

SYNTHESIS, ANTIMICROBIAL AND ANTIOXIDANT ACTIVITY OF 3-ARYL-6,7-DIHYDRO-5H-[1,3] [3,2-*a*] PYRIMIDINES

Vasyl Zhytko¹, Lesya Saliyeva^{1,✉}, Nataliia Slyvka¹, Alina Grozav², Nina Yakovychuk²,
Viktor Tkachuk³, Mykhailo Vovk³

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Abstract. A series of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines was obtained by cyclocondensation of tetrahydropyrimidin-2(1*H*)-one with 2-bromo-1-arylethanones. It was established that the nature of the substituent in the aromatic nucleus of phenacyl bromide significantly affects the course of this type of reaction. In particular, in the case of 2-bromo-1-(4-hydroxyphenyl) ethanone, the target bicyclic product is formed as a result of boiling in ethanol for 4 hours, whereas the reaction time for the cyclocondensation of tetrahydropyrimidine-2(1*H*)-thione with other bromomethylaryl ketones was 10 hours. It was found that the result of the interaction of tetrahydropyrimidine-2(1*H*)-thione and 2-bromo-1-(4-chlorophenyl) ethanone for 4 hours is the *S*-alkylation product, 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl) thio] ethanone, intramolecular cyclization of which leads to 3-(4-chlorophenyl)-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidine under the action of H₃PO₄. The results of bioscreening of the synthesized 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines demonstrated their moderate antimicrobial activity and made it possible to identify a potential synthetic antioxidant, 3-(4-fluorophenyl)-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*]pyrimidine (*I* = 88.2 %).

Keywords: tetrahydropyrimidine-2(1*H*)-thione, 2-bromo-1-arylethanone, cyclocondensation, electrophilic intra-

molecular cyclization, thiazolo [3,2-*a*] pyrimidine, antimicrobial activity, anti-oxidant activity, DPPH.

1. Introduction

Mononuclear heterocyclic compounds and their condensed analogues occupy a prominent place in modern organic synthesis as important building blocks for the construction of bioactive molecules, analogues of natural compounds, drugs^{1, 2} and functional materials that find practical applications as selective organocatalysts, ionic liquids, electroluminescent materials for OLEDs-devices³⁻⁶. In the chemical space of nitrogen-containing condensed structures, azole-azine systems play an important role as key platforms for synthetic purposes and biomedical research^{7, 8}. Among their variety, special attention is attracted to derivatives based on the thiazolo [3,2-*a*] pyrimidine scaffold that is privileged in medical chemistry due to a wide spectrum of biological activity⁹⁻¹¹. For instance, the thiazolopyrimidine core is a key structural fragment of the antidepressants ritanserin (**I**) and setoperone (**II**)¹². Additionally, inhibitors of casein kinase 2 (PKCK2) (**III**)¹³ and diacylglycerol kinase (DG) (**IV**) (Fig. 1)¹⁴, potential antidiabetic¹⁵, antimicrobial^{16,17}, and anti-HIV-1¹⁸ agents, as well as compounds with antitumor^{19, 20}, anti-inflammatory²¹, antinociceptive²², cardiotoxic, inotropic, hypotensive²³ activities were found among thiazolo[3,2-*a*]pyrimidine derivatives.

An important challenge of modern medicine is the search for methods of treatment of infectious diseases caused by resistant strains of microorganisms, as well as the rapid emergence of resistance to old and new antibiotics^{24, 25}. Therefore, the creation of non-toxic and effective antimicrobial agents based on original types of organic compounds is becoming relevant.

An equally promising direction of medical and biological research in recent years is the search and development of powerful antioxidants, as a key protective factor against the effects of free radicals on the body⁶, which play an important role in the prevention of diseases

¹ Department of Organic and Pharmaceutical Chemistry, Lesya Ukrainka Volyn National University, 13, Voli Ave., Lutsk, 43025, Ukraine

² Department of Medical and Pharmaceutical Chemistry, Bukovinian State Medical University, 2, Teatralna Sq., Chernivtsi, 58000, Ukraine

³ Department of Functional Heterocyclic Systems, Institute of Organic Chemistry of National Academy of Sciences of Ukraine, 5, Academician Kuhar str., Kyiv, 02660, Ukraine

✉ saliyeva.lesia@vnu.edu.ua

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caused by the effects of active forms of oxygen in the body^{27–29}. Along with natural products^{26, 30}, representatives of synthetic heterocyclic compounds, particularly functionalized thiazole^{31, 32}, 1,3-thiazine³³ and indole^{34, 35}, are widely used as antioxidants^{36, 37}. The analysis of literature sources clearly proves that thiazolo [3,2-*a*] pyrimidines remain less studied in synthetic and pharmacological aspects compared to their benzannelated analogues^{38–41}. It is therefore necessary to synthesize new partially hydrogenated thiazolo [3,2-*a*] pyrimidines and investigate their antimicrobial and antioxidant effects.

