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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antitumor evaluation of novel fused heterocyclic 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives

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Abstract

In this study, twenty three 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives were synthesized and their antiproliferative activities in vitro were studied against SMMC-7721, HeLa, A549, and L929 by the CCK-8 assay. The bioassay results demonstrated that all tested compounds **8(a–w)** exhibited antiproliferation with different degrees, and some compounds showed better effects than reference drug 5-fluorouracil. Among these screened compounds, compounds **8a**, **8d**, and **8l** displayed significant antitumor activities in inhibiting SMMC-7721cell proliferation with IC_{50} values of 1.64, 1.74, and 1.61 μM, respectively. Compounds **8d** and **8l** were manifested highly effective biological activity versus HeLa cells with IC_{50} values of 2.23 and 2.84 μM, respectively. Compound **8l** was found to have the highest antitumor potency against A549 cells with IC_{50} value of 2.67 μM. Furthermore, all compounds exhibited weaker cytotoxic effects than 5-fluorouracil on normal cell lines L929.

Keywords Triazolo-thiadiazole · Disulfides · Antitumor activity

Introduction

Cancer has become one of the most terrible diseases around the world because of its low cure and high mortality. Therefore, the design and development of new drugs for cancer therapeutics is an important and challenging task for medicinal chemists worldwide (Anand et al. 2008; Alegaon et al. 2017; Chowrasia et al. 2017).

The heterocyclic compounds bearing 1,2,4-triazole or 1,3,4-thiadiazole moieties are of special interest to medicinal chemists because of their exceptional chemical and versatile biological properties including potential antioxidant (Menteşe et al. 2013; Padmaja et al. 2015), antimicrobial (Ceylan 2016; Li et al. 2016), antidepressant (Chelamalla et al. 2017; Khan et al. 2016), antifungal (Miniyar et al. 2017; Er et al. 2017), anticonvulsant (Kahveci et al. 2014; Harish et al. 2014), and anti-inflammatory activities (Liu et al. 2016; Banerjee et al. 2016). In particular, a great number of 1,2,4-triazole and 1,3,4-thiadiazole derivatives have been proved to show potent antitumor activities (Meti et al. 2016; Zhao et al. 2016; Bhatt et al. 2018; Vudhgiri et al. 2017). Moreover, The fused 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole moieties were found to have various biological properties, such as antioxidant (Chidananda et al. 2012), antimicrobial (Almajan et al. 2010; Cui et al. 2017), anticonvulsant (Deng et al. 2012), and anti-inflammatory (Chidananda et al. 2012; Akhter et al. 2014). Particularly, this class of compounds have received considerable attention in the last few decades, owing to their effective anticancer importance (Chowrasia et al. 2017; Xu et al. 2017; Rostom et al. 2017; Husain et al. 2013). Moreoever, disulfide derivatives are also known to display a wide spectrum of biological activities including anti-Alzheimer's (Roldán-Peña et al. 2017), antibacterial (Sheppard et al. 2018; Turos et al. 2008), anti-HIV-1 (Cesarini et al. 2008), antioxidant (Roldán-Peña et al. 2017), and herbicidal properties (Li et al. 2013; Shang et al. 2012). Especially, the antitumor potential of disulfide

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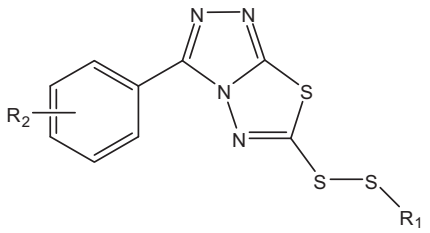


Fig. 1 The structure of target compounds **8(a–w)**

derivatives attracts the great interest of medicinal chemists in recent years (Branowska et al. 2018; Hong et al. 2015; Rubino et al. 2017; Vale et al. 2017) (Fig. 1).

In view of the abovementioned findings, in order to screen out novel antitumor agents bearing disulfide core with high efficiency and low toxicity, hybrid compounds possessing disulfide and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole moieties will be formed, and some cells growth inhibitory effects will be examined in our research.

