

含苯并噻唑的 4-氨基喹唑啉衍生物的合成及抗肿瘤活性研究

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摘要 为了寻找高效低毒的抗肿瘤药物,设计并合成了一系列新型的含苯并噻唑结构的 4-氨基喹唑啉类衍生物,并采用噻唑蓝(MTT)法测定了目标化合物对人乳腺癌细胞系(MCF-7)、人胃癌细胞系(MGC-803)、人前列腺癌细胞系(PC-3)和人高度分化的胃癌细胞系(HGC-27)四种肿瘤细胞的抗增殖活性.结果显示大部分化合物具有较好的抗肿瘤活性,其中 2-((苯并[d]噻唑-2-基甲基)硫亚基)-N-(3-氯-4-氟苯基)-喹唑啉-4-胺(**13n**)对 MCF-7、MGC-803、PC-3 和 HGC-27 四种细胞显示出最好的抗增殖活性,IC₅₀ 值分别为(6.01±0.54), (7.63±0.48), (6.16±0.34)和(7.59±0.62) μmol·L⁻¹,其活性均优于阳性对照物吉非替尼.分子对接结果显示化合物 **13n** 能与表皮生长因子受体(EGFR)很好地结合,为抗肿瘤药物的研究提供了线索.

关键词 苯并噻唑; 4-氨基喹唑啉; 合成; 抗肿瘤活性

Synthesis and Antitumor Activity of Novel 4-Aminoquinazoline Derivatives Containing Benzothiazole

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Abstract In order to find efficient and low toxicity anti-tumor drugs, a series of novel 4-aminoquinazoline derivatives containing benzothiazole were designed and synthesized. And their antiproliferative activities against four human cancer cell lines [human breast cancer cell line (MCF-7), human gastric carcinoma cell line (MGC-803), human prostate cancer cell line (PC-3), human gastric carcinoma cell line (HGC-27)] were evaluated by using methyl thiazolyl tetrazolium (MTT) assay. The results showed that most compounds exhibited good antiproliferative activities against the four human tumor cell lines. Among them, 2-((benzo[d]thiazol-2-ylmethyl)thio)-N-(3-chloro-4-fluorophenyl)-quinazolin-4-amine (**13n**) showed the best antiproliferative activity against MCF-7, MGC 803, PC-3 and HGC-27 cancer cell lines, with IC₅₀ values of (6.01±0.54), (7.63±0.48), (6.16±0.34), (7.59±0.62) μmol·L⁻¹, respectively. Its activity was better than the positive control gefitinib. Molecular docking showed that compound **13n** could bind well with epidermal growth factor receptor (EGFR). In a nutshell, this work provides

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clues to discover antitumor agent based on the quinazoline scaffold.

Keywords benzothiazole; 4-aminoquinazoline; synthesis; antiproliferative activity

1 Introduction

The epidermal growth factor receptor (EGFR) belongs to the ErbB family of receptor tyrosine kinases and plays a crucial role in cell proliferation, survival and differentiation via activation of downstream signaling pathways.^[1-2]

Quinazoline derivatives are important nitrogen-containing heterocycles^[3] with a variety of pharmacological properties such as antimalarial,^[4-5] antibacterial,^[6-7] anti-inflammatory,^[8-9] anticonvulsant,^[10-11] antihypertensive,^[12] anti-diabetic,^[13] cholinesterase inhibition^[14-15] and anti-tumor.^[16-17] Meanwhile, it can specifically block the auto-phosphorylation of the epidermal growth factor receptor and inhibit the epidermal growth factor receptor or its tyrosine kinase ultimately.^[18-19] Remarkable progress has been made in recent years, and researchers have found that 4-aminoquinazoline plays an important role in inhibiting epidermal growth factor receptor tyrosine kinase.^[20] Some of the drugs with 4-aminoquinazoline are effective for the treatment of Non-Small Cell Lung Cancers (NSCLCs) such as erlotinib, gefitinib, lapatinib, afatinib (Figure 1).^[21]

Benzothiazole is an important benzo five-membered heterocyclic ring, which was discovered in 1880. Benzothiazole derivatives have a variety of biological activities, such as deworming,^[22] antiviral,^[23-24] analgesia,^[25-26] anti-tu-

mor,^[27-28] anti-bacterial,^[29-30] anti-inflammatory,^[31-32] anti-tuberculosis^[33] and anti-malarial.^[34] In 2015, Cai *et al.*^[35] reported that compounds **5**~**7** containing benzothiazole had strong cytotoxic effect against six human cancer cell lines. Xie *et al.*^[36] reported that compound **8** had strong cytotoxic effect against A549 with IC₅₀ value of 0.45 $\mu\text{mol}\cdot\text{L}^{-1}$ and benzothiazole was the key pharmacophore for the enhancement of antitumor activity (Figure 1). So, benzothiazole plays an indispensable role in pharmaceutical chemistry.

Therefore, a series of 4-aminoquinazoline derivatives containing benzothiazole by using the combination principles were synthesized and the antiproliferative activity of target compounds was evaluated *in vitro* by methyl thiazolyl tetrazolium (MTT) assay.

