**Preliminary evaluation of thiazolidinone- and pyrazoline-related heterocyclic derivatives as potential antimalarial agents**

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**Aim.** Synthesis of a series of thiazolidinone- and pyrazoline-related compounds. *In vitro* screening of antiplasmodial activity of versatile heterocyclic derivatives. **Methods:** organic wet synthesis, analytical and spectral methods, pharmacological screening, SAR analysis. **Results.** A series of different thiazolidinone- and pyrazoline-based derivatives was screened against *Plasmodium falciparum* in *in vitro* assays. 5-(Z)-Arylidene-2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones showed high growth inhibition rates with the IC₅₀=2.32-2.39 µM. 5-Bromo-1-[2-[3-(4-chlorophenyl)-5-(4-methoxyphenyl)-3,4-dihydropyrazol-2-yl]-2-oxoethyl]indoline-2,3-dione ³ was the most active compound among tested with the IC₅₀=1.81 µM. Based on the screening data some structure-activity relationships were derived. **Conclusions.** A set of different thiazolidinone- and pyrazoline-related derivatives with antitrypanosomal and anticancer properties was screened against *Plasmodium falciparum*. Hit-compounds inhibiting growth of the parasite at micromolar concentrations were identified. The obtained results provide further avenues to develop more potent antimalarial agents on the base of investigated classes of small drug-like molecules. **Keywords:** thiazolidinone, pyrazoline, antimalarial activity, SAR analysis

**Introduction**

The thiazolidinone based molecules had been widely studied and described as a fruitful source of novel drug-like molecules with a variety of pharmacological profiles [1-4]. Recently, the thiazolidinone/thiazole derivatives became interesting in the field of antiparasitic agents search [5-9]. We had designed and synthesized a class of rhodanine derivatives – 5-enamine-2-thioxo-4-thiazolidinone-3-carboxylic acids that showed [the] significant trypanocidal activity towards *Trypanosoma brucei gambiense* along with a good cytotoxicity profile against the myoblast derived cell line (L-6). The selectivity indices for these
compounds were within 158–1396.2 (calculated as the ratio of CC$_{50}$ to IC$_{50}$) designating this class of rhodanine-3-carboxylic acids as perspective in the search for antitrypanosomal agents [10]. For a number of related 5-benzylidenerhodanine-3-acetic acids the inhibitory activity against Trypanosoma brucei dolichol-phosphate mannose synthase and glycosylphosphatidylinositol anchor was studied, these compounds also showed [the] in vitro trypanocidal activity against bloodstream forms [7]. There was also identified a row of hit-compounds among thiazolidinone/thiazole-imidazothiadiazole/phenyl-indole hybrids inhibiting growth of Trypanosoma brucei brucei and Trypanosoma gambiense at submicromolar concentrations. [11]. Encouraged by a significant trypanocidal activity of different thiazolidinone- and thiazole-based compounds we decided to study if these classes of small “drug-like molecules” possess the antimalarial activity.

Malaria is a parasitic infection of the genus Plasmodium, two of its species - Plasmodium falciparum and Plasmodium vivax account for more than 95 % of clinical cases and deaths. Although, in recent years, there has been a reduction in the numbers of deaths from malaria due to the efficiency of Artemisinin combination therapies (ACTs), the latter meet new challenges because of the emerging drug resistance [12]. Traditional directions in search for new antimalarial agents usually cover the study of various artemisinin analogs as well as different aminoquinoline derivatives [13,14]. Despite the fact, that Artemisinin combination therapies (ACTs) play a pivotal role in malaria control programmes as they remain the cornerstone of case management, it is important to develop novel classes of active agents against artemisinin resistant strains of Plasmodium ssp. as well as targeting the multiple stages of the parasite life cycle.

Among various classes of organic compounds being investigated as potential agents to treat malaria, the study of thiazole based molecules indicated this heterocycle as a pharmacophore with antimalarial properties [15]. For example, a row of aminomethylthiazole pyrazole carboxamides showed good in vitro activity against P. falciparum and was orally effective in a P. berghei mouse model [16]. 2-(2-Hydrazinyl)thiazole derivatives with 2-pyridyl moiety inhibited [the] growth of blood stage P. falciparum (NF54) in submicromolar concentrations in vitro [17].

