Supporting information

Design, Synthesis and Biological Evaluation of New Molecules Inhibiting Epidermal Growth Factor Receptor Threonine$^{790}$ → Methionine$^{790}$ mutant

Shilin Xu,ac Lianwen Zhang,bc Shaohua Chang,ac Jinfeng Luo,a Xiaoyun Lu,a Zhengchao Tu,a Yinxue Liu,a Zhang zhang,a Yong Xu,a Xiaomei Rena and Ke Dingad

aKey Laboratory of Regenerative Biology and Institute of Chemical Biology, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, #190 Kaiyuan Avenue, Guangzhou 510530, China
bSchool of Life Science, University of Science and Technology of China, # 96 Jinzhai Road, Hefei 230026, China
cGraduate School of Chinese Academy of Sciences, # 19 Yuquan Road, Beijing 100049, China

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**General Information:**

Reagents and solvents were obtained from commercial suppliers and used without further purification. Flash chromatography was performed using silica gel (200-300 mesh). All reactions were monitored by TLC, silica gel plates with fluorescence F$_{254}$ were used and visualized with UV light. All products were characterized by their NMR, LC/MS. NMR spectras were recorded at 20 °C on a Bruker AC 400 MHz spectrometer working at 400 MHz and 125 MHz for $^1$H and $^{13}$C, respectively. The firstorder peak patterns were indicated as s (singlet), d (doublet), t (triplet), q (quartet) dd (double doublet) and br (broad). Complex non-first-order signals were indicated as m (multiplet). High resolution mass spectral (HRMS) analyses were recorded on AB SCIEX (USA) QSTAR Elite Hybrid LC/MS/MS mass spectrometer using electrospray ionization.

**Cell Lines and Reagents:**

H1975 (NSCLC, EGFR$^{L858R/T790M}$) and HCC827 (NSCLC, EGFR$^{DEL.E746-A750}$) cells were obtained from ATCC. The cells were maintained at 37 °C in a 5% CO2 incubator in RPMI 1640 (Gibco, Invitrogen) containing 10% fetal bovine serum (Gibco, Invitrogen). HL-7702 (diploid human liver cell) cells were gifts from Prof. Duanqing Pei. The HL-7702 was cultured in RPMI 1640 containing 10% FBS. The EGFR gene of every cell line was sequenced before use. Gefitinib and WZ4002 were synthesized in our chemistry laboratory.

**In Vitro Enzymatic Activity Assay:**

Wild-type and different EGFR mutants (T790M, L858R, L861Q and L858R/T790M) and the Z'-Lyte Kinase Assay Kit were purchased from Invitrogen. Ten concentration gradients from $5.1\times10^{-11}$ to $1.0\times10^{-6}$ mol/L were set for all the tested compounds. The experiments were performed according to the instructions of the manufacturer.

**Cell Proliferation and Growth Inhibition Assay:**

Cell proliferation was assessed by MTS assay. The cells were exposed to treatment for 72 h, and the number of cells used per experiment for each cell line was adjusted
to obtain an absorbance of 1.3 to 2.2 at 490nm. Six concentrations (0.1 nM to 10 μM) were set for the compounds. At least six parallels of every concentration were used. All experiments were repeated at least four times. The data was calculated using GraphPad Prism version 4.0. The IC<sub>50</sub> were fitted using a nonlinear regression model with a sigmoidal dose-response.

**Antibodies and Western Blotting:**

Cells were plated in 6-cm dishes. After 24-h growth, the cells were treated with the compounds under the indicated concentrations for 24 h. Cell lysates were collected with 1× lysis buffer (CST) and were briefly sonicated. Western blot analyses were conducted after separation by SDS/PAGE electrophoresis and transfer to PVDF membranes. Membranes were blocked in 5% bovine serum albumin/TBST and probed with the indicated antibodies, followed by a peroxidase-conjugated antimouse or rabbit secondary antibody. Blots were developed by enhanced chemiluminescence (Thermo). Anti-EGFR, anti-phospho specific EGFR (pY1068) and anti-actin antibodies were obtained from Cell Signaling Technology.

**Kinase Profiling Results**

![LeadHunter Discovery Services](image-url)
**GUA012-01-s-00001 Curve Images**

Table 2 - Curve images for GUA012-01-s-00001. The amount of kinase measured by qPCR (y-axis) is plotted against the corresponding compound concentration in nM in log10 scale (x-axis). Data points marked with an "X" were not used for Kd determination.
General Method for the Synthesis of Compounds and Analytical Data:

1. **ethyl 4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)pyrimidine-5-carboxylate (5)**

To a solution of 3 (12.63 g, 54.27 mmol) in DMF (200 mL) was added 4 (11.29 g, 54.27 mmol) and potassium carbonate (15 g, 108.54 mmol). The resulting solution was stirred at 80°C overnight. After cooled to room temperature, the reaction mixture was added with ice-water (500 mL). The precipitate was filtered, and the filtered cake was rinsed with additional cool water and dried in vacuum oven to give the title compound (21.3 g, 97% yield), which was used without further purification. MS (ESI) m/z 405.0 [M+H]+. 1H NMR (400 MHz, CDCl3) δ 10.41 (s, 1H), 8.77 (s, 1H), 7.92 (s, 1H), 7.34 (d, J = 8.8 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 0.8, 8.8 Hz, 1H), 6.49 (s, 1H), 4.38 (q, J = 7.2 Hz, 2H) 2.56 (s, 3H), 1.52 (s, 9H), 1.41 (t, J = 7.2 Hz, 3H)

2. **4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)pyrimidine-5-carboxylic acid (6)**

To a solution of 5 (7 g, 17.33 mmol) in THF (200 mL) and H2O (100 mL) was added LiOH-H2O (1.46 g, 34.66 mmol). The mixture was stirred at room temperature overnight. Most solvents were evaporated in vacuo. The residue was acidified with 1M hydrochloric acid till PH = 2. The solid was collected by suction filtration and washed with H2O (100 mL) to afford a white powder (6.39 g, 98% yield), which was dried in vacuum oven without further purification. MS (ESI) m/z 377.0 [M+H]+. 1H NMR (400 MHz, DMSO) δ 13.76 (br, 1H), 10.56 (s, 1H), 9.45 (s, 1H), 8.72 (s, 1H), 7.90 (s, 1H), 7.38 (d, J = 9.2 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 2.53 (s, 3H), 1.50 (s, 9H).

3. **methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)acetate (7a)**

**General Procedure for Synthesis of 7a-m.**

To a solution of 6 (4.5 g, 11.97 mmol) in anhydrous CH2Cl2 (200 mL) under argon
was added carefully oxalyl chloride (1.5 mL, 17.96 mmol), followed by DMF (500 μL). The solution slowly turned to a light-yellow homogeneous solution over 4 h. The solution was concentrated in vacuo to give tert-butyl 3-(5-chlorocarbonyl)-2-methylthio)pyrimidin-4-lamo)phenylcarbamate as an yellow solid, which was used immediately in the next reaction without characterization. This yellow solid was dissolved in anhydrous CH₂Cl₂ (200 mL) under argon and cooled to 0 °C (ice bath). N-Methylglycine methyl ester hydrochloride (2.51 g, 17.96 mmol) in CH₂Cl₂ (20 mL) and N,N-diisopropylethylamine (8.3 mL, 47.88 mmol) were added with stirring. The reaction was allowed to warm to room temperature. After stirring for 20 h, TLC analysis indicated completion of the reaction. The mixture was poured into a solution of 10% aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layer was separated, washed with 10% aqueous NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography (SiO₂, CH₂Cl₂/Methanol stepwise elution, 500 :1 to 100:1) to give the title compound. (4.68g, 84.8% yield). MS (ESI) m/z 462.1 [M+H]⁺ ¹H NMR (400 MHz, CDCl₃) δ 8.88 (s, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.25 (dd, J = 1.2, 8.0 Hz, 1H), 6.48 (s, 1H), 4.25 (s, 2H), 3.83 (s, 3H), 3.16 (s, 3H), 2.56 (s, 3H), 1.51 (s, 9H).

4. methyl 1-(4-(3-(tert-butoxycarbonylamino) phenylamino)-2-(methylthio) pyrimidine-5-carbonyl)pyrrolidine-2-carboxylate (7b)
MS (ESI) m/z 488.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃) δ 9.61 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.47 (s, 1H), 4.69 (t, J = 6.8 Hz, 1H), 3.80 (s, 3H), 3.78-3.69 (m, 2H), 2.56 (s, 3H), 2.40-2.33 (m, 1H), 2.11-1.92 (m, 3H), 1.51 (s, 9H).

