**Supplementary Fig. S1 Screening of epigenetic inhibitors against blood-stage *P. falciparum.* a A heatmap indicates the percent inhibition of 3D7 asexual growth at 50 nM and 500 nM tested compounds compared to that with the DMSO control. b The EC\textsubscript{50} values of five compounds against *Pf*3D7, HepG2 and 293T cells; SI\textsuperscript{a}, EC\textsubscript{50} HepG2/EC\textsubscript{50} *Pf*3D7; SI\textsuperscript{b}, EC\textsubscript{50} 293T/EC\textsubscript{50} *Pf*3D7. c *In vivo* activity assay against the blood stage of *P. yoelii* in BALB/c mice. Three mice were used in each group. Parasitemia was calculated from at least 5,000 red blood cells (RBCs) by microscopy. Blank, untreated group; PPQ, piperaquine phosphate. The administration route was intraperitoneal (i.p.). The data of a and b are from three independent biological replicates in duplication.
Supplementary Fig. S2 *In vivo* activity of JX21108 against *P. yoelii* in BALB/c mice.  

a The body weight of the tested mice from the experiment described in Fig. 2c.  

b *In vivo* activity of JX21108, (+)-JX21108 and (-)-JX21108 against the blood stage of *P. yoelii* in BALB/c mice. Five mice were used in each group. Parasitemia was calculated from at least 5,000 RBCs by microscopy. Blank, untreated group; PPQ, piperaquine phosphate.  

c and d The body weight and survival ratio of the tested mice from the experiment described in c. All data are the mean ± s.e.m.
**Supplementary Fig. S3 3D structure modeling of PfHDAC1.**

**a** Multiple sequence alignment of PfHDAC1, human HDAC2 and human HDAC8 was utilized for the generation of the PfHDAC1 model.

**b** The template sequence used for model construction, in which reference sequence regions are labeled in pink for human HDAC2 and green for HDAC8.

**c** Cartoon representation of the PfHDAC1 model. Zn$^{2+}$ is shown as blue sphere and its coordinated residues are shown as sticks. The active site is illustrated by pale orange column.

**d** Ramachandran plot of the PfHDAC1 model.

**e** *In silico* docking of a homology model of PfHDAC1 showing that quisinostat could be perfectly accommodated by the catalytic site surface of PfHDAC1. PfHDAC1 is shown as green cartoon. Small molecules and key residues in PfHDAC1 are drawn as sticks. Carbons are shown in pink, cyan and orange, in small molecules and green in key residues. All oxygen, nitrogen and hydrogen atoms (polar hydrogens only) are colored red, blue and white, respectively. Zn$^{2+}$ and π bond centers are represented by blue and yellow spheres, respectively. Metal bonds, hydrogen bonds, π bonds and ionic bonds are shown as blue, purple, yellow and green dashed lines, respectively. The distances of these interactions are also labeled near the dashed lines and shown in angstroms.
Supplementary Fig. S4 Knockdown of *PfHDA1* and *PfHDAC1*. a Schematic of the gene knockdown strategy using the CRISPR/Cas9 system. HR1, the 5’ flanking fragment for homologous recombination. HR2, the 3’ flanking fragment for homologous recombination. *hDHFR*, human dihydrofolate reductase. *BSD*, Blasticidin S Deaminase. 3 × TY1, a tag sequence for detection of the recombinant protein by western blot. *glmS*, sequence of the ribozyme for posttranscriptional degradation of the target gene induced by glucosamine (GlcN). p17/19 and p18/20, primers 17, 18, 19 and 20 used for PCR identification of gene editing (see also in Supplementary information, Table S6). b–e PCR identification of gene editing at the genomic loci of *PfHDA1* (b and c) and *PfHDAC1* (d and e). f Western blot analysis of the histone H3 acetylation levels (H3-Ace) of GlcN-treated 3D7*HDA1-TY1*, 3D7*HDA1-glmS*, 3D7*HDAC1-TY1*, and 3D7*HDAC1-glmS* at the ring, trophozoite and schizont stages. Histone H3 (H3) was used as the loading control.
Supplementary Fig. S5 Gene Ontology (GO) analyses of genes with altered expression after PfHDAC1 knockdown (KD) or JX21108 treatment. GO analyses for downregulated genes (a) or up-regulated genes (b) from PfHDAC1 KD, JX21108 treatment or both in PfHDAC1 KD and JX21108-treated parasites. GO analyses were performed in PlasmoDB.
Supplementary Fig. S6 The PK curve graph of JX21108 and quisinostat in BALB/c mice related to supplementary table S4. Five mice per group were used in this experiment; i.p., intraperitoneal injection.
Supplementary Table S1. Anti-*P. falciparum* activity and cytotoxicity profiles of linker derivatives.

| Entry | Comp. | Linker | Molecular Weight | cLogP | Antiplasmodinal Activity<sup>a</sup>, EC<sub>50</sub> (nM) | Cytotoxicity<sup>a</sup>, EC<sub>50</sub> (nM)/SI |
|-------|-------|--------|------------------|-------|-----------------------------|----------------------------------|
|       |       |        |                  |       | 3D7 | Dd2 | HepG2 | SI<sup>b</sup> | 293T | SI<sup>c</sup> |
| 1     | Quisinostat | ![Quisinostat](image) | 430.94 | -0.98 | 5.2 ± 1.6 | 7.09 ± 0.01 | 42 ± 10 | 8 | 48 ± 1 | 9 |
| 2     | JX21002 | ![JX21002](image) | 428.92 | -1.19 | 4.4 ± 0.2 | 7.0 ± 0.2 | 128 ± 2 | 29 | 307 ± 4 | 70 |
| 3     | JX21003 | ![JX21003](image) | 402.88 | -1.79 | 10.9 ± 0.8 | 15.3 ± 0.4 | 44 ± 7 | 4 | 47 ± 21 | 4 |
| 4     | JX21004 | ![JX21004](image) | 416.91 | -1.36 | 32.9 ± 0.9 | 61.0 ± 0.4 | 294 ± 57 | 9 | 519 ± 112 | 16 |
|   | JX21005  |    |       |          |      |     |       |
|---|---------|----|-------|----------|------|-----|-------|
|   |         |    | 430.94| -1.26    | 73.6 ± 3.5 | 107.5 ± 5.6 | 643 ± 36 | 9 | 1978 ± 407 |
|   |         |    |       |          |      |     |       |
|   | JX21006 | Me |       |          |      |     |       |
|   |         |    | 430.94| -1.26    | 26.5 ± 1.2 | 32.0 ± 2.5 | 37 ± 10 | 1 | 118 ± 24 |
|   |         |    |       |          |      |     |       |
|   | JX21008 |    |       |          |      |     |       |
|   |         |    | 430.94| -1.24    | 13.1 ± 0.6 | 23.6 ± 0.4 | 688 ± 10 | 52 | 253 ± 89 |
|   |         |    |       |          |      |     |       |
|   | JX21022 |    |       |          |      |     |       |
|   |         |    | 430.94| -1.20    | 151.1 ± 2.7 | 125.4 ± 4.5 | >10000 | >66 | >10000 |
|   |         |    |       |          |      |     |       |
|   | JX21024 |    |       |          |      |     |       |
|   |         |    | 485.03| -0.11    | 19.8 ± 2.5 | 54.0 ± 3.8 | 871 ± 61 | 44 | 1547 ± 5 |
|   |         |    |       |          |      |     |       |
|   | JX21010 |    |       |          |      |     |       |
|   |         |    | 471.00| -0.78    | 23.4 ± 2.4 | 31.1 ± 4.6 | 904 ± 18 | 39 | 2212 ± 226 |
|   |         |    |       |          |      |     |       |
|   | JX21011 |    |       |          |      |     |       |
|   |         |    | 442.95| -1.32    | 3.0 ± 0.7  | 3.2 ± 0.1  | 113 ± 1 | 38 | 72 ± 10 |
|   |         |    |       |          |      |     |       |
|   | JX21013 |    |       |          |      |     |       |
|   |         |    | 442.95| -1.32    | 79.2 ± 2.4 | 44.0 ± 10.0 | >10000 | >126 | >10000 |
|   |         |    |       |          |      |     |       |
|   | JX21014 |    |       |          |      |     |       |
|   |         |    | 442.95| -1.32    | 16.9 ± 0.8 | 10.7 ± 0.2 | 348 ± 24 | 21 | 1132 ± 26 |
|   |         |    |       |          |      |     |       |
|   | JX21017 |    |       |          |      |     |       |
|   |         |    | 471.00| -0.78    | 28.9 ± 1.2 | 32.4 ± 1.8 | 2347 ± 93 | 98 | 4497 ± 33 |
|   |         |    |       |          |      |     |       |
|   | JX21019 |   |   |   |   |   |   |   |   |   |
|---|---------|---|---|---|---|---|---|---|---|---|
| 15| JX21019 | 456.98 | -0.79 | 45.2 ± 1.2 | 38.7 ± 0.6 | 875 ± 70 | 19 | 1003 ± 208 | 22 |
| 16| JX21020 | 442.95 | -1.06 | 203.1 ± 23.6 | 243.8 ± 47.8 | 1031 ± 456 | 5 | 4009 ± 223 | 20 |

*Results are expressed as the mean ± SD of at least two independent experiments.*

*b*Selectivity index for HepG2 is defined as IC$_{50}$ (HepG2)/IC$_{50}$ (3D7).

*c*Selectivity index for 293T is defined as IC$_{50}$ (293T)/IC$_{50}$ (3D7).

cLog$_{p}$ was calculated from [www.molinspiration.com](http://www.molinspiration.com)
Supplementary Table S2. Anti *P. falciparum* activity and cytotoxicity profiles of R group derivatives.

