Supporting Information

Selective Degradation of GSPT1 by Cereblon Modulators Identified via a Focused Combinatorial Library

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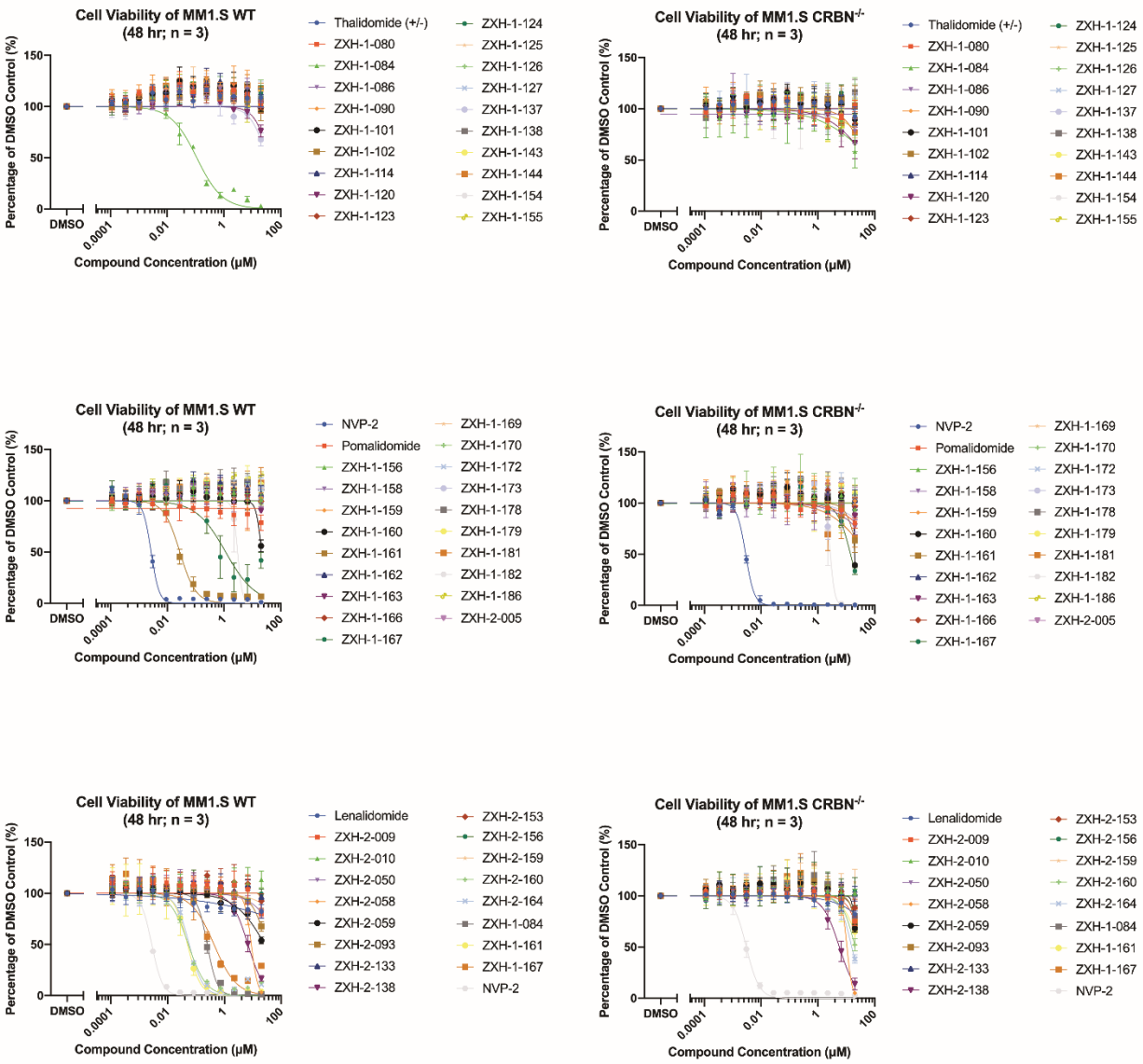


Figure S1. Antiproliferative IC_{50} Curves in MM1.S Wild-Type and $CRBN^{-/-}$ Cells.

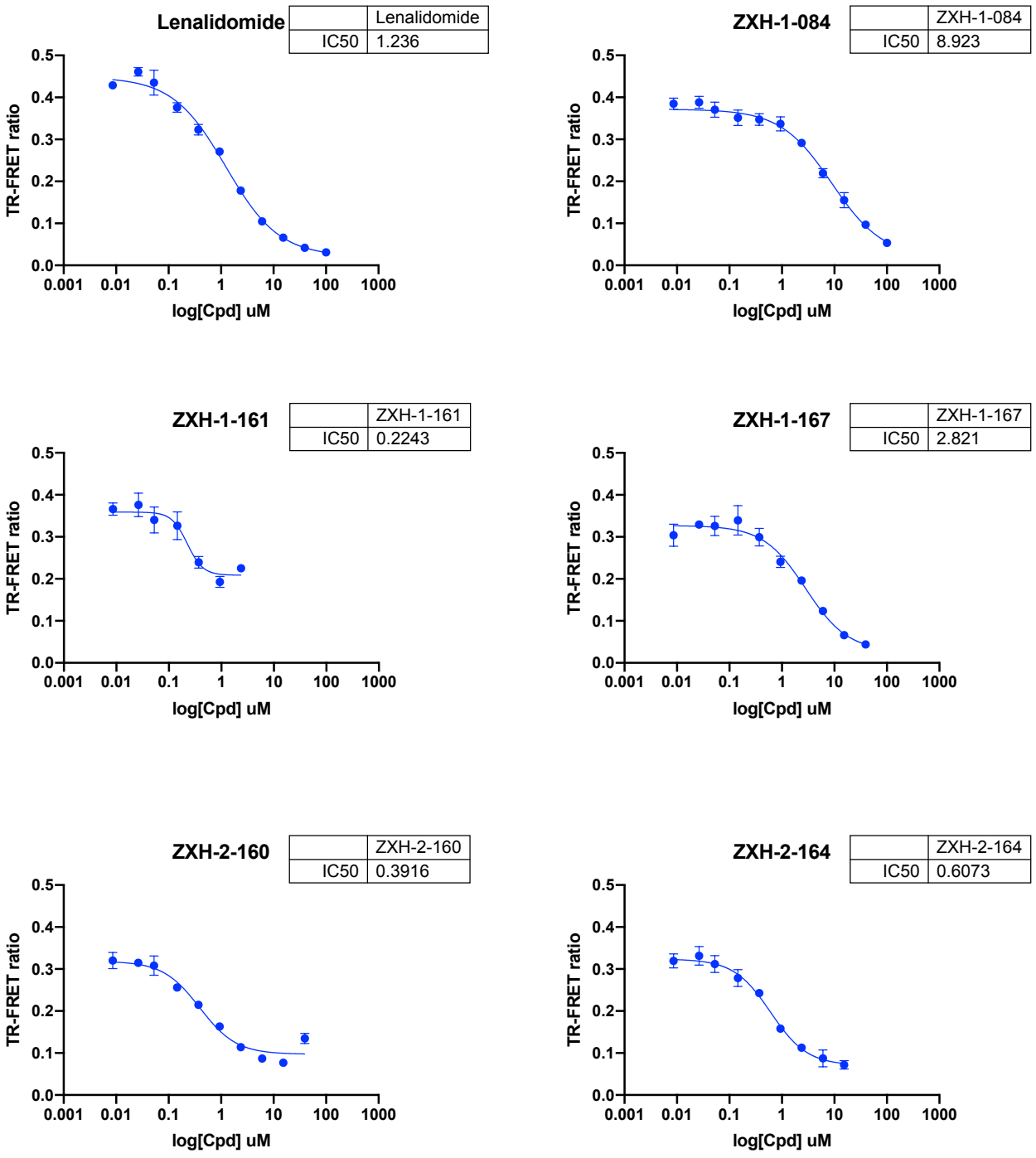


Figure S2. *In vitro* cereblon binding assay data with IC_{50}s for hit compounds.

