Synthesis, Antitumor Activity and Preliminary Structure-activity Relationship of 2-Aminothiazole Derivatives

LI Hongshuang, WANG Xinran, DUAN Guiyun*, XIA Chengcai, XIAO Yuliang, LI Furong, GE Yanqing, YOU Guirong, HAN Junfen, FU Xiaopan, TAN Shanhui and WANG Rongwei

School of Pharmaceutical Sciences, Taishan Medical University, Taian 271016, P. R. China

Abstract In this paper, we described the synthesis of 2-aminothiazole sublibrary containing methyl, bromo, phenyl or butylidene at 4- or/and 5-position of its core. All target compounds were evaluated for their antitumor activities against human lung cancer cell line H1299 and human glioma cell line SHG-44. Among the compounds screened, 4,5,6,7-tetrahydrobenzo[*d*]thiazole(**26**b) exhibited the most potent antitumor activities with IC_{50} values of 4.89 and 4.03 μmol/L against the two tested cell lines, respectively. Preliminary structure-activity relationship(SAR) studies of these compound were subsequently investigated.

Keywords 2-Aminothiazole; Antitumor activity; Structure-activity relationship

1 Introduction

Cancer has sustained cellular proliferative capacity, which has rendered it the second most lethal disease on the earth. About 14 million new cases of cancer per year increase the global burden, especially in those developing countries with growing and aging populations. Although the mechanism of initiation and progression of cancer has been well established, the successful treatment of cancer remains a huge challenge facing the lack of early detection, undefined tumor cell dormancy status and metastatic properties of malignant tumor. Consequently, there is an urgent need for the implementation of efficient prevention and treatment strategies to curb cancer deaths. Investigating small molecular antitumor agents, which could decrease drug resistance and reduce unpleasant side effects is more desirable[1—3].

1,3-Thiazoles with ubiquitous heterocyclic privileged structures have been demonstrated to possess a broad range of pharmaceutical properties, involving antioxidant[4], anti-ulcer[5], anti-HIV[6], antibacterial[7], antifungal[8], diuretic[9], anti-inflammatory[10], antitubercular[11], anticancer[12] and anti-hyperglycemic[13—16]. More importantly, a few compounds with the incorporation of thiazole moieties are currently in clinical trials[17,18]. Recently, extensive efforts have been made to enhance the antitumor activities of 2-aminothiazoles, as exemplified by SNS-032(BMS-387032)[19—21] and Dasatinib[22—24](Fig.1). In particular, El-Subbagh and co-workers[25—27] developed a series of 2-aminothiazole derivatives or their related structural alterations as potential chemotherapeutics against cancer. Although SNS-032 was discontinued during phase II trial due to its low specificity and

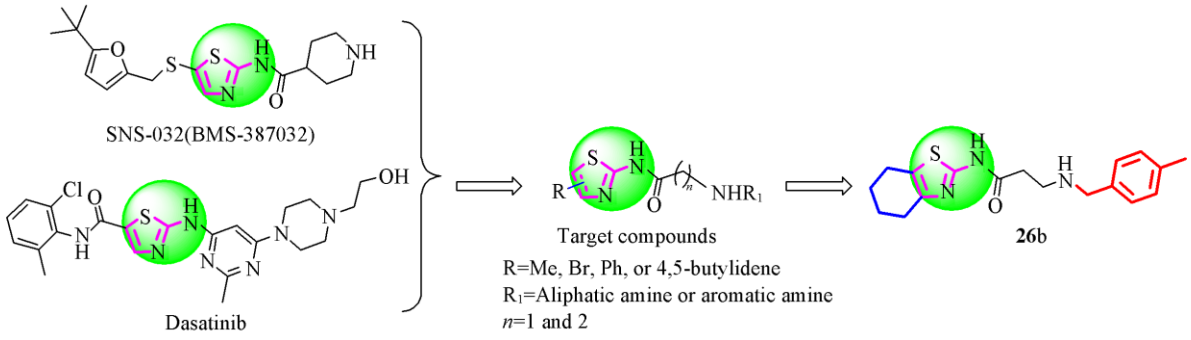


Fig.1 Antitumor molecules encompassing 2-aminothiazole core

*Corresponding author. E-mail: duanguiyun@126.com

Received July 14, 2016; accepted October 19, 2016.

Supported by the Science and Technology Development Project of Shandong Province, China(No.2012GSF11812), the Natural Science Foundation of Shandong Province, China(No.ZR2015BL006) and the Project of Shandong Province Higher Educational Science and Technology Program, China(No.J15LM08).

unfavorable pharmacological properties[20], the preceding reports support the result that the compounds encompassing 2-aminothiazole framework are essential for the effectiveness of the antitumor profiles.

Recent studies have revealed that the introduction of various substituents at 4- or/and 5-position of the 2-aminothiazole core is favorable to improve the antitumor activities[25,26]. In addition, halogen atoms render remarkable changes in the physical, chemical, and biological properties of the compounds. Meanwhile, the incorporation of lipophilic groups, such as alkyl, cycloalkyl or aryl into 2-aminothiazole could enhance the cell permeability of the antitumor agents. As our ongoing interest in the exploration of more potent antitumor heterocyclic compounds[28], herein we described the synthesis of 2-aminothiazoles with different hydrophobic substitution patterns, such as methyl, bromo, phenyl or butylidene at 4- or/and 5-position of the core(Fig.1), yielding 43 compounds. All the target compounds were subjected for the evaluation of antitumor activities against human lung cancer cell line H1299 and human glioma cell line SHG-44 to determine the half maximal inhibitory concentration(IC_{50}). Preliminary structure-activity relationship(SAR) studies of this compound class were subsequently investigated, which may provide a valuable guidance for the generation of much more potent analogs.

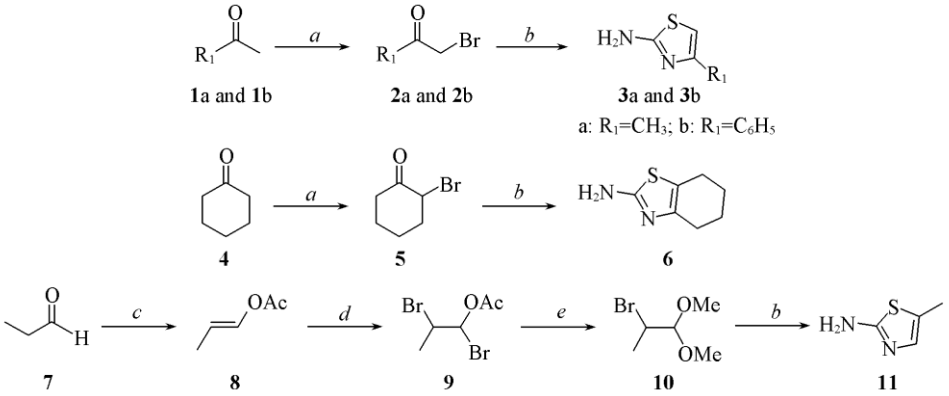
2 Experimental

2.1 Materials and Instruments

All the reagents and solvents were obtained from commercially available sources and were used without further purification. Melting points were determined on an X-4 binocular microscope(Gongyi Tech. Instrument Co., Gongyi, China) and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE III-400 NMR spectrometer(Bruker Biospin Co., Switzerland) with tetramethylsilane (TMS) as the internal standard. MS(ESI) measurement was conducted on an Agilent 1100 LC-MS spectrometer(Agilent, Palo Alto, USA). Column chromatography was carried out on silica gel(200—300 mesh) from Qingdao Ocean Chemicals (Qingdao, China).

