# Synthesis of novel antiproliferative 1,2,3-triazole hybrids using the molecular hybridisation approach

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A series of nine novel 1,2,3-triazole-chalcone derivatives were designed using the molecular hybridisation approach and synthesised by click chemistry. Most of the synthesised compounds exhibited moderate to good antiproliferative activity against oesophagus, gastric and neuroendocrine cancer cell lines, but a compound containing a *p*-bromo group in the A ring and a [(4,5-dihydrothiazol-2-yl)thio]methyl group attached at the 4-position of a *p*-[3-(1,2,3-triazol-1-yl)propyloxy] group in the B ring showed the highest activity with an IC50 value of 8.16 μM against neuroendocrine cancer cells. The structure activity relationships of all nine compounds were discussed.

**Keywords:** 1,2,3-triazole, chalcone, molecular hybridisation, antiproliferative

Heterocyclic scaffolds play important roles in drug design and organic reactions. 1,2,3-Triazoles have received attention in medicinal chemistry and organic chemistry due to their excellent biological activities and easy synthesis *via* click reactions.[1,2] In recent years, 1,2,3-triazoles have gained special attention as antiproliferative agents because several biologically active compounds contain that group such as the spirooxindole-derived morpholine-fused-1,2,3-triazole **1**,[3] and the 1,2,3-triazole linked chalcone **2** (Fig. 1).[4]

Chalcones, which are important constituents of natural products, are abundant in edible plants where they are known to be the precursors of flavonoids and isoflavonoids.[5] There is growing interest in the pharmacological potential of chalcones, which constitute an important group of natural and synthetic products that have been screened for their wide range of pharmacological activities as antibacterial,[6,7] antitumour,[8,9] anti-inflammatory,[10,11] antifungal and antioxidant agents.[12,13] Our group has recently reported four variously substituted chalcone derivatives as antiproliferative agents (Fig. 2). In one series a pyridine ring featured as ring B with ring A containing a 4-amino side chain containing a 1,2,3-triazole ring and a terminal substituted phenyl group (**3**).[14] A recurring feature of three other series was a trimethoxylated B ring, with a side chain containing either a thiocarbamate (**4**),[15] an imidazole group (**5**),[16] or a cyclic amino group (**6**)[17] at the 4-position of ring A.

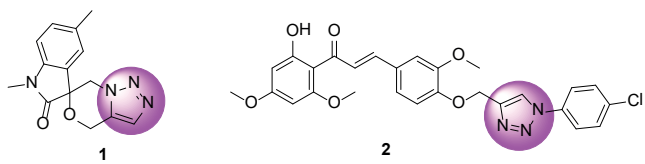

**Fig. 1** The structures of 1,2,3-triazole analogues as antiproliferative agents.

Molecular hybridisation is a strategy of rational design of new ligands or prototypes based on the recognition of pharmacophoric subunits in the molecular structure of two or more known bioactive derivatives.18 The above interesting findings and our continuous quest to synthesise antiproliferative 1,2,3-triazole analogues, led us to carry out the molecular hybridisation of a biologically active chalcone and a bioactive 1,2,3-triazole to integrate them in one molecular platform to generate a new hybrid architecture with the aim of exploring the impact of such modification on the anticancer agents.

## Results and discussion

As shown in Fig. 3, a molecular hybridisation strategy based on the structures of a bioactive highly substituted chalcone and a bioactive 1,2,3-triazole compound **2** yielded a scaffold which has four parts: (i) a 1,2,3-triazole as a central core, (ii) a di-substituted chalcone attached thereto *via* (iii) a medium-chain alkoxyl group for lipophilicity, and (iv) an attachment at the 4-position of the 1,2,3-triazole of a thiomethyl group to which is attached various *N*-heterocycles.

The synthetic routes are shown in Scheme 1 and Scheme 2. Commercially available thiols were treated with propargyl bromide to provide **I** (Scheme 1). Target derivatives were synthesised by a click reaction in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate (Scheme 2). The structures of the synthesised compounds were characterised using spectral methods, and all spectral data corroborated the assumed structures.

