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Synthesis and study of the antimicrobial activity of nifuroxazide derivatives

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ABSTRACT

The number of infections caused by microorganisms that are resistant to antibiotics and synthetic antibacterial drugs is growing fast worldwide. This is one of the most important and urgent problems in health care. The main efforts of researchers around the world are focused on solving this issue. Nitrofurans represent one of the most effective classes of antibacterial drugs. We have synthesized 4 analogues of nifuroxazide – a well known nitrofuran antibiotic – and confirmed their structures by NMR, IR spectroscopy, and mass-spectrometry. All of the obtained compounds were studied for antimicrobial and antifungal activity.

Activity against *Escherichia coli*, *Staphylococcus aureus*, *Staphylococcus haemolyticus*, and *Pseudomonas aeruginosa* was evaluated by the agar diffusion method. The synthesized compounds suppressed the growth of all the studied bacterial strains except *Escherichia coli*; the diameter of the inhibition zones ranged from 13.5 to 28 mm depending on the concentration of the tested compound and bacterial strain. One of the compounds studied in this project – the pyridine analogue of nifuroxazide – exceeded the activity of the standard (nifuroxazide) against the *Staphylococcus aureus*. The inhibitory activity of the synthesized compounds against the *Candida albicans* and *Cryptococcus neoformans* yeasts was determined using the microdilution method. The results were assessed according to the indicator color change. None of the studied compounds showed activity against these cultures.

The obtained results confirm that substituted nifuroxazides have significant antimicrobial activity and, therefore, can be considered as promising candidates for developing new antibacterial drugs.

INTRODUCTION

The increase in the number of microorganisms resistant to antibiotics all over the world has become a serious problem for public health and veterinary medicine [1]. Patients infected with resistant strains have a higher mortality risk than patients with infections caused by non-resistant strains of the same microorganisms [2]. The modification of known antibiotics and the search for new antimicrobial synthetic drugs are the main directions of the modern pharmaceutical science [2, 3].

Over the course of the search for new synthetic antimicrobial drugs, significant attempts of scientists are focused on the discovery of new active nifuroxazide derivatives. Therefore, Rollas *et al.* [4] provides an overview of a large number of structurally similar to nifuroxazide compounds with various substituents in the *para*- and *ortho*- positions of the benzene ring, most of which exhibit high pharmacological activity comparable to modern fluoroquinolone drugs. Thota *et al.* [5] give examples of *o*-nitrofuran derivatives that are used as antibacterial agents (Fig. 1). The authors conclude that acylhydrazones, which include substituted *o*-nitrofurans, are promising compounds for the development of new antibacterial drugs.

Tavares *et al.* [6] described the synthesis and study of the antibacterial activity of nifuroxazide isosteres against *Staphylococcus aureus (S. aureus)*. According to Masunari *et al.* [7], new compounds of the nifuroxazide series have activity against the multi-resistant *S. aureus*. Some thiophene analogues of nifuroxazide exhibited higher antibacterial activity than nifuroxazide itself. Nifuroxazide and its analogues also showed significant activity against the parasites *Trypanosoma cruzi* [8, 9] and *Leishmania donovani* [10]. According to Rando *et al.* [10], the thiophene analogues of nifuroxazide are significantly more active against the *Leishmania donovani* parasite than the corresponding furan derivatives.

Nitrofurans are active against many gram-positive and gram-negative microorganisms as well as against some species of fungi and protozoa. Depending on the concentration, these substances have a bacteriostatic or bactericidal effect [11]. One of the main advantages of nitrofurans is the slow formation of bacterial resistance to this class of compounds [12].

