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[1,2,4]TRIAZOLO[4,3-*a*]QUINAZOLIN-5-ONE DERIVATIVES AS ANTIMALARIAL AGENTS

Five novel [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one derivatives containing an amide group connected to 1 position of triazoloquinazoline moiety via sulfur-carbon or carbon chain were synthesized. The structure was confirmed by elemental analysis and ^{1}H NMR spectroscopy. Their in vitro antiprotozoal activity was evaluated against Leishmania infantum, Plasmodium falciparum, Trypanosoma brucei and Trypanosoma cruzi. 4-Benzyl-1-{4-[4-(4-methoxyphenyl)piperazin-1-yl]-4-oxobutyl}[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one **7e** *with an amide group connected via carbon chain showed noticeable antimalarial activity (IC_{50} 0.2 μM). The lead structure* **7e** *may be promising for further investigations as novel antimalarial agents.*

Key words: 2-hydrazinoquinazolin-4(3*H*)-ones; [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones; in vitro; antiprotozoal; antimalaria activity

INTRODUCTION

In recent years, understanding of the necessity for treatment of tropical diseases has grown among investigators around the world. The lack of effective remedy and drug resistance for known medicines endorses the need for searching of new drug substances. Derivatives of [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one are representatives of important class of condensed heterocycles possessing wide biological activity range. Among their potential pharmacologically significant properties, the antibacterial [2, 10, 13], antitubercular [2, 13], antifungal [2, 10], anti-HIV [2], antihistaminic [3, 4, 5, 6, 14, 15], anticonvulsant [1], anticancer [13], antiasthmatic [12, 14], antiallergic [12], anti-inflammatory [11, 12] bioactivities should be mentioned. Hence, it was of interest to check some [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives against tropical disease protozoa. The aim of this study was to evaluate [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives containing an amide group that was connected to 1 position of triazoloquinazoline moiety via sulfur-carbon or carbon chain against tropical parasitic protozoa *Leishmania*, *Plasmodium* and *Trypanosoma*.

MATERIALS AND METHODS

We used formerly described [9] 2-hydrazinoquinazolin-4(3*H*)-ones **1a-d** as starting materials for [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **7a-e** synthesis (Figure). Condensation of hydrazines **1a-c** with CS_2 resulted in 1-thioxo-2,4-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5(1H)-ones **2a-c** formation. Consequent alkylation by chloroacetic acid amides **3a-d** lead to [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **7a-d,** which contain sulfur-carbon chain. Condensation of hydrazine **1d** with glutaric anhydride **4** produced 4-(4-benzyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-1-yl)butanoic acid **5**. For amide formation we used activation of carboxylic group in obtained acid **5** via getting intermediate imidazolyl amide by CDI in anhydrous dioxane with subsequent reaction with corresponding amine **6** by reflux up to 2 hours. The structure of obtained compounds was verified by elemental analysis and ^{1}H NMR spectroscopy data.

RESULTS AND DISCUSSION

Results of biological screening of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives **7a-e** are presented in Table.

[1,2,4]Triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **7a-d**, which contain the amide group connected via sulfur-carbon chain possess moderate activity. Analogues, which contain amide group connected via carbon chain **7e** may be interesting for further exploration as antimalarial agents in view of the fact that 4-benzyl-1-{4-[4-(4-methoxyphenyl)piperazin-1-yl]-4-oxobutyl}[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one **7e** shows potent (IC_{50} 0.2 μM) and selective antimalarial activity.

EXPERIMENTAL SYNTHETIC PART

^{1}H NMR spectra were recorded on Varian WXR-400 (200 MHz) spectrometer in DMSO-d_6 solution with TMS as

