

UDC 616–093 + 547.789

The novel pyrazolin-5-one bearing thiazolidin-4-ones: synthesis, characterization and biological evaluation

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Aim. Synthesis, structure determination, *in vivo* study of anti-inflammatory (anti-exudative) and ulcerogenic activity, estimation of an impact of novel pyrazolin-5-one bearing thiazolidin-4-ones on liver function. **Methods.** Organic synthesis: multicomponent reactions (MCRs), [2+3]-cycloaddition reactions. Spectral methods: IR, LC-MS, ¹H NMR. Biological methods: study of anti-cancer activity (NCI NIH, USA) protocol for 3-cell line panel); carrageenin-induced inflammatory paw edema model of white rats, biochemical laboratory tests (ALT, AST, ALP, γ -GGT levels determination); evaluation of ulcerogenic action. **Results.** The series of novel C-5 and N-3 substituted 2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl) amino/imino]thiazolidin-4-ones had been synthesized using MCR and [2+3]-cycloaddition reactions as potential biologically active compounds. The results of screening anti-exudative activity revealed that the tested derivatives possess promising anti-inflammatory effect. The SARs were formed and possible mechanisms of their action were discussed. **Conclusions.** The results presented in paper suggest that the design and synthesis of new pyrazolin-5-on/thiazolidin-4-one hybrids as potential molecules are an attractive area for the search for novel agents with promising pharmacological properties.

Key words: antipyrene, pyrazolin-5-one, thiazolidin-4-one, hybrids, multicomponent reactions, tautomers/rotamers; anticancer/anti-inflammatory activity

Introduction

The pyrazolin-5-one scaffold is one of the oldest in medicinal chemistry and at the same time it does not lose its relevance and attractiveness for researchers. It could be aptly demonstrated by the examples of two world-known drugs Antipyrine (Phenazone) [1] and Radicava (Edavaron) [2] (Fig. 1), which belong to the simplest pyrazolin-5-one derivatives but were introduced in pharmaceutical market with a difference of almost 120 years and represent different pharmacological groups. Nowadays pyrazolin-5-ones possess important place as a privilege heterocycles [3, 4]. The pharmacological profile of these compounds is very wide, they are targeted to the treatment and improvement of many difficult pathologies and diseases. The novel molecules with pyrazolin-5-one/antipyryl-4 pharmacophore have been designed, synthesized and successfully studied as selective inhibitors to plausible anti-cancers targets such as vascular endothelial growth factor receptor 2 (VEGFR-2) [5, 6]; c-mesenchymal epithelial transition factor (c-Met) [7,8]; Sirtuins (SIRT) [9]; they display high and selective cytotoxic activity in the *in vitro* models [10]. Noteworthy, some pyrazolin-5-one/antipyr-4-yl bearing compounds are

promising as lipid-lowering [11] and antihyperglycemic [12] agents.

The anti-inflammatory action/activity still remains an actual trend in the design of potential non-steroidal anti-inflammatory drugs (NSAIDs) using pyrazoline-5-one/antipyr-4-yl scaffold for more than 100 years of synthetic work. Nowadays the fragment/structure-based drug design (F/SBDD) [13] and hybrid-pharmacophore approach (HPhA) are useful tools for design of new drug-like molecules in this area of medicinal chemistry [14]. So, the pyrazolin-5-one bearing thiazolidin-4-one hybrids with promising anti-inflammatory (anti-exudative) activity in carrageenan/formaldehyde-induced inflammatory paw edema models of white rats with low-toxicity parameters have been synthesized and reported [15–18] (Fig. 1) using F/SBDD and/or HPhA methodologies.

The oxidative stress [19–21] and redox [22, 23] processes play important role under inflammation condition. The ability of neutralization of the impacts of reactive element species (Oxygen, Nitrogen, free radicals) is a desirable feature for modern NSAIDs [24, 25]. That is why an of the chemical groups with anti-scavenging/anti-oxidant or redox properties into

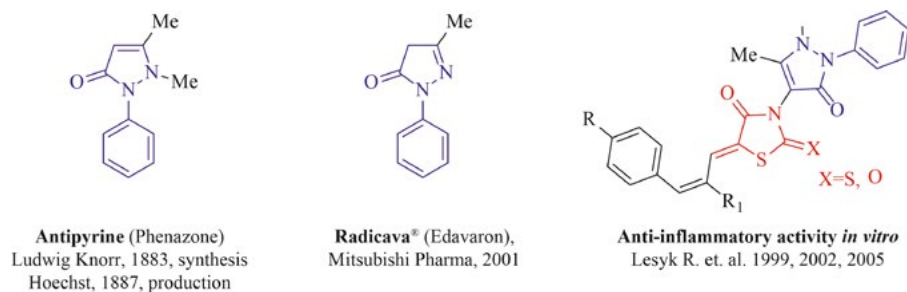


Fig. 1. Pyrazolin-5-one motif in drug design.

the molecular structure of potential NSAIDs seems an attractive strategy for design. Taking into account the above-mentioned reasons and accordingly to our permanent interest to issues of medicinal chemistry of azoles [26–28], here in we report synthetic approaches to novel 5-substituted thiazolidin-4-ones with 4-aminoantipyrine fragments in the C-2 position of heterocycle, their characterization and biological evaluation.

Materials and Methods

Commercial reagents were purchased from Merck and used without purification. Melting points were measured in open capillary tubes on a BÜCHI B-545 melting point apparatus and are uncorrected. The elemental analyses (C, H, N) were performed using the Perkin-Elmer 2400 CHN analyzer; the results were within ± 0.4 % of the theoretical values. The $^1\text{H-NMR}$ spectra were recorded on a Varian Gemini spectrometer at 400 MHz using a mixture of $\text{DMSO-}d_6 + \text{CCl}_4$ as a solvent and TMS as an internal standard. Chemical shift values are reported in ppm units with use of δ scale. Mass spectra were obtained using electrospray ionization (ESI) techniques on Agilent 1100 Series LCMS (column SUPELCO Ascentis Express C18 2.7 μm , 4.6 mm \times 15 cm, solvent — methanol). Infra-red spectra were recorded on OMNIC-510 spectrometer in KBr pellets. The purity of the compounds was checked by thin-layer chromatography performed with Merck Silica Gel 60 F₂₅₄ aluminum sheets. Spots were detected by their absorption under UV light.

