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Research Article

Anti-inflammatory properties of some novel thiazolo[4,5-b]pyridin-2-ones

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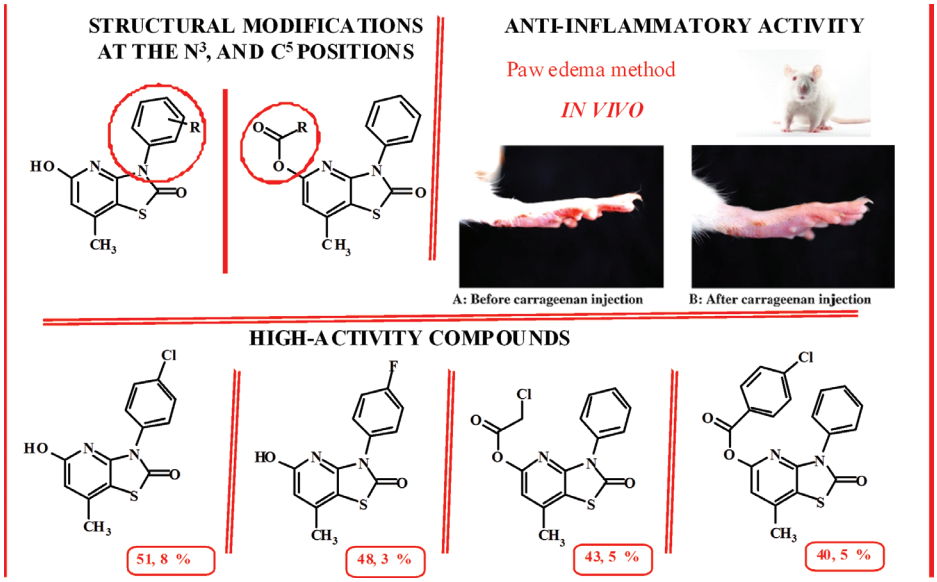
Abstract

Synthesis of novel N^3 and C^5 substituted thiazolo[4,5-*b*]pyridin-2-ones was carried out on the basis of [3+3]-cyclocodensation, acylation and alkylation reactions. The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy, and elemental analysis. The anti-inflammatory action of novel thiazolo[4,5-*b*]pyridine-2-one derivatives was evaluated *in vivo* employing the carrageenan-induced rat paw edema method. When compared with Ibuprofen, some our compounds were found to be more potent.

Graphical abstract



PENSOFT

Keywords

anti-inflammatory activity, organic synthesis, thiazolo[4,5-*b*]pyridines

Introduction

Inflammation is a major pathogenetic component of many diseases of different etiology and one of the most important problems of general pathology and clinic. This reaction of the body to damage, is involved in the formation of many diseases. The problem of the pharmacological regulation of inflammation is relevant to modern medicine (Brenner and Krakauer 2003). There is a considerable amount of medication used to treat inflammation. Non-steroidal anti-inflammatory drugs, which combine a whole range of properties, displaying anti-inflammatory, analgesic, antipyretic activity are in particular demand (Bacchi et al. 2012). However, they all have ulcerogenic properties to varying degrees (Al-Shidhani et al. 2015). In order to overcome these restrictions worldwide, the search for new effective and safe anti-inflammatory drugs is continuing.

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 (Taylor et al. 2016), so the work in this direction is rapidly developing and relevant. In particular, there is growing interest in nitrogen-containing fused heterocyclic systems, as many of them exhibit broad-spectrum biological activity (Smirnova et al. 2006; Chaban et al. 2017a, 2018a). Pyridine derivatives make up a large part of the modern drug arsenal. Of the 1.5 thousand most commonly used drugs, more than 10% account for the compounds having the pyridine ring (Ali Altaf et al. 2015). Equally interesting are 4-thiazolidones (Abhinit et al. 2009; Lozynska et al. 2015; Chhabria et al. 2016; Tymoshuk et al. 2019). Thiazolidone derivatives anelated with the pyridine cycle, in particular thiazolopyridine, are of particular interest to researchers because these compounds exhibit different types of biological activity. Among them were identified substances with antioxidant (Chaban et al. 2013, 2019a; Klenina et al. 2013, 2017), fungicidal (Marzoog and Al-Thebeiti 2000), anti-inflammatory (Chaban et al. 2016, 2017b, 2018b), anti-mitotic (Victor et al. 2017), tuberculostatic (Chaban et al. 2014), herbicidal (Hegde and Mahoney 1993) and antitumor (Chaban et al. 2012a) activities, agonists of H3-histamine receptors (Walczyn´ski et al. 2005), antagonists of metabotropic glutamate receptors 5 (mGluR5) (Lin et al. 2009), substances with high inhibitory activity against epidermal growth factor receptors (Komoriya et al. 2006) and several other enzymes (Singh et al. 1995). Given the above synthesis of new thiazolopyridines, as well as the pharmacological screening of the anti-inflammatory activity of the newly synthesized compounds is an interesting and relevant direction.

