Article

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Synthesis and Cytotoxicity in Vitro of *N*-Aryl-4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine

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A series of novel *N*-aryl-4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amines were synthesized in a green way. H_2O_2-NaBr Brominating circulatory system was used in the synthesis of the key intermediate in a mild condition. All of the target compounds were confirmed by ^{1}H NMR and elemental analysis and tested for their cytotoxicity against two different human cancer cell lines. The cytotoxicity assay revealed that some of the title compounds showed moderate to strong cytotoxic activities. Compound **2i** was the most potent compound with the IC_{50} values of 9 μM against *Hela* cells and 15 μM against *Bel–7402* cells, respectively.

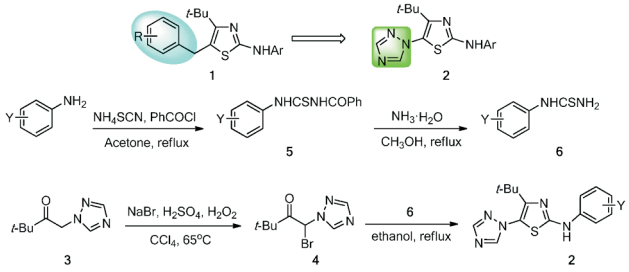
Keywords: Thiazole derivatives; Triazole; Bromination; Synthesis; Cytotoxicity.

INTRODUCTION

Thiazole derivatives, as a class of well known nitrogen-containing heterocyclic compounds, have been studied extensively due to their numerous of pharmacological applications and varied biological activities,[1,2] such as antimicrobial,[3-5] anti-inflammatory,[6] antihypertensive,[7] antifungal,[8-10] antibacterial[11-13] and anti-HIV.[14-16] In recent years, a considerable effort has been made to develop new anti-cancer drugs based on thiazole. U.G. Bhat reported that thiazole antibiotics can induce apoptosis in human cancers.[17] S. Back discovered that 4-aryl-2-substituted aniline-thiazole analogs can inhibit the growth of human prostate cancer *LNCap* cells.[18] Zhengyue Ma found that 1,3-thiazolidin-4-ones have a good inhibitory effect against gastric cancer (*SGC-7901*), cervical cancer cells (*Hela*) and lung cancer cells (*A-549*).[19]

Inspired by these reports, we have previously synthesized various *N*-aryl-5-benzyl-4-(*tert*-butyl)thiazol-2-amines (**1**) and found that they were effective in cytotoxicity.[20] To search for additional promising active compounds, we continued our effort to modify the structure of compound **1** by replacement of the substituted benzyl with triazole. Hereon, several novel *N*-aryl-4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amines (**2**) were synthesized (Scheme 1) and their cytotoxic activities were evaluated against two human cancer cell lines.

Scheme 1 Synthetic route of the target compounds **2**



RESULTS AND DISCUSSION

Chemistry

To the best of our knowledge, this is a new method for the synthesis of 2-aminothiazole. Generally, bromine was used as brominating agent in the synthesis of the key intermediate **4**, but the process was fraught with problems of handling and low atom efficiency of substitution reactions. Although bromination reaction with H_2O_2-NaBr system has been reported,[21-23] there is no a clear way to recycling the bromide which produced from the reaction. Only solving this key issue may reduce the affection to our environment fundamentally. For this reason, we explored H_2O_2-NaBr brominating circulatory system, and the recycling of bromine in the synthesis process of compounds **2** is depicted in Scheme 2. In this system, compound **3** was brominated to α–bromoketones **4** in excellent yield. After work-up, compound **4**, without further purification, was carried forward to react with *N*-arylthiourea in ethanol to

