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

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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(2*H*)-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(2*H*)-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(2*H*)-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(2*H*)-yl) methyl)thiopyrimidines as promising antimicrobial agents.

Conclusions. It was found that the studied derivatives of hybrids of 1,2,4-triazole-3(2*H*)-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(2*H*)-thiol with pyrimidine fragment .

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

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Пошук антибактеріальної активності в ряду нових S-похідних (1,2,4-тріазол-3(2*H*)-іл)метил)тіопіримідинів

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Актуальність дослідження похідних 1,2,4-тріазолу з піримідиновим фрагментом зумовлена синтезом потенційних антибактеріальних лікарських препаратів широкого спектра дії, низькомолекулярних індукторів інтерферону та протипухлинних агентів, пошуком молекулярних дескрипторів їхньої структури, важливих для встановлення закономірностей «структура – біологічна активність».

Мета роботи – комп’ютерний пошук антибактеріальної дії нових гібридів 1,2,4-тріазол-3(2*H*)-тіолів із піримідиновим фрагментом щодо 5 тест-культур, встановити залежність «структура – дія».

Матеріали та методи. Для поглибленого вивчення антибактеріальної дії похідних гібридів 1,2,4-тріазол-3(2*H*)-тіолу з піримідиновим фрагментом обрали 4 тест-культури музейних штамів грампозитивних і грамнегативних бактерій та один вид грибів. *In silico* дослідження виконували за допомогою регресійних і класифікаційних QSAR-моделей.

Результати. Похідні гібридів 1,2,4-тріазол-3(2*H*)-тіолу з піримідиновим фрагментом показали високу антибактеріальну активність щодо грамнегативних мікроорганізмів (*E. coli, P. aeruginosa*). Експериментальні результати дали можливість не тільки встановити роль основних структурних особливостей сполук у прояві антимікробних властивостей, але й оцінити ефективність створених класифікаційних і регресійних QSAR моделей. На підставі наведених параметрів для індивідуальних QSAR моделей для прогнозу можна зробити висновок про ефективність, стабільність, доцільність використання цих моделей для пошуку нових S-похідних (1,2,4-тріазол-3(2*H*)-іл)метил)тіопіримідинів як перспективних антимікробних агентів.

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

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Висновки. Встановили, що досліджувані похідні гібриди 1,2,4-тріазол-3(2*H*)-тіолу з піримідиновим фрагментом показали високу антибактеріальну активність щодо грамнегативних мікроорганізмів. Розроблені класифікаційні QSAR моделі за показником відсотка правильно прогнозованих сполук (70 %) вважаємо найефективнішими порівняно з регресійними (50 %) для пошуку нових антимікробних агентів у ряду похідних гібридів 1,2,4тріазол-3(2*H*)-тіолу з піримідиновим фрагментом.

Ключові слова: 1,2,4-триазол, піримідин, антибактеріальна активність, класифікаційні QSAR моделі, регресійні QSAR моделі.

Актуальні питання фармацевтичної і медичної науки та практики. 2021. Т. 14, № 2(36). С. 173–178

Поиск антибактериальной активности в ряду новых S-производных (1,2,4-триазол-3(2*H*)-ил)метил)тиопиримидинов

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Актуальность исследования производных 1,2,4-триазола с пиримидиновым фрагментом обусловлена синтезом потенциальных антибактериальных лекарственных препаратов широкого спектра действия, низкомолекулярных индукторов интерферона и противоопухолевых агентов, поиском молекулярных дескрипторов их структуры, важных для установления закономерностей «структура – биологическая активность».

Цель работы – компьютерный поиск антибактериального действия новых гибридов 1,2,4-триазол-3(2*H*)-тиолов с пиримидиновым фрагментом относительно 5 тест-культур, установить зависимость «структура – действие».

Материалы и методы. Для углубленного изучения антибактериального действия производных гибридов 1,2,4-триазол-3(2*H*)-тиола с пиримидиновым фрагментом отобрали 4 тест-культуры музейных штаммов грамположительных и грамотрицательных бактерий и один вид грибов. *In silico* исследования проведены с помощью регрессионных и классификационных QSAR-моделей.

