Search for antibacterial activity in a number of new S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

The relevance of the study of 1,2,4-triazole derivatives with pyrimidine fragment is due to the synthesis of potential broad-spectrum antibacterial drugs, low molecular weight inducers of interferon, and antitumor agents, search for molecular descriptors of their structure, important for establishing patterns “structure – biological activity”.

The aim of the work is a computer search for the antibacterial action of new hybrids of 1,2,4-triazole-3(2H)-thiol with a pyrimidine fragment in relation to 5 test cultures, to establish the dependence of “structure – action”.

Materials and methods. For an in-depth study of the antibacterial activity of derivatives of 1,2,4-triazole-3(2H)-thiol hybrids with a pyrimidine fragment, 4 test cultures of museum strains of gram-positive, gram-negative bacteria and one species of fungi were selected. In silico studies were performed using regression and classification QSAR models.

Results. Derivatives of 1,2,4-triazole-3(2H)-thiol hybrids with a pyrimidine moiety showed high antibacterial activity against gram-negative microorganisms (E. coli, P. aeruginosa). The obtained experimental results allowed to establish not only the role of the main structural features of the compounds in the manifestation of antimicrobial properties, but also to evaluate the effectiveness of the created classification and regression QSAR models. Based on the presented parameters for individual predictive QSAR models, it is possible to conclude about the effectiveness, stability and feasibility of using these models to search for new S-derivatives (1,2,4-triazole-3(2H)-yl) methylthiopyrimidines as promising antimicrobial agents.

Conclusions. It was found that the studied derivatives of hybrids of 1,2,4-triazole-3(2H)-thiol with a pyrimidine fragment showed high antibacterial activity against gram-negative microorganisms. The developed QSAR classification models based on the percentage of correctly predicted compounds (70 %) are the most effective in comparison with regression (50 %) for the search for new antimicrobial agents in a number of derivatives of hybrids 1,2,4 triazole-3(2H)-thiol with pyrimidine fragment.

Key words: 1,2,4-triazole, pyrimidines, antibacterial activity, QSAR.

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The relevance of the study of 1,2,4-triazole derivatives with pyrimidine fragment is due to the synthesis of potential antibacterial and antitumor agents in a broad spectrum of drugs, low molecular weight with pyrimidine fragment is due to their potential strong ester bond and good permeability to the cell. Molecular weight alcohol residues are due to good dissociation, rapid absorption, and esters with low toxicity. Salts are due to the peculiarities of their pharmacokinetics and bioavailability. In this regard, the most promising are salts and esters of the most promising substances with high antibacterial activity.

Aim
The aim of the work is a computer search for the antibacterial action of new hybrids of 1,2,4-triazole-3(2H)-thiols with a pyrimidine fragment in relation to 4 test cultures, to establish the dependence of “structure – action”.

Materials and methods
To create predictive QSAR models, individual samples of 1,2,4-triazole derivatives were formed, the main number of which were 1,2,4-triazole-3(2H)-thiol derivatives, and entered into the OCHEM server database [https://ochem.eu/] in Excel format [5]. Sets of experimental data included 110 structures of inhibitors of P. aeruginosa, E. coli, S. aureus and C. albicans. The k-Nearest Neighbor Method (k-NN) was used to construct QSAR regression models. Classification models were built using the random forest (WEKA-RF, Random Forest) algorithm. The k-Nearest Neighbor Method (k-NN) was used to construct QSAR regression models. Classification models were built using the random forest (WEKA-RF, Random Forest) algorithm.

The relevance of the study of 1,2,4-triazole derivatives with pyrimidine fragment is due to the synthesis of potential broad-spectrum antibacterial drugs, low molecular weight inducers of interferon and antitumor agents, search for molecular descriptors of their structure, important for establishing patterns “structure – biological activity”.

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simple descriptors for counting chemical groups, and descriptors of a wide range of possibilities for counting chemical structures, such as: ALOGPS, E-State, ADRIANA. Code, Dragon V6.0, Chemaxon, Inductive descriptors, available on the OCHEM server.

