含脲砌块的 4-氨基喹唑啉衍生物的设计、合成及抗肿瘤活性研究

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摘要 为了寻找新的具有靶向治疗作用的抗肿瘤药物,设计并合成了一系列新型的含脲砌块的 4-氨基喹唑啉类衍生物,并采用噻唑蓝(MTT)法测定目标化合物对 MCF-7(人乳腺癌细胞)、MGC-803(人胃癌细胞)、SW620(人结肠癌细胞)、A549(人肺癌细胞)四种肿瘤细胞的抗肿瘤活性。结果显示大部分化合物具有较好的抗肿瘤活性,其中 2-((4-((3,4,5-三甲氧基苯基)-氨基)喹唑啉-2-基)-硫代)-N-((3,4,5-三甲氧基苯基)氨基甲酰基)乙酰胺(**10p**)对 MGC-803、SW620 和 A549 三种细胞显示出最好的抗肿瘤活性,IC₅₀ 值分别为(7.02±0.46)、(6.00±0.78)和(7.04±1.11) μmol·L⁻¹,其抗肿瘤活性和阳性对照品吉非替尼相当。分子对接结果显示,化合物 **10p** 能与 EGFR 很好地结合,有可能成为潜在的抗肿瘤药物。

关键词 脲砌块; 4-氨基喹唑啉; 合成; 抗肿瘤活性

Design, Synthesis and Antitumor Activity Evaluation of 4-Aminoquinazoline Derivatives Containing Urea Moiety

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Abstract In order to find new anti-tumor drugs with targeted therapeutic effect, a series of novel 4-aminoquinazoline derivatives bearing urea moiety were designed, synthesized and evaluated for antitumor activity against four human cancer cell lines of MCF-7, MGC-803, SW620 and A549 using methyl thiazolyl tetrazolium (MTT) assay. Most of the target compounds exhibited excellent anti-tumor activity against the four human tumor cell lines. Among them, 2-((4-((3,4,5-trimethoxyphenyl)-amino)quinazolin-2-yl)-thio)-N-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10p**) showed the best antitumor activity against MGC-803, SW620 and A549 cancer cell lines with IC₅₀ values of (7.02±0.46), (6.00±0.78) and (7.04±1.11) μmol·L⁻¹, respectively. Its activity was comparable to the positive control of gefitinib. Molecular docking showed that compound **10p** could bind well with EGFR, suggesting that it could be a potential antitumor agent.

Keywords urea moiety; 4-aminoquinazoline; synthesis; antitumor activity

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1 Introduction

Currently, the cancer is the second major cause of human death after cardiovascular disease. Statistics showed that approximately 8.2 million people die from cancer each year.^[1] Although the technology for diagnosis and treatment of cancer has made great progress, the survival rate of cancer patient is still low in the past 5 years. Quinazoline has a wide range of pharmacological activities such as antitumor,^[2] antibacterial,^[3] anti-inflammatory^[4] and antimalarial activities.^[5] In the past few years, quinazoline has been extensively studied as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and many quinazolines have been approved for cancer therapy by US FDA as erlotinib (1), gefitinib (2) and lapatinib (3)^[6–8] (Figure 1). They used to have a good effect on non-small cell lung cancer, but cancer cells have shown resistance to gefitinib and erlotinib due to the T790M mutation. Lapatinib was banned after one year of clinical treatment due to the discovery of fatal liver toxicity in clinical trials and post-marketing test. Therefore, it is urgent to develop targeted antitumor agents with lower toxicity and higher efficacy.

In addition, we found that the urea structure plays an important role in organic synthesis and antitumor during literature research.^[9–12] In 2017, Keating^[13] reported that sorafenib 4 containing a urea structure is a systemic agent approved for the treatment of hepatocellular carcinoma (HCC) with good tolerance and safety. In 2017 Kurt *et al.*^[14] reported that compound 5 had strong cytotoxic effect against H4IIE with IC₅₀ value of 2.07 $\mu\text{mol}\cdot\text{L}^{-1}$ and urea moiety was the key pharmacophore for the enhancement of antitumor activity. Therefore, we considered that the synthesis of quinazoline derivatives containing urea structures may result in more active antitumor inhibitors.

Based on previous studies,^[15–17] 2-mercaptoquinazoline was selected as the core from gefitinib, erlotinib and lapatinib. The urea moiety and the sulfhydryl group were linked to obtain compound 8 by principle of molecular hybridization. After chlorination, 4-position of quinazoline was substituted by different anilines. Finally, the antitumor activity of these compounds was evaluated *in vitro*.

