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Synthesis, Cytotoxic Activity Evaluation of Novel 1,2,3-Triazole Linked Quinazoline Derivatives

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A series of novel 1,2,3-triazole-quinazoline derivatives were synthesized in five steps starting from anthranilamide by conventional methods. All the title compounds **10a**—**10r** were evaluated for cytotoxic activity against four human cancer cell lines (MGC-803, EC-109, MCF-7 and HGC-27) using MTT assay *in vitro*. Some of the synthesized compounds exhibited moderate to potent activity against tested cancer cell lines. Among them, compounds **10h** and **10q** exhibited excellent growth inhibition against HGC-27 and compound **10m** also possessed excellent activity against MCF-7, with IC_{50} values less than 1 μmol/L. Especially, compound **10h** was more cytotoxic than 5-fluorouracil against all tested four human cancer cell lines.

Keywords quinazoline, triazole, synthesis, cytotoxicity

Introduction

Nowadays, cancer is one of the leading causes of death in both developed and developing countries.[1-6] During the last decade, chemotherapy has achieved great success in cancer treatment. But the outlook of exploring the development of new anticancer drugs is still grim. In the path of identifying various chemical substances which may serve as leads for designing novel antitumor agents, nitrogen-containing heterocycles are of particular interest. For example, quinazoline is considered an effective group, its derivatives are potent inhibitors of epidermal growth factor receptor (EGFR),[7,8] such as compounds **1** and **2** (Figure 1). In addition, quinazoline also has a variety of biological activitives, such as antihypertensive, antimicrobial, anti-hyperlipidemic, anti-inflammatory and anticonvulsant activity.[9-11] Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agents.[12-14] Now, the quinazoline derivatives have become a hot spot in the field of cancer research.[15] However, 2-substituted quinazoline derivatives have rarely been researched. From this point of view, here we report the synthesis and biological activitives of 2,4-disubstituted quinazoline derivatives.

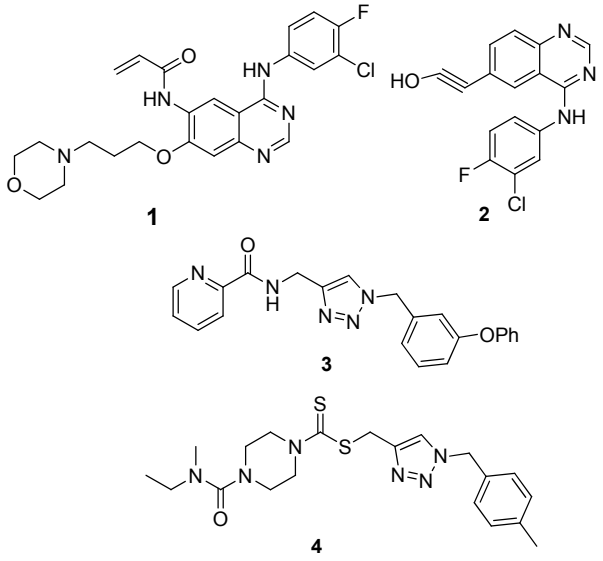

Figure 1 Chemical structures of compounds **1**—**4**.

1,2,3-Triazole has been a fruitful source of inspiration for medicinal chemists for many years and attracted our attention deeply.[16] It was synthesized accessibly by

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click chemistry and has numerous biological activities, such as anti-fungal, anti-bacterial, anti-allergic, anti-HIV, anti-tubercular and anti-inflammatory agents.[17-26] Recently, 1,2,3-triazole was found and used in research as a popular building block in pharmaceutical research. For example, Miller group reported that compound **3** exhibited an IC_{50} value of 46 nmol/L against MCF-7 cancer cell line.[27] Compound **4**, a 1,2,3-triazol-dithiocarbamate-urea hybrid, showed an IC_{50} value of 8.27 μmol/L against MGC-803 cell line.[28]

The study of new hybrid system which combined 1,2,3-triazole with quinazoline is an unexplored field of research. Many papers have reported that some 1,2,3-triazole-dithiocarbamate hybrids and other 1,2,3-triazole derivatives showed impressive anticancer activity.[29-33] These results encouraged us to investigate the potential synergistic effect of 1,2,3-triazole and quinazoline scaffolds. Herein, for the first time, the synthesis of novel 1,2,3-triazole-quinazoline compounds is reported in moderate yields. Besides, their cytotoxic activities were evaluated against tumor cell lines.

Experimental

Materials

All reagents and solvents were purchased from commercial sources and were used without further purification. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel (Qingdao Haiyang Chemical Co., G60F-254) and visualized by UV light (254 nm). The products were purified by column chromatography over silica gel (Qingdao Haiyang Chemical Co, 200－300 mesh). Melting points were determined on an X-5 micromelting apparatus and are uncorrected. All the NMR spectra were recorded with a Bruker DPX 400 MHz spectrometer. Chemical shifts (δ) are given relative to TMS. High-resolution mass spectra (HRMS) were recorded on a Waters Micromass Q-T of Micromass spectrometer by electrospray ionization (ESI). The synthesized compounds were named using ChemDraw Ultra software (v 12.0).

