

Scientific paper

Synthesis, Molecular Docking and Biological Properties of Novel Thiazolo[4,5-*b*]pyridine Derivatives

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Received: 07-24-2019

Abstract

The synthesis, anti-inflammatory and antioxidant properties of novel 5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one derivatives were discussed. Fused thiazolo[4,5-*b*]pyridin-2-ones were synthesized and modified at the N³, C⁵ and C⁶ positions of the main core in order to obtain the compounds with a satisfactory pharmacological profile. The synthesized compounds were preselected via molecular docking for further testing of their anti-inflammatory activity *in vitro*. Evaluation of novel compounds over the carageenin induced rat paw edema revealed strong anti-inflammatory action of some compounds including (thiazolo[4,5-*b*]pyridin-3(2*H*)-yl) propanenitrile (5) and thiazolo[4,5-*b*]pyridin-3(2*H*)-yl) propanoic acid (6) even exceeding the standard – Ibuprofen. The antioxidant activity of the synthesized compounds was measured *in vitro* by the method of scavenging effect on 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals.

Keywords: Organic synthesis; thiazolo[4,5-*b*]pyridin-2-ones; anti-inflammatory activity; antioxidant activity; molecular docking

1. Introduction

Inflammation is an essential response of living organisms to the common ailments starting from traumatic disorder or fever associated with infection to major life-threatening diseases like myocardial infarction or brain haemorrhage or infarct.¹ Literature data survey has revealed that numerous nonsteroidal anti-inflammatory drugs (NSAIDs), which belong to different chemical classes, have been developed to treat inflammatory disorders. During the past few years, the long-term use of NSAIDs has been severely hampered by the emerging of several serious effects such as gastrointestinal ulcers, hepatotoxicity, renal dysfunction, and cardiotoxicity.² Unfortunately all of the proposed medications provoke serious side effects.³

In general, NSAIDs exert their pharmacological action by inhibiting the synthesis of prostaglandins (PGs) by non-selectively *cyclooxygenases 1* and *2* (COX-1 and COX-2), either selective COX-2 blocking. Inhibition of COX-1 is also responsible, in part, for gastrointestinal side effects, which are the most frequent side effects of NSAIDs.⁴ These conditions generate one of the biggest challenges of modern medicinal chemistry for the development of alternative anti-inflammatory drugs with minimal adverse effects.^{5–7}

No less challenging is the search for new antioxidants. Different environmental stress factors like pollution, drought, temperature, excessive light intensities, and nutritional limitation can increase the production of reactive oxygen species (ROS).^{8–9} Oxidative stress is a major contributing factor for developing degenerative diseases

like atherosclerosis, ischemic heart disease, ageing, diabetes mellitus, cancer and others.¹⁰ Antioxidants can interfere with the oxidation process by reacting with free radicals, and also by acting as reactive species scavenger.¹¹ Therefore, various natural well and synthetic antioxidants are used to scavenge free radicals. In this regard, it is important to synthesize new classes of compounds with antioxidant properties.

Fused bicyclic systems with thiazolidine core occupy a prominent place in medicinal chemistry due to their broad spectrum of pharmacological activities.^{12–14} Previously, we have developed convenient and efficient method to form combinatorial libraries of fused azoles such as [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazole,^{15–16} pyrazolo[3,4-*d*]pyridazines,¹⁷ [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines,¹⁸ isoindolo[1,2-*a*]isoquinoline,¹⁹ thiopyrano[2,3-*d*][1,3]thiazoles,²⁰ thieno[3,2-*c*]pyridinone,²¹ triazolo[4,5-*d*]pyridazine,²² and thiazolo[4,5-*b*]pyridines.²³ In summing up the published scientific data fused thiazolopyridines are characterized by herbicidal,²⁴ antioxidant,^{25–28} antimicrobial,²⁹ antifungal,³⁰ and anti-mitotic³¹ activities. They also show potent inhibitory activities for A β 42 fibrillization for Alzheimer's disease treatment.³² It was established that thiazolopyridine derivatives exhibit anti-tuberculosis,³³ anti-inflammatory^{34–36} and significant anticancer³⁷ activity, and also act as agonists of H3-histamine receptors.³⁸

For the time being, exploration of different chemical modifications avenues of thiazolopyridines to obtain novel active compounds, and thus, the development of a new class of anti-inflammatory drugs with optimal pharmacokinetic properties should be continued.

The present work is devoted to the synthesis of a series of novel 3*H*-thiazolo[4,5-*b*]pyridine-2-ones by the structural modification of the core heterocycle in its N³, C⁵ and C⁶ positions for further pharmacological *in vivo* anti-inflammatory activity assay based on the results obtained via computer simulation – molecular docking and *in vitro* antioxidant screenings.

2. Experimental Section

2.1. Materials

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

2.2. Chemistry

All melting points were determined in an open capillary and are uncorrected. ¹H and ¹³C NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ¹H) instrument with TMS or deuterated solvent as an internal reference. Mass spectra were run using Agilent 1100 series LC/MSD, Agilent Technologies Inc. with an API-ES/APCI

ionization mode. Satisfactory elemental analyses were obtained for new compounds (C \pm 0.17, H \pm 0.21, N \pm 0.19).

General procedure for the synthesis 6-arylazo-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (2, 3).