5. methyl 1-(4-(3-(tert-butoxycarbonylamino) phenylamino)-2-(methylthio) pyrimidine-5-carbonyl)piperidine-2-carboxylate (7c)
MS (ESI) m/z 502.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃) δ 8.70 (s, 1H), 8.16 (s, 1H), 7.97 (s, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 8.8 Hz, 1H), 6.99 (dd, J = 1.6, 8.4 Hz, 1H), 6.49 (s, 1H), 5.42 (br, 1H), 3.84 (s, 3H), 3.77-3.73 (m, 1H), 3.27 (br, 1H), 2.56 (s, 3H), 2.38 (d, J = 13.6 Hz, 1H), 1.85-1.67 (m, 3H), 1.51 (s, 9H), 1.43-1.34 (m,
6. methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)propanoate (7d)

MS (ESI) m/z 476.0 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.92 (s, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 6.98 (dd, J = 1.2, 8.0 Hz, 1H), 6.48 (s, 1H), 5.06 (br, 1H), 3.81 (s, 3H), 3.05 (s, 3H), 2.56 (s, 3H), 1.56 (d, J = 7.2 Hz, 3H), 1.51 (s, 9H).

7. methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-methylbutanoate (7e)

MS (ESI) m/z 504.1 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.93 (br, 1H), 8.22 (s, 1H), 7.88 (s, 1H), 7.24-7.20 (m, 2H), 7.00-6.97 (m, 1H), 6.50 (s, 1H), 4.52 (br, 1H), 3.79 (s, 3H), 3.10 (s, 3H), 2.55 (s, 3H), 2.39-2.29 (m, 1H), 1.51 (s, 9H), 1.02 (s, 3H), 0.94 (s, 3H).

8. methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-4-methylpentanoate (7f)

MS (ESI) m/z 518.2 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.92 (br, 1H), 8.18 (s, 1H), 7.90 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.52 (s, 1H), 5.13 (br, 1H), 3.79 (s, 3H), 3.04 (s, 3H), 2.55 (s, 3H), 1.84 (t, J = 7.2 Hz, 2H), 1.75-1.64 (m, 1H), 1.51 (s, 9H), 1.00-0.94 (m, 6H).

9. methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-2-phenylacetate (7g)

MS (ESI) m/z 538.1 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.46-7.40 (m, 3H), 7.37 (d, J = 8.4 Hz, 1H), 7.32-7.30 (m, 2H), 7.25 (t, J = 8.0 Hz, 1H), 7.02 (dd, J = 1.2, 8.0 Hz, 1H), 6.49 (s, 1H), 6.28 (s, 1H), 3.87 (s, 3H), 2.86 (s, 3H), 2.55 (s, 3H), 1.52 (s, 9H).

10. methyl 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)-N-phenylpyrimidine-5-carboxamido)acetate (7h)

MS (ESI) m/z 524.0 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 9.62 (s, 1H), 7.91 (s, 1H), 7.79 (s, 1H), 7.34-7.31 (m, 2H), 7.28-7.27 (m, 1H), 7.25-7.18 (m, 4H), 7.00 (dt, J = 1.6, 7.6 Hz, 1H), 6.48 (s, 1H), 4.58 (s, 2H), 3.82 (s, 3H), 2.47 (s, 3H), 1.52 (s, 9H).
11. methyl 2-(4-(3-(tert-butoxycarbonylamino) phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-phenylpropanoate (7i)
MS (ESI) m/z 552.0 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.68 (br. 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.25-7.19 (m, 7H), 6.99 (dd, J = 1.6, 8.8 Hz, 1H), 6.47 (s, 1H), 5.12 (br, 1H), 3.85 (s, 3H), 3.44 (br, 1H), 3.16 (br, 1H), 2.95 (s, 3H), 2.53 (s, 3H), 1.52 (s, 9H).

12. methyl 2-(4-(3-(tert-butoxycarbonylamino) phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-methoxyphenyl)propanoate (7j)
MS (ESI) m/z 582.2 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.49 (br, 1H), 7.86 (s, 1H), 7.70 (s, 1H), 7.23-7.22 (m, 2H), 7.07-7.05 (m, 3H), 6.79 (s, 2H), 6.52 (s, 1H), 5.11 (br, 1H), 3.84 (s, 3H), 3.66 (br, 3H), 3.36 (br, 1H), 3.08 (br, 1H), 2.97 (s, 3H), 2.53 (s, 3H), 1.52 (s, 9H).

13. methyl 2-(4-(3-(tert-butoxycarbonylamino) phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-chlorophenyl)propanoate (7k)
MS (ESI) m/z 586.0 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.58 (br, 1H), 7.86 (s, 1H), 7.82 (s, 1H), 7.26-7.22 (m, 4H), 7.13 (s, 2H), 7.01-6.98 (m, 1H), 6.50 (s, 1H), 5.07 (s, 1H), 3.84 (s, 3H), 3.41 (d, J = 10.8 Hz, 1H), 3.17-3.11 (m, 1H), 2.95 (s, 3H), 2.53 (s, 3H), 1.52 (s, 9H).

14. methyl 2-(4-(3-(tert-butoxycarbonylamino) phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-fluorophenyl)propanoate (7l)
MS (ESI) m/z 570.2 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.62 (br, 1H), 7.83 (s, 2H), 7.23-7.22 (m, 2H), 7.16 (s, 2H), 7.00-6.97 (m, 3H), 6.47 (s, 1H), 5.07 (s, 1H), 3.84 (s, 3H), 3.43-3.40 (m, 1H), 3.17-3.11 (m, 1H), 2.96 (s, 3H), 2.53 (s, 3H), 1.52 (s, 9H).

15. methyl 2-(N-benzyl-4-(3-(tert-butoxycarbonylamino) phenylamino)-2-(methylthio)pyrimidine-5-carboxamido)acetate (7m)
MS (ESI) m/z 538.0 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.94 (s, 1H), 8.20 (s, 1H), 7.98 (s, 1H), 7.40-7.35 (m, 3H), 7.34-7.31 (m, 1H), 7.28-7.24 (m, 1H), 7.20 (d, J = 7.2 Hz, 2H), 7.02 (dd, J = 1.2, 8.4 Hz, 1H), 6.50 (s, 1H), 4.68 (s, 2H), 4.15(s, 2H), 3.82 (s, 3H), 2.55 (s, 3H), 1.52 (s, 9H).
16. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)acetic acid (8a)

**General Procedure for Synthesis of 8a-m.**

To a solution of 7a (4.98 g, 10.78 mmol) in THF (100 mL) and H₂O (50 mL) was added LiOH·H₂O (0.91 g, 21.56 mmol). The reaction solution was stirred at room temperature overnight. The solution was concentrated in vacuo and acidified with 1M hydrochloric acid till PH = 2. The solid was collected by suction filtration and washed with H₂O (50 mL) to afford a white powder (4.37 g, 90% yield), which was dried in vacuum oven without further purification. MS (ESI) m/z 448.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 13.19 (br, 1H), 9.38 (s, 1H), 8.92 (s, 1H), 7.95 (s, 1H), 7.22-7.19 (m, 2H), 7.08 (d, J = 6.8 Hz, 1H), 4.19 (s, 2H), 3.02 (s, 3H), 2.46 (s, 3H), 1.47 (s, 9H).

17. 1-(4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)pyrimidine-5-carbonyl)pyrrolidine-2-carboxylic acid (8b)

MS (ESI) m/z 472.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 12.95 (br, 1H), 9.39 (s, 2H), 8.31 (s, 1H), 7.88 (s, 1H), 7.24 (d, J = 6.8 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 6.8 Hz, 1H), 4.50 (s, 1H), 3.61 (s, 2H), 2.50 (s, 3H), 2.33-2.28 (m, 1H), 1.89 (s, 3H), 1.47 (s, 9H).

18. 1-(4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)pyrimidine-5-carbonyl)piperidine-2-carboxylic acid (8c)

MS (ESI) m/z 488.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 13.40 (br, 1H), 9.36 (s, 1H), 8.80 (s, 1H), 8.10 (s, 1H), 7.93 (s, 1H), 7.22-7.18 (m, 2H), 7.10 (d, J = 6.8 Hz, 1H), 5.24 (br, 1H), 3.57 (s, 1H), 3.20-3.17 (m, 1H), 2.46 (s, 3H), 2.19 (s, 1H), 1.71-1.60 (m, 3H), 1.47 (s, 9H), 1.31-1.25 (m, 2H).

19. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)propanoic acid (8d)

MS (ESI) m/z 462.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 13.11 (br, 1H), 9.36 (s, 1H), 8.89 (s, 1H), 8.14 (s, 1H), 7.89 (s, 1H), 7.22-7.19 (m, 2H), 7.08 (d, J = 6.8 Hz, 1H), 4.89 (br, 1H), 2.93 (s, 3H), 2.46 (s, 3H), 1.47 (s, 9H), 1.43 (d, J = 6.8 Hz, 3H).

20. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-
**rimidine-5-carboxamido)-3-methylbutanoic acid (8e)**

MS (ESI) m/z 490.1 [M+H]^+. ^1^H NMR (400 MHz, DMSO) δ 13.12 (br, 1H), 9.37 (s, 1H), 8.88 (s, 1H), 8.17 (br, 1H), 7.85 (s, 1H), 7.20 (t, J = 7.6 Hz, 2H), 7.08 (d, J = 7.2 Hz, 1H), 4.56 (br, 1H), 3.00 (s, 3H), 2.45 (s, 3H), 2.25-2.18 (m, 1H), 1.47 (s, 9H), 0.86 (s, 6H).

**21. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-4-methylpentanoic acid (8f)**

MS (ESI) m/z 504.2 [M+H]^+. ^1^H NMR (400 MHz, DMSO, a mixture of rotamers) δ 13.32 (br, 1H), 9.37 (s, 1H), 9.02 (br, 1H), 8.20 (s) and 8.04 (s) (together 1H), 7.92 and 7.85 (s) (together 1H), 7.22-7.15 (m, 2H), 7.09 (d, J = 7.2 Hz, 1H), 4.99 (s, 0.67H) and 4.29 (s, 0.33H), 2.92 (s, 3H), 2.46 (s, 3H), 1.81 (s, 1H), 1.75 (s, 1H), 1.63 (s, 1H), 1.47 (s, 9H), 0.93 (s) and 0.68 (s) (together 6H).

**22. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-2-phenylacetic acid (8g)**

MS (ESI) m/z 524.2 [M+H]^+. ^1^H NMR (400 MHz, DMSO) δ 13.49 (br, 1H), 9.38 (s, 1H), 9.19 (s, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.33-7.27 (m, 4H), 7.23-7.13 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 4.56 (s, 2H), 2.36 (s, 3H), 1.48 (s, 9H).

**23. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)-N-phenylpyrimidine-5-carboxamido)acetic acid (8h)**

MS (ESI) m/z 510.2 [M+H]^+. ^1^H NMR (400 MHz, DMSO) δ 13.27 (br, 1H), 9.36 (s, 1H), 9.19 (s, 1H), 7.96 (s, 1H), 7.80 (s, 1H), 7.33-7.27 (m, 4H), 7.23-7.13 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 4.56 (s, 2H), 2.36 (s, 3H), 1.48 (s, 9H).

**24. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-phenylpropanoic acid (8i)**

MS (ESI) m/z 538.1 [M+H]^+. ^1^H NMR (400 MHz, DMSO, a mixture of rotamers) δ 13.34 (br, 1H), 9.38 (s, 1H), 8.64 (s) and 8.19 (s) (together 1H), 7.87-7.53 (m, 2H), 7.30-7.07 (m, 8H), 5.11 (s, 0.59H) and 4.81 (s, 0.41H), 3.32-3.17 (m, 2H), 2.85 (s, 3H), 2.45 (s, 3H), 1.48 (s, 9H).

**25. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-methoxyphenyl)propanoic acid (8j)**
MS (ESI) m/z 568.1 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, DMSO, a mixture of rotamers) δ 13.42 (br, 1H), 9.37 (s, 1H), 8.62 (s) and 8.26 (s) (together 1H), 7.83 (s) and 7.66 (s) (together 2H), 7.22-7.18 (m, 2H), 7.16-7.07 (m, 3H), 6.84 (s, 1H), 6.69 (s, 1H), 5.07 (s) and 4.79 (s) (together 1H), 3.57 (s, 3H), 3.24 (s, 1H), 3.17 (s, 1H), 2.86 (s, 3H), 2.46 (s, 3H), 1.47 (s, 9H).

26. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-chlorophenyl)propanoic acid (8k)

MS (ESI) m/z 572.1 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, DMSO, a mixture of rotamers) δ 13.39 (br, 1H), 9.37 (s, 1H), 8.64 (s) and 8.24 (s) (together 1H), 7.86 (s) and 7.73-7.67 (m) (together 2H), 7.35-7.06 (m, 7H), 5.09 (s) and 4.86 (s) (together 1H), 3.24 (s) and 3.08 (s) (together 2H), 2.86 (s, 3H), 2.46 (s, 3H), 1.48 (s, 9H).

27. 2-(4-(3-(tert-butoxycarbonylamino)phenylamino)-N-methyl-2-(methylthio)pyrimidine-5-carboxamido)-3-(4-fluorophenyl)propanoic acid (8l)

MS (ESI) m/z 556.2 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, DMSO, a mixture of rotamers) δ 13.44 (br, 1H), 9.38 (s, 1H), 8.67 (s) and 8.24 (s) (together 1H), 7.83 (s) and 7.63 (s) (together 2H), 7.34 (s, 1H), 7.22-7.06 (m, 5H), 6.96 (s, 1H), 5.08 (s) and 4.82 (s) (together 1H), 3.86 (s, 2H), 2.86 (s, 3H), 2.45 (s, 3H), 1.48 (s, 9H).

28. 2-(N-benzyl-4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(methylthio)pyrimidine-5-carboxamido)acetic acid (8m)

MS (ESI) m/z 524.0 [M+H]^+. \textsuperscript{1}H NMR (400 MHz, DMSO) δ 13.30 (br, 1H), 9.43 (s, 1H), 9.37 (s, 1H), 8.14 (s, 1H), 8.06 (s, 1H), 7.36-7.33 (m, 2H), 7.30-7.26 (m, 3H), 7.22-7.18 (m, 3H), 7.11 (s, 1H), 4.54 (s, 2H), 3.99 (s, 2H), 2.45 (s, 3H), 1.47 (s, 9H).

29. tert-butyl 3-(6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido [4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9a)

General Procedure for Synthesis of 9a-m.

To a solution of 8a (6.85 g, 15.3 mmol) in anhydrous CH\textsubscript{2}Cl\textsubscript{2} (1000 mL) was added HATU (17.5 g, 45.9 mmol) at 0 °C (ice bath). N,N-diisopropylethylamine (8 mL, 45.9 mmol) was added dropwise. Then the solution was allowed to warm to room temperature and stirred for 24 h under argon atmosphere. The solution was poured on a solution of 10% NaHCO\textsubscript{3} and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was
separated, washed with 10% aqueous NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography (SiO₂, Petroleum ether/CH₂Cl₂ stepwise elution, 1:1 to 1:3) to give the title compound. (5.25g, 80% yield).

**30. tert-butyl 3-(2-(methylthio)-5,10-dioxo-8,9,9a,10-tetrahydro-5H-pyrimido[4,5-e]pyrrolo[1,2-a][1,4]diazepin-11(7H)-yl)phenylcarbamate (9b)**

MS (ESI) m/z 456.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H), 7.45 (s, 1H), 7.33 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.54 (s, 1H), 4.30-4.28 (m, 1H), 3.85-3.80 (m, 1H), 3.70-3.63 (m, 1H), 2.83-2.79 (m, 1H), 2.16 (s, 3H), 2.13-2.04 (m, 3H), 1.49 (s, 9H).

**31. tert-butyl 3-(2-(methylthio)-5,11-dioxo-7,8,9,10a,11-hexahydropyrido[1,2-a]pyrimido[4,5-e][1,4]diazepin-12(5H)-yl)phenylcarbamate (9c)**

MS (ESI) m/z 470.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃) δ 8.95 (s, 1H), 7.41 (s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.25 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 4.53-4.48 (m, 1H), 4.34 (s, 1H), 3.09-3.02 (m, 1H), 2.36-2.32 (m, 1H), 2.16 (s, 3H), 1.99-1.60 (m, 5H), 1.50 (s, 9H).

**32. tert-butyl 3-(6,7-dimethyl-2-(methylthio)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9d)**

MS (ESI) m/z 444.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 7.42 (s, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.25 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.54 (s, 1H), 4.39 (s, 1H), 3.14 (s, 3H), 2.16 (s, 3H), 1.61 (s, 3H), 1.50 (s, 9H).

**33. tert-butyl 3-(7-isopropyl-6-methyl-2-(methylthio)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9e)**

MS (ESI) m/z 472.1 [M+H]+ ¹H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.00 (s) and 8.96 (s) (together 1H), 7.38-7.29 (m, 3H), 6.82-6.76 (m, 1H), 6.56 (s, 1H), 3.84 (d, J = 11.6 Hz, 0.79H) and 3.69 (d, J = 10.8 Hz, 0.21H), 3.35 (s) and 3.12 (s) (together 3H), 2.19 (s) and 2.10 (s) (together 3H), 1.97-1.86 (m, 1H), 1.49 (s, 9H),
1.06 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.4 Hz, 3H).

34. tert-butyl 3-(7-isobutyl-6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9f)

MS (ESI) m/z 486.2 [M+H]^+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 8.99 (s) and 8.98 (s) (together 1H), 7.37-7.28 (m, 3H), 6.79 (d, J = 7.6 Hz, 1H), 6.55 (s, 1H), 4.35 (t, J = 8.0 Hz, 0.30H) and 4.18 (t, J = 7.2 Hz, 0.70H), 3.33 (s) and 3.10 (s) (together 3H), 2.18 (s) and 2.10 (s) (together 3H), 2.05-2.00 (m), 1.90-1.83 (m) and 1.60-1.55 (m) (together 2H), 1.70-1.62 (m, 1H), 1.49 (s, 9H), 0.97-0.92 (m, 6H).

