

Antitumor properties of thiazolo[4,5-*b*]pyridin-2-one derivatives

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ABSTRACT

In this paper we present synthesis and antitumor activity determination of some thiazolo[4,5-*b*]pyridine-2-ones. In reactions conditions [3+3]cyclocondensation, acylation and alkylation were synthesized the compounds 1-13. The study of the antitumor activity of the obtained substances was carried out within international cooperation with the National Cancer Institute's (Developmental Therapeutic Program). For test compounds established moderate activity against most malignant tumor cells.

Keywords: *synthesis; thiazolo[4,5-*b*]pyridine-2-ones; structural modification; antitumor activity.*

1. INTRODUCTION

Oncological diseases represent one of the most significant global health problems. It is widely known that malignant neoplasms are one of the main causes of death and disability of the population. To date, 1 out of 7 deaths in all the world comes from cancer. In recent years, some progress has been made in the development of drugs used to treat malignant neoplasms [1-2]. However, the effectiveness of pharmacotherapy of cancer remains very small. In this aspect, the development of new antitumor drugs of targeted action is an urgent problem of modern medical chemistry. The development of chemistry of heterocyclic compounds is largely due to the practical direction of research. It is sufficient to note that among the most well-known and widely used drugs, more than 60% belong to heterocyclic compounds. Previously we have successfully developed a lot of methods of design of combinatorial libraries of five- and six-membered nitrogen [3-10] containing heterocycles. Among a variety of such compounds, thiazolidines, which, due to the numerous derivatives wide biological action range, are very important [11, 12]. In particular, there is growing interest in nitrogen-containing fused heterocyclic systems, as many of them exhibit broad-spectrum biological activity [13, 14].

Thiazolidone derivatives condensed with the pyridine cycle, in particular thiazolopyridine, are of high priority in modern medicinal chemistry, because these compounds exhibit different types of biological activity. Among them were identified substances with herbicidal [15], antioxidant [16-19], antimicrobial [20], antifungal [21], and anti-mitotic [22] activities. Also this class of compounds is show potent inhibitory activities for A42 fibrillization for Alzheimer's disease treatment [23]. It was established that these derivatives exhibit anti-tuberculosis [24] and anti-inflammatory [25-27] actions. For these compounds is characteristic there are substances agonists of H3-histamine receptors [28, 29], antagonists of metabotropic glutamate receptors [30] with high inhibitory activity in relation to receptors of epidermal growth factor [31] and a number of other enzymes [32]. Thiazolopyridine derivatives, exhibit significant anti-cancer effect [22, 33-35].

Thus, the research to explore different avenues of chemical modifications of thiazolopyridines as well as the search for new antitumor compounds among the specified class of compounds should continue.

2. MATERIALS AND METHODS

2.1. Materials.

The reagents used in the synthesis were commercially available and of analytical grade. All solvents and reagents was used without further purification.

2.2. Chemistry.

The NMR-spectra were run using Varian Mercury 400 (400 MHz) at 298 K. Chemical shifts are reported as δ (ppm). The coupling constant *J* is expressed in Hz. Elemental analysis was performed on a vario MICRO cube automatic CHNS analyzer. Mass spectra of synthesized compounds were recorded on Agilent 1100 series LC/MSD.

Synthesis of 7-methyl-5-hydroxy-3H-thiazolo[4,5-*b*]pyridin-2-one (compound 1). 2.5 g (109 mmol) of sodium are dissolved in 125 ml of absolute methanol. To the resulting solution was added

6.8 g (50 mmol) of 4-iminothiazolidin-2-one and 8 ml of acetoacetic ester. The mixture is left for 5 days, stirring occasionally at 20 °C. Then it is acidified with acetic acid to pH ~ 5, five-fold diluted with water. The precipitated is filtered. The resulting substance on the filter is washed with cold water and dried. It is a white crystalline powder, readily soluble in DMF, DMSO, solutions of alkali or acid. Slightly soluble in other solvents. Yield: 75 %; mp > 300 °C with dec.; ¹H NMR: δ_{H} = 12.18 (s, 1H, NH), 10.84 (s, 1H, OH), 6.31 (s, 1H, Py), 2.33 (s, 3H, CH₃); ¹³C NMR, δ , ppm: 169.55, 162.91, 147.91, 144.59, 107.84, 104.73, 19.85; ESI-MS: *m/z* 183 [M+H]⁺; anal. calcd. for C₇H₇N₂O₂S: C 46.15, H 3.32, N 15.37; found: C 46.24, H 3.38, N 15.44.