Sodium (0.2 mol) was dissolved in anhydrous methanol (100 mL). To the obtained solution 4-iminothiazolidin-2-one (50 mmol) and α -arylazo-derivative of ethyl acetoacetate (50 mmol) were added at 20 °C. The mixture was left for 7 days with the intermittent stirring. Afterwards, it was acidified with acetic acid to pH 5 and five-fold diluted with water. The precipitate was filtered off, washed with water, and dried at 100–110 °C. The obtained compounds were recrystallized from acetic acid.

4-((5-Hydroxy-7-methyl-2-oxo-2,3-dihydrothiazolo[4,5-*b*]pyridin-6-yl)diazanyl) benzene-sulfonic acid (2):

Red solid; yield: 88 %; mp > 280 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.37 (s, 3H, CH₃), 7.59 (d, *J* = 8.1 Hz, 2H, C₆H₄), 7.69 (d, *J* = 7.9 Hz, 2H, C₆H₄), 13.30 (s, 1H, OH), 14.55 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃) δ 16.88, 116.35, 122.65, 125.27, 127.08, 140.78, 141.58, 145.48, 159.99, 166.28, 177.45; ESI-MS: *m/z* 366 [M+H]⁺; anal. calcd. for C₁₃H₁₀N₄O₅S₂: C 42.62, H 2.75, N 15.29; found: C 43.01, H 2.68, N 15.35.

5-Hydroxy-7-methyl-6-(naphthalen-2-yl)diazanylthiazolo[4,5-*b*]pyridin-2(3*H*)-one (3):

Red solid; yield: 84 %; mp 265 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H, CH₃), 7.67 (d, *J* = 6.8 Hz, 2H, naphthalen), 7.74–7.77 (m, 1H, naphthalen), 7.88–7.90 (m, 1H, naphthalen), 7.98–8.07 (m, 3H, naphthalen), 13.46 (s, 1H, OH), 15.74 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃) δ 16.90, 114.83, 115.86, 121.34, 125.49, 125.96, 127.17, 127.80, 127.84, 129.90, 131.46, 132.12, 133.26, 135.20, 136.17, 139.48, 140.50, 160.54; ESI-MS: *m/z* 336 [M+H]⁺; anal. calcd. for C₁₇H₁₂N₄O₂S: C 60.70, H 3.60, N 16.66; found: C 60.44, H 3.63, N 16.58.

5-Hydroxy-7-methyl-3-phenylthiazolo[4,5-*b*]pyridin-2(3*H*)-one (4):

Sodium (109 mmol) was dissolved in anhydrous methanol (150 mL). To the obtained solution 3-phenyl-4-iminothiazolidin-2-one (50 mmol) and ethyl acetoacetate (8.5 mL) were added at 20 °C. The mixture was left for 5 days with the intermittent stirring. Afterwards it was acidified with acetic acid to pH ~5, five-fold diluted with water; the precipitate was filtered off, washed with water, and dried. Yellow solid; yield: 65 %; mp 244 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.51 (s, 3H, CH₃), 6.96 (t, *J* = 7.3 Hz, 1H, Py), 7.28 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C₆H₅), 7.45 (d, *J* = 8.1 Hz, 3H, C₆H₅), 8.67 (s, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 17.51, 108.34, 114.33, 125.73, 127.90, 128.24, 140.18, 142.06, 145.08, 160.61, 168.96; ESI-MS: *m/z* 258 [M+H]⁺; anal. calcd. for C₁₃H₁₀N₂O₂S: C 60.45, H 3.90, N 10.85; found: C 60.06, H 3.84, N 10.73.

3-(5-Hydroxy-7-methyl-2-oxothiazolo[4,5-b]pyridin-3(2H)-yl) propanenitrile (5):

A mixture of pyridine (50 mL) and water (10 mL) with acrylonitrile (3 mL) was added to the 5-hydroxy-7-methylthiazolo[4,5-*b*]pyridin-2(3*H*)-one (**1**, 10 mmol). The reaction mixture was refluxed for 5 h. On cooling, the precipitation was achieved with petroleum ether-water mixture (3:1). The precipitate was recrystallized from ethanol, filtered off, and dried. This compound was isolated as a white crystalline solid, well soluble in ethanol, chloroform, dioxane, DMF, acetic acid. White solid; yield: 74 %; mp 105 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.27 (s, 3H, CH₃), 3.04 (t, *J* = 6.5 Hz, 2H, CH₂), 4.15 (t, *J* = 6.5 Hz, 2H, CH₂), 6.41 (s, 1H, Py), 11.09 (s, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 15.77, 19.15, 37.48, 105.11, 105.80, 118.12, 144.70, 146.16, 162.53, 167.96; ESI-MS: *m/z* 236 [M+H]⁺; anal. calcd. for C₁₀H₉N₃O₂S: C 51.05, H 3.86, N 17.86; found: C 50.97, H 3.89, N 17.77.

3-(5-Hydroxy-7-methyl-2-oxothiazolo[4,5-b]pyridin-3(2H)-yl) propanoic acid (6):

The mixture of the propanenitrile (**5**, 10 mmol), acetic acid (30 mL), and hydrochloric acid (15 mL) were placed into the round-bottomed flask. The reaction mixture was refluxed 3 h and the product was precipitated with water. The mixture was left for 24 h at ambient temperature. The precipitate was filtered off and treated with toluene. The precipitate was recrystallized from ethanol, filtered off, and dried. This compound was isolated as a white crystalline powdered solid, well soluble in ethanol, chloroform, dioxane, DMF, acetic acid. White solid; yield: 66 %; mp 111 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.25 (s, 3H, CH₃), 2.68 (t, *J* = 7.5 Hz, 2H, CH₂), 4.10 (t, *J* = 7.6 Hz, 2H, CH₂), 6.38 (s, 1H, Py), 11.05 (s, 1H, OH), 12.07 (s, 1H, COOH); ¹³C NMR (101 MHz, CDCl₃) δ 19.17, 31.76, 37.90, 104.77, 105.97, 144.45, 146.62, 162.50, 167.85, 171.90; ESI-MS: *m/z* 254 [M+H]⁺; anal. calcd. for C₁₀H₁₀N₂O₄S: C 47.24, H 3.96, N 11.02; found: C 47.88, H 3.98, N 11.21.

