Supplementary Information

Development of the first non-hydroxamate selective HDAC6 degraders

Tim Keuler, a Beate König, a Nico Bückreiß, a Fabian B. Kraft, a Philipp König, a Christian Steinebach, a Gerd Bendas, a Michael Gütschow a and Finn K. Hansen a

a Pharmaceutical Institute, University of Bonn, 53121 Bonn, Germany.

‡ These authors contributed equally.

Content

1. Supplementary Figures, Schemes and Tables

   Figure S1. HDAC6 inhibitors with a 2-(difluoromethyl)-1,3,4-oxadiazole (DFMO) group .......S2
   Figure S2. Ligand RMSD vs interface score plots for compound I and compound II ..........S2
   Figure S3. Docking pose of ligand II in the CD2 of HDAC6 (PDB: 5EDU) ......................S3
   Figure S4. Determination of the half-degrading concentrations (DC50) for degraders 1 and 4 ......S3
   Scheme S1. Synthesis of the VHL ligand 33 ..........................................................S4
   Table S1. Inhibitory activities (IC50) of PROTACs 1-6 against HDAC1-3 and HDAC6 .........S4

2. Biological Experiments

   2.1. Inhibition Assay for HDAC1-3 and HDAC6 .........................................................S5
   2.2. Cell Culture ........................................................................................................S5
   2.3. Western Blot .......................................................................................................S5
   2.4. Cell Viability Assay ..........................................................................................S6
   2.5. Statistical Analysis ..........................................................................................S6

3. Molecular Docking

   3.1. Procedure ...........................................................................................................S7

4. Physicochemical Experiments

   4.1. Molecular Descriptor Calculations ........................................................................S8
   4.2. HPLC-based Determinations of elogD7.4 .............................................................S8
   4.3. Plasma Protein Binding Studies ..........................................................................S8

5. Chemical Experiments

   5.1. General Information ..........................................................................................S9
   5.2. Preparation of Compounds .................................................................................S10
   5.3. NMR Data ........................................................................................................S36

6. References ...............................................................................................................S76
1. Supplementary Figures, Schemes and Tables

**Figure S1.** Selective HDAC6 inhibitors utilizing a 2-(difluoromethyl)-1,3,4-oxadiazole (DFMO) zinc-binding group. Structures and inhibition data taken from patent literature.\(^1\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC(_{50}) HDAC6</th>
<th>IC(_{50}) HDAC1</th>
</tr>
</thead>
<tbody>
<tr>
<td>cmpd 6</td>
<td>0.057 (\mu)M</td>
<td>&gt;30 (\mu)M</td>
</tr>
<tr>
<td>cmpd 9</td>
<td>0.038 (\mu)M</td>
<td>&gt;30 (\mu)M</td>
</tr>
<tr>
<td>cmpd 43</td>
<td>0.039 (\mu)M</td>
<td>&gt;30 (\mu)M</td>
</tr>
</tbody>
</table>

**Figure S2.** Ligand RMSD vs interface score plots for compound I and compound II. It was plotted against the models with the best scoring from their respective runs.
**Figure S3.** Docking pose of ligand II in the CD2 of HDAC6 (PDB: 5EDU). The catalytic Zn\(^{2+}\)-ion is shown as gray sphere.

**Figure S4.** Determination of the half-degrading concentrations (DC\(_{50}\)) for degraders 1 and 4 in MM.1S cells. Multiple myeloma cells were incubated with several PROTAC concentrations ranging from 0.1 up to 2.0 µM.
Scheme S1. Synthesis of the VHL ligand 33.

Table S1. Inhibitory activities (IC₅₀) of PROTACs 1-6 against HDAC1, HDAC2, HDAC3 and HDAC6.

<table>
<thead>
<tr>
<th>cmpd</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HDAC1</td>
</tr>
<tr>
<td>1</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>2</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>3</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>4</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>5</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>6</td>
<td>&gt;30 µM</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>0.102 ± 0.003</td>
</tr>
</tbody>
</table>

* ≤20% inhibition at 30 µM
2. Biological Experiments

2.1. Inhibition Assay for HDAC1-3 and HDAC6

*In vitro* inhibitory activities against HDAC1-3 and HDAC6 were measured using a previously published protocol. For test compounds and controls, serial dilutions of the respective DMSO stock solution in assay buffer (50 mM Tris–HCl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1.0 mM MgCl₂·6H₂O, 0.1 mg/mL BSA) were prepared, and 5.0 μL of this serial dilution were transferred into OptiPlate-96 black microplates (PerkinElmer). A volume of 35 μL of the fluorogenic substrate ZMAL (Z-Lys(Ac)-AMC) (21.43 μM in assay buffer) and 10 μL enzyme solution were added. Human recombinant HDAC1 (BPS Bioscience, Catalog# 50051), HDAC2 (BPS Bioscience, Catalog# 50052), HDAC3/NcoR2 (BPS Bioscience, Catalog# 50003), or HDAC6 (BPS Bioscience, Catalog# 50006) was applied. The total assay volume of 50 μL (HDAC6 max. 1% DMSO; HDAC1-3 max. 5% DMSO) was incubated at 37 °C for 90 min. Subsequently, 50 μL trypsin solution (0.4 mg/mL trypsin in buffer: 50 mM Tris–HCl, pH 8.0, 100 mM NaCl) was added, followed by additional 30 min of incubation at 37 °C. Fluorescence (excitation: 355 nm, emission: 460 nm) was measured using a FLUOstar OPTIMA microplate reader (BMG LABTECH). All compounds were tested at least twice in duplicates and the 50% inhibitory concentration (IC₅₀) was determined by plotting dose response curves and nonlinear regression with GraphPad Prism.

2.2. Cell Culture

The human multiple myeloma cell line MM.1S (CRL-2974) was obtained from ATCC (Manassas, VA, USA). MM.1S cells were cultivated in RPMI 1640 medium supplemented with 10% FBS, 100 IU/mL penicillin, 0.1 mg/mL streptomycin (PAN Biotech GmbH; Aidenbach, Germany) and 1 mM sodium pyruvate (ThermoFisher Scientific Inc.; Waltham, MA, USA) at 37 °C in a 5% CO₂ atmosphere. The semi-adherent cells were detached mechanically by using a cell scraper. The cell line was tested to exclude mycoplasma contamination every two weeks by qPCR.

2.3. Western Blot

MM.1S cells were seeded to cell culture flasks (75 cm²) and cultured for 96 h. Cells were then incubated for 24 h with the respective PROTACs at a concentration of 1 μM. In case of rescue experiments, cells were pre-incubated with the CRBN, VHL or HDAC6 ligands for 30 min before addition of the PROTACs. The next day, cell protein lysates were prepared from cells while incubating them at 4 °C on a shaker with cell extraction buffer (Life Technologies; Carlsbad, CA, USA) for 30 min. Lysed cells were afterwards centrifuged, the supernatant was collected and protein concentrations of the lysates were quantified by a BCA protein assay kit (ThermoFisher Scientific Inc.). SDS-Page and western blots were conducted as described using stain-free gels. After proteins were transferred to PVDF membranes, western blots were incubated with blocking solution (milk powder-solution 5%) for 1 h at room temperature. Subsequently, rabbit anti-HDAC6, mouse anti-HDAC1, rabbit anti-acetyl-histone H3,
rabbit anti-acetyl-α-tubulin (Cell Signaling Technology; Frankfurt am Main, Germany) or mouse anti-GAPDH (GeneTex; Irvine, USA) antibody solutions were added to membranes, depending on the respective target. Next, HRP-conjugated secondary anti-rabbit (R&D systems; Minneapolis, MN, USA) and anti-mouse (Santa Cruz Biotechnology; Heidelberg, Germany) antibodies were used to quantify the proteins of interest by means of a chemiluminescence reaction. For visualisation and analysis of the western blot, we used the Clarity Western ECL substrate chemiluminescence kit, a ChemiDoc XRS+ imaging acquiring system and Image Lab software v.5.2.1 from BioRad Laboratories GmbH (Munich, Germany). For normalization, stainfree protein normalization and GAPDH as loading control were used.

2.4. Cell Viability Assay
To exclude possible cytotoxic effects of the PROTACs, cell viability of MM.1S cells was determined by using CellTiter-Glo® 2.0 luminescent cell viability assay (Promega; Madison, WI, USA). Cells were seeded in 96-well plates (25,000 tumour cells/well) and incubated with PROTACs for 72 h at a concentration of 1 µM and 10 µM, respectively. FDA-approved HDACi vorinostat (SAHA) was used as a cytotoxic positive control at the same concentrations as PROTACs, and DPBS as a non-cytotoxic negative control. After incubation, 100 µL of CellTiter Glo 2.0 substrate were added to each well. In an ATP-dependent conversion of luciferin by a luciferase, conclusions can be drawn regarding the cytotoxic potential of the compounds. Luminescence readout is directly proportional to the number of viable cells.

2.5. Statistical Analysis
The results are shown as mean ± SD. Statistical analysis was performed by using one-way ANOVA following Dunnett´s test. Statistical significance was indicated with asterisks (* = p < 0.05; ** = p < 0.01; *** = p < 0.001; **** = p < 0.0001).
3. Molecular Docking

3.1. Procedure

The crystal structure of human HDAC6 (PDB: 5EDU)\textsuperscript{2} was obtained from the Protein Data Bank (PDB, www.rcsb.org). Chain A, the maltose-binding periplasmic protein, and trichosatin A were deleted. All heteroatom records were removed, except for the metal ions (one zinc atom and two potassium atoms). The structure was optimized to the closest local energy minimum using RosettaRelax with coordinate constraints on the backbone and metal ion restraints.\textsuperscript{6} Ligand input files for compound I and II were created with ChemDraw. An initial 3D conformer with hydrogen atoms was constructed in Chem3D and energetically minimized using the MM2 force field, followed by the production of an ensemble of 1000 low-energy conformers with BCL:ConformerGenerator.\textsuperscript{7} One conformer was placed in the binding pocket of HDAC6. A constraint file was constructed to ensure binding of the amine of the linker to Ser453.\textsuperscript{8} Ligand docking was performed with RosettaLigand for an initial 5000 models. Those models were clustered according to their similarity in their binding mode. The depicted models are the best scoring models from their respective runs.\textsuperscript{9,11} Rosetta version 3.12 was used. The executed commands used throughout the modeling process are provided by the authors on demand.
4. Physicochemical Experiments

4.1. Molecular Descriptor Calculations
Predicted values for the topological polar surface area (TPSA) and the number of rotatable bonds were calculated using the web service www.swissadme.ch provided by the Swiss Institute of Bioinformatics.

4.2. HPLC-based Determinations of $\text{elog } D_{7.4}$
The determination of the $\text{logD}_{7.4}$ values was performed by a chromatographic method as described previously.\textsuperscript{12,13} The system was calibrated by plotting the retention times of six different drugs (atenolol, metoprolol, labetalol, diltiazem, triphenylene, permethrin) \textit{versus} their literature known $\text{logD}_{7.4}$ values to obtain a calibration line ($R^2 = 0.99$). Subsequently, the mean retention times of the analytes were taken to calculate their $\text{logD}_{7.4}$ values with aid of the calibration line.

4.3. Plasma Protein Binding Studies
Plasma protein binding (\%PPB) was estimated by correlating the logarithmic retention times of the analytes on a CHIRALPAK HSA 50 $\times$ 3 mm, 5 $\mu$m column with the literature known \%PPB values (converted into logK values) of the following drugs, warfarin, ketoprofen, budesonide, nizatidine, indomethacin, acetylsalicylic acid, carbamazepine, piroxicam, nicardipine, and cimetidine (for details, see Valko et al.\textsuperscript{14}). Samples were dissolved in MeCN/DMSO 9:1 to achieve a final concentration of 0.5 mg/mL. The mobile phase A was 50 mM ammonium acetate adjusted to pH 7.4 with aqueous ammonia, while mobile phase B was $i$PrOH. The flow rate was set to 1.0 mL/min, the UV detector was set to 254 nm, and the column temperature was kept at 30 °C. After injecting 3 $\mu$L of the sample, a linear gradient from 100% A to 30% $i$PrOH in 5.4 min was applied. From 5.4 to 18 min, 30% $i$PrOH was kept, followed by switching back to 100% A in 1.0 min and a re-equilibration time of 6 min. With the aid of the calibration line ($R^2 = 0.96$), the logK values of new substances were calculated and converted to their \%PPB values.
5. Chemical Experiments

