Supporting information for

PROTAC degraders of the METTL3-14 m⁶A-RNA methyltransferase

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Supplementary Figures

**Figure S1.** METTL14 Western blot quantification by densitometry from a cellular degradation assay with PROTACs 14, 20, 22, 24 and 30 in the AML cell lines MOLM-13, THP-1, NOMO1, KASUMI-1 and in the prostate cancer cell lines PC3, DU145.

**Figure S2.** Representative Western blot for data in Figure 4. Concentration dependence of METTL3 and METTL14 degradation by PROTAC 30 in MOLM-13 cells.
**Figure S3.** Evaluation of compound 14 and its negative control me-14 in MOLM-13 AML cell line. The stabilization of METTL3 (left) and Cereblon (CRBN, right) was quantified by CETSA at 54°C. Both 14 and me-14 stabilize METTL3 in a concentration-dependent manner. The stabilization of CRBN is visible only with compound 14.

**Figure S4.** Western blot analysis of the *in vitro* ubiquitination assay. The ubiquitination reaction mixture (E1, E2, CUL4A-RBX1, CRBN-DDB1 and METTL3-METTL14 in reaction buffer) was incubated with or without ATP and at different concentrations of compounds 14 and me-14 as indicated at 30°C for 2h. The proteins were separated by SDS-PAGE followed by Western blot analysis with α-METTL3, α-METTL14 and α-Ubiquitin antibodies. Shown here is one representative Western blot of three biological replicates of the experiment. To generate figure 5E, densitometry was performed using the α-METTL3 blots of all three replicates. In the α-METTL14 blot, a weak band appears above the METTL14 band at 32 μM, 8 μM, and 2 μM of compound 14, presumably indicating mono-ubiquitination of METTL14. However, the ubiquitination of METTL3 is clearly more efficient. The band indicated with an asterisk (*) originates from the unspecific detection of METTL3 with the α-METTL14 antibody.
**Figure S5:** Dose-response curves derived from the TR-FRET ternary complex formation assay between METTL3-14, CRBN and 4 PROTACs (a-d) or UZH2 as negative control (e) (mean ± SD, n = 3 technical replicates). 3 biological replicates from independent measurements are shown for Compounds 20, 22, 23 and 30 and 1 for UZH2. The Hook effect is apparent in all curves in panels a-d. The curve in panel a was fitted with the Gaussian function, which was not appropriate for the curves in panels b-d. EC\textsubscript{max} and the amplitude of the curves were either derived from the fitting parameters or from the coordinates of the data point with the highest signal. UZH2 (e) showed no activity in the ternary complex formation assay since it is only able to bind to METTL3 and not to CRBN.
Figure S6. Dose-response curves derived from the reader-based TR-FRET inhibition assay on METTL3-14 (mean ± SD, n = 3 technical replicates) measured for three PROTACs: compound 14 (a), Compound 23 (b), and Compound 30 (c). IC₅₀ and Hill Slope values were obtained from fits with nonlinear regression “log(inhibitor) vs. normalized response with variable slope”. Note that depending on the placement of a compound on the 384-well plate used, the maximal signal can deviate from the expected 100% maximum enzymatic activity.
Table S1. Protein methyltransferases selectivity profile of UZH2 at 10μM.

<table>
<thead>
<tr>
<th>Methyltransferase</th>
<th>Remaining activity [%][a]</th>
<th>Control IC_{50} (M)</th>
<th>Control compound[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Replicate 1</td>
<td>Replicate 2</td>
<td></td>
</tr>
<tr>
<td>DOT1L</td>
<td>84.02</td>
<td>82.97</td>
<td>1.05E-07</td>
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<tr>
<td>G9α</td>
<td>85.07</td>
<td>88.33</td>
<td>7.08E-07</td>
</tr>
<tr>
<td>MLL4 Complex</td>
<td>88.26</td>
<td>86.64</td>
<td>8.16E-07</td>
</tr>
<tr>
<td>PRDM9</td>
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<tr>
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<tr>
<td>SETD2</td>
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<td>87.13</td>
<td>1.38E-06</td>
</tr>
<tr>
<td>SMYD3</td>
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</tr>
<tr>
<td>METTL3-14</td>
<td>0.02</td>
<td>0.02</td>
<td>1.53E-07</td>
</tr>
</tbody>
</table>

[a] The remaining activity is the percentage of enzymatic activity in the presence of 10 μM UZH2 concerning the buffer solution containing DMSO. The closer to 100% these values are, the weaker the inhibitory potency of UZH2.

[b] SAH = S-(5’-adenosyl)-L-homocysteine.

Table S2: Hook curve amplitudes derived from the TR-FRET ternary complex formation assay with all compounds in the paper. n = number of independent measurements (biological replicates).

<table>
<thead>
<tr>
<th>Compound</th>
<th>TCFA amplitude (mean ± SEM)</th>
<th>n</th>
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<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0.3 ± 0.1</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>0.3 ± 0.2</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0.7 ± 0.1</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>1.0 ± 0.0</td>
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</tr>
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<td>11</td>
<td>0.3 ± 0.0</td>
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<tr>
<td>12</td>
<td>0.7 ± 0.1</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>0.8 ± 0.0</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>1.2 ± 0.0</td>
<td>2</td>
</tr>
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<td>15</td>
<td>0.8 ± 0.1</td>
<td>2</td>
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<tr>
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<td>20</td>
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<td>3</td>
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<tr>
<td>21</td>
<td>1.3 ± 0.1</td>
<td>3</td>
</tr>
<tr>
<td>22</td>
<td>1.1 ± 0.1</td>
<td>3</td>
</tr>
<tr>
<td>23</td>
<td>1.0 ± 0.1</td>
<td>3</td>
</tr>
<tr>
<td>24</td>
<td>1.2 ± 0.0</td>
<td>2</td>
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<tr>
<td>25</td>
<td>1.2 ± 0.1</td>
<td>2</td>
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<td>26</td>
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<td>3</td>
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<td>27</td>
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<td>2</td>
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<td>28</td>
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<td>29</td>
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<td>31</td>
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<tr>
<td>33</td>
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<td>34</td>
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</tr>
<tr>
<td>35</td>
<td>0.7 ± 0.2</td>
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</table>
Chemistry

Materials and Methods

All reagents were purchased from commercial suppliers and used as received. Reactions run at elevated temperatures were carried out in the oil bath. All reactions were monitored by thin-layer chromatography (Aluminium plates coated with silica gel 60 F_{254}). Flash column chromatography was carried out over silica gel (0.040-0.063 mm) or aluminium oxide (0.050-0.200 mm). SiliaMetS® TAAcONa (or SiliaMetS® Triaminetetraacetate, sodium salt) is a silica-bound metal scavenger for Pd(II), Ni(II) and Cu. It is the supported version of EDTA in its sodium salt form. \(^1\text{H}\) and \(^{13}\text{C}\) \(^{1}\text{H}\) NMR spectra were recorded on AV2-400 MHz and AV-600 Bruker spectrometers (400 MHz, 101 MHz and 600 MHz, 150 MHz, respectively) in DMSO-\(d_6\), CDCl\(_3\) or MeOD-\(d_4\). Chemical shifts are given in ppm and their calibration was performed to the residual \(^1\text{H}\) and \(^{13}\text{C}\) signals of the deuterated solvents. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), multiplet (m), and broad signal (bs). The purity was acquired by Liquid chromatography high-resolution electrospray ionization mass spectrometry (LC-HR-ESI-MS): Acquity UPLC (Waters, Milford, USA) connected to an Acquity \(\phi\) diode array detector and a Synapt G2 HR-ESI-QTOF-MS (Waters, Milford, USA); injection of 1 \(\mu\)L sample (c = ca. 10-100 \(\mu\)g/mL in the indicated solvent); Acquity BEH C18 HPLC column (1.7 \(\mu\)m particle size, 2.1 \(\times\) 50 mm, Waters) kept at 30\(^{\circ}\)C; elution at a flow rate of 400 \(\mu\)L/min with A: H\(_2\)O + 0.02% TFA and B: CH\(_3\)CN + 0.02% TFA, linear gradient from 10–95% B within 3 min, then isocratic 95% B for 2 min; UV spectra recorded from 190–300 nm at 1.2 nm resolution and 20 points s\(^{-1}\); ESI: positive ionization mode, capillary voltage 3.0 kV, sampling cone 40V, extraction cone 4V, \(\text{N}_2\) cone gas 4 L/h, \(\text{N}_2\) desolvation gas 800 L/min, source temperature 120\(^{\circ}\)C; mass analyzer in resolution mode: mass range 100–2'000 m/z with a scan rate of 1 Hz, mass calibration to <2 ppm within 50–2'500 m/z with a 5mM aq. soln. of HCO\(_2\)Na, lockmasses: m/z 195.0882 (caffein, 0.7 ng/mL) and 556.2771 (Leucineenkephalin, 2 ng/mL). The HPLC analyses were performed on a Shimadzu LC – 9A HPLC system equipped with a Shimadzu SPD – 6A VP UV – Vis detector; Phenomenex RP-HPLC on a Phenomenex InertClone (5 \(\mu\)m particle size, 4.6 mm \(\times\) 150 mm i.d.). HPLC purifications were performed on a Shimadzu LC – 8A HPLC system equipped with a Shimadzu SCL – 10A VP System control and a Shimadzu SPD – 10A VP UV – Vis detector on a Phenomenex Gemini C18-110A preparative column (10-\(\mu\)m particle size, 250 mm \(\times\) 21.2 mm i.d.).

For all isolated intermediates and final compounds \(^1\text{H}\), \(^{13}\text{C}\) NMR and LCMS characterization is included to the synthetic procedures, if they were not previously reported in the literature. For all final compounds \(^1\text{H}\), \(^{13}\text{C}\) NMR spectra and HPLC traces are shown in the SI.
Compounds purity

The final compounds 1-35, me-14 and me-24 have a purity ≥ 95% assessed by HPLC, HPLC traces can be found further on in the Supplemental Information.
Experimental section

General procedure 1: SnAr from compound 39 (synthesis of compounds 40, 41, 42a-47a)

To a solution of compound 39 (1 eq) in DMSO (for 40, 41, 46a) or EtOH (for 42a-45a, 47a) (0.5 M) in a pressure vial were subsequently added amine (1.5 eq) and TEA (4 eq). The resulting reaction mixture was stirred at 120°C (oil bath temperature) until completion (Monitored by TLC).

General procedure 2: Boc-protected amines deprotection (synthesis of compounds 42-47, 49, 51)

To a stirred solution of corresponding Boc-protected amine (1 eq) in MeOH (0.5 M) was added 4M HCl in dioxane (10 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the product was used in the following synthetic step without further purification.

General procedure 3: amide coupling (synthesis of compounds 49a, 1-20, 22-25, 29-31, 33, me-14, me-24)
To a cooled solution (water-ice bath) of carboxylic acid (1 eq) in DMF (0.5 M) was added DIPEA (4 eq), and the reaction mixture was stirred at the same temperature for 10 minutes. After the addition of 1.1 eq of HATU (for compounds 1-4, 8, 9, 29-31) or COMU (for compounds 5-7, 10-28, 32-35), the solution was stirred for an additional 30 minutes after which the amine (1 eq) was added. The resulting reaction mixture was stirred at rt until completion (Monitored by TLC), concentrated in vacuo, and purified using flash column chromatography.

**General procedure 4 (synthesis of compounds S1-S4)**

To a stirred solution of corresponding tert-butyl ester (1 eq) in DCM (0.5 M) was subsequently added TsCl (1.6 eq) and TEA (5 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were removed in vacuo and the product was involved in the next step without further purification.

To a stirred solution of corresponding tosylated tert-butyl ester in DMF (0.5 M), was added potassium phthalimide (2 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the product was used in the following step without further purification.

The compound was then dissolved in methanol (0.5 M), and hydrazine hydrate 50-60% (3 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography.
General procedure 5 (synthesis of compounds S5-S7)

\[ \begin{align*}
\text{X} & = \text{Br, I} \\
n & = 7, 9
\end{align*} \]

To a stirred solution of lenalidomide (1 eq) in NMP (0.5 M) were subsequently added the corresponding tert-butyl ester (1 eq) and DIPEA (10 eq). The resulting reaction mixture was stirred at 110°C (oil bath temperature) until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography.

General procedure 6 (synthesis of compounds 56, 57, S8-S12)

\[ \begin{align*}
\text{R}^1 & \text{NH}_2 + \text{F} & \text{DMSO, 130°C} & \text{DIPEA} & \text{R}^2 = \text{H, CH}_3
\end{align*} \]

To a stirred solution of 4-fluoro-thalidomide (1 eq) in DMSO (0.5 M) was subsequently added the corresponding amine (1 eq) and DIPEA (3 eq). The resulting reaction mixture was stirred at 130°C (if not stated otherwise) until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography.
General procedure 7 (synthesis of compounds S13-S15)

To a stirred solution of tert-butyl ester (1 eq) in DMF (0.5 M) was added sodium azide (1.2 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by $^1$H NMR). The volatiles were then removed in vacuo, taken up with DCM, and filtered through filter paper. The product was involved in the next step without further purification.

Compound 56 (1 eq) was dissolved in THF (0.5 M) followed by the addition of the corresponding tert-butyl ester (1 eq), anhydrous CuSO$_4$ (0.5 eq), and sodium ascorbate (1.1 eq). The resulting reaction mixture was stirred at 40°C (oil bath temperature) until full completion (Monitored by TLC). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography.

General procedure 8 (synthesis of compounds 52 and 53)

In a flame-dried round-bottomed flask equipped with a magnetic stirring bar and under N$_2$-atm, 200 mg of acid (1 eq) were dissolved in 0.5 mL of SOCl$_2$. The mixture was stirred at reflux for 5h and then the solvent was evaporated in vacuo. The residue was dissolved in 1 mL of dry THF and 1 eq of Lenalidomide was added to the flask. The mixture was stirred overnight at reflux under N$_2$-atm. Then the solvent was evaporated under reduced pressure and the residue was treated with water and extracted with EtOAc. The combined organic layers were washed
with water, dried (MgSO₄), filtered, and evaporated. The crude product was purified using flash column chromatography.

**General procedure 9 (synthesis of compounds 54 and 55)**

The Bromo compound (1 eq) was dissolved in DMF (0.5 M), to a stirred solution of it was added sodium azide (1.2 eq). The resulting reaction mixture was stirred at rt until completion (Monitored by ¹H-NMR). The reaction mixture was evaporated and extracted in EtOAc (3x). The combined organic layers were dried over MgSO₄, filtrated, and evaporated.

**General procedure 10: tert-butyl esters deprotection (synthesis of compounds S16-S30)**

To a stirred solution of corresponding tert-butyl esters S1-S15 (1 eq) in DCM (0.5 M) was added TFA (10 eq). The resulting reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were then removed *in vacuo* and the obtained products (S16-S30) were used in the following synthetic step without further purification.
Preparation of 4-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-9-(6-fluoropyrimidin-4-yl)-1,4,9-triazaspiro[5.5]undecan-2-one (39)

4-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-1,4,9-triazaspiro[5.5]undecan-2-one 37 (Ref.1) (100 mg, 0.27 mmol) was dissolved in iPrOH (0.5 M). To the stirred solution were subsequently added 4,6-difluoro pyrimidine (27 µL, 0.32 mmol) and TEA (150 µL, 1.01 mmol). The resulting reaction mixture was stirred at 80°C (oil bath temperature) until full completion (Monitored by TLC). The volatiles were removed in vacuo and the crude product was purified using flash column chromatography (SiO\textsubscript{2}; DCM/MeOH = 9 : 1) providing 112 mg of the desired product (89% yield). \textsuperscript{1}H NMR (400 MHz, DMSO) \( \delta \) 8.30 (d, \( J = 2.8 \) Hz, 1H), 8.22 (s, 1H), 7.15 (dd, \( J = 13.5, 6.6 \) Hz, 1H), 6.93 (dd, \( J = 11.5, 7.3 \) Hz, 1H), 6.58 (s, 1H), 4.00 (s, 2H), 3.60 (s, 2H), 3.58 – 3.47 (m, 2H), 3.42 (s, 2H), 3.28 (s, 2H), 2.33 (s, 3H), 1.83 (m, 2H), 1.68 (m, 2H), 1.30 (t, \( J = 5.3 \) Hz, 4H), 0.87 (s, 6H). \textsuperscript{13}C NMR (101 MHz, DMSO) \( \delta \) 172.5, 170.1, 167.1, 164.9, 164.8, 158.6, 158.4, 156.0, 152.0, 149.7, 107.1, 106.8, 85.9, 85.6, 55.4, 54.5, 53.3, 53.0, 49.5, 46.1, 38.7, 35.1, 28.6. LRMS (ESI) m/z: [M + H]\textsuperscript{+} calcd for C\textsubscript{26}H\textsubscript{34}F\textsubscript{3}N\textsubscript{6}O; 503.270 found, 503.276.

Preparation of 9-(6-((3-aminopropyl)amino)pyrimidin-4-yl)-4-(4-((4,4-dimethyl piperidin-1-yl)methyl)phenyl)-1,4,9-triazaspiro[5.5]undecan-2-one (42)
To a stirred solution of compound 38 (Ref.1) (100 mg, 0.21 mmol) in EtOH (0.5 M) were subsequently added N-Boc-1,3-propanediamine (108 mg, 0.62 mmol) and TEA (86.6 µL, 0.62 mmol). The resulting reaction mixture was refluxed until full completion (Monitored by TLC). The volatiles were removed in vacuo and the crude product was purified using flash column chromatography (SiO2; DCM/MeOH = 9 : 1) providing 117 mg of 42a (91% yield).

The impure product (117 mg, 0.19 mmol) was dissolved in MeOH (0.5 M) followed by the addition of 37% HCl (57.7 µL, 1.9 mmol). The reaction mixture was stirred at rt until full completion (Monitored by TLC). The volatiles were removed in vacuo and the residue was extracted into nBuOH. The organic layer was washed with saturated aq. solution of Na2CO3. The combined organic layers were dried over MgSO4, filtered, and concentrated providing 80 mg of the desired product 42 (81% yield). 1H NMR (400 MHz, MeOD) δ 8.06 (d, J = 0.9 Hz, 1H), 7.38 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 5.77 (d, J = 1.0 Hz, 1H), 4.01 (s, 2H), 3.86 (s, 2H), 3.83 (s, 2H), 3.63 – 3.56 (m, 2H), 3.53 (s, 2H), 3.43 (t, J = 6.5 Hz, 2H), 3.17 (d, J = 0.8 Hz, 1H), 2.98 (t, J = 7.0 Hz, 6H), 1.95 – 1.87 (m, 4H), 1.81 (ddd, J = 13.3, 8.6, 4.1 Hz, 2H), 1.58 (d, J = 5.9 Hz, 4H), 1.29 (d, J = 2.7 Hz, 3H), 1.02 (s, 6H). 13C NMR (101 MHz, DMSO) δ 167.6, 163.7, 162.1, 157.8, 148.6, 130.1, 129.2, 114.7, 65.4, 62.4, 53.3, 52.9, 51.9, 49.7, 38.8, 38.0, 37.9, 34.8, 29.6, 28.8, 28.6, 15.7. LRMS (ESI) m/z: [M + H]+ calcd for C29H44N8O; 520.360 found, 521.371.