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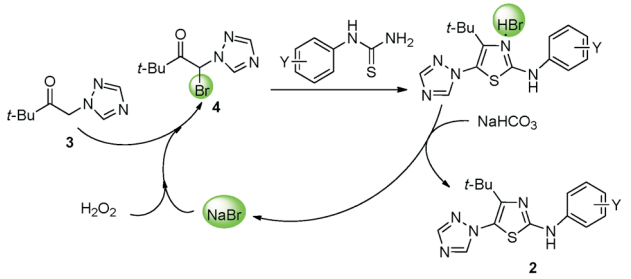
produce *N*-aryl-4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine hydrobromides, which were converted to free-bases **2a-2q** by neutralization with sodium hydrogen carbonate. The overall yield of compounds **2** (based on **3**) is 54-90% (Table 1). At the same time, sodium bromide can be reused as the bromine source in the next run. The H_2O_2-NaBr brominating circulatory system we explored successfully solved the problem of the bromine handling. The process is atom economic and environmental friendly. In addition, all the new compounds were confirmed by ^{1}H NMR spectroscopy and elemental analysis.

Scheme 2 Recycling of bromine in the synthesis of compounds **2**



Cytotoxicity in vitro

The compounds **2a-2q** were tested cytotoxic activities against two cancer cell lines: *Hela* (cervix cancer) and *Bel-7402* (liver cancer), and the IC_{50} values of some active compounds were compared to Cisplatin (Table 2). Compouds **2h**, **2i**, **2o** and **2q** showed moderate to strong cytotoxic activities against *Hela* cell line with IC_{50} values of 25, 9, 25 and 22 μM, respectively, which were close to that of Cisplatin (IC_{50} 20 μM). Meanwhile, they also exhibited potent cytotoxic activities against *Bel-7402* cell line with IC_{50} values of 29, 15, 37 and 33 μM, respectively, which were equivalent to that of Cisplatin (IC_{50} 30 μM). Among them, compound **2i**, with meta-electron-withdrawing group (3-CF_3) on the phenyl ring, is the most potent compound, which may be a good candidate for further study in vitro against a broad panel of human cancer cell lines.

EXPERIMENTAL

Materials and Instruments: All solvents were of reagent grade. All chemicals were analytical reagents and used directly without further purification. Melting point was measured on an X-4 electrothermal digital melting point apparatus and uncorrected. The ^{1}H NMR spectra were recorded on a VARIAN INOVA-400 spectrometer (400 MHz) in $CDCl_3$ with TMS as internal standard. The elemental analysis were carried out on a VARIO EL III instrument.

Synthesis: As described in Scheme 1, compounds **2** were synthesized from the reaction of α–bromoketones (**4**) and *N*-arylthiourea (**6**), while benzoyl arylthiourea (**5**) and *N*-arylthiourea **6** were prepared according to the literature method.[24]

Synthesis of 1-bromo-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-one (4): Sodium bromide (6.6 mmol), water (6.0 mL) and concentrated sulfuric acid (0.3 mL) were added in sequence to a solution of 3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-one (**3**, 6.0 mmol) in CCl_4 (40.0 mL). The mixture was heated to 65 °C, then, 30% hydrogen peroxide (3.6 mL) was

Table 1. The reaction results for the synthesis of compounds **2**

Compd.	Y	m.p. (°C)	Yield (%)
2a	H	187-189	67
2b	4-CH_3	140-141	83
2c	2-CH_3O	128-130	85
2d	2-F	193-195	63
2e	2-Cl	122-124	66
2f	3-Cl	156-159	54
2g	4-Cl	200-202	60
2h	3-Br	148-150	90
2i	3-CF_3	168-170	60
2j	2-NO_2	141-143	58
2k	4-NO_2	229-232	81
2l	2,4-diCH_3	170-172	67
2m	2,6-diCH_3	194-196	86
2n	3,4-diCH_3	166-168	73
2o	3-Cl-4-F	195-198	63
2p	2-Cl-4-NO_2	227-229	74
2q	2,3-CH=CH-CH=CH	145-147	86

Table 2. Cytotoxic activities of selected compounds against *Hela* and *Bel–7402* cells

