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PRIMARY ANTIMICROBIAL SCREENING OF NOVEL [1,2,4]TRIAZOLO[4,3-*a*]QUINAZOLIN-5(4*H*)-ONE DERIVATIVES

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Aim. *The aim of the given study was to conduct primary antimicrobial screening of novel [1,2,4]triazolo [4,3-a]quinazolin-5(4H)-one derivatives.*
Methods. *The set of 169 novel [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one derivatives has been tested for activity against 5 bacteria: Escherihia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus, and 2 fungi: Candida albicans and Cryptococcus neoformans. Primary antimicrobial screening has been conducted by whole cell growth inhibition assays, using the provided samples at a single concentration. Samples were tested in water – 0.3 % DMSO solutions with final sample concentrations 32 μg/ml (70-80 μMol).*
Results. *[1,2,4]Triazolo[4,3-a]quinazolin-5(4H)-ones 5{1}, 7{1}, 7{2}, 7{3} showed more than 80 % inhibition of Acinetobacter baumannii growth and compounds 7{4} showed more than 80 % inhibition of growth fungi Cryptococcus neoformans.*
Conclusions. *For the first time conducted antimicrobial screening of novel [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones showed that compounds, which had no amide group exhibited no antimicrobial activity, but several [1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one derivatives containing amide group attached by carbon or sulfur-carbon chain possess antimicrobial activity against Acinetobacter baumannii or fungi Cryptococcus neoformans*
Keywords: *[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one, antimicrobial activity Escherihia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Cryptococcus neoformans*

Мета. *У даному дослідженні було поставлено за мету провести первинний скринінг на антимікробну активність нових похідних [1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-ону.*
Методи. *Масив 169 нових похідних [1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-ону було тестовано на активність проти 5 видів бактерій: Escherihia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa та Staphylococcus aureus, та 2 видів грибів: Candida albicans та Cryptococcus neoformans. Первинний скринінг на антимікробну активність було проведено тестуванням усього масиву на подавлення росту клітин, за умов однакової концентрації сполук. Зразки сполук було тестовано у водних з 0.3 % ДМСО розчинах при остаточній концентрації сполук 32 μг/мл (70–80 μМол).*

Результати. *Похідні [1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-ону 5{1}, 7{1}, 7{2}, 7{3} показали більш ніж 80 % тамування росту Acinetobacter baumannii, та сполука 7{4} показала більш ніж 80 % тамування росту грибку Cryptococcus neoformans.*

Висновки. *Проведене вперше тестування на антимікробну активність [1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-онів показало, що сполуки, що не мають амідної групи, не проявляють антимікробної дії, проте деякі [1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-они, що містять амідну групу, приєднану за допомогою карбонового, або сульфур-карбонового ланцюгу, мають антимікробну активність проти Acinetobacter baumannii або Cryptococcus neoformans*

Ключові слова: *[1,2,4]триазоло[4,3-а]хіназолін-5(4Н)-он, антимікробна активність, Escherihia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Candida albicans, Cryptococcus neoformans*

1. Introduction

The infection treatment was actual task of medicine both ancient and modern times. A lot of remedies were directed against infectious diseases. But massive use of antimicrobial agents leads to appear microbial resistance to popular drugs.

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The growth of microbial resistance to drugs is serious problem in the infection treatment. The main solution to this problem is the search for new effective antimicrobial agents. Usually, the screening of assays of new derivatives potentially biologically active compounds for antimicrobial activity is efficient way to find new antimicrobial substances.

Derivatives of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one, which are representatives of the important class of condensed heterocycles possessing wide range of the biological activity, attract particular interest in development of innovative drug substances.

3. Analysis of recent studies and publications in which a solution of the problem and which draws on the author

Derivatives of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one showed the H1-antihistaminic [1–9], anticonvulsant [10], antiHIV [11], anticancer [12], anti-asthmatic [8, 13], antiallergic [13], anti-inflammatory [13, 14] bioactivities. 1-Alkyl-3-aryl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones demonstrated moderate antibacterial [11, 12] including antitubercular [12] and antifungal [11] properties. In the previous study [15] we found that containing amide group connected via carbon chain 4-benzyl-1-{4-[4-(4-methoxyphenyl)piperazin-1-yl]-4-oxobutyl}[1,2,4] triazolo[4,3-*a*]quinazolin-5(4*H*)-one showed noticeable antimalarial activity with IC_{50} 0.25 μMol.