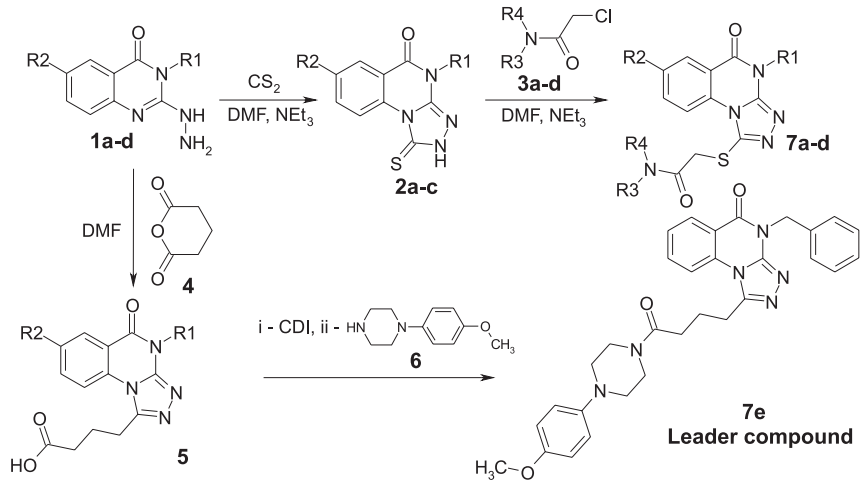
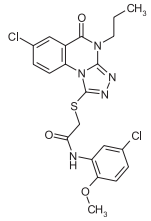
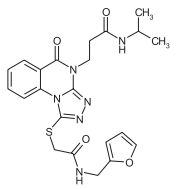
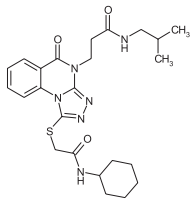
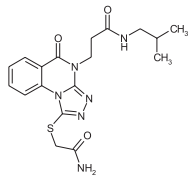
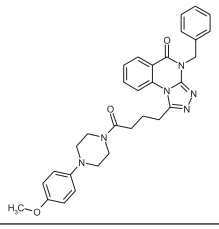


Fig. *Reaction scheme of the [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones* ***7a-e*** *derivatives.*

Table

INTEGRATED *IN VITRO* ACTIVITY SCREENING AGAINST TROPICAL DISEASE PROTOZOA. RESULTS ARE EXPRESSED AS 50 % INHIBITORY CONCENTRATION (IC_{50}-VALUE)

Compound code	Structure of compound	IC_{50} (μM)				
		MRC-5	*T. cruzi*	*L. infantum*	*T. brucei*	*P. falciparum*
7a		> 64	> 64	> 64	> 64	8.7
7b		> 64	> 64	8.1	> 64	3.4
7c		> 64	> 64	> 64	> 64	4.9
7d		> 64	> 64	> 64	> 64	> 64
7e		> 64	9.4	8.0	32.9	0.2

internal standard, chemical shifts are reported in ppm. Melting points were measured with a Buchi B-520 melting point apparatus. Elemental analysis was performed on Euro EA-3000 apparatus. Starting 2-hydrazinoquinazolin-4(3*H*)-ones **1a-c** were obtained according to method [9]. Amides of chloroacetic acid **3a-d**, which were used for alkylation, are commercially available.

General procedure for the synthesis of 1-thioxo-2,4-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5(1H)-ones 2a-c. 0.1 M of corresponding hydrazine **1a-c** was dissolved in 100 ml of DMF. To the clear solution 50 ml (0.35 M) of triethylamine and 5.0 ml (0.2 M) of carbon disulfide was added. The solution was heated at 40 °C during 2 hours then the temperature was raised to 90-100 °C for boiling. The reaction mixture was refluxed during 8 hour. After cooling to room temperature the reaction mixture was acidified by 30 ml of acetic acid and diluted with 200 ml of water. The formed precipitate was filtered off, washed with water and purified by crystallization from a mixture of DMF and *i*-propanol.

7-Chloro-4-propyl-1-thioxo-2,4-dihydro[1,2,4]triazolo[4,3-a]quinazolin-5(1H)-one 2a. Yield – 14.74 g (50 %), orange solids. M. p. > 300 °C. ^{1}H NMR: 0.88 t (J 7.2, 3H, CH_3); 1.70 sext (J 7.2, 2H, 2-CH_2); 3.92 t (J 7.2, 2H, 3-CH_2); 7.90 dd ($J_{8,9}$ 7.8, $J_{6,8}$ 2.0, 1H, H-8); 8.07 d ($J_{6,8}$ 2.0. 1H, H-6); 10.25 d ($J_{8,9}$ 7.8, 1H, H-9); 14.05 s (1H, NH). Found, %: C 48.86; H 3.75; N 18.99. $C_{12}H_{11}ClN_4OS$. Calculated, %: C 48.90; H 3.76; N 19.01.

