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Synthesis and antitumor activities of new *N*-(5-benzylthiazol-2-yl)-2-(heteryl-5-ylsulfanyl)-acetamides

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Aim. Synthesis of a series of new *N*-(5-benzyl-thiazol-2-yl)-2-(heteryl-5-ylsulfanyl)-acetamides and study of their anticancer activity. **Methods.** Organic synthesis, analytical and spectral methods, pharmacological screening. **Results.** [2-chloro-*N*-(5-aryl-1,3-thiazol-2-yl)acetamides **3a-h** have been synthesized by the reaction of 2-amino-5-(*R*-benzyl)thiazoles with the chloroacetyl chloride. The obtained compounds react with 1-phenyl-1*H*-tetrazole-5- **4**, 4-allyl-5-phenyl-4*H*-[1,2,4]triazole-3- 5a, 4-allyl-5-furan-2-yl-4*H*-[1,2,4] triazole-3- 5b thioles, pyrimidine-2- **6a** and 4,6-dimethyl-pyrimidine-2- thioles **6b** to form a series of novel *N*-(5-benzyl-thiazol-2-yl)-2-(heterylsulfanyl)acetamides with yields of 65–96%. These compounds in the concentration of 10 μM have been evaluated for their anticancer activity against 60 human cancer cell lines of nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. The synthesized compounds displayed moderate activity in the *in vitro* screening with the tested cell lines. However, a selective influence of some compounds on several cancer cell lines was observed. The **7c**, **8a**, **8d** and **9c-g** compounds have been found to be active and highly selective towards the HOP-92 Non-Small Cell Lung Cancer cell line (*GP* = 39.45 – 65.63%), whereas 2-(4,6-*R*[1]-pyrimidin-2-ylsulfanyl)-*N*-[(5-*R*-benzyl)-thiazol-2-yl]-acetamides **9c-h** were active towards the *UO*-31 Renal Cancer cell line (*GP* = 34.43 – 60.58%). The **7c** possessed significant activity towards the *SNB*-75 CNS Cancer cell line (*GP* = –3.83 %), the **7f**, towards the *OVCAR*-4 Ovarian Cancer cell line (*GP* = 14.66 %), the **8d**, towards the *HS* 578T Breast Cancer cell line (*GP* = 11.09%), the **9g**, towards the *NCI*-H226 Non-Small Cell Lung Cancer (*GP* = 9.75%) and *UO*-31 Renal Cancer cell lines (*GP* = 16.35%). **Conclusions.** A series of new 2-amino-5-arylmetylthiazole derivatives was synthesized. These compounds have anticancer activity.

K e y w o r d s: organic synthesis, arylation, 2-amino-5-arylmetylthiazole, anticancer activity.

Introduction

2-Aminothiazole derivatives play an important role in medical chemistry. They have a diverse range of biological effects such as antitumor, antimicrobial, anticonvulsant, anti-inflammatory, antidiabetic, antiviral, antihypertensive, antileishmanial, *etc.* The information is summarized in [1–6]. The synthetic drugs belonging to the 2-aminothiazole family include famotidine, abafungin, cefdinir, sudoxicam, meloxicam, pramipexole. 2-aminothiazole is regarded as a privileged structure motif in medicinal chemistry [1–2].

Earlier we have developed a convenient method for the synthesis of 2-amino-5-R-benzylthiazoles [7–9]. Further, these thiazoles were utilized in the synthesis of biologically active compounds. Their high antimicrobal [10–12] and antitumor [13–19] potential was reported. Noteworthy, 2-amino-5-R-benzylthiazole derivatives also play an important role in analytical chemistry [20–23].

On the other hand, 2-sulfanyl-*N*-thiazol-2-yl-acetamides exhibit a wide range of biological activities such as antioxidant [24], cytotoxic [24–26] anticonvulsant [27, 28], anticholinesterase [26], antimicrobial [29], *etc.* These compounds were found to be selective inhibitors of HIF-α prolyl hydroxylase [30], enoyl-acyl carrier protein reductase FabK [31], BACE1 [32], calcium-activated chloride channel TMEM16A/Ano1 [33]. They can be used for treatment of type II diabetes [34].

Materials and Methods

All chemicals used in the study were of the analytical grade and commercially available. All reagents and solvents were used without further purification and drying.

Chemistry

2-Chloro-*N*-[5-(R-benzyl)-thiazol-2-yl]-acetamides 3a-k were prepared according the procedure described in [7].

N*-(5-R-benzylthiazol-2-yl)-2-(heterylylsulfanyl)acetamides (7-9). *General Procedure

A mixture of appropriate 2-chloro-N-[5-(R-benzyl)-thiazol-2-yl]-acetamide **3a-k** (5 mmol) and thiole **4-6** (5.5 mmol) was refluxed for 4h in ethanol (25 ml). The obtained solid products were collected by filtration, washed with ethanol (5–10 ml and recrystallized from the mixture ethanol-DMFA.

***N*-(5-benzyl-1,3-thiazol-2-yl)-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl]acetamide 7a.** Yield 93%. M.p. 186-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.37 (s, 1H, NH), 7.66 (br.s, 5H, C_6H_5), 7.35 – 7.17 (m, 6H, C_6H_4, thiazol), 4.40 (s, 2H, CH_2), 4.07 (s, 2H, CH_2). Calculated, %: C, 55.86; H, 3.95; N, 20.57. $C_{19}H_{16}N_6OS_2$. Found, %: C, 55.38; H, 3.90; N, 20.15.