Compd.	Y	IC_{50} (μM)	
		Hela	*Bel–7402*
2b	4-CH_3	95	ND
2c	2-CH_3O	59	41
2e	2-Cl	75	ND
2h	3-Br	25	29
2i	3-CF_3	9	15
2j	2-NO_2	274	583
2n	3,4-diCH_3	445	687
2o	3-Cl-4-F	25	37
2q	2,3-CH=CH-CH=CH	22	33
Cisplatin		20	30

added dropwise during 2 h. The mixture continued to react for 30 min, poured into $NaHCO_3$ aqueous solution (40.0 mL), and extracted with dichloromethane (3 × 10 mL). The organic phase was washed with saturated NaCl solution, dried over anhydrous Na_2SO_4, and evaporated in vacuum to give compound **4** as an oil.

General procedure for synthesis of *N*-aryl-4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2): A suspension of compound **4** and *N*-arylthiourea **6** (5 mmol) in EtOH (30.0 mL) was heated at reflux (monitored by thin-layer chromatography). Then the mixture was cooled and poured into $NaHCO_3$ aqueous solution. The resultant precipitate was filtered off and purified by recrystallization from ethanol to obtain the target compounds. The filtrate was evaporated to give the recovered sodium bromide, which was reused for the next run. **4-(*tert*-Butyl)-*N*-phenyl-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2a):** Reaction time: 1.0 h, yield: 67%, m.p. 187-189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.83 (bs, 1H), 7.11-7.40 (m, 5H), 8.09 (s, 1H), 8.26 (s, 1H). Anal. Calc. for $C_{15}H_{17}N_5S$: C, 60.18, H, 5.72, N, 23.39 found: C, 60.25, H, 5.73, N 23.42. **4-(*tert*-Butyl)-*N*-(4-methylphenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2b):** Reaction time: 1.0 h, yield: 83%, m.p. 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 2.34 (s, 3H), 7.17 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 8.8 Hz, 2H), 8.08 (s, 1H), 8.24(s, 1H). Anal. Calc. for $C_{16}H_{19}N_5S$: C, 61.31, H, 6.11, N, 22.34 found: C, 61.37, H, 6.11, N, 22.30. **4-(*tert*-Butyl)-*N*-(2-methoxyphenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2c):** Reaction time: 1.0 h, yield: 85%, m.p. 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 3.92 (s, 3H), 6.92 (dd, *J* = 2.0 Hz, *J* = 7.6 Hz, 1H), 6.97-7.03 (m, 2H), 7.70 (bs, 1H), 7.93 (dd, *J* = 2.0 Hz, *J* = 7.6 Hz, 1H), 8.09 (s, 1H), 8.25 (s, 1H). Anal. Calc. for $C_{16}H_{19}N_5OS$: C, 58.34, H, 5.81, N, 21.26 found: C, 58.26, H, 5.80, N, 21.29. **4-(*tert*-Butyl)-*N*-(2-fluorophenyl)-5-(1*H*-1,2,4-triazol-1-yl) thiazol-2-amine (2d):** Reaction time: 5.0 h, yield: 63%, m.p. 193-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 7.03-7.30 (m, 3H), 8.22 (s, 1H), 8.42 (t, *J* = 8.0 Hz, 1H), 8.93 (s, 1H), 10.17 (bs, 1H). Anal. Calc. for $C_{15}H_{16}FN_5S$: C, 56.76, H, 5.08, N, 22.07 found: C, 56.81, H, 5.08, N, 22.02. **4-(*tert*-Butyl)-*N*-(2-chlorophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2e):** Reaction time: 2.0 h, yield: 66%, m.p. 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 7.02 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 7.52 (bs, 1H), 8.08 (dd, *J* = 1.6 Hz, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 8.27 (s, 1H). Anal. Calc. for $C_{15}H_{16}ClN_5S$: C, 53.97, H, 4.83, N, 20.98 found: C, 54.05, H, 4.83, N, 20.94. **4-(*tert*-Butyl)-*N*-(3-chlorophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2f):** Reaction time: 1.5 h, yield: 54%, m.p. 156-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 