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含丙烯酰胺结构的喹唑啉衍生物的合成及抗肿瘤活性研究

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摘要 为了寻找高效低毒的抗肿瘤药物，设计并合成了一系列新型的含 N-(3-丙烯酰胺苯基)乙酰胺结构的喹唑啉类衍生物，并采用 MTT 法测定目标化合物对 H1975（人肺腺癌细胞系）、PC-3（人前列腺癌细胞系）、MGC-803（人胃癌细胞系）三种肿瘤细胞的抗增殖活性。结果显示大部分化合物具有较好的抗肿瘤活性，其中化合物 N-（3-（2-（((4-（(4-氯苯基）氨基）-7-甲氧基喹唑啉-6-基）氧基）乙酰氨基）苯基）丙烯酰胺（**13j**）对 H1975、MGC-803 两种细胞显示出最好的抗增殖活性，IC_{50} 值分别为 6.77±0.65 和（4.06±0.34)μmol/L，其活性均优于阳性对照品吉非替尼，为抗肿瘤药物的研究提供了线索。

关键词 丙烯酰胺；喹唑啉；合成；抗肿瘤活性

Synthesis and Antitumor Activity of Novel Quinazoline Derivatives Containing Acrylamide

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Abstract In order to find efficient and low toxicity anti-tumor drugs, a series of novel quinazoline derivatives containing N-(3-aminophenyl)acrylamide were synthesized and evaluated for their antiproliferative activities against four human cancer cell lines (H1975, PC-3, MGC-803) by using MTT assay. The results showed that most compounds exhibited better antiproliferative activities against the four human tumor cell lines. Among them, N-(3-(2-((4-((4-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（**13j**）showed the best antiproliferative activity against H1975 and MGC-803 cancer cell lines , with the IC_{50} values of 6.77±0.65 and (4.06±0.34)μmol/L, respectively. Its activity was better than the positive control Gefitinib. In a nutshell, this work provided clues to discover antitumor agent based on the quinazoline scaffold.

Keywords Acrylamide, Quinazoline, Synthesis, Antiproliferative activity

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Currently, the cancer is the second major cause of human death after cardiovascular disease[1]. Statistics show that approximately 13.15 million people will die from cancer until 2035[2]. Chemotherapy is a very important method in clinic. However, Many anti-tumor drugs are prone to drug resistance[3]. Therefore, finding efficient and low toxicity anti-tumor drugs is of great significance for the treatment of tumors.

Quinazoline derivatives are important nitrogen -containing heterocycles[4] with a variety of pharmacological properties such as antimalarial[5-6], antibacterial[7-8], anti-inflammatory[9-10], anticonvulsant[11 -12], antihypertensive[13], anti-diabetic[14], cholinesterase inhibition[15-16] and antitumor[17-18]. With the remarkable progress made in recent years, researchers have found that 4-aminoquinazoline plays an important role in inhibiting epidermal growth factor receptor tyrosine kinase. Some of the drugs with 4-aminoquinazolineare are effective for the treatment of Non-Small Cell Lung Cancers (NSCLCs) such as erlotinib, gefitinib, lapatinib, afatinib（Figure 1）[19].

Acrylamide substituted derivatives play an important role in pharmaceutical chemistry. For example, the third generation EGFR inhibitors all have the acrylamide moiety（Figure 1）[20].

Therefore, we synthesized a series of quinazoline derivatives containing N-(3-aminophenyl)acrylamide by using the combination principles and evaluated the antiproliferative activity of target compounds in vitro by MTT assay.