Preparation of 4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)- 9-(6-(prop-2-yn-1-ylamino)pyrimidin-4-yl)-1,4,9-triazaspiro[5.5]undecan-2-one (40)

Compound 40 was prepared according to General procedure 1 using compound 39 (200 mg, 0.4 mmol) and propargylamine (76.46 µL, 3 eq) in DMSO. The reaction mixture was stirred at 100°C (oil bath temperature) for 14 h and then concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO2; EtOAc/MeOH = 90 : 10) providing 150 mg of the desired product (70% yield). 1H NMR (400 MHz, DMSO) δ 8.18 (s, 1H), 8.04 (s, 1H), 7.15 (dd, J = 13.0, 6.7 Hz, 1H), 6.98 (t, J = 6.0 Hz, 1H), 6.93 (dd, J = 11.7, 7.5 Hz, 1H), 5.71 (s, 1H), 4.02 (dd, J = 5.9, 2.5 Hz, 2H), 3.91 – 3.81 (m, 2H), 3.59 (s, 2H), 3.44
(s, 2H), 3.39 – 3.29 (m, 2H), 3.27 (s, 2H), 3.06 (t, \(J = 2.4\) Hz, 1H), 2.35 (s, 4H), 1.83 – 1.73 (m, 2H), 1.72 – 1.61 (m, 2H), 1.31 (t, \(J = 5.5\) Hz, 4H), 0.87 (s, 6H). \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 166.5, 162.7, 161.6, 158.0, 157.3, 155.6, 151.5, 149.2, 138.1, 117.8, 106.6, 106.3, 81.9, 72.7, 54.8, 54.0, 52.8, 52.6, 49.1, 38.2, 34.6, 29.7, 28.1. LRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{29}\)H\(_{38}\)F\(_2\)N\(_7\)O; 538.310 found, 538.310.

**Preparation of tert-butyl (3-((6-((4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)carbamate (43a)**

![Structure of Compound 43a](image)

Compound 43a was prepared according to General procedure 1 using compound 39 (300 mg, 0.6 mmol) and tert-butyl (3-aminopropyl)carbamate (156 mg, 0.9 mmol) in EtOH. The volatiles were removed in vacuo and the crude product was purified using flash column chromatography (SiO\(_2\); DCM/MeOH = 90 : 10) providing 280 mg of the desired product (71% yield). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.18 (s, 1H), 7.97 (s, 1H), 7.17 (s, 1H), 6.94 (dd, \(J = 11.5, 7.3\) Hz, 1H), 6.82 (t, \(J = 5.7\) Hz, 1H), 6.61 (t, \(J = 5.7\) Hz, 1H), 5.60 (s, 1H), 3.86 (d, \(J = 13.5\) Hz, 2H), 3.60 (s, 2H), 3.27 (s, 2H), 3.22 – 3.12 (m, 2H), 2.96 (q, \(J = 6.6\) Hz, 2H), 2.37 (s, 4H), 1.77 (dt, \(J = 14.2, 4.2\) Hz, 2H), 1.70 – 1.52 (m, 5H), 1.37 (s, 9H), 1.34 – 1.28 (m, 4H), 0.88 (s, 6H). \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 166.5, 163.2, 161.6, 157.3, 155.7, 117.9, 106.5, 106.3, 77.5, 54.7, 52.8, 52.7, 49.0, 38.0, 37.7, 34.6, 29.5, 28.3, 28.1. LRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{34}\)H\(_{51}\)F\(_2\)N\(_8\)O\(_3\); 657.404 found, 657.405.
Preparation of tert-butyl (3-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)carbamate (44a)

Compound 44a was prepared according to General procedure 1 using compound 39 (50 mg, 0.1 mmol) and 1-(N-Boc-aminomethyl)-3-(aminomethyl)benzene (35 mg, 0.15 mmol) in EtOH. The volatiles were removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = 90 : 10) providing 51 mg of the desired product (71% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.30 (t, $J = 7.5$ Hz, 1H), 7.23 – 7.18 (m, 3H), 7.12 (dd, $J = 12.8$, 6.6 Hz, 1H), 6.60 – 6.56 (m, 2H), 5.43 (s, 1H), 5.20 (s, 1H), 4.89 (s, 1H), 4.53 (d, $J = 5.8$ Hz, 2H), 4.30 (d, $J = 6.0$ Hz, 2H), 3.73 – 3.66 (m, 4H), 3.50 (s, 2H), 3.27 (s, 2H), 2.41 (s, 3H), 1.93 (m, 2H), 1.77 (m, 2H), 1.44 (s, 8H), 1.40 (t, $J = 7.4$, 6.5 Hz, 4H), 0.90 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.7, 163.2, 162.5, 157.9, 155.9, 139.7, 138.6, 129.1, 126.5, 126.2, 126.1, 105.8, 105.5, 81.3, 56.4, 54.7, 53.5, 53.0, 49.7, 45.7, 44.5, 40.4, 38.5, 35.2, 29.7, 28.4, 28.4. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{39}$H$_{53}$F$_2$N$_8$O$_3$; 719.420 found, 719.422.

Preparation of tert-butyl 4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidine-1-carboxylate (45a)

Compound 45a was prepared according to General procedure 1 using compound 39 (50 mg, 0.1 mmol) and tert-butyl 4-(aminomethyl)piperidine-1-carboxylate (42 mg, 0.15 mmol) in EtOH. The volatiles were removed in vacuo and the crude product was purified using flash
column chromatography (SiO₂; DCM/MeOH = 90 : 10) providing 55 mg of the desired product (79% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 7.11 (dd, J = 12.9, 6.6 Hz, 1H), 6.67 (m, 1H), 6.58 (dd, J = 10.9, 7.1 Hz, 1H), 5.43 (s, 1H), 4.87 (s, 1H), 4.13 (s, 2H), 3.78 – 3.68 (m, 4H), 3.60 (m, 2H), 3.48 (s, 2H), 3.28 (s, 2H), 3.14 (t, J = 6.1 Hz, 2H), 2.70 (t, J = 12.7 Hz, 2H), 2.44 – 2.37 (m, 4H), 1.97 (m, 2H), 1.82 (m, 2H), 1.77 – 1.69 (m, 3H), 1.45 (s, 9H), 1.39 (t, J = 5.6 Hz, 4H), 1.28 – 1.11 (m, 2H), 0.91 (s, 6H).¹³C NMR (101 MHz, CDCl₃) δ 167.8, 163.4, 162.4, 157.8, 156.0, 154.8, 152.2, 137.3, 118.4, 118.2, 105.9, 105.6, 80.7, 79.5, 56.5, 54.7, 53.4, 53.0, 49.8, 47.2, 40.2, 38.6, 36.4, 35.4, 30.0, 28.5, 28.4. LRMS (ESI) m/z: [M + H]+ calcd for C₃₇H₅₅F₂N₈O₃; 697.440 found, 697.438.

Preparation of tert-butyl (3-(((6-((4,4-diethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)carbamate (46a)

Compound 46a was prepared according to General procedure 1 using compound 39 (50 mg, 0.1 mmol) and tert-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (34 mg, 0.15 mmol) in DMSO. After reaction completion, the volatiles were removed in vacuo and the crude mixture was purified using flash column chromatography (SiO₂; DCM/MeOH = 90 : 10) providing 91 mg of the desired product (86% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.16 (s, 1H), 7.26 (s, 1H), 7.14 (dd, J = 12.7, 6.5 Hz, 1H), 6.78 (s, 1H), 6.58 (dd, J = 10.8, 7.2 Hz, 1H), 5.45 (s, 1H), 5.36 (s, 1H), 3.77–3.68 (m, 4H), 3.67-3.58 (m, 2H), 3.53 (s, 2H), 3.44 (t, J = 4.6 Hz, 4H), 3.35-3.24 (m, 4H), 2.51-2.37 (m, 8H), 1.96 (m, 2H), 1.84 (m, 2H), 1.77 (m, 2H), 1.46 (s, 9H), 1.41 (t, J = 5.3 Hz, 4H), 0.92 (s, 6H).¹³C NMR (125 MHz, CDCl₃) δ 172.6, 166.8, 166.1, 162.5, 161.0, 160.5, 159.0, 155.7, 153.8, 142.2, 142.1, 122.9, 122.7, 84.1, 60.3, 59.3, 58.1, 57.2, 56.5, 56.4, 53.2, 44.4, 43.7, 41.8, 41.7, 38.7, 31.9. LRMS (ESI) m/z: [M + H]+ calcd for C₃₇H₅₆F₂N₈O₃; 712.447 found, 712.902.
**Preparation of tert-butyl 4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)phenyl)piperazine-1-carboxylate (47a)**

Compound **47a** was prepared according to General procedure 1 using compound **39** (200 mg, 0.397 mmol) and tert-butyl 4-(4-(aminomethyl)phenyl)piperazine-1-carboxylate (115 mg, 0.397 mmol) in EtOH. The volatiles were removed *in vacuo* and the crude product was purified using flash column chromatography (SiO\(_2\); DCM/MeOH = 90 : 10) providing 181 mg of the desired product (58% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.18 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 7.12 (dd, J = 12.9, 6.6 Hz, 1H), 6.92 – 6.88 (m, 2H), 6.58 (dd, J = 10.8, 7.2 Hz, 1H), 6.42 – 6.28 (m, 1H), 5.46 (s, 1H), 5.07 – 4.98 (m, 1H), 4.36 (d, J = 5.6 Hz, 1H), 3.74 – 3.65 (m, 4H), 3.61 – 3.53 (m, 6H), 3.49 (s, 2H), 3.27 (s, 2H), 3.15 – 3.09 (m, 4H), 2.43 – 2.37 (m, 4H), 1.99 – 1.91 (m, 2H), 1.83 – 1.75 (m, 2H), 1.73 – 1.62 (m, 4H), 1.48 (s, 9H), 1.39 (t, J = 5.6 Hz, 2H), 0.91 (s, 6H), 0.87 – 0.76 (m, 2H). \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 171.2, 168.4, 167.4, 166.9, 162.4, 150.8, 150.2, 150.1, 135.9, 134.3, 129.0, 128.5, 123.5, 116.8, 116.2, 105.6, 81.0, 56.4, 53.6, 52.9, 51.2, 49.6, 49.3, 45.5, 41.1, 40.4, 35.4, 32.1, 31.6, 29.9, 29.8, 29.5, 28.2, 27.4, 22.9, 14.3, 1.2. LRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{42}\)H\(_{58}\)F\(_2\)N\(_9\)O\(_3\); 774.462 found, 774.462.
Preparation of 4-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-9-(6-((2-(4-(4-(piperazin-1-yl)phenyl)piperazin-1-yl)ethyl)amino)pyrimidin-4-yl)-1,4,9-triazaspiro[5.5]undecan-2-one (48a)

To a stirred solution of tert-Butyl 4-(5-bromopyrimidin-2-yl)piperazine-1-carboxylate (170 mg, 0.5 mmol) in DMSO (0.5 M) was subsequently added CuI (19 mg, 0.1 mmol), L-proline (23 mg, 0.2 mmol), and K₂CO₃ (276 mg, 2 mmol). After a few minutes, compound 46 (376 mg, 0.6 mmol) was added. The resulting reaction mixture was stirred at 85°C until completion (Monitored by TLC). The reaction was cooled down to rt, quenched with water and extracted into DCM. The combined organic layers were washed twice with water, once with brine and dried over Na₂SO₄. The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO₂; DCM/MeOH = 90:10) affording 43 mg of the desired product (10% yield). ¹H NMR (500 MHz, CDCl₃) δ 8.13 (s, 3H), 7.19 (m, 1H), 7.08 (m, 1H), 6.99 (dd, J = 10.3, 7.4 Hz, 1H), 5.46 (m, 2H), 3.73 (m, 9H), 3.64 (m, 3H), 3.59-3.47 (m, 9H), 3.35 (s, 2H), 3.30 (s, 2H), 3.07 (s, 3H), 3.00 (s, 3H), 2.67 (m, 4H), 2.63 (s, 4H), 2.48 (s, 4H), 1.96 (m, 2H), 1.86 (m, 2H), 1.50 (s, 9H), 1.44 (s, 2H), 0.93 (s, 6H).¹³C NMR (101 MHz, DMSO) δ 170.1, 167.0, 164.8, 158.4, 157.8, 156.0, 154.9, 152.0, 149.6, 148.1, 138.4, 137.1, 118.3, 118.1, 107.7, 106.7, 80.2, 79.8, 57.2, 55.4, 54.4, 53.3, 52.7, 52.9, 50.4, 49.5, 46.1, 44.5, 38.6, 37.0, 35.1, 28.5, 28.2. LCMS (ESI) m/z: [M + H]⁺ calcd for C₄₅H₆₅F₂N₁₃O₃; 874.533, found: 874.652.
Preparation of tert-butyl 2-(4-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)carbamate (49a)

Compound 49a was prepared according to General procedure 3 (COMU) from compound 45 (108 mg, 0.17 mmol) and N-Boc-glycine (30 mg, 0.17 mmol). After reaction completion, the mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = 95:5) providing 75 mg of the desired product (58% yield). $^1$H NMR (400 MHz, MeOD) $\delta$ 7.99 (d, $J = 0.8$ Hz, 1H), 7.26 (dd, $J = 12.9$, 6.7 Hz, 1H), 6.93 (dd, $J = 11.3$, 7.3 Hz, 1H), 5.72 – 5.68 (m, 1H), 4.49 (d, $J = 13.2$ Hz, 1H), 3.95 – 3.82 (m, 6H), 3.75 (s, 2H), 3.41 (s, 3H), 3.22 – 3.15 (m, 2H), 3.06 (t, $J = 12.9$ Hz, 1H), 2.79 (s, 4H), 2.71 – 2.61 (m, 1H), 2.03 – 1.92 (m, 2H), 1.89 – 1.76 (m, 5H), 1.52 (t, $J = 5.8$ Hz, 4H), 1.45 (s, 9H), 1.32 – 1.09 (m, 4H), 0.98 (s, 6H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 168.7, 167.9, 163.4, 162.0, 157.0, 156.9, 156.7, 119.1, 118.8, 106.1, 105.8, 79.2, 54.6, 54.4, 53.4, 53.2, 52.2, 49.0, 48.45, 45.9, 44.4, 42.4, 42.0, 41.6, 40.3, 36.8, 36.1, 34.4, 29.9, 29.3, 27.5, 27.3, 11.8. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{39}$H$_{58}$F$_2$N$_9$O$_4$; 754.457 found, 754.458.
Preparation of 9-((6-(((1-(2-chloroacetyl)piperidin-4-yl)methyl)amino)pyrimidin-4-yl)-4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-1,4,9-triazaspiro[5.5]undecan-2-one (50)

In a flame-dried flask under N$_2$-atmosphere, 150 mg of 45 (0.237 mmol, 1 eq) were suspended in 1 mL of dry-THF with 82 µL of DIPEA (0.47 mmol, 2 eq). 19 µL of 2-chloroacetyl chloride (0.237 mmol, 1 eq) were added dropwise at 0°C and the reaction was stirred at room temperature under N$_2$-atmosphere overnight. The mixture was then dried under reduced pressure and purified using flash column chromatography (SiO$_2$; DMC/MeOH = 90 : 10), affording 140 mg of impure product that was directly used for the following step. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{34}$H$_{48}$ClF$_2$N$_8$O$_2$; 673.355 found, 673.356.

Preparation of tert-butyl 3-((2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)propanoate (S1)

Compound S1 was prepared according to General procedure 4 using 4-fluoro-thalidomide (82 mg, 0.3 mmol) and the corresponding tert-butyl ester (70 mg, 0.3 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = from 80 : 20 to 90 : 10) providing 64 mg of desired product (57% yield). The analytical results were consistent with data reported in the literature$^2$. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.1 (s, 1H), 7.52 (m, J = 8.4, 7.1 Hz, 1H), 7.12 (d, J = 7.1 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.47 (t, J 5.6 Hz, 1H), 4.85 (dd, J 12.4, 5.3 Hz, 1H), 3.74 (m, 4H), 3.65 (m, 4H), 3.46 (m, 2H), 2.89 (m, 1H), 2.86 (m, 2H), 2.53 (t, J= 6.6 Hz, 2H), 2.18 – 2.10 (m, 1H), 1.40 (s, 9H).
Preparation of tert-butyl 3-(2-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisodolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propanoate (S2)

Compound S2 was prepared according to General procedure 4 using 4-fluoro-thalidomide (68 mg, 0.25 mmol) and the corresponding tert-butyl ester (69 mg, 0.25 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = from 80 : 20 to 90 : 10) providing 52 mg of desired product (39% yield). The analytical results were consistent with data reported in the literature (3). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (s, 1H), 7.55 (t, J= 7.6 Hz, 1H), 7.13 (d, J= 6.8 Hz, 1H), 6.94 (d, J=8.3 Hz, 1H), 6.51 (s, 1H), 4.94 (m, 1H), 3.73 (m, 13H), 3.50 (m, 2H), 2.92 – 2.70 (m, 3H), 2.50 (t, J= 6.2 Hz, 2H), 2.15 (m, 1H), 1.44 (s, 9H).

Preparation of tert-butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisodolin -4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-oate (S3)

Compound S3 was prepared according to General procedure 4 using 4-fluoro-thalidomide (53 mg, 0.2 mmol) and the corresponding tert-butyl ester (62 mg, 0.2 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = from 80 : 20 to 90 : 10) affording 64 mg of desired product (57% yield). The analytical results were consistent with data reported in the literature (3). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (s, 1H), 7.44 (dd, J= 7.32, 8.34 Hz, 1H), 7.04 (d, J= 7.11 Hz, 1H), 6.83 (d, J= 8.54 Hz, 1H), 6.42 (m, 1H), 4.8 (s, 1H), 3.58 (m, 18H), 3.42 – 3.35 (m, 2H), 2.72 (s, 3H), 2.45 – 2.39 (m, 2H), 1.98 (m, 1 H), 1.43 (m, 9H).
Preparation of tert-butyl 1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl) amino)-3,6,9,12,15-pentaoxiaoctadecan-18-oate (S4)

![Chemical Structure of S4]

Compound S4 was prepared according to General procedure 4 using 4-fluoro-thalidomide (56 mg, 0.2 mmol) and the corresponding tert-butyl ester (74 mg, 0.2 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = from 80 : 20 to 90 : 10) affording 61 mg of desired product (49% yield). The analytical results were consistent with data reported in the literature $^3$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.19 (s, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.0 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.50 (m, 1H), 4.92 (m, 1H), 3.76 – 3.58 (m, 18H), 3.46 (m, 2H), 2.94 – 2.73 (m, 3H), 2.52 (t, J = 6.4 Hz, 2H), 2.14 (m, 1H), 1.43 (m, 9H).

Preparation of tert-butyl 9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl) amino) nonanoate (S5)

![Chemical Structure of S5]

Compound S5 was prepared according to General procedure 5 using lenalidomide (267 mg, 1.03 mmol) and the corresponding tert-butyl ester (303 mg, 1.03 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = 70 : 30) providing 200 mg of the desired product (41% yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 11.00 (s, 1H), 7.27 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.3 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.55 (t, J = 5.5 Hz, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.26 – 4.08 (m, 2H), 3.10 (q, J = 6.6 Hz, 2H), 2.92 (ddd, J = 18.3, 13.6, 5.4 Hz, 1H), 2.73 – 2.57 (m, 2H), 2.36 – 2.22 (m, 2H), 2.16 (td, J = 7.3, 3.7 Hz, 2H), 2.08 – 1.97 (m, 1H), 1.56 (m, 2H), 1.47 (m, 2H), 1.38 (s, 9H), 1.25 (m, 8H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.9, 172.2, 170.2, 166.3, 147.5, 131.6, 129.8, 125.72, 116.7, 116.2, 80.3, 55.4, 48.2, 43.6, 35.2, 31.1, 29.3, 28.4, 27.7, 27.2, 26.4, 24.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{22}$H$_{30}$N$_3$O$_5$; 416.22 found, 416.26.
Preparation of tert-butyl 11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)undecanoate (S6)

Compound S6 was prepared according to General procedure 5 using lenalidomide (245 mg, 0.95 mmol) and the corresponding tert-butyl ester (304 mg, 0.95 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = 70 : 30) providing 125 mg of the desired product (26% yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 11.00 (s, 1H), 7.27 (t, J = 7.7 Hz, 1H), 6.95 – 6.88 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.55 (t, J = 5.5 Hz, 1H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.28 – 4.07 (m, 2H), 3.10 (q, J = 6.6 Hz, 2H), 2.92 (dd, J = 18.0, 13.5, 5.3 Hz, 1H), 2.72 – 2.58 (m, 2H), 2.36 – 2.23 (m, 2H), 2.16 (t, J = 7.3 Hz, 2H), 2.07 – 1.98 (m, 1H), 1.57 (m, 2H), 1.46 (m, 2H), 1.38 (s, 9H), 1.24 (m, 14H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.7, 172.5, 170.3, 165.9, 148.1, 131.7, 130.1, 125.6, 117.2, 116.4, 80.5, 56.3, 49.1, 43.6, 35.4, 31.3, 30.8, 29.7, 29.1, 28.2, 27.7, 27.3, 26.7, 23.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{28}$H$_{42}$N$_3$O$_5$; 500.31 found, 500.34.

