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Research Article

A new group of compounds derived from 4-, 5-, 6- and 7-aminoindoles with antimicrobial activity

Irina S. Stepanenko[1], Semen A. Yamashkin[1], Yuliya A. Kostina[1], Alyona A. Batarsheva[1], Mikhail A. Mironov[1]

1 *National Research Ogarev Mordovia State University, 68 Bolshevistskaya St., Saransk 430005, Republic of Mordovia, Russian Federation*

Corresponding author: *Irina S. Stepanenko* (ymahkina@mail.ru)

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Abstract

Introduction. The problem of antibiotic resistance of microorganisms is becoming more urgent in the twenty-first century. Microorganisms possess an evolutionary adaptive capacity. Non-adherence to the basic principles of rational antibiotic therapy leads to menacing consequences. More and more pathogenic microbes are becoming resistant to two or more antibiotics. The search for new compounds with antimicrobial activity is one of the principles for overcoming the antibiotic resistance of microorganisms.

Materials and methods. Eighteen test-strains of microorganisms and more than 2000 clinical strains of microorganisms, representating the families Micrococcaceae, Streptococcaceae, Enterobacteriaceae, Moraxellaceae, Pseudomonadaceae, Sphingomonadaceae, Xanthomonadaceae were studied for sensitivity to the compounds derived from 4-, 5-, 6- and 7-aminoindoles. A method of serial dilutions to determine the minimal inhibitory concentration (MIC) of the compounds under study was used in the study, as well as a disc diffusion method.

Results and discussion. Sensitivity of the test-strains and of clinical strains of microorganisms to the resulting compounds was studied. The compounds based on substituted 4-, 5-, 6-, 7-aminoindoles showed different activity against the test strains and experimental strains of microorganisms *in vitro*. It was found that the marked antibacterial activity was exhibited by the compounds containing a trifluoromethyl group. The most significant activity was noted in amides and pyrroloquinolones based on 4-aminoindole, 6-aminoindole and 7-aminoindole.The most effective compounds with laboratory codes **5D**, **7D**, **39D**, **S3**, **HD**, **4D** showed a pronounced antibacterial activity.

Conclusion. Antimicrobial activity of the substituted amides and pyrroloquinolines on the basis of 4-, 5-, 6-, 7-aminoindoles was etermined in our study, as well as the spectra of their action against Gram-positive and Gram-negative microorganisms, which are causative agents of non-specific and certain specific human infectious diseases. Moreover, we evaluated the synthetic potentials of the substituted 4-, 5-, 6-, 7-aminoindoles as the starting compounds for synthesizing a series of indolylamides and pyrroloquinolines. Also, the prospects for targeted synthesis of biologically active compounds based on indole-type aromatic amines were determined.

Keywords

antimicrobial activity, conditionally pathogenic microorganisms, cyclic aminoindoles, non-cyclic aminoindoles, pyrroloquinolones.

Introduction

The need for a search of new highly effective and safe antimicrobial compounds was stated on the legislative level in the Order of the Government of the Russian Federation of September 25, 2017 No. 2045-r "On the Strategy for Preventing the Spread of Antimicrobial Resistance in the Russian Federation for the Period till 2030".

One of the main modern trends in the development of antimicrobial compounds is synthesis of analogs and derivatives of the known drugs. At present, there are more than fifteen million chemical compounds with antimicrobial activity, isolated from natural sources or obtained by chemical synthesis. However, only a few of them meet the requirements for antimicrobial and biological safety (Ling et al. 2015; Brown et al. 2016).

Resistance to both antibiotics and disinfectants is becoming an urgent and alarming issue in the 21st century, since an uncontrolled use of antimicrobial agents as preservatives in the food industry, as disinfectants and chemotherapeutic agents in animal husbandry and agriculture inevitably results in an increased resistance of microorganisms to most commonly used antimicrobial drugs. In most regions of the world, as well as in Russia among others, antibiotic-resistant strains of both Gram-positive (staphylococci, enterococci) and Gram-negative bacteria (enterobacteria, pseudomonas, etc.) are spreading (Pop-Vicas et al. 2008; Snitkin et al. 2012; Kozlov et al. 2015; Eidelstein et al. 2017; Sukhorukova et al. 2017; Natan and Banin 2017). Annually, in the world about twenty million people die from infectious pathology. Annual incidence of infectious diseases is estimated to be hundreds of millions of cases. Difficulties in the treatment and prevention of infectious diseases caused by diverse biological forms of pathogens, an immense adaptive ability of microorganisms and constant emergence of forms with multiple resistance, as well as emergence of new species of microorganisms, make the development of new antimicrobial agents an urgent issue. The prospects for developing and implementing new antimicrobial agents look, to be frankly, depressing (Saveliev et al. 2012; Tacconelli et al. 2018).

The microbiological monitoring in 2013-2014 showed an increased proportion of multi-drug and methicillin-resistant strains of *S. aureus*, *P. aeruginosa* and multiple-drug resistance of the Enterobacteriaceae family to three or more antimicrobial drugs (Lai et al. 2014; Kozlova et al. 2014; Kozlov et al. 2015; WHO 2015; Eidelstein et al. 2017; Sukhorukova 2017; Petchiappan and Chatterji 2017).

In modern conditions, the studies based on one of the fundamental principles of overcoming the resistance of microorganisms and search for new compounds with antimicrobial activity, perhaps with a different mechanism of action, are undoubtedly of vital importance (Kosinets et al. 2014).