Synthesis of 6-propyl-7-methyl-5-hydroxy-3H-thiazolo[4,5-*b*]pyridin-2-one (compound 2). 50 mmol (6.8 g) of 4-

iminothiazolidin-2-one added to the solution obtained by the interaction 100 ml of anhydrous methanol with 200 mmol (4.6 g) metallic sodium. To the resulting solution add propyl derivative acetoacetic ester (50 mmol) at 20 °C. The mixture was stirred for 7 days. Then it is acidified with acetic acid to pH ~ 5, five-fold diluted with water. The precipitated is filtered. The resulting substance on the filter is washed with cold water and dried. It is a beige crystalline powder solid, readily soluble in DMF and DMSO. Yield: 60 %; mp 249-250 °C; ¹H NMR: δ_H = 11.48 (s, 1H, OH), 2.48 (d, *J* = 7.4 Hz, 2H, CH₂-CH₂-CH₃), 2.19 (s, 3H, CH₃), 1.43 (d, *J* = 7.3 Hz, 2H, CH₂-CH₂-CH₃), 0.90 (t, *J* = 5.1 Hz, *J* = 7.2 Hz, 3H, CH₂-CH₂-CH₃); ¹³C NMR, δ, ppm: 169.48, 160.88, 144.83, 141.73, 116.20, 108.56, 28.02, 22.39, 17.63, 14.42; ESI-MS: *m/z* 225 [M+H]⁺; anal. calcd. for C₁₀H₁₂N₂O₂S: C 53.55, H 5.39, N 12.49; found: C 53.30, H 5.44, N 12.56.

Synthesis of 6-benzyl-7-methyl-5-hydroxy-3H-thiazolo[4,5-*b*]pyridin-2-one (compound 3): Were obtained similarly from 4-iminothiazolidin-2-one and appropriate 2-(4-nitro-benzyl)-3-oxo-butyric acid ethyl ester. White solid; Yield: 86 %; mp 206 °C; ¹H NMR: δ_H = 12.54 (s, 1H, NH), 11.33 (s, 1H, OH), 7.17 (t, *J* = 7.3 Hz, *J* = 7.1 Hz, 2H, C₆H₅), 7.15 (t, *J* = 6.2 Hz, *J* = 7.0 Hz, 1H, C₆H₅), 7.01 (d, *J* = 7.1 Hz, 2H, C₆H₅), 3.87 (s, 2H, CH₂-C₆H₅), 2.24 (s, 3H, CH₃); ¹³C NMR, δ, ppm: 169.01; 168.54, 146.21, 143.87, 138.96, 128.88, 128.01, 125.22, 120.55, 116.89, 20.89, 18.24; ESI-MS: *m/z* 273 [M+H]⁺; anal. calcd. for C₁₄H₁₂N₂O₂S: C 61.75, H 4.44, N 10.29; found: C 61.84, H 4.49, N 10.44.

Synthesis of 6-(2-hydroxy-phenylazo)-7-methyl-5-hydroxy-3H-thiazolo[4,5-*b*]pyridin-2-one (compound 4): Were obtained similarly from 4-iminothiazolidin-2-one and appropriate 2-(2-hydroxy-phenylazo)-3-oxo-butyric acid ethyl ester. Orange solid; Yield: 99 %; mp > 280 °C with dec.; ¹H NMR: δ_H = 14.89 (s, 1H, NH), 13.28 (s, 1H, OH), 10.75 (s, 1H, C₆H₄-OH), 7.71 (d, *J* = 7.7 Hz, 1H, C₆H₄), 7.12 (t, *J* = 7.3 Hz, 1H, C₆H₄), 6.95-6.98 (m, 2H, C₆H₄), 2.40 (s, 3H, CH₃); ¹³C NMR, δ, ppm: 169.79, 163.08, 148.11, 145.12, 130.33, 124.71, 121.25, 119.33, 115.35, 113.44, 107.07, 103.12, 19.44; ESI-MS: *m/z* 303 [M+H]⁺; anal. calcd. for C₁₃H₁₀N₄O₃S: C 51.65, H 3.33, N 18.53; found: C 51.59, H 3.40, N 18.58.

