Supporting Information

Development of p300-targeting degraders with enhanced selectivity and onset of degradation

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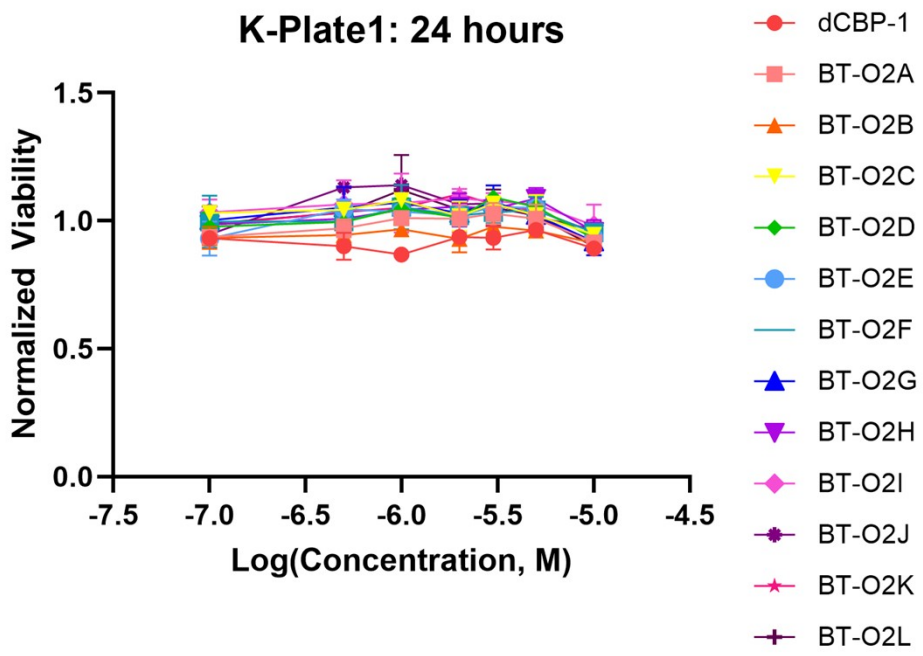
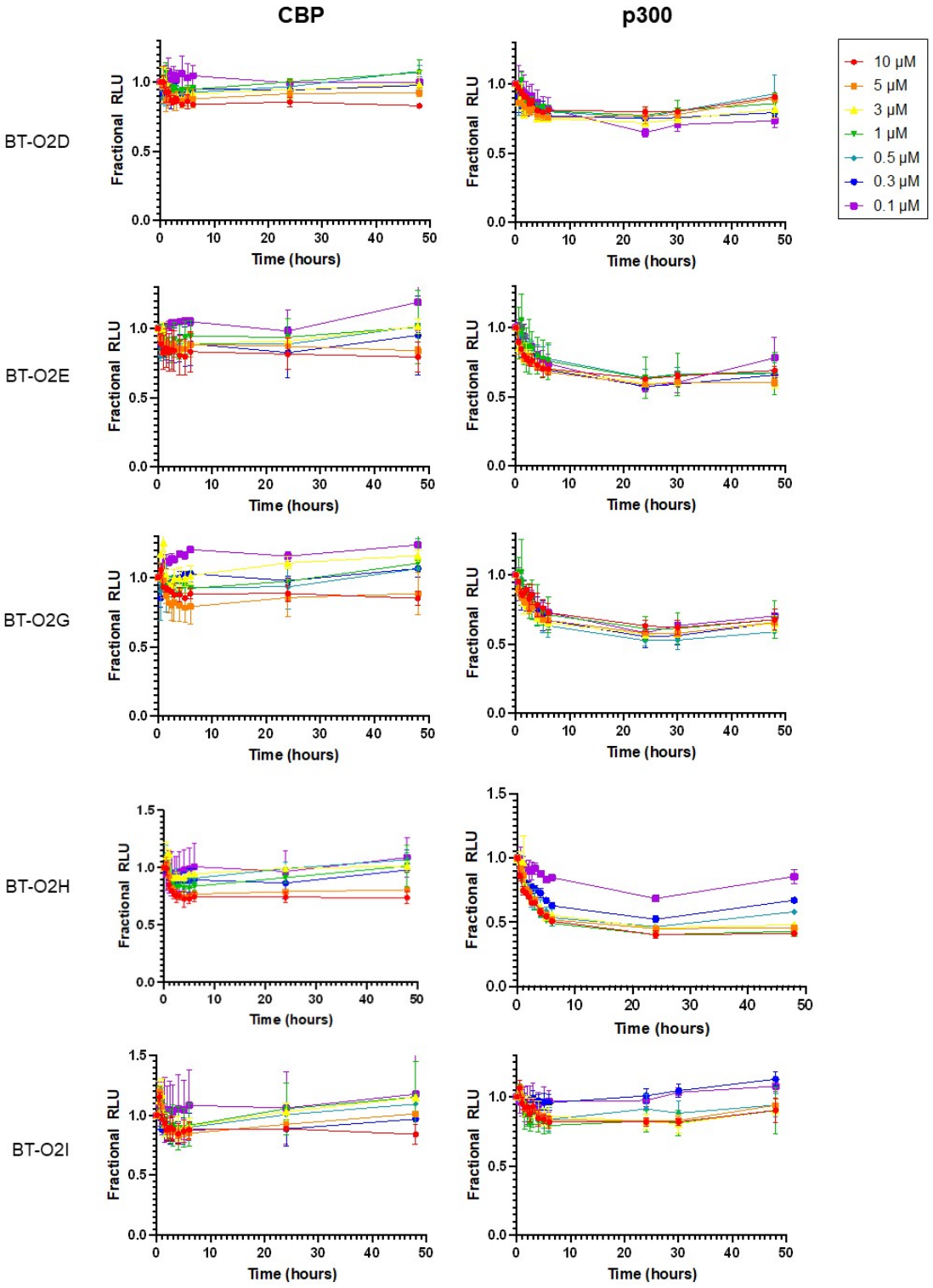


Figure S1. ATP viability assay in the HAP1 cells following treatment with compounds as indicated for 24 hours.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p300
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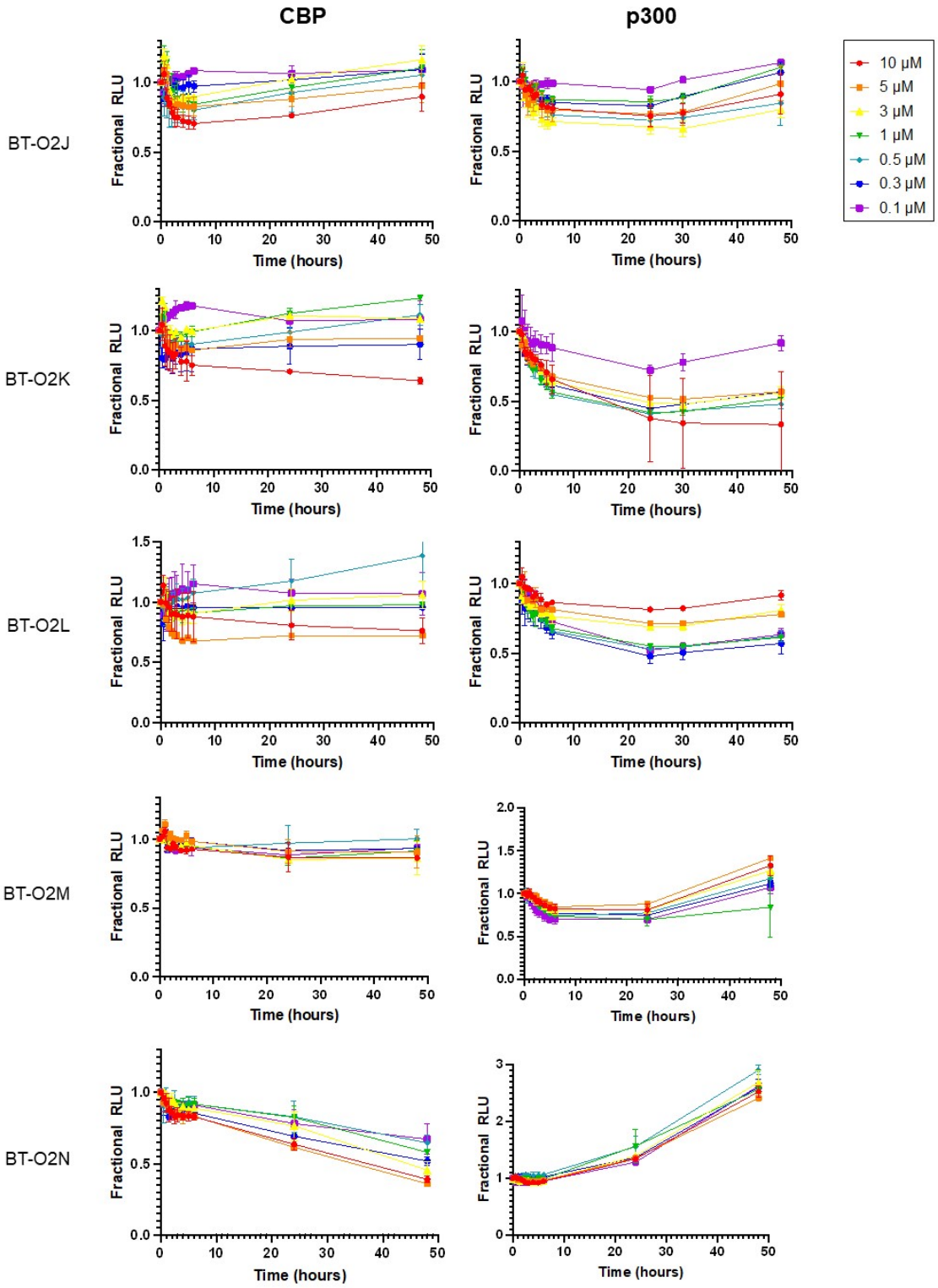
BT-O2E
BT-O2G
BT-O2H
BT-O2I
Fractional RLU
Time (hours)
10 µM
5 µM
3 µM
1 µM
0.5 µM
0.3 µM
0.1 µM


CBP
p300
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BT-O2L
BT-O2M
BT-O2N
Fractional RLU
Time (hours)
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3 µM
1 µM
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0.3 µM
0.1 µM

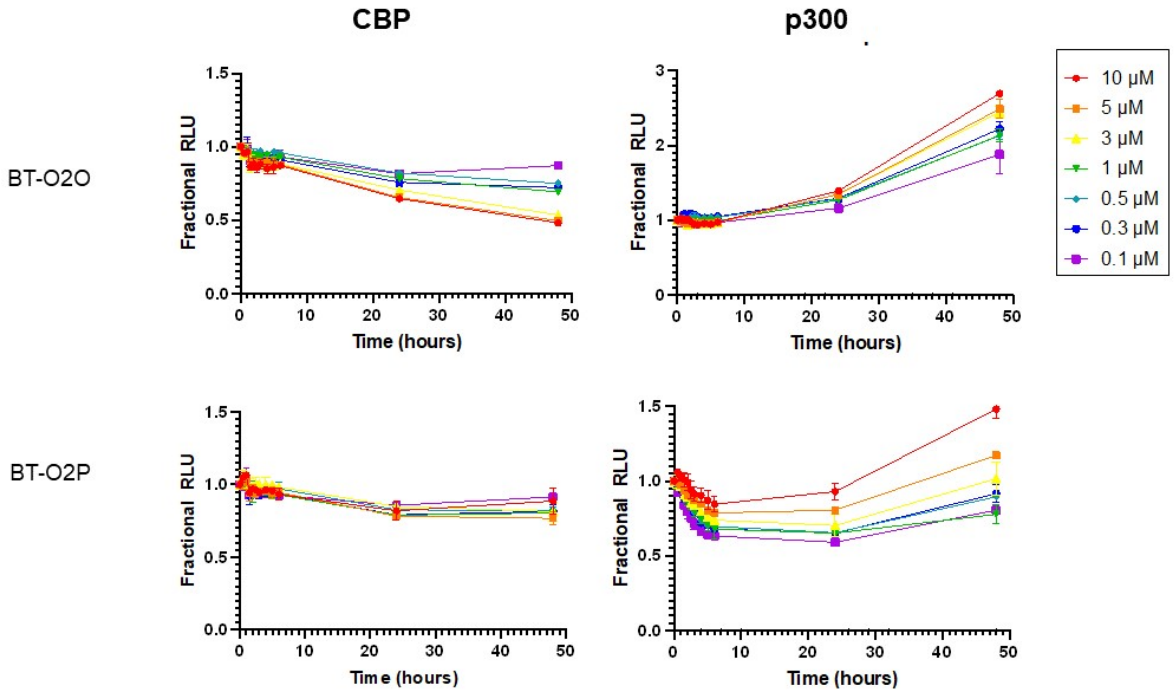


Figure S2. Degradation profiles of p300 and CBP using a HiBiT assay in a HAP1 cell line. PROTACs were dosed from 100 nM to 10 µM. Readout is normalized protein abundance (y axis) versus hours after PROTAC treatment (x axis). A luminescence read-out was used to assess protein levels over a time period of 48 hours following treatment.

