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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*

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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*

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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.

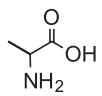
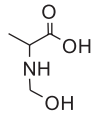
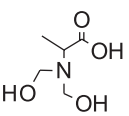
The **aim** of the present study is to determine the quantitative "structure – antibacterial action" relationships in a series of N-substituted amino acids.

Materials and Methods

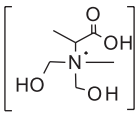
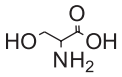
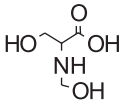
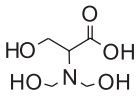
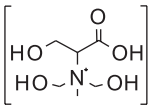
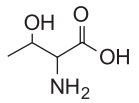
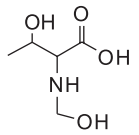
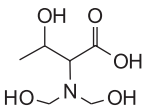
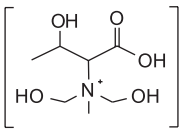
The antibacterial activity of some L-amino acids and their N-substituted derivatives 1-12 was studied (Table) and probable "structure – antibacterial action" relationships in the given series were discussed [13]. Previously [14], the values of the distribution coefficients for N-R-amines

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)						
			S. aureus	*E. coli*	*Pr. vulgaris*	*P. aeruginosa*	*B. subtilis*	*C. albicans*	*Cl. Perfringens*
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.

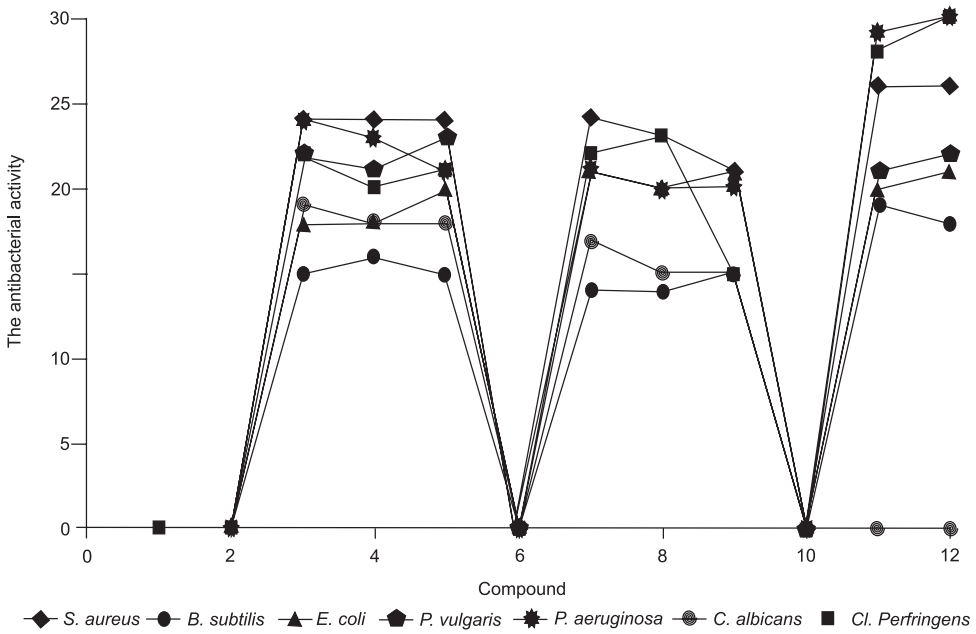


Fig. 1. The levels of the antibacterial action of compounds **1-12**

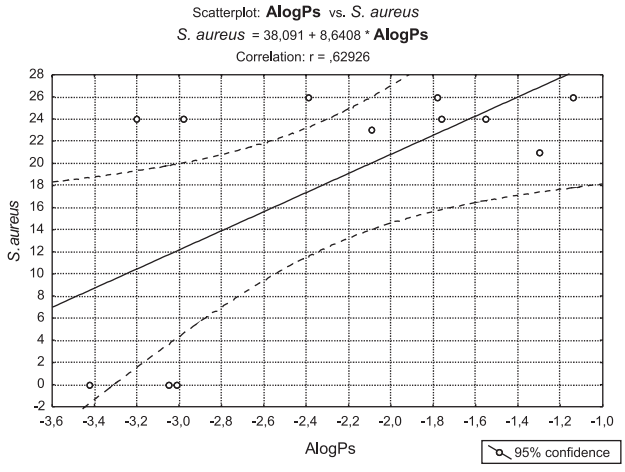


Fig. 2. Correlation of the antimicrobial action against *S. aureus* and AlogPs

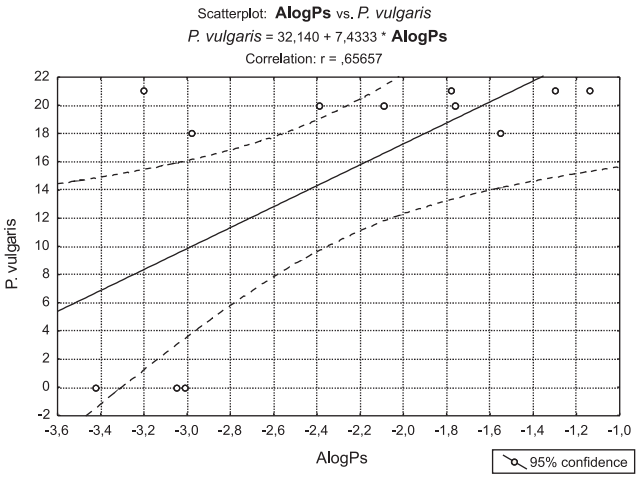


Fig. 4. Correlation of the antimicrobial action against *P. vulgaris* and AlogPs

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 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