Synthesis of 2-mercaptoquinazolin-4-ol (6)

Carbon disulfide (6 mL, 0.1 mol) was added to a stirred solution of potassium hydroxide (6.01 g, 40 mmol) in ethanol (300 mL). The mixture was heated to 30 ℃ for 0.5 h. And compound **5** was added to a stirred solution of mixture. The mixture was heated to 90 ℃ for 5 h. The mixture was cooled to room temperature and filtered through a buchner funnel. Then the filter cake was added to the cold water (50 mL) and adjusted the pH to 6－7 with dilute hydrochloric acid. The mixture was filtered through a buchner funnel. The filter cake was washed with water (3×300 mL) and dried in vacuum. **6** (14.0 g, 78.5%) was obtained as a white solid. m.p. 245－246 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.52 (s, 2H), 7.93 (dd, J=7.9, 1.2 Hz, 1H), 7.73 (ddd, J=8.6, 7.3, 1.5 Hz, 1H), 7.37－7.29 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 174.71, 160.09, 140.84, 135.78, 127.15, 124.78, 116.59, 116.28. HR-MS (ESI) calcd for $C_8H_6N_2OS$ $[M+H]^+$: 179.0119, found 179.0117.

Synthesis of 2-(prop-2-yn-1-ylthio)quinazolin-4-ol (7)

Bromopropyne (1.20 g, 10 mmol) was added to a stirred solution of compound **6** (1.78 g, 10 mmol) and potassium hydroxide (0.67 g, 12 mmol) in the mixed solvent of water and dioxane (50 mL, *V*/*V*, 5∶1). The mixture was heated to 50 ℃ for 0.5 h. The reaction mixture was cooled to room temperature and filtered through a buchner funnel. Then the filter cake was washed with dioxane and dried in vacuum. **7** (1.46 g, 67.6%) was obtained as a white solid. m.p. 167.3－168 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.68 (s, 1H), 8.05 (dd, J=7.9, 1.1 Hz, 1H), 7.81－7.74 (m, 1H), 7.55 (d, J=8.1 Hz, 1H), 7.44 (t, J=7.5 Hz, 1H), 4.10 (d, J=2.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 161.67, 154.54, 148.56, 135.16, 126.54, 126.39, 120.45, 80.10, 74.35, 18.67. HR-MS (ESI) calcd for $C_{11}H_{18}N_2OS$ $[M+H]^+$: 217.0355, found 217.0352.

General procedure for synthesis of 8 (8a, 8b)

To a solution of the different substituents benzylazide (7.63 mmol) and compound **7** (1.50 g, 6.94 mmol) in THF/H_2O (20 mL, *V*/*V*, 2∶1) were added $CuSO_4$ (0.22 g, 1.40 mmol) and VcNa (0.28 g, 1.40 mmol). The mixture was stirred for 3 h at room temperature, than the mixture was extracted twice with ethyl acetate, and dried over Na_2SO_4. The mixture was purified by chromatography on silica gel using petroleum ether/ethyl acetate to give derivatives **8**.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-ol (8a) Yield 70.7%, white solid, m.p. 210－210.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.62 (s, 1H), 8.17 (s, 1H), 8.05 (d, J=7.7 Hz, 1H), 7.78 (t, J=7.4 Hz, 1H), 7.60 (d, J=8.0 Hz, 1H), 7.44 (t, J=7.4 Hz, 1H), 7.35 (dd, J=8.2, 5.6 Hz, 2H), 7.15 (t, J=8.8 Hz, 2H), 5.56 (s, 2H), 4.54 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.00, 160.57, 154.79, 148.26, 134.55, 132.23, 130.19, 130.10, 126.08, 125.97, 125.70, 123.93, 115.58, 115.37, 51.92, 24.47. HR-MS (ESI) calcd for $C_{18}H_{14}ClN_5S$ $[M+H]^+$: 384.0610, found 384.0607.

2-(((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-ol (8b) Yield 73.4%, white solid, m.p. 223－223.7 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.62 (s, 1H), 8.14 (s, 1H), 8.06 (d, J=7.9 Hz, 1H), 7.78 (t, J=7.2 Hz, 1H), 7.61 (dd, J=9.2, 4.6 Hz, 1H), 7.45 (t, J=7.5 Hz, 1H), 7.17 (d, J=7.3 Hz, 2H), 7.11 (d, J=7.8 Hz, 2H), 5.51 (s, 2H), 4.55 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.80, 161.13, 154.80, 150.28, 148.26, 143.02, 137.35, 132.93, 129.15, 127.85, 125.67, 123.82, 122.25, 115.27, 52.54, 24.50, 20.62. HR-MS (ESI) calcd for $C_{19}H_{17}N_5S$ $[M+H]^+$: 364.1159, found 364.1158.