In the recent decades, the studies in the field of indole chemistry and its derivatives have remained invariably of interest. This is due to the fact that the indole structure underlies many natural and synthetic physiologically active substances. A special role in indole chemistry is played by aminoindoles. It is because an indole fragment contains molecules of the irreplaceable protein amino acid tryptophan, the biogenic amine of serotonin. Of particular interest are aminoindoles with an aminogroup in the benzene part of the molecule. These compounds, like any aromatic amines can give various kinds of derivatives with an aminogroup (Yamashkin et al. 2006; 2008; Alyamkina et al. 2017). The authors of the present paper carried out the studies on the interaction of β-dioxo compounds with substituted aminoindoles, with different positions of the amino group in the benzene ring. The resulting amides, enamines, are of interest in themselves as biologically active substances, as well as the starting compounds for the production of tricyclic heterosystems – pyrroloquinolones. These compounds are structural fragments of some alkaloids (for example, the Vomipirin alkaloid) and coenzymes of some bacterial and animal dehydrogenases (eg, Metoxatine – PQQ coenzyme). The new group contains compounds that affect the biological and physiological characteristics of microscopic fungi (Kadimaliev et al. 2014). The derivatives of dihydropyrroloquinoline are used to kill clinically latent microorganisms (Bek et al. 2009). In view of this, the aim of the present study was to evaluate the antimicrobial activity of cyclic, non-cyclic aminoindoles and pyrroloquinolones derived from 4-, 5-, 6- and 7-aminoindoles.

Materials and methods

Antimicrobial activity was studied on the following test-strains of microorganisms: *Staphylococcus aureus 25923 ATCC, Staphylococcus aureus ATCC 6538-P, Staphylococcus aureus 43300 ATCC (MRSA), Escherichia coli 25922 ATCC, Pseudomonas aeruginosa 27853 ATCC, Streptococcus pyogenes 1238 ATCC, Streptococcus pyogenes 19615 ATCC, Streptococcus pneumoniae 49619 ATCC, Salmonella enteritidis 5765 ATCC, Shigella sonnei S-form, Pseudomonas aeruginosa 453, Escherichia coli M-17, Staphylococcus aureus 906, Enterococcus faecalis 19433 ATCC, Citrobacter freundii 101/57, Proteus vulgaris "Tsvetkov", Klebsiella pneumoniae 13883 ATCC, Bacillus cereus 96* and on the experimental microorganisms, representatives of the families Micrococcaceae, Streptococcaceae, Enterobacteriaceae, Moraxellaceae, Pseudomonadaceae, Sphingomonadaceae, and Xanthomonadaceae. Some strains obtained from the collection of the Museum of Living Cultures (Moscow, Obolensk, Becton Dickinson France S.A.S.). were used in the study, The experimental strains were isolated from the material obtained from patients with nonspecific and specific diseases of the respiratory and urinary tracts and intestines, with different sensitivity to the traditional antimicrobial drugs. The identification of the laboratory microorganism strains was carried out by classical bacteriological methods (The order of the Ministry of Healthcare of the USSR № 535 of April 22, 1985). The final verification and determination of the microbial sensitivity to common

antimicrobial agents were performed by means of the automated bacterial system Sensititré (England). For the determination of the antimicrobial activity, the traditional methods were used (Clinical recommendations, 2018): serial dilutions in broth (test tube macro method) and disc diffusion method (DDM). In DDM, paper disks without antibiotics were used as carriers of the test compounds. Immediately before use, the disks were impregnated with the test compound, using a microdoser. To study the antimicrobial activity, the test compounds were used as solutions. Dimexide (DMSO) was used as a solvent. In all the studies conducted, DMSO was also studied in the concentrations used. As an antimicrobial agent, dioxidine (a derivative of di-*N*-oxyquinoxaline), widely used in medical practice, was used as a comparator.

Method of serial dilutions in broth (test tube macro method)

Into each of ten tubes, 0.5 ml of Müller-Hinton broth (MHB) was added. To prepare a solution of the test compounds, into 1 ml of DMSO 5 mg of the test substance was added and then 4 ml of MHB. Into the first tube, 0.5 ml of the resulting work solution of the test compound was added, after which 0.5 ml was transferred to a subsequent tube, except for the last one ("negative" control). As a result of dilution, the following concentrations of the test compounds were obtained: 250 μg, 125 μg, 62.5 μg, 31.3 μg, 15.7 μg, 7.9 μg, 3.9 μg, 1.96 μg, and 0.98 μg. The testing was carried out in 6 series of experiments. To prepare a suspension of microorganisms, a one-day-old culture of microorganisms was diluted in 1 ml of saline solution in accordance with the commercial standard of turbidity of 0.5 McFarland. Then 0.1 ml of the prepared solution with microorganisms was diluted in 10 ml of MHB, and then 0.5 ml of MHB with microorganisms was added into each of 10 tubes. The "negative" control tube was placed into a refrigerator at 4 °C, where it was stored until the results were recorded. To determine the presence of microbial growth, the test tubes with cultures were examined in transmitted light. The culture growth in the presence of the test compound was compared to the control test-tube ("negative" control) containing the original inoculum which had been stored in the refrigerator. The MIC was determined as the lowest concentration of the test compound that suppressed the visible growth of the microorganism.

Disc diffusion method (DDM)

In DDM, paper discs (standardized ND-PMP-1 discs from technical filterboard). Immediately before use, the discs were impregnated with the test compound, using a microdoser; some disks were impregnated with distilled water as controls. In the DDM, a standard inoculum corresponding to a density of 0.5 according to the McFarland standard and containing approximately 1.5x108 CFU/ml was used to determine the sensitivity, for inoculation, industrially manufactured sterile cotton swabs (swab-stick of plastic-cotton) CITOSWAB, sterile in individual packaging, were used. The growth inhibition zones of the microbial strain, which were formed as a result of the diffusion of the test compound from the carrier into the Müller-Hinton agar (MHA) were studied. These zones were determined using a ruler-scale (HiMedia Laboratories P vt.Limited).

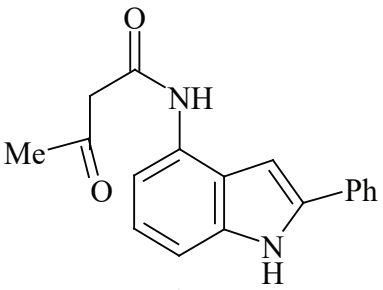
As the result of employing the synthetic potentials of the substituted 4-, 5-, 6-, 7-aminoindoles used as the starting agents, a series of indolylamides and pyrroloquinolones were synthesized. Then the series of the obtained anilide-type compounds containing various substituted cyclic, noncyclic *N*-(indolyl)amides and pyrroloquinolones were studied. Designations for enamines, amides, pyrroloquinolones were brought in compliance with the rules of the ACD LABS IUPAC Name Generator software, and the structural formulas of the compounds were drawn in ISIS Draw 2.4 software.