2.2 General Procedure for the Preparation of Intermediates 3a, 3b and 6

Intermediates **3**a and **6** were prepared *via* a similar method (Scheme 1). Acetone(58 g, 1 mol) was dissolved in ether (300 mL) and the mixture was cooled to 0 °C. Bromine(160 g, 1 mol) was added dropwise during a period of 3 h. Then, the mixture was added to 20 mL of saturated sodium bicarbonate solution and stirred for another 5 min. The reaction mixture was subsequently washed with saturated sodium chloride aqueous solution(30 mL×3). The organic phase was isolated, dried over anhydrous calcium chloride, and concentrated. After vacuum distillation, bromopropanone was separated and dissolved in ethanol(300 mL). Thiourea(79.9 g, 1.05 mol) was added in batches. After refluxing for 2 h, the solvent was removed under reduced pressure to afford a solid. The solid was dissolved in water(300 mL) and the solution was adjusted to pH=10.0 with a 1 mol/L NaOH aqueous solution. The aqueous solution was extracted with dichloromethane. The organic layer was concentrated to obtain the crude product, which was recrystallized from ethanol to yield the desired product.



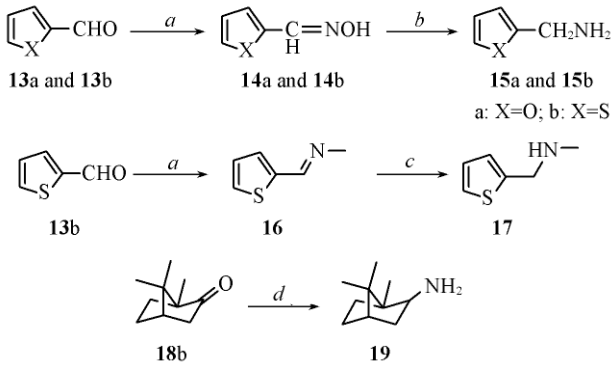
Scheme 1 Synthesis of 2-aminothiazole cores

Reagents and conditions: *a*. For compounds **2**a and **5**: Br_2, Et_2O, 0 °C, 3—4 h; for compound **2**b: Br_2, $AlCl_3$, Et_2O, 0 °C, 3 h; *b*. thiourea, EtOH, reflux, 2—3 h; *c*. Ac_2O, AcONa, reflux, 1 h; *d*. Br_2, DCM, 0 °C, 24 h; *e*. MeOH, 0 °C—r. t., 36 h.

Intermediate **3**b was prepared *via* the same method mentioned above, with the exception of using $AlCl_3$ as the catalyst.

2.3 General Procedure for the Preparation of Amines 15a and 15b

(Furan-2-yl)methanamine(**15**a) and (thiophen-2-yl)methanamine(**15**b) were prepared by the similar method as described in Scheme 2. To a mixture of aldehyde(1 mol) and sodium carbonate(0.5 mol) in water(200 mL) was added hydroxylamine hydrochloride aqueous solution(1 mol) dropwise over a period of 45 min. The reaction mixture was stirred at room temperature for 7 h, and then filtered to obtain the corresponding oxime, which was reduced with zinc powder(4.5 mol) to afford the desired amine.



Scheme 2 Synthesis of amines

Reagents and conditions: *a*. For compounds **14**a and **14**b: $NH_2OH·HCl$, Na_2CO_3, H_2O, r. t., overnight; for compound **16**: methylamine(aq.), Na_2CO_3, H_2O, r. t., 7 h; *b*. Zn, AcOH, 60 °C, 6 h; *c*. $NaBH_4$, MeOH, 0 °C, 3.5 h; *d*. $HCOONH_4$, nitrobenzene, 110—180 °C, 9 h.

2.4 Preparation of *N*-Methyl(thiophen-2-yl)methanamine(17)

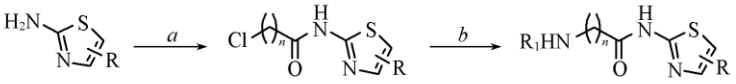
To a stirring mixture of thiophene-2-carbaldehyde(**13**b, 1 mol) and 40% methylamine aqueous solution(85 g) at room temperature was added sodium carbonate aqueous solution (0.5 mol) dropwise over a period of 2 h. The reaction mixture was stirred at room temperature for an additional 5 h, and then filtered to obtain the corresponding imine, which was reduced with sodium borohydride(2 mol) to give *N*-methyl(thiophen-2-yl) methanamine(**17**, Scheme 2).

2.5 Preparation of Camphor Amine(19)

A mixture of camphor(0.2 mol) and ammonium formate (49.7 g, 0.8 mol) in nitrobenzene(30 mL) was heated to 150 ℃ and stirred for 2 h. Subsequently, the reaction mixture was heated to 180 ℃ to remove water. After the completion of the reaction, the mixture was cooled to room temperature and then 80 mL of water was added. Nitrobenzene was removed by steam distillation. The residue was basified with 1 mol/L NaOH aqueous solution to pH=10.0. Finally, the desired product was obtained by steam distillation.

2.6 General Procedure for Preparation of Target Compounds 21a—21h, 22a—22j, 23a—23e, 24a—24f, 25a—25c, 26a—26e and 27a—27f

The target compounds were prepared according to the literature procedure(Scheme 3)[16]. ^{1}H NMR and ^{13}C NMR spectra of these compounds are listed in the Electronic Supplementary Material of this paper.



3a and **3**b, **6**, **11**, **12**

20a: R=5-CH_3, *n*=1;
20b: R=5-Br, *n*=1;
20c: R=4-CH_3, *n*=1;
20d: R=4-CH_3, *n*=2;
20e: R=4-C_6H_5, *n*=1;
20f: R=4,5-butylidene, *n*=2;
20g: R=4,5-butylidene, *n*=1

21a—**21**h: R=5-CH_3, *n*=1;
22a—**22**j: R=5-Br, *n*=1;
23a—**23**e: R=4-CH_3, *n*=1;
24a—**24**f: R=4-CH_3, *n*=2;
25a—**25**c: R=4-C_6H_5, *n*=1;
26a—**26**e: R=4,5-butylidene, *n*=2;
27a—**27**f: R=4,5-butylidene, *n*=1

Scheme 3 Synthesis of target compounds 21—27

Reagents and conditions: *a*. 2-chloroacetyl chloride or 3-chloropropionyl chloride, pyridine, DCM, 0 °C, 4 h; *b*. aliphatic amine or aromatic amine, triethylamine, THF, reflux, 4 h.

N-(5-Methylthiazol-2-yl)-2-(phenethylamino)acetamide (**21**a): a yellow solid; yield 46.6%; m. p. 120—121 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.19—7.33(m, 5H), 3.45(s, 2H), 2.96(t, *J*=6.8 Hz, 2H), 2.83(t, *J*=6.8 Hz, 2H), 2.40(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.7, 36.3, 51.3, 52.0, 126.6, 127.7, 128.8, 134.4, 139.7, 156.3, 169.7. MS(ESI), *m/z*: 276.3$[M+H]^+$.