General procedure for the synthesis 7-methyl-3H-thiazolo[4,5-*b*]pyridin-2-one 5-yl esteri aliphatic derivatives (compounds 5-8). In a flat-bottomed flask, 5 mmol of compound 1 or 2 or 3 was dissolved in 20 ml of anhydrous dioxane. Then, to the solution obtained in the previous step, was added a solution consisting of 5 mmol of the corresponding aliphatic chloroanhydride and 5 mmol of triethylamine in 10 ml of dioxane. The reaction mixture was refluxed 15 min. After recrystallization from methanol, white or yellowish powders are soluble upon heating in ethanol, DMF, and acetic acid.

7-Methyl-2-oxo-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester acetic acid (compound 5): White solid; Yield: 92 %; mp 240-241 °C; ¹H NMR: δ_H = 12.69 (s, 1H, NH), 6.88 (s, 1H, Py), 2.36 (s, 3H, CH₃-CO), 2.30 (s, 3H, CH₃); ¹³C NMR, δ, ppm: 169.30, 168.76, 154.01, 146.07, 143.89, 118.36, 117.33, 18.45, 12.13; ESI-MS: *m/z* 225 [M+H]⁺; anal. calcd. for C₉H₈N₂O₃S: C 48.21, H 3.60, N 12.49; found: C 48.66, H 3.55, N 12.55.

7-Methyl-2-oxo-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester butyric acid (compound 6): White solid; Yield: 56 %; mp 164 °C; ¹H NMR: δ_H = 12.69 (s, 1H, NH), 6.87 (s, 1H, Py), 2.59 (t, *J* = 7.1

Hz, 2H, CH₃-CH₂-CH₂-CO), 2.36 (s, 3H, CH₃), 1.64-1.69 (m, 2H, CH₃-CH₂-CH₂-CO), 0.99 (t, *J* = 7.3 Hz, 3H, CH₃-CH₂-CH₂-CO); ¹³C NMR, δ, ppm: 169.23, 166.14, 154.07, 148.15, 144.52, 118.37, 116.84, 28.15, 22.08, 19.81, 14.81; ESI-MS: *m/z* 253 [M+H]⁺; anal. calcd. for C₁₁H₁₂N₂O₃S: C 52.37, H 4.79, N 11.10; found: C 52.50, H 4.74, N 11.25.

7-Methyl-2-oxo-6-propyl-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester butyric acid (compound 7): White solid; Yield: 62 %; mp 171 °C; ¹H NMR: δ_H = 12.56 (s, 1H, NH), 2.62 (t, *J* = 7.1 Hz, 2H, CH₃-CH₂-CH₂-CO), 2.48 (d, *J* = 7.4 Hz, 2H, CH₃-CH₂-CH₂-C₆H₅), 2.34 (s, 3H, CH₃), 1.67-1.71 (m, 2H, CH₃-CH₂-CH₂-CO), 1.42 (t, *J* = 7.5 Hz, 2H, CH₃-CH₂-CH₂-C₆H₅), 1.00 (t, *J* = 7.3 Hz, 3H, CH₃-CH₂-CH₂-CO), 0.92 (t, *J* = 7.4 Hz, 3H, CH₃-CH₂-CH₂-C₆H₅); ¹³C NMR, δ, ppm: 169.23, 166.14, 154.07, 148.15, 144.52, 118.37, 116.84, 28.10, 22.44, 22.12, 19.77, 17.59, 14.85, 14.44; ESI-MS: *m/z* 295 [M+H]⁺; anal. calcd. for C₁₄H₁₈N₂O₃S: C 57.12, H 6.16, N 9.52; found: C 57.24, H 6.11, N 9.48.