N-isopropyl-3-(5-oxo-1-thioxo-1,2-dihydro[1,2,4]triazolo[4,3-a]quinazolin-4(5H)-yl)propanamide 2b. Yield – 22.53 g (68 %), yellow solids. M. p. > 300 °C. ^{1}H NMR: 0.98 d (J 7.0, 6H, 2CH_3); 2.48 t (J 7.2, 2H, 2-CH_2); 3.65-3.85 m (1H, NCH); 4.20 t (J 7.2, 2H, 3-CH_2); 7.58 t (J 7.8, 1H, H-7); 7.82 d (J 7.0, 1H, CONH); 7.90 t (J 7.8, 1H, H-8); 8.20 d (J 7.8, 1H, H-6); 10.20 d (J 7.8, 1H, H-9); 14.05 s (1H, NH). Found, %: C 54.40; H 5.16; N 21.11. $C_{15}H_{17}N_5O_2S$. Calculated, %: C 54.36; H 5.17; N 21.13.

N-isobutyl-3-(5-oxo-1-thioxo-1,2-dihydro[1,2,4]triazolo[4,3-a]quinazolin-4(5H)-yl)propanamide 2c. Yield – 24.18 g (70 %), yellow solids. M. p. > 300 °C. ^{1}H NMR: 0.80 d (J 7.0, 6H, 2CH_3); 1.55-1.65 m (1H, CH); 2.53 t (J 7.2, 2H, 2-CH_2); 2.93 t (J 7.2, 2H, NCH_2); 4.07 t (J 7.2, 2H, 3-CH_2); 7.58 t (J 7.8, 1H, H-7); 7.82 d (J 7.0, 1H, CONH); 7.90 t (J 7.8, 1H, H-8); 8.20 d (J 7.8, 1H, H-6); 10.20 d (J 7.8, 1H, H-9); 14.05 s (1H, NH). Found, %: C 55.66; H 5.56; N 20.30. $C_{16}H_{19}N_5O_2S$. Calculated, %: C 55.63; H 5.54; N 20.27.

4-(4-Benzyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-1-yl)butanoic acid 5. The mixture of 53.2 g (0.2 M) of 3-benzyl-2-hydrazinoquinazolin-4(3*H*)-one **1d** and 34.2 g (0.3 M) of glutaric anhydride **4** in 200 ml of anhydrous DMF was refluxed for 12 hours. After cooling the reaction mixture was diluted with 500 ml of water. At next day the precipitate was filtered, washed twice with 200 ml of acetone and recrystallized from a mixture of 50 ml of DMF and 200 ml of acetone. Yield – 53.6 g (74 %), white solids. M. p. > 300 °C (dec.). ^{1}H NMR: 2.02 qn (J 7.2, 2H, 3-CH_2); 2.40 t (J 7.2, 2H, 2-CH_2); 3.22 (J 7.2, 2H, 4-CH_2); 5.35 s (2H, CH_2); 7.24-7.36 m (3H, H-3,4,5 Ph); 7.44-7.62 m (3H, H-7, 2,6 Ph); 7.91 t (J 7.8, 1H, H-8); 8.01 d (J 7.8, 1H, H-9); 8.26 d (J 7.8, 1H, H-6); 12.25 br. s (1H, OH). Found, %: C 66.34; H 4.99; N 15.42. $C_{20}H_{18}N_4O_3$. Calculated, %: C 66.29; H 5.01; N 15.46.

General procedure for the synthesis of [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones 7a-d. To an agitated solution of 0.001 M of corresponding thiones **2a-c** and 0.56 ml (0.004 M) of triethylamine in 5 ml of anhydrous DMF 0.0012 M of appropriate alkylating reagent **3a-d** was added. Resulting mixtures were heated and stirred at 70 °C for 20 minutes. After cooling the reaction mixture was diluted with 10 ml of water. The formed precipitate was filtered off, washed with *i*-propanol and purified by crystallization from a mixture of DMF and *i*-propanol.

N-(5-chloro-2-methoxyphenyl)-2-[(7-chloro-5-oxo-4-propyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinazolin-1-yl)thio]acetamide 7a. Yield – 0.41 g (83 %), cream solids. M. p. > 300 °C. ^{1}H NMR: 0.88 t (J 7.2, 3H, CH_3); 1.70 sext (J 7.2, 2H, 2-CH_2); 3.88 s (3H, OCH_3); 4.09 t (J 7.2, 2H, 3-CH_2); 4.35 s (2H, SCH_2); 6.94-7.10 m (2H, H-3,4 Ar); 7.97 dd ($J_{8,9}$ 7.8, $J_{6,8}$ 2.0, 1H, H-8); 8.05 s (1H, H-6 Ar); 8.14 d ($J_{6,8}$ 2.0. 1H, H-6); 8.57 d ($J_{8,9}$ 7.8, 1H, H-9); 9.80 s (1H, CONH). Found, %: C 51.26; H 3.90; N 14.19. $C_{21}H_{19}Cl_2N_5O_3S$. Calculated, %: C 51.23; H 3.89; N 14.22.