| Entry | Comp.     | Linker | Molecular Weight | cLogP | Antiplasmodinal Activity\(a\), EC50 (nM) | Cytotoxicity\(a\), EC50 (nM)/SI |
|-------|-----------|--------|------------------|-------|------------------------------------------|---------------------------------|
| 1     | JX21011   | ![Linker](image1) | 442.95           | -1.32 | 3.0 ± 0.7, 3.2 ± 0.1, 113 ± 1, 38 | 72 ± 10, 24 |
| 2     | JX21131   | ![Linker](image2) | 299.76           | -3.23 | 40.4 ± 9.2, 20.7 ± 2.4, > 10000, > 248 | > 10000, > 248 |
| 3     | JX21121   | ![Linker](image3) | 381.91           | -1.35 | 92.5 ± 11.3, 61.6 ± 4.8, > 10000, > 108 | > 10000, > 108 |
| 4     | JX21112   | ![Linker](image4) | 395.93           | -0.84 | 40.4 ± 4.1, 28.3 ± 3.8, 2493 ± 520 | 62, 607 ± 42, 15 |
| 5     | JX21105   | ![Linker](image5) | 389.88           | -1.54 | 17.8 ± 0.5, 28.6 ± 1.8, 1204 ± 68 | 68, 1787 ± 37, 101 |
| 6     | JX21119   | ![Linker](image6) | 390.87           | -2.77 | 53.3 ± 0.5, 39.0 ± 4.0, 6421 ± 540 | 120, 6998 ± 57, 131 |
|   |     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|-----|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | JX2111 | 379.85 | -2.28 | 45.5 ± 3.3 | 34.0 ± 2.5 | 1105 ± 18 | 24 | 2256 ± 286 | 50 |
| 8 | JX21136 | 379.85 | -2.59 | 84.7 ± 4.3 | 55.9 ± 2.2 | > 10000 | > 118 | > 10000 | > 118 |
| 9 | JX21110 | 395.91 | -1.64 | 49.7 ± 1.1 | 35.4 ± 1.3 | 1693 ± 163 | 34 | 4540 ± 323 | 91 |
| 10 | JX21120 | 395.91 | -1.95 | 18.6 ± 3.9 | 23.2 ± 1.2 | 2115 ± 165 | 114 | 3928 ± 374 | 211 |
| 11 | JX21123 | 442.95 | -1.01 | 6.2 ± 1.3 | 7.2 ± 0.3 | 1254 ± 62 | 202 | 1203 ± 156 | 193 |
| 12 | JX21103 | 442.95 | -1.29 | 13.9 ± 0.9 | 23.7 ± 1.0 | 1284 ± 152 | 93 | 2155 ± 81 | 155 |
| 13 | JX21135 | 442.95 | -1.27 | 67.4 ± 3.9 | 60.6 ± 7.1 | 7742 ± 950 | 115 | 10292 ± 1157 | 153 |
| 14 | JX21133 | 442.95 | -1.29 | 240.8 ± 55.2 | 231.7 ± 9.5 | > 10000 | > 42 | > 10000 | > 42 |
| 15 | JX21118 | 445.97 | -0.33 | 5.61 ± 0.04 | 6.4 ± 1.3 | 1673 ± 230 | 298 | 1638 ± 122 | 292 |
| 16 | JX21117 | 429.91 | -0.97 | 6.4 ± 0.3 | 7.61 ± 0.05 | 1639 ± 25 | 255 | 1614 ± 334 | 252 |
|   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|
|17 | JX21115 | ![Molecule](image) | 445.97 | -0.64 | 4.8 ± 0.1 | 7.2 ± 0.2 | 864 ± 76 | 179 | 482 ± 42 | 100 |
|18 | JX21113 | ![Molecule](image) | 429.91 | -1.28 | 67.5 ± 5.3 | 112.3 ± 13.1 | > 10000 | > 148 | 3018 ± 67 | 45 |
|19 | JX21109 | ![Molecule](image) | 431.92 | -1.51 | 9.8 ± 0.3 | 7.0 ± 0.3 | 1311 ± 73 | 133 | 2561 ± 113 | 260 |
|20 | JX21140 | ![Molecule](image) | 433.89 | -1.65 | 10.5 ± 0.1 | 5.4 ± 0.2 | 493 ± 149 | 47 | 2452 ± 301 | 235 |
|21 | JX21122 | ![Molecule](image) | 429.91 | -1.93 | 72.9 ± 10.0 | 74.4 ± 27.4 | > 10000 | > 137 | > 10000 | > 137 |
|22 | JX21130 | ![Molecule](image) | 443.94 | -2.22 | 8.4 ± 0.4 | 7.5 ± 2.0 | 1179 ± 84 | 140 | 4637 ± 375 | 552 |
|23 | JX21129 | ![Molecule](image) | 443.94 | -2.41 | 8.0 ± 0.5 | 7.8 ± 1.3 | 1532 ± 69 | 192 | 1125 ± 98 | 141 |
|   | Compound   | Molecular Weight | m.p. (°C) | Rf  | TIC (mg/ml) | GC (ppm) | LC (ppm) | IC50 (µM) | EC50 (µM) | DMSO (µM) |
|---|------------|------------------|----------|-----|------------|----------|----------|-----------|-----------|-----------|
| 24| JX21134    | 443.94           | -2.41    | 169.9 ± 17.8 | 131.4 ± 11.9 | > 10000 | > 59     | > 10000   | > 59     |
| 25| JX21128    | 443.94           | -2.22    | 8.7 ± 0.7    | 7.7 ± 0.1    | > 10000 | > 1148   | > 10000   | > 1148   |
| 26| JX21124    | 443.94           | -1.54    | 5.8 ± 0.9    | 4.3 ± 0.5    | 1131 ± 168 | 195      | 1327 ± 29 | 229      |
| 27| JX21141    | 521.84           | -0.53    | 3.3 ± 0.5    | 1.736 ± 0.005 | 294 ± 45 | 88       | 633 ± 209 | 189      |
| 28| JX21104    | 472.97           | -1.29    | 1.6 ± 0.3    | 3.0 ± 0.1    | 534 ± 45 | 176      | 659 ± 128 | 217      |
| 29| JX21139    | 456.98           | -0.89    | 3.1 ± 0.3    | 2.1 ± 0.3    | 866 ± 157 | 283      | 737 ± 109 | 241      |
|   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | JX21108 | ![Chemical Structure](#) | 467.96 | -1.59 | 3.57 ± 0.06 | 4.0 ± 0.9 | 3817 ± 145 | 1069 | 1193 ± 233 | 334 |
| 31 | JX21142 | ![Chemical Structure](#) | 472.97 | -1.29 | 13.6 ± 4.2 | 3.4 ± 2.2 | 975 ± 1 | 72 | 1229 ± 102 | 90 |
| 32 | JX21102 | ![Chemical Structure](#) | 477.39 | -0.66 | 4.2 ± 0.7 | 2.4 ± 0.2 | 514 ± 22 | 123 | 1673 ± 110 | 574 |
| 33 | JX21106 | ![Chemical Structure](#) | 460.94 | -1.18 | 2.0 ± 0.9 | 3.60 ± 0.08 | 178 ± 4 | 88 | 402 ± 96 | 198 |
| 34 | JX21125 | ![Chemical Structure](#) | 439.94 | -0.38 | 6.0 ± 0.4 | 4.9 ± 0.7 | 815 ± 48 | 136 | 1243 ± 185 | 207 |
| 35 | JX21114 | ![Chemical Structure](#) | 440.93 | -1.30 | 45.9 ± 11.8 | 76.2 ± 9.9 | 3932 ± 537 | 86 | 1859 ± 12 | 41 |
|    |      |     |  |  |  |  |  |  |  |  |  |  |
|----|------|-----|---|---|---|---|---|---|---|---|---|---|
| 36 | JX21101 | ![Chemical Structure](image) | 439.94 | -0.35 | 3.5 ± 0.2 | 2.18 ± 0.02 | 651 ± 63 | 186 | 1159 ± 193 | 331 |
| 37 | JX21143 | ![Chemical Structure](image) | 440.93 | -1.46 | 7.9 ± 1.0 | 3.1 ± 0.3 | 388 ± 58 | 49 | 2907 ± 655 | 368 |
| 38 | JX21137 | ![Chemical Structure](image) | 440.93 | -1.55 | 7.0 ± 0.4 | 9.6 ± 0.5 | 1253 ± 190 | 179 | 1773 ± 28 | 254 |
| 39 | JX21138 | ![Chemical Structure](image) | 490.00 | 0.76 | 28.8 ± 18.5 | 21.2 ± 0.9 | 1308 ± 14 | 45 | 1994 ± 559 | 69 |
| 40 | JX21116 | ![Chemical Structure](image) | 465.98 | 0.26 | 21.7 ± 0.2 | 33.9 ± 0.3 | 2961 ± 152 | 137 | 2407 ± 118 | 111 |

*aResults are expressed as the mean ± SD of at least two independent experiments.*

*bSelectivity index for HepG2 is defined as IC₅₀ (HepG2)/IC₅₀ (3D7).*

*cSelectivity index for 293T is defined as IC₅₀ (293T)/IC₅₀ (3D7).*

cLogₚ was calculated from [www.molinspiration.com](http://www.molinspiration.com)
Supplementary Table S3. Activity of Quisinostat and JX21108 to inhibit human HDACs in vitro

| Entry | Comp.     | \( h\text{HDAC1} \) | \( h\text{HDAC2} \) | \( h\text{HDAC3} \) | \( h\text{HDAC8} \) | \( h\text{HDAC6} \) | \( h\text{Sirt2} \) |
|-------|-----------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| 1     | Quisinostat | 0.46                 | 1.1                  | 2.1                  | 9.2                  | 35                   | >10000               |
| 2     | JX21108    | 1.8                  | 4.6                  | 19                   | 62                   | 66                   | >10000               |
**Supplementary Table S4. Primers used in this study**

| Primer name | Sequence |
|-------------|----------|
| **Primers used in gene Knock down (5' to 3')** | |
| P1          | GCGGCCCTAGTCTAGGGCGCGCCGTGGAATATAACAAATTTTCTTGAATATAT | |
| P2          | GCGGCCCGCGCTAGCATTCCAGAAATTATGAATTCCGAATTC | |
| P3          | GCTAGCGCGGGCGCCGCTAACCAAAATTATTAAGCATCAAAAA | |
| P4          | TTTTTTTACAAAAATGCTTAAGGTTAAAAGAAAAATGATGTAATAAAAAC | |
| P5          | GCGGCCCTAGTCTAGGGCGCGCCGCTAATACCTTTTTAACTGTTCTAGGGTG | |
| P6          | GCGGCCGCGCTAGCATAATTGATTAGATCTCTGTTCAGATAA | |
| P7          | GCTAGCGCGCGCGCGTGGAAAAATATATAACCAATGTTG | |
| P8          | TTTTTTTACAAAAATGCTTAAGGTTTCTTACCTTGGGAACATATATT | |
| P9          | ATAAATTTCTGGAATGCTAGCGGAAAGTTGTTCCAGGTGGA | |
| P10         | TTAAATTTCTGGAATGCTAGCGGCTTACTTGTCACTCGTCACTTTG | |
| P11         | ATAAATTTCTGGAATGCTAGCGCTCTGCGGCAACGCGAGC | |
| P12         | TTAAATTTCTGGAATGCTAGCGCTTCTCCTACATGTTTTTTG | |
| P13         | TCTATTTGTACCATATGCTAGCGGAAGTTGTTCCAGGTGGA | |
|   | Primer Sequence |
|---|----------------|
| P14 | TATATATTTTCCACGCGCCGCTTTACTTGTCATCGTCATCCTTGT |
| P15 | TCTATTGTACCATATGCTAGCGGCTCTGGCAGCGGCAGC |
| P16 | TATATATTTTCCACGCGATGCCTCCCCCTCCTACATGTTTTTG |
| P17 | ATAAATATGTCTGAACGTTATTTC |
| P18 | AAATTATAAAGAATATTAAAACGAATCGC |
| P19 | ATCGATTGGGTAGATTTAATTTAAC |
| P20 | TTATTTATTTACCAACTCAGATGC |
| P21 | TAAGTATATAATTATATTATAATTTCTGGAATTGTAGAGCTAGAA |
| P22 | TAAGTATATAATTATTTTTTTAGATTTATCTGACAGTTTTAGAGCTAGAA |

**Primers used in RT-qPCR (5’ to 3’)**

| Primer      | Sequence               |
|-------------|------------------------|
| PfHDA1-FW   | GTATGAAACCTAAAACACCTAC |
| PfHDA1-RV   | AATCGTAAAGATTTGATTGC   |
| PfHDAC1-FW  | CAAAGGAACATTCAACCACAC |
| PfHDAC1-RV  | GGTACAATAGATTGATCCCTG |
### The list of genes in Infection term