4. Allocation of unsolved parts of the general problem, which is dedicated to the article

Only a small part of the vast array of possible [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives, namely, 1-alkyl-3-aryl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones have been systematically screened for antimicrobial activity [11, 12].

5. Formulation of goals (tasks) of article

The aim of the given study was to conduct primary antimicrobial screening of novel [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives, namely, 1-aryl-3-alkyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones and [1,2,4] triazolo[4,3-*a*]quinazolin-5(4*H*)-ones containing amide group.

6. Statement of the basic material of the study (methods and objects) with the justification of the results

We used formerly described [16] 2-hydrazinoquinazolin-4(3*H*)-ones **1** as starting materials for [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones synthesis (Fig. 1).

1-Aryl-3-alkyl[1,2,4]triazolo[4,3-*a*]quinazolin-5 (4*H*)-ones **2** have been synthesized by reaction of 2-hydrazinoquinazolin-4(3*H*)-ones **1** with aromatic aldehydes followed by oxidation in the presence of $FeCl_3$ according [17].

Amides of [(4-substituted-4,5-dihydro-5-oxo[1,2,4] triazolo[4,3-*a*]quinazolin-1-yl)thio]acetic acid **5** have been obtained according [15] by condensation of hydrazines **1** with CS_2 resulted in 1-thioxo-2,4-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-5(1*H*)-ones **3** formation. Consequent alkylation by chloroacetic acid amides **4** lead to [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5**, which contain sulfur-carbon chain.

Amides of 3-(4-substituted-5-oxo-4,5-dihydro [1,2,4]triazolo[4,3-a]quinazolin-1-yl)propanoic acid **7** have been obtained according [15, 18] by condensation of hydrazine **1** with succinic anhydride, that produced 3-(4-substituted-5-oxo-4,5-dihydro[1,2,4]triazolo [4,3-*a*]quinazolin-1-yl)propanoic acids **6**. For amide formation we used activation of carboxylic group in obtained acid **6** via getting intermediate imidazolyl amide by carbonyldiimidazole (CDI) in anhydrous dioxane with subsequent reaction with corresponding amine by reflux up to 2 hours.