Результаты. Производные гибридов 1,2,4-триазол-3(2*H*)-тиола с пиримидиновым фрагментом показали высокую антибактериальную активность в отношении грамотрицательных микроорганизмов (*E. coli, P. aeruginosa*). Экспериментальные результаты позволили не только установить роль основных структурных особенностей соединений в проявлении антимикробных свойств, но и оценить эффективность созданных классификационных и регрессионных QSAR моделей. На основе представленных параметров для индивидуальных прогнозирующих QSAR моделей можно сделать вывод об эффективности, стабильности и целесообразности использования данных моделей для поиска новых S-производных (1,2,4-триазол-3(2*H*)-ил)метил)тиопиримидинов как перспективных антимикробных агентов .

Выводы. Установили, что исследуемые производные гибриды 1,2,4-триазол-3(2*H*)-тиола с пиримидиновым фрагментом показали высокую антибактериальную активность в отношении грамотрицательных микроорганизмов. Разработанные классификационные QSAR модели с показателем процента верно прогнозируемых соединений (70 %) представляются наиболее эффективными по сравнению с регрессионными (50 %) для поиска новых антимикробных агентов в ряду производных гибридов 1,2,4 триазол-3(2*H*)-тиола с пиримидиновым фрагментом.

Ключевые слова: 1,2,4-триазол, пиримидин, антибактериальная активность, классификационные QSAR модели, регрессионные QSAR модели.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2021. Т. 14, № 2(36). С. 173–178

1,2,4-Triazole nucleus is a very interesting azole heterocycle and compounds of its chemical transformation find various biological, pharmaceutical and clinical applications.

At the present stage of development of organic chemistry, many basic synthetic approaches to the synthesis of 1,2,4-triazole [1,2], which exhibits a high antibacterial [3], fungicidal [4] activity. To date, it is known that modification of azole heterocycles leads to increased efficiency and reduced toxicity.

1,2,4-Triazole derivatives are widely known as antibacterial, fungicidal and antiprotozoal drugs, so it is interesting to select and analyze compounds with high antibacterial activity.

It is known that the most biologically active are those compounds whose molecule sizes provide them with optimal bioavailability. In this regard, the most promising salts and esters. Salts – due to the peculiarities of its pharmacokinetics (good dissociation, rapid absorption), and esters with low molecular weight alcohol residues – due to the relatively strong ester bond and good permeability to the cell.

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”.

Aim

The aim of the work is a computer search for the antibacterial action of new hybrids of 1,2,4-triazole-3(2*H*)-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(2*H*)-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 *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 method of random forest (WEKA-RF, Random Forest). To calculate the molecular descriptors used 6 software packages that combine both

Table 1. Parameters of QSAR classification models of antimicrobial activity of S-derivatives (1,2,4-triazole-3(2*H*)-yl)methyl)thiopyrimidines

Parameter models	Sample activity models of S-derivatives (1,2,4-triazole-3(2*H*)-yl)methyl)thiopyrimidines 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. Parameters of regression consensus QSAR models of antimicrobial activity of S-derivatives (1,2,4-triazole-3(2*H*)-yl) methyl)thiopyrimidines

Parameter models	Sample activity models of S-derivatives (1,2,4-triazole-3(2*H*)-yl)methyl)thiopyrimidines 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

q2: coefficient of cross-estimation; **R2:** square of the correlation coefficient; **RMSE:** standard error of the forecast; **MAE:** the average absolute error.

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 Sderivatives (1,2,4-triazole-3(2*H*)-yl)methyl)thiopyrimidines. 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(2*H*)-yl)methyl)thiopyrimidines against the studied cultures are presented in *Table 1*.

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(2*H*)-yl)methyl)thiopyrimidines 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(2*H*)-yl)methyl)thiopyrimidines 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(2*H*)-yl)methyl)thiopyrimidines according to regression QSAR models. General prognosis of

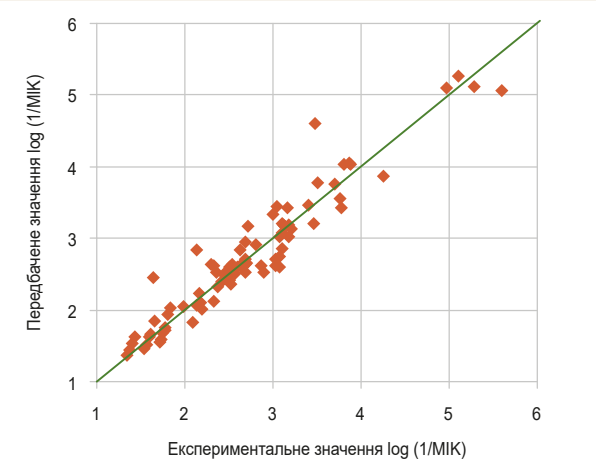

Fig. 1. Distribution of experimental and predicted log values (1/MIC) for inhibitors of *P. aeruginosa.*

