# Supporting Information

# Design and synthesis of novel hydroxamic acid derivatives based on quisinostat as promising antimalarial agents with improved safety

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## Chemistry section

### General information

All reagents and solvents were purchased from commercial suppliers and used directly without purification. Analytical thin-layer chromatography (TLC) was performed using silica gel plate (HSGF254, 0.2 mm thickness; Yantai Jiang you Co., China) and spots were visualized with UV light or iodine staining. $^{1}$H nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker AMX-400 MHz NMR (TMS as internal standard). Chemical shifts were reported in parts per million (ppm, δ) relative to TMS. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). High-resolution mass spectra (HRMS) were obtained on a Waters a Waters XEVO G2 TOF using electrospray ionization (ESI). HPLC analysis of compounds **01–38** was performed on an Agilent 1200 system equipped with a quaternary pump and a diode-array detector (DAD). The peak purity was verified by UV spectroscopy. The column used was Agilent Exlipse XDB-C18. All compounds were confirmed to be ⩾ 95% pure.

### Synthesis of tert-butyl 4-(5-(ethoxycarbonyl)pyrimidin-2-yl)-1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (A)

Ethyl 2-chloropyrimidine-5-carboxylate (18.7 g, 100 mmol) and *tert*-butyl 1-oxa-4,9-diazaspiro[5.5]undecane-9-carboxylate (25.6 g, 100 mmol) were dissolved in 500 mL DCM, and cooled to 0 ℃ under ice bath. DIPEA (18.2 mL, 110 mmol) was added slowly under ice bath and then the mixture was stirred at room temperature until the completion of

reaction was indicated by TLC. The solution was washed with water and brine then evaporated *in vacuo* and the solid residue was separated and purified by silica gel column chromatography to obtain intermediate **A** (37.4 g, 92% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.82 (s, 2H), 4.34 (q, $J$ = 7.1 Hz, 2H), 3.97–3.92 (m, 2H), 3.81 (s, 2H), 3.80–3.76 (m, 2H), 3.68 (s, 2H), 3.23 (t, $J$ = 10.8 Hz, 2H), 1.77 (d, $J$ = 13.4 Hz, 2H), 1.56–1.47 (m, 2H), 1.45 (s, 9H), 1.36 (t, $J$ = 7.1 Hz, 3H).

**Synthesis of ethyl 2-(1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxylate (B)**

Intermediate **A** (37.4 g, 92 mmol) was dissolved in 500 mL DCM, and HCl/1, 4-dioxane solution (4 M, 50 mL, 200 mmol) was added slowly. The mixture was stirred at room temperature until the completion of reaction was indicated by TLC. The solvent was evaporated *in vacuo* and the mixture was extracted with DCM and $H_2O$. The organic phase was dried with anhydrous sodium sulfate and evaporated *in vacuo* to obtain intermediate **B** (23.9 g, 85% yield). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (s, 2H), 4.36 (q, $J$ = 7.1 Hz, 2H), 3.99–3.93 (m, 2H), 3.88 (d, $J$ = 6.9 Hz, 2H), 3.84–3.79 (m, 2H), 2.96–2.87 (m, 2H), 2.83–2.76 (m, 2H), 1.84–1.77 (m, 2H), 1.63–1.53 (m, 2H), 1.39 (t, $J$ = 7.1 Hz, 3H).

**General synthesis of compounds C01–C38**

Intermediate **B** (0.31 g, 1 mmol) and 1-methyl-1*H*-indole-3-carbaldehyde (0.19 g, 1.2 mmol) were dissolved in 15 mL DCE. Acetic acid (0.27 mL, 4.8 mmol) and sodium triacetoxyborohydride (0.76 g, 3.6 mmol) were added in sequence and the mixture was stirred

at room temperature until the completion of reaction was indicated by TLC. The reaction was quenched by saturated aqueous sodium bicarbonate and extracted three times with DCM. The organic phase was dried with anhydrous sodium sulfate and then evaporated *in vacuo*. The solid residue was separated and purified by silica gel column chromatography to obtain compound **C01** (0.31 g, 68% yield). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 8.81 (s, 2H), 7.65 (d, $J$ = 7.9 Hz, 1H), 7.32 (d, $J$ = 8.2 Hz, 1H), 7.27 (s, 1H), 7.23 (d, $J$ = 7.4 Hz, 1H), 7.14 (t, $J$ = 7.2 Hz, 1H), 4.33 (q, $J$ = 7.1 Hz, 2H), 3.97–3.88 (m, 4H), 3.82 (s, 2H), 3.79 (s, 3H), 3.77–3.73 (m, 2H), 2.84 (s, 2H), 2.66 (s, 2H), 1.91–1.78 (m, 4H), 1.36 (t, $J$ = 7.1 Hz, 3H). Compounds **C02**–**C38** were obtained with the same synthetic method as described in the preparation of **C01**.