General synthetic procedure for compounds 4–6, 16–19. A mixture of compound 2 or 3 (10 mmol) and maleic anhydride

(10 mmol) or appropriate N-arylmaleimides (10 mmol) were refluxed for 2 h in 10 ml of glacial acetic acid. After cooling to room temperature, reaction mixtures were filtered off, washed with methanol and recrystallized with acetic acid (5–15 ml).

General synthetic procedure for compounds 7–15. A mixture of compound 2 (10 mmol), chloroacetic acid (10 mmol), the appropriate oxo-compounds (12 mmol) and anhydrous sodium acetate (20 mmol) was refluxed for 3 h in glacial acetic acid (10 ml). The obtained powders were filtered off, washed with mixture DMF:ethanol (1:3).

2-(2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl)-N-phenylacetamide (4). Yield 57 %, mp >250 °C. Ratio of amine:imine forms 60:40. $^1\text{H NMR}$, δ : 13.00 (s, 1H, NH, amid), 11.10, 10.40 (2*brs, 1H, NH, amine/imine), 7.47–7.55, 7.29–7.44 (2*m, 10H, arom), 4.27–4.31, 4.16–4.20 (2*m, 1H, CH-CH₂), 3.07–3.11, 2.76–2.81, 2.59–2.65 (2*m, 2H, CH-CH₂), 3.10, 3.05 (2*s, 3H, N-CH₃), 2.18, 2.26 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 436.3 (M+H)⁺. Anal. Calc. for C₂₂H₂₁N₅O₃S: C, 60.68 %; H, 4.86 %; N, 16.08 %. Found: C, 60.80 %; H, 5.00 %; N, 16.20 %.

N-(4-Chlorophenyl)-2-(2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl)acetamide (5). Yield 72 %, mp >250 °C. Ratio of amine:imine forms 50:50. $^1\text{H NMR}$, δ : 13.30 (s, 1H, NH, amid), 11.20, 10.40, 10.10 (2*brs+s, 1H, NH,

amine/imine), 7.58 (t, 1H, arom), 7.42–7.52, 7.20–7.30 (2*m, 6H, arom) 7.36 (d, 2H, $J = 7.8$ Hz, arom), 4.36–4.40, 4.21–4.27 (2*m, 1H, CH-CH₂), 3.25–3.30, 2.87–2.92, 2.78–2.81 (3*m, 2H, CH-CH₂), 3.20, 3.10 (2*s, 3H, N-CH₃), 2.30, 2.25, 2.20 (3*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 471.2 (M+H)⁺. Anal. Calc. for C₂₂H₂₀ClN₅O₃S: C, 56.23 %; H, 4.29 %; N, 14.90 %. Found: C, 56.40 %; H, 4.50 %; N, 15.10 %.

***N*-(4-Bromophenyl)-2-(2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxo-4,5-dihydrothiazol-5-yl)acetamide (6)**. Yield 79 %, mp >220 °C. Ratio of amine:imine forms 60:40. ¹H NMR, δ : 10.20 (s, 1H, NH, amine/imine), 7.47–7.55, 7.29–7.44 (2*m, 9H, arom), 4.48–4.51, 4.34–4.38 (2*m, 1H, CH-CH₂), 3.30–3.34, 3.24–3.27, 2.76–2.81 (3*m, 2H, CH-CH₂), 3.15, 3.10 (2*s, 3H, N-CH₃), 2.26, 2.18 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 515.4 (M+H)⁺. Anal. Calc. for C₂₂H₂₀BrN₅O₃S: C, 51.37 %; H, 3.92 %; N, 13.61 %. Found: C, 52.40 %; H, 4.00 %; N, 13.80 %.

***(Z)*-5-Benzylidene-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)thiazol-4(5H)-one (7)**. Yield 41 %, mp 237–238 °C. Ratio of amine:imine forms 60:40. ¹H NMR, δ : 13.00, 9.10 (2*brs, 1H, NH, amine/imine), 7.80 (s, 1H, =CH), 7.41–7.54, 7.25–7.39 (2*m, 10H, arom), 3.19, 3.09 (2*s, 3H, N-CH₃), 2.31, 2.21 (2*s, 3H, =C-CH₃). IR (KBr, cm⁻¹): 3376 (vNH), 1720 (vC=O), 1628 (vC=N) imine-form; 3360

(vNH) 1660 (vC=O), 1608 (vC=N) amine-form; 3080 (v CH), 1684, 1576 (vC=O, vC=N pyrazol), 1516 (vC=C), 1344 (δ CH), 716 (vC-S), 652 (vC-S-C), 769, 696 (δ CH, ArH). LC-MS (ESI+) m/z 391.4 (M+H)⁺. Anal. Calc. for C₂₁H₁₈N₄O₂S: C, 64.60 %; H, 4.65 %; N, 14.35 %. Found: C, 64.80 %; H, 4.80 %; N, 14.50 %.

***(Z)*-2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-5-(4-hydroxybenzylidene)thiazol-4(5H)-one (8)**. Yield 54 %, mp >250 °C. Ratio of amine:imine forms 75:25. ¹H NMR, δ : 13.60, 11.80, 10.70 (3*brs, 1H, NH, amine/imine), 10.19, 9.91, 9.90 (3*s, 1H, OH), 7.88 (s, 1H, =CH), 7.43–7.52 m, 7.28–7.40 (m, 5H, arom), 6.91 (d, 2H, $J = 7.9$ Hz, arom), 6.87 (d, 2H, $J = 7.9$ Hz, arom), 3.29, 3.23 (2*s, 3H, N-CH₃), 2.37, 2.24 (2*s, 3H, =C-CH₃). IR (KBr, cm⁻¹): 3384 (vNH), 1720 (vC=O), 1652 (vC=N) imine-form; 3360 (vNH) 1672 (vC=O), 1596 (vC=N) amine-form; 3632 (vOH), 3080 (vCH), 1684, 1524 (vC=O, vC=N pyrazol), 1340 (δ CH), 1508 (v C=C), 1156 (δ C-O), 760 (δ CH, ArH) 720 (vC-S), 656 (vC-S-C). LC-MS (ESI+) m/z 407.3 (M+H)⁺. Anal. Calc. for C₂₁H₁₈N₄O₃S: C, 62.06 %; H, 4.46 %; N, 13.78 %. Found: C, 62.30 %; H, 4.60 %; N, 13.90 %.

