Synthesis and Evaluation of Bioactivity of 6-[(2-Pyridinyloxy)](Benzo)Imidazo[2,1-b][1,3]Thiazine Derivatives

Lesya Salyeva 1,*, Nataliia Slyvka 1, Serhii Holota 1,2, Alina Grozav 3, Nina Yakovychuk 3, Mariia Litvinchuk 4, Mykhailo Vovk 4

1 Department of Organic Chemistry and Pharmacy, Lesya Ukrainka Volyn National University, 43025, Lutsk, Ukraine;
2 Department of Pharmaceutical, Organic and Bioorganic Chemistry, Danylo Haltsky Lviv National Medical University, 79010, Lviv, Ukraine;
3 Department of Medical and Pharmaceutical Chemistry, Bukovinian State Medical University, 58000 Chernivtsi, Ukraine;
4 Department of Mechanism of Organic Reactions, Institute of Organic Chemistry of National Academy of Sciences of Ukraine, 02660 Kyiv, Ukraine;
* Correspondence: esyaNykytyuk@ukr.net (L.S.);

Received: 1.08.2021; Revised: 10.09.2021; Accepted: 15.09.2021; Published: 17.10.2021

Abstract: A series of new 6-[(pyridine-2-yloxy)-6,7-dihydro-5H-imidazo[2,1-b]thiazines 4a-l and their benzoannelated derivatives 4m-r was synthesized by the reaction between 3-hydroxy(benzo)imidazo[2,1-b][1,3]thiazines and substituted 2-chloropyridines under the mild conditions with the yield 53-74 %. The structure of the target compound was proven by the results of 1H NMR, 13C NMR spectrometry, and LC-MS. In silico evaluation of these drug-like compounds proved that many of them comply with the Lipinski ‘rule of five’ and the Veber rule. Antibacterial, antifungal, and anti-inflammatory activity of all synthesized compounds were investigated in the in vitro and in vivo experiments. According to the bio screening results, the compounds 6-[(5-chloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 4a, 6-[(3,5-dichloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 4e and 6-[(3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy]-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 4l proved antifungal activity against Candida albicans. On the other hand, 3-[(3,5-dichloropyridin-2-yl)oxy]-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine 4q proved the best antifungal activity against Aspergillus niger K 9 (MIC=15.62 µg/ml) and comparatively high antiedema activity against the carrageenan-induced edema of the hind paws of albino rats (the inflammation suppression index was 39.1 %).

Keywords: 3-hydroxy-3,4-dihydro-2H-(benzo)imidazo[2,1-b][1,3]thiazines, 6-[(2-pyridinyloxy)]-(benzo)imidazo[2,1-b][1,3]thiazines; evaluation of drug-likeness antibacterial activity; antifungal activity; anti-inflammatory activity.

© 2021 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

The condensed heterocyclic compounds became the key objects of systematic investigations in medicinal and organic chemistry recently. They are used as molecular platforms for developing various commercial medicines and some other prospective bioactive compounds. The construction of the hybrid molecules consisting of several pharmaceutically active fragments is an interesting approach to realizing the syntheses mentioned above. These hybrid compounds may exhibit an increased bio-efficiency while their toxicity remains comparatively mild [1]. Azolo-azine systems [2-9] and, especially, the derivatives of
imidazo[2,1-b][1,3]thiazine [10, 11] are known as the important scaffold for the further modification into such hybrid structures. It should be emphasized that the bicyclic scaffold of the imidazo[2,1-b]thiazine type is a structural part of the strong antagonists of GRP18 I, which inhibit completely the set of β-arrestines induced by ∆9-THC (IC₅₀ = 0.238 μM) [12], while the benzyl-derivatives of imidazo[2,1-b]thiazines II proved their inhibition activity against a group of mycobacteria Mycobacterium tuberculosis complex (MIC 16 μg/mL) [13-15] (see Figure 1). The latter compounds are also effective in the treatment of Chagas disease [16].

The pyridine scaffold is also important for designing various medicines and is used as a basic element in many compounds exhibiting various types of bioactivity [17-19]. For example, a clear antibacterial and antifungal activity was reported for the pyridinyl-containing oxadiazole III [20], while the pyridinyl fragments consisted of 1,3,4-thiadiazole IV is known as a promising medicine for the treatment of Chagas disease [21]. The antiproliferation activity against the human melanoma cells A375 has been reported for dipyridylvinylketone V [22]. Besides, some inhibitors of the enzymes trypsin [23], β-lactamase [24], phosphodiesterase PDE2A [25], and some compounds exhibiting the cytotoxicity against the lines of the human cancer cells were found among the derivatives of pyridine. This cytotoxic activity is caused by the inhibition of tubulin [26] and the ability of these compounds to inhibit the glioma U-87 and T98G cancer cells [27].

![Figure 1. Some examples of the bioactive compounds containing the imidazo[2,1-b][1,3]thiazine cycle (I, II) and the pyridine fragments (III-V).](https://biointerfaceresearch.com/)

Therefore, it seems interesting to synthesize a series of new hybrid molecules containing the pharmacophoric imidazo[2,1-b][1,3]thiazine and pyridinyl fragments and evaluate their antimicrobial and anti-inflammatory activity.

2. Materials and Methods

2.1. Materials.

All the reactants used in this work were of the purity grade ‘chemically pure’. No extra cleaning or treatment of the reactants was applied before the syntheses. All the solvents were cleaned by the standard methods [28] before use.

2.2. Chemistry.

Melting points were measured on a Kofler melting point-device and left uncorrected. 1H NMR spectra were acquired in pulsed Fourier transform mode on a Varian VXR-400
spectrometer (400 MHz), while $^{13}$CNMR spectra were acquired on a Bruker Avance DRX-500 spectrometer (125 MHz), using DMSO-d$_6$ as solvent. Mass spectra were recorded on an Agilent LC/MSD SL chromatograph equipped with Zorbax SB-C$_18$ column (4.6x15mm), particle size 1.8 µm (PN 82(c)75-932), solvent DMSO, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer 2400 CHN Analyzer. The individuality of the obtained compounds was monitored by TLC on Silutol UV-254 plates.