6-Benzyl-7-methyl-2-oxo-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester acetic acid (compound 8): White solid; Yield: 90 %; mp 216 °C; ¹H NMR: δ_H = 12.65 (s, 1H, NH), 7.27 (t, *J* = 7.3 Hz, *J* = 7.1 Hz, 2H, C₆H₅), 7.18 (t, *J* = 6.2 Hz, *J* = 7.0 Hz, 1H, C₆H₅), 7.12 (d, *J* = 7.1 Hz, 2H, C₆H₅), 3.95 (s, 2H, CH₂-C₆H₅), 2.28 (s, 3H, CH₃-CO), 2.26 (s, 3H, CH₃); ¹³C NMR, δ, ppm: 169.31, 168.72, 154.54, 146.77, 144.22, 139.38, 128.91, 128.49, 126.62, 121.08, 117.80, 31.84, 21.06, 18.45; ESI-MS: *m/z* 315 [M+H]⁺; anal. calcd. for C₁₆H₁₄N₂O₃S: C 61.13, H 4.49, N 8.91; found: C 61.10, H 4.45, N 8.88.

General procedure for the synthesis 7-methyl-3H-thiazolo[4,5-*b*]pyridin-2-ones 5-yl esteri aromatic derivatives (compounds 9, 10). The mixture obtained at this stage was refluxed within 30 minutes. The solution was cooled until a precipitate formed, after which it was filtered and washed with acetic acid. The resulting compounds were crystallized from acetic acid or ethanol. These are white substances, poorly soluble in water and organic solvents, soluble in acetate acid, DMF and DMSO.

7-Methyl-2-oxo-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester 4-nitro-benzoic acid (compound 9): White solid; Yield: 72 %; mp 207 °C; ¹H NMR: δ_H = 12.78 (s, 1H, NH), 8.44 (d, *J* = 8.7 Hz, 2H, C₆H₄), 8.38 (d, *J* = 8.7 Hz, 2H, C₆H₄), 7.12 (s, 1H, Py), 2.41 (s, 3H, CH₃); ¹³C NMR, δ, ppm: 168.88, 164.04, 155.86, 148.69, 145.60, 139.94, 132.20, 129.85, 127.67, 116.85, 111.78, 19.98; ESI-MS: *m/z* 332 [M+H]⁺; anal. calcd. for C₁₄H₉N₃O₅S: C 50.76, H 2.74, N 12.68; found: C 51.00, H 2.69, N 12.85.

7-Methyl-2-oxo-6-propyl-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl ester benzoic acid (compound 10): White solid; Yield: 74 %; mp 203 °C; ¹H NMR: δ_H = 12.65 (s, 1H, NH), 8.16 (d, *J* = 7.5 Hz, 2H, C₆H₅), 7.81 (t, *J* = 7.0 Hz, *J* = 6.5 Hz, 1H, C₆H₅), 7.66 (t, *J* = 6.4 Hz, *J* = 7.3 Hz, 2H, C₆H₅), 2.54 (d, *J* = 7.0 Hz, 2H, CH₂-CH₂-CH₃), 2.38 (s, 3H, CH₃), 1.46- 1.51 (m, 2H, CH₂-CH₂-CH₃), 0.86 (t, *J* = 5.1 Hz, *J* = 7.2 Hz, 3H, CH₂-CH₂-CH₃); ¹³C NMR, δ, ppm: 168.11, 167.71, 154.25, 146.18, 144.05, 138.75, 131.15, 128.34, 126.25, 118.31, 117.33, 22.74, 21.21, 18.08, 14.44. ESI-MS: *m/z* 329 [M+H]⁺; anal. calcd. for C₁₇H₁₆N₂O₃S: C 62.18, H 4.91, N 8.53; found: C 62.22, H 4.84, N 8.50.

