Molecular parameters and the antimicrobial activity of some N-substituted amino acids

The concept of "drug likeness" is used when developing drugs for a potential biologically active substance, which must meet some specific criteria, in particular it should be bioavailable. The traditional method of "drug likeness" assessment is verification of compliance with Lipinski's rule.

Aim. To determine the compliance of the "drug likeness" concept for some N-substituted amino acids and identify the quantitative "structure – microbiological activity" relationships.

Materials and methods. Using ChemOffice 2016 software the physicochemical parameters determining the bioavailability of some N-substituted amino acids were calculated. Determination of the possible correlations and quantitative ratios of the biological activity data experimentally obtained with the molar refraction (MR) values calculated was conducted using STATISTIKA 8 program.

Results and discussion. All compounds studied in their physicochemical properties meet the requirements for new BAS at the stage of testing their biological activity (correspond to Lipinski's rule). The dependence of the microbiological action of some N-substituted amino acids on MR is maximal for compounds, which MR value is in the range of 2.13-4.53. The growth of all microorganisms was observed for unsubstituted amino acids (MR < 2.8). The maximum activity of all compounds studied was observed against gram-positive (B. subtilis and S. aureus), and the less activity was against gram-negative microorganisms (E. coli, P. vulgaris, P. aeruginosa) and fungi (C. albicans). It may be associated with the structural peculiarities of the cellular wall. The MR values calculated correlate satisfactorily with the experimental data of the antimicrobial activity of compounds.

Conclusions. Statistically significant values of MR correlation with the values of the antimicrobial activity of some N-substituted amino acids against the microorganisms studied have been determined. It quantitatively confirms the presence of the "structure – activity" relationship in this series of compounds.

Key words: correlation; antimicrobial activity; N-substituted amino acids

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Цель данной работы – установление соответствия концепции «drug likeness» некоторых N-замещенных аминокислот и установление количественных зависимостей «структура - микроbióológica активность».

Материалы и методы. С использованием программного пакета ChemOffice 2016 рассчитаны физико-химические параметры, определяющие биодоступность некоторых N-замещенных аминокислот. Установление возможных корреляций и количественных соотношений данных биохимической активности с рассчитанными значениями молярной рефракции MR проведено с использованием программы STATISTIKA 8.

Результаты и их обсуждение. Все исследованные соединения по совокупности физико-химических свойств удовлетворяют требования к новым биологически активным веществам на стадии тестирования их биохимической активности (отвечают «правилу Липински»). Зависимость биохимического действия некоторых N-замещенных аминокислот от MR является максимальной для соединений, значение MR которых находится в пределах 2,13-4,53. Рост всех микроорганизмов наблюдался для незамещенных аминокислот (MR < 2,8). Максимальная активность всех исследованных соединений наблюдалась для грамположительных (B. subtilis и S. aureus), меньше – для грамотрицательных микроорганизмов (E. coli, P. vulgaris, P. aeruginosa) и грибов (C. albicans), что может быть связано с особенностями строения клеточной стенки. Рассчитанные значения MR удовлетворительно коррелируют с экспериментальными данными противомикробной активности.

Выводы. Установлены статистически достоверные значения корреляции показателя MR со значениями противомикробного действия некоторых N-замещенных аминокислот по отношению к исследованным микроорганизмам, что количественно подтверждает наличие связи «структура-действие» в данном ряду соединений.

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

Данные микробиологической активности соединений 1-12 [9] отражают способность поглощения всех электронов всех молекул, что характеризует способность электронов к поляризации и увеличению скорости перехода электронов в молекулу. Рассчитанные значения MR позволяют определить оптимальные физико-химические параметры, определяющие биодоступность некоторых N-замещенных аминокислот.

Таблица 1: Данные микробиологической активности соединений 1-12 [9]

| No. | S. aureus | E. coli | Pr. vulgaris | P. aeruginosa | B. subtilis | C. albicans | C. Perfringens |
|-----|-----------|---------|--------------|---------------|-------------|-------------|---------------|
| 1   | 5         | 0       | 0            | 0             | 0           | 0           | 0             |
| 2   | 24        | 15      | 18           | 18            | 22          | 19          | 22            |
| 3   | 24        | 16      | 18           | 21            | 23          | 18          | 20            |

*Note. 0 – the growth of microorganisms.
ties of a molecule and its potential bioavailability. Therefore, the next logical step was to determine the possible correlations and quantitative ratios of the biological activity data experimentally obtained with the MR values calculated (Tab. 1, 2). The statistical processing of the results was carried out using STATISTIKA 8 program [12]. According to the requirements of mathematical statistics the correlation coefficient indicates the closeness of the relationship between the signs: with values less than 0.3 – the relationship is absent, within the range of 0.3-0.7 it is medium, and more than 0.7 it is strong [13].