2.2.1. Procedure for the synthesis of 6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-oles 2a,b.

5 mmol of 2-(chloromethyl)oxirane were added to the solution of 5 mmol of the required imidazole-2-thiol 1a,b, and 5 mmol of NaOH in 25 mL of MeOH and stirred at room temperature for 24 h. Then the solvent was vacuum evaporated, 30 mL of the ice-cold water was added to the residue, and then the sediment was filtered off and dried in the air.

2.2.2. 6,7-Dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-ol (2a).

Yield 90%; m.p.: 202-204 °C. $^{13}$C NMR: $\delta = 135.63$ (C$^8a$), 127.68 (C$^2$), 121.26 (C$^3$), 61.52 (C$^6$), 50.45 (C$^5$), 31.73 (C$^7$). LC-MS: m/z = 157 [M+1] (100%). Anal. Calcd. for C$_6$H$_8$N$_2$OS, %: C, 46.13; H, 5.16; N, 17.93. Found, %: C, 46.28; H, 5.11; N, 18.04.

2.2.3. 2,3-Diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-ol (2b).

Yield 89%; m.p.: 218-219 °C. $^{13}$C NMR: $\delta = 137.20$ (C$^8a$), 136.74 (C$^3$), 134.84, 131.08, 130.49 (Ar), 129.77 (C$^2$), 129.48, 129.07, 128.50, 126.55, 126.43 (Ar), 61.79 (C$^6$), 49.71 (C$^5$), 31.50 (C$^7$). LC-MS: m/z = 309 [M+1] (100%). Anal. Calcd. for C$_{18}$H$_{16}$N$_2$OS, %: C, 70.10; H, 5.23; N, 9.08. Found, %: C, 70.25; H, 5.19; N, 9.17.


5.5 mL (7 mmol) of 2-(chloromethyl)oxirane were added to the solution of 10.5 g (7 mmol) of benzimidazole-2-thiol and 9.7 g (7 mmol) of K$_2$CO$_3$ in the dry DMF (30 mL). Then the mixture was heated to 60-70 °C and stirred for 3 h. Afterward, it was poured onto the ice; the sediment was filtered off, washed with 50 mL of water, and dried in the air.

Yield 93%; m.p.: 215-217 °C. $^{13}$C NMR: $\delta = 142.64$ (C$^{10a}$), 138.96 (C$^9a$), 134.23 (C$^5a$), 123.87 (C$^8$), 123.01 (C$^7$), 115.29 (C$^9$), 110.15 (C$^6$), 55.26 (C$^3$), 49.01 (C$^4$), 31.35 (C$^2$). LC-MS: m/z = 207 [M+1] (100%). Anal. Calcd. for C$_{10}$H$_{10}$N$_2$OS, %: C, 58.23; H, 4.89; N, 13.58. Found, %: C, 58.35; H, 4.94; N, 13.44.

2.2.5. General procedure for the synthesis of (2-pyridinyloxy)substituted (benzo)imidazo[2,1-b][1,3]thiazines 4 a-r.

1 mmol of the substituted 2-chloropyridine 3a-f was added to the mixture of 3-hydroxy(benzo)imidazo[2,1-b][1,3]thiazine 2a-c and a 60 % NaH in mineral oil (0.4 g, 1mmol) in the dry DMF (4 mL) and stirred at room temperature for 24 h. Then the mixture was poured onto ice; the sediment was filtered off, washed with water, dried, and recrystallized from MeOH.
2.2.6. 6-[(5-Chloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4a).

Yield 55 %; m.p.: 150–151 °C. 1H NMR: δ = 8.25 (s, 1H, Ar), 7.83 (d, 3J = 8.8 Hz, 1H, Ar), 7.16 (s, 1H, Ar), 6.90 (d, 3J = 8.8 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 5.69-5.70 (m, 1H, CH), 4.32-4.33 (m, 2H, NCH), 3.57-3.60 (m, 1H, SCH2), 3.47 (dd, 3J = 13.2 Hz, 3J = 5.4 Hz, 1H, SCH2). 13C NMR: δ = 160.80 (Py), 145.32 (Py), 140.04 (Py), 135.83 (C8a), 128.20 (C2), 124.54 (Py), 121.80 (C3), 113.35 (Py), 65.33 (C6), 48.56 (C5), 28.86 (C7). LC-MS: m/z = 268 [M+1] (100%). Anal. Calcd. for C11H10ClN3OS, %: C, 49.35; H, 3.76; N, 15.69. Found, %: C, 49.48; H, 3.77; N, 15.54.

2.2.7. 6-[(5-Trifluoromethyl)pyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4b).

Yield 60 %; m.p.: 130–131 °C. 1H NMR: δ = 8.64 (s, 1H, Ar), 8.09 (d, 3J = 8.8 Hz, 1H, Ar), 7.18 (s, 1H, Ar), 7.05 (d, 3J = 8.4 Hz, 1H, Ar), 6.88 (s, 1H, Ar), 5.82-5.85 (m, 1H, CH), 4.37-4.38 (m, 2H, NCH2), 3.61-3.65 (m, 1H, SCH2), 3.52 (dd, 3J = 13.4 Hz, 3J = 5.4 Hz, 1H, SCH2). 13C NMR: δ = 168.58 (Py), 145.31 (q, 3JC = 4.5 Hz, Py), 137.42 (q, 3JC = 3.0 Hz, Py), 135.80 (C8a), 128.21 (C2), 124.42 (d, 1JC = 270.0 Hz, CF3), 121.82 (C3), 119.93 (q, 2JC = 33.0 Hz, Py), 114.55 (Py), 65.73 (C6), 48.52 (C5), 28.80 (C7). LC-MS: m/z = 302 [M+1] (100%). Anal. Calcd. for C12H10F3N3OS, %: C, 47.84; H, 3.35; N, 13.95. Found, %: C, 48.02; H, 3.32; N, 13.89.