Experimental part

Materials and methods

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

All the melting points were determined in an open capillary and are uncorrected. ^{1}H- spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H) 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 ± 0.17, H ± 0.21, N ± 0.19). Ibuprofen was purchased from a medical store.

Chemistry

General procedure for the synthesis of 3-aryl-5-hydroxy-7-methyl-3H-thiazolo[4,5-b]pyridin-2-ones (***1–8***). Metallic Sodium (109 mmol) was dissolved in anhydrous methanol (150 ml), to the resulting solution was added the corresponding 3-aryl-4-iminothiazolidin-2-one (50 mmol) and acetoacetic ether (8.5 ml) at 20 °C. The mixture is left for 5 days, stirring on a magnetic stirrer. Then it is acidified with acetate to pH ~ 5, diluted five times with water, the precipitate is filtered off, washed with water and dried. Recrystallized from acetic acid. The obtained substances are white, gray or yellowish crystalline powders, well soluble in DMF, DMSO, alkali solutions, low in benzene, toluene, alcohols; bad – in other organic solvents and water.

5-Hydroxy-7-methyl-3-phenyl-3H-thiazolo[4,5-b] pyridin-2-one **(*1*).** Yield: 65 %, mp.= 244 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.51 (s, 3H, CH_3), 6.96 (t, J = 7.3 Hz, 1H, Py), 7.28 (t, J = 7.4 Hz, J = 7.7 Hz, 2H, C_6H_5), 7.45 (d, J = 8.1 Hz, 3H, C_6H_5), 8.67 (s, 1H, OH). Anal. calcd. for $C_{13}H_{10}N_2O_2S$%: C 60.45, H 3.90, N 10.85. Found: C 60.06, H 3.84, N 10.73.

5-Hydroxy-7-methyl-3-(4-nitro-phenyl)-3H-thiazolo[4,5-b]pyridin-2-one **(*2*).** Yield: 56%, mp.= 212 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.55 (s, 3H, CH_3), 7.01 (s, 1H, Py), 7.29 (d, 2H, J = 8.2 Hz, C_6H_4), 7.53 (d, 2H, J = 8.2 Hz, C_6H_4), 8.71 (s, 1H, OH). Anal. calcd. for: $C_{13}H_9N_3O_4S$: C 51.48, H 2.99, N 13.85. Found: C 51.16, H 3.05, N 13.69.

3-(4-Chloro-phenyl)-5-hydroxy-7-methyl-3H-thiazolo[4,5-b]pyridin-2-one **(*3*).** Yield: 51%, mp.= 206 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.51 (s, 3H, CH_3), 6.99 (s, 1H, Py), 7.19 (d, 2H, J = 7.8 Hz, C_6H_4), 7.45 (d, 2H, J = 8.1 Hz, C_6H_4), 8.68 (s, 1H, OH). Anal. calcd. for: $C_{13}H_9ClN_2O_2S$: C 53.34, H 3.10, N 9.57. Found: C 52.98, H 3.14, N 9.61.

3-(4-Fluoro-phenyl)-5-hydroxy-7-methyl-3H-thiazolo[4,5-b]pyridin-2-one **(*4*).** Yield: 59%, mp.= 223 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.52 (s, 3H, CH_3), 7.03 (s, 1H, Py), 7.25 (d, 2H, *J* = 7.7 Hz, C_6H_4), 7.51 (d, 2H, *J* = 8.4 Hz, C_6H_4), 8.71 (s, 1H, OH). Anal. calcd. for: $C_{13}H_9FN_2O_2S$: C 56.51, H 3.28, N 10.14. Found: C C 56.08, H 3.21, N 10.07.