***(Z)*-5-(4-Chlorobenzylidene)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)thiazol-4(5H)-one (9)**. Yield 62 %, mp >250 °C. Ratio of amine:imine forms 50:50. ¹H NMR, δ : 11.70, 10.55 (2*brs, 1H, NH,

amine/imine), 7.64 (s, 1H, =CH), 7.47–7.54, 7.32–7.43 (2*m, 5H, arom), 7.25 (d, 2H, $J = 8.1$ Hz, arom), 7.20 (d, 2H, $J = 8.1$ Hz, arom), 3.27, 3.19 (2*s, 3H, N-CH₃), 2.31, 2.19 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 426.5 (M+H)⁺. Anal. Calc. for C₂₁H₁₇ClN₄O₂S: C, 59.36 %; H, 4.03 %; N, 13.19 %. Found: C, 59.50 %; H, 4.20 %; N, 13.30 %.

(Z)-5-(4-Bromobenzylidene)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)thiazol-4(5H)-one (10). Yield 57 %, mp>250 °C. Ratio of amine:imine forms 50:50. ¹H NMR, δ : 14.00, 12.00, 9.50, 9.30 (2*brs+2*s, 1H, NH, amine/imine), 7.68–7.74, 7.48–7.62, 7.33–7.43 (3*m, 10H, =CH+ arom), 3.21, 3.13 (2*s, 3H, N-CH₃), 2.32, 2.22 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 470.2 (M+H)⁺. Anal. Calc. for C₂₁H₁₇BrN₄O₂S: C, 53.74 %; H, 3.65 %; N, 11.94 %. Found: C, 53.90 %; H, 3.80 %; N, 12.10 %.

(Z)-2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-5-(4-methoxybenzylidene)thiazol-4(5H)-one (11). Yield 62 %, mp=201–204 °C. Ratio of amine:imine forms 74:26. ¹H NMR, δ : 13.30, 9.00 (brs+s, 1H, NH, amine/imine), 7.95 (s, 1H, =CH), 7.61 (d, 2H, $J = 7.6$ Hz, arom), 7.45–7.59, 7.30–7.42 (2*m, arom) 7.10 (d, 2H, $J = 7.3$ Hz, arom), 7.05 (t, 1H, $J = 7.9$ Hz, arom), 3.84, 3.83, 3.82 (3*s, 3H, OCH₃), 3.28, 3.22, 3.12 (3*s, 3H, N-CH₃), 2.33, 2.24, 2.23 (3*s, 3H, =C-CH₃). IR (KBr, cm⁻¹): 3384 (vNH), 1720 (vC=O), 1636 (vC=N) imine-form; 3365 (vNH) 1664 (vC=O),

1592 (vC=N) amine-form; 3096 (vCH), 2860 (vO-CH₃), 1680, 1576 (vC=O, vC=N pyrazol), 1512 (vC=C), 1348 (δ CH), 764, 680 (δ CH, ArH), 712 (vC-S), 648 (vC-S-C). LC-MS (ESI+) m/z 421.7 (M+H)⁺. Anal. Calc. for C₂₂H₂₀N₄O₃S: C, 62.84 %; H, 4.79 %; N, 13.32 %. Found: C, 62.90 %; H, 5.00 %; N, 13.50 %.

(Z)-2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-5-(4-hydroxy-3-methoxybenzylidene)thiazol-4(5H)-one (12). Yield 46 %, mp>250 °C. Ratio of amine:imine forms 70:30. ¹H NMR, δ : 13.00, 10.20 (brs+s, 1H, NH, amine/imine), 9.25, 9.00 (2*s, 1H, OH), 7.75 (s, 1H, =CH), 7.40–7.55, 7.20–7.35 (2*m, arom), 7.13 (d, 2H, $J = 7.2$ Hz, arom), 3.75, 3.68 (2*s, 3H, OCH₃), 3.25, 3.13 (2*s, 3H, N-CH₃), 2.29, 2.19 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 437.6 (M+H)⁺. Anal. Calc. for C₂₂H₂₀N₄O₄S: C, 60.54 %; H, 4.62 %; N, 12.84 %. Found: C, 60.70 %; H, 4.90 %; N, 13.00 %.

(Z)-5-(3,4-Dimethoxybenzylidene)-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)thiazol-4(5H)-one (13). Yield 41 %, mp=241–243 °C. Ratio of amine:imine forms 70:30. ¹H NMR, δ : 12.90, 9.00 (2*brs, 1H, NH, amine/imine), 7.70 (s, 1H, =CH), 7.40–7.50, 7.20–7.35 (2*m, arom), 3.85, 3.83, 3.73, 3.68 (4*s, 6H, 2*OCH₃), 3.29, 3.18 (2*s, 3H, N-CH₃), 2.32, 2.23 (2*s, 3H, =C-CH₃). IR (KBr, cm⁻¹): 3368 (vNH) 1681 (vC=O), 1628 (vC=N) imine-form; 3352 (vNH), 1664

($\nu\text{C}=\text{O}$), 1608 ($\nu\text{C}=\text{N}$) amine-form; 3069 (νCH), 2856 ($\nu\text{O}-\text{CH}_3$), 1580 ($\nu\text{C}=\text{N}$ pyrazol), 1518 ($\nu\text{C}=\text{C}$), 1356 (δCH), 772 (δCH , ArH), 716 ($\nu\text{C}-\text{S}$), 664 ($\nu\text{C}-\text{S}-\text{C}$). LC-MS (ESI+) m/z 451.5 ($\text{M}+\text{H}$)⁺. Anal. Calc. for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 61.32 %; H, 4.92 %; N, 12.44 %. Found: C, 61.60 %; H, 5.10 %; N, 12.70 %.