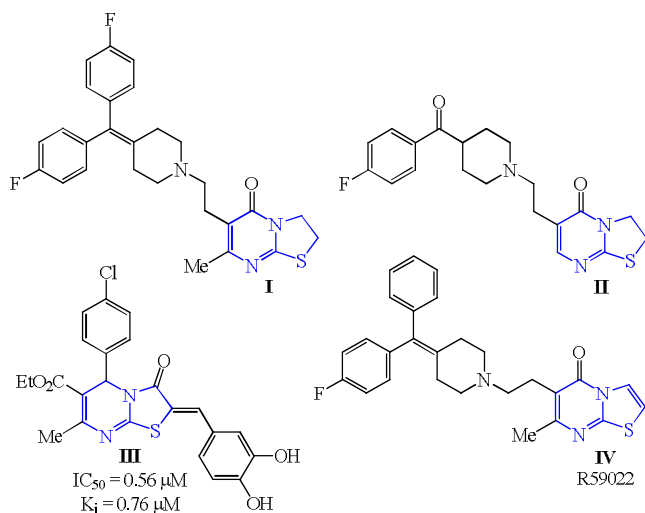


Fig. 1. Structure of ritanserin (**I**), setoperone (**II**), and some kinase inhibitors **III-IV**

In turn, cyclocondensation of heterocycles that contain an endocyclic –HN–C(S)– fragment with halocarbonyl compounds is one of the most common tools for constructing their condensed derivatives with simultaneous functionalization with pharmacophore groups. This methodology additionally makes it possible to solve design problems of complex structures, including analogs of natural compounds, in a fairly convenient and preparatively accessible way^{42–44}.

Synthetic approaches to the construction of bridged thiazolo [3,2-*a*] pyrimidine systems are usually based on the annelation of the thiazole ring to the pyrimidine core or, conversely, on the formation of the pyrimidine ring based on the functionalized thiazole core. Preparatively, the first approach is more convenient due to the fact that available 3,4-dihydropyrimidine-2-thiones, known as Biginelli compounds (**V**), are most often used as a pyrimidine scaffold (Fig. 2)^{45–47}. Their cyclocondensation with such halocarbonyl compounds as bromoketones, chloroacetic acid and its derivatives is characterized by high regioselectivity and leads to the target thiazolo[3,2-

a]pyrimidines with an sp³-hybridized carbon atom in position 5 of the bicyclic structure^{48, 49}.

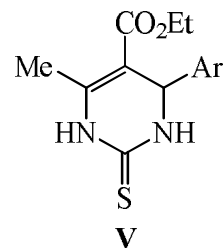


Fig. 2. Structure of the Biginelli compounds **V**

2. Experimental

2.1. Materials and Methods

¹H and ¹³C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 126 MHz, respectively) in a pulsed Fourier mode in DMSO-*d*₆ and CDCl₃, 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*₆ 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. Reagents (tetrahydropyrimidine-2(1*H*)-thione **1** and phenacyl bromides **2a-h**) are of 100 % purity, and dry solvents were purchased from UkrOrgSyntez Ltd.

2.2. Synthesis of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines **4a-h**

2.6 mmol of respective phenacyl bromide **2a-h** was added to a suspension of 0.3 g (2.6 mmol) of tetrahydropyrimidine-2(1*H*)-thione **1** in 10 mL of dry EtOH. The reaction mixture was boiled for 4 h (compound **2a**) or 10 h (compounds **2b-h**), the solvent was evaporated, the solid residue of hydrobromide **3a-h** was dissolved in 30 mL of acetone, neutralized with an aqueous NaHCO₃ solution, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried with Na₂SO₄, evaporated, and the residue was recrystallized from ethyl acetate.