3-[1-({2-[(2-Furylmethyl)amino]-2-oxoethyl}thio)-5-oxo[1,2,4]triazolo[4,3-a]quinazolin-4(5H)-yl]-N-isopropylpropanamide 7b. Yield – 0.38 g (81 %), white solids. M. p. > 300 °C. ^{1}H NMR: 0.98 d (J 7.0, 6H, 2CH_3); 2.48 t (J 7.2, 2H, 2-CH_2); 3.65-3.85 m (1H, NCH); 4.12 s (2H, SCH_2); 4.20 t (J 7.2, 2H, 3-CH_2); 4.30 d (J 7.0, 2H, NCH_2); 6.25 d (J 6.8, 1H, H-3 Ar); 6.38 d (J 6.8, 1H, H-5 Ar); 7.40 t (J 6.8, 1H, H-4 Ar); 7.58 t (J 7.8, 1H, H-7); 7.82 d (J 7.0, 1H, CONH-*i*-Pr); 7.90 t (J 7.8, 1H, H-8); 8.20 d (J 7.8, 1H, H-6); 8.53 d (J 7.0, 1H, CONHCH$_2$); 8.60 d (J 7.8, 1H, H-9). Found, %: C 56.44; H 5.18; N 17.96. $C_{22}H_{24}N_6O_4S$. Calculated, %: C 56.40; H 5.16; N 17.94.

3-[1-{[2-(Cyclohexylamino)-2-oxoethyl]thio}-5-oxo[1,2,4]triazolo[4,3-a]quinazolin-4(5H)-yl]-N-isobutylpropanamide 7c. Yield – 0.44 g (90 %), white solids. M. p. > 300 °C. ^{1}H NMR: 0.80 d (J 7.0, 6H, 2CH_3); 0.90-1.25 m (5H, Ch); 1.40-1.65 m (6H, CH+5H Ch); 2.53 t (J 7.2, 2H, 2-CH_2); 2.93 t (J 7.2, 2H, NCH_2); 3.35-3.45 m (1H, CH Ch); 3.95 s (2H, SCH_2); 4.07 t (J 7.2, 2H, 3-CH_2); 7.58 t (J 7.8, 1H, H-7); 7.82 d (J 7.0, 1H, CONH-*i*-Bu); 7.90 t (J 7.8, 1H, H-8); 8.02 d (J 7.0, 1H, CONH-Ch); 8.25 d (J 7.8, 1H, H-6); 8.62 d (J 7.8, 1H, H-9). Found, %: C 59.43; H 6.68; N 17.36. $C_{24}H_{32}N_6O_3S$. Calculated, %: C 59.48; H 6.66; N 17.34.

3-[1-[(2-Amino-2-oxoethyl)thio]-5-oxo[1,2,4]triazolo[4,3-a]quinazolin-4(5H)-yl]-N-isobutylpropanamide 7d. Yield – 0.34 g (85 %), white solids. M. p. > 300 °C. ^{1}H NMR: 0.80 d (J 7.0, 6H, 2CH_3); 1.55-1.65 m (1H, CH); 2.53 t (J 7.2, 2H, 2-CH_2); 2.93 t (J 7.2, 2H, NCH_2); 4.05 t (J 7.2, 2H, 3-CH_2); 4.12 s (2H, SCH_2); 7.20 br. s (1H, NH_2); 7.58 t (J 7.8, 1H, H-7); 7.66 br. s (1H, NH_2); 7.82 d (J 7.0, 1H, CONH); 7.90 t (J 7.8, 1H, H-8); 8.25 d

(J 7.8, 1H, H-6); 8.60 d (J 7.8, 1H, H-9). Found, %: C 53.73; H 5.48; N 20.85. $C_{18}H_{22}N_6O_3S$. Calculated, %: C 53.72; H 5.51; N 20.88.