Results and discussion

Group of compounds derived from 4-, 5-, 6- and 7-aminoindoles.

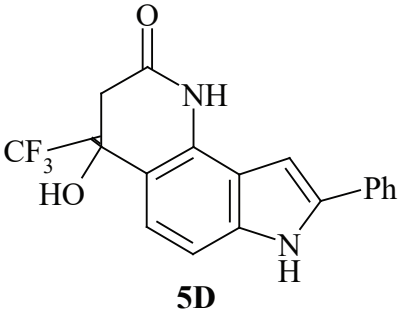
1. Derivatives of substituted 4-amino-2-phenylindole:

3-Oxo-*N*-(2-phenyl-1*H*-indol-4-yl) butanamide (laboratory code **6D**)



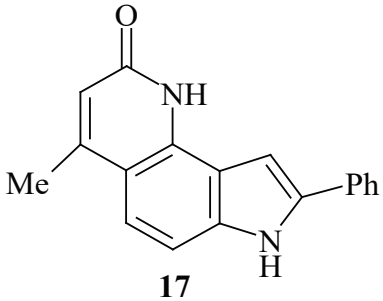
6D

4-hydroxy-8-phenyl-4-(trifluoromethyl)-1,3,4,7-tetrahydro-2*H*-pyrrolo-[2,3-*h*]quinoline-2-one (laboratory code **5D**)



5D

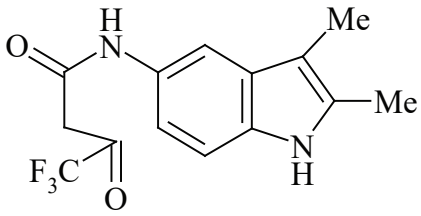
4-methyl-8-phenyl-1,7-dihydro-2*H*-pyrrolo[2,3-*h*]quinolin-2-one (**17**)



17

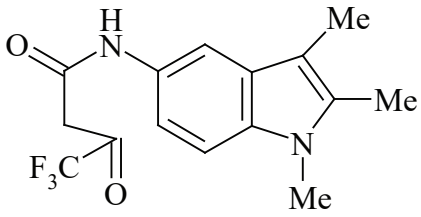
2. Derivatives of substituted 5-aminoindoles:

4,4,4-trifluoro-3-oxo-*N*-(2,3-dimethyl-1*H*-indol-5-yl)butanamide (laboratory code **3D**)



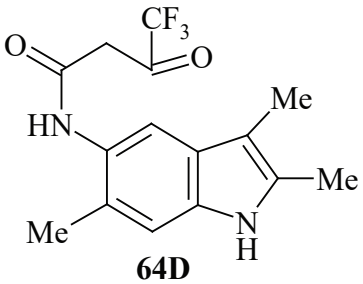
3D

4,4,4-trifluoro-3-oxo-*N*-(1,2,3-trimethyl-1*H*-indol-5-yl) butanamide **(**laboratory code **2D)**



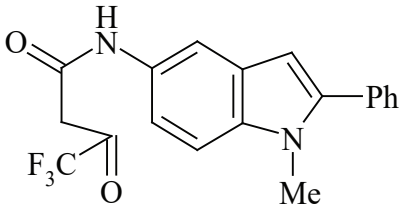
2D

4,4,4-trifluoro-*N*-(1-methyl-2-phenyl-1*H*-indol-5-yl)-3-oxobutanamide **(**laboratory code **64D)**



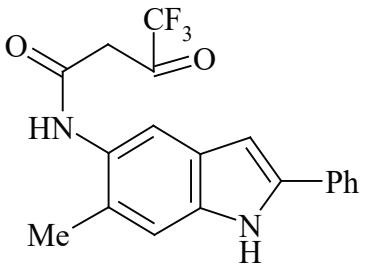
64D

4,4,4-trifluoro-3-oxo-*N*-(2,3,6-trimethyl-1*H*-indol-5-yl) butanamide **(**laboratory code **32D)**



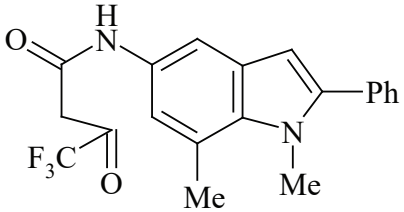
32D

4,4,4-trifluoro-*N*-(6-methyl-2-phenyl-1*H*-indol-5-yl)-3-oxobutanamide **(**laboratory code **43D)**



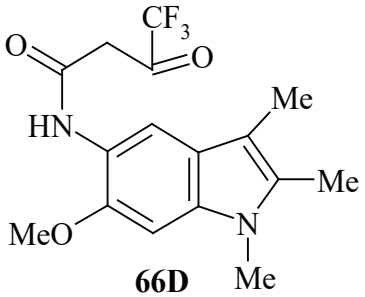
43D

N-(1,7-dimethyl-2-phenyl-1*H*-indol-5-yl)-4,4,4-trifluoro-3-oxobutanamide **(**laboratory code **235D)**



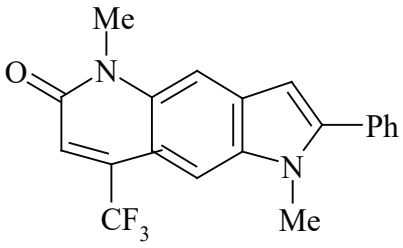
235D

4,4,4-trifluoro-N- (6-methoxy-1,2,3-trimethyl-1H-indol-5-yl) -3-oxobutanamide **(**laboratory code **66D)**



66D

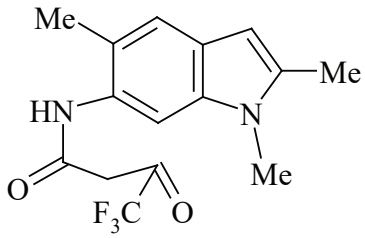
1,5-dimethyl-2-phenyl-8-(trifluoromethyl)-1,5-dihydro-6*H*-pyrrolo-[2,3-g]quinolin-6-one **(**laboratory code **39D)**



