CHEMISTRY GENERAL METHODS

Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on 500 MHz Bruker Avance III spectrometer, and chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Coupling constants (J) are reported in Hz. Spin multiplicities are described as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a Waters Acquity UPLC. Preparative HPLC was performed on a Waters Sunfire C18 column (19 mm × 50 mm, 5 μM) using a gradient of 15 - 95% methanol in water containing 0.05% trifluoroacetic acid (TFA) over 22 minutes (28 minutes run time) at a flow rate of 20 mL/min. Assayed compounds were isolated and tested as TFA salts. Purities of assayed compounds were in all cases greater than 95%, as determined by reverse-phase HPLC analysis.

Abbreviations:

DIEA: diisopropylethyamine

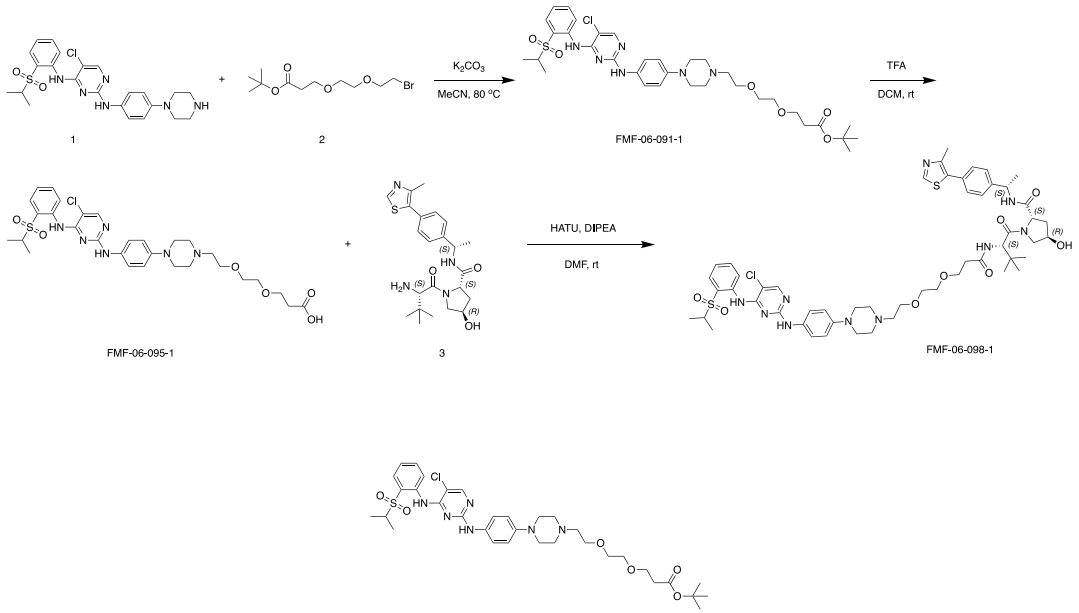
HATU: Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium

DCM: dichloromethane

DMF: dimethylformamide

RT: room temperature

Scheme 1: Synthesis of FMF-06-098-1

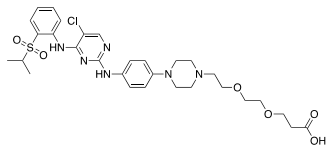


tert-butyl 3-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino) pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)propanoate (FMF-06-091-1)

Intermediate **1** was prepared according to the literature (Huang et al., 2018). Intermediate 1 (25 mg, 0.048 mmol), *tert*-butyl 3-(2-(2-bromoethoxy)ethoxy)propanoate (2) (16 mg, 0.058 mmol) and potassium carbonate (20 mg, 0.144 mmol) were stirred in MeCN (3 mL) at 80 °C and monitored by UPLC/MS. The reaction mixture was cooled to RT, diluted with water (5 mL) and extracted with DCM (3 x 10 mL). The organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1, DCM:MeOH) to yield **FMF-06-091-1** as a colorless oil (31 mg).

^{1}H NMR (500 MHz, MeOD) δ 8.53 (d, *J* = 8.5 Hz, 1H), 7.99 (s, 1H), 7.77 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.53 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.24 – 7.17 (m, 1H), 6.87 – 6.80 (m, 2H), 3.64 – 3.56 (m, 4H), 3.51 (s, 4H), 3.07 (t, *J* = 5.1 Hz, 4H), 2.64 (t, *J* = 5.0 Hz, 4H), 2.57 (dd, *J* = 11.3, 5.7 Hz, 3H), 2.38 (t, *J* = 6.2 Hz, 2H), 1.35 (s, 9H), 1.15 (d, *J* = 6.8 Hz, 6H).

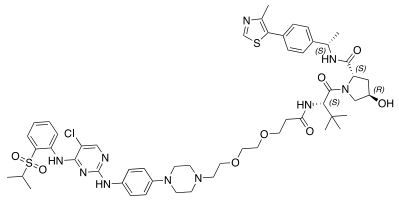
LC/MS (ESI) *m/z* 704.2 [$[M+H]^+$; calcd for $C_{34}H_{47}ClN_6O_6S$: 703.30]



3-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)propanoic acid (FMF-06-095-1)

FMF-06-091-1 (31 mg, 0.044 mmol) was dissolved in 10 mL of DCM, to which was added 1 mL TFA. The reaction was stirred at RT for 2 hours, concentrated under reduced pressure and used without further purification (30 mg, 0.039 mmol).

LC/MS (ESI) *m/z* 648.3 [[M+H]$^+$; calcd for $C_{30}H_{39}ClN_6O_6S$: 647.19]



(2S,4R)-1-((S)-2-(3-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-N-((S)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (FMF-06-098-1)

FMF-06-095-1 (30 mg, 0.039 mmol), VHL ligand **3** (Raina et al., 2016) (23 mg, 0.51 mmol), HATU (21 mg, 0.055 mmol), DIPEA (26 µL, 0.140 mmol) were dissolved in DMF and stirred for 16 hours. The reaction mixture was filtered and purified by preparative phase HPLC to give **FMF-06-098-1** as a colorless oil (46 mg, 0.038 mmol).

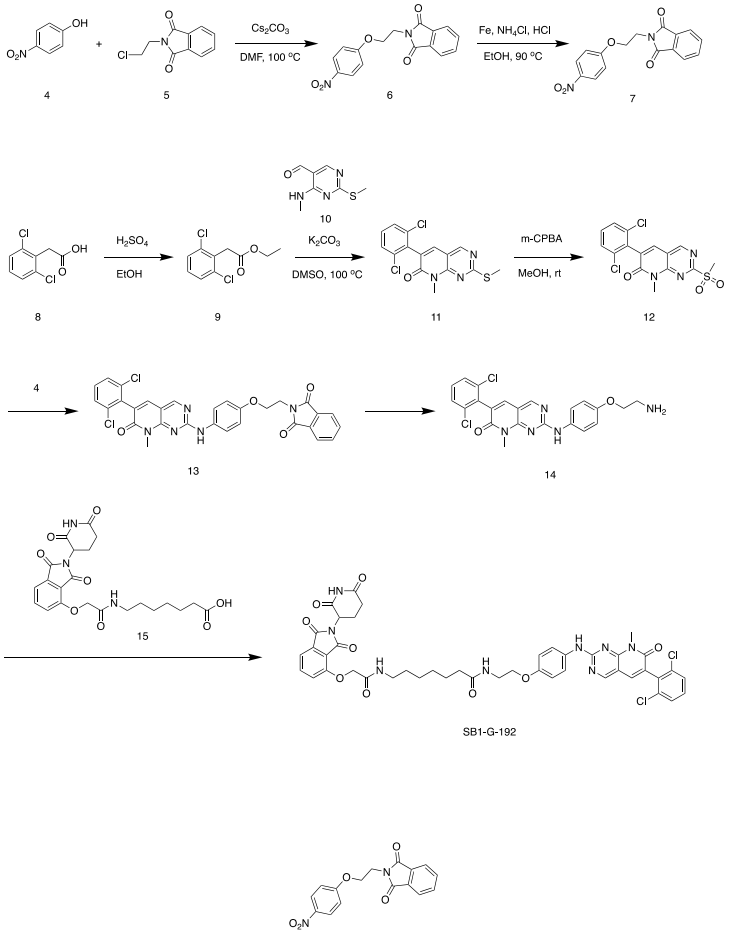
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (s, 2H), 9.51 (s, 1H), 9.40 (s, 1H), 8.98 (d, *J* = 4.3 Hz, 1H), 8.65 (s, 1H), 8.37 (d, *J* = 7.8 Hz, 1H), 8.25 (d, *J* = 1.3 Hz, 1H), 7.91 – 7.83 (m, 2H), 7.77 – 7.72 (m, 1H), 7.50 (d, *J* = 8.7 Hz, 3H), 7.43 (dt, *J* = 7.3, 2.2 Hz, 2H), 7.38 (dt, *J* = 8.3, 3.5 Hz, 4H), 6.95 (dd, *J* = 8.9, 3.7 Hz, 3H), 4.92 (q, *J* = 7.3 Hz, 1H), 4.55 (d, *J* = 9.4 Hz, 1H), 4.43 (t, *J* = 8.1 Hz, 1H), 4.29 (s, 1H), 3.80 (t, *J* = 4.9 Hz, 2H), 3.56 (q, *J* = 5.1, 4.5 Hz, 1H), 3.75 (d, *J* = 12.5 Hz, 1H),

3.45 (p, *J* = 6.8 Hz, 1H), 3.39 (s, 3H), 3.22 (s, 1H), 3.02 (d, *J* = 12.3 Hz, 2H), 2.59 – 2.53 (m, 1H), 2.46 (d, *J* = 3.0 Hz, 4H), 2.40 (dt, *J* = 14.7, 6.1 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.80 (ddd, *J* = 12.9, 8.6, 4.6 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 5H), 0.95 (s, 7H).

^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 171.04, 170.62, 169.89, 162.99, 158.25, 151.97, 129.29, 126.85, 121.61, 116.88, 70.05, 69.67, 69.01, 67.35, 64.75, 59.04, 56.81, 55.35, 54.01, 51.76, 48.17, 46.62, 42.27, 40.50, 40.43, 40.33, 40.28, 40.17, 40.00, 39.83, 39.67, 39.50, 35.87, 26.88, 22.86, 18.53, 17.20, 16.45, 15.33, 12.88.

LC/MS (ESI) *m*/*z* 1074.9 [[M+H]$^+$; calcd for $C_{53}H_{69}ClN_{10}O_8S_2$:1073.77]

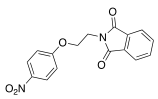
Scheme 2: Synthesis of SB1-G-192



2-(2-(4-nitrophenoxy)ethyl)isoindoline-1,3-dione (6)

The mixture of 4-nitrophenol **4** (5.564 g, 40.0 mmol), 2-(2-chloroethyl)isoindoline-1,3-dione **5** (9.041g, 43.1 mmol) and Cs_2CO_3 (23.4 g, 71.8 mmol) in DMF (80 mL) was stirred at 100 ^oC for 16 hours. The mixture was diluted with water (500 mL) and extracted with DCM (300 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by recrystallization from EtOH to give compound **6** as off-white solid (7.8 g, yield 71%).

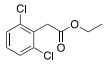
LC/MS (ESI) m/z: 313.1 $[M + H]^+$.



2-(2-(4-aminophenoxy)ethyl)isoindoline-1,3-dione (7)

The mixture of compound **6** (6.6 g, 21.1 mmol), Fe (5.9 g, 105.6 mmol), NH_4Cl (6.7 g, 126.8 mmol) and concentrated HCl solution (10.6 mL, 12 M) in EtOH (200 mL) was stirred at 90 ^oC for 2 hours. The mixture was filtered through celite, the filtrate was concentrated and purified by column chromatography on silica-gel (DCM/MeOH=20/1-5/1) to get compound **7** as off-white solid (5.0 g, yield 84%).

LC/MS (ESI) m/z: 283.1 $[M + H]^+$.

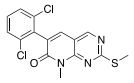


ethyl 2-(2,6-dichlorophenyl)acetate (9)

The mixture of compound **8** (25 g, 121.9 mmol) and concentrated H_2SO_4 (15 mL) in EtOH (200 mL) was heated to reflux for 8 hours. The mixture was concentrated to remove most of the organic solvent, the residue was diluted with water (500 mL), adjusted to pH 8 - 9 with Na_2CO_3 solution and extracted with DCM (300 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by column chromatography on

silica-gel (PE/EtOAc=20/1-4/1) to give compound **9** as off-white solid (23.5 g, yield 83%).

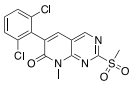
LC/MS (ESI) m/z: 232.9 $[M + H]^+$.



6-(2,6-dichlorophenyl)-8-methyl-2-(methylthio)pyrido[2,3-d]pyrimidin-7(8H)-one (11)

The mixture of compound **9** (5.0 g, 21.4 mmol), compound **10** (2.63 g, 14.3 mmol) and K_2CO_3 (11.8 g, 85.8 mmol) in DMSO (150 mL) was stirred at 100 ^oC for 16 hours. The mixture was concentrated to remove most of the organic solvent, the residue was diluted with water (200 mL) and filtered, the cake was washed with EA/PE=1/3 (50 mL) to give compound **11** as off-white solid (1.85 g, yield 24%).

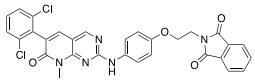
LC/MS (ESI) m/z: 351.9 $[M + H]^+$.



6-(2,6-dichlorophenyl)-8-methyl-2-(methylsulfonyl)pyrido[2,3-d]pyrimidin-7(8H)-one (12)

The mixture of compound **11** (1.6 g, 4.5 mmol) and m-CPBA (1.9 g, 11.3 mmol) in MeOH (50 mL) was stirred at 25 ^oC for 16 hours. The mixture was concentrated to remove most of the organic solvent, the residue was diluted with water (100 mL) and extracted with DCM (200 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by column chromatography on silica-gel (PE/EtOAc=4/1-1/1) to give compound **12** as off-white solid (1.4 g, yield 82%).

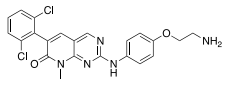
LC/MS (ESI) m/z: 383.8 $[M + H]^+$.



2-(2-(4-((6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)phenoxy)ethyl)isoindoline-1,3-dione (13)

The mixture of compound **12** (3.3 g, 11.9 mmol), compound 9 (0.92 g, 2.4 mmol) and TFA (1.1 g, 9.6 mmol) in 2-BuOH (20 mL) was stirred at 100 ^{o}C for 24 hours. The mixture was diluted with brine (100 mL) and extracted with DCM (200 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by column chromatography on silica-gel (DCM/MeOH=10/1) to give compound **13** as white solid (690 mg, yield 49%).

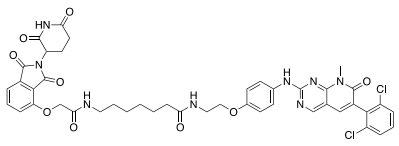
LC/MS (ESI) m/z: 586.1 $[M + H]^+$.



