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Przeciwdrobnoustrojowe właściwości 5-funkcjonalizowanych pochodnych imidazolu

Antimicrobial properties of 5-functionalized imidazole derivatives

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Przeprowadzono porównanie przeciwdrobnoustrojowej aktywności 6 różnych grup imidazoli posiadających różne grupy funkcyjne w pozycji C-5. Aktywność przeciwdrobnoustrojową badano wobec wybranych bakterii Gram-dodatnich i Gram-ujemnych oraz grzybów drożdżopodobnych. Badania umożliwiły wybranie grup imidazoli o najwyższej aktywności wobec badanych drobnoustrojów i przedstawienie zaleceń dotyczących syntezy nowych przeciwdrobnoustrojowych związków chemicznych.

Słowa kluczowe: 5-funkcjonalizowane pochodne imidazolu, właściwości przeciwdrobnoustrojowe, aktywność przeciwgrzybicza

ABSTRACT

Introduction: Resistance of microorganisms to antibiotics is a threat for human health all over the world and is a global issue. New antibiotics are essential for the fight against medical resistance of pathogenic microorganisms. In spite of the fact that certain promising antibacterial agents are now on the development stage, there is an sharp need of new antibiotic compounds, especially effective against multiple medical resistance of microorganisms. Imidazole derivatives are extremely promising group of chemical compounds to find new antibiotics. They can be considered as one of the major classes of biologically active compounds with a wide spectrum of action.

Methods: 75 new synthesized compounds were selected to compare their antimicrobial properties. These compounds belong to six different groups 5-carbofunctionalized imidazoles. Antimicrobial properties of imidazole derivatives were studied *in vitro* by means of two-fold serial dilution method in liquid nutrient medium. Minimal inhibitory concentration and minimal bactericidal or yeasticidal concentrations of chemical compounds were detected concerning reference-strains of Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923), Gram-negative bacteria (*Escherichia coli* ATCC 25922), and simply yeast (*Candida albicans* ATCC 885-653).

Results: 5-carbofunctionalized imidazoles manifest their antimicrobial activity concerning Gram-positive bacteria (*S. aureus* ATCC 25923), Gram-negative bacteria (*E. coli* ATCC 25922), and simply yeast (*C. albicans* ATCC 885-653) which enable to consider them as chemical compounds with a wide spectrum of antimicrobial action. At the same time their anticandidiasis activity is higher than that of antibacterial action. For example, average values of minimal inhibitory concentrations of all the six groups of the compounds examined concerning the reference-strain *C. albicans* ATCC 885-653 were 90,92±32,04 μg/mL, while their average values of minimal inhibitory concentrations were 139,20±29,71 μg/mL concerning *E. coli* ATCC 25922 and 143,45±27,60 μg/mL concerning *S. aureus* ATCC 25923. Similar regularities were found for yeasticidal and bactericidal concentrations of the examined 5-carbofunctionalized imidazoles – their average values were 167,14±46,33, 279,73±42,57 and 284,66±41,26 μg/mL respectively. Antimicrobial activity of 5-carbofunctionalized imidazoles depends on their chemical structure.
Conclusions: Comparison of antimicrobial activity of different six groups of 5-carbofunctionalized imidazoles enabled to select their most promising representatives and substantiate recommendations concerning the following synthesis of new antimicrobial chemical compounds.

Key words: 5-carbonfunctional imidazole, antimicrobial properties, antibacterial activity, anticandidiasis activity.

INTRODUCTION

Resistance of microorganisms to antibiotics is a threat for human health all over the world (2,30) and is a global issue (1,3,21). Multiple medical resistance occurred in the majority of organisms reaching alarming scales in recent years (4,13,16,28,29). It is a great clinical problem during treatment of infectious diseases (10,20,27). This tendency presents a serious danger for the lives of patients (5).

New antibiotics are essential for the struggle against medical resistance of pathogenic microorganisms (11,15,24). Imidazole derivatives are extremely promising group of chemical compounds to find new antibiotics. They can be considered as one of the major classes of biologically active compounds with a wide spectrum of action. Numerous imidazole compounds with a high therapeutic efficacy are widely used in clinical work in the treatment of different groups of diseases as anti-tumor, antifungal, antibacterial, anti-tuberculous, anti-inflammatory, anti-neuropathic, antihypertensive, antihistamine, anti-parasitic, antiviral agents. Although the search for more active and less toxic medical preparations on the base of imidazole seems to be essential (32).

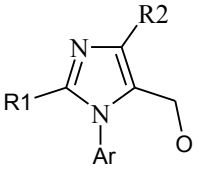
In spite of the fact that certain promising antibacterial agents are now on the development stage, there is an acute need of new antibiotic compounds, especially effective against multiple medical resistance of microorganisms (26).

Objective: to compare antimicrobial activity *in vitro* of various groups of 5-carbofunctionalized imidazoles to establish recommendations for concerning the following synthesis of new antimicrobial chemical compounds.

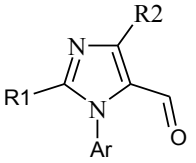
MATERIAL AND METHODS

Seventy five new synthesized compounds were selected to compare their antimicrobial properties belonging to six different groups of 5-carbofunctionalized imidazoles: 13 derivatives of 2,4-disubstituted 1-aryl-imidazole-5-methylcarbonyls (group 1), 8 derivatives of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 2), 8 derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones (group 3), 9 derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-ones (group 4), 12 derivatives of 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid (group 5) and 25 thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and their certain derivatives (group 6).