39D

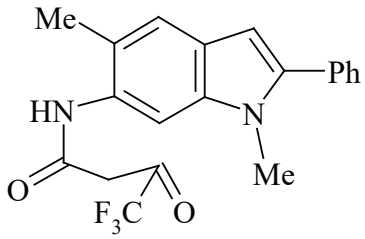
3. Derivatives of substituted 6-aminoindoles:

4,4,4-trifluoro-3-oxo-*N*-(1,2,5-trimethyl-1*H*-indol-6-yl) butanamide (laboratory code **243D**)



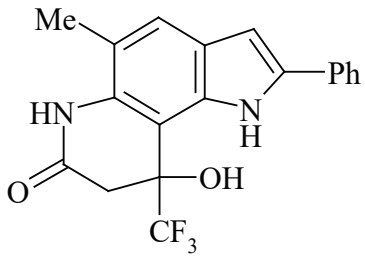
243D

N-(1,5-dimethyl-2-phenyl-1*H*-indol-6-yl)-4,4,4-trifluoro-3-oxobutanamide **(**laboratory code **S3)**



S3

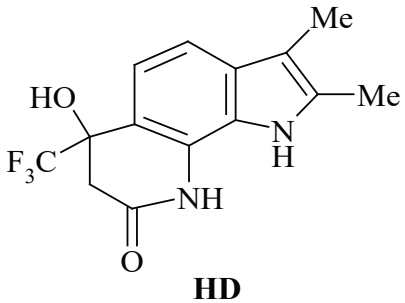
9-hydroxy-5-methyl-2-phenyl-9-(trifluoromethyl)-1,6,8,9-tetrahydro-7*H*-pyrrolo[2,3-*f*]quinolin-7-one **(**laboratory code **7D)**



7D

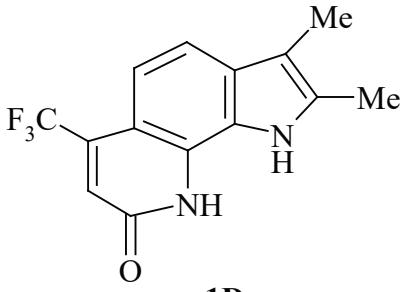
4. Derivatives of substituted 7-aminoindoles:

6-hydroxy-2,3-dimethyl-6-(trifluoromethyl)-1,6,7,9-tetrahydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one **(**laboratory code **HD)**



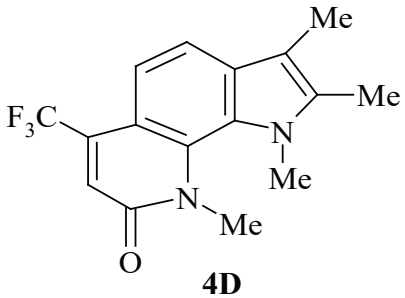
HD

2,3-dimethyl-6-(trifluoromethyl)-1,9-dihydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one (laboratory code **1D**)



1D

1,2,3,9-tetramethyl-6-(trifluoromethyl)-1,9-dihydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one (laboratory code **4D**)



4D

1. Derivatives of substituted 4-amino-2-phenylindole:

3-oxo-*N*-(2-phenyl-1*H*-indol-4-yl) butanamide (compound with laboratory code **6D)** was found to be inactive against the Gram-positive and Gram-negative test strains of microorganisms *in vitro*.

4-hydroxy-8-phenyl-4-(trifluoromethyl)-1,3,4,7-tetrahydro-2*H*-pyrrolo-[2,3-*h*]quinoline-2-one (compound with laboratory code **5D)** showed a wide range of antimicrobial activities and a pronounced antibacterial activity

against the studied strains of Gram-positive microorganisms *in vitro*, and also showed an antimicrobial activity against the studied Gram-negative microorganisms *in vitro*, with the exception of the *P. aeruginosa* .

As for the test strains of microorganisms, the compound with laboratory code **5D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 7.8 μg/ml, against *E. coli* 25922 – 125 μg/ml, against *P. aeruginosa* 27853 – over 250 μg/ml, against *S. pyogenes* 1238 – 31.25 μg/ml, and against *B. cereus* 96 – 62.5 μg/ml. The MICs for the experimental microorganisms were: for *S. aureus* – 3.9-500 μg/ml, for *E. coli* – 62.5-1000 μg/ml, for *S. pyogenes* – 31.25-750 μg/ml, and for *B. cereus* – 62.5-1000 μg/ml.

The test compound **5D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. pyogenes, S. pneumoniae, S. salivarius, S. uberis, S. mitis, S. agalactiae, E. faecalis, E. faecium, B. cereus, E. coli, S. enteritidis, C. freundii, E. cloaceae, E. aerogenes,* and *K. pneumoniae* .

4-methyl-8-phenyl-1,7-dihydro-2*H*-pyrrolo[2,3-*h*] quinolin-2-one (compound with laboratory code **17**) was found to be inactive against the Gram-positive and Gram-negative test strains of microorganisms *in vitro*.

2. Derivatives of substituted 5-aminoindoles:

4,4,4-trifluoro-3-oxo-*N*-(2,3-dimethyl-1*H*-indol-5-yl) butanamide (compound with laboratory code **3D**), 4,4,4-trifluoro-3-oxo-*N*-(1,2,3-trimethyl-1*H*-indol-5-yl)butanamide (compound with laboratory code **2D**), 4,4,4-trifluoro-*N*-(1-methyl-2-phenyl-1*H*-indol-5-yl)-3-oxobutanamide (compound with laboratory code **64D**), 4,4,4-trifluoro-3-oxo-*N*-(2,3,6-trimethyl-1*H*-indol-5-yl) butanamide (compound with laboratory code **32D**) were found to be inactive against Gram-positive and Gram-negative test strains of microorganisms *in vitro*.

4,4,4-trifluoro-*N*-(6-methyl-2-phenyl-1*H*-indol-5-yl)-3-oxobutanamide (compound with laboratory code **43D**) showed antimicrobial activity against the test strains and experimental strains of Gram-positive microorganisms *in vitro*, but its effect was more pronounced with respect to pyogenic streptococcus. The effect on the studied Gram-negative microorganisms *in vitro* was not significant.