Preparation of tert-butyl 15-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)pentadecanoate (S7)

Compound S7 was prepared according to General procedure 5 using lenalidomide (264 mg, 1.02 mmol) and the corresponding tert-butyl ester (432 mg, 1.02 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = 70 : 30) affording 125 mg of the desired product (22% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.98 (s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 6.80 (dd, J = 8.0, 0.9 Hz, 1H), 5.25 (dd, J = 13.2, 5.2 Hz, 1H), 4.36 – 4.09 (m, 2H), 4.05 (t, J = 6.8 Hz, 1H), 3.20 (t, J = 7.3 Hz, 2H), 2.92 – 2.78 (m, 2H), 2.36 – 2.26 (m, 2H), 2.20 (t, J = 7.5 Hz, 2H), 1.69 – 1.53 (m, 6H), 1.44 (s, 9H), 1.31 – 1.22 (m, 18H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 174.4, 173.1, 170.5, 165.6, 149.7, 131.2, 129.5, 126.2, 117.1, 116.3, 79.8, 56.1, 48.4, 43.8, 36.7, 33.4, 30.7, 29.5, 29.2, 28.4,
Preparation of 2-(2,6-dioxopiperidin-3-yl)-4-(prop-2-yn-1-ylamino) isoindoline-1,3-dione (56)

Compound 56 was prepared according to General procedure 6 using 4-fluoro-thalidomide (320 mg, 1.16 mmol) and propargylamine (64 mg, 1.16 mmol). The resulting reaction mixture was stirred at 130°C (oil bath temperature) until full completion (Monitored by TLC). The reaction mixture was quenched by the addition of a saturated aq. solution of NaHCO₃ and extracted into EtOAc (3 x 15ml). The combined organic layers were dried over MgSO₄, filtrated, and evaporated providing 280 mg of desired product 56 (78% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 1H), 7.57 (dd, J = 8.5, 7.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.44 (t, J = 6.5 Hz, 1H), 4.92 (dd, J = 12.2, 5.4 Hz, 1H), 4.09 (dd, J = 6.1, 2.5 Hz, 2H), 2.95 – 2.67 (m, 3H), 2.27 (t, J = 2.4 Hz, 1H), 2.20 – 2.07 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 170.8, 169.2, 168.1, 167.4, 145.6, 136.2, 132.4, 117.2, 112.8, 111.4, 79.1, 72.2, 49.0, 32.3, 31.4, 22.8. LRMS (ESI) m/z: [M + H]⁺ calcd for C₁₆H₁₄N₄O₄; 312.090 found, 312.099.

Preparation of tert-Butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl) -2-(piperazin-1-yl)ethyl)carbamate (57)

Compound 57 was prepared according to General procedure 6 using 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (150 mg, 0.55 mmol) and tert-butyl (2-(piperazin-1-yl)ethyl)carbamate (138 mg, 0.60 mmol). The reaction was heated to 95°C until completion, as determined by TLC. After cooling to room temperature, the mixture was partitioned twice between H₂O and DCM; the combined organic layers were dried over Na₂SO₄, filtered and evaporated. The crude product was purified using flash column chromatography (SiO₂;
DCM/MeOH = 95:5) providing 232 mg of the desired product (87% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.32 (s, 1H), 7.59 (dd, J = 8.1 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 4.96 (dd, J = 12.1, 5.1 Hz, 1H), 3.39 (s, 4H), 3.30 (s, 2H), 2.88 (m, 1H), 2.81 (m, 1H), 2.78 – 2.66 (m, 5H), 2.61 (s, 2H), 2.11 (m, 1H), 1.46 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.5, 169.7, 167.3, 166.6, 156.0, 150.1, 135.7, 134.2, 123.5, 117.2, 115.2, 57.4, 52.9, 50.9, 49.2, 37.5, 31.5, 28.6, 22.6. LCMS (ESI) m/z: [M + H]$^+$ calcd for C$_{24}$H$_{32}$N$_5$O$_6$; 486.227, found: 486.154.

**Preparation of tert-butyl 8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoxindolin-4-yl)amino) octanoate (S8)**

[Chemical structure image]

Compound S8 was prepared according to General procedure 6 using 4-fluoro-thalidomide (258 mg, 0.93 mmol) and the corresponding tert-butyl ester (201 mg, 0.93 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = 2:3) providing 251 mg of the desired product (57% yield). The analytical results were consistent with data reported in the literature (2). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.07 (s, 1H), 7.49 (dd, J = 8.5, 7.1 Hz, 1H), 7.08 (d, J = 7.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.22 (t, J = 5.7 Hz, 1H), 4.91 (dd, J = 12.1, 5.3 Hz, 1H), 3.25 (td, J = 7.1, 5.6 Hz, 2H), 2.96 – 2.67 (m, 3H), 2.20 (t, J = 7.5 Hz, 2H), 2.17 – 2.09 (m, 1H), 1.70 – 1.53 (m, 4H), 1.43 (s, 9H), 1.37 – 1.30 (m, 5H).

**Preparation of tert-butyl 6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoxindolin-4-yl)amino) hexanoate (S9)**

[Chemical structure image]

Compound S9 was prepared according to General procedure 6 using 4-fluoro-thalidomide (516 mg, 1.9 mmol) and the corresponding tert-butyl ester (350 mg, 1.9 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/Hept = 2:3) providing 623 mg of desired product (75% yield). The analytical
results were consistent with data reported in the literature\(^4\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.89 (s, 1H), 7.42 (dd, \(J = 8.5, 7.1\) Hz, 1H), 7.02 (d, \(J = 7.0\) Hz, 1H), 6.81 (d, \(J = 8.5\) Hz, 1H), 6.16 (t, \(J = 5.7\) Hz, 1H), 4.84 (dd, \(J = 12.1, 5.4\) Hz, 1H), 3.20 (td, \(J = 7.1, 5.6\) Hz, 2H), 2.89 – 2.59 (m, 3H), 2.17 (t, \(J = 7.4\) Hz, 2H), 2.10 – 2.04 (m, 1H), 1.68 – 1.53 (m, 4H), 1.37 (s, 9H).

**Preparation of tert-butyl 4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoate (S10)**

![Chemical Structure of S10](image)

Compound S10 was prepared according to General procedure 6 using 4-fluoro-thalidomide (55 mg, 0.2 mmol) and the corresponding tert-butyl ester (34 mg, 0.2 mmol). The volatiles were then removed \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO\(_2\); EtOAc/Hept = 2 : 3) providing 80 mg of the desired product (96\% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.02 (s, 1H), 7.50 (dd, \(J = 8.6, 7.1\) Hz, 1H), 7.10 (d, \(J = 7.0\) Hz, 1H), 6.93 (d, \(J = 8.5\) Hz, 1H), 6.29 (t, \(J = 5.8\) Hz, 1H), 4.96 – 4.84 (m, 1H), 3.33 (q, \(J = 6.6\) Hz, 2H), 2.93 – 2.69 (m, 3H), 2.35 (t, \(J = 7.1\) Hz, 2H), 2.17 – 2.10 (m, 1H), 1.94 (p, \(J = 7.1\) Hz, 2H), 1.45 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.4, 171.1, 169.6, 168.4, 167.7, 147.0, 136.3, 132.7, 116.8, 111.8, 110.2, 80.8, 49.0, 42.0, 32.7, 31.6, 28.3, 24.8, 22.9. LRMS (ESI) \(m/z\): [M + H]\(^+\) calcd for C\(_{21}\)H\(_{26}\)N\(_3\)O\(_6\); 416.181 found, 416.182.

**Preparation of tert-butyl 4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanoate (S11)**

![Chemical Structure of S11](image)

Compound S11 was prepared according to General procedure 6 using 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (70 mg, 0.24 mmol) and the corresponding tert-butyl ester (38 mg, 0.24 mmol). The volatiles were then removed \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO\(_2\); EtOAc/Hept = 2 : 3) providing 53 mg of the desired product (51\% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.49 (dd, \(J = 8.5, 7.1\) Hz, 1H), 7.02 (d, \(J = 7.0\) Hz, 1H), 6.81 (d, \(J = 8.5\) Hz, 1H), 6.16 (t, \(J = 5.7\) Hz, 1H), 4.84 (dd, \(J = 12.1, 5.4\) Hz, 1H), 3.20 (td, \(J = 7.1, 5.6\) Hz, 2H), 2.89 – 2.59 (m, 3H), 2.17 (t, \(J = 7.4\) Hz, 2H), 2.10 – 2.04 (m, 1H), 1.68 – 1.53 (m, 4H), 1.37 (s, 9H).
1H), 7.09 (d, J = 7.1 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.28 (bs, 1H), 4.95 – 4.88 (m, 1H), 3.33 (t, J = 7.1 Hz, 2H), 3.21 (s, 3H), 3.01 – 2.90 (m, 1H), 2.84 – 2.72 (m, 2H), 2.34 (t, J = 7.1 Hz, 2H), 2.13 – 2.05 (m, 1H), 1.93 (p, J = 7.1 Hz, 2H), 1.45 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 172.3, 171.4, 169.8, 169.1, 167.9, 147.0, 136.3, 132.7, 116.7, 111.7, 110.3, 80.8, 49.8, 42.0, 32.7, 32.1, 28.2, 27.4, 24.8, 22.3. LRMS (ESI) m/z: [M + Na]+ calcld for C22H27N3O6Na; 452.180 found, 452.180.

Preparation of tert-butyl 6-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanoate (S12)

Compound S12 was prepared according to General procedure 6 using 4-fluoro-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (70 mg, 0.24 mmol) and the corresponding tert-butyl ester (45 mg, 0.24 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = 2 : 3) providing 41 mg of the desired product (37% yield). 1H NMR (400 MHz, CDCl3) δ 7.48 (t, J = 8.4, 7.3 Hz, 1H), 7.08 (d, J = 7.1 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.22 (t, J = 5.7 Hz, 1H), 4.90 (dd, J = 12.6, 5.3 Hz, 1H), 3.27 (td, J = 7.1, 5.6 Hz, 2H), 3.21 (s, 3H), 3.01 – 2.90 (m, 1H), 2.79 – 2.71 (m, 2H), 2.24 (t, J = 7.4 Hz, 2H), 2.16 – 2.04 (m, 1H), 1.66 (ddt, J = 17.1, 15.1, 7.4 Hz, 4H), 1.57 (s, 2H), 1.44 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 173.0, 171.4, 169.8, 169.2, 167.9, 147.1, 136.2, 132.7, 116.7, 111.5, 110.1, 80.3, 49.8, 42.6, 35.5, 32.1, 29.2, 28.3, 27.4, 26.6, 24.9, 22.3. LRMS (ESI) m/z: [M + H]+ calcld for C24H32N6O6 458.229 found, 458.231.

Preparation of tert-butyl 11-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanoate (S13)

Compound S13 was prepared according to General procedure 4 using compound 56 (80 mg, 0.26 mmol) and the corresponding tert-butyl ester (73 mg, 0.26 mmol). The volatiles were then
removed *in vacuo* and the crude product was purified using flash column chromatography (SiO₂; EtOAc/Hept = from 40 : 60 to 50 : 50) providing 85 mg of desired product (55% yield).

\(^1\)H NMR (400 MHz, CDCl₃) δ 7.99 (s, 1H), 7.49 (dd, J = 8.5, 7.1 Hz, 1H), 7.45 (s, 1H), 7.14 (d, J = 7.1 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.68 (t, J = 6.0 Hz, 1H), 4.92 (dd, J = 12.2, 5.4 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H), 4.31 (t, J = 7.3 Hz, 2H), 2.95 – 2.67 (m, 3H), 2.19 (t, J = 7.5 Hz, 2H), 2.13 (m, 1H), 1.88 (t, J = 7.2 Hz, 2H), 1.44 (s, 9H), 1.33 – 1.21 (m, 14H).

\(^{13}\)C NMR (101 MHz, CDCl₃) δ 173.2, 172.5, 171.0, 164.9, 163.4, 142.7, 140.8, 132.5, 131.6, 122.7, 121.8, 119.8, 113.4, 82.3, 52.5, 49.8, 38.3, 35.1, 30.3, 29.7, 29.2, 28.6, 27.7, 26.8, 26.1, 23.2. LRMS (ESI) m/z: [M + H]⁺ calcd for C₃₁H₄₃N₆O₆; 595.32 found, 595.35.

**Preparation of tert-butyl 9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanoate (S14)**

![Diagram of S14](image)

Compound S14 was prepared according to General procedure 4 using compound 56 (85 mg, 0.27 mmol) and the corresponding tert-butyl ester (70 mg, 0.27 mmol). The volatiles were removed *in vacuo* and the crude product was purified using flash column chromatography (SiO₂; EtOAc/Hept = from 40 : 60 to 50 : 50) affording 73 mg of desired product (47% yield).

\(^1\)H NMR (400 MHz, CDCl₃) δ 8.06 (s, 1H), 7.49 (dd, J = 8.5, 7.2 Hz, 1H), 7.44 (s, 1H), 7.14 (d, J = 7.2, 0.6 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.67 (t, J = 5.9 Hz, 1H), 4.92 (dd, J = 12.1, 5.4 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H), 4.31 (t, J = 7.9, 6.5 Hz, 2H), 2.94 – 2.67 (m, 3H), 2.21 – 2.15 (m, 2H), 2.15 – 2.09 (m, 1H), 1.92 – 1.83 (m, 1H), 1.43 (s, 9H), 1.30 – 1.22 (m, 11H). \(^{13}\)C NMR (101 MHz, CDCl₃) δ 173.8, 172.3, 170.3, 165.5, 164.8, 143.4, 141.0, 131.4, 130.3, 123.1, 121.4, 120.6, 111.5, 80.25, 51.7, 50.2, 37.3, 35.1, 30.5, 29.2, 28.6, 27.7, 26.4, 24.3. LRMS (ESI) m/z: [M + H]⁺ calcd for C₂₉H₃₀N₆O₆; 567.29 found, 567.30.
Preparation of tert-butyl 3-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)propanoate (S15)

Compound S15 was prepared according to General procedure 4 using compound 56 (147 mg, 0.47 mmol) and the corresponding tert-butyl ester (81 mg, 0.47 mmol). The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO2; EtOAc/Hept = from 40 : 60 to 50 : 50) affording 106 mg of desired product (46% yield).

1H NMR (400 MHz, CDCl3) δ 7.94 (s, 1H), 7.56 (s, 1H), 7.49 (dd, J = 7.3, 0.8 Hz, 1H), 7.14 (d, J = 6.6 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.68 (t, J = 6.0 Hz, 1H), 4.91 (dd, J = 12.1, 5.4 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 4.58 (t, J = 6.5 Hz, 2H), 2.99 – 2.68 (m, 6H), 1.38 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 173.3, 170.8, 170.4, 166.2, 165.1, 144.0, 141.5, 132.2, 130.8, 122.7, 121.1, 120.2, 112.7, 80.8, 52.3, 44.9, 37.7, 34.1, 31.4, 27.4, 25.9. LRMS (ESI) m/z: [M + H]+ calcd for C23H27N6O6; 483.20 found, 483.22.

Preparation of 9-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)nonanamide (52)

Compound 52 was prepared according to General procedure 8 starting from 9-bromononanoic acid (200 mg, 0.8 mmol, 1 eq). The crude product was purified using flash column chromatography (SiO2; EtOAc) affording 110 mg of the desired product (27% yield). 1H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 9.76 (s, 1H), 7.81 (dd, J = 6.9 Hz, 2.0 Hz, 1H), 7.53 – 7.38 (m, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.35 (dd, J = 25.6, 17.5 Hz, 2H), 13.53 (t, J = 6.7 Hz, 2H), 2.92 (ddd, J = 18.1, 13.5, 5.4 Hz, 1H), 2.68 – 2.56 (m, 1H), 2.41 – 2.30 (m, 3H), 2.11 – 1.99 (m, 1H), 1.80 (p, J = 6.7 Hz, 2H), 1.61 (t, J = 7.2 Hz, 2H), 1.42 – 1.25 (m, 8H). 13C NMR (101 MHz, DMSO) δ 174.5, 172.9, 171.4, 171.1, 167.8, 133.8, 133.7, 132.7, 128.6, 125.2, 119.0,
Preparation of 11-bromo-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)undecanamide (53)

Compound 53 was prepared according to General procedure 8 starting from 11-bromoundecanoic acid (200 mg, 0.8 mmol, 1 eq). The crude product was purified using flash column chromatography (SiO2; EtOAc/Hept 7 : 3) affording 125 mg of the desired product (31% yield). 1H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 9.75 (s, 1H), 7.80 (dd, J = 6.9, 2.1 Hz, 1H), 7.60 – 7.38 (m, 2H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.35 (dd, J = 25.8, 17.6 Hz, 2H), 3.51 (t, J = 6.7 Hz, 2H), 2.92 (ddd, J = 18.1, 13.5, 5.4 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.39 – 2.30 (m, 3H), 2.10 – 1.97 (m, 1H), 1.78 (p, J = 6.9 Hz, 2H), 1.60 (t, J = 7.0 Hz, 2H), 1.36 – 1.23 (m, 12H). 13C NMR (101 MHz, DMSO) δ 175.0, 172.9, 171.3, 171.1, 168.6, 167.8, 133.8, 132.7, 128.4, 125.1, 122.2, 119.0, 109.1, 51.5, 46.4, 35.8, 35.2, 34.4, 32.2, 31.2, 28.8, 28.7, 28.1, 27.5, 25.1, 22.7. LRMS (ESI) m/z: [M + H]+ calcd for C24H33BrN3O4; 506.164, 508.162 found, 506.165, 508.164.

Preparation of N-(3-((6-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-3-(2-((2,6-dioxopiperidin-3-yl)1,3-dioxoisodolin-4-yl)amino)ethoxy)ethoxy)propenamide (1)

Compound 1 was prepared according to General procedure 3 (HATU) using the corresponding amine (159 mg, 0.306 mmol) and carboxylic acid (132 mg, 0.306 mmol). The crude product was purified first using flash column chromatography (Al2O3; DCM/MeOH = from 90 : 10 to
80 : 20), then using semipreparative HPLC providing 15 mg of the desired product (5% yield).  

$^1$H NMR (500 MHz, DMSO) $\delta$ 11.09 (s, 1H), 8.25 (s, 1H), 7.98 (s, 1H), 7.86 – 7.80 (m, 1H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.15 – 7.09 (m, 3H), 7.03 (d, $J = 7.0$ Hz, 1H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.64 – 6.56 (m, 2H), 5.61 (s, 1H), 5.05 (dd, $J = 12.7$, 5.4 Hz, 1H), 3.81 – 3.74 (m, 2H), 3.65 (s, 2H), 3.59 (t, $J = 6.0$ Hz, 4H), 3.55 – 3.52 (m, 2H), 3.50 – 3.47 (m, 2H), 3.44 (q, $J = 5.6$ Hz, 4H), 3.20 – 3.15 (m, 2H), 3.08 (q, $J = 6.6$ Hz, 2H), 2.87 (ddd, $J = 16.7$, 13.7, 5.4 Hz, 2H), 2.65 – 2.55 (m, 2H), 2.33 – 2.25 (m, 4H), 2.06 – 1.97 (m, 1H), 1.90 (s, 1H), 1.76 – 1.68 (m, 2H), 1.67 – 1.55 (m, 4H), 1.28 (t, $J = 5.6$ Hz, 3H), 1.23 (s, 1H), 0.87 (s, 6H).  