2 Results and discussion

2.1 Chemistry

The synthetic procedure was shown in Scheme 1. In this study, compound 6 was prepared by the reaction of 2-aminobenzamide with carbon disulfide in the presence of potassium hydroxide in ethanol at 90 °C for 24 h. Then, compound 6 reacted with compound 7 to obtain compound 8 in an aqueous solution of potassium hydroxide at 90 °C for 1 h. Next, phosphorus oxychloride was added to compound 8 and the temperature was slowly raised to 70 °C and kept for 4 h to obtained compound 9. Finally, compounds 10a~10r were synthesized using reaction of compound 9 with different substituted anilines in *N,N*-dimethylfor-

Figure 1 EGFR agents and compounds 4 and 5

mamide at 90 °C for 1 h. The structures of target compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS.

2.2 Anti-tumor activity

All compounds were tested for antiproliferative activity against MCF-7 (human breast cancer cell line), MGC-803 (human gastric cancer cell line), SW620 (human colon cancer cell line) and A549 (human lung cancer cell) through methyl thiazolyl tetrazolium (MTT) assay method.^[18–20] Gefitinib was used as reference compounds. The results were summarized in Table 1.

As shown in Table 1, the majority of the compounds exhibited moderate to potent antitumor activity against four cell lines. Comparing compounds 10a~10c with 10m~10o, it could be found that the activity of *ortho*-substitution was better than *meta*-substitution and *para*-substitution, whether it was an electron-withdrawing

Reagents and conditions: (i) KOH, EtOH, 90 °C, 24 h; (ii) KOH, H_2O , 90 °C, 1 h; (iii) POCl_3 , 70 °C, 4 h; (iv) different anilines, *N,N*-dimethylformamide, 90 °C, 1 h

Scheme 1 Synthetic procedure of compounds **10a~10r**

Table 1 Anti-tumor activity of target compounds **8**, **9** and **10a~10r** against four cancer cell lines

Compd.	R	$\text{IC}_{50}^a/(\mu\text{mol}\cdot\text{L}^{-1})$			
		MCF-7	MGC-803	SW620	A549
8	—	17.23 ± 0.85	18.02 ± 0.98	23.25 ± 1.91	25.67 ± 1.78
9	—	18.83 ± 1.07	26.40 ± 1.42	22.02 ± 1.54	25.19 ± 1.20
10a	4-Cl	20.21 ± 1.02	21.31 ± 1.71	11.44 ± 1.06	13.15 ± 1.52
10b	3-Cl	18.04 ± 1.04	17.34 ± 1.48	8.22 ± 0.95	10.76 ± 1.31
10c	2-Cl	10.28 ± 1.25	7.61 ± 0.93	7.66 ± 0.91	8.07 ± 1.02
10d	4-F	25.21 ± 1.35	27.09 ± 1.32	29.89 ± 1.16	21.54 ± 1.93
10e	3-F	20.21 ± 1.42	15.09 ± 1.30	13.68 ± 1.59	14.08 ± 1.08
10f	2-F	15.02 ± 1.21	16.27 ± 1.03	19.92 ± 1.12	18.76 ± 1.94
10g	4-Br	>50	31.05 ± 1.82	35.67 ± 1.24	>50
10h	3-Br	>50	29.48 ± 1.67	39.73 ± 1.43	>50
10i	2-Br	16.24 ± 1.46	17.24 ± 1.51	22.23 ± 0.97	23.20 ± 1.96
10j	4-CH ₃	>50	>50	>50	>50
10k	3-CH ₃	21.06 ± 1.45	23.82 ± 1.80	>50	24.89 ± 1.07
10l	2-CH ₃	10.84 ± 1.03	8.09 ± 1.37	8.38 ± 1.12	16.73 ± 1.81
10m	4-OCH ₃	>50	>50	>50	>50
10n	3-OCH ₃	17.02 ± 1.36	9.71 ± 0.98	12.16 ± 1.00	20.11 ± 1.95
10o	2-OCH ₃	7.88 ± 0.84	5.90 ± 0.69	7.45 ± 0.82	7.92 ± 1.44
10p	3,4,5-(OCH ₃) ₃	7.62 ± 0.63	7.02 ± 0.46	6.00 ± 0.78	7.04 ± 1.11
10q	H	27.05 ± 1.62	25.07 ± 1.96	15.51 ± 1.13	>50
10r	3-Cl-4-F	25.51 ± 1.35	20.08 ± 1.31	34.53 ± 1.21	14.64 ± 1.27
Gefitinib ^b	—	7.34 ± 0.86	8.82 ± 0.63	10.79 ± 0.69	9.28 ± 1.00

^a Anti-tumor activity was assayed by exposure for 72 h to substances and expressed as concentration required to inhibit tumor cells proliferation by 50% (IC_{50}).