High-throughput screening of the AstraZeneca compound library against the asexual blood stage of Plasmodium falciparum led to identification of the active aminoimidazole scaffold. Optimization of the latter yielded an orally bioavailable lead – 2-aminooazabenzimidazole derivative with [the] nanomolar inhibitory activity against P. falciparum and efficiency in the humanized Pf/SCID model of malaria [18] (Fig. 1). The imidazolopiperazine derivatives, representing the next-generation antimalarial therapy with the clinical candidate KAF156, belong to the examples of the active antimalaria compounds bearing [6+5]-scaffolds. The latter is effective against Plasmodium falciparum drug-sensitive and drug-resistant strains in nanomolar concentrations targeting multiple life stages of the parasite like liver, ABS and gametocyte [19]. A series of tripeptides with different heterocycles in the side chains was tested for the falcipain-2 inhibitory activity as well as against Plasmodium
*falciparum* (3D7 culture). Interestingly, the most active compounds in both assays and the less toxic contain indole fragment and different five-membered nitrogen containing heterocyclic moieties (pyrolidine and imidazole) [20].

One of the approaches to search for new antimalarials is the developing of agents with the modes of action distinct from the existing drugs. Thus, a spiroindolone derivative KAE609 (Cipargamin) is characterized by the fastest clearance rates in patients of any anti malaria yet (Fig. 1). Cipargamin targets the P-type Na\(^+\) ATPase PfATP4, affecting Na\(^+\) homeostasis in the parasite and as a result blocking [the] ABS development and transmission to mosquitoes [21]. Similar effects on intraerythrocytic *Plasmodium falciparum* caused a pyrazoleamide compound PA21A092 that could prevent parasite mating and therefore transmission by mosquitoes [22]. Another example of [6+5]-heterocyclic fragment implementation is an inhibitor of the mitochondrion-located DHODH (dihydroorotate dehydrogenase) DSM265 that showed the activity against both hepatic and ABS (intra-erythrocytic asexual blood stages) schizonts and was efficient even in single-dose regimens in human trials [23].

The development of novel small non-toxic molecules able to kill *Leishamania* and *Plasmodium* *ssp.* at different stages as well as
to overcome multidrug resistance in treatment of the leishmaniasis and malaria is of great importance and remains a topical issue in parasitic diseases control. The attempts to develop the agents with dual inhibitory activity against both mentioned parasites had been also made. As follows, thiazolidinone and thiazole cores were utilized to obtain a series of molecules bearing thiazole/thiazolidinone cycle and pyrazole core within the hybrid pharmacophore approach. Although, pyrazolylthiosemicarbazones showed good antimalarial activity, their cyclization to thiazole and thiazolidinone increased and the hit-compounds had significant suppressive effect (> 90 %) against *Plasmodium berghei* in *in vivo* assays and even showed a better activity than chloroquine phosphate against chloroquine resistant (RKL9) strain of *P. falciparum* [24].

**Materials and Methods**

**Chemistry**

All chemicals were of the analytical grade and commercially available. All reagents and solvents were used without further purification and drying. Compounds 1,2 [11], 3 [25] and 4 [26] were synthesized as described previously. NMR spectra were determined with Varian Mercury 400 (400 MHz) spectrometer, in DMSO-*d*₆ using tetramethylsilane as an internal standard. Elemental analyses (C, H, N) were performed at the Perkin-Elmer 2400 CHN analyzer and were within ± 0.4 % of the theoretical values. The melting points were measured in open capillary tubes on a BUCHI B-545 melting point apparatus and were not corrected. The purity of the compounds was checked by thin-layer chromatography performed with Merck silica Gel 60 F254 aluminum sheets.

**General method for synthesis of 5-(Z)-arylidene-2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones (5-7)**

The mixture of 3-(4-hydroxyphenyl)thiosemicarbazide (0.01 mol), chloroacetic acid (0.01 mol), sodium acetate (0.02 mol) and appropriate oxocompound (0.03 mol) in the mixture of 5 mL of DMF and 10 mL of acetic acid was refluxed for 2 h. After cooling, the product of the reaction was filtered off and recrystallized from the mixture of DMF-acetic acid or DMF-ethanol.