2-((4-(2-aminoethoxy)phenyl)amino)-6-(2,6-dichlorophenyl)-8-methylpyrido[2,3-d]pyrimidin-7(8H)-one (14)

The mixture of compound **13** (590 mg, 1.01 mmol) and $N_2H_4.H_2O$ (503 mg, 10 mmol) in EtOH (20 mL) was heated to reflux for 16 hours. The mixture was concentrated to remove the organic solvent, the residue was diluted with water (100 mL) and extracted with EtOAc (100 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by column chromatography on silica-gel (DCM/MeOH=10/1) to give compound **14** as yellow solid (290 mg, yield 63%).

LC/MS (ESI) m/z: 456.1 $[M + H]^+$.



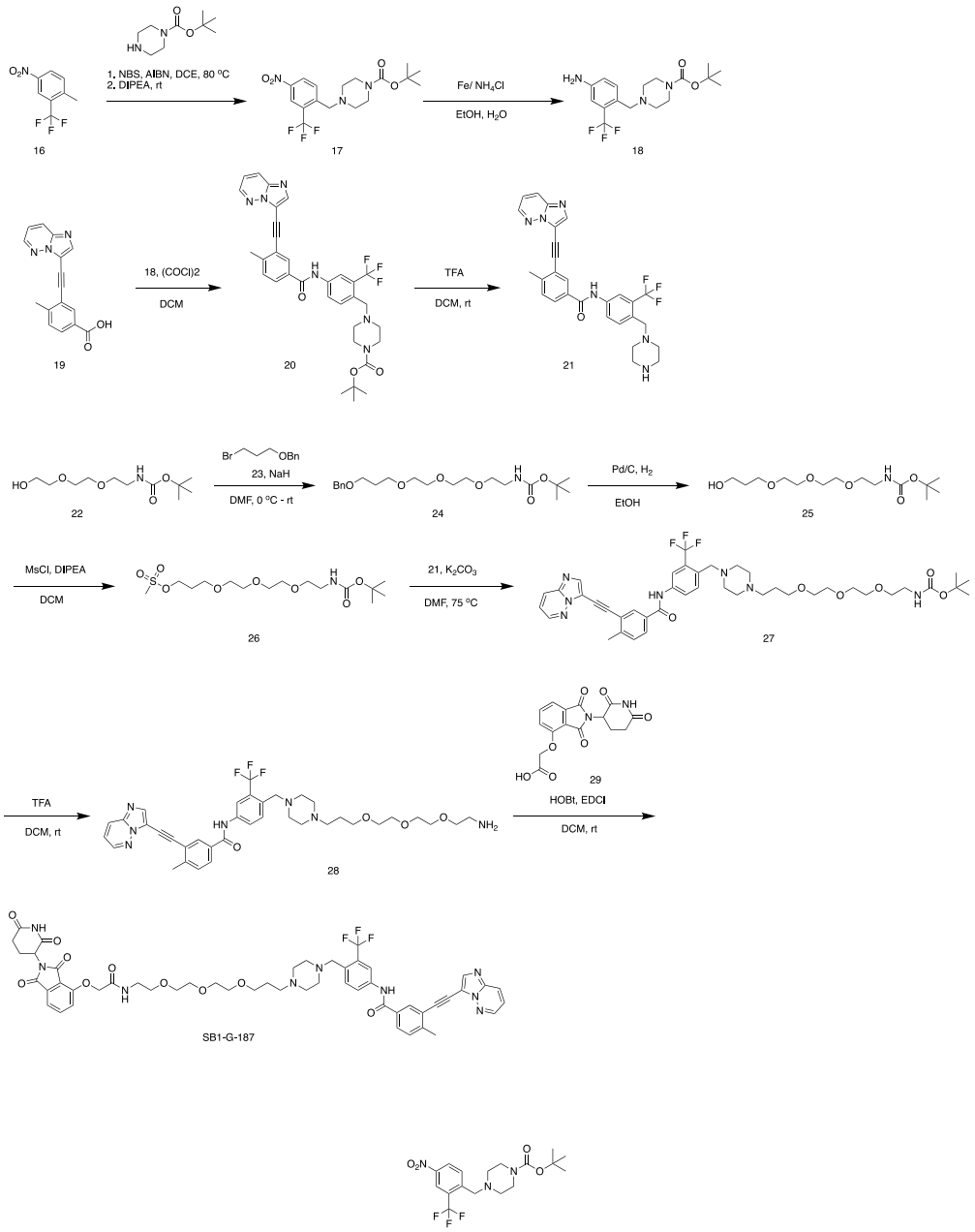
N-(2-(4-((6-(2,6-dichlorophenyl)-8-methyl-7-oxo-7,8-dihydropyrido[2,3-d]pyrimidin-2-yl)amino)phenoxy)ethyl)-7-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)heptanamide (SB1-G-192)

The mixture of compound **14** (109 mg, 0.24 mmol), compound **15** (100 mg, 0.22 mmol), HATU (28.4 mg, 0.07 mmol) and DIPEA (48.3 mg, 0.37 mmol) in DCM (3.0 mL) was stirred at RT for 4 hours, until LC/MS showed full conversion of starting material. The mixture was diluted with water (50 mL) and extracted with DCM (100 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum, the residue was purified by preparative HPLC (C18 column, CH_3CN/H_2O, containing 0.05% NH_4HCO_3) to give compound **SB1-G-192** as off-white solid (35.7 mg).

^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 10.10 (br, 1 H), 8.80 (s, 1 H), 8.04 (t, *J* = 5.6 Hz, 1 H), 7.91 (t, *J* = 5.6 Hz, 1 H), 7.87 (s, 1 H), 7.80 (dd, *J* = 7.2 Hz, 8.4 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.60 (s, 1 H), 7.58 (s, 1 H), 7.52-7.45 (m, 2 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 5.12 (dd, *J* = 12.8 Hz, 5.2 Hz, 1 H), 4.76 (s, 2 H), 3.97 (t, *J* = 5.6 Hz, 2 H), 3.63 (s, 3 H), 3.17-3.08 (m, 2 H), 2.94-2.85 (m, 1 H), 2.69-2.53 (m, 2H), 2.15-1.95 (m, 4 H), 1.54-1.35 (m, 4 H), 1.32-1.16 (m, 7 H).

LC/MS (ESI) m/z: 897.1 $[M + H]^+$

Scheme 3: Synthesis of SB1-G-187

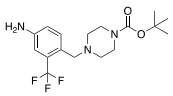


tert-butyl 4-(4-nitro-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (17)

The mixture of 1-methyl-4-nitro-2-(trifluoromethyl)benzene **16** (4.0 g, 19.5 mmol), NBS (3.8 g, 21.4 mmol) and AIBN (639 mg, 3.9 mmol) in DCE (30.0 mL) was stirred at 80 °C for 16 hours, the mixture was cooled down to RT, tert-butyl piperazine-1-carboxylate (4.7 g, 25.3 mmol) and DIPEA (6.7 mL) was added, the resulting mixture was stirred at RT for 2 hours, diluted with water (200 mL) and extracted with DCM (100 mL × 2), the combined organic phase was washed with brine

(100 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, the residue was purified by column chromatography (silica gel, EtOAc/PE = 1/5) to obtain compound **17** as white solid (4.5 g, yield 60%).

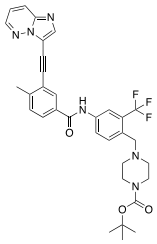
LC/MS (ESI) m/z: 390.0 $[M + H]^+$.



tert-butyl 4-(4-amino-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (18)

The mixture of compound **17** (4.4 g, 11.3 mmol), Fe (3.16 g, 56.5 mmol) and NH_4Cl (3.16 g, 56.5 mmol) in EtOH (30.0 mL) and H_2O (4.0 mL) was stirred at 80 °C for 3 hours, the mixture was filtered, the filtrate was concentrated in vacuum, the residue was diluted with H_2O (200 mL) and extracted with DCM (150 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, the residue was purified by column chromatography (silica gel, MeOH/ DCM = 1/20) to obtain compound **18** as yellow oil (3.5 g, yield 87.5%).

LC/MS (ESI) m/z: 360.0 $[M + H]^+$.

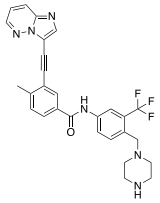


tert-butyl 4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methylbenzamido)-2-(trifluoromethyl)benzyl)piperazine-1-carboxylate (20)

To the solution of compound **19** (300 mg, 1.08 mmol) in DCM (50 mL) was added DMF (0.1 mL), and then $(COCl)_2$ (0.5 mL) was added dropwise at 0 °C, the mixture was stirred at RT for 2 hours and concentrated in vacuum, the residue was dissolved in DCM (10 mL) and added dropwise to the mixture of compound **6** (466 mg, 1.29 mmol) and DIPEA (1.0 mL) in DCM (40 mL) at 0 °C, the

resulting mixture was stirred at RT for 2 hours, diluted with brine (100 mL) and extracted with DCM (100 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum, the residue was purified by preparative HPLC to obtain compound **20** as yellow solid (240 mg, yield 36%).

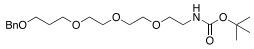
LC/MS (ESI) m/z: 619.0 $[M + H]^+$.



3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-(4-(piperazin-1-ylmethyl)-3-(trifluoromethyl)phenyl)benzamide (21)

The mixture of compound **20** (100 mg, 0.16 mmol) and TFA (2.0 mL) in DCM (2.0 mL) was stirred at RT for 1 hour, the mixture was concentrated in vacuum, the residue was diluted with water (50 mL) and adjusted to pH 8 with $NaHCO_3$, the mixture was extracted with EtOAc (50 mL × 2), the combined organic phase was washed with brine (50 mL × 2), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to leave crude compound **21** as yellow oil (80 mg, yield 96%).

LC/MS (ESI) m/z: 519.0 $[M + H]^+$.

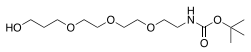


tert-butyl (1-phenyl-2,6,9,12-tetraoxatetradecan-14-yl)carbamate (24)

To the mixture of tert-butyl (2-(2-(2-hydroxyethoxy)ethoxy)ethyl)carbamate **22** (1.5 g, 6.0 mmol) in DMF (15 mL) was added NaH (1.2 g, 30.0 mmol) slowly in portions at 0 °C, after stirred at 0 °C for 1 hour, ((3-bromopropoxy)methyl)benzene **23** (1.5 g, 6.6 mmol) was added, the resulting mixture was stirred at RT for 16 hours, diluted with brine (200 mL) and extracted with DCM (150 mL × 2), the combined organic was dried over anhydrous Na2SO4, filtered and evaporated in

vacuum, the residue was purified by column chromatography (silica gel, EA/PE = 1/5) and preparative HPLC (C18 column, CH3CN/H2O, containing 0.05% TFA) to give compound **24** as colorless oil (380 mg, yield 15%)

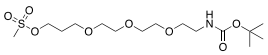
LC/MS (ESI) m/z: 420.1 $[M+Na]^+$, 298.1 $[M - 100 + H]^+$.



tert-butyl (2-(2-(2-(3-hydroxypropoxy)ethoxy)ethoxy)ethyl)carbamate (25)

The mixture of compound **24** (350 mg, 0.8 mmol) and Pd/C (10%, 100 mg) in EtOH (10.0 mL) was stirred at RT under H2 (1 atm) for 2 hours, the mixture was filtered through celite, the filtrate was concentrated to leave crude compound **25** as colorless oil (280 mg, yield 90%).

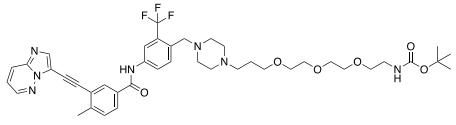
LC/MS (ESI) m/z: 208.1 $[M - 100 + H]^+$, 330.1 $[M+Na]^+$.



2,2-dimethyl-4-oxo-3,8,11,14-tetraoxa-5-azaheptadecan-17-yl methanesulfonate (26)

To the mixture of compound **25** (250 mg, 0.81 mmol) and DIPEA (0.3 mL) in DCM (8 mL) was added MsCl (93 mg, 0.81 mmol) at 0 °C , the mixture was stirred at RT for 2 hours, diluted with saturated $NaHCO_3$ solution (200 mL) and extracted with DCM (150 mL × 2), the combined organic was washed with brine (100 mL × 2), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum to leave crude compound **26** as brown oil (300 mg, yield 95%).

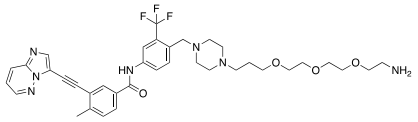
LC/MS (ESI) m/z: 286.0 $[M-100 + H]^+$, 408.0 $[M+Na]^+$.



tert-butyl (2-(2-(2-(3-(4-(4-(3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methylbenzamido)-2-(trifluoromethyl)benzyl)piperazin-1-yl)propoxy)ethoxy)ethoxy)ethyl)carbamate (27)

The mixture of compound **21** (90 mg, 0.17 mmol), compound **26** (100 mg, 0.26 mmol) and K2CO3 (48 mg, 0.34 mmol) in DMF (6.0 mL) was stirred at 70 °C for 16 hours. The mixture was diluted with ethyl acetate (100 mL), washed with brine (50 mL × 2), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum, the residue was purified by column chromatography (silica gel, MeOH/ DCM = 1/20) to afford compound **27** as yellow oil (70 mg, yield 40.4%).

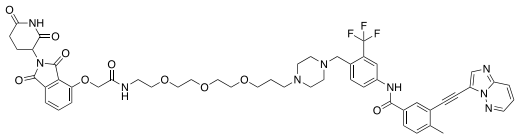
LC/MS (ESI) m/z: 808.1 $[M + H]^+$.



N-(4-((4-(3-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)propyl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methylbenzamide (28)

The mixture of compound **27** (70 mg, 0.08 mmol) and TFA (2.0 mL) in DCM (2.0 mL) was stirred at RT for 1 hour, the mixture was concentrated in vacuum, the residue was diluted with water (20 mL) and adjust to pH 8 with $NaHCO_3$, the mixture was extracted with EtOAc (150 mL × 2), the combined organic phase was washed with brine (50 mL × 2), dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum to leave crude compound **28** as brown oil (80 mg, crude).

LC/MS (ESI) m/z: 708.1 $[M + H]^+$.