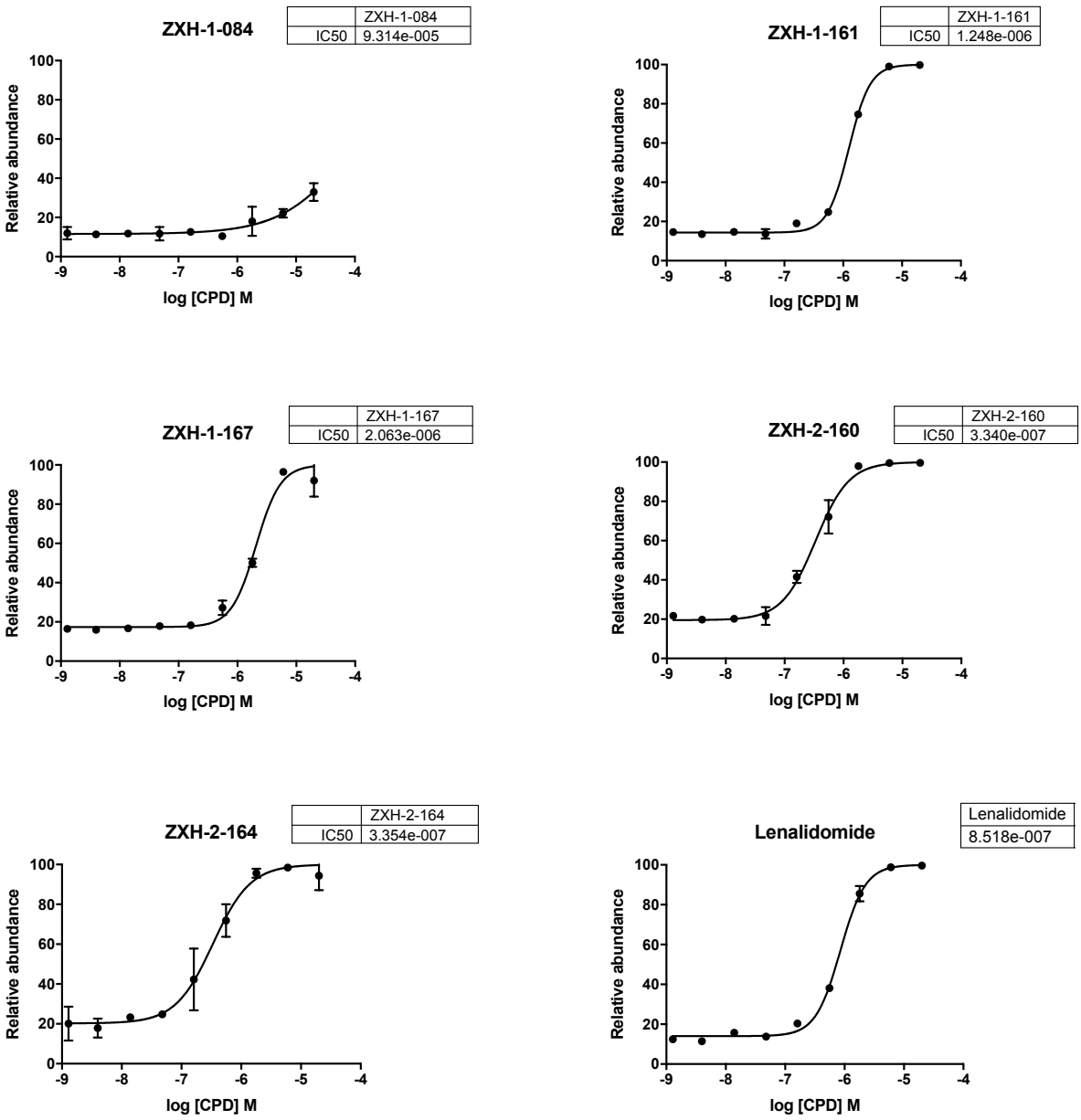


Figure S3. Cellular cereblon engagement data with IC_{50}s for hit compounds.

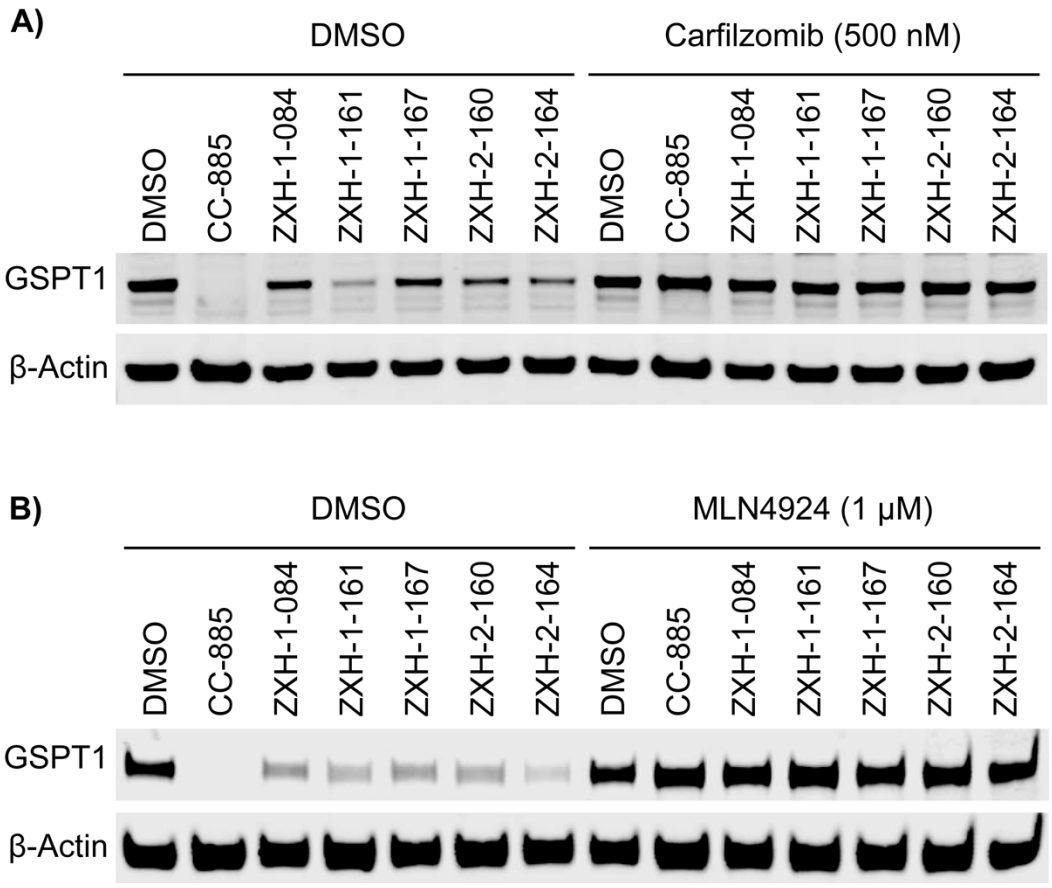


Figure S4. Validation that observed GSPT1 degradation is proteasome dependent. (A) Immunoblot after 4 h co-treatment of carfilzomib and 1 μM compounds in MM1.S cells. (B) Immunoblot after 4 h co-treatment of MLN4924 and 1 μM compounds in MM1.S cells.

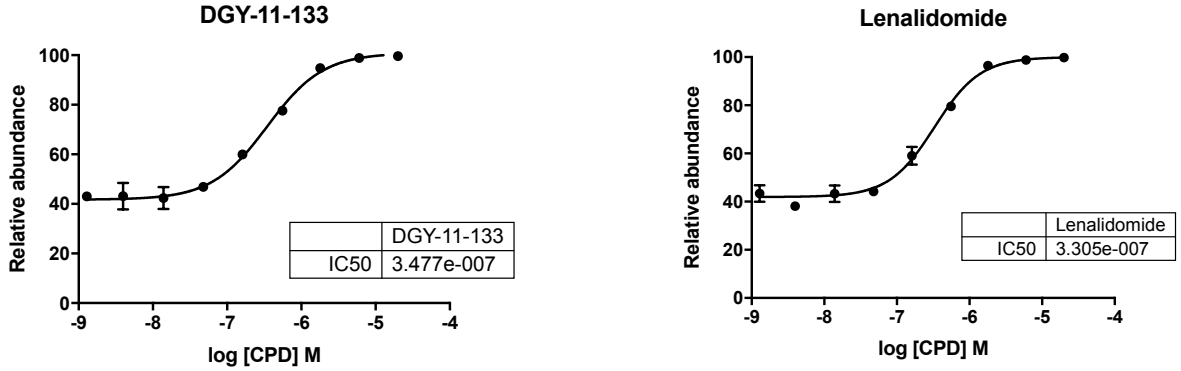


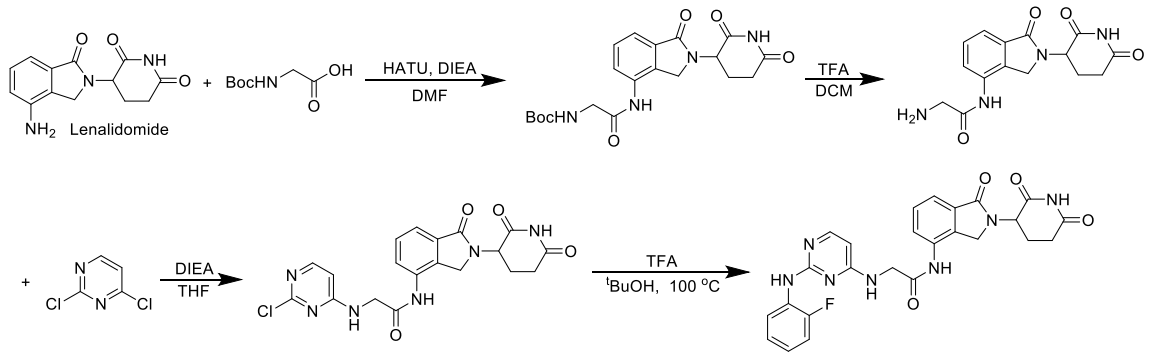
Figure S5. Cellular cereblon engagement data for DGY-11-133 (**52**).

Experimental Methods

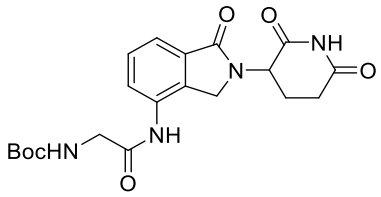
Chemical Synthesis

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 A500), 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 Micromass ZQ instrument. Preparative HPLC was performed on a Waters Sunfire C18 column (19 x 50 mm, 5μM) using a gradient of 15-95% methanol in water containing 0.05% trifluoroacetic acid (TFA) over 22 min (28 min run time) at a flow rate of 20 mL/min. Purities of assayed compounds were in all cases greater than 95%, as determined by reverse-phase HPLC analysis.

Scheme 1. Synthesis of **1**



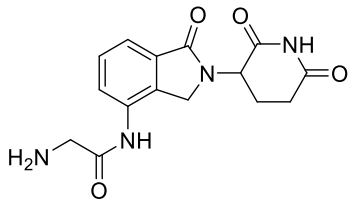
tert-Butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-2-oxoethyl)-carbamate



To a solution of (*tert*-butoxycarbonyl)glycine (2.1 g, 12 mmol), DIEA (5 mL, 30 mmol) in DMF (30 mL) was added 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) (4.94 g, 13 mmol), stirred for 0.5h, and then Lenalidomide (2.59 g, 10 mmol) was added, the mixture was then stirred at room temperature for another 1h. The mixture was then purified by silica gel (MeOH/DCM = 0–10%) to obtain the title compound.

LCMS (m/z): 417 $[M+H]^+$.

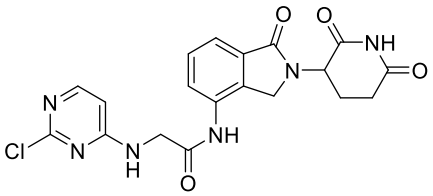
2-Amino-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide



To a solution of *tert*-Butyl (2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-2-oxoethyl)-carbamate in DCM (30 mL) was added TFA (10 mL), and stirred at room temperature for 3h. The mixture was then concentrated *in vacuo*, and purified by silica gel (MeOH/DCM = 0-30%) to obtain the title compound (972 mg, 23% for 2 steps).