Concerning the test strains of microorganisms, the compound with laboratory code **43D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – over 250 μg/ml, against *P. aeruginosa* 27853 – over 250 μg/ml, against *S. pyogenes* 1238 – 62.5 μg/ml, and against *B. cereus* 96–125 μg/ml. The MICs for the experimental microorganisms were: for *Streptococcus* spp. – 62.5–1000 μg/ml, for *Staphylococcus* spp. – 250–1000 μg/ml, and for *B. cereus* – 125-1000 μg/ml.

The test compound **43D** was found to be capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. haemolyticus, S. pyogenes, S. pneumoniae, S. bovis, S. salivarius, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans,* and *B. cereus* .

4,4,4-trifluoro-N-(6-methoxy-1,2,3-trimethyl-1H-indol-5-yl)-3-oxobutanamide (compound with laboratory code **66D**) showed antimicrobial activity against the test strains and experimental strains of Gram-positive microorganisms *in vitro*, but it was more pronounced with respect to pyogenic streptococcus. No significant effect was noted on the Gram-negative microorganisms *in vitro*.

Concerning the test strains of microorganisms, the compound with laboratory code **66D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – over 250 μg/ml, against *P. aeruginosa* 27853 – more than 250 μg/ml, against *S. pyogenes* 1238 – 125 μg/ml, and against *B. cereus* 96 – 250 μg/ml. The MICs for the experimental microorganisms were: for *Streptococcus* spp. – 125-1000 μg/ml, for *Staphylococcus* spp. –125-1000 μg/ml, and for *B. cereus* – 125-1000 μg/ml.

The test compound **66D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. haemolyticus, S. pyogenes, S. pneumoniae, S. bovis, S. salivarius, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans,* and *B. cereus* .

N-(1,7-dimethyl-2-phenyl-1*H*-indol-5-yl)-4,4,4-trifluoro-3-oxobutanamide (compound with laboratory code **235D**) has antimicrobial activity against the test strains and experimental strains of Gram-positive microorganisms *in vitro*.

However, it exhibited lower antimicrobial activity against the studied Gram-negative microorganisms *in vitro*. Only at high concentrations, it becomes able to exert an antimicrobial effect on *P. aeruginosa* .

Concerning the test strains of microorganisms, the compound with laboratory code **235D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – 250 μg/ml, against *P. aeruginosa* 27853 – 250 μg/ml, against *S. pyogenes* 1238 – 62.5 μg/ml, *and* against *B. cereus* 96 – 62.5 μg/ml. The MICs for the experimental microorganisms were: for *Streptococcus* spp. – 62.5-500 μg/ml, for *Staphylococcus* spp. – 125-1000 μg/ml, for *B. cereus* –62.5-750 μg/ml, for *E. coli* – 250-1000 μg/ml, and for *P. aeruginosa* – 500-1500 μg/ml.

The test compound **235D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. pyogenes, S. pneumoniae, S. bovis, S. salivarius, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans, S. dysgalactiae equisimilis, S. constellatus constellatus, E. faecalis, E. faecium, E. coli, C. freundii, E. cloaceae, E. aerogenes, E. cloaceae, K. pneumoniae, K. oxytoca, P. vulgaris, A. lwoffi,* and *P. aeruginosa* .

1,5-dimethyl-2-phenyl-8-(trifluoromethyl)-1,5-dihydro-6*H*-pyrrolo-[2,3-g]quinolin-6-one (compound with laboratory code **39D**) showed antibacterial activity against the strains of Gram-positive microorganisms studied in

vitro, and at high concentrations it can exert an antimicrobial effect against the studied Gram-negative microorganisms *in vitro*, with the exception of the *P. aeruginosa* .

Concerning the test strains of microorganisms, the compound with laboratory code **39D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 31.25 μg/ml, against *E. coli* 25922 – 250 μg/ml, against *P. aeruginosa* 27853 – more than 250 μg/ml, against *S. pyogenes* 1238 – 31.25 μg/ml, *and* against *B. cereus* 96 – 125 μg/ml. The MICs for the experimental microorganisms were: against *Streptococcus* spp. – 15.6-750 μg/ml, against *Staphylococcus* spp. – 31.25-1000 μg/ml, against *B. cereus* –125-750 μg/ml, and against *E. coli* – 500-1500 μg/ml.

The test compound **39D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. pyogenes, S. pneumoniae, S. salivarius, S. bovis, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans, E. faecalis, E. faecium, B. cereus, E. coli, S. enteritidis, S. typhimurium, S. sonnei, C. freundii, E. cloaceae, E. aerogenes, E. aqqlom, K. pneumoniae, K. oxytoca, P. vulgaris,* and *A. baumani* .

3. Derivatives of substituted 6-aminoindoles:

4,4,4-trifluoro-3-oxo-*N*-(1,2,5-trimethyl-1*H*-indol-6-yl) butanamide (compound with laboratory code **243D**) showed antimicrobial activity against the test strains and experimental strains of Gram-positive microorganisms *in vitro.* There was no significant effect noted on the studied Gram-negative microorganisms *in vitro*.

Concerning the test strains of microorganisms, the compound with laboratory code **243D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – more than 250 μg/ml, against *P. aeruginosa* 27853 – more than 250 μg/ml, against *S. pyogenes* 1238 – 125 μg/ml, and against *B. cereus* 96 – 250 μg/ml. The MICs for the experimental microorganisms were: for *Streptococcus* spp. – 125-750 μg/ml, *Staphylococcus* spp. – 125-1000 μg/ml, and *B. cereus* – 250-1000 μg/ml.

The test compound **243D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. pyogenes, S. pneumoniae, S. salivarius, S. bovis, S. mitis, S. mutans, E. faecalis, E. faecium,* and *B. cereus* .

