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ANTIMICROBIAL ACTIVITY OF SYNTHETIC DERIVATES OF CONDENSED HETEROCYCLIC COMPOUNDS WITH PYRIDINE FRAGMENT

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The morbidity rate of infectious and purulent disease remains at present on the high level and no tendency to decrease is observed [1]. The treatment of such diseases is one of the highest priority trends in health protection.

The ecological and economical problems and the low level of social protection of the major population of Ukraine led to the decrease in the innate resistance and compensatory abilities of immune system in the significant part of the population. The specific gravity of infectious and purulent-inflammatory diseases in the general lethality structure is increasing. Since the second half of XX century and until present time the leading role in the treatment of such diseases belongs to antibiotics [2, 3]. The main negative event that stipulates for the decrease in antibiotics effectiveness is the continually progressive resistance or the microorganisms to the antibiotics [4 - 8]. Infections caused by multiresistant strains are characterized by high disease duration, require frequent hospitalization, increase the duration of lying-in period and the prognosis for patients become poorer. The Global Advisory on Antibiotic Resistance Data (GAARD) has published a report on the world-wide research in antibacterial agents «Shadow Epidemic: The Growing Menace of Drug Resistance». The published data have given an opportunity to obtain a modern picture of drug resistance - unfortunately, not very optimistic for the health protection. From Staphylococcus and Pneumococcus to HIV, the drug resistance increases continually. GAARD recommends supporting the national and international researches of the frequency of resistance to antimicrobial agents and development of the new therapeutical agents with new effector mechanisms for treatment and control of infections resistant to traditional therapy [9 - 12].

The mentioned above led to restoration of search for radically different drugs, that wouldn't have structure similarities with antibiotics and, therefore, would not be the target of the present drug resistance mechanisms [13 - 15].

The spreading of the antibiotics resistance, the lack of drugs that are active against new pathogens and naturally resistant species, unsatisfactory pharmacokinetics and adverse reactions of the already developed drugs induce the search for new antibiotics and chemotherapeutical drugs with antimicrobial activity. Therefore in the present conditions of rapid scientific progress the search for new antimicrobial agents is being held and new approaches and agents of direct synthesis of antibiotic substances are being developed [16, 17].

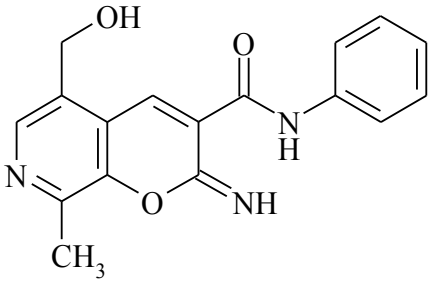
According to the literature data, among 1070 most widespread synthetic drugs 661 (62 %) belong to the heterocyclic compounds [18 - 20]. The heterocyclic compounds are the organic compounds that contain a cycle that besides the carbon atoms contains atoms of other elements (heteroatoms), most often – nitrogen, oxygen and sulfur, rarely – phosphorus, boron, silicon et cetera. The diversity of heterocyclic compounds types is great, as they differ in quantity of atoms in the cycles, nature, quantity and orientation of heteroatoms, presence or absence of substitutes or condensed cycles and the heterocyclic ring features.

In respect of search for highly active compounds with antimicrobial activity one of the perspective candidates is the group of synthetic derivatives of condensed heterocyclic compounds with a pyridine fragment, which remains at present insufficiently explored [21].

Our aim was to perform a microbiological study of the synthetic derivatives of condensed heterocyclic compounds with a pyridine fragment and to determine the samples with the highest antimicrobial activity in order to develop a drug for treatment of infectious and purulent-inflammatory diseases on their basis in future.

