QSAR prediction of toxicity for a new 1,2,4-triazole derivatives with 2-bromo-5-methoxyphenyl fragment

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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

New derivatives of 1,2,4-triazole are promising research targets due to their unique biological properties, including antimicrobial, antifungal, antitumor, and antioxidant activities. The introduction of the 2-bromo-5-methoxyphenyl fragment into the triazole structure potentially enhances these properties. However, the issue of toxicity for such compounds remains a critical factor for their further application. To reduce experimental costs and time, QSAR (Quantitative Structure-Activity Relationship) methods are widely applied, allowing to predict compounds toxicity based on their molecular structure.

The aim of this study was to evaluate the toxicity of new derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols, their acids, and esters using the QSAR method to predict parameters of acute toxicity (LD_{50}) and to assess the influence of various radicals on the toxicity of the compounds.

Materials and methods. The objects of this study were derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols, synthesized at the Department of Toxicological and Inorganic Chemistry of Zaporizhzhia State Medical and Pharmaceutical University. The nearest neighbor method was used for toxicity evaluation, applying the Toxicity Estimation Software Tool (TEST). The prediction of rats lethal dose (LD_{50}) was based on the structural similarity of the studied compounds with known substances that have experimental toxicity data.

Results. The QSAR analysis revealed that structural modifications in the derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols significantly influence their toxicity. Specifically, increasing the size of the radicals, especially through the introduction of aromatic fragments, contributed to the enhanced safety of the compounds, as evidenced by the increase in LD_{50} values. The highest LD_{50} values were observed for compounds containing phenyl radicals.

Conclusions. The results of this study indicate the feasibility of using QSAR models to predict the toxicity of 1,2,4-triazole derivatives containing a 2-bromo-5-methoxyphenyl fragment. The observed trend of increasing safety with the introduction of larger aromatic radicals can be used for the rational design of new compounds with improved toxicological properties.

Keywords: 1,2,4-triazole, QSAR, toxicity, prediction.

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QSAR-прогнозування токсичності нових похідних 1,2,4-тріазолу, що містять 2-бромо-5-метоксифенільний фрагмент

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Нові похідні 1,2,4-тріазолу – перспективні об'єкти для досліджень, оскільки мають унікальні біологічні властивості, включаючи протимікробну, протигрибкову, протипухлинну й антиоксидантну активність. Введення 2-бромо-5-метоксифенільного фрагмента в структуру тріазолу потенційно може покращити ці властивості. Проте питання щодо токсичності таких сполук залишається важливим аспектом для їх застосування надалі. Для зменшення експериментальних витрат і часу на дослідження активно застосовують методи QSAR (Quantitative Structure-Activity Relationship), що дають змогу прогнозувати токсичність сполук на основі їхньої молекулярної структури.

Мета роботи – оцінювання токсичності нових похідних 5-(2-бромо-5-метоксифеніл)-4-R-1,2,4-тріазол-3-тіолів, їхніх кислот та естерів за допомогою методу QSAR для прогнозування параметрів гострої токсичності (LD_{50}) і визначення впливу різних радикалів на токсичність сполук.

Матеріали і методи. Об'єкти дослідження – похідні 5-(2-бромо-5-метоксифеніл)-4-R-1,2,4-тріазол-3-тіолів, синтез яких здійснили на кафедрі токсикологічної та неорганічної хімії Запорізького державного медико-фармацевтичного університету. Для оцінювання токсичності використано метод найближчих сусідів із застосуванням утиліти Toxicity Estimation Software Tool (TEST). Прогнозування летальної дози (LD_{50}) для щурів ґрунтувалося на структурній схожості досліджених сполук з уже відомими речовинами, що мають експериментальні дані щодо токсичності.

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Результати. QSAR-аналіз показав, що структурні зміни в похідних 5-(2-бромо-5-метоксифеніл)-4-R-1,2,4-тріазол-3-тіолів суттєво впливають на їхню токсичність. Так, збільшення розміру радикалів, особливо введення ароматичних фрагментів, сприяє посиленню безпечності сполук. Це підтверджено збільшенням значень LD_{50}. Найвищі значення LD_{50} встановлені для сполук із фенільними радикалами.