**5-(Z)-[(4-Methoxyphenyl)methylene]-2-[(4-methoxyphenyl)methylenehydrazono]-3-(4-hydroxyphenyl)-4-thiazolidinone (5).**

Yield: 57 %, mp >250°C, (DMF/EtOH). ¹H NMR (400 MHz, DMSO-*d*₆), δ, ppm: 3.81 (s, 3H, OCH₃); 3.84 (s, 3H, OCH₃), 6.88 (d, 2H, *J* = 8.3 Hz, arom.), 7.04 (d, 2H, *J* = 8.2 Hz, arom.), 7.15 (d, 2H, *J* = 8.3 Hz, arom.), 7.25 (d, 2H, *J* = 8.3 Hz, arom.), 7.67 (d, 2H, *J* = 8.4 Hz, arom.), 7.69 (s, 1H, CH=), 7.75 (d, 2H, *J* = 8.3 Hz, arom.), 8.36 (s, 1H, CH=N), 9.81 (s, 1H, OH). ¹³C NMR (100 MHz, DMSO-*d*₆), δ, ppm: 166.6, 162.1, 161.0, 159.6, 158.7, 158.1, 132.4, 130.3, 130.2, 129.8, 126.9, 126.7, 126.3, 119.2, 116.0, 115.4, 114.9, 55.9, 55.9. Anal. Calcd for C₂₅H₂₁N₃O₄S, %: C, 65.35; H, 4.61; N, 9.14. Found, %: C, 65.50; H, 4.50; N, 9.40.

**5-(Z)-[(4-Hydroxyphenyl)methylene]-2-[(4-hydroxyphenyl)methylenehydrazono]-3-(4-hydroxyphenyl)-4-thiazolidinone (6).**

Yield: 62 %, mp >250°C, (DMF/AcOH). ¹H NMR (400 MHz, DMSO-*d*₆), δ, ppm: 6.81-6.88 (m, 4H, arom), 6.96 (d, 2H, *J* = 7.2 Hz,
arom), 7.23 (d, 2H, J = 7.2 Hz, arom.), 7.57 (d, 2H, J = 7.0 Hz, arom.), 7.63 (s, 1H, CH=N), 9.77 (s, 1H, OH), 10.08 (brs, 1H, OH), 10.24 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d$_6$), δ, ppm: 166.7, 160.8, 159.8, 158.9, 158.1, 132.7, 130.7, 130.4, 129.8, 129.7, 125.3, 125.1, 117.9, 116.8, 116.2, 116.1, 116.0. Anal. Calcd for C$_{12}$H$_{17}$N$_3$O$_4$S, %: C, 64.03; H, 3.97; N, 9.74. Found, %: C, 64.20; H, 4.00; N, 9.90.

5-(Z)-[(4-Dimethylaminophenyl)methylene]-2-[(4-dimethylaminophenyl)methylene hydrazono]-3-(4-hydroxyphenyl)-4-thiazolidinone (7). Yield: 50 %, mp 252-253°C, (DMF/AcOH). 1H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.96 (s, 6H, 2*CH$_3$), 2.99 (s, 3H, CH$_3$), 3.03 (s, 3H, CH$_3$), 6.72 (d, 2H, J = 7.9 Hz, arom.), 6.88 (d, 2H, J = 7.8 Hz, arom.), 7.12 (d, 2H, J = 7.6 Hz, arom.), 7.22 (d, 2H, J = 7.6 Hz, arom.), 7.54-7.60 (m, 3H, arom.), 7.62-7.64 (m, 2H, arom., =CH), 8.13 (s, 1H, CH=N), 9.78 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d$_6$), δ, ppm: 176.9, 174.8, 167.9, 163.1, 158.2, 156.1, 142.8, 131.7, 130.2, 129.6, 129.5, 127.8, 122.8, 121.7, 120.5, 119.7, 116.0, 115.3, 111.5, 43.6, 38.8, 20.9. Anal. Calcd for C$_{27}$H$_{27}$N$_5$O$_2$S, %: C, 66.78; H, 5.60; N, 14.42. Found, %: C, 66.90; H, 5.70; N, 14.60.

