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Molecular modeling in search of biological activity of 4-thioquinoline derivatives

Summary

Today, molecular modeling of compounds, such as derivatives of nitrogen-containing heterocycles, plays a significant role in the development of bioregulators, with quinoline derivatives being particularly important.

The peculiarities of calculating molecular structure descriptors and assessing the toxicity of quinoline derivatives have been considered. As a result of chemometric studies, molecular structure descriptors have been identified that can reduce the toxicity of compounds and increase their permeability through cell membranes.

Molecular modeling has shown that derivatives of 2-methylquinoline-4-thiol may exhibit high biological potential.

Keywords: 2-methylquinoline-4-thiols, molecular descriptors, solubility, lipophilicity, quantitative structure-activity relationship (QSAR), software for calculating biological activity and physicochemical parameters.

Introduction

The current stage of development in both chemical synthesis technologies and laboratory research techniques, as well as molecular modeling, provides the potential to use an integrated and comprehensive approach to the development of new pharmaceuticals with selective, fast-acting mechanisms and minimal contraindications.

Simultaneous use of laboratory research and computer modeling enables optimization of the workflow in terms of time and economy, making it more detailed, targeted, and understandable, while maximizing the utilization of existing experimental results.

This approach involves transforming objects in chemistry and medicine into mathematical models that can be manipulated by informatics; the reverse conversion of modeling results into datasets acceptable for real experiments, which can be interpreted, drawn conclusions from, and make forecasts. Given the absence of strict boundaries in this field, the most comprehensive application of computer technologies in medicinal chemistry is achieved through the simultaneous use of bioinformatics, cheminformatics, molecular modeling, and mathematical statistics [1-4].

Molecular modeling of biologically active compounds involves several stages that allow understanding their structure, properties, and interactions with biological systems.

The general stages of this process include:

1) Defining the goals and questions under investigation (including studying interactions with biological molecules, establishing structure-function relationships, etc.);

2) Preparation of the initial structure of the object under investigation (this can be the molecular structure of a compound, protein structure, or other biomolecule; using various molecular modeling software, calculations of energy, structure, dynamics, and other properties of the object are performed; methods such as molecular dynamics, quantum computations, virtual screening, etc., are employed; data are analyzed to study the properties and interactions of the object under investigation. This may include structural analysis, energetic properties, dynamics, interactions with other molecules, etc.);

3) Study and interpretation of the obtained results (this may include identifying key properties, interactions, and potential applications of the object under investigation).

The presented stages of molecular modeling help expand our understanding of biological processes and molecule properties, as well as develop new methods for disease diagnosis and treatment [5-8].

Compounds containing a quinoline nucleus, both as natural representatives of quinoline alkaloids and synthetically synthesized, exhibit a wide range of biological activities of varying intensity. This explains the particular interest in these compounds, primarily from medicinal chemistry, aiming to create medications based on them for the prevention and treatment of a wide range of diseases: from bacterial and viral infections to disorders of the central nervous system [9-13].

The purpose, subject and research methods

The aim of this study is to determine the molecular structure factors of 2-methylquinoline-4-thiol derivatives that influence the magnitude of their biological effects.

The object of the research is derivatives of 2-methylquinoline-4-thiol, which were used for computer modeling. These derivatives are represented in Figure 1 and Table 1.

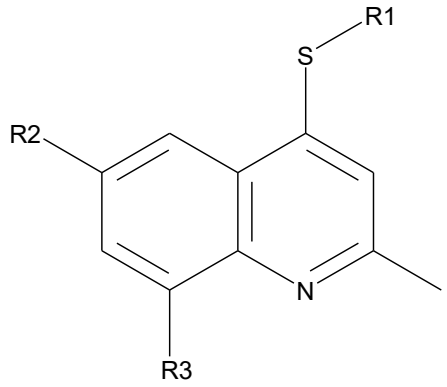

Figure 1. The general structural formula of substituted derivatives of 2-methylquinoline-4-thiol