2 Results and discussion

2.1 Chemistry

The synthetic strategy to prepare the target compounds is depicted in Scheme 2. Firstly, The compound **10** was synthesized by the reaction of 2-aminobenzamide with carbon disulfide in the presence of KOH in ethanol at 90 °C. Then compound **11** was acquired from the reaction of compound **10** with 2-(chloromethyl)-benzothiazole under basic condi-

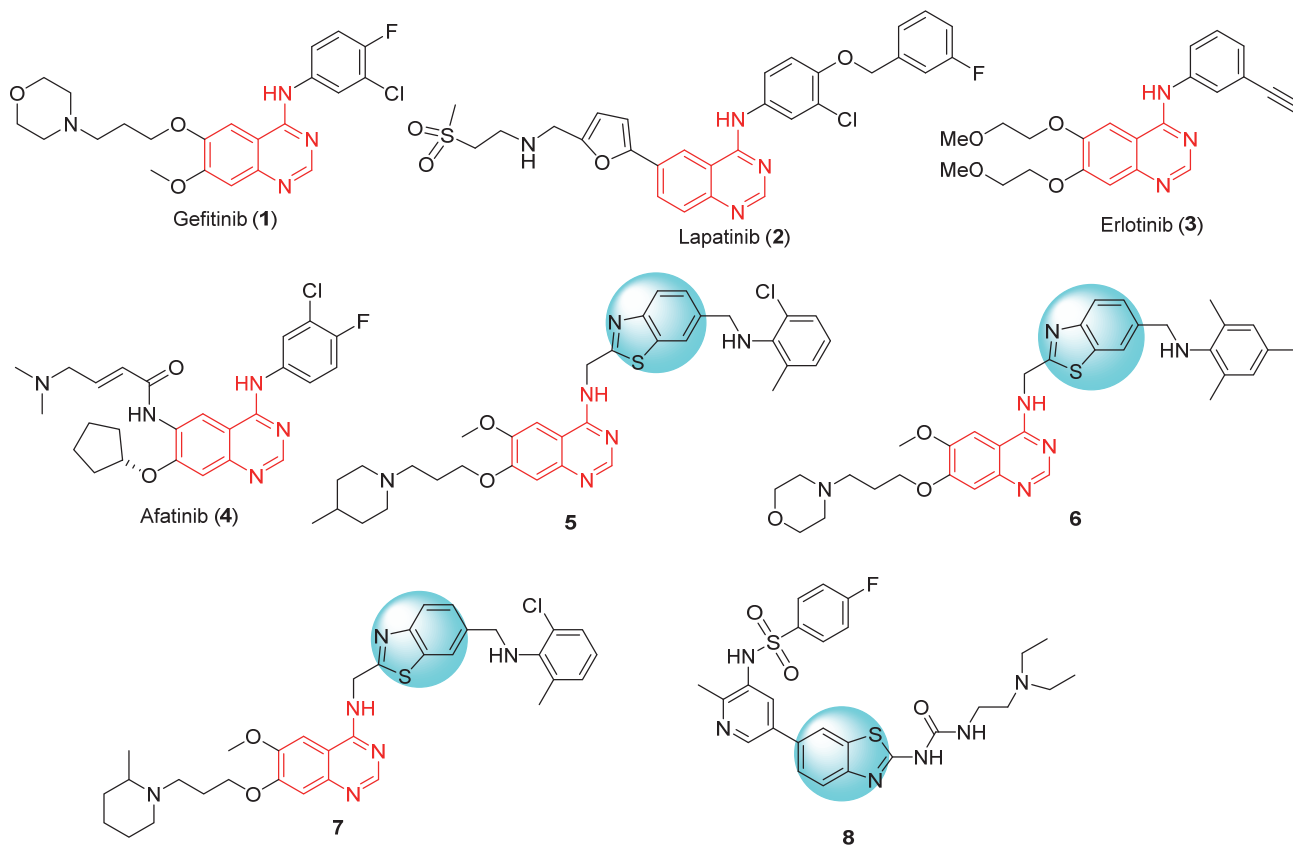
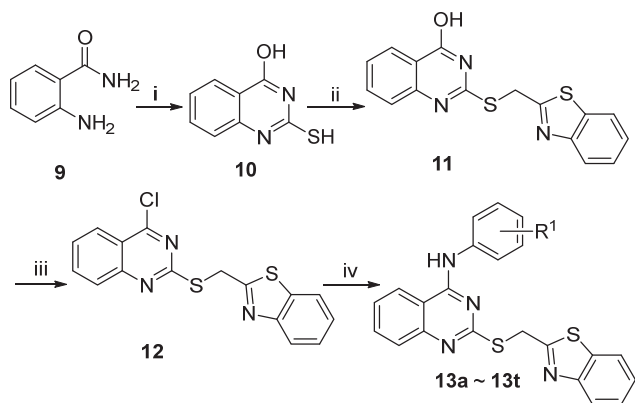


Figure 1 Structures of some 4-aminoquinazoline derivatives and derivatives containing benzothiazole

tion in the mixture of H₂O and acetone at 90 °C. Next, phosphorus oxychloride was added to compound **11** and the temperature was slowly raised to 70 °C and kept for 1 h to obtain compound **12**. Finally, compound **12** and appropriate anilines were added to *N,N*-dimethylformamide (DMF) and the temperature was raised to 90 °C for 2 h to get the target compounds **13a**~**13t**. The structures of target compounds were confirmed by ¹H NMR, ¹³C NMR and HRMS.



Reagents and conditions: (i) KOH, CS₂, EtOH, 90 °C, 24 h; (ii) KOH, H₂O, 2-(chloromethyl)benzothiazole, 90 °C, 1 h; (iii) POCl₃, 70 °C, 1 h; (iv) different anilines, *N,N*-dimethylformamide, 90 °C, 2 h.

Scheme 1 Synthesis of compounds **13a**~**13t**

2.2 Anti-tumor activity

In order to explore the antiproliferative activity of the

target compounds, compounds **13a**~**13t** were evaluated against four human cancer cell lines including human breast cancer cell line (MCF-7), human gastric carcinoma cell line (MGC-803), human prostate cancer cell line (PC-3), human gastric carcinoma cell line (HGC-27) by using MTT assay. Gefitinib was employed as the positive control. The results are shown in Table 1.