Висновки. Результати цього дослідження свідчать про можливість використання QSAR-моделей для прогнозування токсичності похідних 1,2,4-тріазолу, що містять 2-бромо-5-метоксифенільний фрагмент. Виявлена тенденція до підвищення безпечності при введенні більших ароматичних радикалів може бути використана для раціонального дизайну нових сполук із покращеними токсикологічними властивостями.

Ключові слова: 1,2,4-тріазол, QSAR, токсичність, прогнозування.

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The relevance of the study of new 1,2,4-triazole derivatives is determined by their unique properties, in particular, a wide spectrum of biological activity [1,2]. Triazole derivatives demonstrate antimicrobial, antitumor, antifungal and antioxidant effects, which makes them promising candidates for use in pharmacology [3,4,5]. The introduction of a 2-bromo-5-methoxyphenyl fragment into the 1,2,4-triazole structure can improve these properties, but the question of their toxicity remains relevant.

In order to reduce experimental costs and time for studying the toxicity of chemical compounds, QSAR methods (Quantitative Structure-Activity relationship) are widely used. They make it possible to predict the biological activity and toxicity of substances on the basis of the molecular structure, which is especially important at the initial stages of the development of new medicines. QSAR modeling allows not only to predict the toxicity of new 1,2,4-triazole derivatives, but also to determine potential ways of modifying molecules to reduce the negative impact on the body.

QSAR methods are an effective tool for predicting the toxicity of chemical compounds. In particular, studies in recent years have shown the successful use of QSAR models for the prediction of hepatotoxicity, including compounds with triazole derivatives. These models are used to assess the potential hazards of new chemicals, which significantly reduces the cost of experimental research [6]. The article by Dahmani and colleagues describes the structural characterization and QSAR modeling of 1,2,4-triazole derivatives as α-glucosidase inhibitors. The research is aimed at establishing a connection between the structural characteristics of these compounds and their biological activity. The QSAR model was developed based on chemical descriptors, which made it possible to predict the activity of triazole derivatives and their effect on the inhibition of the α-glucosidase enzyme, which is important in the treatment of diabetes [7]. A team of scientists [8] applied the QSAR method to predict the antitumor activity of triazole derivatives, focusing on their low toxicity. The study made it possible to identify the structural features of molecules that contribute to the reduction of toxicity, with a simultaneous increase in antitumor activity.

QSAR methods allow evaluation of various aspects of toxicity, including cardiotoxicity and neurotoxicity. Research of Elhadi and Yassen [9] showed that brominated triazole derivatives can significantly influence the new compounds level toxicity. The purpose of the study was to improve QSAR models for more accurate toxicity prognostication. In addition, X. D. Chen and colleagues [10] considered mechanisms of interaction of brominated derivatives with biological macromolecules that have decisive value during the development of new medical drugs.

Thus, the relevance of this study lies in the further development of QSAR models for predicting the toxicity of new 1,2,4-triazole derivatives containing a 2-bromo-5-methoxyphenyl fragment. These models can help to reduce the risks of toxic effects and ensure the creation of safer medicines.

Aim

Studying of acute toxicity parameters of a raw of new derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols, 2-((5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazol-3-yl)thio)acetic acids and ethers of 2-((5-(2-bromo-5-methoxyphenyl)-4-R-*4H*-1,2,4-triazol-3-yl)thio)acetic acids by using QSAR analysis.

Materials and methods

Compounds whose synthesis was carried out by us earlier at the Department of Toxicological and Inorganic Chemistry of the Zaporizhzhia State Medical and Pharmaceutical University [11] *(Fig. 1)* were chosen as the object of research.

To assess the toxicity of the specified compounds, the nearest neighbor method was used, namely the Toxicity utility Estimate Software Tool (TEST). This method allows to predict the lethal dose (LD_{50}) for rats, based on the similarity between the chemical structures of the substance under study and known compounds that already have experimentally confirmed toxicity values.

The nearest neighbor method uses a database of known toxicological values for chemical compounds. TEST compares the structure of the tested substance with compounds from the database and determines the similarity coefficient (Similarity Coefficient, SC) for each of the found analogues. This coefficient varies from 0 (no similarity) to 1 (complete similarity).

LD_{50} (lethal dose 50 %) is a toxicity indicator that determines the dose of a substance (measured in mg/kg or mol/kg) that causes the death of 50 % of experimental rats. To predict this indicator, TEST uses up to 5 closest analogues with SC ≥0.5.

