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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH ARTICLE

Design, synthesis and antitumor activity evaluation of 2,4,6-trisubstituted quinazoline derivatives containing piperidine moiety

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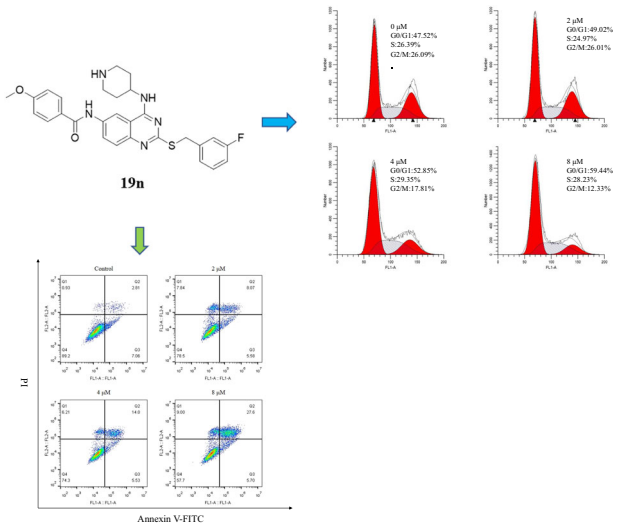
Abstract

In this study, 35 novel 2,4,6-trisubstituted quinazoline derivatives were designed and synthesized, and their anti-tumor activity in vitro were preliminarily explored. Among them, compound **19n** exhibited the best anti-proliferative activity against MGC-803 cells with an IC_{50} of 4.61 μM. Further biological experiments showed that compound **19n** could inhibit the cloning formation of MGC-803 cells. DAPI staining and apoptosis experiments showed that compound **19n** could induce apoptosis of MGC-803 cells in a concentration-dependent manner, and the cell cycle experiment indicated that compound **19n** could also arrest the MGC-803 cell cycle in G0/G1 phase. In addition, the ADME datas of compound **19n** was predicted and the potential target of compound **19n** was explained through molecular docking.



Keywords Quinazoline · Synthesis · Derivatives · Anti-proliferation

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Introduction

Cancer is caused by the loss of normal regulation and over-proliferation of body cells, which is an important cause of human death. According to literature reports, the incidence rate of cancer in China is on the rise. So far, humans have achieved significant results in cancer treatment, in addition to traditional surgical treatment, chemotherapy, and radiation therapy, various emerging treatment methods have also been continuously discovered in recent years, such as immunotherapy [1], DNA precision therapy [2], photothermal therapy [3], and stem cell therapy [4]. However, each treatment method has its limitations and cannot be effectively used for tumor treatment. Among them, chemical drug therapy is the most widely used in the field of cancer treatment, but chemotherapy drugs are prone to develop resistance, and it could cause serious adverse reactions, such as nausea, vomiting, hair loss, anemia, etc. Therefore, searching for safe, efficient, and low-toxicity anti-tumor drugs is still the hot spot of drug research and development [5–8].

Quinazoline is an important nitrogen-containing aromatic heterocyclic compound, with various pharmacological activities, such as anti-tumor [9, 10], antiviral [11, 12], antibacterial [13, 14], and anticonvulsant [15, 16], etc. Because of its diverse biological activities, it has aroused great interest of medical researchers and chemists [17–19], 4-aminoquinazoline can serve as the backbone structure for many kinase inhibitors, and many small molecule anti-tumor drugs based on the 4-aminoquinoline skeleton have been approved by FDA(Food and Drug Administration) for cancer treatment, such as gefitinib(**1**) [20], erlotinib(**2**) [21], afatinib(**3**) [22], etc. In addition, many quinazoline derivatives with anti-tumor activity have also been continuously reported in recent years, such as AURK inhibitor compound **4** [23] and compound LSD1 inhibitor compound **5** [24].

In addition, the amide group can act as the bioisosteres of many groups, such as 1,2,3-triazole, oxadiazole, imidazole, tetrazole, indole, pyridine, pyrazine, sulfonamide, etc, it play an important role in the design of anti-tumor drugs and the optimization or modification of lead compounds [25]. Benzylthiol is an important structural fragment for small drug molecules to exert pharmacological activities and improve pharmacokinetic characteristics, and previous research by our research group found that compounds **6** and **7** containing benzylthio groups have good anti-tumor activity [26, 27]. Furthermore, many compounds containing benzylthio groups were also reported and exhibited good anti-proliferative activity, such as compound **8** [28], it was speculated that the reason for its effectiveness may be that benzylthiol may be oxidized into sulfone in the body, but the true mechanism of action was still being further explored by our research group. In addition, through literature review, we found that there have been few reports on the simultaneous modification of positions 2, 4, and 6 of the quinazoline ring. Therefore, on the basis of extensive literature review and our research group's previous work, further development and exploration were conducted on the quinazoline ring, we chose to design and modify these three sites of the quinazoline ring reasonably to obtain efficient new chemical entities with anti-tumor activity. The detailed design rationale was shown in Figure 1. Thus, we introduced the benzylthio and amide groups into 4-aminoquinazoline skeleton structure based on the combination principles to synthesize a series of 2,4,6-trisubstituted quinazoline derivatives and evaluated their anti-proliferative activities in vitro, and taking

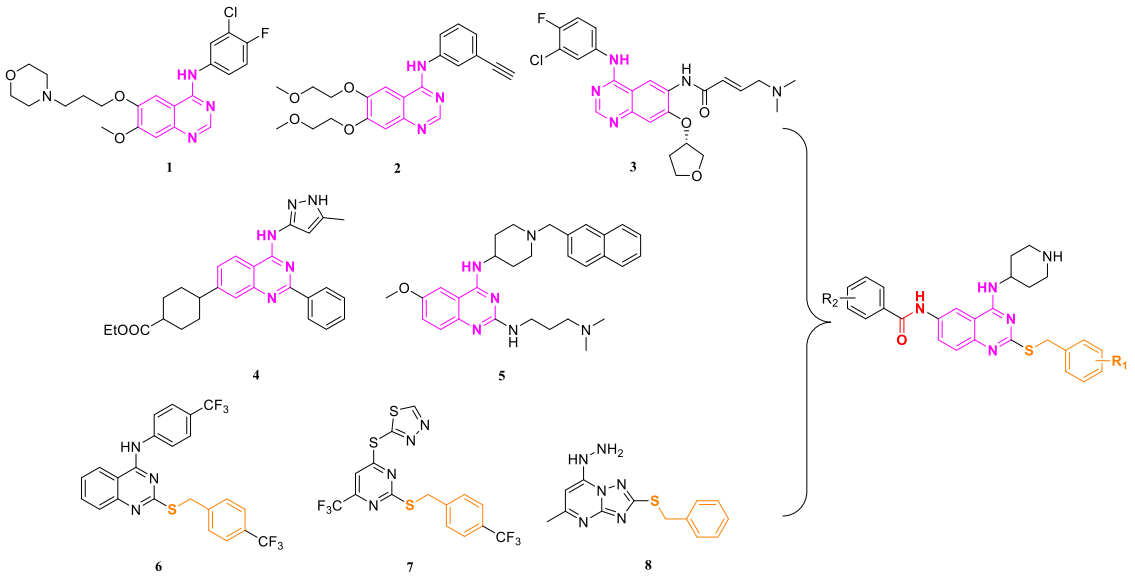
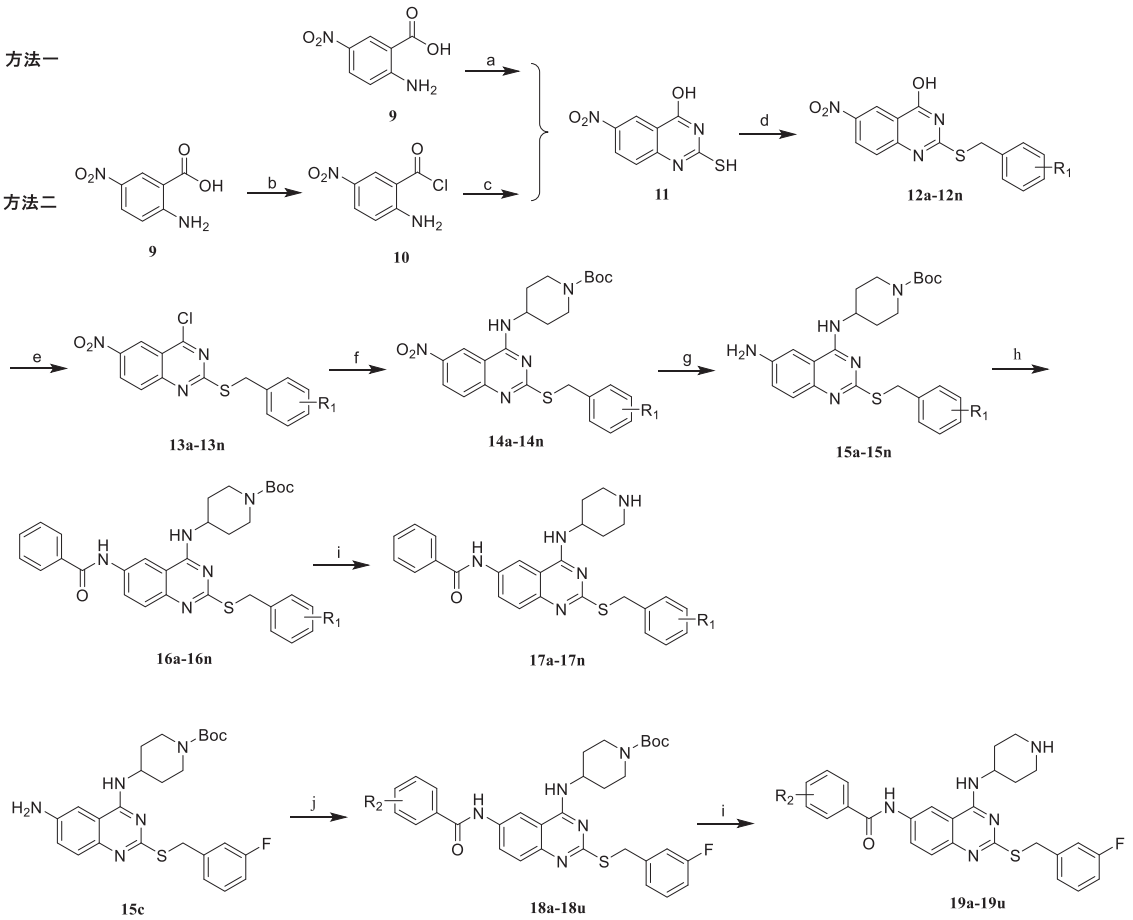


Fig. 1 Design rationale of 2,4,6-triquinazoline quinazoline derivatives



Scheme 1 Reaction conditions and reagents: a) thiourea, polyethylene glycol 400, 140 °C, 8 h; b) $SOCl_2$, 75 °C, 2 h; c) NH_4NCS, acetone, room temperature, 30 min; d) different benzyl chlorides, NaOH, H_2O, 80 °C, 1 h; e) $SOCl_2$, *N,N*-Dimethylformamide, 65 °C, 2 h; f) 4-amino-1-Boc-piperidine, K_2CO_3, 80 °C, 1 h; g) iron, NH_4Cl, ethanol, H_2O, 85 °C, 4 h; h) benzoic acid, HATU, DIPEA, *N,N*-Dimethylformamide, room temperature, 6 h; i) CF_3COOH, CH_2Cl_2, room temperature, 1 h; j) different benzoic acid, HATU, DIPEA, *N,N*-dimethylformamide, room temperature, 6 h

compound **19n** as an example, the potential target of the target compounds was predicted through computer simulation and its ADME data was predicted, hope to obtain some quinazoline derivatives with good anti proliferative activity.

Results and discussion

Chemistry

The preparation of compounds **17a–17n** and **19a–19u** was shown in Scheme 1. There are two synthesis methods for compound **11**. The first method: commercially available compound **9** reacted with thiourea at 140 °C for 8 h to obtain compound **11**. The second method: at first, compound **9** reacted with $SOCl_2$ to synthesize compound **10**, then compound **10** reacted with NH_4NCS for 30 min and cyclized to obtain compound **11**. The compounds **12a–12n** was obtained by a nucleophilic substitution stirred of compound **11** with different benzyl chloride. Next, compounds **12a–12n** were chlorinated with $SOCl_2$ to obtain compounds **13a–13n**. The compounds **13a–13n** were reacted with 4-amino-1-Boc-piperidine in DMF to yield the compounds **14a–14n**, which were reduced by iron powder to obtain compounds **15a–15n**. The compounds **16a–16n** were prepared via condensation stirred of compounds **15a–15n** with benzoic acid. Finally, the final compounds **17a–17n** were prepared by removal of the *N*-Boc protection through CF_3COOH treatment. Compounds **18a–18u** were obtained by condensation stirred of compound **15c** with different substituted benzoic acids under the action of condensation agent HATU. Then, the *N*-Boc protecting group was removed to get compounds **19a–19u**.

