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Synthesis and Evaluation of Anti-inflammatory Activity of some Thiazolo[4,5-*b*]pyridines

Taras Chaban [1], Vasyl Matiychuk [2,*], Zoriana Chulovska [1], Iryna Myrko [1], Iryna Drapak [1], Rostyslav Sogujko [1], Ihor Chaban [1], Volodymyr Ogurtsov [1], Ihor Nektegaev [1]

[1] Danylo Halytsky Lviv National Medical University, Pekarska 69, Zip Code: 79010, Lviv, Ukraine; chabantaras@ukr.net (T.I.);
[2] Ivan Franko National University of Lviv, Kyryla and Mefodia 6, Zip Code: 79005, Lviv, Ukraine; v_matiychuk@ukr.net (V.M.);
* Correspondence: v_matiychuk@ukr.net (V.M.);

Scopus Author ID 57216946847

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Abstract: The 18 new thiazolo[4,5-*b*]pyridin-2-one derivatives have been synthesized using alkylation, cyanethylation, hydrolysis, and acylation reactions. The structures of the obtained compounds have been confirmed by ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis. The study of the *in vivo* anti-inflammatory activity of the synthesized substances was assessed by using the functional model of carrageenan-induced rat paw edema. The present results of anti-inflammatory activity have shown that the synthesized compounds demonstrated considerable anti-inflammatory effects. Some of them approach or exceed the comparative drug Ibuprofen in terms of activity.

Keywords: organic synthesis; thiazolo[4,5-*b*]pyridines; Ibuprofen; anti-inflammatory activity.

1. Introduction

Inflammation is an important pathogenetic component in many diseases of various etiologies, and therefore its pharmacological regulation is an urgent problem in modern medicine. Rational pharmacotherapy during inflammatory diseases includes the application of anti-inflammatory drugs of different action mechanisms [1]. According to the WHO, about 20 % of the world's population regularly uses NSAIDs, based on the most important feature of this group of drugs – their antipyretic, analgesic, and anti-inflammatory action [2]. Despite the centuries-old history of the use of NSAIDs in clinical practice, the issue of eliminating side effects remains unresolved. Among them, the largest share is attributed to ulcerogenicity [1]. New effective and safe anti-inflammatory drugs are being sought worldwide to overcome these limitations [3,4].

The drugs with nitrogen-containing heterocyclic systems are the most widely used [5-7]. Among several such compounds, thiazolidines are very important due to their numerous derivatives' wide range of biological actions [8-11]. However, fused heterocycles' synthesis and biological activity with a thiazolidinone moiety have been insufficiently studied [12-14]. Thiazolopyridines, as purine bioisosteres, are an important type of heterocyclic system. Their intensive study is driven by a considerable range of their pharmacological activity and synthetic capabilities for functionalizing derivatives at different positions. Published scientific data have confirmed that annelated thiazolopyridines have various biological activities. They include substances with antioxidant [15,16], fungicidal [17], anti-inflammatory [18-22], herbicidal

[23], tuberculostatic [24] anti-mitotic [25], antitumor [26] and antimicrobial [27-29] activities. Some of their analogs were recognized as agonists H3-histamine receptors [30], antagonists of metabotropic glutamate receptors 5 (mGluR5) [31], and substances with high inhibitory activity against epidermal growth factor receptors [32] and several other enzymes [33].

In this article, which is the portion of our exploring biologically active heterocycles [34-57] we structural modification of basic 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one and 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one for pharmacological screening of anti-inflammatory activity of synthesized compounds.

2. Materials and Methods

2.1. Materials.

The reagents used for the synthesis of the target compounds were commercially available and of analytical grade. When performing the synthetic part of the work, the reagents of the company Merck (Germany) and Sigma-Aldrich (USA) were used. All solvents and reagents were used without further purification.

2.2. Chemistry.

The melting points of all the compounds were recorded in an open capillary by Melt temp instrument. ^{1}H-NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) [Agilent Technologies, San Francisco, USA] instrument with TMS or deuterated solvent as an internal reference. Chemical shifts were reported as δ (ppm). Mass spectra were run using Agilent 1100 series LC/MSD [Agilent Technologies, San Francisco, USA] with an API–ES/APCI ionization mode. Elemental analysis was performed on a Vario MICRO cube automatic CHNS analyzer [Elementar, Langenselbold, Hesse, Germany]. The elemental analysis data obtained experimentally for carbon, hydrogen, and nitrogen contents were within ±0.3% of the theoretical values.