LCMS (m/z): 317 $[M+H]^+$.

2-((2-chloropyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) acetamide



To a solution of 2-amino-*N*-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (972 mg, 2.26 mmol) and 2,4-dichloropyrimidine (332 mg, 2.26 mmol) in THF (20 mL) was added DIEA (1.1 mL, 6.78 mmol), and then stirred overnight. The mixture was then concentrated *in vacuo*, and purified by silica gel (MeOH/DCM = 0-10%) to obtain the title compound (693 mg, 72%).

LCMS (m/z): 429 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((2-fluorophenyl)amino)pyrimidin-4-yl)amino)acetamide (1)

To a solution of 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) acetamide (50 mg, 0.12 mmol) and 2-fluoroaniline (13 mg, 0.12 mmol) in ^{t}BuOH (1 mL) was added TFA (18 μL, 0.24 mmol), and then the mixture was heated to reflux overnight. The mixture was then concentrated *in vacuo*, and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain compound **1** (4.6 mg, 6%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.18 (s, 1H), 10.06 (s, 1H), 9.38 (t, *J* = 5.7 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.83 – 7.74 (m, 2H), 7.57 – 7.49 (m, 2H), 7.26 – 7.16 (m, 1H), 7.08 – 6.97 (m, 1H), 6.45 (d, *J* = 7.2 Hz, 1H), 5.16 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.31 – 4.22 (m, 4H), 2.93 (ddd, *J* = 17.4, 13.6, 5.4 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.24 (qd, *J* = 13.2, 4.5 Hz, 1H), 2.03 (ddd, *J* = 10.3, 5.4, 2.8 Hz, 1H).

LCMS (m/z): 504 $[M+H]^+$.

2-((2-((2,3-dihydro-1H-inden-5-yl)amino)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (2)

2 (4.4 mg, 6%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 2,3-dihydro-1*H*-inden-5-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.32 (s, 1H), 10.11 (s, 1H), 9.30 (t, *J* = 5.9 Hz, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.34 (s, 1H), 7.26 – 7.18 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.39 (d, *J* = 7.2 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.33 – 4.25 (m, 4H), 2.85 (dt, *J* = 14.5, 7.7 Hz, 2H), 2.73 (q, *J* = 7.5 Hz, 4H), 2.07 – 1.96 (m, 2H), 1.91 (p, *J* = 7.0 Hz, 2H).

LCMS (m/z): 526 $[M+H]^+$.

2-((2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (3)

3 (6.5 mg, 4%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to benzo[*d*][1,3]dioxol-5-ylmethanamine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.85 (d, *J* = 4.6 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.68 (d, *J* = 5.7 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.32 (s, 1H), 6.94 (s, 1H), 6.82 (s, 1H), 6.76 – 6.65 (m, 2H), 5.90 (s, 2H), 5.86 (d, *J* = 6.0 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.36 – 4.22 (m, 4H), 4.09 (d, *J* = 5.9 Hz, 2H), 2.92 (ddd, *J* = 17.2, 13.6, 5.4 Hz, 1H), 2.69 – 2.57 (m, 1H), 2.32 – 2.18 (m, 1H), 2.03 – 1.96 (m, 1H).

LCMS (m/z): 544 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-4-yl)amino)acetamide (4)

4 (1.9 mg, 3%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to (*S*)-pyrrolidin-2-ylmethanol.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.04 (s, 1H), 10.13 (s, 1H), 9.12 (s, 1H), 7.83 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.57 – 7.46 (m, 2H), 6.29 (d, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.42 – 4.26 (m, 4H), 3.64 – 3.34 (m, 4H), 2.94 (ddd, *J* = 18.1, 13.5, 5.4 Hz, 1H), 2.67 – 2.60 (m, 1H), 2.30 (dd, *J* = 13.1, 4.6 Hz, 1H), 2.10 – 1.90 (m, 6H).

LCMS (m/z): 494 $[M+H]^+$.

2-((2-(benzo[d][1,3]dioxol-5-ylamino)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (5)

5 (5.2 mg, 6%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.25 (s, 1H), 10.12 (s, 1H), 9.28 (s, 1H), 7.83 – 7.74 (m, 2H), 7.56 – 7.47 (m, 2H), 7.01 (d, *J* = 2.5 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.37 (d, *J* = 7.2 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.32 (s, 2H), 4.16 – 4.05 (m, 4H), 2.92 (ddd, *J* = 17.2, 13.5, 5.4 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.32 – 2.20 (m, 1H), 2.06 – 1.95 (m, 1H).

LCMS (m/z): 530 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((3-(2-oxopyrrolidin-1-yl)propyl)amino)pyrimidin-4-yl)amino)acetamide (6)

6 (4.1 mg, 5%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 1-(3-aminopropyl)pyrrolidin-2-one.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (s, 1H), 11.04 (d, *J* = 2.3 Hz, 1H), 10.20 – 10.08 (m, 1H), 8.04 – 7.93 (m, 1H), 7.85 (ddd, *J* = 17.0, 7.4, 1.6 Hz, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.58 – 7.46 (m, 2H), 6.30 – 6.23 (m, 1H), 5.17 (ddd, *J* = 13.3, 5.2, 2.9 Hz, 1H), 4.49 – 4.21 (m, 4H), 3.31 (d, *J* = 22.6 Hz, 2H), 3.19 – 3.08 (m, 2H), 2.98 – 2.90 (m, 1H), 2.67 – 2.59 (m, 1H), 2.34 – 2.25 (m, 1H), 2.14 (d, *J* = 7.8 Hz, 1H), 2.08 – 1.99 (m, 1H), 1.81 (s, 1H), 1.62 (s, 1H).

LCMS (m/z): 535 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((4-methoxyphenyl)amino)pyrimidin-4-yl)amino)acetamide (7)

7 (10.9 mg, 7%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 4-methoxyaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.46 (s, 1H), 10.15 (s, 1H), 9.32 (d, *J* = 5.7 Hz, 1H), 7.81 (td, *J* = 9.1, 7.7, 4.1 Hz, 2H), 7.58 – 7.47 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 6.38 (d, *J* = 7.2 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.33 – 4.23 (m, 4H), 3.60 (s, 3H), 2.93 (ddd, *J* = 17.2, 13.5, 5.4 Hz, 1H), 2.65 – 2.56 (m, 1H), 2.23 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.01 (dtd, *J* = 12.4, 7.4, 6.2, 3.7 Hz, 1H).

LCMS (m/z): 516 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-4-yl)amino)acetamide (14)

14 (5.1 mg, 2%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to (*R*)-pyrrolidin-2-ylmethanol.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.15 (s, 1H), 9.13 (s, 1H), 7.83 (d, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.60 – 7.47 (m, 2H), 6.29 (d, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.44 – 4.27 (m, 4H), 3.60 – 3.36 (m, 5H), 2.94 (ddd, *J* = 18.1, 13.5, 5.5 Hz, 1H), 2.68 – 2.58 (m, 1H), 2.30 (tt, *J* = 13.1, 6.7 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.91 (dqd, *J* = 18.5, 12.4, 6.4 Hz, 4H).

LCMS (m/z): 494 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-((2-methoxyphenyl)amino)pyrimidin-4-yl)amino)acetamide (15)

15 (9.5 mg, 5%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 2-methoxyaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.18 (s, 1H), 9.64 (s, 1H), 9.38 (t, *J* = 5.8 Hz, 1H), 7.94 – 7.77 (m, 3H), 7.56 – 7.49 (m, 2H), 7.12 (t, *J* = 7.7 Hz, 1H), 7.09 – 7.07 (m, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.34 – 4.20 (m, 4H), 3.83 (s, 3H), 2.92 (ddd, *J* = 17.2, 13.5, 5.4 Hz, 1H), 2.66 – 2.54 (m, 1H), 2.19 (qd, *J* = 13.1, 4.4 Hz, 1H), 2.00 (dtd, *J* = 12.8, 5.4, 2.2 Hz, 1H).

LCMS (m/z): 516 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)pyrimidin-4-yl)amino)acetamide (16)

16 (12.1 mg, 5%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to 1-(3-(trifluoromethyl)phenyl)piperazine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.27 (s, 1H), 9.27 (t, *J* = 5.6 Hz, 1H), 7.88 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.80 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.47 – 7.43 (m, 1H), 7.29 – 7.22 (m, 1H), 7.17 (t, *J* = 6.9 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.36 (dd, *J* = 34.4, 7.4 Hz, 4H), 3.85 (t, *J* = 5.1 Hz, 4H), 3.37 (dt, *J* = 48.5, 5.2 Hz, 4H), 2.93 (ddd, *J* = 18.0, 13.5, 5.3 Hz, 1H), 2.64 – 2.57 (m, 1H), 2.31 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.04 (ddd, *J* = 13.3, 5.8, 3.4 Hz, 1H).

LCMS (m/z): 623 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-(methyl(phenyl)amino)pyrimidin-4-yl)amino)acetamide (17)

17 (16.5 mg, 6%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to *N*-methylaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.20 (s, 1H), 9.35 (t, *J* = 5.7 Hz, 1H), 7.86 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.49 (d, *J* = 7.4 Hz, 2H), 7.45 (dt, *J* = 8.2, 2.6 Hz, 3H), 6.38 (d, *J* = 7.2 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.46 – 4.28 (m, 4H), 3.44 (s, 3H), 2.99 – 2.87 (m, 1H), 2.67 – 2.58 (m, 1H), 2.31 (qd, *J* = 13.2, 4.5 Hz, 1H), 2.13 – 1.96 (m, 1H).

LCMS (m/z): 500 $[M+H]^+$.