In order to explore the structure-activity relationship, different substituents were introduced to quinazoline scaffold. As shown in Table 1, the majority of the compounds exhibited moderate to potent antiproliferative activity against four human cancer cell lines. Most of the target compounds exerted moderate cytotoxic activity against PC-3 and HGC-27 cell lines. However, most of the target compounds showed moderate to low cytotoxicity against MCF-7 and MGC-803 cell lines. Among all the target compounds, compound **13n** showed the best cytotoxicity against the tested cell lines (MCF-7, PC-3, HGC-27 and MGC-803) with IC₅₀ values of (6.0±0.5), (7.6±0.4), (6.1±0.3), (7.6±0.7) μmol·L⁻¹, which was better than gefitinib.

Comparing **13a**, **13b**, **13e**, **13j**, **13n**, **13o** with **13f**, **13g**, **13h**, **13i**, **13p**, we concluded that compounds with electron-withdrawing groups at R¹ of benzene exhibited better cytotoxicity than compounds with electron-donating groups. Comparing **13a**, **13b**, **13d** with **13e**, **13j**, **13k**, the results indicated that electron-withdrawing groups at 4-position of benzene was favorable for the antitumor activity. From the biological data of compounds **13r**~**13t**, the

Table 1 Antiproliferative activity [IC₅₀/(μmol·L⁻¹)] of target compounds **13a**~**13t** against four cancer cell lines^a

Compd.	R ¹	MCF-7	MGC-803	PC-3	HGC-27
13a	4-Cl	19.05±1.28	8.30±0.92	20.12±1.01	8.49±0.92
13b	3-Cl	27.67±1.44	>50	10.78±1.03	21.44±1.42
13c	H	>50	25.84±1.20	24.42±1.15	22.52±1.35
13d	2-Cl	>50	>50	8.84±0.64	>50
13e	4-F	20.66±1.31	9.55±0.98	10.34±1.01	16.62±1.21
13f	2-OCH ₃	>50	>50	>50	>50
13g	2-OCH ₂ CH ₃	>50	>50	49.92±1.69	>50
13h	4-OCH ₂ CH ₃	>50	>50	19.78±1.29	>50
13i	4-OCH ₃	>50	>50	15.024±1.177	>50
13j	3-F	47.45±1.67	14.18±1.20	8.77±0.34	10.20±1.00
13k	2-F	>50	>50	14.42±1.15	13.24±1.12
13l	3-OCH ₃	37.40±1.57	>50	13.64±1.14	18.76±1.27
13m	2-CH ₂ CH ₃	>50	12.66±1.10	17.16±1.10	12.54±1.09
13n	3-Cl-4-F	6.01±0.54	7.63±0.48	6.16±0.34	7.59±0.62
13o	3-CF ₃	11.71±1.06	9.47±0.97	19.64±0.74	7.80±0.89
13p	3,4,5-(OCH ₃) ₃	>50	>50	18.28±1.26	36.71±156
13q	4-CH ₂ CH ₃	>50	>50	14.99±1.17	23.77±1.37
13r	2-CH ₃	>50	13.57±1.11	9.98±1.02	15.42±1.18
13s	3-CH ₃	>50	>50	17.45±1.23	22.42±1.35
13t	4-CH ₃	>50	14.23±1.15	17.49±1.24	18.88±1.27
Gefitinib ^b	—	7.34±0.86	8.82±0.63	7.99±0.54	12.44±0.87

^a Antiproliferative was assayed by exposure for 72 h to substances and expressed as concentration required to inhibit tumor cells proliferation by 50% (IC₅₀). ^b Used as a positive control.

results revealed that the methyl at 2-position of benzene had better cytotoxic activity for cancer cells than that at 3- or 4-position.

2.3 Molecular modeling

In order to predict the possible binding mode of this series of compounds with EGFR, molecular docking was performed using MOE 2014. EGFR (PDB code: 2ITO) was retrieved from the Protein Data Bank (<http://www.rcsb.org/pdb>) for the docking calculations. Based on the anti-proliferative activity results, compound **13n** (the most potent compound) was selected as ligand. The docking study of compound **13n** with EGFR protein was performed using gefitinib as positive controls (Figure 2). In the binding model, comparing Figure 2A with 2B, compound **13n** can bind to Met793 (0.371 nm) residue by hydrogen bonds and formed π -H interaction with Leu718 (0.365 nm), which is similar to the binding site of gefitinib in EGFR domain. The result suggests that compound **13n** may be a valuable lead compound.

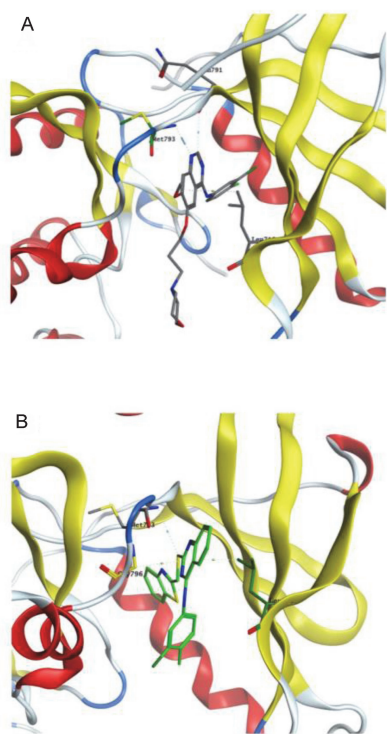


Figure 2 Predicted binding model of (A) gefitinib and (B) compound **13n** with EGFR (selected residues MET793 in EGFR are shown, Dashed lines indicate hydrogen bonds)

3 Conclusion

In conclusion, a series of novel 4-aminoquinazoline quinazolines containing benzothiazole were synthesized and their cytotoxic activity against MCF-7, MGC-803 and PC-3, HGC-27 cells was evaluated by using MTT assay. Among all the tested compounds, compound **13n** showed the most potent anti-proliferative activity against the tested cells. Molecular docking showed that compound **13n** could

bind well with EGFR, suggesting that compound **13n** might be a valuable lead compound. This work provided clues to discover antitumor agent based on the quinazoline scaffold.