**General synthesis of compounds D01–D38**

Compound **C01** (0.31 g, 0.68 mmol) was dissolved in $H_2O$/MeOH (10 mL, 1:1 v/v mixture). Potassium carbonate (0.28 g, 2 mmol) was added and the reaction was sitrred at 65 ℃ for 6 h. The solvent was acidified with aqueous hydrogen chloride (2 M) to pH 1 and evaporated *in vacuo*. The mixture was stirred with HOBt (0.11 g, 0.82 mmol) and EDCI (0.16 g, 0.82 mmol) in dry DMF (10 mL) under nitrogen atmosphere for 10 min. THPONH2 (0.4 g, 3.4 mmol) was then added followed by $Et_3N$ (0.47 mL, 3.4 mmol) The mixture was stirred at room temperature for 64 h. The mixture was then diluted with $H_2O$ (30 mL) and extracted three times with DCM (15 mL x 3). The organic phase was dried with anhydrous sodium sulfate and then evaporated *in vacuo*. The solid residue was separated and purified by silica gel column chromatography to obtain compound **D01** (163 mg, 46% yield). $^1$H NMR (400

MHz, $CDCl_3$) $\delta$ 8.67 (s, 1H), 8.42 (s, 1H), 7.61 (d, $J$ = 7.9 Hz, 1H), 7.45 (s, 1H), 7.33 (d, $J$ = 8.2 Hz, 1H), 7.24 (d, $J$ = 7.4 Hz, 1H), 7.16 (t, $J$ = 7.5 Hz, 1H), 5.06–5.02 (m, 1H), 4.12–3.98 (m, 3H), 3.90–3.83 (m, 2H), 3.79 (s, 3H), 3.79–3.76 (m, 2H), 3.75–3.69 (m, 2H), 3.68–3.62 (m, 1H), 3.01 (s, 2H), 2.78 (s, 2H), 2.03–1.89 (m, 4H), 1.88–1.78 (m, 3H), 1.67–1.52 (m, 3H). Compounds **D02**–**D38** were obtained with the same synthetic method as described in the preparation of **D01**.

**General synthesis of compounds 01-38**

Compounds **D01**–**D38** (0.3 mmol) were dissolved into dry DCM (5 mL). HCl/1, 4-dioxane solution (4 M, 0.18 mL, 0.72 mmol) was added slowly and the mixture was stirred at room temperature for 0.5 h under nitrogen atmosphere. The solution was filtered and washed with large amount of DCM. The filter cake was dired *in vacuo* to obtain target compounds **01**–**38**.

***N*-Hydroxy-2-(9-((1-methyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl )pyrimidine-5-carboxamide hydrochloride (01)**

Compound **01** was prepared according to the above general synthetic method. m. p. 197–201 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.20 (s, 1H), 10.64 (s, 1H), 8.74 (d, $J$ = 8.6 Hz, 2H), 7.88 (d, $J$ = 7.9 Hz, 1H), 7.66 (d, $J$ = 9.6 Hz, 1H), 7.52 (d, $J$ = 8.1 Hz 1H), 7.26 (t, $J$ = 7.2 Hz, 1H), 7.16 (t, $J$ = 7.5 Hz, 1H), 4.47 (d, $J$ = 3.9 Hz, 2H), 3.86 (s, 3H), 3.82 (s, 2H), 3.72 (s, 4H), 3.29 (d, $J$ = 11.4 Hz, 2H), 3.01 (dd, $J$ = 23.0, 11.0 Hz, 2H), 2.05 (d, $J$ = 14.1 Hz, 2H), 1.88 (t, $J$ = 12.3 Hz, 2H) HRMS (ESI) m/z calcd $C_{23}H_{29}N_6O_3^+$ $[M + H]^+$ 437.2296, found

437.2302.

**2-(9-(Cyclopentylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (02)**

Compound **02** was prepared according to the above general synthetic method. m. p. 238–242 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.23 (s, 1H), 10.53 (s, 1H), 8.76 (d, $J$ = 2.1 Hz, 2H), 3.90–3.84 (m, 2H), 3.79–3.70 (s, 4H), 3.34 (d, $J$ = 11.3 Hz, 2H), 3.13–3.03 (m, 2H), 3.02–2.89 (m, 2H), 2.35–2.22 (m, 1H), 2.06–1.83 (m, 6H), 1.68–1.50 (m, 4H), 1.32–1.26 (m, 2H). HRMS (ESI) m/z calcd $C_{19}H_{30}N_5O_3^+$ $[M + H]^+$ 376.2343, found 376.2347.

**2-(9-(Cyclohexylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (03)**

Compound **03** was prepared according to the above general synthetic method. m. p. 234–236 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.57 (s, 2H), 8.79–8.74 (m, 2H), 3.88–3.82 (m, 2H), 3.80–3.71 (d, $J$ = 16.5 Hz, 4H), 3.30 (d, $J$ = 11.2 Hz, 2H), 3.07–2.85 (m, 4H), 2.10 (t, $J$ = 12.1 Hz, 2H), 2.04–1.95 (m, 2H), 1.86 (d, $J$ = 11.4 Hz, 2H), 1.82–1.75 (m, 1H), 1.74–1.57 (m, 4H), 1.31–1.13 (m, 4H). HRMS (ESI) m/z calcd $C_{20}H_{32}N_5O_3^+$ $[M + H]^+$ 390.2500, found 390.2506.

**2-(9-(Furan-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (04)**

Compound **04** was prepared according to the above general synthetic method. m. p.

152–155 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.17 (s, 2H), 8.70 (s, 2H), 7.85–7.79 (m, 1H), 6.73 (s, 1H), 6.59–6.53 (m, 1H), 4.39 (s, 2H), 3.85–3.77 (m, 2H), 3.70 (s, 4H), 3.18 (d, $J$ = 12.3 Hz, 2H), 3.03–2.88 (m, 2H), 2.04 (d, $J$ = 14.2 Hz, 2H), 1.91–1.79 (m, 2H). HRMS (ESI) m/z calcd $C_{18}H_{24}N_5O_4^+$ $[M + H]^+$ 374.1823, found 374.1830.