(Z)-2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-5-(3-nitrobenzylidene)thiazol-4(5H)-one (14). Yield 51 %, mp>250 °C. Ratio of amine:imine forms 25:75. ¹H NMR, δ : 14.06 (s, 1H, NH, amine/imine), 8.40, 8.38 (2*s, 1H, =CH), 8.16–8.24, 7.88–8.00, 7.38–7.60 (3*m, arom) 7.77 (t, 1H, $J = 8.3$ Hz, arom), 7.32 (t, 1H, $J = 8.5$ Hz, arom), 3.26, 3.15 (2*s, 3H, N-CH₃), 2.38, 2.26 (2*s, 3H, =C-CH₃). IR (KBr, cm⁻¹): 3376 (νNH), 1728 ($\nu\text{C}=\text{O}$), 1636 ($\nu\text{C}=\text{N}$) imine-form; 3352 (νNH) 1664 ($\nu\text{C}=\text{O}$), 1608 ($\nu\text{C}=\text{N}$) amine-form; 3064 (νCH), 1577 ($\nu\text{C}=\text{N}$ pyrazol), 1532 ($\nu\text{C}=\text{C}$), 1352 (δCH), 768, 696 (δCH , ArH), 712 ($\nu\text{C}-\text{S}$), 664 ($\nu\text{C}-\text{S}-\text{C}$). LC-MS (ESI+) m/z 436.4 ($\text{M}+\text{H}$)⁺. Anal. Calc. for $\text{C}_{21}\text{H}_{17}\text{N}_5\text{O}_4\text{S}$: C, 57.92 %; H, 3.94 %; N, 16.08 %. Found: C, 58.00 %; H, 4.10 %; N, 16.20 %.

(Z)-2-((1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-5-((E/Z)-3-phenylallylidene)thiazol-4(5H)-one (15). Yield 58 %, mp=194–197 °C. Ratio of amine:imine forms 60:40. ¹H NMR, δ : 13.72, 11.81, 10.69 (s+2*brs, 1H, NH, amine/imine), 7.46–7.60, 7.27–7.43, 7.07–7.15, 6.80–

6.88 (4*m, arom+CH=CH-CH=), 3.20, 3.19, 3.10 (3*s, 3H, N-CH₃), 2.35, 2.21 (2*s, 3H, =C-CH₃). LC-MS (ESI+) m/z 417.3 ($\text{M}+\text{H}$)⁺. Anal. Calc. for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2\text{S}$: C, 66.33 %; H, 4.84 %; N, 13.45 %. Found: C, 66.50 %; H, 5.10 %; N, 13.60 %.

2-(3-Allyl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxothiazolidin-5-yl)acetic acid (16). Yield 74 %, mp=200–203 °C. ¹H NMR, δ : 12.5 (brs, 1H, COOH), 7.50 (t, 1H, $J = 8.5$ Hz, arom), 7.40 (t, 2H, $J = 8.7$ Hz, arom), 7.20 (d, 2H, $J = 7.7$ Hz, arom), 5.86–5.90 (m, 1H, allyl), 5.30 (d, 1H, $J = 1.6$ Hz, allyl), 5.20 (d, 1H, $J = 1.6$ Hz, allyl), 4.40 (d, 2H, $J = 1.7$ Hz, allyl), 4.46–4.50 (m, 1H, CH-CH₂), 3.20 (dd, 1H, $J = 18.0$ Hz, $J = 7.5$ Hz, CH-CH₂), 2.80 (dd, 1H, $J = 18.0$ Hz, $J = 5.0$ Hz, CH-CH₂), 3.00 (s, 3H, N-CH₃), 2.10 (s, 3H, =C-CH₃). LC-MS (ESI+) m/z 403.8 ($\text{M}+\text{H}$)⁺. Anal. Calc. for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 56.70 %; H, 5.51 %; N, 13.92 %. Found: C, 56.80 %; H, 5.70 %; N, 14.00 %.

2-(3-Allyl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxothiazolidin-5-yl)-N-phenylacetamide (17). Yield 63 %, mp=184–186 °C. ¹H NMR, δ : 9.90 (s, 1H, NH), 7.00–7.60 (m, arom), 5.86–5.90 (m, 1H, allyl), (d, 1H, $J = 1.6$ Hz, allyl), 5.20 (d, 1H, $J = 1.6$ Hz, allyl), 4.40 (d, 2H, $J = 1.7$ Hz, allyl), 4.46–4.50 (m, 1H, CH-CH₂), 3.30 (dd, 1H, $J = 17.8$ Hz, $J = 7.6$ Hz, CH-CH₂), 2.50 (dd, 1H, $J = 17.9$ Hz, $J = 4.8$ Hz, CH-CH₂), 3.00 (s, 3H, N-CH₃), 2.20 (s, 3H, =C-CH₃). LC-

MS (ESI+) m/z 478.4 (M+H)⁺. Anal. Calc. for C₂₅H₂₇N₅O₃S: C, 62.87; H, 5.70; N, 14.66 %. Found: C, 63.00 %; H, 5.90 %; N, 14.80 %.

2-(3-Allyl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxothiazolidin-5-yl)-N-(4-chlorophenyl)acetamide (18). Yield 63 %, mp=193–196 °C. ¹H NMR, δ: 10.10 (s, 1H, NH), 7.40–7.60 (m, arom) 7.32 (t, 1H, *J* = 8.7 Hz, arom), 7.18 (t, 2H, *J* = 7.5 Hz, arom), 5.86–5.90 (m, 1H, allyl), (d, 1H, *J* = 1.7 Hz, allyl), 5.20 (d, 1H, *J* = 1.7 Hz, allyl), 4.40 (d, 2H, *J* = 1.7 Hz, allyl), 4.48–4.51 (m, 1H, CH-CH₂), 3.30 (dd, 1H, *J* = 18.2 Hz, *J* = 7.4 Hz, CH-CH₂), 2.80 (dd, 1H, *J* = 18.1 Hz, *J* = 5.1 Hz, CH-CH₂), 3.00 (s, 3H, N-CH₃), 2.10 (s, 3H, =C-CH₃). LC-MS (ESI+) m/z 513.2 (M+H)⁺. Anal. Calc. for C₂₅H₂₆ClN₅O₃S: C, 58.64 %; H, 5.12 %; N, 13.68 %. Found: C, 58.80 %; H, 5.30 %; N, 13.80 %.