5.1. General Information

Chemicals were purchased from ABCR, Acros Organics, BLDpharm, Carl Roth, Fisher Scientific, Fluorochem, Sigma Aldrich, Tokyo Chemical Industry and VWR Chemicals. Thin layer chromatography was carried out with pre-coated silica gel (60 F254) aluminum sheets from Merck. Detection was performed with UV light at 254 and 360 nm or with AgNO3 or ninhydrin staining. Acros Organics silica gel 60 (70–230 mesh) was taken for preparative column chromatography. Preparative silica gel flash column chromatography was performed on an Interchim Puriflash PF420 system with diode-array detection (DAD) from 200 to 400 nm. Uncorrected melting points were measured on a Büchi 510 oil bath apparatus or on a Buchi Melting Point M-565 apparatus. ESI-MS (LC-MS) analyses for compounds 1-6, 18-48 and the chemical negative controls 1(-) and 4(-) respectively, were carried out on an API 2000 mass spectrometer coupled with an Agilent HPLC HP 1100 using an EC50/2 Nucleodur C18 Gravity 3 μm column or on an Agilent Infinity Lab LC/MSD-system coupled with an Agilent HPLC 1260 Infinity II using an EC50/2 Nucleodur C18 Gravity 3 μm column. The purity of synthesized compounds was determined by HPLC-DAD. HPLC measurements for compounds 15 and 16 were performed on a Thermo Fisher Scientific UltiMateTM 3000 UHPLC system with a Nucleodur 100-5 C18 column (250 × 4.6 mm, Macherey Nagel) with a flow rate of 1 mL/min and a temperature of 25 °C with an appropriate gradient. Detection was implemented by UV absorption measurement at a wavelength of λ = 254 nm. Bidest. H2O (A) and MeCN (B) were used as eluents with an addition of 0.1% TFA for eluent A. Low resolution electrospray ionisation mass spectra (LRMS) were acquired with an Advion expression compact mass spectrometer coupled with an automated Advion TLC plate reader Plate Express. HR-ESI-MS spectra were recorded on a Bruker micrOTOF-Q mass spectrometer coupled with a HPLC Dionex UltiMate 3000 or a LTQ Orbitrap XL. NMR spectra were recorded on a Bruker Avance DRX 500 (500 MHz 1H NMR, 126 MHz 13C NMR) and a Bruker Avance III 600 (600 MHz 1H NMR, 151 MHz 13C NMR). Chemical shifts are given in parts per million (ppm) referring to the signal center using the solvent peaks for reference, DMSO-d6 (2.49/39.7).
5.2. Preparation of Compounds

Benzyl (3-(((tert-butoxycarbonyl)amino)methyl)benzyl)carbamate (9). tert-Butyl (3-(aminomethyl)benzyl)carbamate (7, 803 mg, 3.40 mmol, 1.0 eq) was dissolved in THF (34 mL). NaHCO₃ (342 mg, 4.08 mmol, 1.2 eq) was added and the mixture was stirred at 0 °C. Subsequently, benzyl chloroformate (0.523 mL, 628 mg, 3.74 mmol, 1.1 eq) was added slowly and the reaction was allowed to stir for 12 h at room temperature. The mixture was quenched with water (60 mL) and extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine (45 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using cyclohexane/EtOAc (3+1), as eluent to yield 9 as a white solid (1.22 g, 3.31 mmol).

Yield 97%; mp. 99-102 °C; \( R_f = 0.34 \) (cyclohexane/EtOAc (3+1)); \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)) \( \delta 1.38 \) (s, 9H), 4.09 (d, \( J = 6.2 \) Hz, 2H), 4.18 (d, \( J = 6.2 \) Hz, 2H), 5.03 (s, 2H), 7.07 – 7.13 (m, 3H), 7.24 (t, \( J = 7.5 \) Hz, 1H), 7.26 – 7.33 (m, 2H), 7.36 (d, \( J = 6.4 \) Hz, 4H), 7.78 (t, \( J = 6.2 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, DMSO-\( d_6 \)) \( \delta 28.4, 43.5, 44.0, 65.5, 77.9, 125.5, 125.7, 127.8, 127.9, 128.3, 128.5, 137.3, 139.8, 140.4, 155.9, 156.5; LRMS (ESI) \( m/z \) [M+H]⁺ calcd for \( C_{21}H_{26}N_2O_4 \) 371.2, found 371.1.

Benzyl (3-(((5-cyanopyrimidin-2-yl)amino)methyl)benzyl)carbamate (11). Benzyl (3-(((tert-butoxycarbonyl)amino)methyl)benzyl)carbamate (9, 1.22 g, 3.31 mmol, 1.0 eq) was dissolved in CH₂Cl₂ (26 mL), treated with TFA (7 mL) and stirred for 1 h at room temperature. After evaporation of the solvent, the resulting solid was dissolved in EtOH (11 mL), DIPEA (1.73 mL, 1.28 g, 9.93 mmol, 3.0 eq) and 2-chloropyrimidine-5-carbonitrile (924 mg, 6.62 mmol, 2.0 eq) were added and the reaction stirred at 80 °C for 24 h. The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc (200 mL), washed with brine (80 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using cyclohexane/EtOAc (2+1) as eluent to afford 11 as a yellow solid (1.21 g, 3.26 mmol).

Yield 98%; mp. 122-128 °C; \( R_f = 0.26 \) (cyclohexane/EtOAc (2+1)); \(^1\)H NMR (600 MHz, DMSO-\( d_6 \)) \( \delta 4.18 \) (d, \( J = 6.2 \) Hz, 2H), 4.54 (d, \( J = 6.4 \) Hz, 2H), 5.03 (s, 2H), 7.13 (d, \( J = 7.6 \) Hz, 1H), 7.16 (d, \( J = 7.6 \) Hz, 1H), 7.19 (d, \( J = 1.8 \) Hz, 1H), 7.26 (t, \( J = 7.6 \) Hz, 1H), 7.29 – 7.40 (m, 5H), 7.79 (t, \( J = 6.2 \) Hz, 1H), 8.66 – 8.71 (m, 2H), 8.82 (t, \( J = 6.4 \) Hz, 1H); \(^{13}\)C NMR (151 MHz, DMSO-\( d_6 \)) \( \delta 24.3, 44.1, 65.5, 95.6, 117.2, 125.7, 125.8, 125.9, 127.9, 127.9, 128.4, 128.5, 137.3, 139.1, 140.0, 156.5, 161.6, 161.9; LRMS (ESI) \( m/z \) [M+H]⁺ calcd for \( C_{21}H_{19}N_5O_2 \) 374.2, found 374.2.
Benzyl (3-(((5-((1H-tetrazol-5-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (13). Benzyl (3-(((5-cyanopyrimidin-2-yl)amino)methyl)benzyl)carbamate (11, 205 mg, 0.550 mmol, 1.0 eq) was dissolved in DMF (2.2 mL). NaN₃ (71.5 mg, 1.1 mmol, 2.0 eq), NH₄Cl (38.5 mg, 0.720 mmol, 1.3 eq) and LiCl (11.8 mg, 0.280 mmol, 0.5 eq) were added and the reaction mixture was stirred at 100 °C for 18 h. After completion of the reaction, the mixture was quenched with ice water (8 mL) and acidified with 1 M HCl. The precipitated solid was filtered and washed with cold water to obtain the product 13 as a white solid (224 mg, 0.540 mmol).

Yield 98%; mp. 164-169 °C; ¹H NMR (500 MHz, DMSO-d₆) δ 4.18 (d, J = 6.2 Hz, 2H), 4.57 (d, J = 5.9 Hz, 2H), 5.02 (s, 2H), 7.12 (d, J = 7.5 Hz, 1H), 7.18 – 7.25 (m, 3H), 7.25 – 7.39 (m, 5H), 7.78 (t, J = 6.3 Hz, 1H), 8.43 (t, J = 6.5 Hz, 1H), 8.88 (s, 2H); ¹³C NMR (126 MHz, DMSO-d₆) δ 44.0, 44.2, 65.5, 108.0, 125.6, 125.7, 125.9, 127.8, 127.9, 128.4, 128.5, 137.3, 139.8, 140.0, 156.5, 156.7, 157.0, 162.8; LRMS (ESI) m/z [M+H]+ calcd for C₂₁H₂₀N₈O₂ 417.2, found 417.2.

Benzyl (3-(((5-((difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (15). Benzyl (3-(((1H-tetrazol-5-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (13, 454 mg, 1.09 mmol, 1.0 eq) was dissolved in toluene (10 mL). Difluoroacetic anhydride (DFAA, 0.403 mL, 569 mg, 3.27 mmol, 3.0 eq) was added and it was stirred at 70 °C for 18 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel flash column chromatography using a CH₂Cl₂/MeOH gradient (0% to 5% MeOH) as eluent to yield 15 as a white solid (234 mg, 0.502 mmol).

Yield 46%; mp. 148-152 °C; ¹H NMR (600 MHz, DMSO-d₆) δ 4.17 (d, J = 6.2 Hz, 2H), 4.58 (d, J = 6.4 Hz, 2H), 5.01 (s, 2H), 7.12 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 7.7 Hz, 1H), 7.21 – 7.39 (m, 7H), 7.51 (t, J = 51.4 Hz, 1H), 7.78 (t, J = 6.2 Hz, 1H), 8.71 (t, J = 6.4 Hz, 1H), 8.87 (s, 2H); ¹³C NMR (151 MHz, DMSO-d₆) δ 44.3, 44.5, 65.8, 106.8, 107.1 (t, J = 238.3 Hz), 126.1, 126.2, 128.2, 128.8, 128.8, 137.6, 139.7, 140.3, 156.8, 157.5, 157.7, 158.0 (t, J = 28.9 Hz), 163.4, 163.6; ¹⁹F NMR (565 MHz, DMSO-d₆) δ -121.1, -121.2; HRMS (ESI) m/z [M+H]+ calcd for C₂₃H₂₀F₂N₆O₃ 467.1638, found 467.1610; HPLC (95% H₂O 5 min, then to 95% MeCN in 5 min, then 100% MeCN to 20 min, 254 nm), tᵣ = 16.32 min, 99% purity.
tert-Butyl (4-(((benzyloxy)carbonyl)amino)methyl)benzyl)carbamate (10). 1-(N-Boc-aminomethyl)-4-(aminomethyl)benzene (8, 236 mg, 1.00 mmol, 1.0 eq.) was dissolved in THF (15 mL). NaHCO$_3$ (84.0 mg, 1.20 mmol, 1.2 eq) was added and the mixture was stirred at 0 °C. Subsequently, benzyl chloroformate (0.154 mL, 188 mg, 1.10 mmol, 1.1 eq) was added slowly and the reaction was allowed to stir for 12 h at room temperature. The mixture was quenched with water (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using cyclohexane/EtOAc (3+1), as eluent to yield 10 as a white solid (306 mg, 0.830 mmol).

Yield 83%; mp. 129-133 °C; $R_f$ = 0.26 (cyclohexane/EtOAc (3+1)); $^1$H NMR (600 MHz, DMSO-d$_6$) δ 1.38 (s, 9H), 4.08 (d, $J$ = 6.2 Hz, 2H), 4.16 (d, $J$ = 6.2 Hz, 2H), 5.03 (s, 2H), 7.15 – 7.19 (m, 5H), 7.29 – 7.37 (m, 5H), 7.76 (t, $J$ = 6.2 Hz, 1H); $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 28.4, 43.3, 43.8, 65.5, 77.9, 127.0, 127.1, 127.9, 128.5, 137.3, 138.2, 138.9, 155.9, 156.5; LRMS (ESI) m/z [M+H]$^+$ calcd for C$_{21}$H$_{26}$N$_2$O$_4$ 371.2, found 371.1.

**Benzyl (4-(((5-cyanopyrimidin-2-yl)amino)methyl)benzyl)carbamate (12).** tert-Butyl (4-(((benzyloxy)carbonyl)amino)methyl)benzyl)carbamate (10, 519 mg, 1.40 mmol, 1.0 eq) was dissolved in CH$_2$Cl$_2$ (11 mL), treated with TFA (3 mL) and stirred for 1 h at room temperature. After evaporation of the solvent, the resulting solid was dissolved in EtOH (6 mL), DIPEA (0.730 mL, 542 mg, 4.20 mmol, 3.0 eq) and 2-chloropyrimidine-5-carbonitrile (390 mg, 2.80 mmol, 2.0 eq) were added and the reaction stirred at 80 °C for 24 h. The solvent was evaporated under reduced pressure, the residue was dissolved in EtOAc (100 mL), washed with brine (40 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using cyclohexane/EtOAc (3+1) as eluent to afford 12 as a yellow solid (520 mg, 1.30 mmol).

Yield 92%; mp. 160-164 °C; $R_t$ = 0.32 (cyclohexane/EtOAc (1+1)); $^1$H NMR (600 MHz, DMSO-d$_6$) δ 4.15 (d, $J$ = 6.2 Hz, 2H), 4.51 (d, $J$ = 6.3 Hz, 2H), 5.02 (s, 2H), 7.18 (d, $J$ = 7.9 Hz, 2H), 7.22 (d, $J$ = 8.1 Hz, 2H), 7.25 – 7.34 (m, 1H), 7.32 – 7.37 (m, 4H), 7.75 (t, $J$ = 6.2 Hz, 1H), 8.66 (d, $J$ = 3.0 Hz, 1H), 8.68 (d, $J$ = 3.0 Hz, 1H), 8.78 (t, $J$ = 6.4 Hz, 1H); $^{13}$C NMR (126 MHz, DMSO-d$_6$) δ 43.7, 43.9, 65.5, 95.5, 117.2, 127.2, 127.2, 127.8, 127.9, 128.5, 137.3, 137.6, 138.5, 156.5, 161.5, 161.8; LRMS (ESI) m/z [M+H]$^+$ calcd for C$_{21}$H$_{16}$N$_3$O$_2$ 374.2, found 374.2.
Benzyl (4-(((5-(1H-tetrazol-5-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (14). Benzyl (4-(((5-cyanopyrimidin-2-yl)amino)methyl)benzyl)carbamate (12, 281 mg, 0.750 mmol, 1.0 eq) was dissolved in DMF (3 mL). NaN₃ (97.5 mg, 1.50 mmol, 2.0 eq), NH₄Cl (52.4 mg, 0.980 mmol, 1.3 eq) and LiCl (16.0 mg, 0.380 mmol, 0.5 eq) were added and the reaction mixture was stirred at 100 °C for 18 h. After completion of the reaction, the mixture was quenched with ice water (9 mL) and acidified with 1 M HCl. The precipitated solid was filtered and washed with cold water to obtain the product 14 as a white solid (286 mg, 0.690 mmol).