Classification quality was assessed by statistical indicators – total accuracy as a percentage of correctly classified compounds (total accuracy), prediction accuracy for active and inactive compounds (precision), and class efficiency rates (class hit rate). The predictive power of QSAR regression models was estimated using a cross-estimation factor $q^2$.

**Results**

Development of QSAR models of antimicrobial activity of S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines. Classification and regression predictive QSAR models of antimicrobial activity of inhibitors E. coli, P. aeruginosa, S. aureus, C. albicans were created according to MIC indicators. Training samples were formed by [6–10].

When creating QSAR classification models, MIC values were divided into two conditional groups in a ratio of approximately 1:1 for bacteria, where 50% of all compounds were considered active and 50% inactive and in a ratio of 1.0:1.5 for the fungus C. albicans where 40% of all compounds considered active and 60% inactive.

Statistical parameters of the created individual QSAR classification models of antimicrobial activity of S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines against the studied cultures are presented in Table 1.

![Table 1](https://via.placeholder.com/150)

| Parameter models | Sample activity models of S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines as culture inhibitors |
|------------------|--------------------------------------------------------------------------------------------------|
| **P. aeruginosa** | E. coli  | S. aureus | C. albicans |
| Number of descriptors | 146 | 209 | 220 | 191 |
| Precision (active) | 0.86 | 0.82 | 0.82 | 0.78 |
| Precision (inactive) | 0.90 | 0.85 | 0.81 | 0.80 |
| Sensitivity | 0.90 | 0.83 | 0.79 | 0.69 |
| Specificity | 0.86 | 0.84 | 0.84 | 0.87 |
| Accuracy, % | 88.0 ± 4.0 | 83.0 ± 3.0 | 82.0 ± 4.0 | 80.0 ± 5.0 |

Precision (active): the accuracy of predicting compounds as active; Precision (inactive): the accuracy of predicting compounds as inactive; Sensitivity: sensitivity for the active class; Specificity: specificity for the inactive class; Accuracy: the percentage of correctly classified compounds.

![Table 2](https://via.placeholder.com/150)

| Parameter models | Sample activity models of S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines as inhibitors of microbial cultures |
|------------------|--------------------------------------------------------------------------------------------------|
| **P. aeruginosa** | E. coli  | S. aureus | C. albicans |
| Number of descriptors | 246 | 276 | 283 | 262 |
| $q^2$ | 0.91 ± 0.03 | 0.83 ± 0.03 | 0.87 ± 0.03 | 0.84 ± 0.04 |
| $R^2$ | 0.91 ± 0.03 | 0.83 ± 0.03 | 0.87 ± 0.03 | 0.84 ± 0.04 |
| RMSE | 0.26 ± 0.04 | 0.48 ± 0.04 | 0.42 ± 0.03 | 0.44 ± 0.05 |
| MAE | 0.18 ± 0.02 | 0.35 ± 0.03 | 0.32 ± 0.02 | 0.30 ± 0.03 |

$q^2$: coefficient of cross-estimation; $R^2$: square of the correlation coefficient; RMSE: standard error of the forecast; MAE: the average absolute error.

The percentage of correctly classified compounds in relation to all microbial cultures (total accuracy) was 80–88%, which indicates the high predictive power of the constructed QSAR classification models.

Statistical coefficients of the developed regression consensus QSAR models for predicting the activity of new S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines against the studied microorganisms are presented in Table 2 and graphically shown in Fig. 1–4.

Antimicrobial activity, represented as MIC, was transformed into log (1/MIC) and used as a dependent variable to build QSAR models.

This conclusion is confirmed by the graphical results (Fig. 1–4) of the established ratio of experimental values of log (1/MIC) and predicted values of log (1/MIC) activity, the value of which for most compounds (90%) is within 1 log (1/MIC).

Prediction of antimicrobial activity of synthesized S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines according to QSAR classification models. The created QSAR classification models were used to predict the “class” of antimicrobial activity of the synthesized compounds by the criterion of “active” and “inactive”. The results of the prediction by classification models are given in Table 3.