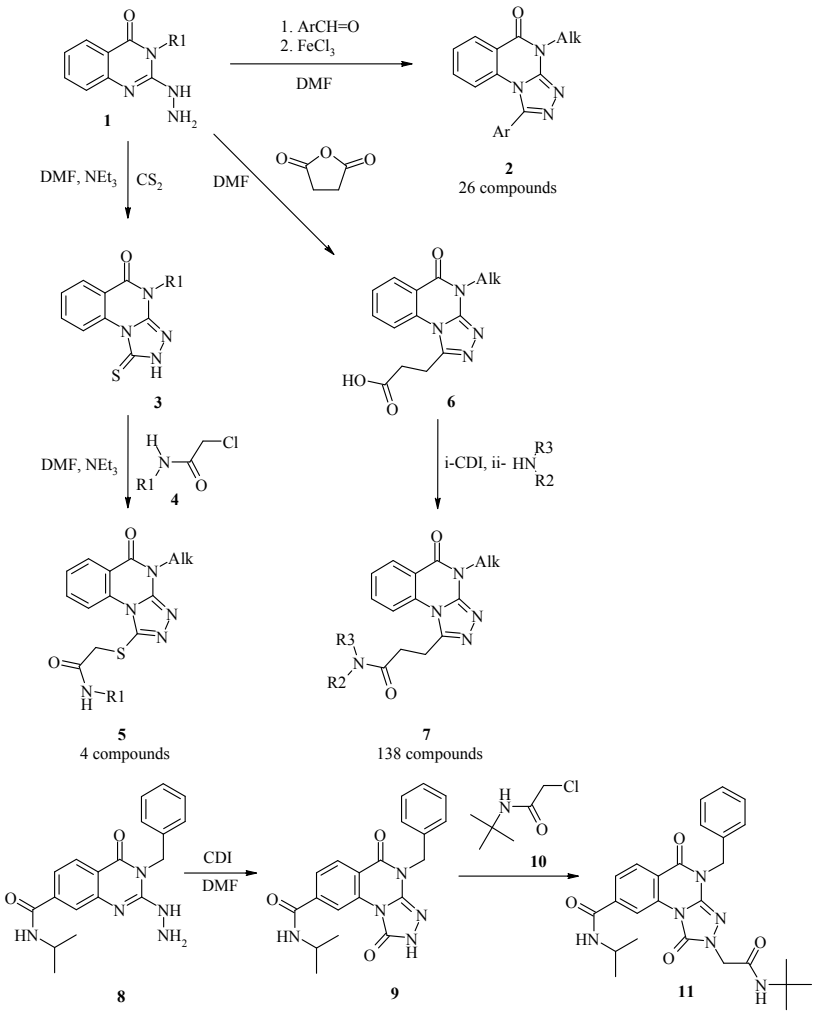

Fig. 1. The synthesis of [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones

Novel 4-benzyl-2-[2-(*tert*-butylamino)-2-oxoethyl]-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro [1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide **11** has been synthesized by reaction of 3-benzyl-2-hydrazino-*N*-isopropyl-4-oxo-3,4-dihydroquinazoline-7-carboxamide **8** with CDI resulted in 4-benzyl-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide **9** formation. Consequent alkylation by *N*-(*tert*-butyl)-2-chloroacetamide **10** lead to [1,2,4]triazolo [4,3-*a*]quinazolin-5(4*H*)-one **11**.

The structures of obtained compounds have been confirmed by the ^{1}H NMR spectroscopy data. Formation of the [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one condensed system led to shift of H-6 protons signals to 8.26–9.22 ppm, that is in good correlation with the known data [19]. ^{1}H NMR-spectra were recorded on Varian WXR-400 (200 MHz) spectrometer in DMSO-d6 solution with TMS as 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.

4-Benzyl-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide 9. Reflux the solution of 0.70 g (0.002 mol) 3-benzyl-2-hydrazino-*N*-isopropyl-4-oxo-3,4-dihydroquinazoline-7-carboxamide **8** and 0.39 g (0.0024 mol) of CDI in anhydrous DMF (5 ml) during 6 hours. After cooling, dilute the reaction mixture with H_2O (20 ml). Filter the precipitate formed, wash it with *i*-propanol (10 ml) and recrystallize from mixture of DMF (5 ml) and *i*-propanol (10 ml). Yields 0.64 g (85 %), white solids, m.p. >300 °C (dec.). ^{1}H NMR (δ, ppm, J, hz): 1.16 (6H, d, J=7.0, $2CH_3$); 4.02-4.12 (1H, m, C<u>H</u>$(CH_3)_2$); 5.18 (2H, s, CH_2); 7.24-7.36 (3H, m, H-3,4,5 Bn); 7.48 (2H, d, J_7=7.8, H-2,6 Bn); 7.86 (1H, dd, $J_{6,7}$=7.8, $J_{7,9}$=2.0, H-7); 8.17 (1H, d, $J_{6,7}$=7.8, H-6); 8.57 (1H, d, J=7.0, CONH); 9.00 (1H, d, $J_{7,9}$=2.0, H-9); 12.00 (1H, s, NH-2). Found, %: C 63.54; H 5.05; N 18.48. $C_{20}H_{19}N_5O_3$. Calculated, %: C 63.65; H 5.07; N 18.56.

4-Benzyl-2-[2-(*tert*-butylamino)-2-oxoethyl]-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro[1,2,4]triazolo [4,3-*a*]quinazoline-8-carboxamide 11. Dissolve 0.38 g (0.001 mol) of 4-benzyl-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide **9** in 5 ml of DMF. Add 0.21 g (0.002 mol) of powder of anhydrous Na_2CO_3 with stirring. Add 0.18 g (0.0012 mol) of *N*-(*tert*-butyl)-2-chloroacetamide **10**. Heat the reaction mixture with stirring at 90 °C for 2 hours. After cooling, dilute the reaction mixture with H_2O (20 ml). Filter the precipitate formed, wash it with *i*-propanol (10 ml) and recrystallize from mixture of DMF (5 ml) and *i*-propanol (10 ml). Yields 0.35 g (71 %),