***N*-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl]acetamide 7b.** Yield 73%. M.p. 204-205 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.42 (s, 1H, NH), 7.67 (br.s, 5H, C_6H_5), 7.44 (d, J = 7.7 Hz, 1H, C_6H_4), 7.41 (d, J = 7.0 Hz, 1H, C_6H_4), 7.33-7.27 (m, 3H, C_6H_4, thiazol), 4.40 (s, 2H, CH_2), 4.18 (s, 2H, CH_2). Calculated, %: C, 51.52; H, 3.41; N, 18.97. $C_{19}H_{15}ClN_6OS_2$. Found, %: C, 51.05; H, 3.39; N, 18.92.

***N*-[5-(3-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl]acetamide 7c.** Yield 81%. M.p. 199-201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.41 (s, 1H, NH), 7.67 (br.s, 5H, C_6H_5), 7.37 – 7.25 (m, 4H, C_6H_4, thiazole), 7.20 (d, J = 7.2 Hz, 1H, C_6H_4),

4.40 (s, 2H, CH_2), 4.14 (s, 2H, CH_2). Calculated, %: C, 51.52; H, 3.41; N, 18.97. $C_{19}H_{15}ClN_6OS_2$. Found, %: C, 50.99; H, 3.37; N, 18.93.

***N*-[5-(4-methoxybenzyl)-1,3-thiazol-2-yl]-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl]acetamide 7d.** Yield 87%. M.p. 179-180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.36 (s, 1H, NH), 7.66 (br.s, 5H, C_6H_5), 7.28 (s, 1H, thiazol), 7.05 (d, *J* = 7.3, 2H, C_6H_4), 6.91 (d, *J* = 7.3, 2H, C_6H_4), 4.39 (s, 2H, CH_2), 4.06 (s, 2H, CH_2), 3.75 (s, 3H, OCH_3). Calculated, %: C, 54.78; H, 4.14; N, 19.16. $C_{20}H_{18}N_6O_2S_2$. Found, %: C, 54.35; H, 4.11; N, 19.02.

2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl]-*N*-{5-[3-(trifluoromethyl)benzyl]-1,3-thiazol-2-yl}acetamide 7e. Yield 76%. M.p. 164-166 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.43 (s, 1H, NH), 7.67 (br.s, 5H, C_6H_5), 7.64 (s, 1H, C_6H_4), 7.61 – 7.47 (m, 3H, C_6H_4), 7.33 (s, 1H, thiazol), 4.41 (s, 2H, CH_2), 4.21 (s, 2H, CH_2). Calculated, %: C, 50.41; H, 3.17; N, 17.64. $C_{20}H_{15}F_3N_6OS_2$. Found, %: C, 49.98; H, 3.16; N, 17.57.

***N*-[5-(2,3-dichlorobenzyl)-1,3-thiazol-2-yl]-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl] acetamide 7f.** Yield 75%. M.p 227-228 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.42 (s, 1H, NH), 7.66 (br.s, 5H, C_6H_5), 7.54 (dd, *J* = 7.3, 1.1 Hz, 1H, C_6H_3), 7.40 (dd, *J* = 7.3, 1.1 Hz, 1H, C_6H_3), 7.28 (s, 1H, thiazol), 4.40 (s, 2H, CH_2), 4.24 (s, 2H, CH_2). Calculated, %: C, 47.80; H, 2.96; N, 17.60. $C_{19}H_{14}Cl_2N_6OS_2$. Found, %: C, 47.34; H, 2.90; N, 17.35.

***N*-[5-(2,6-dichlorobenzyl)-1,3-thiazol-2-yl]-2-[(1-phenyl-1*H*-tetrazol-5-yl)sulfanyl] acetamide 7g.** Yield 69. M.p. 230-231°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.43 (s, 1H, NH), 7.67 (br.s, 5H, C_6H_5), 7.54 (dd, *J* = 7.7, 1.1 Hz, 1H, C_6H_3), 7.40 (dd, *J* = 7.6, 1.0 Hz, 1H, C_6H_3), 7.34 (t, *J* = 7.8 Hz, 1H, C_6H_3), 7.29 (s, 1H, thiazol), 4.41 (s, 2H, CH_2), 4.25 (s, 2H, CH_2). Calculated, %: C, 47.80; H, 2.96; N, 17.60. $C_{19}H_{14}Cl_2N_6OS_2$. Found, %: C, 47.32; H, 2.92; N, 17.49.

***N*-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(5-phenyl-4-prop-2-en-1-yl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide 8a.** Yield 96%. M.p. 189-191°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.32 (br.s, 1H, NH), 8.73 (d, *J* = 5.5 Hz, 2H, Ar), 7.65 – 7.61 (m, 2H), 7.43 (dd, *J* = 7.2, 1.7 Hz, 1H, C_6H_4), 7.39 (dd, *J* = 7.0, 1.7 Hz, 1H, C_6H_4), 7.33 – 7.22 (m, 3H, Ar), 7.25 (s, 1H, thiazol), 6.06 – 5.87 (m, 1H, = CH), 5.22 (d, *J* = 10.6 Hz, 1H, = CH_2), 4.85 (d, *J* = 17.2 Hz, 1H, =CH_2), 4.72 (d, *J* = 4.0, 1H, CH_2), 4.24 (s, 1H, CH_2), 4.17 (s, 1H, CH_2). Calculated, %: C, 57.31; H, 4.18; N, 14.53. $C_{23}H_{20}ClN_5OS_2$. Found, %: C, 56.90; H, 4.16; N, 14.50.