Despite the fact that several nitrofuran compounds are used as drugs in various countries, the mechanism of action of these compounds has not been studied in detail. It

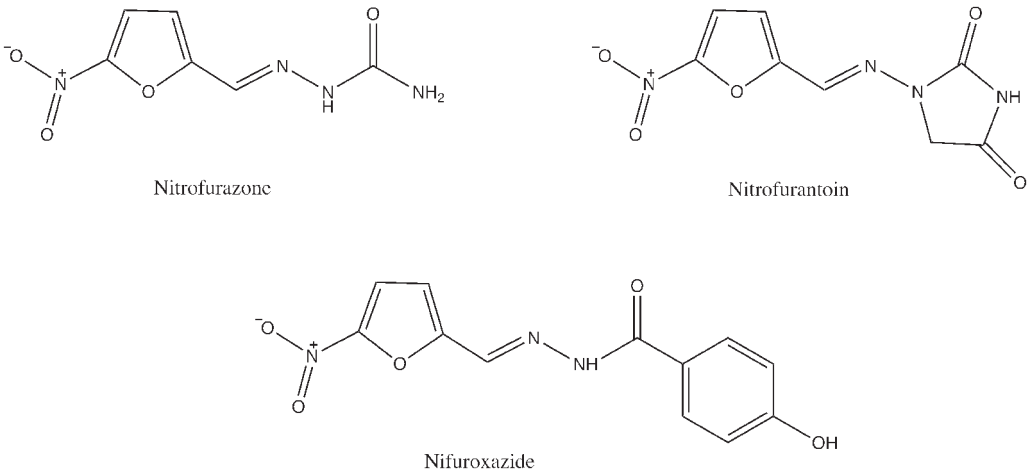

Fig. 1. Antimicrobial drugs – derivatives of *o*-nitrofuran [5].

is believed that the reduction of these substances by the appropriate enzymes in bacteria produces very active intermediates that destroy DNA, RNA, and other macromolecules as well as lead to the disruption of a number of vital processes for bacteria, such as cell wall formation and protein synthesis [13]. A wide range of antimicrobial activity of these compounds is a possible reason for the absence of pronounced bacterial resistance to these drugs.

In addition, the possibility of using substituted nitrofurans as anti-cancer drugs has been widely discussed in recent publications; several publications are devoted to the study of the inhibitory effect of nifuroxazide on the growth of cancer cells and tumors [14-17].

The aim of this study was to search for effective synthetic antimicrobial agents – substituted nitrofurans. Based on literature data analysis, it was decided to synthesize several nifuroxazide isosteres, particularly compounds containing a 4-dimethylaminophenyl fragment, and thiophene analogues of nifuroxazide, and to investigate their antimicrobial activity.

MATERIALS AND METHODS

Synthesis of nifuroxazide analogues

Acylhydrazones were synthesized by the condensation of the corresponding hydrazides with aromatic nitroaldehydes using a modified procedure [10] (Fig. 4). The corresponding aromatic aldehyde was dissolved in ethanol with stirring and heating to 50°C. An equimolar amount of hydrazide was added in portions over 30 min and the reaction mixture was stirred for another 10 min. Reaction progress monitoring was accomplished using thin layer chromatography (TLC). After the reaction completion, the mixture was poured into cold water and the product was crystallized from water.

Confirmation of the structure and purity of the compounds

All the synthesized compounds were analyzed by NMR and IR spectroscopy and mass-spectrometry. The purity of all the synthesized compounds was determined using TLC and LC-MS (liquid chromatography – mass-spectrometry) methods (Schimadzu Analytical HPLC LC10Avp, SPD-10A, autosampler Gilson 215, ELSD Sedex 75 Mass analyzer PE SCIEX API 165, Japan). The NMR spectra (HTLab AG Avance III, Switzerland) and IR spectra (HTLab AG MPA, Switzerland) confirmed the structure of the obtained compounds, while the TLC and LC-MS data proved the high purity of all the reaction products. The spectral data as well as the results of TLC and LC-MS are presented below.

5-Nitro-2-furancarboxaldehyde *p*-dimethylaminobenzoyl hydrazone (furan analogue) is a bright orange powder that is poorly soluble in ethanol and almost insoluble in water. Yield 91%. TLC (ethanol: hexane 1: 5, R_f = 0.6). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.94 (s, 1H), 8.39 (s, 1H), 7.82 (d, J = 8.14 Hz, 2H), 7.79 (d, J = 4.42 Hz, 1H), 7.21 (d, J = 4.42 Hz, 1H), 6.77 (d, J = 8.14 Hz, 2H), 3.00 (s, 6H). IR (KBr) ν (cm^{-1}): 3417 (NH), 1529 (C = O), 1354 (NO_2). LC-MS water/acetonitrile/trifluoroacetic acid: 7.01 min. (m/z): 303.4 (M + 1).

