

UDC 547.789

THE SYNTHESIS AND ANTICANCER PROPERTIES OF 2-(4-AMINO-5-METHYL-4H-[1,2,4]TRIAZOL-3-YLSULFANYL)-N-(5-R-BENZYLTHIAZOL-2-YL)-ACETAMIDES

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Key words: 2-aminothiazole; 1,2,4-triazole derivatives; chloroacetamides; arylation; Meerwein reaction; 4-amino-1,2,4-triazole-3-thiole; anticancer activity

3-Aryl-2-chloropropanals 2a-h have been prepared by the reaction of arenediazonium chlorides 1a-h with acrolein in the conditions of Meerwein arylation (water-acetone, CuCl_2 as a catalyst). These aldehydes react with thiourea by refluxing in ethanol to obtain 2-amino-5-R-benzyl-1,3-thiazoles 3a-h ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 3\text{-CF}_3, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2, 3,4\text{-Cl}_2, 3\text{-Cl-4-Me}$) with high yields. The resulting 2-aminothiazoles were acylated with chloroacetic acid chlorides to form 2-chloro-N-(5-aryl-1,3-thiazol-2-yl)acetamides 4a-h with the yields of 68-91%. By the reaction of compounds 4a-h with 4-amino-5-methyl-4H-1,2,4-triazole-3-thiole 5 a series of novel 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-R-benzylthiazol-2-yl)-acetamides 6a-h (71-86%) have been synthesized. These compounds have been evaluated for their anticancer activity against 60 cancer lines in the concentration of 10 μM . The human tumour cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. Among all the derivatives, compounds 6a-c, 6e,f ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2$) have been found to be active and have a high selectivity in relation to melanoma, while 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-[5-(2-chlorobenzyl)-thiazol-2-yl]-acetamide (6a) and 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-[5-(3,4-dichlorobenzyl)-thiazol-2-yl]-acetamide (6g) are active in relation to breast cancer.

СИНТЕЗ І ПРОТИПУХЛИННА АКТИВНІСТЬ 2-(4-АМІНО-5-МЕТИЛ-4Н-[1,2,4]ТРИАЗОЛ-3-ІЛСУЛЬФАНИЛ)-N-(5-R-БЕНЗИЛТІАЗОЛ-2-ІЛ)-АЦЕТАМІДІВ

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Ключові слова: 2-амінотіазол; похідні 1,2,4-тріазолу; хлорацетаміди; арилювання; реакція Меєрвейна; 4-аміно-[1,2,4]тріазол-3-тіол; протираковий активність

Взаємодією арендіазонієвих солей 1a-h з акролеїном у водно-ацетоновому середовищі за наявності катализатора хлориду міді(II) (умови реакції Меєрвейна) синтезовано 3-арил-2-хлоропропанали 2a-h. Ці альдегіди реагують з тиосечовиною при нагріванні у спирті, утворюючи 2-аміно-5-R-бензил-1,3-тіазоли 3a-h ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 3\text{-CF}_3, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2, 3,4\text{-Cl}_2, 3\text{-Cl-4-Me}$) з високими виходами. Ацилюванням амінотіазолів 3a-h хлорангідридом хлороцтової кислоти за наявності триетиламіну одержано 2-хлор-N-(5-арил-1,3-тіазол-2-іл)ацетаміди 4a-h з виходами 68-91%. Кип'ятінням цих хлорацетамідів з еквімолярною кількістю 4-аміно-5-метил-4H-[1,2,4]тріазол-3-тіолу 5 протягом 4 годин у присутності триетиламіну синтезували серію нових 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-(5-R-бензилтіазол-2-іл)-ацетамідів 6a-h, виходи яких складають 71-86%. Вивчена протиракова активність одержаних сполук. Досліджували протираковий активність щодо 60 ракових ліній в концентрації 10 мкМ. Лінії пухлинних клітин людини були отримані з дев'яти різних типів раку: лейкемії, меланому, раку легень, товстої кишки, ЦНС, яєчників, нирок, простати, молочної залози. Встановлено, що сполуки 6a-c, 6e,f ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2$) найактивніші відносно ліній меланому, а 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-[5-(2-хлорбензил)тіазол-2-іл]ацетамід (6a) і 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-[5-(3,4-дихлорбензил)тіазол-2-іл]ацетамід (6g) – відносно ліній раку молочної залози.

