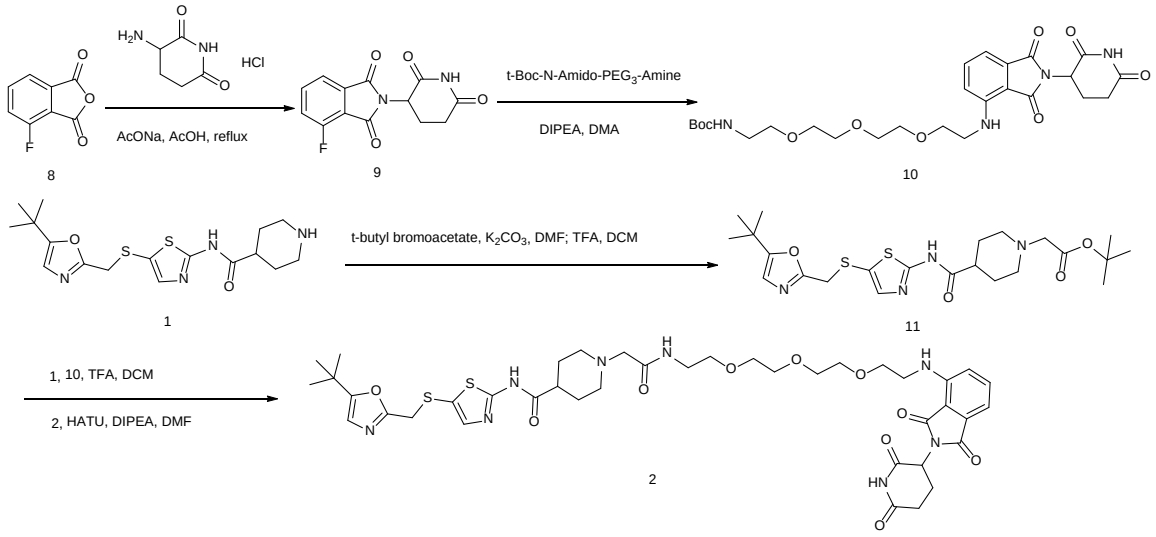
Supplementary Note

Chemical Synthesis of THAL-SNS-032, NVP-2, THAL-NVP-2-02-099, THAL-NVP-2-03-069, HAL-NVP-2-03-099, THAL-NVP-2-03-084, THAL-NVP-2-03-105.

Synthesis of THAL-SNS-032 (2)



Synthesis of 9[1-2]. To a suspension of **8** (1.66 g, 10 mmol), and 3-aminopiperidine-2,6-dione hydrochloride (1.64 g, 10 mmol) in AcOH (20 mL) was added sodium acetate (0.99 g, 12 mmol). The resulting mixture was heated to 120°C for 12h. After cooling to room temperature, most of the AcOH was evaporated and the residue was purified by column chromatography on silica gel (0-10% MeOH in DCM) to give **9** as an off white solid (2.3 g, 83%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.99-7.91 (m, 1H), 7.81-7.71 (m, 2H), 5.17 (dd, J = 12.9, 5.4 Hz, 1H), 2.96-2.86 (m, 1H), 2.67-2.59 (m, 1H), 2.56-2.49 (m, 1H), 2.12-2.05 (m, 1H). ^{13}C NMR (126 MHz, DMSO) δ 172.74, 169.69, 166.09, 163.96, 156.81, 138.04, 133.44, 122.99, 120.03, 117.02, 49.12, 30.93, 21.87. LC-MS: *m/z* 277.1 [M+1].