Synthesis of 2-f(4-Dimethylaminophenyl)methylene]-2-[(4-dimethylaminophenyl)methylene hydrazono]-3-(4-hydroxyphenyl)-4-thiazolidinone (7). Yield: 50 %, mp 252-253°C, (DMF/AcOH). 1H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 2.96 (s, 6H, 2*CH$_3$), 2.99 (s, 3H, CH$_3$), 3.03 (s, 3H, CH$_3$), 6.72 (d, 2H, J = 7.9 Hz, arom.), 6.88 (d, 2H, J = 7.8 Hz, arom.), 7.12 (d, 2H, J = 7.6 Hz, arom.), 7.22 (d, 2H, J = 7.6 Hz, arom.), 7.54-7.60 (m, 3H, arom.), 7.62-7.64 (m, 2H, arom., =CH), 8.13 (s, 1H, CH=N), 9.78 (s, 1H, OH). 13C NMR (100 MHz, DMSO-d$_6$), δ, ppm: 176.9, 174.8, 167.9, 163.1, 158.2, 156.1, 142.8, 131.7, 130.2, 129.6, 129.5, 127.8, 122.8, 121.7, 120.5, 119.7, 116.0, 115.3, 111.5, 43.6, 38.8, 20.9. Anal. Calcd for C$_{27}$H$_{27}$N$_5$O$_2$S, %: C, 66.78; H, 5.60; N, 14.42. Found, %: C, 66.90; H, 5.70; N, 14.60.

Synthesis of 9-(2-methoxyphenyl)-14-phenyl-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0$^{2,10}$.0$^{12,16}$]heptadec-4(8)-ene-6,13,15-trione (9). A mixture of appropriate 5-(2-methoxyphenylmethylidene)-4-thioxo-2-thiazolidinone (10 mmol) and 5-norbornene-2,3-dicarboxylic acid phenylimide (11 mmol) was refluxed for 1 h with a catalytic amount of hydroquinone (2–3 mg) to prevent polymerization processes in 10 ml of glacial acetic acid, and then left overnight at room temperature. The precipitated crystals were filtered off, washed with methanol (5–10 ml), and recrystallized. Yield: 60 %, mp >250°C (BuOH). 1H NMR (400 MHz, DMSO-d$_6$), δ, ppm: 1.70 (d, 1H, J = 10.0 Hz), 2.30 (t, 1H, J = 8.6 Hz), 2.41 (d, 1H, J = 5.3 Hz), 2.52 (m, 1H), 2.71 (d, 1H, J = 4.9 Hz), 3.26 (m, 1H), 3.50 (m, 3H) - norbornane fragment, CHAr; 3.74 (s, 3H, OCH$_3$), 6.90-7.10 (m, 3H, arom.), 7.37-7.42 (m, 2H, arom.), 7.48-7.54 (m, 2H, arom.), 7.62 (d, 2H, J = 7.6 Hz, arom.), 11.47 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d$_6$), δ, ppm: 2.24 (s, 3H, CH$_3$), 3.23 (dd, 1H, CH$_2$, J = 7.6, 16.8 Hz), 3.28 (m, 1H, CH$_2$), 4.70 (m, 1H, CH), 6.68 (t, 1H, arom.), 6.79 (d, 2H, J = 8.5 Hz, arom.), 6.93-6.97 (m, 2H, arom.), 7.10 (d, 1H, J = 7.6 Hz, arom.) 7.24-7.37 (m, 4H, arom.), 7.46 (d, 1H, J = 8.2 Hz, arom.), 7.76 (d, 1H, J = 7.3 Hz, arom.), 9.5 (s, 1H, -OH), 10.63 (s, 1H, NH), 11.21 (s, 1H, NH).
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δ, ppm: 176.8, 176.7, 171.7, 149.4, 148.9, 133.8, 133.3, 131.6, 130.1, 129.6, 121.7, 120.8, 115.7, 112.9, 112.2, 56.0, 52.6, 48.9, 47.6, 45.8, 45.5, 44.9, 39.4, 38.8. Anal. Calcd for C_{26}H_{22}N_{2}O_{4}S_{2}, %: C, 63.65; H, 4.52; N, 5.71. Found, %: C, 65.80; H, 4.60; N, 5.60.