4-(6,7-Dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidin-3-yl)phenol 4a. Yield: 0.40 g (67 %), mp more than 473 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.94–1.97 m (2H, CH₂), 3.43–3.46 m (2H, NCH₂), 3.82–3.85 m (2H,

NCH₂), 6.68 s (1H, SCH), 6.89 d (2H, ³J = 6.0, Ar), 7.32 d (2H, ³J = 6.0, Ar), the OH-group proton is exchanged with water molecules of deuteriosolvent. ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 18.4 (C⁶), 40.0 (C⁵), 45.1 (C⁷), 100.8 (C²), 115.6, 118.8, 130.5 (Ar), 140.7 (C³), 158.9 (Ar), 163.4 (C^{8a}). Mass spectrum, *m/z*: 233 [M+H]⁺. Found, %: C 62.29; H 5.18; N 12.17. C₁₂H₁₁N₂OS. Calculated, %: C 62.04; H 5.21; N 12.06.

3-(4-Chlorophenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4b (method A). Yield: 0.38 g (59 %), mp 398–400 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.71–1.78 m (2H, CH₂), 3.33 t (2H, ³J = 6.0, NCH₂), 3.63 m (2H, ³J = 6.0, NCH₂), 6.25 s (1H, SCH), 7.49 d (2H, ³J = 9.0, Ar), 7.54 d (2H, ³J = 9.0, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 19.3 (C⁶), 43.4 (C⁵), 44.5 (C⁷), 97.1 (C²), 128.7, 128.8, 130.0, 133.8 (Ar), 138.7 (C³), 159.9 (C^{8a}). Mass spectrum, *m/z*: 251 [M+H]⁺. Found, %: C 57.29; H 4.46; N 11.35. C₁₂H₁₁ClN₂S. Calculated, %: C 57.48; H 4.42; N 11.17.

3-(4-Methoxyphenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4c. Yield: 0.32 g (51 %), mp 431–433 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.76–1.84 m (2H, CH₂), 3.36 t (2H, ³J = 6.0, NCH₂), 3.68 m (2H, ³J = 6.0, NCH₂), 3.80 s (3H, OMe), 6.27 s (1H, SCH), 7.04 d (2H, ³J = 9.0, Ar), 7.41 d (2H, ³J = 9.0, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 18.3 (C⁶), 40.0 (C⁵), 45.2 (C⁷), 55.4 (OMe), 102.1 (C²), 114.3, 120.3, 130.6 (Ar), 140.3 (C³), 160.4 (Ar), 163.9 (C^{8a}). Mass spectrum, *m/z*: 247 [M+H]⁺. Found, %: C 63.58; H 5.68; N 11.23. C₁₃H₁₄N₂OS. Calculated, %: C 63.39; H 5.73; N 11.37.

3-(4-Fluorophenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4d. Yield: 0.31 g (52 %), mp 428–430 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.67–1.74 m (2H, CH₂), 3.31 t (2H, ³J = 6.0, NCH₂), 3.58 t (2H, ³J = 6.0, NCH₂), 6.08 s (1H, SCH), 7.27–7.42 m (2H, Ar), 7.48–7.53 m (2H, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 19.9 (C⁶), 44.4 (C⁵), 44.7 (C⁷), 96.1 (C²), 116.1 (*d*, ²J_{CF} = 22.5), 127.2 (*d*, ⁴J_{CF} = 3.0), 131.0 (*d*, ³J_{CF} = 7.5), 139.2 (C³), 159.9 (C^{8a}), 161.8 (*d*, ¹J_{CF} = 94.5). Mass spectrum, *m/z*: 235 [M+H]⁺. Found, %: C 61.76; H 4.75; N 11.85. C₁₂H₁₁FN₂S. Calculated, %: C 61.52; H 4.73; N 11.96.

3-(4-Bromophenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4e. Yield: 0.46 g (61 %), mp 389–391 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.66–1.74 m (2H, CH₂), 3.31 t (2H, ³J = 6.0, NCH₂), 3.60 t (2H, ³J = 6.0, NCH₂), 6.14 s (1H, SCH), 7.41 d (2H, ³J = 9.0, Ar), 7.66 d (2H, ³J = 9.0, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 19.5 (C⁶), 44.0 (C⁵), 44.3 (C⁷), 96.2 (C²), 122.3, 129.4, 130.1, 131.6 (Ar), 138.7 (C³), 159.2 (C^{8a}). Mass

spectrum, *m/z*: 295 [M+H]⁺. Found, %: C 49.01; H 3.72; N 9.61. C₁₂H₁₁BrN₂S. Calculated, %: C 48.82; H 3.76; N 9.49.