General procedure for the synthesis of 3-(5-hydroxy-7-methyl-2-oxothiazolo[4,5-b]pyridin-3(2H)-yl)-*N*-aryl-*l* propanamides (7, 8).

The mixture of the propanoic acid (**6**, 10 mmol), thionyl chloride (57 mmol) and dioxane (30 mL) were placed into the round-bottomed flask. The reaction mixture was refluxed for 30 min and the product was precipitated with *n*-hexane, the precipitate was filtered off. The resulting acyl chlorides were used for further transformations without further purification. Obtained 3-(5-hydroxy-7-methyl-2-oxothiazolo[4,5-*b*]pyridin-3(2*H*)-yl)propanoyl chloride (10 mmol) was dissolved in anhydrous dioxane (10 mL), and appropriate aromatic amine (10 mmol) and triethylamine (10 mmol) were added to the solution. The reaction mixture was refluxed for 15 min. On cooling, the mixture was diluted with water and precipitated crystalline solid filtered off, washed with methanol and dried. The obtained compounds were recrystallized from acetic acid.

3-(5-Hydroxy-7-methyl-2-oxothiazolo[4,5-b]pyridin-3(2H)-yl)-*N*-phenyl propanamide (7):

White solid; yield: 48 %; mp 214 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (s, 3H, CH₃), 2.71 (t, 2H, *J* = 7.1 Hz, CH₂), 4.13 (t, 2H, *J* = 7.2 Hz, CH₂), 6.42 (s, 1H, Py), 7.21–7.26 (m, 2H, C₆H₅), 7.40–7.48 (m, 3H, C₆H₅), 9.96 (s, 1H, NH), 11.09 (s, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 19.21, 31.55, 37.54, 105.06, 105.89, 125.18, 128.32, 128.86, 140.85, 144.41, 146.32, 162.47, 167.79, 170.11; ESI-MS: *m/z* 329 [M+H]⁺; anal. calcd. for C₁₆H₁₅N₃O₃S: C 58.35, H 4.59, N 12.76; found: C 58.43, H 4.67, N 12.88.

3-(5-Hydroxy-7-methyl-2-oxothiazolo[4,5-b]pyridin-3(2H)-yl)-*N*-(4-nitrophenyl) propanamide (8):

Yellow solid; yield: 53 %; mp 202 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.36 (s, 3H, CH₃), 2.85 (t, 2H, *J* = 7.2 Hz, CH₂), 4.24 (t, 2H, *J* = 7.2 Hz, CH₂), 6.54 (s, 1H, Py), 7.35–7.41 (m, 2H, C₆H₄), 7.56–7.62 (m, 2H, C₆H₄), 10.18 (s, 1H, NH), 11.14 (s, 1H, OH); ¹³C NMR (101 MHz, CDCl₃) δ 19.23, 31.65, 37.60, 104.89, 105.78, 122.25, 125.63, 126.97, 140.59, 144.24, 146.51, 162.51, 167.70, 170.24; ESI-MS: *m/z* 375 [M+H]⁺; anal. calcd. for C₁₆H₁₄N₄O₅S: C 51.33, H 3.77, N 14.97; found: C 51.11, H 3.81, N 14.86.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 2-chloroacetate (9):

5-Hydroxy-7-methyl-thiazolo[4,5-*b*]pyridin-2(3*H*)-one (**1**, 5 mmol), an appropriate aliphatic chloroacetyl chloride (5 mmol), and triethylamine (5 mmol) were added to dioxane (20 mL). The reaction mixture was refluxed 15 min. On cooling, the formed crystalline precipitate was filtered off, washed with methanol and dried. The obtained compound was recrystallized from methanol. White solid; yield: 67 %; mp 191 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.37 (s, 3H, CH₃), 4.72–4.74 (m, 2H, CH₂), 6.92 (s, 1H, Py), 12.71 (s, 1H, NH); ¹³C NMR (101 MHz, CDCl₃) δ 19.43, 41.07, 110.76, 116.52, 145.16, 148.09, 154.79, 166.09, 168.31; ESI-MS: *m/z* 259 [M+H]⁺; anal. calcd. for C₉H₇ClN₂O₃S: C 41.79, H 2.73, N 10.83; found: C 41.53, H 2.76, N 10.95.

General procedure for the synthesis of 7-methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 4-carboxylates (10–14).