The general procedure of receiving 5,7-dimethyl-3H-thiazolo[4,5-b]pyridin-2-one N^3 substituted derivatives by alkylation reaction (1-6). An equimolar amount of 5,7-dimethyl-3H-thiazolo[4,5-*b*]pyridin-2-one was added to the solution obtained by heating 0.003 mol of KOH in 20 ml of ethanol and boiled for 15 minutes. 0.003 mol of the corresponding chloroacetamide was added to the resulting solution and boiled for another 60 min, with a significant amount of precipitate observed. After that, the hot mixture was filtered. 100 ml of water was added to the filtrate with stirring, cooled to a temperature of about 50°C; the solution was cooled to 12–15 °C. The precipitate was filtered off, flushed out with water, and dried. The precipitate was recrystallized from acetic acid. Obtained compounds are white or cream-colored crystalline powders soluble in DMF, DMSO, and ethanol and acetic acid when heated; insoluble in water.

2-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-N-phenyl-acetamide (1). Yield 74%, mp 188°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.80 (s, 2H, N-$\underline{CH_2}$), 7.02 (s, 1H, Py), 7.07 (t, 1H, *J* = 7.4 Hz, C_6H_5), 7.32 (t, 2H, *J* = 8.2 Hz, C_6H_5), 7.32 (d, 2H, *J* = 7.7 Hz, C_6H_5), 10.44 (s, 1H, NH). ESI-MS: m/z 314 $[M+H]^+$. Anal. calculated for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41. Found: C, 61.24; H, 4.77; N, 13.55.

N-(4-Chloro-phenyl)-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetamide (2). Yield 70%, mp 172°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.34 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.80 (s, 2H, N-$\underline{CH_2}$), 7.02 (s, 1H, Py), 7.38 (d, 2H, *J* = 8.9 Hz, C_6H_4), 7.59 (d, 2H, *J* =

8.9 Hz, C_6H_4), 10.59 (s, 1H, NH). ESI-MS: m/z 349 $[M+H]^+$. Anal. calculated for $C_{16}H_{14}ClN_3O_2S$: C, 55.25; H, 4.06; N, 12.08. Found: C, 55.28; H, 4.11; N, 12.00.

2-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-N-p-tolyl-acetamide (3). Yield 90%, mp 202°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.25 (s, 3H, C_6H_4-CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.77 (s, 2H, N-CH_2), 7.02 (s, 1H, Py), 7.12 (d, 2H, *J* = 8.3 Hz, C_6H_4), 7.44 (d, 2H, *J* = 8.4 Hz, C_6H_4), 10.34 (s, 1H, NH). ESI-MS: m/z 329 $[M+H]^+$. Anal. calculated for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.23; N, 12.83. Found: C, 62.20; H, 5.33; N, 12.53.

2-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-N-(4-nitro-phenyl)-acetamide (4). Yield 69%, mp 180°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.34 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.87 (s, 2H, N-CH_2), 7.03 (s, 1H, Py), 7.81 (d, 2H, *J* = 9.3 Hz, C_6H_4), 8.24 (d, 2H, *J* = 9.2 Hz, C_6H_4), 11.08 (s, 1H, NH). ESI-MS: m/z 359 $[M+H]^+$. Anal. calculated for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.45; H, 3.69; N, 15.55.

4-[2-(5,7-Dimethyl-2-oxo -thiazolo[4,5-b]pyridin-3-yl)-acetylamino]-benzoic acid ethyl ester (5). Yield 73%, mp 212°C. ^{1}H NMR (400 MHz, DMSO): δ = 1.31 (t, 3H, *J* = 7.1 Hz, CH_2-CH_3), 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.26-4.31 (m, 2H, CH_2-CH_3), 4.84 (s, 2H, N-CH_2), 7.02 (s, 1H, Py), 7.70 (d, 2H, *J* = 8.7 Hz, C_6H_4), 7.93 (d, 2H, *J* = 8.8 Hz, C_6H_4), 10.81 (s, 1H, NH). ESI-MS: m/z 387 $[M+H]^+$. Anal. calculated for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.33; H, 5.02; N, 10.81.

N-(4-Acetylamino-phenyl)-2-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-yl)-acetamide (6). Yield 75%, mp 187°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.02 (s, 3H, CO-CH_3), 2.33 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.77 (s, 2H, N-CH_2), 7.01 (s, 1H, Py), 7.47 (d, 2H, *J* = 9.1 Hz, C_6H_4), 7.52 (d, 2H, *J* = 9.1 Hz, C_6H_4), 9.90 (s, 1H, NH), 10.37 (s, 1H, NH). ESI-MS: m/z 372 $[M+H]^+$. Anal. calculated for $C_{18}H_{18}N_4O_3S$: C, 58.36; H, 4.90; N, 15.12. Found: C, 58.44; H, 4.84; N, 15.20.