Biological activity

Anti-proliferative activity

Using 5-fluorouracil as the positive control, the anti-proliferative activities in vitro of compounds **17a–17n**

Table 1 In vitro anti-proliferative activity data of compounds **17a–17n**

Compd.	R1	IC_{50}(μM)[a]			
		A549	PC-3	MGC-803	Eca-109
17a	H	10.84 ± 0.91	12.23 ± 0.08	8.23 ± 0.59	21.37 ± 1.93
17b	2-F	15.99 ± 1.03	23.70 ± 0.19	7.10 ± 0.04	20.96 ± 0.74
17c	3-F	12.01 ± 0.94	10.17 ± 0.23	6.43 ± 0.38	13.21 ± 2.73
17d	4-F	13.23 ± 0.03	12.17 ± 0.13	7.94 ± 0.35	14.49 ± 1.20
17e	2-Cl	15.00 ± 0.71	20.13 ± 1.50	7.99 ± 0.60	26.75 ± 1.12
17f	3-Cl	11.16 ± 1.14	11.62 ± 0.54	6.97 ± 0.52	9.74 ± 0.87
17g	3-Br	10.12 ± 0.63	11.51 ± 0.87	7.50 ± 1.05	13.95 ± 1.68
17h	2-CH_3	11.14 ± 0.14	10.39 ± 1.22	11.78 ± 0.04	8.66 ± 0.31
17i	3-CH_3	8.93 ± 0.59	8.89 ± 0.63	8.58 ± 0.97	11.31 ± 0.74
17j	2-CF_3	9.97 ± 0.29	12.15 ± 0.11	11.53 ± 0.23	12.40 ± 0.23
17k	3-CF_3	9.86 ± 0.02	9.23 ± 1.01	11.51 ± 0.33	10.65 ± 1.34
17l	2-CN	19.70 ± 1.54	12.88 ± 0.83	12.03 ± 0.09	13.47 ± 0.62
17m	2,4-diCl	20.12 ± 0.54	10.91 ± 0.33	11.42 ± 0.81	15.03 ± 1.01
17n	3,4-diCl	16.40 ± 0.88	10.43 ± 0.51	10.10 ± 0.75	11.24 ± 0.12
5-Fu[b]	-	8.17 ± 0.26	9.35 ± 0.14	7.67 ± 0.54	7.91 ± 0.24

[a]IC_{50} (μM) the concentration of compound required for cell activity to be suppressed by half

[b]5-FUb Positive control

against A549(human non-small cell lung cancer cell line), PC-3(prostate cancer cell line), MGC-803(human gastric cancer cell line), and Eca-109(human esophageal cancer cell line) were determined by MTT method. The results were shown in Table 1.

As shown in Table 1, most target compounds displayed moderate anti-proliferative activities against the four cell lines. By comparing the activity data of compounds **17b–17d, 17e–17f, 17h–17i**, and **17j–17k** against A549 and PC-3, we can see that the anti-proliferative activities of the compounds that substituent in the meta position were superior to that of the ortho- or para- substitution. From the biological data of compounds **17b–17j**, When R_1 were halogen substituent, the anti-proliferative activities against MGC-803 were superior to the other three types of tumor cells. In addition, when R_1 was a double substituent, it would not have a significant impact on the activities of the compounds, such as compounds **17m** and **17n**. The summary of structure-activity relationship of compounds **17a–17n** were shown in Fig. 2. Compound **17c** showed the best anti-proliferative activity against MGC-803 cells, in order to obtain compounds with better activities, further optimization was carried out on the basis of compound **17c**, and different substituents were introduced into the benzamide at position 6 of the quinazoline ring, exploring the effects of electronic effect and the position of different substituents on the anti-proliferative activities of compounds. The results of anti-proliferative activities were shown in Table 2.

As shown in Table 2, when R_2 was a strong electron-withdrawing group, such as -NO_2 or -CN, it was found to have an adverse effect on the anti-proliferative activities of compounds. When R_2 were -Cl, -Br, -CH_3, -OCH_3, and -NO_2, we could conclude that compared to ortho and meta substitutions, compounds exhibit better anti-proliferative activity when the substituent was in the para position, such as compounds **19d–19f, 19g–19i, 19j–19l, 19m–19n**, and **19r–19s**. From the biological data of compounds **19t** and **19u**, we could see that when R_2 was -CN, the activities of meta substitution were always better than that of para substitution. The summary of structure-activity relationship of compounds **19a–19u** were shown in Fig. 2. Among them, compound **19n** showed the best anti-proliferative activity against MGC-803 cells, with the IC_{50} value of 4.61 μM, which was better than the positive control 5-Fu. Therefore, Compound **19n** was selected for further research.

Compound 19n inhibited the colony formation of MGC-803 cells

In order to further evaluate the anti-tumor ability in vitro of compound **19n**, the colony formation experiment was conducted. The MGC-803 cells were treated with drug-containing medium containing different concentrations of compound **19n**(0 μM, 1 μM, 2 μM, and 4 μM), as shown in Fig. 3, it could be seen that as the concentration of compound **19n** gradually increases, the cell community gradually decreases, and the area of the cell community also decreases. This indicated that compound **19n** could effectively inhibit the cloning formation of MGC-803 cells.

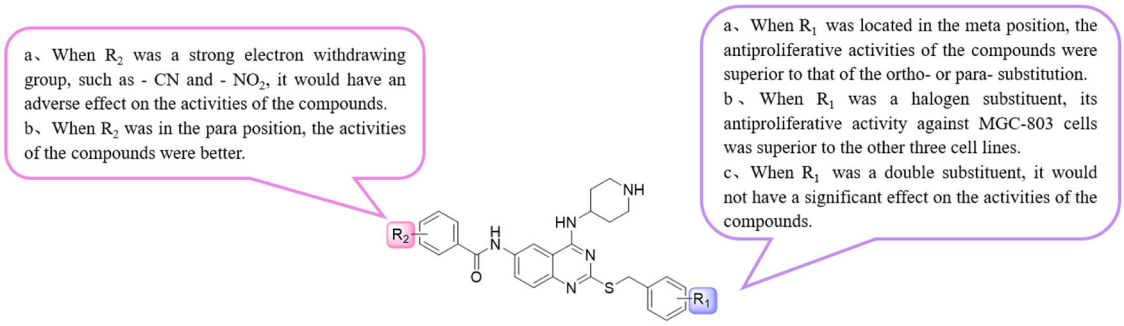


Fig. 2 Summary of structure-activity relationship of target compounds

Table 2 In vitro anti-proliferative activity data of compounds **19a–19u**

Compd.	R_2	$IC_{50}(\mu M)$[a]			
		A549	PC-3	MGC-803	Eca-109
19a	2-F	12.43 ± 0.18	8.62 ± 1.01	11.00 ± 0.87	10.78 ± 0.04
19b	3-F	10.27 ± 0.25	9.65 ± 0.08	11.02 ± 0.83	16.13 ± 1.12
19c	4-F	9.65 ± 0.61	9.47 ± 0.45	11.64 ± 0.06	12.34 ± 1.02
19d	2-Cl	9.26 ± 0.99	10.81 ± 0.59	11.64 ± 0.02	16.79 ± 0.37
19e	3-Cl	11.61 ± 0.18	9.67 ± 0.13	10.02 ± 1.33	14.95 ± 1.29
19f	4-Cl	5.93 ± 0.93	8.62 ± 1.01	9.49 ± 1.03	9.96 ± 0.19
19g	2-Br	12.52 ± 0.35	11.92 ± 0.39	10.37 ± 0.14	17.30 ± 0.19
19h	3-Br	10.86 ± 0.53	9.28 ± 0.48	11.57 ± 0.80	16.26 ± 0.48
19i	4-Br	7.84 ± 0.21	7.53 ± 1.19	9.47 ± 0.29	5.71 ± 0.41
19j	2-CH_3	15.28 ± 0.72	15.11 ± 0.76	12.83 ± 1.82	17.91 ± 0.38
19k	3-CH_3	12.07 ± 0.30	9.46 ± 0.14	9.56 ± 1.02	15.22 ± 1.23
19l	4-CH_3	11.89 ± 0.01	8.30 ± 0.71	8.27 ± 0.70	9.43 ± 0.34
19m	3-OCH_3	11.47 ± 0.39	9.93 ± 0.45	10.60 ± 1.37	13.05 ± 0.32
19n	4-OCH_3	11.43 ± 0.80	5.99 ± 0.12	4.61 ± 0.13	9.19 ± 0.03
19o	2-CF_3	16.88 ± 0.73	10.85 ± 0.69	8.66 ± 0.17	16.19 ± 0.81
19p	3-CF_3	22.46 ± 1.79	9.94 ± 0.07	8.73 ± 0.21	13.16 ± 0.24
19q	4-CF_3	10.96 ± 0.31	10.45 ± 0.51	8.70 ± 0.67	11.71 ± 0.34
19r	2-NO_2	46.31 ± 4.03	27.48 ± 0.33	24.26 ± 2.18	29.25 ± 0.59
19s	3-NO_2	23.44 ± 0.25	17.54 ± 0.28	12.80 ± 0.37	15.43 ± 0.35
19t	3-CN	34.14 ± 6.06	18.97 ± 0.88	13.30 ± 0.23	24.07 ± 0.49
19u	4-CN	> 50	> 50	26.89 ± 0.36	35.81 ± 0.94
5-Fu[b]	-	8.17 ± 0.26	9.35 ± 0.14	7.67 ± 0.54	7.91 ± 0.24

[a]IC_{50} (μM) the concentration of compound required for cell activity to be suppressed by half
[b]5-FUb Positive control

Compound 19n arrested MGC-803 cells at G0/G1 phase

Many anti-tumor drugs can effectively inhibit the development of tumor by arresting the cell cycle [29]. Therefore, the effects of compound **19n** on the cell cycle of MGC-803 were evaluated using flow cytometry. The results were shown in Fig. 4, the cells in G0/G1 phase gradually increased from 47.52% of the blank control group to 59.44% after 24 h of culture in the drug-containing medium with different concentrations of compound **19n**(0 μM, 2 μM, 4 μM, and 8 μM). The results suggested that compound **19n** could arrest the cell cycle of MGC-803 in G0/G1 phase in a concentration-dependent manner.

Compound 19n induced MGC-803 cells apoptosis

Inducing cell apoptosis is an important pathway for many anti-tumor drugs to exert their function [30]. At first, the effects of compound **19n** on the nuclear morphology of MGC-803 were observed through DAPI staining

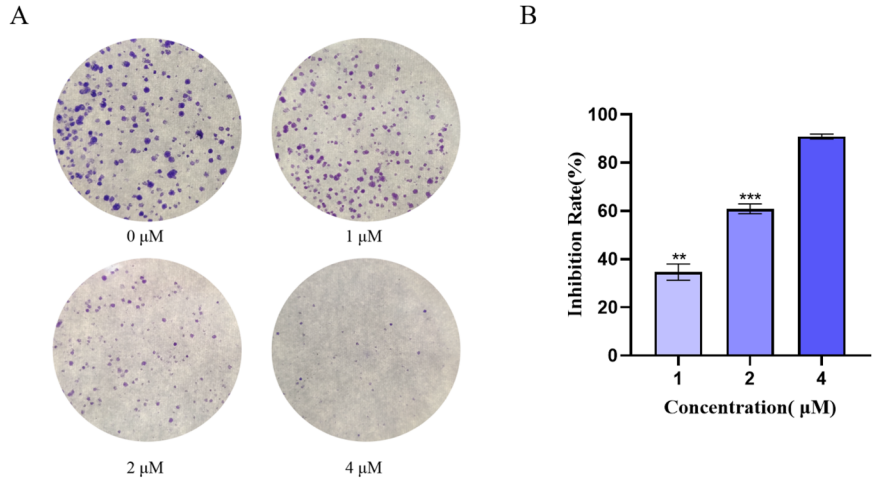


Fig. 3 **A** Effects of compound **19n** on the colony formation for MGC-803 cells. **B** Quantitative analysis of colony formation inhibition rate; Compared with the control group, $^{**}P < 0.01$, $^{***}P < 0.001$

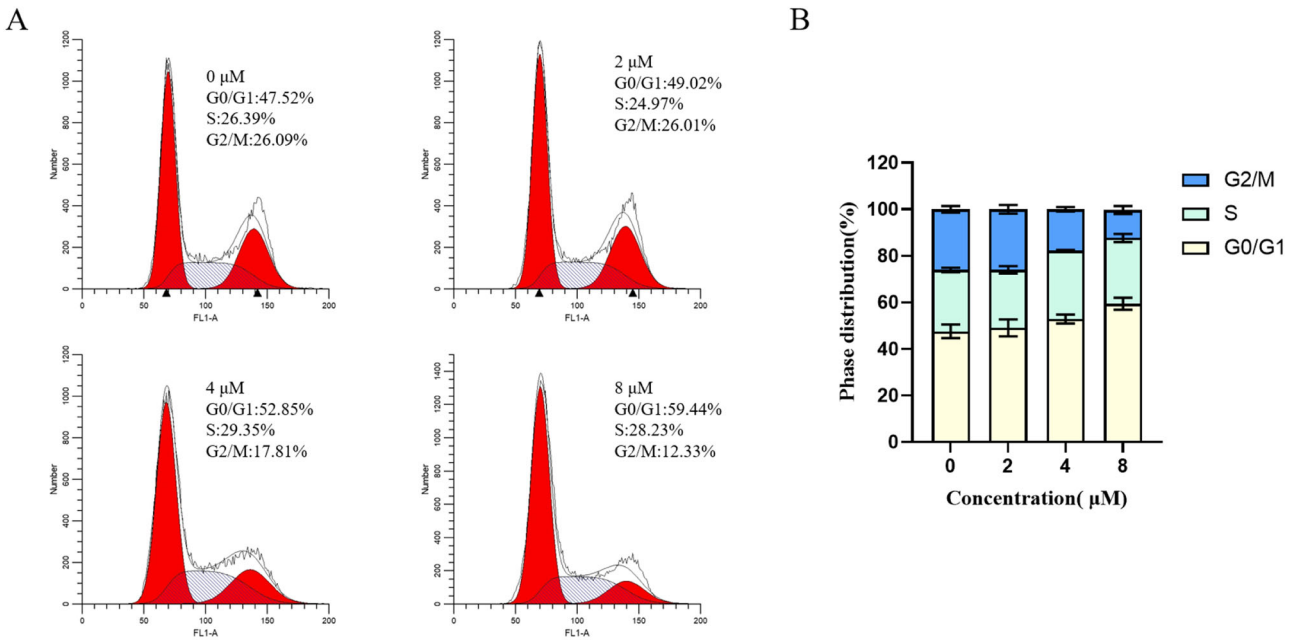


Fig. 4 **A** The effects of compound **19n** on cell cycle for MGC-803 cells. **B** Quantitative analysis of cell cycle distribution; Compared with the control group

experiment. It could be seen from Fig. 5A that with the increase of compound **19n** concentration(0 μM, 1 μM, 2 μM, and 4 μM), the number of cells with nuclear shrinkage and chromatin condensation gradually increases.