Results and discussion

Synthesis

As exhibited in Scheme 1, twenty three novel 1,2,4-triazole [3,4-b]-1,3,4-thiadiazole derivatives **8(a–w)** were synthesized and reported for the frist time. The preparation of *S*-alkyl-thioisothiourea hydrochloride **2** was carried out by the reported literature method (Sirakawa et al. 1970). The 3-substitutedphenyl-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole-6-thiol **7** were obtained according to the reported procedure (Eweiss and Bahajaj 1987). Finally, the target compounds **8 (a–w)** were successfully gained by the reaction of intermediates **2** and compounds **7** in the presence of $NaHCO_3$ in ethanol and water at room temperature. All newly synthesized compounds **8(a–w)** were purified by silica gel column chromatography and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HR-ESI-MS.

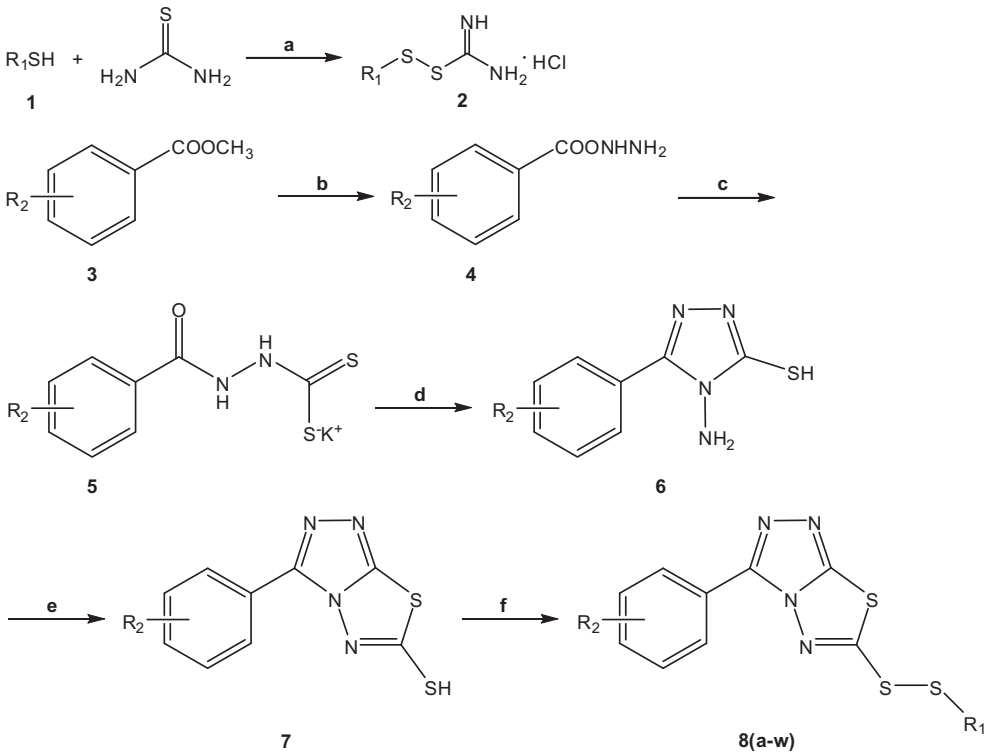
Pharmacology evaluation

Evaluation of the antiproliferative activities in vitro for 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **8(a–w)** was carried out by utilizing the CCK-8 assay against SMMC-7721, HeLa, A549, and L929 cell lines. The inhibitory activities IC_{50} (μM) were expressed in Table 1.