3-Nitrobenzaldehyde *p*-dimethylaminobenzoyl hydrazone (phenyl analogue) is a yellow powder that is soluble in hot ethanol and almost insoluble in water as well as poorly soluble in dioxane. Yield 92%. TLC (ethanol: hexane 1: 5, R_f = 0.4). ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 11.60 (br s, 1H), 8.53 (s, 2H), 8.25 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.75 (m, 1H), 6.75 (d, J = 8.2 Hz, 2H), 3.00 (s, 6H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ (ppm): 163.2, 153.6, 148.3, 143.5, 136.7, 133.2, 130.4, 129.4, 123.9, 120.6, 119.1, 110.9, 39.6. IR (KBr) ν (cm^{-1}): 3039 (CH), 1628 (C = O), 1352 (NO_2). LC-MS: 7.32 min., (m/z): 313.3 (M + 1).

5-Nitro-2-thiophenecarboxaldehyde *p*-dimethylaminobenzoyl hydrazone (thiophene analogue) is a bright red crystalline powder that is soluble in hot ethanol and poorly soluble in water and hexane. Yield 87%. TLC (ethanol: hexane 1: 5, R_f = 0.5). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 11.90 (br s, 1H), 9.62 (s, 1H), 8.11 (d, J = 5.43 Hz, 1H), 7.81 (d, J = 7.84 Hz, 2H), 7.51 (d, J = 5.43 Hz, 1H), 6.26 (d, J = 7.84 Hz, 2H), 3.00 (s, 6H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ (ppm): 163.3, 152.7, 150.4, 147.5, 139.3, 130.6, 129.5, 128.9, 118.7, 110.8, 39.58. IR (KBr) ν (cm^{-1}):

3052 (CH), 1342 (NO_2), 603/682 (C - S). LC-MS: 7.37 min., (m/z): 319.3 (M + 1).

5-Nitro-2-thiophenecarboxaldehyde isonicotinoyl hydrazone (pyridine analogue) is a green-yellow powder that is soluble in hot ethanol and poorly soluble in water and hexane. Yield 91%. TLC (ethanol: hexane 1: 5, R_f = 0.8). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 12.5 (s, 1H), 8.8 (d, 2H), 8.7 (s, 1H), 8.3 (d, 1H), 7.8 (d, 2H), 7.6 (d, 1H). IR (KBr) ν (cm^{-1}): 3392 (NH), 1652 (C = N), 583/672 (C - S). LC-MS: 5.72 min., (m/z): 277.3 (M + 1).

Bacteria and yeast

The activity of all the synthesized compounds was tested against the bacterial strains representing the most common causative agents of infectious diseases and nosocomial infections [18]. All of the strains used in this study were obtained from the I. I. Mechnikov Research Institute for Vaccines and Sera (MRIVS) Collection – *Escherichia coli* (*E. coli* MRIVS 241), *Staphylococcus aureus* (*S. aureus* MRIVS 906), *Staphylococcus haemolyticus* (*S. haemolyticus* MRIVS 209), *Pseudomonas aeruginosa* (*P. aeruginosa* MRIVS 27853), *Candida albicans* (*C. albicans* MRIVS 927), and *Cryptococcus neoformans* (*Cr. neoformans* MRIVS 3465).

Evaluation of antimicrobial activity

The method of diffusion into agar was used for the evaluation of the antimicrobial activity of synthesized compounds. Antimicrobial activity was determined by comparing the sizes of inhibition zones of bacterial growth according to the method described earlier [19, 20]. Since the tested compounds were only slightly soluble in water and poorly diffused into the agar, the concentration of the test solutions was increased to 2 mg/ml (as opposed to 1 mg/ml according to the method described in State Pharmacopoeia [19]). The test solutions were prepared as follows: 0.1 g of the tested compounds were dissolved in 1.3 ml of 37% HCl, followed by the addition of 50 ml of distilled H_2O and heating. Since all the compounds were basic and were protonated in an acidic medium, the pH of the final solutions was close to the physiological. A commercial drug Enterofuryl (Bosnalijek, Bosnia and Herzegovina) was used as a reference compound. Every capsule of this drug contains 200 mg of nifuroxazide.

