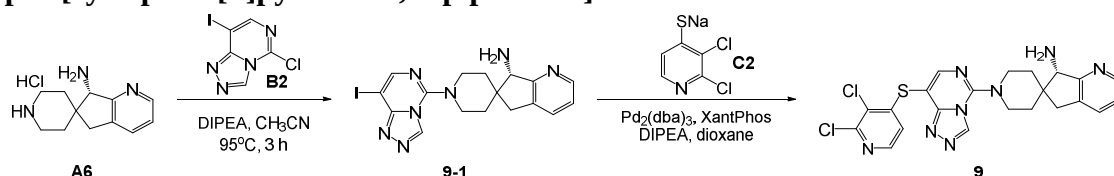


8.0 Hz, 2H), 3.13 (d, $J = 16.4$ Hz, 1H), 2.76 (d, $J = 16.4$ Hz, 1H), 1.98 (d, $J = 11.6$ Hz, 2H), 1.62 (d, $J = 13.6$ Hz, 1H), 1.30 (s, 1H).

LCMS: m/z 479.1 $[M+H]^+$.

5 Example 9: Synthesis of compound 9

(S)-1'-(8-(2,3-dichloropyridin-4-yl)thio-[1,2,4]-triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine



Step 1: (S)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine

hydrochloride (**A6**, 200mg, 1.28mmol) was dissolved in acetonitrile (20mL), DIPEA (1.6mL, 9.68mmol) and 5-chloro-8-iodo-[1,2,4]-triazolo[4,3-c]pyrimidine (**B2**, 180mg, 0.64mmol) were added, the mixture was heated to 90 °C and refluxed for 3 hours under the protection of nitrogen, and the reaction was completed. The reaction liquid was cooled to room temperature, poured into saturated sodium bicarbonate aqueous solution, and extracted twice with dichloromethane (80mL). The organic phases were combined, and washed with saturated brine. The organic phase was separated, and then dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography (DCM: MeOH = 20/1) to obtain

(S)-1'-(8-iodo[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine (**9-1**, 260mg, yield 90%) as a light yellow solid. LCMS: m/z 448.2 $[M+H]^+$

Step 2:

(S)-1'-(8-iodo[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine (**9-1**, 55mg, 0.12mmol) was dissolved in 1,4-dioxane (3mL), and DIPEA (35mg, 0.27mmol) and sodium 2,3-dichloropyridine-4-mercaptan (**C2**, 100mg, crude product) were added. XantPhos (30mg, 0.05mmol) and $Pd_2(dba)_3$ (17mg, 0.02mmol) were added under the protection of nitrogen. After the atmosphere in the reaction system was replaced with nitrogen three times, the mixture was reacted at 100°C for 3 hours, and the reaction was completed. The reaction solution was concentrated and purified by high performance liquid chromatography to obtain

(S)-1'-(8-(2,3-dichloropyridin-4-yl)thio-[1,2,4]-triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine (compound **9**, 27mg, TFA salt, yield: 40%) as a light yellow solid. LCMS: m/z 499.1 $[M+H]^+$

^1H NMR (400 MHz, MeOD) δ 9.35 (s, 1H), 8.56 (d, $J = 4.8$ Hz, 1H), 8.14 (s, 1H), 7.95 (d, $J = 5.2$ Hz, 1H), 7.84 (d, $J = 7.6$ Hz, 1H), 7.44-7.41 (m, 1H), 6.80 (d, $J = 5.2$ Hz, 1H), 4.53 (s,

Step 1: (S)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-5-amine hydrochloride (**A8**, 200mg, 0.83mmol) was dissolved in acetonitrile (20mL), DIPEA (1.07g, 8.3mmol) and 5-chloro-8-iodoimidazo[1,2-c]pyrimidine(**B3**, 208mg, 0.75mmol) were added, the mixture was heated to 90 °C and refluxed for 5 hours under nitrogen protection, and the reaction was

completed. The reaction liquid was cooled to room temperature, poured into saturated sodium bicarbonate aqueous solution, and extracted twice with dichloromethane (50mL). The organic phases were combined and then washed with saturated brine. The organic phase was separated, and then dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography to obtain

