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REGULAR ARTICLE

Efficient click reaction towards novel sulfonamide hybrids by molecular hybridization strategy as antiproliferative agents

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Abstract. Twelve novel sulfonamide hybrids were designed by molecular hybridization strategy. The target sulfonamide hybrids were obtained in the click reaction of azide derivatives and commerciallly available alkynes. All sulfonamide hybrids were evaluated for their antiproliferative activity against three selected cancer cell lines (MGC-803, EC-109 and PC-3). Most of the synthesized compounds exhibited moderate to good activity against all the cancer cell lines selected. Particularly, compound **8c** showed the potent antiproliferative activity with an IC_{50} value of 0.7 μmol against MGC-803 cancer cells. These sulfonamide hybrids might be promising lead compounds to develop antitumor agents in the clinical practice.

Keywords. Molecular hybridization strategy; click reaction; sulfonamide; antiproliferative.

1. Introduction

Sulfonamide derivatives have been used extensively in medicinal chemistry as antibacterial, anticonvulsant, anti-carbonicanhydrase and anticancer activities.[1–3] Much attention has been paid to the antitumor activity of sulfonamide derivatives.[4,5] 1, 3, 4-oxadiazole derivative possessing a sulfonamide moiety **1** showed superior activity than paclitaxel and gefitinib against the T-47D and MDA-MB-468 cells.[6] Piperlongumine derived cyclic sulfonamide **2** significantly reduced the HeLa cells growth.[7] Chromone-based sulfonamide **3** (Figure 1) showed IC_{50} of 0.72 and 0.50 μmol against MCF-7 and A-549 cell lines, respectively.[8]

On the other hand, two series of 1, 2, 3-triazole derivatives in our group have revealed their anticancer activity: Chalcone-1, 2, 3-triazole-azole **4** showed the potent antiproliferative activity with an IC_{50} value of 1.52 μmol against SK-N-SH cancer cells and induced morphological changes;[9] 1, 2, 3-Triazole–chalcone **5** (Figure 2) inhibited the proliferation of SK-N-SH cancer cells by inducing apoptosis and arresting the cell cycle at the G1 phase.[10]

Molecular hybridization strategy is a new concept in drug design and development based on the combination of pharmacophoric moieties of different bioactive substances to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs.[11] Based on the above interesting findings and our continuous quest to synthesize antitumor agents,[12–16] led us to carry out the molecular hybridization of biologically active sulfonamide and 1, 2, 3-triazole to integrate them in one molecular platform to generate new hybrid architecture with the aim of exploring the impact of such modification on the anticancer agents. As shown in Figure 3, a molecular hybridization strategy based on the structures of a bioactive sulfonamide derivative **1** and a bioactive 1, 2, 3-triazole compound**5** yielded a scaffold which has

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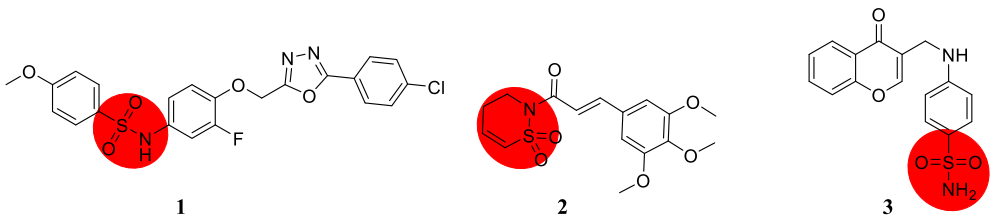


Figure 1. Anticancer sulfonamide derivatives.

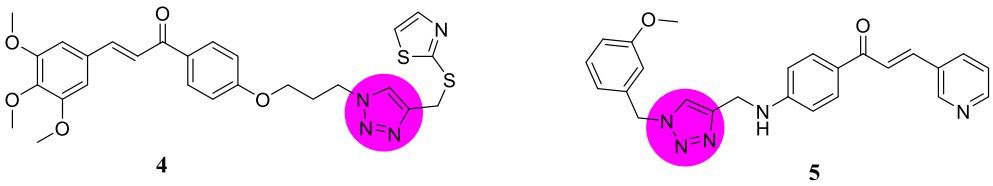


Figure 2. Reported anticancer compounds containing the 1, 2, 3-triazole scaffold in our group.