To a solution of pyridine (20 mL) an appropriate aromatic acyl chloride (5 mmol) and 5-hydroxy-7-methyl-thiazolo[4,5-*b*]pyridin-2(3*H*)-one (**1**, 5 mmol) were added. The reaction mixture was refluxed 30 min. On cooling, formed crystalline precipitate was filtered off, washed with acetic acid and dried. The obtained compounds were recrystallized from acetic acid.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 4-chlorobenzoate (10):

White solid; yield: 65 %; mp 214 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.39 (s, 3H, CH₃), 7.06 (s, 1H, Py), 7.70 (d, *J* = 8.5 Hz, 2H, C₆H₄), 8.13 (d, *J* = 8.5 Hz, 2H, C₆H₄), 12.74

(s, 1H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 19.45, 111.25, 116.31, 127.14, 129.32, 131.67, 139.41, 145.08, 148.15, 155.32, 163.52, 168.35; ESI-MS: m/z 320 $[\text{M}+\text{H}]^+$; anal. calcd. for $\text{C}_{14}\text{H}_9\text{ClN}_2\text{O}_3\text{S}$: C 52.42, H 2.83, N 8.73; found: C 52.68, H 2.85, N 8.79.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 4-(benzyloxy) benzoate (11):

White solid; yield: 71 %; mp 197 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.37 (s, 3H, CH_3), 7.01 (s, 1H, Py), 7.21 (d, $J = 8.4$ Hz, 2H, C_6H_4), 7.41 (d, $J = 7.2$ Hz, 2H, C_6H_5), 7.49 (d, $J = 6.9$ Hz, 3H, C_6H_5), 8.08 (d, $J = 8.3$ Hz, 2H, C_6H_4), 12.75 (s, 1H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 19.37, 69.64, 111.39, 114.56, 115.17, 120.45, 127.82, 128.45, 131.31, 132.08, 136.21, 144.95, 148.08, 155.65, 163.06, 163.91, 168.47; ESI-MS: m/z 393 $[\text{M}+\text{H}]^+$; anal. calcd. for $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$: C 64.27, H 4.11, N 7.14; found: C 64.05, H 4.14, N 7.24.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl-(E)-3-(4-methoxyphenyl) acrylate (12):

White solid; yield: 65 %; mp 169 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.39 (s, 3H, CH_3), 3.79 (s, 3H, $\text{CH}_3\text{-C}_6\text{H}_4$), 6.37 (d, 1H, $J = 16.0$ Hz, CH), 7.07 (s, 1H, Py), 6.97 (d, $J = 8.7$ Hz, 2H, C_6H_4), 7.55 (d, 1H, 16.0 Hz, CH), 7.63 (d, $J = 8.7$ Hz, 2H, C_6H_4), 12.17 (s, 1H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 19.64, 55.12, 105.11, 106.80, 114.29, 116.45, 126.77, 129.87, 143.69, 145.55, 146.82, 158.53, 160.88, 167.79, 169.55; ESI-MS: m/z 343 $[\text{M}+\text{H}]^+$; anal. calcd. for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$: C 59.64, H 4.12, N 8.18; found: C 59.64, H 4.03, N 8.28.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 1-(3,4-dimethylphenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (13):

White solid; yield: 77 %; mp 187 °C; ^1H NMR (400 MHz, CDCl_3) δ 1.99 (s, 3H, $\text{CH}_3\text{-triazole}$), 2.38 (s, 3H, CH_3), 2.40 (s, 3H, $\text{CH}_3\text{-C}_6\text{H}_3$), 2.41 (s, 3H, $\text{CH}_3\text{-C}_6\text{H}_3$), 7.08 (s, 1H, Py), 7.28 (d, $J = 8.0$ Hz, 1H, C_6H_3), 7.36–7.38 (m, 2H, C_6H_3), 12.78 (s, 1H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 9.34, 16.61, 19.46, 20.74, 111.26, 116.31, 127.08, 127.68, 131.33, 131.82, 134.14, 134.67, 140.78, 141.62, 145.08, 148.21, 154.98, 159.20, 168.37; ESI-MS: m/z 398 $[\text{M}+\text{H}]^+$; anal. calcd. for $\text{C}_{19}\text{H}_{17}\text{N}_5\text{O}_3\text{S}$: C 57.71, H 4.33, N 17.71; found: C 57.59, H 4.28, N 17.82.

7-Methyl-2-oxo-2,3-dihydrothiazolo[4,5-b]pyridin-5-yl 1-(2-chlorophenyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate (14):

White solid; yield: 64 %; mp 178 °C; ^1H NMR (400 MHz, CDCl_3) δ 2.01 (s, 3H, $\text{CH}_3\text{-triazole}$), 2.37 (s, 3H, CH_3), 7.01 (s, 1H, Py), 6.94–6.98 (m, 1H, C_6H_4), 7.40–7.45 (m, 1H, C_6H_4), 7.53–7.58 (m, 2H, C_6H_4), 12.78 (s, 1H, NH); ^{13}C NMR (101 MHz, CDCl_3) δ 19.39, 20.70, 104.18, 111.03, 116.02, 144.05, 144.69, 144.71, 147.50, 148.31, 148.33, 148.38, 155.32, 162.36, 168.44, 168.88, 168.11;

ESI-MS: m/z 403 $[\text{M}+\text{H}]^+$; anal. calcd. for $\text{C}_{17}\text{H}_{12}\text{ClN}_5\text{O}_3\text{S}$: C 50.81, H 3.01, N 17.43; found: C 51.07, H 3.06, N 17.51.

2. 3. Molecular Docking

Molecular docking was conducted with OpenEye Scientific Software program package as a computer method approach to the search of molecules with affinity to certain biotargets. Used software includes Fred Receptor, Vida, Flipper, Babel 3, Omega 2 and Fred 2 programs.

2. 4. Anti-inflammatory Activity Evaluation

Assays

Anti-inflammatory activity³⁹ was evaluated using carrageenan induced rat paw edema method in rats. Outbred (male/female) white rats weighing 180–220g were used for the edema test. The experiments were carried out in accordance with the requirements of the European convention for the protection of vertebrate animals used for experimental and other scientific purposes. The experimental protocol was approved by the Danylo Halytsky Lviv National Medical University ethics committee, constituted by the Ministry of Health of Ukraine.