N-(5-Methylthiazol-2-yl)-2-(4-methylbenzylamino)acetamide(**21**b): a yellow solid; yield 48.3%; m. p. 98—99 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.20(d, *J*=8.0 Hz, 2H), 7.14(d, *J*=7.6 Hz, 2H), 7.03(s, 1H), 3.79(s, 2H), 3.49(s, 2H), 2.39(s, 3H), 2.33(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.7, 21.1, 51.2, 53.5, 127.6, 128.3, 129.4, 134.2, 135.9, 137.2, 156.6, 169.7. MS(ESI), *m/z*: 276.3$[M+H]^+$.

2-(4-Methoxybenzylamino)-*N*-(5-methylthiazol-2-yl)acetamide(**21**c): a yellow solid; yield 53.0%; m. p. 110—111 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.23(d, *J*=8.4 Hz, 2H), 7.02(s, 1H), 6.86(dd, J_1=6.8 Hz, J_2=2.0 Hz, 2H), 3.78(s, 3H), 3.73(s, 2H), 3.49(s, 2H), 2.38(s, 3H)；^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.7, 51.2, 53.3, 55.4, 114.1, 127.7, 129.6, 131.0, 134.2, 156.5, 159.1, 169.7. MS(ESI), *m/z*: 292.4$[M+H]^+$.

2-(Benzylamino)-*N*-(5-methylthiazol-2-yl)acetamide(**21**d): a yellow solid; yield 57.2%; m. p. 109—110 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.26—7.35(m, 5H), 7.02—7.03(m, 1H), 3.84(s, 2H), 3.51(s, 2H), 2.37(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.6, 51.2, 53.7, 127.5, 127.6, 128.3, 128.7, 134.0, 138.9, 156.7, 169.9. MS(ESI), *m/z*: 262.1$[M+H]^+$.

2-(4-Methoxyphenylamino)-*N*-(5-methylthiazol-2-yl)aceta-

mide(**21**e): a black solid; yield 64.2%; m. p. 166—167 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 10.24(s, 1H), 7.05(s, 1H), 6.78(dd, J_1=6.8 Hz, J_2=2.0 Hz, 2H), 6.58(dd, J_1=6.8 Hz, J_2=2.0 Hz, 2H), 4.19(s, 1H), 3.96(s, 2H), 3.74(s, 3H), 2.40(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.8, 49.4, 55.9, 114.5, 115.2, 128.1, 134.4, 140.7, 153.6, 156.3, 169.1. MS(ESI), *m/z*: 278.2$[M+H]^+$.

N-(5-Methylthiazol-2-yl)-2-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylamino)acetamide(**21**f): a yellow solid; yield 65.4%; m. p. 154—155 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.09(s, 1H), 3.45(s, 2H), 2.51—2.54(m, 1H), 2.40(s, 3H), 1.70—1.74(m, 5H), 0.84—1.08(m, 11H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.7, 12.6, 20.6, 20.7, 27.2, 36.9, 39.2, 45.1, 46.6, 48.8, 51.5, 67.6, 127.7, 134.6, 156.1, 170.2. MS(ESI), *m/z*: 308.4$[M+H]^+$.

2-(Furan-2-ylmethylamino)-*N*-(5-methylthiazol-2-yl)acetamide(**21**g): an orange solid; yield 74.9%; m. p. 105—106 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.35—7.36(m, 1H), 7.07(d, *J*=1.2 Hz, 1H), 6.30(dd, J_1=2.8 Hz, J_2=2.0 Hz, 1H), 6.21(d, *J*=3.2 Hz, 1H), 3.83(s, 2H), 3.50(s, 2H), 2.40(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 11.6, 45.9, 50.9, 107.9, 110.2, 127.5, 134.1, 142.2, 152.5, 156.6, 169.5. MS(ESI), *m/z*: 251.9$[M+H]^+$.

2-(Methyl(thiophen-2-ylmethyl)amino)-*N*-(5-methylthiazol-2-yl)acetamide(**21**h): a white solid; yield 61.5%; m. p. 95—96 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 10.18(s, 1H), 7.25—7.27 (m, 1H), 7.10(s, 1H), 6.94—6.95(m, 2H), 3.87(s, 2H), 3.26(s, 2H), 2.43(s, 3H), 2.40(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 11.7, 43.4, 56.5, 59.2, 125.8, 126.8, 126.9, 127.8, 134.7, 140.5, 155.8, 168.5. MS(ESI), *m/z*: 282.0$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(*p*-tolylmethanamino)acetamide (**22**a): a red brown solid; yield 67.9%; m. p. 114—115 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.34(s, 1H), 7.19(d, *J*=8.0 Hz, 2H), 7.15(d, *J*=8.0 Hz, 2H), 3.80(s, 2H), 3.50(s, 2H), 2.33(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 21.2, 51.1, 53.7, 103.5, 128.3, 129.5, 135.5, 137.5, 138.2, 158.1, 170.2. MS(ESI), *m/z*: 340.3$[M+H]^+$.

2-(4-Methoxybenzylamino)-*N*-(5-bromothiazol-2-yl)acetamide(**22**b): an orange oil; yield 74.6%; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 9.80(s, 1H), 7.62(s, 1H), 7.45(d, *J*=8.0 Hz, 2H), 6.98(d, *J*=8.4 Hz, 2H), 4.16(s, 2H), 4.00(s, 2H), 3.77(s, 3H), 2.51(s, 1H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 47.1, 50.1, 55.8, 102.8, 114.6, 123.8, 132.4, 139.4, 157.9, 160.4, 165.3. MS(ESI), *m/z*: 356.0$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(phenylamino)acetamide(**22**c): a brown solid; yield 54.9%; m. p. 177—178 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.32(s, 1H), 7.21—7.26(m, 2H), 6.86(t, *J*=7.2 Hz, 1H), 6.63(d, *J*=7.8 Hz, 2H), 4.27(s, 1H), 4.03(s, 2H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 48.8, 104.0, 113.7, 120.3, 129.8, 138.3, 146.5, 158.0, 169.4. MS(ESI), *m/z*: 311.9$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(4-methoxyphenylamino)acetamide(**22**d): a black solid; yield 58.5%; m. p. 144—145 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 6.56—6.81(m, 5H), 3.86(s, 1H), 3.79(s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 49.5, 56.0, 103.8, 115.0, 116.7, 138.4, 140.0, 153.2, 157.8, 169.7. MS(ESI), *m/z*: 341.8$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(4-chlorophenylamino)acetamide(**22**e): a yellow solid; yield 60.4%; m. p. 189—190 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.84(s, 1H), 7.33(s, 1H), 7.20(d, *J*=8.8 Hz, 2H), 6.56(d, *J*=8.8 Hz, 2H), 4.35(s, 1H), 4.01(s, 2H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 48.8, 104.1, 114.2, 129.7, 138.5, 145.0, 157.5, 168.7. MS(ESI), *m/z*: 345.8$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(phenethylamino)acetamide (**22**f): an orange solid; yield 45.2%; m. p. 130—132 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.36(s, 1H), 7.32(t, *J*=7.2 Hz, 2H), 7.19—7.26(m, 3H), 3.47(s, 2H), 2.95(t, *J*=6.8 Hz, 2H), 2.83(t, *J*=6.4 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 36.2, 51.2, 51.7, 103.4, 126.6, 128.7, 128.8, 138.3, 138.9, 158.0, 170.3. MS(ESI), *m/z*: 340.2$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(furan-2-ylmethylamino)acetamide(**22**g): a brown solid; yield 54.0%; m. p. 93—95 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.36(d, *J*=1.6 Hz, 2H), 6.30(dd, J_1=3.2 Hz, J_2=1.6 Hz, 1H), 6.21(dd, J_1=3.2 Hz, J_2=0.8 Hz, 1H), 3.86(s, 2H), 3.54(s, 2H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 46.1, 50.8, 103.5, 108.3, 110.4, 138.2, 142.7, 152.1, 158.1, 170.0. MS(ESI), *m/z*: 315.8$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-[methyl(thiophen-2-ylmethyl)-amino]acetamide(**22**h): an orange oil; yield 49.4%; ^{1}H NMR (400 MHz, DMSO-d_6), δ: 11.25(s, 1H), 7.74(d, *J*=5.2 Hz, 1H), 7.63(s, 1H), 7.41(d, *J*=3.2 Hz, 1H), 7.14(dd, J_1=5.2 Hz, J_2=3.6 Hz, 1H), 4.70(s, 2H), 4.24(s, 2H), 2.87(s, 3H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 53.2, 54.5, 103.1, 128.3, 130.5, 130.8, 133.5, 139.6, 157.9, 164.7. MS(ESI), *m/z*: 345.7$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylamino)acetamide(**22**i): a red solid; yield 50.6%; m. p. 111—112 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.36(s, 1H), 3.47(s, 2H), 2.51—2.54(m, 1H), 1.56—1.76(m, 7H), 1.06(s, 1H), 0.98(s, 1H), 0.85(s, 1H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 12.6, 20.7, 27.2, 36.9, 39.3, 45.0, 46.9, 48.8, 51.2, 67.7, 103.4, 138.4, 157.8, 170.7. MS(ESI), *m/z*: 372.1$[M+H]^+$.