7.03-7.06 (m, 1H), 7.22-7.29 (m, 2H), 7.50-7.51 (m, 1H), 7.62 (bs, 1H), 8.11 (s, 1H), 8.28 (s, 1H). Anal. Calc. for $C_{15}H_{16}ClN_5S$: C, 53.97, H, 4.83, N, 20.98 found: C, 53.91, H, 4.83, N, 21.02. **4-(*tert*-Butyl)-*N*-(4-chlorophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2g):** Reaction time: 1.0 h, yield: 60%, m.p. 200-202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 7.33 (m, 4H), 8.09 (s, 1H), 8.26 (s, 1H). Anal. Calc. for $C_{15}H_{16}ClN_5S$: C, 53.97, H, 4.83, N, 20.98 found: C, 54.02, H, 4.83, N, 20.95. **4-(*tert*-Butyl)-*N*-(3-bromophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2h):** Reaction time: 1.0 h, yield: 90%, m.p. 148-150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 7.17 (bs, 1H), 7.21-7.28 (m, 3H), 7.64 (d, *J* = 1.2 Hz, 1H), 8.09 (s, 1H), 8.26 (s, 1H). Anal. Calc. for $C_{15}H_{16}BrN_5S$: C, 47.62, H, 4.26, N, 18.51 found: C, 47.58, H, 4.27, N, 18.54. **4-(*tert*-Butyl)-5-(1*H*-1,2,4-triazol-1-yl)-*N*-(3-(trifluorometh-yl)phenyl) thiazol-2-amine (2i):** Reaction time: 1.5 h, yield: 60%, m.p. 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 7.32-7.56 (m, 4H), 7.89 (bs, 1H), 8.10 (s, 1H), 8.27 (s, 1H). Anal. Calc. for $C_{16}H_{16}F_3N_5S$: C, 52.31, H, 4.39, N, 19.06 found: C, 52.25, H, 4.38, N, 19.09. **4-(*tert*-Butyl)-*N*-(2-nitrophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2j):** Reaction time: 1.5 h, yield: 58%, m.p. 141-143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 7.08-7.13 (m, 1H), 7.65-7.70 (m, 1H), 8.12 (s, 1H), 8.29 (dd, *J* = 1.6 Hz, *J* = 8.8 Hz, 1H), 8.29 (s, 1H), 8.74 (dd, *J* = 1.6 Hz, *J* = 8.8 Hz, 1H), 10.68 (bs, 1H). Anal. Calc. for $C_{15}H_{16}N_6O_2S$: C, 52.31, H, 4.68, N, 24.40 found: C, 52.36, H, 4.68, N, 24.38. **4-(*tert*-Butyl)-*N*-(4-nitrophenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2k):** Reaction time: 2.0 h. yield: 81%, m.p. 229-232 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 7.60 (d, *J* = 9.2 Hz, 2H), 7.67 (bs, 1H), 8.12 (s, 1H), 8.26 (d, *J* = 9.2 Hz, 2H), 8.29 (s, 1H). Anal. Calc. for $C_{15}H_{16}N_6O_2S$: C, 52.31, H, 4.68, N, 24.40 found: C, 52.37, H, 4.69, N, 24.36. **4-(*tert*-Butyl)-*N*-(2,4-dimethylphenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2l):** Reaction time: 0.5 h, yield: 67%, m.p. 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.85 (bs, 1H), 2.23 (s, 3H), 2.25 (s, 3H), 7.06-7.12 (m, 3H), 8.07 (s, 1H), 8.23 (s, 1H). Anal. Calc. for $C_{17}H_{21}N_5S$: C, 62.36, H, 6.46, N, 21.39 found: C, 62.30, H, 6.46, N, 21.43. **4-(*tert*-Butyl)-*N*-(2,6-dimethylphenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2m):** Reaction time: 1.0 h, yield: 86%, m.p. 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (s, 9H), 2.35 (s, 6H), 6.75 (bs, 1H), 7.12-7.18 (m, 3H), 8.02 (s, 1H), 8.20 (s, 1H). Anal. Calc. for $C_{17}H_{21}N_5S$: C, 62.36, H, 6.46, N, 21.39 found: C, 62.30, H, 6.47, N, 21.42. **4-(*tert*-Butyl)-*N*-(3,4-dimethylphenyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2n):** Reaction time: 0.5 h, yield: 73%, m.p. 166-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 2.23 (s, 3H), 2.25 (s, 3H), 7.04-7.12 (m, 3H), 7.15 (bs, 1H), 8.07 (s, 1H), 8.23 (s, 1H). Anal. Calc. for $C_{17}H_{21}N_5S$: C, 62.36, H, 6.46, N, 21.39 found: C, 62.26,