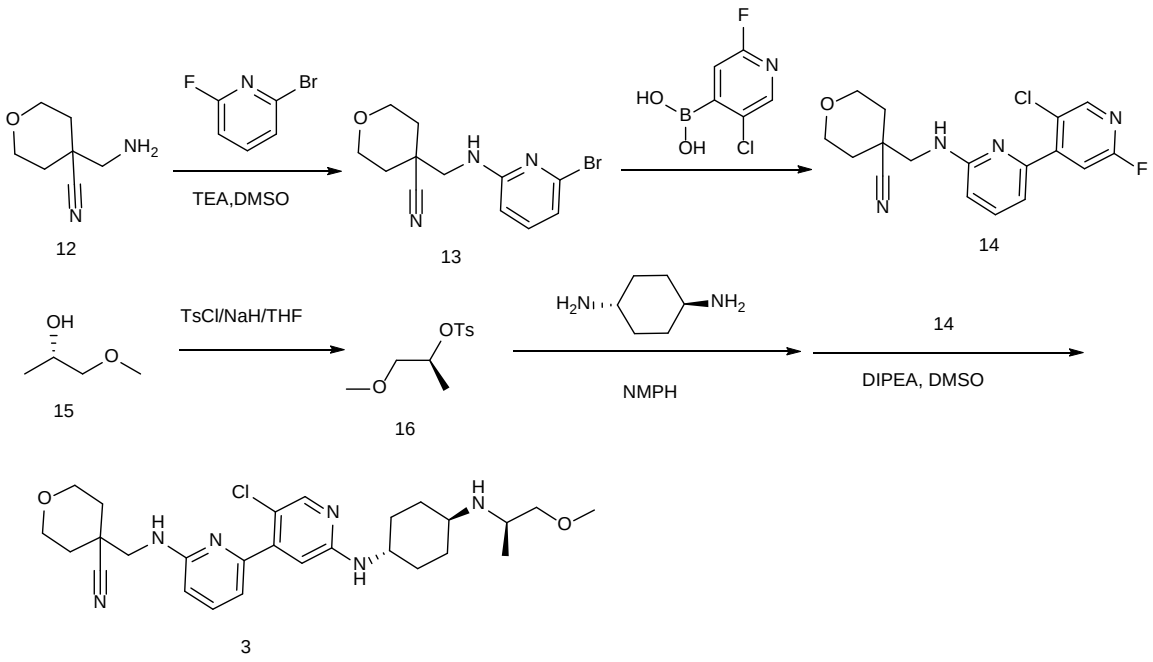
Synthesis of 10. To a solution of 9 (138 mg, 0.5 mmol) in DMA (5 mL) was added *t*-Boc-N-Amido-PEG3-Amine (146 mg, 0.5 mmol) and DIPEA (0.26 mL, 1.5 mmol). The resulting mixture was heated to 90°C for 2h. After cooling to room temperature, the mixture was extracted with EtOAc, evaporated and the residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **10** (TFA salt) as a yellow solid. (219 mg, 80%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 7.61-7.56 (m, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 1H), 6.73 (t, *J* = 5.7 Hz, 1H), 6.60 (br, 1H), 5.10-5.02 (m, 1H), 3.62 (t, *J* = 5.4 Hz, 2H), 3.59-3.43 (m, 10H), 3.35 (t, *J* = 6.1 Hz, 2H), 3.08-3.01 (m, 2H), 2.93-2.84 (m, 1H), 2.63-2.52 (m, 2H), 2.06-1.97 (m, 1H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 172.77, 170.04, 168.91, 167.27, 155.55, 146.39, 136.20, 132.08, 117.44, 110.65, 109.23, 77.56, 69.78, 69.75, 69.67, 69.49, 69.41, 69.13, 68.88, 66.65, 48.55, 41.69, 30.97, 28.21, 22.13. LC-MS: *m/z* 548.6 [M+1].

Synthesis of 11. To a solution of SNS-032 (**1**) (32 mg, 0.0832 mmol) in DMF (0.5 mL) was added *tert*-butyl 2-bromoacetate (24 mg, 0.125 mmol) and K_2CO_3 (58 mg, 0.416 mmol). The mixture was stirred at ambient temperature overnight. The mixture was diluted with EtOAc and H_2O, extracted, and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **11** (TFA salt) as a white solid. (30mg, 75%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (s, 1H), 10.09 (br, 1H), 7.40 (s, 1H), 6.72 (s, 1H), 4.13 (s, 2H), 4.06 (s, 2H), 3.61-3.50 (m, 2H), 3.15-2.98 (m, 2H), 2.78-2.66 (m, 1H), 2.09-2.01 (m, 2H), 1.98-1.85 (m, 2H), 1.48 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 171.96, 164.98, 160.97, 160.82, 158.71, 145.14, 120.11, 118.97, 83.69, 55.74, 51.71, 38.58, 34.00, 30.93, 28.30, 27.62, 25.12. LC-MS: *m/z* 494.9 [M+1].

Synthesis of 2. To a solution of the **10** (24 mg, 0.0422 mmol) and **11** (18 mg, 0.0422 mmol) in DCM (1 mL) was added TFA (1 mL) and the resulting solution was stirred at