^b Used as a positive control.

substituent or an electron donating substituent. From the biological data of compounds **10a~10c** vs **10d~10f** vs **10g~10i**, it could be known that the contribution to enhance antitumor activity was $\text{Cl} > \text{F} > \text{Br}$, although the substituents were all halogen atoms. Compared compounds **10j~10l** and **10m~10o**, it could be concluded that the methoxy-substituted quinazoline activity was better than the methyl substitution, as a result of the methoxy group with stronger electron donating ability than the methyl group. It also be found that unsatisfied antitumor activity was given when substituents were at 4-position (compounds **10g**, **10j** and **10m**). Among all the target compounds, compound **10p**

showed the best antitumor activity against MCF-7, MGC-803, SW620 and A549 with IC_{50} values of (7.62 ± 0.63) , (7.02 ± 0.46) , (6.00 ± 0.78) and $(7.04 \pm 1.11) \mu\text{mol}\cdot\text{L}^{-1}$, respectively. Also, compounds **10c** and **10o** had broad antitumor activity against MCF-7, MGC-803, SW620 and A549 cells and their activity is comparable to the positive control.

2.3 Molecular modeling

To predict the binding mode of target compound to the active site of EGFR, molecular docking was performed using MOE 2014. Based on the antitumor activity results, compound **10p** was selected as ligand. 1xkk was selected

as receptor due to the co-crystal structure of 1xkk is similar to compound **10p**.^[21] As shown in Figure 2A, compound **10p** was able to be tightly embedded in the active pocket of EGFR in the given posture. From Figures 2B & 2C, it could be seen that both compound **10p** and lapatinib could form hydrogen bonds with the residue Asp800 and the length of the hydrogen bond was similar. lapatinib formed a hydrogen bond with residue Leu718 (3.68 Å), while compounds **10p** formed π -H interaction with it. In addition, lapatinib formed hydrogen bond with Met793 (2.96 Å) and π -H interaction with Phe856. Compound **10p** formed hydrogen bonds with Ala743 (3.20 Å), Met1002 (3.66 Å) and P0481(3.14 Å). The results also suggest that compound **10p** may be a potential EGFR inhibitor.

Figure 2 Molecular docking model of compound **10p** with 1xkk (A & B), and binding model of Lapatinib with 1xkk (C) The hydrogen was illustrated as dashed lines and the length of hydrogen bonds was illustrated in numbers (unit in Å)

3 Conclusion

In summary, a series of 4-aminoquinazoline derivatives containing urea moiety were designed, synthesized and evaluated for anti-tumor activity against four human cancer cell lines. The cytotoxicity experiment results showed that compounds **10c**, **10o** and **10p** had broad antitumor activity.

Especially, compound **10p** showed the most excellent activity against MGC-803, SW620 and A549 cancer cell lines and its activity was comparable to the positive control gefitinib. Molecular docking showed that compound **10p** could bind well with EGFR protein, which indicated that compound **10p** could be a potential antitumor agent.

4 Experimental

4.1 Materials

All commercially available starting materials, reagents and solvents were used without further purification. Column chromatography silica gel, Shanghai May Fourth Chemical Reagent Factory. Anhydrous ethanol, Yantai Chemical Co., Ltd. *N,N*-dimethylformamide, Guangdong Guanghua Technology Co., Ltd. ¹H NMR and ¹³C NMR spectra were measured using a DPX-DPX-400 superconducting nuclear magnetic resonance instrument, TMS as internal standard. High-resolution mass spectrometry using a Waters-Micromass Q-ToF Micro high resolution Determination of tetragonal-flight time tandem mass spectrometer.

4.2 Chemistry

4.2.1 Synthesis of 2-mercapto-4-hydroxyquinazoline (**6**)

Compound **6** was synthesized according to the published literature^[11] and the characterization data was consistent with the literature.