2-(3-Allyl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino)-4-oxothiazolidin-5-yl)-N-(4-bromophenyl)acetamide (19). Yield 61 %, mp=196–198 °C. ¹H NMR, δ: 10.00 (s, 1H, NH), 7.40–7.60, 7.25–7.38 (m, 9H, arom), 5.86–5.90 (m, 1H, allyl), (d, 1H, *J* = 1.7 Hz, allyl), 5.20 (d, 1H, *J* = 1.7 Hz, allyl), 4.40 (d, 2H, *J* = 1.7 Hz, allyl), 4.45–4.49 (m, 1H, CH-CH₂), 3.20 (dd, 1H, *J* = 18.0 Hz, *J* = 7.3 Hz, CH-CH₂), 2.70 (dd, 1H, *J* = 18.0 Hz, *J* = 4.9 Hz, CH-CH₂) 3.00 (s, 3H, N-CH₃), 2.15 (s, 3H, =C-CH₃). LC-MS (ESI+) m/z 556.4 (M+H)⁺. Anal. Calc. for C₂₅H₂₆BrN₅O₃S: C, 53.96 %;

H, 4.71 %; N, 12.59 %. Found: C, 54.10 %; H, 5.00 %; N, 12.80 %.

Anticancer assay. A primary anticancer assay was performed in the 3-cell line panel consisting of NCI-H460 (Lung), MCF7 (Breast) and SF-268 (CNS), in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda [29, 30].

Anti-inflammatory (antiexudative) assay. The male albino rats weighing 180–220 g were used for studying the anti-exudative activity. The animals were treated humanely throughout the study period adhering to the guideline for use and care of animals in 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. 4, January 23, 2020. The carrageenan-induced hind paw oedema was produced by the method of Winter *et al.* [31].

Assessment of liver function. The serum collected from the albino rats was used for estimation of biochemical parameters to determine the functional state of the liver.

Estimation of ulcerogenic activity. The estimation of ulcerogenic activity was performed according to recommendations [32].

Results and Discussion

Chemistry

The 4-amino-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (4-aminoantipyrine, **1**) was used as a starting reagent for synthesis of target derivatives **4–19** (Scheme 1) according to selected synthetic strategy. The key

building block 1-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)thiourea (**2**) was synthesized from **1** following two-step approach (**a,b**). The utilization of **2** in [2+3]-cyclocondensation reaction with N-arylmaleimides (**c**) as well as in three-component one-pot process with chloroacetic acid and aromatic aldehydes (**d**) efficiently lead to C-5 modified thiazolidin-4-one derivatives **4–6** and **7–15** respectively. The 1-allyl-3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)thiourea (**3**) has been obtained in reaction **1** with allyl isothiocyanate (**e**). The 3-allyl-substituted thiazolidin-4-ones (**16–19**) were synthesized in [2+3]-cyclocondensation reaction of **3** with maleic anhydride (**f**) and N-arylmaleimides (**c**).

The ¹H NMR, IR spectroscopies and LC-MS spectrometry were used for structure determination of the synthesized compounds. The 2-R-imino/amino-thiazolidin-4-ones possess prototropic amine/imine tautomerism [33]. In the ¹H NMR spectra of compounds **4–15** the signals of both tautomeric forms were observed. The signals of amine-forms protons of compounds were observed at 9.00–10.70 ppm and the signals of imine-forms protons were observed at 11.0–14.06 ppm. The ratio of tautomers based on the integral intensity curve ranges from ~3:1 to ~1:3 (amine-imine forms respectively). The correlation of the prevalence amine- or imine-form with electron nature of substituent in C-5 was observed. The presence of electron withdrawing group (NO₂-group) leads increasing of imine-form whereas the electron releasing groups (OMe, OH) result in [the] prevalence of amine-form. The ¹H NMR spectral patterns of derivatives **5, 8, 10–12, 15** are more complex and the appearance of 3 or

4 groups of signals which belong to possible rotameric forms was observed (Fig. 2). The studies of IR-spectra of compounds **7, 8, 11, 13, 14** confirmed the presence of amine/imine tautomerism in the solid state.

