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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-ARYLIDENE-5,6-DIHYDROIMIDAZO[2,1-*b*]THIAZOLES AND 6,7-DIHYDRO-5*H*-[1,3]THIAZOLO[3,2-*a*]PYRIMIDINES

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**The aim.** The present study is devoted to searching for potential biologically active agents among functionalized imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]pyrimidines.

**Materials and methods.** The interaction of preparatively available 5,6-dihydroimidazo[2,1-*b*]thiazolone and 6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidinone with several substituted benzaldehydes in boiling acetic acid in the presence of anhydrous sodium acetate leads to new 2-arylidene-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines as potential pharmacological agents. Their antimicrobial activity was studied using the micromethod of two-fold serial dilutions in a liquid nutrient medium. The antioxidant activity of the synthesized compounds was evaluated using a DPPH assay.

**Results.** A library of 2-arylidene-5,6-dihydroimidazo[2,1-*b*]thiazolone and 6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidinone was synthesized by condensation of 5,6-dihydroimidazo[2,1-*b*]thiazoles and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines with series of aromatic aldehydes. Pharmacological in vitro screening results revealed that synthesized compounds possess moderate antimicrobial activity with MBC and MFC values of 31.25–62.5 mg/mL. While studying the antioxidant activity, it was found that all derivatives effectively inhibited DPPH radicals with an inhibition rate of 42.3–94.4 %. The best antiradical effect was observed for the molecule's derivatives containing 3-methoxy-4-hydroxy- or 2-hydroxyphenylmethylidene fragments.

**Conclusions.** It was found that the Knevenagel condensation of 5,6-dihydroimidazo[2,1-*b*]thiazolone and 6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidinone with aromatic aldehydes is a convenient approach for structure modification and optimization using pharmacophore fragments for these types of heterocycle. The synthesized arylidene derivatives are characterized by moderate antimicrobial and good antioxidant activity in vitro models

**Keywords:** imidazo[2,1-*b*]thiazoles, thiazolo[3,2-*a*]pyrimidines, Knoevenagel condensation, antimicrobial activity, antioxidant activity, DPPH

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**1. Introduction**

Thiazolo-annelated imidazoles [1–3] and pyrimidines [4, 5] are attractive and prospective objects for biomedical research due to their wide and powerful pharmacological spectrum. In particular, the imidazo[2,1-*b*]thiazole core is a key fragment in the structure of the known anthelmintic and immunomodulatory drug Levamisole **I** [6] and the potential anticancer agent Quizartinib **II**, which has demonstrated good activity toward acute myeloid leukaemia [7]. Thiazolo[3,2-*a*]pyrimidines are also of great interest for drug design, and effective antidepressants Ritanserin **III** and Setoperone **IV** [8] have been discovered among these heterocycles (Fig. 1).

In addition, the imidazothiazole scaffold present in the structures of the anxiolytic agent WAY-181187 (SAX-187) [9], the antineoplastic agent pifitrin-β [10], the sirtuin modulator SRT2140 [11], the enzyme inhibitor 15-lipoxygenase (15-LOX) [12] and recombinant enzyme

IDO1 (rhIDO1) [13]. Whereas inhibitors of casein kinase 2 (CK2) [14] and diacylglycerol kinase (DG) [15] have been identified among the thiazolo[3,2-*a*]pyrimidine derivatives.

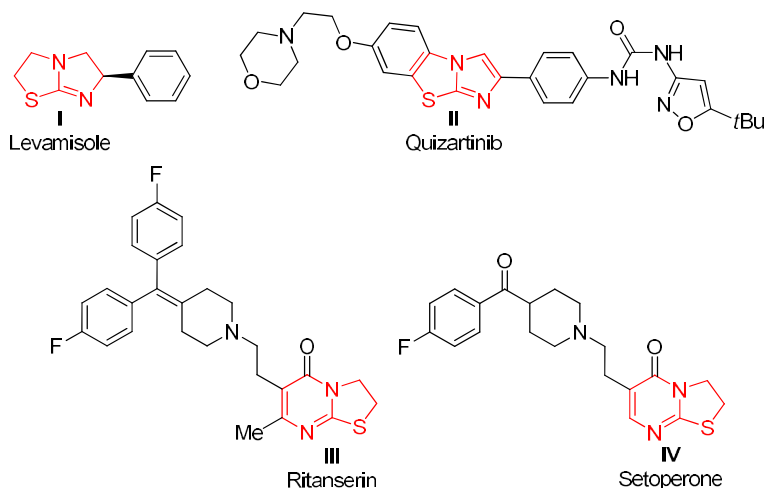


Fig. 1. Structure of some bioactive imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]pyrimidines

Systematic literature analysis suggests that nitrogen- and sulfur-containing heterocyclic systems modified with pharmacophore arylidene fragments are promising scaffolds for the research and development of potential biologically active compounds as antimicrobial [16], anti-inflammatory [16–18], antimalarial [19], anticancer [17, 20] agents. Taking into account the above, it seemed reasonable to carry out focused structural functionalization of 5,6-dihydroimidazo[2,1-*b*]thiazolone and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidinone using pharmacophore arylidene substituents and perform *in vitro* evaluation of biological properties of novel heterocycles.