In order to determine the sensitivity threshold, the activities of solutions with sequential dilutions to 2, 4, and 8 times were estimated. The dilution of samples was performed with a normal saline solution.

Mueller-Hinton agar (MHA) was used for the assessment of bacteria sensitivity following the procedure described previously [21]. In order to prepare the inoculum, bacterial colonies were suspended in sterile isotonic solution to a density of 0.5 according to McFarland turbidity standard. The inoculum was applied to the Petri dishes with the MHA and evenly distributed using a Drygalsky microbiological spatula. Wells with a diameter of 10 mm were made using the sterile punch followed by the addition of 100 µl of solutions of the investigated substances to the corresponding wells. Each Petri dish contained 4 wells; the concentration in the first well was 2 mg/ml, while in the last one – 0.25 mg/ml for each of the 5 tested substances. After the addition of samples to the agar containing bacteria, Petri dishes were incubated at 37°C for 48 h. The antimicrobial activity of the corresponding compound was determined by measuring the diameters of the inhibition zones of bacterial growth.

The determination of antifungal activity of the synthesized products against the strains *C. albicans* and *Cr. neoformans* was accomplished by the microdilution method performed in the round-bottom 96-well plate (Medpolymer, Russia) (Fig. 5) [22-24]. Both *C. albicans* and *Cr. neoformans* cultures were grown on a glucose-peptone-yeast medium at 25°C for 19 h. The 96-well plate was divided into 2 parts. The activity of compounds against *C. albicans* was tested in the upper part while the activity against *Cr. neoformans* – in the lower part of the plate. Each part of the 96-well plate consisted of five rows of wells and each row was used to study the activity of one of the five synthesized compounds. The sixth row contained pure DMSO and served as a control. The solutions of tested compounds in dimethyl sulfoxide (DMSO) were added to the first well in a volume of 10 µl followed by twofold serial dilutions in sterile distilled water. DMSO was diluted in the same way. Then, 190 µl of the yeast suspension in a synthetic nutrient medium with a final cell concentration of 10^3 colony forming units (CFU/ml) containing pH indicator bromocresol blue (pH 5.5, indicator color is blue) were added to each well. The final concentration of the compounds in the first well was 1024 µg/ml, and in the last one – 8 µg/ml. The synthetic nutrient medium used in these experiments was prepared according to the method of Yarrow [25]. The mixing was carried out at the moment of addition of the larger volume of yeast suspension to the smaller volume of the tested compound. The incubation was carried out at 32°C. The activity of the studied compounds was estimated visually after 48 h of incubation. The change in the color of the indicator from blue to yellow reveals the pH change of the medium, which indicates the growth of the yeast culture and the absence of activity of the tested compounds.

Statistical data processing

The antimicrobial and antifungal activity tests were performed 3 times for each studied compound and the average activity values were calculated. All of the data were subjected to statistical analysis. The results were processed using standard Microsoft Excel software for Windows. Data were presented as mean (M) ± standard deviation (SD).

RESULTS

Synthesis and analysis of the chemical compounds

We assumed that it is possible to obtain a more effective analogue of an existing drug nifuroxazide by the directed modification of its structure while preserving the pharmacophore.

After analysis of the structures of active nitrofurans, a pharmacologically significant fragment (pharmacophore) – 2-iminomethyl-5-nitrofuran – was selected (Fig. 2).

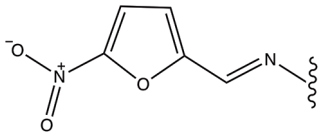

Fig. 2. Structure of pharmacophore (2-iminomethyl-5-nitrofuran).

The basic assumption was that any active analogue of nifuroxazide should have a nitro group in the fifth position and an iminomethyl group in the second position of the furan ring. This approach gives broad possibilities for the structural design of drug candidates among the aromatic and heterocyclic compounds. The structures of the studied drug candidates are shown in Fig. 3.