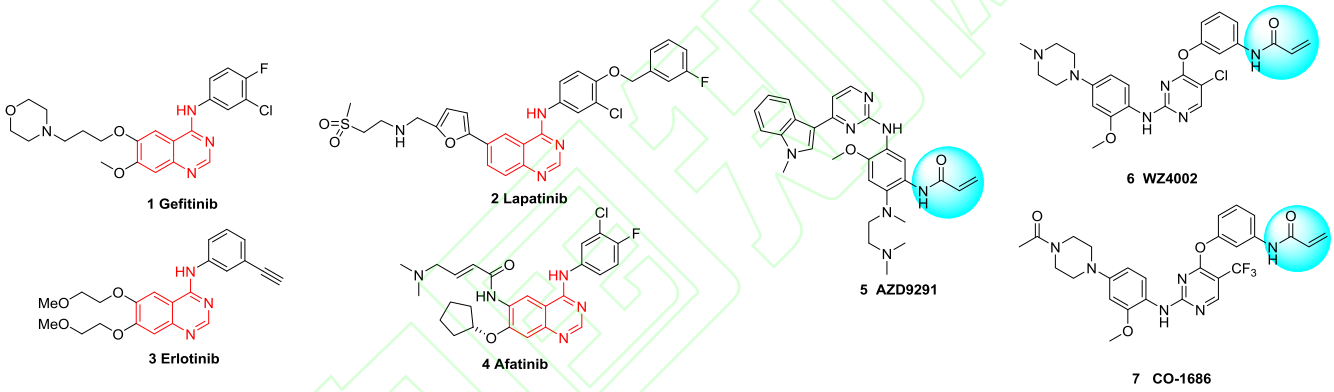
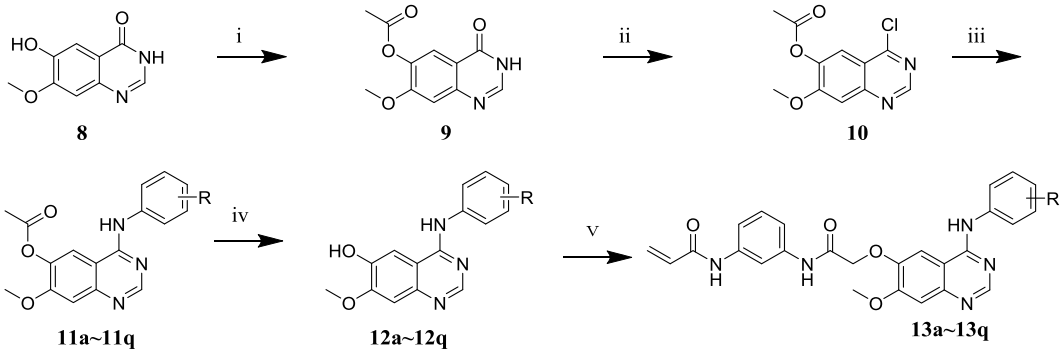


Fig.1. The structures of some 4-aminoquinazoline derivatives and derivatives containing benzothiazole**.**

1 Results and Discussion

1.1 Chemistry

The synthetic strategy to prepare the target compounds is depicted in **Scheme 1**. Firstly, 6-hydroxy-7-methoxyquinazolin-4(3H)-one and pyridine was dissolved in acetic anhydride at 80℃ for 4h to obtained compound **9**. Next, phosphorus oxychloride was added to compound **9** and the temperature was slowly raised to 80℃ and kept for 2 h to obtained compound **10**. Then compound **11a~11v** was acquired from the reaction of compound **10** with substituted aniline in isopropanol at 80℃ for 1h. $NH_3·H_2O$ was added to compound **11a~11q** in CH_3OH at 75℃ for 2h to obtained compound **12a~12q**. Finally, compound **12a~12q** and commercially available N-(3-(2-chloroacetamido)phenyl)acrylamide were added to DMF and the temperature was raised to 90℃ for 2h to get the target compounds **13a-13q**. The structures of target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.



Scheme 1 Reagents and conditions: (i) $(CH_3CO)_2O$, pyridine, 80 ℃, 4 h; (ii) $POCl_3$, 80 ℃, 2 h; (iii) substituted aniline, Isopropanol, 80 ℃, 1 h; (iv) $NH_3·H_2O$, CH_3OH, 75 ℃, 2 h; (v) N-(3-(2-chloroacetamido)phenyl)acrylamide, DMF, 90 ℃, 2h.

1.2 Anti-tumor activity

In order to explore the antiproliferative activity of the target compounds, compounds **13a-13q** were evaluated against four human cancer cell lines including H1975 (Human lung cancer cell line), PC-3 (Human prostate cancer cell line), MGC-803 (Human gastric carcinoma cell line) by using MTT assay. Gefitinib was employed as the positive control. The results are shown in **Table 1.**

Table 1. Antiproliferative activity of target compounds **13a-13q** against three cancer cell lines.

