pr_2NEt (12.4 mg, 0.096 mmol, 7 eq., 0.02 mL) the

reaction was stirred for 15 h at room temperature. The mixture was then diluted with EtOAc (20 mL), separated against 5% LiCl (20 mL), extracted with EtOAc (2x 20 mL) and washed twice with 10% LiCl (2x 20 mL) and brine (2x 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification of the resulting crude product by flash column chromatography (CH_2Cl_2/MeOH gradient, 0→20% MeOH) gave **PHOTAC-II-5** (9.1 mg, 0.009 mmol, 65%) as a yellow solid.

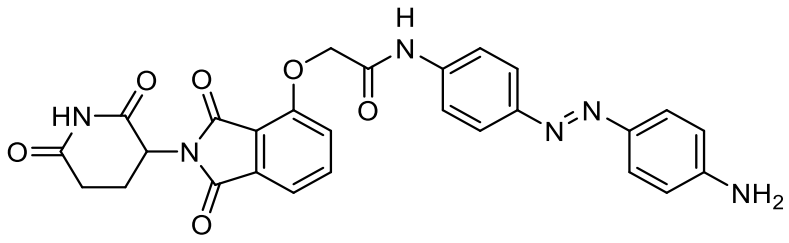
R_f = 0.17 [CH_2Cl_2:MeOH, 19:1].

^{1}H NMR (600 MHz, DMSO-d_6) δ = 11.02 (s, 1H), 8.30 (d, *J* = 5.0 Hz, 1H), 8.21 (d, *J* = 5.3 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 7.29 (q, *J* = 7.9 Hz, 1H), 7.19 – 7.15 (m, 2H), 6.96 (dd, *J* = 4.3, 2.2 Hz, 2H), 6.92 – 6.88 (m, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.73 (m, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 5.71 – 5.65 (m, 1H), 5.16 (m, 2H), 4.78 (d, *J* = 19.0 Hz, 1H), 4.67 (d, *J* = 18.9 Hz, 1H), 4.60 (s, 2H), 4.47 (s, 2H), 3.71 (s, 3H), 3.69 (s, 3H), 3.29 – 3.19 (m, 5H), 3.10 (t, *J* = 12.3 Hz, 1H), 2.94 (ddd, *J* = 17.9, 13.4, 5.4 Hz, 1H), 2.61 (d, *J* = 18.2 Hz, 1H), 2.57 – 2.45 (m, 4H), 2.23 (d, *J* = 13.3 Hz, 1H), 2.20 – 2.08 (m, 1H), 2.06 – 1.98 (m, 2H), 1.74 – 1.50 (m, 4H), 1.40 – 1.29 (m, 1H), 1.14 (s, 3H), 1.12 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 1H), 0.78 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (150 MHz, DMSO) δ = 207.64, 172.91, 171.00, 169.32, 167.92, 167.46, 167.22, 166.82, 160.86, 157.72, 148.63, 147.06, 146.68, 146.58, 141.63, 134.28, 133.74, 133.13, 129.72, 129.57, 128.49, 124.99, 124.74, 119.91, 119.00, 115.41, 114.13, 112.98, 112.10, 111.87, 75.99, 67.10, 66.97, 55.47, 55.32, 51.66, 50.89, 48.24, 46.17, 43.84, 38.23, 38.16, 37.59, 31.93, 31.25, 30.62, 26.06, 24.36, 22.88, 22.60, 22.33, 20.77, 8.58 ppm.

HRMS (APCI):	calcd. for $C_{55}H_{64}N_7O_{13}^+$:	1030.4557 m/z $[M+H]^+$
	found:	1030.4565 m/z $[M+H]^+$.
LCMS (ESI):	t_{ret} = 4.70 min.	1030 m/z $[M+H]^+$.

(*E*)-N-(4-((4-aminophenyl)diazenyl)phenyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide (S21)



To a solution of thalidomide-4-hydroxyacetate(*61*) (16.7 mg, 50 µmol, 1.0 eq.) and 4,4'-diaminoazobenzene (32 mg, 150 µmol, 3.0 eq.) in THF (1.9 mL) was added HOBt (6.8 mg, 50 µmol, 1.0 eq.), PyBOP (52 mg, 100 µmol, 2.0 eq.) and triethylamine (35 µL, 26 mg, 250 µmol, 5.0 eq.) at room temperature. The reaction was stirred overnight, upon which the reaction solution was diluted with EtOAc, washed with water, sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by column chromatography over SiO_2 using 0% → 10% MeOH in CH_2Cl_2 as the eluent to afford the desired product **S21** (21 mg, 40 µmol, 79%) as a highly insoluble brown solid.

R_f = 0.51 [CH_2Cl_2:MeOH, 19:1].

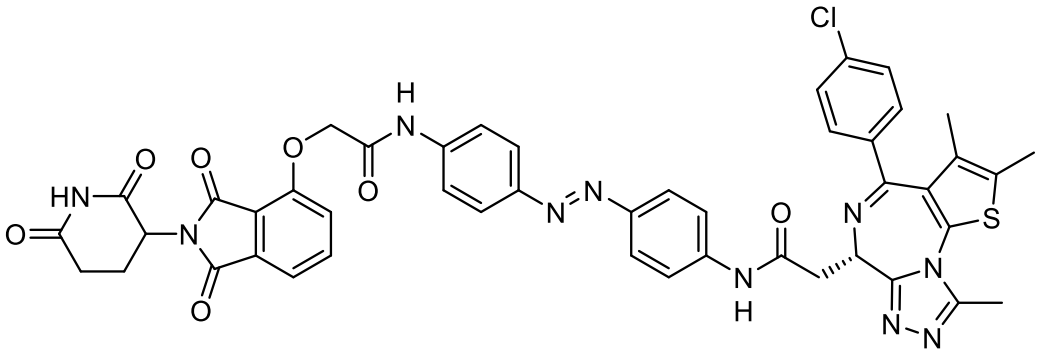
^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.13 (s, 1H), 10.35 (s, 1H), 7.83 (t, *J* = 7.9 Hz, 1H), 7.76 (s, 4H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.05 (s, 2H), 5.15 (dd, *J* = 12.9, 5.4 Hz, 1H), 5.05 (s, 2H), 2.99 – 2.80 (m, 1H), 2.59 (t, 2H), 2.07 (d, *J* = 13.0 Hz, 2H) ppm.

^{13}C NMR (100 MHz, DMSO) δ = 172.8, 169.9, 166.7, 165.9, 165.5, 155.2, 152.5, 148.5, 142.8, 139.4, 137.0, 133.1, 124.9, 122.6, 120.5, 119.6, 116.7, 116.1, 113.4, 67.6, 48.8, 31.0, 22.0 ppm.

HRMS (ESI): calcd. for $C_{27}H_{22}N_6NaO_6^+$: 549.1493 *m/z* $[M+Na]^+$
found: 549.1478 *m/z* $[M+Na]^+$.

LCMS T_R = 3.521 min

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-((E)-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)phenyl)acetamide (PHOTAC-I-10)



To a solution of **S37** (5.0 mg, 9.5 µmol, 1.0 eq.) and (+)-JQ1 free acid (4.2 mg, 10.4 µmol, 1.1 eq.) DCE (1.0 mL) was added TBTU (4.0 mg, 12.3 µmol, 1.3 eq.) and DIPEA (2 µL, 14.2 µmol, 1.5 eq.) at room temperature. The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction was diluted with EtOAc and washed with water, NaHCO3 and brine. The organics were dried over sodium sulfate and concentrated in vacuo. The residue was purified by column chromatography over SiO_2 using 0% →10% MeOH in CH_2Cl_2 as the eluent to afford the desired product **PHOTAC-I-10** (3.0 mg, 3.3 µmol, 35%) as an orange amorphous solid.