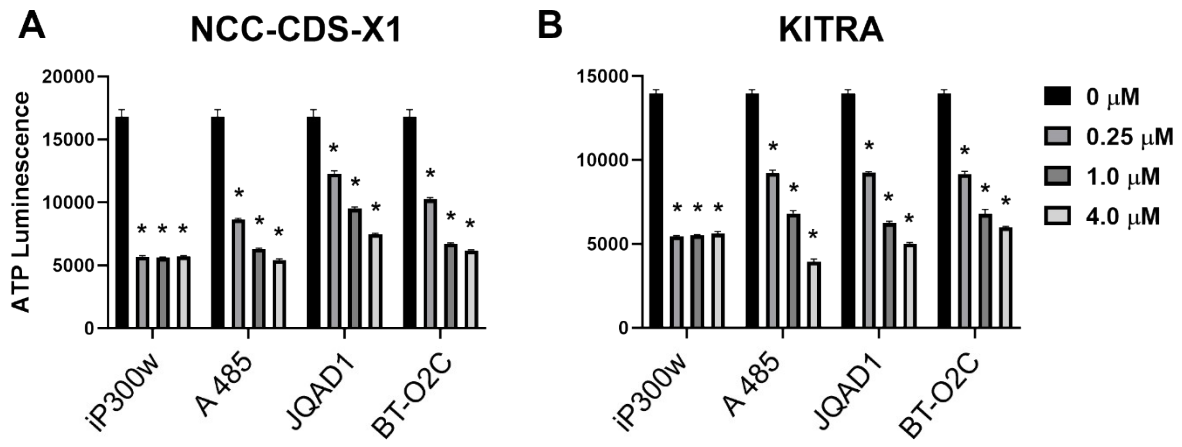


Figure S3. ATP viability assay in CIC::DUX4 sarcoma cell lines following 48 hr treatment with compounds as indicated. (A) NCC-CDS-X1 cell line (B) KITRA cell line.

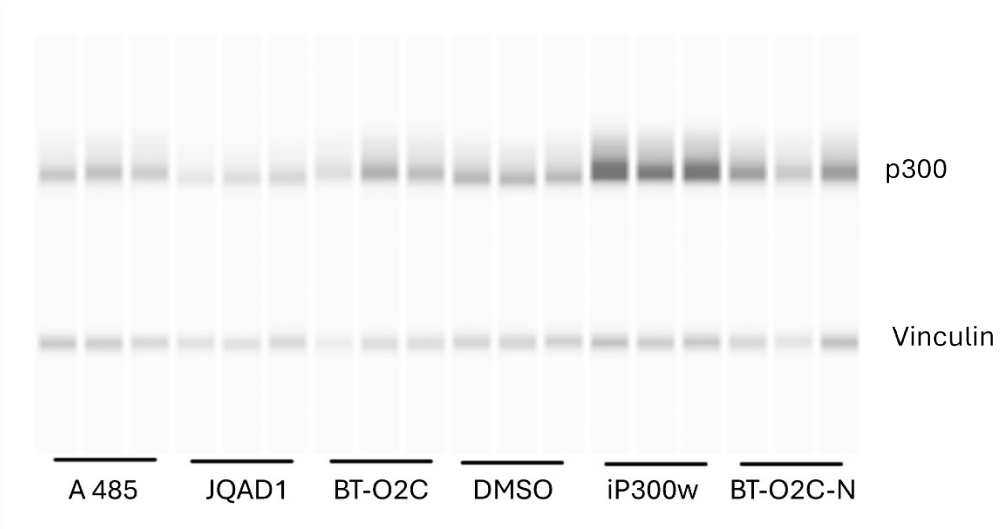


Figure S4. Assessment of p300 degradation in NCC-CDS-X1 cells following compound treatment. Capillary electrophoresis (Wes™ platform, powered by Simple Western technology) measurements of p300 levels were made following 24 hr treatment with compounds as indicated. Compound concentrations are: iP300w and A 485, 250 nM; JQAD1, BT-O2C and BT-O2C-N, 4 µM. Three repeats per condition were tested and shown. Vinculin is shown as the loading control for each.

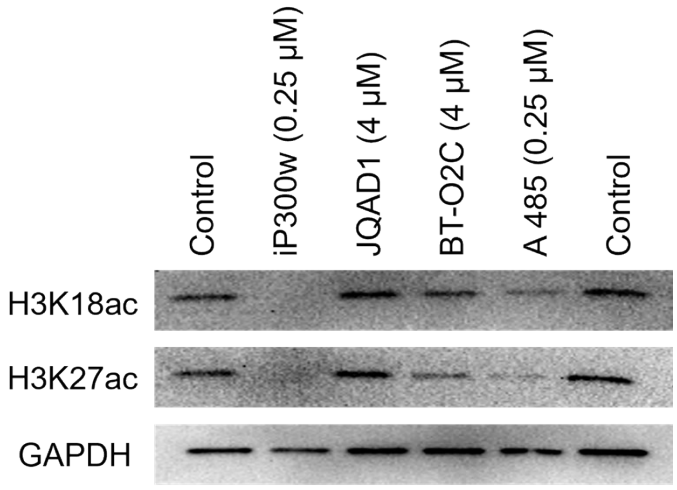
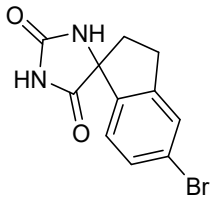


Figure S5. Histone lysine (H3K18 and H3K27) acetylation in NCC-CDS-X1 cells following 24-hour treatment with compounds as indicated.

Chemistry General Methods

Unless otherwise stated, all reagents and solvents were purchased from commercial sources and used without further purification. Nuclear magnetic resonance spectra were recorded on a Bruker Avance III HD spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. ^{1}H NMR and ^{13}C NMR chemical shifts (δ) are reported in parts per million (ppm) and are referenced to residual protium in solvent and to the carbon resonances of the residual solvent peak respectively. DEPT and correlation spectra were run in conjunction to aid assignment. Coupling constants (*J*) are quoted in Hertz (Hz), and the following abbreviations were used to report multiplicity: s= singlet, d= doublet, dd= doublet of doublets, ddd= double doublet of doublets, t= triplet, q= quartet, m= multiplet, br s= broad singlet. Purification by flash column chromatography was carried out using Fisher Scientific silica gel 60Å (35-70 μm), or by using Biotage Selekt, Biotage Isolera, Grace Reveleris or Buchi Pure systems. Analytical thin layer chromatography was performed on glass plates pre-coated with silica gel (Analtech, UNIPLATE™ 250 μm / UV254), with visualization being achieved using UV light (254 nm) and/or by staining with alkaline potassium permanganate dip. Reaction monitoring LC-MS analyses were conducted using Agilent InfinityLab LC/MSD systems. Chiral GC analysis was conducted using an Agilent 7890A GC system. Optical rotations were recorded on a Bellingham & Stanley ADP450 polarimeter. High resolution mass spectral (HRMS) data was collected in the laboratories of the University of Bath Chemistry Department using an Agilent 6545 LC/Q-TOF system. All final compounds were >95% pure by HPLC/LCMS analysis.

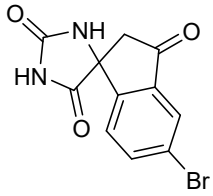
5'-Bromo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-2,5-dione (1)



A stirred suspension of 5-bromoindan-1-one (60.00 g, 284.29 mmol) in ethanol (246 mL) and water (164 mL) at ambient temperature was treated with ammonium carbonate (83.86 g, 872.76 mmol) and potassium cyanide (27.77 g, 426.43 mmol). The reaction mixture was heated to 70 °C and stirred under a flow of nitrogen at this temperature for a total of 161 hours. During this period it was found to be necessary three times to cool and recharge with further portions of ammonium carbonate (1 eq) and potassium cyanide (0.5 eq) before raising the temperature again. Upon completion of the reaction, and after cooling to ambient temperature, the reaction mixture was treated with water (700 mL) and ethyl acetate (500 mL). The mixture was filtered, and the layers of the filtrate separated. The aqueous component was extracted with ethyl acetate (2 × 200 mL), and the combined organics were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by dry flash chromatography, eluting with 2-4% MeOH/DCM, afforded the title compound as a light brown solid (42.80 g, 54%). m/z (ES-): 279.1, 281.1 $[M-H^{+}]^{-}$

^{1}H NMR (DMSO-d_6) δ: 10.81 (br s, 1H), 8.44 (br s, 1H), 7.55 (d, *J*= 1.2, 1H), 7.43 (dd, *J*= 8.4, 1.2, 1H), 7.12 (d, *J*= 8.4, 1H), 3.07-2.94 (m, 2H), 2.56-2.50 (m, 1H), 2.21-2.13 (m, 1H).

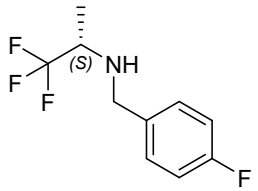
5'-Bromospiro[imidazolidine-4,1'-indene]-2,3',5(2'H)-trione (2)



A stirred mixture of 5'-bromo-2',3'-dihydrospiro[imidazolidine-4,1'-indene]-2,5-dione **(1)** (38.70 g, 137.67 mmol), tetrabutylammonium hydrogen sulfate (9.35 g, 27.53 mmol) and sodium 2-iodobenzenesulfonic acid (2.11 g, 6.88 mmol) in acetonitrile (1450 mL) at ambient temperature was treated with potassium peroxymonosulfate (126.95 g, 413.01 mmol) in portions. The reaction mixture was heated to 65 °C and stirred for a total of 56 hours. During this period it was found necessary to periodically cool and recharge with further portions of potassium peroxymonosulfate (eventually up to a total of 8 equivalents were added) before raising the temperature again. Upon completion of the reaction, and after cooling to ambient temperature, the reaction mixture was filtered and washed with acetone (900 mL). The collected solid was treated with hot acetone (5 × 500 mL), these extracts being concentrated to a solid and triturated with ethyl acetate to give an initial crop of product. All the filtrates were combined and concentrated and purified by flash column chromatography, eluting with 3% MeOH/DCM, to afford a second crop of product. This process afforded the title compound as a white solid (22.15 g, 55%). m/z (ES+): 295.1, 297.1 $[M+H^+]^+$

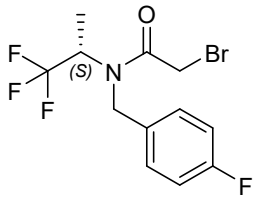
^{1}H NMR (DMSO-d_6) δ: 11.19 (br s,1H), 8.56 (br s, 1H), 7.96 (dd, *J*= 8.2, 2.0, 1H), 7.90 (d, *J*= 2.0, 1H), 7.62 (d, *J*= 8.2, 1H), 3.15 (d, *J*= 18.6, 1H), 2.92 (d, *J*= 18.6, 1H).