| ID          | Symbol | Description                                      | function |
|-------------|--------|--------------------------------------------------|----------|
| PF3D7_1371600 | EBL1   | "erythrocyte binding like protein 1, pseudogene" | invasion |
| PF3D7_0102500 | EBA181 | erythrocyte binding antigen-181                  | invasion |
| PF3D7_1301600 | EBA140 | erythrocyte binding antigen-140                  | invasion |
| PF3D7_0731500 | EBA175 | erythrocyte binding antigen-175                  | invasion |
| PF3D7_0424300 | EBA165 | "erythrocyte binding antigen-165, pseudogene"    | invasion |
| PF3D7_1335300 | RH2b   | reticulocyte binding protein 2 homologue b        | invasion |
| PF3D7_1252400 | RH3    | "reticulocyte binding protein homologue 3, pseudogene" | invasion |
| PF3D7_1335400 | RH2a   | reticulocyte binding protein 2 homologue a        | invasion |
| PF3D7_0424200 | RH4    | reticulocyte binding protein homologue 4          | invasion |
| PF3D7_1335200 | RH6    | "reticulocyte binding protein homologue 6, pseudogene" | invasion |
| PF3D7_0424100 | RH5    | reticulocyte binding protein homologue 5          | invasion |
| PF3D7_1335100 | RH1    | reticulocyte binding protein homologue 1          | invasion |
| PF3D7_1335000 | MSP6   | merozoite surface protein 6                      | invasion |
| PF3D7_1035700 | DBLMSp | duffy binding-like merozoite surface protein      | invasion |
| PF3D7_1036300 | DBLMSp2| duffy binding-like merozoite surface protein 2    | invasion |
| PF3D7_1035400 | MSP3   | merozoite surface protein 3                      | invasion |
| PF3D7_0502400 | MSP8   | merozoite surface protein 8                      | invasion |
| PF3D7_1036000 | MSP11  | merozoite surface protein                         | invasion |
| PF3D7_0620400 | MSP10  | merozoite surface protein 10                     | invasion |
| PF3D7_1335100 | MSP7   | merozoite surface protein 7                      | invasion |
| PF3D7_0930300 | MSP1   | merozoite surface protein 1                       | invasion |
| PF3D7_0206900 | MSP5   | merozoite surface protein 5                       | invasion |
| PF3D7_0207000 | MSP4   | merozoite surface protein 4                       | invasion |
| PF3D7_0206800 | MSP2   | merozoite surface protein 2                       | invasion |
| PF3D7_1228600 | MSP9   | merozoite surface protein 9                       | invasion |
| PF3D7_0613900 | myoE   | "myosin E, putative"                              | invasion |
| PF3D7_1229800 | MyoD   | myosin D                                         | invasion |
| PF3D7_0503600 | MyoB   | myosin B                                         | invasion |
| PF3D7_1342600 | MyoA   | myosin A                                         | invasion |
| PF3D7_1329100 | MyoC   | myosin C                                         | invasion |
| PF3D7_1140500 | MyoF   | "myosin F, putative"                             | invasion |
| PF3D7_1246400 | MTIP   | myosin A tail domain interacting protein          | invasion |
| PF3D7_1361800 | GAC    | glideosome-associated                            | invasion |
| PF3D7_1222700 | GAP45  | glideosome-associated protein                     | invasion |
| PF3D7_0722200 | RALP1  | rhoptry-associated leucine zipper-like protein 1  | invasion |
| PF3D7_0707300 | RAMA   | rhoptry-associated membrane antigen               | invasion |
| PF3D7_0214900 | RON6   | rhoptry neck protein 6                            | invasion |
| PF3D7_0414900 | ARO    | armadillo-domain containing rhoptry protein       | invasion |
| PF3D7_0613300 | ROP14  | rhoptry protein ROP14                            | invasion |
| Accession | Name | Description | Invasion | Egress |
|-----------|------|-------------|---------|--------|
| PF3D7_1452000 | RON2 | rhoptry neck protein 2 | invasion | |
| PF3D7_1116000 | RON4 | rhoptry neck protein 4 | invasion | |
| PF3D7_0817700 | RON5 | rhoptry neck protein 5 | invasion | |
| PF3D7_1252100 | RON3 | rhoptry neck protein 3 | invasion | |
| PF3D7_1012200 | RA | rhoptry associated adhesin | invasion | |
| PF3D7_1410400 | RAP1 | rhoptry-associated protein 1 | invasion | |
| PF3D7_1017100 | RON12 | rhoptry neck protein 12 | invasion | |
| PF3D7_0905400 | RhopH3 | high molecular weight rhoptry protein 3 | invasion | |
| PF3D7_0929400 | RhopH2 | high molecular weight rhoptry protein 2 | invasion | |
| PF3D7_0501600 | RAP2 | rhoptry-associated protein 2 | invasion | |
| PF3D7_0511600 | ARNP | apical rhoptry neck protein | invasion | |
| PF3D7_0501500 | RAP3 | rhoptry-associated protein 3 | invasion | |
| PF3D7_1466900 | N/A | "rhoptry protein, putative" | invasion | |
| PF3D7_1366400 | RHOP148 | rhoptry protein RHOP148 | invasion | |
| PF3D7_1133400 | AMA1 | apical membrane antigen 1 | invasion | |
| PF3D7_0828800 | GAMA | GPI-anchored micronemal | invasion | |
| PF3D7_0316000 | MA | microneme associated antigen | invasion | |
| PF3D7_1030200 | CLAMP | "claudin-like apicomplexan microneme protein, putative" | invasion | |
| PF3D7_0404700 | DPAP3 | dipeptidyl aminopeptidase 3 | invasion | |
| PF3D7_0423400 | AARP | apical asparagine-rich protein AARP | invasion | |
| PF3D7_1431400 | SRA | "conserved Plasmodium protein, unknown function" | invasion | |
| PF3D7_1238900 | pk2 | protein kinase 2 | invasion | |
| PF3D7_0528400 | DHHC3 | palmitoyltransferase DHHC7 | invasion | |
| PF3D7_1337800 | CDPK5 | calcium-dependent protein kinase 5 | egeress | |
| PF3D7_0217500 | CDPK1 | calcium-dependent protein kinase 1 | egeress | |
| PF3D7_1136900 | SUB2 | subtilisin-like protease 2 | egeress | |
| PF3D7_0507500 | SUB1 | subtilisin-like protease 1 | egeress | |
| PF3D7_1028700 | MTRAP | merozoite TRAP-like protein | egeress | |
| PF3D7_1436600 | PKG | cGMP-dependent protein kinase | egeress | |
| PF3D7_0808200 | plasmepsin X | plasmepsin X | egeress | |
### Quality control information of RNAseq

| sample name                        | raw reads | paired reads | aligned concordantly exactly 1 time | aligned concordantly >1 times |
|------------------------------------|-----------|--------------|-------------------------------------|------------------------------|
| 3D7-DMSO-Schizont-rep1             | 24655275  | 24652825     | 20702280                            | 608339                       |
| 3D7-DMSO-Schizont-rep2             | 21919048  | 21971719     | 18574575                            | 451470                       |
| 3D7HDAC1-glms-Glcn-Schizont-rep1   | 27320353  | 27319574     | 24820322                            | 732113                       |
| 3D7HDAC1-glms-Glcn-Schizont-rep2   | 20832241  | 20831010     | 18054228                            | 524288                       |
| 3D7HDAC1-Ty1-Glcn-Schizont-rep1    | 27310681  | 27309879     | 24964200                            | 839321                       |
| 3D7HDAC1-Ty1-Glcn-Schizont-rep2    | 20676886  | 20677064     | 17548123                            | 599342                       |
| 3D7-JX21108-Schizont-rep1          | 23735453  | 23733167     | 20005169                            | 438247                       |
| 3D7-JX21108-Schizont-rep2          | 24727153  | 24726161     | 20722269                            | 457626                       |

**Supplementary Table S6. Quality control information of RNAseq**
Supplementary Materials and Methods

Chemical Synthesis and analytical data

Abbreviation

| Abbreviation | Definition |
|--------------|------------|
| Ac           | acetyl     |
| Boc          | t-butoxycarbonyl |
| calcd.       | calculated |
| Chz          | benzyloxy carbonyl |
| DCM          | dichloromethane |
| DCE          | dichloroethane |
| DIPEA        | N,N-diisopropylethylamine |
| DMF          | N,N-dimethylformamide |
| DMSO         | dimethylsulfoxide |
| EDCI         | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride |
| EA           | ethyl acetate |
| Et           | ethyl       |
| ESI          | electrospray ionization |
| h            | hour        |
| HOBt         | 1-Hydroxybenzotriazole |
| HRMS         | high-resolution mass spectra |
| Me           | methyl      |
| min          | minute      |
| NMR          | nuclear magnetic resonance |
| PE           | petroleum ether |
| rt           | room temperature |
| TEA          | triethylamine |
| THF          | tetrahydrofuran |
| THP          | 2-tetrahydropyranyl |
| TLC          | thin-layer chromatography |

Chemical Synthesis

JL01 sample was purchased from WuXi AppTec. Unless otherwise noted, reagents and solvents were purchased from commercial suppliers and were directly used without further purification. Flash column chromatography was performed using HSGF 254 (150–200 μm thickness; Yantai Huiyou Co., China). Analytical thin-layer chromatography (TLC) was performed using HSGF 254 (150–200 μm thickness; Yantai Huiyou Co., China), and spots were visualized with UV light, iodine, and potassium permanganate staining. Reaction conditions were not optimized. Chiral column chromatography was conducted in Daicel Chiral Technologies (China) CO. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker AMX-400 NMR (IS as TMS). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). High-resolution mass spectra (HRMS) was obtained by electrospray ionization (ESI) using a Waters GCT Premie and Waters LCT. HPLC
analysis was performed on Agilent 1100 with quaternary pump and diode-array detector (DAD), using Agilent Exlipse XDB-C18 (250×4.6 mm, 5 µm particle size) column. Eluent was MeOH/aq. H3PO4 (0.1%, 90/10), flow rate was 0.5 ml/min, and peak purity was checked with UV spectra. Optical activity of enantiopure compound was measured via Rudolph Research Analytical AUTOPOL V automatic polarimeter.

**Synthesis of linker derivatives**

Generally, preparation of linker derivatives is based on the synthetic procedure of **JL01** using corresponding **H-L-Boc** as starting material. H-L-Boc were purchased from commercial suppliers.

**Scheme 1.** Reagents and conditions: (a) ethyl 2-chloropyrimidine-5-carboxylate, DIPEA, DCM, rt, 3-6 h; (b) HCl/1, 4-dioxane (4 M), DCM, rt, 2-5 h; (c) 1-methyl-3-formyliindole, NaBH(OAc)₃, HOAc, DCE, rt, 12 h; (d) NaOH, THF, H₂O, reflux; (e) THPONH₂, EDCI, HOBr, TEA, DMF, rt, 72 h; (f) HCl/1, 4-dioxane (4 M), DCM, rt, 30 min. In the substrate **H-L-Boc** the right-side nitrogen atom of L link to Boc group.
General synthetic method of compounds JX21002-JX21022

General synthesis of S-1:

To a mixture of corresponding H-L-Boc (1 g) and ethyl 2-chloropyrimidine-5-carboxylate (1.2 eq.) in DCM (0.2 M for H-L-Boc) was added DIPEA (1.5 eq.) in one portion at 0 °C under N₂. The mixture was stirred at rt for 3 h. TLC (PE/EA = 2/1) showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by flash column chromatography (SiO₂, PE/EA) to get compound S-1.

General synthesis of S-2:

To a solution of compound S-1 (1 eq) in DCM (0.5 M) was added HCl/1, 4-dioxane (4 M, 6 eq.). The mixture was stirred at rt for 2 h. TLC (PE/EA = 2/1) showed the reaction was complete. The solvent was removed in vacuo. The reaction mixture was washed with saturated NaHCO₃ and filtered. The resulted precipitate was wash with H₂O for 3 times, dried in vacuo to get deprotected mixture which was used directly in the next steps without purification.

To the mixture of deprotected mixture (considered as 1 eq.), N-methyl-3-formylindole (1.2 eq.) was added DCE (0.2 M) and HOAc (2 eq.) under N₂. The mixture was stirred at rt for 30 min. NaBH(OAc)₃ (1.5 eq.) was then added and the mixture stirred for 12 h. TLC (DCM/MeOH = 9/1) showed the reaction was complete. The reaction mixture was quenched by addition saturated aqueous NaHCO₃, and then the reaction mixture was diluted with H₂O and extracted three times with DCM. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, DCM/MeOH) to get compound S-2.

General synthesis of S-3:

To a solution of compound S-2 (1 eq.) in THF (0.1 M) was added aqueous NaOH (1M, 10 eq.). The mixture was stirred at reflux until TLC (DCM/MeOH = 9/1) showed the reaction was complete. The mixture was then acidified to pH = 2–3 with 2 M HCl, causing a solid to precipitate. This solid was collected, washed with large amount of H₂O to pH = ca.7 and dried to get hydrolyzed mixture which was used directly in the next steps without purification.