2.2.8. 2-[(6,7-Dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl)oxy]isonicotinonitrile (4c).

Yield 51 %; m.p.: 106–107 °C. 1H NMR: δ = 8.44-8.46 (m, 1H, Ar), 7.45-7.47 (m, 1H, Ar), 7.43 (s, 1H, Ar), 7.17 (s, 1H, Ar), 6.87 (s, 1H, Ar), 5.76-5.80 (m, 1H, CH), 4.35-4.36 (m, 2H, NCH2), 3.59-3.62 (m, 1H, SCH2), 3.49 (dd, 3J = 13.2 Hz, 3J = 5.6 Hz, 1H, SCH2). 13C NMR: δ = 162.33 (Py), 149.07 (Py), 135.78 (C8a), 128.22 (C2), 122.80 (Py), 121.82 (C3), 119.49 (Py), 116.82 (Py), 114.95 (CN), 65.68 (C6), 48.53 (C5), 28.77 (C7). LC-MS: m/z = 259 [M+1] (100%). Anal. Calcd. for C12H10N4OS, %: C, 55.80; H, 3.90; N, 21.69. Found, %: C, 55.98; H, 3.87; N, 21.74.

2.2.9. 6-[(6,7-Dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl)oxy]nicotinonitrile (4d).

Yield 58 %; m.p.: 182–183 °C. 1H NMR: δ = 8.74 (s, 1H, Ar), 8.18 (d, 3J = 8.8 Hz, 1H, Ar), 7.17 (s, 1H, Ar), 7.04 (d, 3J = 8.8 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 5.81-5.85 (m, 1H, CH), 4.35-4.36 (m, 2H, NCH2), 3.60-3.64 (m, 1H, SCH2), 3.44 (dd, 3J = 13.6 Hz, 3J = 5.2 Hz, 1H, SCH2). 13C NMR: δ = 164.24 (Py), 152.49 (Py), 143.20 (Py), 135.76 (C8a), 128.24 (C2), 121.82 (C3), 117.59 (Py), 112.66 (Py), 103.11 (CN), 65.97 (C6), 48.50 (C5), 28.80 (C7). LC-MS: m/z = 259 [M+1] (100%). Anal. Calcd. for C12H10N4OS, %: C, 55.80; H, 3.90; N, 21.69. Found, %: C, 56.02; H, 3.92; N, 21.60.

2.2.10. 6-[(3,5-Dichloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4e).

Yield 59 %; m.p.: 163–164 °C. 1H NMR: δ = 8.24 (s, 1H, Ar), 8.17 (s, 1H, Ar), 7.17 (s, 1H, Ar), 6.87 (s, 1H, Ar), 5.75-5.77 (m, 1H, CH), 4.36-4.38 (m, 2H, NCH2), 3.58-3.61 (m, 1H, SCH2), 3.46-3.50 (m, 1H, SCH2). 13C NMR: δ = 156.32 (Py), 143.54 (Py), 139.34 (Py), 135.82 (C8a), 128.24 (C2), 124.35 (Py), 121.78 (C3), 118.58 (Py), 66.85 (C6), 48.42 (C5), 28.84 (C7).
LC-MS: m/z = 302 [M+1] (100%). Anal. Calcd. for C_{11}H_{5}Cl_{2}N_{3}O_{3}: %: C, 43.72; H, 3.00; N, 13.91. Found, %: C, 43.88; H, 2.97; N, 14.04.

2.2.11. 6-[[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4f).

Yield 62 %; m.p.: 113-114 °C. ¹H NMR: δ = 8.57 (s, 1H, Ar), 8.37 (s, 1H, Ar), 7.16 (s, 1H, Ar), 6.86 (s, 1H, Ar), 5.85-5.88 (m, 1H, CH), 4.38-4.40 (m, 2H, NCH₂), 3.61-3.64 (m, 1H, SCH₂), 3.51 (dd, ^2J = 10.6 Hz, ^3J = 4.6 Hz, 1H, SCH₂). ¹³C NMR: δ = 159.97 (Py), 143.26 (q, ^3JC_F = 3.75 Hz, Py), 136.87 (q, ^4JC_F = 2.5 Hz, Py), 135.78 (C^8), 128.23 (C^3), 123.52 (d, ^1JC_F = 270.0 Hz, CF₃), 121.79 (C^3), 120.83 (q, ^2JC_F = 33.75 Hz, Py), 118.67 (Py), 67.34 (C^6), 48.37 (C^5), 28.77 (C^7). LC-MS: m/z = 336 [M+1] (100%). Anal. Calcd. for C_{12}H_{5}ClF_{3}N_{3}O_{3}: %: C, 42.93; H, 2.70; N, 12.52. Found, %: C, 43.08; H, 2.67; N, 12.64.

2.2.12. 6-[[5-Chloropyridin-2-yl]oxy]-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4g).

Yield 58 %; m.p.: 152-153 °C. ¹H NMR: δ = 8.20 (s, 1H, Ar), 7.81-7.84 (m, 1H, Ar), 7.46-7.48 (m, 3H, Ar), 7.30-7.35 (m, 4H, Ar), 7.16-7.20 (m, 2H, Ar), 7.11-7.13 (m, 1H, Ar), 6.92 (d, ^3J = 8.8 Hz, 1H, Ar), 5.87-5.71 (m, 1H, CH), 4.10-4.14 (m, 1H, NCH₂), 3.89-3.92 (m, 1H, NCH₂), 3.59-3.62 (m, 1H, SCH₂), 3.50-3.54 (m, 1H, SCH₂). ¹³C NMR: δ = 160.32 (Py), 144.85 (Py), 139.61 (Py), 136.61 (C^8), 136.39 (C^3), 134.23, 130.57, 129.80 (Ar), 129.42 (C^5), 129.13, 128.80, 128.10, 126.24, 125.98 (Ar), 124.17, 112.97 (Py), 65.14 (C^6), 46.91 (C^3), 28.05 (C^7). LC-MS: m/z = 420 [M+1] (100%). Anal. Calcd. for C_{22}H_{18}ClN_{3}OS: %: C, 65.78; H, 4.32; N, 10.01. Found, %: C, 65.92; H, 4.34; N, 9.88.

