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Synthesis of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone with analgesic activity

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Quinazolin-4(3H)-one derivatives are characterized by a wide range of pharmacological properties, among which the most significant one is a pronounced effect on the central nervous system. In this regard, a molecular design of biologically active compounds that have an analgesic activity due to the formation of ligand-receptor complexes with nociceptive and dopamine receptors, has been performed.

The aim of the study was a molecular design and a subsequent targeted synthesis of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone with an analgesic activity, as well as the creation of a mathematical model in order to identify significant molecular descriptors.

Materials and methods. A molecular design was carried out by a logical-structural approach using the PASS program with the identification of the biological activity of the predicted structures, as well as the energy calculation of the ligand-receptor interaction. The synthesis of 2-phenyl derivatives of 4(3H)-quinazolinone was carried out by the reaction of 2-aminobenzamide with aromatic aldehydes in polyphosphoric acid when heated, while the 2-benzyl derivatives were synthesized by fusing amides of anthranilic and homoveratric acids followed by sulfonation with sulfuric acid. The analgesic activity of the synthesized compounds was studied in the models of nociceptive reactions induced by chemical stimuli (a formalin test and “acetic acid writhings”).

Results. A molecular design made it possible to identify promising structures in the series of 4(3H)-quinazolinone derivatives that affect nociceptive and dopamine receptors and have an analgesic activity. A modification was made to the synthesis of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone in order to increase the yield of the target products by a simpler and more cost-effective method. The predicted compounds were synthesized by cyclocondensation of anthranilic acid amide with aromatic aldehydes or with homoveraic acid amide. It follows from the primary pharmacological studies results that the synthesized substances are promising from the point of view of creating painkillers based on them. A structure-activity relationship between the molecular descriptors, which are largely responsible for the analgesic activity, and the results of biological tests, has been revealed.

Conclusion. The use of computer modelling made it possible to identify the amino acid residues involved in the formation of the ligand-receptor complex with the nociceptive receptor, and to construct a mathematical model to explain the analgesic activity of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone. Modified procedures for the synthesis of target compounds have been proposed. The obtained coefficients of the approximation between the theoretical values and the data of the pharmacological experiment make it possible to state a sufficient reliability of the carried out studies.

Keywords: molecular design; quinazolin-4(3H)-one derivatives; dopaminergic compounds; nociceptive receptors; analgesic activity; cyclocondensation; anthranilamide; aromatic aldehydes; homoveratric acid amide; molecular descriptors

Abbreviations: CNS – central nervous system; BACs – biologically active compounds; PPA – polyphosphoric acid; LUMO – lowest unoccupied molecular orbital; DMSO – dimethyl sulfoxide.

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Синтез 2-фенил- и 2-бензилпроизводных хиназолин-4(3*H*)-она, обладающих анальгезирующей активностью

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Известно, что производные хиназолин-4(3*H*)-она обладают широким спектром фармакологических свойств, среди которых наиболее значимым является выраженное влияние на центральную нервную систему. В связи с этим нами выполнено молекулярное конструирование биологически активных соединений, обладающих анальгезирующей активностью за счет образования лиганд-рецепторных комплексов с ноцицептивными и дофаминовыми рецепторами.

Цель. Молекулярное конструирование и последующий целенаправленный синтез 2-фенил- и 2-бензилпроизводных хиназолин-4(3*H*)-она, обладающих анальгезирующей активностью, а также создание математической модели с целью выявления значимых молекулярных дескрипторов.

Материалы и методы. Молекулярное конструирование проводилось с помощью логико-структурного подхода посредством программы PASS с выявлением биологической активности прогнозируемых структур, а также расчетом энергии лиганд-рецепторного взаимодействия. Синтез 2-фенилпроизводных хиназолин-4(3*H*)-она осуществляли взаимодействием 2-аминобензамида с ароматическими альдегидами в полифосфорной кислоте при нагревании, а 2-бензилпроизводных – сплавлением амидов антраниловой и гомовератровой кислот с последующим сульфированием серной кислотой. Анальгезирующую активность синтезированных соединений изучали на моделях ноцицептивных реакций, вызванных химическими стимулами (формалиновый тест и «уксусные корчи»).

Результаты. Молекулярное конструирование позволило выявить перспективные структуры в ряду производных хиназолин-4(3*H*)-она, влияющие на ноцицептивные и дофаминовые рецепторы и обладающие анальгезирующей активностью. Осуществлена модификация синтеза 2-фенил- и 2-бензилпроизводных хиназолин-4(3*H*)-она с целью повышения выхода целевых продуктов посредством более простого и экономически выгодного способа. Прогнозируемые соединения синтезированы циклоконденсацией амида антраниловой кислоты с ароматическими альдегидами или с амидом гомовератровой кислоты. Из результатов первичных фармакологических исследований следует, что синтезированные вещества перспективны с точки зрения создания на их основе обезболивающих средств. Выявлена взаимосвязь структура-активность между молекулярными дескрипторами, в значительной степени отвечающими за анальгезирующую активность, и результатами биологических тестов.