[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetic acid ethyl ester (7). An equimolar amount of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one was added to a solution obtained by mixing 0.005 mol KOH in 20 ml of ethanol, and the resulting mixture was boiled for 20 min until complete dissolving. 0.005 mol of monochloroacetic acid ethyl ester was added to the resulting solution and boiled for another 60 minutes. The hot mixture was filtered. 150 ml of water was added to the filtrate, cooled to a temperature of about 40°C, and then the solution was cooled to 10–15°C. The precipitate was filtered off, flushed out with water, and dried. The precipitate was recrystallized from acetic acid. It is a cream-colored crystalline powder readily soluble in DMF and DMSO. It is insoluble in water.

Yield 69%, mp 108°C. ^{1}H NMR (400 MHz, DMSO): δ = 1.15 (s, 3H, CH_2-CH_3), 2.33 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.07-4.12 (m, 2H, CH_2-CH_3), 4.18 (s, 2H, S-CH_2), 5.40 (s, 2H, N-CH_2), 7.05 (s, 1H, Py). ESI-MS: m/z 382 $[M+H]^+$. Anal. calculated for $C_{15}H_{16}N_4O_4S_2$: C, 47.36; H, 4.24; N, 14.73. Found: C, 47.12; H, 4.58; N, 14.55.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-propionitrile (8). A mixture of 50 ml of pyridine and 10 ml of water containing 3 ml of acrylonitrile was added to 0.01 mol of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one. The reaction mixture was heated in a flask under reflux for 5 h. Crystalline precipitate was obtained by precipitation with a mixture of petroleum ether and water (3:1). After recrystallization from ethanol, the white powder is soluble in ethanol, chloroform, dioxane, DMF, and acetic acid. Yield 54%, mp 135°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.34 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 3.00 (t, 2H, *J* = 6.3 Hz, CH_2),

4.28 (t, 2H, *J* = 6.3 Hz, CH_2), 5.34 (s, 2H, N-$\underline{CH_2}$), 7.07 (s, 1H, Py). ESI-MS: m/z 349 $[M+H]^+$. Anal. calculated for $C_{14}H_{13}N_5O_2S_2$: C, 48.40; H, 3.77; N, 20.16. Found: C, 48.34; H, 3.74; N, 20.33.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-propionic acid (9). A mixture of 0.01 mol of compound 8, 30 ml of acetic acid, and 15 ml of hydrochloric acid was added in a round-bottom flask. The reaction mixture was refluxed for 3 h and precipitated with water. The solid precipitate filtered after 24 hours was treated with toluene. It was recrystallized from ethanol. The white powder is soluble in DMF, DMSO, and in ethanol and acetic acid when heated; it is insoluble in water. Yield 80%, mp 107°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.33 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 2.72 (t, 2H, *J* = 7.0 Hz, CH_2), 4.17 (t, 2H, *J* = 7.0 Hz, CH_2), 5.31 (s, 2H, N-$\underline{CH_2}$), 7.06 (s, 1H, Py), 12.55 (s, 1H, COOH). ESI-MS: m/z 368 $[M+H]^+$. Anal. calculated. for $C_{14}H_{14}N_4O_4S_2$: C, 45.89; H, 3.85; N, 15.29. Found: C, 46.02; H, 3.77; N, 15.35.