СИНТЕЗ И ПРОТИВООПУХОЛЕВАЯ АКТИВНОСТЬ 2-(4-АМИНО-5-МЕТИЛ-4Н-[1,2,4]ТРИАЗОЛ-3-ІЛСУЛЬФАНИЛ)-N-(5-R-БЕНЗИЛТІАЗОЛ-2-ІЛ)-АЦЕТАМИДОВ

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Ключевые слова: 2-амінотіазол; производные 1,2,4-тріазола; хлорацетаміди; арилювання; реакція Меєрвейна; 4-аміно-[1,2,4]тріазол-3-тіол; противоопухолева активність

Взаимодействием арендиазониевых солей 1a-h с акролеином в водно-ацетоновой среде в присутствии катализатора хлорида меди(II) (условия реакции Меєрвейна) синтезированы 3-арил-2-хлоропропанали 2a-h. Эти альдегиды реагируют с тиомочевинной при нагревании в спирте, образуя 2-аміно-5-R-бензил-1,3-тіазоли 3a-h ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 3\text{-CF}_3, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2, 3,4\text{-Cl}_2, 3\text{-Cl-4-Me}$) с высокими выходами. Ацилированием амінотіазолов 3a-h хлорангідридом хлороцтової кислоти в присутствии триетиламіна получили 2-хлор-N-(5-арил-1,3-тіазол-2-іл)ацетаміди 4a-h с виходами 68-91%. Кип'ятінням останніх з еквімолярним количеством 4-аміно-5-метил-4H-[1,2,4]тріазол-3-тіола 5 на протязенні 4 годин в присутствии триетиламіна синтезували серію нових 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-(5-R-бензилтіазол-2-іл)-ацетамідів 6a-h, виходи которых составляют 71-86%. Изучена противоопухолева активність полученных соединений. Исследование противоопухолева активности соединений проводили на 60 линиях раковых клеток в концентрации 10 мкМ. Линии опухолевых клеток человека были получены из девяти различных типов рака: лейкемии, меланомы, рака легких, толстой кишки, ЦНС, яичников, почек, простаты, молочной железы. Установлено, что соединения 6a-c, 6e,f ($R = 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 2,4\text{-Cl}_2, 2,5\text{-Cl}_2$) наиболее активны относительно линий меланомы, а 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-[5-(2-хлорбензил)тіазол-2-іл]ацетамід (6a) и 2-(4-аміно-5-метил-4H-[1,2,4]тріазол-3-ілсульфаніл)-N-[5-(3,4-дихлорбензил)тіазол-2-іл]ацетамід (6g) – относительно линий рака молочной железы.

2-Aminothiazole is regarded as a privileged structure motif in medicinal chemistry due to its presence in the numerous pharmaceuticals and agrochemicals [1]. Their anti-inflammatory activity, as well as antiparasitic and antimicrobial action have led to three classes of these compounds with the trade names: Sudoxicam, Nitridazole and Sulfadimethoxine.

2-Aminothiazole derivatives possess the antimycobacterial [2] antiplasmodial [3], antifungal [4], antiplatelet [5], antiviral [6], hypoglycemic [7] and other activities. The anticancer studies of different 2-acylaminothiazole derivatives exhibited their potent inhibitory activity against a wide range of human cancerous cell lines [8–14]. Here we describe the synthesis and the anticancer evaluation of some novel 2-acylamino-5-arylmethylthiazole derivatives **6a-h**, several of which exhibited good activities.

Chemistry

Our syntheses of the corresponding 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-R-benzylthiazol-2-yl)-acetamides **6** are illustrated in Schemes 1 and 2. At the first stage acrolein was chloro-arylated by diazonium salts in the presence of copper(II) chloride under Meerwein arylation conditions. Refluxing of 3-aryl-2-chloropropanals **2a-h** and thiourea in ethanol gave 5-substituted 2-aminothiazoles **3a-h** [15, 16],

To obtain chloroacetamides **4a-h** the corresponding 5-substituted 2-aminothiazoles **3a-h** were acylated with chloroacetyl chloride in a dry dioxane in the presence of triethylamine [10]. By the interaction of thiocarbonohydrazide with acetic acid 4-amino-5-methyl-4H-[1,2,4]triazole-3-thiole **5** was obtained.

The treatment of **4a-h** with 4-amino-5-methyl-4H-[1,2,4]triazole-3-thiole **5** gave the target compounds **6a-h** in the yields of 70-86%.