Compounds	R	IC_{50} (μM) [a]		
		H1975	PC-3	MGC-803
13a	2-F	>50	23.11±0.54	32.54±0.92
13b	2-Cl	>50	9.79±0.61	30.73±1.21
13c	2-Br	>50	8.42±0.70	16.85±0.54
13d	3-F	29.75±0.56	28.24±0.86	18.63±1.18
13e	3-Cl	>50	>50	24.28±0.89
13f	3-Br	>50	30.81±0.58	>50
13g	3-NO_2	>50	>50	49.03±0.72
13h	3-OCH_3	8.94±1.02	14.53±0.64	10.84±0.71
13i	4-F	>50	>50	20.79±1.19
13j	4-Cl	6.77±0.65	9.89±0.75	4.06±0.34
13k	4-Br	15.89±1.24	23.28±0.87	42.00±1.03
13l	4-CH_3	16.41±1.14	13.4±0.98	9.98±1.36
13m	4-OCH_3	13.2±0.79	41.92±0.74	40.14±1.45
13n	2,4-diCl	>50	28.42±0.97	49.61±0.78
13o	3,4-diCl	>50	29.69±1.04	14.81±1.15
13p	3-Cl-4-F	>50	34.80±0.53	12.84±1.08
13q	3,4,5-triOCH_3	>50	33.62±0.81	41.30±0.55
Gefitinib[b]	-	9.20±0.76	8.92±0. 41	8.19±0.67

[a] Antiproliferative 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.

In order to explore the structure-activity relationship, different substituents were introduced to quinazoline scaffold. As shown in Table 1, the majority of the compounds exhibited moderate antiproliferative activity against three human cancer cell lines. Among all the target compounds, compound **13j** showed the best cytotoxicity against the tested cell lines (H1975, MGC-803) with IC_{50} values of 6.77±0.65 and 4.06±0.34 μM, which was better than Gefitinib.

From the biological data of compounds **13a**、**13b**、**13c**, we could know that the contribution to enhance antitumor activity was F<Cl<Br, when the halogen atoms at 2-position of benzene. From the biological data of compound **13g**, we concluded that compounds with nitro at R of benzene exhibited low cytotoxicity. From the biological data of compounds **13h** and **13m**, the results revealed that the methoxy at 3-position of benzene had better cytotoxic activity for cancer cells than that at 4-position. From the biological data of compounds **13l** and **13m**, the results revealed that the methyl at 4-position of benzene had better cytotoxic activity against the tested cell lines (PC-3, MGC-803) than the methoxy at 4-position.

2 Conclusion

In conclusion, a series of novel quinazoline derivatives containing acrylamide were synthesized and evaluated for their cytotoxic activity against H1975, PC-3 and MGC-803 cancer cells using MTT assay. Among all the tested compounds, compound **13j** showed the most potent anti-proliferative activity against the tested cells. This work provided clues to discover antitumor agent based on the quinazoline scaffold.

3 Experimental

3.1 Materials

Reagents and solvents were purchased from commercial sources and were used without further purification. Column chromatography was carried out on 200−300 mesh silica gel (Qingdao Haiyang Chemical, China). Reactions were monitored by thin-layer chromatography (TLC) on 0.25mm silicagel plates (GF254) and visualized under UV light. Melting points were determined on an X-5 micro-melting apparatus and are uncorrected. ^{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) of all derivatives were recorded on a Waters Micro-mass Q-T of Micro-mass spectrometer by electrospray ionization (ESI).

3.2 Chemistry

3.2.1 7-methoxy-4-oxo-3,4-dihydroquinazolin-6-yl-acetate (9)

Compound **8** was synthesized according to the published literature [21]and the characterization data was consistent with the literature.

3.2.2 4-chloro-7-methoxyquinazolin-6-yl acetate（10）

Compound **9** was synthesized according to the published literature[21] and the characterization data was consistent with the literature.