Source: The research was conducted. 1) Mikhail Zavhorodnii Khortytsia National Academy, 59, Naukove mistechko St., Khortytsia island, Zaporizhzhia, Ukraine; 2) Oleksandr Brazhko Zaporizhzhia National University, Faculty of Biology, 66, Zhukovs'ky St., Zaporizhzhia, Ukraine; 3) Viktoriia Gencheva Zaporizhzhia National University, Faculty of Biology, 66, Zhukovs'ky St., Zaporizhzhia, Ukraine

The subject of the study is the physicochemical properties of derivatives of 2-methylquinoline-4-thiol, as well as the spatial characteristics of their molecular structure factors with the selected direction for investigation aimed at enhancing biological (primarily toxicological) properties.

Table 1. The list of compounds used for molecular modeling includes

The cipher or code for the compounds.	The IUPAC name (in English)
(1)	2-Methyl-quinoline-4-thiol
(2)	6-Methoxy-2-methyl-quinoline-4-thiol
(3)	6-Ethoxy-2-methyl-quinoline-4-thiol
(4)	6-Chloro-2-methyl-quinoline-4-thiol
(5)	6-Bromo-2-methyl-quinoline-4-thiol
(6)	6-Ethoxy-2-methyl-4-methylsulfanyl-quinoline
(7)	(2-Methyl-quinolin-4-ylsulfanyl)-acetic acid
(8)	3-(2-Methyl-quinolin-4-ylsulfanyl)-propionic acid
(9)	(6-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-acetic acid
(10)	3-(6-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(11)	(6-Ethoxy-2-methyl-quinolin-4-ylsulfanyl)-acetic acid
(12)	3-(6-Fluoro-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(13)	3-(6-Chloro-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(14)	3-(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(15)	Sodium (2-methyl-quinolin-4-ylsulfanyl)-acetate
(16)	(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetic acid
(17)	Sodium (6-bromo-2-methyl-quinolin-4-ylsulfanyl)-acetate

(18)	(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetic acid ethyl ester
(19)	2-(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetamide
(20)	(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetic acid hydrazide
(21)	2-(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-N-phenyl-acetamide
(22)	(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetic acid benzylidene-hydrazide
(23)	(6-Bromo-2-methyl-quinolin-4-ylsulfanyl)-acetic acid (4-dimethylamino-benzylidene)-hydrazide
(24)	(8-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-acetic acid
(25)	2-(8-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(26)	3-(8-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(27)	2-Amino-3-(2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(28)	2-Amino-3-(6-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(29)	2-Amino-3-(6-ethoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(30)	2-Amino-3-(6-fluoro-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(31)	2-Amino-3-(6-chloro-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(32)	2-Amino-3-(6-bromo-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(33)	2-Amino-3-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(34)	2-Amino-3-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(35)	2-Carboxyamino-3-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(36)	2-(2-Chloro-acetylamino)-3-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(37)	2-Benzoylamino-3-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(38)	3-[1-Carboxy-2-(8-methoxy-2-methyl-quinolin-4-ylsulfanyl)-ethylcarbamoyl]-acrylic acid
(39)	2-Amino-3-(5,8-dimethoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid
(40)	Sodium 2-amino-3-(2-methyl-quinolin-4-ylsulfanyl)-propionate
(41)	Sodium 2-amino-3-(6-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionate
(42)	Sodium 2-amino-3-(6-ethoxy-2-methyl-quinolin-4-ylsulfanyl)-propionate
(43)	Sodium 2-amino-3-(6-fluoro-2-methyl-quinolin-4-ylsulfanyl)-propionate
(44)	Sodium 2-amino-3-(6-chloro-2-methyl-quinolin-4-ylsulfanyl)-propionate
(45)	Sodium 2-amino-3-(6-bromo-2-methyl-quinolin-4-ylsulfanyl)-propionate
(46)	Sodium 3-(2-methyl-quinolin-4-ylsulfanyl)-propionate
(47)	Sodium 3-(6-methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionate
(48)	Sodium 3-(6-ethoxy-2-methyl-quinolin-4-ylsulfanyl)-propionate
(49)	Sodium 3-(6-fluoro-2-methyl-quinolin-4-ylsulfanyl)-propionate
(50)	Sodium 3-(6-chloro-2-methyl-quinolin-4-ylsulfanyl)-propionate
(51)	Sodium 3-(6-bromo-2-methyl-quinolin-4-ylsulfanyl)-propionate
(52)	3-(2-Methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(53)	3-(6-Methoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(54)	3-(6-Ethoxy-2-methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(55)	3-(6-Fluoro-2-methyl-quinolin-4-ylsulfanyl)-propionic acid methyl ester
(56)	4-[(2-aminoethyl)sulfanyl]-2-methylquinoline dihydrochloride