To the hydrolyzed mixture (considered as 1 eq.) was stirred with EDCI (3 eq.) and HOBT (3 eq.) in DMF (0.2 M) at rt under a nitrogen atmosphere for 30 min. THPONH₂ (5 eq.) was then added followed by TEA (5 eq.) and the mixture allowed to stirred at rt for 72 h. TLC (DCM/MeOH = 9/1) showed the reaction was complete. The mixture was then diluted with H₂O and extracted three times with DCM. The combined organic layers were wash twice with H₂O, once with brine, dried (Na₂SO₄), and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO₂, DCM/MeOH) to get...
compound S-3.

General synthesis of compounds JX21002-JX21022

To a solution of compound S-3 (1 eq.) in DCM (0.1 M) was added HCl/dioxane (4 M, 2.5 eq.). The mixture was stirred at rt for 30 min under a nitrogen atmosphere. TLC showed the reaction was complete. The reaction mixture was filtered and the resulted precipitate was wash with large amount of DCM and ether, dried in vacuo to get compound.

\[
N\text{-Hydroxy-2-}(5\text{-}(1\text{-methyl-1H-indol-3-yl})\text{methyl})\text{hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl}\text{pyrimidine-5-carboxamide hydrochloride (JX21002)}
\]

Compound JX21002 was synthesized according to the above general synthetic method. 112 mg (5.5% yield from H-L-Boc); \[^1^H\text{NMR (400 MHz, DMSO-}d_6\text{)} \delta 11.19 \text{ (m, 1H), 8.71 (m, 2H), 7.85 (t, } J=7.8 \text{ Hz, 1H), 7.51–7.43 (m, 1H), 7.22 (q, } J=7.6 \text{ Hz, 1H), 7.13 (dt, } J=11.5, 7.5 \text{ Hz, 1H), 4.52 (m, 2H), 3.81 (m Hz, 4H), 3.75 (m, 1H), 3.70–3.53 (m, 3H), 3.41 (m, 2H), 3.25 (m, 1H), 3.09 (m, 1H), 3.01 (m, 1H); HRMS (ESI) m/z calcd. for C\(_{21}\)H\(_{23}\)N\(_6\)O\(_2\) [M-H]\(^+\) 391.1882, found 391.1884; Purity: 97% (254 nm, RT = 4.066 min)

\[
N\text{-Hydroxy-2-}(4\text{-}(1\text{-methyl-1H-indol-3-yl})\text{methyl})\text{piperazin-1-yl}\text{pyrimidine-5-carboxamide hydrochloride (JX21003)}
\]

Compound JX21003 was synthesized according to the above general synthetic method. 101 mg (4.7% yield from H-L-Boc); \[^1^H\text{NMR (400 MHz, DMSO-}d_6\text{)} \delta 11.19 \text{ (s, 1H), 10.47–10.35 (m, 1H), 9.08 (s, 1H), 8.74 (s, 2H), 7.81 (d, } J=7.9 \text{ Hz, 1H), 7.60 (s, 1H), 7.51 (d, } J=8.2 \text{ Hz, 1H), 7.24 (t, } J=7.6 \text{ Hz, 1H), 7.16 (t, } J=7.4 \text{ Hz, 1H), 4.80 (m, 2H), 4.49 (m, 2H), 3.84 (s, 3H), 3.50 (m, 2H), 3.33 (m, 2H), 3.10 (m, 2H); HRMS (ESI) m/z calcd. for C\(_{19}\)H\(_{23}\)N\(_6\)O\(_2\) [M+H]\(^+\) 367.1882, found 367.1883; Purity: 99% (254 nm, RT = 4.017 min).
Compound **JX21004** was synthesized according to the above general synthetic method. 103 mg (4.9% yield from H-L-Boc); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.32 (m, 1H), 8.71 (s, 2H), 7.81 (d, $J$=7.9 Hz, 1H), 7.63 (s, 1H), 7.48 (d, $J$=8.2 Hz, 1H), 7.22 (t, $J$=7.6 Hz, 1H), 7.13 (t, $J$=7.4 Hz, 1H), 4.79 (m, 2H), 4.32 (m, 2H), 3.81 (s, 3H), 3.40–3.00 (m, 1H), 2.99 (m, 2H), 2.38–2.14 (m, 2H), 1.63 (m, 2H); HRMS (ESI) m/z calcd. for C$_{20}$H$_{25}$N$_6$O$_2$ [M+H]$^+$ 381.203, found 381.2038; Purity: 98% (254 nm, RT = 4.055 min).

**N-Hydroxy-2-(4-(((1-methyl-1H-indol-3-yl)methyl)amino)piperidin-1-yl)pyrimidine-5-carboxamide hydrochloride (JX21005)**

Compound **JX21005** was synthesized according to the above general synthetic method. 110 mg (5.5% yield from H-L-Boc); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.63 (s, 1H), 8.74 (s, 2H), 7.81 (d, $J$=7.9 Hz, 1H), 7.71 (s, 1H), 7.50 (d, $J$=8.2 Hz, 1H), 7.23 (t, $J$=7.6 Hz, 1H), 7.14 (t, $J$=7.4 Hz, 1H), 4.89 (m, 2H), 4.57 (m, 1H), 4.38 (m, 1H), 3.83 (s, 3H), 3.57 (m, 1H), 2.94 (m, 2H), 2.61 (m, 3H), 2.35 (m, 1H), 2.24 (m, 1H), 1.77 (m, 2H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 395.219, found 395.2194; Purity: 99% (254 nm, RT = 3.978 min).

**N-Hydroxy-2-(methyl(((1-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)amino)pyrimidine-5-carboxamide hydrochloride (JX21006)**

Compound **JX21006** was synthesized according to the above general synthetic method. 108 mg (5.4% yield from H-L-Boc); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.13 (s, 1H), 10.27 (s, 1H), 8.69 (s, 2H), 7.83 (d, $J$=7.9 Hz, 1H), 7.61 (s, 1H), 7.51 (d, $J$=8.2 Hz, 1H), 7.24 (t, $J$=7.5 Hz, 1H), 7.16 (t, $J$=7.4 Hz, 1H), 4.87 (m, 1H), 4.44 (m, 2H), 3.84 (s, 3H), 3.57 – 3.45 (m, 3H), 3.24 – 3.11 (m, 2H), 2.99 (s, 3H), 2.17 (m, 2H), 1.79 (m, 2H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 395.2195, found 395.2196; Purity: 99% (254 nm, RT = 4.049 min).
N-hydroxy-2-(((1-(1-methyl-1H-indol-3-yl)methyl)piperidin-4-yl)methyl)amino)pyrimidine-5-carboxamide hydrochloride (JX21008)

Compound JX21008 was synthesized according to the above general synthetic method. 116 mg (5.8% yield from H-L-Boc); 1H NMR (400 MHz, DMSO-d6) δ 10.06 (s, 1H), 8.76–8.33 (m, 2H), 7.91–7.75 (m, 1H), 7.60 (m, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.22 (t, J=7.5 Hz, 1H), 7.13 (t, J=7.3 Hz, 1H), 4.38 (m, 2H), 3.83 (s, 3H), 3.41 (m, 2H), 3.20 (m, 2H), 2.97 (m, 1H), 2.88 (m, 2H), 1.81 (m, 3H), 1.48 (m, 2H); HRMS (ESI) m/z calcd. for C21H27N6O2 [M+H]+ 395.2195, found 395.2194; Purity: 99% (254 nm, RT = 4.004 min)

N-Hydroxy-2-((9-(1-methyl-1H-indol-3-yl)methyl)-3,9-diazaspiro[5.5]undecan-3-yl)pyrimidine-5-carboxamide hydrochloride (JX21010)

Compound JX21010 was synthesized according to the above general synthetic method. 123 mg (6.6% yield from H-L-Boc); 1H NMR (400 MHz, DMSO-d6) δ 10.24 (s, 1H), 8.67 (s, 2H), 7.86 (d, J=7.9 Hz, 1H), 7.62 (s, 1H), 7.50 (d, J=8.2 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.15 (t, J=7.4 Hz, 1H), 4.44 (m, 2H), 3.82 (s, 3H), 3.23 (m, 2H), 3.12 (m, 2H), 1.87 (m, 2H), 1.76–1.62 (m, 4H), 1.35 (m, 2H); HRMS (ESI) m/z calcd. for C24H31N6O2 [M+H]+ 435.2508, found 435.2507; Purity: 99% (254 nm, RT = 4.068 min)

N-Hydroxy-2-((7-(1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21011)

Compound JX21011 was synthesized according to the above general synthetic method. 129 mg (6.6% yield from H-L-Boc); 1H NMR (400 MHz, DMSO-d6) δ 11.11 (m 1H), 8.69 (m, 2H), 7.86 (d, J=8.0 Hz, 1H), 7.65 (s, 1H), 7.49 (d, J=8.2 Hz, 1H), 7.22 (td, J=7.7, 3.1 Hz, 1H), 7.14 (q, J=7.4 Hz, 1H), 4.52 (m, 2H), 3.82 (s, 3H), 3.67–3.39 (m, 6H), 3.33 (m, 1H), 3.23 (m, 1H), 2.05 (m, 4H); 13C NMR (151 MHz, DMSO) δ 161.93, 161.88, 159.84, 159.80, 157.07, 156.80, 136.40, 136.37, 132.32, 132.29, 127.45, 127.41, 121.78, 121.75, 119.68, 119.64, 118.87, 118.83, 114.40, 110.12, 103.13, 103.10, 66.36, 59.52, 59.03, 56.57, 56.15, 51.84, 51.80, 48.11, 47.96, 47.16, 47.13, 45.75, 45.69, 45.56, 35.21, 33.80, 33.44, 32.71; HRMS (ESI) m/z calcd. for C22H27N6O2 [M+H]+ 407.2195, found 407.2196; Purity: 96% (254 nm, RT = 4.052 min).
**N-Hydroxy-2-(7-((1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21013)**

Compound JX21013 was synthesized according to the above general synthetic method. 132 mg (6.7% yield from **H-L-Boc**); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.65 (s, 1H), 8.68 (s, 2H), 7.86 (d, $J$=7.9 Hz, 1H), 7.64 (s, 1H), 7.50 (d, $J$=8.2 Hz, 1H), 7.23 (t, $J$=7.6 Hz, 1H), 7.14 (t, $J$=7.4 Hz, 1H), 4.41 (m, 2H), 3.93 (s, 2H), 3.83 (s, 5H), 3.3 (m, 2H), 3.01 (m, 2H), 2.20–1.98 (m, 4H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 407.2195, found 407.2200; Purity: 99% (254 nm, RT = 3.995 min).

**N-Hydroxy-2-((1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21014)**

Compound JX21014 was synthesized according to the above general synthetic method. 135 mg (6.9% yield from **H-L-Boc**); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.20 (m, 1H), 8.68 (s, 2H), 7.89 (d, $J$=7.9 Hz, 1H), 7.66 (s, 1H), 7.48 (d, $J$=8.2 Hz, 1H), 7.22 (t, $J$=7.6 Hz, 1H), 7.13 (t, $J$=7.4 Hz, 1H), 4.53 (m, 2H), 3.95–3.77 (m, 10H), 3.72 (m, 2H), 1.90 (m, 2H), 1.79 (m, 2H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 407.2195, found 407.2196; Purity: 97% (254 nm, RT = 4.039 min).

