ISSN 1993-6842 (on-line); ISSN 0233-7657 (print)
Biopolymers and Cell. 2020. Vol. 36. N 1. P 48–60
doi: http://dx.doi.org/10.7124/bc.000A20

UDC 616-093 + 547.789

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 IC_{50}–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 IC_{50}–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

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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 amino imidazole scaffold. Optimization of the latter yielded an orally bioavailable lead – 2-aminoazabenzimidazole 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*

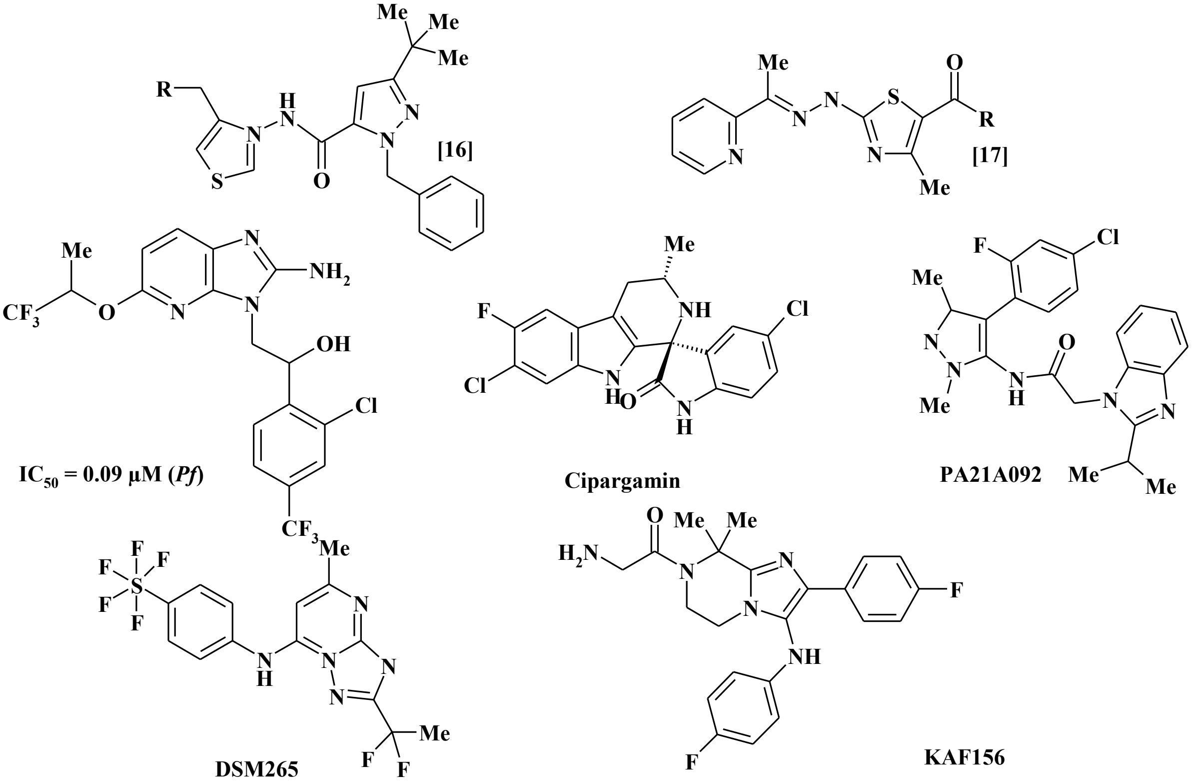


Fig.1. Examples of thiazole derivatives and different [6+5]-heterocyclic compounds active against *P. falciparum.*

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 antimalarial 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). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.81 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3), 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). ^{13}C 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 $C_{25}H_{21}N_3O_4S$, %: 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). ^{1}H 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=), 7.64 (d, 2H, *J* = 8.0 Hz, arom.), 8.29 (s, 1H, CH=N), 9.77 (s, 1H, OH), 10.08 (brs, 1H, OH), 10.24 (s, 1H, OH). ^{13}C 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 $C_{12}H_{17}N_3O_4S$, %: C, 64.03; H, 3.97; N, 9.74. Found, %: C, 64.20; H, 4.00; N, 9.90.

5-(Z)-[(4-Dimethylaminohenyl)methylene]-2-[(4-dimethylaminophenyl)methylene hydrazono]-3-(4-hydroxyphenyl)-4-thiazolidinone (7). Yield: 50 %, mp 252-253°C, (DMF/AcOH). ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 172.5, 158.2, 157.9, 152.5, 150.2, 147.3, 132.7, 132.4, 131.1, 129.9, 129.8, 129.7, 126.7, 126.4, 121.9, 116.0, 112.2, 32.5. Anal. Calcd for $C_{27}H_{27}N_5O_2S$, %: C, 66.78; H, 5.60; N, 14.42. Found, %: C, 66.90; H, 5.70; N, 14.60.

Synthesis of 2-[(3-(4-hydroxyphenyl)-4-oxo-2-[(2-oxoindolin-3-ylidene)hydrazono]thiazolidin-5-yl]-N-(p-tolyl)acetamide (8). Equimolar amounts (0.01 mol) of 1-(2-oxoindolin-3-ylidene)-4-(4-hydroxyphenyl)thiosemicarbazone, (*p*-tolyl)maleimide and acetic acid (20 mL) were put into round bottom flask and heated under reflux for 2 h. After cooling the reaction mixture to room temperature, the formed precipitate was filtered off and recrystallized. Yield: 81 %, mp 212-213°C, (DMF/EtOH). ^{1}H NMR (400 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). ^{13}C 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 $C_{26}H_{21}N_5O_4S$, %: C, 62.51; H, 4.24; N, 14.02. Found, %: C, 62.40; H, 4.10; N, 14.20.

Synthesis of 9-(2-methoxyphenyl)-14-phenyl-3,7-dithia-5,14-diazapentacyclo-[9.5.1.0^{2,10}.0^{4,8}.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). ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d_6), 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 $C_{26}H_{22}N_2O_4S_2$, %: 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). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.51-2.56 (m, 4H, CH_2CH_2), 3.53-3.56 (m, 4H, CH_2CH_2), 3.88 (s, 2H, CH_2Ph), 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.). ^{13}C NMR (100 MHz, DMSO-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 $C_{23}H_{23}N_3OS$, %: C, 70.92; H, 5.95; N, 10.79. Found, %: C, 71.00; H, 5.80; N, 10.70.

Synthesis of 5-(Z)-(4-dimethylamino-phenylmethylene)-2-(thiazol-2-yl)imino-thiazolidin-4-one (11). The mixture of 2-(thiazol-2-yl)imino-4-thiazolidinone (0.01 mol), 4-dimethylaminobenzaldehyde (0.015 mol) and sodium acetate (0.01 mol) in 10 mL of acetic acid was refluxed for 3 h. The precipitate formed after cooling the reaction mixture was filtered off and recrystallized. Yield: 73 %, mp 249-251°C (AcOH). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.12 (s, 6H, 2*CH_3), 6.78 (d, 2H, J = 8.2 Hz, arom.), 7.21 (d, 1H, J = 4.6 Hz, thiazol), 7.46 (d, 2H, J = 8.2 Hz, arom.), 7.54 (s, 1H, CH=), 7.64 (d, 1H, J = 4.7 Hz, thiazol), 12.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 173.8, 164.9, 152.4, 146.6, 141.3, 134.1, 133.3, 122.5, 121.2, 117.9, 113.2, 36.7. Anal. Calcd for $C_{15}H_{14}N_4OS_2$, %: C, 54.52; H, 4.27; N, 16.96. Found, %: C, 54.60; H, 4.30; N, 16.70.

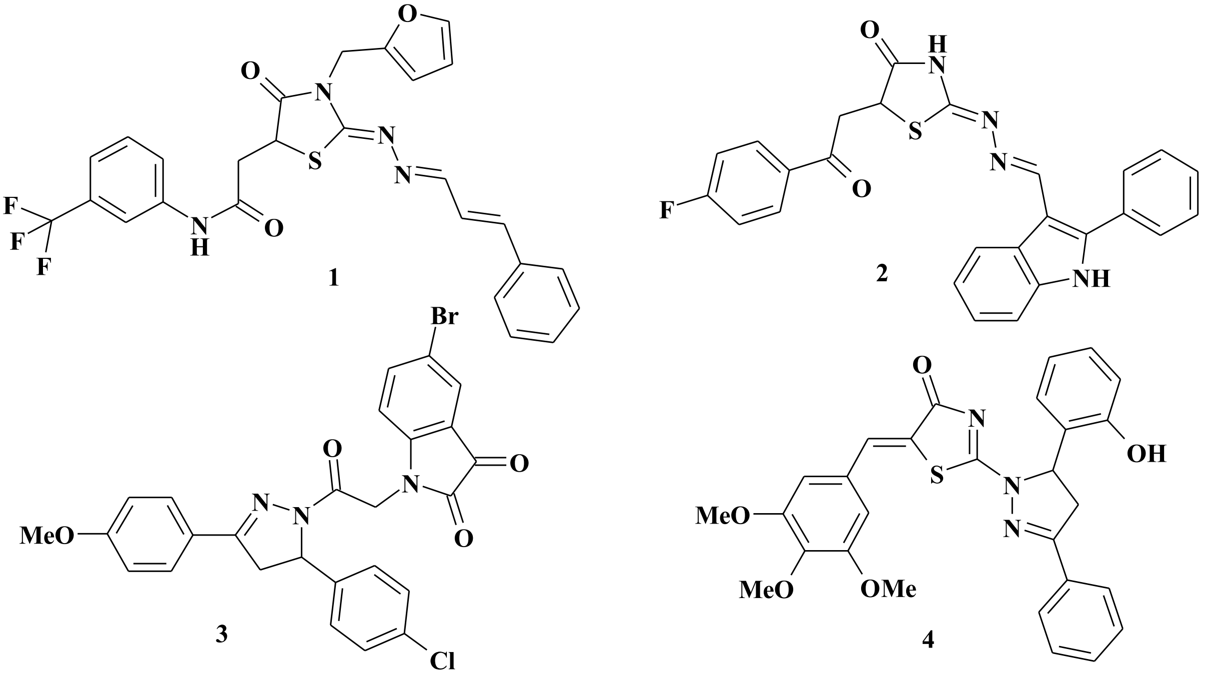
Pharmacology

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. Stock solutions of chloroquine diphosphate and test compounds were prepared in sterile, distilled water and DMSO, respectively. 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 ^{o}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_{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 Discusion

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-1*H*-pyrazol-1-yl]-1,3-thiazol-4(5*H*)-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).



1

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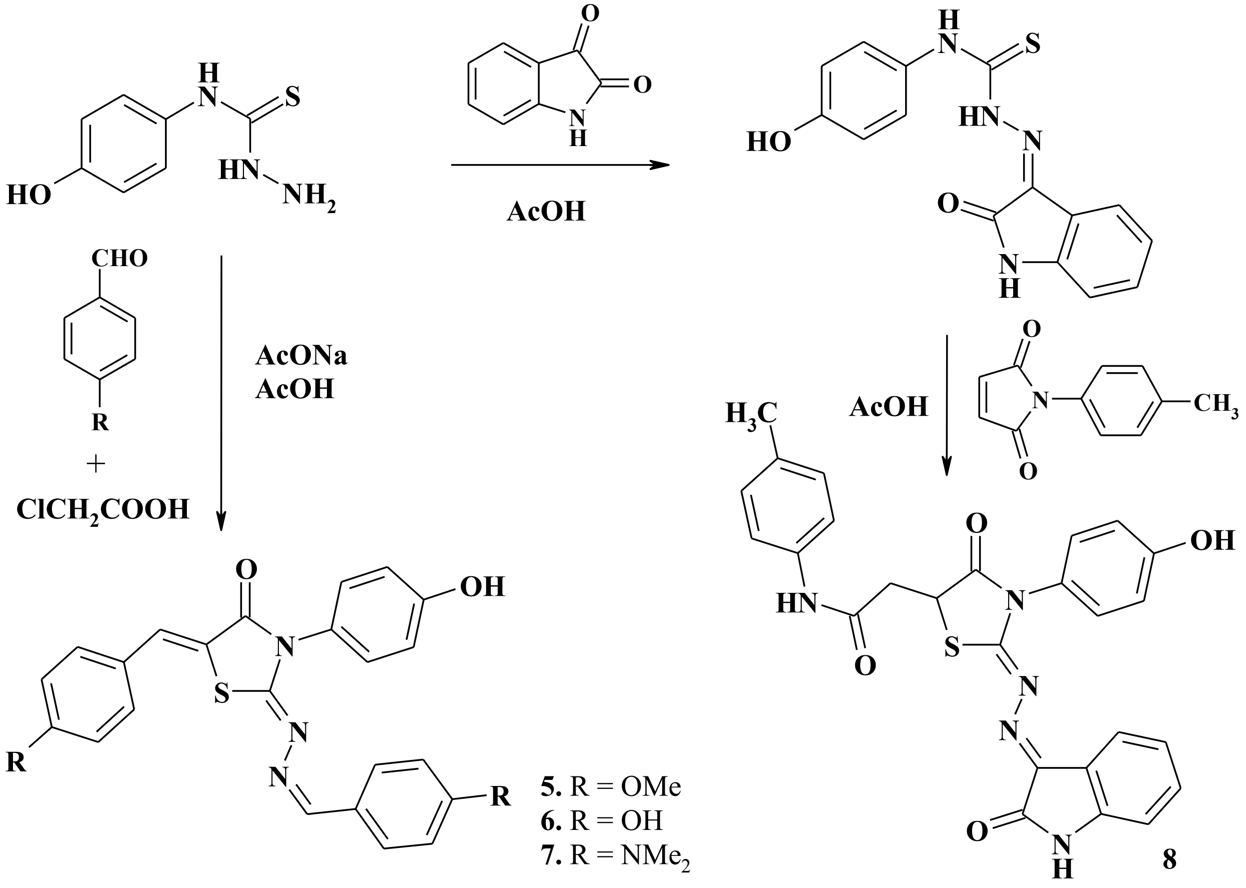
Fig. 2. The selected compounds resynthesized for antiplasmodium assay.



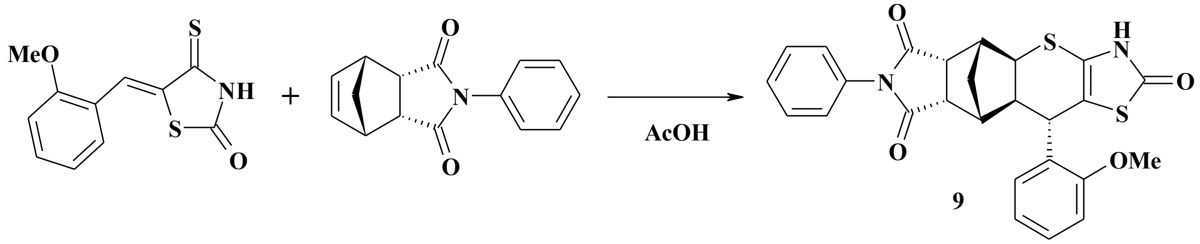
Scheme 1. General scheme of the 5-substituted 2-arylidenehydrazono-3-(4-hydroxyphenyl)-4-thiazolidinones synthesis.

3,7-Dithia-5,14-diazapentacyclo[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadecene **9** was synthesized in the *hetero*-Diels-Alder reaction of 5-norbornene-2,3-dicarboxylic acid phenylimide 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).

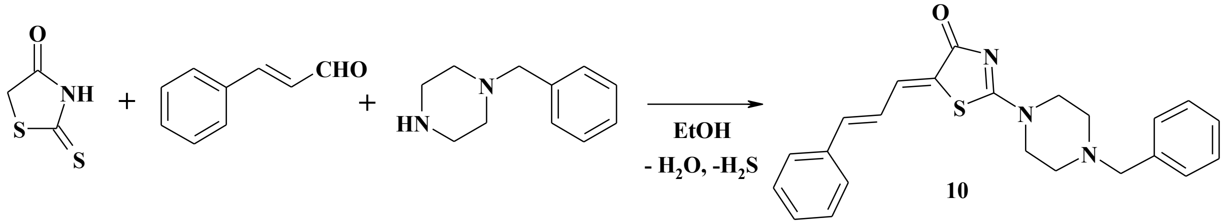
2-(4-Benzylpiperazin-1-yl)-5-(3-phenylprop-2-enylidene)thiazol-4-one **10** was synthesized in the one-pot three-component reaction of the rhodanine, cynnamaldehyde and 1-benzylpiperazine (Scheme 3).

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).

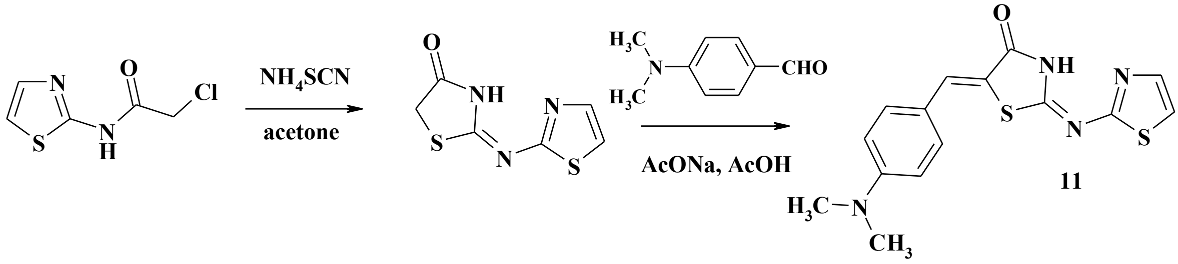
In general, all tested compounds possessed moderate and good antiplasmodial properties, although, it is rather complicated to outline any structure-activity peculiarities as the hit-



Scheme 2. Synthesis of 9-(2-methoxyphenyl)-14-phenyl-3,7-dithia-5,14-diazapentacyclo-[9.5.1.$0^{2,10}$.$0^{4,8}$.$0^{12,16}$]heptadec-4(8)-ene-6,13,15-trione **9**.



Scheme 3. Synthesis 2-(4-benzylpiperazin-1-yl)-5-arylidene-thiazol-4-one **10.**



Scheme 4. Synthesis of 5-(*Z*)-(4-dimethylaminophenylmethylene)-2-(thiazol-2-yl)imino-thiazolidin-4-one **11.**

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 10μM/mL, although the calculated IC_{50} values were within 1.81-13.29 μM. 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 μM). 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 compond **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.

Table 1. **Antimalarial activity of studied heterocyclic derivatives**

Compound	Inhibition, % (10 μg/mL)	IC_{50} μg/ml	IC_{50}, μM
1	83.00	7.00 ± 0.40	13.29 ± 0.76
2	82.19	2.50 ± 0.60	5.31 ± 1.28
3	96.40	1.00 ± 0.10	1.81 ± 0.18
4	88.15	4.50 ± 0.30	8.97 ± 0.60
5	82.19	1.10 ± 0.10	2.39 ± 0.22
6	96.00	1.00 ± 0.10	2.32 ± 0.23
7	83.07	1.70 ± 0.10	3.50 ± 0.21
8	83.77	3.50 ± 0.10	7.01 ± 0.20
9	85.64	2.10 ± 0.10	4.28 ± 0.20
10	96.40	2.70 ± 0.20	6.93 ± 0.51
11	92.56	2.00 ± 0.10	6.05 ± 0.30
Chloroquine			0.065 ± 0.001

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 гетероциклічних 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 гетероциклічних 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 концентрацій IC_{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-іл]-2-оксоетил]індолін-2,3-діон (IC_{50}–1.81 мкМ). **Результати** скринігу дозволили окреслити деякі закономірності взаємозв'язку структура-активність. **Висновки.** Ряд структурно різноманітних похідних тіазолідинону та піразоліну із раніше встановленими протитрипаносомною та протипухлинною активністю були дослідженні у тесті на *Plasmodium falciparum.* Виявлено сполуки-хіти, що інгібували ріст збудника малярії у мікромолярних концентраціях. Отримані результати забезпечують подальші шляхи розробки потенційних протималярійних агентів на основі досліджених класів малих «лікоподібних» молекул.

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

Предварительная оценка гетероциклических производных тиазолидинона и пиразолина как потенциальных противомалярийных агентов

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Цель. Синтез ряда производных тиазолидинона и пиразолина. *In vitro* скрининг противомалярийной активности различных гетероциклических производных на их основе. **Методы:** органический синтез, аналитические и спектральные методы, фармакологический скрининг, анализ взаимосвязи структура-активность. **Результаты.** Проведено *in vitro* исследования ингибирования роста *Plasmodium falciparum* различными производными тиазолидинона и пиразолина. 5-(Z)-Арилиден-2-арилиденгидразоно-3-(4-гидроксифенил)-4-тиазолидиноны обладали высокой антиплазмодийной активностью с показателями полумаксимальных ингибирующих концентраций IC_{50} - 2.32-2.39 мкМ. Самым активным соединением среди исследуемых оказался 5-бром-1-[2- [3-(4-хлорофенил)-5-(4-метоксифенил)-3,4-дигидропиразол-2-ил]-2-оксоетил]-индолин-2,3-дион (IC_{50} - 1.81 мкМ). **Результаты** скрининга позволили очертить некоторые закономерности взаимосвязи структура-активность. **Выводы.** Ряд структурно различных производных тиазолидинона и пиразолина с ранее установленными противотрипаносомной и противоопухолевой активностью были исследованы в тесте на *Plasmodium falciparum*. Выявлены соединения-хиты, что ингибировали рост возбудителя малярии в микромолярных концентрациях. Полученные результаты обеспечивают дальнейшие пути разработки потенциальных противомалярийных агентов на основе исследованных классов малых «drug-like» молекул.

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

Received 01.10.2019