Pharmacology

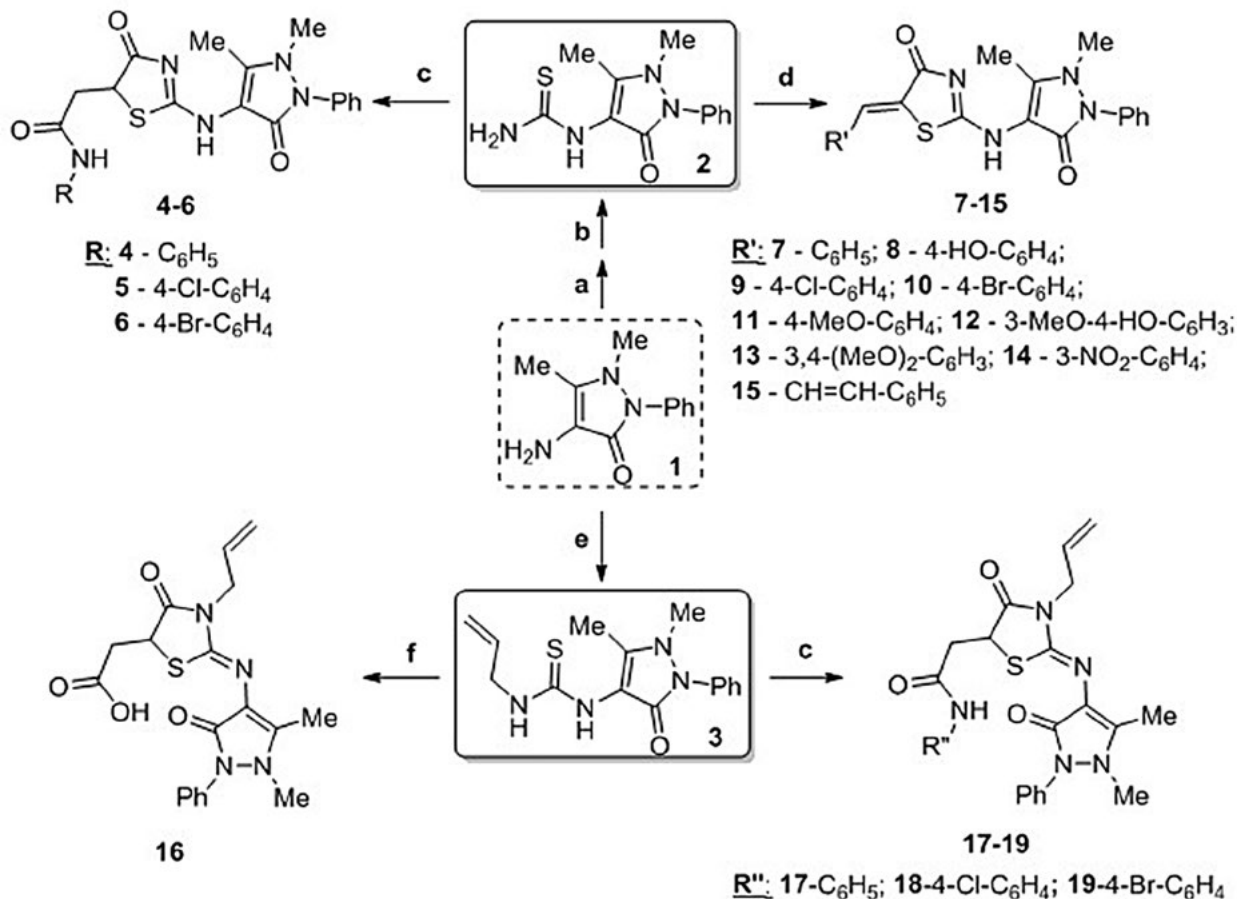
Anticancer activity

The last decades have witnessed a growing interest in the studies of anticancer properties of NSAIDs and compound with anti-inflammatory activity [34, 35]. The prescreening of anti-cancer activity of compounds **7, 11, 13** was performed according to the US NCI protocol, as described elsewhere [29, 30]. These substances were evaluated in the 3-cell line panel consisting of NCI-H460 (Lung), MCF7 (Breast), and SF-268 (CNS) cell lines. As a result all tested compounds were found inactive and in the pre-screening phase (Table 1). Only compound **11** showed moderate growth inhibition activity (69 %) against Lung cancer cell line NCI-H460.

Table 1. Anticancer screening (3 cell lines assay) data of compounds **7, 11, 13** in 10 μM concentration

Compound/ NCI number	Cell lines and growth percent of treated cells, %		
	NCI-H460, Lung cancer	SF-268, CNS cancer	MCF7, breast cancer
7 / S730128	96	117	114
11 / S729939	69	87	97
13 / S730129	89	115	108

Despite, that presented anti-cancer activity results indicate that only derivative **11** possesses low activity, but the presence of one, as well as the prevailing impact on NCI-H460 line (Lung cancer), give opportunities for perspectives of rational design of anticancer



Scheme 1. Synthesis of thiazolidin-4-ones with pyrazolin-5-one moiety in molecules (**2–19**). Reagents and conditions: (a) **1** (10 mmol), NH₄SCN (10 mmol), HCl (conc.) (10 mmol), C₆H₅COCl (10 mmol), acetone, 30 min, heating; (b) 10% NaOH (aq.), reflux, 1h, 61%; (c) **2** or **3** (10 mmol), N-arylmaleimides (10 mmol), EtOH (20 mL), reflux, 2 h, 57–89%; (d) **2** (10 mmol), ClCH₂COOH (10 mmol), R'-CHO (10 mmol), AcONa (20 mmol), AcOH (10 mL), 3 h, reflux, 51–64%; (e) **1** (10 mmol), allyl isothiocyanate (12 mmol), i-PrOH, 2 h, reflux, 65%; (f) **3** (10 mmol), maleic anhydride (10 mmol), EtOH (20 mL), reflux, 2 h, 74%.

agents among such type of pyrazolin-5-one/thiazolidin-4-one hybrids.

Anti-inflammatory (anti-exudative) activity

Fourteen novel synthesized pyrazolin-5-one/thiazolidin-4-one hybrids have been studied for their anti-inflammatory activity *in vivo* on

carrageenin-induced paw oedema in rats (Table 2). All tested derivatives possess anti-exudative activity at different level. Five derivatives (34.5% from total amount) **9**, **10**, **15**, **16**, **18** have demonstrated the effect, which was $\geq 50\%$ compared to reference-drug (Diclofenac sodium) one. The derivatives **9** and **15** were found as the most active in the

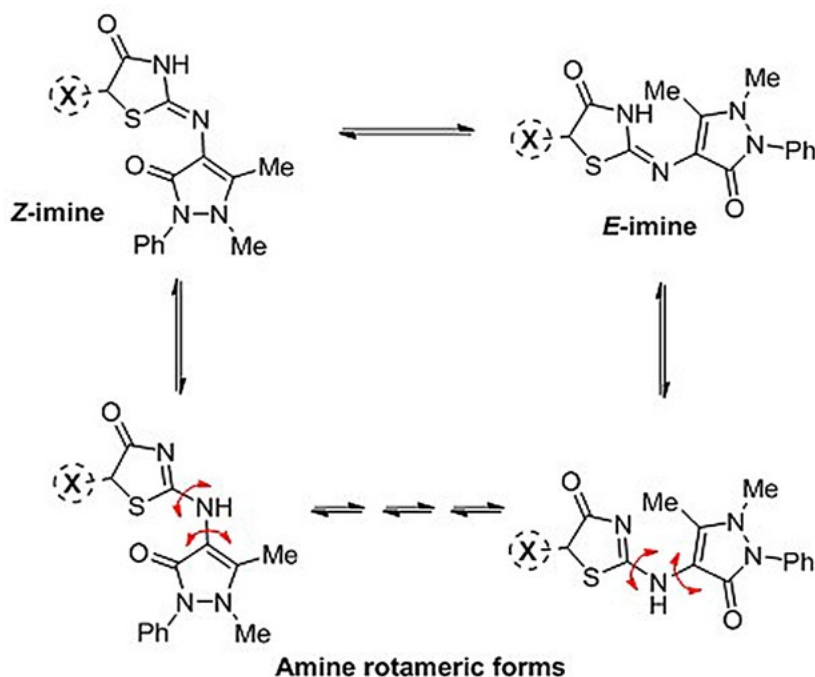


Fig. 2. Possible tautomeric/rotameric forms for compounds **4–15**.

experiment with the inhibition values of 48.3 % and 50.6 % respectively compared to the untreated (carrageenin) group. Their activity levels were almost equal to Diclofenac sodium effect.