The synthesis of the nifuroxazide derivatives is shown in Fig. 4. Reactions were carried out in ethanol at boiling.

The structure of all obtained compounds was confirmed by NMR and IR spectroscopy, and the TLC and LC-MS data showed their high purity. The analytical data are presented in the Materials and Methods section.

Inhibitory activity of compounds against bacteria and yeast

The sizes of zones of bacterial growth inhibition are shown in Table 1. The commercial drug Enterofuryl served as a positive control. The measurement of bacterial growth inhibition zones showed that the control drug Enterofuryl inhibited the growth of *S. aureus*, *S. haemolyticus*, and *P. aeruginos* at a concentration of 2.0 mg/ml and did not suppress the growth of these microorganisms at lower concentrations (1.0 mg/ml and 0.5 mg/ml). In all of the studied concentrations, Enterofuryl did not inhibit the growth of *E. coli*. The lack of Enterofuryl activity against the non-enteropathogenic *E. coli* MRIVS 241 strain used in our study does not exclude the sensitivity of other *E. coli* strains, including pathogenic strains, to this drug. Similar results were obtained for analogues 1, 2, and 3. Unlike Enterofuryl and analogues 1, 2, and 3, the pyridine analogue (analogue 4) inhibited the growth of *S. aureus* not only at a concentration of 2.0 mg/ml but also at concentrations of 1.0 mg/ml and 0.5 mg/ml. The inhibitory activity of analogue 4 against *P. aeruginosa*, *S. haemolyticus*, and *E. coli* did not differ from that of other compounds.

The results of the study of the inhibitory activity of the synthesized compounds against *C. albicans* and *Cr. neoformans* are shown in Fig. 5. The color change of the indicator from blue to yellow in the course of 48 h incubation in the control wells with the DMSO solution as well as in all of the wells with the tested compounds indicated the acidification of the medium by the products of yeast metabolism, i.e. their unimpeded growth. Consequently, none of the studied samples or the control drug Enterofuryl were active against *C. albicans* and *Cr. neoformans* in the studied concentration range.

DISCUSSION

The antimicrobial activity of four synthesized nifuroxazide analogues was studied against the strains of *S. aureus*, *S. haemolyticus*, *P. aeruginosa*, and *E. coli* as well as against the clinically significant yeast species *C. albicans* and *Cr. neoformans*. The experiments conducted in this study showed that all of the tested compounds were

Table 1. The diameter of the growth inhibition zones of the bacterial test-cultures for the studied compounds

Nifuroxazide derivatives, concentration used (mg/ml)	Diameter of the growth inhibition zones of test cultures (mm)			
	S. aureus	*S. haemolyticus*	*P. aeruginosa*	*E. coli.*
1. Phenyl analogue (analogue 1)				
2 mg/ml	15.5±0.5	17.5±0.5	14.0±0.5	0
1 mg/ml	0	0	0	0
0.5 mg/ml	0	0	0	0
2. Thiophene analogue (analogue 2)				
2 mg/ml	15.3±0.6	20.0±0	18.3±0.3	0
1 mg/ml	0	0	0	0
0.5 mg/ml	0	0	0	0
3. Furan analogue (analogue 3)				
2 mg/ml	18.5±0.5	22.3±0	16.0±0	0
1 mg/ml	0	0	0	0
0.5 mg/ml	0	0	0	0
4. Pyridine analogue (analogue 4)				
2 mg/ml	25.3±0.6	27.8±0.3	18.0±0	0
1 mg/ml	18.3±0.3	0	0	0
0.5 mg/ml	16±0	0	0	0
5. Enterofuryl				
2 mg/ml	19.7±0.3	21.2±0.3	21.5±0.5	0
1 mg/ml	0	0	0	0
0.5 mg/ml	0	0	0	0