4 Experimental

4.1 Materials

Reagents and solvents were purchased from commercial sources and were used without further purification. Column chromatography was carried out on 200~300 mesh silica gel (Qingdao Haiyang Chemical, China). Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silicagel plates (GF254) and visualized under UV light. Melting points were determined on an X-5 micro-melting apparatus and were uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz and 101 MHz spectrometer, respectively. High resolution mass spectra (HRMS) of all derivatives were recorded on a Waters Micro-mass Q-T of Micro-mass spectrometer by electrospray ionization (ESI).

4.2 Chemistry

4.2.1 Synthesis of 2-mercapto-4-hydroxyquinazoline (**10**)

Compound **10** was synthesized according to the published literature^[38] and the characterization data was consistent with the literature.

4.2.2 Synthesis of 2-((benzo[d]thiazol-2-ylmethyl)-thio)quinazolin-4-o-l (**11**)

Compound **10** (0.01 mol) was dissolved in 50 mL of aqueous solution of KOH (0.01 mmol) at room temperature. 2-(Chloromethyl)benzothiazole (0.012 mol) was dissolved in acetone (10 mL) and the solution was added slowly to the above reaction, then the temperature was raised to 90 °C for 1 h, the reaction was completed (TLC detection reaction). The reaction solution was cooled to room temperature. Then, the precipitate was collected by filtration, washed three times with water and acetone and dried in vacuo to give compound **11** as white solid (yield 75%). m.p. 165~166 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 12.80 (s, 1H), 8.05 (dd, $J=14.5$, 7.4 Hz, 2H), 7.97 (d, $J=6.7$ Hz, 1H), 7.84~7.77 (m, 1H), 7.61 (d, $J=8.1$ Hz, 1H), 7.53~7.44 (m, 2H), 7.42 (dd, $J=11.2$, 4.0 Hz, 1H), 4.98 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 174.3, 168.2, 161.1, 154.1, 152.2, 148.0, 135.3, 134.8, 126.2, 126.1, 126.0, 125.3, 122.4, 122.2, 120.0, 31.5.

4.2.3 Synthesis of 2-(((4-chloroquinazolin-2-yl)thio)-methyl)benzo[d]-thiazole (**12**)

Compound **11** (0.01 mol) was added to a 25 mL round bottom flask, followed by addition of phosphorus oxychloride (0.08 mol), then the temperature was raised to 70 °C for 1 h. The reaction system was cooled to room temperature, and added to the stirred ice water mixture. The precipitate was collected by filtration and washed three times with water, dried to give compound **12** as yellow solid, yield 77%. m.p. 169~170 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 8.05 (dd, $J=14.5$, 7.4 Hz, 2H), 7.97 (d, $J=8.1$ Hz,

1H), 7.84~7.77 (m, 1H), 7.61 (d, $J=8.1$ Hz, 1H), 7.54~7.44 (m, 2H), 7.42 (dd, $J=11.2, 4.0$ Hz, 1H), 4.98 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 174.3, 168.2, 161.10, 154.1, 152.2, 148.0, 135.3, 134.8, 126.2, 126.1, 126.0, 125.3, 122.4, 122.2, 120.0, 31.5.

4.2.4 General procedure for synthesis of target compounds **13a**~**13t**

Compound **12** (0.35 mmol) was dissolved in 4 mL of DMF at room temperature. Then, aniline (0.39 mmol) was added dropwise to the above system. The reaction was carried out at 90 °C for 2 h. After the reaction was completed (TLC detection reaction), it was cooled to room temperature. An appropriate amount of water was added to the system to get white solid. The precipitate was collected by filtration. Next, crude compound was subjected to column chromatography (petroleum ether/ethyl acetate, $V:V=3:1$). Concentrated eluent to give solid compounds **13a**~**13t**.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(4-chlorophenyl)-quinazolin-4-amine (**13a**): White solid, yield 56%. m.p. 166~167 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 10.03 (s, 1H), 8.49 (d, $J=8.2$ Hz, 1H), 7.97 (t, $J=8.9$ Hz, 2H), 7.87~7.78 (m, 3H), 7.70 (d, $J=8.3$ Hz, 1H), 7.55 (dd, $J=11.2, 4.1$ Hz, 1H), 7.51~7.46 (m, 1H), 7.39 (dd, $J=15.4, 8.4$ Hz, 3H), 4.87 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.1, 164.3, 157.2, 152.6, 150.0, 137.5, 135.1, 133.8, 128.3, 127.8, 126.4, 126.1, 125.4, 125.0, 124.1, 123.3, 122.3, 122.1, 113.2, 32.3; HRMS calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 435.0505, found 435.0507.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3-chlorophenyl)-quinazolin-4-amine (**13b**): White solid, yield 51%. m.p. 136~137 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 10.05 (s, 1H), 8.51 (d, $J=8.2$ Hz, 1H), 8.04~7.93 (m, 3H), 7.86 (t, $J=7.6$ Hz, 1H), 7.79 (d, $J=8.1$ Hz, 1H), 7.71 (d, $J=8.2$ Hz, 1H), 7.58 (t, $J=7.6$ Hz, 1H), 7.48 (t, $J=7.6$ Hz, 1H), 7.39 (q, $J=7.9$ Hz, 2H), 7.19 (d, $J=7.0$ Hz, 1H), 4.90 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 169.7, 164.2, 157.22, 152.5, 150.1, 140.1, 135.2, 133.9, 132.8, 130.1, 126.5, 126.1, 125.5, 125.0, 123.7, 123.3, 122.3, 122.0, 121.9, 120.7, 113.2, 32.2; HRMS calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 435.0505, found 435.0502.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-phenylquinazolin-4-amine (**13c**): White solid, yield 50%. m.p. 159~160 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 9.97 (s, 1H), 8.51 (d, $J=8.2$ Hz, 1H), 7.96 (dd, $J=7.9, 4.7$ Hz, 2H), 7.82 (t, $J=7.6$ Hz, 1H), 7.75 (d, $J=7.9$ Hz, 2H), 7.68 (d, $J=8.2$ Hz, 1H), 7.54 (t, $J=7.6$ Hz, 1H), 7.47 (t, $J=7.7$ Hz, 1H), 7.37 (t, $J=7.8$ Hz, 3H), 7.14 (t, $J=7.4$ Hz, 1H), 4.87 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.1, 164.3, 157.4, 152.6, 150.1, 138.5, 135.2, 133.6, 128.5, 126.4, 126.1, 125.3, 125.0, 124.2, 123.4, 122.7, 122.3, 122.0, 113.3, 32.2; HRMS calcd for $\text{C}_{22}\text{H}_{17}\text{N}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 401.0895, found 401.0892.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(2-chlorophenyl)-quinazolin-4-amine (**13d**): White solid, yield 54%. m.p. 176~177 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 10.12 (s,