3.2.3 General procedure for synthesis of target compounds 11a-11q

Compounds **11a**、**11d**、**11e**、**11f**、**11g**、**11i**、**11l**、**11m**、**11o**、**11p**、**11q** were synthesized according to the published literature[21] and the characterization data was consistent with the literature.

Compounds **11b**、**11c**、**11j**、**11k** were synthesized according to the published literature[22] and the characterization data was consistent with the literature.

Compounds **11n**、**11h** were synthesized according to the published literature[23] and the characterization data was consistent with the literature.

3.2.4 General procedure for synthesis of target compounds 12a-12q

Compounds **12a**、**12d**、**12e**、**12f**、**12g**、**12i**、**12l**、**12m**、**12o**、**12p**、**12q** were synthesized according to the published literature[21] and the characterization data was consistent with the literature.

Compounds **12b**、**12c**、**12j**、**12k** were synthesized according to the published literature[22] and the characterization data was consistent with the literature.

Compounds **12n**、**12h**were synthesized according to the published literature[23] and the characterization data was consistent with the literature.

3.2.5 General procedure for synthesis of target compounds 13a-13q

N-(3-(2-chloroacetamido)phenyl)acrylamide (0.35mmol)

was dissolved in 4mL of N, N-dimethylformamide at room temperature. Then, Compounds **12a-12q** (0.39mmol) was added dropwise to the above system. The reaction was carried out at 90 ℃ for 2 h. After the reaction was completed (TLC detection reaction), it was cooled to room temperature and an 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_{PE}: V_{EA} = 3:1). Concentrated eluent to give solid compounds **13a-13q.**

N-(3-(2-((4-((2-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13a） white solid, yield 78.2%. m.p.258-259 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.14 (s, 1H), 9.50 (s, 1H), 8.38 (s, 1H), 8.10 (s, 1H), 7.94 (s, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.31 (dt, *J* = 11.9, 4.8 Hz, 3H), 7.26 (s, 2H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.75 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.90 (s, 2H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9 (d, *J* =276.7 Hz), 158.1, 157.3, 155.6, 154.4, 153.4, 147.5, 147.2, 139.6, 138.67, 131.8, 129.0, 128.4, 127.1, 126.9, 126.5, 124.4 (d, *J* =3.0 Hz), 116.0 (d, *J* =20.2. Hz), 114.7, 110.6, 108.4, 107.4, 103.9, 68.2, 55.9. HRMS (ESI) calcd for $C_{26}H_{23}FN_5O_4$ $[M+H]^+$: 488.1734, found: 488.1733.

N-(3-(2-((4-((2-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13b） white solid, yield 77.1%. m.p.236-237 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.18 (s, 1H), 10.13 (s, 1H), 9.50 (s, 1H), 8.34 (s, 1H), 8.09 (s, 1H), 7.94 (s, 1H), 7.60 – 7.55 (m, 2H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.26 (s, 1H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.26 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.75 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.89 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 157.5, 154.4, 153.4, 147.5, 147.2, 139.4, 138.7, 136.1, 131.8, 130.8, 129.7, 129.0, 127.6, 127.5, 126.8, 114.7, 114.7, 110.6, 108.3, 107.4, 103.9, 68.2, 55.9. HRMS (ESI) calcd for $C_{26}H_{23}ClN_5O_4$ $[M+H]^+$: 504.1439, found: 504.1440.

N-(3-(2-((4-((2-bromophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13c） white solid, yield 73.8%. m.p.236-237 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.18 (s, 1H), 10.13 (s, 1H), 9.48 (s, 1H), 8.33 (s, 1H), 8.09 (s, 1H), 7.93 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.44 (dd, *J* = 15.4, 7.8 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 3H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.30 – 6.21 (m, 1H), 5.75 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.89 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 157.5, 154.4, 153.4, 147.4, 139.4, 138.7, 137.5, 132.8, 131.8, 123.0, 129.0, 128.2, 127.9, 126.8, 121.9, 114.7, 114.7, 110.6, 108.3, 107.4, 103.8, 68.1, 55.9. HRMS (ESI) calcd for $C_{26}H_{23}BrN_5O_4$ $[M+H]^+$: 548.0933, found: 548.0932.