$^{13}$C NMR (126 MHz, DMSO) $\delta$ 172.8, 172.1, 170.1, 170.1, 169.0, 167.3, 167.1, 163.3, 161.7, 157.4, 148.2, 146.4, 136.3, 132.1, 129.7, 128.6, 117.5, 114.3, 110.7, 109.3, 69.7, 69.6, 68.9, 66.9, 61.9, 52.8, 52.4, 51.4, 49.2, 48.6, 41.7, 38.3, 38.0, 36.3, 36.2, 34.3, 31.0, 29.1, 28.3, 22.2, 22.1, 21.1. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{49}$H$_{66}$N$_{11}$O$_8$; 936.500 found, 936.512.

**Preparation of N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-3-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propenamide (2)**

Compound 2 was prepared according to General procedure 3 (HATU) using the corresponding amine (69 mg, 0.13 mmol) and carboxylic acid (64 mg, 0.13 mmol). The crude product was purified first using flash column chromatography (Al$_2$O$_3$; DCM/MeOH = from 90 : 10 to 80 : 20), then using semipreparative HPLC providing 28 mg of the desired product (22% yield).  

$^1$H NMR (500 MHz, DMSO) $\delta$ 11.09 (s, 1H), 8.25 (s, 1H), 7.98 (s, 1H), 7.84 (t, $J = 5.6$ Hz, 1H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.16 – 7.09 (m, 3H), 7.03 (d, $J = 7.0$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 2H), 6.60 (dt, $J = 11.5$, 5.9 Hz, 2H), 5.61 (s, 1H), 5.05 (dd, $J = 12.8$, 5.5 Hz, 1H), 3.78 (d, $J = 13.8$ Hz, 2H), 3.65 (s, 2H), 3.59 (dt, $J = 17.1$, 6.0 Hz, 4H), 3.56 – 3.49 (m, 4H), 3.47 (h, $J = 5.7$ Hz, 8H), 3.21 – 3.15 (m, 2H), 3.08 (q, $J = 6.6$ Hz, 2H), 2.87 (ddd, $J = 16.8$, 13.7, 5.4 Hz, 2H), 2.65 – 2.54 (m, 2H), 2.28 (q, $J = 5.9$, 5.2 Hz, 4H), 2.02 (ddd, $J = 12.2$, 6.9, 4.4 Hz, 1H), 1.90 (s, 1H), 1.72 (dd, $J = 14.2$, 5.1 Hz, 2H), 1.61 (qd, $J = 13.9$, 11.3, 5.5 Hz, 4H), 1.28 (t, $J = 5.6$ Hz, 3H), 1.23 (s, 1H), 0.87 (s, 6H).  

$^{13}$C NMR (126 MHz, DMSO) $\delta$ 172.8, 170.1, 170.1, 169.0, 167.3,
167.1, 163.3, 161.7, 157.4, 148.1, 146.4, 136.3, 132.1, 129.7, 128.7, 117.5, 114.3, 110.7, 109.3, 69.8, 69.7, 68.9, 66.9, 62.0, 52.8, 52.4, 51.4, 49.3, 48.6, 41.7, 38.4, 36.3, 36.2, 34.3, 31.0, 29.0, 28.3, 22.2, 21.2. LRMS (ESI) m/z: [M + H]^+ calcd for C_{51}H_{70}N_{11}O_{9}; 980.530 found, 980.537.

**Preparation of N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-1-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoinolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide (3)**

Compound 3 was prepared according to General procedure 3 (HATU) using the corresponding amine (50 mg, 0.096 mmol) and carboxylic acid (50 mg, 0.096 mmol). The crude product was purified first using flash column chromatography (Al_{2}O_{3}; DCM/MeOH = from 90 : 10 to 80 : 20), then using semipreparative HPLC providing 20 mg of the desired product (20% yield). ^1^H NMR (500 MHz, DMSO) δ 11.09 (s, 1H), 8.25 (s, 1H), 7.98 (s, 1H), 7.84 (t, J = 5.7 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.15 – 7.10 (m, 3H), 7.04 (d, J = 7.1 Hz, 1H), 6.89 (d, J = 8.4 Hz, 2H), 6.64 – 6.57 (m, 2H), 5.61 (s, 1H), 5.05 (dd, J = 12.8, 5.5 Hz, 1H), 3.81 – 3.75 (m, 2H), 3.65 (s, 2H), 3.63 – 3.53 (m, 5H), 3.53 – 3.41 (m, 12H), 3.19 (h, J = 4.9 Hz, 2H), 3.08 (q, J = 6.5 Hz, 2H), 2.87 (ddd, J = 16.8, 13.8, 5.4 Hz, 2H), 2.65 – 2.54 (m, 2H), 2.33 – 2.25 (m, 4H), 2.06 – 1.97 (m, 1H), 1.90 (s, 1H), 1.76 – 1.68 (m, 2H), 1.67 – 1.56 (m, 4H), 1.28 (t, J = 5.6 Hz, 3H), 1.24 (s, 1H), 0.87 (s, 6H). ^13^C NMR (126 MHz, DMSO) δ 172.8, 172.1, 170.1, 170.1, 169.0, 167.3, 167.1, 163.3, 161.7, 157.4, 149.8, 148.2, 146.4, 136.3, 134.7, 132.1, 132.0, 129.8, 123.4, 122.1, 117.5, 114.3, 110.7, 109.3, 69.8, 69.8, 69.8, 69.7, 69.5, 68.9, 66.9, 61.9, 52.8, 52.4, 51.4, 49.2, 48.6, 41.7, 38.3, 38.0, 36.3, 36.2, 34.3, 31.0, 29.1, 28.3, 22.2. LRMS (ESI) m/z: [M + H]^+ calcd for C_{53}H_{74}N_{11}O_{10}; 1024.550 found, 1024.564.
Preparation of \( \text{N}-(3-((6-(4-(4,4\text{-dimethylpiperidin-1-yl})\text{methyl})\text{phenyl})-2\text{-oxo}-1,4,9\text{-triazaspiro[5.5]undecan-9-yl}$$\text{pyrimidin-4-yl}$$\text{amino})$$\text{propyl})-1-((2,6\text{-dioxpiperidin-3-yl})$$1,3\text{-dioxoisindolin-4-yl}$$\text{amino})-3,6,9,12,15\text{-pentaaxoctadecan-18-amide (4)}\)

![Chemical Structure](image)

Compound 4 was prepared according to General procedure 3 (HATU) using the corresponding amine (51 mg, 0.098 mmol) and carboxylic acid (56 mg, 0.096 mmol). The crude product was purified first using flash column chromatography (Al\(_2\)O\(_3\); DCM/MeOH = from 90 : 10 to 80 : 20), then using semipreparative HPLC providing 13 mg of the desired product (12% yield). \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 11.09 (s, 1H), 8.25 (s, 1H), 7.98 (s, 1H), 7.89 – 7.80 (m, 1H), 7.58 (t, \(J = 7.9\) Hz, 1H), 7.16 – 7.09 (m, 3H), 7.04 (d, \(J = 7.0\) Hz, 1H), 6.89 (d, \(J = 8.3\) Hz, 2H), 6.64 – 6.57 (m, 2H), 5.61 (s, 1H), 5.05 (dd, \(J = 12.7, 5.4\) Hz, 1H), 3.81 – 3.73 (m, 2H), 3.65 (s, 2H), 3.63 – 3.54 (m, 6H), 3.54 – 3.43 (m, 17H), 3.21 – 3.15 (m, 2H), 3.08 (q, \(J = 6.6\) Hz, 2H), 2.87 (ddd, \(J = 16.9, 13.8, 5.4\) Hz, 2H), 2.65 – 2.54 (m, 2H), 2.32 – 2.24 (m, 4H), 2.06 – 1.97 (m, 1H), 1.90 (s, 1H), 1.76 – 1.68 (m, 2H), 1.67 – 1.55 (m, 4H), 1.28 (t, \(J = 5.6\) Hz, 3H), 1.23 (s, 1H), 0.87 (s, 6H). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 172.8, 172.1, 170.1, 170.1, 169.0, 167.3, 167.1, 163.3, 161.7, 157.4, 148.1, 146.4, 136.3, 134.5, 132.1, 131.6, 129.7, 128.7, 123.1, 117.5, 114.3, 110.7, 109.3, 69.9, 69.8, 69.8, 69.7, 69.5, 68.9, 66.9, 62.0, 52.9, 52.4, 51.4, 49.3, 48.6, 48.6, 41.7, 38.4, 38.0, 36.3, 36.2, 34.3, 31.0, 29.1, 28.3, 22.2, 21.2. LRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{55}\)H\(_{78}\)N\(_{11}\)O\(_{11}\); 1068.580 found, 1068.591.
Preparation of N-(3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoiindolin-4-yl)amino)nonanamide (5)

Compound 5 was prepared according to General procedure 3 (COMU) using the corresponding amine (63 mg, 0.12 mmol) and carboxylic acid (50 mg, 0.12 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using two consecutive preparative thin layer chromatography (SiO$_2$; DCM/MeOH = 84 : 16) providing 6 mg of the desired product (5% yield). $^1$H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 8.27 (s, 1H), 7.98 (s, 1H), 7.78 (t, J = 5.6 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.14 (d, J = 8.2 Hz, 2H), 6.91 (m, 3H), 6.72 (d, J = 8.0 Hz, 1H), 6.64 (m, 1H), 5.61 (s, 1H), 5.54 (t, J = 5.5 Hz, 1H), 5.10 (dd, J = 13.2, 5.1 Hz, 1H), 4.22 (d, J = 17.3 Hz, 1H), 4.12 (d, J = 17.2 Hz, 1H), 3.77 (m, 2H), 3.66 (t, J = 7.4 Hz, 2H), 3.17 (m, 2H), 3.08 (p, J = 6.6 Hz, 4H), 2.92 (dd, J = 18.0, 13.4, 5.6 Hz, 2H), 2.69 – 2.57 (m, 2 H), 2.36 – 2.23 (m, 2H), 2.04 (t, J = 7.4 Hz, 2H), 1.72 (m, 2H), 1.58 (m, 6H), 1.47 (t, J = 7.1 Hz, 2H), 1.31 (m, 4H), 1.25 (m, 8H), 0.88 (s, 6H). $^{13}$C NMR (151 MHz, MeOD) δ 176.4, 174.7, 172.4, 172.3, 170.7, 164.5, 163.3, 163.2, 162.9, 158.2, 150.7, 145.1, 132.8, 132.8, 132.8, 132.8, 132.8, 127.9, 115.6, 113.6, 111.7, 62.3, 54.3, 54.1, 53.4, 52.1, 50.1, 47.2, 44.4, 41.5, 39.7, 39.5, 39.4, 39.3, 39.1, 37.8, 37.8, 37.1, 35.4, 32.3, 30.7, 30.2, 30.2, 30.1, 30.0, 28.9, 28.0, 26.9, 26.9, 24.1, 23.6, 14.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{51}$H$_{73}$N$_{11}$O$_5$; 918.560 found, 918.574.
Preparation of N-((3-(6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindo- lin-4-yl)amino)undecanamide (6)

Compound 6 was prepared according to General procedure 3 (COMU) using the corresponding amine (47 mg, 0.090 mmol) and carboxylic acid (40 mg, 0.090 mmol). The reaction mixture was evaporated and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 80 : 20) providing 36 mg of the desired product (42% yield). $^1$H NMR (500 MHz, DMSO) $\delta$ 11.00 (s, 1 H), 8.32 (s, 1H), 7.98 (s, 1H), 7.84 (t, J = 5.7 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.27 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 8.3 Hz, 2H), 6.91 (d, J = 7.4 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.67 (m, 1H), 5.62 (s, 1H), 5.57 (t, J = 5.5 Hz, 1H), 5.10 (dd, J = 13.3, 5.1 Hz, 1H), 4.23 (d, J = 17.2 Hz, 1H), 4.12 (d, J = 17.2 Hz, 1H), 3.81 – 3.74 (m, 2 H), 3.72 (s, 2H), 3.59 (m, 2H), 3.51 (m, 2H), 3.45 (s, 2H), 3.17 (m, 2H), 3.08 (dq, J = 13.0, 6.5 Hz, 4H), 2.91 (ddd, J = 15.1, 9.8, 5.2, 4.7 Hz, 2H), 2.61 (m, 2H), 2.29 (m, 2H), 2.03 (t, J = 7.0 Hz, 2H), 1.70 (m, 2H), 1.59 (m, 6H), 1.46 (m, 4H), 1.34 (m, 2H), 1.25 (m, 14 H), 0.94 (s, 6H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 173.0, 172.2, 171.3, 169.0, 166.9, 163.2, 161.7, 158.0, 157.8, 157.3, 143.8, 132.1, 129.2, 126.5, 118.6, 116.2, 113.8, 111.7, 109.9, 69.8, 53.3, 52.4, 51.9, 50.7, 47.7, 45.8, 42.8, 41.6, 38.0, 36.2, 35.5, 34.2, 31.3, 29.1, 29.0, 28.9, 28.8, 28.7, 28.6, 27.8, 26.7, 25.4, 22.8, 22.1, 18.6, 18.0, 16.8, 12.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{55}$H$_{77}$N$_{11}$O$_5$; 946.600 found, 946.605.
Preparation of \(N-(3-((6-(4-(4-(4,4\text{-dimethylpiperidin-1-yl})methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-15-((2-(2,6\text{-dioxopiperidin-3-yl})-1\text{-oxoisooindolin-4-yl})amino)pentadecanamide (7)\)

Compound 7 was prepared according to General procedure 3 (COMU) using the corresponding amine (117 mg, 0.224 mmol) and carboxylic acid (112 mg, 0.224 mmol). The reaction mixture was concentrated \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO\(_2\); DCM/MeOH = from 90 : 10 to 80 : 20) providing 120 mg of the desired product (53% yield). \(^1\)H NMR (400 MHz, MeOD) \(\delta\) 8.11 (s, 1H), 7.42 (d, \(J = 8.7\) Hz, 2H), 7.31 (t, \(J = 7.8\) Hz, 1H), 7.08 – 6.99 (m, 3H), 6.81 (d, \(J = 8.0\) Hz, 1H), 5.81 (s, 1H), 5.15 (dd, \(J = 13.3, 5.1\) Hz, 1H), 4.32 (d, \(J = 16.9\) Hz, 1H), 4.26 (d, \(J = 17.1\) Hz, 1H), 4.22 (s, 2H), 3.96 – 3.86 (m, 4H), 3.80 – 3.71 (m, 2H), 3.55 (s, 2H), 3.28 – 3.25 (m, 2H), 3.20 (t, \(J = 7.2\) Hz, 2H), 3.15 – 3.04 (m, 2H), 2.91 (ddd, \(J = 18.4, 13.4, 5.3\) Hz, 1H), 2.48 (qd, \(J = 13.2, 4.7\) Hz, 1H), 2.19 (t, \(J = 7.4\) Hz, 2H), 1.98 – 1.90 (m, 2H), 1.88 – 1.78 (m, 4H), 1.70 – 1.56 (m, 8H), 1.35 – 1.26 (m, 20H), 1.05 (d, \(J = 15.1\) Hz, 6H). \(^{13}\)C NMR (101 MHz, MeOD) \(\delta\) 176.6, 174.7, 172.5, 172.4, 170.4, 151.6, 145.2, 133.7, 133.0, 130.6, 128.0, 120.4, 115.7, 113.8, 111.8, 61.0, 54.0, 53.8, 53.6, 51.8, 47.5, 44.5, 42.0, 40.1, 37.6, 37.2, 36.6, 35.5, 32.4, 31.5, 30.6, 30.5, 30.4, 30.3, 30.2, 29.8, 28.8, 28.2, 27.0, 24.3, 23.5. LRMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{57}\)H\(_{84}\)N\(_{11}\)O\(_5\); 1002.670 found, 1002.664.

Preparation of \(N-(3-((6-(4-(4-(4,4\text{-dimethylpiperidin-1-yl})methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((4-((2-(2,6\text{-dioxopiperidin-3-yl})-1\text{-oxoisooindolin-4-yl})amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (8)\)

\[\text{Diagram of Chemical Structure}\]
Compound 8 was prepared according to General procedure 3 (HATU) using the corresponding amine (80 mg, 0.15 mmol) and carboxylic acid (83 mg, 0.15 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 80 : 20) providing 7 mg of the desired product (5% yield).

$^1$H NMR (600 MHz, MeOD) δ 8.04 (t, J = 5.6 Hz, 1H), 7.98 (s, 1H), 7.90 (s, 1H), 7.51 (dd, J = 8.5, 7.1 Hz, 1H), 7.27 (d, J = 8.7 Hz, 2H), 7.06 (dd, J = 7.8, 2.4 Hz, 2H), 6.98 (t, J = 6.1 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 5.66 (s, 1H), 5.04 (dd, J = 12.5, 5.5 Hz, 1H), 4.63 (d, J = 6.1 Hz, 2H), 4.34 (t, J = 7.0 Hz, 2H), 3.81 (s, 2H), 3.72 – 3.67 (m, 2H), 3.56 – 3.50 (m, 2H), 3.48 (s, 2H), 3.29 – 3.22 (m, 4H), 2.87 – 2.78 (m, 2H), 2.75 – 2.72 (m, 1H), 2.70 (s, 1H), 2.69 – 2.64 (m, 2H), 2.16 (t, J = 7.4 Hz, 2H), 2.10 – 2.02 (m, 2H), 1.92 – 1.86 (m, 2H), 1.85 – 1.81 (m, 2H), 1.77 – 1.73 (m, 2H), 1.62 – 1.55 (m, 4H), 1.47 (t, J = 5.7 Hz, 4H), 1.32 – 1.27 (m, 16H), 0.95 (s, 6H).

$^{13}$C NMR (151 MHz, MeOD) δ 176.4, 174.6, 171.6, 170.8, 170.4, 169.1, 164.5, 163.3, 163.2, 162.9, 162.7, 158.2, 150.4, 147.4, 147.3, 146.5, 137.0, 133.8, 132.6, 124.0, 118.2, 115.7, 112.4, 111.9, 54.3, 53.2, 52.3, 51.2, 50.5, 50.1, 41.5, 39.6, 38.9, 38.2, 37.9, 37.1, 33.0, 32.1, 31.6, 31.5, 31.0, 30.7, 30.6, 30.2, 30.1, 30.1, 30.0, 29.8, 29.8, 29.0, 27.2, 26.9, 23.7, 18.4.

LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{56}$H$_{78}$N$_{14}$O$_6$: 1041.610 found, 1041.615.

Preparation of N-((3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (9)

Compound 9 was prepared according to General procedure 3 (HATU) using the corresponding amine (67 mg, 0.13 mmol) and carboxylic acid (66 mg, 0.13 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 80 : 20) providing 100 mg of the desired product (76% yield).

$^1$H NMR (400 MHz, MeOD) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.51 (dd, J = 8.5, 7.1 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.07 (t, J = 7.9 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 5.68 (s, 1H), 5.04 (dd, J = 12.5, 5.4 Hz, 1H), 4.62 (s, 2H), 4.34 (t, J = 7.0 Hz, 2H), 4.11 (s, 2H), 3.86 (s, 2H), 3.83 – 3.77 (m, 2H), 3.59 – 3.54 (m, 2H), 3.52 (s, 2H), 3.29 – 3.22 (m, 4H), 3.11 – 3.06 (m, 4H),
2.75 – 2.66 (m, 2H), 2.16 (t, J = 7.4 Hz, 2H), 1.89 – 1.73 (m, 8H), 1.61 (t, J = 5.8 Hz, 4H), 1.56 (t, J = 7.3 Hz, 2H), 1.40 – 1.36 (m, 4H), 1.27 – 1.23 (m, 6H), 1.03 (s, 6H). 13C NMR (101 MHz, MeOD) δ 176.4, 174.6, 171.6, 170.6, 170.5, 169.2, 164.6, 163.4, 158.3, 151.4, 147.4, 146.5, 137.2, 133.9, 133.5, 124.1, 118.4, 115.6, 112.5, 112.0, 61.4, 55.8, 54.3, 53.9, 51.9, 51.3, 50.2, 41.6, 39.6, 37.9, 37.1, 36.9, 35.5, 32.2, 31.1, 30.2, 30.1, 29.9, 29.7, 28.9, 27.2, 26.9, 23.8, 13.2. LRMS (ESI) m/z: [M + H]+ calcd for C54H53N14O6; 1013.580 found, 1013.584.