N-(5-Bromothiazol-2-yl)-2-(adamantanamino)acetamide (**22**j): an orange solid; yield 53.4%; m. p. 134—136 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.36(s, 1H), 3.47(s, 2H), 1.60—1.69(m, 15H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 29.5, 36.4, 42.6, 43.6, 51.4, 103.4, 138.3, 157.9, 171.6. MS(ESI), *m/z*: 369.8$[M+H]^+$.

2-(Benzylamino)-*N*-(4-methylthiazol-2-yl)acetamide(**23**a): a white solid; yield 61.1%; m. p. 196—198 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 9.85(s, 1H), 7.57—7.59(m, 2H), 7.41—7.42(m, 3H), 6.67(s, 1H), 4.25(s, 2H), 4.00(s, 2H), 2.30(s, 3H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 17.4, 47.8, 51.0, 108.5, 129.2, 129.6, 130.9, 131.9, 147.2, 157.4, 165.0. MS(ESI), *m/z*: 262.1$[M+H]^+$.

2-(4-Methoxybenzylamino)-*N*-(4-methylthiazol-2-yl)acetamide(**23**b): a white solid; yield 73.2%; m. p. 201—203 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 9.78(s, 1H), 7.50(d, *J*=8.8 Hz, 2H), 6.93(d, *J*=8.4 Hz, 2H), 6.71(s, 1H), 4.18(s, 2H), 3.98(s, 2H), 3.80(s, 3H), 2.31(s, 3H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 16.6, 47.7, 50.6, 55.9, 109.3, 114.7, 123.6, 132.6, 146.0, 160.8, 165.0, 165.8. MS(ESI), *m/z*: 292.0$[M+H]^+$.

2-(4-Methylbenzylamino)-*N*-(4-methylthiazol-2-yl)acetamide(**23**c): a white solid; yield 71.2%; m. p. 207—209 °C; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 12.47(s, 1H), 9.68(s, 1H), 7.43(d, *J*=7.6 Hz, 2H), 7.22(d, *J*=8.0 Hz, 2H), 6.69(s, 1H), 4.19(s, 2H), 3.96(s, 2H), 2.35(s, 3H), 2.29(s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6), δ: 17.4, 21.6, 47.6, 50.7, 108.6, 128.8,

129.8, 131.0, 139.3, 147.3, 157.3, 164.6. MS(ESI), *m/z*: 276.2[M+H]$^+$.

2-(Furan-2-ylmethylamino)-*N*-(4-methylthiazol-2-yl)acetamide(**23**d): a gray solid; yield 68.7%; m. p. 179—181 °C; ^{1}H NMR(400 MHz, DMSO-d$_6$), *δ*: 9.97(s, 1H), 7.77(s, 1H), 6.84(d, *J*=1.2 Hz, 1H), 6.67(d, *J*=1.2 Hz, 1H), 6.51—6.53 (m, 1H), 4.30(s, 2H), 4.00(s, 2H), 2.27(s, 3H); ^{13}C NMR (100 MHz, DMSO-d$_6$), *δ*: 17.5, 43.2, 47.6, 109.1, 111.9, 113.4, 145.0, 146.4, 147.4, 157.4, 165.0. MS(ESI), *m/z*: 252.3 [M+H]$^+$.

N-(4-Methylthiazol-2-yl)-2-(adamantanamino)acetamide (**23**e): a yellow solid; yield 84.5%; m. p. 113—115 °C; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 6.52(s, 1H), 3.46(s, 2H), 2.36(s, 3H), 1.58—1.69(m, 15H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 17.2, 29.5, 36.5, 42.7, 43.8, 51.4, 108.1, 147.3, 157.0, 171.4. MS(ESI), *m/z*: 306.1[M+H]$^+$.

3-(4-Methoxybenzylamino)-*N*-(4-methylthiazol-2-yl)propanamide(**24**a): an orange oil; yield 47.8%; ^{1}H NMR (400 MHz, DMSO-d$_6$), *δ*: 10.96(s, 1H), 7.59(d, *J*=8.8 Hz, 2H), 7.02(d, *J*=8.4 Hz, 2H), 6.77(s, 1H), 4.33(s, 2H), 3.79(s, 3H), 3.35(t, *J*=7.6 Hz, 2H), 3.09(t, *J*=7.2 Hz, 2H), 2.26(s, 3H); ^{13}C NMR(100 MHz, DMSO-d$_6$), *δ*: 17.2, 29.9, 47.7, 55.8, 56.5, 108.5, 114.8, 121.9, 133.5, 146.6, 157.7, 160.7, 168.5. MS(ESI), *m/z*: 306.0[M+H]$^+$.

N-(4-Methylthiazol-2-yl)-3-(phenethylamino)propanamide (**24**b): a white solid; yield 45.8%; m. p. 150—152 °C; ^{1}H NMR (400 MHz, CDCl$_3$), *δ*: 11.88(s, 1H), 7.06—7.20(m, 5H), 6.46(s, 1H), 3.02(t, *J*=5.6 Hz, 2H), 2.79(t, *J*=5.6 Hz, 2H), 2.61(t, *J*=5.6 Hz, 2H), 2.36(s, 3H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 17.1, 32.8, 33.9, 50.8, 55.8, 108.0, 126.4, 128.6, 128.7, 139.2, 147.5, 157.5, 170.0. MS(ESI), *m/z*: 289.9[M+H]$^+$.

3-(4-Methylbenzylamino)-*N*-(4-methylthiazol-2-yl)propanamide(**24**c): a white solid; yield 52.3%; m. p. 131—133 °C; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 7.20(d, *J*=8.0 Hz, 2H), 7.03(d, *J*=7.6 Hz, 2H), 6.45(s, 1H), 3.67(s, 2H), 2.96(t, *J*=5.2 Hz, 2H), 2.60(t, *J*=5.2 Hz, 2H), 2.35(s, 3H), 2.26(s, 3H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 17.1, 21.1, 33.4, 49.8, 58.5, 107.9, 129.3, 129.5, 133.2, 137.5, 147.1, 157.6, 169.9. MS(ESI), *m/z*: 290.0 [M+H]$^+$.