**N-Hydroxy-2-((1-methyl-1H-indol-3-yl)methyl)-2,9-diazaspiro[5.5]undecan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21017)**

Compound JX21017 was synthesized according to the above general synthetic method. 113 mg (6.1% yield from **H-L-Boc**); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.81–10.63 (m, 1H), 8.66 (m, 2H), 7.89 (dd, $J$=13.6, 7.9 Hz, 1H), 7.66 (d, $J$=8.6 Hz, 1H), 7.49 (dd, $J$=12.0, 8.2 Hz, 1H), 7.27–7.19 (m, 1H), 7.14 (dt, $J$=15.4, 7.5 Hz, 1H), 4.44 (m, 2H), 3.82 (m, 6H), 3.61 (s, 1H), 3.20 (m, 3H), 3.06 (m, 1H), 1.80–1.49 (m, 8H), 1.44 (m, 1H). HRMS (ESI) m/z calcd. for C$_{24}$H$_{31}$N$_6$O$_2$ [M+H]$^+$ 435.2508, found 435.2509. Purity: 99% (254 nm, RT = 4.031 min).
N-Hydroxy-2-((1-methyl-1H-indol-3-yl)methyl)-1,8-diazaspiro[4.5]decan-1-yl)pyrimidine-5-carboxamide hydrochloride (JX21019)

Compound JX21019 was synthesized according to the above general synthetic method. 98 mg (5.2% yield from H-L-Boc); 1H NMR (400 MHz, DMSO-d$_6$) δ 10.12 (s, 1H), 8.71 (s, 2H), 7.90 (m, 1H), 7.73 (m, 1H), 7.51 (dd, J=8.5, 5.1 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.15 (t, J=7.5 Hz, 1H), 4.62 (m, 2H), 3.85 (s, 3H), 3.63 (m, 2H), 3.43–3.18 (m, 6H), 2.16 (m, 2H), 1.86 (m, 2H), 1.53 (m, 2H); HRMS (ESI) m/z calcd. for C$_{23}$H$_{29}$N$_6$O$_2$ [M+H]$^+$ 421.2352, found 421.2354; Purity: 99% (254 nm, RT = 4.059 min).

N-Hydroxy-2-(((1R,4R)-4-(((1-methyl-1H-indol-3-yl)methyl)amino)cyclohexyl)amino)pyrimidine-5-carboxamide hydrochloride (JX21022)

Compound JX21022 was synthesized according to the above general synthetic method. 126 mg (6.3% yield from H-L-Boc); 1H NMR (400 MHz, DMSO-d$_6$) δ 9.22 (s, 1H), 8.67 (s, 2H), 8.10–7.96 (m, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.63 (s, 1H), 7.48 (d, J=8.2 Hz, 1H), 7.22 (t, J=7.6 Hz, 1H), 7.13 (t, J=7.5 Hz, 1H), 4.30 (m, 2H), 3.82 (m, 4H), 3.10–2.96 (m, 1H), 2.25 (m, 2H), 2.08–1.93 (m, 2H), 1.62 (m, 2H), 1.40–1.26 (m, 2H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 395.2195, found 395.2196; Purity: 96% (254 nm, RT = 4.129 min).
2. Synthesis of R derivatives

Scheme 2. Synthesis of R derivatives. *Reagents and conditions: (a) ethyl 2-chloropyrimidine-5-carboxylate, DIPEA, DCM, rt, 6 h; (b) HCl/1, 4-dioxane (4 M), DCM, rt, 0.5 h; (c) Cbz-Cl, DIPEA, DCM, rt, 6 h; (d) K₂CO₃, MeOH, H₂O, 65 °C, 12 h; (e) THPONH₂, EDCI, HOBT, TEA, DMF, rt, 72 h; (f) Et₃SiH, Pd/C, MeOH, DCM, rt, 2 h; (g) R-CHO, NaBH₃(CN), MeOH, rt, 24 h; (h) HCl/1, 4-dioxane 1, 4-dioxane(4 M), DCM, rt, 30 min.

General synthetic method of compounds JX21101-JX21143

Synthesis of S-1-011

To a mixture of H-L-Boc-011 (6 g, 26.5 mmol) and ethyl 2-chloropyrimidine-5-carboxylate (5.9 g, 32 mmol 1.2 eq.) in DCM (130 mL, 0.2 M for H-L-Boc) was added DIPEA (6.6 mL, 40 mmol, 1.5 eq.) in one portion at 0 °C under N₂. The mixture was stirred at rt for 6 h. TLC (PE/EA = 2/1) showed the
reaction was complete. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was purified by flash column chromatography (SiO$_2$, PE/EA) to get compound S-1-011 (9.7 g, 98% yield).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.87 (m, 2H), 4.35 (q, $J=7.1$ Hz, 1H), 3.87–3.24 (m, 8H), 1.98 (m, 4H), 1.46 (s, 9H), 1.37 (t, $J=7.1$ Hz, 3H).

Synthesis of S-4

To a solution of compound S-1-011 (9.5 g, 25.4 mmol) in DCM (51 mL, 0.5 M) was added HCl/1, 4-dioxane (4 M, 64 mL, 256 mmol, 10 eq.). The mixture was stirred at rt for 0.5 h. TLC (PE/EA = 2/1) showed the reaction was complete. The solvent was removed in vacuo. To the resultant mixture was added DCM (130 mL, 0.2 M), DIPEA (12.6 mL, 76.2 mmol, 3 eq.), then Cbz-Cl (4.4 mL, 30.8 mmol, 1.2 eq.) was added slowly to the mixture. The mixture was stirred at rt for 6 h. TLC (PE/EA = 2/1) showed the reaction was complete. The reaction mixture was poured into saturated NaHCO$_3$ and the aqueous phase was extracted three times with DCM (300 mL in total). The combined organic layers was washed once with brine, dried (Na$_2$SO$_4$), and the solvent was removed in vacuo. The residue was purified by flash column chromatography (SiO$_2$, PE/EA) to get compound S-4 (10 g, 96% yield).

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.86 (m, 2H), 7.35 (m, 5H), 5.14 (m, 2H), 4.34 (q, $J=7.1$ Hz, 2H), 3.83–3.62 (m, 3H), 3.57 (m, 3H), 3.50–3.36 (m, 2H), 2.11–1.87 (m, 4H), 1.37 (t, $J=7.1$ Hz, 3H).

Synthesis of S-5

To a mixture of S-4 (10 g, 24.5 mmol), and potassium carbonate (8.5 g, 61.5 mmol, 2.5 eq.) was added H$_2$O (60 mL) and MeOH (60 mL). The mixture was heated to 65 $^\circ$C for 18 h. TLC (PE/EA = 2/1) showed the reaction was complete. The reaction mixture was concentrated under reduced pressure to remove solvent. The mixture was then acidified to pH = 2–3 with 2 M HCl, causing a solid to precipitate. This solid was collected, washed with large amount of H$_2$O to pH = ca.7 and dried in vacuo. To the dried mixture was added HOBT (9.9 g, 73.5 mmol, 3 eq.), DCM (120 mL, 0.2 M) and stirred at rt under a nitrogen atmosphere until all the solid dissolved. EDCI (14 g, 73.5 mmol, 3 eq.) was added and stirred for 30 min. THPONH$_2$ (5.7 g, 49 mmol, 2 eq.) and TEA (6.8 mL, 49 mmol, 2 eq.) and the mixture was allowed to stirred at rt for 72 h. TLC (DCM/MeOH = 9/1) showed the reaction was complete. The mixture was then diluted with H$_2$O and extracted three times with DCM. The combined organic layers were wash twice with H$_2$O, once with brine, dried (Na$_2$SO$_4$), and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO$_2$, DCM/MeOH) to get compound S-5 (10.6 g, 90% yield).

$^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.52 (s, 1H), 8.68 (m, 2H), 7.54–7.16 (m, 5H), 5.07 (m, 2H), 4.96 (m, 1H), 4.20–3.93 (m, 1H), 3.63 (m, 2H), 3.58–3.40 (m, 5H), 3.34 (m, 3H), 1.93 (m, 4H), 1.72 (m, 3H), 1.55 (m, 3H).

Synthesis of S-6
S-5 (0.48 g 1 mmol) was dissolved into DCM (5 mL) and MeOH (5 mL). To the solvent was added 10% Pd/C (0.19 g, wetted with ca. 55% water) and Et₃SiH (96 μL, 0.6 mmol). The mixture was allowed to stirred at rt for 1 h, and Et₃SiH (96 μL, 0.6 mmol) was added to the mixture. After 1 h, the mixture was filter through celite, and the solid residure was washed with MeOH. The solvent was rotavaporied to dryness, and the residue was purified by column chromatography (SiO₂, DCM/MeOH) to get compound S-6 (0.29 g, 84% yield).

¹H NMR (400 MHz, DMSO-d₆) δ 8.73 (s, 2), 5.01 (m, 1H), 4.10 (m, 1H), 3.75–3.43 (m, 6H), 3.09 (m, 2H), 3.00–2.83 (m, 2H), 2.02 (m, 2H), 1.82 (m, 5H), 1.61 (m, 3H).

Synthesis of JX21101-JX21143

S-5 (0.48 g 1 mmol) was hydrogenated via Pd/C-Et₃SiH, and the crude residure was directly used without purification. To the crude mixture was add MeOH (10 mL), R-CHO (1.2 mmol), NaBH₃(CN) (5 mmol) and stirred for 24 h. The reaction mixture was poured into saturated NaHCO₃ and the aqueous phase was extracted three times with DCM (75 mL in total). The combined organic layers was washed once with brine, dried (Na₂SO₄), and the solvent was removed in vacuo. The residue was purified by flash column chromatography (SiO₂, DCM/MeOH) and the product was dissolved into DCM (0.05 M) under a nitrogen atmosphere and HCl/1, 4-dioxane (4 M, 2.4 eq.) was add in one portion. The mixture was stirred at rt for 30 min and TLC showed the reaction was complete. The reaction mixture was filtered and the resulted precipitate was wash with large amount of DCM and ether, dried in vacuo to get compound. Similarly treated with HCl/1, 4-dioxane solution in DCM, JX21131 was synthesized from S-5.

N-Hydroxy-2-(7-(naphthalen-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21101)

Compound JX21101 was synthesized according to the above general synthetic method.

190 mg (43% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 12.02–11.82 (m, 1H), 8.98–8.66 (m, 2H), 8.17 (s, 1H), 8.09–7.83 (m, 4H), 7.59 (m, 2H), 4.58 (m, 2H), 3.76 – 3.50 (m, 5H), 3.39 (m, 2H), 3.33–3.25 (m, 1H), 2.34–1.92 (m, 4H); HRMS (ESI) m/z calcd. for C₂₃H₂₆N₄O₂ [M+H]⁺ 404.2087, found 404.2084; Purity: 96% (254 nm, RT = 4.007 min).
2-(7-((6-Chloro-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21102)

Compound JX21102 was synthesized according to the above general synthetic method. 169 mg (35% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.47–11.08 (m, 1H), 8.69 (m, 2H), 7.90 (d, J=8.5 Hz, 1H), 7.69 (s, 1H), 7.63 (s, 1H), 7.15 (d, J=7.7 Hz, 1H), 4.50 (m, 2H), 3.81 (s, 3H), 3.57 (m, 5H), 3.42 (m, 1H), 3.31 (m, 1H), 3.21 (m, 1H), 2.06 (m, 4H); HRMS (ESI) m/z calcd. for C₂₂H₂₆ClN₆O₂ [M+H]+ 441.1806, found 441.1807; Purity: 97% (254 nm, RT = 4.095 min).

N-Hydroxy-2-(7-((5-methoxy-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21104)

Compound JX21104 was synthesized according to the above general synthetic method. 192 mg (41% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.36–10.93 (m, 2H), 8.68 (m, 2H), 7.57 (s, 1H), 7.43 (s, 1H), 7.37 (d, J=8.9 Hz, 1H), 6.89–6.81 (m, 1H), 4.49 (m, 2H), 3.81 (d, 3H), 3.78 (s, 3H), 3.64 (m, 1H), 3.60–3.47 (m, 4H), 3.42 (m, 1H), 3.32 (m, 1H), 2.05 (m, 4H); HRMS (ESI) m/z calcd. for C₂₃H₂₉N₆O₃ [M+H]+ 437.2301, found 437.2300; Purity: 99% (254 nm, RT = 4.064 min).