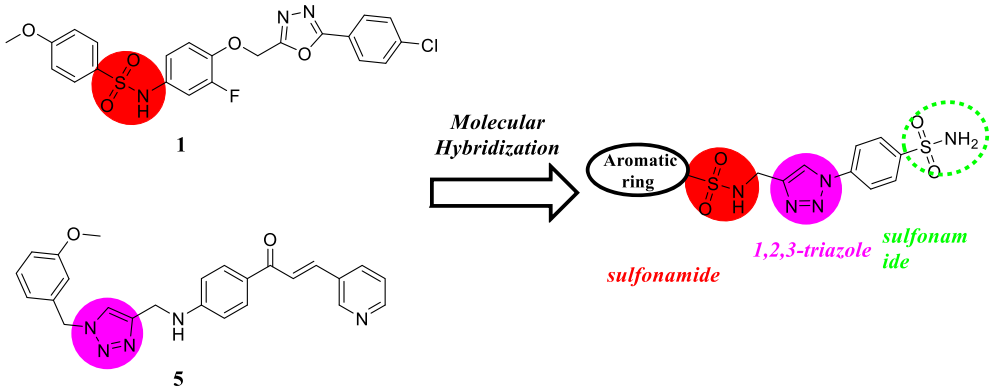


Figure 3. Illustration of the design strategy for target compounds.

three parts: (i) a 1, 2, 3-triazole as a central core, (ii) a substituted phenylsulfonamide (iii) another phenyl sulfonamide attached throughcarbon 4 (Figure 3).

2. Experimental

2.1 *Materials and methods*

All reagents and solvents used were of analytical grade and were purchased from Zhengzhou Research Biotechnology Co., Ltd. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel and visualized by UV light (254 nm). Melting points were determined on a Beijing Keyi XT4A apparatus and are uncorrected. NMR spectra were obtained on a Bruker DPX 400 MHz spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) in DMSO-d_6 using TMS as internal standard. Chemical shifts are given in ppm and coupling constants are given in Hz. Mass spectra (MS) were recorded on a Bruker 3000 mass spectrometer by electrospray ionisation (ESI). The purity of all target compounds was determined to be $>$ 95% by reverse phase high performance liquid chromatography (HPLC) analysis. HPLC measurement was performed with a Phenomenex column (C_{18}, 5.0 μm, 4.60 mm × 250 mm) on Dionex UltiMate 3000 UHPLC instrument from Thermo-Fisher. The signal was monitored at 254 nm with a UV detector. A flow rate of 0.6 mL/min was used with mobile phase of CH_3CN in H_2O (65:35, v/v).

2.2 *Synthesis of target compounds* **8a-8l**

Alkyne derivatives **6a-6l** (1 mmol), compound **7** (1 mmol), $CuSO_4.5H_2O$ (0.3 mmol) and sodium ascorbate (0.15 mmol) were dissolved in THF/H_2O (5 mL/5 mL) to stir for 10 h at room temperature. Upon completion, the precipitated product was filtered off and washed with ethanol to afford the crude product, which was purified with column chromatography (hexane: EtOAc = 10:1) to obtain analogue **8a-8l.** The usage of ethanol and column chromatography (hexane: EtOAc = 10:1) in the post-processing reduced the yields.

2.2a *4-Fluoro-N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl] benzenesulfonamide (***8a***)*: Yield: 21%, white solid, M.p.188–189 °C. Purity: 96.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.36 (t, J = 6.0 Hz, 1H), 8.16–7.97 (m, 4H), 7.89 (dd, J = 8.7, 5.2 Hz, 2H), 7.58 (s, 2H), 7.40 (t, J = 8.8 Hz, 2H), 4.23 (d, J = 5.9 Hz, 2H). ^{13}C NMR (100MHz, DMSO-d_6) δ 165.30, 162.81, 144.61,

143.78, 138.42, 136.78, 136.75, 129.68, 129.58, 127.52, 121.81, 120.15, 116.23, 116.01, 37.88. HRMS (ESI) calcd for $C_{15}H_{14}FN_5O_4S_2Na$ $[M+Na]^+$: 434.0369, found: 434.0367.