white solids, m.p. 294-296 °C. ^{1}H NMR (δ, ppm, J, hz): 1.08 (9H, d, *J*=7.0, $3CH_3$); 1.16 (6H, d, *J*=7.0, $2CH_3$); 4.02-4.12 (1H, m, $C\underline{H}(CH_3)_2$); 5.20 (2H, s, CH_2); 5.20 (2H, s, CH_2); 7.24-7.36 (3H, m, H-3,4,5 Bn); 7.48 (2H, d, J_7=7.8, H-2,6 Bn); 7.86 (1H, dd, $J_{6,7}$=7.8, $J_{7,9}$=2.0, H-7); 8.05 (1H, d, *J*=7.0, CONH); 8.17 (1H, d, $J_{6,7}$=7.8, H-6); 8.57 (1H, d, *J*=7.0, CONH); 9.00 (1H, d, $J_{7,9}$=2.0, H-9). Found, %: C 63.54; H 6.18; N 17.08. $C_{26}H_{30}N_6O_4$. Calculated, %: C 63.66; H 6.16; N 17.13.

Hereby sinthesized set of 169 novel [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives consisted of 26 1-aryl-3-alkyl[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **2**, 4 amides of [(4-substituted-4,5-dihydro-5-oxo [1,2,4]triazolo[4,3-*a*]quinazolin-1-yl)thio]acetic acid **5**, 138 amides of 3-(4-substituted-5-oxo-4,5-dihydro[1,2,4] triazolo[4,3-*a*]quinazolin-1-yl)propanoic acid **7** and 4-benzyl-2-[2-(*tert*-butylamino)-2-oxoethyl]-*N*-isopropyl-1,5-dioxo-1,2,4,5-tetrahydro[1,2,4]triazolo[4,3-*a*]quinazoline-8-carboxamide **11**.

This set of compounds has been tested for activity against 5 bacteria: *Escherihia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, and 2 fungi: *Candida albicans* and *Cryptococcus neoformans*.

Samples of 2 mg of each compound were dissolved in 0.2 ml of DMSO that gave 10mg/ml solution in DMSO. An aliquot of each sample was diluted to 320 μg/ml in water, and plated in 384-well polypropylene plates (PP), 5 μl was plated in duplicate (n=2) into a 384-well non-binding surface plate (NBS) for each strain or cell type assayed against. Once cells were added this gave a final compound concentration range of 32 μg/ml (70–80 μMol). Final concentration of DMSO was 0.3 %.

All bacteria were cultured in Cation-adjusted Mueller Hinton broth (CAMHB) at 37 °C overnight. The resultant mid-log phase cultures was added to each well of the compound containing plates, giving a cell density of $5\cdot10^5$ CFU/ml. All the plates were covered and incubated at 37 °C for 18 h without shaking. Inhibition of bacterial growth was determined by measuring absorbance at 600 nm using a Tecan M1000 Pro monochromator plate reader.

Fungi strains were cultured for 3 days on Yeast Extract-Peptone Dextrose (YPD) agar at 30 °C. A yeast suspension of $1\cdot10^6$ to $5\cdot10^6$ cells/ml (as determined by OD530) was prepared from five colonies. These stock suspensions were diluted with Yeast Nitrogen Base (YNB) broth to a final concentration of $2.5\cdot10^3$ CFU/ml. Then, 45 μl of the fungi suspension was added to each well of the compound-containing plates. Plates were covered and incubated at 35°C for 24 h without shaking. Growth inhibition of *Candida albicans* was determined measuring absorbance at 530 nm (OD530), while the growth inhibition of *Cryptococcus neoformans* was determined measuring the difference in absorbance between 600 and 570 nm (OD600-570), after the addition of resazurin (0.001 % final concentration) and incubation at 35 °C for additional 2 h. The absorbance was measured using a Biotek Synergy HTX plate reader.

Colistin and Vancomycin were used as positive bacterial inhibitor standards for Gramnegative and Grampositive bacteria, respectively. Fluconazole was used as a positive fungal inhibitor standard for *Candida albicans* and *Cryptococcus neoformans.*

The tests have been carried out in CO-ADD laboratory (Brisbane, Australia).