Yield 92%; mp. 210 - 216 °C; \( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)) \( \delta \) 4.17 (d, \( J = 6.1 \) Hz, 2H), 4.56 (d, \( J = 6.3 \) Hz, 2H), 5.03 (s, 2H), 7.20 (d, \( J = 7.9 \) Hz, 2H), 7.24 – 7.32 (m, 4H), 7.24 – 7.39 (m, 3H), 7.76 (t, \( J = 6.3 \) Hz, 1H), 8.41 (t, \( J = 6.3 \) Hz, 1H), 8.85 (s, 2H); \( ^13C \) NMR (151 MHz, DMSO-\( d_6 \)) \( \delta \) 43.8, 44.0, 65.6, 108.1, 127.3, 127.3, 127.3, 128.0, 128.0, 128.6, 137.4, 138.3, 138.5, 156.6, 156.8, 157.1, 162.9; \( ^{19}F \) NMR (565 MHz, DMSO-\( d_6 \)) \( \delta \) -121.1, -121.2; HRMS (ESI) \( m/z \) [M+H]+ calcd for C₂₁H₂₀N₈O₂ 417.2, found 417.2.

Benzyl (4-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (16). Benzyl (4-(((5-(1H-tetrazol-5-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (14, 286 mg, 0.690 mmol, 1.0 eq) was dissolved in toluene (7 mL). Difluoroacetic anhydride (DFAA, 0.260 mL, 364 mg, 2.07 mmol, 3.0 eq) was added and it was stirred at 70 °C for 18 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel flash column chromatography using a CH₂Cl₂/MeOH gradient (0% to 5% MeOH) as eluent to yield 16 as a white solid (236 mg, 0.506 mmol).

Yield 72%; mp. 174-177 °C; \( ^1H \) NMR (500 MHz, DMSO-\( d_6 \)) \( \delta \) 4.17 (d, \( J = 6.2 \) Hz, 2H), 4.58 (d, \( J = 6.3 \) Hz, 2H), 5.03 (s, 2H), 7.20 (d, \( J = 7.9 \) Hz, 2H), 7.27 (d, \( J = 7.9 \) Hz, 2H), 7.28 – 7.39 (m, 5H), 7.50 (t, \( J = 51.6 \) Hz, 1H), 7.76 (t, \( J = 6.1 \) Hz, 1H), 8.70 (t, \( J = 6.4 \) Hz, 1H), 8.87 (s, 2H); \( ^13C \) NMR (126 MHz, DMSO-\( d_6 \)) \( \delta \) 43.7, 44.0, 65.5, 106.5, 106.7 (t, \( J(C,F) = 237.6 \) Hz), 127.2, 127.2, 127.8, 127.9, 128.5, 137.3, 137.9, 138.5, 156.5, 157.1, 157.3, 157.7 (t, \( J(C,F) = 29.4 \) Hz), 163.1, 163.3; \( ^{19}F \) NMR (565 MHz, DMSO-\( d_6 \)) \( \delta \) -121.1, -121.2; HRMS (ESI) \( m/z \) [M+H]+ calcd for C₂₃H₂₀F₂N₆O₃ 467.1638, found 467.1635; HPLC (95% H₂O 5 min, then to 95% MeCN in 5 min, then 100% MeCN to 20 min, 254 nm), \( t_R = 12.77 \) min, 98% purity.
Compound 18 was synthesized as described.\textsuperscript{15}

\[
\begin{align*}
\text{HO} & \text{-} \text{O} \text{-} \text{NHCbz} \\
\text{t-BuO}_2\text{C} & \text{-} \text{O} \text{-} \text{O} \text{-} \text{NHCbz}
\end{align*}
\]

Compound 19 was synthesized as described.\textsuperscript{15}

2-(2,6-Dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (25). This compound was synthesized similar to a previously reported procedure.\textsuperscript{16} 3-Fluorophthalic anhydride (1.24 g, 7.5 mmol) and 3-aminoglutarimide × HCl (0.82 g, 5 mmol) were put in a flask. A solution of sodium acetate (492 mg, 6 mmol) in glacial acetate (20 mL) was added and the reaction mixture was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature and was then poured onto H\textsubscript{2}O (100 mL). The precipitate was collected, washed with H\textsubscript{2}O (3 × 5 mL) and petroleum ether (3 × 5 mL) and it was dried under high vacuum to yield 25 as a light purple solid (1.00 g, 3.62 mmol). Yield 72%; \(R_f = 0.67\) (petroleum ether/EtOAc (1+2)); mp. > 230 °C, lit.\textsuperscript{16} mp. 236-238 °C; \(^1\text{H NMR}\) (600 MHz, DMSO-\text{d}_6) \(\delta 2.04 - 2.10\) (m, 1H), \(2.51 - 2.57\) (m, 1H), \(2.58 - 2.64\) (m, 1H), \(2.85 - 2.93\) (m, 1H), \(5.15\) (dd, \(J = 12.9, 5.4\) Hz, 1H), \(7.73\) (d, \(J = 8.7\) Hz, 1H), \(7.79\) (d, \(J = 7.3\) Hz, 1H), \(7.92 - 7.97\) (m, 1H), 11.13 (s, 1H); \(^{13}\text{C NMR}\) (151 MHz, DMSO-\text{d}_6) \(\delta 21.8, 30.9, 49.1, 117.0\) (d, \(^3\)\(J\) (C,F) = 12.5 Hz), 120.0 (d, \(^4\)\(J\) (C,F) = 2.8 Hz), 123.0 (d, \(^5\)\(J\) (C,F) = 19.6 Hz), 133.4 , 138.0 (d, \(^3\)\(J\) (C,F) = 7.7 Hz), 156.8 (d, \(^1\)\(J\) (C,F) = 262.3 Hz), 163.9 , 166.1 (d, \(^5\)\(J\) (C,F) = 2.6 Hz), 169.6, 172.7; LC-MS (ESI) (90% H\textsubscript{2}O + 2 mM NH\textsubscript{4}OAc to 100% MeCN in 10 min, then 100% MeCN to 20 min, DAD 220-500 nm), \(t_R = 6.99\) min, 100% purity, \(m/z\) [M+H]\(^+\) calcd for C\textsubscript{13}H\textsubscript{9}FN\textsubscript{2}O\textsubscript{4} 277.1, found 277.0.

\[
\begin{align*}
\text{t-BuO}_2\text{C} & \text{-} \text{O} \text{-} \text{NH} \\
\text{O} & \text{-} \text{O} \text{-} \text{NH}
\end{align*}
\]

\textit{tert-Butyl} 2-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisodolin-4-yl)amino)ethoxy)ethoxy)acetate (26). This compound was synthesized similar to a previously reported procedure.\textsuperscript{17} The orthogonally protected linker \textit{tert}-butyl 3-oxo-1-phenyl-2,7,10-trioxo-4-azadodecan-12-oate (19, 1.06 g, 3 mmol) was dissolved in dry EtOAc (30 mL) and treated with 10% m/m Pd/C. The mixture was
stirred under H\textsubscript{2} (1 atm, balloon) for 18 h. The mixture was filtered through celite and the filtrate was concentrated. The residue, compound 20, was taken up in dry DMSO (30 mL), DIPEA (0.78 g, 6 mmol) and 2-(2,6-dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione (25, 0.83 g, 3 mmol) were added. The reaction mixture was stirred at 90 °C for 18 h. It was allowed to cool to room temperature. Then it was poured onto half-saturated brine (300 mL) and it was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with 5% aqueous LiCl solution (150 mL) and brine (150 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The crude product was purified by silica gel column chromatography using a gradient from petroleum ether/EtOAc (1+1) to petroleum ether/EtOAc (1+2) to yield 26 as a yellow solid (581 mg, 1.22 mmol).

Yield 41%; \textit{R}\textsubscript{f} = 0.20 (petroleum ether/EtOAc (1+1)); mp. 66-68 °C, lit.\textsuperscript{17} mp. 66-68 °C;

\textsuperscript{1}H NMR (600 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 1.41 (s, 9H), 2.00 – 2.05 (m, 1H), 2.52 – 2.63 (m, 2H), 2.84 – 2.92 (m, 1H), 3.47 (q, \(J = 5.6\) Hz, 2H), 3.59 (s, 4H), 3.63 (t, \(J = 5.5\) Hz, 2H), 3.97 (s, 2H), 5.05 (dd, \(J = 12.8, 5.4\) Hz, 1H), 6.60 (t, \(J = 5.8\) Hz, 1H), 7.04 (d, \(J = 7.0\) Hz, 1H), 7.15 (d, \(J = 8.6\) Hz, 1H), 7.58 (dd, \(J = 8.5, 7.1\) Hz, 1H), 11.07 (s, 1H); \textsuperscript{13}C NMR (151 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 22.1, 27.7, 31.0, 41.7, 48.5, 68.2, 68.9, 68.9, 69.6, 80.6, 109.2, 110.6, 117.4, 132.1, 136.2, 146.4, 167.3, 168.9, 169.3, 170.0, 172.7; LC-MS (ESI) (90% H\textsubscript{2}O + 2 mM NH\textsubscript{4}OAc to 100% MeOH + 2 mM NH\textsubscript{4}OAc in 10 min, then 100% MeOH + 2 mM NH\textsubscript{4}OAc to 20 min, DAD 220-500 nm), \(t_R = 10.19\) min, 97% purity, \(m/z\) [M+H]\textsuperscript{+} calcd for C\textsubscript{23}H\textsubscript{29}N\textsubscript{3}O\textsubscript{8} 476.2, found 476.2.

\textit{t}-Butyl 8-bromooctanoate (22). This compound was synthesized similar to a previously reported procedure.\textsuperscript{18} 8-Bromooctanoic acid (21, 4.46 g, 20 mmol) was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (50 mL) and cooled to 0 °C under nitrogen. Trifluoroacetic anhydride (4.62 g, 22 mmol) was added dropwise at 0 °C and the mixture was allowed to stir for 2.5 h. \textit{t}-Butanol (5.19 g, 70 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 h at 0 °C. It was allowed to warm to room temperature and was stirred for 16 h. The reaction was quenched by the addition of water (50 mL). The organic phase was separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (39+1) as eluent to yield 22 as a colourless liquid (4.09 g, 14.6 mmol).

Yield 73%; \(R_f = 0.43\) (petroleum ether/EtOAc (39+1)); \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 1.24 – 1.30 (m, 4H), 1.34 – 1.38 (m, 2H), 1.39 (s, 9H), 1.45 – 1.52 (m, 2H), 1.75 – 1.82 (m, 2H), 2.17 (t, \(J = 7.3\) Hz, 2H), 3.52 (t, \(J = 6.7\) Hz, 2H); \textsuperscript{13}C NMR (126 MHz, DMSO-\textit{d}\textsubscript{6}) \(\delta\) 24.4, 27.3, 27.7, 27.7, 28.1, 32.1, 34.7, 35.0, 79.3, 172.2; LC-MS (ESI) (90% H\textsubscript{2}O + 2 mM NH\textsubscript{4}OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min), \(t_R = 9.35\) min, \(m/z\) [M+NH\textsubscript{4}]+ calcd for C\textsubscript{12}H\textsubscript{23}BrO\textsubscript{2} 296.1, found 296.2.
tert-Butyl 8-azidooctanoate (23). tert-Butyl 8-bromoocanoate (22, 4.05 g, 14.5 mmol) was dissolved in dry DMF (20 mL). Sodium azide (1.13 g, 17.4 mmol) was added in one portion. The reaction mixture was stirred at 80 °C for 24 h. The reaction mixture was concentrated under high vacuum. The residue was diluted with water (30 mL). The aqueous phase was extracted with Et2O (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na2SO4, filtered and concentrated to yield 23 as a colourless oil (3.31 g, 13.7 mmol).

Yield 94%; Rf = 0.41 (petroleum ether/EtOAc (39+1)); 1H NMR (500 MHz, DMSO-d6) δ 1.23 – 1.33 (m, 6H), 1.39 (s, 9H), 1.44 – 1.56 (m, 4H), 2.17 (t, J = 7.3 Hz, 2H), 3.31 (t, J = 6.9 Hz, 2H); 13C NMR (126 MHz, DMSO-d6) δ 24.4, 25.9, 27.7, 28.1, 28.1, 28.2, 34.7, 50.5, 79.2, 172.2.

tert-Butyl 8-aminooctanoate (24). tert-Butyl 8-azidooctanoate (23, 3.26 g, 13.5 mmol) was dissolved in a mixture of THF (20 mL) and H2O (10 mL). Triphenylphosphine (3.89 g, 14.9 mmol) was added in one portion and the reaction mixture was allowed to stir for 18 h at room temperature. The reaction mixture was diluted with H2O (30 mL) and was extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were dried over Na2SO4, filtered and concentrated. The crude product was purified by silica gel column chromatography using CH2Cl2 + 7 N NH3 in MeOH (9+1) as eluent to yield 24 as a colourless liquid (2.47 g, 11.5 mmol).