According to table 3 almost 90% of compounds according to the classification models of activity are provided as active. Prediction of antimicrobial activity of synthesized S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines according to regression QSAR models. General prognosis of
Table 3. Prediction of antimicrobial activity of the studied S-derivatives (1,2,4-triazole-3(2H)-yl)methyl)thiopyrimidines according to QSAR classification models

| №   | Prediction of the activity inhibitors of microbial cultures |
|-----|----------------------------------------------------------|
|     | E. coli | S. aureus | P. aeruginosa | C. albicans |
| 2.2 | +       | +         | +             | +           |
| 2.3 | +       | –         | +             | +           |
| 2.4 | +       | –         | +             | +           |
| 2.7 | +       | –         | –             | +           |
| 2.9 | +       | +         | –             | +           |
| 2.10| +       | –         | +             | –           |
| 2.11| +       | –         | +             | +           |
| 2.12| +       | –         | +             | –           |
| 2.13| –       | –         | +             | +           |
| 2.14| +       | –         | +             | –           |
| 2.15| +       | –         | +             | –           |
| 2.16| +       | –         | +             | –           |

Fig. 1. Distribution of experimental and predicted log values (1/MIC) for inhibitors of P. aeruginosa.

Fig. 2. Distribution of experimental and predicted log values (1/MIC) for E. coli inhibitors.

Fig. 3. Distribution of experimental and predicted log values (1/MIC) for S. aureus inhibitors.

Fig. 4. Distribution of experimental and predicted values of log (1/MIC) for inhibitors of C. albicans.
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Cont. of table 3.

| №  | Prediction of the activity inhibitors of microbial cultures |  |  |  |
|----|-----------------------------------------------------------|---|---|---|
|    | **E. coli**                                               | **S. aureus**                      | **P. aeruginosa**                  | **C. albicans** |
| 2.17 | +                                                         | –                                        | +                                    | +               |
| 2.18 | +                                                         | –                                        | +                                    | +               |
| 2.19 | +                                                         | –                                        | +                                    | +               |
| 2.20 | +                                                         | –                                        | –                                    | +               |
| 2.21 | +                                                         | –                                        | –                                    | +               |
| 2.22 | +                                                         | –                                        | –                                    | +               |
| 2.23 | +                                                         | +                                        | –                                    | +               |
| 2.24 | +                                                         | +                                        | –                                    | +               |

*: compound intended as active; –: the compound is intended to be inactive.

Table 4. The results of the prediction of the activity of S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines by regression QSAR models, log(1/MIC)