***N*-[5-(4-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(5-phenyl-4-prop-2-en-1-yl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide 8b.** Yield 95%. M.p. 187-188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.31 (br.s, 1H, NH), 7.63 – 7.57 (m, 2H, Ar), 7.54 (s, 3H, Ar), 7.36 (d, *J* = 8.2 Hz, 2H, C_6H_4), 7.30 – 7.21 (m, 3H, Ar, thiazole), 6.04 – 5.88 (m, 1H, = CH), 5.22 (d, *J* = 10.3 Hz, 1H, = CH_2), 4.83 (d, *J* = 17.1 Hz, 1H, = CH_2), 4.63 (d, *J* = 4.0, 2H, NCH_2), 4.22 (s, 2H, CH_2), 4.08 (s, 2H, CH_2). Calculated, %: C, 57.31; H, 4.18; N, 14.53. $C_{23}H_{20}ClN_5OS_2$. Found, %: C, 57.07; H, 4.15; N, 14.39.

***N*-[5-(3-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(5-furan-2-yl-4-prop-2-en-1-yl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide 8c.** Yield 84%. M.p. 184-185°C. ^{1}H NMR (400 MHz,

DMSO-d_6) δ: 12.33 (br.s, 1H, NH), 7.92 (br.s, 1H, furyl), 7.40 – 7.24 (m, 4H, C_6H_4, thiazole), 7.21 (d, *J* = 7.0 Hz, 1H, C_6H_4), 7.01 (d, *J* = 2.9 Hz, 1H, furyl), 6.71-6.68 (m, 1H, furyl), 6.03 – 5.87 (m, 1H, = CH), 5.16 (d, *J* = 10.3 Hz, 1H, = CH_2), 4.85 (d, *J* = 17.3 Hz, 1H, = CH_2), 4.79 (d, *J* = 3.6 Hz, 2H, NCH_2), 4.19 (s, 1H, CH_2), 4.09 (s, 1H, CH_2). Calculated, %: C, 53.44; H, 3.84; N, 14.84. $C_{21}H_{18}ClN_5O_2S_2$. Found, %: C, 53.09; H, 3.81; N, 14.71.

***N*-[5-(4-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(5-furan-2-yl-4-prop-2-en-1-yl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide 8d.** Yield 84%. M.p. 193-194°C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.29 (br.s, 1H, NH), 7.93 (br.s, 1H, furyl), 7.35 (d, *J* = 8.1 Hz, 2H, C_6H_4), 7.28-7.25 (m, 3H, C_6H_4, thiazole), 7.02 (d, *J* = 3.3 Hz, 1H, furyl), 6.71-6.69 (m, 1H, furyl), 5.99-5.92 (m, 1H, = CH), 5.17 (d, *J* = 10.3 Hz, 1H, = CH_2), 4.86 (d, *J* = 17.2 Hz, 1H, = CH_2), 4.79 (d, *J* = 3.6 Hz, 2H, NCH_2), 4.19 (s, 2H, CH_2), 4.08 (s, 2H, CH_2). Calculated, %: C, 53.44; H, 3.84; N, 14.84. $C_{21}H_{18}ClN_5O_2S_2$. Found, %: C, 53.02; H, 3.80; N, 14.69.

***N*-[5-(4-fluorobenzyl)-1,3-thiazol-2-yl]-2-[(5-furan-2-yl-4-prop-2-en-1-yl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetamide 8e.** Yield 83%. M.p. 190-191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.27 (br.s, 1H, NH), 7.92 (br.s, 1H, furyl), 7.32 – 7.24 (m, 3H, Ar, thiazol), 7.11 (t, *J* = 8.6 Hz, 2H, C_6H_4), 7.01 (d, *J* = 3.3 Hz, 1H, furyl), 6.71-6.69 (m, 1H, furyl), 6.03 – 5.88 (m, 1H, = CH), 5.17 (d, *J* = 10.4 Hz, 1H, = CH_2), 4.86 (d, *J* = 17.3 Hz, 1H, = CH_2), 4.79 (d, *J* = 3.7 Hz, 2H, NCH_2), 4.18 (s, 2H, CH_2), 4.06 (s, 2H, CH_2). Calculated, %: C, 55.37; H, 3.98; N, 15.37. $C_{21}H_{18}FN_5O_2S_2$. Found, %: C, 54.97; H, 3.94; N, 15.23.

N-[5-(4-methylbenzyl)-1,3-thiazol-2-yl]-2-(pyrimidin-2-ylsulfanyl)acetamide 9a. Yield 77%. M.p. 153-154°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.24 (s, 1H, NH), 8.59 (d, *J* = 4.8 Hz, 2H, 4,6H-pyrymidine), 7.26 (s, 1H, thiazole), 7.21 (t, *J* = 4.8 Hz, 1H, 5H-pyrymidine), 7.14 (d, *J* = 7.2, 2H, C_6H_4), 7.07 (d, *J* = 7.2, 2H, C_6H_4), 4.16 (s, 2H, CH_2), 4.11 (s, 2H, CH_2), 2.33 (s, 3H, CH_3). Calculated, %: C, 57.28; H, 4.52; N, 15.72. $C_{17}H_{16}N_4OS_2$. Found, %: C, 56.96; H, 4.46; N, 15.60.

***N*-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-2-(pyrimidin-2-ylsulfanyl)acetamide 9b.** Yield 83%. M.p. 150-152 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.27 (s, 1H, NH), 8.60 (d, *J* = 4.8 Hz, 2H, 4,6H-pyrymidine), 7.44 (dd, *J* = 7.4, 1.6 Hz, 1H, C_6H_4), 7.41 (dd, *J* = 7.5, 1.7 Hz, 1H, C_6H_4), 7.33 – 7.26 (m, 2H, C_6H_4), 7.25 (s, 1H, thiazole), 7.21 (t, *J* = 4.8 Hz, 1H, 5H-pyrymidine), 4.17 (s, 2H, CH_2), 4.15 (s, 2H, CH_2). Calculated, %: C, 50.99; H, 3.48; N, 14.87. $C_{16}H_{13}ClN_4OS_2$. Found, %: C, 50.73; H, 3.42; N, 14.79.