5-Hydroxy-7-methyl-3-p-tolyl-3H-thiazolo[4,5-b]pyridin-2-one (***5*).** Yield: 63%, mp.= 232 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.49 (s, 3H, CH_3), 2.67 (s, 3H, C_6H_4-CH_3), 6.99 (s, 1H, Py), 7.23 (d, 2H, *J* = 7.8 Hz, C_6H_4), 7.57 (d, 2H, *J* = 8.3 Hz, C_6H_4), 8.69 (s, 1H, OH). Anal. calcd. for: $C_{14}H_{12}N_2O_2S$: C 61.75, H 4.44, N 10.29. Found: C 62.05, H 4.12, N 10.34.

5-Hydroxy-3-(4-hydroxy-phenyl)-7-methyl-3H-thiazolo[4,5-b]pyridin-2-one (***6*).** Yield: 68%, mp.= 208 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.52 (s, 3H, CH_3), 7.00 (s, 1H, Py), 7.30 (d, 2H, *J* = 8.2 Hz, C_6H_4), 7.58 (d, 2H, *J* = 7.9 Hz, C_6H_4), 8.70 (s, 1H, OH), 9.83 (s, 1H, C_6H_4-OH). Anal. calcd. for: $C_{13}H_{10}N_2O_3S$: C 56.92, H 3.67, N 10.21. Found: C 57.12, H 3.61, N 10.25.

5-Hydroxy-7-methyl-3-m-tolyl-3H-thiazolo[4,5-b]pyridin-2-one (***7*).** Yield: 54%, mp.= 244 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.46 (s, 3H, CH_3), 2.61 (s, 3H, C_6H_4-CH_3), 7.00 (s, 1H, Py), 7.08 (d, 1H, *J* = 9.7 Hz, C_6H_4), 7.16 (t, 1H, *J* = 8.0 Hz, C_6H_4), 7.25 (t, 1H, *J* = 8.0 Hz, C_6H_4), 7.84 (d, 1H, *J* = 7.5 Hz, C_6H_4), 8.66 (s, 1H, OH). Anal. calcd. for: $C_{14}H_{12}N_2O_2S$: C 61.75, H 4.44, N 10.29. Found: C 61.88, H 4.35, N 10.28.

5-Hydroxy-3-(3-hydroxy-phenyl)-7-methyl-3H-thiazolo[4,5-b]pyridin-2-one (***8*).** Yield: 60%, mp.= 215 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.49 (s, 3H, CH_3), 6.96 (s, 1H, Py), 7.87 (d, 1H, *J* = 8.3 Hz, C_6H_4), 7.94 (d, 1H, *J* = 7.0 Hz, C_6H_4), 8.43–8.45 (m, 2H, C_6H_4), 8.68 (s, 1H, OH), 10.01 (s, 1H, C_6H_4-OH). Anal. calcd. for: $C_{13}H_{10}N_2O_3S$: C 56.92, H 3.67, N 10.21. Found: C 57.12, H 3.61, N 10.25.

*General procedure for the production of acylation products of 5-hydroxy-7-methyl-3-phenyl-3H-thiazolo[4,5-b]pyridin-2-one by aliphatic chloroanhydride to form compounds **9–11*.** In a flat bottom flask dissolve 10 mmol of compound **1** in 10 ml of anhydrous dioxane. To the resulting solution was added a solution consisting of 10 mmol of the corresponding aliphatic chloroanhydride and 10 mmol of triethylamine in 10 ml of dioxane. Maintain for 10 minutes in a drying oven at a temperature of 100 °C and poured into water. After recrystallization from acetic acid, the white or yellowish powders are soluble when heated in ethanol, DMF, acetic acid.

Acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***9*).** Yield: 76 %, mp.= 235 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.30 (s, 3H, CH_3), 2.36 (s, 3H, CH_3-CO), 6.92 (s, 1H, Py), 7.30 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.48 (d, *J* = 8.1 Hz, 3H, C_6H_5). Anal. calcd. for: $C_{15}H_{12}N_2O_3S$: C 59.99, H 4.03, N 9.33. Found: C 60.18, H 4.12, N 9.39.

