

Recommended by Doctor of Pharmacy, Professor V. S. Bondar

UDC 311.16:547.233.1/4

M. Yu. Golik, O. S. Kryskiv, A. M. Komissarenko, O. V. Kolisnyk, K. I. Dudka

National University of Pharmacy

The quantitative “structure – antibacterial activity” relationships in a series of N-substituted amino acids

The presence of the antibacterial and antifungal activity in derivatives of amino acids is determined by different mechanisms; therefore, a promising field of research is to obtain new N-substituted amino acids and study their antibacterial action.

Aim. To determine the quantitative “structure – antibacterial action” relationships in a series of N-substituted amino acids.

Materials and methods. The quantitative dependencies of the antibacterial action of the compounds studied on AlogPs values were calculated using the STATISTIKA 8 program.

Results and discussion. The satisfactory values of the levels of correlation of AlogPs parameters calculated with the experimental data of the antibacterial activity of N-substituted amino acids against *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *B. subtilis*, and *Cl. perfringens* are statistically significant. The absence of the relationship between the antibacterial effect against *C. albicans* and the structure of threonine derivatives may indicate a possible role of the latter in the metabolism of these fungi.

Conclusions. The statistically significant correlation values of AlogPs with the values of the antibacterial action of N-substituted amino acids against the microorganisms studied have been determined, and it quantitatively confirms the earlier assumptions of the existence of the “structure – action” relationship in this series of compounds and the degree of its manifestation.

Key words: lipophilicity; correlation; antibacterial action; N-substituted amino acids

М. Ю. Голік, О. С. Криський, А. М. Комісаренко, О. В. Колісник, К. І. Дудка

Кількісні залежності «структура – антибактеріальна дія» у ряду N-заміщених амінокислот

Наявність антибактеріальної та протигрибкової активності похідних амінокислот визначається різноманітними механізмами, тому одержання нових N-заміщених амінокислот та вивчення їх антибактеріальної дії є перспективним напрямком досліджень.

Мета роботи – встановлення кількісних співвідношень «структура – антибактеріальна дія» у ряду N-заміщених амінокислот.

Матеріали та методи. Розрахунки кількісних залежностей антибактеріальної дії досліджуваних сполук від значень AlogPs проведені з використанням програми STATISTICA 8.

Результати та їх обговорення. Задовільні значення рівнів кореляцій розрахованих значень AlogPs з експериментальними даними антибактеріальної активності N-заміщених амінокислот щодо *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *B. subtilis* та *Cl. perfringens* є статистично достовірними. Відсутність зв'язку між антибактеріальною дією відносно *C. albicans* та структурою похідних треоніну може свідчити про можливу роль останніх у метаболізмі цих грибів.

Висновки. Встановлені статистично достовірні значення кореляції показника AlogPs зі значеннями антибактеріальної дії N-заміщених амінокислот щодо досліджуваних мікроорганізмів, що кількісно підтверджує висловлені раніше припущення стосовно наявності зв'язку «структура-дія» у даному ряду сполук та ступінь його прояву.

Ключові слова: ліпофільність; кореляція; антибактеріальна дія; N-заміщені амінокислоти

Н. Ю. Голик, О. С. Крыськив, А. Н. Комиссаренко, Е. В. Колесник, К. И. Дудка

Количественные зависимости «структура – антибактериальное действие» в ряду N-замещенных аминокислот

Наличие антибактериальной и противогрибковой активности производных аминокислот определяется различными механизмами, поэтому получение новых N-замещенных аминокислот и изучение их антибактериального действия является перспективным направлением исследований.

Цель работы – установление количественных соотношений «структура – антибактериальное действие» в ряду N-замещенных аминокислот.

Материалы и методы. Расчеты количественных соотношений антибактериального действия исследуемых соединений от значений AlogPs проведены с использованием программы STATISTICA 8.

Результаты и их обсуждение. Удовлетворительные значения уровней корреляций рассчитанных значений AlogPs с экспериментальными данными антибактериальной активности N-замещенных аминокислот относительно *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *B. Subtilis* и *Cl. perfringens* являются статистически достоверными. Отсутствие связи между антибактериальным действием относительно *C. albicans* и структурой производных треонина может свидетельствовать о возможной роли последних в метаболизме данных грибов.

Выводы. Установлены статистически достоверные значения корреляции показателя AlogPs со значениями антибактериального действия N-замещенных аминокислот относительно исследуемых микроорганизмов, что количественно подтверждает высказанные ранее предположения о наличии связи «структура-действие» в данном ряду соединений и степень ее проявления.

Ключевые слова: липофильность; корреляция; антибактериальное действие; N-замещенные аминокислоты

Since discovery of antibiotics there has been a considerable number of bacteria resistant to their action because of ill-considered use and misuse, therefore, traditional antibiotics are not able to meet the needs of clinical medicine [1]. Hence, there is a need to search for novel antimicrobial agents with new mechanisms of action.