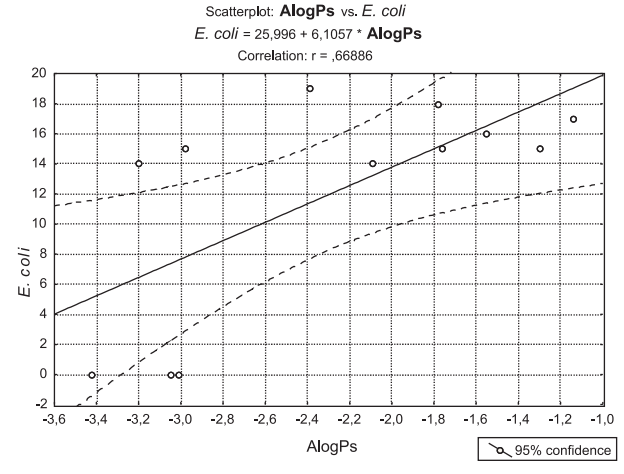


Fig. 3. Correlation of the antimicrobial action against *E. coli* and AlogPs

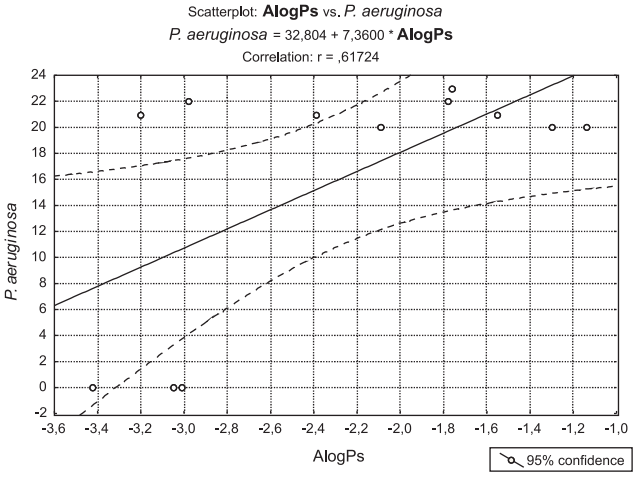


Fig. 5. Correlation of the antimicrobial action against *P. aeruginosa* and AlogPs

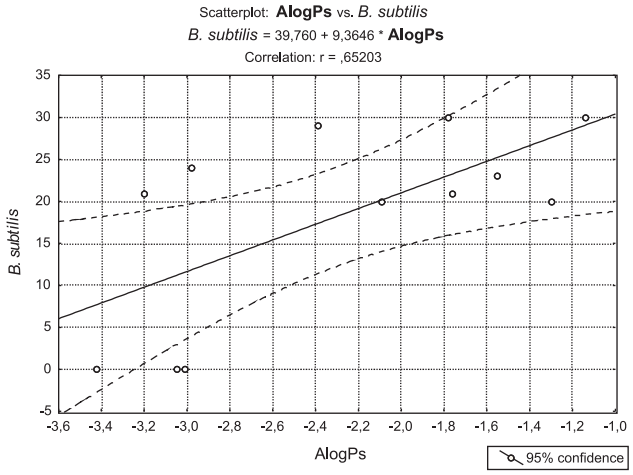


Fig. 6. Correlation of the antimicrobial action against *B. subtilis* and AlogPs

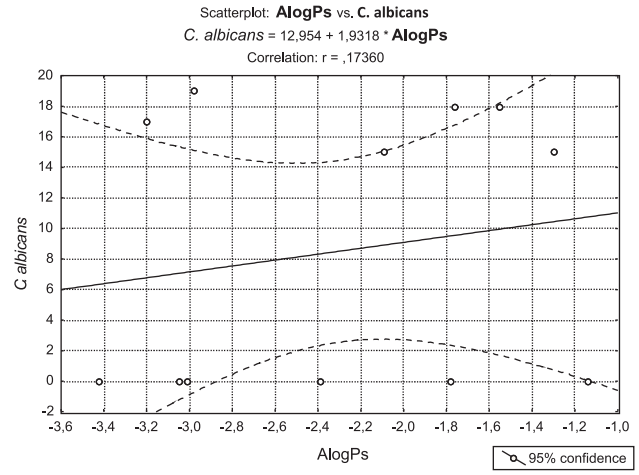


Fig. 7. Correlation of the antimicrobial action against *C. albicans* and AlogPs

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.

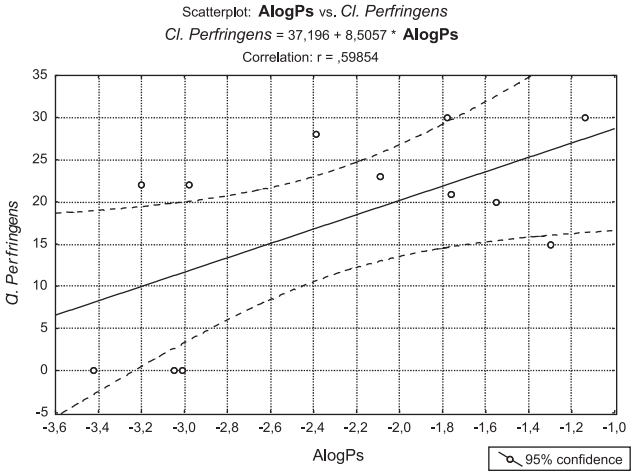


Fig. 8. Correlation of the antimicrobial action against *Cl. Perfringens* and AlogPs

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.

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