ambient temperature for 1 h. The mixture was concentrated and the residue was then dissolved in DMF (0.3 mL) followed by adding DIPEA (37 µL, 0.211 mmol) and HATU (33 mg, 0.0844 mmol). The reaction was stirred for 1h at ambient temperature. The mixture was filtered and purified by reverse phase HPLC (5-95% MeOH in H_2O) to give compound **2** (TFA salt) as a yellow solid (31 mg, 86%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.22 (s, 1H), 11.08 (s, 1H), 7.68 (t, *J* = 5.9 Hz, 1H), 7.57 (dd, *J* = 8.5, 7.0 Hz, 1H), 7.37 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.70 (s, 1H), 6.59 (t, *J* = 5.8 Hz, 1H), 5.05 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.04 (s, 2H), 3.61 (t, *J* = 5.4 Hz, 2H), 3.58-3.44 (m, 8H), 3.41 (t, *J* = 5.9 Hz, 2H), 3.24 (q, *J* = 5.9 Hz, 2H), 2.88 (s, 2H), 2.82 (d, *J* = 11.6 Hz, 2H), 2.66-2.57 (m, 2H), 2.48-2.37 (m, 2H), 2.11-1.97 (m, 3H), 1.79-1.66 (m, 4H), 1.17 (s, 9H). ^{13}C NMR (125 MHz, DMSO) δ 173.75, 172.77, 170.04, 169.34, 168.90, 167.27, 161.24, 160.80, 158.72, 146.38, 145.10, 136.19, 132.08, 120.09, 118.53, 117.42, 110.65, 109.23, 69.84, 69.79, 69.53, 68.99, 68.87, 61.46, 54.91, 52.62, 48.54, 41.69, 40.88, 38.03, 33.98, 30.97, 30.91, 28.29, 28.27, 28.06, 22.14. LC-MS: *m/z* 869.3 [M+1].

Synthesis of NVP-2 (3)



Synthesis of 13. To a solution of 12 (1.9 g, 13.62 mmol) in DMSO (15 ml) at ambient temperature was sequentially added 2-bromo-6-fluoropyridine (2.0 g, 11.35 mmol) and triethylamine (4 ml, 28.4 mmol). The resulting light brown mixture was heated to 110°C and kept stirring for 18 hours. The reaction mixture then was cooled to ambient temperature, reaction mixture diluted with EtOAc, washed with saturated $NaHCO_3$ solution and brine, dried over sodium sulfate and concentrated. The crude was purified by column chromatography on silica gel to afford **13** as a light yellow solid (2.06 g, 61.0%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.36-7.28 (m, 2H), 6.69 (d, *J* = 7.3 Hz, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 3.93-3.84 (m, 2H), 3.56 (d, *J* = 6.4 Hz, 2H), 3.46 (td, *J* = 12.0, 2.1 Hz, 2H), 1.88-1.78 (m, 2H), 1.70-1.61 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 158.96, 139.55, 139.06, 122.18, 114.78, 107.23, 79.15, 63.79, 47.41, 47.36, 38.53, 32.33. LC-MS: *m/z* 296.0 [M+1].

Synthesis of 14. A mixture of 13 (2.06 g, 6.9 mmol), 5-chloro-2-fluoropyridin-4-ylboronic acid (1.81 g, 10.5 mmol), Pd(dppf)Cl_2 (0.565 g, 0.7 mmol), 1,4-dioxane (30 mL) and 2M aqueous Na_2CO_3 (10 mL) was sealed and stirred at 110 °C for 3 hours. After cooling to room temperature, the mixture was extracted with EtOAc, filtered and concentrated. The crude was purified by column chromatography on silica gel to afford **14** as a light yellow solid (1.8 g, 75.0%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (s, 1H), 7.55-7.49 (m, 1H), 7.20 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 4.01-3.94 (m, 2H), 3.76 (d, *J* = 6.9 Hz, 2H), 3.71-3.63 (m, 2H), 1.93-1.86 (m, 2H), 1.78-1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.42, 161.52, 157.91, 150.91, 147.76, 137.72, 122.31, 114.42, 111.20, 109.35, 64.58, 48.52, 39.71, 33.11. LC-MS: *m/z* 347.1 [M+1].

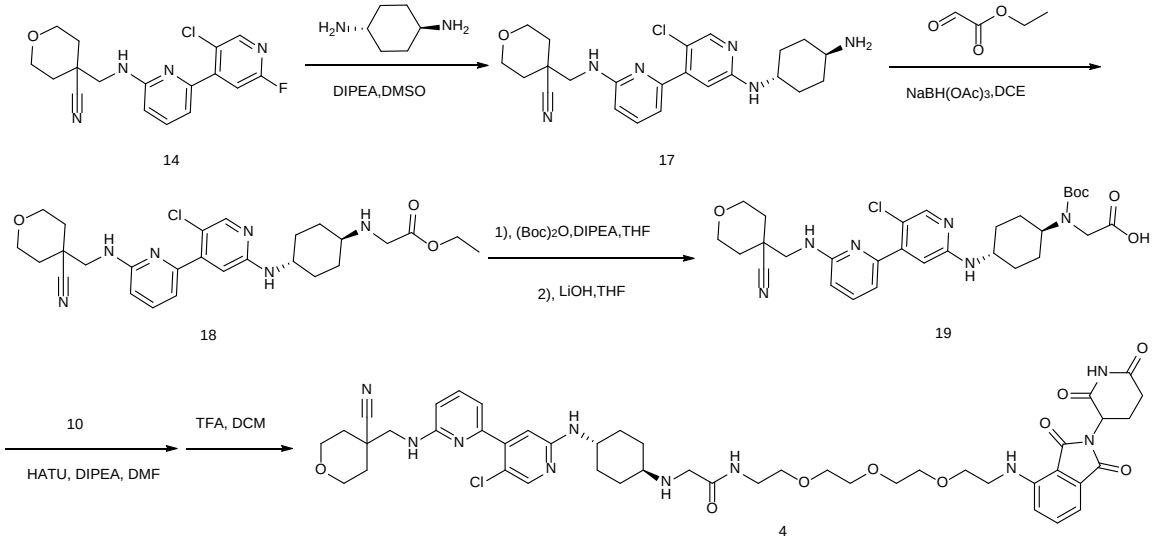
Synthesis of 16. To a suspension of sodium hydride (1.22 g, 30 mmol) in 10 mL of THF was added (S)-1-methoxypropan-2-ol (0.9 g, 10 mmol) in 20 mL of THF at ambient temperature. The mixture was stirred for 20 min. and followed by addition of 4-