4.2.2 Synthesis of 2-((4-hydroxyquinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**8**)

Compound **6** (1.12 mmol) was dissolved in 20 mL of an aqueous solution of KOH (1.23 mmol) at room temperature. Compound **7** (1.10 mmol) was dissolved in acetone (2 mL) and added to the above solution. After reacting at 90 °C, the reaction was completed (TLC detection reaction). The reaction solution was cooled to room temperature. Then, the precipitate was collected by filtration, washed three times with water and acetone and dried in vacuo to give compound **8**. White solid, yield 69.4%. m.p. 248.1~248.9 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ : 12.76 (s, 1H), 11.04 (s, 1H), 10.29 (s, 1H), 8.08~8.01 (m, 1H), 7.82~7.74 (m, 1H), 7.44 (dd, *J*=15.3, 7.6 Hz, 2H), 6.92 (s, 2H), 4.24 (s, 2H), 3.75 (s, 6H), 3.62 (s, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ : 170.55, 161.07, 156.15, 154.89, 152.85, 150.41, 148.06, 134.71, 133.67, 133.54, 126.06, 125.83, 119.85, 97.45, 60.03, 55.78, 34.53. HRMS (ESI) calcd for C₂₀H₂₀N₄O₆Na [M+Na]⁺: 467.1001, found 467.1004.

3.2.3 Synthesis of 2-((4-chloroquinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**9**)

Compound **8** (1.13 mmol) was added to a 25 mL round bottom flask, followed by addition of phosphorus oxychloride (8 mL). The reaction was completed after reacting at 70 °C for 4 h. The mixture was cooled to room temperature and added to the stirred ice water mixture. The precipitate was collected by filtration and washed three times with water. The filter cake was purified by column chromatog-

raphy ($V_{\text{DCM}} : V_{\text{EA}} = 15 : 1$) and the eluent was concentrated to give compound **9**. White solid, yield 67.2%. m.p. 164.8~165.3 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 11.04 (s, 1H), 10.35 (s, $J=17.2$ Hz, 1H), 8.07 (dd, $J=20.7, 7.9$ Hz, 1H), 7.81~7.73 (m, 1H), 7.47 (dd, $J=8.6, 4.1$ Hz, 2H), 6.91 (s, 2H), 4.28 (d, $J=6.7$ Hz, 2H), 3.86~3.78 (m, 3H), 3.75 (s, 6H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 170.42, 161.07, 154.96, 152.85, 150.41, 147.92, 134.66, 133.68, 133.61, 126.04, 125.79, 125.61, 119.84, 97.42, 60.02, 55.78, 34.59. HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{19}\text{ClN}_4\text{O}_5\text{SNa}$ $[\text{M}+\text{Na}]^+$: 485.0622, found 485.0663.

3.2.4 General procedure for the synthesis of 4-chloroquinazoline derivatives (**10a**~**10r**)

Compound **9** (0.35 mmol) was dissolved in 4 mL of N,N -dimethylformamide at room temperature. Then, aniline (0.39 mmol) was added dropwise to the above system. The reaction was carried out at 90 °C for 1 h. After the reaction was completed (TLC detection reaction), the reaction mixture was cooled to room temperature. Then appropriate amount of water was added to the system to get white solid. The precipitate was collected by filtration. Next, crude compound was subjected to column chromatography ($V_{\text{PE}} : V_{\text{EA}} = 2 : 1$), and the eluent was concentrated to give solid compound **10**.

2-((4-((4-Chlorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10a**): White solid, yield 83.1%. m.p. 243.3~244.3 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.93 (s, 1H), 10.27 (s, 1H), 9.99 (s, 1H), 8.45 (d, $J=8.3$ Hz, 1H), 7.81 (d, $J=8.7$ Hz, 3H), 7.61 (d, $J=8.3$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 1H), 7.44 (d, $J=8.8$ Hz, 2H), 6.88 (s, 2H), 4.12 (s, 2H), 3.73 (s, 6H), 3.60 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.23, 165.04, 157.05, 152.84, 150.47, 149.94, 137.49, 133.76, 133.70, 133.51, 128.38, 127.85, 126.22, 125.32, 123.92, 123.22, 113.01, 97.52, 60.05, 55.78, 35.00. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{ClN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 554.1265, found 554.1266.