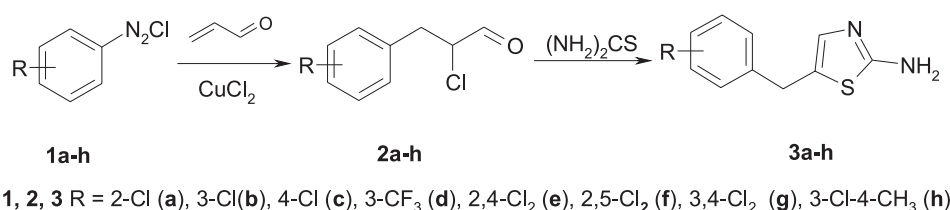
The composition and structure of the compounds synthesized were elucidated by ¹H NMR and microanalyses. In ¹H NMR spectrum, all protons were seen according to expected chemical shifts and integral values. The protons of the CH₃ and NH₂ group were observed at δ 2.29-2.30 and 5.78-5.79 ppm, respectively, while two methylene groups at δ 4.03-4.18 ppm.

Biological Activity

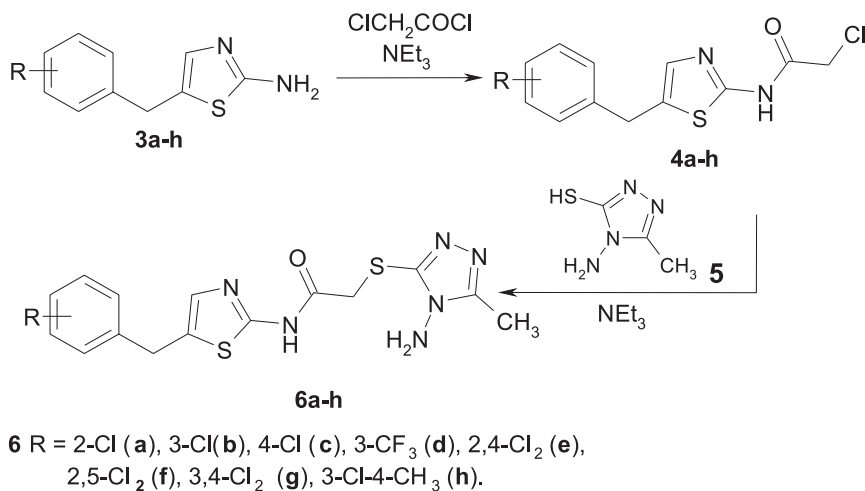
The 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-R-benzylthiazol-2-yl)-acetamides **5** synthesized were selected by the National Cancer Institute (NCI) Developmental Therapeutic Programme (www.dtp.nci.nih.gov) for the *in vitro* cell line screening to investigate their anticancer activity. Anticancer assays were performed according to the NCI protocol [17-20]. The compounds were evaluated for the antitumor activity against 60 cancer lines in the concentration of 10 μM. The human tumour cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. The screening results are shown in Table.

The compounds tested showed different levels of activity on various cancer cell lines. Compounds **5a-c**, **3e,f** have a selective effect on the growth of MDA-MB-435 (Melanoma) cancer cell lines and **5a,g** on MCF7 (breast cancer) in comparison with others.

Thus, the preparative method for obtaining of 2-chloro-N-(5-aryl-1,3-thiazol-2-yl) acetamides was developed, and 2-(4-amino-5-methyl-4H-[1,2,4]tri-



Scheme 1. Preparation of 2-amino-5-arylmethylthiazoles **2**.



Scheme 2. Preparation of 2-(4-amino-5-methyl-4H-[1,2,4]triazol-3-ylsulfanyl)-N-(5-R-benzylthiazol-2-yl)-acetamides **6**.

Table

The cytotoxic activity of the compounds tested in the concentration of 10^{-5} M against 60 cancer cell lines