All the synthesised derivatives were evaluated for their cytotoxic activity *in vitro* against three cancer cell lines, MGC-803 (human gastric cancer cell line), SK-N-SH (human

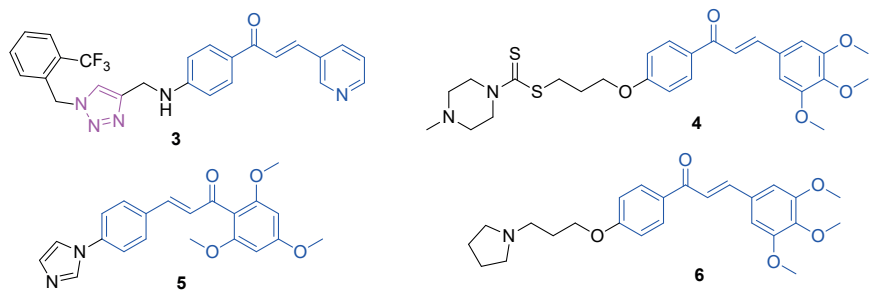

**Fig. 2** Reported chalcones as antiproliferative agents.

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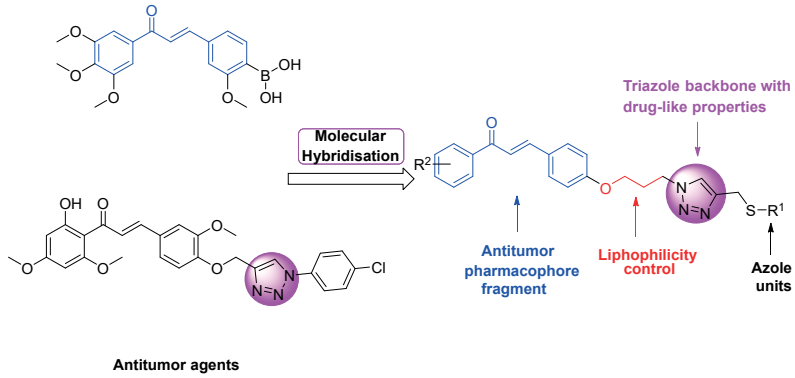
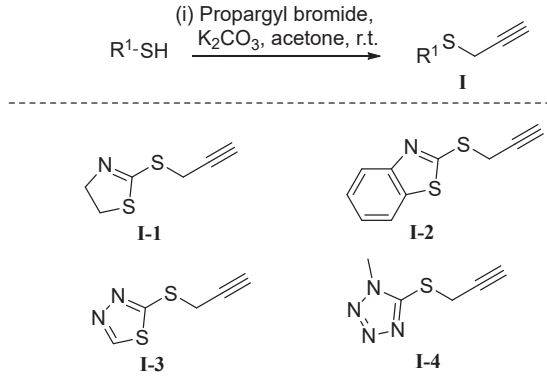
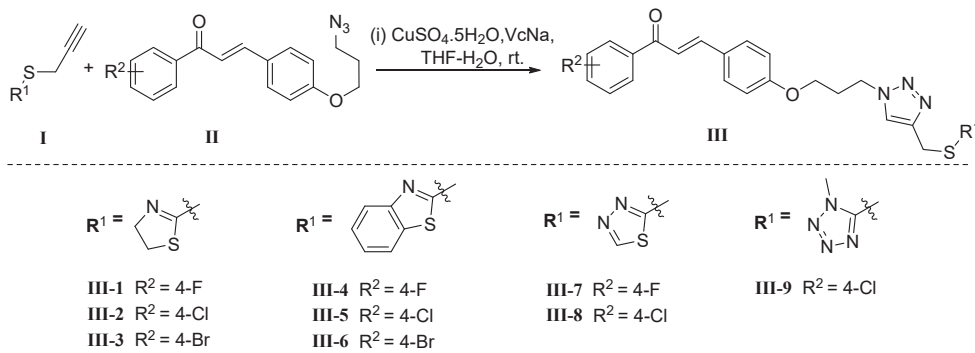



**Fig. 3** Illustration of the design strategy for target compounds.




**Scheme 1**




**Scheme 2**

neuroendocrine cancer cell line), and EC-109 (human oesophagus cancer cell line) using the MTT assay method and compared with the well-known anticancer drug 5-fluorouracil.[19] The antiproliferative activity results of compounds **III-1–9** are shown in Table 1. All compounds exhibited moderate antiproliferative activity against at least one of the three selected cancer cell lines. Among them, compound **III-3** showed the highest antiproliferative activity with an $IC_{50}$ value of 8.16 μM, better than 5-FU, against SK-N-SH cells (Table 1).