2-((4-((3-Chlorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10b**): White solid, yield 76.1%. m.p. 216.3~217.0 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.95 (s, 1H), 10.32 (s, 1H), 10.00 (s, 1H), 8.49 (d, $J=8.3$ Hz, 1H), 7.99 (s, 1H), 7.83 (d, $J=8.5$ Hz, 1H), 7.63 (d, $J=8.3$ Hz, 1H), 7.56 (t, $J=7.6$ Hz, 1H), 7.44 (t, $J=8.1$ Hz, 1H), 7.37 (s, 1H), 7.21 (d, $J=8.0$ Hz, 1H), 6.90 (s, 2H), 4.16 (s, 2H), 3.74 (s, 6H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.36, 164.94, 158.19, 156.99, 152.87, 152.65, 150.46, 150.00, 140.23, 134.44, 132.78, 130.10, 126.33, 125.37, 123.60, 123.29, 121.66, 120.53, 113.11, 97.52, 60.04, 55.81, 34.90. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{ClN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 554.1265, found 554.1265.

2-((4-((2-Chlorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10c**): White solid, yield 76.5%. m.p. 208.2~209.0 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.82 (s, 1H), 10.29 (s, 1H), 9.97 (s, 1H), 8.41 (d, $J=8.2$ Hz, 1H), 7.82 (t, $J=7.6$ Hz, 1H), 7.61 (d, $J=8.3$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 2H), 7.38~7.29

(m, 2H), 7.26 (t, $J=6.5$ Hz, 1H), 6.90 (s, 2H), 4.01 (s, 2H), 3.75 (s, 6H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.19, 165.29, 158.07, 155.60, 152.88, 150.45, 149.92, 133.72, 128.33, 127.81, 126.17, 125.52, 125.27, 124.38, 123.33, 116.07, 115.87, 112.77, 97.44, 90.65, 60.04, 55.81, 34.93. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{ClN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 554.1265, found 554.1265.

2-((4-((4-Fluorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10d**): White solid, yield 79.7%. m.p. 228.2~229.2 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.94 (s, 1H), 10.30 (s, 1H), 9.98 (s, 1H), 8.48 (d, $J=8.2$ Hz, 1H), 7.84 (d, $J=8.8$ Hz, 2H), 7.63~7.60 (m, 1H), 7.54 (t, $J=7.4$ Hz, 1H), 7.46 (d, $J=8.8$ Hz, 2H), 7.16 (t, $J=8.9$ Hz, 1H), 6.90 (s, 2H), 4.13 (d, $J=7.1$ Hz, 2H), 3.74 (s, 6H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.24, 165.06, 159.41, 157.03, 152.86, 150.46, 149.98, 137.59, 133.56, 128.39, 127.78, 126.26, 125.25, 123.86, 123.30, 115.50, 113.07, 97.55, 60.04, 55.81, 35.03. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{FN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 538.1560, found 538.1561.

2-((4-((3-Fluorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10e**): White solid, yield 78.6%. m.p. 229.9~230.7 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.97 (s, 1H), 10.32 (s, 1H), 10.02 (s, 1H), 8.50 (d, $J=8.2$ Hz, 1H), 7.87~7.78 (m, 2H), 7.65 (dd, $J=16.6, 8.3$ Hz, 2H), 7.56 (t, $J=7.5$ Hz, 1H), 7.44 (dd, $J=15.3, 7.9$ Hz, 1H), 6.99 (t, $J=7.4$ Hz, 1H), 6.90 (s, 2H), 4.16 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.35, 164.96, 156.99, 152.85, 150.47, 149.96, 140.45, 133.80, 133.67, 133.59, 130.07, 129.97, 126.32, 125.35, 123.32, 117.85, 113.11, 110.5, 109.00, 97.46, 60.03, 55.79, 34.96. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{FN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 538.1560, found 538.1558.

2-((4-((2-Fluorophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10f**): White solid, yield 72.4%. m.p. 222.0~223.0 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.82 (s, 1H), 10.29 (s, 1H), 9.97 (s, 1H), 8.41 (d, $J=8.2$ Hz, 1H), 7.82 (t, $J=7.6$ Hz, 1H), 7.61 (d, $J=8.3$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 2H), 7.33 (dd, $J=5.9, 4.0$ Hz, 2H), 7.26 (t, $J=6.5$ Hz, 1H), 6.90 (s, 2H), 4.01 (s, 2H), 3.75 (s, 6H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.19, 165.29, 158.07, 155.60, 152.88, 150.45, 149.92, 133.72, 133.63, 128.33, 127.74, 126.17, 125.64, 125.52, 125.27, 124.38, 123.33, 116.07, 112.77, 97.44, 60.04, 55.81, 34.93. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{25}\text{FN}_5\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$: 538.1560, found 538.1561.