The current studies in their search are conducted, in particular in the direction of modification of natural metabolites, among which amino acids are the leaders [2].

Schiff bases on the basis of 2-hydroxy-1-naphthaldehyde and some amino acids, as well as their complexes with manganese (III) were studied against certain bacteria and fungi; it was shown that the antimicrobial action decreased with the increase of the amino acid residues in size [3]. It was found that that beta-lactam derivatives of 6-aminopenicillin and 7-aminocephalosporanic acids were more active against bacteria, while Schiff bases of the same amino acids were active against fungi [4]. Derivatives of pyrido[1,2-a]pyrimidine containing Schiff bases of some amino acids (glycine, alanine, glutamic acid, histidine, tryptophan or leucine) appeared to be promising antibacterial and antifungal agents [5].

N-substituted derivatives of 3-aminobutyric acid revealed a high antimicrobial and antifungal activity at low concentrations [6]. The authors [7] synthesized some α -phthalimide and acetamide amino acid derivatives and determined their antimicrobial, antifungal and antitumor activity.

Derivatives of D-amino acids with a positive charge at neutral pH were obtained. They can be a good combination with negatively charged fragments of phospholipids affecting membrane structures [8].

The high antimicrobial activity of 39 derivatives of L- and D-forms of amino acids against microorganisms and fungi was found [9]; it was determined that the mechanism of this action was due to reduced availability of oxygen for the cells adsorbed by the compounds studied.

The authors [10] associate the antimicrobial activity of N-(2-amino-4-phenylthiazole)- and N-(2-amino-4-(4'-chlorophenyl)thiazole) derivatives of amino acids with the action of the amino acid residue on the cell wall, in which the thiazole fragment disturbs the metabolic functions of bacteria and fungi. There are similar data describing 2-amino-4-metolazone and N-aminoazoles fragments combined in the molecule of amino acids [11].

N-derivatives of tryptophan and histidine with a fragment of 4-(2-methyl-1H-imidazol-5-yl) benzoic acid were found to have a significant activity against pathogenic fungi and dermatophytes and low toxicity; it was also shown that specific activity of esters with the similar structure was lower [12].

Therefore, to obtain new derivatives of amino acids and study their antibacterial action is a promising field of research.

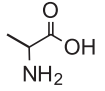
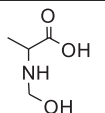
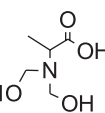
The aim of the present study is to determine the quantitative "structure – antibacterial action" relationships in a series of N-substituted amino acids.

Materials and Methods

The antibacterial activity of some L-amino acids and their N-substituted derivatives 1-12 was studied (Table) and probable "structure – antibacterial action" relationships in the given series were discussed [13]. Previously [14], the values of the distribution coefficients for N-R-amines

Table

Structures, AlogPs values calculated and data of the antibacterial action [13] for compounds 1-12

Compounds	Structure	AlogPs	Diameter of the growth inhibition zone, mm (mean)						
			<i>S. aureus</i>	<i>E. coli</i>	<i>Pr. vulgaris</i>	<i>P. aeruginosa</i>	<i>B. subtilis</i>	<i>C. albicans</i>	<i>Cl. Perfringens</i>
1	2	3	4	5	6	7	8	9	10
1		-3.05	0	0	0	0	0	0	0
2		-2.98	24	15	18	22	24	19	22
3		-1.55	24	16	18	21	23	18	20

Continuation of Table

1	2	3	4	5	6	7	8	9	10
4		-1.76	24	15	20	23	21	18	21
5		-3.42	0	0	0	0	0	0	0
6		-3.20	24	14	21	21	21	17	22
7		-2.09	23	14	20	20	20	15	23
8		-1.30	21	15	21	20	20	15	15
9		-3.01	0	0	0	0	0	0	0
10		-2.39	26	19	20	21	29	0	28
11		-1.78	26	18	21	22	30	0	30
12		-1.14	26	17	21	20	30	0	30

Notes. 0 – the growth of microorganisms.