N-(1,5-dimethyl-2-phenyl-1*H*-indol-6-yl)-4,4,4-trifluoro-3-oxobutanamide (compound with laboratory code **S3**) showed a pronounced antibacterial activity against the studied strains of both Gram-positive and Gram-negative microorganisms *in vitro.*

Concerning the test strains of microorganisms, the compound with laboratory code **S3** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 62.5 μg/ml, against *E. coli* 25922 – 31.25 μg/ml, against *P. aeruginosa* 27853 – 62.5 μg/ml, against *S. pyogenes* 1238 – 250 μg/ml, and against *B. cereus* 96 – 250 μg/ml. The MIC for the experimental microorganisms were: for *Staphylococcus* spp. it was 31.25-1000 μg/ml, for *E. coli* – 31.25-500 μg/ml, for *Streptococcus* spp. – 125-1000 μg/ml, for *B. cereus* – 250-500 μg/ml, and for *P. aeruginosa* – 62.5-1000 μg/ml.

The test compound **S3** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. mitis, S. salivarius, S. agalactiae, S. uberis, S. pneumoniae, S. pyogenes, S. aureus, S. epidermidis, E. faecalis, E. faecium, B. cereus, E. aerogenes, E. cloaceae, K. pneumonia, E. coli, C. freundii, P. vulgaris, P. mirabilis P. aeruginosa* .

9-hydroxy-5-methyl-2-phenyl-9-(trifluoromethyl)-1,6,8,9-tetrahydro-7*H*-pyrrolo[2,3-*f*]quinolin-7-one (compound with laboratory code **7D**) was noted to have a pronounced antibacterial effect against the studied strains of Gram-negative microorganisms *in vitro*, with the exception of *P. aeruginosa* . It exhibited an antimicrobial effect against the studied Gram-positive microorganisms *in vitro.*

Concerning the test strains of microorganisms, the compound with laboratory code **7D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – 62.5 μg/ml, against *P. aeruginosa* 27853 – over 250 μg/ml, against *S. pyogenes* 1238 – 250 μg/ml, and against *B. cereus* 96 – 62,5 μg/ml. The MICs for the experimental microorganisms were: for *Staphylococcus* spp. – 62.5-1000 μg/ml, for *E. coli* – 31.25-500 μg/ml, for *Streptococcus* spp. – 250-1000 μg/ml, and for *B. cereus* – 62.5-500 μg/ml.

The test compound **7D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. pyogenes, S. pneumoniae, S. agalactiae, B. cereus, E. coli, E. cloaceae,* and *K. pneumoniae* .

4. Derivatives of substituted 7-aminoindoles:

6-hydroxy-2,3-dimethyl-6-(trifluoromethyl)-1,6,7,9-tetrahydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one (compound with laboratory code **HD**) showed antibacterial activity against the studied strains of both Gram-positive and Gram-negative microorganisms *in vitro.*

Concerning the test strains of microorganisms, the compound with laboratory code **HD** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 59.0 μg/ml, against *E. coli* 25922 – 108.0 μg/ml, against *P. aeruginosa* 27853 – 184.0 μg/ml, against *S. pyogenes* 1238 – 117.0 μg/ml, and against *B. cereus* 96 – 117.0 μg/ml. The MICs for the experimental microorganisms were: for *Staphylococcus* spp. – 14.25-1000 μg/ml, for *E. coli* – 59.0-1000 μg/ml, for *P. aeruginosa* – 117-1000 μg/ml, for *Streptococcus* spp. – 28.5-1000 μg/ml, and for *B. cereus* – 117-1000 μg/ml.

The test compound **HD** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. pyogenes, S. salivarius, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans, E. faecalis, E. faecium, E. coli, S. enteritidis, S. typhimurium, S. sonnei,*

C. freundii, E. cloaceae, E. aerogenes, E. gergoviae, E. amnigenes, E. hormaechei, K. pneumoniae, K. oxytoca, P. vulgaris, M. morganii, P. agglomerans, A. baumani, and *P. aeruginosa* .

1,2,3,9-tetramethyl-6-(trifluoromethyl)-1,9-dihydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one (compound with laboratory code **4D**) showed a wide spectrum of antimicrobial activity and a pronounced antibacterial activity against the studied strains of both Gram-positive and Gram-negative microorganisms in vitro, but is not very active against *P. aeruginosa* .

Concerning the test strains of microorganisms, the compound with laboratory code **4D** showed the following activity: against *S. aureus* 29213 – MIC of the test compound was 125 μg/ml, against *E. coli* 25922 – 125 μg/ml, against *P. aeruginosa* 27853 – over 250 μg/ml, against *S. pyogenes* 1238 – 125 μg/ml, and against *B. cereus* 96 – 125 μg/ml. The MICs for the experimental microorganisms were: for *Staphylococcus* spp. – 125-1000 μg/ml, for *E. coli* – 125-1000 μg/ml, for *P. aeruginosa* – 500-1500 μg/ml, for *Streptococcus* spp. – 62.5-1000 μg/ml, and for *B. cereus* – 125-1000 μg/ml.

The test compound **4D** is capable of slowing down or suppressing the growth and multiplication of clinical strains of *S. aureus, S. epidermidis, S. saprophyticus, S. haemolyticus, S. warneri, S. pyogenes, S. pneumoniae, S. salivarius, S. uberis, S. mitis, S. agalactiae, S. sanguinis, S. mutans, E. faecalis, E. faecium, E. coli, S. enteritidis, S. typhimurium, S. sonnei, C. freundii, E. cloaceae, E. aerogenes, E. gergoviae, E. amnigenes, E. hormaechei, K. pneumoniae, K. oxytoca, P. vulgaris, P. mirabilis, M. morganii, H. alvei, P. agglomerans, A. baumani,* and *P. aeruginosa* .

2,3-dimethyl-6-(trifluoromethyl)-1,9-dihydro-8*H*-pyrrolo[3,2-*h*]quinolin-8-one (compound with laboratory code **1D**) showed an antimicrobial effect against the test strains and experimental strains of some Gram-positive microorganisms *in vitro*, which was more pronounced with respect to pyogenic streptococcus and *B. cereus* .

There was no significant effect noted on the studied Gram-negative microorganisms *in vitro*. Its activity is the lowest among all the active compounds, both with narrow and wide spectra of action.