2-((4-((4-Bromophenyl)amino)quinazolin-2-yl)thio)- N -((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10g**): White solid, yield 69.2%. m.p. 237.8~238.4 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.95 (s, 1H), 10.30 (s, 1H), 9.97 (s, 1H), 8.48 (d, $J=8.2$ Hz, 1H), 7.84 (d, $J=7.4$ Hz, 1H), 7.79 (d, $J=8.9$ Hz, 2H), 7.60 (t, $J=9.5$ Hz, 3H), 7.54 (t, $J=7.5$ Hz, 1H), 6.90 (s, 2H), 4.15 (s, 2H), 3.74 (s, 6H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.23, 165.05, 156.99, 152.86, 150.46, 149.97, 138.04, 133.74, 133.72, 133.56, 131.30, 126.26, 125.26, 124.17, 123.30, 115.87, 113.09, 97.55, 60.04, 55.82, 35.02. HRMS (ESI) calcd for

$C_{26}H_{25}BrN_5O_5S$ $[M+H]^+$: 598.0760, found 598.0761.

2-((4-((3-Bromophenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10h**): White solid, yield 80.1%. m.p. 227.9~228.9 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.97 (s, 1H), 10.33 (s, 1H), 10.00 (s, 1H), 8.49 (d, $J=8.3$ Hz, 1H), 8.13 (s, 1H), 7.88 (d, $J=8.0$ Hz, 1H), 7.83 (d, $J=7.2$ Hz, 1H), 7.63 (d, $J=8.2$ Hz, 1H), 7.56 (t, $J=7.6$ Hz, 1H), 7.41~7.33 (m, 2H), 6.90 (s, 2H), 4.16 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.38, 164.92, 156.95, 152.86, 150.46, 149.99, 140.37, 133.80, 133.57, 131.68, 130.40, 128.62, 126.46, 125.38, 124.49, 123.29, 121.16, 120.90, 113.10, 97.46, 60.03, 55.79, 34.89. HRMS (ESI) calcd for $C_{26}H_{25}BrN_5O_5S$ $[M+H]^+$: 598.0760, found 598.0762.

2-((4-((2-Bromophenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10i**): White solid, yield 81.4%. m.p. 207.7~208.7 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.76 (s, 1H), 10.29 (s, 1H), 10.02 (s, 1H), 8.41 (d, $J=8.2$ Hz, 1H), 7.82 (t, $J=7.5$ Hz, 1H), 7.73 (d, $J=7.5$ Hz, 1H), 7.60 (d, $J=8.3$ Hz, 1H), 7.53 (dd, $J=6.8$, 4.1 Hz, 2H), 7.45 (t, $J=7.5$ Hz, 1H), 7.28 (t, $J=7.0$ Hz, 1H), 6.90 (s, 2H), 3.96 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.12, 165.29, 158.26, 152.87, 150.42, 149.92, 136.73, 133.74, 133.69, 133.65, 132.82, 129.92, 128.52, 128.21, 126.13, 125.21, 123.25, 121.97, 112.66, 97.40, 60.04, 55.81, 34.93. HRMS (ESI) calcd for $C_{26}H_{25}BrN_5O_5S$ $[M+H]^+$: 598.0760, found 598.0762.

2-((4-(*p*-Tolylamino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10j**): White solid, yield 69.8%. m.p. 243.8~244.8 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.93 (s, 1H), 10.32 (s, 1H), 9.87 (s, 1H), 8.47 (d, $J=8.2$ Hz, 1H), 7.80 (t, $J=7.3$ Hz, 1H), 7.63 (d, $J=8.3$ Hz, 2H), 7.59 (d, $J=8.2$ Hz, 1H), 7.51 (t, $J=7.5$ Hz, 1H), 7.21 (d, $J=8.3$ Hz, 2H), 6.91 (s, 2H), 4.11 (s, 2H), 3.77 (d, $J=19.5$ Hz, 6H), 3.61 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.32, 165.19, 157.18, 152.86, 150.48, 149.89, 135.89, 133.66, 133.62, 133.50, 133.33, 128.92, 126.16, 125.07, 123.27, 122.69, 113.10, 97.43, 60.04, 55.79, 34.97, 20.54. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_5S$ $[M+H]^+$: 534.1811, found 534.1812.