**_N_-Hydroxy-2-(9-(thiophen-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (05)**

Compound **05** was prepared according to the above general synthetic method. m. p. 224–225 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.37 (s, 2H), 8.75 (d, $J$ = 8.5 Hz, 2H), 7.76–7.69 (m, 1H), 7.46 (s, 1H), 7.23–7.14 (m, 1H), 4.57 (s, 2H), 3.89–3.81 (m, 2H), 3.74 (s, 4H), 3.21 (d, $J$ = 10.5 Hz, 2H), 3.00 (dd, $J$ = 22.3, 10.7 Hz, 2H), 2.08 (d, $J$ = 14.1 Hz, 2H), 2.00–1.84 (m, 2H). HRMS (ESI) m/z calcd $C_{18}H_{24}N_5O_3S^+$ $[M + H]^+$ 390.1594, found 390.1601.

**2-(9-(Furan-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-_N_-hydroxypyrimidine-5-carboxamide hydrochloride (06)**

Compound **06** was prepared according to the above general synthetic method. m. p. 168–169 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.18 (s, 2H), 8.75–8.72 (m, 2H), 7.89 (d, $J$ = 10.2 Hz, 1H), 7.85–7.78 (m, 1H), 6.84–6.76 (d, $J$ = 16.4 Hz, 1H), 4.19 (s, 2H), 3.87–3.83 (m, 2H), 3.83–3.77 (m, 2H), 3.75 (s, 2H), 3.30–3.17 (m, 2H), 3.06–2.90 (m, 2H), 2.07 (d, $J$ = 15.1 Hz, 2H), 1.96–1.82 (m, 2H). HRMS (ESI) m/z calcd $C_{18}H_{24}N_5O_4^+$ $[M + H]^+$ 374.1823, found 374.1827.

**_N_-Hydroxy-2-(9-(thiophen-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (07)**

Compound **07** was prepared according to the above general synthetic method. Oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.32 (s, 2H), 8.77–8.71 (m, 2H), 7.86–7.81 (m, 1H), 7.71–7.64 (m, 1H), 7.46 (t, $J$ = 6.4 Hz, 1H), 4.32 (d, $J$ = 4.8 Hz, 2H), 3.89–3.82 (m, 2H), 3.82–3.71 (m, 4H), 3.23–3.09 (m, 2H), 2.96 (dd, $J$ = 22.3, 10.2 Hz, 2H), 2.06 (d, $J$ = 13.8 Hz, 2H), 2.00–1.87 (m, 2H). HRMS (ESI) m/z calcd $C_{18}H_{24}N_5O_3S^+$ $[M + H]^+$ 390.1594, found 390.1602.

**2-(9-Benzyl-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-_N_-hydroxypyrimidine-5-carboxamid e hydrochloride (08)**

Compound **08** was prepared according to the above general synthetic method. m. p. 225–228 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.15 (s, 2H), 8.71 (d, $J$ = 11.6 Hz, 2H), 7.63 (s, 2H), 7.53–7.41 (m, 3H), 4.37–4.22 (m, 2H), 3.87–3.74 (m, 3H), 3.70 (s, 3H), 3.13 (d, $J$ = 10.3 Hz, 2H), 3.05–2.91 (m, 2H), 2.02 (d, $J$ = 14.2 Hz, 2H), 1.92 (d, $J$ = 13.9 Hz, 2H). HRMS (ESI) m/z calcd $C_{20}H_{26}N_5O_3^+$ $[M + H]^+$ 384.2030, found 384.2037.

**_N_-Hydroxy-2-(9-(pyridin-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (09)**

Compound **09** was prepared according to the above general synthetic method. m. p. 162–165 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.23 (s, 1H), 10.81 (s, 1H), 8.79–8.71 (m,

3H), 8.07–7.98 (m, 1H), 7.82–7.70 (m, 1H), 7.62–7.50 (m, 1H), 4.56 (s, 2H), 3.85 (t, *J* = 4.9 Hz, 2H), 3.82–3.73 (m, 4H), 3.34–3.09 (m, 4H), 2.11–1.87 (m, 4H). HRMS (ESI) m/z calcd $C_{19}H_{25}N_6O_3^+$ $[M + H]^+$ 385.1983, found 385.1989.

***N*-Hydroxy-2-(9-(pyridin-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (10)**

Compound **10** was prepared according to the above general synthetic method. Oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.85 (s, 1H), 11.22 (s, 1H), 9.15 (s, 1H), 9.00–8.94 (m, 1H), 8.80–8.76 (m, 1H), 8.74 (d, *J* = 2.7 Hz, 2H), 8.09–8.01 (m, 1H), 4.56 (d, *J* = 4.1 Hz, 2H), 3.91–3.85 (m, 2H), 3.84–3.79 (m, 2H), 3.78–3.74 (m, 2H), 3.32–3.19 (m, 2H), 3.17–3.04 (d, *J* = 10.7 Hz, 1H), 2.06 (d, *J* = 14.3 Hz, 2H), 2.01–1.89 (m, 2H). HRMS (ESI) m/z calcd $C_{19}H_{25}N_6O_3^+$ $[M + H]^+$ 385.1983, found 385.1989.

***N*-Hydroxy-2-(9-(pyridin-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (11)**

Compound **11** was prepared according to the above general synthetic method. m. p. 228–232 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.08 (s, 1H), 11.20 (s, 1H), 8.97 (s, 2H), 8.73 (s, 2H), 8.29 (s, 2H), 4.60 (s, 2H), 3.90–3.83 (m, 2H), 3.86–3.73 (m, 4H), 3.33–3.16 (m, 2H), 3.15–2.97 (m, 2H), 2.07–1.97 (m, 4H). HRMS (ESI) m/z calcd $C_{19}H_{25}N_6O_3^+$ $[M + H]^+$ 385.1983, found 385.1989.

