chemistry proceedings

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Proceeding Paper

Synthetic Approach to Diversified Imidazo[2,1-*b*][1,3]thiazines and Its Evaluation as Non-Steroidal Anti-Inflammatory Agents †

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† Presented at the 25th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2021; Available online: https://ecsoc-25.sciforum.net/.

Abstract: The present work is devoted to the synthesis of imidazo[2,1-*b*][1,3]thiazine derivatives as possible anti-inflammatory agents. The synthetic approach to (2-pyridinyloxy) substituted imidazo[2,1-*b*][1,3]thiazines based on the interaction of the polysubstituted 2-chloropyridines with 3-hydroxy-imidazo[2,1-*b*][1,3]thiazines was proposed. Selective nucleophilic substitution in position 2 of a pyridine ring was observed in the mentioned reaction. The synthesized (2-pyridinyloxy) substituted imidazo[2,1-*b*][1,3]thiazines drug-like properties were studied in silico using SwissADME and anti-inflammatory activity in the carrageenan test in vivo. Hit-compounds with satisfactory drug-like and pharmacological features were identified as promising objects for forthcoming structure optimization and in-depth studies.

Keywords: imidazo[2,1-*b*][1,3]thiazine; pyridine; small molecules; alkylation; drug-like; anti-inflammatory activity; NSAIDs

Citation: Slyvka, N.; Holota, S.; Saliyeva, L.; Vovk, M. Synthetic Approach to Diversified Imidazo[2,1-*b*][1,3]thiazines and Its Evaluation as Non-Steroidal Anti-Inflammatory Agents. *Chem. Proc.* **2022**, *8*, 82. https://doi.org/10.3390/ecsoc-25-11692

Academic Editor: Julio A. Seijas

Published: 14 November 2021

1. Introduction

Imidazo[2,1-*b*][1,3]thiazine scaffold is the attractive matrix for the design of small molecules with a wide activity spectrum. The application of modern drug design methodologies and strategies allowed the identification of the mentioned heterocycles' potential agents with trypanocidal [1,2], anti-tuberculosis [3–5], antioxidant [6] antiviral [7,8], antitumor [9] and antifungal [10] activities (Figure 1).

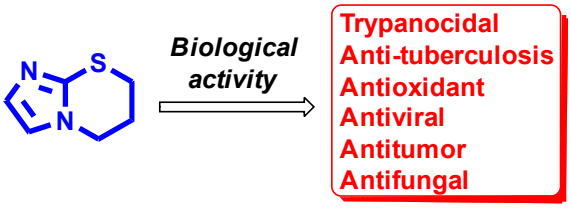


Figure 1. Pharmacology profile of imidazo[2,1-*b*][1,3]thiazine scaffold.

Inflammation is an important part of many pathology processes and an attractive pathway/target in modern drug design for the modulation and obtaining of the appropriate and satisfactory therapeutic effects [11–13].

Taking into account the synthesis of the hybrid molecules containing two or more pharmacophores is a promising and interesting approach to the design of potential pharmacological active small molecules, it was interesting to work out the straightforward

and convenient protocol for the synthesis of new hybrid molecules containing diversified imidazo[2,1-*b*][1,3]thiazine scaffolds linked with a potential pharmacophore–pyridine ring and evaluate their drug-like and anti-inflammatory properties.

2. Methods

2.1. General Information

Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus (BÜCHI Labortechnik AG, Flawil, Switzerland) and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin–Elmer 2400 CHN analyzer (PerkinElmer, Waltham, MA, USA) and were within ±0.4% of the theoretical values. The 400 MHz-^{1}H and 126 MHz-^{13}C spectra were recorded on a Varian Unity Plus 400 (400 MHz) spectrometer (Varian Inc., Paulo Alto, CA, USA). All spectra were recorded at room temperature except where indicated otherwise and were referenced internally to solvent reference frequencies. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are reported in Hz. LC–MS spectra were obtained on a Finnigan MAT INCOS-50 (Thermo Finnigan LLC, San Jose, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (Merck Kieselgel 60 F_{254}). Solvents and reagents that are commercially available were used without further purification. The 3-hydroxy-imidazo[2,1-*b*][1,3]thiazines **2a**–**c** were prepared using the similar protocol described in [5].

2.2. Synthesis and Characterization of Compounds **3a**–**m**

To the mixture of compounds **2a**–**c** and a 60% NaH in mineral oil (10 mmol) in the dry DMF (4 mL), 10 mmol of the appropriate substituted derivate of 2-chloropiridine was added 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.