Chloro-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***10*).** Yield: 73%, mp.= 188 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.35 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 6.94 (s, 1H, Py), 7.28 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.46 (d, *J* = 8.1 Hz, 3H, C_6H_5). Anal. calcd. for: $C_{15}H_{11}ClN_2O_3S$: C 53.82, H 3.31, N 8.37. Found: C 53.71, H 3.28, N 8.41.

Butyric acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***11*).** Yield: 60%, mp. = 172 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 1.02 (t, *J* = 7.3 Hz, 3H, CH_3- CH_2- CH_2-CO), 1.66–1.71 (m, 2H, CH_3- CH_2- CH_2-CO), 2.35 (s, 3H, CH_3), 4.72 (s, 2H, CH_2), 2.62 (t, *J* = 7.1 Hz, 3H, CH_3- CH_2- CH_2-CO), 6.90 (s, 1H, Py), 7.31 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.47 (d, *J* = 8.1 Hz, 3H, C_6H_5). Anal. calcd. for: $C_{16}H_{17}N_2O_3S$: C 62.18, H 4.91, N 8.53. Found: C 62.32, H 5.00, N 8.60.

*General procedure for the production of acylation products of 5-hydroxy-7-methyl-3-phenyl-3H-thiazolo[4,5-b]pyridin-2-one by aromatic chloroanhydride to form compounds **12–16*.** Compound **1** (5 mmol) was added to a solution of pyridine (20 ml) and the corresponding aromatic chloroanhydride (5 mmol). The reaction mixture was refluxed for 30 min. Upon cooling, the crystalline precipitate was filtered off, washed with acetate and dried. The compounds obtained were crystallized from acetate or ethanol. These are white, gray or cream substances, poorly soluble in water and organic solvents, soluble in acetate, DMF and DMSO.

4-Chloro-benzoic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***12*).** Yield: 63%, mp. = 221 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.37 (s, 3H, CH_3), 7.07 (s, 1H, Py), 7.28 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.44 (d, *J* = 8.1 Hz, 3H, C_6H_5), 7.66 (d, *J* = 8.5 Hz, 2H, C_6H_4), 8.09 (d, *J* = 8.5 Hz, 2H, C_6H_4). Anal. calcd. for: $C_{20}H_{13}ClN_2O_3S$: C 60.53, H 3.30, N 7.06. Found: C 60.66, H 3.27, N 6.99.

4-Benzyloxy-benzoic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***13*).** Yield: 65 %, mp.= 191 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3), 7.02 (s, 1H, Py), 7.19 (d, *J* = 8.4 Hz, 2H, C_6H_4),7.25 (t, *J* = 7.3 Hz, *J* = 7.6 Hz, 2H, C_6H_5), 7.39 (d, *J* = 8.0 Hz, 3H, C_6H_5), 7.44 (d, *J* = 7.2 Hz, 2H, CH_2-C_6H_5), 7.49 (d, *J* = 6.9 Hz, 3H, CH_2-C_6H_5), 8.08 (д, *J* = 8.3 Гц, 2H, C_6H_4). Anal. calcd. for: $C_{27}H_{20}N_2O_4S$: C 69.22, H 4.30, N 5.98. Found: C C 70.01, H 4.25, N 6.02.

1-(2,4-Dimethyl-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***14*).** Yield: 75%, mp. = 180 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.01 (s, 3H, C_6H_3-CH_3), 2.12 (s, 3H, C_6H_3-CH_3), 2.37 (s, 3H, CH_3), 3.08 (s, 3H, triazole-CH_3), 6.96 (d, 1H, *J* = 8.0 Hz, C_6H_3), 7.04 (s, 1H, Py), 7.30 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.32–7.35 (m, 1H, C_6H_3), 7.46 (d, *J* = 8.1 Hz, 3H, C_6H_5), 7.83–7.85 (m, 1H, C_6H_3). Anal. calcd. for: $C_{25}H_{21}N_5O_3S$: C 63.68, H 4.49, N 14.85. Found: C 63.57, H 4.52, N 14.71.