Preparation of N-(3-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)nonanamide (10)

Compound 10 was prepared according to General procedure 3 (COMU) using the corresponding amine (85 mg, 0.14 mmol) and carboxylic acid (60 mg, 0.24 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO2; DCM/MeOH = from 95 : 5 to 90 : 10), followed by a second flash column chromatography (SiO2; EtOAc/MeOH = from 90 : 10 to 80 : 20) providing 100 mg of the desired product (72% yield). 1H NMR (400 MHz, CDCl3) δ 10.31 (bs, 1H), 8.14 (s, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.11 (dd, J = 12.9, 6.6 Hz, 1H), 7.02 (s, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.57 (dd, J = 10.9, 7.1 Hz, 1H), 6.36 (s, 1H), 5.74 (s, 1H), 5.43 (s, 1H), 5.20 (dd, J = 13.2, 5.2 Hz, 1H), 4.29 (d, J = 15.6 Hz, 1H), 4.12 (d, J = 15.6 Hz, 1H), 3.71 (m, 4H), 3.60 – 3.53 (m, 2H), 3.50 (s, 2H), 3.29 (m, 4H), 3.25 (s, 2H), 3.18 (q, J = 7.1, 6.6 Hz, 2H), 2.85 – 2.75 (m, 2H), 2.47 – 2.38 (m, 4H), 2.33 – 2.19 (m, 2H), 2.19 – 2.07 (m, 4H), 1.98 – 1.86 (m, 2H), 1.84 – 1.69 (m, 4H), 1.66 – 1.53 (m, 4H), 1.44 – 1.36 (m, 4H), 1.35 – 1.21 (m, 7H), 0.90 (s, 6H). 13C NMR (101 MHz, CDCl3) δ 173.8, 172.2, 171.1, 170.3, 168.3, 163.1, 162.3, 157.4, 156.2, 152.0, 149.9, 143.4, 137.6, 132.0, 129.8, 126.3, 118.6, 113.3, 112.5, 105.9, 105.7, 56.6, 56.5, 54.7, 53.5, 53.1, 51.9, 51.0, 49.8, 45.2, 43.7, 40.3, 38.9, 38.6, 38.3, 38.3, 36.9, 36.5, 35.3, 31.8, 29.8, 29.3, 29.2, 29.0, 28.9, 28.5, 26.8, 25.7, 23.7. LRMS (ESI) m/z: [M + H]+ calcd for C51H70F2N14O6; 954.552 found, 954.552.
Preparation of N-(3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)undecanamide (11)

Compound 11 was prepared according to General procedure 3 (COMU) using the corresponding amine (40 mg, 0.07 mmol) and carboxylic acid (30 mg, 0.07 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = from 90 : 10 to 80 : 20) providing 37 mg of the desired product (56% yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 11.00 (s, 1H), 10.87 (s, 1H), 8.36 (s, 1H), 8.29 (s, 1H), 7.99 (t, $J$ = 5.5 Hz, 1H), 7.73 (dd, $J$ = 13.4, 6.8 Hz, 1H), 7.27 (t, $J$ = 7.7 Hz, 1H), 7.05 (dd, $J$ = 11.7, 7.4 Hz, 1H), 6.91 (d, $J$ = 7.4 Hz, 1H), 6.72 (d, $J$ = 8.0 Hz, 1H), 5.94 (s, 1H), 5.10 (dd, $J$ = 13.2, 5.1 Hz, 1H), 4.27 – 4.20 (m, 2H), 4.12 (d, $J$ = 17.2 Hz, 1H), 3.69 (s, 2H), 3.40 – 3.33 (m, 3H), 3.34 – 3.27 (m, 2H), 3.21 – 3.01 (m, 8H), 2.92 (ddd, $J$ = 18.0, 13.4, 5.2 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.29 (qd, $J$ = 13.4, 4.9 Hz, 1H), 2.13 – 1.97 (m, 3H), 1.91 – 1.70 (m, 5H), 1.66 (t, $J$ = 6.8 Hz, 2H), 1.60 – 1.51 (m, 2H), 1.51 – 1.39 (m, 4H), 1.38 – 1.16 (m, 17H), 0.96 (d, $J$ = 26.8 Hz, 6H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 172.9, 172.3, 171.3, 168.9, 166.4, 158.3, 158.0, 156.5, 143.8, 140.5, 132.0, 129.2, 126.5, 120.5, 118.4, 115.5, 112.5, 111.7, 109.9, 54.6, 52.8, 52.2, 51.5, 50.9, 47.7, 45.8, 42.8, 35.9, 35.4, 34.6, 31.2, 31.1, 29.0, 28.9, 28.9, 28.8, 28.7, 28.5, 27.5, 26.7, 25.3, 23.1, 22.8. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{53}$H$_{74}$F$_2$N$_{11}$O$_5$; 982.583 found, 982.584.
Preparation of N-((3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (12)

Compound 12 was prepared according to General procedure 3 (COMU) using the corresponding amine (34.9 mg, 0.063 mmol) and carboxylic acid (32.0 mg, 0.063 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO2; DCM/MeOH = from 100 : 5 to 100 : 20) providing 15 mg of the desired product (22% yield). 1H NMR (400 MHz, CDCl3) δ 10.38 (bs, 1H), 8.14 (s, 1H), 7.49 (s, 1H), 7.47 (dd, J = 8.5, 7.1 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.11 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.90 (s, 1H), 6.70 (t, J = 5.9 Hz, 1H), 6.58 (dd, J = 10.9, 7.2 Hz, 1H), 6.28 (bs, 1H), 5.79 (bs, 1H), 5.44 (s, 1H), 4.91 (dd, J = 12.1, 5.4 Hz, 1H), 4.63 (d, J = 5.9 Hz, 2H), 4.32 (t, J = 7.0 Hz, 2H), 3.75 – 3.49 (m, 8H), 3.35 – 3.26 (m, 5H), 2.87 – 2.81 (m, 3H), 2.49 (bs, 4H), 2.17 – 2.05 (m, 2H), 1.95 – 1.91 (m, 8H), 1.60 – 1.51 (m, 2H), 1.45 – 1.38 (m, 4H), 1.28 – 1.17 (m, 10H), 0.92 (s, 6H). 13C NMR (101 MHz, CDCl3) δ 173.8, 171.8, 169.8, 169.6, 168.1, 167.7, 162.5, 162.3, 158.7, 157.2, 156.3, 152.3, 146.3, 145.2, 136.4, 132.5, 121.8, 118.9, 117.3, 112.4, 110.9, 105.9, 105.6, 63.9, 56.7, 54.5, 53.5, 53.0, 50.5, 49.7, 49.1, 40.3, 38.9, 38.3, 36.8, 36.5, 35.4, 32.1, 31.6, 31.1, 30.1, 29.8, 29.5, 29.3, 28.8, 28.4, 28.4, 26.2, 25.6, 23.0. LRMS (ESI) m/z: [M + H]+ calcd for C54H71F2N14O6; 1049.564 found, 1049.565.
Preparation of $N$-((3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-(4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (13)

Compound 13 was prepared according to General procedure 3 (COMU) using the corresponding amine (33.08 mg, 0.059 mmol) and carboxylic acid (32.0 mg, 0.059 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 100 : 10 to 100 : 20) providing 14 mg of the desired product (21% yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.38 (bs, 1H), 8.14 (s, 1H), 7.49 (s, 1H), 7.46 (dd, $J$ = 8.5, 7.1 Hz, 1H), 7.15 – 7.12 (m, 1H), 7.10 (d, $J$ = 7.1 Hz, 1H), 7.05 (s, 1H), 6.98 (d, $J$ = 8.5 Hz, 1H), 6.70 (t, $J$ = 5.9 Hz, 1H), 6.58 (dd, $J$ = 10.9, 7.2 Hz, 1H ), 6.28 (bs, 1H ), 5.79 (bs, 1H ), 5.44 (s, 1H), 4.91 (dd, $J$ = 12.1, 5.4 Hz, 1H), 4.63 (d, $J$ = 5.9 Hz, 2H), 4.32 (t, $J$ = 7.0 Hz, 2H), 3.75 – 3.49 (m, 8H), 3.35 – 3.23 (m, 5H), 2.87 – 2.81 (m, 3H), 2.49 (bs, 4H), 2.17 – 2.05 (m, 2H), 1.95 – 1.91 (m, 8H), 1.60 – 1.51 (m, 2H), 1.45 – 1.38 (m, 4H), 1.28 – 1.17 (m, 14H), 0.92 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 173.9, 171.9, 169.5, 168.2, 167.7, 162.9, 162.3, 158.7, 157.2, 156.3, 152.3, 149.9, 146.3, 145.1, 137.8, 136.3, 132.5, 121.7, 118.6, 117.3, 112.4, 110.9, 105.9, 105.6, 63.9, 56.6, 54.6, 53.5, 53.0, 50.6, 49.7, 49.1, 40.3, 38.9, 38.4, 36.9, 36.5, 35.3, 31.6, 30.2, 29.8, 29.5, 29.4, 29.1, 29.1, 28.7, 28.4, 26.3, 25.8, 22.9, 14.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{56}$H$_{75}$F$_2$N$_{14}$O$_6$; 1077.596 found, 1077.593.
Preparation of \( N-((6-(4-(4,4\text{-dimethylpiperidin-1-yl})methyl)-2,5\text{-difluorophenyl})-2\text{-oxo-1,4,9-triazaspiro}[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-4-((2-(2,6\text{-dioxopiperidin-3-yl})-1,3\text{-dioxoisooindolin-4-yl)amino})butanamide (14) \)

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\begin{align*}
\text{Compound 14} \text{ was prepared according to General procedure 3 (COMU) using the corresponding amine (55 mg, 0.08 mmol) and carboxylic acid (30 mg, 0.08 mmol). The reaction mixture was concentrated \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO}_2; \text{EtOAc/MeOH = 90 : 10} \text{ providing 47 mg of the desired product (59\% yield).}^{1}\text{H NMR (400 MHz, CDCl}_3) \delta 10.85 (\text{bs, 1H}), 8.16 (\text{s, 1H}), 7.43 (\text{dd, } J = 8.5, 7.1 \text{ Hz, 1H}), 7.25 – 7.17 (\text{m, 3H}), 7.15 – 7.07 (\text{m, 2H}), 7.04 (\text{d, } J = 7.1 \text{ Hz, 1H}), 6.92 – 6.84 (\text{m, 2H}), 6.57 (\text{dd, } J = 10.9, 7.1 \text{ Hz, 1H}), 6.26 (\text{t, } J = 5.9 \text{ Hz, 1H}), 6.09 – 6.04 (\text{m, 1H}), 5.77 (\text{bs, 1H}), 5.34 (\text{s, 1H}), 4.89 (\text{dd, } J = 12.2, 5.3 \text{ Hz, 1H}), 4.38 (\text{dd, } J = 13.1, 5.7 \text{ Hz, 4H}), 3.71 (\text{s, 1H}), 3.66 – 3.50 (\text{m, 4H}), 3.33 (\text{q, } J = 6.5 \text{ Hz, 2H}), 3.25 (\text{s, 2H}), 2.90 – 2.69 (\text{m, 3H}), 2.46 (\text{bs, 4H}), 2.31 (\text{t, } J = 6.9 \text{ Hz, 2H}), 2.15 – 2.06 (\text{m, 1H}), 2.05 – 1.96 (\text{m, 2H}), 1.94 – 1.83 (\text{m, 2H}), 1.81 – 1.70 (\text{m, 4H}), 1.45 – 1.38 (\text{m, 4H}), 0.92 (\text{s, 6H}).^{13}\text{C NMR (101 MHz, CDCl}_3) \delta 172.0, 171.9, 170.4, 169.8, 168.2, 167.8, 162.5, 157.6, 147.0, 139.1, 138.8, 136.4, 132.6, 129.1, 127.0, 126.7, 126.3, 116.9, 111.8, 110.3, 56.7, 54.3, 53.5, 53.0, 49.8, 49.1, 45.7, 43.6, 41.8, 40.3, 38.5, 35.2, 33.3, 31.7, 29.9, 28.5, 24.8, 23.0. \text{LRMS (ESI) m/z: [M + H]}^+ \text{ calcd for } \text{C}_{51}\text{H}_{60}\text{F}_{2}\text{N}_{11}\text{O}_{6}; 960.469 \text{ found, 960.469.} \)
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Preparation of N-(3-(((6-(4-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)nonanamide (16)

Compound 15 was prepared according to General procedure 3 using the corresponding amine (124 mg, 0.19 mmol) and carboxylic acid (95 mg, 0.19 mmol). The reaction mixture was evaporated and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = from 85 : 15 to 80 : 20) providing 113 mg of the desired product (60% yield).

$^1$H NMR (400 MHz, MeOD) $\delta$ 7.98 (s, 1H), 7.51 (t, 1H), 7.29 – 7.20 (m, 3H), 7.18 (d, J = 6.7 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.03 – 6.97 (m, 2H), 6.86 (dd, J = 11.2, 7.3 Hz, 1H), 5.62 (s, 1H), 5.03 (dd, J = 12.4, 5.5 Hz, 1H), 4.45 (s, 2H), 4.34 (s, 2H), 3.89 – 3.81 (m, 2H), 3.70 (s, 2H), 3.60 (s, 2H), 2.90 – 2.62 (m, 3H), 2.54 (bs, 3H), 2.24 (t, J = 7.3 Hz, 2H), 2.13 – 2.03 (m, 1H), 1.97 – 1.87 (m, 2H), 1.82 – 1.71 (m, 2H), 1.71 – 1.60 (m, 4H), 1.43 (t, J = 4.9, 3.7 Hz, 6H), 1.36 – 1.27 (m, 1H), 0.93 (s, 6H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 173.4, 172.7, 170.6, 169.4, 167.8, 167.2, 163.6, 162.0, 158.5, 157.8, 156.1, 146.9, 140.1, 136.8, 132.6, 128.7, 126.4, 126.1, 126.0, 117.7, 110.9, 109.4, 54.3, 53.1, 49.4, 49.0, 44.1, 42.4, 42.2, 38.4, 35.7, 35.0, 31.4, 28.9, 28.5, 26.4, 25.5, 22.6. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{58}$H$_{79}$F$_2$N$_{12}$O$_6$; 988.50 found, 988.56.

Preparation of N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)nonanamide (16)
Compound 16 was prepared according to General procedure 3 (COMU) using the corresponding amine (25 mg, 0.04 mmol) and carboxylic acid (17 mg, 0.04 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO\(_2\); EtOAc/MeOH = from 90 : 10 to 80 : 20) providing 25 mg of the desired product (61% yield). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.01 (s, 1H), 8.35 (t, \(J = 6.0\) Hz, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.31 – 7.20 (m, 3H), 7.20 – 7.12 (m, 3H), 7.08 (d, \(J = 7.5\) Hz, 1H), 6.97 – 6.86 (m, 2H), 6.71 (d, \(J = 8.0\) Hz, 1H), 5.69 (s, 1H), 5.60 (t, \(J = 5.6\) Hz, 1H), 5.10 (dd, \(J = 13.3, 5.1\) Hz, 1H), 4.41 (d, \(J = 6.2\) Hz, 2H), 4.28 – 4.09 (m, 4H), 3.83 (d, \(J = 13.3\) Hz, 2H), 3.58 (s, 2H), 3.47 – 3.37 (m, 4H), 3.25 (s, 2H), 3.09 (q, \(J = 6.6\) Hz, 2H), 2.92 (ddd, \(J = 18.1, 13.5, 5.4\) Hz, 1H), 2.67 – 2.57 (m, 1H), 2.40 – 2.22 (m, 4H), 2.11 (t, \(J = 7.4\) Hz, 2H), 2.06 – 1.97 (m, 1H), 1.81 – 1.72 (m, 2H), 1.69 – 1.60 (m, 1H), 1.60 – 1.44 (m, 4H), 1.38 – 1.20 (m, 14H), 0.87 (s, 6H). \(^{13}\)C NMR (101 MHz, DMSO) \(\delta\) 172.9, 172.1, 172.0, 171.3, 168.9, 166.5, 163.2, 161.6, 157.4, 156.2, 156.2, 143.8, 139.8, 132.0, 129.2, 128.1, 126.5, 126.0, 125.5, 125.5, 111.7, 109.8, 106.3, 69.8, 62.8, 59.8, 54.7, 54.2, 52.8, 52.6, 51.5, 49.0, 45.8, 43.6, 42.7, 41.9, 38.1, 35.3, 34.6, 31.2, 28.9, 28.8, 28.7, 28.5, 28.1, 26.7, 25.3, 22.8, 21.1, 20.8, 14.1. LRMS (ESI) \(\text{m/z: } [M + H]^+\) calcd for C\(_{56}\)H\(_{72}\)F\(_2\)N\(_{11}\)O\(_5\); 1016.568 found, 1016.566.

**Preparation of N-(3-(((6-((4-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)undecanamide (17)**

![Compound 17](image)

Compound 17 was prepared according to General procedure 3 (COMU) using the corresponding amine (18.6 mg, 0.04 mmol) and carboxylic acid (26 mg, 0.04 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO\(_2\); DCM/MeOH = from 90 : 10 to 80 : 20) providing 32 mg of the desired product (73% yield). \(^1\)H NMR (400 MHz, MeOD) \(\delta\) 8.06 (s, 1H), 7.47 – 7.38 (m, 1H), 7.33 – 7.25 (m, 3H), 7.22 (d, \(J = 7.8\) Hz, 1H), 7.17 (d, \(J = 7.5\) Hz, 1H), 7.03 (d, \(J = 7.5\) Hz, 1H), 6.98 (dd, \(J = 11.4, 7.2\) Hz, 1H), 6.79 (d, \(J = 8.0\) Hz, 1H), 5.69 (s, 1H), 5.13 (dd, \(J = 13.3, 5.1\) Hz, 1H), 4.48 (s, 2H), 4.34 (s, 2H), 4.30 – 4.26 (m, 3H), 3.94 – 3.86 (m, 2H), 3.76 (s, 2H), 3.72 (t, \(J = 6.7\) Hz, 1H), 3.64 (s, 1H), 3.57 (dd, \(J = 10.8, 8.1\) Hz, 2H), 3.49 – 3.43 (m, 1H), 3.41 (s,
2H), 3.26 – 3.16 (m, 6H), 2.96 – 2.84 (m, 1H), 2.81 – 2.73 (m, 1H), 2.46 (qd, J = 13.1, 4.7 Hz, 1H), 2.23 – 2.14 (m, 3H), 1.97 – 1.89 (m, 2H), 1.78 (m, 2H), 1.70 – 1.57 (m, 6H), 1.39 – 1.36 (m, 14H), 1.05 (s, 5H). $^{13}$C NMR (101 MHz, MeOD) δ 176.2, 174.7, 172.5, 172.4, 169.8, 162.6, 160.9, 145.2, 142.5, 140.1, 133.0, 130.6, 129.9, 128.0, 127.5, 127.3, 127.2, 121.3, 113.8, 111.8, 110.3, 107.6, 55.8, 54.4, 53.6, 53.3, 50.0, 47.5, 46.0, 44.4, 43.9, 43.8, 41.9, 37.1, 36.5, 35.7, 32.4, 30.8, 30.6, 30.5, 30.3, 30.2, 30.2, 28.7, 28.2, 27.0, 24.2, 18.7, 17.3, 13.2. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{58}$H$_{76}$F$_2$N$_{11}$O; 1044.600 found, 1044.600.