We found that the nature of the substituent on the benzene ring of chalcone has a remarkable effect on their antiproliferative activity. Of the tested compounds against the EC-109 cell line, compound **III-3** with the bromine atom on the A ring of the chalcone showed more potent antiproliferative activity (30.35 μM) than the corresponding fluoro- and chloro-compounds **III-1** and **III-2**. For the MGC-803 cell line, compound **III-6** with the chlorine atom on the benzene ring of chalcone showed higher activity (15.43 μM) than all other derivatives.

To determine whether the azole rings might affect the activity, compounds containing 4,5-dihydrothiazole-2-thiol (**III-1–3**),

**Table 1** The antiproliferative activity against oesophagus (EC109), human neuroendocrine (SK-N-SH) and gastric (MGC-803) cancer cell lines of the synthesised 1,2,3-triazole-chalcone derivatives **III-1–9** (Scheme 2)

| Compound | $IC_{50}$ (μM)[a] | | |
|---|---|---|---|
| | EC-109 | SK-N-SH | MGC-803 |
| **III-1** | >100 | 13.59 ± 0.72 | 24.38 ± 0.63 |
| **III-2** | >100 | >100 | 68.72 ± 1.88 |
| **III-3** | 30.35 ± 0.84 | 8.16 ± 0.49 | 18.56 ± 0.61 |
| **III-4** | 58.39 ± 0.68 | 12.28 ± 1.22 | 49.07 ± 1.69 |
| **III-5** | >100 | 14.45 ± 1.25 | 48.61 ± 0.62 |
| **III-6** | 29.17 ± 0.59 | 14.44 ± 1.68 | 15.43 ± 0.94 |
| **III-7** | 86.24 ± 1.68 | 12.53 ± 0.26 | 36.43 ± 1.57 |
| **III-8** | 37.80 ± 1.79 | 26.13 ± 0.68 | 23.27 ± 1.59 |
| **III-9** | 34.65 ± 0.72 | 10.45 ± 0.84 | 37.94 ± 0.68 |
| **5-FU**[b] | 10.30 ± 0.32 | 9.85 ± 0.76 | 7.14 ± 0.28 |

[a]Antiproliferative activity was assayed by exposure for 48 h to the tested substances and expressed as the concentration required to inhibit tumour cell proliferation by 50% ($IC_{50}$). The data are presented as the means with standard deviation from the dose–response curves of three independent experiments. [b]5-FU = 5-fluorouracil.

benzo[*d*]thiazole-2-thiol (**III-4**–**6**), 1,3,4-thiadiazole-2-thiol (**III-7**–**8**) and 1-methyl-1*H*-tetrazole-5-thiol (**III-9**) were synthesised and their antiproliferative activities are shown in Table 1. Replacing the 1,3,4-thiadiazole-2-thiol scaffold of compound **III-7** (12.53 μM) with 1-methyl-1*H*-tetrazole-5-thiol (**III-9**, 10.45 μM) led to a small increment of activity against SK-N-SH cancer cells, whereas, changing the benzo[*d*] thiazole-2-thiol (**III-5**, 48.61 μM) to a 1,3,4-thiadiazole-2-thiol (**III-8**, 23.27 μM) or a 1-methyl-1*H*-tetrazole-5-thiol (**III-9**, 37.94 μM) led to an improvement of activity against MGC-803 cells, indicating the significance of the azole rings in their antiproliferative activity.

In summary, a series of chalcone-1,2,3-triazole derivatives were synthesised, and their structures characterised by $^1$H NMR, $^{13}$C NMR, and HRMS. Their *in vitro* antiproliferative activities were then tested, using a MTT assay, against three selected cancer cell lines (SK-N-SH, EC-109 and MGC-803) and compared with the well-known anticancer drug 5-fluorouracil. Most of the synthesised compounds exhibited moderate to good activity against all the cancer cell lines selected. In particular, the promising compound **III-3** showed the highest antiproliferative activity with an $IC_{50}$ value of 8.16 μM against SK-N-SH cancer cells.

## Experimental

All reagents and solvents used were of analytical grade and were purchased from commercial sources. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel and visualised 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 $CDCl_3$ or 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).