All synthesized compounds **8(a–w)** showed different degrees of antitumor activities, and some compounds showed better effects than positive control 5-fluorouracil against various cancer cell. The substituent groups R_1 and R_2 played important roles in the potency of biologically active compounds. In SMMC-7721 cells, except compound **8e** bearing 4-methoxyl substituent at the phenyl ring while R_1 is *n*-butyl group, showed moderate antitumor activity with IC_{50} value of 14.42 μM, the other compounds exhibited good antiproliferative effects with IC_{50} values ranging from 1.61 to 9.45 μM. Meanwhile, the majority of the tested compounds showed better activities than positive control 5-fluorouracil. In particular, compounds **8a**, **8d**, and **8l** displayed significant antitumor activities against SMMC-7721 cells with IC_{50} values of 1.64, 1.74, and 1.61 μM, respectively. As compared with compound **8a** ($IC_{50} = 1.64$ μM), which has no substituent at the phenyl ring while R_1 is *n*-butyl group, compounds **8(b–h)** all showed weaker activities against SMMC-7721 cells. In HeLa cells, compounds **8c**, **8e**, **8j**, **8m**, and **8u** showed moderate antiproliferative activity with IC_{50} values of 12.67, 21.29, 14.25, 24.30, and 21.49 μM, respectively. The other compounds all showed good antiproliferative effects with IC_{50} values ranging from 2.23 to 9.71 μM, and displayed higher activities than positive control 5-fluorouracil. Among them, compounds **8d** and **8l** exhibited highly effective biological activity against HeLa cells with IC_{50} values of 2.23 and 2.84 μM, respectively. In A549 cells, except compounds **8g**, **8q**, and **8w**, showed moderate antiproliferative activity with IC_{50} values of 25.26, 14.85 and 17.07 μM, respectively. The other compounds all exhibited good antitumor effects with IC_{50} values ranging from 2.67 to 9.07 μM, and most of the tested compounds showed better activities than positive control 5-fluorouracil. As compared with compound **8i** ($IC_{50} = 7.35$ μM), which has no substituent at the phenyl ring while R_1 is 2-butyl group, compounds **8(j–p)** all displayed better activities against A549 cells. Among them, compound **8l** possessing 4-methyl substituent at the phenyl while R_1 is 2-butyl group, exhibited the best inhibitory effect against A549 cells with IC_{50} value of 2.67 μM. Furthermore, all compounds exhibited weaker cytotoxic effects than 5-fluorouracil on normal cell lines L929.

Conclusion

The present study comprises the synthesis of some novel 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles and screening for their antiproliferative activities against SMMC-7721, HeLa, A549, and L929 cell lines via the CCK-8 assay. The preliminary investigation revealed that the tested compounds have potency of inhibition for three tumor cell lines, and the effects of substituents on anticancer efficacy have been observed. Interestingly, some compounds showed stronger antitumor effects than reference drug 5-fluorouracil, and several screened compounds, such as **8a**, **8d**, and **8l**, displayed promising biological activities. Furthermore, all tested compounds exhibited weaker cytotoxic effects than 5-fluorouracil on the normal cell lines



R_2 (R_1 = n-C_4H_9): H (**8a**), 4-Cl (**8b**), 4-F (**8c**), 4-CH_3 (**8d**), 4-OCH_3 (**8e**), 4-OH (**8f**), 4-$C(CH_3)_3$ (**8g**), 3,4,5-$(OCH_3)_3$ (**8h**); R_2 (R_1 = 2-C_4H_9): H (**8i**), 4-Cl (**8j**), 4-F (**8k**), 4-CH_3 (**8l**), 4-OCH_3 (**8m**), 4-OH (**8n**), 4-$C(CH_3)_3$ (**8o**), 3,4,5-$(OCH_3)_3$ (**8p**); R_2 (R_1 = i-C_4H_9): H (**8q**), 4-Cl (**8r**), 4-F (**8s**), 4-CH_3 (**8t**), 4-OCH_3 (**8u**), 4-OH (**8v**), 4-$C(CH_3)_3$ (**8w**)

Scheme 1 Synthesis of target compounds **8(a–w)**. Reaction conditions and reagents: **a** Conc. HCl, H_2O_2 (30%), 0–5 °C, 8–10 h; **b** $NH_2NH_2{\cdot}H_2O$ (85%), EtOH, reflux, 5–8 h; **c** KOH, CS_2, EtOH, 0–5 °C, 4–6 h; **d** $NH_2NH_2{\cdot}H_2O$ (85%), EtOH, reflux, 5–8 h; **e** KOH, CS_2, MeOH, reflux, 10–15 h; **f** compound **2**, EtOH, $NaHCO_3/H_2O$, rt, 4–6 h

L929. Therefore, the pharmacological results could be helpful for improving the potency and selectivity of this class of compounds.

Material and methods

Synthesis

Unless otherwise noted, all solvents and reagents were used as received without further purification. Melting points were determined by an X-6 microscope melting point apparatus and are uncorrected. Infrared spectra were obtained in KBr pellets on a Nicolet Avatar 370 spectrometer. NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer (^{1}H, 400 MHz; ^{13}C, 100 MHz) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. Chemical shifts are given in ppm downfield from tetramethylsilane and the coupling constants (*J*) are in hertz (Hz). The high-resolution mass spectra were taken with a Waters Xevo G2 spectrometer. The reaction progress of some intermediates, such as compounds **5**, **6**, and **7**, was monitored by thin layer chromatography.