N-(4-((4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-2-oxo-6,9,12-trioxa-3-azapentadecan-15-yl)piperazin-1-yl)methyl)-3-(trifluoromethyl)phenyl)-3-(imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methylbenzamide (SB1-G-187)

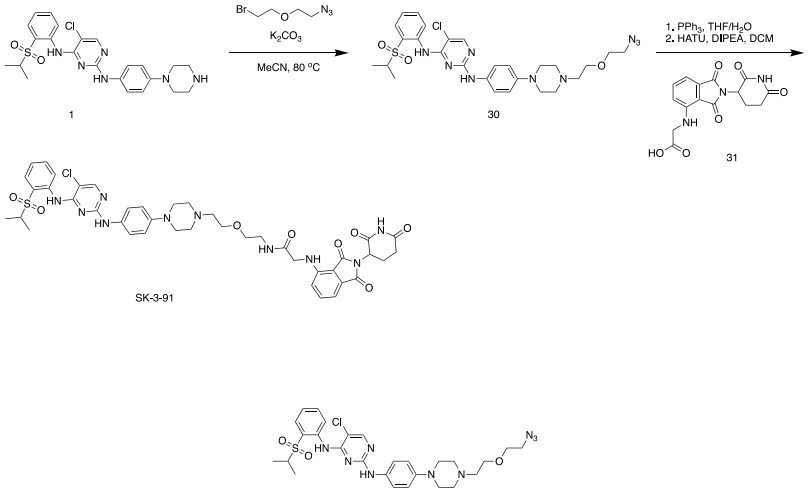
The mixture of compound **29** (43 mg, 0.12 mmol) and HOBt (20 mg, 0.14 mmol) in DCM (5.0 mL) was stirred at RT for 15 minutes, and then EDCI (38 mg, 0.19 mmol) was added, the mixture

was stirred for another 15 minutes, compound **28** (70 mg, 0.09 mmol) was added, the resulting mixture was stirred at RT for 2 hours, diluted with water (20 mL) and extracted with DCM (50 mL × 2), the combined organic was dried over anhydrous Na_2SO_4, filtered and evaporated in vacuum, the residue was purified by preparative HPLC (C18 column, CH_3CN/H_2O, containing 0.05% NH_4HCO_3) to give **SB1-G-187** as light yellow solid (38 mg, yield 37.6%).

1H NMR (CDCl3, 400 MHz): δ (ppm) 8.49 (dd, J1 = 1.2 Hz, J2 = 4.4 Hz, 1 H), 8.32-8.28 (m, 1 H), 8.08-8.07 (m, 2 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.92-7.88 (m, 2 H), 7.83 (dd, J1 = 2.0 Hz, J2 = 8.0 Hz, 1 H), 7.76-7.67 (m, 3 H), 7.52 (d, J = 7.2 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.17-7.12 (m, 2 H), 4.96-4.92 (m, 1 H), 4.64 (s, 2 H), 3.69-3.63 (m, 10 H), 3.60-3.56 (m, 4 H), 3.50 (t, J = 6.4 Hz, 2 H), 2.90-2.72 (m, 3 H), 2.64 (s, 3 H), 2.45-2.44 (m, 3 H), 2.17-2.11 (m, 1H), 1.81-1.66 (m, 9 H).

LC/MS (ESI) m/z: 511.6 $[M/2 + H]^+$

Scheme 4: Synthesis of SK-3-91

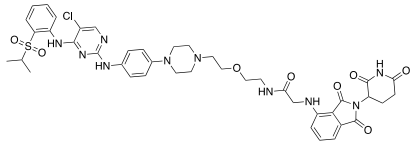


N^2-(4-(4-(2-(2-azidoethoxy)ethyl)piperazin-1-yl)phenyl)-5-chloro-N^4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (30)

Intermediate **1** was prepared according to Scheme 1 (590 mg, 1.0 mmol) and dissolved in acetonitrile (5 mL), to which was added 1-azido-2-(2-bromoethoxy)ethane (300 mg, 1.2 mmol) and potassium carbonate (414 mg, 3.0 mmol). The resulted mixture was stirred under 80 °C

overnight, then cooled down to RT and diluted with 50 mL of dichloromethane. The precipitation was filtered, and the filtrate was concentrated and purified by column chromatography (dichloromethane:methanol = 10:1) to yield **30** as a colorless oil (446 mg).

LC/MS (ESI) m/z 600 $[M+H]^+$.



N-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamide (SK-3-91)

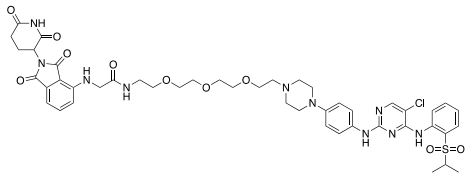
Intermediate **31** was prepared according to the literature (Huang et al., 2018). Under a nitrogen atmosphere, to **30** (30 mg, 0.05 mmol) in tetrahydrofuran (4.5 mL) and water (0.45 mL) was added triphenylphosphine (16 mg, 0.06 mmol). The reaction mixture was stirred overnight, then concentrated and dried under vacuum. To the obtained crude oil in anhydrous dichloromethane (3 mL) was added **31** (18 mg, 0.055 mmol) and (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) and DIEA (27 µL, 0.15 mmol). The reaction mixture was stirred for 2 hours, then concentrated and purified by preparative phase HPLC to give **SK-3-91** as a yellow oil (35 mg, trifluoroacetate salt, 69%).

^{1}H NMR (400 MHz, Methanol-d_4, TFA salt) δ 8.59 (d, J = 8.4 Hz, 1H), 8.16 (s, 1H), 7.92 (dd, J = 8.0, 1.6 Hz, 1H), 7.69 (t, J = 8.0 Hz, 1H), 7.58 (dd, J = 8.5, 7.2 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.39 – 7.32 (m, 1H), 7.11 (d, J = 7.1 Hz, 1H), 7.02 – 6.86 (m, 3H), 4.98 (dd, J = 12.5, 5.5 Hz, 1H), 4.08 (s, 2H), 3.86 – 3.65 (m, 9H), 3.51 (m, 2H), 3.49 – 3.34 (m, 4H), 2.21 (m, 2H), 2.10 – 1.93 (m, 2H), 1.62 (m, 2H), 1.27 (d, J = 6.9 Hz, 6H).

LC/MS (ESI) m/z 887 $[M+H]^+$.

Synthesis of SK-3-87

SK-3-87 was synthesized with similar procedures as **SK-3-91**.



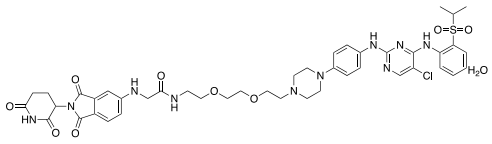
N-(2-(2-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamide (SK-3-87)

^{1}H NMR (400 MHz, Methanol-d_4, TFA salt) δ 8.36 (d, *J* = 8.4 Hz, 1H), 8.00 (s, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.5, 7.1 Hz, 1H), 7.35 – 7.17 (m, 3H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.86 (d, *J* = 8.5 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 4.93 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.84 (m, 2H), 3.76 (dd, *J* = 5.8, 4.1 Hz, 2H), 3.66 – 3.54 (m, 7H), 3.50 (m, 4H), 3.44 (m, 2H), 3.39 – 3.21 (m, 6H), 3.00 (m, 2H), 2.81 – 2.48 (m, 4H), 2.16 – 1.84 (m,2H), 1.13 (d, *J* = 6.8 Hz, 6H).

LC/MS (ESI) m/z 975 $[M+H]^+$.

Synthesis of LT2-49

LT2-49 was synthesized with similar procedures as **SK-3-91**.



N-(2-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)acetamide (LT2-49)

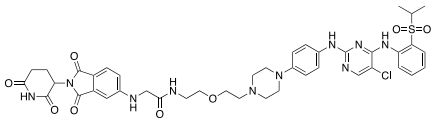
^{1}H NMR (400 MHz, DMSO-d_6, TFA salt) δ 11.07 (s, 1H), 9.70 (s, 1H), 9.51 (s, 1H), 9.39 (s, 1H), 8.63 (s, 1H), 8.25 (s, 1H), 8.12 (t, *J* = 5.7 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.75 (td, *J* = 8.4,

7.9, 1.6 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 (td, *J* = 7.7, 1.2 Hz, 1H), 7.01 – 6.86 (m, 3H), 6.86 (dd, *J* = 8.4, 2.2 Hz, 1H), 5.03 (dd, *J* = 12.8, 5.4 Hz, 1H), 3.85 (s, 2H), 3.82 – 3.66 (m, 4H), 3.57 (dt, *J* = 11.7, 6.1 Hz, 6H), 3.50 – 3.36 (m, 6H), 3.34 – 3.11 (m, 4H), 3.09 – 2.78 (m, 2H), 2.65 – 2.53 (m, 2H), 2.06 – 1.92 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 6H).

LC/MS (ESI) m/z 931 $[M+H]^+$.

Synthesis of SK-3-93

SK-3-93 was synthesized with similar procedures as **SK-3-91**.



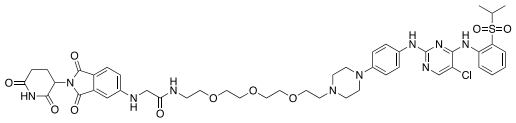
N-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)acetamide (SK-3-93)

^{1}H NMR (400 MHz, Methanol-d_4, TFA salt) δ 8.42 (d, *J* = 8.4 Hz, 1H), 8.04 (s, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 1H), 7.36 – 7.21 (m, 3H), 6.93 – 6.72 (m, 4H), 4.93 (dd, *J* = 12.4, 5.5 Hz, 1H), 3.86 (m, 2H), 3.71 (t, *J* = 4.9 Hz, 2H), 3.50 (m, 6H), 3.38 (m, 2H), 3.32 – 3.24 (m, 4H), 2.80 – 2.59 (m, 4H), 2.17 – 2.02 (m, 1H), 1.94 (dd, *J* = 8.2, 5.1 Hz, 2H), 1.15 (d, *J* = 6.8 Hz, 6H).

LC/MS (ESI) m/z 887 $[M+H]^+$.

Synthesis of SK-3-89

SK-3-89 was synthesized with similar procedures as **SK-3-91**.



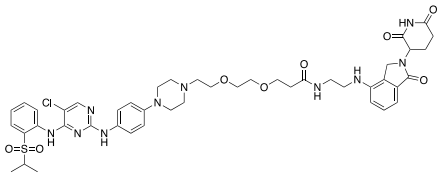
N-(2-(2-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5-yl)amino)acetamide (SK-3-89)

^{1}H NMR (400 MHz, Methanol-d_4, TFA salt) δ 8.34 (d, *J* = 8.3 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.96 – 6.79 (m, 3H), 6.74 (dd, *J* = 8.3, 2.1 Hz, 1H), 4.92 (dd, *J* = 12.4, 5.5 Hz, 1H), 3.79 (m, 2H), 3.76 (m, 2H), 3.70 – 3.51 (m, 10H), 3.47 (m, 8H), 3.45 – 3.25 (m, 2H), 2.75 – 2.58 (m, 2H), 2.03 – 1.89 (m, 1H), 1.13 (d, *J* = 6.8 Hz, 6H).

LC/MS (ESI) m/z 975 $[M+H]^+$.

Synthesis of TL13-97

TL13-97 was synthesized with similar procedures as **SK-3-91**.

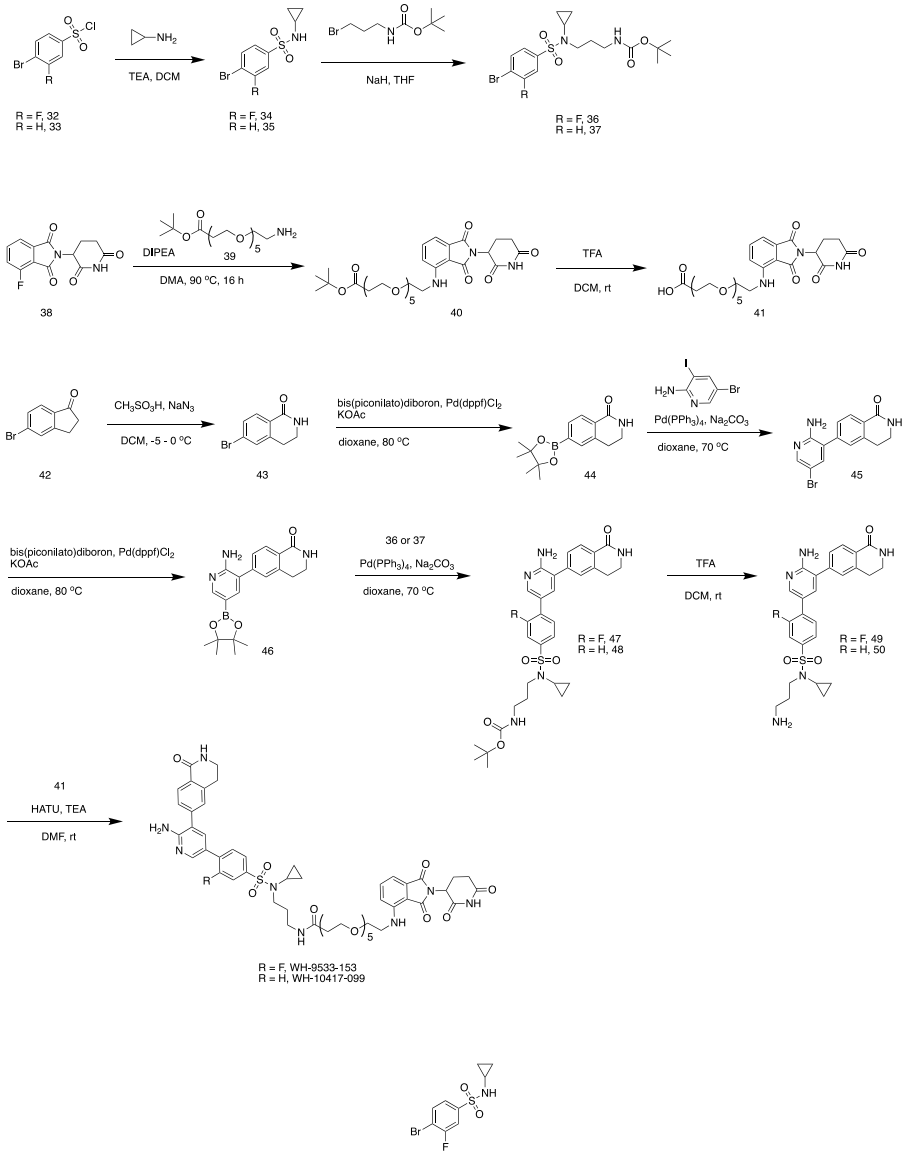


3-(2-(2-(4-(4-((5-chloro-4-((2-(isopropylsulfonyl)phenyl)amino)pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)ethoxy)ethoxy)-N-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)ethyl)propenamide (TL13-97)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.69 (s, 1H), 9.52 (s, 1H), 9.41 (s, 1H), 8.64 (s, 1H), 8.26 (s, 1H), 8.06 (t, *J* = 5.6 Hz, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.80 – 7.68 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.42 – 7.34 (m, 1H), 7.28 (t, *J* = 7.7 Hz, 1H), 7.07 – 6.87 (m, 3H), 6.82 (d, *J* = 8.1 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.29 – 4.04 (m, 2H), 3.83 – 3.70 (m, 4H), 3.64 (t, *J* = 6.4 Hz, 2H), 3.61 – 3.51 (m, 6H), 3.49 – 3.41 (m, 1H), 3.37 (d, *J* = 5.1 Hz, 2H), 3.30 – 3.14 (m, 6H), 3.03 – 2.88 (m, 3H), 2.66 – 2.57 (m, 1H), 2.35 (t, *J* = 6.4 Hz, 2H), 2.29 (dd, *J* = 13.2, 4.6 Hz, 1H), 2.08 – 1.98 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 6H).