The SAR studies revealed that the activity level depends on the nature of C-5 as well as N-3 attached substituents in thiazolidin-4-one ring. The C-5-ylidene derivatives (**7–15**) resulted in a higher activity level than [the] C-5-N-phenylacetamide ones (**4–6**) in series of [the] N-3-unsubstituted compounds (**4–15**). The derivative **15** with [the] C-5-propenylidene fragment was found to be the most active among all tested compounds (50.6 % inhibition, activity relative Diclofenac sodium 97.7 %). The derivative **9** with the C-5-(*p*-chloro)-benzylidene substituent demonstrated a lower level of activity and its inhibition

value was 48.3 % (93.2 % compared] to the reference drug activity). The introduction of both acetic acid residue in C-5 position and allyl group in position N-3 (compounds **16–19**) did not provide for significant improvement of anti-exudative properties (Table 2). However noteworthy, the presence of carboxylic group in structure (**16**) is eventually an advantage feature and could be used for the properties optimization through the synthesis of water-soluble organic/inorganic salts and thus an increase in the bioavailability/activity. The most active derivatives **9**, **15**, **18** were evaluated for their impact on the liver enzyme function and ulcerogenic activity (Table 3).

Thus, the compounds **9**, **15**, **18** do not lead to the appearance of negative changes in the key liver enzymes function as well as do not induce ulcerogenic action.

Table 2. *In vivo* anti-inflammatory activity of compounds 4–11, 13, 15–19 on carrageenin-induced paw oedema 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, %	Activity relative to Diclofenac sodium, %
Carrageenin	127.9±6.3	-	-
Diclofenac sodium	61,6±3.8	51.8	-
4	109.6±7.7	14.3	27.6
5	96.2±8.1	24.8	47.8
6	104.1±9.3	18.6	35.9
7	111.8±10.2	12.6	24.3
8	99.1±7.4	22.5	43.3
9	66.1±4.3	48.3	93.2
10	94.6±8.0	26.0	50.2
11	98.1±6.9	23.3	44.9
13	103.1±9.9	19.4	37.5
15	63.2±4.6	50.6	97.7
16	89.9±8.6	29.7	57.3
17	105.5±10.0	17.5	33.8
18	87.7±6.3	31.4	60.6
19	97.3±8.4	23.9	46.1

Summarizing our studies on the search for potential anti-inflammatory agents among antipyryl-4 based thiazolidin-4-ones we have observed the next SAR (Fig. 3): a) the hybrids with antipyryl-4 fragment linked in N-3 position of thiazolidin-4-one nucleus are optimal and possess anti-exudative activity higher than the relevant reference drugs; b) cinnamic aldehydes and *p*-chloro-benzaldehyde moieties in C-5 position of thiazolidin-4-one are pivotal and optimal for their activity; c) 2-thioxo-derivatives of 3-(antipyryl-4)-thiazolidin-4-ones demonstrate a higher activity level compare[d] to 2-oxoanalogs; d) replacement of the aromatic aldehyde fragments at C-5 position by acetic acid or R-phenylacetamides residues provoke attenuation of the anti-exudative effect; e) introduction of the second

pyrazolone fragment linked via imine/amine linker as well as its replacement from position 3 to 2 in the position 2 of thiazolidin-4-one does not enhance the anti-exudative effect; f) introduction of allyl group in N-3 position does not cause a positive impact on the effect.

The mechanism of anti-exudative action for 5-substituted antipyryl-4 based thiazolidin-4-ones (Fig. 3) seems very attractive for study due to the presence of set potential pharmacophore fragments in their molecules. It is known that pyrazolones act by the inhibition of both isoforms of cyclooxygenase (COX-1, COX-2, and COX-3) enzymes involved in the prostaglandin (PG) synthesis [4, 36]. The inhibition of 5-lipoxygenase (5-LOX), COX-2 and phospholipases A2 (PLA2s) has been reported for 5-ene-thiazolid-4-one scaffold [37]. Nowadays

Table 3. Studies of key liver enzymes function and ulcerogenic action in treatment with compounds 9, 15, 18 and Diclofenac sodium under carrageenin-induced paw oedema 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/ Parameters	ALT ^a , U/l	AST ^b , U/l	ALP ^c , IU/l	γ-GGT ^d , IU/l	Animals with ulcers, n ^e	Ulcer degree, points
Intact animals*	61.1–84.5	139.3–194.6	180.2–281.9	1.8–4.8	0	0±0.00
Diclofenac sodium	79.7±6.2	184.1±19.7	233.0±23.9	3.0±0.5	2	1.0±0.1
9	67.5±5.9	149.9±15.2	206.7±20.9	2.6±0.6	0	0±0.00
15	74.0±7.1	168.3±20.4	212.4±22.7	2.1±0.4	0	0±0.00
18	75.5±8.3	152.7±23.6	221.3±25.8	2.9±0.6	0	0±0.00

* — the data for intact male albino rats groups from LNMU vivarium were used; ^a — 1 U = 0.0165 μkat/L; ^b — 1 U = 0.0167 μkat/L; ^c — 1 IU = 0.1667 μkat/L; ^d — 1 U = 0.1667 μkat/L

the modulation of nuclear factor kappa-light-chain-enhancer of the activated B cells (NF-κB) signaling pathway is considered as the potential target for 5-ene-thiazolidin-4-ones and as a promising molecular mechanism for anti-inflammatory effect [38]. Also, it is also important and worth to note that the presence of cinnamic aldehydes residues resulting in the best activity level for **15** (as well as for previously reported analogues [15–18]) is a com-

mon structure feature with known pharmacological agent Epalrestat (ONO-2235), which was originally developed as the aldose reductase (ALR) inhibitor and used for the treatment of diabetic neuropathy. According to modern insights the inhibition of aldose reductase is one of the prospective strategies for design of potential anti-inflammatory agents [39]. Thus, for the all above-mentioned reasons the multi-target anti-inflammatory action might be ex-