Synthesis of 5,7-dimethyl-3H-thiazolo[4,5-*b*]pyridin-2-one (compound 11): In 25 ml of anhydrous methanol 0.5 g (22 mmol) of sodium was dissolved, and to the solution obtained at 20°C was added 1.36 g (10 mmol) of 4-iminothiazolidin-2-one and 10 mmol

of acetylacetone. The mixture is left for 5 days, stirring occasionally at 20 °C. The resulting solution was acidified acetic acid to pH ~5. After which the solution five-fold diluted with water. The precipitated is filtered. The resulting substance on the filter is washed with cold water and dried. White crystalline powder, well soluble in DMF, DMSO, solutions of alkali and mineral acids, sparingly soluble in the other organic solvents. ¹H NMR, δ_H: 12.44 s (1H, NH), 6.91 s (1H, Py), 2.40 s (3H, CH₃), 2.27 s (3H, CH₃); ¹³C NMR, δ, ppm : 168.64; 141.38, 139.25, 137.43, 127.38, 118.65, 23.16, 19.29; ESI-MS: m/z 181 [M+H]⁺; anal. calcd. for C₈H₈N₂O₃S, C 53.02; H, 4.49; N, 15.44. found: C, 53.31; H, 4.47; N, 15.54.

6-Ylazo-benzenesulfonamide-4-(5,7-dimethyl-2-oxo-2,3-dihydro-thiazolo[4,5-b]pyridin-2-one (compound 12). Were obtained similarly from of 4-iminothiazolidin-2-one and appropriate α-benzenesulfonamideazoacetylacetone. Orange solid; Yield: 95 %; mp > 280 °C with dec.; ¹H NMR: δ_H = 13.99 (s, 1H, NH), 7.79 (d, J = 8.5 Hz, 2H, C₆H₄), 7.68 (d, J = 8.5 Hz, 2H, C₆H₄), 7.36 (s, 2H, NH₂), 2.36 (s, 3H, CH₃), 2.22 s (3H, CH₃); ¹³C NMR, δ, ppm: 177.15, 167.05, 161.12, 146.12, 142.21, 141.44, 127.55, 125.23, 123.22, 116.75, 23.12, 19.18; ESI-MS: m/z 365 [M+H]⁺ anal. calcd. for C₁₄H₁₃N₅O₃S₂: C 46.27, H 3.61 N 19.27; found: C 46.01, H 3.55, N 19.21.

3-(4-Nitrobenzyl)-5,7-dimethyl-3H-thiazolo-[4,5-b]pyridin-2-one (compound 13): In a flat-bottomed flask, 9 mmol of compound **11** and 9 mmol of and 1-chloromethyl-4-nitro-benzene was dissolved in 20 ml of ethanol. To the cooled filtrate to ~50°C was added 100 ml of water with stirring. After which the mixture is cooled to 12–15°C. The precipitated is filtered. The resulting

3. RESULTS

Synthesis of some thiazolo[4,5-b]pyridines. Continuing systematic study of thiazolopyridines as potential drug candidates we spent synthesis and antitumor activity screening of some compounds. In our previous works we have developed method of synthesis 3H-thiazolo[4,5-b]pyridine-2-one [6-8]. The specified method was based on [3+3]cyclocondensation of of 4-iminothiazolidin-2-one on account of its N,C-binucleophilic properties with dielectrophilic reagents. By using 4-iminothiazolidin-2-one as the initial compound that was reacted with acetoacetic ester, it was possible to obtain 7-methyl-5-hydroxy-3H-thiazolo[4,5-b]pyridin-2-one (**1**) (scheme 1).

We found that the high yield of compound **1** received at stirring for 5 days the reagent mixture on a magnetic stirrer in the presence of sodium methylate over 5 days. Under the chosen conditions we looked at a possibility behavior in this reaction of acetoacetic ester alkylated and arylazo derivatives. The corresponding thiazolo[4,5-b]pyridin-2-ones (**2-4**) were obtained in good yields (scheme).