1H), 8.45 (d, $J=8.2$ Hz, 1H), 7.94 (s, 2H), 7.85 (t, $J=7.6$ Hz, 1H), 7.70 (t, $J=8.3$ Hz, 1H), 7.55 (d, $J=7.7$ Hz, 3H), 7.48 (d, $J=7.9$ Hz, 1H), 7.39 (s, 2H), 7.36~7.33 (m, 1H), 4.72 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 169.9, 164.4, 158.4, 152.4, 150.1, 135.2, 135.1, 133.9, 130.9, 129.7, 129.6, 128.1, 127.6, 126.3, 126.0, 125.4, 125.0, 123.3, 122.3, 121.9, 112.8, 32.0; HRMS calcd for $\text{C}_{22}\text{H}_{16}\text{ClN}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 435.0505, found 435.0504.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(4-fluorophenyl)-quinazolin-4-amine (**13e**): White solid, yield 54%. m.p. 129~130 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 10.01 (s, 1H), 8.49 (d, $J=8.2$ Hz, 1H), 7.97 (t, $J=7.6$ Hz, 2H), 7.83 (t, $J=7.6$ Hz, 1H), 7.76 (dd, $J=8.9, 5.0$ Hz, 2H), 7.69 (d, $J=8.2$ Hz, 1H), 7.55 (t, $J=7.6$ Hz, 1H), 7.49 (t, $J=7.7$ Hz, 1H), 7.38 (t, $J=7.6$ Hz, 1H), 7.21 (t, $J=8.8$ Hz, 2H), 4.86 (s, 2H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.1, 164.3, 159.9 (d, $J=256.5$ Hz), 152.6, 150.0, 135.2, 134.8 (d, $J=3.0$ Hz), 133.7, 126.4, 126.1, 125.3, 125.0, 124.8 (d, $J=8.1$ Hz), 123.3, 122.3, 122.0, 115.2, 115.0, 113.1, 32.3; HRMS calcd for $\text{C}_{22}\text{H}_{16}\text{FN}_4\text{S}_2$ $[\text{M}+\text{H}]^+$ 419.0800, found 419.0802.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(2-methoxyphenyl)quinazolin-4-amine (**13f**): White solid, yield 51%. m.p. 144~145 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 9.65 (s, 1H), 8.44 (d, $J=7.8$ Hz, 1H), 7.95 (dd, $J=13.9, 7.8$ Hz, 2H), 7.84~7.78 (m, 1H), 7.66 (d, $J=7.7$ Hz, 1H), 7.55~7.45 (m, 3H), 7.40~7.35 (m, 1H), 7.27~7.22 (m, 1H), 7.11 (dd, $J=8.3, 1.0$ Hz, 1H), 6.97 (td, $J=7.6, 1.2$ Hz, 1H), 4.75 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.0, 164.5, 158.2, 153.6, 152.4, 150.0, 135.2, 133.5, 127.3, 127.0, 126.4, 126.3, 126.0, 125.2, 125.0, 123.3, 122.3, 122.0, 120.2, 113.1, 111.9, 55.6, 32.1; HRMS calcd for $\text{C}_{23}\text{H}_{19}\text{N}_4\text{OS}_2$ $[\text{M}+\text{H}]^+$ 431.1000, found 431.0998.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(2-ethoxyphenyl)quinazolin-4-amine (**13g**): White solid, yield 47%. m.p. 127~128 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 9.61 (s, 1H), 8.40 (d, $J=6.4$ Hz, 1H), 7.94 (s, 2H), 7.82 (s, 1H), 7.68 (s, 1H), 7.51 (d, $J=26.6$ Hz, 3H), 7.38 (s, 1H), 7.22 (s, 1H), 7.10 (s, 1H), 6.96 (s, 1H), 4.77 (s, 2H), 4.03 (d, $J=5.9$ Hz, 2H), 1.19 (s, 3H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.0, 164.4, 158.0, 152.7, 152.4, 149.8, 135.2, 133.5, 126.9, 126.2, 126.0, 125.4, 125.3, 125.0, 124.5, 123.2, 122.3, 122.0, 120.2, 113.1, 113.0, 63.8, 32.1, 14.6; HRMS calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{OS}_2$ $[\text{M}+\text{H}]^+$ 445.1157, found 445.1156.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(4-ethoxyphenyl)quinazolin-4-amine (**13h**): White solid, yield 50%. m.p. 150~151 °C; ^1H NMR (DMSO- d_6 , 400 MHz) δ : 9.89 (s, 1H), 8.47 (d, $J=8.2$ Hz, 1H), 7.97 (dd, $J=15.4, 6.5$ Hz, 2H), 7.81 (t, $J=7.3$ Hz, 1H), 7.66 (d, $J=8.1$ Hz, 1H), 7.59 (d, $J=9.0$ Hz, 2H), 7.55~7.46 (m, 2H), 7.39 (dd, $J=11.1, 4.0$ Hz, 1H), 6.92 (t, $J=6.1$ Hz, 2H), 4.85 (s, 2H), 4.01 (q, $J=6.9$ Hz, 2H), 1.33 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (DMSO- d_6 , 101 MHz) δ : 170.2, 164.4, 157.4, 155.4, 152.6, 149.9, 135.2, 133.5, 131.1, 126.3, 126.0, 125.1, 125.0, 124.5, 123.3, 122.3, 122.0, 114.1, 113.2, 63.1, 32.2, 14.6; HRMS calcd for $\text{C}_{24}\text{H}_{21}\text{N}_4\text{OS}_2$ $[\text{M}+\text{H}]^+$ 445.1157, found