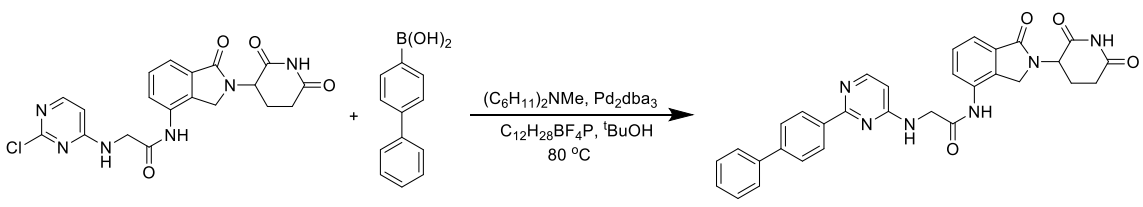
2-((2-(benzyl(ethyl)amino)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (18)

18 (1.4 mg, 0.8%) was obtained according to the synthetic route of **1**, changing from 2-fluoroaniline to *N*-benzylethanamine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.05 (s, 1H), 7.77 (dt, *J* = 13.2, 7.1 Hz, 2H), 7.54 – 7.46 (m, 2H), 7.40 – 7.18 (m, 6H), 6.33 (d, *J* = 6.6 Hz, 1H), 5.15 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.78 (d, *J* = 16.6 Hz, 2H), 4.30 (d, *J* = 5.7 Hz, 4H), 3.52 (s, 2H), 2.93 (ddd, *J* = 17.4, 13.6, 5.4 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.17 (d, *J* = 16.2 Hz, 1H), 2.01 (s, 1H), 1.03 (t, *J* = 7.0 Hz, 3H).

LCMS (m/z): 528 $[M+H]^+$.

Scheme 2. Synthesis of **8**



2-((2-([1,1'-biphenyl]-4-yl)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (8)

To a solution of 2-((2-chloropyrimidin-4-yl)amino)-*N*-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) acetamide (110 mg, 0.24 mmol) and [1,1'-biphenyl]-4-ylboronic acid (54 mg, 0.28 mmol) in ^{t}BuOH (2 mL) were added *N*,*N*-Dicyclohexylmethylamine (52 mg, 0.26 mmol), Pd_2dba_3 (22 mg, 0.024 mmol) and Tri-*tert*-butylphosphonium tetrafluoroborate (20 mg, 0.048 mmol). The mixture was heated to 80 ℃ and stirred under N_2 atmosphere overnight. The mixture was then filtered, concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain **8** (4.4 mg, 3%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.30 (s, 1H), 8.77 (dd, *J* = 4.4, 1.4 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 2H), 8.31 – 8.27 (m, 1H), 7.90 – 7.72 (m, 5H), 7.56 – 7.50 (m, 4H), 7.49 – 7.39 (m, 1H), 6.88 (d, *J* = 6.7 Hz, 1H), 5.11 (dd, *J* = 13.4, 5.0 Hz, 1H), 4.49 (d, *J* = 5.4 Hz, 2H), 4.37 (s, 2H), 2.87 (t, *J* = 13.9 Hz, 1H), 2.64 (d, *J* = 5.1 Hz, 1H), 2.17 (d, *J* = 13.4 Hz, 1H), 1.96 (s, 1H).

LCMS (m/z): 547 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-(3-methoxyphenyl)pyrimidin-4-yl)amino)acetamide (9)

9 (4.0 mg, 3%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to (3-methoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.31 (s, 1H), 9.79 (s, 1H), 8.24 (d, *J* = 7.2 Hz, 1H), 8.19 – 8.17 (m, 1H), 7.81 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.68 (ddd, *J* = 8.9, 7.3, 1.8 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.50 (d, *J* = 5.5 Hz, 2H), 4.36 – 4.25 (m, 2H), 3.98 (s, 3H), 2.92 (ddd, *J* = 18.3, 13.4, 5.5 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.15 – 2.07 (m, 1H), 2.00 – 1.96 (m, 1H).

LCMS (m/z): 501 $[M+H]^+$.

2-((2-(2,4-dimethoxyphenyl)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (10)

10 (2.8 mg, 1%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to (2,4-dimethoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.30 (s, 1H), 9.60 (s, 1H), 8.23 (d, *J* = 9.3 Hz, 1H), 8.16 (d, *J* = 7.2 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.59 – 7.49 (m, 2H), 6.88 (d, *J* = 7.1 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.66 (dt, *J* = 8.9, 2.0 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.47 (d, *J* = 5.5 Hz, 2H), 4.32 (s, 2H), 4.01 (s, 3H), 3.89 (s, 3H), 2.92 (ddd, *J* = 18.3, 13.5, 5.4 Hz, 1H), 2.58 (d, *J* = 17.5 Hz, 1H), 2.20 – 2.08 (m, 1H), 2.01 – 1.90 (m, 1H).

LCMS (m/z): 531 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-(4-fluorophenyl)pyrimidin-4-yl)amino)acetamide (11)

11 (10.0 mg, 3%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to (4-fluorophenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.30 (s, 1H), 9.30 (s, 1H), 8.36 – 8.23 (m, 2H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.57 – 7.49 (m, 3H), 7.42 (t, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 6.8 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.47 (d, *J* = 5.3 Hz, 2H), 4.34 (s, 2H), 2.92 (ddt, *J* = 18.1, 13.6, 4.7 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.19 – 2.12 (m, 1H), 1.98 (d, *J* = 10.2 Hz, 1H).

LCMS (m/z): 489 $[M+H]^+$.

2-((2-(4-acetylphenyl)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (12)

12 (3.6 mg, 3%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to (4-acetylphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.22 (s, 1H), 8.75 (s, 1H), 8.40 (d, *J* = 8.4 Hz, 2H), 8.29 (d, *J* = 6.4 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 2H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.47 (m, 2H), 6.82 (d, *J* = 6.4 Hz, 1H), 5.11 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.43 – 4.38 (m, 2H), 4.33 (s, 2H), 2.90 (ddd, *J* = 18.2, 13.5, 5.4 Hz, 1H), 2.63 (s, 3H), 2.57 (d, *J* = 19.1 Hz, 1H), 2.14 (d, *J* = 13.6 Hz, 1H), 2.00 – 1.91 (m, 1H).

LCMS (m/z): 513 $[M+H]^+$.

2-((2-(benzofuran-2-yl)pyrimidin-4-yl)amino)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide (13)

13 (12.3 mg, 6%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to benzofuran-2-ylboronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.20 (s, 1H), 8.22 (d, *J* = 5.8 Hz, 1H), 8.14 (s, 1H), 7.83 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.66 (s, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.43 – 7.38 (m, 1H), 7.29 (s, 1H), 6.67 (s, 1H), 5.07 (dd, *J* = 13.4, 4.9 Hz, 1H), 4.36 (d, *J* = 22.3 Hz, 4H), 2.92 – 2.79 (m, 1H), 2.46 (s, 1H), 2.13 (d, *J* = 13.9 Hz, 1H), 1.89 (s, 1H).

LCMS (m/z): 511 $[M+H]^+$.

N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-2-((2-(4-fluoro-2-methoxyphenyl)pyrimidin-4-yl)amino)acetamide (19)

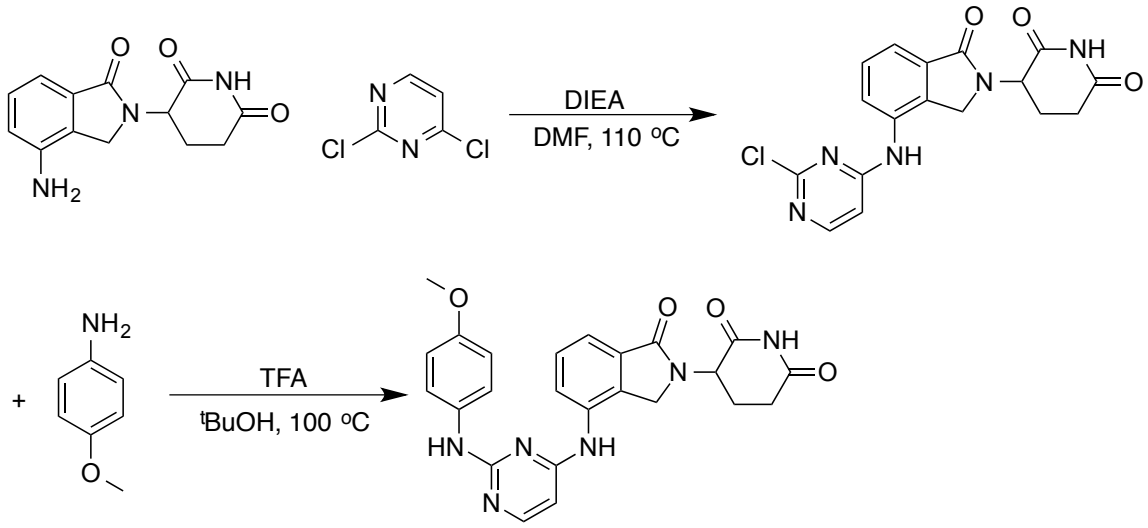
19 (1.6 mg, 1%) was obtained according to the synthetic route of **8**, changing from [1,1'-biphenyl]-4-ylboronic acid to (4-fluoro-2-methoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.27 (s, 1H), 9.73 (s, 1H), 8.65 (s, 1H), 8.21 (d, *J* = 7.0 Hz, 1H), 8.12 (s, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.55 (m, 2H), 7.28 (d, *J* = 10.3 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 5.13 (dd, *J* = 12.2, 5.3 Hz, 1H), 4.52 (d, *J* = 5.2 Hz, 2H), 4.35 – 4.23 (m,

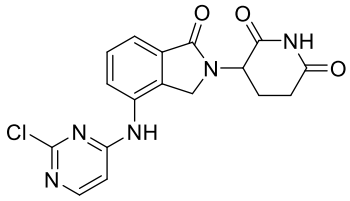
2H), 3.95 (s, 3H), 2.90 (ddd, *J* = 18.0, 12.9, 5.3 Hz, 1H), 2.61 – 2.57 (m, 1H), 2.14 – 2.03 (m, 1H), 2.02 – 1.92 (m, 1H).

LCMS (m/z): 519 $[M+H]^+$.

Scheme 3. Synthesis of **20**



3-(4-((2-Chloropyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



To a solution of Lenalidomide (777 mg, 3 mmol) and 2,4-dichloropyrimidine (882 mg, 6 mmol) in DMF (6 mL) was added DIEA (1.5 mL, 9 mmol), and then the mixture was heated to 110 ℃ overnight. The mixture was concentrated *in vacuo* and then purified by silica gel (MeOH/DCM = 0-6%) to obtain the title compound (321 mg, 29%) as pale white solid.