N-(3-(2-((4-((3-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13d） white solid, yield 76.8%. m.p.183-184 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.13 (s, 1H), 9.58 (s, 1H), 8.56 (s, 1H), 8.12 (s, 1H), 7.98 (s, 1H), 7.90 (dt, *J* = 11.9, 2.4 Hz, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.43 (dt, *J* = 7.2, 3.4 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 4.1 Hz, 2H), 6.93 (td, *J* = 8.5, 2.4 Hz, 1H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.91 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) 165.8, 163.1 (d, *J* =237.3 Hz), 156.2, 154.5, 153.0, 147.5, 147.4, 141.2, 139.4, 138.6, 131.8, 129.9 (d, *J* =10.1 Hz), 129.0, 126.8, 117.5, 114.7, 110.6, 109.6, 109.4, 108.8, 108.5, 107.6, 104.2, 68.6, 56.0. HRMS (ESI) calcd for $C_{26}H_{23}FN_5O_4$ $[M+H]^+$: 488.1734, found: 488.1735.

N-(3-(2-((4-((3-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13e） white solid, yield 72.9%. m.p.270-271 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.13 (s, 1H), 9.55 (s, 1H), 8.56 (s, 1H), 8.11 (s, 1H), 8.04 (t, *J* = 2.0 Hz, 1H), 7.97 (s, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 9.5 Hz, 1H), 7.29 (s, 2H), 7.18 – 7.13 (m, 1H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.91 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 156.1, 154.5, 153.0, 147.5, 147.4, 141.0, 139.4, 138.6, 132.7 131.8, 130.0, 129.0, 126.9, 122.8, 121.2, 120.2, 114.8, 110.6, 108.7, 107.6, 104.1, 68.6, 56.0. HRMS (ESI) calcd for $C_{26}H_{23}ClN_5O_4$ $[M+H]^+$: 504.1439, found: 504.1438.

N-(3-(2-((4-((3-bromophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13f）

white solid, yield 71.5%. m.p.246-247 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.20 (s, 1H), 10.12 (s, 1H), 9.54 (s, 1H), 8.56 (d, *J* = 2.6 Hz, 1H), 8.18 – 8.10 (m, 2H), 7.96 (s, 1H), 7.88 – 7.83 (m, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 3H), 6.47 (dd, *J* = 17.0, 10.0 Hz, 1H), 6.28 (dd, *J* = 17.0, 2.3 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.91 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 156.1, 154.5, 153.0, 147.5, 147.5, 141.1, 139.4, 138.6, 131.8, 130.3, 129.0, 126.9, 125.7, 124.0, 121.2, 120.6, 114.8, 110.6, 108.7, 107.6, 104.1, 68.6, 56.0. HRMS (ESI) calcd for $C_{26}H_{23}BrN_5O_4$ $[M+H]^+$: 548.0933, found: 548.0932.

N-(3-(2-((7-methoxy-4-((3-nitrophenyl)amino)quinazolin-6-yl)oxy)acetamido)phenyl)acrylamide （13g） white solid, yield 67.6%. m.p.247-248 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.16 (s, 1H), 9.96 (s, 1H), 8.66 (s, 1H), 8.29 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 8.11 (s, 1H), 8.00 (s, 1H), 7.39 (t, *J* = 8.4 Hz, 2H), 7.34 (s, 1H), 7.28 (t, *J* = 8.1 Hz, 1H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.26 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.76 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.93 (s, 2H), 4.02 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) ^{13}C NMR (101 MHz, DMSO) δ 165.7, 163.1, 155.7, 155.2, 154.9, 152.8, 152.7, 147.9, 147.8, 146.2, 141.5, 139.4, 138.6, 131.8, 129.1, 126.9, 124.6, 120.5, 114.8, 114.7, 110.6, 107.6, 104.1, 68.6, 56.1. HRMS (ESI) calcd for $C_{26}H_{23}N_6O_6$ $[M+H]^+$: 515.1679, found: 515.1677.