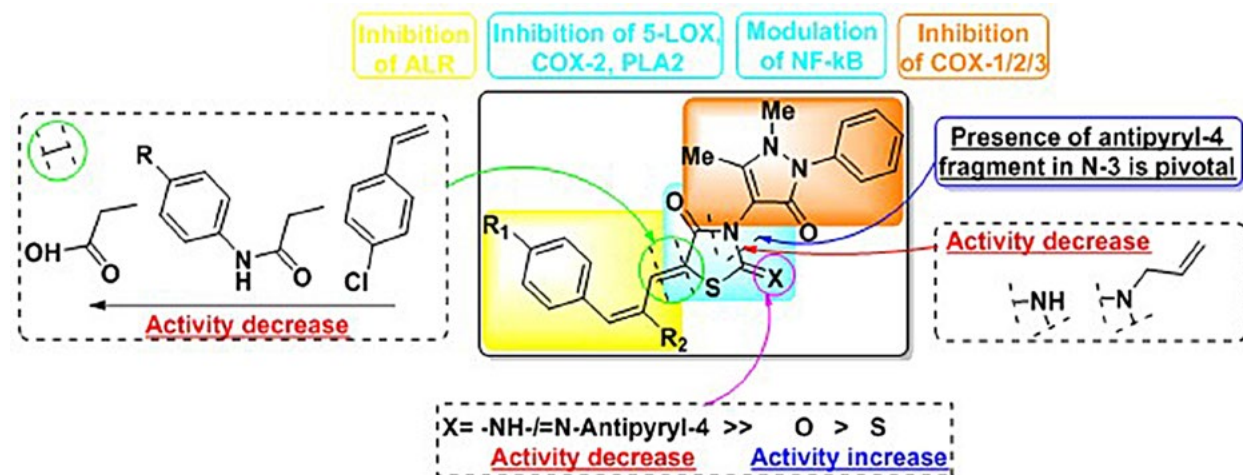


Fig. 3. Possible potential anti-inflammatory pharmacophores and structure - anti-inflammatory activity relationships for antipyryl-4 based thiazolidin-4-ones.

pected for this class of molecular hybrids and, undoubtedly, more comprehensive additional research is required.

Conclusions

In this paper the synthetic approaches to series of novel 2-imine/amine-(antipyryl-4)-thiazolidin-4-ones were proposed. The structure and tautomerism of synthesized compounds were confirmed and studied using LC-MS and ¹H NMR, IR spectra. The selected compounds were evaluated for their anticancer and anti-inflammatory activities. The lead-compounds were identified, which were equal to the reference drug Diclofenac sodium by the anti-inflammatory activity but had neither negative impact on the key liver enzymes function nor ulcerogenic action. The SARs were formed and possible mechanisms of action were discussed. The obtained results are promising for the future design and synthesis of new pyrazolin-5-on/thiazolidin-4-one hybrids as the potential molecules with promising pharmacological properties.

Funding

This work was partially supported by COST Action NutRedOx-CA161112 “Personalized Nutrition in ageing society: redox control of major aged-related diseases” (for Holota S.) and Ministry of Healthcare of Ukraine (project 0121U100690).

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Синтез, характеристика та біологічна оцінка нових піразолін-5-он-заміщених тiazолідин-4-онів

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Мета. Синтез, визначення структури, дослідження *in vivo* протизапальної (антиексудативної) та ульцерогенної активності, оцінка впливу на функцію печінки нових піразолін-5-он заміщених тiazолідин-4-онів. **Методи.** Традиційний органічний синтез: мультикомпонентні реакції (МКР), реакції [2+3]-циклоприєднання. Спектральні методи: ІЧ, РХ-МС, ¹H ЯМР. Біологічні методи: дослідження протиракової активності (протокол NCI (НИН, США) 3 лінії ракових клітин); карагенін-індукована модель запального набряку лапи білих шурів, біохімічні лабораторні дослідження (визначення рівня АЛТ, АСТ, ЛФ, γ-ГГТ); оцінка ульцерогенної дії. **Результати.** Серію нових С-5 і N-3 заміщених 2-[(1,5-диметил-3-оксо-2-феніл-2,3-дигідро-1H-піразол-4-іл)аміно/іміно]tiazолідин-4-онів, як потенційних біологічно активних сполук, було синтезовано з використанням МКР та реакцій [2+3]-циклоприєднання. За результати скринінгу антиексудативної активності встановлено, що тестовані похідні виявляють протизапальний ефект. Визначені залежності “структура-протизапальна активність” для антипірин-заміщених тiazолідин-4-онів та обговорені можливі механізми дії. **Висновки.** Отримані і представлені в роботі результати свідчать про те, що дизайн та синтез нових піразолін-5-он/tiazолідин-4-онових гібридів є перспективним напрямком для пошуку нових молекул/агентів з потенційними фармакологічними властивостями.

Ключові слова: антипірин, піразолін-5-он, тiazолідин-4-он, гібридні молекули, багатокомпонент-

ні реакції, таутомери/ротамери, протиракова/проти-
запальна активність.

**Синтез, характеристика и биологическая
оценка новых пиразолина-5-он-замещенных
тиазолидин-4-онов**

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Цель. Синтез, определение структуры, исследования *in vivo* противовоспалительной (антиэкссудативной) и ulcerогенной активности, оценка влияния на функцию печени новых пиразолина-5-он замещенных тиазолидин-4-онов. **Методы.** Традиционный органический синтез: мультикомпонентные реакции (МКР), реакции [2+3]-циклоприсоединения. Спектральные методы: ИК, ЖХ-МС, ¹Н ЯМР. Биологические методы: исследование противораковой активности (протокол NCI (НИН, США) 3 линии раковых клеток); карагенин-индуцированная модель воспалительного отека лапы белых крыс; биохимические лабораторные исследования (определение уровня АЛТ, АСТ, ЩФ, γ-ГТТ) оценка ulcerогенного действия. **Результаты.**

Серию новых С-5 и N-3 замещенных 2-[(1,5-диметил-3-оксо-2-фенил-2,3-дигидро-1*H*-пиразол-4-ил)амино/имино]тиазолидин-4-онов, как потенциальных биологически активных соединений, было синтезировано с использованием МКР и реакций [2+3]-циклоприсоединения. По результатам скрининга антиэкссудативного активности установлено, что тестируемые производные проявляют противовоспалительный эффект. Определены зависимости «структура-противовоспалительная активность» для антипирин-замещенных тиазолидин-4-онов и обсуждены возможные механизмы действия. **Выводы.** Полученные и представленные в работе результаты свидетельствуют о том, что дизайн и синтез новых пиразолин-5-он/тиазолидин-4-оновых гибридов является перспективным направлением для поиска новых молекул/агентов с потенциальными фармакологическими свойствами.

Ключевые слова: антипирин, пиразолин-5-он, тиазолидин-4-он, гибридные молекулы, многокомпонентные реакции, таутомеры/ротамеры, противораковая/противовоспалительная активность.

Received 15.10.2020