Заключение. Использование компьютерного моделирования позволило выявить аминокислотные остатки, участвующие в образовании лиганд-рецепторного комплекса с ноцицептивным рецептором и построить математическую модель, позволяющую объяснить обезболивающую активность 2-фенил- и 2-бензилпроизводных хиназолин-4(3*H*)-она. Предлагаются модифицированные методики синтеза целевых соединений. Полученные коэффициенты аппроксимации между теоретическими значениями и данными фармакологического эксперимента позволяют констатировать достаточную достоверность проведенных исследований.

Ключевые слова: молекулярное конструирование; производные хиназолин-4(3*H*)-она; дофаминергические соединения; ноцицептивные рецепторы; анальгезирующая активность; реакция циклоконденсации; антраниламид; ароматические альдегиды; амид гомовератровой кислоты; молекулярные дескрипторы

Список сокращений: ЦНС – центральная нервная система; БАС – биологически активные соединения; ПФК – полифосфорная кислота; НСМО – низшая свободная молекулярная орбиталь; ДМСО – диметилсульфоксид

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INTRODUCTION

The targeted search for new highly effective and safe drug substances that affect the CNS is an urgent task of pharmacy [1-3]. The empirical approach used in the synthetic preparation of new compounds with a biological activity is insufficiently productive and efficient [4–7]. It is possible to significantly increase the effectiveness of the search for biologically active compounds (BACs) with the molecular modeling aimed at finding structures with the targeted pharmacological action [8–11]. When designing substances that affect the CNS, special attention is paid to the prediction of ligand-receptor interactions, which makes possible not only to purposefully synthesize new pharmacologically active compounds, but also to effectively plan a pharmacological experiment.

The neurotropic effect of a number of 4(3H)-quinazolinone derivatives has been shown, and the search for BACs substances that exhibit analgesic an activity in this group, is of considerable interest [12, 13]. The modified synthesis procedure given in the article, makes possible to expand the boundaries of the preparative possibilities for obtaining 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone, which leads to the synthesis of the target products with desired pharmacological properties. The introduction of substituents in position 2 of the pyrimidine ring containing hydroxy and methoxy groups, leads to the modeling and completion of additional cycles in the creation of a significant series of polyheterocyclic and coordination compounds. The revealed structure-activity relationships and molecular descriptors responsible for the effect on the central nervous system will further make possible a more efficient search for BACs with an analgesic action containing classical pharmacophore fragments inherent in anesthetics.

The choice of hydroxy and methoxy substituents in the 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone synthesized in the phenyl and benzyl fragments is due to their similarity in electronic effects, which made it possible to reveal a correlation between the values obtained in the course of the molecular design and the results of the pharmacological experiment. In addition, since the hydroxy and methoxy substituents are electron-donating, this will make it possible to vary the structure of the resulting quinazolinones over a fairly wide range due to the electrophilic substitution in the phenyl and benzyl fragments in position 2, including, with a subsequent heterocyclization, to one of the nitrogen atoms [14–17]. It is noteworthy that in one of the latest works, in which the prospects of using a number of nitrogen-containing heterocycles were evaluated *in silico*, 2-(4-methoxyphenyl)-3-amino(3,4,5-trihydroxybenzylidene)-4(3H)-quinazolinone was identified as the leader having just such substituents [18].

The unrelenting interest in quinazolinone derivatives is caused by a wide range of their biological activity, which began with a pharmacognostic study of the plant extracts containing alkaloids, the structural basis of which is the core of this heterocycle. One of the first alkaloids of this kind, which was isolated in a pure form from the extract of *Glycosmis arborea* (Roxb.) DC. and other plants of this genus [19], is arborine, which is 2-benzylquinazolinon.

The possibility of using quinaline and quinazoline alkaloids in the fight against COVID-19 is being intensively studied [20], including the study on the basis of a theoretical structure-activity study.

In recent years, interest in quinazolinone derivatives has been significantly stimulated by the search for and study of their luminescent properties [21]. A new trend in this area is the synthesis of ligand systems and the preparation of multifunctional coordination compounds based on them, which have a number of practically significant properties [22, 23].

THE AIM of the study was a molecular design and a subsequent targeted synthesis of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone with an analgesic activity, as well as the creation of a mathematical model in order to identify significant molecular descriptors.

MATERIALS AND METHODS

Prognostic part

A preliminary prediction of a biological activity was carried out using the web service of the PASS program (Prediction of Activity Spectra for Substances, Russia; Protected Online PASS Application) [24].

Geometry optimization, calculation of the enthalpy and the lowest unoccupied molecular orbital (LUMO) of the structures under study were carried out by semi-empirical AM1 and Monte Carlo methods and using the HyperChem 6.0.9 program (in free access). To model the ligand-receptor interaction with dopamine and nociceptive receptors using the molecular docking method, the Molegro Virtual Docker 6.0.1 program (a demo version) was used, the calculations of which are based on the molecular calculation algorithm – MolDockScore. This program was used to simulate the 50 most stable conformations of the studied substances in the active center of the dopamine and nociceptive receptors. The results obtained were optimized in accordance with the published experimental data of the

X-ray diffraction analysis of the protein-ligand complex [25]. To study the energy components of the spatial-conformational interactions of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone with the dopamine receptor binding site, the 3D structure of the protein-ligand complex with the identification code 5WIU and the nociceptive receptor 4EA3 was used. These protein-ligand complexes are presented in the RCSB Protein Data Bank.