General formulas of the six different groups of 5-carbofunctionalized imidazoles are the following:



group 1



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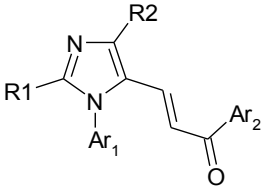
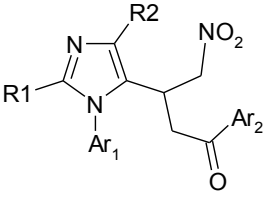
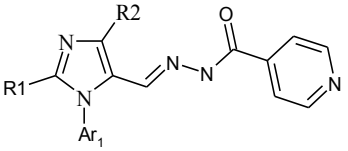


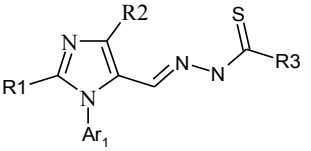
group 3



group 4



group 5



group 6

The substances examined are original substances first synthesized at the Department of Medical and Pharmaceutical Chemistry, the Higher State Educational Establishment of Ukraine "Bukovina State Medical University" (Chernivtsi, Ukraine) by PhD, associate professor Chornous V.O. (6-8,17). The substances are solid, crystal compounds of white or yellowish-red colour, odorless, insoluble in water, moderately soluble in 96% ethyl alcohol, well soluble – in dimethylsulphoxide (DMSO) and dimethylformamide (DMF). The structure of the synthesized compounds was proved by NMR methods, and their content – by quantitative element analysis.

The names of these compounds are presented in Tables 1-6. To prepare solutions of synthesized 5-carbofunctionalized imidazoles 0,1 ml of DMSO and sterile distilled water were used, bringing a matrix solution to 1000 μg/mL.

Table 1. Antimicrobial activity of 2,4-disubstituted (1-aryl-1*H*-imidazole-5-yl) methanoles (μg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1868	(4-chloro-1-phenyl-1*H*-imidazol-5-yl) methanol	125	250	125	250	31,25	62,5
1503	[4-chloro-1-(2-methylphenyl)-1*H*-imidazol-5-yl]methanol	250	500	250	500	15,62	31,25
1501	[4-chloro-1-(4-methylphenyl)-1*H*-imidazol-5-yl]methanol	250	500	250	500	62,5	250
1506	[4-chloro-1-(3-methylphenyl)-1*H*-imidazol-5-yl]methanol	125	250	250	500	31,25	31,25
1869	[4-chloro-1-(4-chlorophenyl)-1*H*-imidazol-5-yl]methanol	125	250	500	>1000	31,25	250
2787	[1-(2-bromophenyl)-4-chloro-1*H*-imidazol-5-yl]methanol	125	250	250	500	15,62	31,25
2788	[1-(2-bromo-4-methylphenyl)-4-chloro-1*H*-imidazol-5-yl]methanol	125	250	250	500	15,62	31,25
1815	(2,4-dichlor o-1-phenyl-1*H*-imidazol-5-yl)methanol	125	250	250	500	31,25	62,5
1812	[2,4-dichloro-1-(4-methylphenyl)-1*H*-imidazol-5-yl]methanol	250	500	125	250	62,5	125
2274	{[5-(hydroxymethyl)-1-(3-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	250	500	125	250	31,25	31,25
2273	{[5-(hydroxymethyl)-1-(4-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	250	500	250	500	15,62	31,25

Notes:
MIC - minimal inhibitory concentration
MBC - minimum bactericidal concentration
MYC - minimum yeasticidal concentration

Examination of antimicrobial properties of different groups of 5-carbofunctionalized imidazoles was made *in vitro* by means of two-fold serial dilution method in liquid nutrient medium (18). Minimal inhibitory concentration (MIC) and minimal bactericidal or yeasticidal concentrations (MBC, MYC) of chemical compounds were detected concerning reference-strains of Gram-positive bacteria (*Staphylococcus aureus* ATCC 25923), Gram-negative bacteria (*Escherichia coli* ATCC 25922), and simply yeast

(*Candida albicans* ATCC 885-653). Optic density while preparing microbial suspension of an examined microorganism (10^5 CFU/ml for bacteria and 10^4 CFU/ml for yeast) was controlled by means of the densitometer DEN-1 Biosan. The temperature of incubation of microorganisms was 37°C, time - 24 hours (for yeast – 28°C, and 48 hours respectively).

Table 2. Antimicrobial activity of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (μg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1880	4-chloro-1-(2-chlorophenyl)-1*H*-imidazole-5-carbaldehyde	250	500	250	500	125	250
2898	2-(benzylthio)-4-chloro-1-phenyl-1*H*-imidazole-5-carbaldehyde	250	500	250	500	125	500
2853	4-chloro-5-formyl-1-(4-methylphenyl)-1*H*-imidazole-2-sulfonic acid	250	500	250	500	250	500
2895	4-chloro-5-formyl-1-phenyl-1*H*-imidazole-2-sulfonamide	125	250	250	500	125	250
1423	{[1-(4-fluorophenyl)-5-formyl-1*H*-imidazol-4-yl]thio}acetic acid	250	500	125	250	250	500
2471	{[5-formyl-1-(4-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	250	500	125	250	125	250
2843	4-[(4-chlorophenyl)thio]-1-(4-methylphenyl)-1*H*-imidazole-5- carbaldehyde	250	500	250	500	250	500
2899	5-formyl-1-(3-methylphenyl)-1*H*-imidazole-4-sulfonic acid	250	500	250	500	250	500

Notes:
MIC - minimal inhibitory concentration
MBC - minimum bactericidal concentration
MYC - minimum yeasticidal concentration

Minimal inhibitory concentration was the least concentration of a substance examined with the presence of which there was no culture growth seen. Bactericidal (yeasticidal) concentration of the examined substances was detected by the results of inoculation on appropriate dense nutrient media.