Yield 85%; Rf = 0.22 (CH2Cl2/7 N NH3 in MeOH (19+1)); 1H NMR (500 MHz, DMSO-d6) δ 1.21 – 1.37 (m, 10H), 1.39 (s, 9H), 1.44 – 1.52 (m, 2H), 2.16 (t, J = 7.3 Hz, 2H), one signal (2H) is missing due to proton exchange; 13C NMR (126 MHz, DMSO-d6) δ 24.5, 26.2, 27.7, 28.4, 28.6, 33.3, 34.7, 41.6, 79.2, 172.2; LC-MS (ESI) (90% H2O + 2 mM NH4OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min), tR = 5.12 min, m/z [M+H]+ calcd for C12H25NO2 216.2, found 216.2, lit.19 m/z [M+H]+ found 216.2.

tert-Butyl 8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)octanoate (27). tert-Butyl 8-aminooctanoate (24, 646 mg, 3 mmol) was dissolved in dry DMF (10 mL). DIPEA (595 mg, 4.6 mmol) was added. 2-(2,6-Dioxopiperidin-3-yl)-4-fluoroisindoline-1,3-dione (25, 635 mg, 2.3 mmol) was added and the mixture was stirred at 90 °C for 18 h. The organic layer was concentrated under high
vacuum. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (2+1) as eluent to yield 27 as a yellow solid (383 mg, 0.81 mmol).

Yield 27%; Rf = 0.24 (petroleum ether/EtOAc (2+1)); mp. 68-70 °C; 1H NMR (500 MHz, DMSO-d6) δ 1.25 – 1.35 (m, 6H), 1.38 (s, 9H), 1.45 – 1.52 (m, 2H), 1.53 – 1.60 (m, 2H), 1.99 – 2.06 (m, 1H), 2.16 (t, J = 7.4 Hz, 2H), 2.53 – 2.62 (m, 2H), 2.83 – 2.93 (m, 1H), 5.04 (dd, J = 12.7, 5.4 Hz, 1H), 6.50 (t, J = 6.0 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H), 7.57 (dd, J = 8.5, 7.2 Hz, 1H), 11.06 (s, 1H), one signal (2H) is obscured by the solvent signal; 13C NMR (126 MHz, DMSO-d6) δ 22.1, 24.5, 26.1, 27.7, 28.3, 28.6, 30.9, 34.7, 41.8, 48.5, 79.3, 109.0, 110.3, 117.1, 132.1, 136.2, 146.4, 164.4, 167.2, 168.9, 170.0, 172.2, 172.7; LC-MS (ESI) (90% H2O + 2 mM NH4OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), tR = 8.46 min, 100% purity, m/z [M-H]+ calcd for C25H33N3O6 470.2, found 470.3.

*tert*-Butyl 1-phenyl-2,5,8,11-tetraoxatridecan-13-oate (29). Potassium butoxide (1.18 g, 10.5 mmol) was dispersed in dry THF (60 mL) at 0 °C. 2-(2-(2-(Benzyloxy)ethoxy)ethoxy)ethanol (28, 2.40 g, 10 mmol) was added to the mixture. The solution was heated to 40 °C for 30 min. Afterwards the reaction was cooled to 0 °C. tert-Butyl 2-bromoacetate (1.95 g, 10 mmol) was added. The reaction mixture was stirred for 1 h at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 18 h. The reaction mixture was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was separated. The aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na2SO4, filtered and concentrated. The residue was purified by silica gel column chromatography using a gradient from petroleum ether/EtOAc (4+1) to petroleum ether/EtOAc (2+1) to yield 29 as a colourless oil (1.21 g, 3.41 mmol).

Yield 34%; Rf = 0.30 (petroleum ether/EtOAc (2+1)); 1H NMR (500 MHz, DMSO-d6) δ 1.42 (s, 9H), 3.51 – 3.57 (m, 12H), 3.97 (s, 2H), 4.49 (s, 2H), 7.25 – 7.37 (m, 5H); 13C NMR (126 MHz, DMSO-d6) δ 27.7, 68.1, 69.1, 69.7, 69.7, 69.8, 69.8, 72.0, 80.6, 127.3, 127.4, 128.1, 138.5, 169.3, one signal is missing due to overlapping peaks; LC-MS (ESI) (90% H2O + 2 mM NH4OAc to 100% MeOH + 2 mM NH4OAc in 10 min, then 100% MeOH + 2 mM NH4OAc to 20 min), tR = 11.12 min, 90% purity, m/z [M+NH4]⁺ calcd for C19H30O6 372.2, found 372.2.

*tert*-Butyl 2-(2-(2-(2-hydroxyethoxy)ethoxy)ethoxy)acetate (30). This compound was synthesized similar to a previously reported procedure.20 *tert*-Butyl 1-phenyl-2,5,8,11-tetraoxatridecan-13-oate (29, 1.24 g, 3.5 mmol) was dissolved in dry EtOH (10 mL) and treated with 10% m/m Pd/C under H2 (1 atm, balloon) and was stirred for 18 h. The mixture was diluted with EtOAc (20 mL), filtered through celite and concentrated to yield 30 as a colourless oil.
Quantitative yield; \( R_t = 0.48 \) (CH\(_2\)Cl\(_2\)/MeOH (9+1)); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.41 – 1.43 (m, 9H), 3.40 – 3.43 (m, 2H), 3.47 – 3.59 (m, 10H), 3.97 – 3.99 (m, 2H), 4.51 – 4.55 (m, 1H); \(^1^3\)C NMR (126 MHz, DMSO-\(d_6\)) \( \delta \) 27.7, 60.2, 68.1, 69.7, 69.7, 69.7, 69.8, 72.3, 80.6, 169.3; LC-MS (ESI) (90% H\(_2\)O + 2 mM NH\(_4\)OAc to 100% MeOH + 2 mM NH\(_4\)OAc in 10 min, then 100% MeOH + 2 mM NH\(_4\)OAc to 20 min), \( t_R = 8.58 \) min, \( m/z \) [M+NH\(_4\)]\(^+\) calcd for C\(_{12}\)H\(_{24}\)O\(_6\) 282.2, found 282.2.

13,13-Dimethyl-11-oxo-3,6,9,12-tetraoxatetradecanoic acid (31). This compound was synthesized similar to a previously reported procedure.\(^{20}\) tert-Butyl 2-(2-((2-hydroxyethoxy)ethoxy)-ethoxy)acetate (30, 925 mg, 3.5 mmol) was dissolved in MeCN (6 mL) and water (6 mL). TEMPO (120 mg, 0.77 mmol) was added. (Diacetoxyiodo)benzene (2.48 g, 7.7 mmol) was added portionwise. The reaction mixture was stirred at room temperature for 16 h. It was quenched by the addition of saturated NaHCO\(_3\) solution (85 mL) and the aqueous layer was washed with EtOAc (2 × 50 mL). The aqueous phase was acidified with 2 N HCl until pH~1. The mixture was then extracted with EtOAc (2 × 50 mL) and the combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by silica gel column chromatography using a gradient of CH\(_2\)Cl\(_2\) to CH\(_2\)Cl\(_2\)/MeOH (19+1) to yield 31 as a colourless oil (460 mg, 1.65 mmol).

Yield 47%; \( R_t = 0.19 \) (CH\(_2\)Cl\(_2\)/MeOH (9+1)); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.42 (s, 9H), 3.52 – 3.59 (m, 8H), 3.98 (s, 2H), 4.01 (s, 2H), one signal (1H) is missing due to proton exchange; \(^1^3\)C NMR (126 MHz, DMSO-\(d_6\)) \( \delta \) 27.7, 67.6, 68.1, 69.6, 69.7, 69.8, 69.8, 80.6, 169.3, 171.6; LC-MS (ESI) (90% H\(_2\)O + 0.1% AcOH to 100% MeCN + 0.1% AcOH in 10 min, then 100% MeCN +0.1% AcOH to 20 min), \( t_R = 6.22 \) min, \( m/z \) [M+NH\(_4\)]\(^+\) calcd for C\(_{12}\)H\(_{22}\)O\(_7\) 296.2, found 296.2.

tert-Butyl (S)-(1-(4-bromophenyl)ethyl)carbamate (37). This compound was synthesized similar to a previously reported procedure.\(^{21}\) (S)-1-(4-Bromophenyl)ethan-1-amine (36, 5.00 g, 25 mmol) and NaHCO\(_3\) (1.58 g, 18.8 mmol) were dissolved in H\(_2\)O (15 mL) and EtOAc (10 mL) and cooled to 0 °C. Boc\(_2\)O (6.55 g, 30 mmol) was dissolved in EtOAc (3 mL) and was added dropwise. The reaction mixture was stirred for 2 h at 0 °C. The precipitate was collected, resuspended in H\(_2\)O/hexane (1+1) (25 mL), stirred for further 30 min and was again collected. The residue was washed with hexane (3 × 15 mL) and dried under high vacuum to yield 37 as a white solid (6.90 g, 23 mmol).

Yield 92%; mp. 141-143 °C; \( R_t = 0.71 \) (petroleum ether/EtOAc (4+1)); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \( \delta \) 1.27 (d, \( J = 7.0 \) Hz, 3H), 1.35 (s, 9H), 4.53 – 4.62 (m, 1H), 7.24 (d, \( J = 8.3 \) Hz, 2H), 7.39 (d, \( J = 8.2 \) Hz, 1H), 7.47 – 7.51 (m, 2H); \(^1^3\)C NMR (151 MHz, DMSO-\(d_6\)) \( \delta \) 22.6, 28.2, 49.1, 77.7, 119.4, 128.1, 131.0, 144.9, 154.7; LC-MS (ESI) (90% H\(_2\)O + 2 mM NH\(_4\)OAc to 100% MeCN in 10 min, then 100% MeCN +2 mM NH\(_4\)OAc to 20 min), \( t_R = 6.84 \) min, \( m/z \) [M]+ calcd for C\(_{18}\)H\(_{19}\)N\(_2\)Br 340.0, found 340.1.
MeCN to 20 min, DAD 205-400 nm), \( t_R = 9.86 \) min, 100% purity, \( m/z [M+H]^+ \) calcd for C_{13}H_{18}BrNO_2 302.1, found 302.0.

**tert-Butyl (S)-(1-((4-methylthiazol-5-yl)phenyl)ethyl)carbamate (38).** This compound was synthesized similar to a previously reported procedure.21 tert-Butyl (S)-(1-(4-bromophenyl)ethyl)carbamate (37, 6.00 g, 20 mmol), Pd(OAc)_2 (45 mg, 0.2 mmol) and KOAc (3.93 g, 40 mmol) were dissolved in dry DMA (20 mL). 4-Methylthiazole (3.97 g, 40 mmol) was added and the mixture was heated to 130 °C under argon for 4 h. The mixture was allowed to cool to room temperature and was concentrated under high vacuum. The residue was diluted with water (80 mL) and was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4+1) as eluent to yield 38 as a white solid (5.34 g, 16.8 mmol).

Yield 84%; mp. 124-126 °C; \( R_I = 0.15 \) (petroleum ether/EtOAc (4+1)); \(^1\)H NMR (500 MHz, DMSO-d_6) \( \delta 1.33 (d, J = 7.0 \text{ Hz}, 3H), 1.37 (s, 9H), 2.45 (s, 3H), 4.60 – 4.71 (m, 1H), 7.37 – 7.46 (m, 5H), 8.97 (s, 1H); \(^{13}\)C NMR (126 MHz, DMSO-d_6) \( \delta 15.9, 22.7, 28.2, 49.2, 77.7, 126.3, 128.7, 129.6, 131.1, 145.3, 147.7, 151.3, 154.8; \) LC-MS (ESI) (90% H_2O + 2 mM NH_4OAc to 100% MeOH + 2 mM NH_4OAc in 10 min, then 100% MeOH + 2 mM NH_4OAc to 20 min, DAD 220-400 nm), \( t_R = 11.11 \) min, 96% purity, \( m/z [M+H]^+ \) calcd for C_{17}H_{22}N_{2}O_{2}S 319.1, found 318.9.

**Benzyl (2S,4R)-1-((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-pyrrolidine-2-carboxylate (41).** Boc-Tle-OH (39, 4.63 g, 20 mmol) was dissolved in dry DMF (18 mL). HATU (8.03 g, 21.1 mmol) and DIPEA (9.05 g, 70 mmol) were added at 0°C and the mixture was stirred for 30 min under nitrogen. H-Hyp-OBzl×HCl (40, 5.15 g, 20 mmol) was dissolved in dry DMF (18 mL) and was added to the reaction mixture. The mixture was stirred under nitrogen at room temperature for 18 h. The reaction was quenched by the addition of H_2O (50 mL) and was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaHCO_3 solution (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by
silica gel column chromatography using petroleum ether/EtOAc (1+1) as eluent to yield 41 as a white solid (5.91 g, 13.6 mmol). Yield 68%; mp. 118-120 °C; Rf = 0.33 (petroleum ether/EtOAc (1+1)); ¹H NMR (500 MHz, DMSO-d₆) δ 0.89 (s, 9H), 1.38 (s, 9H), 1.88 – 1.96 (m, 1H), 2.10 – 2.16 (m, 1H), 3.58 – 3.64 (m, 1H), 3.67 (dd, J = 10.6, 4.1 Hz, 1H), 4.15 (d, J = 9.4 Hz, 1H), 4.34 (br s, 1H), 4.42 (t, J = 8.3 Hz, 1H), 5.06 – 5.15 (m, 2H), 5.19 (d, J = 3.8 Hz, 1H), 6.47 (d, J = 9.4 Hz, 1H), 7.29 – 7.39 (m, 5H); ¹³C NMR (126 MHz, DMSO-d₆) δ 26.1, 28.1, 35.1, 37.2, 55.9, 57.7, 58.2, 65.8, 68.7, 78.1, 127.8, 127.9, 128.3, 135.8, 155.3, 170.1, 171.6; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeOH + 2 mM NH₄OAc in 10 min, then 100% MeOH + 2 mM NH₄OAc to 20 min, DAD 200-400 nm), tR = 11.41 min, 100% purity, m/z [M+H]+ calcd for C₂₃H₃₄N₂O₆ 435.2, found 435.4.

**tert-Butyl ((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (33).** This compound was synthesized similar to a previously reported procedure.²² Benzyl (2S,4R)-1-(((S)-2-((tert-butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-pyrrolidine-2-carboxylate (41, 2.17 g, 5 mmol) was dissolved in dry EtOH (50 mL) and treated with 10% m/m Pd/C under H₂ (1 atm, balloon) for 18 h. The reaction mixture was filtered through celite and was concentrated to yield a white solid. tert-Butyl (S)-(1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamate (38, 1.59 g, 5 mmol) was dissolved in dry CH₂Cl₂ (15 mL) and TFA (5 mL) was added. The mixture was stirred for 2 h at room temperature. The mixture was concentrated under high vacuum. The obtained intermediate from the hydrogenolytic deprotection (2S,4R)-1-((S)-2-((tert-Butoxycarbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxy-pyrrolidine-2-carboxylic acid (1.72 g, 5 mmol) was dissolved in dry DMF (5 mL) and HATU (2.09 g, 5.5 mmol) and DIPEA (2.26 g, 17.5 mmol) were added. The concentrated residue of the TFA mediated deprotection was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was stirred at room temperature under argon for 18 h. The reaction was quenched by the addition of H₂O (25 mL) and was then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (75 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by silica gel column chromatography using EtOAc as eluent to yield 33 as a white solid (1.75 g, 3.21 mmol). Yield 64%; mp. 208-210 °C; Rf = 0.29 (EtOAc); ¹H NMR (600 MHz, DMSO-d₆) δ 0.93 (s, 9H), 1.36 – 1.40 (m, 12H), 1.75 – 1.82 (m, 1H), 2.00 – 2.05 (m, 1H), 2.45 (s, 3H), 3.52 – 3.63 (m, 2H), 4.14 (d, J = 9.3 Hz, 1H), 4.28 (br s, 1H), 4.45 (t, J = 8.0 Hz, 1H), 4.87 – 4.93 (m, 1H), 5.10 (d, J = 3.6 Hz, 1H), 6.37 (d, J = 9.3 Hz, 1H), 7.36 – 7.39 (m, 2H), 7.42 – 7.44 (m, 2H), 8.38 (d, J = 7.6 Hz, 1H), 8.98 (s, 1H); ¹³C NMR (151 MHz, DMSO-d₆) δ 15.9, 22.4, 26.3, 28.2, 35.3, 37.7, 47.7, 56.2, 58.4, 58.5, 68.8, 78.1, 126.3,
128.8, 129.6, 131.1, 144.7, 147.7, 151.4, 155.3, 169.7, 170.6; **LC-MS (ESI)** (90% H$_2$O + 2 mM NH$_4$OAc to 100% MeOH + 2 mM NH$_4$OAc in 10 min, then 100% MeOH + 2 mM NH$_4$OAc to 20 min, DAD 220-400 nm), $t_R = 11.32$ min, 97% purity, $m/z$ [M+H]$^+$ calcld for C$_{28}$H$_{40}$N$_4$O$_5$S 545.3, found 545.1.

**tert-Butyl** (S)-13-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoate (34). **tert-Butyl** ((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (33, 872 mg, 1.6 mmol) was dissolved in dry CH$_2$Cl$_2$ (15 mL) and was treated with TFA (5 mL). The mixture was stirred for 2 h at room temperature. The mixture was concentrated under high vacuum. 13,13-Dimethyl-11-oxo-3,6,9,12-tetraoxatetradecanoic acid (31, 445 mg, 1.6 mmol) was dissolved in dry DMF (5 mL), HATU (669 mg, 1.76 mmol) and DIPEA (724 mg, 5.6 mmol) were added under argon. The deprotected VHL-ligand was dissolved in dry DMF (5 mL) and was added to the mixture, containing the activated acid compound. The reaction mixture was allowed to stir at room temperature under argon for 18 h. The reaction mixture was concentrated under high vacuum. The residue was diluted with water (25 mL) and was extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography using CH$_2$Cl$_2$/MeOH (19+1) as eluent to yield 34 as a colourless resin (902 mg, 1.28 mmol). Yield 80%; $R_f = 0.24$ (CH$_2$Cl$_2$/MeOH (19+1)); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 0.94 (s, 9H), 1.38 (d, $J = 7.0$ Hz, 3H), 1.42 (s, 9H), 1.75 – 1.82 (m, 1H), 2.01 – 2.07 (m, 1H), 2.45 (s, 3H), 3.53 – 3.65 (m, 10H), 3.96 (d, $J = 1.9$ Hz, 2H), 3.98 (s, 2H), 4.28 (br s, 1H), 4.45 (t, $J = 8.2$ Hz, 1H), 4.55 (d, $J = 9.5$ Hz, 1H), 4.88 – 4.94 (m, 1H), 5.11 (d, $J = 3.5$ Hz, 1H), 7.34 – 7.39 (m, 3H), 7.41 – 7.46 (m, 2H), 8.41 (d, $J = 7.7$ Hz, 1H), 8.98 (s, 1H); $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 15.9, 22.4, 26.2, 27.7, 35.7, 37.7, 47.7, 55.7, 56.5, 58.5, 68.1, 68.7, 69.5, 69.6, 69.7, 69.9, 70.4, 80.6, 126.3, 128.8, 129.7, 131.1, 144.7, 147.7, 151.4, 168.5, 169.0, 169.3, 170.4; **LC-MS (ESI)** (90% H$_2$O + 2 mM NH$_4$OAc to 100% MeOH + 2 mM NH$_4$OAc in 10 min, then 100% MeOH + 2 mM NH$_4$OAc to 20 min, DAD 220-400 nm), $t_R = 11.47$ min, 98% purity, $m/z$ [M+H]$^+$ calcld for C$_{35}$H$_{52}$N$_4$O$_9$S 705.4, found 705.6.
**tert-Butyl 11-(((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)-carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoate** (35). *tert-Butyl* ((S)-1-((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)-pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (33, 490 mg, 0.9 mmol) was dissolved in dry CH$_2$Cl$_2$ (5 mL) and was treated with TFA (5 mL). The mixture was stirred for 2 h at room temperature. The mixture was concentrated under high vacuum. 11-(tert-Butoxy)-11-oxoundecanoic acid (32, 245 mg, 0.9 mmol) was dissolved in dry DMF (5 mL). HATU (376 mg, 0.99 mmol) and DIPEA (407 mg, 3.15 mmol) were added under argon. The deprotected VHL ligand was dissolved in dry DMF (5 mL) and was added to the mixture containing the activated acid compound. The reaction mixture was allowed to stir at room temperature under argon for 3 h. The reaction mixture was concentrated under high vacuum. The residue was diluted with water (50 mL) and was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography using CH$_2$Cl$_2$/MeOH (19+1) as eluent to yield 35 as a colourless resin (441 mg, 0.63 mmol).

Yield 70%; $R_f = 0.28$ (CH$_2$Cl$_2$/MeOH (9+1)); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 0.93 (s, 9H), 1.22 – 1.25 (m, 10H), 1.37 – 1.39 (m, 12H), 1.43 – 1.51 (m, 4H), 1.77 – 1.83 (m, 1H), 1.97 – 2.03 (m, 1H), 2.06 – 2.13 (m, 1H), 2.14 – 2.18 (m, 2H), 2.21 – 2.28 (m, 1H), 2.45 (s, 3H), 3.57 – 3.64 (m, 2H), 4.26 – 4.30 (m, 1H), 4.42 (t, $J = 8.0$ Hz, 1H), 4.52 (d, $J = 9.3$ Hz, 1H), 4.89 – 4.95 (m, 1H), 5.07 (d, $J = 3.5$ Hz, 1H), 7.38 (d, $J = 8.2$ Hz, 2H), 7.43 (d, $J = 8.2$ Hz, 2H), 7.75 (d, $J = 9.3$ Hz, 1H), 8.34 (d, $J = 7.8$ Hz, 1H), 8.98 (s, 1H); $^{13}$C NMR (151 MHz, DMSO-$d_6$) $\delta$ 15.9, 22.4, 24.6, 25.4, 26.4, 27.7, 28.3, 28.6, 28.6, 28.7, 34.7, 34.9, 35.2, 37.7, 38.2, 47.7, 56.2, 56.3, 58.5, 68.7, 79.3, 126.4, 128.8, 129.7, 131.1, 144.6, 147.7, 151.4, 169.6, 170.6, 172.0, 172.3; **LC-MS (ESI)** (90% H$_2$O + 2 mM NH$_4$OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), $t_R = 8.48$ min, 95% purity, $m/z$ [M+H]$^+$ calced for C$_{38}$H$_{58}$N$_4$O$_6$S 699.4, found 699.6.
N-(3-(((5-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)acetamide (1). Benzyl (3-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (15, 117 mg, 0.25 mmol) was dissolved in a mixture of dry EtOH (10 mL) and dry EtOAc (5 mL). The mixture was treated with 10% m/m Pd/C under H2 (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl 2-((2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)acetate (26, 119 mg, 0.25 mmol) was dissolved in dry CH2Cl2 (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (97 mg, 0.75 mmol) and HATU (105 mg, 0.28 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH2Cl2/MeOH gradient (0% to 4% MeOH) to yield 1 as a yellow solid (49 mg, 0.07 mmol).

Yield 27%; mp. 106-110 °C; Rf = 0.31 (CH2Cl2/MeOH (19+1)); 1H NMR (600 MHz, DMSO-d6) δ 1.99 – 2.05 (m, 1H), 2.52 – 2.62 (m, 2H), 2.82 – 2.90 (m, 1H), 3.40 – 3.43 (m, 2H), 3.58 – 3.61 (m, 6H), 3.93 (s, 2H), 4.28 (d, J = 6.2 Hz, 2H), 4.57 (d, J = 6.3 Hz, 2H), 5.03 (dd, J = 12.8, 5.4 Hz, 1H), 6.56 (t, J = 5.9 Hz, 1H), 7.02 (d, J = 7.0 Hz, 1H), 7.08 – 7.13 (m, 2H), 7.16 – 7.26 (m, 3H), 7.51 (t, J = 51.3 Hz, 1H), 7.53 – 7.57 (m, 1H), 8.15 (t, J = 6.2 Hz, 1H), 8.70 (t, J = 6.4 Hz, 1H), 8.86 (s, 2H), 11.07 (s, 1H); 13C NMR (151 MHz, DMSO-d6) δ 22.1, 31.0, 41.6, 41.6, 44.0, 48.5, 68.9, 69.4, 70.0, 70.3, 106.3, 106.5 (t, 1J (C,F) = 238.6 Hz), 109.2, 110.6, 117.3, 125.5, 125.7, 125.9, 128.2, 132.0, 136.2, 139.2, 139.5, 146.3, 157.0, 157.1, 157.5 (t, 3J (C,F) = 29.4 Hz), 162.9, 163.1, 167.2, 168.9, 169.2, 170.0, 172.7; LC-MS (ESI) (90% H2O + 2 mM NH4OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 200-600 nm), tR = 5.84 min, 96% purity, m/z [M+H]+ calcld for C34H33F2N9O8 734.2, found 734.4; HRMS (ESI) m/z [M+H]+ calcld for C34H33F2N9O8 734.2493, found 734.2492.
**Scheme S24**

**N-(3-(((5-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-y1)pyrimidin-2-y1)amino)methyl)benzyl)-8-((2,6-dioxopiperidin-3-y1)-1,3-dioxoisindolin-4-y1)amino)octanamide (2).** Benzyl (3-(((5-(difluoromethyl)-1,3,4-oxadiazol-2-y1)pyrimidin-2-y1)amino)methyl)benzyl)carbamate (15, 93 mg, 0.2 mmol) was dissolved in dry THF (10 mL). The mixture was treated with 10% m/m Pd/C under H₂ (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum.

tert-Butyl 8-((2-(2,6-dioxopiperidin-3-y1)-1,3-dioxoisindolin-4-y1)amino)octanoate (27, 94 mg, 0.2 mmol) was dissolved in dry CH₂Cl₂ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (78 mg, 0.6 mmol) and HATU (84 mg, 0.22 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH₂Cl₂/MeOH gradient (0% to 4% MeOH) to yield 2 as a yellow solid (36 mg, 0.05 mmol).