35. tert-butyl 3-(6-methyl-2-(methylthio) -5,8-dioxo-7-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9g)

MS (ESI) m/z 506.2 [M+H]^+ 1H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 7.40-7.37 (m, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.24-7.16 (m, 3H), 6.90 (d, J = 8.0 Hz, 1H), 6.60 (s, 1H), 5.60 (s, 1H), 3.55 (s, 3H), 2.00 (s, 3H), 1.51 (s, 9H).

36. tert-butyl 3-(2-(methylthio) -5,8-dioxo-6-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9h)

MS (ESI) m/z 492.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 7.50 (d, J = 7.6 Hz, 3H), 7.44 (t, J = 7.6 Hz, 2H), 7.38-7.29 (m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 6.61 (s, 1H), 4.54 (s, 2H), 2.18 (s, 3H), 1.50 (s, 9H).

37. tert-butyl 3-(7-benzyl-6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9i)

MS (ESI) m/z 520.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.13 (s) and 8.97 (s) (together 1H), 7.35-7.24 (m, 7H), 7.08 (d, J = 7.2 Hz, 1H), 6.75-6.69 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 4.57-4.47 (m, 1H), 3.61-3.56 (m), 3.28-3.23 (m) and 3.07-3.02 (m) (together 2H), 3.17 (s) and 2.98 (s) (together 3H), 2.14 (s) and 2.13 (s) (together 3H), 1.50 (s, 9H).

38. tert-butyl 3-(7-(4-methoxybenzyl)-6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9j)

MS (ESI) m/z 550.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.12 (s) and 8.97 (s) (together 1H), 7.36-7.29 (m, 2H), 7.23 (s, 1H), 7.17 (d, J = 7.6 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.87 (t, J = 8.4 Hz, 2H), 6.76-6.69 (m, 1H), 6.52 (d,
J = 7.2 Hz, 1H), 4.52-4.48 (m) and 4.41 (br) (together 1H), 3.80 (s, 3H), 3.56-3.51 (m), 3.19 (s) and 2.98-2.89 (m) (together 2H), 3.16 (s) and 3.01 (s) (together 3H), 2.14 (s) and 2.13 (s) (together 3H), 1.50 (s, 9H).

39. tert-butyl 3-(7-(4-chlorobenzyl)-6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9k)

MS (ESI) m/z 554.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.11 (s) and 8.97 (s) (together 1H), 7.40-7.27 (m, 4H), 7.25-7.19 (m) and 7.03 (d, J = 8.4 Hz) (together 3H), 6.73 (d, J = 8.4 Hz) and 6.68 (d, J = 7.6 Hz) (together 1H), 6.54 (d, J = 8.8 Hz, 1H), 4.53-4.49 (m) and 4.43-4.39 (m) (together 1H), 3.62-3.56 (m), 3.22-3.18 (m) and 3.01-2.90 (m) (together 2H), 3.16 (s) and 3.03 (s) (together 3H), 2.14 (s, 3H), 1.50 (s, 9H).

40. tert-butyl 3-(7-(4-fluorobenzyl)-6-methyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9l)

MS (ESI) m/z 538.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.12 (s) and 8.97 (s) (together 1H), 7.42-7.29 (m, 2H), 7.25-7.18 (m, 2H), 7.07-6.99 (m, 3H), 6.73 (d, J = 7.6 Hz) and 6.68 (d, J = 7.6 Hz) (together 1H), 6.56 (s) and 6.53 (s) (together 1H), 4.52-4.48 (m) and 4.43-4.39 (m) (together 1H), 3.61-3.55 (m), 3.23-3.19 (m) and 2.99-2.90 (m) (together 2H), 3.17 (s) and 3.02 (s) (together 3H), 2.14 (s, 3H), 1.50 (s) and 1.49 (s) (together 9H).

41. tert-butyl 3-(6-benzyl-2-(methylthio) -5,8-dioxo-7,8-dihydro-5H-pyrimido [4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (9m)

MS (ESI) m/z 506.1 [M+H]^+ 1H NMR (400 MHz, CDCl₃) δ 9.06 (s, 1H), 7.45 (s, 1H), 7.38-7.32 (m, 6H), 7.23 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 7.6 Hz, 1H), 6.56 (s, 1H), 4.87 (s, 2H), 4.03 (s, 2H), 2.15 (s, 3H), 1.50 (s, 9H).

42. tert-butyl 3-(6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido [4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10a)

General Procedure for Synthesis of 10a-m.

To a solution of 9a (4.59 g, 10.7 mmol) in anhydrous CH₂Cl₂ (50 mL) was added 85% m-CPBA (6.52 g, 32.1 mmol) at 0 °C under argon. The reaction mixture was allowed to warm to room temperature, stirred for 4 h. The solution was diluted with CH₂Cl₂,
and was then treated with 50% \( \text{Na}_2\text{S}_2\text{O}_3/\text{NaHCO}_3 \) solution. The organic phase was washed with saturated aqueous NaCl, was dried over \( \text{Na}_2\text{SO}_4 \), and was then filtered. After removal of solvent under vacuum, the resulting white solid (4.44 g, 90% yield) was recrystallized from a minimum amount of ethyl acetate and petroleum ether, which was used for the next step without further purification. \( ^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.39 (s, 1H), 7.56 (s, 1H), 7.37 (t, \( J = 8.0 \) Hz, 1H), 7.19 (dd, \( J = 1.2, 8.0 \) Hz, 1H), 6.85 (dd, \( J = 1.2, 8.0 \) Hz, 1H), 6.62 (s, 1H), 4.18 (s, 2H), 3.36 (s, 3H), 2.99 (s, 3H), 1.49 (s, 9H).

43. tert-butyl 3-(2-(methylsulfonyl)-5,10-dioxo-8,9,9a,10-tetrahydro-5H-pyrrimido[4,5-e]pyrrolo[1,2-a][1,4]diazepin-11(7H)-yl)phenylcarbamate (10b)
\( ^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.41 (s, 1H), 7.55 (s, 1H), 7.36 (t, \( J = 8.0 \) Hz, 1H), 7.17 (dd, \( J = 1.2, 8.0 \) Hz, 1H), 6.83 (d, \( J = 8.0 \) Hz, 1H), 6.64 (s, 1H), 4.34 (d, \( J = 6.4 \) Hz, 1H), 3.92-3.86 (m, 1H), 3.73-3.66 (m, 1H), 2.96 (s, 3H), 2.87-2.84 (m, 1H), 2.25-2.10 (m, 3H), 1.49 (s, 9H).

44. tert-butyl 3-(2-(methylsulfonyl)-5,11-dioxo-7,8,9,10a,11-hexahydropyrido[1,2-a]pyrimido[4,5-e][1,4]diazepin-12(5H)-yl)phenylcarbamate (10c)
\( ^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.34 (s, 1H), 7.52 (s, 1H), 7.36 (t, \( J = 8.0 \) Hz, 1H), 7.21 (d, \( J = 8.0 \) Hz, 1H), 6.82 (d, \( J = 8.0 \) Hz, 1H), 6.59 (s, 1H), 4.55-4.50 (m, 1H), 4.33 (s, 1H), 3.13-3.06 (m, 1H), 3.00 (s, 3H), 2.39-2.35 (m, 1H), 2.00-1.57 (m, 5H), 1.49 (s, 9H).

45. tert-butyl 3-(6,7-dimethyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10d)
\( ^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 9.36 (s, 1H), 7.52 (s, 1H), 7.36 (t, \( J = 8.0 \) Hz, 1H), 7.20 (dd, \( J = 1.2, 8.0 \) Hz, 1H), 6.83 (d, \( J = 8.0 \) Hz, 1H), 6.62 (s, 1H), 4.38 (d, \( J = 4.8 \) Hz, 1H), 3.18 (s, 3H), 3.00 (s, 3H), 1.65 (s, 3H), 1.49 (s, 9H).

46. tert-butyl 3-(7-isopropyl-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10e)
\( ^1\text{H} \) NMR (400 MHz, CDCl\textsubscript{3}, a mixture of rotamers) \( \delta \) 9.41 (s) and 9.35 (s) (together 1H), 7.43-7.34 (m, 2H), 7.28-7.22 (m, 1H), 6.83-6.78 (m, 1H), 6.60 (s, 1H), 3.92 (d, \( J = 12.0 \) Hz, 0.78Hz) and 3.66 (d, \( J = 10.8 \) Hz, 0.22Hz), 3.39 (s) and 3.16 (s) (together
3H), 3.02 (s) and 2.93 (s) (together 3H), 1.83-1.73 (m, 1H), 1.49 (s, 9H), 1.11-1.00 (m, 6H).