***N*-Hydroxy-2-(9-(naphthalen-1-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimi**

**dine-5-carboxamide hydrochloride (12)**

Compound **12** was prepared according to the above general synthetic method. m. p. 168–171 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.37 (s, 2H), 8.72 (d, $J$ = 22.2 Hz, 2H), 8.45 (d, $J$ = 8.4 Hz, 1H), 8.08–7.99 (m, 3H), 7.67–7.56 (m, 3H), 4.82 (d, $J$ = 4.9 Hz, 2H), 3.81 (s, 2H), 3.77–3.63 (m, 4H), 3.22–3.13 (m, 4H), 1.99 (s, 4H). HRMS (ESI) m/z calcd $C_{24}H_{28}N_5O_3^+$ $[M + H]^+$ 434.2187, found 434.2193.

***N*-Hydroxy-2-(9-(naphthalen-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimi dine-5-carboxamide hydrochloride (13)**

Compound **13** was prepared according to the above general synthetic method. m. p. 233–238 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.26–10.99 (m, 2H), 8.71 (d, $J$ = 16.9 Hz, 2H), 8.16 (d, $J$ = 12.5 Hz, 1H), 8.03–7.96 (m, 2H), 7.94–7.90 (m, 1H), 7.81 (d, $J$ = 8.4 Hz, 1H), 7.63–7.55 (m, 2H), 4.47 (d, $J$ = 5.0 Hz, 2H), 3.87–3.77 (m, 2H), 3.71 (d, $J$ = 6.8 Hz, 4H), 3.26–3.16 (m, 2H), 3.11–2.98 (m, 2H), 2.03 (d, $J$ = 13.9 Hz, 2H), 1.91 (t, $J$ = 13.6 Hz, 2H). HRMS (ESI) m/z calcd $C_{24}H_{28}N_5O_3$ $[M+H]^+$ 434.2187, found 434.2191.

**2-(9-(Anthracen-9-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidi ne-5-carboxamide hydrochloride (14)**

Compound **14** was prepared according to the above general synthetic method. m. p. 198–201 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.22 (s, 1H), 9.78 (s, 1H), 8.89 (d, $J$ = 7.1 Hz, 1H), 8.71 (s, 2H), 8.66 (t, $J$ = 7.3 Hz, 2H), 8.24 (t, $J$ = 8.0 Hz, 2H), 7.82–7.73 (m, 2H), 7.66 (dd, $J$ = 14.4, 6.3 Hz, 2H), 5.49 (d, $J$ = 5.1 Hz, 2H), 3.91–3.79 (m, 4H), 3.74–3.65 (m, 2H),

3.49 (dd, *J* = 22.2, 10.5 Hz, 2H), 3.33 (d, *J* = 11.0 Hz, 2H), 2.01 (d, *J* = 13.9 Hz, 2H), 1.93–1.83 (m, 2H). HRMS (ESI) m/z calcd $C_{28}H_{30}N_5O_3^+$ $[M + H]^+$ 484.2343, found 484.2350.

**2-(9-([1,1'-Biphenyl]-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (15)**

Compound **15** was prepared according to the above general synthetic method. m. p. 232–237 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.19 (s, 2H), 8.75 (d, *J* = 14.1 Hz, 2H), 7.79 (s, 1H), 7.77 (s, 3H), 7.75–7.71 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.3 Hz, 1H), 4.37 (d, *J* = 5.1 Hz, 2H), 3.89–3.82 (m, 2H), 3.82–3.69 (m, 4H), 3.21 (d, *J* = 11.5 Hz, 2H), 3.10–2.98 (m, 2H), 2.07 (d, *J* = 13.6 Hz, 2H), 2.02–1.90 (t, *J* = 11.8 Hz, 2H). HRMS (ESI) m/z calcd $C_{26}H_{30}N_5O_3^+$ $[M + H]^+$ 460.2343, found 460.2348.

***N*-Hydroxy-2-(9-(isoquinolin-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (16)**

Compound **16** was prepared according to the above general synthetic method. m. p. 211–214 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.40 (s, 2H), 9.93 (s, 1H), 9.16 (s, 1H), 8.80 (d, *J* = 8.9 Hz, 1H), 8.73 (s, 2H), 8.57 (d, *J* = 8.2 Hz, 1H), 8.27 (t, *J* = 7.5 Hz, 1H), 8.09–8.03 (m, 1H), 5.00 (d, *J* = 4.8 Hz, 2H), 3.90–3.83 (s, 2H), 3.83–3.76 (m, 2H), 3.73 (s, 2H), 3.39–3.23 (m, 4H), 2.12–1.92 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2144.

***N*-Hydroxy-2-(9-(quinolin-4-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin**

**e-5-carboxamide hydrochloride (17)**

Compound **17** was prepared according to the above general synthetic method. m. p. 192–196 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.97 (s, 1H), 11.18 (s, 1H), 9.42 (d, $J$ = 4.9 Hz, 1H), 8.82 (d, $J$ = 8.5 Hz, 1H), 8.79–8.67 (m, 3H), 8.54 (d, $J$ = 7.1 Hz, 1H), 8.19 (t, $J$ = 7.6 Hz, 1H), 8.08–7.99 (m, 1H), 5.15 (s, 2H), 3.91–3.82 (m, 2H), 3.82–3.66 (m, 4H), 3.32 (s, 4H), 2.20–1.96 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2144.