All the experiments were accompanied by appropriate control: control of the medium for sterility, control of culture growth in the medium without a compound. In order to obtain reliable results the experiments were conducted three times with every concentration of a compound and examined culture of microorganisms.

Antimicrobial action was compared separately for each of the three different reference-strains (*S. aureus* ATCC 25923, *E. coli* ATCC 25922 and *C. albicans* ATCC 885-653). At the same time, minimal inhibitory concentrations and bactericidal (yeasticidal) activity of the examined compounds was analyzed. Mean value (X) and standard error of the mean value (Sx) of inhibitory and bactericidal (yeasticidal) concentrations were calculated for every of 6 groups of 5-carbofunctionalized imidazoles.

RESULTS

The obtained results of studies *in vitro* antibacterial properties of 5-carbofunctionalized imidazoles concerning reference-strains of Gram-positive (*S. aureus* ATCC 25923) and Gram-negative bacteria (*E. coli* ATCC 25922) and their anticandidiasis activity concerning the reference-strain of simply yeast (*C. albicans* ATCC 885-653) (Tables 1-6) enabled to compare antimicrobial action of different groups of 5-carbofunctionalized imidazoles.

Table 3. Antimicrobial activity of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one (μg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
2652	3- (4-chloro-1-fenilimidazol-5-yl) -1- (2,4-dychlorofenyl) prop-2-en-1-one	62,5	125	62,5	250	31,25	31,25
2653	3- (4-chloro-1-fenilimidazol-5-yl) -1- (2,4-dyftorofenyl) prop-2-en-1-one	62,5	125	62,5	125	31,25	62,5
2654	3- (4-chloro-1-fenilimidazol-5-yl) -1- (pyrazine-1-yl) prop-2-en-1-one	62,5	250	31,25	125	31,25	250
2661	3- [4-chloro-1- (3-methylphenyl) imidazole-5-yl] -1- (2,4-dyftorofenyl) prop-2-en-1-one	125	250	62,5	125	15,62	31,25
2663	3- [4-chloro-1-(4-methoxyphenyl) imidazole-5-yl] -1- (2,4-dyftorofenyl) prop-2-en-1-one	31,25	125	31,25	125	15,62	31,25
2810	3- [4-chloro-1- (3-methylphenyl) imidazole-5-yl] -1- (4-chlorophenyl) prop-2-en-1-one	62,5	250	62,5	250	15,62	31,25
2001	{[5- [3- (3-chlorophenyl) -3-oksoprop-1-en-1-yl] -1- (1-naphthyl) -1H-imidazole-4-yl] thio} acetic acid	31,25	62,5	31,25	125	15,62	15,62
2664	3- (4-chloro-1-fenylimidazol-5-yl) -1- (4-ftorofenyl) prop-2-en-1-one	125	250	62,5	250	15,62	31,25

Notes:

MIC - minimal inhibitory concentration

MBC - minimum bactericidal concentration

MYC - minimum yeasticidal concentration

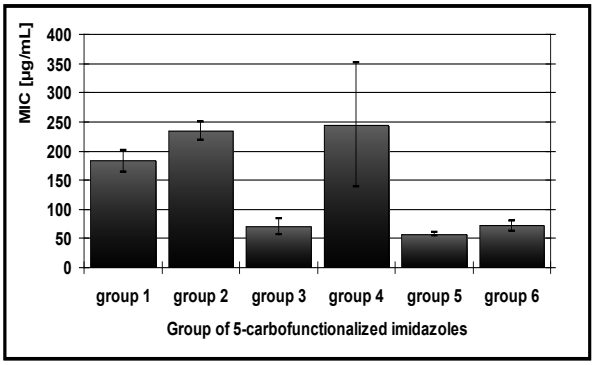


Fig. 1. Average values of minimal inhibitory concentration (MIC) of different groups of 5-carbofunctionalized imidazoles concerning reference-strain of *S. aureus* ATCC 25923 (µg/mL)

Fig. 1 demonstrates that the lowest average values of MIC (57,29±3,51 µg/mL) are specific for 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid (group 5), and the highest ones (244,80±106,50 µg/mL) – derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-ones (group 4). It should be noted that the compounds forming group 4 manifest antibacterial activity concerning *S. aureus* ATCC 25923 within rather wide ranges – from 15,62 to 1000 µg/mL (Table 4). The indicated above stipulates rather great importance of the standard error of MIC for this group as a result of a considerable effect of substitutes on the activity of the examined compounds.

The derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones (group 3) and thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and their certain derivatives (group 6) also manifest greater antibacterial activity concerning *S. aureus* ATCC 25923 (Fig. 1). Their average values of MIC are 70,31±12,87 and 71,25±9,11 µg/mL respectively. Rather less activity was manifested by the derivatives of 2,4-disubstituted 1-aryl-imidazole-5-methylcarbonyls (group 1) and derivatives of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 2), the average values of MIC of which are 182,69±17,99 and 234,37±15,63 µg/mL respectively.

Similar regularities are found in comparison of bactericidal activity of the examined 5-carbofunctionalized imidazoles concerning the reference-strain of *S. aureus* ATCC 25923 (Fig. 2).

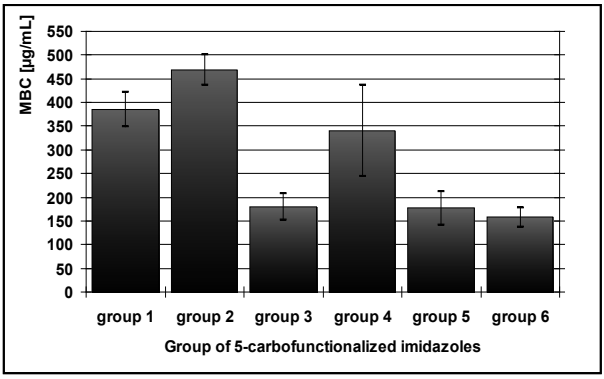


Fig. 2. Average values of minimal bactericidal concentrations (MBC) of different groups of 5-carbofunctionalized imidazoles concerning the reference-strain *S. aureus* ATCC 25923 (µg/mL)

Fig. 2 demonstrates that the highest bactericidal activity is manifested by the representatives of the groups 3, 5 and 6 – average values of their MBC are within the limits from 157,50±20,45 to 179,70±27,54 μg/mL. On the contrary, the representatives of the groups 1, 2 and 4 manifest less bactericidal action – from 340,30±97,22 to 468,75±31,25 μg/mL were their average values of MBC.

The regularities found in comparison of antibacterial action of different groups of 5-carbofunctionalized imidazoles concerning the reference-strain of *S. aureus* ATCC 25923, were characteristic for the reference-strain of *E. coli* ATCC 25922 (Fig. 3 and 4).

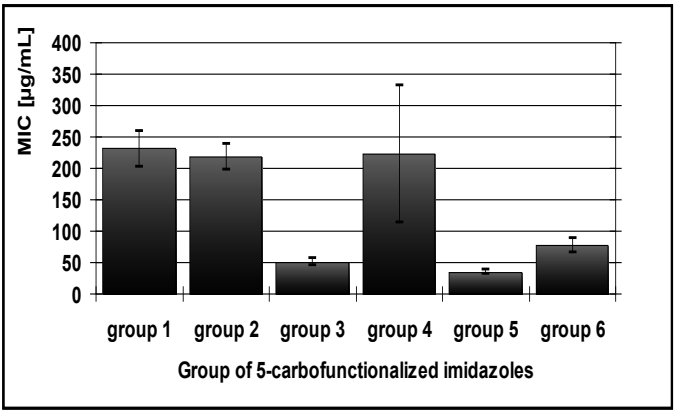


Fig. 3. Average values of minimal inhibitory concentration (MIC) of different groups of 5-carbofunctionalized imidazoles concerning the reference-strain *E.coli* ATCC 25922 (μg/mL)

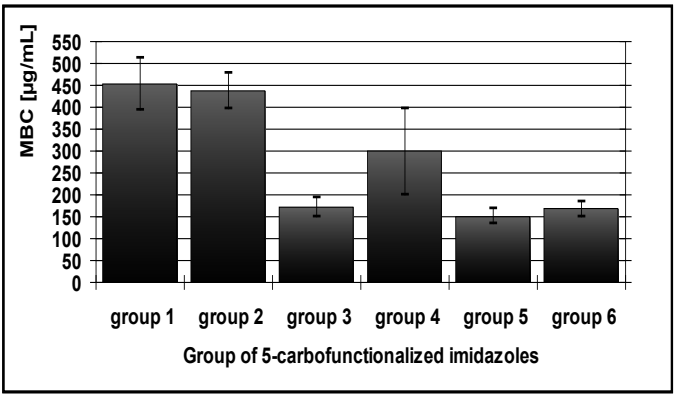


Fig. 4. Average values of minimal bactericidal concentrations (MBC) of different groups of 5-carbofunctionalized imidazoles concerning the reference-strain *E.coli* ATCC 25922 (μg/mL)

As to *E. coli* ATCC 25922 the most active were the derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones (group 3), derivatives of 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid (group 5), and thiosemicarbazones of

2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 6). Average values of their MIC were from 35,16±3,91 (group 5) to 77,50±11,71 (group 6) μg/mL (Fig. 3), and MBC - from 151,00±17,97 (group 5) to 171,90±22,87 (group 3) μg/mL (Fig. 4).

The derivatives of 2,4-disubstituted 1-aryl-imidazole-5-methylcarbonyls (group 1) and derivatives of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 2), 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-ones (group 4) similar to the case with *S. aureus* ATCC 25923, manifested rather less antibacterial activity concerning *E.coli* ATCC 25922. Average values of their MIC were from 218,80±20,46 to 230,77±27,76 μg/mL (Fig. 3), and MBC - from 298,60±97,59 to 451,93±59,27 μg/mL (Fig. 4).

Examination of anticandidiasis action of different groups of 5-carbofunctionalized imidazoles found that the representatives of the 4 and 6 examined groups have MIC concerning the reference-strain *C. albicans* ATCC 885-653 lower than 50 μg/mL (Fig. 5).