Yield 25%; mp. 108-112 °C; Rf = 0.33 (CH₂Cl₂/MeOH (19+1)); **¹H NMR** (600 MHz, DMSO-δ₆) δ 1.22 – 1.34 (m, 6H), 1.46 – 1.52 (m, 2H), 1.52 – 1.59 (m, 2H), 2.00 – 2.05 (m, 1H), 2.10 (t, J = 7.4 Hz, 2H), 2.52 – 2.62 (m, 2H), 2.84 – 2.91 (m, 1H), 3.25 – 3.30 (m, 2H), 4.22 (d, J = 5.9 Hz, 2H), 4.58 (d, J = 6.3 Hz, 2H), 5.04 (dd, J = 12.8, 5.4 Hz, 1H), 6.50 (t, J = 6.0 Hz, 1H), 7.01 (d, J = 7.0 Hz, 1H), 7.06 – 7.12 (m, 2H), 7.16 – 7.21 (m, 2H), 7.25 (t, J = 7.5 Hz, 1H), 7.52 (t, J = 51.3 Hz, 1H), 7.56 (dd, J = 8.5, 7.1 Hz, 1H), 8.24 (t, J = 6.1 Hz, 1H), 8.71 (t, J = 6.4 Hz, 1H), 8.87 (s, 2H), 11.07 (s, 1H); **¹³C NMR** (151 MHz, DMSO-δ₆) δ 22.1, 25.2, 26.2, 28.4, 28.6, 31.0, 35.3, 41.8, 41.9, 44.0, 48.5, 106.3, 106.5 (t, J(C,F) = 238.2 Hz), 109.0, 110.3, 117.1, 125.4, 125.7, 125.8, 128.2, 132.2, 136.2, 139.2, 139.9, 146.4, 157.0, 157.1, 157.5 (t, J(C,F) = 29.5 Hz), 162.9, 163.1, 167.3, 168.9, 170.0, 172.0, 172.8; **LC-MS (ESI)** (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), tᵣ = 6.99 min, 98% purity, m/z [M+H]+ caled for C₃₆H₃₇F₂N₉O₆ 730.3, found 730.5; **HRMS (ESI)** m/z [M+H]+ caled for C₃₆H₃₇F₂N₉O₆ 730.2908, found 730.2907.
\[ N-(\text{4-(((5-(5-\text{(Difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)-2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)acetamide}) \text{ (3). Benzyl (4-(((5-(difu}rormethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (16, 117 mg, 0.25 mmol) was dissolved in a mixture of dry EtOAc (10 mL), dry EtOH (2 mL) and dry THF (2 mL). The mixture was treated with 10% m/m Pd/C under H\textsubscript{2} (1 atm, balloon) for 4 days. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl 2-(\text{2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)acetate (26, 119 mg, 0.25 mmol) was dissolved in dry CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (97 mg, 0.75 mmol) and HATU (105 mg, 0.28 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH\textsubscript{2}Cl\textsubscript{2}/MeOH gradient (0% to 6% MeOH) to yield 3 as a yellow solid (47 mg, 0.06 mmol).

Yield 26%; mp. 106-110 °C; \( R_t = 0.61 \) (CH\textsubscript{2}Cl\textsubscript{2}/MeOH (9+1)); \textsuperscript{1}H NMR (600 MHz, DMSO-\text{d}_6) \( \delta \) 1.99 – 2.05 (m, 1H), 2.52 – 2.62 (m, 2H), 2.83 – 2.91 (m, 1H), 3.41 (q, \( J = 5.6 \) Hz, 2H), 3.58 – 3.62 (m, 6H), 3.93 (s, 2H), 4.26 (d, \( J = 6.1 \) Hz, 2H), 4.55 (d, \( J = 6.3 \) Hz, 2H), 5.03 (dd, \( J = 12.9, 5.5 \) Hz, 1H), 6.56 (t, \( J = 5.9 \) Hz, 1H), 7.02 (d, \( J = 7.1 \) Hz, 1H), 7.09 (d, \( J = 8.6 \) Hz, 1H), 7.19 (d, \( J = 8.0 \) Hz, 2H), 7.24 (d, \( J = 7.9 \) Hz, 2H), 7.51 (t, \( J = 51.4 \) Hz, 1H), 7.54 – 7.57 (m, 1H), 8.12 (t, \( J = 6.2 \) Hz, 1H), 8.68 (t, \( J = 6.4 \) Hz, 1H), 8.86 (s, 2H), 11.07 (s, 1H); \textsuperscript{13}C NMR (151 MHz, DMSO) \( \delta \) 22.1, 30.9, 41.4, 41.6, 43.8, 48.5, 68.8, 69.4, 70.0, 70.3, 106.3, 106.5 (t, \( J (C,F) = 238.7 \) Hz), 109.2, 110.6, 117.3, 127.0, 127.2, 132.0, 136.1, 137.7, 137.9, 146.3, 157.0, 157.1, 157.5 (t, \( J (C,F) = 29.4 \) Hz), 162.9, 163.1, 167.2, 168.9, 169.1, 170.0, 172.7; LC-MS (ESI) (90% H\textsubscript{2}O + 2 mM NH\textsubscript{4}OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 200-600 nm), \( t_R = 6.01 \) min, 99% purity, \( m/z \) [M+H]\textsuperscript{+} calcd for C\textsubscript{34}H\textsubscript{33}F\textsubscript{2}N\textsubscript{9}O\textsubscript{7} 734.2, found 734.4; HRMS (ESI) \( m/z \) [M+H]\textsuperscript{+} calcd for C\textsubscript{34}H\textsubscript{33}F\textsubscript{2}N\textsubscript{9}O\textsubscript{7} 734.2493, found 734.2482.
(2S,4R)-1-(((S)-15-(tert-Butyl)-1-(3-(((5-((difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)phenyl)-3,13-dioxo-5,8,11-trioxa-2,14-diazahexadecan-16-oyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (4). Benzyl (3-(((5-((difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (15, 117 mg, 0.25 mmol) was dissolved in dry THF (10 mL). The mixture was treated with 10% m/m Pd/C under H₂ (1 atm, balloon) for 18 h. The mixture was filtered through celite and was concentrated under high vacuum. tert-Butyl (5-S)-13-(((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoate (34, 176 mg, 0.25 mmol) was dissolved in dry CH₂Cl₂ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (97 mg, 0.75 mmol) and HATU (105 mg, 0.28 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH₂Cl₂/MeOH gradient (0% to 20% MeOH) to yield 4 as a white solid (117 mg, 0.12 mmol).

Yield 49%; mp. 88-92 °C; Rf = 0.30 (CH₂Cl₂/MeOH (9+1)); ¹H NMR (600 MHz, DMSO-d₆) δ 0.93 (s, 9H), 1.37 (d, J = 7.0 Hz, 3H), 1.75 – 1.81 (m, 1H), 2.02 – 2.08 (m, 1H), 2.45 (s, 3H), 3.54 – 3.62 (m, 10H), 3.87 – 3.97 (m, 4H), 4.27 – 4.32 (m, 3H), 4.45 (t, J = 8.2 Hz, 1H), 4.54 (d, J = 9.6 Hz, 1H), 4.59 (d, J = 6.3 Hz, 2H), 4.87 – 4.93 (m, 1H), 5.11 (d, J = 3.5 Hz, 1H), 7.12 – 7.28 (m, 4H), 7.33 – 7.39 (m, 3H), 7.41 – 7.61 (m, 3H), 8.19 (t, J = 6.3 Hz, 1H), 8.41 (d, J = 7.6 Hz, 1H), 8.72 (t, J = 6.4 Hz, 1H), 8.87 (s, 2H), 8.97 (s, 1H); ¹³C NMR (151 MHz, DMSO-d₆) δ 15.9, 22.4, 26.2, 35.7, 37.7, 41.6, 44.0, 47.7, 55.7, 58.5, 68.7, 69.6, 70.0, 70.3, 70.4, 106.3, 106.6 (t, ¹J (C,F) = 238.8 Hz), 125.5, 125.8, 125.9, 126.3, 128.2, 128.8, 129.7, 131.1, 139.2, 139.5, 144.7, 147.7, 151.4, 157.0, 157.2, 157.5 (t, ²J (C,F) = 29.3 Hz), 162.9, 163.1, 168.5, 169.0, 169.2, 170.4, one signal is missing due to overlapping signals; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 200-600 nm), tᵣ = 6.22 min, 96% purity, m/z [M+H]⁺ calcd for C₄₆H₅₆F₂N₁₀O₉S 963.4, found 963.5; HRMS (ESI) m/z [M+H]⁺ calcd for C₄₆H₅₆F₂N₁₀O₉S 963.3993, found 963.3990.
$N^{1}$-((5-(5-(Difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)ethyl)benzyl-$N^{11}$-((5S)-1-((2S,4R)-4-hydroxy-2-((5S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)undecanediamide (5). Benzyl (3-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (15, 70 mg, 0.15 mmol) was dissolved in dry THF (10 mL). The mixture was treated with 10% m/m Pd/C under H$_2$ (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl 11-(((2S)-1-((4-(4-hydroxy-2-((5S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-11-oxoundecanoate (35, 105 mg, 0.15 mmol) was dissolved in dry CH$_2$Cl$_2$ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (58 mg, 0.45 mmol) and HATU (63 mg, 0.17 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH$_2$Cl$_2$/MeOH (0% to 20% MeOH) to yield 5 as a white solid (29 mg, 0.03 mmol).

Yield 20%; $R_i$ = 0.32 (CH$_2$Cl$_2$/MeOH (9+1)); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 0.92 (s, 9H), 1.21 (s, 10H), 1.37 (d, $J$ = 7.0 Hz, 3H), 1.42 – 1.50 (m, 4H), 1.76 – 1.82 (m, 1H), 1.96 – 2.03 (m, 1H), 2.05 – 2.12 (m, 3H), 2.19 – 2.26 (m, 1H), 2.44 (s, 3H), 3.55 – 3.63 (m, 2H), 4.22 (d, $J$ = 5.9 Hz, 2H), 4.25 – 4.29 (m, 1H), 4.42 (t, $J$ = 8.0 Hz, 1H), 4.51 (d, $J$ = 9.3 Hz, 1H), 4.58 (d, $J$ = 6.3 Hz, 2H), 4.87 – 4.94 (m, 1H), 5.05 (d, $J$ = 3.6 Hz, 1H), 7.10 (d, $J$ = 7.4 Hz, 1H), 7.16 – 7.20 (m, 2H), 7.25 (t, $J$ = 7.5 Hz, 1H), 7.35 – 7.38 (m, 2H), 7.40 – 7.62 (m, 3H), 7.72 (d, $J$ = 9.3 Hz, 1H), 8.22 (t, $J$ = 6.0 Hz, 1H), 8.32 (d, $J$ = 7.8 Hz, 1H), 8.69 (t, $J$ = 6.4 Hz, 1H), 8.86 (s, 2H), 8.96 (s, 1H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ 15.9, 22.0, 22.3, 25.2, 25.4, 26.4, 28.6, 28.6, 28.7, 28.8, 34.9, 35.1, 35.3, 37.7, 41.9, 44.0, 47.6, 56.2, 56.3, 58.5, 68.7, 106.3, 106.5 (t, $^1$J(C,F) = 238.9 Hz), 125.4, 125.6, 125.8, 126.3, 128.2, 128.8, 129.7, 131.1, 139.2, 139.9, 144.6, 147.7, 151.4, 156.9, 157.1, 157.5 (t, $^2$J(C,F) = 29.3 Hz), 162.9, 163.1, 169.6, 170.6, 172.0, 172.0; LC-MS (ESI) (90% H$_2$O + 2 mM NH$_4$OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 200-600 nm), $t_R$ = 7.17 min, 96% purity, $m/z$ [M+H]$^+$ calcd for C$_{49}$H$_{62}$F$_2$N$_{10}$O$_6$S 957.5, found 957.7; HRMS (ESI) $m/z$ [M+H]$^+$ calcd for C$_{49}$H$_{62}$F$_2$N$_{10}$O$_6$S 957.4615, found 957.4615.
(2S,4R)-1-((S)-15-(tert-Butyl)-1-(4-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)phenyl)-3,13-dioxo-5,8,11-trioxa-2,14-diazahexadecan-16-oyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (6). Benzyl (4-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (16, 93 mg, 0.2 mmol) was dissolved in dry THF (10 mL). The mixture was treated with 10% m/m Pd/C under H₂ (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl (S)-13-(((2S,4R)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxa-12-azapentadecanoate (34, 141 mg, 0.2 mmol) was dissolved in dry CH₂Cl₂ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (78 mg, 0.6 mmol) and HATU (84 mg, 0.22 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 2 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH₂Cl₂/MeOH gradient (0% to 20% MeOH) to yield 6 as a white solid (52 mg, 0.05 mmol).

Yield 27%; mp. 88-92 °C; Rᵣ = 0.30 (CH₂Cl₂/MeOH (9+1)); ′H NMR (600 MHz, DMSO-d₆) δ 0.93 (s, 2H), 1.37 (d, J = 7.0 Hz, 3H), 1.75 – 1.81 (m, 1H), 2.02 – 2.08 (m, 1H), 2.45 (s, 3H), 3.55 – 3.63 (m, 10H), 3.88 – 3.97 (m, 4H), 4.26 – 4.31 (m, 3H), 4.44 (t, J = 8.2 Hz, 1H), 4.54 (d, J = 9.5 Hz, 1H), 4.57 (d, J = 6.3 Hz, 2H), 4.87 – 4.94 (m, 1H), 5.11 (d, J = 3.5 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 8.3 Hz, 2H), 7.33 – 7.39 (m, 3H), 7.41 – 7.61 (m, 3H), 8.17 (t, J = 6.2 Hz, 1H), 8.41 (d, J = 7.7 Hz, 1H), 8.70 (t, J = 6.3 Hz, 1H), 8.87 (s, 2H), 8.97 (s, 1H); ′C NMR (151 MHz, DMSO) δ 15.9, 22.4, 26.2, 35.7, 37.7, 41.4, 43.8, 47.7, 55.7, 56.5, 58.5, 68.7, 69.5, 69.6, 69.6, 70.0, 70.3, 70.4, 106.3, 106.5 (t, J (C,F) = 238.0 Hz), 126.3, 127.1, 127.3, 128.8, 129.7, 131.1, 137.7, 138.0, 144.7, 147.7, 151.4, 157.0, 157.1, 157.5 (t, J (C,F) = 29.3 Hz), 162.9, 163.1, 168.5, 169.0, 169.2, 170.4; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 200-600 nm), tᵣ = 6.20 min, 97% purity, m/z [M+H]+ calcd for C₄₆H₅₉F₂N₁₀O₉S 963.4, found 963.7; HRMS (ESI) m/z [M+H]+ calcd for C₄₆H₅₉F₂N₁₀O₉S 963.3993, found 963.3991.
**tert-Butyl (2,6-dioxopiperidin-3-yl)carbamate (42).** This compound was synthesized similar to a previously reported procedure.16 Boc-Gln-OH (4.93 g, 20 mmol) was dissolved in dry THF (75 mL). 1,1'-Carbonyldiimidazole (3.89 g, 24 mmol) and DMAP (0.005 g) were added. The reaction mixture was refluxed for 10 h. The mixture was concentrated and the residue was taken up in EtOAc (300 mL). The organic layer was washed with H₂O (75 mL) and brine (75 mL). The organic layer was dried over Na₂SO₄ and loaded onto a pad of silica gel. The product was eluted with EtOAc. The solvent was evaporated to yield 42 as a white solid (3.08 g, 13.5 mmol).