Animals were divided into 15 groups comprising five rats per group. One group was kept as the control and remaining 14 groups (test groups) were used to determine the anti-inflammatory activity elicited by the 13 drug candidates, respectively. Rats were kept in the animal house under standard conditions of light and temperature on the general diet prior to the experiment. The standard drug, Ibuprofen (50 mg/kg body weight) and the test compounds (50 mg/kg body weight) were dissolved in DMSO and administered through intraperitoneal route. DMSO was injected to the control group. At 30 minutes later, 0.1 ml of 2 % carrageenan solution in saline was injected in the sub-plantar region of the right hind paw of each rat. After 4 h of the carrageenan injection, the volume of paw edema (in ml) was measured using water plethysmometer and decrease in paw edema was compared between the control group and the test groups. The inflammatory reaction inhibition was expressed as a percent of paw volume reduction and it was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{V_{\text{control}} - V}{V_{\text{control}}} \cdot 100 \% \quad (1)$$

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

2. 5. Antioxidant Activity Evaluation Assays

The antioxidant activity was determined on the basis of free radical scavenging activity of stable 2,2-diphe-

nyl-1-picrylhydrazyl (DPPH). The effect of the studied compounds on DPPH radicals was estimated according to the method of Blois^{40–41} with minor modifications. The solution of DPPH in ethanol with the concentration of 150 $\mu\text{moles/L}$ (4 mL) was mixed with the compound or control solution in ethanol its concentration been 250 $\mu\text{moles/L}$ (0.2 mL). The reaction mixture was vortex mixed thoroughly and incubated at room temperature in the dark for 60 min. Simultaneously, a control was prepared as ascorbic acid solution in ethanol (0.2 mL) mixed with of DPPH solution in ethanol (4 mL) without sample fraction. Reduction in the absorbance of the mixture was measured at 517 nm using ethanol as blank. Ascorbic acid was used as a standard. Also, the absorbance of DPPH solution was measured. Percentage of free-radical-scavenging activity was expressed as percent inhibition and it was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{A_{\text{DPPH}} - A_c}{A_{\text{DPPH}}} \cdot 100\% ; \quad (2)$$

where A_{DPPH} is the absorbance of DPPH free radicals solution, and A_c is the absorbance of a sample. Each experiment was performed in triplicate and average values were recorded. Results are expressed as the means \pm S.D.

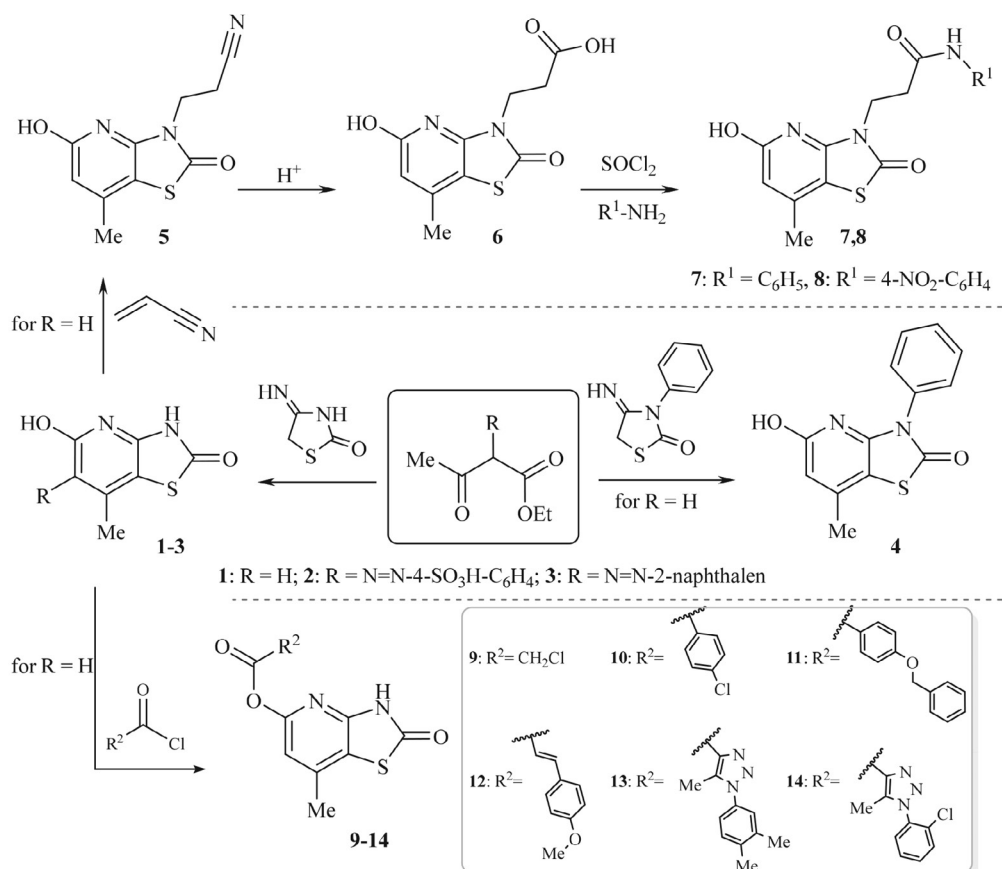
3. Results and Discussion

3.1. Chemistry

Continuing systematic study of fused bicyclic systems as potential drug candidates we represented synthesis, anti-inflammatory and antioxidant activity evaluation of some thiazolo[4,5-*b*]pyridin-2-ones. The efficient synthetic approach for 3*H*-thiazolo[4,5-*b*]pyridin-2-one^{23,36} system construction had been developed earlier and is based on [3 + 3] cyclocondensation of 4-iminothiazolidone-2 due its N,C-binucleophilic properties with dielectrophilic reagents like ethyl acetoacetate forming the above-mentioned fused heterocycle (1).³³