R_F = 0.32 [CH_2Cl_2:MeOH, 95:5].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.46 (s, 1H), 9.36 (d, *J* = 6.0 Hz, 1H), 8.21 (d, *J* = 10.7 Hz, 1H), 7.82 (d, *J* = 1.9 Hz, 4H), 7.75 (dd, *J* = 8.9, 2.3 Hz, 2H), 7.69 (ddd, *J* = 8.5, 7.5, 2.0 Hz, 1H), 7.66 – 7.60 (m, 2H), 7.51 (dd, *J* = 7.4, 3.5 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 1.3 Hz, 1H), 4.97 (ddd, *J* = 12.3, 5.4, 2.0 Hz, 1H), 4.71 (s, 2H), 4.63 (dd, *J* = 8.7, 5.4 Hz, 1H), 3.87 – 3.76 (m, 1H), 3.49 (dd, *J* = 14.3, 5.3 Hz, 1H), 2.92 – 2.85 (m, 1H), 2.85 – 2.78 (m, 1H), 2.78 – 2.71 (m, 1H), 2.63 (s, 3H), 2.35 (s, 3H), 2.17 – 2.08 (m, 1H), 1.63 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 170.9, 169.1, 168.1, 166.7, 166.5, 165.0, 164.4, 155.8, 154.4, 150.3, 149.6, 149.0, 140.9, 139.6, 137.4, 137.2, 136.5, 133.6,

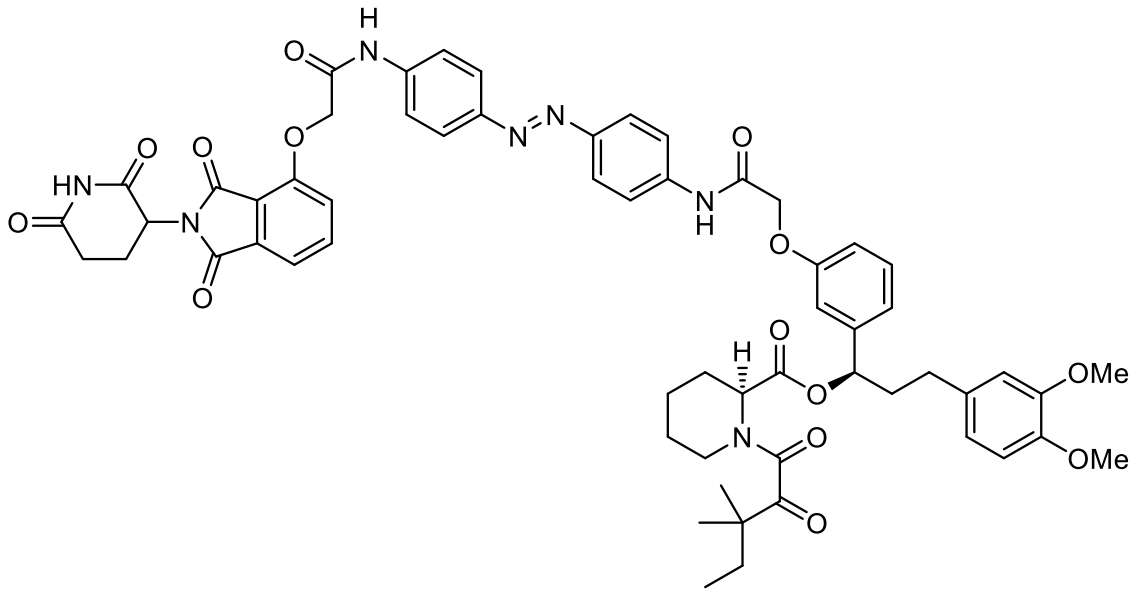
132.2, 131.3, 131.1, 130.6, 130.1, 128.9, 124.0, 123.9, 120.1, 120.0, 119.9, 118.0, 68.5, 54.7, 49.6, 40.8, 31.6, 22.7, 14.6, 13.3, 12.0 ppm.

HRMS (ESI): calcd. for $C_{46}H_{37}ClN_{10}O_7SNa^+$: 931.2148 *m/z* $[M+Na]^+$

found: 931.2167 *m/z* $[M+Na]^+$.

LCMS T_R = 4.642 min

(1R)-3-(3,4-dimethoxyphenyl)-1-(3-(2-((4-((E)-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)phenyl)amino)-2-oxoethoxy)phenyl)propyl (2S)-1-(3,3-dimethyl-2-oxopentanoyl)piperidine-2-carboxylate (PHOTAC-II-6)



To a solution of **S37** (6.0 mg, 11.4 µmol, 1.0 eq.) and SLF free acid (7.3 mg, 12.5 µmol, 1.1 eq.) in DMF (1.2 mL) was added HATU (5.6 mg, 14.8 µmol, 1.3 eq.) and DIPEA (3 µL, 17.1 µmol, 1.5 eq.) at room temperature. The reaction was allowed to stir at room temperature overnight. Upon completion, the reaction was diluted with EtOAc and washed with water, $NaHCO_3$ and brine. The organics were dried over sodium sulfate and concentrated to afford an orange amorphous solid. The residue was purified by column chromatography using 0% →50% acetone in CH_2Cl_2 to afford

the desired product **PHOTAC-II-6** (8.1 mg, 7.4 µmol, 65%) as an orange amorphous solid.

R_f = 0.15 [CH_2Cl_2:Acetone, 9:1].

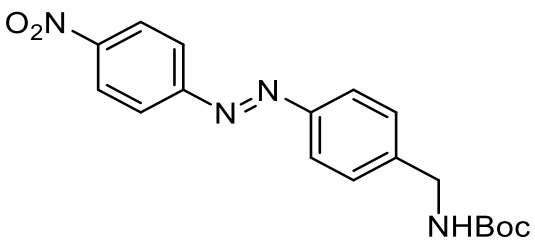
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.55 (s, 1H), 8.55 (d, *J* = 22.1 Hz, 1H), 8.24 (d, *J* = 3.7 Hz, 1H), 7.98 – 7.90 (m, 6H), 7.82 – 7.72 (m, 3H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.24 (s, 1H), 7.11 – 7.03 (m, 1H), 7.03 – 6.99 (m, 1H), 6.93 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.82 – 6.73 (m, 1H), 6.67 (d, *J* = 6.2 Hz, 2H), 5.81 (dd, *J* = 8.0, 5.3 Hz, 1H), 5.34 (d, *J* = 5.6 Hz, 1H), 5.04 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.79 (s, 2H), 4.65 (s, 2H), 3.85 (d, *J* = 5.9 Hz, 6H), 3.35 (s, 2H), 3.22 – 3.11 (m, 1H), 3.01 – 2.74 (m, 4H), 2.67 – 2.51 (m, 2H), 2.39 – 2.20 (m, 2H), 2.17 (d, *J* = 2.1 Hz, 4H), 2.07 (td, *J* = 9.0, 7.2, 3.9 Hz, 1H), 1.84 – 1.56 (m, 5H), 1.52 – 1.28 (m, 0H), 1.25 (s, 7H), 1.21 (d, *J* = 1.8 Hz, 5H), 0.87 (t, *J* = 7.4 Hz, 4H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 208.1, 170.9, 169.9, 168.0, 167.4, 166.6, 166.5, 166.3, 165.0, 157.3, 154.4, 149.5, 149.5, 149.0, 147.5, 142.2, 139.9, 139.3, 137.4, 133.6, 133.4, 130.3, 124.1, 124.0, 120.7, 120.3, 120.3, 120.1, 120.1, 118.6, 118.0, 114.1, 113.8, 111.9, 111.9, 111.4, 76.5, 68.5, 67.7, 56.1, 56.0, 53.9, 53.6, 51.4, 49.6, 46.9, 44.3, 38.3, 32.6, 31.6, 31.3, 31.1, 29.4, 26.5, 25.1, 23.5, 23.4, 22.7, 21.2, 14.3, 8.9 ppm.