General procedure for synthesis of 9 (9a, 9b)

The compound **8** (1.92 g, 5 mmol) was added to a stirred solution of phosphorus oxychloride and phosphorus trichloride (15 mL, *V*/*V*, 2∶1). The mixture was heated to 110 ℃ for 1 h. After the reaction was completed (monitored by TLC), the reaction mixture was cooled to room temperature and added dropwise to crushed ice with stirring for 10 min. Then the mixture was filtered through a buchner funnel. The filter cake was washed with H_2O until neutral and dried in vacuum.

4-Chloro-2-(((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazoline (9a) Yield 88.5%, yellow solid, m.p. 134－135 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.17 (d, J=7.2 Hz, 2H), 8.05 (d, J=7.3 Hz, 1H), 7.93 (d, J=8.4 Hz, 1H), 7.75 (d, J=7.6 Hz, 1H), 7.35 (d, J=8.3 Hz, 2H), 7.27 (d, J=8.3 Hz, 2H), 5.55 (s, 2H), 4.53 (d, J=8.9 Hz, 2H); ^{13}CNMR (100 MHz, DMSO-d_6) δ: 165.61, 161.84, 151.50, 143.76, 136.74, 135.45, 133.25, 130.24, 129.13, 128.71, 127.38, 126.33, 124.47, 121.01, 52.42, 25.89. HR-MS (ESI) calcd for $C_{18}H_{13}Cl_2N_5S$ [M＋H]$^+$: 402.0266, found 402.0265.

4-Chloro-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazoline (9b) Yield 86.7%, yellow solid, m.p. 171.7－172.9 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.13 (s, 1H), 8.04 (d, J=7.2 Hz, 1H), 7.78 (t, J=7.3 Hz, 1H), 7.59 (d, J=8.0 Hz, 1H), 7.44 (t, J=7.4 Hz, 1H), 7.16 (d, J=8.2 Hz, 2H), 7.11 (d, J=7.7 Hz, 2H), 5.50 (s, 2H), 4.54 (d, J=9.9 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.79, 161.19, 154.95, 150.24, 148.08, 142.99, 137.36, 134.56, 129.17, 127.86, 123.87, 122.26, 119.94, 115.30, 52.53, 24.49, 20.64. HR-MS (ESI) calcd for $C_{19}H_{16}Cl_2N_5S$ [M＋H]$^+$: 382.0818, found 382.0816.

Synthesis of novel 1,2,3-triazole–quinazoline hybrids (10a－10r)

To a well stirred solution of the appropriate amine (0.50 mmol) in isopropanol (4 mL), equimolar amount of compound **9a** or **9b** (0.50 mmol) was added. The reaction mixture was stirred at 90 ℃ for 10 h. Upon completion, the solid was filtrated and washed with ethanol or by silica gel column chromatography to yield the pure products **10a－10r.**

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(4-chlorophenyl)quinazolin-4-amine (10a) Yield 82.3%, white solid, m.p. 231－232 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.41 (s, 1H), 8.78 (d, J=8.3 Hz, 1H), 7.97 (t, J=7.6 Hz, 1H), 7.76 (dd, J=11.1, 8.9 Hz, 4H), 7.68 (t, J=7.7 Hz, 1H), 7.39 (dd, J=11.7, 8.6 Hz, 4H), 7.27 (d, J=8.4 Hz, 2H), 5.51 (s, 2H), 4.46 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.84, 157.84, 143.79, 136.37, 136.04, 135.31, 133.37, 130.36, 130.27, 129.22, 128.91, 127.21, 126.42, 125.08, 124.09, 121.24, 112.55, 52.49, 25.50. HR-MS (ESI) calcd for $C_{24}H_{18}Cl_2N_6S$ [M＋H]$^+$: 493.0667, found 493.0665.

***N*-(4-Chlorophenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10b)** Yield 79.4%, white solid, m.p. 158－158.8 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.53 (s, 1H), 8.85 (d, J=8.2 Hz, 1H), 7.97 (t, J=7.6 Hz, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.77－7.72 (m, 3H), 7.68 (t, J=7.6 Hz, 1H), 7.38 (d, J=8.6 Hz, 2H), 7.14 (s, 4H), 5.45 (s, 2H), 4.45 (s, 2H), 2.27 (s, 3H), 1.04 (d, J=6.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.22, 157.27, 143.07, 137.38, 135.80, 135.48, 132.77, 129.82, 129.17, 128.34, 127.79, 126.63, 125.91, 124.66, 123.34, 111.99, 52.55, 24.95, 20.60. HR-MS (ESI) calcd for $C_{25}H_{21}ClN_6S$ [M＋H]$^+$: 473.1315, found 473.1313.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(3-chlorophenyl)quinazolin-4-amine (10c) Yield 80.5%, white solid, m.p. 158－58.4 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.43 (s, 1H), 8.84 (d, J=8.2 Hz, 1H), 7.97 (t, J=7.4 Hz, 2H), 7.88 (s, 1H), 7.80 (d, J=8.3 Hz, 1H), 7.74－7.65 (m, 2H), 7.43－7.33 (m, 3H), 7.26 (d, J=8.3 Hz, 3H), 5.52 (s, 2H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.90, 157.87, 143.75, 139.12, 135.95, 135.37, 133.30, 133.20, 130.59, 130.24, 129.18, 127.12, 125.93, 125.15, 124.22, 123.00, 121.64, 112.67, 52.47, 25.51. HR-MS (ESI) calcd for $C_{24}H_{18}Cl_2N_6S$ [M＋H]$^+$: 493.0769, found 493.0768.