2.2b *N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl]benzenesul fonamide (**8b**)*: Yield: 27%, white solid, M.p. 189–190 °C. Purity: 96.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.28 (t, J = 6.0 Hz, 1H), 8.14–7.95 (m, 4H), 7.82 (dd, J = 7.9, 1.5 Hz, 2H), 7.66–7.46 (m, 5H), 4.17 (d, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.77, 143.77, 140.32, 138.42, 132.39, 129.06, 127.50, 126.57, 121.79, 120.17, 37.92. HRMS (ESI) calcd for $C_{15}H_{15}N_5O_4S_2Na[M+Na]^+$: 416.0463, found: 416.0464.

2.2c *2-Chloro-N-[(1-(4-sulfamoylphenyl)-1H-1, 2, 3-triazol-4-yl) Methyl]benzenesulfonamide (**8c**)*: Yield: 34%, white solid, M.p. 235–236 °C. Purity: 97.1%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, J = 10.2 Hz, 1H), 8.55 (s, 1H), 8.08–7.98 (m, 4H), 7.95 (dd, J = 7.8, 1.3 Hz, 1H), 7.61–7.50 (m, 4H), 7.50–7.41 (m, 1H), 4.30 (d, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.53, 143.76, 138.37, 137.97, 133.78, 131.48, 130.65, 130.44, 127.51, 127.36, 121.76, 120.19, 37.64. HRMS (ESI) calcd for $C_{15}H_{14}ClN_5O_4S_2Na[M+Na]^+$: 450.0073, found: 450.0071.

2.2d *N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl]thiophene-2-sulfonamide(**8d**)*: Yield: 33%, yellow solid, M.p.191–192 °C. Purity: 95.7%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.48 (t, J = 5.9 Hz, 1H), 8.09 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.92 (dd, J = 5.0, 1.2 Hz, 1H), 7.64 (dd, J = 3.7, 1.2 Hz, 1H), 7.54 (s, 2H), 7.17 (dd, J = 4.9, 3.8 Hz, 1H), 4.25 (d, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.70, 143.79, 141.11, 138.46, 132.64, 131.89, 127.62, 127.53, 121.80, 120.21, 38.13. HRMS (ESI) calcd for $C_{13}H_{13}N_5O_4S_3Na[M+Na]^+$: 422.0027, found: 422.0024.

2.2e *5-Chloro-N-[(1-(4-sulfamoylphenyl)-1H-1, 2, 3-triazol-4-yl)methyl] thiophene-2-sulfonamide (**8e**)*: Yield:29%, yellow solid, M.p. 180–182 °C. Purity: 98.0%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.67 (t, J = 5.8 Hz, 1H), 8.13–8.06 (m, 2H), 8.05–8.00 (m, 2H), 7.54 (s, 2H), 7.49 (d, J = 4.0 Hz, 1H), 7.21 (d, J = 4.0 Hz, 1H), 4.28 (d, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.41, 143.82, 139.65, 138.44, 134.55, 131.77, 127.81, 127.52, 121.91, 120.20, 38.04. HRMS (ESI) calcd for $C_{13}H_{12}ClN_5O_4S_3Na[M+Na]^+$: 455.9638, found: 455.9640.

2.2f *4-Methoxy-N-[(1-(4-sulfamoylphenyl)-1H-1, 2, 3-triazol-4-yl)methyl] benzenesulfonamide (**8f**)*: Yield: 29%, 36%, yellow solid, M.p. 200–201 °C. Purity: 96.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.10 (t, J = 6.1 Hz, 1H), 8.06–7.98 (m, 4H), 7.75–7.68 (m, 2H), 7.53 (s, 2H), 7.07–7.01 (m, 2H), 4.14 (d, J = 6.0 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.09, 144.79, 143.76, 138.40, 131.98, 128.79, 127.47, 121.72, 120.08, 114.14, 55.51, 37.93. HRMS (ESI) calcd for $C_{16}H_{17}N_5O_5S_2Na[M+Na]^+$: 446.0569, found: 446.0565.