Synthetic part

General procedure for compounds III–VII synthesis. A mixture solution consisting of 0.01 mol of 2-aminobenzamide (**I**) and 0.01 mol of the corresponding aromatic aldehyde (**II**) in 50 g of polyphosphoric acid was heated for 30 minat the temperature of 80–90°C. The precipitation formed after the reaction mixture hydrolysis, was filtered off and recrystallized from glacial acetic acid. The yields of the reaction products were 75–82%.

Synthesis of 2-(3,4-dimethoxybenzyl)-4(3H)quinazolinone VIII. The mixture melt – 19.5 g (0.1 mol) of homoveratric (3,4-dimethoxyphenylacetic) acid amide and 15.2 g (0.11 mol) of 2-aminobenzamide (**I**) – was heated in an open vessel at 110–120°C until the release of the water vapor (~40–60 min). The melt was cooled to 90–70°C and diluted with 100 ml of acetic acid heated to the same temperature. The crystalline precipitate formed after cooling was filtered off, washed twice with cold isopropyl alcohol, and dried at room temperature. The yield was 79-82%, melting point (m.p.) was 225–226°C (colorless crystals).

^{1}H NMR spectrum (300 MHz), δ, ppm, DMSO-d6: 3.70 (s, 3H, OCH3), 3.74 (s, 3H, OCH3), 3.00 (s, 2H, CH2), 6.91 (d, 1H, Ar), 6.93 (d, 1H, Ar), 7.07 (s, 1H, Ar), 7.58 (t, 1H, Ar), 7.67 (d, 1H, Ar), 7.88 (t, 1H, Ar), 8.11 (d, 1H, Ar).

Synthesis of 6-sulfo-2-(3,4-dimethoxybenzyl)-4(3H)-quinazolinone IX. At room temperature and stirring, 3.0 g (0.01 mol) of 2-(3,4-dimethoxybenzyl)quinazolin-4(3H)-one (**VIII**) was dissolved in 15 ml of concentrated sulfuric acid. The homogeneous reaction mixture was kept for 10-12 h at room temperature and introduced into 150 g of an ice water mixture. The colorless precipitate formed was filtered off and washed thoroughly with water and isopropyl alcohol. The yield was 80%, m.p. >300°C.

^{1}H NMR (600 MHz), δ, ppm, DMSO-d6: 3.55 (s, 6H, 2OCH3), 4.70 (s, 2H, CH2), 6.94 (s, 1H, Ar) , 7.38 (s, 1H, Ar), 7.20–7.55 (d+t, 2H, Ar), 7.83 (t, 1H, Ar), 8.25 (d, 2H, Ar).

The air-dried product was used further without any further purification.

In vivo studies

Study animals

A primary pharmacological screening was performed on adult white Wistar female rats weighing 200–220 g (178 animals, 9–10 animals in a randomly formed group). The animals were kept with a free access to water and food under standard vivarium conditions. The requirement for the care of animals was accomplished in accordance with European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes.

The experiments were performed in accordance with the standards of the Russian Federation legislation (GOST R 33044-2014, GOST R 33647-2015), the technical standards of Good Laboratory Practice of the Eurasian Economic Union (ICH GCP). The studies were carried out in compliance with the bioethical standards, approved by the local ethics committee of Stavropol State Medical University (Protocol No. 89 dated March 18, 2020).

Study of specific activity

The assessment of the peripheral level of the pain sensitivity and, consequently, the magnitude of the analgesic activity of the synthesized compounds was determined using models of nociceptive reactions[1] induced by chemical stimuli (a formalin test and "acetic acid writhings") [26].

A formalin test was used to assess the somatic pain. In this test, hyperalgesia was modeled by a subplantar injection – 50 µl of a 2% formalin aqueous solution (CJSC Base No. 1 Himreaktivov, Russia) with an insulin syringe (Elets MPK, Russia) into the dorsal surface of the right hind paw. The phases of the nociceptive response were recorded by a number of pain reactions ("flinches": raising the paw, licking, biting the injection site) from the moment of the formalin administration and throughout the entire observation time – 60 min. The magnitude of the analgesic activity of the studied substances was assessed in total, as well as separately for phases I (the first 10 min) and II (10–60 min) of the nociceptive response to reduce the number of pain reactions in comparison with the indicators in control animals taken as 100%.

The "acetic acid writhings" test was used to evaluate the peritovisceral pain caused by algogens. This test is a model of visceral nociception and is used to study the peripheral analgesic activity of new substances through the chemical stimulation method of peritoneal nociceptors and the corresponding motor responses[2].