methylbenzenesulfonyl chloride (2.9 g, 15 mmol). The white cloudy solution was stirred at ambient temperature for 18 hours. The reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. The crude was purified by column chromatography on silica gel to afford **16** as a colorless oil (1.4 g, 59.5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.79 (d, *J* = 10 Hz, 2H), 7.45 (d, *J* = 10 Hz, 2H), 4.71-4.63 (m, 1H), 3.37-3.27 (m, 2H), 3.13 (s, 3H), 2.40 (s, 3H), 1.14 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 144.55, 133.75, 129.89, 127.43, 78.28, 73.83, 58.17, 20.99, 16.91. LC-MS: *m/z* 245.1 [M+1].

Synthesis of 3. To a solution of **16** (1.4 g, 5.7 mmol) in DMSO (5 mL) was added *trans*-cyclohexane-1,4-diamine (1.3 g, 11.4 mmol). The resulting mixture was heated at 110^{o}C for 1h. LC/MS showed nearly complete consumption of 16. The mixture was then cooled to ambient temperature, diluted with water and extracted with DCM. The DCM extracts were combined, dried and concentrated to give mono-alkylated intermediate (82% purity by LC-MS) which was used in the next step without further purification. The intermediate (373 mg, 2 mmol) was added to a solution of **14** (347 mg, 1 mmol), DIPEA (0.52 mL, 3 mmol) in DMSO (2 mL). The resulting mixture was heated to 120^{o}C and kept stirring for 12h, then cooled to room temperature and diluted with EtOAc, washed with water and brine, dried (Na_2SO_4) and concentrated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **NVP-2** (TFA salt) as an off-white solid (30.2 mg, 35.5% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.39-7.58 (m, 1H), 6.97 (d, *J*=7.2 Hz, 1H), 6.54 (s, 1H), 6.49 (d, *J*=8.0 Hz, 1H), 4.94-4.61 (m, 1H), 4.42 (d, *J*=8.2 Hz, 1H),4.00-3.90 (m, 2H), 3.85-3.63 (m, 3H), 3.59-3.41 (m, 2H), 3.39-3.20 (m, 5H), 3.09-3.06 (m, 1H), 2.67-2.52 (m, 1H), 2.24-2.12 (m, 2H), 2.07-2.01 (m, 2H), 1.99-1.82 (m, 1H), 1.79-1.71 (m, 2H), 1.38-1.11 (m, 5H), 1.06 (d, *J*=6.2 Hz, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 158.32,

157.27, 152.36, 147.13, 146.85, 137.17, 122.54, 115.08, 112.48, 109.36, 108.67, 76.66, 58.24, 52.79, 49.35, 48.63, 47.25, 38.69, 32.48, 31.26, 31.11, 17.75. LC-MS: *m/z* 513.3 [M+1].

Synthesis of THAL-NVP-2-03-099 (4)



Synthesis of 17. To a solution of 14 (1.45 g, 4.2 mmol) in DMSO (10 mL) was added *trans*-cyclohexane-1,4-diamine (0.96 g, 8.4 mmol) and DIPEA (2.2 mL, 12.6 mmol) at 120ºC for 12 hours. The reaction mixture was cooled to room temperature and diluted with EtOAc, washed with water and brine, dried (Na_2SO_4) and concentrated. The resulting residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to afford **17** (TFA salt) as a light brown solid (1.4 g, 76%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.14-8.06 (m, 1H), 7.99-7.83 (br, 3H), 7.60-7.49 (m, 1H), 7.37-7.18 (br, 1H), 6.86-6.77 (m, 3H), 3.94-3.87 (m, 2H), 3.67 (s, 2H), 3.64-3.54 (m, 1H), 3.50-3.43 (m, 2H), 3.09-2.98 (m, 1H), 2.06-2.00 (m, 2H), 1.97 (d, *J* = 12.3 Hz, 2H), 1.84 (dd, *J* = 13.8, 2.0 Hz, 2H), 1.72-1.62 (m, 2H), 1.49-1.38 (m, 2H), 1.36-1.22 (m, 2H). ^{13}C NMR (126 MHz, DMSO) δ 158.12, 158.07, 137.60, 122.42, 119.41, 117.08, 115.56, 115.51, 114.75, 112.63, 112.58, 63.85, 48.69, 48.64, 47.25, 38.57, 32.40, 29.93, 29.87, 29.11, 29.06. LC-MS: *m/z* 441.2 [M+1].