*Synthesis of 2-(prop-2-yn-1-ylthio) derivatives* (**I-1**–**4**); *general procedure*

To a stirred solution of mercaptan (3 mmol) in acetone (15 mL), propargyl bromide (3 mmol) and $K_2CO_3$ (3 mmol) were added carefully and the reaction mixture was refluxed for 5 h. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc (30 mL) and washed with water and brine, dried over anhydrous $Na_2SO_4$ and concentrated under vacuum to afford compounds **I-1**–**4**, which were used in the next reaction without further purification.

*2-(Prop-2-yn-1-ylthio)-4,5-dihydrothiazole* (**I-1**): Colourless oil; yield 74%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.16 (t, *J* = 8.0 Hz, 2H), 3.94 (d, *J* = 2.6 Hz, 2H), 3.48 (t, *J* = 8.0 Hz, 2H), 3.21 (t, *J* = 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 161.8, 79.5, 74.1, 63.9, 35.5, 20.1; HRMS (ESI) calcd for $C_6H_8NS_2$ [M + H]$^+$: 158.0095; found: 158.0098.

*2-(Prop-2-yn-1-ylthio)benzo[*d*]thiazole* (**I-2**): Yellow solid; yield 47%; m.p. 50–52 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 7.75–7.62 (m, 2H), 7.41–7.30 (m, 2H), 4.23 (d, *J* = 2.6 Hz, 2H), 3.31 (t, *J* = 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 162.7, 151.4, 141.2, 124.7, 124.5, 118.5, 110.3, 79.2, 74.6, 20.3; HRMS (ESI) calcd for $C_{10}H_8NS_2$ [M + H]$^+$: 206.0010; found: 206.0098.

*2-(Prop-2-yn-1-ylthio)-1,3,4-thiadiazole* (**I-3**): Colourless oil; yield 78%; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.59 (dd, *J* = 3.5, 1.6 Hz, 1H), 4.23 (dd, *J* = 2.2, 1.6 Hz, 2H), 3.25 (ddd, *J* = 7.9, 4.9, 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.0, 154.5, 79.0, 74.8, 22.2; HRMS (ESI) calcd for $C_5H_5N_2S_2$ [M + H]$^+$: 156.9899; found: 156.9894.

*1-Methyl-5-(prop-2-yn-1-ylthio)-1*H*-tetrazole* (**I-4**): White solid; yield 83%; m.p. 61–62 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 4.12 (d, *J* = 2.6 Hz, 2H), 3.99 (s, 3H), 3.26 (t, *J* = 2.6 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 152.3, 78.9, 74.9, 33.8, 21.6; HRMS (ESI) calcd for $C_5H_7N_4S$ [M + H]$^+$: 155.0393; found: 155.0391.

*Preparation of compounds* (**III-1**–**9**); *general procedure*

Compound **I** (1.05 mmol), compound **II** (1 mmol), $CuSO_4{\cdot}5H_2O$ (0.2 mmol) and sodium ascorbate (0.1 mmol) were dissolved in THF/$H_2O$ (5 mL/5 mL) and stirred at room temperature. The reaction was monitored by TLC until the reaction was finished. Upon completion, the reaction mixture was concentrated under vacuum, the residue was dissolved in EtOAc and washed with water and brine, and then dried over anhydrous $Na_2SO_4$ and concentrated under vacuum to afford compounds **III-1**–**9** which were purified by column chromatography (petroleum ether:EtOAc = 6:1).

*(*E*)-3-{4-[3-(4-{[(4,5-dihydrothiazol-2-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl}-1-(4-fluorophenyl)prop-2-en-1-one* (**III-1**): Yellow solid; yield 85%; m.p. 129–131 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.54 (s, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.18 (t, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.57 (t, *J* = 6.7 Hz, 2H), 4.41 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 2H), 4.00 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 8.0 Hz, 2H), 2.54–2.31 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.8, 164.8, 164.3, 160.5, 144.6, 134.8, 131.1, 130.3, 127.9, 123.2, 119.5, 115.6, 114.9, 64.2, 64.1, 47.0, 35.8, 29.8, 27.1; HRMS (ESI) calcd for $C_{24}H_{23}FN_4NaO_2S_2$ [M + Na]$^+$: 505.1148, found: 505.1144.