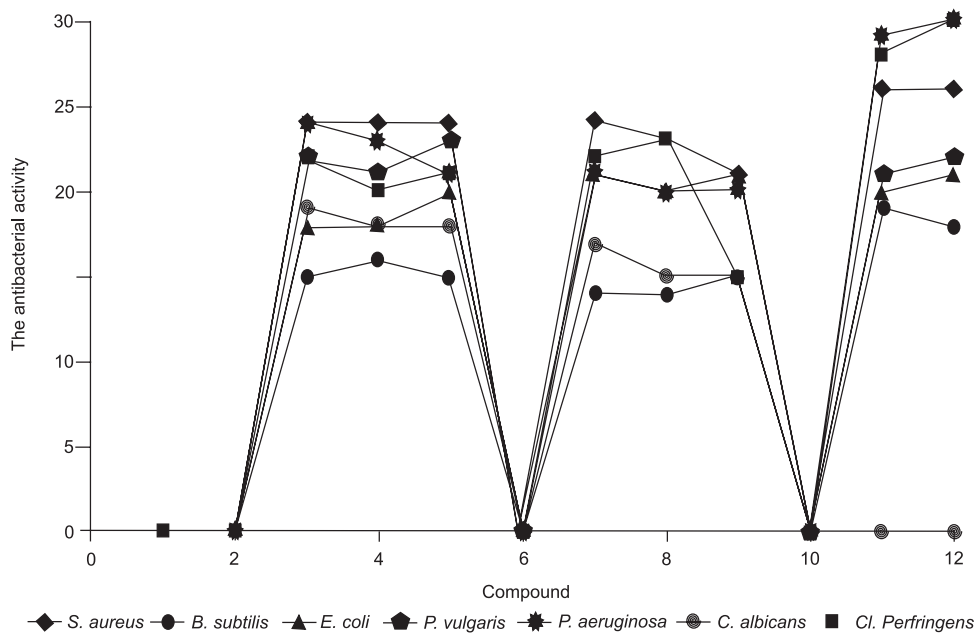


Fig. 1. The levels of the antibacterial action of compounds 1-12

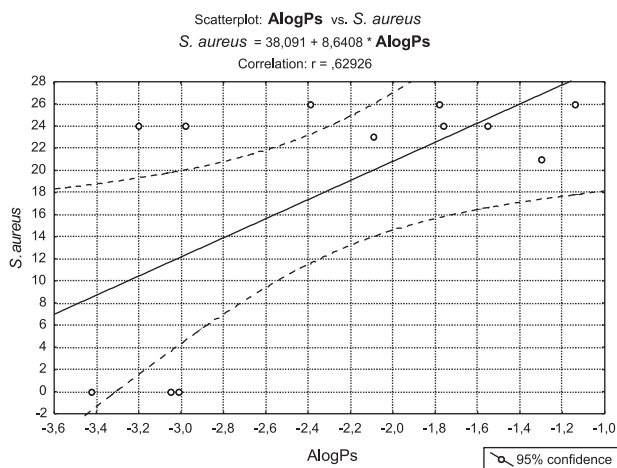


Fig. 2. Correlation of the antimicrobial action against *S. aureus* and AlogPs

were calculated by different algorithms, and expediency of further use of the AlogPs values obtained was shown to determine the quantitative correlations with the experimental data of the biological activity.

Since amino acids are structural analogs of N-R-amines, the AlogPs calculation algorithm can also be applied to them. Thus, further obvious step was to determine possible correlations and quantitative ratios of the data of the biological activity of N-substituted amino acids experimentally obtained with the calculated values of the AlogPs distribution coefficient (Tab.). It is known that the correlation and regression analysis is a reliable tool for determining quantitative relationships between independent variables and the dependent variable, in particular the biological activity [15, 16].

The quantitative dependencies of the antibacterial action of compounds 1-12 on AlogPs values was calculated using the STATISTIKA 8 program [17-20]. According to the requirements of mathematical statistics the coefficient of correlation shows the strength of relationships between characteristics: at values less than 0.3 – the relationship is absent, in the range of 0.3-0.7 – it is moderate, more than 0.7 – the relationship is strong [21, 22].

Results and Discussion

In total, 12 compounds were included in the statistical sample. During statistical processing of the research