3-(2-Fluorophenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4f. Yield: 0.35 g (57 %), mp 453–455 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.82–1.87 m (2H, CH₂), 3.40 t (2H, ³J = 6.0, NCH₂), 3.60 t (2H, ³J = 6.0, NCH₂), 6.56 s (1H, SCH), 7.32–7.42 m (2H, Ar), 7.47–7.50 m (1H, Ar), 7.55–7.62 m (1H, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 18.8 (C⁶), 42.1 (C⁵), 43.8 (C⁷), 100.9 (C²), 116.0 (*d*, ²J_{CF} = 21.3), 117.1 (*d*, ⁴J_{CF} = 15.0), 125.0 (*d*, ⁵J_{CF} = 2.5), 132.0 (Ar), 132.3 (*d*, ³J_{CF} = 16.3), 133.6, (C³), 158.5 (C^{8a}), 160.7 (*d*, ¹J_{CF} = 67.5). Mass spectrum, *m/z*: 235 [M+H]⁺. Found, %: C 61.74; H 4.70; N 11.89. C₁₂H₁₁FN₂S. Calculated, %: C 61.52; H 4.73; N 11.96.

3-(3-Nitrophenyl)-6,7-dihydro-5H-[1,3]

thiazolo [3,2-*a*] pyrimidine 4g. Yield: 0.44 g (65 %), mp 413–415 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.67–1.71 m (2H, CH₂), 3.31 t (2H, ³J = 6.0, NCH₂), 3.62 t (2H, ³J = 6.0, NCH₂), 6.26 s (1H, SCH), 7.75 t (1H, ³J = 6.0, Ar), 7.92 d (1H, ³J = 6.0, Ar), 8.24–8.28 m (2H, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 19.5 (C⁶), 44.3 (C⁵), 44.5 (C⁷), 97.1 (C²), 122.5, 123.4, 130.3, 131.9, 134.3, 137.6 (Ar), 147.9, (C³), 158.5 (C^{8a}). Mass spectrum, *m/z*: 262 [M+H]⁺. Found, %: C 55.38; H 4.20; N 15.96. C₁₂H₁₁N₃O₂S. Calculated, %: C 55.16; H 4.24; N 16.08.

3-(2,4-Dichlorophenyl)-6,7-dihydro-5H-

[1,3]thiazolo [3,2-*a*] pyrimidine 4h. Yield: 0.45 g (61 %), mp 403–405 K. Crystallize from ethyl acetate. ¹H NMR spectrum, DMSO-*d*₆, δ, ppm (*J*, Hz): 1.67–1.74 m (2H, CH₂), 3.27–3.35 m (4H, 2NCH₂), 6.07 s (1H, SCH), 7.48–7.56 m (2H, Ar), 7.80 s (1H, Ar). ¹³C NMR spectrum, DMSO-*d*₆, δ, ppm: 19.4 (C⁶), 42.7 (C⁵), 44.4 (C⁷), 96.6 (C²), 127.8, 128.5, 129.2, 133.5, 134.4, 134.7 (Ar), 135.2 (C³), 158.2 (C^{8a}). Mass spectrum, *m/z*: 286 [M+H]⁺. Found, %: C 50.78; H 3.50; N 9.63. C₁₂H₁₀Cl₂N₂S. Calculated, %: C 50.54; H 3.53; N 9.82.

2.3. Synthesis of 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio]ethanone 6

1.0 g (2.6 mmol) of 2-bromo-1-(4-chlorophenyl) ethanone **2b** was added to a suspension of 0.3 g (2.6 mmol) of tetrahydropyrimidine-2(1*H*)-thione **1** in 10 mL of EtOH. The reaction mixture was boiled for 4 h, the solvent was evaporated, the solid residue of hydrobromide **5** was dissolved in 30 mL of acetone, neutralized with an aqueous NaHCO₃ solution, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried with Na₂SO₄, evaporated, and the residue was recrystallized from ethyl acetate.

Yield: 0.53 g (76 %), mp 453–455 K. Crystallize from ethyl acetate. ^1H NMR spectrum, DMSO- d_6 , δ , ppm (J , Hz): 1.77–1.83 m (1H, CH₂), 1.95–1.98 m (1H, CH₂), 2.94–2.97 m (1H, NCH₂), 3.21–3.25 m (2H, NCH₂), 3.67 s (2H, SCH₂), 7.52 d (2H, $J = 6.0$, Ar), 7.60 d (2H, $J = 6.0$, Ar), 7.81 br. s (1H, NH). ^{13}C NMR spectrum, DMSO- d_6 , δ , ppm: 18.4 (C⁵), 40.7 (CH₂), 42.5 (C⁴+C⁶), 128.2, 128.7, 133.8, 138.1 (Ar), 164.7 (C²), 170.4 (C=O). Mass spectrum, m/z : 269 [M+H]⁺. Found, %: C 53.87; H 4.90; N 10.23. C₁₂H₁₃ClN₂OS. Calculated, %: C 53.63; H 4.88; N 10.42.