[1] Voronina TA, Guzevatykh LS. Metodicheskiye rekomendatsii po izucheniyu anal'geticheskoy aktivnosti lekarstvennykh sredstv [Methodical recommendations for the study of the analgesic activity of drugs]. Guidelines for conducting preclinical studies of drugs. Mironov A.N. editor; Moscow: Grif and K, 2012. – P. 197–218. Russian

[2] Ibid.

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This pain reaction was induced by an intraperitoneal injection of a 1% acetic acid (Laverna, Russia). An analgesic activity was assessed by a decrease in the number of "writhings" ("writhings" are contractions of the abdominal muscles, alternating with their relaxation, stretching of the hind limbs, arching of the back, resembling pain in peritonitis) for a 15-minute observation period after the administration of an acetic acid solution in the % relative to the indicators of the control group of animals, taken as 100%.

The compounds under study (lab codes: III, IV, V, VI, VII, VIII, IX) investigated at the dose of 2/10 of the molecular weight in mg/kg (III – 47.6 mg/kg; IV – 53.6 mg/kg; V – 53.6 mg/kg; VI – 53.6 mg/kg; VII – 56.4 mg/kg; VIII – 59.2 mg/kg; IX – 75.2 mg/kg).

Lidocaine (the injection solution of 20 mg/ml, 2 ml, Dalchimpharm, Russia) at the dose of 1 mg/kg was used as a reference drug. All compounds of the studied series, the reference drug, the saline solution (OJSC "Borisov Plant of Medical Preparations", Belarus) were administered to the control animals (0.4 ml) intraperitoneally once 40 min before the administration of chemical stimuli. The doses of the studied substances and the reference drug were selected taking into account the literature data [27, 28] and the dose titration method.

Statistical processing of results

A statistical analysis of the results was carried out using the following software packages: "Microsoft Excel 2010" (Microsoft Office, USA), "Statistica 10" (Statsoft, USA), "BIOSTAT" (Glantz, McGraw Hill, USA). The normality of the obtained data distribution was determined using the Shapiro-Wilk test. When comparing independent normally distributed data, a one-way analysis of variance with the Dunnett's test (a multiple comparison with the control group) was used. When the distribution of study data was different from the normal, the Kruskal-Wallis test the post hoc Dunn's test was used. The differences were considered statistically significant at $p < 0.05$.

Predictive experiment *in silico*

Molecular descriptors were calculated using the T.E.S.T. (Toxicity Estimation Software Tool. EPA, USA – An official website of the United States government), which makes it possible to obtain information about 794 descriptors associated with the 2D compounds structure. A correlation analysis was carried out between dependent variables representing biological activity data and independent variables, including the energy of interaction with amino acid residues, energy values (Total Energy), as well as molecular descriptors. In constructing the mathematical model, methods of a linear regression and the least squares regression, as well as a sliding control over individual objects (leave-one-outcross-validation), were used.

RESULTS

Based on the logical-structural approach, a group of virtual quinazolin-4(3H)-one derivatives was formed. At the first stage of a computer modeling of the structures, the biological activity was predicted using the PASS program, the results of which for the most promising compounds are shown in Table 1.

Table 1 shows that almost all hydroxyphenyl derivatives isolated from the total array can be characterized by an effect on the central nervous system, have broncholytic, antiulcer and anti-ischemic effects. In addition to the structure of 2-dimethoxyphenyl substituted VII, the structures containing hydroxymethoxyphenyl residues (IV, V, VI) and a dimethoxybenzyl fragment, can affect the release of dopamine. All the predicted compounds, except substance VII, can have an antiviral activity and cardioprotective effects. The introduction of the 2-dimethoxybenzyl fragment of the sulfo group into the aromatic nucleus can lead to an increase in the antiulcer activity and the loss of a stimulating effect on the release of neurotransmitters – dopamine and serotonin.

The results of the molecular docking in a series of 4(3H)-quinazolinone derivatives with nociceptive and dopamine receptors are presented in Table 2.

The values of the minimum and average energies of interaction with nociceptive and dopamine receptors for 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone suggest that compound IX should exhibit the greatest dopaminergic activity, since its ligand-receptor complex with the dopamine receptor is characterized by the greatest sustainability. This compound appears to be superior to other predicted 2-phenyl derivatives, and compound VIII forms less stable ligand-receptor complexes than compound IX.

For the synthesis of 2-phenyl derivatives III–VII, a modified procedure was developed that does not require the use of an oxidizing agent.

Syntheses of 2-phenyl-substituted derivatives of 4(3H)-quinazolinone , realized by the cyclocondensation of anthranilic acid azomethines, which are easily formed by the interaction of aldehydes and its N-acylated amides, are described. However, the cyclization process itself proceeds rather difficultly in the presence of strong oxidizing agents (diacetoxyiodo)benzene or potassium permanganate [29, 30].

The proposed optimized procedure for the synthesis of hydroxy- and methoxyphenyl derivatives of 4(3H)-quinazolinone is based on the interaction of equimolar amounts of anthranilic acid amide and the

corresponding aromatic aldehydes in a polyphosphoric acid (PPA) medium. The desired effect is achieved due to the fact that, unlike aromatic carboxylic acids, their corresponding aldehydes are highly soluble in PPA.