N-(3-(2-((7-methoxy-4-((3-methoxyphenyl)amino)quinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13h） white solid, yield 72.8%. m.p.187-188 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.13 (s, 1H), 9.44 (s, 1H), 8.50 (d, *J* = 2.6 Hz, 1H), 8.11 (s, 1H), 7.99 (s, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.35 (m, 3H), 7.32 – 7.29 (m, 1H), 7.27 (d, *J* = 6.1 Hz, 2H), 6.70 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.75 (dd, *J* = 9.9, 2.2 Hz, 1H), 4.91 (s, 2H), 4.00 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 163.1, 159.4, 156.4, 154.4, 153.2, 147.4, 140.5, 139.4, 138.6, 131.8, 129.1, 129.0, 126.8, 114.8, 114.5, 113.8, 110.6, 108.7, 108.6, 108.1, 107.6, 104.3, 68.6, 56.0, 55.1. HRMS (ESI) calcd for $C_{27}H_{26}N_5O_5$ $[M+H]^+$: 500.1934, found: 500.1935.

N-(3-(2-((4-((4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide （13i） white solid, yield 75.7%. m.p.251-252 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.12 (s, 1H), 9.50 (s, 1H), 8.46 (s, 1H), 8.11 (d, *J* = 2.2 Hz, 1H), 7.96 (s, 1H), 7.81 – 7.74 (m, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.20 (m, 4H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.90 (s, 2H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 163.1 (d, *J* =363.4 Hz), 157.13, 156.5, 154.4, 153.2, 147.4, 147.3, 139.4, 138.6, 135.6, 131.8, 129.0, 126.8, 124.5 (d, *J* =8.1 Hz), 115.1 (d, *J* =22.2Hz), 114.7, 110.6, 108.5, 107.6, 104.2, 68.5, 55.9. HRMS (ESI) calcd for $C_{26}H_{23}FN_5O_4$ $[M+H]^+$: 488.1734, found: 488.1733.

N-(3-(2-((4-((4-chlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide （13j） white solid, yield 74.9%. m.p.259-260 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.69 (s, 1H), 10.51 (s, 1H), 10.22 (s, 1H), 8.52 (s, 1H), 8.25 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.57 (d, *J* = 2.3 Hz, 1H), 6.48 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.30 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.79 (dd, *J* = 10.1, 2.2 Hz, 1H), 5.07 (s, 2H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.7, 163.2, 162.7, 156.7, 155.1, 155.0, 153.5, 139.5, 138.5, 138.3, 131.9, 129.2 128.4, 126.8, 126.8, 123.0, 114.8, 110.5, 101.3, 100.7, 99.4, 67.9, 55.7. HRMS (ESI) calcd for $C_{26}H_{23}ClN_5O_4$ $[M+H]^+$: 504.1439, found: 504.1440.

N-(3-(2-((4-((4-bromophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13k） white solid, yield 71.9%. m.p.178-179 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.13 (s, 1H), 9.53 (s, 1H), 8.51 (s, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 7.39 (dd, *J* = 15.4, 8.1 Hz, 2H), 7.27 (s, 2H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.26 (dd, *J* = 16.9, 2.2 Hz, 1H), 5.75 (dd, *J* = 9.8, 2.2 Hz, 1H), 4.90 (s, 2H), 4.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 156.2, 154.5, 153.0, 147.5, 147.4, 139.4, 138.8, 138.6, 131.8, 131.2, 129.1, 126.9, 124.0, 114.9, 114.8, 110.6, 108.7, 107.6, 104.2, 68.5, 56.0. HRMS (ESI) calcd for $C_{26}H_{23}BrN_5O_4$ $[M+H]^+$: 548.0933, found: 548.0933.

N-(3-(2-((7-methoxy-4-(p-tolylamino)quinazolin-6-

yl)oxy)acetamido)phenyl)acrylamide（13l） white solid, yield 75.3%. m.p.157-158 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.12 (s, 1H), 9.40 (s, 1H), 8.45 (s, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.23 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.1 Hz, 1H), 5.76 (dd, *J* = 10.0, 2.1 Hz, 1H), 4.89 (s, 2H), 3.99 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 163.1, 156.5, 154.2, 153.3, 147.3, 147.2, 139.4, 138.6, 136.6, 132.5, 131.8, 129.0, 128.8, 126.9, 122.6, 114.8, 110.6, 108.6, 107.5, 104.2, 68.5, 55.9, 20.5. HRMS (ESI) calcd for $C_{27}H_{26}N_5O_4$ $[M+H]^+$: 484.1985, found: 484.1986.