1-(2-Chloro-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***15*).** Yield: 69%, mp. = 171 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3), 3.05 (s, 3H, triazole -CH_3), 6.91–6.96 (m, 1H, C_6H_4), 7.00 (s, 1H, Py), 7.28 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.41–7.49

(m, 1H, C_6H_4), 7.43 (d, *J* = 8.1 Hz, 3H, C_6H_5), 7.55–7.58 (m, 2H, C_6H_4). Anal. calcd. for: $C_{23}H_{16}ClN_5O_3S$: C 57.80, H 3.37, N 14.65. Found: C 57.88, H 3.35, N 14.59.

1-(3,4-Dimethyl-phenyl)-5-methyl-1H-[1,2,3]triazole-4-carboxylic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***16).*** Yield: 69%, mp.= 171 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.08 (s, 3H, C_6H_3-CH_3), 2.13 (s, 3H, C_6H_3-CH_3), 2.34 (s, 3H, CH_3), 3.07 (s, 3H, triazole-CH_3), 6.86 (d, 1H, *J* = 8.0 Hz, C_6H_3), 7.05 (s, 1H, Py), 7.13–7.17 (m, 2H, *J* = 7.2 Hz, C_6H_3), 7.25 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.44 (d, *J* = 8.1 Hz, 3H, C_6H_5). Anal. calcd. for: $C_{25}H_{21}N_5O_3S$: C 63.68, H 4.49, N 14.85. Found: C 63.75, H 4.43, N 14.80.

General procedure for the preparation of s-alkylation products 7-methyl-2-oxo-3-phenyl-2,3-dihydrothiazolo[4,5-b] pyridin-5-yl ester of monochloroacetic acid (**17–20**). Into a round bottom flask was added 50 mmol of compound **10**, 50 mmol of the corresponding thiol and 20 ml of ethanol. The reaction mixture is refluxed for 1 hour. White crystalline precipitates that precipitate after cooling are filtered off and washed with ethanol. The compounds obtained are recrystallized from ethanol or acetic acid.

[4-Amino-5-(4-methyl-furan-3-yl)-4H-pyrazol-3-ylsulfanyl]-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***17).*** Yield: 75%, mp. = 176 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.08 (s, 3H, furan-CH_3), 2.31 (s, 3H, CH_3), 4.14 s (2H, CH_2), 6.14 (s, 2H, NH_2), 7.01 (s, 1H, Py), 7.11 (s, 1H, aryl), 7.28 (t, *J* = 7.3 Hz, *J* = 7.6 Hz, 2H, C_6H_5), 7.44 (d, *J* = 8.0Hz, 3H, C_6H_5), 7.72 (s, 1H, aryl). Anal. calcd. for: $C_{23}H_{19}N_5O_4S_2$: C 55.97, H 3.88, N 14.19. Found: C 56.23, H 3.84, N 14.21.

(5-Phenyl-[1,3,4]oxadiazol-2-ylsulfanyl)-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***18).*** Yield: 68%, mp. = 193 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.35 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 7.00 (s, 1H, Py), 7.25 (t, *J* = 7.3 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.39 (s, 2H, oxadiazol-C_6H_5), 7.46 (d, *J* = 8.0Hz, 3H, C_6H_5), 7.55 (s, 1H, oxadiazol-C_6H_5), 7.80 (s, 2H, oxadiazol-C_6H_5). Anal. calcd. for: $C_{23}H_{16}N_4O_4S_2$: C 57.97, H 3.38, N 11.76. Found: C 58.09, H 3.36, N 11.64.

(1-p-Tolyl-1H-tetrazol-5-ylsulfanyl)-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***19).*** Yield: 75%, mp. = 169 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.01 (s, 3H, aryl-CH_3), 2.33 (s, 3H, CH_3), 4.11 (s, 2H, CH_2), 6.98 (s, 1H, Py), 7.24 (t, *J* = 7.4 Hz, *J* = 7.7 Hz, 2H, C_6H_5), 7.48 (d, *J* = 8.0Hz, 3H, C_6H_5), 7.54 (d, 2H, *J* = 8.8 Hz, aryl), 7.71 (d, 2H, *J*=8.8 Hz, aryl). Anal. calcd. for: $C_{23}H_{18}N_6O_3S_2$: C 56.31, H 3.70, N 17.13. Found: C 56.25, H 3.74, N 17.21.