In order to further evaluate the ability of compound **19n** to induce cell apoptosis, propidium iodide (PI) and Annexin V-FITC double staining experiment was performed. The result was shown in Fig. 5B and C, the percentage of MGC-803 cells in G0/G1 phase increased from 9.21 to 38.64% after treatment of various concentrations compound **19n**(0 μM, 2 μM, 4 μM, and 8 μM) for 48 h. The above results indicated that compound **19n** could induce apoptosis of MGC-803 cells in a concentration-dependent manner.

ADME properties of compound 19n

The process in vivo (absorption, distribution, metabolism, excretion) of a compound is an important index to evaluate whether it has druggability [31]. We predicted the ADME properties of compound **19n** through pkCSM server (https://biosig.lab.uq.edu.au/pkcsm/). The predicted results were shown in Table 3. Absorption: The predicted results showed that compound **19n** had moderate Caco-2(human colorectal adenocarcinoma cells)

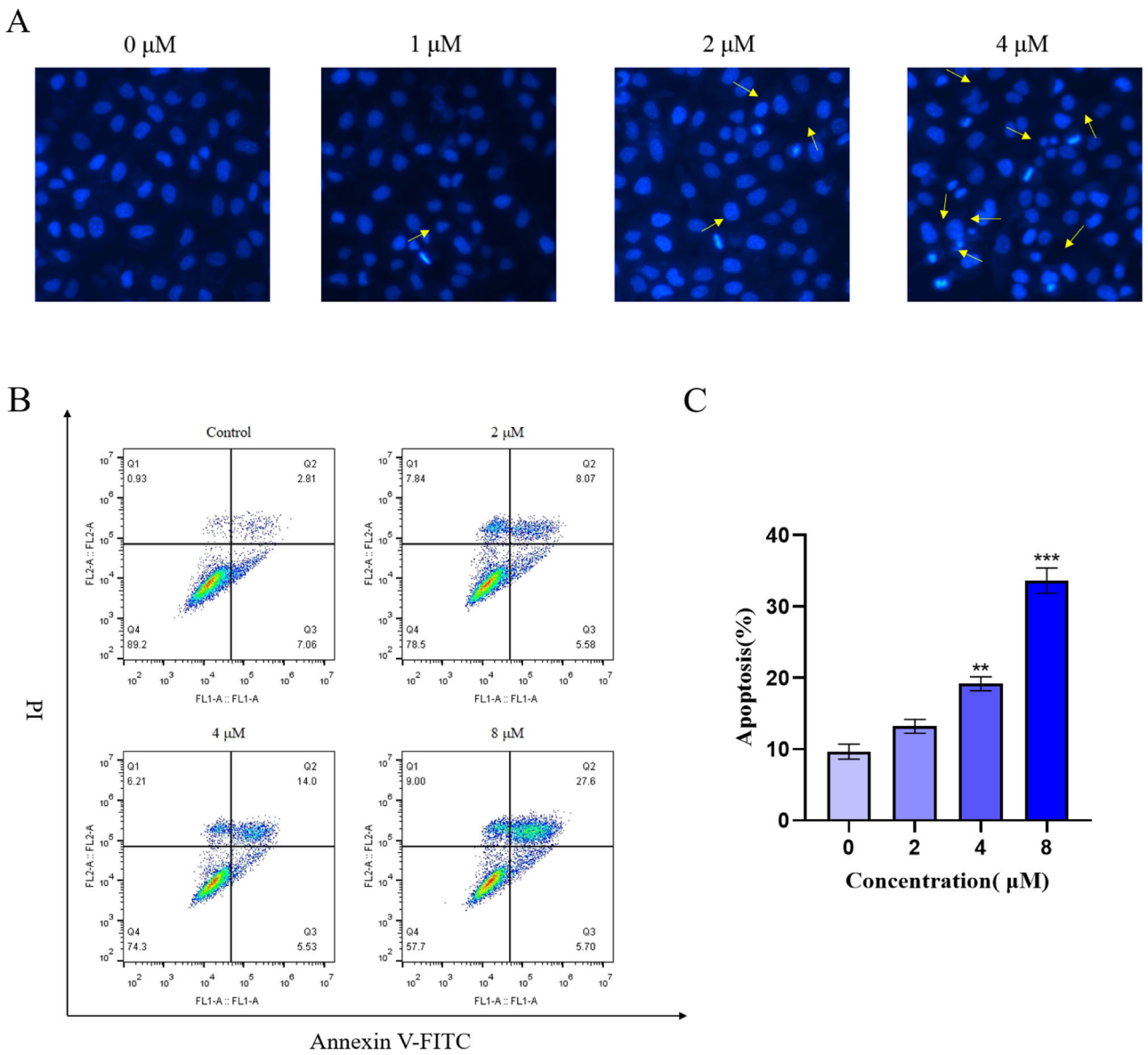


Fig. 5 **A** Effects of compound **19n** on nuclear morphology of MGC-803 cells. The arrows in the figure indicate the cells whose nuclei have shrunk or broken. **B** Effects of compound **19n** on apoptosis of MGC-803 cells **C** Quantitative analysis of apoptotic cells; Compared with the control group, $^{**}P < 0.01$, $^{***}P < 0.001$

permeability (log Papp in 10^{-6} cm/s = 0.709), moderate water solubility (log mol/L = −4.356) and good intestinal absorption (%Absorbed >90%). P-glycoprotein (P-gp) is a transmembrane transport protein, it can reduce the concentration of drugs in cells and related to the formation of tumor drug resistance [32], and the results showed that compound **19n** was an inhibitor of P-gp. Distribution: The logBB value and VDss value (log L/kg) were −1.225 and 0.523, respectively. The results meant that compound **19n** was poorly distributed in the brain and had good distribution. Metabolism: CYP2D6 is involved in the metabolism of multiple drugs. And the metabolic prediction of compound **19n** showed that compound **19n** was neither substrate nor inhibitor of CYP2D6. Excretion: OCT2 (Renal organic cation transporter 2) plays a crucial role in the disposal of drugs and endogenous compounds, as well as in renal clearance, the prediction results showed that compound **19n** was Renal OCT2 substrate.

Molecular docking

The quinazoline framework has been successfully used in the development of EGFR inhibitor. Therefore, in order to explore the potential target of the target compounds and discuss the pharmacophore of target compounds and the interaction leading to its antiproliferative activity, we

Table 3 Absorption, Distribution, Metabolism and Excretion data of compound **19n** predicted by pkCSM server

	Indexes	Value/ Result
Absorption	Water solubility (log mol/L)	−4.356
	Caco-2 permeability (log Papp in 10^{-6} cm/s)	0.709
	Intestinal absorption(human) (% Absorbed)	91.416
	P-glycoprotein inhibitor	Yes
Distribution	BBB permeability (log BB)	−1.225
	VDss (human) (log L/kg)	0.523
Metabolism	CYP2D6 substrate	No
	CYP2D6 inhibitor	No
Excretion	Total clearance (log ml/min/kg)	0.696
	Renal OTC2 substrate (YES/NO)	No

conducted docking studies on compound **19n** with EGFR kinase (PDB code: 3UG2) though MOE 2020. As shown in Fig. 6A and B, it can be seen that compound **19n** could effectively bind to the catalytic pocket of EGFR and interacted with multiple amino acid residues. The N atom on the piperidine ring could form ionic and hydrogen bonding interactions with Asp855 and Asn842, respectively. The benzyl sulfide group: the S atom could interact with residues Cys797 and Asp800 through a hydrogen bond, respectively; the benzene ring can form an H-π conjugated interaction with residue Gly796. In addition, the oxygen atom on the amide bond could form a hydrogen bond interaction with Met793. The above results indicated that the target compound may exert anti proliferative activity by inhibiting EGFR activity, but the specific mechanism need to be further exploration in our future study.

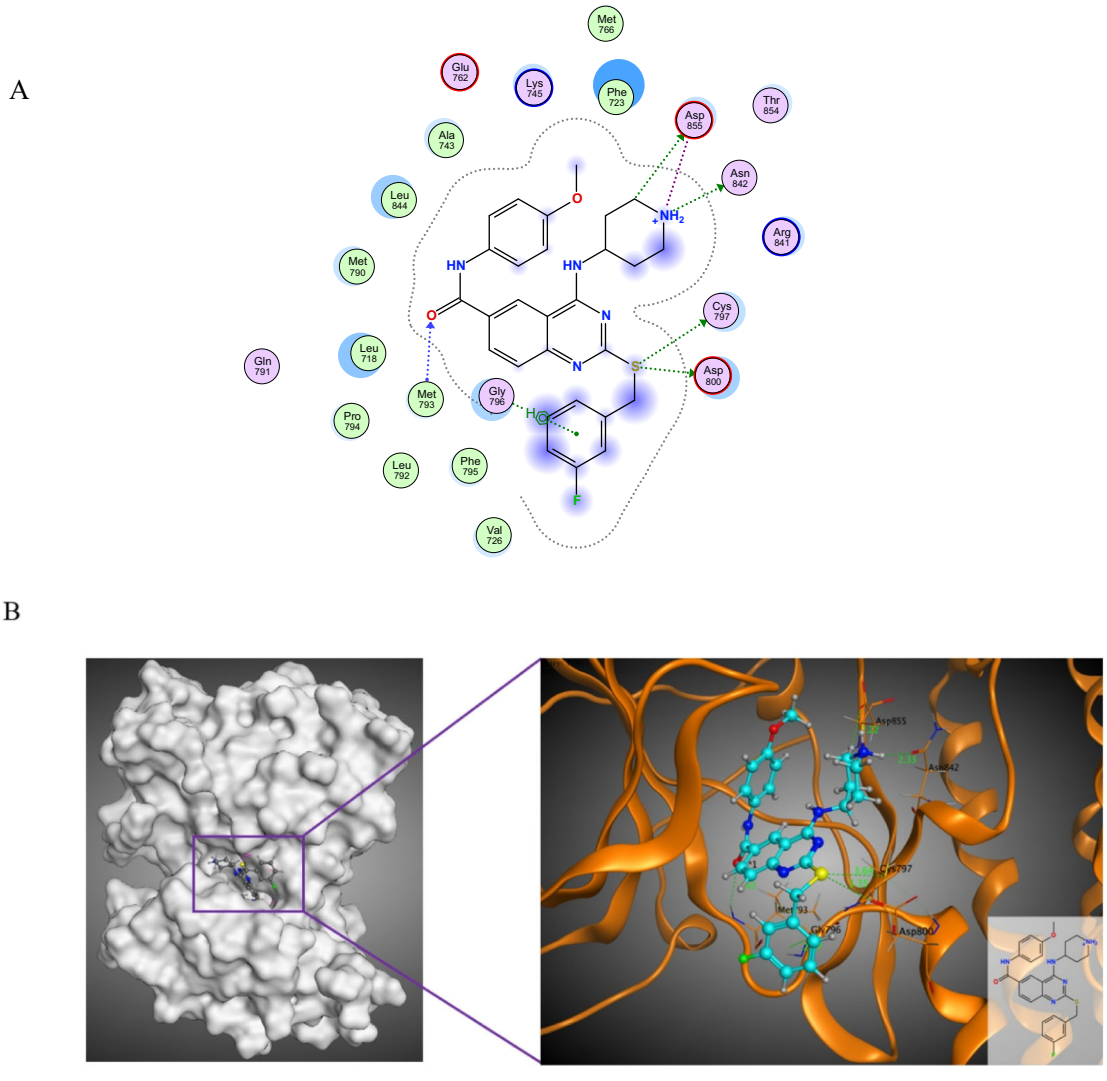


Fig. 6 Predicted binding modes of compound **19n** with EGFR(PDB code: 3UG2). **A** The 2D combination mode of compound **19n** with EGFR. **B** The 3D combination mode of compound **19n** with EGFR. (Hydrogen bonds: Green dashed line; Ionic bonds: Purple dashed line)

Conclusions

In summary, we have designed, synthesized, and identified a novel series of 2,4,6-trisubstituted quinazoline derivatives. In vitro anti-proliferation experiments showed that most of the target compounds exhibited moderate to good anti-proliferation activity against the tested tumor cell lines, compound **19n** exhibited the best activity against MGC-803 cells, with an IC_{50} value of 4.61 μM. Further biological experiments showed that compound **19n** could inhibit the cloning of MGC-803 cells. DAPI staining and propidium iodide (PI) and Annexin V-FITC double staining experiments revealed that compound **19n** could induce apoptosis of MGC-803 cells in a concentration-dependent manner. In addition, cell cycle experiments indicated that compound **19n** could also arrest the cell cycle of MGC-803 cells in G0/G1 phase. The ADME prediction results showed that compound **19n** had good druggability. Molecular docking experiment indicated that compound **19n** may exert its antiproliferative activity by inhibiting EGFR kinase activity. Taken together, these results suggested that compound **19n** might act as a promising lead compound to provide new ideas for the research and development of anti-tumor drugs.