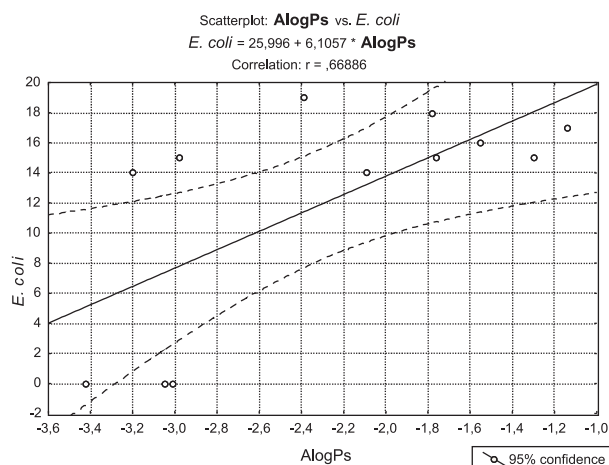


Fig. 3. Correlation of the antimicrobial action against *E. coli* and AlogPs

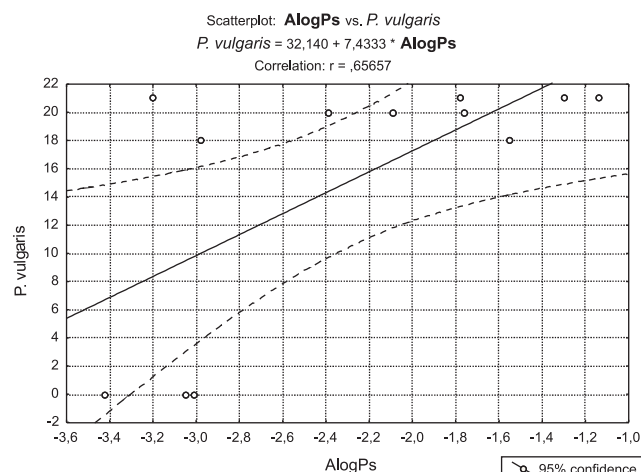


Fig. 4. Correlation of the antimicrobial action against *P. vulgaris* and AlogPs

results when analyzing a sample with the length of 12 cases the values of the Pearson correlation coefficients more than 0.40 ($p \leq 0.05$) were considered to be statistically significant [23].

The antibacterial action of compounds 1-12 greatly depends on the presence of substituents at the nitrogen atom and reaches maximum values with the increase in their number (Tab., Fig. 1). The growth of all microorganisms was observed in case of unsubstituted amino acids (compounds 1, 5 and 9), and it could be explained by their participation in the metabolic processes. Other N-substituted amino acids studied showed a high activity against gram-positive microorganisms (*B. subtilis*, *S. aureus* and *Cl. Perfringens*), and a slightly lower activity against the gram-negative (*E. coli*, *P. vulgaris*, *P. aeruginosa*) and fungi (*C. albicans*). It may be associated with the structure of the cell wall [24]. It should be noted that all threonine derivatives studied (10-12) contributed to the growth of *C. albicans* regardless of the presence of substituents at the nitrogen atom. Probably, it is due to the metabolism peculiarity of the amino acid mentioned, in particular as a substrate for the synthesis of glycine [25] and formation of some specific proteins [26].

When analyzing the results of statistical processing the satisfactory positive values of the levels of correlation (%) of the parameters of the coefficient of lipophilicity AlogPs

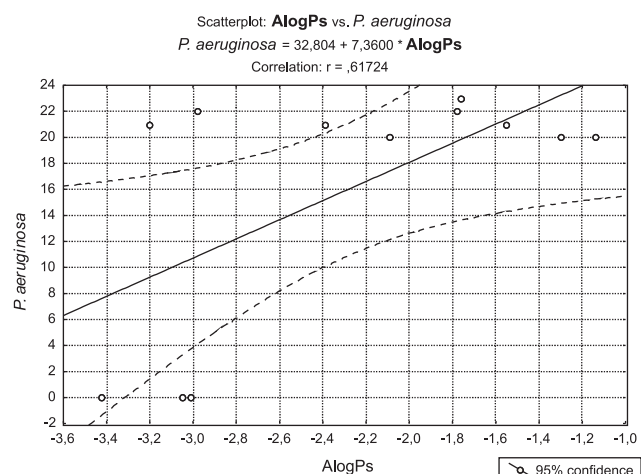


Fig. 5. Correlation of the antimicrobial action against *P. aeruginosa* and AlogPs

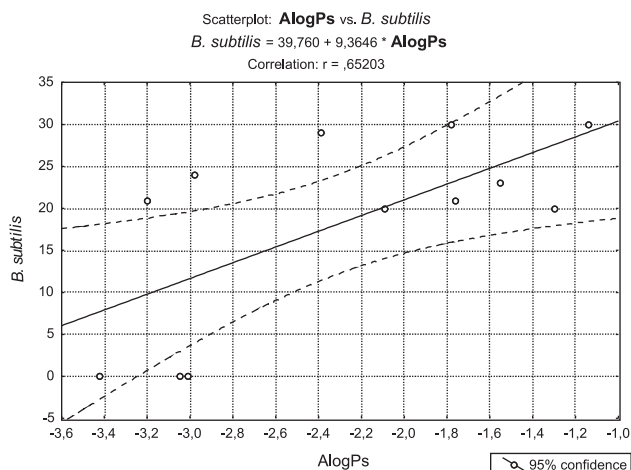


Fig. 6. Correlation of the antimicrobial action against *B. subtilis* and AlogPs

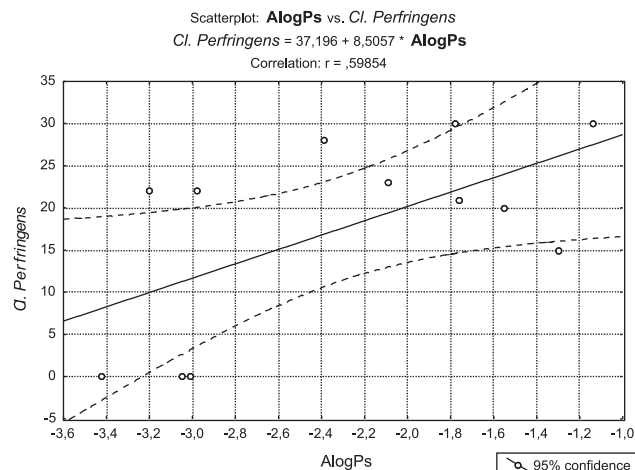


Fig. 8. Correlation of the antimicrobial action against *Cl. Perfringens* and AlogPs