*6-[(5-Chloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3a***).* M.p.: 150–151 °C. ^{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.

*6-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3b***).* M.p.: 130–131 °C. ^{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.

*6-[(6,7-Dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl)oxy]nicotinonitrile (***3c***).* M.p.: 182–183 °C. ^{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.

*6-[(3,5-Dichloropyridin-2-yl)oxy]-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3d***).* M.p.: 163–164 °C. ^{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.

*6-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3e***).* 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.

*2,3-Diphenyl-6-{[5-(trifluoromethyl)pyridin-2-yl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3f***).* 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.

*6-[(2,3-Diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazin-6-yl)oxy]nicotinonitrile (***3g***).* 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.

*6-[(3,5-Dichloropyridin-2-yl)oxy]-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine (***3h***).* 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; N, 9.25. Found, %: C, 60.94; H, 3.73; N, 9.16.

*6-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-2,3-diphenyl-6,7-dihydro-5H-imidazo[2,1-b][1,3] thiazine (***3i***).* 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.

*3-{[5-(Trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine (***3j***).* M.p.: 140–141 °C. ^{1}H NMR: δ = 8.66 (s, 1H, Ar), 8.08 (d, ^3J = 9.2 Hz, 1H, Ar), 7.48 (d, ^3J = 7.6 Hz, 1H, Ar), 7.43–7.45 (m, 1H, Ar), 7.13–7.19 (m, 2H, Ar), 7.05 (d, ^3J = 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, ^2J = 13.4 Hz, ^3J = 5.4 Hz, 1H, SCH_2). ^{13}C NMR: δ = 164.50 (Py), 146.24 (C^{10a}), 145.33 (q, $^3J_{CF}$ = 4.5 Hz, Py), 143.05 (C^{9a}), 137.47 (q, $^4J_{CF}$ = 3.0 Hz, Py), 136.20 (C^{5a}), 124.42 (d, $^1J_{CF}$ = 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 $C_{16}H_{12}F_{3}N_{3}OS$, %: C, 54.70; H, 3.44; N, 11.96. Found, %: C, 54.88; H, 3.47; N, 11.84.

*6-[(3,4-Dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazin-3-yl)oxy]nicotinonitrile (***3h***).* 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 $C_{16}H_{12}N_{4}OS$, %: C, 62.32; H, 3.92; N, 18.17. Found, %: C, 62.45; H, 3.89; N, 18.29.

*3-[(3,5-dichloropyridin-2-yl)oxy]-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3]thiazine (***3l***).* 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 $C_{15}H_{11}Cl_{2}N_{3}OS$, %: C, 51.15; H, 3.15; N, 11.93. Found, %: C, 51.36; H, 3.11; N, 11.82.

*3-{[3-Chloro-5-(trifluoromethyl)pyridin-2-yl]oxy}-3,4-dihydro-2H-benzo[4,5]imidazo[2,1-b][1,3] thiazine (***3m***).* 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 $C_{16}H_{11}ClF_{3}N_{3}OS$, %: C, 49.81; H, 2.87; N, 10.89. Found, %: C, 50.01; H, 2.89; N, 10.97.

2.3. Anti-Inflammatory (Anti-Exudative) Activity

The male albino rats, weighing 180–220 g, were used for the anti-exudative activity studies. 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, Lviv, Ukraine, protocol No.10, 17 March 2021. The carrageenin-induced hind paw edema was produced by the method of Winter et al. [14]. The synthesized compounds were intraperitoneally injected in a dose of 50 mg/kg (in saline solution with one drop of Tween-80™). Diclofenac (tablets "Diclofenac sodium", "Zdorovja narodu", Ukraine) in a dose of 8 mg/kg was used as reference drug. The antiexudative activity (inflammation inhibition) was expressed as a decrease in the rats' paw edema and was calculated using the equation and was given in a percentage:

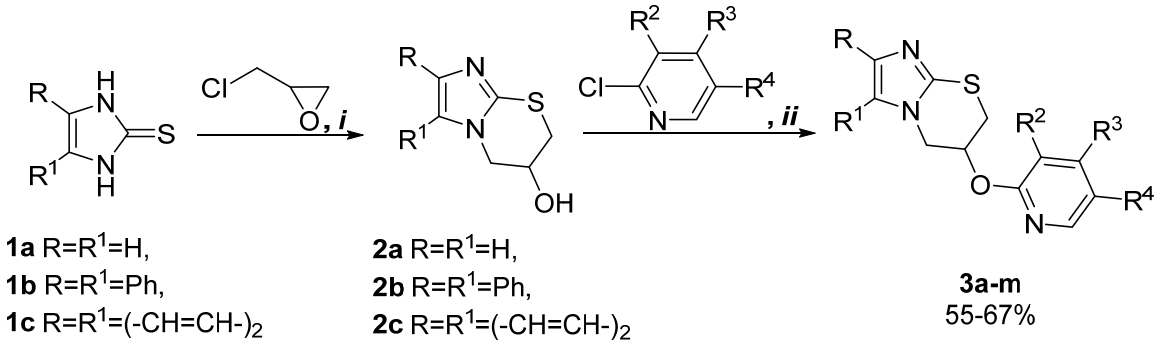
$$Inhibition = (\Delta V_{control} - \Delta V_{experiment})/\Delta V_{control} \times 100\%$$

where, $\Delta V_{control}$ and $\Delta V_{experiment}$—the mean values of the volume difference for control and experimental animal hinds, respectively.

3. Results and Discussion

Used in the present work, the synthetic approach is based on the utilization of structure-modified imidazolinthiones as starting the building blocks for the formation of the imidazo[2,1-*b*][1,3]thiazine core. The interaction of the last ones in the soft conditions with epichlorohydrin led to the key 3-hydroxy-imidazo[2,1-*b*][1,3]thiazines **2a–c** [5]. The various polysubstituted 2-chloropyridines were studied in the alkylation reaction with

early synthesized compounds **2a–c** (Scheme 1). As a result, the target (2-pyridinyloxy) substituted imidazo[2,1-*b*][1,3]thiazines **3a–m** were obtained with satisfied yields (in the presence of equimolar amounts of 60% sodium hydride in an anhydrous DMF medium) at room temperature, and the selective nucleophilic substitution in position 2 of the pyridine ring was observed.



Scheme 1. Synthesis of compounds **3a–m**. Reagents and conditions: (*i*) **1a–c** (10 mmol), 2-(chloromethyl)oxirane (10 mmol), NaOH (10 mmol), MeOH (25 mL), stirring, r.t. 24 h; (*ii*) **2a–c** (10 mmol), 60% NaH in mineral oil (10 mmol), appropriate derivate of 2-chloropiridine (10 mmol), DMF (4 mL), stirring, r.t. 24 h.

The control of reaction process and products formation was monitored by TLC. The compounds' structure characterization and yield are presented in the Table 1.

Table 1. Structure characterization and yeilds of synthesized compounds **3a–m**.

Compound	R	R^1	R^2	R^3	R^4	Yield, %
3a	H	H	H	H	Cl	55
3b	H	H	H	H	CF_3	60
3c	H	H	H	H	CN	58
3d	H	H	Cl	H	Cl	59
3e	H	H	Cl	H	CF_3	62
3f	Ph	Ph	H	H	CF_3	67
3g	Ph	Ph	H	H	CN	57
3h	Ph	Ph	Cl	H	Cl	61
3i	Ph	Ph	Cl	H	CF_3	66
3j	(-CH=CH-)$_2$		H	H	CF_3	67
3k	(-CH=CH-)$_2$		H	H	CN	59
3l	(-CH=CH-)$_2$		Cl	H	Cl	62
3m	(-CH=CH-)$_2$		Cl	H	CF_3	65

The structure of compounds was studied and confirmed using 1H, 13C NMR spectroscopy and LC-MS spectrometry.

3.1. In Silico Evaluation of Drug-Likeness Properties

The drug-likeness properties of the derivatives **3a–m** were determined based on Lipinski and Veber rules and evaluated in silico using the SwissAdme of the Swiss Institute of Bioinformatics website [15] (Table 2).

Table 2. Drug-likeness parameters of derivatives 3a-m according to Lipinski and Veber rules.