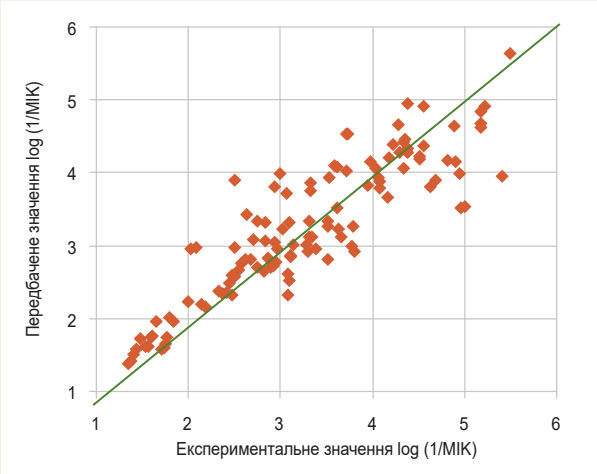

Fig. 2. Distribution of experimental and predicted log values (1/MIC) for *E. coli* inhibitors.

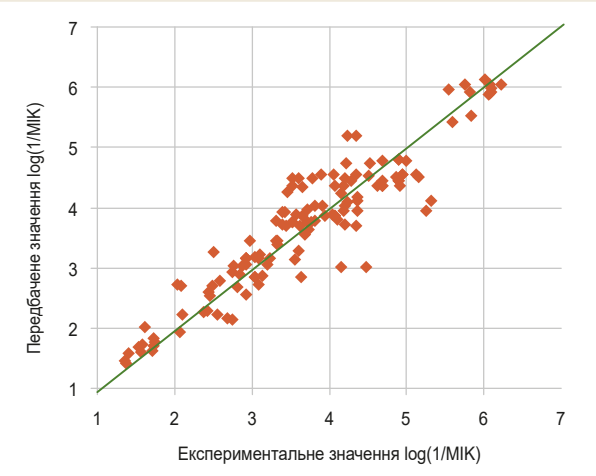

Fig. 3. Distribution of experimental and predicted log values (1/MIC) for *S. aureus* inhibitors.

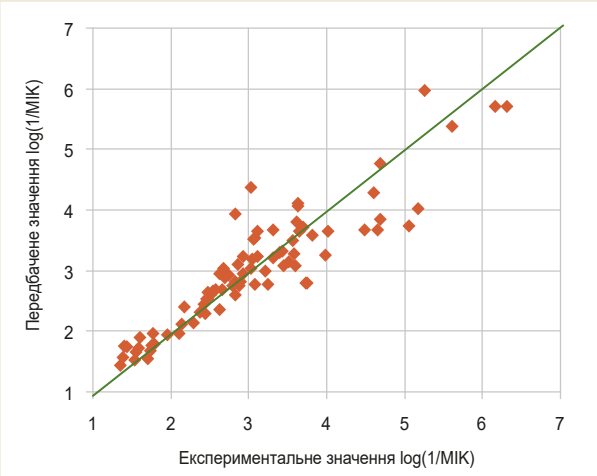

Fig. 4. Distribution of experimental and predicted values of log (1/MIC) for inhibitors of *C. albicans.*

Table 3. Prediction of antimicrobial activity of the studied Sderivatives (1,2,4triazole-3(2*H*)-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	+	–	+	+

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(2*H*)-yl)methyl)thiopyrimidines 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(2*H*)-yl)methyl)thiopyrimidines 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(2*H*)-yl)methyl) thiopyrimidines 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(2*H*)-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(2*H*)-yl)methyl)thiopyrimidines.

Conclusions

1. It was found that the studied derivatives of hybrids of 1,2,4-triazole-3(2*H*)-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(2*H*)-thiol with pyrimidine fragment .

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