2.4. Synthesis of 3-(4-chlorophenyl)-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidine 4b (method B)

10 g of H₃PO₄ was added to 0.5 g of 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio] ethanone **6** and heated at 75 °C for 1 h, cooled, poured on ice, neutralized with an aqueous solution of K₂CO₃, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried over Na₂SO₄ and evaporated. Yield: 0.33 g (52 %).

2.5. Antimicrobial Activity

Antimicrobial activity was studied by the micromethod of two-time serial dilutions in a liquid nutrient medium. The minimum inhibitory concentrations of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines against reference strains of bacteria (*Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Proteus vulgaris* ATCC 4636) and fungi (*Candida albicans* ATCC 885/653) 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 µg/mL), using dimethyl sulfoxide (DMSO) as a solvent and the antimicrobial agent “Furacilin” produced by JSC “Halychpharm” as a control. To obtain reliable results, the experiments were performed three times with each concentration of the compound and the investigated culture of microorganisms⁵⁰.

2.6. Anti-Oxidant Activity (DPPH Assay)

Antioxidant activity of the synthesized compounds was assessed using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical inhibition assay⁵¹. 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:

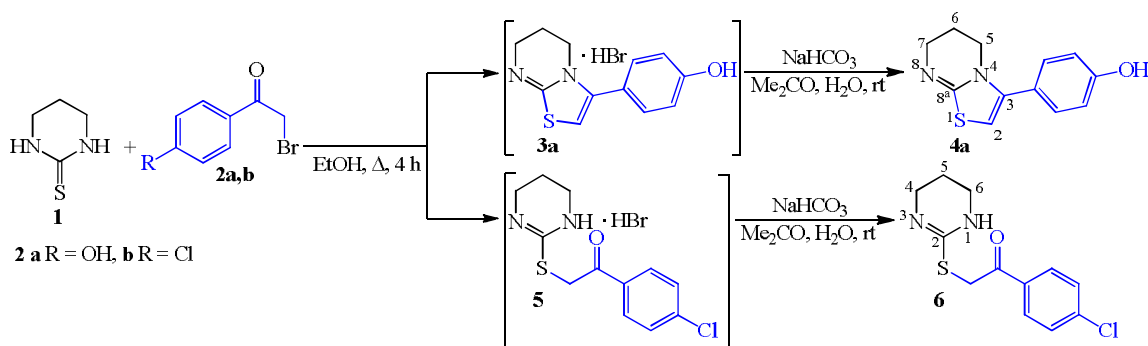
$$I\% = ((A_{\text{blank}} - (A_{\text{sample+DPPH}} - A_{\text{sample}})) / A_{\text{blank}}) \cdot 100\%$$

where A_{blank} is the absorption of the control reaction (includes all reagents except for the studied compounds); $A_{\text{sample+DPPH}}$ is the absorption of the studied compounds after 60 min incubation with DPPH solution; A_{sample} is the absorption of the investigated compounds without DPPH solution.