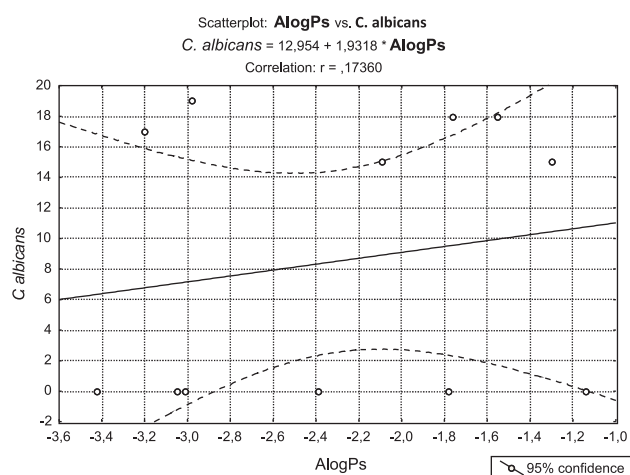


Fig. 7. Correlation of the antimicrobial action against *C. albicans* and AlogPs

calculated with the experimental data of the antibacterial activity of compounds 1-12 against *S. aureus* ($r = 0.62926$), *E. coli* ($r = 0.66886$), *P. vulgaris* ($r = 0.65657$), *P. aeruginosa* ($r = 0.61724$), *B. subtilis* ($r = 0.65203$), and *Cl. perfringens* ($r = 0.59854$) were observed, and they were statistically significant (Fig. 2-8). The absence of the relationship between the antibacterial effect against *C. albicans* ($r = 0.17360$) and the structure of threonine derivatives (10-12) confirmed the abovementioned arguments concerning the role of the latter in the metabolism of these fungi.

These combinations of the Pearson correlation coefficient and indicators of significance prove the reliability of the plots and equations shown in Fig. 2-8.

Therefore, arguments about the presence of the “structure – action” relationship and the degree of its manifestation were confirmed quantitatively by calculations. The results obtained give the possibility to predict the presence and the level of detection of the biological action in a series of N-substituted amino acids and carry out a purposeful search of biologically active substances in the given series.

CONCLUSIONS

1. To determine the quantitative “structure – antibacterial action” relationships the correlation and regression analysis of the AlogPs values calculated for N-substituted amino acids taking into account the results of the experimental study of the antibacterial action of the compounds under research has been conducted.

2. The statistically significant correlation values of AlogPs with the values of the antibacterial action of N-substituted amino acids against *S. aureus*, *E. Coli*, *Pr. Vulgaris*, *P. Aeruginosa*, *B. Subtilis*, *C. Albicans* and *Cl. perfringens* have been determined, and it quantitatively confirms the earlier assumptions of the existence of the “structure – action” relationship in this series of compounds and the degree of its manifestation.

Conflicts of Interest: authors have no conflict of interest to declare.

REFERENCES

1. Antifungal effect and action mechanism of antimicrobial peptide polybia-cp / K. Wang, F. Jia, W. Dang et al. // J. Pept. Sci. – 2016. – Vol. 22, Issue 1. – P. 28–35. doi: 10.1128/aac.05995-11
2. Industrial Biotechnology of Vitamins, Biopigments, and Antioxidants / ed. E. Vandamme, J. Revuelta. – New York : Wiley–VCH Verlag GmbH & Co. KGaA, 2016. – 581 p. doi: 10.1002/9783527681754
3. Antimicrobial activities of N-(2-hydroxy-1-naphthalidene)-amino acid (glycine, alanine, phenylalanine, histidine, tryptophane) Schiff bases and their manganese (III) complexes / I. Sakiyan., E. Logoglu, S. Arslan et al. // Biometals. – 2004. – Vol. 17, Issue 2. – P. 115–120. doi: 10.1023/b:biom.0000018380.34793.df
4. Synthesis and antimicrobial activities of new higher amino acid Schiff base derivatives of 6-aminopenicillanic acid and 7-aminocephalosporanic acid / O. Ozlem, G. Perihan, O. Berrin, O. Oyardi // J. Mol. Struc. – 2016. – Vol. 1106. – P. 181–191. doi: 10.1016/j.molstruc.2015.10.074
5. Alwan, S. Synthesis and Preliminary Antimicrobial Activity of New Schiff Bases of Pyrido [1,2-a] Pyrimidine Derivatives with Certain Amino Acids / S. Alwan, J. Al-Kaabi, R. Hashim // Med. Chem. – 2014. – Vol. 4, Issue 9. – P. 635–639. doi: 10.4172/2161-0444.1000206