General method for the synthesis of 3,6-disubstituted 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles 8(a–w)

S-Alkyl-thioisothiourea hydrochloride **2** (2.2 mmol) and 3-substitutedphenyl-1,2,4-triazole-[3,4-b]-1, 3,4-thiadiazole-6-thiol **7** (2.0 mmol) were dissolved in water (5 mL) and ethanol (15 mL). Then, a solution of saturated $NaHCO_3$ (20 mL) was added dropwise with stirring for 4 h at room temperature. Solid crude products were obtained by filtration. The insoluble solid was collected and purified by silica gel column chromatography with petroleum ether/ethyl acetate (8:1, volume ratio) as eluent to afford the desired products.

3-Phenyl-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8a)

White solid, Yield 76.5%, m.p.: 92.3–93.7 °C; IR (KBr) cm^{-1}: 2930, 1613, 1452, 1381, 1230, 685, 504; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.18 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.55–7.62 (m, 3H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.67–11.74 (m, 2H, CH_2), 1.33–1.43 (m, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ

Table 1 Inhibition (IC_{50}) of SMMC-7721, HeLa, A549, and L929 cells proliferation by compounds **8(a–w)**

Compound	IC_{50} (μM)			
	SMMC-7721	HeLa	A549	L929
8a	1.64 ± 0.11	8.15 ± 0.92	6.52 ± 0.21	3.85 ± 0.27
8b	5.46 ± 0.26	9.71 ± 0.45	3.84 ± 0.09	7.75 ± 0.31
8c	5.38 ± 0.29	12.67 ± 0.66	5.56 ± 0.19	14.13 ± 0.89
8d	1.74 ± 0.09	2.23 ± 0.13	4.18 ± 0.22	3.15 ± 0.12
8e	14.42 ± 1.25	21.29 ± 1.35	7.61 ± 0.38	19.09 ± 1.29
8f	2.63 ± 0.11	3.88 ± 0.22	8.63 ± 0.35	6.68 ± 0.28
8g	2.29 ± 0.13	3.82 ± 0.29	25.26 ± 1.57	8.13 ± 0.41
8h	4.56 ± 0.39	8.45 ± 0.48	4.47 ± 0.23	5.10 ± 0.26
8i	3.22 ± 0.12	7.33 ± 0.34	7.35 ± 0.29	4.31 ± 0.21
8j	6.19 ± 0.25	14.25 ± 1.01	5.89 ± 0.23	6.85 ± 0.37
8k	2.49 ± 0.09	7.76 ± 0.23	7.06 ± 0.42	3.71 ± 0.23
8l	1.61 ± 0.10	2.84 ± 0.19	2.67 ± 0.17	3.16 ± 0.18
8m	5.20 ± 0.36	24.30 ± 1.59	6.27 ± 0.35	22.32 ± 1.87
8n	2.64 ± 0.13	3.34 ± 0.22	3.08 ± 0.16	4.62 ± 0.33
8o	6.23 ± 0.47	5.73 ± 0.33	7.02 ± 0.37	9.34 ± 0.63
8p	3.30 ± 0.14	9.01 ± 0.45	3.14 ± 0.16	15.64 ± 1.01
8q	5.58 ± 0.31	9.67 ± 0.63	14.85 ± 1.03	16.39 ± 1.11
8r	9.45 ± 0.78	9.58 ± 0.56	7.64 ± 0.48	15.43 ± 0.89
8s	2.80 ± 0.12	3.41 ± 0.27	8.07 ± 0.42	6.94 ± 0.34
8t	3.50 ± 0.15	9.20 ± 0.88	8.03 ± 0.38	6.43 ± 0.49
8u	6.74 ± 0.37	21.49 ± 1.24	6.20 ± 0.38	12.49 ± 0.70
8v	5.91 ± 0.36	3.42 ± 0.21	9.07 ± 0.77	9.93 ± 0.65
8w	2.11 ± 0.09	7.09 ± 0.34	17.07 ± 1.25	7.62 ± 0.43
5–FU	5.62 ± 0.28	17.21 ± 0.27	8.13 ± 0.34	2.98 ± 0.15

(ppm): 173.84, 154.47, 145.33, 130.76, 129.55 (2C), 126.23 (2C), 125.72, 39.18, 30.91, 21.34, 13.87; HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4S_3$ $[M + H]^+$ 323.0465, found 323.0459.