N-(3-(2-((7-methoxy-4-((4-methoxyphenyl)amino)quinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13m） white solid, yield 70.8%. m.p.150-151 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.11 (s, 1H), 9.39 (s, 1H), 8.41 (s, 1H), 8.11 (s, 1H), 7.95 (s, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.23 (s, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.75 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.89 (s, 2H), 3.99 (s, 3H), 3.77 (d, *J* = 2.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 163.1, 156.7, 155.7, 154.2, 153.38, 147.2, 147.1, 139.4, 138.6, 132.0, 131.8, 129.0, 126.9, 124.5, 114.8, 113.6, 110.6, 108.5, 107.5, 104.2, 68.4, 55.9, 55.2. HRMS (ESI) calcd for $C_{27}H_{26}N_5O_5$ $[M+H]^+$: 500.1934, found: 500.1933.

N-(3-(2-((4-((2,4-dichlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamid（13n） white solid, yield 73.7%. m.p.163-164 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.17 (s, 1H), 10.14 (s, 1H), 9.53 (s, 1H), 8.35 (s, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 8.6 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.41 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.26 (q, *J* = 6.6, 5.0 Hz, 2H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.25 (dd, *J* = 17.0, 2.2 Hz, 1H), 5.75 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.88 (s, 2H), 3.99 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 157.3, 154.47, 153.2, 147.5, 147.3, 139.3, 138.7, 135.3, 131.8, 131.7, 130.7, 129.1, 129.0, 127.7, 126.9, 114.7, 114.6, 110.5, 108.3, 107.4, 103.8, 68.1, 56.0. HRMS (ESI) calcd for $C_{26}H_{22}Cl_2N_5O_4$ $[M+H]^+$: 538.1049, found: 538.1049.

N-(3-(2-((4-((3,4-dichlorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylamide（13o） white solid, yield 75.4%. m.p.275-276 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.19 (s, 1H), 10.12 (s, 1H), 9.60 (s, 1H), 8.58 (d, *J* = 2.3 Hz, 1H), 8.25 (d, *J* = 2.5 Hz, 1H), 8.12 (s, 1H), 7.94 (s, 1H), 7.86 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.29 (s, 2H), 6.47 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.1, 2.2 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.2 Hz, 1H), 4.91 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8, 163.1, 155.9, 154.6, 152.9, 147.6, 147.5, 139.7, 139.4, 138.6, 131.8, 130.6, 130.2, 129.0, 126.8, 124.4, 122.7, 121.6, 114.8, 110.6, 108.7, 107.6, 104.1, 68.6, 56.0. HRMS (ESI) calcd for $C_{26}H_{22}Cl_2N_5O_4$ $[M+H]^+$: 538.1049, found: 538.1048.

N-(3-(2-((4-((3-chloro-4-fluorophenyl)amino)-7-methoxyquinazolin-6-yl)oxy)acetamido)phenyl)acrylami（13p） white solid, yield 73.6%. m.p.257-258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.18 (s, 1H), 10.11 (s, 1H), 9.56 (s, 1H), 8.54 (s, 1H), 8.12 (dd, *J* = 7.0, 2.5 Hz, 2H), 7.94 (s, 1H), 7.77 (ddd, *J* = 9.2, 4.4, 2.5 Hz, 1H), 7.44 (t, *J* = 9.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.46 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 16.9, 2.1 Hz, 1H), 5.76 (dd, *J* = 10.1, 2.1 Hz, 1H), 4.90 (s, 2H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.8 (d, *J* =271.7 Hz), 156.1, 154.5, 153.0, 152.0, 147.5, 147.4, 139.4, 138.6, 136.7, 131.8, 129.0, 126.8, 123.5, 122.3, 118.9, 116.6 (d, *J* =21.2 Hz), 114.8, 114.7, 110.6, 108.6, 107.6, 104.1, 68.6, 56.0. HRMS (ESI) calcd for $C_{26}H_{22}ClFN_5O_4$ $[M+H]^+$: 522.1344, found: 522.1342.