Compounds	Lipinski Rules					Veber Rules	Violations of Rules
	MW $\leq$ 500	log P/Mlog P $\leq$ 5/$\leq$ 4.15 [1]	NHD $\leq$ 5 [2]	NHA $\leq$ 10 [3]	NBR $\leq$ 10 [4]	TPSA $\leq$ 140 [5]	
3a	267.73	2.09/1.41	0	3	2	65.24	0
3b	301.29	2.25/1.82	0	6	3	65.24	0
3c	258.30	1.94/0.23	0	4	2	89.03	0
3d	302.18	2.58/1.95	0	3	2	65.24	0
3e	353.73	2.41/2.34	0	6	3	65.24	0
3f	453.48	3.61/4.11	0	6	5	65.24	0
3g	410.49	3.03/2.63	0	4	4	89.03	0
3h	454.37	3.91/4.28	0	3	4	65.24	1
3i	487.92	3.65/4.69	0	6	5	65.24	1
3j	351.35	2.74/3.15	0	6	3	65.24	0
3k	308.36	2.33/1.62	0	4	2	89.03	0
3l	352.24	2.96/3.30	0	3	2	65.24	0
3m	385.79	2.84/3.66	0	6	3	65.24	0

[1] Mlog P: Moriguchi log P [16,17]; [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 **3h** and **3i**, for which the calculated MlogP values were higher (4.69 and 4.28, accordingly) than limited for the Mlog P parameter (accepted $\leq$ 4.15), in line with the Lipinski's rules.

3.2. Study of Anti-Inflammatory (Anti-Exudative) Activity of Synthesized Compounds **3a–m**

The anti-inflammatory (anti-exudative) activity of all synthesized compounds **3a–m** was investigated on the in vivo carrageenin model of the total edema of the hind paws of albino rats [14]. The study results are presented in Table 3.

Table 3. In vivo anti-inflammatory activity of compounds **3a–m** on carrageenin-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 $\pm$ m; n = 6 in each group).

Compounds/Reference Drug, Doses	Rat Hind Limb Volume Increase, 4 h, %	Inflammation Inhibition, %
Carrageenin	122.9 $\pm$ 10.8	-
Diclofenac sodium	65.9 $\pm$ 5.3	46.3
3a	81.6	33.8
3b	82.1	33.2
3c	78.9	35.8
3d	84.8	31.0
3e	90.4	26.4
3f	96.2	21.7
3g	118.4	3.7
3h	114.9	6.5
3i	104.1	15.3
3j	105.8	13.9
3k	101.6	17.3
3l	74.8	39.1
3m	96.1	21.8

The synthesized compounds **3a–m** possess different levels of anti-inflammatory activity (inhibition index was in the range of 3.7 to 39.1%). From the point of view of the "structure—anti-inflammatory activity" derivatives **3a–d** with an unsubstituted imidazole ring in the imidazo[2,1-*b*][1,3]thiazine core, they are characterized with a total higher activity level. The compound **3c** containing cyano-group in the pyridine ring was the most active among derivatives **3a–d**, whereas the change of cyano-group on the chlorine or threefluormethyl-group led to an insignificant activity decrease. Derivative **3l** was found to be the most active inside the tested group, with an inflammation inhibition value of 39.1%, which is only 15.5% less compared to the same data for the reference drug, diclofenac.

4. Conclusions

In the present work, a synthetic approach to (2-pyridinyloxy) substituted imidazo[2,1-*b*][1,3]thiazines is described. The polysubstituted 2-chloropyridines were studied in the alkylation reaction with some 3-hydroxy-imidazo[2,1-*b*][1,3]thiazines, and the selective nucleophilic substitution in position 2 of pyridine ring was observed. The synthesized (2-pyridinyloxy) substituted imidazo[2,1-*b*][1,3]thiazines comply with Lipinski's rules of five and Veber's rules and possess promising anti-inflammatory properties in the carrageenan test in vivo. Such drug-like and pharmacological features of synthesized derivatives argue for forthcoming studies as potential non-steroidal anti-inflammatory agents.

Author Contributions: Conceptualization, N.S. and M.V.; methodology and experimental work, N.S., S.H., L.S. and M.V.; data analysis, N.S., S.H., L.S. and M.V.; writing—review and editing, N.S., S.H., L.S. and M.V.; project administration and supervision, N.S. and M.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethic Committee of the Danylo Halytsky Lviv National Medical University, Lviv, Ukraine (protocol No. 10 from 17 March 2021).

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available in this article.