3-(4-Cholorophenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8b)

White solid, Yield 65.2%, m.p.: 95.6–96.7 °C; IR (KBr) cm^{-1}: 2930, 1610, 1449, 1381, 1230, 684, 505; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.19 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.68 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.66–1.74 (m, 2H, CH_2), 1.37–1.43 (m, 2H, CH_2), 0.89 (t, $J =$ 7.2 Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.32, 155.11, 143.08, 135.01, 129.06 (2C), 127.75 (2C), 125.06, 39.18, 30.90, 21.34, 13.87; HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3Cl$ $[M + H]^+$ 357.0072, found 357.0069.

3-(4-Fluorophenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8c)

Yellow solid, Yield 60.7%, m.p.: 64.7–65.3 °C; IR (KBr) cm^{-1}: 2932, 1613, 1450, 1382, 1230, 685, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.22 (dd, $J = 8.8$ Hz, 2H, Ar-H), 7.46 (dd, $J = 8.8$ Hz, 2H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.66–1.74 (m, 2H, CH_2), 1.36–1.45 (m, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 164.78, 162.31, 154.48, 144.58, 128.67 (2C) ($J_{C\text{-}F} = 8.7$ Hz), 122.35 ($J_{C\text{-}F} = 2.9$ Hz), 116.67 (2C) ($J_{C\text{-}F} = 22.0$ Hz), 39.16, 30.89, 21.33, 13.87; HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3F$ $[M + H]^+$ 341.0386, found 341.0365.

3-(4-Methylphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8d)

White solid, Yield 78.5%, m.p.: 83.9–84.2 °C; IR (KBr) cm^{-1}: 2931, 1612, 1451, 1380, 1233, 682, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.86 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar-H), 2.97 (t, $J = 7.2$ Hz, 2H, CH_2), 2.37 (s, 3H, Ar-CH_3), 1.64–1.74 (m, 2H, CH_2), 1.33–1.41 (m, 2H, CH_2), 0.87 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 160.36, 156.23, 140.85, 131.04, 130.14 (2C), 129.75, 126.52 (2C), 38.62, 30.57, 21.49, 21.28, 13.92; HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4S_3$ $[M + H]^+$ 337.0635, found 337.0615.

3-(4-Methoxyphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8e)

White solid, Yield 66.8%, m.p.: 90.3–91.6 °C; IR (KBr) cm^{-1}: 2933, 1613, 1451, 1379, 1230, 681, 505; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.10 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.15 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.66–1.73 (m, 2H, CH_2), 1.37–1.43 (m, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.48, 161.17, 154.02, 145.09, 127.88 (2C), 118.23, 114.95 (2C), 55.81, 39.20, 30.90, 21.33, 13.86; HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4OS_3$ $[M + H]^+$ 353.0577, found 353.0565.

3-(4-Hydroxyphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8f)

White solid, Yield 82.5%, m.p.: 108.5–109.4 °C; IR (KBr) cm^{-1}: 2931, 1614, 1455, 1384, 1231, 682, 505; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.07 (s, H, OH), 8.01 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.96 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.66–1.72 (m, 2H, CH_2), 1.38–1.43 (m, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.28, 159.67, 153.90, 145.34, 127.99 (2C), 116.89, 116.29 (2C), 39.18, 30.88, 21.32, 13.87; HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4OS_3$ $[M + H]^+$ 339.0422, found 339.0408.

3-(4-Tert-butylphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8g)

White solid, Yield 79.6%, m.p.: 92.7–93.4 °C; IR (KBr) cm^{-1}: 2935, 1613, 1451, 1380, 1230, 682, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.10 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.61 (d, $J = 8.4$ Hz, 2H, Ar-H), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.63–1.73 (m, 2H, CH_2), 1.36–1.45 (m, 2H, CH_2), 1.32 (s, 9H, CH_3), 0.88 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.65, 154.41, 153.37, 145.15, 126.31 (2C), 126.10 (2C), 123.22, 39.17, 35.09, 31.37 (3C), 30.90, 21.32, 13.87; HR-ESI-MS m/z: calcd for $C_{17}H_{22}N_4S_3$ $[M + H]^+$ 379.1097, found 379.1085.