Materials and methods

Materials

RPMI-1640 and MTT were purchased from Solarbio. Fetal Bovine Serum (FBS) was obtained from Biological Industries. Annexin V-FITC/PI Apoptosis Detection Kit and Cell Cycle Detection Kit were purchased from Keygen Biotech. All the other reagents used were of analytical grade.

MTT assay

The MTT experiment was conducted according to the methods in the literature [33]. After digestion and centrifugation, the tumor cells were inoculated into 96 well plate with 1500 to 3300 cells per well. After 24 h, the old culture medium was discarded, and 200 μL fresh medicinal culture media with different concentrations were added. After 72 h, under dark conditions, 5% MTT solution was added with 20 μL per well and incubated in constant temperature incubator at 37 °C with 5% CO_2. After 4 h, remove the old culture medium and add 150 μL DMSO to each well. Finally, the absorbance value at 490 nm wavelength was tested through an enzyme-linked immunosorbent assay (ELISA), and the IC_{50} value was calculated using Graph Pad Prism 8.0.1. Three composite pores were set for each concentration.

Colony formation assay

Colony formation assay was conducted according to the methods in the literature [34]. The MGC-803 cells were seeded in a 6 well plate, after 24 h of cultivation, discard the old culture medium and add the medicated culture medium containing different concentrations of compound **19n**. The drug-containing culture medium was discarded when the cells grows into a visible cell community. After carefully washing twice with PBS, add 1 mL of 4% paraformaldehyde to each well for 20 min, then discard the paraformaldehyde and add 1 mL of 0.1% crystalline violet dye to each well. After the plate drying, images were photographed. The experiment was repeated three times.

Cell morphology assay and DAPI staining

DAPI staining assay was conducted according to the methods in the literature [35]. MGC-803 cells were plated in a 6 well plate. After overnight, the cells were incubated with different concentrations (0, 0.5, 1, 2 μM) of compound **19n** for 48 h. Afterward, the cells were fixed with ice-cold methanol at 4 °C for 10 min and treated with the DAPI dye solution in the dark. Then, the cells were photographed with fluorescence microscope, and the pictures were processed by Photoshop and Illustartor software. The experiment was repeated three times.

Cell cycle assay

Cycle experiments was conducted according to the instructions of the kit. MGC-803 cells were inoculated into a 6 well plate, and after 24 h of cultivation, replace the old medium with a drug-containing medium containing different concentrations of compound **19n**. After 24 h, the cells were digested and collected, and washed twice with pre-cooled PBS. Then, 1 mL of DNA staining solution and 10 μL membrane breaker were added and incubate the cells in dark for 30 min. Finally, the cells were detected through the flow cytometer. The experiment was repeated three times.

Cell apoptosis assay

Cell apoptosis experiment was conducted according to the instructions of the kit. According to the manufacturer's instructions of the apoptosis detection kit. MGC-803 cells were seeded in a 6 well culture plate and treated with compound **19n** for 48 h. Then cells were harvested and resuspended in Annexin V-FITC solution and propidium iodide (PI) solution, then incubated for 15 min in a dark place. After that, samples were analyzed with flow cytometry. The experiment was repeated three times.

Molecular docking

The molecular docking experiment was conducted through MOE2020. The co-crystal structure of EGFR protein(PDB code: 3UG2) was downloaded from RCSB Protein Date Bank(https://www.rcsb.org/). At first, the protein was prepared through the 'QuickPrep' function. The 3D structure energy of compound **19n** was minimized, and the molecular list was obtained by conformational search function. Next, the binding mode of compound **19n** and with EGFR protein(PDB code: 3UG2) was obtained by docking the molecular list with the catalytic pocket position of protein.

Experimental section

General procedure

Reagents and solvents were purchased from commercial sources and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 101 MHz spectrometer respectively. High resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer by electrospray ionization (ESI). Melting points were determined by the X-5 micromelting apparatus. The purity was determined by E2695 high-performance liquid chromatography, detection wavelength: 254 nm, mobile phase: compounds **17a–17n, 19a, 19c–19h** and **19k–19u**: MeOH: $H_2O = 70:30$; compounds **19b, 19i**, and **19j**: MeOH: $H_2O = 90:10$.

General procedure for the synthesis of compounds 11

Compound **11** was synthesized according to the method described in the literature [36]. Compound **9** (5.00 g, 27.45 mmol) was transferred to a 100 mL round-bottomed flask, and 40 mL thionyl chloride was added, and reacted at 75 °C for 2 h. Then, the excess thionyl chloride was removed by rotary evaporation to obtain compound **10**. NH_4NCS (2.09 g, 27.45 mmol) were dissolved in appropriate amounts of acetone, and then the acetone solution of compound **10** was slowly dropped into the NH_4NCS acetone solution, stirred at room temperature for 30 min, filtered and dried to obtain compound **11**, no need for purification, can directly proceed to the next step. The total yield of two-steps: 63.4%.

General procedure for the synthesis of compounds 12a–12n

Compound **12a–12n** was synthesized according to the literature [37]. Compound **11** (5.00 g, 22.60 mmol) and sodium hydroxide (1.39 g, 24.86 mmol) were dissolved in water, and different substituted benzyl chlorides (24.86 mmol) were added, compounds **12a–12n** were obtained by reacting at 80 °C for 1 h. After the reaction was completed, filtered, dried to obtain compounds **11a–11s**, no need for purification, can directly proceed to the next step, yield: 80.1–89.2%.

General procedure for the synthesis of compounds 13a–13n

Compound **13a–13n** was synthesized according to the method described in the literature [38]. Taking the synthesis of compound **13a** as an example. Compound **12a** (2.00 g, 6.39 mmol) was dissolved in 20 mL $SOCl_2$, then adding 2 drops of *N,N*-dimethylformamide. Stirred on at 65 °C for 2 h., after the reaction was completed, the reaction solution was slowly dropped into ice water and filtered out the resulting precipitate to obtain compound **13a**, no need for purification, can directly proceed to the next step. The synthesis method of compound **13b–13n** was consistent with the preparation of compound **13a**, yield: 85.2–90.7%.

General procedure for the synthesis of compounds 14a–14n

Compound **14a–14n** was synthesized according to the method described in the literature [39]. Taking the synthesis of compound **14a** as an example, compound **13a** (1.00 g, 3.01 mmol), *N*-Boc-4-aminopiperidine (0.61 g, 3.32 mmol), and anhydrous potassium carbonate (0.46 g, 3.32 mmol) were transferred to a 25 mL round bottom flask. 10 mL of *N, N*-dimethylformamide was added as the solvent and reacted at 80 °C for 1 h. After the reaction was completed, the reaction system was extracted three times with ethyl acetate, concentrated, and purified by column chromatography to obtain yellow solid compound **14a**. The synthesis method of compound **14b–14n** was consistent with the preparation of compound **14a**, yield: 78.2–87.5%.

General procedure for the synthesis of compounds 15a–15n

Compound **15a–15n** was synthesized according to the method described in the literature [40]. Taking the synthesis of compound **15a** as an example, compound **14a** (1.00 g, 2.09 mmol), iron powder (0.82 g, 14.60 mmol), and ammonium chloride (0.33 g, 6.26 mmol) were weighed and transferred to a 50 mL circular bottom flask. 20 mL of a mixed solution of ethanol and water (V_{EtOH}: $VH_2O = 4:1$) was added, and the reaction was refluxed at 85 °C for 4 h. After the reaction was completed, the iron powder residue was removed by suction filtration, the crude product was extracted using ethyl acetate as the extraction solution, concentrated, and purified by column chromatography to

obtain compound **15a**, the preparation method of compound **15b**–**15n** was consistent with that of compound **15a**, with a yield of 75.3–86.2%.

General procedure for the synthesis of compounds 16a–16n

Compound **16a**–**16n** was synthesized according to the method described in the literature [41]. At first, benzoic acid (0.16 g, 1.29 mmol), HATU (0.49 g, 1.29 mmol), compound **15a** (0.50 g, 1.07 mmol) and diisopropylethylamine (281 μL, 1.61 mmol) were transferred to a 25 mL reaction flask and dissolved in 10 mL of *N,N*-dimethylformamide, stirred at room temperature for 6 h. Then, the reaction solution was extracted with ethyl acetate, and purified with column chromatography to obtain compound **16a**. The preparation method of compound **16b**–**16n** was consistent with that of compound **16a**, with a yield of 75.3–88.2%.

General procedure for the synthesis of compounds 17a

Compound **17a** was synthesized according to the method described in the literature [42]. Compound **16a** (0.50 g, 0.90 mmol) was dissolved in 5 mL dichloromethane, and then trifluoroacetic acid (1 mL) was slowly added and reacted at room temperature for 1 h. After the reaction was completed, the reaction solution was extracted with ethyl acetate, after adjusting the pH, the crude product was purified using column chromatography to give the **17a**. White solid, yield: 90.2%, mp: 131.4–132.0 °C, purity: 95.05%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H, -NH-C = O), 8.64–8.44 (m, 1H, Ar-NH-), 8.10 (d, J = 7.6 Hz, 1H, Ar-H), 8.04 (d, J = 7.4 Hz, 2H, Ar-H), 7.86 (dd, J = 8.9, 2.2 Hz, 1H, Ar-H), 7.65–7.60 (m, 1H, Ar-H), 7.57 (d, J = 7.9 Hz, 3H, Ar-H), 7.47 (d, J = 7.5 Hz, 2H, Ar-H), 7.31 (t, J = 7.4 Hz, 2H, Ar-H), 7.23 (t, J = 7.3 Hz, 1H, Ar-H), 4.43 (s, 2H, -S-CH_2-), 4.24 (m, 1H, Piperidine-H), 3.06 (d, J = 12.2 Hz, 2H, Piperidine-H), 2.63 (t, J = 12.1 Hz, 2H, Piperidine-H), 1.86 (d, J = 11.9 Hz, 2H, Piperidine-H), 1.68–1.53 (m, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.34(-NH-C = O), 164.89(Ar-C), 157.78, 146.94, 138.84, 134.74, 134.35, 131.73, 128.70, 128.47, 128.25, 127.54, 126.72, 126.32, 114.97, 112.77, 47.62(-S-CH_2-), 44.36(Piperidine-C), 33.99(Piperidine-C), 30.76(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{27}N_5OS$ $[M + H]^+$: 470.2015, found: 470.2020.