(Benzothiazol-2-ylsulfanyl)-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl ester (***20).*** Yield: 66%, mp. = 160 °C. ^{1}H NMR (400 MHz, DMSO-d6) d 2.33 (s, 3H, CH_3),), 4.07 (s, 2H, CH_2), 7.00 (s, 1H, Py), 7.25 (t, *J* = 7.3 Hz, *J* = 7.6 Hz, 2H, C_6H_5), 7.36 (t, 1H, *J* = 7.0 Hz, *J* = 6,7 Hz, Ar), 7.44 (d, *J* = 8.0Hz, 3H, C_6H_5), 7.50 (t, 1H, *J* = 7.2 Hz, *J* = 6,7 Hz, Ar), 7.88 (d, 1H, Ar), 8.11 (d, 1H, Ar). Anal. calcd. for: $C_{22}H_{15}N_3O_3S_3$: C 56.76, H 3.25, N 9.03. Found: C 56.89, H 3.33, N 8.98.

Anti-inflammatory activity

The experiment was performed on nonlinear white rats of both sexes weighing 180–200 g. Rats were kept in the animal house under standard conditions of light and temperature on the general diet prior to the experiment. Total swelling was caused by aseptic injection of 0.1 ml of a 2% solution of carrageenan under aponeurosis of the sole of the hind limb of the rat for 0.5 h. animals were intraperitoneally injected with the test substance at a dose of 50 mg/kg prior to administration of the carrageenan solution. The presence of an inflammatory reaction was determined by changing the volume of the limb oncometric method at the beginning of the experiment and 4 hours after the introduction of the phlogogenic agent. For comparison, the anti-inflammatory effect of a known anti-inflammatory drug-ibuprofen in medium therapeutic doses was studied in similar conditions. The Ethics Committee of the Danylo Halytsky National Medical University, established by the Ministry of Health of Ukraine, approved the experimental protocol. The suppression of the inflammatory reaction was expressed as a percentage reduction in the volume of the paw, and it was calculated by the following equation:

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

where Vcontrol is the increase in paw volume in control group animals;

V is the increase in paw volume in animals injected with the test substances.

Results and discussion

Chemistry

Continuing the systematic study of thiazolo[4,5-*b*]pyridines as potential anti-inflammatory agents, we have synthesized novel N^3 and C^5 substituted derivatives of 5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one. Our new approach to the synthesis of thiazolo[4,5-*b*]pyridines, which was based on the ability of 4-iminothiazolidin-2-one to react to [3+3]cyclocondensation with dielectrophilic reagents (Chaban et al. 2012b, 2019b) was previously proposed synthesis of novel N-aryl-substituted thiazolo[4,5-*b*] pyridin-2-ones. Previously obtained 3-aryl-4-iminothiazolidin-2-ones (Chaban et al. 2019c) due to their N,C-binucleophilic properties are able to cyclize with acetoacetic ether to form the corresponding 3-aryl-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones (**1–8**) (**Figure 1**). This conversion takes place in a methanol medium in the presence of sodium methylate and allows the introduction of aryl residues at the N^3 position of the base scaffold. Experiments have shown that it is optimal to obtain compounds **1–8** with constant stirring of the reaction mixture for 5 days at a temperature of 20–25 °C.

To expand the combinatorial library of thiazolo[4,5-*b*] pyridines, the transformation of 3-phenyl-5-hydroxy-7-me-

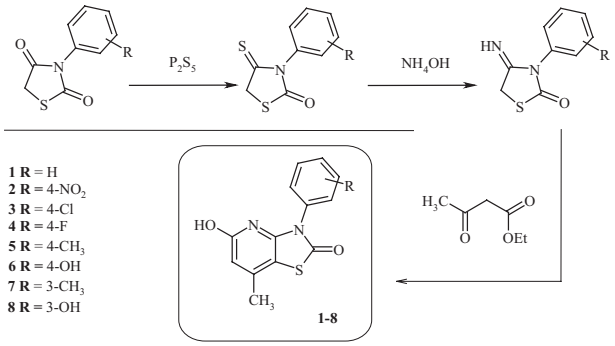


Figure 1. Synthesis of 3-aryl-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones.

thyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one (**1**) at position C^5 was performed. The synthetic potential of the hydroxy group of compound **1** is represented by its interaction with a series of carboxylic acid chlorides in an acylation reaction. It is established that the optimum conditions for obtaining the corresponding acylated derivatives of 3-phenyl-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one (**9–16**) are the reaction in the environment of dioxane under interaction with aliphatic chlorides and pyridine in the case of interaction with aromatic chlorides **(Figure 2**).