3-(3,4,5-Trimethoxyphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8h)

White solid, Yield 65.2%, m.p.: 106.6–107.3 °C; IR (KBr) cm^{-1}: 2931, 1613, 1452, 1380, 1233, 685, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.48 (s, 2H, Ar-H), 3.87 (s, 6H, CH_3O), 3.75 (s, 3H, CH_3O), 3.09 (t, $J = 7.2$ Hz, 2H, CH_2), 1.62–1.72 (m, 2H, CH_2), 1.33–1.45 (m, 2H, CH_2), 0.89 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 167.41, 153.76 (2C), 139.78, 131.96, 129.12, 121.06, 103.90 (2C), 60.67, 56.54 (2C), 39.07, 30.91, 21.32, 13.87; HR-ESI-MS m/z: calcd for $C_{16}H_{20}N_4O_3S_3$ $[M + H]^+$ 413.0797, found 413.0776.

3-Phenyl-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8i)

White solid, Yield 62.7%, m.p. 89.3–90.1 °C; IR (KBr) cm^{-1}: 2930, 1612, 1451, 1380, 1231, 684, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.17 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.55–7.63 (m, 3H, Ar-H), 3.26–3.31 (m, 1H, CH), 1.62–1.75 (m, 2H, CH_2), 1.37 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.14, 154.47, 145.36, 130.83, 129.60 (2C), 126.29 (2C), 125.70, 49.91, 28.83, 20.06, 11.64; HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4S_3$ $[M + Na]^+$ 345.0297, found 345.0278.

3-(4-Chlorophenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8j)

White solid, Yield 82.5%, m.p.: 90.7–92.3 °C; IR (KBr) cm^{-1}: 2931, 1612, 1450, 1381, 1229, 684, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.18 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.68 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.26–3.31 (m, 1H, CH), 1.58–1.78 (m, 2H, CH_2), 1.36 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.50, 154.57, 144.39, 135.43, 129.70 (2C), 127.84 (2C), 124.52, 49.93, 28.85, 20.06, 11.65; HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3Cl$ $[M + H]^+$ 357.0083, found 357.0069.

3-(4-Fluorophenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8k)

Yellow solid, Yield 68.6%, m.p. 62.5–63.1 °C; IR (KBr) cm^{-1}: 2932, 1611, 1453, 1381, 1230, 684, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.22 (dd, $J = 8.8$ Hz, 2H, Ar-H), 7.46 (t, $J = 8.8$ Hz, 2H, Ar-H), 3.24–3.30 (m, 1H, CH), 1.60–1.75 (m, 2H, CH_2), 1.36 (d, $J = 6.8$ Hz, 3H, CH_3), 0.97–1.01 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 164.79, 162.32, 154.40, 144.57, 128.70 (2C) ($J_{C\text{-}F} = 8.7$ Hz), 122.35 ($J_{C\text{-}F} = 3.1$ Hz), 116.66 (2C) ($J_{C\text{-}F} = 22.0$ Hz), 49.92, 28.84, 20.07, 11.65; HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3F$ $[M + H]^+$ 341.0382, found 341.0365.

3-(4-Methylphenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8l)

White solid, Yield 58.3%, m.p.: 85.7–86.2 °C; IR (KBr) cm^{-1}: 2932, 1610, 1450, 1383, 1231, 683, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.86 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.35 (d, $J = 8.0$ Hz, 2H, Ar-H), 3.08–3.14 (m, 1H, CH), 2.36 (s, 3H, Ar-CH_3), 1.51–1.75 (m, 2H, CH_2), 1.31 (d, $J = 6.8$ Hz, 3H, CH_3), 0.93 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 160.08, 156.24, 140.46,

131.91, 130.04 (2C), 129.53, 126.40 (2C), 48.43, 28.44, 21.39, 20.11, 11.50; HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4S_3$ $[M + H]^+$ 337.0631, found 337.0615.

3-(4-Methoxyphenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8m)

White solid, Yield 88.2%, m.p.: 87.8–88.6 °C; IR (KBr) cm^{-1}: 2930, 1616, 1450, 1381, 1235, 683, 505; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.11 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.15 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.25–3.32 (m, 1H, CH), 1.58–1.76 (m, 2H, CH_2), 1.35 (d, $J = 6.8$ Hz, 3H, CH_3), 0.99 (t, $J = 7.6$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.63, 161.10, 154.08, 145.02, 127.87 (2C), 118.42, 114.96 (2C), 55.82, 49.90, 28.84, 20.07, 11.65; HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4OS_3$ $[M + H]^+$ 353.0590, found 353.0565.