4-Benzyl-1-{4-[4-(4-methoxyphenyl)piperazin-1-yl]-4-oxobutyl}[1,2,4]triazolo-[4,3-a]quinazolin-5(4H)-one 7e. The mixture of 1.81 g (0.005 M) of corresponding acid **5** and 0.81 g (0.0055 M) of 1-(*1H*-imidazol-1-ylcarbonyl)-1H-imidazole (CDI) in 10 ml of anhydrous dioxane was refluxed with stirring for 1 hour. Then 1.15 g (0.006 M) of 1-(4-methoxyphenyl)piperazine **6** was added. The resulting mixture was refluxed for 2 hours. After cooling the mixture was diluted with 20 ml of water and allowed to stand for 2 days to form a precipitate, which was filtered, washed with water and recrystallized from a mixture of 5 ml of DMF and 20 ml of *i*-propanol. Yield – 2.25 g (84 %), cream solids. M. p. – 223-225 °C. ^{1}H NMR: 2.05 qn (J 7.2, 2H, 3-CH_2); 2.40 t (J 7.2, 2H, 2-CH_2); 2.95-3.20 m (6H, 4H-pip + 4-CH_2); 3.55-3.75 m (7H, 4H-pip + OCH_3); 5.35 s (2H, CH_2); 6.80 d (J 7.8, 2H, H-3,5 Ar); 6.92 d (J 7.8, 2H, H-2,6 Ar);7.24-7.36 m (3H, H-3,4,5 Ph); 7.44-7.62 m (3H, H-7, 2,6 Ph); 7.92 t (J 7.8, 1H, H-8); 8.04 d (J 7.8, 1H, H-9); 8.28 d (J 7.8, 1H, H-6). Found, %: C 69.33; H 5.99; N 15.64. $C_{31}H_{32}N_6O_3$. Calculated, %: C 69.38; H 6.01; N 15.66.

EXPERIMENTAL BIOLOGICAL PART

Stock solutions were prepared in 100 % DMSO at 20 mg/ml just prior to screening. For the different tests, appropriate reference drugs were used as positive control: tamoxifen for MRC-5, chloroquine for *P. falciparum*, miltefosine for *L. infantum*, benznidazole for *T. cruzi* and suramin for *T. brucei*. All reference drugs were either obtained from the fine chemical supplier Sigma or from WHO-TDR.

The integrated panel of microbial screens and standard screening methodologies were adopted as previously described [8]. All assays were performed in triplicate at the Laboratory of Microbiology, Parasitology and Hygiene at the University of Antwerp, Belgium. Plant extracts were tested at 5 concentrations (64, 16, 4, 1 and 0.25 μg/ml) to establish a full dose-titration and determination of the IC_{50} (inhibitory concentration 50 %). The in-test concentration of DMSO did not exceed 0.5 %. The selectivity antiprotozoal potential as assessed by simultaneous evaluation of cytotoxicity on a fibroblast (MRC-5) cell line. The criterion for activity was an IC_{50} < 10μg/ml (< 5μg/ml for *T. brucei*) and a selectivity index of > 4.

Antileishmanial activity. *L. infantum* MHOM/MA (BE)/67 amastigotes were collected from the spleen of an infected donor hamster and used to infect primary peritoneal mouse macrophages. To determine *in vitro* antileishmanial activity, 3×10^4 macrophages were seeded in each well of a 96-well plate. After 2 days outgrowth, 5×10^5 amastigotes/well were added and incubated for 2 h at 37 °C. Prediluted plant extracts were subsequently added and the plates were further incubated for 5 days at 37 °C and 5 % CO_2. Parasite burdens (mean number of amastigotes/macrophage) were microscopically assessed after Giemsa staining, and expressed as a percentage of the blank controls without plant extract.

Antiplasmodial activity. Chloroquine-resistant *P. falciparum* 2/K 1-strain was cultured in human erythrocytes O^+ at 37 °C under a low oxygen atmosphere (3 % O_2, 4 % CO_2, and 93 % N_2) in RPMI-1640, supplemented with 10 % human serum. Infected human red blood cells (200 μl, 1 % parasitaemia, 2 % haematocrit) were added to each well and incubated for 72 h. After incubation, test plates were frozen at –20 °C. Parasite multiplication was measured by the Malstat method [8, 17].

Antitrypanosomal activity. *T. brucei* Squib-427 strain (suramin-sensitive) was cultured at 37 °C and 5 % CO_2 in Hirumi-9 medium [16], supplemented with 10 % fetal calf serum (FCS). About 1.5×10^4 trypomastigotes/well were added to each well and parasite growth was assessed after 72 h at 37 °C by adding resazurin [18]. For Chagas disease, *T. cruzi* Tulahuen CL2 (benznidazole-sensitive) was maintained on MRC-5 cells in minimal essential medium (MEM) supplemented with 20 mM L-glutamine, 16.5 mM sodium hydrogen carbonate and 5 % FCS. In the assay, 4×10^3 MRC-5 cells and 4×10^4 parasites were added to each well and after incubation at 37 °C for 7 days, parasite growth was assessed by adding the *β*-galactosidase substrate chlorophenol red *β-D*-galactopyranoside [7]. The color reaction was read at 540 nm after 4 h and absorbance values were expressed as a percentage of the blank controls.