(57)	2-[(6-Methoxy-2-methyl-4-quinolinyl)sulfanyl]ethanamine dihydrochloride
(58)	2-[(6-Ethoxy-2-methyl-4-quinolinyl)sulfanyl]ethanamine
(59)	2-[(6-Fluoro-2-methyl-4-quinolinyl)sulfanyl]ethanamine
(60)	N-[1-Carboxy-2-(6-ethoxy-2-methyl-quinolin-4-ylsulfanyl)-ethyl]-succinamic acid
(61)	N-[1-Carboxy-2-(5;8-dimethoxy-2-methyl-quinolin-4-ylsulfanyl)-ethyl]-succinamic acid
(62)	8-Methoxy-2-methyl-quinoline-4-thiol
(63)	Sodium (6-methoxy-2-methyl-quinolin-4-ylsulfanyl)-acetate
(64)	5,8-Dimethoxy-2-methyl-quinoline-4-thiol

Source: The research was conducted. 1) Mikhail Zavhorodnii Khortytsia National Academy, 59, Naukove mistechko St., Khortytsia island, Zaporizhzhia, Ukraine; 2) Oleksandr Brazhko Zaporizhzhia National University, Faculty of Biology, 66, Zhukovs'ky St., Zaporizhzhia, Ukraine

The synthesis of derivatives of 2-methylquinoline-4-thiol, which served as the basis for virtual screening based on the structural features of the biological target and QSAR studies, constitutes a part of the laboratory's long-standing experimental database in the Biotechnology of Physiologically Active Substances at Zaporizhzhia National University [14-24].

Calculation of molecular structure descriptors

Determination of physicochemical characteristics and biological activity indicators based on selected parameters. Based on a series of publications, the main physicochemical indicators and indicators of biological activity were selected to determine the fundamental possibility of compounds under investigation exhibiting a biological effect (i.e., to determine the probability that these compounds are biologically active and affect the metabolism of living organisms) and the likelihood that this effect will be toxic in nature. It is reasonable to hypothesize that a compound showing signs of being biologically active while simultaneously having low predicted toxicity levels may potentially serve as a prototype for a therapeutic agent [25-28].

The set of compounds under investigation was prepared in advance for the study. The selection of conformers for the presented compounds was performed using the AmberTools16 software. Energy minimization was carried out using the molecular mechanics method with force field parameters assigned to atoms in the MMFF94 force field. The average calculated potential energy value of the obtained conformations of the investigated compounds was approximately 140 kJ/mol, indicating good spatial geometry minimization. Alignment of the compounds was conducted using the OBFIT program, which is part of the OpenBabel software suite.

The root-mean-square deviation (RMSD) value for atomic positions, indicating the average deviation between aligned structures, was 0.26, which is indicative of good structural alignment

despite significant differences in the length of the carbon ring and the degree of substituent branching. The shape similarity index for neutral compounds (excluding salts) averaged at 0.77. The charge-weighted shape similarity index averaged at 0.58, indicating significant differences in the localization of electronic density on corresponding functional groups among the investigated compounds.