**Synthesis of 2-(4-benzylpiperazin-1-yl)-5-(3-phenylprop-2-enylidene)thiazol-4-one (10).** The mixture of 2-thioxo-4-thiazolidinone (0.01 mol), 1-benzylpiperazine (0.011 mol) and cinnamaldehyde (0.01 mol) in 10 mL of ethanol is refluxed for 3 h. Formed precipitate is filtered off and recrystallized from 2-propanol or acetic acid.

Yield: 75 %, mp 139-141°C (i-PrOH). 1H NMR (400 MHz, DMSO-\textit{d}_{6}), δ, ppm: 2.51-2.56 (m, 4H, CH\textsubscript{2}CH\textsubscript{2}), 3.53-3.56 (m, 4H, CH\textsubscript{2}CH\textsubscript{2}), 3.88 (s, 2H, CH\textsubscript{2}Ph), 6.91-6.96 (m, 1H, arom.), 7.15-7.20 (m, 1H, arom.), 7.26-7.40 (m, 9H, arom.), 7.59-7.64 (m, 2H, arom.). 13C NMR (100 MHz, DMSO-\textit{d}_{6}), δ, ppm: 179.3, 173.6, 141.9, 138.1, 136.3, 131.5, 131.1, 129.8, 129.4, 128.8, 127.9, 127.6, 125.5, 61.9, 52.4, 52.1, 48.8, 48.2. Anal. Calcd for C\textsubscript{23}H\textsubscript{23}N\textsubscript{3}OS, %: C, 70.92; H, 5.95; N, 10.79. Found, %: C, 71.00; H, 5.80; N, 10.70.

**Pharmacology**

Antimalarial activity assay. *P. falciparum* strain FcB1/colombia was maintained continuously in culture on human erythrocytes as described by Trager and Jensen [27]. [*The in vitro* antiplasmodial activity was determined using a modification of the semi-automated microdilution technique [28]. Chloroquine diphosphate was used as a reference drug. Drug solutions were serially diluted with the culture medium and added to asynchronous parasite cultures (1 % parasitemia and 1 % final hematocrite) in 96-well plates for 24 h, at 37 °C, prior to the addition of 0.5 ACi of [3H]hypoxanthine (1 to 5 Ci/mmol; Amersham, Les Ulis, France) per well, for 24 h. The growth inhibition for each drug concentration was determined by comparison of the radioactivity incorporated into the treated culture with that in the control culture (without drug) maintained on the same plate. The concentration causing 50 % inhibition (IC\textsubscript{50}) was obtained from the drug concentration-response curve and the results were expressed as the mean of the standard deviations determined from several independent experiments. The DMSO concentration never exceeded 0.1 % and did not inhibit the parasite growth.
Results and Discussion

Taking into account high antitrypanosomal activity of some groups of thiazolidinone derivatives, we intended to study possible antimalarial activity of some thiazolidinones. Different 4-thiazolidinone- and pyrazoline-based compounds from our in-home library [1] were investigated in the in vitro study against *Plasmodium falciparum* at the concentration of 10µg/mL. 11 derivatives out of 40 studied ones inhibited growth of the parasites by more than 80 % (Table 1); for these hit-compounds the IC$_{50}$ values were estimated. Compounds 1 and 2 were selected from a series studied in the antitrypanosomal assays [11]; 5-bromo-1-[2-[3-(4-chlorophenyl)-5-(4-methoxyphenyl)-3,4-dihydropyrazol-2-yl]-2-oxo-ethyl]indoline-2,3-dione 3 was synthesized as described elsewhere [25] as well as 5-(4-hydroxy-3,5-dimethoxybenzylidene)-2-[5-(2-hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl]-1,3-thiazol-4(5H)-one 4 was synthesized according to the known method [26] (Fig. 2).