N-(4-Methylthiazol-2-yl)-3-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-ylamino)propanamide(**24**d): an orange oil; yield 56.4%; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 6.65(s, 1H), 3.12—3.73 (m, 5H), 2.52(s, 3H), 1.49—2.26(m, 7H), 1.20(s, 3H), 1.13(s, 3H), 0.89(s, 3H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 12.9, 14.4, 18.6, 19.5, 20.2, 21.0, 26.2, 27.6, 28.3, 32.9, 36.7, 108.7, 138.7, 160.8, 170.8. MS(ESI), *m/z*: 322.1[M+H]$^+$.

N-(4-Methylthiazol-2-yl)-3-(adamantanamino)propanamide (**24**e): a white solid; yield 63.9%; m. p. 166—168 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$), *δ*: 9.07(s, 1H), 6.78(s, 1H), 3.17(s, 2H), 2.95(t, *J*=6.8 Hz, 2H), 2.51(s, 3H), 1.59—2.26(m, 15H); ^{13}C NMR(100 MHz, DMSO-d$_6$), *δ*: 17.4, 36.1, 29.3, 32.6, 35.2, 38.4, 39.8, 40.0, 40.2, 40.4, 40.7, 40.9, 57.2, 108.8, 146.6, 158.2, 169.0. MS(ESI), *m/z*: 320.1[M+H]$^+$.

3-(2-Ethoxyphenylamino)-*N*-(4-methylthiazol-2-yl)propanamide(**24**f): a yellow oil; yield 47.2%; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 10.43(s, 1H), 6.77(d, *J*=8.8 Hz, 2H), 6.63(d, *J*=8.8 Hz, 2H), 6.52(s, 1H), 3.95(q, *J*=6.8 Hz, 2H), 3.48(t, *J*=6.8 Hz, 2H), 2.67(t, *J*=6.0 Hz, 2H), 2.30(s, 1H), 1.37(t, *J*=6.8 Hz, 3H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 15.1, 17.2, 35.6, 41.1, 64.2, 108.4, 115.4, 115.9, 141.3, 146.9, 152.3, 158.1, 169.9. MS(ESI), *m/z*: 306.2[M+H]$^+$.

2-(Methyl(thiophen-2-ylmethyl)amino)-*N*-(4-phenylthiazol-2-yl)acetamide(**25**a): an orange oil; yield 46.5%; ^{1}H NMR(400 MHz, DMSO-d$_6$), *δ*: 11.20(s, 1H), 7.90(d, *J*=7.6 Hz, 2H), 7.74(d, *J*=3.6 Hz, 2H), 7.42—7.47(m, 3H), 7.34(t, *J*=7.2 Hz, 1H), 7.16(q, *J*=3.2 Hz, 1H), 4.72(s, 2H), 4.42(s, 2H), 2.90 (s, 3H); ^{13}C NMR(100 MHz, DMSO-d$_6$), *δ*: 53.4, 54.8, 109.6, 126.5, 128.4, 128.7, 129.6, 130.6, 130.9, 133.6, 134.8, 149.8, 157.5, 164.4. MS(ESI), *m/z*: 343.9[M+H]$^+$.

2-(Benzylamino)-*N*-(4-phenylthiazol-2-yl)acetamide(**25**b): a yellow solid; yield 47.9%; m. p. 97—99 °C; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 7.84(d, *J*=7.2 Hz, 2H), 7.28—7.43(m, 8H), 7.13(s, 1H), 3.84(s, 2H), 3.50(s, 2H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 51.3, 53.9, 107.8, 126.2, 127.6, 128.1, 128.2, 128.79, 128.83, 134.5, 138.7, 150.1, 157.4, 170.1. MS(ESI), *m/z*: 324.2[M+H]$^+$.

2-(4-Methylbenzylamino)-*N*-(4-phenylthiazol-2-yl)acetamide(**25**c): an orange oil; yield 50.1%; ^{1}H NMR(400 MHz, DMSO-d$_6$), *δ*: 9.89(s, 1H), 7.90(d, *J*=7.6 Hz, 2H), 7.73(s, 1H), 7.42—7.47(m, 4H), 7.34(t, *J*=7.6 Hz, 1H), 7.25(d, *J*=8.0 Hz, 2H), 4.20(s, 2H), 4.02(s, 2H), 2.33(s, 3H); ^{13}C NMR(100 MHz, DMSO-d$_6$), *δ*: 21.6, 47.6, 50.6, 109.5, 126.6, 128.8, 129.3, 129.6, 130.0, 131.1, 134.9, 139.3, 149.9, 157.7, 165.2. MS(ESI), *m/z*: 338.1[M+H]$^+$.

3-(4-Methoxybenzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)propanamide(**26**a): an orange oil; yield 79.8%; ^{1}H NMR(400 MHz, DMSO-d$_6$), *δ*: 9.46(s, 1H), 7.51(d, *J*=8.4 Hz, 2H), 6.98(d, *J*=8.4 Hz, 2H), 4.08(t, *J*=7.6 Hz, 1H), 3.77(s, 3H), 2.50—2.55(m, 4H), 1.76(s, 4H); ^{13}C NMR(100 MHz, DMSO-d$_6$), *δ*: 23.2, 23.3, 23.7, 26.4, 32.2, 40.9, 50.4, 56.2, 114.9, 122.6, 124.7, 132.7, 143.3, 156.1, 160.6, 169.1. MS(ESI), *m/z*: 346.2[M+H]$^+$.

3-(4-Methylbenzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)propanamide(**26**b): a yellow solid; yield 64.1%; m. p. 99—100 °C; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 7.25(d, *J*=8.0 Hz, 2H), 7.14(d, *J*=7.6 Hz, 2H), 3.85(s, 2H), 2.96(t, *J*=7.6 Hz, 1H), 2.66—2.71(m, 4H), 2.56(t, *J*=6.0 Hz, 2H), 2.33(s, 3H), 1.84—1.85(m, 4H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 22.9, 23.1, 23.4, 26.5, 29.7, 34.7, 43.8, 52.8, 122.5, 128.4, 129.3, 135.6, 137.6, 144.1, 155.3, 170.2. MS(ESI), *m/z*: 329.8[M+H]$^+$.

N-(4,5,6,7-Tetrahydrobenzo[*d*]thiazol-2-yl)-3-(thiophen-2-ylmethylamino)propanamide(**26**c): a brown solid; yield 48.1%; m. p. 104—105 °C; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 7.23(dd, J_1=4.8 Hz, J_2=1.6 Hz, 2H), 6.95—6.98(m, 2H), 4.09(s, 2H), 3.00(t, *J*=5.6 Hz, 2H), 2.68(d, *J*=5.2 Hz, 4H), 2.55(t, *J*=5.6 Hz, 2H), 1.84—1.85(m, 4H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 23.0, 23.2, 23.4, 26.6, 35.0, 43.7, 47.5, 122.7, 124.9, 125.8, 126.9, 142.4, 144.2, 155.3, 170.0. MS(ESI), *m/z*: 322.0[M+H]$^+$.