## 2. Planning of research

Considering the pharmacophoric nature of imidazo[2,1-*b*]thiazole and thiazolo[3,2-*a*]pyrimidine scaffolds and arylidene fragments, our task involved using the Knoevenagel reaction to construct new potential bioactive derivatives. The choice of aldehydes with different positions and the nature of substituents in the aromatic nucleus is based on the goal of elucidating the structure-activity relationships (SAR) (Fig. 2).

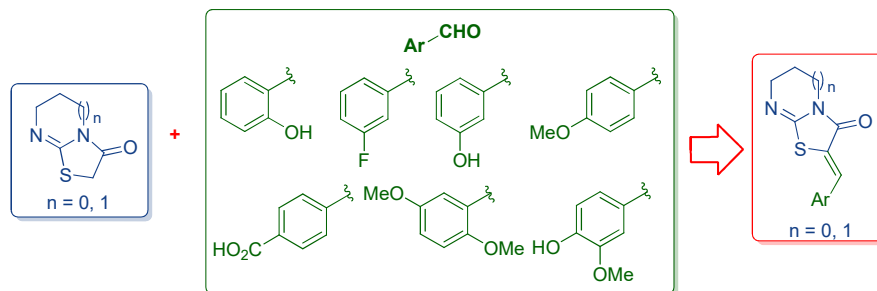


Fig. 2. Design of 2-arylidene substituted imidazo[2,1-*b*]thiazoles and thiazolo[3,2-*a*]pyrimidines

*In vitro* screening studies of their antimicrobial and antioxidant properties were performed to assess the synthesized compounds' biological potential.

## 3. Materials and methods

### 3.1. Synthesis

<sup>1</sup>H spectra were recorded on a Varian VXR-400 spectrometer and Bruker AVANCE DRX 500 (400 and 500 MHz, respectively) and <sup>13</sup>C NMR spectra were recorded on a Varian VXR-400 spectrometer (126 MHz) in pulsed Fourier mode in DMSO-*d*<sub>6</sub>, with TMS as the internal standard. Mass spectra were recorded on an Agilent LC/MSD SL instrument, Zorbax SB-C18 column, 4.6×15 mm, 1.8 μm (PN 82(c)75-932), DMSO-*d*<sub>6</sub> as the solvent, electrospray ionization at atmospheric pressure. Elemental analysis was performed on a PerkinElmer CHN Analyzer 2400 series in the analytical laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine. Melting points were determined according to a Kofler bench and are uncorrected.

**General procedure for the synthesis of 2-arylidene substituted imidazo[2,1-*b*]thiazoles (3a–c).** To the solution of 0.5 g (3.5 mmol), 5,6-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-one **1a** in 5 mL AcOH was added 0.32 g (0.39 mmol) NaOAc and 0.39 mmol of respective aldehyde **2a,d,g**. The

reaction mixture was boiled for 3 h; the solution was cooled, and the obtained precipitate was filtered off, washed with water, dried, and recrystallized from EtOH.

**(Z)-2-(3-Hydroxybenzylidene)-5,6-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-one (3a).** Yield 62 %; M.p. >250 °C. <sup>1</sup>H NMR, δ: 3.79 (*t*, 2H, <sup>3</sup>*J*=10.0 Hz, NCH<sub>2</sub>), 4.28 (*t*, 2H, <sup>3</sup>*J*=10.0 Hz, NCH<sub>2</sub>), 6.85 (*d*, 1H, <sup>3</sup>*J*=10.0 Hz, Ar), 6.96 (*s*, 1H, Ar), 7.01 (*d*, 1H, <sup>3</sup>*J*=10.0 Hz, Ar), 7.30–7.33 (*m*, 1H, Ar), 7.54 (*s*, 1H, CH=), 9.81 (*s*, 1H, OH). <sup>13</sup>C NMR, δ: 41.6 (C<sup>5</sup>), 60.9 (C<sup>6</sup>), 115.4, 117.1, 120.7 (Ar), 127.3 (C<sup>2</sup>), 129.8, 130.3 (Ar), 134.3 (CH=), 156.6 (Ar), 157.8 (C<sup>7a</sup>), 159.5 (C<sup>3</sup>). LC-MS, *m/z*: 247 [M+H]<sup>+</sup>. Anal. Calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S (%): C, 58.52; H, 4.09; N, 11.37. Found, %: C, 58.77; H, 4.06; N, 11.52.