HRMS (ESI):	calcd. for $C_{59}H_{62}N_7O_{14}^+$:	1092.4355 *m/z* $[M+H]^+$
	found:	1092.4334 *m/z* $[M+H]^+$.

LCMS T_R = 5.265 min

tert-butyl (_E_)-(4-((4-nitrophenyl)diazenyl)benzyl)carbamate (S22)



The following procedure was carried out in two steps:

Oxone Oxidation:

To a solution of 4-nitroaniline (566 mg, 4.1 mmol, 1.0 eq) in CH_2Cl_2 (14.6 mL) was added a solution of oxone (2.5 g, 4.1 mmol, 1.0 eq) in water (14.6 mL). The biphasic mixture was stirred vigorously under N_2 atmosphere. After 3 hours, phases were separated and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined and then washed with 1 M HCl, sat. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to approximately 5 mL. The resulting yellow-black solution of nitrosobenzene in CH_2Cl_2 was carried on to the next step immediately.

Mills Reaction:

To the nitrosobenzene solution in CH_2Cl_2, prepared as described above, was added sequentially tert-butyl (4-aminobenzyl)carbamate(*62*) (910 mg, 4.1 mmol, 1.0 eq) and glacial AcOH (1.2 mL, 20 mmol, 5.000 eq). The reaction mixture was allowed to stir for 15 hours under N2 atmosphere, after which time the reaction mixture was found to be an orange-black suspension. EtOAc was added and the organic phase was washed with 1 M NaOH, sat. $NaHCO_3$, sat. NaCl. The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure. Crude material was purified by flash column chromatography over SiO_2 using a gradient from 1% → 5% → 10% EtOAc in Hexanes as the eluent, affording **S22** (900 mg, 2.5 mmol, 62%) as a crystalline red solid.

$\mathbf{R}_f$ = 0.24 [Hexanes:EtOAc, 85:15].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.37 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.9 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 4.98 (s, 1H), 4.42 (d, *J* = 5.3 Hz, 2H), 1.48 (s, 2H) ppm.

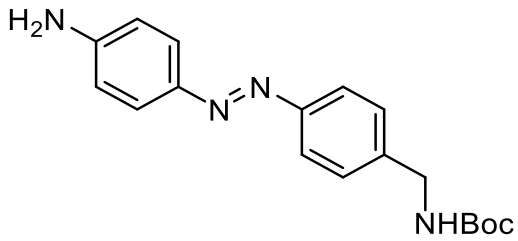
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 155.8, 151.8, 148.8, 144.0, 128.2, 124.9, 123.9, 123.6, 80.0, 44.5, 28.5 ppm.

HRMS (APCI): calcd. for $C_{13}H_{13}N_4O_2^+$: 257.1033 *m/z* $[M\text{-Boc+H}]^+$

found: 257.1041 *m/z* $[M\text{-Boc+H}]^+$.

LCMS T_R = 4.736 min

***tert*-butyl (*E*)-(4-((4-aminophenyl)diazenyl)benzyl)carbamate (S23)**



To a solution of **S22** (100.0 mg, 270 µmol, 1.0 eq.) in dioxane (4.0 mL) and water (0.4 mL) in a pressure tube was added $Na_2S{\cdot}9H_2O$ (202 mg, 842 µmol, 3.0 eq.). The reaction was sealed and heated to 85 °C. After 1 hour, the reaction was diluted with water and the aqueous layer was extracted 3 times with EtOAc. The organics were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo to afford an orange-red solid. The reaction was loaded onto isolute and purified by column chromatography over SiO_2 using a stepped gradient from 9:1 →1:1 Hexanes/EtOAc as the eluent to afford **S23** (70.0 mg, 215 µmol, 76%) as a pale orange solid.

R_f = 0.14 [Hexanes:EtOAc, 8:2].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.80 (dd, *J* = 8.6, 3.0 Hz, 4H), 7.37 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 4.96 (s, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 4.21 – 3.92 (m, 2H), 1.47 (s, 10H).

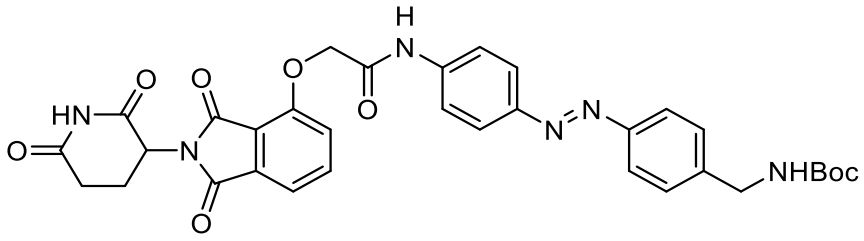
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 152.3, 149.8, 145.6, 140.8, 128.1, 125.2, 122.7, 114.7, 79.7, 44.5, 28.5.

HRMS (APCI): calcd. for $C_{18}H_{23}N_4O_4^+$: 327.1816 *m/z* $[M+H]^+$

found: 327.1804 *m/z* $[M+H]^+$.

LCMS T_R = 4.032 min

***tert*-butyl (*E*)-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)benzyl)carbamate (S24)**



Thalidomide-4-hydroxyacetate (*61*) (20.0 mg, 60.2 µmol, 1.0 eq) and **S23** (29.5 mg, 90.3 µmol, 1.5 eq) were dissolved in DMF (600 µL) followed by the addition of HATU (25.2 mg, 66.2 µmol, 1.1 eq) and DIPEA (21 µL, 120 µmol, 2.0 eq) at rt. The reaction was allowed to stir at rt overnight. The reaction was diluted with water, extracted 3 times with EtOAc, organics were combined, washed with bicarb and brine and dried over sodium sulfate. Concentration of organics and purification by column chromatography over SiO_2 using 8:1.5:0.5 DCM/EtOAc/MeOH as the mobile phase afforded **S24** (37 mg, 57.8 µmol, 96%) as an orange amorphous solid.

R_f = 0.06 [Hexanes:EtOAc, 1:1].