We studied the behavior of 4-iminothiazolidin-2-one with α -arylozo- derivatives of ethyl acetoacetate in [3+3] cyclocondensation reaction. Under the chosen conditions the corresponding 6-arylozo-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (2, 3) were obtained in good yields (Scheme).

We looked at a possibility to use the reported method for preparation of 3-phenyl-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one (4) from above mentioned ethyl acetoacetate and 3-phenyl-4-iminothiazolidone-2-one. It was found that compound 4 was easily accessed with a high yield at the same conditions (Scheme).



Scheme 1. Synthesis of novel thiazolo[4,5-*b*]pyridine derivatives.

The further strategy included the core heterocycle structural modification at its N³ position. Core thiazolo[4,5-*b*]pyridine scaffold had been extensively studied as electrophilic reagent due the presence of NH-group hydrogen atom. Therefore, the functionalization of thiazolo[4,5-*b*]pyridine could be easily performed via the addition reaction to the acrylonitrile. We have found out that the high yield of the product **5** could be achieved while treatment of the equimolar amounts of the thiazolo[4,5-*b*]pyridine (**1**) with acrylonitrile in pyridine – water medium (5:1). 3-(5-Hydroxy-7-methyl-2-oxothiazolo[4,5-*b*]pyridin-3(2*H*)-yl) propanenitrile (**5**) prepared in this way was subjected to hydrolysis leading to 3-(5-hydroxy-7-methyl-2-oxothiazolo[4,5-*b*]pyridin-3(2*H*)-yl) propanoic acid (**6**) formation (Scheme).

Besides, propanamides are highly reactive substances, hence suitable for creating and broadening the collection of building blocks useful for combinatorial chemistry including the design of biologically active compounds. The carboxyl group present in N³ position of thiazolo[4,5-*b*]pyridinyl-propanoic acid (**6**) provides an entry to 3-(5-hydroxy-7-methyl-2-oxothiazolo[4,5-*b*]pyridin-3(2*H*)-yl)-*N*-aryl propanamides (**7**, **8**). Dioxane was established to be the most suitable medium for the reaction of compound **6** with thionyl chloride. Prepared in this way, 3-(5-hydroxy-7-methyl-2-oxothiazolo[4,5-*b*]pyridin-3(2*H*)-yl) propanoyl chloride was reacted with corresponding aromatic amines. Refluxing the reaction mixture for 30 min in dioxane medium was defined as optimal condition for propanamides (**7**, **8**) formation in good yields (Scheme).

Furthermore, compound **1**, 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 (**9–14**) generation via acylation reaction by chloroacetyl chloride or appropriate aromatic acyl chlorides (Scheme). Powders of these products are well soluble in DMF, DMSO and acetic acid, and sparingly soluble in water and in other organic solvents.

Structures of the obtained compounds were confirmed by ¹H and ¹³C NMR spectroscopy, mass spectroscopy and elemental analysis. All these new compounds possess spectroscopic data in accordance with the proposed structures.

3. 2. Molecular Docking

Previously we have shown a good correlation between results obtained in computer simulation using OpenEye Software with that obtained in the corresponding *in vitro* assays.^{42,43}

Crystallographic models of COX-1 and COX-2 (4O1Z and 5IKR correspondingly) were obtained from Protein Data Bank (www.rcsb.org). As research objects thiazolo[4,5-*b*]pyridine derivatives, common NSAIDs (aspirin, mefenamic acid, diclofenac, ibuprofen, indomethacin, ketoprofen, ketorolac, others) and well-known selective COX-2 inhibitors, such as parecoxib, lumiracoxib, etoricoxib and others, were chosen. To estimate *in silico* COX-2-compound and COX-1-compound binding seven scoring function values (Chemgauss 2, Chemscore, PLP, Screenshot, Shapegauss, Zapbind and Consensus) were calculated. Cumulative (Consensus) scoring function ranking allowed us to select compounds, which could prospectively be selective COX-2 inhibitors. Fred receptor program allows to extract the active sites (biotarget) of COX-2 and COX-1 from crystallographic models for molecular docking.

Molecular docking studies included generation of *R*-, *S*- and *cis-trans* isomers of ligands using program Flipper with further 3D optimization of isomers using program Hyper Chem 7.5 (www.hyper.com) (molecular mechanics method MM+ and semi-empirical quantum-mechanical method PM3). Conformers were generated via Omega 2. Further program Fred 2 choose minimum energy conformation for each molecule and 3D molecular docking was performed.