LC/MS (ESI) m/z 931$[M+H]^+$.

Scheme 5: Synthesis of WH099 and WH153



4-bromo-*N*-cyclopropyl-3-fluorobenzenesulfonamide (34)

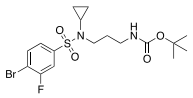
Solution of 4-bromo-3-fluorobenzenesulfonyl chloride **32** (0.55 g, 2.0 mmol, 1.0 eq) in DCM was added dropwise to a stirring solution of cyclopropanamine (0.15 g, 2.6 mmol, 1.3 eq) and TEA (0.84 mL, 6.0 mmol, 3 eq) in DCM at 5-10°C. After addition completed, the mixture was warmed up to room temperature and stirred for 1 hour. The mixture was concentrated, and the residue was purified by flash column chromatography (0% to 30%

EtOAc in hexanes) to afford desired product in high yields. (0.54 g, 92%): LC/MS (ESI) *m*/*z* 293.98 $[M+H]^+$; calcd for $C_9H_{10}BrFNO_2S^+$: 294.14.

4-bromo-N-cyclopropylbenzenesulfonamide (35)

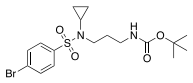
The mixture of 4-bromobenzene-1-sulfonyl chloride (2.56 g, 10.0 mmol, 1.0 eq), cyclopropanamine (0.58 g, 10.0 mmol, 1.0 eq) and Et_3N (1.17 g, 11.0 mmol, 1.1 eq) in DCM (20 mL) was stirred at rt for 22 hours. The mixture was concentrated in vacuum, the residue was purified by flash column chromatography on silica gel (PE: ethyl acetate = 4:1) to give the target compound as a white solid. (2.24 g, 81%)

LC/MS (ESI) *m/z* 277.9 (isotope) $[M+H]^+$; calcd for $C_9H_{11}BrNO_2S^+$: 275.97.



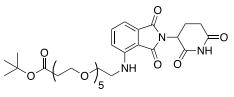
***tert*-butyl(3-((4-bromo-*N*-cyclopropyl-3-fluorophenyl)sulfonamido)propyl)carbamate (36)**

Under N_2 atmosphere, to a stirring suspension of 60% NaH in anhydrous THF was added dropwise the solution of sulfonamide (0.50 g, 1.7 mmol) in anhydrous THF (5 mL) at 5-10℃. After addition completed, the mixture was warmed up to room temperature and stirred for 20 min. A solution of *tert*-butyl (3-bromopropyl)carbamate (0.61 g, 2.5 mmol) in anhydrous THF was added to the above mixture. Then the mixture was heated at 55°C overnight. The mixture was quenched with saturated NH_4Cl aqueous and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (0% to 30% EtOAc in hexanes) to afford desired products (0.44 g, 58%) LC/MS (ESI) *m*/*z* 351.07 $[M-99]^+$; calcd for $C_{17}H_{25}BrFN_2O_4S^+$: 451.35.



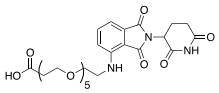
***tert*-butyl(3-((4-bromo-*N*-cyclopropylphenyl)sulfonamido)propyl)carbamate (37)**

The mixture of 4-bromo-N-cyclopropylbenzenesulfonamide (1.91 g, 7.0 mmol, 1.0 eq), *tert*-butyl (3-bromopropyl)carbamate (1.67 g, 14.0 mmol, 2.0 eq) and K_2CO_3 (4.80 g, 35.0 mmol, 5.0 eq) in DMF (70 mL) was stirred at rt for 17 hours. Then 200 mL of water was added and the mixture was extracted with ethyl acetate (200 mL× 3), the combined organic phase was washed with saturated brine (250 mL× 3), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by flash column chromatography on silica gel (PE: ethyl acetate = 9:1) to give the target compound as a white solid (3.12 g, quant.) LC/MS (ESI) *m/z* 332.9 $[M-99]^+$, 454.8 $[M+Na]^+$; calcd for $C_{17}H_{26}BrN_2O_4S^+$ 433.08.



Compound 40

(2,6-dioxopiperidin-3-yl)-4-fluoroisoindoline-1,3-dione (0.28 g, 1.0 mmol), amino-PEG-tert-butyl ester [0.36 g (PEG5), 1.0 mmol], N,N-diisopropylethylamine (DIPEA) (0.24 mL, 1.5 mmol) were mixed in 3 mL dimethylacetamide (DMA). The reaction mixture was heated at 90°C in sealed reaction tube overnight. Then the reaction was cooled to room temperature. The crude was directly subjected to preparative HPLC purification ($MeCN/H_2O$ v/v 0.5‰ TFA). Isolated product was then purified again using flash column chromatography (80% to 100% EtOAc in hexanes). Final product was collected as condensed yellow oil (0.28 g, 44%). LC/MS (ESI) *m/z* 622.23 $[M+H]^+$; calcd for $C_{30}H_{44}N_3O_{11}^+$: 622.30.

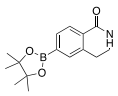


Compound 41

To a solution of A (0.21 g, 0.3 mmol) in DCM 8 mL was added TFA 4 mL, then stirred at room temperature for 1 h. The mixture was concentrated and the crude was purified by preparative HPLC (C18 column, CH_3CN/H_2O, neutral condition) to afford building block B (0.13 g, 68%) LC/MS (ESI) *m*/*z* 566.32 $[M+H]^+$; calcd for $C_{26}H_{36}N_3O_{11}^+$: 566.23

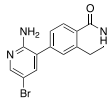
6-bromo-3,4-dihydroisoquinolin-1(2H)-one (43)

Under N_2 atmosphere, to a solution of 5-bromo-2,3-dihydro-1H-inden-1-one (10.00 g, 47.4 mmol) and methanesulfonic acid (45.50 g, 473.9 mmol) in DCM (75 mL) was added NaN_3 (6.20 g, 94.8 mmol) slowly in portions at -5~0℃ with stirring. After addition completed, the mixture was kept at 0°C for 3 hours. The reaction mixture was adjusted to pH=10 with 20% NaOH aqueous solution and extracted with DCM. The combined organic layers were washed with water three times and then with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (0% to 70% EtOAc in hexanes) to afford product (6.9 g, 64%). LC/MS (ESI) *m*/*z* 226.08 $[M+H]^+$; calcd for $C_9H_9BrNO^+$: 226.07.



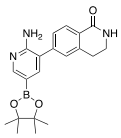
6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2H)-one (44)

Under N_2 atmosphere, a mixture of 6-bromo-3,4-dihydroisoquinolin-1(2H)-one (3.40 g, 15.0 mmol), bis(pinacolato)diboron (5.73 g, 22.5 mmol), potassium acetate (2.95 g, 30.0 mmol) and $Pd(dppf)Cl_2$ (1.10 g, 1.5 mmol) in dioxane (75 mL) was heated at 85°C for 20 hours. The mixture was concentrated, and the residue was purified by flash column chromatography (0% to 80% EtOAc in hexanes) to afford product (3.4 g, 83%). LC/MS (ESI) *m*/*z* 274.28 $[M+H]^+$; calcd for $C_{15}H_{21}BNO_3^+$: 274.16.



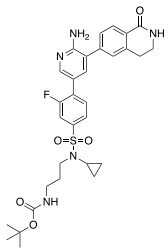
6-(2-amino-5-bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (45)

Under N_2 atmosphere, a mixture of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroisoquinolin-1(2H)-one (3.40 g, 12.5 mmol), 5-bromo-3-iodopyridin-2-amine (4.50 g, 14.9 mmol), sodium carbonate (2.64 g, 24.9 mmol) and $Pd(PPh_3)_4$ (1.44 g, 1.3 mmol) in 1,4-dioxane (80 mL) and water (10 mL) was heated at 70°C for 64 hours. The mixture was concentrated, and the residue was purified by flash column chromatography (0% to 25% MeOH in DCM) to afford product (2.1 g, 53%). LC/MS (ESI) *m/z* 318.18 $[M+H]^+$; calcd for $C_{14}H_{13}BrN_3O^+$: 318.17.



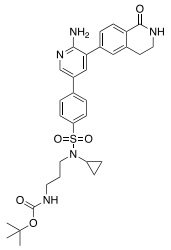
6-(2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (46)

Under N_2 atmosphere, a mixture of 6-(2-amino-5-bromopyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (1.00 g, 3.1 mmol), Bis(pinacolato)diboron (1.20 g, 4.7 mmol), potassium acetate (0.62 g, 6.3 mmol) and $Pd(dppf)Cl_2$ (0.23 g, 0.3 mmol) in 1,4-dioxane (30 mL) was heated at 90°C for 20 hours. The mixture was concentrated. The residue was dissolved in DCM and washed with water two times and brine, dried over $MgSO_4$, filtered and concentrated to afford 2 g crude product, which was used in next step without further purification.



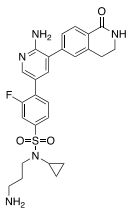
tert-butyl (3-((4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-cyclopropyl-3-fluorophenyl)sulfonamido)propyl)carbamate (47)

Under N_2 atmosphere, A mixture of tert-butyl (3-((4-bromo-N-cyclopropyl-3-fluorophenyl)sulfonamido)propyl)carbamate (0.25 g, 0.56 mmol, 1.0 eq.), 6-(2-amino-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl)-3,4-dihydroisoquinolin-1(2H)-one (0.34 g, 0.56 mmol, 1.0 eq.), sodium carbonate (0.12 g, 1.12 mmol, 2.0 eq.) and $Pd(PPh_3)_4$ (0.065 g, 0.056 mmol, 0.1 eq.) in 1,4-dioxane and water (12 mL, v/v=5:1) was heated at 90°C overnight. The mixture was concentrated, and the residue was purified by flash column chromatography to afford desired products (18 mg, 5.2%): LCMS (ESI) *m*/*z* 610.39 $[M+H]^+$; calcd for $C_{31}H_{37}FN_5O_5S^+$: 610.25.



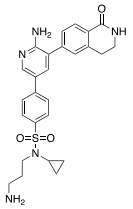
tert-butyl (3-((4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-cyclopropylphenyl)sulfonamido)propyl)carbamate (48)

When R=H: The mixture of (6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)boronic acid (0.5 g, 1.94 mmol, 1.0 eq), *tert*-butyl (3-(4-bromo-*N*-cyclopropylphenylsulfonamido)propyl)carbamate (0.86 g, 1.94 mmol, 1.0 eq), $Pd(PPh_3)_2Cl_2$ (0.27 g, 0.39 mmol, 0.2 eq) and K_2CO_3 (1.08 g, 7.76 mmol, 4.0 eq) in DMF (25 mL) was stirred at 110°C for 4.5 hours. LC-MS showed 41% of target compound. The mixture was cooled down to rt, diluted with water (30 mL) and extracted with EtOAc (60 mL×3). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, concentrated and purified by flash column chromatography on silica gel (PE: ethyl acetate = 9:1 to MeOH:EtOAc = 2:8) to give the target compound (200 mg) as a yellow solid with only 80% purity. The crude compound was further purified by preparative HPLC (C18 column, CH_3CN/H_2O/HCOOH(0.01%)) to give the target compound as a white solid (0.17 g, 15%): LCMS (ESI) *m*/*z* 592.0 $[M+H]^+$; calcd for $C_{31}H_{38}N_5O_5S^+$: 592.26.



4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-(3-aminopropyl)-N-cyclopropyl-3-fluorobenzenesulfonamide (49)

To the solution of Boc-protected products in DCM were added respectively TFA 2 mL, then stirred at room temperature for 30 min. The mixtures were concentrated and dried *in vacuo* to afford free amines in the form of TFA salts, which were used in next step directly. LCMS (ESI) *m*/*z* 510.28 [[M+H]$^+$; calcd for $C_{26}H_{28}FN_5O_3S^+$: 509.60].



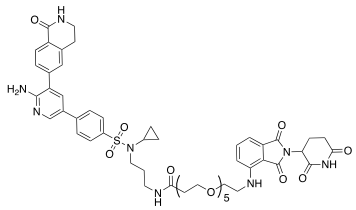
4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-(3-aminopropyl)-N-cyclopropylbenzenesulfonamide (50)

To the solution of Boc-protected products in DCM were added respectively TFA 2 mL, then stirred at room temperature for 30 min. The mixtures were concentrated and dried *in vacuo* to afford free amines in the form of TFA salts, which were used in next step directly. LCMS (ESI) *m*/*z* 492.28 [M+H]$^+$; calcd for $C_{26}H_{30}N_5O_3S^+$: 492.21.

WH-9533-153, WH-10417-099

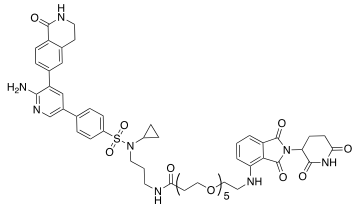
The amine compounds (49: 0.02 g, 0.03 mmol, 1.0 eq; 50: 0.05 g, 0.08 mmol, 1.0 eq.) and PEG5-linked pomalidomide (R=F: 0.02 g, 0.03 mmol, 1.0 eq; R=H: 0.05 g, 0.08 mmol, 1.0 eq) were mixed in DMSO with HATU (1.5 eq) and Et_3N (4.0 eq.) The reactions were stirred at room temperature for 1 hour. The crudes were purified by preparative HPLC (C18 column, CH_3CN/H_2O, neutral condition or with 0.05% TFA) and normal phase flash

chromatography [0% to 20% MeOH in EtOAc/DCM (v/v=1:1)] to afford final products: WH-9533-153 (14 mg, 45%) and WH-10417-099 (47 mg, 51%).



N-(3-((4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-cyclopropyl-3-fluorophenyl)sulfonamido)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide. (WH-9533-153)

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.36 (s, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.75 – 7.55 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.37 (s, 1H), 7.10 (d, *J* = 7.1 Hz, 1H), 7.00 (t, *J* = 5.7 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.51 (dd, *J* = 12.3, 6.7 Hz, 1H), 5.34 (s, 1H), 4.94 (dd, *J* = 12.1, 5.3 Hz, 1H), 3.72 (dt, *J* = 17.4, 8.9 Hz, 3H), 3.69 – 3.57 (m, 9H), 3.54 – 3.42 (m, 2H), 3.35 – 3.22 (m, 2H), 3.07 (t, *J* = 6.5 Hz, 1H), 2.94 – 2.68 (m, 2H), 2.49 (t, *J* = 5.7 Hz, 1H), 2.22 – 2.01 (m, 1H), 1.91 – 1.77 (m, 1H), 0.88 (t, *J* = 7.7 Hz, 1H), 0.73 (q, *J* = 6.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.46, 171.84, 169.36, 169.27, 167.72, 165.73, 160.16, 158.15, 155.81, 146.83, 141.05, 140.02, 138.41, 136.05, 132.52, 130.35, 129.07, 128.72, 127.59, 127.33, 123.74, 120.45, 116.83, 115.85, 115.64, 111.61, 110.29, 70.64, 70.48, 70.43, 70.36, 70.25, 70.10, 69.41, 67.35, 48.95, 48.80, 42.36, 42.26, 40.15, 40.01, 36.89, 36.40, 36.27, 31.56, 30.72, 28.46, 28.37, 22.81, 7.11. LC/MS (ESI) *m*/*z* 1057.54 $[M+H]^+$; calcd for $C_{52}H_{62}FN_8O_{13}S^+$: 1057.41.