*(*E*)-1-(4-chlorophenyl)-3-{4-[3-(4-{[(4,5-dihydrothiazol-2-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl}prop-2-en-1-one* (**III-2**): Yellow solid; yield 62%; m.p. 129–131 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 2H), 7.54 (s, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 15.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.57 (t, *J* = 6.7 Hz, 2H), 4.41 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 2H), 4.00 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 8.0 Hz, 2H), 2.54–2.33 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.1, 164.8, 160.6, 145.0, 144.4, 139.0, 136.7, 130.4, 129.9, 128.9, 127.9, 123.2, 119.4, 114.9, 64.2, 64.1, 47.0, 35.8, 29.7, 27.1; HRMS (ESI) calcd for $C_{24}H_{23}ClN_4NaO_2S_2$ [M + Na]$^+$: 521.0842; found: 521.0849.

*(*E*)-1-(4-bromophenyl)-3-{4-[3-(4-{[(4,5-dihydrothiazol-2-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl}prop-2-en-1-one* (**III-3**): Yellow solid; yield 87%; m.p. 138–140 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.62 (dd, *J* = 16.4, 8.6 Hz, 4H), 7.53 (s, 1H), 7.37 (d, *J* = 15.6 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.57 (t, *J* = 6.7 Hz, 2H), 4.41 (s, 2H), 4.14 (t, *J* = 8.0 Hz, 2H), 4.00 (t, *J* = 5.7 Hz, 2H), 3.36 (t, *J* = 8.0 Hz, 2H), 2.54–2.28 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.3, 164.8, 160.6, 145.0, 144.4, 137.1, 131.9, 130.4, 130.0, 127.9, 123.2, 119.4, 114.9, 64.2, 64.1, 47.0, 35.8, 29.8, 27.1; HRMS (ESI) calcd for $C_{24}H_{23}BrN_4NaO_2S_2$ [M + Na]$^+$: 565.0347; found: 565.0343.

*(*E*)-3-[4-(3-{4-[(benzo[*d*]thiazol-2-ylthio)methyl]-1*H*-1,2,3-triazol-1-yl}propoxy)phenyl]-1-(4-fluorophenyl)prop-2-en-1-one* (**III-4**): Yellow solid; yield 80%; m.p. 140–142 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.7, 5.5 Hz, 2H), 7.90–7.68 (m, 3H), 7.64 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.36 (ddd, *J* = 30.8, 13.3, 7.7 Hz, 3H), 7.18 (t, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.68 (s, 2H), 4.55 (t, *J* = 6.7 Hz, 2H), 3.96 (t, *J* = 5.7 Hz, 2H), 2.50–2.27 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.8, 165.9, 164.3, 160.5, 153.0, 144.7, 135.5, 134.8, 131.1, 130.3, 127.9, 126.1, 124.4, 123.4, 121.4, 121.2, 119.5, 115.8, 114.8, 64.2, 47.0, 29.7, 27.7; HRMS (ESI) calcd for $C_{28}H_{23}FN_4NaO_2S_2$ [M + Na]$^+$: 553.1148; found: 553.1144.

*(*E*)-3-[4-(3-{4-[(benzo[*d*]thiazol-2-ylthio)methyl]-1*H*-1,2,3-triazol-1-yl}propoxy)phenyl]-1-(4-chlorophenyl)prop-2-en-1-one* (**III-5**): White solid; yield 84%; m.p. 156–158 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 11.8 Hz, 2H), 7.61 (s, 1H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.42–7.25 (m, 3H), 6.82 (d, *J* = 8.7 Hz, 2H), 4.66 (s, 2H), 4.53 (t, *J* = 6.7 Hz, 2H), 3.94 (t, *J* = 5.7 Hz, 2H), 2.51–2.28 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.1, 165.9, 160.5, 153.0, 145.0, 144.2, 139.0, 136.7, 135.5, 130.4, 129.9, 128.9, 127.8, 126.1, 124.4, 123.4, 121.4, 121.2, 119.4, 114.8, 64.2, 47.0, 29.7, 27.7; HRMS (ESI) calcd for $C_{28}H_{23}ClN_4NaO_2S_2$ [M + Na]$^+$: 569.0842; found: 569.0849.