Concerning the test strains of microorganisms, the compound with laboratory code **1D** showed the following activity: against *S. aureus* 29213, *E. coli* 25922, *P. aeruginosa* 27853 MIC of the test compound was over 250 μg/ml, against *S. pyogenes* 1238 *ATCC* – 125 μg/ml, and against *B. cereus* 96 – 125 μg/ml. The MICs for the experimental microorganisms were: for *S. pyogenes* – 65.2-1000 μg/ml and for *B. cereus* – 125-1000 μg/ml.

Conclusion

The sensitivity of the test strains of microorganisms to new compounds was studied on *Staphylococcus aureus 25923 ATCC, S. aureus ATCC 6538-P, Staphylococcus aureus 43300 ATCC (MRSA), Escherichia coli 25922 ATCC, Pseudomonas aeruginosa 27853 ATCC, Streptococcus pyogenes 1238 ATCC, Streptococcus pyogenes 19615 ATCC, Streptococcus pneumoniae 49619 ATCC, Salmonella enteritidis 5765 ATCC, Shigella sonnei S-form, Pseudomonas aeruginosa 453, Escherichia coli M-17, Staphylococcus aureus 906, Enterococcus faecalis 19433 ATCC, Citrobacter freundii 101/57, Proteus vulgaris "Tsvetkov", Klebsiella pneumoniae 13883 ATCC,* and *Bacillus cereus 96*. Also the sensitivity to more than 3,000 strains of experimental microorganisms representating the families Micrococcaceae, Streptococcaceae, Enterobacteriaceae, Moraxellaceae, Pseudomonadaceae, Sphingomonadaceae, and Xanthomonadaceae which are causative agents of nonspecific and some specific human infectious diseases was studied.

The conducted study of the antimicrobial activity of substituted amides and pyrroloquinolines on the basis of 4-, 5-, 6-, 7-aminoindoles and of the spectra of their action against the Gram-positive and Gram-negative microorganisms, causative agents of nonspecific and some specific infectious diseases in man indicates potential prospects of a targeted synthesis of biologically active compounds based on aromatic amines of the indole series. Compounds **5D**, **7D**, **39D**, **HD**, **S3**, **4D** are of interest for further investigation as antimicrobial agents.

References

- Alyamkina EA, Stepanenko IS, Yamashkin SA, Yurovskaya MA (2017) 4-amino-2-phenylindole, amides, antibacterial activity, ethyl 4,4,4-trifluoroacetate, ethylacetoacetate, pyrrolo[2,3-*h*]quinoline. Moscow University Chemistry Bulletin 72(1): 24–28. https://doi.org/10.3103/S0027131417010023
- Bek PK, Braun MB, Rlark DE, Koutes E, Dajk KD, KhU J, Londesbro DD, Mills K, Pallin TD, Rejd GP, Stoddart G (2009) Application of pyrroloquinoline compounds for killing clinically latent microorganisms. Patent of invention RU 2404982 C2 Priority: 08.11.2005 GB 0522715.2
- Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J (2009) Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clinical infectious diseases 48(1): 1–12. https://doi.org/10.1086/595011 [PubMed]
- Brown ED, Wright GD (2016) Antibacterial drug discovery in the resistance era. Nature 529(7586): 336–343. https://doi.org/10.1038/nature17042 [PubMed]
- Determination of sensitivity of microorganisms to antibiotics (Practical policies MUK 4.2. 1890-04) (2004) Clinical Microbiology and Antimicrobial Chemotherapy [Klinicheskaya Mikrobiologiya i Antimikrobnaya Khimioterapiya] 6(4): 306-359. [in Russian]
- Determination of sensitivity of microorganisms to antimicrobial agents (2018) Clinical recommendations. Smolensk, 206 pp. [in Russian]