(*S*)-1,1,1-Trifluoro-*N*-(4-fluorobenzyl)propan-2-amine (3)



To a stirred solution of (2*S*)-1,1,1-trifluoropropan-2-amine hydrochloride (34.50 g, 230.70 mmol, $[\alpha]_D^{22}$ = +5.8° (c=1.0, MeOH)) and potassium carbonate (127.54 g, 922.81 mmol) in DMF (345 mL) at ambient temperature was added 1-(bromomethyl)-4-fluoro-benzene (34.50 mL, 276.84 mmol) in a dropwise fashion over a period of 10 minutes, and the resulting reaction mixture was stirred for 18 hours. The reaction mixture was poured into water (2.8 L) and extracted with ethyl acetate (3 × 1 L). The combined organic extracts were washed with water (3 × 1 L), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a colourless oil. Purification by flash column chromatography, eluting with 4% ethyl actetate/petroleum ether (40:60), afforded the title compound as a colourless oil (30.79 g, 60%). ^{1}H NMR ($CDCl_3$) δ: 7.33-7.28 (m, 2H), 7.04-6.99 (m, 2H), 3.93-3.84 (m, 2H), 3.22-3.11 (m, 1H), 1.26-1.24 (m, 3H). Chiral GC (β-DEX™ 120, 30 m x 250 mm, 0.25 µm): 99.7%*ee.* $[\alpha]_D^{26}$ = +22.5° (c = 1, $CHCl_3$).

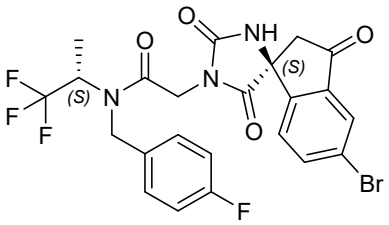
(*S*)-2-Bromo-*N*-(4-fluorobenzyl)-*N*-(1,1,1-trifluoropropan-2-yl)acetamide (4)



To a stirred solution of (*S*)-1,1,1-trifluoro-*N*-(4-fluorobenzyl)propan-2-amine **(3)** (30.50 g, 137.89 mmol) in DCM (350 mL) at ambient temperature was added a solution of bromoacetyl bromide (55.66 g, 275.78 mmol) in DCM (50 mL) in a dropwise fashion over a period of 15 minutes, and the resulting reaction mixture was stirred at ambient temperature for 2 hours. After treatment with $NaHCO_3$ (sat. aq.) (470 mL) and a further hour of stirring, the organic phase was separated. The aqueous component was extracted with DCM (2 × 200mL), and the combined organics were washed with $NaHCO_3$ (sat. aq.) (250 mL), brine (250 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a pale yellow oil. Purification by flash column chromatography, eluting with 4-10% ethyl actetate/petroleum ether (40:60), afforded the title compound as a colourless oil (16.90 g, 36%). m/z (ES+): 367.3 [M+Na+]+

^{1}H NMR (DMSO-d_6) δ: 7.32-7.10 (m, 4H), 5.34-5.28 (m, 0.5H), 4.96-4.88 (m, 0.5H), 4.81-4.66 (m, 1.5H), 4.56 (d, *J*= 12.0, 0.5H), 4.38 (d, *J*= 16.4, 0.5H), 4.26 (d, *J*= 12.0, 0.5H), 4.09-3.95 (m, 1H), 1.39-1.29 (m, 3H). *Observed as a mixture of rotamers.*

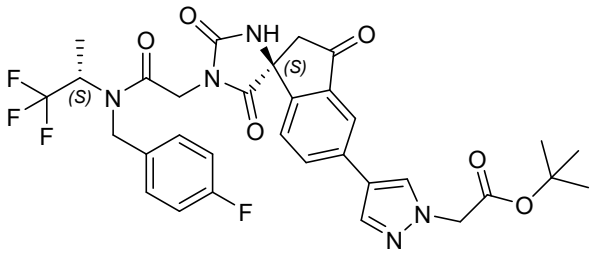
2-((*S*)-5'-Bromo-2,3',5-trioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (5)



To a stirred solution of 5'-bromospiro[imidazolidine-4,1'-indene]-2,3',5(2'H)-trione **(2)** (22.70 g, 76.93 mmol) and potassium carbonate (21.26 g, 153.85 mmol) in DMF (200 mL) at 2 °C was dropwise added a solution of (*S*)-2-bromo-*N*-(4-fluorobenzyl)-*N*-(1,1,1-trifluoropropan-2-yl)acetamide **(4)** (26.32 g, 76.93 mmol) in DMF (50 mL) at such a rate so as to keep the temperature below 5 °C during the course of the addition. The reaction mixture was then allowed to warm to ambient temperature and stirred for 6 hours before being partitioned between water (450 mL) and ethyl acetate (450 mL). The organic phase was separated, and the aqueous component was extracted with ethyl acetate (3 × 200 mL). The combined organics were washed with brine (4 × 200 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 1-2% MeOH/DCM afforded an off-white solid which was triturated with diethyl ether/petroleum ether (40:60) (1:1) to give the title compound as a white solid (33.08 g, 77%). Separation by preparative chromatography afforded the desired *(S)-(S)*-diastereomer (12.49g). m/z (ES+): 578.1, 580.1 $[M+Na^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 8.58 (br s, 1H), 7.98-7.92 (m, 1H), 7.88-7.86 (m, 1H), 7.67-7.63 (m, 1H), 7.36-7.33 (m, 2H), 7.13 (t, *J*= 8.8, 2H), 5.22-5.15 (m, 1H), 4.82 (d, *J*= 17.6, 1H), 4.65-4.50 (m, 2H), 4.35-4.28 (m, 1H), 3.13 (d, *J*= 18.6, 1H), 2.98 (d, *J*= 18.6, 1H), 1.37 (d, *J*= 7.2, 3H). $[\alpha]_D^{21}$ = +23.6° (c = 1, MeOH)

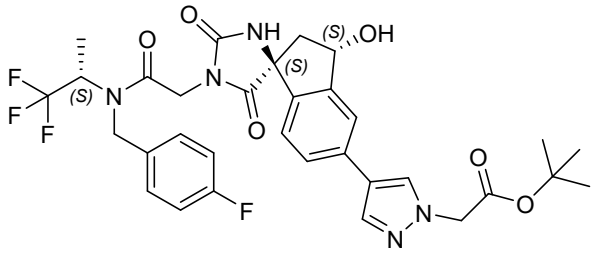
<u>*tert*-Butyl 2-(4-((*S*)-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,3',5-trioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate (6)</u>



To a stirred solution of 2-((*S*)-5'-bromo-2,3',5-trioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide **(5)** (3.00 g, 5.39 mmol) and *tert*-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazol-1-yl]acetate (2.08 g, 6.74 mmol) in 1,4-dioxane (45 mL) at ambient temperature was added water (9 mL), and the resulting reaction mixture was degassed with nitrogen. Potassium carbonate (2.24 g, 16.18 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloropalladium (II) DCM complex (0.35 g, 0.43 mmol) were added, nitrogen was bubbled through the reaction mixture for 5 minutes, and then the entire reaction mixture was transferred to a sealed stainless-steel vessel and stirred under nitrogen atmosphere at 95°C for 12 hours. Upon cooling to ambient temperature, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 2% MeOH/DCM, afforded the title compound as a light brown solid (2.86 g, 81%). m/z (ES+): 658.30 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100°C) δ: 8.64 (s, 1H), 8.26 (s, 1H), 8.03 – 7.97 (m, 2H), 7.87 (d, *J*= 1.4, 1H), 7.67 (d, *J*= 8.1, 1H), 7.40 – 7.31 (m, 2H), 7.14 (t, *J*= 8.6, 2H), 5.21 (br s, 1H), 4.92 (s, 2H), 4.84 (d, *J*= 17.4, 1H), 4.69 – 4.44 (m, 2H), 4.30 (d, *J*= 16.0, 1H), 3.11 (d, *J*= 18.4, 1H), 2.95 (d, *J*= 18.4, 1H), 1.46 (s, 9H), 1.37 (d, *J*= 7.0, 3H).

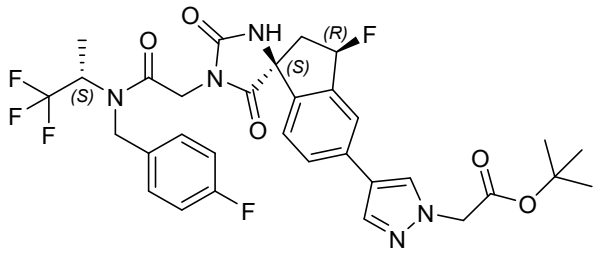
<u>*tert*-Butyl 2-(4-((3'*S*,4*S*)-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-3'-hydroxy-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate (7)</u>



To a stirred solution of *tert*-butyl 2-(4-((*S*)-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,3',5-trioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate **(6)** (2.80 g, 4.26 mmol) in THF (87 mL) and MeOH (87 mL) at 0°C was added sodium borohydride (0.96 g, 25.42 mmol) in a portion-wise fashion. After stirring at 0°C for 30 minutes, the reaction mixture was allowed to warm to ambient temperature with acetone (5 mL) being added, before being concentrated under reduced pressure. Purification by flash column chromatography, eluting with 2% MeOH/DCM, afforded the title compound as a beige solid (2.18 g, 78%). m/z (ES+): 660.30 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100°C) δ: 8.46 (s, 1H), 8.09 (s, 1H), 7.84 (s, 1H), 7.58 (s, 1H), 7.52 (d, *J*= 8.8, 1H), 7.40 – 7.33 (m, 2H), 7.29 (d, *J*= 8.0, 1H), 7.15 (t, *J*= 8.8, 2H), 5.34 (t, *J*= 6.5, 1H), 5.22 (br s, 1H), 4.92 – 4.81 (m, 3H), 4.68 – 4.45 (m, 2H), 4.29 (d, *J*= 16.3, 1H), 2.55 (dd, *J*= 13.5, 6.3, 1H), 2.40 (dd, *J*= 13.5, 6.3, 1H), 1.45 (s, 9H), 1.37 (d, *J*= 7.0, 3H).

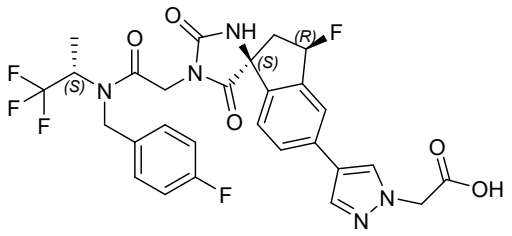
<u>*tert*-Butyl 2-(4-((3'*R*,4*S*)-3'-fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate (8)</u>



To a stirred solution of *tert*-butyl 2-(4-((3'*S*,4*S*)-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-3'-hydroxy-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate **(7)** (2.10 g, 3.18 mmol) in DCM (140 mL) at -70°C was added DAST (1.03 g, 6.37 mmol) in a dropwise fashion, and stirring was maintained at this temperature for 30 minutes. The reaction mixture was allowed to warm to -30°C over 10 minutes, at which point calcium carbonate (1.00 g) was added. The reaction mixture was warmed to ambient temperature and then concentrated under reduced pressure. Purification by flash column chromatography, eluting with 1% MeOH (5% NH_4OH)/DCM, afforded the title compound as a white solid (1.43 g, 68%). m/z (ES+): 662.10 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100°C) δ: 8.73 (s, 1H), 8.17 (s, 1H), 7.92 (s, 1H), 7.75 – 7.68 (m, 2H), 7.40 – 7.31 (m, 3H), 7.14 (t, *J*= 8.4, 2H), 6.16 (ddd, *J*= 57.7, 6.6, 4.9, 1H), 5.21 (s, 1H), 4.92 (s, 2H), 4.83 (d, *J*= 17.8, 1H), 4.67 – 4.41 (m, 2H), 4.26 (d, *J*= 17.8, 1H), 3.08 (ddd, *J*= 14.3, 12.8, 6.9, 1H), 2.42 (ddd, *J*= 25.7, 14.5, 4.6, 1H), 1.46 (s, 9H), 1.36 (d, *J*= 7.0, 3H).