General synthesis method of 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-aryl-propionamides (10-18). A mixture of 0.057 mol of thionyl chloride was added to 0.01 mol of compound 9 in dioxane medium; the mixture was boiled for 30 minutes and precipitated with petroleum ether. The obtained untreated acid chloride is used for further transformations. A solution of 0.01 mol of the corresponding amine and 0.01 mol of triethylamine in 10 ml of dioxane was added to the obtained acid chloride. It was incubated for 10 min in an oven at 100°C and poured into water. The filtered precipitate is recrystallized from acetic acid. These are white, gray, or cream-colored substances, poorly soluble in water and organic solvents, soluble in DMF and DMSO.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-phenyl-propionamide (10). Yield 62%, mp 204°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.32 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.81 (t, 2H, *J* = 7.1 Hz, CH_2), 4.26 (t, 2H, *J* = 7.0 Hz, CH_2), 5.31 (s, 2H, N-$\underline{CH_2}$), 7.02 (s, 1H, Py), 7.04 (d, 1H, *J* = 7.4 Hz, C_6H_5), 7.28 (t, 2H, *J* = 8.1 Hz, C_6H_5), 7.51 (d, 2H, *J* = 7.9 Hz, C_6H_5), 10.03 (s, 1H, NH). ESI-MS: m/z 443 $[M+H]^+$. Anal. calculated for $C_{20}H_{19}N_5O_3S_2$: C, 54.41; H, 4.34; N, 15.86. Found: C, 54.56; H, 4.40; N, 15.77.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-p-tolyl-propionamide (11). Yield 48%, mp 223°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.24 (s, 3H, C_6H_4-$\underline{CH_3}$), 2.27 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.76 (t, 2H, *J* = 7.1 Hz, CH_2), 4.20 (t, 2H, *J* = 7.1 Hz, CH_2), 5.33 (s, 2H, N-$\underline{CH_2}$), 6.98 (s, 1H, Py), 7.09 (d, 2H, *J* = 7.7 Hz, C_6H_4), 7.43 (d, 2H, *J* = 8.1 Hz, C_6H_4), 9.88 (s, 1H, NH). ESI-MS: m/z 457 $[M+H]^+$. Anal. calculated for $C_{21}H_{21}N_5O_3S_2$: C, 55.37; H, 4.65; N, 15.37. Found: C, 55.48; H, 4.58; N, 15.45.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-fluoro-phenyl)-propionamide (12). Yield 53%, mp 215°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.31 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.80 (t, 2H, *J* = 7.0 Hz, CH_2), 4.22 (t, 2H, *J* = 7.1 Hz, CH_2), 5.29 (s, 2H, N-$\underline{CH_2}$), 7.03 (s, 1H, Py), 7.18 (d, 2H, *J* = 7.6 Hz, C_6H_4), 7.44 (d, 2H, *J* = 8.0 Hz, C_6H_4), 10.04 (s, 1H, NH). ESI-MS: m/z 461 $[M+H]^+$. Anal. calculated for $C_{20}H_{18}FN_5O_3S_2$: C, 52.28; H, 3.95; N, 15.24. Found: C, 52.11; H, 3.86; N, 15.33.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-chloro-phenyl)-propionamide (13). Yield 61%, mp 236°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.32 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.81 (t, 2H, *J* = 7.1 Hz, CH_2), 4.24 (t, 2H, *J* = 7.1 Hz, CH_2), 5.32 (s, 2H, N-$\underline{CH_2}$), 7.01 (s, 1H, Py), 7.23 (d, 2H, *J* = 7.5 Hz, C_6H_4),

7.49 (d, 2H, *J* = 8.1 Hz, C_6H_4), 9.98 (s, 1H, NH). ESI-MS: m/z 477 $[M+H]^+$. Anal. calculated for $C_{20}H_{18}ClN_5O_3S_2$: C, 50.47; H, 3.81; N, 14.71. Found: C, 50.55; H, 3.87; N, 14.62.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(4-nitro-phenyl)-propionamide (14). Yield 55%, mp 198°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.31 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 2.80 (t, 2H, *J* = 7.1 Hz, CH_2), 4.24 (t, 2H, *J* = 7.1 Hz, CH_2), 5.32 (s, 2H, N-$\underline{CH_2}$), 7.01 (s, 1H, Py), 7.18 (d, 2H, *J* = 7.6 Hz, C_6H_4), 7.46 (d, 2H, *J* = 8.1 Hz, C_6H_4), 10.06 (s, 1H, NH). ESI-MS: m/z 488 $[M+H]^+$. Anal. calculated for $C_{20}H_{18}N_6O_5S_2$: C, 49.37; H, 3.73; N, 17.27. Found: C, 49.54; H, 3.71; N, 17.14.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(2-fluoro-phenyl)-propionamide (15). Yield 51 %, mp 206°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.23 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 2.82 (t, 2H, *J* = 7.3 Hz, CH_2), 4.21 (t, 2H, *J* = 7.5 Hz, CH_2), 5.33 (s, 2H, N-$\underline{CH_2}$), 6.98 (s, 1H, Py), 7.24 (t, 1H, *J* = 7.6 Hz, C_6H_4), 7.35 (t, 1H, *J* = 7.7 Hz, C_6H_4), 7.51 (d, 1H, *J* = 8.1 Hz, C_6H_4), 7.66 (d, 1H, *J* = 7.9 Hz, C_6H_4), 9.96 (s, 1H, NH). ESI-MS: m/z 461 $[M+H]^+$. Anal. calculated for $C_{20}H_{18}FN_5O_3S_2$: C, 52.28; H, 3.95; N, 15.24. Found: C, 52.06; H, 4.02; N, 15.35.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(2-chloro-phenyl)-propionamide (16). Yield 55 %, mp 227°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.26 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.84 (t, 2H, *J* = 7.3 Hz, CH_2), 4.21 (t, 2H, *J* = 7.5 Hz, CH_2), 5.32 (s, 2H, N-$\underline{CH_2}$), 6.96 (s, 1H, Py), 7.19 (t, 1H, *J* = 7.6 Hz, C_6H_4), 7.31 (t, 1H, *J* = 7.8 Hz, C_6H_4), 7.47 (d, 1H, *J* = 8.0 Hz, C_6H_4), 7.64 (d, 1H, *J* = 7.8 Hz, C_6H_4), 9.87 (s, 1H, NH). ESI-MS: m/z 477 $[M+H]^+$. Anal. calculated for $C_{20}H_{18}ClN_5O_3S_2$: C, 50.47; H, 3.81; N, 14.71. Found: C, 50.25; H, 3.88; N, 14.75.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(2-trifluoromethyl-phenyl)-propionamide (17). Yield 52 %, mp 180°C. ^{1}H NMR (400 MHz, DMSO): δ = 2.27 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.81 (t, 2H, *J* = 7.2 Hz, CH_2), 4.22 (t, 2H, *J* = 7.6 Hz, CH_2), 5.32 (s, 2H, N-$\underline{CH_2}$), 6.96 (s, 1H, Py), 7.21 (t, 1H, *J* = 7.3 Hz, C_6H_4), 7.39 (t, 1H, *J* = 7.7 Hz, C_6H_4), 7.53 (d, 1H, *J* = 7.8 Hz, C_6H_4), 7.73 (d, 1H, *J* = 7.8 Hz, C_6H_4), 10.07 (s, 1H, NH). ESI-MS: m/z 511 $[M+H]^+$. Anal. calculated for $C_{21}H_{18}F_3N_5O_3S_2$: C, 49.50; H, 3.56; N, 13.74. Found: C, 49.05; H, 3.81; N, 13.66.