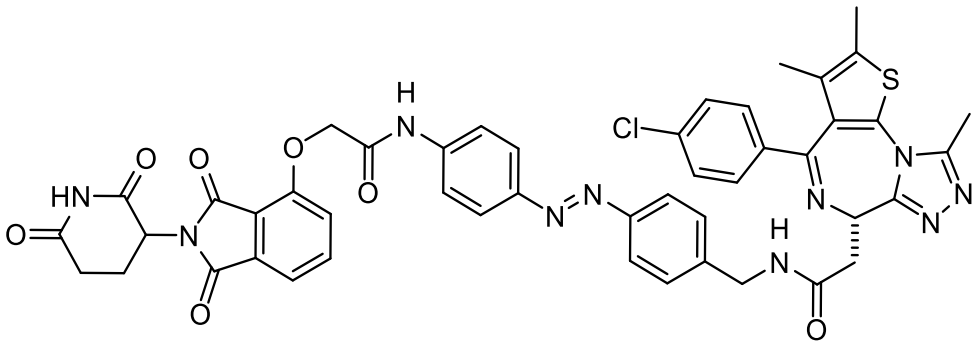
^{1}H NMR (400 MHz, Acetone-d_6) δ = 10.03 (s, 1H), 9.84 (s, 1H), 8.05 – 7.93 (m, 4H), 7.93 – 7.82 (m, 3H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 5.25 (dd, *J* = 12.5, 5.4 Hz, 1H), 5.00 (s, 2H), 4.39 (d, *J* = 6.3 Hz, 2H), 3.09 – 2.91 (m, 1H), 2.92 – 2.78 (m, 3H), 2.39 – 2.20 (m, 1H), 1.46 (s, 9H) ppm.

^{13}C NMR (101 MHz, Acetone) δ = 172.7, 170.1, 167.7, 167.6, 166.8, 157.0, 155.8, 152.6, 149.8, 144.7, 142.0, 138.1, 134.4, 128.9, 124.7, 123.6, 122.1, 120.5, 119.3, 117.9, 79.1, 69.7, 50.5, 44.6, 32.1, 28.7, 23.4 ppm ppm.

HRMS (ESI): calcd. for $C_{33}H_{32}N_6NaO_8^+$: 663.2174 *m/z* $[M+Na]^+$
found: 663.2178 *m/z* $[M+Na]^+$.

LCMS T_R = 4.505 min

2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-((*E*)-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)benzyl)acetamide (PHOTAC-I-11)



S24 (10.0 mg, 15.6 µmol, 1.0 eq) was dissolved in formic acid (1.6 mL), immediately turning the solution to a deep red color, and allowed to stir overnight at rt. After this period, the solvent was evaporated in vacuo to afford an orange amorphous solid. To this was added (+)-JQ1 free acid (6.6 mg, 16.4 µmol, 1.05 eq) in DMF (0.66 mL), HATU (8.9 mg, 23.4 µmol, 1.5 eq), followed by DIPEA (5 µL, 31.2 µmol, 2.0 eq) and the reaction was allowed to stir overnight at room temperature. The reaction was diluted with water, extracted 3 times with EtOAc, organics were combined, washed with bicarb and brine and dried over sodium sulfate. The organic layer was concentrated in vacuo and the residue was purified by semi-preparative reverse phase HPLC (50% → 70% MeCN gradient + 0.01% formic acid) affording **PHOTAC-I-11** (6.0 mg, 6.5 µmol, 42%) as a yellow orange amorphous solid.

R_f = 0.29 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.58 (d, *J* = 8.8 Hz, 1H), 8.29 (d, *J* = 18.0 Hz, 1H), 7.96 (qd, *J* = 9.0, 2.8 Hz, 4H), 7.89 – 7.76 (m, 3H), 7.61 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.26 (d, *J* = 8.8 Hz, 1H), 5.06 (dd, *J* = 12.2, 5.2 Hz, 1H), 4.82 (d, *J* = 4.0 Hz, 2H), 4.79 – 4.65 (m, 2H), 4.46 (dd, *J* = 15.3, 5.3 Hz, 1H), 3.67 – 3.49 (m, 2H), 3.03 – 2.76 (m, 3H), 2.70 (s, 3H), 2.42 (s, 3H), 2.30 – 2.16 (m, 1H), 1.68 (s, 3H) ppm.

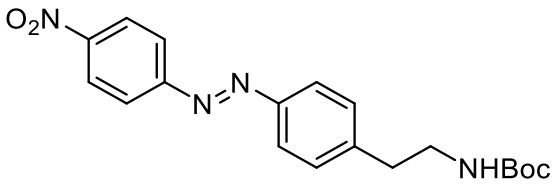
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.9, 170.9, 170.7, 168.0, 166.6, 166.5, 165.1, 164.3, 155.7, 154.4, 152.1, 150.1, 149.5, 141.5, 140.0, 137.4, 137.1, 136.5, 133.6, 132.3, 131.1, 130.6, 130.0, 128.9, 128.5, 124.2, 123.2, 120.0, 120.0, 118.0, 68.5, 54.6, 49.6, 43.4, 41.2, 39.4, 31.6, 22.8, 14.6, 13.3, 12.0 ppm.

HRMS (APCI): calcd. for $C_{47}H_{43}ClN_{11}O_7S^+$: 940.2751 *m/z* $[M+NH_4]^+$

found: 940.2736 *m/z* $[M+NH_4]^+$.

LCMS T_R = 4.422 min

***tert*-butyl (*E*)-(4-((4-nitrophenyl)diazenyl)phenethyl)carbamate (S25)**



The following procedure was carried out in two steps:

Oxone Oxidation:

To a solution of 4-nitroaniline (462 mg, 3.3 mmol, 1.0 eq.) in CH_2Cl_2 (12.0 mL) was added a solution of oxone (2.1 g, 3.3 mmol, 1.0 eq.) in water (12.0 mL). The biphasic mixture was stirred vigorously under N_2 atmosphere. After 3 hours, phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined and then washed with 1 M HCl, sat. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to approximately 5 mL. The resulting yellow-black solution of nitrosobenzene in CH_2Cl_2 was carried on to the next step immediately.

Mills Reaction:

To the nitrosobenzene solution in DCM, prepared as described above, was added sequentially *tert*-butyl (4-aminophenethyl)carbamate(*63*) (791.0 mg, 3.3 mmol, 1.0 eq.) and glacial AcOH (0.96 mL, 17 mmol, 5.0 eq.). The reaction mixture was allowed to stir for 15 hours under N2 atmosphere, after which time the reaction mixture was found to be an orange-black suspension. EtOAc was added and the organic phase was washed with 3x 1-M-NaOH, 2x sat. $NaHCO_3$, 2x sat. NaCl. The organic phase was then dried over Na_2SO_4 and concentrated under reduced pressure. Crude material was purified by flash column chromatography over SiO_2 using a gradient

from 1% → 5% → 10% EtOAc in Hexanes as the eluent, affording affording **S25** (724.0 mg, 1.955 mmol, 58%) as a crystalline red solid.

R$_f$ = 0.23 [Hexanes:EtOAc, 9:1].

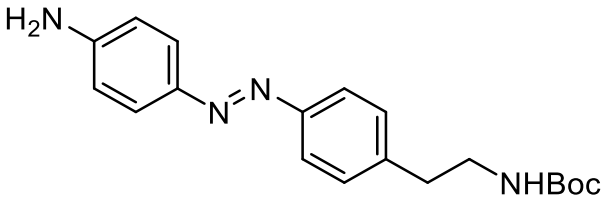
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.36 (dd, *J* = 8.8, 1.6 Hz, 2H), 8.00 (dd, *J* = 8.7, 1.4 Hz, 2H), 7.91 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 2H), 4.62 (s, 1H), 3.43 (d, *J* = 5.1 Hz, 2H), 2.90 (t, *J* = 7.0 Hz, 2H), 1.44 (s, 9H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 155.9, 151.3, 148.7, 144.3, 129.9, 124.8, 123.8, 123.5, 79.6, 41.7, 36.4, 28.5 ppm.