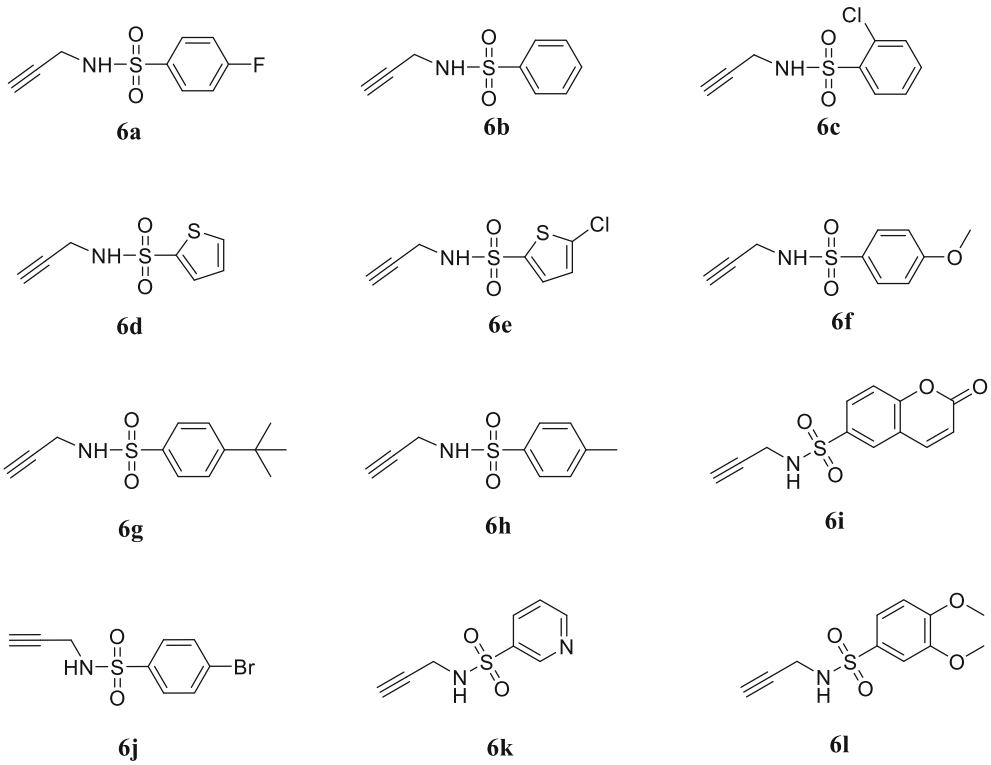
2.2g *4-(Tert-butyl)-N-[(1-(4-sulfamoylphenyl)-1H-1, 2,3-triazol-4-yl)methyl]benzenesulfonamide (**8g**)*: Yield: 37%, white solid, M.p. 203–204 °C. Purity: 97.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.21 (t, J = 6.0 Hz, 1H), 8.12–7.92 (m, 4H), 7.73 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.6 Hz, 4H), 4.18 (d, J = 6.0 Hz, 2H), 1.22 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.37, 144.74, 143.79, 138.40, 137.52, 127.48, 126.47, 125.81, 121.67, 120.02, 37.94, 34.69, 30.66. HRMS (ESI) calcd for $C_{19}H_{23}N_5O_4S_2Na[M+Na]^+$: 472.1089, found: 472.1093.

2.2h *4-Methyl-N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl]benzenesulfonamide (8h)*: Yield: 38%, white solid, M.p. 200–202 °C. Purity: 95.8%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.11 (s, 1H), 8.08–8.01 (m, 4H), 7.76–7.69 (m, 2H), 7.55 (s, 2H), 7.06 (t, J = 5.9 Hz, 2H), 4.16 (d, J = 4.7 Hz, 2H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.09, 144.78, 143.75, 138.40, 131.98, 128.80, 127.48, 121.72, 120.08, 114.13, 55.50, 37.93. HRMS (ESI) calcd for $C_{19}H_{23}N_5O_4S_2Na[M+Na]^+$: 472.1089, found: 472.1093.