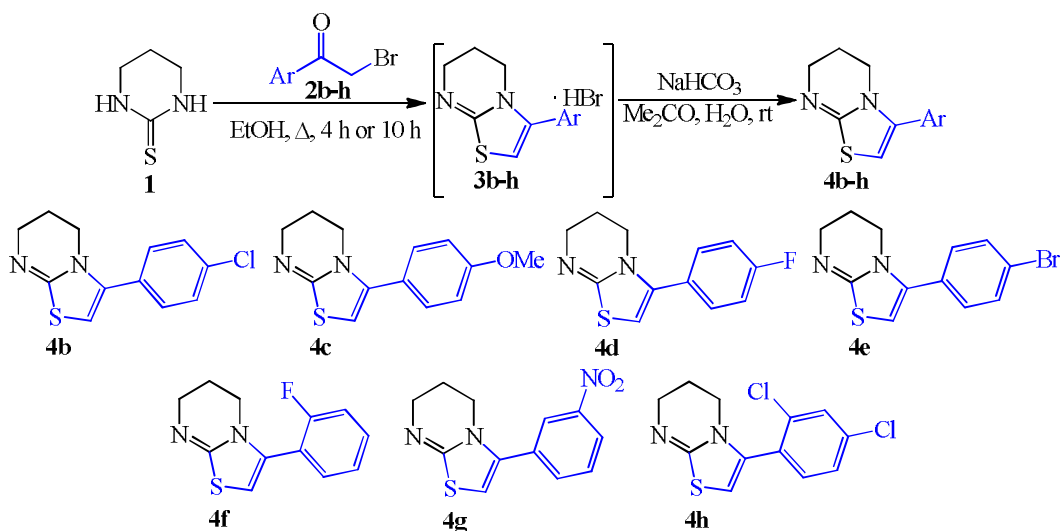
3. Results and Discussion

Considering the substantial role of the conformational flexibility of heterocyclic compounds in modern strategies for the rational design of bioactive chemotypes, tetrahydropyrimidine-2(1H)-thione **1** with three tetragonal carbon atoms in positions 3, 4 and 5 of the nucleus were used as key substrates for the preparation of new thiazolo [3,2-*a*] pyrimidines. Several phenacyl bromides **2a-h** were tested in cyclocondensation, with various aryl substituents, the nature of which affects the speed of the cyclization process. For instance, optimal reaction conditions were selected on the example of the interaction of tetrahydropyrimidine-2(1H)-thione **1** with 2-bromo-1-(4-hydroxyphenyl)ethanone **2c** and 2-bromo-1-(4-chlorophenyl)ethanone **2f**. It was found that boiling for 4 hours tetrahydropyrimidine-2(1H)-thione **1** with phenacyl bromide **2c**, which contains a donor hydroxyl group, results in annelation of the thiazole cycle with the formation of thiazolopyrimidine hydrobromide **3a**. On the other hand, the interaction under similar reaction conditions of tetrahydropyrimidine-2(1H)-thione **1** with 2-bromo-1-(4-chlorophenyl)-ethanone **2f** resulted only in the hydrobromide of *S*-alkylated derivative **5**. Further treatment of hydrobromides **3a** and **5** in acetone with an aqueous solution of NaHCO₃ at room temperature produced 4-(6,7-dihydro-5H-thiazolo[3,2-*a*]pyrimidin-3-yl)phenol **4a** and 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio] ethanone **6**, respectively (Scheme 1).

The structure of the synthesized compounds **4a** and **6** was reliably confirmed by a set of physico-chemical analysis methods. For instance, the ^1H NMR spectrum of thiazolo [3,2-*a*] pyrimidine **4a** is characterized by multiplets of three CH₂ groups at 1.94–1.97, 3.43–3.46, and 3.82–3.85 ppm, a singlet proton of the thiazole ring at 6.68 ppm, and also by doublets of protons of the aromatic nucleus at 6.89 and 7.32 ppm. The presence in the ^1H NMR spectrum of the alkylation product **6** of the SCH₂-group singlet at 3.67 ppm and the broadened singlet of the NH group at 7.81 ppm clearly confirm its structure.



Scheme 1. Synthesis of 4-(6,7-dihydro-5H-thiazolo [3,2-*a*] pyrimidin-3-yl)phenol **4a** and 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio]ethanone **6**



Scheme 2. Synthesis of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines **4b-h**

It was experimentally determined that extending the heating time of tetrahydropyrimidin-2(1*H*)-thione **1** with 2-bromo-1-(4-chlorophenyl)ethanone **2b** to 10 hours leads to the formation of the target 3-(4-chlorophenyl)-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidine **4b** (Scheme 2). Analogous reaction conditions turned out to be optimal for the interaction of tetrahydropyrimidin-2(1*H*)-thione **1** with phenacyl bromide, which contains an electron-donating methoxy group **2c**, as well as its analogues **2d-h** with acceptor substituents in the phenyl nucleus, for the formation of hydrobromides **3b-h**. Their subsequent treatment with an aqueous solution of NaHCO₃ in acetone at room temperature produces the target 3-aryl-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidines **4b-h** with yields of 51–67 % (Scheme 2).

The composition and structure of the synthesized 3-aryl-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidines **4** were proven by a set of physico-chemical analysis methods, in particular by ¹H and ¹³C NMR spectroscopy, chromatography-mass spectrometry, as well as elemental

analysis data. For instance, the presence in the ¹H NMR spectra of a proton singlet of the C² atom of the thiazole ring at 6.07–6.68 ppm serves as a reliable confirmation of the annelation of the thiazole ring. The corresponding C² atom is recorded in the region of 96.1–102.1 ppm in the ¹³C NMR spectra.

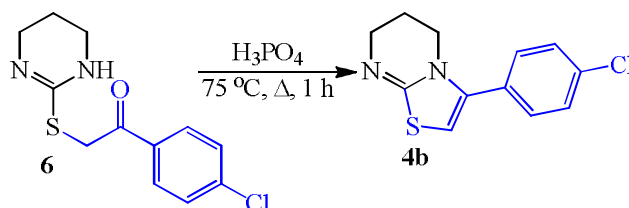
The reaction of electrophilic intramolecular cyclization (EIC) under the action of H₃PO₄⁵² was used to obtain 3-(4-chlorophenyl)-6,7-dihydro-5*H*-[1,3]thiazolo [3,2-*a*] pyrimidine **4b** from the synthesized 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio]ethanone **6**. Heating the derivative **6** in 10 mL of H₃PO₄ at 75 °C for 1 h resulted in intramolecular cyclization and the formation of the target 3-(4-chlorophenyl)-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine **4b** with a yield of 52 % (Scheme 3).

The formation of the thiazole nucleus in the process of intramolecular cyclization is reliably confirmed by the disappearance of the singlet of the SCH₂ group and the broadened singlet of the NH group in the ¹H NMR

spectra and the appearance of the proton singlet of the C² atom of the thiazole ring at 6.25 ppm.

Results of bioscreening of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines **4a-h** proved their moderate antibacterial activity against strains of *S. aureus* ATCC 25923, *E. coli* ATCC 25922, and *P. Vulgaris* ATCC 4636 with minimum inhibitory concentration values of 62.5–125 µg/mL. Testing the synthesized compounds against the fungus *C. albicans* ATCC 885/653, which is

the causative agent of opportunistic human infections, produced more interesting results. For instance, the minimum inhibitory concentrations of derivatives **4a-h** are 31.25 µg/mL and are at the level of the antimicrobial drug “Furacilin” used as a control in this research (Table). The obtained screening results lead us to conclude that further in-depth studies of 3-aryl-6,7-dihydro-5H-[1,3] thiazolo [3,2-*a*] pyrimidines **4a-h** are highly advisable.



Scheme 3. Synthesis of the 3-(4-chlorophenyl)-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine **4b**

Table. Antimicrobial activity of 3-aryl-6,7-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidines **4a-h**

Compounds	<i>Staphylococcus aureus</i> ATCC 25923	<i>Escherichia coli</i> ATCC 25922	<i>Proteus vulgaris</i> ATCC 4636	<i>Candida albicans</i> ATCC 885/653
	MIC, µg/mL	MIC, µg/mL	MIC, µg/mL	MIC, µg/mL
4a	62.5	62.5	62.5	31.25
4b	62.5	62.5	62.5	31.25
4c	62.5	62.5	62.5	31.25
4d	125	62.5	62.5	31.25
4e	62.5	62.5	62.5	31.25
4f	62.5	62.5	62.5	31.25
4g	125	62.5	62.5	31.25
4h	62.5	62.5	62.5	31.25
DMSO	+	+	+	+
Furacilin	3.91	7.81	7.81	31.25

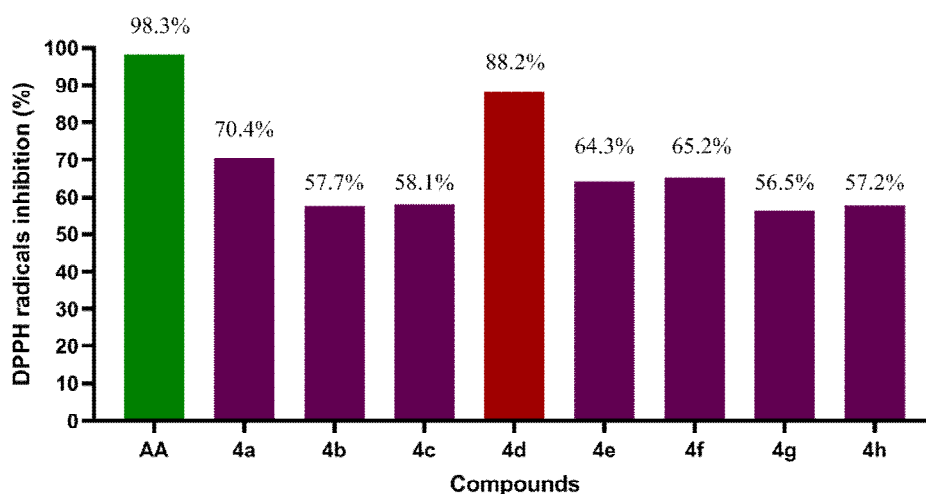


Fig. 3. Rate of inhibition of DPPH radicals by the compounds **4a-h** at 5 mM concentration. Ascorbic acid (AA) was employed as a positive control (green). The highest activity was observed for compound **4d** (red)