**(Z)-4-[(3-Oxo-5,6-dihydroimidazo[2,1-*b*]thiazol-2(3*H*)-ylidene)methyl]benzoic acid (3b).** Yield 81 %; M.p. >250 °C. <sup>1</sup>H NMR, δ: 3.82 (*t*, 2H, <sup>3</sup>*J*=10.0 Hz, NCH<sub>2</sub>), 4.31 (*t*, 2H, <sup>3</sup>*J*=10.0 Hz, NCH<sub>2</sub>), 7.68–7.70 (*m*, 3H, Ar+CH=), 8.04 (*d*, 2H, <sup>3</sup>*J*=10.0 Hz, Ar), 13.18 (*s*, 1H, CO<sub>2</sub>H). <sup>13</sup>C NMR, δ: 42.2 (C<sup>5</sup>), 61.5 (C<sup>6</sup>), 128.8 (C<sup>2</sup>), 129.9, 130.5, 130.6, 131.8 (Ar), 137.6 (CH=), 156.8 (C<sup>7a</sup>), 159.7 (C<sup>3</sup>), 167.1 (CO<sub>2</sub>H). LC-MS, *m/z*: 275 [M+H]<sup>+</sup>. Anal. Calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>S (%): C, 56.92; H, 3.67; N, 10.21. Found, %: C, 57.19; H, 3.69; N, 10.03.

**(Z)-2-(4-Hydroxy-3-methoxybenzylidene)-5,6-dihydroimidazo[2,1-*b*]thiazol-3(2*H*)-one (3c).** Yield 63 %; M.p. 220–222 °C. <sup>1</sup>H NMR, δ: 3.77 (*t*, 2H, <sup>3</sup>*J*=8.0 Hz, NCH<sub>2</sub>), 3.82 (*s*, 3H, OMe), 4.27 (*t*, 2H, <sup>3</sup>*J*=8.0 Hz, NCH<sub>2</sub>), 6.92 (*d*, 1H, <sup>3</sup>*J*=8.0 Hz, Ar), 7.03 (*d*, 1H, <sup>3</sup>*J*=8.0 Hz, Ar), 7.14 (*s*, 1H, Ar), 7.54 (*s*, 1H, CH=), OH (H/D exchange). <sup>13</sup>C NMR, δ: 41.5 (C<sup>5</sup>), 55.6 (OMe), 60.8 (C<sup>6</sup>), 113.7, 116.0, 123.1 (Ar), 123.2 (C<sup>2</sup>), 124.5, 130.3 (Ar), 147.9 (CH=), 148.7 (Ar), 156.8 (C<sup>7a</sup>), 159.8 (C<sup>3</sup>). LC-MS, *m/z*: 277 [M+H]<sup>+</sup>. Anal. Calcd. For C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S (%): C, 56.51; H, 4.38; N, 10.14. Found, %: C, 56.74; H, 4.35; N, 9.98.

**General procedure for the synthesis of 2-arylidene substituted thiazolo[3,2-*a*]pyrimidines (3d–j).** To the solution of 0.5 g (3.2 mmol) 6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-3(5*H*)-one **1b** in 5 mL AcOH was added 0.29 g (0.35 mmol) NaOAc and 0.35 mmol of respective aldehyde **2a–g**. The reaction mixture was boiled for 3 h; the solution was cooled, and the obtained precipitate was filtered off, washed with water, dried, and recrystallized from EtOH.

**(Z)-2-(2-Hydroxybenzylidene)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-3(5*H*)-one (3d).** Yield 71 %; M.p. 223–225 °C. <sup>1</sup>H NMR, δ: 1.82–1.88 (*m*, 2H, CH<sub>2</sub>), 3.53 (*t*, 2H, <sup>3</sup>*J*=8.0 Hz, NCH<sub>2</sub>), 3.71 (*t*, 2H, <sup>3</sup>*J*=8.0 Hz, NCH<sub>2</sub>), 6.95 (*t*, 2H, <sup>3</sup>*J*=8.0 Hz, Ar), 7.27 (*t*, 1H, <sup>3</sup>*J*=8.0 Hz, Ar), 7.34 (*d*, 1H, <sup>3</sup>*J*=8.0 Hz, Ar), 7.92 (*s*, 1H, CH=), 10.38 (*s*, 1H, OH). <sup>13</sup>C NMR, δ: 19.1 (C<sup>6</sup>), 40.2 (C<sup>5</sup>), 46.3 (C<sup>7</sup>), 115.9, 119.6, 120.0, 120.6, 123.4 (Ar), 127.9 (C<sup>2</sup>), 131.3 (Ar), 148.4 (CH=), 156.8 (C<sup>8a</sup>), 164.8 (C<sup>3</sup>). LC-MS, *m/z*: 261 [M+H]<sup>+</sup>. Anal. Calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S (%): C, 59.98; H, 4.65; N, 10.76. Found, %: C, 60.22; H, 4.68; N, 10.57.