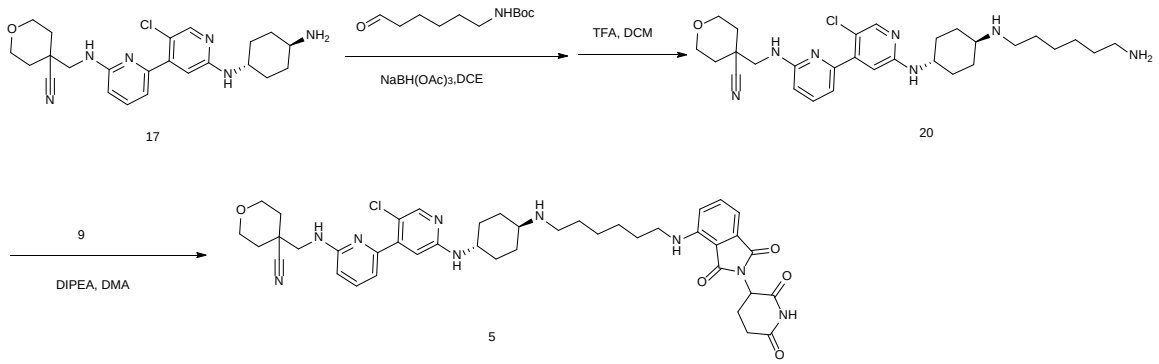
Synthesis of 18. To a solution of 17 (440 mg, 1 mmol) in 1,2-dichloro-ethane (5 mL) was added ethyl glyoxylate in toluene (50%) (0.2 mL, 1 mmol) and acetic acid (3 drops). The mixture was stirred for 15 min at ambient temperature and then sodium tris(acetoxy)borohydride (275 mg, 1.3 mmol) was added in one portion and kept stirring for another 2 hours. Then the reaction mixture was poured to saturated $NaHCO_3$ solution (20 mL) and extracted DCM (3X30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **18** (TFA salt) as a brown oil (174 mg, 33% over two steps). LC-MS: *m/z* 527.2 [M+1].

Synthesis of 19. To a solution of **18** (105 mg, 0.2 mmol) and DIPEA (0.1 mL, 0.6 mmol) in anhydrous THF (3 mL) was added $(Boc)_2O$ (48 mg, 0.22 mmol) in THF (1 mL) dropwise at 0^oC. After addition, the mixture was warmed to room temperature and kept stirring overnight. Then the mixture was diluted with EtOAc and H_2O, extracted, and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography on silica gel to give the Boc-protected compound which was then dissolved in THF (3 mL) and 1 N aqueous LiOH (1 mL) was added. The resulting mixture was stirred at room temperature for 3h, acidified with 1 N HCl solution (PH=6) and the solvent was evaporated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give the acid **19** (TFA salt) (72 mg, 60% over two steps). LC-MS: *m/z* 599.3 [M+1].

Synthesis of 4. To a solution of **10** (46 mg, 0.083 mmol) in DCM (1 mL) was added TFA (1 mL) and stirred for 1h at ambient temperature. Then the solvent was evaporated and added to a solution of the acid 19 (50 mg, 0.083 mmol), DIPEA (44 µL, 0.25 mmol) and HATU (46 mg, 0.125 mmol) in DMF (2 mL). The mixture was stirred for 1h at ambient temperature, then evaporated and the residue was dissolved in DCM (1 mL) followed by