***N*-Hydroxy-2-(9-(quinolin-5-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (18)**

Compound **18** was prepared according to the above general synthetic method. Oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.60 (s, 1H), 11.27 (s, 1H), 9.78–9.71 (m, 1H), 9.38 (d, $J$ = 5.2 Hz, 1H), 8.73 (s, 2H), 8.59 (d, $J$ = 8.6 Hz, 1H), 8.42 (d, $J$ = 7.2 Hz, 1H), 8.26–8.20 (m, 1H), 8.16 (dd, $J$ = 8.5, 5.2 Hz, 1H), 4.99 (d, $J$ = 5.0 Hz, 2H), 3.90–3.83 (m, 2H), 3.82–3.76 (m, 2H), 3.72 (s, 2H), 3.37–3.21 (m, 4H), 2.03 (s, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2146.

***N*-Hydroxy-2-(9-(isoquinolin-8-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimid ine-5-carboxamide hydrochloride (19)**

Compound **19** was prepared according to the above general synthetic method. Oil. $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.63 (s, 1H), 11.26 (s, 1H), 10.48 (s, 1H), 8.77 (d, $J$ = 6.4 Hz, 1H), 8.73 (s, 2H), 8.63 (d, $J$ = 6.4 Hz, 1H), 8.46 (dd, $J$ = 13.6, 7.7 Hz, 2H), 8.28 (t, $J$ = 7.7 Hz, 1H), 5.07 (d, $J$ = 4.7 Hz, 2H), 3.90–3.83 (m, 2H), 3.84–3.78 (m, 2H), 3.72 (s, 2H), 3.30 (s,

4H), 2.08–1.97 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2147.

**_N_-Hydroxy-2-(9-(quinolin-8-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (20)**

Compound **20** was prepared according to the above general synthetic method. m. p. 198–202 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.03 (s, 2H), 9.14–9.09 (m, 1H), 8.79–8.71 (m, 2H), 8.64 (d, $J$ = 8.2 Hz, 1H), 8.31 (d, $J$ = 6.8 Hz, 1H), 8.22 (d, $J$ = 8.3 Hz, 1H), 7.80–7.75 (m, 2H), 5.00 (d, $J$ = 3.6 Hz, 2H), 3.91–3.78 (m, 3H), 3.77–3.69 (m, 3H), 3.28 (d, $J$ = 11.0 Hz, 2H), 3.20–3.09 (m, 2H), 2.07–1.90 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2146.

**_N_-Hydroxy-2-(9-(quinolin-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (21)**

Compound **21** was prepared according to the above general synthetic method. m. p. 186–189 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.97 (s, 2H), 8.71 (s, 2H), 8.53 (d, $J$ = 8.5 Hz, 1H), 8.08 (t, $J$ = 9.1 Hz, 2H), 7.86 (t, $J$ = 7.5 Hz, 2H), 7.70 (t, $J$ = 7.4 Hz, 1H), 4.73 (s, 2H), 3.88–3.69 (m, 6H), 3.35 (s, 2H), 3.24 (s, 2H), 2.09–1.92 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2146.

**_N_-Hydroxy-2-(9-(quinolin-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (22)**

Compound **22** was prepared according to the above general synthetic method. m. p. 210–212 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.77 (s, 2H), 9.49 (s, 1H), 9.18 (s, 1H), 8.74 (d, $J$ = 3.2 Hz, 2H), 8.35 (d, $J$ = 8.6 Hz, 1H), 8.29–8.23 (m, 1H), 8.17–8.09 (m, 1H), 8.00–7.91 (m, 1H), 4.68 (d, $J$ = 5.0 Hz, 2H), 3.89–3.81 (m, 3H), 3.80–3.74 (m, 3H), 3.34 (d, $J$ = 11.2 Hz, 2H), 3.23–3.09 (m, 2H), 2.07 (d, $J$ = 14.1 Hz, 2H), 2.00–1.91 (m, 2H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2146.

**_N_-Hydroxy-2-(9-(quinolin-6-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidin e-5-carboxamide hydrochloride (23)**

Compound **23** was prepared according to the above general synthetic method. m. p. 205–208 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.82 (s, 1H), 11.23 (s, 1H), 9.35 (d, $J$ = 5.0 Hz, 1H), 9.10 (d, $J$ = 8.6 Hz, 1H), 8.73 (s, 2H), 8.60 (d, $J$ = 7.3 Hz, 1H), 8.49 (d, $J$ = 5.3 Hz, 2H), 8.10 (dd, $J$ = 8.3, 5.0 Hz, 1H), 4.64 (d, $J$ = 4.9 Hz, 2H), 3.92–3.80 (m, 3H), 3.78–3.73 (m, 3H), 3.34–3.20 (m, 2H), 3.18–3.07 (m, 2H), 2.10–1.95 (m, 4H). HRMS (ESI) m/z calcd $C_{23}H_{27}N_6O_3^+$ $[M + H]^+$ 435.2139, found 435.2147.

**2-(9-(Benzofuran-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-_N_-hydroxypyrimid ine-5-carboxamide hydrochloride (24)**

Compound **24** was prepared according to the above general synthetic method. m. p. 157–160 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.63 (s, 1H), 10.41 (s, 1H), 8.78–8.71 (m, 2H), 7.80–7.72 (m, 1H), 7.65 (dd, $J$ = 8.0, 3.0 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.36 – 7.31 (m, 1H), 7.28 (s, 1H), 4.62 (s, 2H), 3.83 (s, 2H), 3.74 (s, 4H), 3.34 (d, $J$ = 11.1 Hz, 2H), 3.15–3.05

(m, 2H), 2.09 (d, *J* = 13.7 Hz, 2H), 2.01–1.89 (m, 2H). HRMS (ESI) m/z calcd $C_{22}H_{26}N_5O_4^+$ $[M + H]^+$ 424.1979, found 424.1986.