3-(4-Hydroxyphenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8n)

White solid, Yield 78.4%, m.p.: 103.4–104.2 °C; IR (KBr) cm^{-1}: 2932, 1611, 1450, 1382, 1231, 683, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.08 (s, H, OH), 8.01 (d, $J = 8.4$ Hz, 2H, Ar-H), 6.96 (d, $J = 8.4$ Hz, 2H, Ar-H), 3.25–3.30 (m, 1H, CH), 1.61–1.76 (m, 2H, CH_2), 1.36 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.36, 159.87, 153.55, 145.63, 128.10 (2C), 116.55, 116.34 (2C), 49.89, 28.83, 20.07, 11.66; HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4OS_3$ $[M + H]^+$ 339.0426, found 339.0408.

3-(4-Tert-butylphenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8o)

White solid, Yield 78.6%, m.p.: 83.4–84.1 °C; IR (KBr) cm^{-1}: 2932, 1615, 1452, 1382, 1233, 684, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.08 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.62 (d, $J = 8.4$ Hz, 2H, Ar-H), 3.25–3.30 (m, 1H, CH), 1.60–1.76 (m, 2H, CH_2), 1.36 (d, $J = 7.2$ Hz, 3H, CH_3), 1.33 (s, 9H, CH_3), 0.98 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.81, 154.09, 153.55, 145.39, 126.32 (2C), 126.15 (2C), 122.95, 49.89, 35.09 (3C), 31.34, 28.84, 20.06, 11.65; HR-ESI-MS m/z: calcd for $C_{17}H_{22}N_4S_3$ $[M + H]^+$ 379.1099, found 379.1085.

3-(3,4,5-Trimethoxyphenyl)-6-(2-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8p)

White solid, Yield 70.3%, m.p. 114.6–115.3 °C; IR (KBr) cm^{-1}: 2931, 1613, 1451, 1385, 1233, 685, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.48 (s, 2H, Ar-H), 3.88 (s, 6H, CH_3O), 3.75 (s, 3H, CH_3O), 3.28 (t, $J = 7.2$ Hz, 1H, CH), 1.60–1.78 (m, 2H, CH_2), 1.37 (d, $J = 6.4$ Hz, 3H, CH_3), 0.99 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.87, 153.76 (2C), 145.16, 139.83, 129.11, 121.02, 103.96 (2C), 60.67, 56.56 (2C), 49.64, 28.83, 20.04, 11.61; HR-ESI-MS m/z: calcd for $C_{16}H_{20}N_4O_3S_3$ $[M + H]^+$ 413.0797, found 413.0776.

3-Phenyl-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8q)

White solid, Yield 81.4%, m.p. 105.1–106.3 °C; IR (KBr) cm^{-1}: 2931, 1610, 1451, 1380, 1232, 683, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.8 (d, $J = 7.2$ Hz, 2H, Ar-H), 7.55–7.62 (m, 3H, Ar-H), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.93–2.03 (m, 1H, CH), 1.01 (d, $J = 6.4$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.44, 154.62, 145.15, 130.65, 129.52 (2C), 126.20 (2C), 125.88, 48.38, 28.24, 21.66 (2C); HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4S_3$ $[M + H]^+$ 323.0480, found 323.0459.

3-(4-Chlorophenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8r)

White solid, Yield 79.8%, m.p. 101.1–102.3 °C; IR (KBr) cm^{-1}: 2930, 1612, 1450, 1381, 1230, 685, 503; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.18 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.68 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.94–2.01 (m, 1H, CH), 1.01 (d, $J = 6.8$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.29, 154.78, 144.45, 135.45, 129.76 (2C), 127.9 (2C), 124.54, 48.37, 28.23, 21.65 (2C); HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3Cl$ $[M + H]^+$ 357.0077, found 357.0069.