Test compounds	Average growth, %	Range of growth, %	Most sensitive cell line growth, % (cancer line/type)
5a	76	19.36-110.14	KM12 54.45/Colon Cancer MDA-MB-435 37.22/Melanoma IGROV1 47.62/Ovarian Cancer OVCAR-5 51.68/Ovarian Cancer MCF7 19.36/Breast Cancer 786-0 3.81/Renal Cancer
5b	81	25.33-126.56	CCRF-CEM 51.42/Leukemia MOLT-4 58.84/Leukemia MDA-MB-435 25.33/Melanoma HCT-15 44.27/Colon Cancer
5c	79	22.21-108.95	CCRF-CEM 41.44/Leukemia HOP-62 54.14/Non-Small Cell Lung Cancer MDA-MB-435 22.21/Melanoma SF-268 70.84/CNS Cancer
4d	102	62.38-133.44	MALME-3M 62.38/ Melanoma
5e	88	35.77-126.56	RPMI-8226 59.22/Leukemia SR 58.21/Leukemia MDA-MB-435 35.67/Melanoma
5f	89	13.89-121.78	RPMI-8226 49.26/Leukemia SR 48.12/Leukemia NCI-H226 40.37/Non-Small Cell Lung Cancer MDA-MB-435 13.89/Melanoma
5g	91	24.75-110.99	PC-3 49.15/Prostate Cancer MCF7 24.75/Breast Cancer MDA-MB-231/ATCC 42.44/Breast Cancer
5h	110	42.27-146.81	MALME-3M 42.27/Melanoma

azol-3-ylsulfanyl)-N-(5-R-benzylthiazol-2-yl)-acetamides with the anticancer activity were synthesized.

Experimental Part

All starting materials were purchased from the commercial sources and used without purification. Melting points were uncorrected and were measured in open capillary tubes. The $^1\text{H-NMR}$ spectra were recorded on a Varian Gemini (400 MHz) in DMSO-d_6 , TMS was the internal standard.

The general procedure for the synthesis of 3-aryl-2-chloropropanals 2. Charge a three-necked flask equipped with a stirrer, a dropping funnel, and a gas-outlet tube (attached to a bubble counter) with 0.2 Mol (13.5 ml) of acrolein, 10 g of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$, and 50 ml of acetone. Add dropwise a cold aqueous solution of arenediazonium chloride **1** (prepared by diazotization of 0.2 Mol of the corresponding aromatic amine) with vigorous stirring. Maintain the temperature in the range of 10-30°C. When the reaction is complete, the organic layer is separated. Extract the aqueous layer with chloroform. Combine the extract with the organic phase, dry over MgSO_4 , evaporate, and distill the residue under reduced pressure. Compounds **2a, c-g** were described earlier [15, 16].

2-Chloro-3-(3-chlorophenyl)propanal 2b. Yield – 38%. B.p. – 114°C/3 mm Hg. n_D^{20} 1.5500.

2-Chloro-3-(3-chloro-4-methylphenyl)propanal 2h. Yield – 45%. B.p. – 119°C/3 mm Hg. n_D^{20} 1.5380.

The general procedure for the synthesis of 2-amino-5-arylmethylthiazoles (3a-h). Heat the mixture of 0.8 g of thiourea and 0.01 Mol of aldehyde **2** in 10 ml of ethanol for 1.5-2 h under reflux. Cool the mixture, dilute with 100 ml of water, and make alkaline by adding aqueous ammonia. Filter the precipitate and recrystallize from CCl_4 or $\text{C}_6\text{H}_6\text{-CCl}_4$. Compounds **3a, c-g** were described earlier [15, 16].

5-(3-Chlorobenzyl)-1,3-thiazol-2-ylamine 3b. Yield – 86%. M.p. – 99-101°C. $^1\text{H-NMR}$, d, ppm, (J, Hz): 3.89 (s, 2H, CH_2), 6.68 (s, 1H, $\text{H}_{\text{thiazol}}$), 6.55 (s, 2H, NH_2), 7.02–7.12 (m, 3H, C_6H_4), 7.13-7.16 (m, 1H, C_6H_4). Calculated, %: C 53.45, H 4.04, N 12.47. $\text{C}_{10}\text{H}_9\text{ClN}_2\text{S}$. Found: C 53.10, H 3.98, N 12.32.

5-(3-Chloro-4-methylbenzyl)-1,3-thiazol-2-ylamine 3h. Yield – 80%. M.p. – 115-117°C. $^1\text{H-NMR}$, d, ppm, (J, Hz): 2.28 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 6.67 (s, 1H, $\text{H}_{\text{thiazol}}$), 6.54 (s, 2H, NH_2), 6.98–7.11 (m, 2H, C_6H_3), 7.17 (s, 1H, C_6H_3). Calculated, %: C 55.34, H 4.64, N 11.73. $\text{C}_{11}\text{H}_{11}\text{ClN}_2\text{S}$. Found: C 55.07, H 4.49, N 11.68.