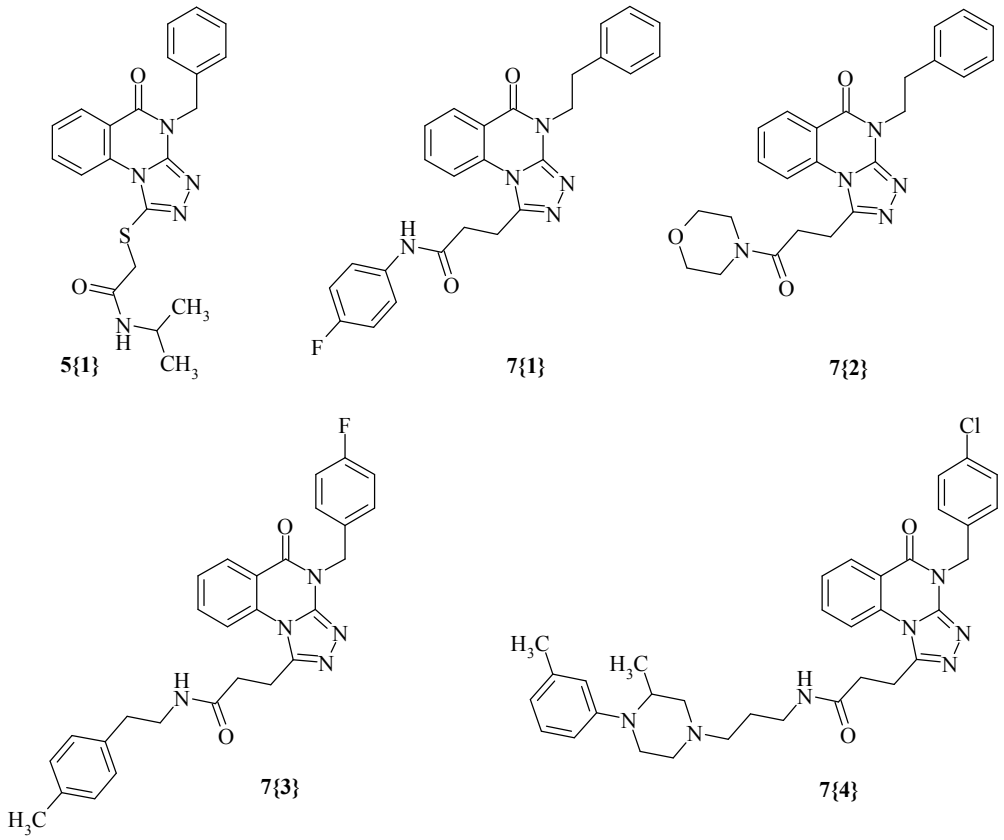

Fig. 2. [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones with antimicrobial activity

2-[(4-Benzyl-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-1-yl)thio]-*N*-isopropylacetamide **5{1}**, *N*-(4-fluorophenyl)-3-[5-oxo-4-(2-phenylethyl)-4,5-dihydro [1,2,4]triazolo[4,3-*a*]quinazolin-1-yl]propanamide **7{1}**, 1-(3-morpholin-4-yl-3-oxopropyl)-4-(2-phenylethyl)[1,2,4] triazolo[4,3-*a*]quinazolin-5(4*H*)-one **7{2}** and 3-[4-(4-fluorobenzyl)-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-1-yl]-*N*-[2-(4-methylphenyl)ethyl]propanamide **7{3}** showed more than 80 % inhibition of *Acinetobacter baumannii* growth and 3-[4-(4-chlorobenzyl)-5-oxo-4,5-dihydro[1,2,4]triazolo[4,3-*a*]quinazolin-1-yl]-*N*-{3-[3-methyl-4-(3-methylphenyl)piperazin-1-yl]propyl} propanamide **7{4}** showed more than 80 % inhibition of growth fungi *Cryptococcus neoformans* (Fig. 2).

7. Conclusions

For the first time conducted antimicrobial screening of novel [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones showed that compounds, which had no amide group exhibited no antimicrobial activity, but several [1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-one derivatives containing amide group attached by carbon or sulfur-carbon chain possess antimicrobial activity against *Acinetobacter baumannii* or fungi *Cryptococcus neoformans*.

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