Toxicity assessment

For the initial stage of the study, the following software was utilized for calculating biological activity and physicochemical parameters:

TEST (Toxicity Estimation Software Tool) – Developed by a scientific group within the United States Environmental Protection Agency (US EPA), TEST is a software suite comprising:

– Built-in QSAR models for toxicity prediction QSPR models for predicting physicochemical properties;

– An automated algorithm (without user customization options) for constructing QSAR models using multiple statistical approaches Built-in databases with reliable information on certain physicochemical properties and toxicological characteristics of thousands of organic compounds.

For the initial stage of the investigation, the following software was employed for calculating biological activity and physicochemical parameters:

This software tool implements the following algorithms for building mathematical models and calculating predicted values: Fisher Discriminant Analysis, hierarchical method, single-model method based on genetic algorithm, additive method (Group Contribution Method), nearest neighbor method, Random Forest Method, and consensus prediction method - averaging the results obtained by all the mentioned methods.

Among the selected final investigation parameters, the following indicators are included:

1) Fathead minnow LC50 96 hr – represents the concentration of the compound being studied in the water phase, which kills half of the Pimephales promelas over four days (96 hours). Data for predicting this value were borrowed from the ECOTOX water phase toxicant database (filtered by parameters such as “clean water”, “laboratory study, 96 hours”, “compounds consisting only of elements C, H, O, N, F, Cl, Br, I, S, P, Si, As”, “pure compounds, not salts”), which includes 823 compounds of various classes.

2) Daphnia magna LC50 48 hr - represents the concentration of the compound in the water phase that kills half of the Daphnia magna population within 48 hours. The database and filtration criteria are similar to the “Fathead minnow LC50 96hr” parameter, with a total sample size of 353 compounds.

3) Tetrahymena pyriforms IGC50 48 hr – represents the concentration of the compound that inhibits the development of Tetrahymena pyriforms by 50% after 48 hours. The total compound sample size is 1792.

4) Bioaccumulation factor (bioconcentration factor – BCF) – determines the concentration of a chemical substance in biota as a result of absorption through respiratory surfaces, relative to the concentration in water in a steady state. Data were collected from several different databases. The final dataset consists of 676 chemical compounds (after removal of salts and mixtures).

5) Developmental Toxicity – a test for negative effects on intrauterine development. It is determined by a substance's ability to cause toxic effects in the organism of humans or animals. Experimentally defined as any influence that disrupts normal development both before and after birth. The sample size consists of 293 compounds.

6) Mutagenicity (Ames test) – a genetic test using Salmonella typhimurium bacteria as the test object. It is used to assess the mutagenic potential of chemical compounds. A positive result in the test indicates that the chemical compound may have carcinogenic effects. The sample size consists of 5743 compounds.

7) Water solubility – a parameter indicating the compound's solubility, calculated based on data for 5020 compounds.

ALogP/S (from VCCLab) – This software is presented as a service for calculating lipophilicity (LogP) and water solubility (LogS) parameters. The principal advantage of this service is that the final result represents the arithmetic mean among the obtained values of these parameters calculated using different methods.

For the second stage of the research, which involved systematic molecular docking, the following software tools were utilized:

AutoDock Vina – Software for conducting molecular docking directly. Among its features compared to similar software tools are its widespread use in scientific circles, relative ease of use, and speed of operation. Additionally, this software allows for both "rigid" docking (where only the ligand molecule is conformationally labile) and "flexible" docking (where the receptor itself can change its relative spatial positions of its structural components).

PaDEL-ADV – Software for automating part of the molecular docking process, namely: technical preparation of files with ligand and receptor structures for the AutoDock Vina program, automatic renaming of files, and packaging them into archives for more convenient further work with the final results.