N-(2-((2-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17b)

White solid, yield: 89.3%, mp: 132.3–132.9 °C, purity: 95.12%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H, -NH-C = O), 8.57 (s, 1H, Ar-H), 8.14 (d, J = 7.6 Hz, 1H, Ar-H), 8.05 (d, J = 7.4 Hz, 2H, Ar-H), 7.90 (d, J = 8.8 Hz, 1H, Ar-H), 7.65–7.53 (m, 4H, Ar-H), 7.26 (d, J = 12.5 Hz, 2H, Ar-H), 7.20 (d, J = 7.3 Hz, 1H, Ar-H), 7.04 (d, J = 7.6 Hz, 1H, Ar-H), 4.43 (d, J = 19.2 Hz, 2H, -S-CH_2-), 4.28 (m, 1H, Piperidine-H), 3.19 (s, 1H, Piperidine-H), 3.12 (d, J = 12.0 Hz, 2H, Piperidine-H), 2.71 (t, J = 12.5 Hz, 2H, Piperidine-H), 1.92 (d, J = 12.9 Hz, 2H, Piperidine-H), 1.67 (t, J = 12.2 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.27(-NH-C = O), 164.60(Ar-C), 163.18(d, J = 244.1 Hz), 157.75, 146.94, 142.22(d, J = 7.5 Hz), 140.97, 134.78, 134.40, 131.68, 130.11(d, J = 8.6 Hz), 128.44, 127.55, 126.26, 124.74, 115.23(d, J = 20.6 Hz), 115.08, 113.55(d, J = 21.2 Hz), 112.85, 48.67(-S-CH_2-), 45.36(Piperidine-C), 33.41(Piperidine-C), 32.38(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}FN_5OS$ $[M + H]^+$: 488.1920, found: 488.1907.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17c)

White solid, yield: 85.3%, mp: 147.6–148.3 °C, purity: 94.10%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H, -NH-C = O), 8.57 (s, 1H, Ar-H), 8.15 (d, J = 7.6 Hz, 1H, Ar-H), 8.05 (d, J = 7.5 Hz, 2H, Ar-H), 7.89 (dd, J = 8.8, 2.2 Hz, 1H, Ar-H), 7.62 (d, J = 7.5 Hz, 2H, Ar-H), 7.58 (d, J = 7.1 Hz, 3H, Ar-H), 7.30 (q, J = 7.0, 6.6 Hz, 1H, Ar-H), 7.20 (t, J = 9.2 Hz, 1H, Ar-H), 7.14 (t, J = 7.5 Hz, 1H, Ar-H), 4.46 (s, 2H, -S-CH_2-), 4.23 (m, 1H, Piperidine-H), 3.04 (d, J = 12.0 Hz, 2H, Piperidine-H), 2.59 (t, J = 12.1 Hz, 2H, Piperidine-H), 1.88–1.79 (m, 2H, Piperidine-H), 1.57 (qd, J = 12.1, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.26(-NH-C = O), 164.40(Ar-C), 161.60(d, J = 246.0 Hz), 157.84, 146.89, 134.87, 134.36, 131.71, 131.02(d, J = 3.9 Hz), 128.97(d, J = 8.4 Hz), 128.50, 128.45, 127.57, 126.32, 125.71(d, J = 21.2 Hz), 124.24, 115.23(d, J = 21.7 Hz), 115.05, 112.83, 47.48(-S-CH_2-), 44.12(Piperidine-C), 30.52(Piperidine-C), 27.43(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}FN_5OS$ $[M + H]^+$: 488.1920, found: 488.1906.

N-(2-((4-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17d)

White solid, yield: 83.2%, mp: 144.6–145.4 °C, purity: 95.10%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H, -NH-C = O), 8.58 (d, J = 8.4 Hz, 1H, Ar-H), 8.23–8.11 (m, 1H, Ar-H), 8.05 (d, J = 7.4 Hz, 2H, Ar-H), 7.90 (d, J = 8.7 Hz, 1H, Ar-H), 7.61 (d, J = 8.0 Hz, 2H, Ar-H), 7.53 (dd, J = 28.0, 7.2 Hz, 4H, Ar-H), 7.12 (t, J = 8.6 Hz, 2H, Ar-H), 4.43 (s, 2H, -S-CH_2-), 4.24 (m, 1H, Piperidine-H), 3.09 (d, J = 12.2 Hz, 2H, Piperidine-H), 1.89 (d, J = 12.6 Hz, 2H, Piperidine-H), 1.62 (q, J = 12.2 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.30(-

NH-C = O), 164.74(Ar-C), 162.26 (d, $J = 243.5$ Hz), 157.80, 146.90, 135.22 (d, $J = 3.03$ Hz), 135.19, 134.84, 134.37, 131.70, 130.61 (d, $J = 8.08$ Hz), 128.44, 127.55, 126.31, 115.03 (d, $J = 21.2$ Hz), 114.96, 112.83, 47.80(-S-CH_2-), 44.53(Piperidine-C), 33.14(Piperidine-C), 31.08(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}FN_5OS$ $[M + H]^+$: 488.1920, found: 488.1920.

N-(2-((2-chlorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17e)

White solid, yield: 87.3%, mp: 166.1–167.0 °C, purity: 95.19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.52 (s, 1H, -NH-C = O), 8.57 (s, 1H, Ar-H), 8.15 (d, $J = 7.6$ Hz, 1H, Ar-H), 8.05 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.92 (d, $J = 9.0$ Hz, 1H, Ar-H), 7.68 (dd, $J = 6.4$, 3.3 Hz, 1H, Ar-H), 7.60 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.54 (t, $J = 7.5$ Hz, 2H, Ar-H), 7.47 (dd, $J = 6.2$, 3.3 Hz, 1H, Ar-H), 7.29 (dt, $J = 6.0$, 3.0 Hz, 2H, Ar-H), 4.52 (s, 2H, -S-CH_2-), 4.23–4.07 (m, 1H, Piperidine-H), 3.00 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 2.56 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 1.80 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 1.54 (q, $J = 12.1$ Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.25(-NH-C = O), 164.41(Ar-C), 157.77, 146.85, 136.13, 134.88, 134.37, 133.16, 131.67, 130.90, 129.23, 128.72, 128.42, 128.31, 127.57, 127.11, 126.25, 115.06, 112.87, 48.38(-S-CH_2-), 45.05(Piperidine-C), 31.91(Piperidine-C), 22.55(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}ClN_5OS$ $[M + H]^+$: 504.1625, found: 504.1611.

N-(2-((3-chlorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17f)

White solid, yield: 86.1%, mp: 117.2–117.9 °C, purity: 95.15%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H, -NH-C = O), 8.56 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.15 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.08–7.98 (m, 2H, Ar-H), 7.88 (dd, $J = 8.9$, 2.2 Hz, 1H, Ar-H), 7.65–7.60 (m, 1H, Ar-H), 7.60–7.54 (m, 4H, Ar-H), 7.45 (d, $J = 7.4$ Hz, 1H, Ar-H), 7.32 (dt, $J = 16.2$, 8.2 Hz, 2H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.27–4.15 (m, 1H, Piperidine-H), 3.02 (d, $J = 11.9$ Hz, 2H, Piperidine-H), 2.61–2.52 (m, 2H, Piperidine-H), 1.86–1.79 (m, 2H, Piperidine-H), 1.55 (qd, $J = 12.1$, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.26(-NH-C = O), 164.49(Ar-C), 157.82, 146.90, 141.89, 134.86, 134.36, 132.72, 131.70, 130.04, 128.48, 128.44, 127.57, 127.39, 126.62, 126.26, 115.05, 112.83, 47.86(-S-CH_2-), 44.55(Piperidine-C), 33.29(Piperidine-C), 31.16(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}ClN_5OS$ $[M + H]^+$: 504.1625, found: 504.1623.

N-(2-((3-bromobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17g)

White solid, yield: 82.0%, mp: 129.1–129.5 °C, purity: 96.62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H, -NH-C = O), 8.56 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.15 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.05 (d, $J = 7.4$ Hz, 2H, Ar-H), 7.89 (dd, $J = 9.0$, 2.1 Hz, 1H, Ar-H), 7.70 (s, 1H, Ar-H), 7.65–7.60 (m, 1H, Ar-H), 7.58 (d, $J = 8.1$ Hz, 3H, Ar-H), 7.49 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.45–7.39 (m, 1H, Ar-H), 7.27 (t, $J = 7.8$ Hz, 1H, Ar-H), 4.43 (s, 2H, -S-CH_2-), 4.20 (ddp, $J = 11.6$, 7.9, 3.9 Hz, 1H, Piperidine-H), 3.00 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.60–2.51 (m, 2H, Piperidine-H), 1.89–1.79 (m, 2H, Piperidine-H), 1.54 (qd, $J = 12.1$, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.26(-NH-C = O), 164.49(Ar-C), 157.79, 146.90, 142.21, 134.85, 134.37, 131.70, 131.38, 130.33, 129.50, 128.44, 127.77, 127.57, 126.24, 121.36, 115.06, 112.85, 48.25(-S-CH_2-), 44.93(Piperidine-C), 33.25(Piperidine-C), 31.70(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{26}BrN_5OS$ $[M + H]^+$: 548.1120, found: 548.1108.

N-(2-((2-methylbenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17h)

White solid, yield: 81.9%, mp: 150.2–150.8 °C, purity: 95.21%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.66 (s, 1H, -NH-C = O), 8.65 (s, 1H, Ar-H), 8.23 (d, $J = 7.6$ Hz, 1H, Ar-H), 8.08 (d, $J = 7.5$ Hz, 2H, Ar-H), 8.00–7.93 (m, 1H, Ar-H), 7.65–7.59 (m, 1H, Ar-H), 7.55 (t, $J = 8.0$ Hz, 3H, Ar-H), 7.49–7.41 (m, 1H, Ar-H), 7.19 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.16–7.09 (m, 2H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.25–4.13 (m, 1H, Piperidine-H), 2.98 (d, $J = 12.2$ Hz, 2H, Piperidine-H), 2.52 (d, $J = 10.7$ Hz, 2H, Piperidine-H), 2.40 (s, 3H, Piperidine-H), 1.86–1.76 (m, 2H, Piperidine-H), 1.55 (td, $J = 11.9$, 4.1 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.24(-NH-C = O), 164.97(Ar-C), 157.72, 146.88, 136.31, 136.12, 134.88, 134.41, 131.67, 130.07, 129.46, 128.41, 128.14, 127.59, 127.02, 126.18, 125.82, 115.07, 112.91, 48.78(-S-CH_2-), 45.44(Piperidine-C), 32.45(Piperidine-C), 32.28(Piperidine-C), 18.94(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{29}N_5OS$ $[M + H]^+$: 484.2171, found: 484.2173.

N-(2-((3-methylbenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17i)

White solid, yield: 84.6%, mp: 125.2–125.8 °C, purity: 95.60%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H, -NH-C = O), 8.60–8.52 (m, 1H, Ar-H), 8.14 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.04 (d, $J = 7.5$ Hz, 2H, Ar-H), 7.88 (dd, $J = 8.8$, 2.1 Hz, 1H, Ar-H), 7.66–7.60 (m, 1H, Ar-H), 7.56 (dd,

$J = 8.6$, 5.5 Hz, 3H, Ar-H), 7.26 (d, $J = 13.4$ Hz, 2H, Ar-H), 7.18 (t, $J = 7.5$ Hz, 1H, Ar-H), 7.04 (d, $J = 7.5$ Hz, 1H, Ar-H), 4.39 (s, 2H, -S-CH_2-), 4.30–4.17 (m, 1H, Piperidine-H), 3.01 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.56 (t, $J = 12.0$ Hz, 2H, Piperidine-H), 2.27 (s, 3H, Piperidine-H), 1.90–1.79 (m, 2H, Piperidine-H), 1.57 (td, $J = 11.9$, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.25(-NH-C = O), 164.95(Ar-C), 157.73, 146.97, 138.72, 137.30, 134.75, 134.39, 131.68, 129.33, 128.44, 128.34, 128.13, 127.56, 127.36, 126.24, 125.82, 115.05, 112.83, 48.47(-S-CH_2-), 45.14(Piperidine-C), 33.98(Piperidine-C), 32.00(Piperidine-C), 20.95(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{29}N_5OS$ $[M + H]^+$: 484.2171, found: 484.2156.

N-(4-(piperidin-4-ylamino)-2-((2-(trifluoromethyl) benzyl)thio)quinazolin-6-yl)benz-amide(17j)

White solid, yield: 85.2%, mp: 181.9–182.5 °C, purity: 96.17%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H, -NH-C = O), 8.59 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.22 (d, $J = 7.6$ Hz, 1H, Ar-H), 8.05 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.91 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.83 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.75 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.63 (dd, $J = 10.0$, 6.9 Hz, 2H, Ar-H), 7.60–7.53 (m, 3H, Ar-H), 7.48 (t, $J = 7.7$ Hz, 1H, Ar-H), 4.64 (s, 2H, -S-CH_2-), 4.17 (m, 1H, Piperidine-H), 3.00 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 1.86–1.76 (m, 2H, Piperidine-H), 1.55 (qd, $J = 12.1$, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.25(-NH-C = O), 164.28(Ar-C), 157.84, 146.84, 136.96, 134.96, 134.37, 132.70, 131.69, 131.32, 128.43, 128.37, 127.51, 127.08(d, $J = 29.6$ Hz,), 126.27, 125.88(d, $J = 281.3$ Hz), 125.83, 115.01, 112.90, 48.33(-S-CH_2-), 44.93(Piperidine-C), 31.75(Piperidine-C), 30.56(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{26}F_3N_5OS$ $[M + H]^+$: 538.1888, found: 538.1883.

N-(4-(piperidin-4-ylamino)-2-((4-(trifluoromethyl) benzyl)thio)quinazolin-6-yl)benz-amide(17k)

White solid, yield: 85.3%, mp: 112.8–113.4 °C, purity: 96.18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.47 (s, 1H, -NH-C = O), 8.56 (s, 1H, Ar-H), 8.12 (d, $J = 7.8$ Hz, 1H, Ar-H), 8.05 (d, $J = 7.4$ Hz, 2H, Ar-H), 7.89 (d, $J = 9.3$ Hz, 2H, Ar-H), 7.80 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.59 (dt, $J = 13.9$, 9.1 Hz, 6H, Ar-H), 4.53 (s, 2H, -S-CH_2-), 4.27–4.10 (m, 1H, Piperidine-H), 3.20 (s, 2H, Piperidine-H), 2.98 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.51 (d, $J = 10.3$ Hz, 2H, Piperidine-H), 1.81 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 1.53 (qd, $J = 12.1$, 4.1 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.35(-NH-C = O), 164.47(Ar-C), 157.77, 146.88, 140.95, 134.87, 134.38, 132.87, 131.73, 129.20, 129.04(d, $J = 31.6$ Hz), 128.44, 128.40, 127.54, 126.20, 125.52(d, $J = 273.3$ Hz), 125.24(q, $J = 3.74$ Hz), 123.33, 114.99, 112.85, 48.68(-S-CH_2-), 45.28(Piperidine-C), 33.33(Piperidine-C), 32.27(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{26}F_3N_5OS$ $[M + H]^+$: 538.1888, found: 538.1876.