***N*-(3-Chlorophenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10d)** Yield 89.6%, white solid, m.p. 172.4－173 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.34 (s, 1H), 8.80 (s, 1H), 8.05－7.91 (m, 2H), 7.81 (s, 2H), 7.69 (dd, J=16.4, 8.4 Hz, 2H), 7.38 (t, J=8.1 Hz, 1H), 7.26 (dd, J=8.0, 1.1 Hz, 1H), 7.13 (s, 4H), 5.45 (s, 2H), 4.49 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.50, 157.37, 143.10, 138.72, 137.42, 135.45, 132.86, 132.72, 130.12, 129.20, 127.82, 126.62, 124.58, 123.42, 122.37, 112.22, 52.58, 25.02, 20.66. HR-MS (ESI) calcd for $C_{25}H_{21}ClN_6S$ [M＋H]$^+$: 473.1315, found 473.1313.

***N*-(4-Bromophenyl)-2-(((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10e)** Yield 90.7%, white solid, m.p. 160－161 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.37 (s, 1H), 8.82 (d, J=8.0 Hz, 1H), 7.96 (t, J=7.6 Hz, 1H), 7.79 (d, J=7.4 Hz, 2H), 7.74－7.64 (m, 4H), 7.52 (d, J=8.7 Hz, 2H), 7.41 (d, J=8.4 Hz, 2H), 7.27 (d, J=8.4 Hz, 2H), 5.52 (s, 2H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.88, 157.76, 143.91, 136.99, 135.89, 135.35, 133.35, 131.82, 130.28, 129.23, 127.07, 126.59, 125.11, 124.16, 118.44, 112.68, 52.49, 25.52. HR-MS (ESI) calcd for $C_{24}H_{18}BrClN_6S$ [M＋H]$^+$: 537.0264, found 537.0262.

***N*-(4-Bromophenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10f)** Yield 76.1%, white solid, m.p. 168－168.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.13 (s, 1H), 8.72 (d, J=8.4 Hz, 1H), 7.95 (t, J=7.5 Hz, 1H), 7.76 (s, 2H), 7.68 (t, J=8.2 Hz, 3H), 7.52 (d, J=8.8 Hz, 2H), 7.17－7.10 (m, 4H), 5.44 (s, 2H), 4.45 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.50, 157.37, 143.10, 138.72, 137.42, 135.45, 132.86, 132.72, 130.12, 129.20, 127.82, 126.62, 124.58, 123.42, 122.37, 112.22, 52.58, 25.02, 20.66. HR-MS (ESI) calcd for

$C_{25}H_{21}BrN_6S$ $[M+H]^+$: 517.0810, found 517.0810.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(4-(trifluoromethyl)phenyl)quinazolin-4-amine (10g) Yield 77.8%, white solid, m.p. 143—144 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.38 (s, 1H), 8.85 (d, J=7.6 Hz, 1H), 7.99 (dd, J=21.1, 7.2 Hz, 3H), 7.90 (s, 1H), 7.81 (d, J=7.7 Hz, 1H), 7.69 (d, J=7.2 Hz, 3H), 7.38 (d, J=6.6 Hz, 2H), 7.27 (d, J=6.5 Hz, 2H), 5.52 (s, 2H), 4.49 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.05, 157.91, 144.07, 141.62, 135.84, 135.37, 133.32, 130.27, 129.16, 127.01, 126.09, 126.05, 125.09, 124.31, 124.19, 123.27, 122.33, 112.87, 52.47, 25.55. HR-MS (ESI) calcd for $C_{25}H_{18}ClF_3N_6S$ $[M+H]^+$: 527.1032, found 527.1031.

2-(((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(4-(trifluoromethyl)phenyl)quinazolin-4-amine (10h) Yield 76.7%, white solid, m.p. 173.1—174 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.40 (s, 1H), 8.85 (d, J=8.3 Hz, 1H), 7.99 (t, J=7.3 Hz, 3H), 7.88—7.77 (m, 2H), 7.68 (d, J=8.6 Hz, 3H), 7.13 (d, J=1.9 Hz, 4H), 5.45 (s, 2H), 4.48 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.48, 157.45, 143.24, 140.97, 137.43, 135.48, 132.85, 129.18, 127.86, 126.61, 125.58, 125.54, 124.74, 124.05, 123.40, 122.76, 121.30, 112.28, 52.60, 25.06, 20.62. HR-MS (ESI) calcd for $C_{26}H_{21}F_3N_6S$ $[M+H]^+$: 507.1578, found 507.1577.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(4-isopropylphenyl)quinazolin-4-amine (10i) Yield 69.9%, white solid, m.p. 173—174 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.07 (s, 1H), 8.68 (d, J=8.3 Hz, 1H), 7.93 (t, J=7.5 Hz, 1H), 7.71 (d, J=8.3 Hz, 1H), 7.65 (t, J=7.6 Hz, 1H), 7.60—7.56 (m, 3H), 7.39 (t, J=7.1 Hz, 2H), 7.26 (d, J=8.4 Hz, 2H), 7.19 (d, J=8.4 Hz, 2H), 5.48 (s, 2H), 4.42 (s, 2H), 2.82 (dt, J=13.7, 6.9 Hz, 1H), 1.12 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.89, 157.82, 144.08, 133.34, 130.24, 129.19, 126.89, 126.77, 124.78, 124.69, 123.96, 112.66, 52.45, 33.43, 25.40, 24.25. HR-MS (ESI) calcd for $C_{25}H_{20}ClN_5O_2S$ $[M+H]^+$: 501.1628, found 501.1627.