47. tert-butyl 3-(7-isobutyl-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10f)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) δ 9.41 (s) and 9.37 (s) (together 1H), 7.44 (s, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 9.2$ Hz, 1H), 6.81 (d, $J = 7.6$ Hz, 1H), 6.59 (s, 1H), 4.43 (t, $J = 8.0$ Hz, 0.25H), and 4.15 (t, $J = 7.2$ Hz, 0.75H), 3.38 (s) and 3.14 (s) (together 3H), 3.02 (s) and 2.94 (s) (together 3H), 2.09-2.04 (m), 1.92-1.89 (m), and 1.56-1.55 (m) (together 2H), 1.69-1.63 (m, 1H), 1.49 (s, 9H), 0.99-0.93 (m, 6H).

48. tert-butyl 3-(6-methyl-2-(methylsulfonyl)-5,8-dioxo-7-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10g)

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.13 (s, 1H), 7.52 (s, 1H), 7.42 (t, $J = 8.0$ Hz, 1H), 7.31-7.22 (m, 4H), 7.15 (s, 2H), 6.92 (d, $J = 7.6$ Hz, 1H), 6.65 (s, 1H), 5.68 (s, 1H), 3.60 (s, 3H), 2.82 (s, 3H), 1.50 (s, 9H).

49. tert-butyl 3-(2-(methylsulfonyl)-5,8-dioxo-6-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10h)

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.45 (s, 1H), 7.59 (s, 1H), 7.51-7.45 (m, 4H), 7.41-7.35 (m, 2H), 7.24 (d, $J = 8.4$ Hz, 1H), 6.89 (d, $J = 7.6$ Hz, 1H), 6.65 (s, 1H), 4.58 (s, 2H), 3.01 (s, 3H), 1.49 (s, 9H).

50. tert-butyl 3-(7-benzyl-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10i)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) δ 9.52 (s) and 9.35 (s) (together 1H), 7.46-7.28 (m, 5H), 7.24-7.22 (m, 2H), 7.18 (d, $J = 8.4$ Hz and 7.05 (d, $J = 6.8$ Hz) (together 1H), 6.73-6.68 (m, 1H), 6.59 (s, 1H), 4.66-4.61 (m, 0.30H) and 4.49-4.45 (m, 0.70H), 3.64-3.58 (m), 3.32-3.27 (m) and 2.91-2.81 (m) (together 2H), 3.21 (s) and 3.04 (s) (together 3H), 2.97 (s, 3H), 1.49 (s, 9H).

51. tert-butyl 3-(7-(4-methoxybenzyl)-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10j)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) δ 9.50 (s) and 9.34 (s) (together
1H), 7.43-7.31 (m, 2H), 7.25-7.16 (m, 2.40H) and 6.96 (d, J = 8.8 Hz, 0.60H), 6.87 (t, J = 8.0 Hz, 2H), 6.75-6.67 (m, 1H), 6.58 (s, 1H), 4.61-4.57 (m) and 4.40-4.37 (m) (together 1H), 3.80 (s) and 3.79 (s) (together 3H), 3.59-3.53 (m), 3.23-3.19 (m) and 2.86-2.80 (m) (together 2H), 3.21 (s) and 3.07 (s) (together 3H), 2.97 (s) and 2.96 (s) (together 3H), 1.49 (s, 9H).

52. tert-butyl 3-(7-(4-chlorobenzyl)-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10k)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) $\delta$ 9.52 (s) and 9.34 (s) (together 1H), 7.50-7.28 (m, 4H), 7.24-7.14 (m, 2.60H) and 7.05 (d, J = 8.0 Hz, 0.4H), 6.73 (d, $J$ = 8.0 Hz) and 6.67 (d, J = 8.0 Hz) (together 1H), 6.59 (s, 1H), 4.62-4.58 (m) and 4.41-4.38 (m) (together 1H), 3.65-3.59 (m), 3.26-3.24 (m) and 2.90-2.76 (m) (together 2H), 3.22 (s) and 3.09 (s) (together 3H), 2.97 (s, 3H), 1.49 (s, 9H).

53. tert-butyl 3-(7-(4-fluorobenzyl)-6-methyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10l)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) $\delta$ 9.51 (s) and 9.32 (s) (together 1H), 7.51-7.31 (m, 2H), 7.24-7.14 (m, 2H), 7.15-7.00 (m, 3H), 6.73-6.65 (m, 1H), 6.61 (s, 1H), 4.61-4.57 (m, 0.23H) and 4.43-4.39 (m, 0.77H), 3.64-3.58 (m), 3.26-3.25 (m) and 2.90-2.84 (m) (together 2H), 3.21 (s) and 3.08 (s) (together 3H), 2.95 (s, 3H), 1.49 (s, 9H).

54. tert-butyl 3-(6-benzyl-2-(methylsulfonyl)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (10m)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.33 (s, 1H), 7.42 (s, 1H), 7.29-7.22 (m, 5H), 7.14 (s, 1H), 7.06 (dd, J = 1.2, 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.48 (s, 1H), 4.78 (s, 2H), 3.95 (s, 2H), 2.86 (s, 3H), 1.37 (s, 9H).

55. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11a)

**General Procedure for Synthesis of 11a-m.**

To a solution of 10a (1 g, 2.17 mmol), in 2-butyl alcohol (10 mL) was added 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (529 mg, 2.39 mmol), followed by
trifluoroacetic acid (177 µL, 2.39 mmol). The reaction mixture was stirred for 18 h at 110 ℃ in a seal tube. The reaction mixture was cooled to room temperature and poured into a solution of 10% aqueous NaHCO\textsubscript{3} and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was separated, washed with 10% aqueous NaHCO\textsubscript{3} and brine, dried with Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography (SiO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2}/Methanol stepwise elution, 100 :1 to 10 :1) to give the title compound. (0.88 g, 67% yield).

**56. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl) phenylamino)-5,10-dioxo-8,9,9a,10-tetrahydro-5H-pyrimido[4,5-e]pyrrolo[1,2-a][1,4]diazepin-11(7H)-yl)phenylcarbamate (11b)**

MS (ESI) m/z 629.2 [M+H]\textsuperscript{+}\n
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.95 (s, 1H), 7.81 (s, 1H), 7.46-7.40 (m, 2H), 7.32 (s, 1H), 7.09 (s, 1H), 6.89 (d, J = 7.2 Hz, 1H), 6.64 (s, 1H), 6.41 (s, 1H), 6.12 (s, 1H), 4.33-4.32 (m, 1H), 3.81 (s, 3H), 3.79-3.76 (m, 1H), 3.69-3.64 (m, 1H), 3.27 (br, 4H), 2.83 (br, 4H), 2.80 (s, 1H), 2.53 (s, 3H), 2.14-2.03 (m, 3H), 1.48 (s, 9H).

**57. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl) phenylamino)-5,11-dioxo-7,8,9,10,10a,11-hexahydropyrido[1,2-a]pyrimido[4,5-e][1,4]diazepin-12(5H)-yl)phenylcarbamate (11c)**

MS (ESI) m/z 643.2 [M+H]\textsuperscript{+}\n
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.87 (s, 1H), 7.81 (s, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.14 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.66 (s, 1H), 6.41 (s, 1H), 6.12 (s, 1H), 4.52-4.47 (m, 1H), 4.41-4.38 (m, 1H), 3.81 (s, 3H), 3.16 (t, J = 4.8 Hz, 4H), 3.08-3.01 (m, 1H), 2.64 (t, J = 4.8 Hz, 4H), 2.40 (s, 3H), 2.34-2.30 (m, 1H), 1.98-1.93 (m, 1H), 1.85-1.59 (m, 4H), 1.48 (s, 9H).

**58. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl) phenylamino)-6,7-dimethyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl...**
carbamate (11d)

MS (ESI) m/z 617.2 [M+H]+ 1H NMR (400 MHz, CDCl3) δ 8.90 (s, 1H), 7.82 (s, 1H), 7.49 (s, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.28 (s, 1H), 7.14 (s, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.62 (s, 1H), 6.41 (s, 1H), 6.12 (s, 1H), 4.44 (dd, J = 6.8, 13.6 Hz, 1H), 3.82 (s, 3H), 3.24 (br, 4H), 3.11 (s, 3H), 2.77 (br, 4H), 2.50 (s, 3H), 1.59 (s, 3H), 1.48 (s, 9H).

59. tert-butyl 3-(7-isopropyl-2- (2-methoxy-4- (4-methylpiperazin-1-yl) phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9 (6H)-yl)phenylcarbamate (11e)

MS (ESI) m/z 645.3 [M+H]+ 1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 8.97 (s) and 8.92 (s) (together 1H), 7.90-7.82 (m, 1H), 7.58 (s, 1H), 7.47-7.42 (m, 1H), 7.18 (s, 1H), 6.99 (s, 1H), 6.87 (d, J = 6.8 Hz, 1H), 6.65 (s) and 6.63 (s) a(together 1H), 6.41 (s, 1H), 6.09 (s, 1H), 3.90-3.86 (m, 1H), 3.81 (s, 3H), 3.46 (s) and 3.32 (s) (together 3H), 3.17 (br, 4H), 2.65 (br, 4H), 2.41 (s, 3H), 2.11-2.04 (m, 1H), 1.48 (s, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H).