Cytotoxicity assay. MRC-5 SV2 cells were cultivated in MEM, supplemented with L-glutamine (20 mM), 16.5 mM sodium hydrogen carbonate and 5 % FCS. For the assay, 10^4 MRC-5 cells/well were seeded onto the test plates containing the pre-diluted sample and incubated at 37 °C and 5 % CO_2 for 72 h. Cell viability was assessed fluorimetrically after 4 hours of addition of resazurin. Fluorescence was measured (excitation 550 nm, emission 590 nm) and the results were expressed as % reduction in cell viability compared to control.

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CONCLUSIONS

4-Benzyl-1-{4-[4-(4-methoxyphenyl)piperazin-1-yl]-4-oxobutyl}[1,2,4]triazolo-[4,3-*a*]quinazolin-5(4*H*)-one **7e**, containing the amide group connected via carbon chain, shows noticeable antimalarial activity with IC_{50} 0.2 μM. Further exploration of other [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones containing the amide group connected to 1 position of triazoloquinazoline moiety via carbon chain could be interesting for identification of novel antimalarial lead structures.

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ПРОИЗВОДНЫЕ [1,2,4]ТРИАЗОЛО[4,3-*a*]ХИНАЗОЛИН-5-ОНОВ КАК ПРОТИВОМАЛЯРИЙНЫЕ СРЕДСТВА

Синтезировано пять новых производных [1,2,4]триазоло[4,3-*a*]хиназолин-5(4*H*)-онов, содержащих амидную группу, присоединенную к первому положению триазолхиназолинового фрагмента с помощью серо-углеродной или углеродной цепи. Строение синтезированных соединений доказано с помощью элементного анализа и данных ^{1}H ЯМР-спектроскопии. Их *in vitro* антипротозойная активность была оценена против *Leishmania infantum*, *Plasmodium falciparum*, *Trypanosoma brucei* и *Trypanosoma cruzi*. 4-Бензил-1-{4-[4-(4-метоксифенил)пиперазин-1-ил]-4-оксобутил}[1,2,4]триазоло[4,3-*a*]хиназолин-5(4*H*)-он **7e**, содержащий амидную группу, соединенную через углеродную цепь, проявил заметную противомалярийную активность с IC_{50} 0,2 мкмоль. Соединение-лидер **7e** может быть перспективным объектом для будущих исследований как новое противомалярийное средство.

Ключевые слова: 2-гидразинохиназолин-4(3*H*)-оны; [1,2,4]триазоло[4,3-*a*]хиназолин-5(4*H*)-оны; *in vitro*; антипротозойный; антималярийная активность

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ПОХІДНІ [1,2,4]ТРИАЗОЛО[4,3-*a*]ХІНАЗОЛІН-5-ОНІВ ЯК ПРОТИМАЛЯРІЙНІ ЗАСОБИ

Синтезовано п'ять нових похідних [1,2,4]триазоло[4,3-*a*]хіназолін-5(4*H*)-онів, що містять амідну групу, приєднану до першого положення триазолхіназолінового фрагменту за допомогою сірко-вуглецевого або вуглецевого ланцюга. Будову синтезованих сполук доведено за допомогою елементного аналізу та даних ^{1}H ЯМР-спектроскопії. Їх *in vitro* антипротозойна активність була оцінена проти *Leishmania infantum*, *Plasmodium falciparum*, *Trypanosoma brucei* та *Trypanosoma cruzi*. 4-Бензил-1-{4-[4-(4-метоксифеніл)піперазин-1-іл]-4-оксобутил}[1,2,4]триазоло[4,3-*a*]хіназолін-5(4*H*)-он **7e**, що містить амідну групу, з'єднану через вуглецевий ланцюг, проявив помітну протималярійну активність з IC_{50} 0,2 мкмоль. Сполука-лідер **7e** може бути перспективним об'єктом для майбутніх досліджень як новий протималярійний засіб.

Ключові слова: 2-гідразинохіназолін-4(3*H*)-они; [1,2,4]триазоло[4,3-*a*]хіназолін-5(4*H*)-они; *in vitro*; антипротозойний; антималярійна активність

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