***N*-(4-Isopropylphenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10j)** Yield 74.3%, white solid, m.p. 159—160 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.57 (s, 1H), 8.84 (d, J=8.2 Hz, 1H), 7.97 (t, J=7.7 Hz, 1H), 7.79 (d, J=8.2 Hz, 1H), 7.68 (t, J=7.6 Hz, 1H), 7.58 (d, J=8.4 Hz, 2H), 7.47 (s, 1H), 7.19 (d, J=8.4 Hz, 2H), 7.14 (s, 4H), 5.41 (s, 2H), 4.42 (s, 2H), 2.82 (dt, J=13.7, 6.8 Hz, 1H), 2.27 (s, 3H), 1.12 (d, J=6.9 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.04, 157.35, 146.63, 143.11, 137.44, 135.59, 134.38, 132.83, 130.08, 129.22, 128.69, 127.83, 127.14, 126.75, 126.28, 124.66, 123.32, 111.91, 52.59, 32.96, 24.95, 23.73, 20.66. HR-MS (ESI) calcd for $C_{28}H_{28}N_6S$ $[M+H]^+$: 481.2174, found 481.2175.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(3-(trifluoromethyl)phenyl)quinazolin-4-amine (10k) Yield 73.2%, white solid, m.p. 160—161 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.48 (s, 1H), 8.85 (d, J=8.2 Hz, 1H), 8.27 (s, 1H), 8.07 (d, J=7.6 Hz, 1H), 7.97 (t, J=7.5 Hz, 1H), 7.90 (s, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.69 (t, J=7.6 Hz, 1H), 7.62—7.53 (m, 2H), 7.40 (d, J=8.3 Hz, 2H), 7.25 (d, J=8.3 Hz, 2H), 5.52 (s, 2H), 4.48 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.99, 157.95, 143.68, 138.61, 135.93, 135.37, 133.29, 130.20, 129.85, 129.54, 129.16, 128.07, 127.11, 125.77, 125.10, 124.23, 123.06, 122.37, 120.95, 112.74, 52.45, 25.51. HR-MS (ESI) calcd for $C_{25}H_{18}ClF_3N_6S$ $[M+H]^+$: 527.1032, found 527.1031.

2-(((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(3-(trifluoromethyl)phenyl)quinazolin-4-amine (10l) Yield 77.0%, white solid, m.p. 156—157 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.71 (s, 1H), 8.93 (d, J=8.3 Hz, 1H), 8.27 (s, 1H), 8.06 (d, J=7.1 Hz, 1H), 7.99 (t, J=7.7 Hz, 1H), 7.85—7.80 (m, 1H), 7.70 (t, J=7.6 Hz, 1H), 7.58 (d, J=7.5 Hz, 1H), 7.13 (s, 2H), 5.45 (s, 1H), 4.48 (s, 1H), 2.27 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.32, 157.45, 142.66, 137.84, 137.35, 135.58, 132.78, 129.63, 129.30, 129.12, 128.98, 127.82, 127.72, 126.70, 125.20, 124.77, 123.37, 122.49, 122.07, 120.67, 112.05, 52.50, 24.98, 20.58. HR-MS (ESI) calcd for $C_{26}H_{21}F_3N_6S$ $[M+H]^+$: 507.1578, found 507.1580.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(3,4,5-trimethoxyphenyl)quinazolin-4-amine (10m) Yield 71.1%, white solid, m.p. 153.8—154 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.48 (s, 1H), 8.63 (d, J=8.0 Hz, 1H), 7.93—7.86 (m, 2H), 7.71 (d, J=8.2 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.39 (d, J=8.3 Hz, 2H), 7.25 (d, J=10.2 Hz, 4H), 5.52 (s, 2H), 4.50 (s, 2H), 3.75 (s, 6H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 165.31, 157.60, 153.01, 135.42, 135.25, 134.88, 134.35, 133.27, 130.18, 129.17, 126.31, 124.23, 113.15, 101.67, 99.99, 60.62, 56.33, 52.41, 25.44. HR-MS (ESI) calcd for $C_{27}H_{25}ClN_6O_3S$ $[M+H]^+$: 549.1475, found 549.1475.