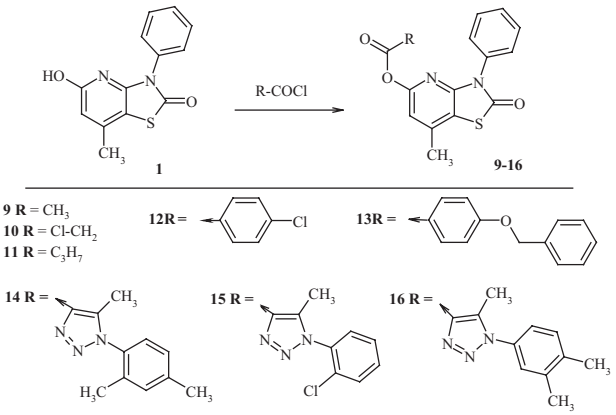


Figure 2. Synthesis of 7-methyl-3-phenyl-2-oxo-2,3-dihydro-thiazolo[4,5-*b*]pyridin-5-yl 4-carboxylates.

Compound **10** may be considered as a key intermediate in 5-hetarylsulfanyl-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridin-5-yl esters obtaining being treated with appropriate thiols. The reaction mixture reflux for 60 min in 96% ethanol medium were optimal conditions for compounds **17–20** formation proceeding in good yields (**Figure 3**). Thus the series of thiazolo[4,5-*b*]pyridin-2-one acetamides has been diversified by alkylation reactions applying compound **10** as alkylating agent employing it into the reactions with heteryl moiety thiols which can be considered an effective and general route to a wide range of acetamides preparation.

The structure of the compounds obtained and the interpretation of the chemical studies were confirmed by elemental analysis and 1H NMR spectroscopy. All these new compounds gave spectroscopic data in accordance with the proposed structures.

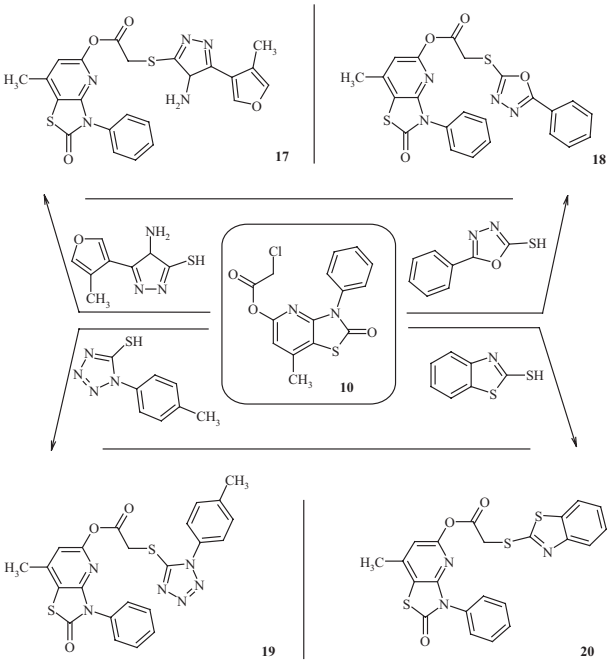


Figure 3. Synthesis of hetarylsulfanyl derivatives of chloro-acetic acid 7-methyl-2-oxo-3-phenyl-2,3-dihydro-thiazolo[4,5-*b*] pyridin-5-yl ester under the alkylation reaction.

Anti-inflammatory activity in vivo evaluation

Exudative is considered to be a classic example of acute inflammation. The effect of the synthesized substances on the course of the exudative phase of inflammation was studied on the basis of a carrageenan model of inflammatory edema of the paws of white rats (Pillai et al. 2004).