**(Z)-2-(3-Hydroxybenzylidene)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyrimidin-3(5*H*)-one (3e).** Yield 69 %;

M.p. 231–233 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.82–1.87 (*m*, 2H,  $\text{CH}_2$ ), 3.54 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 3.71 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 6.82–6.85 (*m*, 1H, Ar), 6.96 (*s*, 1H, Ar), 7.01 (*d*, 1H,  $^3J=5.0$  Hz, Ar), 7.29–7.32 (*m*, 1H, Ar), 7.55 (*s*, 1H, CH=), OH (H/D exchange).  $^{13}\text{C}$  NMR,  $\delta$ : 19.1 ( $\text{C}^6$ ), 40.3 ( $\text{C}^5$ ), 46.3 ( $\text{C}^7$ ), 115.6, 117.0, 120.9, 121.4 (Ar), 128.5 ( $\text{C}^2$ ), 130.2, 134.7 (Ar), 148.2 (CH=), 157.9 ( $\text{C}^{8a}$ ), 164.5 ( $\text{C}^3$ ). LC-MS, *m/z*: 261  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$  (%): C, 59.98; H, 4.65; N, 10.76. Found, %: C, 60.18; H, 4.61; N, 10.59.

(*Z*)-2-(3-Fluorobenzylidene)-6,7-dihydro-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (**3f**). Yield 56 %; M.p. 116–118 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.83–1.88 (*m*, 2H,  $\text{CH}_2$ ), 3.55 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 3.72 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 7.27–7.31 (*m*, 1H, Ar), 7.40–7.43 (*m*, 2H, Ar), 7.55–7.59 (*m*, 1H, Ar), 7.66 (*s*, 1H, CH=).  $^{13}\text{C}$  NMR,  $\delta$ : 19.1 ( $\text{C}^6$ ), 40.4 ( $\text{C}^5$ ), 46.4 ( $\text{C}^7$ ), 116.3 (*q*,  $^1J_{\text{CF}}=31.25$  Hz, Ar), 123.5 ( $\text{C}^2$ ), 125.2 (*d*,  $^4J_{\text{CF}}=3.75$  Hz, Ar), 126.9 (*d*,  $^4J_{\text{CF}}=3.75$  Hz, Ar), 131.3 (*d*,  $^3J_{\text{CF}}=7.5$  Hz, Ar), 136.0 (*d*,  $^2J_{\text{CF}}=8.75$  Hz, Ar), 147.8 (CH=), 161.3 ( $\text{C}^{8a}$ ), 163.3 (Ar), 164.3 ( $\text{C}^3$ ). LC-MS, *m/z*: 263  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{13}\text{H}_{11}\text{FN}_2\text{OS}$  (%): C, 59.53; H, 4.23; N, 10.68. Found, %: C, 59.76; H, 4.20; N, 10.85.

(*Z*)-2-(4-Methoxybenzylidene)-6,7-dihydro-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (**3g**). Yield 63 %; M.p. 184–186 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.82–1.87 (*m*, 2H,  $\text{CH}_2$ ), 3.53 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 3.70 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 3.81 (*s*, 3H, OMe), 7.08 (*d*, 2H,  $^3J=10.0$  Hz, Ar), 7.52 (*d*, 2H,  $^3J=10.0$  Hz, Ar), 7.60 (*s*, 1H, CH=).  $^{13}\text{C}$  NMR,  $\delta$ : 19.6 ( $\text{C}^6$ ), 40.7 ( $\text{C}^5$ ), 46.8 ( $\text{C}^7$ ), 55.9 (OMe), 115.2, 119.0 (Ar), 126.6 ( $\text{C}^2$ ), 128.8, 132.0 (Ar), 148.7 (CH=), 160.8 ( $\text{C}^{8a}$ ), 165.2 ( $\text{C}^3$ ). LC-MS, *m/z*: 275  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$  (%): C, 61.29; H, 5.14; N, 10.21; O, 11.66. Found, %: C, 61.53; H, 5.18; N, 10.05.

(*Z*)-4-[(3-Oxo-3,5,6,7-tetrahydro-2H-thiazolo[3,2-*a*]pyrimidin-2-ylidene)methyl]benzoic acid (**3h**). Yield 74 %; M.p. >250 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.84–1.88 (*m*, 2H,  $\text{CH}_2$ ), 3.56 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 3.72 (*t*, 2H,  $^3J=5.0$  Hz,  $\text{NCH}_2$ ), 7.67–7.68 (*m*, 3H, Ar+CH=), 8.05 (*d*, 2H,  $^3J=5.0$  Hz, Ar), 13.15 (*s*, 1H,  $\text{CO}_2\text{H}$ ).  $^{13}\text{C}$  NMR,  $\delta$ : 19.1 ( $\text{C}^6$ ), 40.4 ( $\text{C}^5$ ), 46.4 ( $\text{C}^7$ ), 124.2 (Ar), 127.0 ( $\text{C}^2$ ), 129.6, 130.0, 131.0 (Ar), 137.6 (CH=), 147.8 ( $\text{C}^{8a}$ ), 164.3 ( $\text{C}^3$ ), 166.7 ( $\text{CO}_2\text{H}$ ). LC-MS, *m/z*: 289  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$  (%): C, 58.32; H, 4.20; N, 9.72. Found, %: C, 58.56; H, 4.18; N, 9.53.