Preparation of N-((3-(((6-(((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-3-((4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisodolin-4-yl)amino)methyl)-IH-1,2,3-triazol-1-yl)propenamide (18)

Compound 18 was prepared according to General procedure 3 (COMU) using the corresponding amine (48.5 mg, 0.07 mmol) and carboxylic acid (40 mg, 0.07 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 80 : 20) providing 26 mg of the desired product (34% yield). $^1$H NMR (600 MHz, MeOD) δ 7.96 (s, 1H), 7.80 (s, 1H), 7.47 (dd, J = 8.5, 7.1 Hz, 1H), 7.24 – 7.14 (m, 4H), 7.06 – 6.98 (m, 3H), 6.88 (dd, J = 11.2, 7.2 Hz, 1H), 5.61 (s, 1H), 5.03 (dd, J = 12.8, 5.5 Hz, 1H), 4.65 (t, J = 6.4 Hz, 2H), 4.56 (s, 2H), 4.42 (s, 2H), 4.24 (s, 2H), 3.85 – 3.78 (m, 2H), 3.71 (s, 2H), 3.68 (s, 2H), 3.34 (s, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.75 – 2.66 (m, 2H), 2.66 – 2.58 (m, 4H), 2.10 – 2.05 (m, 1H), 1.92 – 1.87 (m, 2H), 1.78 – 1.71 (m, 2H), 1.46 (t, J = 5.7 Hz, 4H), 1.31 – 1.28 (m, 6H), 0.95 (s, 6H). $^{13}$C NMR (151 MHz, MeOD) δ 174.7, 171.9, 171.6, 170.5, 170.3, 169.2, 164.4, 163.4, 159.9, 158.3, 153.1, 151.5, 147.4, 146.4, 140.8, 140.4, 140.1, 137.2, 133.9, 129.7, 127.1, 127.1, 124.6, 120.2, 120.0, 118.3, 112.5, 111.9, 107.4, 107.2, 71.5, 61.6, 56.0, 55.1, 54.6, 53.7, 50.4, 50.2, 47.6, 45.7, 43.9, 41.7, 38.8, 38.7, 37.0, 35.7, 33.1, 32.2, 31.8, 30.8, 29.0, 23.8, 14.5. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{53}$H$_{61}$F$_2$N$_{14}$O$_6$; 1028.159 found, 1028.509.
Preparation of N-(3-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-((4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (19)

Compound 19 was prepared according to General procedure 3 (COMU) using the corresponding amine (18.2 mg, 0.03 mmol) and carboxylic acid (15 mg, 0.03 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO₂; DCM/MeOH = from 90 : 10 to 80 : 20) providing 10 mg of desired product (31% yield). ¹H NMR (500 MHz, CDCl₃) δ 10.24 (bs, 1H), 8.16 (s, 1H), 7.51 – 7.41 (m, 2H), 7.30 – 7.26 (m, 1H), 7.20 (s, 1H), 7.17 (t, J = 7.4 Hz, 2H), 7.11 (d, J = 7.1 Hz, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.81 (s, 1H), 6.67 (t, J = 6.0 Hz, 1H), 6.58 (dd, J = 10.9, 7.0 Hz, 1H), 6.03 (t, J = 6.0 Hz, 1H), 5.37 (s, 1H), 4.89 (dd, J = 12.2, 5.4 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.47 – 4.35 (m, 3H), 4.31 (t, J = 6.9, 2.4 Hz, 2H), 3.71 (s, 2H), 3.70 – 3.62 (m, 2H), 3.54 – 3.45 (m, 2H), 3.28 (s, 2H), 2.90 – 2.69 (m, 3H), 2.56 (bs, 2H), 2.12 (t, J = 7.1, 6.5 Hz, 2H), 1.91 – 1.81 (m, 4H), 1.79 – 1.71 (m, 3H), 1.57 (t, J = 7.8, 7.1 Hz, 2H), 1.50 – 1.43 (m, 2H), 1.26 (m, 16H), 0.94 (s, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 171.9, 169.6, 169.6, 167.8, 162.8, 162.5, 157.2, 156.6, 152.0, 150.1, 146.3, 145.2, 139.4, 138.7, 136.4, 132.5, 129.1, 126.9, 126.3, 126.0, 121.8, 118.9, 117.3, 112.4, 110.9, 105.8, 105.6, 81.1, 56.3, 53.6, 53.0, 50.5, 49.1, 45.7, 43.4, 40.6, 38.9, 36.7, 35.1, 32.1, 31.6, 30.1, 29.9, 28.9, 28.9, 28.5, 28.3, 26.2, 25.6, 23.0, 22.8, 14.3. LRMS (ESI) m/z: [M + H]⁺ calcd for C₅₉H₇₃F₂N₁₄O₆; 1111.580 found, 1111.581.
**Preparation of N-(3-(((6-(4-(4-(4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-11-(4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (20)**

Compound 20 was prepared according to General procedure 3 (COMU) using the corresponding amine (17 mg, 0.03 mmol) and carboxylic acid (15 mg, 0.03 mmol). The reaction mixture was concentrated *in vacuo* and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 80 : 20) providing 12 mg of desired product (37% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 10.08 (bs, 1H), 8.16 (s, 1H), 7.50 – 7.43 (m, 2H), 7.21 (s, 1H), 7.17 (t, J = 7.3 Hz, 2H), 7.10 (d, J = 7.2 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.83 (s, 1H), 6.68 (t, J = 5.9 Hz, 1H), 6.58 (dd, J = 10.9, 7.1 Hz, 1H), 6.07 (s, 1H), 5.93 (bs, 1H), 5.40 – 5.32 (m, 2H), 4.90 (dd, J = 11.9, 5.3 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.42 (m, 3H), 4.31 (t, J = 7.0 Hz, 2H), 3.71 (s, 2H), 3.67 – 3.62 (m, 2H), 3.59 – 3.45 (m, 4H), 3.27 (s, 2H), 2.90 – 2.69 (m, 3H), 2.48 (bs, 2H), 2.18 – 2.13 (m, 2H), 2.05 – 1.97 (m, 2H), 1.93 – 1.83 (m, 4H), 1.80 – 1.71 (m, 2H), 1.65 – 1.55 (m, 4H), 1.44 – 1.39 (m, 4H), 1.28 – 1.25 (m, 12H), 0.92 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.3, 171.9, 169.6, 169.4, 167.9, 167.7, 162.5, 146.3, 139.4, 138.7, 136.3, 132.5, 129.1, 126.8, 126.3, 126.0, 121.7, 117.3, 112.4, 110.9, 56.4, 53.6, 53.0, 50.6, 49.7, 49.1, 45.7, 43.4, 40.6, 38.9, 38.4, 36.7, 35.1, 32.1, 31.6, 30.2, 29.9, 29.5, 29.2, 29.1, 28.8, 28.4, 27.4, 26.3, 25.8, 22.9, 22.8, 14.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{61}$H$_{77}$F$_2$N$_{14}$O$_6$; 1139.610 found, 1139.608.
Preparation of 4-((4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (22)

Compound 22 was prepared according to General procedure 3 (COMU) using the corresponding amine (53 mg, 0.08 mmol) and carboxylic acid (30 mg, 0.08 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO₂; DCM/MeOH = from 95 : 5 to 90 : 10), followed by a second flash column chromatography (SiO₂; EtOAc/MeOH = from 90 : 10 to 80 : 20) providing 32 mg of the desired product (41% yield). ¹H NMR (400 MHz, MeOD) δ 7.99 (s, 1H), 7.55 (dd, J = 8.6, 7.1 Hz, 1H), 7.18 (dd, J = 12.9, 6.6 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.03 (d, J = 7.1 Hz, 1H), 6.88 (dd, J = 11.2, 7.3 Hz, 1H), 5.66 (s, 1H), 5.05 (dd, J = 12.4, 5.4 Hz, 1H), 4.53 (d, J = 13.1 Hz, 1H), 3.97 – 3.90 (m, 3H), 3.72 (s, 2H), 3.60 (s, 2H), 3.43 – 3.35 (m, 6H), 3.15 – 3.08 (m, 2H), 3.03 (t, J = 12.8 Hz, 1H), 2.91 – 2.79 (m, 1H), 2.78 – 2.67 (m, 2H), 2.63 – 2.43 (m, 7H), 2.14 – 2.06 (m, 1H), 2.02 – 1.91 (m, 4H), 1.88 – 1.72 (m, 5H), 1.43 (t, J = 5.6 Hz, 4H), 1.15 – 1.01 (m, 2H), 0.93 (s, 6H). ¹³C NMR (101 MHz, MeOD) δ 174.7, 173.1, 171.7, 170.7, 170.3, 169.3, 164.8, 163.4, 158.3, 148.2, 137.3, 134.0, 120.1, 119.9, 118.1, 111.9, 111.2, 107.4, 107.1, 56.2, 55.3, 54.6, 53.7, 50.5, 50.2, 47.3, 46.9, 43.0, 42.8, 41.8, 39.0, 37.4, 35.9, 32.2, 31.6, 31.2, 31.0, 30.8, 29.1, 25.9, 23.8. LRMS (ESI) m/z: [M + H]⁺ calcd for C₄₉H₆₂F₂N₁₁O₆; 938.484 found, 938.492.
Compound 24 was prepared according to General procedure 3 (COMU) using the corresponding amine (26 mg, 0.042 mmol) and carboxylic acid (17 mg, 0.042 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = 2 : 0.6) providing 32 mg of the desired product (79% yield). $^1$H NMR (400 MHz, MeOD) δ 7.99 (s, 1H), 7.54 (dd, $J = 8.5, 7.1$ Hz, 1H), 7.22 (dd, $J = 12.9, 6.7$ Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 1H), 6.92 (dd, $J = 11.3, 7.2$ Hz, 1H), 5.68 (s, 1H), 5.02 (dd, $J = 13.1, 6.0$ Hz, 1H), 4.52 (d, $J = 13.3$ Hz, 1H), 3.98 – 3.86 (m, 3H), 3.847 – 3.78 (bs, 2H), 3.74 (s, 2H), 3.42 – 3.38 (m, 4H), 3.34 (d, $J = 5.6$ Hz, 2H), 3.21 – 3.13 (m, 2H), 3.05 (t, $J = 12.4$ Hz, 1H), 2.81 – 2.70 (m, 6H), 2.63 – 2.5744 (m, 1H), 2.44 – 2.38 (m, 2H), 2.11 – 2.06 (m, 1H), 1.98 – 1.95 (m, 2H), 1.84 – 1.78 (m, 5H), 1.71 – 1.62 (m, 5H), 1.52 – 1.49 (m, 6H), 1.20 – 1.06 (m, 2H), 0.97 (s, 6H). $^{13}$C NMR (101 MHz, MeOD) δ 174.7, 173.7, 171.7, 170.8, 170.1, 169.3, 164.8, 163.4, 160.5, 158.3, 158.1, 151.0, 148.3, 137.3, 133.9, 120.2, 118.0, 111.8, 111.0, 107.4, 107.1, 56.0, 54.8, 54.6, 53.6, 50.4, 50.2, 47.3, 47.1, 43.2, 43.0, 41.7, 38.3, 37.5, 35.8, 34.0, 32.2, 31.7, 30.8, 30.0, 29.0, 27.6, 26.4, 23.8. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{51}$H$_{66}$F$_2$N$_{11}$O$_6$: 966.545 found, 966.545.

Preparation of 4-((8-(4-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-8-oxooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (25)
Compound 25 was prepared according to General procedure 3 (COMU) using the corresponding amine (50 mg, 0.08 mmol) and carboxylic acid (33 mg, 0.08 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO2; EtOAc/MeOH = from 85 : 15 to 80 : 20) providing 25 mg of the desired product (32% yield). 1H NMR (400 MHz, MeOD) δ 7.99 (s, 1H), 7.53 (dd, J = 8.6, 7.1 Hz, 1H), 7.18 (dd, J = 13.0, 6.6 Hz, 1H), 7.03 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 7.1 Hz, 1H), 6.88 (dd, J = 11.2, 7.2 Hz, 1H), 5.68 (s, 1H), 5.04 (dd, J = 12.5, 5.5 Hz, 1H), 4.53 (d, J = 13.2 Hz, 1H), 4.02 – 3.85 (m, 3H), 3.72 (s, 2H), 3.63 (m, 2H), 3.39 (m, 4H), 3.17 (d, J = 6.4 Hz, 2H), 3.05 (t, J = 12.8 Hz, 1H), 2.85 (ddd, J = 17.6, 14.2, 5.0 Hz, 1H), 2.76 (m, 1H), 2.74 – 2.68 (m, 1H), 2.58 (m, 5H), 2.38 (td, J = 7.4, 4.9 Hz, 2H), 2.10 (td, J = 12.9, 4.9, 2.3 Hz, 1H), 1.98 (m, 2H), 1.81 (m, 6H), 1.67 (t, J = 6.8 Hz, 2H), 1.60 (t, J = 7.1 Hz, 2H), 1.44 (t, J = 5.7 Hz, 6H), 1.38 (m, 5H), 1.32 – 1.28 (m, 2H), 0.94 (s, 6H). 13C NMR (101 MHz, MeOD) δ 174.7, 174.0, 171.7, 170.8, 170.3, 169.3, 164.8, 163.4, 158.3, 148.3, 140.0, 137.3, 133.9, 119.9, 118.0, 111.7, 111.0, 107.4, 107.1, 56.2, 55.2, 54.6, 53.7, 50.5, 50.2, 47.3, 47.1, 43.4, 43.0, 41.7, 38.9, 37.6, 35.9, 34.1, 32.2, 31.7, 30.9, 30.2, 30.2, 30.1, 29.1, 27.8, 26.5, 23.8. LRMS (ESI) m/z: [M + H]+ calcd for C53H70F2N11O6; 994.550 found, 994.549.

Preparation of N-(3-(((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)-4-(2-aminoethyl)piperazin)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoidolin-4-yl)amino)butanamide (29)

![Chemical Structure of 29]

Compound 29 was prepared according to General procedure 3 (HATU) using the corresponding amine (74 mg, 0.11 mmol) and carboxylic acid (40 mg, 0.11 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO2; EtOAc/MeOH = 90 : 10) providing 61 mg of the desired product (59% yield). 1H NMR (500 MHz, MeOD) δ 8.57 (s, 1H), 8.03 (s, 1H), 7.57 (dd, J = 8.4, 7.2 Hz, 1H), 7.22 (dd, J = 12.9, 6.7 Hz, 1H), 7.12 (d, J = 8.5, 1H), 7.06 (d, J = 7.0, 1H), 6.92 (dd, J = 11.1, 7.3 Hz, 1H), 5.73 (s,
1H), 5.07 (dd, J = 12.5, 5.4 Hz, 1H), 3.96 (m, 2H), 3.76 (s, 2H), 3.71 (s, 2H), 3.66-3.53 (m, 4H), 3.50-3.37 (m, 9H), 2.91-2.61 (m, 8H), 2.59 (t, J = 6.2, 2H), 2.53 (t, J = 6.8, 1H), 2.48 (m, 4H), 2.12 (m, 1H), 1.99 (m, 4H), 1.84 (m, 2H), 1.49 (t, J = 5.6, 4H), 1.21 (s, 3H), 0.97 (s, 6H).

$^{13}$C NMR (101 MHz, MeOD) $\delta$ 173.2, 171.8, 170.2, 169.3, 168.8, 167.8, 163.0, 162.1, 158.9, 156.8, 156.5, 152.1, 149.7, 148.5, 146.7, 138.9, 138.8, 135.8, 132.5, 118.7, 118.5, 116.7, 110.5, 109.8, 106.0, 105.7, 81.23, 56.2, 54.7, 53.7, 53.1, 52.7, 52.3, 49.0, 48.8, 45.2, 41.3, 41.3, 40.3, 37.6, 37.3, 34.4, 30.8, 29.47, 27.6, 24.4, 22.4. LCMS (ESI) m/z: [M + H]$^+$ calcd for C_{49}H_{63}F_{12}O_{6}; 953.469, found: 953.584.

Preparation of N-((3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanamide (30)

Compound 30 was prepared according to General procedure 3 (HATU), the corresponding amine (74 mg, 0.11 mmol) and carboxylic acid (42 mg, 0.11 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = 90 : 10) providing 53 mg of desired product (50% yield). $^1$H NMR (500 MHz, MeOD) $\delta$ 8.58 (s, 1H), 8.02 (s, 1H), 7.92 (s, 1H), 7.56 (dd, J = 8.2, 7.3 Hz, 1H), 7.20 (dd, J = 12.9, 6.5 Hz, 1H), 7.06 (dd, J = 10.4, 8.7 Hz, 2H), 6.90 (dd, J = 11.1, 7.2 Hz, 1H), 5.74 (s, 1H), 5.06 (dd, J = 12.4, 5.4 Hz, 1H), 3.97 (m, 2H), 3.75 (s, 2H), 3.66-3.54 (m, 6H), 3.49-3.36 (m, 8H), 2.91-2.67 (m, 3H), 2.60 (t, J = 6.1, 2H); 2.59-2.46 (m, 7H), 2.44 (t, J = 7.0, 2H), 2.12 (m, 1H), 2.01 (m, 2H), 1.84 (m, 2H), 1.70 (m, 4H), 1.54-1.42 (m, 6H), 1.31 (s, 3H), 0.93 (s, 6H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 173.2, 172.5, 170.2, 169.4, 168.8, 167.9, 163.0, 162.1, 158.8, 156.8, 156.4, 146.9, 138.6, 135.8, 132.5, 118.6, 118.4, 116.6, 110.3, 109.6, 105.9, 105.7, 78.0, 56.2, 54.7, 53.8, 53.1, 52.9, 52.4, 52.3, 49.1, 48.7, 45.4, 41.7, 41.3, 40.3, 37.6, 37.6, 34.4, 32.3, 30.8, 29.3, 28.5, 27.6, 26.1, 24.8, 22.4. LCMS (ESI) m/z: [M + H]$^+$ calcd for C_{51}H_{66}F_{2}N_{12}O_{6}; 980.520, found: 981.584.
Preparation of \( \text{N-}((6-(4-((4,4\text{-dimethylpiperidin-1-yl})\text{methyl})-2,5\text{-difluorophenyl})\text{-2-oxo-1,4,9-triaza}\text{spiro}[5.5]\text{undecan-9-yl})\text{pyrimidin-4-yl})\text{-4-(2-aminoethyl)piperazin})\text{-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)octanamide (31)} \)

Compound 31 was prepared according to General procedure 3 (HATU) using the corresponding amine (74 mg, 0.11 mmol) and carboxylic acid (45 mg, 0.11 mmol). The reaction mixture was concentrated \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO\(_2\); EtOAc/MeOH = 90 : 10) providing 73 mg of desired product (66% yield). \(^1\)H NMR (500 MHz, DMSO) \( \delta \) 8.56 (s, 1H), 8.03 (s, 1H), 7.56 (dd, \( J = 8.3, 7.0 \text{ Hz, 1H} \)), 7.27 (dd, \( J = 12.6, 6.4 \text{ Hz, 1H} \)), 7.05 (dd, \( J = 8.5, 6.3 \text{ Hz, 2H} \)), 6.95 (dd, \( J = 11.1, 7.2 \text{ Hz, 1H} \)), 5.74 (s, 1H), 5.07 (dd, \( J = 12.6, 5.5 \text{ Hz, 1H} \)), 3.95 (m, 2H), 3.90 (s, 2H), 3.77 (s, 2H), 3.70-3.55 (m, 4H), 3.50-3.39 (m, 8H), 2.89-2.71 (m, 6H), 2.66 (s, 1H), 2.63 (t, \( J = 6.2, 2H \)), 2.53 (m, 4H), 2.40 (t, \( J = 7.4, 1H \)), 2.13 (m, 1H), 2.00 (m, 2H), 1.85 (m, 2H), 1.70 (m, 2H), 1.62 (m, 2H), 1.55 (t, \( J = 5.3, 4H \)), 1.50-1.37 (m, 9H), 1.31 (s, 6H), 1.01 (s, 6H). \(^{13}\)C NMR (125 MHz, DMSO) \( \delta \) 173.2, 172.7, 170.2, 169.4, 168.7, 167.9, 163.0, 162.1, 158.8, 156.8, 156.5, 151.8, 146.9, 135.8, 132.5, 119.0, 116.6, 110.3, 109.6, 106.0, 105.8, 56.5, 54.6, 53.3, 53.1, 52.9, 52.4, 52.2, 48.9, 48.8, 45.4, 41.9, 41.2, 40.2, 39.0, 37.6, 37.4, 32.5, 30.8, 29.3, 28.7, 27.5, 26.3, 25.0, 22.4. LCMS (ESI) m/z: [M + H]\(^+\) calcd for C\(_{53}\)H\(_{71}\)F\(_2\)N\(_{12}\)O\(_6\): 1009.559, found: 1009.712.
Preparation of \(N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-\text{oxo}-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)4-(5-bromopyrimidin-2-yl)piperazine-4-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butanamide (33)