2-(7-Benzyl-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21105)

Compound JX21105 was synthesized according to the above general synthetic method. 192 mg (49% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.52–11.28 (m, 1H), 8.68 (m, 2H), 7.65 (m, 2H), 7.44 (m, 3H), 4.48–4.31 (m, 2H), 3.73–3.54 (m, 4H), 3.49 (m, 1H), 3.34 (m, 2H), 3.25–3.14 (m, 1H), 2.07 (m, 4H); HRMS (ESI) m/z calcd. for C₁₉H₁₅N₅O₂ [M+H]+ 354.1930, found 354.1932; Purity: 96% (254 nm, RT = 3.954 min).
2-(7-((6-Fluoro-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21106)

Compound JX21106 was synthesized according to the above general synthetic method. 171 mg (37% yield from S-5); 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.41 (m, 1H), 8.71 (d, 2H), 7.91 (dd, $J$=8.8, 5.3 Hz, 1H), 7.67 (s, 1H), 7.37 (d, $J$=9.8 Hz, 1H), 6.99 (q, $J$=8.0 Hz, 1H), 4.51 (m, 2H), 3.79 (s, 3H), 3.69–3.49 (m, 5H), 3.43 (m, 1H), 3.32 (m, 1H), 3.22 (m, 1H), 2.05 (m, 4H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{26}$FN$_6$O$_2$ [M+H]$^+$ 425.2101, found 425.2102; Purity: 96% (254 nm, RT = 4.074 min).

2-(7-((5-Cyano-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21108)

Compound JX21108 was synthesized according to the above general synthetic method. 205 mg (44% yield from S-5); 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.41–11.13 (m, 2H), 8.69 (m, 2H), 8.52 (s, 1H), 7.87 (s, 1H), 7.70 (d, $J$=8.5 Hz, 1H), 7.58 (d, $J$=8.5 Hz, 1H), 4.57 (m, 2H), 3.88 (s, 3H), 3.65 (m, 1H), 3.55 (m, 4H), 3.43 (m, 1H), 3.34 (m, 1H), 3.28–3.18 (m, 1H), 2.19–1.93 (m, 4H); 13C NMR (151 MHz, DMSO) $\delta$ 161.94, 161.88, 159.83, 159.80, 157.07, 156.77, 137.97, 134.92, 134.88, 127.14, 127.11, 125.18, 125.15, 124.36, 124.33, 120.53, 120.51, 114.40, 111.60, 104.75, 104.73, 101.75, 59.71, 59.19, 56.58, 56.23, 52.06, 52.03, 47.64, 47.49, 47.18, 47.14, 45.76, 45.71, 35.56, 35.26, 33.86, 33.47, 33.05; HRMS (ESI) m/z calcd. for C$_{23}$H$_{26}$N$_7$O$_2$ [M+H]$^+$ 432.2148, found 432.2149; Purity: 99% (254 nm, RT = 4.013 min).

2-(7-((2,3-Dihydrobenzofuran-5-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21109)

Compound JX21109 was synthesized according to the above general synthetic method. 138 mg (32% yield from S-5); 1H NMR (400 MHz, DMSO-d$_6$) $\delta$ 11.53–11.32 (m, 1H), 8.70 (m, 2H), 7.51 (s, 1H), 7.42–7.30 (m, 1H), 6.80 (d, $J$=8.1 Hz, 1H), 4.55 (t, $J$=8.7 Hz, 1H), 4.27 (m, 2H), 3.74–3.52 (m, 4H), 3.45 (m, 1H), 3.40–3.23 (m, 2H), 3.22–3.10 (m, 3H), 2.07 (m, 4H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{26}$N$_5$O$_3$ [M+H]$^+$ 396.2036, found 396.2035; Purity: 97% (254 nm, RT = 3.986 min).
**N-Hydroxy-2-(7-(thiophen-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21110)**

Compound JX21110 was synthesized according to the above general synthetic method.

130 mg (33% yield from S-5); \( ^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 11.65 (d, \( J=41.7 \) Hz, 1H), 8.70 (m, 2H), 7.67 (d, \( J=5.1 \) Hz, 1H), 7.44 (s, 1H), 7.12 (t, \( J=4.4 \) Hz, 1H), 4.62 (m, 2H), 3.70–3.46 (m, 5H), 3.41 (m, 1H), 3.31 (m, 1H), 3.22 (m, 1H), 2.23–1.92 (m, 4H); HRMS (ESI) m/z calcd. for \( \text{C}_{17}\text{H}_{22}\text{N}_{5}\text{O}_2\text{S} \ [\text{M+H}]^+ \) 360.1494, found 360.1495; Purity: 98% (254 nm, RT = 4.009 min).

**2-(7-(Furan-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21111)**

Compound JX21111 was synthesized according to the above general synthetic method.

128 mg (34% yield from S-5); \( ^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 11.52 (m, 1H), 8.70 (m, 2H), 7.80 (d, \( J=2.3 \) Hz, 1H), 6.74 (d, \( J=3.3 \) Hz, 1H), 6.61–6.52 (m, 1H), 4.46 (m, 2H), 3.69–3.40 (m, 6H), 3.30 (m, 1H), 3.25–3.16 (m, 1H), 2.20–1.92 (m, 4H); HRMS (ESI) m/z calcd. for \( \text{C}_{17}\text{H}_{22}\text{N}_{5}\text{O}_3 \ [\text{M+H}]^+ \) 344.1723, found 344.1724; Purity: 95% (254 nm, RT = 3.972 min).

**2-(7-(Cyclohexylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21112)**

Compound JX21112 was synthesized according to the above general synthetic method.

160 mg (40% yield from S-5); \( ^1\)H NMR (400 MHz, DMSO-\(d_6\)) \( \delta \) 10.80 (d, 1H), 8.70 (s, 2H), 3.81–3.51 (m, 5H), 3.29–2.94 (m, 3H), 2.06 (m, 3H), 1.89 (m, 1H), 1.81 (m, 1H), 1.76–1.56 (m, 3H), 1.22 (m, 4H), 0.94 (m, 2H); HRMS (ESI) m/z calcd. for \( \text{C}_{19}\text{H}_{30}\text{N}_{5}\text{O}_2 \ [\text{M+H}]^+ \) 360.2400, found 360.2401; Purity: 96% (254 nm, RT = 3.996 min).
2-(7-(Benzofuran-3-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21113)

Compound JX21113 was synthesized according to the above general synthetic method. 202 mg (47% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.93–11.59 (m, 1H), 8.71 (m, 2H), 8.32 (s, 1H), 8.03 (d, $J=7.5$ Hz, 1H), 7.65 (d, $J=7.9$ Hz, 1H), 7.37 (m, 2H), 4.58 (m, 2H), 3.80–3.46 (m, 6H), 3.39 (m, 1H), 3.32–3.20 (m, 1H), 2.31–1.89 (m, 4H). HRMS (ESI) m/z calcd. for C$_{21}$H$_{24}$N$_5$O$_3$ [M+H]$^+$ 394.1879, found 394.1880; Purity: 99% (254 nm, RT = 3.994 min).

N-Hydroxy-2-(7-(quinolin-4-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21114)

Compound JX21114 was synthesized according to the above general synthetic method. 185 mg (42% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.44–12.10 (m, 1H), 9.33 (m, 1H), 8.68 (m, 3H), 8.6–8.38 (m, 2H), 8.13 (t, $J=7.5$ Hz, 1H), 7.98 (t, $J=7.8$ Hz, 1H), 5.26 (m, 2H), 3.80–3.44 (m, 7H), 3.43–3.32 (m, 1H), 2.32–1.91 (m, 4H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{25}$N$_6$O$_2$ [M+H]$^+$ 405.2039, found 405.2040; Purity: 95% (254 nm, RT = 4.099 min).

2-(7-(Benzothiophen-3-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21115)

Compound JX21115 was synthesized according to the above general synthetic method. 189 mg (42% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.50 (m, 1H), 8.70 (m, 2H), 8.26 (d, $J=5.3$ Hz, 1H), 8.18 (d, $J=7.9$ Hz, 1H), 8.07 (d, $J=7.8$ Hz, 1H), 7.47 (m, 2H), 4.71 (m, 2H), 3.76–3.46 (m, 6H), 3.40 (m, 1H), 3.33–3.19 (m, 1H), 2.23–1.94 (m, 4H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{23}$N$_5$O$_3$S [M+H]$^+$ 410.1651, found 410.1652; Purity: 97% (254 nm, RT = 4.112 min).
2-(7-((1,1’-Biphenyl)-4-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21116)

Compound JX21116 was synthesized according to the above general synthetic method. 202 mg (43% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.70 (m, 1H), 8.70 (m, 2H), 7.84–7.66 (m, 6H), 7.49 (t, 2H), 7.39 (t, J = 7.3 Hz, 1H), 4.53–4.34 (m, 2H), 3.74–3.50 (m, 5H), 3.47–3.29 (m, 2H), 3.29–3.17 (m, 1H), 2.11 (m, 4H); HRMS (ESI) m/z calcd for C_{25}H_{28}N_{5}O_{2} [M+H]^+ 430.2243, found 430.2244; Purity: 99% (254 nm, RT = 3.970 min).

2-(7-(Benzo[3]furan-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21117)

Compound JX21117 was synthesized according to the above general synthetic method. 174 mg (40% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.87 (m, 1H), 8.70 (m, 2H), 7.72 (d, J = 7.7 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.23 (s, 1H), 4.77–4.60 (m, 2H), 3.61 (m, 6H), 3.42 (m, 1H), 3.32 (m, 1H), 2.09 (m, 4H); HRMS (ESI) m/z calcd for C_{21}H_{24}N_{5}O_{3} [M+H]^+ 394.1879, found 394.1880; Purity: 97% (254 nm, RT = 4.060 min).

2-(7-(Benzo[b]thiophen-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21118)

Compound JX21118 was synthesized according to the above general synthetic method. 184 mg (41% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 12.09–11.84 (m, 1H), 8.70 (m, 2H), 8.09–8.00 (m, 1H), 7.90 (m, 1H), 7.75 (s, 1H), 7.52–7.31 (m, 2H), 4.82–4.63 (m, 2H), 3.71–3.55 (m, 5H), 3.49 (m, 1H), 3.38 (m, 1H), 3.28 (m, 1H), 2.10 (m, 4H); HRMS (ESI) m/z calcd. for C_{21}H_{24}N_{5}O_{2}S [M+H]^+ 410.1651, found 410.1652; Purity: 96% (254 nm, RT = 4.009 min).
N-Hydroxy-2-(7-(pyridin-3-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21119)

![Chemical structure image]

Compound JX21119 was synthesized according to the above general synthetic method. 176 mg (45% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 12.23 (m, 1H), 9.15 (s, 1H), 8.93 (d, J=5.5 Hz, 1H), 8.78 (m, 1H), 8.69 (m, 2H), 8.02 (t, J=6.9 Hz, 1H), 4.63 (m, 2H), 3.77–3.52 (m, 5H), 3.49–3.19 (m, 3H), 2.09 (m, 4H); HRMS (ESI) m/z calcd for C18H23N6O2 [M+H]+ 355.1882, found 355.1885; Purity: 97% (254 nm, RT = 4.072 min).

N-Hydroxy-2-(7-(thiophen-3-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21120)

![Chemical structure image]

Compound JX21120 was synthesized according to the above general synthetic method. 146 mg (37% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.76 (m, 1H), 8.71 (m, 2H), 7.82 (d, J=3.0 Hz, 1H), 7.63 (dd, J=5.0, 3.0 Hz, 0H), 7.44 (t, J=5.0 Hz, 1H), 4.45–4.32 (m, 2H), 3.70–3.54 (m, 4H), 3.47 (m, 1H), 3.36 (m, 1H), 3.27 (m, 1H), 3.18 (m, 1H), 2.23–1.93 (m, 4H); 1HRMS (ESI) m/z calcd for C17H22N6O2S [M+H]+ 360.1494, found 360.1495; Purity: 95% (254 nm, RT = 3.996 min).