HRMS (APCI): calcd. for $C_{14}H_{15}N_4O_2^+$: 271.1195 *m/z* $[M\text{-}Boc+H]^+$
found: 271.1190 *m/z* $[M\text{-}Boc+H]^+$.

LCMS T_R = 4.858 min

***tert*-butyl (*E*)-(4-((4-aminophenyl)diazenyl)phenethyl)carbamate (S26)**



To a solution of **S25** (100.0 mg, 270 µmol, 1.0 eq.) in dioxane (4.0 mL) and water (0.4 mL) in a pressure tube was added $Na_2S{\cdot}9H_2O$ (195 mg, 810 µmol, 3.0 eq.). The reaction was sealed and heated to 85 °C. After 1 hour, the reaction was diluted with water and the aqueous layer was extracted 3 times with EtOAc. The organics were combined, washed with brine, dried over sodium sulfate and concentrated in vacuo to afford an orange-red solid. The reaction was loaded onto isolute and purified by column chromatography over SiO_2 using a stepped gradient from 9:1 →1:1 Hexanes/EtOAc as the eluent to afford **S26** (77.0 mg, 226 µmol, 84%) as a pale orange solid.

R$_f$ = 0.64 [Hexanes:EtOAc, 6:4].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 7.80 (d, *J* = 4.5 Hz, 2H), 7.78 (d, *J* = 3 .9 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.58 (s, 1H), 4.06 (s, 2H), 3.41 (d, *J* = 6.7 Hz, 1H), 2.86 (t, *J* = 7.0 Hz, 2H), 1.44 (s, 9H) ppm.

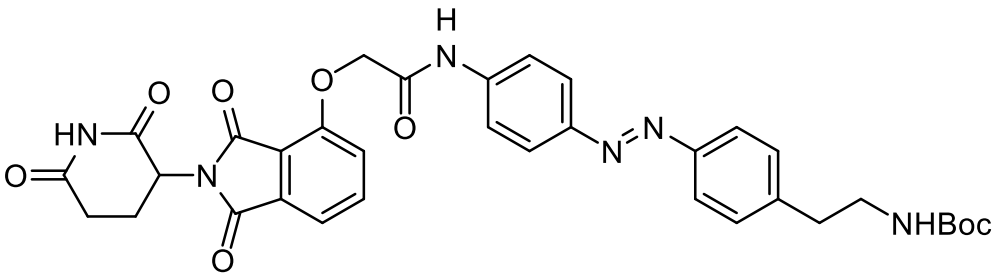
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.0, 151.8, 149.7, 145.7, 141.1, 129.5, 125.2, 122.7, 114.7, 79.4, 41.8, 36.1, 28.5 ppm.

HRMS (APCI): calcd. for $C_{19}H_{25}N_4O_2^+$: 341.1972 *m/z* $[M+H]^+$

found: 341.1973 *m/z* $[M+H]^+$.

LCMS T_R = 4.141 min

***tert*-butyl (*E*)-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)phenethyl)carbamate (S27)**



Thalidomide-4-hydroxyacetate(*61*) (20.0 mg, 60.2 µmol, 1.0 eq.) and **S26** (20.0 mg, 60.2 µmol, 1.0 eq.) were dissolved in DMF (600 µL) followed by the addition of TBTU (25 mg, 66.2 µmol, 1.10 eq.) and DIPEA (21 µL, 120.4 µmol, 2.0 eq.) at rt. The reaction was allowed to stir at room temperature overnight upon which the reaction was diluted with EtOAc, the organics were washed three times with equal portions of water, saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and concentrated. The crude product was purified by column chromatography over SiO_2 using a gradient of 9:1 hexanes/EtOAc to 100% EtOAc as the eluent to afford product **S27** (38.0 mg, 58.0 µmol, 96%) as an orange amorphous solid.

R_f = 0.29 [Hexanes:EtOAc, 6:4].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.54 (s, 1H), 8.41 (d, *J* = 13.7 Hz, 1H), 7.92 (t, *J* = 2.8 Hz, 4H), 7.83 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.80 – 7.70 (m, 1H), 7.63 – 7.51 (m, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 1H), 5.04 (dd, *J* = 12.3, 5.3 Hz, 1H), 4.78 (d, *J* = 1.9 Hz, 2H), 4.60 (s, 1H), 3.41 (t, *J* = 6.7 Hz, 2H), 2.97 – 2.78 (m, 6H), 2.25 – 2.15 (m, 1H), 1.44 (s, 9H) ppm.

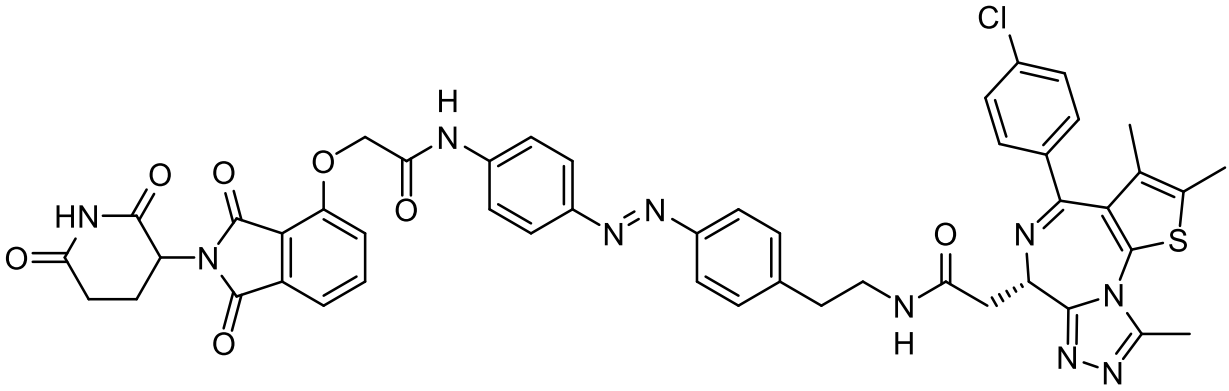
^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.0, 168.1, 166.6, 166.5, 165.1, 156.0, 154.4, 151.5, 149.5, 142.4, 139.9, 137.4, 133.6, 129.7, 124.1, 123.1, 120.0 (overlap of two signals), 118.6, 118.0, 79.5, 68.5, 49.6, 41.8, 36.2, 31.6, 28.5, 22.7 ppm.

HRMS (ESI): calcd. for $C_{34}H_{35}N_6O_8^+$: 655.2511 *m/z* $[M+H]^+$

found: 655.2530 *m/z* $[M+H]^+$.

LCMS T_R = 4.599 min

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(4-((E)-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)phenyl)diazenyl)phenethyl)acetamide (PHOTAC-I-12)



S27 (5.0 mg, 9.0 µmol, 1.0 eq) was dissolved in formic acid (1.5 mL0 and allowed to stir overnight. After this period the reaction was concentrated and azeotroped to afford an orange residue. This crude material and (+)-JQ1-free acid (4.0 mg, 9.9 µmol, 1.1 eq) were dissolved in DMF (400 µL) followed by the addition of HATU (4.5 mg, 11.7 µmol, 1.3 eq) and DIPEA (2.0 µL, 13.5 µmol, 1.5 eq) at rt. The reaction was allowed to stir at rt overnight. The reaction was diluted with water and extracted 3 times with EtOAc. The organic layers were combined, washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. Concentration of organics and

purification by column chromatography over SiO_2 using 8:1.5:0.5 DCM/EtOAc/MeOH as the mobile phase afforded **PHOTAC-I-12** (7.9 mg, 8.4 µmol, 94%) as an orange amorphous solid.