***N*-(5-benzyl-1,3-thiazol-2-yl)-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9c.** Yield 89%. M.p. 177-178 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.21 (s, 1H, NH), 7.33-7.29 (m, 3H, C_6H_5), 7.27-7.23 (m, 3H, C_6H_5, thiazole), 6.95 (s, 1H, pyrymidine), 4.12 (s, 2H, CH_2), 4.07 (s, 2H, CH_2), 2.30 (s, 6H, CH_3). Calculated, %: C, 58.35; H, 4.90; N, 15.12. $C_{18}H_{18}N_4OS_2$. Found, %: C, 57.89; H, 4.83; N, 15.00.

***N*-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9d.** Yield 65%. M.p. 186-187 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.27 (s, 1H, NH), 7.38 (dd, *J* = 7.4, 1.7 Hz, 1H, C_6H_4), 7.35

(dd, J = 7.6, 1.7 Hz, 1H, C_6H_4), 7.30 – 7.27 (m, 2H, C_6H_4), 7.23 (s, 1H, thiazole), 6.95 (s, 1H, pyrymidine), 4.08 (s, 4H, CH_2), 2.29 (s, 6H, CH_3). Calculated, %: C, 53.39; H, 4.23; N, 13.84. $C_{18}H_{17}ClN_4OS_2$. Found, %: C, 52.96; H, 4.18; N, 13.71.

***N*-[5-(3-chlorobenzyl)-1,3-thiazol-2-yl]-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9e.** Yield 69%. M.p. 184-185 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.25 (s, 1H, NH), 7.33 (d, J = 7.8 Hz, 1H, C_6H_4), 7.31 (d, J = 2.2 Hz, 1H, C_6H_4), 7.28-7.25 (m, 2H, C_6H_4, thiazole), 7.21 (d, J = 7.4 Hz, 1H, C_6H_4), 6.93 (s, 1H, pyrymidine), 4.07 (s, 4H, CH_2), 2.28 (s, 6H, CH_3). Calculated, %: C, 53.39; H, 4.23; N, 13.84. $C_{18}H_{17}ClN_4OS_2$. Found, %: C, 52.99; H, 4.19; N, 13.74.

***N*-[5-(2,3-dichlorobenzyl)-1,3-thiazol-2-yl]-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9f.** Yield 91%. M.p. 127-128 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.19 (s, 1H, NH), 7.22 (s, 1H, thiazole), 7.12 (d, J = 7.8 Hz, 1H, C_6H_4), 7.09 (d, J = 7.9 Hz, 1H, C_6H_4), 6.94 (s, 1H, pyrymidine), 4.07 (s, 2H, CH_2), 4.00 (s, 2H, CH_2), 2.28 (s, 6H, CH_3), 2.25 (s, 3H, CH_3). Calculated, %: C, 59.35; H, 5.24; N, 14.57. $C_{19}H_{20}N_4OS_2$. Found, %: C, 58.95; H, 5.17; N, 14.39.

***N*-[5-(2,3-dichlorobenzyl)-1,3-thiazol-2-yl]-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9g.** Yield 88%. M.p. 184-185 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.30 (br.s, 1H, NH), 7.53 (dd, J = 7.8, 1.6 Hz, 1H, C_6H_3), 7.39 (dd, J = 7.7, 1.6 Hz, 1H, C_6H_3), 7.34-7.30 (m, 1H, C_6H_3), 7.25 (s, 1H, thiazole), 6.94 (s, 1H, pyrymidine), 4.23 (s, 2H, CH_2), 4.08 (s, 2H, CH_2), 2.27 (s, 6H, CH_3). Calculated, %: C, 49.20; H, 3.67; N, 12.75. $C_{18}H_{16}Cl_2N_4OS_2$. Found, %: C, 48.94; H, 3.62; N, 12.66.

***N*-[5-(3,4-dichlorobenzyl)-1,3-thiazol-2-yl]-2-[(4,6-dimethylpyrimidin-2-yl)sulfanyl]acetamide 9h.** Yield 89%. M.p. 165-167 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.28 (s, 1H, NH), 7.56 (d, J = 8.2 Hz, 1H, C_6H_4), 7.53 (s, 1H, C_6H_4), 7.28 (s, 1H, thiazole), 7.25 (d, J = 8.1 Hz, 1H, C_6H_4), 6.94 (s, 1H, pyrymidine), 4.09 (s, 4H, CH_2), 2.28 (s, 6H, CH_3). Calculated, %: C, 49.20; H, 3.67; N, 12.75. $C_{18}H_{16}Cl_2N_4OS_2$. Found, %: C, 48.88; H, 3.63; N, 12.70.

Pharmacology

Cytotoxic activity against malignant human tumor cells

A primary anticancer screening was performed on a panel of approximately 60 human tumor cell lines derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda. The tested compounds of 10^{-5}M concentration were added to the culture with subsequent incubation for 48 h. Endpoint determinations were made with a protein binding dye, sulforhodamine B (SRB). The results for each tested compound were reported as the evaluated spectrophotometrically percent growth of the treated cells versus the control untreated cells. The cytotoxic and/or growth inhibitory effects of the most active selected compounds were tested in vitro against the full panel of about 60 human tumor cell lines at 10-fold dilutions of five concentrations ranging from 10^{-4} to 10^{-8}M. The 48-h continuous drug exposure protocol was followed and an SRB protein assay was used to estimate the cell viability or growth.