(*Z*)-2-(2,5-Dimethoxybenzylidene)-6,7-dihydro-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (**3i**). Yield 85 %; M.p. 181–183 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.82–1.87 (*m*, 2H,  $\text{CH}_2$ ), 3.53 (*t*, 2H,  $^3J=10.0$  Hz,  $\text{NCH}_2$ ), 3.70 (*t*, 2H,  $^3J=10.0$  Hz,  $\text{NCH}_2$ ), 3.75 (*s*, 3H, OMe), 3.82 (*s*, 3H, OMe), 6.91 (*s*, 1H, Ar), 7.03 (*d*, 1H,  $^3J=10.0$  Hz, Ar), 7.07 (*d*, 1H,  $^3J=10.0$  Hz, Ar), 7.81 (*s*, 1H, CH=).  $^{13}\text{C}$  NMR,  $\delta$ : 19.1 ( $\text{C}^6$ ), 40.3 ( $\text{C}^5$ ), 46.3 ( $\text{C}^7$ ), 55.5 (OMe), 56.1 (OMe), 112.9, 113.1, 116.4, 122.0, 122.6 (Ar), 122.8 ( $\text{C}^2$ ), 148.1 (CH=), 152.0 (Ar), 153.0 ( $\text{C}^{8a}$ ), 164.5 ( $\text{C}^3$ ). LC-MS, *m/z*: 305  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3\text{S}$  (%): C, 59.19; H, 5.30; N, 9.20. Found, %: C, 59.43; H, 5.34; N, 9.03.

(*Z*)-2-(4-Hydroxy-3-methoxybenzylidene)-6,7-dihydro-2H-thiazolo[3,2-*a*]pyrimidin-3(5H)-one (**3j**). Yield 68 %; M.p. 220–222 °C.  $^1\text{H}$  NMR,  $\delta$ : 1.81–1.86 (*m*, 2H,  $\text{CH}_2$ ), 3.52 (*t*, 2H,  $^3J=10.0$  Hz,  $\text{NCH}_2$ ), 3.69 (*t*, 2H,  $^3J=10.0$  Hz,  $\text{NCH}_2$ ), 3.82 (*s*, 3H, OMe), 6.91 (*d*, 1H,

$^3J=10.0$  Hz, Ar), 7.02 (*d*, 2H,  $^3J=10.0$  Hz, Ar), 7.14 (*s*, 1H, OH), 7.57 (*s*, 1H, CH=).  $^{13}\text{C}$  NMR,  $\delta$ : 19.6 ( $\text{C}^6$ ), 40.7 ( $\text{C}^5$ ), 46.8 ( $\text{C}^7$ ), 56.0 (OMe), 114.3, 116.6, 117.9 (Ar), 123.8 ( $\text{C}^2$ ), 125.4, 129.6 (Ar), 148.4 (CH=), 148.9 (Ar), 149.2 ( $\text{C}^{8a}$ ), 165.3 ( $\text{C}^3$ ). LC-MS, *m/z*: 291  $[\text{M}+\text{H}]^+$ . Anal. Calcd. for  $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3\text{S}$  (%): C, 57.92; H, 4.86; N, 9.65. Found, %: C, 58.16; H, 4.85; N, 9.47.

### 3. 2. Biological studies

**Antimicrobial activity.** Antimicrobial activity was studied by the micromethod of two-time serial dilutions in a liquid nutrient medium. The minimum inhibitory concentrations of 2-arylidene substituents imidazo[2,1-*b*]thiazoles **3a–c** and thiazolo[3,2-*a*]pyrimidines **3d–j** against reference strains of bacteria (*Staphylococcus aureus* ATCC 25923, *Pseudomonas aeruginosa* ATCC 27853, *Escherichia coli* ATCC 25928) and fungi (*Candida albicans* ATCC 885/653, *Aspergillus niger* K 9) were determined. The study used bacteria and fungi from the Museums of Living Microorganisms of the State University “I. I. Mechnikov Institute of Microbiology and Immunology of the National Academy of Medical Sciences of Ukraine” and the Department of Microbiology, Virology and Immunology of Bukovinian State Medical University. Solutions of the studied compounds were prepared for the micromethod of serial dilutions (at a concentration of 1000  $\mu\text{g}/\text{ml}$ ), using dimethyl sulfoxide (DMSO) as a solvent and the antimicrobial agent Decasan produced by “Yuria-Pharm” as a control. To obtain reliable results, the experiments were performed three times with each concentration of the compound and the investigated culture of microorganisms [21].