2.2i *2-Oxo-N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl]-2H-chromene-6-sulfonamide (**8i**)*: Yield: 32%, yellow solid, M.p. 104–106 °C. Purity: 97.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.42 (t, J = 6.0 Hz, 1H), 8.20 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 9.6 Hz, 1H), 8.01 (d, J = 2.4 Hz,4H), 7.96 (dd, J = 8.7, 2.2 Hz, 1H), 7.58–7.49 (m, 3H), 6.58 (d, J = 9.6 Hz, 1H), 4.23 (d, J = 6.0 Hz,2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.13, 155.48, 144.48, 143.79, 143.50, 138.33, 136.42, 129.74, 127.54, 127.47, 121.87, 120.05, 118.66, 117.42, 117.41, 37.91. HRMS (ESI) calcd for $C_{18}H_{15}N_5O_6S_2Na[M+Na]^+$: 484.0361, found: 484.0363.

2.2j *4-Bromo-N-[(1-(4-sulfamoylphenyl)-1H-1,2,3-triazol-4-yl)methyl] benzenesulfonamide (**8j**)*: Yield: 22%, yellow solid, M.p. 227–230 °C. Purity: 96.4%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.41 (t, J = 5.9 Hz, 1H), 8.03 (s, 4H), 7.72 (q, J = 8.6 Hz, 4H), 7.54 (s, 2H), 4.21 (d, J = 5.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 144.47, 143.79, 139.75, 138.38, 132.07, 128.64, 127.51, 126.20, 121.82, 120.16, 37.84. HRMS (ESI) calcd for $C_{15}H_{14}BrN_5O_4S_2Na[M+Na]^+$: 493.9568, found: 493.9566.

2.2k *N-[(1-(4-sulfamoylphenyl)-1H-1, 2, 3-triazol-4-yl)methyl]pyridine-3-sulfonamide (8k)*: Yield: 39%, yellow solid, M.p. 169–170 °C. Purity: 97.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.75 (s, 1H), 8.69 (s, 1H), 8.57 (t, J = 5.8 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.08–7.97 (m, 4H), 7.58 (dd, J = 7.9, 4.8 Hz, 1H), 7.53 (s, 2H), 4.26 (d, J = 5.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.88, 147.11, 144.37, 143.81, 138.38, 136.92, 134.55, 127.50, 124.05, 121.93, 120.23, 37.77. HRMS (ESI)



Scheme 1. The structures of alkynes used in this work.

calcd for $C_{14}H_{14}N_6O_4S_2Na[M + Na]^+$: 417.0416, found: 417.0414.

2.2l *3,4-Dimethoxy-N-[(1-(4-sulfamoylphenyl)-1H-1, 2,3-triazol-4-yl) methyl]benzenesulfonamide (**8l**)*: Yield: 40%, yellow solid, M.p. 151–152 °C. Purity: 98.6%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.09 (t, J = 6.1 Hz, 1H), 8.01 (s, 4H), 7.53 (s, 2H), 7.36 (dd, J = 8.4, 2.1 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 4.14 (d, J = 6.0 Hz, 2H), 3.78 (s, 3H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.81, 148.48, 144.76, 143.76, 138.37, 131.89, 127.45, 121.71, 120.35, 120.04, 110.89, 109.47, 55.66, 37.96, 30.65. HRMS (ESI) calcd for $C_{17}H_{19}N_5NaO_6S_2[M + Na]^+$: 476.0674, found: 476.0677.

2.3 *Anticancer testing with MTT method* [17]

MGC-803 cells (human gastric cancer), EC-109 (human esophagus cancer) and PC-3 (human prostate Cancer) were seeded into 96-well plates at a concentration of 3000 cells per well. Cancer cell lines were purchased from the China Centre for Type Culture Collection (CCTCC, Shanghai, China). After 24 h of incubation, the culture medium (RPMI 1640 medium with 10% FBS and 100 U/mL penicillin and 0.1 mg/mL streptomycin) was removed and fresh medium containing various concentrations of the candidate compounds was added to each well. 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 at 37 °C for 4 h. Discarded the suspension and added DMSO (150μL) to each well and shook the plates to dissolve the dark blue crystals (formazan); 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}) was determined from the dose-response curves according to the inhibition ratio for each concentration.