***N*-(3-Chloro-4-fluorophenyl)-2-(((1-(4-chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10n)** Yield 78.6%, white solid, m.p. 157—158 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.65 (s, 1H), 8.88 (d, J=8.2 Hz, 1H), 8.10 (dd, J=6.8, 2.5 Hz, 1H), 8.01—7.95 (m, 1H), 7.94 (s, 1H), 7.82 (d, J=8.3 Hz, 1H), 7.74 (ddd, J=8.8, 4.1, 2.7 Hz, 1H), 7.69. (t, J=7.6 Hz, 1H), 7.43—7.36 (m, 3H), 7.28 (d, J=8.4 Hz, 2H), 5.54 (s, 2H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.32, 157.41, 143.11, 135.64, 134.87, 134.12, 132.82, 129.75, 128.67, 126.77, 126.24, 124.80, 123.68, 119.09, 118.91, 116.69, 116.47, 111.98, 51.97, 25.04. HR-MS (ESI) calcd for $C_{24}H_{17}Cl_2FN_6S$ $[M+H]^+$: 511.0674, found 511.0672.

2-(((1-(4-Chlorobenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(3,4-dichlorophenyl)quinazolin-4-amine (10o) Yield 77.5%, white solid, m.p. 154.3—155 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (s, 1H), 8.91 (d, J=8.3 Hz, 1H), 8.20 (d, J=2.3 Hz, 1H), 8.00—7.95 (m, 2H), 7.85—7.77 (m, 3H), 7.68 (t, J=7.6 Hz, 1H), 7.57 (d, J=8.7 Hz, 1H), 7.40 (d, J=8.4 Hz, 2H), 7.28

(d, J=8.4 Hz, 2H), 5.54 (s, 2H), 4.53 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.37, 157.31, 143.09, 137.16, 135.65, 134.85, 132.83, 130.67, 130.22, 129.75, 128.68, 127.53, 126.77, 125.57, 124.83, 124.04, 123.72, 112.08, 51.99, 25.09. HR-MS (ESI) calcd for $C_{24}H_{17}Cl_3N_6S$ $[M+H]^+$: 527.0379, found 527.0377.

***N*-(4-Fluorophenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10p)** Yield 77.9%, white solid, m.p. 157−158 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.62 (s, 1H), 8.86 (d, J=8.3 Hz, 1H), 7.98 (t, J=7.7 Hz, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.73−7.67 (m, 4H), 7.16 (d, J=7.7 Hz, 6H), 5.45 (s, 2H), 4.43 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.68, 157.98, 143.50, 137.97, 136.13, 133.49, 133.35, 129.72, 128.37, 127.28, 127.19, 125.30, 123.87, 115.87, 115.65, 112.40, 53.11, 25.50, 21.16. HR-MS (ESI) calcd for $C_{25}H_{21}FN_6S$ $[M+H]^+$: 457.1610, found 457.1611.

2-(((1-(4-Methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)-*N*-(4-nitrophenyl)quinazolin-4-amine (10q) Yield 88.4%, white solid, m.p. 177−178 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.11 (s, 1H), 8.77 (d, J=8.3 Hz, 1H), 8.22 (d, J=9.2 Hz, 2H), 8.12 (d, J=9.2 Hz, 2H), 7.99−7.91 (m, 2H), 7.78 (d, J=8.1 Hz, 1H), 7.67 (t, J=7.4 Hz, 1H), 7.11 (d, J=2.8 Hz, 4H), 5.45 (s, 2H), 4.51 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.82, 157.19, 144.35, 143.59, 143.02, 137.40, 135.01, 132.91, 130.12, 129.16, 127.84, 126.24, 124.29, 123.46, 122.60, 119.88, 112.75, 61.98, 25.46, 20.64. HR-MS (ESI) calcd for $C_{25}H_{21}N_7O_2S$ $[M+H]^+$: 484.1555, found 484.1554.

***N*-(4-Methoxyphenyl)-2-(((1-(4-methylbenzyl)-1*H*-1,2,3-triazol-4-yl)methyl)thio)quinazolin-4-amine (10r)** Yield 63.5%, white solid, m.p. 153−154 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.30 (s, 1H), 8.72 (d, J=8.4 Hz, 1H), 7.96 (dd, J=16.9, 8.3 Hz, 2H), 7.74 (d, J=8.2 Hz, 1H), 7.67 (t, J=7.7 Hz, 1H), 7.59−7.55 (m, 2H), 7.27 (d, J=8.7 Hz, 1H), 7.14 (s, 3H), 6.91 (d, J=9.0 Hz, 2H), 5.43 (s, 2H), 4.42 (s, 2H), 3.71 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 164.17, 157.28, 143.14, 137.46, 135.39, 132.86, 130.13, 129.50, 129.23, 127.85, 126.65, 126.03, 124.48, 123.41, 122.73, 119.89, 113.72, 111.97, 55.24, 52.59, 24.97, 20.66. HR-MS (ESI) calcd for $C_{26}H_{24}N_6OS$ $[M+H]^+$: 469.1810, found 469.1811.