**Antioxidant activity.** The antioxidant activity of the synthesized compounds was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical inhibition assay [22]. 1 ml of DPPH solution (8 mg/100 ml) was added to solutions of the tested compounds and ascorbic acid in methanol as a standard and left at room temperature in a dark place for 1 hour. The amount of absorption of radicals was determined at 517 nm relative to the standard on a UV-1800 spectrophotometer (Shimadzu, Japan). Each sample was analyzed in triplicate. The percentage of inhibition was calculated relative to the blank sample (1):

$$I \% = \frac{(A_{\text{blank}} - (A_{\text{sample+DPPH}} - A_{\text{sample}}))}{A_{\text{blank}}} \cdot 100 \%, \quad (1)$$

where  $A_{\text{blank}}$  is the absorption of the control reaction (includes all reagents except for the studied compound);

$A_{\text{sample+DPPH}}$  is the absorption of the studied compound after 60 min incubation with DPPH solution;

$A_{\text{sample}}$  is the absorption of the investigated compounds without DPPH solution.

## 4. Results

### 4. 1. Chemistry assay

As model substrates for synthetic research to implement the task, we used available 5,6-dihydroimidazo[2,1-*b*]thiazol-3(2H)-one **1a** [23] and 6,7-dihydro-2H-thiazolo[3,2-*a*]pyrimidine-3(5H)-one **1b** [24], which contain in their structures an activated methylene component at-



tractive for further transformations. It was found that the Knoevenagel condensation of starting compounds **1a,b** with aromatic aldehydes **2a–g** proceeds smoothly upon boiling in acetic acid in the presence of anhydrous NaOAc and leads to the formation of target compounds **3a–j** with yields of 56–85 % (Fig. 3).

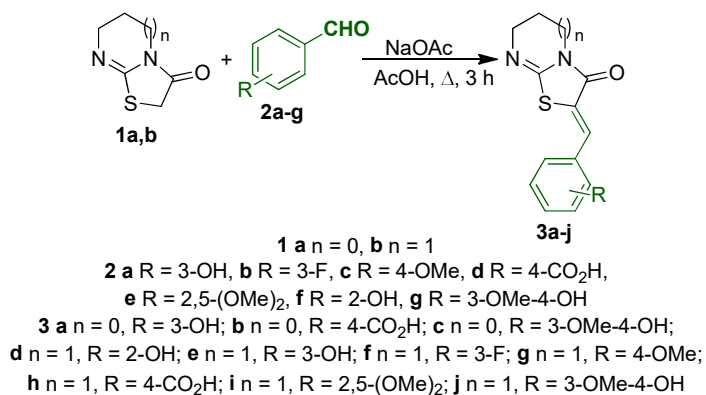


Fig. 3. Synthesis of 2-arylidene substituted imidazo[2,1-*b*]thiazoles **3a–c** and thiazolo[3,2-*a*]pyrimidines **3d–j**

The composition and structure of the synthesized arylidene derivatives **3a–j** were reliably confirmed by a comprehensive physicochemical study, which included elemental analysis,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and LC-MS spectra. It is worth noting that the condensation products **3a–j** are formed stereoselectively in the form of *Z*-isomers, which is confirmed by the position of the singlet proton of the  $-\text{CH}=\text{CH}-$  group of the arylidene fragment in the range of 7.54–7.92 ppm and is consistent with the data for structural analogues [25, 26].

#### 4. 2. Biological assay

The search for treatment for infectious diseases caused by resistant strains of microorganisms, as well as the rapid emergence of resistance to known and new antibiotics, is a crucial problem of modern medicine [27, 28].

Due to this, research and development of non-toxic and effective antimicrobial agents based on original types of organic compounds is of urgent importance. Given the above, *in vitro* screening of antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* strains, as well as antifungal activity against *Candida albicans*, was carried out for synthesized 2-arylidene-substituted 5,6-dihydroimidazo[2,1-*b*]thiazoles **3a–c** and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines **3d–j**. The study results are outlined in Table 1.

An important problem of modern pharmacy and medicine is the search and development of powerful antioxidants as a key protective factor against the effects of free radicals on the human body [29]. In recent years, representatives of synthetic heterocyclic compounds, in particular, functionalized and condensed thiazole derivatives [30, 31], which are characterized by relatively pronounced activity and stability [32, 33], have become widely used as potential antioxidants. That is why it seemed reasonable to evaluate the antioxidant activity of the synthesized derivatives **3a–j** for their inhibition of DPPH radicals (Fig. 4).

