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ANTIMICROBIAL PROPERTIES OF NEW DERIVATIVES OF IMIDAZOLE

Objective: *to study in vitro antimicrobial activity of new derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one and propane-1-one as the base for further purposeful synthesis of new antimicrobial drugs.* ***Methods.*** *Examination of antimicrobial properties of new chemical synthesis compounds – 8 derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one and 9 derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-one was carried out by means of generally accepted method of two-time serial dilution in a fluid nutritious medium and detection of minimal bacterio(fungi) static and bactri(fungi)cidal concentrations of compounds concerning reference-strains Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922 and Candida albicans ATCC 885-653.* ***Results.*** *Minimal bacteriostatic concentrations of the majority of the studied derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one and propane-1-one concerning reference-strains Staphylococcus aureus ATCC 25923 and Escherichia coli ATCC 25922 were found to be within the limits of 31,25 – 125 mkg/ml. Anticandidal activity of the examined compounds was found to prevail over their antibacterial action. Minimal fungistatic concentrations for the majority of the above mentioned compounds concerning Candida albicans ATCC 885-653 were within the limits from 15,62 to 31,25 mkg/ml, and minimal fungicidal concentrations were from 15,62 to 250 mkg/ml respectively. Introduction of tolyl substitute into the position of 1 imidazole cycle and fluor atoms into the aryl fragment was found to result in increased antimicrobial activity of the examined compounds concerning gram-positive bacteria.* ***Conclusions.*** *The compounds examined manifest moderate anti-microbial activity concerning both gram-positive and gram-negative bacteria, and yeast-like fungi as well. Antimicrobial activity of the examined compounds was found to depend on their chemical structure. The results obtained enable to recommend further purposeful synthesis of new compounds with predicted antimicrobial properties.*

Keywords: derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propene-1-ones and propane-1-ones, antimicrobial properties, antibacterial activity, antifungal action

The problem of antibiotic administration and resistance of new strains of microorganisms to them is one of the most serious threats of the global health care [1,2,3]. Resistance of pathogenic microorganisms to antibiotics increase from year to year, and in the long term a complete loss of their efficacy is possible. It might result in massive deaths of people due to incurable bacterial infections [3]. For example, the WHO estimates that during following 35 years approximately 300 million of people will die suddenly due to antibiotic resistance, and its economic consequences for the world economy will constitute about 100 billion dollars in case no measures are taken [4]. According to the results of the study conducted in Great Britain till 2050

antibiotic resistance may become a global cause of mortality in case new effective antibiotics are not obtained in a sufficient amount.

Scientists from many countries of the world have a good reason to focus their attention on the search of new antimicrobial agents, as only few antibiotics are synthesized every year, while the rates of antibiotic resistance increase very fast [4,5,6,7]. For example, since the beginning of this century no more than 5 new antibiotics have been synthesized, which is rather threatening statistics considering the rates of microorganism resistance to them.

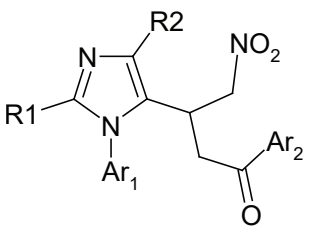
Intensification of the development and introduction of new antimicrobial drugs is one of the ways out of the situation [8]. Therefore the search for new antibiotics and modification of the available ones in order to improve them is one of the main directions of modern medicine [9].

Imidazole derivatives is an extremely promising group of chemical compounds to find new effective antimicrobial means. A great number of them has been used in clinical practice for decades as antifungal, antibacterial and antiviral agents. Although, their wide and long administration has caused an increasing resistance of microorganisms to them which affected the therapeutic effect of these medical preparations [10]. Therefore, the search for structurally new imidazole derivatives with more effective and less toxic properties, less ability to form microbial resistance remains rather complicated but real task due to a unique structural characteristics of the imidazole ring [11].

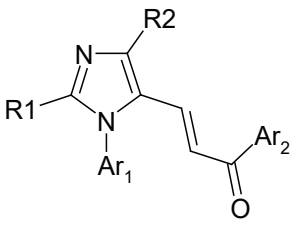
Considering everything mentioned above as well as the fact that a considerable number of functionalized including carbon functionalized imidazole derivatives possess antifungal and antibacterial action, the investigation of antimicrobial properties of their new representatives is topical and practically important.

Objective: to investigate *in vitro* antimicrobial activity of new derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propen-1-ones and 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propane-1-ones as the basis for the following purposeful synthesis of new antimicrobial drugs.

Materials and methods. To investigate antimicrobial properties 17 new compounds of chemical synthesis have been selected: 8 derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propen-1-ones and 9 derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propane-1-ones of the following general formula:



derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propan-1-ones



derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propen-1-ones

Derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl)propen-1-ones and propane-1-ones are original substances first synthesized in the department of Medical and Pharmaceutical Chemistry HSEE of Ukraine Bukovinian State Medical University by the Candidate of Chemical Sciences Chornous V.O. the structure of the compounds is proved by physical-chemical methods of analysis: NMR-1H spectroscopy, chromate-mass spectrometry. They are solid crystalline compounds of a white or yellowish colours, odorless, poorly soluble in water, 96% ethyl alcohol, and well soluble in dimethyl sulfoxide (DMSO), dimethyl formamide (DMFA). The chemical formulas of the chemical synthesis investigated compounds are presented in Table 1 and 2. Their antimicrobial properties were examined by means of the common methods of two-phase serial dilution in a liquid nutrient medium [12] and detection of minimal bacteriostatic or fungistatic (MBsC, MFsC) and minimal bactericidal or fungicidal (MBcC, MFcC) concentrations of the compounds concerning reference-strains of gram-positive bacteria (*Staphylococcus aureus* ATCC 25923), gram-negative bacteria (*Escherichia coli* ATCC 25922) and yeast-like fungi (*Candida albicans* ATCC 885-653). The reference strains of microorganisms were obtained from the museum of living microorganisms of the droplet infection prophylaxis laboratory at the State Institution "I.I.Mechnikov Institute of Microbiology and Immunology, the National Academy of Medical Sciences of Ukraine".

96 socket polystyrene dishes were filled with 0,05 ml of 4-hour culture of microorganisms (1 ml of beef-extract broth contained 10^5 CFU/ml; for fungi 10^4 CFU/ml was used in Sabouraud liquid medium). The optic density in preparing microbial suspension of the examined microorganism was controlled by means of the densitometer DEN-1 Biosan. After that the first socket was filled with 0,05 ml of matrix solution of the experimental substance with the concentration equal 2000 mkg/ml. After mixing 0,05 ml was filled into the following sockets of the first row, thus the dilution from 1000 mkg/ml to 7,8 mkg/ml was obtained. Similar experiment was conducted in the next rows of sockets with the following experimental compounds, and on other dishes – with the next test-cultures of microorganisms. Then the dishes were placed into a moist thermostat camera at the temperature of 37 °C, incubated during 24 hours (for fungi – 28 °C, 48 hours respectively).

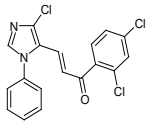
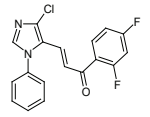
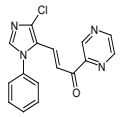
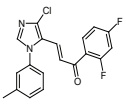
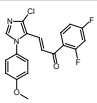
The lowest concentration of the experimental substance at the presence of which the culture growth was not noticed, was considered as bacteriostatic (fungistatic) concentration. Bactericidal (fungicidal) concentration of the experimental substances was determined by the results of inoculation of the content from the sockets with dilution into appropriate dense nutrient media.

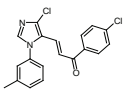
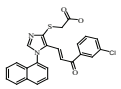
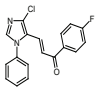
All the experiments were accompanied by appropriate control: sterility control of the medium, the control of culture growth in the medium without a compound. In order to obtain reliable results the experiments were conducted three times with detection of the concentration of every compound and experimental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

Results and discussion. The results of the investigation of antibacterial and antifungal activity of derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one are presented in Table 1.

Table 1

Structure and antimicrobial activity of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one (mkg/ml)

Cipher compound	The chemical formula of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MBsC	MBcC	MBsC	MBcC	MFsC	MFcC
2652	 3- (4-chloro-1-phenylmidazol-5-yl) -1-(2,4-dychlorophenyl) prop-2-en-1-one	62,5	125	62,5	250	31,25	31,25
2653	 3- (4-chloro-1-phenylmidazol-5-yl) -1-(2,4-dyfluorophenyl) prop-2-en-1-one	62,5	125	62,5	125	31,25	62,5
2654	 3- (4-chloro-1-phenylmidazol-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-dyfluorophenyl) 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-dyfluoro) prop-2-en-1-one	31,25	125	31,25	125	15,62	31,25

Cipher compound	The chemical formula of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MBsC	MBcC	MBsC	MBcC	MFsC	MFcC
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-oxoprop-1-en-1-yl] -1-(1-naphthyl) - imidazole-4-yl] thio} acetic acid	31,25	62,5	31,25	125	15,62	15,62
2664	 3- (4-chloro-1-phenylmidazol-5-yl) -1-(4-ftorophenyl) prop-2-en-1-one	125	250	62,5	250	15,62	31,25

Notes: MBsC - minimum bacteriostatic concentration

MBcC - minimum bactericidal concentration

MFsC - minimal fungistatic concentration

MFcC - minimum fungicidal concentration

As it is illustrated in Table 1, minimal bacteriostatic concentrations (MBsC) of the experimental compounds concerning reference-strains of both gram-positive*s (S. aureus* ATCC 25923) and gram-negative bacteria (*E. coli* ATCC 25922) are within the limits of 31,25 – 125 mkg/ml. As to the reference-strain *S.aureus* ATCC 25923 the highest activity was demonstrated by the compounds 2663 and 2001. Both presented compounds and the compound 2654 manifested the highest action concerning the reference strain *E. coli* ATCC 25922.

Minimal bactericidal concentrations of derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propene-1-one two-four times increase their minimal bacteriostatic concentrations and are on the level of 62,5 - 250 mkg/ml.

Investigation of anti-candidiasis activity of the derivatives has detected their higher action as compared to the antibacterial one – minimal fungiostatic concentrations of the compounds concerning *Candida albicans* ATCC 885-653 were from 15,62 to 31,25 mkg/ml, and minimal fungicidal concentrations were from 15,62 to 250 mkg/ml respectively (Table 1).

A wider as compared to derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propene-1-one range of antimicrobial activity was found in derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propane-1-one. The results of investigation of their antibacterial and antifungal activity are

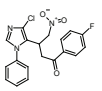
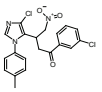
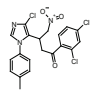
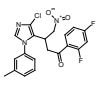
presented in Table 2.

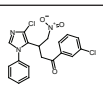
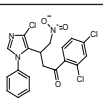
As it is seen from the data presented in Table 2, minimal bacteriostatic concentration of the examined derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propane-1-one concerning gram-positive bacteria (*S. aureus* ATCC 25923) was within rather wide ranges – from 15,62 (compound 2671) to 1000 mkg/ml (compound 2668). The majority of the experimental compounds of this group possessed MBsC concerning the reference-strain on the level of 62,5 - 125 mkg/ml.

Similar regularities were found while investigating antibacterial action concerning *E. coli* ATCC 25922. MBsC was within wide ranges – from 31,25 (compounds 2667 and 2669) to 1000 mkg/ml (compound 2668).

Table 2

Structure and antimicrobial activity of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-one (mkg/ml)

Cipher compound	The chemical formula of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MBsC	MBcC	MBsC	MBcC	MFsC	MFcC
2665	 3- (4-chloro-1-phenylmidazol-5-yl) -1- (4-ftorophenyl) -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-chlorophenyl) -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-dyfluorophenyl) -4-nitrobutan-1-one	125	125	31,25	62,5	15,62	15,62

Cipher compound	The chemical formula of the compound	*S.aureus* ATCC 25923		*E.coli* ATCC 25922		*C.albicans* ATCC 885-653	
		MBsC	MBcC	MBsC	MBcC	MFsC	MFcC
2672	 3- (4-chloro-1-phenylmidazol-5-yl] -1- (2,4-dyfluorophenyl) -4-nitrobutan-1-one	250	500	125	250	31,25	62,5
2673	 3- (4-chloro-1-phenylmidazol-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-dyfluorophenyl) -4-nitrobutan-1-one	15,62	62,5	62,5	125	31,25	62,5
2674	 3- (4-chloro-1-phenylmidazol-5-yl] -1- (3-chlorophenyl) -4-nitrobutan-1-one	62,5	250	125	125	15,62	500
2668	 3- (4-chloro-1-phenylmidazol-5-yl] -1- (2,4-dychlorophenyl) -4-nitrobutan-1-one	1000	1000	1000	1000	1000	1000

Notes: MBsC - minimum bacteriostatic concentration

MBcC - minimum bactericidal concentration

MFsC - minimal fungistatic concentration

MFcC - minimum fungicidal concentration

Minimal bactericidal concentrations of derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-one, as a rule, were two-four times higher than their minimal bacteriostatic concentrations (Table 2).

It should be noted that anti-candidiasis activity of derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propane-1-one as in case of derivatives of 2,4-disubstituted 3-(1-aryl-imidazole-5-il) propene-1-one prevailed over their antibacterial action. Minimal fungistatic concentration

(MFsC) for the majority of the mentioned compounds concerning *C. albicans* ATCC 885-653 was within the range from 15,62 to 31,25 mkg/ml. Only compounds 2666 and 2668 manifested minimal antifungal action – their MFcC was 1000 mkg/ml (Table 2).

While investigating the effect of chemical structure of the synthesized derivatives on their antimicrobial activity we have determined that the range of antimicrobial action is very much affected by the type of a substitute in the position 1 of imidazole cycle and the type of halogen in the aryl substitute (Fig.).

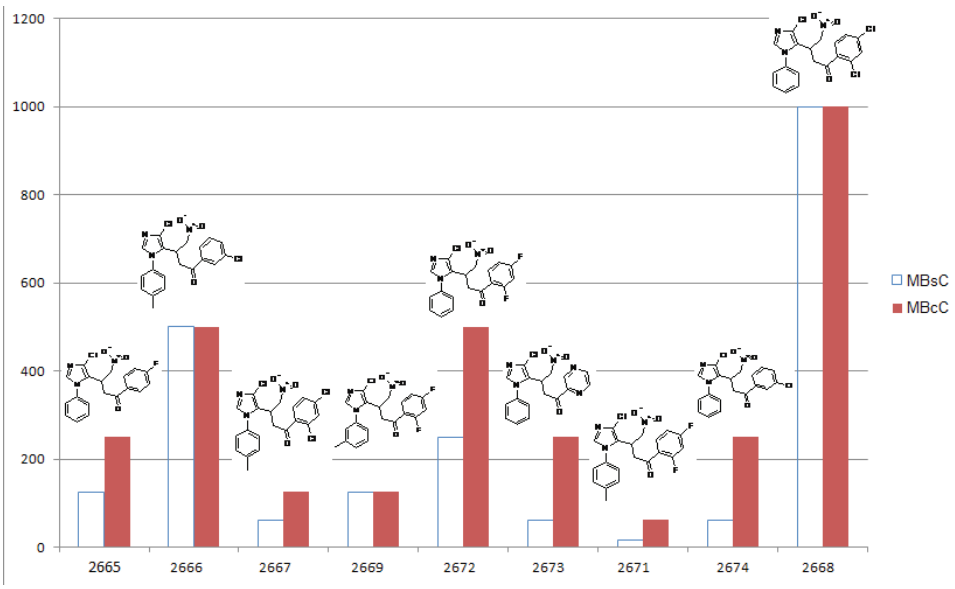


Fig. The dependence of the antimicrobial activity of derivatives 2,4-disubstituted 3- (1-aryl-imidazole-5-yl) propane-1-ones of their structure (reference strain *Staphylococcus aureus* ATCC 25923, mkg/ml).

Thus, the presence of methyl group in benzene cycle of imidazole substitute was reliably found to increase the activity in 25-50 times. The derivatives containing fluor atom in the aromatic radical manifest twice as much bactericidal action as compared to other compounds.

Therefore, the investigation conducted has found that the examined compounds possess a moderate antimicrobial action. Thus, minimal bacteriostatic concentrations of the majority of the examined of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propene-1-one and propane-1-one concerning reference-strains *S. aureus* ATCC 25923 and *E. coli* ATCC 25922 are within the ranges 31,25 – 125 mkg/ml. Anti-candidiasis activity of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propane-1-one similar to of derivatives 2,4-disubstituted 3-(1-aryl-imidazole-5-yl) propene-1-one prevails over their antibacterial action. Minimal fungistatic concentrations for the majority of the examined compounds concerning *C. albicans* ATCC 885-653 are within the range from 15,62 to 31,25 mkg/ml, and minimal fungicidal concentrations are from 15,62 to 250 mkg/ml respectively. Introduction of tolil substitute into the position 1 of imidazole cycle and fluor atoms into aryl fragment result in increased antimicrobial activity of the examined compounds concerning gram-positive bacteria.

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АНТИМІКРОБНІ ВЛАСТИВОСТІ НОВИХ ПОХІДНИХ ІМІДАЗОЛУ

Резюме

Мета. Вивчити *in vitro* антимікробну активність нових похідних 2,4-дизаміщених 3-(1-арил-імідазол-5-іл)пропен-1-онів та пропан-1-онів як основу для наступного цілеспрямованого синтезу нових протимікробних препаратів. **Методи.** Дослідження антимікробних властивостей нових сполук хімічного синтезу − 8 похідних 2,4-дизаміщених 3-(1-арил-імідазол-5-іл)пропен-1-онів та 9 похідних 2,4-дизаміщених 3-(1-арил-імідазол-5-іл)пропан-1-онів − проведено з використанням загальноприйнятої методики дворазових серійних розведень у рідкому живильному середовищі та визначенням мінімальних бактеріо(фунгі)статичних і бактери(фунгі)цидних концентрацій сполук щодо референс-штамів *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 та *Candida albicans* ATCC 885-653. **Результати.** Встановлено, що мінімальні бактеріостатичні концентрації переважної більшості досліджених похідних 2,4-дизаміщених 3-(1-арил-імідазол-5-іл)пропен-1-онів та пропан-1-онів щодо референс-штамів *Staphylococcus aureus* ATCC 25923 та *Escherichia coli* ATCC 25922 знаходяться в межах 31,25 – 125 мкг/мл. Показано, що антикандидозна активність досліджених сполук переважає над їх антибактеріальною дією. Мінімальні фунгістатичні концентрації для переважної більшості вказаних сполук щодо *Candida albicans* ATCC 885-653 знаходилися в межах від 15,62 до 31,25 мкг/мл, а мінімальні фунгіцидні концентрації відповідно від 15,62 до 250 мкг/мл. Встановлено, що введення толільного замісника в положення 1 імідазольного циклу та атомів Флуору в арильний фрагмент приводить до збільшення антимікробної активності досліджуваних сполук по відношенню до грампозитивних бактерій. **Висновки.** Досліджені сполуки проявляють помірну протимікробну активність як до грампозитивних і грамнегативних бактерій, так і до дріжджоподібних грибів. Встановлено, що антимікробна активність досліджених сполук залежить від їх хімічної структури. Отримані результати дозволяють рекомендувати подальший цілеспрямований синтез нових сполук з прогнозованими протимікробними властивостями.

Ключові слова: похідні 2,4-дизаміщених 3-(1-арил-імідазол-5-іл)пропен-1-онів та пропан-1-онів, антимікробні властивості, антибактеріальна активність, протигрибкова дія.

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АНТИМИКРОБНЫЕ СВОЙСТВА НОВЫХ ПРОИЗВОДНЫХ ИМИДАЗОЛА

Резюме

Цель. Изучить *in vitro* антимикробную активность новых производных 2,4-дизамещенных 3- (1-арил-имидазол-5-ил) пропен-1-онов и пропан-1-онов в качестве основы для последующего целенаправленного синтеза новых противомикробных препаратов. **Методы.** Исследование антимикробных свойств новых соединений химического синтеза − 8 производных 2,4-дизамещенных 3-(1-арил-имидазол-5-ил) пропен-1-онов и 9 производных 2,4-дизамещенных 3-(1-арил-имидазол-5-ил) пропан-1-онов − проведено с использованием общепринятой методики двукратных серийных разведений в жидкой питательной среде и определением минимальных бактерио(фунги)статических и бактери(фунги)цидных концентраций соединений по отношению к референс-штаммам *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922 и *Candida albicans* ATCC 885-653. **Результаты.** Установлено, что минимальные бактериостатические концентрации подавляющего большинства исследованных производных 2,4-дизамещенных 3-(1-арил-имидазол-5-ил) пропен-1-онов и пропан-1-онов по отношению к референс-штаммам *Staphylococcus aureus* ATCC 25923 и *Escherichia coli* ATCC 25922 находятся в пределах 31,25 − 125 мкг/мл. Показано, что антикандидозная активность исследованных соединений преобладает над их антибактериальным действием. Минимальные фунгистатические концентрации для подавляющего большинства указанных соединений по отношению к *Candida albicans* ATCC 885-653 находились в пределах от 15,62 до 31,25 мкг/мл, а минимальные фунгицидные концентрации соответственно от 15,62 до 250 мкг/мл. Установлено, что введение толильного заместителя в положение 1 имидазольного цикла и атомов Фтора в арильный фрагмент приводит к увеличению антимикробной активности исследуемых соединений в отношении грамположительных бактерий. **Выводы.** Исследованные соединения проявляют умеренную противомикробную активность как в отношении грамположительных и грамотрицательных бактерий, так и в отношении дрожжеподобных грибов. Установлено, что антимикробная активность исследованных соединений зависит от их химической структуры. Полученные результаты позволяют рекомендовать дальнейший целенаправленный синтез новых соединений с прогнозируемыми противомикробными свойствами.

Ключевые слова: производные 2,4-дизамещенных 3-(1-арил-имидазол-5-ил) пропен-1-онов и пропан-1-онов, антимикробные свойства, антибактериальная активность, противогрибковое действие.

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