In addition to the above, the following software tools were used at each stage:

1) AMBER (Assisted Model Building with Energy Refinement) – A molecular dynamics software package that models AMBER force fields. AMBER is a family of force fields

specifically designed for molecular dynamics of biomolecules. The AmberTools16 software package was used to optimize the geometry of the investigated ligands (2-methylquinolin-4-thiols) as well as the investigated receptor - superoxide dismutase SOD1.

2) OpenBabel – An expert system and file converter for chemical data between different formats. This software suite was used for internal conversion of molecule structures between different formats and for further processing of structures (e.g., removing water molecules, protons, centering molecules about the origin, etc.).

3) UCFS Chimera – Software developed with the ability to flexibly extend functionality for interactive visualization and analysis of molecular structures and related data, including density maps, supramolecular ensembles, molecule alignments, analysis of docking results, molecular dynamics trajectories, and conformational ensembles. Among its features, UCFS Chimera also integrates other software, including AutoDock Vina and AMBER. Another functional capability of this software is the visual analysis and editing of spatial images of structures and recording video analysis of molecular structures dynamically.

Results of the research

The computer experiment involved conducting molecular modeling.

For a comprehensive analysis of the investigated compounds, we calculated both selected physicochemical properties (solubility and lipophilicity) and biological activity indicators.

The first step was the calculation of lipophilicity and solubility indicators using the ALogP/S software from VCCLab. The results are presented in Table 2.

Table 2. The indicators of lipophilicity (LogP) and water solubility (LogS) were calculated using the ALogP/S software

The cipher or code for the compounds.	LogP	LogS	№№ compounds	LogP	LogS
(1)	2.83	-3.78	(33)	-0.66	-3.67
(2)	2.83	-3.89	(34)	2.32	-3.67
(3)	3,36	-4.15	(35)	1.79	-4.21
(4)	3.43	-4.32	(36)	1.81	-4.84
(5)	3.37	-4.52	(37)	3.15	-5.45
(6)	3.89	-4.33	(38)	1.7	-4.88
(7)	2.1	-3.73	(39)	-0.6	-3.6
(8)	2.42	-3.93	(40)	1.95	-3.38
(9)	2.24	-3.99	(41)	1.93	-3.41
(10)	2.54	-4.18	(42)	2.6	-3.62
(11)	2.92	-4.25	(43)	1.98	-3.58

(12)	2.63	-4.0	(44)	2.48	-3.8
(13)	3.2	-4.45	(45)	2.87	-4.4
(14)	3.24	-4.9	(46)	3.14	-3.84
(15)	2.83	-3.51	(47)	3.11	-4.23
(16)	2.98	-4.59	(48)	3.59	-4.49
(17)	3.37	-4.57	(49)	2.9	-3,92
(18)	4.21	-5.15	(50)	3.54	-4.57
(19)	2.83	-4.53	(51)	2.9	-3.92
(20)	2.79	-4.54	(52)	3.54	-4.57
(21)	4.84	-5.88	(53)	3.85	-4.91
(22)	3.72	-5.84	(54)	3.67	-4.31
(23)	4.25	-5.77	(55)	3.39	-4.48
(24)	2.17	-3.96	(56)	2.42	-3.27
(25)	2.71	-4.15	(57)	2.51	-3.39
(26)	3.38	-4.44	(58)	3.07	-3.65
(27)	-0.67	-3.43	(59)	2.51	-3.79
(28)	-0.67	-3.71	(60)	1.46	-4.66
(29)	-0.19	3.95	(61)	1.35	-4.44
(30)	-0.67	-3.57	(62)	2.8	-3.87
(31)	-0.14	-4.13	(63)	2.85	-3.96
(32)	-0.03	-4.5	(64)	2.79	-3.81

Source: The research was conducted. 1) Mikhail Zavhorodnii Khortytsia National Academy, 59, Naukove mistechko St., Khortytsia island, Zaporizhzhia, Ukraine; 2) Oleksandr Brazhko Zaporizhzhia National University, Faculty of Biology, 66, Zhukovs'ky St., Zaporizhzhia, Ukraine

The values of lipophilicity indicators (LogP) of the investigated compounds range from -0.03 to 4.84. The average value is approximately 2.50, which falls within the intermediate range of LogP = 2-3 optimal for oral pharmaceuticals.