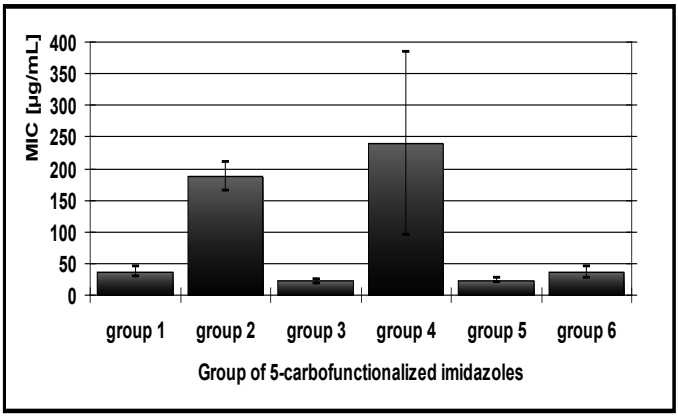


Fig. 5. Average values of minimal inhibitory concentration (MIC) of 5-carbofunctionalized imidazoles concerning the reference-strain *C.albicans* ATCC 885-653 (μg/mL)

The highest anticandidiasis action is manifested by the derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones (group 3), derivatives of 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid (group 5). Average values of their MIC were 21,48±2,86 and 23,43±4,08 μg/mL (Fig. 5). Lower anticandidiasis activity was manifested by the derivatives of 2,4-disubstituted 1-aryl-imidazole-5-methylcarbonyls (group 1) and thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 6). Average values of their MIC were 37,27±8,58 and 36,25±9,41 μg/mL. The derivatives of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes (group 2) and 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-ones (group 4) have average values of MIC 187,50±23,62 and 239,60±143,70 μg/mL (Fig. 5).

Average values of MYC of different groups of 5-carbofunctionalized imidazoles are presented in Fig.6.

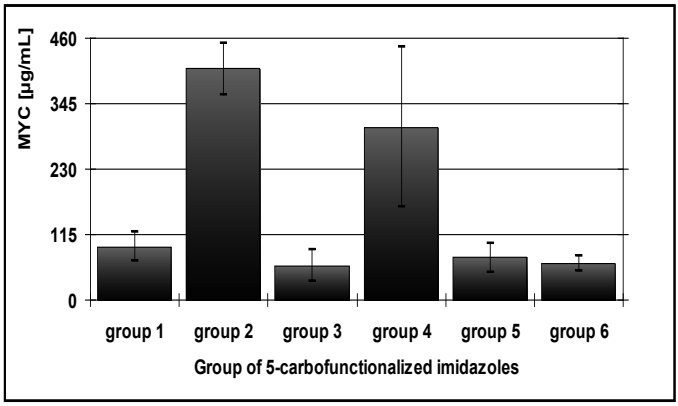


Fig. 6. Average values of minimal yeasticidal concentrations (MYC) of different groups of 5-carbofunctionalized imidazoles concerning the reference-strain *C.albicans* ATCC 885-653 (µg/mL)

Fig. 6 demonstrates that the highest yeasticidal activity is manifested by the representatives of the groups 3, 6, 5 and 1 – average values of their MYC were within the limits from 60,55±27,45 to 93,75±25,76 µg/mL. On the contrary, the representatives of the groups 4 and 2 manifest less yeasticidal action - 303,80±140,90 and 406,20±45,75 µg/mL respectively were their average values of MYC.

Table 4. Antimicrobial activity of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-one (µg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
2665	3- (4-chloro-1-fenilimidazol-5-yl) -1- (4-ftorofenil) -4-nitrobutan-1-one	125	250	62,5	250	15,62	31,25
2666	3- [4-chloro-1- (4-methylphenyl) imidazole-5-yl] -1- (3-chlorophenyl) -4-nitrobutan-1-one	500	500	500	500	1000	1000
2667	3- [4-chloro-1- (4-methylphenyl) imidazole-5-yl] -1- (2,4-dyhlorofenil) -4-nitrobutan-1-one	62,5	125	31,25	125	15,62	31,25
2669	3- [4-chloro-1- (3-methylphenyl) imidazole-5-yl] -1- (2,4-dyftorofenil) -4-nitrobutan-1-one	125	125	31,25	62,5	15,62	15,62

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
2672	3- (4-chloro-1-fenilimidazol-5-yl] -1- (2,4-dyftorofenil) -4-nitrobutan-1-one	250	500	125	250	31,25	62,5
2673	3- (4-chloro-1-fenilimidazol-5-yl] -1- (pyrazine-2-yl) -4-nitrobutan-1-one	62,5	250	62,5	250	31,25	31,25
2671	3- [4-chloro-1- (4-methylphenyl) imidazole-5-yl] -1- (2,4-dyftorofenil) -4-nitrobutan-1-one	15,62	62,5	62,5	125	31,25	62,5
2674	3- (4-chloro-1-fenilimidazol-5-yl] -1- (3-chlorophenyl) -4-nitrobutan-1-one	62,5	250	125	125	15,62	500
2668	3- (4-chloro-1-fenilimidazol-5-yl] -1- (2,4-dyhlorofenil) -4-nitrobutan-1-one	1000	1000	1000	1000	1000	1000

Notes:
MIC - minimal inhibitory concentration
MBC - minimum bactericidal concentration
MYC - minimum yeasticidal concentration

Comparison of antibacterial action of different groups of 5-carbofunctionalized imidazoles has found the following. Average values of minimal inhibitory concentration (MIC) concerning reference-strain of *S. aureus* ATCC 25923 were within wide scales (Fig. 1).