Using seven absorbance measurements [time zero, (Tz), control growth in the absence

of drug, (C), and test growth in the presence of drug at five concentration levels (Ti)], the percent growth was calculated at each level of the drug concentrations. The percent growth inhibition was calculated as:

- $[(Ti - Tz)/(C - Tz)] \times 100$ for concentrations for which $Ti \geq Tz$
- $[(Ti - Tz)/Tz] \times 100$ for concentrations for which $Ti < Tz$.

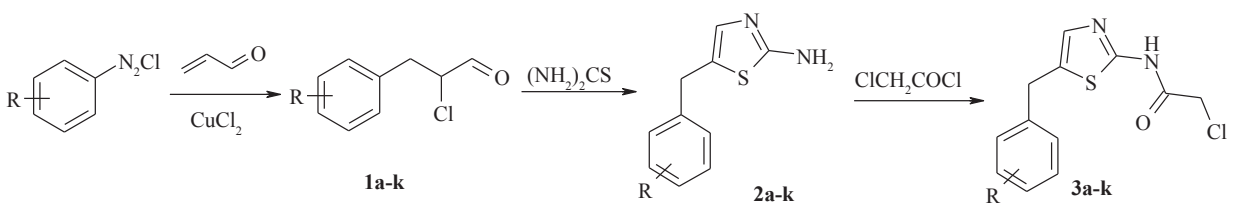
Three dose-response parameters were calculated for each compound. Growth inhibition of 50% (GI_{50}) was calculated from $[(Ti - Tz)/(C - Tz)] \times 100 - 50$, which is the drug concentration resulting in a 50% lower net protein increase in the treated cells (measured by SRB staining) as compared to the net protein increase in the control cells. The drug concentration resulting in the total growth inhibition (TGI) was calculated from Ti = Tz. The LC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from $[(Ti - Tz)/Tz] \times 100 = -50$. Values were calculated for each of these three parameters if the level of activity was reached; however, if the effect was not reached or was exceeded, the value for that parameter was expressed as more or less than the maximum or minimum concentration was tested..

Results and Discussion

Chemistry

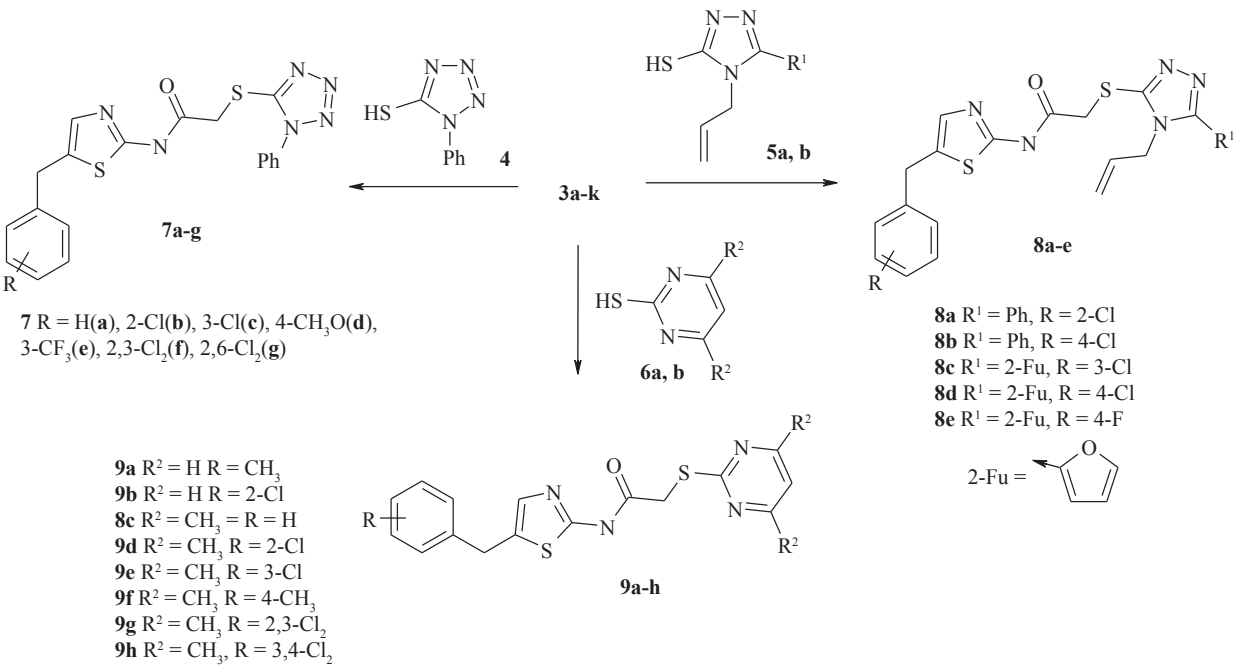
In this work we reported about the antitumor activity of the new 2-(1-phenyl-*1H*-tetrazol-5-ylsulfanyl)- **7**, 2-(4-Allyl-5-phenyl-*4H*-[1,2,4]triazol-3-ylsulfanyl)- **8**, 2-(4,6-Dimethyl-pyrimidin-2-ylsulfanyl)- **9**, *N*-[5-(3-R-benzyl)-thiazol-2-yl]-acetamides. Their synthesis is presented in the Schemes 1 and 2. At the first step the acrolein was chloroarylated by diazonium salts in the presence of copper (II) chloride in condition of Meerwein reaction [35]. Refluxing of 3-aryl-2-chloro-propanals **1a-h** and thiourea in ethanol gives 5-substituted 2-aminothiazoles [7]. To obtain chloroacetamides **3a-h** 2-amino function of corresponding 5-substituted 2-aminothiazoles **3a-h** were acylated with chloroacetyl chloride in dry dioxane in the presence of triethylamine [7].