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. Carrageenan-induced paw edema is the most common animal model of acute inflammation. Marked paw edema was caused in rats with sub-planter injection of 0.1 ml of 2% carrageenan. Investigated compounds were dissolved in DMSO and injected intraperitoneally 50 mg/kg body weight 0.5 h prior to carrageenan injection. The NSAID drug Ibuprofen in its effective therapeutic dose was tested simultaneously as an activity reference. Anti-inflammatory activity was estimated by measuring the paw edema volume 4 h after the carrageenan injection. Results of paw edema decreasing were expressed as the average ± 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).

According to the anti-inflammatory activity pharmacological screening for synthesized products, in a significant number of cases the anti-inflammatory effect is equivalent to that of the reference drug Ibuprofen. For some compounds, the anti-inflammatory effect was less than the of the reference drug. The inflammatory response inhibition for them are in the range of 20.2–35.4%. However, some substances activity exceeds Ibuprofen, which gives reason

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	1.27 ± 0.020	42.1	*104.7*
2	1.69 ± 0.035	23.2	*57.7*
3	1.06 ± 0.015	51.8	*128.9*
4	1.14 ± 0.015	48.3	*120.2*
5	1.66± 0.035	24.4	*60.7*
6	1.39 ± 0.025	36.7	*91.3*
7	1.71 ± 0.040	22.2	*55.2*
8	1.42 ± 0.040	35.4	*88.1*
9	1.68 ± 0.035	23.6	*58.7*
10	1.24 ± 0.020	43.5	*108.2*
11	1.74 ± 0.040	21.1	*52.5*
12	1.31 ± 0.020	40.5	*100.8*
13	1.75 ± 0.040	20.6	*51.3*
14	1.51 ± 0.030	31.2	*77.6*
15	1.38 ± 0.025	37.2	*92.5*
16	1.52 ± 0.030	30.8	*76.6*
17	1.71± 0.040	22.1	*55.0*
18	1.69 ± 0.035	23.4	*58.2*
19	1.76 ± 0.040	20.2	*50.3*
20	1.72 ± 0.040	21.8	*54.2*
Ibuprofen	1.32 ± 0.035	40.2	*100*

to consider this condensed system as a promising molecular framework for the design of potential anti-inflammatory agents.

The results of pharmacological screening and analysis of the structure of molecules and the nature of the substituents in different positions of the thiazolopyridine cycle allow us to distinguish a number of patterns of dependence «structure – anti-inflammatory action» among the derivatives of thiazolo[4,5-*b*]pyridin-2-one.

5-Hydroxy-7-methyl-3-phenyl-3*H*-thiazolo[4,5-*b*]pyridin-2-one exhibits relatively not very high anti-inflammatory activity – 36.2% (Chaban et al. 2019b). However, the possibility of its structural modification according to the N^3 and C^5 positions of the base scaffold creates prerequisites for rational design in order to search for "drug-like" compounds with a high level of anti-inflammatory activity. Carrying out structural modification by positioning N^3 allowed to obtain the corresponding 3-aryl-5-hydroxy-7-methyl-3*H*-thiazolo[4,5-*b*]pyridin-2-ones, which increases activity compared to the base scaffold. Structural modification at C^5 allows to isolate only 2 compounds that, in terms of activity, approach or exceed the Ibuprofen comparator. The acylation products exhibited different anti-inflammatory activity as determined by the nature of the substituent. The resulting S-alkylation products of 7-methyl-2-oxo-3-phenyl-2,3-dihydrothiazolo[4,5-*b*]pyridin-5-yl ester of monochloroacetic acid (**17–20**) have no anti-inflammatory activity.

The results obtained demonstrate that the anti-inflammatory effect of the synthesized compounds is probably due to the contribution of 5-hydroxy-7-methyl-3-phenyl-3*H*-thiazolo[4,5-*b*]pyridine nucleus and a number of structural fragments that are pharmacophore for the class heterocycles and the type of pharmacological activity.

Conclusions

As a result of the [3 +3]cyclocodensation, acylation and alkylation reactions, the synthesis of novel thiazolo[4,5-*b*]pyridin-2-ones has been carried out. For the synthesized compounds, *in vivo* screening of anti-inflammatory activity was conducted, the results of which indicate that the test substances in terms of activity approach or exceed the preparation of the comparison Ibuprofen. Thus the core thiazolo[4,5-*b*]pyridine heterocyclic system may be regarded as a promising scaffold for the effective anti-inflammatory a drug candidates development.

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