The DPPH method is known as a simple, fast, and convenient screening option for radical scavenging activity for various substances, which makes it very useful for testing newly synthesized compounds for their ability to scavenge radicals and searching for promising antioxidant drugs. Screening of antioxidant activity of synthesized thiazolo [3,2-*a*] pyrimidines **4a-h** demonstrated that the inhibition of DPPH radicals reaches 56.5–88.2 % (Fig. 3). The highest antioxidant effect was found for 3-(4-fluorophenyl)-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidine **4d** which absorbs 88.2 % of radicals, whereas its isomer 2-fluorophenylthiazolo [3,2-*a*] pyrimidine **4f** inhibits only 65.2 % of DPPH radicals. 3-(4-nitrophenyl)-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidine **4g** has the lowest radical inhibition value (56.5 %). A relatively lower rate of radical scavenging for compound **4a** (70.4 %), which contains a phenol fragment usually characterized by a pronounced antioxidant effect, was somewhat unexpected⁵³.

4. Conclusions

We have shown that the reaction of tetrahydropyrimidin-2(1*H*)-one with phenacyl bromides is a convenient approach to obtaining biooriented 3-aryl-6,7-dihydro-5*H*-[1,3] thiazolo [3,2-*a*] pyrimidines, and optimal conditions for its course were selected. It was established that the *S*-alkylation product obtained in the case of 2-bromo-1-(4-chlorophenyl)ethanone is 1-(4-chlorophenyl)-2-[(1,4,5,6-tetrahydropyrimidin-2-yl)thio] ethanone that easily undergoes electrophilic intramolecular cyclization under the action of H₃PO₄ to form the target bicyclic system. The screening of the antimicrobial and antioxidant activities of the synthesized compounds proved their promise for further in-depth biological research.

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СИНТЕЗ, АНТИМІКРОБНА Й АНТИ-ОКСИДАНТНА АКТИВНІСТЬ 3-АРИЛ-6,7-ДИГІДРО-5*H*-[1,3] ТІАЗОЛО [3,2-*a*] ПІРИМІДИНІВ

Анотація. Циклоконденсацією тетрагідропіримідин-2(1*H*)-ону з 2-бромо-1-арилетаноном отримано низку 3-арил-6,7-дигідро-5*H*-[1,3] тіазоло [3,2-*a*] піримідинів. Встановлено, що природа замісника в ароматичному ядрі фенацилброміду істотно позначається на перебігу такого типу реакції. Зокрема, у разі 2-бромо-1-(4-гідроксифеніл)етанону цільовий біциклічний продукт утворюється внаслідок 4 год кип'ятіння в етанолі, натомість для циклоконденсації тетрагідропіримідин-2(1*H*)-тіону з іншими бромометиларилкетонами час реакції становив 10 год. Виявлено, що результатом взаємодії тетрагідропіримідин-2(1*H*)-тіону та 2-бромо-1-(4-хлорофеніл)етанону впродовж 4 год є продукт *S*-алкілювання – 1-(4-хлорофеніл)-2-[(1,4,5,6-тетрагідропіримідин-2-іл)тіо]етанон, внутрішньомолекулярна циклізація якого під дією H_3PO_4 приводить до 3-(4-хлорофеніл)-6,7-дигідро-5*H*-[1,3] тіазоло [3,2-*a*] піримідину. Результати біоскрінінгу синтезованих 3-арил-6,7-дигідро-5*H*-[1,3] тіазоло [3,2-*a*] піримідинів продемонстрували їхню помірну антимікробну активність і дали змогу виявити потенційний синтетичний антиоксидант – 3-(4-фторофеніл)-6,7-дигідро-5*H*-[1,3]тіазоло[3,2-*a*]піримідин ($I = 88.2\%$).

Ключові слова: тетрагідропіримідин-2(1*H*)-тіон, 2-бром-1-арилетанон, циклоконденсація, електрофільна внутрішньомолекулярна циклізація, тіазоло [3,2-*a*] піримідин, антимікробна активність, антиоксидантна активність, DPPH.