N-(2-((2-cyanobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benzamide(17l)

White solid, yield: 82.5%, mp: 208.6–209.1 °C, purity: 96.05%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H, -NH-C = O), 8.61 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.18 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.07 (d, $J = 7.4$ Hz, 2H, Ar-H), 7.95 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.81 (dd, $J = 16.0$, 7.8 Hz, 2H, Ar-H), 7.67–7.59 (m, 3H, Ar-H), 7.56 (t, $J = 7.3$ Hz, 2H, Ar-H), 7.42 (t, $J = 7.6$ Hz, 1H, Ar-H), 4.59 (s, 2H, -S-CH_2-), 4.16 (m, 1H, Piperidine-H), 2.97 (dt, $J = 12.5$, 3.3 Hz, 2H, Piperidine-H), 2.59–2.50 (m, 2H, Piperidine-H), 1.80–1.74 (m, 2H, Piperidine-H), 1.52 (qd, $J = 12.1$, 4.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.24(-NH-C = O), 163.95(Ar-C), 157.79, 146.77, 142.67, 135.04, 134.38, 133.08, 132.77, 131.67, 129.96, 128.42, 128.24, 127.65, 127.59, 126.23, 117.70, 115.05, 112.97, 111.81, 48.67(-S-CH_2-), 45.39(Piperidine-C), 32.57(Piperidine-C), 32.43(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{27}N_6OS$ $[M + H]^+$: 495.1967, found: 495.1964.

N-(2-((2,4-dichlorobenzyl)thio)-4-(piperidin-4-ylamino)quinazolin-6-yl)benza-mide(17m)

White solid, yield: 83.6%, mp: 167.1–167.5 °C, purity: 95.19%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.44 (s, 1H, -NH-C = O), 8.52 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.08 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.05–8.01 (m, 2H, Ar-H), 7.86 (dd, $J = 8.9$, 2.2 Hz, 1H, Ar-H), 7.69 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.63 (d, $J = 2.3$ Hz, 1H, Ar-H), 7.61 (d, $J = 7.9$ Hz, 2H, Ar-H), 7.58–7.54 (m, 2H, Ar-H), 7.37 (dd, $J = 8.3$, 2.2 Hz, 1H, Ar-H), 4.48 (s, 2H, -S-CH_2-), 4.20–4.05 (m, 1H, Piperidine-H), 2.95 (dd, $J = 9.6$, 6.4 Hz, 2H, Piperidine-H), 2.50–2.44 (m, 2H, Piperidine-H), 1.75 (dd, $J = 12.4$, 3.7 Hz, 2H, Piperidine-H), 1.49 (qd, $J = 12.0$, 4.1 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.28(-NH-C = O), 164.18(Ar-C), 157.76, 146.86, 135.45, 134.84, 134.37, 134.05, 132.24, 132.07, 131.71, 128.63, 128.45, 128.42, 127.54, 127.20, 126.30, 115.03, 112.86, 48.67(-S-CH_2-), 45.32(Piperidine-C), 32.32(Piperidine-C), 31.47(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}Cl_2N_5OS$ $[M + H]^+$: 538.1235, found: 538.1224.

N-(2-((3,4-dichlorobenzyl)thio)-4-(piperidin-4-ylamino)quinazolin-6-yl)benzami-de(17n)

White solid, yield: 79.8%, mp: 125.6–126.3 °C, purity: 95.51%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H,

-NH-C = O), 8.55 (s, 1H, Ar-H), 8.14 (d, $J = 8.0$ Hz, 1H, Ar-H), 8.04 (d, $J = 7.7$ Hz, 2H, Ar-H), 7.87 (d, $J = 9.2$ Hz, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 7.68–7.61 (m, 2H, Ar-H), 7.57 (dd, $J = 8.3$, 5.6 Hz, 3H, Ar-H), 7.48 (d, $J = 8.6$ Hz, 1H, Ar-H), 4.43 (d, $J = 10.2$ Hz, 2H, -S-CH_2-), 4.24–4.05 (m, 1H, Piperidine-H), 2.99 (d, $J = 12.2$ Hz, 2H, Piperidine-H), 2.55 (s, 2H, Piperidine-H), 1.79 (d, $J = 12.3$ Hz, 2H, Piperidine-H), 1.54 (td, $J = 12.1$, 4.4 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.26(-NH-C = O), 164.33(Ar-C), 157.78, 146.87, 140.75, 134.85, 134.37, 131.69, 130.60, 130.52, 130.28, 129.17, 129.01, 128.44, 127.55, 126.24, 115.05, 112.86, 48.58(-S-CH_2-), 45.26(Piperidine-C), 32.72(Piperidine-C), 32.23(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}Cl_2N_5OS$ $[M + H]^+$: 538.1235, found: 538.1237.

General procedure for the synthesis of compounds 18a–18u

The synthesis methods of compounds **18a**–**18u** were consistent with the preparation of compounds **16a**–**16n**.

General procedure for the synthesis of compounds 19a–19u

The synthesis methods of compounds **19a**–**19u** were consistent with the preparation of compounds **17a**–**17n**.

2-fluoro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19a)

White solid, yield: 90.1%, mp: 182.3–182.9 °C, purity: 95.56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H, -NH-C = O), 8.54 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.14 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.81 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.73 (td, $J = 7.5$, 1.7 Hz, 1H, Ar-H), 7.59 (dd, $J = 16.5$, 8.2 Hz, 2H, Ar-H), 7.42–7.36 (m, 2H, Ar-H), 7.35–7.27 (m, 3H, Ar-H), 7.11–7.00 (m, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.26–4.12 (m, 1H, Piperidine-H), 3.02–2.94 (m, 2H, Piperidine-H), 2.54 (d, $J = 2.2$ Hz, 2H, Piperidine-H), 1.79 (d, $J = 10.0$ Hz, 2H, Piperidine-H), 1.52 (qd, $J = 12.0$, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.63(-NH-C = O), 163.17(d, $J = 244.1$ Hz, Ar-C), 162.64(d, $J = 244.3$ Hz), 160.22, 157.74, 146.97, 142.17(d, $J = 7.5$ Hz), 134.46, 132.71(d, $J = 8.2$ Hz), 130.12(d, $J = 8.7$ Hz), 129.90, 127.57, 126.47, 124.74, 124.59, 124.44, 116.32(d, $J = 22.5$ Hz), 115.42(d, $J = 22.1$ Hz), 114.15, 113.56(d, $J = 20.2$ Hz), 112.88, 48.66(-S-CH_2-), 45.38(Piperidine-C), 33.38(Piperidine-C), 32.36(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}F_2N_5OS$ $[M + H]^+$: 506.1826, found: 506.1814.

3-fluoro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19b)

White solid, yield: 90.2%, mp: 201.3–201.9 °C, purity: 98.05%. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.55 (s, 1H, -NH-C = O), 8.62 – 8.50 (m, 1H, Ar-H), 8.13 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.98–7.81 (m, 3H, Ar-H), 7.69–7.55 (m, 2H, Ar-H), 7.48 (td, $J = 8.5$, 2.7 Hz, 1H, Ar-H), 7.32 (td, $J = 10.9$, 9.2, 5.4 Hz, 3H, Ar-H), 7.12–7.00 (m, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.27–4.14 (m, 1H, Piperidine-H), 3.00 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 2.56 (d, $J = 11.3$ Hz, 2H, Piperidine-H), 1.87–1.76 (m, 2H, Piperidine-H), 1.55 (qd, $J = 11.2$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.73(-NH-C = O), 163.87(d, $J = 244.4$ Hz, Ar-C), 163.85(d, $J = 244.6$ Hz), 163.17, 157.74, 147.04, 142.19(d, $J = 7.5$ Hz), 136.73(d, $J = 6.8$ Hz), 134.46, 130.71(d, $J = 8.4$ Hz), 130.12(d, $J = 8.0$ Hz), 128.42, 126.33, 124.75, 123.78, 123.76, 118.73(d, $J = 23.0$ Hz), 115.44, 115.23, 114.47(d, $J = 23.1$ Hz), 113.56(d, $J = 21.1$ Hz), 48.55(-S-CH_2-), 45.23(Piperidine-C), 33.38(Piperidine-C), 32.18(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}F_2N_5OS$ $[M + H]^+$: 506.1826, found: 506.1817.

4-fluoro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benz-amide(19c)

White solid, yield: 91.2%, mp: 116.0–116.5 °C, purity: 95.89%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.54 (s, 1H, -NH-C = O), 8.55 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.13 (dd, $J = 8.5$, 5.7 Hz, 3H, Ar-H), 7.88 (dd, $J = 8.9$, 2.2 Hz, 1H, Ar-H), 7.57 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.40 (t, $J = 8.7$ Hz, 2H, Ar-H), 7.32 (td, $J = 11.2$, 9.5, 4.2 Hz, 3H, Ar-H), 7.05 (td, $J = 8.0$, 7.0, 2.7 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.24–4.12 (m, 1H, Piperidine-H), 2.97 (dd, $J = 12.6$, 3.3 Hz, 2H, Piperidine-H), 2.53 (s, 2H, Piperidine-H), 1.84–1.73 (m, 2H, Piperidine-H), 1.51 (qd, $J = 11.9$, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.37(d, $J = 250.5$ Hz), 164.63(-NH-C = O), 164.15(Ar-C), 163.17(d, $J = 244.2$ Hz), 157.74, 146.94, 142.21(d, $J = 7.47$ Hz), 134.69, 130.82(d, $J = 2.7$ Hz), 130.34(d, $J = 9.1$ Hz), 130.11(d, $J = 7.9$ Hz), 128.42, 126.26, 124.75, 115.52(d, $J = 22.0$ Hz), 115.44(d, $J = 21.9$ Hz), 115.18, 113.55(d, $J = 21.5$ Hz), 112.85, 48.62(-S-CH_2-), 45.36(Piperidine-C), 33.38(Piperidine-C), 32.36(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}F_2N_5OS$ $[M + H]^+$: 506.1826, found: 506.1815.

2-chloro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19d)

White solid, yield: 89.2 %, mp: 131.1–131.6 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H, -NH-C = O), 8.58 (d,

$J = 2.3$ Hz, 1H, Ar-H), 8.19 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.78 (dd, $J = 8.8$, 2.2 Hz, 1H, Ar-H), 7.59 (q, $J = 9.8$, 8.3 Hz, 3H, Ar-H), 7.51 (dt, $J = 20.5$, 6.8 Hz, 2H, Ar-H), 7.10–6.99 (m, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.18–4.28 (m, 1H, Piperidine-H), 3.06 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 2.62 (t, $J = 12.1$ Hz, 2H, Piperidine-H), 1.91–1.78 (m, 2H, Piperidine-H), 1.60 (qd, $J = 12.3$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.83(-NH-C = O), 164.53(Ar-C), 163.17(d, $J = 244.1$ Hz), 157.81, 146.93, 142.12(d, $J = 7.47$ Hz), 136.70, 134.65, 131.17, 130.14(d, $J = 8.69$ Hz), 129.95, 129.71, 128.90, 127.30, 127.26, 126.57, 124.76, 115.45(d, $J = 20.5$ Hz), 113.57(d, $J = 20.9$ Hz), 113.55, 112.92, 48.06(-S-CH_2-), 44.73(Piperidine-C), 33.40(Piperidine-C), 31.35(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}ClFN_5OS$ $[M + H]^+$: 522.1531, found: 522.1511.

3-chloro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19e)

White solid, yield: 89.7%, mp: 191.2–191.8 °C, purity: 97.68%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.60 (s, 1H, -NH-C = O), 8.54 (d, $J = 2.3$ Hz, 1H, Ar-H), 8.19–8.06 (m, 2H, Ar-H), 8.00 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.89 (dd, $J = 8.9$, 2.2 Hz, 1H, Ar-H), 7.75–7.67 (m, 1H, Ar-H), 7.60 (dd, $J = 14.3$, 8.3 Hz, 2H, Ar-H), 7.33 (ddt, $J = 14.7$, 9.4, 5.2 Hz, 3H, Ar-H), 7.06 (td, $J = 7.8$, 6.9, 2.6 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.20 (s, 1H, Piperidine-H), 3.00 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.62–2.52 (m, 2H, Piperidine-H), 1.86–1.77 (m, 2H, Piperidine-H), 1.55 (qd, $J = 12.0$, 3.0 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.72(-NH-C = O), 163.78(Ar-C), 163.17(d, $J = 244.1$ Hz), 157.77, 147.01, 142.19(d, $J = 7.6$ Hz), 136.35, 134.54, 133.29, 131.53, 130.47, 130.11(d, $J = 8.4$ Hz), 128.29, 127.33, 126.38, 126.31, 124.75, 115.43(d, $J = 19.6$ Hz), 115.13, 113.55(d, $J = 21.1$ Hz), 112.85, 48.35(-S-CH_2-), 45.09(Piperidine-C), 33.40(Piperidine-C), 31.97(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}ClFN_5OS$ $[M + H]^+$: 522.1531, found: 522.1514.