1-(8-iodoimidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-4-amine (**14-1**, 250mg, yield: 74%) as a light yellow solid. LCMS: m/z 447.1 [M+H]⁺

Step2:
1'-(8-iodoimidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-4-amine (**14-1**, 50mg, 0.11mmol) was dissolved in 1,4-dioxane (10mL), DIPEA (36mg, 0.28mmol) and sodium 2-amino-3-chloropyridine-4-mercaptan (**C1**, 31mg, 0.17mmol) were added. XantPhos (13mg, 0.02mmol) and Pd₂(dba)₃ (10mg, 0.01mmol) were added under the protection of nitrogen. After the atmosphere in the reaction system was replaced with nitrogen for three times, the mixture was reacted at 100 °C for 3 hours, and the reaction was completed. The reaction liquid was concentrated, and then purified by high performance liquid

chromatography to obtain

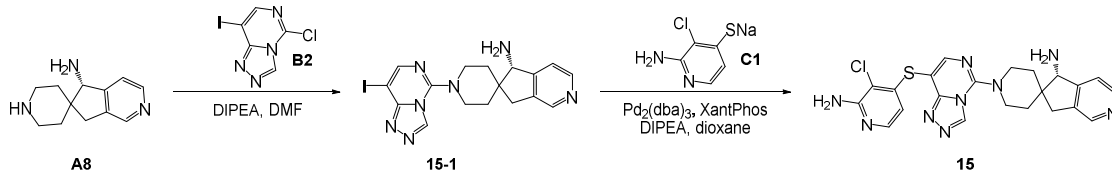
(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)imidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-5-amine (**14**, 12mg, yield: 22.4%) as a light yellow solid.

LCMS: m/z 479.2 [M+H]⁺

¹H NMR (400 MHz, MeOD) δ 8.64 (s, 1H), 8.56 (d, *J* = 4.4 Hz, 1H), 8.09 (s, 1H), 7.62-7.60(m, 2H), 7.60-7.50 (m, 1H), 5.95-5.94 (m, 1H), 4.64 (s, 1H), 4.22-4.07 (m, 2H), 3.60 (s, 2H), 3.6-3.49 (m, 2H), 2.20-2.10(m, 2H), 2.10-2.00 (m, 1H), 1.85-1.63(m, 2H).

Example 15: Synthesis of compound 15

(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-5-amine



(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[c]pyridine-6,4'-piperidine]-5-amine (**15**) was synthesized through two steps according to the synthesis protocol of compound 14, using intermediate B2 instead of

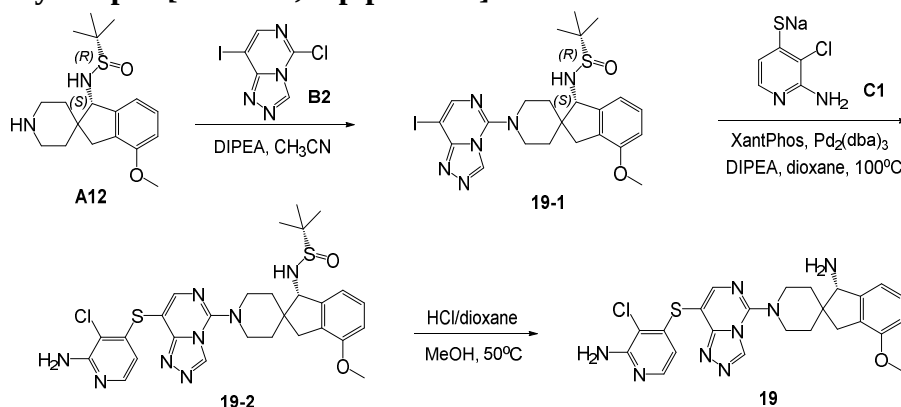
glass seal tube, DIPEA (1.78g, 13.8mmol), sodium 2-amino-3-chloropyridine-4-mercaptan (**C1**, 1.26g, 6.9mmol), XantPhos (797mg, 1.38mmol) and Pd₂(dba)₃ (630mg, 0.69mmol) were added successively, the reaction mixture was sparged with argon for 30 seconds, and was heated to 100 °C under argon and maintained for 3 hours until the reaction was completed. The mixture was cooled to room temperature, diluted with dichloromethane and filtered by suction filtration. The filtrate was spin-dried and passed through the column. The obtained pure point was spin-dried, mixed with dichloromethane/n-hexane (1/1) and pulped overnight, and then filtered and dried to obtain