3. Results and Discussion

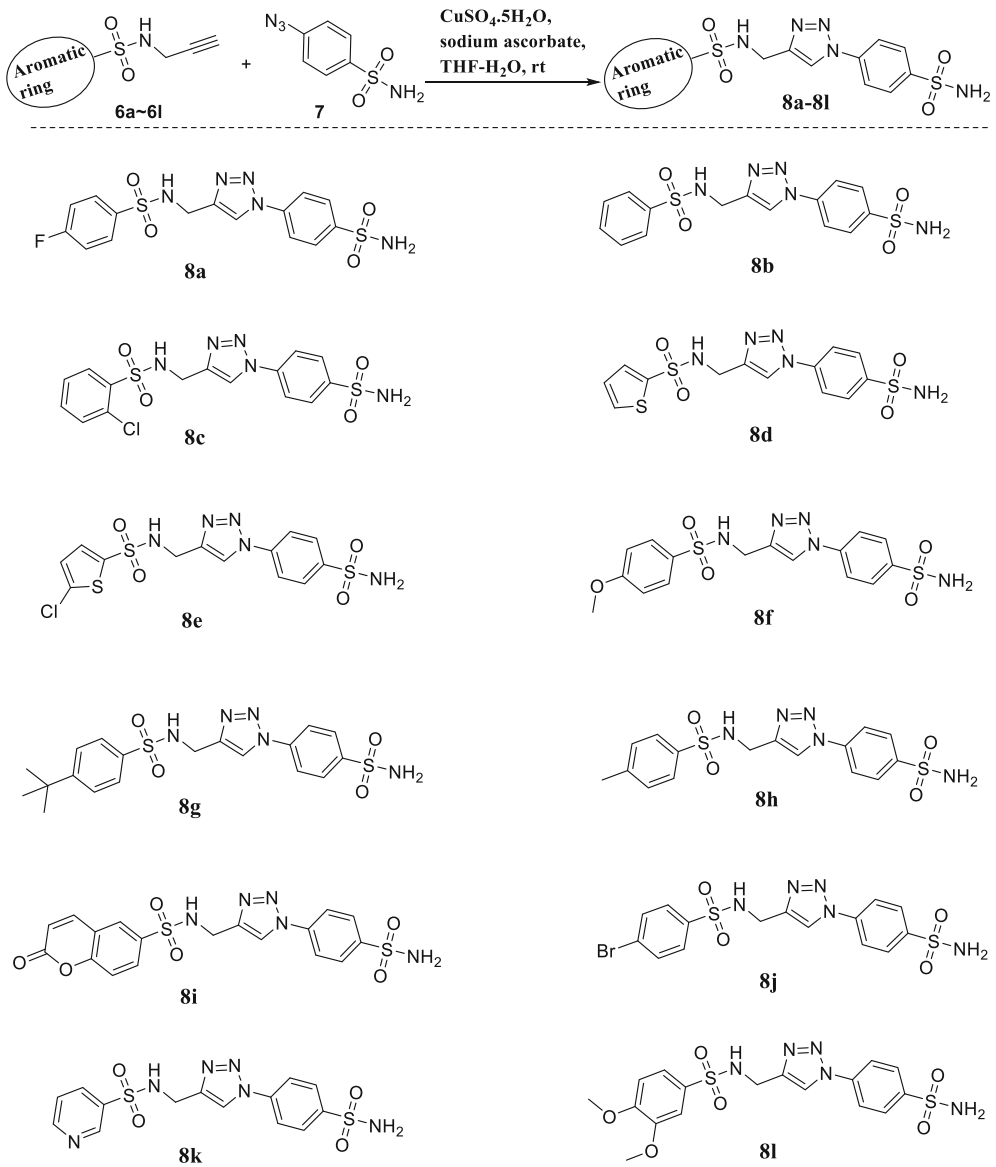
3.1 *Chemistry*

The alkynes were purchased from Zhengzhou Research Biotechnology Co., Ltd. The structures of alkynes used in this work were shown in Scheme 1.