5-(Z)-Arylidene-2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones 5-7 were synthesized in the one-step modified Knoevenagel reaction of 4-(4-hydroxyphenyl) thiosemicarbazide with appropriate aromatic aldehydes and chloroacetic acid in the acetic acid medium in the presence of sodium acetate. Compound 8 was obtained following the reaction of 1-(2-oxoindolin-3-ylidene)-4-(4-hydroxyphenyl)thiosemicarbazone with (p-tolyl) maleimide in the glacial acetic acid medium (Scheme 1).

![Fig. 2](image-url) The selected compounds resynthesized for antiplasmodium assay.
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3,7-Dithia-5,14-diazapentacyclo[9.5.1.0^{2,10}.0^{12}.0^{16}]heptadecene 9 was synthesized in the hetero-Diels-Alder reaction of 5-norbornene-2,3-dicarboxylic acid phenyl-imide and 5-(2-methoxybenzylidene)-4-thioxo-2-thiazolidinone in glacial acetic acid with adding a catalytic amount of hydroquinone to inhibit a side polymerization reaction (Scheme 2).

2-(4-Benzylpiperazin-1-yl)-5-(3-phenylprop-2-enylidene)thiazol-4-one 10 was synthesized in the one-pot three-component reaction of the rhodanine, cinnamaldehyde and 1-benzylpiperazine (Scheme 3).

Compound 11 was synthesized in the two step synthetic protocol via formation of 2-(thiazol-2-yl)imino-4-thiazolidinone in the reaction of appropriate chloroacetamide with ammonium rhodanide and acetone and further Knoevenagel condensation (Scheme 4).

In general, all tested compounds possessed moderate and good antiplasmodial properties, although, it is rather complicated to outline any structure-activity peculiarities as the hit-
compounds selected in antimalarial primary assays are represented by different classes of thiazolidinone- and pyrazoline-based compounds. The best inhibition activity towards *Plasmodium falciparum* was observed for 5-\((Z)\)-arylidene-2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones 5, 6 and pyrazoline derivative 3. In general, all studied groups of thiazolidinone-based compounds showed significant *Plasmodium* growth inhibition in the concentration of 10\(\mu\)M/mL, although the calculated IC\(_{50}\) values were within 1.81-13.29 \(\mu\)M. The IC\(_{50}\) of 5-bromo-1-[2-[3-(4-chlorophenyl)-5-(4-methoxyphenyl)-3,4-dihydropyrazol-2-yl]-2-oxo-ethyl]indoline-2,3-dione 3 was one of the lowest among all tested compounds (1.81 \(\mu\)M). This pyrazoline containing molecule was also highly effective in the anticancer activity assay; at the micromolar concentrations it inhibited the growth of majority of the tested cancer cell lines and moreover showed certain selectivity towards Leukemia panel [25]. Such a promiscuous behaviour makes it a promising object within
the concepts of polypharmacological approach and multitarget drugs design [29-33]. The studied 5-(Z)-arylidene-2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones 5-7 were characterized by the comparable IC$_{50}$ values proving [a] positive impact of combination of thiazolidinone core and hydrazine moiety on the antiparasitic activity [6]. On the other hand, such an impact strongly depends on other fragments in the molecule, e.g. the compound 1 bearing also a cinnamoyl fragment did not show high antimalarial activity. Interestingly, the compounds 1 and 2 earlier tested against Trypanosoma brucei brucei [11] showed analogous results regarding the antiplasmodial activity levels: i) compound 1 inhibited the growth of Trypanosoma brucei brucei by more than 90 % (by 83 % for Plasmodium falciparum) and was not active at 1 µg/mL; ii) the IC$_{50}$ calculated for compound 2 was 10.63 µM (comparing to 5.31 µM calculated in antimalarial assay). 3,7-Dithia-5,14-diazapentacyclo[9.5.1.0$^{2,10}$0$^{4,8}$0$^{12,16}$]heptadecene 9 was chosen for the screening as an example of fused thiopyranothiazole scaffold that retains pharmacological profile of its precursors – 5-ene-4-thiazolidinones, but at the same time does not keep the undesirable Michael acceptor properties [29]. Indeed, compound 9 showed a high rate of parasites growth inhibition at the concentration of 10µg/mL and the IC$_{50}$ value comparable with that for other derivatives.