2-((4-(*m*-Tolylamino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10k**): White solid, yield 75.1%. m.p. 231.4~232.4 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.94 (s, 1H), 10.32 (s, 1H), 9.86 (s, 1H), 8.49 (d, $J=8.3$ Hz, 1H), 7.81 (t, $J=7.6$ Hz, 1H), 7.61 (t, $J=9.5$ Hz, 2H), 7.53 (dd, $J=16.0$, 8.4 Hz, 2H), 7.29 (t, $J=7.8$ Hz, 1H), 6.99 (d, $J=7.5$ Hz, 1H), 6.90 (s, 2H), 4.13 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.44, 165.11, 157.15, 152.86, 150.46, 149.94, 138.45, 137.70, 133.68, 133.59, 133.56, 128.31, 126.22, 125.15, 124.91, 123.28, 123.09, 119.79, 113.14, 97.46, 60.04, 55.80, 34.86, 21.08. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_5S$ $[M+H]^+$: 534.1811, found 534.1812.

2-((4-(*o*-Tolylamino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10l**): White solid, yield 76.4%. m.p. 235.1~236.1 °C; 1H NMR (400 MHz,

DMSO- d_6) δ : 10.81 (s, 1H), 10.31 (s, 1H), 9.83 (s, 1H), 8.42 (d, $J=8.1$ Hz, 1H), 7.80 (t, $J=7.4$ Hz, 1H), 7.58 (d, $J=8.2$ Hz, 1H), 7.51 (t, $J=7.3$ Hz, 1H), 7.32 (d, $J=6.5$ Hz, 2H), 7.28~7.20 (m, 2H), 6.91 (s, 2H), 3.97 (s, 2H), 3.75 (s, 6H), 3.62 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.33, 165.41, 158.16, 152.88, 150.44, 149.81, 136.45, 134.80, 133.65, 133.47, 130.42, 127.45, 126.65, 126.17, 126.11, 125.05, 123.27, 112.83, 97.40, 71.34, 60.04, 55.80, 34.88, 17.93. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_5S$ $[M+H]^+$: 534.1811, found 534.1810.

2-((4-((4-Methoxyphenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10m**): White solid, yield 73.8%. m.p. 228.9~229.5 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.93 (s, 1H), 10.32 (s, 1H), 9.84 (s, 1H), 8.45 (d, $J=8.3$ Hz, 1H), 7.79 (t, $J=7.6$ Hz, 1H), 7.63 (d, $J=8.9$ Hz, 2H), 7.58 (d, $J=8.3$ Hz, 1H), 7.50 (t, $J=7.6$ Hz, 1H), 6.98 (d, $J=9.0$ Hz, 2H), 6.91 (s, 2H), 4.09 (s, 2H), 3.78 (s, 3H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.32, 165.24, 157.21, 156.08, 152.86, 150.49, 149.85, 133.68, 133.42, 131.28, 128.63, 126.13, 124.99, 124.36, 123.20, 113.66, 113.05, 97.46, 60.04, 55.79, 55.12, 34.96. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_6S$ $[M+H]^+$: 550.1760, found 550.1762.

2-((4-((3-Methoxyphenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10n**): White solid, yield 68.3%. m.p. 230.5~230.9 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.96 (s, 1H), 10.33 (s, 1H), 9.87 (s, 1H), 8.50 (d, $J=8.2$ Hz, 1H), 7.82 (t, $J=7.5$ Hz, 1H), 7.61 (d, $J=8.2$ Hz, 1H), 7.53 (dd, $J=15.0$, 7.3 Hz, 2H), 7.43 (d, $J=8.1$ Hz, 1H), 7.31 (t, $J=8.1$ Hz, 1H), 6.90 (s, 2H), 6.74 (d, $J=6.6$ Hz, 1H), 4.14 (s, 2H), 3.79 (s, 3H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.42, 165.07, 159.34, 157.05, 152.86, 150.48, 149.92, 139.82, 133.67, 133.61, 129.21, 126.27, 125.20, 123.31, 123.29, 114.52, 113.18, 109.57, 108.07, 97.44, 60.04, 55.79, 55.03, 34.96. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_6S$ $[M+H]^+$: 550.1760, found 550.1762.