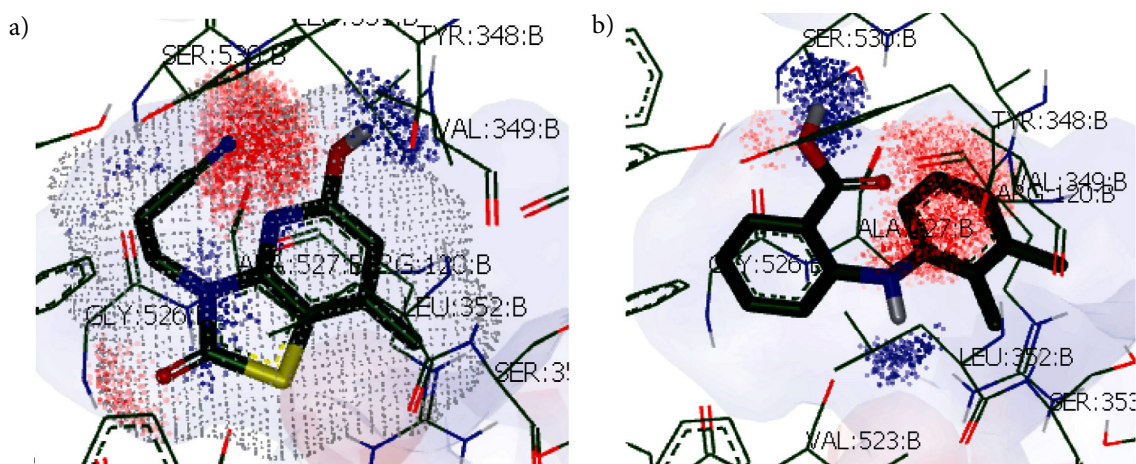


Figure 1. Compound **5** docked in the active site of COX-2 (a) in comparison with inhibitor mefenamic acid docked in the active site of COX-2. (b).

Values of the seven scoring functions (Chemgauss 2, Chemscore, PLP, Screenscore, Shapegauss, Zapbind and Consensus) were obtained as a result. Ranking property (compound ranking) of the consensus scoring function, which includes values of all scoring functions, allowed to analyze the results easily.

Ranking and analysis of the molecular docking results were obtained using the selected compounds and crystallographic model of COX-2 with cumulative scoring function (consensus). Consensus results allowed us to select compounds, which could prospectively be selective COX-2 inhibitors at the level of mefenamic acid and Ibuprofen for future (in-depth) pharmacological studies for further evaluation of *in vitro* anti-inflammatory activity. The interactions between COX-2 active site and the most active compound **5** in comparison with selective inhibitor mefenamic acid is shown in Figure. Moreover, it should be noted that results predicted via docking correlate quite well with that obtained in the *in vitro* assay. The selected “lead” compound **5** based on the *in vitro* screening results was also predicted to be the most active in the docking studies.

On the contrast, generated conformations of thiazolo[4,5-*b*]pyridine derivatives did not possess the necessary parameters for successful binding to the target COX-1 active site and were found to be bad substrates of cyclooxygenase-1 during docking experiment.

3. 3. Anti-inflammatory Activity in Vivo Evaluation

Carrageenan-induced paw edema is the most widely used animal model of acute inflammation. *In vivo* studies of novel thiazolo[4,5-*b*]pyridine-2-one derivatives were carried out for anti-inflammatory activity employing the

carrageenan-induced rat paw edema method. The NSAID drug Ibuprofen in its effective therapeutic dose was tested in parallel as an activity reference. Results of paw edema decreasing were expressed as the mean \pm standard deviation and compared statistically with the control group using Student's *t*-test. A level of $p < 0.05$ was adopted as the test of significance (Table 1). The percentage protection against inflammation was calculated as % inhibition by comparison between DMSO injected control group and drugs-tested groups.

Evaluation of anti-inflammatory activity indicated that 8 compounds (**2**, **3**, **7**, **8**, **10**, **11**, **12** and **13**) showed no significant decrease in edema; the inhibition rate for them was observed at the level of 22.6–30.1 % as compared to control group. The compounds **4**, **9** and **14** possessed the anti-inflammatory activity in the range of 35.6–42.1 % which is comparable to the effect of Ibuprofen. The anti-inflammatory evaluation test for compounds **5** and **6** gave the result at the level of 45.3–48.8 % inhibition indicating that the compounds **5** and **6** were more potent than Ibuprofen.

The results of the pharmacological tests were analyzed concerning the structure of the compounds. Among the two arylazo substituted derivatives **2-3** none of them was defined as active indicating the nature and position of the substituted arylazo groups did not noticeably influence on their anti-inflammatory activity. It was found out that for N^3 -substituted 5-hydroxy-7-methyl-3*H*-thiazolo [4,5-*b*]pyridin-2-one derivative (**4**), obtained via [3+3]cyclocondensation 3-phenyl-4-iminothiazolidone-2-one with ethyl acetoacetate, the presence of phenyl group in the N^3 position contributed to the inflammation inhibition efficiency. The presence of cyano and carboxy groups substituents (**5**, **6**) in the core scaffold N^3 position lead to the high anti-inflammatory activity even exceeding the Ibuprofen