6. Synthesis and Antimicrobial Activity of N-Substituted- β -amino Acid Derivatives Containing 2-Hydroxyphenyl, Benzo[b]phenoxazine and Quinoxaline Moieties / K. Mickeviciene, R. Barauskaite, K. Kantminiene et al. // *Molecules*. – 2015. – Vol. 20. – P. 3170–3189. doi: 10.3390/molecules20023170
7. Synthesis and antimicrobial activity of α N-phthalimido and acetimido derivatives from amino acids and anhydrides / C. Uma, M. Reddy, B. Jayakar, R. Srinivasan // *Int. J. of Pharma and Bio Sci.* – 2010. – Vol. 1, Issue 4. – P. 81–86.
8. Membrane active antimicrobial activity and molecular dynamics study of a novel cationic antimicrobial peptide polybia-MPI, from the venom of *Polybia paulista* / K. Wang, J. Yan, W. Dang et al. // *Peptides*. – 2013. – Vol. 39. – P. 80–88. doi: 10.1016/j.peptides.2012.11.002
9. Antimicrobial activities of amino acid derivatives of monascus pigments / C. Kim, H. Jung, Y. Kim, C. Shin // *FEMS Microbiol. Lett.* – 2006. – Vol. 264, Issue 1. – P. 117–124. doi: 10.1111/j.1574-6968.2006.00451.x
10. Design, synthesis and antimicrobial screening of amino acids conjugated 2-amino-4-arylthiazole derivatives / K. Prakasha, G. Raghavendra, R. Harisha, D. Gowda // *Int. J. Pharm. Pharm. Sci.* – 2011. – Vol. 3, Suppl. 3. – P. 120–125.
11. Synthesis and antimicrobial evaluation of some amino acid derivatives of 2-amino-4-methylthiazole / H. Hassan, A. El-Haddad, F. Kora, A. El-Naggar // *Analele Universita Nii din București – Chimie (serie noua)*. – 2010. – Vol. 19, Issue 2. – P. 23–30.
12. Dahiya, R. Synthesis, Characterization and Antimicrobial Studies on Some Newer Imidazole Analogs / R. Dahiya // *Sci. Pharm.* – 2008. – Vol. 76. – P. 217–239. doi: 10.3797/scipharm.0803-04
13. The search of compounds with the antimicrobial activity among derivatives of aliphatic α -amino acids / A. N. Komissarenko, M. Yu. Golik, O. P. Osolodchenko et al. // *The Scientific Heritage*. – 2017. – Vol. 1, № 8 (8). – P. 68–71.
14. The quantitative relationships of the partition coefficients calculated in the series of N-R-amine functional derivatives / M. Golik, O. Kryskiv, A. Komissarenko et al. // *Вісник фармації*. – 2016. – № 1 (85). – С. 19–23.
15. Draper, N. Applied Regression Analysis / N. Draper, H. Smith. – 2nd ed. – New York : John Wiley & Sons, 1998. – 736 p. doi: 10.1002/9781118625590
16. Mekenyan, O. Dynamic QSAR Techniques Application in Drug Design and Toxicology / O. Mekenyan // *Curr. Pharm. Design*. – 2002. – Vol. 8. – P. 1605–1621. doi: 10.2174/1381612023394278
17. Statistica. – Available at: <http://www.statsoft.com/Products/STATISTICA-Features>
18. Боровиков, В. П. STATISTICA: искусство анализа данных на компьютере. Для профессионалов. – 2-е изд. / В. П. Боровиков. – СПб. : Питер, 2003. – 688 с.
19. Вуколов, Э. А. Основы статистического анализа / Э. А. Вуколов. – М : Форум, 2008. – 464 с.
20. Халафян, А. А. Статистический анализ данных. STATISTICA 6 : учеб. / А. А. Халафян. – 3-е изд. – М. : Бином-Пресс, 2007. – 512 с.
21. Fujita, T. Recent success stories leading to commercializable bioactive compounds with the aid of traditional QSAR procedures / T. Fujita // *QSAR*. – 1997. – Vol. 16. – P. 107–112. doi: 10.1002/qsar.19970160202
22. Rivere, P. Quality et Statistique / P. Rivere // *Courrier des statistique*. – Paris: INSEE. – 1999. – Vol. 90. – P. 47–58.
23. Гублер, Е. В. Применение непараметрических критериев статистики в медико-биологических исследованиях / Е. В. Гублер, А. А. Генкин. – Л. : Медицина, 1973. – 141 с.
24. Brock Biology of Microorganisms / M. Madigan, J. Martinko, D. Stahl, D. Clark. – 13th ed. – New York : Pearson Education, 2012. – 1155 p.
25. *C. albicans* Pathway: glycine biosynthesis from threonine. – Available at: <http://pathway.candidagenome.org/CALBI/NEW-IMAGE?object=GLYSYN-THR-PWY>
26. Unexpected Role for a Serine/Threonine-Rich Domain in the *Candida albicans* Iff Protein Family / A. Boisrame, A. Cornu, G. Costa, L. Richard // *Eukaryot Cell*. – 2011. – Vol. 10, Issue 10. – P. 1317–1330. doi: 10.1128/EC.05044-11

REFERENCES

1. Wang, K., Jia, F., Dang, W., Zhao, Y., Zhu, R., Sun, M., Wang, R. (2015). Antifungal effect and action mechanism of antimicrobial peptide polybia-CP. *Journal of Peptide Science*, 22 (1), 28–35. doi: 10.1002/psc.2835
2. Vandamme, E. J., Revuelta, J. L. (Eds.). (2016). *Industrial Biotechnology of Vitamins, Biopigments, and Antioxidants*. New York: Wiley-VCH Verlag GmbH & Co. KGaA, 581. doi: 10.1002/9783527681754
3. Sakıyan, I., Logoglu, E., Arslan, S., Sari, N., Şakıyan, N. (2004). Antimicrobial activities of N-(2-hydroxy-1-naphthalidene)-amino acid (glycine, alanine, phenylalanine, histidine, tryptophane) Schiff bases and their manganese (III) complexes. *BioMetals*, 17 (2), 115–120. doi: 10.1023/b:biom.0000018380.34793.df
4. Özdemir (nee Güngör), Ö., Gürkan, P., Özçelik, B., Oyardı, Ö. (2016). Synthesis and antimicrobial activities of new higher amino acid Schiff base derivatives of 6-aminopenicillanic acid and 7-aminocephalosporanic acid. *Journal of Molecular Structure*, 1106, 181–191. doi: 10.1016/j.molstruc.2015.10.074
5. Alwan, S. M. (2014). Synthesis and Preliminary Antimicrobial Activity of New Schiff Bases of Pyrido [1,2-A] Pyrimidine Derivatives with Certain Amino Acids. *Medicinal Chemistry*, 4 (9), 635–639. doi: 10.4172/2161-0444.1000206
6. Mickevicienė, K., Barauskaitė, R., Kantminienė, K., Stasevych, M., Komarovska-Porokhnyavets, O., Novikov, V. (2015). Synthesis and Antimicrobial Activity of N-Substituted- β -amino Acid Derivatives Containing 2-Hydroxyphenyl, Benzo[b]phenoxazine and Quinoxaline Moieties. *Molecules*, 20 (2), 3170–3189. doi: 10.3390/molecules20023170
7. Uma, C. Reddy, M., Jayakar, B., Srinivasan, R. (2010). Synthesis and antimicrobial activity of α N-phthalimido and acetimido derivatives from amino acids and anhydrides. *Int. J. of Pharma and Bio Sci.*, 1 (4), 81–86.
8. Wang, K., Yan, J., Dang, W., Liu, X., Chen, R., Zhang, J., Wang, R. (2013). Membrane active antimicrobial activity and molecular dynamics study of a novel cationic antimicrobial peptide polybia-MPI, from the venom of *Polybia paulista*. *Peptides*, 39, 80–88. doi: 10.1016/j.peptides.2012.11.002
9. Kim, C., Jung, H., Kim, Y. O., Shin, C. S. (2006). Antimicrobial activities of amino acid derivatives of monascus pigments. *FEMS Microbiology Letters*, 264 (1), 117–124. doi: 10.1111/j.1574-6968.2006.00451.x