*(*E*)-3-[4-(3-{4-[(benzo[*d*]thiazol-2-ylthio)methyl]-1*H*-1,2,3-triazol-1-yl}propoxy)phenyl]-1-(4-bromophenyl)prop-2-en-1-*

*one* (**III-6**): Yellow solid; yield 70%; m.p. 159–162 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.85–7.71 (m, 3H), 7.64 (d, *J* = 7.7 Hz, 3H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.35 (ddd, *J* = 19.4, 15.3, 7.5 Hz, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.68 (s, 2H), 4.55 (t, *J* = 6.7 Hz, 2H), 3.96 (t, *J* = 5.7 Hz, 2H), 2.52–2.29 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.3, 165.9, 160.5, 153.0, 145.1, 137.2, 135.5, 131.9, 130.4, 130.0, 127.8, 127.7, 126.1, 124.4, 123.4, 122.6, 121.4, 121.2, 119.3, 114.8, 64.2, 47.0, 29.7, 27.7; HRMS (ESI) calcd for $C_{28}H_{23}BrN_4NaO_2S_2$ $[M + Na]^+$: 613.0347; found: 613.0343.

*(*E*)-3-{4-[3-(4-{[(1,3,4-thiadiazol-2-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl}-1-(4-fluorophenyl)prop-2-en-1-one* (**III-7**): Yellow solid; yield 75%; m.p. 139–141 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.16–7.93 (m, 2H), 7.78 (d, *J* = 15.6 Hz, 1H), 7.72 (s, 1H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 15.6 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.67 (s, 2H), 4.55 (t, *J* = 6.8 Hz, 2H), 3.98 (t, *J* = 5.7 Hz, 2H), 2.55–2.25 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 188.8, 166.8, 164.3, 160.5, 151.8, 144.7, 143.3, 134.8, 130.3, 127.9, 123.8, 119.5, 115.8, 115.6, 114.9, 64.2, 47.1, 29.8, 28.2; HRMS (ESI) calcd for $C_{23}H_{20}FN_5NaO_2S_2$ $[M + Na]^+$: 504.0946; found: 504.0940.

*(*E*)-3-{4-[3-(4-{[(1,3,4-thiadiazol-2-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl)-1-(4-chlorophenyl)prop-2-en-1-one* (**III-8**): Yellow solid; yield 80%; m.p. 171–173 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 2H), 7.81 (d, *J* = 15.6 Hz, 1H), 7.74 (s, 1H), 7.61 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 15.6 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.70 (s, 2H), 4.57 (t, *J* = 6.8 Hz, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 2.53–2.32 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.2, 165.1, 160.6, 151.8, 145.0, 143.4, 139.0, 136.7, 130.4, 129.9, 128.9, 127.9, 123.8, 119.4, 114.9, 64.2, 47.1, 29.8, 28.2; HRMS (ESI) calcd for $C_{23}H_{20}ClN_5NaO_2S_2$ $[M + Na]^+$: 520.0649; found: 520.0645.

*(*E*)-1-(4-chlorophenyl)-3-{4-[3-(4-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-1*H*-1,2,3-triazol-1-yl)propoxy]phenyl}prop-2-en-1-one* (**III-9**): White solid; yield 84%; m.p. 135–137 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 13.9 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 15.6 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.64 (s, 2H), 4.57 (t, *J* = 6.9 Hz, 2H), 4.01 (t, *J* = 5.7 Hz, 2H), 3.88 (s, 3H), 2.51–2.33 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 189.1, 160.6, 153.7, 145.0, 142.8, 139.0, 136.7, 130.4, 129.9, 128.9, 127.9, 124.0, 119.5, 114.9, 64.2, 47.1, 33.4, 29.7, 27.4; HRMS (ESI) calcd for $C_{23}H_{22}ClN_7NaO_2S$ $[M + Na]^+$: 518.1146; found: 518.1142.

*Antiproliferative activity assays*

All cancer cell lines were maintained in minimal essential medium supplemented with 10% foetal bovine serum (FBS) and 1% penicillin-streptomycin in a humidified atmosphere of 5% $CO_2$ and 95% air at 37 °C. Cancer cells were maintained in RPMI1640 medium. Cancer cell lines were purchased from the China Centre for Type Culture Collection (CCTCC, Shanghai, China). For pharmacological investigations, 10 mM stock solutions of the tested compounds were prepared with DMSO. The highest DMSO concentration of the medium (0.1%) did not have any substantial effect on the determined cellular functions.

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## Electronic Supplementary Information

Additional data and spectra are available through: stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data

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