adding TFA (1 mL). The resulting mixture was stirred at ambient temperature for 0.5h and concentrated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **4** (TFA salt) as a light yellow solid (31 mg, 40% over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.83 (d, *J* = 6.5 Hz, 2H), 8.52 (t, *J* = 5.6 Hz, 1H), 8.06 (s, 1H), 7.59 (dd, *J* = 8.6, 7.0 Hz, 1H), 7.56-7.48 (m, 1H), 7.14 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 7.1 Hz, 1H), 6.74-6.66 (m, 2H), 6.60 (s, 1H), 3.99-3.81 (m, 2H), 3.72 (t, *J* = 5.9 Hz, 3H), 3.66 (d, *J* = 5.5 Hz, 2H), 3.62 (t, *J* = 5.4 Hz, 2H), 3.59 (dd, *J* = 5.6, 2.9 Hz, 2H), 3.57-3.52 (m, 4H), 3.50-3.40 (m, 6H), 3.30 (q, *J* = 5.5 Hz, 2H), 3.05 (s, 1H), 2.98-2.74 (m, 1H), 2.66-2.57 (m, 1H), 2.54 (s, 1H), 2.10-1.97 (m, 6H), 1.84 (dd, *J* = 14.0, 2.1 Hz, 3H), 1.78-1.61 (m, 2H), 1.53-1.38 (m, 3H), 1.33-1.21 (m, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.81, 170.07, 168.96, 167.27, 165.29, 158.35, 158.15, 158.06, 157.78, 156.18, 146.40, 137.41, 136.25, 132.09, 122.45, 117.46, 115.47, 112.51, 110.73, 109.25, 69.78, 69.63, 68.89, 68.82, 63.85, 55.27, 48.57, 48.48, 47.21, 45.06, 41.70, 38.86, 38.58, 32.39, 30.99, 29.96, 27.16, 22.15. LC-MS: *m/z* 929.4 [M+1].

Synthesis of 5

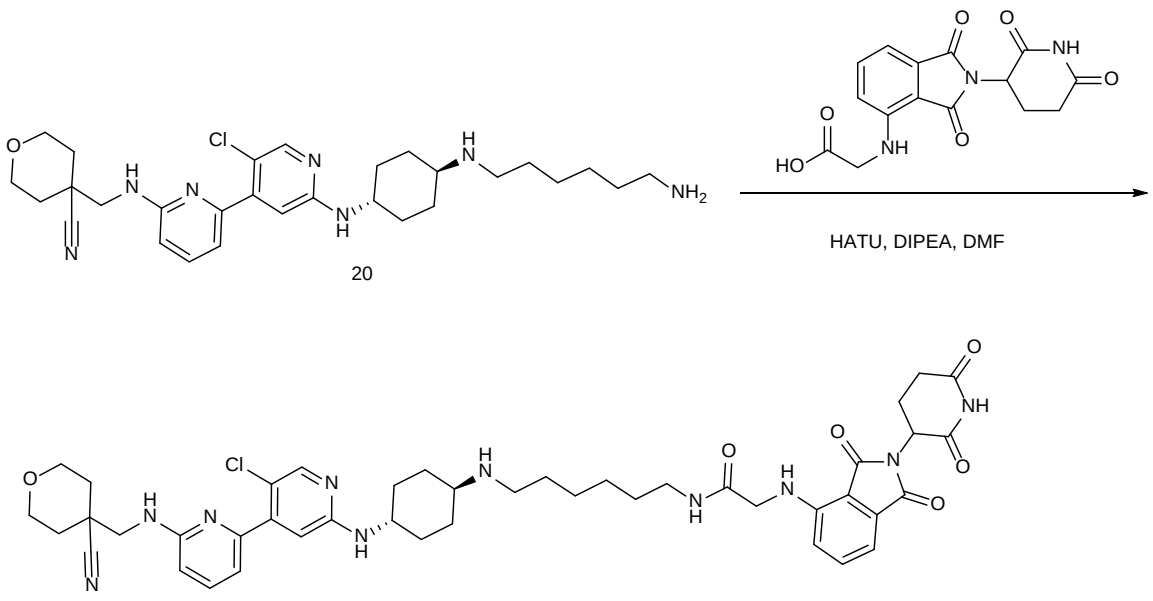


Synthesis of 20. To a solution of **17** (440 mg, 1 mmol) in 1,2-dichloro-ethane (5 mL) was added *tert*-butyl 6-oxohexylcarbamate (215 mg, 1 mmol) and acetic acid (3 drops). The mixture was stirred for 15 min at ambient temperature and then sodium tris(acetoxy)borohydride (275 mg, 1.3 mmol) was added in one portion and kept stirring

for another 2 hours. Then the reaction mixture was poured to saturated $NaHCO_3$ solution (20 mL) and extracted DCM (3X30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was then dissolved in DCM (3 mL) followed by addition of TFA (1.5 mL). The mixture was stirred at ambient temperature for 0.5h and evaporated under vacuum. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give 20 (TFA salt) as a brown oil (227 mg, 42% over two steps). LC-MS: *m/z* 540.3 [M+1].