The general procedure for the synthesis of *N*-(5-(*R*-benzyl)-1,3-thiazol-2-yl)-2-chloroacetamides (4a-h). To the mixture of appropriate 2-amino-5-arylmethylthiazole **3** (10 mmol) and 1.4 ml triethylamine in dioxane (25 ml) add dropwise chloroacetyl chloride (0.8 ml, 10 mmol) at 20–25°C. Dilute the mixture with 100 ml of water. Collect by filtration the solid product obtained, wash with water (10–20 ml) and recrystallize from the mixture of ethanol-DMF.

2-Chloro-*N*-[5-(2-chlorobenzyl)-1,3-thiazol-2-yl]acetamide 4a. Yield – 85%. M.p. – 175°C. ¹H-NMR, d, ppm, (J, Hz): 4.17 (s, 4H, 2CH₂), 7.08 (s, 1H, H_{thiazol}), 7.14–7.21 (m, 2H, C₆H₄), 7.28–7.35 (m, 2H, C₆H₄), 12.19 (s, 1H, NH). Calculated, %: C 47.85, H 3.35, N 9.30. C₁₂H₁₀Cl₂N₂OS. Found: C 47.54, H 3.18, N 9.07.

2-Chloro-*N*-[5-(3-chlorobenzyl)-1,3-thiazol-2-yl]acetamide 4b. Yield – 80%. M.p. – 158°C. ¹H-NMR, d, ppm, (J, Hz): 4.11 (s, 2H, CH₂), 4.17 (s, 2H, CH₂), 7.25–7.36 (m, 5H, H_{thiazol}, C₆H₄), 12.17 (s, 1H, NH). Calculated, %: C 47.85, H 3.35, N 9.30. C₁₂H₁₀Cl₂N₂OS. Found: C 47.80, H 3.29, N 9.29.

2-Chloro-*N*-[5-(4-chlorobenzyl)-1,3-thiazol-2-yl]acetamide 4c. Yield – 87%. M.p. – 159°C. ¹H-NMR, d, ppm, (J, Hz): 4.13 (s, 2H, CH₂), 4.17 (s, 2H, CH₂), 7.10–7.22 (m, 3H, H_{thiazol}, C₆H₄), 7.35 (d, 2H, J = 7.8, C₆H₄), 12.19 (s, 1H, NH). Calculated, %: C 47.85, H 3.35, N 9.30. C₁₂H₁₀Cl₂N₂OS. Found: C 47.48, H 3.13, N 9.09.

2-Chloro-*N*-[5-(3-trifluoromethylbenzyl)-1,3-thiazol-2-yl]acetamide 4d. Yield – 75%. M.p. – 146°C. ¹H-NMR, d, ppm, (J, Hz): 4.20 (s, 2H, CH₂), 4.23 (s, 2H, CH₂), 7.19 (s, 1H, H_{thiazol}), 7.48–7.63 (m, 4H, C₆H₄), 12.15 (brs, 1H, NH). Calculated, %: C 46.65, H 3.01, N 8.37. C₁₃H₁₀ClF₃N₂OS. Found: C 46.30, H 2.90, N 8.08.

2-Chloro-*N*-[5-(2,4-dichlorobenzyl)-1,3-thiazol-2-yl]acetamide 4e. Yield – 90%. M.p. – 180°C. ¹H-NMR, d, ppm, (J, Hz): 4.19 (s, 2H, CH₂), 4.23 (s, 2H, CH₂), 7.18 (s, 1H, H_{thiazol}), 7.24 (d, 1H, ³J = 8.8, ⁴J = 2.0, 4-H C₆H₂), 7.40 (d, 1H, ³J = 8.8, 3-H C₆H₂), 7.44 (d, 1H, ⁴J = 2.0, 6-H C₆H₂), 12.19 (s, 1H, NH). Calculated, %: C 42.94, H 2.70, N 8.35. C₁₂H₉Cl₃N₂OS. Found: C 42.74, H 2.58, N 8.11.

2-Chloro-*N*-[5-(2,5-dichlorobenzyl)-1,3-thiazol-2-yl]acetamide 4f. Yield – 91%. M.p. – 207°C. ¹H-NMR, d, ppm, (J, Hz): 4.20 (s, 2H, CH₂), 4.23 (s, 2H, CH₂), 7.19 (s, 1H, H_{thiazol}), 7.25 (d, 1H, ³J = 8.8, ⁴J = 2.0, 4-H C₆H₂), 7.41 (d, 1H, ³J = 8.8, 3-H C₆H₂), 7.44 (d, 1H, ⁴J = 2.0, 6-H C₆H₂), 12.19 (s, 1H, NH). Calculated, %: C 42.94, H 2.70, N 8.35. C₁₂H₉Cl₃N₂OS. Found: C 42.60, H 2.50, N 8.05.