(S)-1'-((8-((2-amino-3-chloropyridin-4-yl)thio)imidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyrazine-6,4'-piperidine]-5-amine (compound **18**, 440mg, yield: 19.9%). LCMS: m/z 480.1 [M+H]⁺

¹H NMR (400 MHz, MeOD): δ 8.44-8.39 (m, 2 H), 8.05 (s, 1 H), 7.85 (d, J = 1.6 Hz, 1 H), 7.56 (d, J = 1.6 Hz, 1 H), 7.49 (d, J = 5.6 Hz, 1 H), 5.89 (d, J = 5.6 Hz, 1 H), 4.14 (s, 1 H), 4.06-4.02 (m, 2 H), 3.49-3.40 (m, 2 H), 3.33 (s, 1 H), 3.01 (d, J = 16.8 Hz, 1H), 2.24-2.10 (m, 2 H), 1.82 (d, J = 13.2 Hz, 1 H), 1.50 (d, J = 13.6 Hz, 1 H).

Example 19: Synthesis of compound 19

(S)-1'-((8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1-amine



Step1:

(S)-1-(((R)-tert-butylsulfinyl)amino)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine] (**A12**, 520mg, 1.55mmol) was dissolved in acetonitrile (20mL), DIPEA (2.0g, 15.5mmol) and 5-chloro-8-iodo-[1,2,4]triazolo[4,3-c]pyrimidine (**B2**, 435mg, 1.55mmol) were added, the mixture was reacted at 85 °C for 3 hours under the protection of nitrogen, and the reaction was completed. The residue obtained by concentration under reduced pressure was purified by silica gel chromatography (0-10% gradient of methanol/ethyl acetate) to obtain (R)-N-((S)-1'-((8-iodo-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-tert-butylsulfonamide (**19-1**, 420mg, yield: 46.8%) as a yellow solid.

LCMS: m/z 581.1 [M+H]⁺.

Step2:

(R)-N-((S)-1'-(8-iodo-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-tert-butylsulfonamide (**19-1**, 420mg, 0.72mmol) was dissolved in 1,4-dioxane (10mL), and DIPEA (234mg, 1.81mmol) and sodium 2-amino-3-chloropyridine-4-mercaptan (**C1**, 198mg, 1.09mmol) were added. XantPhos (83mg, 0.144mmol) and Pd₂(dba)₃ (66mg, 0.072mmol) were added under the protection of nitrogen. After the atmosphere in the reaction system was replaced with nitrogen for three times, the mixture was reacted at 100°C for 3 hours, and the reaction was completed. The reaction solution was concentrated and then purified by silica gel chromatography to obtain (R)-N-((S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-tert-butylsulfonamide (**19-2**, 310mg, yield: 69.9%) as a white solid.

LCMS: m/z 613.2 [M+H]⁺.

Step3:

(R)-N-((S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidin]-1-yl)-2-tert-butylsulfonamide (**19-2**, 310mg, 0.51mmol) and methanol (6mL) were added to a 50mL single-necked flask under the protection of nitrogen successively, hydrochloric acid 1,4-dioxane solution (2mL, 4M) was added dropwise at room temperature, and the mixture was stirred at room temperature for 1 hour. After the reaction was completed, the mixture was cooled to room temperature, filtered and concentrated under reduced pressure. The obtained residue was purified by preparative high performance liquid chromatography to obtain

(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-4-methoxy-1,3-dihydrospiro[indene-2,4'-piperidine]-1-amine (compound **19**, 114mg, yield: 44.3%).

¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 7.95(s, 1H), 7.65 (d, *J* = 5.6 Hz, 1H), 7.26 (t, 2H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.02 (d, *J* = 5.6 Hz, 1H), 4.89 (s, 2H), 4.13-4.04 (m, 4H), 3.86 (s, 3H), 3.53-3.48 (m, 2H), 3.11 (d, *J* = 16 Hz, 1H), 2.70 (d, *J* = 16 Hz, 1H), 2.08-2.01 (m, 3H), 1.76 (d, *J* = 14 Hz, 1H), 1.53 (d, *J* = 14 Hz, 2H).

LCMS: m/z 509.2 [M+H]⁺.

Example 20: Synthesis of compound 20

(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)-[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyrazine-6,4'-piperidine]-5-amine

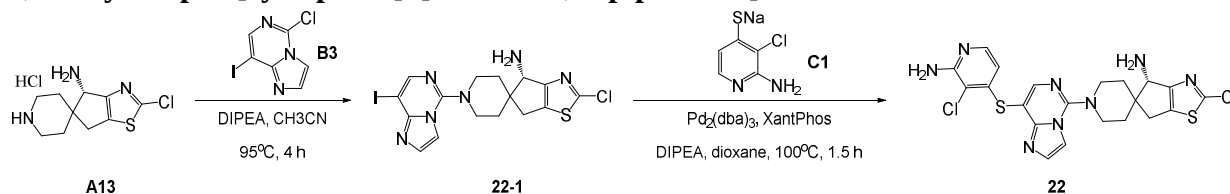
(S)-1'-(8-iodo[1,2,4]triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine (**9-1**, 100mg, 0.22mmol) was dissolved in 1,4-dioxane (12mL), and DIPEA (300mg, 2.32mmol) and sodium 2-(trifluoromethyl)pyridine-3-mercaptan (**C3**, 200mg, crude product) were added. XantPhos (100mg, 0.17mmol) and Pd₂(dba)₃ (100mg, 0.11mmol) were added under the protection of nitrogen. After the the atmosphere in the reaction system was replaced with nitrogen for three times, the mixture was reacted at 100 °C for 3 hours, and the reaction was completed. The reaction solution was passed through the column (EA:MeOH=5/1, 0.5% of ammonium hydroxide) to obtain

(S)-1'-(8-((2-(trifluoromethyl)pyridin-3-yl)thio)-[1,2,4]-triazolo[4,3-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopenta[b]pyridine-6,4'-piperidine]-7-amine (compound **21**, 35mg, yield: 31%) as a white solid. LCMS: m/z 499.1 [M+H]⁺

¹H NMR (400 MHz, MeOD) δ 9.32 (s, 1H), 8.41-8.37 (m, 2H), 8.03 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.38-7.35 (m, 1H), 7.28-7.25 (m, 1H), 4.18 – 4.14 (m, 2H), 4.04 (s, 1H), 3.62-3.59 (m, 2H), 3.23 (d, *J* = 16.4 Hz, 1H), 2.90 (d, *J* = 16.4 Hz, 1H), 2.11-2.06(m, 2H), 1.79-1.75 (m, 1H), 1.56-1.53(m, 1H).