Materials and methods

The object of research was synthetic derivatives of condensed heterocyclic compounds with a pyridine fragment that were synthesized in Kharkov National Pharmaceutical University in the chair of organic chemistry:



For the microbiological screening of the new synthetic compounds were used reference strains of the microorganisms test cultures that belonged to the infectious and purulent-inflammatory diseases pathogens according to their morphological and functional characteristics. The set of standard test cultures consisted of Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Proteus vulgaris ATCC 4636, Bacillus anthracoides 1312. The bacterial load of the museums strains was 10^6 and 10^7 CFU (CFU/ml).

The determination of antimicrobial activity of the studied compounds was carried out by performing series of dilutions in the liquid nutrient mediums, allowing the quantitative evaluation of antimicrobial activity [22]. The microorganisms cultures were incubated in the thermostat at the temperature of 37 ºC for 18 – 24 hours. The results were obtained according to the absence of the growth in the last probe that corresponds with the minimum inhibiting concentration (MIBC). For the evaluation of the minimum bactericidal concen-

tration (MBC) from 2-3 probes from the end of the row 0,1 ml of the corresponding cultures was inoculated onto Petri dishes with solid nutrient medium (MPA, blood agar, et cetera). In 18 – 24 hours of incubation at the temperature 37 ºC a minimal concentration, that did not give growth on the agar that corresponded to the MBC was evaluated.

In the course of the study 24-hours cultures of the microorganisms grown on the corresponding nutrient mediums mentioned in the State Pharmacy of Ukraine were used. The research carried out in the five repeated experiments.

Results and discussion

For the microbiological research standard test cultures of both gram-positive and gram-negative bacteria were used, that belonged to the clinically important groups of pathogens of infectious and purulent-inflammatory diseases according to their morphological and physiological features: Staphylococcus aureus ATCC 25923, Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Proteus vulgaris ATCC 4636, Bacillus anthracoides 1312. Individual codes were assigned to the studied compounds according to the radicals they contained.

According to the order № 167 from 05.04.2007 «About the affirmation of methodical instructions «Evaluation of the microorganisms sensitivity to the antibacterial agents» the synthetic antibacterial preparation, the nalidix acid derivative - nevigramon was used as a control (K) of the antimicrobial activity of the studied compounds. The research results are displayed in the table 1.

Table 1. Antibacterial activity of synthetic derivatives of condensed heterocyclic compounds with a pyridine fragment

The compound code	Radical	Antibacterial activity (mkg/ml) towards the strains									
		Staphylococcus aureus ATCC 25923		Escherichia coli ATCC 25922		Pseudomonas aeruginosa ATCC 27853		Proteus vulgaris ATCC 4636		Bacillus anthracoides ATCC 1312	
		MIBC	MBC	MIBC	MBC	MIBC	MBC	MIBC	MBC	MIBC	MBC
1	2	3	4	5	6	7	8	9	10	11	12
1{1}	H	100,0	100,0	25,0	25,0	50,0	100,0	100,0	100,0	50,0	50,0
1{2}	2-F	100,0	100,0	50,0	100,0	50,0	100,0	100,0	100,0	50,0	50,0
1{3}	3-F	100,0	100,0	50,0	50,0	50,0	100,0	100,0	100,0	50,0	100,0
1{4}	2-Cl	100,0	200,0	25,0	50,0	100,0	200,0	100,0	100,0	25,0	100,0
1{5}	3-Cl	100,0	100,0	25,0	50,0	25,0	100,0	100,0	100,0	25,0	50,0
1{6}	4-Cl	100,0	100,0	50,0	50,0	50,0	100,0	50,0	100,0	25,0	50,0
1{7}	4-OMe	50,0	100,0	12,5	50,0	25,0	100,0	100,0	100,0	50,0	100,0
1{8}	3,5-diMe	50,0	100,0	25,0	50,0	50,0	100,0	100,0	200,0	50,0	100,0
1{9}	3,4-diMe	100,0	200,0	25,0	100,0	50,0	100,0	100,0	100,0	50,0	100,0
1{10}	3-CF_3	100,0	200,0	50,0	100,0	50,0	100,0	100,0	100,0	12,5	100,0
1{11}	2-F-4-Me	200,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	100,0	100,0
1{12}	3-Cl-4-Me	200,0	200,0	100,0	100,0	100,0	200,0	100,0	200,0	100,0	200,0
1{13}	3-Cl-4-OMe	200,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0
1{14}	4-COOMe	200,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0
1{15}	2,5-diCl	200,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	25,0	100,0
1{16}	2,4-diOMe	200,0	200,0	200,0	200,0	100,0	200,0	100,0	200,0	50,0	100,0
1{17}	3,5-diOMe	100,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	50,0	200,0
1{18}	2-Cl-4-F	25,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	50,0	100,0
1{19}	2,3-diCl	25,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	50,0	100,0
1{20}	2,4-diF	25,0	200,0	50,0	200,0	100,0	100,0	100,0	200,0	12,5	100,0
1{21}	2-Me	100,0	200,0	100,0	200,0	200,0	200,0	200,0	200,0	100,0	100,0
1{22}	3,4diCl	50,0	200,0	50,0	200,0	100,0	200,0	200,0	200,0	100,0	100,0
1{23}	3,4-diF	50,0	200,0	50,0	200,0	100,0	200,0	100,0	200,0	100,0	100,0
3{1}	H	100,0	200,0	100,0	100,0	100,0	200,0	100,0	200,0	50,0	100,0