Compounds **1-3** due to the presence of hydroxyl- moiety in position 5 of thiazolo[4,5-b]pyridine core represents a convenient reagent for thiazolo[4,5-b]pyridin-5-yl 4-carboxylates (**5-10**) via acylation reaction. It is established that the optimum conditions for obtaining the corresponding acylated derivatives of compounds **1-3** are the reaction in the environment of dioxane under interaction with aliphatic chloroanhydrides (**5-8**) and pyridine in the case of interaction with aromatic chloroanhydrides (**9, 10**).

The next stage of our strategy includes synthesis and structural modification 5,7-dimethyl-3H-thiazolo[4,5-b]pyridine-2-one (**11**). The compound **11** were obtained similarly compound **1** from 4-

substance on the filter is washed with cold water and dried. Yield 72%, mp 180°C (DMF). ¹H NMR, δ_H: 8.20 d (2H, J =10.5 Hz, C₆H₄), 7.56 d (2H, J=10.5 Hz, C₆H₄), 7.04 s (1H, Py), 5.29 s (2H, CH₂), 2.44 s (3H, CH₃), 2.33 s (3H, CH₃); ¹³C NMR, δ, ppm : 168.21, 163.87, 148.08, 145.44, 139.01, 137.24, 132.11, 129.71, 127.22, 118.61, 19.31, 14.81; ESI-MS: m/z 316 [M+H]⁺; anal. calcd. for C₁₅H₁₃N₃O₃S, C 57.13; H 4.16; N 13.33. found, %: C 57.25; H 4.05; N 13.40.

2.3. Pharmacology.

Anticancer activity was performed in National Cancer Institute, Bethesda (Drug Evaluation Branch) [36-39]. Within 48 hours, test compounds were added to the culture at a single concentration (10⁻⁵ M) and cultures were incubated. The dye binding protein sulforhodamine B (SRB), made the determination of the endpoint. For each test compound, results were presented as the percentage of growth of treated cells compared to untreated control cells. Versus controls the percentage growth was evaluated spectrophotometrically not treated with test agents. For this were used the seven absorbance measurements [time zero, (Tz), control growth in the absence of drug, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percent growth was calculated at each of the drug concentrations levels. Percent growth inhibition was calculated as:

$$\begin{aligned} & [(Ti - Tz) / (C - Tz)] \times 100 \text{ when } Ti \geq Tz, \\ & [(Ti - Tz) / Tz] \times 100 \text{ when } Ti < Tz. \end{aligned}$$

spectrophotometrically compared to control not treated with the test agents.

iminothiazolidin-2-one and acetylacetone. We also studied the behavior α-benzenesulfonamideazoacetylacetone as a dielectrophilic agent. It appeared that 6-ylazo-benzenesulfonamide-4-(5,7-dimethyl-2-oxo-2,3-dihydro-thiazolo[4,5-b]pyridin-2-one (**12**) was accessed at the same conditions with a high yield (scheme 1).

The high electrophilicity of the basic scaffold N³ position makes it possible to use its functionalization as a fairly convenient method for obtaining a variety of N³-substituted derivatives, thereby extending the number of thiazolo[4,5-b]pyridines. The compound **11** exhibited nucleophilic properties and under mild conditions through the stage of formation of potassium salt reacted with 1-chloromethyl-4-nitro-benzeneto give compound **13** (scheme 1).

Quantitative elemental analysis, ¹H, ¹³C NMR and mass spectroscopy were used to confirm the structure and individuality of the synthesized substances. All spectroscopic data of the synthesized compounds correspond to the proposed structures.

Evaluation of the antitumor activity in vitro. For in vitro screening of cell lines to study their antitumor activity (therapeutic development program of the National Cancer Institute) among all the synthesized compounds, substances **2, 4-10, 12, 13** were selected. The test compounds were submitted and evaluated at the single concentration of 10⁻⁵ M towards a panel of the approximately sixty cancer cell lines.

The human tumor cell lines were derived from the nine different cancer types: leukemia, non-small cell lung, colon, CNS, melanoma, ovarian, renal, prostate and breast cancers. Primary

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anticancer assays were performed according to the US NCI protocol, which was described elsewhere [36-39]. For each test compound, results are reported as percent growth (GP) (table 1). The lowest and highest growth that was found among the tested cancer cells shows the range of growth (%) that was found among different cancer cell.