Table 5. Antimicrobial activity of 2,4-disubstituted 1-aryl-imidazole-5-ylidene-hydrazones of isonicotinic acid (μg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1853	({1-(4-fluorophenyl)-5-[(*E*)-(isonicotinoylhydrazono)methyl]-1*H*-imidazol-4-yl}thio)acetic acid	62,5	125	31,25	125	62,5	125
1861	*N*'-{(1*E*)-[4-chloro-2-(2-chlorophenyl)-1-phenyl-1*H*-imidazol-5-yl]methylene} isonicotinohydrazide	62,5	250	31,25	250	31,25	250
1575	*N*'-{(1*E*)-[4-chloro-1-(2-methylphenyl)-1*H*-imidazol-5-yl] methylene}isonicotinohydrazide	31,25	62,5	15,62	62,5	15,62	31,25

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1587	*N*'-{(1*E*)-[2,4-dichloro-1-(4-fluorophenyl)-1*H*-imidazol-5-yl] methylene}isonicotinohydrazide	62,5	125	62,5	250	31,25	31,25
1604	*N*'-{(1*E*)-[4-(benzylthio)-1-phenyl-1*H*-imidazol-5-yl]methylene} isonicotinohydrazide	62,5	500	31,25	125	15,62	31,25
1848	({5-[(*E*)-(isonicotinoylhydrazono) methyl]-1-phenyl-1*H*-imidazol-4-yl} thio)acetic acid	62,5	250	31,25	125	15,62	31,25
1849	{[5-[(*E*)-(isonicotinoylhydrazono) methyl]-1-(1-naphthyl)-1*H*-imidazol-4-yl]thio}acetic acid	62,5	125	31,25	125	15,62	31,25
1850	{[5-[(*E*)-(isonicotinoylhydrazono) methyl]-1-(3-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	62,5	125	31,25	125	15,62	31,25
1851	{[5-[(*E*)-(isonicotinoylhydrazono) methyl]-1-(4-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	62,5	125	31,25	125	15,62	31,25
1854	{[5-[(*E*)-(isonicotinoylhydrazono) methyl]-1-(2-methylphenyl)-1*H*-imidazol-4-yl]thio}acetic acid	62,5	125	62,5	125	15,62	31,25
2618	*N*'-((1*Z*)-{3-[4-(trifluoromethyl) phenyl]-1*H*-pyrazol-4-yl}methylene) isonicotinohydrazide	31,25	62,5	31,25	125	15,62	15,62

Notes:
MIC - minimal inhibitory concentration
MBC - minimum bactericidal concentration
MYC - minimum yeasticidal concentration

Table 6. Antimicrobial activity of thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and some of their derivatives (μg/mL).

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1574	4-chloro-1-(2-methylphenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	31,25	62,5	31,25	62,5
1576	2,4-dichloro-1-(4-fluorophenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	250	31,25	62,5	31,25	62,5

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
1577	2-azido-4-chloro-1-(4-methylphenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	31,25	62,5	31,25	62,5	62,5	125
1578	4-chloro-1-methyl-2-(3-nitrophenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	31,25	62,5	31,25	62,5
1579	4-mercapto-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	31,25	62,5	62,5	250	15,62	15,62
1580	[(5-{(*E*)-[(aminocarbonothioyl) hydrazono]methyl}-1-phenyl-1*H*-imidazol-4-yl)thio]acetic acid	62,5	125	62,5	125	31,25	62,5
1581	4-chloro-2-(2-chlorophenyl)-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	31,25	62,5	31,25	62,5	15,62	15,62
1582	4-chloro-2-methoxy-1-methyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	62,5	31,25	62,5	15,62	31,25
1583	4-chloro-2-(cyclohexylthio)-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	31,25	62,5	62,5	62,5	15,62	31,25
1584	4-(benzylthio)-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	31,25	125	62,5	125	15,62	31,25
1585	2-amino-4-chloro-1-(4-methylphenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	62,5	250	31,25	125
1898	4-chloro-1-(4-fluorophenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	250	250	250	15,62	15,62
1899	4-chloro-1-(4-methylphenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	250	62,5	250	15,62	15,62
1900	2,4-dichloro-1-(4-chlorophenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	62,5	125	31,25	62,5
1901	2,4-dichloro-1-(4-fluorophenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	62,5	125	31,25	31,25
1902	2,4-dichloro-1-(4-methylphenyl)-1*H*-imidazole-5-carbaldehyde thiosemicarbazone	62,5	125	62,5	125	31,25	62,5
2280	{[5-{(*E*)-[(aminocarbonothioyl) hydrazono]methyl}-1-(2-methylphenyl)-1*H*-imidazol-4-yl] thio}acetic acid	62,5	250	62,5	250	15,62	15,62

Cipher compound	The name of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MIC	MBC	MIC	MBC	MIC	MYC
2282	{[5-{(*E*)-[(aminocarbonothioyl) hydrazono]methyl}-1-(1-naphthyl)-1*H*-imidazol-4-yl]thio}acetic acid	62,5	62,5	62,5	250	15,62	15,62
2283	{[5-{(*E*)-[(aminocarbonothioyl) hydrazono]methyl}-1-(4-chlorophenyl)-1*H*-imidazol-4-yl] thio}acetic acid	125	250	125	250	15,62	15,62
2279	{[5-{(*E*)-[(aminocarbonothioyl) hydrazono]methyl}-1-(4-methylphenyl)-1*H*-imidazol-4-yl] thio}acetic acid	62,5	125	125	250	15,62	31,25
1911	[(2*Z*)-2-((2*E*)-{[4-chloro-1-(4-fluorophenyl)-1*H*-imidazol-5-yl] methylene}hydrazono)-4-oxo-1,3-thiazolidin-5-yl]acetic acid	62,5	125	62,5	250	62,5	250
2331	[(1-(1-naphthyl)-5-{(*E*)-[(4-oxo-4,5-dihydro-1,3-thiazol-2-yl)hydrazono] methyl}-1*H*-imidazol-4-yl)thio] acetic acid	62,5	62,5	250	250	250	250
2344	{[5-((*E*)-{(2*Z*)-[5-(carboxymethyl)-4-oxo-1,3-thiazolidin-2-ylidene] hydrazono}methyl)-1-(4-fluorophenyl)-1*H*-imidazol-4-yl] thio}acetic acid	125	250	125	250	31,25	62,5
1865	((2*Z*)-2-{(2*E*)-[(4-chloro-1-phenyl-1*H*-imidazol-5-yl)methylene] hydrazono}-4-oxo-1,3-thiazolidin-5-yl)acetic acid	125	500	62,5	250	15,62	31,25
1913	[(2*Z*)-2-((2*E*)-{[2,4-dichloro-1-(4-fluorophenyl)-1*H*-imidazol-5-yl] methylene}hydrazono)-4-oxo-1,3-thiazolidin-5-yl]acetic acid	250	250	62,5	125	62,5	125