R_f = 0.17 [CH_2Cl_2:EtOAc:MeOH, 8:1.5:0.5].

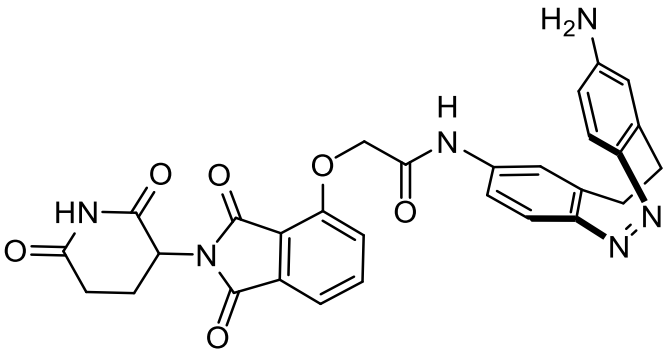
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.57 (d, *J* = 2.4 Hz, 1H), 8.13 (d, *J* = 2.8 Hz, 1H), 8.03 – 7.89 (m, 4H), 7.78 (dd, *J* = 8.0, 4.0 Hz, 3H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.40 – 7.26 (m, 7H), 6.77 (s, 1H), 5.05 (dd, *J* = 11.9, 5.0 Hz, 1H), 4.81 (s, 2H), 4.56 (t, *J* = 6.9 Hz, 1H), 3.76 – 3.45 (m, 3H), 3.31 (dd, *J* = 14.2, 5.8 Hz, 1H), 3.02 – 2.76 (m, 5H), 2.66 (s, 3H), 2.37 (s, 3H), 2.27 – 2.18 (m, 1H), 1.66 (s, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 170.8, 170.5, 167.9, 166.6, 166.5, 165.1, 164.2, 155.6, 154.4, 151.4, 150.0, 149.5, 142.3, 139.9, 137.4, 137.1, 136.4, 133.6, 132.1, 131.2, 131.1, 130.6, 130.0, 129.6, 128.9, 124.1, 123.0, 120.1 (overlap 2 peaks), 118.7, 118.1, 68.5, 54.6, 49.6, 40.5, 39.6, 35.6, 31.6, 22.8, 14.5, 13.2, 12.0 ppm.

HRMS (ESI): calcd. $C_{48}H_{42}ClN_{10}O_7S^+$: 937.2642 *m/z* $[M+H]^+$
found: 937.2675 *m/z* $[M+H]^+$.

LCMS T_R = 4.599 min

(Z)-N-(9-amino-11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide (S28)



Thalidomide-4-hydroxyacetate (20.0 mg, 60 µmol, 1.0 eq.) and (Z)-11,12-dihydrodibenzo[c,g][1,2]diazocine-2,9-diamine(*64*) (21.5 mg, 90 µmol, 1.5 eq.) were

dissolved in DMF (0.6 mL) followed by the addition of TBTU (21.3 mg, 66 µmol, 1.1 eq.) and DIPEA (21 µL, 120 µmol, 2.0 eq.) at rt. The reaction was allowed to stir at rt overnight. The reaction was diluted with CH_2Cl_2 and successively washed with water, saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography over silica using a 1% to 3% MeOH in CH_2Cl_2 as the eluent to afford **S28** (17.0 mg, 31 µmol, 51%) as an amorphous yellow solid. This product was contaminated with an unknown impurity and used in the next step.

R_f = 0.08 [CH_2Cl_2:MeOH, 95:5].

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 10.10 (s, 1H), 7.80 (ddd, *J* = 8.5, 7.3, 4.2 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.30 (m, 1H), 6.81 (dd, *J* = 30.2, 8.4 Hz, 1H), 6.63 – 6.51 (m, 1H), 6.36 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.20 (d, *J* = 2.3 Hz, 1H), 5.13 (q, *J* = 6.5, 5.5 Hz, 2H), 4.96 (d, *J* = 3.2 Hz, 2H), 2.90 (s, 2H), 2.76 – 2.55 (m, 6H), 2.08 – 1.92 (m, 1H) ppm.

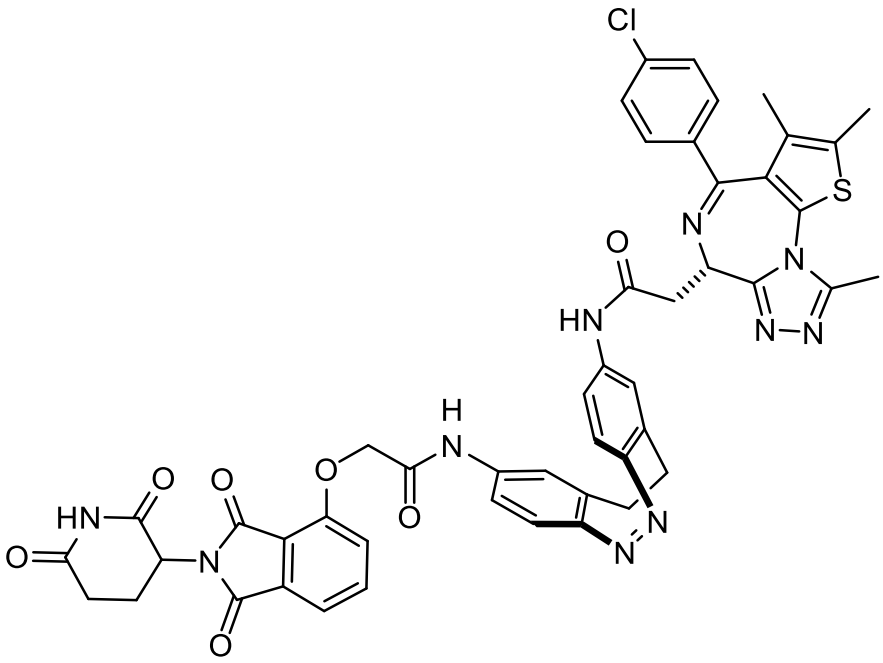
^{13}C NMR (101 MHz, DMSO) δ = 172.8, 169.9, 166.7, 165.6, 165.5, 162.3, 155.2, 151.4, 147.9, 145.4, 136.9, 136.7, 133.0, 129.5, 128.5, 121.0, 120.5, 119.5, 117.4, 116.7, 116.0, 113.6, 111.9, 67.4, 48.8, 31.6, 31.2, 30.9, 22.0 ppm.

HRMS (APCI): calcd. $C_{29}H_{25}N_6O_6^+$: 553.1836 *m/z* $[M+H]^+$

found: 553.1828 *m/z* $[M+H]^+$.

LCMS T_R = 2.931 min

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-((Z)-9-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)-11,12-dihydrodibenzo[c,g][1,2]diazocin-2-yl)acetamide (PHOTAC-I-13)



To a solution of **S28** (5.0 mg, 9.0 µmol, 1.0 eq.) and (+)-JQ1 free acid (4.0 mg, 10 µmol, 1.1 eq.) in DCE (1.8 mL) was added TBTU (3.8 mg, 11.8 µmol, 1.3 eq.) followed by DIPEA (1.8 mg, 2.0 µL, 13.6 µmol, 1.5 eq.) at room temperature. The reaction was allowed to stir overnight upon which the reaction was diluted with EtOAc, washed with equal portions of water, saturated sodium bicarbonate, and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography over SiO_2 using a gradient of 0% → 10% MeOH in CH_2Cl_2 as the eluent to afford **PHOTAC-I-13** (5.9 mg, 5.9 µmol, 65%) as a amorphous yellow solid.