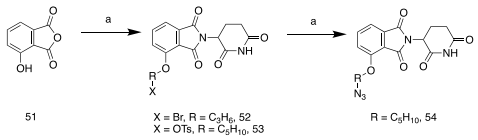
N-(3-(4-(6-amino-5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)pyridin-3-yl)-N-cyclopropylphenylsulfonamido)propyl)-1-((2-(2,6-dioxopiperidin-3-yl)-1,3-

dioxoisoindolin-4-yl)amino)-3,6,9,12,15-pentaoxaoctadecan-18-amide. (WH-10417-099)

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.19 (s, 1H), 8.55 (s, 1H), 8.13 – 8.01 (m, 5H), 7.94-7.91 (m, 3H), 7.71 – 7.55 (m, 3H), 7.21 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 6.68 (t, *J* = 5.8 Hz, 1H), 5.14 (dd, *J* = 12.8, 5.5 Hz, 1H), 3.75 – 3.46 (m, 22H), 3.23 (t, *J* = 7.6 Hz, 2H), 3.11 (q, *J* = 6.7 Hz, 2H), 3.06 (t, *J* = 6.6 Hz, 2H), 2.97 (ddd, *J* = 17.8, 13.7, 5.5 Hz, 1H), 2.73 – 2.52 (m, 4H), 2.38 (t, *J* = 6.4 Hz, 2H), 2.11 (dq, *J* = 7.1, 4.3 Hz, 2H), 1.73 (p, *J* = 7.1 Hz, 2H), 0.89 – 0.68 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 173.29, 170.54, 170.49, 169.40, 167.77, 164.70, 155.59, 146.87, 142.73, 141.40, 140.48, 140.04, 138.39, 136.69, 136.49, 132.55, 129.39, 128.41, 128.36, 128.21, 127.52, 126.77, 123.72, 122.01, 117.90, 111.15, 109.71, 70.29, 70.24, 70.12, 69.98, 69.35, 67.30, 49.03, 48.96, 42.17, 36.68, 36.66, 31.45, 30.74, 28.69, 28.29, 22.62, 7.32.

LC/MS (ESI) *m*/*z* 1038.64 $[M+H]^+$; calcd for $C_{52}H_{63}N_8O_{13}S^+$: 1039.42.

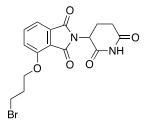
Scheme 6: Synthesis of intermediate 54



Reagent and condition: (a) 3-Aminopiperidine-2,6-dione hydrochloride, KOAc, AcOH, 120 ^{o}C; ii) 1,3-dibromopropane or pentane-1,5-diyl bis(4-methylbenzenesulfonate), DIPEA, DMF, 80 ^{o}C; (b) NaN_3, DMF, 80 ^{o}C.

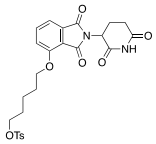
General procedure A for the synthesis of compound (52-53) To a solution of compound **51** (20 g, 122 mmol) in AcOH (400 mL) was added 3-aminopiperidine-2,6-dione hydrochloride (24 g, 146 mmol), KOAc (36 g, 366 mmol) at RT. The reaction mixture was then stirred for 24 hours at 120 ^{o}C, concentrated under reduced pressure. The residue was solidified by swirling in H_2O and filtered out to give black solid and used for next reaction without any further purification. To a solution of black solid (1.0 equiv) in DMF (5.0 mL) was added 1,3-dibromopropane or pentane-

1,5-diyl bis(4-methylbenzenesulfonate) (3.0 equiv), DIPEA (3.0 equiv) at RT. The reaction mixture was then stirred for 30 minutes at 60 ^{o}C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 - 40% THF/hexane) to give compound **52-53** (79-83%).



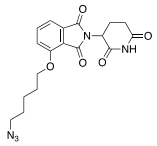
4-(3-Bromopropoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (52) Black solid (498 mg, 1.59 mmol) was converted to the target compound using general procedure A. The residue was purified by flash column chromatography on silica gel (30-40% THF/hexane) to give compound **52** (498 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 5.10 (dd, J = 12.7, 5.1 Hz, 1H), 4.33 (t, J = 5.6 Hz, 2H), 3.82-3.66 (m, 2H), 2.98-2.80 (m, 1H), 2.67-2.52 (m, 2H), 2.37-2.21 (m, 2H), 2.16-1.96 (m, 1H).

LRMS (ESI) *m/z* 395 $[M + H]^+$.



5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)pentyl 4-methylbenzenesulfonate (53) Black solid (527 mg, 1.69 mmol) was converted to the target compound using general procedure A. The residue was purified by flash column chromatography on silica gel (30 - 40% THF/hexane) to give compound **53** (721 mg, 83%).

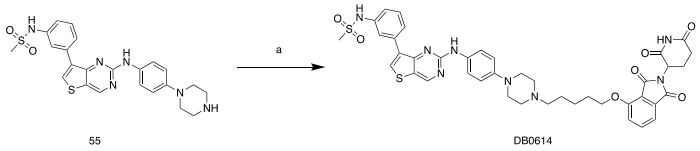
LRMS (ESI) *m/z* 515 $[M + H]^+$.



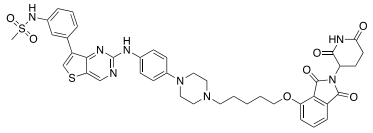
4-((5-Azidopentyl)oxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (54) To a solution of compound **3** (319 mg, 0.62 mmol) in DMF (5.0 mL) was added NaN_3 (201 mg, 3.10 mmol) at RT. The reaction mixture was then stirred for 1 hour at 60 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 - 40% THF/hexane) to give compound **54** (212 mg, 89%).

LRMS (ESI) *m/z* 386 $[M + H]^+$.

Scheme 7: Synthesis of DB0614



Reagent and condition: (a) **53**, DIPEA, DMF, 80 ^oC.



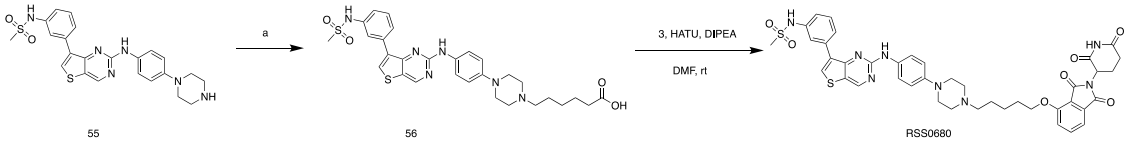
***N*-(3-(2-((4-(4-(5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)pentyl)piperazin-1-yl)phenyl)amino)thieno[3,2-*d*]pyrimidin-7-yl)phenyl)methanesulfonamide (DB0614)**

To a solution of compound **5** (100 mg, 0.21 mmol) in DMF (2.0 mL) was added compound **3** (321 mg, 0.62 mmol), DIPEA (0.11 mL, 0.62 mmol) at RT. The reaction mixture was then stirred for 30 minutes at 60 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 - 40% THF/hexane) to give compound **6** (156 mg, 91%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 9.85 (s, 1H), 9.47 (s, 1H), 9.18

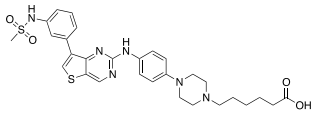
(s, 1H), 8.48 (s, 1H), 7.89-7.78 (m, 3H), 7.72 (d, *J* = 8.6 Hz, 2H), 7.59-7.42 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 5.09 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.24 (t, *J* = 6.2 Hz, 2H), 3.37-3.30 (m, 8H), 3.14-3.01 (m, 5H), 2.64-2.54 (m, 3H), 2.08-1.96 (m, 1H), 1.87-1.76 (m, 2H), 1.70-1.45 (m, 4H).

LRMS (ESI) *m/z* 823 $[M + H]^+$.

Scheme 8: Synthesis of RSS0680



Reagent and condition: (a) i) Ethyl 6-bromohexanoate, DIPEA, DMF, rt; ii) NaOH, MeOH, rt; (b) **3**, HATU, DIEPA, DMF, rt.

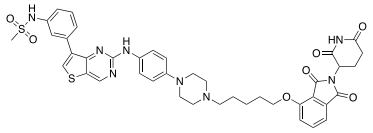


6-(4-(4-((7-(3-(Methylsulfonamido)phenyl)thieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)piperazin-1-yl)hexanoic acid (56)

To a solution of compound **55** (309 mg, 0.64 mmol) in DMF (5.0 mL) was added ethyl 6-bromohexanoate (430 mg, 1.93 mmol), DIPEA (0.34 mL, 1.93 mmol) at RT. The reaction mixture was then stirred for 30 minutes at 60 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the solution of crude ester in MeOH (10.0 mL) was added aqueous NaOH solution (129 mg, 3.21 mmol) at 0 ^oC. The reaction mixture was then stirred for 1 hour at RT, diluted with EtOAc, and neutralized with aqueous citric acid. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was solidified by

swirling in CH_2Cl_2/Et_2O and concentrated to give compound **56** and used for next reaction without any further purification.

LRMS (ESI) *m/z* 595 $[M + H]^+$.

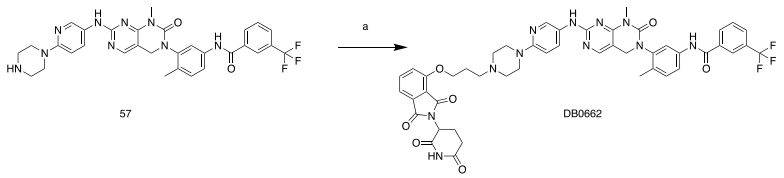


(2*S*,4*R*)-1-((*S*)-3,3-Dimethyl-2-(6-(4-(4-((7-(3-(methylsulfonamido)phenyl) thieno[3,2-*d*]pyrimidin-2-yl)amino)phenyl)piperazin-1-yl) hexanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (RSS0680)

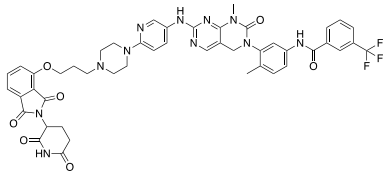
To a solution of compound **56** (116 mg, 0.20 mmol) in DMF (10 mL) was added (*S*,*R*,*S*)-AHPC-Me hydrochloride (104 mg, 0.23 mmol), HATU (222 mg, 0.59 mmol), and DIPEA (0.17 mL, 0.98 mmol) at 0 ^oC. The reaction mixture was then stirred for 30 minutes at 0 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give **RSS0680** (121 mg, 61%). ^1H NMR (400 MHz, Acetone-d_6) δ 9.08 (s, 1H), 8.83 (s, 1H), 8.69 (s, 1H), 8.56 (s, 1H), 8.36 (s, 1H), 8.08 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.75-7.67 (m, 1H), 7.53-7.36 (m, 6H), 7.13-7.07 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.08-4.98 (m, 1H), 4.69-4.56 (m, 2H), 4.47 (brs, 1H), 3.85 (s, 1H), 3.70 (d, *J* = 11.1 Hz, 1H), 3.27-3.12 (m, 4H), 3.02 (s, 3H), 2.95-2.69 (m, 9H), 2.46 (s, 3H), 2.36-2.20 (m, 2H), 1.68-1.52 (m, 4H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.41-1.32 (m, 2H), 1.02 (s, 9H).

LRMS (ESI) *m/z* 1021 $[M + H]^+$.

Scheme 9: Synthesis of DB0662



Reagent and condition: (a) **52**, DIPEA, DMF, 80 °C.

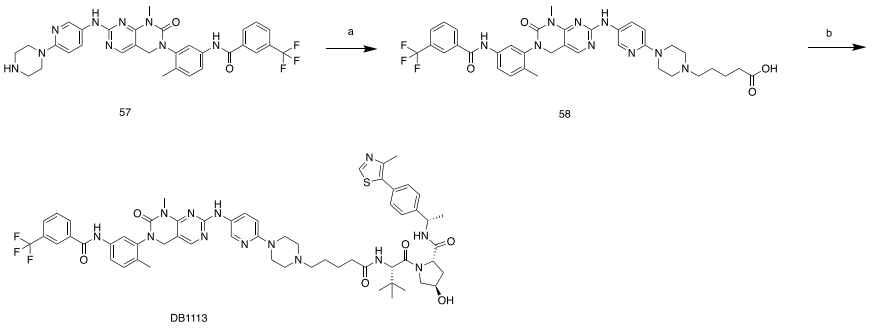


***N*-(3-(7-((6-(4-(3-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)propyl)piperazin-1-yl)pyridin-3-yl)amino)-1-methyl-2-oxo-1,4-dihydropyrimido[4,5-*d*]pyrimidin-3(2*H*)-yl)-4-methylphenyl)-3-(trifluoromethyl)benzamide (DB0662)**

To a solution of compound **57** (108 mg, 0.17 mmol) in DMF (3.0 mL) was added compound **52** (207 mg, 0.52 mmol), DIPEA (0.09 mL, 0.52 mmol) at RT. The reaction mixture was then stirred for 30 minutes at 60 °C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 - 40% THF/hexane) to give **DB0662** (143 mg, 88%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.96 (s, 1H), 9.83 (s, 1H), 8.52 (s, 1H), 8.44 (s, 1H), 8.31 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 8.03 (d, J = 10.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.82-7.75 (m, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 6.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 9.2 Hz, 1H), 5.12-5.10 (m, 1H), 4.76 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 14.0 Hz, 1H), 4.37 (m, 2H), 3.51 (m, 4H), 3.34 (s, 3H), 2.78 (m, 2H), 2.63 (m, 4H), 2.22-2.18 (m, 2H), 2.18 (s, 3H), 2.09-2.08 (m, 2H), 1.27 (m, 2H).

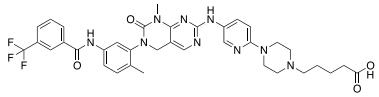
LRMS (ESI) *m/z* 932 $[M + H]^+$.

Scheme 10: Synthesis of DB1113



Reagent and condition: (a) i) Br-R-COOEt, DIPEA, DMF, rt; ii) NaOH, MeOH, rt; (b) **3**, HATU, DIEPA, DMF, rt.