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

| compound ID | paw edema volume (mL) \pm SEM* | inhibition, % | activity relative to Ibuprofen, % |
|------------------|----------------------------------|---------------|-----------------------------------|
| control | 2.20 \pm 0.050 | – | – |
| 2 | 1.62 \pm 0.035 | 26.3 | 65.4 |
| 3 | 1.60 \pm 0.035 | 27.5 | 68.4 |
| 4 | 1.27 \pm 0.020 | 42.1 | 104.7 |
| 5 | 1.13 \pm 0.020 | 48.8 | 121.4 |
| 6 | 1.20 \pm 0.020 | 45.3 | 112.7 |
| 7 | 1.65 \pm 0.040 | 25.2 | 62.7 |
| 8 | 1.68 \pm 0.040 | 23.7 | 59.0 |
| 9 | 1.42 \pm 0.030 | 35.6 | 88.6 |
| 10 | 1.54 \pm 0.030 | 30.1 | 74.9 |
| 11 | 1.64 \pm 0.040 | 25.5 | 63.4 |
| 12 | 1.70 \pm 0.040 | 22.6 | 56.2 |
| 13 | 1.62 \pm 0.035 | 26.3 | 65.4 |
| 14 | 1.41 \pm 0.030 | 36.1 | 89.8 |
| Ibuprofen | 1.32 \pm 0.035 | 40.2 | 100 |

effect. Notably, among the six C⁵-substituted 5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one derivatives, prepared by the acylation reaction, only two compounds: chloro-acetic acid (**9**) and 1-(2-chloro-phenyl)-5-methyl-1*H*-[1,2,3]triazole-4-carboxylic acid (**14**) possessed inflammation inhibition. The rest of substituents in the C⁵ position did not notably affect on the anti-inflammatory activity of thiazolo[4,5-*b*]pyridin-2-ones.

3. 4. In Vitro Antioxidant Assay

The antioxidant activity was determined on the basis of free radical scavenging activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. The DPPH method is described as a simple, rapid and convenient method for screening of many samples for radical scavenging activity. These advantages make the DPPH method interesting for testing newly synthesized compounds to scavenge radicals and to find out antioxidant drug candidates.

DPPH radical had found many applications due to its high stability in a methanolic solution and intense purple color. In its oxidized form, the DPPH radical has an absorbance maximum at a wavelength of 540 nm. The absorbance decreases when the radical is reduced by antioxidants. Its reduction affords 2,2-diphenyl-1-picrylhydrazine (DPPH-H), or the corresponding anion(DPPH⁻) in basic medium. The DPPH radical acts as a scavenger for other odd-electron species which afford *para*-substitution products at phenyl rings. In the present paper, we demonstrate modified spectrophotometric method making use of the DPPH radical and its specific absorbance properties. The free-radical-scavenging activity of each compound was assayed using a stable DPPH and was quantified by decolorization the solution being mixed with DHHP at a wavelength of 540 nm. The absorbance of DPPH solution in ethanol (150 mmol/l) was measured as 0.77. The ab-

Table 2. Values of Absorbance and % of inhibition of thiazolo[4,5-*b*]pyridine-2-ones.

| compound / standard | Absorbance of a sample, A _s | inhibition, % |
|---------------------|--|---------------|
| ascorbic acid | 0.220 ± 0.010 | 71.5 |
| 2 | 0.718 ± 0.025 | 6.7 |
| 3 | 0.700 ± 0.025 | 9.1 |
| 4 | 0.671 ± 0.020 | 12.8 |
| 5 | 0.742 ± 0.025 | 3.7 |
| 6 | 0.759 ± 0.030 | 1.5 |
| 7 | 0.525 ± 0.015 | 31.8 |
| 8 | 0.549 ± 0.015 | 28.7 |
| 9 | 0.559 ± 0.020 | 27.4 |
| 10 | 0.546 ± 0.015 | 29.1 |
| 11 | 0.745 ± 0.030 | 3.3 |
| 12 | 0.523 ± 0.015 | 32.0 |
| 13 | 0.702 ± 0.025 | 8.8 |
| 14 | 0.571 ± 0.020 | 25.8 |

sorbances and free-radical-scavenging activities % inhibitions of standard (ascorbic acid) and each compound are listed in Table 2.

The antioxidant activity evaluation results showed that, in general, most of the tested compounds possess insignificant free radical scavenging effect being in the range of 1.5%–32.0%.

4. Conclusions

In summary, we presented an efficient synthetic approaches to a number of thiazolo[4,5-*b*]pyridin-2-one derivatives for their anti-inflammatory and antioxidant activity evaluation. We have shown that the proposed synthetic protocols provided the possibility to design 5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones diversity with a considerable chemical novelty involving [3+3]cyclocondensation, cyanoethylation, hydrolysis, and acylation reactions. The obtained results of the performed biological activity evaluation suggested the core fused heterocycle as a promising scaffold in anti-inflammatory drug development. On the contrary, the free radical scavenging effect was found to be insignificant. Further optimization of the structure to improve biological activity is currently in progress.

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Povzetek

V prispevku je predstavljena sinteza ter protivnetne in antioksidativne lastnosti novih derivatov 5-hidroksi-7-metil-3H-tiazolo[4,5-*b*]piridin-2-ona. Kondenzirani tiazolo[4,5-*b*]piridin-2-oni so bili sintetizirani in modificirani na položajih N³, C⁵ in C⁶ glavnega obroča in s tem dobili spojine z zadovoljivim farmakološkim profilom. Sintetizirane spojine so bile predhodno izbrane s pomočjo molekulskega modeliranja za nadaljnje testiranje njihove protivnetne aktivnosti *in vitro*. Vrednotenje novih spojin pri edemu podganjih tačk, ki ga povzroča karagenin, je pokazalo močno protivnetno delovanje nekaterih spojin, vključno s tiazolo [4,5-*b*]piridin-3(2*H*)-il) propanenitriplom (5) in tiazolo[4,5-*b*]piridin-3(2*H*)-il) propanojsko kislino (6), ki celo presega standard – Ibuprofen. Antioksidativno aktivnost sintetiziranih spojin so izmerili *in vitro* z metodo lovljenja na 2,2-difenil-1-pikrilhidrazil (DPPH) radikalih.



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