3-[5-(5,7-Dimethyl-2-oxo-thiazolo[4,5-b]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-N-(2-ethyl-phenyl)-propionamide (18). Yield 44 %, mp 203°C. ^{1}H NMR (400 MHz, DMSO): δ = 1.10 (s, 3H, CH_2-$\underline{CH_3}$), 2.27 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.82 (t, 2H, *J* = 7.2 Hz, CH_2), 3.15 (s, 2H, $\underline{CH_2}$-CH_3), 4.24 (t, 2H, *J* = 7.4 Hz, CH_2), 5.29 (s, 2H, N-$\underline{CH_2}$), 6.85 (s, 1H, Py), 7.21 (t, 1H, *J* = 7.3 Hz, C_6H_4), 7.30 (t, 1H, *J* = 7.5 Hz, C_6H_4), 7.46 (d, 1H, *J* = 8.0 Hz, C_6H_4), 7.58 (d, 1H, *J* = 7.9 Hz, C_6H_4), 9.22 (s, 1H, NH). ESI-MS: m/z 471 $[M+H]^+$. Anal. calculated for $C_{22}H_{23}N_5O_3S_2$: C, 56.27; H, 4.94; N, 14.91. Found: C, 56.44; H, 4.99; N, 15.07.

2.3. Pharmacology.

The requirements of the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes, we carried out a study of anti-inflammatory activity using the method of paw edema in rats caused by carrageenan. The Ethical Committee of the Danylo Halytsky Lviv National Medical University approved the experimental protocol (Ethical Committee or Institutional Animal Care and Use Committee Approval: March 18, 2013; № 3). White Wistar rats weighing 180–200 g were used for this study. The laboratory animals were divided into 20 groups. Each group consisted of 5 animals.

To test the anti-inflammatory activity of 18 synthesized compounds and Ibuprofen, 19 test groups were used, and the 20th test group was a control group.

Tested compounds (50 mg/kg body weight) and Ibuprofen (50 mg/kg body weight) were dissolved in DMSO and administered intraperitoneally. Only DMSO was administered to the animals from the control group.

After 30 minutes, the general edema was induced by an aseptic injection of 0.1 ml of 2 % carrageenan solution under the aponeurosis of the sole of the rat's hind limb. Inflammatory reaction was determined by the change in limb volume by the oncometric method at the beginning of the experiment and 4 hours after the administering flogogenic agent. Inhibition of the inflammatory reaction was determined as a percentage of the reduction in paw volume and calculated using the following formula:

$$\%\ \text{Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \cdot 100\ \%$$

where V_{control} is the increase in paw volume in the control group of animals;
V is the increase in paw volume in animals injected with the test substances.