General procedure B for the synthesis of compound (58-59) To a solution of compound **57** (1.0 equiv) in DMF (5.0 mL) was added corresponding chain bearing bromo compound (3.0 equiv), DIPEA (3.0 equiv) at RT. The reaction mixture was then stirred for 30 minutes at 60 ^{o}C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. To the solution of crude ester in MeOH (10.0 mL) was added aqueous NaOH solution (5.0 equiv) at 0 ^{o}C. The reaction mixture was then stirred for 1 hour at RT, diluted with EtOAc, and neutralized with aqueous citric acid. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was solidified by swirling in CH_2Cl_2/Et_2O and concentrated to give compound **11-12** and used for next reaction without any further purification.



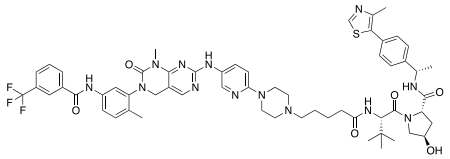
5-(4-(5-((8-Methyl-6-(2-methyl-5-(3-(trifluoromethyl)benzamido)phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)amino)pyridin-2-yl)piperazin-1-yl)pentanoic acid (58)

Compound **9** (350 mg, 0.57 mmol) was converted to the target compound using general procedure B. The residue was solidified by swirling in CH_2Cl_2/Et_2O and concentrated to give compound **11** and used for next reaction without any further purification.

LRMS (ESI) *m/z* 718 $[M + H]^+$.

General procedure C for the synthesis of compound (DB1113-DB1114)

To a solution of compound **58** or **59** (1.0 equiv) in DMF (10 mL) was added **3** (1.2 equiv), HATU (3.0 equiv), and DIPEA (5.0 equiv) at 0 ^oC. The reaction mixture was then stirred for 30 minutes at 0 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give compound **DB1113-DB1114** (49 - 52%).



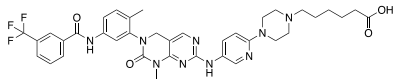
(2*S*,4*R*)-1-((*S*)-3,3-Dimethyl-2-(5-(4-(5-((8-methyl-6-(2-methyl-5-(3-(trifluoromethyl)benzamido)phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)amino)pyridin-2-yl)piperazin-1-yl)pentanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (DB1113)

Compound **58** (121 mg, 0.17 mmol) was converted to the target compound using general procedure C. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give **DB1113** (95 mg, 49%). ^1H NMR (400 MHz, Acetone-d_6) δ 9.86 (s, 1H), 8.83 (s, 1H), 8.52 (s, 1H), 8.46 (d, *J* = 10.9 Hz, 1H), 8.29 (d, *J* = 9.1 Hz, 2H), 8.06 (s, 1H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.86 (s, 1H), 7.81-7.61 (m, 3H), 7.49-7.37 (m, 4H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.19-7.05 (m, 1H), 6.78 (d, *J* = 9.2 Hz, 1H), 5.12-4.98 (m, 1H), 4.79-4.40

(m, 5H), 3.87 (d, *J* = 10.6 Hz, 1H), 3.70 (d, *J* = 7.0 Hz, 1H), 3.52-3.38 (m, 4H), 3.33 (s, 3H), 2.54-2.45 (m, 4H), 2.45 (s, 3H), 2.39-2.21 (m, 4H), 2.16 (s, 3H), 2.13-2.06 (m, 3H), 1.70-1.45 (m, 4H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.02 (s, 9H).

LRMS (ESI) *m/z* 1145 $[M + H]^+$.

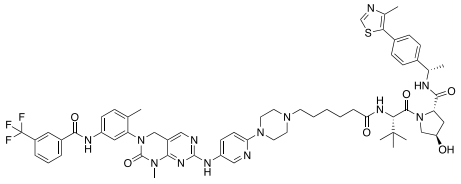
DB1114 was synthesized using similar procedures to DB1113



6-(4-(5-((8-Methyl-6-(2-methyl-5-(3-(trifluoromethyl)benzamido)phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)amino)pyridin-2-yl)piperazin-1-yl)hexanoic acid (59)

Compound **9** (394 mg, 0.64 mmol) was converted to the target compound using general procedure B. The residue was solidified by swirling in CH_2Cl_2/Et_2O and concentrated to give compound **12** and used for next reaction without any further purification.

LRMS (ESI) *m/z* 732 $[M + H]^+$.



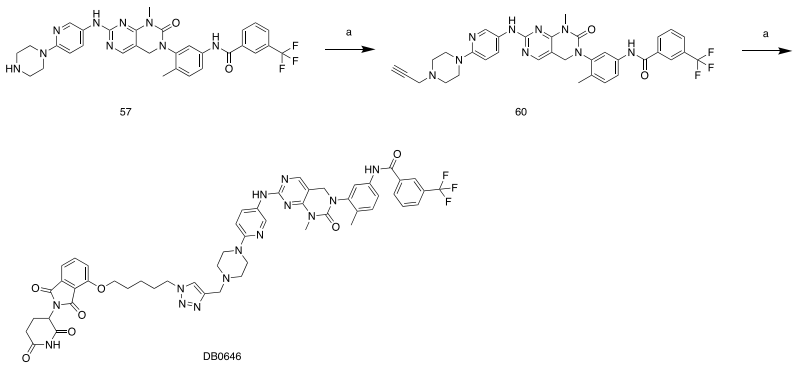
(2*S*,4*R*)-1-((*S*)-3,3-Dimethyl-2-(6-(4-(5-((8-methyl-6-(2-methyl-5-(3-(trifluoromethyl)benzamido)phenyl)-7-oxo-5,6,7,8-tetrahydropyrimido[4,5-*d*]pyrimidin-2-yl)amino)pyridin-2-yl)piperazin-1-yl)hexanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (DB1114)

Compound **59** (118 mg, 0.16 mmol) was converted to the target compound using general procedure C. The residue was purified by flash column chromatography on silica gel (20% EtOAc/hexane) to give compound **DB1114** (97 mg, 52%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.86

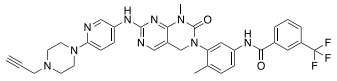
(s, 1H), 8.83 (s, 1H), 8.52 (s, 1H), 8.46 (s, 1H), 8.33-8.24 (m, 2H), 8.06 (s, 1H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.86 (s, 1H), 7.81-7.70 (m, 2H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.50-7.37 (m, 4H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 9.1 Hz, 1H), 6.80 (d, *J* = 9.2 Hz, 1H), 5.10-4.97 (m, 1H), 4.76 (d, *J* = 13.9 Hz, 1H), 4.69-4.51 (m, 3H), 4.46 (s, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.70 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.56-3.42 (m, 4H), 3.34 (s, 3H), 2.60-2.51 (m, 4H), 2.46 (s, 3H), 2.42-2.34 (m, 2H), 2.33-2.30 (m, 2H), 2.17 (s, 3H), 2.12-2.04 (m, 3H), 1.68-1.50 (m, 4H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.39-1.27 (m, 2H), 1.02 (s, 9H).

LRMS (ESI) *m/z* 1158 $[M + H]^+$.

Scheme 11: Synthesis of DB0646



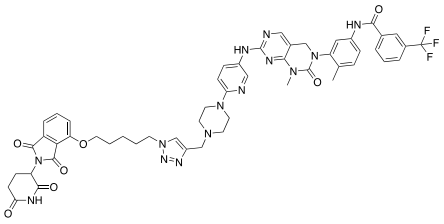
Reagent and condition: (a) Propargyl bromide, DIPEA, DMF, 80 ^oC, (b) **54**, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF/H_2O (4:1), 60 ^oC.



***N*-(4-Methyl-3-(1-methyl-2-oxo-7-((6-(4-(prop-2-yn-1-yl)piperazin-1-yl)pyridin-3-yl)amino)-1,4-dihydropyrimido[4,5-*d*]pyrimidin-3(2*H*)-yl)phenyl)-3-(trifluoromethyl)benzamide (60)**

To a solution of compound **57** (200 mg, 0.32 mmol) in DMF (2.0 mL) was added propargyl bromide (38.5 mg, 0.32 mmol), DIPEA (0.56 mL, 3.24 mmol) at RT. The reaction mixture was then stirred for 1 hour at 80 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed

with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4 - 7% MeOH/CH_2Cl_2) to give compound **60** (168 mg, 79%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 9.78 (s, 1H), 8.48 (d, J = 2.4 Hz, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 8.02 (s, 1H), 7.98 (dd, J = 7.2, 2.4 Hz, 1H), 7.87 (d, J = 6.0 Hz, 1H), 7.82 (d, J = 1.6 Hz, 1H), 7.72 (t, J = 6.4 Hz, 1H), 7.63 (dd, J = 6.4, 1.6 Hz, 1H), 7.21 (d, J = 6.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 4.71 (d, J = 10.0 Hz, 1H), 4.51 (d, J = 10.0 Hz, 1H), 3.47 (m, 4H), 3.31 (s, 3H), 3.30 (s, 2H), 2.67 (t, J = 0.8 Hz, 1H), 2.58 (m, 4H), 2.10 (s, 3H). LRMS (ESI) *m/z* 656 $[M + H]^+$.



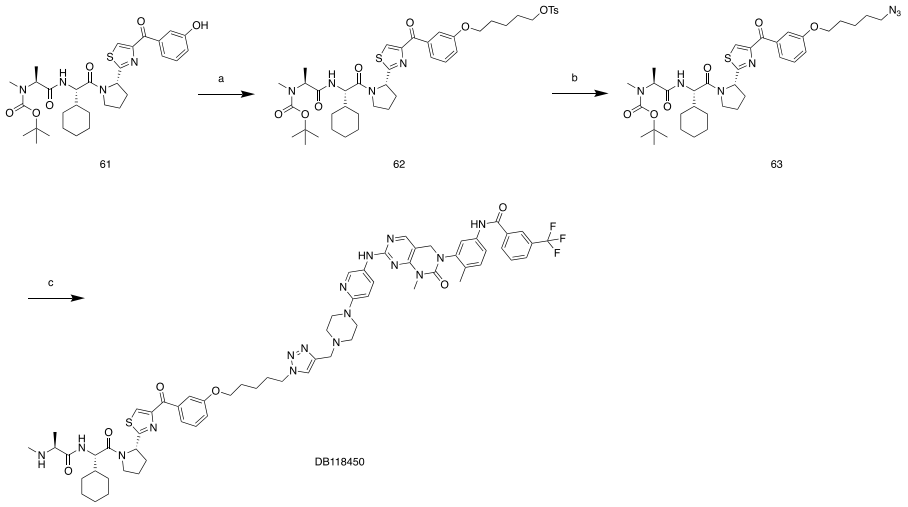
***N*-(3-(7-((6-(4-((1-(5-((2-(2,6-Dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)pentyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)pyridin-3-yl)amino)-1-methyl-2-oxo-1,4-dihydropyrimido[4,5-*d*]pyrimidin-3(2*H*)-yl)-4-methylphenyl)-3-(trifluoromethyl)benzamide (DB0646)**

To a solution of compound **60** (30 mg, 0.05 mmol) in DMF/H_2O (4:1, 2.0 mL) was added compound **4** (1.2 equiv), sodium ascorbate (1.5 equiv) and $CuSO_4 \cdot 5H_2O$ (1.5 equiv) at RT. The reaction mixture was then stirred for 3 hours at 60 ^{o}C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4-7% MeOH/CH_2Cl_2) to give **DB0646** (38 mg, 79%). ^{1}H NMR (400 MHz, Acetone-d_6) δ 10.39 (s, 1H), 9.83 (s, 1H), 8.50 (s, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 8.28 (s, 1H), 8.07 (s, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.88 (m, 1H), 7.78 (dd, J = 16.0, 8.0 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.44 (dd, J = 16.0, 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H),

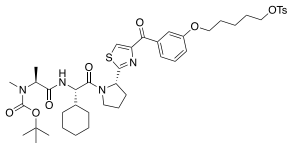
5.10 (dd, *J* = 16.0, 8.0 Hz, 2H), 4.77 (d, *J* = 14.0 Hz, 1H), 4.56 (d, *J* = 14.0 Hz, 1H), 4.47-4.44 (m, 2H), 4.26 (m, 2H), 3.67 (s, 2H), 3.48 (s, 3H), 3.34 (s, 3H), 2.59 (s, 3H), 2.19 (s, 3H), 1.92-1.89 (m, 2H), 1.62-1.59 (m, 2H).

LRMS (ESI) *m/z* 1042 $[M + H]^+$.

Scheme 12: Synthesis of DB118450



Reagent and condition: (a) Pentane-1,5-diyl bis(4-methylbenzenesulfonate), DIPEA, DMF, 50 ^oC; (b) NaN_3, DMF, 50 ^oC; (c) i) **57**, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, DMF/H_2O (4:1), 60 ^oC, ii) TFA, CH_2Cl_2, RT.

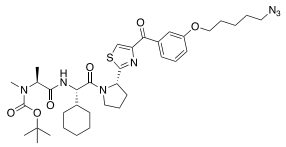


5-(3-(2-((*S*)-1-((*S*)-2-(2-((*tert*-Butoxycarbonyl)(methyl)amino)acetamido)-2-cyclohexylacetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)pentyl 4-methylbenzenesulfonate (62)

To a solution of compound **61** (100 mg, 0.17 mmol) in DMF (10.0 mL) was added pentane-1,5-diyl bis(4-methylbenzenesulfonate) (206 mg, 0.50 mmol), K_2CO_3 (46 mg, 0.33 mmol) at RT. The

reaction mixture was then stirred for 3 hours at 50 °C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 - 30% THF/hexane) to give compound **62** (131 mg, 93%).

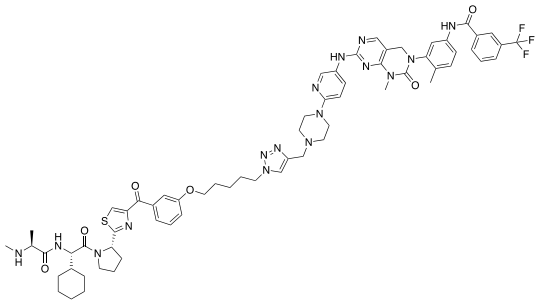
LRMS (ESI) *m/z* 826 $[M+H]^+$.



***tert*-butyl (2-(((*S*)-2-((*S*)-2-(4-(3-((5-azidopentyl)oxy)benzoyl)thiazol-2-yl)pyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl)amino)-2-oxoethyl)(methyl)carbamate (63)**

To a solution of compound **62** (100 mg, 0.12 mmol) in DMF (10.0 mL) was added NaN_3 (46 mg, 0.72 mmol) at RT. The reaction mixture was then stirred for 2 hours at 50 °C, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15 - 20% THF/hexane) to give compound **19** (65 mg, 80%).

LRMS (ESI) *m/z* 697 $[M+H]^+$.