Identification of analogues: The TEST utility finds chemical compounds in the database, the structure of which is as

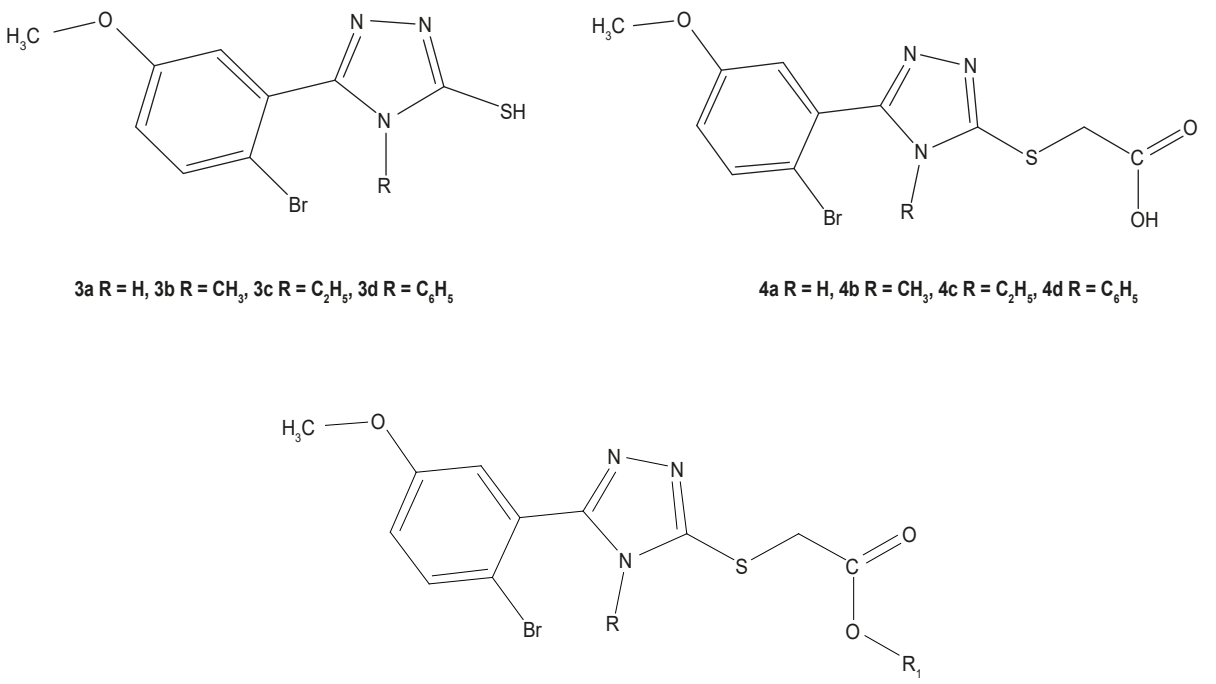

Fig. 1. Structural formulas of derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R -1,2,4-triazole-3-thiols (**3a–3d**), 2-((5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazol-3-yl)thio)acetic acids (**4a–4c**) and ethers 2-((5-(2-bromo-5-methoxyphenyl)-4-R-*4H*-1,2,4-triazol-3-yl)thio)acetic acids (**5a–5t**).

similar as possible to the structure of the substance under investigation.

Similarity Coefficient (SC): TEST calculates the SC value for each compound, showing how similar the test substance is to others for which experimental data are available.

Prediction of LD_{50}: Based on the LD_{50} values of the nearest neighbors, the utility makes a prediction for the substance under study, considering the SC value [12,13,14].

Results

As a result of the conducted QSAR analysis, it was established that changes in the structure of derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols (**3a–3d**) have a significant impact on their predicted toxicity. The main factor determining the change in LD_{50} values are various radicals at the 4th position of the 1,2,4-triazole ring *(Table 1)*.

Discussion

Alkyl substituents at the N_4 position of the 1,2,4-triazole core demonstrate increased safety (higher LD_{50} value) with increasing radical size. For example, the base compound (**3a**) has an LD_{50} value 1090.50 mg/kg, while the introduction of a methyl group (**3b**) slightly increases safety (LD_{50} 1143.96 mg/kg). Further elongation of the radical to the ethyl group (**3c**) more increases the safety (LD_{50} 1197.42 mg/kg). The lowest level of toxicity in this group is observed in compounds with phenyl group (**3d**), where the value of LD_{50} reaches 1380.49 mg/kg.