Effect of compounds on cell viability

Exponentially growing cells were seeded at 4×10^3 cells per well into 96-well plates. After 24 h incubation at 37 ℃, the culture medium was removed and replaced with fresh medium containing the candidate compounds in different concentrations. The cells were incubated for another 72 h. Then, 20 μL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (5 mg/mL) was added to all wells and incubated for 4 h at 37 ℃. The medium containing MTT was discarded, 150 μL dimethyl sulfoxide (DMSO) was added to each well and the plates were agitated until the dark blue crystals (formazan) completely dissolved; the absorbance was measured using a microplate reader at a wavelength of 490 nm. Each concentration was analyzed in triplicate and the experiment was repeated three times. The average 50% inhibitory concentration (IC_{50}) values were determined from the concentration-response curves according to the inhibition ratio for each concentration.

Results and Discussion

Chemistry

The synthetic strategy to prepare the target compounds was depicted in Scheme 1. A series of novel 1,2,3-triazole–quinazoline derivatives were finally obtained in five steps from available anthranilamide and different substituents benzyl chloride. In earlier report,[34] the compound **6** was prepared by the reaction of anthranilamide and carbon disulfide in the presence of potassium hydroxide in ethanol for a long period. In this letter, we also synthesized the compound in a higher yield under the condition of reflux in the presence of potassium hydroxide and excess carbon disulfide in ethanol at 90 ℃ for 5 h. The next part of this synthesis involved the preparation of the compound **7** which was stirred by condensation of compound **6** with propargyl bromide in the mixed solvent of water and dioxane. To a solution of the different substituents benzylazide and compound **7** in THF/H_2O (*V*/*V*, 2∶1) were added $CuSO_4$ and VcNa. The solution was stirred for 3 h at room temperature, then the mixture was extracted twice with ethyl acetate, and dried over Na_2SO_4. The solvent was purified on silica gel (petroleum ether/ethyl acetate, 5∶4, *V*/*V*) to give the desired compound **8**. Subsequently, compound **8** was halogenated by the reaction with $POCl_3$ and PCl_3 to yield the compound **9**. The highly activated intermediate was then reacted with different substituted anilines to obtain compounds **10a**−**10r**. The results were summarized in Table 1. Finally, all the structures of **10a**−**10r** were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS.

Cytotoxic activity *in vitro*

All synthesized compounds were evaluated for the cytotoxic activities against four human cancer cell lines, MCF-7 (human breast cancer cell line), MGC-803 (human gastric cancer cell line), EC-109 (human esophageal cancer cell line) and HGC-27 (human gastric cancer cell line) using MTT[35,36] assay method. 5-Fluorouracil (5-Fu) was used as positive control. Table 2 reported the IC_{50} (μmol•L^{-1}) values of the tested compounds and the standard.

From the screening results in Table 2, most of the synthesized compounds exhibited good anticancer activity on all the tested cell lines. Regarding the activity of the tested compounds against HGC-27 cell line, compounds (**10b**, **10d**, **10f**, **10h**, **10j** and **10l**) with electron-donating groups exhibited better activity effects