Example 22: Synthesis of compound 22

(S)-1'-(8-((2-amino-3-chloropyridin-4-yl)thio)imidazo[1,2-c]pyrimidin-5-yl)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-4-amine



Step 1: (S)-2-chloro-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-4-amine hydrochloride (**A13**, 155mg, 0.35mmol) was dissolved in acetonitrile (10mL), and DIPEA (450mg, 3.5mmol) and 5-chloro-8-iodoimidazo[1,2-c]pyrimidine (**B3**, 108mg, 0.39mmol) were added, the mixture was heated to 100°C and refluxed for 5 hours under the protection of nitrogen, and the reaction was completed. The reaction solution was cooled to room temperature, poured into saturated sodium bicarbonate aqueous solution and extracted with dichloromethane (50mL x 2). The organic phases were combined, and then washed with saturated brine. The organic phase was separated, and then dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by silica gel chromatography to obtain

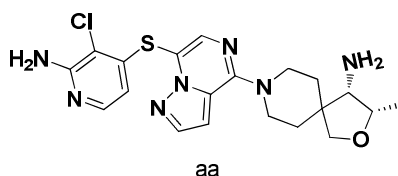
(S)-2-chloro-1'-(8-iodoimidazo[1,2-c]pyrimidin-5-yl)-4,6-dihydrospiro[cyclopenta[d]thiazole-5,4'-piperidine]-4-amine (**22-1**, 72mg, yield: 43%) as a light yellow solid. LCMS: m/z 487 [M+H]⁺

Step2: Under the protection of nitrogen, HCl/dioxane (4 M, 1.3mL, 5.20mmol) was slowly added to a solution of

(R)-2-methyl-N-((5S)-1'-((8-((1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[3,4-b]pyridin-4-yl)thio)imidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopentadiene[b]pyridine-6,4'-piperidin]-5-yl)propane-2-sulfonamide (**23-1**, 176mg, 0.26mmol) in dichloromethane (10mL) at 0 °C, the mixture was stirred at room temperature for 2 h, and TLC (dichloromethane/methanol=8/1) and LCMS indicated the reaction was completed. The reaction solution was cooled to 0 °C, ammonia methanol solution was slowly added to adjust the PH to about 10, and then the mixture was concentrated under reduced pressure and purified by prep-TLC to obtain (S)-1'-((8-(((1H-pyrazolo[3,4-b]pyridin-4-yl)thio)imidazo[1,2-c]pyrimidin-5-yl)-5,7-dihydrospiro[cyclopentadiene[b]pyridine-6,4'-piperidine]-5-amine (**23**, 73.01mg, yield: 58.1%). LCMS: m/z 470.5 [M+H]⁺

¹H NMR (400 MHz, MeOD): δ 8.42 (d, *J* = 4.0 Hz, 1 H), 8.16 ~ 8.14 (m, 2 H), 8.10 (s, 1H), 7.91 ~ 7.87 (m, 2 H), 7.56 (d, *J* = 1.2 Hz, 1 H), 7.34 ~ 7.31 (m, 1 H), 4.26 (s, 1 H), 4.11 ~ 4.06 (m, 1 H), 3.49 ~ 3.43 (m, 2 H), 3.28 (s, 1 H), 3.07 (d, *J* = 16.8 Hz, 1 H), 2.15 ~ 2.07 (m, 2 H), 1.76 (d, *J* = 12.8 Hz, 2 H), 1.64 (d, *J* = 13.6 Hz, 2 H).

Synthesis of control compound: At the time of application of the disclosure, the closest control compound to the disclosure is Example 25 of WO2018136265. According to the synthetic route and operation steps of Example 25 of WO2018136265, the control compound aa was obtained.



The biological function of the compound of the disclosure has been proved by the tests on enzyme activity and at the cellular level. For example, in the SHP2 enzyme activity inhibition test, the compound of the disclosure can achieve strong inhibition activity (IC₅₀ can reach 1nM). At the cellular level, the compound of the disclosure also showed a very good activity on inhibiting the proliferation of cancer cells, and the inhibitory activity on the proliferation of MV4-11 cell line can reach 1nM. Compared with SHP099 (6-(4-amino-4-methylpiperidine-1-yl)-3-(2,3-dichlorophenyl)pyrazine-2-amine) or the control compound aa, the compound of the disclosure showed superior activity both at the enzymatic level and at the cellular level.

Test example 1: Test method of SHP2 enzyme activity

Test method of SHP2 enzyme activity: