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

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Abstract: A series of new 6-[(pyridine-2-yl)oxy]-6,7-dihydro-5*H*-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 ^{1}H NMR, ^{13}C 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-5*H*-imidazo[2,1-*b*][1,3]thiazine 4a, 6-[(3,5-dichloropyridin-2-yl)oxy]-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 4e and 6-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-2,3-diphenyl-6,7-dihydro-5*H*-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-2*H*-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-2*H*-(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.

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-artestines induced by Δ^9-THC (IC_{50} = 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].

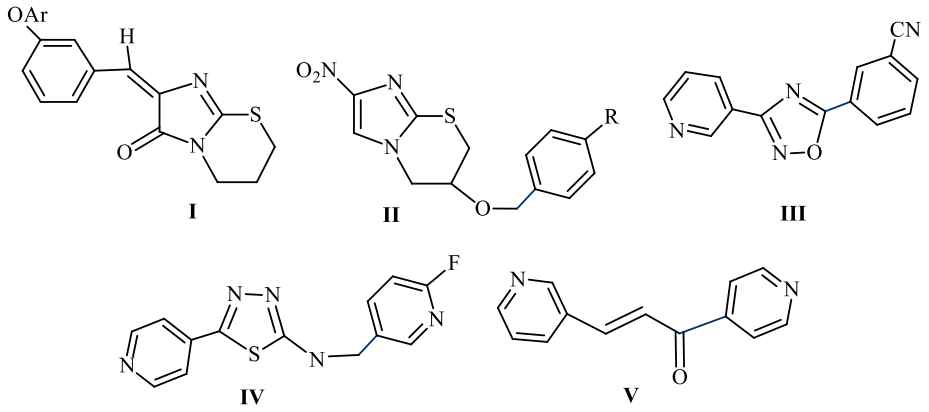


Figure 1. Some examples of the bioactive compounds containing the imidazo[2,1-*b*][1,3]thiazine cycle (I, II) and the pyridine fragments (III-V).

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. ^{1}H 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-5*H*-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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-ol (2a).

Yield 90 %; m.p.: 202-204 ºC. ^{13}C NMR: δ = 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 $C_6H_8N_2OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-ol (2b).

Yield 89 %; m.p.: 218-219 ºC. ^{13}C NMR: δ = 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 $C_{18}H_{16}N_2OS$, %: C, 70.10; H, 5.23; N, 9.08. Found, %: C, 70.25; H, 5.19; N, 9.17.

2.2.4. Procedure for the synthesis of 3-hydroxy-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine 2c.

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_2CO_3 in the dry DMF (30 mL). Then the mixture was heated to 60-70 ºC 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 ºC. ^{13}C NMR: δ = 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 $C_{10}H_{10}N_2OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4a).

Yield 55 %; m.p.: 150-151 ºC. ^{1}H NMR: δ = 8.25 (s, 1H, Ar), 7.83 (d, ^{3}J = 8.8 Hz, 1H, Ar), 7.16 (s, 1H, Ar), 6.90 (d, ^{3}J = 8.8 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 5.69-5.70 (m, 1H, CH), 4.32-4.33 (m, 2H, NCH_2), 3.57-3.60 (m, 1H, SCH_2), 3.47 (dd, ^{2}J = 13.2 Hz, ^{3}J = 5.4 Hz, 1H, SCH_2). ^{13}C NMR: δ = 160.80 (Py), 145.32 (Py), 140.04 (Py), 135.83 (C^{8a}), 128.20 (C^{2}), 124.54 (Py), 121.80 (C^{3}), 113.35 (Py), 65.33 (C^{6}), 48.56 (C^{5}), 28.86 (C^{7}). LC-MS: m/z = 268 [M+1] (100%). Anal. Calcd. for $C_{11}H_{10}ClN_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4b).

Yield 60 %; m.p.: 130-131 ºC. ^{1}H NMR: δ = 8.64 (s, 1H, Ar), 8.09 (d, ^{3}J = 8.8 Hz, 1H, Ar), 7.18 (s, 1H, Ar), 7.05 (d, ^{3}J = 8.4 Hz, 1H, Ar), 6.88 (s, 1H, Ar), 5.82-5.85 (m, 1H, CH), 4.37-4.38 (m, 2H, NCH_2), 3.61-3.65 (m, 1H, SCH_2), 3.52 (dd, ^{2}J = 13.4 Hz, ^{3}J = 5.4 Hz, 1H, SCH_2). ^{13}C NMR: δ = 168.58 (Py), 145.31 (q, $^{3}J_{CF}$ = 4.5 Hz, Py), 137.42 (q, $^{4}J_{CF}$ = 3.0 Hz, Py), 135.80 (C^{8a}), 128.21 (C^{2}), 124.42 (d, $^{1}J_{CF}$ = 270.0 Hz, CF_3), 121.82 (C^{3}), 119.93 (q, $^{2}J_{CF}$ = 33.0 Hz, Py), 112.45 (Py), 65.73 (C^{6}), 48.52 (C^{5}), 28.80 (C^{7}). LC-MS: m/z = 302 [M+1] (100%). Anal. Calcd. for $C_{12}H_{10}F_3N_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl)oxy]isonicotinonitrile (4c).

Yield 51 %; m.p.: 106-107 ºC. ^{1}H 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, NCH_2), 3.59-3.62 (m, 1H, SCH_2), 3.49 (dd, ^{2}J = 13.2 Hz, ^{3}J = 5.6 Hz, 1H, SCH_2). ^{13}C NMR: δ = 162.33 (Py), 149.07 (Py), 135.78 (C^{8a}), 128.22 (C^{2}), 122.80 (Py), 121.82 (C^{3}), 119.49 (Py), 116.82 (Py), 114.95 (CN), 65.68 (C^{6}), 48.53 (C^{5}), 28.77 (C^{7}). LC-MS: m/z = 259 [M+1] (100%). Anal. Calcd. for $C_{12}H_{10}N_4OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl)oxy]nicotinonitrile (4d).

Yield 58 %; m.p.: 182-183 ºC. ^{1}H NMR: δ = 8.74 (s, 1H, Ar), 8.18 (d, ^{3}J = 8.8 Hz, 1H, Ar), 7.17 (s, 1H, Ar), 7.04 (d, ^{3}J = 8.8 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 5.81-5.85 (m, 1H, CH), 4.35-4.36 (m, 2H, NCH_2), 3.60-3.64 (m, 1H, SCH_2), 3.44 (dd, ^{2}J = 13.6 Hz, ^{3}J = 5.2 Hz, 1H, SCH_2). ^{13}C NMR: δ = 164.24 (Py), 152.49 (Py), 143.20 (Py), 135.76 (C^{8a}), 128.24 (C^{2}), 121.82 (C^{3}), 117.59 (Py), 112.66 (Py), 103.11 (CN), 65.97 (C^{6}), 48.50 (C^{5}), 28.80 (C^{7}). LC-MS: m/z = 259 [M+1] (100%). Anal. Calcd. for $C_{12}H_{10}N_4OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4e).

Yield 59 %; m.p.: 163-164 ºC. ^{1}H 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, NCH_2), 3.58-3.61 (m, 1H, SCH_2), 3.46-3.50 (m, 1H, SCH_2). ^{13}C NMR: δ = 156.32 (Py), 143.54 (Py), 139.34 (Py), 135.82 (C^{8a}), 128.24 (C^{2}), 124.35 (Py), 121.78 (C^{3}), 118.58 (Py), 66.85 (C^{6}), 48.42 (C^{5}), 28.84 (C^{7}).

LC-MS: m/z = 302 [M+1] (100%). Anal. Calcd. for $C_{11}H_9Cl_2N_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4f).

Yield 62 %; m.p.: 113-114 °C. ^{1}H 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, NCH_2), 3.61-3.64 (m, 1H, SCH_2), 3.51 (dd, ^2J = 10.6 Hz, ^3J = 4.6 Hz, 1H, SCH_2). ^{13}C NMR: δ = 159.97 (Py), 143.26 (q, $^3J_{CF}$ = 3.75 Hz, Py), 136.87 (q, $^4J_{CF}$ = 2.5 Hz, Py), 135.78 (C^{8a}), 128.23 (C^2), 123.52 (d, $^1J_{CF}$ = 270.0 Hz, CF_3), 121.79 (C^3), 120.83 (q, $^2J_{CF}$ = 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 $C_{12}H_9ClF_3N_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4g).

Yield 58 %; m.p.: 152-153 °C. ^{1}H 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), 5.67-5.71 (m, 1H, CH), 4.10-4.14 (m, 1H, NCH_2), 3.89-3.92 (m, 1H, NCH_2), 3.59-3.62 (m, 1H, SCH_2), 3.50-3.54 (m, 1H, SCH_2). ^{13}C NMR: δ = 160.32 (Py), 144.85 (Py), 139.61 (Py), 136.61 (C^{8a}), 136.39 (C^3), 134.23, 130.57, 129.80 (Ar), 129.42 (C^2), 129.13, 128.80, 128.10, 126.24, 125.98 (Ar), 124.17, 112.97 (Py), 65.14 (C^6), 46.91 (C^5), 28.05 (C^7). LC-MS: m/z = 420 [M+1] (100%). Anal. Calcd. for $C_{23}H_{18}ClN_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4h).

Yield 67 %; m.p.: 154-155 °C. ^{1}H 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, NCH_2), 3.92-3.95 (m, 1H, NCH_2), 3.62-3.64 (m, 1H, SCH_2), 3.53-3.57 (m, 1H, SCH_2). ^{13}C NMR: δ = 164.49 (Py), 145.22 (q, $^3J_{CF}$ = 4.5 Hz, Py), 137.38 (q, $^4J_{CF}$ = 3.0 Hz, Py), 137.01 (C^{8a}), 136.83 (C^3), 134.62, 130.97, 130.19 (Ar), 129.85 (C^2), 129.54, 129.22, 128.51, 126.67, 126.40 (Ar), 124.39 (d, $^1J_{CF}$ = 270.0 Hz, CF_3), 119.95 (q, $^2J_{CF}$ = 33.0 Hz, Py), 112.47 (Py), 65.92 (C^6), 47.33 (C^5), 28.40 (C^7). LC-MS: m/z = 454 [M+1] (100%). Anal. Calcd. for $C_{24}H_{18}F_3N_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl)oxy]isonicotinonitrile (4i).

Yield 63 %; m.p.: 184-185 °C. ^{1}H 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, NCH_2), 3.90-3.94 (m, 1H, NCH_2), 3.62-3.65 (m, 1H, SCH_2), 3.51-3.56 (m, 1H, SCH_2). ^{13}C NMR: δ = 162.31 (Py), 149.05 (Py), 137.03 (C^{8a}), 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 $C_{24}H_{18}N_4OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazin-6-yl)oxy]nicotinonitrile (4j).

Yield 57 %; m.p.: 235-236 °C. ^{1}H NMR: δ = 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: δ = 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 $C_{24}H_{18}N_4OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4k).

Yield 61 %; m.p.: 165-166 °C. ^{1}H NMR: δ = 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: δ = 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 $C_{23}H_{17}Cl_2N_3OS$, %: 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-5*H*-imidazo[2,1-*b*][1,3]thiazine (4l).

Yield 66 %; m.p.: 159-160 °C. ^{1}H NMR: δ = 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: δ = 159.47 (Py), 142.79 (q, $^3J_{CF}$ = 3.75 Hz, Py), 136.65 (C^{8a}+C^3), 136.45 (q, $^4J_{CF}$ = 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, $^2J_{CF}$ = 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 $C_{24}H_{17}ClF_3N_3OS$, %: 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-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (4m).

Yield 60 %; m.p.: 144-145 °C. ^{1}H NMR: δ = 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: δ = 160.72 (Py), 146.30 (C^{10a}), 145.34 (Py), 143.04 (C^{9a}), 140.08 (Py), 136.20 (C^{5a}), 124.63 (Py), 122.41 (C^8), 121.46 (C^7), 117.58 (C^9), 113.36 (Py), 109.23 (C^6), 64.64 (C^3), 46.61 (C^4), 28.54 (C^2). LC-MS: m/z = 318 [M+1] (100%). Anal. Calcd. for $C_{15}H_{12}ClN_3OS$, %: C, 56.69; H, 3.81; N, 13.22. Found, %: C, 56.68; H, 3.77; N, 13.34.

2.2.19. 3-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (4n).

Yield 67 %; m.p.: 140-141 °C. ^{1}H NMR: δ = 8.66 (s, 1H, Ar), 8.08 (d, ^{3}J = 9.2 Hz, 1H, Ar), 7.48 (d, ^{3}J = 7.6 Hz, 1H, Ar), 7.43-7.45 (m, 1H, Ar), 7.13-7.19 (m, 2H, Ar), 7.05 (d, ^{3}J = 8.4 Hz, 1H, Ar), 6.87 (s, 1H, Ar), 6.00-6.04 (m, 1H, CH), 4.57-4.61 (m, 1H, NCH_2), 4.48-4.52 (m, 1H, NCH_2), 3.75-3.78 (m, 1H, SCH_2), 3.66 (dd, ^{2}J = 13.4 Hz, ^{3}J = 5.4 Hz, 1H, SCH_2). ^{13}C NMR: δ = 164.50 (Py), 146.24 (C^{10a}), 145.33 (q, $^{3}J_{CF}$ = 4.5 Hz, Py), 143.05 (C^{9a}), 137.47 (q, $^{4}J_{CF}$ = 3.0 Hz, Py), 136.20 (C^{5a}), 124.42 (d, $^{1}J_{CF}$ = 270.0 Hz, CF_3), 122.42 (C^{8}), 121.47 (C^{7}), 120.02 (q, $^{2}J_{CF}$ = 33.0 Hz, Py), 117.61 (Py), 112.47 (C^{9}), 109.25 (C^{6}), 65.06 (C^{3}), 46.59 (C^{4}), 28.48 (C^{2}). LC-MS: m/z = 352 [M+1] (100%). Anal. Calcd. for $C_{16}H_{12}F_3N_3OS$, %: C, 54.70; H, 3.44; N, 11.96. Found, %: C, 54.88; H, 3.47; N, 11.84.

2.2.20. 2-[(3,4-Dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazin-3-yl)oxy]isonicotinonitrile (4o).

Yield 56 %; m.p.: 109-110 °C. ^{1}H 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, NCH_2), 4.47-4.50 (m, 1H, NCH_2), 3.73-3.77 (m, 1H, SCH_2), 3.61-3.66 (m, 1H, SCH_2). ^{13}C NMR: δ = 161.85 (Py), 148.68 (Py), 145.81 (C^{10a}), 142.64 (C^{9a}), 135.78 (C^{5a}), 122.42 (Py), 122.01 (C^{8}), 121.06 (C^{7}), 119.17 (C^{6}), 117.20 (C^{9}), 116.38 (CN), 114.56 (Py), 108.83 (Py), 64.61 (C^{3}), 46.17 (C^{4}), 28.06 (C^{2}). LC-MS: m/z = 309 [M+1] (100%). Anal. Calcd. for $C_{16}H_{12}N_4OS$, %: C, 62.32; H, 3.92; N, 18.17. Found, %: C, 62.19; H, 3.93; N, 18.25.

2.2.21. 6-[(3,4-Dihydro-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazin-3-yl)oxy]nicotinonitrile (4p).

Yield 59 %; m.p.: 161-162 °C. ^{1}H 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, NCH_2), 4.46-4.48 (m, 1H, NCH_2), 3.73-3.75 (m, 1H, SCH_2), 3.61-3.63 (m, 1H, SCH_2). ^{13}C NMR: δ = 164.14 (Py), 152.49 (Py), 146.19 (C^{10a}), 143.14 (Py), 143.01 (C^{9a}), 136.16 (C^{5a}), 122.45 (C^{8}), 121.51 (C^{7}), 117.62 (Py), 117.60 (Py), 112.66 (C^{9}), 109.24 (C^{6}), 103.19 (CN), 65.26 (C^{3}), 46.56 (C^{4}), 28.48 (C^{2}). LC-MS: m/z = 309 [M+1] (100%). Anal. Calcd. for $C_{16}H_{12}N_4OS$, %: 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-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (4q).

Yield 62 %; m.p.: 203-204 °C. ^{1}H 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, NCH_2), 4.54-4.56 (m, 1H, NCH_2), 3.70-3.73 (m, 1H, SCH_2), 3.58-3.62 (m, 1H, SCH_2). ^{13}C NMR: δ = 155.81 (Py), 145.83 (C^{10a}), 143.32 (Py), 142.64 (C^{9a}), 138.89 (Py), 135.78 (C^{5a}), 124.04 (Py), 121.99 (C^{8}), 121.05 (C^{7}), 118.19 (Py), 117.20 (C^{9}), 108.87 (C^{6}), 65.63 (C^{3}), 46.07 (C^{4}), 28.06 (C^{2}). LC-MS: m/z = 352 [M+1] (100%). Anal. Calcd. for $C_{15}H_{11}Cl_2N_3OS$, %: 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-2*H*-benzo[4,5]imidazo[2,1-*b*][1,3]thiazine (4r).

Yield 65 %; m.p.: 165-166 °C. ^{1}H 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, NCH_2), 4.51-4.54 (m, 1H, NCH_2), 3.74-3.77 (m, 1H, SCH_2), 3.63-3.67 (m, 1H, SCH_2). ^{13}C NMR: δ = 159.87 (Py), 146.19 (C^{10a}), 143.34 (q, $^{3}J_{CF}$ = 3.75 Hz, Py), 143.05 (C^{9a}), 136.97 (q, $^{4}J_{CF}$ = 2.5 Hz, Py), 136.19 (C^{5a}), 123.52 (d, $^{1}J_{CF}$ = 270.0 Hz, CF_3), 122.42 (C^{8}), 121.47 (C^{7}), 120.92 (q, $^{2}J_{CF}$ = 33.75 Hz, Py), 118.68 (Py), 117.63 (C^{9}), 109.31 (C^{6}), 66.54 (C^{3}), 46.50 (C^{4}), 28.27 (C^{2}). LC-MS: m/z = 386 [M+1] (100%). Anal. Calcd. for $C_{16}H_{11}ClF_3N_3OS$, %: 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:

$$\text{Inhibition}, \% = \frac{\Delta V control - \Delta V experiment}{\Delta V control} * 100\ \%$$

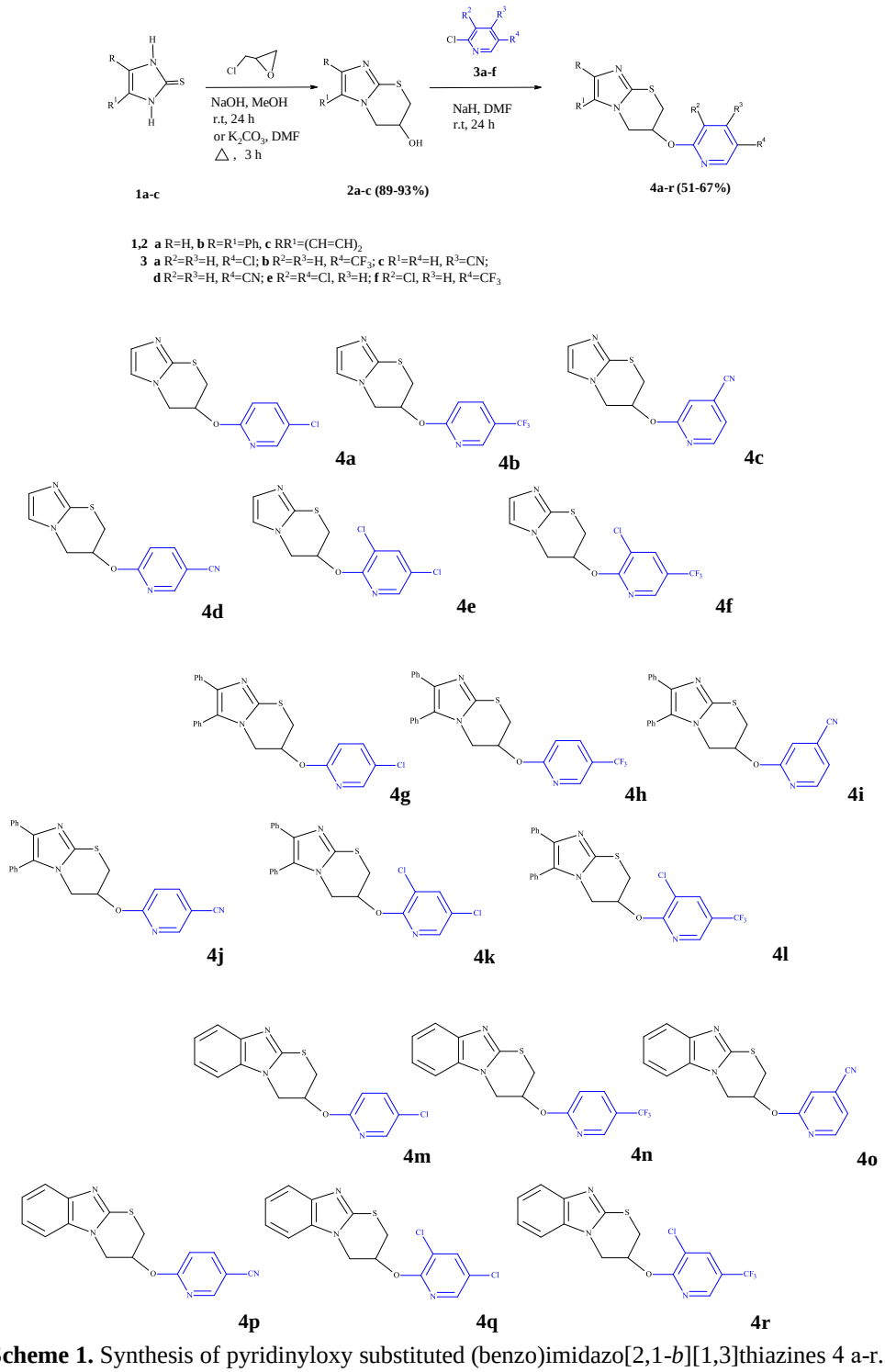
where ΔV*control* and ΔV*experiment* – the mean values of the volume difference for control and experimental animals hinds respectively.

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-5*H*-imidazo[2,1-*b*][1,3]thiazines 4a-l 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-l 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.

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

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

Compounds	*Staphylococcus aureus*	*Escherichia coli*	*Bacillus cereus*	*Candida albicans*	*Aspergillus niger*
	MIK (µg/ml)				
4a	125	62.5	31.25	15.62	31.25
4b	62.5	62.5	31.25	31.25	62.5
4c	62.5	62.5	31.25	31.25	62.5
4d	125	62.5	31.25	31.25	62.5
4e	62.5	62.5	31.25	15.62	31.25
4f	125	31.25	31.25	31.25	31.25
4g	500	62.5	62.5	31.25	31.25
4h	125	62.5	62.5	31.25	31.25
4i	62.5	62.5	31.25	31.25	31.25
4j	125	62.5	62.5	31.25	31.25
4k	500	62.5	62.5	31.25	31.25
4l	125	62.5	62.5	15.62	31.25
4m	125	62.5	125	62.5	31.25
4n	125	62.5	125	62.5	31.25
4o	125	62.5	62.5	31.25	31.25

Compounds	*Staphylococcus aureus*	*Escherichia coli*	*Bacillus cereus*	*Candida albicans*	*Aspergillus niger*
	MIK (µg/ml)				
4p	125	62.5	31.25	31.25	31.25
4q	125	62.5	62.5	31.25	15.62
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)

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

4. Conclusions

A new series of 6-(2-pyridinyloxy)derivatives 4a-r was synthesized by the interaction between 3-hydroxy-3,4-dihydro-2*H*-(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.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Shaveta; Mishra, S.; Singh, P. Hybrid molecules: The privileged scaffolds for various pharmaceuticals. *Eur. J. Med. Chem.* **2016**, *124*, 500-536, https://doi.org/10.1016/j.ejmech.2016.08.039.
2. Muhammad, Z.A.; Farghaly, T.A.; Althagafi, I.; Al-Hussain, S.A.; Zaki, M.E.A.; Harras, M.F. Synthesis of antimicrobial azoloazines and molecular docking for inhibiting COVID-19. *J. Het. Chem.* **2021**, *58*, 1286-1301, https://doi.org/10.1002/jhet.4257.
3. Ulomskiy, E.N.; Ivanova, A.V.; Gorbunov, E.B.; Esaulkova, I.L.; Slita, A.V.; Sinegubova, E.O.; Voinkov, E.K.; Drokin, R.A.; Butorin, I.I.; Gazizullina, E.R.; Gerasimova, E.L.; Zarubaev, V.V.; Rusinov, V.L. Synthesis and biological evaluation of 6-nitro-1,2,4-triazoloazines containing polyphenol fragments possessing antioxidant and antiviral activity. *Bioorg. Med. Chem. Lett.* **2020,** *30*, https://doi.org/10.1016/j.bmcl.2020.127216.
4. Abdel-Mohsen, H.T.; Abood, A.; Flanagan, K.J.; Meindl, A.; Senge, M.O.; El Diwani, H.I. Synthesis, crystal structure, and ADME prediction studies of novel imidazopyrimidines as antibacterial and cytotoxic agents. *Arch. Pharm.* **2020,** *353*, https://doi.org/10.1002/ardp.201900271.
5. Alizadeh, S.R.; Ebrahimzadeh, M.A. Pyrazolotriazines: Biological activities, synthetic strategies and recent developments. *Eur. J. Med. Chem.* **2021,** *223*, https://doi.org/10.1016/j.ejmech.2021.113537.
6. Bernat, Z.; Szymanowska, A.; Kciuk, M.; Kotwica-Mojzych, K.; Mojzych, M. Review of the Synthesis and Anticancer Properties of Pyrazolo[4,3-*e*][1,2,4]triazine Derivatives. *Molecules* **2020,** *25*, https://doi.org/10.3390/molecules25173948.
7. Aouad, M.R.; Al-Mohammadi, H.M.; Al-blewi, F.F.; Ihmaid, S.; Elbadawy, H.M.; Althagfan, S.S.; Rezki, N. Introducing of acyclonucleoside analogues tethered 1,2,4-triazole as anticancer agents with dual epidermal growth factor receptor kinase and microtubule inhibitors. *Bioorg. Chem.* **2020,** *94*, https://doi.org/10.1016/j.bioorg.2019.103446.
8. Al-azmi, A. Pyrazolo[1,5-*a*]pyrimidines: A Close Look into their Synthesis and Applications. *Curr. Org. Chem.* **2019**, *23*, 721-743, https://doi.org/10.2174/1385272823666190410145238.
9. Maji, P.K. Synthesis of Pyrimidine-Annulated Five-Membered Heterocycles: An Overview. *Curr. Org. Chem.* **2019**, *23*, 2204-2269, https://doi.org/10.2174/1385272823666191019111627.
10. Radini, A.M.; Abdel-Wahab, B.F.; Khidre, R.E. Synthetic routes to imidazothiazines. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191*, 844-856, https://doi.org/10.1080/10426507.2015.1119148.
11. Tales A.C.Goulart, T.A.C.; Kazmirski, J.A.G.; Back, D.F.; Zeni, G. Cyclization of Thiopropargyl Benzimidazoles by Combining Iron(III) Chloride and Diorganyl Diselenides. *J. Org. Chem.* **2019,** *84*, 14113-14126, https://doi.org/10.1021/acs.joc.9b02276.
12. Schoeder, C.T.; Kaleta, M.; Mahardhika, A.B.; Olejarz-Maciej, A.; Łażewska, D.; Kieć-Kononowicz, K.; Müller, C.E. Structure-activity relationships of imidazothiazinones and analogs as antagonists of the cannabinoid-activated orphan G protein-coupled receptor GPR18. *Eur. J. Med. Chem.* **2018**, *155*, 381-397, https://doi.org/10.1016/j.ejmech.2018.05.050.
13. Gong, J.-X.; Cui, Y. He, Z.-L.; Guo, Y.-W. Synthesis, spectral characterization, and antituberculosis activity of thiazino[3,2-*a*]benzimidazole derivatives. *Phosphorus, Sulfur, Silicon.* **2016**, *191*, 1036-1041, https://doi.org/10.1080/10426507.2015.1135149.
14. Kim, P.; Kang, S.; Boshoff, H.I.; Jiricek, J.; Collins, M.; Singh, R.; Manjunatha, U.H.; Niyomrattanakit, P.; Patel, S.; Zhang, L.; Goodwin, M.; Dick, T.; Keller, T.H.; Dowd, C.S.; Barry, C.E. Structure-Activity Relationships of Antitubercular Nitroimidazoles. 2. Determinants of Aerobic Activity and Quantitative Structure−Activity Relationships. *J. Med. Chem.* **2009**, *52*, 1329-1344, https://doi.org/10.1021/jm801374t.

15. Thompson, A.M.; Marshall, A.J.; Maes, L.; Yarlett, N.; Bacchi, C.J. Assessment of a pretomanid analogue library for African trypanosomiasis: Hit-to-lead studies on 6-substituted 2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]thiazine 8-oxides. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 207-213, https://doi.org/10.1016/j.bmcl.2017.10.067.
16. Thompson, A.M.; O'Connor, P.D.; Marshall, A.J.; Francisco, A.F.; Kelly, J.M.; Riley, J.; Read, K.D.; Perez, C.J.; Cornwall, S.; Thompson, R.C.A.; Keenan, M.; White, K.L.; Charman, S.A.; Zulfiqar, B.; Sykes, M.L.; Avery, V.M.; Chatelain, E.; Denny, W.A. Re-evaluating pretomanid analogues for Chagas disease: Hit-to-lead studies reveal both in vitro and in vivo trypanocidal efficacy. *Eur. J. Med. Chem.* **2020**, *207*, https://doi.org/10.1016/j.ejmech.2020.112849.
17. Cordeiroa, N.D.M.; Freitas, Rosana H.C.N.; Fragab, C.A.M.; Fernandesa, P.D. New 2-amino-pyridinyl-N-acylhydrazones: Synthesis and identification of their mechanism of anti-inflammatory action. *Biomedicine and Pharmacotherapy* **2020**, *123*, https://doi.org/10.1016/j.biopha.2019.109739.
18. Leoni, A.; Frosini, M.; Locatelli, A.; Micucci, M.; Carotenuto, C.; Durante, M.; Cosconati, S.; Budriesi, R. 4-Imidazo[2,1-*b*]thiazole-1,4-DHPs and neuroprotection: preliminary study in hits searching. *Eur. J. Med. Chem.* **2019**, *169*, 89-102, https://doi.org/10.1016/j.ejmech.2019.02.075.
19. Bai, H.; Liu, X.; Chenzhang, P.; Xiao, Y.; Fu, B.; Qin, Z. Design, Synthesis and Fungicidal Activity of New 1,2,4-Triazole Derivatives Containing Oxime Ether and Phenoxyl Pyridinyl Moiety. *Molecules* **2020**, *25*, 5852-5864, https://doi.org/10.3390/molecules25245852.
20. Ticona, L.A.; Sánchez, Á.R.; Gonzáles, Ó.O.; Doménech, M.O. Antimicrobial compounds isolated from Tropaeolum tuberosum. *Natural Product Research.* **2020**, 1-5, https://doi.org/10.1080/14786419.2019.1710700.
21. Freitas, R.H.C.N.; Barbosa, J.M.C.; Bernardino, P.; Sueth-Santiago, V.; Wardell, S.M.S.V.; Wardell, J.L.; Decoté-Ricardo, D.; Melo, T.G.; da Silvah E.F.; Salomão, K.; Fraga, C.A.M. Synthesis and trypanocidal activity of novel pyridinyl-1,3,4-thiadiazole derivatives. *Biomedicine and Pharmacotherapy.* **2020**, *127*, https://doi.org/10.1016/j.biopha.2020.110162.
22. Kotowski, K.; Supplitt, S.; Wiczew, D.; Przystupski, D.; Bartosik, W.; Saczko, J.; Rossowska, J.; Drąg-Zalesińska, M.; Michel, O.; Kulbacka, J. 3PO as a Selective Inhibitor of 6-Phosphofructo2-Kinase/Fructose-2,6-Biphosphatase 3 in A375 Human Melanoma Cells. *Anticancer Research.* **2020**, *40*, 2613-2625, https://doi.org/10.21873/anticanres.14232.
23. Al-Hadhrami, N.A.; Ladwig, A.; Rahman, A.; Rozas, I.; Malthouse, J.P.G.; Evans, P. Synthesis of 2-Guanidinyl Pyridines and their Trypsin Inhibition and Docking. *Bioorg. Med. Chem.* **2020**, *28*, https://doi.org/10.1016/j.bmc.2020.115612.
24. Reddy, N.; Shungube, M.; Arvidsson, P.I.; Baijnath, S.; Kruger, H.G. Govender, T.; Naicker, T. A 2018-2019 patent review of metallo betalactamase inhibitors. Expert *Opinion on Therapeutic Patents.* **2020**, *30*, 541-555, https://doi.org/10.1080/13543776.2020.1767070.
25. Ritawidya, R.; Ludwig, F-A.; Briel, D.; Brust, P.; Scheunemann, M. Synthesis and In Vitro Evaluation of 8-Pyridinyl-Substituted Benzo[*e*]imidazo[2,1-*c*][1,2,4]triazines as Phosphodiesterase 2A Inhibitors. *Molecules.* **2019**, *24*, 2791-2811, https://doi.org/10.3390/molecules24152791.
26. Álvarez, R.; Aramburu, L.; Gajate, C.; Vicente-Blázquez, A.; Mollinedo, F.; Medarde, M.; Peláez, R. Methylsulfanylpyridine based diheteroaryl isocombretastatin analogs as potent anti-proliferative agents. *Eur. J. Med. Chem.* **2021**, *209*, https://doi.org/10.1016/j.ejmech.2020.112933.
27. Mironov, M.E.; Oleshko, O.S.; Pokrovskii, M.A.; Rybalova, T.V.; Pechurov, V.K.; Pokrovskii, A.G.; Cheresis, S.V.; Mishinov, S.V.; Vyacheslav V.Stupak, V.V.; Shults, E.E. 6-(4′-Aryl-1′,2′,3′-triazolyl)-spirostan-3,5-diols and 6-(4′-Aryl-1′,2′,3′-triazolyl)-7-hydroxyspirosta-1,4-dien-3-ones: Synthesis and analysis of their cytotoxicity. *Steroids.* **2019**, *151*, https://doi.org/10.1016/j.steroids.2019.108460.
28. Armarego W.L.F.; Chai C. *Purification of Laboratory Chemicals*. 7th ed.: Elsevier: Oxford, UK, **2013**; pp. 1-1024, https://doi.org/10.1016/C2009-0-64000-9.
29. Yakovychuk N.D.; Deyneka S.Y.; Grozav A.M.; Humenna A.V.; Popovych V.B.; Djuiriak V.S. Antifungal activity of 5-(2-nitrovinyl) imidazoles and their derivatives against the causative agents of vulvovaginal candidiasis. *Regulatory Mechanisms in Biosystems* **2018**, *9*, 369-373, https://doi.org/10.15421/021854.
30. Winter, C.A.; Risley, E.A.; Nuss, G.W. Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544-547, https://doi.org/10.3181/00379727-111-27849.
31. Thompson, A.M.; Sutherland, H.S.; Palmer, B.D.; Kmentova, I.; Blaser, A.; Franzblau, S.G.; Wan, B.; Wang, Y.; Ma, Z.; Denny, W.A. Synthesis and structure-activity relationships of varied ether linker analogues of the antitubercular drug (6S)-2-nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5h-imidazo[2,1-b][1,3]oxazine (PA-824). *J. Med. Chem.* **2011**, *54*, 6563-6585, https://doi.org/10.1021/jm200377r.
32. Liu, G.; Campbell, B.T.; Holladay, M.W.; Julia M. Ford Pulido, J.M.; Hua, H.; Gitnick, D.; Gardner, M.F.; James, J.; Breider, M.A.; Brigham, D.; Belli, B.; Armstrong, R.C.; Treiber, D.K. Discovery of AC710, a Globally Selective Inhibitor of Platelet-Derived Growth Factor Receptor-Family Kinases. *ACS Med. Chem. Lett.* **2012**, *3*, 997-1002, https://doi.org/10.1021/ml300214g.