**2-(9-(Benzo[*b*]thiophen-2-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxyp yrimidine-5-carboxamide hydrochloride (25)**

Compound **25** was prepared according to the above general synthetic method. m. p. 196–200 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.62–11.08 (m, 2H), 8.75 (d, *J* = 12.0 Hz, 2H), 8.10–8.03 (m, 1H), 7.97–7.90 (m, 1H), 7.77 (s, 1H), 7.48–7.43 (m, 2H), 4.70 (d, *J* = 3.9 Hz, 2H), 3.90–3.81 (m, 2H), 3.75 (s, 4H), 3.29 (d, *J* = 10.4 Hz, 2H), 3.09 (dd, *J* = 22.1, 10.8 Hz, 2H), 2.09 (d, *J* = 13.9 Hz, 2H), 1.95 (t, *J* = 13.8 Hz, 2H). HRMS (ESI) m/z calcd $C_{22}H_{26}N_5O_3S^+$ $[M + H]^+$ 440.1751, found 440.1757.

**2-(9-(Benzo[*b*]thiophen-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxyp yrimidine-5-carboxamide hydrochloride (26)**

Compound **26** was prepared according to the above general synthetic method. m. p. 227–231 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.33–10.80 (m, 2H), 8.71 (d, *J* = 13.0 Hz, 2H), 8.29–8.18 (m, 2H), 8.08 (t, *J* = 7.1 Hz, 1H), 7.55–7.40 (m, 2H), 4.61 (d, *J* = 3.5 Hz, 2H), 3.85–3.78 (m, 2H), 3.76–3.65 (m, 4H), 3.24 (d, *J* = 10.6 Hz, 2H), 3.17–3.04 (m, 2H), 2.03 (d, *J* = 14.3 Hz, 2H), 1.96–1.81 (m, 2H). HRMS (ESI) m/z calcd $C_{22}H_{26}N_5O_3S^+$ $[M + H]^+$ 440.1751, found 440.1757.

***N*-Hydroxy-2-(9-(imidazo[1,2-*a*]pyridin-3-ylmethyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-**

**yl)pyrimidine-5-carboxamide hydrochloride (27)**

Compound **27** was prepared according to the above general synthetic method. m. p. 202–205 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.85 (d, $J$ = 32.2 Hz, 1H), 11.21 (s, 1H), 9.38 (d, $J$ = 6.8 Hz, 1H), 8.84–8.71 (m, 2H), 8.58–8.48 (m, 1H), 8.13–8.03 (m, 2H), 7.70–7.58 (m, 1H), 4.91 (s, 2H), 3.91–3.83 (m, 3H), 3.82–3.72 (m, 3H), 3.50–3.40 (m, 2H), 3.33–3.15 (m, 2H), 2.07 (d, $J$ = 13.3 Hz, 2H), 2.02–1.89 (m, 2H). HRMS (ESI) m/z calcd $C_{21}H_{26}N_7O_3^+$ $[M + H]^+$ 424.2092, found 424.2098.

***N*-Hydroxy-2-(9-((1-methyl-1*H*-benzo[*d*]imidazol-2-yl)methyl)-1-oxa-4,9-diazaspiro[5.5] undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (28)**

Compound **28** was prepared according to the above general synthetic method. m. p. 225–227 ℃; H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.23 (s, 2H), 8.75 (s, 2H), 7.80 (d, $J$ = 8.9 Hz, 2H), 7.51–7.40 (m, 2H), 4.85 (s, 2H), 4.04 (s, 3H), 3.91–3.85 (m, 2H), 3.84–3.72 (m, 4H), 3.54 (s, 2H), 3.35 (s, 2H), 2.14–1.93 (m, 4H). HRMS (ESI) m/z calcd $C_{22}H_{28}N_7O_3^+$ $[M + H]^+$ 438.2248, found 438.2255.

***N*-Hydroxy-2-(9-((1-methyl-1*H*-indazol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4 -yl)pyrimidine-5-carboxamide hydrochloride (29)**

Compound **29** was prepared according to the above general synthetic method. m. p. 182–186 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.01 (s, 2H), 8.74 (d, $J$ = 4.5 Hz, 2H), 8.15–8.08 (m, 1H), 7.78–7.72 (m, 1H), 7.54–7.46 (m, 1H), 7.30–7.24 (m, 1H), 4.70 (d, $J$ = 3.9 Hz, 2H), 4.14 (d, $J$ = 4.7 Hz, 3H), 3.83 (t, $J$ = 8.2 Hz, 2H), 3.78–3.66 (m, 4H), 3.41 (d, $J$ =

10.9 Hz, 2H), 3.15–3.01 (m, 2H), 2.07 (d, *J* = 14.3 Hz, 2H), 1.96–1.85 (m, 2H). HRMS (ESI) m/z calcd $C_{22}H_{28}N_7O_3^+$ $[M + H]^+$ 438.2248, found 438.2255.

**_N_-Hydroxy-2-(9-((1-methyl-1_H_-pyrrolo[3,2-_b_]pyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (30)**

Compound **30** was prepared according to the above general synthetic method. m. p. 184–186 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.19 (s, 1H), 10.92 (s, 1H), 8.83 (d, *J* = 7.6 Hz, 2H), 8.73 (s, 2H), 8.44 (s, 1H), 7.81 (dd, *J* = 8.1, 5.8 Hz, 1H), 4.75 (s, 2H), 4.08 (s, 3H), 3.87 (s, 2H), 3.79–3.73 (m, 4H), 3.44–3.36 (m, 2H), 3.19–3.08 (m, 2H), 2.07 (d, *J* = 13.6 Hz, 2H), 1.86 (t, *J* = 12.5 Hz, 2H).. HRMS (ESI) m/z calcd $C_{22}H_{28}N_7O_3^+$ $[M + H]^+$ 438.2248, found 438.2253.