Notes:

MIC - minimal inhibitory concentration

MBC - minimum bactericidal concentration

MYC - minimum yeasticidal concentration

It should be noted that examined 5-carbofunctionalized imidazoles in general manifest anticandidiasis action higher than that of their antibacterial activity (Tables 1-6). For example, average values of MIC of all the six groups of examined compounds concerning the reference-strain *C. albicans* ATCC 885-653 were 90,92±32,04 μg/mL, while their average values of MBC - 139,20±29,71 μg/mL concerning *E. coli* ATCC 25922 and 143,45±27,60 μg/mL concerning *S. aureus* ATCC 25923. Similar regularities were found concerning yeasticidal and bactericidal concentrations of the examined 5-carbofunctionalized imidazoles - their average values were 167,14±46,33, 279,73±42,57 and 284,66±41,26 μg/mL respectively.

Antimicrobial activity of the examined compound was found to depend on their chemical structure. For example, examination of the influence of chemical structure of the derivatives of 2,3-disubstituted 1-aryl-imidazole-5-methylcarbonyls and 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes on their antimicrobial activity found that the level of biological activity is affected by the group of a substitute in the position of 5-imidazole cycle and the substitutes in the positions of 1, 2 and 4 (Tables 1-2). In particular, the compounds of a similar structure having in the position 5 alcohol-hydroxyl, demonstrated twofold activity as compared to the compounds with aldehyde group. Introduction of aryl substitute of fluorine lipophilic atom into the aromatic cycle decreases bactericidal action while introduction of methyl group intensifies it. Changing hydrogen atom in the position 2 into chlorine atom does not practically influence on the value of antimicrobial action of compounds.

DISCUSSION

Ever since the discovery of imidazole as early as the 1840s, the research and development of imidazole-based compounds have been quite a rapidly developing and increasingly active field due to their wide potential applications as medicinal drugs, agrochemicals, artificial materials, artificial acceptors, supramolecular ligands, biomimetic catalysts, etc. Applications of pharmacological imidazole derivatives in medicinal chemistry (as anticancer, antifungal, antibacterial, antituberculous, antiparasitic, antihistaminic, antineuropathic, antihypertensive, antiinflammatory, antiviral, and other medicinal agents) have especially achieved great progress (32). Azole compounds such as imidazoles and triazoles are the first class of synthetic antifungal agents. However, along with a widespread use of current antifungal drugs, the increasing fungal resistance has largely influenced on their therapeutic effects (10,26). Thus, the search of structurally new imidazoles with more effective, less toxic, and less resistance remains to be a highly challenging task and has aroused great interest to medicinal chemistry (14).

In addition to investigation of structural modifications of clinical drugs, development of imidazole antifungal compounds with a new structural skeleton is one more significant direction (32).

Taking into account the mentioned above, 75 new synthesized compounds were selected to compare their antimicrobial properties belonging to six different groups of 5-carbofunctionalized imidazoles. Comparison of antimicrobial activity of different groups of 5-carbofunctionalized imidazoles enabled to select their most promising groups (thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and their certain derivatives, 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid, and 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones) and representatives (*N*'-{(1*E*)-[4-chloro-1-(2-methylphenyl)-1*H*-imidazol-5-yl]methylene}isonicotinohydrazide, *N*'-((1*Z*)-{3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methylene)isonicotinohydrazide, 4-chloro-2-(2-chlorophenyl)-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone, 3-[4-chloro-1-(4-methoxyphenyl) imidazole-5-yl]-1-(2,4-dyftorofenyl) prop-2-en-1-one, and {[5- [3-(3-chlorophenyl)-3-oksoprop-1-en-1-yl]-1-(1-naphthyl)-1*H*-imidazole-4-yl] thio} acetic acid). In the indicated representatives of 5-carbofunctionalized imidazoles a minimal inhibiting concentrations concerning the reference-strain *C. albicans* ATCC

885-653 were 15,62 μg/mL, concerning *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 - 15,62 - 31,25 μg/mL.

The obtained results of antimicrobial activity of 5-carbofunctionalized imidazoles were compared with the values of antimicrobial activity of other imidazole derivatives presented in scientific literature. Comparison of anticandidiasis activity has found the following.

Fluconazole is a well-known first-line antifungal drug recommended by the World Health Organization (WHO). Its exceptional therapeutic record for *Candida* infections has received special attention. However, several disadvantages including increase of fluconazole-resistant *C. albicans* isolates together with a wide clinical use of fluconazole, low water solubility, ineffectiveness against invasive aspergillosis and non-fungicide limit its clinical use. Therefore, much work has been devoted to further structural modification of fluconazole. Fluconazole analogues manifest antifungal activity with MIC values of 32 μg/mL against *C. albicans, C. mycoderma, C. utilis*, and *Beer yeast* (33).

We have determined that 33 out of 75 examined representatives of 5-carbofunctionalized imidazoles possess minimal inhibiting concentration concerning the reference-strain *C. albicans* ATCC 885-653 on the level of 15,62 μg/mL, which is twice as less than MIC of fluconazole analogues.