445.1154.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(4-methoxyphenyl)quinazolin-4-amine (**13i**): White solid, yield 54%. m.p. 152~153 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.91 (s, 1H), 8.47 (d, *J*=8.2 Hz, 1H), 7.96 (t, *J*=7.4 Hz, 2H), 7.80 (t, *J*=7.3 Hz, 1H), 7.66 (d, *J*=8.1 Hz, 1H), 7.61 (d, *J*=9.0 Hz, 2H), 7.53~7.49 (m, 1H), 7.49~7.45 (m, 1H), 7.36 (dd, *J*=11.5, 4.5 Hz, 1H), 6.92 (d, *J*=9.0 Hz, 2H), 4.84 (s, 2H), 3.75 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 170.2, 164.4, 157.4, 156.1, 152.6, 149.9, 135.2, 133.5, 131.2, 126.3, 126.1, 125.1, 125.0, 124.5, 123.3, 122.3, 122.0, 113.6, 113.2, 55.2, 32.2; HRMS calcd for C₂₃H₁₉N₄OS₂ [M+H]⁺ 431.1000, found 431.1003.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3-fluorophenyl)quinazolin-4-amine (**13j**): White solid, yield 54%. m.p. 148~149 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.07 (s, 1H), 8.53 (d, *J*=8.1 Hz, 1H), 7.97 (t, *J*=8.6 Hz, 2H), 7.86 (dd, *J*=11.2, 4.1 Hz, 1H), 7.83~7.78 (m, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 7.65 (dd, *J*=8.2, 1.1 Hz, 1H), 7.61~7.56 (m, 1H), 7.51~7.46 (m, 1H), 7.45~7.36 (m, 2H), 6.98 (td, *J*=8.4, 2.2 Hz, 1H), 4.91 (s, 2H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.7, 164.2, 163.12 (d, *J*=242.4 Hz), 157.2, 152.5, 150.0, 135.2, 133.8, 130.0 (d, *J*=9.1 Hz), 126.4, 126.1, 125.5, 125.0, 123.4, 122.3, 122.0, 118.0, 117.9, 113.2, 110.6 (d, *J*=21.2 Hz), 109.2, 32.2; HRMS calcd for C₂₂H₁₆FN₄S₂ [M+H]⁺ 419.0800, found 419.0802.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(2-fluorophenyl)quinazolin-4-amine (**13k**): White solid, yield 52%. m.p. 177~178 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.07 (s, 1H), 8.45 (d, *J*=7.9 Hz, 1H), 7.98~7.92 (m, 2H), 7.88~7.83 (m, 1H), 7.70 (d, *J*=7.8 Hz, 1H), 7.55 (td, *J*=8.3, 1.1 Hz, 2H), 7.50~7.46 (m, 1H), 7.40~7.36 (m, 1H), 7.35~7.29 (m, 2H), 7.26~7.21 (m, 1H), 4.76 (s, 2H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.8, 164.4, 158.2 (d, *J*=265.6 Hz), 152.4, 150.0, 135.2, 133.8, 128.4, 127.8 (d, *J*=8.1 Hz), 126.3, 126.0, 125.6, 125.5, 125.4, 125.0, 124.4 (d, *J*=3.0 Hz), 123.4, 122.3, 122.0, 116.1 (d, *J*=20.2 Hz), 112.9, 32.1; HRMS calcd for C₂₂H₁₆FN₄S₂ [M+H]⁺ 419.0800, found 419.0803.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3-methoxyphenyl)quinazolin-4-amine (**13l**): White solid, yield 48%. m.p. 147~148 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.94 (s, 1H), 8.53 (d, *J*=8.1 Hz, 1H), 7.97 (t, *J*=7.6 Hz, 2H), 7.83 (d, *J*=7.2 Hz, 1H), 7.71 (d, *J*=7.9 Hz, 1H), 7.56 (t, *J*=7.6 Hz, 1H), 7.52~7.46 (m, 2H), 7.41 (t, *J*=8.1 Hz, 2H), 7.28 (t, *J*=8.1 Hz, 1H), 6.74 (dd, *J*=8.1, 2.0 Hz, 1H), 4.90 (s, 2H), 3.78 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.9, 164.3, 159.3, 157.3, 152.5, 150.0, 139.7, 135.2, 133.7, 129.2, 126.4, 126.1, 125.3, 125.0, 123.3, 122.3, 122.0, 114.7, 113.3, 109.7, 108.2, 55.0, 32.2; HRMS calcd for C₂₃H₁₉N₄OS₂ [M+H]⁺ 431.1000, found 431.1002.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(2-ethylphenyl)quinazolin-4-amine (**13m**): White solid, yield 49%. m.p. 75~76 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.92 (s, 1H), 8.47 (d, *J*=8.2 Hz, 1H), 7.94 (dd, *J*=12.9, 8.0 Hz, 2H), 7.82 (t, *J*=7.6 Hz, 1H), 7.67 (d, *J*=8.2 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 1H), 7.47 (t, *J*=7.3 Hz, 1H), 7.38 (t, *J*=7.4 Hz,