| №  | Prediction of the activity inhibitors of microbial cultures |  |  |  |
|----|-----------------------------------------------------------|---|---|---|
|    | **P. aeruginosa**                                         | **E. coli**                           | **S. aureus**                        | **C. albicans** |
| 2.2 | 1.92 ± 0.27                                              | 2.65 ± 0.47                            | 4.80 ± 0.66                           | 1.19 ± 0.41     |
| 2.3 | 1.91 ± 0.18                                              | 2.61 ± 0.31                            | 4.29 ± 0.16                           | 1.77 ± 0.23     |
| 2.4 | 2.17 ± 0.12                                              | 3.09 ± 0.08                            | 4.62 ± 0.38                           | 2.16 ± 0.21     |
| 2.7 | 3.30 ± 1.42                                              | 3.53 ± 0.83                            | 4.50 ± 1.52                           | 1.73 ± 1.53     |
| 2.9 | 2.68 ± 0.09                                              | 4.36 ± 0.12                            | 5.12 ± 0.27                           | 2.39 ± 0.23     |
| 2.10 | 3.11 ± 0.34                                             | 4.76 ± 0.22                            | 5.43 ± 0.37                           | 2.68 ± 0.32     |
| 2.11 | 3.70 ± 0.76                                              | 4.30 ± 0.23                            | 5.65 ± 0.59                           | 2.88 ± 0.62     |
| 2.12 | 3.14 ± 0.35                                              | 4.80 ± 0.20                            | 5.44 ± 0.36                           | 2.75 ± 0.33     |
| 2.13 | 3.20 ± 0.45                                              | 4.88 ± 0.31                            | 5.22 ± 0.53                           | 2.96 ± 0.39     |
| 2.14 | 2.85 ± 0.11                                              | 4.80 ± 0.12                            | 5.29 ± 0.20                           | 2.63 ± 0.21     |
| 2.15 | 2.68 ± 0.09                                              | 4.36 ± 0.12                            | 5.12 ± 0.27                           | 2.39 ± 0.23     |
| 2.16 | 3.20 ± 0.45                                              | 4.88 ± 0.31                            | 5.22 ± 0.53                           | 2.96 ± 0.39     |
| 2.17 | 2.16 ± 0.11                                              | 3.10 ± 0.14                            | 4.74 ± 0.22                           | 2.16 ± 0.23     |
| 2.18 | 2.97 ± 0.19                                              | 4.52 ± 0.06                            | 5.26 ± 0.22                           | 2.34 ± 0.13     |
| 2.19 | 2.70 ± 0.28                                              | 3.95 ± 0.16                            | 5.35 ± 0.40                           | 2.28 ± 0.32     |
| 2.20 | 3.14 ± 0.35                                              | 4.80 ± 0.21                            | 5.44 ± 0.36                           | 2.75 ± 0.33     |
| 2.21 | 3.19 ± 0.39                                              | 4.88 ± 0.24                            | 5.38 ± 0.39                           | 2.76 ± 0.32     |
| 2.22 | 3.18 ± 0.43                                              | 4.94 ± 0.18                            | 5.29 ± 0.45                           | 2.84 ± 0.36     |
| 2.23 | 3.20 ± 0.45                                              | 4.88 ± 0.31                            | 5.22 ± 0.53                           | 2.96 ± 0.39     |
| 2.24 | 2.87 ± 0.11                                              | 4.80 ± 0.12                            | 5.29 ± 0.20                           | 2.63 ± 0.21     |

the activity of the synthesized S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines as inhibitors *P. aeruginosa*, *E. coli*, *S. aureus* and *C. albicans* according to all constructed regression QSAR models are presented in Table 4.

**Discussion**

Based on the presented parameters for individual predictive QSAR models (Table 2), we can conclude about the efficiency, stability and feasibility of using these models to search for new S-derivatives (1,2,4-triazole-3(2H)-yl)methylthiopyrimidines as promising antimicrobial agents. This is evidenced by the high value of the cross-estimation coefficient – *q*², determined for all consensus models in the range of 0.84–0.91 and the optimal range of values of the standard error of the forecast – RMSE 0.26–0.48.

The use of regression QSAR models to predict the antimicrobial activity of the compounds allowed to divide them into 4 conditional groups by activity value (MIC) in the range of
10 μmol, 100 μmol, 1000 μmol and 10000 μmol. Moreover, for each type of microorganism there was a different level of predicted activity of S-derivatives (1,2,4-triazole-3(2H)-yl) methyl)thiopyrimidines.

The obtained experimental results allowed to establish not only the role of the main structural features of the compounds in the manifestation of antimicrobial properties, but also to evaluate the effectiveness of the created classification and regression QSAR models.

Developed QSAR classification models based on the percentage of correctly predicted compounds (70 %) are the most effective compared to regression (50 %) for the search for new antimicrobial agents in a number of S-derivatives (1,2,4-triazole-3(2H)-yl) methyl)thiopyrimidines.

Conclusions

1. It was found that the studied derivatives of hybrids of 1,2,4-triazole-3(2H)-thiol with a pyrimidine moiety showed high antibacterial activity against gram-negative microorganisms.

2. The developed QSAR classification models based on the percentage of correctly predicted compounds (70 %) are the most effective in comparison with regression (50 %) for the search for new antimicrobial agents in a number of derivatives of hybrids 1,2,4 triazole-3(2H)-thiol with pyrimidine fragment.

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

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