2-Chloro-*N*-[5-(3,4-dichlorobenzyl)-1,3-thiazol-2-yl]acetamide 4g. Yield – 80%. M.p. – 200°C. ¹H-NMR, d, ppm, (J, Hz): 4.19 (s, 2H, CH₂), 4.22 (s, 2H, CH₂), 7.16 (s, 1H, H_{thiazol}), 7.21 (d, 1H, ³J = 8.8, ⁴J = 2.0, 6-H C₆H₂), 7.41 (d, 1H, ³J = 8.8, 5-H C₆H₂), 7.48 (d, 1H, ⁴J = 2.0, 2-H C₆H₂), 12.19 (s, 1H, NH). Calculated, %: C 42.94, H 2.70, N 8.35. C₁₂H₉Cl₃N₂OS. Found: C 42.65, H 2.53, N 8.09.

2-Chloro-*N*-[5-(3-chloro-4-methylbenzyl)-1,3-thiazol-2-yl]acetamide 4h. Yield – 68%. M.p. – 148°C. ¹H-NMR, d, ppm, (J, Hz): 4.16 (s, 2H, CH₂), 4.20 (s, 2H, CH₂), 7.05–7.20 (m, 4H, H_{thiazol}, C₆H₄), 12.16 (brs, 1H, NH). Calculated, %: C 49.53, H 3.84, N 8.89. C₁₃H₁₂Cl₂N₂OS. Found: C 49.24, H 3.50, N 8.61.

The general procedure for the synthesis of 2-(4-amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-(5-*R*-benzylthiazol-2-yl)-acetamides (6a-h). Reflux the mixture of the corresponding *N*-(5-benzyl-1,3-thiazol-2-yl)-2-chloroacetamide **4** (5 mmol), 0.84 g of (5.5 mmol) of 4-amino-5-methyl-4*H*-[1,2,4]triazole-3-thiole **5**, and 1.2 ml of triethylamine for **4h** in ethanol (25 ml). Collect by filtration the solid products obtained, wash with ethanol (5–10 ml) and recrystallize from the mixture of ethanol-DMF.

2-(4-Amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-[5-(2-chloro-benzyl)-thiazol-2-yl]-acetamide (6a). Yield – 73%. M.p. – 205–207°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 4.17 (s, 2H, CH₂), 5.79 (s, 2H, NH₂), 7.15 (s, 1H, H_{thiazol}), 7.24–7.28 (m, 2H, C₆H₄), 7.35 (d, J = 7.2 Hz, 1H, C₆H₄), 7.39 (d, J = 7.6 Hz, 1H, C₆H₄), 12.22 (brs, 1H, NHCO). Calculated, %: C 45.62, H 3.83, N 21.28. C₁₅H₁₅ClN₆OS₂. Found: C 45.34, H 3.65, N 20.97.

2-(4-Amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-[5-(3-chloro-benzyl)-thiazol-2-yl]-acetamide (6b). Yield – 78%. M.p. – 212–214°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 4.08 (s, 2H, CH₂), 5.80 (s, 2H, NH₂), 7.18–7.26 (m, 3H, H_{thiazol} + C₆H₄), 7.27 (d, J = 6.8 Hz, 1H, C₆H₄), 7.31 (d, J = 8.0 Hz, 1H, C₆H₄), 12.25 (brs, 1H, NHCO). Calculated, %: C 45.62, H 3.83, N 21.28. C₁₅H₁₅ClN₆OS₂. Found: C 45.28, H 3.61, N 21.05.

2-(4-Amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-[5-(4-chloro-benzyl)-thiazol-2-yl]-acetamide (6c). Yield – 80%. M.p. – 224–225°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.05 (s, 2H, CH₂), 4.06 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.15 (s, 1H, H_{thiazol}), 7.24 (d, J = 8.0 Hz, 2H, C₆H₄), 7.29 (d, J = 8.8 Hz, 2H, C₆H₄), 12.22 (s, 1H, NHCO). Calculated, %: C 45.62, H 3.83, N 21.28. C₁₅H₁₅ClN₆OS₂. Found: C 45.41, H 3.70, N 20.99.