**Conclusions.** A versatile row of thiazolidinone and pyrazoline derivatives was studied against Plasmodium falciparum in the in vitro assay. The calculated IC$_{50}$ values were within 1.81-13.29 µM indicating the suitability of the described class of small molecules for the purposes of medicinal chemistry. For some of the investigated compounds a significant trypanocidal activity against Trypanosoma brucei brucei and Trypanosoma gambiense had been earlier established that can warrant the in-depth study of the above-mentioned molecules as promising antiparasitic agents.

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Попередня оцінка гетероцикличних похідних тіазолідинону та піразоліну як потенційних протималярійних агентів

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Мета. Синтез ряду похідних тіазолідинону та піразоліну. *In vitro* скринінг протималярійної активності різноманітних гетероцикличних похідних на їх основі.

Методи: органічний синтез, аналітичні та спектральні методи, фармакологічний скринінг; аналіз взаємозв’язку структура-активність. Результати: Проведено *in vitro* дослідження інгібування росту *Plasmodium falciparum* різноманітними похідними тіазолідинону та піразоліну. 5-(Z)-Ариліден-2-ариліденгідразоно-3-(4-гідроксифеніл)-4-тіазолідинони володіли високою антиплазмодійною активністю із показниками напівмаксимальних інгібуючих концен-
трацій IC\textsubscript{50} – 2.32–2.39 мкМ. Найактивнішою сполукою серед досліджуваних виявився 5-бромо-1-[2-[3-(4-хлорофеніл)-5-(4-метоксифеніл)-3,4-дигідропіразол-2-ил]-2-оксоетил]індолін-2,3-діон (IC\textsubscript{50} – 1.81 мкМ). 
Результати скринігу дозволили окреслити деякі за
кономірності взаємозв’язку структура-активність.

Результати скринігу дозволили окреслити деякі за
кономірності взаємозв’язку структура-активність.

Висновки. Ряд структурно різноманітних похідних тіазолідинону та піразоліну із раніше встановленими противтрипаносомною та протипухлинною активністю були досліджені у тесті на \textit{Plasmodium falciparum}.
Виявлено сполуки-хіти, що інгібували ріст збудника маляриї у мікромолярних концентраціях. Отримані результати забезпечують подальші шляхи розробки потенційних противмалярійних агентів на основі досліджених класів малих «лікоподібних» молекул.

Ключові слова: тіазолідинон, піразолін, противмалярійна активність, аналіз структура-активність.

Предварительна оценка гетероциклических производных тиазолидинона и пиразолина как потенциальных противомалярных агентов
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Цель. Синтез ряда производных тиазолидинона и пиразолина. In vitro скрининг противомалярной активности различных гетероциклических производных на их основе. Методы: органический синтез, аналитические и спектральные методы, фармакологическій скрининг; аналіз взаємосвязи структура-активность. Результаты. Проведено in vitro исследование ингибирования роста \textit{Plasmodium falciparum} различ
ными производными тиазолидинона и пиразолина. 5-(Z)-Арилиден-2-арилиденгидразоно-3-(4-гидроксифенил)-4-тиазолидиноны обладали высокой антиплазмодийной активностью с показателями полумаксимальных ингибитирующих концентраций IC\textsubscript{50} - 2.32–2.39 мкМ. Самым активным соединением среди исследуемых оказался 5-бром-1-[2- [3-(4-хлорофенил)-5-(4-метоксифенил)-3,4-дигідропіразол-2-ил]-2-оксоетил]індолін-2,3-діон (IC\textsubscript{50} – 1.81 мкМ). Результаты скрининга позволили очер	иться некоторые закономерности взаємосвязі структура-активность. Выводы. Ряд структурно различных производных тиазолидинона и пиразолина с ранее установленными противотрипаносомной и противопухоловой активностью были исследованы в тесте на \textit{Plasmodium falciparum}.
Выявлены соединения-хіти, що інгібировали рост возбудителя маляриї в мікромолярних концентраціях. Полу
ченные результаты обеспечивают дальнейшие пути разработки потенциальных противомалярных агентов на основе исследованных клас
сов малих «drug-like» молекул.

Ключевые слова: тиазолидинон, пиразолин, противомалярная активность, анализ структура-активность.

Received 01.10.2019