60. tert-butyl 3-(7-isobutyl-2- (2-methoxy-4- (4-methylpiperazin-1-yl) phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9 (6H)-yl)phenylcarbamate (11f)

MS (ESI) m/z 659.2 [M+H]+ 1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 8.93 (s) and 8.92 (s) (together 1H), 7.90-7.82 (m, 1H), 7.58 (s, 1H), 7.47-7.42 (m, 1H), 7.18 (s, 1H), 6.99 (s, 1H), 6.87 (d, J = 6.8 Hz, 1H), 6.65 (s) and 6.63 (s) a(together 1H), 6.41 (s, 1H), 6.09 (s, 1H), 4.32 (t, J = 7.6 Hz, 0.3H) and 4.22 (t, J = 6.0 Hz, 0.7H), 3.82 (s, 3H), 3.26 (br, 4H), 3.09 (s, 3H), 2.80 (br, 4H), 2.08-2.01 (m, 1H), 1.87-1.80 (m, 1H), 1.70-1.65 (m, 1H), 1.48 (s, 9H), 0.96-0.94 (m, 6H).

61. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl -5,8-dioxo-7-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11g)

MS (ESI) m/z 679.0 [M+H]+ 1H NMR (400 MHz, CDCl3) δ 8.67 (s, 1H), 7.61 (s, 2H), 7.48 (t, J = 8.0 Hz, 1H), 7.27-7.24 (m, 3H), 7.19 (s, 3H), 6.97 (d, J = 8.0 Hz, 2H), 6.62 (s, 1H), 6.38 (s, 1H), 6.09 (s, 1H), 5.58 (s, 1H), 3.76 (s, 3H), 3.54 (s, 3H), 3.14 (t, J = 4.0 Hz, 4H), 2.62 (t, J = 4.0 Hz, 4H), 2.39 (s, 3H), 1.49 (s, 9H).
62. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5,8-dioxo-6-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11h)

MS (ESI) m/z 665.2 [M+H]^+ 1H NMR (400 MHz, CDCl3) δ 8.99 (s, 1H), 7.88 (s, 1H), 7.55-7.50 (m, 3H), 7.46-7.41 (m, 3H), 7.35 (s, 1H), 7.30 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.66 (s, 1H), 6.43 (S, 1H), 6.12 (s, 1H), 4.55 (s, 2H), 3.83 (s, 3H), 3.15 (br, 4H), 2.60 (br, 4H), 2.38 (s, 3H), 1.49 (s, 9H).

63. tert-butyl 3-(7-benzyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11i)

MS (ESI) m/z 693.2 [M+H]^+ 1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 9.05 (s) and 8.90 (s) (together 1H), 7.89 (s) and 7.80 (s) (together 1H), 7.54 (s, 1H), 7.44-7.20 (m, 6H), 7.11-7.03 (m, 2H), 6.81 (d, J = 8.4 Hz, 0.36H) and 6.76 (d, J = 8.0 Hz, 0.64H), 6.59 (s) and 6.56 (s) (together 1H), 6.43 (s) and 6.40 (s), (together 1H), 6.10 (s) and 6.07 (s) (together 1H), 4.57-4.49 (m, 1H), 3.83 (s and 3.80 (s) (together 3H), 3.61-3.56 (m), 3.25-3.22 (m) and 3.07-3.04 (m) (together 2H), 3.18 (br, 4H), 3.14 (s) and 2.97 (s) (together 3H), 2.65 (br, 4H), 2.42 (s) and 2.41 (s) (together 3H), 1.48 (s, 9H).

64. tert-butyl 3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-7-(4-methoxybenzyl)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11j)

MS (ESI) m/z 723.2 [M+H]^+ 1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 9.04 (s) and 8.89 (s) (together 1H), 7.89 (s) and 7.80 (s) (together 1H), 7.53 (s, 1H), 7.43-7.37 (m, 1H), 7.18-7.00 (m, 4H), 6.87-6.75 (m, 3H), 6.66 (s and 6.63 (s) (together 1H), 6.42 (s) and 6.40 (s) (together 1H), 6.10 (s) and 6.06 (s) (together 1H), 4.49-4.44 (m, 1H), 3.83 (s and 3.79 (s) (together 3H), 3.79 (s) and 3.77 (s) (together 3H), 3.15 (s, 3H), 3.12 (br, 4H), 2.99 (s, 2H), 2.62 (br, 4H), 2.39 (s) and 2.38 (s) (together 3H), 1.48 (s, 9H).

65. tert-butyl 3-(7-(4-chlorobenzyl)-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9...
(6H)-yl)phenylcarbamate (11k)

MS (ESI) m/z 727.2 [M+H]+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 9.04 (s) and 8.89 (s) (together 1H), 7.90 (s) and 7.81 (s) (together 1H), 7.50 (s, 1H), 7.40 (dd, J = 8.4, 16.8 Hz, 1H), 7.33-7.27 (m, 2H), 7.22-7.19 (m, 2H), 7.13-7.04 (m, 2H), 6.81 (d, J = 7.20 Hz, 0.3H) and 6.75 (d, J = 7.60 Hz, 0.7 Hz) (together 1H), 6.60 (s) and 6.57 (s) (together 1H), 6.43 (s) and 6.40 (s) (together 1H), 6.10 (s) and 6.06 (s) (together 1H), 4.50-4.46 (m, 1H), 3.83 (s) and 3.80 (s) (together 3H), 3.61-3.55 (m), 3.19-3.17 (m) and 3.05 (br) (together 2H), 3.15 (s) and 3.02 (s) (together 3H), 3.14 (br, 4H), 2.62 (br, 4H), 2.41 (s) and 2.39 (s) (together 1H), 1.48 (s, 9H).

66. tert-butyl 3-(7-(4-fluorobenzyl)-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11l)

MS (ESI) m/z 711.3 [M+H]+ 1H NMR (400 MHz, CDCl₃, a mixture of rotamers) δ 7.90 (s) and 7.81 (s) (together 1H), 7.52-7.36 (m, 2H), 7.25-7.22 (m, 2H), 7.12-6.97 (m, 4H), 6.80 (d, J = 6.8 Hz, 0.32H) and 6.74 (d, J = 8.0 Hz, 0.68H), 6.62 (s) and 6.58 (s) (together 1H), 6.43 (s) and 6.39 (s) (together 1H), 6.10 (s) and 6.06 (s) (together 1H), 4.49-4.46 (m, 1H), 3.83 (s) and 3.80 (s) (together 3H), 3.61-3.55 (m), 3.25-3.22 (m) and 3.06-3.03 (m) (together 2H), 3.18 (br, 4H), 3.16 (s) and 3.00 (s) (together 3H), 2.69 (br, 4H), 2.45 (s) and 2.44 (s) (together 3H), 1.48 (s, 9H).

67. tert-butyl 3-(6-benzyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenylcarbamate (11m)

MS (ESI) m/z 679.2 [M+H]+ 1H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 7.85 (s, 1H), 7.49 (s, 1H), 7.43-7.31 (m, 7H), 7.09 (s, 1H), 6.88 (d, J = 7.6 Hz, 1H), 6.65 (s, 1H), 6.41 (s, 1H), 6.11 (s, 1H), 4.86 (s, 2H), 4.04 (s, 2H), 3.81 (s, 3H), 3.19 (br, 4H), 2.68 (br, 4H), 2.43 (s, 3H), 1.48 (s, 9H).

68. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2a)

General Procedure for Synthesis of 2a-m.