2.2.13. 2,3-Diphenyl-6-[[5-(trifluoromethyl)pyridin-2-yl]oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (4h).

Yield 67 %; m.p.: 154-155 °C. ¹H NMR: δ = 8.54 (s, 1H, Ar), 8.05 (d, ^3J = 9.0 Hz, 1H, Ar), 7.43-7.44 (m, 3H, Ar), 7.33-7.34 (m, 2H, Ar), 7.28-7.29 (m, 2H, Ar), 7.14-7.17 (m, 2H, Ar), 7.07-7.10 (m, 1H, Ar), 7.05 (d, ^3J = 8.4 Hz, 1H, Ar), 5.80-5.82 (m, 1H, CH), 4.13-4.16 (m, 1H, NCH₂), 3.92-3.95 (m, 1H, NCH₂), 3.62-3.64 (m, 1H, SCH₂), 3.53-3.57 (m, 1H, SCH₂). ¹³C NMR: δ = 164.49 (Py), 145.22 (q, ^3JC_F = 4.5 Hz, Py), 137.38 (q, ^4JC_F = 3.0 Hz, Py), 137.01 (C^8), 136.83 (C^3), 134.62, 130.97, 130.19 (Ar), 129.85 (C^5), 129.54, 129.22, 128.51, 126.67, 126.40 (Ar), 124.39 (d, ^1JC_F = 270.0 Hz, CF₃), 119.95 (q, ^2JC_F = 33.0 Hz, Py), 112.47 (Py), 65.92 (C^6), 47.33 (C^3), 28.40 (C^7). LC-MS: m/z = 454 [M+1] (100%). Anal. Calcd. for C_{24}H_{18}F_{3}N_{3}OS: %: C, 63.57; H, 4.00; N, 9.27. Found, %: C, 63.75; H, 3.97; N, 9.19.

2.2.14. 2-[[2,3-Diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl]oxy]isonicotinonitrile (4i).

Yield 63 %; m.p.: 184-185 °C. ¹H NMR: δ = 8.38-8.40 (m, 1H, Ar), 7.44-7.48 (m, 5H, Ar), 7.31-7.35 (m, 4H, Ar), 7.16-7.20 (m, 2H, Ar), 7.09-7.13 (m, 1H, Ar), 5.76-5.79 (m, 1H, CH), 4.12-4.16 (m, 1H, NCH₂), 3.90-3.94 (m, 1H, NCH₂), 3.62-3.65 (m, 1H, SCH₂), 3.51-3.56 (m, 1H, SCH₂). ¹³C NMR: δ = 162.31 (Py), 149.05 (Py), 137.03 (C^8), 136.88 (C^3), 134.67, 131.05, 130.24 (Ar), 129.89 (C^2), 129.64, 129.30, 128.61, 126.76, 126.47 (Ar), 122.81 (Py), 119.58 (Py), 116.87 (CN), 115.08 (Py), 65.87 (C^6), 47.43 (C^5), 28.39 (C^7). LC-MS: m/z = 411
[M+1] (100%). Anal. Calcd. for C$_2$H$_{18}$N$_4$OS, %: C, 70.22; H, 4.42; N, 13.65. Found, %: C, 70.38; H, 4.37; N, 13.55.

2.2.15. 6-{(2,3-Diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl)oxy}nicotinonitrile (4j).

Yield 57 %; m.p.: 235-236 °C. $^1$H NMR: $\delta = 8.69$ (s, 1H, Ar), 8.16-8.19 (m, 1H, Ar), 7.45-7.49 (m, 5H, Ar), 7.33-7.35 (m, 4H, Ar), 7.17-7.20 (m, 1H, Ar), 7.06-7.13 (m, 1H, Ar), 5.79-5.85 (m, 1H, CH), 4.14-4.17 (m, 1H, NCH$_2$), 3.90-3.94 (m, 1H, NCH$_2$), 3.63-3.66 (m, 1H, SCH$_2$), 3.52-3.57 (m, 1H, SCH$_2$). $^{13}$C NMR: $\delta = 164.22$ (Py), 152.50 (Py), 143.19 (Py), 136.99 (C$_{8a}$), 136.88 (C$_3$), 134.65, 131.05, 130.22 (Ar), 129.90 (C$_2$), 129.65, 129.32, 128.61, 126.77, 126.47 (Ar), 117.64 (CN), 112.76, 103.19 (Py), 66.15 (C$_6$), 47.41 (C$_5$), 28.39 (C$_7$). LC-MS: m/z = 411 [M+1] (100%). Anal. Calcd. for C$_2$H$_{18}$N$_4$OS, %: C, 70.22; H, 4.42; N, 13.65. Found, %: C, 70.32; H, 4.44; N, 13.58.

2.2.16. 6-{(3,5-Dichloropyridin-2-yl)oxy}-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin (4k).