R_f = 0.39 [CH_2Cl_2: MeOH, 95:5].

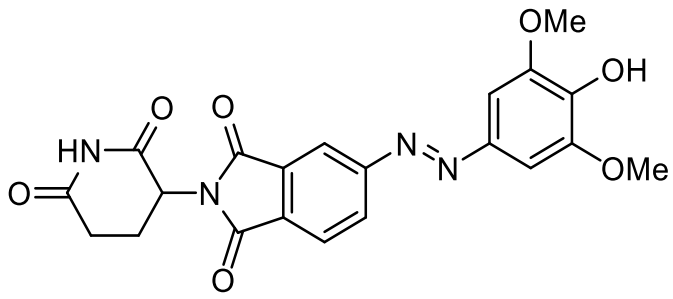
^{1}H NMR (400 MHz, Chloroform-*d*) δ = 9.23 (d, *J* = 122.5 Hz, 2H), 7.84 – 7.74 (m, 1H), 7.75 – 7.63 (m, 1H), 7.60 (dd, *J* = 7.4, 3.4 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.6 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.25 (dd, *J* = 8.5, 6.2 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 5.12 – 4.93 (m, 1H), 4.73 (d, *J* = 8.6 Hz, 2H), 4.61 (dd, *J* = 9.2,

4.7 Hz, 1H), 3.79 (ddd, *J* = 22.4, 14.1, 9.1 Hz, 1H), 3.44 (ddd, *J* = 19.4, 14.0, 4.8 Hz, 1H), 3.04 – 2.75 (m, 7H), 2.68 (d, *J* = 4.3 Hz, 3H), 2.64 (d, *J* = 0.8 Hz, 5H), 2.42 (d, *J* = 2.4 Hz, 3H), 2.31 – 2.15 (m, 1H), 1.72 – 1.60 (m, 3H) ppm.

^{13}C NMR (101 MHz, Chloroform-*d*) δ = 168.5, 168.3, 166.5, 164.8, 164.7, 155.4, 154.4, 152.1, 150.1, 137.2, 136.2, 133.5, 131.3, 131.0, 130.5, 129.9, 129.9, 129.2, 128.8, 120.5, 120.2, 118.7, 118.0, 117.8, 68.8, 68.5, 54.6, 54.4, 49.4, 41.0, 31.5, 31.5, 22.6, 14.4, 14.4, 13.1, 11.7 ppm.

HRMS (APCI): calcd. $C_{48}H_{40}ClN_{10}O_7S^+$: 935.2491 *m/z* $[M+H]^+$
found: 935.2478 *m/z* $[M+H]^+$.

(E)-2-(2,6-dioxopiperidin-3-yl)-5-((4-hydroxy-3,5-dimethoxyphenyl)diazenyl)isoindoline-1,3-dione (S29)



To a solution of 5-aminothalidomide (200 mg, 0.73 µmol, 1.0 eq) and $NaNO_2$ (424 µl, 848 µmol, 1.16 equiv) in acetone/water (4:1, 8 mL) was added 4 equiv. of HCl (4.0 M in 1,4-dioxane, 732 µL, 2.9 mmol, 4.0 equiv) at 0 °C. After stirring for 1 h, the solution was added in a dropwise fashion to a mixture of 2,6-dimethoxyphenol, (135 mg, 0.88 mmol, 1.2 equiv), $NaHCO_3$ (1.5 g, 18.1 mmol, 24.7 equiv), Na_2CO_3 (3.7 g, 34.5 mmol, 47.2 equiv) in water/MeOH (5:2, 28 mL) at 0 °C and allowed to stir for an additional hour. After this time period, the reaction was quenched with sat. NH_4Cl and extracted with EtOAc. The organic layers were combined and washed with brine and concentrated under reduced pressure. The residue was purfied by column chromatography over SiO_2 using 4:6 Hexanes/EtOAc as the eluent to afford **S29** (49.0 mg, 112 µmol, 15%) as a red solid.

R$_f$ = 0.23 [Hexanes:EtOAc, 4:6].

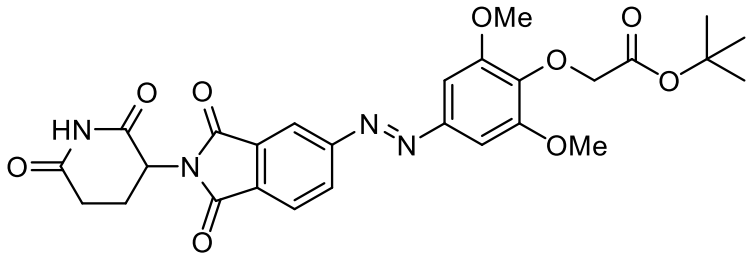
^{1}H NMR (400 MHz, Acetone-d_6) δ = 9.96 (s, 1H), 8.31 (dd, *J* = 5.3, 2.6 Hz, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.43 (s, 2H), 5.21 (dd, *J* = 12.6, 5.5 Hz, 1H), 3.98 (s, 6H), 2.99 (m, 1H), 2.88 – 2.77 (m, 2H), 2.32 – 2.25 (m, 1H).

^{13}C NMR (101 MHz, Acetone) δ = 172.6, 169.9, 167.5, 167.5, 157.6, 149.1, 145.8, 142.0, 134.2, 133.0, 130.6, 125.4, 116.0, 102.6, 56.7, 50.5, 32.0, 23.2.

HRMS (APCI): calcd. for $C_{21}H_{19}N_4O_7^+$: 439.1248 *m/z* $[M+H]^+$
found: 439.1251 *m/z* $[M+H]^+$.

LCMS T_R = 3.180 min

tert-butyl (E)-2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)diazenyl)-2,6-dimethoxyphenoxy)acetate (S30)



S29 (35.0 mg, 78.8 µmol, 1.0 eq) was dissolved in DMF (0.8 mL) at room temperature. To this was added K_2CO_3 (16.6 mg, 0.12 mmol, 1.5 equiv), immediately turning the solution a blue-black color, followed by the addition of *tert*-butyl bromoacetate (16.4 mg, 83.8 µmol, 1.05 eq). The reaction was allowed to stir at room temperature for 2 hours upon which the reaction was quenched with saturated aqueous NH_4Cl. The aqueous layer was extracted three times with EtOAc, the organics were combined, washed with brine, dried over sodium sulfate and concentrated. The residue was purified by column chromatography over SiO_2 using a gradient of 0 → 30% EtOAc in DCM to afford **S30** (17.0 mg, 30.8 µmol, 39%) as an orange film.

R_f = 0.47 [CH_2Cl_2:EtOAc, 7:3].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.37 (d, *J* = 1.6 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.00 (s, 1H), 7.34 (s, 2H), 5.05 (dd, *J* = 12.4, 5.4 Hz, 1H), 4.74 (s, 2H), 3.99 (s, 6H), 3.02 – 2.70 (m, 4H), 2.31 – 2.14 (m, 1H), 1.51 (s, 9H) ppm.