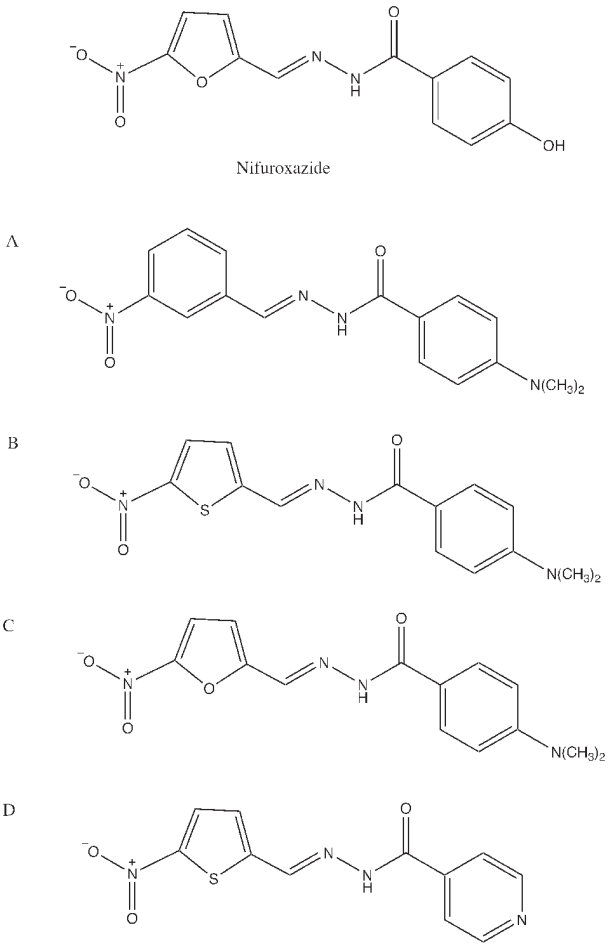

Fig. 3. Chemical structures of the studied compounds. A – phenyl analogue (analogue 1), heterocyclic analogues: B – thiophene analogue (analogue 2), C – furan analogue (analogue 3), D – pyridine analogue (analogue 4).