**_N_-Hydroxy-2-(9-((1-methyl-1_H_-pyrrolo[2,3-_c_]pyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (31)**

Compound **31** was prepared according to the above general synthetic method. m. p. 184–187 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.07 (s, 2H), 8.74 (d, *J* = 10.0 Hz, 2H), 8.52–8.46 (m, 1H), 8.43–8.38 (m, 1H), 7.93–7.87 (m, 1H), 7.34–7.27 (m, 1H), 4.49 (d, *J* = 4.3 Hz, 2H), 3.92 (d, *J* = 5.5 Hz, 3H), 3.85 – 3.80 (m, 2H), 3.78–3.68 (m, 4H), 3.28 (d, *J* = 10.6 Hz, 2H), 3.02 (dd, *J* = 22.6, 10.9 Hz, 2H), 2.05 (d, *J* = 14.0 Hz, 2H), 1.98–1.87 (m, 2H). HRMS (ESI) m/z calcd $C_{22}H_{28}N_7O_3^+$ $[M + H]^+$ 438.2248, found 438.2257.

**_N_-Hydroxy-2-(9-((1-methyl-1_H_-pyrrolo[2,3-_b_]pyridin-3-yl)methyl)-1-oxa-4,9-diazaspiro[**

**5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (32)**

Compound **32** was prepared according to the above general synthetic method. m. p. 188–191 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.26 (s, 2H), 8.78–8.70 (m, 2H), 8.44–8.38 (m, 1H), 7.98–7.85 (m, 2H), 7.38–7.27 (m, 1H), 4.49 (d, $J$ = 4.4 Hz, 2H), 3.98–3.90 (m, 3H), 3.89–3.78 (m, 3H), 3.73 (s, 3H), 3.28 (d, $J$ = 11.1 Hz, 2H), 3.02 (dd, $J$ = 22.4, 10.8 Hz, 2H), 2.04 (d, $J$ = 14.1 Hz, 2H), 1.99–1.86 (m, 2H). HRMS (ESI) m/z calcd $C_{22}H_{28}N_7O_3^+$ $[M + H]^+$ 438.2248, found 438.2256.

**2-(9-((1*H*-Indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (33)**

Compound **33** was prepared according to the above general synthetic method. m. p. 178–182 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.56 (s, 1H), 10.75 (s, 1H), 8.74 (d, $J$ = 7.8 Hz, 2H), 7.85 (d, $J$ = 7.8 Hz, 1H), 7.69 (d, $J$ = 2.1 Hz, 1H), 7.47 (d, $J$ = 7.9 Hz, 1H), 7.15 (dt, $J$ = 14.7, 7.1 Hz, 2H), 4.47 (d, $J$ = 3.7 Hz, 2H), 3.85–3.78 (m, 2H), 3.76–3.65 (m, 4H), 3.28 (d, $J$ = 11.8 Hz, 2H), 3.00 (dd, $J$ = 22.1, 10.5 Hz, 2H), 2.05 (d, $J$ = 13.5 Hz, 2H), 1.90 (t, $J$ = 12.5 Hz, 2H). HRMS (ESI) m/z calcd $C_{22}H_{27}N_6O_3^+$ $[M + H]^+$ 423.2139, found 423.2146.

***N*-Hydroxy-2-(9-((5-methoxy-1-methyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (34)**

Compound **34** was prepared according to the above general synthetic method. m. p. 187–192 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.17 (s, 1H), 10.35 (s, 1H), 8.73 (d, $J$ = 8.0 Hz, 2H), 7.57 (s, 1H), 7.48–7.38 (m, 2H), 6.88 (dd, $J$ = 8.8, 2.3 Hz 1H), 4.44 (d, $J$ = 3.9 Hz,

2H), 3.83 (d, *J* = 3.3 Hz, 5H), 3.82 (s, 3H), 3.73 (s, 4H), 3.29 (d, *J* = 11.2 Hz, 2H), 3.03 (d, *J* = 12.1 Hz, 2H), 2.07 (d, *J* = 14.2 Hz, 2H), 1.91–1.80 (m, 2H). HRMS (ESI) m/z calcd $C_{24}H_{31}N_6O_4^+$ $[M + H]^+$ 467.2401, found 467.2408.

**2-(9-((1,6-Dimethyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (35)**

Compound **35** was prepared according to the above general synthetic method. m. p. 168–171 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.18 (s, 1H), 10.52 (s, 1H), 8.73 (d, *J* = 4.2 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.55 (s, 1H), 7.32 (d, *J* = 5.4 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 4.43 (d, *J* = 3.9 Hz, 2H), 3.82 (d, *J* = 4.6 Hz, 5H), 3.76–3.67 (m, 4H), 3.27 (d, *J* = 10.8 Hz, 2H), 3.00 (dd, *J* = 22.9, 11.0 Hz, 2H), 2.48 (d, *J* = 5.7 Hz, 3H), 2.05 (d, *J* = 14.4 Hz, 2H), 1.91–1.80 (m, 2H). HRMS (ESI) m/z calcd $C_{24}H_{31}N_6O_3^+$ $[M + H]^+$ 451.2452, found 451.2460.