3-(Benzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)propanamide(**26**d): an orange oil; yield 45.6%; ^{1}H NMR(400 MHz, CDCl$_3$), *δ*: 7.25—7.38(m, 5H), 3.88(s, 2H), 2.97(t, *J*=6.0 Hz, 2H), 2.64—2.69(m, 4H), 2.55(t, *J*=6.0 Hz, 2H), 1.84—1.85 (m, 4H); ^{13}C NMR(100 MHz, CDCl$_3$), *δ*: 22.9, 23.1, 23.4, 26.5,

34.7, 43.9, 53.1, 122.5, 127.4, 128.4, 128.6, 138.8, 144.1, 155.2, 170.1. MS(ESI), *m/z*: 316.3[M+H]$^+$.

3-(Furan-2-ylmethylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)propanamide(**26**e): an orange oil; yield 55.4%; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 9.52(s, 1H), 7.77—7.78(m, 1H), 6.67(d, J=3.2 Hz, 1H), 6.53(q, J=2.0 Hz, 1H), 3.15—3.19(m, 2H), 2.92(t, J=7.2 Hz, 2H), 2.50—2.55(m, 4H), 1.76(s, 4H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 27.6, 27.7, 28.1, 30.7, 36.6, 46.9, 47.7, 116.4, 117.7, 127.0, 147.6, 149.5, 151.1, 160.6, 173.5. MS(ESI), *m/z*: 305.9[M+H]$^+$.

2-(4-Methoxyphenylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)acetamide(**27**a): a yellow solid; yield 53.5%; m. p. 150—151 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 9.91(s, 1H), 6.78(dd, J_1=6.8 Hz, J_2=2.0 Hz, 2H), 6.56(dd, J_1=6.8 Hz, J_2=2.0 Hz, 2H), 4.13(s, 1H), 3.93(s, 2H), 3.74(s, 3H), 2.69—2.70(m, 2H), 2.60—2.61(m, 2H), 1.82—1.85(m, 4H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 23.09, 23.11, 23.4, 26.5, 49.6, 55.8, 114.7, 115.2, 123.4, 140.6, 144.5, 153.7, 154.5, 169.1. MS(ESI), *m/z*: 318.3[M+H]$^+$.

2-(Furan-2-ylmethylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)acetamide(**27**b): a yellow solid; yield 66.7%; m. p. 102—104 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.35—7.36(m, 1H), 6.29—6.31(m, 1H), 6.20—6.21(m, 1H), 3.81(s, 2H), 3.47(s, 2H), 2.64—2.70(m, 4H), 1.83—1.87(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 23.0, 23.1, 23.4, 26.4, 46.0, 50.8, 107.9, 110.3, 122.9, 142.4, 144.3, 152.2, 154.6, 169.4. MS(ESI), *m/z*: 292.1[M+H]$^+$.

2-[Methyl(thiophen-2-ylmethyl)amino]-*N*-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)acetamide(**27**c): an orange oil; yield 61.6%; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 11.11(s, 1H), 7.74(dd, J_1=5.2 Hz, J_2=1.2 Hz, 1H), 7.39(d, J=3.2 Hz, 1H), 7.14(dd, J_1=5.2 Hz, J_2=3.6 Hz, 1H), 4.69(s, 2H), 4.19(s, 2H), 2.86(s, 3H), 2.51—2.65(m, 4H), 1.77(s, 4H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 23.1, 23.3, 23.7, 26.5, 41.1, 53.3, 55.0, 122.9, 128.5, 130.5, 131.0, 133.6, 144.0, 155.4, 164.5. MS(ESI), *m/z*: 322.0[M+H]$^+$.

2-(Benzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]thiazol-2-yl)acetamide(**27**d): a yellow solid; yield 65.4%; m. p. 101—103 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.26—7.37(m, 5H), 3.83(s, 2H), 3.48(s, 2H), 2.65—2.71(m, 4H), 1.83—1.87(m, 4H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 21.1, 23.1, 23.4, 26.5, 51.2, 53.6, 122.9, 128.2, 129.4, 135.7, 137.2, 144.3, 154.5, 169.5. MS(ESI), *m/z*: 301.9[M+H]$^+$

2-(4-Methylbenzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)acetamide(**27**e): an orange solid; yield 64.6%; m. p. 114—116 °C; ^{1}H NMR(400 MHz, $CDCl_3$), δ: 7.13—7.20(m, 4H), 3.78(s, 2H), 3.46(s, 2H), 2.64—2.70(m, 4H), 2.33(s, 3H), 1.84—1.87(m, 4H); ^{13}C NMR(100 MHz, $CDCl_3$), δ: 21.1, 23.0, 23.1, 23.4, 26.5, 51.2, 53.6, 123.0, 128.2, 129.4, 135.7, 137.2, 144.3, 154.5, 169.5. MS(ESI), *m/z*: 316.1[M+H]$^+$.

2-(4-Methoxybenzylamino)-*N*-(4,5,6,7-tetrahydrobenzo[*d*]-thiazol-2-yl)acetamide(**27**f): an orange oil; yield 63.6%; ^{1}H NMR(400 MHz, DMSO-d_6), δ: 9.68(s, 1H), 7.47(d, J=8.4 Hz, 2H), 6.98(d, J=8.8 Hz, 2H), 4.14(s, 2H), 3.94(s, 2H), 3.77(s, 3H), 2.50—2.65(m, 4H), 1.77(s, 4H); ^{13}C NMR(100 MHz, DMSO-d_6), δ: 23.2, 23.4, 23.8, 26.7, 47.7, 50.4, 56.2, 114.9, 123.0, 124.3, 133.0, 144.4, 155.3, 160.7, 165.1. MS(ESI), *m/z*: 332.2[M+H]$^+$.

2.7 Biological Evaluation

All the forty-three synthesized compounds were subjected for the evaluation of antitumor activities against human lung cancer cell line H1299 and human glioma cell line SHG-44. Teniposide, a cancer chemotherapeutic agent[3], was utilized as the positive control. For a typical screening, the cells were cultured in a DMEM media supplemented with 10% fetal bovine serum, and then plated in 96-well plates in 180 μL at a plating density of 10000 cells per well. After incubating at 37 °C for 24 h under an atmosphere of 5% CO_2 and 100% relative humidity, the cells were treated with the tested compounds. The plates were cultured for an additional 48 h. Subsequently, the growth inhibition rate was assessed *via* the methyl thiazolyl tetrazolium(MTT) assay[29,30]. The absorbance was measured on an RT6100 Microplate Reader at 492 nm. All the compounds were tested three times for each cell lines, and the results expressed as IC_{50}s were the averages of three determination.

3 Results and Discussion

3.1 Synthesis

The synthesis of 2-aminothiazole core was outlined in Scheme 1[16]. Initial α-bromination of ketones(**1**a, **1**b and **4**) with subsequent condensation with thiourea established 2-aminothiazoles(**3**a, **3**b and **6**) with different hydrophobic substitutions. Followed previously disclosed protocol, 5-methyl-2-aminothiazole(**11**) was obtained *via* a four-step procedure[31]. Briefly, the reaction of propanal **7** with acetic anhydride in the presence of sodium acetate afforded enol acetate(**8**), which was subjected to the addition reaction by treating with bromine. Subsequent alcoholysis and condensation with thiourea delivered the target intermediate **11**. It should be mentioned that 5-bromo-2-aminothiazole(**12**) was commercially available.