H, 6.45, N, 21.43. **4-(*tert*-Butyl)-*N*-(3-chloro-4-fluorophenyl)-5-(1*H*-1,2,4-tria-zol-1-yl)thiazol-2-amine (2o):** Reaction time: 1.5 h, yield: 63%, m.p. 195-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 9H), 7.37-7.48 (m, 2H), 8.08 (dd, J = 2.4 Hz, J = 6.8 Hz, 1H), 8.23 (s, 1H), 8.94 (s, 1H), 10.58 (bs, 1H). Anal. Calc. for $C_{15}H_{15}ClFN_5S$: C, 51.21, H, 4.30, N, 19.91 found: C, 51.29, H, 4.31, N, 19.94. **4-(*tert*-Butyl)-*N*-(2-chloro-4-nitrophenyl)-5-(1*H*-1,2,4-triaz-ol-1-yl)thiazol-2-amine (2p):** Reaction time: 1.5 h, yield: 74%, m.p. 227-229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 9H), 8.25 (s, 1H), 8.29 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.81 (d, J = 9.6 Hz, 1H), 8.97 (s, 1H), 10.46 (bs, 1H). Anal. Calc. for $C_{15}H_{15}ClN_6O_2S$: C, 47.56, H, 3.99, N, 22.18 found: C, 47.51, H, 3.99, N, 22.16. **4-(*tert*-Butyl)-*N*-(naphthalen-1-yl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amine (2q):** Reaction time: 1.5 h, yield: 86%, m.p. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 7.47-8.09 (m, 7H), 8.04 (s, 1H), 8.20 (s, 1H). Anal. Calc. for $C_{19}H_{19}N_5S$: C, 65.30, H, 5.48, N, 20.04 found: C, 65.24, H, 5.47, N, 20.09.

MTT Assay of Cytotoxicity: The target compounds **2a-2q** were measured cytotoxic activities against two human cancer cell lines including *Hela* (cervix cancer) and *Bel-7402* (liver cancer) by the MTT (3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) assay[25] with Cisplatin as the positive control. MTT solution (10.0 μL/well) in RPMI-1640 (Sigma, St. Louis, MO) was added after the cells were treated with the title compound (concentration ranging from 0 to 0.5 μM) for 48 h, and then the cells were further incubated for 4 h at 37 °C in 5% CO_2 incubator. The purple formazan crystals were dissolved in 100.0 μL DMSO and well-mixed. The absorbance of each well at 570 nm was measured by Multiskan MK3 microplate reader. The assay was performed three times in the same manner, and the IC_{50} (50% inhibition) was calculated by SPSS statistical software.

CONCLUSIONS

In summary, a series of novel *N*–aryl–4-(*tert*-butyl)-5-(1*H*-1,2,4-triazol-1-yl)thiazol-2-amines were synthesized from 3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-one. H_2O_2-NaBr Brominating circulatory system was used in the synthesis of the key intermediate 1-bromo-3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)-butan-2-one, and the sodium bromide was recovered and reused. The process is efficient, low toxicity and high atom economy. The cytotoxicity assay showed that some of the title compounds exhibited moderate to strong cytotoxic activities against *Hela* and *Bel-7402* cell lines, while compound **2i** was the most potent compound and could be used as a lead compound for further study.

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