Scheme 1 Synthesis of compounds **5**—**9** and **10a**—**10r**

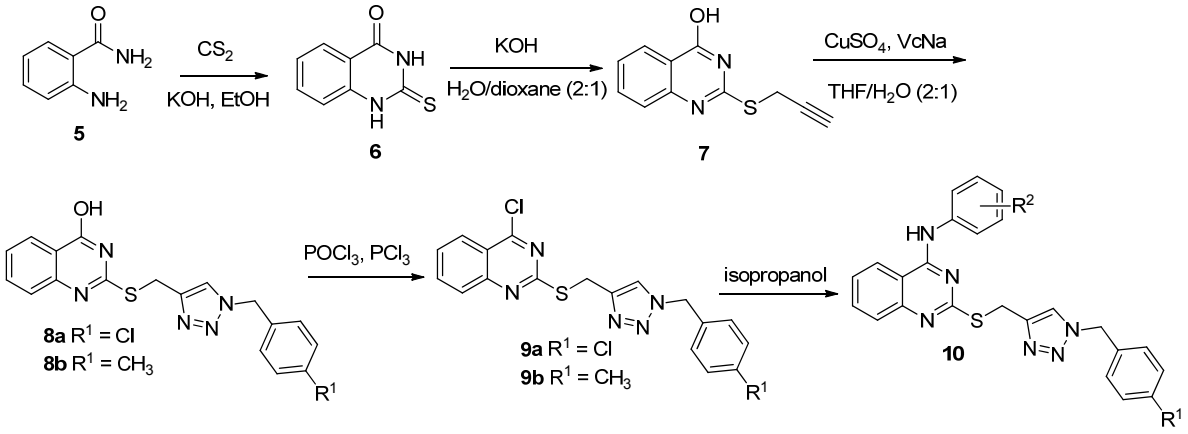

Table 1 Synthesis of 1,2,3-triazole-quinazoline derivatives **10a**—**10r**

Compd.	R^1	R^2	Yield/%
10a	Cl	*p*-Cl	82.3
10b	CH_3	*p*-Cl	79.4
10c	Cl	*m*-Cl	80.5
10d	CH_3	*m*-Cl	76.1
10e	Cl	*p*-Br	90.7
10f	CH_3	*p*-Br	89.1
10g	Cl	*p*-CF_3	77.8
10h	CH_3	*p*-CF_3	76.7
10i	Cl	*p*-$CH(CH_3)_2$	69.9
10j	CH_3	*p*-$CH(CH_3)_2$	74.3
10k	Cl	*m*-CF_3	73.2
10l	CH_3	*m*-CF_3	77.0
10m	Cl	*m*,*p*,*m*-OCH_3	71.1
10n	Cl	*m*-Cl,P-F	78.6
10o	Cl	*m*,*p*-Cl	77.5
10p	CH_3	*p*-F	77.9
10q	CH_3	*p*-NO_2	88.4
10r	CH_3	*p*-OCH_3	63.5

Table 2 *In vitro* cytotoxicity evaluation of 1,2,3-triazole-quinazoline derivatives

Compd.	IC_{50}[a]/(μmol•L^{-1})			
	MCF-7	MGC-803	EC-109	HGC-27
10a	21.36±1.27	25.21±1.08	15.27±1.49	12.43±1.22
10b	15.63±1.36	14.03±1.14	7.96±0.90	4.05±0.65
10c	24.68±1.85	23.38±1.38	11.22±1.50	29.71±1.27
10d	1.23±0.09	2.32±0.36	9.79±0.99	7.24±0.86
10e	3.17±0.50	3.17±0.52	15.97±1.20	5.18±0.71
10f	27.38±1.43	9.33±0.97	8.83±0.94	2.89±0.46
10g	15.69±1.38	1.52±0.27	9.10±1.01	4.38±0.58
10h	7.13±0.96	2.17±0.33	4.91±0.69	0.57±0.08
10i	15.78±0.56	4.64±0.62	13.87±1.14	4.54±0.55
10j	13.11±1.11	3.48±0.41	8.26±0.91	1.31±0.13
10k	1.29±1.11	10.42±1.05	16.65±1.22	9.59±0.88
10l	4.13±0.61	16.51±1.21	14.07±1.14	4.60±0.66
10m	0.84±0.07	2.15±0.06	15.55±1.19	6.60±0.66
10n	20.75±1.24	35.40±1.74	10.28±1.26	5.77±1.03
10o	28.12±1.36	22.42±1.35	11.49±1.26	7.85±0.76
10p	13.66±1.13	6.41±0.80	15.79±1.19	7.47±0.87
10q	11.79±1.07	17.22±1.23	23.19±1.36	0.74±0.12
10r	20.01±1.84	37.01±1.88	6.82±0.83	1.21±0.08
5-Fu[b]	10.18±0.87	7.13±0.28	14.61±1.12	6.50±0.38

[a] Inhibitory activity was assayed by exposure for 72 h to substances and expressed as concentration required to inhibit tumor cell proliferation by 50% (IC_{50}). [b] Positive control.

(0.57—7.24 μmol/L) than compounds (**10a**, **10c**, **10e**, **10g**, **10i** and **10k**) with electron-withdrawing groups on the substituent group R^1. In particular, compounds (**10a** and **10c**; **10b** and **10d**; **10g** and **10k**; **10h** and **10l**) with electron-withdrawing groups on the 4-substituent group R^2 showed more potent inhibitory effects than those with the 3-substituent group R^2. Among them, compounds (**10h**, **10q** and **10m**) showed excellent inhibitory effects with IC_{50} values of 0.57, 0.74 and 0.84 μmol/L against HGC-27 and MCF-7, respectively. Compound **10h** was more cytotoxic than 5-fluorouracil against all tested four human cancer cell lines.

Some structure–activity relationships could be observed, mainly related to the influence of different R^1 on phenyl ring and different 4-substituted anilines. It is worthy to mention that electron donating group with $-CH_3$ on the substituent group R^1 is more effective than electron withdrawing group —Cl. Moreover, comparing the activities of compounds (**10b** and **10d**; **10g** and **10k**; **10h** and **10l**), we can have a conclusion that the analogues with *para*-substituted anilines were found to be more effective as compared to compounds

meta-substituted anilines.

Conclusions

In summary, we have successfully synthesized a series of 1,2,3-triazole-quinazoline hybrids which were stating from the readily available anthranilamide and different substituents benzyl chloride. Among them, compounds **10h** and **10q** exhibited excellent growth inhibition against HGC-27, compound **10m** possessed excellent activity against MCF-7, with an IC_{50} value less than 1 μmol/L. Especially, compound **10h** was more cytotoxic than 5-fluorouracil against all tested four human cancer cell lines. Moreover, the mechanisms of action of the compounds with excellent activities remain to be investigated.

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