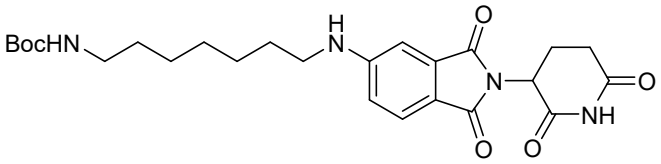
<u>2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (9)</u>



tert-Butyl 2-(4-((3'*R*,4*S*)-3'-fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetate **(8)** (0.11 g, 0.17 mmol) was treated with hydrogen chloride (2 mL, 4M solution in 1,4-dioxane) and the resulting solution was stirred at ambient temperature for 6 hours before being concentrated under reduced pressure to give the title compound as a white solid (100 mg, quant). m/z (ES+): 606.10 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100°C) δ: 8.73 (s, 1H), 8.18 (s, 1H), 7.91 (s, 1H), 7.75 – 7.67 (m, 2H), 7.40 – 7.31 (m, 3H), 7.14 (t, *J*= 8.9, 2H), 6.16 (ddd, *J*= 57.2, 6.3, 4.7, 1H), 5.21 (br s, 1H), 4.95 (s, 2H), 4.83 (d, *J*= 17.7, 1H), 4.68 – 4.41 (m, 2H), 4.26 (d, *J*= 18.1, 1H), 3.13 – 3.02 (m, 1H), 2.47 – 2.34 (m, 1H), 1.36 (d, *J*= 6.9, 3H).

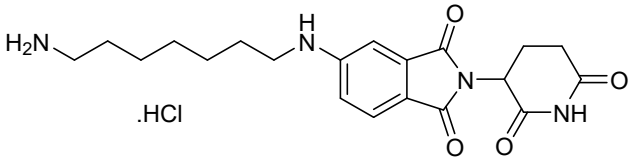
<u>*tert*-Butyl (7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl)carbamate</u>



To a stirred mixture of 2-(2,6-dioxo-3-piperidyl)-5-fluoro-isoindoline-1,3-dione (0.25 g, 0.91 mmol) and DIPEA (0.23 g, 1.81 mmol) in NMP (5 mL) was added *tert*-butyl *N*-(7-aminoheptyl)carbamate (0.23 g, 0.99 mmol) and the reaction mixture was stirred at 90°C for 19.5 hours. After cooling to ambient temperature, the dark green reaction mixture was poured into water (30 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were sequentially washed with water (20 mL) and brine (3 x 20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 1 % MeOH/DCM (containing 0.1% NH_4OH), afforded the title compound as a thick oil (118 mg, 41%). m/z (ES+): 387.20 $[M_{-Boc}+H^+]^+$

^{1}H NMR ($CDCl_3$) δ: 7.95 (s, 1H), 7.63 (d, *J*= 8.3, 1H), 7.01 (d, *J*= 1.7, 1H), 6.80 (d, *J*= 8.1, 1H), 4.99 – 4.86 (m, 1H), 4.50 (s, 2H), 3.32 – 3.19 (m, 2H), 3.11 (t, *J*= 6.8, 2H), 2.93 – 2.63 (m, 3H), 2.16 – 2.08 (m, 2H), 1.75 – 1.57 (m, 2H), 1.54 – 1.23 (m, 16H).

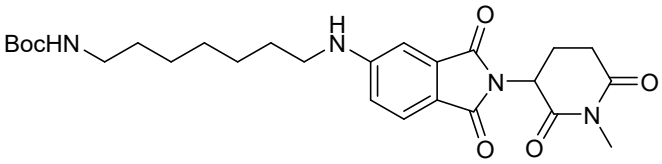
<u>5-((7-Aminoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride</u>



tert-Butyl (7-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl)carbamate (113 mg) was treated with hydrogen chloride (1.2 mL, 4M solution in 1,4-dioxane) and the reaction mixture was stirred at ambient temperature for 16 hours. The resulting suspension was treated with diethyl ether (5 mL) before being filtered, washed with further diethyl ether (2 mL) and dried, to afford the title compound as a yellow-green solid (110 mg) which was used directly in the next stage without further purification. m/z (ES+): 387.20 $[M_{free\ base}+H^+]^+$

^{1}H NMR (DMSO-d_6) δ: 11.05 (br s, 1H), 7.85 (br s, 3H), 7.56 (d, *J*= 8.4, 1H), 6.95 (d, *J*= 1.8, 1H), 6.85 (dd, *J*= 8.4, 1.8, 1H), 5.02 (dd, *J*= 8.4, 2.0, 1H), 3.16 (t, *J*= 8.4, 2H), 2.93-2.82 (m, 1H), 2.80-2.71 (m, 2H), 2.61-2.45 (m, 2H), 2.04-1.95 (m, 1H), 1.62-1.50 (m, 4H), 1.40-1.28 (m, 6H).

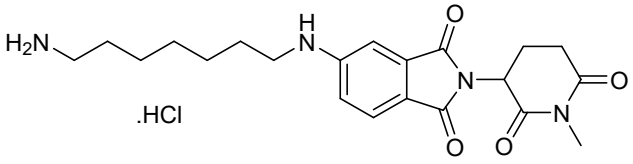
<u>*tert*-Butyl (7-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl)carbamate</u>



To a stirred mixture of 5-fluoro-2-(1-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione (5.00 g, 17.2 mmol) and DIPEA (6.00 mL g, 34.45 mmol) in NMP (50 mL) was added *tert*-butyl *N*-(7-aminoheptyl)carbamate (4.36 g, 18.95 mmol) and the reaction mixture was stirred at 90°C for 17 hours. After cooling to ambient temperature, the dark green reaction mixture was poured into water (200 mL), and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were sequentially washed with water (2 x 250 mL) and brine (3 x 250 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 1-3% MeOH/DCM (with 0.1% NH_4OH) afforded the title compound as a green solid (1.1 g) which was used directly in the next stage without further purification. m/z (ES+): 401.3 $[M_{-Boc}+H^+]^+$

^{1}H NMR (DMSO-d_6) δ: 7.61 (d, *J*= 8.3, 1H), 6.96 (d, *J*= 2.0, 1H), 6.75 (dd, *J*= 8.3, 2.0, 1H), 4.95 – 4.88 (m, 1H), 4.51 (s, 1H), 3.24 – 3.18 (m, 4H), 3.15 – 3.05 (m, 2H), 2.99 – 2.90 (m, 1H), 2.84 – 2.68 (m, 2H), 2.12 – 2.06 (m, 1H), 1.70 – 1.59 (m, 2H), 1.53 – 1.28 (m, 19H).

<u>5-((7-Aminoheptyl)amino)-2-(1-methyl-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione</u>



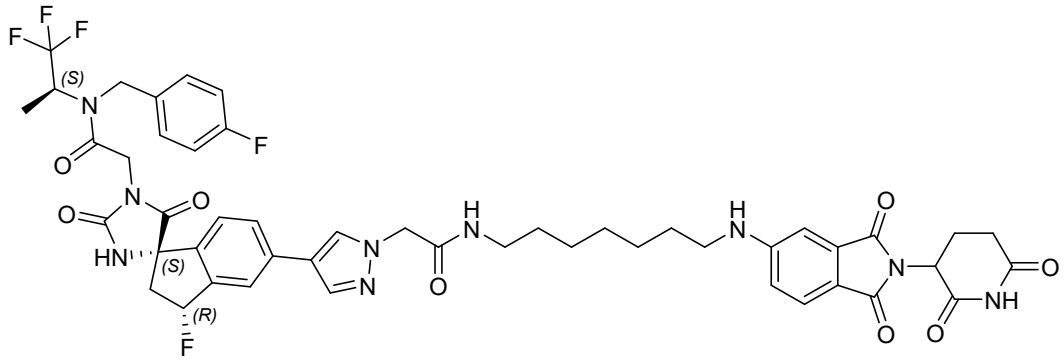
tert-Butyl(7-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl) carbamate (378 mg, 0.76 mmol) was treated with hydrogen chloride (3.78 mL, 4M solution in 1,4-dioxane) and the resulting mixture was stirred for 2 hours, treated with diethyl ether and filtered, affording the title compound as a pale blue solid (265 mg, 80%) which was used directly in the next stage without further purification. m/z (ES+): 401.2 $[M_{(free\ base)}+H^+]^+$

^{1}H NMR (DMSO-d_6) δ: 7.81 (br s, 1H), 7.56 (d, *J*= 8.4, 1H), 6.95 (s, 1H), 6.85 (dd, *J*= 8.4, 2.0, 1H), 5.09 (dd, *J*= 13.0, 5.4, 1H), 4.25 (s, 1H), 3.16 (t, *J*= 7.0, 2H), 3.02 – 2.88 (m, 4H), 2.79 – 2.70 (m, 3H), 2.60 – 2.52 (m, 1H), 2.05 – 1.97 (m, 1H), 1.62 – 1.50 (m, 5H), 1.41 – 1.24 (m, 7H).

GENERAL PROCEDURE A

To a stirred solution of 2-(4-((3'*R*,4*S*)-3'-fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (1 eq) in DMF was added the amine coupling partner (1 eq), DIPEA (2.5 to 4.5 eq) and HATU (1.1 eq) and the reaction mixture stirred at ambient temperature until the reaction was complete. The reaction mixture was diluted with water (10 volumes) and extracted with ethyl acetate. The organic extracts were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Purification by flash column chromatography followed by lyophilisation afforded the product.

2-((3'*R*,4*S*)-5'-(1-(2-((7-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2C)



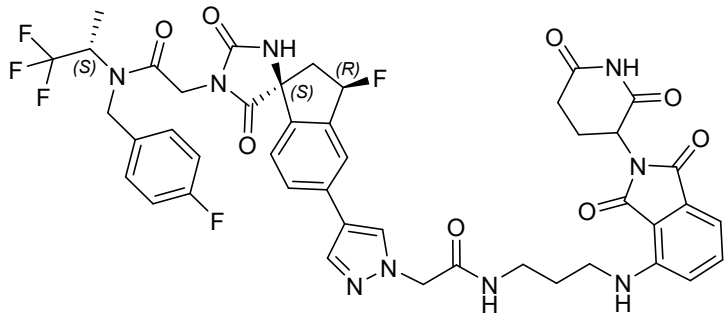
2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (95.0 mg, 0.16 mmol) was coupled with 5-((7-aminoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 3% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (97 mg, 64%, >99% LCMS purity). m/z (ES+): 974.30 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 10.51 (br s, 1H), 8.61 (s, 1H), 8.13 (s, 1H), 7.88 (d, *J*= 0.67, 1H), 7.71 (m, 1H), 7.69 - 7.66 (m, 1H), 7.54 (d, *J*= 8.2, 1H), 7.38 - 7.32 (m, 3H), 7.13 (t, *J*=

8.7, 2H), 6.98 (d, *J*= 2.1, 1H), 6.87 (dd *J*= 8.4, 2.2, 1H), 6.62, (t, *J*= 5.2, 1H), 6.14 (ddd, *J*= 57.7, 6.8, 4.6, 1H), 5.18 (m, 1H), 4.96 (m, 1H), 4.82 (d, *J*= 17.2, 1H), 4.78 (s, 2H) 4.61 (d, *J*= 17.6, 1H), 4.47 (d, *J*= 17.6, 1H), 4.26 (d, *J*= 16.7, 1H), 3.23 - 3.12 (m, 4H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.90 - 2.79 (m, 1H), 2.67 - 2.52 (m, 2H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.09 - 2.01 (m, 1H), 1.66 - 1.58 (m, 1H), 1.54 - 1.45 (m, 1H), 1.44 - 1.28 (m, 6H), 1.37 (d, *J*= 7.1, 3H)

HRMS (ES+) calculated for $[C_{48}H_{48}F_5N_9O_8+H^+]^+$ 974.9670, found: 974.3638

2-((3'*R*,4*S*)-5'-(1-(2-((3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2D)