The target sulfanylamides **7-9** were synthesized by the reaction of **3a-h** with 1-phenyl-1*H*-tetrazole-5- **4**, 4-allyl-5-phenyl-4*H*-[1,2,4]triazole-3- **5a**, 4-allyl-5-furan-2-yl-*4H*-[1,2,4]triazole-3- **5b** thioles and pyrimidine-2- **6a** and 4,6-dimethyl-pyrimidine-2- thioles in the presence of triethylamine. Overall yields for the amides **7**, **8** and **9** were 65– 96% that allowed the creation of a library of such compounds without additional chromatographic purification.



1 – 3 R = H(**a**), CH_3(**b**), CH_3O(**c**), 4-F(**d**), 2-Cl(**e**), 3-Cl(**f**), 4-Cl(**g**), 3-CF_3(**h**), 2,3-Cl_2(**i**), 2,6-Cl_2(**j**), 3,4-Cl_2(**k**)

Scheme 1. Synthesis of 2-Chloro-N-[5-(R-benzyl)-thiazol-2-yl]-acetamides **3a-k**



Scheme 2. Synthesis of N-(5-benzyl-thiazol-2-yl)-2-(heteryl-sulfanyl)acetamides **7** – **9**

The structure of synthesized compounds was elucidated by ^{1}H NMR and microanalyses. In ^{1}H NMR spectra, all protons were seen according to expected chemical shifts and integral values. In ^{1}H NMR spectra, there appeared a singlet at δ 12.19-12.43 ppm indicative of H–N amide protons and two other singlets at δ 4.00-4.25 and 4.07-4.72 for methylene groups of benzyl radical and amide fragments respectively. The proton of thiazole ring was observed at δ 7.22-7.33 ppm.

Anticancer activity

The synthesized compounds were selected by the National Cancer Institute (NCI) Developmental Therapeutic Program (www.dtp.nci.nih.gov) for the *in vitro* cell line screening to investigate their anticancer activity. Anticancer assays were performed according to the NCI protocol, which is described elsewhere [36–39]. The screening results are shown in Table 1.

The synthesized compounds displayed moderate activity in the *in vitro* screening on the tested cell lines. However, it was observed a selective influence of some compounds on several cancer cell lines (Table 1). Compounds **7c, 8a, 8d** and **9c-g** have been found to be active and to have a high selectivity on the HOP-92 Non-Small Cell Lung Cancer cell line (GP = 39.45 – 65.63%), whereas 2-(4,6-R^1-pyrimidin-2-ylsulfanyl)-N-[(5-R-benzyl)-thiazol-2-yl]-acetamides **9c-h** are active on [the] UO-31 Renal Cancer cell line (GP = 34.43– 60.58%). Compound **7c** was highly active on the leukemia SNB-75 CNS Cancer cell line (GP = –3.83 %), **7f** – on the renal cancer OVCAR-4 Ovarian Cancer cell line (GP = 14.66 %), **8d** – on the HS 578T Breast Cancer cell line (GP =

Table 1. **Cytotoxic activity of the tested compounds in the concentration of 10^{-5} M against 60 cancer cell lines**

Test compounds	Average growth, %	Range of growth, %	The most sensitive cell line (cancer line/type) GP%
7a	95.95	54.15 – 121.62	SNB-75 (CNS Cancer) 54.15; MALME-3M (Melanoma) 71.10; A498 (Renal Cancer) 66.27; TK-10 (Renal Cancer) 74.05; UO-31 (Renal Cancer) 73.00
7b	104.46	81.23 – 146.87	UO-31 (Renal Cancer) 81.23
7c	83.98	-3.83 – 120.15	HOP-92 (Non-Small Cell Lung Cancer) 60.58; SF-539 (CNS Cancer) 30.16; SNB-19 (CNS Cancer) 59.12; **SNB-75 (CNS Cancer) -3.83;** U251 (CNS Cancer) 59.56; UO-31 (Renal Cancer) 56.56; HS 578T (Breast Cancer) 54.92
7d	94.33	70.38– 111.68	SR (Leukemia) 70.38; NCI-H522 (Non-Small Cell Lung Cancer) 70.33
7f	81.69	14.66 – 112.04	HCT-116 (Colon Cancer) 24.68; SNB-75 (CNS Cancer) 47.17; OVCAR-4 (**Ovarian Cancer) 14.66;** SK-OV-3 (Ovarian Cancer) 26.95; MDA-MB-231/ ATCC (Breast Cancer) 48.55
7g	86.25	31.75– 107.96	SR (Leukemia) 73.88; HCT-116 (Colon Cancer) 48.47; OVCAR-4 (Ovarian Cancer) 31.75; SK-OV-3 (Ovarian Cancer) 43.22
8a	96.06	65.74 – 123.84	HOP-92 (Non-Small Cell Lung Cancer) 53.62; CAKI-1 (Renal Cancer) 74.02; UO-31 (Renal Cancer) 65.74
8b	87.78	31.61 – 120.10	HOP-62 (Non-Small Cell Lung Cancer) 68.75; NCI-H460 (Non-Small Cell Lung Cancer) 60.28; HCT-116 (Colon Cancer) 58.56; SF-539 (CNS Cancer) 48.51; SNB-19 (CNS Cancer) 65.56; SNB-75 (CNS Cancer) 31.61; U251 (CNS Cancer) 55.80
8c	94.15	66.36 – 121.48	SR (Leukemia) 66.47; UACC-62 (Melanoma) 66.36; CAKI-1 (Renal Cancer) 71.94
8d	63.05	11.09 – 131.81	HOP-62 (Non-Small Cell Lung Cancer) 27.52; HOP-92 (Non-Small Cell Lung Cancer) 39.45; NCI-H460 (Non-Small Cell Lung Cancer) 42.83; NCI-H522 (Non-Small Cell Lung Cancer) 28.62; SF-539 (CNS Cancer) 23.05; SNB-75 (CNS Cancer) 17.02; LOX IMVI (Melanoma) 74.21; SK-MEL-28 (Melanoma) 36.74; UACC-62 (Melanoma) 38.99; OVCAR-8 (Ovarian Cancer) 36.26; NCI/ADR-RES (Ovarian Cancer) 27.20; SK-OV-3 (Ovarian Cancer) 63.12; MDA-MB-231/ATCC (Breast Cancer) 63.88; **HS 578T (Breast Cancer) 11.09;** BT-549 (Breast Cancer) 31.96; T-47D (Breast Cancer) 68.00
8e	93.24	75.48– 115.58	UACC-62 (Melanoma) 75.48
9a	80.91	26.42 – 110.58	CCRF-CEM (Leukemia) 60.81; K-562 (Leukemia) 42.18; MDA-MB-435 (Melanoma) 26.42
9b	82.09	22.50 – 106.19	K-562 (Leukemia) 43.32; HCT-116 (Colon Cancer) 63.22; MDA-MB-435 (Melanoma) 22.50; MDA-MB-468 (Breast Cancer) 48.57
9c	91.90	56.27 – 107.33	HOP-92 (Non-Small Cell Lung Cancer) 61.89; SN12C (Renal Cancer) 69.96; UO-31 (Renal Cancer) 56.27
9d	86.08	53.99 – 118.32	HOP-62 (Non-Small Cell Lung Cancer) 67.62; HOP-92 (Non-Small Cell Lung Cancer) 54.70; SNB-75 (CNS Cancer) 61.50; A498 (Renal Cancer) 53.99; UO-31 (Renal Cancer) 60.58

