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

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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, representing 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- and 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 pyrroloquinolones on the basis of 4-, 5-, 6-, 7-aminoindoles was determined 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; Smitkin 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).


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 amino group (Yamashkin et al. 2006; 2008; Aiyamikina 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 amidines, 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 V omipirin 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 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 Micrococccaceae, Streptococccaeae, 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 microorganisms 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 Sensititre (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-oxyquinoloxaline), 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 inoculati-

As the result of employing the synthetic potentials of the substituted 4-, 5-, 6-, 7-aminoidoles 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-aminoidoles.

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

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

   ![6D](image)

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

   ![5D](image)
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)

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

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

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

4,4,4-trifluoro-\(N\)-(6-methoxy-1,2,3-trimethyl-1\(H\)-indol-5-yl)-3-oxobutanamide (laboratory code 66D)
1. Derivatives of substituted 4-amino-2-phenylindole:

3-oxo-N-(2-phenyl-1H-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-2H-pyrrolo-[2,3-h]quinoline-2-one (compound with laboratory code 5D) showed a wide range of antimicrobial activities and a pronounced antibacterial activity.

2. Derivatives of substituted 6-aminoindoles:

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

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

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

3. Derivatives of substituted 6-aminoindoles:

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

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

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

4. Derivatives of substituted 7-aminoindoles:

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

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

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


4-methyl-8-phenyl-1,7-dihydro-2H-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-1H-indol-5-yl) butanamide (compound with laboratory code 3D), 4,4,4-trifluoro-3-oxo-N-(1,2,3-trimethyl-1H-indol-5-yl)butanamide (compound with laboratory code 2D), 4,4,4-trifluoro-N-(1-methyl-2-phenyl-1H-indol-5-yl)-3-oxobutanamide (compound with laboratory code 64D), 4,4,4-trifluoro-3-oxo-N-(2,3,6-trimethyl-1H-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-1H-indol-5-yl)-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, and for B. cereus – 62.5-750 μg/ml, for E. coli – 250-1000 μg/ml, and for P. aeruginosa – 500-1500 μg/ml.


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.


N-(1,7-dimethyl-2-phenyl-1H-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.

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 S. pyogenes 1238 – 125 μg/ml, and against B. cereus 96 – 250 μg/ml. The MICs for the experimental microorganisms were: for Streptococcus spp. – 62.5-500 μg/ml, for Staphylococcus spp. – 125-1000 μg/ml, and for P. aeruginosa – 500-1500 μg/ml.


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


3. Derivatives of substituted 6-aminooindoles:

4,4,4-trifluoro-3-oxo-N-(1,2,5-trimethyl-1H-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 – 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 *Streptococcus* spp. – 15.6-750 μg/ml, for *Staphylococcus* spp. – 125-1000 μg/ml, and for *B. cereus* – 500-1500 μg/ml.


4. Derivatives of substituted 7-aminooindoles:

6-hydroxy-2,3-dimethyl-6-(trifluoromethyl)-1,6,7,9-tetrahydro-8H-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. mitis, S. agalactiae, S. sanguinis, S. mutans, E. faecalis, E. faecium, E. coli, S. enteritidis, S. typhimurium, S. sonnei,
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. intim, 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 representing the families Micrococcaceae, Streptococcaceae, Enterobacteraeae, 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 substituted amides and pyrroloquinolines on the basis of 4-, 5-, 6-, 7-aminoindoles and of the spectra of their antimicrobial activity 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.

References

Author contributions

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