Compound 33 was prepared according to General procedure 3 (HATU) using the corresponding deprotected amine (31 mg, 0.04 mmol) and carboxylic acid (14 mg, 0.04 mmol). The reaction mixture was concentrated \textit{in vacuo} and the crude product was purified using flash column chromatography (SiO\(\mathbf{2};\) EtOAc/MeOH = 90 : 10) providing 23 mg of the desired product (53\% yield). \(^1\)H NMR (400 MHz, CDCl\(\mathbf{3}\)) \(\delta\) 8.13 (s, 3H), 7.63-7.47 (m, 2H), 7.09 (d, \(J = 7.0\) Hz, 1H), 6.99 (d, \(J = 8.5\) Hz, 1H), 6.61 (dd, \(J = 11.3, 7.1\) Hz, 1H), 6.47 (s, 1H), 6.32 (t, \(J = 5.6\) Hz, 1H), 5.51 (s, 1H), 4.90 (dd, \(J = 12.2, 5.5\) Hz, 1H), 3.95 (s, 2H), 3.82-3.61 (m, 9H), 3.57-3.49 (m, 2H), 3.46-3.32 (m, 4H), 3.11 (m, 3H), 2.98-2.93 (m, 4H), 2.82-2.68 (m, 6H), 2.49 (t, \(J = 6.6\) Hz, 1H), 2.39-1.89 (m, 18H), 1.88-1.77 (m, 3H), 1.68 (s, 4H), 1.01 (s, 6H). \(^{13}\)C NMR (176 MHz, DMSO) \(\delta\) 172.8, 170.4, 170.1(3x), 168.8, 167.3, 166.4, 166.5, 163.2, 157.5, 157.3, 155.9, 151.2, 147.0, 146.4, 138.0, 136.3, 132.2, 117.8, 117.3, 110.4, 109.1, 106.5, 59.8, 54.9, 54.8, 54.1, 53.0, 52.8, 52.7, 52.5, 49.2, 49.1, 48.6, 48.5, 44.8, 41.6, 41.1, 40.0, 38.3, 34.6, 31.0, 29.4, 29.0, 28.1, 24.2, 22.1. LCMS (ESI) m/z: [M + H]\(^{+}\) calcd for C\(_{57}H_{73}F_{2}N_{16}O_{6}\); 1115.582, found: 1115.654.
Preparation of N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)pyridin-1-yl)-6-oxohexyl)amino)-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (me-24)

Compound **me-14** was prepared according to General procedure 3 (COMU) using the corresponding amine (56 mg, 0.09 mmol) and carboxylic acid (40 mg, 0.1 mmol). The reaction mixture was concentrated *in vacuo* and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = 90 : 10) providing 43 mg of desired product (41% yield).$^1$H NMR (400 MHz, MeOD) $\delta$ 7.98 (s, 1H), 7.49 (dd, $J = 8.6, 7.1$ Hz, 1H), 7.30 – 7.13 (m, 6H), 7.03 – 6.96 (m, 2H), 6.90 (dd, $J = 11.3, 7.2$ Hz, 1H), 5.61 (s, 1H), 5.06 (dd, $J = 12.8, 5.4$ Hz, 1H), 4.45 (s, 2H), 4.34 (d, 2H), 3.86 – 3.79 (m, 4H), 3.72 (s, 2H), 3.39 – 3.35 (m, 4H), 3.11 (s, 3H), 2.86 (dd, $J = 7.1, 3.7$ Hz, 2H), 2.76 (s, 4H), 2.72 – 2.60 (m, 1H), 2.33 (t, $J = 7.2$ Hz, 2H), 2.10 – 2.03 (m, 1H), 1.97 – 1.86 (m, 5H), 1.79 – 1.69 (m, 2H), 1.50 (d, $J = 7.2$ Hz, 5H), 0.97 (s, 6H). $^{13}$C NMR (101 MHz, MeOD) $\delta$ 175.1, 173.7, 171.4, 170.7, 170.1, 169.3, 164.5, 163.4, 163.0, 158.3, 148.1, 140.6, 137.3, 133.9, 129.8, 127.4, 127.1, 127.1, 127.1, 119.9, 118.0, 111.9, 111.1, 107.2, 54.6, 53.6, 50.8, 50.4, 49.6, 49.5, 49.4, 49.3, 49.2, 49.1, 49.0, 48.9, 48.8, 48.6, 48.4, 44.0, 42.8, 41.7, 38.3, 35.7, 34.1, 32.5, 30.8, 29.0, 27.3, 26.4, 23.0. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{52}$H$_{62}$F$_2$N$_{11}$O$_6$; 974.485 found, 974.485.

Preparation of 4-((6-(4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-6-oxohexyl)amino)-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (me-24)
Compound **me-24** was prepared according to General procedure 3 (COMU) using the corresponding amine (25 mg, 0.040 mmol) and carboxylic acid (17 mg, 0.04 mmol). The reaction mixture was concentrated *in vacuo* and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 100:5 to 100:10) providing 6 mg of desired product (15% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.14 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.17-7.13 (m, 1H), 7.07 (d, J = 7.1 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 6.59 (dd, J = 10.9, 7.0 Hz, 1H), 6.38 (s, 1H), 6.23 – 6.21 (m, 1H), 5.44 (s, 1H), 4.93 – 4.89 (m, 1H), 4.66 (d, J = 13.3 Hz, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.76 – 3.51 (m, 4H), 3.31 – 3.13 (m, 6H), 3.04 – 2.95 (m, 2H), 2.78 – 2.73 (m, 2H), 2.55 – 2.42 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 2.09 – 2.07 (m, 1H), 2.01 – 1.92 (m, 2H), 1.87 – 1.77 (m, 4H), 1.72 – 1.62 (m, 4H), 1.50 – 1.39 (m, 6H), 1.18 – 1.10 (m, 2H), 0.92 (s, 6H), 0.86 – 0.77 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 169.9, 169.2, 167.9, 167.8, 163.3, 163.1, 162.5, 157.9, 147.1, 136.3, 132.7, 118.8, 116.7, 111.5, 110.1, 105.9, 56.6, 54.7, 53.6, 53.1, 49.8, 49.8, 47.1, 45.6, 42.6, 41.7, 40.4, 38.4, 36.6, 35.5, 33.2, 32.1, 30.8, 29.9, 29.8, 29.3, 28.4, 27.4, 26.9, 25.1, 22.3. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{52}$H$_{68}$F$_2$N$_{11}$O$_6$; 980.532 found, 980.531.

**Preparation of N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)dione (32)**

![Diagram of Compound 32](image)

Compound **32** was prepared according to General procedure 1 using compounds **57** (86 mg, 0.22 mmol), **39** (75 mg, 0.15 mmol) and DIPEA (0.6 mmol). The reaction mixture was concentrated *in vacuo* and the crude product was purified using flash column chromatography (SiO$_2$; EtOAc/MeOH = 90 : 10) providing 57 mg of the desired product (44% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (s, 1H), 7.5 (t, J = 7.7 Hz, 1H), 7.38 (d, J = 7.0 Hz, 1H), 7.21-7.09 (m, 4H), 6.96 (s, 1H), 6.58 (dd, J =10.7, 7.3 Hz, 1H), 5.55 (s, 1H), 5.45 (s, 1H), 4.95 (m, 1H), 3.72 (m, 4H), 3.64 (m, 2H), 3.52 (m, 2H), 3.34 (m, 6H), 3.28 (m, 2H), 2.91-2.65 (m, 9H), 2.45 (s, 4H), 2.09 (m, 1H), 1.89 (m, 4H), 1.41 (s, 4H), 0.91 (s, 6H).$^{13}$C NMR (101 MHz, CDCl$_3$) δ 171.4, 168.7, 167.9, 167.3, 166.7, 163.0, 162.4, 158.5, 157.7, 156.1, 152.1, 150.2, 149.7, 138.0.
135.6, 134.1, 123.3, 118.8, 117.4, 115.7, 105.7, 105.4, 80.7, 56.5, 56.3, 54.3, 53.4, 52.9, 52.7, 50.9, 49.6, 40.1, 38.0, 35.3, 31.4, 28.2, 22.7. LCMS (ESI) m/z: [M + H]+ calcd for C_{45}H_{55}F_{11}N_{11}O_{5}; 868.439, found: 868.554.

**Preparation of 5-((4-(4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (23)**

The reaction sequence started with General procedure 6 using 5-fluoro-thalidomide (813 mg, 2.95 mmol) and the corresponding tert-butyl ester (469 mg, 2.95 mmol). The volatiles were then removed in vacuo and the crude product was used in the next synthetic step without further purification. To a stirred solution of the tert-butyl ester (1 eq) in DCM (0.5 M) was added TFA (10 eq). The resulting reaction mixture was stirred at rt until full completion. The free carboxylic acid was used in the next step without further purification. (Monitored by TLC). Compound 23 was prepared according to General procedure 3 (COMU) using the corresponding amine (79 mg, 0.125 mmol) and carboxylic acid (44 mg, 0.125 mmol). The reaction mixture was concentrated in vacuo and the crude product was purified using flash column chromatography (SiO_{2}; DCM/MeOH = 2 : 0.1 to 2 : 0.2), followed by a second flash column chromatography (SiO_{2}; EtOAc/MeOH = 2 : 0.4) providing 7 mg of the desired product (0.2% yield after three steps). $^1$H NMR (400 MHz, MeOD) δ 7.99 – 7.96 (bs, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 12.9, 6.6 Hz, 1H), 6.98 (d, J = 2.2 Hz, 1H), 6.91 (dd, J = 11.3, 7.2 Hz, 1H), 6.86 (dd, J = 8.4, 2.2 Hz, 1H), 5.67 (s, 1H), 5.03 (dd, J = 12.8, 5.5 Hz, 1H), 4.60 (s, 4H), 4.54 (d, J = 13.7 Hz, 1H), 3.97 – 3.90 (m, 4H), 3.74 – 3.72 (m, 4H), 3.48 – 3.43 (m, 4H), 3.30 – 3.26 (m, 1H), 3.15 – 3.12 (m, 2H), 3.06 – 3.01 (m, 1H), 2.88 – 2.80 (m, 2H), 2.75 – 2.59 (m, 8H), 2.55 – 2.46 (m, 2H), 2.08 (ddt, J = 13.0, 5.6, 2.8 Hz, 1H), 2.00 – 1.91 (m, 3H), 1.86 – 1.79 (m, 3H), 1.50 – 1.46 (m, 4H), 1.14 – 1.06 (m, 2H), 0.96 (s, 6H). $^{13}$C NMR (151 MHz, MeOD) δ 174.7, 173.2, 171.8, 170.2, 169.6, 169.3, 164.9, 164.7, 163.2, 160.0, 158.4, 158.3, 156.1, 153.1, 151.8, 140.6, 136.0, 126.6, 120.2, 118.2, 116.8, 107.4, 107.2, 106.7, 56.1, 55.0, 54.6, 53.6, 50.4, 50.3, 49.6.
Preparation of 4-((2-(4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21)

Compound 21 was prepared according to General procedure 6 with 4-fluoro-thalidomide (14 mg, 0.052 mmol, 1 eq) and the corresponding amine (40 mg, 0.052 mmol, 1 eq). The reaction was stirred at 80°C for 24 hours, evaporated and the crude product was purified using flash column chromatography (SiO$_2$; DCM/MeOH = from 90 : 10 to 87 : 13), followed by a second flash column chromatography (SiO$_2$; EtOAc/MeOH = from 90 : 10 to 80 : 20) providing 23 mg of the desired product (48% yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 11.09 (s, 1H), 8.17 (s, 1H), 7.98 (s, 1H), 7.60 (t, $J$ = 7.8 Hz, 1H), 7.19 – 7.08 (m, 3H), 7.06 (d, $J$ = 7.0 Hz, 1H), 6.93 (dd, $J$ = 11.5, 7.4 Hz, 1H), 6.78 (bs, 1H), 5.66 (s, 1H), 5.06 (dd, $J$ = 12.9, 5.4 Hz, 1H), 4.38 (d, $J$ = 12.8 Hz, 1H), 4.16 (dd, $J$ = 9.5, 4.5 Hz, 1H), 3.86 (d, $J$ = 15.9 Hz, 3H), 3.59 (s, 2H), 3.43 (s, 2H), 3.26 (s, 3H), 3.18 – 3.08 (m, 2H), 3.00 (t, $J$ = 12.4 Hz, 1H), 2.95 – 2.83 (m, 1H), 2.69 – 2.56 (m, 2H), 2.34 (s, 4H), 2.08 – 1.97 (m, 1H), 1.85 – 1.60 (m, 9H), 1.22 – 1.08 (m, 5H), 1.07 – 0.96 (m, 2H), 0.87 (s, 6H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 172.9, 170.1, 168.8, 167.4, 166.6, 166.0, 163.5, 158.0, 157.8, 157.3, 151.3, 149.4, 145.4, 136.2, 132.0, 118.5, 118.3, 116.2, 110.8, 109.5, 106.5, 106.5, 106.3, 106.3, 69.8, 54.7, 52.8, 52.7, 49.0, 48.6, 45.5, 43.7, 41.6, 40.4, 37.9, 35.7, 35.5, 34.6, 31.0, 29.9, 29.3, 29.1, 29.0, 28.1, 22.2, 14.0. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{49}$H$_{62}$F$_2$N$_{11}$O$_6$; 938.485 found, 938.495.
Preparation of 4-(4-(4-(((6-4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-
2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)phenyl)piperazin-1-
yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (34)

To a stirred solution of compound 47a (150 mg, 0.193 mmol) in DCM (1.9 mL) was added
TFA (0.147 mL, 1.9 mmol). The reaction mixture was stirred at rt for two hours. The volatiles
were removed in vacuo and compound 47 was used in the next step without further purification.
The final compound 34 was prepared using General procedure 6 using 47 (57 mg, 0.086 mmol)
and 4-fluoro thalidomide (0.024 g, 0.083 mmol). The crude product was purified using flash column chromatography (SiO2; DCM/MeOH = from 100 : 5 to 100 : 10) followed
by preparative TLC (EtOAc/MeOH 2 : 0.3) providing 5 mg of desired product (0.01% yield).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.16 (s, 1H), 7.63 (dd, $J = 8.4$, 7.2 Hz, 1H), 7.44 (d, $J = 7.3$ Hz,
1H), 7.27 – 7.25 (m, 1H), 7.22 (dd, $J = 8.4$ Hz, 2H), 6.96 (d, $J = 8.7$ Hz, 2H), 6.60 (dd, $J = 10.9$,
7.0 Hz, 1H), 6.24 (s, 1H), 5.43 (s, 1H), 4.97 (dd, $J = 12.4$, 5.4 Hz, 1H), 4.38 (d, $J = 5.6$ Hz, 2H),
3.74 (s, 2H), 3.69 – 3.63 (m, 2H), 3.60 – 3.55 (m, 2H), 3.53 – 3.49 (m, 3H), 3.39 (t, $J = 5.1$ Hz,
3H), 2.91 – 2.70 (m, 4H), 2.14 – 2.12 (m, 1H), 1.96 – 1.92 (m, 2H), 1.80 – 1.76 (m, 2H), 0.96
(s, 6H), 0.89 – 0.83 (m, 5H). $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$ 171.2, 168.4, 167.4, 162.4, 150.8,
150.4, 150.2, 135.9, 134.3, 129.0, 128.5, 123.5, 117.9, 116.8, 116.2, 105.6, 81.0, 56.4, 53.6,
52.9, 51.2, 49.6, 49.3, 45.5, 41.1, 40.4, 37.2, 35.4, 32.1, 31.6, 29.9, 29.8, 29.5, 28.2, 27.4, 22.9,
14.3, 1.2. LRMS (ESI) m/z: [M + H]$^+$ calcd for C$_{50}$H$_{58}$F$_2$N$_{11}$O$_5$; 930.486 found, 930.461.
Preparation of 4-(4-(2-(4-(((6-(4-(4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (35)

Compound 50 (61 mg, 0.09 mmol, 1 eq) and tert-butyl piperazine-1-carboxylate (25 mg, 0.135 mmol, 1.5 eq) were dissolved in 1 mL of DMSO. TEA (3 eq) was added to the mixture and the reaction was stirred at 50°C overnight. The volatiles were then removed in vacuo and the crude product was used in the next synthetic step without further purification. To a stirred solution of the Boc-protected amine (1 eq) in DCM (0.5 M) was added TFA (10 eq). The resulting reaction mixture was stirred at rt until full completion. The free amine 51 was used in the next step without further purification (Monitored by TLC). Compound 35 was prepared according to General procedure 6 using 51, 4-fluoro thalidomide (9 mg, 0.09 mmol, 1 eq) and DIPEA (3 eq). The reaction mixture was stirred at 110 °C for 1 hour. The volatiles were then removed in vacuo and the mixture was purified with flash column chromatography twice (SiO₂; DMC/MeOH = 90:10m, then EtOAc/MeOH = 2:1). Affording 5 mg of desired product (5% yield after three steps). ¹H NMR (400 MHz, MeOD) δ 7.98 (s, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.37 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.18 (dd, J = 13.0, 6.6 Hz, 1H), 6.87 (dd, J = 11.2, 7.2 Hz, 1H), 5.69 (s, 1H), 5.09 (dd, J = 12.5, 5.4 Hz, 1H), 4.55 – 4.50 (m, 1H), 4.18 (d, J = 11.5 Hz, 1H), 3.91 – 3.88 (m, 2H), 3.71 (s, 2H), 3.60 (s, 2H), 3.44 – 3.33 (m, 8H), 3.21 – 3.17 (m, 3H), 3.07 (t, J = 12.6 Hz, 1H), 2.91 – 2.63 (m, 8H), 2.57 – 2.47 (m, 4H), 2.13 – 2.09 (m, 1H), 1.97 – 1.76 (m, 7H), 1.21 – 1.11 (m, 2H), 0.93 (s, 6H). ¹³C NMR (126 MHz, MeOD) δ 174.6, 171.6, 170.2, 169.9, 168.9, 168.0, 164.9, 163.4, 160.1, 158.3, 158.2, 153.3, 151.5, 136.9, 135.5, 130.9, 130.2, 129.9, 124.7, 120.2, 119.9, 118.8, 116.3, 107.4, 107.2, 61.7, 56.1, 55.1, 54.6, 54.2, 53.7, 51.9, 50.5, 47.2, 47.0, 43.3, 41.7, 38.7, 37.7, 36.5, 35.8, 33.1, 32.2, 31.8, 30.9, 30.8, 30.3, 29.0, 23.7, 14.4. LRMS (ESI) m/z: [M + H]+ for C₅₁H₆₅F₂N₁₂O₆; 979.511 found, 979.512.
Preparation of 9-(4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)nonanamide (26)

Intermediates 54 was prepared according to General procedure 9 starting from 52 (40 mg, 83 µmol, 1 eq) and sodium azide (6.5 mg, 100 µmol, 1.2 eq). The desired product was obtained in quantitative yield and used as such without further purification (37 mg).