Yield 61 %; m.p.: 165-166 °C. $^1$H NMR: $\delta = 8.20$ (s, 2H, Ar), 7.46-7.49 (m, 3H, Ar), 7.30-7.35 (m, 5H, Ar), 7.16-7.20 (m, 2H, Ar), 7.11-7.13 (m, 1H, Ar), 5.72-5.76 (m, 1H, CH), 4.09-4.12 (m, 1H, NCH$_2$), 3.93-3.98 (m, 1H, NCH$_2$), 3.61-3.64 (m, 1H, SCH$_2$), 3.50-3.55 (m, 1H, SCH$_2$). $^{13}$C NMR: $\delta = 155.86$, 143.23, 138.86 (Py), 136.65 (C$_{8a}$), 136.39 (C$_3$), 134.23, 130.57, 129.84 (Ar), 129.45 (C$_2$), 129.16, 128.83, 128.10, 126.24, 125.92 (Ar), 124.00, 118.17 (Py), 66.98 (C$_6$), 46.63 (C$_5$), 28.17 (C$_7$). LC-MS: m/z = 455 [M+1] (100%). Anal. Calcd. for C$_2$H$_{18}$Cl$_2$N$_3$OS, %: C, 60.80; H, 3.77; Cl, 15.61; N, 9.25. Found, %: C, 60.94; H, 3.73; N, 9.16.

2.2.17. 6-{(3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy}-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin (4l).

Yield 66 %; m.p.: 159-160 °C. $^1$H NMR: $\delta = 8.49$ (s, 1H, Ar), 8.36 (s, 1H, Ar), 7.42-7.44 (m, 3H, Ar), 7.29-7.34 (m, 4H, Ar), 7.08-7.15 (m, 3H, Ar), 5.83-5.87 (m, 1H, CH), 4.12-4.14 (m, 1H, NCH$_2$), 3.98-4.00 (m, 1H, NCH$_2$), 3.64-3.66 (m, 1H, SCH$_2$), 3.54-3.56 (m, 1H, SCH$_2$). $^{13}$C NMR: $\delta = 159.47$ (Py), 142.79 (q, $^3J_{CF} = 3.75$ Hz, Py), 136.65 (C$_{8a}$+C$_3$), 136.45 (q, $^3J_{CF} = 2.5$ Hz, Py), 134.20, 130.55, 129.81 (Ar), 129.47 (C$_2$), 129.14, 128.83, 128.09, 126.24, 125.94 (Ar), 123.03 (d, $^1J_{CF} = 270.0$ Hz, CF$_3$), 120.47 (q, $^3J_{CF} = 33.75$ Hz, Py), 118.28 (Py), 67.50 (C$_6$), 46.61 (C$_5$), 28.15 (C$_7$). LC-MS: m/z = 488 [M+1] (100%). Anal. Calcd. for C$_4$H$_{17}$ClF$_3$N$_3$OS, %: C, 59.08; H, 3.51; N, 8.61. Found, %: C, 59.25; H, 3.47; N, 8.49.

2.2.18. 3-{(5-Chloropyridin-2-yl)oxy]-3,4-dihydro-2H-benzol[4,5]imidazo[2,1-b][1,3]thiazin (4m).

Yield 60 %; m.p.: 144-145 °C. $^1$H NMR: $\delta = 8.25$ (s, 1H, Ar), 7.81-7.84 (m, 1H, Ar), 7.40-7.46 (m, 2H, Ar), 7.12-7.14 (m, 2H, Ar), 6.87 (d, $^3J = 7.2$ Hz, 1H, Ar), 5.85-5.87 (m, 1H, CH), 4.52-4.54 (m, 1H, NCH$_2$), 4.44-4.46 (m, 1H, NCH$_2$), 3.70-3.72 (m, 1H, SCH$_2$), 3.59-3.61 (m, 1H, SCH$_2$). $^{13}$C NMR: $\delta = 160.72$ (Py), 146.30 (C$_{8a}$), 145.34 (Py), 143.04 (C$_{9a}$), 140.08 (Py), 136.20 (C$_{8a}$), 124.63 (Py), 122.41 (C$_6$), 121.46 (C$_7$), 117.58 (C$_6$), 113.36 (Py), 109.23 (C$_6$), 64.64 (C$_3$), 46.61 (C$_5$), 28.54 (C$_2$). LC-MS: m/z = 318 [M+1] (100%). Anal. Calcd. for C$_{15}$H$_{12}$ClN$_3$OS, %: C, 56.69; H, 3.81; N, 13.22. Found, %: C, 56.68; H, 3.77; N, 13.34.

Yield 67 %; m.p.: 140-141 °C. 1H NMR: δ = 8.66 (s, 1H, Ar), 8.08 (d, J = 9.2 Hz, 1H, Ar), 7.48 (d, J = 7.6 Hz, 1H, Ar), 7.43-7.45 (m, 1H, Ar), 7.13-7.19 (m, 2H, Ar), 7.05 (d, J = 8.4 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 6.00-6.04 (m, 1H, CH), 4.57-4.61 (m, 1H, NCH2), 4.48-4.52 (m, 1H, NCH2), 3.75-3.78 (m, 1H, SCH2), 3.66 (dd, J = 13.4 Hz, J = 5.4 Hz, 1H, SCH2). 13C NMR: δ = 164.50 (Py), 146.24 (C10a), 145.33 (q, 3JCF = 4.5 Hz, Py), 143.05 (C8a), 137.47 (q, 4JCF = 3.0 Hz, Py), 136.20 (C5a), 124.42 (d, 1JCF = 270.0 Hz, CF3), 122.42 (C8), 121.47 (C7), 120.02 (q, 2JCF = 33.0 Hz, Py), 117.61 (Py), 112.47 (C9), 109.25 (C6), 65.06 (C9), 46.59 (C4), 28.48 (C2). LC-MS: m/z = 352 [M+1] (100%). Anal. Calcd. for C16H12F3N3OS, %: C, 54.70; H, 3.44; N, 11.96. Found, %: C, 54.88; H, 3.47; N, 11.84.