2-(7-(Cyclopentylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21121)

![Chemical structure image]

Compound JX21121 was synthesized according to the above general synthetic method. 133 mg (35% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 10.94 (m, 1H), 8.71 (s, 2H), 3.89–3.52 (m, 6H), 3.29–3.03 (m, 4H), 2.33–1.96 (m, 5H), 1.83 (m, 2H), 1.69–1.48 (m, 4H), 1.26 (m, 3H); HRMS (ESI) m/z calcd. for C18H26N6O2 [M+H]+ 346.2243, found 346.2244; Purity: 96% (254 nm, RT = 4.046 min).
**N-Hydroxy-2-(7-(imidazo[1,2-a]pyridin-3-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21122)**

Compound JX21122 was synthesized according to the above general synthetic method. 128 mg (30% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.11 (d, 1H), 11.13 (s, 1H), 9.33 (d, $J=$6.8 Hz, 1H), 8.69 (s, 1H), 8.01 (m, 2H), 7.58 (td, $J=$6.8, 2.1 Hz, 2H), 5.00 (m, 2H), 3.89–3.32 (m, 8H), 2.10 (m, 4H); HRMS (ESI) m/z calcd. for C$_{20}$H$_{24}$N$_7$O$_2$ [M+H]$^+$ 394.1991, found 394.1992; Purity: 99% (254 nm, RT = 4.009 min).

**N-Hydroxy-2-(7-((1-methyl-1H-indol-2-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21123)**

Compound JX21123 was synthesized according to the above general synthetic method. 131 mg (30% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.58 (m, 1H), 8.69 (m, 2H), 7.58 (d, $J=$7.9 Hz, 1H), 7.50 (d, $J=$8.3 Hz, 1H), 7.21 (t, $J=$7.7 Hz, 1H), 7.07 (t, $J=$7.4 Hz, 1H), 6.84 (s, 1H), 4.76–4.60 (m, 2H), 3.88 (s, 3H), 3.75–3.47 (m, 6H), 3.40 (m, 1H), 3.34 (m, 1H), 2.26–1.97 (m, 4H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{27}$N$_6$O$_2$ [M+H]$^+$ 407.2195, found 407.2194; Purity: 97% (254 nm, RT = 4.131 min).

**N-Hydroxy-2-(7-((1-methyl-1H-indazol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21124)**

Compound JX21124 was synthesized according to the above general synthetic method. 142 mg (32% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 11.21 (m, 2H), 8.68 (m, 2H), 8.05 (d, $J=$8.2 Hz, 1H), 7.71 (d, $J=$8.5 Hz, 1H), 7.54–7.33 (m, 1H), 7.25 (td, $J=$7.5, 4.6 Hz, 1H), 4.78 (m, 2H), 4.10 (s, 3H), 3.73–3.48 (m, 6H), 3.44 (m, 1H), 3.33 (m, 1H), 2.25–1.89 (m, 4H); HRMS (ESI) m/z calcd. for C$_{21}$H$_{26}$N$_7$O$_2$ [M+H]$^+$ 408.2148, found 408.2149; Purity: 98% (254 nm, RT = 3.915 min).
N-Hydroxy-2-(7-(naphthalen-1-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21125)

Compound JX21125 was synthesized according to the above general synthetic method. 146 mg (33% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.01–10.76 (m, 1H), 8.74–8.63 (m, 2H), 8.39 (d, J=8.4 Hz, 1H), 8.04 (t, J=8.2 Hz, 2H), 7.93 (t, J=7.3 Hz, 1H), 7.71–7.57 (m, 3H), 4.92 (m, 2H), 3.77–3.44 (m, 7H), 3.37 (m, 1H), 2.14 (m, 2H), 2.01 (m, 1H); HRMS (ESI) m/z calcd for C23H26N5O2 [M+H]+ 404.2087, found 404.2088; Purity: 100% (254 nm, RT = 4.015 min).

N-Hydroxy-2-(7-((1-methyl-1H-pyrrolo[2,3-c]pyridin-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21129)

Compound JX21129 was synthesized according to the above general synthetic method. 122 mg (27% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.43 (m, 1H), 8.70 (m, 2H), 8.47 (d, J=7.9 Hz, 1H), 8.37 (d, J=4.8 Hz, 1H), 7.88 (s, 1H), 7.27 (dt, J=7.9, 4.8 Hz, 1H), 4.55 (m, 2H), 3.69–3.50 (m, 5H), 3.44 (m, 1H), 3.37–3.29 (m, 1H), 3.23 (m, 1H), 2.20–1.92 (m, 4H); HRMS (ESI) m/z calcd for C21H26N7O2 [M+H]+ 408.2148, found 408.2149; Purity: 99% (254 nm, RT = 4.002 min).

N-Hydroxy-2-(7-((1-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21130)

Compound JX21130 was synthesized according to the above general synthetic method. 126 mg (28% yield from S-5); 1H NMR (400 MHz, DMSO-d6) δ 11.22 (m, 2H), 8.68 (m, 2H), 8.41 (d, J=7.9 Hz, 1H), 8.35 (d, J=4.7 Hz, 1H), 7.86 (s, 1H), 7.24 (dt, J=7.9, 4.7 Hz, 1H), 4.54 (m, 2H), 3.87 (s, 3H), 3.69–3.50 (m, 5H), 3.43 (m, 1H), 3.33 (m, 1H), 3.22 (m, 1H), 2.06 (m, 4H); HRMS (ESI) m/z calcd for C21H26N7O2 [M+H]+ 408.2148, found 408.2149; Purity: 97% (254 nm, RT = 4.080 min).
**N-Hydroxy-2-(2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21131)**

Compound JX21131 was synthesized according to the above general synthetic method.  
126 mg (42% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 9.49 (m, 2H), 8.70 (s, 2H), 3.72–3.51 (m, 4H), 3.28 (m, 2H), 3.16 (m, 2H), 2.21–1.89 (m, 4H); HRMS (ESI) m/z calcd. for C$_{12}$H$_{18}$N$_5$O$_2$ [M+H]$^+$ 264.1460, found 264.1461; Purity: 100% (254 nm, RT = 4.044 min).

**N-Hydroxy-2-(7-(quinolin-6-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21137)**

Compound JX21137 was synthesized according to the above general synthetic method.  
137 mg (31% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 12.06 (m, 1H), 9.28 (m, 1H), 8.99 (m, 1H), 8.68 (m, 2H), 5.63–5.51 (m, 2H), 3.87–3.29 (m, 9H), 2.24–1.86 (m, 4H); HRMS (ESI) m/z calcd. for C$_{22}$H$_{25}$N$_6$O$_2$ [M+H]$^+$ 405.2039, found 405.2040; Purity: 96% (254 nm, RT = 3.966 min).

**2-(7-(Anthracen-9-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21138)**

Compound JX21138 was synthesized according to the above general synthetic method.  
125 mg (26% yield from S-5); $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 10.38 (m, 1H), 8.84 (s, 1H), 8.69 (m, 4H), 2.24–1.86 (m, 4H); HRMS (ESI) m/z calcd. for C$_{27}$H$_{28}$N$_5$O$_2$ [M+H]$^+$ 454.2243, found 454.2244; Purity: 98% (254 nm, RT = 3.966 min).

**2-(7-(Benzo[d][1,3]dioxol-5-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21140)**

Compound JX21140 was synthesized according to the above general synthetic method.
152 mg (35% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.78–11.46 (m, 1H), 8.90–8.48 (m, 2H), 7.35 (d, J=5.6 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 6.96 (d, J=7.7 Hz, 1H), 6.06 (s, 2H), 4.39–4.18 (m, 2H), 3.70–3.53 (m, 4H), 3.51–3.42 (m, 1H), 3.39–3.09 (m, 3H), 2.07 (m, 4H); HRMS (ESI) m/z calcd. for C₂₅H₂₇N₅O₄ [M+H]⁺ 398.1828, found 398.1829; Purity: 100% (254 nm, RT = 4.051 min).

2-(7-(5-Bromo-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)-N-hydroxypyrimidine-5-carboxamide hydrochloride (JX21141)

Compound JX21141 was synthesized according to the above general synthetic method. 161 mg (31% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 10.96 (m, 1H), 8.81–8.58 (m, 2H), 8.13 (d, J=1.9 Hz, 1H), 7.71 (s, 1H), 7.48 (d, J=8.7 Hz, 1H), 7.33 (dt, J=8.7, 1.9 Hz, 1H), 4.51 (m, 2H), 3.82 (s, 3H), 3.69–3.37 (m, 7H), 3.39–3.29 (m, 1H), 3.26–3.14 (m, 1H), 2.21–1.90 (m, 4H); HRMS (ESI) m/z calcd. for C₂₂H₂₆BrN₆O₂ [M+H]⁺ 485.1301, found 485.1302; Purity: 99% (254 nm, RT = 4.094 min).

N-Hydroxy-2-(7-((6-methoxy-1-methyl-1H-indol-3-yl)methyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21142)

Compound JX21142 was synthesized according to the above general synthetic method. 144 mg (30% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.3–10.98 (m, 1H), 8.69 (m, 2H), 7.73 (dd, J=8.4, 2.0 Hz, 1H), 7.50 (s, 1H), 7.01 (d, J=2.2 Hz, 1H), 6.77 (td, J=8.4, 2.2 Hz, 1H), 4.47 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 3.67–3.47 (m, 5H), 3.41 (m, 1H), 3.30 (m, 1H), 3.21 (m, 1H), 2.20–1.91 (m, 4H); HRMS (ESI) m/z calcd. for C₂₃H₂₉N₆O₃ [M+H]⁺ 437.2301, found 437.2302; Purity: 98% (254 nm, RT = 4.057 min).

N-Hydroxy-2-(7-(quinolin-2-ylmethyl)-2,7-diazaspiro[4.4]nonan-2-yl)pyrimidine-5-carboxamide hydrochloride (JX21143)

Compound JX21143 was synthesized according to the above general synthetic method. 139 mg (32% yield from S-5); ¹H NMR (400 MHz, DMSO-d₆) δ 11.50 (s, 1H), 8.71 (s, 2H), 8.52 (d, J= 8.5 Hz, 1H), 8.08 (dd, 2H), 7.93–7.79 (m, 2H), 7.69 (t, J= 7.4 Hz, 1H), 4.83 (m, 2H), 3.79–3.39 (m, 10H), 2.14 (m, 4H); HRMS (ESI) m/z calcd. for C₂₂H₂₅N₆O₂ [M+H]⁺ 405.2039, found 405.2040; Purity: 97% (254 nm, RT = 4.007 min).
3. Synthesis of enantiomeric JX21108

3.1 Synthetic route

Because of the failure to separate the chiral antipodes of JX21108 via chiral column chromatography, both enantiomeric JX21108 were prepared from enantiopure S-1-011 using procedures in the synthesis of linker derivatives. (+)-JX21108 was synthesized from (+)-S-1-011, and (-)-JX21108 was synthesized from (-)-S-1-011. The enantiopurity of products was guaranteed by original substrate materials since no chiral manipulation was introduced during synthetic process.

![Scheme 4. Synthesis of enantiomeric JX21108](image)

3.2 Chiral column separation of S-1-011

3.2.1 Separation and analysis of S-1-011

Both 1.45 g (+)-S-1-011 and (-)-S-1-011 were obtain from 3.00 g racemic S-1-011.