2-((4-((2-Methoxyphenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10o**): White solid, yield 76.2%. m.p. 202.5~202.9 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.84 (s, 1H), 10.29 (s, 1H), 9.55 (s, 1H), 8.39 (d, $J=8.1$ Hz, 1H), 7.80 (t, $J=7.6$ Hz, 1H), 7.60~7.54 (m, 2H), 7.50 (t, $J=7.6$ Hz, 1H), 7.30~7.25 (m, 1H), 7.13 (d, $J=7.5$ Hz, 1H), 7.01 (t, $J=7.6$ Hz, 1H), 6.90 (s, 2H), 4.01 (s, 2H), 3.80 (s, 3H), 3.74 (s, 6H), 3.62 (s, 3H). ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.36, 165.31, 158.02, 153.42, 152.86, 150.44, 149.78, 133.65, 133.59, 133.50, 127.01, 126.41, 126.10, 125.19, 125.12, 123.16, 120.19, 112.95, 111.90, 97.42, 60.05, 55.80, 55.61, 34.90. HRMS (ESI) calcd for $C_{27}H_{28}N_5O_6S$ $[M+H]^+$: 550.1760, found 550.1758.

2-((4-((3,4,5-Trimethoxyphenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10p**): White solid, yield 70.4%. m.p. 217.3~218.3 °C; 1H NMR (400 MHz, DMSO- d_6) δ : 10.97 (s, 1H), 10.33 (s, 1H), 9.82 (s, 1H), 8.49 (d, $J=8.3$ Hz, 1H), 7.82 (t, $J=7.6$ Hz, 1H), 7.61 (d, $J=8.2$ Hz, 1H), 7.54 (t, $J=7.6$ Hz, 1H), 7.32

(s, 2H), 6.90 (s, 2H), 4.15 (s, 2H), 3.82 (s, 6H), 3.73 (d, $J=7.7$ Hz, 6H), 3.69 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.55, 164.97, 156.88, 152.86, 152.47, 150.44, 149.79, 134.67, 134.05, 133.69, 133.57, 126.32, 125.22, 123.15, 113.23, 100.12, 97.46, 60.13, 60.04, 55.79, 55.74, 34.90. HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{32}\text{N}_5\text{O}_8\text{S} [\text{M} + \text{H}]^+$: 610.1972, found 610.1970.

2-((4-(Phenylamino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10q**): White solid, yield 78.4%. m.p. 224.7~225.7 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.95 (s, 1H), 10.32 (s, 1H), 9.91 (s, 1H), 8.50 (d, $J=8.3$ Hz, 1H), 7.82~7.76 (m, 3H), 7.60 (d, $J=8.3$ Hz, 1H), 7.53 (t, $J=7.6$ Hz, 1H), 7.41 (t, $J=7.8$ Hz, 2H), 7.16 (t, $J=7.4$ Hz, 1H), 6.90 (s, 2H), 4.12 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.36, 165.13, 157.15, 152.86, 152.53, 150.48, 149.95, 138.56, 133.67, 133.59, 128.48, 126.22, 125.16, 124.16, 123.31, 122.51, 113.12, 97.46, 60.04, 55.80, 34.97. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_5\text{O}_5\text{S} [\text{M} + \text{H}]^+$: 520.1655, found 520.1652.

2-((4-((3-Chloro-4-fluorophenyl)amino)quinazolin-2-yl)thio)-*N*-((3,4,5-trimethoxyphenyl)carbamoyl)acetamide (**10r**): White solid, yield 72.9%. m.p. 239.5~240.3 °C; ^1H NMR (400 MHz, DMSO- d_6) δ : 10.94 (s, 1H), 10.30 (s, 1H), 10.03 (s, 1H), 8.46 (d, $J=8.2$ Hz, 1H), 8.06 (dd, $J=6.8, 2.6$ Hz, 1H), 7.84 (t, $J=5.4$ Hz, 1H), 7.80 (dd, $J=5.2, 3.7$ Hz, 1H), 7.62 (d, $J=8.2$ Hz, 1H), 7.55 (t, $J=7.4$ Hz, 1H), 7.46 (t, $J=9.1$ Hz, 1H), 6.90 (d, $J=5.2$ Hz, 2H), 4.14 (s, 2H), 3.74 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO- d_6) δ : 171.30, 164.93, 157.02, 152.85, 150.45, 149.95, 135.84, 133.81, 133.68, 133.57, 126.30, 125.36, 123.98, 123.24, 122.83, 122.76, 118.99, 116.73, 112.97, 97.46, 60.03, 55.78, 34.91. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{24}\text{ClFN}_5\text{O}_5\text{S} [\text{M} + \text{H}]^+$: 572.1171, found 572.1170.

Supporting Information ^1H NMR and ^{13}C NMR of compounds **8**, **9** and **10a~10r** are available for free download from our website (<http://sioc-journal.cn/>).

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