Yield 56 %; m.p.: 109-110 °C. 1H NMR: δ = 8.48-8.49 (m, 1H, Ar), 7.44-7.50 (m, 4H, Ar), 7.13-7.19 (m, 2H, Ar), 5.95-5.99 (m, 1H, CH), 4.56-4.60 (m, 1H, NCH2), 4.47-4.50 (m, 1H, NCH2), 3.73-3.77 (m, 1H, SCH2), 3.61-3.66 (m, 1H, SCH2). 13C NMR: δ = 161.85 (Py), 148.68 (Py), 145.81 (C10a), 142.64 (C9a), 135.78 (C3a), 122.42 (Py), 122.01 (C8), 121.06 (C7), 119.17 (C6), 117.20 (C9), 116.38 (CN), 114.56 (Py), 108.83 (Py), 64.61 (C3), 46.17 (C4), 28.06 (C2). LC-MS: m/z = 309 [M+1] (100%). Anal. Calcd. for C16H12N4OS, %: C, 62.32; H, 3.92; N, 18.17. Found, %: C, 62.19; H, 3.93; N, 18.25.


Yield 59 %; m.p.: 161-162 °C. 1H NMR: δ = 8.74 (s, 1H, Ar), 7.46 (s, 1H, Ar), 7.40 (s, 1H, Ar), 7.00-7.13 (m, 4H, Ar), 5.97-6.00 (m, 1H, CH), 4.55-4.57 (m, 1H, NCH2), 4.46-4.48 (m, 1H, NCH2), 3.73-3.75 (m, 1H, SCH2), 3.61-3.63 (m, 1H, SCH2). 13C NMR: δ = 164.14 (Py), 152.49 (Py), 146.19 (C10a), 143.14 (Py), 143.01 (C9a), 136.16 (C3a), 122.45 (C8), 121.51 (C7), 117.62 (Py), 117.60 (Py), 112.66 (C9), 109.24 (C6), 103.19 (CN), 65.26 (C4), 46.56 (C4), 28.48 (C2). LC-MS: m/z = 309 [M+1] (100%). Anal. Calcd. for C16H12N4OS, %: C, 62.32; H, 3.92; N, 18.17. Found, %: C, 62.45; H, 3.89; N, 18.29.

2.2.22. 3-{[3,5-dichloropyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine (4q).

Yield 62 %; m.p.: 203-204 °C. 1H NMR: δ = 8.25 (s, 1H, Ar), 8.14 (s, 1H, Ar), 7.41-7.46 (m, 2H, Ar), 7.11-7.16 (m, 2H, Ar), 5.90-5.94 (m, 1H, CH), 4.48-4.50 (m, 1H, NCH2), 4.54-4.56 (m, 1H, NCH2), 3.70-3.73 (m, 1H, SCH2), 3.58-3.62 (m, 1H, SCH2). 13C NMR: δ = 155.81 (Py), 145.83 (C10a), 143.32 (Py), 142.64 (C9a), 138.89 (Py), 135.78 (C3a), 124.04 (Py), 121.99 (C8), 121.05 (C7), 118.19 (Py), 117.20 (C9), 108.87 (C6), 65.63 (C3), 46.07 (C4), 28.06 (C2). LC-MS: m/z = 352 [M+1] (100%). Anal. Calcd. for C15H11Cl2N3OS, %: C, 51.15; H, 3.15; N, 11.93. Found, %: C, 51.36; H, 3.11; N, 11.82.

2.2.23. 3-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine (4r).

https://doi.org/10.33263/BRIAC124.50315044
Yield 65%; m.p.: 165-166 °C. 1H NMR: δ = 8.61 (s, 1H, Ar), 8.39 (s, 1H, Ar), 7.42-7.47 (m, 2H, Ar), 7.11-7.16 (m, 2H, Ar), 6.04-6.07 (m, 1H, CH), 4.58-4.61 (m, 1H, NCH2), 4.51-4.54 (m, 1H, NCH2), 3.74-3.77 (m, 1H, SCH2), 3.63-3.67 (m, 1H, SCH2). 13C NMR: δ = 159.87 (Py), 146.19 (C10a), 143.34 (q, 3JCF = 3.75 Hz, Py), 143.05 (C9a), 136.97 (q, 4JCF = 2.5 Hz, Py), 136.19 (C5a), 123.52 (d, 1JCF = 270.0 Hz, CF3), 122.42 (C8), 121.47 (C7), 120.92 (q, 2JCF = 33.75 Hz, Py), 118.68 (Py), 117.63 (C9), 109.31 (C6), 66.54 (C3), 46.50 (C4), 28.27 (C2).

LC-MS: m/z = 386 [M+1] (100%). Anal. Calcd. for C16H11ClF3N3O, %: C, 49.81; H, 2.87; N, 10.89. Found, %: C, 50.01; H, 2.89; N, 10.97.

2.3. Antimicrobial activity.

The antibacterial and antifungal activity of the synthesized compounds were investigated by the micro-method of double sequential dilutions in the liquid nutritional medium [29]. The minimal inhibition concentrations (MIC) against some gram-positive and gram-negative bacteria (Staphylococcus aureus 25923, Escherichia coli 25922, Bacillus cereus 10702) and fungi (Candida albicans ATCC 885/653 and Aspergillus niger K 9) were determined for the synthesized 2-(pyridinyloxy) substituted (benzo)imidazo[2,1-b][1,3]thiazines 4a-r.

2.4. Anti-inflammatory (anti-exudative) activity.

The male albino rats weighing 180-220 g were used for anti-exudative activity studying. The animals were treated humanely throughout the study period adhering to the guideline for the use and care of animals in the declaration of Helsinki (National Research Council, 2011). The experiment design and study protocol were approved by the Animal Ethics Committee of the Danylo Halytsky Lviv National Medical University, protocol No.10, March 17, 2021. The carrageenin-induced hind paw edema was produced by the method of Winter et al. [30]. The compounds synthesized were intraperitoneally injected in a dose 50 mg/kg (in saline solution with one drop of Tween-80™). Diclofenac (tablets “Diclofenac sodium”, “Zdorovja narodu”, Ukraine) in dose 8 mg/kg was used as reference drug. The antiexudative activity (inflammation inhibition) was expressed as a decrease of rats paw edema, was calculated using the equation, and was given in percentage:

\[
\text{Inhibition, \%} = \frac{\Delta V_{\text{control}} - \Delta V_{\text{experiment}}}{\Delta V_{\text{control}}} \times 100 \% 
\]

where \( \Delta V_{\text{control}} \) and \( \Delta V_{\text{experiment}} \) – the mean values of the volume difference for control and experimental animals hinds respectively.