4-chloro-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19f)

White solid, yield: 87.2%, mp: 216.2–217.0 °C, purity: 97.86%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H, -NH-C = O), 8.53 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.09 (dd, $J = 22.5$, 7.9 Hz, 3H, Ar-H), 7.86 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.65 (d, $J = 8.2$ Hz, 2H, Ar-H), 7.58 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.32 (td, $J = 11.1$, 9.1, 4.4 Hz, 3H, Ar-H), 7.05 (t, $J = 8.3$ Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.27–4.10 (m, 1H, Piperidine-H), 3.02 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.63–2.52 (m, 2H, Piperidine-H), 1.89–1.75 (m, 2H, Piperidine-H), 1.55 (qd, $J = 12.1$, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.68(-NH-C = O), 164.17(Ar-C), 163.17(d, $J = 244.1$ Hz), 157.76, 147.00, 142.18(d, $J = 7.5$ Hz), 136.57, 134.57, 133.07, 130.11(d, $J = 8.08$ Hz), 129.51, 128.54, 128.46, 126.30, 124.74, 115.45, 115.23, 113.56(d, $J = 20.9$ Hz), 112.83, 48.28(-S-CH_2-), 44.98(Piperidine-C), 33.39(Piperidine-C), 31.81(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}ClFN_5OS$ $[M + H]^+$: 522.1531, found: 522.1515.

2-bromo-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19g)

White solid, yield: 92.1%, mp: 151.7–152.4 °C, purity: 95.18%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H, -NH-C = O), 8.59 (s, 1H, Ar-H), 8.26 (d, $J = 7.5$ Hz, 1H, Ar-H), 7.77 (dd, $J = 17.0$, 8.5 Hz, 2H, Ar-H), 7.61–7.56 (m, 2H, Ar-H), 7.53 (d, $J = 7.4$ Hz, 1H, Ar-H), 7.45 (t, $J = 7.7$ Hz, 1H, Ar-H), 7.37–7.29 (m, 3H, Ar-H), 7.06 (s, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.28–4.10 (m, 1H, Piperidine-H), 3.18 (d, $J = 12.3$ Hz, 2H, Piperidine-H), 2.80 (t, $J = 12.3$ Hz, 2H, Piperidine-H), 1.92 (d, $J = 12.8$ Hz, 2H, Piperidine-H), 1.78–1.69 (m, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.74(-NH-C = O), 164.48(Ar-C), 163.16(d, $J = 244.02$ Hz), 157.91, 146.92, 142.06(d, $J = 7.47$ Hz), 138.84, 134.76, 132.80, 131.28, 130.16(d, $J = 8.9$ Hz), 128.83, 127.73, 127.34, 126.62, 124.78, 118.96, 115.49(d, $J = 23.3$ Hz), 113.60(d, $J = 19.8$ Hz), 113.42, 112.90, 46.93(-S-CH_2-), 43.54(Piperidine-C), 33.40(Piperidine-C), 29.54(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}BrFN_5OS$ $[M + H]^+$: 566.1025, found: 566.1011.

3-bromo-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19h)

White solid, yield: 90.4%, mp: 134.2–134.9 °C, purity: 95.27%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H, -NH-C = O), 8.51 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 8.11 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.03 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.91–7.80 (m, 2H, Ar-H), 7.59–7.51 (m, 2H, Ar-H), 7.31 (td, $J = 11.4$, 9.6, 4.4 Hz, 3H, Ar-H), 7.05 (td, $J = 7.9$, 6.9, 2.4 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.22–4.12 (m, 1H, Piperidine-H), 3.03–2.95 (m, 2H, Piperidine-H), 2.55 (s, 2H, Piperidine-H), 1.84–1.76 (m, 2H, Piperidine-H), 1.53 (qd, $J = 11.9$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.74(-NH-C = O), 163.71(Ar-C), 163.17(d, $J = 244.32$ Hz), 157.74, 147.04, 142.19(d, $J = 7.58$ Hz), 136.54, 134.46, 134.42, 130.72, 130.16, 130.03(d, $J = 8.38$ Hz), 128.35, 126.75, 126.31, 124.74, 121.74, 115.44(d, $J = 22.6$ Hz), 115.16, 113.55(d, $J = 20.6$ Hz), 112.84, 48.57(-S-CH_2-), 45.30(Piperidine-C), 33.40(Piperidine-C), 32.29(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}BrFN_5OS$ $[M + H]^+$: 566.1025, found: 566.1012.

4-bromo-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19i)

White solid, yield: 86.4%, mp: 211.2–212.1 °C, purity: 99.61%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H, -NH-C = O), 8.51 (d, J = 2.2 Hz, 1H, Ar-H), 8.10 (d, J = 7.7 Hz, 1H, Ar-H), 7.98 (d, J = 8.2 Hz, 2H, Ar-H), 7.85 (dd, J = 8.9, 2.1 Hz, 1H, Ar-H), 7.79 (d, J = 8.2 Hz, 2H, Ar-H), 7.57 (d, J = 8.8 Hz, 1H, Ar-H), 7.32 (ddt, J = 14.9, 9.5, 5.1 Hz, 3H, Ar-H), 7.10–7.01 (m, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.23–4.13 (m, 1H, Piperidine-H), 3.02–2.93 (m, 2H, Piperidine-H), 2.55–2.51 (m, 2H, Piperidine-H), 1.79 (d, J = 12.3 Hz, 2H, Piperidine-H), 1.53 (qd, J = 12.0, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.70(-NH-C = O), 164.29(Ar-C), 163.17(d, J = 244.22 Hz), 157.73, 147.02, 142.20(d, J = 7.47 Hz), 134.52, 133.45, 131.49, 130.11(d, J = 8.0 Hz), 129.67, 128.43, 126.31, 125.53, 124.73, 115.43, 115.23, 113.55(d, J = 20.6 Hz), 112.84, 48.67(-S-CH_2-), 45.35(Piperidine-C), 33.40(Piperidine-C), 32.35(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}BrFN_5OS$ $[M + H]^+$: 566.1025, found: 566.1011.

***N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-2-methylbenza-mide(19j)**

White solid, yield: 88.6%, mp: 139.4–140.2 °C, purity: 98.11%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H, -NH-C = O), 8.62 (s, 2H, Ar-H), 8.24 (d, J = 7.3 Hz, 1H, Ar-H), 7.78 (d, J = 8.9 Hz, 1H, Ar-H), 7.59 (d, J = 8.9 Hz, 1H, Ar-H), 7.50 (d, J = 7.4 Hz, 1H, Ar-H), 7.42 (t, J = 7.5 Hz, 1H, Ar-H), 7.33 (q, J = 8.0, 7.2 Hz, 4H, Ar-H), 7.06 (t, J = 8.6 Hz, 1H, Ar-H), 4.46 (s, 2H, -S-CH_2-), 4.42–4.35 (m, 1H, Piperidine-H), 3.17 (d, J = 3.4 Hz, 2H, Piperidine-H), 3.04 (t, J = 12.5 Hz, 2H, Piperidine-H), 2.43 (s, 3H, Piperidine-H), 2.04 (d, J = 13.3 Hz, 2H, Piperidine-H), 1.83 (q, J = 12.2 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.73(-NH-C = O), 164.30, 163.15(d, J = 244.2 Hz, Ar-C), 157.97, 146.75, 142.04(d, J = 7.4 Hz), 136.79, 135.36, 135.13, 130.60, 130.16(d, J = 8.1 Hz), 129.76, 127.67, 127.20, 126.50, 125.65, 124.81, 115.53(d, J = 21.0 Hz), 113.60(d, J = 21.0 Hz), 113.40, 112.85, 46.13(-S-CH_2-), 42.87(Piperidine-C), 33.40(Piperidine-C), 28.53(Piperidine-C), 19.36(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{28}FN_5OS$ $[M + H]^+$: 502.2077, found: 502.2064.

***N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-3-methylbenza-mide(19k)**

White solid, yield: 88.6%, mp: 208.7–209.6 °C, purity: 95.01%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H, -NH-C = O), 8.52 (d, J = 2.2 Hz, 1H, Ar-H), 8.10 (d, J = 7.7 Hz, 1H, Ar-H), 7.92–7.78 (m, 3H, Ar-H), 7.57 (d, J = 8.9 Hz, 1H, Ar-H), 7.44 (d, J = 6.2 Hz, 2H, Ar-H), 7.33 (ddt, J = 14.4, 9.2, 5.1 Hz, 3H, Ar-H), 7.11–7.00 (m, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.30–4.15 (m, 1H, Piperidine-H), 2.99 (d, J = 12.1 Hz, 2H, Piperidine-H), 2.54 (d, J = 12.1 Hz, 2H, Piperidine-H), 2.42 (s, 3H, Piperidine-H), 1.80 (d, J = 12.2 Hz, 2H, Piperidine-H), 1.54 (qd, J = 11.6, 2.8, Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.35(-NH-C = O), 164.54(Ar-C), 163.17(d, J = 244.2 Hz), 157.75, 146.88, 142.21(d, J = 7.5 Hz), 137.72, 134.86, 134.40, 132.26, 130.12(d, J = 8.8 Hz), 128.38, 128.35, 128.03, 126.24, 124.74, 115.43(d, J = 21.5 Hz), 114.99, 113.55(d, J = 21.3 Hz), 112.85, 48.48(-S-CH_2-), 45.20(Piperidine-C), 33.40(Piperidine-C), 32.13(Piperidine-C), 20.98(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{28}FN_5OS$ $[M + H]^+$: 502.2077, found: 502.2064.

***N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-4-methylbenza-mide(19l)**

White solid, yield: 89.3%, mp: 193.5–194.2 °C, purity: 95.52%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H, -NH-C = O), 8.52 (d, J = 2.3 Hz, 1H, Ar-H), 8.09 (d, J = 7.7 Hz, 1H, Ar-H), 7.95 (d, J = 7.9 Hz, 2H, Ar-H), 7.86 (dd, J = 8.9, 2.2 Hz, 1H, Ar-H), 7.56 (d, J = 8.9 Hz, 1H, Ar-H), 7.36 (d, J = 7.9 Hz, 2H, Ar-H), 7.31 (q, J = 9.4, 8.3 Hz, 3H, Ar-H), 7.09–7.01 (m, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.23–4.15 (m, 1H, Piperidine-H), 2.99 (d, J = 12.0 Hz, 2H, Piperidine-H), 2.58–2.51 (m, 2H, Piperidine-H), 2.40 (s, 3H, -CH_3), 1.85–1.75 (m, 2H, Piperidine-H), 1.52 (qd, J = 11.9, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.06(-NH-C = O), 164.51(Ar-C), 163.17(d, J = 244.2 Hz), 157.75, 146.85, 142.14(d, J = 7.5 Hz), 141.72, 134.88, 131.50, 130.04(d, J = 8.2 Hz), 128.97, 128.45, 127.59, 126.21, 124.75, 115.44(d, J = 20.8 Hz), 115.03, 113.55(d, J = 20.5 Hz), 112.84, 48.46(-S-CH_2-), 45.19(Piperidine-C), 33.38(Piperidine-C), 32.11(Piperidine-C), 20.96(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{28}FN_5OS$ $[M + H]^+$: 502.2077, found: 502.2061.