Chromene-based imidazole manifested anti-*C. albicans* activity with MIC value of 12,5 μg/mL as compared to ketoconazole (MIC = 12,5 μg/mL) (25). The indicated results of anticandidiasis activity of chromene-based imidazoleare close to those obtained for 5-carbofunctionalized imidazoles (15,62 μg/mL).

Experimental MIC values of substituted imidazole derivatives concerning *Candida albicans* (ATCC 10231), *Candida albicans* (ATCC 24433) were found to be on the level of 16 – 32 μg/mL (12). These results are close to our obtained data as well.

Minimal inhibitory concentration of 4-chloro-5-(2-nitrovinyl)-1h-imidazoles and products of their interaction with 3-methyl-2-pyrazolin-5-one concerning *C. albicans* was found to be on the level of 125 – 500 μg/mL (9). The investigations performed by us demonstrated that 5-carbofunctionalized imidazoles manifest 8-16 times higher anticandidiasis activity as compared to 4-chloro-5-(2-nitrovinyl)-1h-imidazoles and products of their interaction with 3-methyl-2-pyrazolin-5-one.

Anticandidiasis activity of 5-carbofunctionalized imidazoles is on the level of anticandidiasis activity of ketoconazole (MIC = 12,5 μg/mL) (25), but it is less than that of clotrimazole (MIC = 5 μg/mL) (19) and fluconazole (MIC = 1 μg/mL) (12).

Comparison of antibacterial activity has found the following. Carbazole-based imidazoles bearing alkyl or aralkyl linker displayed compatible or even superior antibacterial activities with MIC values in the range of 1-8 μg/mL to chloramphenicol and norfloxacin toward *S. aureus*, methicillin-resistant *S. aureus* (MRSA), *Bacillus subtilis*, *Escherichia coli, Pseudomonas aeruginosa*, and *B. proteus* (31). Antibacterial activity of the examined 5-carbofunctionalized imidazoles concerning *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 is 2-16 times lower than that of indicated carbazole-based imidazoles.

Triphenyl imidazole derivatives can effectively inhibit the growth of *E. coli* and *S. aureus* with MIC values in the range of 500-250 μg/mL, which was comparable to tetracycline (MIC = 250 μg/mL) (22,23). The studies performed by us demonstrated that

5-carbofunctionalized imidazoles manifest antibacterial activity 16-32 times as much as compared to triphenyl imidazole derivatives.

Therefore, review of scientific literature showed that investigated 5-carbofunctionalized imidazoles manifest in a number of cases antibacterial activity higher or equal to that of new synthetic derivatives of imidazole and medicines applied in clinical practical work. Although in a part of cases they demonstrate lower activity. From one side, it is indicative of availability of 5-carbofunctionalized imidazoles as antimicrobial means (first of all anticandidal compounds), and on the other hand, it stipulates the need of further search of new representatives of 5-carbofunctionalized imidazoleswith more pronounced antimicrobial activity.

Successful strategies and structure-activity relationships are discussed (32). Therefore, we have studied the effect of chemical structure of 5-carbofunctionalized imidazoles on their antimicrobial activity. At the same time we have determined that antimicrobial activity of 5-carbofunctionalized imidazoles depends on their chemical structure. Comparison of antimicrobial activity of different representatives of 5-carbofunctionalized imidazoles determined by us regularities of «chemical structure - antimicrobial activity» dependence enabled to substantiate recommendations concerning the following synthesis of new antimicrobial chemical compounds.

CONCLUSIONS

1. 5-carbofunctionalized imidazoles manifest their antimicrobial activity concerning Gram-positive bacteria (*S. aureus* ATCC 25923), Gram-negative bacteria (*E. coli* ATCC 25922), and simply yeast (*C. albicans* ATCC 885-653) which enable to consider them as chemical compounds with a wide spectrum of antimicrobial action. At the same time their anticandidiasis activity is higher than that of antibacterial action.

2. Minimal yeasticidal concentration of 5-carbofunctionalized imidazoles in an average was 1,84 times higher and minimal bactericidal concentration was in an average twice as much their minimal inhibitory concentration.

3. Comparison of antimicrobial activity of different groups of 5-carbofunctionalized imidazoles enabled to select their most promising groups (thiosemicarbazones of 2,4-disubstituted 1-aryl-imidazole-5-carbaldehydes and their certain derivatives, 2,4-disubstituted 1-aryl-imidazole-5-ilidenhydrazones of isonicotinic acid, and 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-ones) and representatives (*N*'-{(1*E*)-[4-chloro-1-(2-methylphenyl)-1*H*-imidazol-5-yl]methylene}isonicotinohydrazide, *N*'-((1*Z*)-{3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazol-4-yl}methylene)isonicotinohydrazide, 4-chloro-2-(2-chlorophenyl)-1-phenyl-1*H*-imidazole-5-carbaldehyde thiosemicarbazone, 3-[4-chloro-1-(4-methoxyphenyl) imidazole-5-yl]-1-(2,4-dyftorofenyl) prop-2-en-1-one, and {[5- [3-(3-chlorophenyl)-3-oksoprop-1-en-1-yl]-1-(1-naphthyl)-1*H*-imidazole-4-yl] thio} acetic acid).

4. Antimicrobial activity of 5-carbofunctionalized imidazoles depends on their chemical structure. The regularities of «chemical structure - antimicrobial activity» dependence and comparison of antimicrobial activity of different representatives of 5-carbofunctionalized imidazoles enabled us to substantiate recommendations concerning the following synthesis of new antimicrobial chemical compounds.

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