33. Hwang, S.H.; Wecksler, A.T.; Zhang, G.; Morisseau, C.; Nguyen, L.V.; Fu, S.H.; Hammock, B.D. Synthesis and biological evaluation of sorafenib- and regorafenib-like sEH inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3732-3737, https://doi.org/10.1016/j.bmcl.2013.05.011.
34. Sato, K.; Sugimoto, H.; Rikimaru, K.; Imoto, H.; Kamaura, M.; Negoro, N.; Tsujihata, Y.; Miyashita, H.; Odani, T.; Murata, T. Discovery of a novel series of indoline carbamate and indolinylpyrimidine derivatives as potent GPR119 agonists. *Bioorg. Med. Chem.* **2014**, *22*, 1649-1666, https://doi.org/10.1016/j.bmc.2014.01.028.
35. Han, S.; Narayanan, S.; Kim, S.H.; Calderon, I.; Zhu, X.; Kawasaki A.; Yue D.; Lehmann, J.; Wong, A.; Buzard, D.J.; Semple, G.; Carroll, C.; Chu, Z.L.; Al-Sharmma, H.; Shu, H.H.; Tung, S.F.; Unett, D.J.; Behan, D.P.; Yoon, W.H.; Morgan, M.; Usmani, K.A.; Chen, C.; Sadeque, A.; Leonard, J.N.; Jones, R.M. Discovery of a novel *trans*-1,4-dioxycyclohexane GPR119 agonist series. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3034-3038, https://doi.org/10.1016/j.bmcl.2015.04.102.
36. McDermott, L.A.; Iyer, P.; Vernetti, L.; Rimer, S.; Sun, J.; Boby, M.; Yang, T.; Fioravanti, M.; O'Neill, J.; Wang, L.; Drakes, D.; Katt, W.; Huang, Q.; Cerione, R. Design and evaluation of novel glutaminase inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 1819-1839, https://doi.org/10.1016/j.bmc.2016.03.009.
37. Alper, H.; Keung, E.C.H. New synthesis of the 1,3-thiazine ring system. *J Org Chem.* **1972**, *37*, 1464-1466, https://doi.org/10.1021/jo00974a047.
38. SwissADME. Available online: http://www.swissadme.ch/ (accessed on 28/04/2021).
39. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. **2001**, *46*, 3-26, https://doi.org/10.1016/s0169-409x(00)00129-0.
40. Moriguchi, I.; Hirono, S.; Nakagome, I.; Hirano, H. Comparison of Reliability of log P Values for Drugs Calculated by Several Methods. *Chem. Pharm. Bull*. **1994**, *42*, 976-978, https://doi.org/10.1248/cpb.42.976.
41. Sloan, B.; Scheinfeld, N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. *Expert Opin Drug Saf*. **2008**, *7*, 571-577, https://doi.org/10.1517/14740338.7.5.571.
42. Crowley, P.D.; Gallagher, H.C. Clotrimazole as a pharmaceutical: past, present and future. *J. Appl. Microbiol.* **2014**, *117*, 611-617, https://doi.org/10.1111/jam.12554.