Yield 68%; mp. 192-194 °C, lit.23 mp. 193.7-194.4 °C; Rᵣ = 0.31 (petroleum ether/EtOAc (1+1)); ¹H NMR (500 MHz, DMSO-d₆) δ 1.40 (s, 9H), 1.86 – 1.99 (m, 2H), 2.44 – 2.49 (m, 1H), 2.66 – 2.75 (m, 1H), 4.17 – 4.28 (m, 1H), 7.09 (d, J = 8.5 Hz, 1H), 10.70 (s, 1H); ¹³C NMR (126 MHz, DMSO-d₆) δ 24.4, 28.1, 30.9, 50.4, 78.1, 155.4, 172.4, 172.9; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, tᵣ = 3.02 min, m/z [M-H]⁺ calcd for C₁₀H₁₆N₂O₄ 227.1, found 227.0.

**tert-Butyl (1-methyl-2,6-dioxopiperidin-3-yl)carbamate (43).** This compound was synthesized similar to a previously reported procedure.16 tert-Butyl (2,6-dioxopiperidin-3-yl)carbamate (42, 2.97 g, 13 mmol) was dissolved in dry DMF (30 mL). K₂CO₃ (3.59 g, 26 mmol) and iodomethane (1.85 g, 13 mmol) were added. The reaction mixture was sonicated for 2 h. The mixture was concentrated under high vacuum. The residue was taken up in EtOAc (15 mL). The organic layer was washed with 1 N NaOH (2 × 40 mL), H₂O (40 mL) and brine (40 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (2+1) as eluent to yield 43 as a white solid (1.55 g, 6.40 mmol).

Yield 49%; mp. 86-88 °C, lit.16 mp. 84-86 °C; Rᵣ = 0.41 (petroleum ether/EtOAc (2+1)); ¹H NMR (500 MHz, DMSO-d₆) δ 1.40 (s, 9H), 1.85 – 2.00 (m, 2H), 2.60 – 2.68 (m, 1H), 2.75 – 2.84 (m, 1H), 2.97 (s, 3H), 4.22 – 4.37 (m, 1H), 7.16 (d, J = 8.6 Hz, 1H); ¹³C NMR (126 MHz, DMSO) δ 23.5, 26.4, 28.1, 31.1, 50.9, 78.1, 155.4, 172.0, 172.2; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, tᵣ = 4.05 min, m/z [M-H]⁺ calcd for C₁₁H₁₆N₂O₄ 241.1, found 241.1.
4-Fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (44). This compound was synthesized similar to a previously reported procedure. 3-Fluorophthalic anhydride (1.28 g, 9 mmol) and tert-butyl (1-methyl-2,6-dioxopiperidin-3-yl)carbamate (43, 1.45 g, 6 mmol) were put in a flask. A solution of sodium acetate (995 mg, 7.2 mmol) in glacial acetate (20 mL) was added and the reaction mixture was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature and was then poured onto H₂O (100 mL). The precipitate was collected, washed with H₂O (3 × 5 mL) and petroleum ether (3 × 5 mL) and it was dried under high vacuum to yield 44 as a light purple solid (1.30 g, 4.48 mmol). Yield 75%; mp. 200–202 °C, lit. mp. 196–198 °C; Rₛ = 0.23 (petroleum ether/EtOAc (2+1)); ¹H NMR (500 MHz, DMSO-d₆) δ 2.05 – 2.12 (m, 1H), 2.52 – 2.59 (m, 1H), 2.74 – 2.81 (m, 1H), 2.91 – 3.00 (m, 1H), 3.03 (s, 3H), 5.22 (dd, J = 13.1, 5.4 Hz, 1H), 7.74 (t, J = 8.9 Hz, 1H), 7.79 (d, J = 7.3 Hz, 1H), 7.92 – 7.98 (m, 1H); ¹³C NMR (126 MHz, DMSO-d₆) δ 21.0, 26.6, 31.0, 49.6, 117.0 (d, 2J(C,F) = 12.6 Hz), 120.0 (d, 4J(C,F) = 3.0 Hz), 123.0 (d, 2J(C,F) = 19.6 Hz), 133.4, 138.0 (d, 3J(C,F) = 7.7 Hz), 156.8 (d, 1J(C,F) = 262.4 Hz), 163.9, 166.0 (d, 3J(C,F) = 2.9 Hz), 169.3, 171.6; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), tᵣ = 4.51 min, 100% purity, m/z [M+H]⁺ calcd for C₁₄H₁₁FN₂O₄ 291.1, found 291.0.

tert-Butyl 2-(2-(2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)-ethoxyacetate (45). The orthogonally protected linker tert-butyl 3-oxo-1-phenyl-2,7,10-troixa-4-azadodecan-12-oate (19, 1.06 g, 3 mmol) was dissolved in dry EtOAc (30 mL) and treated with 10% m/m Pd/C. The reaction mixture was stirred under H₂ (1 atm, balloon) for 18 h. The mixture was filtered through celite and the filtrate was concentrated. The residue was redissolved in dry DMSO (30 mL) and DIPEA (0.776 g, 6 mmol) and 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (44, 871 mg, 3 mmol) were added. The reaction mixture was stirred at 90 °C for 18 h. The reaction mixture was allowed to cool to room temperature. Then it was poured onto half-saturated brine (300 mL) and it was extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with 5% aqueous LiCl solution (150 mL) and brine (150 mL), dried over Na₂SO₄, filtered and concentrated. The crude
product was purified by silica gel column chromatography using a gradient from petroleum ether/EtOAc (1+1) to petroleum ether/EtOAc (1+2) to yield 45 as a yellowish-green resin (665 mg, 1.36 mmol). Yield 45%; \( R_f = 0.33 \) (petroleum ether/EtOAc (1+1)); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.41 (s, 9H), 2.01 – 2.08 (m, 1H), 2.51 – 2.59 (m, 1H), 2.72 – 2.79 (m, 1H), 2.90 – 2.99 (m, 1H), 3.02 (s, 3H), 3.47 (q, \( J = 5.6 \) Hz, 2H), 3.57 – 3.60 (m, 4H), 3.63 (t, \( J = 5.4 \) Hz, 2H), 3.97 (s, 2H), 5.12 (dd, \( J = 13.0, 5.4 \) Hz, 1H), 6.60 (t, \( J = 5.9 \) Hz, 1H), 7.04 (d, \( J = 7.0 \) Hz, 1H), 7.15 (d, \( J = 8.5 \) Hz, 1H), 7.59 (dd, \( J = 8.5, 7.1 \) Hz, 1H); \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \( \delta \) 21.3, 26.5, 27.7, 31.1, 41.7, 49.1, 68.2, 68.8, 69.6, 69.9, 80.6, 109.2, 110.6, 117.4, 132.0, 136.2, 146.4, 167.2, 168.9, 169.3, 169.7, 171.7; LC-MS (ESI) (90% \( \text{H}_2\text{O} + 2 \text{mM NH}_4\text{OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm} \), \( t_R = 6.83 \) min, 99% purity, \( \text{m/z} \) [M–H] – calcd for \( \text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_8 488.2 \), found 488.2.

\begin{align*}
\text{N-} & (3-(5-(5-(\text{Difluoromethyl})-1,3,4-\text{oxadiazol}-2-\text{yl})\text{pyrimidin}-2-\text{yl})\text{amino})\text{methyl})\text{benzyl)}-2-(2-(2-(1\text{methyl-2,6-}\text{dioxopiperidin-3-yl})-1,3\text{-dioxoisindolin-4-yl})\text{amino})\text{ethoxy}}\text{ethoxy)acetamide (1(-))}. \text{ Benzyl (3-((5-(\text{difluoromethyl})-1,3,4-oxadiazol-2-yl)\text{pyrimidin-2-yl})\text{amino})methyl)}\text{benzyl)-carbamate (15, 93 mg, 0.2 mmol) was dissolved in dry THF (10 mL) and was treated with 10% m/m Pd/C under H2 (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl 2-(2-(2-(1\text{methyl-2,6-}\text{dioxopiperidin-3-yl})-1,3\text{-dioxoisindolin-4-yl})\text{amino})\text{ethoxy}}\text{ethoxy)acetate (45, 98 mg, 0.2 mmol) was dissolved in dry CH2Cl2 (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (78 mg, 0.6 mmol) and HATU (84 mg, 0.22 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added. The reaction mixture was allowed to stir at room temperature under argon for 18 h. The mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH2Cl2/MeOH gradient (0% to 4% MeOH) to yield 1(-) as a yellow solid (72 mg, 0.096 mmol). Yield 48%; mp. 82-88 °C; \( R_f = 0.24 \) (CH2Cl2/MeOH (19+1)); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \( \delta \) 2.00 – 2.06 (m, 1H), 2.51 – 2.57 (m, 1H), 2.72 – 2.77 (m, 1H), 2.88 – 2.96 (m, 1H), 3.01 (s, 3H), 3.41 (q, \( J = 5.6 \) Hz, 2H), 3.58 – 3.61 (m, 6H), 3.92 (s, 2H), 4.28 (d, \( J = 6.2 \) Hz, 2H), 4.57 (d, \( J = 6.3 \) Hz, 2H), 5.10 (dd, \( J = 13.0, 5.4 \) Hz, 1H), 6.56 (t, \( J = 5.9 \) Hz, 1H), 7.02 (d, \( J = 7.0 \) Hz, 1H), 7.08 – 7.13 (m, 2H), 7.16 – 7.26 (m, 3H), 7.51 (t, \( J = 51.3 \) Hz, 1H), 7.56 (dd, \( J = 8.6, 7.1 \) Hz, 1H), 8.15 (t, \( J = 6.2 \) Hz, 1H), 8.70 (t, \( J = 6.4 \) Hz, 1H), 8.86 (s, 2H); \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \( \delta \) 21.3, 26.6, 31.1, 41.6, 41.6, 44.0, 49.1, 68.8, 69.4, 70.0, 70.3, 106.3, 106.5 (t, \(^1\)J (C,F) = 238.3 Hz), 109.2, 110.7, 117.4, 125.5, 125.7,
125.9, 128.2, 132.0, 139.2, 139.5, 146.3, 157.0, 157.1, 157.5 (t, \( J(C,F) = 29.3 \) Hz), 162.9, 163.1, 167.2, 168.9, 169.2, 169.8, 171.7; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), \( t_R = 6.34 \) min, 99% purity, \( m/z [M+H]^+ \) calcd for C₃₅H₃₅F₂N₉O₈ 748.3, found 748.5; HRMS (ESI) \( m/z [M+H]^+ \) calcd for C₃₅H₃₅F₂N₉O₈ 748.2649, found 748.2649.

tert-Butyl (2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)-pyrrolidine-1-carboxylate (46). tert-Butyl \((S)-(1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamate (38, 1.27 g, 4 mmol) was dissolved in dry CH₂Cl₂ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. (2S,4S)-1-(tert-Butyloxycarbonyl)-4-hydroxy-2-carboxylic acid (925 mg, 4 mmol) was dissolved in dry DMF (10 mL). DIPEA (1.81 g, 14 mmol) and HATU (1.67 g, 4.4 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (10 mL) and was added to the reaction mixture. The reaction mixture was stirred under argon for 4 h. The reaction mixture was concentrated under high vacuum.

The residue was diluted with water (50 mL) and was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated NaHCO₃ solution (50 mL) and brine (50 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel column chromatography using CH₂Cl₂/MeOH (19+1) as eluent to yield 46 as a white solid (449 mg, 1.04 mmol).