***N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-3-methoxybenz-amide(19m)**

White solid, yield: 86.2%, mp: 144.6–145.3 °C, purity: 95.14%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (s, 1H, -NH-C = O), 8.53 (d, J = 2.2 Hz, 1H, Ar-H), 8.11 (d, J = 7.4 Hz, 1H, Ar-H), 7.87 (dd, J = 8.8, 2.2 Hz, 1H, Ar-H), 7.64–7.55 (m, 3H, Ar-H), 7.48 (t, J = 7.9 Hz, 1H, Ar-H), 7.36–7.27 (m, 3H, Ar-H), 7.18 (dd, J = 8.2, 2.6 Hz, 1H, Ar-H), 7.05 (td, J = 9.4, 2.5 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.24–4.13 (m, 1H, Piperidine-H), 3.86 (s, 3H, -CH_3),

2.97 (d, $J = 12.0$ Hz, 2H, Piperidine-H), 2.53 (s, 2H, Piperidine-H), 1.84–1.72 (m, 2H, Piperidine-H), 1.52 (qd, $J = 11.9$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.93(-NH-C = O), 164.62(Ar-C), 163.17(d, $J = 244.0$ Hz), 159.21, 157.73, 146.93, 142.14(d, $J = 7.47$ Hz), 135.75, 134.71, 130.12(d, $J = 19.7$ Hz), 129.61, 128.48, 126.22, 124.75, 119.79, 117.47, 115.44, 115.19, 113.55(d, $J = 20.7$ Hz), 112.84, 112.75, 55.35, 48.69(-S-CH_2-), 45.38(Piperidine-C), 33.41(Piperidine-C), 32.39(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{28}FN_5O_2S$ $[M + H]^+$: 518.2026, found: 518.2014.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-4-methoxybenz-amide(19n)

White solid, yield: 87.3%, mp: 216.0–216.7 °C, purity: 96.01%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H, -NH-C = O), 8.51 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.10 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.04 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.90–7.79 (m, 1H, Ar-H), 7.56 (d, $J = 8.8$ Hz, 1H, Ar-H), 7.39–7.27 (m, 3H, Ar-H), 7.14–7.02 (m, 3H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.27–4.16 (m, 1H, Piperidine-H), 3.85 (s, 3H, -CH_3), 3.03 (d, $J = 12.2$ Hz, 2H, Piperidine-H), 2.59 (t, $J = 12.0$ Hz, 2H, Piperidine-H), 1.82 (dd, $J = 12.7$, 3.7 Hz, 2H, Piperidine-H), 1.56 (qd, $J = 12.1$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.64(-NH-C = O), 164.43(Ar-C), 163.17(d, $J = 244.1$ Hz), 161.97, 157.77, 146.77, 142.20(d, $J = 7.5$ Hz), 135.03, 130.12(d, $J = 8.7$ Hz), 129.51, 128.50, 126.38, 126.20, 124.76, 115.44(d, $J = 21.0$ Hz), 114.96, 113.67, 113.36(d, $J = 20.6$ Hz), 112.83, 55.37(Piperidine-C), 48.13(-S-CH_2-), 44.87(Piperidine-C), 33.39(Piperidine-C), 31.63(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{28}FN_5O_2S$ $[M + H]^+$: 518.2026, found: 518.2017.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin)-2-(trifluoromethyl)-benzamide(19o)

White solid, yield: 86.3%, mp: 167.9–168.7 °C, purity: 95.13%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H, -NH-C = O), 8.51 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.18 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.88 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.85–7.77 (m, 2H, Ar-H), 7.74 (t, $J = 7.8$ Hz, 2H, Ar-H), 7.58 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.39–7.27 (m, 3H, Ar-H), 7.06 (dt, $J = 9.6$, 4.6 Hz, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.26–4.16 (m, 1H, Piperidine-H), 3.10–2.96 (m, 2H, Piperidine-H), 2.64–2.54 (m, 2H, Piperidine-H), 1.90–1.77 (m, 2H, Piperidine-H), 1.58 (qd, $J = 12.1$, 3.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.51(-NH-C = O), 164.58(Ar-C), 163.18(d, $J = 244.3$ Hz), 157.78, 147.00, 142.14(d, $J = 7.6$ Hz), 136.00(d, $J = 2.1$ Hz), 134.67, 132.59, 130.13, 130.04, 128.54, 127.28, 126.61, 126.41(q, $J = 4.7$ Hz), 126.03(d, $J = 31.5$ Hz), 125.11(d, $J = 274.7$ Hz), 124.75, 115.44(d, $J = 22.0$ Hz), 113.57(d, $J = 21.1$ Hz), 113.52, 112.93, 48.55(-S-CH_2-), 48.33(Piperidine-C), 44.99(Piperidine-C), 33.40(Piperidine-C), 31.72(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{25}F_4N_5OS$ $[M + H]^+$: 556.1794, found: 556.1780.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin)-3-(trifluoromethyl)-benzamide(19p)

White solid, yield: 88.2%, mp: 125.6–125.9 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H, -NH-C = O), 8.51 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.40 (s, 1H, Ar-H), 8.34 (d, $J = 7.9$ Hz, 1H, Ar-H), 8.13 (d, $J = 7.7$ Hz, 1H, Ar-H), 8.01 (d, $J = 7.8$ Hz, 1H, Ar-H), 7.91 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.83 (t, $J = 7.8$ Hz, 1H, Ar-H), 7.59 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.32 (td, $J = 11.2$, 9.6, 4.2 Hz, 3H, Ar-H), 7.05 (tt, $J = 7.0$, 2.2 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.25–4.15 (m, 1H, Piperidine-H), 2.98 (d, $J = 12.2$ Hz, 2H, Piperidine-H), 2.55 (s, 2H, Piperidine-H), 1.84–1.76 (m, 2H, Piperidine-H), 1.52 (qd, $J = 12.1$, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.82(-NH-C = O), 163.72(Ar-C), 163.17(d, $J = 243.8$ Hz), 157.73, 147.11, 142.12(d, $J = 7.6$ Hz), 135.21, 134.37, 131.75, 130.03(d, $J = 8.4$ Hz), 129.83, 129.40, 128.48, 128.26(d, $J = 2.42$ Hz), 126.34, 125.29, 124.74, 124.12(q, $J = 3.74$ Hz), 115.39, 115.22(d, $J = 20.8$ Hz), 113.55(d, $J = 20.9$ Hz), 112.86, 48.55(-S-CH_2-), 45.32(Piperidine-C), 33.38(Piperidine-C), 32.32(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{25}F_4N_5OS$ $[M + H]^+$: 556.1794, found: 556.1782.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin)-4-(trifluoromethyl)-benzamide(19q)

White solid, yield: 87.1%, mp: 175.9–176.4 °C, purity: 93.43%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H, -NH-C = O), 8.56 (d, $J = 2.2$ Hz, 1H, Ar-H), 8.23 (d, $J = 8.1$ Hz, 2H, Ar-H), 8.14 (d, $J = 7.7$ Hz, 1H, Ar-H), 7.96 (d, $J = 8.1$ Hz, 2H, Ar-H), 7.88 (dd, $J = 8.9$, 2.1 Hz, 1H, Ar-H), 7.59 (d, $J = 8.9$ Hz, 1H, Ar-H), 7.33 (ddt, $J = 14.6$, 9.4, 5.3 Hz, 3H, Ar-H), 7.06 (dd, $J = 9.5$, 6.8 Hz, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.25–4.12 (m, 1H, Piperidine-H), 3.00 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 2.56 (d, $J = 12.1$ Hz, 2H, Piperidine-H), 1.88–1.76 (m, 2H, Piperidine-H), 1.54 (qd, $J = 12.1$, 2.9 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.79(-NH-C = O), 164.10(Ar-C), 163.17(d, $J = 243.61$ Hz), 157.76, 147.09, 142.18(d, $J = 7.6$ Hz), 138.19, 134.40, 131.64(d, $J = 31.9$ Hz), 130.12(d, $J = 8.1$ Hz), 128.49, 128.37, 126.37, 125.49(q, $J = 3.7$ Hz), 125.22, 124.74, 115.45, 115.27, 113.56(d, $J = 21.3$ Hz), 112.84, 48.43(-S-CH_2-), 45.13(Piperidine-C), 33.39(Piperidine-C), 32.03(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{25}F_4N_5OS$ $[M + H]^+$: 556.1794, found: 556.1783.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-2-nitrobenz-amide(19r)

White solid, yield: 89.3%, mp: 162.5–162.9 °C, purity: 96.94%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.74 (s, 1H, -NH-C = O), 8.58 (s, 1H, Ar-H), 8.49 (s, 1H, Ar-H), 8.33 (d, J = 8.0 Hz, 1H, Ar-H), 8.18 (d, J = 7.8 Hz, 1H, Ar-H), 8.10 (d, J = 7.7 Hz, 1H, Ar-H), 7.91 (d, J = 9.1 Hz, 1H, Ar-H), 7.79 (t, J = 7.8 Hz, 1H, Ar-H), 7.58 (d, J = 8.9 Hz, 1H, Ar-H), 7.33 (ddt, J = 15.7, 10.0, 5.1 Hz, 3H, Ar-H), 7.05 (dd, J = 9.6, 7.0 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.24–4.09 (m, 1H, Piperidine-H), 2.98 (d, J = 12.2 Hz, 2H, Piperidine-H), 2.65–2.56(m, 2H, Piperidine-H), 1.86–1.76 (m, 2H, Piperidine-H), 1.53 (qd, J = 11.6, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.78(-NH-C = O), 163.36(Ar-C), 163.17(d, J = 244.12 Hz), 157.75, 147.04, 142.19(d, J = 7.6 Hz), 135.41, 135.10, 134.43, 132.40, 131.20, 130.13(d, J = 8.3 Hz), 129.93, 128.10, 126.36, 124.76, 118.26, 115.44(d, J = 23.0 Hz), 113.56(d, J = 20.7 Hz), 112.87, 111.60, 48.62(-S-CH_2-), 45.28(Piperidine-C), 33.37(Piperidine-C), 32.26(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}FN_6O_3S$ $[M + H]^+$: 533.1771, found: 533.1761.

N-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)-3-nitrobenz-amide(19 s)

White solid, yield: 86.2%, mp: 132.1–132.7 °C, purity: 94.97%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H, -NH-C = O), 8.48 (d, J = 2.2 Hz, 1H, Ar-H), 8.18 (d, J = 7.9 Hz, 2H, Ar-H), 7.90 (t, J = 7.5 Hz, 1H, Ar-H), 7.84–7.76 (m, 3H, Ar-H), 7.59 (d, J = 8.9 Hz, 1H, Ar-H), 7.33 (ddt, J = 14.4, 9.0, 5.1 Hz, 3H, Ar-H), 7.06 (dt, J = 9.7, 4.6 Hz, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.26–4.16 (m, 1H, Piperidine-H), 3.03 (d, J = 12.0 Hz, 2H, Piperidine-H), 2.65–2.54 (m, 2H, Piperidine-H), 1.89–1.78 (m, 2H, Piperidine-H), 1.57 (qd, J = 12.2, 2.8 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.64(-NH-C = O), 164.05(Ar-C), 163.17(d, J = 244.1 Hz), 157.77, 147.01, 146.51, 142.13(d, J = 7.6 Hz), 134.60, 134.05, 132.43, 131.06, 130.12(d, J = 8.1 Hz), 129.22, 127.23, 126.66, 124.76, 124.28, 115.45(d, J = 21.8 Hz), 113.53, 113.36, 112.95, 48.29(-S-CH_2-), 44.94(Piperidine-C), 33.41(Piperidine-C), 31.66(Piperidine-C). HRMS (ESI) calcd for $C_{27}H_{25}FN_6O_3S$ $[M + H]^+$: 533.1771, found: 533.1761.

3-cyano-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benza-mide(19t)

White solid, yield: 90.6%, mp: 139.6–140.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H, -NH-C = O), 8.89 (d, J = 2.1 Hz, 1H, Ar-H), 8.61–8.44 (m, 3H, Ar-H), 8.22 (d, J = 7.5 Hz, 1H, Ar-H), 7.99–7.84 (m, 2H, Ar-H), 7.61 (d, J = 8.9 Hz, 1H, Ar-H), 7.44–7.25 (m, 3H, Ar-H), 7.13–6.93 (m, 1H, Ar-H), 4.45 (s, 2H, -S-CH_2-), 4.32–4.22 (m, 1H, Piperidine-H), 3.14 (d, J = 12.2 Hz, 2H, Piperidine-H), 2.75 (t, J = 12.2 Hz, 2H, Piperidine-H), 1.90 (d, J = 12.7 Hz, 2H, Piperidine-H), 1.73–1.57 (m, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.83(-NH-C = O), 163.14(Ar-C), 160.75(d, J = 244.0 Hz), 157.84, 147.81, 147.13, 142.13(d, J = 7.6 Hz), 135.76, 134.35, 134.05, 130.30, 130.14(d, J = 6.7 Hz), 128.48, 126.41, 126.31, 124.77, 122.30, 115.44, 115.37, 115.23, 113.58(d, J = 19.8 Hz), 112.84, 47.53(-S-CH_2-), 44.21(Piperidine-C), 33.42(Piperidine-C), 30.68(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{25}FN_6OS$ $[M + H]^+$: 513.1873, found: 513.1863.

4-cyano-*N*-(2-((3-fluorobenzyl)thio)-4-(piperidin-4-ylamino) quinazolin-6-yl)benz-amide(19u)

White solid, yield: 89.1%, mp: 142.6–143.4 °C, purity: 95.36%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H, -NH-C = O), 8.66 (s, 1H, Ar-H), 8.39 (d, J = 8.5 Hz, 2H, Ar-H), 8.29 (d, J = 8.5 Hz, 3H, Ar-H), 7.97 (d, J = 9.0 Hz, 1H, Ar-H), 7.58 (d, J = 8.9 Hz, 1H, Ar-H), 7.35–7.28 (m, 3H, Ar-H), 7.05 (dd, J = 9.5, 6.9 Hz, 1H, Ar-H), 4.44 (s, 2H, -S-CH_2-), 4.22–4.12 (m, 1H, Piperidine-H), 2.98 (d, J = 12.0 Hz, 2H, Piperidine-H), 2.65–2.54(m, 2H, Piperidine-H), 1.83–1.74 (m, 2H, Piperidine-H), 1.53 (qd, J = 12.0, 3.2 Hz, 2H, Piperidine-H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.82(-NH-C = O), 163.56(Ar-C), 163.17(d, J = 244.2 Hz), 157.79, 149.18, 147.02, 142.19(d, J = 7.5 Hz), 140.06, 134.53, 130.11(d, J = 8.3 Hz), 129.15, 129.10, 127.97, 126.26, 124.73, 123.54, 115.43(d, J = 22.7 Hz), 115.27, 113.54(d, J = 21.3 Hz), 112.92, 48.68(-S-CH_2-), 45.33(Piperidine-C), 33.40(Piperidine-C), 32.33(Piperidine-C). HRMS (ESI) calcd for $C_{28}H_{25}FN_6OS$ $[M + H]^+$: 513.1873, found: 513.1862.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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