The scheme for obtaining target compounds (III–VII) is shown below (Fig. 1).

In order to increase the yield of target 2-phenyl derivatives of 4(3*H*)-quinazolinone, a synthesis method using polyphosphoric acid is used. This method is simpler and makes it possible to obtain target products with the yields varying from 79 to 82%.

The synthesis of 2-benzyl derivatives of 4(3H)-quinazolinone was carried out by fusing amides of anthranilic and homoveraic acids and led to the formation of compound VIII, followed by sulfonation with sulfuric acid and the formation of compound IX (Fig. 2).

To confirm the molecular design reliability, a study of the pharmacological properties of the synthesized substances was carried out. Previously, the anticataleptic effect of the predicted 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone, as well as the effect on the blood coagulation, was experimentally shown [12, 31].

With reference to these studies, to research their analgesic activity was considered appropriate. Under the influence of the studied compounds in the female animals, a statistically significant decrease in the number of pain responses was observed when substance VIII was used throughout all stages of testing with formalin (Table 3).

In the "acetic acid writhings" test, 4(3H)-quinazolinone derivatives III, VIII, and IX significantly limited the frequency of pain responses in the female rats. At the same time, the effect of substance III was most pronounced, and compounds VIII, IX outperformed the reference drug lidocaine.

Based on the data of the pharmacological studies, it follows that compounds III, VIII, IX reduce the frequency of nociceptive responses in the female rats, showing an analgesic effect.

Next, a study of quantitative structure-activity relationships in the series of 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone, which made it possible to identify molecular descriptors characterizing an analgesic activity, was carried out.

The assessment of the results reliability of the molecular design should be confirmed by a correlation analysis. This analysis was carried out between the theoretically calculated formation energies of the ligand-receptor complex and molecular descriptors with the experimentally obtained results of the analgesic activity. The values of pain responses in female rats had been used as experimental values for these calculations.

The approximation coefficient (R^2) between the minimum binding energies of the studied molecules with the nociceptive receptor and the results of the formalin test is 93.9%, and the average values of the formation energies of ligand-receptor complex – 82.3%. The approximation coefficient between the minimum binding energy of the predicted structures with the dopamine receptor and the results of the formalin test are a great deal less, so they are not given. This fact suggests a great interaction contribution of the studied substances with the nociceptive receptor, which manifests itself in the analgesic activity of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone. The most stable ligand-receptor complexes of the leader compound (VIII) in the binding site with dopamine and nociceptive receptors are shown in Fig. 3.

The approximation coefficient between the minimum binding energy of the studied molecules with the nociceptive receptor and the values of the "acetic acid writhings" test is 75.48%. At the same time, the coefficient of approximation between the binding energies of the investigated molecules with the dopamine receptor and the results of the "acetic acid writhings" test is insignificant, i.e., there is no correlation.

Subsequently, to identify the correlation between quantum-chemical and topological descriptors with the results of the analgesic activity, the HyperChem (energy calculation) and T.E.S.T. (Toxicity Estimation Software Tool) programs were used [32]. (Table 4).

Table 5 shows the energies of the most stable conformations with isolated amino acid residues in the binding site of BACs and the nociceptive receptor.

To select the most significant amino acid residues when constructing a mathematical model in the Molegro Data Modeler program, a correlation matrix was calculated for the results of the tests. The matrix is shown in Table 6 below.

Based on the number of substances in the sample and the data of the formalin test correlation matrix, the following amino acid residues were selected to build a mathematical model: **Gln 280, Ile 219, Met 134, Phe 215,** and for the "acetic acid writhing" test – **Asp 130, Phe 215, Met 134 , Val 202.** In addition to the indicated interaction energies, two independent variables – Total Energy and SdO – turned out to be the most relevant in constructing the predictive model (Table 7).

The proposed predictive model can be used for the molecular design of highly effective and safe BACs, since it is characterized by sufficiently high approximation coefficients and makes it possible to judge the significant reliability of the studies carried out.

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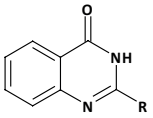
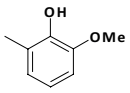
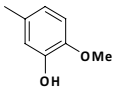
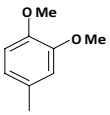
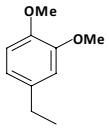
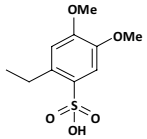
Table 1 – Predicted types of biological activity of hydroxy- and methoxyphenyl, as well as dimethoxybenzyl derivatives of 4(3H)-quinazolinone



R substituent / Biological activities	III	IV	V	VI	VII	VIII	IX
							
	Pa, %						
Broncholytic	86.3	81.2	75.1	75.1	80.7	55.7	40.5
Psychotropic (dopamine release stimulant)	39.8	57.4	64.2	64.2	–	60.5	35.9
Psychotropic (stimulator of serotonin release)	54.6	50.3	56.5	56.5	61.2	44.7	–
Antiviral	89.4	84.2	73.4	73.4	–	64.8	52.4
Anti-ischemic	61.2	65.4	70.3	70.3	67.4	59.7	64.8
Histamine inhibitor	54.1	50.3	51.2	51.2	–	50.1	46.5
Neuroprotective	51.6	52.7	56.8	56.8	63.5	57.3	32.7
Antiulcer	47.3	61.4	62.6	62.6	62.1	–	85.7
Cardioprotective	54.6	58.9	65.7	65.7	–	57.6	51.9

Note: Pa (%) characterizes the probability of an pharmacological activity manifestation.