1H), 7.33~7.29 (m, 2H), 7.24 (dd, *J*=15.4, 7.5 Hz, 2H), 4.70 (s, 2H), 2.54 (dd, *J*=15.1, 7.5 Hz, 2H), 1.05 (t, *J*=7.5 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.9, 164.6, 158.8, 152.4, 149.8, 140.6, 135.8, 135.2, 133.6, 128.6, 128.2, 127.1, 126.2, 126.0, 125.2, 124.9, 123.3, 122.3, 121.9, 112.9, 54.9, 32.0, 24.0, 14.0; HRMS calcd for C₂₄H₂₁N₄S₂ [M+H]⁺ 429.1208, found 429.1208.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3-chloro-4-fluorophenyl)quinazolin-4-amine (**13n**): White solid, yield 45%. m.p. 199~200 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.07 (s, 1H), 8.47 (d, *J*=8.1 Hz, 1H), 8.08 (dd, *J*=6.8, 2.6 Hz, 1H), 7.96 (dd, *J*=12.4, 8.0 Hz, 2H), 7.85 (t, *J*=7.6 Hz, 1H), 7.77 (ddd, *J*=9.0, 4.2, 2.7 Hz, 1H), 7.71 (d, *J*=8.0 Hz, 1H), 7.57 (t, *J*=7.6 Hz, 1H), 7.50~7.46 (m, 1H), 7.42~7.36 (m, 2H), 4.88 (s, 2H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.7, 164.2, 159.6 (d, *J*=238.4 Hz), 152.5, 150.0, 140.4, 135.2, 133.8, 126.5, 126.1, 125.5, 125.0, 124.2, 123.3, 123.0, 122.9, 122.3, 122.0, 116.6 (d, *J*=21.2 Hz), 115.8, 113.1, 32.2; HRMS calcd for C₂₂H₁₅ClFN₄S₂ [M+H]⁺ 453.0411, found 453.0411.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3-(trifluoromethyl)phenyl)quinazolin-4-amine (**13o**): White solid, yield 48%. m.p. 104~105 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 10.20 (s, 1H), 8.54 (d, *J*=8.3 Hz, 1H), 8.30 (s, 1H), 8.15 (d, *J*=8.2 Hz, 1H), 7.96 (t, *J*=7.6 Hz, 2H), 7.87 (t, *J*=7.6 Hz, 1H), 7.73 (d, *J*=8.2 Hz, 1H), 7.61 (dt, *J*=10.9, 7.8 Hz, 2H), 7.48 (t, *J*=7.4 Hz, 2H), 7.38 (t, *J*=7.6 Hz, 1H), 4.90 (s, 2H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.6, 164.2, 157.3, 152.4, 150.1, 139.5, 135.2, 133.9, 129.6, 129.4, 129.1, 126.5, 126.1, 125.9, 125.5, 125.0, 123.3, 122.3, 122.0, 120.2, 118.6, 113.2, 32.2; HRMS calcd for C₂₃H₁₆F₃N₄S₂ [M+H]⁺ 469.0768, found 469.0769.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(3,4,5-trimethoxyphenyl)quinazolin-4-amine (**13p**): White solid, yield 53%. m.p. 172~173 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.87 (s, 1H), 8.51 (dd, *J*=8.5, 1.3 Hz, 1H), 7.98~7.93 (m, 2H), 7.84 (ddd, *J*=8.3, 6.9, 1.3 Hz, 1H), 7.70 (dd, *J*=8.4, 1.2 Hz, 1H), 7.60~7.54 (m, 1H), 7.48 (ddd, *J*=8.3, 7.2, 1.3 Hz, 1H), 7.38 (td, *J*=7.6, 7.2, 1.2 Hz, 1H), 7.28 (s, 2H), 4.90 (s, 2H), 3.80 (s, 6H), 3.66 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.6, 164.3, 157.2, 152.5, 152.3, 149.9, 135.2, 134.6, 134.2, 133.6, 126.5, 126.0, 125.3, 125.0, 123.2, 122.3, 122.0, 113.3, 100.5, 60.1, 55.8, 32.2; HRMS calcd for C₂₅H₂₃N₄O₃S₂ [M+H]⁺ 491.1212, found 491.1210.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(4-ethylphenyl)quinazolin-4-amine (**13q**): White solid, yield 53%. m.p. 127~128 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.99 (s, 1H), 8.53 (d, *J*=8.1 Hz, 1H), 7.97 (t, *J*=7.5 Hz, 2H), 7.81 (dd, *J*=11.2, 4.1 Hz, 1H), 7.70~7.63 (m, 3H), 7.51 (ddd, *J*=15.4, 8.2, 1.1 Hz, 2H), 7.41~7.35 (m, 1H), 7.18 (d, *J*=8.5 Hz, 2H), 4.87 (s, 2H), 2.59 (q, *J*=7.6 Hz, 2H), 1.17 (t, *J*=7.6 Hz, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 170.2, 164.4, 157.4, 152.6, 150.0, 139.7, 136.2, 135.2, 133.5, 127.6, 126.3, 126.0, 125.2, 125.0, 123.4, 122.8, 122.3, 122.0, 113.3, 32.2, 27.6, 15.6; HRMS calcd for C₂₄H₂₁N₄S₂ [M+H]⁺ 429.1208, found 429.1206.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(*o*-tolyl)quinazolin-4-amine (**13r**): White solid, yield 53%. m.p. 146~147 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.99 (s, 1H), 8.52 (d, *J*=8.2 Hz, 1H), 7.95 (dd, *J*=14.2, 8.0 Hz, 2H), 7.82 (t, *J*=7.6 Hz, 1H), 7.67 (d, *J*=8.2 Hz, 1H), 7.53 (t, *J*=7.5 Hz, 1H), 7.48 (t, *J*=7.5 Hz, 1H), 7.38 (p, *J*=7.5 Hz, 1H), 7.35~7.27 (m, 2H), 7.22 (p, *J*=7.0 Hz, 2H), 4.72 (s, 2H), 2.16 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 169.9, 164.5, 158.4, 152.4, 150.0, 136.5, 135.2, 134.8, 133.5, 130.4, 127.6, 126.6, 126.3, 126.1, 126.0, 125.1, 124.9, 123.5, 122.3, 122.0, 113.0, 32.1, 17.9; HRMS calcd for C₂₃H₁₉N₄S₂ [M+H]⁺ 415.1051, found 415.1052.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(*m*-tolyl)quinazolin-4-amine (**13s**): White solid, yield 48%. m.p. 168~169 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.91 (s, 1H), 8.52 (d, *J*=8.2 Hz, 1H), 8.00~7.93 (m, 2H), 7.83 (t, *J*=7.3 Hz, 1H), 7.68 (d, *J*=8.1 Hz, 1H), 7.61 (s, 1H), 7.56 (dd, *J*=16.2, 8.1 Hz, 2H), 7.48 (dd, *J*=11.2, 4.1 Hz, 1H), 7.38 (t, *J*=7.2 Hz, 1H), 7.25 (t, *J*=7.8 Hz, 1H), 6.97 (d, *J*=7.4 Hz, 1H), 4.89 (s, 2H), 2.30 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 170.0, 164.3, 157.4, 152.5, 150.1, 138.4, 137.7, 135.2, 133.6, 128.3, 126.4, 126.1, 125.2, 125.0, 124.9, 123.3, 123.3, 122.3, 122.0, 119.9, 113.3, 32.2, 21.0; HRMS calcd for C₂₃H₁₉N₄S₂ [M+H]⁺ 415.1051, found 415.1053.