Synthesis of 5. To a solution of **20** (100 mg, 0.19 mmol) in DMA (2 mL) was added 9 (53 mg, 0.19 mmol) and DIPEA (66 µL, 0.38 mmol). The reaction mixture was heated to 90^{o}C and kept stirring for 2h. Then the mixture was cooled to ambient temperature, filtered and purified by reverse phase HPLC (5-95% MeOH in H_2O) to give compound **5** (TFA salt) as a yellow solid (42 mg, 28%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.09 (s, 1H), 8.41 (s, 2H), 8.04 (s, 1H), 7.69-7.56 (m, 1H), 7.54-7.42 (m, 1H), 7.14 (br, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 7.03 (d, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 1H), 6.54 (s, 1H), 5.15-5.09 (m, 1H), 3.66 (d, *J* = 6.0 Hz, 3H), 3.58-3.39 (m, 2H), 3.31 (q, *J* = 6.2 Hz, 2H), 3.03 (s, 1H), 2.97-2.78 (m, 4H), 2.66-2.52 (m, 2H), 2.10-1.99 (d, *J* = 11.0 Hz, 5H), 1.94-1.85 (m, 2H), 1.78-1.62 (m, 2H), 1.58 (q, *J* = 6.9, 6.3 Hz, 4H), 1.49-1.32 (m, 6H), 1.30-1.18 (m, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.82, 170.10, 168.97, 167.28, 158.24, 158.18, 157.92, 156.68, 147.14, 146.41, 137.23, 136.31, 132.21, 122.48, 117.10, 115.39, 112.45, 110.46, 109.05, 108.83, 63.95, 55.23, 48.55, 48.42, 47.20, 44.02, 41.70, 38.60, 32.40, 30.98, 30.06, 28.47, 27.42, 25.81, 25.74, 25.70, 22.16. LC-MS: *m/z* 796.4 [M+1].

Synthesis of 6

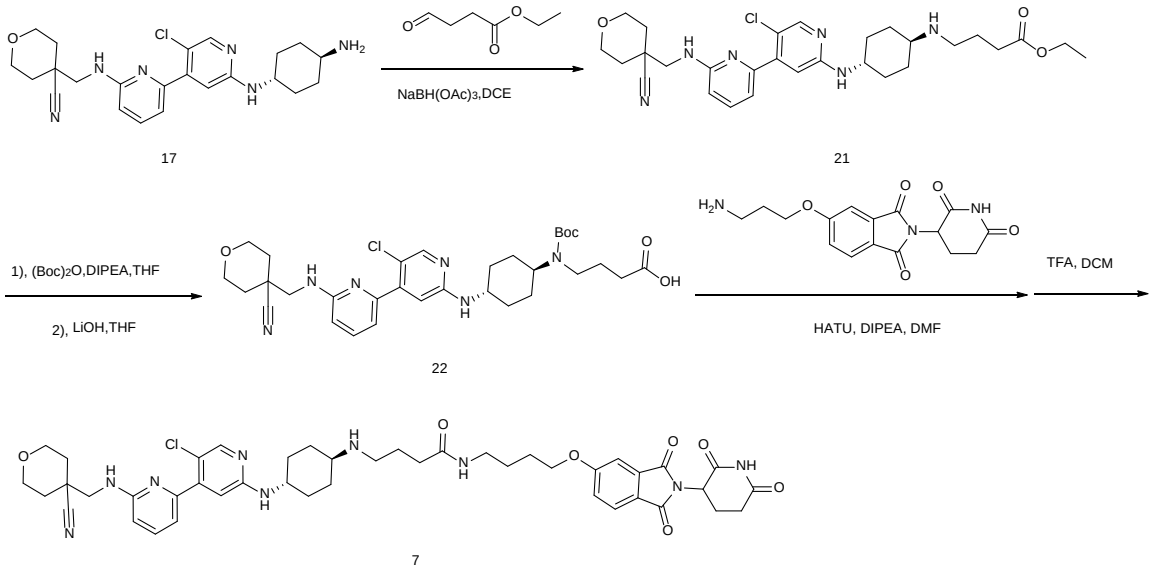


20

6

To a solution of the **20** (100 mg, 0.19 mmol) in DMF (2 mL) was added 2-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-ylamino)acetic acid[1] (56 mg, 0.17 mmol), DIPEA (0.1 mL, 0.57 mmol) and HATU (97mg, 0.26 mmol). The mixture was stirred for 1h at ambient temperature, filtered and purified by reverse phase HPLC (5-95% MeOH in H_2O) to give compound **6** (TFA salt) as a yellow solid (50 mg, 31%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.35 (s, 2H), 8.11 (t, *J* = 5.7 Hz, 1H), 8.06 (d, *J* = 2.2 Hz, 1H), 7.62-7.57 (m, 1H), 7.54-7.39 (m, 1H), 7.19 (s, 1H), 7.08 (d, *J* = 7.0 Hz, 1H), 6.94 (s, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.76-6.64 (m, 2H), 3.98-3.85 (m, 3H), 3.72-3.55 (m, 2H), 3.52-3.43 (m, 3H), 3.15-2.98 (m, 2H), 2.94-2.78 (m, 2H), 2.64-2.52 (m, 2H), 2.14-1.97 (m, 6H), 1.93-1.78 (m, 2H), 1.76-1.62 (m, 2H), 1.59-1.52 (m, 2H), 1.47-1.35 (m, 4H), 1.35-1.18 (m, 9H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.81, 170.05, 168.71, 168.26, 167.30, 158.36, 158.15, 158.08, 145.80, 137.43, 136.18, 132.07, 122.45, 117.42, 115.48, 112.52, 110.97, 109.88, 63.85, 60.64, 55.22, 48.57, 48.52, 17.21, 45.18, 44.08, 38.57, 38.43, 32.39, 30.98, 29.99, 28.87, 27.39, 25.81, 25.72, 25.67, 22.16. LC-MS: *m/z* 853.4 [M+1].