LCMS (m/z): 372 $[M+H]^+$.

3-(4-((2-((4-methoxyphenyl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (20)

To a solution of 3-(4-((2-chloropyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (112 mg, 0.3 mmol) and 4-methoxyaniline (37 mg, 0.3 mmol) in ^{t}BuOH (2 mL) was added TFA (45 μL, 0.6 mmol), and then the mixture was heated to reflux overnight. The mixture was then concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain compound **20** (64.3 mg, 38%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.36 (d, *J* = 51.4 Hz, 2H), 7.94 (dd, *J* = 41.2, 7.4 Hz, 2H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.43 (d, *J* = 6.9 Hz, 1H), 5.14 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.46 (d, *J* = 17.5 Hz, 1H), 4.33 (d, *J* = 17.4 Hz, 1H), 3.74 (s, 3H), 2.90 (ddd, *J* = 18.1, 13.6, 5.4 Hz, 1H), 2.62 – 2.53 (m, 1H), 2.35 – 2.24 (m, 1H), 1.87 (d, *J* = 11.2 Hz, 1H).

LCMS (m/z): 459 $[M+H]^+$.

3-(4-((2-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (21)

21 (15.9 mg, 10.1%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.41 (d, *J* = 52.9 Hz, 2H), 7.94 (dd, *J* = 57.8, 7.2 Hz, 2H), 7.69 – 7.49 (m, 2H), 6.99 (s, 1H), 6.85 – 6.71 (m, 2H), 6.43 (d, *J* = 6.9 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.3 Hz, 1H), 4.46 (d, *J* = 17.5 Hz, 1H), 4.30 (d, *J* = 17.4 Hz, 1H), 4.20 (s, 4H), 2.97 – 2.85 (m, 1H), 2.57 (s, 1H), 2.25 (s, 1H), 1.82 (s, 1H).

LCMS (m/z): 487 $[M+H]^+$.

3-(4-((2-((2-fluorophenyl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (23)

23 (11.0 mg, 9%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 2-fluoroaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.31 (s, 1H), 10.01 (s, 1H), 8.07 (d, *J* = 6.8 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.59 (dd, *J* = 9.9, 7.0 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.30 (ddd, *J* = 10.5, 8.3, 1.4 Hz, 1H), 7.24 (tdd, *J* = 7.9, 5.2, 1.6 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 6.49 (d, *J* = 6.7 Hz, 1H), 5.14 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.45 (d, *J* = 17.5 Hz, 1H), 4.33 (d, *J* = 17.4 Hz, 1H), 2.96 – 2.84 (m, 1H), 2.59 (dt, *J* = 17.0, 3.3 Hz, 1H), 2.31 (qd, *J* = 13.2, 4.4 Hz, 1H), 1.97 – 1.84 (m, 1H). LCMS (m/z): 447 $[M+H]^+$.

3-(1-oxo-4-((2-((3-(2-oxopyrrolidin-1-yl)propyl)amino)pyrimidin-4-yl)amino)isoindolin-2-yl)piperidine-2,6-dione (24)

24 (8.6 mg, 6%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 1-(3-aminopropyl)pyrrolidin-2-one.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.58 (s, 1H), 8.32 (s, 1H), 7.93 (d, *J* = 6.9 Hz, 2H), 7.65 (dd, *J* = 18.8, 7.5 Hz, 2H), 6.38 (s, 1H), 5.19 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.48 (d, *J* = 17.7 Hz, 1H), 4.38 (d, *J* = 17.8 Hz, 1H), 3.17 (d, *J* = 21.2 Hz, 6H), 2.94 (ddd, *J* = 18.0, 13.7, 5.4 Hz, 1H), 2.60 (d, *J* = 17.2 Hz, 1H), 2.39 (qd, *J* = 13.2, 4.5 Hz, 1H), 2.14 (s, 2H), 2.02 (d, *J* = 12.2 Hz, 1H), 1.73 (d, *J* = 83.3 Hz, 4H).

LCMS (m/z): 478 $[M+H]^+$.

3-(1-oxo-4-((2-(4-(3-(trifluoromethyl)phenyl)piperazin-1-yl)pyrimidin-4-yl)amino)isoindolin-2-yl)piperidine-2,6-dione (25)

25 (10.9 mg, 7%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 1-(3-(trifluoromethyl)phenyl)piperazine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.53 (s, 1H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.22 (t, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.41 (d, *J* = 6.9 Hz, 1H), 5.19 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.47 (d, *J* = 17.6 Hz, 1H), 4.37 (d, *J* = 17.5 Hz, 1H), 3.76 (q, *J* = 4.0 Hz, 4H), 3.39 (t, *J* = 4.3 Hz, 4H), 2.93 (ddd, *J* = 17.4, 13.7, 5.4 Hz, 1H), 2.58 (dt, *J* = 17.2, 3.1 Hz, 1H), 2.38 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.02 (ddq, *J* = 10.5, 5.6, 3.3, 2.7 Hz, 1H).

LCMS (m/z): 566 $[M+H]^+$.

3-(4-((2-((2,3-dihydro-1H-inden-5-yl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (26)

26 (15.6 mg, 11%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 2,3-dihydro-1*H*-inden-5-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.47 (d, *J* = 32.6 Hz, 2H), 8.03 (d, *J* = 6.9 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 7.4 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.32 (s, 1H), 7.09 (q, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 6.9 Hz, 1H), 5.12 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.46 (d, *J* = 17.5 Hz, 1H), 4.31 (d, *J* = 17.5 Hz, 1H), 2.88 (ddd, *J* = 18.0, 13.6, 5.4 Hz, 1H), 2.79 (t, *J* = 7.4 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 2.57 – 2.55 (m, 1H), 2.22 (qd, *J* = 13.3, 4.4 Hz, 1H), 1.98 (p, *J* = 7.4 Hz, 2H), 1.75 (d, *J* = 12.2 Hz, 1H).

LCMS (m/z): 469 $[M+H]^+$.

3-(4-((2-(benzyl(ethyl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (27)

27 (7.6 mg, 5%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to *N*-benzylethanamine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.38 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.38 – 7.24 (m, 4H), 7.18 (s, 2H), 6.43 (s, 1H), 5.17 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.74 (s,

2H), 4.50 – 4.28 (m, 2H), 3.55 (s, 2H), 2.93 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.61 (dt, *J* = 17.2, 3.3 Hz, 1H), 2.36 (qd, *J* = 12.9, 4.4 Hz, 1H), 2.07 – 1.93 (m, 1H), 1.10 (s, 3H).

LCMS (m/z): 471 $[M+H]^+$.

3-(4-((2-(methyl(phenyl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (28)

28 (17.4 mg, 14%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to *N*-methylaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.05 (s, 1H), 10.50 (s, 1H), 7.86 (dd, *J* = 22.4, 7.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.47 – 7.39 (m, 4H), 6.50 (d, *J* = 7.0 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.47 (d, *J* = 17.5 Hz, 1H), 4.37 (d, *J* = 17.5 Hz, 1H), 3.39 (s, 3H), 2.94 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.62 (dt, *J* = 17.2, 3.4 Hz, 1H), 2.37 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.02 (dtd, *J* = 12.8, 5.3, 2.3 Hz, 1H).

LCMS (m/z): 443 $[M+H]^+$.

3-(4-((2-(mesitylamino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (29)

29 (4.7 mg, 4%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 2,4,6-trimethylaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.74 – 9.65 (m, 2H), 7.98 (d, *J* = 50.4 Hz, 1H), 7.76 – 7.57 (m, 2H), 7.01 (d, *J* = 36.2 Hz, 2H), 6.47 (s, 1H), 5.17 (dd, *J* = 37.4, 13.3 Hz, 1H), 4.33 (dd, *J* = 28.6, 16.4 Hz, 2H), 2.95 (d, *J* = 15.1 Hz, 1H), 2.68 – 2.57 (m, 1H), 2.45 – 2.34 (m, 1H), 2.30 (s, 3H), 2.12 (d, *J* = 7.0 Hz, 6H).

LCMS (m/z): 471 $[M+H]^+$.

3-(4-((2-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (30)

30 (6.3 mg, 5%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to (*S*)-pyrrolidin-2-ylmethanol.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.46 (s, 2H), 8.12 – 7.87 (m, 2H), 7.63 (dd, *J* = 20.9, 7.6 Hz, 2H), 6.44 (s, 1H), 5.19 (dt, *J* = 13.3, 5.2 Hz, 1H), 4.57 – 4.31 (m, 2H), 4.11 (s, 1H), 3.47 (d, *J* = 38.9 Hz, 4H), 2.94 (ddd, *J* = 18.2, 13.9, 5.0 Hz, 1H), 2.66 – 2.56 (m, 1H), 2.40 – 2.31 (m, 1H), 2.09 (s, 1H), 2.05 – 1.84 (m, 4H).

LCMS (m/z): 437 $[M+H]^+$.

3-(4-((2-((R)-2-(hydroxymethyl)pyrrolidin-1-yl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (31)

31 (12.0 mg, 10%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to (*R*)-pyrrolidin-2-ylmethanol.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.49 (s, 1H), 8.22 – 7.88 (m, 2H), 7.74 – 7.37 (m, 2H), 6.44 (s, 1H), 5.18 (dt, *J* = 13.3, 5.2 Hz, 1H), 4.56 – 4.28 (m, 2H), 4.11 (s, 1H), 3.63 – 3.37 (m, 4H), 2.99 – 2.85 (m, 1H), 2.67 – 2.56 (m, 1H), 2.43 – 2.32 (m, 1H), 2.11 (d, *J* = 15.7 Hz, 1H), 2.06 – 1.83 (m, 5H).

LCMS (m/z): 437 $[M+H]^+$.

3-(4-((2-(((R)-1-hydroxy-3-methylbutan-2-yl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (37)

37 (4.5 mg, 3%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to (*R*)-2-amino-3-methylbutan-1-ol.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.50 (s, 1H), 8.21 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 6.37 (s, 1H), 5.17 (dd, *J* = 13.1, 5.1 Hz, 1H),

4.59 – 4.34 (m, 2H), 3.48 (d, *J* = 9.0 Hz, 2H), 2.99 – 2.87 (m, 1H), 2.62 (dd, *J* = 15.3, 11.7 Hz, 1H), 2.44 – 2.31 (m, 1H), 2.01 (d, *J* = 16.2 Hz, 1H), 1.84 (s, 1H), 0.86 (d, *J* = 42.6 Hz, 6H).