3. Results and Discussion

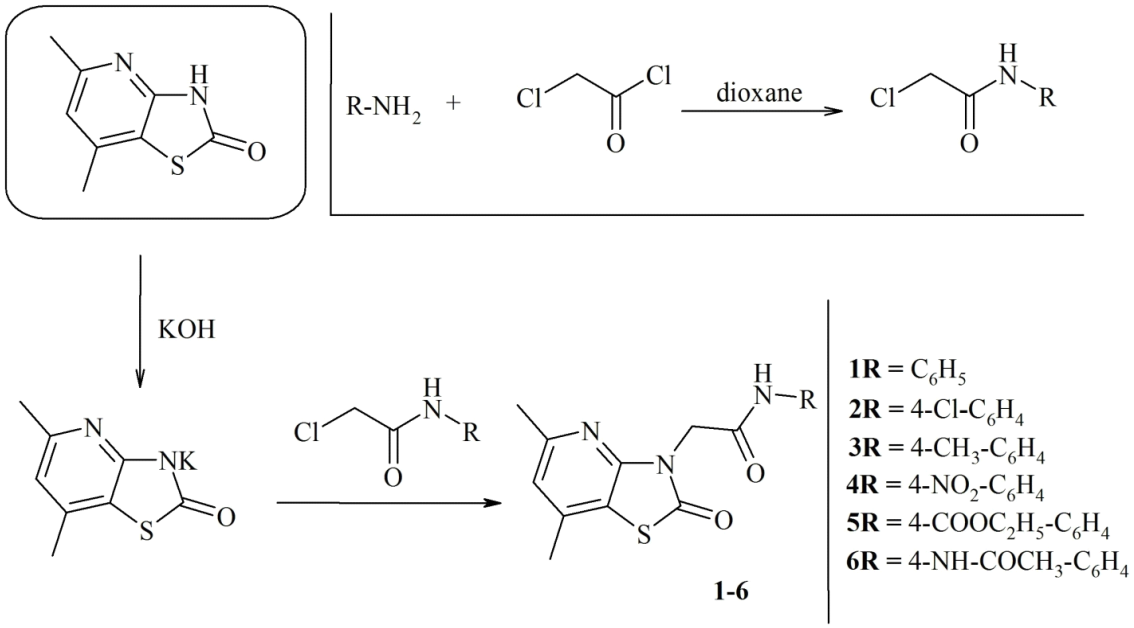
3.1. Chemistry.

In order to study the effect of various substituents in the molecules on the nature of the pharmacological activity of thiazolo[4,5-*b*]pyridin-2-ones, a series of new compounds were synthesized based on the previously obtained 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one [58] and 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one [59].

The high electrophilicity of the N^3 position in 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one allows to use of its functionalization as a convenient method for obtaining various N^3-substituted derivatives to expand the range of thiazolo[4,5-*b*]pyridines. In particular, an NH center with a mobile hydrogen atom at the N^3 position in 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one allows conducting a synthesis based on 3-substituted derivatives. This conversion was carried out through the stage of obtaining potassium salt. Several chloroacetamides were tested as alkylating agents, which allowed to obtain the corresponding 2-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-yl)-N-aryl-acetamides (1-6) (Scheme 1).

The next step in this work was to carry out the structural modification of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one. SH-nucleophilic center with a mobile hydrogen atom of this scaffold allows synthesizing S-substituted derivatives. In particular, the thiol group of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one makes it possible to synthesize the corresponding derivative based on it in an alkylation reaction with monochloroacetic acid ethyl ester. The reaction was carried out in ethanol by boiling for 75 min, which resulted in the corresponding [5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-acetic acid ethyl ester (7) (Scheme 2).

Implementation of transformations leading to the appearance of a chemically versatile cyano group in the base scaffold is known to expand the synthetic capabilities of the original organic compound significantly. It makes it possible to obtain various derivatives of interest in terms of finding new biologically active substances.



Scheme 1. Synthesis of N^3 substituted 3*H*-thiazolo[4,5-*b*]pyridin-2-ones by alkylation reaction (1-6).

In order to obtain 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-propionitrile which is a reagent in the transformations of thiazolo[4,5-*b*]pyridine, we investigated the cyanethylation reaction of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one. One of the conditions for this transformation is the use of basic catalysts. The use of a pyridine mixture with water leads to an increase in basicity, which positively affects the course of this reaction. It was found that the most optimal conditions for the introduction of β-cyanethyl moiety on the thiol group of the base scaffold imply interaction of equimolar amounts of 3-(5-mercapto-[1,3,4]oxodiazol-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one with acrylonitrile in pyridine and water with a ratio of 5:1, which made it possible to obtain the corresponding 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxodiazol-2-ylsulfanyl-propionitrile (8) (Scheme 2). This transformation occurs as a conjugate nucleophilic 1,4-addition (Scheme 2).