Table 2

| No. | Compound | Parameters | The number of H-bond acceptors | The number of H-bond donors |
|-----|----------|------------|-------------------------------|----------------------------|
|     |          | MW, g/mol  | MR, cm³                       | AlogPs [10]                |
| 1   |          | 89.05      | 2.13                          | -3.05                      | 2                           | 2                           |
| 2   |          | 119.06     | 2.74                          | -2.98                      | 3                           | 3                           |
| 3   |          | 149.07     | 3.36                          | -1.55                      | 4                           | 3                           |
| 4   |          | 164.09     | 3.91                          | -1.76                      | 3                           | 3                           |
| 5   |          | 105.04     | 2.28                          | -3.42                      | 3                           | 3                           |
| 6   |          | 135.05     | 2.90                          | -3.20                      | 4                           | 4                           |
| 7   |          | 165.06     | 3.51                          | -2.09                      | 5                           | 4                           |
| 8   |          | 180.09     | 4.06                          | -1.30                      | 4                           | 4                           |
| 9   |          | 119.06     | 2.74                          | -3.01                      | 3                           | 3                           |
| 10  |          | 149.07     | 3.36                          | -2.39                      | 4                           | 4                           |
| 11  |          | 179.08     | 3.98                          | -1.78                      | 5                           | 4                           |
| 12  |          | 194.10     | 4.53                          | -1.14                      | 4                           | 4                           |

The range of values: 89.05-194.10, 2.13-4.53, -3.42-1.14, 2-5, 2-4
The mean value: 146.65, 3.29, -2.31, 4, 3
The maximum permitted value: 460, 130, 5.6, 5, 10
Results and discussion

All compounds studied in their physicochemical properties meet the requirements for new BAS at the stage of testing their biological activity (correspond to Lipinski’s rule) (Tab. 2).

In general, the statistical sampling included 12 compounds. During the statistical processing of the research results when analyzing a sample with the length of 12 cases the values of Pearson correlation coefficients more than 0.40 ($p \leq 0.05$) are considered to be statistically significant [14].

The dependence of the microbiological action of compounds 1-12 on MR has a nonlinear character, and reaches the maximum values for compounds, which MR value is in the range close to the mean value (2.13-4.53) (Tab. 1, 2). The growth of all microorganisms was observed for unsubstituted amino acids (compounds 1, 5 and 9) with MR values less than 2.8. The maximum activity of all compounds studied was observed against gram-positive (B. subtilis and S. aureus), and the less activity was against gram-negative microorganisms (E. coli, P. vulgaris, P. aeruginosa) and fungi (C. albicans). It may be associated with the structural peculiarities of the cellular wall [15].

The analysis of the statistical processing of the results obtained indicates that the MR values calculated correlate satisfactorily (%) negative values of correlation coefficients) with the experimental data of the antimicrobial activity of compounds 1-12 in relation to S. aureus ($r = -0.73481$), E. coli ($r = -0.75928$), P. vulgaris ($r = -0.77000$), P. aeruginosa ($r = -0.71342$), B. subtilis ($r = -0.76287$), and Cl. Perfringens ($r = -0.74181$); they are statistically significant (Fig. 1-7). The relationship is absent only in the case of C. albicans ($r = -0.13588$), and its possible causes are mentioned above [15].

These combinations of Pearson correlation coefficient and the significance values indicate the reliability of plots 1-7 and equations given in Fig.

Therefore, the earlier considerations [9, 10] about the presence of the “structure – activity” relationship and the degree of its manifestation were confirmed quantitatively by calculations. The results obtained allow to predict the presence and the level of detection of the biological action of some N-substituted amino acids and...
to carry out a purposeful search of biologically active substances in the series.

CONCLUSIONS

1. Some N-substituted amino acids have been tested for compliance with the concept of “drug likeness”. The results obtained have shown that the compounds can be recommended for further study as those that have favorable physicochemical parameters according to Lipinski’s rule.

2. With the purpose of revealing QSAR the correlation and regression analysis of MR values calculated and the results of the experimental study of the antimicrobial activity of the compounds studied has been conducted.

3. Statistically significant values of MR correlation with the values of the antimicrobial activity of some N-substituted amino acids against *S. aureus*, *E. coli*, *P. vulgaris*, *P. aeruginosa*, *B. subtilis* and *C. albicans* have been determined. It quantitatively confirms earlier assumptions about the presence of the “structure – activity” relationship in this series of compounds and the degree of its manifestation.

Conflict of Interests: authors have no conflict of interests to declare.

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