3. Results and Discussion

3.1. Chemistry.

Taking into account the significant role of the pyridinyloxy substitutes in the structure of the pharmaceutically active compounds [31-36], it was required to insert these substitutes into the composition of new functional derivatives of (benzo)imidazo[2,1-b][1,3]thiazines. According to our approach to the construction of such systems, 3-hydroxy(benzo)imidazo[2,1-b][1,3]thiazines 2a-c were used as the key substrates. The modified methods synthesized these compounds from (benzo)imidazolinthiones 1a-c [13, 37]. It was found that 3-
hydroxyimidazo[2,1-b][1,3]thiazines 2a,b, and their benzo-analogon 2c can selectively react with the substituted chloropyridines 3a-f in the dry DMF at room temperature and in the presence of NaH (see Scheme 1). As a result of the 24 h, long interaction, 6-[(pyridine-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazines 4a-1 and their benzoannelated derivatives 4m-r were obtained with the yield 53-74%. The structure of the synthesized compounds is proven by the $^1$H NMR, $^{13}$C NMR, and LC-MS spectra given in the Experimental section of this paper. In particular, the response of the pyridine series protons is characteristic for all imidazothiazines 4a-r. These responses can be identified within the range 8.74-6.86 m.n. for the compounds 4a-f, while for the diphenyl compounds 4g-i and the benzo-analogs 4m-r, they overlap on the responses of the phenyl protons.

Scheme 1. Synthesis of pyridinyloxy substituted (benzo)imidazo[2,1-b][1,3]thiazines 4 a-r.
3.2 In silico evaluation of drug-likeness properties.

The drug-likeness properties of the derivatives 4 b,d,e,f,h,j-n,p-r were determined based on Lipinski and Veber rules and evaluated in silico using the SwisAdme of Swiss Institute of Bioinformatics website [38] (see Table 1).

### Table 1. Drug-likeness parameters of derivatives 4 b,d,e,f,h,j-n,p-r according to Lipinski and Veber rules.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MW ≤ 500</th>
<th>log P/Mlog P ≤ 5/≤ 4.15</th>
<th>NHD ≤ 5</th>
<th>NHA ≤ 10</th>
<th>NBR ≤ 10</th>
<th>TPSA ≤ 140</th>
<th>Violations of rules</th>
</tr>
</thead>
<tbody>
<tr>
<td>4b</td>
<td>301.29</td>
<td>2.25/1.82</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4d</td>
<td>258.30</td>
<td>1.94/0.23</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>89.03</td>
<td>0</td>
</tr>
<tr>
<td>4e</td>
<td>302.18</td>
<td>2.58/1.95</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4f</td>
<td>353.73</td>
<td>2.41/2.34</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4h</td>
<td>453.48</td>
<td>3.61/4.11</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4j</td>
<td>410.49</td>
<td>3.03/2.63</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>89.03</td>
<td>0</td>
</tr>
<tr>
<td>4k</td>
<td>454.37</td>
<td>3.91/4.28</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td>65.24</td>
<td>1</td>
</tr>
<tr>
<td>4l</td>
<td>487.92</td>
<td>3.65/4.69</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>65.24</td>
<td>1</td>
</tr>
<tr>
<td>4n</td>
<td>351.35</td>
<td>2.74/3.15</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4p</td>
<td>308.36</td>
<td>2.33/1.62</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>89.03</td>
<td>0</td>
</tr>
<tr>
<td>4q</td>
<td>352.24</td>
<td>2.96/3.30</td>
<td>0</td>
<td>3</td>
<td>2</td>
<td>65.24</td>
<td>0</td>
</tr>
<tr>
<td>4r</td>
<td>385.79</td>
<td>2.84/3.66</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>65.24</td>
<td>0</td>
</tr>
</tbody>
</table>

1Mlog P: Moriguchi log P [39, 40]; 2NHD: number of hydrogen bond donors; 3NHA: number of hydrogen acceptors; 4NBR: number of rotatable bonds; 5TPSA: total polar surface area.

All tested compounds comply with Lipinski’s rules of five and Veber’s rules, except derivatives 4l and 4k, for which calculated MlogP values were higher (4.69 and 4.28 accordingly) than limited for Mlog P parameter (accepted ≤4.15) in line with the Lipinski’s rules.

3.3. Investigation of antimicrobial activity.

As seen from the results of our investigation, the synthesized compounds 4а-r exhibit some moderate antimicrobial activity with MIC ranging between 15.62 to 500 µg/mL (see Table 2). On the other hand, their antifungal efficiency is higher, and the corresponding MIC’s are 15.62-62.5 µg/mL. It should be noted that the compounds 4а, 4е, and 4l proved the best efficiency against Candida albicans, while the compound 4q ensured the highest antifungal activity against Aspergillus niger K 9 (MIC=15.62 µg/mL). These compounds may be used for further extended investigations in this field.