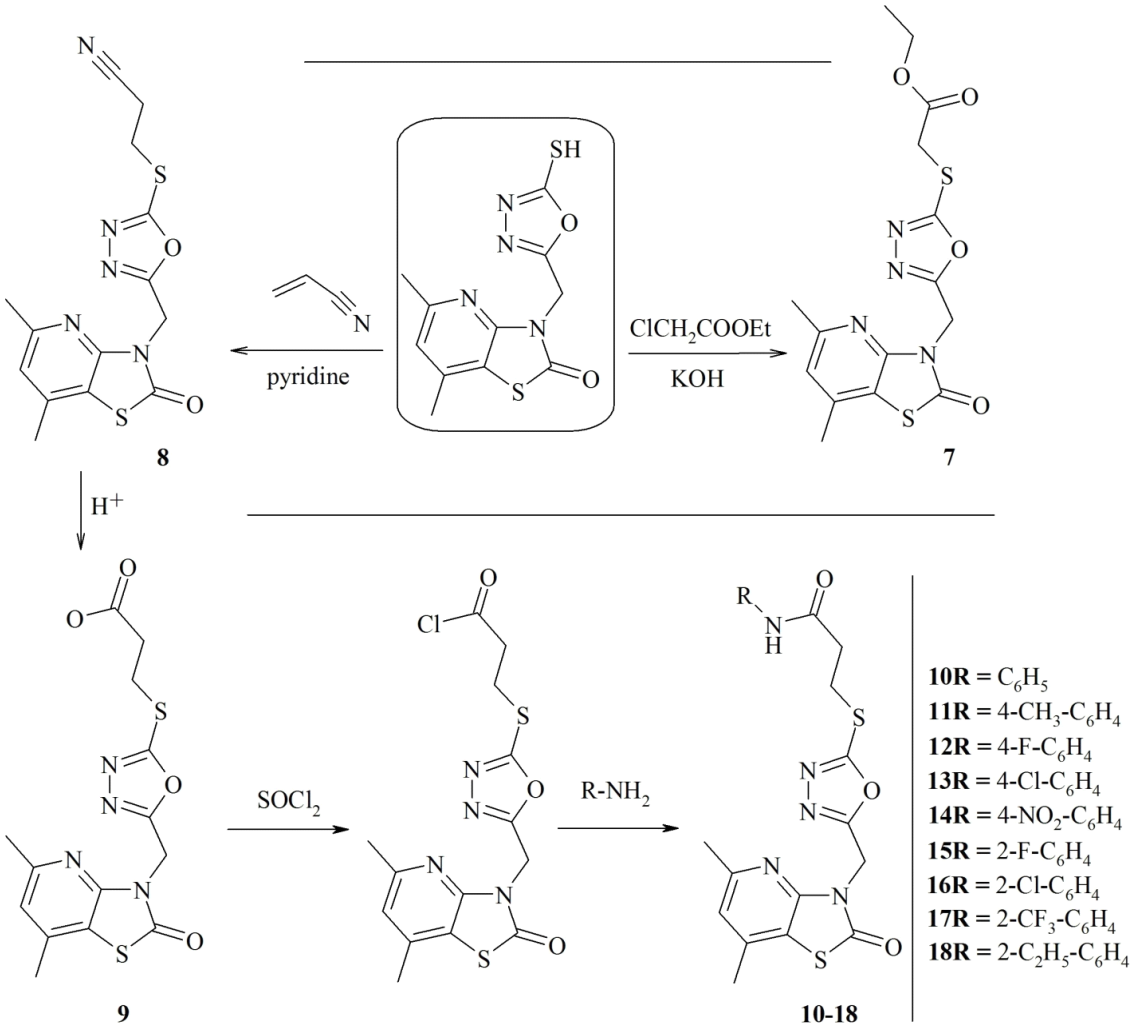
The compound 8 obtained by this reaction was hydrolyzed, which allowed obtaining 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-propionic acid (9). To transform the compound 9 carboxyl group, the corresponding acid chloride was obtained, which belongs to the unstable, highly reactive reagents. Thus, its use in further transformations was carried not isolating *in situ* by introducing aromatic amines into the acylation reaction. This transformation allowed obtaining several suitable propionamides (10-18) (Scheme 2).

Methods of quantitative elemental analysis, mass spectrometry, and ^{1}H NMR spectroscopy were used to confirm the structure and individuality of the synthesized substances. Interpretation of the spectra revealed that the signals for protons of all structural units were observed in their characteristic ranges.

3.2. Pharmacology.

Exudative inflammation is considered a classic example of acute inflammation. A study of the effect of the synthesized substance on the course of the exudative phase during

inflammation was performed based on the carrageenan model of inflammatory edema of the white Wistar rat's paws [60,61].



Scheme 2. Synthesis of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-ones (7-18).

For comparison, the anti-inflammatory effect of a known anti-inflammatory drug, Ibuprofen, was studied in medium therapeutic doses in similar conditions. Inhibition of the inflammatory response was determined as a percentage of the reduction in paw volume. The anti-inflammatory activity results for the synthesized compounds and Ibuprofen are shown in table 1.