The presence of thioacetate substituents in acids **4a–4d** shows a greater impact on safety. Thus, compound **4a**, which contains a thioacetate fragment without a substituent at the N_4 position of the 1,2,4-triazole nucleus, shows the highest LD_{50} value of 1687.16 mg/kg, which indicates the highest safety among the compounds of this group. The introduction of a methyl group (**4b**) decreases the safety, with an LD_{50} of 842.38 mg/kg, and an ethyl group in **4c** gives a slight increase in safety with an LD_{50} of 858.73 mg/kg. The phenyl radical in compound **4d** increases toxicity to 656.50 mg/kg, which indicates the opposite trend in cases with thiol **3d**.

Esters of 2-((5-(2-bromo-5-methoxyphenyl)-4-R-*4H*-1,2,4-triazol-3-yl)thio)acetic acids (**5a–5t**) show even more pronounced dependence between the type of substitute and the level of safety. The predicted LD_{50} value is 1457.16 mg/kg for compound **5a** with methyl substitute, which is high indicator safety. Replacing the methyl group with an ethyl group (**5g**) increases toxicity up to 941.35 mg/kg, while the

Table 1. The obtained data of QSAR analysis of LD_{50} for derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols (**3a–3d, 4a–4c, 5a–5t**)

Compound	Oral rat LD_{50} mg/kg	Oral rat LD_{50} -Log10 (mol/kg)	Coefficient similarities (SC)
3a	1090.50	2.42	0.86–0.83
3b	1143.96	2.42	0.89–0.82
3c	1197.42	2.42	0.89–0.80
3d	1380.49	2.42	0.89–0.74
4a	1687.16	2.31	0.59–0.58
4b	842.38	2.63	0.76–0.63
4s	858.73	2.64	0.77–0.75
4d	656.50	2.81	0.83–0.72
5a	1457.16	2.39	0.63–0.61
5b	875.37	2.63	0.79–0.66
5c	908.36	2.63	0.79–0.67
5d	1316.73	2.52	0.84–0.74
5e	1514.23	2.39	0.64–0.62
5f	908.36	2.63	0.79–0.67
5g	941.35	2.63	0.79–0.68
5h	1359.26	2.52	0.83–0.75
5i	1730.84	2.35	0.65–0.63
5j	941.35	2.63	0.79–0.68
5k	974.34	2.63	0.79–0.69
5l	1401.79	2.52	0.83–0.77
5m	1730.84	2.35	0.65–0.63
5n	941.35	2.63	0.79–0.68
5o	974.34	2.63	0.79–0.69
5p	1401.79	2.52	0.82–0.76
5q	1793.71	2.35	0.66–0.64
5r	974.34	2.63	0.79–0.68
5s	1007.33	2.63	0.79–0.69
5t	1444.33	2.52	0.82–0.78

introduction of the phenyl radical (**5d**) significantly increases level safety – LD_{50} is 1316.73 mg/kg.

We observe a similar picture in the case bigger radicals, such as propyl (**5i**), where the LD_{50} value reaches 1730.84 mg/kg, which is one of the highest safety indicators in this group. Introduction of aromatic fragments (**5p, 5t**) continues upward trend safety, where predicted LD_{50} value goes to 1401.79 mg/kg and 1444.33 mg/kg respectively.

Coefficient similarity (SC) was estimated for all compounds, evaluated using the nearest-neighbor method, which reflects the structural similarity degree of the studied compounds with analogues that already have experimental value toxicity, as mentioned above. For most of the studied derivatives, SC ranged from 0.59 to 0.89. Higher SC values indicate that the test compound has greater structural similarity to known analogues, which increases the reliability of the prediction. For example, esters with available radicals of the phenyl group (**5d, 5h**) had SC similarity coefficients of 0.84–0.74, which indicates a high correspondence to the structure of their closest ones *(Table 1)*.

Conclusions

1. As a result of the research, it was established that changes in the structure of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols and their derivatives significantly affect their predicted toxicity. There is a clear trend toward increased safety (higher numerical LD_{50} values) with larger substituent size, especially when bigger aromatic radicals are introduced.

2. The obtained results of the predicted activity of the specified compounds had high similarity coefficients, which indicates a high correspondence to the structure of their closest analogues and the validity of the obtained data.

3. The described results can be used for the rational design of new derivatives with optimal toxic properties, which will allow to improve their safety profile.

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