LCMS (m/z): 439 $[M+H]^+$.

3-(4-((2-((2-methoxyphenyl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (38)

38 (20.6 mg, 13%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 2-methoxyaniline.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.64 (s, 1H), 9.86 – 9.75 (m, 1H), 8.04 (d, *J* = 7.0 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.65 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.82 (t, *J* = 7.8 Hz, 1H), 6.51 (d, *J* = 7.1 Hz, 1H), 5.14 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.47 (d, *J* = 17.5 Hz, 1H), 4.34 (d, *J* = 17.5 Hz, 1H), 3.82 (s, 3H), 2.90 (ddd, *J* = 17.3, 13.7, 5.4 Hz, 1H), 2.57 (dt, *J* = 17.2, 3.4 Hz, 1H), 2.28 (qd, *J* = 13.2, 4.4 Hz, 1H), 1.87 (d, *J* = 12.6 Hz, 1H).

LCMS (m/z): 459 $[M+H]^+$.

4-((4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)pyrimidin-2-yl)amino)benzenesulfonamide (40)

40 (9.0 mg, 9%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 4-aminobenzenesulfonamide.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.39 (s, 1H), 10.17 (s, 1H), 8.12 (d, *J* = 6.5 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H), 7.72 – 7.55 (m, 6H), 7.24 (s, 2H), 6.48 (d, *J* = 6.6 Hz, 1H), 5.15 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.48 (d, *J* = 17.5 Hz, 1H), 4.37 (d, *J* = 17.5 Hz, 1H), 2.90 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.56 (dt, *J* = 16.9, 3.4 Hz, 1H), 2.30 (qd, *J* = 13.2, 4.5 Hz, 1H), 1.90 (dtd, *J* = 12.9, 5.4, 2.3 Hz, 1H).

LCMS (m/z): 508 $[M+H]^+$.

3-(4-((2-(indolin-5-ylamino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (41)

41 (10.4 mg, 13%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to *tert*-butyl 5-aminoindoline-1-carboxylate.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.48 (d, *J* = 30.2 Hz, 2H), 8.02 (d, *J* = 6.9 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.66 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.07 (s, 1H), 7.01 (s, 2H), 6.46 (d, *J* = 6.9 Hz, 1H), 5.15 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.49 (d, *J* = 17.5 Hz, 1H), 4.34 (d, *J* = 17.5 Hz, 1H), 3.56 (t, *J* = 8.2 Hz, 2H), 2.99 (t, *J* = 8.1 Hz, 2H), 2.94 – 2.85 (m, 1H), 2.64 – 2.55 (m, 1H), 2.33 (ddd, *J* = 26.6, 13.2, 3.2 Hz, 1H), 2.25 (s, 1H), 1.90 (dd, *J* = 11.1, 5.2 Hz, 1H).

LCMS (m/z): 470 $[M+H]^+$.

3-(4-((2-(((3s,5s,7s)-adamantan-1-yl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (42)

42 (4.1 mg, 3%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to (3*s*,5*s*,7*s*)-adamantan-1-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.61 (s, 1H), 7.99 (s, 1H), 7.93 (d, *J* = 7.2 Hz, 1H), 7.72 (dd, *J* = 10.6, 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 6.33 (d, *J* = 7.2 Hz, 1H), 5.16 (dd, *J* = 13.3, 5.2 Hz, 1H), 4.40 (d, *J* = 17.6 Hz, 1H), 4.30 (d, *J* = 17.6 Hz, 1H), 2.92 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.44 – 2.36 (m, 1H), 2.09 (s, 1H), 1.96 – 1.91 (m, 1H), 1.86 (s, 3H), 1.76 (s, 6H), 1.50 (d, *J* = 12.2 Hz, 3H), 1.33 (d, *J* = 11.9 Hz, 3H).

LCMS (m/z): 487 $[M+H]^+$.

3-(4-((2-(naphthalen-2-ylamino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (43)

43 (16.8 mg, 21%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to naphthalen-2-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.79 (s, 1H), 10.61 (s, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 8.03 – 8.00 (m, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.84 (t, *J* = 8.3 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.55 – 7.39 (m, 4H), 6.52 (d, *J* = 6.9 Hz, 1H), 5.08 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.49 (d, *J* = 17.6 Hz, 1H), 4.35 (d, *J* = 17.6 Hz, 1H), 2.81 (ddd, *J* = 17.2, 13.7, 5.4 Hz, 1H), 2.45 (s, 1H), 2.16 (dt, *J* = 11.5, 5.3 Hz, 1H), 1.62 (s, 1H).

LCMS (m/z): 479 $[M+H]^+$.

3-(4-((2-((9H-fluoren-3-yl)amino)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (44)

44 (30.0 mg, 37%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 9*H*-fluoren-3-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.79 (s, 1H), 10.64 (s, 1H), 8.10 (d, *J* = 6.9 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.74 – 7.70 (m, 2H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.28 (td, *J* = 7.4, 1.2 Hz, 1H), 6.50 (d, *J* = 7.0 Hz, 1H), 5.12 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.51 (d, *J* = 17.6 Hz, 1H), 4.36 (d, *J* = 17.5 Hz, 1H), 2.85 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.54 (d, *J* = 11.7 Hz, 1H), 2.30 – 2.15 (m, 1H), 1.80 – 1.67 (m, 1H).

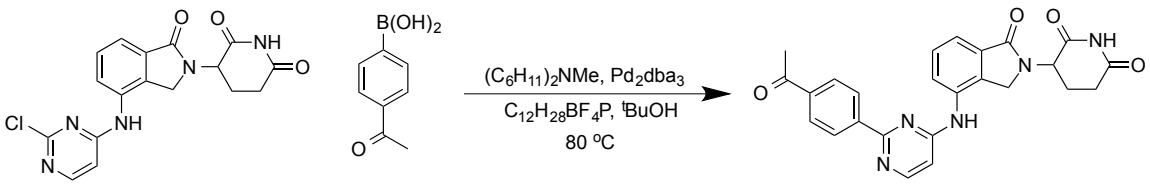
LCMS (m/z): 517 $[M+H]^+$.

3-(1-oxo-4-((2-((5,6,7,8-tetrahydronaphthalen-2-yl)amino)pyrimidin-4-yl)amino)isoindolin-2-yl)piperidine-2,6-dione (45)

45 (70.4 mg, 44%) was obtained according to the synthetic route of **20**, changing from 4-methoxyaniline to 5,6,7,8-tetrahydronaphthalen-2-amine.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 10.62 (s, 1H), 10.54 (s, 1H), 8.03 (d, *J* = 7.0 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 2.2 Hz, 1H), 7.04 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 1H), 6.46 (d, *J* = 7.0 Hz, 1H), 5.12 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.45 (d, *J* = 17.6 Hz, 1H), 4.29 (d, *J* = 17.5 Hz, 1H), 2.89 (ddd, *J* = 17.3, 13.7, 5.4 Hz, 1H), 2.64 (d, *J* = 6.2 Hz, 2H), 2.55 (d, *J* = 2.6 Hz, 1H), 2.45 (s, 2H), 2.20 (qd, *J* = 13.4, 4.3 Hz, 1H), 1.68 (dd, *J* = 7.6, 4.3 Hz, 4H). LCMS (m/z): 483 $[M+H]^+$.

Scheme 4. Synthesis of **22**



3-(4-((2-(4-acetylphenyl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (22)

To a solution of 3-(4-((2-chloropyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (115 mg, 0.3 mmol) and (4-acetylphenyl)boronic acid (61 mg, 0.36 mmol) in ^{t}BuOH (2 mL) were added N,N-dicyclohexylmethylamine (64 mg, 0.33 mmol), Pd_2dba_3 (27 mg, 0.03 mmol) and Tri-*tert*-butylphosphonium tetrafluoroborate (18 mg, 0.06 mmol). The mixture was heated to 80 ℃ and stirred under N_2 atmosphere overnight. The mixture was then filtered, concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain compound **22** (10.0 mg, 6%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 9.65 (s, 1H), 8.49 (d, *J* = 5.8 Hz, 1H), 8.37 (d, *J* = 8.3 Hz, 2H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.67 – 7.53 (m, 2H), 6.87 (d, *J* = 5.9 Hz, 1H), 5.17 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.52 (d, *J* = 17.3 Hz, 1H), 4.43 (d, *J* = 17.3 Hz, 1H), 2.92 (ddd, *J* = 17.2, 13.6, 5.4 Hz, 1H), 2.63 (s, 3H), 2.61 – 2.55 (m, 1H), 2.35 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.01 (dtd, *J* = 12.7, 5.3, 2.2 Hz, 1H).

LCMS (m/z): 456 $[M+H]^+$.

3-(4-((2-([1,1'-biphenyl]-4-yl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (32)

32 (4.0 mg, 2%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to [1,1'-biphenyl]-4-ylboronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.99 (s, 1H), 8.47 (d, *J* = 6.1 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.10 (dd, *J* = 7.3, 1.6 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.79 – 7.75 (m, 2H), 7.67 – 7.61 (m, 2H), 7.51 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.44 – 7.39 (m, 1H), 6.88 (d, *J* = 6.2 Hz, 1H), 5.18 (dd, *J* = 13.4, 5.1 Hz, 1H), 4.54 (d, *J* = 17.4 Hz, 1H), 4.44 (d, *J* = 17.4 Hz, 1H), 2.92 (ddd, *J* = 18.0, 13.6, 5.4 Hz, 1H), 2.64 – 2.54 (m, 1H), 2.35 (qd, *J* = 13.2, 4.5 Hz, 1H), 2.07 – 1.96 (m, 1H).

LCMS (m/z): 490 $[M+H]^+$.