### Table 2. Antibacterial and antifungal activities of the synthesized compounds 4 a-r.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Staphylococcus aureus</th>
<th>Escherichia coli</th>
<th>Bacillus cereus</th>
<th>Candida albicans</th>
<th>Aspergillus niger</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>125</td>
<td>62.5</td>
<td>31.25</td>
<td>15.62</td>
<td>31.25</td>
</tr>
<tr>
<td>4b</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
<td>62.5</td>
</tr>
<tr>
<td>4c</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
<td>62.5</td>
</tr>
<tr>
<td>4d</td>
<td>125</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
<td>62.5</td>
</tr>
<tr>
<td>4e</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>15.62</td>
<td>31.25</td>
</tr>
<tr>
<td>4f</td>
<td>125</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4g</td>
<td>500</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4h</td>
<td>125</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4i</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4j</td>
<td>125</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4k</td>
<td>500</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
</tr>
<tr>
<td>4l</td>
<td>125</td>
<td>62.5</td>
<td>62.5</td>
<td>15.62</td>
<td>31.25</td>
</tr>
<tr>
<td>4m</td>
<td>125</td>
<td>62.5</td>
<td>125</td>
<td>62.5</td>
<td>31.25</td>
</tr>
<tr>
<td>4n</td>
<td>125</td>
<td>62.5</td>
<td>125</td>
<td>62.5</td>
<td>31.25</td>
</tr>
<tr>
<td>4o</td>
<td>125</td>
<td>62.5</td>
<td>62.5</td>
<td>31.25</td>
<td>31.25</td>
</tr>
</tbody>
</table>
Compounds | Staphylococcus aureus | Escherichia coli | Bacillus cereus | Candida albicans | Aspergillus niger
---|-----------------|-----------------|-----------------|-----------------|------------------|
4p | 125 | 62.5 | 31.25 | 31.25 | 31.25 |
4q | 125 | 62.5 | 62.5 | 31.25 | 13.62 |
4r | 125 | 62.5 | 62.5 | 31.25 | 31.25 |
Solvent (DMSO)* | + | + | + | + | + |
Control series** | 7.8 | 3.9 | 3.9 | 7.8 | 0.9 |

*proliferation of the bacteria takes place
** doxycycline was used as a reference for evaluating antibacterial activity [41], and Clotrimazole was used as a reference in the antifungal activity determination series [42].

3.4. Investigation of anti-inflammatory (anti-exudative) activity.

The anti-inflammatory (anti-exudative) activity of all synthesized compounds 4 a,b,d-f,h,j-l,n,p-r was investigated on the in vivo carrageenan model of the total edema of hind paws of albino rats [30]. All results of this investigation are shown in Table 3.

As seen from Table 3, 2-(pyridyloxy)imidazo[2,1-b][1,3]thiazines 4 a,b,d-f showed the highest activity among the entire series of the synthesized compounds. Their inflammation inhibition indexes were between 26.4 to 35.8 %, while the highest index, 39.1%, was found for the benzoannealed derivative 4q. This value is almost the same as that for the reference medicine. The anti-inflammatory activity of the other synthesized compounds was worse, and their inflammation inhibition indexes ranged between 3.7 to 21.8 %. Taking into account the relation “compound structure – anti-inflammatory activity”, one can note that the most active compound 4q consists of both benzo[4,5]imidazo[2,1-b][1,3]thiazine and 3,5-dichloropyridinyl elements.

Table 3. In vivo anti-inflammatory activity of compounds 4 a,b,d-f,h,j-l,n,p-r on carrageenan-induced paw edema in white rats (intraperitoneally use; doses: carrageenin 1%, 0.1 mL; Diclofenac sodium – 8 mg/kg, tested compounds – 50 mg/kg; M±m; n=6 in each group)

<table>
<thead>
<tr>
<th>Compounds/Reference drug, Doses</th>
<th>Rat hind limb volume increase,4 hours, %</th>
<th>Inflammation inhibition, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrageenin</td>
<td>122.9±10.8</td>
<td>-</td>
</tr>
<tr>
<td>Diclofenac sodium</td>
<td>65.9±5.3</td>
<td>46.3</td>
</tr>
<tr>
<td>4a</td>
<td>81.6</td>
<td>33.8</td>
</tr>
<tr>
<td>4b</td>
<td>82.1</td>
<td>33.2</td>
</tr>
<tr>
<td>4d</td>
<td>78.9</td>
<td>35.8</td>
</tr>
<tr>
<td>4e</td>
<td>84.8</td>
<td>31.0</td>
</tr>
<tr>
<td>4f</td>
<td>90.4</td>
<td>26.4</td>
</tr>
<tr>
<td>4h</td>
<td>96.2</td>
<td>21.7</td>
</tr>
<tr>
<td>4j</td>
<td>118.4</td>
<td>3.7</td>
</tr>
<tr>
<td>4k</td>
<td>114.9</td>
<td>6.5</td>
</tr>
<tr>
<td>4l</td>
<td>104.1</td>
<td>15.3</td>
</tr>
<tr>
<td>4n</td>
<td>105.8</td>
<td>13.9</td>
</tr>
<tr>
<td>4p</td>
<td>101.6</td>
<td>17.3</td>
</tr>
<tr>
<td>4q</td>
<td>74.8</td>
<td>39.1</td>
</tr>
<tr>
<td>4r</td>
<td>96.1</td>
<td>21.8</td>
</tr>
</tbody>
</table>

4. Conclusions

A new series of 6-(2-pyridinloyloxy)derivatives 4a-r was synthesized by the interaction between 3-hydroxy-3,4-dihydro-2H-(benzo)imidazo[2,1-b][1,3]thiazones 2a-c and the substituted 2-chloropyridines. The antibacterial, antifungal, and anti-inflammatory activity of all synthesized compounds were investigated, and the most active representatives were identified. The compounds 4a, 4e, and 4l proved the best efficiency against the fungi Candida albicans, while the compound 4q was found the most effective against Aspergillus niger K 9 (MIC=15.62 µg/ml). Besides, it has been shown that the benzoannealed derivative 4q can
inhibit carrageenan-induced inflammation with an efficiency of 39.1%. The results of in silico evaluation of the drug-like synthesized compounds are also reported.

**Funding**

This research received no external funding.

**Acknowledgments**

This research has no acknowledgment.

**Conflicts of Interest**

The authors declare no conflict of interest.

**References**