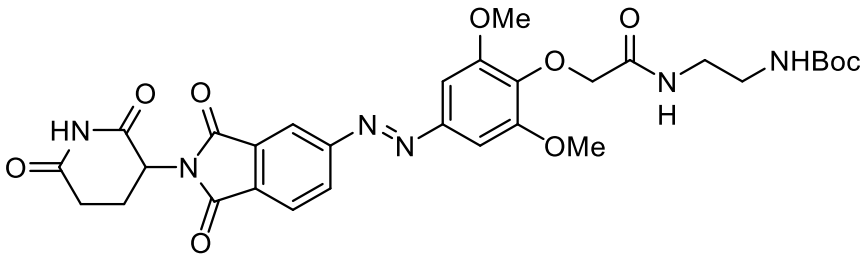
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.7, 168.3, 167.8, 166.8, 166.7, 156.9, 152.8, 147.9, 140.6, 133.2, 132.3, 130.1, 129.8, 125.2, 125.0, 119.4, 117.0, 101.5, 81.9, 70.0, 56.5, 49.7, 31.6, 29.9, 28.3, 22.8 ppm.

HRMS (APCI): calcd. for $C_{23}H_{21}N_4O_9^+$: 497.1303 *m/z* $[M\text{-}t\text{Bu+H}]^+$

found: 497.1292 *m/z* $[M\text{-}t\text{Bu+H}]^+$.

LCMS T_R = 3.383 min

<u>*tert*</u>-butyl (*E*)-(2-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)ethyl)carbamate (S31)



S30 (8.0 mg, 14.5 µmol, 1.0 eq.) was dissolved in formic acid (1.4 mL), immediately turning the solution to a deep red color, and allowed to stir overnight at rt. After this period, the solvent was evaporated in vacuo to afford an orange-red amorphous solid. To this was added *N*-Boc-ethylene diamine (2.8 mg, 17.4 µmol, 1.2 eq.) in DMF (1.4 mL), HATU (8.3 mg, 21.7 µmol, 1.5 eq.), followed by DIPEA (5 µL, 3.7 mg, 28.7 µmol, 2.0 eq.) and the reaction was allowed to stir overnight at room temperature. The reaction was diluted with water, extracted 3 times with EtOAc, organics were combined, washed with bicarb and brine and dried over sodium sulfate. The organic layer was concentrated in vacuo and the residue was purified column chromatography over SiO_2 using 0% → 3% MeOH in CH_2Cl_2 as the eluent to affod **S31** (5.7 mg, 8.9 µmol, 62%) as an orange film.

R_f = 0.09 [CH_2Cl_2:MeOH, 97:3].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.35 (d, *J* = 1.5 Hz, 1H), 8.28 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.17 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.83 (m, 1H), 7.33 f(s, 2H), 5.03 (dd, *J* = 12.2, 5.5 Hz, 1H), 4.90 (s, 1H), 4.63 (s, 2H), 4.01 (s, 6H), 3.49 (d, *J* =

6.0 Hz, 2H), 3.38 – 3.24 (m, 2H), 3.02 – 2.63 (m, 3H), 2.28 – 2.09 (m, 1H), 1.43 (s, 9H) ppm.

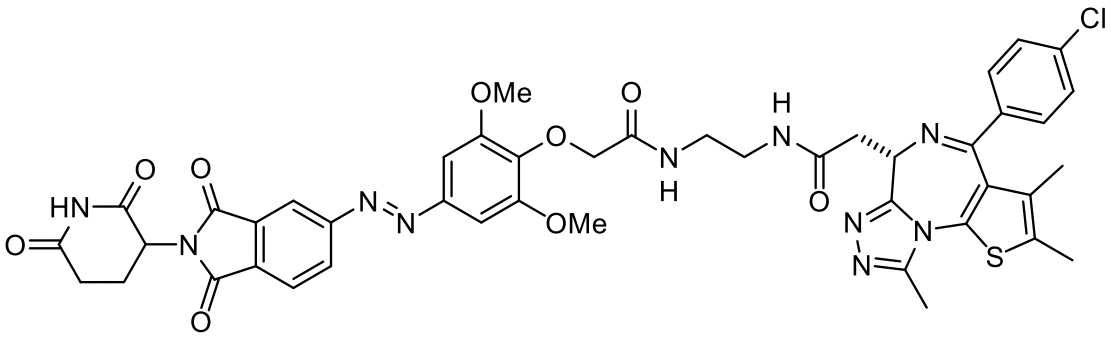
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.8, 170.3, 167.9, 166.7, 166.7, 156.7, 156.2, 152.8, 148.6, 140.4, 133.2, 132.6, 130.2, 125.0, 116.9, 101.3, 79.7, 72.8, 56.5, 49.7, 40.9, 39.2, 31.6, 28.5, 22.8 ppm.

HRMS (APCI): calcd. for $C_{25}H_{27}N_6O_8^+$: 539.1885 *m/z* $[M\text{-Boc+H}]^+$

found: 539.1873 *m/z* $[M\text{-Boc+H}]^+$.

LCMS T_R = 3.953 min

2-((S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)-N-(2-(2-(4-((E)-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)diazenyl)-2,6-dimethoxyphenoxy)acetamido)ethyl)acetamide (PHOTAC-I-9)



S31 (5.7 mg, 8.9 µmol, 1.0 equiv) was dissolved in formic acid and allowed to stir at room temperature for 30 min. After this period, the reaction was concentrated *in vacuo* and azeotroped. The crude residue was used immediately without further purification. This crude material and (+)-JQ1-free acid (3.9 mg, 9.8 µmol, 1.1 eq) were dissolved in DMF (400 µL) followed by the addition HATU (3.7 mg, 9.8 µmol, 1.1 eq) and DIPEA (2.3 µL, 17.9 µmol, 2.0 eq) at rt. The reaction was allowed to stir at rt overnight. The reaction was diluted with water and extracted 3 times with EtOAc. The organic layers were combined, washed with saturated sodium bicarbonate and brine and dried over sodium sulfate. Concentration of organics and purification by column chromatography over SiO_2 using 0% → 10% MeOH in DCM as the mobile phase afforded **PHOTAC-I-9** (4.1 mg, 4.4 µmol, 50%) as an orange amorphous solid.

R_f = 0.23 [CH_2Cl_2:MeOH, 9:1].

^{1}H NMR (400 MHz, Chloroform-*d*) δ = 8.32 (d, *J* = 1.5 Hz, 1H), 8.26 (dd, *J* = 7.9, 1.6 Hz, 1H), 8.16 (s, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.90 (d, *J* = 6.4 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 3H), 7.31 (s, 2H), 5.03 (dd, *J* = 12.3, 5.4 Hz, 1H), 4.69 (t, *J* = 6.8 Hz, 1H), 4.62 (s, 2H), 3.99 (s, 6H), 3.65 – 3.35 (m, 6H), 3.02 – 2.71 (m, 3H), 2.69 (s, 3H), 2.40 (s, 3H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.67 (s, 3H), 1.67 – 1.55 (m, 1H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 176.9, 171.0, 170.8, 170.5, 167.9, 166.8, 166.7, 164.7, 156.7, 155.4, 152.8, 150.3, 148.6, 140.5, 137.5, 136.0, 135.9, 133.1, 132.5, 131.3, 130.2, 130.2, 129.0, 129.0, 125.0, 117.0, 101.4, 72.8, 56.6, 53.6, 49.7, 40.0, 38.8, 33.7, 32.1, 31.6, 24.9, 22.8, 22.8, 14.6, 13.3, 11.9 pmm.

HRMS (APCI): calcd. for $C_{44}H_{42}ClN_{10}O_9S^+$: 921.2545 *m/z* $[M+H]^+$

found: 921.2519 *m/z* $[M+H]^+$.

LCMS T_R = 4.089 min