Tested compounds displayed a low antitumor activity in the *in vitro* screening on the tested cell lines with average values of GP = 93.80–105.36 %. It is noteworthy that the synthesized compounds demonstrated a selective influence on several cell lines (table 1). Most test compounds inhibition growth on the UP-31 renal cancer cell line (**4**, **6-9**, **12**, **13**) and CNS cancer cell line SNB-75 (**5**, **6**, **8-10**, **12**, **13**). The compounds **5**, **7**, **8** and **10** were slightly active on breast cancer MDA-MB-468 cell line (GP = 83.11%, 75.99%, 84.35%, 82.98%, respectively), and the compound **5** also possessed slightly active on CNS cancer SF-268 cell line and renal cancer RXF 393 cell line (GP = 73.52% and GP = 82.75%, respectively). The compound **13** was moderate to slightly active on lung cancer NCI-H522 cell line (GP = 70.87%), prostate cancer PC-3 cell line

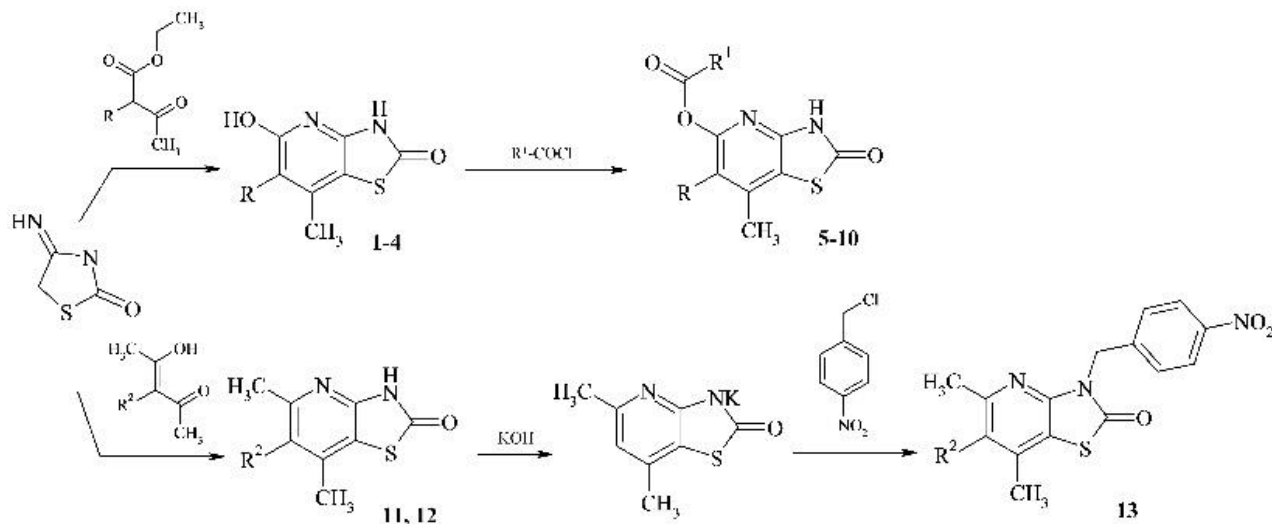
(GP = 77.16%), leukemia CCRF-CEM cell line (GP = 83.74%) and melanoma LOX IMVI cell line (GP = 84.89%).

The most promising compound **12** showed moderate activity on CNS cancer cell line SNB-75 with GP = 68.26% and a number of leukemia cancer cell lines with average values of GP = 66.14–77.69 %. (table 1).

The SAR analysis study revealed that: (1) acylation of OH group in C⁵ position of thiazolo[4,5-*b*]pyridine moiety enhanced potency of compounds **5-10** compared to the least active non-acylated derivatives **2** and **4**; (2) derivatives with 5-alkylcarbonyloxy group (compounds **5-8**) are more active than 5-benzoyloxy substituted analogues **9** and **10**; (3) the presence of alkyl substituents in C⁶ position (compounds **7**, **8**, **10**) did not essentially influence antitumor activity compared to the unsubstituted derivatives **5**, **6**, **9**; and (4) introduction of 4-sulfonamidephenylazo group (compound **12**) in C⁶ position of thiazolo[4,5-*b*]pyridine core leads to increase of activity in particular towards all leukemia panel cell lines.