(+)S-1-011

\[ [\alpha]_{20}^D = 68 (c=0.01 g mL^{-1} in MeOH); \]  
\[ {^1}H NMR (400 MHz, Chloroform-d) \delta 8.87 (m, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.88–3.25 (m, 8H), 1.98 (m, 4H), 1.46 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H). \]

(-)S-1-011

\[ [\alpha]_{20}^D = -66.3 (c=0.01 g mL^{-1} in MeOH); \]  
\[ {^1}H NMR (400 MHz, Chloroform-d) \delta 8.87 (m, 1H), 4.35 (q, J = 7.1 Hz, 1H), 3.84 – 3.27 (m, 8H), 1.98 (m, 4H), 1.46 (s, 9H), 1.37 (t, J = 7.1 Hz, 3H). \]

The conditions of chiral separation and analysis were listed as follows:

| Column: CHIRALPAK ID |  |
|---------------------|--|
| Column size         | 5.0 cm I.D. × 25 cm L, 10 μm |
| Sample solution     | 15 mg/ml in Mobile phase |
| Injection           | 15 ml |
| Mobile phase        | EtOH/MeCN = 95/5(V/V) |
| Flow rate           | 60 ml/min |
| Wave length         | UV 214 nm |
| Temperature         | 35 °C |

| Separation conditions |  |
|-----------------------|--|
| Column                | CHIRALPAK ID (ID00CD-TB002) |
| Column size           | 0.46 cm I.D. × 15 cm L |
| Injection             | 1 μl |
| Mobile phase          | EtOH/MeCN = 95/5(V/V) |
| Flow rate             | 0.5 ml/min |
| Wave length           | UV 254nm |
| Temperature           | 25 °C |

| HPLC equipment        | Shimadzu LC-20AD, CP-HPLC-05 |

Analyse conditions
### S-01-011

**Chromatogram of racemic S-01-011**

| Peak# | Ret. Time | Area     | Area%  | T.Plate#  | Tailing F. | Resolution |
|-------|-----------|----------|--------|-----------|------------|------------|
| 1     | 9.254     | 12161198 | 49.2951| 4653.218  | 1.644      | --         |
| 2     | 14.063    | 12509010 | 50.7049| 3294.776  | 2.050      | 6.316      |

---

### S-011-1

**Chromatogram of S-011-1**

| Peak# | Ret. Time | Area     | Area%  | T.Plate#  | Tailing F. | Resolution |
|-------|-----------|----------|--------|-----------|------------|------------|
| 1     | 9.340     | 3482762  | 99.8337| 5448.383  | 1.404      | --         |
| 2     | 14.407    | 5801     | 0.1663 | 4694.278  | 1.610      | 7.522      |
Chromatogram of S-1-011-2

| Peak# | Ret. Time | Area | Area% | T.Plate# | Tailing F. | Resolution |
|-------|-----------|------|-------|----------|------------|------------|
| 1     | 9.362     | 10814| 0.2275| 5843.085 | 1.141      | --         |
| 2     | 14.123    | 4743378 | 99.7725 | 4181.857 | 1.652  | 6.983      |

3.3 Characterization data of (+)-JX21108 and (-)-JX21108

(+)-JX21108

Compound (+)-JX21108 was synthesized according to the above general synthetic method.

232 mg (19% from (+)-S-1-011); $[\alpha]^{20}_D$ (deg mL$^2$ g$^{-1}$ dm$^{-1}$)=22.3 (c=0.01 g mL$^{-1}$ in MeOH); $^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.50–11.22 (m, 1H), 8.70 (m, 2H), 8.53 (s, 1H), 7.87 (s, 1H), 7.70 (d, $J$ = 8.5 Hz, 1H), 7.58 (d, $J$ = 8.5 Hz, 1H), 4.57 (m, 2H), 3.88 (s, 3H), 3.66 (m, 1H), 3.62–3.48 (m, 4H), 3.42 (m, 1H), 3.34 (m, 1H), 3.29 (m, 1H), 2.19–1.93 (m, 4H); $^{13}$C NMR (151 MHz, DMSO) δ 161.90, 159.78, 157.05, 156.86, 137.97, 134.92, 134.90, 127.14, 127.11, 125.17, 124.36, 120.53, 114.39, 111.59, 111.57, 104.75, 104.72, 101.75, 59.71, 59.19, 56.59, 56.23, 52.06, 52.03, 47.64, 47.48, 47.18, 47.14, 45.76, 45.72, 35.56, 35.26, 33.86, 33.46, 33.05; HRMS (ESI) m/z calcd. for C$_{23}$H$_{26}$N$_7$O$_2$ [M+H]$^+$ 432.2148, found 432.2149; Purity: 99% (254 nm, RT = 4.043 min).

(-)-JX21108

Compound (-)-JX21108 was synthesized according to the above general synthetic method.

226 mg (18% from (-)-S-1-011); $[\alpha]^{20}_D$ (deg mL$^2$ g$^{-1}$ dm$^{-1}$)=23.8 (c=0.01 g mL$^{-1}$ in MeOH); $^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.46–11.19 (m, 1H), 8.69 (m, 2H), 8.53 (s, 1H), 7.87 (s, 1H), 7.70 (d, $J$ = 8.5 Hz, 1H), 7.58 (d, $J$ = 8.5 Hz, 1H), 4.57 (m, 2H), 3.88 (s, 3H), 3.65 (m, 1H), 3.55 (m, 4H), 3.42 (m, 1H), 3.34 (m, 1H), 3.29–3.19 (m, 1H), 2.19–1.93 (m, 4H); $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 161.92, 159.84, 157.05, 156.74, 137.97, 134.92, 134.87, 127.14, 127.11, 125.17, 124.36, 120.53, 114.40, 111.59, 104.75, 104.72, 101.75, 59.72, 59.20, 56.58, 56.23, 52.06, 52.03, 47.64, 47.49, 47.18, 47.14, 45.75, 45.70, 35.56, 35.26, 33.86, 33.46, 33.05; HRMS (ESI) m/z calcd. for C$_{23}$H$_{26}$N$_7$O$_2$ [M+H]$^+$ 432.2148, found 432.2149; Purity: 99% (254 nm, RT = 4.084 min).
Reference

1. Dickens, J. W. J. *et al.* New mono-hydrochloric salt of N-hydroxy-2-(4-(((1-methyl-1H-indol-3-yl)methyl)amino)methyl)-1-piperidinyl)-5-pyrimidin-carboxamide useful in a medicament for treating e.g. leukemia, lung cancer, pancreatic cancer, prostate cancer. WO2008138918-A1.

2. Verdonck, M. G. C. *et al.* New substituted indolyl alkyl amino derivatives useful for treating e.g. cancer, osteoarthritis, conjunctivitis, asthma, Adult respiratory distress syndrome and diabetes. WO2006010750-A1.
4. Data of characterization

Compound JX21011 $^1$H NMR
Compound JX21011 HRMS
Compound JX21011 HPLC

操作者：LRX
仪器：仪器 1
进样日期：2019/12/4 20:55:49
采集方法：C:\CHEM32\1\METHODS\LJH\LC.M
最后修改：2019/12/4 20:55:49：LRX
分析方法：C:\CHEM32\1\METHODS\LJH\LC.M
最后修改：2019/12/29 22:55:18：ZC
样品信息：MeOH:H3PO4(c=0.1)=50:10, 0.5mL/min

面积百分比报告

信号：1
乘积因子：1.0000
稀释因子：1.0000
样品量：10.0000 [ng/ul] （校正中没有使用）
内标使用乘积因子和稀释因子

信号 1: DAD1 A, Sig=254,4 Ref=360,100

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1 0.858 BB 0.2025 25.65597 1.91384 0.4412
2 2.643 BB 0.2134 24.22771 1.68889 0.4165
3 3.672 BV 0.1022 12.79882 1.08737 0.2599
4 4.052 VB 8.1831 5559.62580 502.52358 95.5792
5 4.834 BV 0.1750 72.59579 6.36869 1.2480
6 5.123 W 8.1356 67.24868 7.03936 1.1560

仪器 1 2020/1/2 9:17:22 MLH
Compound JX21108 \(^1\)H NMR
Compound JX21108 $^{13}$C NMR

![Chemical Structure of JX21108]
Compound JX21108 HRMS
## Compound JX21108 HPLC

数据文件：C:\CHEMS2\1\DATA\LRX\JX21108-1-A0379.D

### 操作者：LRX

### 仪器：仪器1

### 选样日期：2019/12/5 19:07:35

### 采集方法：C:\CHEMS2\1\METHODS\LYL_LC.M

### 最后修改：2019/12/5 17:40:18

### 分析方法：C:\CHEMS2\1\METHODS\LYL_C.LC.M

### 最后修改：2019/12/29 22:55:18

### 样品信息：MeOH: H3PO4(c=0.1)=98:10, 0.5ml/min

### 面积百分比报告

| 排序 | 信号 | 乘积因子 | 积分因子 | 样品量 | [ng/μl] | [校正中没有使用] |
|------|------|----------|----------|--------|---------|----------------|
| 信号1: DAD1 A, Sig=254,4 Ref=360,100 |

| 峰保留时间 | 类型 | 宽度 | 峰面积 | 峰高 | 峰面积 |
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| [min]     | [min] | [nAU%] | [nAU] | %    |        |
|-----------|------|--------|------|------|--------|
| 1 3.684  | BV   | 0.1625 | 7.80931 | 1.17259 | 0.256 |
| 2 4.013  | YY   | 0.1958 | 5999.89029 | 568.11118 | 0.2542 |
| 3 4.769  | VB   | 0.1701 | 40.93482 | 3.31476 | 0.6724 |
| 4 6.374  | BB   | 0.1953 | 25.16251 | 1.82028 | 0.4133 |
| 5 7.789  | BB   | 0.2190 | 14.02817 | 1.02924 | 0.2384 |

| 总量 | 6887.82801 | 515.44837 |

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页 1/2
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Compound (+)-JX21108 $^{13}$C NMR
Compound (+)-JX21108 HRMS
Compound (+)-JX21108 HPLC

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样品名称：108-1-1-A

操作者：LRX
仪器：仪器 1
选择日期：2019/12/5 19:23:11
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最后修改：2019/12/5 17:46:18 : LRX
分析方法：C:\CHEM32\DATA\METHODS\2C\LC__M
最后修改：2019/12/29 22:55:18 : 2C
样品信息：MeOH:H2O:0.1%H3PO4=99:1, 0.5mL/min

面积百分比报告

排序  信号
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稀释因子：1.0000
样品量：10.0000 [ng/μl] （校正中没有使用）
内标使用乘积因子和稀释因子

信号 1: DAD1 A, λg=254.4 Ref=360,100

| 峰号 | 保留时间 | 类型 | 峰宽 | 峰面积 | 峰高 | 峰面积 |
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| 2    | 4.043  | VV   | 0.2184 | 8983.01855 | 678.78870 | 98.6946 |
| 3    | 4.657  | VV   | 0.1184 | 23.74992 | 2.87441 | 0.2607 |
| 4    | 4.804  | VB   | 0.1370 | 28.70254 | 3.07344 | 0.3151 |
| 5    | 6.384  | BB   | 0.1866 | 29.12960 | 2.25600 | 0.2397 |
| 6    | 7.822  | BB   | 0.2486 | 19.96937 | 1.33468 | 0.2192 |
| 7    | 9.639  | BB   | 0.2268 | 16.21591 | 1.09510 | 0.1780 |

仪器 1 2020/1/2 9:19:15 HLM
Compound (-)-JX21108 $^1$H NMR
Compound (-)-JX21108 $^{13}$C NMR
Compound (+)-JX21108 HRMS
Compound (-)-JX21108 HPLC

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**Operator:** LRX
**Instrument:** 1
**Location:** Sample Bottle 1
**Injection Date:** 2019/12/5 19:37:33
**Injection Method:** C:\CHEMS\1\DATA\LRX\108-2-1-0000381.D
**Last Modified:** 2019/12/20 22:55:18
**Sample Information:** MeOH: H3PO4 (c=0.1)+98:10, 0.5mL/min

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**Data Analysis Report**

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**Signal:** 信号
**Signal Factor:** 1.0000
**Signal Ratio:** 1.0000
**Sample Volume:** 10.000000 [ng/ul] (corrected with a factor of 1)

**Signal 1:** DAD1 A, Sig=254.4 Ref=360,100

| Time (min) | Width (min) | Area (nA*s) | Height (nA) | % |
|------------|-------------|-------------|-------------|---|
| 1          | 0.1064      | 9.7936      | 1.45865     | 0.1107 |
| 2          | 0.3070      | 815.78125   | 993.69473   | 98.7993 |
| 3          | 0.2038      | 65.2654     | 3.52836     | 0.6351 |
| 4          | 0.1782      | 23.14072    | 1.98251     | 0.2616 |
| 5          | 0.2469      | 17.10029    | 1.11498     | 0.1933 |

**Total:** 8845.99923 781.74863

**Instrument:** 1 2020/1/2 9:22:10 MLH