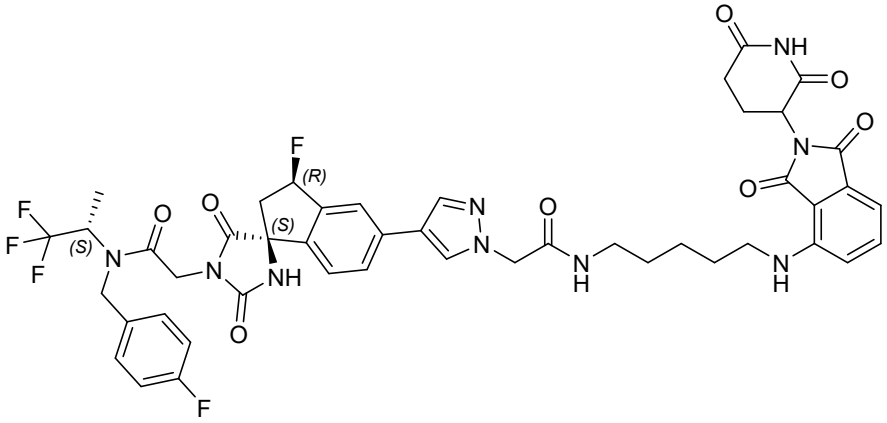


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (100 mg, 0.17 mmol) was coupled with 4-((3-aminopropyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 3% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (77 mg, 51%, 99% LCMS purity). m/z (ES+): 918.30 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 10.56 (br s, 1H), 8.63 (s, 1H), 8.14 (d, *J*= 0.65, 1H), 7.89 (d, *J*= 0.76, 1H), 7.78 - 7.71 (m, 1H),7.72 (m, 1H), 7.70 - 7.66 (m, 1H), 7.57 (dd, *J*= 8.4, 7.1, 1H), 7.39 - 7.33 (m, 3H), 7.13 (t, *J*= 8.8, 2H), 7.07 (d, *J*= 8.5, 1H), 7.03 (d, *J*= 7.1, 1H), 6.45 (t, *J*= 6.2, 1H), 6.15 (ddd, *J*= 57.5, 6.7, 4.5, 1H), 5.19 (m, 1H), 5.00 (m, 1H), 4.83 (d, *J*= 17.2, 1H), 4.82 (s, 2H), 4.62 (d, *J*= 17.2, 1H), 4.48 (d, *J*= 17.2, 1H), 4.27 (d, *J*= 16.7, 1H), 3.38 (q, *J*= 6.7, 2H), 3.28 (q, *J*= 6.7, 2H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.91 - 2.81 (m, 1H), 2.68 - 2.53 (m, 2H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.13 - 2.04 (m, 1H), 1.87 - 1.78 (m, 1H), 1.37 (d, *J*= 6.9, 3H)

HRMS (ES+) calculated for $[C_{44}H_{40}F_5N_9O_8+H^+]^+$ 918.2998, found: 918.3005

2-((3'*R*,4*S*)-5'-(1-(2-((5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)pentyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2E)

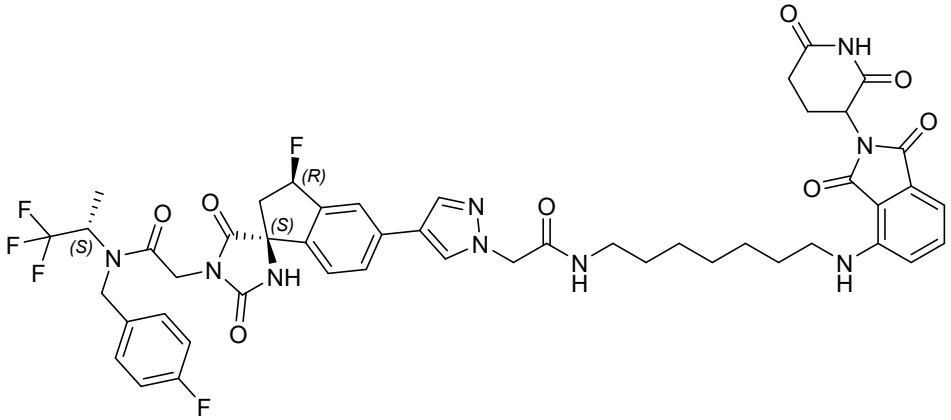


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with 4-((5-aminopentyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with EtOAc, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (43 mg, 34%, 96% LCMS purity). m/z (ES+): 946.20 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 10.67 (s, 1H), 8.71 (s, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.73 – 7.66 (m, 3H), 7.57 (dd, *J*= 8.3, 7.3, 1H), 7.39-7.33 (m, 2H), 7.13 (t, *J*= 8.3, 2H), 7.07 (d, *J*= 8.5, 1H), 7.02 (d, *J*= 7.0, 1H), 6.42 – 6.35 (m, 1H), 6.14 (ddd, *J*= 58.4, 6.9, 4.7, 1H), 5.19 (br s, 1H), 5.00 (dd, *J*= 12.5, 5.5, 1H), 4.86 – 4.77 (m, 3H), 4.66 – 4.42 (m, 2H), 4.26 (d, *J*= 16.3, 1H), 3.31 (dd, *J*= 12.8, 6.5, 2H), 3.16 (dd, *J*= 12.8, 6.6, 2H), 3.12 – 3.01 (m, 1H), 2.91 – 2.80 (m, 2H), 2.67 – 2.55 (m, 2H), 2.41 (ddd, *J*= 25.0, 14.1, 4.4, 1H), 2.11 – 2.02 (m, 1H), 1.65 – 1.59 (m, 2H), 1.58 – 1.49 (m, 2H), 1.46 – 1.39 (m, 2H), 1.36 (d, *J*= 7.0, 3H).

HRMS (ES+) calculated for $[C_{46}H_{44}F_5N_9O_8+H^+]^+$ 946.3311, found: 946.3320

2-((3'*R*,4*S*)-5'-(1-(2-((7-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)heptyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2F)

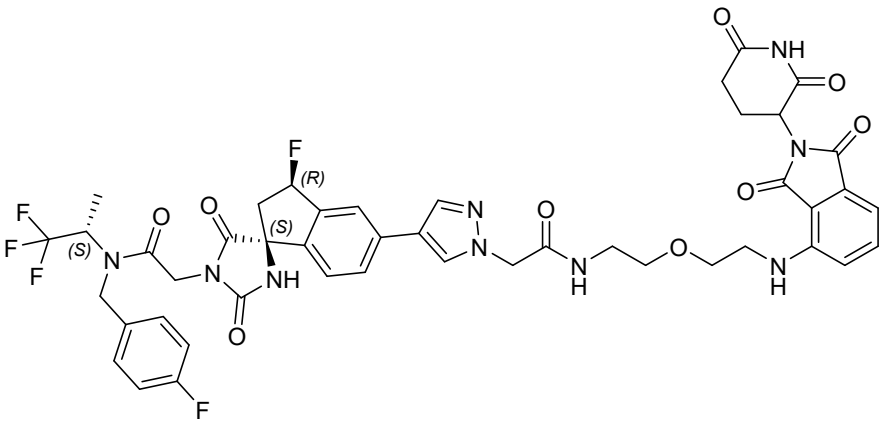


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with 4-((5-aminoheptyl)amino)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 50% EtOAc/petroleum ether (40:60) increased to 100% EtOAc, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (79 mg, 61%, >95% LCMS purity). m/z (ES+): 974.10 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 10.69 (s, 1H), 8.72 (s, 1H), 8.15 (s, 1H), 7.89 (s, 1H), 7.73 – 7.65 (m, 3H), 7.57 (dd, *J*= 8.2, 7.5, 1H), 7.39 – 7.30 (m, 3H), 7.13 (t, *J*= 8.6, 2H), 7.07 (d, *J*= 8.6, 1H), 7.02 (d, *J*= 7.0, 1H), 6.38 (t, *J*= 5.8, 1H), 6.14 (ddd, *J*= 58.0, 7.2, 5.0, 1H), 5.20 (br s, 1H), 5.00 (dd, *J*= 12.4, 5.6, 1H), 4.86 – 4.76 (m, 3H), 4.69 – 4.37 (m, 2H), 4.25 (d, *J*= 15.8, 1H), 3.31 (dd, *J*= 13.2, 6.7, 2H), 3.16 – 3.02 (m, 3H), 2.91 – 2.81 (m, 1H), 2.67 – 2.52 (m, 2H), 2.40 (ddd, *J*= 25.5, 14.4, 4.5, 1H), 2.13 – 1.99 (m, 1H), 1.67 – 1.57 (m, 2H), 1.51 – 1.43 (m, 2H), 1.43 – 1.22 (m, 9H).

HRMS (ES+) calculated for $[C_{48}H_{48}F_5N_9O_8+H^+]^+$ 974.3624, found: 974.3632

2-((3'*R*,4*S*)-5'-(1-(2-((2-(2-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2G)



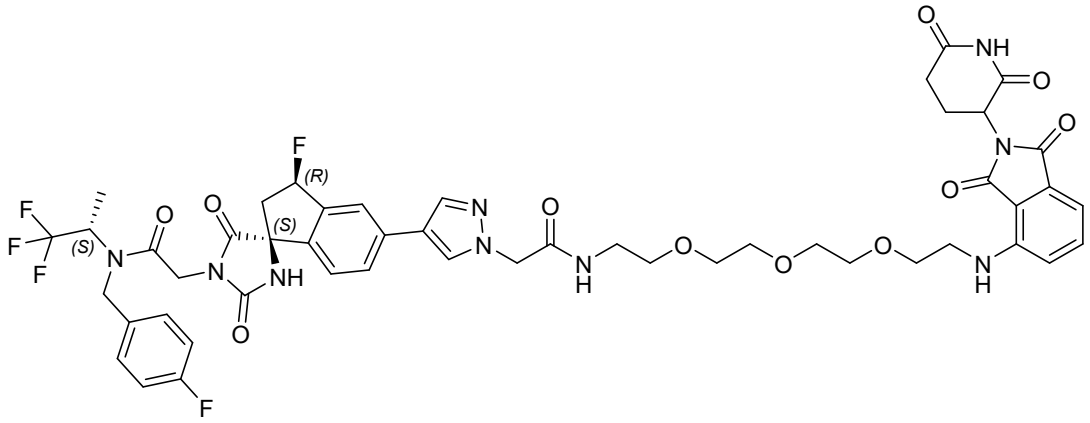
2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with 4-[2-(2-aminoethoxy)ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 3% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (88 mg, 70%, 99% LCMS purity). m/z (ES+): 948.30 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 10.56 (br s, 1H), 8.62 (s, 1H), 8.12 (d, *J*= 0.5, 1H), 7.87 (d, *J*= 0.7, 1H), 7.70 (s, 1H), 7.67, (dt, *J*= 8.0, 1.7, 1H), 7.64 (br s, 1H), 7.57 (dd, *J*= 8.5, 7.2, 1H), 7.39 - 7.32 (m, 3H) 7.13 (m, 3H), 7.04 (d, *J*= 7.0, 1H), 6.51 (t, *J*= 5.2, 1H), 6.14 (ddd, *J*=

57.6, 6.7, 4.5, 1H), 5.18 (m, 1H), 5.00 (m, 1H), 4.82 (d, *J*= 17.2, 1H), 4.82 (s, 2H), 4.62 (d, *J*= 17.2, 1H), 4.48 (d, *J*= 17.2, 1H), 4.27 (d, *J*= 16.7, 1H), 3.68 (t, *J*= 5.5, 2H), 3.56 (t, *J*= 5.5, 2H), 3.49 (q, *J*= 5.6, 2H), 3.34 (q, *J*= 5.6, 2H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.90 - 2.80 (m, 1H), 2.67 - 2.53 (m, 2H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.12 - 2.03 (m, 1H), 1.37 (d, *J*= 6.9, 3H)

HRMS (ES+) calculated for $[C_{45}H_{42}F_5N_9O_9+H^+]^+$ 948.3104, found: 948.3113

2-((3'*R*,4*S*)-5'-(1-(14-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-2-oxo-6,9,12-trioxa-3-azatetradecyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2H)