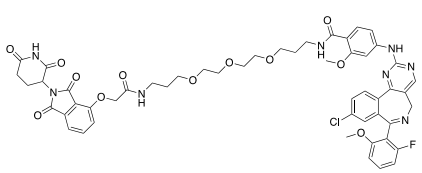


***N*-(3-(7-((6-(4-((1-(5-(3-(2-((*S*)-1-((*S*)-2-cyclohexyl-2-((*S*)-2-(methylamino)propanamido)acetyl)pyrrolidin-2-yl)thiazole-4-carbonyl)phenoxy)pentyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)pyridin-3-yl)amino)-1-methyl-2-oxo-1,4-**

dihydropyrimido[4,5-*d*]pyrimidin-3(2*H*)-yl)-4-methylphenyl)-3-(trifluoromethyl)benzamide (DB118450)

To a solution of compound **63** (61 mg, 0.09 mmol) in DMF/H_2O (4:1, 5.0 mL) was added compound **57** (99 mg, 0.14 mmol), sodium ascorbate (28.0 mg, 0.14 mmol) and $CuSO_4 \cdot 5H_2O$ (35 mg, 0.14 mmol) at RT. The reaction mixture was then stirred for 30 minutes at 60 ^oC, quenched with water and diluted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was solidified by swirling in CH_2Cl_2/Et_2O and concentrated to give a white solid. To the solution of residue in CH_2Cl_2 (10.0 mL) was added TFA (10.0 equiv) at 0 ^oC. The reaction mixture was then stirred for 36 hours at RT, diluted with EtOAc, and neutralized with aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (4 - 7% MeOH/ CH_2Cl_2) to give **DB118450** (90 mg, 50% overall yield for 2 steps). LRMS (ESI) *m/z* half mass 633 $[M + H]^+$; ^1H NMR (400 MHz, Methanol-d_4) δ 8.48 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 2H), 8.27 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 8.03 (s, 1H), 8.00-7.87 (m, 2H), 7.87-7.71 (m, 3H), 7.72-7.60 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.23 (d, *J* = 5.6 Hz, 1H), 6.84 (d, *J* = 9.5 Hz, 1H), 5.51 (d, *J* = 7.0 Hz, 1H), 4.82 (d, *J* = 14.1 Hz, 1H), 4.71-4.46 (m, 4H), 4.34-4.19 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.89-3.75 (m, 2H), 3.47-3.48 (m, 4H), 3.46 (s, 3H), 3.41-3.39 (m, 4H), 3.30-3.19 (m, 1H), 2.74-2.62 (m, 4H), 2.48-2.36 (m, 2H), 2.33-2.15 (m, 7H), 2.14-2.04 (m, 2H), 1.98-1.69 (m, 7H), 1.65-1.44 (m, 3H), 1.42-1.21 (m, 6H).

LRMS (ESI) *m/z* 633 $[M/2+H]^+$.



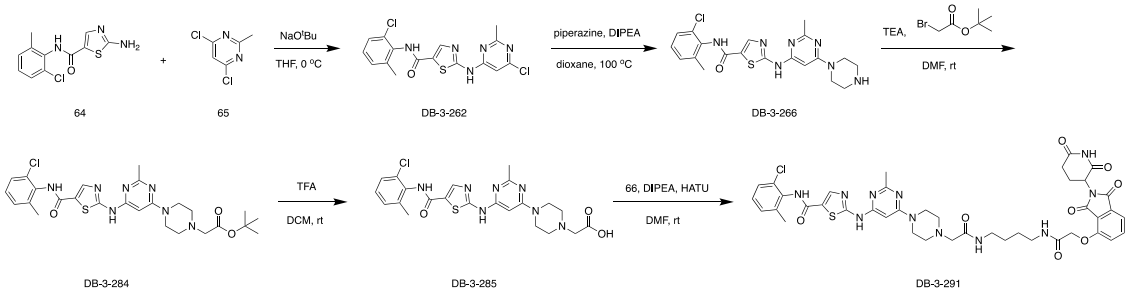
4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-benzo[*c*]pyrimido[4,5-*e*]azepin-2-yl)amino)-*N*-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)-2-oxo-7,10,13-trioxa-3-azahexadecan-16-yl)-2-methoxybenzamide (dAURK-4)

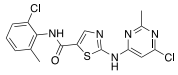
N-(3-(2-(2-(3-aminopropoxy)ethoxy)ethoxy)propyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide trifluoroacetate salt (12.4 mg, 0.0191 mmol, 1 eq) was added to 4-((9-chloro-7-(2-fluoro-6-methoxyphenyl)-5*H*-benzo[*c*]pyrimido[4,5-*e*]azepin-2-yl)amino)-2-methoxybenzoic acid (MLN8237) (9.9 mg, 0.0191 mmol, 1 eq) as a solution in DMF (0.191 mL). DIPEA (0.010 mL, 0.0572 mmol, 3 eq) was added, followed by HATU (7.3 mg, 0.191 mmol, 1 eq). After 24 hours, the mixture was diluted with EtOAc and washed sequentially with saturated sodium bicarbonate, water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (0 - 10% MeOH/DCM) gave the desired product (11.03 mg, 0.0107 mmol, 56%) as a yellow solid.

^{1}H NMR (400 MHz, 1:1 MeOD:$CDCl_3$) δ 8.52 (s, 1H), 8.27 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 1.9 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.61 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.56 (s, 2H), 7.48 (d, *J* = 7.4 Hz, 1H), 7.38 - 7.21 (m, 4H), 6.80 (broad s, 2H), 5.01 (dd, *J* = 11.9, 6.1 Hz, 1H), 4.63 (s, 2H), 3.98 (s, 6H), 3.57 (dddd, *J* = 27.7, 15.3, 10.9, 7.0 Hz, 13H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.85 - 2.68 (m, 3H), 2.12 (d, *J* = 8.3 Hz, 1H), 1.85 (dp, *J* = 19.9, 7.1 Hz, 4H).

LC/MS (ESI) *m/z* 1035.6 $[M+H]^+$

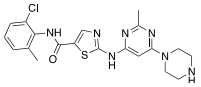
Scheme 13: Synthesis of DB-3-291





2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (DB-3-262).

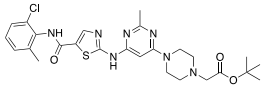
2-amino-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide 64 (1.34 g, 5 mmol, 1 eq) and 4,6-dichloro-2-methylpyrimidine 65 (0.978 g, 6 mmol, 1.2 eq) were dissolved in THF (17 mL) and cooled to 0 degrees C. After 0.5 hours, sodium *tert*-butoxide (1.68 g, 17.5 mmol, 3.5 eq) was added. After 2 hours, 1M HCl was added to adjust pH to ~5-6. The mixture was stirred for 15 minutes, and then filtered through fluted filter paper. The soild was washed twice with methanol and once with water, then air dried to give the desired product (1.26 g, 3.20 mmol, 64%) as a white solid, which was used without further purification. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 12.24 (s, 1H), 10.00 (s, 1H), 8.31 (s, 1H), 7.44 - 7.39 (m, 1H), 7.27 (ddd, *J* = 19.8, 12.4, 7.0 Hz, 2H), 6.93 (s, 1H), 2.59 (s, 3H), 2.24 (s, 3H). **LC/MS (ESI)**: 394.25 $[M+H]^+$



***N*-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (DB-3-266)**

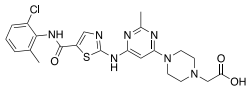
2-((6-chloro-2-methylpyrimidin-4-yl)amino)-*N*-(2-chloro-6-methylphenyl)thiazole-5-carboxamide (0.56 g, 1.42 mmol, 1 eq) and piperazine (1.22 g, 14.2 mmol, 10 eq) were dissolved in dioxane (18 mL, 0.08 M). DIPEA (0.49 mL, 2.84 mmol, 2 eq) was added. The flask was fitted with a vigreaux condenser and the mixture was heated to 100 degrees C. After 20 hours, the mixture was cooled to room temperature and concentrated under reduced pressure. The material was triturated twice with 25 mL of 1:1 MeOH:water, once with 25 mL of 1:1 MeOH:Et_2O and once with 25 mL Et_2O. The washes were then concentrated, and triturate three times with 20 mL of 1:4

MeOH:water to isolate additional material, which was combined with the previously isolated material. The desired product was isolated as a white solid (533.9 mg, 1.20 mmol, 85%) and used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.86 (s, 1H), 8.21 (s, 1H), 7.46 - 7.34 (m, 1H), 7.27 (dt, J = 15.3, 7.1 Hz, 2H), 6.02 (s, 1H), 3.44 (d, J = 4.6 Hz, 4H), 2.79 - 2.70 (m, 4H), 2.40 (s, 3H), 2.24 (s, 3H). LC/MS (ESI): 444.34 $[M+H]^+$



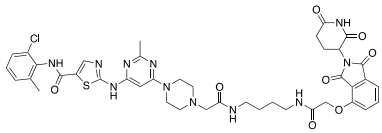
***tert*-butyl 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetate (DB-3-284).**

N-(2-chloro-6-methylphenyl)-2-((2-methyl-6-(piperazin-1-yl)pyrimidin-4-yl)amino)thiazole-5-carboxamide (236 mg, 0.532 mmol, 1 eq) was dissolved in DMF (5.3 mL, 0.1 M) at room temperature. Triethylamine (0.222 mL, 1.59 mmol, 3 eq) was added, followed by *tert*-butyl bromoacetate (0.118 mL, 0.797 mmol, 1.5 eq). After 15 hours, the mixture was diluted with 25 mL sat. aq. sodium bicarbonate, then extracted three times with EtOAc. The organic layers were combined and washed three times with brine, then dried with sodium sulfate, filtered and condensed. The desired product was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.44 (s, 1H), 9.86 (s, 1H), 8.21 (s, 1H), 7.40 (d, J = 6.4 Hz, 1H), 7.27 (dt, J = 15.3, 7.1 Hz, 2H), 6.05 (s, 1H), 3.52 (s, 4H), 3.17 (s, 2H), 2.61 - 2.54 (m, 4H), 2.40 (s, 3H), 2.24 (s, 3H), 1.42 (s, 9H). LC/MS (ESI): 558.46 $[M+H]^+$



2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetic acid (DB-3-285).

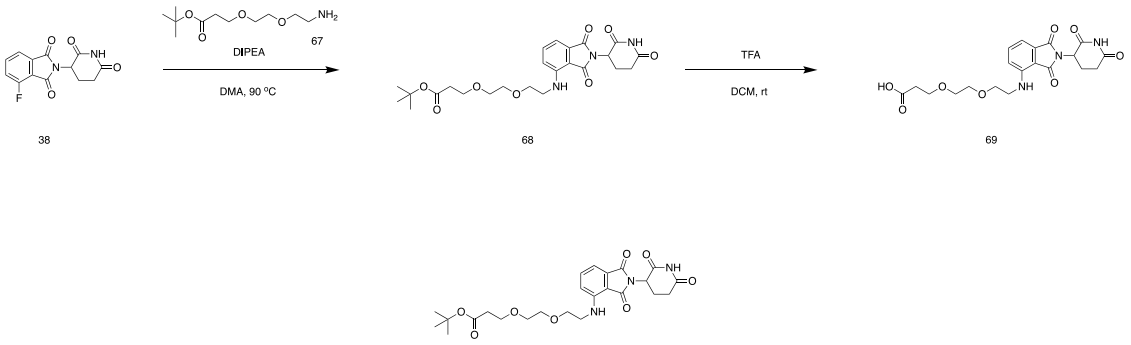
The material isolated from the previous step, *tert*-butyl 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetate, was dissolved in DCM (50 mL) and TFA (10 mL) at room temperature. After 18 hours, the material was concentrated under reduced pressure, and precipitated with Et_2O and dried under high vacuum. The desired product was isolated as a white solid (257 mg, 0.512 mmol, 98% yield over 2 steps0 and used without further purification. LC/MS (ESI): 502.37 ($[M+H]^+$



***N*-(2-chloro-6-methylphenyl)-2-((6-(4-(2-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)amino)-2-oxoethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (DB-3-291)**

N-(4-aminobutyl)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamide trifluoroacetate salt **66** (12.9 mg, 0.025 mmol, 1 eq) was added to 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)acetic acid (15.4 mg, 0.025 mmol, 1 eq) as a 0.1M solution in DMF (0.25 mL) at room temperature. DIPEA (0.131 mL, 0.075 mmol, 3 eq) was added, followed by HATU (9.5 mg, 0.025 mmol, 1 eq). After 13 hours, the material was diluted with MeOH and purified by preparative HPLC. The desired product (11.16 mg, 0.0112 mmol, 45%) was isolated as a yellow solid. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.17 (s, 1H), 7.82 (dd, *J* = 8.4, 7.4 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.38 - 7.34 (m, 1H), 7.28 - 7.22 (m, 2H), 6.16 (s, 1H), 5.14 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.78 (s, 2H), 3.95 (s, 6H), 3.52 - 3.39 (m, 4H), 3.38 - 3.32 (m, 4H), 2.88 (ddd, *J* = 17.5, 13.9, 5.2 Hz, 1H), 2.80 - 2.68 (m, 2H), 2.52 (s, 3H), 2.32 (s, 3H), 2.16 (dtd, *J* = 13.0, 5.7, 2.7 Hz, 1H), 1.67 - 1.54 (m, 4H). LC/MS (ESI): 886.61 $[M+H]^+$

Scheme 14: Synthesis of intermediate 69



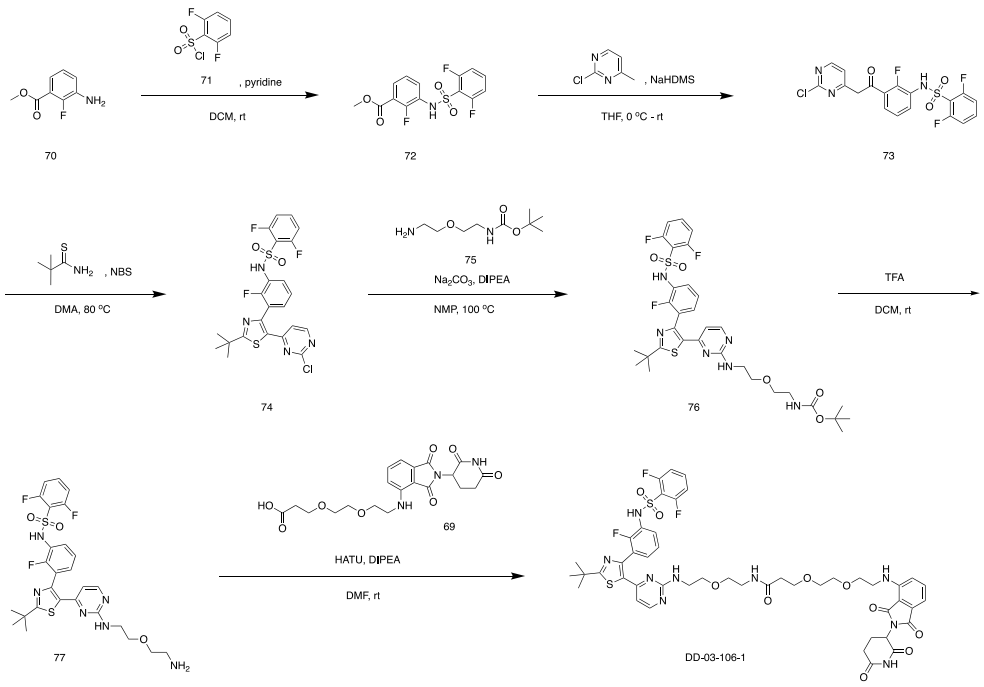
tert-butyl 3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy) ethoxy)propanoate (68)

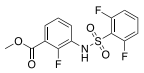
Compound **38** (455 mg, 1.74 mmol), **2** (405 mg, 1.74 mmol), and DIPEA (1.21 mL, 6.94 mmol) were stirred in DMA (2 mL) at 90 °C for 20 h. The reaction was diluted with H_2O (10 mL) and extracted with ethyl acetate (4 x 20 mL). The organics were combined, washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (0 - 70% ethyl acetate /hexanes) gave the desired product (250 mg, 0.51 mmol, 29 %) as a yellow solid. LC/MS (ESI) m/z 490.5 $[M+H]^+$.