1	2	3	4	5	6	7	8	9	10	11	12
3{2}	4-Br	100,0	200,0	100,0	100,0	100,0	200,0	100,0	100,0	100,0	200,0
3{4}	3-F	100,0	200,0	100,0	200,0	100,0	200,0	200,0	200,0	100,0	200,0
3{5}	3,5-diMe	200,0	200,0	25,0	100,0	100,0	200,0	100,0	100,0	100,0	100,0
3{23}	4-Ph	50,0	100,0	50,0	250,0	25,0	100,0	50,0	250,0	50,0	250,0
3{25}	4-OCH_2Ph	100,0	100,0	50,0	100,0	50,0	50,0	50,0	250,0	50,0	250,0
3{26}	3,4,5-tri-OMe	25,0	100,0	50,0	250,0	25,0	25,0	50,0	100,0	50,0	100,0
3{28}	4-$CONH_2$	50,0	100,0	100,0	250,0	50,0	50,0	50,0	100,0	50,0	100,0
3{29}	4-COOEt	50,0	100,0	50,0	250,0	25,0	50,0	50,0	250,0	100,0	250,0
3{30}	4-Ph-Et	50,0	100,0	50,0	250,0	50,0	100,0	50,0	250,0	100,0	100,0
4{1}	2-Cl	50,0	200,0	25,0	100,0	100,0	200,0	100,0	200,0	100,0	100,0
4{2}	4-Cl	50,0	200,0	50,0	200,0	100,0	200,0	50,0	200,0	100,0	100,0
4{3}	4-COOMe	100,0	200,0	100,0	200,0	100,0	200,0	200,0	200,0	25,0	200,0
4{4}	3-Me	100,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0	100,0	200,0
4{6}	3-CF_3	100,0	200,0	100,0	200,0	100,0	200,0	200,0	200,0	100,0	200,0
4{7}	3,5-diMe	100,0	200,0	100,0	100,0	100,0	200,0	100,0	200,0	100,0	200,0
4{9}	3-Cl-4-F	50,0	200,0	100,0	200,0	100,0	200,0	100,0	100,0	100,0	200,0
4{10}	3-Cl-4-OMe	50,0	200,0	100,0	100,0	100,0	200,0	100,0	200,0	50,0	100,0
K	nevigramon	50,0	50,0	6,25	50,0	50,0	50,0	50,0	50,0	6,25	50,0

It was established that against Staphylococcus aureus ATCC 25923 the compounds 1{7}, 1{8}, 1{22}, 1{23}, 3{20}, 3{23}, 3{28}, 3{29}, 4{1}, 4{2}, 4{9}, 4{10} exhibited a moderate bacteriostatic activity that was comparable with the control. In compounds 1{18}, 1{19}, 1{20}, 3{26} bacteriostatic activity was higher than that of the control value and amounted to 25,0 mkg/ml. All other compounds that were studied exhibited insignificant bacteriostatic activity (MIBC = 100,0 mkg/ml and more). Bactericidal activity of all the compounds regarding Staphylococcus aureus ATCC 25923 was not high.

The sufficient bacteriostatic activity against Escherichia coli ATCC 25922 was exhibited by compounds 1{1}, 1{4}, 1{5}, 1{7} - 1{9}, 3{5}, 4{1}, 4{2} (MIBC amounted to 12,5 - 25 mkg/ml), moderate bacteriostatic activity was exhibited by compounds 1{2}, 1{3}, 1{10}, 1{22}, 1{23}, 1{20}, 3{30}, 3{23}, 3{25}, 3{26}, 3{29} (MIBC amounted to 50,0 mkg/ml), but it was lower than the control value (nevigramon 6,25 mkg/ml). The sufficiently high bactericidal activity towards ATCC 25922 was exhibited by compound 1{1} (MBC = 25 mkg/ml). At the same time the moderate bactericidal activity that was equal to the control value towards this pathogen was exhibited by compounds 1{3} - 1{5}, 1{7}, 1{8} (MBC = 50, 0 mkg/ml).

The compounds 1{5}, 1{7}, 3{23}, 3{29} exhibited high bacteriostatic activity, and compound 3{26} – exhibited both a significant bacteriostatic and bactericidal activity (MBC and MIBC amounted to 25,0 mkg/ml) against the standard strain of Pseudomonas aeruginosa ATCC 27853. All described above compounds exhibited higher bacteriostatic activity than that of the control. The moderate bacteriostatic activity towards Pseudomonas aeruginosa ATCC 27853 was exhibited by compounds 1{1} - 1{3}, 1{8} - 1{10}, 3{20}, moderate bactericidal activity was exhibited by compound 3{29}. Compounds 3{25}, 3{28} exhibited moderate both bacteriostatic and bactericidal activity (MBC and MBIC amounted to 50 mkg/ml, that was equal to the control value).

In course of the study it was established that against Proteus vulgaris ATCC 4636 a moderate bacteriostatic activity equal to that of the control was exhibited by compounds 1{6}, 3{23}, 3{25}, 3{26}, 3{28} - 3{30}, 4{2} (MIBC of the studied compounds amounted to 50,0 mkg/ml). All other compounds exhibited moderate antimicrobial activity towards that pathogen. The minimal bactericidal concentration in all compounds was higher than the control value.

Against the standard strain Bacillus anthracoides ATCC 1312 sufficiently high bacteriostatic activity was exhibited by compounds 1{4}, 1{10}, 1{15}, 1{20}, 4{3} (MBC amounted to 25,0 mkg/ml). The moderate bacteriostatic activity (MBC amounted to 50,0 mkg/ml) was exhibited by compounds 1{3}, 1{7} - 1{9}, 1{16}, 1{17}, 1{19}, 3{1}, 3{23}, 3{25}, 3{26}, 3{28}. The compounds 1{5}, 1{6} exhibited significant bacteriostatic and moderate bactericidal activity against Bacillus anthracoides ATCC 1312, and compounds 1{1},

1{2} exhibited moderate both bacteriostatic and bactericidal activity (MBIC amounted to 50,0 mkg/ml).

Conclusion

1. The carried out research of the new compounds in the series of synthetic derivatives of condensed heterocyclic compounds that contain a pyridine fragment has established an antimicrobial activity against Staphylococcus aureus ATCC 25923 for compounds 1{18}, 1{19}, 1{20}, 3{26}, which MBC amounted to 25,0 mkg/ml and against Bacillus anthracoides ATCC 1312 for compounds 1{1} - 1{3}, 1{4} - 1{6}, 1{7} - 1{9}, 1{10}, 1{15}, 1{16} - 1{20}, 3{1}, 3{23} - 3{28}, 4{3}, 4{10}, compounds, that were also active in concentration 25,0 – 50,0 mkg/ml.

2. An antimicrobial activity against gram-negative microorganisms was also established. A high antimicrobial activity against Escherichia coli ATCC 25922, was exhibited by compounds: 1{4}, 1{5}, MBC was in range 2,5 - 25,0 mkg/ml; compounds 1{1} - 1{3}, 1{5} - 1{7}, 1{8} - 1{10}, 3{25}, 3{26}, 3 {28} - 3{30} were active in concentrations 25,0 – 50,0 mkg/ml against Pseudomonas aeruginosa ATCC 27853; compounds 1{6}, 3{25}, 3{26}, 3 {28} - 3{30}, 4{2}, were active in concentrations 25,0 – 50,0 mkg/ml against Proteus vulgaris ATCC 4636.

3. A number of perspective compounds were chosen for future research in order to develop a drug.

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An experimental study of the level and range of antimicrobial activity was carried out among the synthetic derivates of condensed heterocyclic compounds with pyridine fragment. A hign antimicrobial activity of the studied compounds against gram-negative (Escherichia coli AECC 25922) and gram-positive (Staphylococcus aureus ATCC 25923, Bacillus anthracoides ATCC 1312) bacteria was proved. The experimental data have proven the perspectivity of the further research of the range and level of antimicrobial activity of the compounds chosen in the course of primary screening against the reference strains pathogens of infectious and purulent-inflammatory diseases.

Key words: microorganisms, condensed heterocyclic compounds, antimicrobial activity, infectious and purulent inflammatory diseases.

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ПРОТИМІКРОБНА АКТИВНІСТЬ СИНТЕТИЧНИХ ПОХІДНИХ КОНДЕНСОВАНИХ ГЕТЕРОЦИКЛІЧНИХ СПОЛУК З ПІРИДИНОВИМ ФРАГМЕНТОМ

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Проведено експериментальне вивчення ступеню та спектру протимікробної дії серед синтетичних похідних конденсованих гетероциклічних сполук з піридиновим фрагментом. Доведена висока протимікробна активність досліджуваних речовин щодо грамнегативних (Escherichia coli AECC 25922) та грампозитивних (Staphylococcus aureus ATCC 25923, Bacillus anthracoides ATCC 1312) мікроорганізмів. Експериментальні дані довели перспективність подальшого вивчення спектру і рівня протимікробної активності відібраних в процесі первинного скринінгу сполук щодо референтних штамів мікроорганізмів - збудників інфекційних та гнійно-запальних захворювань.

Ключові слова: мікроорганізми, конденсовані гетероциклічні сполуки, протимікробна активність, інфекційні і гнійно-запальні захворювання.

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ПРОТИВОМИКРОБНАЯ АКТИВНОСТЬ СИНТЕТИЧЕСКИХ ПРОИЗВОДНЫХ КОНДЕНСИРОВАННЫХ ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ С ПИРИДИНОВЫМ ФРАГМЕНТОМ

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Проведено экспериментальное изучение степени и спектра противомикробного действия синтетических производных конденсированных гетероциклических соединений с пиридиновым фрагментом. Доказана высокая протимикробная активность исследуемых веществ относительно грамнегативних (Escherichia coli AECC 25922) и грампозитивних (Staphylococcus aureus ATCC 25923, Bacillus anthracoides ATCC 1312) микроорганизмов. Экспериментальные данные доказали перспективность дальнейшего изучения спектра и уровня противомикробной активности отобранных в процессе первичного скрининга соединений относительно музейных штаммов микроорганизмов - возбудителей инфекционных и гнойно-воспалительных заболеваний.

Ключевые слова: микроорганизмы, конденсированные гетероциклические соединения, противомикробная активность, инфекционные и гнойно-воспалительные заболевания.