Table 2 – Minimum and average mean energies of interaction with nociceptive and dopamine receptors of 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone

Substances	Minimum energy (nociceptive receptor), kcal/mol	Average energy (nociceptive receptor), kcal/mol	Minimum energy (dopamine receptor), kcal/mol	Average energy (dopamine receptor), kcal/mol
III	-98.443	-75.808	-94.905	-83.205
IV	-99.098	-74.455	-110.399	-93.380
V	-106.250	-78.909	-108.822	-93.935
VI	-99.595	-73.997	-108.96	-92.002
VII	-105.502	-81.574	-106.676	-94.181
VIII	-111.212	-87.347	-110.732	-99.709
IX	-115.508	-91.058	-126.920	-111.839
Lidocaine	-88.152	-68.476	-87.250	-70.356

Table 3 – Influence of 2-phenyl and 2-benzyl derivatives of 4(3H)quinazolinone on parameters of the formalin test and the number of "acetic acid writhings" in female rats (in the % data of the control group)

Substances	Formalin test			Acetic acid writhings
	Whole period	Phase 1 (10 min)	Phase 2 (50 min)	
III	68.0	65.9	69.3	11.7*
IV	71.3	64.5	75.2	45.6
V	111.0	42.9	150.7	63.6
VI	96.7	71.9	111.1	75.6
VII	96.2	71.0	110.8	82.0
VIII	17.0*	29.1*	10.0*	19.5*
IX	43.5	49.2	40.2	32.0*
Lidocaine	50.3	61.4	43.8	39.4*

Note: significant relative to the control group of female rats: * – p <0.05 (Kruskal-Wallis test with Dunn's test).

Table 4 – Total energy of formation calculated by the Monte Carlo method and molecular electrotopological indices for 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone

Substances	Energy, kcal/mol	SdO	SHssNH	Formalin writhings	Acetic writhings
III	-3216.51	11.907	2.0492	68.0	11.7
IV	-3582.71	11.9981	2.0621	71.3	45.6
V	-3582.87	12.0181	2.0631	111.0	63.6
VI	-3836.77	12.0989	2.0662	96.7	75.6
VII	-3574.60	12.0302	2.0866	96.2	82.0
VIII	-4115.67	12.073	2.0158	17.0	19.5
IX	-4471.47	35.7029	2.1112	43.5	32.0
Lidocaine	-3232.35	11.8923	1.8784	50.3	39.4

Table 5 – Interaction energies of 2-phenyl and 2-benzyl 4(3H)-quinazolinone derivatives with amino acid residues of the nociceptive receptor

Substances	Amino acid residues								
	Ala216	**Gln280**	**Ile219**	Leu284	**Met134**	**Phe215**	Phe220	Ser223	**Val202**
III	-0.655	-7.449	-20.062	-9.307	-6.349	-3.098	-9.962	-4.889	0
IV	-13.857	-9.791	-17.865	-1.903	-1.694	-19.934	-3.943	-0.903	-0.3986
V	-11.549	-10.136	-19.453	-8.007	-0.311	-22.050	-9.408	-0.661	-1.7388
VI	-11.974	-5.023	-13.882	-10.253	0	-23.701	-6.637	-0.811	-3.7199
VII	-8.713	-4.146	-19.999	-8.621	0	-22.635	-9.043	-0.581	-3.9376
VIII	-7.605	-22.105	-8.656	-9.932	-12.806	-4.417	-8.089	-2.506	0
IX	-8.843	-13.104	-13.042	-5.753	-6.222	-10.783	-5.317	-1.357	0
Lidocaine	-9.059	-19.582	-14.256	-9.166	-2.763	-3.876	-8.039	-1.298	0

Table 6 – Results of the mathematical model for significant amino acid residues of 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone

Biological activity	Amino acid residues								
	Ala216	**Asp130**	**Gln280**	**Ile219**	**Met134**	Phe135	**Phe215**	Ser223	**Val202**
Formalin writhings	0.099	0.421	0.670	0.570	0.780	0.039	0.648	0.162	0.553
Acetic acid writhings	0.390	0.583	0.356	0.115	0.682	0.453	0.801	0.633	0.834

Table 7 – Results of building a predictive model of analgesic activity for 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone

Biological activity	R^2	R^2 for sliding control	Model
Formalin test	0.915	0.877	Activity=0.00398328×Total Energy–0.271986×SdO+1.24195×Gln280–1.58577×Ile219+2.06023×Met134–1.04422×Phe215+70.3678
"Acetic acid writhings" test	0.954	0.886	Activity=-0.00667588×Total Energy–0.158964×SdO+1.72064×Asp130+1.14011×Met134–0.852054×Phe215–5.75385×Val202+12.5588

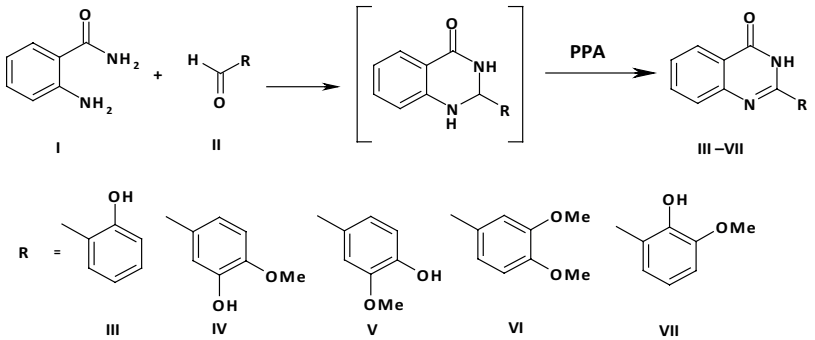


Figure 1 – Scheme for synthesis of 2-phenyl derivatives of 4(3H)-quinazolinone III–VII
Note: PPA – polyphosphoric acid.

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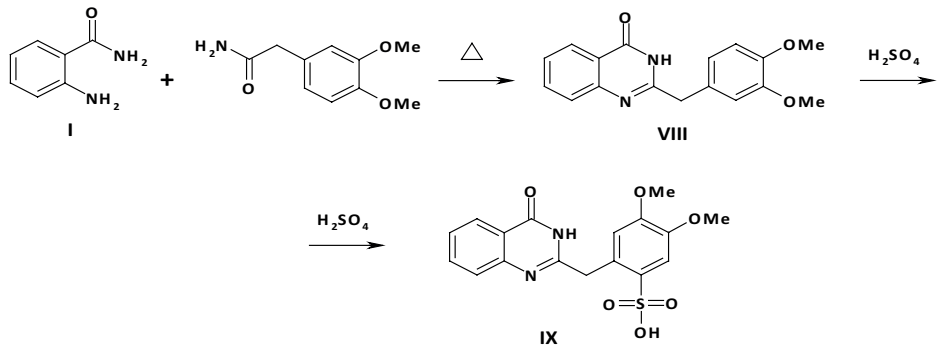
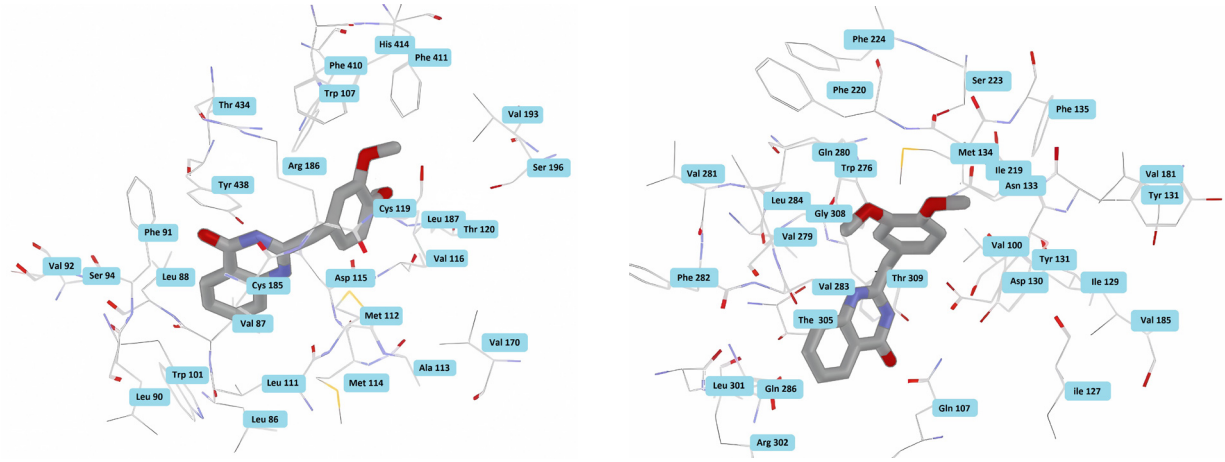


Figure 2 – Scheme for the synthesis of 2-benzyl derivatives of 4(3H)-quinazolinone VIII and IX



A B

Figure 3 – Ligand-receptor complexes of the leader compound (VIII), which have the most stable, with dopamine (A) and nociceptive (B) receptors

DISCUSSION

A neuroprotective activity can manifest itself in a stimulating effect on neurotransmitter systems, which became the basis for a molecular docking of the predicted substances with nociceptive and dopamine receptors.