To a solution of 11a (687 mg, 1.14 mmol) in CH₂Cl₂ (5 mL) was added trifluoroacetic
acid (0.85 mL, 11.4 mmol). The reaction mixture was stirred for 4 h at room temperature. The reaction mixture was diluted with CH₂Cl₂, and basified with saturated aqueous NaHCO₃ till pH = 9 and extracted with CH₂Cl₂. The organic layer was separated, washed with 10% aqueous NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography (SiO₂, CH₂Cl₂/Methanol stepwise elution, 100 :1 to 10 :1) to give 9-(3-aminophenyl)-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-6,7-dihydro-5H-pyrimido[4,5-e][1,4]diazepine-5,8(9H)-dione 12a as an yellow solid (487 mg, 85% yield), which was used in the next reaction without characterization. This yellow solid 12a (428 mg, 0.85 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL) under argon and cooled to 0 °C (ice bath). N,N-diisopropylethylamine (221 μL, 1.28 mmol) and acryloyl chloride (105 μL, 1.28 mmol) were added with stirring. The reaction was allowed to warm to room temperature. After stirring for 4 h, the reaction mixture was poured into a solution of 10% aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layer was separated, washed with 10% aqueous NaHCO₃ and brine, dried with Na₂SO₄, filtered, and concentrated in vacuo. The resultant crude material was purified by column chromatography (SiO₂, CH₂Cl₂/Methanol stepwise elution, 100 :1 to 10 :1) to give the title compound. (388 mg, 82% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.90 (s, 1H), 7.98 (s, 2H), 7.74 (s, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.00-6.91 (m, 2H), 6.43-6.39 (m, 2H), 6.31-6.25 (m, 1H), 6.08 (d, J = 8.0 Hz, 1H), 5.74 (dd, J = 1.2, 10.0 Hz, 1H), 4.06 (s, 2H), 3.81 (s, 3H), 3.26 (s, 3H), 3.18 (t, J = 4.4 Hz, 4H), 2.71 (s, 4H), 2.46 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 167.70, 165.16, 163.33, 162.97, 159.35, 158.47, 158.89, 147.78, 139.21, 139.16, 139.99, 130.22, 128.12, 124.29, 120.22, 120.08, 119.83, 119.57, 109.46, 107.53, 99.35, 55.60, 55.07, 53.65, 49.47, 46.07, 35.96. HRMS (ESI) Calcd for [M+H]⁺ = 557.2619, found: [M+H]⁺ = 557.2621.
7.44 (t, \( J = 7.6 \) Hz, 1H), 7.38 (s, 1H), 7.00 (s, 1H), 6.93 (d, \( J = 7.2 \) Hz, 1H), 6.42-6.38 (m, 2H), 6.22-6.16 (m, 1H), 6.09 (s, 1H), 5.74 (d, \( J = 10.0 \) Hz, 1H), 4.34 (d, \( J = 5.2 \) Hz, 1H), 3.80 (s, 3H), 3.77 (s, 1H), 3.67-3.65 (m, 1H), 3.12 (br, 4H), 2.79 (s, 1H), 2.60 (br, 4H), 2.38 (s, 3H), 2.14-2.05 (m, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.16, 163.27, 162.40, 159.46, 158.28, 148.79, 147.51, 140.23, 139.17, 131.05, 130.10, 127.96, 124.35, 120.46, 120.31, 119.64, 119.53, 113.04, 110.43, 107.76, 99.61, 58.04, 55.60, 55.02, 49.42, 47.00, 45.92, 26.95, 23.81.

HRMS (ESI) Calcd for [M+H]\(^+\) = 583.2776, found: [M+H]\(^+\) = 583.2773.

70. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5,11-dioxo-7,8,9,10,10a,11-hexahydropyrido[1,2-a]pyrimido[4,5-e][1,4]diazepin-12(5H)-yl)phenyl)acrylamide (2c)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.87 (s, 1H), 7.97 (s, 1H), 7.90 (s, 1H), 7.43 (t, \( J = 8.0 \) Hz, 1H), 7.40 (s, 1H), 7.08 (s, 1H), 6.92 (d, \( J = 7.6 \) Hz, 1H), 6.40-6.36 (m, 2H), 6.27-6.20 (m 1H), 6.09 (s, 1H), 5.72 (d, \( J = 10.8 \) Hz, 1H), 4.50-4.47 (m, 1H), 4.43-4.40 (m, 1H), 3.79 (s, 3H), 3.15 (br, 4H), 3.06-2.99 (m, 1H), 2.67 (br, 4H), 2.42 (s, 3H), 2.27 (s, 1H), 1.95-1.90 (m, 1H), 1.83-1.62 (m, 4H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.68, 166.07, 163.26, 162.49, 159.44, 158.26, 148.78, 147.61, 139.42, 139.06, 131.02, 130.05, 127.95, 124.47, 120.39, 120.33, 119.70, 119.47, 110.55, 107.69, 99.55, 55.60, 55.02, 52.63, 49.51, 46.01, 39.88, 23.27, 22.84, 18.83. HRMS (ESI) Calcd for [M+H]\(^+\) = 597.2932, found: [M+H]\(^+\) = 597.2929.

71. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6,7-dimethyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2d)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.89 (s, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.77 (s, 1H), 7.47-7.41 (m, 2H), 7.06 (s, 1H), 6.92 (d, \( J = 7.6 \) Hz, 1H), 6.41-6.23 (m, 3H), 6.15-6.06 (m, 1H), 5.72 (dd, \( J = 1.2 \), 10.0 Hz, 1H), 4.45 (dd, \( J = 6.8 \), 13.6 Hz, 1H), 3.80 (s, 3H), 3.17 (br, 4H), 3.10 (s, 3H), 2.72 (br, 4H), 2.45 (s, 3H), 1.57 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 169.25, 165.99, 163.45, 162.65, 159.50, 158.16, 148.85, 147.17, 139.61, 139.30, 134.60, 131.13, 129.99, 127.92, 124.25, 120.94, 120.40, 119.69, 110.35, 108.11, 100.08, 55.61, 54.69, 52.47, 49.12, 45.36, 28.37, 12.65. HRMS (ESI)
Calcd for [M+H] + = 571.2776, found: [M+H] + = 571.2770.

72. N-(3-(7-isopropyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2e)

1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 8.97 (s) and 8.92 (s) (together 1H), 8.04-7.96 (m and 7.80 (s (together 3H), 7.51-7.33 (m, 2H), 7.04 (d, J = 6.8Hz) and 6.91 (d, J = 6.8Hz) (together 2H), 6.41-6.35 (m, 2H), 6.20-6.06 (m, 2H), 5.73-5.70 (m, 1H), 3.82 (s, 1H), 3.80 (s, 3H), 3.45 (s, 0.70H) and 3.33 (s, 2.30H), 3.10 (br, 4H), 2.59 (br, 4H), 2.37 (s, 3H), 2.13-2.05 (m, 1H), 1.07-0.96 (m, 6H). 13C NMR (125 MHz, CDCl3) δ 169.45, 163.60, 163.28, 162.62, 162.42, 157.16, 148.77, 147.49, 140.26, 139.57, 131.08, 130.24, 130.12, 127.87, 124.47, 120.42, 120.19, 119.71, 119.39, 107.73, 99.52, 74.31, 55.61, 54.99, 49.39, 45.93, 39.73, 28.76, 20.12, 19.96, 19.48, 19.28. HRMS (ESI) Calcd for [M+H] + = 599.3089, found: [M+H] + = 599.3087.

73. N-(3-(7-isobutyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2f)

1H NMR (400 MHz, CDCl3, a mixture of rotamers) δ 8.92 (s) and 8.90 (s) (together 1H), 7.92-7.79 (m, 3H), 7.49-7.42 (m, 1H), 7.36 (s, 1H), 7.05-6.91 (m, 2H), 6.41-6.37 (m, 2H), 6.26-6.19 (m, 1H), 6.10 (s, 1H), 5.73 (d, J = 10.4 Hz, 1H), 4.32 (t, J = 7.6 Hz, 0.3H) and 4.27 (t, J = 7.6 Hz, 0.7H), 3.80 (s, 3H), 3.32 (s) and 3.08 (s) (together 3H), 3.14 (br, 4H), 2.66 (br, 4H), 2.41 (s, 3H), 2.07-1.61 (m, 3H), 0.96-0.91 (m, 3H). 13C NMR (125 MHz, CDCl3) δ 169.82, 168.67, 166.38, 163.81, 163.35, 162.76, 162.60, 158.31, 148.86, 147.38, 139.58, 139.26, 131.10, 130.05, 127.90, 124.38, 120.57, 120.27, 119.80, 107.92, 99.81, 55.62, 55.25, 54.88, 49.30, 45.71, 38.83, 38.59, 35.42, 28.84, 25.69, 25.18, 22.59, 22.32. HRMS (ESI) Calcd for [M+H] + = 613.3245, found: [M+H] + = 613.3237.

74. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2g)
\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.67 (s, 1H), 8.48 (s, 1H), 7.97 (d, \( J = 6.4 \) Hz, 1H), 7.63 (s, 1H), 7.56 (s, 1H), 7.47 (t, \( J = 7.6 \) Hz, 1H), 7.24 (d, \( J = 7.2 \) Hz, 2H), 7.18 (d, \( J = 6.8 \) Hz, 3H), 6.98 (d, \( J = 7.6 \) Hz, 1H), 6.87 (s, 1H), 6.39-6.37 (m, 2H), 6.32 (s, 1H), 6.10 (s, 1H), 5.73-5.70 (m, 1H), 5.57 (s, 1H), 3.73 (s, 3H), 3.52 (s, 3H), 3.23 (br, 4H), 2.85 (br, 4H), 2.54 (s, 3H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 168.99, 165.02, 163.67, 162.41, 158.81, 156.75, 148.66, 146.52, 139.84, 139.61, 133.36, 131.27, 130.05, 129.18, 128.41, 127.89, 124.12, 121.37, 120.36, 119.78, 119.36, 108.41, 100.30, 69.08, 55.57, 54.44, 48.70, 44.86, 29.66. HRMS (ESI) Calcd for [M+H]\(^+\) = 633.2932, found: [M+H]\(^+\) = 633.2927.

75. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5,8-dioxo-6-phenyl-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2h)

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 8.96 (s, 1H), 8.07 (s, 1H), 7.94 (s, 1H), 7.48-7.46 (m, 3H), 7.41 (t, \( J = 8.0 \) Hz, 2H), 7.31-7.27 (m, 2H), 6.96 (d, \( J = 7.2 \) Hz, 2H), 6.40-6.36 (m, 2H), 6.19-6.06 (m, 2H), 5.70 (d, \( J = 10.8 \) Hz, 1H), 4.44 (s, 2H), 3.83 (s, 3H), 3.09 (br, 4H), 2.56 (br, 4H), 2.36 (s, 3H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 168.30, 164.26, 163.31, 159.35, 158.37, 148.87, 147.86, 141.72, 139.33, 138.96, 131.01, 130.30, 129.27, 127.95, 127.30, 125.35, 124.05, 120.18, 119.95, 119.86, 119.60, 109.75, 107.47, 99.21, 55.62, 55.07, 54.54, 49.33, 46.10. HRMS (ESI) Calcd for [M+H]\(^+\) = 619.2776, found: [M+H]\(^+\) = 619.2770.

76. N-(3-(7-benzyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2i)

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, a mixture of rotamers) \( \delta \) 9.04 (s) and 8.89 (s) (together 1H), 7.92-7.75 (m, 3H), 7.43-7.39 (m, 1H), 7.35-7.27 (m, 3H), 7.25-7.09 (m, 3H), 6.96 (s, 1H), 6.86-6.81 (m, 1H), 6.40-6.35 (m, 2H), 6.16-6.04 (m, 2H), 5.70 (d, \( J = 10.4 \) Hz, 1H), 4.61-4.58 (m, 0.64H) and 4.51 (t, \( J = 8.4 \) Hz, 0.36H), 3.81 (s) and 3.78 (s) (together 3H), 3.63-3.52 (m), 3.26-3.21 (m) and 3.04 (br) (together 2H), 3.14 (s) and 2.98 (s) (together 3H), 3.12-3.06 (m, 4H), 2.60-2.55 (m, 4H), 2.37-2.35 (s, 3H). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 168.88, 167.96, 166.06, 163.64, 163.21, 162.98,
162.69, 158.23, 139.05, 136.06, 135.15, 130.96, 130.17, 129.08, 128.98, 128.89, 128.09, 127.59, 127.17, 124.53, 120.07, 107.65, 107.5, 99.48, 68.88, 58.25, 55.63, 55.58, 55.07, 49.54, 46.11, 38.82, 35.41, 32.87, 29.06.


77. N-(3-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-7-(4-methoxybenzyl)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2j)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) $\delta$ 9.04 (s) and 8.99 (s) (together 1H), 8.08-7.75 (m, 3H), 7.43 (t, $J = 8.0$ Hz, 1H), 7.34-7.24 (m, 2H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.03-6.82 (m, 4H), 6.41-6.37 (m, 2H), 6.30-6.21 (m, 1H), 6.10-6.06 (m, 1H), 5.73 (d, $J = 9.6$ Hz, 1H), 4.53-4.45 (m, 1H), 3.84-3.78 (m, 6H), 3.55-3.46 (m), 3.24-3.22 (m) and 2.99 (s) (together 2H), 3.21-3.18 (m, 4H), 3.15 (s) and 3.01 (s) (together 3H), 2.76-2.72 (m, 4H), 2.53-2.46 (m, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.00, 168.09, 166.05, 163.64, 163.37, 163.00, 162.69, 158.99, 158.65, 158.19, 148.95, 147.16, 139.40, 131.10, 130.13, 130.04, 127.95, 126.96, 124.37, 120.10, 119.81, 114.53, 114.32, 108.26, 108.09, 100.19, 100.07, 68.99, 58.50, 55.65, 55.60, 55.28, 54.71, 49.08, 45.38, 38.81, 34.56, 32.02, 29.05. HRMS (ESI) Calcd for [M+H]^+ = 677.3194, found: [M+H]^+ = 677.3190.

78. N-(3-(7-(4-chlorobenzyl)-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2k)

$^1$H NMR (400 MHz, CDCl$_3$, a mixture of rotamers) $\delta$ 9.03 (s) and 8.89 (s) (together 1H), 7.96-7.87 (m, 2H), 7.59 (s, 1H), 7.45-7.43 (m, 1H), 7.32 (d, $J = 8.4$ Hz, 1H), 7.25-7.16 (m, 3H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.96 (s, 1H), 6.88-6.82 (m, 1H), 6.43-6.37 (m, 2H), 6.22-6.15 (m, 1H), 6.10-6.03 (m, 1H), 5.75 (d, $J = 10.8$ Hz, 1H), 4.53-4.47 (m, 1H), 3.82 (s) and 3.78 (s) (together 3H), 3.58-3.53 (m), 3.20-3.19 (m) and 3.05 (br) (together 2H), 3.15 (s) and 3.03 (s) (together 3H), 3.09 (br, 4H), 2.58 (br, 4H), 2.39 (s) and 2.37 (s) (together 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 168.57, 167.84, 166.00, 163.57, 163.30, 162.97, 162.69, 159.53, 159.35, 158.13, 157.24, 148.91, 147.64, 139.33, 134.52, 133.63, 133.59, 133.03, 130.97, 130.55, 130.33,
130.15, 129.31, 129.00, 128.01, 124.31, 120.17, 119.88, 119.59, 107.75, 107.61, 99.63, 68.63, 58.20, 55.58, 54.93, 49.37, 45.87, 38.83, 34.81, 32.34, 29.05.


**79.** N-(3-(7-(4-fluorobenzyl)-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-6-methyl-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2l)

**¹H NMR** (400 MHz, CDCl₃, a mixture of rotamers) δ 9.04 (s) and 8.89 (s) (together 1H), 7.93-7.66 (m, 3H), 7.44 (s, 1H), 7.36-6.93 (m, 6H), 6.87-6.81 (m, 1H), 6.42 (s) and 6.38 (s) (together 2H), 6.20 (d, J = 10.0 Hz) and 6.16 (d, J = 10.0 Hz) (together 1H), 6.10-6.03 (m, 1H), 5.74 (d, J = 10.4 Hz, 1H), 4.53-4.45 (m, 1H), 3.82 (s) and 3.78 (s) (together 3H), 3.58-3.52 (m), 3.21-3.17 (m) and 3.05-3.02 (m) (together 2H), 3.15 (s) and 3.01 (s) (together 3H), 3.10 (br, 4H), 2.63-2.58 (br, 4H), 2.40 (s) and 2.37 (s) (together 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 167.88, 166.02, 163.58, 163.30, 162.88, 162.68, 160.92, 158.15, 148.92, 147.69, 139.37, 131.73, 131.70, 130.97, 130.79, 130.72, 130.58, 130.52, 130.13, 128.03, 124.36, 120.17, 119.97, 119.85, 119.63, 116.18, 116.01, 115.83, 115.66, 107.81, 107.66, 99.64, 68.89, 58.38, 55.63, 55.58, 54.96, 49.41, 45.91, 38.81, 34.61, 32.16, 29.04. HRMS (ESI) Calcd for [M+H]⁺ = 665.2995, found: [M+H]⁺ = 665.2982.

**80.** N-(3-(6-benzyl-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5,8-dioxo-7,8-dihydro-5H-pyrimido[4,5-e][1,4]diazepin-9(6H)-yl)phenyl)acrylamide (2m)

**¹H NMR** (400 MHz, CDCl₃) δ 8.97 (s, 1H), 7.96 (s, 1H), 7.77 (d, J = 13.2 Hz, 2H), 7.44 (t, J = 8.0 Hz, 1H), 7.36-7.30 (m, 6H), 7.01-6.96 (m, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.41-6.37 (m, 2H), 6.19-6.10 (m, 1H), 6.07 (d, J = 6.4 Hz, 1H), 5.72 (dd, J = 1.2, 6.4 Hz, 1H), 4.84 (s, 2H), 4.00 (s, 2H), 3.81 (s, 3H), 3.12 (t, J = 4.8 Hz, 4H), 2.60 (t, J = 4.8 Hz, 4H), 2.38 (s, 3H). **¹³C NMR** (125 MHz, CDCl₃) δ 167.77, 165.23, 163.22, 159.34, 158.51, 148.86, 147.59, 139.19, 135.90, 131.07, 130.19, 128.90, 128.39, 128.10, 127.95, 124.09, 120.27, 119.85, 119.62, 109.31, 107.71, 99.54, 55.61, 54.99, 51.44, 51.09, 49.34, 45.89. HRMS (ESI) Calcd for [M+H]⁺ = 633.2932, found: [M+H]⁺ = 633.2929.