3-(4-Fluorophenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8s)

Yellow solid, Yield 67.5%, m.p. 78.3–79.2 °C; IR (KBr) cm^{-1}: 2930, 1609, 1451, 1381, 1229, 684, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.22 (dd, $J = 8.8$ Hz, 2H, Ar-H), 7.45 (dd, $J = 8.8$ Hz, 2H, Ar-H), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.91–2.02 (m, 1H, CH), 1.01 (d, $J = 6.8$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 164.83, 162.35, 154.64, 144.14, 128.78 (2C) ($J_{C\text{-}F} = 8.8$ Hz), 122.17 ($J_{C\text{-}F} = 2.8$ Hz), 116.66 (2C) ($J_{C\text{-}F} = 22.1$ Hz), 48.37, 28.23, 21.67 (2C); HR-ESI-MS m/z: calcd for $C_{13}H_{13}N_4S_3F$ $[M + H]^+$ 341.0378, found 341.0365.

3-(4-Methylphenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8t)

White solid, Yield 63.2%, m.p.: 90.4–91.2 °C; IR (KBr) cm^{-1}: 2931, 1614, 1451, 1382, 1231, 680, 504; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.86 (d, $J = 8.0$ Hz, 2H, Ar-

H), 7.36 (d, $J = 8.0$ Hz, 2H, Ar-H), 2.87 (d, $J = 6.8$ Hz, 2H, CH_2), 2.37 (s, 3H, Ar-CH_3), 1.97–2.06 (m, 1H, CH), 0.97 (d, $J = 6.8$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 160.30, 156.26, 140.84, 131.95, 130.12 (2C), 129.11, 126.47 (2C), 48.18, 27.73, 21.82, 21.44 (2C); HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4S_3$ $[M + H]^+$ 337.063, found 337.0615.

3-(4-Methoxyphenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8u)

White solid, Yield 83.6%, m.p.: 85.6–86.3 °C; IR (KBr) cm^{-1}: 2932, 1612, 1453, 1383, 1233, 680, 504; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.12 (d, $J = 8.8$ Hz, 2H,Ar-H), 7.15 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.84 (s, 3H, OCH_3), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.94–2.01 (m, 1H, CH), 1.01 (d, $J = 6.8$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 173.15, 161.07, 154.32, 144.72, 127.88 (2C), 118.50, 114.96 (2C), 55.82, 48.36, 28.22, 21.67 (2C); HR-ESI-MS m/z: calcd for $C_{14}H_{16}N_4OS_3$ $[M + H]^+$ 353.0596, found 353.0565.

3-(4-Hydroxyphenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8v)

White solid, Yield 70.5%, m.p.: 105.7–106.3 °C; IR (KBr) cm^{-1}: 2933, 1612, 1450, 1382, 1232, 685, 504; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.09 (s, H, OH), 8.01 (d, $J = 8.8$ Hz, 2H, Ar-H), 6.96 (d, $J = 8.8$ Hz, 2H, Ar-H), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.94–2.01 (m, 1H, CH), 1.01 (d, $J = 6.8$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.19, 159.89, 153.75, 145.60, 128.11 (2C), 116.53, 116.38 (2C), 48.38, 28.22, 21.68 (2C); HR-ESI-MS m/z: calcd for $C_{13}H_{14}N_4OS_3$ $[M + H]^+$ 339.0429, found 339.0408.

3-(4-Tert-butylphenyl)-6-(i-butyldisulfanyl)-1,2,4-triazole-[3,4-b]-1,3,4-thiadiazole (8w)

White solid, Yield 82.6%, m.p. 88.2–89.7 °C; IR (KBr) cm^{-1}: 2931, 1614, 1450, 1383, 1231, 683, 505; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.10 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.61 (d, $J = 8.4$ Hz, 2H, Ar-H), 3.01 (d, $J = 6.8$ Hz, 2H, CH_2), 1.93–2.03 (m, 1H, CH), 1.32 (s, 9H, CH_3), 1.02 (d, $J = 6.4$ Hz, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 174.14, 154.47, 153.42, 145.12, 126.31 (2C), 126.12 (2C), 123.14, 48.37, 35.10, 31.37 (3C), 28.23, 21.66 (2C); HR-ESI-MS m/z: calcd for $C_{17}H_{22}N_4S_3$ $[M + H]^+$ 379.1085, found 379.1085.

Tumor cell growth inhibitory assay

The cell lines (SMMC-7721, HeLa, A549, and L929) were cultured in proper medium in a 5% CO_2 at 37 °C during the experiment. The inhibition (IC_{50}) of the selected cells proliferation by target compounds **8(a–w)** and reference drug was measured by our previous method as described in the literature (Xuan et al. 2015).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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