Primarily, formalin exerts its pharmacological action through the activation of channels of the variable receptor potential of ankyrin 1, TRPA1, which normally respond to cold and stimulate the development of inflammation [33–35]. According to the experimental studies, two phases can be distinguished in the formalin test mechanism. The drugs related to local anesthetics, affect the first phase of the nociceptive response, while non-steroidal anti-inflammatory drugs suppress mainly the second phase of the formalin test [26, 36–38].

The studied compounds presumably have a dopaminergic activity, which is expressed in the anticataleptic effect revealed for 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone in previous studies [12]. Two groups of dopamine receptors are known: the D_1-type group (D_1 and D_5) and the D_2-type group (D_2, D_3 and D_4), which are opposite in their mechanism of action and affect cellular processes in different ways. The dopamine receptors are associated with G proteins. A group of D_1-type receptors has an activating effect on the adenylate cyclase, while D_2-type receptors inhibit its activity, which leads to a decrease in the concentration of cAMP in the cells and the activation of potassium channels [39, 40].

In relation to the nociceptive receptor, all the predicted structures are characterized by a higher binding energy with the receptor than the reference drug, lidocaine. Comparing the results of the molecular docking of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone, an assumption about the pronounced analgesic activity of the latter can be made. The values of the minimum and average energies of the ligand-receptor complex with the nociceptive receptor formation, are comparable for structures VIII and IX.

The modification of preparative studies consists in carrying out the reaction in a polyphosphoric acid medium, which allows the resulting intermediate dihydroquinazolinone to be converted into the target 4(3H)-quinazolinone heterocycle without an additional oxidation step. We have shown that

When the reaction is carried out in the PPA medium, an additional oxidation process is eliminated. The fact

that the reaction yields exceed 50% at an equimolar ratio of reactants makes it possible to exclude the possibility of the reaction proceeding through a disproportionation. Perhaps the role of the oxidizing agent is performed by atmospheric oxygen, or pentavalent phosphorus PPA.

An important requirement for drug candidates is their water solubility, the increase of which consists, among other things, in the introduction of highly polar groups into the molecule. On this basis, to increase the solubility of the substance in water, the structures that form internal salts, were obtained. The simplest way to achieve this goal is to sulfonate the activated aromatic ring of the nitrogen-containing heterocycle, the heterocyclic fragment of which plays the role of a proton acceptor. Quinazolinones containing two nitrogen atoms seem to be a good model in this respect.

From the data in Table 3 show that the analgesic activity is observed in 2-phenyl and 2-benzyl derivatives of 4(3H)-quinazolinone in the formalin test and in the "acetic acid writhing" test. It should be noted that compared with the activity of other studied compounds and the reference drug lidocaine, the analgesic effect of substance VIII was stable and expressed in the both test methods used. In the "acetic acid writhing" test, the greatest analgesic effect is noted for substance III, and here, the effect is more pronounced than that of lidocaine.

Since compound VIII is active in the first phase of the formalin test, it can be assumed that it exhibits an antineoceptive action, exerting a local anesthetic effect. Compound VIII also blocks the second phase of the test in animals, which suggests a combination of a local anesthetic and anti-inflammatory activity in the mechanism of the analgesic action of this substance. It is possible that the analgesic activity of the studied compound is realized by acting on C-polymodal nociceptors that are sensitive to chemical stimuli, in particular, to formalin.

A correlation analysis of the quantum-chemical parameters of the structures and the results of the pharmacological tests showed that the highest approximation coefficient is observed for 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone and the reference drug lidocaine when used in the calculations of the total energy, and the results of the formalin test (96.08%). However, for the "acetic acid writhing" test, the coefficient is much lower (69.58%). Accordingly, these data make it possible to reveal the differences between the formalin and acetic acid writhing tests for assessing the analgesic activity and the prospects for their use in predicting the analgesic activity for 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone.

CONCLUSION

By means of the molecular design, a targeted synthesis of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone with an analgesic activity was carried out. The results of correlation studies made it possible to identify molecular descriptors and create a predictive model for the search for new analgesic compounds in the series of 4(3H)-quinazolinone derivatives. The reliability of the molecular design of virtual molecules with the given pharmacological properties has been experimentally proven to a certain extent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Ivan P. Kodonidi –research idea and molecular design methodology of biologically active substances and QSAR calculations of molecular descriptors; Alexander V. Bicherov – synthesis methods development of 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone; Eleonora A. Manvelyan – working out a pharmacological research strategy, results interpretation; editing and approval of manuscript pharmacological part; Aleksandra A. Kolodina – NMR spectra interpretation, 4(3H)-quinazolinone derivatives purification; Aleksandr A. Bicherov – 2-phenyl- and 2-benzyl derivatives of 4(3H)-quinazolinone synthesis; Mikael M. Manvelyan – pharmacological studies conducting; statistical analysis results and interpretation, pharmacological part of the manuscript writing; Aleksandr V. Ivchenko – analysis of the relationship structure-analgesic activity; Natalia N. Vdovenko-Martynova – results interpretation of molecular descriptors calculation; Aida T. Navalieva – predictive models analysis; Maria M. Manvelyan – pharmacological studies conducting.

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