2-((Benzo[d]thiazol-2-ylmethyl)thio)-*N*-(*p*-tolyl)quinazolin-4-amine (**13t**): White solid, yield 52%. m.p. 150~151 °C; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 9.92 (s, 1H), 8.50 (d, *J*=8.1 Hz, 1H), 7.97 (t, *J*=7.5 Hz, 2H), 7.81 (dd, *J*=11.2, 4.0 Hz, 1H), 7.68 (d, *J*=7.9 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 2H), 7.56~7.51 (m, 1H), 7.49 (dd, *J*=11.7, 4.7 Hz, 1H), 7.38 (dd, *J*=11.5, 4.6 Hz, 1H), 7.17 (d, *J*=8.3 Hz, 2H), 4.87 (s, 2H), 2.30 (s, 3H); ¹³C NMR (DMSO-*d*₆, 101 MHz) δ: 170.2, 164.4, 157.4, 152.6, 150.0, 135.8, 135.2, 133.6, 133.4, 128.9, 126.4, 126.1, 125.2, 125.0, 123.3, 122.8, 122.3, 122.1, 113.3, 32.2, 20.5; HRMS calcd for C₂₃H₁₉N₄S₂ [M+H]⁺ 415.1051, found 415.1052.

4.2.5 Cell culture and treatment

Human cancer cells MCF-7, MGC-803 and PC-3, HGC-27 was purchased from the China Center for Type Culture Collection and maintained in RPMI-1640 and DMEM complete medium at 37 °C in a humidified atmosphere with CO₂ in 5% volume ratio.

4.2.6 MTT assay

Cells in the logarithmic growth phase were seeded in 96-well plates at 3000~5000 cells per well. After the cells were cultured for 24 h, different concentrations of compounds **13a**~**13t** were treated for 72 h, respectively. MTT was added to each well at a final concentration of 0.5 mg/mL. After 4 h in a 37 °C incubator, the medium was aspirated. 150 μL of dimethyl sulfoxide (DMSO) was then added to each well to dissolve the formazan, and the plate was shaken on a shaker for 10 min. The absorbance was measured by an enzyme-linked immunosorbent assay reader (BioTek, USA) at a wavelength of 490 nm, and the cell survival rate was measured. Viability rate = Abs 490

treated cells/Abs 490 control cells × 100%. The concentration-response curve generated by SPSS 16.0 software was used to determine the concentration of compound (IC₅₀) required to inhibit cell growth by 50%. Cell viability curves were generated using GraphPad Prism 7.0 software at various concentrations of all compounds. Results were Mean ± SD of three independent experiments.

Supporting Information ¹H NMR and ¹³C NMR spectra of compounds **11**, **12** and **13a**~**13t**. The Supporting Information is available free of charge via the Internet at <http://sioc-journal.cn>.

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