It can be noted that compounds with the main functional group being the residue of propionic acid with an amino group at the 2nd position exhibit significant deviation from the average LogP value into the negative range. Moreover, the complication or substitution of the amino group at the second position increases the LogP value. The compound (21) – 2-(6-Bromo-2-methylquinolin-4-ylsulfanyl)-N-phenylacetamide, which has the maximum LogP value, can be explained by the presence of a phenyl residue.

The solubility index ranges from -5.88 to -3.27, with an average value of approximately -4.22. Among the features, minimal values are observed in compounds (21, 22, 23), which have aromatic residues.

The next step involved calculating the indicators of biological activity using the TEST software. The primary results of the analysis of biological activity indicators are presented in Table 3.

Table 3. Report Information for the Values of Biological Activity Indicators Calculated Using the TEST Software

Parameter	Minimum	Maximum	Examples of compounds with maximum or minimum values"
Bioaccumulation factor (log units)	0.31	56.79	Compounds (53, 54) have maximum values.
LC50 for Daphnia magna at 48 hours (mg/L)	0.16	56.54	Compounds (22, 23) have minimum values.
Developmental Toxicity (arbitrary units)	All compounds have positive values, except compounds (2-5, 59, 62).		
LC50 for Fathead minnow at 96 hours (mg/L)	0.00375	8.15	Compounds (22, 23) have the minimum values.
Mutagenicity, Ames test	Among the compounds predicted as non-mutagenic (13, 21-23, 31, 35-38, 60, 61)		
LD50 for rats, oral (mg/kg)	360.19	4274.19	Compounds (1, 7, 20, 23) have minimum values.
Water solubility (mg/L)	0.38	413.41	Compounds (21-23) have minimum values

Source: The research was conducted. 1) Mikhail Zavhorodnii Khortytsia National Academy, 59, Naukove mistechko St., Khortytsia island, Zaporizhzhia, Ukraine; 2) Oleksandr Brazhko Zaporizhzhia National University, Faculty of Biology, 66, Zhukovs'ky St., Zaporizhzhia, Ukraine

In summary, compounds (20-23, 53, 54) were identified as the most toxic (while having some of the highest LogP values and some of the lowest LogS values).

It can be summarized that there is a tendency for toxicity to increase (decreasing the concentration of the compound causing the toxic effect) with an increase in the bioaccumulation factor and a decrease in water solubility. The likelihood of a toxic effect increases if the LogP value exceeds one, and the total number of atoms is less than 30.

At the same time, an increase in the number of carboxyl and methyl groups correlates with a decrease in toxic effect. This trend is generalized and applies only to the majority of the compounds investigated, indicating a more complex relationship between the toxic effects and the metabolism of compounds in living organisms.

Comparing the obtained data with the LD50 values for compounds in mice [23, 27], a pattern emerges where compounds with the highest affinity generally have higher LD50 values, indicating lower toxicity. Additionally, 8 out of 11 compounds predicted as potentially non-mutagenic have the highest degree of affinity. Conversely, a decrease in affinity correlates with a decrease in LD50 values for mice.

Thus, the following generalizations can be made:

1) Compounds with the highest toxicity values tend to have the lowest water solubility, while moderate LogP values ranging from 0.0 to 2.5 correlate with lower toxicity.

2) Compounds (31, 32, 35, 38, 60, 6) are identified as the most promising candidates for potential drug agents.

Conclusion

The chemometric studies conducted have allowed the identification of molecular descriptors of structure that decrease the toxicity of compounds and increase their permeability through cell membranes. The data obtained from molecular modeling indicate that the compounds under investigation exhibit high biological potential.

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