continued on next page

Table 1. (continue)

Test compounds	Average growth, %	Range of growth, %	The most sensitive cell line (cancer line/type) GP%
9e	95.16	58.30 – 118.25	HOP-92 (Non-Small Cell Lung Cancer) 65.63; CAKI-1 (Renal Cancer) 74.81; UO-31 (Renal Cancer) 58.30
9f	79.93	42.10 – 110.42	CCRF-CEM (Leukemia) 46.50; HOP-92 (Non-Small Cell Lung Cancer) 56.10; MALME-3M (Melanoma) 65.47; SK-MEL-5 (Melanoma) 42.63; A498 (Renal Cancer) 42.10; UO-31 (Renal Cancer) 34.43
9g	77.42	16.35 – 104.41	HOP-92 (Non-Small Cell Lung Cancer) 48.51; **NCI-H226 (Non-Small Cell Lung Cancer) 9.75;** SK-MEL-5 (Melanoma Renal Cancer) 59.15; A498 (Renal Cancer) 42.69; SN12C (Renal Cancer) 47.55; **UO-31 (Renal Cancer) 16.35**
9h	88.20	52.08 – 121.09	NCI-H322M (Non-Small Cell Lung Cancer) 66.05; SN12C (Renal Cancer) 71.92; UO-31 (Renal Cancer) 52.08

11.09%), **9g** – on the NCI-H226 Non-Small Cell Lung Cancer (GP = 9.75%) and UO-31 Renal Cancer (GP = 16.35%) cell lines.

Finally, compound **8d** was selected for *in vitro* testing against a full panel of about 60 tumor cell lines at 10-fold dilutions of five concentrations (100 μM, 10 μM, 1 μM, 0.1 μM, and 0.01 μM). Based on the cytotoxicity assays, three antitumor activity dose-response parameters were calculated for each experimental agent against each cell line: GI_{50} – molar concentration of the compound that inhibits 50% net cell growth; TGI – molar concentration of the compound leading to total inhibition; and LC_{50} – molar concentration of the compound leading to 50% net cell death.

The most potent and selective cytotoxic activity of compound **8d** against separate tumor cell lines is shown in Table 2.

We have found that compound **8d** possesses moderate activity against the CNS cancer cell lines SNB-75and U251 (GI_{50} = 2.87, and 82.2), Non-small cell lung cancer cell lines HOP-62 (GI_{50} = 32.5), Melanoma cell line LOX IMVI (GI50 = 28.0), Ovarian Cancer cell lines OVCAR-8 and SK-OV-3 (GI_{50} = 9.32, and 3.05) and Breast Cancer cell line HS 578T (GI_{50} = 46.7).

Table 2. **Influence of compound 8d on the growth of tumor cell lines**

Panel	Cell line	GI_{50} (μM)	TGI(μM)
Non-small cell lung cancer	HOP-62	32.5	>100
CNS Cancer	SNB-75	2.87	10.4
CNS Cancer	U251	82.2	>100
Melanoma	LOX IMVI	28.0	>100
Ovarian Cancer	OVCAR-8	9.32	>100
CNS Cancer	SK-OV-3	3.05	>100
Breast Cancer	HS 578T	46.7	>100

Conclusions

A series of novel *N*-(5-R-benzylthiazol-2-yl)-2-(heterylylsulfanyl)acetamide derivatives were synthesized and their anticancer activity was investigated. The compounds with a significant level of anticancer activity towards the selected cancer cell lines have been found and may be used for further optimization.