The synthetic route of sulfonamide hybrids **8a–8l** was shown in Scheme 2. Target sulfonamide hybrids were synthesized from various alkynes **6a–6l** and 4-azidobenzenesulfonamide **7** by a click reaction in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate at room temperature. The structures of the synthesized sulfonamides were characterized using spectral methods, and all spectral data corroborated the assumed structures.

3.2 *Antiproliferative activity*

All the synthesized sulfonamide hybrids **8a–8l** in Scheme 2 were evaluated for their antiproliferative activity against three cancer cell lines, EC-109 (human



Scheme 2. Synthetic strategy of sulfonamide hybrids **8a–8l**.

esophageal cancer cell line), MGC-803 (human gastric cancer cell line), and PC-3 (human prostate cancer cell line) by MTT method and compared with the well-known antitumor drug 5-fluorouracil. The inhibitory results of compounds **8a–8l** were shown in Table 1. All compounds exhibited moderate to good antiproliferative activity against at least one of the three selected cancer cell lines. Among them, compound **8c** showed the potent antiproliferative activity with an IC_{50} value of 0.7μmol, better than 5-FU (5-fluorouracil), against MGC-803 cells (Table 1).

Based on the structure activity relationship studies, the effect of substituent on the phenyl ring was explored (**8a–8c, 8f–8h, 8j** and**8l**). Replacement of the methyl on the phenyl ring of compound **8h** with a 3, 4-dimethoxy on the phenyl ring (**8l**) led to a decrease of the inhibitory activity against MGC-803 cells. However, changing the bromine atom (compound **8j**) to a 4-methoxy group (compound **8f**) led to a significant improvement for the inhibitory activity against all the tested cell lines. These SAR studies suggested that substituent on the phenyl ring of sulfonamide hybrids displayed an important role for the inhibitory activity. To determine whether the benzene ring and heterocycles have an effect on the inhibitory activity, compounds with a thiofuran ring (**8d** and **8e**), a coumarin ring (**8i**), and a pyridine ring (**8k**) were synthesized and evaluated their antiproliferative activity. In terms of MGC-803 cancer cell line, sulfonamide hybrid **8c** with a 2-chlorophenyl moiety displayed a better antiproliferative activity than sulfonamide hybrids with aromatic heterocycle (**8d**, **8e**,**8i** and**8k**).

Table 1. Anticancer activity in vitro of sulfonamide hybrids **8a-8l**.

Compound	IC_{50}(μmol)[a]		
	MGC-803	EC-109	PC-3
8a	5.0 ± 0.7	46.3 ± 1.7	> 100
8b	2.9 ± 0.5	58.3 ± 1.8	36.1 ± 1.6
8c	0.7 ± 0.5	32.1 ± 1.5	93.2 ± 1.9
8d	2.2 ± 0.3	25.7 ± 1.5	61.0 ± 1.8
8e	10.8 ± 1.3	> 100	> 100
8f	2.7 ± 0.4	29.2 ± 1.5	30.8 ± 1.5
8g	9.8 ± 1.0	60.7 ± 1.8	27.3 ± 1.4
8h	1.4 ± 0.1	58.1 ± 1.8	92.9 ± 1.9
8i	22.7 ± 1.4	32.6 ± 1.5	81.7 ± 1.9
8j	6.6 ± 0.8	51.8 ± 1.7	72.2 ± 1.5
8k	5.0 ± 0.7	42.6 ± 1.6	46.6 ± 1.7
8l	31.0 ± 1.5	31.6 ± 1.5	88.7 ± 1.9
5-Fu	17.4 ± 1.2	10.1 ± 0.9	16.3 ± 1.7

[a]Antiproliferative activity was assayed by exposure for 48 h. The data are presented as the means of three independent experiments

4. Conclusions

In summary, we designed a series of sulfonamide derivatives by molecular hybridization strategy and synthesized them by click chemistry. All hybrids possessed moderate to good growth inhibition against the tested cancer cells. Especially, compound **8c** exhibited excellent growth inhibition against MGC-803 cells with an IC50 value of 0.7 μmol. These hybrids in this work might serve as bioactive fragments and lead compounds for developing more potent antitumor drugs.

Acknowledgements

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