3-(4-((2-(3-methoxyphenyl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (33)

33 (13.7 mg, 12%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to (3-methoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.19 (s, 1H), 11.02 (s, 1H), 8.44 (d, *J* = 7.1 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.73 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.67 (td, *J* = 7.8, 7.3, 1.3 Hz, 2H), 7.32 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.17 (td, *J* = 7.5, 1.0 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.52 (d, *J* = 17.6 Hz, 1H), 4.42 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 3H),

2.93 (ddd, *J* = 17.3, 13.7, 5.4 Hz, 1H), 2.64 – 2.55 (m, 1H), 2.38 – 2.29 (m, 1H), 2.00 (ddq, *J* = 10.3, 5.4, 3.1, 2.6 Hz, 1H).

LCMS (m/z): 444 $[M+H]^+$.

3-(4-((2-(4-fluoro-2-methoxyphenyl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (34)

34 (17.1 mg, 11%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to (4-fluoro-2-methoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.14 (s, 1H), 11.03 (s, 1H), 8.43 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.89 (dd, *J* = 8.8, 6.7 Hz, 1H), 7.72 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.26 (dd, *J* = 11.3, 2.4 Hz, 1H), 7.03 (td, *J* = 8.5, 4.1 Hz, 2H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.50 (d, *J* = 17.6 Hz, 1H), 4.41 (d, *J* = 17.6 Hz, 1H), 3.98 (s, 3H), 2.93 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.33 (qd, *J* = 13.2, 4.4 Hz, 1H), 2.00 (dtd, *J* = 12.6, 5.1, 2.1 Hz, 1H).

LCMS (m/z): 462 $[M+H]^+$.

3-(4-((2-(2,4-dimethoxyphenyl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (35)

35 (9.3 mg, 6%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to (2,4-dimethoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 11.11 (s, 1H), 11.02 (s, 1H), 8.35 (d, *J* = 7.1 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.7 Hz, 1H), 6.99 (s, 1H), 6.82 (d, *J* = 2.3 Hz, 1H), 6.80 – 6.76 (m, 1H), 5.18 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.51 (d, *J* = 17.6 Hz, 1H), 4.40 (d, *J* = 17.6 Hz, 1H), 4.03 (s, 3H), 3.89 (s, 3H), 2.92 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.33 (qd, *J* = 12.9, 4.2 Hz, 1H), 2.00 (td, *J* = 6.0, 2.3 Hz, 1H).

LCMS (m/z): 474 $[M+H]^+$.

3-(4-((2-(benzofuran-2-yl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (36)

36 (5.0 mg, 3%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to benzofuran-2-ylboronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 9.75 (s, 1H), 8.44 (d, *J* = 5.9 Hz, 1H), 8.08 (d, *J* = 7.7 Hz, 1H), 7.78 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.68 (dq, *J* = 8.3, 0.9 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.61 – 7.57 (m, 2H), 7.43 (ddd, *J* = 8.4, 7.2, 1.4 Hz, 1H), 7.34 – 7.30 (m, 1H), 6.83 (d, *J* = 6.0 Hz, 1H), 5.16 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.60 (d, *J* = 17.4 Hz, 1H), 4.44 (d, *J* = 17.4 Hz, 1H), 2.90 (ddd, *J* = 17.3, 13.6, 5.4 Hz, 1H), 2.59 – 2.53 (m, 1H), 2.37 (ddd, *J* = 15.6, 12.4, 4.5 Hz, 1H), 2.03 (ddq, *J* = 10.6, 5.6, 3.3, 2.7 Hz, 1H).

LCMS (m/z): 454 $[M+H]^+$.

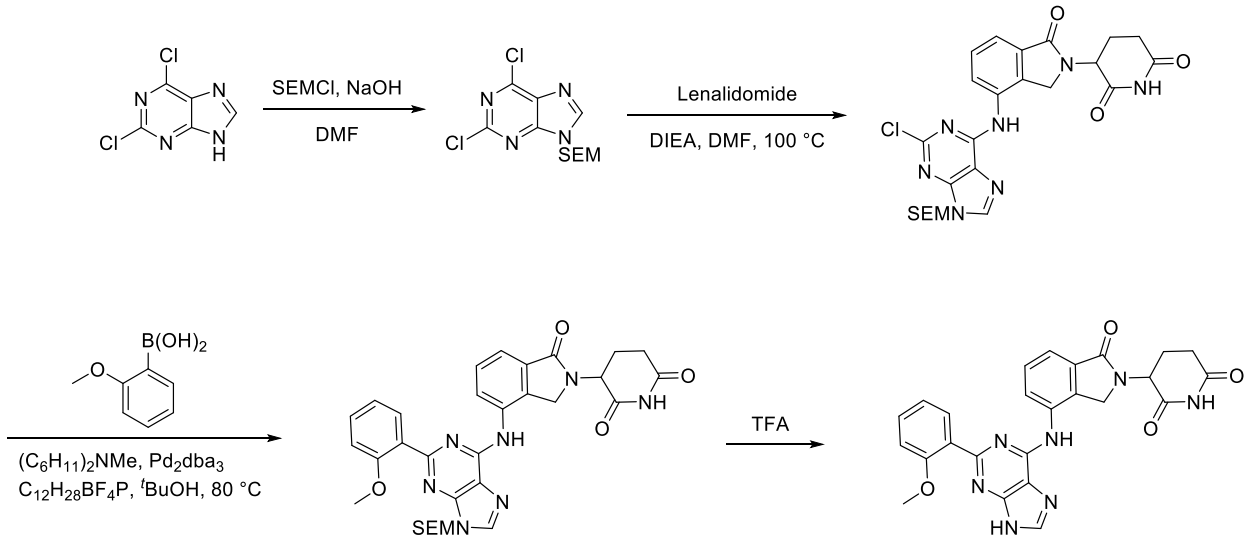
3-(4-((2-(4-fluorophenyl)pyrimidin-4-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (39)

39 (1.5 mg, 2%) was obtained according to the synthetic route of **22**, changing from (4-acetylphenyl)boronic acid to (4-fluorophenyl)boronic acid.

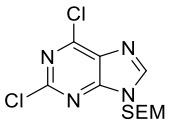
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.96 (s, 1H), 8.44 (d, *J* = 6.1 Hz, 1H), 8.25 (dd, *J* = 8.6, 5.7 Hz, 1H), 8.04 (dd, *J* = 7.0, 1.9 Hz, 1H), 7.84 (dd, *J* = 8.3, 6.3 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 8.7 Hz, 1H), 7.15 (t, *J* = 8.9 Hz, 1H), 6.86 (d, *J* = 6.1 Hz, 1H), 5.17 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.50 (d, *J* = 17.4 Hz, 1H), 4.42 (d, *J* = 17.4 Hz, 1H), 2.92 (ddd, *J* = 18.2, 13.5, 5.4 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.34 (qd, *J* = 13.3, 4.6 Hz, 1H), 2.03 – 1.97 (m, 1H).

LCMS (m/z): 432 $[M+H]^+$.

Scheme 5. Synthesis of **46**



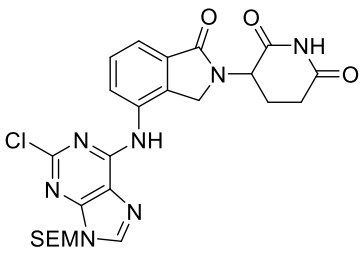
2,6-Dichloro-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purine



To a solution of 2,6-dichloro-9H-purine (1.89 g, 10 mmol) and NaOH (1.2 g, 30 mmol) in DMF (30 mL) was added 2-(Trimethylsilyl)ethoxymethyl chloride (3.5 mL, 20 mmol), and then the mixture was stirred for 4h. The mixture was then extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to next step without any purification.

LCMS (m/z): 319 $[M+H]^+$.

3-(4-((2-Chloro-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



To a solution of 2,6-dichloro-9-((2-(trimethylsilyl)ethoxy)methyl)-9H-purine (10 mmol) and lenalidomide (2.6 g, 10 mmol) in DMF (30 mL) was added DIEA (3.3 mL, 20 mmol), and then heated up to 110 ℃, stirred overnight. The mixture was purified by silica gel (MeOH/DCM = 0-4%) directly to provide the title compound (1.0 g, 19% for 2 steps) as yellow solid.

LCMS (m/z): 542 $[M+H]^+$.

3-(4-((2-(2-methoxyphenyl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (46)

To a solution of 3-(4-((2-chloro-9-((2-(trimethylsilyl)ethoxy)methyl)-9*H*-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (83 mg, 0.15 mmol) and (2-methoxyphenyl)boronic acid (27 mg, 0.18 mmol) in ^{t}BuOH (2 mL) were added *N*,*N*-Dicyclohexylmethylamine (32 mg, 0.17 mmol), Pd_2dba_3 (14 mg, 0.015 mmol) and Tri-*tert*-butylphosphonium tetrafluoroborate (9 mg, 0.03 mmol). The mixture was heated to 80 ℃ and stirred under N_2 atmosphere overnight. The mixture was then filtered, concentrated *in vacuo* and purified by silica gel (MeOH/DCM = 0-4%) to provide the intermediate. The intermediate was then concentrated *in vacuo*, dissolved in TFA/DCM = 1/1, stirred for 2h, and then concentrated again *in vacuo*, purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to provide compound **46** (26.0 mg, 29%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.99 (s, 1H), 8.50 (s, 1H), 8.05 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.62 – 7.50 (m, 4H), 7.45 (ddd, *J* = 8.9, 7.5, 1.8 Hz, 1H), 7.17 – 7.12 (m, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.60 (d, *J* = 17.5 Hz, 1H), 4.45 (d, *J* = 17.4 Hz, 1H), 2.92 (ddd, *J* = 17.2, 13.6, 5.4 Hz, 1H), 2.60 (d, *J* = 3.3 Hz, 1H), 2.55 (s, 3H), 2.32 (qd, *J* = 13.3, 4.6 Hz, 1H), 1.95 (dt, *J* = 10.0, 4.0 Hz, 1H).

LCMS (m/z): 484 $[M+H]^+$.