10. Prakasha, K., Raghavendra, G., Harisha, R., Gowda, D. (2011). Design, synthesis and antimicrobial screening of amino acids conjugated 2-amino-4-arylthiazole derivatives. *Int. J. Pharm. Pharm. Sci.* 3 (3), 120–125.
11. Hassan, H. M., El-Haddad, A. F., Kora, F. A., El-Naggar, A. M. (2010). Synthesis and antimicrobial evaluation of some amino acid derivatives of 2-amino-4-methylthiazole. *Analele Universita Nii din Bucuresti – Chimie (serie noua)*, 19 (2), 23–30.
12. Dahiya, R. (2008). Synthesis, Spectral and Antimicrobial Studies on some Newer Imidazole Analogs. *Scientia Pharmaceutica*, 76 (2), 217–239. doi: 10.3797/scipharm.0803-04
13. Komissarenko, A. N., Golik, M. Yu., Osolodchenko, O. P., Leonova, S. G., Dudka, K. I. (2017). The search of compounds with the antimicrobial activity among derivatives of aliphatic α -amino acids. *The scientific heritage*, 1 (8 (8)), 68–71.
14. Golik, M. Yu., Kryskiv, O. S., Komissarenko, A. M., Kolisnyk, O. V., Dudka, K. I. (2016). The quantitative relationships of the partition coefficients calculated in the series of N-R-amine functional derivatives. *Visnyk farmatsii – News of Pharmacy*, 1 (85), 19–23.
15. Draper, N. R., Smith, H. (1998). *Applied Regression Analysis*. (2–nd ed.). New York: John Wiley & Sons, 736. doi: 10.1002/9781118625590
16. Mekenyan, O. (2002). Dynamic QSAR Techniques: Applications in Drug Design and Toxicology. *Current Pharmaceutical Design*, 8(17), 1605–1621. doi: 10.2174/1381612023394278
17. *Statistica*. Available at: <http://www.statsoft.com/Products/STATISTICA-Features>
18. Borovikov, V. P. (2003). *STATISTICA: iskusstvo analiza dannyh na computere. Dlya professionalov*. (2–nd ed.). St. Petersburg : Piter, 688.
19. Vukolov, E. A. (2008). *Osnovy statisticheskogo analiza*. Moscow : Forum, 464.
20. Halafian, A. A. (2007). *Statisticheskii analiz dannyh. STATISTICA 6*. (3–rd ed.). Moscow : Binom–Press, 512.
21. Fujita, T. (1997). Recent Success Stories Leading to Commercializable Bioactive Compounds with the Aid of Traditional QSAR Procedures. *Quantitative Structure-Activity Relationships*, 16 (2), 107–112. doi: 10.1002/qsar.19970160202
22. Rivere, P. (1999). Quality et Statistique. *Courrier des statistique*. 90, 47–58.
23. Gubler, E. V., Genkin, A. A. (1973). *Primenenie neparametricheskikh kriteriev statistiki v mediko–biologicheskikh issledovaniyah*. Leninhrad: Meditsina, 141.
24. Madigan, M., Martinko, J., Stahl, D., Clark, D. (2012). *Brock Biology of Microorganisms*. (13–th ed.). New York : Pearson Education, 1155.
25. *C. albicans Pathway : glycine biosynthesis from threonine*. Available at : <http://pathway.candidagenome.org/CALBI/NEW-IMAGE?object=GLYSYN-THR-PWY>
26. Boisrame, A., Cornu, A., Da Costa, G., Richard, M. L. (2011). Unexpected Role for a Serine/Threonine-Rich Domain in the Candida albicans Iff Protein Family. *Eukaryotic Cell*, 10 (10), 1317–1330. doi: 10.1128/ec.05044-11

Information about authors:

Golik M. Yu., Candidate of Chemistry (Ph. D.), associate professor of the Analytical Chemistry Department, National University of Pharmacy. E-mail: aptekar4009@gmail.com

Kryskiv O. S., Candidate of Pharmacy (Ph. D.), associate professor of the Inorganic Chemistry Department, National University of Pharmacy

Komissarenko A. M., Doctor of Pharmacy (Dr. habil.), professor of the Chemistry of Natural Compounds Department, National University of Pharmacy

Kolisnyk O. V., Candidate of Pharmacy (Ph. D.), associate professor of the Pharmaceutical Chemistry Department, National University of Pharmacy

Dudka K. I., Master's Degree student, National University of Pharmacy

Відомості про авторів:

Голік М. Ю., канд. хім. наук, доцент кафедри аналітичної хімії, Національний фармацевтичний університет. E-mail: aptekar4009@gmail.com

Криськів О. С., канд. фарм. наук, доцент кафедри неорганічної хімії, Національний фармацевтичний університет

Комісаренко А. М., д-р фарм. наук, професор кафедри хімії природних сполук, Національний фармацевтичний університет

Колісник О. В., канд. фарм. наук, доцент кафедри фармацевтичної хімії, Національний фармацевтичний університет

Дудка К. І., магістрант, Національний фармацевтичний університет

Сведения об авторах:

Голік Н. Ю., канд. хім. наук, доцент кафедры аналитической химии, Национальный фармацевтический университет. E-mail: aptekar4009@gmail.com

Крыськів О. С., канд. фарм. наук, доцент кафедры неорганической химии, Национальный фармацевтический университет

Комиссаренко А. Н., д-р фарм. наук, профессор кафедры химии природных соединений, Национальный фармацевтический университет

Колесник Е. В., канд. фарм. наук, доцент кафедры фармацевтической химии, Национальный фармацевтический университет

Дудка К. И., магистрант, Национальный фармацевтический университет

Надійшла до редакції 01.12.2016 р.