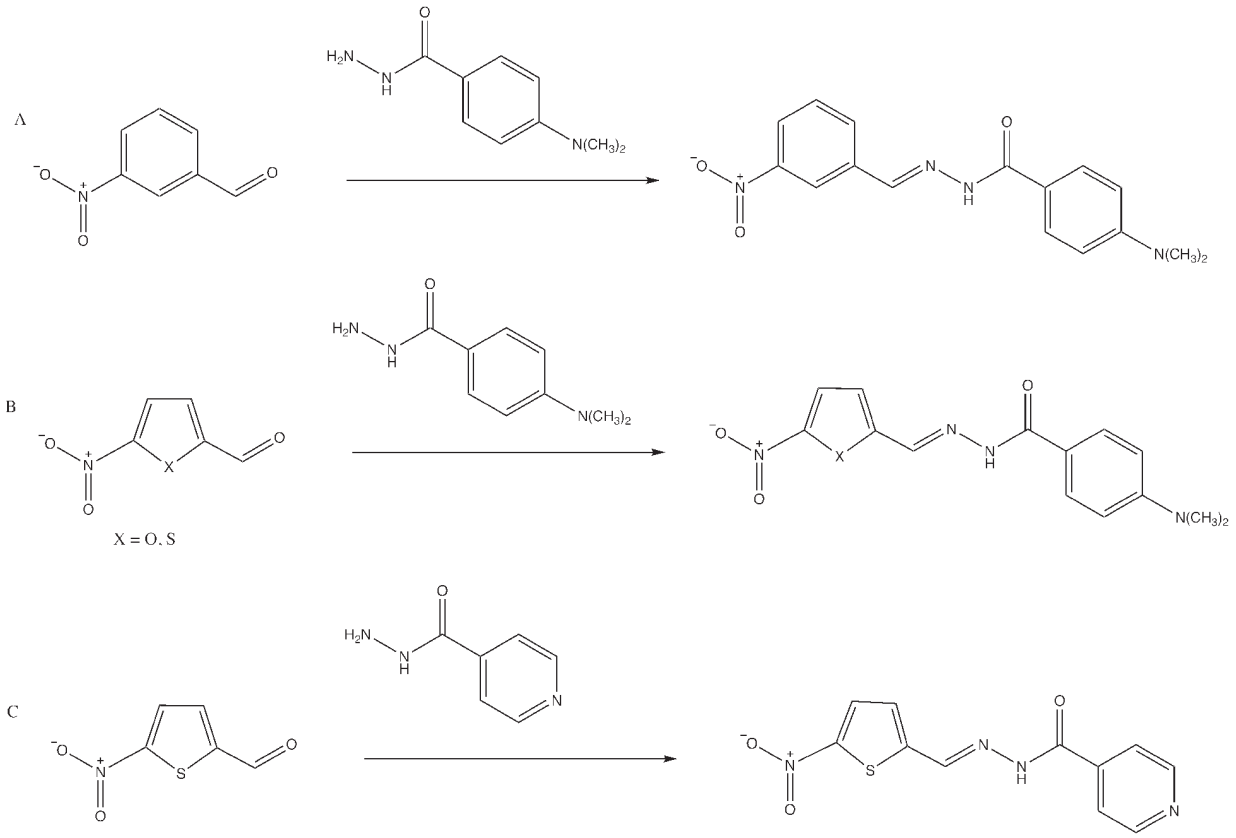

Fig. 4. Schemes for the synthesis of nifuroxazide derivatives. A – synthesis of the phenyl analogue (analogue 1), B – synthesis of the thiophene and furan analogues (analogues 2 and 3), C – synthesis of the pyridine analogue (analogue 4).

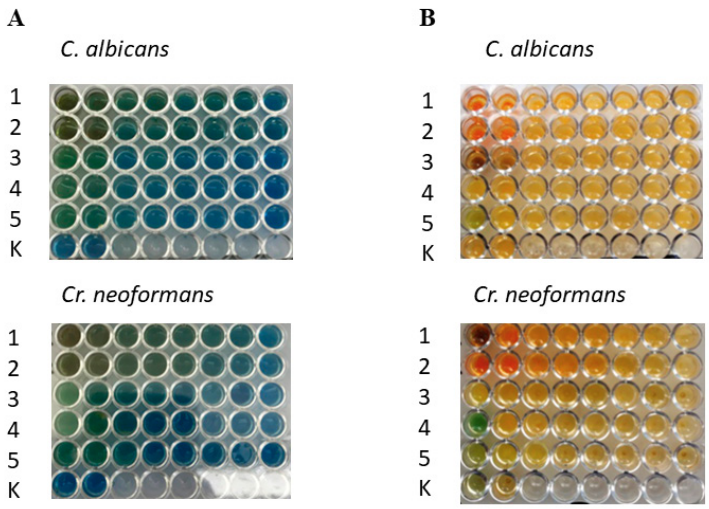

Fig. 5. The growth of the yeast *C. albicans* MRIVS 927 and *Cr. neoformans* MRIVS 3465 in the presence of the studied compounds: A – 0 h of incubation, B – 48 h of incubation. In the first well of every row on the 96-well plate the concentration of compounds is equal to 1024 μg/ml and then the concentration decreases with a step of 2 to 8 μg/ml in the last well. The numbers denote the compounds: 1 – thiophene analogue (analogue 2), 2 – furan analogue (analogue 3), 3 – pyridine analogue (analogue 4), 4 – phenyl analogue (analogue 1), 5 – Enterofuryl. K – negative control (wells 1 and 2) containing pure DMSO.

active against *S. aureus*, *S. haemolyticus*, and *P. aeruginosa* strains at a concentration of 2 mg/ml while only the pyridine analogue (analogue 4) inhibited the growth of the *S. aureus* strain at lower concentrations of 1 mg/ml and 0.5 mg/ml. None of the studied compounds had an inhibitory effect on the *E. coli* strain. In addition, none of the tested compounds were active against the yeast *C. albicans* and *Cr. neoformans* in the studied concentration range.