3-(4-((2-([1,1'-biphenyl]-4-yl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (47)

47 (1.7 mg, 2%) was obtained according to the synthetic route of **46**, changing from (2-methoxyphenyl)boronic acid to [1,1'-biphenyl]-4-ylboronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.91 (s, 1H), 8.36 – 8.24 (m, 3H), 8.01 – 7.96 (m, 1H), 7.75 (dd, *J* = 9.9, 7.9 Hz, 4H), 7.64 – 7.59 (m, 2H), 7.49 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.42 – 7.35 (m, 1H), 5.13 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.64 (d, *J* = 17.4 Hz, 1H), 4.51 (d, *J* = 17.4 Hz, 1H), 2.93 – 2.78 (m, 1H), 2.51 (d, *J* = 1.9 Hz, 1H), 2.34 (qd, *J* = 13.2, 4.8 Hz, 1H), 1.96 (dd, *J* = 14.9, 8.4 Hz, 1H).

LCMS (m/z): 530 $[M+H]^+$.

3-(4-((2-(4-fluoro-2-methoxyphenyl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (48)

48 (16.4 mg, 18%) was obtained according to the synthetic route of **46**, changing from (2-methoxyphenyl)boronic acid to (4-fluoro-2-methoxyphenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 9.74 (s, 1H), 8.30 (s, 1H), 8.11 – 7.99 (m, 1H), 7.58 – 7.48 (m, 3H), 6.98 (dd, *J* = 11.6, 2.4 Hz, 1H), 6.82 (td, *J* = 8.4, 2.4 Hz, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.59 (d, *J* = 17.4 Hz, 1H), 4.45 (d, *J* = 17.3 Hz, 1H), 3.77 (s, 3H), 2.91 (ddd, *J* = 17.9, 13.5, 5.4 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.36 (qd, *J* = 13.2, 4.5 Hz, 1H), 1.94 (d, *J* = 12.8 Hz, 1H).

LCMS (m/z): 502 $[M+H]^+$.

3-(4-((2-(4-fluorophenyl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (49)

49 (6.3 mg, 7%) was obtained according to the synthetic route of **46**, changing from (2-methoxyphenyl)boronic acid to (4-fluorophenyl)boronic acid.

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.94 (s, 1H), 9.89 (s, 1H), 8.34 (s, 1H), 8.27 – 8.20 (m, 2H), 7.95 (dd, *J* = 6.0, 2.9 Hz, 1H), 7.61 (q, *J* = 3.9, 3.1 Hz, 2H), 7.31 – 7.19 (m, 2H), 5.13 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.58 (d, *J* = 17.4 Hz, 1H), 4.48 (d, *J* = 17.3 Hz, 1H), 2.88 (ddd, *J* = 18.0, 11.5, 5.4 Hz, 1H), 2.55 (s, 1H), 2.33 (qd, *J* = 13.1, 4.4 Hz, 1H), 2.01 – 1.91 (m, 1H).

LCMS (m/z): 472 $[M+H]^+$.

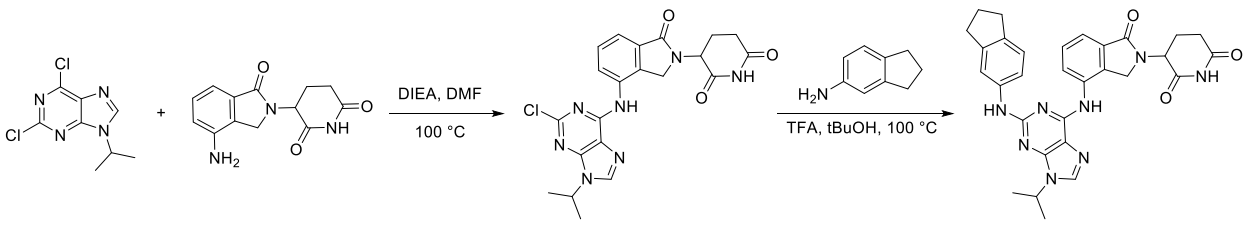
3-(4-((2-(3,5-dimethoxyphenyl)-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (50)

50 (4.5 mg, 4%) was obtained according to the synthetic route of **46**, changing from (2-methoxyphenyl)boronic acid to (3,5-dimethoxyphenyl)boronic acid.

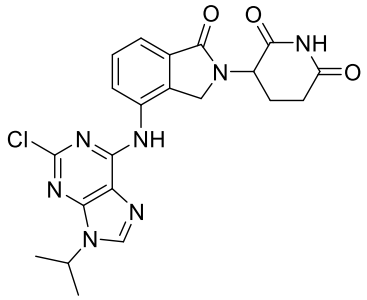
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.46 (s, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 7.73 – 7.40 (m, 3H), 6.69 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 8.6, 2.3 Hz, 1H), 5.16 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 4.47 (s, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.92 (ddd, *J* = 17.2, 13.5, 5.3 Hz, 1H), 2.68 – 2.54 (m, 1H), 2.33 (qd, *J* = 13.2, 4.4 Hz, 1H), 1.96 (ddd, *J* = 9.6, 5.4, 2.6 Hz, 1H).

LCMS (m/z): 514 $[M+H]^+$.

Scheme 6. Synthesis of **51**



3-(4-((2-chloro-9-isopropyl-9*H*-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione



To a solution of Lenalidomide (78 mg, 0.34 mmol) and 2,6-dichloro-9-isopropyl-9*H*-purine (88 mg, 0.34 mmol) in DMF (2 mL) was added DIEA (169 µL, 1.02 mmol), and then the mixture was heated to 100 ℃overnight. The mixture was then concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain the title compound.

LCMS (m/z): 454 $[M+H]^+$.

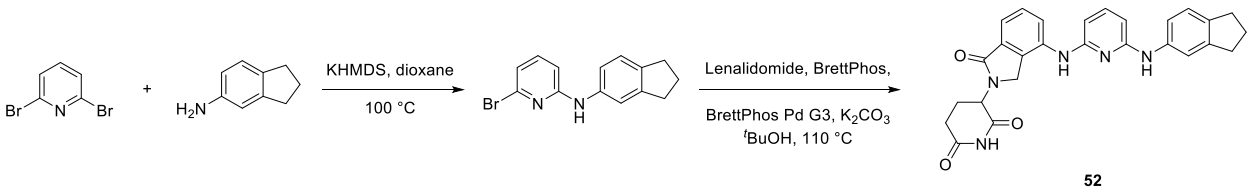
3-(4-((2-((2,3-dihydro-1H-inden-5-yl)amino)-9-isopropyl-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (51)

To a solution of 3-(4-((2-chloro-9-isopropyl-9H-purin-6-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (60 mg, 0.13 mmol) and 2,3-dihydro-1*H*-inden-5-amine (18 mg, 0.13 mmol) in ^{t}BuOH (1 mL) was added TFA (20 µL, 0.26 mmol), and then the mixture was heated to reflux overnight. The mixture was then concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain compound **51** (19.8 mg, 23%).

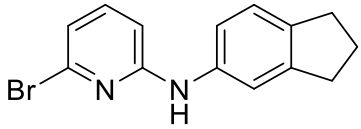
^{1}H NMR (500 MHz, DMSO-d_6) δ 10.93 (s, 1H), 9.74 (s, 1H), 9.03 (s, 1H), 8.31 (s, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.69 – 7.50 (m, 3H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 1H), 5.08 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.78 – 4.68 (m, 1H), 4.57 (d, *J* = 17.3 Hz, 1H), 4.34 (d, *J* = 17.3 Hz, 1H), 2.85 (ddd, *J* = 18.3, 13.6, 5.4 Hz, 1H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.48 (s, 1H), 2.20 (dd, *J* = 13.3, 4.5 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.74 – 1.67 (m, 1H), 1.57 (d, *J* = 6.7 Hz, 6H).

LCMS (m/z): 551 $[M+H]^+$.

Scheme 7. Synthesis of **52**.

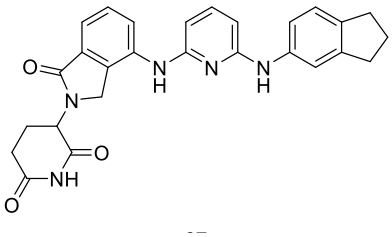


6-bromo-N-(2,3-dihydro-1H-inden-5-yl)pyridin-2-amine



To the solution of 2,3-dihydro-1*H*-inden-5-amine (50 mg, 0.375 mmol) in dioxane (2 mL) was added KHMDS (0.45 mL, 1 M in THF, 0.45 mmol) slowly under an ice bath for 30 mins. 2,6-dibromopyridine was added to the reaction mixture under an ice bath. The reaction mixture was warmed up to room temperature and then heated up to 100 ℃ for 10 mins. The residue was purified by HPLC to afford the title compound (32 mg, 0.11 mmol, 30%). LCMS (m/z): 289, 291 $[M+H]^+$.

3-(4-((6-((2,3-dihydro-1H-inden-5-yl)amino)pyridin-2-yl)amino)-1-oxoisoindolin-2-yl)piperidine-2,6-dione (**52**)



To a solution of 6-bromo-*N*-(2,3-dihydro-1*H*-inden-5-yl)pyridin-2-amine (32 mg, 0.11 mmol) and lenalidomide (43 mg, 0.17 mmol) in ^{t}BuOH (2 mL) were added BrettPhos (9 mg, 0.017 mmol), BrettPhos Pd G3 (10 mg, 0.011 mmol) and K_2CO_3 (76 mg, 0.55 mmol). The mixture was heated to 110℃ and stirred under N_2 atmosphere for 2 hours. The mixture was then filtered,

concentrated *in vacuo* and purified by prep-HPLC (MeOH/H_2O, 0.05% TFA) to obtain compound **53** (19 mg, 0.041 mmol, 37%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.70 (s, 1H), 8.56 (s, 1H), 8.04 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.49 (d, *J* = 2.0 Hz, 1H), 7.45 – 7.32 (m, 3H), 7.10 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.23 (t, *J* = 8.1 Hz, 2H), 5.10 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.46 (d, *J* = 17.2 Hz, 1H), 4.30 (d, *J* = 17.2 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.75 (t, *J* = 7.3 Hz, 2H), 2.67 (t, *J* = 7.5 Hz, 2H), 2.59 – 2.56 (m, 1H), 2.21 (qd, *J* = 13.2, 4.4 Hz, 1H), 1.96 (p, *J* = 7.4 Hz, 2H), 1.84 – 1.76 (m, 1H). LCMS (m/z): 468 $[M+H]^+$.