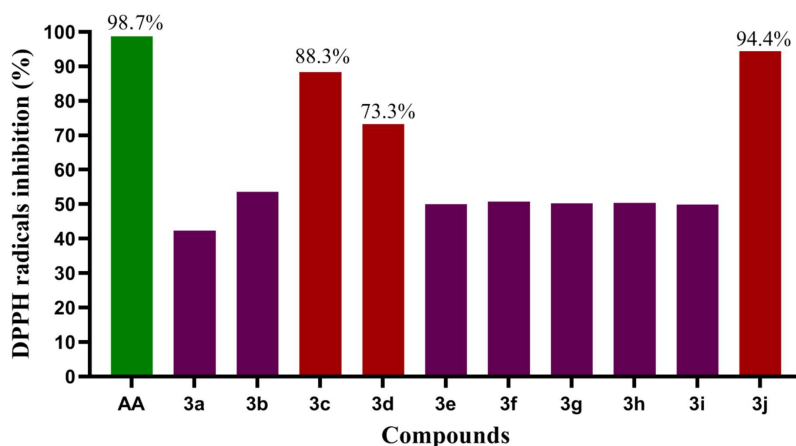


Fig. 4. The inhibition of DPPH radicals by the derivatives **3a–j** at 5 mM concentration. Ascorbic acid (AA) was employed as a positive control (green). The highest activity was observed for compounds **3c,d,j** (red)

Table 1

Antimicrobial activity of 2-arylidene-imidazo[2,1-*b*]thiazoles **3a–c** and thiazolo[3,2-*a*]pyrimidines **3d–j**

Compounds	<i>S. aureus</i> ATCC 25923		<i>P. aeruginosa</i> ATCC 27853		<i>E. coli</i> ATCC 25928		<i>C. albicans</i> ATCC 885/653		<i>A. niger</i> K 9	
	MBC <sup>a</sup>	MBC <sup>b</sup>	MBC <sup>a</sup>	MBC <sup>b</sup>	MBC <sup>a</sup>	MBC <sup>b</sup>	MFC <sup>a</sup>	MFC <sup>b</sup>	MFC <sup>a</sup>	MFC <sup>b</sup>
<b>3a</b>	62.5	62.5	62.5	62.5	62.5	125	62.5	62.5	62.5	125
<b>3b</b>	62.5	62.5	62.5	62.5	31.25	62.5	31.25	31.25	62.5	125
<b>3c</b>	62.5	62.5	62.5	62.5	31.25	62.5	62.5	62.5	62.5	125
<b>3d</b>	62.5	62.5	62.5	62.5	62.5	125	62.5	62.5	62.5	62.5
<b>3e</b>	62.5	62.5	62.5	62.5	31.25	62.5	31.25	31.25	62.5	125
<b>3f</b>	62.5	62.5	62.5	62.5	62.5	62.5	31.25	31.25	62.5	125
<b>3g</b>	62.5	62.5	62.5	62.5	31.25	62.5	31.25	31.25	62.5	125
<b>3h</b>	62.5	62.5	62.5	62.5	31.25	62.5	62.5	62.5	62.5	62.5
<b>3i</b>	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	125
<b>3j</b>	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5	125
DMSO	+		+		+		+		+	
Decasan*	1.95	7.81	15.62	31.25	1.95	7.81	3.9	7.81	3.9	7.81

Note: \*Decasan (a solution consisting of 0.2 mg/mL of decamethoxin) produced by "Yuria-Pharm"; <sup>a</sup> – bacterio/fungistatic action;

<sup>b</sup> – bacterio/fungicidal action.

## 5. Discussion

The Knoevenagel condensation is a powerful and preparatively efficient method for building carbon-carbon bonds and structural modification of organic molecules. Varying the methylene and carbonyl components allows for the creation of large libraries of potential bioactive compounds for combinatorial chemistry [34]. The aforementioned synthetic pathway was successfully used by us for the decoration of 2-methyl-2,3-dihydroimidazo[2,1-*b*]thiazol-5(6H)-one scaffold in order to create antimicrobial and anti-inflammatory agents [16], which became a key idea in the selection of reaction conditions for the synthesis of novel 2-arylidene-5,6-dihydroimidazo[2,1-*b*]thiazoles and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines

The antimicrobial activity of compounds **3a–j** was evaluated by the value of minimum bacteria/fungistatic and bacteria/fungicidal (MBC/MFC) concentrations against strains of the gram-positive bacterium *S. aureus*, the gram-negative bacterium *P. aeruginosa* and *E. coli*, and the fungus *C. albicans* and *A. niger*.