3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy) propanoic acid (69)

Compound **69** (250 mg, 0.51 mmol), was dissolved in 3 mL TFA and 3 mL DCM and stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and used without further purification. LC/MS (ESI) m/z 434.4 $[M+H]^+$.

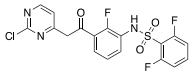
Scheme 15: Synthesis of DD-03-106-1





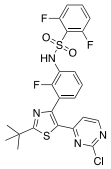
methyl 3-((2,6-difluorophenyl)sulfonamido)-2-fluorobenzoate (72)

Compound **71** (2.4 mL, 17.7 mmol) was added dropwise to a solution of compound **70** (3.0 g, 17.7 mmol), and pyridine (1.6 mL, 19.5 mmol) in DCM (15 mL). The reaction mixture was stirred at rt for 16 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (30 - 100% hexanes/ ethyl acetate) to afford the desired product (5.79 g, 16.7 mmol, 94 %). LC/MS (ESI) m/z 346.3 $[M+H]^+$.



***N*-(3-(2-(2-chloropyrimidin-4-yl)acetyl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide (73)**

Compound **72** (450 mg, 1.30 mmol) was stirred under N_2 in anhydrous THF. The reaction mixture was cooled to 0 ^oC and a 1 M solution of NaHDMS in THF added (4.17 mL, 4.17 mmol). 2-chloro-4-methylpyrimidine (217 mg, 1.69 mmol) in 3 mL THF was added to the reaction mixture, which was stirred at 0 ^oC - rt for 1 h. The reaction mixture was quenched at 0 ^oC by dropwise addition of 6 M HCl (10 mL), followed by extraction with ethyl acetate (3 x 50 mL). The organics were combined, washed with brine (10 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (0 - 70% ethyl acetate /hexanes) gave the desired product (140 mg, 0.32 mmol, 24 %) as a yellow solid. LC/MS (ESI) m/z 442.9 $[M+H]^+$.

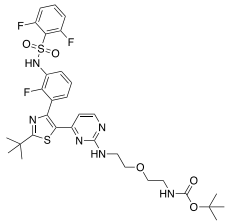


N-(3-(2-(tert-butyl)-5-(2-chloropyrimidin-4-yl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide (74)

To a stirred solution of compound **73** (1.51 g, 3.42 mmol) in anhydrous DMA under N_2 was added NBS (635 mg, 3.57 mmol). The reaction mixture was stirred at rt for 15 min, followed by addition of 2,2-dimethylpropanethioamide (401 mg, 3.42 mmol). The reaction was heated at 80 ^oC for 2 h, allowed to cool to rt, diluted with 60 mL H_2O and extracted with ethyl acetate (4 x 120 mL).

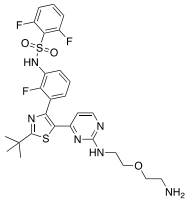
The organics were combined, washed with H_2O (5 x 5 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. Purification by column chromatography (0 - 70% ethyl acetate /hexanes) gave the desired product (620 mg, 1.15 mmol, 34 %)

LC/MS (ESI) m/z 540.0 $[M+H]^+$.



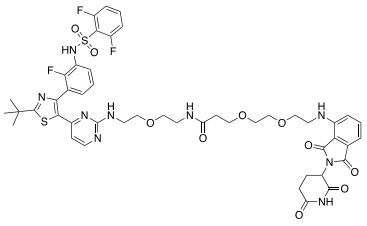
tert-butyl (2-(2-((4-(2-(tert-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)ethoxy)ethyl)carbamate (76)

Compound **74** (86 mg, 0.16 mmol), compound 7**5** (63 mg, 0.32 mmol), sodium carbonate (34 mg, 0.32 mmol), and DIPEA (56 µL, 0.32 mmol) were stirred at 100 ºC in NMP (80 µL) for 1 h. The reaction mixture was diluted with brine (10 mL) and extracted with ethyl acetate (3 x 20 mL). The organics were dried over sodium sulfate, filtered and concentrated under reduced pressure and used without further purification.



***N*-(3-(5-(2-((2-(2-aminoethoxy)ethyl)amino)pyrimidin-4-yl)-2-(*tert*-butyl)thiazol-4-yl)-2-fluorophenyl)-2,6-difluorobenzenesulfonamide (77)**

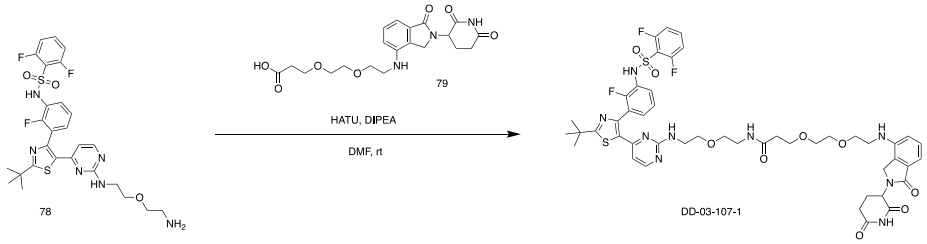
Compound **76** was dissolved in 2 mL DCM and 1 mL TFA and stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure, and purified by HPLC to afford the title compound (76 mmol, 0.105 mmol, 66 % over 2 steps). LC/MS (ESI) m/z 608.0 $[M+H]^+$.

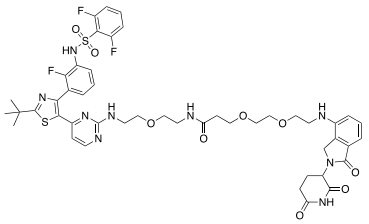


***N*-(2-(2-((4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)ethoxy)ethyl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethoxy)ethoxy)propenamide (DD-03-106-1)**

Compound **77** (36 mg, 0.05 mmol), compound **69** (20 mg, 0.05 mmol), HATU (25 mg, 0.065 mmol) and DIPEA (26 µL, 0.15 mmol) in 1 mL DMF were stirred at rt for 30 mins. The reaction mixture was purified by HPLC to afford the title compound (14 mg, 0.013 mmol, 26%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD) δ 8.05 (d, *J* = 6.3 Hz, 1H), 7.62 (tt, *J* = 8.4, 5.9 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.39 (ddd, *J* = 7.9, 6.2, 1.7 Hz, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 7.15 – 7.07 (m, 2H), 7.07 – 6.98 (m, 2H), 5.05 (dd, *J* = 12.7, 5.5 Hz, 1H), 3.73 (dt, *J* = 20.3, 5.6 Hz, 4H), 3.66 – 3.62 (m, 4H), 3.55 (t, *J* = 5.4 Hz, 2H), 3.46 (t, *J* = 5.2 Hz, 2H), 3.37 (t, *J* = 5.4 Hz, 2H), 2.86 (ddd, *J* = 17.5, 13.9, 5.3 Hz, 1H), 2.79 – 2.64 (m, 2H), 2.46 (t, *J* = 6.0 Hz, 2H), 2.10 (dtd, *J* = 13.1, 5.6, 2.8 Hz, 1H), 1.49 (s, 9H). LC/MS (ESI) m/z 1023.2 $[M+H]^+$.

Scheme 16: Synthesis of DD-03-107-1



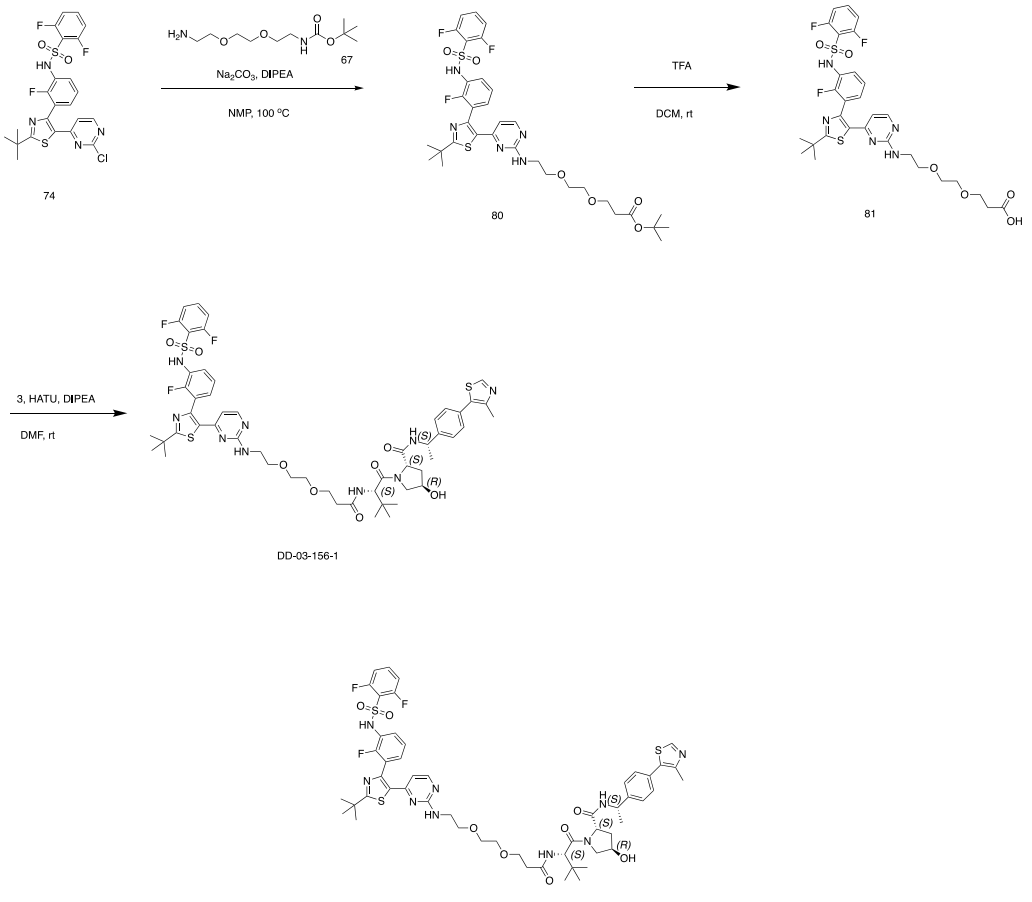


***N*-(2-(2-((4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)ethoxy)ethyl)-3-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)ethoxy)ethoxy)propenamide (DD-03-107-1)**

Compound **78** (31 mg, 0.043 mmol), compound **79** (18 mg, 0.043 mmol), HATU (21 mg, 0.056 mmol) and DIPEA (22 µL, 0.13 mmol) were stirred in DMF (1 mL) for 1 h. The reaction mixture was purified by HPLC to afford the title compound (20 mg, 0.018 mmol, 41%).

^{1}H NMR (500 MHz, MeOD) δ 8.05 (s, 1H), 7.62 (tt, *J* = 8.5, 5.9 Hz, 1H), 7.52 (td, *J* = 7.7, 1.7 Hz, 1H), 7.44 – 7.37 (m, 1H), 7.30 (q, *J* = 8.1 Hz, 3H), 7.11 (ddd, *J* = 11.7, 7.9, 2.3 Hz, 4H), 6.87 (s, 1H), 6.45 (s, 2H), 5.17 (dd, *J* = 13.4, 5.2 Hz, 1H), 4.39 – 4.25 (m, 2H), 3.72 (dt, *J* = 18.0, 5.8 Hz, 4H), 3.63 (q, *J* = 1.5 Hz, 3H), 3.52 (t, *J* = 5.5 Hz, 2H), 3.43 – 3.34 (m, 3H), 2.92 (ddd, *J* = 17.5, 13.5, 5.4 Hz, 1H), 2.80 (ddd, *J* = 17.6, 4.6, 2.4 Hz, 1H), 2.55 – 2.41 (m, 3H), 2.18 (dtd, *J* = 12.9, 5.3, 2.4 Hz, 1H), 1.50 (s, 9H). LC/MS (ESI) m/z 1009.1 $[M+H]^+$.

Scheme 17: Synthesis of DD-03-156-1



(2*S*,4*R*)-1-((*S*)-2-(3-(2-(2-((4-(2-(*tert*-butyl)-4-(3-((2,6-difluorophenyl)sulfonamido)-2-fluorophenyl)thiazol-5-yl)pyrimidin-2-yl)amino)ethoxy)ethoxy)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (DD-03-156-1)

Compound 81 (36 mg, 0.05 mmol), VHL-amine 3 (22 mg, 0.05 mmol), HATU (25 mg, 0.065 mmol) and DIPEA (26 µL, 0.15 mmol) were stirred in DMF (1 mL) for 1 h. The reaction mixture was purified by HPLC to afford the title compound (5 mg, 0.004 mmol, 8%). LC/MS (ESI) m/z 1107.4 $[M+H]^+$.

^{1}H NMR (500 MHz, MeOD) δ 8.92 (d, J = 3.2 Hz, 1H), 8.05 (d, J = 6.1 Hz, 1H), 7.63 (ddd, J = 15.9, 9.4, 6.8 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.43 (dd, J = 9.0, 6.7 Hz, 4H), 7.35 – 7.26 (m, 1H), 7.11 (td, J = 9.0, 4.8 Hz, 3H), 6.39 (s, 1H), 5.00 (q, J = 7.0 Hz, 1H), 4.68 (s, 1H), 4.63 – 4.56 (m, 1H), 4.45 (s, 1H), 3.89 (d, J = 11.1 Hz, 1H), 3.82 – 3.70 (m, 4H), 3.66 (td, J = 5.5, 3.4 Hz, 8H), 3.52 (s, 4H), 2.68 (s, 1H), 2.64 – 2.50 (m, 1H), 2.48 (d, J = 1.8 Hz, 4H), 2.22 (dd, J = 13.3, 7.8 Hz, 1H), 1.99 (ddd, J = 13.4, 9.2, 4.5 Hz, 1H), 1.50 (s, 9H), 1.06 (s, 9H).

LC/MS (ESI) m/z 1007.4 $[M+H]^+$.