***N*-Hydroxy-2-(9-((6-methoxy-1-methyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)pyrimidine-5-carboxamide hydrochloride (36)**

Compound **36** was prepared according to the above general synthetic method. m. p. 197–201 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.19 (s, 1H), 10.54 (s, 1H), 8.74 (d, *J* = 9.7 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.49 (s, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.7, 2.1 Hz, 1H), 4.42 (d, *J* = 3.8 Hz, 2H), 3.85 (d, *J* = 4.0 Hz, 3H), 3.81 (d, *J* = 4.1 Hz, 5H), 3.76–3.66 (m, 4H), 3.28 (d, *J* = 11.8 Hz, 2H), 2.99 (dd, *J* = 22.8, 10.6 Hz, 2H), 2.05 (d, *J* = 13.9 Hz, 2H), 1.93–1.81 (m, 2H). HRMS (ESI) m/z calcd $C_{24}H_{31}N_6O_4^+$ $[M + H]^+$ 467.2401, found 467.2406.

**2-(9-((6-Bromo-1-methyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (37)**

Compound **37** was prepared according to the above general synthetic method. m. p. 185–188 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.21 (s, 1H), 10.74 (s, 1H), 8.72 (s, 2H), 7.87 (d, $J$ = 8.5 Hz, 1H), 7.81 (d, $J$ = 1.5 Hz, 1H), 7.67 (s, 1H), 7.29 (dd, $J$ = 8.5, 1.6 Hz, 1H), 4.46 (d, $J$ = 4.2 Hz, 2H), 3.85 (d, $J$ = 4.3 Hz, 5H), 3.72 (s, 4H), 3.26 (d, $J$ = 10.1 Hz, 2H), 3.00 (dd, $J$ = 22.5, 10.4 Hz, 2H), 2.04 (d, $J$ = 13.8 Hz, 2H), 1.92–1.83 (m, 2H) HRMS (ESI) m/z calcd $C_{23}H_{28}N_6O_3Br^+$ $[M + H]^+$ 515.1401, found 515.1406.

**2-(9-((6-Cyano-1-methyl-1*H*-indol-3-yl)methyl)-1-oxa-4,9-diazaspiro[5.5]undecan-4-yl)-*N*-hydroxypyrimidine-5-carboxamide hydrochloride (38)**

Compound **38** was prepared according to the above general synthetic method. m. p. 217–219 ℃; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.18 (s, 1H), 10.73 (s, 1H), 8.73 (d, $J$ = 7.1 Hz, 2H), 8.20 (d, $J$ = 4.9 Hz, 1H), 8.09 (d, $J$ = 8.3 Hz, 1H), 7.95 (s, 1H), 7.54–7.50 (m, 1H), 4.51 (d, $J$ = 4.3 Hz, 2H), 3.93 (s, 3H), 3.85–3.81 (m, 2H), 3.76–3.70 (m, 4H), 3.27 (d, $J$ = 10.5 Hz, 2H), 3.07–2.97 (m, 2H), 2.05 (d, $J$ = 13.8 Hz, 2H), 1.93–1.82 (m, 2H). HRMS (ESI) m/z calcd $C_{24}H_{28}N_7O_3^+$ $[M + H]^+$ 462.2248, found 462.2253.

## HPLC analysis data of compound purity

**Table S1**. HPLC analysis method and data of compounds **01–38**

| | |
|---|---|
| Equipment | Agilent 1100 with quaternary pump, diode-array detector (DAD) |
| Column | Agilent Exlipse XDB-C18 (250×4.6 mm, 5 μm particle size) |
| System condition | $CH_3OH$:0.1% $H_3PO_4$($H_2O$) = 85:15 (v/v) as eluent, flow rate: 0.5 mL/min |

| Results | Compd. | Retention time (min) | Relactive purity (%) |
|---|---|---|---|
| | **01** | 4.472 | 99.23 |
| | **02** | 4.244 | 99.18 |
| | **03** | 4.287 | 99.07 |
| | **04** | 4.355 | 97.94 |
| | **05** | 4.201 | 98.40 |
| | **06** | 4.121 | 97.18 |
| | **07** | 4.283 | 99.23 |
| | **08** | 4.311 | 99.53 |
| | **09** | 4.201 | 98.06 |
| | **10** | 4.202 | 96.61 |
| | **11** | 4.133 | 95.78 |
| | **12** | 4.228 | 99.13 |
| | **13** | 4.288 | 99.92 |
| | **14** | 4.416 | 95.05 |
| | **15** | 4.332 | 99.73 |
| | **16** | 4.191 | 97.89 |
| | **17** | 4.303 | 96.76 |
| | **18** | 4.156 | 97.36 |
| | **19** | 4.320 | 99.25 |
| | **20** | 4.143 | 97.67 |
| | **21** | 4.894 | 98.65 |
| | **22** | 4.343 | 98.07 |
| | **23** | 4.251 | 97.38 |
| | **24** | 4.262 | 99.29 |
| | **25** | 4.254 | 97.01 |
| | **26** | 4.282 | 95.25 |
| | **27** | 4.104 | 97.33 |
| | **28** | 4.221 | 98.43 |

| | | | |
|---|---|---|---|
| | **29** | 4.316 | 98.76 |
| | **30** | 4.123 | 98.95 |
| | **31** | 4.212 | 97.91 |
| | **32** | 4.286 | 95.45 |
| | **33** | 4.182 | 95.97 |
| | **34** | 3.741 | 97.54 |
| | **35** | 3.587 | 96.94 |
| | **36** | 3.287 | 98.99 |
| | **37** | 4.467 | 97.63 |
| | **38** | 4.217 | 98.19 |