Analysis of the antibacterial activity data of the studied compounds allows us to conclude that the replacement of the five-membered heteroaromatic ring with a six-membered phenyl ring led to a significant decrease in antimicrobial activity, while all of the furan and thiophene analogues inhibited the growth of microorganisms at a rate close to the standard (nifuroxazide). This result probably indicates the fundamental importance of the presence of the five-membered electron rich aromatic fragment in the structure of these compounds. The transition from the furan ring to the thiophene in the presence of a bulky substituent (dimethylamino group) had little effect on antimicrobial activity, while the furan and thiophene analogues showed a small difference in inhibitory activity against the growth of microorganisms compared to the standard (nifuroxazide). The most promising compound appeared to be compound 4 – the pyridine analogue of nifuroxazide. The combination of a thiophene ring and pyridine fragment with the absence of a large substituent in the side chain in this compound led to the highest antimicrobial activity compared to all of the tested compounds. This substance showed a higher inhibition rate against *S. aureus* strain than the standard (nifuroxazide).

Over the course of the study of antibacterial activity of a number of heterocyclic molecules that belong to the same class of compounds, it is usually possible to find a correlation between the molecular structure and the distribution of the electron density in the molecule and its antimicrobial activity. In the case of nifuroxazide derivatives, the analysis of literature data and our results did not allow us to draw concrete conclusions in this regard.

According to the modern concept about the mechanism of action of nifuroxazide and its analogues, the active form of the drug is produced by the reduction of the drug molecule by the corresponding enzymes in bacteria [13]. Therefore, it is logical to assume that the activity of nifuroxazide analogues depends upon their redox potential and, accordingly, upon the presence of electron-donor or electron-acceptor substituents in the molecule. Indeed, according to Masunari and Tavares [7], the introduction of electron-acceptor substituents in the *para*-position of the phenyl ring of the thiophene analogues of nifuroxazide leads to the increased activity of these drugs against *S. aureus*, while the introduction of electron-donor substituents, respectively, decreases the activity of these analogues. However, this contradicts the data of Rando *et al.* [26], who studied the effect of these compounds on *Mycobacterium tuberculosis* and showed that analogues with donor substituents are significantly more active than the corresponding halogen-containing analogue against this bacterial strain. This assumption is also not supported by the results obtained by Popiolek and Biernasiuk [27] and Zorzi *et al.* [28], who studied the activity of furan analogues of nifuroxazide. According to their data, the biological activity of these compounds against *S. aureus* does not depend on the introduction of electron-donor or electron-acceptor substituents in the *para*-position of phenyl ring. The lack of this correlation was also confirmed by the results of Paula *et al.* [29], who determined the

redox potentials of furan and thiophene analogues of nifuroxazide. The authors concluded that the introduction of various substituents into the molecule has very little effect on its redox potential, and that the redox potentials of the substituted furan and thiophene nifuroxazide analogues have a very small difference. These findings may explain the opposite results obtained in the studies of Tavares *et al.* [30] and Alsaeedi *et al.* [31] who compared the activity of the substituted furan and thiophene analogues against the different strains of bacteria.

The activity tests of all the synthesized compounds against the clinically significant strains of yeast *C. albicans* MRIVS 927 and *Cr. neoformans* MRIVS 3465 showed that all of the four synthesized nifuroxazide analogues and the standard – Enterofuryl – did not inhibit the growth of these yeast strains in the studied range of concentrations. This result corresponds to the literature data. Therefore, Popiolek and Biernasiuk [27] showed that the replacement of the hydroxy group in the nifuroxazide molecule with substituents, such as halogen, methoxy group, amino group, or dimethylamino group, did not lead to the emergence of activity against *C. albicans* ATTC 10231. The only aromatic analogue of nifuroxazide the authors described with a very weak activity against this yeast contained a fragment of nicotinic acid hydrazide. Only half of the twenty-two aromatic analogues of nifuroxazide, studied by Zorzi *et al.* [28], showed very weak activity against *C. albicans* ATCC 537Y.

Since it is impossible to find a correlation between the structure of the molecule and its antimicrobial activity based on our current knowledge, the search for new active drug candidates among nifuroxazide analogues is no trivial task. The discovery of a new active compound as a result of our study – the pyridine analogue of nifuroxazide – is of considerable interest for the development of new heterocyclic antimicrobial drug candidates in the series of furan and thiophene derivatives.

CONFLICT OF INTEREST

The authors do not pursue commercial or financial interests.

CITATION

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