Synthesis of 7



Synthesis of 21. To a solution of 17 (440 mg, 1 mmol) in 1,2-dichloro-ethane (5 mL) was added ethyl 4-oxobutanoate (130 mg, 1 mmol) and acetic acid (3 drops). The mixture was stirred for 15 min at ambient temperature and then sodium tris(acetoxy)borohydride (275 mg, 1.3 mmol) was added in one portion and kept stirring for another 2 hours. Then the reaction mixture was poured to saturated $NaHCO_3$ solution (20 mL) and extracted DCM (3X30 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give 21 (TFA salt) as a brown oil (194 mg, 35% over two steps). LC-MS: *m/z* 555.3 [M+1].

Synthesis of 22. To a solution of **21** (111 mg, 0.2 mmol) and DIPEA (0.1 mL, 0.6 mmol) in anhydrous THF (3 mL) was added $(Boc)_2O$ (48 mg, 0.22 mmol) in THF (1 mL) dropwise at 0^oC. After addition, the mixture was warmed to room temperature and kept stirring overnight. Then the mixture was diluted with EtOAc and H_2O, extracted, and washed with brine. The organic layer was dried (Na_2SO_4) and concentrated. The crude was purified by column chromatography on silica gel to give the Boc-protected compound which was then dissolved in THF (3 mL) and 1 N aqueous LiOH (1 mL) was added. The resulting mixture

was stirred at room temperature for 3h, acidified with 1 N HCl solution (PH=6) and solvent was evaporated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give the acid **22** (TFA salt) (78 mg, 62% over two steps). LC-MS: m/z 627.3 [M+1].

Synthesis of 7. To a solution of the acid 22 (52 mg, 0.083 mmol) in DMF (2 mL) was added 5-(3-aminopropoxy)-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione[1-2] (27 mg, 0.083 mmol), DIPEA (44 µL, 0.25 mmol) and HATU (46 mg, 0.125 mmol). The mixture was stirred for 1h at ambient temperature, then evaporated and the residue was dissolved in DCM (2 mL) followed by addition of TFA (1 mL). The resulting mixture was stirred at ambient temperature for 0.5h and concentrated. The residue was purified by reverse phase HPLC (5-95% MeOH in H_2O) to give **7** (TFA salt) as a light yellow solid (35 mg, 49% over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.11 (s, 1H), 8.50 (d, *J* = 6.2 Hz, 2H), 8.06 (s, 1H), 8.00 (t, *J* = 5.7 Hz, 1H), 7.91-7.83 (m, 1H), 7.63-7.55 (m, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.38-7.27 (m, 1H), 7.19 (s, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 6.72-6.70 (m, 2H), 5.11 (dd, *J* = 12.9, 5.4 Hz, 1H), 4.19 (t, *J* = 6.4 Hz, 2H), 3.99-3.76 (m, 2H), 3.66 (d, *J* = 5.4 Hz, 2H), 3.50-3.42 (m, 3H), 3.13 (q, *J* = 6.6 Hz, 2H), 2.93 (q, *J* = 6.1, 5.4 Hz, 3H), 2.22 (t, *J* = 7.1 Hz, 2H), 2.10-2.01 (m, 5H), 1.87-1.79 (m, 4H), 1.76 (dd, *J* = 8.7, 6.3 Hz, 2H), 1.77-1.68 (m, 3H), 1.62-1.51 (m, 2H), 1.47-1.35 (m, 2H), 1.30-1.21 (m, 3H). ^{13}C NMR (125 MHz, DMSO-*d6*) δ 172.76, 171.13, 169.92, 166.89, 166.79, 164.02, 158.64, 158.35, 158.15, 158.07, 156.18, 137.39, 133.96, 125.33, 122.92, 122.45, 120.73, 120.28, 116.93, 115.46, 114.61, 112.51, 109.07, 108.81, 108.41, 99.52, 68.52, 68.41, 63.85, 55.05, 52.05, 51.25, 48.97, 48.51, 47.21, 43.84, 38.57, 38.15, 32.39, 32.07, 30.95, 30.51, 29.96, 27.42, 25.89, 25.62, 22.07, 21.84. LC-MS: *m/z* 853.4 [M+1].

References

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