*In vitro* screening results demonstrated moderate antimicrobial activity of derivatives **3a–j** with MBC and MFC values of 31.25–125 mg/mL. It was found that the nature of the substituents in the arylidene fragment does not have a significant effect on the antibacterial activity of the tested compounds. When studying the antifungal activity, it was found that imidazo[2,1-*b*]thiazole **3b** and thiazolo[3,2-*a*]pyrimidines **3e–g** stop the visible growth of the fungus already at a concentration of 31.25 mg/mL (Table 1).

The antioxidant activity of the synthesized compounds was evaluated using a DPPH assay with stock solutions at a concentration of 5 mM and ascorbic acid (AA) as a control. It was shown that all tested derivatives are characterized by antioxidant activity, absorbing 42.3–94.4 % of DPPH radicals. According to the screening results, three potential hit-compounds **3c, d, j** were identified with inhibition percentages of 88.3, 73.3 and 94.4 %, respectively.

The SAR analysis demonstrated a significant influence of the nature of the arylidene substituent on the antioxidant activity of derivatives **3a–j**. Compounds containing the phenolic hydroxy group in the ylidene moiety were found to be the most active. Additionally, the position of the hydroxy group plays a crucial role in the activity level. Thus, compounds **3c** and **3j** containing a 3-methoxy-4-hydroxybenzylidene fragment in the structure are characterized by the highest antiradical activity level. A somewhat lower rate of radical inhibition was demonstrated by derivative **3d** with a 2-hydroxybenzylidene fragment. In contrast, benzylidene fragments of

different nature (derivatives **3a, b, e–i**) do not contribute significantly to the antioxidant activity.

Summarizing effects of arylidene fragments in 5,6-dihydroimidazo[2,1-*b*]thiazolones and 6,7-dihydro-

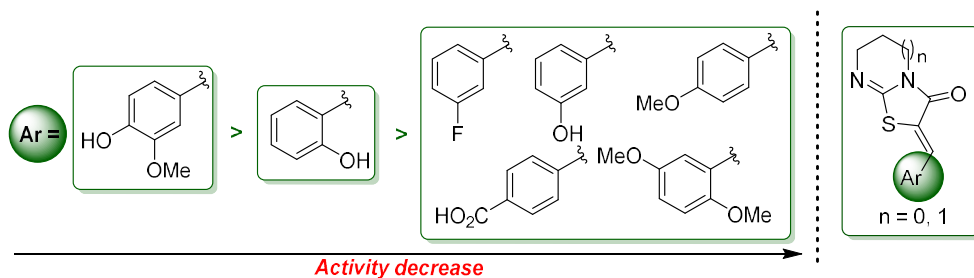


Fig. 5. Structure-anti-radical activity relationships of 2-arylidene-imidazo[2,1-*b*]thiazoles **3a–c** and thiazolo[3,2-*a*]pyrimidines **3d–j**

dro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidinones on antiradical activity are presented on Fig. 5.

The combination of antimicrobial and antioxidant properties enhances treatment efficacy by reducing oxidative stress, which contributes to infections and tissue damage. It can also help minimize microbial resistance and protect healthy cells from the side effects of antimicrobial agents. Additionally, this synergy broadens the spectrum of action, making it beneficial for treating chronic infections. Dihydrofolate reductase inhibition could be considered a plausible molecular pathway for the antibacterial activity of the tested derivatives; however, in-depth computational and *in vitro* studies are needed to validate the hypothesis [35].

**Practical importance.** The obtained results can be used to design structural analogues of 5,6-dihydroimidazo[2,1-*b*]thiazolones and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines with other arylidene and heterocyclic pharmacophore subunits, as well as to conduct in-depth studies of the biological potential of these types of heterocyclic systems.

**Study limitation.** The presented study is limited by the examples of bacterial strains used and the method of free radical inhibition.

**Prospects for further research.** Expansion of the library of 5,6-dihydroimidazo[2,1-*b*]thiazolones and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidines modified with pharmacophore (het)arylidene moieties.

## 5. Conclusions

In the present paper, Knoevenagel condensation was used as a convenient and effective tool for the modification of 5,6-dihydroimidazo[2,1-*b*]thiazolone and 6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine with pharmacological arylidene groups. The *in vitro* screening of the synthesized 2-arylidene derivatives revealed their moderate antimicrobial and antioxidant activity. It was found that compounds **3e–g** inhibit the visible growth of the opportunistic human infection fungus *Candida albicans* at a concentration of 31.25 mg/mL. Whereas, derivatives **3c,d,j** are characterized by good antiradical activity (*I*=73.3–94.4 %) in the DPPH assay.

Identified hits present an interest in in-depth pharmacological studies and the design of potential synthetic antioxidants.

### Conflict of interest

The authors declare that they have no conflict of interest regarding this study, including financial, personal, authorship or other, that could influence the study and its results presented in this article.

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The study was conducted without financial support.

### Data availability

The manuscript has no associated data.

### Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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