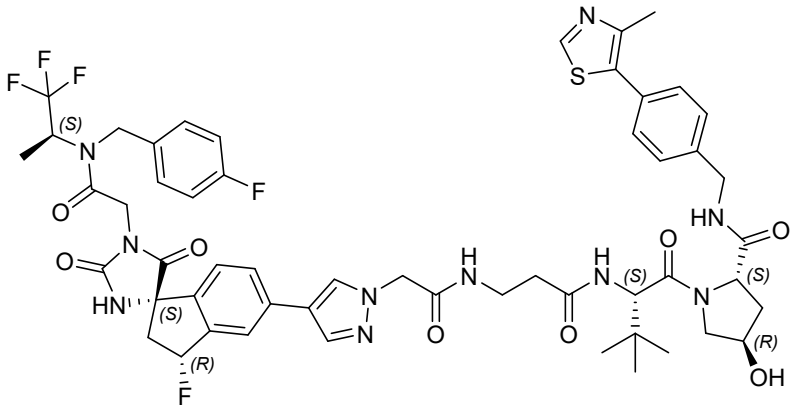
2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with 4-[2-[2-[2-(2-aminoethoxy)ethoxy]ethoxy]ethylamino]-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 2.5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a yellow solid (67 mg, 49%, 98% LCMS purity). m/z (ES+): 1036.40 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 10.55 (br s, 1H), 8.61 (s, 1H), 8.13 (d, *J*= 0.5, 1H), 7.88 (d, *J*= 0.7, 1H), 7.71 (s, 1H), 7.67, (dt, *J*= 8.0, 1.7, 1H), 7.57 (br s, 1H), 7.56 (dd, *J*= 8.8, 7.1, 1H), 7.38 - 7.32 (m, 3H) 7.12 (m, 3H), 7.03 (d, *J*= 7.0, 1H), 6.50 (t, *J*= 5.7, 1H), 6.14 (ddd, *J*= 57.8, 6.8, 4.7, 1H), 5.18 (m, 1H), 4.99 (m, 1H), 4.82 (d, *J*= 17.5, 1H), 4.81 (s, 2H), 4.61 (d, *J*= 17.2, 1H), 4.47 (d, *J*= 17.2, 1H), 4.26 (d, *J*= 16.6, 1H), 3.68 (t, *J*= 5.5, 2H), 3.62 - 3.56 (m, 4H), 3.56 - 3.53 (m, 4H), 3.52 - 3.46 (m, 4H), 3.30 (q, *J*= 5.8, 2H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.90 - 2.80 (m, 1H), 2.68 - 2.52 (m, 2H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.12 - 2.04 (m, 1H), 1.37 (d, *J*= 7.1, 3H)

HRMS (ES+) calculated for $[C_{49}H_{50}F_5N_9O_{11}+H^+]^+$ 1036.3628, found: 1036.3637

(2*S*,4*R*)-1-((*S*)-2-(3-(2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-

4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetamido)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (BT-O2I)

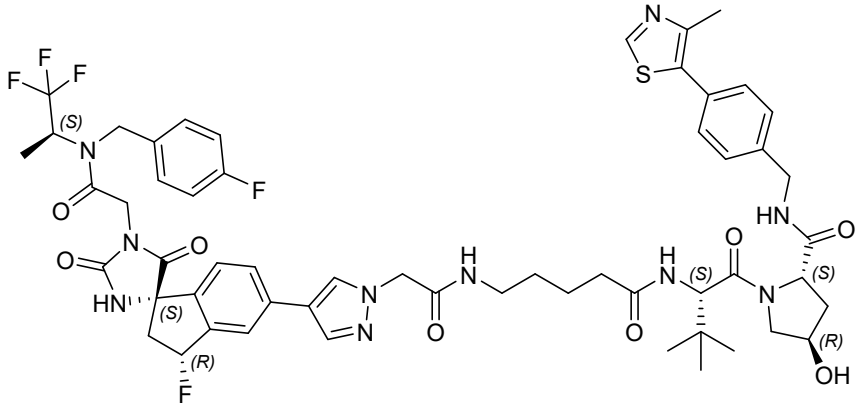


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with (2*S*,4*R*)-1-((*S*)-2-(3-aminopropanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 0-10% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (110 mg, 76%, 98.5% LCMS purity). m/z (ES+): m/z (ES+): 1111.20 $[M+Na^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 8.89 (s, 1H), 8.72 (s, 1H), 8.14 (s, 1H), 8.07 (br s, 1H), 7.89 (s, 1H), 7.74 – 7.65 (m, 3H), 7.50 (br d, *J*= 9.3, 1H), 7.44 – 7.31 (m, 7H), 7.13 (t, *J*= 8.6, 2H), 6.14 (ddd, *J*= 57.6, 6.7, 4.7, 1H), 5.20 (br s, 1H), 4.87 – 4.74 (m, 4H), 4.67 – 4.20 (m, 9H), 3.68 (dd, *J*= 23.6, 10.0, 1H), 3.36 (dd, *J*= 12.5, 6.5, 2H), 3.07 (ddd, *J*= 14.2, 12.7, 6.8, 1H), 2.48 – 2.35 (m, 6H), 2.03 (s, 2H), 1.35 (d, *J*= 7.0, 3H), 0.96 (s, 9H).

HRMS (ES+) calculated for $[C_{53}H_{57}F_5N_{10}O_8S+H^+]^+$ 1089.4080, found: 1089.4080

(2*S*,4*R*)-1-((*S*)-2-(5-(2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetamido)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide (BT-O2J)

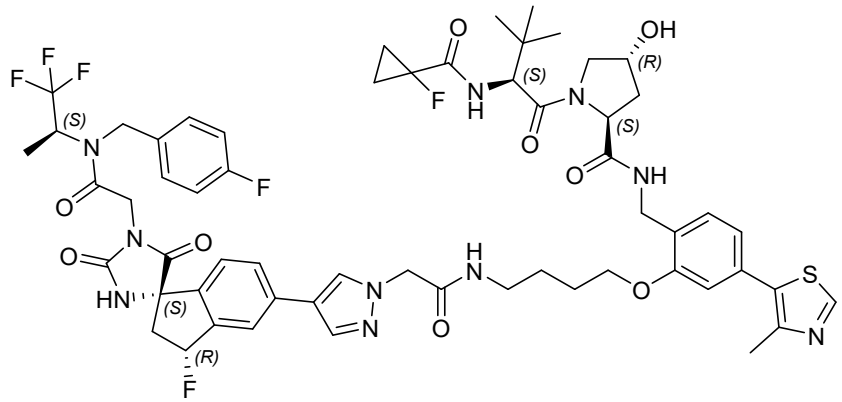


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with (2*S*,4*R*)-1-((*S*)-2-(5-aminopentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-(4-(4-methylthiazol-5-yl)benzyl)pyrrolidine-2-carboxamide dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 0-10% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (78 mg, 53%, 95% LCMS purity). m/z (ES+): 1117.20 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 8.90 (s, 1H), 8.72 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.89 (s, 1H), 7.74 – 7.66 (m, 3H), 7.43 – 7.30 (m, 8H), 7.14 (t, *J*= 8.4, 2H), 6.15 (ddd, *J*= 57.8, 6.7, 4.7, 1H), 5.20 (br s, 1H), 4.86 – 4.72 (m, 4H), 4.68 – 4.56 (m, 1H), 4.57 – 4.45 (m, 3H), 4.44 – 4.33 (m, 2H), 4.33 – 4.19 (m, 2H), 3.75 – 3.62 (m, 2H), 3.17 – 3.02 (m, 3H), 2.45 (s, 3H), 2.43 – 2.34 (m, 1H), 2.30 – 2.13 (m, 3H), 2.06 – 1.98 (m, 2H), 1.60 – 1.44 (m, 4H), 1.35 (d, *J*= 7.0, 3H), 0.96 (s, 9H).

HRMS (ES+) calculated for $[C_{55}H_{61}F_5N_{10}O_8S+H^+]^+$ 1117.4393, found: 1117.4405

(2*S*,4*R*)-*N*-(2-(4-(2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetamido)butoxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (BT-O2K)

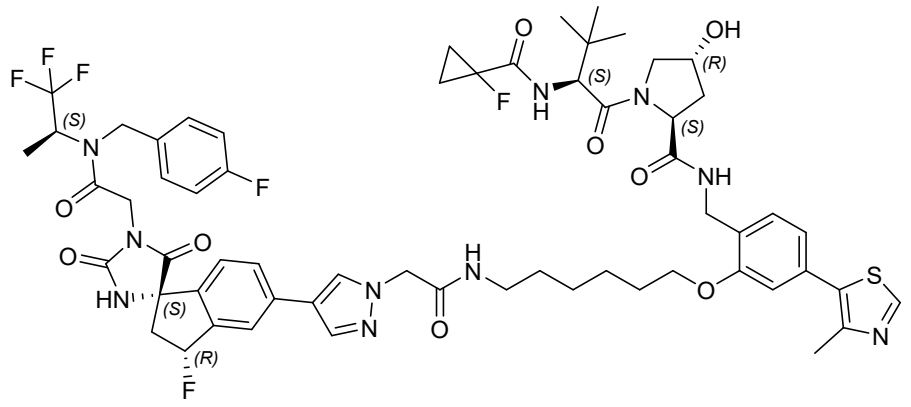


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with (2*S*,4*R*)-*N*-[[2-(4-aminobutoxy)-4-(4-methylthiazol-5-yl)phenyl]methyl]-1-[(2*S*)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 2.5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (98mg, 62%, >99% LCMS purity). m/z (ES-): 1189.4 $[M-H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 8.87 (s, 1H), 8.61 (br s, 1H), 8.13 (s, 1H), 7.87 (s, 1H), 7.82 (m, 1H), 7.71 (s, 1H), 7.67 (dt, *J*= 8.0, 1.7, 1H), 7.65 (br s, 1H), 7.41 - 7.32 (m, 4H), 7.13 (t, *J*= 8.6, 2H), 7.06 (br s, 1H), 7.02 (d, *J*= 1.4, 1H), 6.98 (d, *J*= 8.0, 1H6.14 (ddd, *J*= 57.7, 6.8, 4.6, 1H), 5.18 (m, 1H), 4.82 (d, *J*= 18.1, 1H), 4.79 (s, 2H), 4.70 (br s, 1H), 4.65 - 4.58 (m, 3H), 4.47 (d, *J*= 16.6, 1H), 4.41 (br s, 1H), 4.34 (br s, 2H), 4.27 (d, *J*= 16.6, 1H), 4.10 (t, *J*= 6.4, 2H), 3.77 - 3.56 (m, 2H), 3.24 (q, *J*= 6.8, 2H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.47 (s, 3H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.08 (m, 1H), 1.83 (m, 2H), 1.69 (m, 2H), 1.37 (d, *J*= 7.2, 3H), 1.37 - 1.21 (m, 5H), 0.99 (s, 9H)

HRMS (ES+) calculated for $[C_{58}H_{64}F_6N_{10}O_9S+H^+]^+$ 1191.4561, found: 1191.4576

(2*S*,4*R*)-*N*-(2-((6-(2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetamido)hexyl)oxy)-4-(4-methylthiazol-5-yl)benzyl)-1-((*S*)-2-(1-fluorocyclopropane-1-carboxamido)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxamide (BT-O2L)

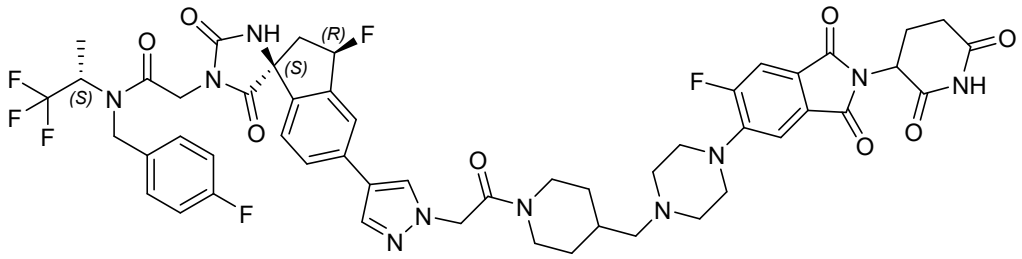


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (80 mg, 0.13 mmol) was coupled with (2*S*,4*R*)-*N*-[[2-(6-aminohexoxy)-4-(4-methylthiazol-5-yl)phenyl]methyl]-1-[(2*S*)-2-[(1-fluorocyclopropanecarbonyl)amino]-3,3-dimethyl-butanoyl]-4-hydroxy-pyrrolidine-2-carboxamide dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 2.5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (108 mg, 67%, >98% LCMS purity). m/z (ES+): 1219.4 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 120 °C) δ: 8.88 (s, 1H), 8.62 (br s, 1H), 8.13 (s, 1H), 7.88 (d, *J*= 0.7, 1H), 7.82 (m, 1H), 7.71 (s, 1H), 7.68 (dt, *J*= 8.0, 1.7, 1H), 7.58 (br s, 1H), 7.41 - 7.32 (m, 4H), 7.13 (t, *J*= 8.6, 2H), 7.07 (br s, 1H), 7.02 (d, *J*= 1.6, 1H), 6.98 (d, *J*= 8.0, 1H), 6.15 (ddd, *J*= 57.7, 6.7, 4.6, 1H), 5.19 (m, 1H), 4.83 (d, *J*= 17.7, 1H), 4.79 (s, 2H), 4.70 (br s, 1H), 4.66 - 4.58 (m, 3H), 4.48 (d, *J*= 16.6, 1H), 4.41 (br s, 1H), 4.34 (br s, 2H), 4.27 (d, *J*= 16.6, 1H), 4.09 (t, *J*= 6.5, 2H), 3.76 - 3.57 (m, 2H), 3.17 (q, *J*= 6.8, 2H), 3.08 (ddd, *J*= 14.4, 12.4, 6.8, 1H), 2.48 (s, 3H), 2.42 (ddd, *J*= 25.5, 14.4, 4.6, 1H), 2.09 (m, 1H), 1.81 (m, 2H), 1.58 - 1.46 (m, 4H) 1.45 - 1.22 (m, 7H), 1.37 (d, *J*= 7.2, 3H), 1.00 (s, 9H)