Table 1. Anticancer screening data at single concentration 10⁻⁵ M.

COMPOUND	60 cancer cell lines assay in 1-dose 10 ⁻⁵ M			
	Mean growth, %	Range of growth, %	The most sensitive cell lines	
			Cell line (Panel)	Growth, %
2	105.36	94.77 to 124.17		-
3	104.23	87.35 to 115.44	UO-31 (Renal Cancer)	87.35
4	96.12	73.52 to 119.10	SF-268 (CNS Cancer) SNB-75 (CNS Cancer) RXF 393 (Renal Cancer) MDA-MB-468 (Breast Cancer) HS 578T (Breast Cancer)	73.52 80.09 82.75 83.11 83.33
5	98.65	83.54 to 117.01	UO-31 (Renal Cancer) SNB-75 (CNS Cancer)	83.54 85.80
6	96.94	75.99 to 111.04	MDA-MB-468 (Breast Cancer) NCI-H226 (Lung Cancer) UO-31 (Renal Cancer) NCI/ADR-RES (Breast Cancer) HOP-92 (Lung Cancer)	75.99 82.71 83.25 85.49 85.75
8	96.51	76.88 to 110.50	SNB-75 (CNS Cancer) UO-31 (Renal Cancer) MDA-MB-468 (Breast Cancer) NCI-H226 (Lung Cancer)	76.88 80.66 82.98 83.57
9	102.38	82.07 to 116.34	UO-31 (Renal Cancer)	82.07
10	98.88	82.33 to 114.99	UO-31 (Renal Cancer) MDA-MB-468 (Breast Cancer)	82.33 84.35
12	93.80	66.14 to 118.30	K-562 (Leukemia) SNB-75 (CNS Cancer) SR (Leukemia) HL-60(TB) (Leukemia) CCRF-CEM (Leukemia) MOLT-4 (Leukemia) PC-3 (Prostate Cancer) UO-31 (Renal Cancer) RPMI-8226 (Leukemia)	66.14 68.26 69.37 74.54 76.86 76.96 77.18 77.72 77.69
13	98.96	70.87 to 129.87	NCI-H522 (Lung Cancer) SNB-75 (CNS Cancer) PC-3 (Prostate Cancer) UO-31 (Renal Cancer) MDA-MB-231/ATCC (Breast C.) CCRF-CEM (Leukemia) LOX IMVI (Melanoma)	70.87 76.07 77.16 77.22 83.67 83.74 84.89



1: R = H; **2:** R = C₃H₇; **3:** R = C₆H₅-CH₂; **4:** R = 2-OH-C₆H₄-N=N-; **5:** R = H, R¹ = CH₃;
6: R = H, R¹ = C₃H₇; **7:** R = C₃H₇, R¹ = C₃H₇; **8:** R = C₆H₅-CH₂, R¹ = CH₃; **9:** R = H, R¹ = 4-NO₂-C₆H₄;
10: R = C₃H₇, R¹ = C₆H₅; **11:** R² = H; **12:** R² = 4-NO₂-SO₂-C₆H₄-N=N-; **13:** R² = H

Scheme 1. Synthesis of some thiazolo[4,5-*b*]pyridines.

4. CONCLUSIONS

As a result of the [3+3]cyclocondensation, acylation and alkylation reactions, the synthesis of some thiazolo[4,5-*b*]pyridin-2-ones has been carried out. Their structures were confirmed by ¹H, ¹³C NMR, mass spectroscopy and elemental analysis. Within the framework of the antitumor activity screening of synthesized

compounds was carried out. The test compounds had moderate antitumor activity on the tested cell lines. These results of selectivity on some cell lines that are important for further optimization of the structure and the creation of more selective and active anticancer agents.

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