As depicted in Scheme 2, commercially available hetero-aromatic aldehydes **13**a and **13**b were smoothly converted to the key intermediate amines(**15**a, **15**b and **17**) by treatment with hydroxylamine hydrochloride or methylamine aqueous solution followed by reduction under Zn/AcOH and $NaBH_4$/MeOH, respectively. Alternatively, the strategy of reductive amination could be utilized for the access to camphor amine(**19**) in the presence of $HCOONH_4$ at a high temperature.

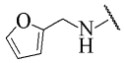
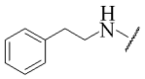
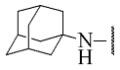
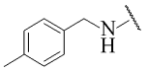
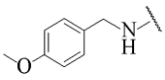
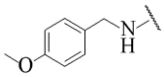
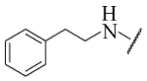
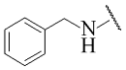
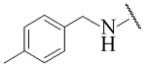
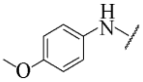
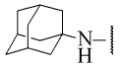
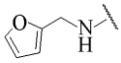
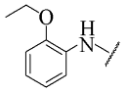
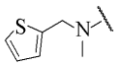
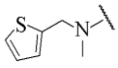
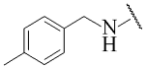
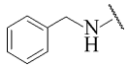
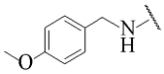
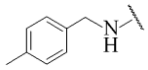
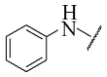
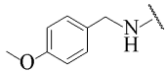
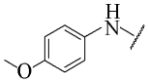
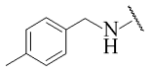
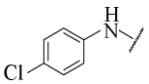
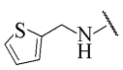
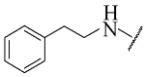
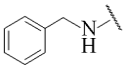
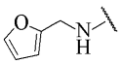
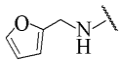
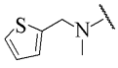
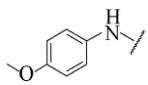
Finally, 2-aminothiazoles(**3**a, **3**b, **6**, **11** and **12**) were acylated with either 2-chloroacetyl chloride or 3-chloropropionyl chloride under basic conditions to give the corresponding alkyl chlorides(**20**a—**20**g, Scheme 3), which were then coupled with aliphatic amines or aromatic amines to produce the target compounds(**21**—**27**).

3.2 Antitumor Activity

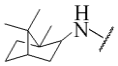
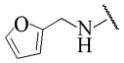
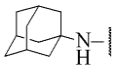
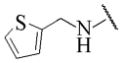
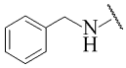
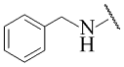
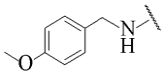
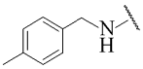
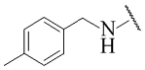
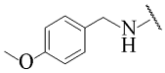
As summarized in Table 1, some of the tested compounds present remarkable sensitivity profiles against the two tumor cell lines. Compounds **22**a—**22**d, **26**b—**26**d and **27**d have IC_{50} values against H1299 cell line at micromolar level. Meanwhile,

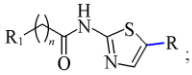
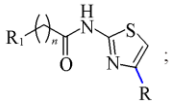
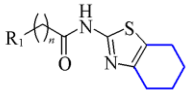
compounds **22**a, **26**b—**26**d, **27**a and **27**f show comparable activities against SHG-44 cell line. These results also indicate that the inhibitory activities against one cell line displayed by the active compounds is not in compliance with those against the other, and H1299 cell line proves a better selectivity towards the synthesized compounds. Inspiringly, compound **26**b exhibits the most potent antitumor activities against both of the cell lines with IC_{50} values of 4.89 and 4.03 μmol/L, respectively. Other counterparts, such as compounds **26**c and **26**d, also exhibit good inhibitory activities against the two cell lines used in the assay.

Table 1 Antitumor activities of compounds 21—27 against H1299 cell line and SHG-44 cell line

Compd.[a]	R	R_1	*n*	IC_{50}[b]/(μmol·L^{-1})		Compd.[a]	R	R_1	*n*	IC_{50}[b]/(μmol·L^{-1})	
				H1299	SHG-44					H1299	SHG-44
Teniposide	/	/	/	0.95	0.68	**23**d	Me		1	25.97	36.67
21a	Me		1	37.98	40.52	**23**e	Me		1	21.43	13.72
21b	Me		1	26.34	29.56	**24**a	Me		2	22.85	17.33
21c	Me		1	31.85	46.29	**24**b	Me		2	30.46	32.31
21d	Me		1	24.43	30.52	**24**c	Me		2	22.96	15.73
21e	Me		1	26.63	48.59	**24**d	Me		2	28.02	24.58
21f	Me		1	23.76	38.86	**24**e	Me		2	24.19	22.47
21g	Me		1	31.81	49.82	**24**f	Me		2	37.18	45.91
21h	Me		1	44.70	44.17	**25**a	Ph		1	23.84	18.65
22a	Br		1	6.61	9.78	**25**b	Ph		1	19.80	44.21
22b	Br		1	7.66	12.93	**25**c	Ph		1	24.27	23.22
22c	Br		1	9.31	14.29	**26**a	/		2	12.30	15.22
22d	Br		1	9.34	14.41	**26**b	/		2	4.89	4.03
22e	Br		1	8.71	13.66	**26**c	/		2	6.19	7.04
22f	Br		1	10.25	18.35	**26**d	/		2	6.05	8.14
22g	Br		1	10.31	17.05	**26**e	/		2	11.81	12.90
22h	Br		1	13.89	21.76	**27**a	/		1	13.33	9.67

To be continued on the next page.

Compd.[a]	R	R_1	*n*	IC_{50}[b]/(μmol·L^{-1}) H1299	SHG-44	Compd.[a]	R	R_1	*n*	IC_{50}[b]/(μmol·L^{-1}) H1299	SHG-44
22i	Br		1	12.65	25.22	**27**b	/		1	18.11	27.86
22j	Br		1	10.92	16.80	**27**c	/		1	13.63	16.68
23a	Me		1	25.44	27.22	**27**d	/		1	9.80	14.42
23b	Me		1	17.42	29.03	**27**e	/		1	12.58	10.13
23c	Me		1	29.01	34.73	**27**f	/		1	14.26	9.64

a.  ;  ;  ; *b*. each experiment was carried out in triplicate.

21a—**21**h, **22**a—**22**j **23**a—**23**c, **24**a—**24**f, **25**a—**25**c **26**a—**26**c, **27**a—**27**f

Subsequently, we explored the preliminary structure-activity relationships(SARs) around the 2-aminothiazoles. From Table 1, it can be concluded that the cell growth inhibitory activities exhibited by the compounds appear to be closely dependent on the substitution patterns on the 2-aminothiazole core. The introduction of methyl group at the C_4- or C_5-position of the thiazoles leads to analogs with decreased potency(**21**a—**21**h, **22**f—**22**j, **23**a—**23**e and **24**a—**24**f) with the IC_{50} values of most of the compounds being more than 10 μmol/L. Meanwhile, the similar substituent effect on the potency can also be observed when the phenyl groups(**25**a—**25**c) have been introduced at the C_4-position. However, the replacement of methyl group by bromo at the C_5-position of the thiazoles results in marginal enhancement of potency, and the IC_{50} values vary from 6.61 μmol/L to 9.34 μmol/L(**22**a—**22**e). It is noteworthy that 4,5,6,7-tetrahydrobenzo[*d*]thiazoles(**26**b—**26**d) exhibit promising antitumor activities at micromolar level, whereas other counterparts only show moderate levels of activities against either H1299 cell line or SHG-44 cell line.