- Eidelshtein MV, Sukhorukova MV, Skleenova E.Yu., Ivanchik NV, Mikotina AV, Shek EA, Dehnich AV, Azizov IS, Kozlov R .S., Popov DA (2017) Antibiotic resistance of nosocomial strains of *Pseudomonas aeruginosa* in Russian hospitals: results of a multicenter epidemiological study "Marathon" 2013–2014. Clinical Microbiology and Antimicrobial Chemotherapy [Klinicheskaya Mikrobiologiya i Antimikrobnaya Khimioterapiya] 19(1): 37–41. [in Russian]
- Kadimaliev DA, Stepanenko IS, Nadezhina OS, Yamashkin SA (2014) Influence of different substituted pirrolohinolons on physiological and biochemical characteristics of lignolytic fungus lentinus tigrinus. Mycology and Phytopathology [Mikologiya I Fitopatologiya] 48(5): 309–314. [in Rissian]
- Kosinets AN, Frolova AV, Bulavkin VP, Okulich VC (2014) Antibiotic resistance. New possibilities of antibacterial influence. Bulletin of Vitebsk State Medical University [Vestnik Vitebskogo Gosudarstvennogo Meditsinskogo Universiteta] 13(2): 70–77. [in Rissian]
- Kozlov RS, Golub AV, Dehnich AV, Sukhorukova MV, SMART research group (2015) Antibiotic resistance Gram-positive pathogens of complicated intra-abdominal infections in Russia. Clinical Microbiology and Antimicrobial Chemotherapy [Klinicheskaya Mikrobiologiya i Antimikrobnaya Khimioterapiya] 17(3):227–234. [in Russian]
- Kozlova NS, Barantsevich EP, Barantsevich NE (2014) Antibiotic resistance of staphylococci isolated from blood. Scientific Review 3: 184–189. [in Russian]
- Lai CC, Lee K, Xiao Y, Ahmad N, Veeraraghavan B, Thamlikitkul V, Tambyah PA, Nelwan RH, Shibl AM, Wu JJ, Seto WH, Hsueh PR. (2014) High burden of antimicrobial drug resistance in Asia. Journal of Global Antimicrobial Resistance 2(3): 141–147. https://doi.org/10.1016/j.jgar.2014.02.007 [PubMed]
- Ling LL, Schneider T, Peoples AJ, Spoering AL, Engels I, Conlon BP, Mueller A, Schäberle TF, Hughes DE, Epstein S, Jones M, Lazarides L, Steadman VA, Cohen DR, Felix CR, Fetterman KA, Millett WP, Nitti AG, Zullo AM, Chen C, Lewis K (2015) A new antibiotic kills pathogens without detectable resistance. Nature 517(7535): 455-459. https://doi.org/10.1038/nature14098 [PubMed]
- Natan M, Banin E (2017) From Nano to Micro: using nanotechnology to combat microorganisms and their multidrug resistance. FEMS Microbiology Reviews 41(3): 302–322. https://doi.org/10.1093/femsre/fux003 [PubMed]
- Petchiappan A, Chatterji D (2017) Antibiotic Resistance: Current Perspectives. ACS Omega 2(10): 7400–7409. https://doi.org/10.1021/acsomega.7b01368
- Pop-Vicas A, Strom J, Stanley K, D'Agata EM (2008) Multidrug-resistant gram-negative bacteria among patients who require chronic hemodialysis. Clinical Journal of the American Society of Nephrology 3(3): 752–758. https://doi.org/10.2215/CJN.04651107 [PubMed] [PMC]
- Saveliev VS, Herfeld BR, Yakovlev SV (2012) Strategy and tactics of antimicrobial use in medical institutions in Russia: Russian national recommendations. BORGES Company Ltd, Moscow, 96 pp. [in Russian]
- Snitkin ES, Zelazny AM, Thomas P, Stock F, NISC Comparative Sequencing Program, Henderson DK, Palmore TN, Segre JA (2012) Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumonia* with whole-genome sequencing. Science Translational Medicine 4(148): 148ra16. https://doi.org/10.1126/scitranslmed.3004129 [PMC] [PubMed]
- Sukhorukova MV, Eidelshtein MV, Skleenova E.Yu., Ivanchik NV, Mikotina AV, Dehnich AV, Kozlov RS, Popov DA (2017) Antibiotic resistance of nosocomial strains of Enterobacteriaceae in Russian hospitals: results of a multicenter epidemiological study "Marathon" 2013-2014. Clinical Microbiology and Antimicrobial Chemotherapy [Klinicheskaya Mikrobiologiya i Antimikrobnaya Khimioterapiya] 19(1): 49–56. [in Russian]
- Sukhorukova MV, Eidelshtein MV, Skleenova E.Yu., Ivanchik NV, Shek EA, Dehnich AV, Kozlov RS (2017) Antibiotic resistance of nosocomial strains of *Acinetobacter* spp. in the Russian hospitals: the results of a multicenter epidemiological study "Marathon" 2013-2014. Clinical Microbiology and Antimicrobial Chemotherapy [Klinicheskaya Mikrobiologiya i Antimikrobnaya Khimioterapiya] 19(1): 42–48. [in Russian]
- Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, Pulcini C, Kahlmeter G, Kluytmans J, Carmeli Y, Ouellette M, Outterson K, Patel J, Cavaleri M, Cox EM, Houchens CR, Grayson ML, Hansen P, Singh N, Theuretzbacher U, Magrini N; WHO Pathogens Priority List Working Group (2018) Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious Diseases 18(3): 318–327. https://doi.org/10.1016/S1473-3099(17)30753-3 [PubMed]
- The order of the Ministry of Healthcare of the USSR № 535 "On the unification of microbiological (bacteriological) research methods used in clinical diagnostic laboratories of medical and preventive institutions" (1985). [in Russian]
- World Health Organization (2018) The top 10 causes of death. http://www.who.int/mediacentre/factsheets/fs310/en/index1.html
- Yamashkin SA, Zhukova NV, Romanova IS (2008) Synthesis of pyrroloquinolines from substituted 6-aminoindoles and oxalacetic ester. Chemistry of Heterocyclic Compounds 44(7): 793–801. https://doi.org/10.1007/s10593-008-0111-8
- Yamashkin, SA, Oreshkina EA, Romanova IS, Yurovskaya MA (2006) The potential use 6-amino-5-methoxy(methyl)-2,3-dimethyl- and 6-amino-5-methoxy(methyl)-1,2,3-trimethylindoles in synthesis pyrrolo[2,3-f]quinolines. Chemistry of Heterocyclic Compounds 42(1): 86–91. https://doi.org/10.1007/s10593-006-0051-0

Author contributions

- **Irina S. Stepanenko,** PhD in Medicine, Associated Professor of the Department of Immunology, Microbiology and Virology, National Research Ogarev Mordovia State University, Saransk, Russia, e-mail: ymahkina@mail.ru, ORCID ID 0000-0001-5793-438X. The author defined the idea of research, made the final verification of the experimental strains of microorganisms and studied their sensitivity to the test compounds, was also engaged in analysis of the laboratory materials.

- **Semen A. Yamashkin,** Doctor of Chemical Sciences, Full Professor, Department of Chemistry, Technology and Methods of Training, Mordovian State Pedagogical Institute named after M.E. Evseviev, Saransk, Russia, e-mail: yamashk@yandex.ru, ORCID ID 0000-0001-8601-2640. The author was engaged in the synthesis of the test compounds and consulted on the research idea.

- **Yuliya A. Kostina,** PhD in Medicine, Associated Professor of the Department of Immunology, Microbiology and Virology, National Research Ogarev Mordovia State University, Saransk, Russia, e-mail: bazunova.2013@mail.ru, ORCID ID 0000-0002-7825-7856. The author was engaged in the design of the article and analysis of the laboratory materials.

- **Alyona A. Batarsheva,** post-graduate student of the Department of Immunology, Microbiology and Virology, National Research Ogarev Mordovia State University, Saransk, Russia, e-mail: minibat@mail.ru, ORCID ID 0000-0001-7604-0680. The author studied sensitivity of microorganisms to the test compounds.

- **Mikhail A. Mironov**, post-graduate student of the Department of Faculty Surgery with a course of topographic anatomy, National Research Ogarev Mordovia State University, Saransk, Russia, e-mail: doctorm@list.ru. The author studied sensitivity of microorganisms to the test compounds.