Yield 26%; mp. 62-64 °C; \( R_f = 0.28 \) (CH₂Cl₂/MeOH (19+1)); \(^1H\) NMR (600 MHz, DMSO-\(d_6\)) \( \delta 1.32 \) (s, 6H), \( 1.37 - 1.43 \) (m, 6H), \( 1.64 - 1.70 \) (m, 1H), \( 2.28 - 2.37 \) (m, 1H), \( 2.45 \) (s, 3H), \( 3.15 - 3.24 \) (m, 1H), \( 3.46 - 3.50 \) (m, 1H), \( 4.10 - 4.18 \) (m, 2H), \( 4.93 - 5.03 \) (m, 1H), \( 5.14 - 5.22 \) (m, 1H), \( 7.38 - 7.47 \) (m, 4H), \( 8.30 \) and \( 8.39 \) (each d, \( J = 7.5 \) Hz, \( J = 7.8 \) Hz, 1H, major and minor rotamer), \( 8.98 \) (s, 1H); \(^13C\) NMR (151 MHz, DMSO-\(d_6\)) \( \delta 15.9, 21.8, 27.9, 38.6, 47.5, 54.4, 58.8, 68.0, 78.7, 126.5, 128.8, 129.9, 131.0, 144.1, 147.8, 151.5, 153.3, 172.1; LC-MS (ESI) (90% H₂O + 2 mM NH₄OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), \( t_R = 5.69 \) min, 96% purity, \( m/z [M-H]^- \) calcd for C₂₂H₂₉N₃O₄S 430.2, found 430.2.
tert-Butyl ((S)-1-((2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (47). tert-Butyl (2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrroli dine-1-carboxylate (46, 432 mg, 1 mmol) was dissolved in dry CH2Cl2 (5 mL) and was treated with TFA (5 mL) for 2 h. The mixture was concentrated under high vacuum. Boc-Tle-OH (39, 231 mg, 1 mmol) was dissolved in dry DMF (5 mL). HATU (418 mg, 1.1 mmol) and DIPEA (452 mg, 3.5 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was stirred for 18 h under argon. The mixture was concentrated under high vacuum. The crude product was purified by silica gel column chromatography using EtOAc as eluent to yield 47 as a white solid (339 mg, 0.62 mmol).

Yield 62%; mp. 100-102 °C; Rf = 0.24 (CH2Cl2 + MeOH (19+1)); 1H NMR (500 MHz, DMSO-d6) δ 0.95 (s, 9H), 1.36 – 1.40 (m, 12H), 1.62 – 1.68 (m, 1H), 2.29 – 2.36 (m, 1H), 2.46 (s, 3H), 3.38 (dd, J = 10.1, 5.3 Hz, 1H), 3.81 – 3.90 (m, 1H), 4.10 (d, J = 8.7 Hz, 1H), 4.17 – 4.24 (m, 1H), 4.36 (dd, J = 8.8, 6.0 Hz, 1H), 4.88 – 4.96 (m, 1H), 5.31 (d, J = 6.7 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 7.37 – 7.40 (m, 2H), 7.42 – 7.45 (m, 2H), 8.33 (d, J = 7.6 Hz, 1H), 8.98 (s, 1H); 13C NMR (126 MHz, DMSO-d6) δ 15.9, 22.2, 26.3, 28.1, 34.7, 36.7, 47.8, 55.4, 58.4, 58.6, 69.0, 78.1, 126.3, 128.8, 129.7, 131.0, 144.3, 147.7, 151.4, 155.5, 170.1, 171.0; LC-MS (ESI) (90% H2O + 2 mM NH4OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), tR = 6.55 min, 95% purity, m/z [M+H]+ calcd for C28H40N4O5S 545.3, found 545.5.

tert-Butyl ((S)-13-((2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-1-oxo-3,6,9-trioxa-12-azapentadecanoate (48). tert-Butyl ((S)-1-((2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (47, 327 mg, 0.6 mmol) was dissolved in dry CH2Cl2 (5 mL) and was treated with TFA (5 mL). The mixture was stirred for 2 h at room temperature. The mixture was concentrated under high vacuum. 13,13-Dimethyl-1-oxo-3,6,9,12-tetraoxatetradecanoic acid (31, 167 mg, 0.6 mmol) was dissolved in dry DMF (5 mL). HATU (251 mg, 0.66 mmol) and DIPEA (271 mg, 2.1 mmol) were added under argon. The deprotected (-)VHL-ligand was dissolved in dry DMF (5
mL) and was added to the mixture, containing the activated acid compound. The reaction mixture was stirred at room temperature under argon for 18 h. The mixture was concentrated under high vacuum. The crude product was purified by silica gel column chromatography using CH$_2$Cl$_2$/MeOH (19+1) as eluent to yield **48** as a white solid (267 mg, 0.38 mmol).

Yield 63%; $R_f = 0.18$ (CH$_2$Cl$_2$/MeOH (19+1)); $^1$H NMR (600 MHz, DMSO-$d_6$) $\delta$ 0.95 (s, 9H), 1.38 (d, $J = 7.0$ Hz, 3H), 1.62 – 1.67 (m, 1H), 2.30 – 2.36 (m, 1H), 2.46 (s, 3H), 3.40 (dd, $J = 10.1$, 5.4 Hz, 1H), 3.86 (dd, $J = 10.1$, 5.7 Hz, 1H), 3.95 (d, $J = 4.2$ Hz, 2H), 3.97 (s, 2H), 4.18 – 4.24 (m, 1H), 4.35 (dd, $J = 8.7$, 6.3 Hz, 1H), 4.50 (s, 2H), 4.90 – 4.96 (m, 1H), 5.32 (d, $J = 6.7$ Hz, 1H), 7.35 – 7.40 (m, 3H), 7.42 – 7.46 (m, 2H), 8.37 (d, $J = 7.7$ Hz, 1H), 8.98 (s, 1H);

$^{13}$C NMR (151 MHz, DMSO) $\delta$ 15.9, 22.2, 26.2, 27.7, 35.1, 36.8, 47.8, 55.5, 55.8, 58.5, 68.1, 68.9, 69.5, 69.7, 69.9, 70.4, 80.6, 126.4, 128.8, 129.8, 131.1, 144.3, 147.8, 151.4, 168.8, 169.3, 169.3, 170.9, one signal is missing due to overlapping signals; LC-MS (ESI) (90% H$_2$O + 2 mM NH$_4$OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), $t_R = 6.55$ min, 99% purity, $m/z$ [M+H]$^+$ calcd for C$_{35}$H$_{52}$N$_4$O$_9$S 705.4, found 705.6.

(2S,4S)-1-((S)-15-(tert-Butyl)-1-(3-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)phenyl)-3,13-dioxo-5,8,11-trioxa-2,14-diazahexadecan-16-oyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (4(-)). Benzyl (3-(((5-(5-(difluoromethyl)-1,3,4-oxadiazol-2-yl)pyrimidin-2-yl)amino)methyl)benzyl)carbamate (15, 70 mg, 0.15 mmol) was dissolved in dry THF (10 mL). The mixture was treated with 10% m/m Pd/C under H$_2$ (1 atm, balloon) for 18 h. The mixture was filtered through celite and concentrated under high vacuum. tert-Butyl (S)-13-((2S,4S)-4-hydroxy-2-(((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidine-1-carbonyl)-14,14-dimethyl-11-oxo-3,6,9-trioxia-12-azapentadecanoate (48, 106 mg, 0.15 mmol) was dissolved in dry CH$_2$Cl$_2$ (5 mL) and was treated with TFA (5 mL) for 2 h at room temperature. The mixture was concentrated under high vacuum. The deprotected acid compound was dissolved in dry DMF (5 mL). DIPEA (58 mg, 0.45 mmol) and HATU (63 mg, 0.165 mmol) were added under argon. The deprotected amine compound was dissolved in dry DMF (5 mL) and was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature under argon for 18 h. The reaction mixture was concentrated under high vacuum. The crude product was purified by silica gel flash column chromatography using a CH$_2$Cl$_2$/MeOH gradient (0% to 20% MeOH) to yield 4(-) as a white solid (71 mg, 0.074 mmol).
Yield 49%; mp. 80-86 °C; \( R_f = 0.49 \) (CH\(_2\)Cl\(_2\)/MeOH (9+1)); \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \( \delta \) 0.94 (s, 9H), 1.37 (d, \( J = 6.9 \) Hz, 3H), 1.61 – 1.67 (m, 1H), 2.28 – 2.35 (m, 1H), 2.45 (s, 3H), 3.39 (dd, \( J = 10.1, 5.4 \) Hz, 1H), 3.53 – 3.62 (m, 8H), 3.85 (dd, \( J = 10.2, 5.7 \) Hz, 1H), 3.88 – 3.96 (m, 4H), 4.17 – 4.23 (m, 1H), 4.29 (d, \( J = 6.2 \) Hz, 2H), 4.34 (dd, \( J = 8.7, 6.3 \) Hz, 1H), 4.50 (d, \( J = 9.3 \) Hz, 1H), 4.59 (d, \( J = 6.4 \) Hz, 1H), 4.89 – 4.95 (m, 1H), 5.31 (d, \( J = 6.7 \) Hz, 1H), 7.11 – 7.28 (m, 4H), 7.35 – 7.40 (m, 3H), 7.42 – 7.61 (m, 3H), 8.19 (t, \( J = 6.3 \) Hz, 1H), 8.37 (d, \( J = 7.6 \) Hz, 1H), 8.72 (t, \( J = 6.4 \) Hz, 1H), 8.87 (s, 2H), 8.97 (s, 1H); \(^{13}\)C NMR (151 MHz, DMSO-\(d_6\)) \( \delta \) 15.9, 22.2, 26.2, 35.2, 36.8, 41.6, 44.0, 47.8, 55.5, 55.8, 58.5, 68.9, 69.5, 69.6, 70.0, 70.3, 70.3, 106.3, 106.6 (t, \( ^1J(C,F) = 238.3 \) Hz), 125.5, 125.8, 125.9, 126.4, 128.2, 128.8, 129.8, 131.0, 139.2, 139.5, 144.3, 147.8, 151.4, 157.0, 157.2, 157.5 (t, \( ^2J(C,F) = 29.3 \) Hz), 162.9, 163.1, 168.8, 169.2, 169.3, 170.9, one signal is missing due to overlapping signals; LC-MS (ESI) (90% H\(_2\)O + 2 mM NH\(_4\)OAc to 100% MeCN in 10 min, then 100% MeCN to 15 min, DAD 220-600 nm), \( t_R = 6.34 \) min, 97% purity, \( m/z \) [M+H]\(^+\) calcd for C\(_{46}\)H\(_{56}\)F\(_2\)N\(_{10}\)O\(_9\)S 963.4, found 963.7; HRMS (ESI) \( m/z \) [M+H]\(^+\) calcd for C\(_{46}\)H\(_{56}\)F\(_2\)N\(_{10}\)O\(_9\)S 963.3993, found 963.3991.
5.3. NMR Data

$^1$H NMR spectrum of 9 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 9 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 11 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 11 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 13 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 13 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 15 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 15 (151 MHz, DMSO-$d_6$)
$^{19}$F NMR spectrum of 15 (565 MHz, DMSO-$d_6$)
$^{1}H$ NMR spectrum of 10 (600 MHz, DMSO-$d_6$)

$^{13}C$ NMR spectrum of 10 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 12 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 12 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 14 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 14 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 16 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 16 (126 MHz, DMSO-$d_6$)
$^{19}$F NMR spectrum of 16 (565 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 25 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 25 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 26 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 26 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 22 (500 MHz, DMSO-$d_6$)

$t$-BuO$_2$C$\cdots$Br

$^{13}$C NMR spectrum of 22 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 23 (500 MHz, DMSO-$d_6$)

t-BuO$_2$C$_n$N$_3$

$^{13}$C NMR spectrum of 23 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 24 (500 MHz, DMSO-$d_6$)

t-BuO$_2$C\[\text{---}\][\text{---}\][\text{---}]\text{NH}_2

$^{13}$C NMR spectrum of 24 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 27 (500 MHz, DMSO-$d_6$)

$t$-BuO$_2$C

$^{13}$C NMR spectrum of 27 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 29 (500 MHz, DMSO-$d_6$)

$t$-BuO$_2$C$\text{O}$$\text{O}$O$\text{OBn}$

$^{13}$C NMR spectrum of 29 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 30 (500 MHz, DMSO-$d_6$)

$t$-BuO$_2$C\(\text{-}\)O\(\text{-}\)O\(\text{-}\)OH

$^{13}$C NMR spectrum of 30 (126 MHz, DMSO-$d_6$)
\(^1\text{H NMR}\) spectrum of 31 (500 MHz, DMSO-\(d_6\))

\[ \text{t-BuO}_2\text{C} \ O \ O \ O \text{CO}_2\text{H} \]

\(^{13}\text{C NMR}\) spectrum of 31 (126 MHz, DMSO-\(d_6\))
$^1$H NMR spectrum of 37 (600 MHz, DMSO-$d_6$)

13C NMR spectrum of 37 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 38 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 38 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 41 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 41 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 33 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 33 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 34 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 34 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 35 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 35 (151 MHz, DMSO-$d_6$)
$^{1}$H NMR spectrum of 1 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 1 (151 MHz, DMSO-$d_6$)
1H NMR spectrum of 2 (600 MHz, DMSO-d6)

13C NMR spectrum of 2 (151 MHz, DMSO-d6)
$^1$H NMR spectrum of 3 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 3 (151 MHz, DMSO-$d_6$)

S63
$^1$H NMR spectrum of 4 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 4 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 5 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 5 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 6 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 6 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 42 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 42 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 43 (500 MHz, DMSO-$d_6$)

13C NMR spectrum of 43 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 44 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 44 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 45 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 45 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 1(-) (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 1(-) (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 46 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 46 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 47 (500 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 47 (126 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 48 (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 48 (151 MHz, DMSO-$d_6$)
$^1$H NMR spectrum of 4(-) (600 MHz, DMSO-$d_6$)

$^{13}$C NMR spectrum of 4(-) (151 MHz, DMSO-$d_6$)
6. References