20 mg of compound 54 (0.065 mmol, 1 eq) were dissolved in 1 mL of THF, followed by the addition of 40 (25 mg, 0.065 mmol, 1 eq), anhydrous CuSO₄ (4 mg, 0.5 eq) and sodium ascorbate (14 mg, 1.1 eq). The resulting reaction mixture was stirred at 70°C (oil bath temperature) for 48h. The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO₂; DCM/MeOH = 90 : 10). 27 mg of the resulting product were dissolved in DCM and stirred overnight with 500 mg of SiliaMetS® TAAcONa. The mixture was then filtered and washed with DCM. The solution was evaporated affording 20 mg of desired product (45% yield).

$^1$H NMR (400 MHz, DMSO) δ 11.02 (s, 1H), 9.76 (s, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.91 (s, 1H), 7.81 (dd, $J = 7.1, 1.9$ Hz, 1H), 7.53 – 7.43 (m, 3H), 7.22 – 7.11 (m, 0H), 7.08 (t, $J = 5.9$ Hz, 1H), 6.93 (dd, $J = 11.5, 7.3$ Hz, 1H), 5.71 (s, 1H), 5.14 (dd, $J = 13.3, 5.1$ Hz, 1H), 4.45 (d, $J = 5.8$ Hz, 2H), 4.35 (dd, $J = 27.0, 17.5$ Hz, 2H), 4.29 (t, $J = 7.1$ Hz, 2H), 3.84 (d, $J = 13.5$ Hz, 2H), 3.59 (s, 2H), 3.44 (s, 2H), 3.31 (s, 2H), 3.25 (s, 2H), 2.92 (ddd, $J = 17.2, 13.5, 5.3$ Hz, 1H), 2.67 – 2.58 (m, 1H), 2.41 – 2.27 (m, 6H), 2.08 – 1.96 (m, 1H), 1.81 – 1.72 (m, 4H), 1.69 – 1.53 (m, 4H), 1.36 – 1.25 (m, 10H), 0.87 (s, 6H).

$^{13}$C NMR (101 MHz, DMSO) δ 172.9, 171.4, 171.1, 167.8, 166.5, 163.0, 161.6, 157.4, 155.7, 145.3, 133.8, 133.67, 132.7, 128.6, 125.2, 122.6, 119.0, 106.5, 103.4, 69.8, 54.8, 52.8, 52.6, 51.5, 49.2, 49.04, 46.5, 35.8, 34.6, 31.2, 29.8, 28.6, 28.3, 28.1, 25.8, 25.0, 22.6. LRMS (ESI) m/z: [M + H]$^+$ calcd for C₅₁H₆₆F₂N₁₃O₅; 978.527 found, 978.528.
Preparation of 11-(4-(((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-ylamino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoinolin-4-yl)undecanamide (27)

Compound 55 was prepared according to General procedure 9 starting from 53 (40 mg, 79 µmol, 1 eq) and sodium azide (6.2 mg, 95 µmol, 1.2 eq). The desired product was obtained in quantitative yield and used as such without further purification (37 mg).

30 mg of compound 58 (0.065 mmol, 1 eq) were dissolved in 1 mL of THF, followed by the addition of 40 (35 mg, 0.065 mmol, 1 eq), anhydrous CuSO₄ (5 mg, 0.5 eq) and sodium ascorbate (20 mg, 1.1 eq). The resulting reaction mixture was stirred at 40°C (oil bath temperature) for 48h. The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO₂; DCM/MeOH = 90 : 10). 20 mg of the resulting product were dissolved in 2 mL of DCM and stirred overnight with 400 mg of SiliaMetS® TAAcONa. The mixture was then filtered and washed with DCM. The solution was evaporated affording 16 mg of desired product (25% yield). ¹H NMR (400 MHz, MeOD) δ 8.02 (d, J = 0.8 Hz, 1H), 7.85 (s, 1H), 7.70 (dd, J = 8.0, 1.0 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.7 Hz, 1H), 7.21 (dd, J = 12.9, 6.7 Hz, 1H), 6.90 (dd, J = 11.3, 7.3 Hz, 1H), 5.74 (d, J = 1.0 Hz, 1H), 5.16 (dd, J = 13.3, 5.2 Hz, 1H), 4.54 (s, 2H), 4.47 (d, J = 2.3 Hz, 2H), 4.35 (t, J = 6.9 Hz, 2H), 3.94 – 3.85 (m, 2H), 3.76 (s, 2H), 3.73 (s, 2H), 3.47 – 3.33 (m, 2H), 2.91 (ddd, J = 18.3, 13.4, 5.3 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.70 (s, 4H), 2.42 (t, J = 7.5 Hz, 2H), 2.24 – 2.13 (m, 1H), 1.99 – 1.90 (m, 2H), 1.91 – 1.73 (m, 4H), 1.70 (p, J = 7.4 Hz, 2H), 1.48 (t, J = 5.7 Hz, 4H), 1.29 (q, J = 4.8 Hz, 13H), 0.96 (s, 6H). ¹³C NMR (101 MHz, MeOD) δ 174.7, 174.6, 172.1, 171.1, 170.1, 164.3, 163.5, 158.4, 146.9, 136.3, 134.7, 134.0, 130.1, 127.8, 124.1, 121.4, 107.5, 107.3, 56.0, 54.9, 54.6, 53.6, 51.3, 50.44, 41.7, 38.4, 37.5, 37.3, 35.8, 32.4, 31.2, 31.0, 30.8, 30.3, 30.3, 30.2, 29.9, 29.0, 28.1, 27.31, 26.7, 24.2, 23.7. LRMS (ESI) m/z: [M + H]⁺ calcd for C₅₃H₇₀F₂N₁₃O₅; 1006.559 found, 1006.558.
Preparation of 4-(((1-(12-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)dodecyl)-1H-1,2,3-triazol-4-yl)methyl)(amino)-2-(2,6-dioxygenpiperidin-3-yl)isoindoline-1,3-dione (28)

For the synthesis of 28, intermediate 41 was prepared following General procedure 1 using compound 39 (37 mg, 0.073 mmol) and 12-azidododecan-1-amine (35 mg, 0.15 mmol, 2 eq). The volatiles were removed in vacuo and the crude product was purified using flash column chromatography (SiO2; DCM/MeOH = 90 : 10) providing 20 mg of compound 41. 18 mg of compound 41 (0.025 mmol, 1 eq) were dissolved in 1 mL of THF, followed by the addition of 56 (16 mg, 0.05 mmol, 2 eq), anhydrous CuSO4 (4 mg) and sodium ascorbate (20 mg, 1.1 eq). The resulting reaction mixture was stirred at 40°C (oil bath temperature) for 48h. The volatiles were then removed in vacuo and the crude product was purified using flash column chromatography (SiO2; EtOAc/MeOH = from 90:10 to 80:20), followed by preparative TLC (DCM/MeOH 90 : 10). 14 mg of the resulting product were dissolved in and stirred overnight with 200 mg of SiliaMetS® TAAcONa. The mixture was then filtered and washed with DCM. The yellow solution was evaporated affording 10 mg of the desired product (13% yield after 2 steps). 1H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.20 (bs, 1H), 8.00 (s, 1H), 7.97 (s, 1H), 7.56 (dd, J = 8.6, 7.1 Hz, 1H), 7.19 (bs, 1H), 7.15 (d, J = 8.6 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.96 (bs, 1H), 6.61 (t, J = 5.6 Hz, 1H), 5.60 (s, 1H), 5.06 (dd, J = 12.9, 5.3 Hz, 1H), 4.58 (d, J = 6.0 Hz, 2H), 4.29 (t, J = 7.0 Hz, 2H), 3.89 – 3.81 (m, 2H), 3.61 (s, 2H), 3.28 (s, 2H), 3.20 – 3.09 (m, 2H), 2.95 – 2.81 (m, 1H), 2.56 (s, 3H), 2.07 – 1.96 (m, 2H), 1.82 – 1.70 (m, 4H), 1.70 – 1.59 (m, 3H), 1.50 – 1.41 (m, 4H), 1.38 – 1.29 (m, 4H), 1.27 – 1.06 (m, 19H), 0.89 (s, 6H). 13C NMR (101 MHz, DMSO) δ 172.8, 170.1, 168.8, 167.3, 163.3, 145.8, 144.4, 136.1, 132.1, 122.7, 117.6, 110.9, 109.7, 69.8, 52.6, 49.3, 48.6, 37.7, 34.6, 31.3, 31.0, 29.7, 29.0, 29.0, 28.9, 28.9, 28.8, 28.3, 26.5, 25.8, 22.2, 14.0. LRMS (ESI) m/z: [M + H]+ calcd for C54H72F2N13O5: 1020.574 found, 1020.575.
References


$^1$H and $^{13}$C NMR spectra of target compounds 1-35, me-14 and me-24

$N$-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-3-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisodolin-4-yl)amino)ethoxy)ethoxy)propenamide (1)

$^1$H NMR (DMSO, 500 mHz)

$^{13}$C NMR (DMSO, 126 mHz)
$N$-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-3-(2-(2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)ethoxy)ethoxy)ethoxy)propenamide (2)

$^1$H NMR (DMSO, 500 MHz)

$^1$C NMR (DMSO, 126 MHz)
$N$-$(3-((6-(4-(4,4\text{-}dimethylpiperidin\text{-}1\text{-}yl)methyl)phenyl)-2\text{-}oxo-1,4,9\text{-}triazaspiro[5.5]undecan\text{-}9\text{-}yl)pyrimidin\text{-}4\text{-}yl)amino)propyl)-1-((2-(2,6-dioxopiperidin\text{-}3\text{-}yl)-1,3-dioxoisoiindolin\text{-}4\text{-}yl)amino)-3,6,9,12\text{-}tetraoxapentadecan\text{-}15\text{-}amide$ (3)
N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-
triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide (4)

$^1$H NMR (DMSO, 500 mHz)

$^{13}$C NMR (DMSO, 126 mHz)
N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)nonanamide (5)

1H NMR (DMSO, 400 mHz)

13C NMR (CD3OD, 151 mHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triaza[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)undecanamide (6)

$^1$H NMR (DMSO, 500 mHz)

$^{13}$C NMR (DMSO, 126 mHz)
N-(3-((6-(4-(4-(4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-15-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)pentadecanamide (7)

\(^1\)H NMR (CD\(_3\)OD, 400 mHz)

\(^{13}\)C NMR (CD\(_3\)OD, 101 mHz)
$N$-$(3-((6-(4-((4,4$-dimethyl)piperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-(4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (8)

$^1$H NMR (CD$_3$OD, 600 mHz)

$^1$C NMR (CD$_3$OD, 151 mHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (9)

$^1$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 101 mHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)nonanamide (10)

$^1$H NMR (CDCl$_3$, 400 mHz)

$^{13}$C NMR (CDCl$_3$, 101 mHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisodolin-4-yl)amino)undecanamide (11)

$^1$H NMR (DMSO, 400 MHz)

$^{13}$C NMR (DMSO, 101 MHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (12)

$^1$H NMR (CDCl$_3$, 400 MHz)

$^13$C NMR (CDCl$_3$, 101 MHz)
$N$-((3-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (13)

$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoloindolin-4-yl)amino)butanamide (14)

$^1$H NMR (CDCl$_3$, 400 mHz)

$^{13}$C NMR (CDCl$_3$, 101 mHz)
$N$-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-
triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-6-((2-(2,6-
dioxopiperidin-3-yl)-1,3-dioisoindolin-4-yl)amino)hexanamide (15)

$^1$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 101 mHz)
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-((2-(6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)nonanamide (16)

$^1$H NMR (DMSO, 400 MHz)

$^{13}$C NMR (DMSO, 101 MHz)
N-(3-(((6-((4-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-11-((2,(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)undecanamide (17)

$^1$H NMR (CD$_3$OD, 400 MHz)

$^1$C NMR (CD$_3$OD, 101 MHz)
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-3-(4-(((2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)propenamide (18)

$^1$H NMR (CD$_3$OD, 600 MHz)

$^{13}$C NMR (CD$_3$OD, 151 MHz)
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (19)
N-(3-(((6-((4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (20)

$^{1}$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
4-((2-(4-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21)

\[ \text{H NMR (DMSO, 400 mHz)} \]

\[ \text{C NMR (DMSO, 126 mHz)} \]

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4-((4-((4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (22)

$\text{H NMR (CD}_3\text{OD, 400 mHz)}$

$\text{C NMR (CD}_3\text{OD, 101 mHz)}$
5-((4-(4-((6-(4-(4-(4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindole-1,3-dione (23)

$^1$H NMR (CD$_3$OD, 400 MHz)

$^{13}$C NMR (CD$_3$OD, 151 MHz)
4-((6-((6-(4-(((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-6-oxohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (24)

$^1$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 101 mHz)
4-((8-((4-(((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluoro phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-8-oxooctyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (25)

$^1$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 101 mHz)
9-(4-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)nonamide (26)

$^1$H NMR (DMSO, 400 mHz)

$^{13}$C NMR (DMSO, 101 mHz)
11-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-
triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-
(2,6-dioxopiperidin-3-yl)-3-oxoisindolin-5-yl)undecanamide (27)

$^1$H NMR (CD$_3$OD, 400 MHz)

$^{13}$C NMR (CD$_3$OD, 101 MHz)
4-(((1-(12-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)dodecyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (28)

$^1$H NMR (DMSO, 400 MHz)

$^{13}$C NMR (DMSO, 101 MHz)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butanamide (29)

$^1$H NMR (MeOD, 500 MHz)

$^{13}$C NMR (MeOD, 101 MHz)
N-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)hexanamide (30)

$^1$H NMR (MeOD, 500 MHz)

$^{13}$C NMR (MeOD, 400 MHz)
$N$-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)octanamide (31)

$^1$H NMR (MeOD, 500 MHz)

$^{13}$C NMR (MeOD, 125 MHz)
4-(4-(2-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (32)

$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (CDCl$_3$, 101 MHz)
4-((3-(4-(5-(4-(2-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)ethyl)piperazin-1-yl)pyrimidin-2-yl)piperazin-1-yl)-3-oxopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (33)

$^1$H NMR (CDCl$_3$, 400 MHz)

$^{13}$C NMR (DMSO-d$_6$, 176 MHz)
4-(4-(4-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)phenyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (34)

$^1$H NMR (CDCl$_3$, 400 mHz)

$^{13}$C NMR (CDCl$_3$, 151 mHz)
4-(4-(2-(4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (35)

$^1$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 126 mHz)
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butanamide (me-14)

$^{1}$H NMR (CD$_3$OD, 400 mHz)

$^{13}$C NMR (CD$_3$OD, 101 mHz)
$4-((6-((6-((6-((4,4\text{-dimethylpiperidin-1-yl})\text{methyl})-2,5\text{-difluorophenyl})-2\text{-oxo}-1,4,9\text{-triazaspiro}[5.5]\text{undecan-9-yl})\text{pyrimidin-4-yl})\text{amino})\text{methyl)piperidin-1-yl})-6\text{-oxohexyl})\text{amino})-2-(1\text{-methyl-2,6-dioxopiperidin-3-yl})\text{isoindoline-1,3-dione (me-24)}$
HPLC traces of target compounds 1-35, me-14 and me-24.

\[ N-(3-((6-(4-(4-(4,4\text{-}dimethylpiperidin\text{-}1\text{-}yl})\text{methyl})phenyl)-2\text{-}oxo-1,4,9\text{-}triazaspiro[5.5]\text{undecan}\text{-}9\text{-}yl)pyrimidin\text{-}4\text{-}yl)amino)propyl)-3-(2-(2-(2,6\text{-}dioxopiperidin-3\text{-}yl)-1,3\text{-}dioxoisooindolin-4\text{-}yl)amino)ethoxy)ethoxy)propenamide (1) \]

\[ N-(3-((6-(4-(4-(4,4\text{-}dimethylpiperidin\text{-}1\text{-}yl})\text{methyl})phenyl)-2\text{-}oxo-1,4,9\text{-}triazaspiro[5.5]\text{undecan}\text{-}9\text{-}yl)pyrimidin\text{-}4\text{-}yl)amino)propyl)-3-(2-(2-(2,6\text{-}dioxopiperidin-3\text{-}yl)-1,3\text{-}dioxoisooindolin-4\text{-}yl)amino)ethoxy)ethoxy)ethoxy)propenamide (2) \]
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-3,6,9,12-tetraoxapentadecan-15-amide (3)

N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide (4)
$N$-((4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)nonanamide(5)

$N$-((4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)undecanamide(6)
N-(3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-15-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoiindolin-4-yl)amino)pentadecanamide(7)

N-(3-((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoiindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide(8)
N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)phenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisooindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (9)

N-(3-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisooindolin-4-yl)amino)nonanamide (10)
N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-11-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)undecanamide (11)

N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)propyl)-9-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (12)
4-((6-(4-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-6-oxohexyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (13)

N-(3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)butanamide (14)
N-((6-((4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-6-((2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)hexanamide (15)

N-((6-((4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-((2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)amino)nonanamide (16)
$N\-((6\-((4\-((4,4\-dimethylpiperidin\-1\-yl)methyl)-2,5\-difluorophenyl)\-2\-oxo-1,4,9\-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)\-11\-((4\-(((2,6\-dioxopiperidin-3-yl)-1,3\-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3\-triazol-1\-yl)undecanamide (17)$

$N\-((6\-((4\-((4,4\-dimethylpiperidin\-1\-yl)methyl)-2,5\-difluorophenyl)\-2\-oxo-1,4,9\-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)\-3\-((4\-(((2,6\-dioxopiperidin-3-yl)-1,3\-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3\-triazol-1\-yl)propenamide (18)$
N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-9-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)nonanamide (19)

N-(3-(((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-11-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)undecanamide (20)
4-((2-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (21)

4-((4-(4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (22)

5-((4-(4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-4-oxobutyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (23)
4-((6-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-6-oxohexylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (24)

4-((8-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-8-oxooctylamino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (25)

9-((6-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)nonanamide (26)
11-((4-(6-(6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-4-yl)undecanamide (27)

4-(((1-((12-(6-(6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)dodecyl)-1H-1,2,3-triazol-4-yl)methyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (28)
N-(3-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioioisoindolin-4-yl)amino)butanamide (29)

HPLC profile of 29 (95% H₂O 0.1% HCOOH to 95% MeCN in 20 min), t_R = 10.64 min, 99% purity, detection at 254 nm.

N-(3-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-6-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioioisoindolin-4-yl)amino)hexanamide (30)

HPLC profile of 30 (95% H₂O 0.1% HCOOH to 95% MeCN in 20 min), t_R = 11.11 min, 99% purity, detection at 254 nm.
N-((3-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)4-(2-aminoethyl)piperazin)-8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)octanamide (31)

HPLC profile of 31 (95% H₂O 0.1% HCOOH to 95% MeCN in 20 min), t_R = 11.73 min, 98% purity, detection at 254 nm.

4-((4-2-((6-(4-((4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)ethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (32)

HPLC profile of 32 (95% H₂O 0.1% HCOOH to 95% MeCN in 30 min), t_R = 11.08 min, 97% purity, detection at 254 nm.

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4-((3-(4-(5-(2-((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperazin-1-yl)pyrimidin-2-yl)piperazin-1-yl)-3-oxopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (33)

HPLC profile of 33 (95% H₂O 0.1% HCOOH to 95% MeCN in 30 min), \( t_R = 13.64 \) min, 98% purity, detection at 254 nm.

4-(4-(((6-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)phenyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (34)
4-(4-(2-(4-(((6-(4-(4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-2-oxoethyl)piperazin-1-yl)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (35)

N-(3-(((6-(4-(4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)benzyl)-4-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisindolin-4-yl)amino)butanamide (me-14)
4-((6-(4-(((6-(4-(4-(4,4-dimethylpiperidin-1-yl)methyl)-2,5-difluorophenyl)-2-oxo-1,4,9-triazaspiro[5.5]undecan-9-yl)pyrimidin-4-yl)amino)methyl)piperidin-1-yl)-6-oxohexyl)amino)-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (me-24)