Table 1. Anti-inflammatory effect of thiazolo[4,5-*b*]pyridine-2-ones on carrageenan-induced rat paw edema (ml) *in vivo* evaluation, % protection from inflammation.

Compound ID	Paw edema volume (mL) ± SEM*	% Inhibition	Activity relative to Ibuprofen, %
Control	2.20 ± 0.050	-	
1	1.69 ± 0.045	23.2	*57.7*
2	1.35± 0.035	38.6	*96.0*
3	1.56± 0.040	29.0	*72.1*
4	1.78± 0.045	19.3	*48.0*
5	1.66 ± 0.045	24.4	*60.7*
6	1.70 ± 0.045	22.7	*56.5*
7	1.16 ± 0.020	47.2	*117.4*
8	1.03 ± 0.015	53.4	*132.8*
9	1.20 ± 0.020	45.6	*113.4*
10	1.58 ± 0.040	28.1	*69.9*
11	1.62 ± 0.045	26.4	*65.7*

Compound ID	Paw edema volume (mL) ± SEM*	% Inhibition	Activity relative to Ibuprofen, %
12	1.40 ± 0.035	36.5	*90.8*
13	1.37 ± 0.035	37.9	*94.3*
14	1.72 ± 0.045	22.0	*54.7*
15	1.47 ± 0.040	33.1	*82.3*
16	1.38 ± 0.035	37.1	*92.3*
17	1.29 ± 0.025	41.3	*102.7*
18	1.75 ± 0.045	20.6	*51.3*
Ibuprofen	1.32 ± 0.035	40.2	*100*

***SEM denotes standard error of the mean.

The synthesized compounds induce various anti-inflammatory activities – from almost complete absence to a pronounced anti-inflammatory effect. For some compounds, the anti-inflammatory effect is equivalent to the effect of the reference drug Ibuprofen. The values of which in the inflammatory reaction inhibition range from 36.5 % to 40.9 %. The anti-inflammatory activity of several synthesized substances is lower in comparison to the reference drug, the inflammatory reaction suppression indicators for them are within the range of 19.3–33.1 %. However, the anti-inflammatory activity of the other three substances exceeds the inhibitory effect of Ibuprofen and total 47.2 % for compound 7, 53.4 % for compound 8, and 45.6 % for compound 9.

Retrospective analysis of the anti-inflammatory activity results of the studied thiazolo[4,5-*b*]pyridin-2-ones allowed identifying the following vectors of chemical optimization. Modification of 5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one allowed introducing a number of chloroacetamide substituents in N^3 position. However, the anti-inflammatory effect increased compared to unsubstituted thiazolo[4,5-*b*]pyridine only in the case of 2-chloro-N-(4-chloro-phenyl)-acetamide alkylation. The introduction of an ethyl acetate substituent in the thiol group 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one leads to an increase in activity compared with the comparative drug. Moreover, a significant increase in activity is observed for the cyanethylation product, namely 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxadiazole-2-ylsulfanyl]-propionitrile, which allows concluding that the propionitrile moiety has pharmacophore properties. The subsequent modification of compound 8 in the hydrolysis reaction leads to a slight decrease in anti-inflammatory activity; however, this effect is more prominent compared to the comparative drug. The obtained 3-[5-(5,7-dimethyl-2-oxo-thiazolo[4,5-*b*]pyridin-3-ylmethyl)-[1,3,4]oxadiazol-2-ylsulfanyl]-*N*-aryl-propionamides (10-18) reveal different activity depending on the substituent. Compounds 10, 11, 14, 15, and 18 reveal anti-inflammatory activity at the level of 20.6–33.1 %, while the effect of compounds with halogen-containing substituents ranges from 36.5 to 41.3 %. Thus, a significant increase in the anti-inflammatory effect compared to Ibuprofen is achieved by modification of 3-(5-mercapto-[1,3,4]oxodiazole-2-yl-methyl)-5,7-dimethyl-3*H*-thiazolo[4,5-*b*]pyridine-2-one, by the introduction of ethyl acetate or propionitrile substituent.

4. Conclusions

Based on the alkylation, cyanethylation, hydrolysis, and acylation reactions, the synthesis of new thiazolo[4,5-*b*]pyridin-2-ones was carried out. The structure of the obtained compounds and the interpretation of the performed chemical studies were confirmed by elemental analysis and NMR ^{1}H spectroscopy. During the study of newly synthesized substances' anti-inflammatory activity in the carrageenan model of inflammatory edema of

white rats paws, we distinguished four highly active compounds with a pronounced anti-inflammatory effect that exceeded the activity of the comparative drug Ibuprofen. It is a strong argument for studying "thiazolo[4,5-*b*]pyridine" structural "matrix" for developing potential anti-inflammatory agents.

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Conflicts of Interest

The authors declare no conflict of interest.

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