N-(3-(2-((7-methoxy-4-((3,4,5-trimethoxyphenyl)amino)quinazolin-6-yl)oxy)acetamido)phenyl)acrylamid（13q） white solid, yield 77.9%. m.p.234-235 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 10.18 (s, 1H), 10.11 (s, 1H), 9.39 (s, 1H), 8.49 (s, 1H), 8.11 (s, 1H), 7.96 (s, 1H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.26 (s, 1H), 7.17 (s, 2H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.26 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.75 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.91 (s, 2H), 4.00 (s, 3H), 3.80 (s, 6H), 3.67 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 165.9, 163.1, 156.6, 154.3, 153.2, 152.5, 147.3, 147.2, 139.4, 138.6, 135.3, 133.8, 131.8, 129.0, 126.9, 114.8, 110.6, 108.7, 107.6, 104.4, 100.5, 68.6, 60.1, 55.9, 55.9. HRMS (ESI) calcd for $C_{29}H_{30}N_5O_7$ $[M+H]^+$: 560.2145,

found: 560.2145.

3.2.6 Cell culture and treatment

Human cancer cells MCF-7, MGC-803 and PC-3, HGC-27 was purchased from the China Center for Type Culture Collection (CCTCC, China) and maintained in RPMI-1640 (Solarbio, China) and DMEM (Solarbio) complete medium (which supplemented with 10% FBS and 100 U/ml penicillin and 100 g/ml streptomycin antibiotics) at 37 ℃ in a humidified atmosphere of 5% CO_2.

3.2.7 MTT assay

Cells in the logarithmic growth phase were seeded in 96-well plates at 3,000-5,000 cells per well. After the cells were cultured for 24h, different concentrations of compounds **13a-13q** were treated for 72 h, respectively. MTT(3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, Solarbio) was added to each well at a final concentration of 0.5 mg/ml. After 4 h in a 37℃ incubator, the medium was aspirated. 150 μL DMSO was then added to each well to dissolve the formazan, and the plate was shaken on a shaker for 10 minute. The absorbance was measured by an enzyme-linked immunosorbent assay reader (BioTek, USA) at a wavelength of 490 nm, and the cell survival rate was measured. Viability rate = Abs 490 treated cells/Abs 490 control cells×100%. The concentration-response curve generated by SPSS 16.0 software was used to determine the concentration of compound (IC_{50}) required to inhibit cell growth by 50%. Cell viability curves were generated using GraphPad Prism 7.0 software at various concentrations of all compounds. Results were Mean ± SD of three independent experiments.

Supporting Information

The ^{1}H NMR, ^{13}C NMR and HRMS of **13a-13q** are available for free download from our website (http://sioc-journal.cn/).

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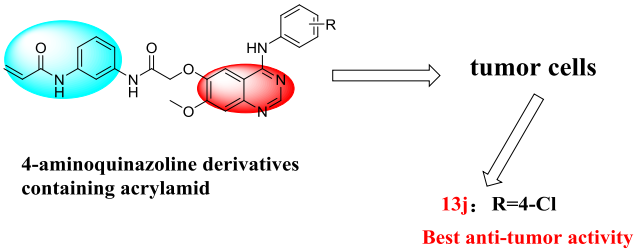
图文摘要

Synthesis and Antitumor Activity of Novel Quinazoline Derivatives Containing Acrylamide



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A series of novel 4-aminoquinazoline derivatives containing N-(3-aminophenyl)acrylamid were designed, synthesized and evaluated for antitumor activities against four human cancer cell lines (H1975, PC-3, MGC-803). Among them, compound **13j** showed the best antitumor activity against H1975, PC-3 and MGC-803 cancer cell lines, with the IC_{50} values of 6.77±0.65、9.89±0.75、4.06±0.34μmol/L.