4 Conclusions

In this work, an antitumor activity oriented 2-aminothiazole sublibrary bearing lipophilic substituents at 4- or/and 5-position was constructed. Several compounds showed moderate to good activities against human lung cancer cell line H1299 and human glioma cell line SHG-44. In particular, the promising compound **26**b exhibited the most potent antitumor activities with IC_{50} values of 4.89 and 4.03 μmol/L against H1299 and SHG-44 cell lines, respectively. The analysis of preliminary SARs suggested that 2-aminothiazoles encompassing 4,5-butylidene moieties with the introduction of benzylic amines at the end of the chain are beneficial in promoting the cytotoxicity of the compounds. Future studies will be focused on the further structurally modification to obtain more potent compounds and their *in vivo* screening panel assay.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-016-6304-2.

References

[1] Stewart B. W., Wild C. P., *World Cancer Report 2014*, International Agency for Research on Cancer(IARC), Lyon, France, **2015**

[2] Jin C., Liang Y. J., He H., Fu L., *Eur. J. Med. Chem.*, **2011**, *46*(1), 429

[3] Xie X., Yan Y., Zhu N., Liu G., *Eur. J. Med. Chem.*, **2014**, *76*, 67

[4] Jaishree V., Ramdas N., Sachin J., Ramesh B., *J. Saudi. Chem. Soc.*, **2012**, *16*, 371

[5] Mohareb R. M., Zaki M. Y., Abbas N. S., *Steroids*, **2015**, *98*, 80

[6] Xu Z., Ba M., Zhou H., Cao Y., Tang C., Yang Y., He R., Liang Y., Zhang X., Li Z., Zhu L., Guo Y., Guo C., *Eur. J. Med. Chem.*, **2014**, *85*, 27

[7] Qin Y., Wang P., Makawana J. A., Wang Z. C., Wang Z. N., Yan G., Jiang A. Q., Zhu H. L., *Bioorg. Med. Chem. Lett.*, **2014**, *24*(22), 5279

[8] Ramírez J., Svetaz L., Quiroqa J., Abonia R., Raimondi M. Zacchino S., Insuasty B., *Eur. J. Med. Chem.*, **2015**, *92*, 866

[9] Andreani A., Rambaldi M., Mascellanib G., Rugarlib P., *Eur. J. Med. Chem.*, **1987**, *22*, 19

[10] Helal M. H. M., Salem M. A., El-Gaby M. S. A., Aljahdali M., *Eur. J. Med. Chem.*, **2013**, *65*, 517

[11] Jeankumar V. U., Kotagiri S., Janupally R., Suryadevara P., Sridevi J. P., Medishetti R., Kulkarni P., Yoqeeswari P., Sriram D., *Bioorg. Med. Chem.*, **2015**, *23*(3), 588

[12] Koppireddi S., Chilaka D. R., Avula S., Komsani J. R., Kotamraju S., Yadla R., *Bioorg. Med. Chem. Lett.*, **2014**, *24*(23), 5428

[13] Luo J., Zhao G. L., Wang Y. L., Shao H., Qu B. H., Tang L. D., *Chin. J. Med. Chem.*, **2010**, *20*(6), 496

[14] Luo J., Zhao G. L., Wang Y. L., Shao H., Qu B. H., Tang L. D., *Chin. J. Syn. Chem.*, **2011**, *19*(1), 41

[15] Zhan F. X., Wang Y. L., Zhao G. L., Xu W. R., Li Y. L., Zou M. X., Tang L. D., Wang J. W., *Chin. J. Org. Chem.*, **2009**, *29*(8), 1236

[16] Zhan F. X., Zhao G. L., Wang Y. L., Xu W. R., Tang L. D., Wang J. W., *Chin. J. Med. Chem.*, **2009**, *19*(5), 334

[17] Ayati A., Emami S., Asadipour A., Shafiee A., Foroumadi A., *Eur. J. Med. Chem.*, **2015**, *97*, 699

[18] Mishra C. B., Kumari S., Tiwari M., *Eur. J. Med. Chem.*, **2015**, *92*, 1

[19] Misra R. N., Xiao H. Y., Kim K. S., Lu S., Han W. C., Barbosa S. A., Hunt J. T., Rawlins D. B., Shan W., Ahmed S. Z., Qian L., Chen B. C., Zhao R., Bednarz M. S., Kellar K. A., Mulheron J. G., Batorsky R., Roongta U., Kamath A., Marathe P., Ranadive S. A., Sack J. S., Tokarski J. S., Pavletich N.P., Lee F. Y., Webster K. R., Kimball S. D., *J. Med. Chem.*, **2004**, *47*(7), 1719

[20] Sánchez-Martínez C., Gelbert L. M., Lallena M. J., Dios A., *Bioorg. Med. Chem. Lett.*, **2015**, *25*(17), 3420

[21] Conroy A., Stockett D. E., Walker D., Arkin M. R., Hoch U., Fox J. A., Hawtin R. E., *Cancer Chemother. Pharmacol.*, **2009**, *64*(4), 723

[22] Das J., Chen P., Norris D., Padmanabha R., Lin J., Moquin R. V., Shen Z., Cook L. S., Doweyko A. M., Pitt S., Pang S., Shen D. R., Fang Q., de Fex H. F., McIntyre K. W., Shuster D. J., Gillooly K. M., Behnia K., Schieven G. L., Wityak J., Barrish J. C., *J. Med. Chem.*, **2006**, *49*(23), 6819

[23] Lombardo L. J., Lee F. Y., Chen P., Norris D., Barrish J. C., Behnia K., Castaneda S., Cornelius L. A., Das J., Doweyko A. M., Fairchild C., Hunt J. T., Inigo I., Johnston K., Kamath A., Kan D., Klei H., Marathe P., Pang S., Peterson R., Pitt S., Schieven G. L., Schmidt R. J., Tokarski J., Wen M. L., Wityak J., Borzilleri R. M., *J. Med. Chem.*, **2004**, *47*(27), 6658

[24] Vizirianakis I. S., Chatzopoulou M., Bonovolias I. D., Nicolaou I., Demopoulos V. J., Tsiftsoglou A. S., *J. Med. Chem.*, **2010**, *53*(19), 6779

[25] El-Messery S. M., Hassan G. S., Al-Omary F. A., El-Subbaqh H. I., *Eur. J. Med. Chem.*, **2012**, *54*, 615

[26] Al-Omary F. A., Hassan G. S., El-Messery S. M., El-Subbaqh H. I., *Eur. J. Med. Chem.*, **2012**, *47*, 65

[27] Hassan G. S., El-Messery S. M., Al-Omary F. A., El-Subbaqh H. I., *Bioorg. Med. Chem. Lett.*, **2012**, *22*(20), 6318

[28] Ge Y. Q., Hao B. Q., Duan G. Y., Wang J. W., *J. Lumin.*, **2011**, *131*(5), 1070

[29] Hu H., Jiang M. Y., Xie L. J., Hu G., Zhang C. R., Zhang L. X., Zhou S. G., Zhang M. H., Gong P., *Chem. Res. Chinese Universities*, **2015**, *31*(5), 746

[30] Zhou H., Duan Z. G., Zhao S., Bao M. Y., Li Z. W., Pei Y. Z., *Chem. J. Chinese Universities*, **2015**, *36*(9), 1694

[31] Zhang R. H., Li Y. J., Ni Y. M., *Fine Chemicals*, **2000**, *17*(1), 45