HRMS (ES+) calculated for $[C_{60}H_{68}F_6N_{10}O_9S+H^+]^+$ 1219.4874, found: 1219.4884

2-((3′*R*,4*S*)-5'-(1-(2-(4-((4-(2-(2,6-Dioxopiperidin-3-yl)-6-fluoro-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2M)

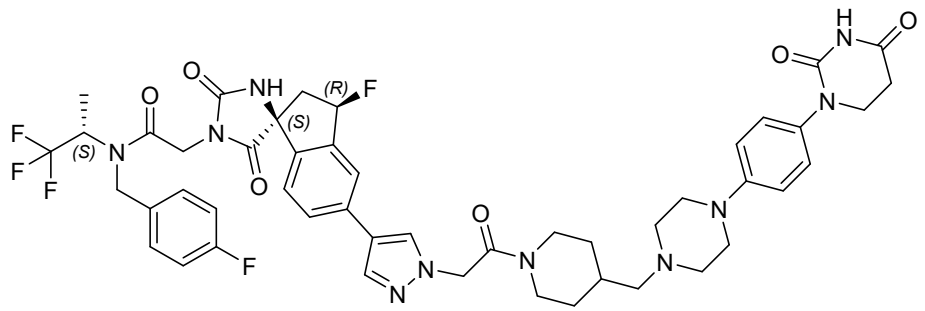


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (63 mg, 0.10 mmol) was coupled with 2-(2,6-dioxo-3-piperidinyl)-5-fluoro-6-[4-(4-piperidinylmethyl)-1-piperazinyl]-1*H*-isoindole-1,3(2*H*)-dione dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 2.5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (97 mg, 89%, >99% LCMS purity). m/z (ES+): 1067.30 $[M+Na^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 10.70 (s, 1H), 8.72 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 7.74 – 7.66 (m, 2H), 7.60 (d, *J*= 11.7, 1H), 7.43 (d, *J*= 7.6, 1H), 7.39-7.30 (m, 3H), 7.13 (t, *J*= 8.3, 2H), 6.15 (ddd, *J*= 57.3, 5.9, 4.7, 1H), 5.28-5.13 (m, 1H), 5.11 – 5.00 (m, 3H), 4.82 (d, *J*= 18.4, 1H), 4.66-4.42 (m, 2H), 4.30 – 4.02 (m, 4H), 3.35-3.27 (m, 4H), 3.12 – 3.02 (m, 2H), 2.89 – 2.80 (m, 1H), 2.68-2.53 (m, 5H), 2.46-2.31 (m, 2H), 2.27 (d, *J*= 6.7, 2H), 2.12 – 2.02 (m, 1H), 1.89-1.75 (m, 3H), 1.35 (d, *J*= 7.1, 3H), 1.20-1.06 (m, 2H).

HRMS (ES+) calculated for $[C_{51}H_{50}F_6N_{10}O_8+H^+]^+$ 1045.3796, found: 1045.3786

2-((3'*R*,4*S*)-5'-(1-(2-(4-((4-(4-(2,4-Dioxotetrahydropyrimidin-1(2H)-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2N)



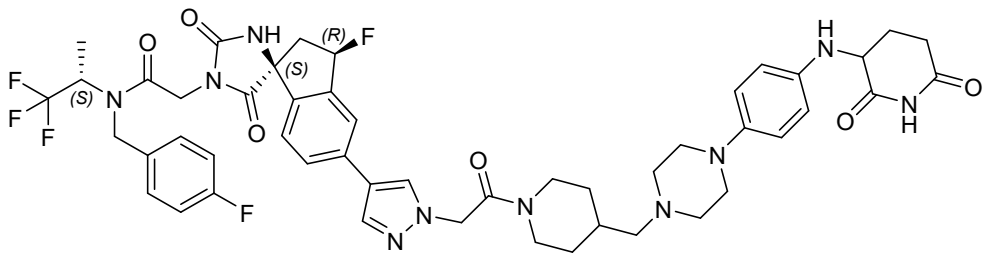
2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (63 mg, 0.10 mmol) was coupled with 1-[4-[4-(4-piperidylmethyl)piperazin-1-

yl]phenyl]hexahydropyrimidine-2,4-dione trihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (41 mg, 42%, 97% LCMS purity). m/z (ES+): 959.40 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 9.79 (s, 1H), 8.73 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 7.74 – 7.66 (m, 2H), 7.39 – 7.30 (m, 3H), 7.21 – 7.09 (m, 4H), 6.93 (d, *J*= 7.9, 2H), 6.15 (ddd, *J*= 57.5, 6.7, 4.4, 1H), 5.20 (br s, 1H), 5.09 (s, 2H), 4.83 (d, *J*= 17.8, 1H), 4.68-4.40 (m, 2H), 4.30-4.01 (m, 3H), 3.71 (t, *J*= 6.7, 2H), 3.25 – 3.02 (m, 5H), 2.70 (t, *J*= 6.7, 2H), 2.65-2.50 (m, 4H), 2.47 – 2.17 (m, 4H), 1.82 (d, *J*= 12.5, 3H), 1.35 (d, *J*= 7.1, 3H), 1.22-1.05 (m, 2H).

HRMS (ES+) calculated for $[C_{48}H_{51}F_5N_{10}O_6+H^+]^+$ 959.3991, found: 959.3975

2-((3'*R*,4*S*)-5'-(1-(2-(4-((4-(4-((2,6-Dioxopiperidin-3-yl)amino)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2O)

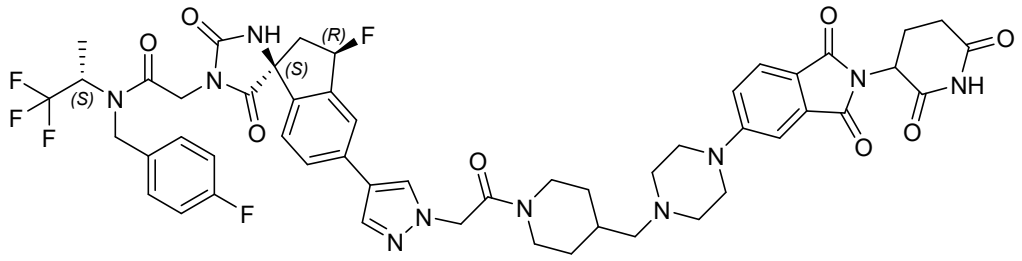


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (63 mg, 0.10 mmol) was coupled with 3-[4-[4-(4-piperidylmethyl)piperazin-1-yl]anilino]piperidine-2,6-dione trihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 30-100% acetone/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (21 mg, 91%, >99% LCMS purity), m/z (ES+): 973.40 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 10.34 (s, 1H), 8.72 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 7.74 – 7.67 (m, 2H), 7.44 – 7.25 (m, 3H), 7.14 (t, *J*= 8.0, 2H), 6.93 (t, *J*= 8.1, 1H), 6.32 – 6.28 (m, 1H), 6.25 – 6.05 (m, 3H), 5.31 (d, *J*= 6.6, 1H), 5.20 (br s, 1H), 5.08 (s, 2H), 4.82 (d, *J*= 17.4, 1H), 4.71-4.41 (m, 2H), 4.31 – 3.97 (m, 4H), 3.14 – 3.01 (m, 5H), 2.80 – 2.59 (m, 2H), 2.55 – 2.50 (m, 4H), 2.48-2.34 (m, 2H), 2.27 – 2.15 (m, 3H), 1.95-1.76 (m, 4H), 1.35 (d, *J*= 7.1, 3H), 1.22 – 1.02 (m, 2H).

HRMS (ES+) calculated for $[C_{49}H_{53}F_5N_{10}O_6 + H^+]^+$ 973.4148, found: 973.4128

2-((3'*R*,4*S*)-5'-(1-(2-(4-((4-(2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)piperazin-1-yl)methyl)piperidin-1-yl)-2-oxoethyl)-1H-pyrazol-4-yl)-3'-fluoro-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2P)

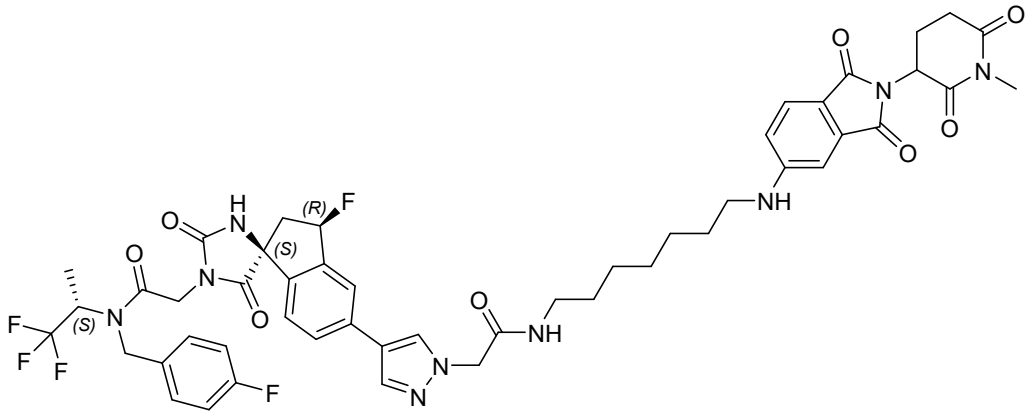


2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (63 mg, 0.10 mmol) was coupled with 2-(2,6-dioxo-3-piperidinyl)-5-[4-(4-piperidinylmethyl)-1-piperazinyl]-1*H*-isoindole-1,3(2*H*)-dione dihydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 3-5% MeOH/DCM, the residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (54.4 mg, 51%, 98% LCMS purity), m/z (ES+): 1027.4 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 10.67 (s, 1H), 8.72 (s, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 7.74 – 7.63 (m, 3H), 7.38 – 7.28 (m, 4H), 7.23 (dd, *J*= 8.6, 1.7, 1H), 7.14 (t, *J*= 8.1, 2H), 6.15 (ddd, *J*= 57.7, 5.8, 4.5, 1H), 5.28 – 5.14 (m, 1H), 5.09 (s, 2H), 5.01 (dd, *J*= 12.5, 5.2, 1H), 4.83 (d, *J*= 17.5, 1H), 4.67 – 4.41 (m, 2H), 4.32 – 4.00 (m, 3H), 3.50 – 3.42 (m, 4H), 3.07 (ddd, *J*= 13.7, 12.7, 6.9, 1H), 2.91 – 2.81 (m, 2H), 2.69 – 2.53 (m, 7H), 2.41 (ddd, *J*= 25.9, 14.6, 4.8, 1H), 2.26 (d, *J*= 6.7, 2H), 2.10 – 2.02 (m, 1H), 1.92 – 1.76 (m, 3H), 1.35 (d, *J*= 7.0, 3H), 1.19 – 1.06 (m, 2H).