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Синтез та протипухлинна активність нових *N*-(5-бензилтіазол-2-іл)-2-(гетерил-5-ілсульфаніл)ацетамідів

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Мета. Синтез та вивчення протипухлинної активності ряду нових *N*-(5-бензилтіазол-2-іл)-2-(гетерил-5-ілсульфаніл)ацетамідів. **Методи.** Органічний синтез, аналітичні та спектральні методи, фармакологічний скринінг. **Результати.** Реакцією 2-аміно-5-(*R*-бензил) тіазолів з хлорацетилхлоридом отримано 2-хлор-*N*-(5-арил-1,3-тіазол-2-іл)ацетаміди **3a-h** з добрими виходами. Вони взаємодіють з 1-феніл-*1H*-тетразол-5-**4**, 4-аліл-5-феніл-4*H*-[1,2,4] триазол-3-**5a**, 4-аліл-5-фуран-2-іл-*4H*-[1,2,4]триазол-3-**5b**, тіолами, а також піримідин-2-**6a** та 4,6-диметилпіримідин-2-**6b** тіолами з утворенням ряду нових *N*-(5-бензилтіазол-2-іл)-2-(гетерилсульфаніл)ацетамідів з виходом 65–96%. Для цих сполук у концентрації 10 мкМ вивчено протипухлинну активність на 60 лініях раку. Клітини пухлин людини було отримано з дев'яти різних типів раку: лейкемії, меланоми, легенів, епітелію, ЦНС, яєчників, нирок, простати та молочної залози. Зазначені сполуки проявили помірковану активність при скринінгу *in vitro* на більшості клітинних лініях. Проте спостерігалася селективність дії деяких сполук. Встановлено, що сполуки **7c, 8a, 8d** та **9c-g** були активними та виявили високу селективність відносно клітинної лінії раку легенів HMC-92 (*GP* = 39,45–65,63%), тоді як 2-(4,6-R^1-піримідін-2-іл-сульфаніл)-*N*-[(5-*R*-бензил) тіазол-2-іл]ацетати (**9c-h)** активні щодо клітинної лінії *UO*-31. (*GP* = 34,43–60,58%). Сполука **7c** є високоактивною щодо клітинної лінії раку ЦНС *SNB*-75 (*GP* = –3,83%), **7f** – до лінії раку яєчників *OVCAR*-4 (*GP* = 14,66%), **8d** – до лінії раку молочної залози *HS* 578T (*GP* = 11,09%), а **9g** – до ліній недрібноклітинного раку легень *NCM*-H226 (*GP* = 9,75%) та раку нирок *UO*-31 (*GP* = 16,35%). **Висновки.** Синтезовано ряд нових похідних 2-аміно-5-арилметилтіазолу. Встановлено, що ці сполуки є перспективними для пошуку інноваційних протиракових агентів.

Ключові слова: органічний синтез, арилювання, 2-аміно-5-арилметилтіазол, протипухлинна активність.

Синтез и противоопухолевая активность новых *N*-(5-бензилтиазол-2-ил)-2-(гетерил-5-илсульфанил)ацетамидов

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Цель. Синтез и изучение противоопухолевой активности ряда новых *N*-(5-бензилтиазол-2-ил)-2-(гетерил-5-илсульфанил)ацетамидов. **Методы.** Органический синтез, аналитические и спектральные методы, фармакологический скрининг. **Результаты.** Реакцией 2-амино-5-(*R*-бензил)тиазолов с хлорацетилхлоридом получены 2-хлор-*N*-(5-арил-1,3-тиазол-2-ил)ацетамиды **3a-h** с хорошими выходами. Они взаимодействуют с 1-фенил-*1H*-тетразол-5-**4**, 4-аллил-5-фенил-4*H*-[1,2,4] триазол-3-**5a**, 4-аллил-5-фуран-2-ил-*4H*-[1,2,4]триазол-3-**5b** тиолами, а также пиримидин-2-**6a** и 4,6-диметилпиримидин-2-**6b** тиолами с образованием ряда новых *N*-(5-бензилтиазол-2-ил)-2(гетерилсульфанил) ацетамидов с выходом 65–96%. Для этих соединений в концентрации 10 мкм изучено противоопухолевую

активность на 60 линиях рака. Клетки опухолей были получены из девяти различных типов рака: лейкемии, меланомы, легких, эпителия, ЦНС, яичников, почек, простаты и молочной железы. Полученные соединения проявили умеренную активность при скрининге *in vitro* на большинстве клеточных линий. Однако наблюдалось селективное влияние некоторых соединений. Установлено, что соединения **7c, 8a, 8d** и **9c-g** активны и обнаружили высокую селективность по отношению к клеточной линии рака легких НМС-92 (*GP* = 39,45–65,63%), тогда как 2-(4,6-*R*[1]-пиримидин-2-илсульфанил)-*N*-[(5-*R*-бензил)тиазол-2-ил]ацетаты (**9c-h)** активны в отношении клеточной линии рака опухолей *UO*-31. (*GP* = 34,43–60,58%). Соединение **7c** высокоактивно относительно линии рака ЦНС *SNB*-75 (*GP* = –3,83%), **7f** – к линии рака яичников *OVCAR*-4 (*GP* = 14,66%), **8d** – к линии рака молочной железы *HS* 578T (*GP* = 11,09%), а **9g** – к линиям немелкоклеточного рака легких *NCM-H*226 (*GP* = 9,75%) и рака почек *UO*-31 (*GP* = 16,35%). **Выводы.** Синтезирован ряд новых производных 2-амино-5-арилметилтиазола. Установлено, что эти соединения являются перспективными для поиска инновационных противораковых агентов.

Ключевые слова: органический синтез, арилирование, 2-амино-5-арилметилтиазол, противоопухолевая активность.

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