2-(4-Amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-[5-(3-trifluoromethylbenzyl)-thiazol-2-yl]-acetamide (6d). Yield – 83%. M.p. – 192–193°C. ¹H-NMR, d, ppm, (J, Hz): 2.28 (s, 3H, CH₃), 4.05 (s, 2H, CH₂), 4.17 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.19 (s, 1H, H_{thiazol}), 7.50–7.55 (m, 3H, C₆H₄), 7.56–7.58 (m, 1H, C₆H₄), 12.23 (s, 1H, NHCO). Calculated, %: C 44.85, H 3.53, N 19.61. C₁₆H₁₅F₃N₆OS₂. Found: C 44.54, H 3.29, N 19.34.

2-(4-Amino-5-methyl-4*H*-[1,2,4]triazol-3-ylsulfanyl)-*N*-[5-(2,4-dichlorobenzyl)-thiazol-2-yl]-acetamide (6e). Yield – 75%. M.p. – 253–254°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.05 (s, 2H, CH₂), 4.15 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.14 (s,

1H, H_{thiazol}), 7.30 (dd, $J_3 = 8.4$ Hz, $J_4 = 1.6$ Hz, 1H, C₆H₄), 7.37 (d, $J = 8.4$ Hz, 1H, C₆H₄), 7.45 (d, $J_4 = 2.4$ Hz, 1H, C₆H₄), 12.25 (s, 1H, NHCO). Calculated, %: C 41.96, H 3.29, N 19.57. C₁₅H₁₄Cl₂N₆OS₂. Found: C 41.66, H 3.18, N 19.35.

2-(4-Amino-5-methyl-4H-[1,2,4]triazol-3-yl-sulfanyl)-N-[5-(2,5-dichlorobenzyl)-thiazol-2-yl]-acetamide (6f). Yield – 85.7%. M.p. – 235-236°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 4.17 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.18 (s, 1H, H_{thiazol}), 7.27 (dd, $J_3 = 8.2$ Hz, $J_4 = 2.9$ Hz, 1H, C₆H₄), 7.41 (d, $J = 2.8$ Hz, 1H, C₆H₄), 7.42 (d, $J = 8.2$ Hz, 1H, C₆H₄), 12.27 (s, 1H, NHCO). Calculated, %: C 41.96, H 3.29, N 19.57. C₁₅H₁₄Cl₂N₆OS₂. Found: C 41.60, H 3.16, N 19.63.

2-(4-Amino-5-methyl-4H-[1,2,4]triazol-3-yl-sulfanyl)-N-[5-(3,4-dichlorobenzyl)-thiazol-2-

yl]-acetamide (6g). Yield – 78%. M.p. – 225-227°C. ¹H-NMR, d, ppm, (J, Hz): 2.30 (s, 3H, CH₃), 4.06 (s, 2H, CH₂), 4.08 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.18 (s, 1H, H_{thiazol}), 7.21 (dd, $J_3 = 8.4$ Hz, $J_4 = 1.6$ Hz, 1H, C₆H₄), 7.43-7.48 (m, 2H, C₆H₄), 12.25 (s, 1H, NHCO). Calculated, %: C 41.96, H 3.29, N 19.57. C₁₅H₁₄Cl₂N₆OS₂. Found: C 42.03, H 3.38, N 19.40.

2-(4-Amino-5-methyl-4H-[1,2,4]triazol-3-yl-sulfanyl)-N-[5-(3-chloro-4-methylbenzyl)thiazol-2-yl]-acetamide (6h). Yield – 71%. M.p. – 204-206°C. ¹H-NMR, d, ppm, (J, Hz): 2.29 (s, 3H, CH₃), 2.31 (s, 3H, CH₃), 4.03 (s, 2H, CH₂), 4.05 (s, 2H, CH₂), 5.78 (s, 2H, NH₂), 7.07 (d, $J = 6.8$ Hz, 1H, C₆H₄), 7.15 (s, 1H, H_{thiazol}), 7.19-7.23 (m, 2H, C₆H₄), 12.22 (s, 1H, NHCO). Calculated, %: C 46.99, H 4.19, N 20.55. C₁₆H₁₇ClN₆OS₂. Found: C 46.75, H 3.98, N 20.85.

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Надійшла до редакції 05.11.2015 р.