HRMS (ES+) calculated for $[C_{51}H_{51}F_5N_{10}O_8+H^+]^+$ 1027.3890, found: 1027.3882

2-((3'*R*,4*S*)-3'-Fluoro-5'-(1-(2-((7-((2-(1-methyl-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)heptyl)amino)-2-oxoethyl)-1H-pyrazol-4-yl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-1-yl)-*N*-(4-fluorobenzyl)-*N*-((*S*)-1,1,1-trifluoropropan-2-yl)acetamide (BT-O2C-N)



2-(4-((3'*R*,4*S*)-3'-Fluoro-1-(2-((4-fluorobenzyl)((*S*)-1,1,1-trifluoropropan-2-yl)amino)-2-oxoethyl)-2,5-dioxo-2',3'-dihydrospiro[imidazolidine-4,1'-inden]-5'-yl)-1H-pyrazol-1-yl)acetic acid (58 mg, 0.10 mmol) was coupled with 5-(7-aminoheptylamino)-2-(1-methyl-2,6-dioxo-3-piperidyl)isoindoline-1,3-dione;hydrochloride according to general procedure A. After purification by flash column chromatography, eluting with 3-5% MeOH/DCM, the

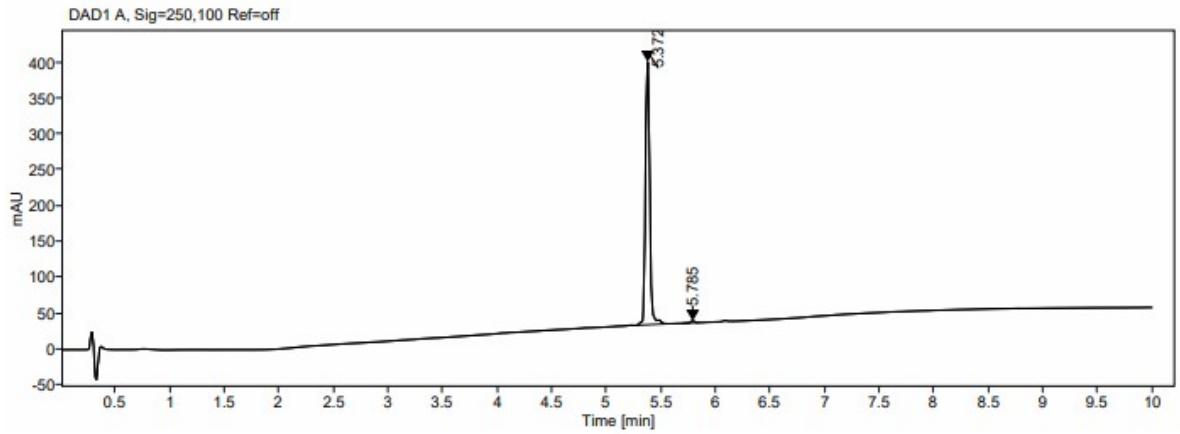
residue was lyophilised from MeCN/H_2O to afford the title compound as a white solid (14 mg, 15%, 98% LCMS purity). m/z (ES+): 988.4 $[M+H^+]^+$

^{1}H NMR (DMSO-d_6, 100 °C) δ: 8.72 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.74 – 7.65 (m, 3H), 7.54 (d, *J*= 8.4, 1H), 7.39 – 7.31 (m, 3H), 7.13 (t, *J*= 8.8, 2H), 6.97 (d, *J*= 2.0, 1H), 6.87 (dd, *J*= 8.4, 2.1, 1H), 6.74 (t, *J*= 5.2, 1H), 6.14 (ddd, *J*= 57.8, 6.8, 5.0, 1H), 5.19 (br s, 1H), 5.05 (dd, *J*= 12.5, 5.6, 1H), 4.86 – 4.76 (m, 3H), 4.67 – 4.41 (m, 2H), 4.25 (d, *J*= 17.7, 1H), 3.16 (ddd, *J*= 19.3, 12.9, 6.7, 4H), 3.10 – 3.02 (m, 4H), 2.94 – 2.87 (m, 1H), 2.81 – 2.73 (m, 1H), 2.63 – 2.52 (m, 1H), 2.41 (ddd, *J*= 25.8, 14.6, 4.6, 1H), 2.08 – 2.01 (m, 1H), 1.65 – 1.56 (m, 2H), 1.53 – 1.44 (m, 2H), 1.35 (d, *J*= 7.2, 3H), 1.37 – 1.31 (m, 6H).

HRMS (ES+) calculated for $[C_{49}H_{50}F_5N_9O_8+H^+]^+$ 988.3781 found: 988.3804

BT-O2C Data

Sample name:	MC-21-II0316B		
Description:	WalkUp method: '5-95% Formic Acid (Non-Polar)' Product Number: C10595-02 Sample Solvent: MeCN		
Acq. method:	5-95 FORMIC ECLIPSE COL OVEN 50C NP.M		
Injection date:	2021-02-08 11:54:52+00:00	**Injection volume:**	1.000
Analysis method:	5-95 FORMIC ECLIPSE COL OVEN 50C NP.M	**Acq. operator:**	Admin



Signal: DAD1 A, Sig=250,100 Ref=off

RT [min]	Width [min]	Area	Height	Area%
5.372	0.04	1021.81	366.17	99.33
5.785	0.04	6.88	2.61	0.67

Figure S6. BT-O2C LCMS purity.

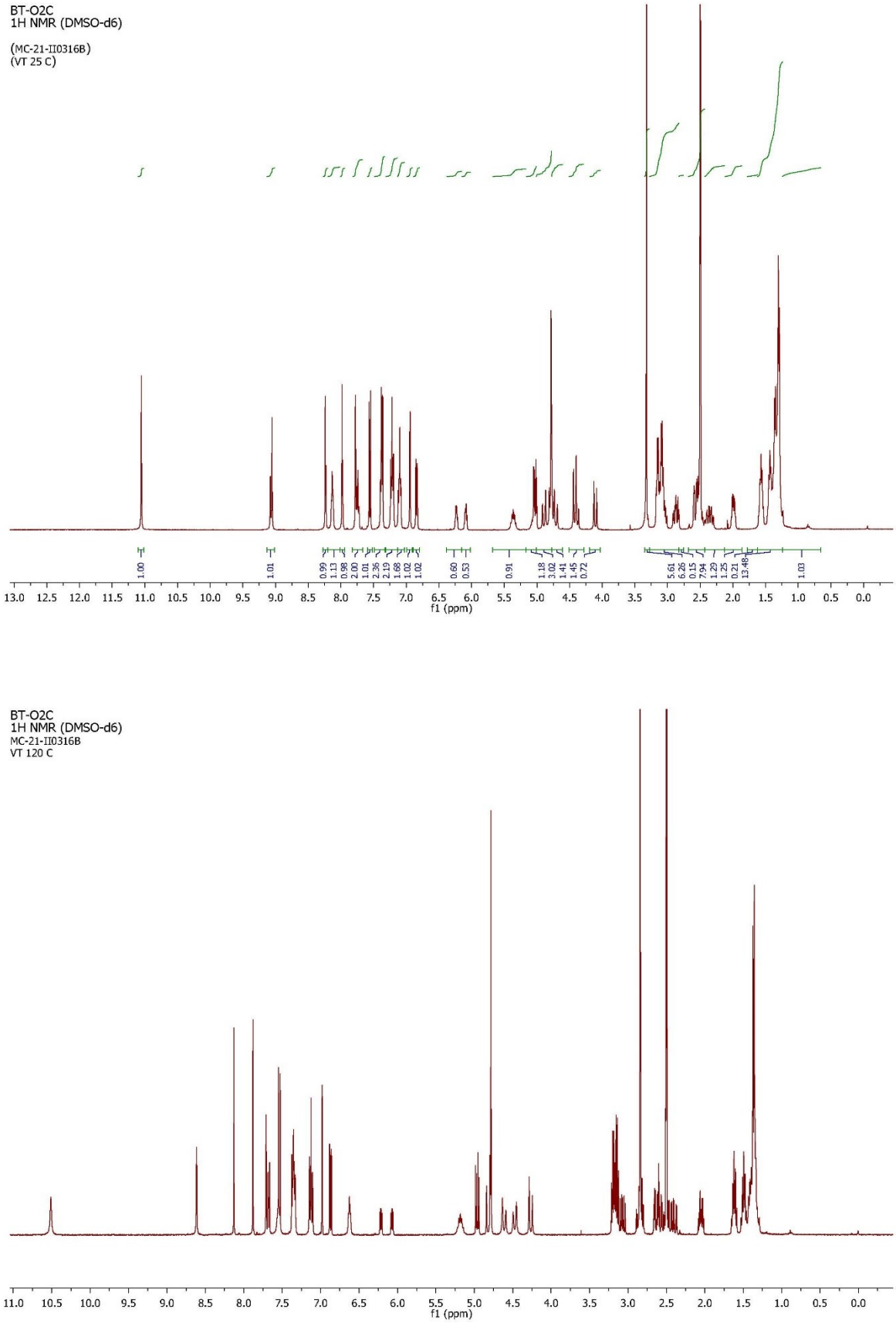


Figure S7. BT-O2C ^{1}H NMR (DMSO-d6) spectra at 25 °C and at elevated temperature (120 °C).

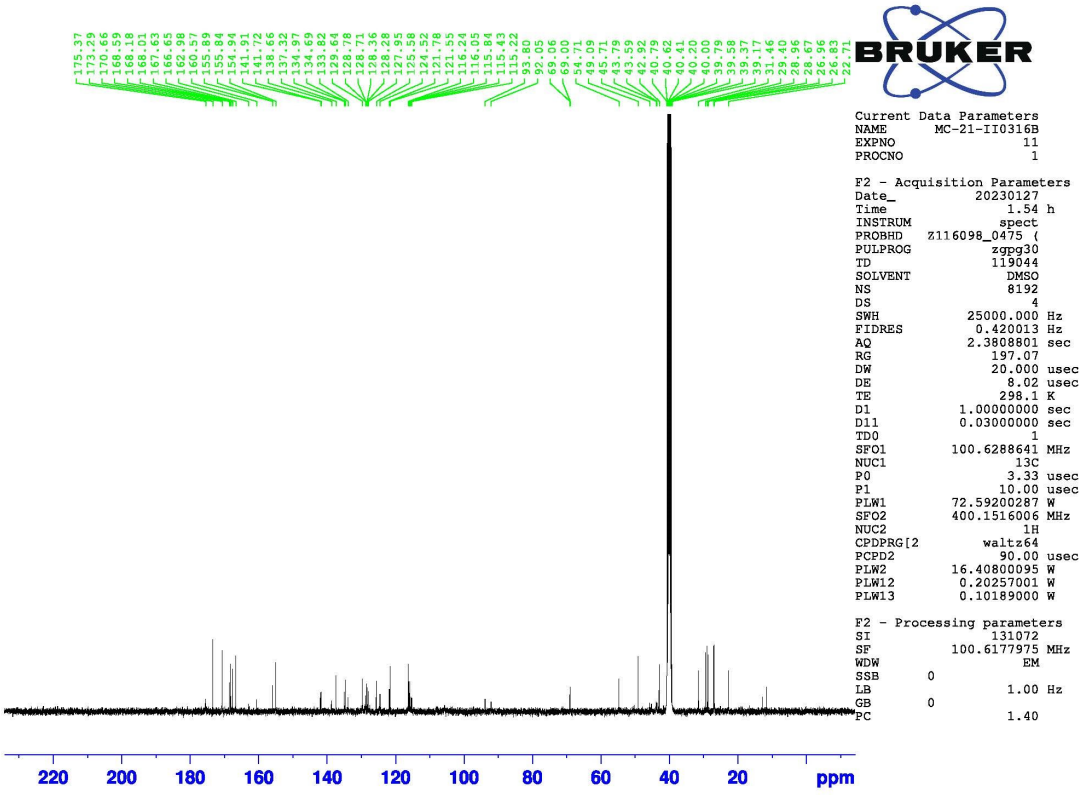


Figure S8. BT-O2C ^{13}C NMR (DMSO-d6) spectrum.