Acknowledgments: This research was supported by the Lesya Ukrainka Volyn National University, Danylo Halytsky Lviv National Medical University and Institute of Organic Chemistry of National Academy of Sciences of Ukraine, which is gratefully acknowledged.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Volkov, O.A.; Cosner, C.C.; Brockway, A.J.; Kramer, M.; Booker, M.; Zhong, S.; Ketcherside, A.; Wei, S.; Longgood, J.; McCoy, M.; et al. Identification of Trypanosoma brucei AdoMetDC Inhibitors Using a High-Throughput Mass Spectrometry-Based Assay. *ACS Infect. Dis.* **2017**, *3*, 512–526. [CrossRef] [PubMed]
2. Thompson, A.M.; Marshall, A.J.; Maes, L.; Yarlett, N.; Bacchi, C.J.; Gaukel, E.; Wringd, S.A.; Launaye, D.; Braillarde, S.; Chatelaine, E.; et al. Assessment of a pretomanid analogue library for African trypanosomiasis: Hit-to-lead studies on 6-substituted 2-nitro-6,7-dihydro-5H-imidazo[2,1-b][1,3]thiazine 8-oxides. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 207–213. [CrossRef] [PubMed]
3. Tawari, N.R.; Degani, M.S. Pharmacophore modeling and density functional theory analysis for a series of nitroimidazole compounds with antitubercular activity. *Chem. Biol. Drug. Des.* **2011**, *78*, 408–417. [CrossRef] [PubMed]
4. Thompson, A.M.; Robert, A.B.; Anderson, F.; Shinde, S.S.; Franzblau, S.G.; Ma, Z.; Denny, W.A.; Palmer, B.D. Synthesis, Reduction Potentials, and Antitubercular Activity of Ring A/B Analogues of the Bioreductive 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.* **2009**, *52*, 637–645. [CrossRef] [PubMed]
5. Gong, J.-X.; He, Y.; Cui, Z.-L.; Guo, Y.-W. Synthesis, spectral characterization, and antituberculosis activity of thiazino[3,2-A]benzimidazole derivatives. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, *191*, 1036–1041. [CrossRef]
6. Rodríguez, O.A.R.; Vergaraa, N.E.M.; Sánchez, J.P.M.; Martínez, M.T.S.; Sandoval, Z.G.; Cruz, A.; Organillo, A.R. Synthesis, crystal structure, antioxidant activity and dft study of 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-a]benzimidazol-4-One. *J. Mol. Struct.* **2020**, *1199*, 127036. [CrossRef]
7. Mickleburgh, I.; Geng, F.; Tiley, L. Mesoionic heterocyclic compounds as candidate messenger RNA cap analogue inhibitors of the influenza virus RNA polymerase cap-binding activity. *Antivir. Chem. Chemother.* **2009**, *19*, 213–218. [CrossRef] [PubMed]
8. Nikolova, I.; Slavchev, I.; Ravutsov, M.; Dangalov, M.; Nikolova, Y.; Zagranyarska, I.; Stoyanova, A.; Nikolova, N.; Mukova, L.; Grozdanov, P.; et al. Anti-enteroviral activity of new MDL-860 analogues: Synthesis, in vitro/in vivo studies and QSAR analysis. *Bioorg Chem.* **2019**, *85*, 487–497. [CrossRef] [PubMed]
9. Hamama, W.S.; Waly, M.A.; El-Hawary, I.I.; Zoorob, H.H. Utilization of 2-Chloronicotinonitrile in the Syntheses of Novel Fused Bicyclic and Polynuclear Heterocycles of Anticipated Antitumor Activity. *J. Heterocycl. Chem.* **2016**, *53*, 953–957. [CrossRef]
10. LaFleur, M.D.; Lucumi, E.; Napper, A.D.; Diamond, S.L.; Lewis, K. Novel high-throughput screen against Candida albicans identifies antifungal potentiators and agents effective against biofilms. *J. Antimicrob. Chemother.* **2011**, *66*, 820–826. [CrossRef] [PubMed]
11. Hori, H.; Kim, Y. Inflammation and post-traumatic stress disorder. *Psychiatry. Clin. Neurosci.* **2019**, *73*, 143–153. [CrossRef] [PubMed]

12. Azab, A.; Nassar, A.; Azab, A.N. Anti-Inflammatory Activity of Natural Products. *Molecules* **2016**, *21*, 1321. [CrossRef] [PubMed]
13. Mishchenko, M.; Shtrygol', S.; Lozynskyi, A.; Khomyak, S.; Novikov, V.; Karpenko, O.; Holota, S.; Lesyk, R. Evaluation of Anticonvulsant Activity of Dual COX-2/5-LOX Inhibitor Darbufelon and Its Novel Analogues. *Sci. Pharm.* **2021**, *89*, 22. [CrossRef]
14. 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. [CrossRef] [PubMed]
15. SwissADME. Available online: http://www.swissadme.ch/ (accessed on 15 September 2021).
16. 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. [CrossRef]
17. 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. [CrossRef]